Supporting Information

Structural and Synthetic Investigations of Tanikolide Dimer, a SIRT2 Selective Inhibitor, and Tanikolide *Seco* Acid from the Madagascar Marine Cyanobacterium *Lyngbya majuscula*

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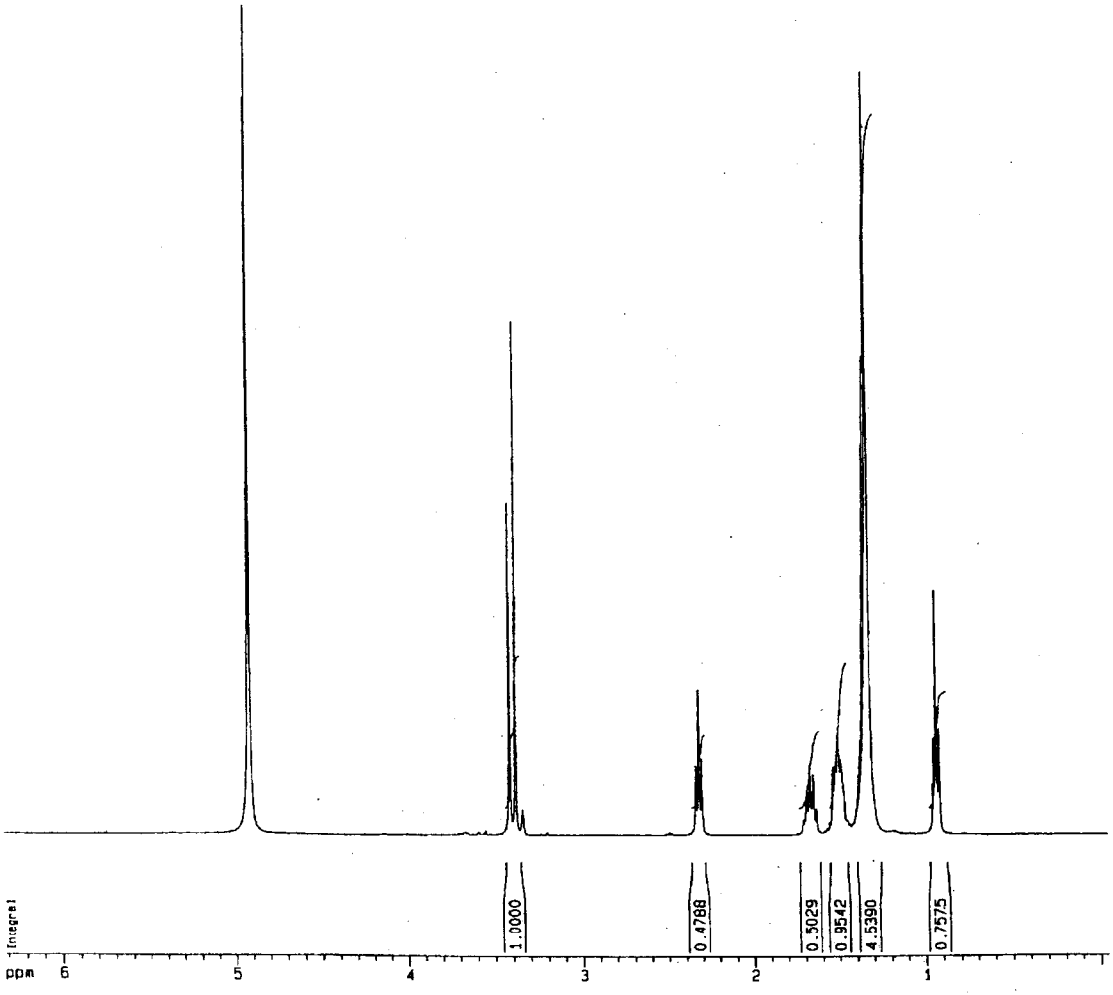
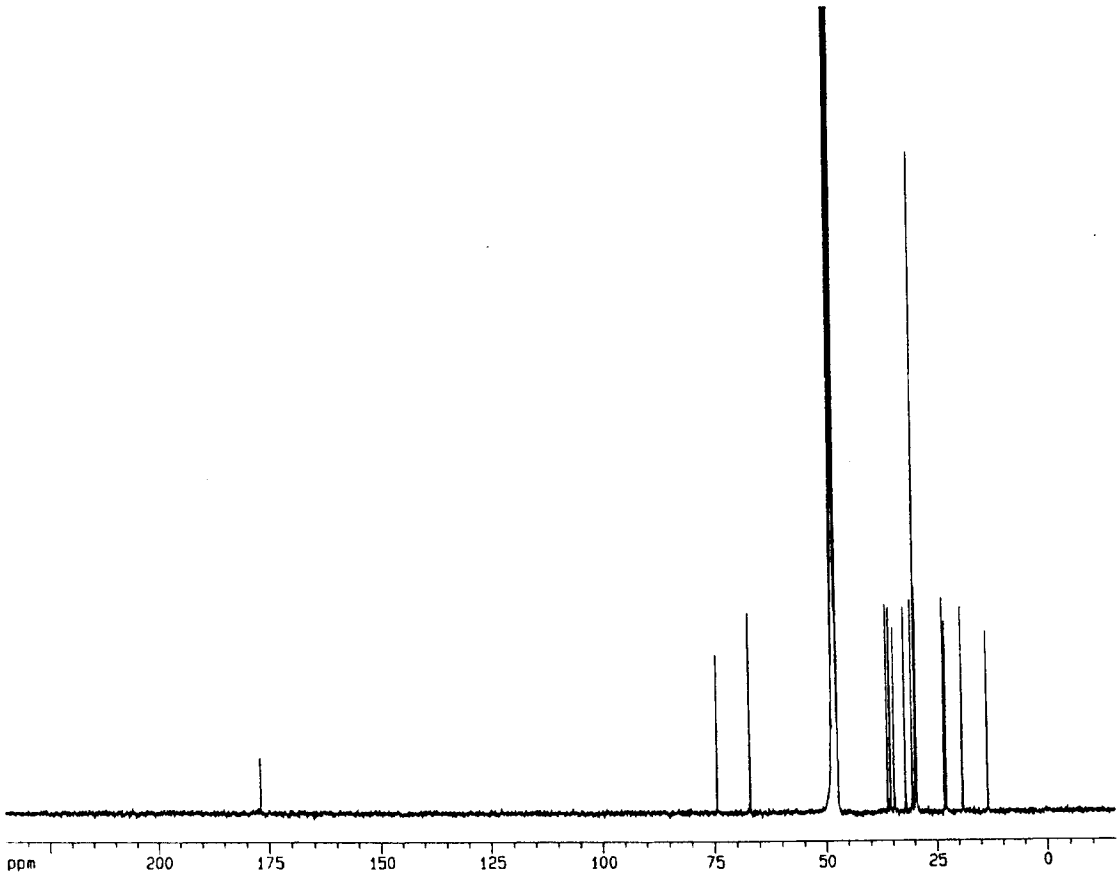
General Experimental Methods – Natural Products: NMR spectra were referenced to residual solvent signal with resonances at $\delta_{H/C}$ 7.26 / 77.1 ($CDCl_3$) and $\delta_{H/C}$ 3.31/49.15 (CD_3OD). X-ray diffraction data were collected on a diffractometer with a HiStar Cu Kα radiation area dectector. Structure solution and refinement was carried out using SHELXS and SHELXL, respectively. Chiral GC-MS analyses was performed on a Cyclosil-B chiral column (30m x 0.250 mm).

General Experimental Methods – Synthesis: NMR chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. The progress of chemical reactions were checked on Merck TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or by charring after dipping the TLC plate into a vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated H_2SO_4 in 300 mL of MeOH), a $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of H_2O), or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL EtOH). Column chromatography was performed on Merck silica gel (9385 Kiesel gel 60) using hexanes-EtOAc (v/v). The solvents were simple distilled unless otherwise noted. Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry N_2. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhyd $MgSO_4$ and evaporating under reduced pressure using a rotary evaporator. Solvents used in the reactions were dried under a N_2 atmosphere. THF was distilled from Nabenzophenone, and CH_2Cl_2 was distilled from P_2O_5. Benzene was washed with conc. H_2SO_4, distilled from Na-benzophenone, and stored over 4 Å molecular sieves. Et_2O was distilled from $LiAlH_4$. CH_3CN was distilled from CaH_2 and stored over 4 Å molecular sieves. Pyridine and triethylamine were distilled over KOH and stored over 4 Å molecular sieves.

400 MHz ^{1}H NMR of compound **2** in CD_3OD



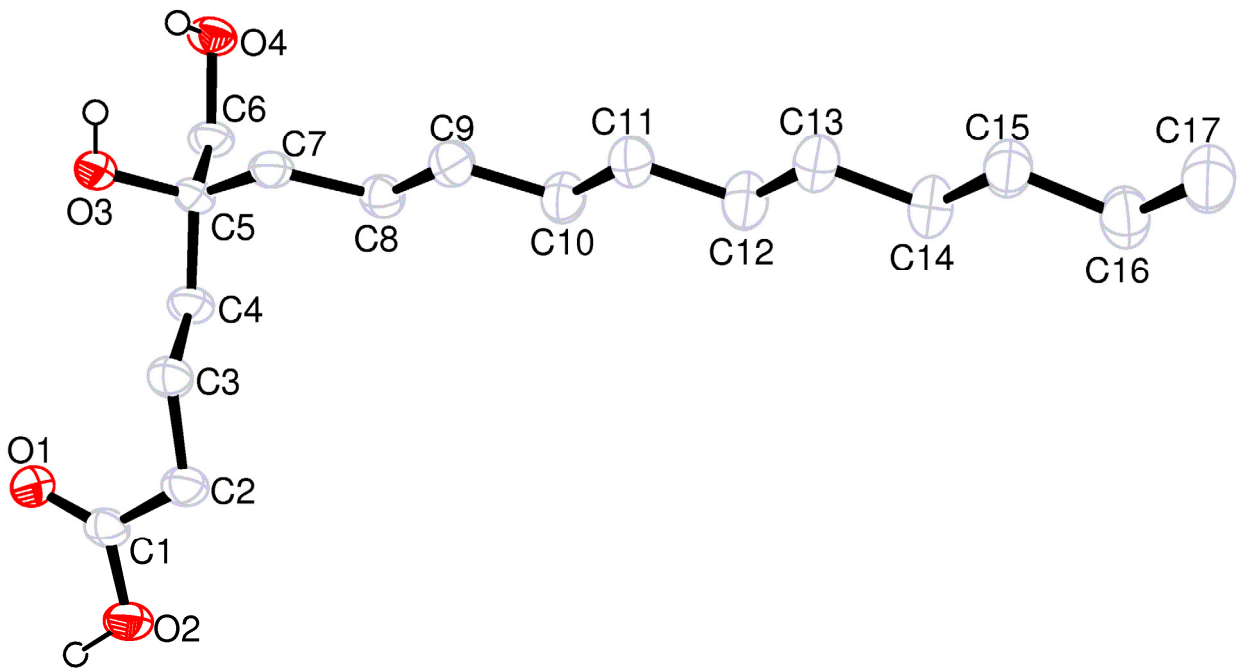
100 MHz ^{13}C NMR of compound **2** in CD_3OD



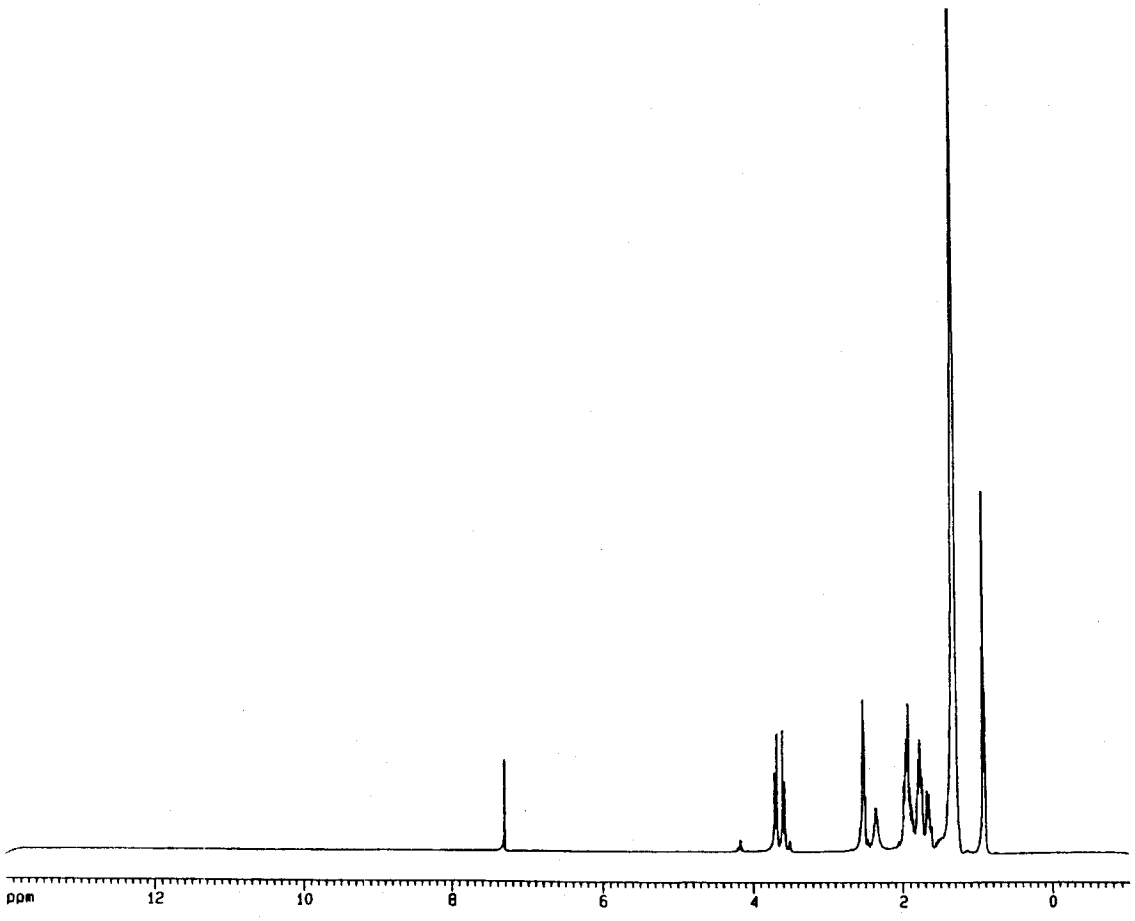
X-ray crystallographic data and structure refinement for compound **2**

Identification code	WG112003	
Empirical formula	$C_{17}H_{34}O_4$	
Formula weight	302.44	
Temperature	100(2) K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 5.524(4) Å	α = 90°
	b = 8.048(5) Å	β= 97.180(14)°
	c = 20.295(12) Å	γ = 90°
Volume	895.2(10) $Å^3$	
Z	2	
Density (calculated)	1.122 Mg/m^3	
Absorption coefficient	0.618 mm^{-1}	
F(000)	336	
Crystal size	0.30 x 0.10 x 0.02 mm^3	
Theta range for data collection	4.39 to 71.19°.	
Index ranges	0<=h<=6, -9<=k<=9, -24<=l<=24	
Reflections collected	8951	
Independent reflections	2294 [R(int) = 0.1640]	
Completeness to theta = 71.19°	85.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.1337	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2294 / 1 / 196	
Goodness-of-fit on F^2	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0882, wR2 = 0.2253	
R indices (all data)	R1 = 0.0975, wR2 = 0.2358	
Absolute structure parameter	0.5(7)	
Largest diff. peak and hole	0.274 and -0.339 $e.Å^{-3}$	

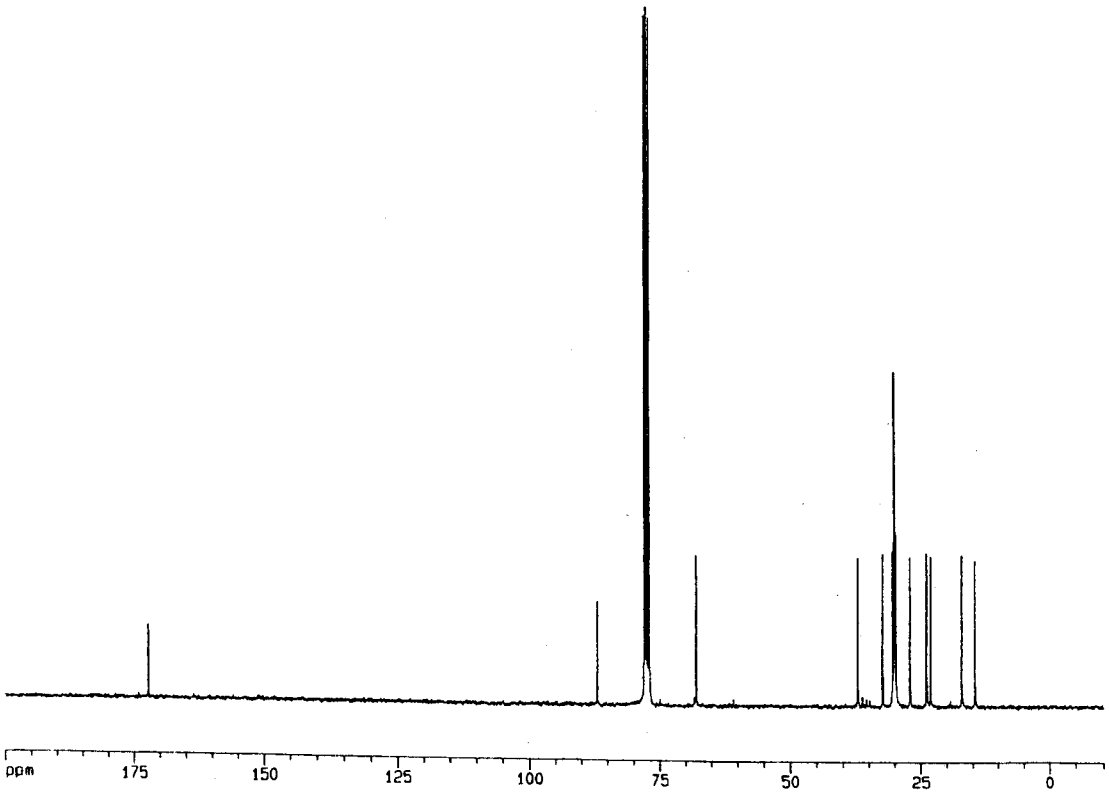
ORTEP of tanikolide *seco* acid **2** with 50% displacement ellipsoids



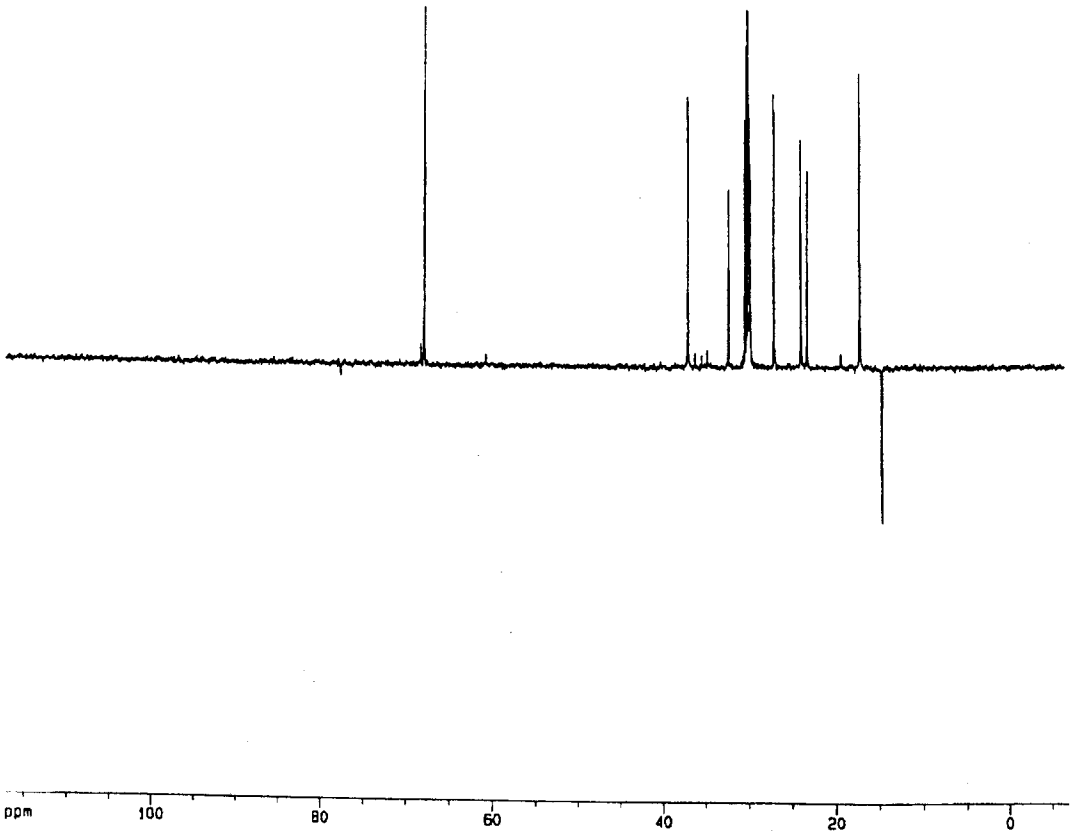
400 MHz ^{1}H NMR of compound **3** in $CDCl_3$



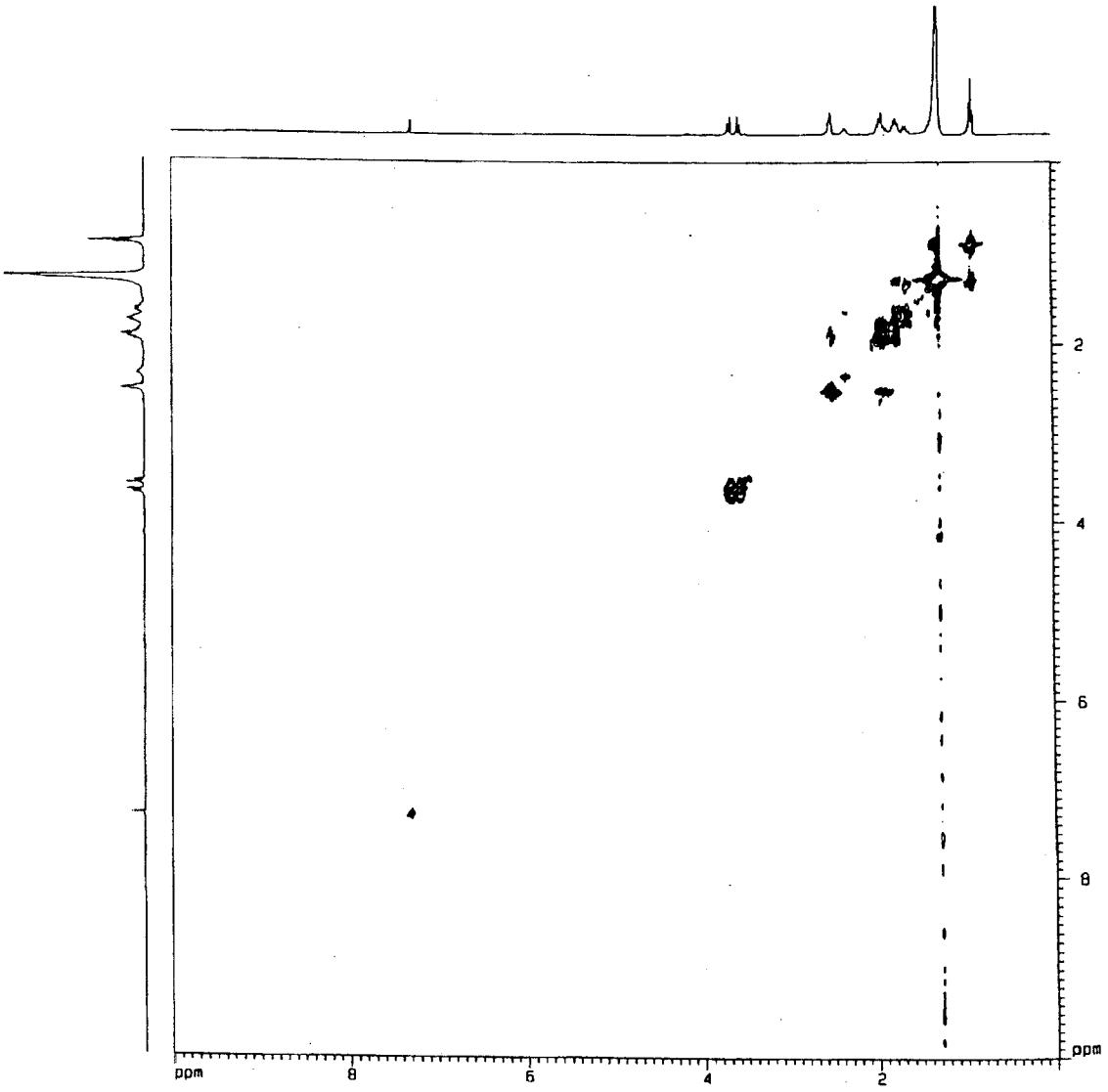
100 MHz ^{13}C NMR of compound **3** in $CDCl_3$



