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A base modulated synthesis of indoles and quinolines, an expedient synthesis of salviadione, and chemoselective couplings en route to indoles and pyrroloindoles

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A Base Modulated Synthesis of Indoles and Quinolines, An Expedient Synthesis of Salviadione, and Chemoselective Couplings en route to Indoles and Pyrroloindoles

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ABSTRACT

A Base Modulated Synthesis of Indoles and Quinolines, An Expedient Synthesis of

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Matthew Marshall Cummings

Palladium-catalyzed reductive *N*-heteroannulation of *ortho*-nitrostyrenes has become a synthetically useful method for the construction of indoles and indole-based heterocycles. Söderberg's elaboration of this methodology has been utilized in the synthesis of indoles and quinolines from a common precursor. The same protocol has also been employed in the synthesis of the indole alkaloid Salviadione. A systematic investigation of chemoselectivity in Kosugi-Migita-Stille coupling reactions provided the basis for the synthesis of isomeric pyrroloindoles through palladium-catalyzed reductive double *N*-heteroannulation of dinitro-dialkenyl benzenes

Acknowledgements

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Chapter 1

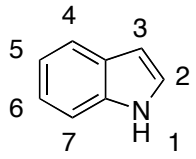
Introduction to Indole, History of Indole, and Historical Routes to the Indole Core

1.1 Indole Background and Notable Indoles

Indole (**1**) is the common name for the molecule featuring a pyrrole ring fused to a benzene ring along the 2- and 3-positions of the pyrrole.[1] The name indole itself is in relation to indigo, which is the parent compound from which indole was originally isolated through treatment with oleum.

The atoms of indole are numbered according to the following scheme[2]: the nitrogen atom is designated atom 1 and proceeds around the pyrrole portion of the molecule in a counter-clockwise fashion (Figure 1). The carbons where the pyrrole is fused to the benzene ring are often times denoted "3a" and "7a".

Figure 1: Structure and Numbering of Indole

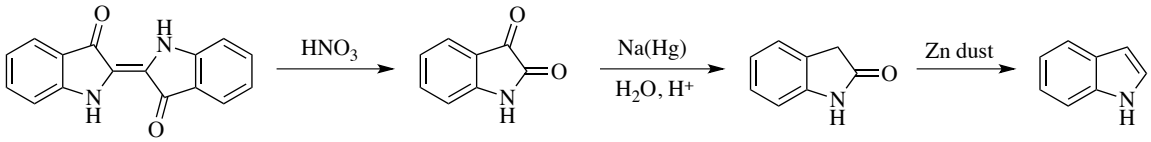


1

Indole is a planar heteroaromatic molecule composed of a ten-electron pi-system made up of two electrons from the nitrogen atom and eight electrons from the remaining eight carbon atoms.[3] Due to it having more pi-electrons than atoms, indole is often referred to as a "pi-excessive" aromatic compound.[4] Typically, the 3-position of indole is highly reactive towards electrophilic species on the basis of pi-electron density, localization energy, and molecular orbital calculations.[3] As expected, the amino-group of indoles is fairly acidic with a pKa of 17, possessing the ability to form an anion in the presence of a strong base.[4] While the resulting electron pair of the anion does not lie within the pi-system, it still serves as a basis for the increased reactivity of the 3-position toward electrophiles.[5]

The preparation of indoles and indole-based derivatives has been a topic of interest for more than a century, beginning with the initial development of indole triggered by the dye industry. Oxidation of indigo (**2**) to isatin (**3**) was achieved by Baeyer and Knopp[6], who then reduced isatin (**3**) to oxindole (**4**) (Scheme 1). Pyrolysis of **4** in the presence of zinc dust afforded indole (**1**). Baeyer[7] first reported the formula of indole, which is still accepted today, in 1869.

Scheme 1: Initial Preparation of Indole from Indigo



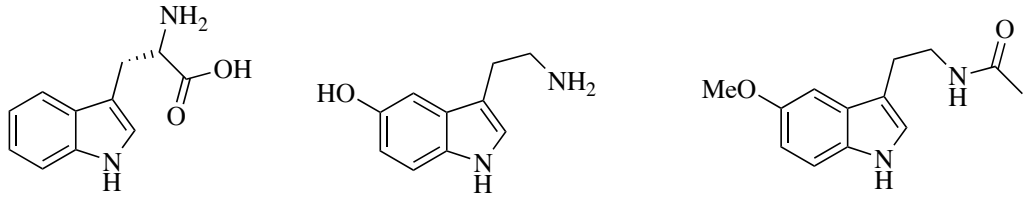
2 **3** **4** **1**

The main use of indoles through the end of the 19th century was within the dyestuff industry. While the dye applications of indoles declined in the early 20th century, organic dyes still account for approximately $14.4 billion in global production.[8]

Interest in indole-based molecules was re-ignited in the 1930's as interest in alkaloid chemistry grew.[9] The diverse structures of indole alkaloids leads to their wide range of biological activities and in turn triggered an increase in research toward the preparative methods of indoles.[3]

A number of indole-based molecules are involved in processes within the human body. The amino acid *L*-tryptophan (**5**)[10] is essential to the human diet while also functioning as a precursor for the neurotransmitter serotonin (**6**)[11], which can be further converted to the neurohormone melatonin (**7**)[12] (Figure 2).

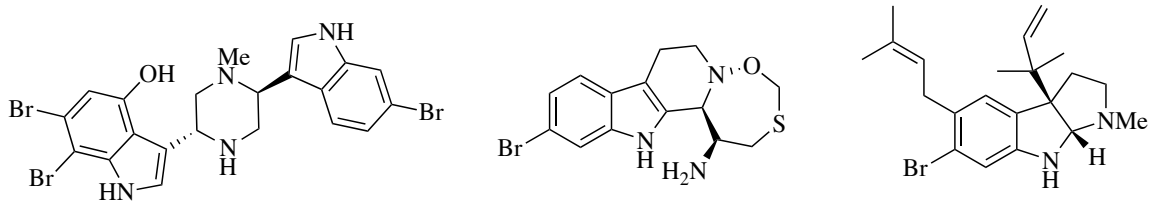
Figure 2: Structures of L-tryptophan, Serotonin, and Melatonin



5 **6** **7**

Indole alkaloids make up a quarter of the marine alkaloids and are considered to be the most structurally complex molecules of this class.[13] Indole alkaloids have been isolated from a number of marine species, including sponges, tunicates, red algae, acorn worms, and symbiotic bacteria.[13] In addition, marine alkaloids often possess structural features uncommon to terrestrial species, such as halides (Figure 3). Dragmacidin (**8**)[14], isolated from the deep water sponge *Dragmacidin* sp., has exhibited *in vitro* cytotoxic activity against a number of cancer cell lines including lung, colon, and mammary.[11] The novel oxathiazepine containing alkaloid Eudistomin K (**9**)[15], isolated from the Caribbean tunicate *E. olivaceum*, inhibits herpes simplex virus-1 growth.[13] Flustramine D (**10**)[16], isolated from the marine bryozoan *F. foliacea*, exhibits inhibition of a wide spectrum of bacterial including *E. coli*, *S. typhimurium*, *S. aureus*, and *S. epidermidis*.[13]

Figure 3: **Structures of Dragmacidin, Eudistomin K, and Flustramine D**

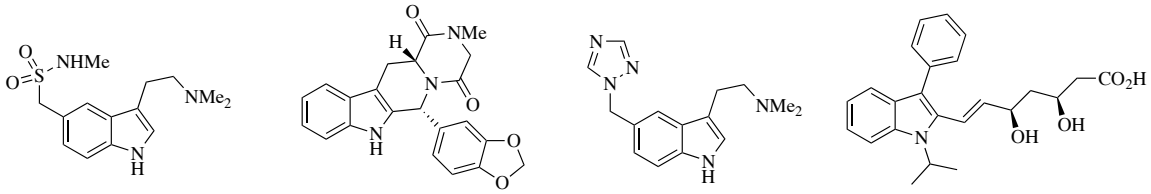


8 **9** **10**

Synthetic indoles have also found applications in the medicinal field. Sumatriptan (**11**)[17], tadalafil (**12**)[18], rizatriptan (**13**)[19], and fluvastatin (**14**)[20], all containing an indole motif, accounted for over $3.2 billion in sales in 2010 (Figure 4).[21] Sumatriptan and rizatriptan have found use as anti-migrane drugs[21], tadalafil (commonly known as Cialis)

is used to treat erectile dysfunction[22], and fluvastatin is used to prevent cardiovascular disease[23].

Figure 4: Structures of Sumtriptan, Tadalafil, Rizatriptan, and Fluvastatin



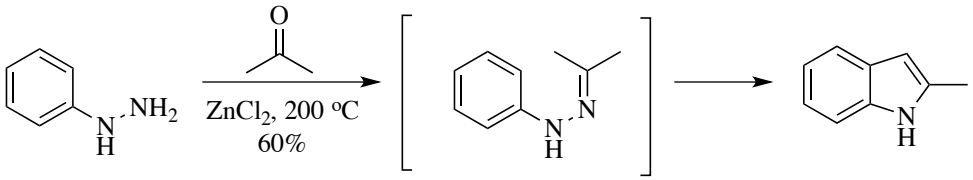
11 **12** **13** **14**

Indoles have found applications in a number of areas. Their initial use as dyestuffs gradually progressed to exploration of their uses as biological compounds. With advances in isolation and characterization techniques, numerous novel indole alkaloids are reported annually. This has in turn triggered a heightened interest in preparative methods of indoles, which will be discussed in the following section.

1.2 Classical Routes to the Indole Core

One of the most widely applied methods for the preparation of indole intermediates en route to biologically active compounds[25] is the Fischer indole synthesis.[26, 27] Developed in 1883, it allowed for the relatively simple conversion of enolizable *N*-arylhydrazones to indoles. In a simplistic example, condensation of aryl hydrazine **15** with 2-butanone afforded intermediate hydrazone **16** which then underwent cyclization to afford indole **17** (Scheme 2). Addition of a protic or Lewis acid (typically $ZnCl_2$) served two purposes: to assist in the tautomerization in order to form the enehydrazine as well as to facilitate cleavage of the N-N bond.[4, 25]

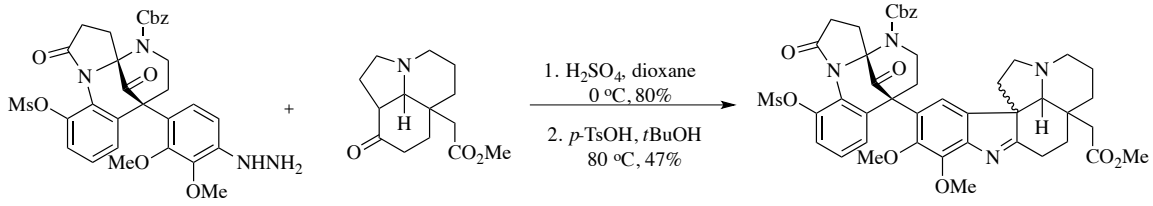
Scheme 2: Fischer Indole Synthesis



15 **16** **17**

A Fischer cyclization was employed as a key step in Fukuyama's synthesis of haplophytine.[28] Condensation of tricyclic ketone **18** with aryl hydrazine **19** followed by heating in the presence of *p*-toluenesulfonic acid afforded indoline **20** which was then converted to haplophytine in six additional steps (Scheme 3). The structural complexity of both substrates highlights the broad scope and functional group tolerance of the Fischer method.

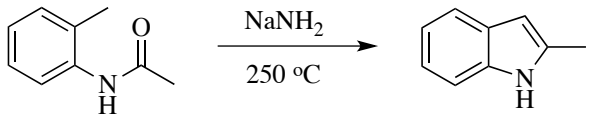
Scheme 3: **Fischer Cyclization en route to Haplophytine**



18 **19** **20**

The Madelung indole synthesis used high temperatures to convert *N*-phenylamides to indoles through intramolecular cyclization in the presence of a strong base.[29] The first reported example prepared 2-methylindole (**18**) from *o*-methylacetanilide (**21**) through treatment with sodium amide and heating at 250°C (Scheme 4).[30]

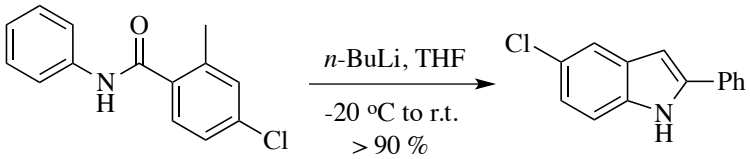
Scheme 4: Madelung Indole Synthesis



21 **17**

One downfall of these conditions was that they were extremely harsh and in turn limited the scope of functionality.[4] However, a number of modifications which utilized much milder conditions were also been reported. The Houlihan modification[31] employed the use of either *n*-butyllithium (*n*-BuLi) or lithium *N,N*-diisopropylamide (LDA) as the base and required much lower reaction temperatures. Using these conditions, *N*-(4-chloro-2-methylphenyl)benzamide (**22**) was converted to 5-chloro-2-phenylindole (**23**) through treatment with two equivalents of *n*-BuLi in tetrahydrofuran at -20°C (Scheme 5).[32]

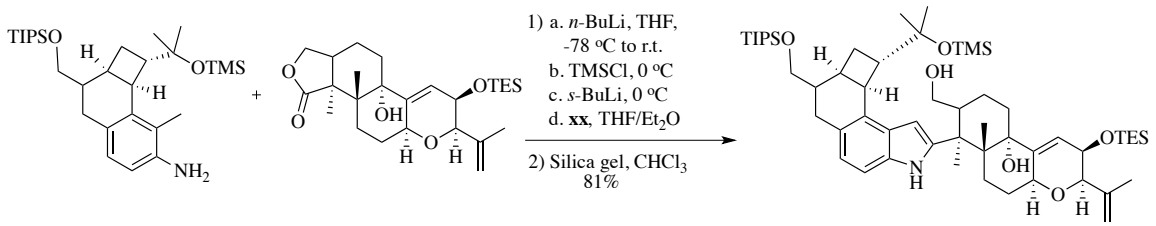
Scheme 5: Houlihan Modification of Madelung Indole Synthesis



22 **23**

An elegant application of the Madelung route was presented in the synthesis of penitrem D.[33] This approach was daring in that it was applied at a late stage in the synthetic route. Condensation of aniline **24** with cyclic ester **25** was afforded heptacyclic indole **26** in excellent yield (Scheme 6).

Scheme 6: Madelung Methodology in the Synthesis of Penitrem D

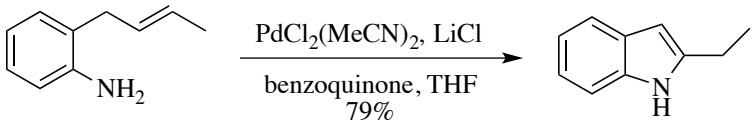


24 **25** **26**

1.3 Transition Metal Catalyzed Indole Synthesis

An early example of palladium-catalyzed indole preparation was reported by Hegedus *et al*. in 1976.[34] This intramolecular elaboration of their earlier finding of palladium-assisted amination of olefins[35] involved cyclization of an *o*-allylaniline **27** in the presence of palladium (II) catalysts to afford 2-substituted indole **28** (Scheme 7). The relatively mild reaction conditions accommodated a number of functional groups and was later applied in the preparation of ergot alkaloids.[36]

Scheme 7: Hegedus Palladium-catalyzed Cyclization of *o*-Allylanilines

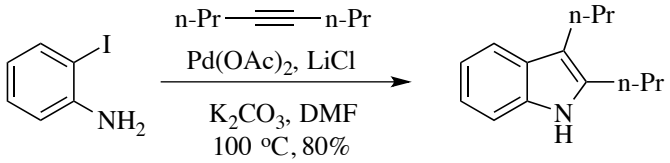


27 **28**

Larock *et al.*[37] described a convenient preparation of 2,3-disubstituted indoles **31** via palladium-catalyzed heteroannulation between *o*-iodoaniline (**30**) and internal alkynes (Scheme 8). This methodology allowed for the preparation of highly functionalized indoles with regioselective control based on the identities of the substituents on the alkyne. The reaction's versatility has led to its application in the synthesis of a number of pharmaceutical compounds including Maxalt[19] and Avitriptan.[38] However, the Larock cyclization has been limited by the requirement of iodoaniline substrates, which are often

more expensive or not commercially-available in comparison to the corresponding bromo- or chloroanilines.[39]

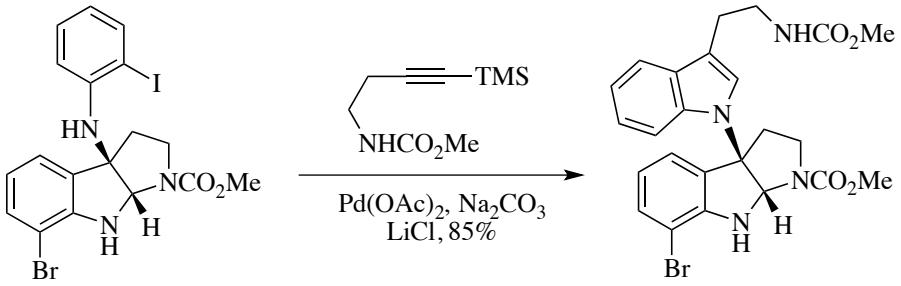
Scheme 8: Larock Heteroannulation of Internal Alkyne with *o*-Iodoaniline



30 **31**

A practical application of Larock methodology was in the synthesis of psychotrimine by Baran *et al*.[40] Attempts to use pre-formed indoles as nucleophiles to prepare intermediate **33** were unsuccessful, however, a Larock cyclization between 2-iodoaniline derivative **32** and the properly substituted alkyne afforded bis-indole **33** in gram amounts (Scheme 9).

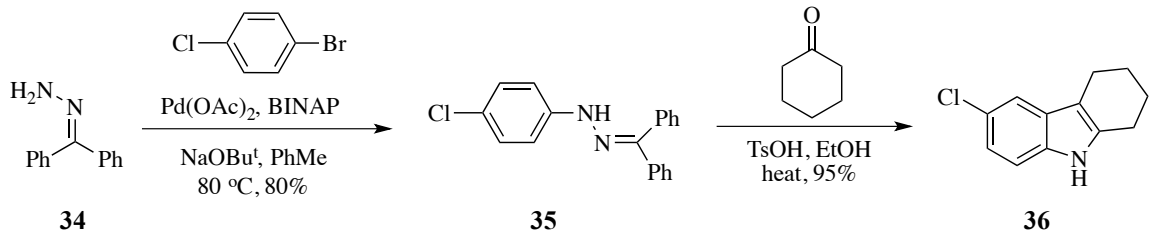
Scheme 9: **Baran's Synthesis of Psychotrimine via Larock Cyclization**



32 **33**

Buchwald's aryl amination methodology[41] has also been applied toward the synthesis of indoles and indole derivatives. Palladium-catalyzed intermolecular amination of aryl bromide with inexpensive benzophenone hydrazone **34** afforded hydrazone **35**, which was converted to indole **36** upon heating under acidic conditions (Scheme 10).[42] This method broadens the scope of the Fischer cyclization by providing an alterative method to prepare the requisite *N*-arylhydrazone precursors.

Scheme 10: Buchwald Indole Synthesis via Intramolecular Amination

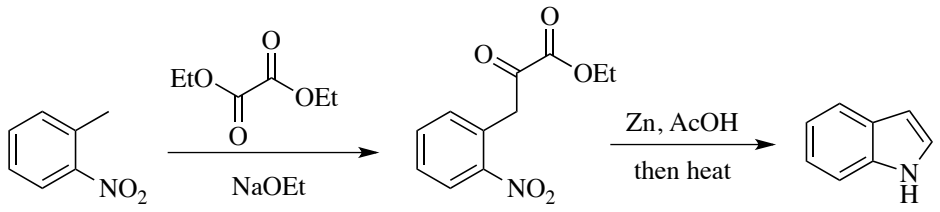


34 **35** **36**

1.4 Indole Synthesis via Reductive Cyclization

An early example of indole synthesis via reductive heterocyclization was the Reissert method.[43] In this route, an *o*-nitrobenzylcarbonyl compound **38**, prepared through the condensation of an *o*-nitrotoluene (**37**) and an oxalic ester, underwent reductive cyclization the presence of zinc to afford indole-2-carboxylic acid derivatives, which then decarboxylated to give indole (**1**) (Scheme 11).

Scheme 11: Reissert Method for Indole Preparation

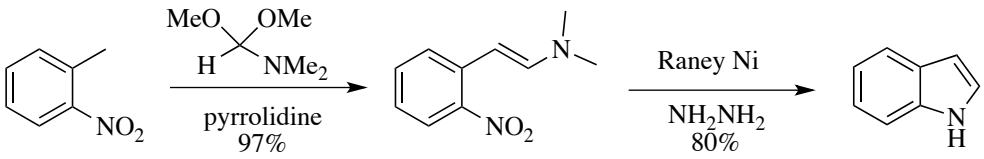


37 **38** **1**

Another commonly used method in indole synthesis was the Leimgruber-Batcho route.[44] This method, similar to the Reissert route, involved the condensation of *o*-nitrotoluenes **37** with dimethylformamide dimethyl acetal (DMFDMA), affording an intermediate *B*-(dimethylamino)-2-nitrostyrene **38** which then underwent reductive heterocyclization to afford indole (**1**) (Scheme 12). The success of the initial condensation was attributed to the increased acidity of the benzylic protons on account of the *ortho* nitro substituent.[44] The addition of pyrrolidine resulted in the generation of a

more reactive aminomethylenating reagent and was found to significantly shorten reaction times.[44]

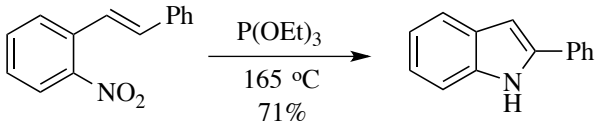
Scheme 12: Leimgruber-Batcho Indole Synthesis



37 **38** **1**

Another method for indole synthesis that has received considerable attention involves reductive cyclization of *o*-nitrostyrenes. This method was pioneered by Cadogan[45], who used trivalent phosphorous compounds to form indoles through deoxygenation of nitroaromatics. An early example involved heating *o*-nitrostyrene **39** in triethylphosphite, affording 2-phenylindole (**40**) in good yield (Scheme 13).[45]

Scheme 13: Cadogan and Sundberg's Reductive Heterocyclization

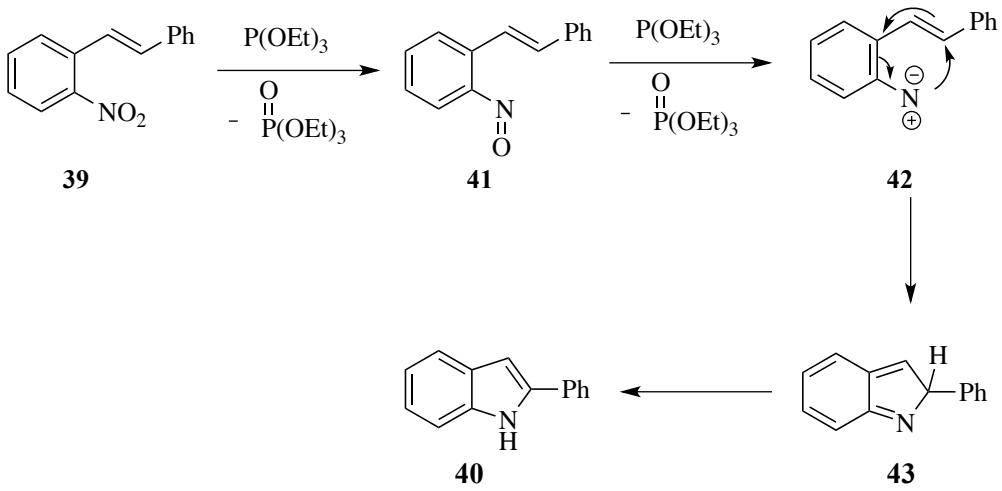


39 **40**

While this method is broadly applicable, it has been limited to small-scale applications due to its requirement of high temperatures (>150 °C) as well as the generation of phosphorous waste. These conditions were also successful in preparing indoles from 2-nitrosobiphenyl compounds[46], lending mechanistic evidence to the cyclization of analogous nitroaromatics proceeding through a nitroso intermediate. It was presumed that this cyclization proceeded through a nitrene intermediate generated by the sequential deoxygenation of the nitro group[45] (Scheme 14). Addition of triethyl phosphite to nitroaromatic **39** followed by elimination of triethyl phosphite provides nitrosoarene **41**, which was reduced to nitrene **42** through repetition of the addition-

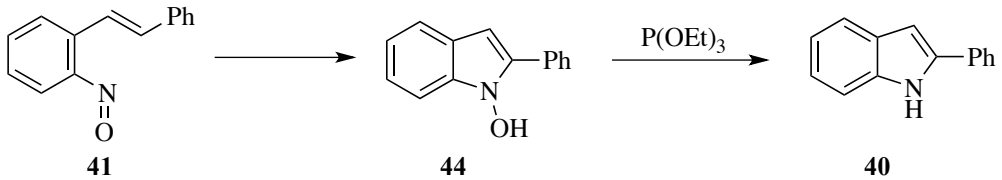
elimination sequence. Nitrene **42** then rapidly attacked the alkene to form heterocycle **43**. Aromaticity was restored through [1,5]-sigmatropic rearrangement, producing indole **40**.

Scheme 14: Mechanism of Cadogan-Sundberg Indole Synthesis



An alternative mechanism has been proposed based on the isolation of hydroxy- and ethoxy-indole by-products (Scheme 15).[46] While the initial deoxygenation to afford nitroso compound **41** is widely accepted, the observation of oxy-indole side products could arise from direct cyclization of nitrosoaromatic **41** to afford hydroxyindole **44**. It is then possible that hydroxyindole **44** could be further reduced to indole **40** by triethylphosphite.

Scheme 15: Alternative Mechanism of Sundberg-Cadogan Cyclization



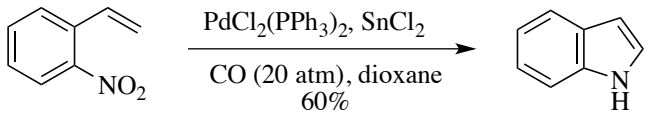
1.5 Indole Preparation via Palladium-Catalyzed Reductive Heterocyclization

Within the past few decades, interest in methods for indole synthesis has led to the discovery of numerous transition-metal catalysts capable of inducing the reductive

heterocyclization of *o*-nitrostyrenes.[47] While numerous metals have been found useful in such transformations, palladium-catalyzed routes employing carbon monoxide as a reducing agent have become the most popular. It is believed that these cyclizations proceed analogously to those reported by Cadogan and Sundberg, meaning that a nitrenoid intermediate likely forms *via* reduction of the nitro group by palladium/carbon monoxide. This transition-metal nitrene then attacks the *ortho* alkene to form the heterocycle, which undergoes [1,5]-sigmatropic rearrangement to give the indole.[48] This mechanistic rationale is based on the proposed similarities between such reductive cyclizations and analogous cyclizations of azido aromatics.[49]

An early palladium-catalyzed reductive *N*-heterocyclization route to indoles and indazoles was reported by Watanabe *et al*.[50] This method improved on the previous routes by providing milder reaction conditions involving palladium(II) and tin(II) chloride catalysts along with pressurized carbon monoxide. Under these conditions, *o*-nitrostyrene (**45**) was converted to indole (**1**) in moderate yield (Scheme 16). A selection of substituted indoles were prepared using this method, although yields were moderate at best even under fairly high carbon monoxide pressures.

Scheme 16: Watanabe Palladium(II)-Catalyzed Reductive Heterocyclization

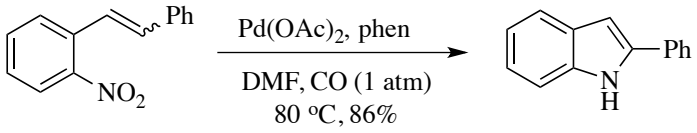


45 **1**

Davies[51] reported an improved route for similar reductive heterocyclizations at significantly lower carbon monoxide pressures. Such reactions were achieved using 0.1% catalyst loadings under 1 atm carbon monoxide (as opposed to 20 atm used by Watanabe[50]). It was also observed that the stereochemistry of the olefin did not have an

effect on the reaction. Reaction of a 1:1 mixture of both *E*- and *Z*-nitrostilbene isomers (**39**) afforded indole **40** in excellent yield (Scheme 17).

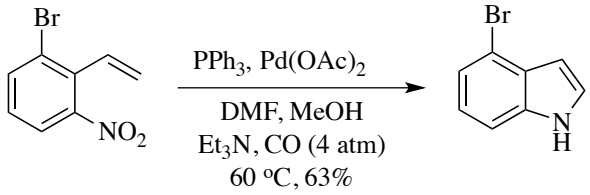
Scheme 17: Davies Reductive *N*-Heterocyclization of Isomeric Nitrostilbenes



39 **40**

A similar transformation was reported by Söderberg in 1997.[52] In an attempted methoxycarbonylation of styrene **46**, indole **47** was isolated as the sole product (Scheme 18). While this result was unexpected, it was also not unprecedented based on the previously mentioned examples.

Scheme 18: Söderberg Reductive Heterocyclization



46 **47**

Through a detailed optimization study of the reaction conditions, it was found that methanol and triethylamine were not required to induce the cyclization.[52] It was also found that a number of solvents, including DMF, acetonitrile, and methanol, all resulted in formation of the desired indole product. Numerous palladium sources were also found successful, including $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $Pd(dba)_2$, and 10% Pd/C. The array of plausible conditions makes this method highly attractive and broadly applicable.

The Söderberg method provides a number of significant improvements over previously reported conditions. In comparison to Watanabe's system[50], the Söderberg conditions require significantly lower temperatures while also eliminating the need for a Lewis acid additive. It is also an improvement over alternative routes involving aniline

derivatives[34] in that (a) anilines are typically prepared through the reduction of the corresponding nitroarene, introducing an additional step to the route. In addition, the use of palladium (0) catalysts eliminates the need for an oxidant required when using palladium (II). From an environmental standpoint, the main by-product of the reaction is carbon dioxide, which is a significant improvement over previous routes using tin[50] or phosphorous[45] additives. This also leads to simplified workup procedures.

The plausible mechanisms for the reductive heterocyclization of *o*-nitrostyrenes are presented in Scheme 19.[53] The difficulty of isolating intermediates has prevented researchers from fully understanding the exact mechanism, so multiple plausible routes have been proposed based on numerous observations.

The mechanism initially proceeds through the palladium-catalyzed reduction of nitrostyrene **45** by carbon monoxide to give intermediate **48**. Carbon monoxide insertion into one of the palladium-oxygen bonds affords palladacycle **49**, which, upon reductive elimination of carbon dioxide, affords palladium-bound nitrosarene **50**. From this point, the mechanism could proceed in three ways:

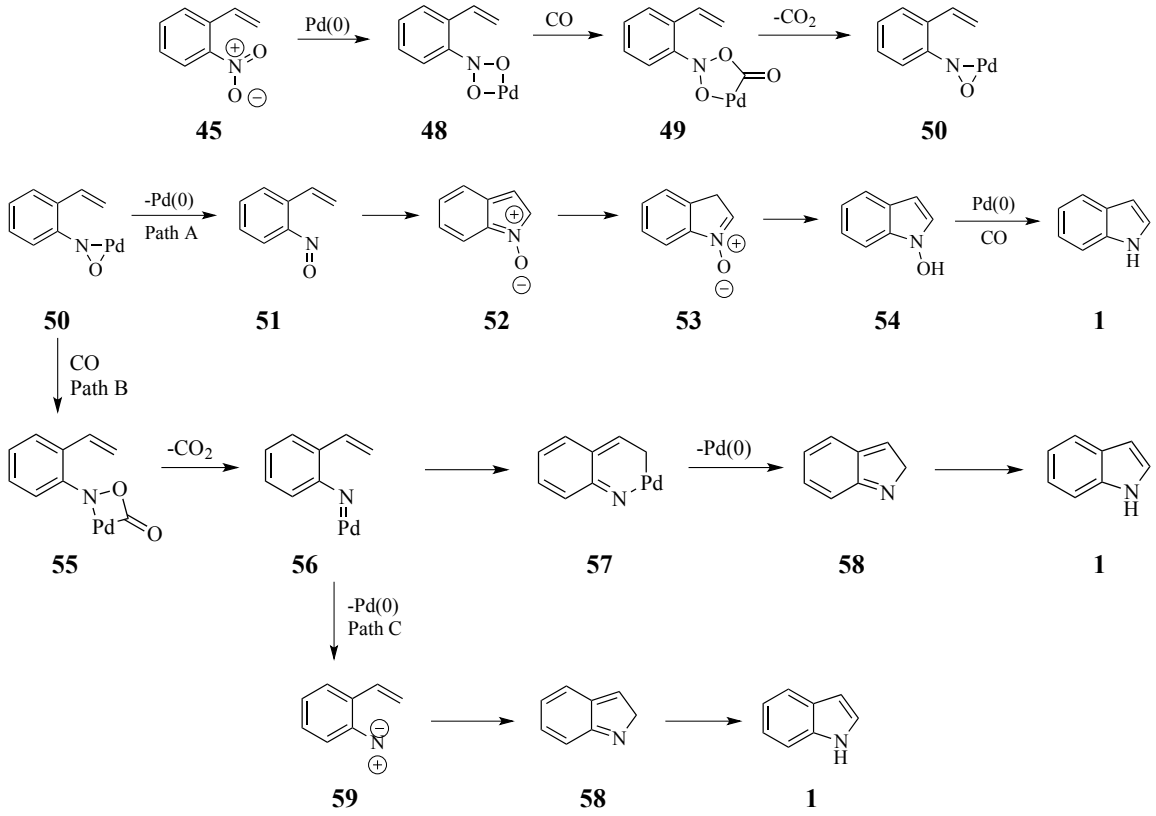
Path A[51] involves liberation of palladium from nitrosarene **50** to afford nitrosostyrene **51**, which can undergo 6-pi electrocyclization to afford nitronate **52**. [1,5]-hydride shift of **53** followed by isomerization of intermediate **53** produces *N*-hydroxyindole (**54**). Reduction of **54** by another equivalent of carbon monoxide then affords indole (**1**).

Path B begins with insertion of carbon monoxide to palladium-bound nitrosarene **50** to give palladacycle **55**. Subsequent reductive elimination of carbon dioxide produces palladium-bound nitrene **56**, which could undergo 6 pi-electrocyclization to afford six-

membered palladacycle **57**. Reductive elimination of palladium from **57** would furnish heterocycle **58**, which could then isomerize to indole (**1**) through a [1,5]-hydrogen shift.

Path C is similar to Path B, although initial reductive elimination of palladium from **56** affords free nitrene **59**. Nitrene **59** could then undergo an electrocyclization-isomerization process (as described for Path B) to ultimately afford indole (**1**).

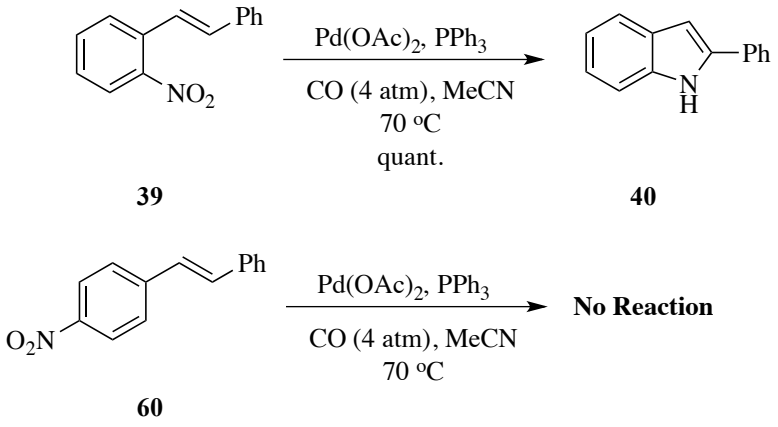
Scheme 19: Proposed Mechanism(s) of Reductive *N*-Heteroannulation



While the exact mechanism of this transformation is not fully understood, several observations lend some evidence to potential intermediates. It is believed that the proximity of the nitro group to the alkene is crucial in facilitating the reaction, as observed for two isomeric nitrostilbenes.[52] While 2-nitrostilbene (**39**) reacts to give 2-phenylindole (**40**) in quantitative yield, 4-nitrostilbene (**60**) is recovered unchanged, also

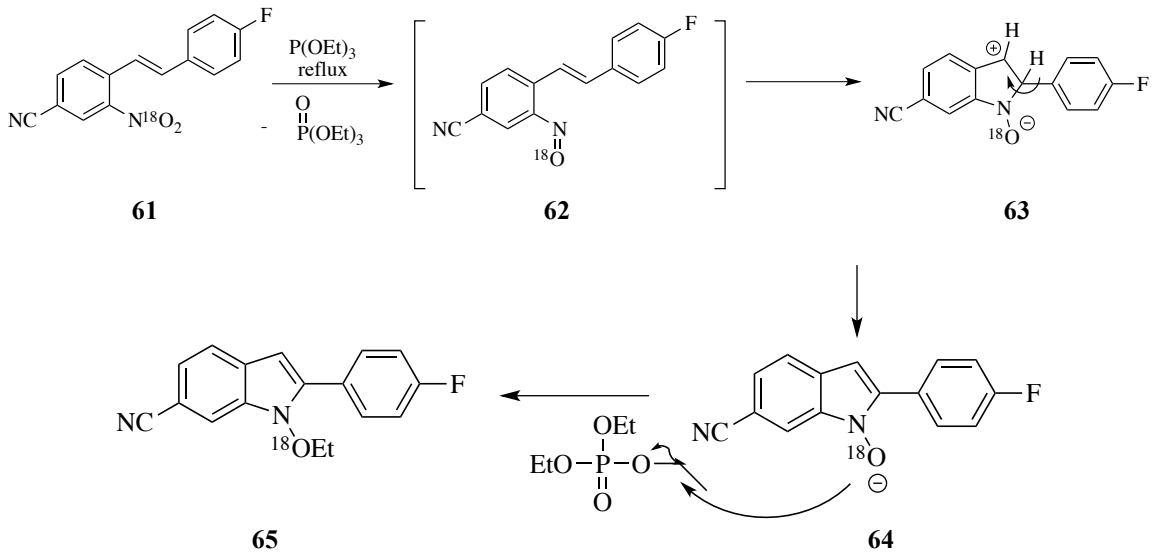
in quantitative yield (Scheme 20). This result hints that initial coordination of the metal to the alkene is necessary for the initial reduction of the nitro group.[52]

Scheme 20: Potential Palladium-Olefin Coordination-Mediated Reduction



The prevalence of *N*-ethoxyindoles as side products of the Cadogan-Sundberg indole synthesis provides justification for path A.[54,55] While the origin of these products was not initially studied, recent work by Peet *et al*.[47] determined through ^{18}O labeling experiments that the oxygen found in the *N*-alkoxyindole originates from the nitro group, not from triethylphosphite (Scheme 21). This means that the labeled nitro group of **61** is only reduced to the corresponding nitroso compound **62** and not further reduced to the nitrene. Nitroso intermediate **62** then cyclizes to afford intermediate **63**, which could lose a proton to give deprotonated *N*-hydroxyindole **64**, which then attacks an ethyl group from the triethyl phosphate (produced in the initial deoxygenation of **61**) to afford *N*-ethoxyindole **65**.

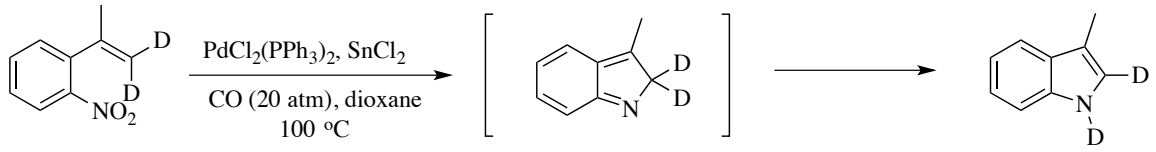
Scheme 21: ^{18}O Labeling Study of Cadogan-Sundberg Reductive Cyclization



Watanabe[50] postulated that formation of the free nitrene (path C, Scheme 19) was likely based on the evolution of carbon dioxide over the course of the reaction, although carbon dioxide is also generated in the initial reduction of the nitro group to the corresponding nitroso compound as well as in the reduction of nitrosarene **50** to palladium-bound nitrene **56** (path B, Scheme 19). This nitroso/nitrene species could then cyclize to form the five-membered ring, followed by a [1,5]-hydride shift to afford the indole product.

The aforementioned [1,5]-hydride shift was also studied by Watanabe[50] (Scheme 22). Through deuterium labeling of *o*-nitrostyrene **65**, it was determined that the 3-methylindole product **67** was deuterated at both the 1- and 2-positions. This means that the nitrogen atom must abstract a deuterium from the β-carbon of the olefin during the cyclization process. This then became the basis for the proposed [1,5]-sigmatropic rearrangement of proposed intermediate **66** to afford indole **67**.

Scheme 22: Deuterium-Labeling Study of [1,5]-Sigmatropic Rearrangement



65 **66** **67**

Söderberg's work over the past number of years has focused on applying this methodology toward the synthesis of a number of compounds including tryptophan derivatives[56], bicyclic heteroaromatics[57], carbazole alkaloids[58], mushroom metabolites[59], and various natural products[60,61,62,63]. The ensuing sections will discuss novel applications of palladium-catalyzed reductive *N*-heterocyclizations in the preparation of indoles and indole derivatives.

Chapter 2

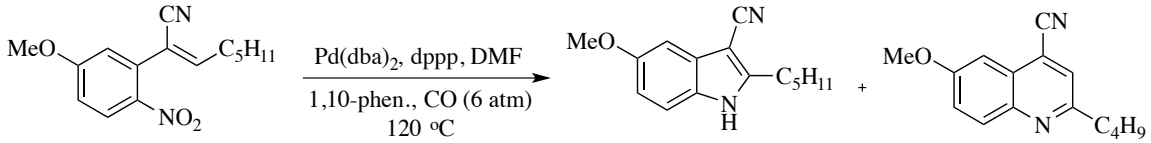
A Base Modulated Synthesis of Indoles and Quinolines

2.1 Introduction

One of the most challenging tasks in synthetic organic chemistry is finding selectivity in reactions. Often times, researchers struggle to target one specific functional group in the presence of other similar functionalities. The ideal reaction would only alter the desired functionality while leaving other reactive moieties untouched. In the same sense, the ability to prepare different products from a common starting material is also of great use.

Through previous work within Söderberg's group aimed at the preparation of 2,3-substituted indoles, an interesting result was obtained. Upon cyclization of cyano-substituted alkene **68**, the expected indole **69** was isolated in moderate yield along with a small amount of quinoline **70** (Scheme 23).[64] This unexpected result was of interest for it presented the potential for preparation of two different yet useful products from a common starting material.

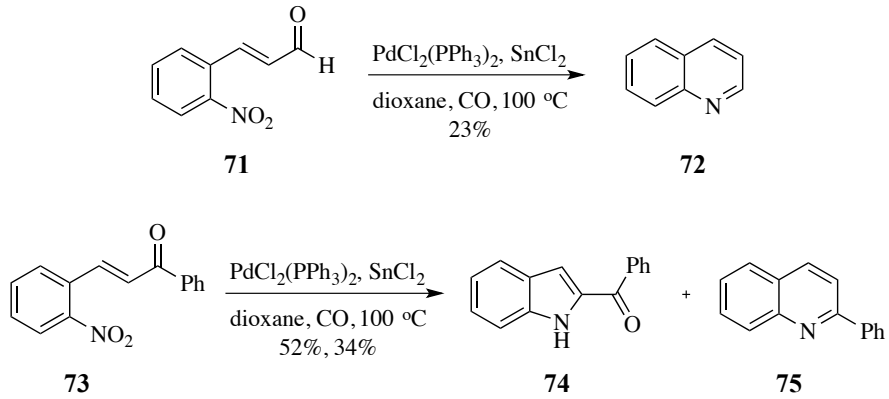
Scheme 23: Initial Cyclization of Cyanoalkene



68 **69** (45%) **70** (10%)

Upon examination of the literature, Akazome *et al.*[50] reported a similar result. In the attempted cyclization of *o*-nitrocinnamaldehyde (**71**) using $PdCl_2(PPh_3)_2$ and $SnCl_2$ under carbon monoxide, quinoline **72** was isolated albeit in low yield (Scheme 24). Similar reaction of *o*-nitrochalcone (**73**) afforded both indole **74** and quinoline **75**.

Scheme 24: Akazome's Synthesis of Indoles and Quinolines



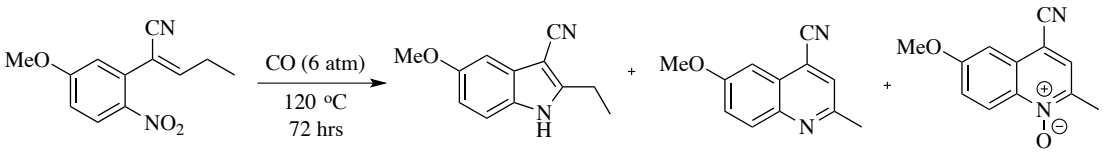
Although it can be envisioned that the aforementioned cyclizations may proceed through reduction of the nitro group to the corresponding aniline in a similar fashion to analogous indole syntheses reported by Hegedus,[34] Akazome found that treatment of 2-aminostilbene with the established conditions afforded neither indole **74** or quinoline **75**.[50] This clearly demonstrates a different mechanism, likely involving the reduction of the nitro group to a nitroso or nitrene (as discussed in Chapter 1).

2.2 Results and Discussion

An investigative study was launched based based on both Akazome's results[50] as well as Söderberg's[64]. The formation of quinoline **70** from cyanoalkene **68** was unexpected, however, upon consideration of the reaction conditions, it was proposed that the presence of a base, specifically 1,10-phenanthroline, could have altered the predicted selectivity. It was decided to examine whether simply varying the additives used in the reaction could alter the selectivity. In screening various conditions for the cyclization of **76**, Banini *et al.* found that the combination of $Pd(OAc)_2$ and PPh_3 (deemed "conditions A") produced exclusively indole **77**, while the addition of DBU to the aforementioned conditions (deemed "conditions B") afforded exclusively quinoline **78** (Scheme 25). This

led to the proposition that the reaction selectivity and product observed could be modulated through addition or exclusion of base in the reaction mixture.

Scheme 25: Investigation of Cyclization Conditions



		76	**77**	**78**	**79**
1	$Pd(dba)_2$ – dppp		6%	8%	7%
2	$Pd(dba)_2$ – dppp – NEt_3		3%	5%	---
3	$Pd(dba)_2$ – dppp – phen – DBU		---	11%	---
4	**$Pd(OAc)_2$ – PPh_3**		**79%**	---	---
5	**$Pd(OAc)_2$ – PPh_3 – DBU**		---	**88%**	---

dppp= 1,3-bis(diphenylphosphino)propane, phen= 1,10-phenanthroline, DBU= 1,8-diazabicyclo[5.4.0]-undec-7-ene

To expand the scope of these findings, Banini *et al*. prepared a number of additional substrates to then subject to the two sets of cyclization conditions. Four unsaturated nitriles (**81**, **68**, **83, 85**) were prepared through Knoevenagel condensation[65] of the corresponding 2-arylacetonitrile with ethanal or hexanal (Table 1).

