CYCLOADDITION APPROACH TO INDOLE-N-GLYCOSIDES

by

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A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

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Naturally occurring indole-N-glycosides, such as Neosidomycin (**1**) and SF-2140 (**2**), have been shown to exhibit antibiotic activity. Many traditional methods for the synthesis of indole-N-glycosides have been investigated by other groups. Our approach to indole-N-glycosides involves the key inverse electron demand Diels-Alder cycloaddition reaction, which proceeds *via* an *ortho*-thiono-imino-quinone intermediate **85**. When chlorine was present at C-5 of the *ortho*-thiono-imino-quinone **129**, the cycloaddition reaction yield improved.

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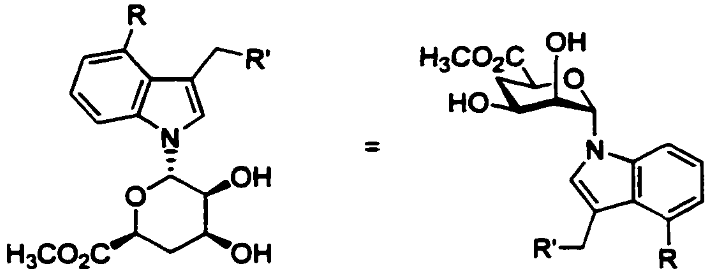
I. Introduction

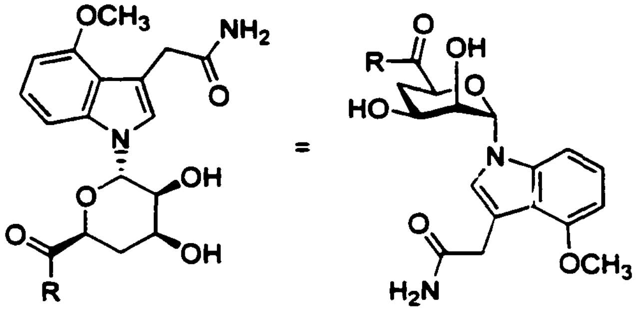
A. Some Representatives of Indole-N- and Indolocarbazole-N-glycosides

The indole unit occurs naturally in a wide variety of structures.[1] Neosidomycin (**1**) was the first example of a naturally occurring nucleoside containing the indole ring system. It was isolated from the fermentation broth of a strain of *Streptomyces hygroscopicus*, and it possessed weak activity against Gram negative bacteria.[2,3] A few years later, another indole nucleoside, with antiviral properties, was described as a metabolite of an *Actinomadura* species isolated from a Japanese soil sample. This compound was termed SF-2140 (**2**).[3,4]

More recently, two new indole nucleosides kahakamides A (**3**) and B (**4**) were isolated from the actinomycete *Nocardiopsis dassonvillei*, obtained from a shallow water sediment sample collected on the island of Kauai, Hawaii.[5] Compound **3** exhibited antimicrobial activity toward the Gram positive bacterium *Bacillus subtilis*. All these four compounds, **1-4** (Figure 1), were identified to be rare N-glycosyl indoles. They all have a single indole-N-glycosidic bond α-linked to the anomeric carbon (C-1) of the sugar.



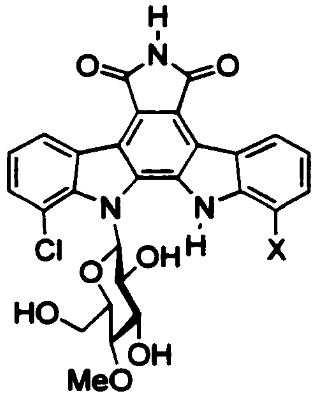
1 R = H; R' = $CONH_2$
2 R = OCH_3; R' = CN



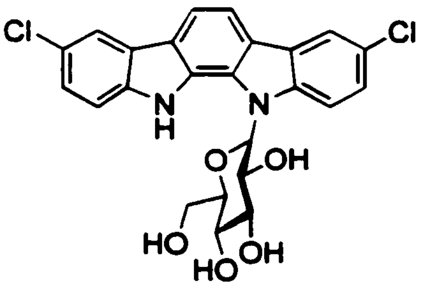
3 R = OCH_3
4 R = NH_2

Figure 1. Structures of Neosidomycin (**1**), SF-2140 (**2**), kahakamide A (**3**), and kahakamide B (**4**).

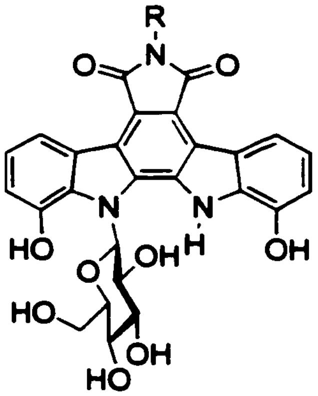
There are other natural products in which indolocarbazoles are glycosidically linked to various sugars. Rebeccamycin (**5**), isolated from fermentation of *Nocardia aercoligenes*, strain C38383-RK-2, is such an example.[6] Compound **5** possesses a single indolocarbazole-N-glycosidic bond β-linked to the C-1 of the sugar. 11-Dechlororebeccamycin (**6**) has a similar structure but lacks the chlorine at C-11. Both compounds are potent antitumor agents.[7] Some other examples of similar structures containing single indolocarbazole-N-glycosidic bonds include tjipanazole-E (**7**), ED-110 (**8**), and NB-506 (**9**) (Figure 2).[8]



Rebeccamycin (**5**) X = Cl
11-Dchlororebeccamycin (**6**) X = H



Tjipanazole E (**7**)

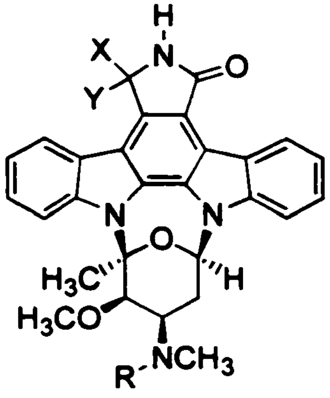


ED-110 (**8**) R = H
NB-506 (**9**) R = NHCHO

Figure 2. Indolocarbazole glycosides containing single β-N-glycosidic bonds.

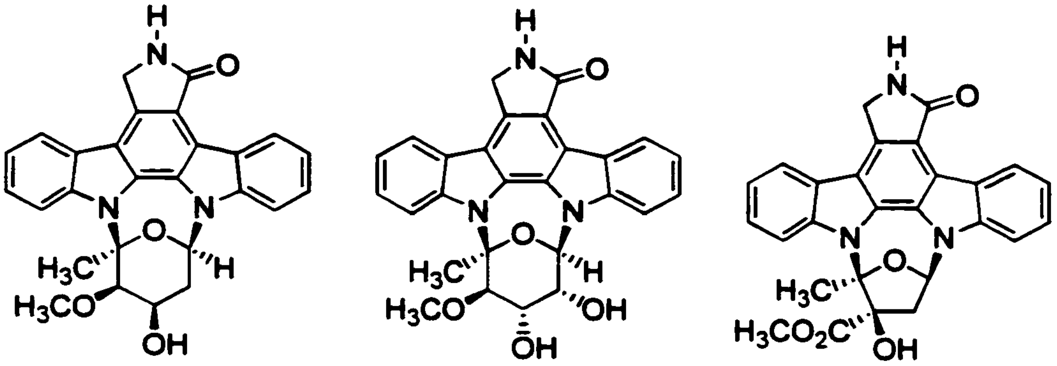
B. Indolocarbazole-N-Glycosides Containing Bis-N-Glycosidic Linkages

Before discussing some existing glycosidation methods of indoles and indolocarbazoles with sugars, some other interesting indolocarbazole glycosides are also mentioned. These compounds display bis-N-glycosidic linkages, which are more complicated than the previously mentioned indole and indolocarbazole glycosides. These include staurosporine (**10**),[9] UCN-01 (**11**), UCN-02 (**12**),[10] 7-*O*-methyl UCN-01 (**13**),[11] CGP41-251 (**14**),[12] NA-382 (**15**),[13] RK-1409 (7-oxo-staurosporine) (**16**),[14] RK286c (**17**),[15] MLR-52 (**18**),[16] and K252a (**19**)[17] (Figures 3 and 4). These compounds are potent inhibitors of protein kinase C. The most active member of this group is staurosporine.[18]



Staurosporine (**10**)	X = Y = H; R = H
UCN-01 (**11**)	X = α-OH; Y = H; R = H
UCN-02 (**12**)	X = H; Y = β-OH; R = H
7-O-Methyl UCN-01 (**13**)	X = α-OMe; Y = H; R = H
GCP41-251 (**14**)	X = Y = H; R = Benzoyl
NA-382 (**15**)	X = Y = O; R = $COOCH_2CH_3$
RK-1409 (**16**)	X = Y = O; R = H

Figure 3. Some indolocarbazole glycosides displaying bis-N-glycosidic linkages.

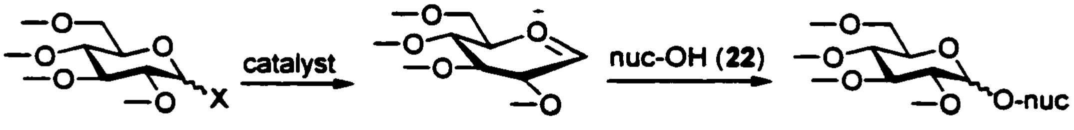


RK286c (**17**) MLR-52 (**18**) K252a (**19**)

Figure 4. Some indolocarbazole glycosides displaying bis-N-glycosidic linkages.

C. A Century of Glycosyl Transfer Chemistry

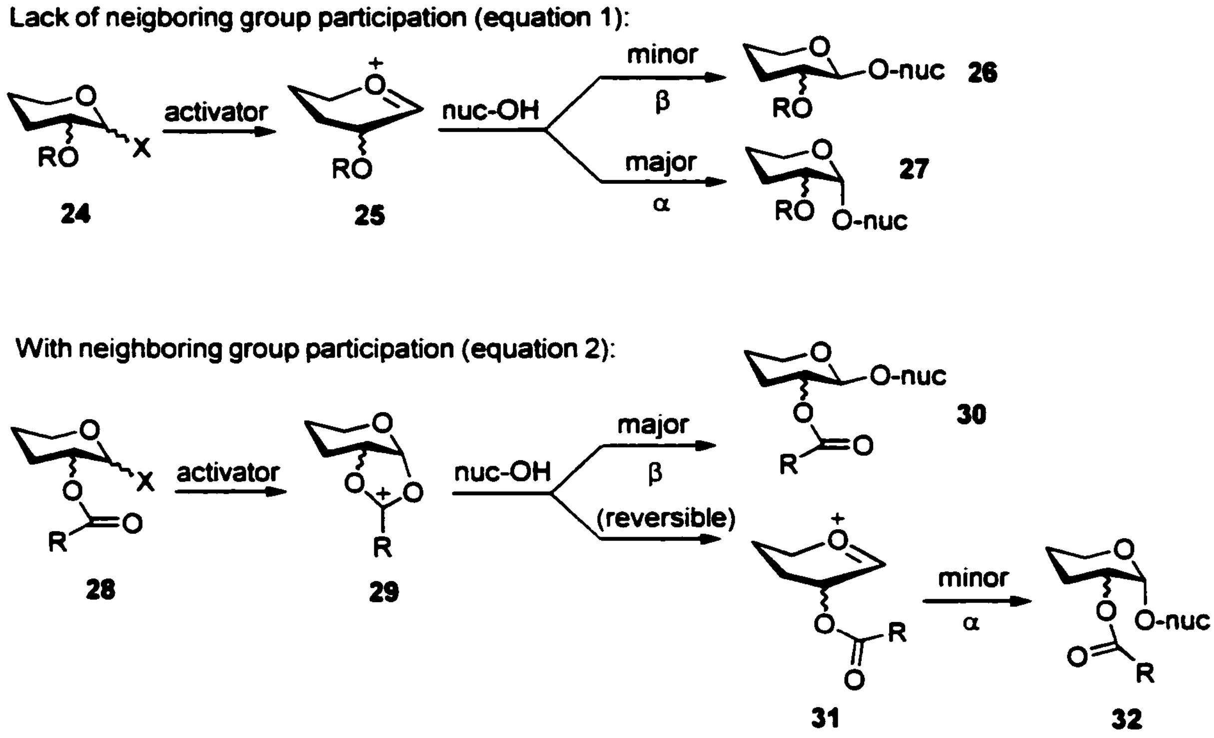
There is a tremendous number of literature articles about glycosidation methodologies.[19] Most glycosyl transfer processes involve a carbohydrate precursor **20** which is activated to become an electrophile **21**, which is transferred to a nucleophile **22** to afford a glycoside product **23** (Scheme 1).



20 **21** **23**

Scheme 1. A century of glycosyl transfer chemistry.

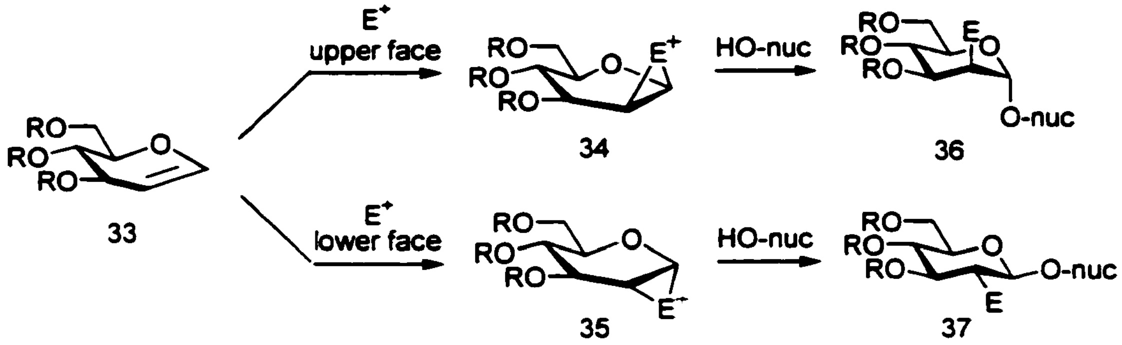
There are two principal modes for production of electrophilic transfer species. Most common is the modification of anomeric functionality. The key problem of stereochemical control of glycosyl transfer is regulated most frequently by neighboring group participation, or lack thereof, by a function at C-2 of the sugar (Scheme 2). In the first equation, because of the lack of neighboring group participation of the group at C-2 of the sugar, the major product is the α species **27**. This is caused by a phenomenon called the anomeric effect. However, in the second equation, the β product **30** is favored over the α product **32** due to the neighboring group participation of the ester group at C-2 of the sugar.


Lack of neigboring group participation (equation 1):

With neighboring group participation (equation 2):

Scheme 2. Modification of anomeric functionality.

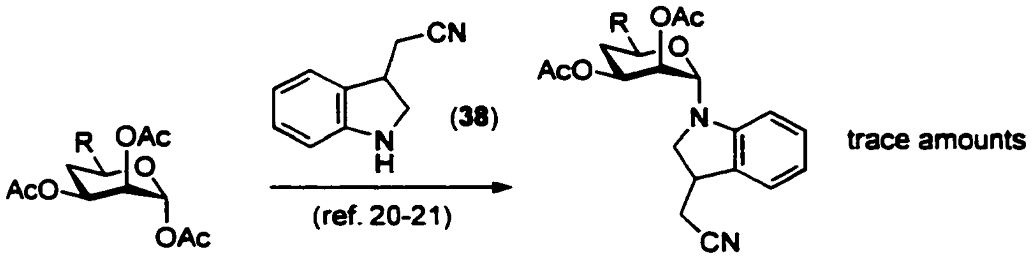
The second general approach for glycosyl transfer is to activate a glycal by electrophilic attack with oxygen, sulfur, selenium, halogen, proton, mercury, or nitrogen electrophiles (Scheme 3). In this strategy, the stereochemistry of the anomeric carbon is regulated by the preferred facial attack of the electrophile on the particular glycal substrate. Glycal **33** reacts with an electrophile E$^+$ to produce species **34**, resulting from the upper face attack of the sugar, and species **35**, as a consequence of the attack of the electrophile E$^+$ on the lower face of the sugar. Nucleophilic species, HO-nuc, then attacks at C-1 of **34** or **35** to produce an α-glycoside **36** and a β-glycoside **37**, respectively.



Scheme 3. Glycal activation by electrophiles.

D. Some Existing Glycosidation Methods for Indoles and Indolocarbazoles with Sugars

A well-established method for the synthesis of indole-N-glycosides is the indole-indoline method, originally developed by Preobrazhenskaya *et al*,[20] and also employed by others.[21] In this method, the indole is reduced to the corresponding indoline (2,3-dihydroindole), which is then linked to a sugar unit, and the resulting indoline-N-glycoside is then oxidized to the indole-N-glycoside. The application of this method to the synthetic studies of neosidomycin and SF-2140 was utilized by Wightman *et al.*[3] Attempted coupling of indoline **38**, which was cleanly reduced using pyridine-borane in trifluoroacetic acid (TFA), with triacetates **39** and **40**, under various conditions, gave no more than trace amounts of product (Scheme 4).[20-22]

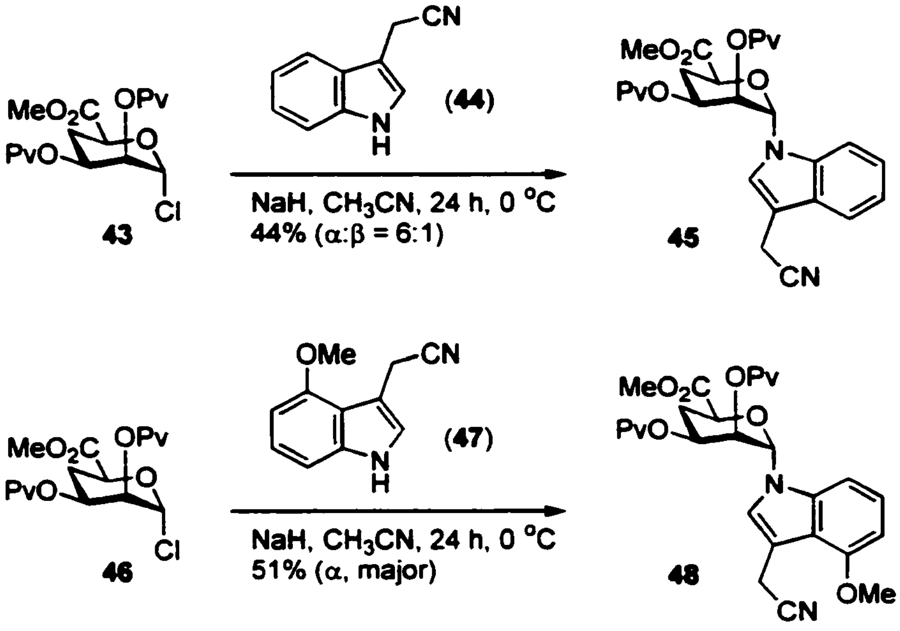


39 R = CH_2OBz
40 R = CO_2Me

41 R = CH_2OBz
42 R = CO_2Me

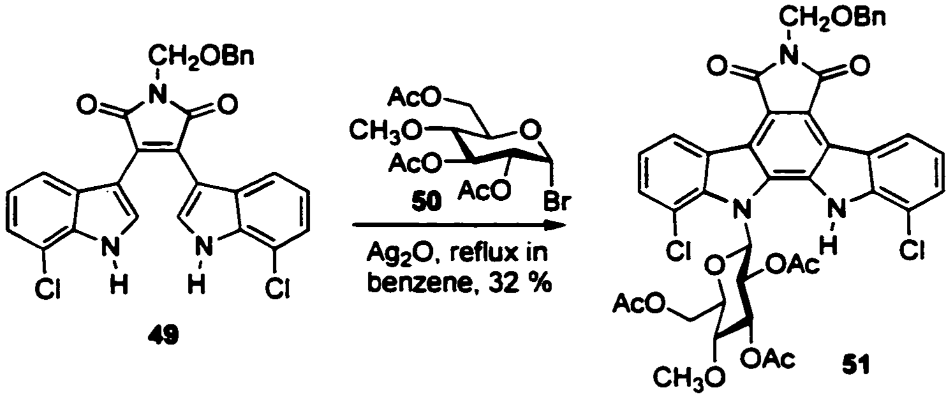
Scheme 4. Indole-indoline method used by Wightman *et al.*

However, using the sodium salt of the indole, Wightman[3] was able to obtain moderate yields of the indole-N-glycosides (scheme 5). The major products of this step were the α isomers (**45** and **48**) due to the neighboring group participation of the pivaloyl group at C-2 of the sugar.



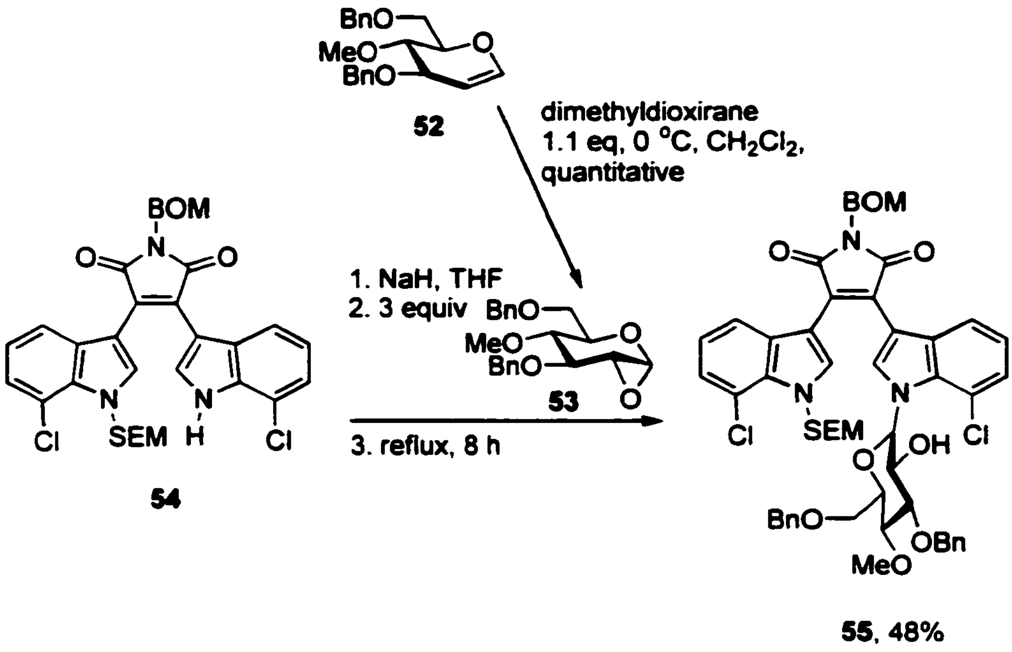
Scheme 5. Sodium salt method used by Wightman *et al.*

Several syntheses of rebeccamycin have been reported. In the first synthesis, Kaneko and Clardy utilized the Koenigs-Knorr technique to effect the glycosidation step.[6b] Treatment of **49** with Ag_2O and 1-bromo-2,3,6-tri-*O*-acetyl-4-*O*-methyl-D-glucose (**50**) in refluxing benzene accomplished the oxidation and glycosidaion in one step to afford **51** in 32% yield (Scheme 6). It was presumed that the triene system **49** was thermally cyclized and Ag_2O was acting as an oxidizing agent.



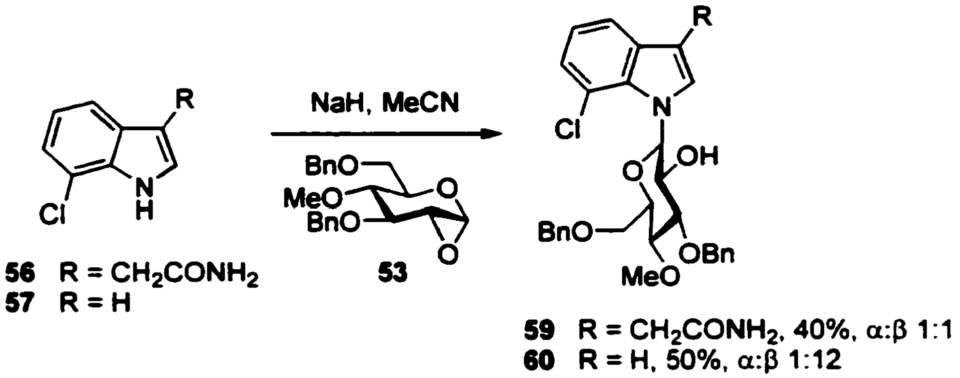
Scheme 6. Koenigs-Knorr glycosidation.

Danishefsky's group has utilized 1,2-anhydrosugars (glycals) as glycosyl donors toward a variety of nucleophiles, and applied this methodology to the total synthesis of rebeccamycin. In the glycosidation step, three equivalents of the 1,2-epoxysugar **53**, obtained from the epoxidation of glucal **52** by dimethyldioxirane, was added to the sodium salt of the monoprotected bisindole **54**, generated by treatment with 1.1 equivalents of sodium hydride. Refuxing the reaction mixture produced the desired β-glucopyranoside **55** in 48% yield (Scheme 7).[18a]



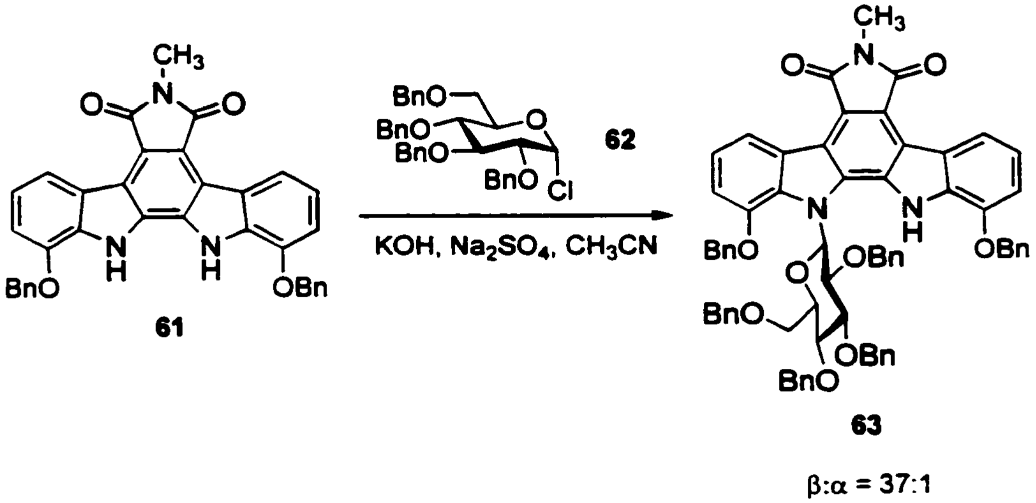
Scheme 7. Danishefsky's glycosidation step.

Faul *et al.* utilized the method of Danishefsky for the selective formation of the β-N-glycosides of 7-chloroindole-3-acetamide (**56**) and 7-chloroindole (**57**). Deprotonation of **56** and **57** (2.0 eq) with NaH (2.1 eq) in acetonitrile, followed by treatment with **53** (1.0 eq) at 50 °C overnight, afforded β-N-glycosides **59** and **60** in 40% and 50% yield, respectively (Scheme 8).[7a]



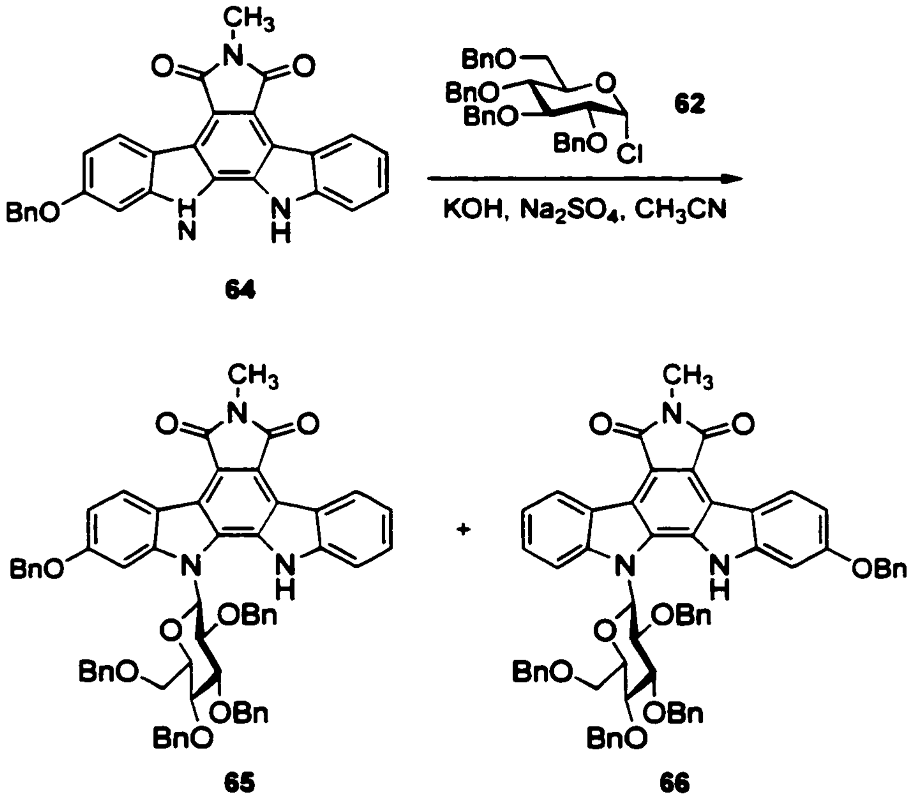
Scheme 8. Faul's use of Danishefsky's method.

In a paper on the synthesis of NB-506 (**9**), the key step, glycosidation of indolocarbazole, was investigated by Ohkubo *et al* to develop a practical synthesis using potassium hydroxide as a base.[8a] The indolyl dianion of **61**, generated by powdered potassium hydroxide in acetonitrile in the presence of sodium sulfate, reacted with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**62**) under a nitrogen atmosphere to form the desired β-glucoside **63** in 90% yield with high stereoselectivity (β:α = 37:1, Scheme 9).



Scheme 9. Ohkubo's glycosidation using KOH as a base.

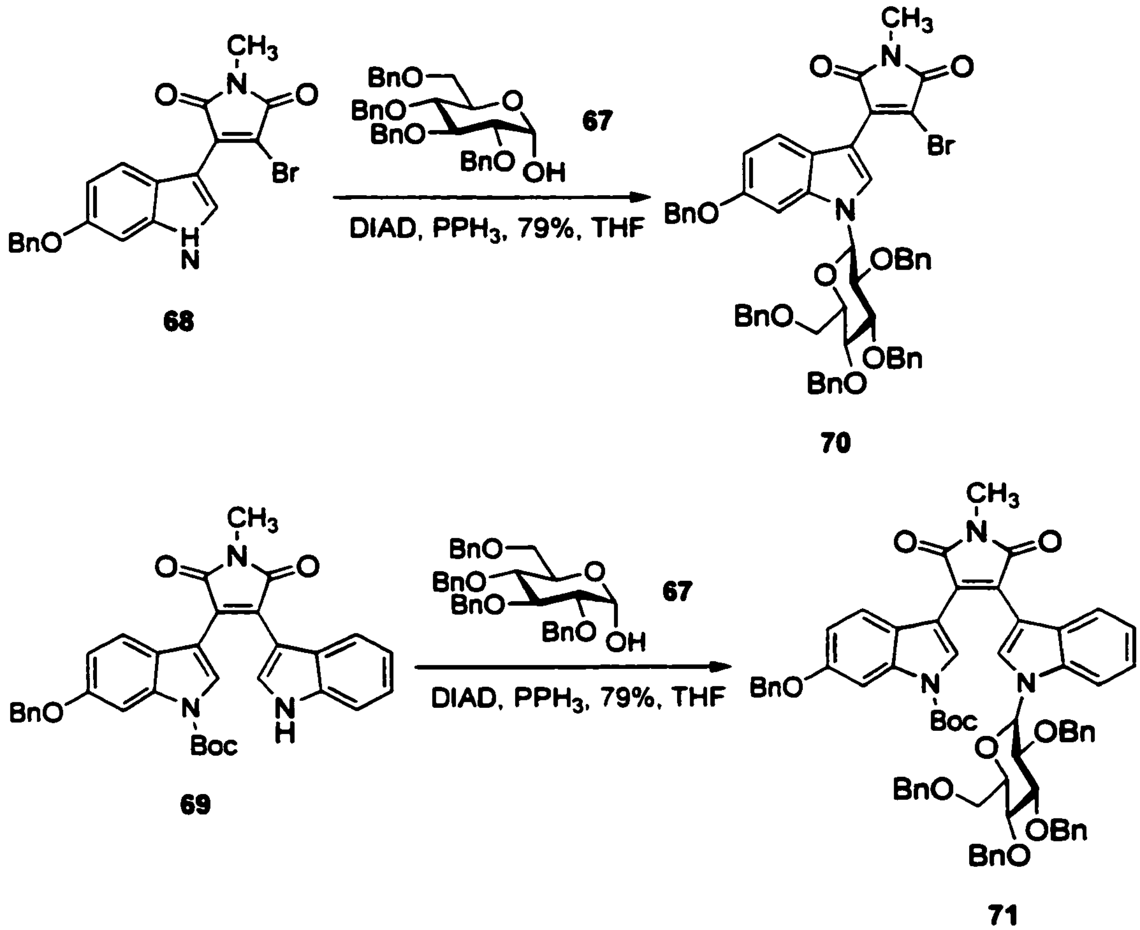
However, the glycosidation method utilized in the synthesis of NB-506 shown in Scheme 9 could not be applied to the synthesis of a dissymmetric indolocarbazole glycoside because of lack of regioselectivity (**65**:**66** = 1:1, Scheme 10).[9]



65:**66** = 1:1

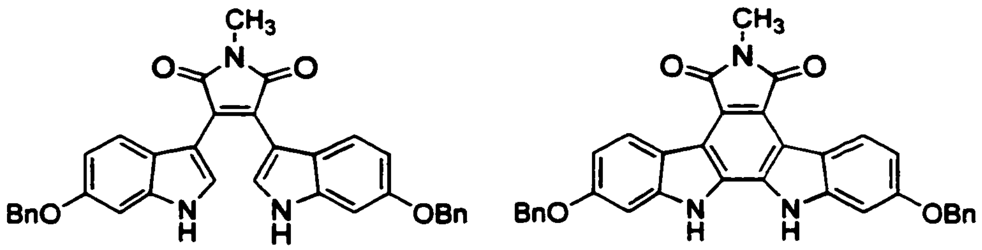
Scheme 10. Ohkubo's glycosidation: Lack of regioselectivity.

The glycosidation of compounds **68** and **69** was also unsuccessful because these compounds were unstable to potassium hydroxide. Glycosidation reactions proceeding under neutral conditions were subsequently investigated, and the Mitsunobu reaction was found to be applicable to the glycosidation of compounds **68** and **69**. An example of the application of this Mitsunobu method is illustrated in Scheme 11.[8b]



Scheme 11. Mitsunobu's application to glycosidation.

This Mitsunobu method failed to glycosidate bisindolylmaleimide **72** and indolocarbazole **73**.[8b] Ohkubo reasoned that the absence of an electron-withdrawing group such as Br or Boc in these compounds may have caused the decrease in reactivity (Figure 5).

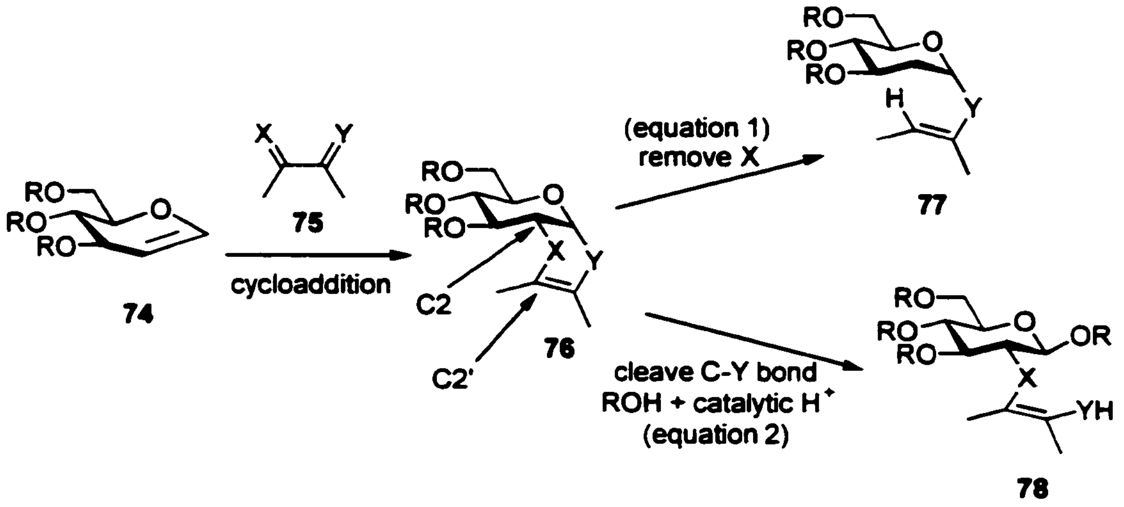


72 **73**

Figure 5. Structures of Bisindolylmaleimide **72** and Indolocarbazole **73**.

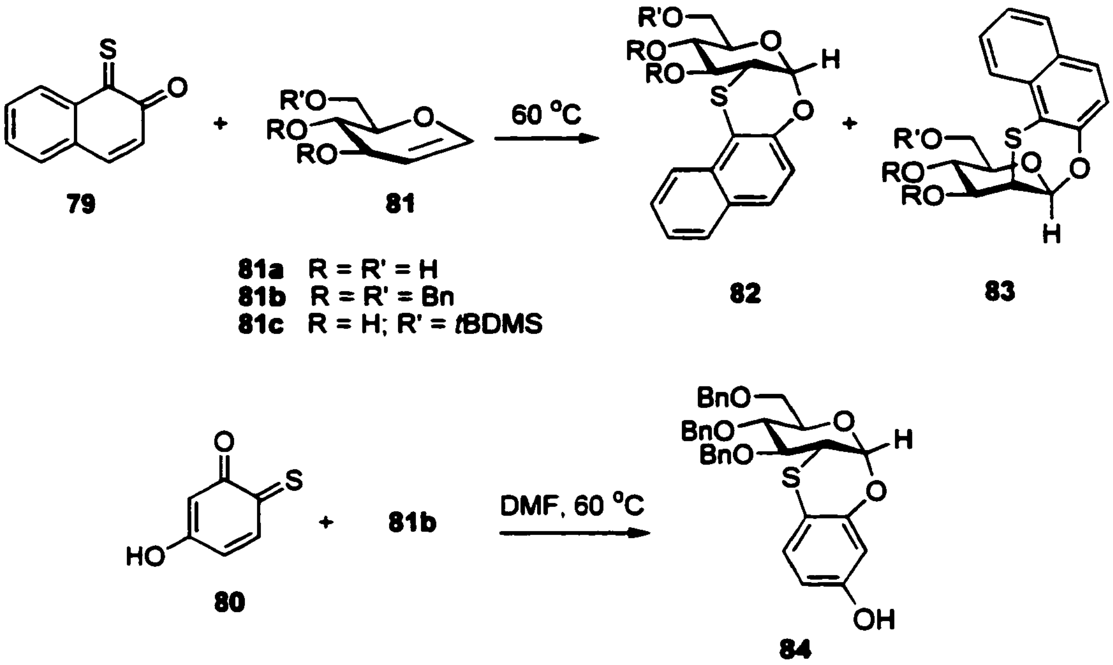
E. Cycloaddition Approach to Indole-N-Glycosides: Objective of This Research Project

Dr. Franck's group at Hunter College of the City University of New York, with the collaboration of Dr. Capozzi's group at the Universita' di Firenze in Italy, has successfully developed a novel concept of glycosyl transfer, a cycloaddition method which is illustrated in general form in Scheme 12.[23] Sugar dienophile **74** undergoes cycloaddition with heterodiene **75** to afford a versatile adduct **76**. Extrusion (reduction, cleavage) of the X-C2 bond and/or the X-C2' bond from **76** will form a glycoside **77** (Scheme 12, equation 1). Or, a transfer step with ring opening at the Y-C1 bond will convert **76** to **78** (Scheme 12, equation 2).

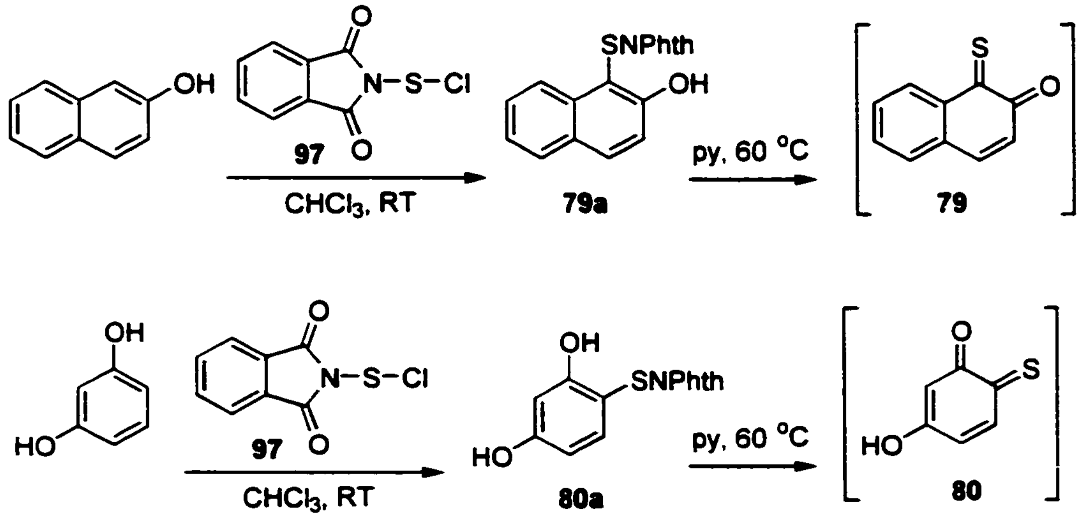


Scheme 12. The Cycloaddition Way to Glycosyl Transfer: General Concept.

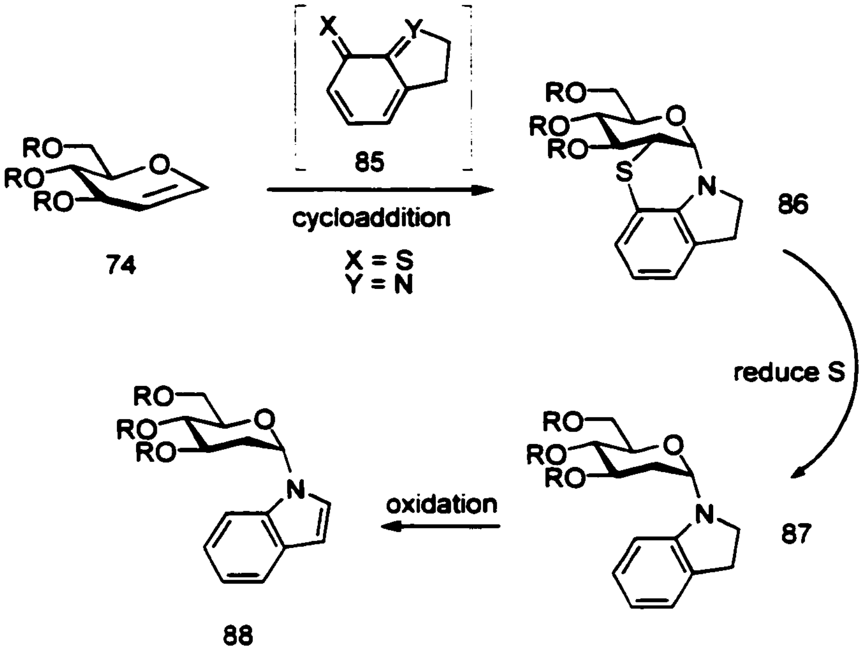
Capozzi and Franck reported the synthesis of 2-deoxy-α-O-aryl glucosides *via* the totally regio- and highly stereo-selective [4+2] cycloadditions of *ortho*-thioquinones **79** and **80** to substituted-D-glucals **81** (Scheme 13).[24] The *ortho*-thioquinones **79** and **80** were generated *in situ* from the corresponding thiophthalimide derivatives **79a** and **80a**, respectively (Scheme 14). Application of this reaction to the synthesis of indole-N-glycosides requires intermediate **85** (Scheme 15). Investigation of this variation of the Capozzi-Franck reaction is the subject of this thesis.