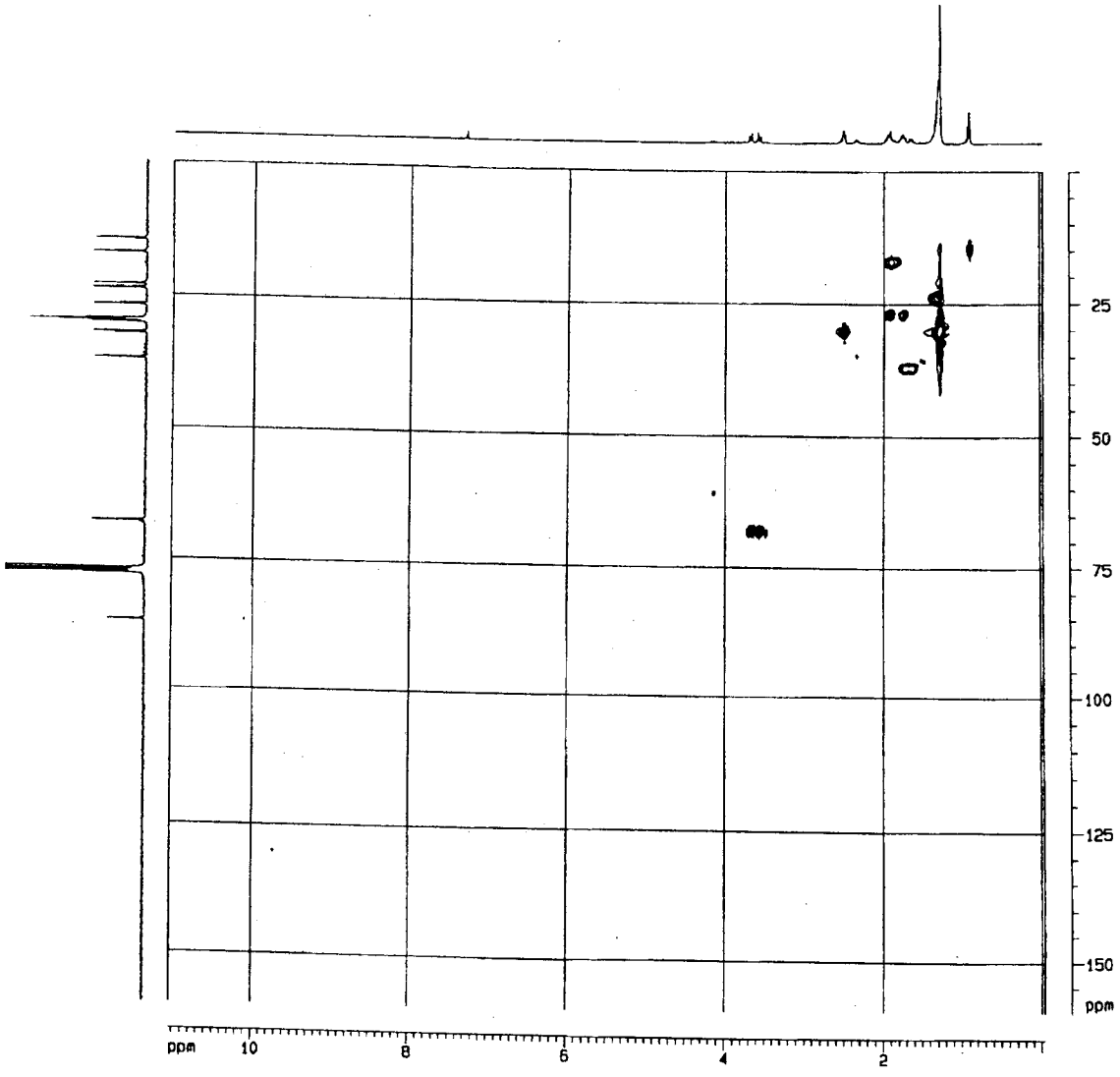
100 MHz DEPT 135 spectrum of compound **3** in $CDCl_3$



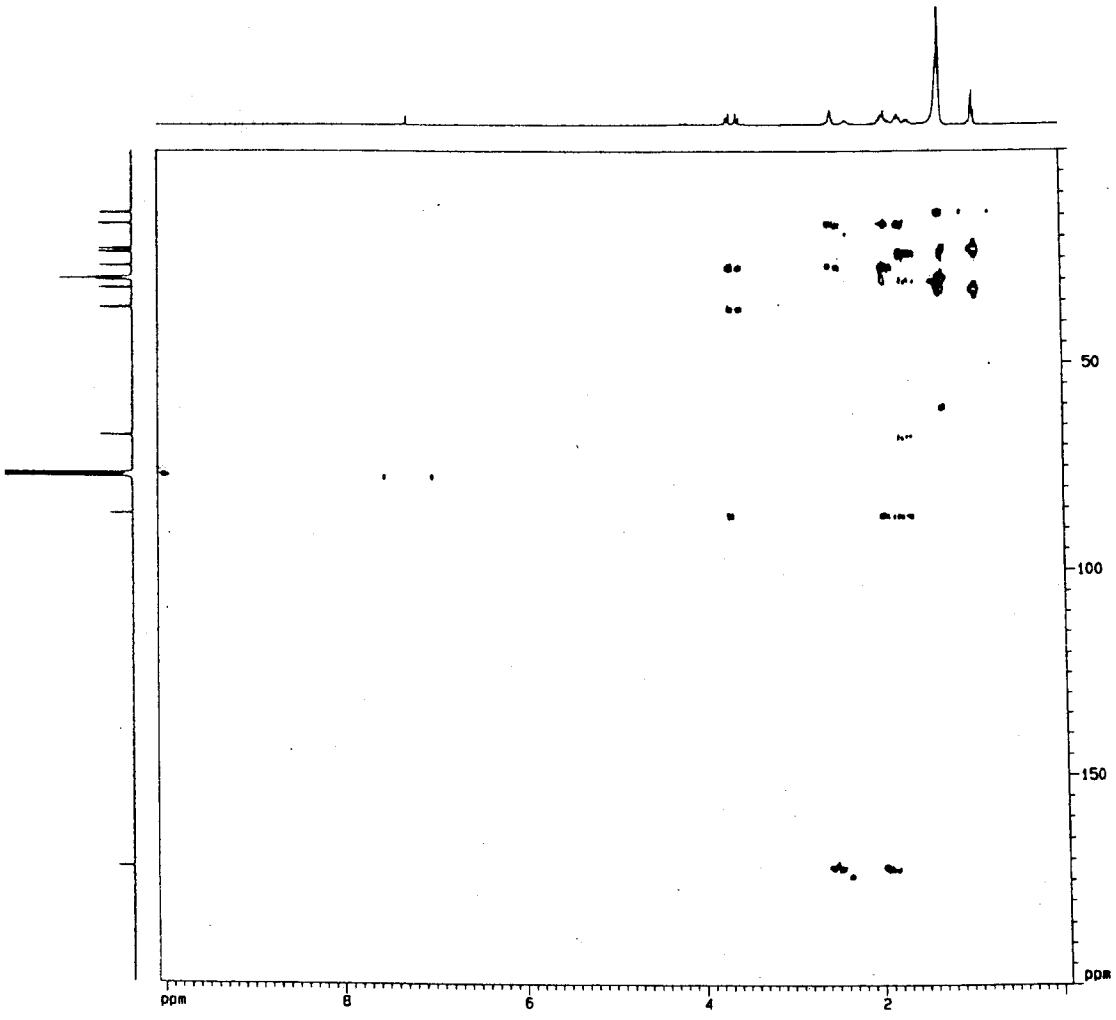
400 MHz ^{1}H-^{1}H COSY spectrum of compound **3** in $CDCl_3$



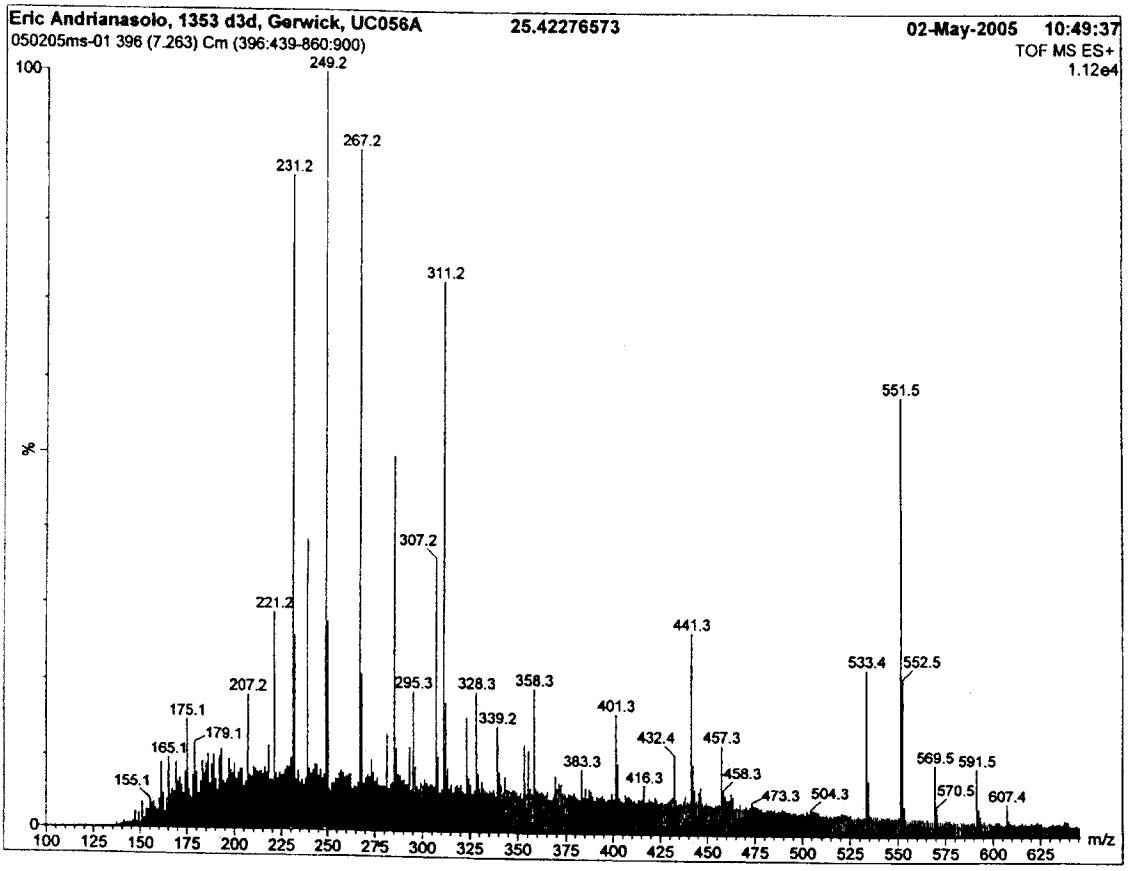
400 MHz Multi-edited HSQC spectrum of compound **3** in $CDCl_3$



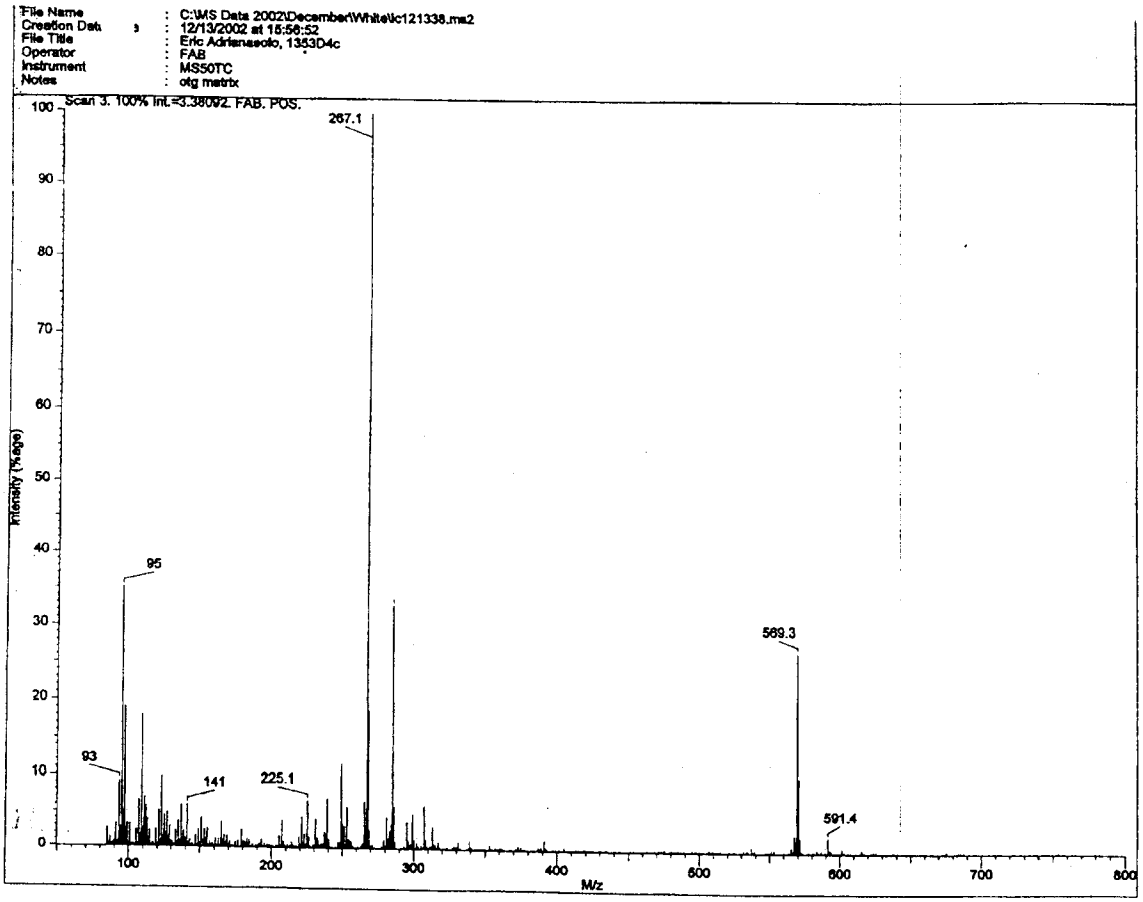
400 MHz HMBC spectrum of compound **3** in $CDCl_3$ optimized for J = 8 Hz



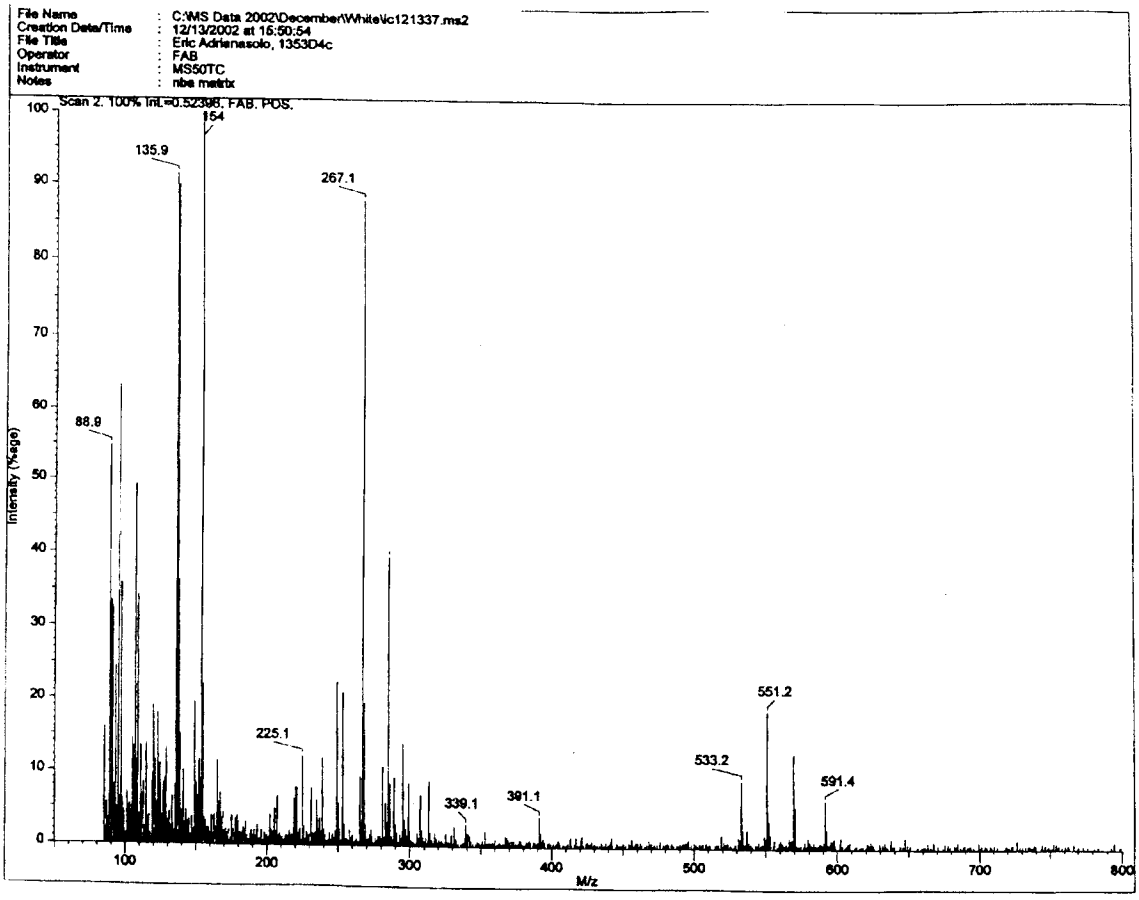
LR TOF MS ES+ spectrum of compound **3**