Table 1: Knoevenagel Condensation of 2-Arylacetonitrile[a]

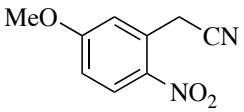
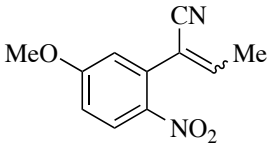
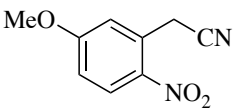
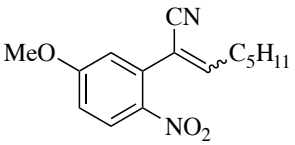
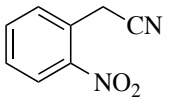
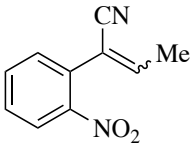
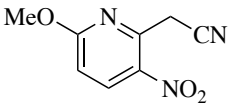
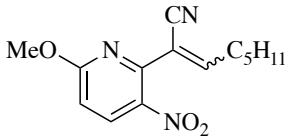
Entry	**Substrate**	**Aldehyde**	**Product (yield)**
1	 **80**	MeCHO	 **81** (41%)
2	 **80**	$C_5H_{11}CHO$	 **68** (89%)

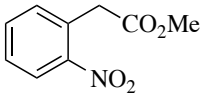
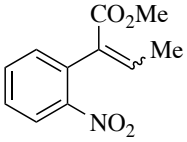
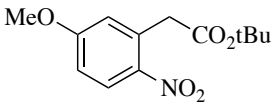
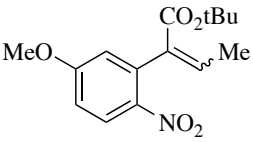
Table 1: Knoevenagel Condensation of 2-Arylacetonitrile[a] (cont'd)

Entry	Substrate	Aldehyde	Product (yield)
3	 **82**	MeCHO	 **83** (21%)
4	 **84**	$C_5H_{11}CHO$	 **85** (62%)

a) Conditions: AcOH, piperidine, PhH

In addition to the cyanoalkenes, two ester-functionalized alkenes (**87, 89**) were prepared using similar methodology[65] (Table 2).

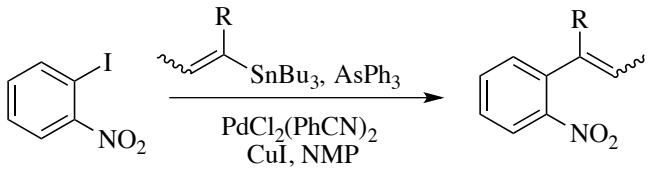
Table 2: Preparation of Ester-Substituted Alkenes[a]

Entry	Substrate	Aldehyde	Product (yield)
1	 **86**	MeCHO	 **87** (23%)
2	 **88**	MeCHO	 **89** (73%)

a) Conditions: AcOH, piperidine, PhH

Two additional substrates were prepared via Kosugi-Migita-Stille cross-coupling between 1-iodo-2-nitrobenzene (**90**) and either 1-propene-1-yltributyltin and 1-phenyl-1-propen-1-yltributyltin (Scheme 26).

Scheme 26: Preparation of 2-Nitrostyrenes via Stille Coupling



90

91 (R=Ph, 84%)

92 (R=H, 73%)

With a number of substrates prepared, Banini *et al.* then examined the base-modulated cyclization. Cyclization of each *ortho*-nitrostyrene derivative using conditions A afforded exclusively indoles (**69**, **77**, and **93-98, 17**) in good isolated yields (Table 3, entries 1-6 and 10, 11, 13). The corresponding quinolines were not observed in the crude spectra from these reactions. Reaction of the same substrates using Conditions B gave different results depending on the substituent on the alkene. As anticipated, the cyano-substituted substrates furnished the corresponding quinolines **70**, **78**, **99-101** (entries 1-5). Disappointingly, ester **87** did not undergo cyclization to afford a quinoline under the basic conditions B. Three additional bases were examined for ester **87**, however, indole **96** was formed in all cases (entries 6-9). This made it apparent that the formation of quinolines was limited to the cyano-substituted alkenes. In contrast, azaquinoline **103** was formed upon reaction of the pyridine derivative **89** (entry 10). In addition to **103**, one additional product was isolated and identified as the azaindole **102**. It is worth noting that **102** had lost a methyl group compared to azaindole **97** formed through reaction of **89** under conditions A. It was apparent that DBU was sufficiently basic to deprotonate all nitriles and esters examined as evidenced by the immediate change in color of the reaction mixtures upon addition of base, indicative of anion formation. In contrast, no color change was observed for the significantly less acidic substrates **91** and **92** upon addition of base. Reaction of **91** using DBU as the base furnished only indole **98** in 95%

yield (entry 11). However, reaction of **91** under conditions B using *t*-BuOK as the base (as opposed to DBU) initially produced a deep blue color (indicative of anion formation) and furnished quinoline **104** (entry 12). The least acidic substrate studied (**92**) afforded exclusively indole **17** under both conditions A and conditions B, regardless of what base was used (entry 13), indicating that neither *t*-BuOK nor DBU were basic enough deprotonate the substrate.

Table 3. Cyclizations to Afford Substituted Indoles and/or Quinolines

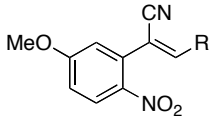
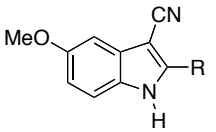
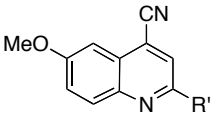
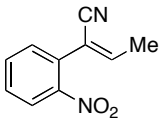
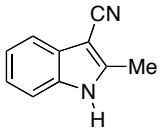
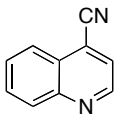
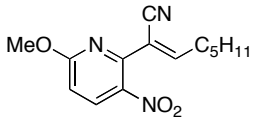
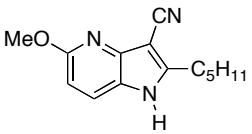
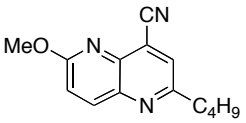
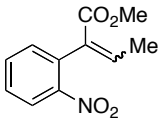
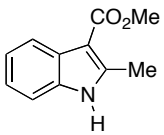
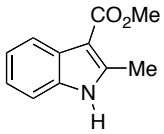
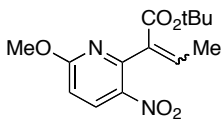
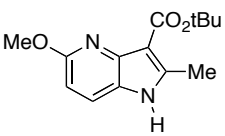
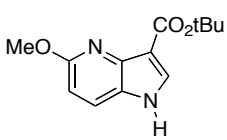
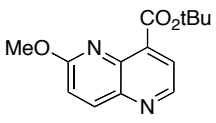
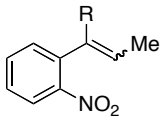
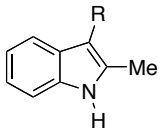
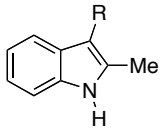
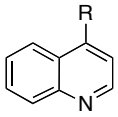
Entry	Nitroalkene	Conditions A[a]	Conditions B[b]	
				
1	**76** (R=Et)	**77** (79%)	**78** (R'=Me, 88%)	
2	**81** (R=Me)	**93** (82%)	**99** (R'=H, 88%)	
3	**68** (R=Pent)	**69** (91%)	**70** (R'=Bu, 79%)	
				
4	**83**	**94** (80%)	**100** (83%)	
				
5	**85**	**95** (74%)	**101** (69%)	
				
6	**87**	**96** (85%)	**96** (DBU, 87%)	
7			**96** (NEt_3, 78%)	
8			**96** (t-BuOK, 35%)	
9			**96** (NaHMDS, 84%)	
				
10	**89**	**97** (89%)	**102** (24%)[c]	**103** (63%)[c]

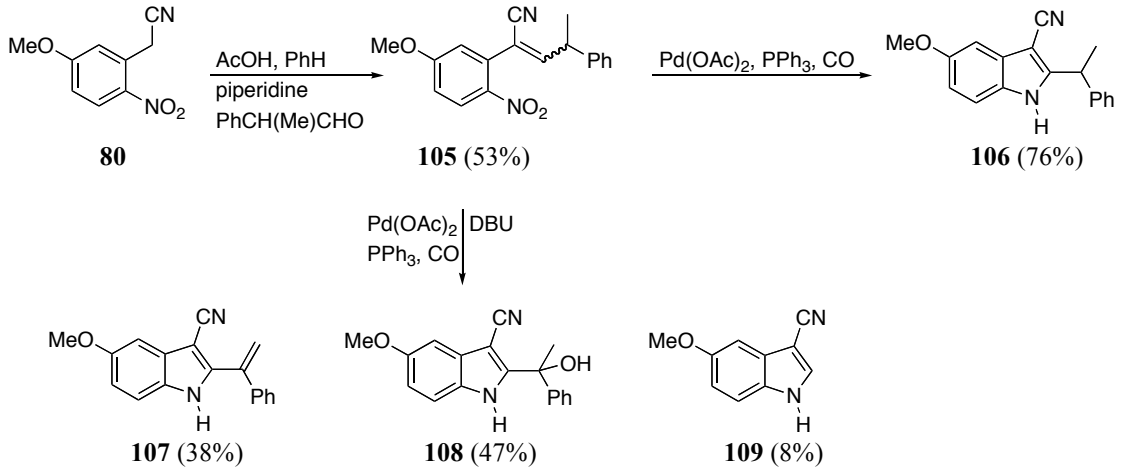
Table 3. Cyclizations to Afford Substituted Indoles and/or Quinolines (cont'd)

Entry	Nitroalkene	Conditions A[a]	Conditions B[b]	
				
11	**91** (R=Ph)	**98** (98%)	**98** (95%)	-----
12			-----	**104** (79%)[c]
13	**92** (R=H)	**17** (96%)[d]	**17** (89%)[c]	-----

a) Conditions A: $Pd(OAc)_2$, PPh_3, DMF, CO (6 atm), 120 ^oC, 72 h.
b) Conditions B: $Pd(OAc)_2$, PPh_3, DBU, DMF, CO (6 atm), 120 ^oC, 72 h.
c) t-BuOK in place of DBU.
d) $Pd(OAc)_2$, PPh_3, MeCN, CO (4 atm), 70 ^oC, 15 h.

Two additional substrates **105** and **111**, which cannot form fully aromatic quinolines without migration or loss of a carbon chain were also examined. Cyanoalkene **105** was prepared through condensation of 2-nitro-5-methoxy-1-cyanomethylbenzene (**80**) with 2-phenylpropanal (Scheme 27). Nitrile **105** was then subjected to reaction conditions A and B. Not surprisingly, under conditions A, the expected indole **106** was isolated in good yield (Scheme 27). In contrast, three different indoles, **107** and an inseparable mixture of **108** and **109** were obtained under the basic conditions B. The structures of **108** and **109** were elucidated using 2D NMR techniques including COSY, HMQC, HMBC, and NOESY. Interestingly, a significant part of the starting material was lost in the formation of indole **109**.

Scheme 27: Preparation and Cyclization of Cyanoalkene 105

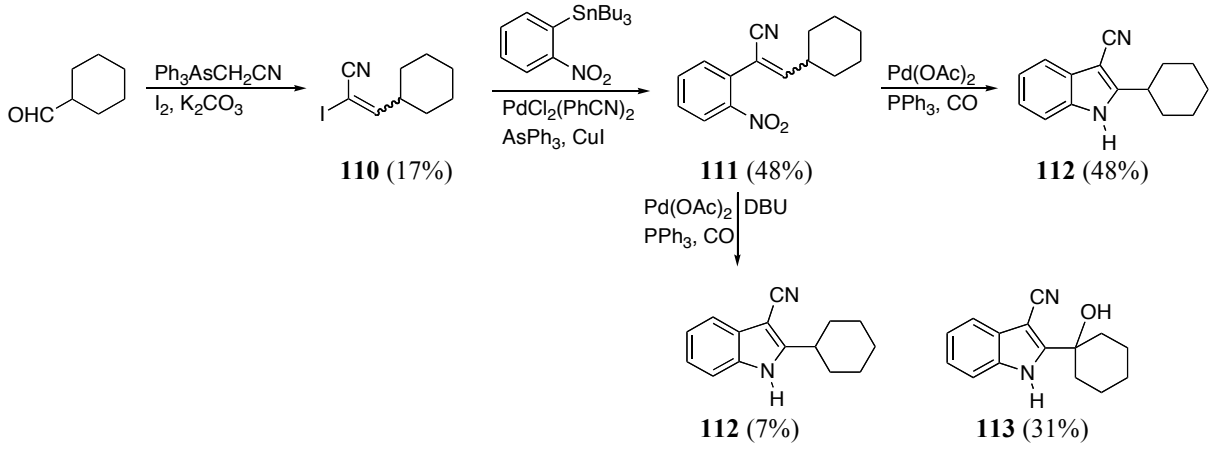


80 **105** (53%) **106** (76%)

107 (38%) **108** (47%) **109** (8%)

Wittig reaction of cyclohexane carbaldehyde formed iodoalkene **110**, which then underwent Kosugi-Migita-Stille cross-coupling with 2-nitrophenyl stannane to afford cyanoalkene **111** (Scheme 28). As anticipated, indole **112** was formed under conditions A, albeit in relatively low isolated yield. Under the basic conditions B, a low yield of indole **112** in addition to indole **113** featuring an oxidized cyclohexyl group were isolated. This outcome was interpreted as the result of a competing cyclization of **111** to **112** and cyclization of the anion formed through deprotonation of **111** to give **113**.

Scheme 28: Preparation and Cyclization of Cyanoalkene 111



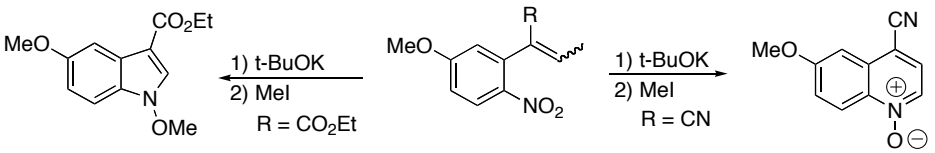
110 (17%) **111** (48%) **112** (48%)

112 (7%) **113** (31%)

The difference in chemoselectivity between the nitriles and the esters was puzzling. It was unclear why either indoles or quinolines were obtained from the nitrile-substituted substrates, while the esters afforded exclusively indoles under both sets of conditions. Presumably, the pKa for the substrates having either a nitrile or an ester moiety must be very similar in magnitude. For example, the pKa values for CH_3CN and CH_3CO_2Et have been reported as 24.5 and 25.0, respectively.[66] In addition, the color changes observed upon addition of base to both the ester and nitrile-substituted substrates likely indicated that the conjugate base was formed, thus raising questions regarding the resonance forms of each anion.

To probe the electronic distribution of anions formed, two similar substrates **81** and **114**, differing only in the electron-withdrawing group, CN vs. CO_2Et, respectively, were compared. Each substrate was deprotonated with *t*-BuOK in *t*-BuOH, then methyl iodide was added to the mixture with the intent of trapping the intermediate to determine the identity of the anion formed through the initial deprotonation (Scheme 29). In doing such, two different products were obtained. After workup and purification, ester **114** gave exclusively *N*-methoxyindole **115**, while on the other hand, nitrile **81** furnished quinoline-*N*-oxide **116**. As was noticed for two previous indole products (**25** and **32**), part of the alkyl chain was lost during the formation of indole **115**. The drastically different results obtained through these two experiments under identical reaction conditions confirmed that esters and the nitriles have different chemoselectivity. The reason for this difference is presently unknown.

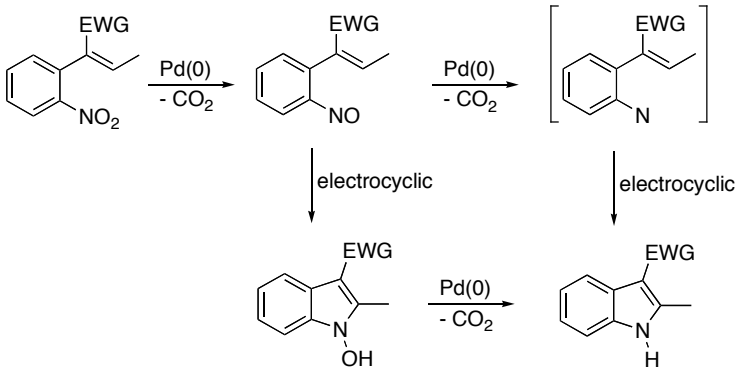
Scheme 29: Attempt to Trap Reactive Intermediates



-- **115** (83%) | **81** (R=CN) **114** (R=CO_2Et) | **116** (53%) --

The mechanisms for the reactions leading to either indole or quinoline products and indoles wherein a carbon-carbon bond has been broken and/or a side-chain oxidized are not clear at this time. In the absence of a base, the reaction likely proceeds via a deoxygenation producing a nitroso compound followed by either a) a second deoxygenation to give a nitrenenoid intermediate and ultimately an indole or b) an electrocyclic ring closure to afford an *N*-hydroxy indole followed by a palladium-catalyzed deoxygenation as discussed in Chapter 1 (Scheme 30). However, this mechanistic rationale accounts for the formation of indoles without carbon-carbon bond cleavage or side-chain oxidation, both of which were observed in a few of the previously mentioned examples.

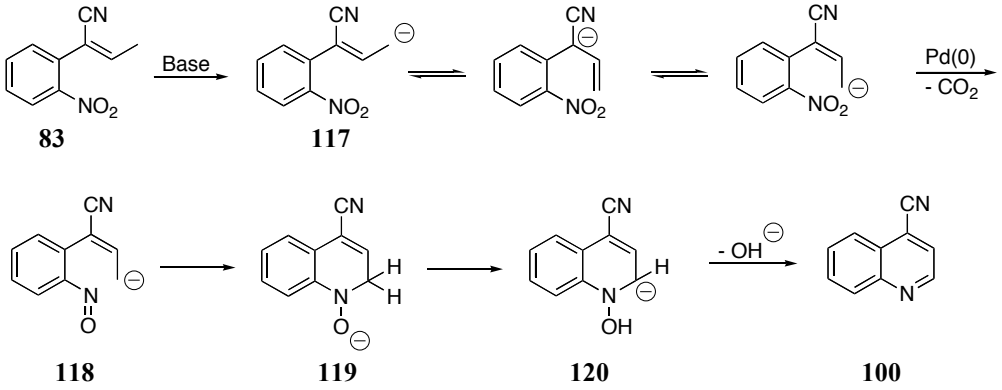
Scheme 30: Potential Mechanism(s) for Cyclization in Absence of Base



The mechanistic picture is slightly more complex in the presence of a base. Addition of a sufficiently strong base to cyanoalkene **83** results in the formation of the conjugate base **117** as evidenced by the immediate formation of a deep blue solution

(Scheme 31). The nitro group of **117** is likely deoxygenated by the catalyst system to form nitrosarene **118**. Nucleophilic addition of the carbanion of **118** to the nitroso group followed by protonation-deprotonation and elimination of hydroxide (**119** to **120**) would furnish quinoline **100**.

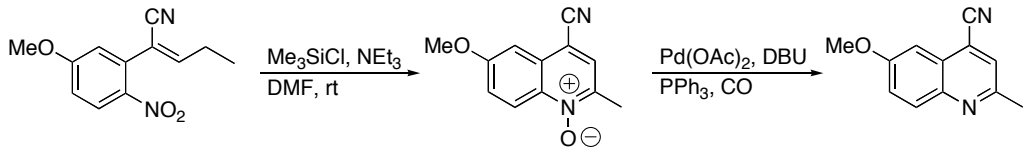
Scheme 31: Proposed Mechanism for Quinoline Formation



83 **117** **118** **119** **120** **100**

Makosza *et al*[67] have reported the formation of quinoline-*N*-oxides (such as **79**, Scheme 25) by treatment of compound **76**, and related substrates, with triethylamine and trimethylsilyl chloride (Scheme 32). This result raised the question of whether the base-modulated cyclization forming quinolines (conditions B) was simply a palladium-catalyzed reduction of the quinoline *N*-oxide **79** formed through nucleophilic attack of the initially formed carbanion to the nitro group of **76** without prior reduction of the nitro group to a nitrosarene. Submitting quinioline *N*-oxide **79** to conditions B did indeed furnish quinoline **76**, however, the yield of quinoline **78** was only 24% after the same length of time required to produce quinoline **78** in 88% yield directly from **76** using our palladium-catalyzed methodology.

Scheme 32: Mechanistic Analysis of Quinoline Formation

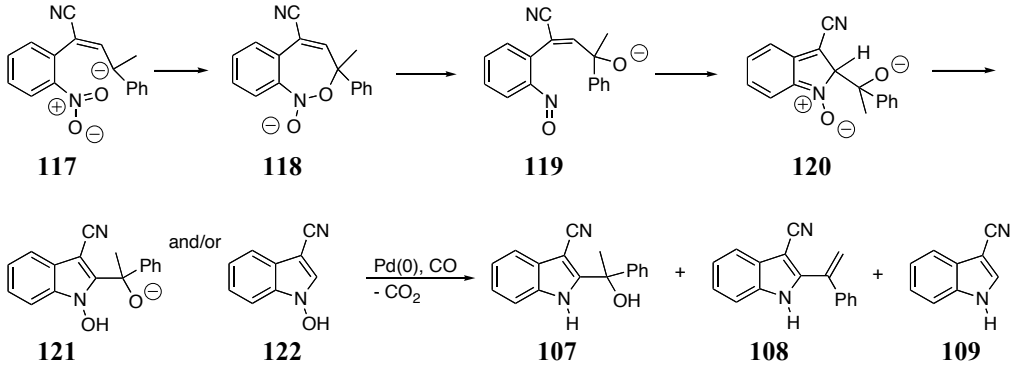


76 **79** (90%) **78** (24%)

While this result is not conclusive, it indicates that the palladium-catalyzed reaction likely involves a different pathway than substrate (**76**) → quinoline-*N*-oxide (**79**) → quinoline (**78**). It is feasible that the palladium-catalyzed reduction of nitroaromatic **76**, resulting in the formation of the nitroso-intermediate is faster in relation to nucleophilic addition to the nitro group in cases wherein a quinoline is formed. In the event, carbanion addition could then occur to the nitroso group (as depicted in Scheme 31) as opposed to the nitro group as reported by Makosza.[67] Another explanation could be that nucleophilic addition to the nitro group may also be a reversible reaction under basic conditions while the reduction to a nitrosarene is not.

The final mechanistic question involved the formation of indoles with concurrent carbon-carbon bond fission (**102**, **109**), oxidation (**108**, **113**), or alkene formation (**107**). The transformation may occur via addition of allylic carbanion **117** to one of the nitro group oxygens, affording the seven-membered intermediate **118** (Scheme 33). Ring-opening of **118** would give nitrosarene **119**, which following electrocyclic ring-closure would produce **120**. Rearomatization of **120** either by loss of a proton would afford *N*-hydroxyindole **121** or through loss of acetophenone and subsequent protonation would provide *N*-hydroxyindole **122**. Palladium-catalyzed deoxygenation of **121** would afford alcohol **107** after subsequent protonation. Elimination of water from **107** could then produce **108**. Deoxygenation of **122** would result in the formation of indole **109**.

Scheme 33: Proposed Mechanism Accounting for Fission, Oxidation, Elimination



The addition of the carbanion to the nitro group of **117** proposed in Scheme 33 is supported by related observations reported in the literature. Nyerges *et al*.[68.69] reported novel 1,7 electrocyclizations of azomethine ylide to pendant nitro groups in their preparation of indazole-*N*-oxides. In addition, attack of carbanions to aromatic nitro groups has been proposed as one of the steps in the Bartoli indole synthesis using nitroarenes and excess alkenyl Grignard reagents.[70]

2.3 Conclusions

A synthetic methodology for the formation of various 4-cyanoquinolines and 3-cyanoindoles from a common 1-cyano-1-(2-nitrophenyl)alkene precursor has been established. In the absence of a base, indoles are formed through palladium-catalyzed reductive *N*-heteroannulation. Quinolines are formed in the presence of a base, presumably through intramolecular nucleophilic addition of a carbanion to a nitrosarene. Analogous esters afford exclusively indoles regardless of the conditions used. Mechanistic rationales for the formation of both products and side products have been presented on the basis of literature precedence and experimental findings.

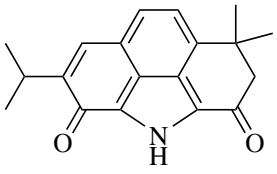
Chapter 3

An Expedient Synthesis of Salviadione

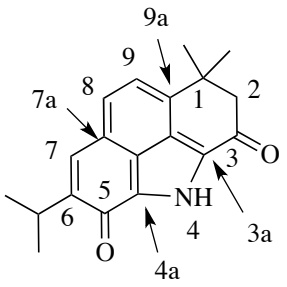
3.1 Introduction to Salviadione

Traditional Chinese folk medicine has employed the use of the dried root of *Salvia miltiorrhiza* as treatment for a wide array of illnesses as Danshen or Tanshen. A number of biologically active compounds have been isolated from the dried root and can be classified as either water-soluble phenolic acids or lipophilic abietane-type diterpenes. These compounds have shown biological activity ranging from antioxidant, anti-inflammatory, antifungal, anticoagulant, anti-HIV, antitumor, and antibacterial activity.[71] Another structurally unique alkaloid, Salviadione, 1,1-dimethyl—6-(1-methylethyl)-1*H*-benzo[*def*]carbazole-3,5-(2*H*,4*H*)-dione (**123**), was also isolated from these dried roots in 2005 (Figure 5).[72] It is believed that this is the only naturally isolated benzo[*def*]carbazole.[73] and one of a small number prepared synthetically.[74] The unique structure inspired us to commence a synthetic study.

Figure 5: Structure and Atom Numbering of Salviadione



123



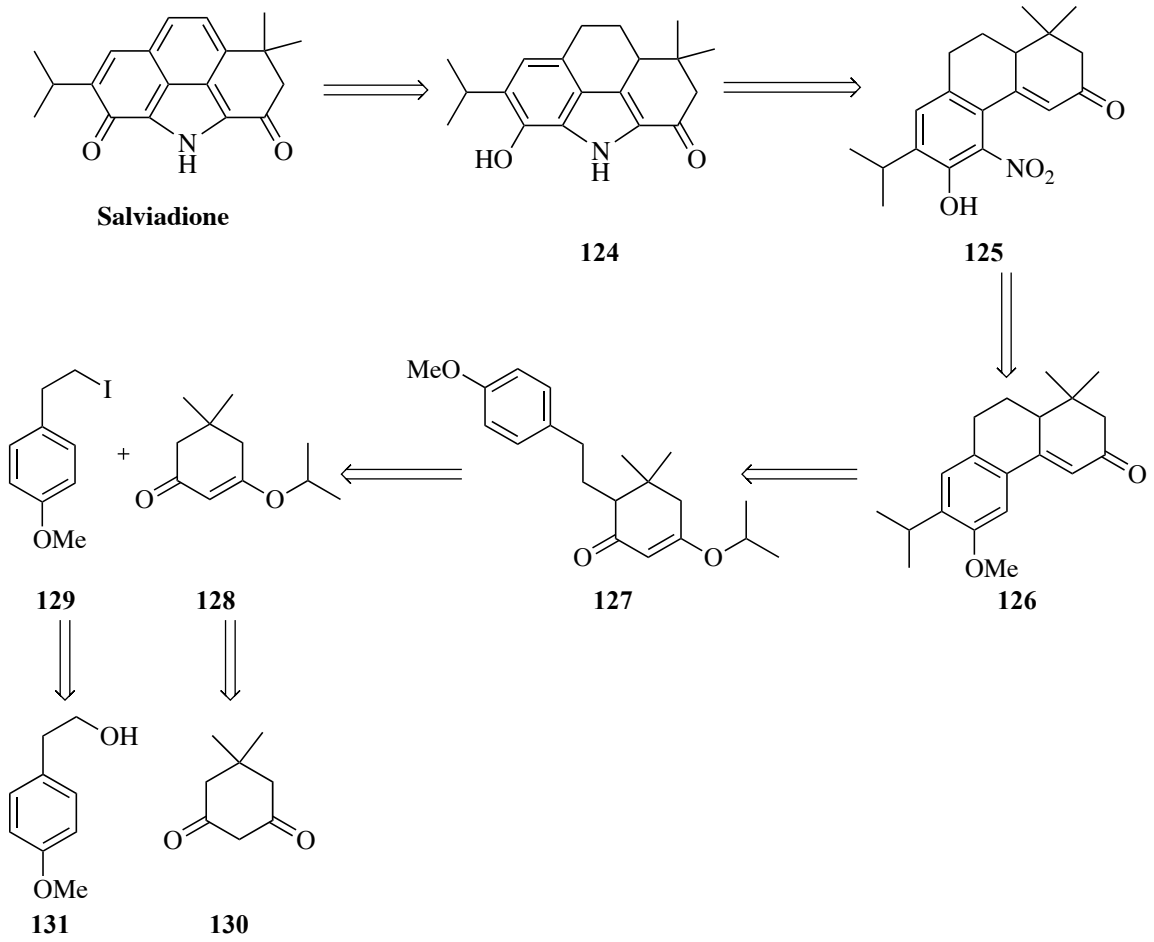
3.2 Expedient Synthesis of Salviadione

The unique structure of Salviadione made it an attractive candidate for a synthetic study. It was proposed that formation of the *N*-heterocyclic ring of the molecule could result from a Söderberg palladium-catalyzed reductive *N*-heterocyclization reaction. The goal was to highlight this methodology as a key step in the synthetic route.

3.2.1 Retrosynthetic Analysis

The structure of Salviadione is deceptively complex, allowing us to propose a relatively concise synthetic route (Scheme 34). It was envisioned that Salviadione (**123**) could result from benzylic oxidation of phenol **124**. The indole core of **124** could be prepared through reductive heterocyclization of nitroaromatic **125**. Nitration of the tricyclic diterpenoid **126** would be expected to occur *ortho* to the methoxy group to give desired nitroaromatic **125**. This tricyclic core could be prepared using the procedure previously outlined by Pan *et al.*[75] Diterpenoid **126** would result from the acid-induced cyclization- Friedel-Craft's alkylation of *para*-substituted anisole **127**, which could be prepared through reaction between iodide **129** and the carbanion derived from **128**. Iodide **129** could be achieved through a simple iodination of commercially available alcohol **131**, while isopropyl enol ether **128** could be prepared from *O*-alkylation of 5,5-dimethyl-1,3-cyclohexanedione **130**.

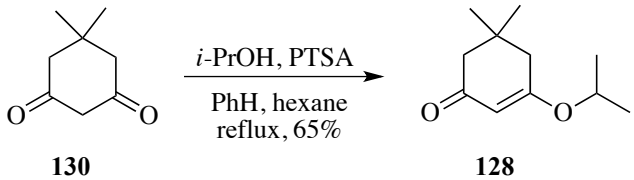
Scheme 34: Proposed Retrosynthetic Outline for Salviadione



3.2.2 Results and Discussion

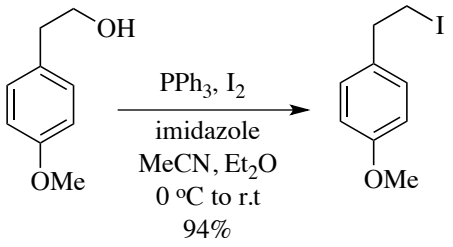
The synthetic route began with the alkylation of commercially available dimedone (5,5-dimethyl-1,3-cyclohexanedione) **130** to afford isopropyl enol ether **131**[76] through reaction with isopropanol and a catalytic amount of *p*-toluenesulfonic acid (Scheme 35).

Scheme 35: Alkylation of Dimedone



Alcohol **131** was then converted to the corresponding iodide **129**[77] using typical Appel conditions (Scheme 36).

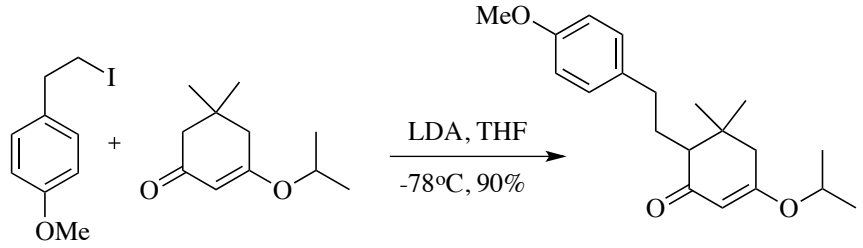
Scheme 36: Preparation of Alkyliodide



131 **129**

Iodide **129** then underwent alkylation with the carbanion formed through treatment of **128** with lithium *N,N*-diisopropylamine to give **127** (Scheme 37).[78,79]

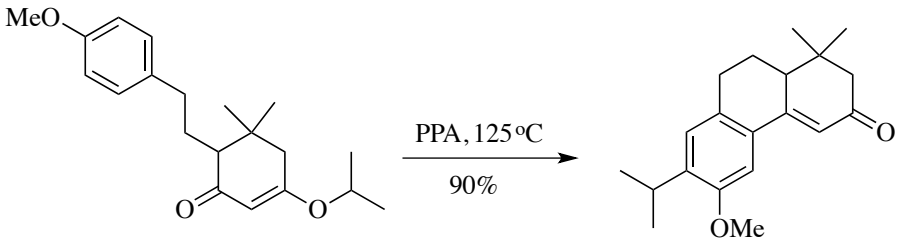
Scheme 37: Preparation of Cyclization Precursor



129 **128** **127**

Intramolecular cyclization-Friedel-Crafts alkylation[75] of **127** was achieved through heating in polyphosphoric acid, furnishing tricyclic terpenoid **126** (Scheme 38).

Scheme 38: Acid-Induced Intramolecular Cyclization-Friedel-Crafts Alkylation

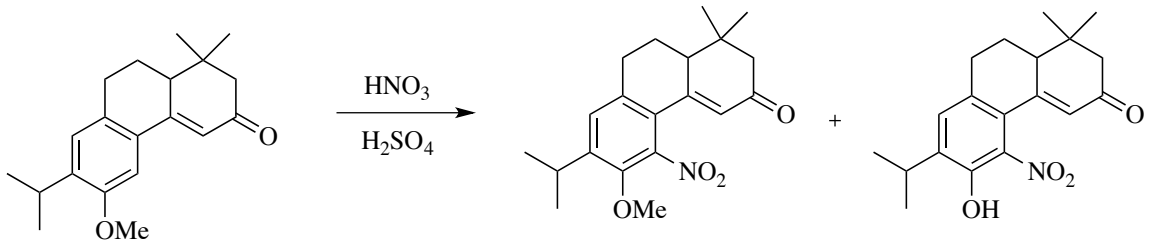


127 **126**

The next major challenge was the nitration of tricyclic diterpenoid **126**. The regioselectivity of the nitration was *ortho* to the methoxy-group as was expected,[80] however, the observed product(s) were very sensitive to reaction conditions, work-up procedure, and speed of chromatographic purification. Given these variables, it was very hard to control the outcome of a given reaction even when using similar conditions.

Nitration of **126** with a mixture of fuming nitric acid and sulfuric acid at -78 °C provided nitro-phenol **125** in addition to desired anisole product **132** (Scheme 39). The absence of demethylation product **125** in reactions where the starting material was not fully consumed leads us to believe that the demethylation must occur after introduction of the nitro-group. Though unexpected, the demethylation turned out to be beneficial, as nitrophenol **125** provided a more direct route to salviadione (**123**).

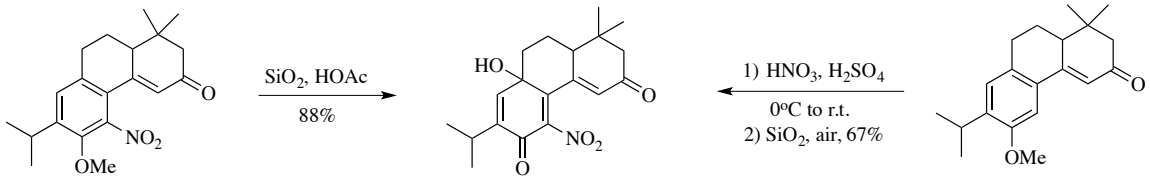
Scheme 39: Nitration of Tricyclic Diterpinoid Core



126	**Temp (°C)**	**132**	**125**
	-78 °C	25%	32%
	-20 °C	---	77%

When the nitration was performed at -20 °C, nitro-phenol **125** was the major product observed along with a trace amount of **132**. Upon separation by column chromatography, both **126** and **132** were moderately stable, however, exposure to acidic conditions and open air or leaving the products absorbed onto silica gel for an extended amount of time resulted in oxidation to quinole **133** as a mixture of diastereomers (14:1 ratio). As an example, treatment of **132** with acetic acid while absorbed on silica gel afforded quinole **133** in 88% yield. This product was also observed when the nitration of **126** was performed at 0 °C and allowed to warm to room temperature, after which the crude product was absorbed onto silica gel and left open to the air (Scheme 40).

Scheme 40: Oxidation of Products to Quinole 133

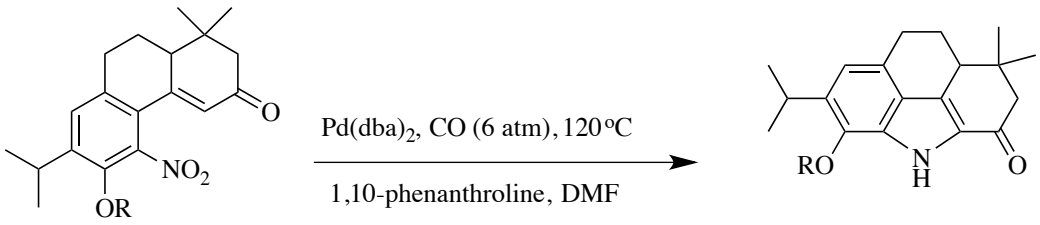


132 **133** **126**

The relative stereochemistry of the major diastereomer of **133** was concluded through NOE, COSY, and selective decoupling NMR experiments. The H9-axial proton and the hydroxy group displayed a four-bond spin-spin coupling (*J*=1.5 Hz), which is in accordance with values observed for similar compounds.[81]

Each of the three nitration products (**125, 132, 133**) were subjected to the previously discussed palladium-catalyzed reductive *N*-heteroannulation conditions[60] in hope of obtaining the expected benzo[*def*]carbazoles. Reaction of both anisole **132** and phenol **125** with carbon monoxide in the presence of a catalytic amount of palladium bis(dibenzylidenacetone) and 1,10-phenanthroline provided **134** and **124** in 87% and 75% yield, respectively (Scheme 41). Unlike their precursors, both cyclization products were stable towards oxidation when treated with acetic acid, air, and when adsorbed onto silica gel.

Scheme 41: Palladium-Catalyzed Reductive *N*-Heteroannulation



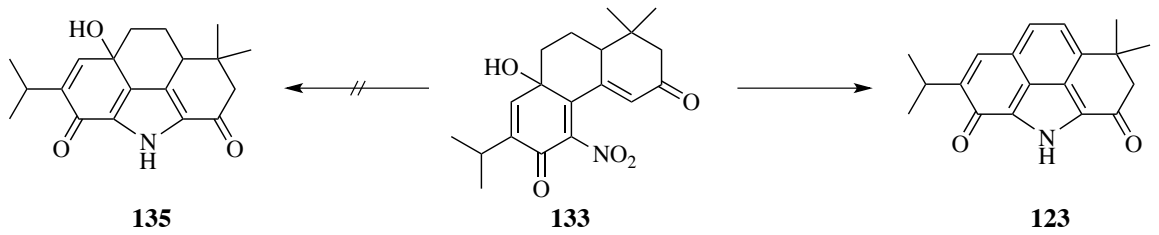
132 (R= Me)
125 (R= H)

134 (R= Me, 87%)
124 (R= H, 75%)

Attempted palladium-catalyzed cyclization of quinole **133** was not as successful as the two previous cases. Although a small amount (10%) of salviadione (**123**) was isolated from a complex reaction mixture of which all of the starting material had been

consumed, none of the expected cyclization product **135** was obtained (Scheme 42). Multiple attempts to improve the yield of this direct route to salviadione (**123**) were unsuccessful.

Scheme 42: Attempted Cyclization of Quinole

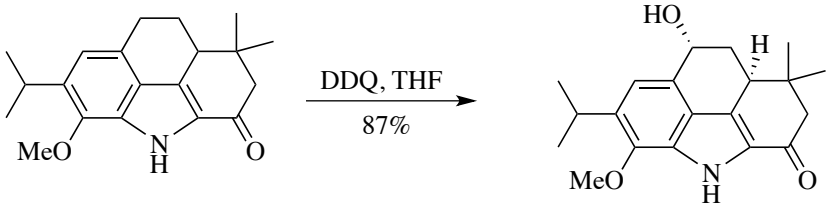


135 **133** **123**

Conditions: 1,10-phenanthroline, $Pd(dba)_2$, CO (6 atm), DMF, 120 ºC

Methoxy-substituted compound **134** was also treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), resulting in benzylic oxidation to afford hydroxy substituted benzo[*def*]carbazole **136** (Scheme 43).[82] Interestingly, **136** possesses the same relative stereochemistry between the hydroxy group and the C9-axial proton as reported for a number of similar naturally occurring compounds.[83] In the case of **136**, this relative stereochemistry was determined through NOE NMR experiments. Unfortunately, conversion of this compound to salviadione (**123**) would require demethylation, elimination of water, and oxidation, so the route was not pursued.

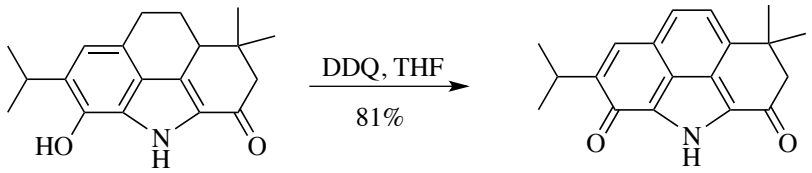
Scheme 43: Benzylic Oxidation of Anisole Using DDQ



134 **136**

A more synthetically-useful route to salviadione (**123**) was achieved through treatment of hydroxy compound **124** with a four-fold excess of DDQ in tetrahydrofuran (THF), affording salviadione (**123**) in good yield (Scheme 44).

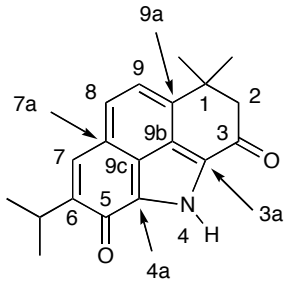
Scheme 44: DDQ Oxidation to Afford Salviadione



124 **123**

The structure of salviadione was confirmed through comparison of experimentally obtained melting point, IR, HRMS, and ^{1}H NMR data with that reported for the natural product.[72] Table 4 provides a comparison of ^{1}H NMR data while ^{13}C NMR data is provided in Table 5. Every carbon resonance was found to be within 1 ppm of the natural product aside from one (C3a), which was 1.2 ppm off.

Table 4: ^{1}HNMR Shift Comparison Between Synthetic and Natural Salviadione



Proton	δ (ppm)[a,c]	J (Hz)[a,c]	$\Delta\delta$ (ppm)
NH	13.24 (14.23)[b]		
H-2	2.95 (2.95)		0
H-6	7.55 (7.56)		0.01
H-8	7.66 (7.66)	7.0 (7.5)	0
H-9	7.31 (7.30)	7.0 (7.5)	-0.01
iPr-CH	3.49 (3.54)	6.9 (7.0)	0.05
iPr-Me	1.29 (1.31)	6.9 (7.0)	0.02
1-Me	1.51 (1.49)		-0.02

a) In $CDCl_3$ b) In DMSO-d_6 c) Literature values in parenthesis.

Table 5: ^{13}CNMR Shift Comparison Between Synthetic and Natural Salviadione

Carbon	δ (ppm)[a]	$\Delta\delta$ (ppm)
1	41.3 (41.3)	0
2	57.3 (57.4)	0.1
3	187.7 (188.0)	0.3
3a	127.0 (128.2)	1.2
4a	126.7 (126.9)	0.2
5	175.8 (175.9)	0.1
6	151.3 (151.4)	0.1
7	128.9 (129.1)	0.2
7a	128.2 *(127.9)*	-0.3
8	129.5 (129.7)	0.2
9	121.2 (121.0)	-0.2
9a	144.9 (145.3)	0.4
9b	124.0 *(123.9)*	-0.1
9c	124.2 (124.3)	0.1
iPr-Me	22.7 (22.8)	0.1
iPr-CH	27.3 (27.4)	0.1
C1-Me	30.0 (30.1)	-0.1

a) In $CDCl_3$; Literature values in parenthesis.

To probe the potential biological uses of these compounds, salviadione (**123**), along with methoxy and hydroxy analogs **134** and **124**, respectively, were tested for potential activity against liver cancer cell lines. However, initial results showed LD_{50} values similar to those typical for DMSO, which was used as the carrier solvent in the assays. Therefore, any cell death was attributed to the DMSO rather than the synthesized compounds. However, this preliminary examination was very narrow in focus and it is possible that compounds **123**, **124**, and **134** possess other biological uses.

3.3 Conclusions

A novel, concise synthetic route to Salviadione and two related derivatives has been developed utilizing a key palladium-catalyzed reductive *N*-heterocyclization to form the indole core. Through an unexpected yet advantageous demethylation encountered in

the nitration of the tricyclic terpenoid intermediate, a more direct route than initially envisioned was established. This reaction sequence may allow facile preparation of additional structural analogues, which could prove useful in a wide array of biological applications.

Chapter 4

Investigation of Chemoselectivity in Kosugi-Migita-Stille Coupling Reactions

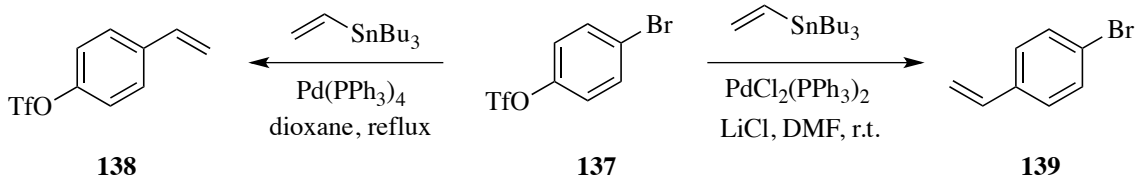
4.1 Kosugi-Migita-Stille Reaction Background

Carbon-carbon bond forming reactions have been a key focus of many synthetic organic chemists over the past number of decades. Kosugi, Shimizu, and Migita[84,85,86] reported the first examples of palladium-catalyzed coupling between organotin compounds and carbon electrophiles in 1977. Stille's first study of similar reactions was published in 1978.[87] While his work was preceded by that of Kosugi, Shimizu, and Migita, the coupling of organotin reagents with carbon electrophiles using palladium catalysts is often referred to as simply the "Stille Coupling" reaction as Stille's comprehensive mechanistic and synthetic investigations provided the basis for more recent studies.[88]

4.2 Chemoselective Stille Coupling Reactions

Selectivity is an ever-important yet challenging issue when employing a particular reaction. Chemoselectivity refers to the ability to react with one particular functional group in the presence of other potentially reactive groups.[89] A specific example of chemoselectivity was reported by Echavarren[90], who studied Stille cross-coupling reactions between organostannanes and arenes featuring both a halide and a triflate. Through use of different palladium catalysts and additives, selective couplings were achieved through either the carbon-halide or carbon-triflate bond of bromophenyl triflate **137**. These results are summarized in Scheme 45. The use of tetrakis(triphenylphosphine)palladium(0) as the catalyst in 1,4-dioxane favored reaction with the bromine, affording styrene **138**, while using bis(triphenylphosphine)palladium(II) dichloride as the catalyst along with a three-fold excess of lithium chloride in *N,N*-dimethylformamide (DMF) afforded exclusively styrene **139** through reaction with the trifloxy group.

