

The Development of a Tandem Stille-Oxaelectrocyclization Reaction

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

Master of Science

California Institute of Technology

Pasadena, California

2004

(August 6, 2003)

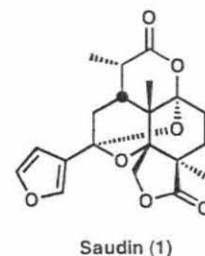
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## Research Summary: The Development of a Tandem Stille-Oxaelectrocyclization Reaction

### Introduction

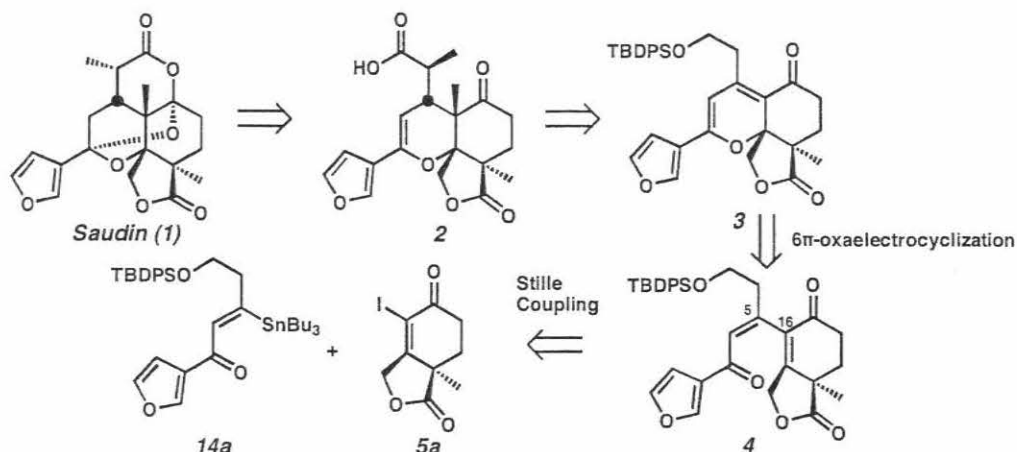
Metal-mediated coupling reactions are an essential tool for the synthetic chemist, and are among the most important methods for forming carbon-carbon bonds. Tandem reactions are also useful since they can rapidly and efficiently build up complex structures. With these key features in mind, a palladium-catalyzed tandem Stille-oxaelectrocyclization has been developed in our labs based upon work toward the total synthesis of saudin (**1**).

Saudin, a labdane diterpenoid, was isolated from the leaves of *Cutia richardiana*, a toxic plant indigenous to Saudi Arabia<sup>1</sup>. Saudin is interesting both for its unique structural features and its potent bioactivity. Saudin possesses seven stereogenic centers, including two quaternary carbons and its caged, highly oxygenated, polycyclic framework presents a formidable synthetic challenge. Saudin is a potent hypoglycemic agent and therefore could be a promising lead structure for discovering therapeutics for the treatment of diabetes<sup>1</sup>.



Since the isolation of saudin in 1985, the molecule has been the subject of considerable synthetic effort. These efforts have resulted in elegant syntheses of ( $\pm$ )-saudin by Winkler<sup>2</sup> and (–)-saudin by Boeckman<sup>3</sup>. Research by my colleagues in the Stoltz group has explored an alternative strategy for the enantioselective synthesis of saudin (Scheme 1)<sup>4</sup>.

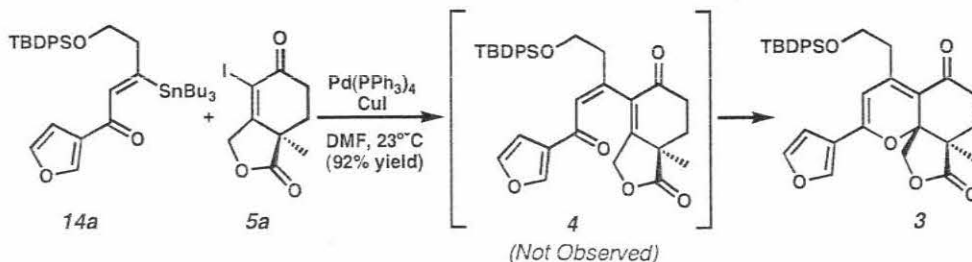
**Scheme 1: Retrosynthetic Analysis of Saudin**



The key disconnection in this sequence is the opening of the 2H-pyran **3** via a retro-oxaelectrocyclization to reveal oxatriene **4**, followed by disconnection across the C(5)-C(16) bond via a Stille coupling. This reveals the relatively simple coupling partners **5a** and **14a** which are each accessible in three steps from readily available starting materials.

When stannane **14a** and iodoenone **5a** were subjected to Cu(I)-accelerated Stille coupling conditions, it was found that the desired coupling reaction occurred. However, product **4** was not observed. Instead, the substrates reacted further, undergoing an oxaelectrocyclization to yield furan appended tricycle **3** (Scheme 2). This tandem reaction, which rapidly builds up the core of saudin, was selected for further investigation to evaluate its utility as a more general synthetic methodology.

**Scheme 2**



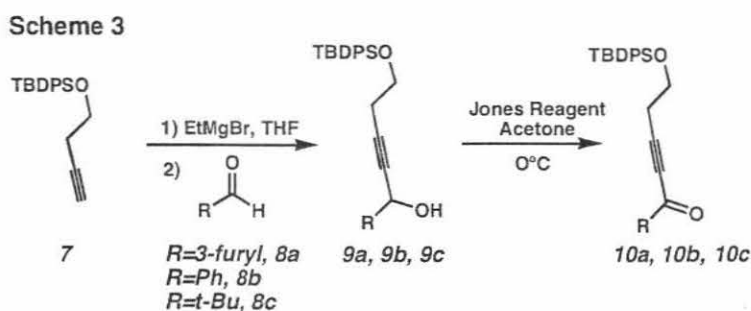
## *From Total Synthesis to Synthetic Methodology*

The tandem Stille-oxaelectrocyclization has several interesting features. It is highly diastereoselective, convergent, and requires mild reaction conditions with low catalyst loading. These mild conditions are particularly noteworthy given the rather sterically hindered nature of the coupling partners. The reaction is also of interest since oxaelectrocyclizations are currently a relatively under-utilized transformation in organic synthesis. Recently, there have been notable, although isolated, examples used in the syntheses of Torreyanic Acid by Porco<sup>5</sup>, Arisugacin A by Hsung<sup>6</sup>, and Sterekunthal A by Trauner<sup>7</sup>.

In pursuing this reaction as part of a general synthetic method for the formation of 2H-pyrans, the key issues examined were the substrate scope of the reaction, the factors affecting the efficiency of the Stille coupling, and the variables that affect the equilibrium between the 2H-pyran and the 1-oxatriene.

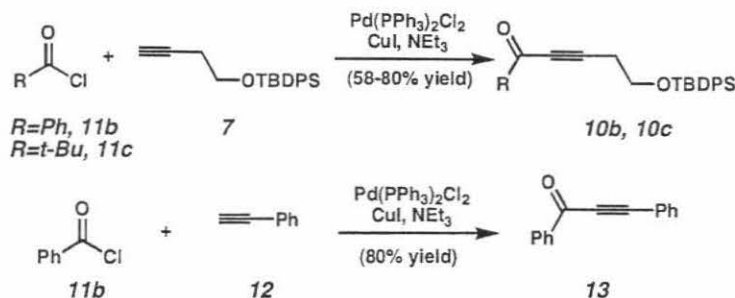
### *Synthesis of Stannane and Iodoenone Substrates*

Several different routes were utilized to obtain the stannane coupling partners. The initial method involved addition of a Grignard reagent into an aldehyde followed by a Jones oxidation (Scheme 3).

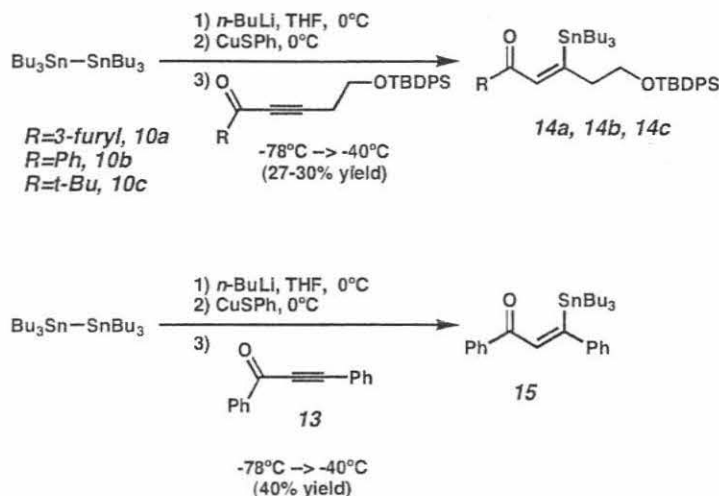


Alternatively, the alkynones could be formed directly via a Sonagashira coupling between a terminal acetylene and an acid chloride<sup>8</sup> (Scheme 4).

Scheme 4

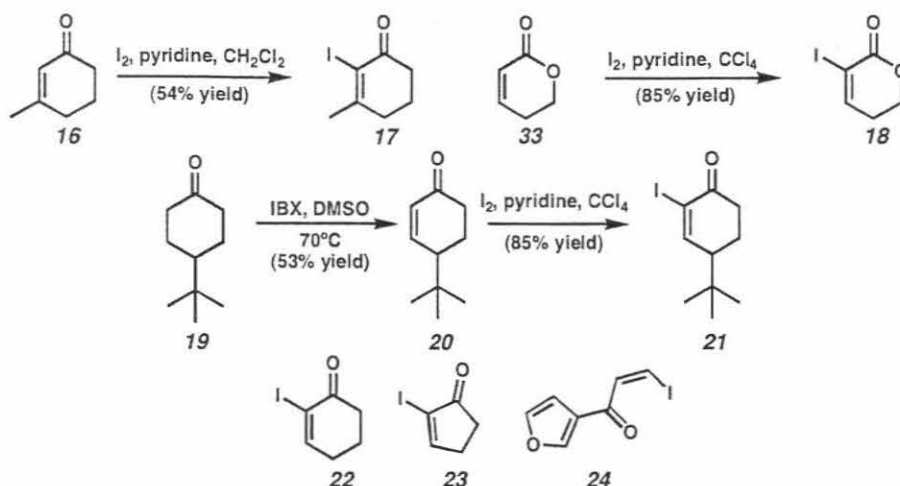


Next, these alkynones were converted to (*Z*)-vinyl stannanes. This transformation was accomplished by first treating hexabutylditin with *n*-butyl lithium, followed by the addition of copper thiophenol. This generated (Bu<sub>3</sub>Sn)CuSPhLi *in situ*, which was then reacted with an alkynone, to give exclusively the desired olefin geometry<sup>9</sup> (Scheme 5).

Scheme 5: Synthesis of (*Z*)-Stannanes

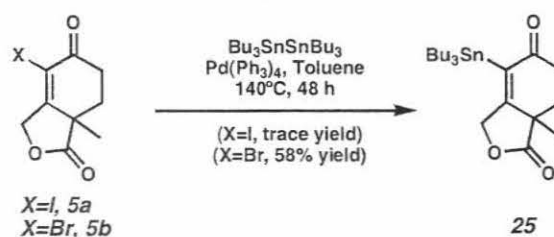
In order to examine the scope of the reaction, several iodoenones were synthesized from readily available enones<sup>10</sup> (Scheme 6). These iodoenones feature varying ring sizes, differing amounts of steric bulk around the ring, and **18** features a lactone. From work toward the synthesis of saudin, it was known that the bicyclic enone **5a** and the acyclic iodoenone **24** were also useful substrates for the tandem Stille-oxaelectrocyclization reaction.

**Scheme 6: Iodoenones**



The bicyclic stannane **25** was synthesized from bicyclic bromoenone **5b** through a cross coupling with hexabutylditin (Scheme 7). In examining this reaction, it was found that using the iodoenone gave primarily non-specific decomposition and only a trace amount of the desired product. The purity of bromoenone **5b** was a critical factor in the success of the reaction, with slightly impure material leading to significant erosions in yield.

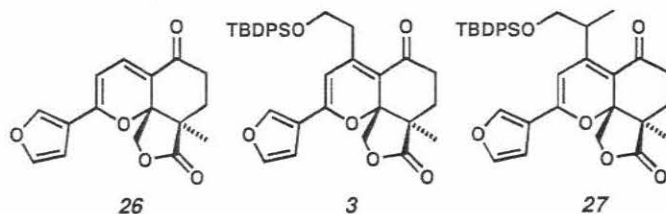
**Scheme 7**



### *Exploring the Tandem Stille-oxaelectrocyclization Reaction*

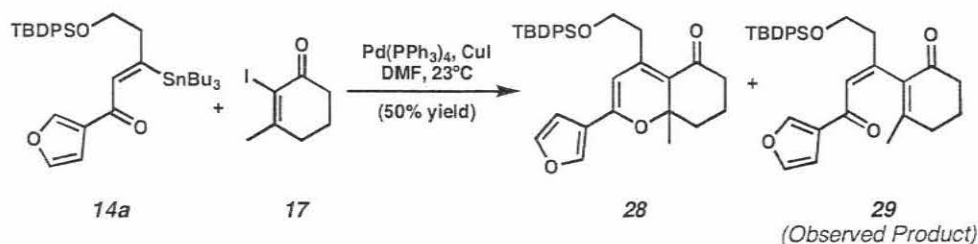
With a variety of stannanes and iodoenones in hand, the substrate scope of the reaction was investigated. Work toward the synthesis of saudin resulted in the syntheses of several different furan appended tricycles (Figure 1). From these studies, it was shown that substrates with varying alkyl substituents in the 4-position of the 2H-pyran successfully underwent the stille-oxaelectrocyclization.

Figure 1



As a starting point, the coupling between iodoenone **17** and stannane **14a** was attempted to explore the substrate scope for the iodoenone (Scheme 8). These substrates successfully underwent the Stille coupling. However, upon examination of the  $^{13}\text{C}$  spectrum, it was clear that two carbonyl peaks were present, indicating that the oxaelectrocyclization did not occur.

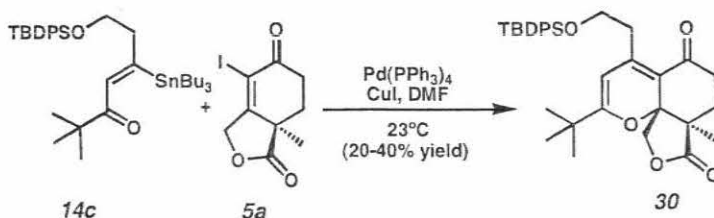
Scheme 8



Since iodoenone **17** was not a useful substrate for the oxaelectrocyclization, the bicyclic iodoenone **5a** served as a better test substrate to examine various substituents in the 6-position of the resulting 2H-pyran. Stannane **14c** successfully underwent both the Stille coupling and the oxaelectrocyclization in tandem when coupled to iodoenone **5a**. However, a new problem emerged – the reaction conditions that

Scheme 9

produced furan appended tricycles in good yield produced *tert*-butyl appended tricycles in low and variable yields (Scheme 9).



In an effort to alleviate this problem, a number of reaction parameters were screened to further optimize the reaction (Table 1). A variety of ligands and palladium sources did little to improve the reaction.

**Table 1: Optimization Studies**

14c + 5a			Pd Source, ligand, additive solvent <sup>a</sup>			30		
Entry	Pd Source	Ligand	Solvent	Additive	Other	Iodoenone consumed?	Stannane consumed?	Yield
1	Pd(PPh <sub>3</sub> ) <sub>4</sub>		DMF	CuI	Argon	no	yes	43% <sup>c</sup>
2	Pd(PPh <sub>3</sub> ) <sub>4</sub>		DMF	CuI	50 °C	no	yes	trace
3	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub> (10 mol%)	DMF	CuI		no	yes	11% <sup>b</sup>
4	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	DMF	CuI		no	yes	45% <sup>b</sup>
5	Pd <sub>2</sub> (dba) <sub>3</sub>	AsPh <sub>3</sub>	DMF	CuI		no	yes	trace
6	Pd <sub>2</sub> (dba) <sub>3</sub>	o-tolyl	DMF	CuI		no	yes	trace
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>		DMSO	CuCl, LiCl	50 °C	no	yes	0% <sup>a</sup>
8	Pd(DPPF)Cl <sub>2</sub>		DMF	CuI		no	yes	0% <sup>d</sup>
9	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub>		DMF	CuI		no	yes	0%

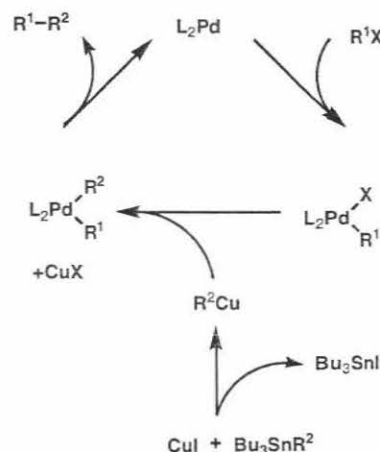
<sup>a</sup> 5 mol% Pd, 20 mol% ligand, 0.1M in 5a, 1 equiv CuI. 1 equiv. 5a, 1.2 equiv 14c <sup>b</sup> Yield measured by NMR with 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Isolated yield. <sup>d</sup> DPPF=1,2-bis(diphenylphosphino)ferrocene.