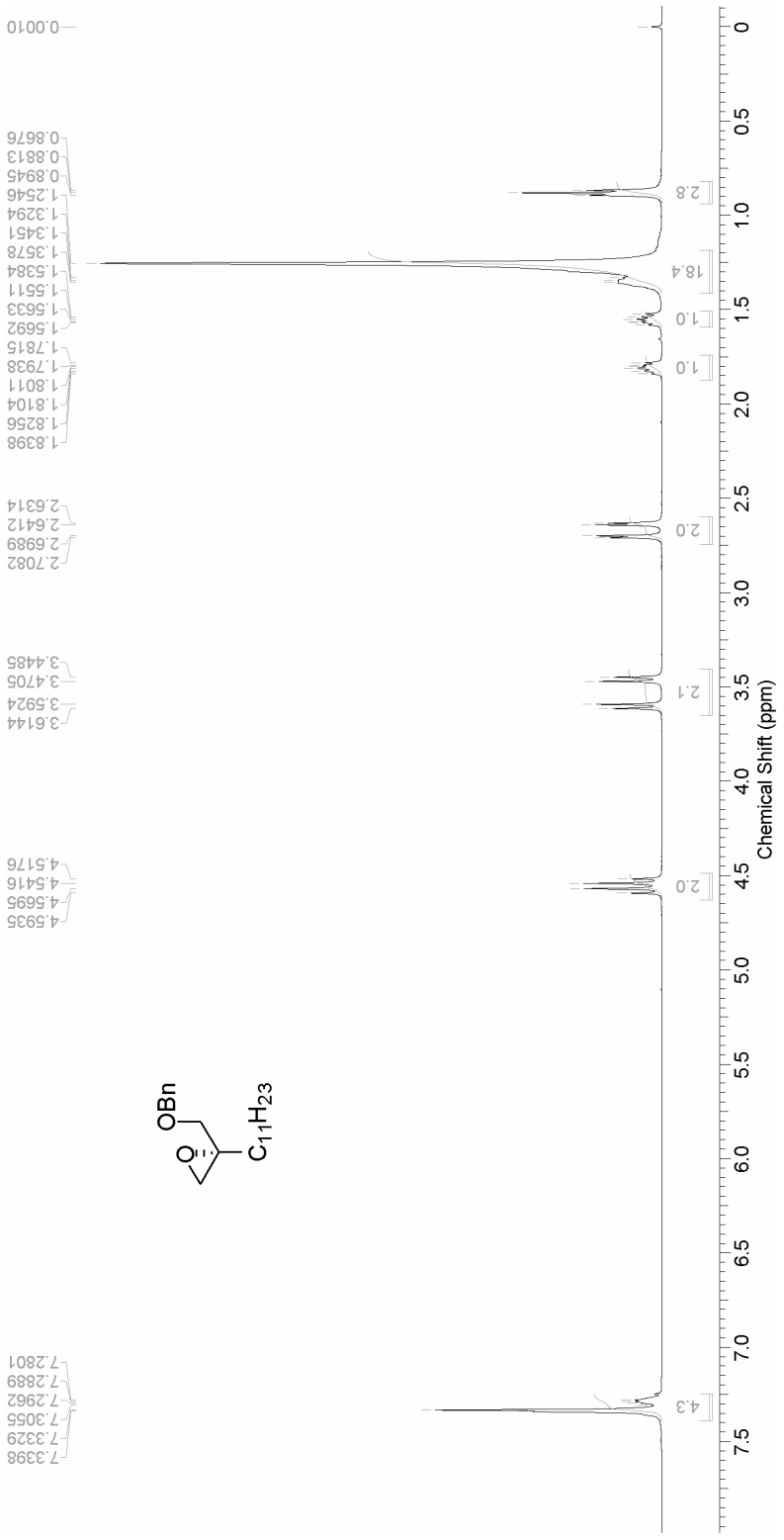


LR FAB (otg matrix) spectrum of compound **3**

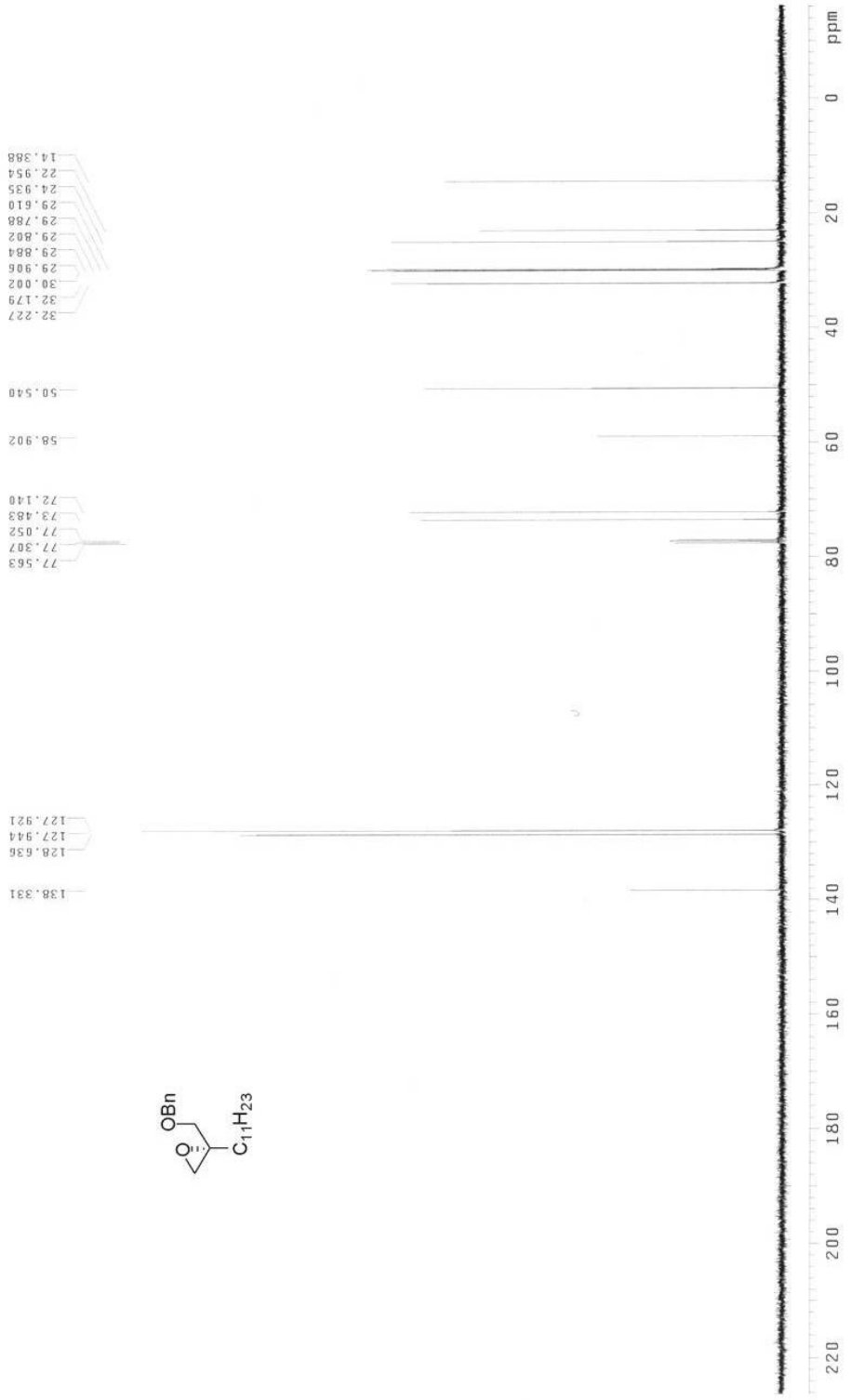


LR FAB (nba matrix) spectrum of compound **3**

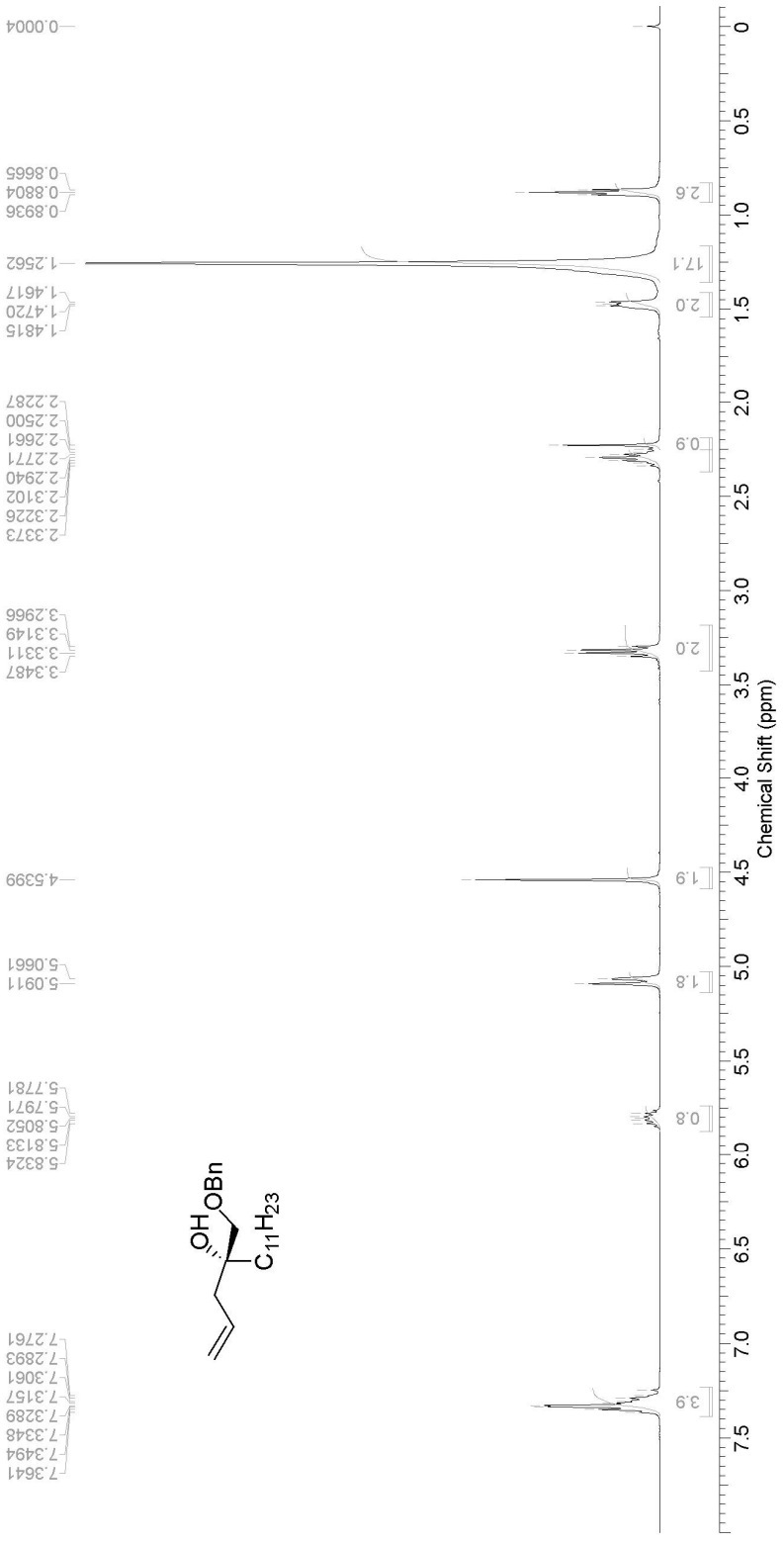




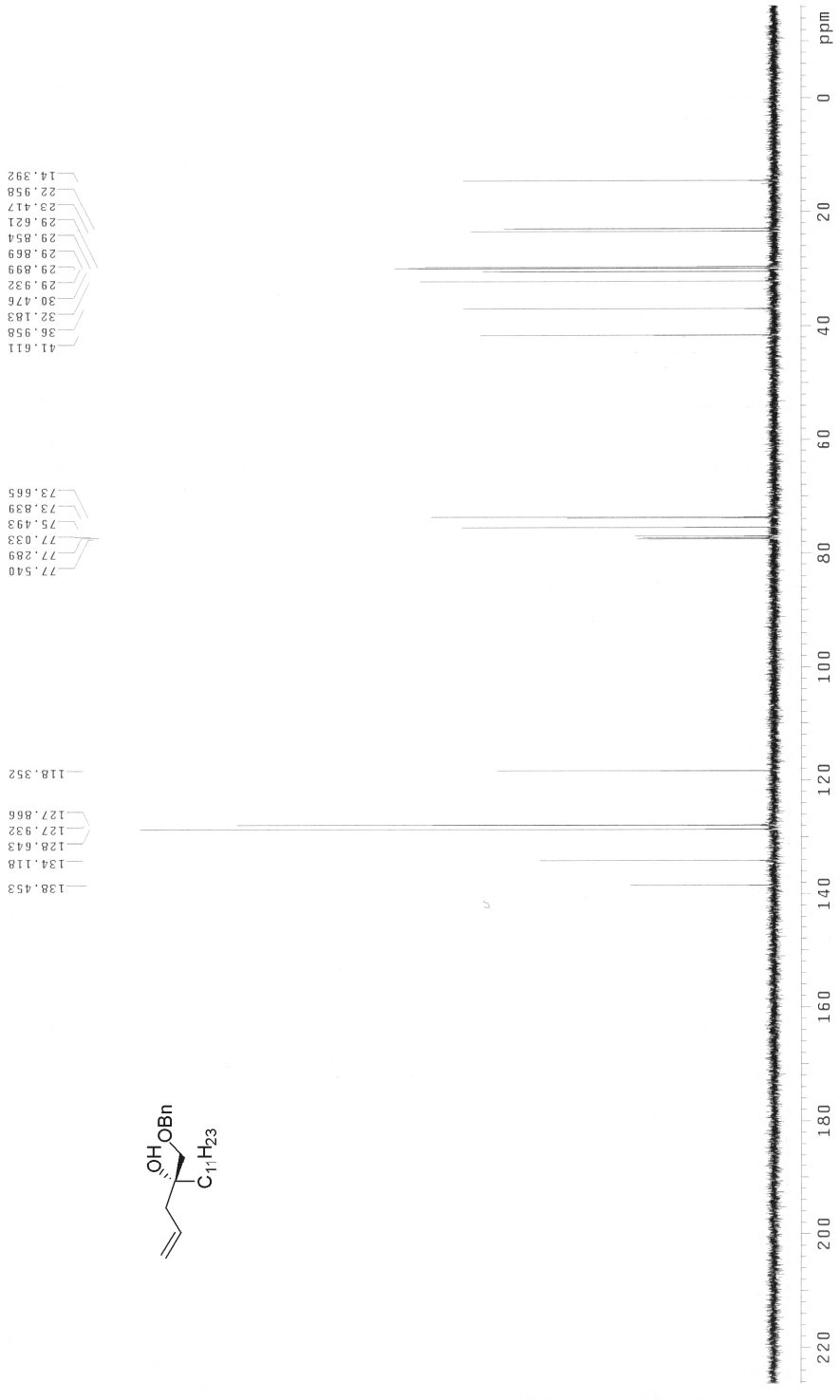
^{1}H-NMR (500MHz, CDCl3) of the benzyl ether of epoxide **6**



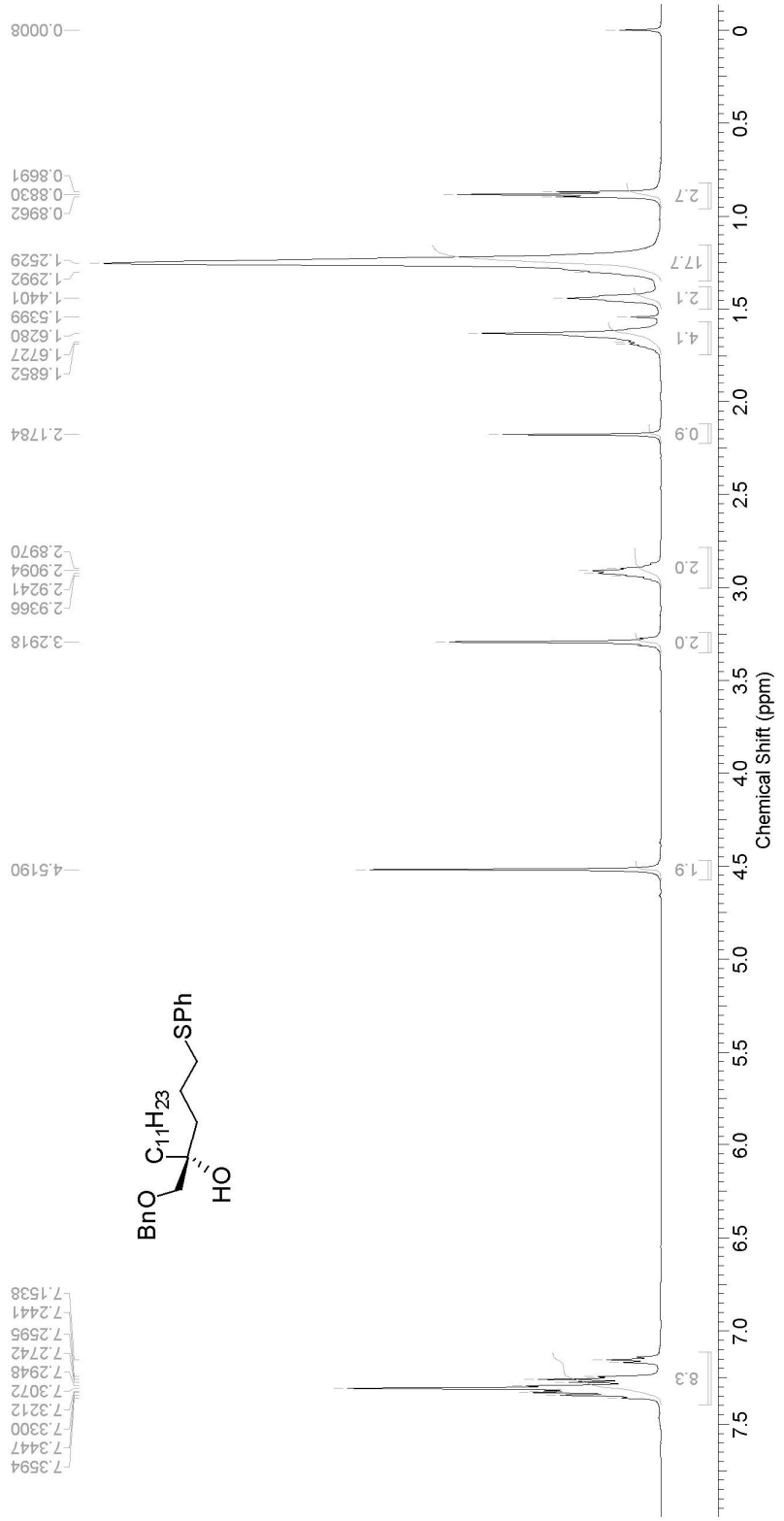
^{13}C-NMR (125 MHz, CDCl3) of the benzyl ether of epoxide **6**



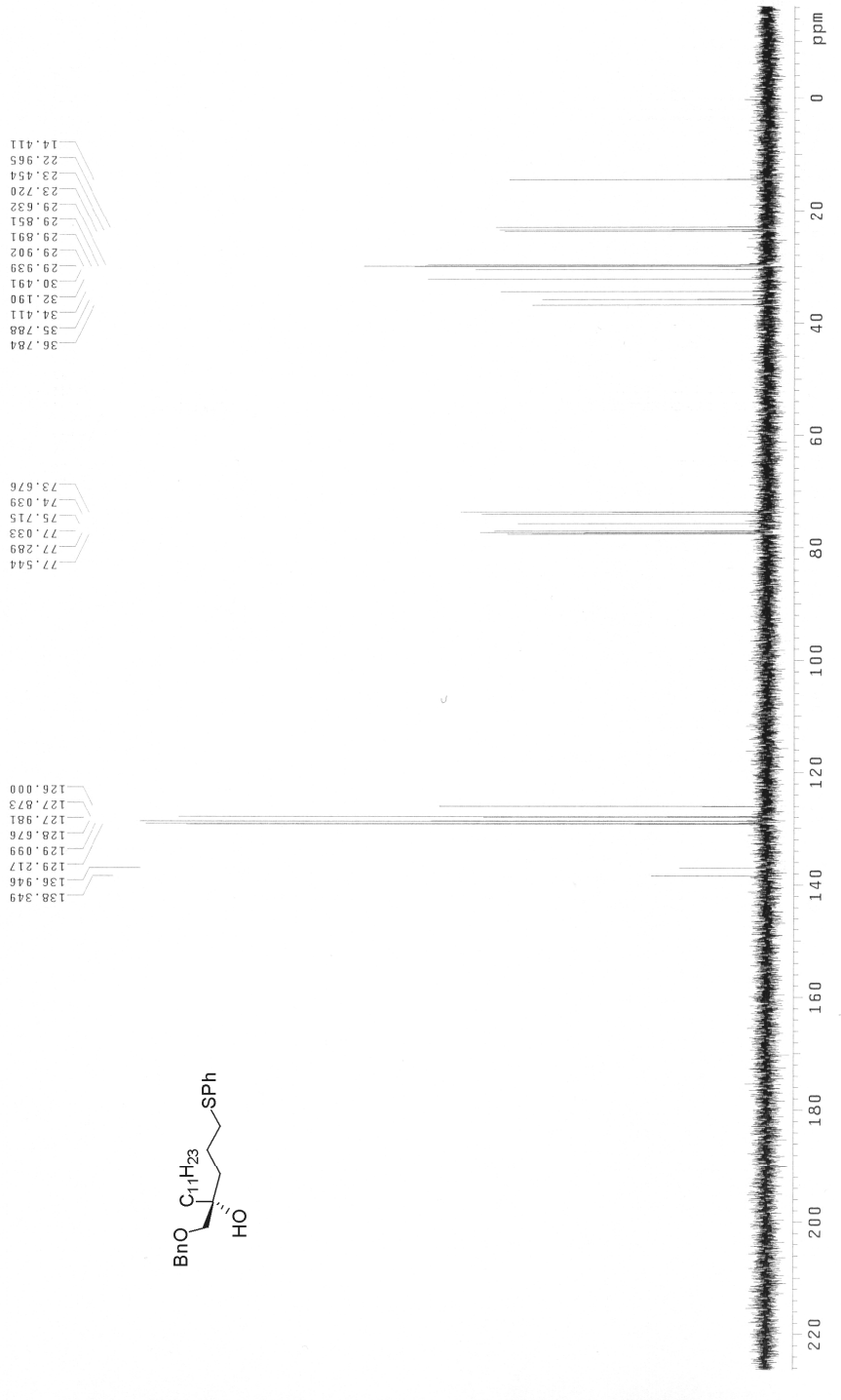
^{1}H-NMR (500 MHz, $CDCl_3$) of **7**



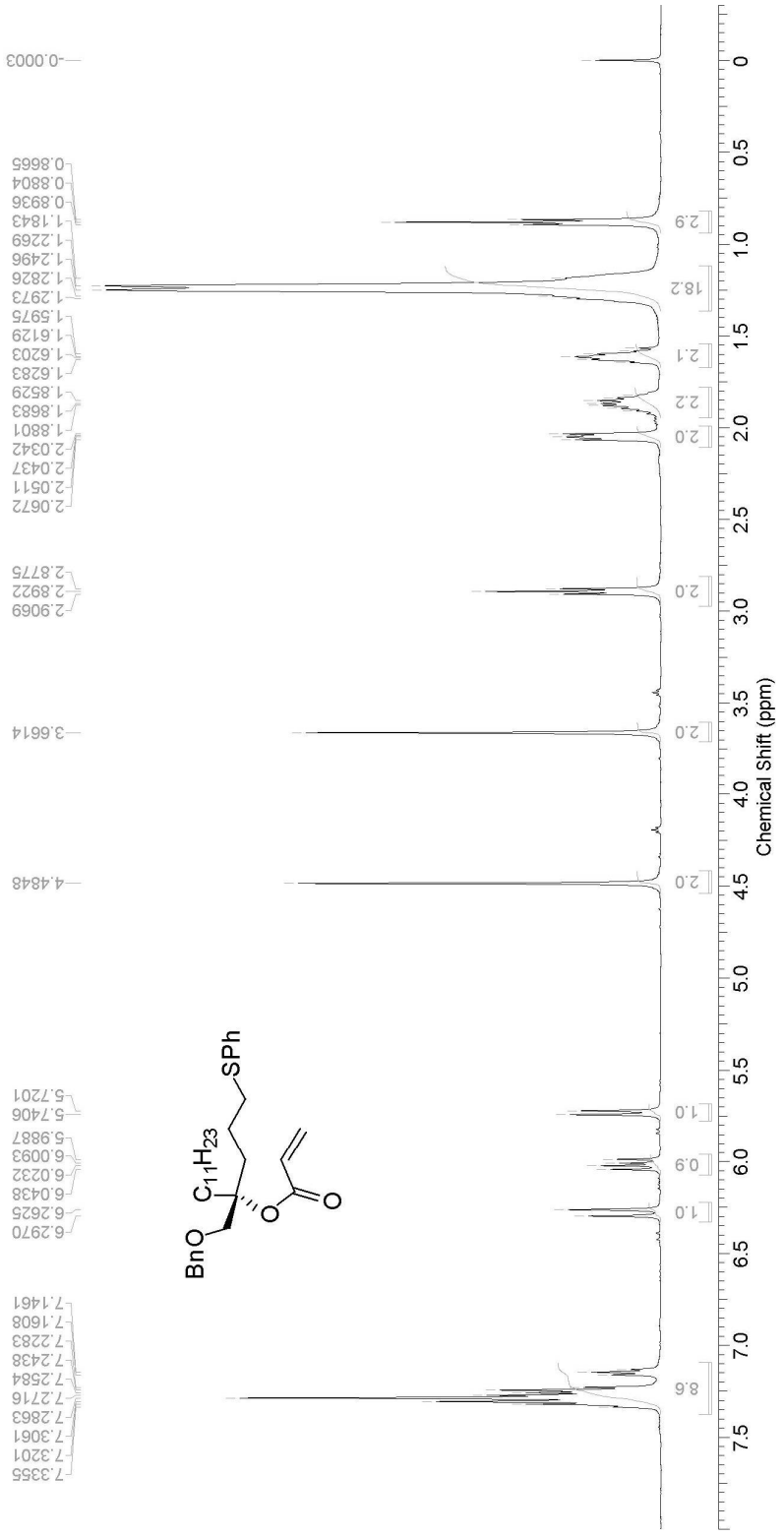
^{13}C-NMR (125 MHz, $CDCl_3$) of **7**



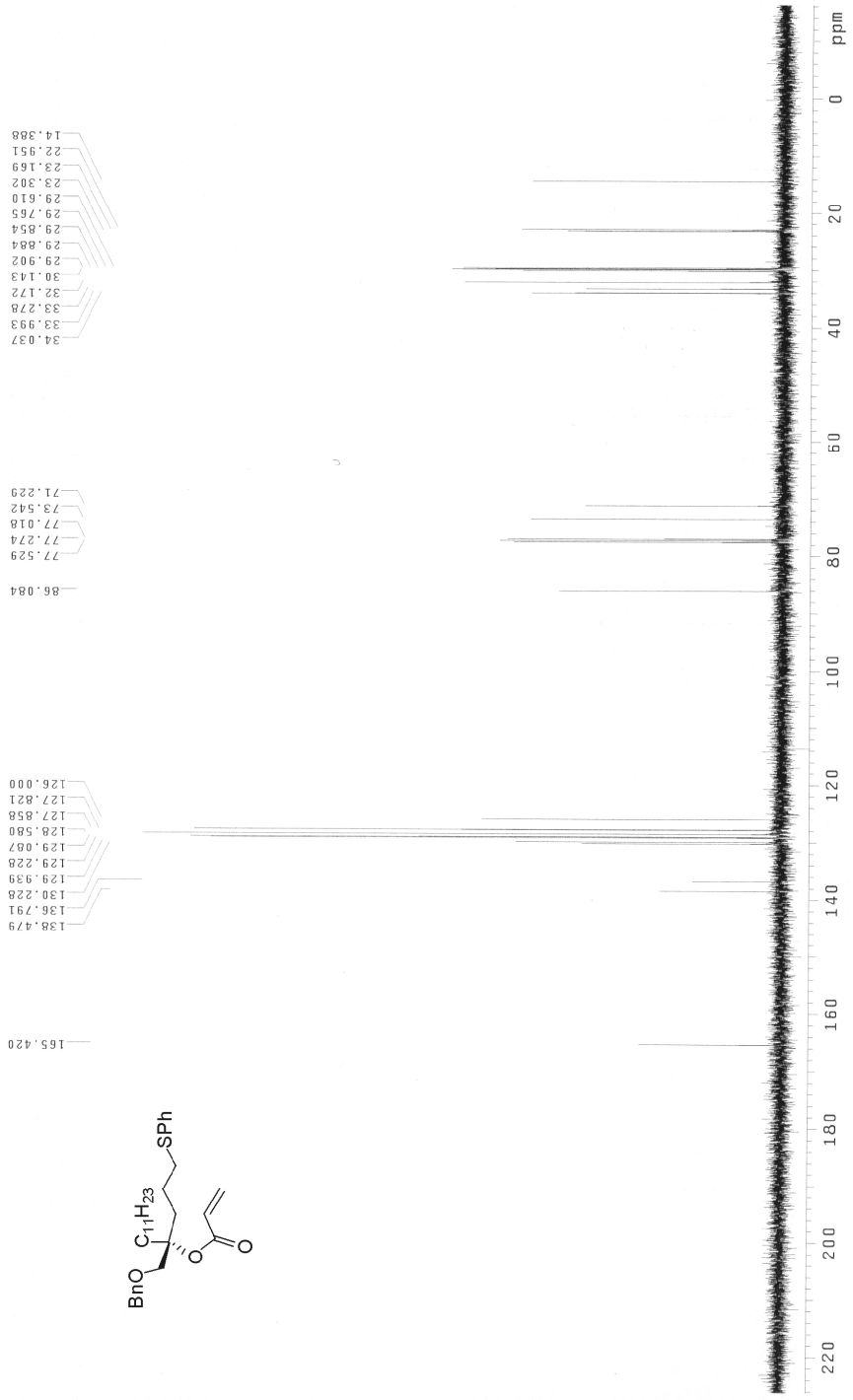
^{1}H-NMR (500MHz, CDCl3) of sulfide derivative of **7**