Scheme 45: Echavarren's Chemoselective Stille Coupling Conditions

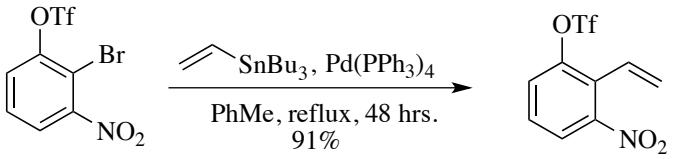


138 **137** **139**

These initial studies suggest that using a palladium (II) catalyst as well as the addition of lithium chloride facilitates insertion of palladium into the carbon-oxygen bond of the triflate to afford bromostyrene **139**. It was also proposed[90] that coordination of the catalyst to the basic trifloxy group could direct the oxidative addition to occur into the triflate carbon-oxygen bond rather than to the carbon-bromine bond. The addition of lithium chloride facilitates ligand exchange of the trifluoromethanesulfonyloxy group for a chloride upon oxidative addition of palladium into the carbon-oxygen bond of the triflate, rendering the intermediate more reactive for subsequent transmetallation.[91]

Only one example of a chemoselective coupling reaction involving a nitrated bromophenyl triflate has been reported by Krolski.[92] Using conditions similar to those previously discussed[90] for the selective coupling of aryl bromides, chemoselective coupling through the carbon-bromine bond of 2-bromo-3-nitrophenyl triflate (**140**) accomplished, affording styrene **141** (Scheme 46).

Scheme 46: Krolski Selective Coupling of 2-Bromo-3-Nitrophenyl Triflate



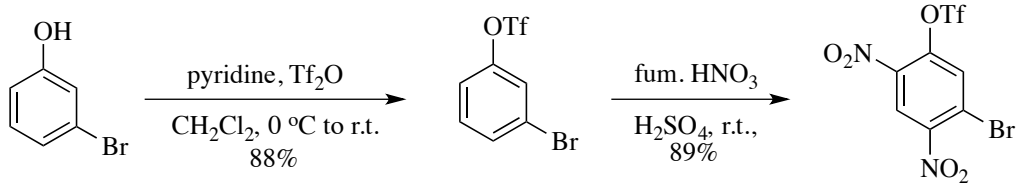
140 **141**

4.3 Investigation of Nitro Effect in Stille Coupling Reactions

Selective couplings were of interest for the potential use in the preparation of substrates en route to pyrroloindoles via reductive double *N*-heteroannulations. The first

system examined was 2,4-dinitro-5-bromophenyl triflate (**144**), which was prepared in two steps from 3-bromophenol (**142**) (Scheme 47). Conversion of phenol **142** to the corresponding triflate **143** followed by nitration eliminated the formation of trinitrophenol as observed in the direct nitration of phenol **142**.

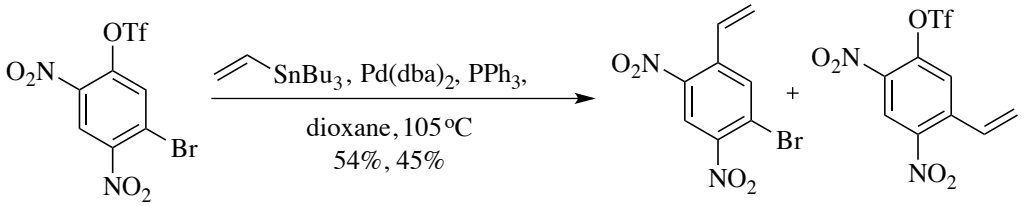
Scheme 47: Preparation of 2,4-Dinitro-5-Bromophenyl Triflate



142 **143** **144**

Application of Echavarren's conditions[90] that should result in coupling through the carbon-bromine bond (Conditions A) using substrate **144** afforded a near 1:1 mixture of triflate-coupled product **145** along with bromine-coupled **146** (Scheme 48).

Scheme 48: Attempted Selective Coupling of Dinitro-Bromophenyl Triflate



144 **145** **146**

The lack of selectivity observed in the coupling of dinitroarene **144** was puzzling. It was concluded that additional factors must have been influencing the erosion of chemoselectivity observed for the dinitro substrate **144**. Considering that electron-withdrawing substituents often enhance the reactivity of C-X bonds (with X referring to either a halide or pseudohalide) in coupling reactions,[90] it was proposed that the nitro groups were the root of the eroded selectivity. The effect was believed to be due to the nitro groups being in conjugation with the *ortho* and *para* X-groups, reducing the electron density at those positions. The more electrophilic X-groups would then be more

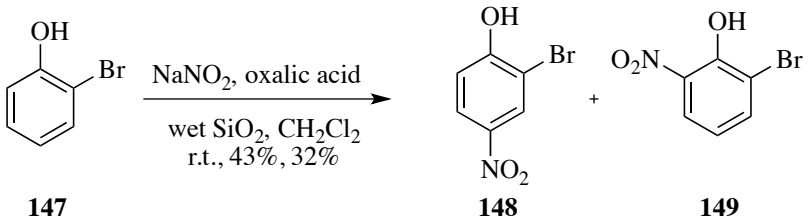
prone to oxidative addition, potentially causing the observed loss of selectivity. Another proposal, based off Echavarren's explanation[90] for the selectivity observed under triflate-selective conditions B, was that the nitro-group could facilitate the oxidative addition into each C-X bond through coordination with the catalyst. In the case of substrate **144** where each C-X bond is *ortho* to a nitro group, potential coordination between palladium and the nitro group could facilitate oxidative addition into either C-X bond. To more explicitly examine the influence that placement of nitro groups had on coupling selectivity, it was deemed necessary to prepare each of the ten bromo-trifloxy nitrobenzene isomers in order to determine what effect the position of the nitro group relative to the triflate or bromine had on the selectivity of the coupling reaction. The plan was to subject each isomer to both the halide-selective conditions A (PPh_3, $Pd(PPh_3)_4$, dioxane, reflux) and triflate-selective conditions B ($PdCl_2(PPh_3)_2$, LiCl, DMF, room temperature) as established by Echavarren.[90]

4.3.1 Preparation of Isomeric Substrates

The first challenge was the preparation of the ten substitutional isomers using a variety of nitration and halogenation reactions.

2-bromo-4-nitrophenol **148** and 2-bromo-6-nitrophenol **149** were prepared through the nitration of 2-bromophenol **147** using sodium nitrite and oxalic acid along with wet silica gel (Scheme 49).[93] The relatively mild reaction conditions provided solely mono-nitrated products with no evidence of di-nitration.

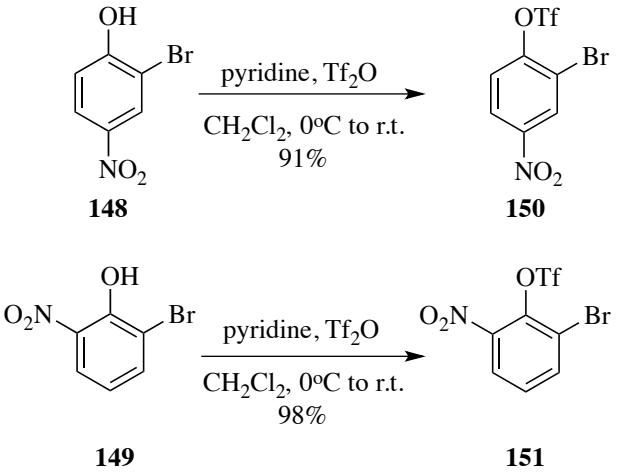
Scheme 49: Nitration of 2-Bromophenol



147 **148** **149**

Conversion to the corresponding triflates **150** and **151** was then accomplished through treatment with pyridine and triflic anhydride (Scheme 50). Filtration of the crude reaction mixture removed the pyridine salt byproduct, and evaporation of solvent provided nearly pure product in both cases.

Scheme 50: Preparation of Isomeric Nitrophenyl Triflates

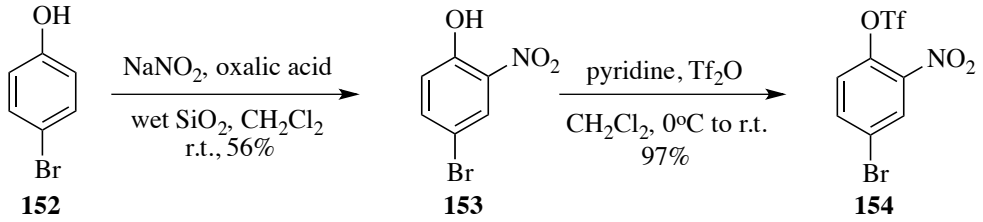


148 **150**

149 **151**

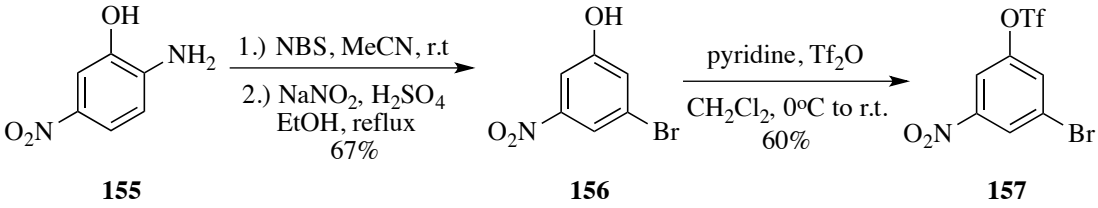
Nitration of 4-bromophenol (**152**) using the same conditions as above[93] provided exclusively 2-nitro-4-bromophenol **153** (Scheme 51). Conversion to the corresponding triflate (as above) provided isomer **154**.

Scheme 51: Preparation of 2-Nitro-4-Bromophenyl Triflate



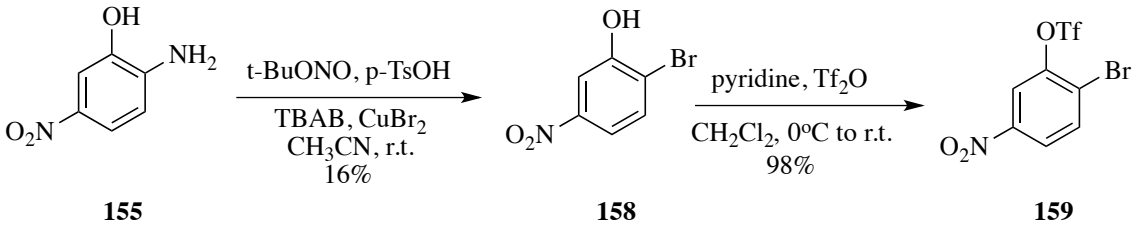
3-nitro-5-bromophenol **156** was prepared in a two-step process from 2-amino-5-nitrophenol **155** (Scheme 52).[94] Regioselective bromination using *N*-bromosuccinimide (NBS) followed by de-amination provided phenol **156**, which was converted to triflate **157** through treatment with pyridine and triflic anhydride.

Scheme 52: Preparation of 3-Nitro-5-Bromophenyl Triflate



2-bromo-5-nitrophenyl triflate **159** was also prepared from 2-amino-5-nitrophenol (**155**) (Scheme 53). Initial halogenation[95] with copper (II) bromide provided aryl bromide **158**, which was subsequently converted to triflate **159** using previously established conditions.

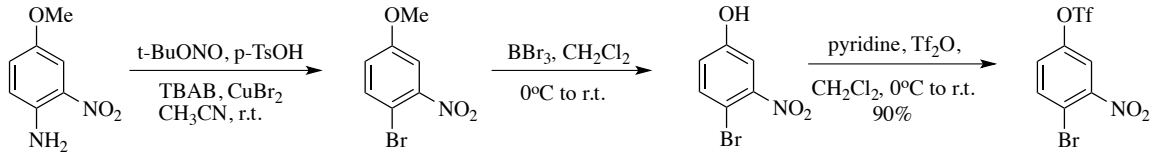
Scheme 53: Preparation of 2-Bromo-5-Nitrophenyl Triflate



3-nitro-4-bromophenyl triflate **163** was prepared in three steps from 3-nitro-4-aminoanisole **160** (Scheme 54). Halogenation[95] of aniline **160** using Sandmeyer-type

conditions provided aryl bromide **161**, which was then treated with boron tribromide to cleave the phenyl methyl ether, providing phenol **162**. Treatment of **162** with base and triflic anhydride afforded triflate **163**.

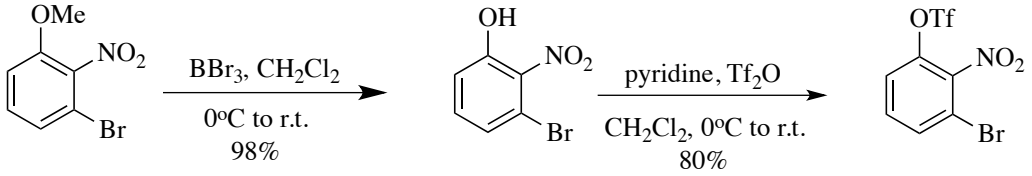
Scheme 54: Preparation of 4-Bromo-3-Nitrophenyl Triflate



160 **161** **162** **163**

Boron tribromide demethylation[95] of anisole **164** provided phenol **165**, which was then converted to triflate **166** using previously discussed conditions (Scheme 55).

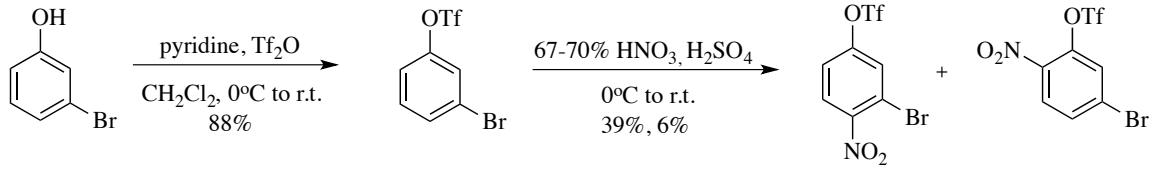
Scheme 55: Preparation of 3-Bromo-2-Nitrophenyl Triflate



164 **165** **166**

Two additional isomers (**167** and **168**) were prepared through the mono-nitration of 3-bromophenyl triflate **143** (Scheme 56).

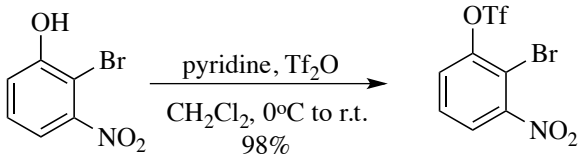
Scheme 56: Preparation of 167 and 168



142 **143** **167** **168**

The final isomer **140** was prepared in near quantitative yield from phenol **169**, which was on hand from previous work within the laboratory (Scheme 57).

Scheme 57: Preparation of 2-Bromo-3-Nitrophenyl Triflate



169 **140**

4.3.2 Results and Discussion

With each of the possible structural isomers in hand, focus was turned to the coupling reaction, each substrate was treated with vinyl stannane in the presence of either bromine-selective conditions A ($Pd(PPh_3)_4$, dioxane, reflux) and triflate-selective conditions B ($PdCl_2(PPh_3)_2$, LiCl, DMF, r.t). The results of this systematic investigation are summarized in Table 6. In some cases, unreacted starting material and/or coupled product was isolated as the corresponding phenol due to hydrolysis during column chromatography. In addition, minor amounts of di-coupled products were also detected in some cases. All reactions were run for 24 hours to allow direct comparison between substrates by limiting potential variables. In a slight variation from Echavarren's work[90] which directly used $Pd(PPh_3)_4$, the same complex was generated *in situ* by mixing $Pd(dba)_2$ with PPh_3. For clarity, the substrates in Table 6 are arranged according to the position of the bromine relative to the nitro group. Entries 1-4 are isomers where the bromine is *ortho* to the nitro group, entries 5-8 possess a *meta* relationship between the bromine and nitro group, and entries 9-10 feature the bromine *para* to the nitro group.

Table 6: Isolated Yields From Reaction Under Conditions A and B

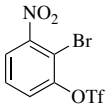
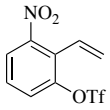
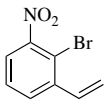
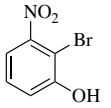
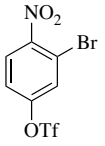
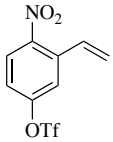
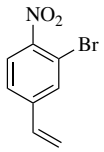
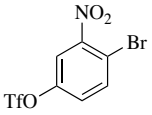
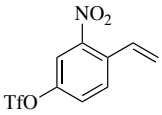
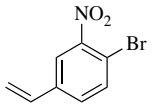
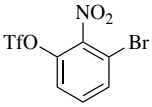
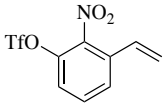
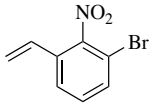
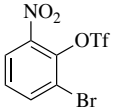
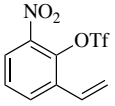
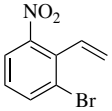
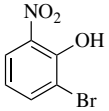
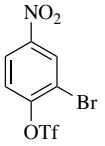
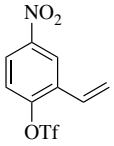
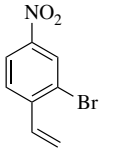
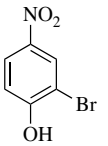
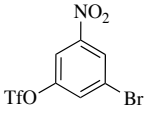
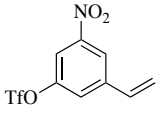
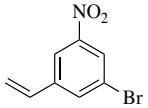
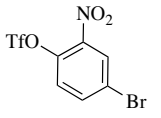
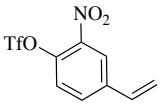
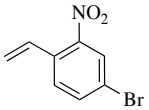
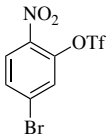
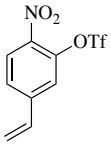
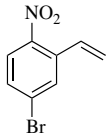
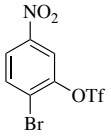
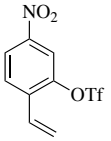
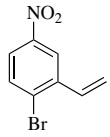
Entry	Substrate	Br-coupling	TfO-coupling	Hydrolysis
				
1A	**140**	**141** (36%)		**169** (62%)
1B	**140** (27%)	**141** (20%)	**170** (38%)	**169** (12%)
				
2A	**167**	**171** (82%)		
2B	**167**	**171** (9%)	**172** (37%)	
				
3A	**163**	**173** (68%)		
3B	**163** (17%)[a]	**173** (23%)[a]	**174** (36%)	
				
4A[b]	**166**	**175** (60%)	**176** (3%)	
4B	**166**		**176** (61%)	
				
5A	**151** (9%)	**177** (24%)	**46** (5%)	**149** (18%)
5B	**151** (5%)		**46** (43%)	**149** (12%)
				
6A	**150** (7%)	**178** (22%)		**148** (8%)
6B	**150** (8%)		**179** (57%)	**148** (16%)
				
7A	**157** (4%)	**180** (78%)		
7B	**157**		**181** (66%)	

Table 6: Isolated Yields From Reaction Under Conditions A and B (cont'd)

Entry	Substrate	Br-coupling	TfO-coupling	Hydrolysis
				
8A		**154** (10%)	**182** (44%)[a]	**183** (3%)
8B		**154**		**183** (78%)
				
9A		**168**	**184** (64%)	
9B		**168**	**184** (26%)	**185** (24%)
				
10A		**159** (20%)[a]	**186** (48%)[a]	
10B		**159** (31%)	**186** (31%)[a]	**187** (7%)

Cond. A: vinyl stannane, PPh_3, $Pd(dba)_2$, 1,4-dioxane, 105 °C
Cond. B: vinyl stannane, $PdCl_2(PPh_3)_2$, LiCl, DMF, r.t.
a) Yield calculated based on integration of ^1H NMR spectrum; b) Also isolated was 31% di coupled product

Under conditions A, all but one substrate featuring a bromine *ortho* to the nitro group (table 6, entries 1-4) exhibited high selectivity, affording exclusively bromine-coupled products (**141, 171, 173**). The only isomer of this group that was not completely selective was that which had both a bromine and a trifloxy group *ortho* to the nitro group (entry 4). In this case, a small amount of trifloxy-coupled product **176** was isolated in addition to the expected bromine-coupled product **175**. This result could be explained by the trifloxy group also being activated toward oxidative addition through conjugation with the *ortho* nitro substituent.

Interestingly, substrates with a bromine *meta* to the nitro group (entries 5-8) also exhibited high selectivity under bromine-selective conditions A. Only isomer **151** (entry

5) was not completely selective for bromine coupling. It can be envisioned that the trifloxy group *ortho* to the nitro group would be activated through conjugation with the nitro group, while the bromine *meta* to the nitro group would not, leading to erosion of selectivity. However, substrates **150** and **154** (entries 6 and 8, respectively) in which the trifloxy group was also in conjugation with the nitro group do not exhibit the same erosion of selectivity. Also of interest is entry 7 where both the bromine and trifloxy group were *meta* to the nitro group. Surprisingly, the isolated yield of bromine-coupled **180** (78%) was among the highest of any isomer examined. This result may be attributed to the overall electron-deficient nature of the nitro-substituted aromatic system even though the nitro group was not in conjugation with the bromine or trifloxy group.

The last two substrates, **168** and **159** (entries 9 and 10, respectively), in which the bromine was positioned *para* to the nitro group were completely selective for bromine coupling under bromine-selective conditions A. This was surprising for isomer **168** in which the trifloxy group was activated *ortho* to the nitro group, although the bromine was in the *para* position, which would also be activated through conjugation with the nitro group. In this case, the observed selectivity could be attributed to a faster transmetalation between palladium and tin upon oxidative addition of the catalyst to the carbon-bromine bond as opposed to the carbon-oxygen bond of the triflate.[91]

Under triflate-selective conditions B, three of the four isomers in which the trifloxy group was *ortho* to the nitro group (entries 4, 5, 8) exhibited absolute selectivity for triflate coupling. In contrast, isomer **168** (entry 9) was actually counter-selective, affording bromine-coupled **184** in higher yield than triflate-coupled **185**. This lack of selectivity could be attributed to the bromine being activated through conjugation with

the *para* nitro group, although the trifloxy group would also be activated *ortho* to the nitro group.

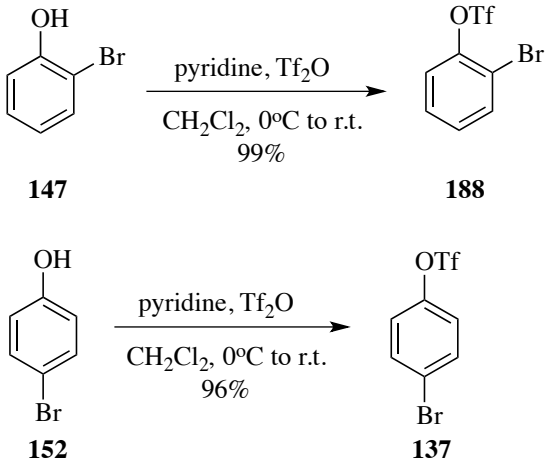
With the exception of entry 7 (where both the triflate and bromine were *meta* to the nitro group), isomers in which the trifloxy group was *meta* to the nitro group (entries 1, 3, 10) exhibited the lowest selectivities out of all of the substrates studied under conditions B. While this could be attributed to each substrate featuring an activated bromine *ortho* or *para* to the nitro group, it is also an indication that conditions B were not ideal for triflate-selective coupling. However, isomer **157** (entry 7) afforded exclusively triflate-coupled **181** on account of the bromine also being in an inactivated *meta* position relative to the nitro group.

The last two substrates were those where the trifloxy group was *para* to the nitro group (entries 2, 6). While isomer **150** was completely selective for triflate-coupling, isomer **167** exhibited eroded selectivity. This contrast could be attributed to the orientation of the bromine relative to the nitro group in each substrate, with the bromine of isomer **150** being in an unactivated *meta* position while the bromine of isomer **167** was activated by the *ortho* nitro group.

From the numerous examples presented in Table 6, it was apparent that the nitro group was key in influencing the selectivity of the reaction. In general, substrates in which the nitro group was *ortho* or *para* to the triflate or bromine exhibited significantly higher conditions-dependent selectivity than those where the nitro-group was *meta* relative to the targeted coupling moiety. In cases where the targeted C-X bond was *meta* to the nitro group, the selectivity was reduced and, in some cases, reversed from what was expected. The reversal of predicted selectivity in these cases could then attributed to electronic activation of the other C-X bond through conjugation with the nitro group.

In addition to the ten mono-nitrated cases mentioned above, two additional isomeric bromophenyl triflates **188** and **137** were prepared in near quantitative yield from the corresponding phenols (Scheme 58).

Scheme 58: Preparation of Bromophenyl Triflates



Each of these substrates (along with 3-bromophenyl triflate **143** from above) were then subjected to coupling conditions A and B. The selectivity observed in each of these reactions is summarized in Table 7.

Table 7: Selective Coupling of Bromophenyl Triflates

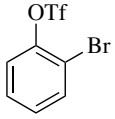
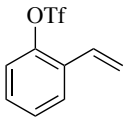
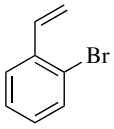
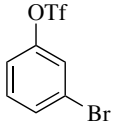
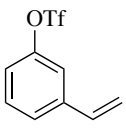
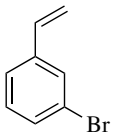
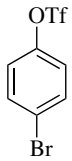
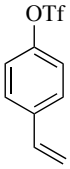
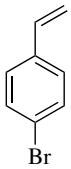
Entry	Substrate	Br-coupling	TfO-coupling
			
1A	**188**	**189** (1.0)	
1B	**188**	**189** (0.15)	**190** (0.85)
			
2A	**143**	**191** (1.0)	
2B	**143**	**191** (0.15)	**192** (0.85)

Table 7: Selective Coupling of Unsubstituted Bromophenyl Triflates (cont'd)

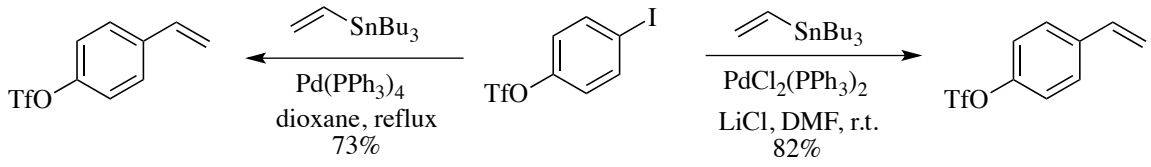
Entry	Substrate	Br-coupling	TfO-coupling
			
3A	**137**	**138** (0.85)	**139** (0.15)
3B	**137**	**138** (0.15)	**139** (0.85)

Cond. A: PPh_3, $Pd(dba)_2$, 1,4-dioxane, 105 ºC
Cond. B: $PdCl_2(PPh_3)_2$, LiCl, DMF, r.t.

Each of these substrates exhibited high selectivity under bromine-selective conditions A. However, conditions B were not as selective, with each substrate affording an approximately 6:1 ratio of the expected triflate-coupled product to the bromide-coupled product. This again demonstrated that conditions B were not ideal for selective coupling of triflates. Pure products were only isolated in some cases, however, due to the tendency of the styrene products to polymerize upon purification, particularly the bromostyrenes. In these cases, the coupled products were present in the NMR spectra obtained after work-up of the reaction mixture; however, no product was isolated upon purification using column chromatography regardless of whether silica gel, basic alumina, or neutral alumina were used as the stationary phase. For these substrates, the selectivities were inferred from integration of the ^1H NMR spectra.

Echavarren[90] also examined the cross-coupling of iodophenyl triflate **193** (Scheme 59). In contrast to the results obtained for bromophenyl triflate **137**, styrene **138** was the only product observed regardless of the catalyst conditions used. This was also in accordance with the established trend[97] that iodides undergo oxidative addition faster than triflates.

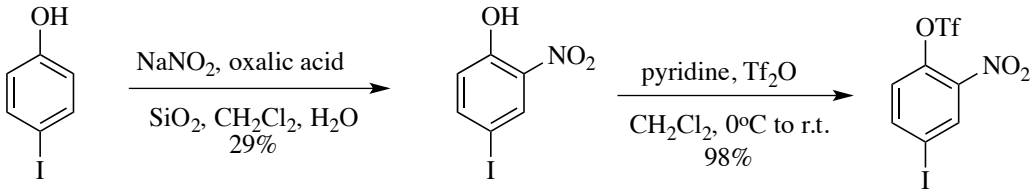
Scheme 59: Echavarren's Coupling of *p*-Iodophenyl Triflate



138 **193** **138**

4-iodo-2-nitrophenyl triflate **196** was prepared as a model to examine whether an iodide would still be more reactive than a trifloxy group even if the iodide was in an unactivated position (*meta* to the nitro group) and the trifloxy group was in an activated position (*ortho* to the nitro group). Nitration[93] of 4-iodophenol (**194**) afforded nitrophenol **195**, which was then converted to triflate **196** using previously established conditions (Scheme 60).

Scheme 60: Preparation of 4-Iodo-2-Nitrophenyl Triflate

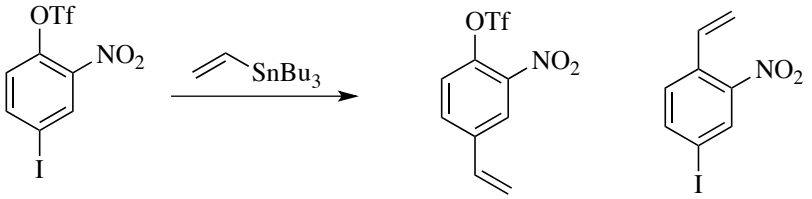


194 **195** **196**

Under both conditions A and B, iodine-coupled **197** was the major product isolated (Scheme 61). Even though the triflate was in an activated position *ortho* to the nitro group, the iodine was still more reactive towards coupling, even under triflate-selective conditions B, which afforded only a trace amount of triflate-coupled product **198**. This result was drastically different than that observed for the analogous bromide **154** (table 6, entry 8), which afforded exclusively triflate-coupled **183** in 78% yield under conditions B. In addition, iodide **196** afforded exclusively iodine-coupled **197** under conditions A, whereas the analogous bromide **154** (table 6, entry 8) exhibited erosion of

selectivity under the same conditions. This direct comparison demonstrated the substantial difference in reactivity between aryl bromides and aryl iodides.

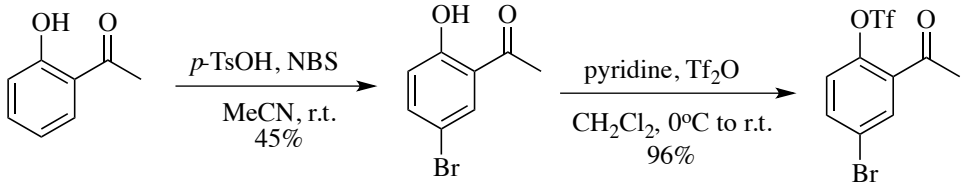
Scheme 61: Coupling of 4-Iodo-2-Nitrophenyl Triflate



196	**197**	**198**
$Pd(dba)_2$, PPh_3, dioxane, reflux	40%	--
$PdCl_2(PPh_3)_2$, LiCl, DMF, r.t.	50%	4%

To examine whether the generalized chemoselectivity could be extended to electron-withdrawing substituents aside from a nitro group, 5-bromo-2-trifloxy acetophenone (**201**) was prepared (Scheme 62). Bromination of phenol **199** afforded the desired bromide **200**, which was then converted to triflate **201**.

Scheme 62: Preparation of 5-Bromo-2-Trifloxy Acetophenone

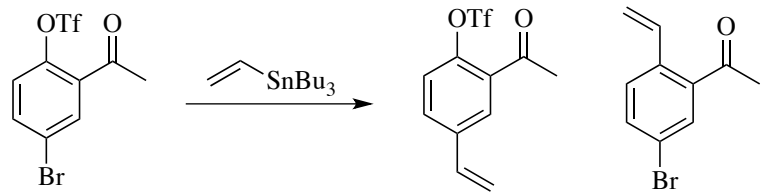


199 **200** **201**

Based on the observations for nitro-substituted arenes, it was proposed that coupling of **201** under conditions A would exhibit erosion of selectivity due to the triflate being activated by the *ortho* electon withdrawing substituent. However, conditions A afforded only **202** (albeit in poor yield), and conditions B afforded only **203**, as expected (Scheme 63). This suggests that weaker electron-withdrawing substituents have little influence on the overall selectivity. However, it is also important to note that for the analogous nitro substrate **154** (Table 6, entry 8), conditions A were not completely selective for bromine-coupling, while conditions B were completely selective for triflate-

coupling. This result is in accordance with the weaker electron-withdrawing acetyl group present in **201** having a smaller activation effect relative to the nitro group in **154**.

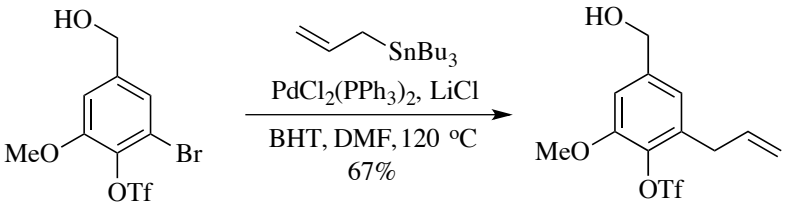
Scheme 63: Selectivity Under Conditions A and B



201	**202**	**203**
$Pd(dba)_2$, PPh_3, dioxane, reflux	14%	--
$PdCl_2(PPh_3)_2$, LiCl, DMF, r.t.	--	58%

Previous work[98] reported bromine-selective coupling under "Conditions B" for bromo-trifloxybenzene **204**, affording **205** in moderate yield (Scheme 64). The observed selectivity was postulated to be due to the trifloxy group being deactivated by the *ortho* and *para* electron-donating methoxy and alkyl substituents, as well as the increased steric crowding around the triflate. The bromine positioned *meta* to the donating groups would be unaffected electronically, rendering it more reactive regardless of the catalyst conditions.

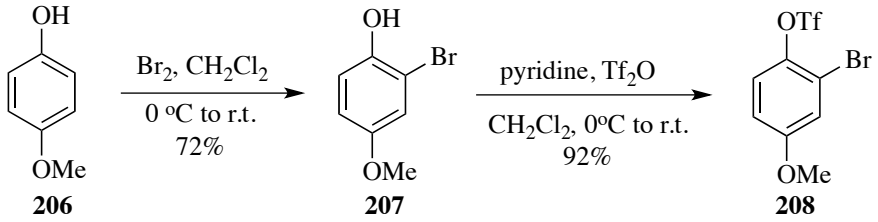
Scheme 64: Bromine-Selective Coupling Under Conditions B



204 **205**

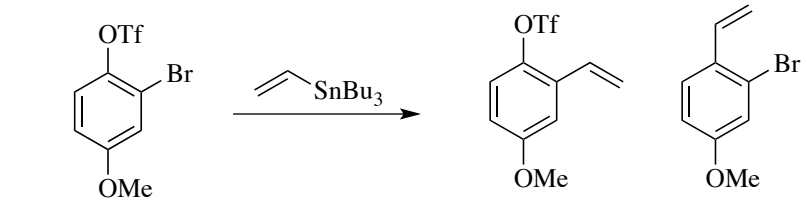
To study the effect of electron-donating substituents in a more simple, direct example, 3-bromo-4-trifloxy anisole (**208**) was prepared (Scheme 65). Bromination of phenol **206** exhibited high regioselectivity, affording bromide **207**, which was then converted to triflate **208**.

Scheme 65: Preparation of 3-Bromo-4-Trifloxy Anisole



Based on previously reported results,[98] it was proposed that the electron-donating methoxy group would deactivate the *para*-trifloxy substituent, while the *meta*-bromine would be unaffected since it was not in conjugation with the methoxy group. Indeed, bromine-coupled **209** was the only product observed under conditions A, while erosion of selectivity was observed under conditions B, resulting in a mixture of both **209** and **210** (Scheme 66). While the ratio of **210** : **209** under conditions B was nearly 11:1, it was apparent that the *para*-methoxy group did indeed deactivate the triflate.

Scheme 66: Selectivity Under Conditions A and B



While this study of the selectivity in Stille coupling reactions allowed direct comparison between numerous substituted aromatics, there are still some issues that remain. For one, the yield in some cases was moderate at best. Although the goal was to study the selectivity only using the previously established conditions,[90] it would be careless to make broad generalizations based on examples that were completely selective, yet the coupled product was isolated in poor yield. In addition, the role of the different reaction conditions is not fully explained. Though conditions B use a palladium (II)

catalyst, this complex is presumably rapidly reduced to palladium (0) to afford a similar $Pd(PPh_3)_x$ species to that formed under conditions A.[99] Rather, the major difference between the two catalysts is the ratio of ligand : palladium in solution.[100] The use of a more polar solvent (DMF vs. dioxane) under conditions B may also play a key role in stabilizing the intermediate formed through oxidative addition of palladium to the carbon-oxygen bond of the triflate.[101] These numerous factors presumably had an effect on the observed selectivity.

4.4 Conclusions

Through this exhaustive study of selectivity in Stille coupling reactions, some important conclusions were drawn. It was clear that the presence of a nitro group as well as the positioning of the nitro group relative to the halide or trifloxy group had a direct effect on the chemoselectivity of the Stille coupling reaction. It was observed that reactivity was enhanced for groups positioned *ortho* and *para* to the nitro group, while groups *meta* to the nitro group were not affected. In the absence of a nitro group, selectivities were the direct result of the conditions themselves. In these cases, halide-selective conditions A were highly selective, while triflate-selective conditions B exhibited slight erosion of selectivity, affording approximately 6:1 ratios of the expected triflate-coupled products relative to the bromine-coupled products. In accordance with the general reactivity series, iodides were more reactive than triflates regardless of the conditions used and independent the location of a nitro group in the molecule. In contrast to nitro groups, the weaker deactivating acetyl group did not exhibit a similar trend in activating *ortho* and *para* groups towards coupling reaction. On the contrary, an electron-donating group such as a methoxy group was found to deactivate the *ortho* and

para positions through resonance. Based on these observations, the selectivity (or lack thereof) of a coupling reaction may be predicted.

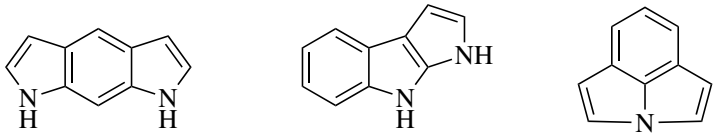
Chapter 5

Preparation of Pyrroloindoles via Palladium-Catalyzed Reductive Double *N*-Heterocyclization

5.1 Pyrroloindole Introduction and Background

Pyrroloindoles have been attractive synthetic targets over the past few decades particularly due to their wide array of potential uses as biological agents as well as electroconductive materials[102] and bidentate ligands.[103] The name pyrroloindole refers to a molecule that features a pyrrole moiety fused onto an indole core. This fusion can come in one of three ways: Type I are those in which the pyrrole is attached to the benzene portion of the indole, Type II feature a pyrrole fused to the nitrogen-containing heterocyclic portion of the indole, and Type III which involve a common nitrogen atom (Figure 6).

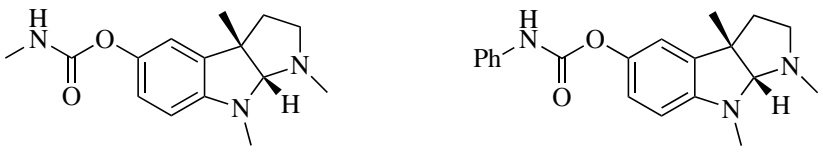
Figure 6: Types of Isomeric Pyrroloindoles



Type I **Type II** **Type III**

A number of pyrroloindoles have gained attention on account of their biological activities. Physostigmine (**211**), a natural product of Type II, is believed to possess therapeutic effects in the treatment of Alzheimer's disease (Figure 7).[104] Phenserine (**212**), also a natural product of Type II, was another potential Alzheimer drug, although it failed in Phase III development (Figure 7).

Figure 7: Physostigmine and Phenserine

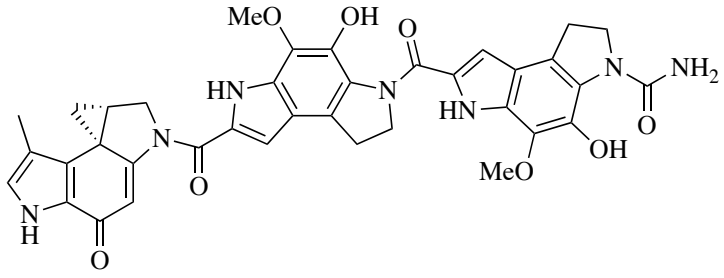


211 **212**

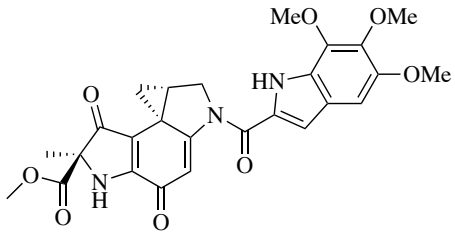
One field in which pyrroloindole based compounds of Type I have found recent application is in the preparation of biological agents, specifically in anti-tumor

treatments. Recent work focusing on the preparation of pyrroloindole based natural products CC-1065 (**213**), Duocarmycin (**214**) and Yatakemycin (**215**) has been reported by Boger *et al* (Figure 8).[105] These compounds and their derivatives are members of a class of anti-tumor compounds whose mode of action centers around the sequence-selective alkylation of duplex DNA within the tumor through nucleophilic opening of the cyclopropane functionality of the anti-tumor agent.

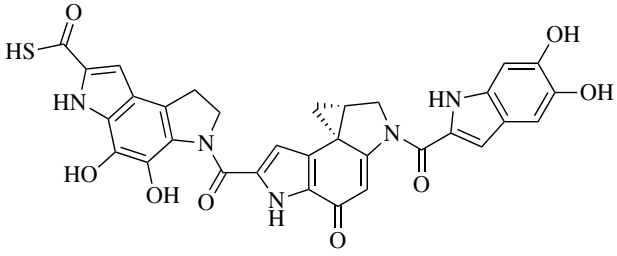
Figure 8: **CC-1065, Duocarmycin, and Yatakemycin**



213



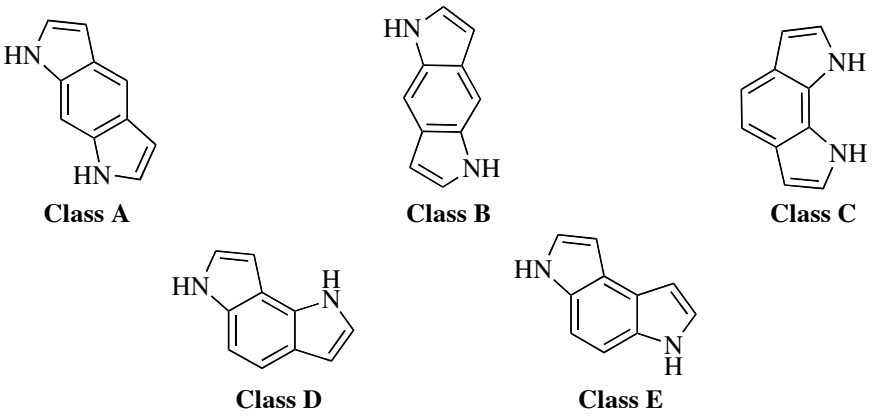
214



215

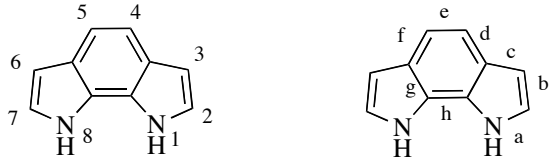
Recent work in Soderberg's laboratory has focused on the preparation of pyrroloindoles of Type I in which the pyrrole is fused to the benzene portion of the indole. Within this class, there are five different isomers, which are shown in Figure 9.

Figure 9: Isomeric Pyrroloindoles of Type I



Pyrroloindoles of type I are named based on the orientation of the pyrrole ring relative to the indole core (Figure 10). Similar to the numbering of the atoms of simple indole, the numbering ascends counter-clockwise around the heterocycle with the nitrogen being atom 1. In a similar fashion, each bond of the indole core is assigned a letter, with the bond between atoms 1 and 2 being bond A. The manner in which the pyrrole unit is fused to the indole core is represented by [x,y-*z*], where x and y are the atoms of the pyrrole and z is the bond of the indole core that atoms x and y are attached to. For example, pyrroloindoles of class C are named 1,8-dihydropyrrolo[3,2-*g*]indoles.

Figure 10: Pyrroloindole Numbering

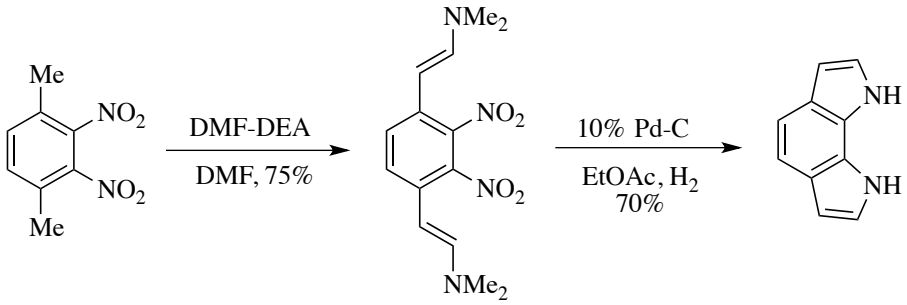


5.2 <u>Historical Routes to Pyrroloindoles of Type I</u>

One of the earliest preparations of symmetrical pyrroloindoles was reported by Berlin *et al*. in 1987 in the study of oxidative polymerization to afford electroconductive materials.[106] This two-step route involved condensation of di-nitro xylene (**216**) with *N,N*-dimethylformamide diethyl acetal (DMF-DEA) to give the bis-enamine **217** which then

underwent reductive cyclization catalyzed by palladium on carbon to afford dihydropyrroloindole **218** (Scheme 67). Although the route was concise, it was quite limited in scope in that only symmetrical, non-substituted pyrroloindoles were accessible.

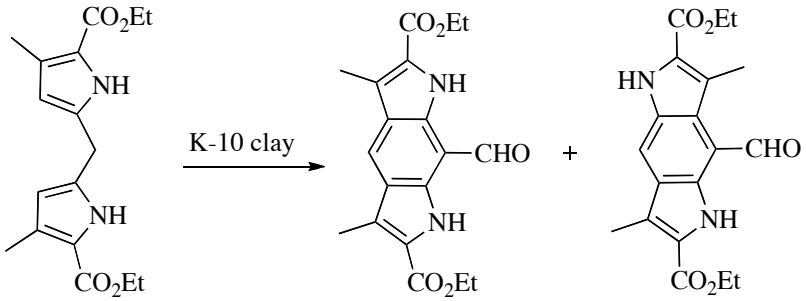
Scheme 67: Berlin's Approach to Pyrroloindoles



216 **217** **218**

Shannon *et al*. prepared pyrrolo[3,2-*f*]- (**220**) and –[2,3-*f*]-indoles (**221**) through the Montmorillonite K-10 clay catalyzed Vilsmeier formylation of dipyrrole **219** (Scheme 68).[107] A mixture of isomers was obtained due to free-rotation about the methylene bridge.