Scheme 13. Totally regio- and highly stereo-selective [4+2] cycloaddition of *ortho*-thioquinones **79** and **80** to substituted-D-glucals **81**.



Scheme 14. *In situ* generation of *ortho*-thioquinones **79** and **80**.



Scheme 15. Proposed Cycloaddition Approach to Indole-N-Glycosides.

Sugar dieneophile **74** undergoes an inverse-electron-demand Diels-Alder cycloaddition with heterodiene **85** to afford adduct **86**. This proposed cycloaddition is similar to the general cycloaddition reaction shown in Scheme 12, where, in this case, X = S and Y = N. Reduction of the sulfur atom in the cycloadduct **86** generates an indoline-N-glycoside **87**. Subsequent oxidation converts the indoline-N-glycoside **87** into an indole-N-glycoside **88**.

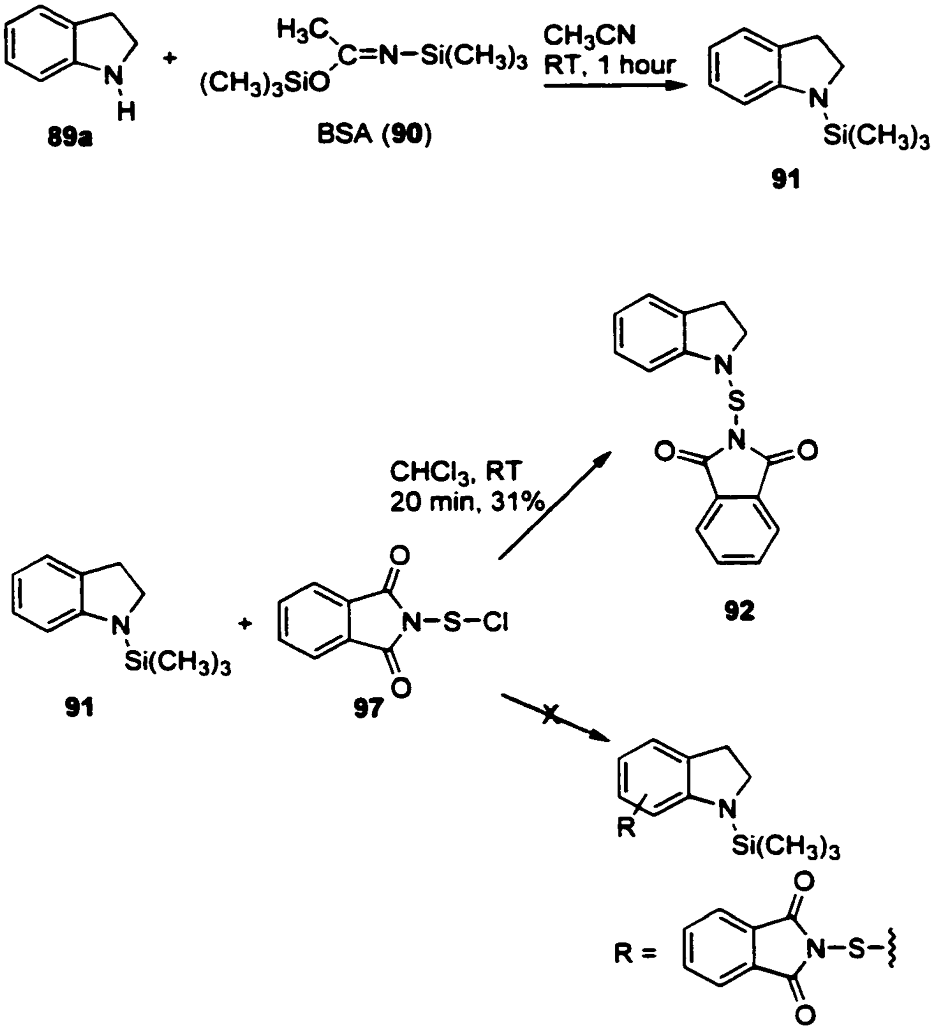
II. Results and Discussion

A. Preparation of the Key Starting Material 103

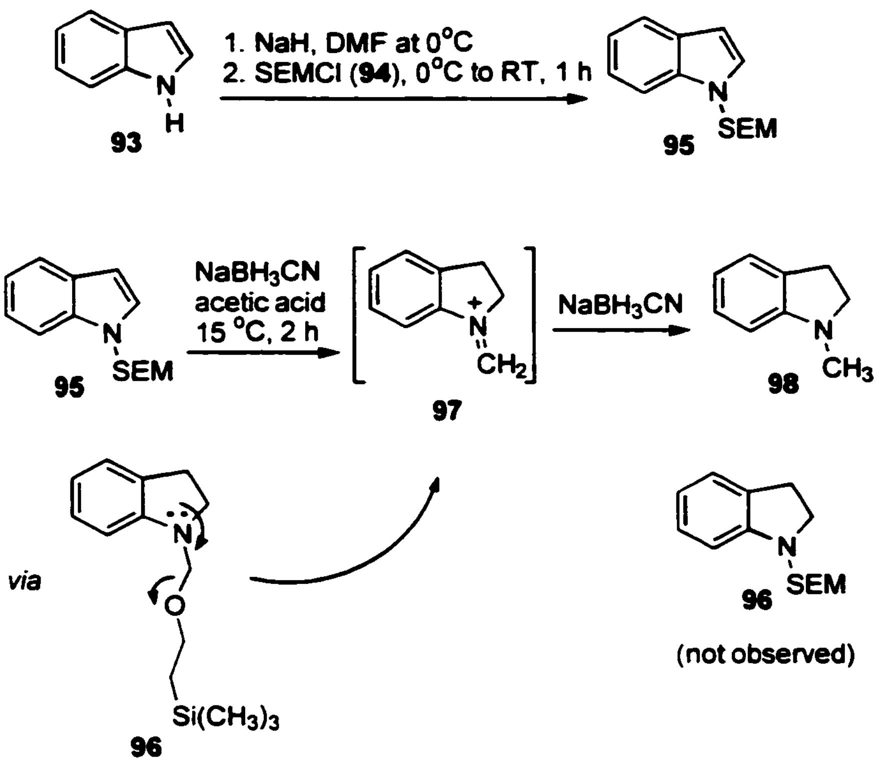
Heterodiene **85** (Scheme 15) requires that sulfur to be introduced at position C-7 of the indole ring system. In order to effect this transformation, reactions that effectively and conveniently performed this operation were required.

Preliminary studies on the preparation of starting material **103** were investigated. Indoline (**89a**) was reacted with bis(trimethylsilyl)acetamide (BSA, **90**) to form N-trimethylsilylindoline (**91**), indicated by ^{1}H nmr data.[25] As **91** was hydrolytically unstable, it was not isolated, and after concentration under vacuo, phthalimide-N-sulfenyl chloride (**97**) was added.[26] No electrophilic aromatic substitution product was observed however. The only product that was obtained was 2-indolinylthioisoindoline-1,3-dione (**92**, Scheme 16).

N-SEM protected indoline was investigated next. 1[[2-Trimethylsilyl)ethoxy]methyl]indoline (**95**) was prepared by reacting the anion of indole (**93**) with [2-(trimethylsilyl)ethoxy]methyl chloride (SEMCl, **94**).[27] Reduction of **95** with sodium cyanoborohydride in acetic acid did not produce the desired indoline species **96**.[28] Instead N-methyl indoline (**98**) was formed *via* the sequence shown in Scheme 17. After the initial reduction of the double bond of the N-SEM protected indole (**95**), the nucleophilic nitrogen of reduced indoline **96** attacks the adjacent carbon of the SEM group, and in the process, displaces the 2-(trimethylsilyl)ethoxy group to form intermediate **97**. Subsequent reduction of compound **97** by sodium cyanoborohydride produces N-methyl indoline (**98**).



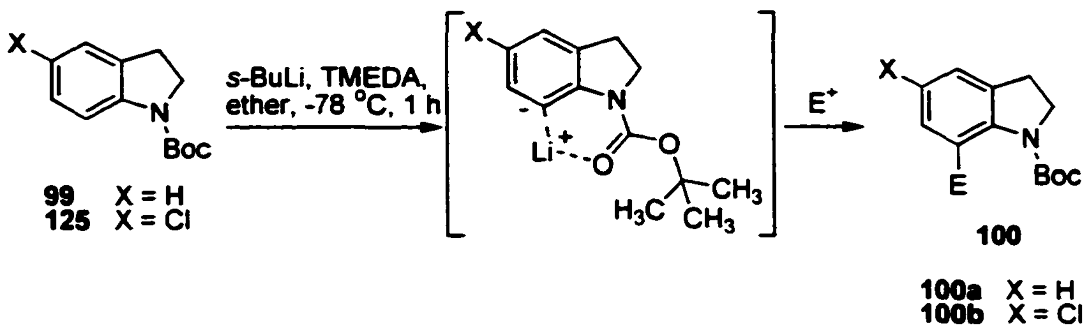
Scheme 16. **Attempted Electrophilic Aromatic Substitution on N-trimethylsilyl indoline (91).**



Scheme 17. Reduction of 1[[2-(Trimethylsilyl)ethoxy]methyl]indoline (**95**).

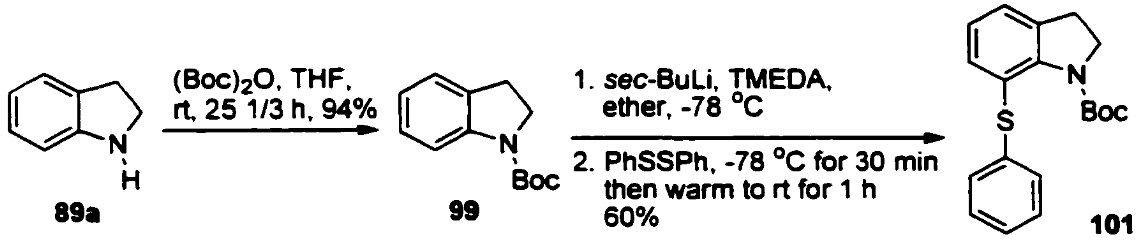
Somei *et al.* developed a procedure for 7-selective functionalization of indole.[29] However, utilization of the toxic thallium reagent was not deemed practical.

In a 1992 paper, Iwao *et al* reported a very convenient route to 7-substituted indolines *via* directed lithiation of 1-(*tert*-butoxycarbonyl)indolines.[30] The C-7 selective lithiation of 1-(*tert*-butoxycarbonyl)indolines (**99** and **125**) was accomplished with *sec*-BuLi/TMEDA in ether or THF at -78 °C for 1 hour. Quenching the lithio species with an appropriate electrophile E^+ afforded 7-substituted compounds **100** (Scheme 18).



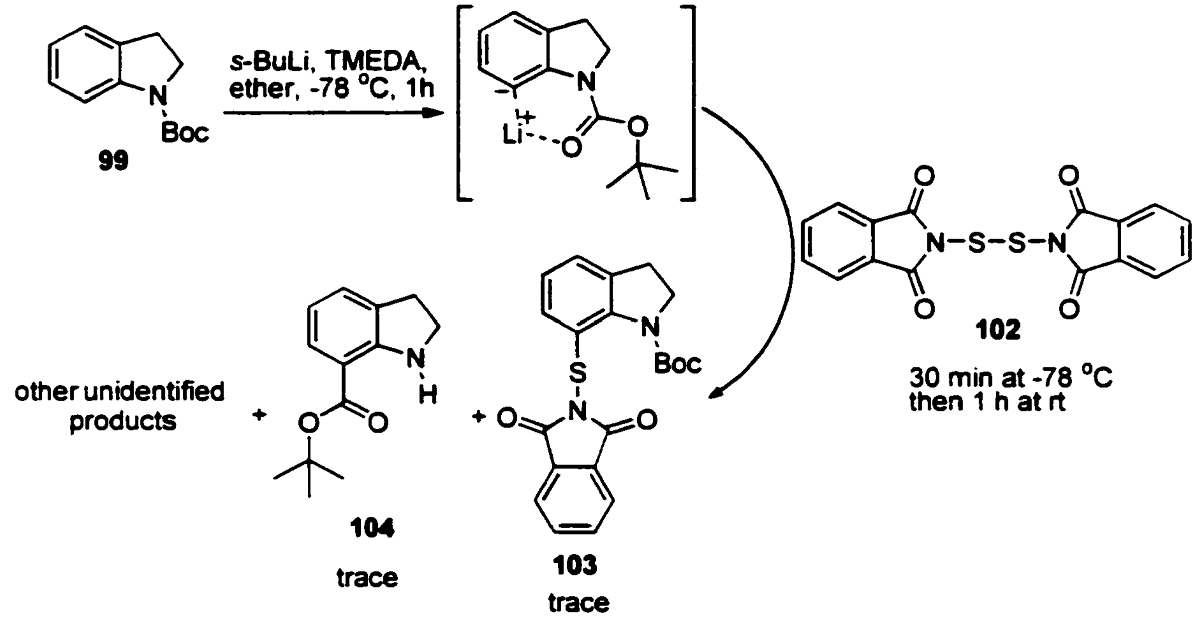
Scheme 18. Directed Lithiation of 1-(*tert*-Butoxycarbonyl)indolines.

As preliminary model work, we followed the Iwao procedure and we were able to reproduce and obtain 1-(*tert*-butoxycarbonyl)-7-phenylthioindoline (**101**) in 60% yield (Scheme 19). N-Boc substituted indoline **99** was prepared by adding di-*tert*-butyl dicarbonate, $(Boc)_2O$, to a stirred solution of indoline **89a** in THF which was then stirred overnight at room temperature.



Scheme 19. 7-Lithiation followed by sulfenylation with phenyl disulfide.

In order to insert the sulfur atom at C-7 of indoline **99** with a good leaving group attached to it, such as the phthalimide group, we attempted this Iwao method with a different electrophile, namely N,N'-dithiobis(phthalimide) (**102**, Scheme 20). The reaction produced a very complex mixture of products. This procedure was repeated many times but the same result was always obtained in each case. Separation by column and radial chromatography, which proved to be very difficult and impractical, yielded only trace amounts of the desired product **103**.



20. 7-Lithiation followed by sulfenylation with N,N'-dithiobis(phthalimide).

Interestingly, trace amounts of the 7-Boc indoline **104** were also detected by ^{1}H nmr (Figure 6). This compound was probably formed *via* a hypothetically feasible rearrangement shown in Scheme 21. The negative charge at C-7 of species **104a** attacks the carbonyl carbon of the Boc group to form a strained tricyclic species **104b**, which is converted to the anionic species **104c** by breaking of the C-N bond of the smallest ring. This completes the transfer of Boc from the nitrogen to C-7 of the indoline. Quenching of **104c** with H^+/H_2O affords **104**.

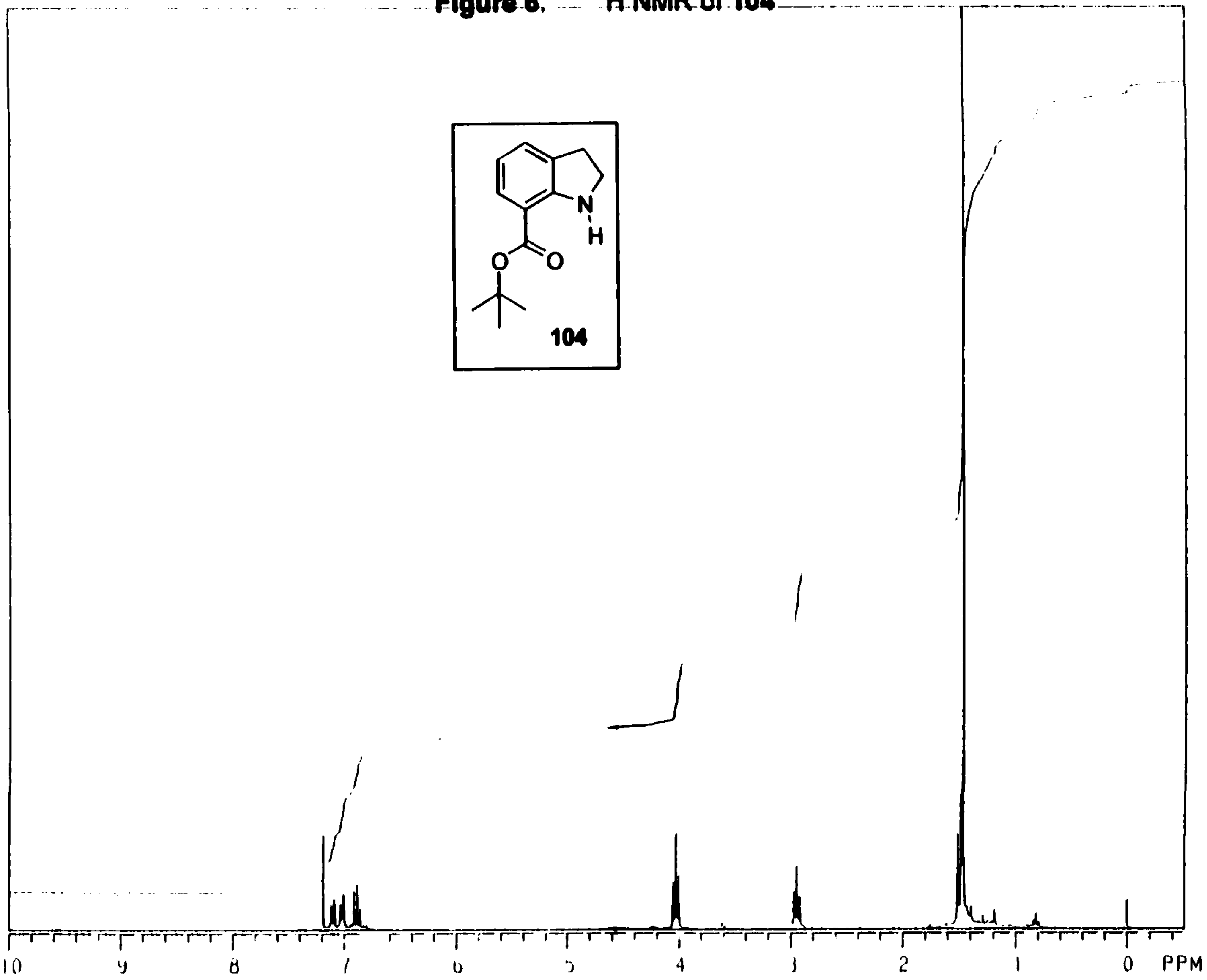
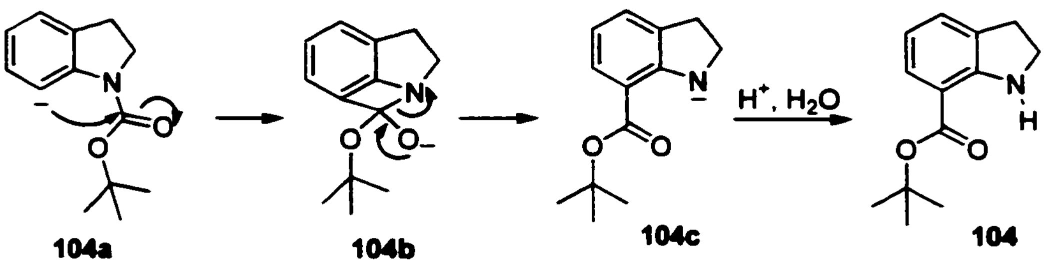
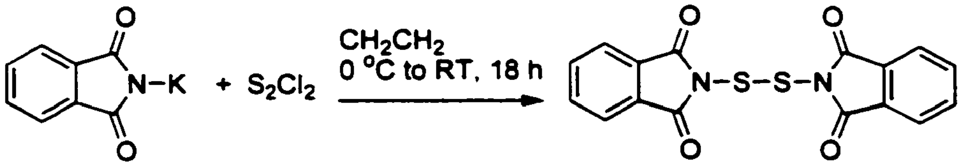


Figure 6. ^{1}H NMR of 104



Scheme 21. Rearrangement to 7-(*tert*-butoxyxarbonyl)indoline (**104**).

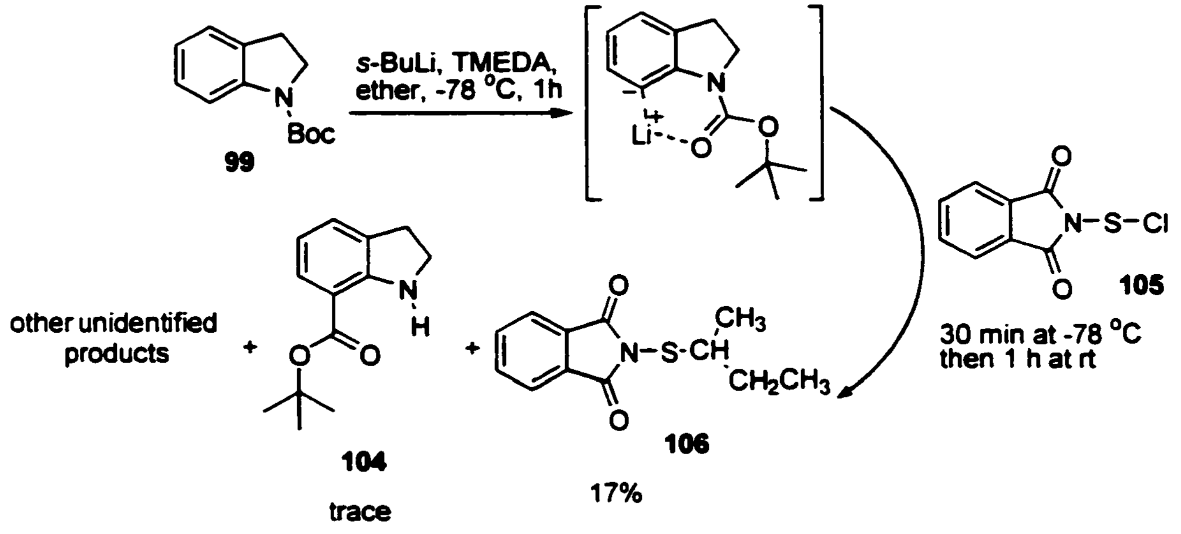
N,N'-dithiobis(phthalimide) (**102**) was prepared by the method of Ley *et al.* (Scheme 22).[31]



102

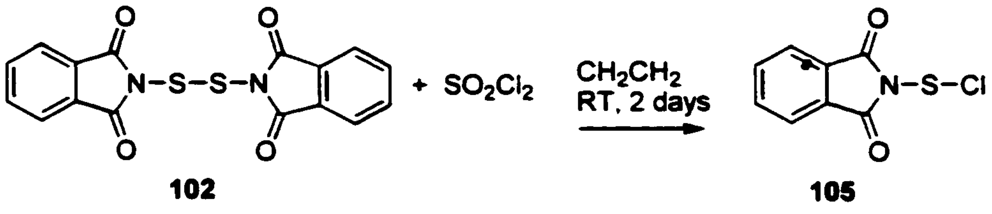
Scheme 22. Preparation of N,N'-dithiobis(phthalimide)(**102**).

Reasoning that phthalimide-N-sulfenyl chloride (**105**) was a better electrophile than the disulfide **102**, we attempted 7-lithiation of 1-(*tert*-butoxycarbonyl)indoline (**99**) to be followed by sulfenylation with electrophile **105**. Unfortunately, change of electrophile still produced trace amounts of the desired product **103**. According to ^{1}H nmr, compound **106** (Figure 7) was also formed, where the *sec*-butyl group apparently displaced the Cl of **97** (Scheme 23). Compound **104** was also detected by ^{1}H nmr in this case.



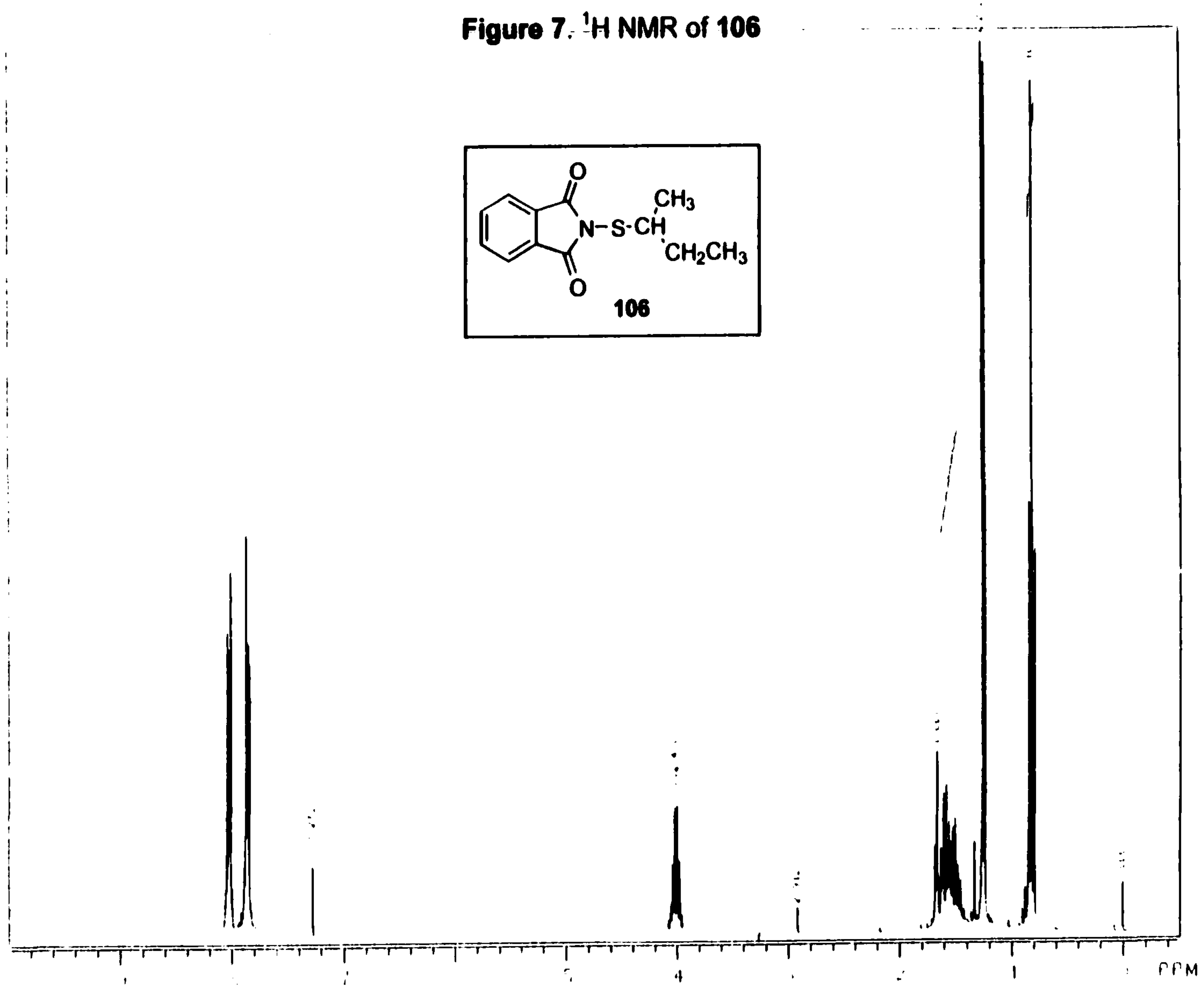
Scheme 23. 7-Lithiation followed by sulfenylation with phthalimide-N-sulfenyl chloride.

Phthalimide-N-sulfenyl chloride (97) was prepared by the method of Butler *et al* (Scheme 24).[32]

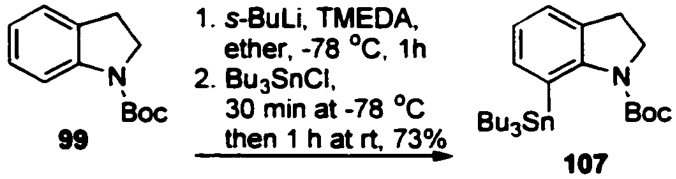


Scheme 24. Preparation of phthalimide-N-sulfenyl chloride (105).

Figure 7. ^{1}H NMR of 106

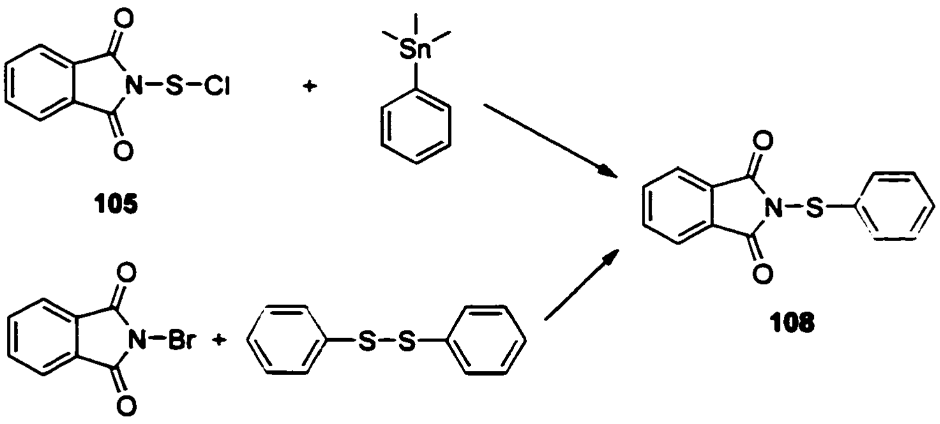


In the same paper by Iwao, 1-(*tert*-butoxycarbonyl)-7-tributylstannylindoline (**107**) was easily prepared by the same 7-lithiation method. We were able to reproduce and obtain **107** in good yield (Scheme 25). Compound **107** proved to be a very useful precursor for the preparation of compound **103**.



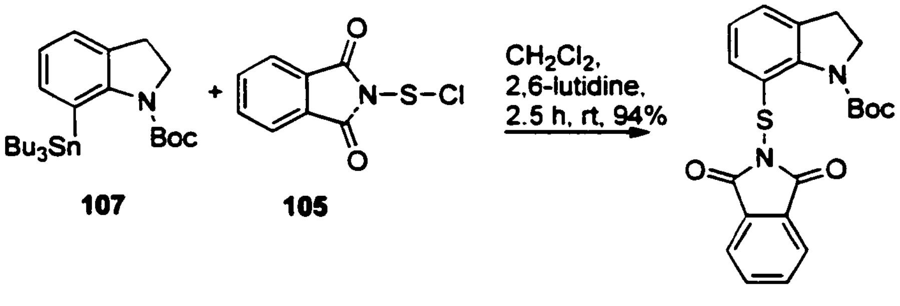
Scheme 25. 7-lithiation followed by stannylation with tributyltin chloride.

Before proceeding to prepare **103**, we experimented on a simpler model compound. Phthalimide-N-sulfenyl chloride (**105**) was reacted with phenyltrimethyltin to produce N-phenylmercaptophthalimide (**108**). This compound (**108**) was also prepared by refluxing phenyldisulfide with N-bromophthalimide in dry benzene (Scheme 26).[33]



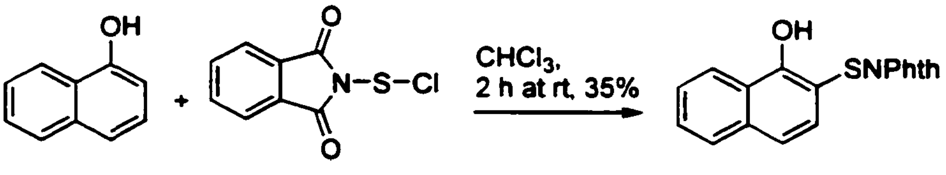
Scheme 26. Preparation of N-phenylmercaptophthalimide (**108**).

With the ease of getting 1-(*tert*-butoxycarbonyl)-7-tributylstannylindoline (**107**), we were finally able and successful in obtaining the desired starting material **103** (Scheme 27). Simple electrophilic displacement of the tributyltin group by phthalimide-N-sulfenyl chloride (**105**) provided **103** in very good yield. In a typical experiment, 2,6-lutidine was first added to the starting material **107** in CH_2Cl_2, followed by addition of phthalimide-N-sulfenyl chloride (**105**). 2,6-lutidine functions as a base to neutralize any acid (HCl) that is present in the phthalimide-N-sulfenyl chloride solution so that the reaction could achieve maximum yield.



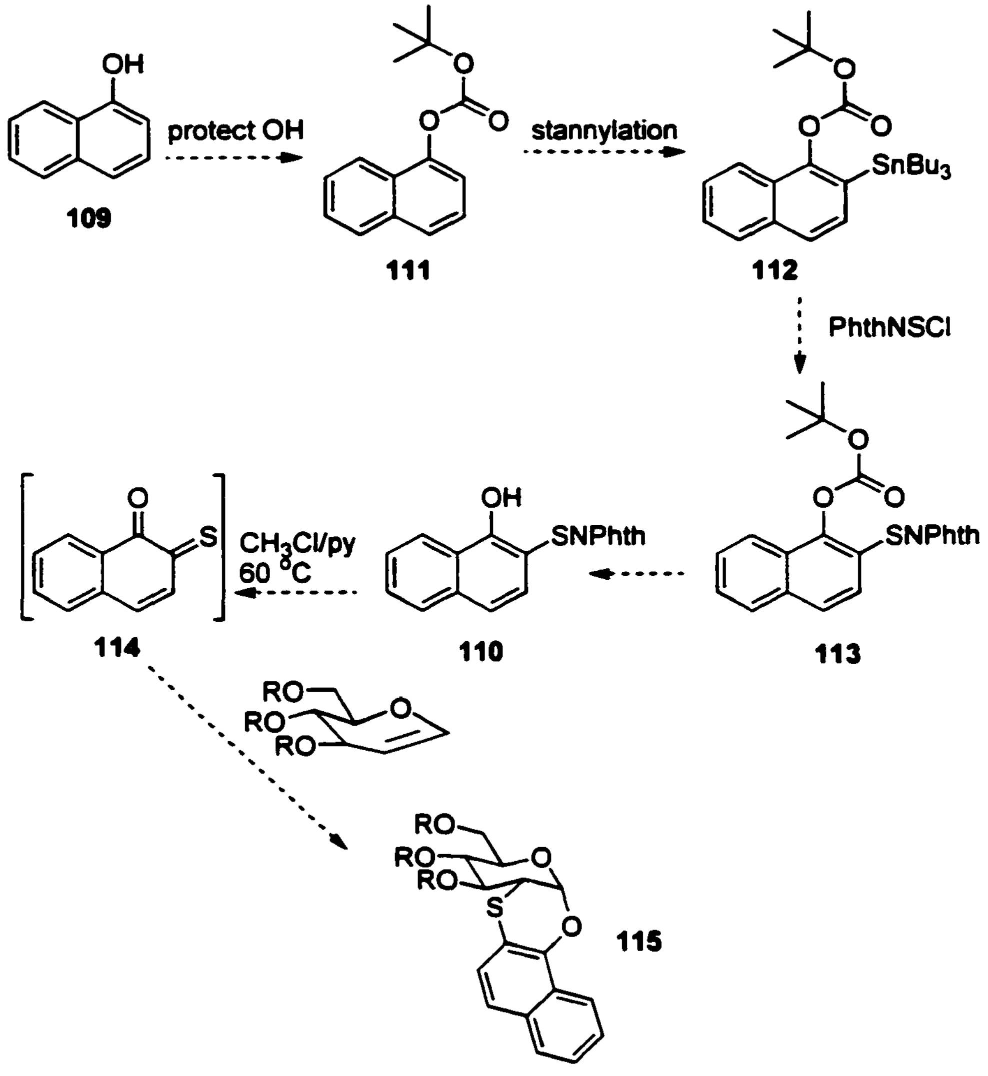
Scheme 27. Preparation of the key starting material **103**.

The stannylation-sulfenylation sequence seems to be very practical. The phthalimide-N-sulfenyl group could be introduced onto any aromatic system where *ortho*-lithiation and stannylation can take place. This could be utilized in the preparation of precursors for the stereo-controlled *O*-aryl glycosidation in the synthesis of a wide number of naturally occurring products.[34] Typical examples are the 2-deoxy-α-*O*-aryl glucosides. We envision cases such as α-napthol **109**, which does not *ortho*-sulfenylate in good yield (Scheme 28), as a substrate for our new stannylation-sulfenylation method (Scheme 29).



109 **102** **110**

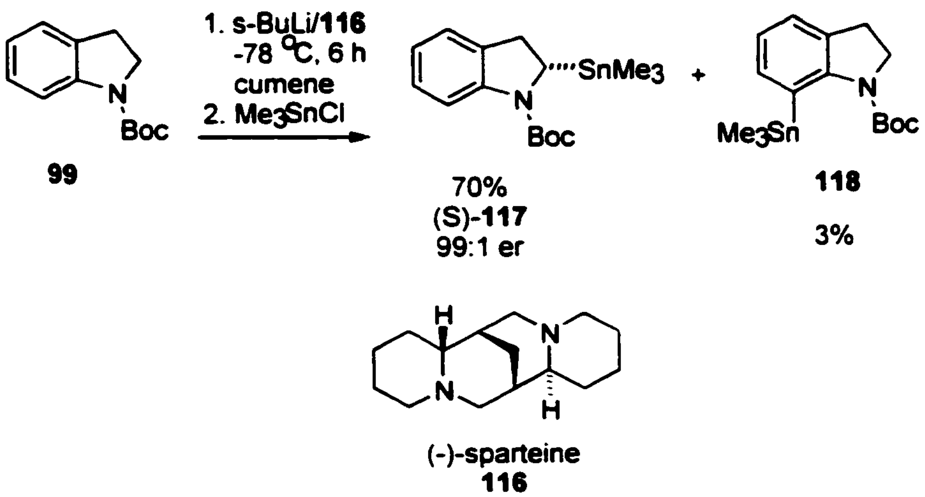
Scheme 28. *Ortho*-sulfenylation where yield is poor.[34]



Scheme 29. *Ortho*-lithiation-stannylation-sulfenylation sequence in other aromatic system?

In a recent paper, Beak *et al* reported an interesting result concerning the lithiation of 1-(*tert*-butoxycarbonyl)indoline (**99**) with *s*-BuLi/(-)-Sparteine (**116**). His group showed that lithiation of **99** with *s*-BuLi in the presence of (-)-sparteine followed by substitution by electrophiles resulted in the formation of (S)-2-substituted N-Boc indolines. The reason for the regioselective lithiation to form the 2-substituted N-Boc indolines is that the complex between **99** and *s*-BuLi/(-)-

Sparteine at the C-7 region of **99** would lead to the transition state that is too sterically hindered. Hence, the complex leading to removal of H-2 is more favorable. The bulky and chiral characters of (-)-sparteine result in high regio- and stereoselectivity for the 2-lithiation of N-Boc indolines. An example to illustrate this method is shown in Scheme 30.[35]



Scheme 30. Dissymmetric lithiation of 1-(*tert*-butoxycarbonyl)indoline (**99a**).

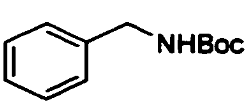
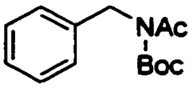
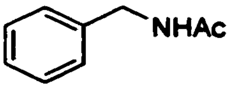
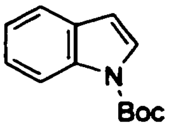
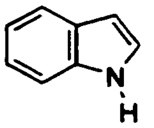
B. Deprotection of Boc

With the key starting material **103** in hand, we were ready to carry out our cycloaddition reaction. First we needed to deprotect the Boc group. Our first attempt of deprotecting the Boc group using the procedure by Masui[36] was unsuccessful. The phthalimide-N-sulfenyl group could not withstand the harsh conditions of concentrated trifluoracetic acid.

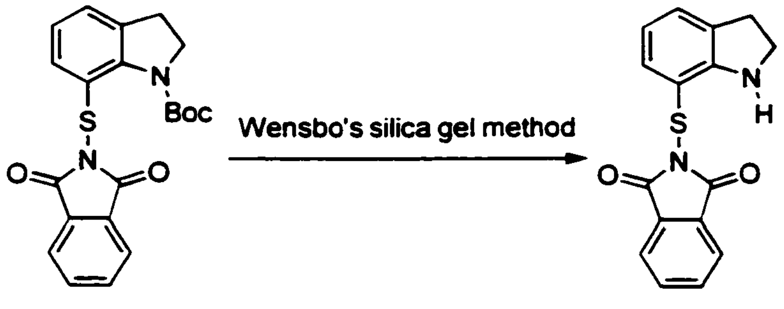
A paper by Wensbo appeared shortly after this failed attempt in which he used silica gel at low pressure to selectively remove the N-Boc protecting group.[37] Boc groups attached to nitrogen atoms which are part of an aromatic system or in conjugation with an aromatic or carbonyl group, were removed in high yields. Boc substituents at aliphatic amines were left unaffected (Table 1).

Our starting material **103** was a candidate for this new procedure of deprotecting Boc. In a typical experiment, the substrate was dissolved in methylene chloride, was evaporated onto 10 times its weight of silica gel (preheated overnight). After treatment at 50 °C/0.2 mmHg for an appropriate period, the product was purified by column chromatography. However, attempts were made to follow this procedure resulted in no recovery of deblocked material after column (or radial) chromatography, although, ^{1}H nmr did show that the deblocked indoline **119** was present (Scheme 31).

Table 1.[32] Removal of Boc from different N-Boc substituted amines.[a]

substrate	product	reaction time, h	isolated yield, %
	No reaction	>144	
		15	92
		8	93

[a] The substrate dissolved in methylene chloride, was evaporated onto 10 times its weight of silica gel (35-70 Mesh). After treatment at 50 °C/0.2 mmHg for the time indicated the product was purified by flash chromatography.



103 **119**

seen in ^1H nmr

Scheme 31. Deprotection of Boc using Wensbo's method.

C. Studies on Cycloaddition Between 3,4,6-Tri-*O*-benzyl-D-glucal (81b) and *t*-Boc Heterodiene Precursor 103 (and N-H Heterodiene Precursor 119)

We continued to experiment with this silica gel method by carrying out the deprotection-cycloaddition sequence in one pot by adsorbing both the starting material **103** and 3,4,6-tri-*O*-benzyl-D-glucal (**81b**) onto the silica gel. We then heated the silica gel mixture to ~50 °C at low pressure for a period of 2 days, and we were able to detect formation of cycloadduct **120** (Scheme 32). Different conditions were explored and are summarized in Table 2.

Some conclusions can be drawn from Table 2. There was no difference whether the silica gel was preheated overnight or not. Commonly used column chromatrography silica gel and Davisil silica gel worked similarly, and for every equivalent increase of 3,4,6-tri-*O*-benzyl-D-glucal (**81b**), the % yield of the cycloadduct **120** increased by about 3-4%, and the amount of the dimer **121** (or **122**) diminished.

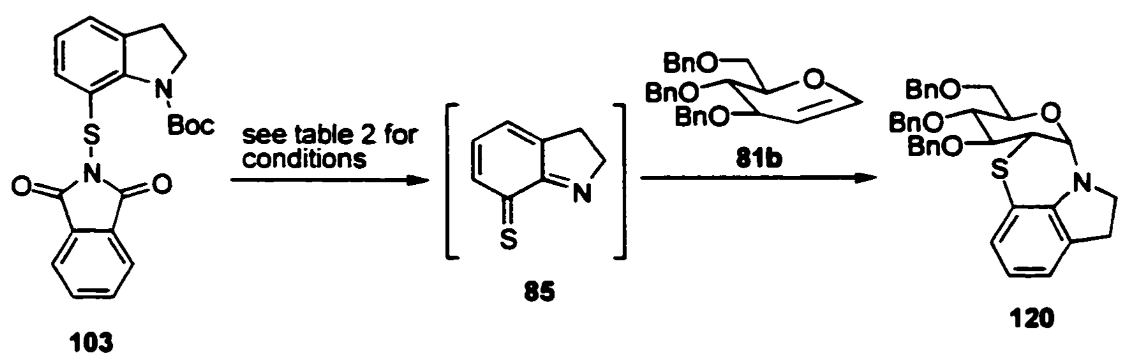
Other solids were used, such as Amberlyst and Amberlite, but the reaction did not produce any significant amount of cycloadduct. Perhaps these resins are too acidic for this reaction system.

Diglyme was used to deprotect Boc at elevated temperature with no success.