<sup>e</sup> 10 mol% Pd, 5 equiv CuCl, 6 equiv LiCl.

A pattern did emerge that illustrated the key problem facing the reaction. Although the stannane was present in slight excess, it was always consumed before the iodoenone. This decomposition of the stannane led to low yields of the desired product and the recovery of unreacted iodoenone.

Previous studies in our lab have demonstrated that copper(I) iodide was necessary for this Stille coupling to proceed. This copper effect in Stille couplings has been well studied<sup>11,12</sup>, and two distinct mechanisms have been proposed depending upon the reaction medium.<sup>13,14</sup> In the case of very polar solvents such as DMF or NMP, copper(I) salts are believed to undergo Cu/Sn

**Scheme 10: Proposed Catalytic Cycle**





transmetallation, resulting in the formation of an organocopper species (Scheme 10). In the case of less polar solvents such as THF, the copper(I) is believed to act as a ligand scavenger of free phosphine, thus accelerating the Sn/Pd transmetallation.

In an attempt to further optimize the reaction, the amount of copper iodide was varied. When using substoichiometric amounts, the reaction became very sluggish and even lower yields were observed. However, these experiments did lead to a useful observation. When catalytic amounts of copper iodide were used, the stannane did not decompose (Table 2, entries 2 and 3). In a control experiment, iodoenone **5a** was excluded from the reaction. Decomposition was observed in the presence of copper iodide (Table 2, Entry 4), while no reaction was seen in the absence of copper iodide (table 2, entry 5). From these results, it was hypothesized that copper(I) was undergoing oxidation to a copper(II) species, which is known to facilitate the homocoupling of stannanes<sup>15</sup>. In order to test this hypothesis, the reaction was run in an inert atmosphere glovebox, thus rigorously excluding oxygen. To our delight, the desired product was obtained in high yield (table 2, entry 6).

**Table 2: Examining the Role of Copper Iodide**

		14c + 5a		Pd Source, ligand, CuI DMF <sup>a</sup> →	30	
Entry	Pd Source	Ligand	CuI (mol%)	Other	Stannane consumed?	Yield
1	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	100%		yes	45% <sup>b</sup>
2	Pd <sub>2</sub> (dba) <sub>3</sub>	PPh <sub>3</sub>	5%		no	trace
3	Pd(PPh <sub>3</sub> ) <sub>4</sub>		0%		no	no reaction
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>		100%	no iodoenone 5a	yes	decomposition
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>		0%	no iodoenone 5a	no	no reaction
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>		100%	in glovebox	no	94% <sup>b</sup>

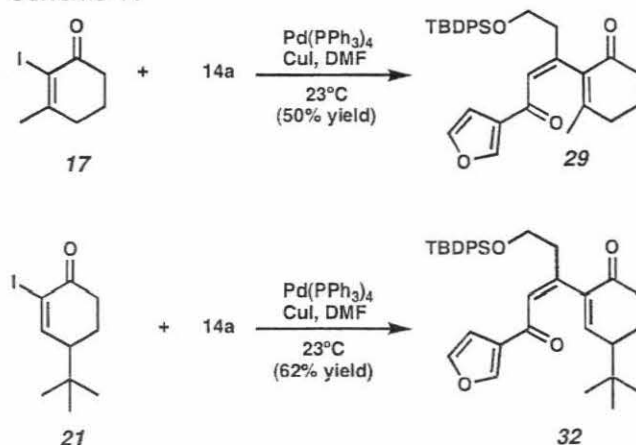
<sup>a</sup> 5 mol% Pd, 20 mol% ligand, 0.1 M in **5a**, 1 equiv **5a**, 1.2 equiv **14c**. <sup>b</sup> Isolated yield.

Having found that rigorously anaerobic conditions were optimal for this reaction, a variety of other substrates were examined. It was discovered that subtle changes in molecular

structure had a large impact on the effectiveness of the oxaelectrocyclization. For some substrates the Stille coupling was successful, but the product would exist primarily as the 1,3,5-oxatriene (Scheme 11).

In other cases, the Stille coupling was successful, and the oxaelectrocyclization yielded an equilibrium mixture of products (Table 3). These equilibrium mixtures were difficult to characterize because the species in solution were rapidly interconverting on the NMR timescale, causing the peaks in the NMR

**Scheme 11**



spectrum to be very broad. To alleviate this problem, the  $^1\text{H}$  NMR spectra were taken at  $-30\text{ }^\circ\text{C}$ . These products were obtained in useful yields and often in a good ratio of cyclized to uncyclized product.

**Table 3**

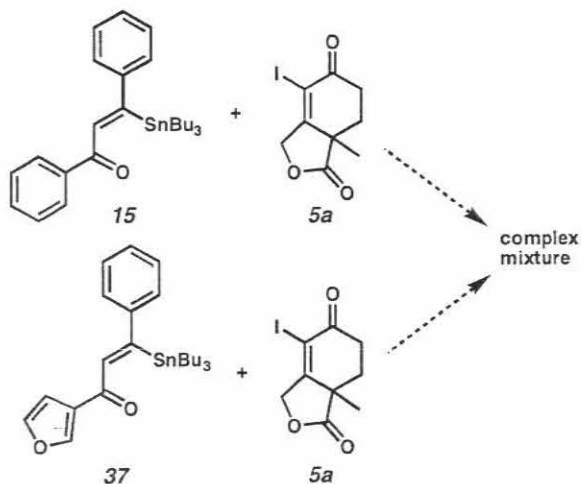
Cyclized Product	Uncyclized Product	Ratio (Cyclized:Uncyclized) <sup>a</sup>	Yield <sup>b</sup>
		7 : 1	90%
		10 : 1	66%
		10 : 1	73%
		1 : 3	62%

<sup>a</sup> Ratio determined by  $^1\text{H}$  NMR spectroscopy. <sup>b</sup> Isolated yield.

When varying the substitution at the 4-position of the resulting pyran ring, it was found that a phenyl ring was not well tolerated in the reaction. These reactions yielded complex mixtures of products (Scheme 13).

The most successful substrates were those incorporating iodoenones **5a** or **18** with a stannane that had alkyl substitution in the 4-position of the resulting pyran ring, while both alkyl and aromatic substitution worked well in the 2-position. These products could be obtained in good to excellent yields and resulted in the exclusive formation of the desired 2H-pyran product (Table 4).

**Scheme 12**



**Table 4**

Product	Yield <sup>a</sup>	Product	Yield <sup>a</sup>
 <b>3</b>	92%	 <b>40</b>	65%
 <b>30</b>	94%	 <b>41</b>	67%
 <b>39</b>	94%	 <b>42</b>	92%

<sup>a</sup> Isolated Yield

## Theoretical Calculations

One of the key difficulties in developing oxaelectrocyclizations as a useful synthetic tool is a typically small (or even unfavorable) thermodynamic driving force for the reaction. This often leads to the formation of uncyclized products or equilibrium mixtures of products. Rather than relying solely on trial and error, we turned to theoretical calculations to examine substrates for the tandem Stille-oxaelectrocyclization reaction.

Using Spartan '02 for Macintosh, AM1 calculations were used to evaluate the enthalpy of reaction for the conversion of 1,3,5-oxatriene to 2H-pyran. In order to simplify the calculations, methyl groups were used to approximate longer alkyl groups

**Table 5: Enthalpy of Reaction for Oxaelectrocyclizations**

Entry	1,3,5-oxatriene	2H-pyran	$\Delta H$ (kcal/mol) <sup>a</sup>
1			2.046
2			0.083
3			-3.71
4			-3.84
5			-1.62

<sup>a</sup> AM1 result based on lowest energy conformation of 1,3,5-hexatriene and 2H-pyran.

in the 4-position of the pyran ring. The results agreed well with the observed experimental observation. In the cases where the calculated enthalpy was endothermic, the 2H-pyran product was not observed experimentally (Table 5, entries 1, 2). In the cases where the calculated enthalpy was exothermic, the 2H-pyrans were obtained as the major products from the tandem stille-oxaelectrocyclization process (Table 5, entries 3,4,5). While these methods are not as

precise as higher level calculations<sup>16</sup>, they clearly offer some degree of predictive power for evaluating potential oxaelectrocyclization substrates.

## *Conclusions*

While the tandem Stille-oxaelectrocyclization reaction is not yet a general method for the synthesis of 2H-pyrans, many interesting subtleties of the reaction have been explored. The key problem with this process is that unfavorable thermodynamics limit the substrate scope of the oxaelectrocyclization. Nonetheless, several highly substituted 2H-pyrans were synthesized using this reaction. This work demonstrates the utility of tandem reactions for the construction of complex molecular architectures, and also shows the potential, and inherent difficulties, of using oxaelectrocyclizations as a synthetic tool.

## *Experimental Section*

**Material and Methods.** Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen atmosphere, using deoxygenated solvents dried over activated alumina. All other commercially available reagents were used as received. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts are reported relative to Me<sub>4</sub>Si ( $\delta$  0.0). Mass spectra were performed at the California Institute of Technology mass spectrometry facilities.

**General Procedure for the Preparation of Propargyl Alcohols.** A terminal alkyne (18 mmol, 1 equiv) was added to a stirred solution of ethyl magnesium bromide (18 mmol, 1 equiv) in

diethyl ether (10 mL) at 23 °C. This reaction mixture was stirred for 30 minutes. Aldehyde (21 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred until the reaction reached completion as determined by TLC. After quenching with 1 M HCl, the organic layer was washed three times with water and once with brine. The organic layer was separated and dried over  $\text{MgSO}_4$ . Following concentration *in vacuo*, a portion of the resulting crude mixture was carried on to the oxidation step.

**General Procedure for the Preparation of Ynones by Jones Oxidation.** The crude alcohol (7.2 mmol, 1 equiv) was dissolved in acetone (15 mL). This solution was cooled to 0 °C and Jones reagent (15 mmol, 2.1 equiv) was added slowly to the stirred reaction mixture. After stirring 30 minutes, the excess Jones reagent was quenched with isopropanol. The reaction mixture was extracted three times with ether, washed once with aqueous  $\text{NaHCO}_3$ , and once with brine. After drying over  $\text{MgSO}_4$  and concentrating *in vacuo*, the crude ynone was purified by flash column chromatography on silica gel.

**General Procedure for the Preparation of Ynones via the Sonagashira Reaction.** A Schlenk tube was charged with CuI (0.2 mmol, 2 mol%),  $\text{Pd(PPh}_3)_2\text{Cl}_2$  (0.06 mmol, 0.5 mol%), and terminal alkyne (10.8 mmol, 1 equiv). Next, triethylamine (22 mL) was added to the Schlenk tube and the mixture was degassed by the freeze-pump-thaw method. Then, an acid chloride (14.2 mmol, 1.3 equiv) was added dropwise to the stirred reaction mixture at 23 °C. The reaction mixture was stirred 12 hours. Once the reaction was complete, water was added to the reaction mixture and the organic material extracted three times with pentane. The organic layer was then

washed thrice with water and once with brine and then dried over  $\text{MgSO}_4$ . After concentrating *in vacuo*, the crude ynone was purified by flash column chromatography on silica gel.

**General Procedure for the Preparation of (Z)-Vinyl Stannanes.** n-Butyllithium (4.5 mmol, 1.2 equiv) was added to a stirred solution of bis(tributyltin) (4.5 mmol, 1.2 equiv) in THF (40 mL) at 0 °C. After stirring 30 minutes, CuSPh (4.5 mmol, 1.2 equiv) was added. After an additional 30 minutes of stirring, the reaction mixture was cooled to -78 °C. Alkynone (3.8 mmol, 1 equiv) was added slowly to the reaction mixture and stirred for 30 minutes at -78 °C. The reaction was then warmed to -40 °C and stirred for an hour and then allowed to warm to room temperature. Aqueous ammonium chloride was added to quench the reaction, and the organic material was extracted with ether. After separating the organic layer, methanol was added, forming a yellow slurry that was filtered through celite. The filtrate was concentrated *in vacuo* to provide the crude (Z)-vinyl stannane, which was then purified by flash column chromatography on silica gel.

**General Procedure for Tandem Stille-oxaelectrocyclization Reactions.**  $\text{Pd}(\text{PPh}_3)_4$  ( $3.3 \times 10^{-6}$  moles, 5 mol%), CuI ( $5.7 \times 10^{-5}$  moles, 1 equiv) and iodoenone ( $5.7 \times 10^{-5}$  moles, 1 equiv) were weighed into a oven-dried vial. The stannane ( $6.8 \times 10^{-5}$  moles, 1.2 equiv) was concentrated *in vacuo* from benzene in a separate flask. These materials were then taken into the glovebox. Next, the stannane was dissolved in DMF (0.7 mL) and the resulting solution was transferred into the vial containing the other reagents. The reaction was stirred for 24 hours. Then, water was added and the reaction mixture extracted with ether. The organic layer was dried by passing it over a short silica plug. The material was concentrated *in vacuo* to yield the crude product,

which could then be purified by flash column chromatography on silica gel. Sometimes after flashing a compound, some alkyl tin contaminants remained. These were removed by dissolving the material in acetonitrile and washing three times with hexane. Concentrating the acetonitrile layer *in vacuo* produced the desired product free of alkyl tin byproducts.

**Furan Appended Tricycle 3.** Prepared using the general procedure for the tandem Stille-oxaelectrocyclization reaction using **5a** (43.5 mg, 0.15 mmol) and **14a** (130.7 mg, .018 mmol). Purified by flash chromatography on silica gel (10:1 hexanes:EtOAc → 7:1 hexanes:EtOAc). 80-92% yield, yellow foam/oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.714 (s, 1H), 7.656-7.612 (comp. m, 4H), 7.448-7.317 (comp. m, 7H), 6.4565 (d, J=2.1 Hz, 1H), 5.817 (s, 1H), 4.7435 (d, J=11.1 Hz, 1H), 3.967-3.880 (comp. m, 3H), 3.095 (dt, J=2.4, 6 Hz, 2H), 2.68-2.2.368 (comp. m, 2H), 2.044-1.996 (comp. m, 2H), 1.542 (s, 3H), 1.071 (s 9); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 194.666, 179.206, 151.477, 144.311, 143.059, 135.579, 133.654, 133.595, 129.722, 172.707, 120.713, 113.925, 107.301, 105.496, 86.5143, 71.5361, 63.3087, 44.9139, 36.6156, 34.9895, 27.8237, 26.8780, 19.2637, 14.8827; IR (film) 2932.0, 2857.7, 1785.0, 1659.4, 1112.1 cm<sup>-1</sup>; HRMS (FAB+) *m/z* calc'd for [C<sub>34</sub>H<sub>37</sub>O<sub>6</sub>Si]<sup>+</sup>: 569.2359, found 569.2346.

**Bicyclic Iodoenone 5a.** Used as received from Taichi Kano. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.97 (d, J=15 Hz, 1H), 4.83 (d, J=15 Hz, 1H), 2.86-2.81 (comp. m, 2H), 2.31-2.13 (comp. m, 2H), 1.56 (s, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 189.20, 176.80, 166.48, 99.13, 73.16, 45.96, 31.97, 29.48, 21.59; HRMS (FAB+) *m/z* calc'd for [C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>I]<sup>+</sup>: 292.9675, found 292.9685.



**Ynone 10b.** Prepared using the general procedure for the preparation of ynones via a Sonagashira coupling with **11b** (1.65 mL, 14.0 mmol) and **7** (3.3g, 10.8 mmol). Purified by flash chromatography on silica gel (8:1 hexanes:EtOAc eluent). 27%, clear, brownish oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.174-8.143 (comp. m, 2H), 7.725-7.686 (comp. m, 4H), 7.583 (tt,  $J=9.6$ , 1.5 Hz, 1H), 7.467-7.354 (comp. m, 8H), 3.918 (t,  $J=6.6$  Hz, 2H), 2.748 (t,  $J=6.6$  Hz, 2H), 1.12 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  178.138, 136.814, 135.584, 133.969, 133.240, 129.876, 129.685, 128.515, 127.831, 93.796, 80.369, 61.510, 26.802, 23.482, 19.232; IR (film) 2931.3, 2857.7, 2237.9, 2207.1, 1645.4, 1645.4, 1263.9, 1112.6  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{27}\text{H}_{27}\text{O}_2\text{Si}]^+$ : 411.1780, found 411.1792.