Scheme 68: Montmorillonite K-10 Catalyzed Synthesis of Pyrroloindoles

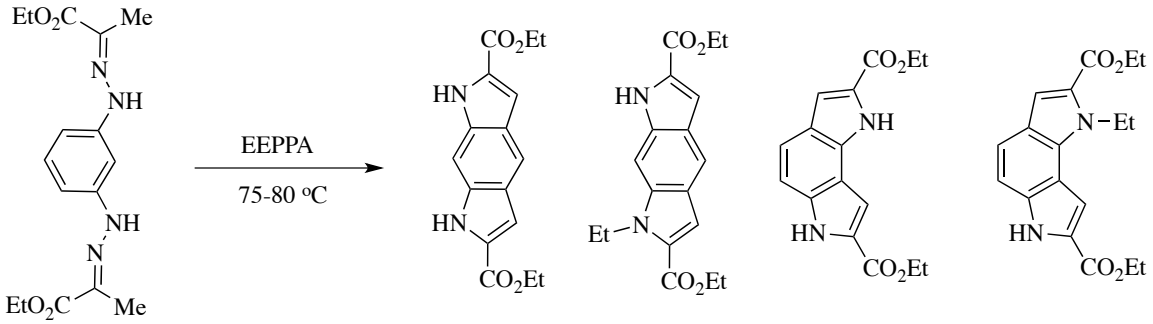


219 **220** **221**

Samsoniya *et al*. reported numerous methods to prepare and characterize isomeric pyrroloindoles.[108, 109] The first method utilized a Fischer-type bicyclization of bishydrazone **222** to form the two pyrrole rings (Scheme 69).[108] The authors noted that due to the harsh conditions required for this transformation, a considerable amount of tar formed over the course of the reaction, presumably from decomposition of the reactants

and/or products. Another drawback was that due to the nature of the cyclization, one starting material **222** produced four isomeric pyrroloindole products (**223-226**) with little control over selectivity.

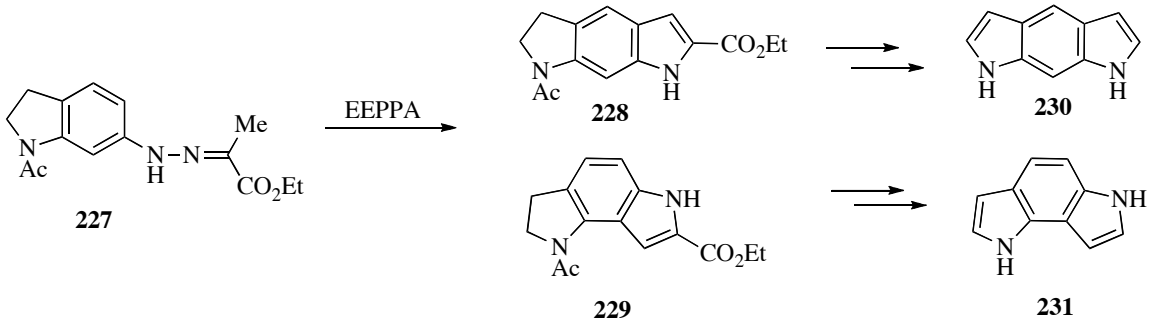
Scheme 69: Samsoniya Route to Isomeric Pyrroloindoles



222 **223** **224** **225** **226**

The second method reported by Samsoniya *et al*. circumvented the previously mentioned issue of isomer formation by using a pre-formed aminoindoline **227** (Scheme 70).[109] Fischer-type cyclization of hydrazone **227** produced two isomeric pyrroloindolines **228** and **229** with a preference for linear isomer **228**. Hydrolysis of the ester and acetyl groups followed by decarboxylation and dehydrogenation then afforded the non-substituted pyrroloindoles **230** and **231**.

Scheme 70: Pyrroloindole Preparation from Aminoindoline

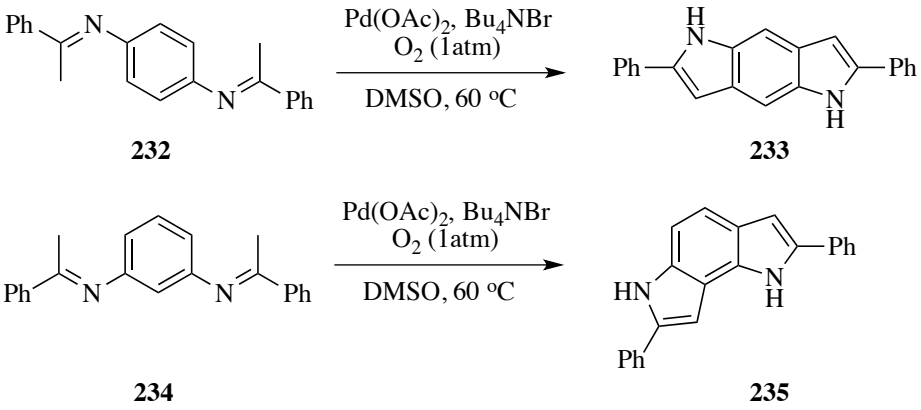


227 **228** **229** **230** **231**

Yoshikai *et al*. have applied their palladium-catalyzed aerobic oxidative bicyclization method to the preparation of pyrroloindoles from *N*-aryl imines.[110]

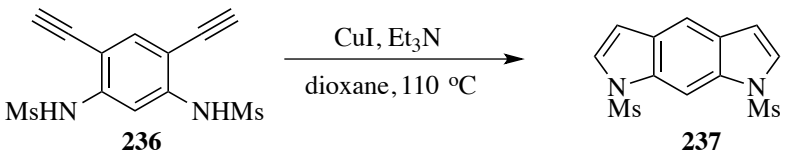
Palladium(II)-catalyzed dicyclization of diimines **232** and **234** afforded corresponding pyrroloindoles **233** and **235** (Scheme 71). While the authors did not attempt to prepare non-symmetrical compounds, the ease of preparation and wide range of aniline and ketone starting materials afford this method a very broad scope, although the yields of the pyrroloindole products were modest at best. In addition, the regioselectivities observed in the cyclizations were not explained

Scheme 71: **Oxidative Bicyclization of Diimines**



Fujii and Ohno reported the preparation of mesylated pyrroloindole **237** through copper-catalyzed bis-cyclization of di-alkynyl-dimesylamide **236** (Scheme 72).[111] The authors state that the cyclization was highly dependent on the substituents on the nitrogen atoms, with mesylates giving the highest conversion. In addition, this approach was limited to terminal alkynes, affording only non-substituted pyrroloindoles.

Scheme 72: Intramolecular Hydroamination of Di-yne



One inherent limitation of many previous synthetic routes is that they only allow for preparation of symmetrical pyrroloindoles. This is in part due to limitations

associated with the methods used to prepare the required starting materials, most of which also involve symmetrical compounds. Therefore, methods to prepare non-symmetrical substrates that can be converted to non-symmetrical pyrroloindoles are highly desirable.

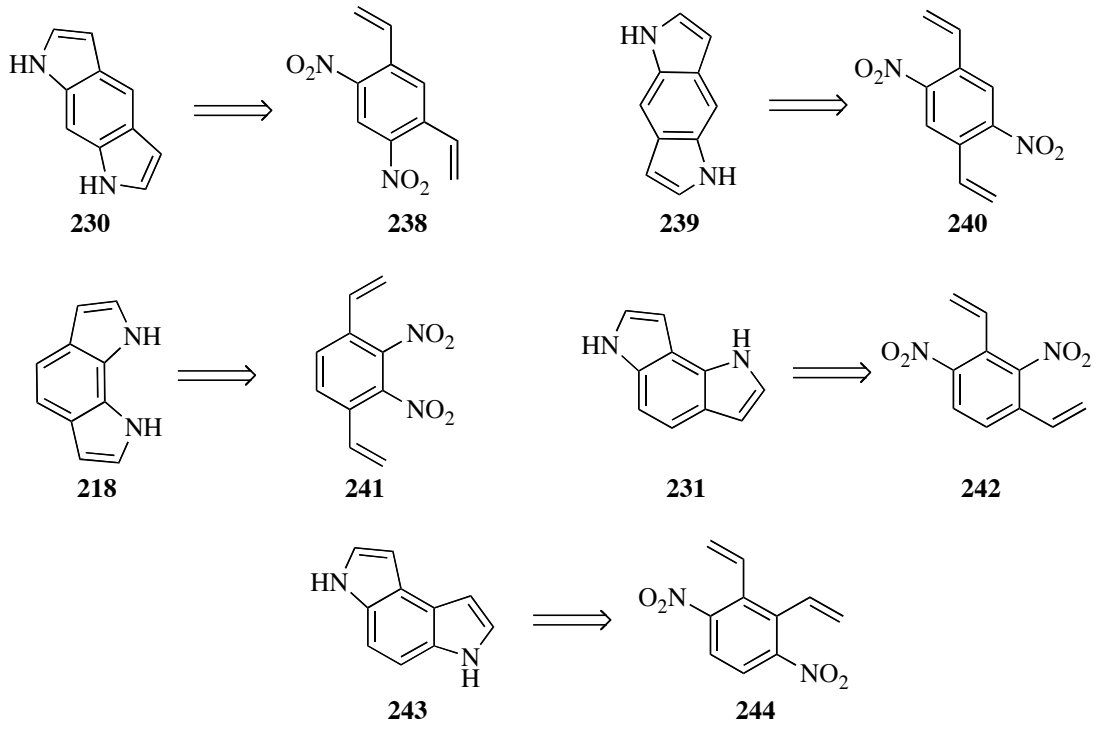
5.3 Pyrroloindole Preparation via Reductive Double *N*-Heteroannulation

As discussed in the preceding chapters, Soderberg's laboratory has studied the applications of palladium-catalyzed reductive *N*-heterocyclizations extensively. It was envisioned that this methodology could be applied in the synthesis of pyrroloindoles from dinitro-dialkenyl benzenes. The generally mild conditions used in such reactions could allow for broad functional group compatibility and offer significant improvements over the previously discussed methods.

5.3.1 Retrosynthetic Analysis

Retrosynthetically, it was proposed that each of the five isomeric pyrroloindoles of type I could be prepared through the palladium-catalyzed reductive double heterocyclization of the corresponding dinitro-dialkenyl benzene (Scheme 73).

Scheme 73: Retrosynthetic Analysis of Pyrroloindoles



230 **238** **239** **240**

218 **241** **231** **242**

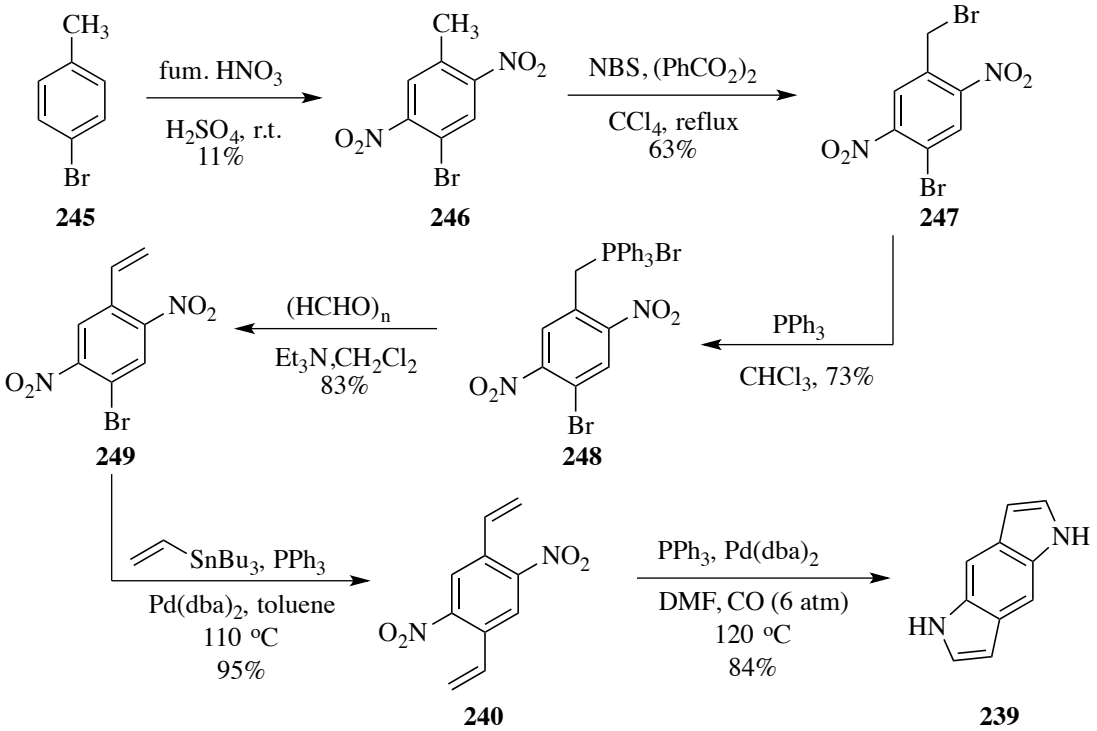
243 **244**

5.3.2 Banini Route To Pyrroloindoles

Banini *et al*. successfully prepared pyrroloindoles using Soderberg's palladium-catalyzed reductive *N*-heteroannulation methodology. Pyrroloindoles of class B such as **239** were achieved in six steps from *p*-bromotoluene (**245**) (Scheme 74). Nitration[112] of **245** afforded a four-product mixture from which isomer **246** was separated and subjected to radical benzylic bromination[113] using *N*-bromosuccinimide and benzoyl peroxide. Benzyl bromide **247** was then converted to phosphine salt **248** before undergoing Wittig condensation to afford styrene **249**. Kosugi-Migita-Stille coupling between bromide **249** and vinyl stannane then afforded dinitro-dialkenyl benzene **240**. Reductive double *N*-heterocyclization was achieved through reaction with PPh_3 and $Pd(dba)_2$ in DMF at 120 ºC in a sealed tube pressurized with carbon monoxide gas, affording pyrroloindole **239** in

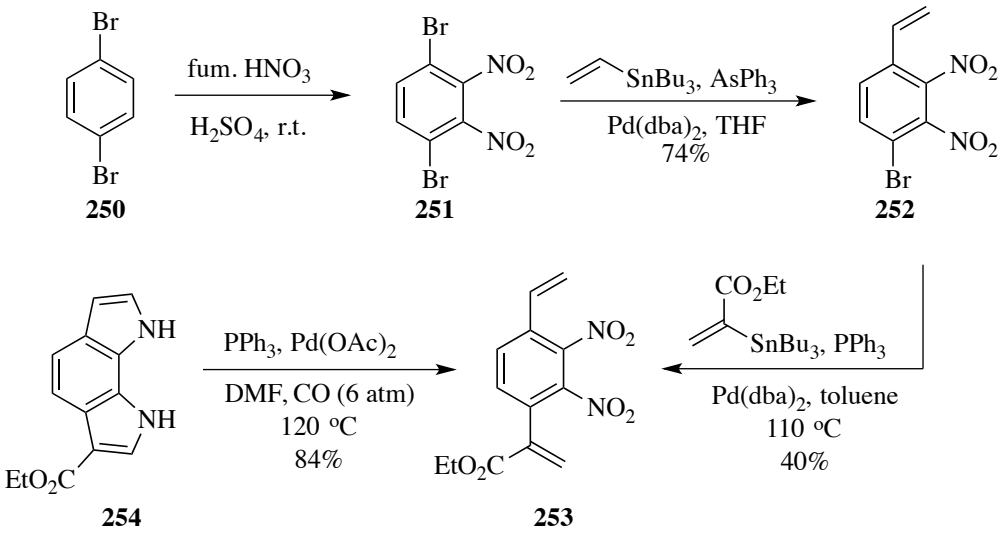
excellent yield. In addition to symmetrical pyrroloindole **239**, non-symmetrical pyrroloindoles were also prepared using this route.

Scheme 74: **Banini Route to Pyrroloindoles of Class B**



A slightly different approach was employed to prepare pyrroloindoles of class C (Scheme 75). Nitration of 1,4-dibromobenzene (**250**) provided three dinitrobenzene isomers, including 2,3-dinitro-1,4-dibromobenzene (**251**). Kosugi-Migita-Stille cross-coupling between **251** and vinyl stannane afforded bromostyrene **252**, which underwent a second Kosugi-Migita-Stille coupling with α-stannyl ester to afford cyclization precursor **253**. Exposure of **253** to altered Soderberg reductive heteroannulation conditions (PPh_3, $Pd(OAc)_2$) afforded pyrroloindole **254** in excellent yield.

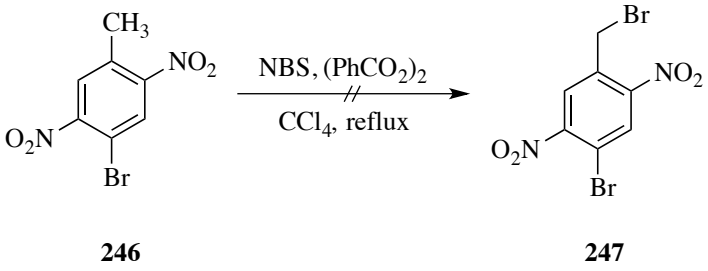
Scheme 75: **Banini Route to Pyrroloindoles of Class C**



5.3.3 Synthesis of Symmetrical Pyrroloindoles

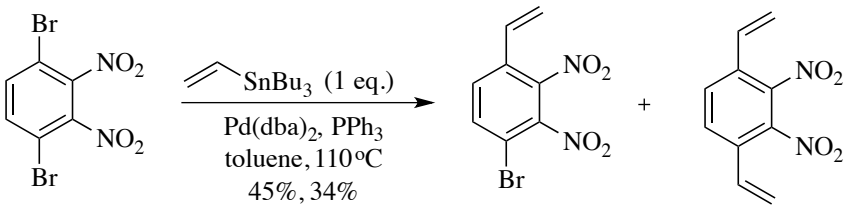
Initial attempts to elaborate on Banini's work encountered a number of issues. While Banini reported the benzylic bromination of dinitrotoluene **246** to afford benzyl bromide **247** in moderate yield, in our hands, the reaction afforded near quantitative recovery of starting material (Scheme 76).

Scheme 76: Failed Preparation of Benzyl Bromide



Replication of the reported mono-Kosugi-Migita-Stille cross-coupling of dinitro-dibromobenzene **251** with vinyl stannane was also unsuccessful (Scheme 77). While Banini achieved styrene **252** in moderate yield, in our hands, a mixture of mono- and di-coupled products **252** and **241** was obtained.

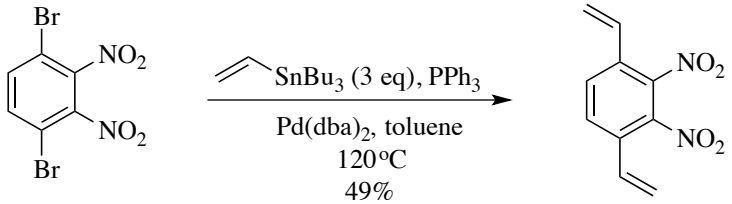
Scheme 77: Attempted Mono-Coupling of Dibromide



251 **252** **241**

To circumvent this issue, the coupling reaction was attempted using a three-fold excess of stannane with the goal of preparing exclusively di-coupled arene **241**. In the event, di-vinyl compound **241** was prepared in moderate yield (Scheme 78).

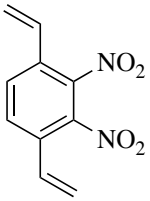
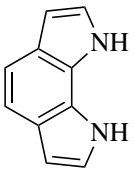
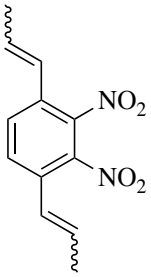
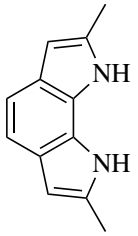
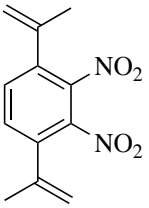
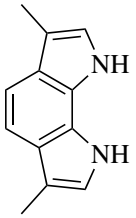
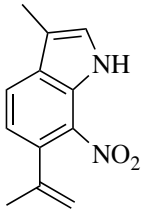
Scheme 78: Preparation of Dialkenyl-Dinitrobenzene



251 **241**

Reductive double *N*-heteroannulation of **241** was achieved using alternate conditions reported by Banini to afford pyrroloindole **218** in moderate yield (table 8, entry 1). Two additional cyclization precursors **255** and **257** were also prepared through dicoupling of **241** with propenyl- and isopropenyl stannane, respectively. Palladium-catalyzed cyclization of **255** afforded exclusively symmetrical pyrroloindole **256** in moderate yield (entry 2). Cyclization of **257** afforded solely indole **259** when the catalyst conditions were 1,10-phenanthroline and $Pd(OAc)_2$, however, pyrroloindole **258** was achieved through use of PPh_3 and $Pd(dba)_2$, although indole **259** was the major product.

Table 8: Reductive Double *N*-Heteroannulation[a]

Entry	Substrate	Product(s)
1[b]	 **241**	 **218** (56%)
2[c]	 **255**	 **256** (43%)
3	 **257**	 +  -- **259** (12%)
3[d]	**257**	**258** (25%) **259** (54%)

a) 1,10-phenanthroline, $Pd(OAc)_2$, CO (6 atm), DMF, 120 ºC; b) Reaction run for 143 hours; c) Reaction run for 20 hours; d) PPh_3, $Pd(dba)_2$, CO (6 atm), DMF, 120 ºC, 96 hours

Dihydropyrroloindole **218** (entry 1) was isolated in moderate yield after 143 hours, although the cyclization was likely complete at an earlier time on account of the lack of unreacted starting material or mono-cyclized product. It was expected that the simple vinyl groups would present less steric repulsion toward the palladium in comparison to propenyl-substituted substrates **255** and **257** and would therefore react faster. Surprisingly, di-propenyl substrate **255** (entry 2) afforded pyrroloindole **256** in moderate yield after only 20 hours. On the contrary, **257** (entry 3) appeared to undergo mono-cyclization with ease, producing indole **259**, however, the second cyclization to afford pyrroloindole **258** was much slower as evidenced by the significantly lower yield

relative to indole **259**. The decreased rate of the second cyclization could potentially be attributed to weaker coordination of the catalyst to the isopropenyl moiety of **259**.

5.4.1 Synthesis of Non-Symmetrical Pyrroloindoles

While symmetrical pyrroloindoles were prepared using Soderberg's palladium-catalyzed reductive double *N*-heteroannulation methodology, numerous limitations were apparent, including the inability to prepare non-symmetrical pyrroloindoles and the incomplete conversion to pyrroloindoles. In addition, only two of the five isomeric pyrroloindoles were achieved through the routes. Efforts to overcome the limitations in the preparation of non-symmetrical pyrroloindoles are presented in the sections hereafter.

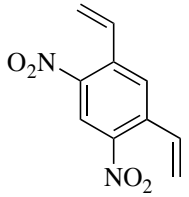
5.4.1 Preparation of Cyclization Precursors

With the goal of preparing non-symmetrical pyrroloindoles using Soderberg's reductive annulation methodology, efforts were made to establish routes to prepare the requisite dinitro-dialkenyl benzenes. Specifically, efforts focused on synthesizing non-symmetrical cyclization precursors in a controlled, sequential manner. For organizational clarity, each isomeric substrate is presented separately, although numerous commonalities were encountered in the preparation of each substrate.

5.4.1 2,4-Dinitro-1,5-Dialkenyl Benzene Isomer

The first and most extensively examined cyclization precursors were 2,4-dinitro-1,5-dialkenyl benzenes, such as **238** (Figure 11).

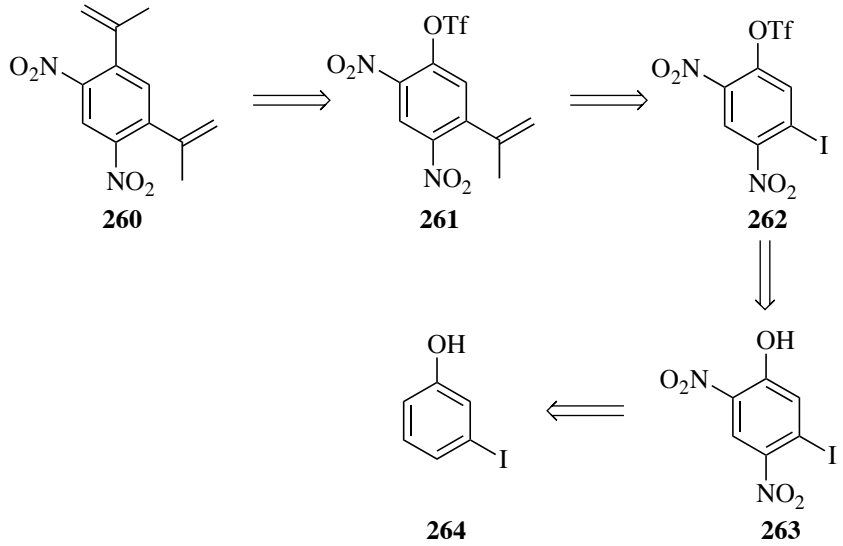
Figure 11: 2,4-Dinitro-1,5-Dialkenyl Benzene



238

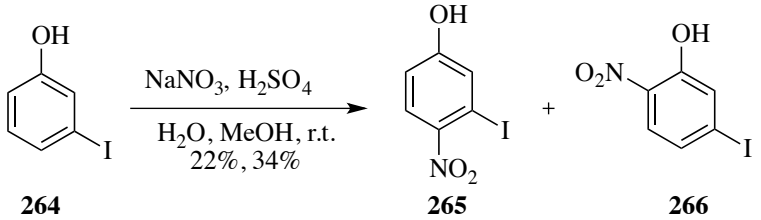
Retrosynthetically, it was envisioned that dinitro-dialkenyl benzene **260** could be prepared through Kosugi-Migita-Stille coupling reaction of triflate **261** (Scheme 79). The isopropenyl moiety of **261** could be introduced by Kosugi-Migita-Stille cross coupling between aryl iodide **262** and isopropenyl stannane. Dinitrophenyl triflate **262** could arise from dinitrophenol **263**, which could be prepared through the nitration of 3-iodophenol (**264**).

Scheme 79: Proposed Retrosynthetic Outline to Cyclization Precursor



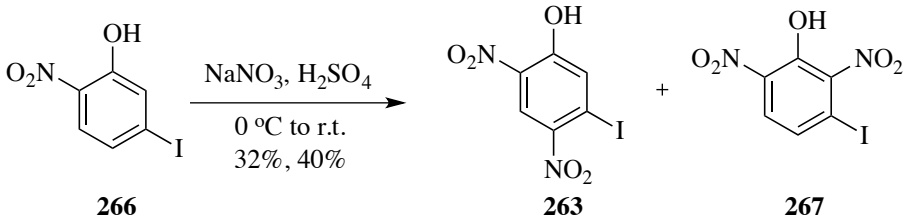
Banwell *et al*.[114] have reported the nitration of 3-iodophenol (**264**) using sodium nitrate in a solution of aqueous methanol and sulfuric acid, providing both 3-iodo-4-nitrophenol (**265**) and 5-iodo-2-nitrophenol (**266**) (Scheme 80). The relatively mild conditions employed prevent the formation of trinitrophenols as reported under harsher conditions.[115,116]

Scheme 80: Nitration of 3-Iodophenol



With isomers **265** and **266** in hand, a second nitration was examined. The methanol/water conditions used in the initial nitration (Scheme 80) proved to be too mild for a second nitration to occur, as evidenced by the absence of di-nitrated products. Therefore, a solution of sodium nitrate in sulfuric acid, believed to be slightly more acidic than the conditions used to introduce the first nitro group, yet milder than the fuming nitric acid/sulfuric acid system, was used. Gratifyingly, treatment of 5-iodo-2-nitrophenol (**266**) with sodium nitrate in sulfuric acid provided di-nitrophenols **263** and **267** with no evidence of tri-nitration (Scheme 81). It should be noted that in some cases, solely isomer **263** was formed, while in other cases, a near 1:1 mixture of isomers **263** and **267** was obtained.

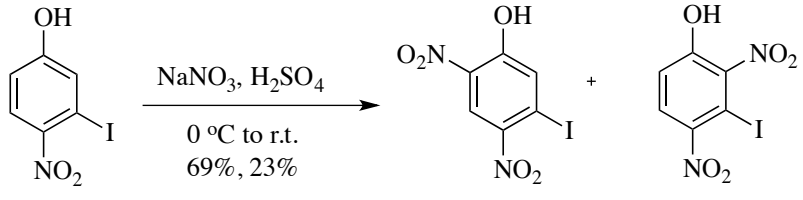
Scheme 81: Nitration of 5-Iodo-2-Nitrophenol



266 **263** **267**

Nitration of 3-iodo-4-nitrophenol (**265**) using these same conditions afforded dinitrophenols **263** and **268** (Scheme 82). Once again, 5-iodo-2,4-dinitrophenol (**263**) was the major product observed in most reactions, although in some cases, isomer **268** was also formed. Unfortunately, dinitrophenols **263** and **268** were nearly inseparable using column chromatography.

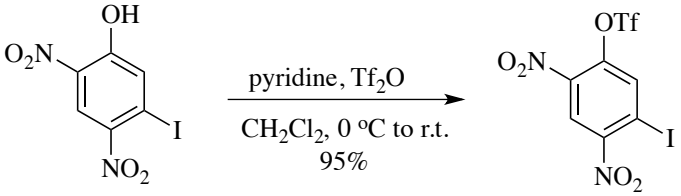
Scheme 82: Nitration of 3-Iodo-4-Nitrophenol



265 **263** **268**

Subsequent treatment of dinitrophenol **263** with pyridine and triflic anhydride afforded aryl triflate **262** in near quantitative yield (Scheme 83).

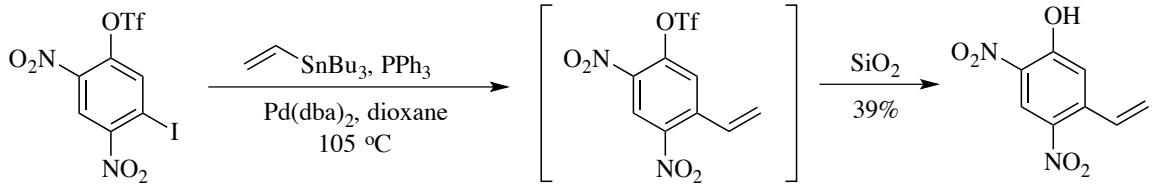
Scheme 83: Preparation of Aryl Triflate



263 **262**

With the desired functionalized starting material in hand, focus was turned to the coupling reactions to prepare the target non-symmetrical dialkenyl-dinitrobenzenes. Attempts to selectively couple the iodine of substrate **262** were successful in producing styrene **146**, however, purification using column chromatography resulted in the hydrolysis of the trifloxy group of **146** and lead to the isolation of phenol **247** (Scheme 84). Similar hydrolysis of electron-deficient aryl triflates has been documented in the literature.[117]

Scheme 84: Attempted Kosugi-Migita-Stille Coupling

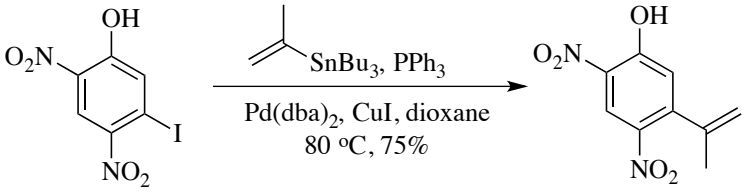


262 **146** **270**

This counter-productive result forced reconsideration of the proposed synthetic route. While phenols are typically poor substrates for Stille coupling reactions due to the electron-rich nature of the aromatic system, the two nitro-groups of phenol **263** would potentially provide enough activation to allow for coupling of the dinitro-iodophenol and circumvent the issue of hydrolysis. This hypothesis was tested using 4,6-dinitro-3-iodophenol (**263**) (Scheme 85). Initially, attempted Kosugi-Migita-Stille coupling of

iodophenol **263** under conditions A[90] (PPh_3, $Pd(dba)_2$, dioxane, reflux) afforded no product. Subsequently, copper (I) iodide was added and the solution was heated at reflux. Delightfully, complete conversion of the starting material to coupled phenol **271** was achieved in four hours. However, after workup with aqueous ammonia, no product was detected in the crude mixture via ^1H NMR. On account of the *ortho* and *para* nitro groups, the acidity phenolic hydrogen of **271** was substantially lower than that of phenol itself, rendering the phenol soluble in aqueous base. In the event, lowering the pH of the aqueous phase from ~10 to ~4 followed by extraction provided the desired coupled phenol **271**. Optimization of conditions led to shortened reaction times (3 hours) while affording phenol **271** in good yield.

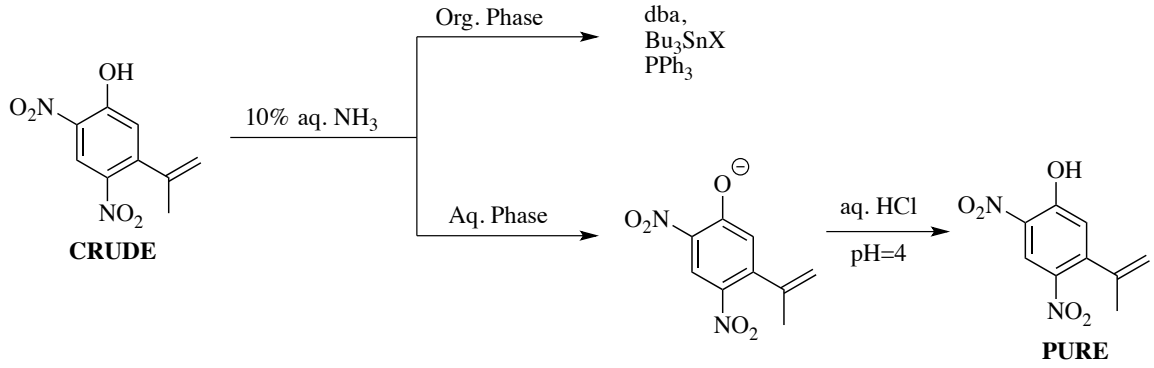
Scheme 85: Kosugi-Migita-Stille Coupling of Iodophenol



263 **271**

This result not only afforded the desired compound, but it also resulted in purification of the product using a simple extraction process, which is depicted in Figure 12. Initially, the phenol product was extracted using an aqueous base, "washing" away the unwanted organic components from the reaction including dba and tributyltin iodide. Acidification of the aqueous phase protonated the phenoxide, allowing for extraction of the nearly pure phenol product prior to chromatography.

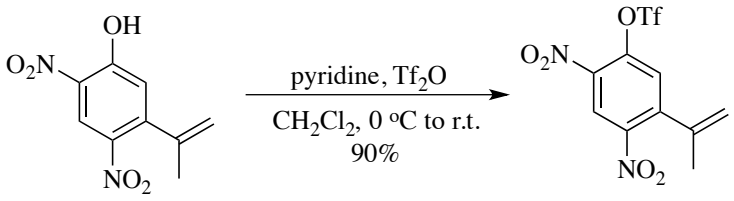
Figure 12: Modified Work-up Procedure for Coupling of Phenol



The success of the coupling reaction was attributed to the addition of copper iodide. The role of copper salts in Stille coupling reactions has been studied extensively.[118,119,120] Liebeskind *et al*. reported significant rate enhancement when adding CuI to Pd(0)/PPh_3 catalyst systems, however, no rate enhancement was observed when using soft ligands such as $AsPh_3$.[120] This has been attributed to CuI acting as a ligand scavenger, so the reported rate enhancement in the Pd(0)/PPh_3 system is presumably due to scavenging of excess PPh_3, as PPh_3 is known to inhibit the rate-limiting transmetalation step. Generation of organocopper species could also be generated through initial tin-copper transmetalation.[118] The formed organocopper complex would then undergo tranmetalation to palladium faster in comparison to the initial stannane. Similar palladium-copper co-catalytic Stille conditions were employed by Hudgens *et al*.[121] in the preparation of novel methylated tyrosine derivates.

Conversion of phenol **271** to triflate **261** was achieved using standard conditions (Scheme 86). Rapid purification using column chromatography afforded triflate **261** with no evidence of hydrolysis.

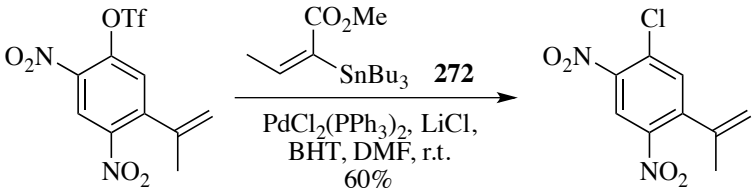
Scheme 86: Conversion of Phenol to Triflate



271 **261**

Initially, issues were encountered in applying conditions B[90] ($PdCl_2(PPh_3)_2$, LiCl, DMF, r.t.) to couple the trifloxy group of **261**. The attempted coupling of triflate **261** with stannane **272** afforded exclusively aryl chloride **273** (Scheme 87).

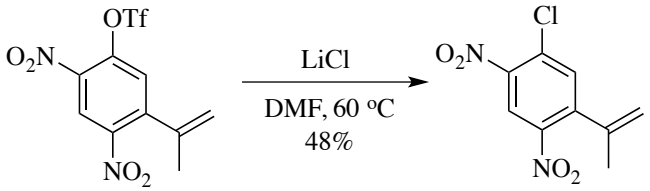
Scheme 87: Attempted Kosugi-Migita-Stille Coupling of Aryl Triflate



261 **273**

To probe the mechanism of this unexpected result, triflate **261** was treated with excess lithium chloride in DMF without the addition of palladium (Scheme 88). This would reveal whether the reaction involved a simple nucleophilic aromatic substitution mechanism or whether it was a palladium-catalyzed process. Interestingly, chloride **273** was achieved in moderate yield in the absence of a palladium catalyst, confirming the nucleophilic aromatic substitution mechanism. While unexpected, this result was reasonable considering highly activated nature of the trifloxy group on the basis of the *ortho* and *para* nitro substituents. Exploration of the literature also produced examples of similar observations.[122]

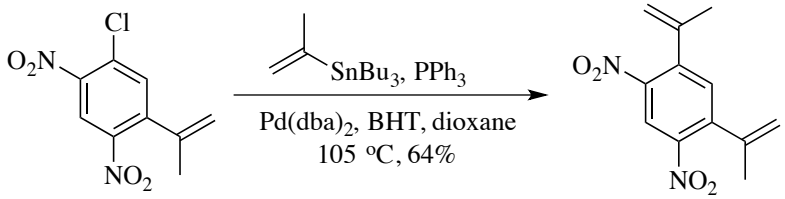
Scheme 88: Conversion of Aryl Triflate to Aryl Chloride



261 **273**

Aryl chloride **273** was then coupled with isopropenyl stannane under conditions A[90] to afford the desired dinitro-dialkenyl substrate **260** (Scheme 89). This result is significant in that aryl chlorides are typically sluggish in Kosugi-Migita-Stille reactions and often require more tailored catalyst and ligand systems. The electron-deficient nature of the system on account of the two nitro groups likely augments the reactivity of the chloride towards oxidative addition of palladium.

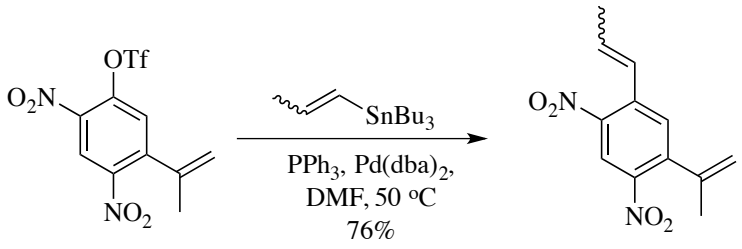
Scheme 89: Kosugi-Migita-Stille Coupling of Aryl Chloride



273 **260**

While the successful coupling of aryl chloride **273** was encouraging, the overall process was not atomically efficient in going from phenol **271** to triflate **261** then to chloride **273**. Rather, direct coupling of triflate **261** was desired. Gratifyingly, use of conditions A[90] in DMF rather than dioxane afforded coupled product **274** in good yield (Scheme 90). While the role of changing solvent was not investigated, the exclusion of lithium chloride from the reaction mixture avoided potential triflate replacement.

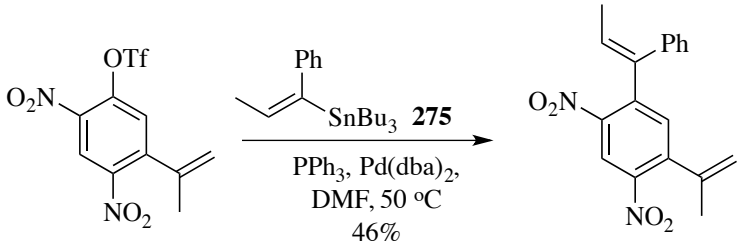
Scheme 90: Kosugi-Migita-Stille Coupling of Aryl Triflate



261 **274**

Similarly, cross-coupling between triflate **261** and α-phenyl alkenylstannane **275** afforded cyclization precursor **276** (Scheme 91).

Scheme 91: Preparation of Cyclization Precursor



261 **276**

Some of the advantages of Stille coupling reactions include the vast array of stannanes, their ease of preparation either from Grignard reagents[123] or hydrostannation of alkynes,[124] and their stability[125] relative to alternative reagents. Rather than delve too far into these different options, only the readily available stannanes described above were employed. However, variation of the alkenyl stannane used in either coupling step would allow for preparation of a number of structurally diverse pyrroloindoles.

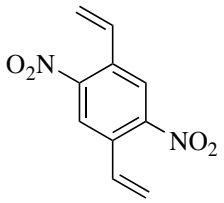
A straightforward method to prepare non-symmetrical 2,4-dinitro-1,5-dialkenyl benzene derivatives has been established. This concise process involving sequential Kosugi-Migita-Stille cross-coupling reactions overcomes a number of obstacles previously encountered in the preparation of the described substrates. In addition, the

generality of cross-coupling reaction allows for preparation of a diverse array of novel highly functionalized substrates.

5.4.2 2,5-Dinitro-1,4-Dialkenyl Benzene Isomer

The next isomeric cyclization precursor examined was 2,5-dinitro-1,4-dialkenyl benzene, such as divinylbenzene **240** (Figure 13). While Banini prepared compounds of this type (Section 3, this chapter), a more synthetically useful route was desired.

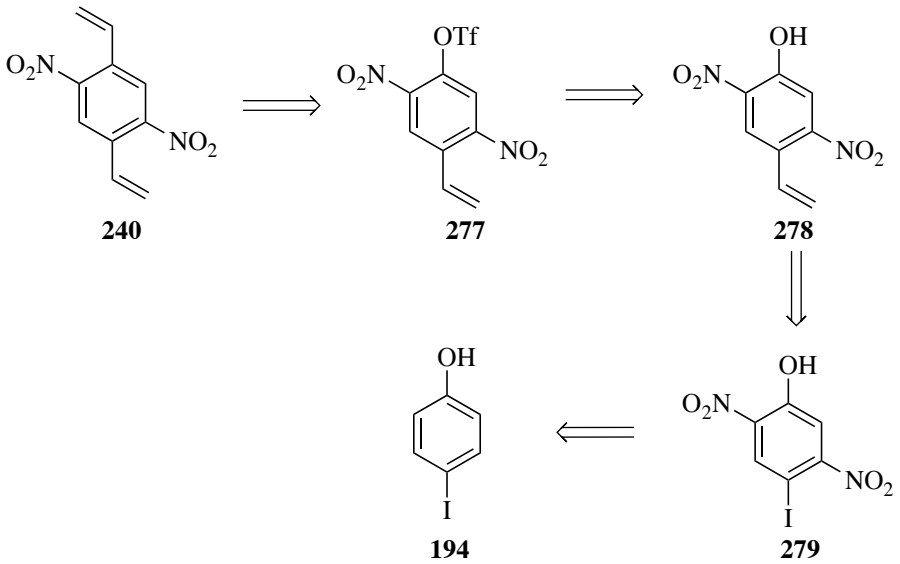
Figure 13: 2,5-Dinitro-1,4-Dialkenyl Benzene



240

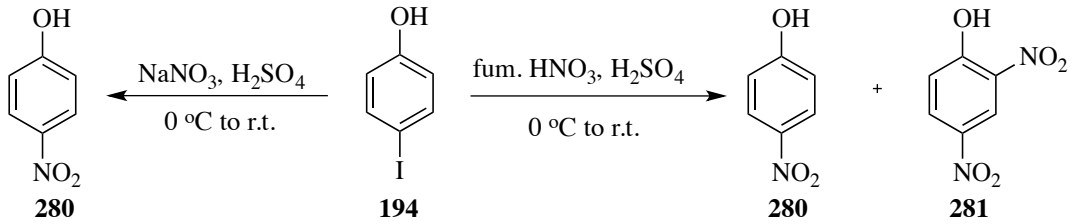
Retrosynthetically, it was envisioned that cyclization precursor **240** could be prepared through Kosugi-Migita-Stille coupling between triflate **277** and vinyl stannane (Scheme 92). Triflate **277** could be achieved from phenol **278**. Styrene **278** would result from Kosugi-Migita-Stille cross-coupling between iodophenol **279** and vinyl stannane. Dinitrophenol **279** could arise through the di-nitration of 4-iodophenol (**194**)

Scheme 92: Proposed Retrosynthetic Outline to Cyclization Precursor



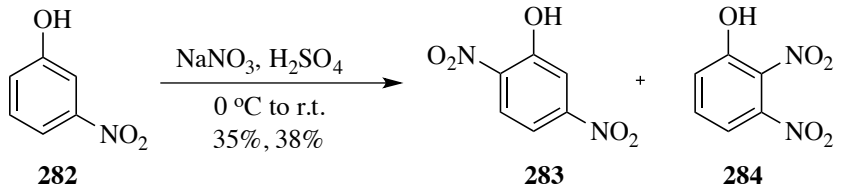
Preparation of isomer **240** was not as simple as initially proposed. It was envisioned that this isomer would be achieved through di-nitration of 4-iodophenol (**194**) (Scheme 93). However, after multiple attempts using a number of conditions, none of the desired di-nitrated product **279** was isolated. Rather, it appeared that the electron-donating hydroxy group *para-* to the iodine activated the iodine for *ipso* substitution, with 4-nitrophenol (**280**) being the isolated product. Under forcing conditions, 2,4-dinitrophenol (**281**) was also isolated. Similar substitutions of aryl halides has also been reported by Hodgson[126] in his exhaustive examination of nitration reactions.

Scheme 93: Nitration of 4-Iodophenol



Based on these results, a revised route was proposed that capitalized on the position *para-* to the alcohol being activated through conjugation with the electron-donating hydroxyl group. The proposed route involved preparation of 2,5-dinitrophenol (**283**), then introducing the iodine in order to overcome the issue of *ipso* substitution encountered in the case of 4-iodophenol (**194**). Nitration of 3-nitrophenol (**282**) using sodium nitrate in sulfuric acid afforded both the desired 2,5-dinitrophenol (**283**) along with 2,3-dinitrophenol (**284**) (Scheme 94).[127] Fortunately, these isomers were separable using column chromatography, as it was envisioned that isomer **284** could be used in the preparation of another substrate (Section 5.4.3).