Table 2. Summary of cycloaddition reaction between 3,4,6-tri-*O*-benzyl-D- glucal (**81b**) and *t*-Boc heterodiene precursor **103**.

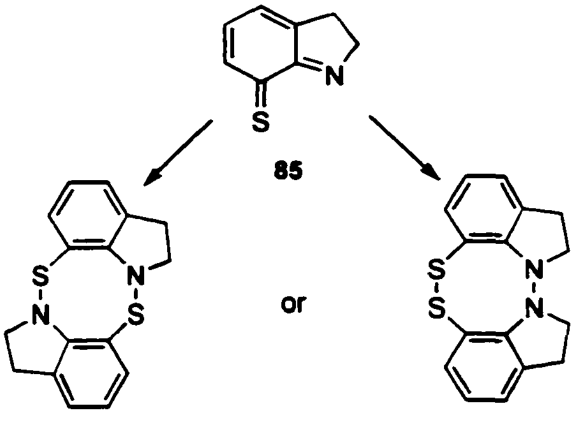
Entry	81b:103	silica gel	solvent	base	temp, °C	vacuum pump	time	yield %	dimer %[a]
1	5:1	Davisil[b]	none	none	50-55	Yes	69.5 hrs	18.8	trace
2	2:1	Davisil (pre)[c]	none	none	50-55	Yes	48 hrs	8.7	17
3	2:1	Davisil	none	none	50-55	Yes	44 hrs	8.9	20
4	1.2:1	Silica gel[d] (pre)	none	none	50-55	Yes	40 hrs	2.9	42
5	1.1:1	Silica gel	none	none	50-55	Yes	125 hrs	3.3	40
6	2.9:1	Silica gel	none	none	50-55	Yes	86 hrs	11.2	23
7	1.1:1	Silica gel & Amberlyst[e]	none	none	50-55	Yes	22 hrs	trace	trace
8	1.5:1	Amberlite[f]	CH_3CN	none	80-85	No	14 days	trace	trace
9	1.1:1	none	diglyme	none	50-80	No	7 days	none	none
10	1.1:1	none	diglyme	none	150-170		8.5 days	none	none

[a] dimer **121** (or **122**)
[b] Davisil, grade 634, 100-200 mesh, 60 A, 99+%
[c] Silica gel was preheated (pre) at reaction temperature overnight (24 hours)
[d] Merck, grade 9385, 230-240 mesh, 60 A
[e] Amberlyst, 15 ion-exchange resin, strongly acidic, macroreticular resin
[f] Amberlite, GC-50 ion-exchange, weakly acidic, 100-200 dry mesh



Scheme 32. Cycloaddition reaction of N-Boc heterodiene precursor **103** with 3,4,6-tri-*O*-benzyl-D-glucal (**81b**).

In some experiments a significant amount of dimer **121** (or **122**) was observed. The mass spectrum (m/z 299) and simple ^1H and ^{13}C nmr spectra support the presence of the dimer, and not the monomer **85** (Scheme 33). Dr. Dannenberg performed DFT calculations on the two dimers, **121** and **122**, which provided two sets of IR data that were compared with the IR that was obtained experimentally (Table 3, Figures 8-10). Interestingly, the experimental IR values of the dimer matched better with those of the calculated IR values of compound **121** than with those of compound **122**. Based on the IR comparisons, we concluded that compound **121** was indeed the dimer.



121

122

Scheme 33. Which dimer is present?

Table 3. Calculated and experimental IR values of the dimer.

Entry	Experimental, **121** (cm^{-1})	Calculated, **121** (cm^{-1})	Calculated, **122** (cm^{-1})
1	739.1	732.1	718.0, 755.4
2	768.0	762.0	758.8
3	948.8	931.8	815.2
4	1057.7	1043.1, 1059.6	1021.4
5	1216.9	1213.6	
6	1244.2	1239.3	1272.1, 1282.0
7	1418.2	1414.0, 1451.3	1434.6, 1451.7, 1458.2
8	1592.1	1601.3	1591.9

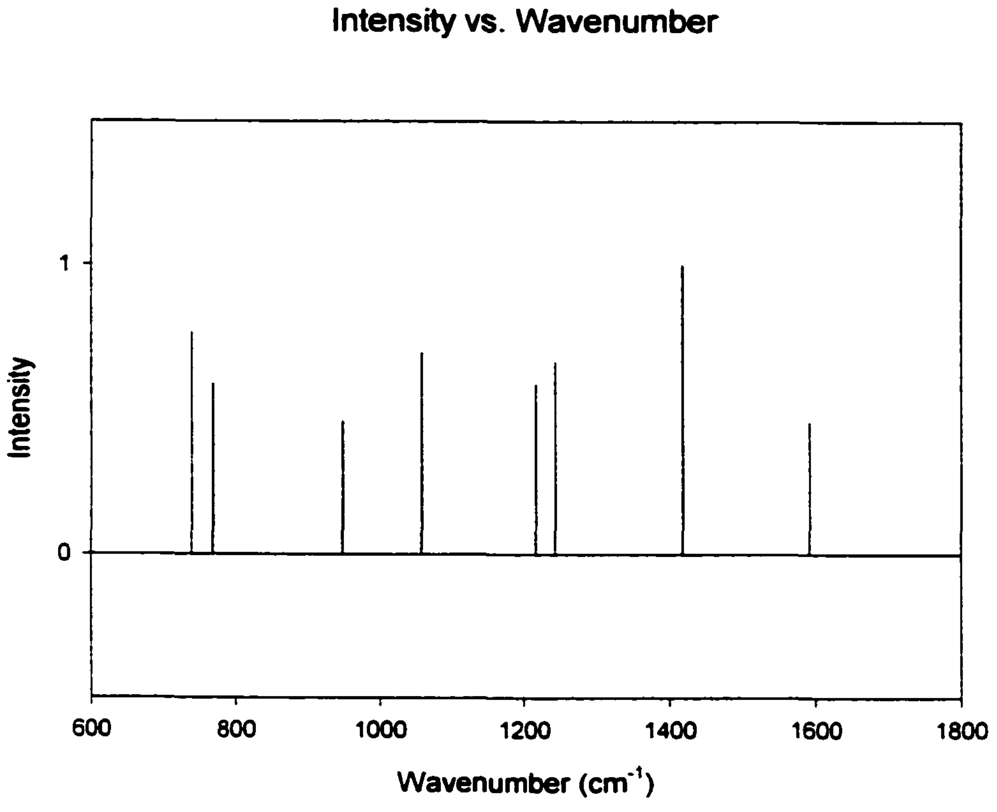


Figure 8. Experimental IR of dimer **121**.

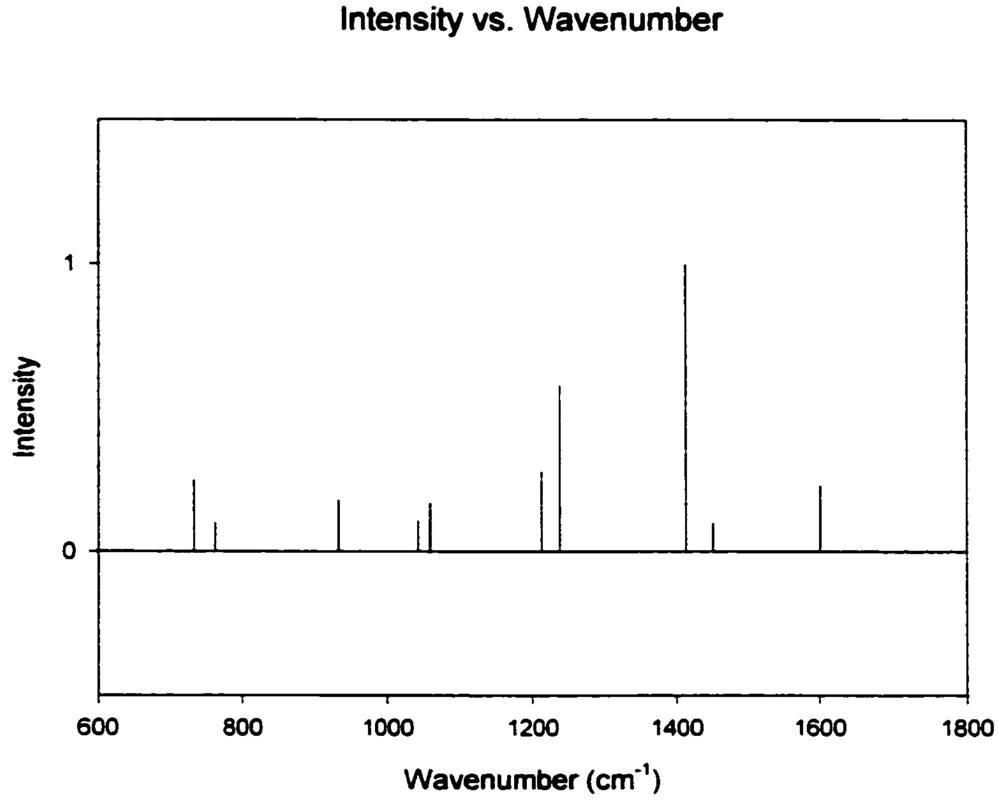


Figure 9. Calculated IR of dimer **121**.

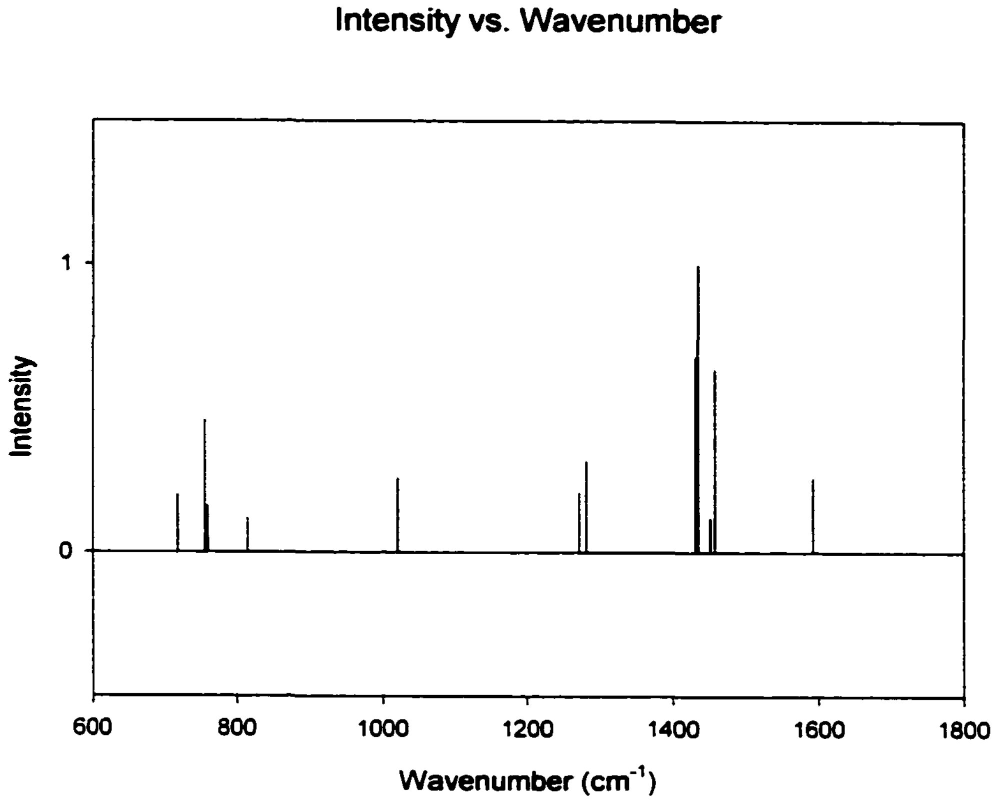
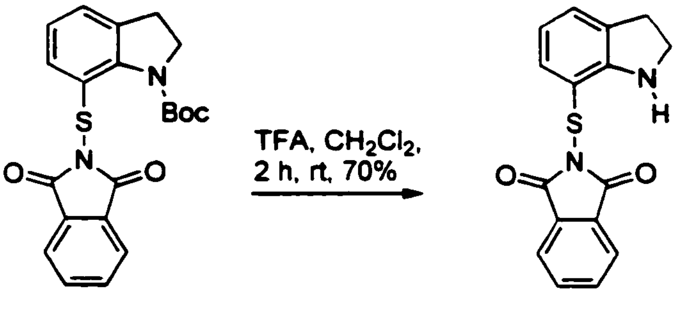


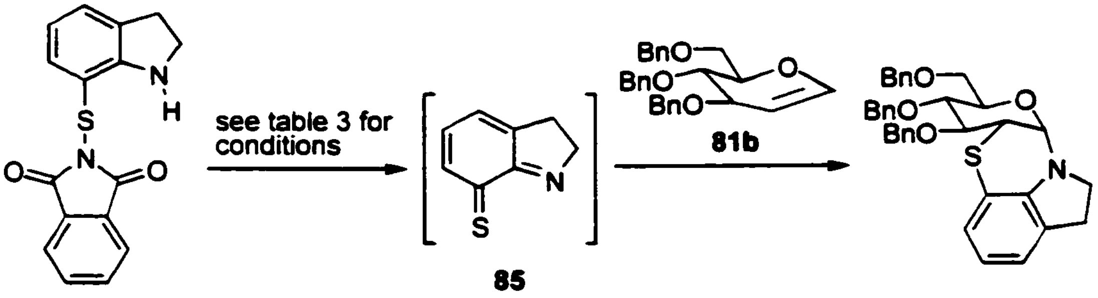
Figure 9. Calculated IR of dimer **122**.

Also, trace amounts of the deprotected amine **119** were obtained. Now that we knew the tlc properties of deprotected **119**, we again repeated the TFA deprotection of **103**. This time a much smaller amount of TFA was used and the reaction successfully afforded the free amine **119** (Scheme 34). This was then used to carry out similar cycloaddition reaction with/without silica gel under reduced pressure and the results are summarized in Table 4 (Scheme 35).



103 **119**

Scheme 34. Deprotection of Boc using TFA.



119 **85** **120**

Scheme 35. Cycloaddition reaction of N-H heterodiene precursor **119** with 3,4,6-tri-*O*-benzyl-D-glucal (**81b**).

Table 4. Summary of cycloaddition reaction between 3,4,6-tri-*O*-benzyl-D- glucal (**81b**) and N-H heterodiene precursor **119**.

Entry	81b:119	silica gel	solvent used	base added	temp, °C	vacuum pump	time	yield %	dimer %
1	5:1	Davisil (pre)[a]			55-58	Yes	50 hrs	18.6	
2	2:1	Davisil			50-55	Yes	70 hrs	20.2	14
3	5.2:1	Davisil			50-55	Yes	50 hrs	20.2	7.4
4	2:1	Davisil		Hunig's base (2.2 eq)	57	Yes	49 hrs	none	
5	2:1	TLC[b]			50	Yes	48 hrs	10.8	
6	2:1	Montmorillontie K10			57	Yes	49 hrs	none	
7	5:1	Aluminum oxide[c]			50-55	Yes	48 hrs	trace	
8	2:1		CH_2Cl_2		RT		72 hrs	9.4	
9	2:1		CH_2Cl_2		RT		18 hrs	7.0	
10	2:1		CH_2Cl_2		RT		12 hrs	6.4	
11	3:1		CH_2Cl_2		Reflux		8 days	trace	
12	2:1		CH_2Cl_2	2,6-lutidine (0.11 eq)	43-57		22 hrs	trace	
13	2:1		CH_2Cl_2	$Et_2O{\cdot}BF_3$	RT		72 hrs	trace	

Table 4. Continued.

14	2:1		CH_2Cl_2	Yb(Otf)$_3$ (0.01 eq)	RT		8 days	none	
15	2:1		DMF		50		42 hrs	3.6	42
16	2:1		DMF	2,6-lutidine (0.94 eq)	57-43		23 hrs	trace	
17	2:1		DMF	NaH (2.7 eq)	RT		7 days	none	
18	2:1		DMF	NaH (2.2 eq)	RT		98 hrs	none	
19	5:1	Davisil	DMF		50-55		48 hrs	trace	
20	5:1		$CHCl_3$		47		48 hrs	trace	
21	5:1	Davisil	$CHCl_3$		47		48 hrs	trace	
22	1.1:1		CH_3CN	Hunig's base (0.53 eq)	RT		116 hrs	none	
23	1.1:1		Hunig's base (34 eq)		RT		48 hrs	none	
24	2:1		THF		Reflux		48 hrs	trace	
25	1:3		THF		Reflux		92 hrs	trace	

[a] preheated silica gel for 12 hours

[b] Silica gel, TLC standard grade without binder

[c] Aluminum oxide, activated, weakly acidic, Brockman I, ~ 150 mesh, 58 A, CAMAG-C-I, surface area 155 m^2/g

When Davisil silica gel was used, the maximum yield obtained was 20% for a 2-day reaction time where a ratio of 5 equivalents of 3,4,6-tri-*O*-benzyl-D-glucal (**81b**) to one of N-H heterodiene precursor **119** were used. Again, preheating the silica gel overnight did not improve the yield. A 2:1 of **81b**:**119** ratio at a longer reaction time also yielded 20% of the desired cycloadduct **120**. When TLC silica gel was used, the yield was about 11%. Other solids (Montmorillonite K10 and aluminum oxide) were also tested, but the results were not successful.

When the cycloaddition reaction was carried out at room temperature, without the use of silica gels and at normal atmospheric pressure, the best result was obtained when methylene chloride was used as the sole solvent without any base added. However, the yield of the cycloadduct **120** was at best 9.4%.

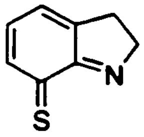
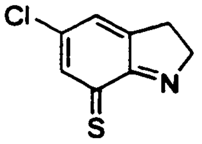
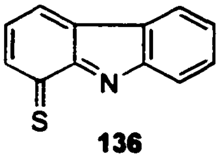
D. Studies on Cycloaddition between 3,4,6-Tri-*O*-benzyl-D-glucal (81b) and N-H Heterodiene Precursor 128

1. LUMO-HOMO Semi-empirical AM1 Calculations

Even though the cycloaddition in part C above did proceed, the yield was not satisfactory. Other heterodiene systems should be explored.

Semi-empirical AM1 calculations of the LUMO's and HOMO's of three different heterodienes are summarized in Table 5. The HOMO-LUMO gap between 3,4,6-tri-*O*-benzyl-D-glucal (**81b**) and heterodiene **129** is 7.43 eV, which is less than that for the gap between **81b** and **85** (7.62 eV). It appeared reasonable to perform the cycloaddition reaction of the precursor to heterodiene **129** with 3,4,6-tri-O-benzyl-D-glucal (**81b**).

Table 5. Semi-empirical AM calculations of LUMO and HOMO.

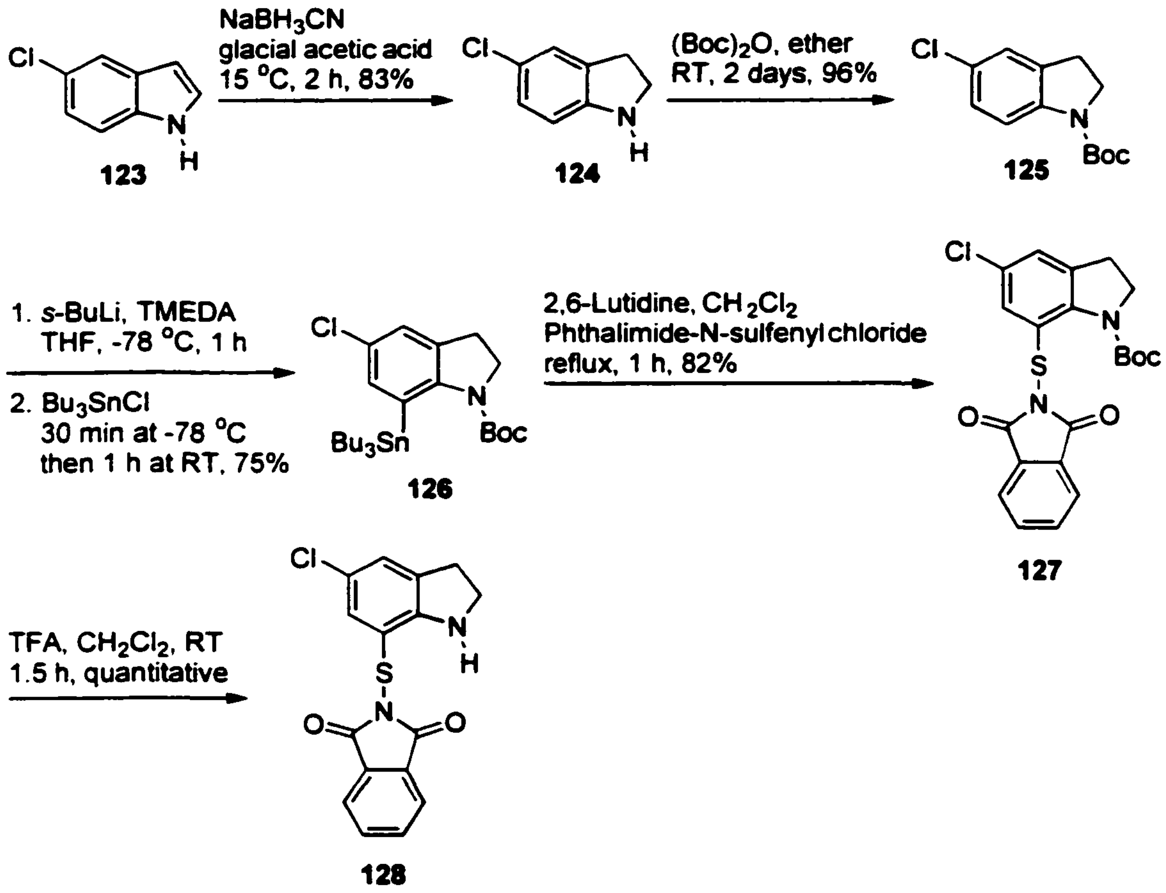
Entry	Heterodiene	HOMO (eV)	LUMO (eV)	HOMO[a] (eV)	HOMO-LUMO gap[b] (eV)
1	 **85**	-8.57	-1.80	-9.42	7.62
2	 **129**	-8.72	-1.99	-9.42	7.43
3	 **136**	-8.73	-2.26	-9.42	7.16

[a] HOMO of 3,4,6-Tri-O-benzyl-D- glucal (**81b**).

[b] HOMO of 3,4,6-Tri-O-benzyl-D- glucal (**81b**), LUMO of heterodiene.

2. Preparation of Key Starting Material 128

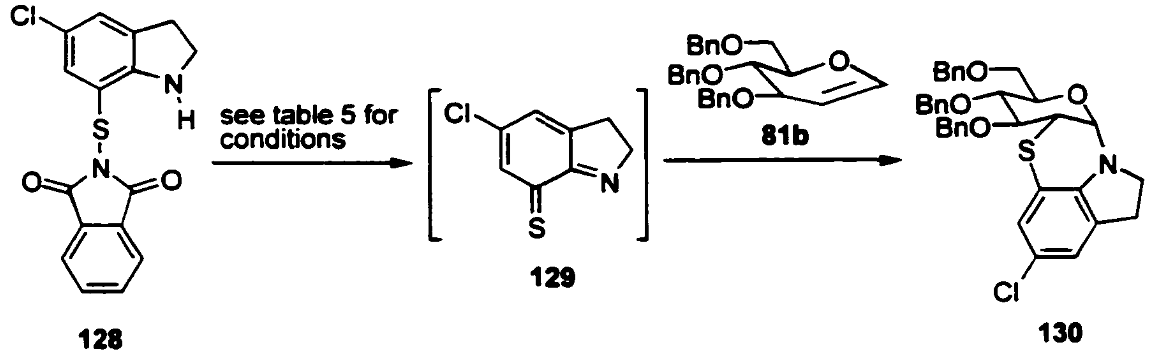
5-Chloro-7-Phthalimide-N-sulfenylindoline (**128**) was prepared using the same sequence for the preparation of **119** (Scheme 36).



Scheme 36. Preparation of Key Starting Material **128**

3. Cycloaddition between 3,4,6-Tri-*O*-benzyl-D-glucal (81b) and N-H Heterodiene Precursor 128

Cycloaddition between 5-Chloro-7-Phthalimide-N-sulfenylindoline (**128**) and 3,4,6-tri-*O*-benzyl-D-glucal (**81b**) was performed and is summarized in Table 6 (Scheme 37).



Scheme 37. Cycloaddition between 3,4,6-Tri-O-benzyl-D-glucal (**81b**) and N-H heterodiene precursor **128**

Table 6. Summary of cycloaddition reaction between 3,4,6-tri-O-benzyl-D-glucal (**81b**) and N-H heterodiene precursor **128**.

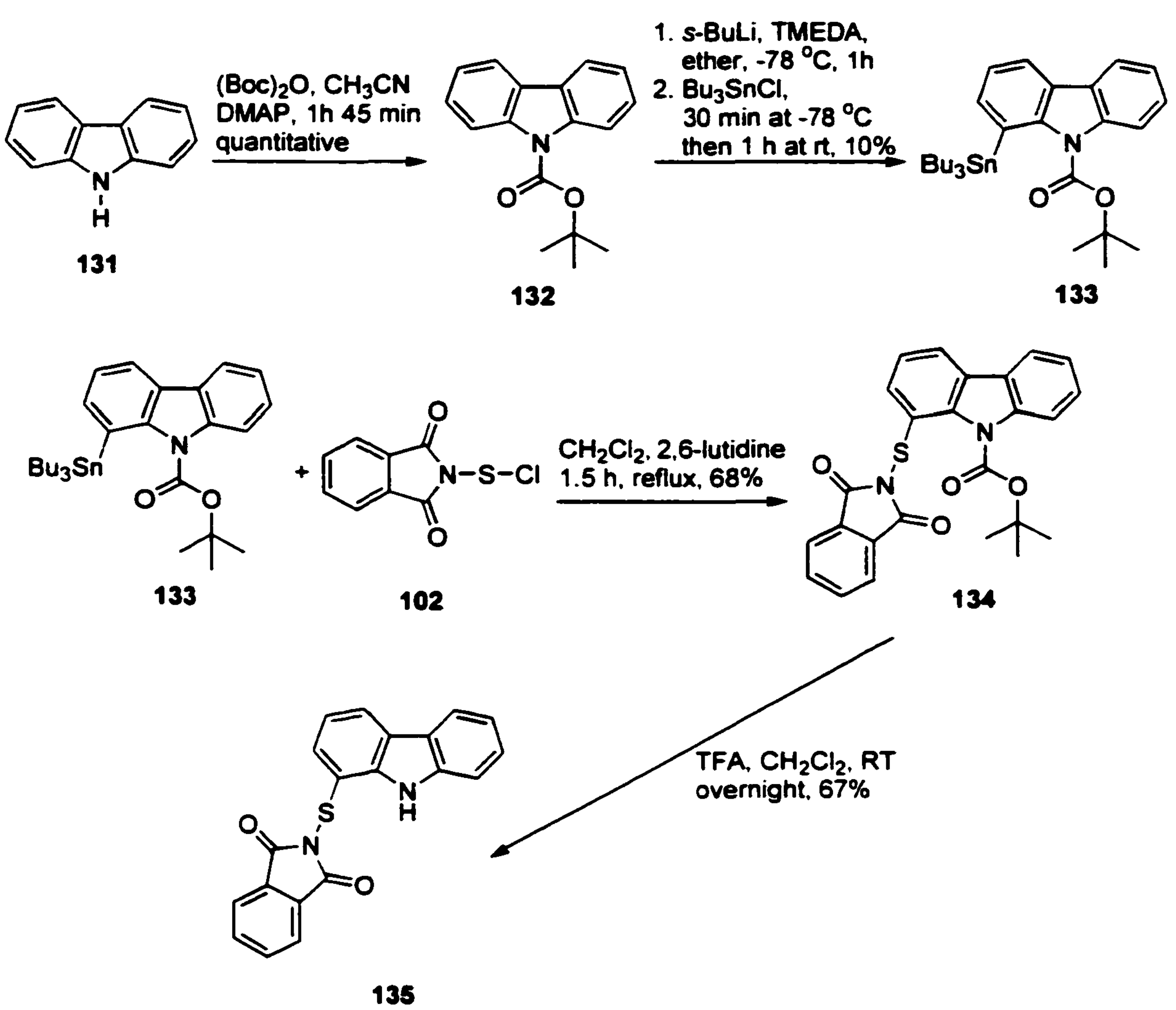
Entry	TBG:128	Solvent	Temp, °C	time	yield %
1	2:1	CH_2Cl_2	Reflux	1 day	58
2	2:1	CH_2Cl_2	Reflux	1 day	53
3	2:1	CH_2Cl_2	Reflux	7 days	39
4	2:1	CH_2Cl_2	Reflux	12 days	39
5	5:1	CH_2Cl_2	Reflux	14 days	17
6	2:1	$CHCl_3$	Reflux	7days	5.6
7	2:1	THF	Reflux	67 hours	Trace

The yield of the cycloaddition reaction between 3,4,6-tri-O-benzyl-D-glucal (**81b**) and N-H heterodiene precursor **128** was more respectable than the one between 3,4,6-Tri-O-benzyl-D-glucal (**81b**) and N-H heterodiene precursor **119**. The best condition for this reaction was refluxing both starting materials in methylene chloride for 1 day. Increasing the reaction time decreased the yield. Other solvents ($CHCl_3$ and THF) that were tried were not as successful as methylene chloride. The electron-withdrawing effect of the chlorine at the C-5 position on the indoline increased the reactivity of the cycloaddition, as predicted by our simple FMO calculations.

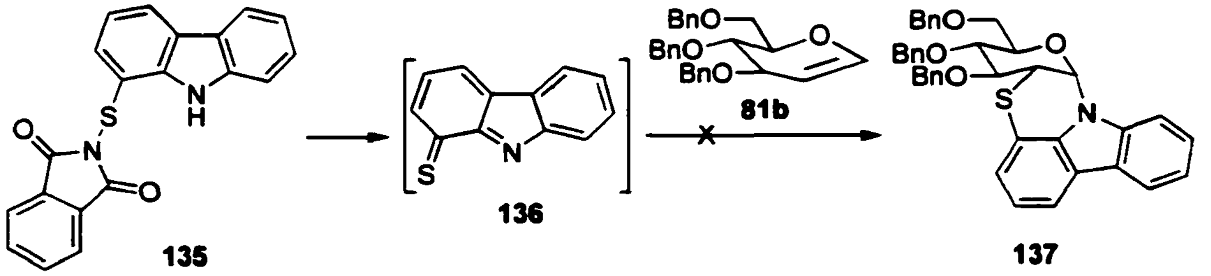
E. Cycloaddition Between 3,4,6-Tri-*O*-benzyl-D-glucal (81b) and N-H Heterodiene Precursor 135

From Table 5, it was conceivable that the cycloaddition could be extended to heterodiene **136**, and that the cycloaddtion could react more readily than that in the first two cases. The gap between the HOMO of 3,4,6-tri-*O*-benzyl-D-glucal (**81b**, HOMO = -9.42 eV) and the LUMO of carbazolethione (**136**, -2.26 eV) is 7.16 eV, which is smaller than those of the other two (Table 4, entries 1 and 2).

Heterodiene precursor 2-carbazolylthioisoindoline-1,3-dione (**135**)[38], which was prepared by deprotection of Boc of *tert*-butyl-1-(1,3-dioxoisoindolin-2-ylthio)carbazole-9-carboxylate (**134**, Scheme 38), was allowed to react with 3,4,6-tri-*O*-benzyl-D-glucal (**81b**, Scheme 39). Unfortunately, no cycloadduct was observed.



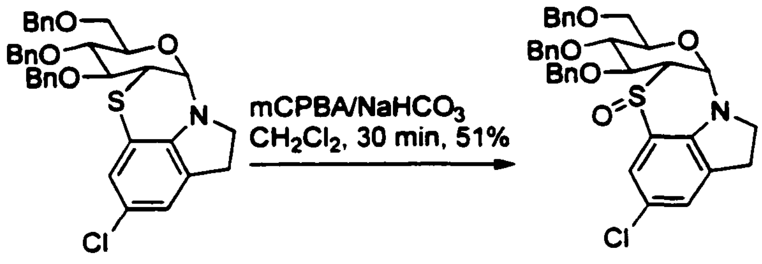
Scheme 38. Preparation of 2-carbazolylthioisoindoline-1,3-dione (**135**).



Scheme 39. Attempted cycloaddition between 3,4,6-tri-O-benzyl-D-glucal (**81b**) and N-H heterodiene precursor **135**.

F. Oxidation of Cycloadduct 130 to Sulfoxide Cycloadduct 138.

Attempted oxidation of cycloadduct **130** using mCPBA, MMPP, or $NaIO_4$[39] failed to produce the sulfone cycloadduct. Instead, oxidation stopped at the sulfoxide stage. Mass spectroscopy showed the presence of **138**, showing peaks at 616 ($M+H^+$) and 638 ($M+Na^+$). Infrared spectroscopy also indicated the presence of compound **138**. A strong IR peak at 1032.9 cm^{-1} is indicative of a sulfoxide.



130 **138**

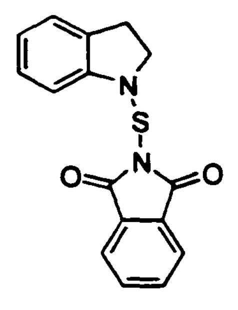
Scheme 40. Oxidation of cycloadduct **130** to sulfoxide cycloadduct **138**.

III. Conclusion

A new glycosidation approach for the construction of indole-N-glycoside linkage has been developed. The key reaction involves an inverse electron demand Diels-Alder cycloaddition reaction, which proceeds *via* an *ortho*-thiono-imino-quinone intermediate **85**. When chlorine was present at C-5 of the *ortho*-thiono-imino-quinone **129**, the cycloaddition reaction yield improved.

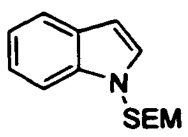
IV. Experimental

All reactions were carried out under a dry argon/nitrogen atmosphere at ambient temperature unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} (E. Merck) plates unless otherwise stated, and short/long wave ultraviolet (UV) light was used to visualize the spots. Flash column chromatography was carried out on silica gel 60 (230-400 mesh). Chromatotron (radial chromatography) plates were prepared by using Kiesegel 60 F_{254} gipshaltig (E. Merck). Petroleum ether, dichloromethane, and ethyl acetate used as eluting solvents were ACS reagent grade. Molecular sieves (Aldrich Chemical Co.) were activated by heating in an oven (>100 °C) overnight or by heating them with a Bunsen burner under high vacuum. The following reaction solvents were purified and dried by using standard distillation procedures: tetrahydrofuran (THF, refluxing over sodium metal with benzophenone as indicator), ether (refluxing over sodium metal with benzophenone as indicator), and methylene chloride (CH_2Cl_2, refluxing over P_2O_5. NMR spectra were measured on a GE QE (300 MHz) instrument with $CDCl_3$ as the solvent unless otherwise stated. Chemical shifts were reported in δ units, and coupling constants in Hz. Tetramethylsilane (TMS, δ 0.0ppm) was used as an internal reference for spectra measured in $CDCl_3$. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer. Melting points were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, New Jersey.



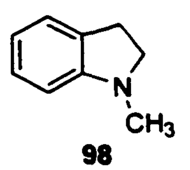
92

92) 2-Indolinylthioisoindoline-1,3-dione. To a stirred solution of indoline (0.056 mL, 0.50 mmol, 2.0 eq) in dry acetonitrile (1mL) was added BSA (0.062 mL, 0.25 mmol, 1.0 eq) and the reaction mixture was stirred for 1 hour at room temperature. After concentration, phthalimide-N-sulfenyl chloride (125 mg, 0.583 mmol, 1.2 eq, in 2.5 mL CH_3Cl) was then added. The reaction mixture was allowed to stir for 20 more minutes at room temperature. The reaction mixture was separated using a 1-mm chromatotron plate (pre-developed with BSA) affording 46.3 mg (31%) of 1-phthalimide-N-sulfenylindoline. R_f 0.44 (CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 3.01 (2H, broad, H-3), 3.94 (1H, broad, H-2), 4.14 (1H, broad, H-2), 6.82 (1H, t, H-5), 7.03 (1H, d, H-4), 7.22 (1H, t, H-6), 7.62 (1H, d, H-7), 7.7-7.9 (4H, m, phth-H).

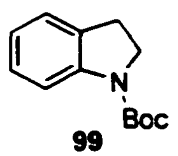


95

95) 1[[2-(Trimethylsilyl)ethoxy]methyl]indole. To a stirred suspension of sodium hydride (60% in mineral oil, 0.450 g, 11.2 mmol, 1.1 eq) in anhydrous THF (10 mL) was added indole (1.17 g, 9.99 mmol, 1.0 eq, in THF) dropwise at 0 °C. When hydrogen evolution had stopped, [2-(trimethylsilyl)ethoxy]methyl chloride (SEMCl, 1.77 mL, 10.0 mmol, 1.0 eq) was added droprwise. The reaction mixture was warmed up to room temperature and stirred for 1 hour. The mixture was poured into 10% ice-cold sodium bicarbonate solution and the two layers were separated. The aqueous layer was washed with ether (3 x 30 mL), and the extract was dried over anhydrous magnesium sulfate. The solvent was removed with a rotary evaporator. After column chromatography (5% ethyl acetate/pet. ether), an oil was obtained (0.984 g, 40%). R_f 0.47 (10% ethyl acetate/pet. ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.077 (9H, s, $Si(CH_3)_3$), 0.88 (2H, t, J = 8.1 Hz, CH_2Si, 3.46 (2H, t, J = 8.1 Hz, OCH_2), 5.46 (2H, s, NCH_2O), 6.52 (1H, d, J = 3.0 Hz, H-3), 7.16 (1H, d, J = 3 Hz, H-2), 7.14 (1H, t, aryl), 7.24 (1H, t, aryl), 7.49 (1H, d, aryl), 7.63 (1H, d, aryl).

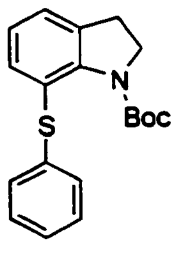

98

98) Reduction of 1[[2-(Trimethylsilyl)ethoxy]methyl]indole. Sodium cyanoborohydride (0.764 g, 12.2 mmol, 3.1 eq) was added in one portion at 11 °C to a solution of indole (0.984 g, 3.98 mmol, 1.0 eq) in glacial acetic acid (10.4 mL). After stirring for 2 hours at 15 °C, the mixture was poured into distilled water (50 mL) and was cooled in an ice bath. Sodium hydroxide pellets were added to make the mixture strongly basic. The mixture was extracted with ether (4 x 50 mL). The combined ether layers were extracted with water, brine (2 x 50 mL), then was dried over anhydrous sodium sulfate. The mixture was then concentrated using the rotary evaporator, pumped under high vacuum to give 0.384 g of the crude product (1-methylindoline, 72% yield according to the crude mass). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (3H, s, CH_3), 3.00 (2H, t, J = 8.1 Hz, H-3), 3.35 (2H, t, J = 8.1 Hz, H-2), 6.55 (1H, d, J = 8.1 Hz, aryl), 6.73 (1H, t, J = 7.2 Hz, aryl), 7.15 (2H, m, aryl).



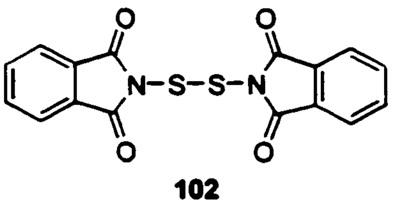
99

99) 1-(*tert*-Butoxycarbonyl)indoline. To a stirred solution of indoline (1.7 mL, 15 mmol1.0 eq) in THF (18 mL) was added di-*tert*-butyldicarbonate (3.7 mL, 16 mmol, 1.1 eq). The reaction mixture was stirred overnight (25 1/3 h) at room temperature and the solvent was removed with a rotary evaporator. The residual liquid was distilled under reduced pressure (Kugelrohr distillation) to give the product as a colorless oil (3.14 g, 94%), bp 148 °C (oven temperature)/0.20-0.15 mmHg, which on standing solidifies. R_f 0.5 (20% ethyl acetate/petroleum ether); mp 44-45 °C (lit. 42-45 °C[30]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (9H, s, *t*-Bu), 3.09 (2H, t, J = 8.7 Hz, H-3), 3.97 (2H, t, J = 8.7 Hz, H-2), 6.92 (1H, t, J = 7.5 Hz, H-5), 7.13-7.18 (2H, m, H-4, H-6), 7.3-7.8 (1H, broad, H-7); ^{13}C NMR (300 MHz, $CDCl_3$) δ 27.4, 28.6, 47.7, 80.7, 114.7, 122.1, 124.7, 127.3, 131.2, 142.5, 152.6; IR (KBr, cm^{-1}) 1703.7.



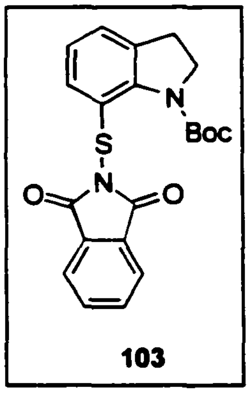
101

101) 1-(*tert*-Butoxycarbonyl)-7-phenylthioindoline. Under an argon (or nitrogen) atmosphere, a 1.3 M solution of *s*-BuLi in cyclohexane (1.2 mL, 1.6 mmol, 1.3 eq) was added dropwise to a stirred solution of 1-(*tert*-butoxycarbonyl)indoline (*tert*-butylindoline carboxylate, 0.27 g, 1.2 mmol, 1.0 eq) and TMEDA (0.25 mL, 1.7 mmol, 1.4 eq, dry) in 6 mL of ether at -78 °C. A yellow-orange mixture was formed. After stirring for 1 hour, phenyl disulfide (0.40 g, 1.8 mmol, 1.5 eq) was added as an ether (2 mL) solution *via* a syringe. The reaction mixture was stirred for 30 minutes at -78 °C, then the dry ice-acetone bath was removed and the reaction mixture was stirred for an additional 1 hour. The reaction mixture was quenched with water and the products were extracted with ether (4 x 10 mL). The combined ether extracts were washed with water (50 mL) and then with saturated NaCl solution (50 mL), dried over Na_2SO_4, and evaporated. Separation was performed using a 2-mm chromatotron plate (2-10% ethyl acetate in petroleum ether) to give a white solid after removal of the solvent (0.24 g, 60%). R_f 0.29 (10% ethyl acetate in petroleum ether; 0.55 in CH_2Cl_2); mp 114-116 °C (lit. 114-115 °C[30a]); ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (9H, s, *t*-Bu), 3.04 (2H, t, J = 7.8 Hz, H-3), 4.14 (2H, t, J = 7.8 Hz, H-2), 6.87 (1H, dd, J = 7.8 Hz, 7.0 Hz, H-5), 6.92 (1H, dd, J = 7.8 Hz, 0.9 Hz, H-6), 7.02 (1H, dd, J = 7.0 Hz, 0.9 Hz, H-4), 7.20-7.30 (3H, m, SPh), 7.30-7.36 (2H, m, SPh); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.6, 29.9, 51.0, 81.7, 122.5, 124.9, 127.2, 129.1, 130.5, 132.4, 134.7, 137.3, 142.6, 154.0.



102

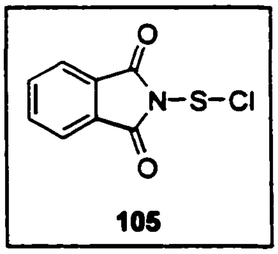
102) N,N'-Dithiobis(phthalimide). Into an ice-chilled suspension of potassium phthalimide (73.3 g, 0.396 mmol, 2.1 eq) in dry methylene chloride (400 mL) was added a solution of sulfur monochloride (15.2 mL, 0.190 mmol, 1.0 eq) in dry methylene chloride (15 mL) *via* a dropping funnel over 5 minutes. The mixture was stirred mechanically. After stirring for 10 minutes at 0 °C, the mixture was allowed to warm to room temperature and stirred overnight (~18 h). The mixture was filtered using methylene chloride and the filtrate was concentrated to give a yellow solid. After recrystalization from chloroform (450 mL), a white solid was obtained (29.5 g, 42%); mp 226-230 °C (lit. 229-230 °C[31]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8-7.9 (8H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 124.6, 132.5, 135.2, 166.8.