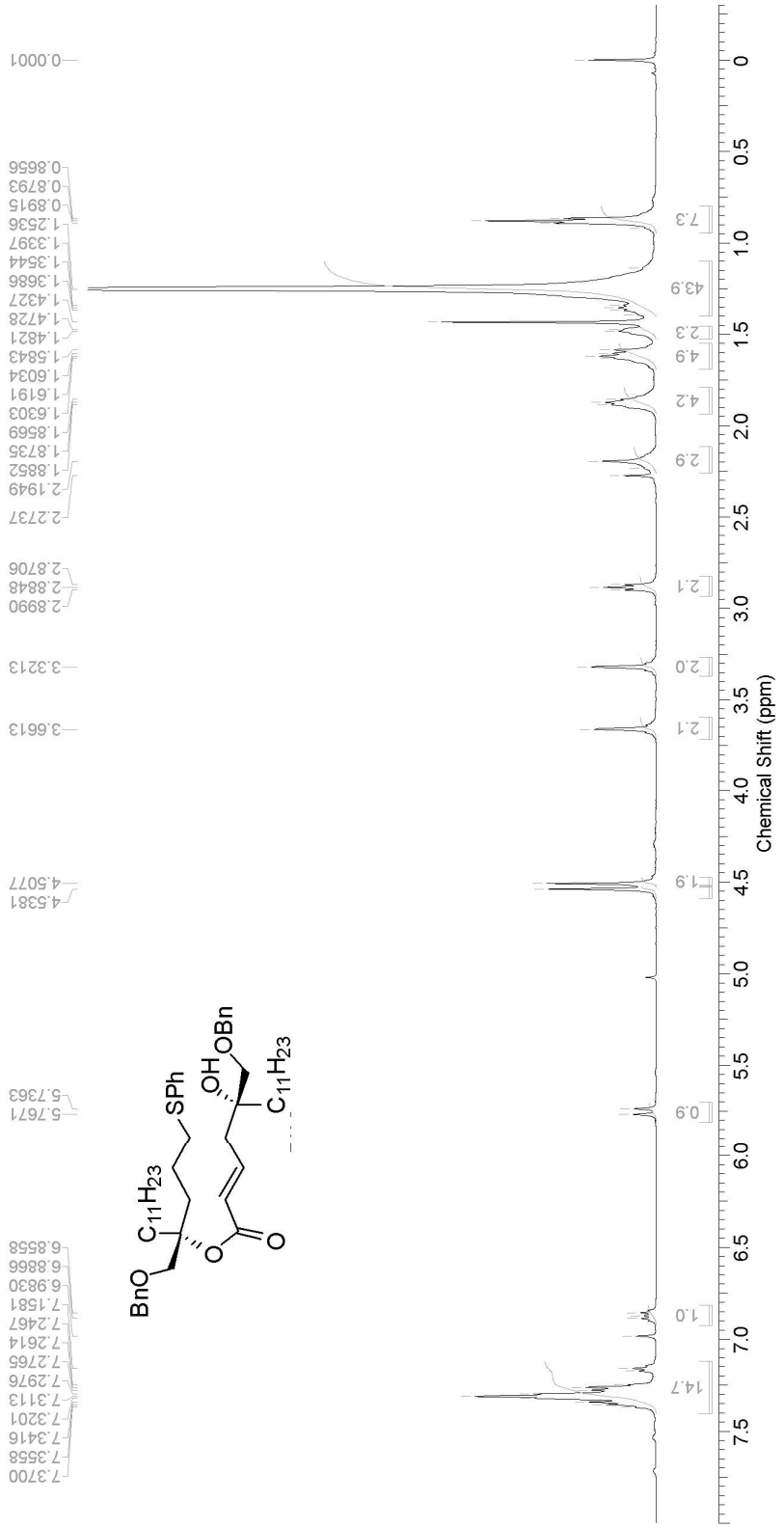
^{13}C-NMR (125 MHz, CDCl3) of sulfide derivative of **7**



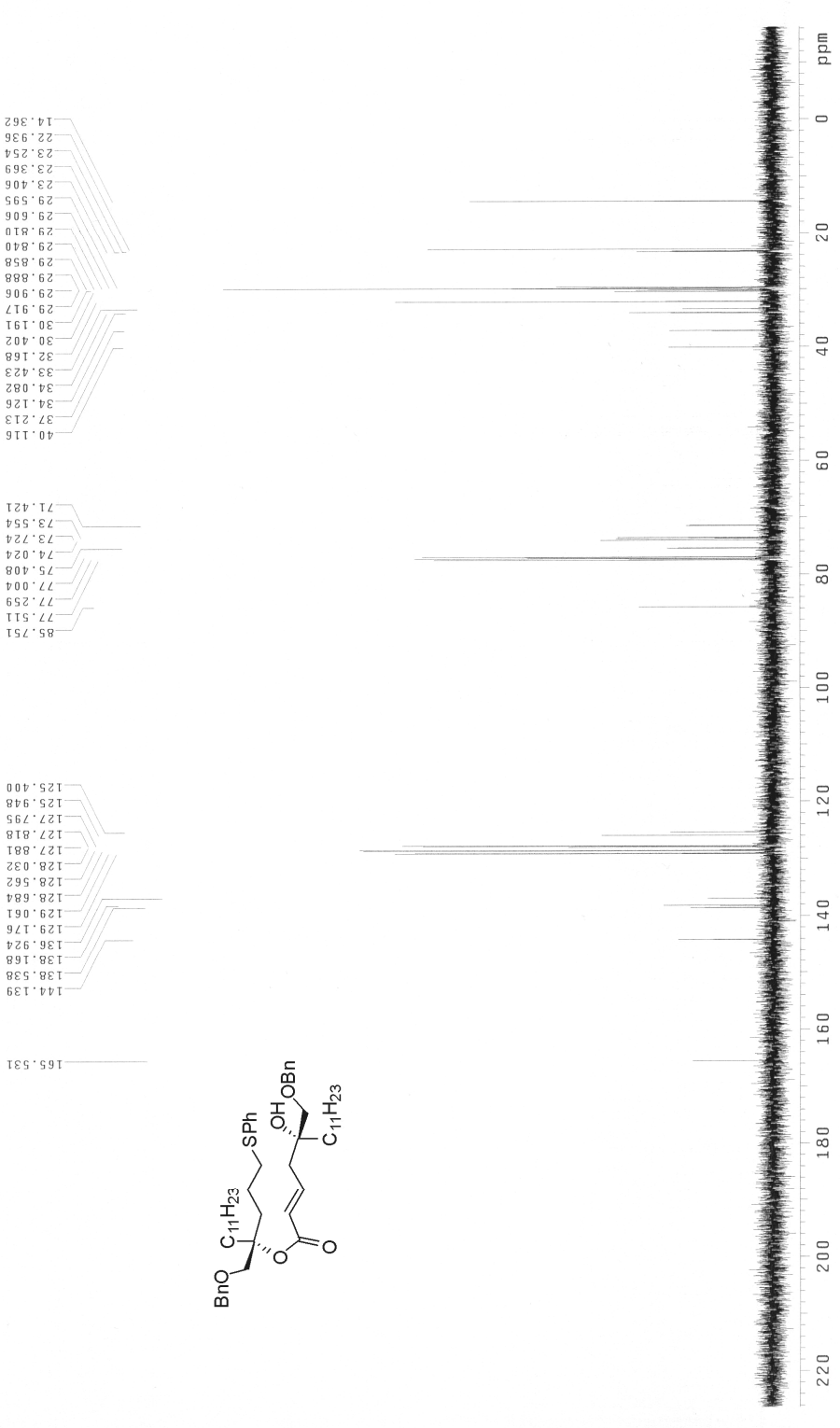
^{1}H-NMR (500 MHz, $CDCl_3$) of **8**



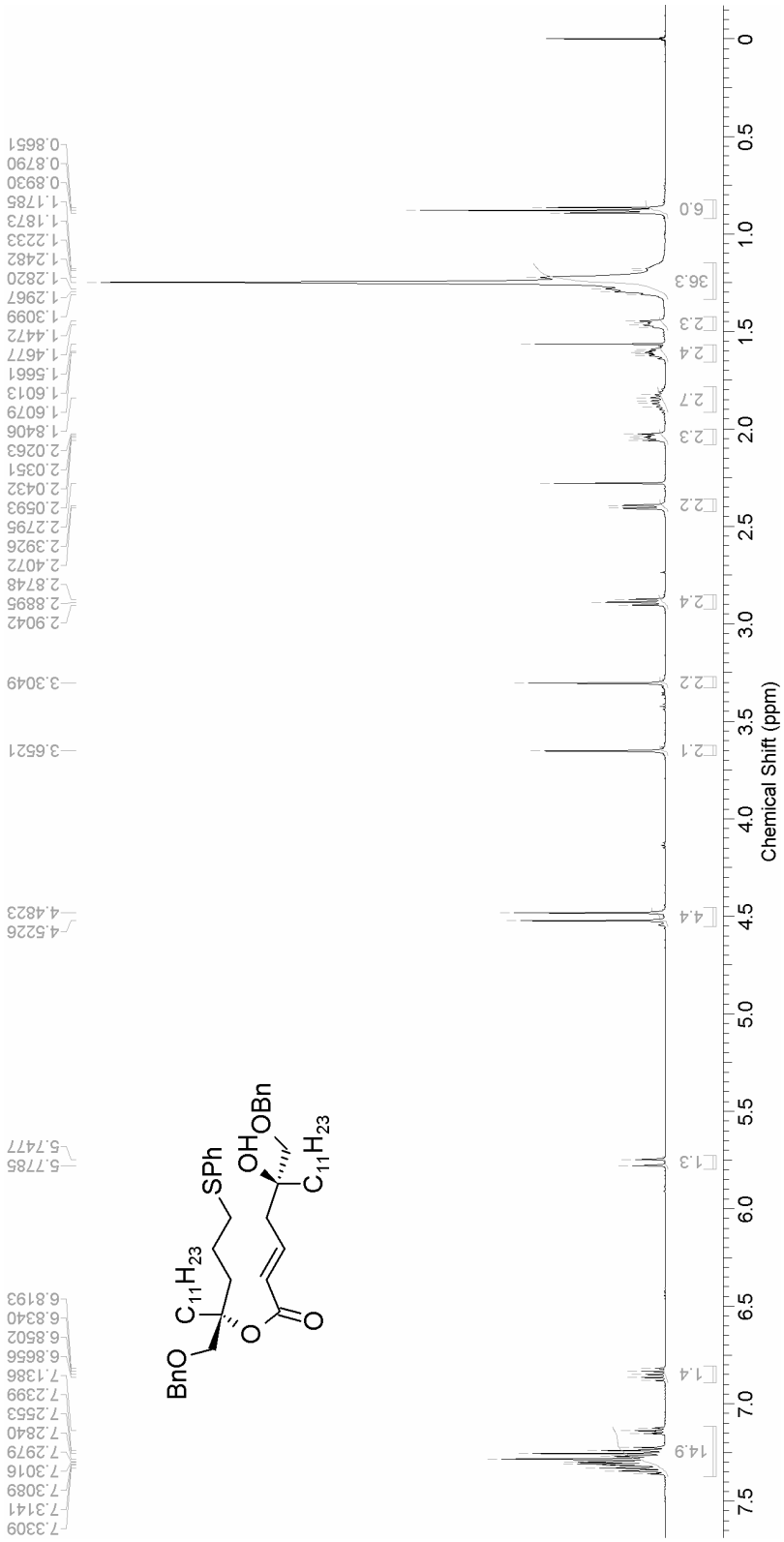
^{13}C-NMR (125 MHz, $CDCl_3$) of **8**



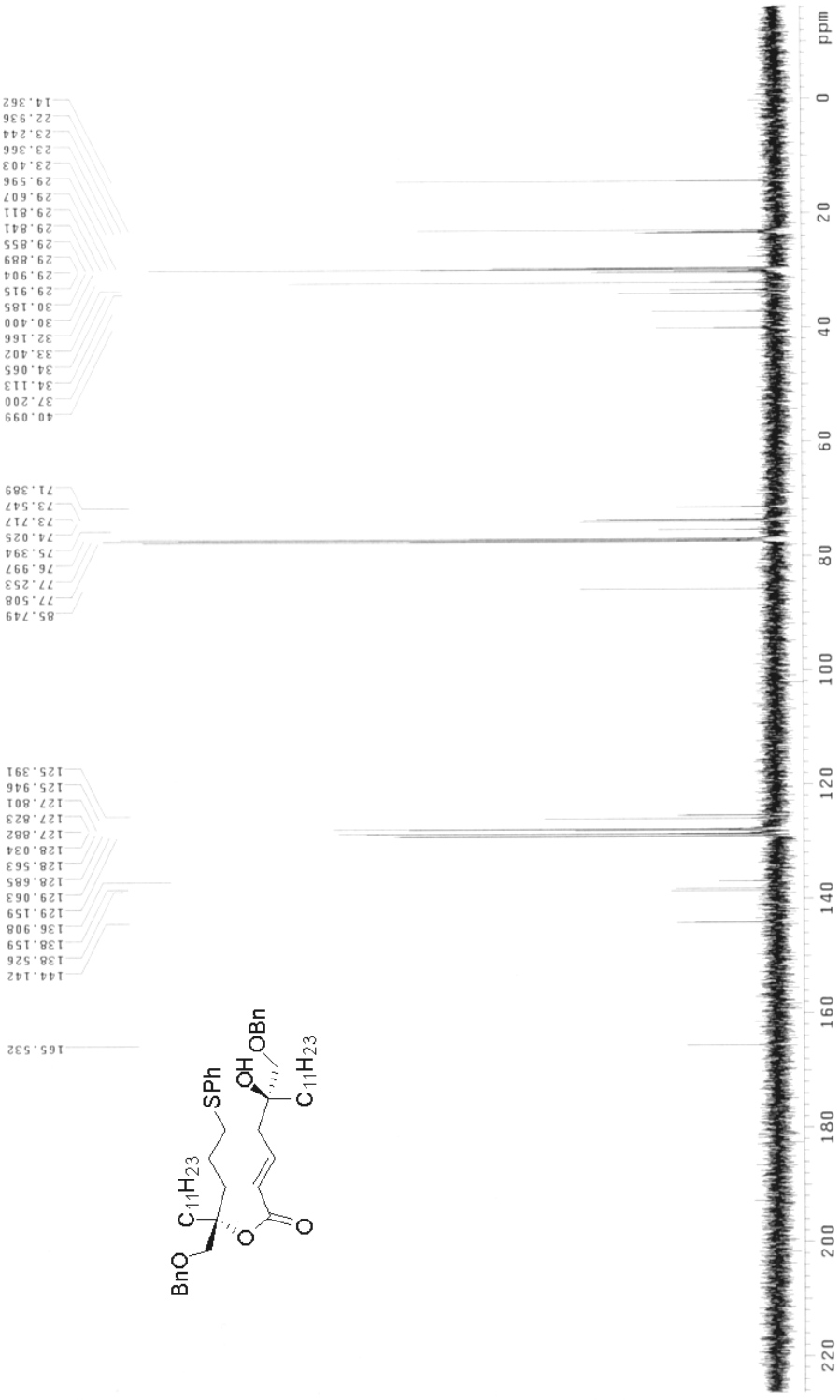
^{1}H-NMR (500 MHz, $CDCl_3$) of **10**



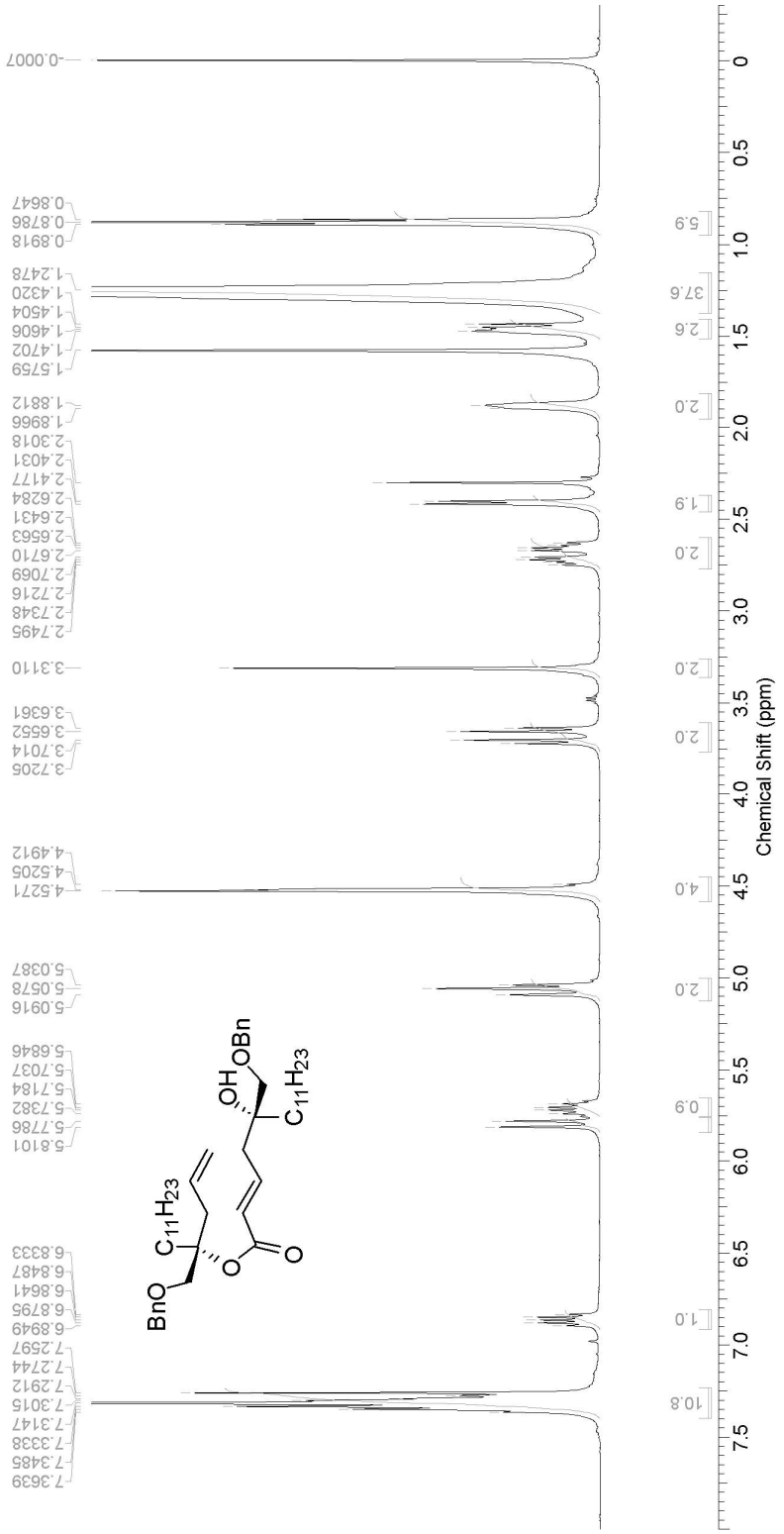
^{13}C-NMR (125 MHz, $CDCl_3$) of **10**