**Ynone 10c.** Prepared using the general procedure for the preparation of ynones via a Sonagashira coupling with **11c** (1.8 mL, 14.2 mmol) and **7** (3.36g, 10.8 mmol). Purified by flash chromatography on silica gel (1:1 hexanes:DCM eluent). 58%, clear, brownish oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.700-7.662 (comp. m, 4H), 7.470-7.364 (comp. m, 6H), 3.828 (t,  $J=6.6$  Hz, 2H), 2.632 (t,  $J=6.6$  Hz, 2H), 1.197 (s, 9H), 1.051 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  194.345, 135.563, 133.265, 129.839, 127.796, 92.624, 79.536, 61.523, 44.639, 26.760, 26.068, 23.260, 19.188; IR (film) 2932.2, 2858.7, 2210.5, 1809.8, 1670.4  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{25}\text{H}_{31}\text{O}_2\text{Si}]^+$ : 391.2093, found 391.2098.

**Stannane 14b.** Prepared using the general procedure for the preparation of (Z)-vinyl stannane from ynone **10b** (1.1 g, 2.5 mmol). Purified by flash chromatography on silica gel (10:1 hexanes:EtOAc  $\rightarrow$  6:1 hexanes:EtOAc). 31% yield, clear, light brown oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.977-7.947 (comp. m, 2H), 7.702-7.670 (comp. m, 4H), 7.634 (s, 1H), 7.551 (comp.

m, 1H), 7.481-7.353 (comp. m, 8H), 3.794 (t, J=6.6 Hz, 2H), 2.830 (t, J=6.6,  $J_{\text{SnH}}=42$  Hz, 2H), 1.479-1.416 (comp. m, 6H), 1.271 (m, J=7.2 Hz, 6H), 1.058 (s, 9H), 0.985-0.931 (comp. m, 6H), 0.848 (t, 7.5H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  189.487, 175.368, 138.328, 135.614, 134.100, 133.812, 132.575, 129.670, 128.519, 128.496, 127.696, 62.856, 43.504, 29.321, 27.493, 26.884, 19.273, 13.752, 11.151; IR (film)  $1651.2\text{ cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{39}\text{H}_{55}\text{O}_2\text{SnSi}]^+$ :  $m/e$  703.2993, found 703.3007.

**Stannane 14c.** Prepared using the general procedure for the preparation of (Z)-vinyl stannane using ynone **10c** (2.3 g, 5.8 mmol). Purified by flash chromatography on silica gel (50:1 hexanes:EtOAc). 28% yield, clear, light brown oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.715-7.683 (comp. m, 4H), 7.455-7.3477 (comp. m, 6H), 7.105 (s, 1H), 3.7003 (t, J=6.65 Hz, 2H), 2.692 (t, J=6.65,  $J_{\text{SnH}}=43.56$  Hz, 2H), 1.4385-1.33658 (comp. m, 6H), 1.240 (m, J=7.7 Hz, 7H), 1.1337 (s, 9H), 1.04245 (s, 9H), 0.894-0.813 (comp m., 14H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  204.562, 171.438, 135.601, 133.812, 133.564, 129.645, 127.665, 62.882, 43.239, 42.518, 29.278, 27.477, 26.859, 26.427, 19.239, 13.748, 11.016; IR (film) 2956.1, 2857.3, 1671.1, 1113.1  $\text{cm}^{-1}$ ; HRMS (EI+)  $m/z$  calc'd for  $[\text{C}_{33}\text{H}_{51}\text{O}_2\text{SiSn}]^+$ : 627.2680, found 627.2666.

**Iodopyranone 18.** Compound **33** (0.1 mL, 1.16 mmol) was dissolved in  $\text{CCl}_4$  (1 mL) and pyridine (1 mL). Then, a solution of iodine (0.9 g, 3.4 mmol), in 1:1 pyridine/ $\text{CCl}_4$  (6 mL) was slowly added at 0 °C. The reaction was quenched with aqueous sodium thiosulfate and the organic material was extracted using  $\text{CH}_2\text{Cl}_2$ . The organic layer was then washed once with brine and dried over  $\text{MgSO}_4$ . Following concentration *in vacuo*, the crude product was purified by flash chromatography on silica gel (10:1 hexanes:EtOAc). 85% yield, yellowish solid.  $^1\text{H}$

NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.595 (t,  $J=4.65$  Hz, 1H), 4.484 (t,  $J=6$  Hz, 2H), 2.515 (dt,  $J=4.65$ , 6 Hz, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  159.654, 154.392, 89.487, 67.044, 28.238; IR (NaCl,  $\text{CCl}_4$ )  $1723.7\text{ cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_5\text{H}_6\text{O}_2\text{I}]^+$ : 224.9413, found 224.9405.

**Iodocyclohexenone 22.** Used as received from David Ebner.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.790 (t,  $J=4.5$  Hz, 1H), 2.704-2.659 (comp. m, 2H), 2.466 (dt,  $J=4.5$ , 6 Hz, 2H), 2.149-2.064 (comp m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  192.233, 159.518, 103.874, 37.275, 29.964, 22.871; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_6\text{H}_8\text{OI}]^+$ : 222.9620, found 222.9622.

**Iodocyclopentenone 23.** Used as received from David Ebner.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.003 (dt,  $J=0.9$ , 3 Hz, 1H), 2.782-2.739 (comp. m, 2H), 2.495-2.464 (comp. m, 2H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  204.080, 169.694, 102.879, 31.299, 30.966.

**Bicyclic Stannane 25.** Bromoenone **5b** (4g, 16.3 mmol), bis(tributyltin) (16.5 ml, 32.6 mmol), and  $\text{Pd}(\text{PPh}_3)_4$  (280 mg, 1.5 mol%) were added to toluene (210 mL) under an atmosphere of argon. The reaction mixture was stirred at reflux for 48 h. Following filtration through celite and concentration *in vacuo*, the crude product was purified by flash column chromatography (10:1 hexanes:EtOAc  $\rightarrow$  7:1 hexanes:EtOAc). 58% yield, brownish-orange oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.028 (d,  $J=14.65$  Hz, 1H), 4.790 (d,  $J=14.65$  Hz, 1H), 2.666-2.468 (comp. m, 2H), 2.2318 (ddd,  $J=13.3$ , 5.3, 2.1 Hz, 1H), 2.040 (td,  $J=13.3$ , 6.6 Hz, 1H), 1.663-1.581 (comp. m, 3H), 1.483 (s, 3H), 1.471-1.240 (comp. m, 13H), 1.029-0.861 (comp. m, 14H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  178.361, 169.627, 139.507, 69.887, 42.200, 32.142, 29.199, 28.292, 27.244,

26.800, 21.580, 17.307, 13.655, 10.964; IR (film) 1783.6, 1654.0  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{21}\text{H}_{35}\text{O}_3\text{Sn}]^+$ : 455.1608, found 455.1603.

***tert*-Butyl Appended Tricycle 30.** Prepared using the general procedure for the tandem Stille-oxaelectrocyclization reaction using **14c** (43 mg, .063 mmol) and **5a** (15.3 mg, 0.0525 mmol). Purified by flash chromatography on silica gel (hexanes  $\rightarrow$  5:1 Hexanes/EtOAc). 94% yield, yellow oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.658-7.620 (comp. m, 4H), 7.46-7.33 (comp. m, 6H), 5.4527 (s, 1H), 4.6363 (d,  $J=10.8$  Hz, 1H), 3.971-3.828 (comp. m, 3H), 3.11 (app. dt,  $J=12, 5$  Hz, 1H), 2.83745-2.75063 (comp. m, 1H), 2.620-2.460 (m,  $J=9$  Hz, 1H), 2.38 (app. dt, 1H), 1.95 (app. q,  $J=5$  Hz, 2H), 1.4696 (s, 3H), 1.10635 (s, 9H), 1.04435 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  194.790, 179.381, 168.713, 151.825, 135.568, 133.675, 129.707, 127.681, 112.935, 103.354, 85.983, 71.353, 63.514, 44.869, 36.735, 35.692, 34.986, 27.801, 27.185, 26.882, 19.286, 14.677; IR (film) 2932.3, 2858.1, 1787.3, 1663.2  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{34}\text{H}_{43}\text{O}_5\text{Si}]^+$ : 559.2880, found 559.2878.

**Phenyl Appended Tricycle 39.** Prepared by the general procedure for the tandem Stille-oxaelectrocyclization reaction using **5a** (16.6 mg, 0.057 mmol) and **14b** (48 mg, 0.068 mmol). Purified by flash chromatography on silica gel (hexanes  $\rightarrow$  5:1 Hexanes/EtOAc eluent). 94% yield, yellow oil  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.620 (m, 5H), 7.3875 (m, 10H), 6.149 (s,  $^1\text{H}$ ), 4.759 (d,  $J=11$  Hz, 1H), 3.950 (m, 3H), 3.103 (t,  $J=6$  Hz, 2H), 2.579 (m, 1H), 2.443 (dt,  $J=7.4, 13.5$  Hz, 1H), 2.051 (m, 2H), 1.566 (s, 3H), 1.031 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  194.855, 179.327, 156.397, 151.482, 135.580, 133.670, 132.074, 131.001, 129.708, 128.769, 127.700, 126.089, 114.161, 105.541, 86.686, 71.479, 63.330, 45.006, 36.652, 35.029, 27.830,

26.884, 19.273, 14.945; IR (thin film) 2931.9, 2857.4, 1785.6, 1661.5  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{36}\text{H}_{39}\text{O}_5\text{Si}]^+$ : 579.2567, found 579.2565.

**Furan Appended Bicycle 40.** Prepared using the general procedure for the tandem Stille-oxaelectrocyclization reaction using **14a** (53 mg, 0.076 mmol) and **33** (14 mg, 0.063 mmol). Purified by flash chromatography on silica gel (hexanes  $\rightarrow$  10:1 hexanes:EtOAc). 65% yield, yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.732 (s, 1H), 7.645 (app. d,  $J=6.5$  Hz, 4H), 7.414-7.262 (comp. m, 7H), 6.488 (s, 1H), 5.912 (s, 1H), 4.667 (t,  $J=5$  Hz, 1H), 4.365-4.217 (comp. m, 2H), 3.925 (t,  $J=6$  Hz, 2H), 3.111-3.011 (comp. m, 2H), 2.329 (app. q,  $J=5$  Hz, 2H), 1.03387 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  164.95, 153.886, 153.084, 144.219, 142.95, 135.864, 134.018, 131.14, 129.816, 127.867, 120.775, 107.969, 106.427, 73.1035, 63.8558, 63.3764, 35.8515, 29.2876, 27.1138, 19.4388; IR (film) 2930.8, 28.56.9, 1702.7, 1529.5, 1112.8  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{30}\text{H}_{33}\text{O}_5\text{Si}]^+$ : 501.2097, found 501.2105.

**tert-Butyl Appended Bicycle 41.** Prepared using the general procedure for the tandem Stille-oxaelectrocyclization reaction using **14c** (87 mg, 0.127 mmol) and **33** (24 mg, 0.106 mmol). Purified by flash chromatography on silica gel (hexanes  $\rightarrow$  5:1 hexanes:EtOAc). 67% yield, yellow oil;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.666-7.6352 (comp. m, 4H), 7.435-7.3313 (comp. m, 6H), 5.5386 (s, 1H), 4.444 (t,  $J=5.3$  Hz, 1H), 4.3222 (m,  $J=6$  Hz, 1H), 4.1835 (m,  $J=6$  Hz, 1H), 3.06775 (m,  $J=5.4$  Hz, 1H), 2.8792 (m,  $J=5.4$  Hz, 1H), 2.260 (app. q,  $J=5.3$  Hz, 2H), 1.118 (s, 9H), 1.04343 (s, 9H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  172.294, 164.904, 153.152, 135.662, 133.793, 129.58, 127.621, 105.032, 103.956, 72.8219, 63.6526, 63.4769, 35.6848, 35.61,

29.0423, 27.9097, 26.8967, 19.2263; IR (film) 2960.8, 2857.9, 1706.3, 1542.9, 1113.3  $\text{cm}^{-1}$ ;  
HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{30}\text{H}_{37}\text{O}_4\text{Si}]^+$ : 489.2461, found 489.2473.

**Phenyl Appended Bicycle 42.** Prepared by the general procedure for tandem Stille-oxaelectrocyclization reactions using **14b** (32.9 mg, 0.046 mmol) and **33** (8.7 mg, 0.038 mmol). Purified by flash chromatography on silica gel (Hexane  $\rightarrow$  5:1 Hexane/EtOAc eluent). 92%, yellow oil;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.629-7.672 (comp. m, 5H), 7.306-7.418 (comp. m, 10H), 6.249 (s, 1H), 4.703 (t,  $J=5.5$  Hz, 1H), 4.387 (comp. m, 1H), 4.256 (comp. m, 1H), 3.952 (t,  $J=6$  Hz, 2H), 3.149 (comp. m, 1H), 3.054 (comp. m, 1H), 2.392 (t,  $J=6$  Hz, 2H), 1.029 (s, 9H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  165.027, 159.058, 153.132, 135.868, 133.956, 132.371, 130.731, 129.808, 128.764, 127.865, 126.384, 106.533, 106.394, 73.288, 63.925, 63.603, 35.901, 29.319, 27.109, 19.433; IR (thin film) 2930.6, 2856.8, 1702.9, 1532.1, 1103.8  $\text{cm}^{-1}$ ; HRMS (FAB+)  $m/z$  calc'd for  $[\text{C}_{32}\text{H}_{35}\text{O}_4\text{Si}]^+$ : 511.2305, found 511.2315.

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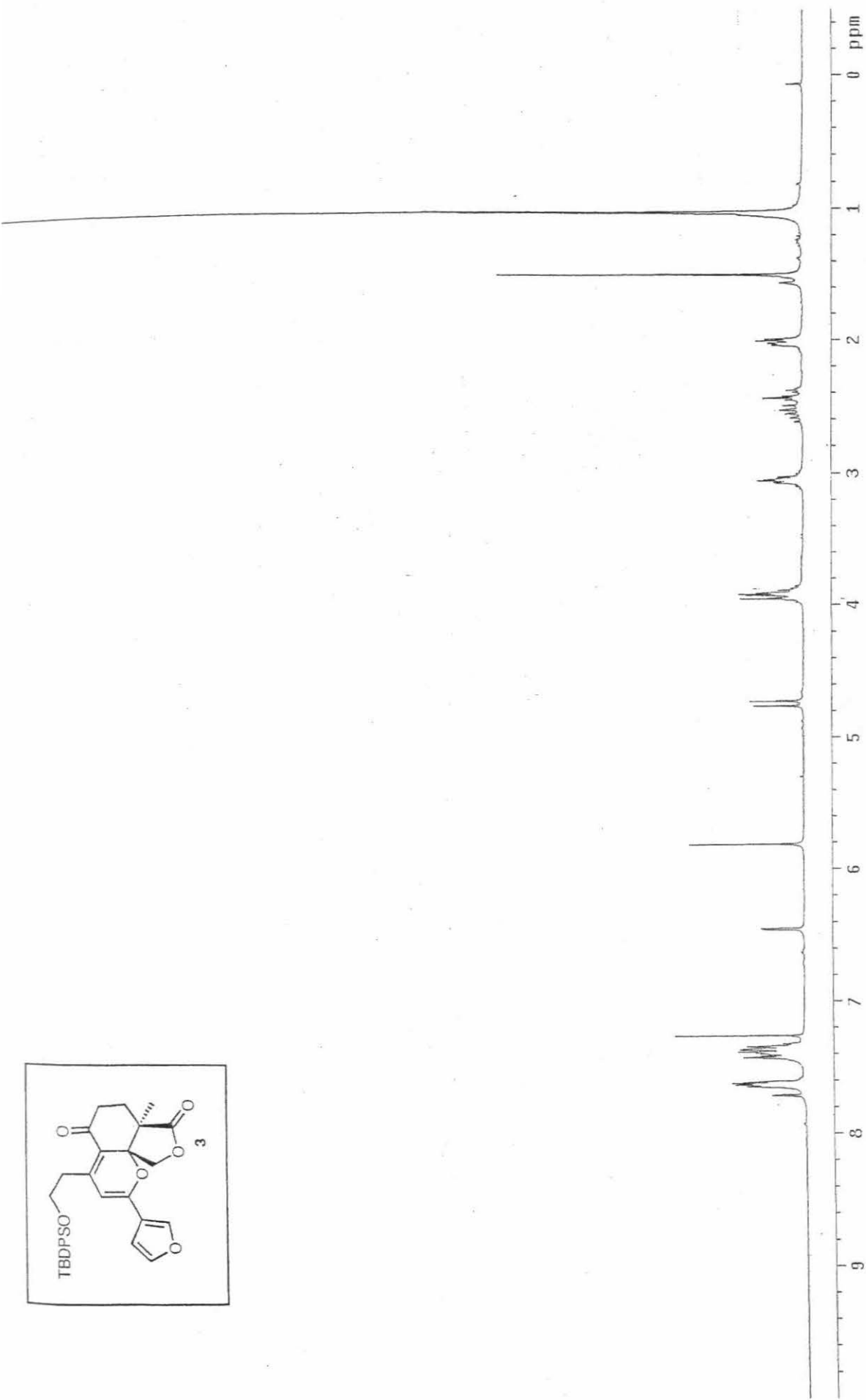
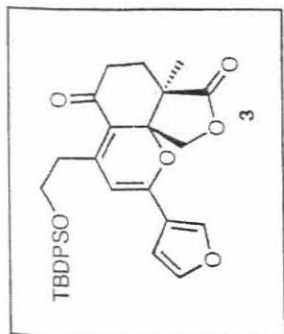


Figure 2.1a:  $^1\text{H}$  NMR Spectrum of Furan Appended Tricycle **3** (300 MHz,  $\text{CDCl}_3$ ).