103

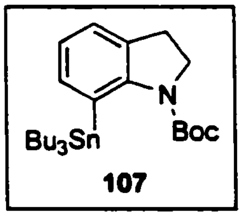
103) ***tert*-Butyl-7-(1,3-dioxoisoindolin-2-ylthio)indoline carboxylate.** To a stirred solution of 1-(*tert*-butoxycarbonyl)-7-tributylstannyl indoline (0.27 g, 0.53 mmol, 1.0 eq) and 2,6-lutidine (0.1 mL, 0.86 mmol, 1.6 eq) in methylene chloride (1 mL, dry) was added phthalimide-N-sulfenyl chloride (0.57 g, 2.3 mmol, 4.3 eq). After stirring for 2.5 hours at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, separated, and the aqueous layer was washed with CH_2Cl_2. The CH_2Cl_2 layers were combined, washed with potassium fluoride solution (10 g KF/100 mL H_2O solution), dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. Purification was done using silica gel column chromatography (20% ethyl acetate/petroleum ether) (0.20 g, 94%). R_f 0.37 (30% ethyl acetate/petroleum ether); mp ~140 °C (decomposition); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (9H, s, *t*-Bu), 3.07 (2H, t, J = 8.1 Hz, H-3), 4.15 (2H, t, J = 8.1 Hz, H-2), 6.86 (1H, t, J = 7.5 Hz, H-5), 6.93 (1H, d, J = 7.5 Hz, H-4), 6.99 (1H, d, J = 6.9 Hz, H-6), 7.76-7.79 (4H, m, Phth-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.5, 29.4, 49.5, 82.3, 123.3, 125.5, 124.0, 125.2, 126.1, 132.5, 133.7, 134.5, 140.5, 154.7, 168.6; IR (KBr, cm^{-1}) 1734.8; MS Calcd for $C_{21}H_{20}N_2O_4S$:

396.1144. Found: *m/z* 397 (M+H$^+$), 414 (M+NH$_4^+$); *Anal.* Calcd for $C_{21}H_{20}N_2O_4S$: C, 63.62; H, 5.08; N, 7.07; S, 8.09. Found: C, 62.85; H, 5.05; N, 6.80; S, 8.00.



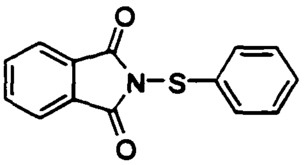
105

105) Phthalimide-N-sulfenyl chloride. To a stirred solution of N,N'-dithiobis(phthalimide) (6.81 g, 19.1 mmol, 1.0 eq, in 250 mL of dry CH_2Cl_2) was added pyridine (0.04 mL, 0.49 mmol, 0.026 eq, dry) and sulfuryl chloride (10.0 mL, 124 mmol, 6.5 eq) *via* a syringe. After stirring for 2 days (48 h) at room temperature, the reaction mixture was concentrated with a rotary evaporator, affording a yellow solid (7.08 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.8-8.1 (8H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 125.1, 132.0, 136.0, 165.6.



107

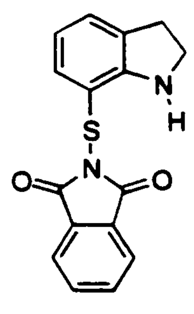
107) 1-(*tert*-Butoxycarbonyl)-7-tributylstannylindoline. Under an argon atmosphere, a 1.3 M solution of *s*-BuLi in cyclohexane (3.0 mL, 3.9 mmol, 1.3 eq) was added dropwise to a stirred solution of 1-(*tert*-butoxycarbonyl)indoline (0.66 g, 3.0 mmol, 1.0 eq) and TMEDA (0.59 mL, 3.9 mmol, 1.3 eq, dry) in 15 mL of ether at -78 °C. After stirring for 1 hour, Bu_3SnCl (4.6 mmol, 1.5 eq) was added as a neat liquid *via* a syringe. After stirring for another 30 minutes at -78 °C, the reaction mixture was removed from the dry ice-acetone bath and was allowed to stir for an additional 1 hour. The reaction mixture was quenched with water and the products were extracted with ether. The combined ether extracts were washed with water and then with saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated. This compound was purified by basic alumina column chromatography (petroleum ether) to give a colorless oil (73%). R_f 0.58 (petroleum ether, on neutral alumina), ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (9H, t, J = 7.2 Hz, $-CH_3$ of Bu), 0.97 (6H, m, $-CH_2-$ of Bu), 1.32 (6 H, sextet, J = 7.2 Hz, $-CH_2-$ of Bu), 1.4-1.6 (6H, m), 1.51 (9H, s, *t*-Bu), 3.00 (2H, t, J = 8.4 Hz, H-3), 3.96 (2H, t, J = 8.4 Hz, H-2), 6.93 (1H, t, J = 7.2 Hz, H-5), 7.10 (1H, dd, J = 7.5 Hz, 1.2 Hz, H-4), 7.32 (1H, dd, J = 6.6 Hz, 1.2 Hz, H-6); ^{13}C NMR (300 MHz, $CDCl_3$) 13.2, 14.0, 27.9, 28.2, 28.8, 29.6, 48.2, 80.7, 122.8, 124.5, 130.5, 131.5, 136.6, 149.2, 153.7; IR (KBr, cm^{-1}) 1693.8; MS Calcd for $C_{25}H_{43}NO_2Sn$: 507.2312. Found *m/z* 506.1 (36), 507.2 (31), 508.1 (71), 509.1 (38), 510.2 (98), 511.2 (25), 512.2 (15), 513.2 (6), 514.2 (14).



108

108) N-Phenylmercaptophthalimide. Method a) To a solution of phenyldisulfide (0.22 g, 1.0 mmol, 1.0 eq) in dry benzene (2 mL) was added N-bromophthalimide (2-bromoisoindoline-1,3-dione, 0.45 g, 2.0 mmol, 2.0 eq). The reaction mixture was refluxed for 30 minutes. The reaction mixture turned red. Cold hexane was added after allowing the reaction mixture to cool to room temperature. Light yellow precipitate formed. The reaction mixture was filtered and the residue was washed twice with cold hexane. The solid was recrystallized from ethanol (23.5 mg, 46%). R_f 0.60 (1:1 ethyl acetate/petroleum ether); mp 165-166 °C (lit. 165-166 °C[33]); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (3H, d, J = 2.1 Hz), 7.32 (2H, d, J = 1.8 Hz), 7.76-7.94 (4H, m); ^{13}C NMR (300 MHz, $CDCl_3$)

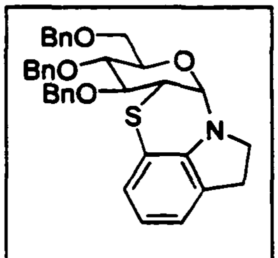
124.2, 129.4 (2 C's), 131.1, 132.2, 134.8, 135.2, 167.7; IR (KBr, cm^{-1}) 1731.6, 1707.2, 1281.6, 1054.3; MS Calcd for $C_{14}H_9NO_2S$: 255.0354. Found *m/z* 256 (M+H$^+$), 278 (M+Na$^+$). Method b) Phthalimide-N-sulfenyl chloride (29.8 mg, 0.139 mmol, 1.3 eq) was dissolved in 1 ml of deuterated chloroform in a vial. Phenyltrimethyltin (2-methyl-2-phenyl-2-stannapropane, 20 mL, 26.5 mg, 0.11 mmol, 1.0 eq) was then added to the vial. The reaction mixture was transferred to an NMR tube and a ^{1}H NMR spectrum was taken periodically to monitor the progress of the reaction. ^{1}H NMR and TLC analyses showed the formation of **2**. Column chromatography was done and the pure product was obtained in 33% yield (9.2 mg).



119

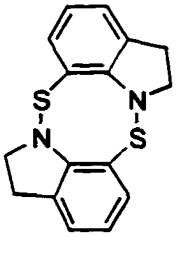
119) 2-Indolin-7-ylthioindoline-1,3-dione. To a solution of *tert*-butyl-7-(1,3-dioxoisoindolin-2-ylthio)indolinecarboxylate (**103**, 1.35 g, 3.40 mmol, 1.0 eq) in methylene chloride (25 mL) was added trifluoroacetic acid (2.6 mL, 34 mmol, 10 eq). After stirring for 2 hours at room temperature, the reaction mixture was quenched with saturated sodium carbonate solution. The aqueous layer was washed 4 times with methylene chloride and the organic layers were combined, dried over anhydrous sodium sulfate, concentrated, and after column chromatography (15% ethyl acetate/petroleum ether), the desired product was obtained (0.703 g, 70%). R_f 0.48 (20% ethyl acetate/petroleum ether); mp 160-170 °C (decomposition); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (2H, t, J = 8.5 Hz, H-3), 3.66 (2H, t, J = 8.5 Hz, H-2), 5.69 (1H, broad singlet, N-H), 6.52

(1H , t, J = 7.35 Hz, H-5), 7.08 (1H, d, J = 7.2 Hz, H-6), 7.47 (1H, d, J = 8.1 Hz, H-4), 7.72-7.89 (4H, m, Phth-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 30.8, 46.9, 110.8, 117.6, 124.1, 128.1, 130.5, 132.4, 134.7, 136.0, 156.7, 168.8; IR (KBr, cm-1) 3357.8 (broad), 1728.1, 1703.1; MS Calcd for $C_{16}H_{12}N2O_2S$: 296.0619. Found *m/z* 297 ($M+H^+$); *Anal.* Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82. Found: C, 64.97; H, 4.24; N, 9.35; S, 10.83.



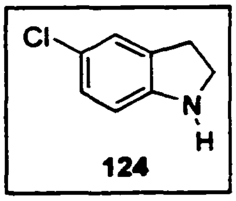
120

120) Method a) Cycloaddition between N-Boc heterodiene **103** and 3,4,6-tri-*O*-benzyl-D-glucal (**81b**). In a typical experiment, **103** and 3,4,6-tri-*O*-benzyl-D-glucal (1-5 eq) were dissolved in dry CH_2Cl_2. The appropriate silica gel (10 x mass of 3,4,6-Tri-*O*-benzyl-D-glucal) was then added. The solvent was then removed to dryness using a rotary evaporator. The flask containing the dry mixture of **103**, 3,4,6-Tri-*O*-benzyl-D-glucal, and silica gel was subject to low pressure by attaching it to a vacuum pump and heated to 50-55 °C for the desired reaction time. Method b) Cycloaddition between 2-indolin-7-ylthioindoline-1,3-dione (**119**) and 3,4,6-tri-*O*-benzyl-D- glucal (**81b**). When silica gel was used, the procedure was the same as that for the cycloaddtition between **103** and 3,4,6-Tri-*O*-benzyl-D-glucal. When no silica gel was used, the procedure was as follow: 2-Indolin-7-ylthioindoline-1,3-dione (**119**, 45 mg, 0.15 mmol, 1.0 eq) and 3,4,6-tri-*O*-benzyl glucal (127 mg, 0.31 mmol, 2.0 eq) were dissolved in methylene chloride (1 mL, dry) and stirred at room temperature for 3 days. The reaction mixture was concentrated and after separation on a 1-mm chromatotron plate, 8.1 mg (9%) of the cycloadduct was obtained. ^1H NMR (300 MHz, $CDCl_3$) δ 2.93 (2H, t, J = 9.5 Hz), 3.14 (1H, quartet, J = 10.1 Hz), 3.35 (1H, dd, J = 10.8 Hz, 3.6 Hz), 3.58 (1H, m), 3.73 (3H, m), 3.91 (1H, m), 4.11 (1H, m), 4.52 (2H, t, J = 11.1 Hz), 4.65 (1H, d, J = 12.3 Hz), 4.78 (1H, d, J = 10.5 Hz), 4.84 (1H, d, J = 10.8 Hz), 4.90 (1H, d, J = 3.6 Hz), 5.00 (1H, d, J = 10.2 Hz), 6.66 (1H, t, J = 7.5 Hz), 6.86 (2H, t, J = 8.7 Hz), 7.12-7.73 (15 H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.37, 46.38, 51.20, 69.11, 69.77, 71.80, 73.84, 75.27, 79.63, 81.44, 82.31, 112.15, 120.43, 121.21, 123.57, 127.92, 127.98, 128.06, 128.14, 128.24, 128.32, 128.61, 129.23, 130.23, 138.27, 138.39, 145.11; MS Calcd for $C_{35}H_{35}NO_4S$: 565.2282. Found m/z 566 ($M+H^+$), 434 (TBG + NH_4^+); *Anal.* Calcd for $C_{35}H_{35}NO_4S$: C, 74.31; H, 6.24; N, 2.48; S, 5.67. Found: C, 74.03; H, 6.28; N, 2.35; S, 5.60.

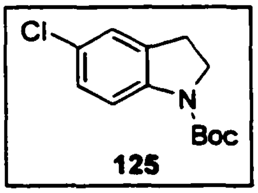


121

121) ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (2H, m), 3.06 (2H, m), 3.69 (4H, m), 6.64 (2H, t, J = 7.5 Hz), 7.03 (2H, d, J = 7.2 Hz), 7.23 (2H, d, J = 7.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 29.1, 58.1, 118.6, 119.4, 127.2, 132.3, 135.9, 151.4; IR (KBr, cm-1) 739.1, 768.0, 948.8, 1057.7, 1216.9, 1244.2, 1418.2, 1592.1; MS Calcd for $C_{16}H_{14}N_2S_2$: 298.0598. Found *m/z* 299 ($M+H^+$).

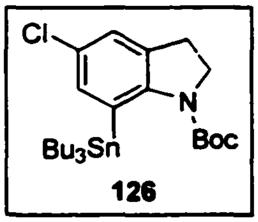

124

124) 5-Chloroindoline. 5-Chloroindole (253 mg, 1.67 mmol, 1.0 eq) was dissolved in glacial acetic acid (2.7 mL). Sodium cyanoborohydride (207 mg, 95%, 3.30 mmol, 2.0 eq) was added in one portion at 15 °C. After stirring at 15 °C for 2 hours, the reaction mixture was poured into water. The mixture was cooled in an ice bath and sodium hydroxide pellets were added until the solution turned basic (blue to litmus paper). The mixture was washed with ether (4 x 15 mL), then with brine (2 x 50 mL). The ether layers were combined and dried over anhydrous sodium sulfate, filtered, and concentrated. Silica gel chromatography (8% ethyl acetate/petroleum ether) was performed and the desired product was obtained in 83% yield (212 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.01 (2H, t, J = 8.4 Hz, H-3), 3.56 (2H, t, J = 8.4 Hz, H-2), 3.71 (1H, broad singlet, N-H), 6.53 (1H, d, J = 8.1 Hz, H-7), 6.95 (1H, dd, J = 8.4 Hz, 2.1 Hz, H-6), 7.05 (1H, d, J = 0.9 Hz, H-4).


125

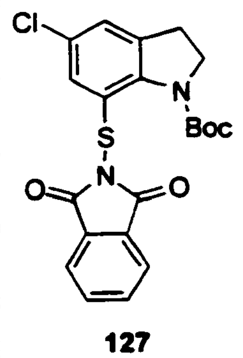
125) 1-(*tert*-Butoxycarbonyl)-5-chloroindoline. A mixture of 5-chloroindoline (0.21 g, 1.4 mmol, 1.0 eq) and di-*tert*-butyl dicarbonate (0.38 mL, 1.7 mmol, 1.2 eq) in ether (5 mL) was stirred overnight at room temperature for 2 days. After silica gel column chromatography (2.5 % ethyl acetate/petroleum ether), 0.34 g (96%) of the desired product was obtained. R_f 0.58 (20% ethyl acetate/petroleum ether); mp 129-130 °C (lit. 130-130.5 °C)[30a]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (9H, s, *t*-Boc), 3.05 (2H, t, J = 8.7 Hz, H-3), 3.97 (2H, t, J = 8.7 Hz, H-2), 7.08 (1H, s, H-6), 7.09 (1H, d, J = 8.4 Hz, H-4), 7.73 (1H, broad singlet, H-7); ^{13}C NMR (300 MHz,

$CDCl_3$) δ 27.4, 28.7, 48.0, 81.0, 115.6, 124.9, 127.1, 127.3, 133.0, 142.0, 152.4; IR (KBr, cm^{-1}) 1707.8, 1479.8, 1390.0, 1329.9, 1255.6, 1142.0, 1019.5, 873.6, 823.2, 762.5.



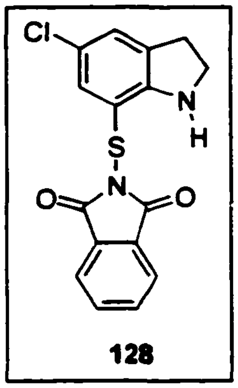
126

126) 1-(*tert*-Butoxycarbonyl)-7-tributylstannyl-5-chloroindoline. Under an inert (N_2) atmosphere, a 1.3 M solution of *s*-BuLi in cyclohexane (2.0 mL, 2.6 mmol, 1.7 eq) was added dropwise to a stirred solution of 1-(*tert*-butoxycarbonyl)-5-chloroindoline (0.38 g, 1.5 mmol, 1.0 eq) and TMEDA (0.30 mL, 2.0 mmol, 1.3 eq, dry) in 15 mL of THF at -78 °C. After stirring for 1 hour, Bu_3SnCl (0.81 mL, 3.0 mmol, 2.0 eq) was added as a neat liquid *via* a syringe. After stirring for another 30 minutes at -78 °C, the reaction mixture was allowed to warm to room temperature and stirred for an additional 1 hour. The reaction mixture was quenched with water and the products were extracted with ether. The combined ether extracts were washed with water and then with saturated NaCl solution, dried over anhydrous sodium sulfate, and evaporated. This compound was purified by basic alumina column chromatography (petroleum ether) to give a colorless oil (75%). ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (9H, t, J = 7.2 Hz, CH_3 of Bu), 0.98 (6H, t, J = 8.2 Hz, $-CH_2-$ of Bu), 1.31 (6 H, sextet, J = 7.2 Hz, $-CH_2-$ of Bu), 1.4-1.6 (6H, m, $-CH_2-$ of Bu), 1.51 (9H, s, CH_3 of *t*-Bu), 2.97 (2H, t, J = 8.4 Hz, H-3), 3.96 (2H, t, J = 8.4 Hz, H-2), 7.05 (1H, d, J = 1.5 Hz, H-4), 7.24 (1H, d, J = 2.1 Hz, H-6). ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.3, 13.9, 27.7, 28.0, 28.7, 29.4, 48.3, 81.1, 124.5, 128.4, 132.7, 133.5, 135.8, 147.8, 153.7. IR (KBr, cm^{-1}) 1694.0.



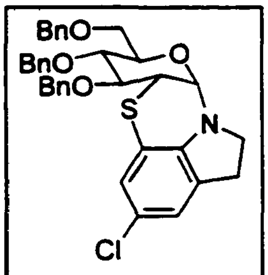
127

127) *tert*-Butyl-7-(1,3-dioxoisoindolin-2-ylthio)-5-chloroindolinecarboxylate. To a stirred solution of 1-(*tert*-butoxycarbonyl)-5-chloro-7-tributylstannylindoline (**126**, 0.18 g, 0.32 mmol, 1.0 eq) and 2,6-lutidine (0.38 mL, 0.33 mmol, 1.0 eq) in methylene chloride (2 mL, dry) under reflux was added phthalimide-N-sulfenyl chloride (0.19 g, 75% pure, 0.67 mmol, 2.1 eq, in 3 mL of dry methylene chloride). After stirring for 1 hour with reflux, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, separated, and the aqueous layer was washed with CH_2Cl_2. The CH_2Cl_2 layers were combined, washed with potassium fluoride solution (10 g KF/100 mL H_2O solution), dried over anhydrous sodium sulfate, and concentrated with a rotary evaporator. Purification was done using silica gel column chromatography (20% ethyl acetate/petroleum ether) (0.11 g, 82%). R_f 0.54 (1:1 ethyl acetate/pet. ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (9H, s, *t*-Bu), 3.06 (2H, t, J = 8.1 Hz, H-3), 4.15 (2H, t, J = 8.1 Hz, H-2), 6.88 (1H, d, J = 1.5 Hz, H-4), 6.97 (1H, d, J = 1.5 Hz, H-6), 7.77-7.95 (4H, m, Phth-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.6, 29.4, 49.7, 82.7, 123.6, 124.2, 124.9, 127.4, 130.0, 132.3, 134.8, 135.4, 139.2, 154.5, 168.2; MS Calcd for $C_{21}H_{19}ClN_2O_4S$: 430.0754. Found *m/z* 453 ($M+Na^+$).



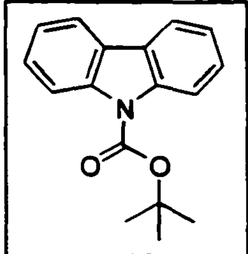
128

128) 2-(5-Chloroindolin-7-ylthio)isoindoline-1,3-dione. To a solution of *tert*-butyl-7-(1,3-dioxoisoindolin-2-ylthio)-5-chloroindolinecarboxylate (**127**, 0.43 g, 0.99 mmol, 1.0 eq) in methylene chloride (18 mL) was added trifluoroacetic acid (1.5 mL, 19 mmol, 19 eq) *via* a syringe in one portion. After stirring for 1.5 hours at room temperature, the reaction mixture was quenched with saturated aqueous sodium carbonate solution (saturated). The aqueous layer was washed 3 times with methylene chloride and the organic layers were combined, dried over anhydrous sodium sulfate, concentrated, and after column chromatography (20-25% ethyl acetate/pet. ether), quantitative yield of the desired product was obtained; ^{1}H NMR (300 MHz, CDCl$_3$) δ 3.05 (2H, t, J = 8.5 Hz. H-3), 3.68 (2H, t, J = 8.5 Hz, H-2), 5.67 (1H, s, N-H), 7.01 (1H , s, H-4), 7.45 (1H, s, H-6), 7.73-7.90 (4H, m, Phth-H); ^{13}C NMR (300 MHz, CDCl$_3$) δ 30.2, 47.2, 110.9, 121.2, 124.1, 128.3, 132.2, 132.3, 134.4, 134.7, 155.3, 168.5; *Anal.* Calcd for $C_{16}H_{11}ClN_2O_2S$: C, 58.09; H, 3.35; Cl, 10.72; N, 8.47; S, 9.69. Found: C, 57.89; H, 3.36; Cl, 11.14; N, 8.28; S, 9.29; MS Calcd for $C_{16}H_{11}ClN_2O_2S$: 330.0230. Found m/z 331 (M+H$^+$), 353 (M+Na$^+$).



130

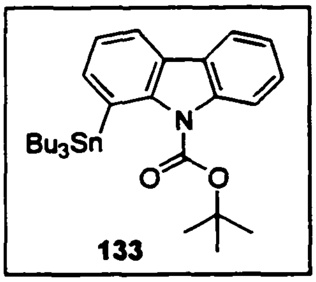
130) Cycloaddition between 2-(5-chloroindolin-7-ylthio)isoindoline-1,3-dione (**128**) and 3, 4, 6-tri-*O*-benzyl-D-glucal (**81b**). A typical experiment: 2-(5-chloroindolin-7-ylthio)isoindoline-1,3-dione (**128**, 66.5 mg, 0.201 mmol, 1.0 eq) and 3,4,6-tri-*O*-benzyl-D-glucal (168.8 mg, 0.405 mmol, 2.0 eq) were dissolved in methylene chloride (2 mL, dry) and stirred under reflux for 1 day. The reaction mixture was concentrated and after silica gel column chromatography (pet ether to 5% ethyl acetate/pet ether), 70.4 mg (58%) of the cycloadduct was obtained. R_f 0.41 (20% ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (2H, t, J = 10.4 Hz), 3.15 (1H, quartet, J = 10.3 Hz), 3.33 (1H, dd, J = 10.8 Hz, 3.5 Hz), 3.58 (1H, t, J = 8.25 Hz), 3.72 (3H, m), 3.86 (1H, t, J = 9.7 Hz), 4.09 (1H, t, J = 7.8 Hz), 4.51 (1H, d, J = 10.7 Hz), 4.55 (1H, d, J = 12.4 Hz), 4.64 (1H, d, J = 12.1 Hz), 4.79 (1H, d, J = 10.5 Hz), 4.83 (1H, d, J = 10.8 Hz), 4.87 (1H, d, J = 3.5 Hz), 4.96 (1H, d, J = 10.2 Hz), 6.81-7.41 (17 H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.23, 46.35, 51.31, 69.04, 71.94, 73.87, 75.34, 76.74, 79.62, 81.31, 82.10, 113.41, 121.48, 122.94, 124.85, 127.88, 127.99, 128.14, 128.26, 128.56, 128.63, 128.97, 131.50, 138.13, 138.18, 138.37, 143.68; *Anal.* Calcd for $C_{35}H_{34}NO_4S$: C, 70.04; H, 5.71; N, 2.33. Found: C, 69.10; H, 5.66; N, 2.14.



132

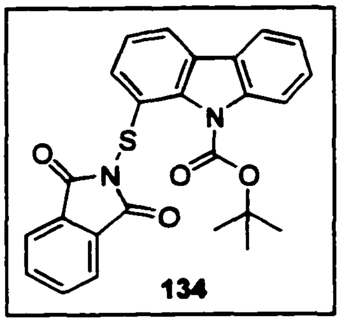
132) *tert*-Butylcarbazole-9-carboxylate. Carbazole (1.00 g, 5.99 mmol, 1.0 eq) was dissolved in dry acetonitrile(25 mL). Di-*tert*-butyldicarbonate (2.60 mL, 11.32 mmol, 1.9 eq) was added as a neat liquid. DMAP (0.735 g, 6.01 mmol, 1.0 eq) was added in one portion. The reaction mixture was stirred for 1h 45min. After column chromatography (2% ethyl acetate/ pet. ether), a colorless oil was obtained in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (9H, s, t-Bu), 7.34 (2H, t, J = 7.5 Hz), 7.46 (2H, t, J = 7.8 Hz), 7.96 (2H, d, J = 7.8 Hz), 8.30

(2H, d, J = 8.4 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.7, 84.1, 116.4, 119.7, 123.1, 125.9, 127.2, 138.7, 151.2.



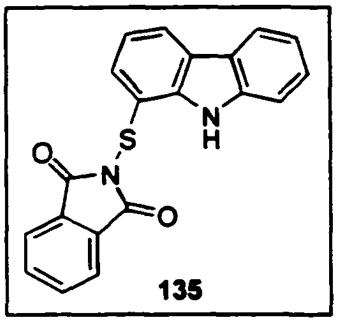
133

133) *tert*-Butyl-1-(1,1-dibutyl-1-stannapentyl)carbazole-9-carboxylate. Under an argon atmosphere, a 1.3 M solution of *s*-BuLi in cyclohexane (1.35 mL, 1.76 mmol, 1.57 eq) was added dropwise to a stirred solution of *tert*-butylcarbazole-9-carboxylate (**132**, 0.298 g, 1.12 mmol, 1.0 eq) and TMEDA (0.22 mL, 1.47 mmol, 1.3 eq) in 5 mL of ether at -78 °C. After stirring for 1 hour, Bu_3SnCl (0.46 mL, 1.6 mmol, 1.5 eq) was added as a neat liquid *via* a syringe. After stirring for another 30 minutes at -78 °C, the reaction mixture was removed from the dry ice-acetone bath and was allowed to stir for an additional 1 hour. The reaction mixture was quenched with water and the products were extracted with ether (3 x 15 mL). The combined ether extracts were washed with water (25 mL) and then with saturated NaCl solution (25 mL), dried over Na_2SO_4, and evaporated. This compound was purified by basic alumina column chromatography (petroleum ether) to give a colorless oil (10%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (9H, t, J = 7.05 Hz), 1.08 (6H, t, J = 8.25 Hz), 1.33 (6H, sextet, J = 7.32 Hz), 1.55 (6H, quintet, J = 7.51 Hz), 1.72 (9H, singlet), 7.32 (2H, t, J = 7.46 Hz), 7.40 (1H, t, J = 7.87 Hz), 7.64 (1H, d, J = 6.95 Hz), 7.93 (2H, t, J = 7.69 Hz), 8.07 (1H, d, J = 8.43 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 13.9, 14.0, 27.9, 28.8, 29.5, 84.3, 117.1, 119.4, 119.5, 123.3 (2), 126.0, 126.7, 126.7, 131.4, 137.2, 138.4, 146.1, 152.2.

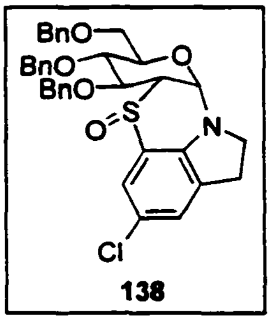


134

134) *tert*-Butyl-1-(1,3-dioxoisointolin-2-ylthio)carbazole-9-carboxylate. To a stirred solution of *tert*-butyl-1-(1,1-dibutyl-1-stannapentyl)carbazole-9-carboxylate (**133**, 69.8 mg, 0.125 mmol, 1.0 eq) and 2,6-lutidine (0.0145 mL, 0.124 mmol, 1.0 eq) in methylene chloride (1 mL, dry) under reflux was added phthalimide-N-sulfenyl chloride (115 mg, 0.54 mmol, 4.35 eq, in 3 mL of dry methylene chloride). After stirring for 1.5 hours with reflux, the reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL), separated, and the aqueous layer was washed with CH_2Cl_2 (3 x 10 mL). The CH_2Cl_2 layers were combined, washed with potassium fluoride solution (10 g KF/100 mL H_2O solution), dried over anhydrous Na_2SO_4, and concentrated with a rotary evaporator. Purification was done using silica gel column chromatography (25% ethyl acetate/petroleum ether) to give 38.1 mg (68%) of the desired product. ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (9H, s), 7.22 (2H, m), 7.35 (1H, t, J = 7.51 Hz), 7.48 (1H, t, J = 8.43 Hz), 7.76 (3H, t of d, J = 2.93 Hz, J = 5.86 Hz), 7.91 (3H, m), 8.08 (1H, d, J = 8.05 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.5, 85.6, 116.5, 118.6, 120.1, 123.7, 124.1, 124.8, 125.4, 126.0, 126.3, 127.5, 127.6, 132.3, 134.7, 136.8, 139.4, 152.5, 168.3.

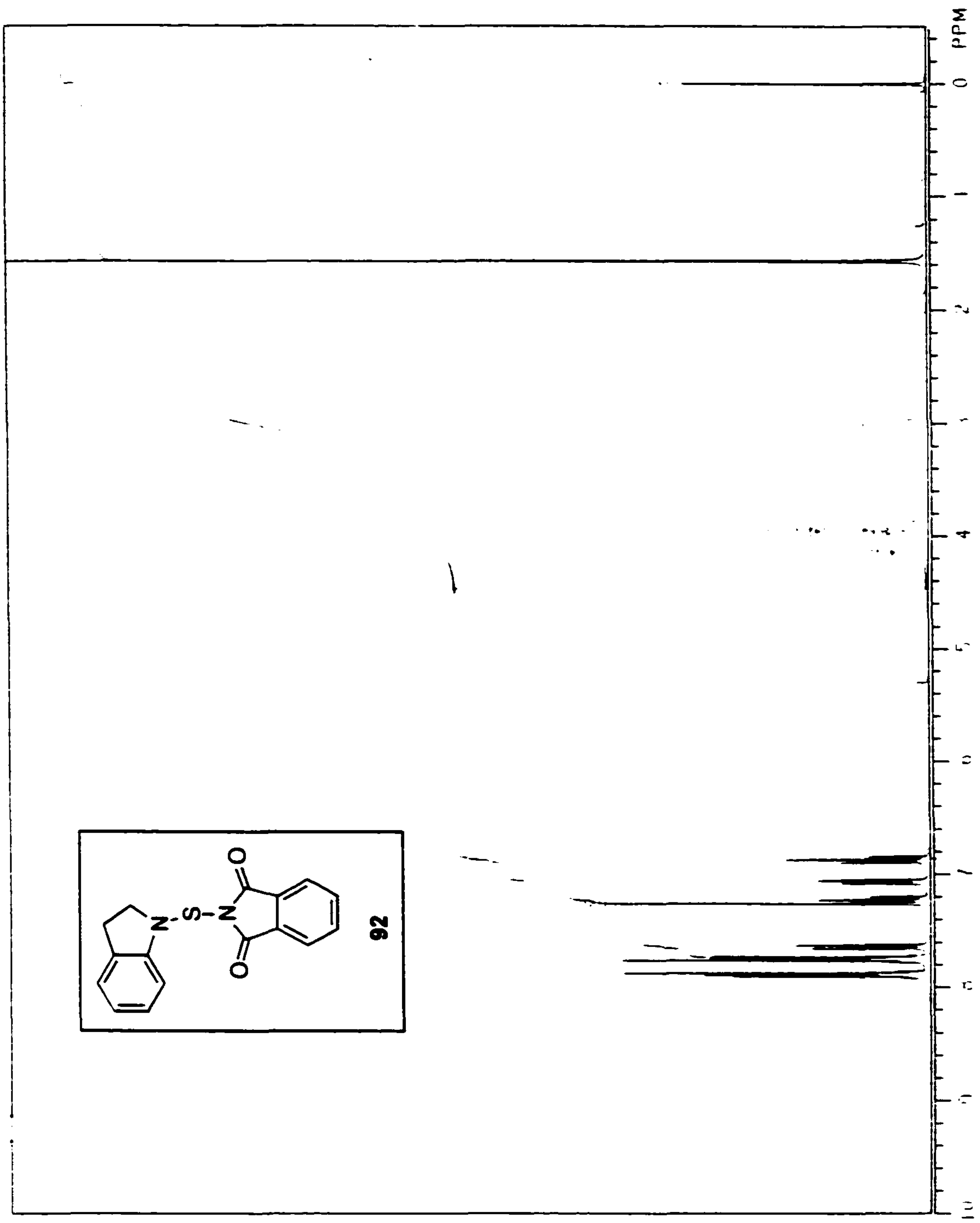

135

135) 2-Carbazolylthioisoindoline-1,3-dione. To a solution of *tert*-butyl-1-(1,3-dioxoisointolin-2-ylthio)carbazole-9-carboxylate (**134**, 26.7 mg, 0.060 mmol, 1.0 eq) in methylene chloride (1 mL) was added trifluoroacetic acid (0.50 mL, 0.65 mmol, 11 eq). After stirring for 23 hours at room temperature, the reaction mixture was quenched with saturated sodium carbonate solution. The aqueous layer was washed 3 times with methylene chloride and the organic layers were combined, dried over anhydrous sodium sulfate, concentrated, and after column chromatography (10% ethyl acetate/petroleum ether), the desired product was obtained (13.8 mg, 67%). R_f 0.33 (20% ethyl acetate/pet. ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (1H, t, J = 7.69 Hz), 7.26 (1H, t, J = 3.45 Hz), 7.48 (1H, t of d, J = 8.1 Hz, J = 1.2 Hz), 7.64 (1H, d, J = 8.1 Hz), 7.71 (2H, dd, J = 5.4 Hz, J = 3.0 Hz), 7.87 (2H, dd, J = 5.4 Hz, J = 3.0 Hz), 7.99 (1H, dd, J = 7.69 Hz, J = 1.10 Hz), 8.03 (1H, d, J = 7.8 Hz), 8.15 (1H, d, J = 7.69 Hz or 7.8 Hz), 9.92 (1H, s, N-H).


138

138) To a solution of Cl-cycloadduct (**130**, 46.5 mg, 0.0775 mmol, in CH_2Cl_2) was addded $NaHCO_3$ (15.3 mg, 0.182 mmol, 2.3 eq) and the reaction mixture was cooled to 5 °C (ice bath). MCPBA (46.3 mg, 0.268 mmol, 3.5 eq, 57-86%) was then added in one portion and stirred for 30 minutes. After 30 minutes, the reaction mixture was quenched with $NaHCO_3$ (aq), and extracted with CH_2Cl_2. The organic layers were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to give a crude weight of 54.6 mg. Column chromatography (20-50% ethyl acetate/ petroleum ether) gave 51% yield of the sulfoxide cycloadduct (24.8 mg). R_f 0.24 (1:1 ethyl acetate/pet. ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (2H, m), 3.41 (3H, m), 3.58 (1H, dd, J = 4.0 Hz, 11.5 Hz), 3.76 (3H, m), 3.96 (1H, dd, J = 2.0 Hz, 9.9 Hz), 4.43 (1H, d, J = 11 Hz), 4.54 (1H, d, J = 11 Hz), 4.58 (1H, d, J = 12 Hz), 4.66 (1H, d, J = 12 Hz), 4.68 (1H, d, J = 11 Hz), 4.79 (1H, d, J = 10.5 Hz), 5.25 (1H, d, J = 3.5 Hz), 7.10-7.40 (17H, m). ^{13}C NMR (500 MHz, $CDCl_3$) δ 27.70, 50.72, 62.20, 68.74, 72.73, 73.93, 75.58, 75.87, 76.98, 78.46, 79.56, 117.84, 124.21, 127.83, 127.95, 128.00, 128.13, 128.32, 128.51, 128.58, 128.61, 128.64, 129.09, 134.26, 137.05, 137.65, 137.92, 145.21; IR (KBr, cm^{-1}) 1032.9; MS Calcd for $C_{35}H_{34}ClNO_5S$: 615.1846. Found *m/z* 616 (M+H$^+$), 638 (M+Na$^+$); *Anal.* Calcd for $C_{35}H_{34}ClNO_5S$: C, 68.22; H, 5.56; N, 2.27. Found: C, 68.22; H, 5.52; N, 2.19.

V. Appendix



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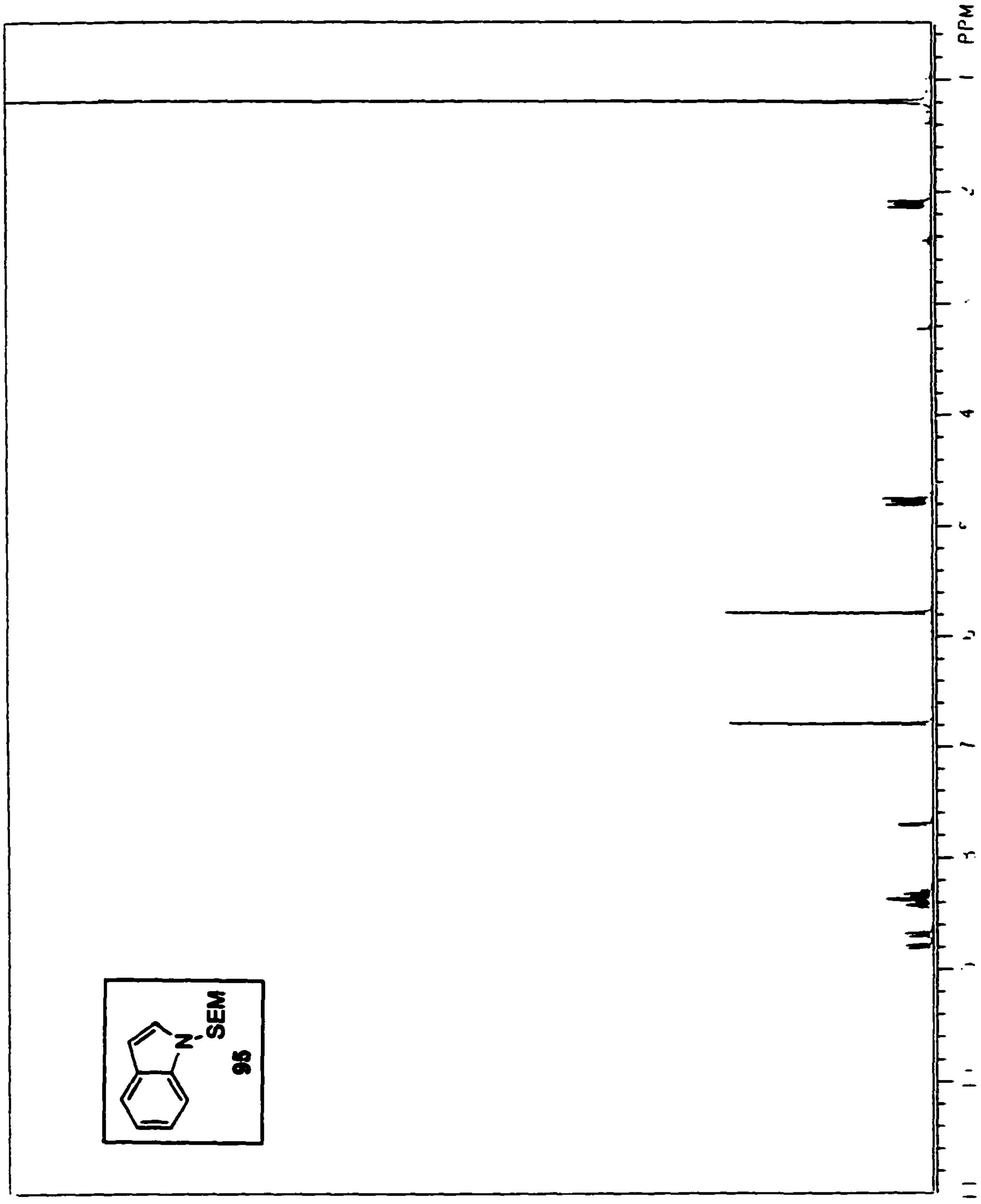
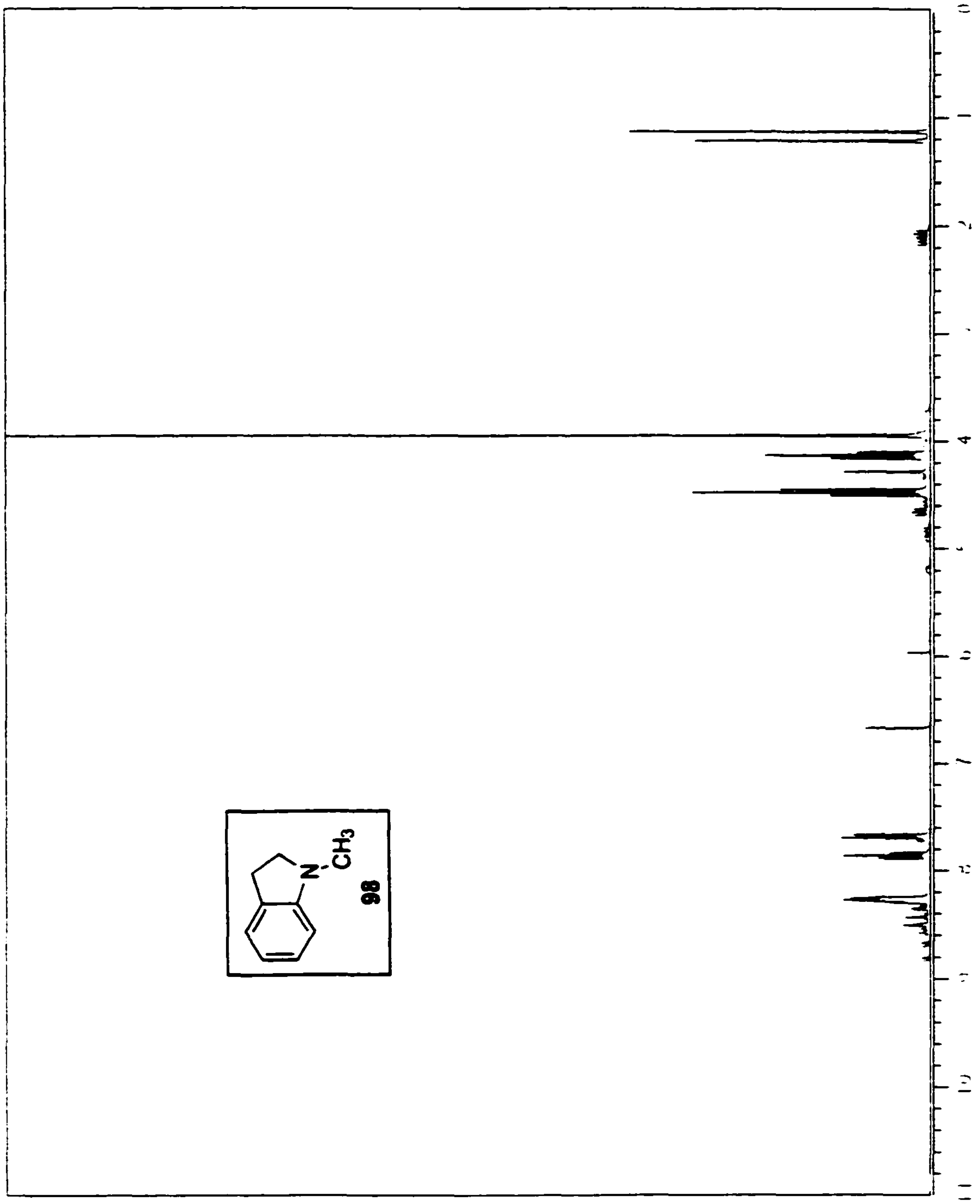
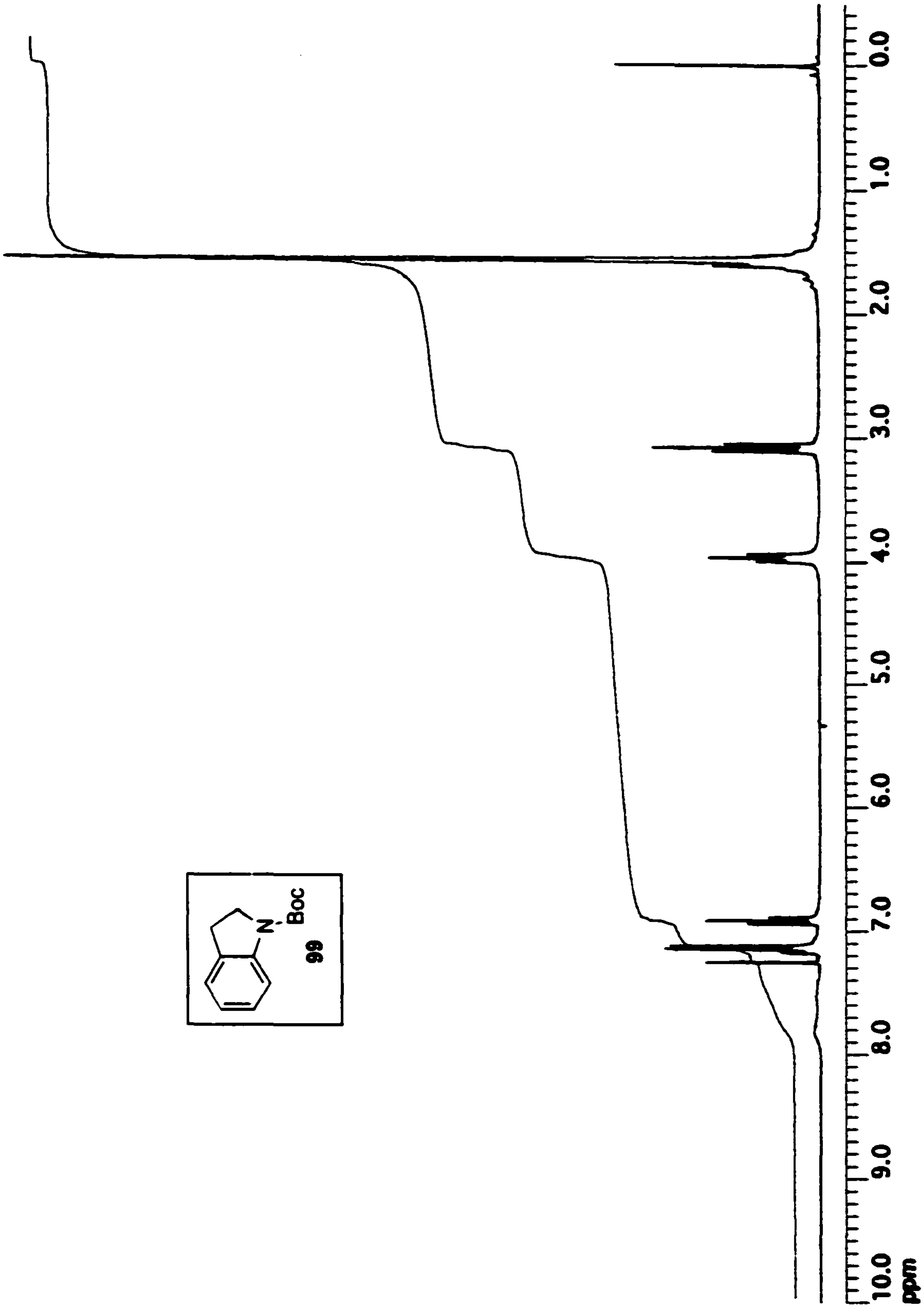