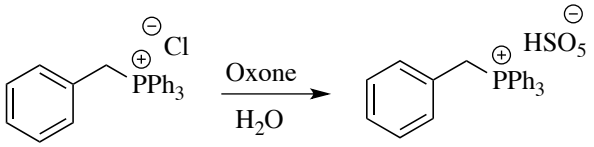
Scheme 94: Nitration of 3-Nitrophenol



282 **283** **284**

Oxidative iodination of phenols has been reported using a number of oxidants, with one of the most recent being benzyltriphenylphosphonium peroxymonosulfate (BTPPMS) (**286**), prepared through treatment of benzyltriphenylphosphonium chloride (**285**) with Oxone (Scheme 95).[128]

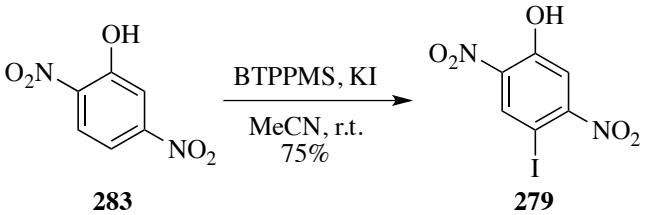
Scheme 95: Preparation of Benzyltriphenylphosphonium Peroxymonosulfate



285 **286**

Hajipour[129] has reported the *para*-selective iodination of a number of phenols using postassium iodide (KI) and BTPPMS (**286**). In fact, it was reported that 4-iodo-2,5-dinitrophenol (**279**) was prepared in good yield from 2,5-dinitrophenol (**283**) using these conditions (Scheme 96).

Scheme 96: Oxidative Iodination of 2,5-Dinitrophenol



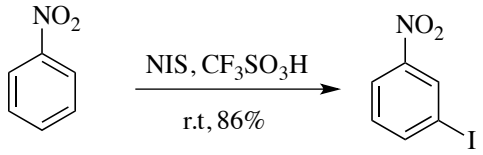
283 **279**

Attempts to replicate these results were unsuccessful in our hands. It was suspected that reagent **286** was highly impure and therefore not capable of oxidizing the substrate **283**. The reported preparation of BTPPMS (**286**) (also reported by Hajipour[128])

provided no specific work-up or characterization data, leaving questions regarding this reagent.

Iodination of deactivated aromatics using *N*-iodosuccinimide (NIS) under acidic conditions has been reported by Olah.[130] Treatment of nitrobenzene (**287**) with NIS and two equivalents of trifluoromethanesulfonic acid afforded 3-nitroiodobenzene (**288**) in excellent yield, confirming that the reaction proceeded through an electrophilic mechanism based on the regioselectivity observed in the product (Scheme 97). It was proposed that a super electrophilic iodine-trifluoromethanesulfonate, generated *in situ*, was the highly reactive iodinating species.

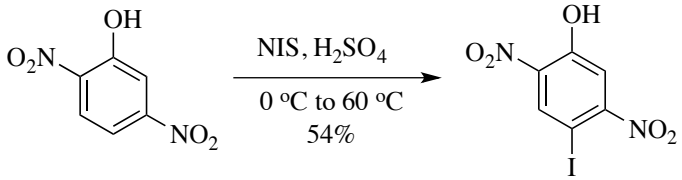
Scheme 97: Iodination of Deactivated Arene



287 **288**

In a slight modification of Olah's protocol,[130] treatment of 2,5-dinitrophenol (**283**) with NIS in sulfuric acid afforded the desired iodophenol **279** (Scheme 98). The ability to substitute expensive trifluoromethanesulfonic acid with sulfuric acid was an improvement to Olah's[130] conditions.

Scheme 98: Electrophilic Iodination of 2,5-Dinitrophenol

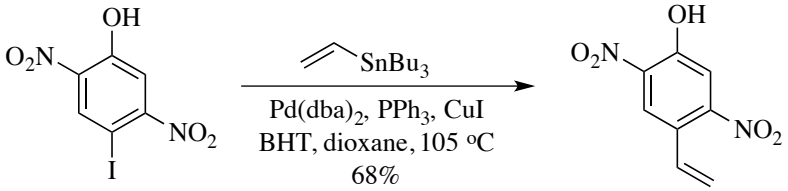


283 **279**

Coupling of iodophenol **279** was then attempted using the previously discussed modified Kosugi-Migita-Stille conditions (Scheme 85, Chapter 5). In the event, coupling

between iodophenol **279** and vinyl stannane afforded styrene **278** in good yield (Scheme 99). Typical radical inhibitor 2,6-di-*t*-butyl-4-methylphenol (BHT) was added to the reaction in order to prevent polymerization of the styrene product.

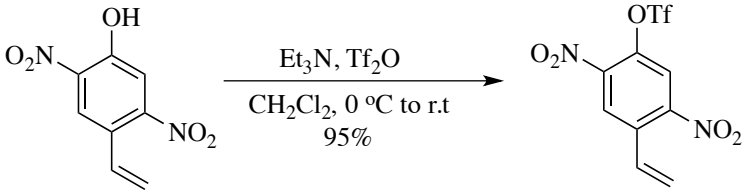
Scheme 99: Kosugi-Migita-Stille Coupling of 4-Iodo-2,5-Dinitrophenol



279 **278**

Phenol **278** was then converted to the corresponding triflate **277** using typical conditions (Scheme 100).

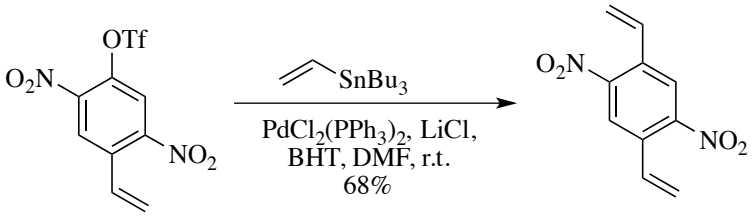
Scheme 100: Preparation of Aryl Triflate



278 **277**

Kosugi-Migita-Stille cross-coupling of triflate **277** with vinyl stannane was achieved using typical conditions B.[90] In contrast to the case of **261** (Scheme 87, Chapter 5), no chloride product was observed and the cross-coupled product **240** was achieved in moderate yield (Scheme 101).

Scheme 101: Kosugi-Migita-Stille Coupling of Aryl Triflate



277 **240**

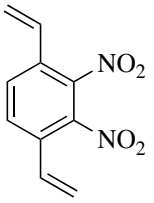
The established method employing sequential cross-coupling reactions offers a number of improvements in comparison to Banini's method to prepare substrate **240** (Scheme 74, Chapter 5). Though both methods employed an initial nitration step, the nitration of 3-nitrophenol **282** (Scheme 94) afforded isomers **283** and **284** in moderate yield, whereas Banini's nitration step afforded a mixture of four isomers, each in low yield. Additionally, 2,3-dinitrophenol (**284**) was of interest for preparation of another isomer. This method also avoids the often unsuccessful benzyl bromination step employed by Banini to convert dinitrotoluene **246** to benzyl bromide **247**.

The desired 2,5-dinitro-1,4-diethenyl isomer **240** was achieved in five steps from 3-nitrophenol (**282**) using a series of electrophilic aromatic substitution and Kosugi-Migita-Stille coupling reactions. While only one symmetrical substrate was prepared, non-symmetrical cyclization precursors would be accessible by varying the stannane used in either coupling step.

5.4.3 2,3-Dinitro-1,4-Dialkenyl Benzene Isomer

Efforts were made to establish a synthetically useful route to prepare non-symmetrical 2,3-dinitro-1,4-dialkenyl cyclization precursors, such as divinylbenzene **241** (Figure 14).

Figure 14: 2,3-Dinitro-1,4-Dialkenyl Benzene



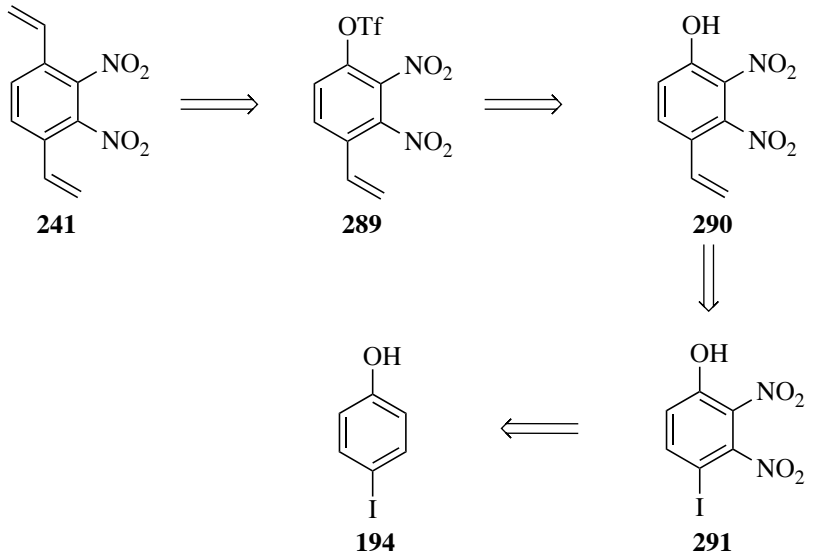
241

Initial attempts to prepare non-symmetrical substrates based on **241** through Kosugi-Migita-Stille coupling between 1,4-dibromo-2,3-dinitrobenzene (**251**) and vinyl

stannane failed due to the inability to achieve selectivity for mono-coupling (as discussed in Section 5.3.3). Based on the successful coupling of halophenols in the preparation of other isomers in this study (Sections 5.4.1 and 5.4.2), a route involving similar ideology was sought.

Retrosynthetically, it was envisioned that cyclization precursor **241** could be prepared through Kosugi-Migita-Stille coupling between aryl triflate **289** and vinyl stannane (Scheme 102). Aryl triflate **289** could arise from dinitrophenol **290**. Styrene **290** could result from the Kosugi-Migita-Stille coupling between iodophenol **291** and vinyl stannane. Dinitrophenol **291** was envisioned through di-nitration of 4-iodophenol (**194**).

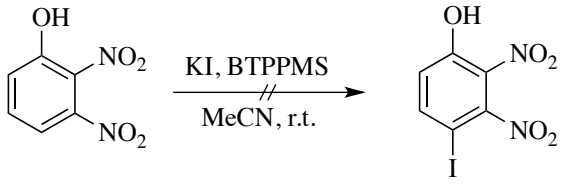
Scheme 102: Proposed Retrosynthetic Outline to Cyclization Precursor



Unfortunately, attempts to prepare 2,3-dinitro-4-iodophenol (**291**) through nitration of *p*-iodophenol (**194**) were unsuccessful (as discussed in Section 5.4.2). It became clear that iodoarenes were highly prone to substitution, therefore, alternative routes to prepare iodophenol **291** were explored. One such route involved using Hajipour's[129] methodology for the oxidative *para* iodination of phenols (described in

greater detail in Section 5.4.2). 2,3-dinitrophenol (**284**) was prepared through the nitration[127] of 3-nitrophenol (**282**) using sodium nitrate in sulfuric acid (as also described in Section 5.4.2). However, treatment of dinitrophenol **284** with BTPPMS and potassium iodide failed to produce the desired iodophenol **291** (Scheme 103).

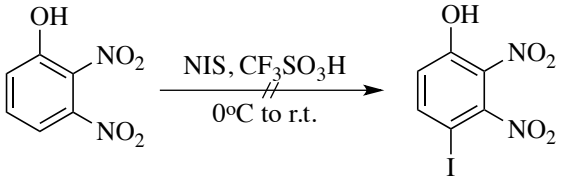
Scheme 103: Attempted Oxidative Iodination of 2,3-Dinitrophenol



284 **291**

Similar to the analogous case of 2,5-dinitrophenol (**283**) (Section 5.4.2), electrophilic iodination of **284** was also attempted using *N*-iodosuccinimide in triflic acid[130] (Scheme 104). While the crude ^{1}H NMR spectrum appeared to show evidence of two iodinated products, neither was isolable through chromatographic purification. Trials using sulfuric acid in place of triflic acid were also unsuccessful.

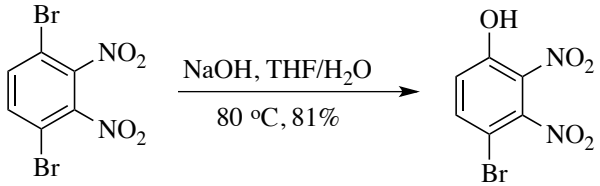
Scheme 104: Attempted Electrophilic Iodination of 2,3-Dinitrophenol



284 **291**

It was envisioned that the two nitro groups of **251** would render the bromines highly activated towards nucleophilic aromatic substitution (S_NAr). Upon examination of the literature, examples of S_NAr reactions using sodium hydroxide as a hydroxide source were discovered.[116] Using this ideodology, treatment of di-bromide **251** with excess sodium hydroxide provided 4-bromo-2,3-dinitrophenol **292** in good yield (Scheme 105).

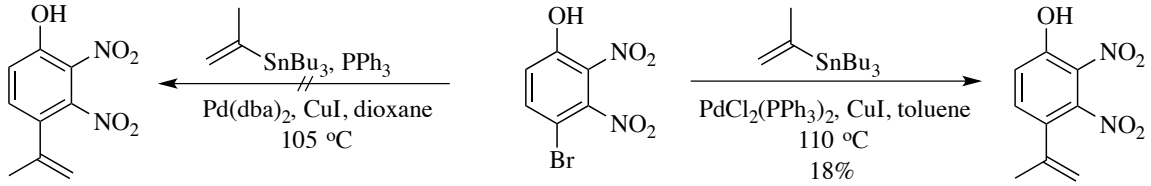
Scheme 105: **Preparation of 4-Bromo-2,3-Dinitrophenol**



251 **292**

With phenol **292** in hand, Kosugi-Migita-Stile coupling was attempted using modified conditions A[90] (PPh_3, $Pd(dba)_2$, CuI, dioxane, reflux), which were successful in coupling 2,4-dinitro-5-iodophenol **263** (Section 5.4.1) as well as 2,5-dinitro-4-iodophenol **279** (Section 5.4.2). Regrettably, the established conditions proved unsuccessful in the coupling of bromophenol **292**, returning only unreacted starting material (Scheme 106). Interestingly, treatment of **292** with $PdCl_2(PPh_3)_2$ and CuI in toluene afforded isopropenyl-substituted phenol **293**, albeit in poor yield.

Scheme 106: Kosugi-Migita-Stille Coupling of Bromophenol



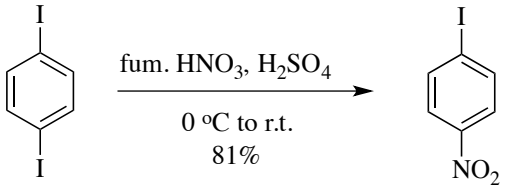
293 **292** **293**

The drastic difference in reactivity observed for bromophenol **292** compared to coupling of iodophenol **279** (Section 5.4.2) was puzzling. Both **292** and **279** were expected to be similar in electronics on account of the bromine of **292** and the iodine of **279** being *ortho* and *meta* to nitro groups and *para* to a hydroxy group. However, iodophenol **279** underwent coupling while the coupling of bromophenol **292** was extremely sluggish. Therefore, it was postulated that the difference in reactivity must have been the result of using an aryl bromide rather than an aryl iodide. It is widely accepted that aryl iodides are more reactive than aryl bromides under a range of typical

coupling conditions,[97] so it was plausible that the combination of a less reactive aryl bromide that was also deactivated through conjugation with an electron-donating hydroxyl group caused the lack of reactivity observed for aryl bromide **292**.

In an attempt to explore whether the analogous iodophenol would prove successful in the coupling step, a similar route to that previously presented was pursued using 1,4-diiodobenzene (**294**). Unfortunately, attempts to di-nitrate **294** afforded 4-nitroiodobenzene (**295**) as the lone product (Scheme 107).

Scheme 107: Nitration of 1,4-Diiodobenzene



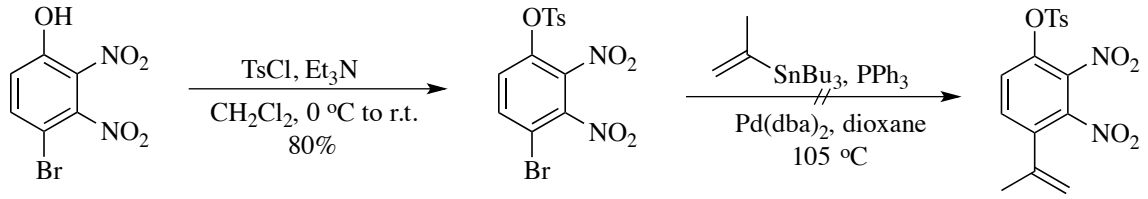
294 **295**

This result provided more insight into the highly reactive nature of aryl iodides relative to bromides. Comparison of the nitrations of 1,4-dibromobenzene **250** and 1,4-diiodobenzene **294** provides a direct example. Di-nitration of dibromide **250** using mixed acid 90 °C afforded three di-nitrated isomers, whereas treatment of diiodide **294** with the same mixed acid conditions at room temperature resulted in *ipso* substitution of iodine by a nitro group. Considering these drastically different results, the differences in reactivity encountered in the aforementioned coupling reaction were not so surprising.

A revised route was sought to increase the reactivity of bromophenol **292** while limiting the number of additional steps required. It was envisioned that conversion of phenol **292** to tosylate **296** would decrease the electron-donor ablility of the phenolic oxygen and potentially render the bromine less deactivated. This could then facilitate the oxidative addition necessary for coupling while also adding only one additional step as

tosylates are potentially suitable substrates for Kosugi-Migita-Stille coupling.[132, 133] Phenol **292** was converted to the corresponding tosylate **296** through treatment with *p*-toluenesulfonyl chloride in the presence of triethylamine[134] (Scheme 108). Unfortunately, Kosugi-Migita-Stille coupling between aryl bromide **296** and isopropenyl stannane using conditions A[90] did not afford isopropenylbenzene **297**. However, a more extensive examination of conditions may provide conditions capable of facilitating coupling reaction of this substrate.

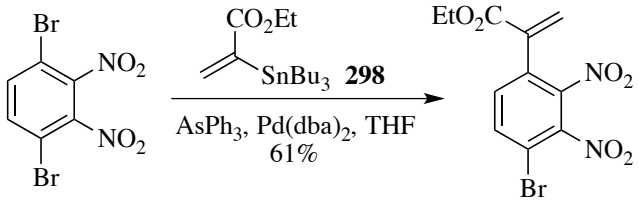
Scheme 108: **Attempted Kosugi-Migita-Stille Coupling of Aryl Bromide**



292 **296** **297**

Re-examination of previous work by Banini turned up an initially overlooked example. Kosugi-Migita-Stille coupling between dibromobenzene **251** and α-stannyl ester **298** afforded exclusively mono-coupled product **299** (Scheme 109).

Scheme 109: Selective Mono-Coupling of Dibromide by Banini



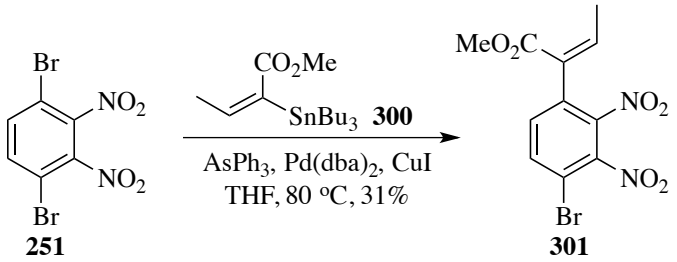
251 **299**

It was envisioned that the presence of an electron-withdrawing substituent on the benzyl position of **299** rendered the mono-coupled product less reactive towards a second coupling reaction. This was in contrast to other examples employing simple alkenyl

stannanes (as discussed in Section 5.3), in which the mono-coupled product appeared to be more reactive than the starting material (**251**) towards a second coupling reaction.

Gratifyingly, Kosugi-Migita-Stille coupling between 1,4-dibromo-2,3-dinitrobenzene **251** and α-stannyl ester **300** was achieved using Banini's conditions afforded mono-coupled arene **301** in moderate yield with no detected di-coupling (Scheme 110). Though not employed in Banini's example, it was also found that the addition of copper iodide aided the reaction, presumably through generation of a more reactive organocopper complex through tin-copper transmetalation.[118]

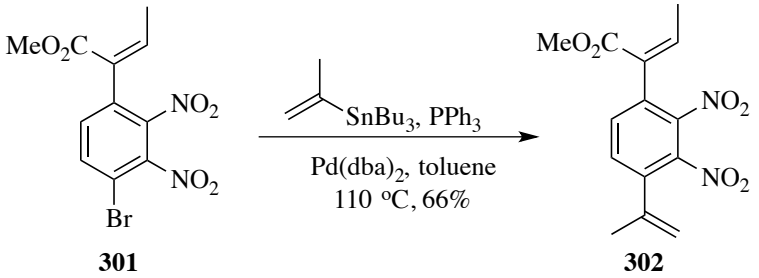
Scheme 110: Mono-Coupling Using α-Stannyl Ester



While the requirement of an electron-deficient stannane such as **300** was viewed as a limitation of this route, the broad range of functional groups that could still be employed provide a wide range of possible substrates that could be prepared using this method.

Cross-coupling between substrate **301** and isopropenyl stannane was achieved using previously described Kosugi-Migita-Stille conditions,[90] affording the desired non-symmetrical cyclization precursor **302** in moderate yield (Scheme 111).

Scheme 111: Preparation of Non-Symmetrical Substrate

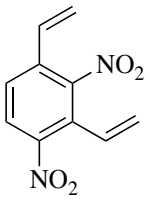


Ultimately, non-symmetrical dinitro-dialkenyl benzene **302** was prepared in three steps from 1,4-dibromobenzene (**250**) through sequential Kosugi-Migita-Stille coupling reactions. While the first coupling step requires the use of an electron-withdrawing substituted stannane, a number of functional groups are still tolerated, providing a concise route to prepare otherwise inaccessible non-symmetrical substrates. The unusual reactivity of iodoarenes prevented the preparation of cyclization precursors such as **302** through coupling of 4-iodo-2,3-dinitrophenol (**291**).

5.4.4 2,4-Dinitro-1,3-Dialkenyl Benzene Isomer

The next target isomer was consisting of alternating nitro and alkenyl substituents, such as **242** (Figure 15). While this class could potentially lead to two different types of pyrroloindoles, they both faced the same obstacles in both the preparation of the substrate as well as the subsequent coupling steps.

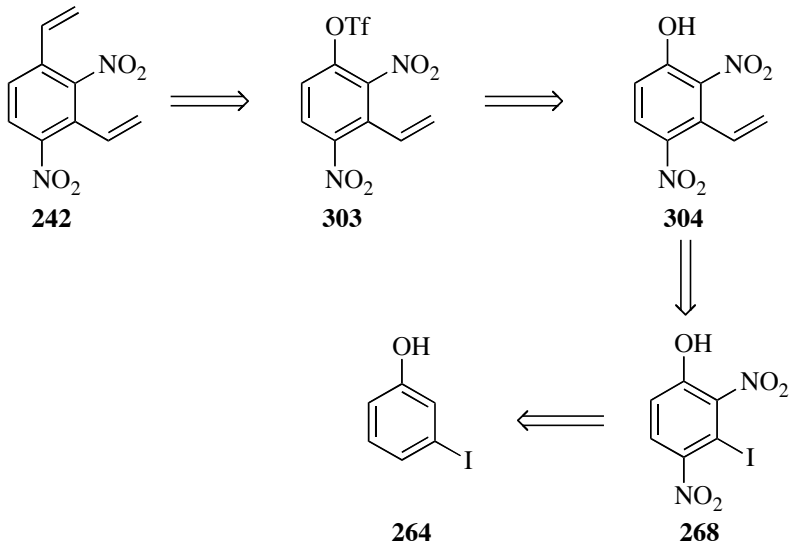
Figure 15: 2,4-Dinitro-1,3-Dialkenyl Benzene



242

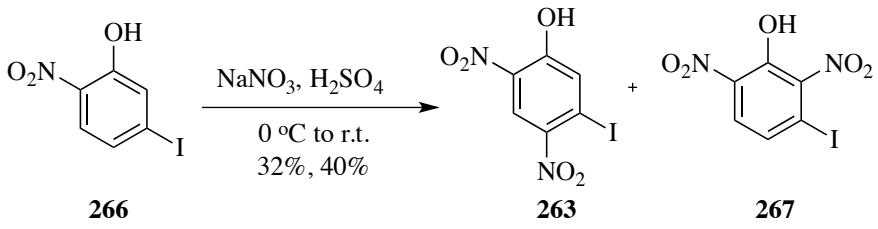
Retrosynthetically, it was initially envisioned that cyclization precursor **242** could be prepared through Kosugi-Migita-Stille coupling between aryl triflate **303** and vinyl stannane (Scheme 112). Aryl triflate **303** could be accessed through phenol **304**. Styrene **304** would result from Kosugi-Migita-Stille coupling between iodophenol **268** and vinyl stannane. Dinitrophenol **268** was previously prepared through nitration of 3-iodophenol (**264**).

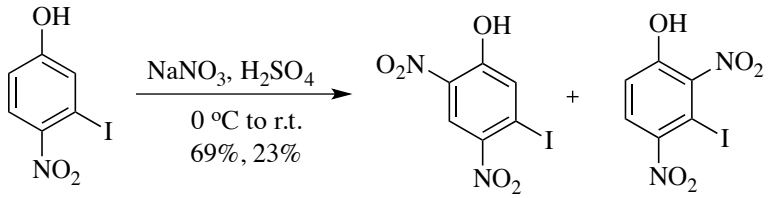
Scheme 112: Proposed Retrosynthetic Outline to Cyclization Precursor



The sequential nitration[114] of 3-iodophenol (**264**) (as discussed in Section 5.4.1). afforded a separable mixture of mono-nitrated isomers **265** and **266**, which then underwent a second nitration using slightly stronger conditions (Scheme 113). Once again, 4,6-dinitro isomer **263** was the major product obtained, however, tailoring the conditions resulted in a slight increase in the amount of desired isomers **267** and **268** obtained (based on the starting material used). Unfortunately, the nitration of 3-iodo-4-nitrophenol (**265**) afforded an inseparable mixture of isomers **263** and **268**. Surprisingly, in the nitration of 2-nitro-5-iodophenol (**266**), dinitro isomer **267** in which the nitro group adds to the more hindered carbon was the major product and was also separable from **263**.

Scheme 113: Preparation of Dinitrophenol Isomers

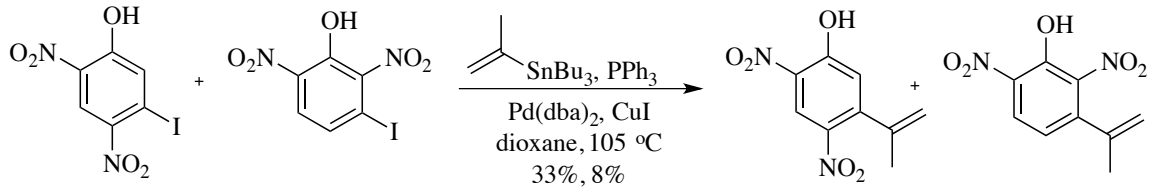




265 **263** **268**

A mixture of phenols **263** and **268** were subjected to coupling conditions A[90] with the addition of copper (I) iodide (as discussed in Chapter 5.4.1) (Scheme 114). While coupled products **271** and **305** were isolated, the yield of desired phenol **305** was very low (8%). Attempts to improve yields were futile, partially because the starting material consisted of two isomers, which made it difficult to optimize conditions.

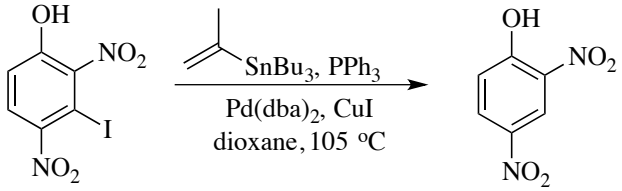
Scheme 114: Attempted Coupling of Isomeric Mixture



263 **268** **271** **305**

Attempted Kosugi-Migita-Stille coupling between 3-iodo-2,4-dinitrophenol (**268**) and isopropenyl stannane using conditions A[90] in addition to copper (I) iodide afforded none of the coupled product (Scheme 115). Rather, 2,4-dinitrophenol (**281**) was isolated.

Scheme 115: Attempted Coupling of Iodophenol



268 **281**

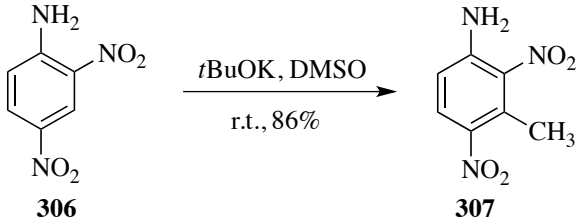
While it was suspected that the iodine of 3-iodo-2,4-dinitrophenol (**268**) would be highly activated towards oxidative addition on account the two *ortho* nitro substituents, it appeared that the neighboring nitro groups also provided steric hindrance, preventing the

transmetalation of the isopropenyl group from tin to palladium. However, the formation of dinitrophenol **281** was evidence that oxidative addition of palladium had occurred. The sensitivity of Kosugi-Migita-Stille reactions to steric demands has been previously noted.[135] This shortcoming, in addition to the difficulties discussed for isomer **267**, resulted in this route's abandonment.

Based on the issues encountered in the previously mentioned examples, a route was sought which did not require coupling of a group positioned between two nitro groups. The goal was to find examples of condensation reactions of toluene or benzaldehyde derivatives in order to overcome the issue of dehalogenation while also avoiding potential selectivity issues experienced when using sequential coupling reactions.

In a unique aromatic substitution reaction, Kawakami[136] reported the regioselective methylation of 2,4-dinitroaniline (**306**) through reaction with dimethyl sulfoxide (DMSO) and excess potassium *tert*-butoxide, affording 3-methyl-2,4-dinitroaniline (**307**) (Scheme 116). The mechanism involves deprotonation of the amine followed by formation of an imino-aromatic system, which is then attacked by the methanesulfonyl anion. Interestingly, the authors state that the analogous reaction using 2,4-dinitrophenol affords none of the desired methylated product, though a similar mechanism can be envisioned.

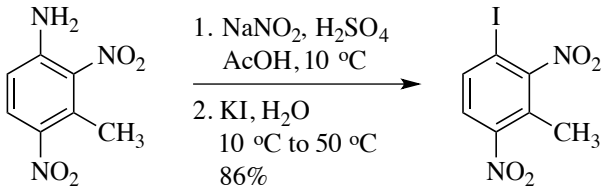
Scheme 116: Kawakami Methylation of 2,4-Dinitroaniline



306 **307**

Aniline **307** was then converted to aryl iodide **308** using modified Sandmeyer-type conditions[137] (Scheme 117). The initially formed diazonium salt was displaced with potassium iodide in order to produce the more reactive aryl iodide for subsequent coupling reaction.

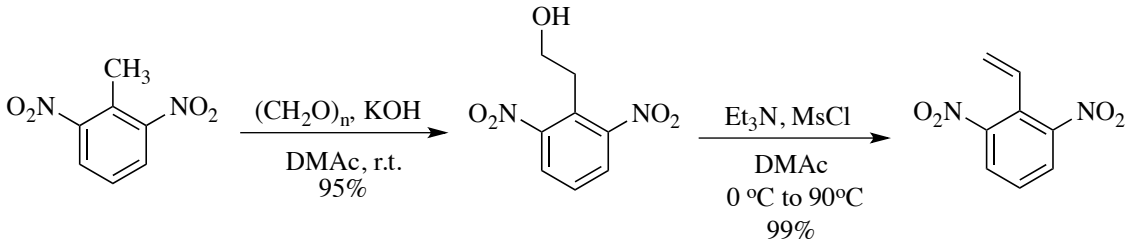
Scheme 117: Preparation of Aryl Iodide



307 **308**

Condensation reactions of 2,6-dinitrotoluene (**309**) as well as the subsequent elimination to afford di-nitrostyrene have been reported by Mundla (Scheme 118).[138] The initial condensation of **309** with *para*-formaldehyde in the presence of a catalytic amount of potassium hydroxide afforded alcohol **310**. Conversion of alcohol **310** to mesylate **311** (which was not isolated) followed by subsequent elimination then afforded dinitrostyrene **311**.

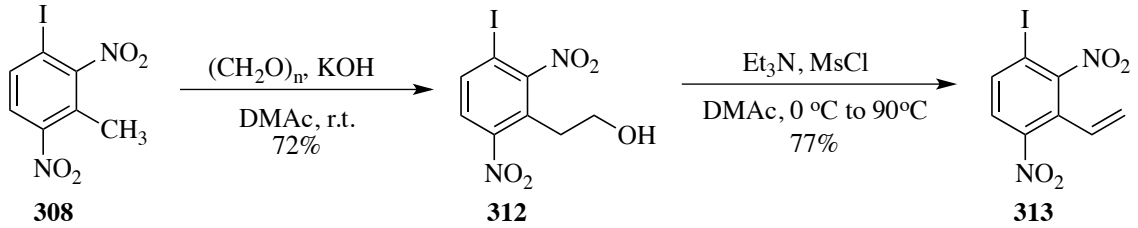
Scheme 118: Mundla's Preparation of 2,6-Dinitrostyrene



309 **310** **311**

Employing Mundla's methodology[138] using toluene **308** afforded desired di-nitrostyrene **313** in moderate yield over two steps (Scheme 119).

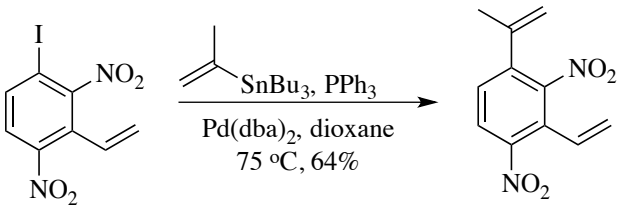
Scheme 119: Synthesis of Styrene



308 **312** **313**

Palladium-catalyzed Kosugi-Migita-Stille coupling between iodide **313** and isopropenyl stannane was achieved using typical conditions A,[90] affording bis-alkenyl substrate **314** (Scheme 120).

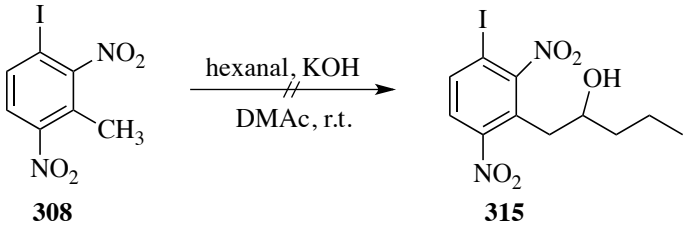
Scheme 120: **Kosugi-Migita-Stille Coupling of Aryl Iodide**



313 **314**

Attempts to broaden the scope of Mundla's[138] methodology to prepare dinitrostyrenes sought to employ different aldehydes. However, substitution of *para*-formaldehyde with hexanal were unsuccessful, likely due to steric hinderance from the nitro groups neighboring the anion formed from **308** and the more bulky aldehyde, preventing the formation of alcohol **315** (Scheme 121).

Scheme 121: Attempted Condensation with Hexanal



308 **315**

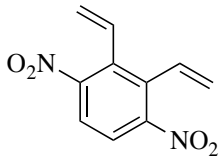
Taking advantage of unique properties of dinitroarenes, a method was established to prepare non-symmetrical cyclization precursors in a straightforward manner. Initial

issues involving failed coupling of halides situated between two nitro groups were overcome through use of a condensation-elimination sequence to install the alkene moiety. While the condensation step is currently limited to formation of an ethenyl group, further investigations may allow more broad elaboration.

5.4.5 1,4-Dinitro-2,3-Dialkenyl Benzene Isomer

While four of the five desired cyclization precursors were successfully prepared, the final isomer has proved elusive. This cyclization precursor **244** would feature two nitro groups oriented *para* to each other, as well as two neighboring alkenyl substituents (Figure 16).

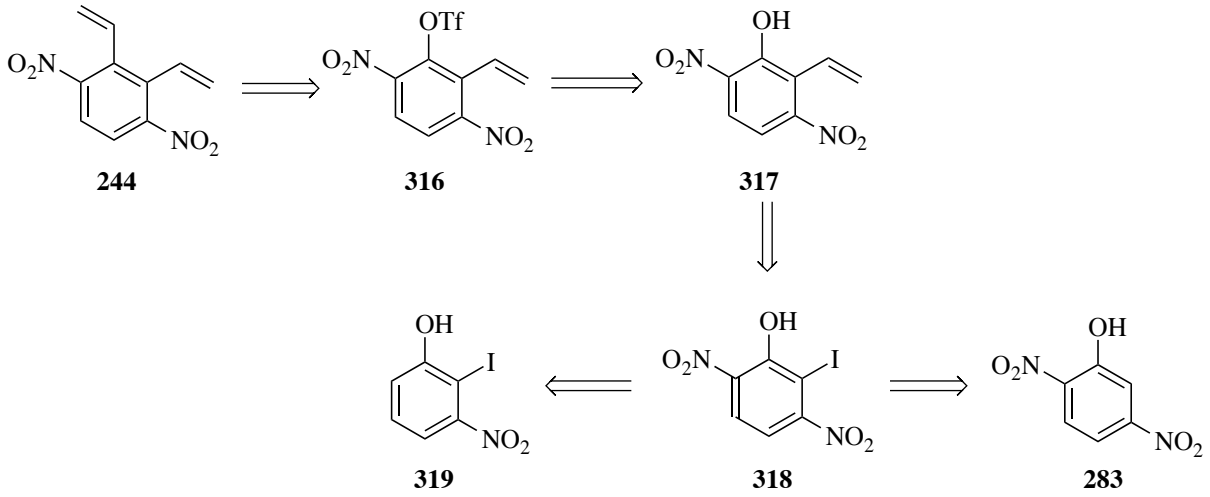
Figure 16: 1,4-Dinitro-2,3-Dialkenyl Benzene



244

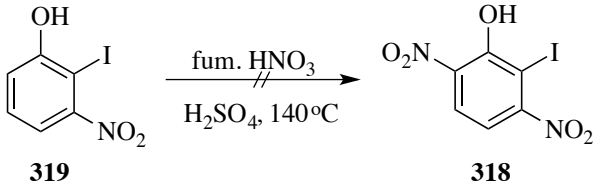
Retrosynthetically, dinitro-dialkenyl benzene **244** could result from Kosugi-Migita-Stille coupling between aryl triflate **316** and vinyl stannane (Scheme 122). Aryl triflate **316** could be achieved from dinitrophenol **317**. Dinitrostyrene **317** could be envisioned from Kosugi-Migita-Stille coupling between iodophenol **318** and vinyl stannane. Dinitrophenol **318** could arise through either the nitration of 2-iodo-3-nitrophenol (**319**) or the iodination of 2,5-dinitrophenol (**283**).

Scheme 122: Proposed Retrosynthetic Outline to Cyclization Precursor



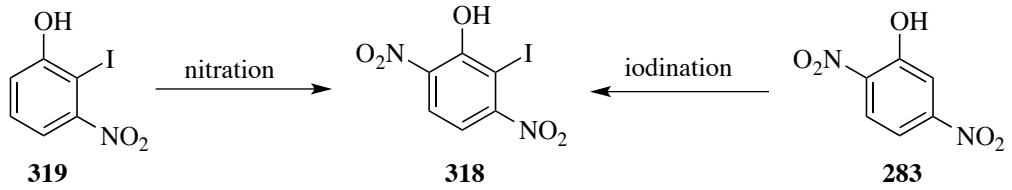
It was initially envisioned that dinitrophenol **318** could be prepared through the nitration of 2-iodo-3-nitrophenol **319** (Scheme 123). In the event, it was found that rather forcing conditions were necessary for reaction to take place, as starting material was recovered in near quantitative yield in reactions using mixed acid at lower temperatures or under milder nitration conditions (such as $NaNO_3$, H_2SO_4). Unfortunately, attempts to force the reaction along by heating phenol **319** in mixed acid resulted in the decomposition of starting material and afforded none of the desired dinitrophenol product **318**.

Scheme 123: Attempted Nitration of 2-Iodo-3-Nitrophenol



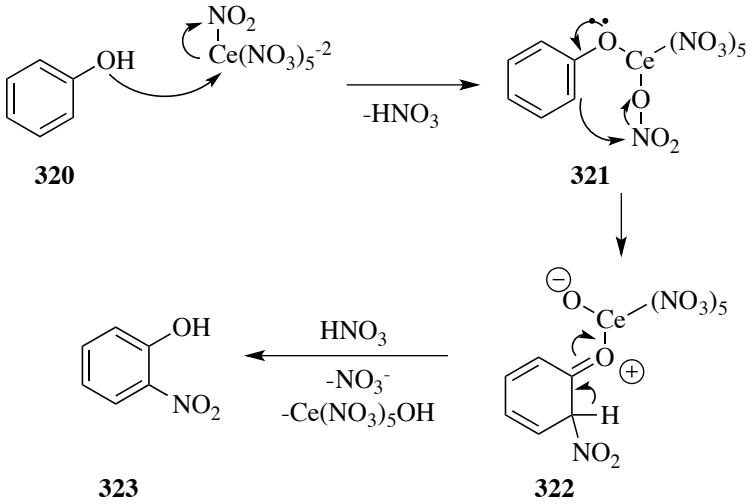
Ortho directed functionalization reactions of phenols were then examined as potential routes to prepare dinitrophenol **318**. It was proposed that the electron-rich hydroxy substituent could be used to direct nitration[139] or iodination[140] to the positions *ortho* to it (Scheme 124).

Scheme 124: Proposed *ortho*-Functionalization of Phenol



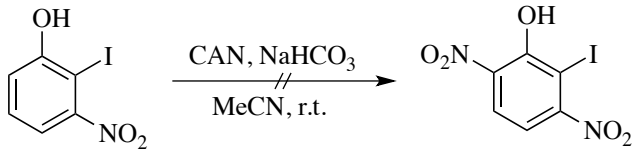
Ortho-selective mono-nitration of substituted phenols using cerium (VI) ammonium nitrate (CAN) has been reported by Sathunuru *et al*.[139] The regioselectivity of these reactions was attributed to the interaction of cerium with the hydroxyl oxygen of **320**, leading to subsequent Fries-type rearrangement of intermediate **321** to afford the *o*-nitrophenol **323** upon re-aromatization of intermediate **322** (Scheme 125).

Scheme 125: Mechanism of *ortho*-Selective Nitration of Phenol



While Sathunuru's study[139] reported the successful nitration of a number of electron-withdrawing substituted phenols, the authors reported that cyano- and nitro-substituted phenols were unreactive, presumably due to the highly electron-deficient nature of arene. However, Sathunuru's methodology[139] was applied in an attempt to nitrate phenol **319** (Scheme 126). In the event, the conditions appeared to be too mild and only unreacted starting material was recovered.

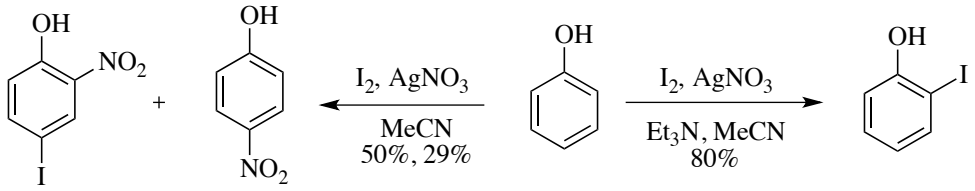
Scheme 126: Attempted *ortho*-Selective Nitration of Phenol



319 **318**

Similarly, *ortho*-selective halogenation of phenols was also explored. Previous work by Gaude *et al*.[140] explored the halogenation and nitration of phenols by either iodine nitrate or bromine nitrate (generated *in situ* using silver nitrate and either iodine or bromine) and reported that in the presence of pyridine or triethylamine, selective *ortho* halogenation of phenol (**320**) was achieved, affording 2-iodophenol (**324**) (Scheme 127). In the absence of amine, a mixture of halogenated and nitrated products was isolated.

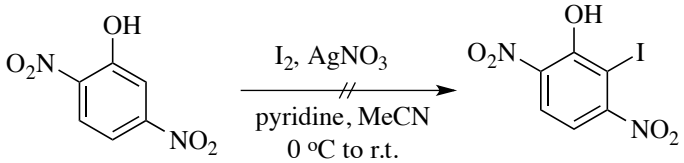
Scheme 127: Gaude's *ortho*-Iodination of Phenol



195 **280** **320** **324**

Gaude's methodology[140] was applied to dinitrophenol **283** in hope of producing *ortho*-iodinated phenol **318** (Scheme 128). Unfortunately, no product was isolated, and starting material was recovered.

Scheme 128: Attempted *ortho*-Iodination of Dinitrophenol



283 **318**

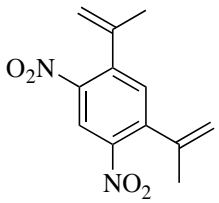
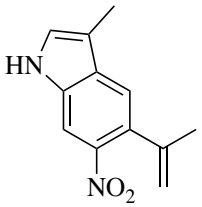
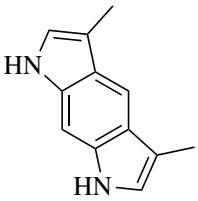
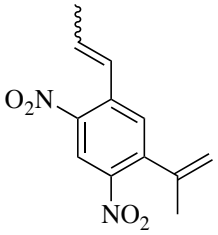
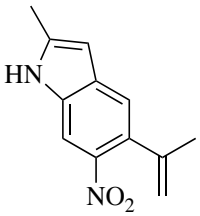
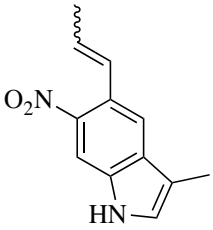
Ultimately, attempts to prepare 1,4-dinitro-2,3-dialkenyl benzene isomer **244** were unsuccessful. As apparent through the attempted routes, this isomer featuring

"mismatched" electronic effects was highly elusive. The mismatched electronics rendered intermediate substrates highly unreactive and posed an obstacle to prepare the targeted isomer. Although this isomer was not pursued further, the importance of pyrrolo[3,2-e]indole frameworks as demonstrated by their use in anti-tumor compounds[105] such as CC-1065, duocarmycin, and yatakemycin makes this isomer still highly sought after.

5.4.2 Pyrroloindole Synthesis via Reductive Double *N*-Heteroannulation

With a number of isomeric substrates in hand, focus was turned to the palladium-catalyzed reductive double *N*-heterocyclizations to prepare each isomeric pyrroloindole. Using conditions previously established by Banini (PPh_3, $Pd(dba)_2$, CO (6 atm), DMF, 120 °C), pyrroloindoles were prepared, although mono-cyclized products were also isolated even after extended reaction times (5 days). These results are outlined in Table 9.