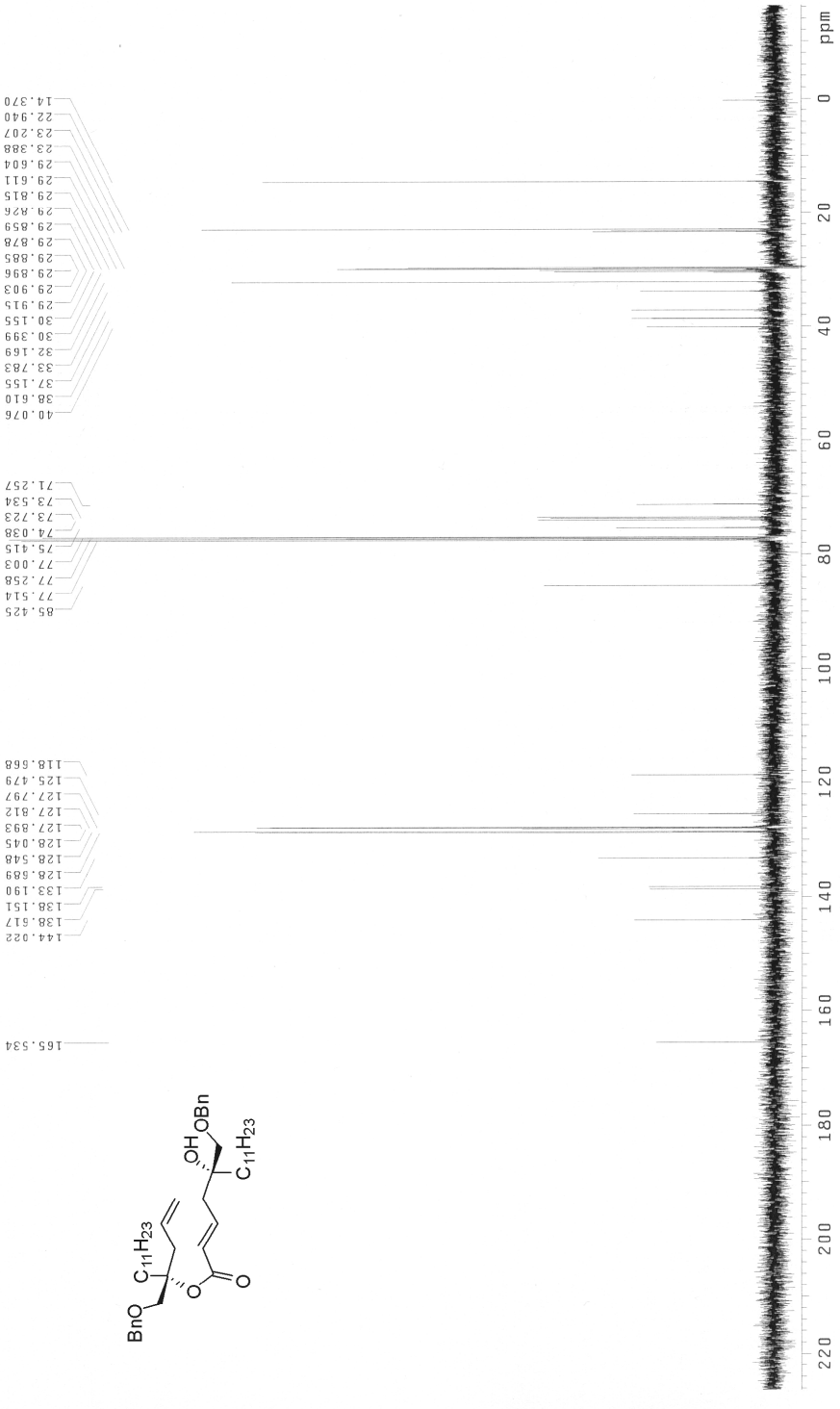
^{1}H-NMR (500 MHz, $CDCl_3$) of **13**



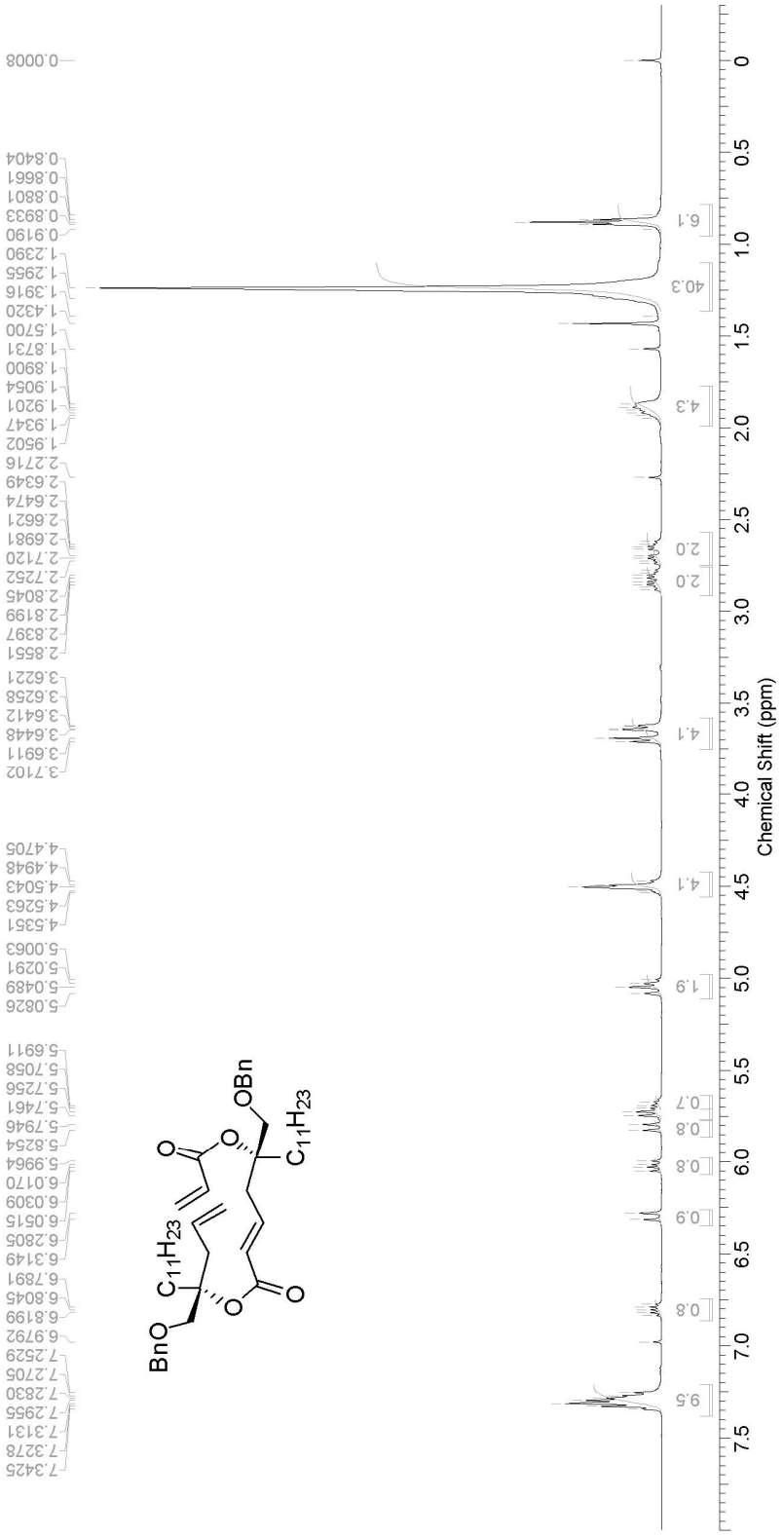
^{13}C-NMR (125 MHz, $CDCl_3$) of **13**



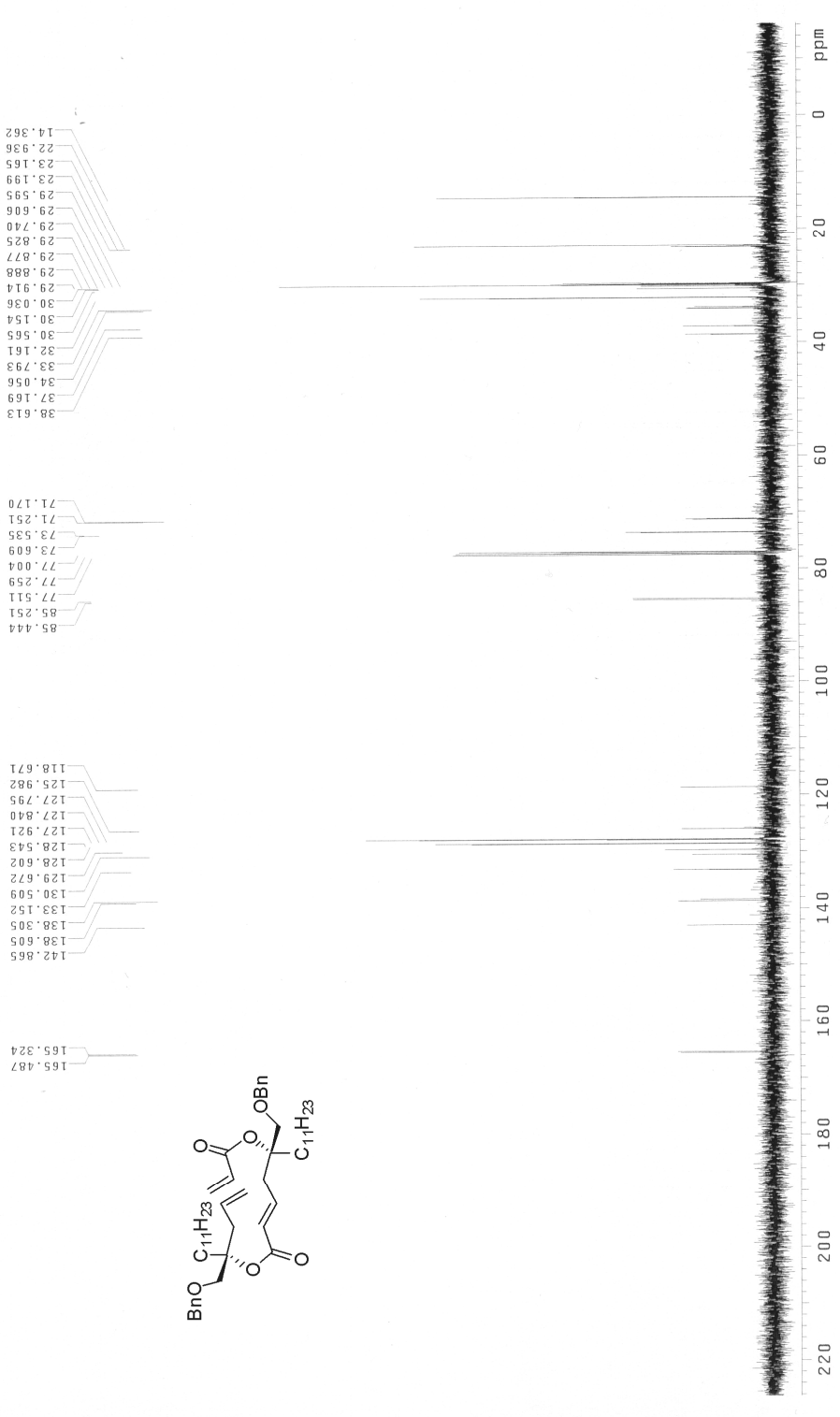
^{1}H-NMR (500MHz, CDCl3) of diene product of **10**



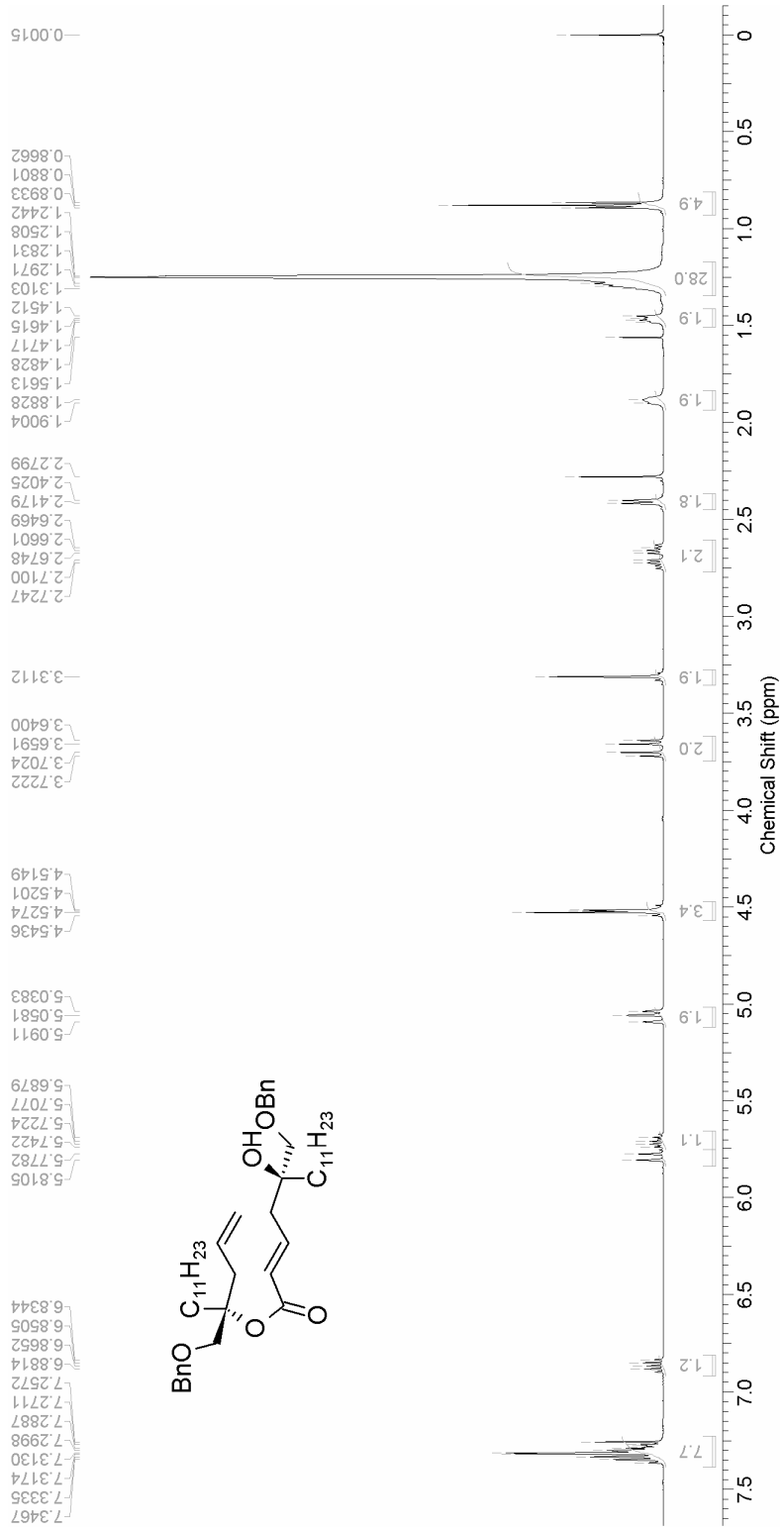
^{13}C-NMR (125 MHz, CDCl3) of diene product of **10**



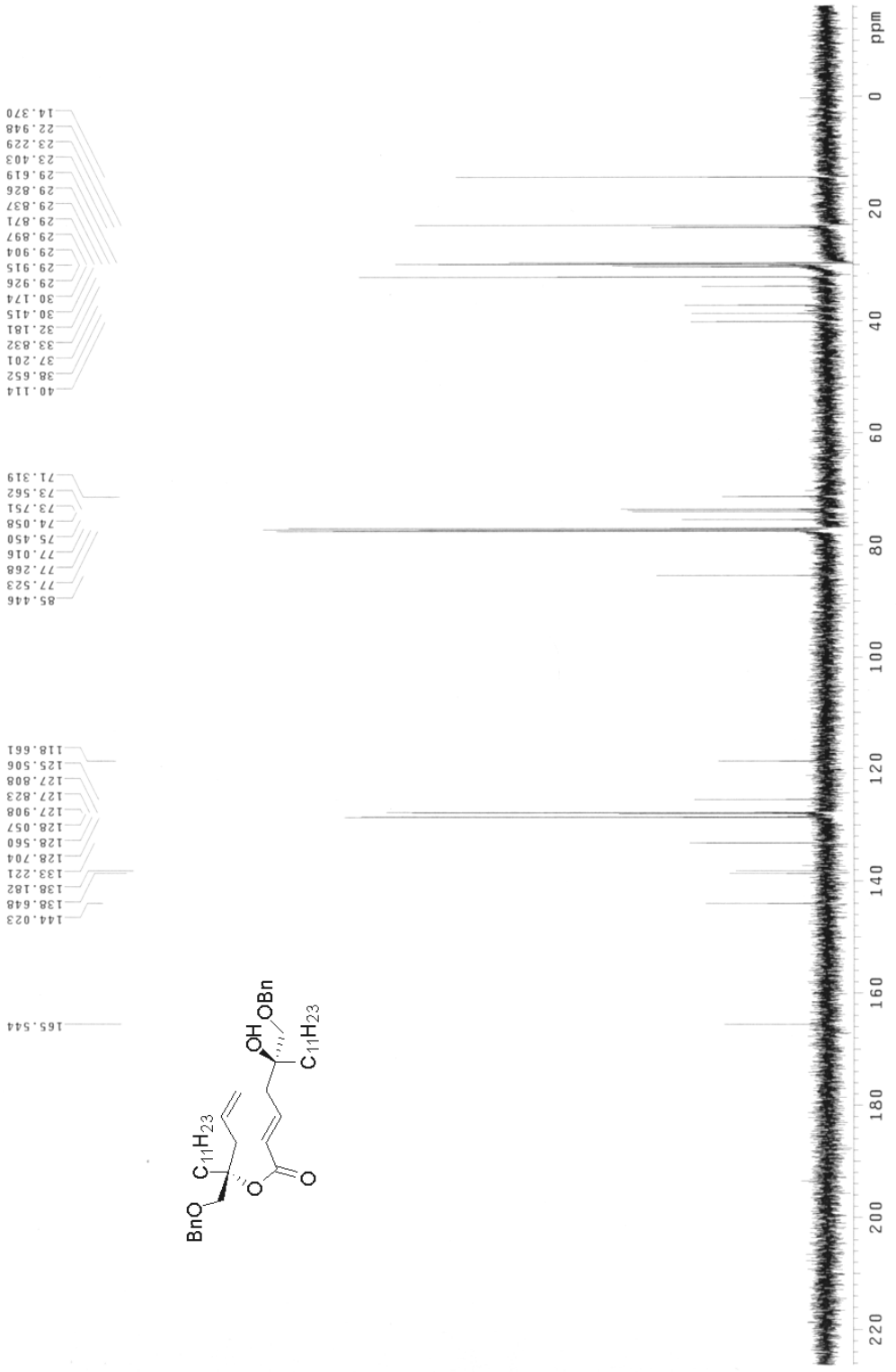
^{1}H-NMR (500 MHz, $CDCl_3$) of **11**



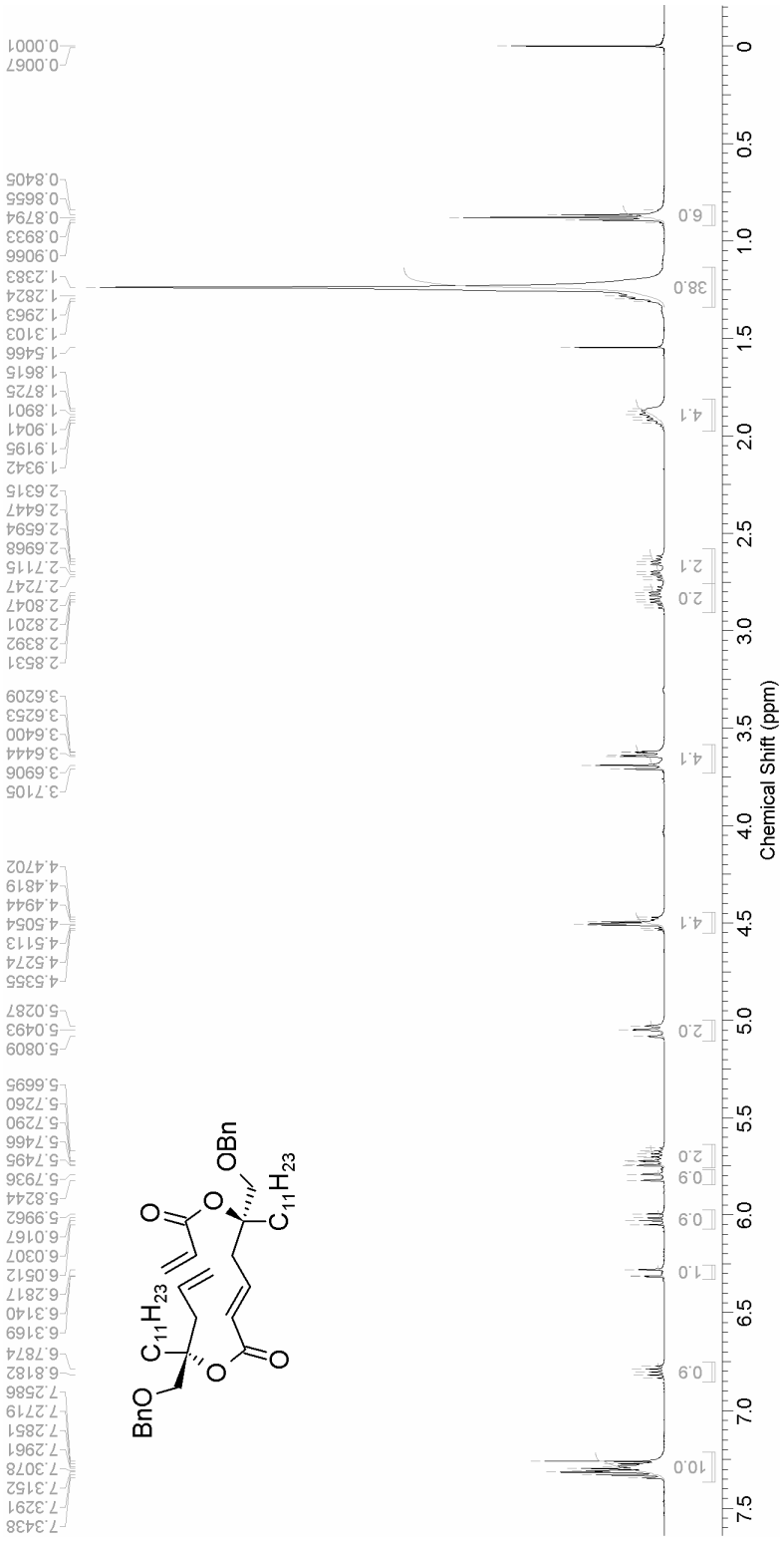
^{13}C-NMR (125 MHz, $CDCl_3$) of **11**



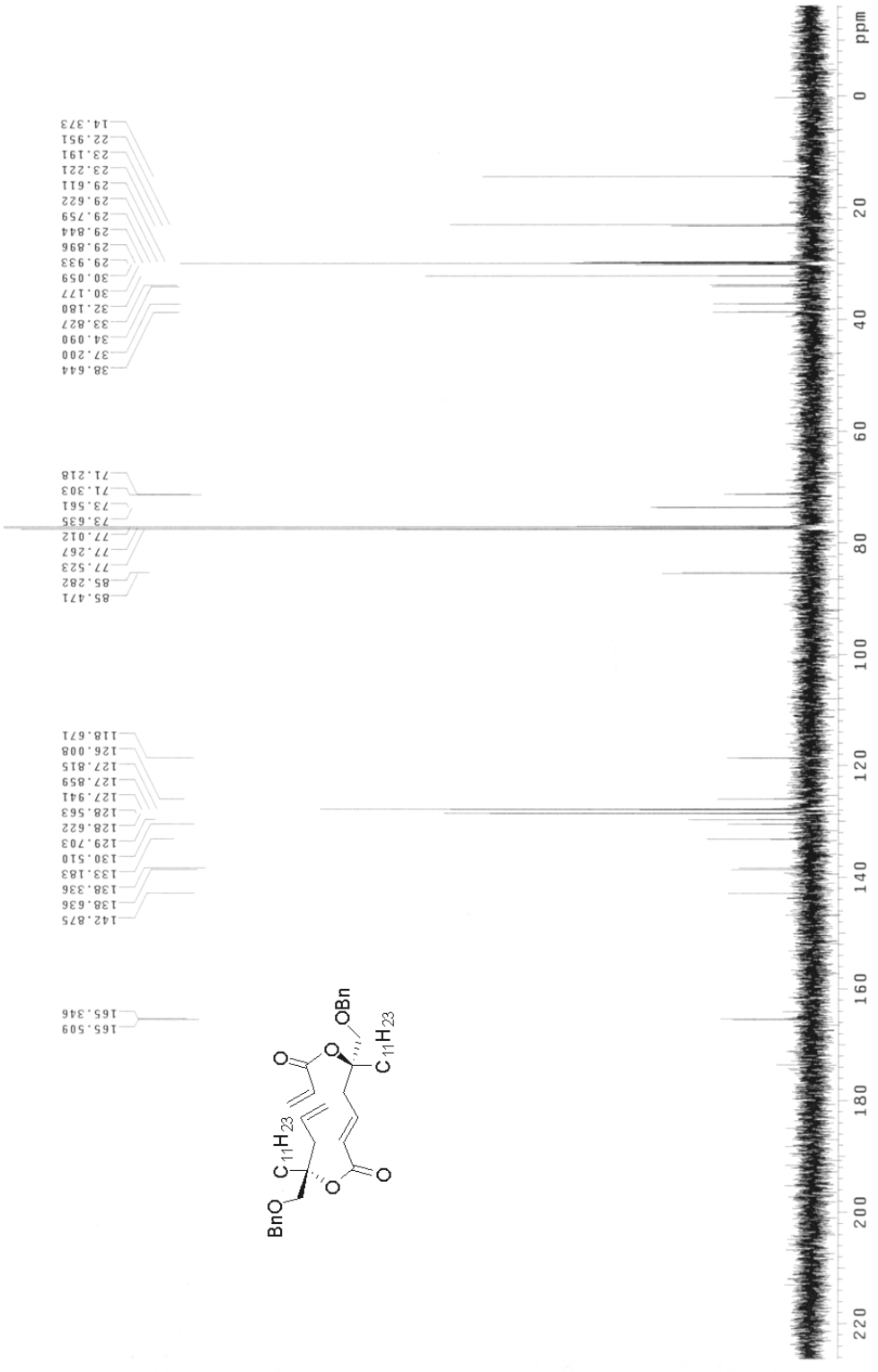
^{1}H-NMR (500MHz, CDCl3) of diene product of **13**