PPM
N
SEM
95


N
CH3
98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Boc
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5.0
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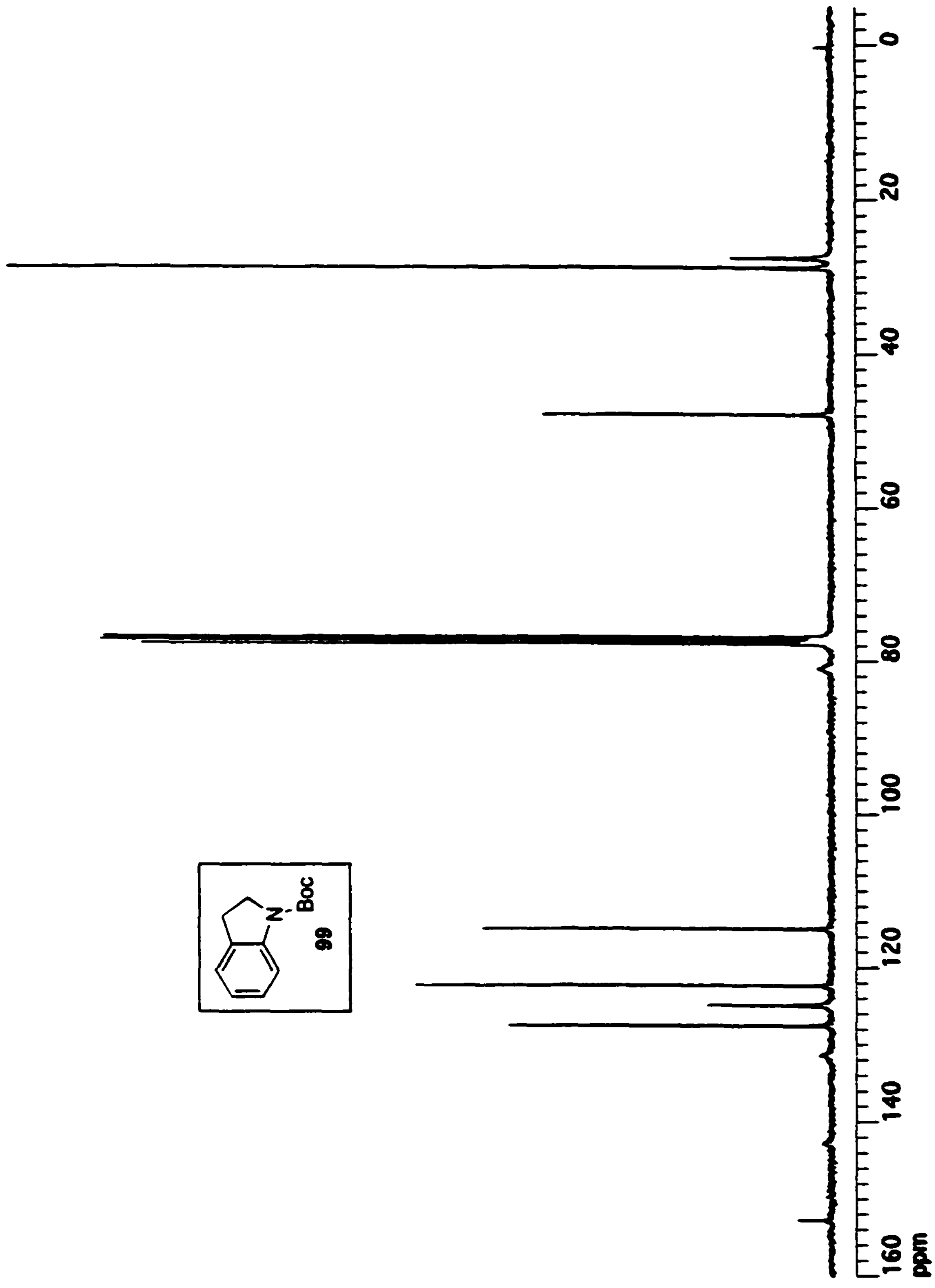
7.0
8.0
9.0
10.0
ppm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Boc
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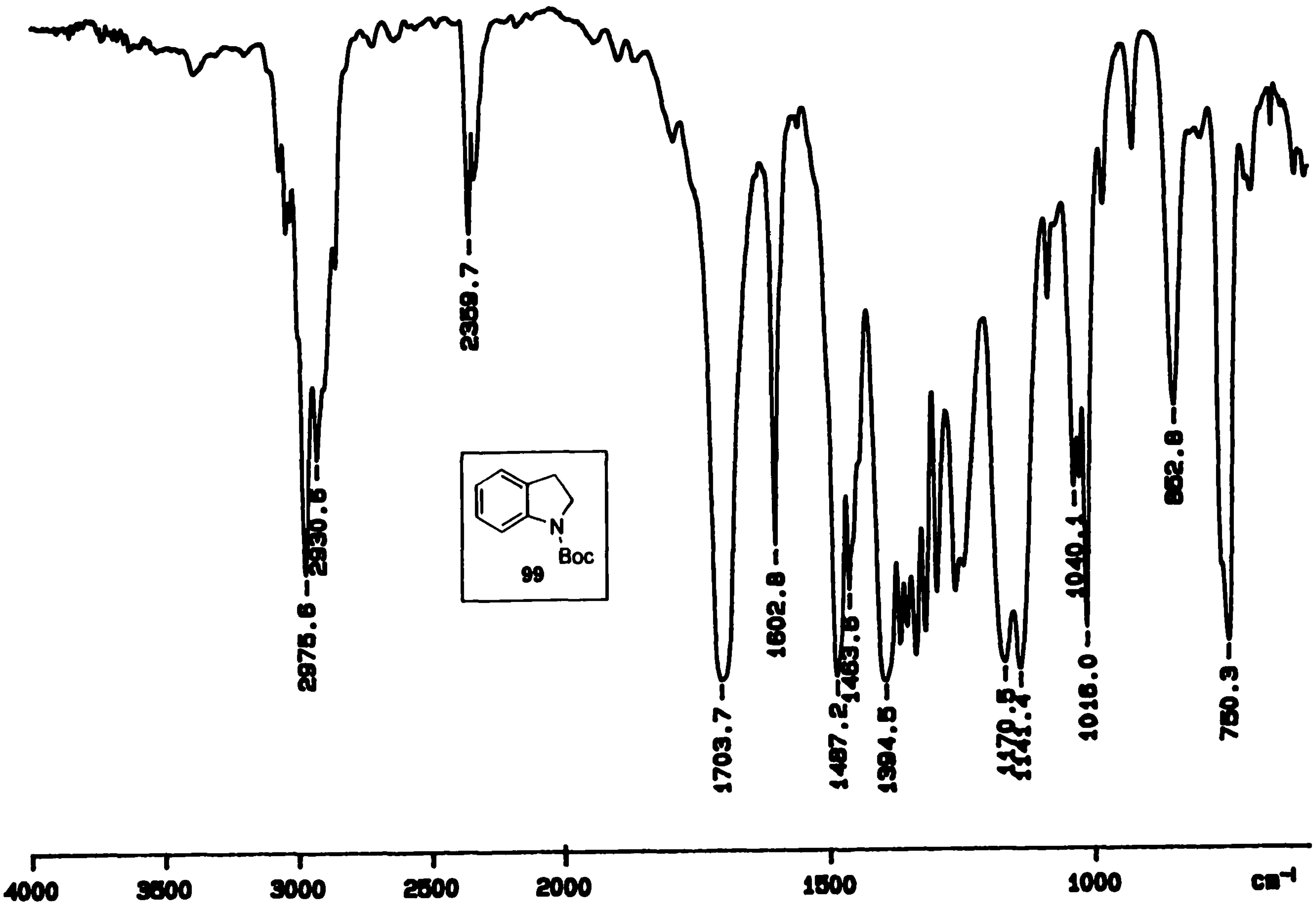
20
40
60
80
100
120
140
160
ppm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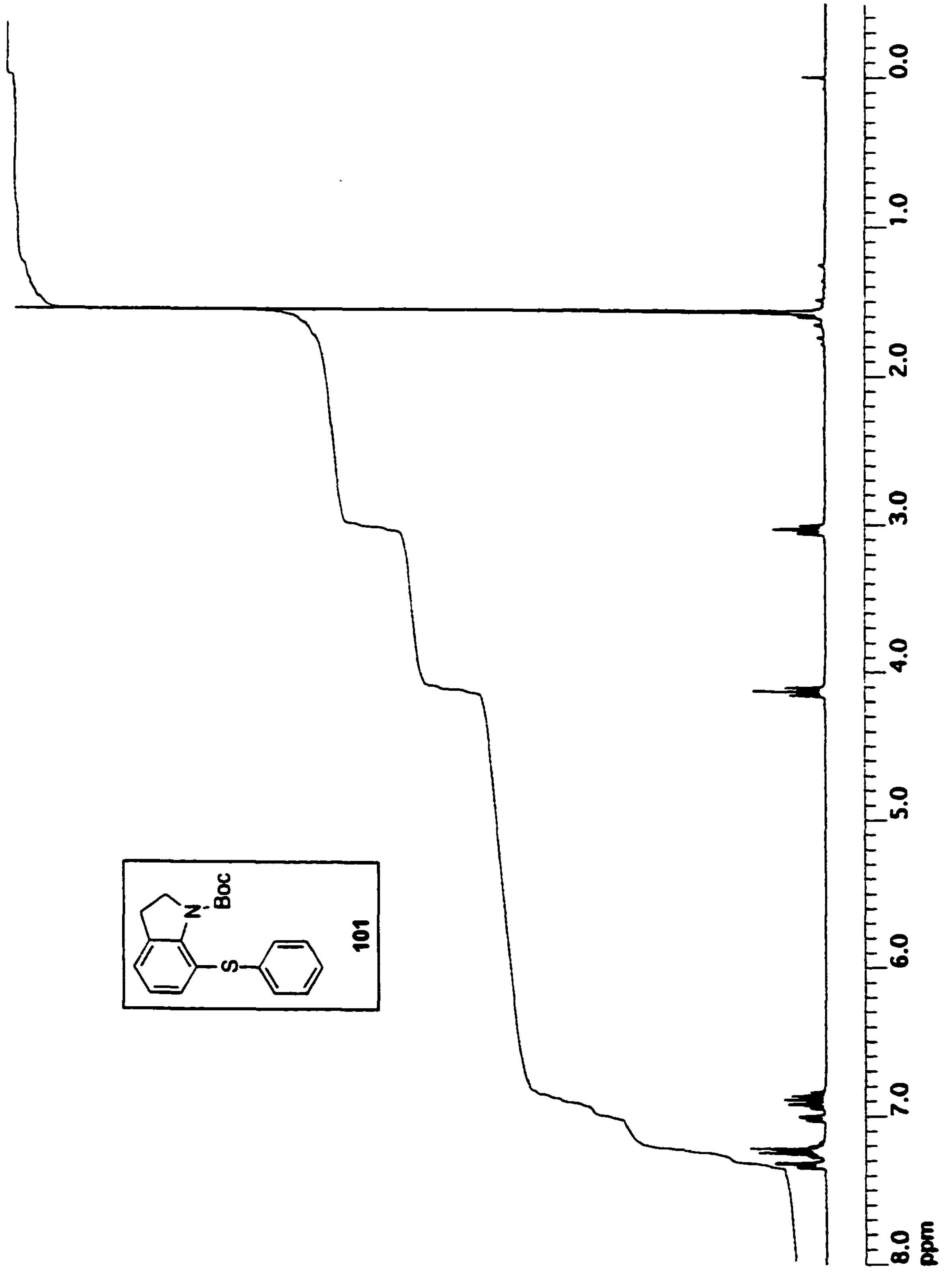
2930.5
2359.7
1703.7
1602.8
1487.2
1463.5
1394.5
1170.5
1141.4
1040.1
1016.0
862.8
750.3
N
Boc
99
4000
3500
3000
2500
2000
1500
1000
cm-1



N-Boc
S
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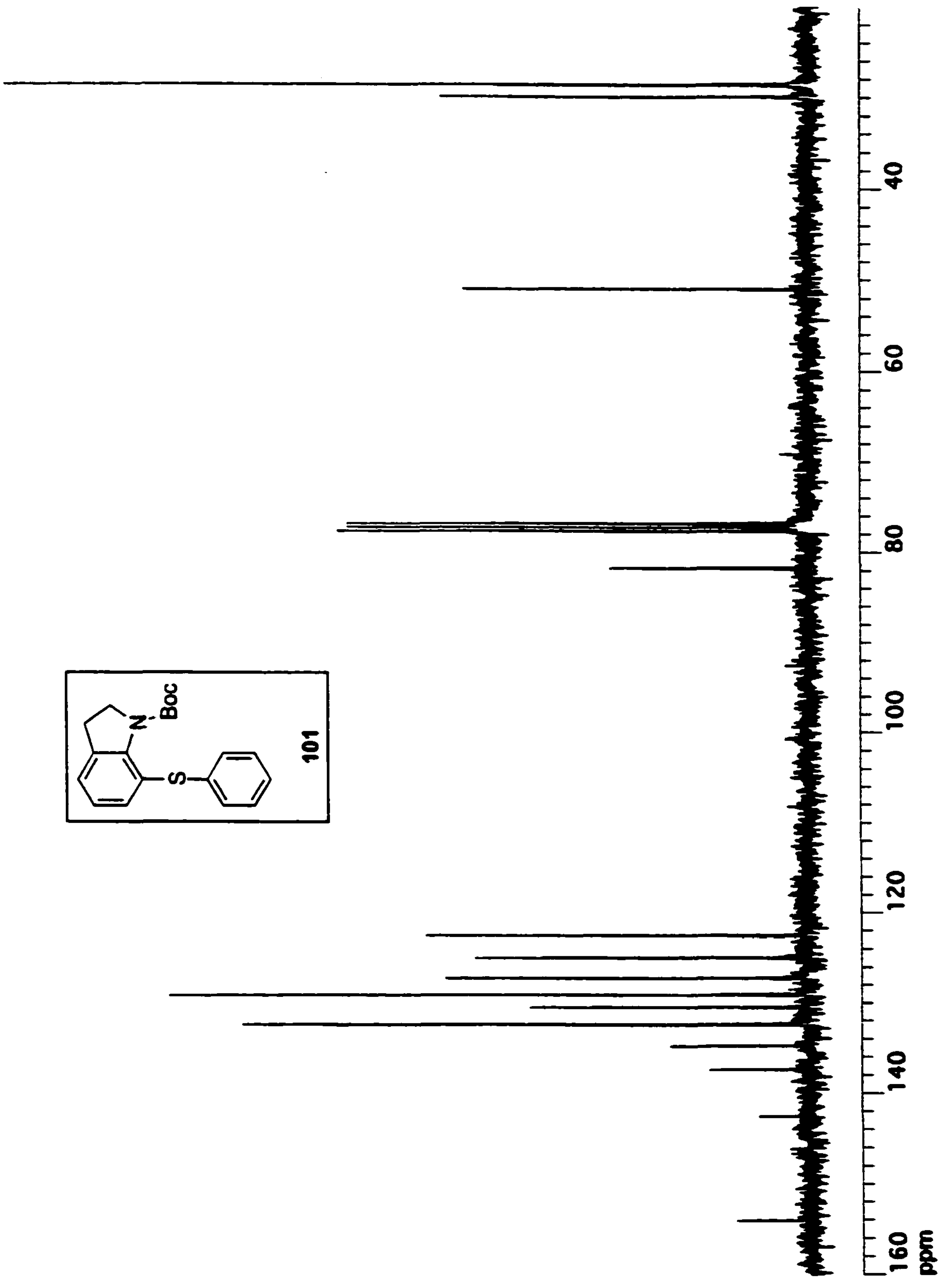
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm



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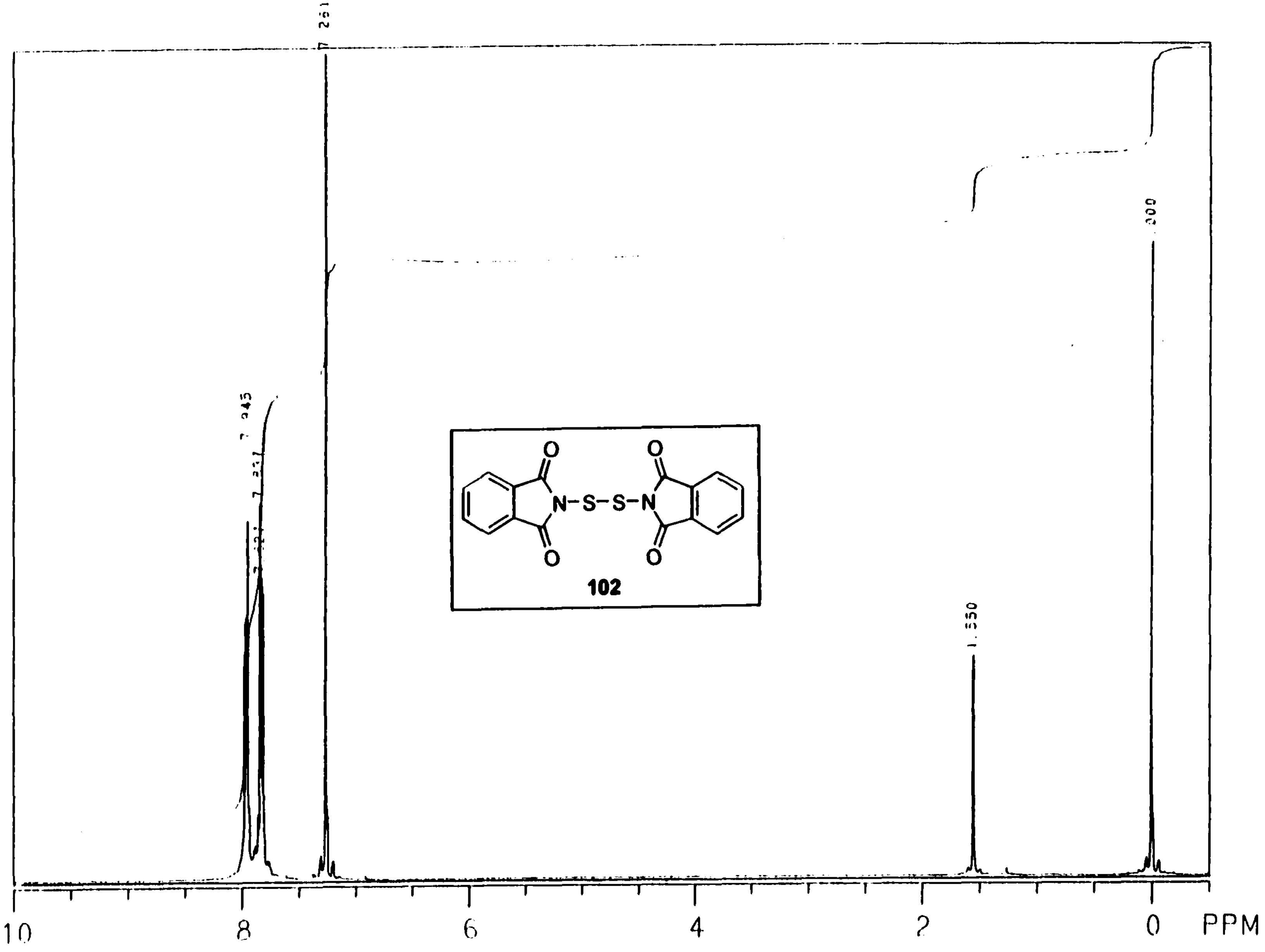

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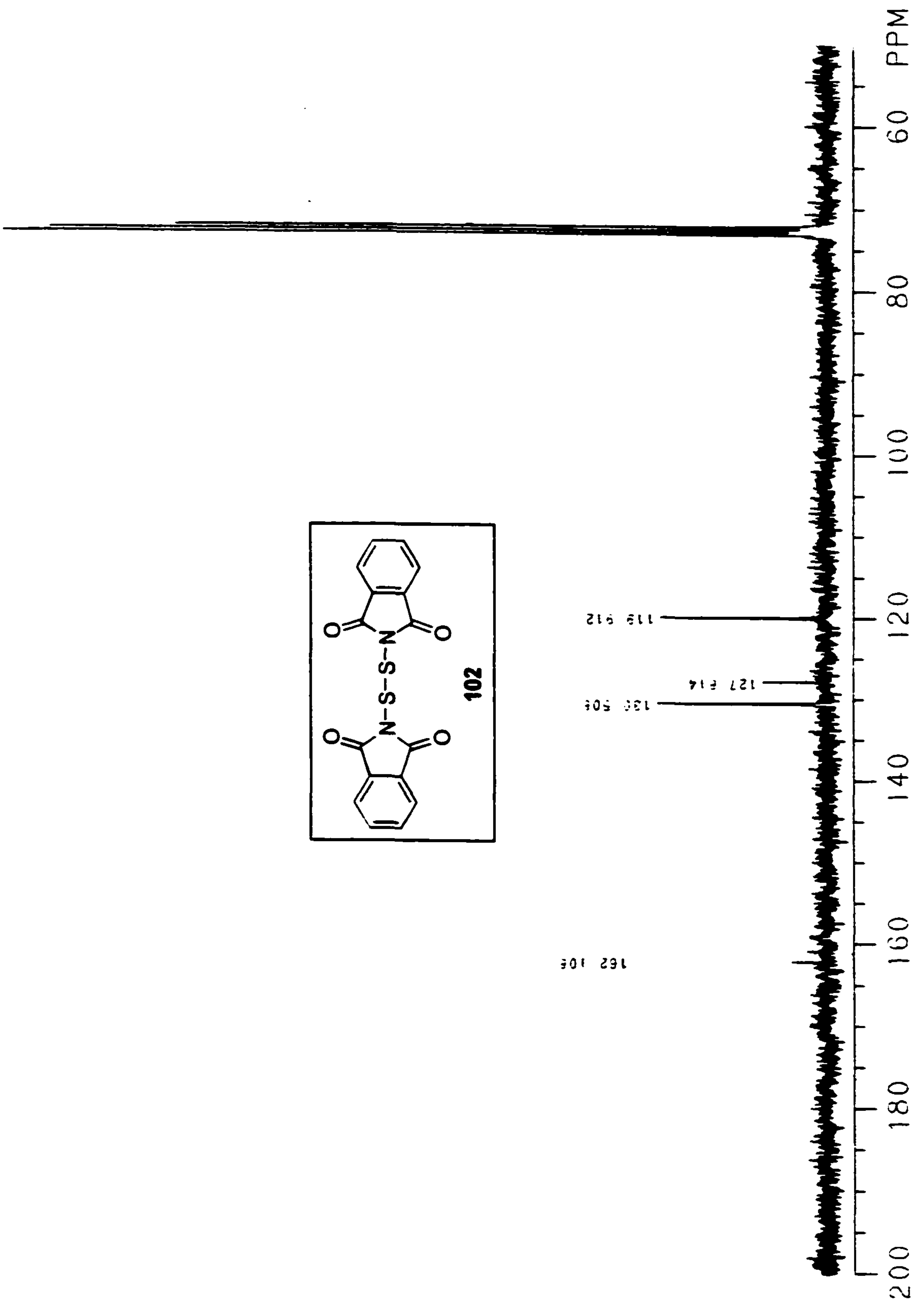
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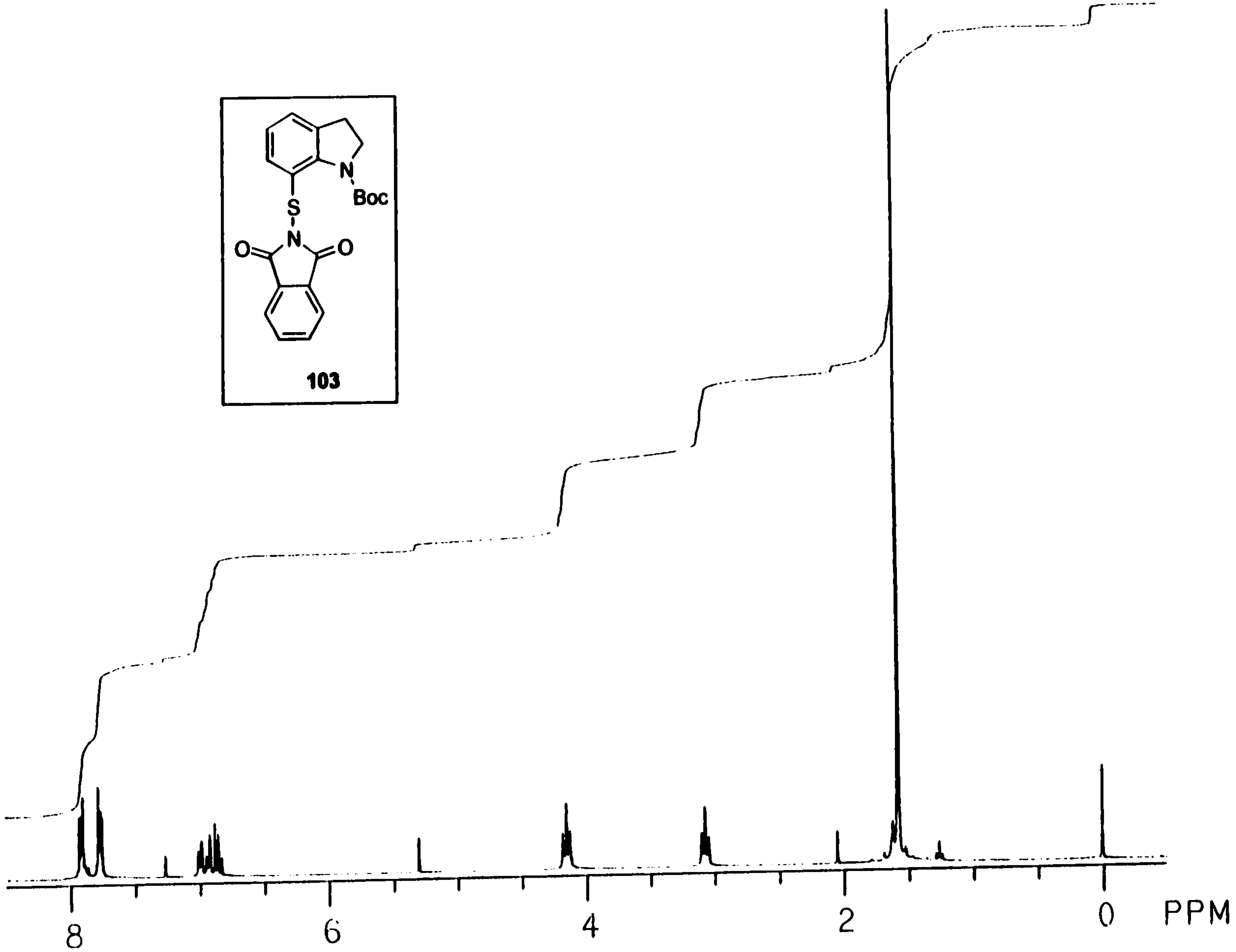
80
100
120
140
160
180
200
119 512
127 614
130 505
162 105
O
N
S
S
N
O
O
O
102



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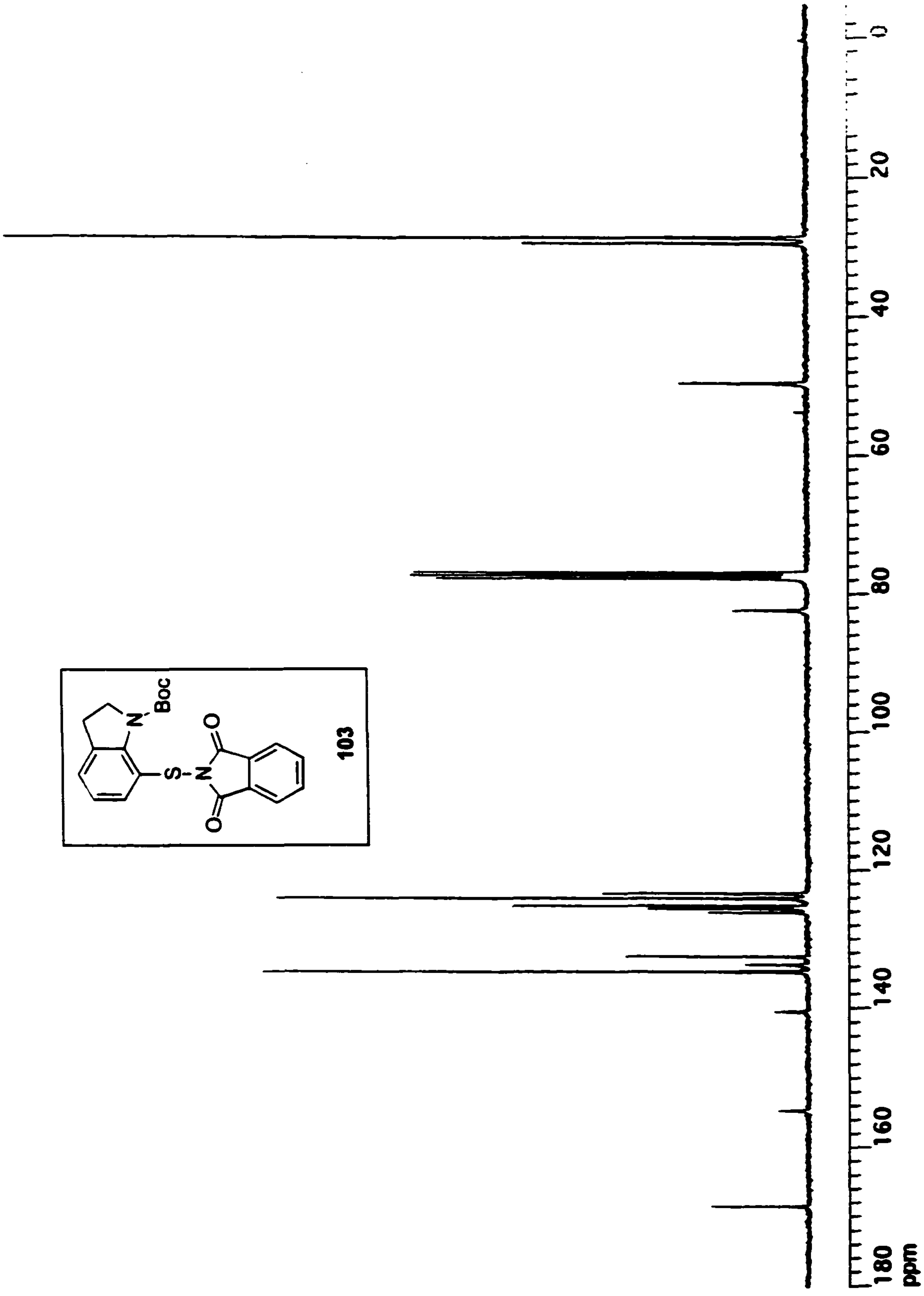

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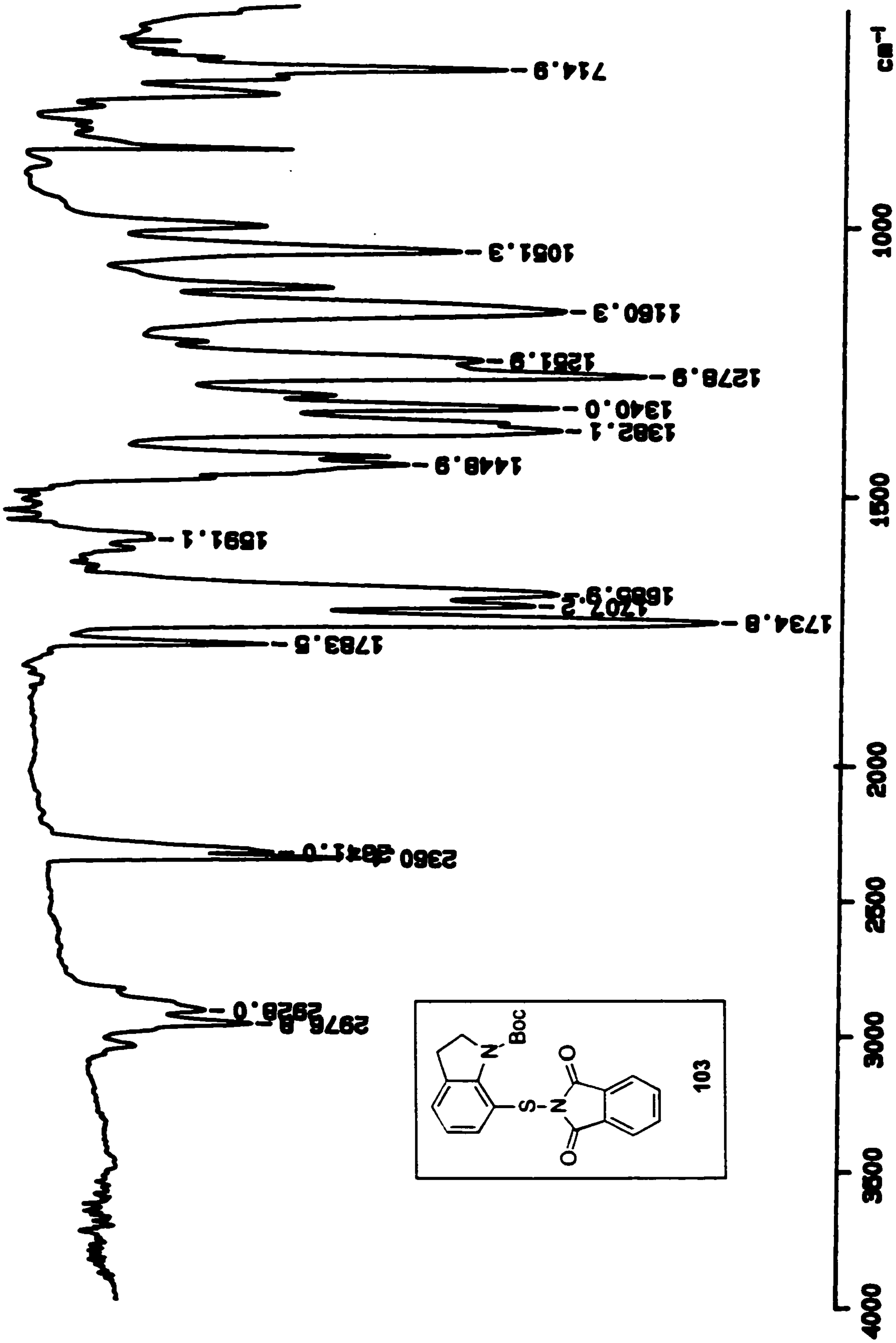
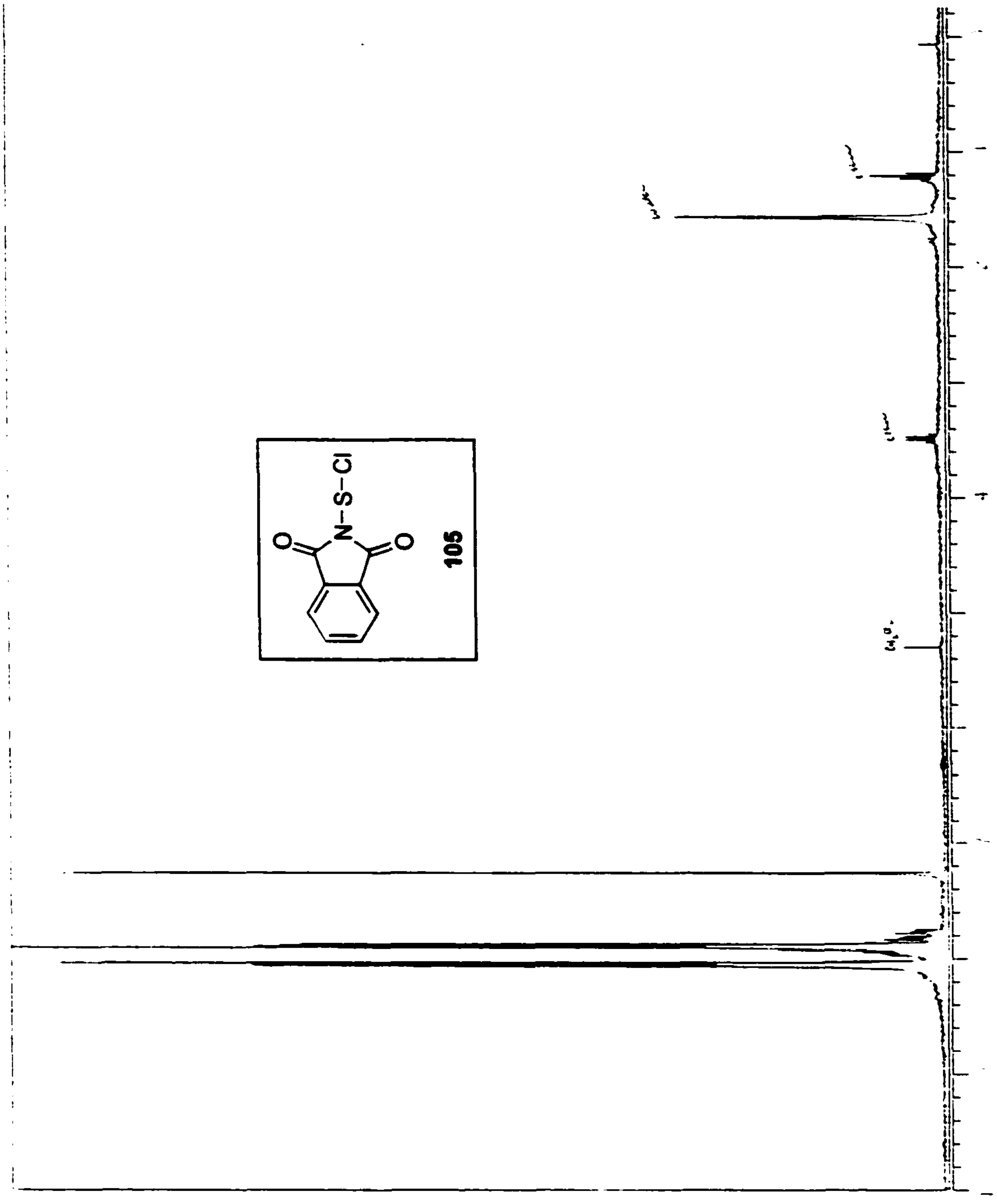
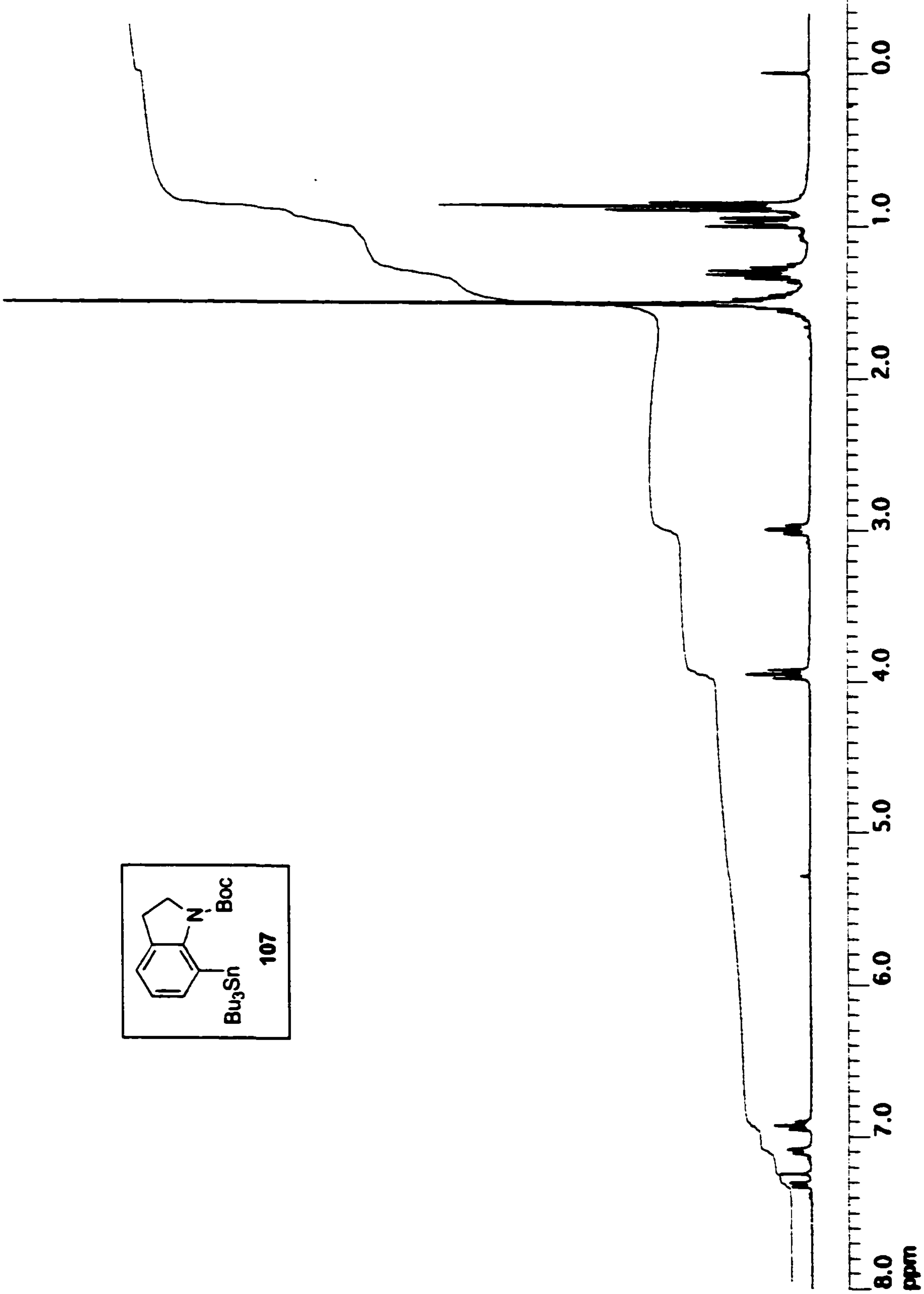