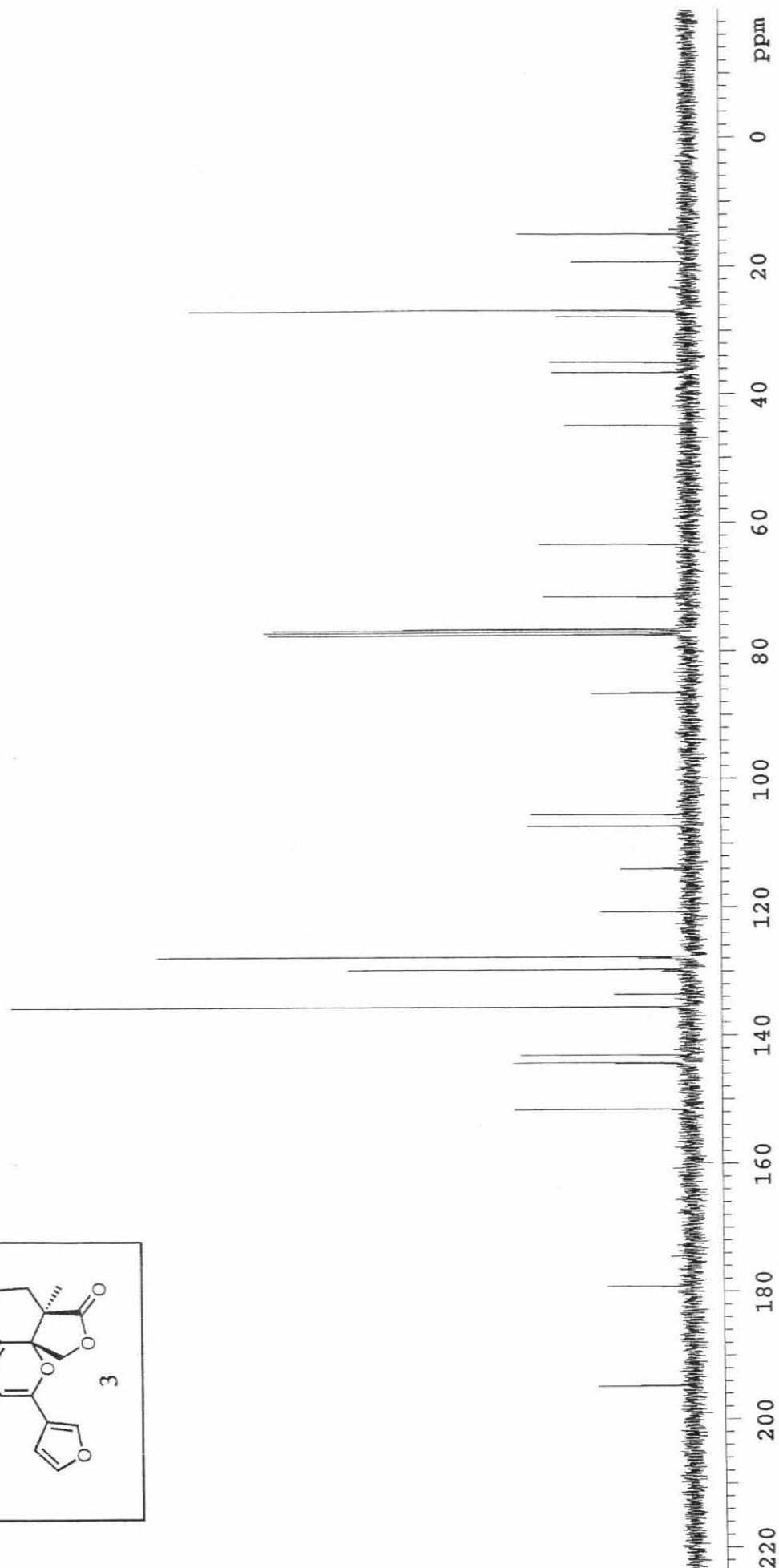
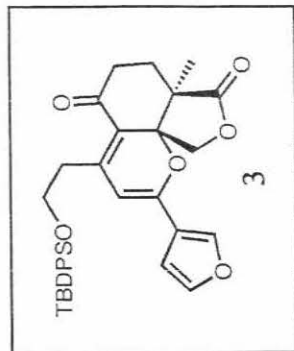


Figure 2.1b:  $^{13}\text{C}$  NMR Spectrum of Furan Appended Tricycle **3** (75 MHz,  $\text{CDCl}_3$ ).

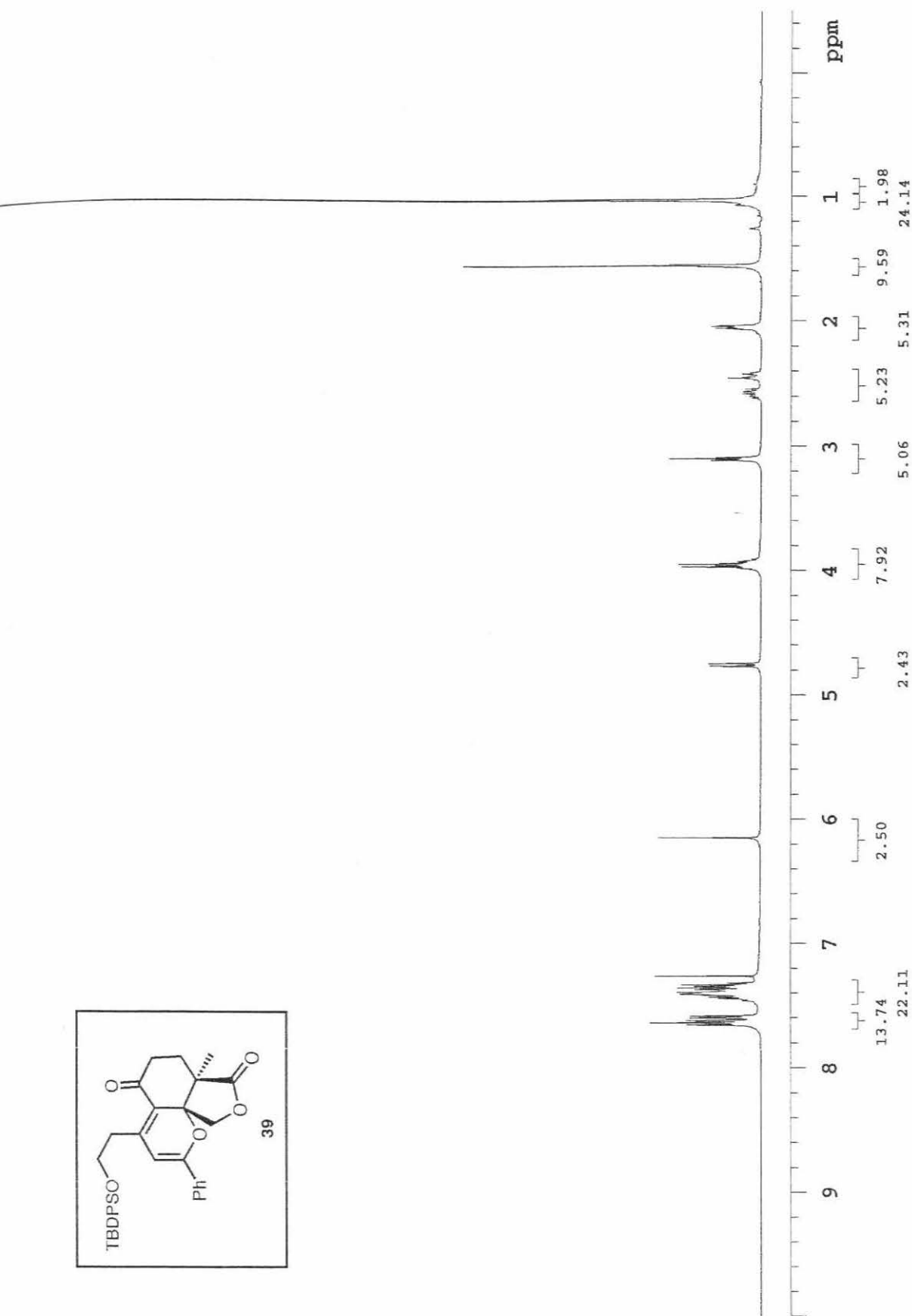
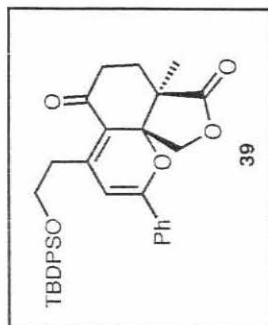


Figure 2.2a: <sup>1</sup>H NMR Spectrum of Phenyl Appended Tricycle 39 (500 MHz, CDCl<sub>3</sub>).

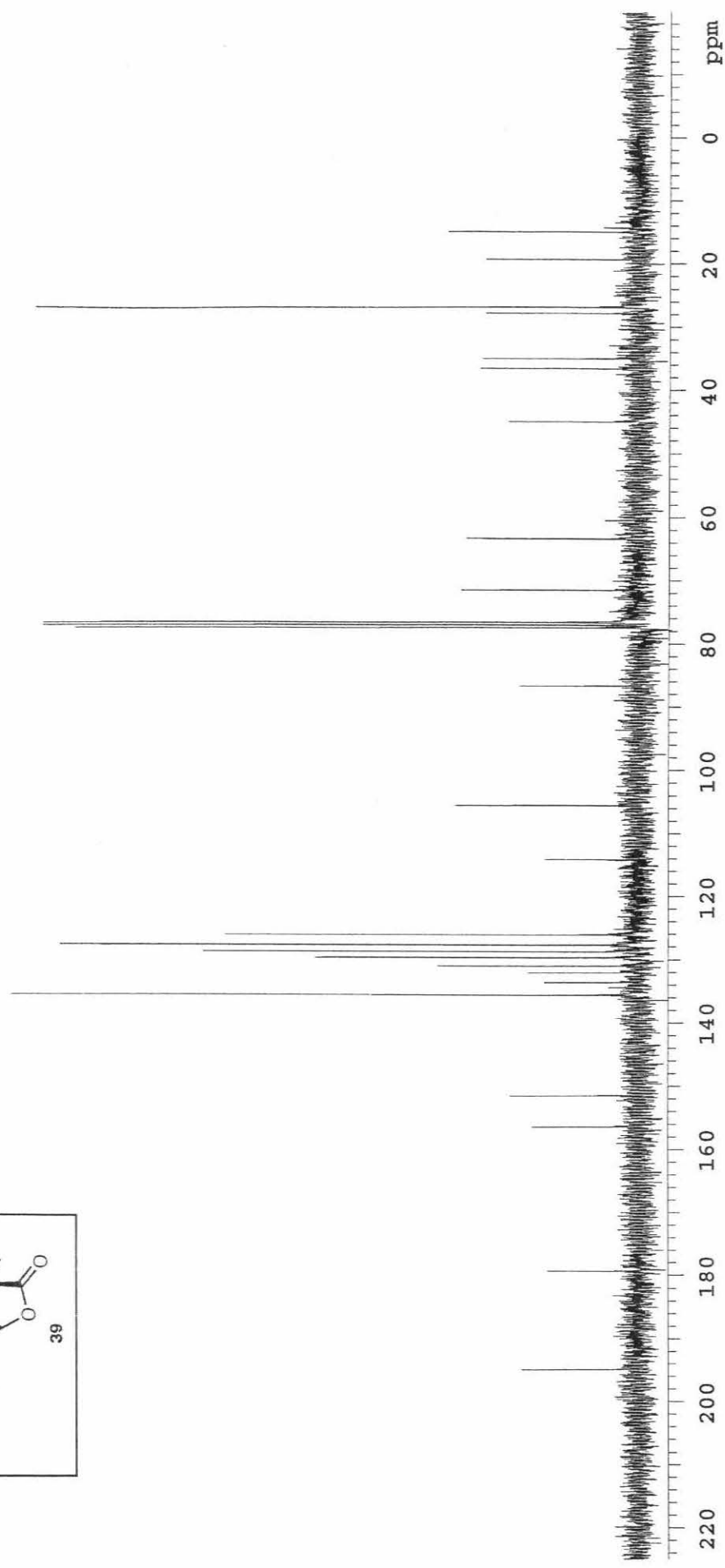
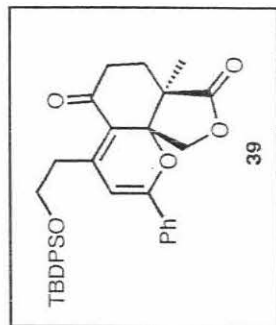


Figure 2.2b:  $^{13}\text{C}$  NMR Spectrum of Phenyl Appended Tricycle 39 (75 MHz,  $\text{CDCl}_3$ ).

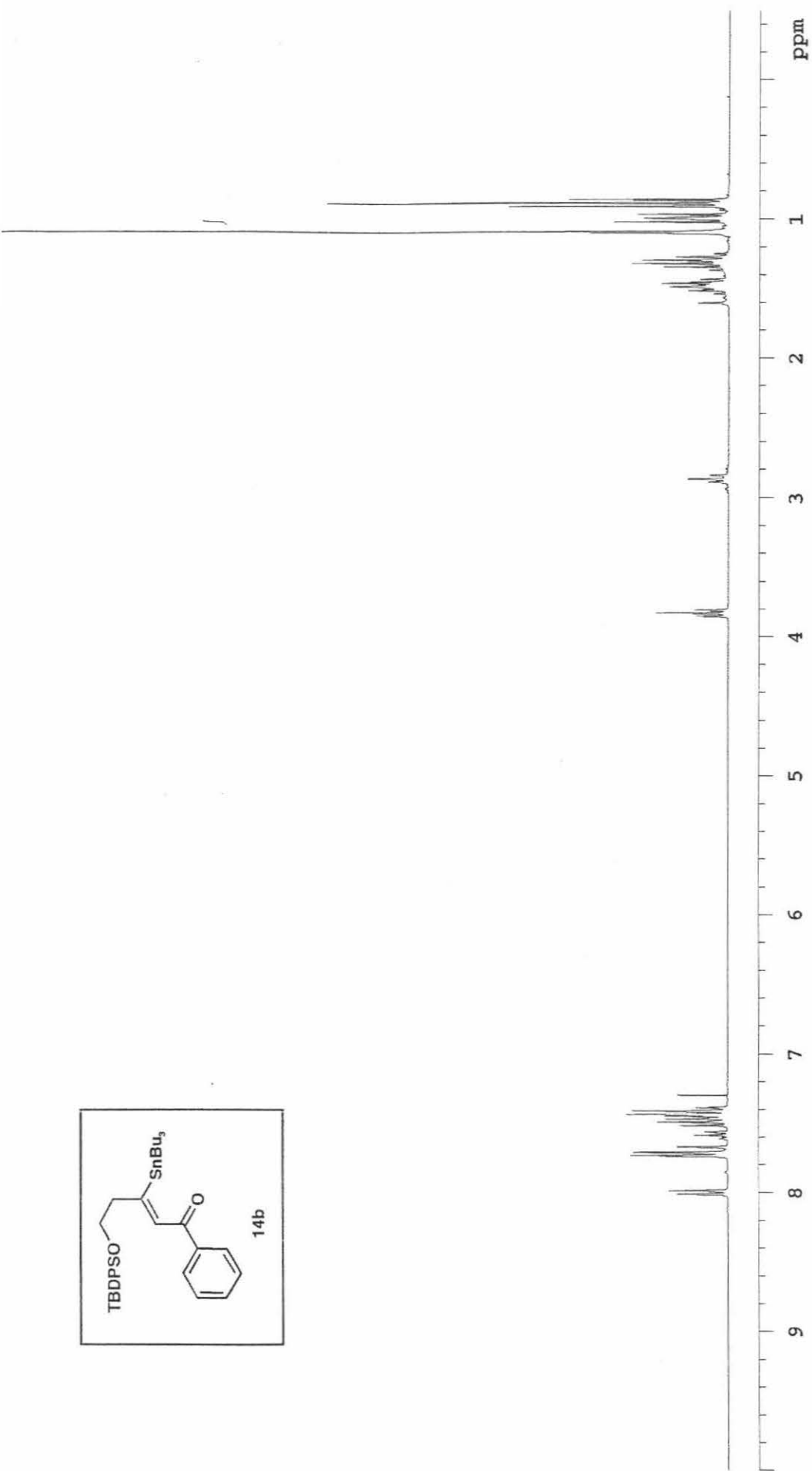
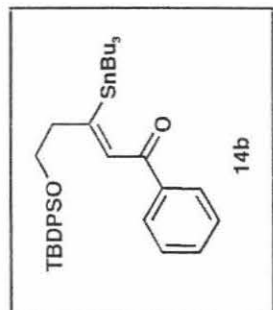


Figure 2.3a: <sup>1</sup>H NMR Spectrum of Stannane **14b** (300 MHz, CDCl<sub>3</sub>).