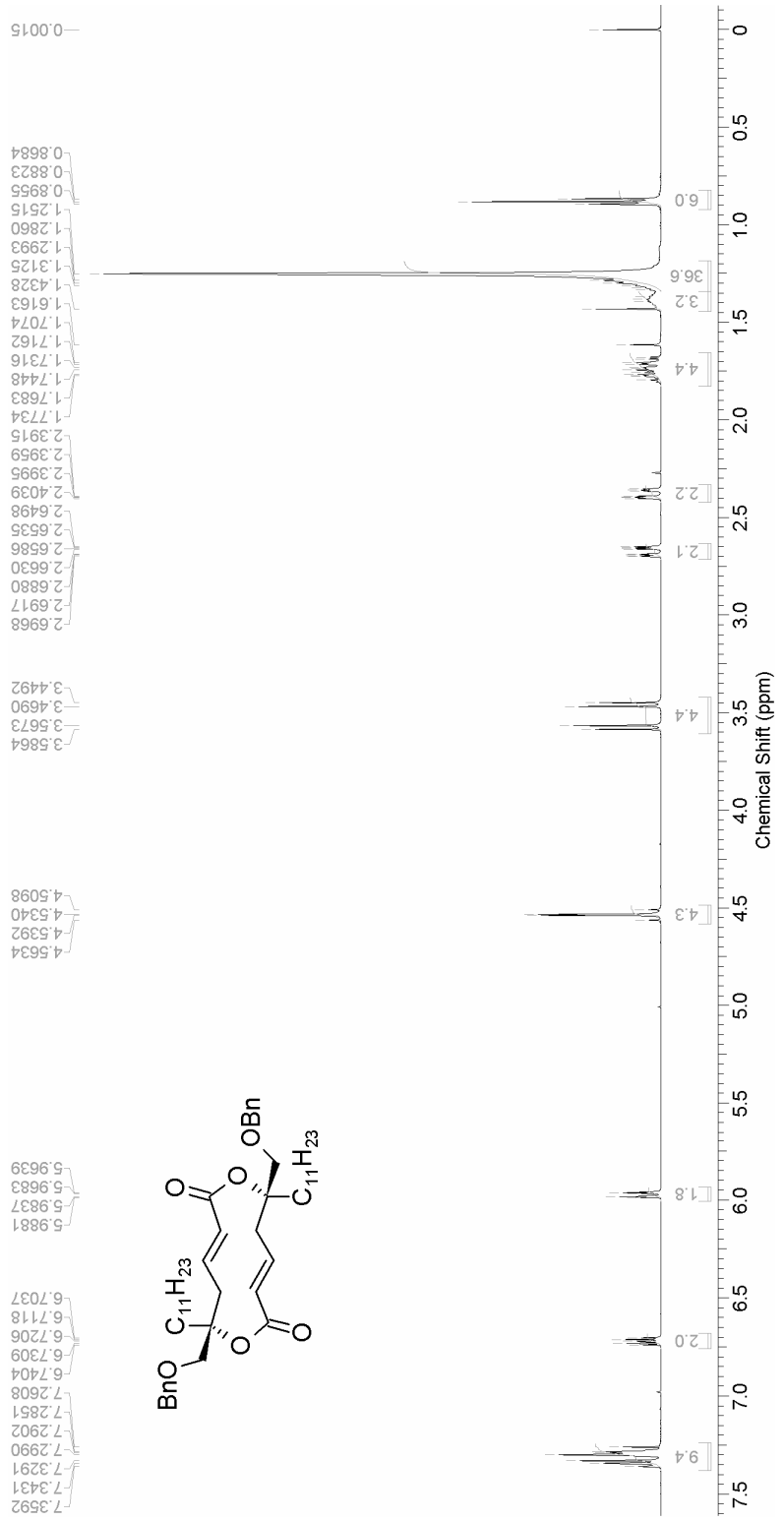
^{13}C-NMR (125 MHz, CDCl3) of diene product of **13**



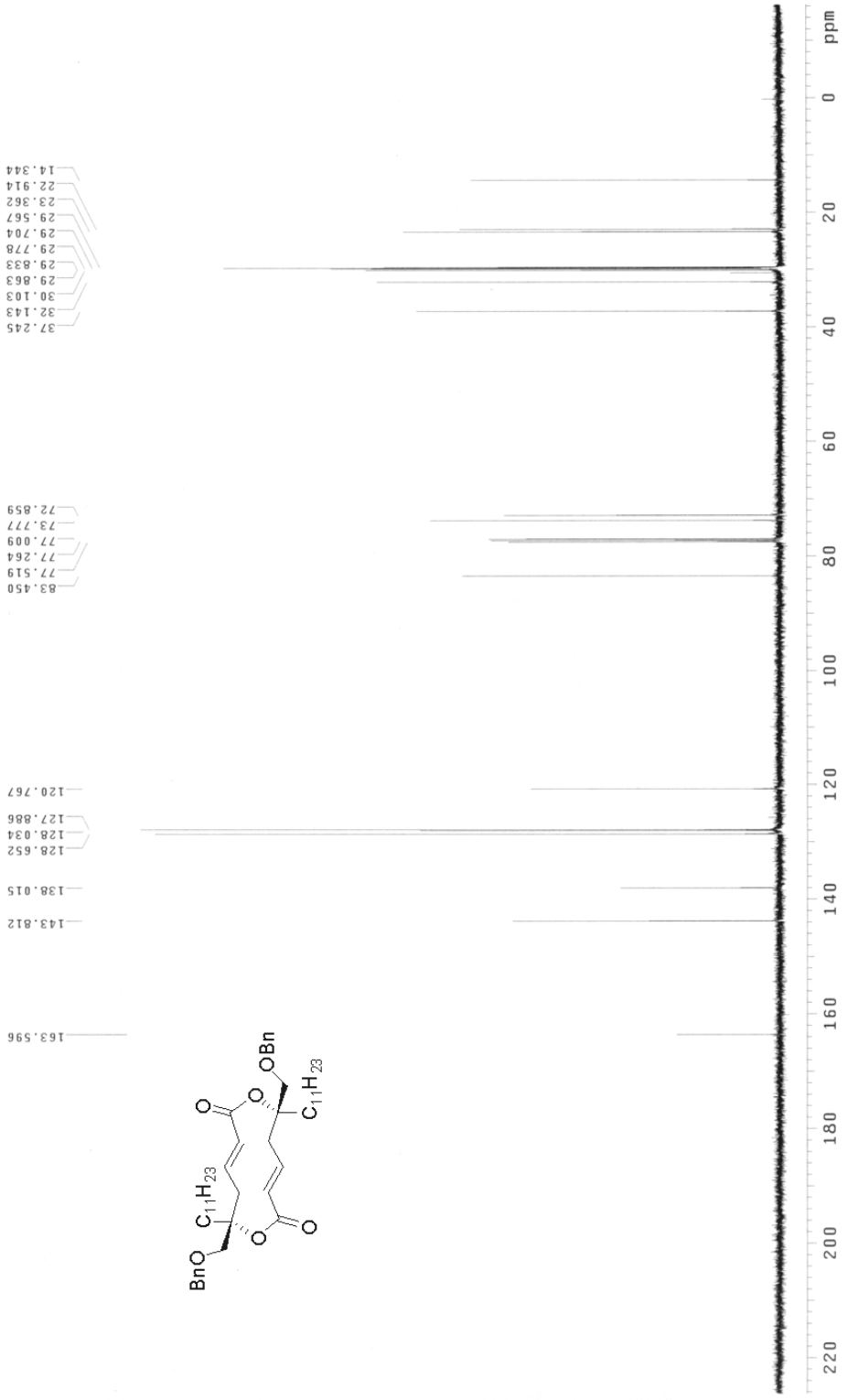
^{1}H-NMR (500 MHz, $CDCl_3$) of **14**



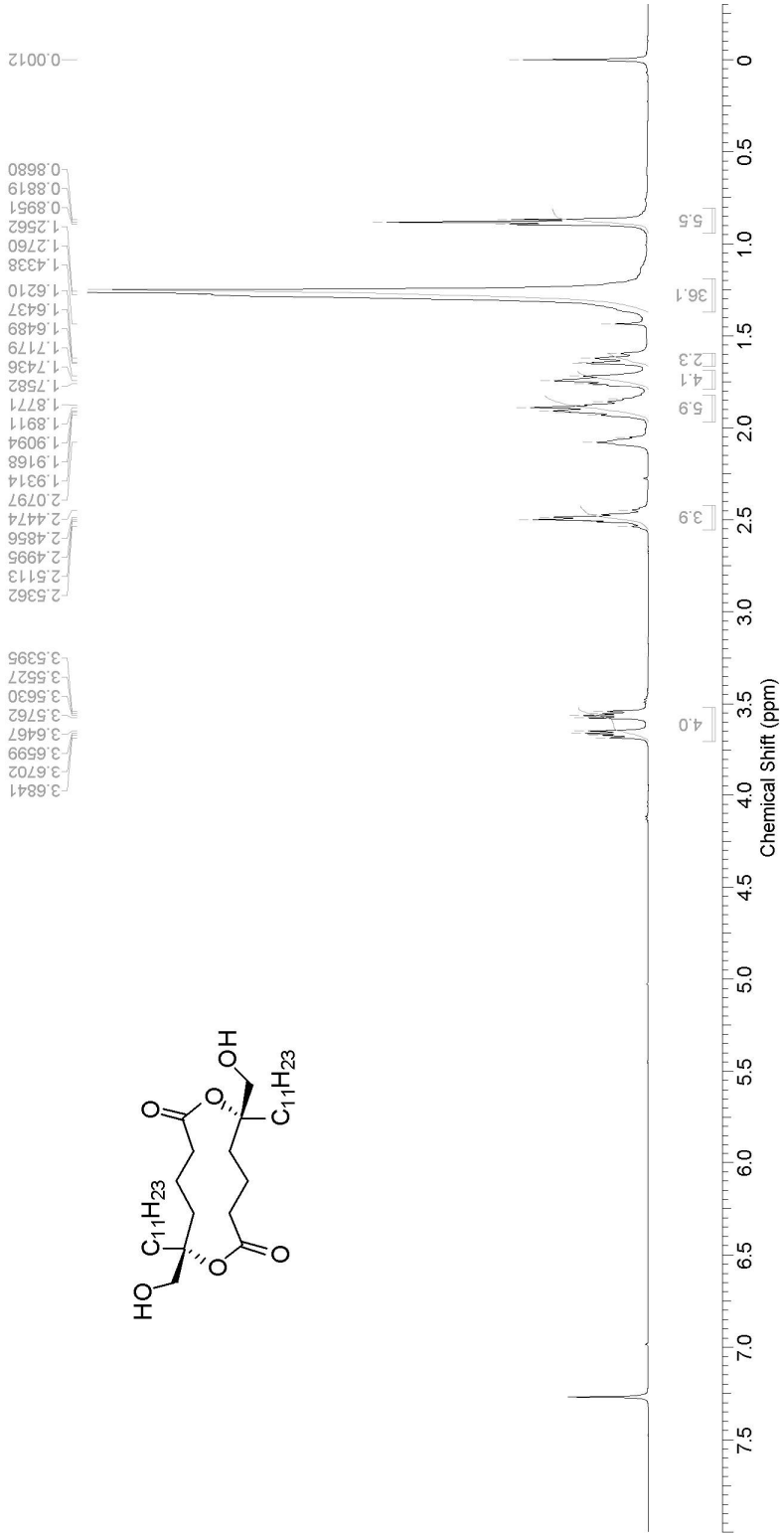
^{13}C-NMR (125 MHz, $CDCl_3$) of **14**



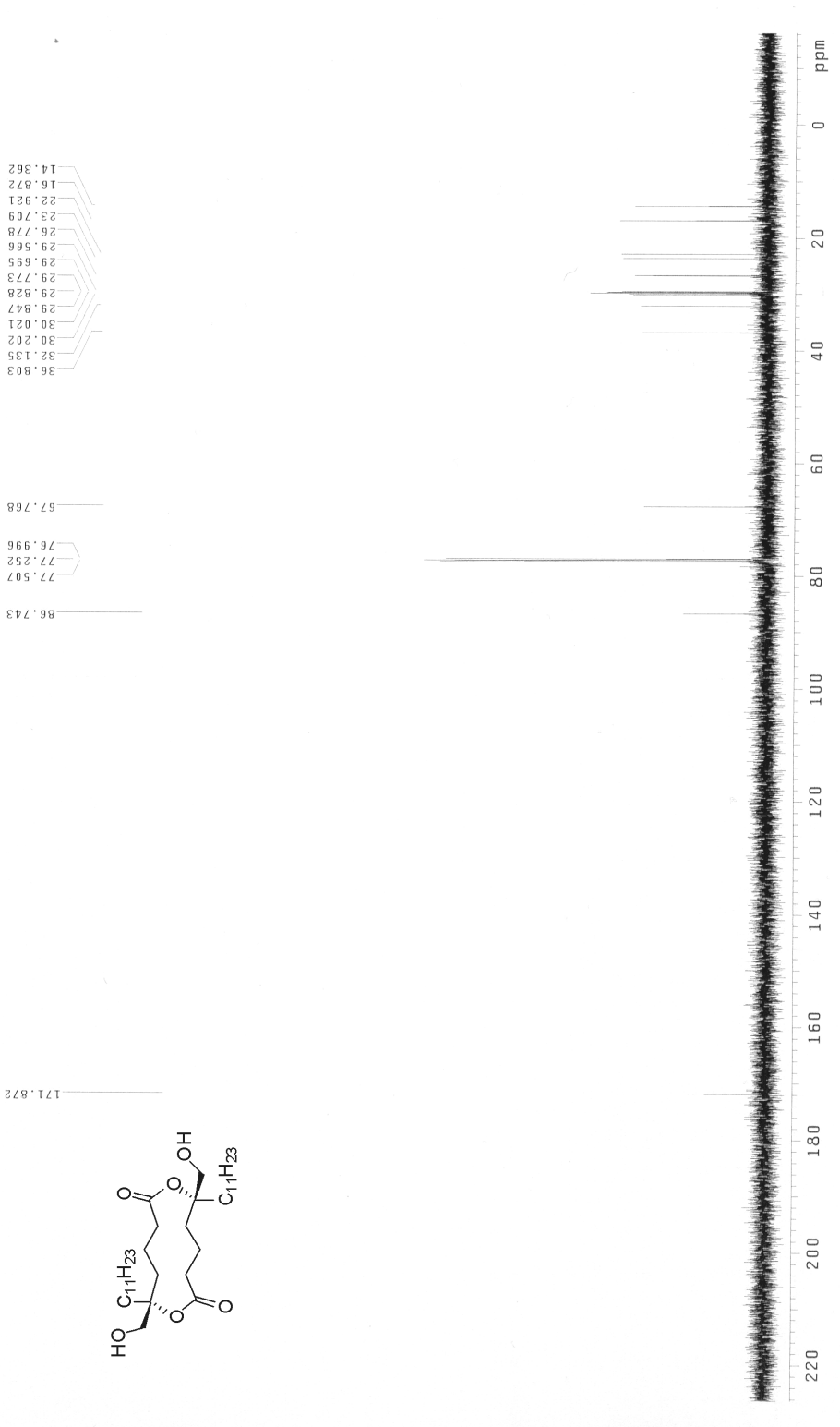
^{1}H-NMR (500 MHz, $CDCl_3$) of **12**



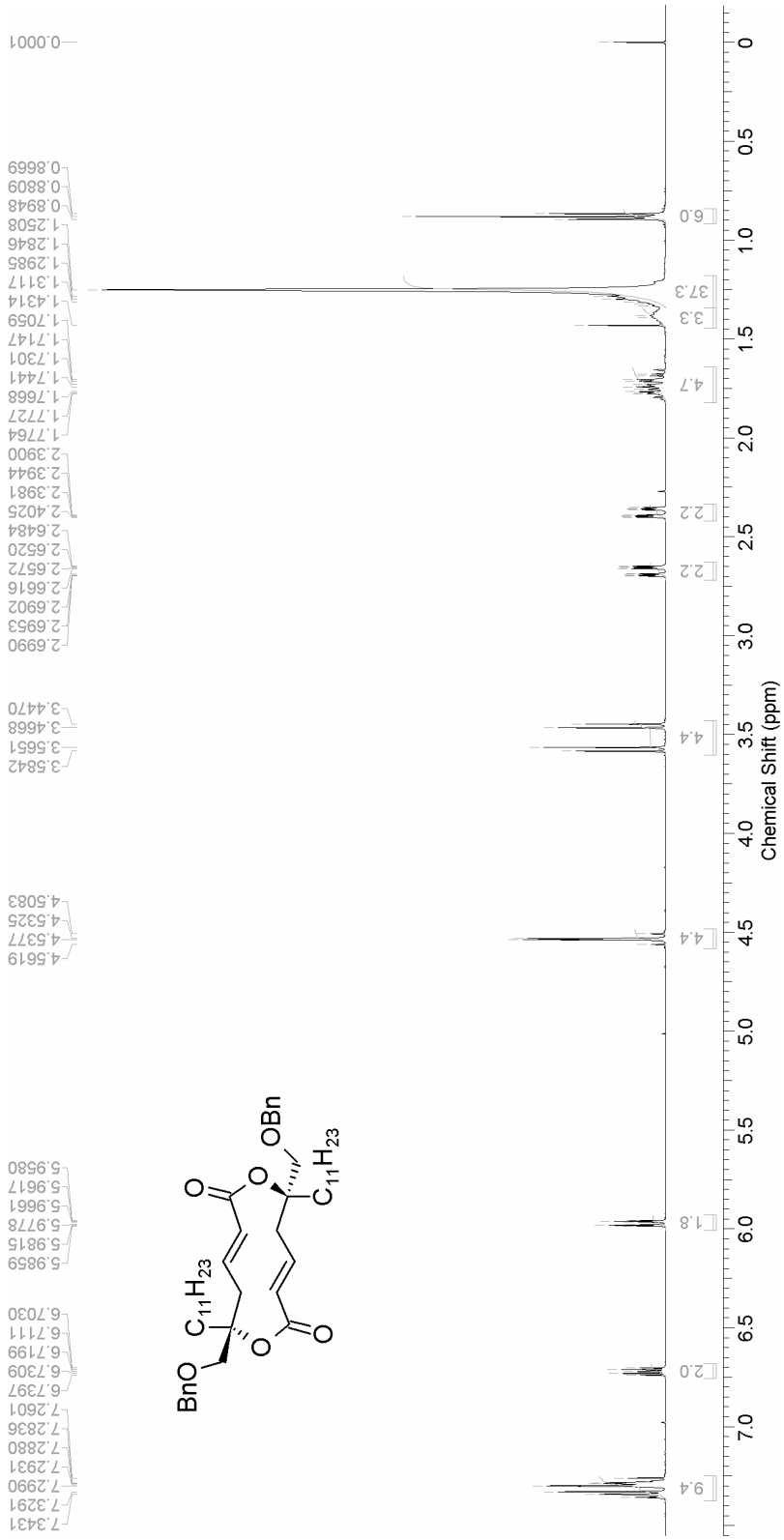
^{13}C-NMR (125 MHz, $CDCl_3$) of **12**