714.9
1051.3
1160.3
1251.9
1278.9
1340.0
1382.1
1448.9
1591.1
1688.9
1707.2
1734.8
1783.5
2360
2341.0
2928.0
2976.8
1000
1500
2000
2500
3000
3500
4000
cm-1
N
Boc
S
N
O
O
103


N–S–Cl
O
O
105


Bu3Sn
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Boc
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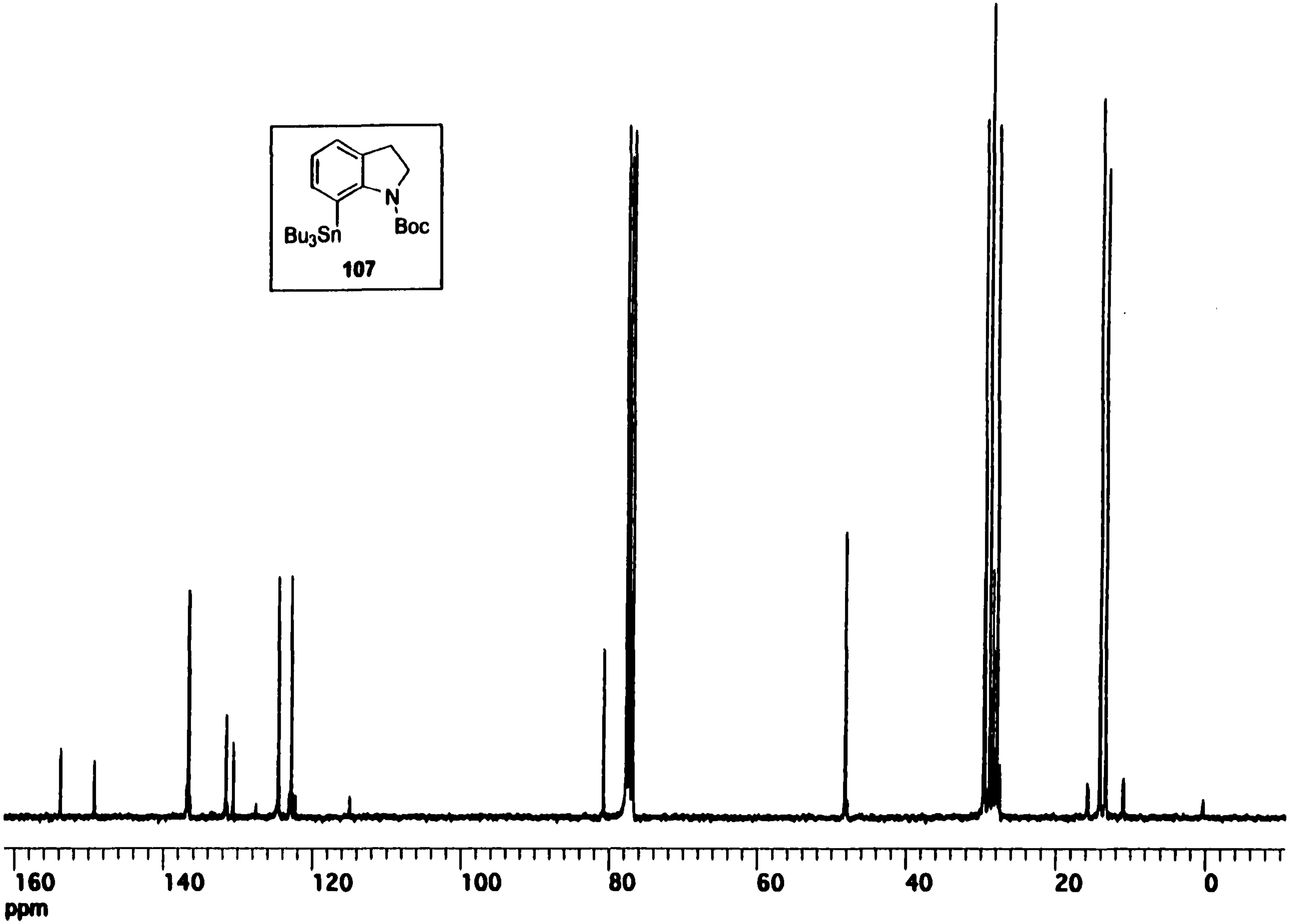
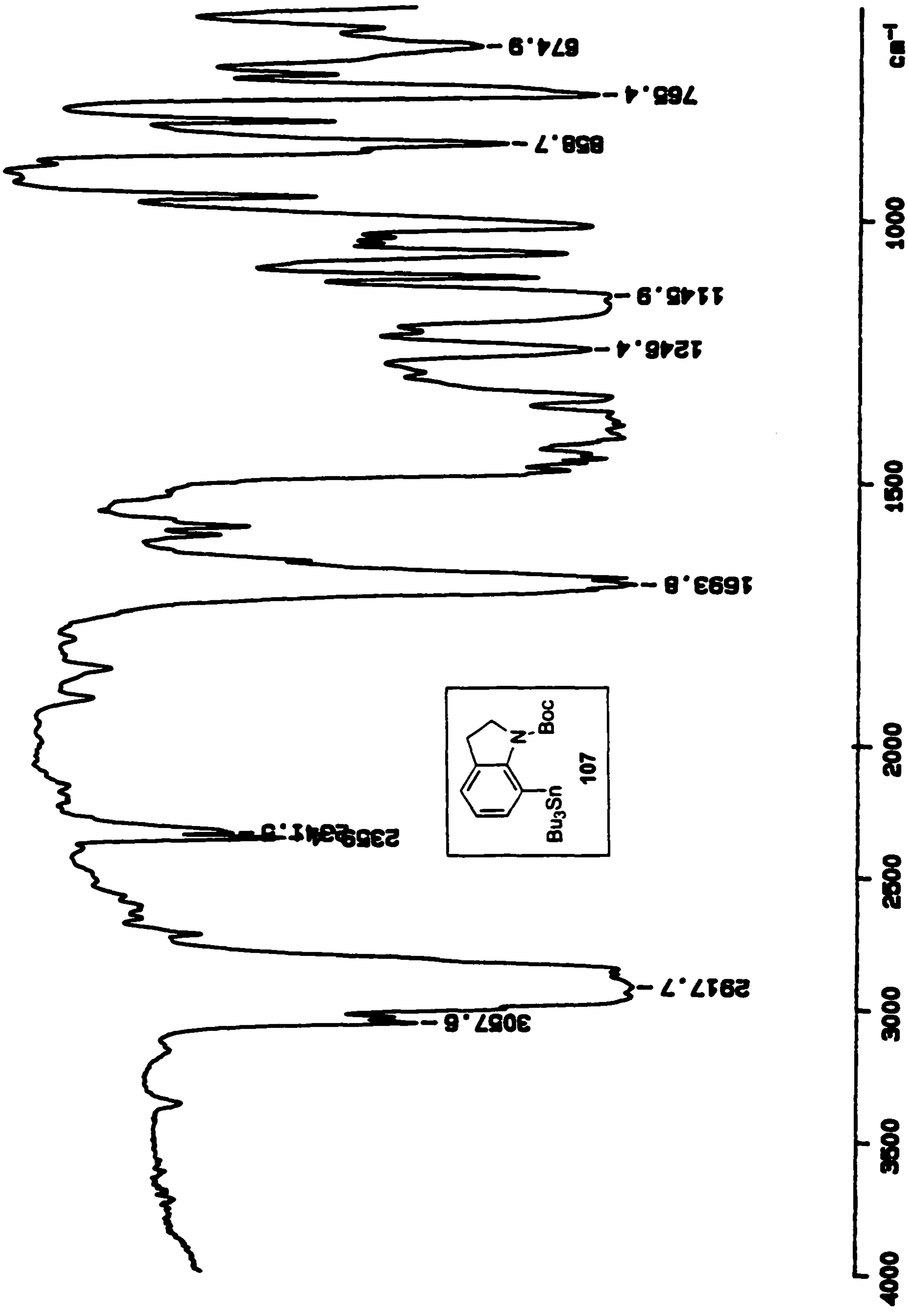
5.0
6.0
7.0
8.0
ppm


Bu$_3$Sn
N
Boc
107
160
140
120
100
80
60
40
20
0
ppm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765.4
858.7
1145.9
1245.4
1693.8
2358
2341.5
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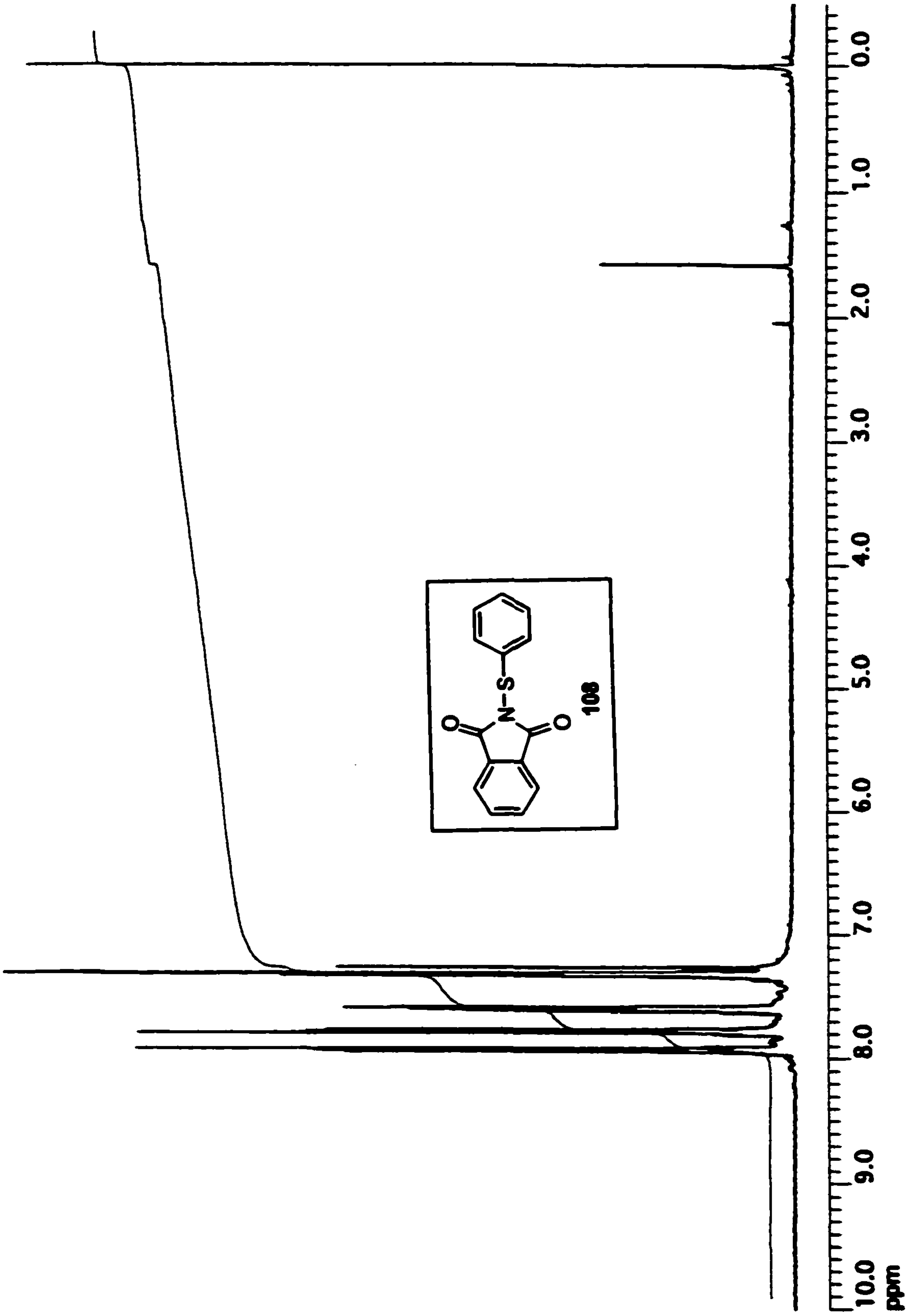
3500
3000
2500
2000
1500
1000
cm-1
Bu3Sn
N
Boc
107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1.0
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7.0
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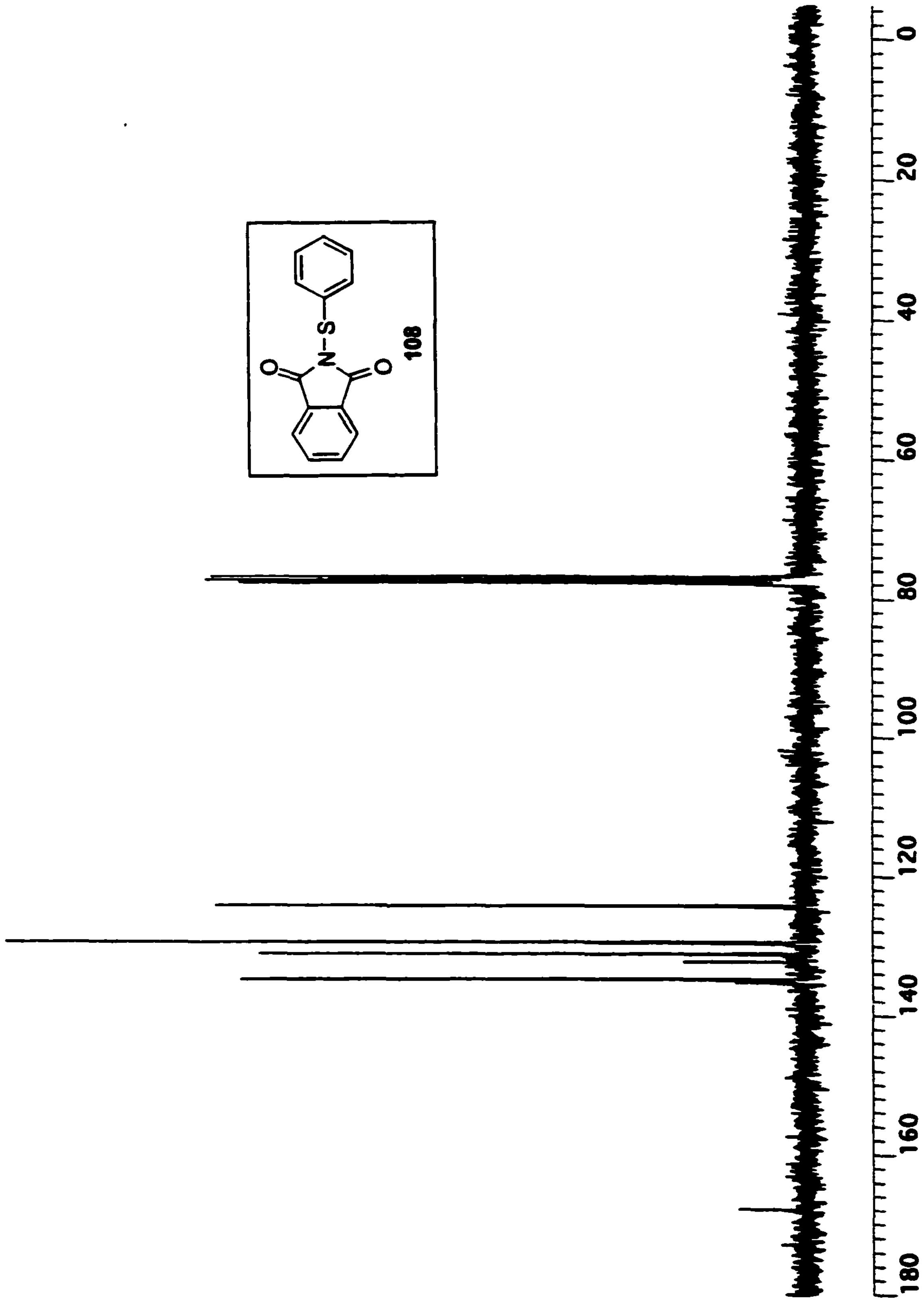
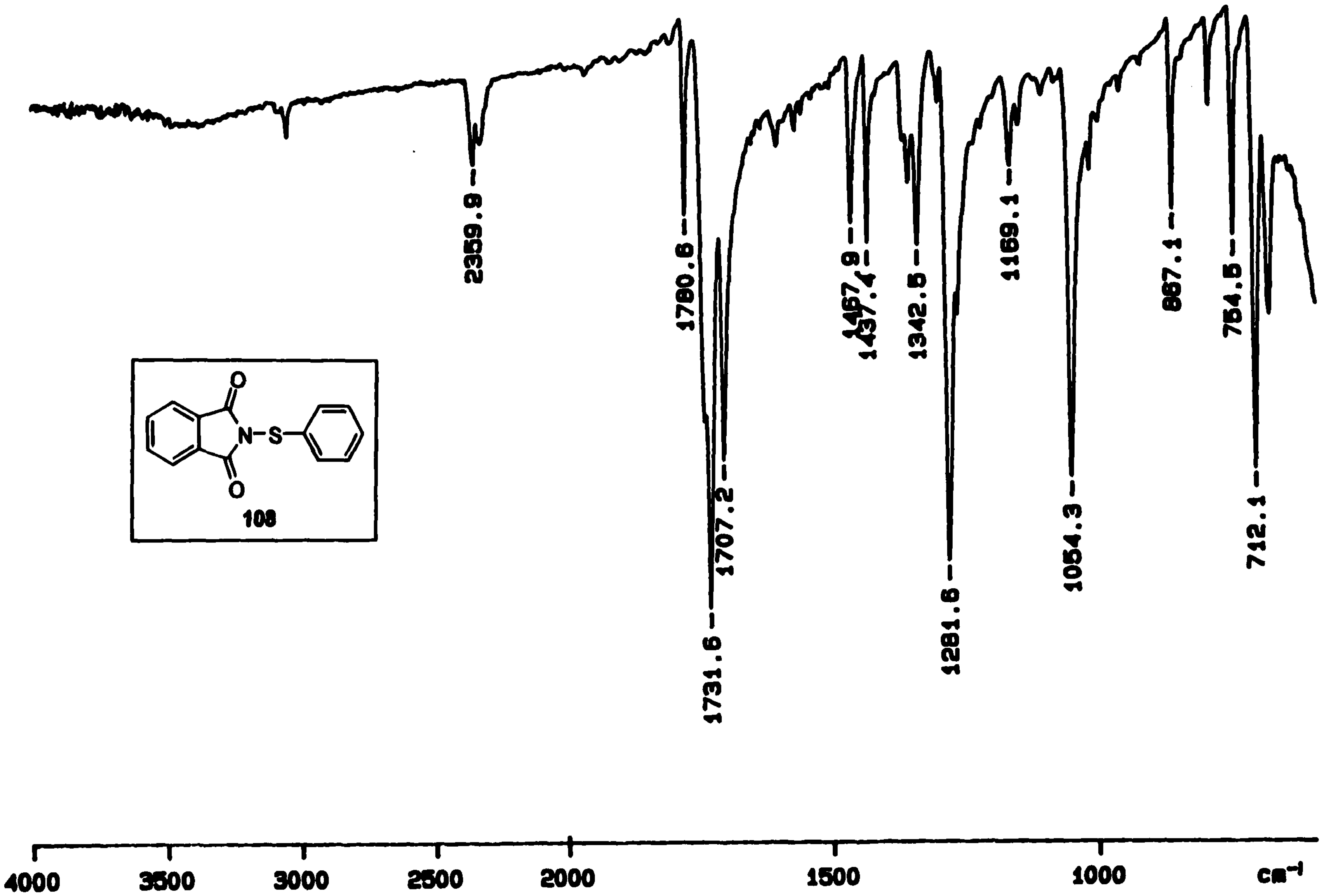
10.0
ppm
O
N-S
O
108


N–S
O
O
108
0
20
40
60
80
100
120
140
160
180
ppm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1731.6
1707.2
1467.9
1437.4
1342.5
1281.6
1169.1
1054.3
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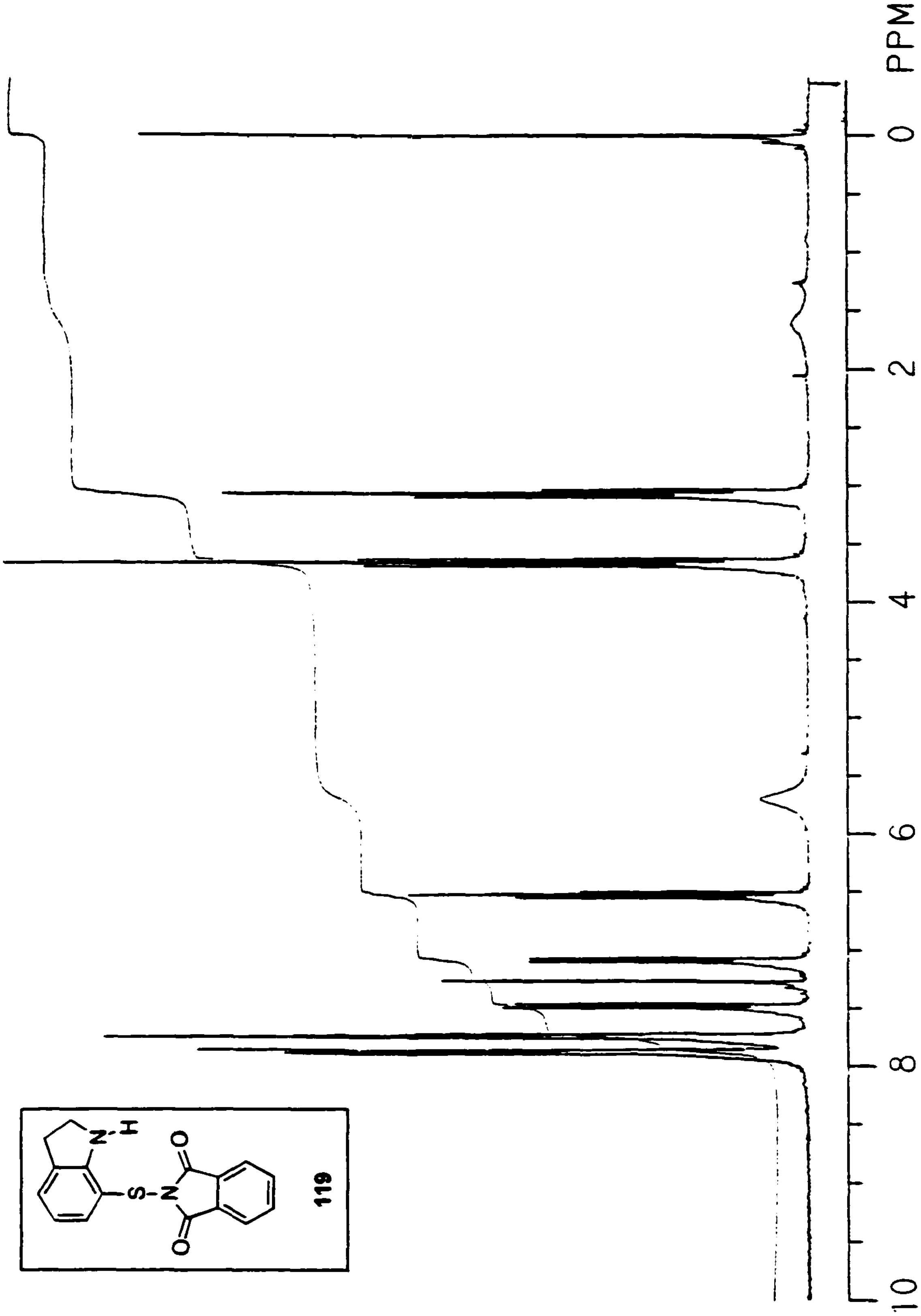
2500
2000
1500
1000
cm⁻¹



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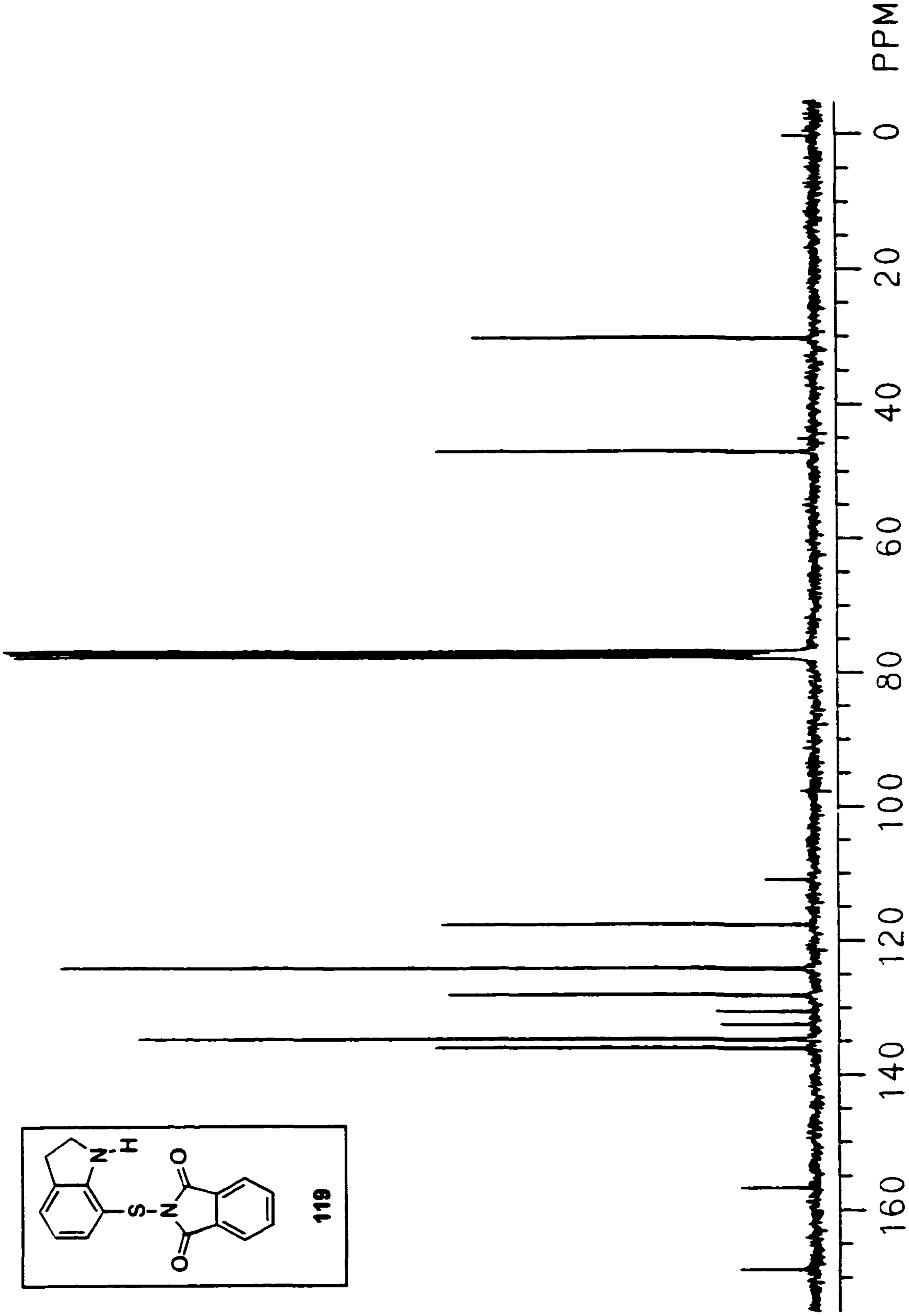
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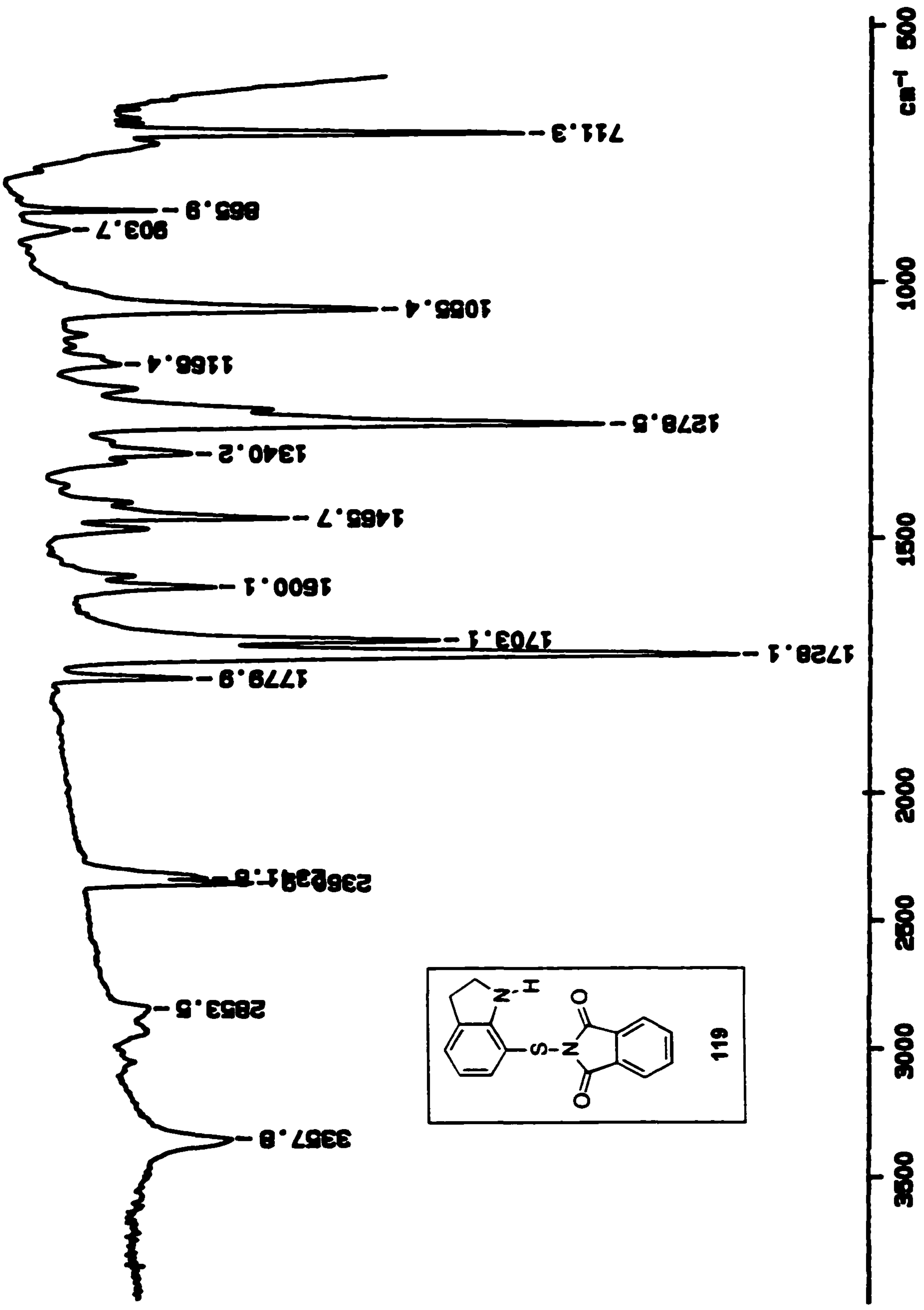
40
60
80
100
120
140
160
119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865.9
903.7
1055.4
1166.4
1278.5
1340.2
1465.7
1600.1
1703.1
1728.1
1779.9
2362
2341.5
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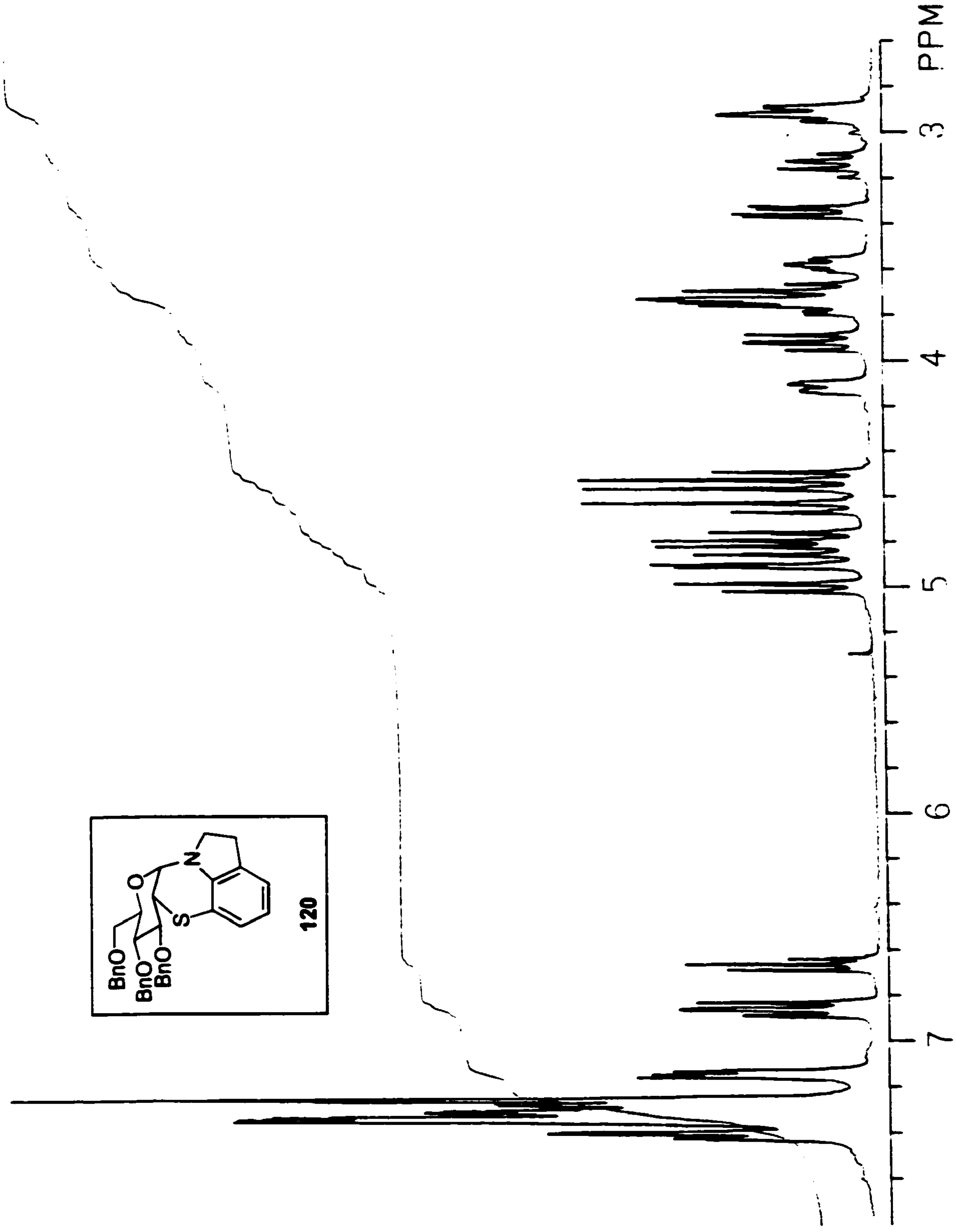
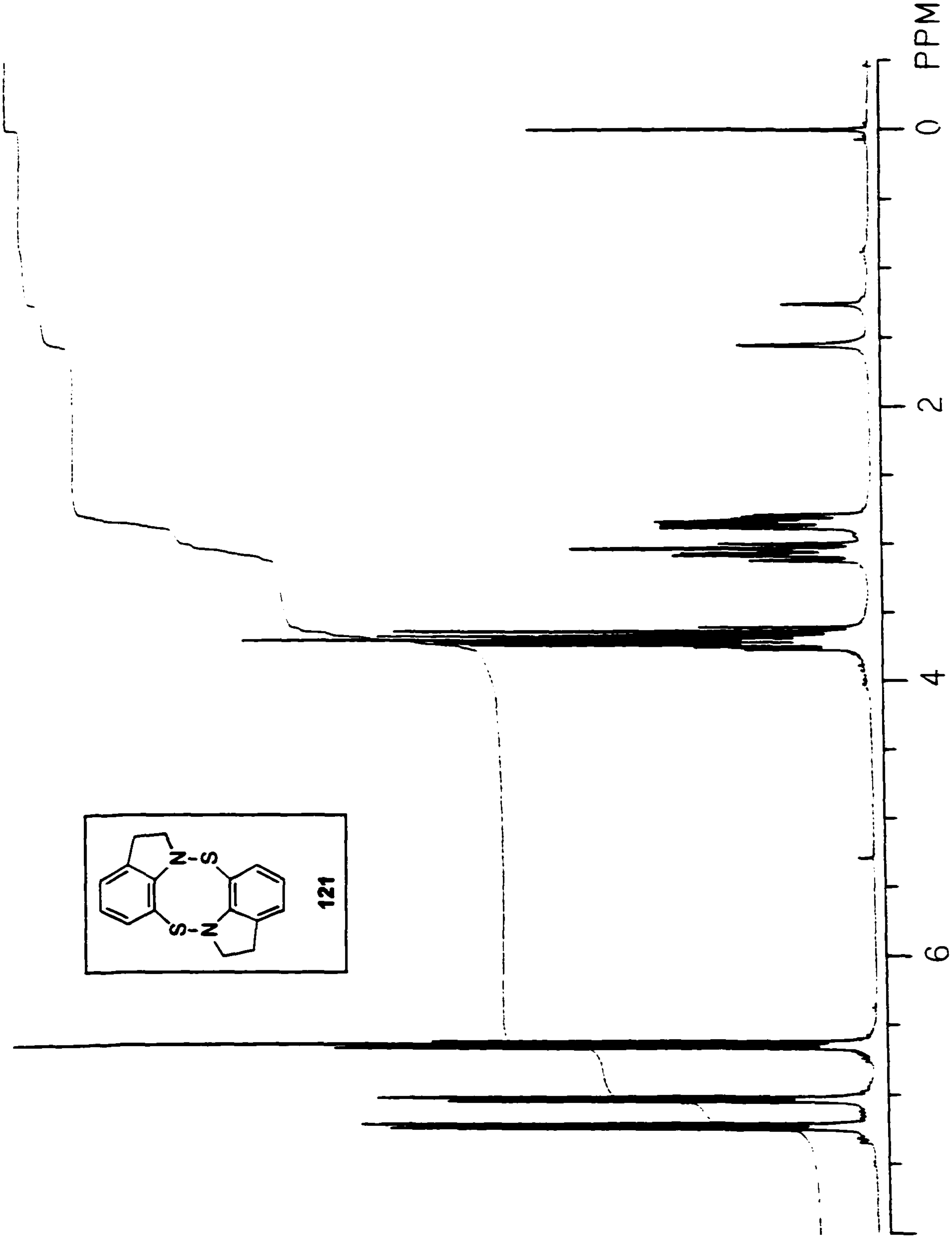
3357.8
cm-1 500
1000
1500
2000
2500
3000
3500
119