Table 9: Double Cyclization Using Banini's Conditions

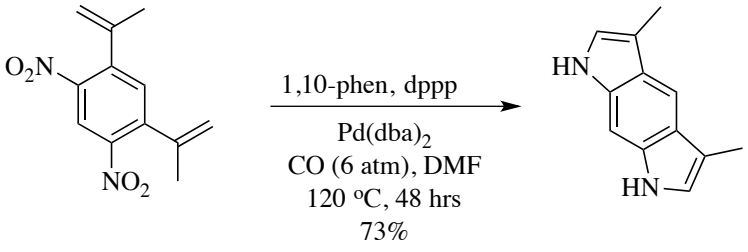
Entry	Substrate	Product(s)	
1	 **260**	 **325** (32%)	 **326** (59%)
2	 **274**	 **327** (34%)	 **328** (28%)

Conditions: PPh_3, $Pd(dba)_2$, CO (6 atm), 120 °C, 120 hours

While these initial cyclizations were not completely successful in producing the desired pyrroloindoles, useful insight was still gained. Substrate **260** (Table 9, entry 1) was converted to pyrroloindole **326** in moderate yield although a fair amount of indole **325** resulting from mono-cyclization was also isolated. The incomplete conversion of **260** to pyrroloindole **326** suggested that the second cyclization step was significantly slower than the initial cyclization, since no unreacted starting material was recovered. Substrate **274** (table 9, entry 2) provided insight into how substituents affect the rate of cyclization. Indole **327**, formed through the cyclization of the propenyl moiety of **274**, was isolated in slightly higher yield than indole **328**, which was the result of cyclization of the isopropenyl substituent. Though the isolated yields were not drastically different, this result suggests that the propenyl substituent may provide less hinderance for coordination of palladium to induce the cyclization, meaning the propenyl substituent cyclizes faster than the isopropenyl group.

With the hope of shortening reaction times while at the same time improving the yield of pyrroloindole products, other ligand systems were also explored. Alternative Soderberg annulation conditions using a two ligand system comprised of 1,10-phenanthroline (1,10-phen) and 1,3-(bis)-diphenylphosphinopropane (dppp) as opposed to simply triphenylphosphine were employed in order to overcome potential catalyst degradation due to the longer time scale of these reactions. Under these modified conditions, diisopropenylarene **260** was converted to pyrroloindole **326** in good yield with no evidence of mono-cyclization (Scheme 129). In addition, the reaction time was reduced to 48 hours.

Scheme 129: Double Cyclization Using 1,10-phenanthroline/dppp



260 **326**

These modified Soderberg cyclization conditions were then applied to each of the substrates prepared in Chapter 5.4. The results of these reactions are summarized in Table 10.

Table 10: Reductive Double *N*-Heterocyclizations[a]

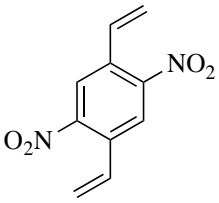
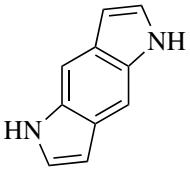
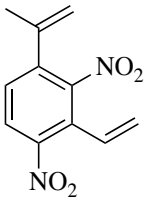
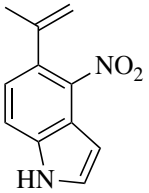
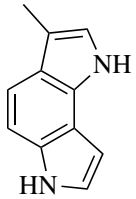
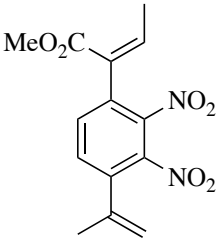
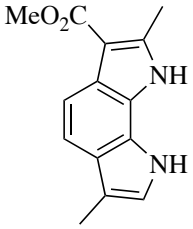
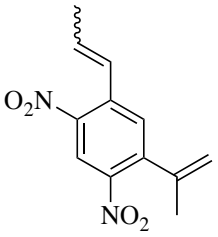
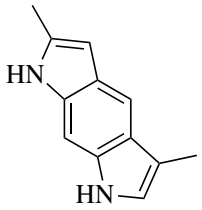
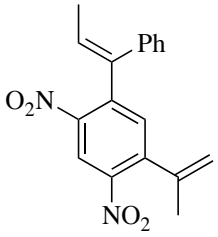
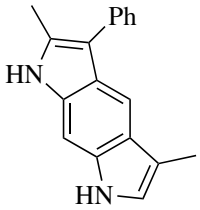
Entry	Substrate	Product(s)	
1	 **240**[b]		 **239** (78%)
2	 **314**	 **329** (47%)	 **330** (30%)
3	 **302**		 **331** (77%)

Table 10: Reductive Double *N*-Heterocyclizations[a]

Entry	Substrate	Product(s)
4	 **274**	 **332** (23%)
5	 **276**	 **333** (17%)

a) Conditions: 1,10-phenanthroline, dppp, $Pd(dba)_2$, CO (6 atm), DMF, 120 °C, 120 hrs
b) Reaction run for 87 hours

Pyrroloindole **239** was obtained in moderate yield after 87 hours (Table 10, entry 1). It was anticipated that di-vinyl substrate **240** would cyclize faster than the other examples, which featured various substituents on the double bonds that could interfere with the coordination of palladium to the alkene. It is possible that the cyclization was complete in a shorter amount of time, however, difficulties in monitoring the reaction via TLC limited the certainty with which progress could be monitored. The modified catalyst conditions also improved on Banini's preparation of **239** (which used PPh_3 and $Pd(dba)_2$ in DMF under CO (6 atm)) to obtain the pyrroloindole **239** in 84% yield after 144 hours). Although the yield was slightly lower in our hands, reducing the reaction time by nearly three days was a modest improvement.

In the case of vinyl-isopropenyl substrate **314** (Table 10, entry 2), it appeared as though the added steric bulk of the methyl group slowed down the cyclization of the

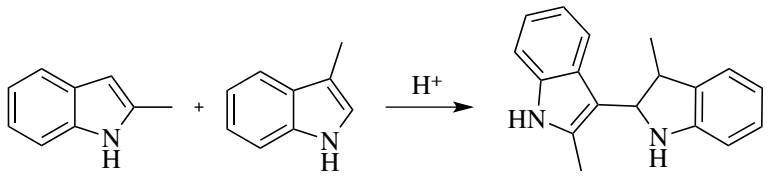
isopropenyl moiety as evidenced by the moderate amount of indole **329** isolated. However, desired pyrroloindole **330** was also isolated, albeit in poor yield on account of the isolation of indole **329**. It is notable that the vinyl group of **314** reacts regioselectively with the 4-nitro group and not with the other neighboring nitro substituent. The structure of indole **329** was confirmed through observed NOE between the C7 proton of the indole core and the indole N-H. This inherent regioselectivity could potentially be attributed to the less hindered nitro group being more accessible to interaction with the palladium catalyst.

The cyclization of 2,3-dinitro substrate **302** (Table 10, entry 3) afforded pyrroloindole **331** in good yield with no detected mono-cyclization. In comparison to the cyclization of di-isopropenyl substrate **257** which afforded mono-cyclized indole **259** as the major product along with pyrroloindole **258** (Section 5.3.3), substrate **302** featuring more substituted double bond cyclized at a faster rate with no mono-cyclized product isolated. The rate enhancement could be attributed to the altered catalyst conditions with the two ligand system employed herein producing a more active catalyst.

Issues arose in the cyclization of propenyl-isopropenyl substrate **274** (Table 10, entry 4). While no starting material was detected or recovered at the end of three different trials, only trace amounts of pyrroloindole **332** was isolated. It is believed that the unsubstituted 3-position of the propenyl-cyclized portion of the product could render the pyrroloindole product prone to oligomerization, as evidenced by a substantial amount of insoluble brown material upon crude work-up. Studies on the acid-induced dimerization and oligomerization of indoles reported that the 3-position of 2-methylindole (**17**) is more nucleophilic than that of indole (**1**) on account of the added

electron-donating methyl group.[141] Also reported is the reaction of 2-methylindole (**17**) and skatole (3-methylindole) (**334**) to afford mixed dimer **335** (Scheme 130).

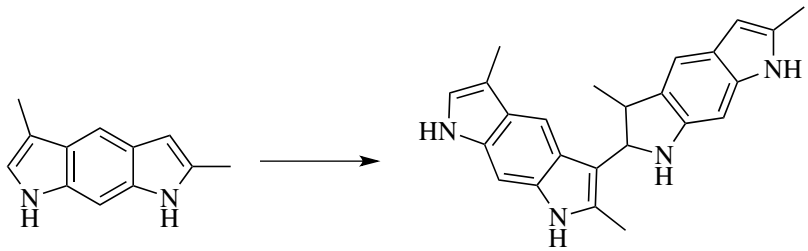
Scheme 130: Formation of Mixed Indole Dimer



17 **334** **335**

A similar transformation could be envisioned for pyrroloindole **332**. In the event that pyrroloindole **332** is formed, intermolecular nucleophilic addition of the 2-methylindole portion of the molecule to the 3-methylindole portion of a second molecule would afford dimer **336** (Scheme 131). However, the inability to characterize the insoluble residue that was obtained prevented the confirmation of this dimerization.

Scheme 131: Intermolecular Dimerization of Pyrroloindole



332 **336**

The last substrate examined **276** (Table 10, entry 5) cyclized to afford pyrroloindole **333** in moderate yield. The added bulk on account of the phenyl and methyl substituents on the alkenyl group of **276** appeared to have little effect on the overall rate of the double annulation, as no mono-cyclized indole products were obtained.

5.5 Conclusions

Novel non-symmetrical pyrroloindoles were prepared from dialkenyl-dinitro benzenes. Four of the five highly functionalized isomeric cyclization precursors were

prepared through use of aromatic substitution along with Kosugi-Migita-Stille coupling reactions. Using Soderberg's palladium-catalyzed reductive double *N*-heteroannulation methodology, the structurally complex cyclization precursors were converted to the corresponding pyrroloindoles. The generally mild catalyst conditions offer significant improvements over previously reported methods using harsh[108, 109] conditions. Catalyst degradation due to extended reaction times was also prevented through use of a two ligand system, protecting the integrity of the catalyst while also reducing the time needed for the double annulations to reach completion. This methodology provides synthetic routes to previously elusive highly functionalized non-symmetrical pyrroloindoles, which are of interest in a number of applications.

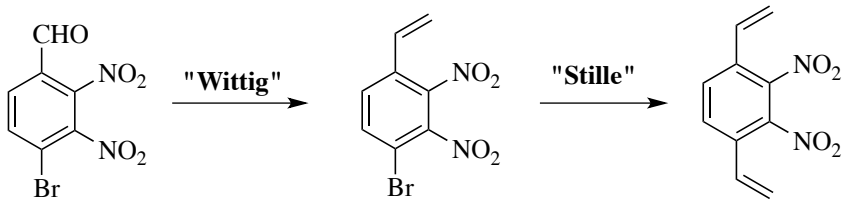
Chapter 6

Synthesis of Functionalized Aromatics

6.1 Brominations of 2-Nitrobenzaldehyde

In the search for alternate routes to prepare non-symmetrical dinitro-dialkenyl aromatic compounds en route to the preparation of pyrroloindoles, the halogenation of nitrobenzaldehyde was explored. It was envisioned that the selectivity issues (discussed in Chapter 4) could be circumvented through use of a route that only required one coupling step. Therefore, halobenzaldehydes were sought as potential intermediates to prepare the desired cyclization precursors though Wittig condensation of the aldehyde and cross-coupling of the halide (Scheme 132).

Scheme 132: Proposed Substrate Preparation From Halobenzaldehyde



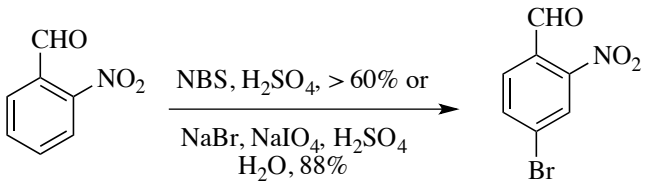
337 **252** **241**

6.1.1 Introduction

A mild method for the bromination of deactivated aromatic compounds[142] using *N*-bromosuccinimide (NBS) in sulfuric acid was reported by Saiganesh *et al* in 2007.[143] Nine different substrates were examined and 60-92% yields of single products were reported. For eight of the starting materials, the directing effect of the functional groups present on the aromatic ring for electrophilic aromatic bromination coincided in the same position. Thus, the regioselectivity of the incoming electrophile was not an issue. The last substrate examined by the authors, 2-nitrobenzaldehyde (**338**), did not have this luxury. Nevertheless, 4-bromo-2-nitrobenzaldehyde (**339**) was reported as the only

product in over 60% yield (Scheme 133). In addition to the reaction of **338** with NBS in sulfuric acid, a related regioselective bromination using sodium bromide and sodium periodate in sulfuric acid – water to afford **339** in 88% isolated yield was reported by Kumar *et al* in 2012 (Scheme 133).[144]

Scheme 133: Regioselective Bromination of 2-Nitrobenzaldehyde



338 **339**

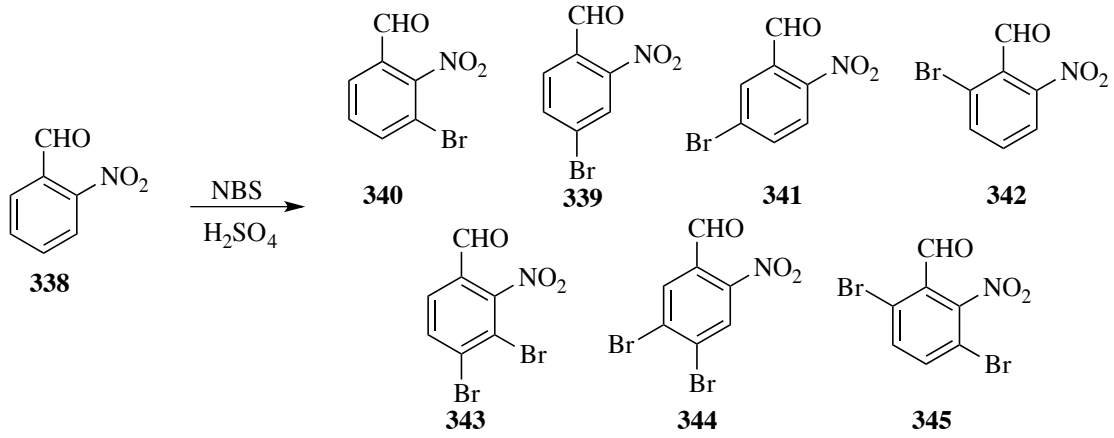
The experimental procedures, as described in the literature, were repeated a number of times. However, in our hands, the results reported could not be duplicated. The reactions with NBS gave a complex mixture of up to seven brominated products along with unreacted starting material. Reactions attempted using NaBr-$NaIO_4$ resulted only in quantitative recovery of starting material. The complex reaction mixtures obtained in the experiments using NBS were examined in order to assign structures to each product. It should be noted that each of the brominated products obtained are potentially useful building blocks in organic chemistry on account of their high degree of functionality, although each was obtained in relatively low yield.

6.1.2 Results and Discussion

In an attempt to deconvolute the complex reaction mixtures obtained, 2-nitrobenzaldehyde (**338**) was reacted with NBS in sulfuric acid at both the originally reported reaction temperature (25 ºC) and at 60 ºC. In addition, experiments employing different amounts of NBS were performed. Complex mixtures containing the four

possible monobrominated compounds (**339-342**) and three dibrominated products (**343-345**) were observed in the crude reaction mixtures in all cases (Scheme 134).

Scheme 134: Bromination of 2-Nitrobenzaldehyde



The molar ratios of products in each trial were extrapolated from integration of the crude ^{1}H NMR spectra and are presented in Table 11. Purification of the crude mixtures afforded pure products along with two or three component mixtures. The isolated yields of each product in each trial are reported in Table 12.

Table 11: Molar Ratios of Brominated Products[a]

Equivalents NBS	338	339	340	341	342	343	344	345
0.75	45.1	17.8	2.9	10.6	19.3	1.6	1.2	1.6
1.25	18.4	24.9	4.0	14.4	24.9	5.0	3.5	5.0
1.25[b]	17.6	25.9	3.2	12.1	20.9	5.2	10.3	4.8
2.5	2.6	27.0	3.1	12.0	17.1	14.0	9.7	13.8
5.0	-	13.5	0.6	3.4	1.1	28.7	26.7	26.1

a) Reactions were performed at ambient temperature. Ratios were calculated from ^{1}H NMR spectra of the crude reaction mixtures. b) Reaction at 60 ºC.

Table 12: Isolated Yields of Brominated Products[a]

Equivalents NBS	338	339	340	341	342	343	344	345	Total Brominated
0.75	38	19	4	12	24	-	1	2	62%
1.25	17	21	4	9	20	5	1	3	63%
1.25[b]	4	10	3	3	8	9	2	1	36%
2.5	3	8	8	20	14	12	9	13	84%
5.0	-	4	-	-	-	24	19	17	64%

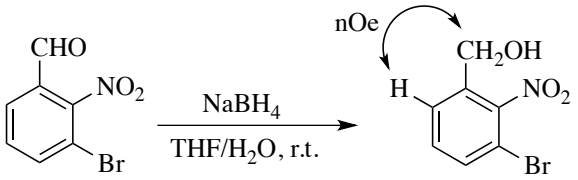
Starting material (**338**) was detected in all reactions aside from the reaction using 5 equivalents of NBS. Chromatographic separation using silica gel was partially successful in separating the isomers. Monobrominated isomer **340** was isolated from the mixture when five equivalents of NBS was added. Pure **344** was isolated regardless of the amount of NBS used, and pure **343** and **345** were separated from the crude mixture when five equivalents of NBS was used. Monobrominated compounds **339**, **341**, and **342** were always isolated as inseparable mixtures. The identities of compounds **340**, **342**, **344,** and **345** were verified through comparison with literature NMR and/or melting point data.

In order to correctly identify each isomeric compound as well as to aide in the separation of the mixtures, all pure compounds and some of the mixtures were reduced to the corresponding benzylalcohols using sodium borohydride.

Reduction of **340** using sodium borohydride afforded known benzylalcohol **346** (Scheme 135). The aromatic ^{1}H NMR splitting pattern consiting of two doublets and a triplet along with a nuclear Overhauser effect (nOe) between the methylene protons and one of the aromatic doublets confirmed the structure of **346** and thus of isomer **340**. This

transformation also verified the structure of the other monobrominated product with the same doublet-doublet-triplet ^{1}H NMR splitting pattern assigned as **342**.

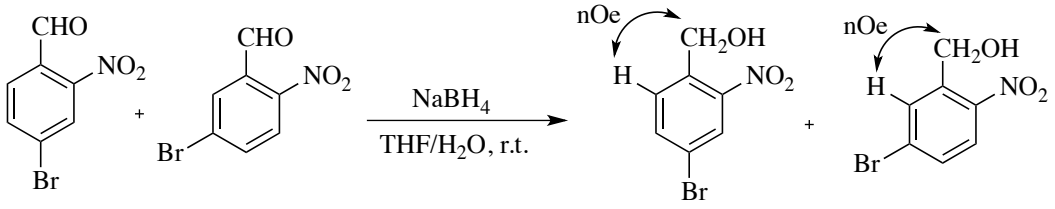
Scheme 135: Sodium Borohydride Reduction of 340



340 **346**

Aldehydes **339** and **341** were inseparable, however, treatment of the mixture with sodium borohydride provided a separable mixture of known benzylalcohols **347** and **348**. These benzylalcohols also corroborated the structure of **339** and **341** by nOe experiments (Scheme 136).

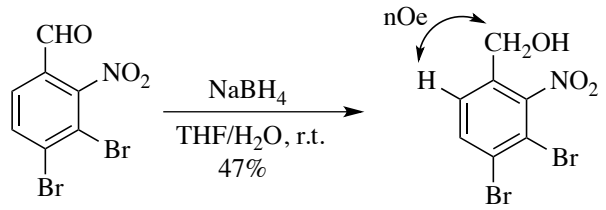
Scheme 136: Reduction of Inseparable Mixture



339 **341** **347** **348**

Similarly, reduction of aldehyde **343** afforded benzylalcohol **349** (Scheme 137). The structure of **343** was then confirmed by and observed nOe between the benzyl protons and the *ortho* proton on the benzene ring of **349**.

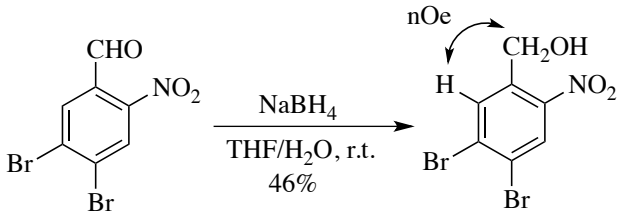
Scheme 137: Reduction of Aldehyde to Confirm Structure



343 **349**

Aldehyde **344** was also reduced using sodium borohydride (Scheme 138). The structure of **350** and subsequently **344** were again confirmed through nOe experiments.

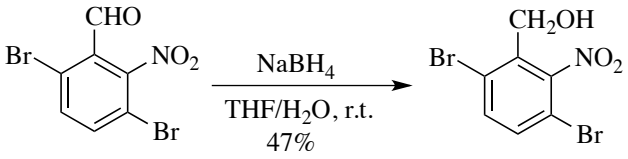
Scheme 138: Reduction of Aldehyde 344



344 **350**

Similar reduction of aldehyde **345** afforded benzylalcohol **351** (Scheme 139). As expected, no nOe was observed between the methylene of **351** and any of the aromatic protons.

Scheme 139: Reduction of Aldehyde 345



345 **351**

As anticipated, predominately monobrominated products were obtained from reactions using lower amounts of NBS and, not surprisingly, dibrominated products were

the major components when a large excess of NBS was used. Interestingly, the total yield of brominated products was roughly the same regardless of the amount of NBS used. A significantly lower yield was obtained from the reaction using 2.5 equivalents of NBS at 60 ºC, even though little starting material was present in the crude mixture. The combination of elevated temperature and the acidic reaction medium may have caused decomposition of the starting material. Because only a small amount of dibrominated products were formed when less than one equivalent of NBS was used, the ratios of **339**, **340**, and **341** provided a measure of the reactivity of the different positions in **338** toward electrophilic aromatic bromination. The reactivity was normalized to compound **340**, the minor monobrominated product, and was calculated to be 6.1 : 1 : 3.7 : 6.7 (in order from **339** to **342**). This order of reactivity likely reflects the electron-withdrawing ability of the nitro group as compared to the aldehyde. Presumably the nitro group more effectively deactivates the *meta* positions (relative to the nitro group), in turn rendering the *ortho* and *para* positions (relative to the nitro group) more reactive. The results from the reactions using 0.75 and 5.0 equivalents of NBS also suggest that compounds **340**, **341**, and **342** undergo a second bromination at a much faster rate compared to **339**, since a significant amount of the latter remains even at 5.0 equivalents of NBS. A rough order of reactivity for the second bromination of each monobrominated product was calculated by comparing the ratios of monobrominated products at 0.75 and 5.0 equivalents of NBS. The resulting order of **342**> **340** > **341** > **339** potentially reflects the minimized steric congestion of **342** and **340** relative to **339** and **340**.

6.1.3 Conclusions

In summary, the reported results for the selective bromination of 2-nitrobenzaldehyde (**338**) using NBS in sulfuric acid to give 4-bromo-2-nitrobenzaldehyde (**339**) reported in the literature were unable to be duplicated. However, the complex mixture of four monobrominated and three dibrominated products obtained in the attempts were isolated and identified. Pure products were achieved through chromatographic separation along with reduction of the aldehydes to the corresponding benzylalcohols, also aiding in the structural elucidation of each isomer. Based on the ratios achieved in each trial, the relative reactivity of each position of 2-nitrobenzaldehyde towards electrophilic bromination was inferred and found to reflect the greater deactivating ability of the nitro group in comparision to the aldehyde. Each mono and dibrominated product possessed a high degree of functionality with the potential to be synthetically useful building blocks.

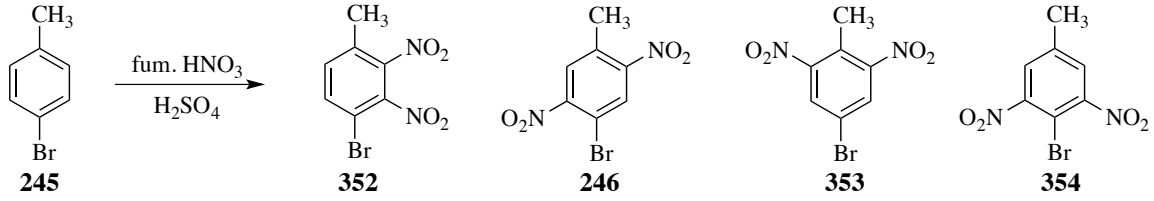
6.2 Synthesis of Functionalized Indoles

Through extensive efforts to prepare non-symmetrical cyclization precursors in the synthesis of pyrroloindoles, a number number of highly functionalized nitroaromatic compounds were prepared. While these compounds were ultimately not used in the established routes to prepare pyrroloindoles, it was envisioned that nitro-substituted indoles could be prepared from some of the intermediate compounds that were synthesized. These functionalized indoles would provide a diverse array of starting materials for a number of further transformations.

6.2.1 Synthesis of 6-Methyl-Nitroindoles

The first functionalized indoles that were prepared arose from the dinitration of *p*-bromotoluene (**245**) (Scheme 140). Due to the harsh conditions used in this reaction, all four possible dinitrated isomers **246** and **352-354** were observed. Although separation of isomers **246** and **353** proved to be very difficult, **352** and **354** were separable using column chromatography.

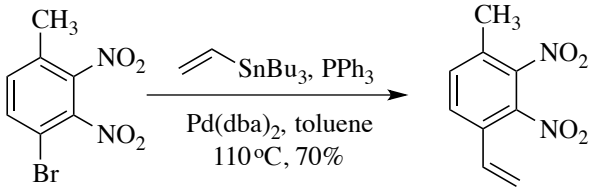
Scheme 140: Nitration of *p*-Bromotoluene



245 **352** **246** **353** **354**

Under Kosugi-Migita-Stille cross-coupling conditions, aryl bromide **352** was coupled with vinyl stannane to afford dinitrostyrene **355** (Scheme 141).

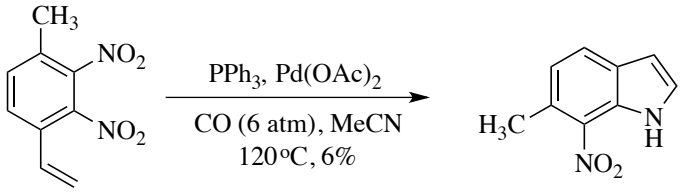
Scheme 141: Kosugi-Migita-Stille Coupling of Aryl Bromide



352 **355**

Using modified Söderberg conditions, reductive *N*-heterocyclization of *o*-nitrostyrene **355** was achieved through treatment with triphenylphosphine and palladium (II) acetate in acetonitrile while heating in a sealed tube pressurized with carbon monoxide, affording 6-methyl-7-nitroindole (**356**), albeit in poor yield (Scheme 142).

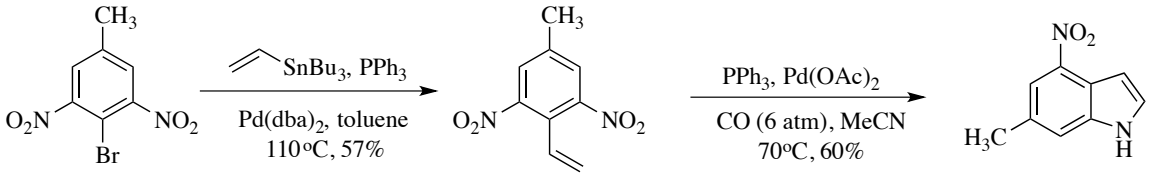
Scheme 142: Reductive *N*-Heterocyclization of Nitrostyrene 355



355 **356**

Similar methodology was applied to 3,5-dinitrotoluene isomer **354** (Scheme 143). Initial Kosugi-Migita-Stille coupling between aryl bromide **354** and vinyl stannane afforded styrene **357**. Subsequent exposure of nitrostyrene **357** to the previously discussed reductive *N*-heterocyclization conditions afforded 6-methyl-4-nitroindole **358** in moderate yield over two steps.

Scheme 143: Synthesis of 6-Methyl-4-Nitroindole



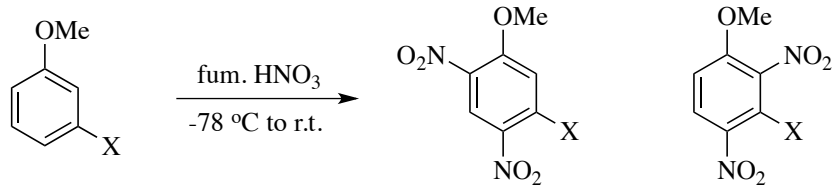
354 **357** **358**

6.2.2 Synthesis of 5-Methoxy-Nitroindoles

In the attempted synthesis of pyrroloindoles starting from either 3-bromoanisole (**359**) or 3-iodoanisole (**362**), dinitro-haloanisoles **360**, **361**, **363**, and **364** were prepared through treatment of the corresponding anisole with fuming nitric acid (Scheme 144). Interestingly, none of the 2,6-dinitroanisole product was formed from either substrate. On account of this, it was presumed that the first nitro group likely added to the 4-

position (relative to the methoxy group), then a second nitro group added to either of the positions *ortho* to the methoxy group. The substantial difference in the ratio of products **360:361** and **363:364** is also intriguing. While the iodine would be larger than the bromine and would pose a greater steric effect, the electronic effect in going from bromine to iodine likely influenced the observed differences in regioselectivity.

Scheme 144: Dinitration of 3-Haloanisole



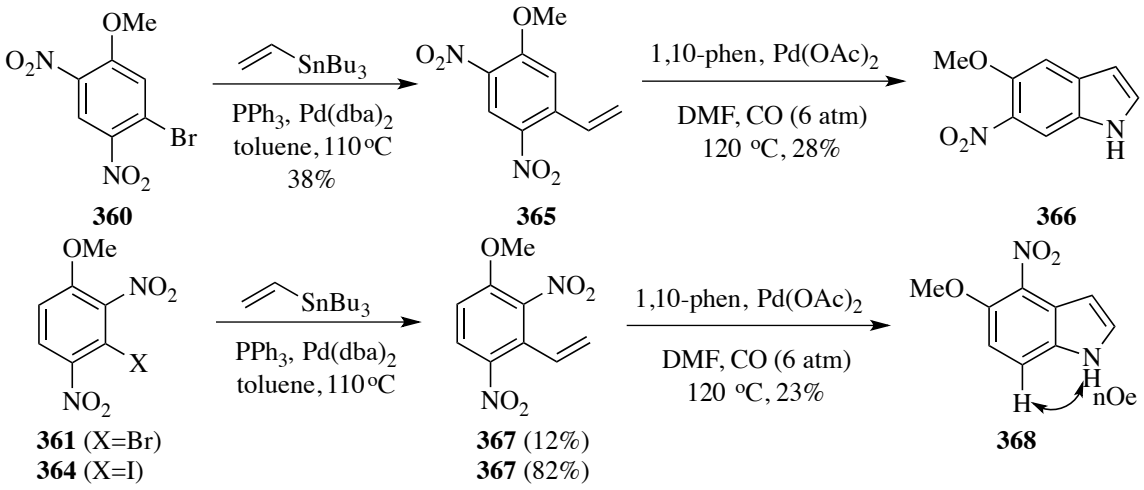
359 (X=Br)
362 (X=I)

360 (89%)
363 (30%)

361 (6%)
364 (35%)

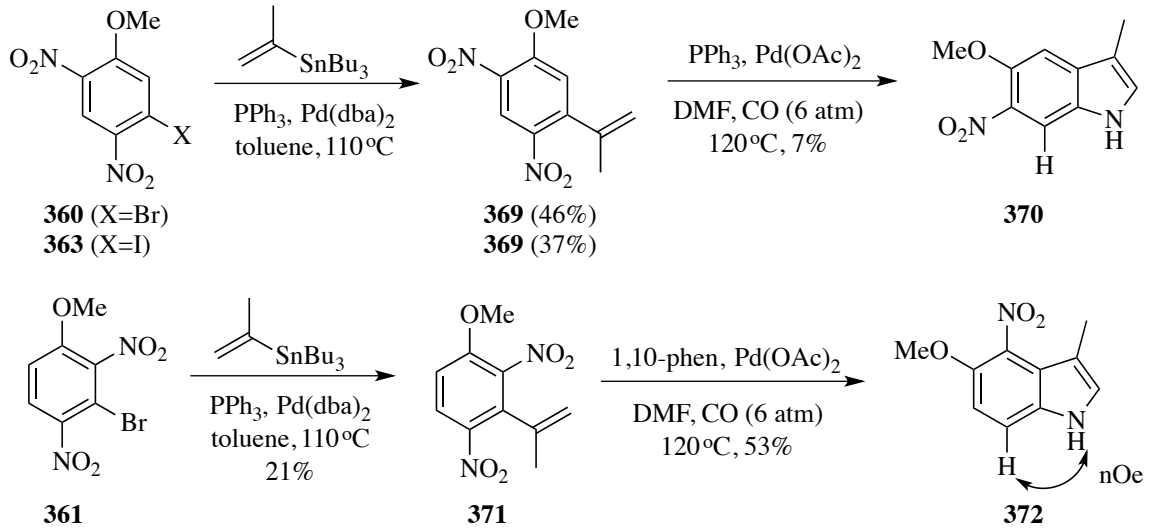
These isomers were then subjected to previously discussed Kosugi-Migita-Stille coupling conditions in the presence of vinyl stannane to afford dinitrostyrenes **365** and **367**, which were then cyclized using Söderberg's palladium-catalyzed reductive *N*-heteroannulation conditions. This sequence afforded two isomeric methoxy-nitroindoles **366** and **368**, albeit in low yield (Scheme 145). The structure of indole **368** was confirmed through the observed nOe between the C7 proton and the indole H.

Scheme 145: Preparation of 5-Methoxy-Nitroindoles



A similar route afforded 3-methylindoles **370** and **372** from intermediates **369** and **371**, which resulted from Kosugi-Migita-Stille coupling between the requisite haloanisole and isopropenyl stannane (Scheme 146). The structure of indole **372** was again confirmed through the observed NOE between the C7 proton and the indole N-H.

Scheme 146: Preparation of 3-Methyl-5-Methoxy-Nitroindoles



While the yields of the indole products were moderate at best, a number of significant observations were made. As observed in prior cases,[52] the *ortho* alkenyl group is necessary for reduction of a nitro group; nitro groups lacking an *ortho* alkenyl substituent were inert to the reductive conditions. The regioselectivity observed in the cyclization of isomers **367** and **371** was also of interest. While cyclization of these could occur through either of the two *ortho* nitro groups relative to the alkenyl substituent, only one indole product (**368** and **372**) was isolated in each case. This infers that sterics influence the initial coordination-mediated nitro group reduction, as only the presumably more accessible nitro group reacted in these examples.

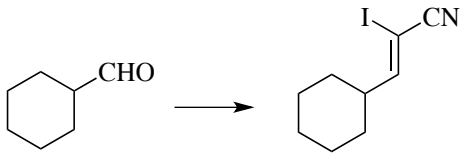
6.2.3 Conclusions

A number of substituted indoles were prepared through palladium-catalyzed reductive *N*-heterocyclization of the requisite *o*-nitrostyrene precursor. These examples expand the already broad substrate scope of Söderberg's palladium-catalyzed reductive *N*-heteroannulation methodology and exemplify the functional group compatibility of the relatively mild reaction conditions. Insight was also gained regarding the regioselectivity of the initial nitro group reduction, confirming previously proposed principles that a neighboring alkenyl group mediates nitro group reduction.

Chapter 7

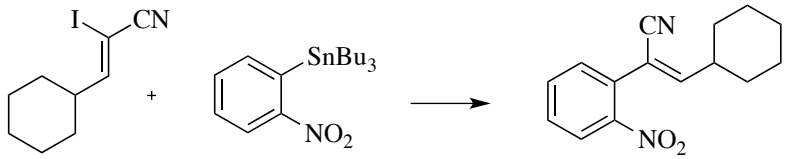
Supporting Information: Experimental Procedures

General Procedures. NMR spectra were determined in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR), 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR), or at 270 MHz (^{1}H NMR) and 67.5 MHz (^{13}C NMR). The chemical shifts are expressed in d values relative to $SiMe_4$ (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. ^{1}H-^{1}H coupling constants are reported as calculated from spectra, thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually observed. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Hexanes and ethyl acetate were distilled from calcium hydride. Anhydrous acetonitrile, benzene, dichloromethane, 1,4-dioxane, *N*,*N*-dimethylformamide, and toluene were used as received. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure unless otherwise stated. Chromatography was performed on silica gel 60 (40-63 μm, Sorbtech). Melting points (uncorrected) were recorded directly from products obtained by chromatography.



110

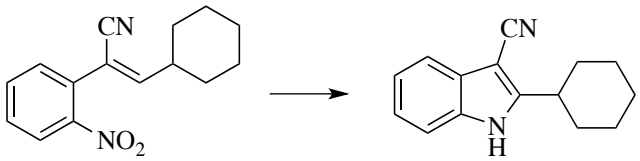
3-Cyclohexyl-2-iodo-2-propenenitrile (110): To a solution of triphenylarsonium ethanenitrile (1.66 g, 3.90 mmol) in MeCN (15 mL) at 10 ºC was added potassium carbonate (536 mg, 3.88 mmol) and iodine (997 mg, 3.93 mmol). The solution was stirred under a nitrogen atmosphere (ambient temp., 30 h) where after potassium carbonate (564 mg, 4.08 mmol), cyclohexylcarboxaldehyde (556 mg, 5.00 mmol) and H_2O (0.5 mL) were added. After an additional 48 h, the solvents were removed under reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **110** (171 mg, 0.65 mmol, 17%) as a brown oil. ^{1}H NMR δ 6.89 (d, *J*=10.2 Hz, 1H), 2.54 (qt, *J*=10.8, 3.6 Hz, 1H), 1.77-1.73 (m, 6H), 1.25-1.14 (m, 4H); ^{13}C NMR δ 167.3, 116.1, 49.7, 45.7, 45.0, 31.4, 25.3, 25.0; IR (ATR) 2935, 2851, 2211, 1447, 1148 cm^{-1}; HRMS (ESI) calcd for $C_9H_{12}NaNI$ ($M+Na^+$) 283.9912; found, 283.9906.



110 **111**

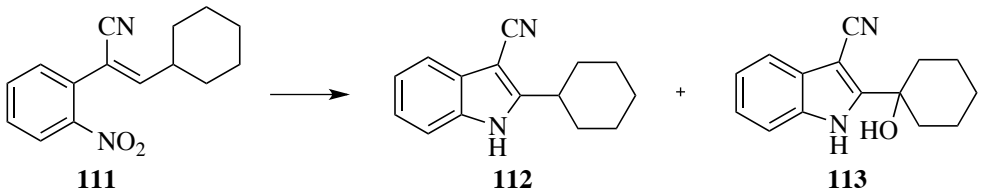
3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile (111): Reaction of tributyl(2-nitrophenyl) stannane (273 mg, 0.66 mmol), **110** (171 mg, 0.65 mmol), $PdCl_2(PhCN)_2$ (16 mg, 0.04 mmol), $AsPh_3$ (22 mg, 0.07 mmol) and CuI (22 mg, 0.12 mmol) in NMP (3 mL), as described for **91** (80 ºC, 76 h), gave after chromatography (hexanes/EtOAc, 9:1) **111** (82 mg, 0.32 mmol, 48%, as a 14:1 mixture of isomers) as a pale brown oil.[i] ^{1}H

NMR δ 8.03 (d, *J*=9.6 Hz, 1H), 7.65 (t, *J*=7.2 Hz, 1H), 7.55 (t, *J*=7.2 Hz, 1H), 7.41 (d, *J*=7.8 Hz, 1H), 6.31 (d, *J*=10.2 Hz, 1H), 2.78 (tq, *J*=4.2, 0.8 Hz, 1H), 1.87 (d, *J*= 2.6 Hz, 2H), 1.79 (dt, *J*=13.8 Hz, 3.0 Hz, 2H), 1.72 (dt, *J*=13.2, 3.6 Hz, 1H), 1.40 (tq, *J*= 12.6, 3.6 Hz, 2H), 1.23 (m, 3H); ^{13}C NMR δ 156.7, 147.8, 133.5, 131.7, 129.9, 129.7, 124.9, 115.2, 110.6, 41.2, 31.6, 25.5, 25.1; IR (ATR) 2928, 2853, 2221, 1526, 1345, 854, 731 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2O_2$ (M+Na$^+$) 279.1110; found 279.1104.



111 **112**

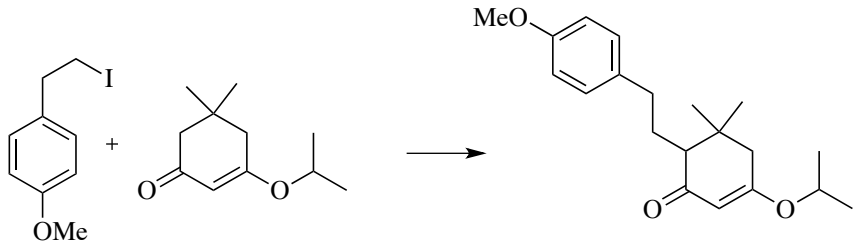
3-Cyano-2-cyclohexylindole (112): Reaction of **111** (73 mg, 0.31 mmol), PPh_3 (26.2 mg, 0.10 mmol), Pd(OAc) (7.6 mg, 0.03 mmol), and CO (6 atm) in DMF (5 mL), as described in for **77**, gave after chromatography (hexanes/EtOAc, 7:3) **112** (34 mg, 0.15 mmol, 48%) as a pale yellow solid. mp 171-173 ºC; ^{1}H NMR δ 8.54 (br s, 1H), 7.67 (d, *J*=4.8 Hz, 1H), 7.38 (d, *J*=7.2 Hz, 1H), 7.26-7.23 (m, 2H), 3.05 (tt, *J*=8.4, 3.6 Hz, 1H), 2.08 (d, *J*=12.0 Hz, 2H), 1.90 (dt, *J*= 13.8, 3.0 Hz, 2H), 1.80 (d, *J*=12.6 Hz, 1H), 1.61 (dq, *J*=12.6, 3.6 Hz, 2H), 1.46 (tq, *J*=13.2, 3.6 Hz, 2H), 1.31 (tq, *J*= 12.6, 3.6 Hz, 1H); ^{13}C NMR δ 153.4, 134.1, 127.8, 123.3, 122.0, 119.0, 116.4, 111.3, 83.4, 37.6, 32.4, 26.1, 25.7; IR (ATR) 3227, 2919, 2849, 2215, 1439, 737 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2$ (M+Na$^+$) 247.1211, found 247.1199.



111 **112** **113**

3-Cyano-2-cyclohexylindole (112) and 3-cyano-2-(1-hydroxycyclohexyl)indole (113). Reaction of **111** (82 mg, 0.32 mmol), PPh_3 (42 mg, 0.16 mmol), DBU (53 mg, 0.36 mmol), and $Pd(OAc)_2$ (10 mg, 0.05 mmol) in DMF (5 mL) as described for **78** gave after chromatography (hexanes/EtOAc, 8:2) **112** (5 mg, 0.02 mmol, 7%) and **113** (24 mg, 0.10 mmol, 31%) as a pale yellow oil. ^{1}H NMR δ 9.25 (br s, 1H), 7.68 (d, *J*=6.6 Hz, 1H), 7.40 (d, *J*=6.6 Hz, 1H), 7.25 (m, 2H), 2.47 (br s, 1H), 2.25 (dt, *J*=13.8, 4.8, 2H), 1.89 (d, *J*=13.8 Hz, 2H), 1.82-1.64 (m, *J*= 16.2 Hz, 5H), 1.43 (m, 1H); ^{13}C NMR δ 154.6, 133.1, 129.2, 123.7, 122.3, 119.4, 116.8, 112.0, 80.7, 72.3, 37.4, 24.9, 21.6; IR (ATR) 3330, 2938, 2214, 1737, 1241, 1044 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NaN_2O$ ($M+Na^+$) 263.1160, found 263.1155.

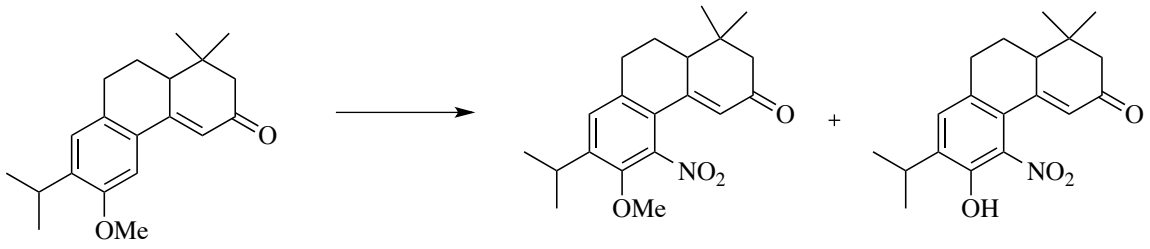
7.2 Supporting Information for Chapter 3: Salviadione



129 **128** **127**

5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (127): 5,5-Dimethyl-3-(1-methylethoxy)-2-cyclohexen-1-one (**128**)[146] (4.133 g, 22.68 mmol) was dissolved in THF (25 mL) and cooled to -78 ºC under a positive flow of nitrogen. Lithium diisopropylamide (2.0 M, 13.6 mL, 27.21 mmol) was added drop wise *via* a cannula over 15 min. The resulting yellow solution was stirred for 1 h at -78 ºC before slowly adding the solution drop wise *via* a cannula to a solution of 1-(2-iodoethyl)-4-methoxybenzene (**129**)[145] (7.132 g, 27.21 mmol) in THF (25 mL) cooled to -78 ºC. The solution was allowed to stir up to ambient temperature (12 h) followed by addition of a solution of NH_4Cl (sat. aqueous, 50 mL) was carefully added and stirred for 5 min. The phases were separated and the aqueous portion was extracted with EtOAc (3 x 200 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The resulting orange oil was purified by chromatography (hexanes/EtOAc, 95:5 followed by 9:1) to afford **127** as a yellow oil (6.429 g, 20.32 mmol, 90%). ^{1}H NMR (270 MHz) δ 7.13 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.3 Hz, 2H), 5.34 (s, 1H), 4.42 (sept, *J*=6.2 Hz, 1H), 3.78 (s, 3H), 2.76 (ddd, *J*=13.4, 9.7, 5.7 Hz, 1H), 2.54 (ddd, *J*=13.9, 9.7, 7.3, 1H), 2.26 (d, *J*=17.6 Hz, 1H), 2.18 (d, *J*=17.6 Hz, 1H), 1.97 (dd, *J*=8.7, 4.3 Hz, 1H), 1.83-1.69 (m, 2H), 1.28 (d, *J*=6.1 Hz, 6H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (67.5 MHz) δ 202.4 (+), 173.1 (+), 157.7 (+), 134.6 (+), 129.4 (-), 113.7 (-), 100.9 (-), 70.7 (-), 56.2 (-), 55.2 (-), 42.2 (+), 35.0 (+), 34.0 (+),

28.5 (-), 28.4 (+), 24.4 (-), 21.5 (-); IR (ATR) 2957, 2932, 1648, 1604, 1517, 1378, 1243, 1107 cm $^{-1}$.