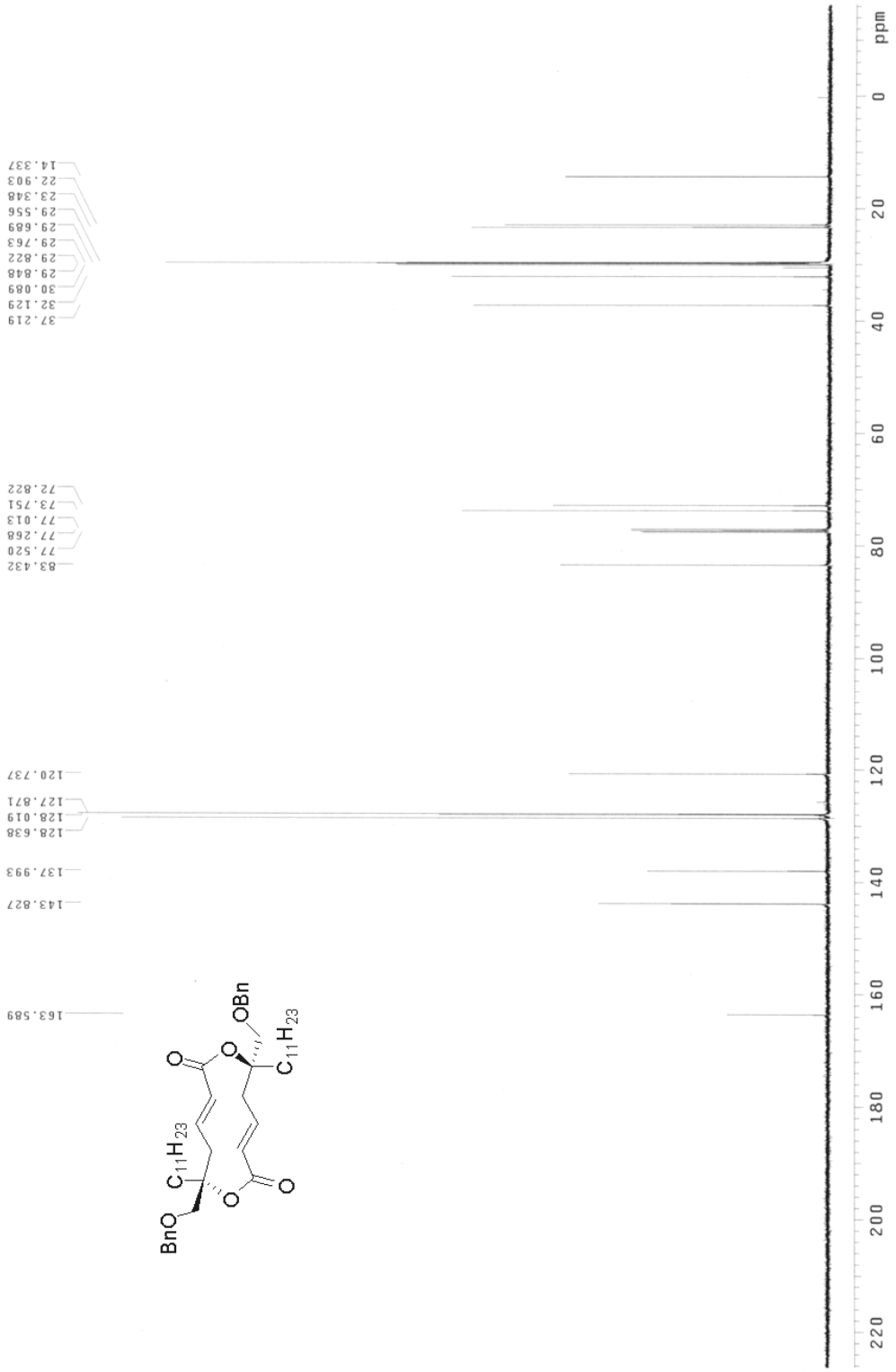
^{1}H-NMR (500 MHz, $CDCl_3$) of **5**



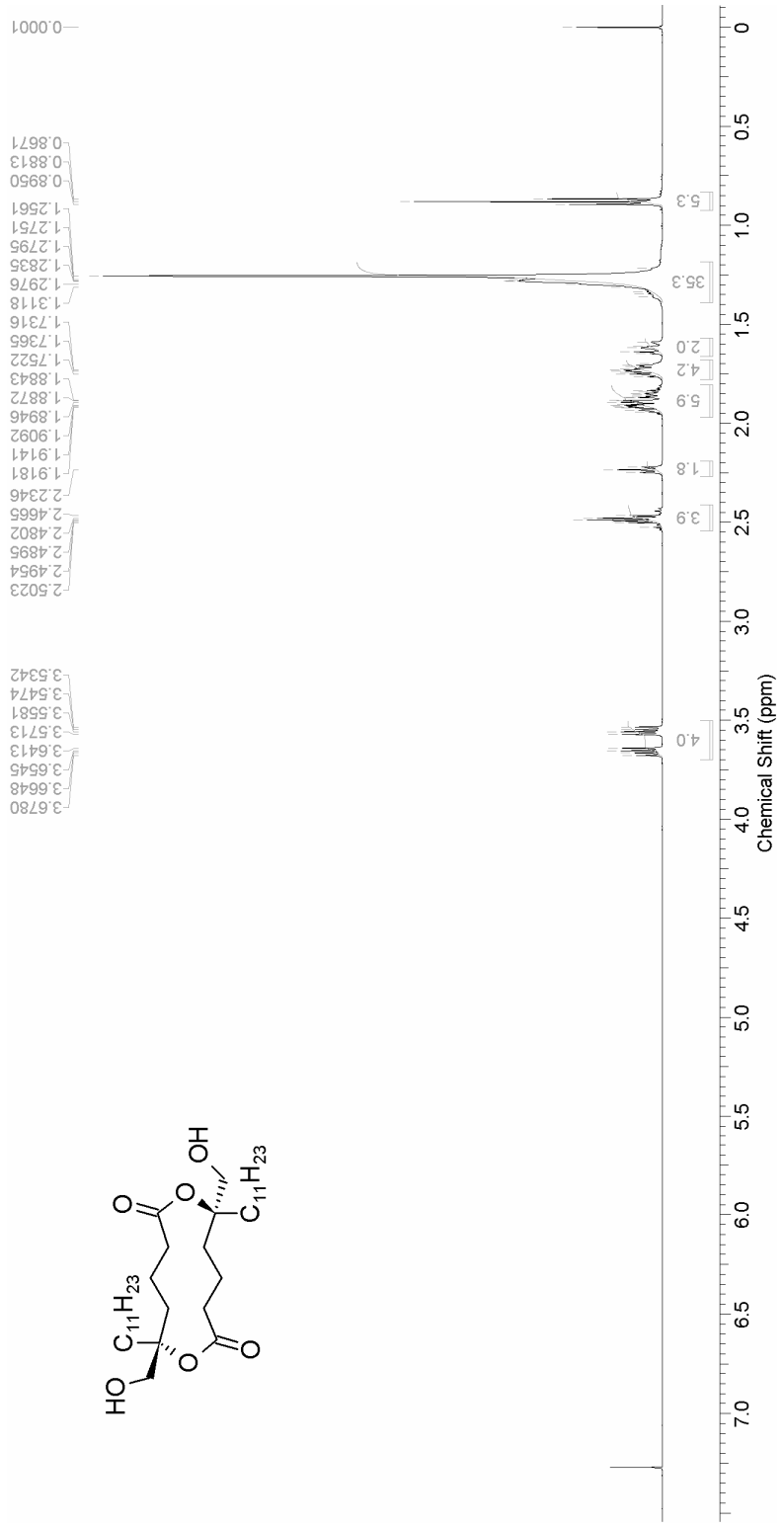
^{13}C-NMR (125 MHz, $CDCl_3$) of **5**



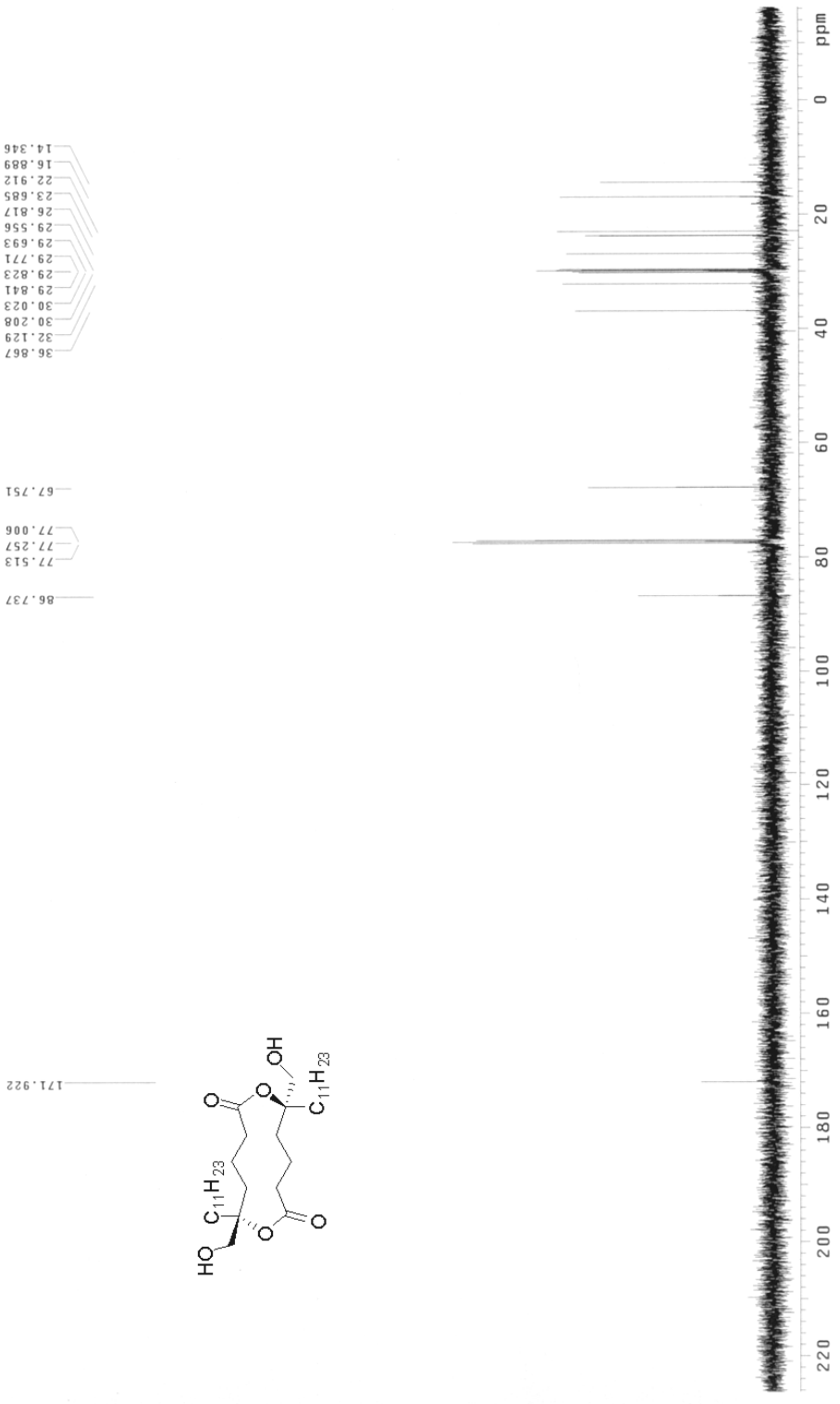
^{1}H-NMR (500MHz, CDCl3) of initial olefin metathesis product of triene **14**



^{13}C-NMR (125 MHz, CDCl3) of initial olefin metathesis product of triene **14**



^{1}H-NMR (500 MHz, $CDCl_3$) of **4**

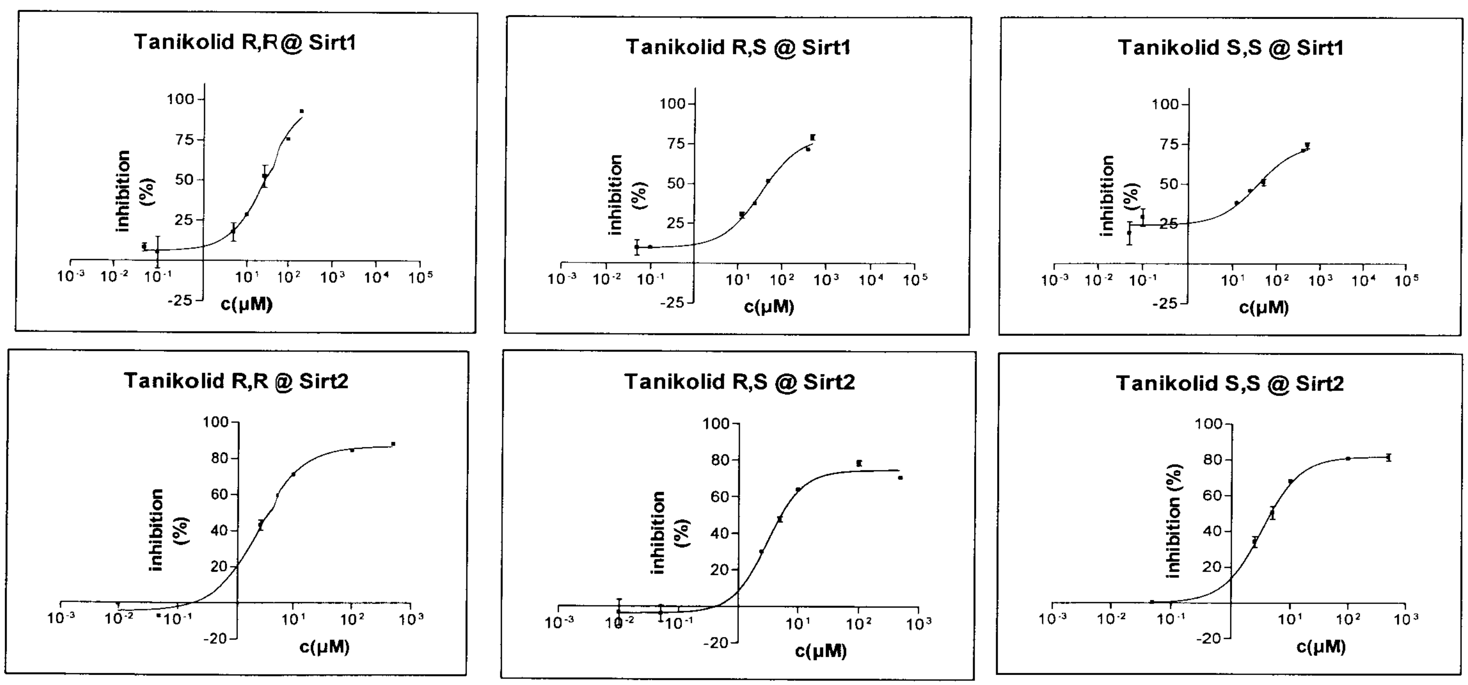


^{13}C-NMR (125 MHz, $CDCl_3$) of **4**

Inhibition dose response curves for compounds **4, 5** and *ent*-**5** to SIRT1 and SIRT2

Test results of Tanikolide Dimers Against Sirt1 and Sirt2

	IC50 ± SE [µM] @ Sirt1	IC50 ± SE [µM] @ Sirt2
R,R	28,8 ± 4,3	2,4 ± 0,2
S,S	36,4 ± 8,1	3,3 ± 0,2
R,S	34,5 ± 3,5	3,1 ± 0,3



C:\Xcalibur\...\TanikolideDIMER_RS 6/28/2007 1:05:38 PM

Copy

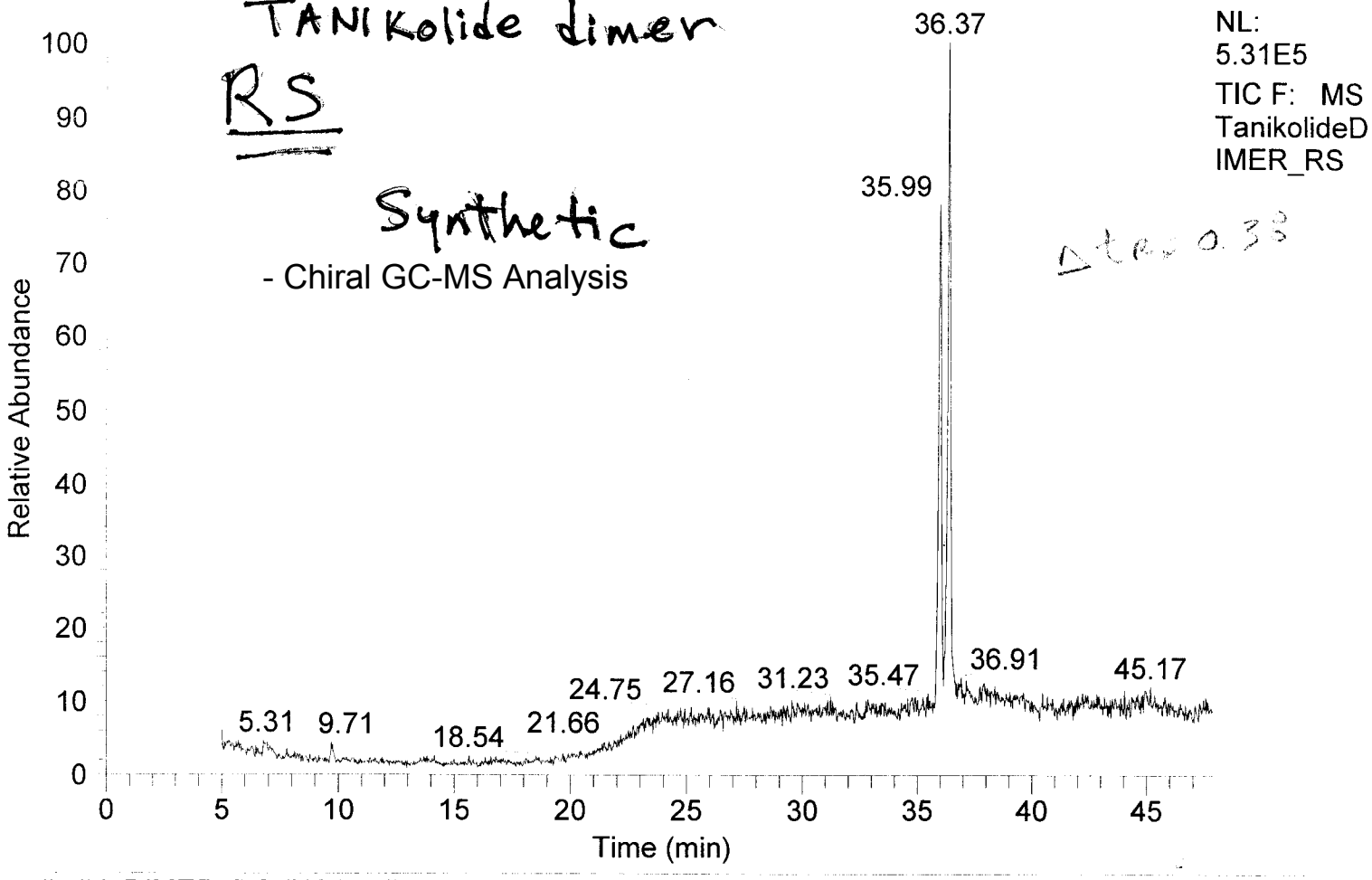
RT: 0.00 - 47.88

TANIKolide dimer

RS

Synthetic

- Chiral GC-MS Analysis



Δtr = 0.38

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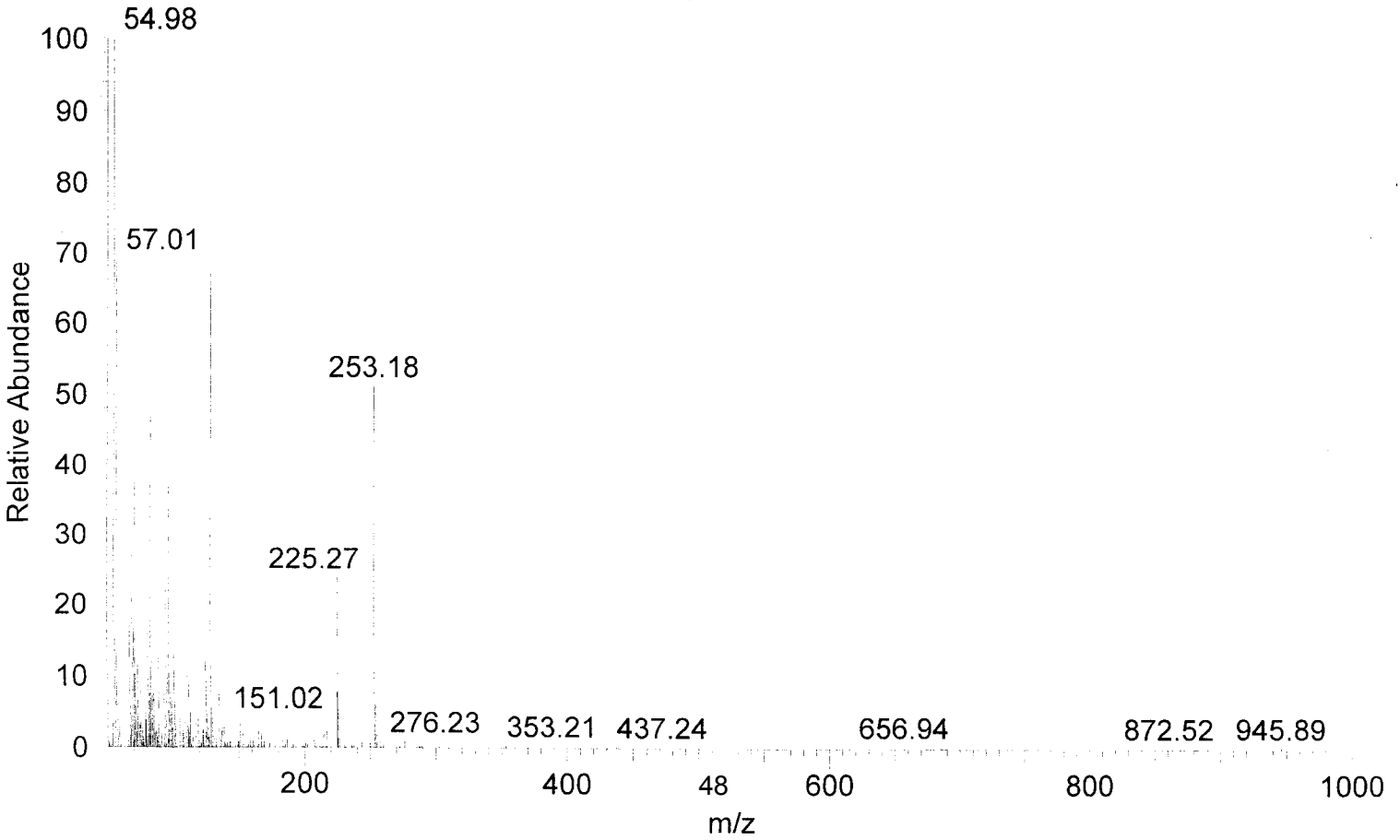

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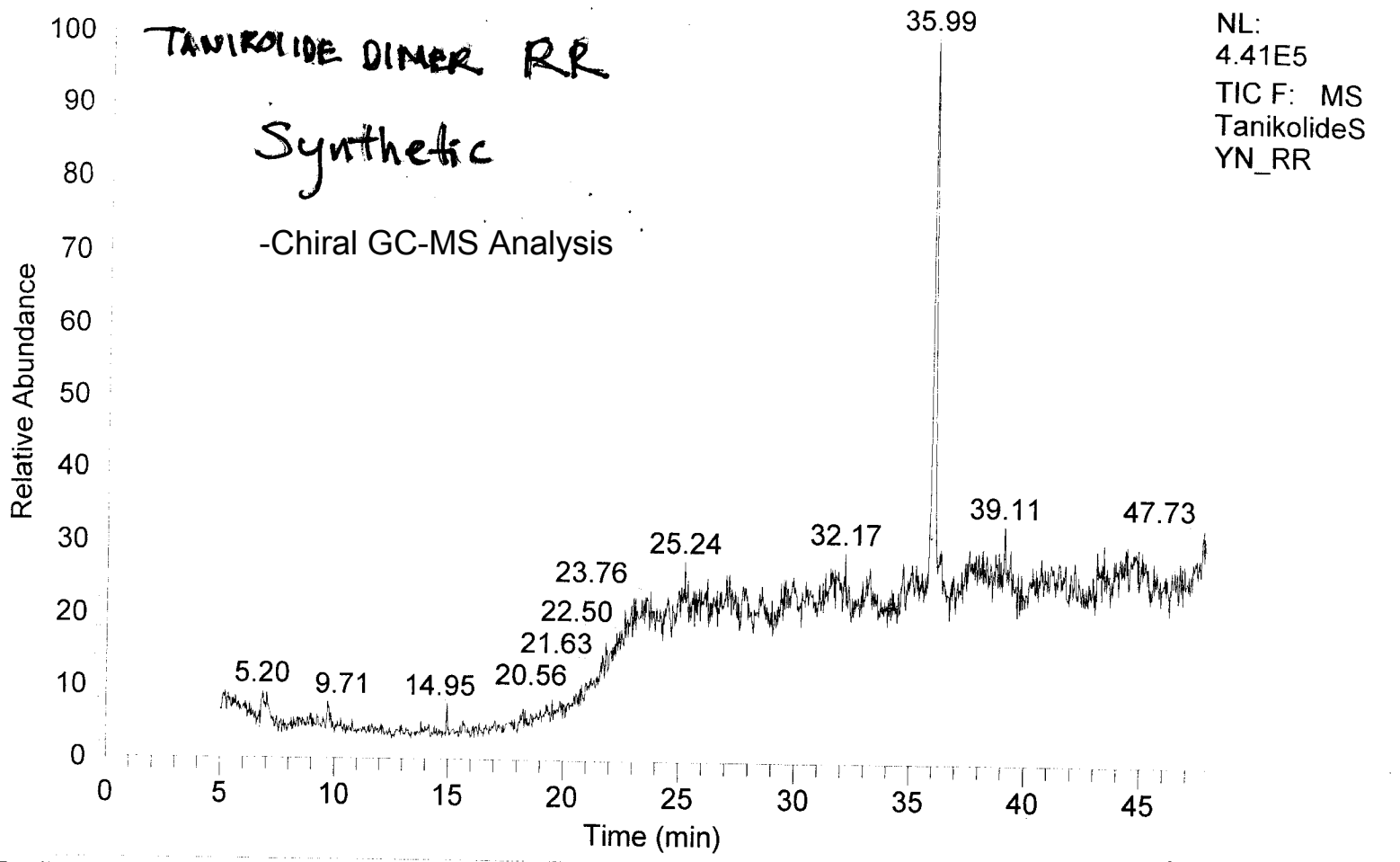