BnO
BnO
BnO
O
N
S
120
PPM
3
4
5
6
7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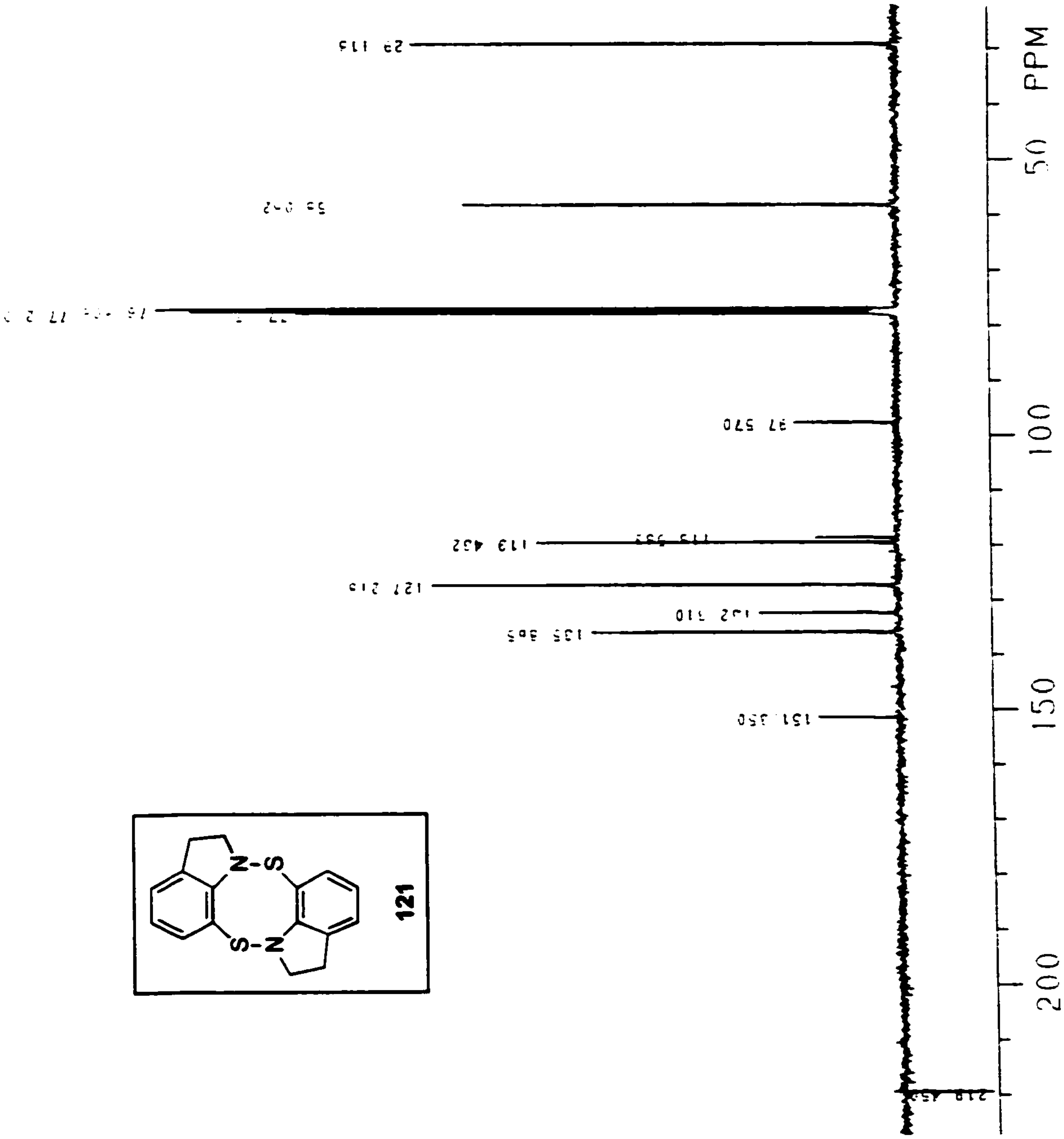
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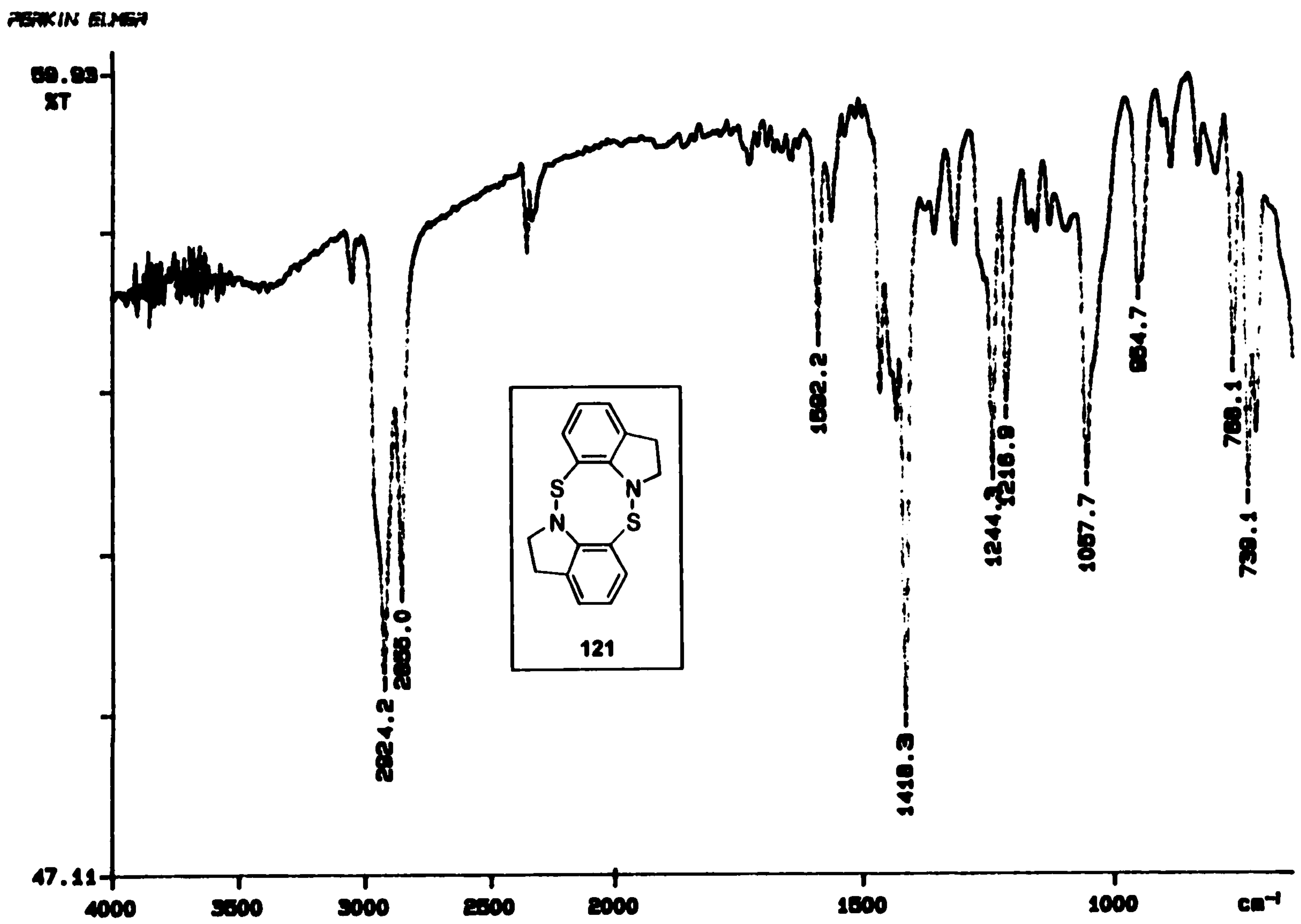
113.432
121.213
132.710
135.365
151.350
200
150
100
50
PPM
N-S
S-N

121


PERKIN ELMER
59.93
%T
47.11
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
2924.2
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1244.3
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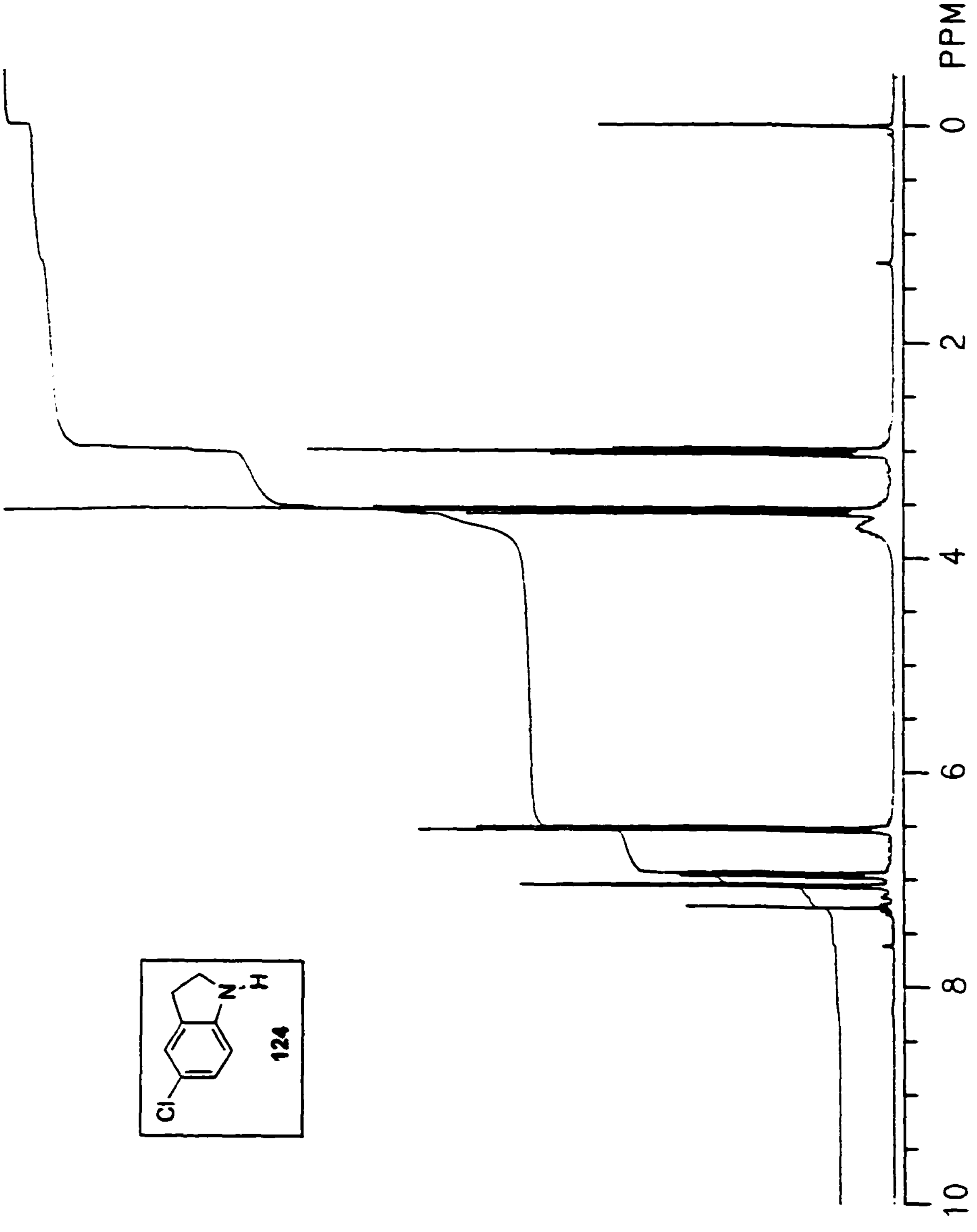
1057.7
954.7
768.1
738.1
S
N
121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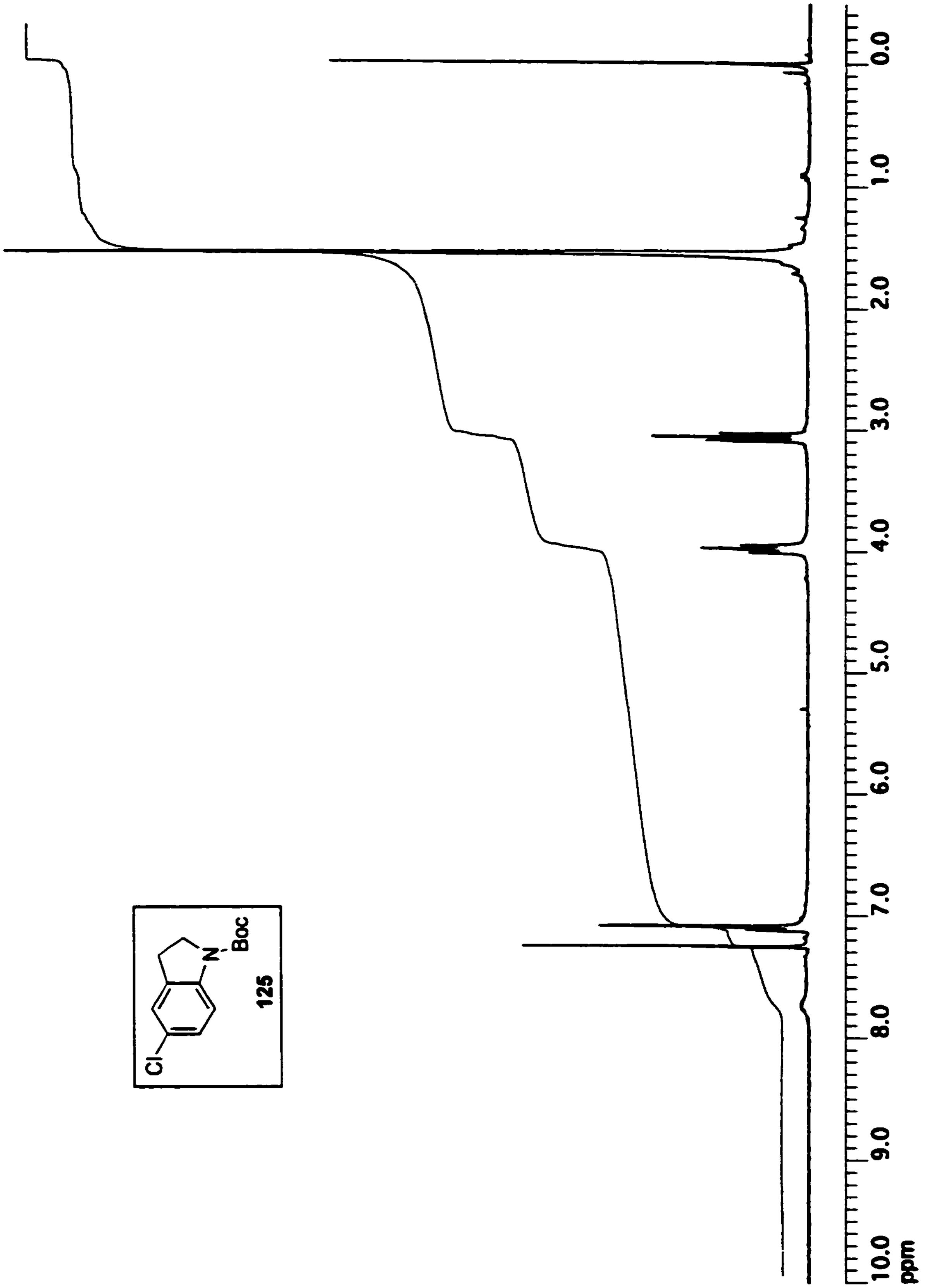
2
4
6
8
10
Cl
N
H
124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N
Boc
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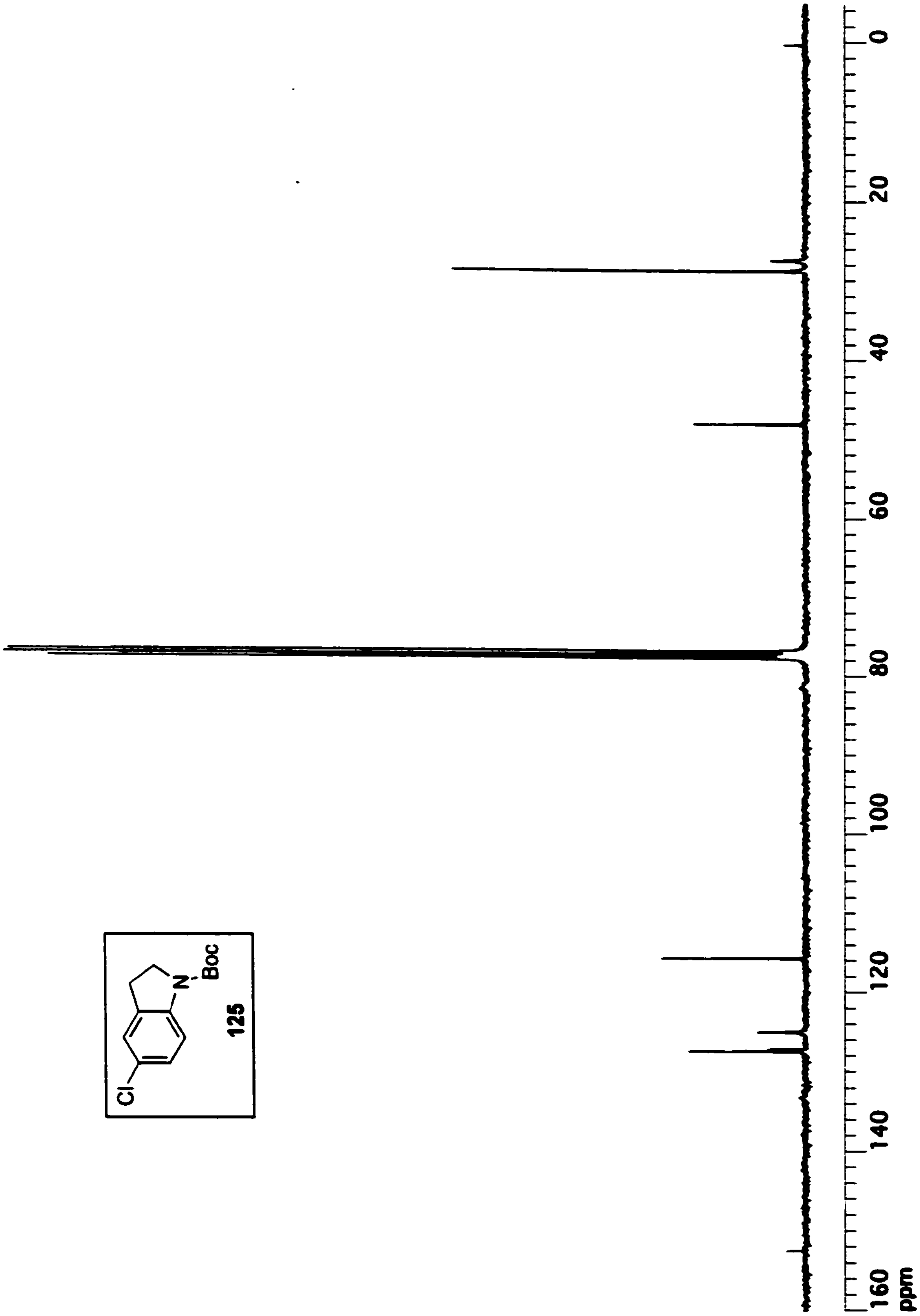
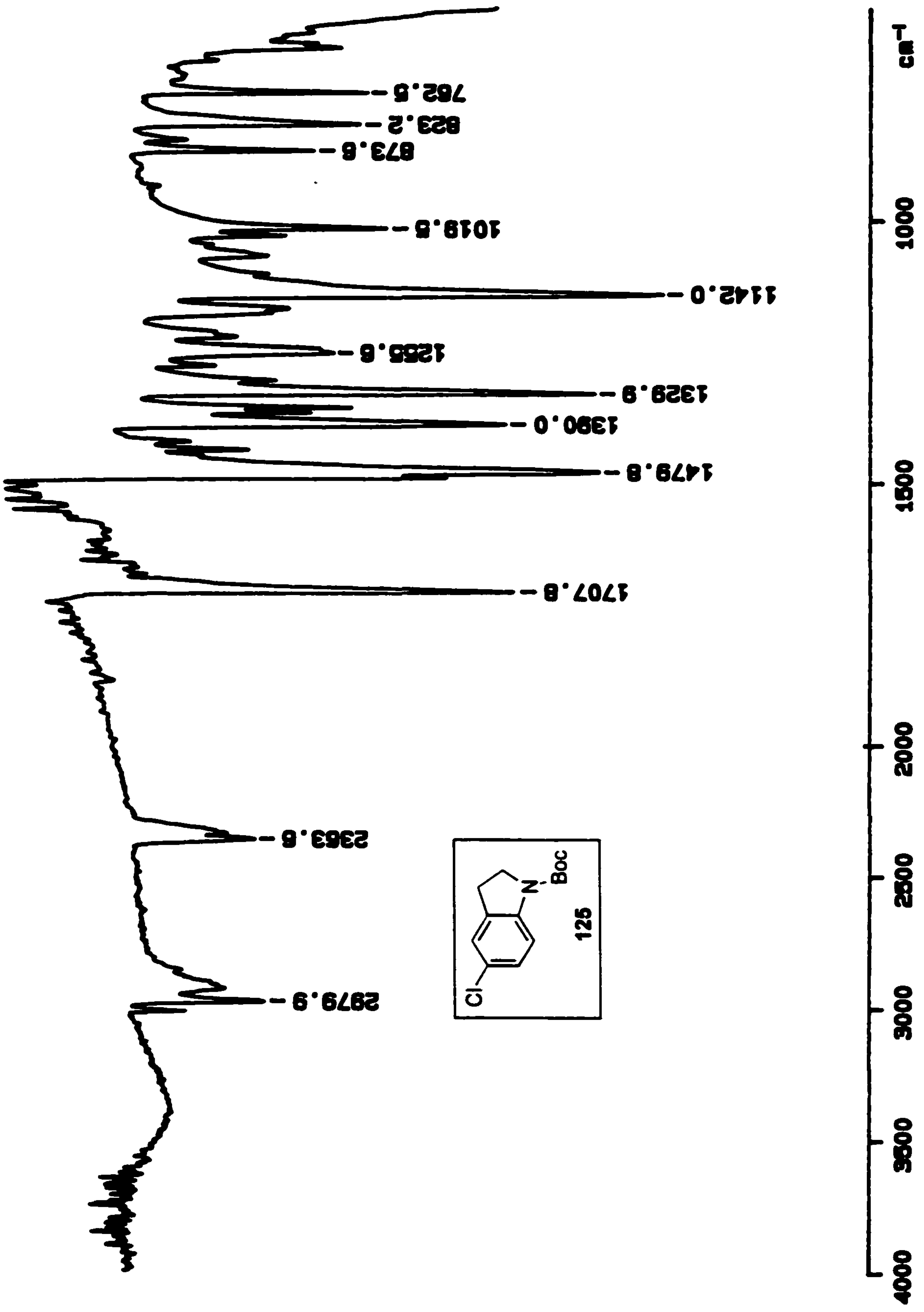
4.0
5.0
6.0
7.0
8.0
9.0
10.0
ppm



Cl
N
Boc
125
0
20
40
60
80
100
120
140
160
ppm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1019.5
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1255.6
1329.9
1390.0
1479.8
1707.8
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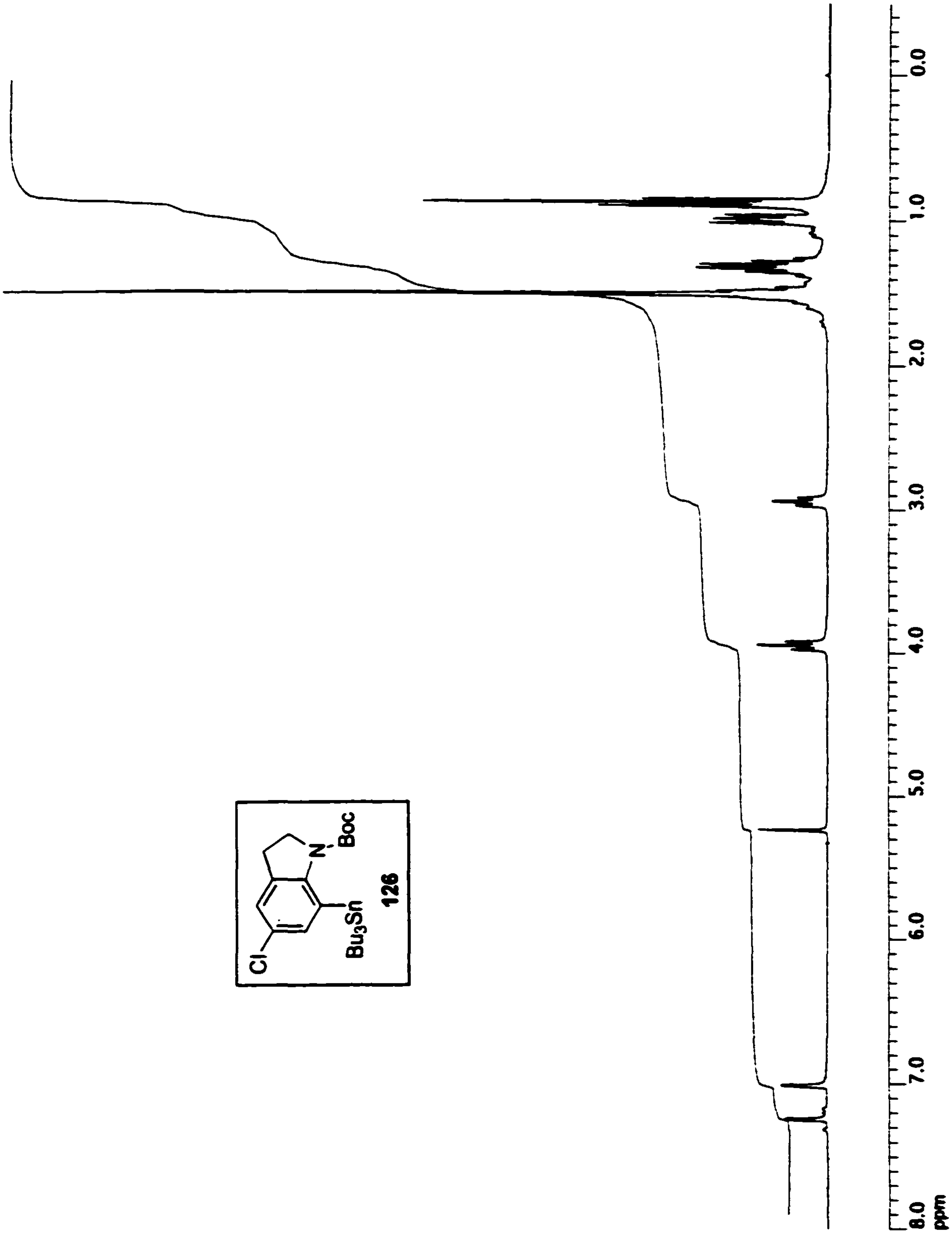
3000
2500
2000
1500
1000
cm-1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N
Boc
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3.0
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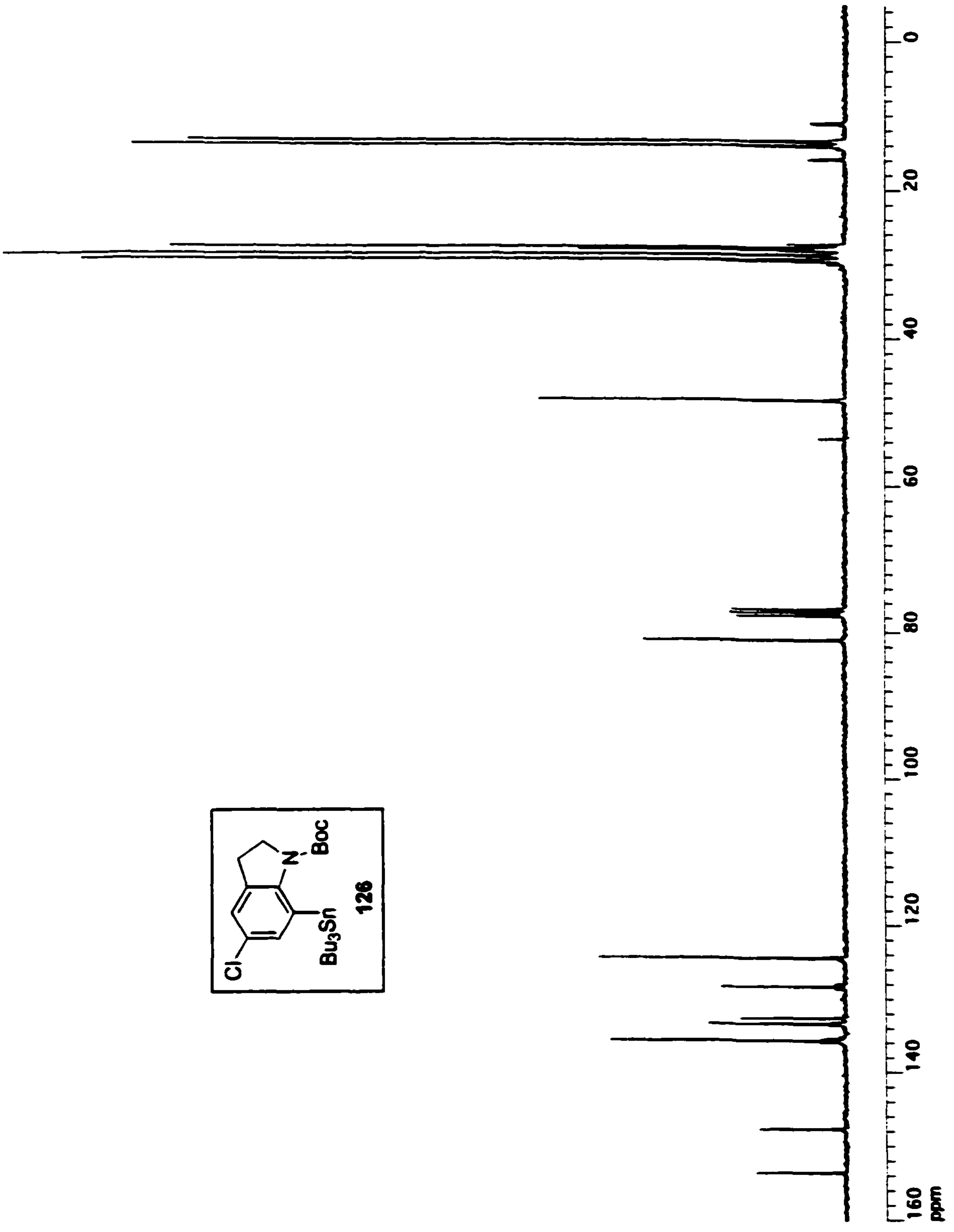
7.0
8.0
ppm



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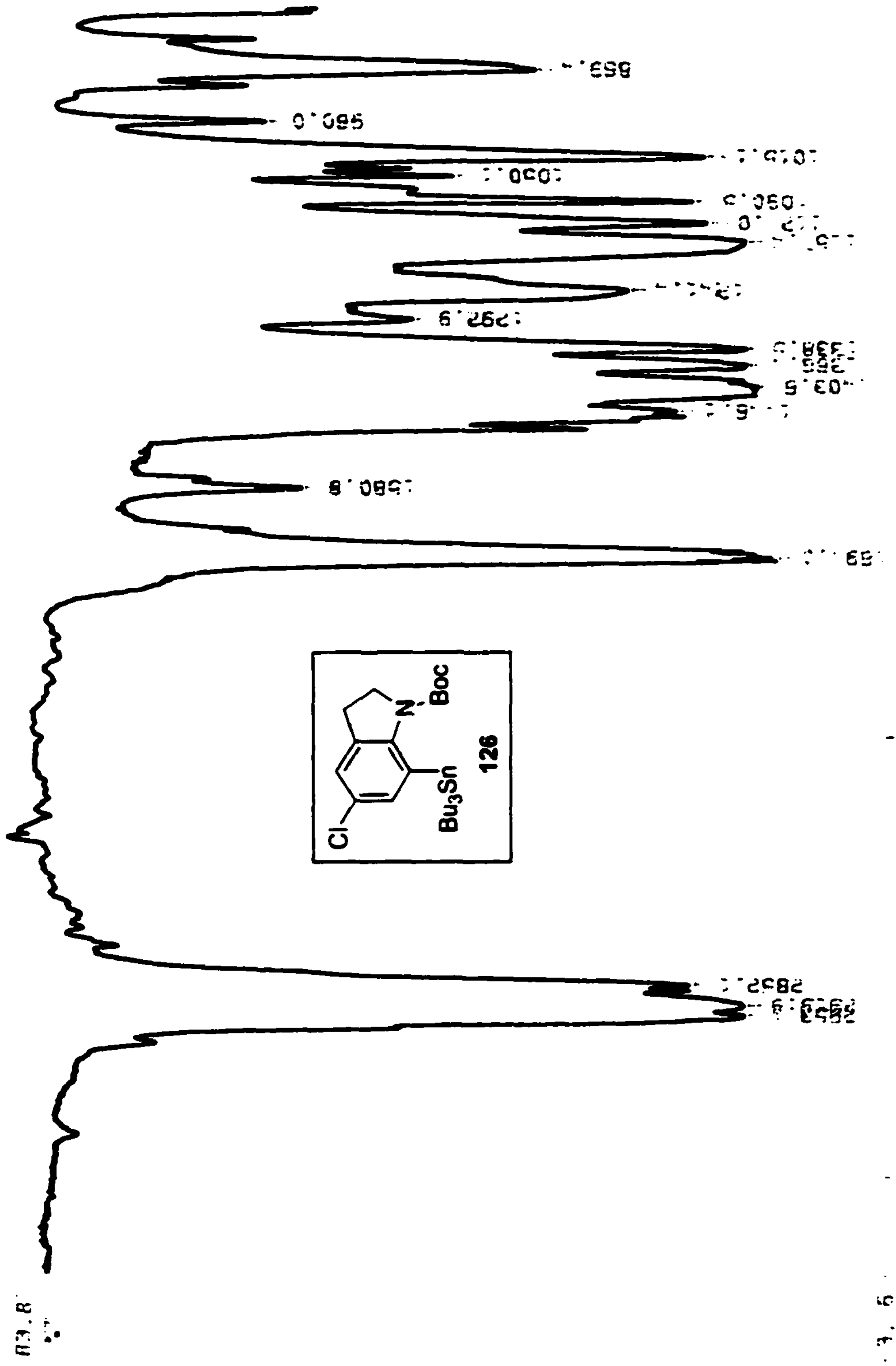

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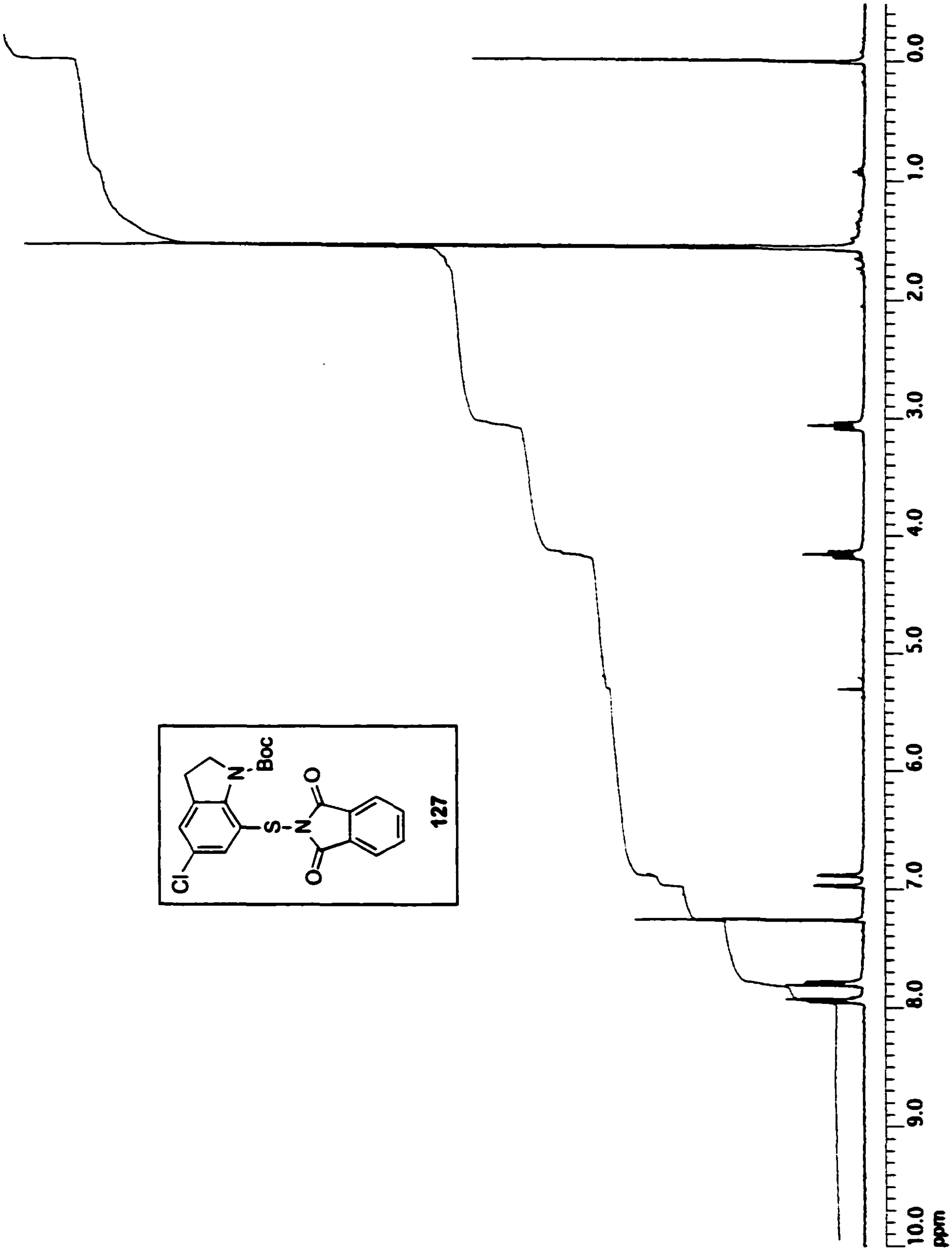
Cl
N
Boc
S
N
O
O
127
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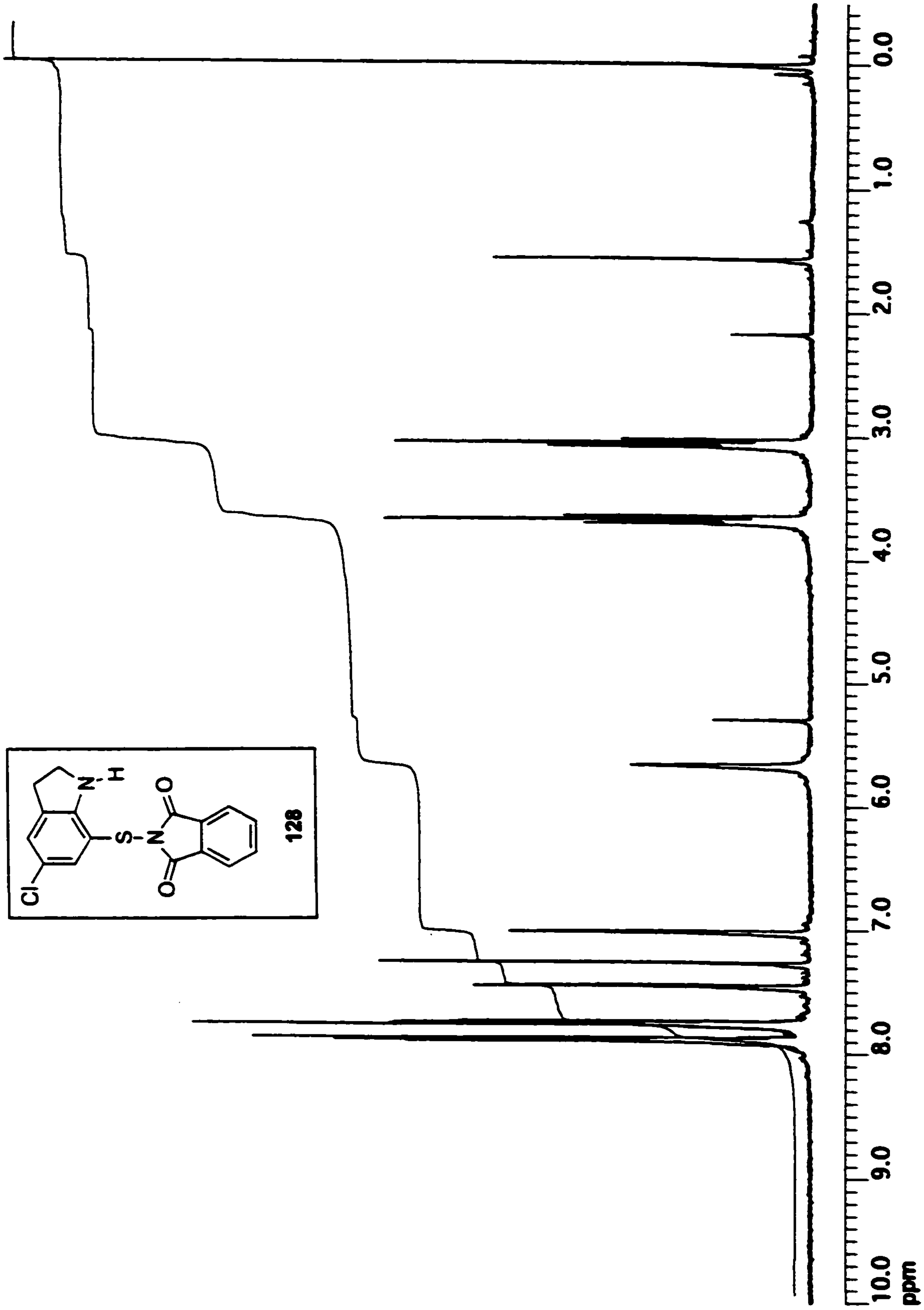
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm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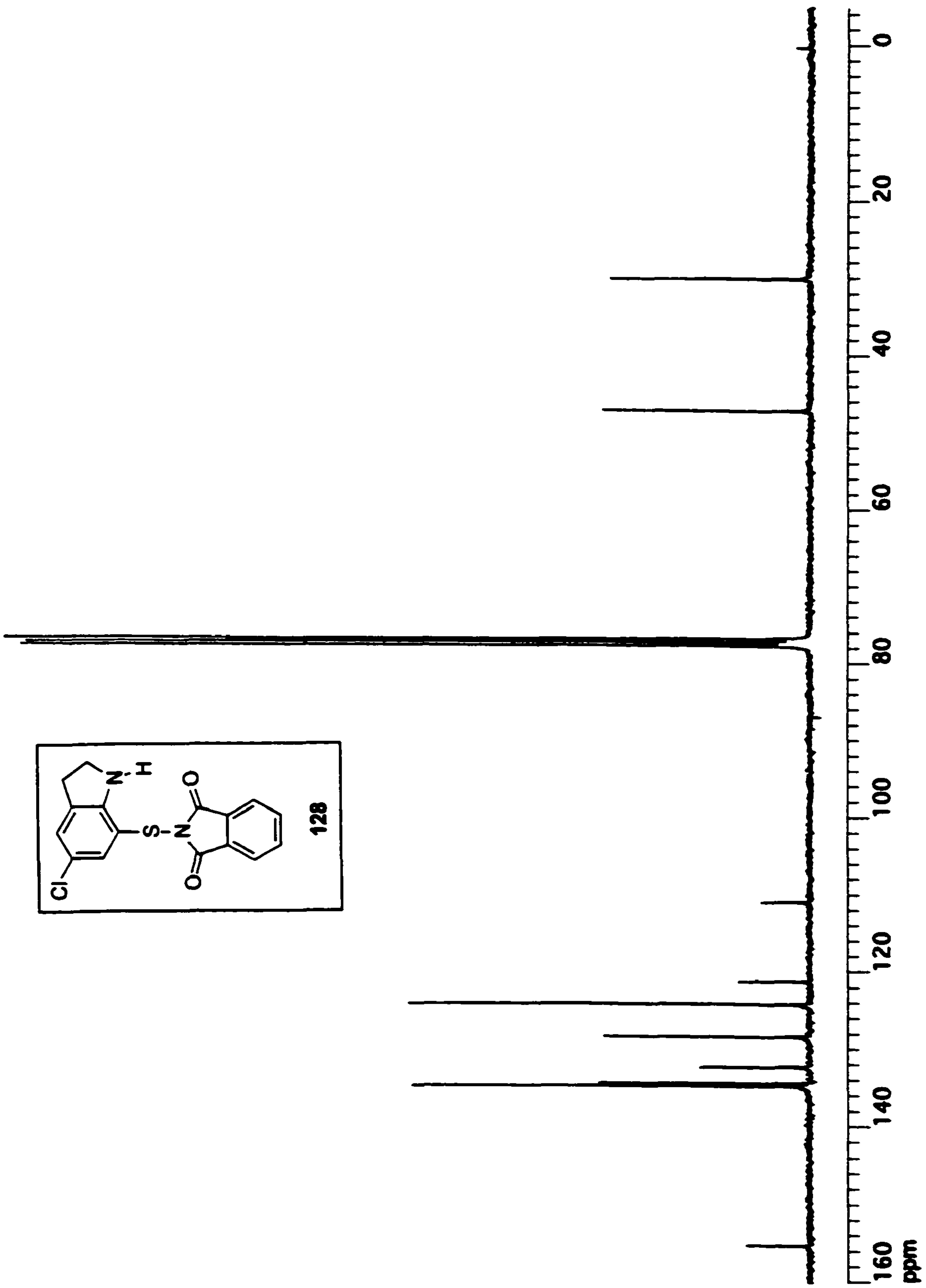
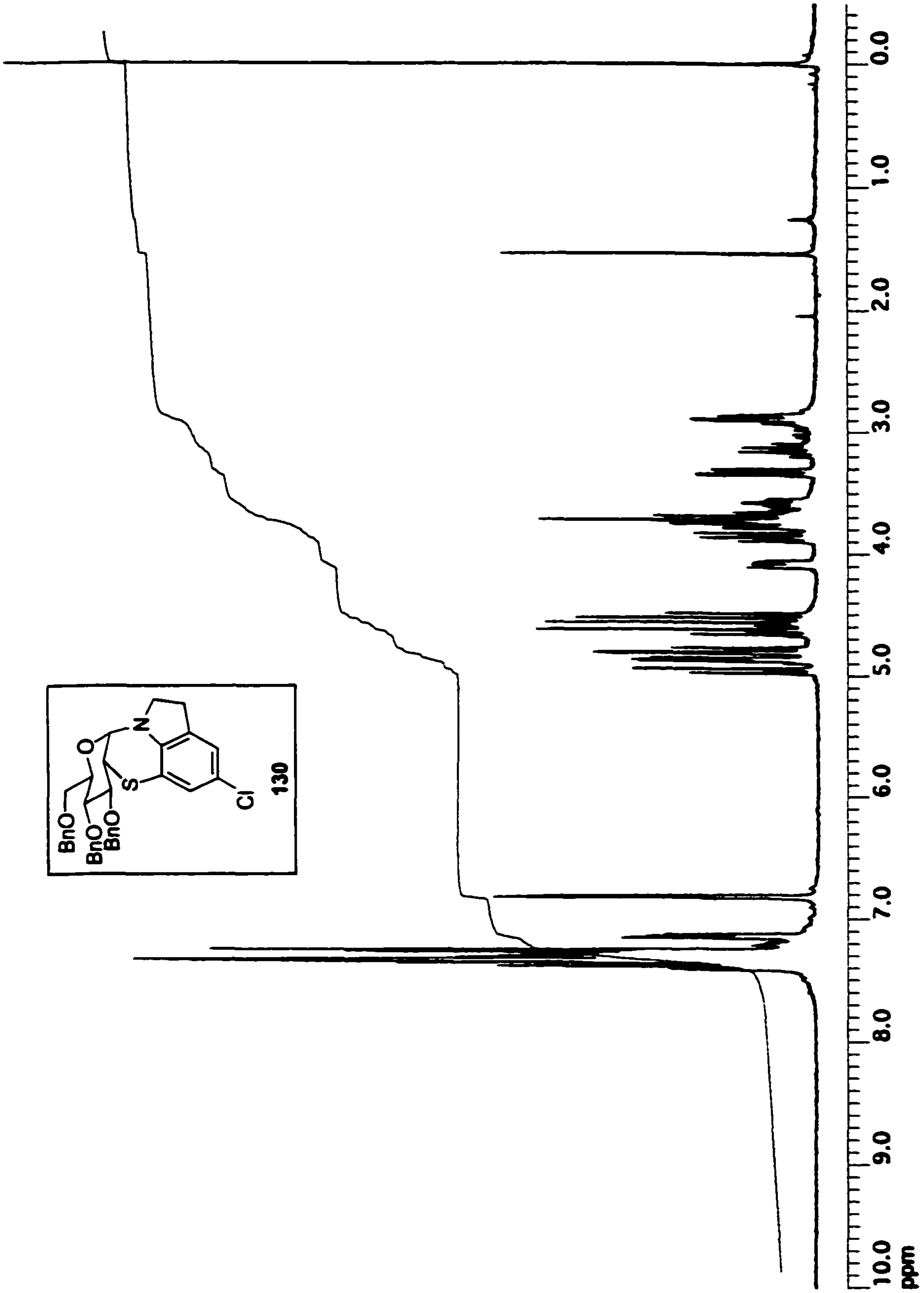
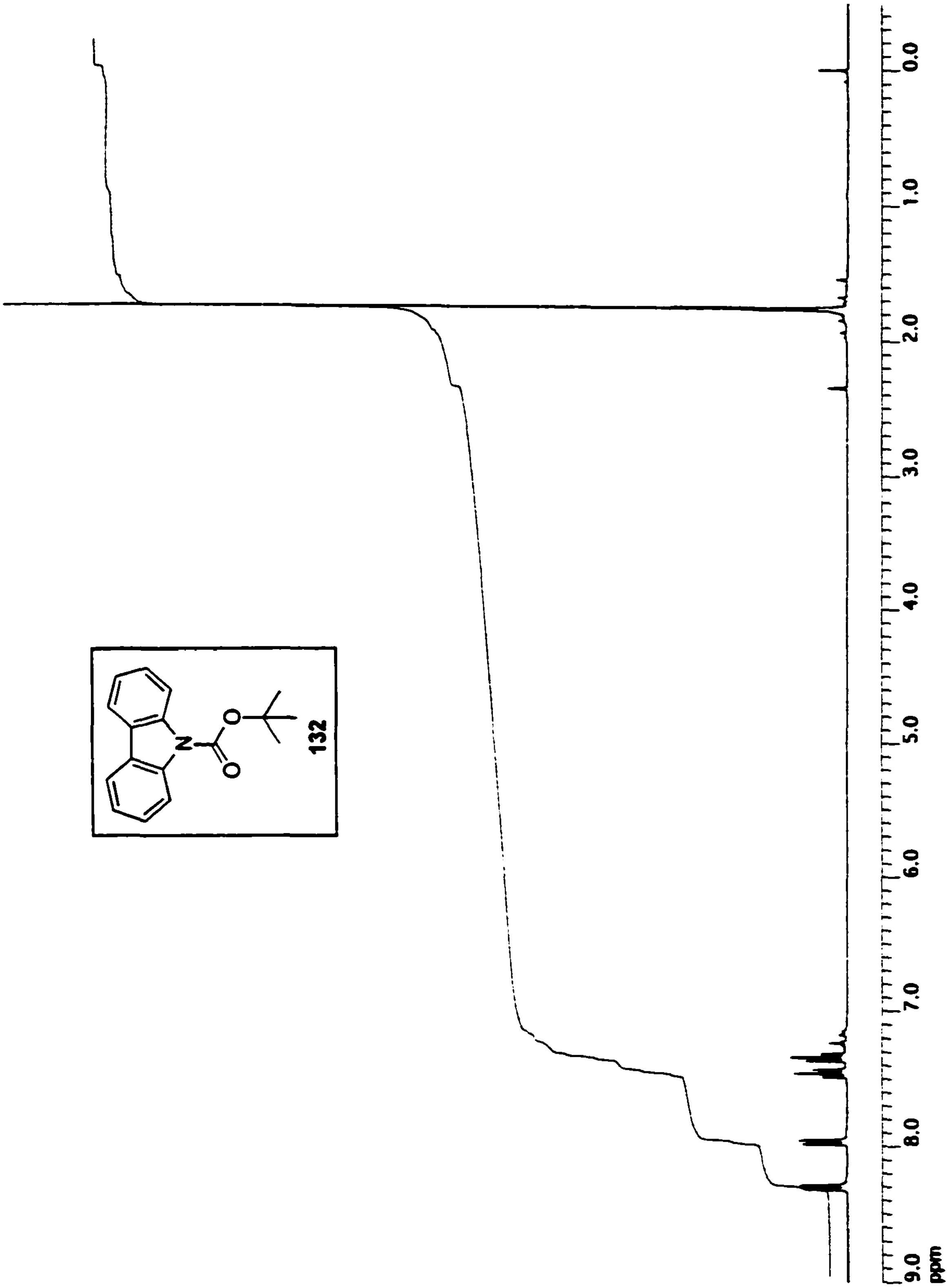