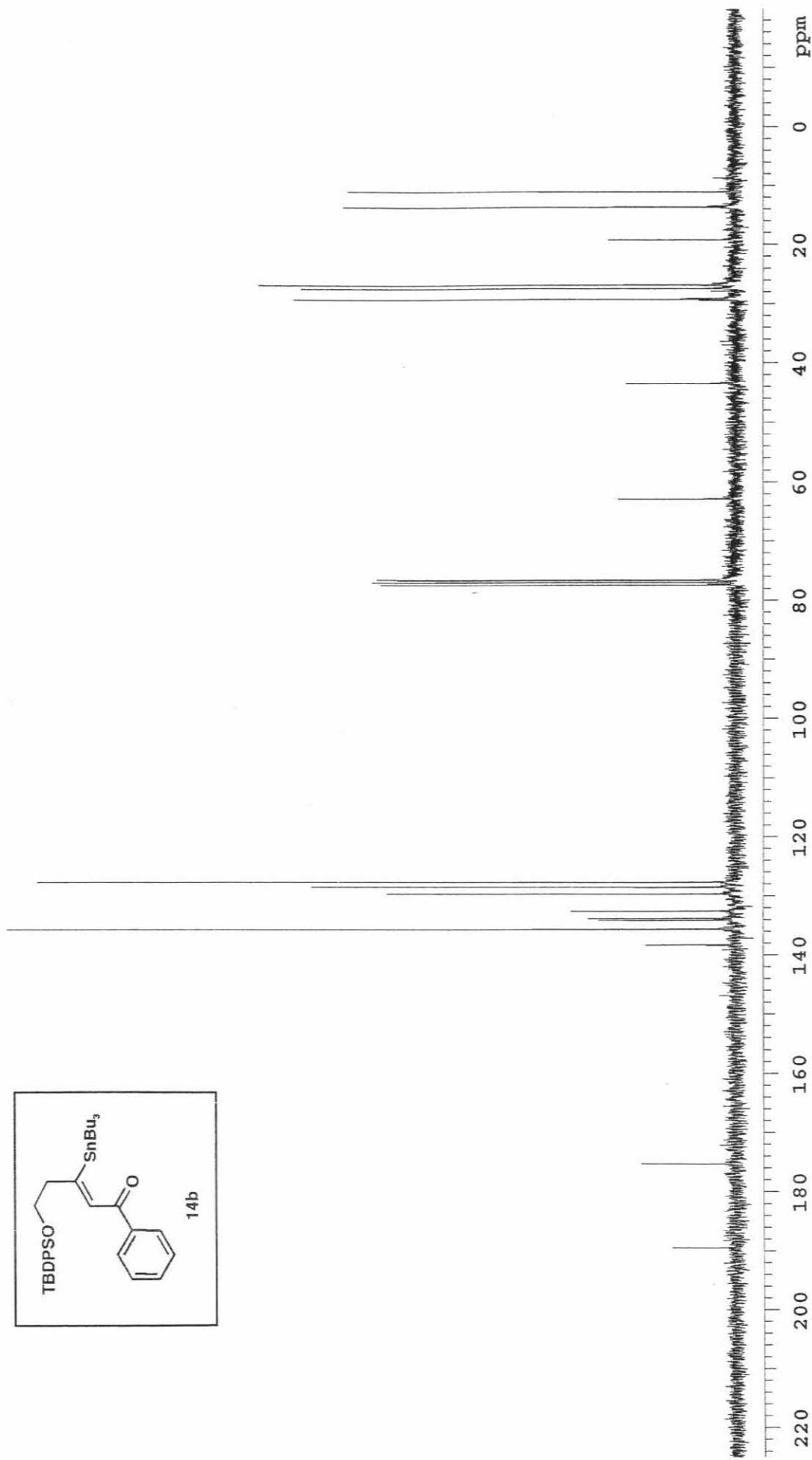


Figure 2.3b:  $^{13}\text{C}$  NMR Spectrum of Stannane 14b (75 MHz,  $\text{CDCl}_3$ ).

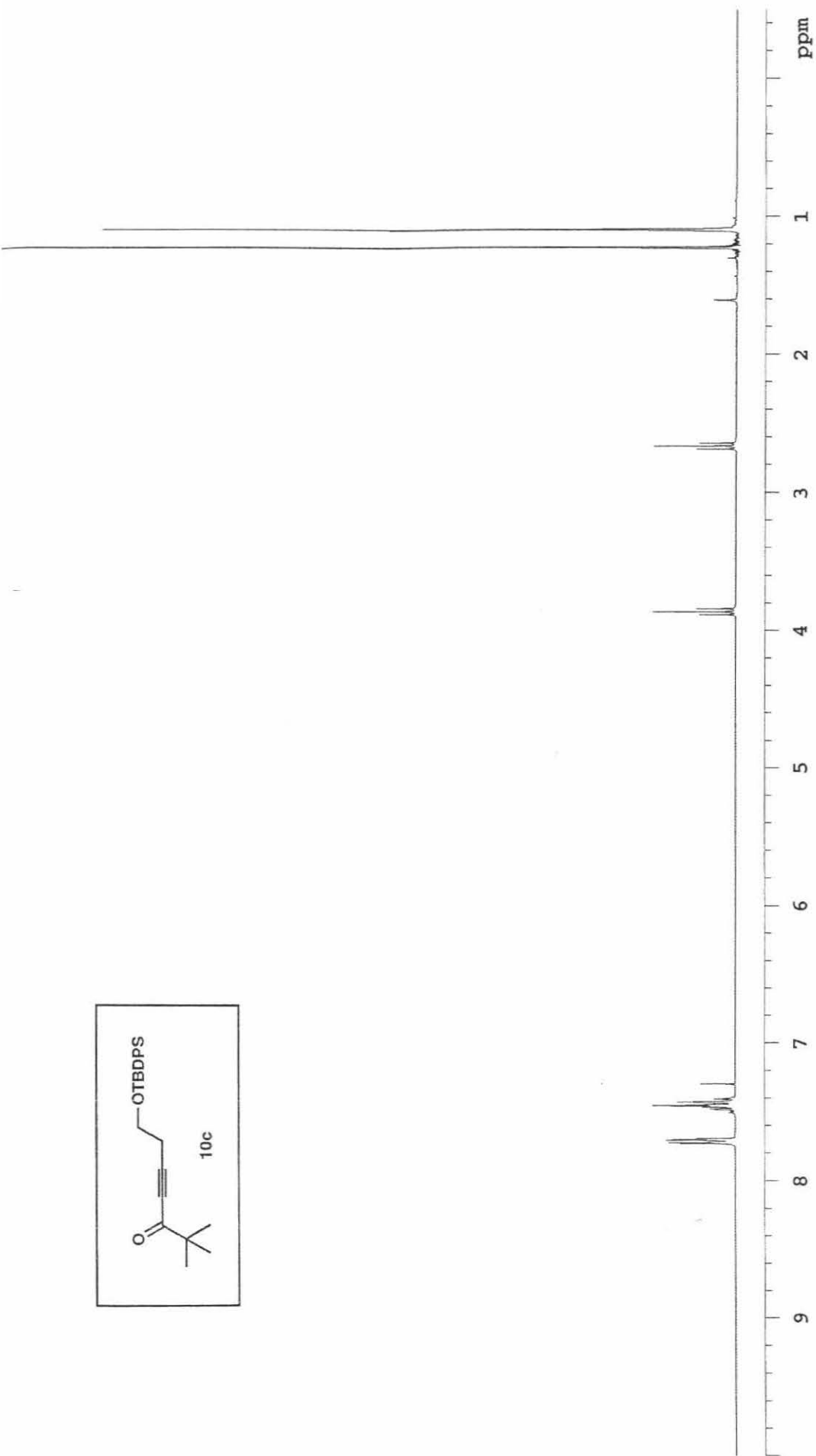
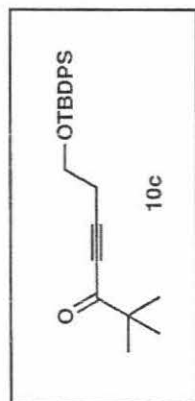


Figure 2.4a: <sup>1</sup>H NMR Spectrum of Alkynone 10c (300 MHz, CDCl<sub>3</sub>).

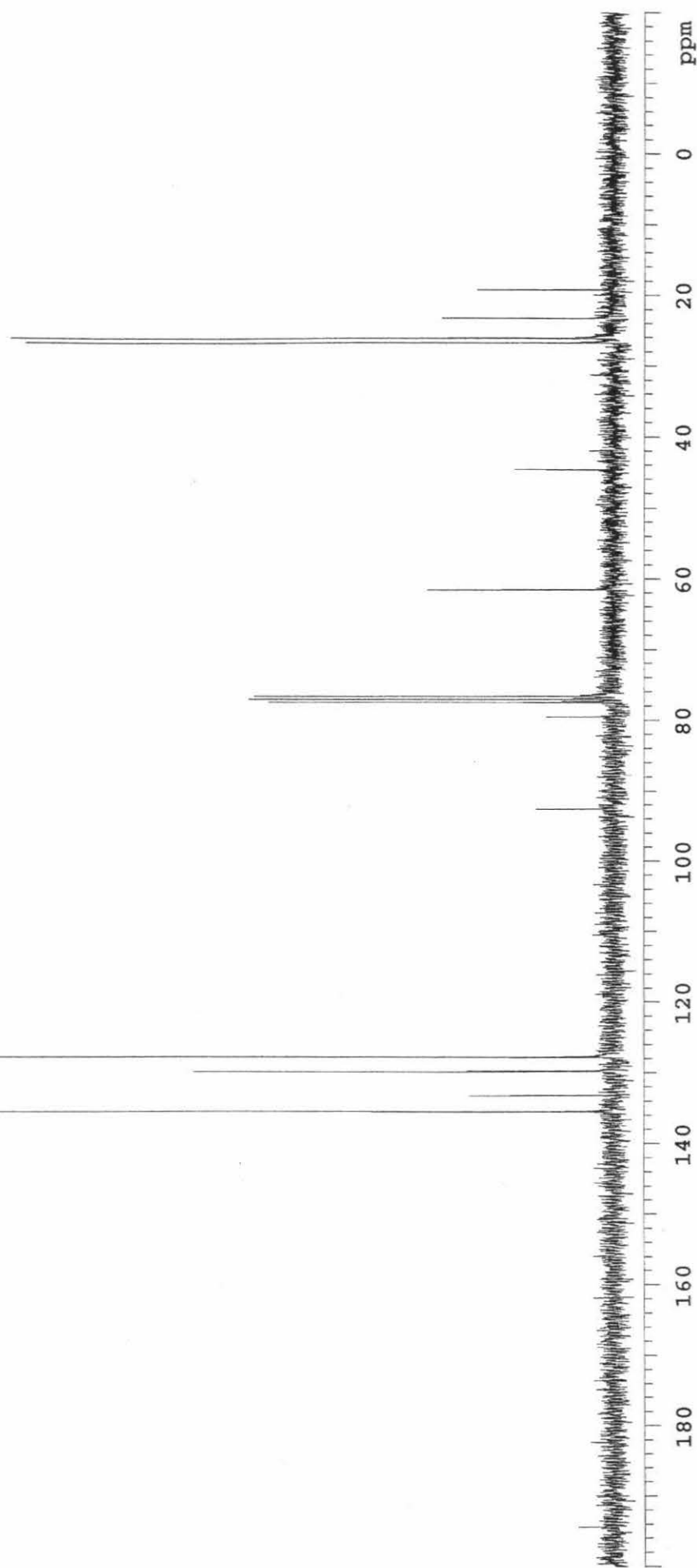
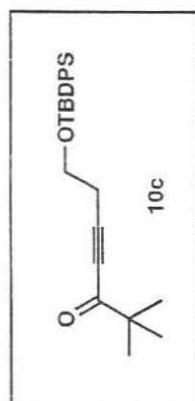


Figure 2.4b:  $^{13}\text{C}$  NMR Spectrum of Alkynone 10c (75 MHz,  $\text{CDCl}_3$ ).

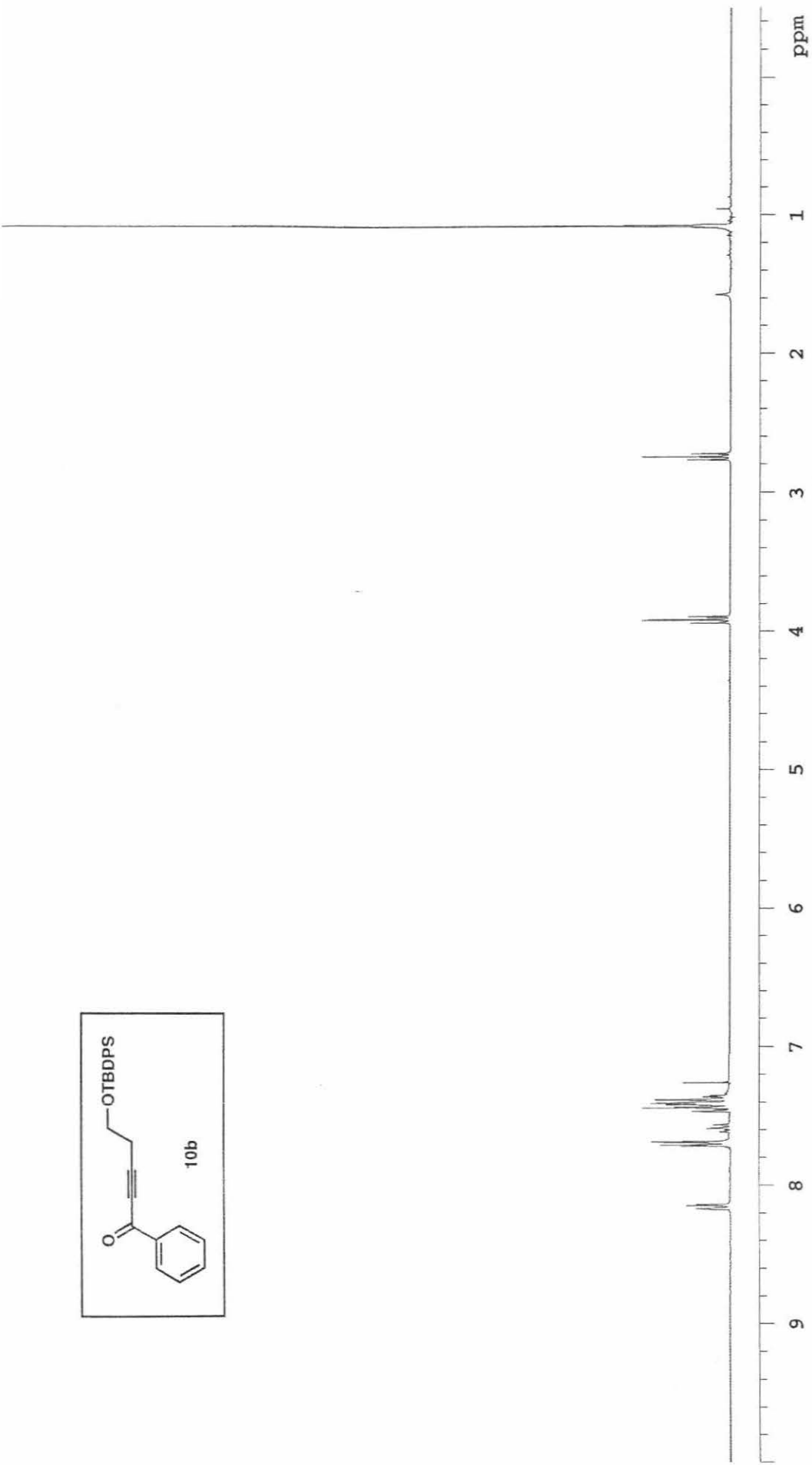
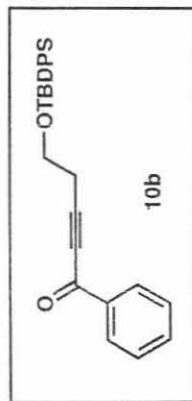


Figure 2.5a:  $^1\text{H}$  NMR Spectrum of Alkynone **10b** (300 MHz,  $\text{CDCl}_3$ ).