TanikolideSYN_RR #1212 RT: 35.99 AV: 1 NL: 3.19E4
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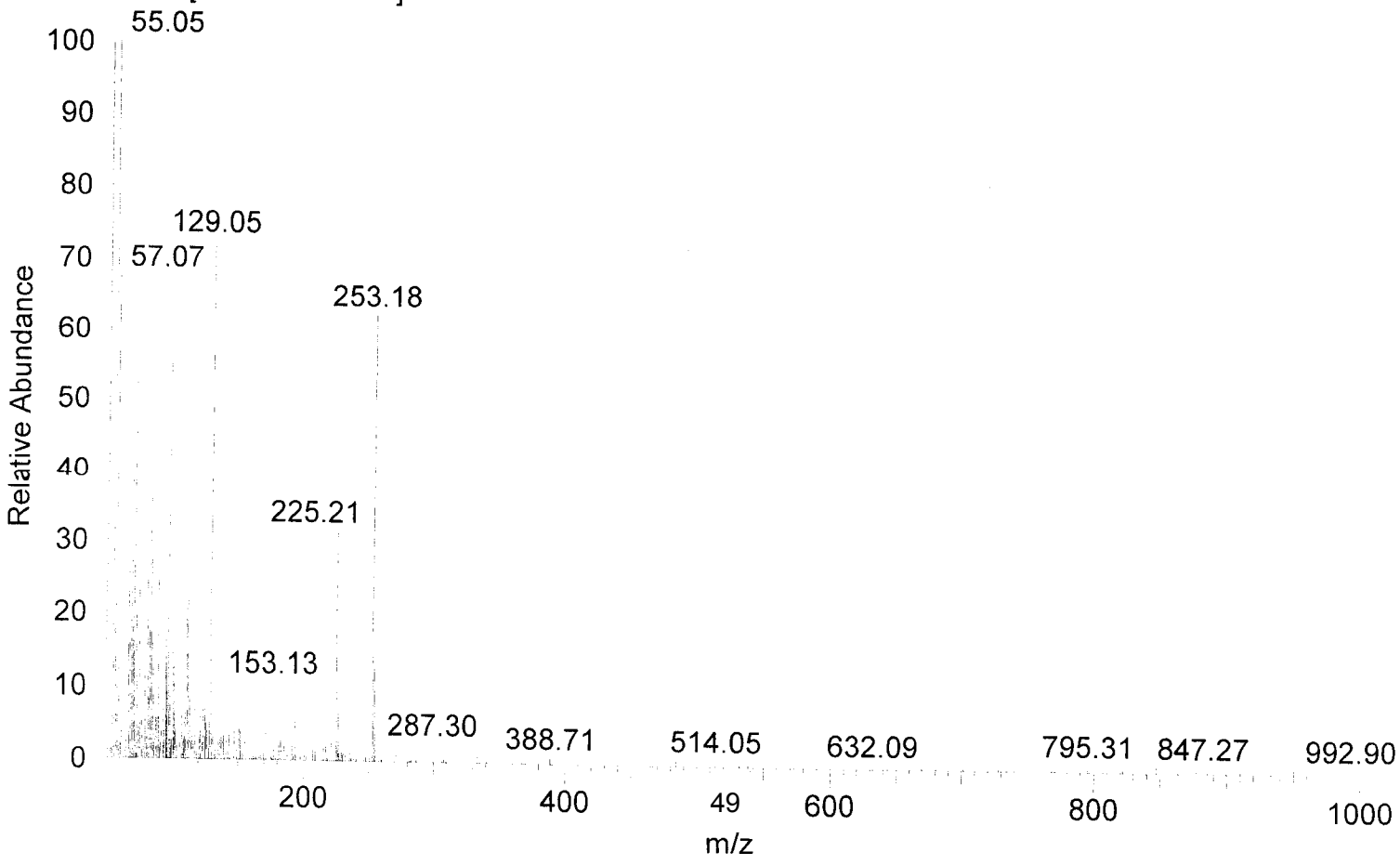
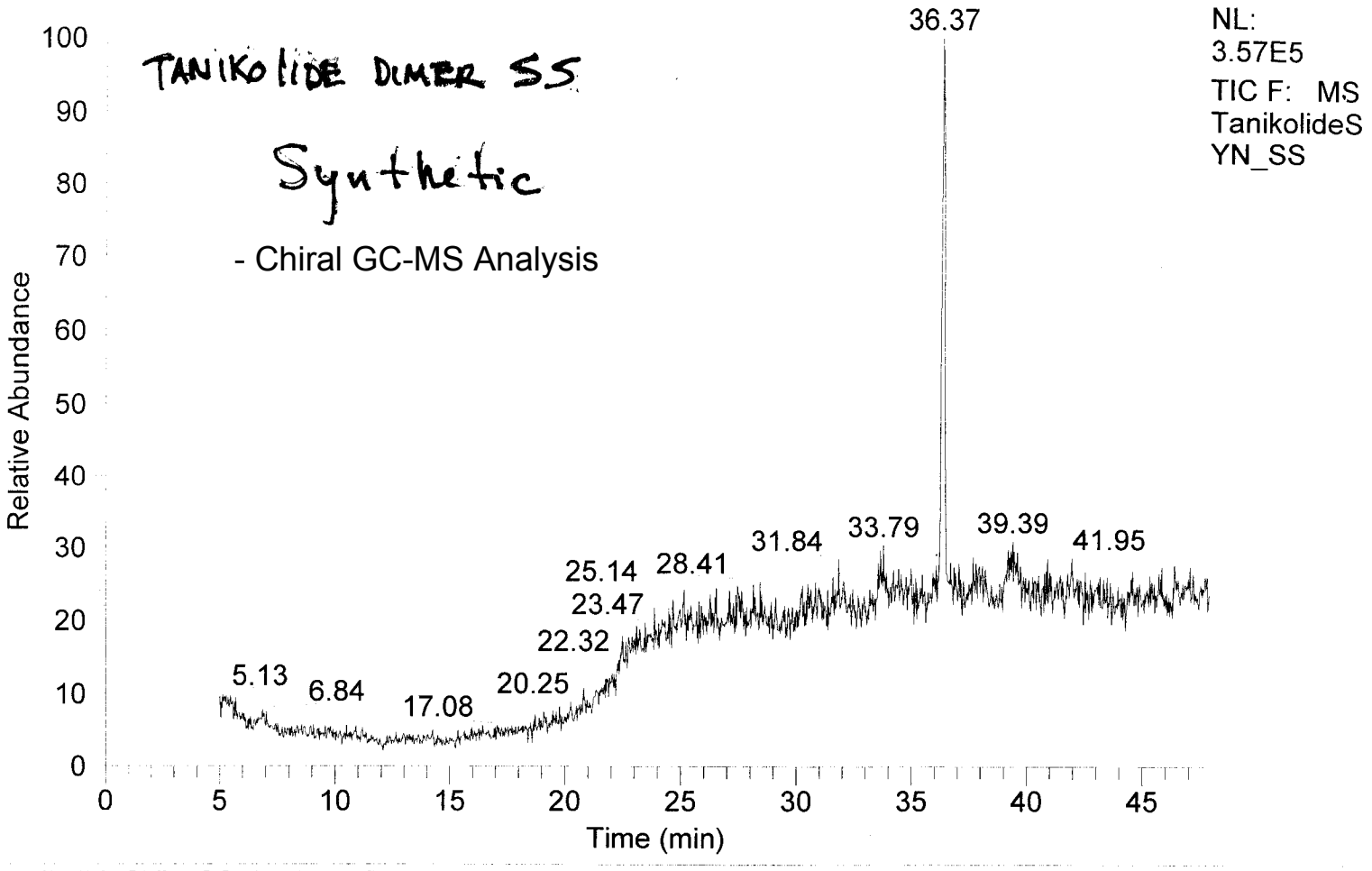
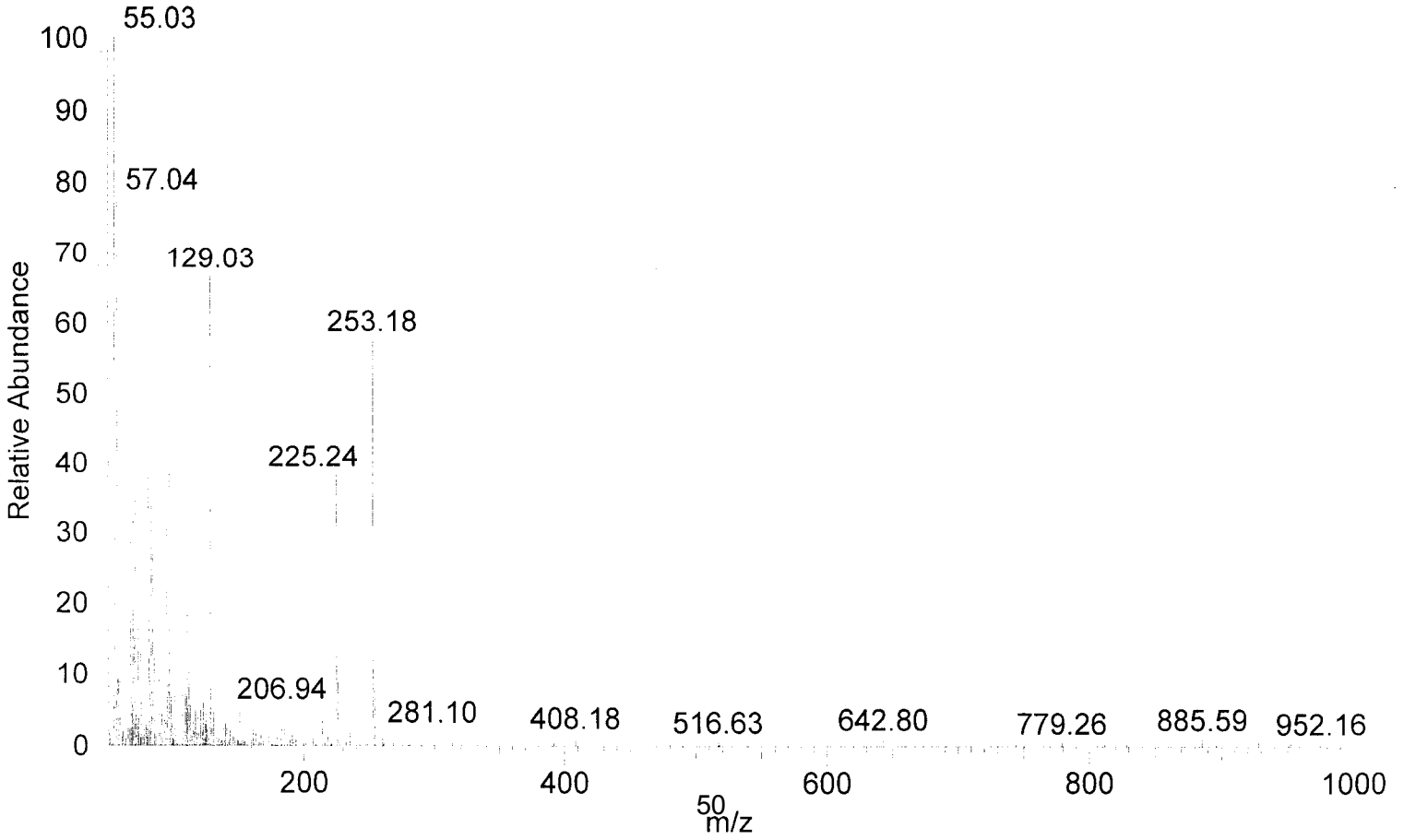


RT: 0.00 - 47.86



TanikolideSYN_SS #1227 RT: 36.37 AV: 1 NL: 3.03E4
T: + c Full ms [50.00-1000.00]



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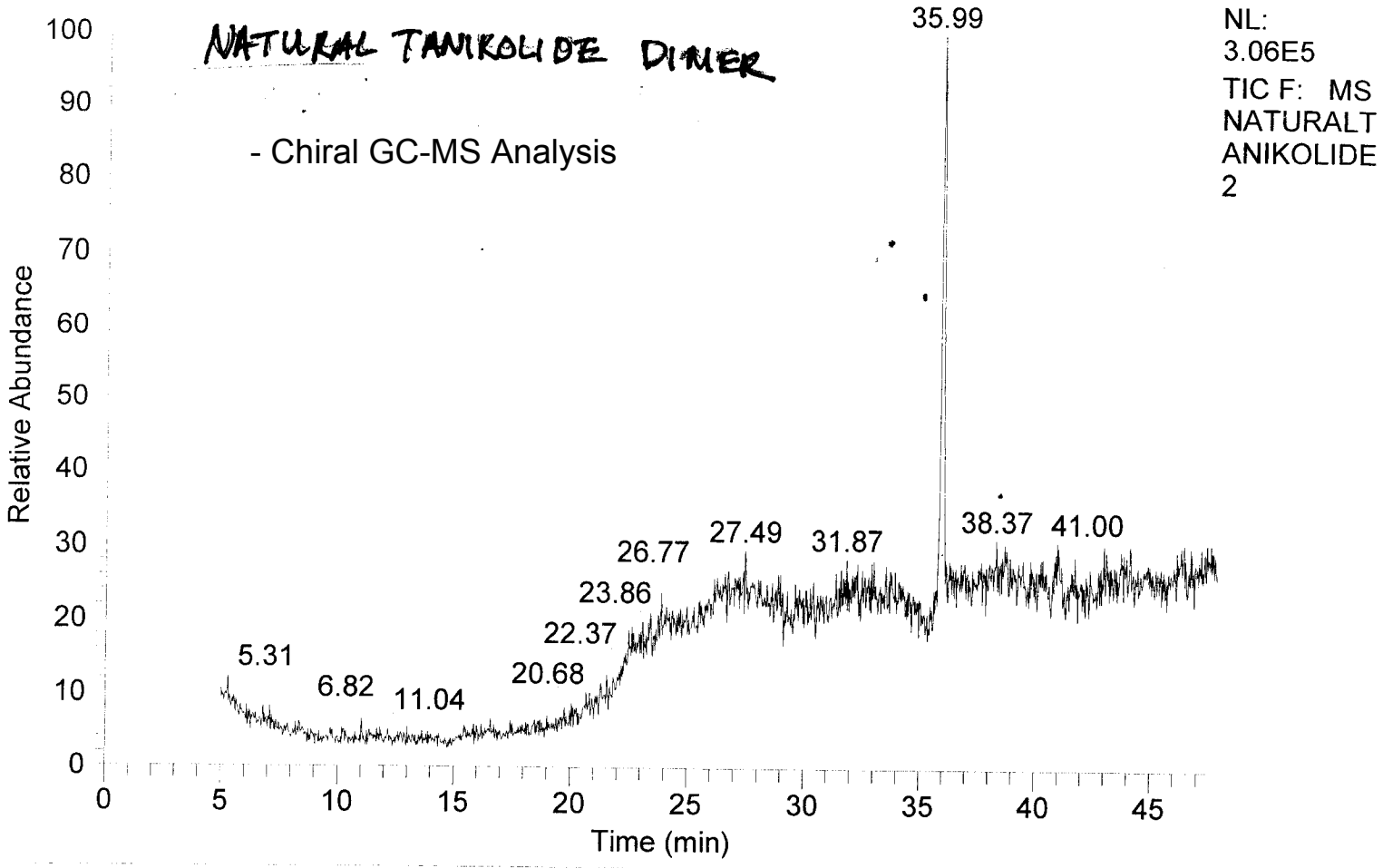
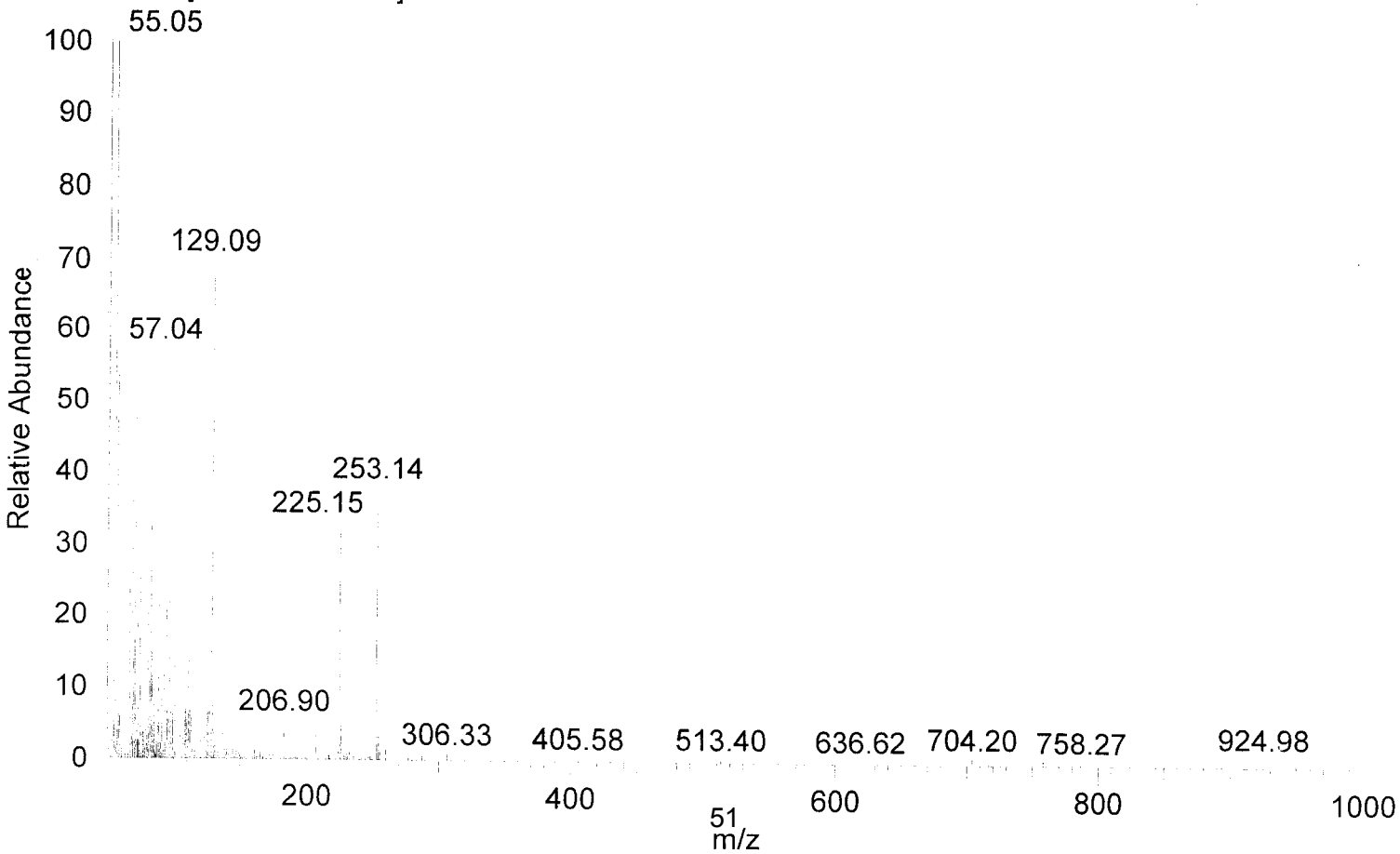
RT: 0.00 - 47.88

NATURAL TANIKOLIDE DIMER

- Chiral GC-MS Analysis

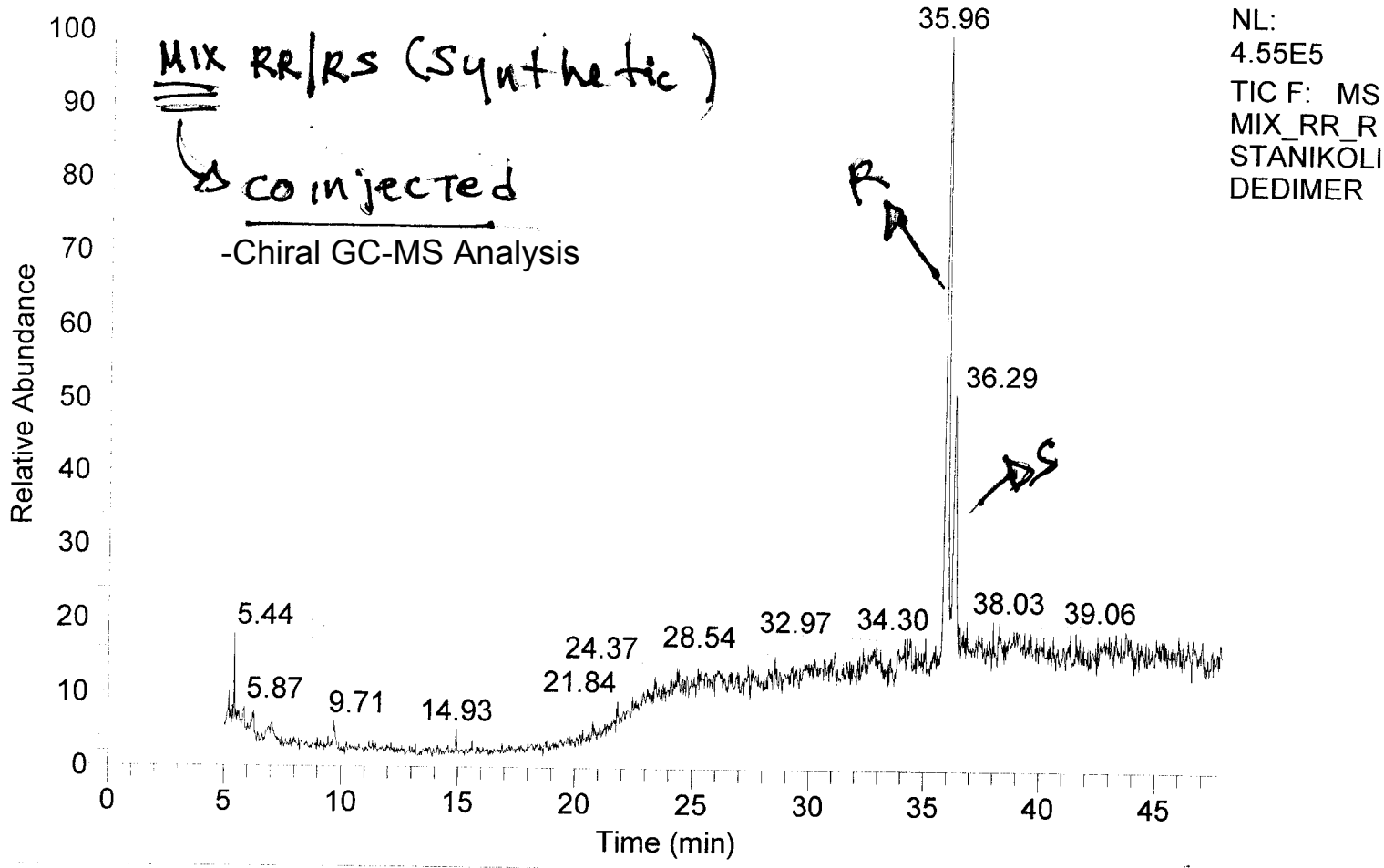


NATURALTANIKOLIDE2 #1212 RT: 35.99 AV: 1 NL: 2.82E4
T: + c Full ms [50.00-1000.00]



C:\Xcalibur\...\MIX_RR_RSTANIKOLIDEDIMER 6/27/2007 6:12:27 PM

RT: 0.00 - 47.88



MIX_RR_RSTANIKOLIDEDIMER #1211 RT: 35.96 AV: 1 NL: 4.89E4
T: + c Full ms [50.00-1000.00]