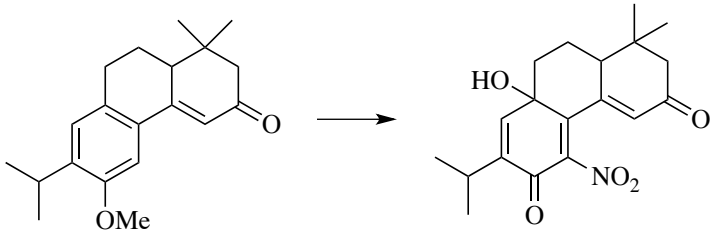
126 **132** **125**

10,10*a*-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1*H*,2*H*,9*H*)-one (132) and 10,10*a*-Dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1*H*,2*H*,9*H*)-one (**125**): Fuming nitric acid (5.0 mL, 144 mmol) was cooled to -78 ºC and concentrated sulfuric acid (13 drops) was slowly added drop wise. After stirring for 20 min, **126** (166 mg, 0.556 mmol) was added in one portion to the nitration solution. The resulting dark red solution was removed from the cold bath and allowed to stir for 10 min. at ambient temperature. The mixture was poured into 200 mL of ice, neutralized with Na_2CO_3 (s) and extracted with EtOAc (3 x 75 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The resulting crude product was purified by chromatography (hexanes/acetone, 6:4) to afford in order of elution **132** (47.9 mg, 0.140 mmol, 25%) as a colorless solid followed by **125** (59.6 mg, 0.181 mmol, 32%) as a yellow solid.

Analytical data for **132**: mp 174-175 ºC; ^{1}H NMR (600 MHz) δ 7.15 (s, 1H), 6.14 (d, *J*=0.8 Hz, 1H), 3.83 (s, 3H), 3.30 (sept, *J*=7.0 Hz, 1H), 2.81 (dddd, *J*=16.0, 7.3, 5.0, 0.6, 1H), 2.71 (dddd, *J*=16.0, 8.1, 5.0, 0.8 Hz, 1H) 2.61 (dt, *J*=7.1, 2.4 Hz, 1H), 2.35 (dd, *J*=16.0, 0.4 Hz, 1H), 2.27 (dd. *J*=16.0, 0.8 Hz, 1H), 1.99 (dddd, *J*=13.5, 7.3, 7.1, 7.1 Hz, 1H), 1.87 (dddd, *J*=13.5, 8.1, 5.0, 5.0 Hz, 1H), 1.26 (d, *J*=7.0 Hz, 3H), 1.24 (*J*=7.0 Hz, 3H), 1.16 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (150 MHz) δ 198.5, 151.8, 147.5, 145.5, 144.4,

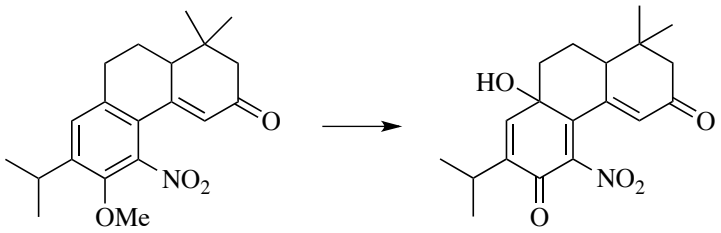
137.4, 127.6, 125.3, 124.8, 63.9, 51.6, 45.7, 37.1, 29.4, 28.9, 26.6, 23.4, 23.4, 23.2, 22.0; IR (ATR) 2968, 1664, 1525, 1283, 1254 cm^{-1}. HRMS (ESI) calcd for $C_{20}H_{26}NO_4$ ($M+H^+$) 344.1862, found 344.1862. Analytical data for **125**: mp 154-156 ºC (dec); ^1H NMR (270 MHz) δ 9.20 (br s, 1H), 7.17 (s, 1H), 5.84 (d, *J*=2.2 Hz, 1H), 3.37 (sept, *J*=6.9 Hz, 1H), 2.82-2.57 (m, 4H), 2.40 (d, *J*=16.0 Hz, 1H), 2.28 (d, *J*=15.8 Hz, 1H), 2.04-1.97 (m, 1H), 1.26 (d, *J*=6.7 Hz, 3H), 1.25 (d, *J*=6.9 Hz, 3H), 1.23 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (67.5 MHz) *δ* 198.2 (+), 154.2 (+), 149.2 (+), 139.7 (+), 134.0 (+), 133. 6 (+), 130.4 (-), 129.0 (+), 125.3 (-), 50.8 (+), 45.3 (-), 37.2 (+), 28.7 (-), 28.6 (+), 27.2 (-), 23.4 (+), 22.7 (-), 22.2 (-), 22.0 (-); IR (ATR) 3280, 2959, 1660, 1645, 1544, 726 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_4$ ($M+H^+$) 330.1705; found, 330.1705.

Alternative procedure to 125. Fuming HNO_3 (500 mL, 12.0 mmol) was stirred at -20 ºC for 5 min before concentrated H_2SO_4 (8 drops) was slowly added drop wise. The solution was stirred for 30 min before **126** (79 mg, 0.26 mmol) was added. The resulting dark red solution was stirred for 90 min before quenching with ice (30 mL). The mixture was neutralized with Na_2CO_3 (aqueous, saturated) and extracted with EtOAc (3 x 50 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The resulting brown oil was immediately purified by chromatography (hexanes/EtOAc, 9:1) affording **125** (66 mg, 0.20 mmol, 77%) as a yellow solid.



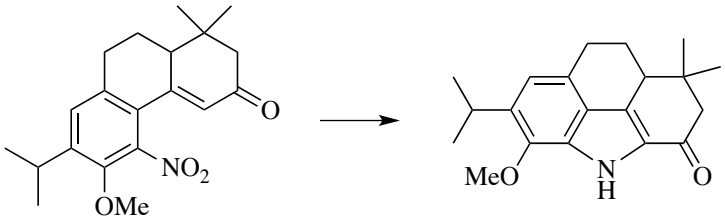
126 **133**

8*a*,9,10,10*a*-Tetrahydro-1,1-dimethyl-8*a*-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1*H*,2*H*)-dione (133): Fuming HNO_3 (6.9 mL, 164.0 mmol) was stirred at 0 ºC for 5 min before concentrated H_2SO_4 (14 drops) was slowly added drop wise. After 30 min at 0 ºC, the solution was added drop wise *via* a pipette to **126** (1.078 g, 3.61 mmol) at ambient temperature. The resulting dark red solution was stirred for 4 h wherafter H_2O (5 mL) and NH_4Cl (sat., aqueous, 40 mL) was added sequentially. The precipitate was removed by filtration, dissolved in acetone (50 mL) and adhered to silica gel (≈1.0 g) and allowed to stand for 1 h. The solvent was removed under reduced pressure and purification by chromatography (hexanes/acetone, 9:1 followed by 7:3) gave **133** (0.832 g, 2.41 mmol, 67%, 14:1 diastereomeric ratio) as an orange solid. mp 239-240 ºC; IR (ATR) 2952, 1663, 1530, 1266, 1253 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{24}NO_5$ ($M+H^+$) 346.1654, found 346.1655. Spectral data of the major diastereomer **133** from the mixture: ^1H NMR (600 MHz, $CDCl_3$/DMSO-d_6) δ 6.66 (d, *J*=1.1 Hz, 1H), 6.02 (d, *J*=2.4 Hz, 1H), 5.49 (d, *J*=1.5 Hz, 1H), 2.94 (dsept, *J*=6.8, 1.0 Hz, 1H), 2.41 (ddd, *J*=12.3, 5.7, 2.4 Hz, 1H), 2.32 (ddd, *J*=13.8, 3.5, 2.3 Hz, 1H), 2.30 (d. *J*=15.3 Hz, 1H), 2.26 (d, *J*=15.3 Hz, 1H), 2.08 (dq, *J*=13.2, 4.0 Hz, 1H), 1.97-1.92 (m, 1H), 1.67 (ddt, *J*=13.2, 4.2, 1.2 Hz, 1H), 1.12 (d, *J*=7.2 Hz, 3H), 1.11 (d, *J*=7.2 Hz, 3H), 1.11 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 198.0, 175.5, 152.1, 147.9, 145.6, 143.4, 142.2, 126.5, 68.9, 50.9, 49.0, 37.4, 35.6, 28.4, 26.4, 23.0, 21.3, 21.0, 20.5. Partial spectral data for minor diastereomer **133** from the mixture: ^1H NMR (600 MHz, $CDCl_3$/DMSO-d_6) δ 6.80 (d, *J*=1.0 Hz, 1H), 6.22 (d, *J*=2.8 Hz, 1H), 5.46 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$/DMSO-d_6) δ 198.1, 175.6, 153.4, 146.2, 145.8, 145.6, 139.8, 127.7, 67.7, 53.6, 45.1, 37.2, 37.1, 30.7, 28.7, 26.2, 23.0, 19.7, 19.6.



132 **133**

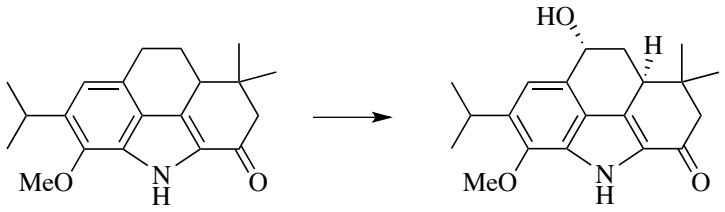
Alternative procedure to 133. To a solution of **132** (81 mg, 0.236 mmol) in acetone (5 mL) and acetic acid (1 mL) was added silica gel (0.5 g). The solvent was removed at reduced pressure and the yellow residue was allowed to stand open to air for 14 h. A slight yellow tint was noticed after this time and the residue was purified by chromatography (hexanes/acetone, 6:4) to afford **133** (72.0 mg, 0.208 mmol, 88%).



132 **134**

1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one (134): To a solution of **132** (22 mg, 0.065 mmol) in anhydrous DMF (1.0 mL) in a threaded ACE glass pressure tube was added 1,10-phenanthroline monohydrate (1.6 mg, 0.008 mmol), 1,3-bis(diphenylphosphino)propane (1.7 mg, 0.004 mmol), and bis(dibenzylideneacetone)palladium (2.3 mg, 0.004 mmol). The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (4 cycles of 6 atm). The reaction mixture was heated at 120 ºC under carbon monoxide (6 atm) for 168 h. The solvent was removed via bulb-to bulb distillation affording a brown residue. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by chromatography

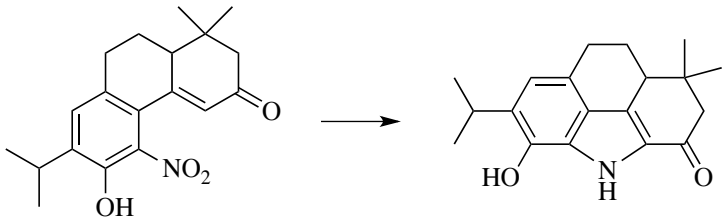
(hexanes/acetone, 9:1) to give **134** (17.3 mg, 0.057 mmol, 87%) as a yellow solid. mp 228-230 ºC; ^{1}H NMR (600 MHz) δ 8.64 (br s, 1H), 6.81 (s, 1H), 3.94 (s, 3H), 3.52 (sept, *J*=7.0 Hz, 1H), 3.03 (dd, *J*=12.1, 5.0 Hz, 1H), 3.02-2.95 (m, 2H), 2.77 (d, *J*=15.8 Hz, 1H), 2.33 (d, *J*=15.8 Hz, 1H), 2.21 (m, 1H), 1.62 (m, 1H), 1.27 (d, *J*=7.0 Hz, 3H), 1.27 (d, *J*=7.0 Hz, 3H), 1.24 (s, 3H), 0.85 (s, 3H); ^{13}C NMR δ 190.0, 140.9, 140.4, 134.3, 130.0, 129.5, 127.6, 126.4, 115.7, 60.9, 55.8, 41.8, 41.2, 28.4, 27.4, 26.8, 25.1, 24.2, 23.9, 20.4; IR (ATR) 3264, 2958, 2930, 1653, 1620 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ (M+H$^+$) 312.1964, found 312.1959.



134 **136**

1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**136**): To a solution of **134** (39.0 mg, 0.124 mmol) in THF (4 mL) was added DDQ (115 mg, 0.496 mmol) over a period of 5 min. The resulting mixture was allowed to stir at ambient temperature for 4 h where after the solvent was removed under reduced pressure. The color of the residue changed from purple to orange over 30 min. The crude product was purified by chromatography (hexanes/EtOAc, 7:3) to give **136** (36.0 mg, 87%) as a brown solid. mp = 141-143 ºC; ^{1}H NMR (600 MHz) δ 8.60 (br s, 1H), 7.03 (s, 1H), 5.18 (t, *J*=2.7 Hz, 1H), 3.95 (s, 3H), 3.53 (sept, *J*=7.2 Hz, 1H), 3.37 (dd, *J*=12.0, 4.8 Hz, 1H), 2.81 (d, *J*=5.2, 0.6, 1H), 2.41 (ddd, *J*=13.8, 5.4, 3.0 Hz, 1H), 2.37 (d, *J*=16.8, 1H), 1.64 (ddd, *J*=16.8, 12.0, 3.0 Hz, 1H), 1.60 (br s, 1H), 1.28 (d, *J*=7.2 Hz, 3H), 1.27 (d, *J*=7.2, 3H), 1.26 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz) δ 189.2, 143.0, 140.3, 132.8, 129.9, 128.9, 128.0, 125.5,

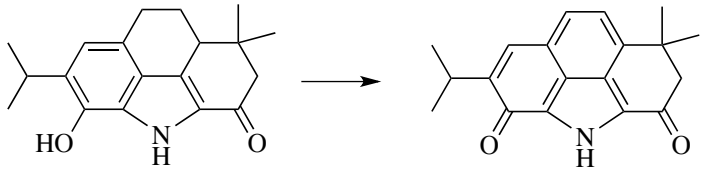
116.8, 67.7, 60.7, 55.9, 41.6, 35.7, 32.5, 28.3, 27.0, 24.1, 23.8, 20.7; IR (ATR) 3279 (br), 2959, 1650, 1624 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ ($M+H^+$) 328.1913, found 328.1909.



125 **124**

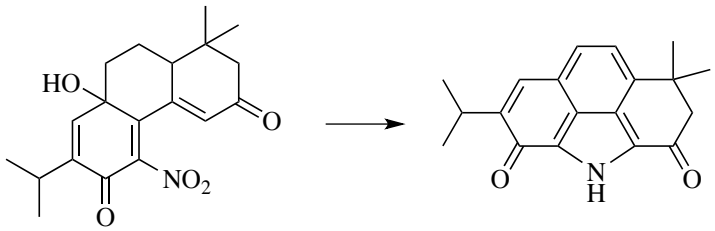
1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**124**): Reaction of **125** (140 mg, 0.566 mmol), bis(dibenzylideneacetone)palladium (20 mg, 0.034 mmol), 1,3-bis-(diphenylphosphino)propane (14 mg, 0.034 mmol), and 1,10-phenanthroline (13 mg, 0.068 mmol) were dissolved in anhydrous DMF (2 mL) in a threaded ACE glass pressure tube. The tube was fitted with a pressure head, and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction was heated at 120 ºC under CO (6 atm) for 32 h. DMF was removed via vacuum distillation before water (10 mL) was added to the brown residue. The brown solution was extracted with ethyl acetate (3 x 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was removed. The resulting crude product was purified by chromatography (pentanes/acetone, 8:2 followed by 1:1) to afford **124** (91 mg, 0.423 mmol, 75%) as a light yellow solid. mp 234-236 ºC; ^{1}H NMR (600 MHz, THF-d_8) δ 9.94 (s, 1H), 7.72 (s, 1H), 6.69 (s, 1H), 3.50 (sept, *J*=7.5 Hz, 1H), 3.03 (dd, *J*=12.6, 4.4 Hz, 1H), 2.96-2.88 (m, 2H), 2.7 (m, 1H), 2.20-2.14 (m, 2H), 1.53 (dq, *J*=11.9, 5.4 Hz, 1H), 1.24 (d, *J*=7.0 Hz, 3H), 1.22 (d, *J*=7.0 Hz, 3H), 1.19 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (150 MHz, THF-d_6) δ 187.9, 138.9, 133.6, 133.2, 129.5, 128.6, 126.8, 125.8, 115.7, 56.8, 42.4, 42.1, 28.7, 28.3,

27.8, 26.5, 24.0, 23.9, 20.6; IR (ATR) 3394 (br), 3260, 2962, 2928, 1617 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{24}NO_2$ ($M+H^+$) 298.1807, found 298.1802.



124 **123**

Salviadione (123): To a solution of **124** (35 mg, 0.118 mmol) in THF (5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (107 mg, 0.471 mmol) slowly in 2 approximately equal portions with a 5 min interval. The reaction mixture was stirred for 4 h at ambient temperature. The solvent was removed under reduced pressure from the resulting dark red-purple solution. The residue was dissolved in acetone (10 mL) and silica gel (≈1.0 g) was added. The solvent was removed under reduced pressure and the resulting solid was allowed to stand open to the air (4 h). Purification by chromatography (hexanes/acetone, 9:1) gave salviadione (**123)** (28 mg, 0.095 mmol, 81%) as an orange solid. Physical (mp) and spectroscopical data (^1H, ^{13}C, COSY, HMBC, HMQC) were in accordance with literature values. HRMS (ESI) calcd for $C_{19}H_{20}NO_2$ ($M+H^+$) 294.1494, found 294.1494.

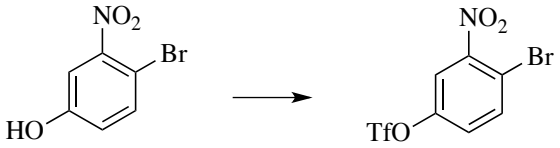


133 **123**

Alternative method to 123 To a solution of **133** (101 mg, 0.29 mmol) in anhydrous DMF (7.0 mL) in a threaded ACE glass pressure tube was added dppp (7.7 mg, 0.019 mmol), phen (19 mg, 0.095 mmol) and $Pd(dba)_2$ (15 mg, 0.027 mmol). The tube was

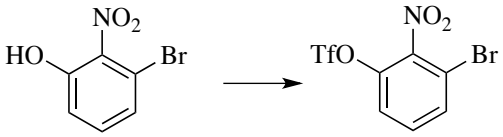
fitted with a pressure head and the solution was saturated with carbon monoxide (3 cycles of 6 atm). The reaction mixture was heated at 120 ºC under carbon monoxide for 168 hours. The solvent was removed via bulb-to-bulb distillation affording a brown oil. Water (5 mL) was added to this residue and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were dried ($MgSO_4$), filtered, and solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/ethyl acetate 7:3) to afford salviadione **(123)** (8.7 mg, 0.029 mmol, 10%).

7.3 Supporting Information for Chapter 4: Chemoselective Coupling



162 **163**

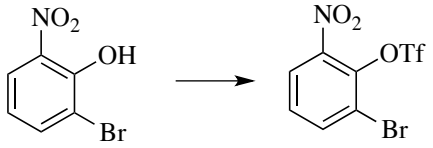
2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (163): To an ice-cooled solution of **162**[147] (269 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) was added pyridine (200 μL, 2.48 mmol) and trifluoromethanesulfonic anhydride (Tf_2O, 250 μL, 1.48 mmol). The mixture was removed from the cold bath and allowed to stir at ambient temperature for 30 min. The resulting mixture was filtered through a small plug of silica gel and the solvent was removed under reduced pressure from the filtrate. Purification by chromatography (hexanes/EtOAc, 9:1) afforded **3** (391 mg, 1.12 mmol, 90%) as a yellow oil. ^{1}H NMR δ 7.89 (d, *J*=9.0 Hz, 1H), 7.83 (d, *J*=3.0 Hz, 1H), 7.42 (dd, *J*=9.0, 3.0 Hz, 1H); ^{13}C NMR δ 150.1, 147.9, 136.8, 126.3, 119.3, 118.6 (q, *J*=319 Hz, C-F), 114.6; IR (ATR) 3103, 1541, 1428, 1208, 1132 cm $^{-1}$. HRMS (ESI) calcd for $C_7H_3BrNO_5F_3S$ ($M+Na^+$) 371.8759; found 371.8760.



165 **166**

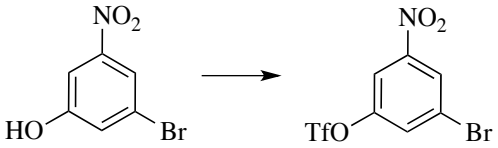
2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (166): Treatment of **165**[116] (298 mg, 1.37 mmol) in CH_2Cl_2 (5 mL) with pyridine (250 μL, 3.10 mmol) and Tf_2O (300 μL, 1.77 mmol), as described for **163**, gave after chromatography (hexanes/EtOAc, 8:2) **166** (394 mg, 1.13 mmol, 80%) as a red solid. mp 52-53 ºC; ^{1}H NMR δ 7.73 (dd, *J*=6.6, 3.0 Hz, 1H), 7.49 (m, 2H); ^{13}C NMR δ 144.3, 140.7, 133.4, 132.1, 121.6, 118.3 (q, *J*=319

Hz, C-F), 115.2; IR (ATR) 3099, 1538, 1434, 1360, 1219, 1132 cm $^{-1}$; HRMS (ESI) calcd for $C_7H_3BrNO_5F_3S$ ($M+Na^+$) 371.8759; found 371.8767.



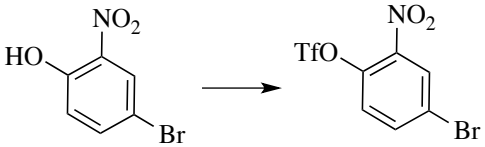
149 **151**

3-Bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (151): Treatment of **149**[93] (189 mg, 0.87 mmol) in CH_2Cl_2 (5 mL) with pyridine (150 μL, 1.85 mmol) and Tf_2O (200 μL, 1.18 mmol), as described for **163**, gave after chromatography (hexanes/EtOAc, 7:3) **151** (299 mg, 0.85 mmol 98%) as a colorless oil. ^{1}H NMR δ 8.04 (dd, *J*=8.4, 1.8 Hz, 1H), 7.99 (dd, *J*=8.4, 1.8 Hz, 1H), 7.46 (t, *J*=7.8 Hz, 1H); ^{13}C NMR δ 143.6, 139.4, 139.1, 129.3, 125.6, 119.0, 118.4 (q, *J*=320 Hz, C-F); IR (ATR) 3093, 1588, 1540, 1431, 1347, 1207 cm $^{-1}$; HRMS (ESI) calcd for $C_7H_3BrNO_5F_3S$ ($M+Na^+$) 371.8759; found 371.8761.



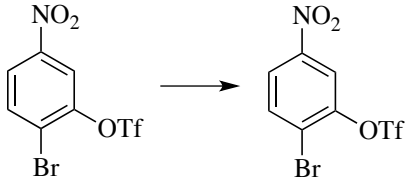
156 **157**

3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene (157): Treatment of **156**[148] (329 mg, 1.51 mmol) in CH_2Cl_2 (10 mL) with pyridine (250 μL, 3.10 mmol) and Tf_2O (300 μL, 1.78 mmol), as described for **163**, gave after chromatography (hexanes/EtOAc, 7:3) **157** (316 mg, 0.90 mmol, 60%) as a red oil. ^{1}H NMR δ 8.44 (t, *J*=1.8 Hz, 1H), 8.11 (t, *J*=1.8 Hz, 1H), 7.80 (t, *J*=1.8 Hz, 1H); ^{13}C NMR δ 149.1, 149.0, 130.7, 126.7, 123.8, 118.5 (q, *J*=319 Hz, C-F),116.0; IR (ATR) 3097, 1732, 1542, 1427, 1344, 1210, 1134 cm $^{-1}$; HRMS (ESI) calcd for $C_7H_3BrNO_5F_3S$ ($M+Na^+$) 371.8760; found 371.8764.



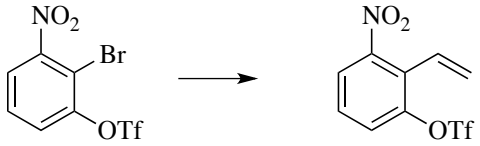
153 **154**

3-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene (154): Treatment of **153**[149] (353 mg, 1.60 mmol) in CH_2Cl_2 (5 mL) with pyridine (260 μL, 3.22 mmol) and Tf_2O (330 μL, 1.95 mmol), as described for **163**, gave after chromatography (hexanes/EtOAc, 7:3) **154** (540 mg, 1.54 mmol, 97%) as a yellow oil. ^{1}H NMR δ 8.30 (d, *J*=2.4 Hz, 1H), 7.88 (dd, *J*=9.0, 2.4 Hz, 1H), 7.36 (d, *J*=9.0 Hz, 1H); ^{13}C NMR δ 141.9, 140.5, 138.2, 129.7, 125.6, 122.3, 118.5 (q, *J*=319 Hz, C-F); IR 3105, 1540, 1431, 1207, 1131 cm^{-1};



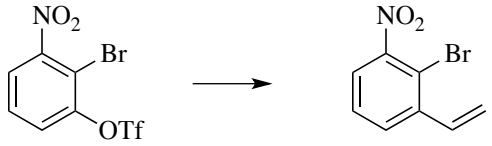
158 **159**

4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene (159): Treatment of **158**[150] (119 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) with pyridine (90.0 μL, 1.12 mmol) and Tf_2O (120 μL, 0.71 mmol), as described for **163**, gave without further purification **159** (188 mg, 0.54 mmol, 98%) as a brown oil. ^{1}H NMR δ 8.22 (d, *J*=2.4 Hz, 1H), 8.16 (dd, *J*=8.4, 2.4 Hz, 1H), 7.93 (d, *J*=8.4 Hz, 1H); ^{13}C NMR δ 147.7, 147.0, 135.2, 124.1, 123.9, 118.5 (q, *J*=319 Hz, C-F), 118.4; IR (ATR) 3104, 1534, 1431, 1348, 1211, 1134 cm $^{-1}$; HRMS (ESI) calcd for $C_7H_3BrNO_5F_3S$ (M+Na$^+$) 373.8739; found 373.8740.



140 **141**

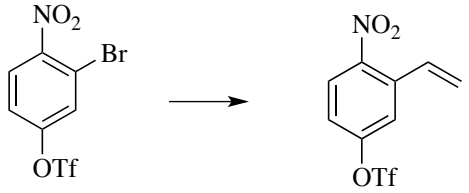
2-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (141):[92] To a solution of PPh_3 (6.5 mg, 0.03 mmol) and $Pd(dba)_2$ (3.7 mg, 0.006 mmol) in dioxane (1.5 mL), stirred for 5 min under an atmosphere N_2, was added **140** (105 mg, 0.30 mmol) and ethenyl(tributyl)stannane (119 mg, 0.38 mmol). The solution was heated at reflux for 24 h. The solvent was removed under reduced pressure. The resulting crude oil was dissolved in EtOAc (10 mL) and washed with NH_4OH (10% aq., 3 x 20 mL), H_2O (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed under reduced pressure. Purification using chromatography (hexanes/EtOAc, 97:3) gave in order of elution, **141** (39.3 mg, 0.13 mmol, 36%) as a yellow oil, a mixture of **140** and dba (9.8 mg), and **169** (40.8 mg, 0.19 mmol, 62%). Spectral data were in accordance with literature values.



140 **170**

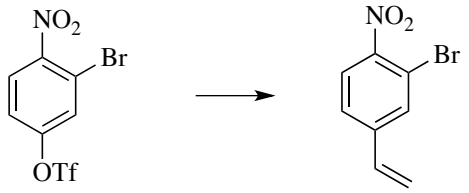
2-Bromo-3-ethenyl-nitrobenzene (170): To a solution of LiCl (40.9 mg, 0.96 mmol) and $Pd(PPh_3)_2Cl_2$ (4.8 mg, 0.007 mmol) in DMF (1.5 mL) under an atmosphere of N_2 was added **140** (110 mg, 0.32 mmol) and ethenyl(tributyl)stannane (123 mg, 0.39 mmol). The resulting solution was stirred at ambient temperature for 24 h. The solution was diluted with EtOAc (10 mL) and washed with NH_4OH (10% aq., 3 x 20 mL), H_2O (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 97:3) affording in order of elution, **11** (18.5 mg, 0.06 mmol, 20%), **170** (27.6 mg, 0.12 mmol, 38%) as a colorless oil. ^{1}H NMR δ 7.70 (d, *J*=7.8 Hz, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.42 (t, *J*=7.8 Hz, 1H), 7.10 (dd, J=16.8, 11.4 Hz, 1H), 5.76 (d, *J*=17.4

Hz, 1H), 5.52 (dd, *J*=10.8 Hz, 1H); ^{13}C NMR δ 147.2, 128.9, 128.3, 126.2, 125.7, 124.8, 123.8, 119.5; IR (ATR) 3110, 1533, 1423, 1358, 1210, 1135 cm $^{-1}$; HRMS (ESI) calcd for $C_8H_6NO_2Br$ (M+Na$^+$) 249.9474; found 249.9473.



167 **171**

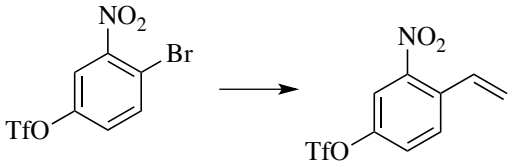
2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (171): Treatment of **167** (67.6 mg, 0.19 mmol) with ethenyl(tributyl)stannane (72.8 mg, 0.23 mmol), PPh_3 (4.5 mg, 0.02 mmol) and $Pd(dba)_2$ (2.2 mg, 0.004 mmol) in dioxane (1.0 mL), as described for **141**, gave after chromatography (hexanes/EtOAc, 97:3) **171** as a colorless oil (47.3 mg, 0.16 mmol, 82%). ^{1}H NMR δ 8.06 (d, *J*= 9.0 Hz, 1H), 7.52 (d, *J*= 2.4 Hz, 1H), 7.34 (dd, *J*= 9.0, 3.0 Hz, 1H), 7.18 (dd, *J*= 16.8, 10.8 Hz, 1H), 5.81 (d, *J*= 17.4 Hz, 1H), 5.63 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 151.7, 146.6, 136.4, 131.1, 127.0, 121.4, 121.3, 121.1, 118.7 (q, *J*= 319 Hz, C-F); IR (ATR) 3118, 1530, 1424, 1350, 1207, 1131 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ (M+Na$^+$) 319.9811; found 319.9809.



167 **172**

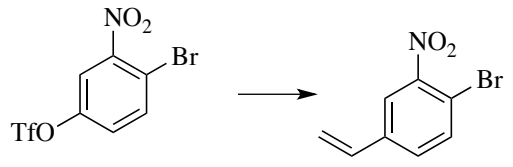
2-Bromo-4-ethenyl-nitrobenzene (172): Treatment of **167** (75.2 mg, 0.22 mmol) with ethenyl(tributyl)stannane (85.5 mg, 0.27 mmol), LiCl (28.1 mg, 0.66 mmol) and

$Pd(PPh_3)_2Cl_2$ (3.6 mg, 0.005 mmol) in DMF (1.0 mL), as described for **170**, gave after chromatography (hexanes/EtOAc, 97:3) a mixture of **172** and **171** (calculated from ^1H NMR spectrum: 18.0 mg of **172**, 0.08 mmol, 37% , 5.8 mg of **171**, 9%) as a yellow oil. ^1H NMR δ 7.86 (d, *J*=7.8 Hz, 1H), 7.74 (d, *J*=1.2 Hz, 1H), 7.45 (dd, *J*=8.4, 1.8 Hz, 1H), 6.69 (dd, *J*= 18.0, 11.4 Hz, 1H), 5.90, (d, *J*=17.4 Hz, 1H), 5.52 (d, *J*=10.8 Hz, 1H); ^{13}C NMR δ 142.9, 136.4, 133.7, 132.6, 126.1, 125.5, 119.3, 115.1; IR (ATR) 3095, 1573, 1526, 1346, 1217, 1139 cm^1; HRMS (ESI) calcd for $C_8H_6NO_2Br$ ($M+Na^+$) 249.9474; found 249.9474.



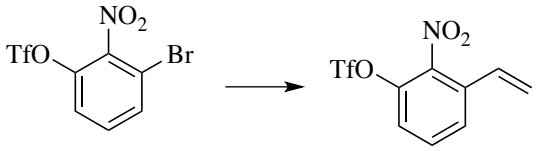
163 **173**

2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (173): Treatment of **163** (110 mg, 0.32 mmol) with ethenyl(tributyl)stannane (134 mg, 0.42 mmol), PPh_3 (6.9 mg, 0.03 mmol) and $Pd(dba)_2$ (3.6 mg, 0.006 mmol) in dioxane (1.5 mL), as described for **11**, gave after chromatography (hexanes/EtOAc, 97:3) **15** (63.3 mg, 0.21 mmol, 68%) as a colorless oil. ^1H NMR δ 7.90 (d, *J*= 2.4 Hz, 1H), 7.74 (d, *J*= 9.0 Hz, 1H), 7.53 (dd, *J*= 9.0, 2.4 Hz, 1H), 7.18 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.79 (d, *J*= 16.8 Hz, 1H), 5.61 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 148, 147.7, 133.8, 131.1, 130.5, 126.2, 121, 118.6 (q, *J*= 319 Hz, C-F), 118; IR (ATR) 3110, 1533, 1426, 1351, 1208, 1133 cm^{-1}; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9810.



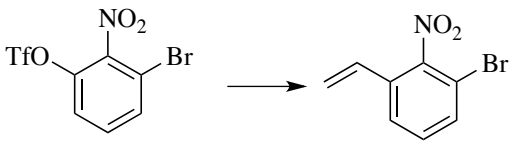
163 **174**

2-Bromo-5-ethenyl-nitrobenzene (174):[151] Treatment of **163** (120 mg, 0.34 mmol) with ethenyl(tributyl)stannane (135 mg, 0.43 mmol), LiCl (48.2 mg, 1.13mmol) and $Pd(PPh_3)_2Cl_2$ (4.8 mg, 0.007 mmol) in DMF (1.5 mL), as described for **170**, gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **174** (27.8 mg, 0.12 mmol, 36%) as a colorless oil and a mixture of **173** and **163** (calculated from ^{1}H NMR spectrum 22 mg, 23% and 20 mg, 17%). Spectral data were in accordance with literature values.



166 **175**

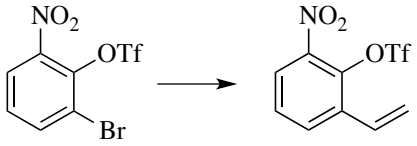
2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (175): Treatment of **166** (104 mg, 0.30 mmol) with ethenyl(tributyl)stannane (121 mg, 0.38 mmol), PPh_3 (6.7 mg, 0.03 mmol) and $Pd(dba)_2$ (3.7 mg, 0.006 mmol) in dioxane (1.5 mL) as described for **141**, gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **176** (2.3 mg, 0.01 mmol, 3%), and **175** (52.9 mg, 0.18 mmol, 60%) as a yellow solid. Spectral data for **175:** mp=38-39 ºC; ^{1}H NMR δ 7.67 (d, *J*= 8.4 Hz, 1H), 7.57 (t, *J*= 8.4 Hz, 1H), 7.41 (dd, *J*= 8.4, 1.2 Hz, 1H), 6.68 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.91 (d, *J*= 17.4 Hz, 1H), 5.61 (d, *J*= 11.4 Hz, 1H); ^{13}C NMR δ 142.0, 140.2, 133.2, 131.6, 128.6, 126.4, 121.9, 121.4, 118.4 (q, *J*= 319 Hz, C-F); IR (ATR) 3090, 1533, 1427, 1361, 1211, 1138 cm $^{-1}$. HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9809.



166 **176**

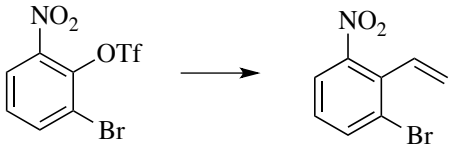
2-Bromo-6-ethenyl-nitrobenzene (176): Treatment of **166** (119 mg, 0.34 mmol) with ethenyl(tributyl)stannane (138 mg, 0.44 mmol), LiCl (45.6 mg, 1.08 mmol) and

$Pd(PPh_3)_2Cl_2$ (5.0 mg, 0.007 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) **176** as an off-white solid (47.1 mg, 0.21 mmol, 61%) (mp=42-44ºC). ^{1}H NMR δ 7.57 (d, *J*=7.8 Hz, 1H), 7.56 (d, *J*=7.8 Hz, 1H), 7.33 (t, *J*=7.8 Hz, 1H), 6.57 (dd, *J*=16.8, 11.4 Hz, 1H), 5.85 (d, *J*=16.8 Hz, 1H), 5.51 (d, *J*=10.8 Hz, 1H); ^{13}C NMR δ 150.1, 132.6, 131.6, 130.9, 129, 125.6, 120.8, 112.9; IR (ATR) 3077, 1557, 1521, 1460, 1365, 1187 cm^1. HRMS (ESI) calcd for $C_8H_6NO_2Br$ ($M+Na^+$) 251.9454; found 251.9454.



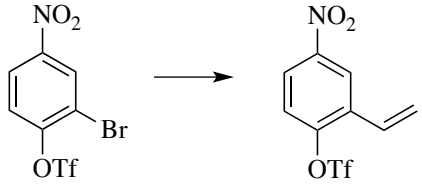
151 **177**

3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (177): Treatment of **151** (135 mg, 0.39 mmol) with ethenyl(tributyl)stannane (129 mg, 0.41 mmol), PPh_3 (8.2 mg, 0.03 mmol) and $Pd(dba)_2$ (4.5 mg, 0.008 mmol) in dioxane (2 mL) before adding as described for **141** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **46** and dicoupled (8.5 mg, 1:1 mixture, 5 mg Tf-coupled, 3.5 mg dicoupled), **149**[92] (22.7 mg mixed with dba), and a mixture of 1**51** and **177** (95.1 mg). The latter fraction was re-chromatographed (hexanes/EtOAc, 97:3) to give in order of elution, **177** as a colorless oil (27.8 mg, 0.09 mmol, 24%) and **151** (12.3 mg, 0.04 mmol, 9%). Analytical data for **177**: ^{1}H NMR δ 7.98 (dd, *J*= 8.4, 1.8 Hz, 1H), 7.91 (dd, *J*= 8.4, 1.8 Hz, 1H), 7.48 (t, *J*= 8.4 Hz, 1H), 6.99 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.95 (d, *J*= 17.4 Hz, 1H), 5.67 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 143.0, 137.8, 134.4, 132, 128.5, 128.0, 125.5, 121.4, 118.3 (q, *J*= 319 Hz, C-F); IR (ATR) 3103, 1539, 1429, 1351, 1210, 1131 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9808.



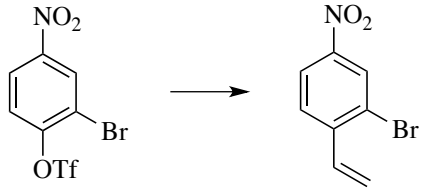
151 **46**

3-Bromo-2-ethenyl-nitrobenzene (46):[36] Treatment of **151** (99.8 mg, 0.29 mmol) with ethenyl(tributyl)stannane (97.5 mg, 0.31 mmol), LiCl (36.6 mg, 0.86 mmol) and $Pd(PPh_3)_2Cl_2$(4.1 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** afforded after chromatography (hexanes/EtOAc, 9:1) in order of elution, **46** as a yellow oil (28.3 mg, 0.12 mmol, 43%), **149**[92] (7.4 mg, 0.03 mmol, 12%), and **151** (5.0 mg, 0.01 mmol, 5%). Spectral data were in accordance with literature values.



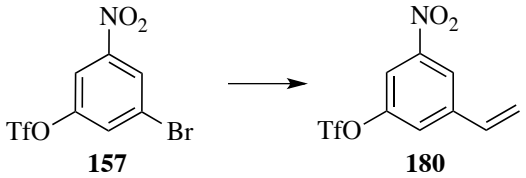
150 **178**

3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene (178): Treatment of **150** (102 mg, 0.29 mmol) with ethenyl(tributyl)stannane (116 mg, 0.37 mmol), PPh_3 (6.5 mg, 0.03 mmol) and $Pd(dba)_2$ (4.1 mg, 0.007 mmol) in dioxane (1.5 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 97:3) order of elution, **178** (19.3 mg, 0.06 mmol, 22%) as a light pink oil, **150** (7.0 mg, 0.02 mmol, 7%), and 148[93] (5.2 mg, 0.02 mmol, 7%). Analytical data for **178**: ^{1}H NMR δ 8.53 (d, *J*= 3.0 Hz, 1H), 8.21 (dd, *J*= 9.0, 2.4 Hz, 1H), 7.48 (d, *J*= 9.0 Hz, 1H), 6.94 (dd, *J*= 17.4, 11.4 Hz, 1H), 6.04 (d, *J*= 17.4 Hz, 1H), 5.70 (d, *J*= 11.4 Hz, 1H); ^{13}C δ 149.9, 147.2, 132.7, 127.3, 124.0, 122.9, 122.7, 121.7, 118.5 (q, *J*= 319 Hz, C-F); IR (ATR) 3107, 1536, 1424, 1347, 1209, 1134 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9809.



150 **179**

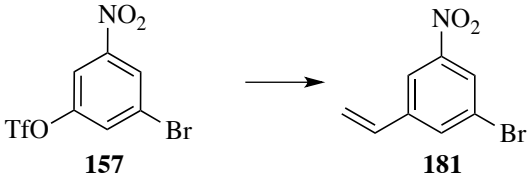
3-Bromo-4-ethenyl-nitrobenzene (179): Treatment of **150** (110 mg, 0.32 mmol) with ethenyl(tributyl)stannane (138 mg, 0.43 mmol), LiCl (42.6 mg, 1.0 mmol) and $Pd(PPh_3)_2Cl_2$ (4.5 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **179** (40.7 mg, 0.18 mmol, 57%) as a yellow oil, **150** (8.7 mg, 0.02 mmol, 8%), and 148 (11.1 mg, 0.05 mmol, 16%). Analytical data for **179**: ^{1}H NMR δ 8.43 (d, *J*=2.4 Hz, 1H), 8.14 (ddd, *J*= 8.4, 2.4, 0.6 Hz, 1H), 7.69 (d, *J*=9.0 Hz, 1H), 7.09 (dd, *J*=17.4, 11.4 Hz, 1H), 5.88 (d, *J*=18.0 Hz, 1H), 5.60 (dd, *J*=10.8, 0.6 Hz, 1H); ^{13}C NMR δ 147.2, 143.7, 134.3, 128.2, 127.1, 123.4, 122.4, 120.9; IR (ATR) 3099, 1520, 1342, 1116, 1035 cm $^{-1}$; HRMS (ESI) calcd for $C_8H_6NO_2Br$ ($M+Na^+$) 251.9454; found 251.9456.



157 **180**

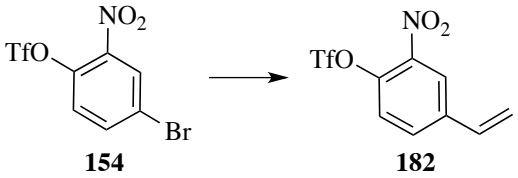
3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene (180): Treatment of **157** (106 mg, 0.30 mmol) with ethenyl(tributyl)stannane (130 mg, 0.41 mmol), PPh_3 (6.4 mg, 0.02 mmol) and $Pd(dba)_2$ (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **157** (4.1 mg, 0.01 mmol, 4%) and **180** (70.0 mg, 0.24 mmol, 78%) as a colorless oil. ^{1}H NMR δ 8.30 (t, *J*= 1.8 Hz, 1H), 8.02 (t, *J*= 1.8 Hz, 1H), 7.61 (t, *J*= 1.8 Hz, 1H), 6.78 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.98 (d, *J*= 17.4 Hz, 1H), 5.61 (d, *J*= 10.8 Hz, 1H); ^{13}C

NMR δ 149.4, 149.2, 141.7, 133.2, 124.6, 120.6, 119.8, 118.6 (q, *J*= 319 Hz, C-F), 115.6; IR (ATR) 3103, 1540, 1425, 1348, 1213, 1132 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9813.



157 **181**

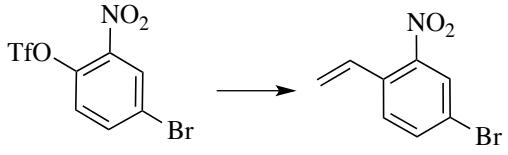
3-Bromo-5-ethenyl-nitrobenzene (181): Treatment of **157** (109 mg, 0.31 mmol) with ethenyl(tributyl)stannane (139 mg, 0.44 mmol), LiCl (45.0 mg, 1.1 mmol) and $Pd(PPh_3)_2Cl_2$ (4.7 mg, 0.007 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) **181** (47.1 mg, 0.21 mmol, 66%) as an off-white solid. mp=37-39 °C; ^{1}H NMR δ 8.23 (t, *J*=1.8 Hz, 1H), 8.17 (t, *J*=1.8 Hz, 1H), 7.83 (t, *J*=1.8 Hz, 1H), 6.71 (dd, *J*=17.4, 10.8 Hz, 1H), 5.91 (d, *J*=17.4 Hz, 1H), 5.50 (d, *J*=11.4 Hz, 1H); ^{13}C NMR δ 149, 140.8, 134.8, 133.6, 125.3, 122.9, 119.6, 118.5; IR (ATR) 3079, 1531, 1339, 1301, 1214 cm^1; HRMS (ESI) calcd for $C_8H_6NO_2Br$ ($M+Na^+$) 251.9454; found 251.9452.



154 **182**

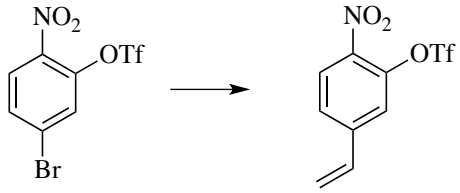
3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene (182): Treatment of **154** (103 mg, 0.29 mmol) with ethenyl(tributyl)stannane (112.4 mg, 0.35 mmol), PPh_3 (6.8 mg, 0.03 mmol) and $Pd(dba)_2$ (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, **154** (10%) followed by **182** as a yellow oil mixed with dibenzylideneacetone (34.6 mg, 0.12 mmol, 44% based on ^{1}H NMR integration). Spectral data from the mixture of **182** and dba: ^{1}H NMR δ

8.15 (d, *J*= 2.4 Hz, 1H), 7.72 (dd, *J*= 9.0, 2.4 Hz, 1H), 7.41 (d, *J*= 9.0 Hz, 1H), 6.75 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.92 (d, *J*= 17.4 Hz, 1H), 5.55 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 141.7, 140.3, 139.2, 133.1, 132.2, 124.3, 123.8, 119.2, 118.5 (q, *J*= 319 Hz, C-F); IR (ATR) 3094, 1541, 1429, 1346, 1205, 1134 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9812.



154 **183**

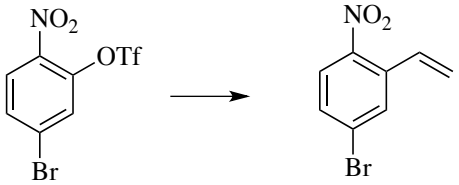
5-Bromo-2-ethenyl-nitrobenzene (183): Treatment of **154** (111 mg, 0.32 mmol) with ethenyl(tributyl)stannane (131 mg, 0.41 mmol), LiCl (44.5 mg, 0.86 mmol) and $Pd(PPh_3)_2Cl_2$ (4.2 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 9:1) **183** as a yellow solid (56.3 mg, 0.25 mmol, 78%). mp=40-41ºC; ^{1}H NMR δ 8.07 (d, *J*=2.4 Hz, 1H), 7.70 (dd, *J*= 8.4, 2.4 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 7.11 (dd, *J*=17.4, 11.4 Hz, 1H), 5.76 (d, *J*=17.4 Hz, 1H), 5.55 (d, *J*=11.4 Hz, 1H); ^{13}C NMR δ 148.0, 136.1, 132.2, 131.5, 129.7, 127.3, 121.4, 119.7; IR (ATR) 3097, 1552, 1514, 1341, 1149 cm $^{-1}$; HRMS (ESI) calcd for $C_8H_6NO_2Br$ ($M+Na^+$) 251.9454; found 251.9455.