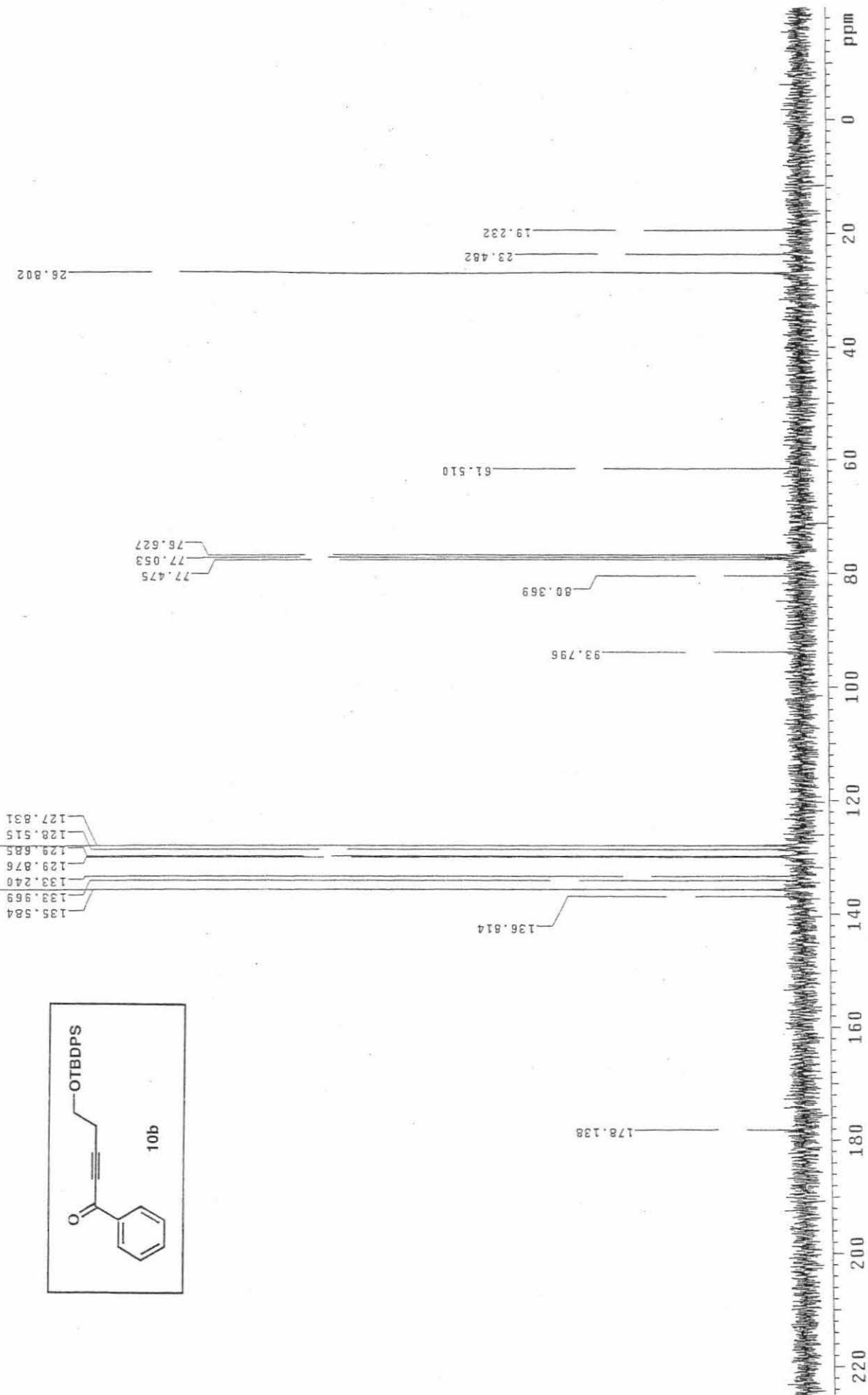


Figure 2.5b: <sup>13</sup>C NMR Spectrum of Alkynone 10b (75 MHz, CDCl<sub>3</sub>).

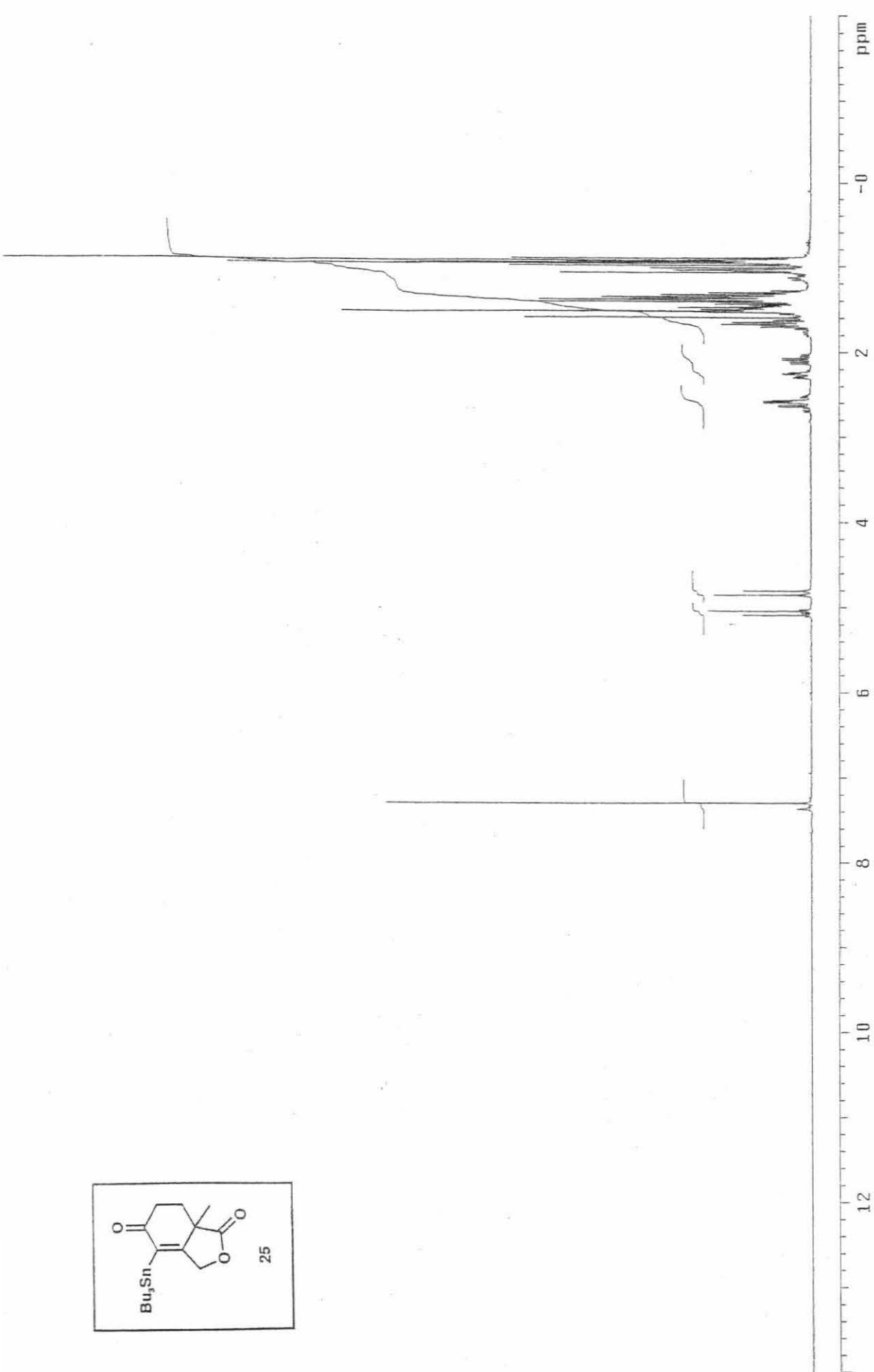
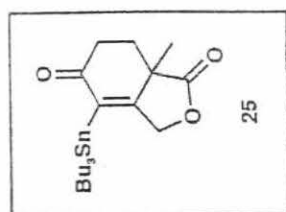


Figure 2.6a:  $^1\text{H}$  NMR Spectrum of Bicyclic Stannane 25 (300 MHz,  $\text{CDCl}_3$ ).

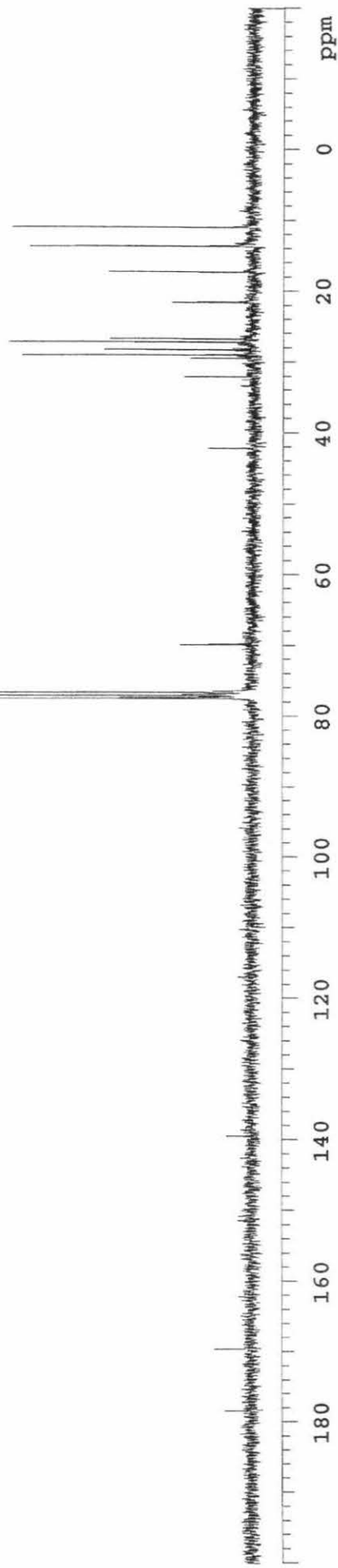
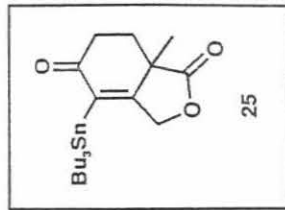


Figure 2.6b:  $^{13}\text{C}$  NMR Spectrum of Bicyclic Stannane 25 (75 MHz,  $\text{CDCl}_3$ ).

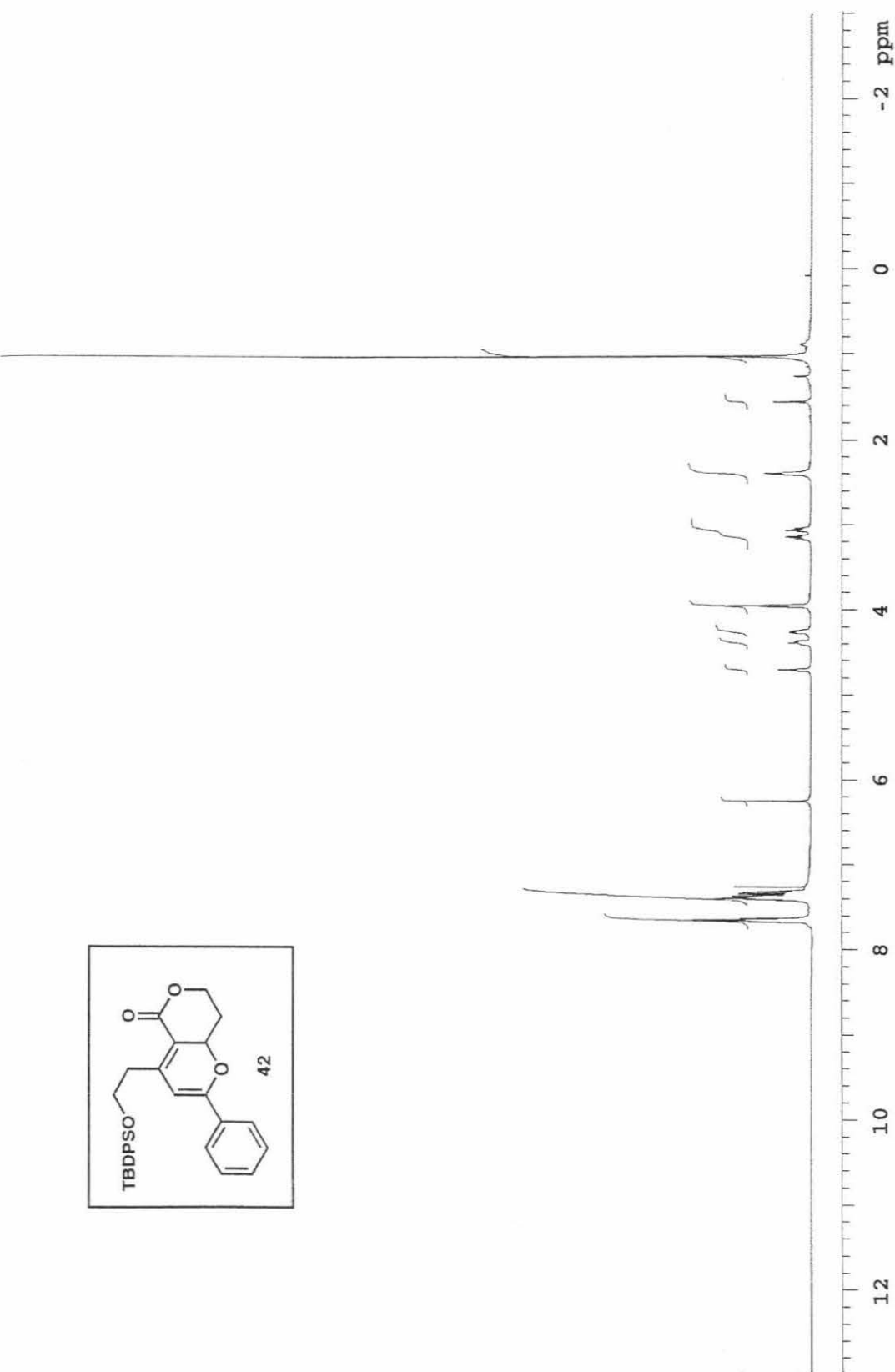
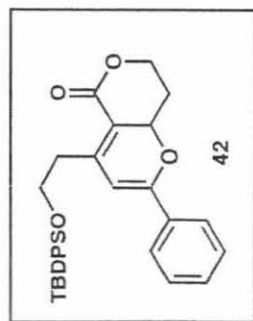


Figure 2.7a:  $^1\text{H}$  NMR Spectrum of Compound 42 (500 MHz,  $\text{CDCl}_3$ ).

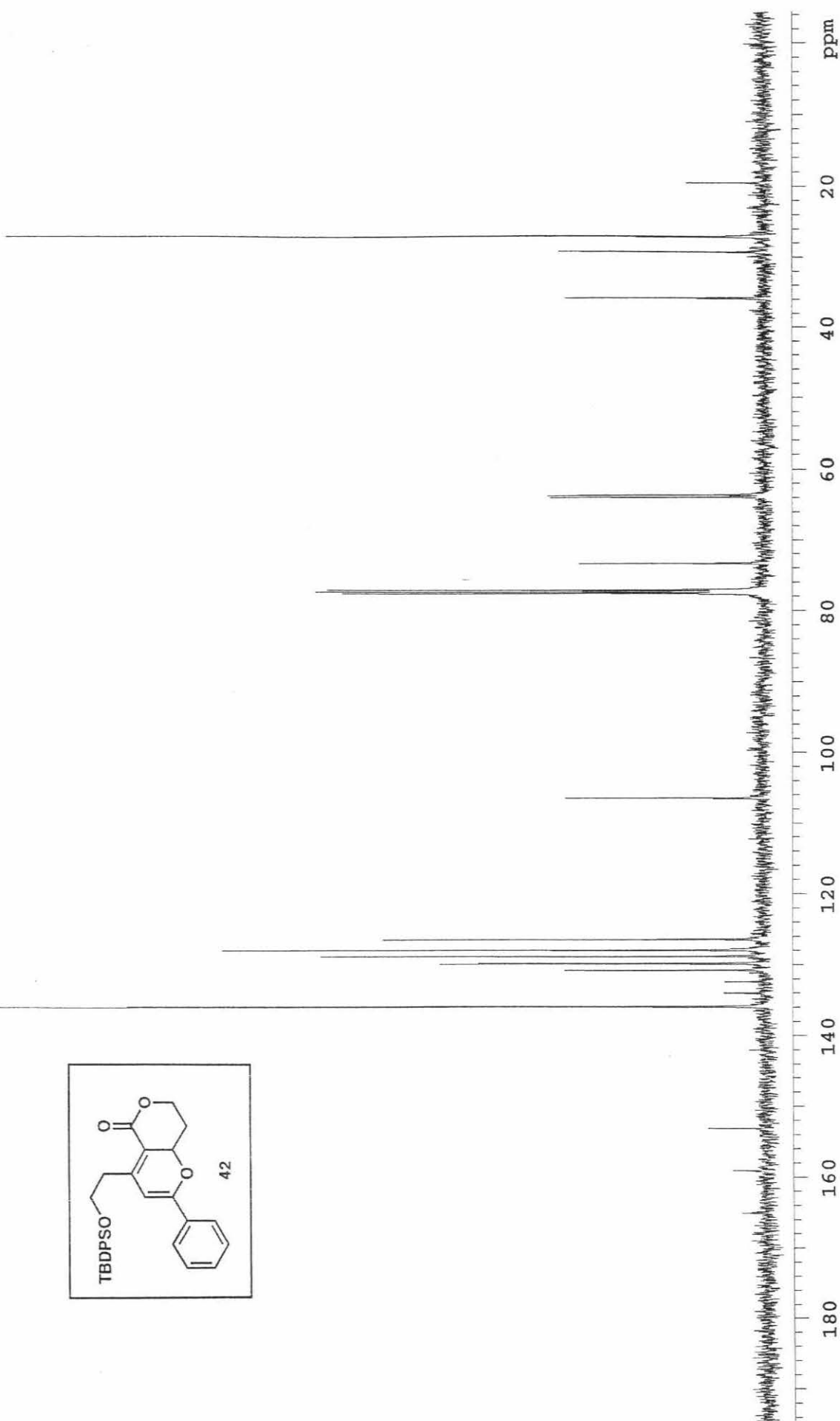
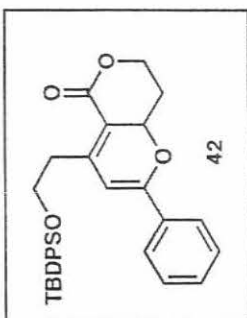


Figure 2.7b:  $^{13}\text{C}$  NMR Spectrum of Compound 42 (125 MHz,  $\text{CDCl}_3$ ).