0
20
40
60
80
100
120
140
160
ppm
Cl
N
H
S
N
O
O
128



0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
ppm
BnO
BnO
BnO
O
N
S
Cl
130



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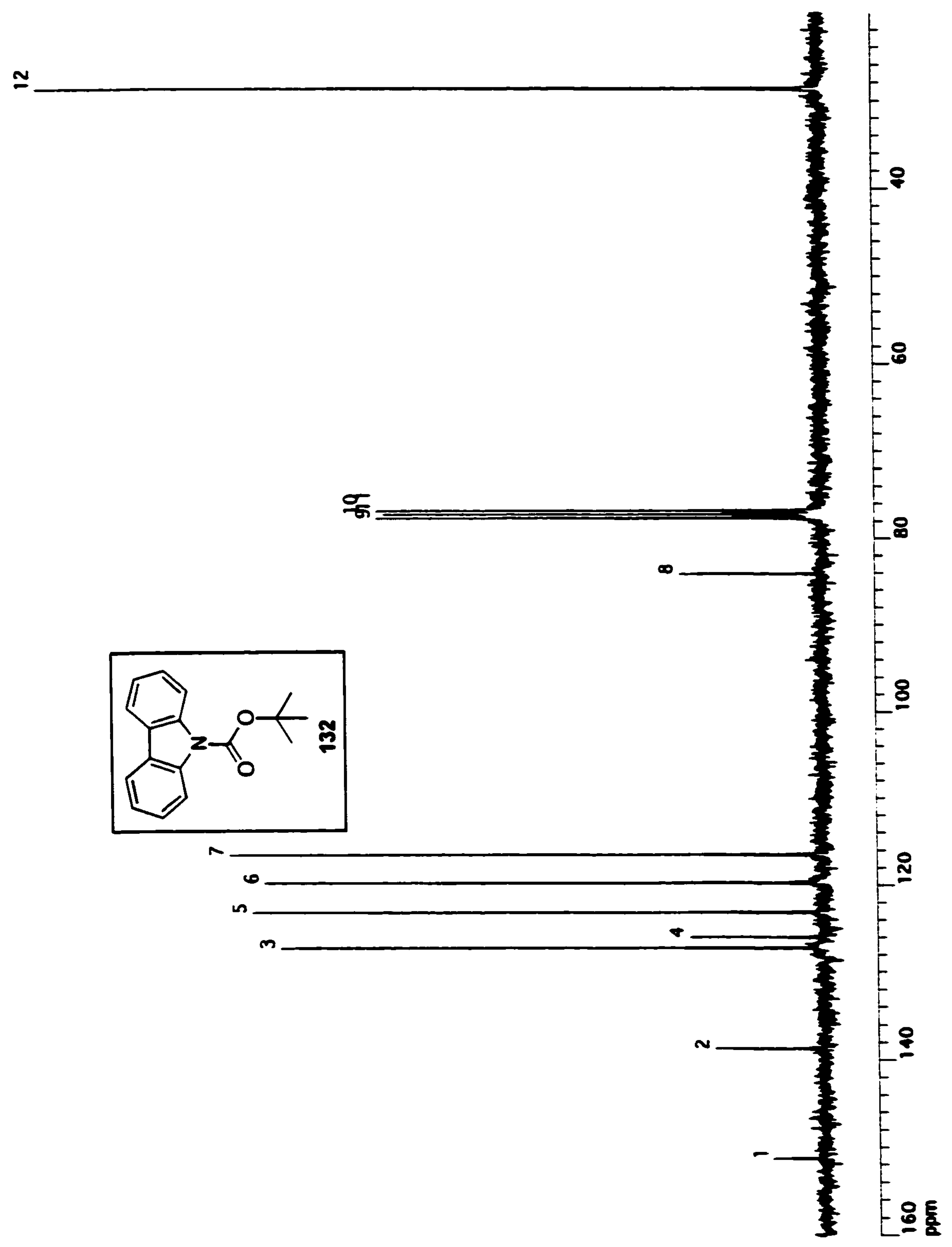
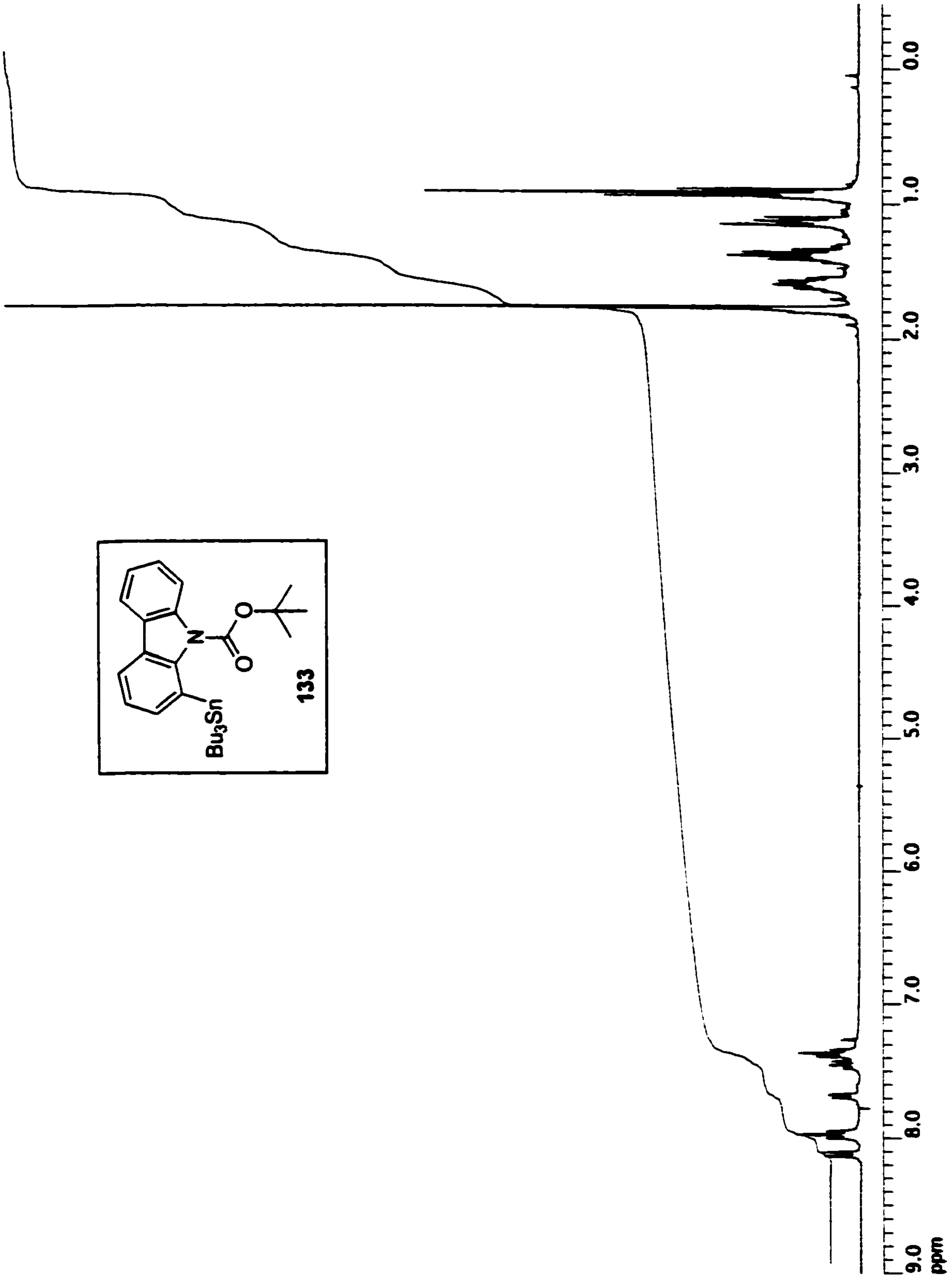

12
10
9
11
8
7
6
5
4
3
2
1
O
N
132
40
60
80
100
120
140
160
ppm


Bu$_3$Sn
N
O
O
133
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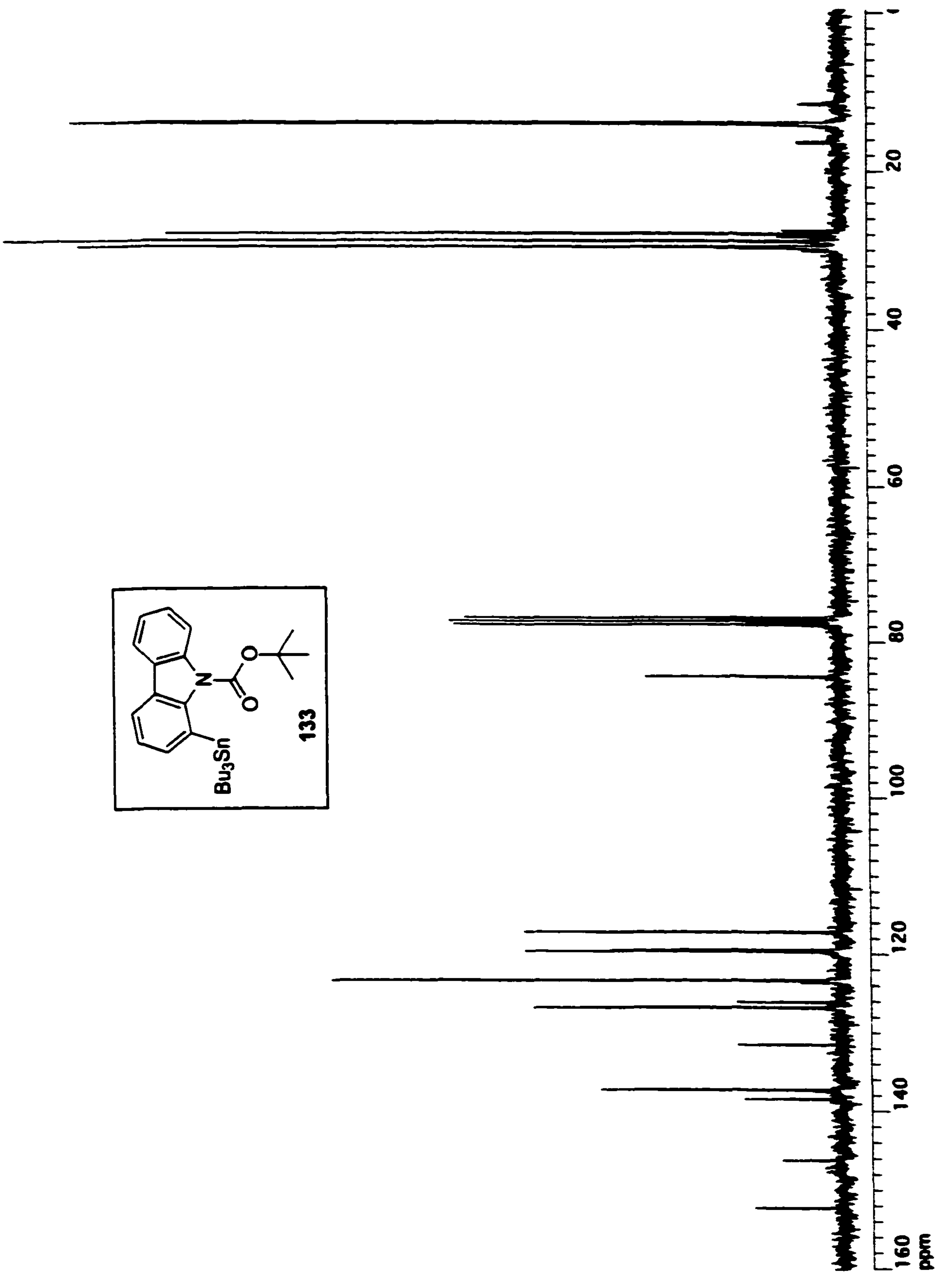
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm



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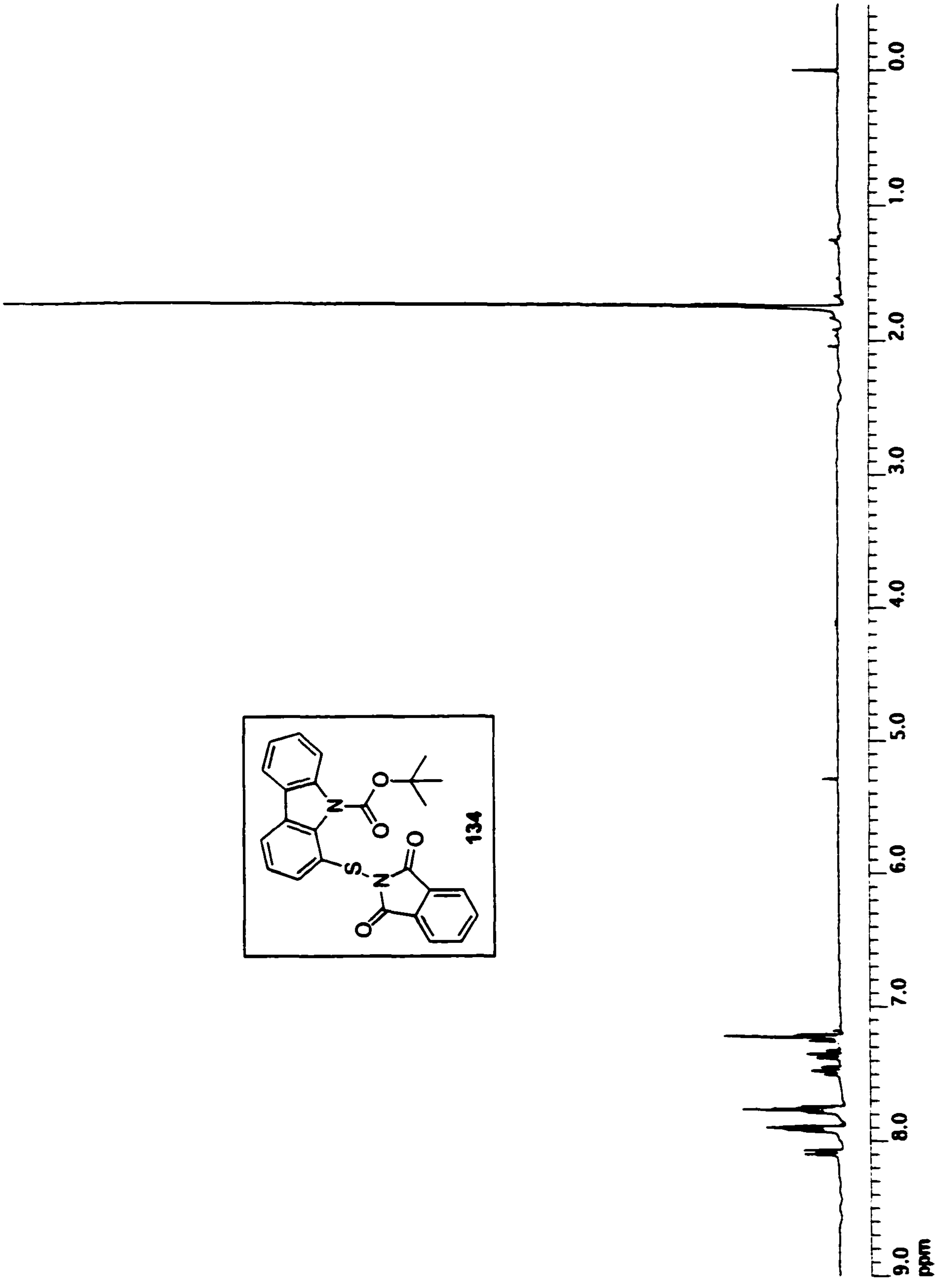
134
S
N
O
O
N
O
O
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7.0
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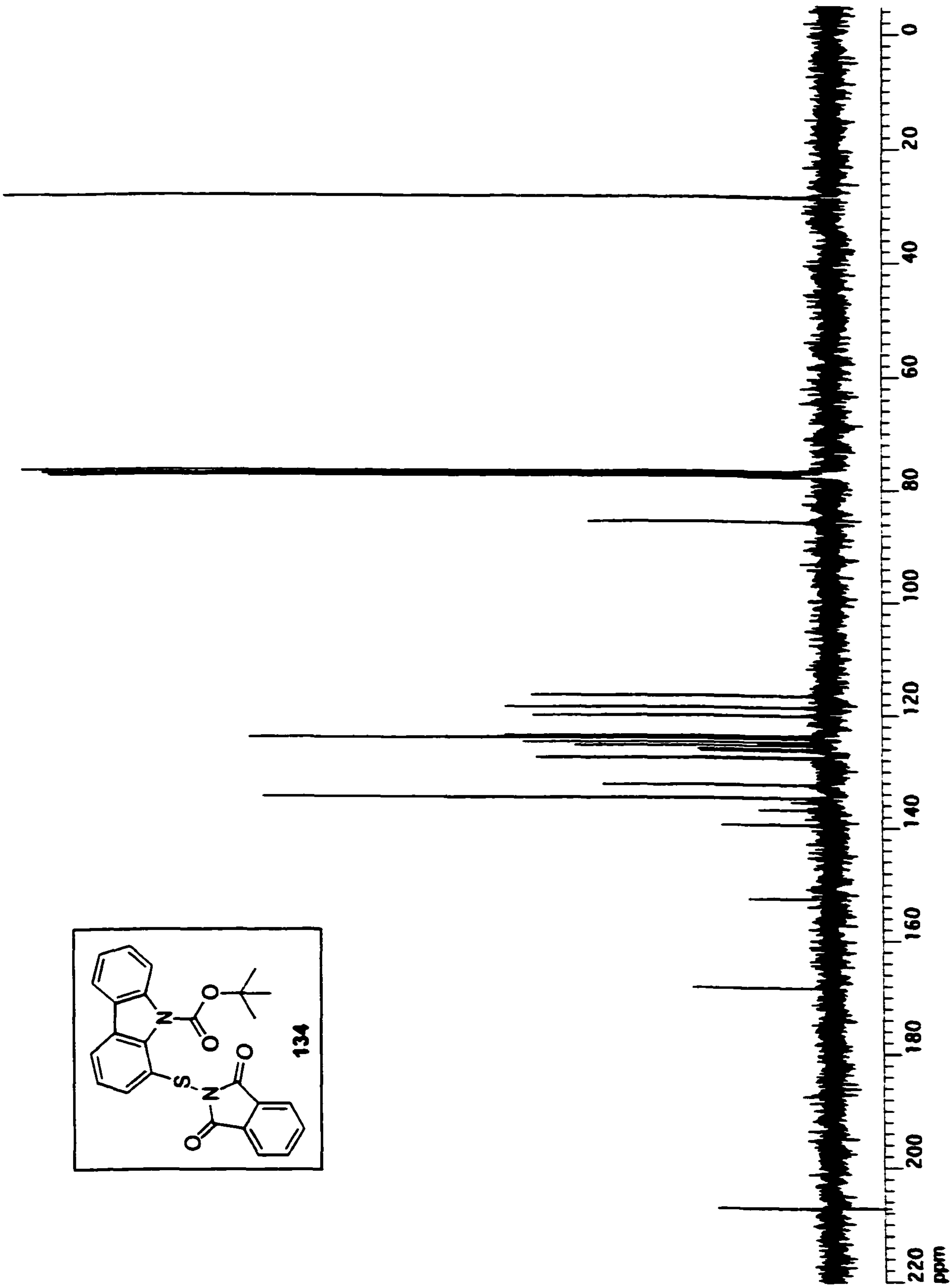
2.0
1.0
0.0
ppm


134
N
O
O
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N
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O
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20
40
60
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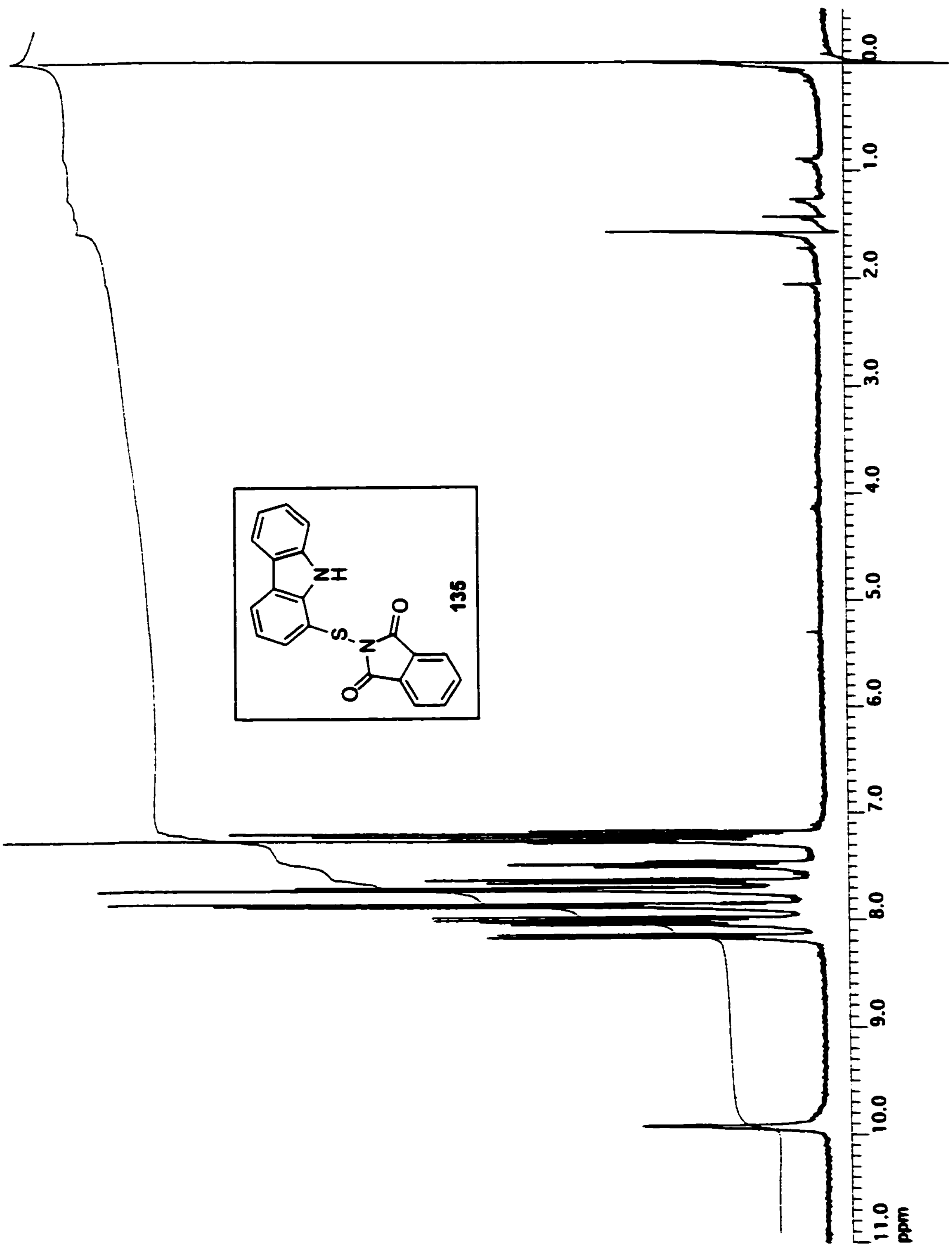
100
120
140
160
180
200
220
ppm



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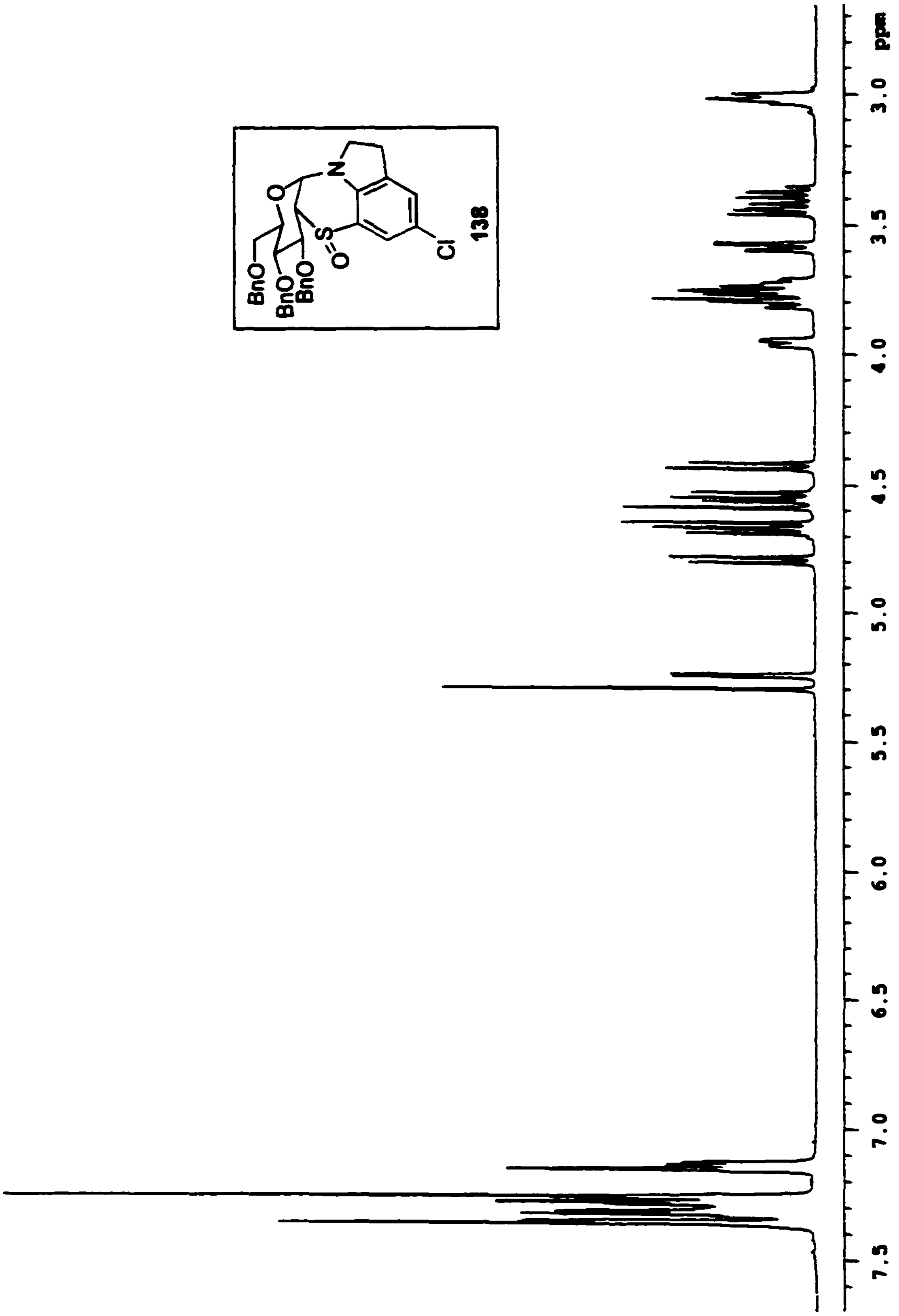
BnO
BnO
BnO
O
N
S
O
Cl
138
ppm
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3.5
4.0
4.5
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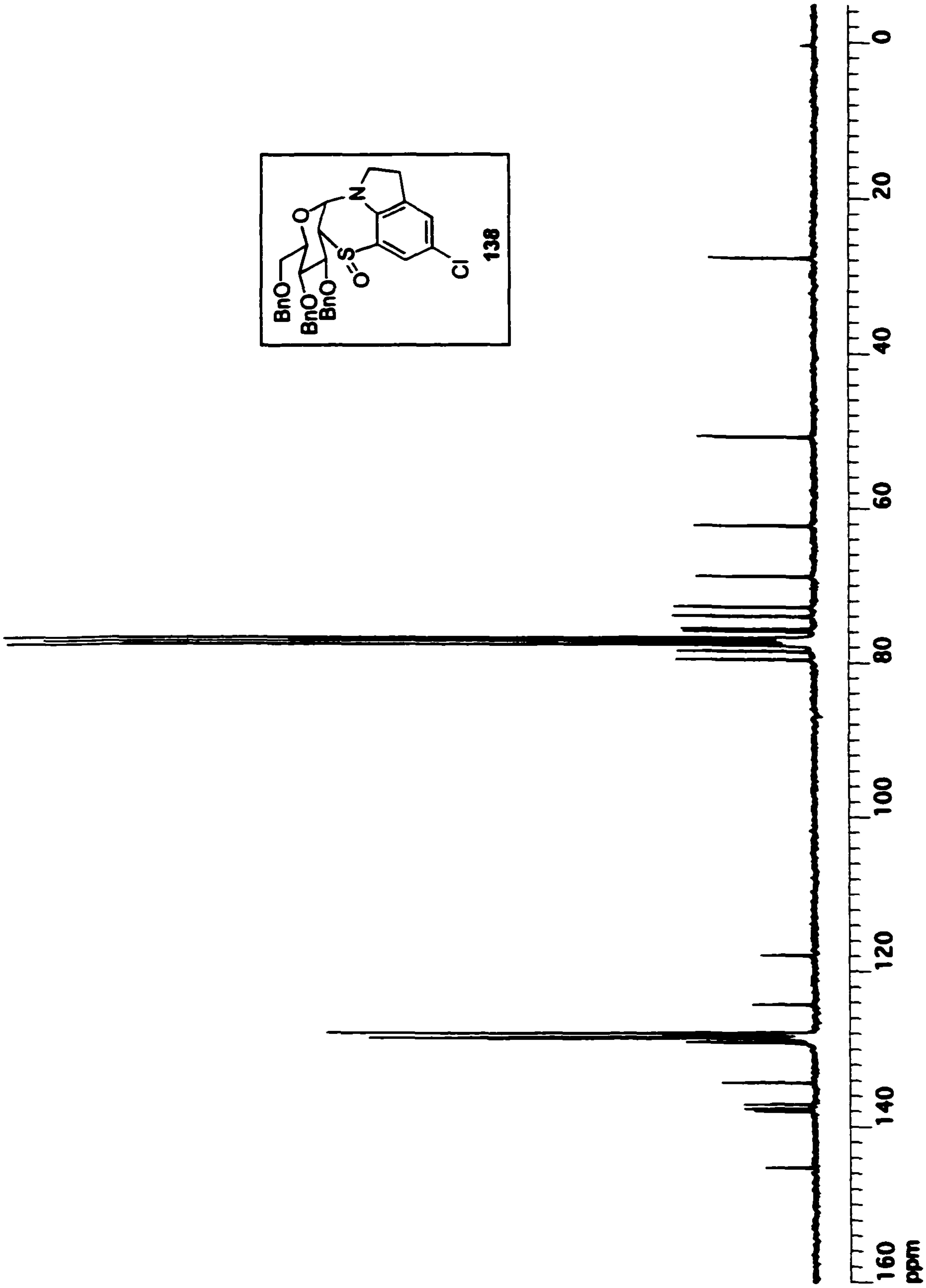
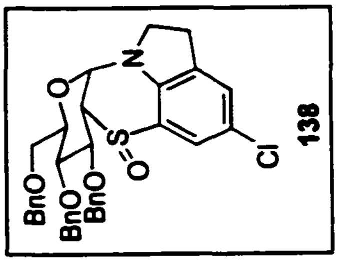
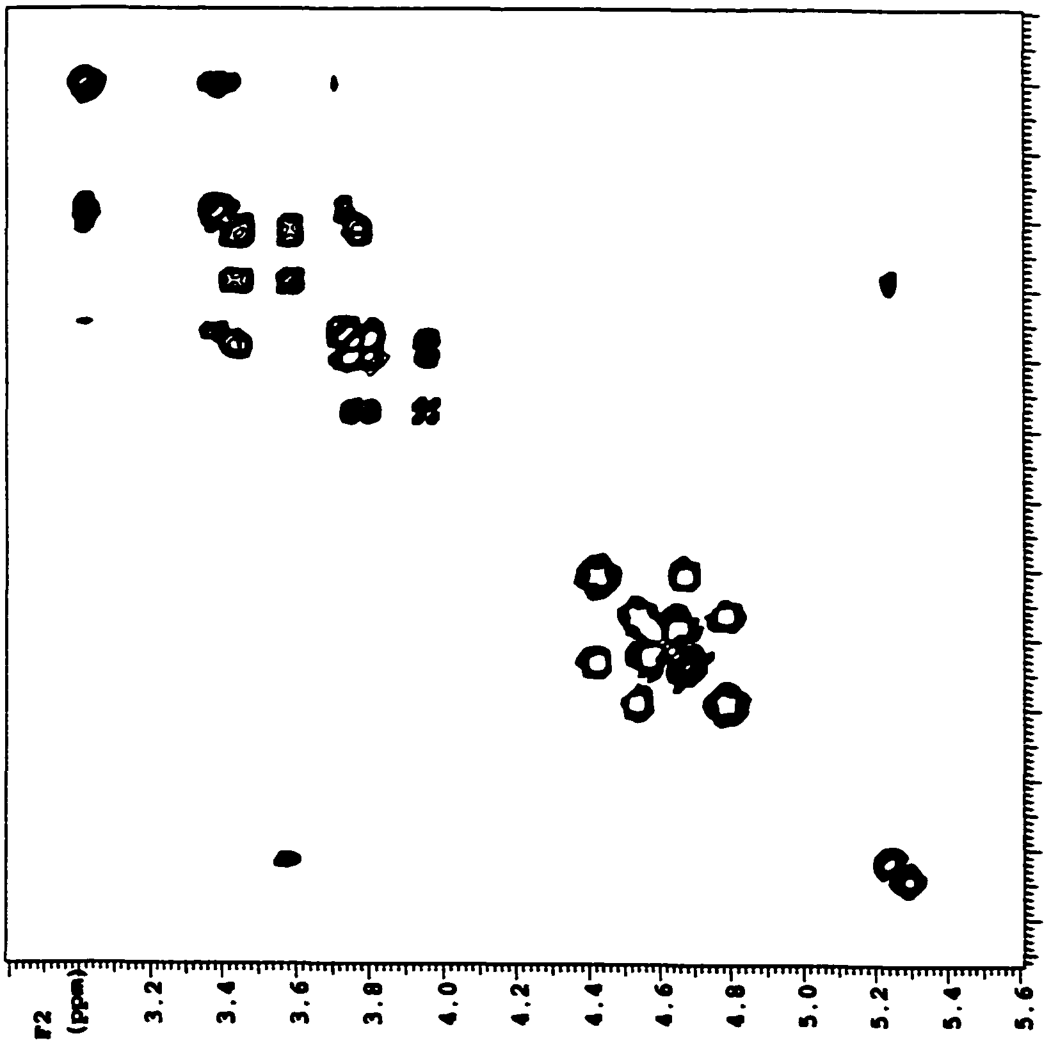
5.5
6.0
6.5
7.0
7.5

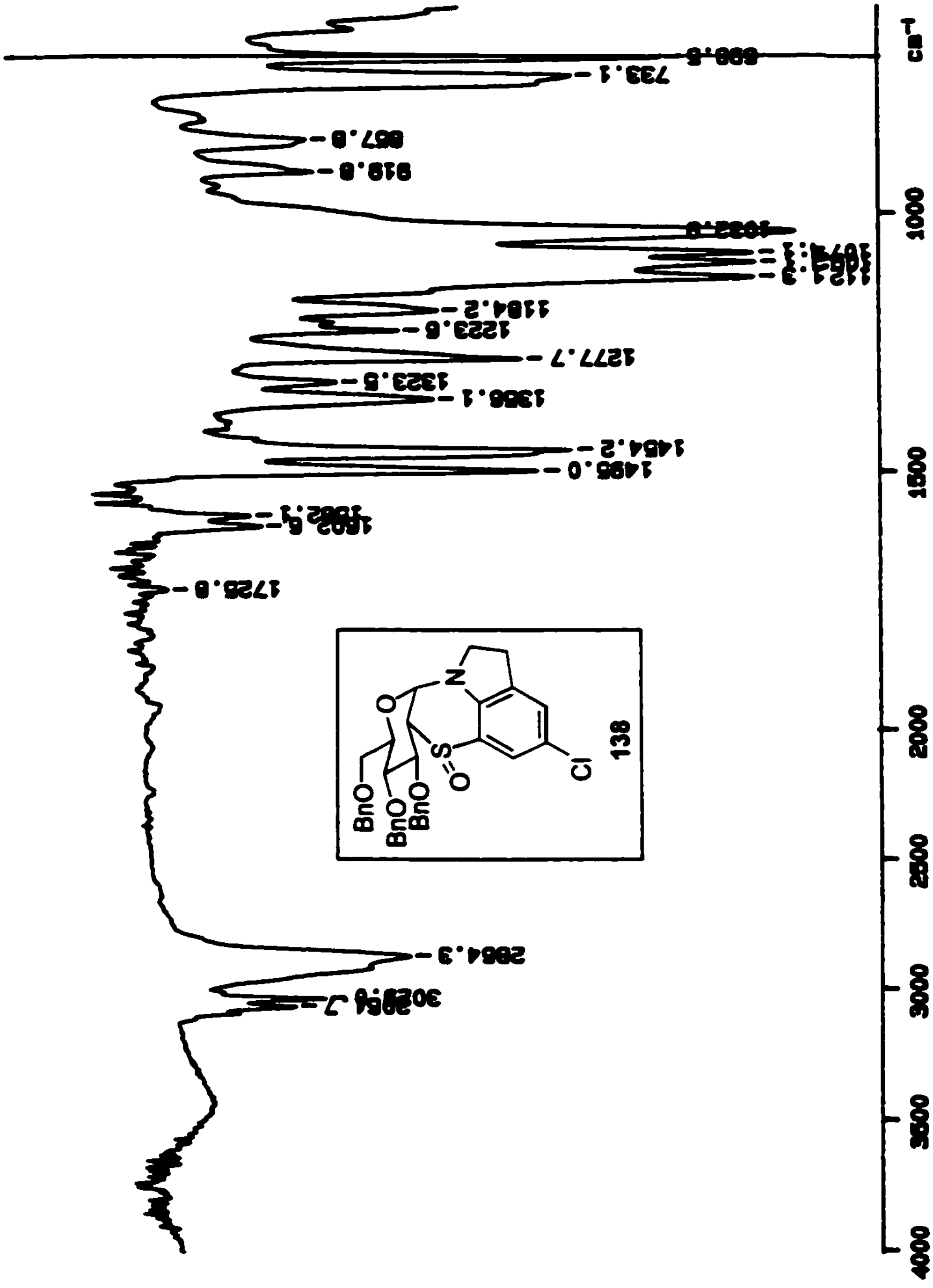


138


BnO
BnO
BnO
O
S
O
N
Cl

138


F1 (ppm)
3.0
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
F2 (ppm)
3.2
3.4
3.6
3.8
4.0
4.2
4.4
4.6
4.8
5.0
5.2
5.4
5.6


cm^{-1}
1000
1500
2000
2500
3000
3500
4000
698.5
733.1
857.8
919.8
1032.0
1074.1
1094.1
1121.3
1184.2
1223.6
1277.7
1323.5
1366.1
1454.2
1495.0
1582.1
1602.6
1725.8
2864.3
3029.6
3064.7
BnO
BnO
BnO
O
S
O
N
Cl
138

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