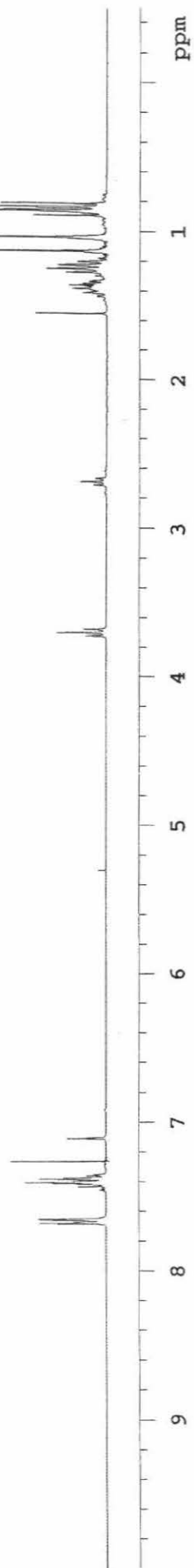
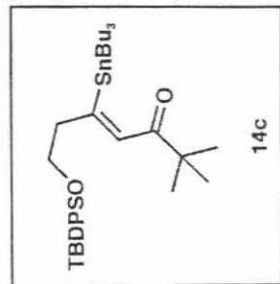


Figure 2.8a:  $^1\text{H}$  NMR Spectrum of Stannane **14c** (300 MHz,  $\text{CDCl}_3$ ).

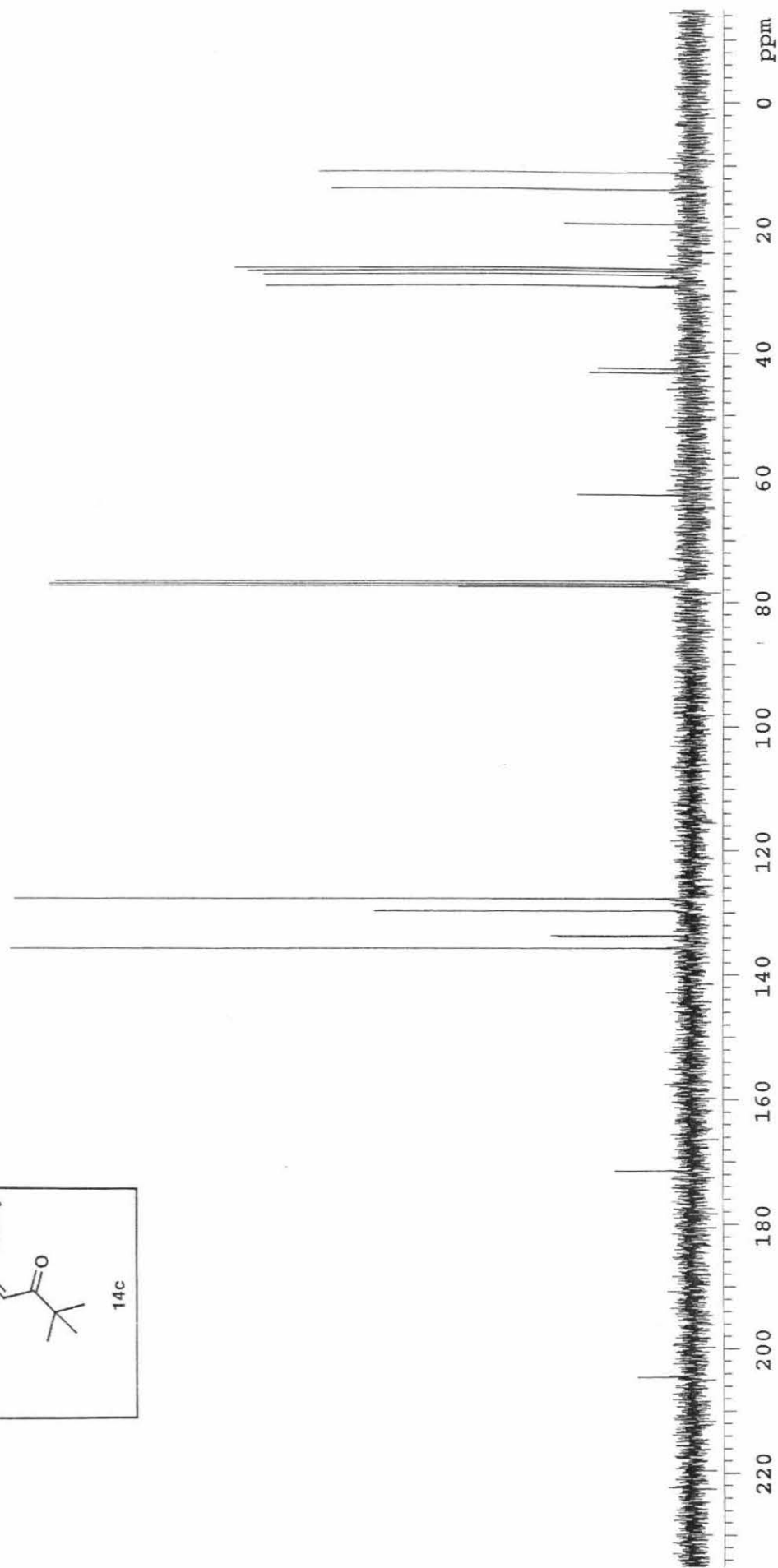
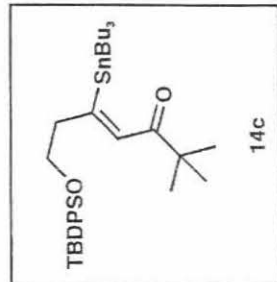


Figure 2.8b:  $^{13}\text{C}$  NMR Spectrum of Stannane **14c** (75 MHz,  $\text{CDCl}_3$ ).

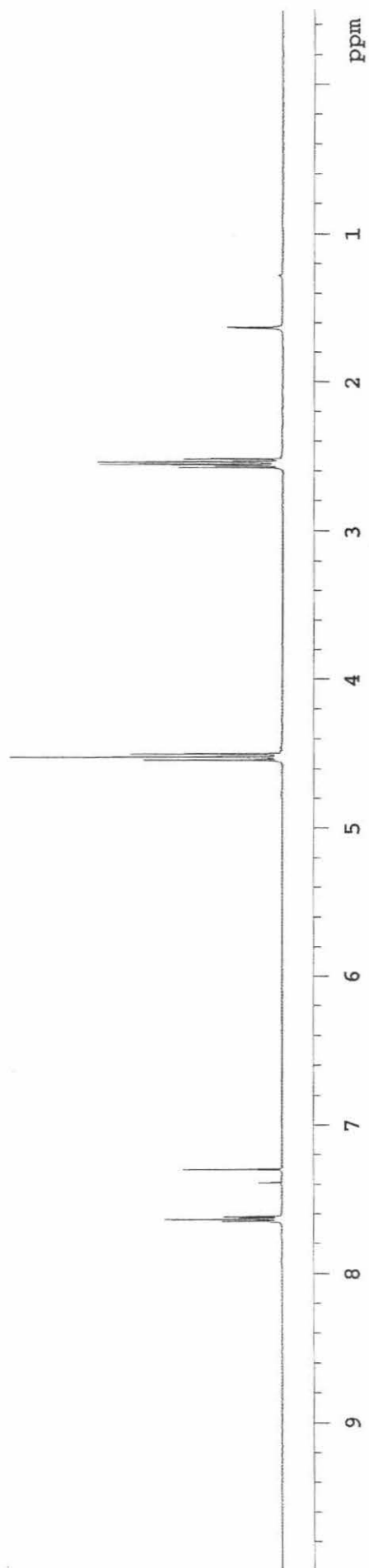
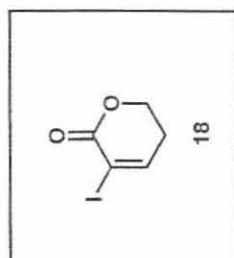


Figure 2.9a:  $^1\text{H}$  NMR Spectrum of Compound 18 (300 MHz,  $\text{CDCl}_3$ ).



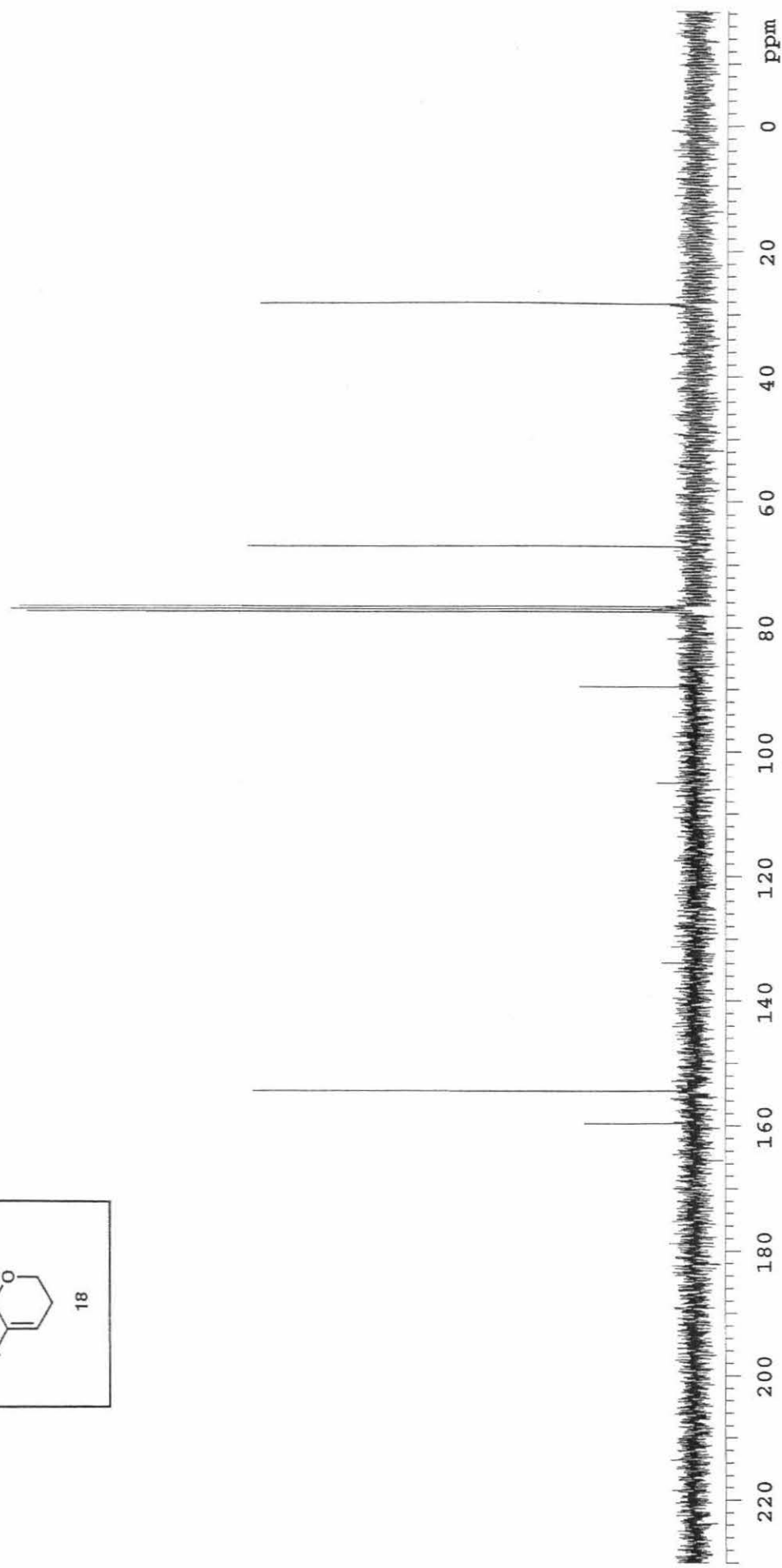
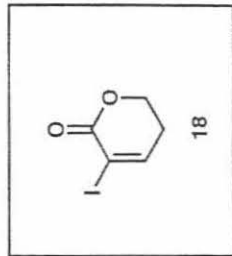


Figure 2.9b:  $^{13}\text{C}$  NMR Spectrum of Compound 18 (75 MHz,  $\text{CDCl}_3$ ).

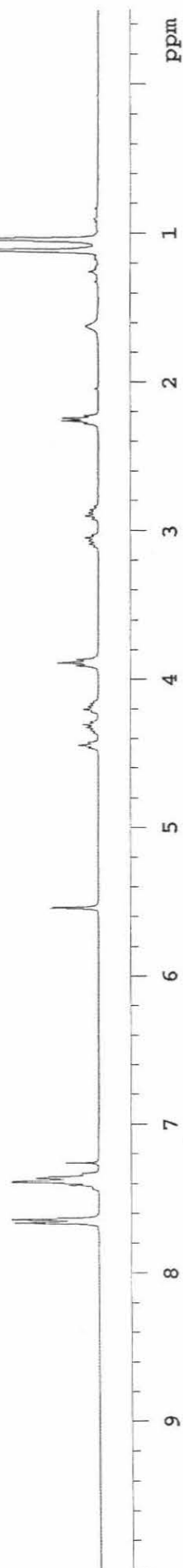
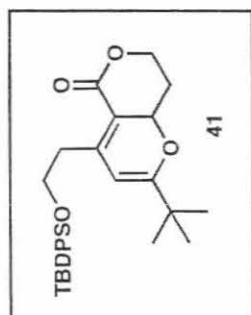


Figure 2.10a: <sup>1</sup>H NMR Spectrum of Compound 41 (300 MHz, CDCl<sub>3</sub>).

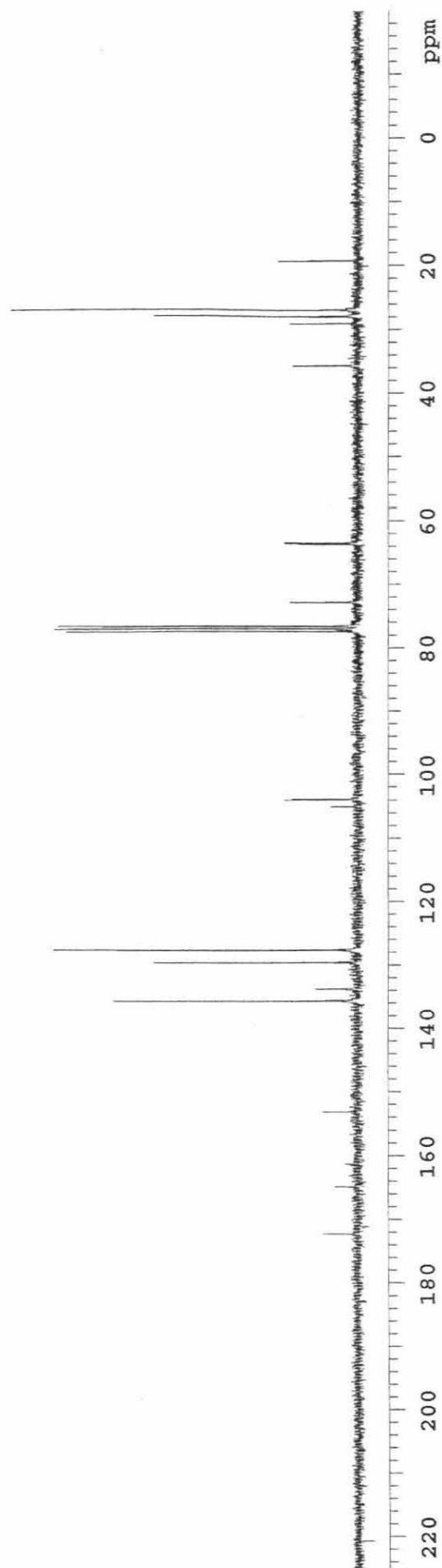
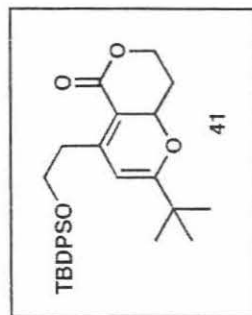


Figure 2.10b:  $^{13}\text{C}$  NMR Spectrum of Compound 41 (75 MHz,  $\text{CDCl}_3$ ).

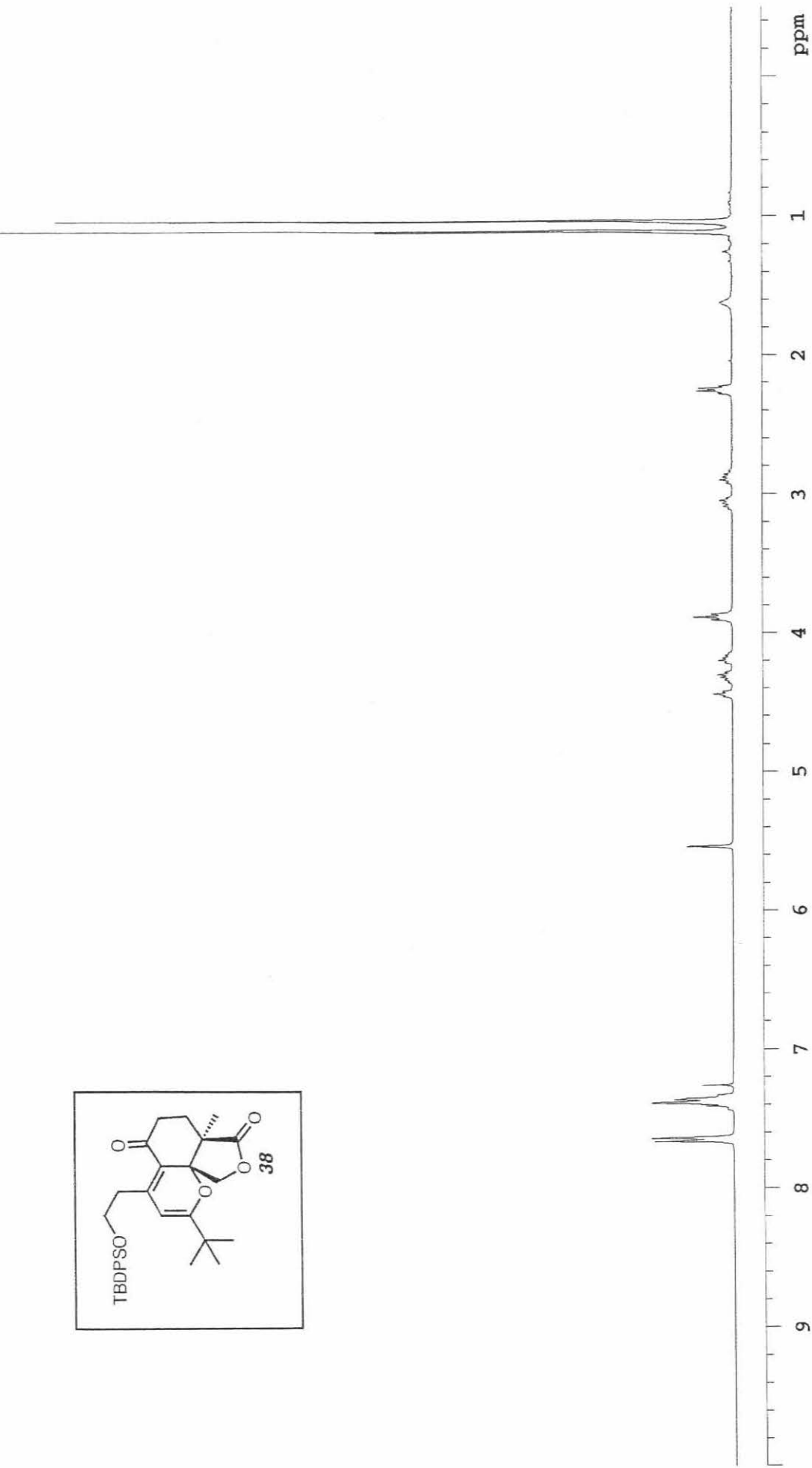
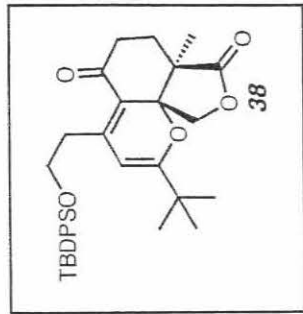


Figure 2.11a:  $^1\text{H}$  NMR Spectrum of *tert*-Butyl Appended Tricycle 30 (300 MHz,  $\text{CDCl}_3$ ).

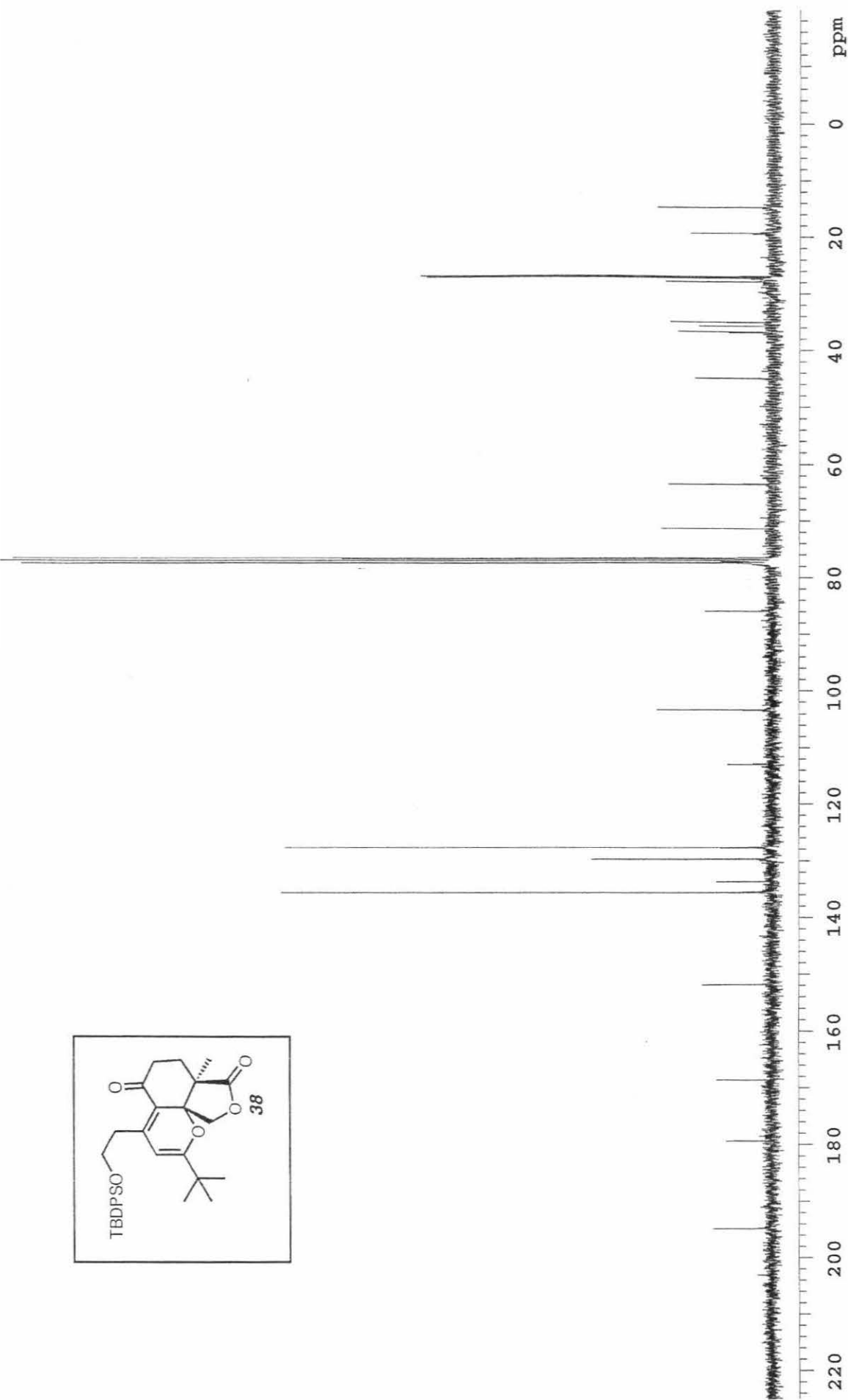
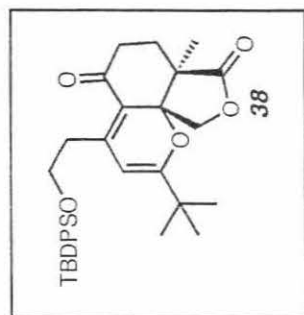


Figure 2.11b:  $^{13}\text{C}$  NMR Spectrum of tert-Butyl Appended Tricycle 30 ( $75\text{ MHz}$ ,  $\text{CDCl}_3$ ).

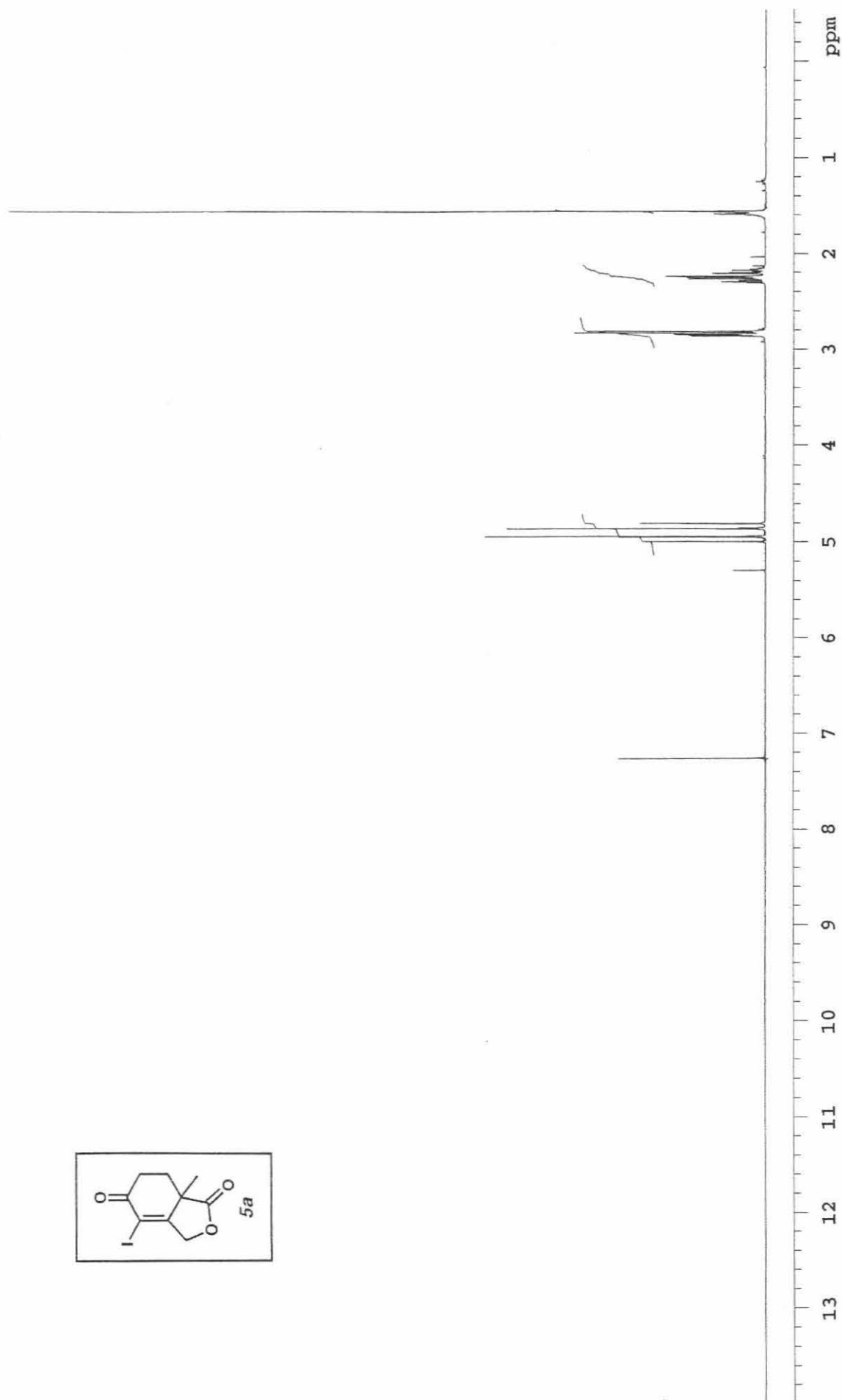
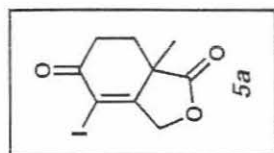


Figure 2.12a: <sup>1</sup>H NMR Spectrum of Iodoenone 5a (300 MHz, CDCl<sub>3</sub>).

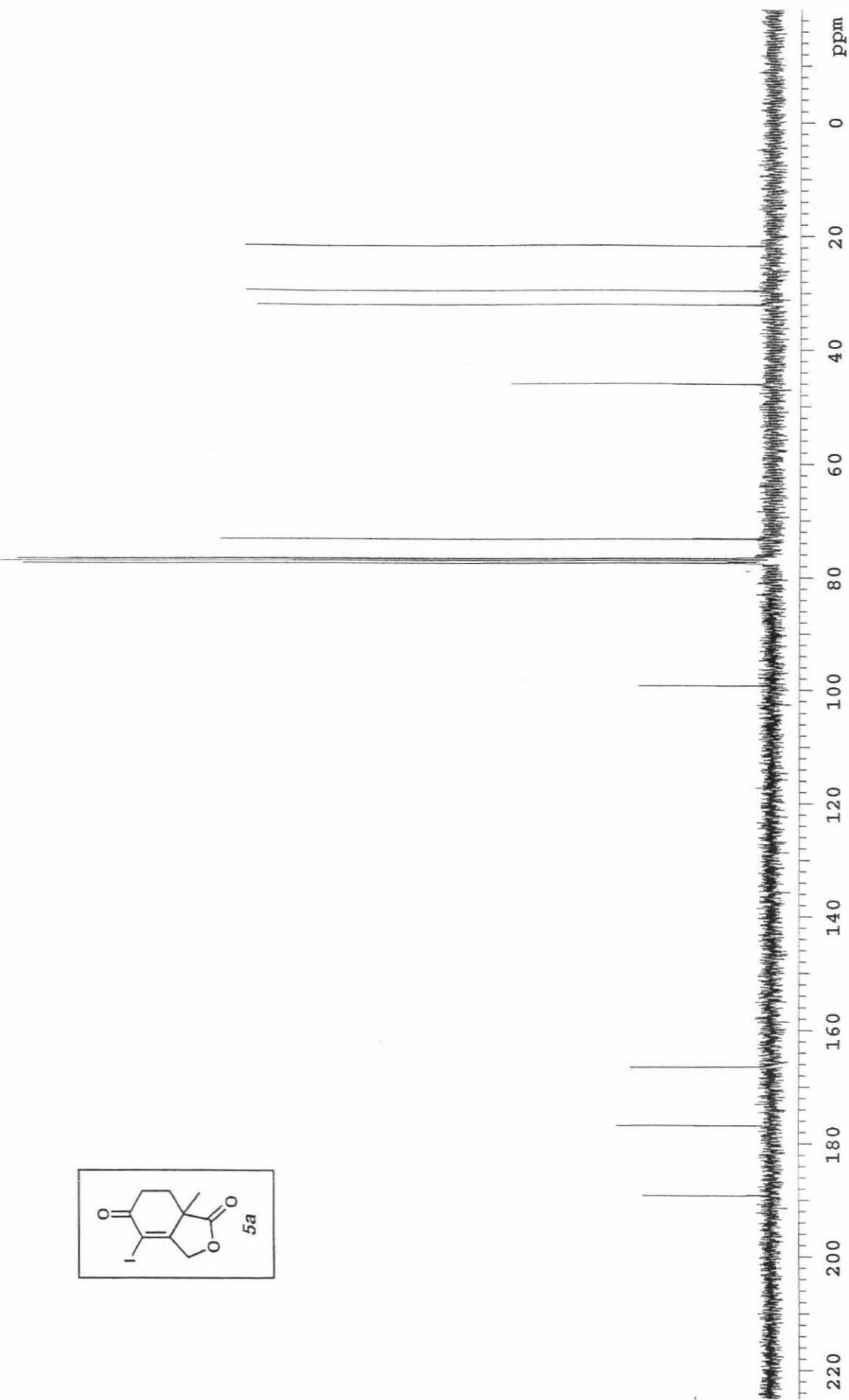
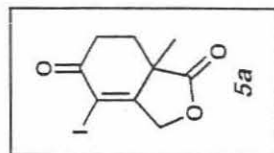


Figure 2.12b:  $^{13}\text{C}$  NMR Spectrum of Iodoenone 5a (75 MHz,  $\text{CDCl}_3$ ).

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