168 **184**

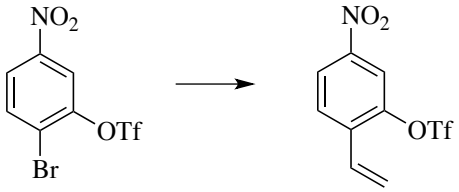
4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene (184): Treatment of **168**[52] (104 mg, 0.29 mmol) with ethenyl(tributyl)stannane (121 mg, 0.38 mmol), PPh_3 (6.8 mg, 0.03 mmol) and $Pd(dba)_2$ (3.4 mg, 0.006 mmol) in dioxane (1.5 mL) as described for **141** gave

after chromatography (hexanes/EtOAc, 97:3) a mixture of **184** and dba (62.3 mg, calculated 55.9 mg, 64% **184** and 6.6 mg dba) as a yellow oil. Analytical data for **184**: ^{1}H NMR δ 8.16 (d, *J*= 8.4 Hz, 1H), 7.55 (dd, *J*= 8.4, 1.8 Hz, 1H), 7.41 (d, *J*= 1.8 Hz, 1H), 6.76 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.97 (d, *J*= 17.4 Hz, 1H), 5.63 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 145.2, 141.9, 140.1, 133.4, 127.1, 126.2, 121.4, 120.9, 118.6 (q, *J*= 319 Hz, C-F); IR (ATR) 3114, 1587, 1529, 1429, 1341, 1209 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ ($M+Na^+$) 319.9811; found 319.9808.



168 **185**

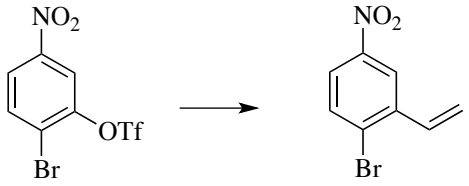
4-Bromo-2-ethenyl-nitrobenzene (185):[152] Treatment of **168** (99.5 mg, 0.29 mmol) with ethenyl(tributyl)stannane (98.1 mg, 0.31 mmol), LiCl (37.0 mg, 0.87 mmol) and $Pd(PPh_3)_2Cl_2$ (4.0 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, **185** (11.0 mg, 0.05 mmol, 17%) as an off-white solid, **168** (22.9 mg, 0.07 mmol, 22%) and **184** (19.4 mg, 0.07 mmol, 23%). Spectral data for **185** were in accordance with literature values.



159 **186**

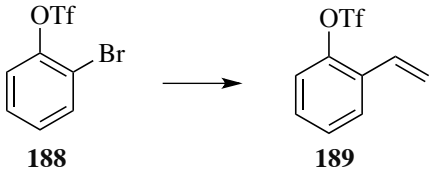
4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene (186): Treatment of **159** (74.7 mg, 0.21 mmol) with ethenyl(tributyl)stannane (83.2 mg, 0.26 mmol), PPh_3 (5.0 mg, 0.02 mmol) and $Pd(dba)_2$ (2.7 mg, 0.005 mmol) in dioxane (1.5 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **159** (14.8 mg, 0.04

mmol, 20%) and **186** (30.2 mg, 0.10 mmol, 48%) as a yellow oil. Analytical data for **186**: ^{1}H NMR δ 8.25 (dd, *J*= 8.4, 1.8 Hz, 1H), 8.17 (d, *J*= 1.8 Hz, 1H), 7.83 (d, *J*= 8.4 Hz, 1H), 6.98 (dd, *J*= 17.4, 10.8 Hz, 1H), 6.05 (d, *J*= 17.4 Hz, 1H), 5.75 (d, *J*= 10.8 Hz, 1H); ^{13}C NMR δ 147.4, 146, 137.5, 127.9, 127.6, 123.3, 122.9, 118.5 (q, J C-F=319 Hz, C-F), 117.8; IR (ATR) 3118, 1528, 1425, 1346, 1210, 1132 cm $^{-1}$; HRMS (ESI) calcd for $C_9H_6NO_5F_3S$ (M+Na$^+$) 319.9811; found 319.9809.



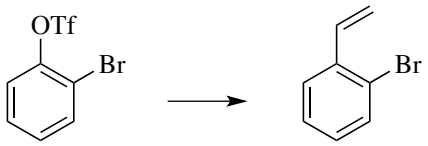
159 **187**

4-Bromo-3-ethenyl-nitrobenzene (187): Treatment of **159** (85.9 mg, 0.25 mmol) with ethenyl(tributyl)stannane (98.2 mg, 0.31 mmol), LiCl (32.2 mg, 0.76 mmol) and $Pd(PPh_3)_2Cl_2$ (3.6 mg, 0.005 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **187** (3.8 mg, 0.02 mmol, 7%) as an off-white solid, **159** (27.0 mg, 0.08 mmol, 31%) and **186** (22.4 mg, 0.08 mmol, 31%). Spectral data for **186**: mp=38-40 ºC; ^{1}H NMR δ 8.39 (d, *J*=2.4 Hz, 1H), 7.97 (dd, *J*=8.4, 2.4 Hz, 1H), 7.74 (d, *J*=9.0 Hz, 1H), 7.06 (dd, *J*=17.4, 10.8 Hz, 1H), 5.99 (d, *J*=17.4 Hz, 1H), 5.56 (d, *J*=10.8 Hz, 1H); ^{13}C NMR δ 143.5, 139.1, 134.2, 133.9, 131.4, 123.1, 121.5, 119.7; IR (ATR) 3099, 2926, 1525, 1341, 1030 cm^{1}; HRMS (ESI) calcd for $C_8H_6NO_2Br$ (M+Na$^+$) 251.9454; found 251.9452.



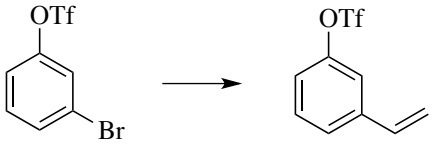
188 **189**

2-ethenyl-trifluoromethanesulfonyloxybenzene (189): Treatment of **188** (96.5 mg, 0.32 mmol) with ethenyl(tributyl)stannane (124 mg, 0.39 mmol), PPh_3 (7.2 mg, 0.03 mmol) and $Pd(dba)_2$ (3.5 mg, 0.006 mmol) in dioxane (1 mL) as described for **141** afforded after chromatography (hexanes/EtOAc, 97:3) a mixture of **189** and unreacted **188** (32.0 mg) (calculated from ^{1}H NMR spectrum 8.0 mg, 10% and 24.0 mg, 24%) as a colorless oil. ^{1}H NMR d 7.65 (dd, *J*=7.2, 2.4 Hz, 1H), 7. (dd, *J*=8.4, 1.8 Hz, 1H), 7.48 (t, *J*=8.4 Hz, 1H), 6.93 (dd, *J*=17.4, 11.4 Hz, 1H), 5.85 (dd, *J*=17.4, 0.6 Hz, 1H), 5.49 (d, *J*=10.8, 0.6 Hz, 1H); ^{13}C NMR d 146.9, 131.1, 129.3, 128.9, 128.4, 127.3, 121.6, 118.6, 118.5 (q, *J*=319.1 Hz, C-F); IR (ATR) 2963, 1469, 1258, 1135, 875 cm $^{-1}$.



188 **190**

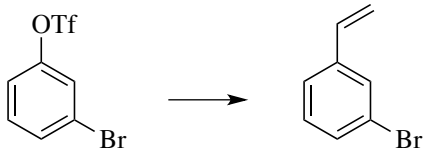
2-ethenyl-bromobenzene (190): Treatment of **188** (88.3 mg, 0.25 mmol) with vinyl(tributyl)stannane (98.0 mg, 0.31 mmol), LiCl (32.2 mg, 0.76 mmol) and $Pd(PPh_3)_2Cl_2$ (3.8 mg, 0.005 mmol) in DMF (1 mL) as described for **170** afforded crude yellow oil (108 mg) which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled **190** to bromine-coupled **189**.



143 **191**

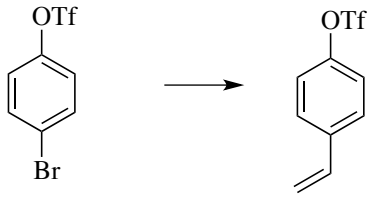
3-ethenyl-trifluoromethanesulfonyloxybenzene (191): Treatment of **143** (105 mg, 0.34 mmol) with vinyl(tributyl)stannane (127 mg, 0.40 mmol), PPh_3 (7.6 mg, 0.03 mmol), and

$Pd(dba)_2$ (4.0 mg, 0.007 mmol) in dioxane (1.5 mL) as described for **141** afforded after chromatography (hexanes/ethyl acetate, 97:3) a mixture of **191** and unreacted **143** (49.2 mg) (calculated from ^{1}H NMR spectrum 28.8 mg, 33% and 20.2 mg, 19%) as a colorless oil. ^{1}H NMR d 7.40 (m, 2H), 7.29 (d, *J*=0.6 Hz, 1H), 7.15 (dt, *J*=7.2, 1.8 Hz, 1H), 6.60 (dd, *J*=17.4, 10.8 Hz, 1H), 5.80 (d, *J*=18.0 Hz, 1H), 5.38 (d, *J*=10.8 Hz, 1H); ^{13}C NMR d 149.9, 140.3, 135.0, 130.3, 126.1, 120.2, 118.8, 118.7 (q, *J*=319.1 Hz, C-F), 116.5; IR (ATR) 3103, 1539, 1429, 1351, 1210, 1131 cm $^{-1}$.



143 **192**

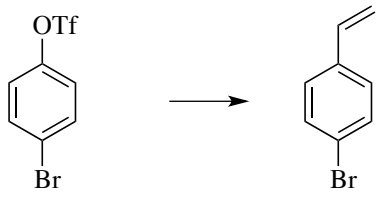
3-bromostyrene (192): Treatment of **143** (108 mg, 0.36 mmol) with vinyl(tributyl)stannane (141 mg, 0.44 mmol), LiCl (45.6 mg, 1.08 mmol) and $Pd(PPh_3)_2Cl_2$ (5.4 mg, 0.008 mmol) in DMF (1.5 mL) as described for **170** afforded crude yellow oil (175 mg) which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled **192** to bromine-coupled **191**.



137 **138**

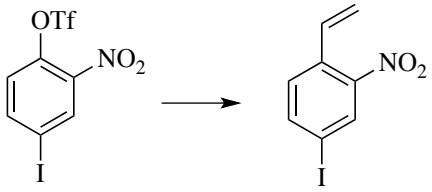
4-ethenyl-trifluoromethanesulfonyloxybenzene (138)[90]: Treatment of **137** (102 mg, 0.34 mmol) with vinyl(tributyl)stannane (128 mg, 0.40 mmol), PPh_3 (7.5 mg, 0.03 mmol), and $Pd(dba)_2$ (4.3 mg, 0.007 mmol) in dioxane (1.5 mL) as described for **141**

afforded after chromatography (hexanes/ethyl acetate, 97:3) **138** (25.2 mg, 0.10 mmol, 30%) as a colorless oil. Spectral data were in accordance with literature values.



137 **139**

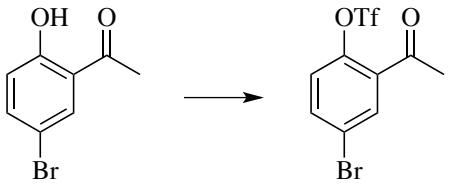
4-bromostyrene (139)[90]: Treatment of **137** (108 mg, 0.35 mmol) with vinyl(tributyl)stannane (141 mg, 0.44 mmol), LiCl (45.5 mg, 1.07 mmol) and $Pd(PPh_3)_2Cl_2$ (4.7 mg, 0.007 mmol) in DMF (1.5 mL) as described for **170** afforded crude yellow oil which was purified by column chromatography (hexanes/ethyl acetate, 9:1), however, the product reacted on the silica gel so no product was isolated. Crude spectral data were in accordance with literature values with a 6:1 ratio of triflate-coupled **139** to bromine-coupled **138**.



196 **198**

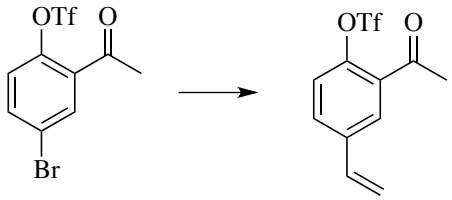
3-Iodo-6-ethenyl-nitrobenzene (198): Treatment of **196** (116 mg, 0.29 mmol) with ethenyl(tributyl)stannane (120 mg, 0.38 mmol), LiCl (39.7 mg, 0.94 mmol) and $Pd(PPh_3)_2Cl_2$ (4.1 mg, 0.006 mmol) in DMF (1.5 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 97:3) in order of elution, **198** (3.2 mg, 0.01 mmol, 4%) as a brown oil, 195 (8.7 mg, 0.03 mmol, 14%), and a mixture of **196** and **197** (67.1 mg). Spectral data for **198**: ^{1}H NMR δ 8.25 (d, *J*=1.8 Hz, 1H), 7.89 (dd, *J*=7.8, 1.8 Hz, 1H), 7.35 (d, *J*=7.8 Hz, 1H), 7.10 (dd, *J*=16.8, 10.8 Hz, 1H), 5.77 (d, *J*=16.8 Hz, 1H), 5.52 (d,

J=10.8 Hz, 1H); ^{13}C NMR δ 148.0, 142.0, 133.0, 132.8, 131.6, 129.8, 119.7, 91.8; IR (ATR) 3094, 2925, 1519, 1341, 1261, 1086 cm $^{-1}$; HRMS (ESI) calcd for $C_8H_6NO_2I$ (M+Na$^+$) 297.9335; found 297.9333.



200 **201**

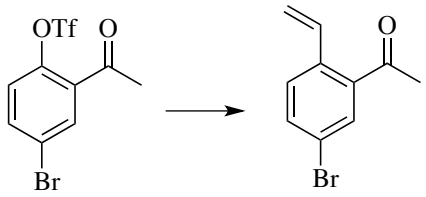
3-Bromo-6-trifluoromethanesulfonyloxy acetophenone (201): Treatment of **200** (381 mg, 1.77 mmol) in CH_2Cl_2 (10 mL) with pyridine (275 μL, 3.41 mmol) and Tf_2O (325 μL, 1.92 mmol) as described for **163,** gave without further purification **201** (590 mg, 1.70 mmol, 96%) as an orange oil. ^{1}H NMR δ 7.92 (d, *J*= 2.4 Hz, 1H), 7.72 (dd, *J* =8.4, 2.4 Hz, 1H), 7.23 (d, *J*= 8.4 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR d 195.1, 145.5, 136.4, 133.5, 133.4, 124.3, 122.0, 118.4 (q, *J*=320 Hz, C-F), 29.2; IR (ATR) 3101, 1701, 1424, 1202, 1133 cm $^{-1}$.



201 **202**

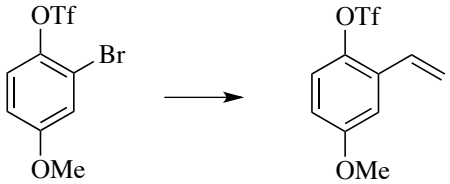
3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone (202): Treatment of **201** (101 mg, 0.29 mmol) with ethenyl(tributyl)stannane (116 mg, 0.37 mmol), PPh_3 (6.4 mg, 0.02 mmol) and $Pd(dba)_2$ (3.8 mg, 0.007 mmol) in dioxane (2 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 9:1) **202** (11.6 mg, 0.04 mmol, 14%) as a colorless oil. ^{1}H NMR δ 7.78 (d, *J*= 2.4 Hz, 1H), 7.61 (dd, *J*= 8.4, 2.4 Hz, 1H), 7.30 (d, *J*= 8.4 Hz, 1H), 6.73 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.83 (d, *J*= 17.4 Hz, 1H), 5.44 (d, *J*=

10.8 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR δ 196.6, 145.9, 138.1, 134.3, 132.3, 130.7, 128.3, 122.9, 118.5 (q, *J*= 319 Hz, C-F), 117.3, 29.6; IR (ATR) 3096, 1698, 1421, 1202, 1134 cm^{-1};



201 **203**

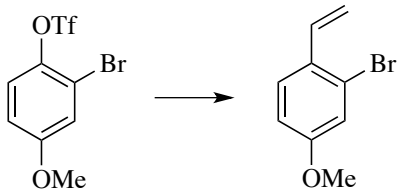
6-Ethenyl-3-bromoacetophenone (203): Treatment of **201** (112 mg, 0.32 mmol) with ethenyl(tributyl)stannane (129 mg, 0.41 mmol), LiCl (43.5 mg, 1.03 mmol) and $Pd(PPh_3)_2Cl_2$ (4.8 mg, 0.007 mmol) in DMF (2 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 8:2) **203** (42.6 mg, 0.19 mmol, 58%) as a colorless oil. ^{1}H NMR δ 7.73 (d, *J*=1.8 Hz, 1H), 7.57 (dd, *J*=8.4, 1.8 Hz, 1H), 7.43 (d, *J*=8.4 Hz, 1H), 7.09 (dd, *J*=17.4, 10.8 Hz, 1H), 5.64 (dd, *J*=17.4, 1.2 Hz, 1H), 5.37 (dd, *J*=11.4, 1.2 Hz, 1H), 2.56 (s, 3H); ^{13}C NMR δ 200.5, 138.9, 136.4, 134.7, 134.4, 131.3, 129.1, 121.1, 117.4, 29.8; IR (ATR) 3088, 1686, 1472, 1355, 1235, 830 cm $^{-1}$;



208 **209**

3-Ethenyl-4-trifluoromethanesulfonyloxy anisole (209): Treatment of **208**[153] (106 mg, 0.32 mmol) with vinyl(tributyl)stannane (126 mg, 0.40 mmol), PPh_3 (7.0 mg, 0.03 mmol) and $Pd(dba)_2$ (3.7 mg, 0.006 mmol) in dioxane (2 mL) as described for **141** gave after chromatography (hexanes/EtOAc, 9:1) **209** (29.6 mg, 0.10 mmol, 33%) as a colorless oil. ^{1}H NMR δ 7.18 (d, *J*= 9.0 Hz, 1H), 7.09 (d, *J*= 3.0 Hz, 1H), 6.89 (dd, *J*= 17.4, 11.4 Hz, 1H), 6.84 (dd, *J*= 9.0, 3.0 Hz, 1H), 5.83 (d, *J*= 18.0 Hz, 1H), 5.49 (d, *J*= 11.4 Hz, 1H),

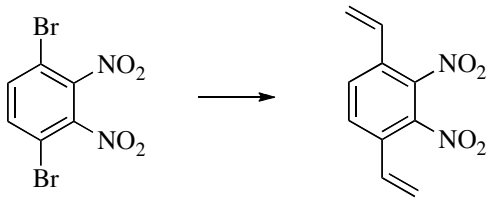
3.84 (s, 1H); ^{13}C NMR δ 158.9, 140.5, 132.1, 129.1, 122.6, 118.6, 118.3 (q, *J*= 319 Hz, C-F), 114.5, 111.6, 55.7; IR (ATR) 2968, 1485, 1419, 1206, 1137, 868 cm $^{-1}$;



208 **210**

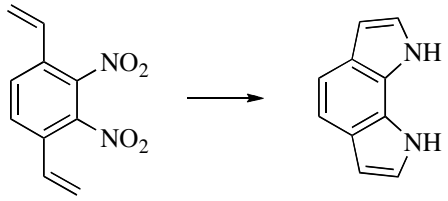
3-Bromo-4-ethenylanisole (210):[154] Treatment of **208** (103 mg, 0.31 mmol) with ethenyl(tributyl)stannane (119 mg, 0.38 mmol), LiCl (38.9 mg, 0.92 mmol) and $Pd(PPh_3)_2Cl_2$ (4.5 mg, 0.006 mmol) in DMF (2 mL) as described for **170** gave after chromatography (hexanes/EtOAc, 9:1) in order of elution, **210** (26.3 mg, 0.12 mmol, 43%) as an orange oil and **209** (3.3 mg, 0.01 mmol, 4%). Spectral data were in accordance with literature values.

7.4: Supporting Information for Chapter 5: Pyrroloindoles



251 **241**

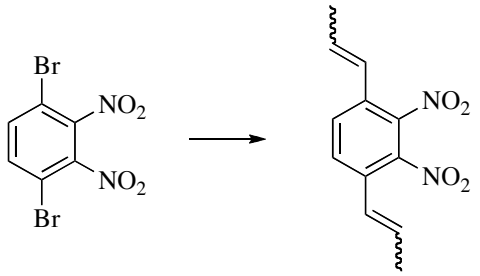
2,3-dinitro-1,4-ethenylbenzene (241): To a solution of PPh_3 (42.3 mg, 0.16 mmol) and $Pd(dba)_2$ (14.8 mg, 0.03 mmol) in toluene (5 mL) were added **251** (99.2 mg, 0.30 mmol) and a solution of tributyl(vinyl) stannane (274.8 mg, 0.87 mmol) in toluene (2 mL). Mixture heated at 110°C for 68 hours. Resulting brown solution filtered through Celite, diluted with EtOAc (20 mL), washed with NH_4OH (10% aq, 3x30 mL), H_2O (30 mL), then brine (30 mL). Organic layer dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. The resulting crude brown oil was purified using column chromatography (hexanes:EtOAc, 8:2) to afford **241** (32.5 mg, 0.15 mmol, 49%) as a yellow solid. ^1H NMR ($CDCl_3$) δ 7.78 (s, 2H), 6.74 (dd, 2H, *J*=17.5, 11.1 Hz), 5.93 (d, 2H, *J*= 17.2 Hz), 5.64 (d, 2H, *J*= 11.1 Hz); HRMS (ESI) calcd for $C_{10}H_8N_2O_4Na$ ($M+Na^+$) 243.0376, found 243.0375.



241 **218**

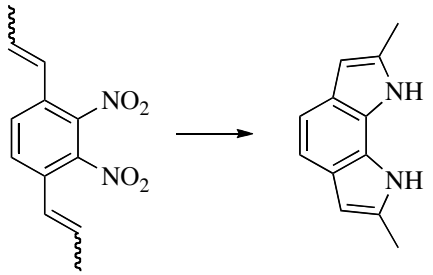
1,8-dihydropyrrolo[3,2-*g*]indole (218)[103]: In an oven-dried ACE glass pressure tube was mixed **241** (31.5 mg, 0.14 mmol), $Pd(OAc)_2$ (3.2 mg, 0.01 mmol), 1,10-phenanthroline (1.8 mg, 0.01 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The

tube was then allowed to heat at 120 ^{0}C for 143 h. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude material which was subsequently diluted with H_2O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. Resulting crude brown oil purified by chromatography (hexanes: EtOAc, 85:15, then 7:3) to give **218** (12.3 mg, 0.08 mmol, 56%) as a dark grey solid. HRMS (ESI) calcd for $C_{10}H_8N_2H$ ($M+H^+$) 157.0760, found 157.0758.



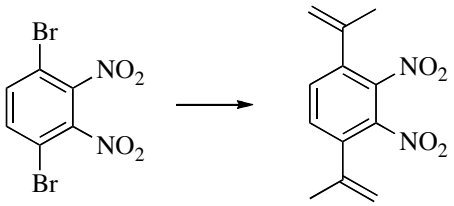
251 **255**

2,3-dinitro-1,4-di(prop-1-enyl)benzene (255): To a solution of PPh_3 (56.7 mg, 0.22 mmol) and $Pd(dba)_2$ (20.9 mg, 0.04 mmol) in toluene (5 mL) were added **251** (154 mg, 0.47 mmol) and a solution of tributyl(prop-1-enyl)stannane (430 mg, 1.3 mmol) in toluene (5 mL). Mixture heated at 110^{o}C for 72 hours. Resulting brown solution filtered through Celite, diluted with EtOAc (20 mL), washed with NH_4OH (10% aq, 3x30 mL), H_2O (30 mL), then brine (30 mL). Organic layer dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. The resulting crude brown oil was purified using column chromatography (hexanes:EtOAc, 9:1) to afford **255** (75.8 mg, 0.31 mmol, 65%) as a yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.50 (s, 2H), 6.42 (dd, *J*= 11.4, 1.8 Hz, 2H), 6.08 (dq, 2H, *J*= 11.4, 6.6 Hz), 1.78 (dd, 6H, *J*= 7.2, 1.8 Hz); ^{13}C NMR δ 133.5, 132.9, 131.0, 122.4, 14.8; IR (ATR) 3041, 2954, 1649, 1528, 1358, 859, 820 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}N_2O_4Na$ ($M+Na^+$) 271.0689, found 271.0688.



255 **256**

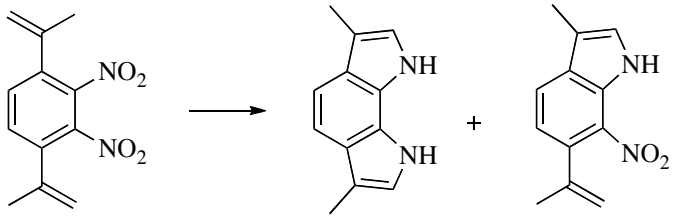
2,7-dimethyl-1,8-dihydropyrrolo[3,2-*g*]indole (256)[103]**:** In an oven-dried ACE glass pressure tube was mixed **255** (29.9 mg, 0.12 mmol), $Pd(OAc)_2$ (3.1 mg, 0.01 mmol), 1,10-phenanthroline (2.9 mg, 0.01 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The tube was then allowed to heat at 120 ^{0}C for 20 h until all starting material was consumed as judged by TLC. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude which was subsequently diluted with H_2O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. Resulting crude brown oil purified by chromatography (hexanes: EtOAc, 8:2) to give **256** (9.5 mg, 0.05 mmol, 43.0%) as a dark grey solid. HRMS (ESI) calcd for $C_{12}H_{12}N_2H$ ($M+H^+$) 185.1073, found 185.1071.



251 **257**

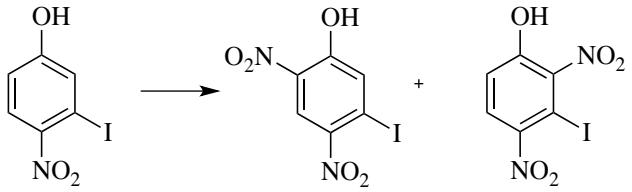
2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene (257): To a solution of PPh_3 (64.9 mg, 0.25 mmol) and $Pd(dba)_2$ (28.2 mg, 0.05 mmol) in toluene (10 mL) were added **251** (198 mg, 0.61 mmol) and a solution of tributyl(prop-1-en-2-yl)stannane (487 mg, 1.47 mmol). Mixture heated at 110 ^{o}C for 45 hours. Resulting brown solution filtered through Celite,

diluted with EtOAc (30 mL), washed with NH_4OH (10% aq, 3x30 mL), H_2O (30 mL), then brine (30 mL). Organic layer dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. The resulting crude green residue was purified using column chromatography (hexanes:EtOAc, 7:3) to afford **257** (93.0 mg, 0.37 mmol, 64%) as a yellow solid (mp= 135-137 ^oC). ^1H NMR ($CDCl_3$) δ 7.44 (s, 2H), 5.27 (m, 2H), 5.03 (m, 2H), 2.11 (m, 6H); ^{13}C NMR δ 142.1, 139.2, 137.4, 131.5, 118.1, 23.1; IR (ATR) 3094, 2973, 1643, 1543, 1526, 1355, 911, 847 cm^{-1}



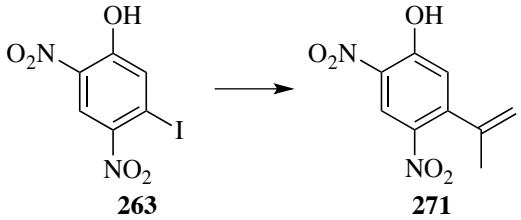
257 **258** **259**

3,6-dimethyl-1,8-dihydropyrrolo[3,2-*g*]indole (258)[103]**:** In an oven-dried ACE glass pressure tube was mixed **257** (26.3 mg, 0.11 mmol), $Pd(dba)_2$ (4.8 mg, 0.008 mmol), PPh_3 (12.1 mg, 0.05 mmol), and anhydrous DMF (3 mL). The tube was fitted with a pressure head, and the solution was saturated with CO (four cycles, 6 atm). The tube was heated at 120 ^0C for 96 hours until all starting material was consumed as judged by TLC. The solvent was then removed by a bulb-to-bulb resulting in a dark brown crude material which was subsequently diluted with H_2O (15 mL) and extracted with EtOAc (3x25 mL). Combined organic layers dried ($MgSO_4$), filtered, then solvent removed under reduced pressure. Resulting crude brown oil was purified by chromatography (hexanes: EtOAc, 8:2) to afford in order of elution **258** (5.1 mg, 0.03 mmol, 25%) as a dark grey solid and **259** (12.9 mg, 0.06 mmol, 54%) as a brown solid (mp= 72-74 ^oC) . HRMS of **258** (ESI) calcd for $C_{12}H_{12}N_2H$ ($M+H^+$) 185.1073, found 185.1071.



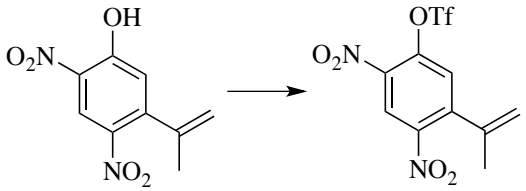
5-iodo-2,4-dinitrophenol (263) and 3-iodo-2,4-dinitrophenol (268)

To an ice-cooled solution of **265**(256 mg, 1.45 mmol) in H_2SO_4 (4 mL) was added $NaNO_3$ (215 mg, 2.53 mmol). The resulting brown solution was stirred at ambient temperature (4 hours). Solution quenched with ice, then extracted with EtOAc (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, then the solvents were removed under reduced pressure. Purification using column chromatography (Hexanes/EtOAc, 8:2) afforded in order of elution **263** (307 mg, 0.99 mmol, 69%) and **268** (103 mg, 0.33 mmol, 23%). Spectral data for **263**: ^{1}H NMR (600 MHz) δ 10.74 (s, 1H), 8.78 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (150 MHz) δ 155.9, 134.1, 133.7, 122.7, 122.5, 97.2; IR (ATR) 3268, 3098, 1607, 1567, 1520, 1315 cm^{-1}; HRMS (ESI) calcd for $C_6H_3N_2O_4I$ (M-H) 308.90084, found 308.90105.Spectral data for **268** ^{1}H NMR (600 MHz) δ 7.83 (d, *J*= 9.0 Hz, 1H), 7.24 (d, *J*= 9.0 Hz, 1H); ^{13}C NMR (150 MHz) δ 152.4, 145.2, 127.9, 127.2, 117.3, 81.5; IR (ATR) 3232, 3097, 1525, 1336, 1296 cm^{-1};



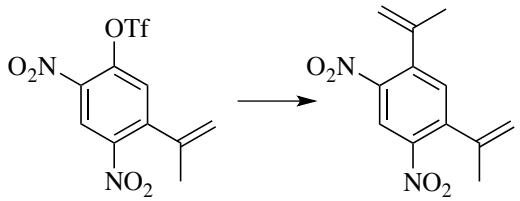
2,4-dinitro-5-(prop-1-en-2-yl)phenol (271): To a solution of **263** (363 mg, 1.17 mmol) in dioxane (4 mL) was added PPh_3 (24.7 mg, 0.09 mmol), $Pd(dba)_2$ (13.3 mg, 0.02 mmol), CuI (225 mg, 1.18 mmol), BHT (26.8 mg, 0.12 mmol), and tributyl(prop-1-en-2-yl)stannane (396 mg, 1.2 mmol). The resulting solution was heated at 105 °C (16 hours).

Solvents were removed under reduced pressure, then the residue was purified using column chromatography (hexanes/EtOAc, 1:1 with 5% Et_3N followed by hexanes/EtOAc, 9:1 with 5% AcOH) to afford **271** (44.7 mg, 0.20 mmol, 17%) as a brown solid. ^{1}H NMR (600 MHz) δ 10.83 (s, 1H), 8.83 (s, 1H), 7.11 (s, 1H), 5.26 (s, 1H), 5.02 (s, 1H), 2.08 (s, 3H); ^{13}C NMR (150 MHz) δ 157.2, 148.8, 141.5, 140.1, 131.4, 122.8, 121.9, 116.6, 22.7. IR (ATR) 3115, 2960, 1582, 1330 cm^{-1}; HRMS (ESI) calcd for $C_9H_8N_2O_5$ (M-H) 223.03550, found 223.03562.



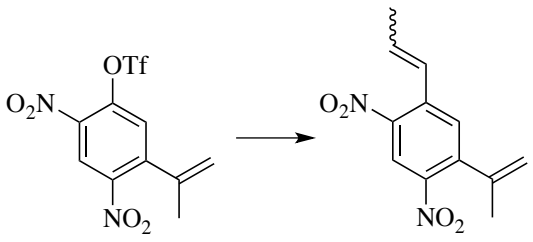
271 **261**

2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (261): To an ice-cooled solution of **271** (118 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) was added pyridine (90.0 μL, 1.11 mmol), and Tf_2O (100 μL, 0.59 mmol) and the solution stirred while warming to ambient temperature over 30 minutes. Solvents were removed under reduced pressure and the crude product purified using column chromatography (hexanes/EtOAc, 85:15) to afford **261** (160 mg, 45 mmol, 86%) as a yellow oil. ^{1}H NMR (600 MHz) δ 8.71 (s, 1H), 7.45 (s, 1H), 5.39 (d, *J*= 1.8 Hz, 1H), 5.11 (s, 1H), 2.13 (s, 3H); ^{13}C (150 MHz) δ 146.3, 146.2, 143.1, 139.8, 139.6, 126.7, 123.2, 118.9, 118.5 (q, *J*= 319 Hz), 22.5; IR (ATR) 3144, 2928, 1590, 1538, 1435, 1340 cm^{-1};



261 **260**

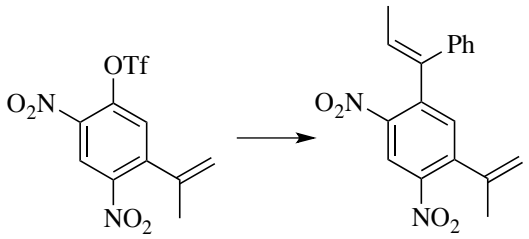
1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (260): To a solution of **261** (149 mg, 0.34 mmol) in DMF (2 mL) was added $PdCl_2(PPh_3)_2$ (5.3 mg, 0.007 mmol), LiCl (50.3 mg, 1.19 mmol), BHT (7.0 mg, 0.03 mmol), and tributyl(prop-1-en-2-yl)stannane (293 mg, 0.88 mmol). The resulting solution was heated at 60 ºC (16 hours). The resulting brown solution was quenched with NH_4OH (10% aq., 15 mL), then extracted with EtOAc (20 mL). The organic layer was washed with NH_4OH (10% aq., 20 mL), H_2O (20 mL), and brine (20 mL), then dried ($MgSO_4$), filtered, then solvents were removed under reduced pressure. Purification using column chromatography (hexanes/EtOAc, 85:15) afforded **260** (73.3 mg, 0.29 mmol, 87%) as a white solid (mp= 77-78 ºC). ^{1}H NMR (600 MHz) δ 8.45 (s, 1H), 7.33 (s, 1H), 5.29 (d, *J*= 1.2 Hz, 2H), 5.03 (d, *J*= 1.2 Hz, 2H), 2.11 (d, *J*= 1.2 Hz, 6H); ^{13}C NMR (150 MHz) δ 146.3, 143.3, 141.1, 133.0, 120.6, 117.0, 22.9; IR (ATR) 3101, 2983, 1584, 1525, 1345 cm^{-1};



261 **274**

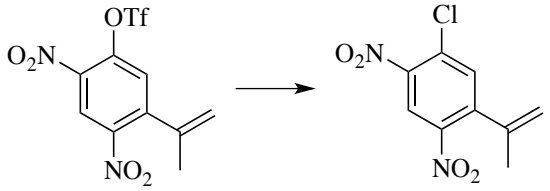
1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene (274): Reaction of **261** (86.3 mg, 0.24 mmol), tributyl(prop-1-enyl)stannane (117 mg, 0.35 mmol), $PdCl_2(PPh_3)_2$ (4.3 mg, 0.006 mmol), LiCl (38.6 mg, 0.91 mmol) in DMF (2 mL) as described for **260** afforded after purification using column chromatography (hexanes/EtOAc, 9:1) **274** (52.1

mg, 0.21 mmol, 87%) as a yellow oil (~2:1 ratio of Z/E isomers). ^{1}H NMR for *Z*-isomer (400 MHz) δ 8.61 (s, 1H), 7.38 (s, 1H), 6.76 (dq, *J*= 11.6, 2.0 Hz, 1H), 6.11 (dq, *J*= 11.6, 7.2 Hz, 1H), 5.29 (t, *J*= 1.6 Hz, 1H), 5.03 (t, *J*= 1.2 Hz, 1H), 2.11 (t, *J*= 1.2 Hz, 3H), 1.80 (dd, *J*= 7.6, 2.0 Hz, 3H); ^{1}H NMR for *E*-isomer (400 MHz) δ 8.52 (s, 1H), 7.55 (s, 1H), 6.94 (dq, *J*= 15.6, 1.6 Hz, 1H), 6.47 (dq, *J*= 15.6, 6.8 Hz, 1H), 5.28 (t, *J*=1.2 Hz, 1H), 5.02 (t, *J*= 1.2 Hz, 1H), 2.11 (t, *J*=0.8 Hz, 3H), 2.01 (dd, *J*= 7.2, 2.0 Hz, 3H); ^{13}C NMR (combined isomers, 100 MHz) δ 146.2, 145.8, 145.4, 145.2, 143.4, 143.1, 141.6, 141.3, 137.6, 137.1, 136.0, 134.3, 131.7, 130.7, 124.7, 124.5, 121.3, 121.2, 116.9, 116.6, 23.0, 22.9, 19.1, 14.6; IR (ATR) 3105, 2978, 1581, 1520, 1341 cm^{-1};



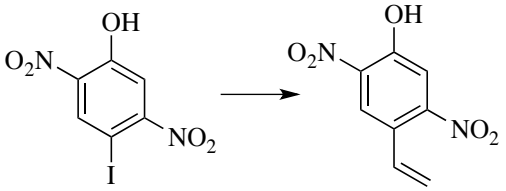
261 **276**

(*E*)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene (276): Reaction of **261** (83.5 mg, 0.23 mmol), (*E*)-tributyl(1-phenylprop-1-enyl)stannane (117 mg, 0.29 mmol), PPh_3 (13.4 mg, 0.05 mmol), and $Pd(dba)_2$ (7.3 mg, 0.01 mmol) in DMF (2 mL) at 50 °C as described for **260** afforded after purification using column chromatography (hexanes/EtOAc, 85:15) **276** (34.9 mg, 0.11 mmol, 46%) as a yellow solid (mp= 92-94 °C). ^{1}H NMR (400 MHz) δ 8.33 (s, 1H), 7.39 (s, 1H), 7.34-7.29 (m, 3H), 7.17-7.15 (m, 2H), 6.01 (q, *J*= 7.6 Hz, 1H), 5.27 (m, 1H), 5.03 (m, 1H), 2.11 (m, 3H), 1.93 (d, *J*= 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 147.3, 146.0, 143.1, 142.8, 141.2, 137.2, 136.4, 134.5, 129.8, 129.7, 128.2, 127.9, 120.7, 117.0, 23.0, 15.7; IR (ATR) 2954, 1583, 1525, 1346 cm^{-1};



261 **273**

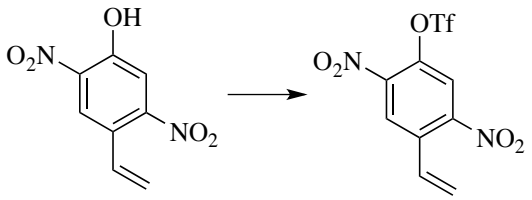
1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene (273): To a solution of **261** (198 mg, 0.55 mmol) in DMF (1 mL) was added LiCl (79.0 mg, 1.86 mmol) and the solution stirred at 60 ºC (8 hours). The resulting solution was diluted with EtOAc (15 mL) and washed with H_2O (5 x 20 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed. Purification using column chromatography (hexanes/EtOAc, 7:3) afforded **273** (64.2 mg, 0.26 mmol, 48%) as a white solid (mp= 128-130 ºC). ^{1}H NMR (400 MHz) δ 8.50 (s, 1H), 7.59 (s, 1H), 5.33 (s, 1H), 5.07 (s, 1H), 2.11 (s, 3H); ^{13}C NMR (100 MHz) δ 145.8, 145.7, 143.9, 140.1, 134.2, 131.7, 122.1, 117.8, 22.6; IR (ATR) 3091, 1593, 1568, 1507, 1338 cm^{-1};



279 **278**

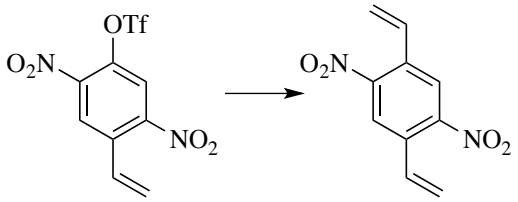
2,5-dinitro-4-ethenylphenol (278): Reaction of **279**[129] (122 mg, 0.39 mmol), PPh_3 (10.3 mg, 0.04 mmol), $Pd(dba)_2$ (5.2 mg, 0.01 mmol), CuI (74.3 mg, 0.39 mmol), BHT (9.7 mg, 0.04 mmol), and tri-n-butyl(ethenyl)stannane (168 mg, 0.64 mmol in dioxane (3 mL) 105 ºC (5 hours) as described for **271** afforded after purification using column chromatography (hexanes/EtOAc, 95:5 w/ 5% AcOH) **278** (55.8 mg, 0.27 mmol, 68%) as a yellow solid (mp= 97-98 ºC). ^{1}H NMR (600 MHz) δ 10.44 (s, 1H), 8.40 (s, 1H), 7.64 (s, 1H), 6.93 (dd, *J*= 17.4, 10.8 Hz, 1H), 5.80 (d, *J*= 16.8 Hz, 1H), 5.55 (d, *J*= 11.4 Hz,

1H); ^{13}C NMR (150 MHz) δ 153.7, 152.3, 135.3, 129.4, 125.1, 125.0, 120.0, 115.9; IR (ATR) 2245, 2080, 1630, 1525, 1263 cm^{-1};



278 **277**

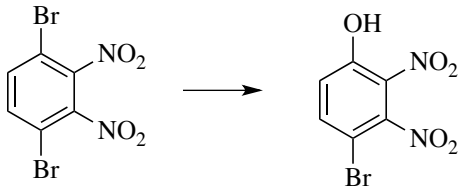
2,5-dinitro-4-vinylphenyl trifluoromethanesulfonate (277): Reaction of **278** (56.3 mg, 0.27 mmol), Et_3N (100 μL, 0.72 mmol), and Tf_2O (60 μL, 0.36 mmol) in CH_2Cl_2 (5 mL) as described for **261** afforded after purification using column chromatography (hexanes/EtOAc, 7:3) **277** (90.8 mg, 0.26 mmol, 98%) as an orange oil. ^{1}H NMR (400 MHz) δ 8.40 (s, 1H), 8.02 (s, 1H), 7.16 (dd, *J*= 17.2, 11.2 Hz, 1H), 5.99 (d, *J*= 17.2 Hz, 1H), 5.80 (d, *J*= 11.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 148.8, 143.4, 139.5, 126.7, 123.8, 121.6, 120.6, 118.5, 118.2 (q, *J*= 319. Hz, C-F); IR (ATR) 3117, 1557, 1436, 1344, 1225 cm^{-1}; HRMS



277 **240**

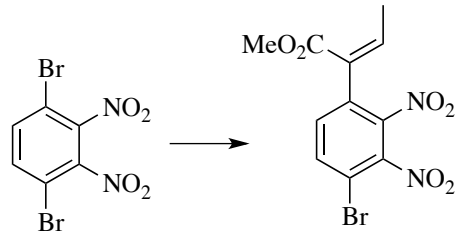
2,5-dinitro-1,4-diethenylbenzene (240): Reaction of **277** (92.9 mg, 0.27 mmol), tri-n-butyl(ethenyl)stannane (105 mg, 0.33 mmol), $PdCl_2(PPh_3)_2$ (4.2 mg, 0.006 mmol), and LiCl (39.1 mg, 0.92 mmol) in DMF (3 mL) at ambient temperature (18 hours) as described for **260** afforded after purification using column chromatography (hexanes/EtOAc, 9:1) **240** (38.8 mg, 0.18 mmol, 65%) as a yellow solid (mp= 140-141 ^{o}C).^{1}H NMR (600 MHz) δ 8.14 (s, 2H), 7.10 (dd, *J*= 17.4, 10.8 Hz, 2H), 5.91 (d, *J*= 17.4

Hz, 2H), 5.65 (d, *J*= 10.8 Hz, 2H); ^{13}C NMR (150 MHz) δ 149.3, 132.9, 129.9, 124.2, 121.5; IR (ATR) 3112, 3075, 1517, 1348, 1283 cm^{-1};



251 **292**

4-bromo-2,3-dinitrophenol (292): To a solution of **251**[155] (730 mg, 2.24 mmol) in THF (8 mL) and H_2O (0.5 mL) was added NaOH (1.04 g, 26.1 mmol). Solution heated at 80 ºC in sealed pressure tube for 18 hours. Resulting brown solution diluted with H_2O (25 mL) and acidified with HCl then extracted with EtOAc (3x30 mL). Combined organic layers dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. Crude brown oil was purified using column chromatography (hexanes/EtOAc, 7:3 w/ 5% AcOH) to afford **292** (554 mg, 2.11 mmol, 94%) as a yellow solid (mp= 59-61 ºC). ^{1}H NMR (400 MHz) δ 7.55 (d, *J*= 8.4 Hz, 1H), 7.20 (d, *J*= 8.8 Hz, 1H); ^{13}C NMR (100 MHz) δ149.0, 138.3, 136.1, 126.5, 114.5, 111.5; IR (ATR) 3391, 1566, 1535, 1456, 1374 cm^{-1}; HRMS (ESI) calcd for $C_6H_3N_2O_5Br$ (M-H) 260.91471, found 260.91484.

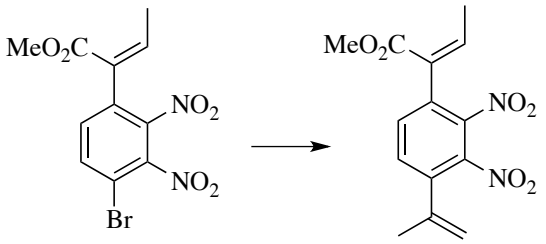


251 **301**

(*Z*)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate (301)

To a solution of **251**[a] (309 mg, 0.95 mmol) in THF (5 mL) was added (*E*)-methyl 2-(tributylstannyl)but-2-enoate (599 mg, 1.54 mmol), $AsPh_3$ (115 mg, 0.38 mmol), $Pd(dba)_2$ (46.2 mg, 0.08 mg), and CuI (187 mg, 0.98 mmol). The resulting solution was

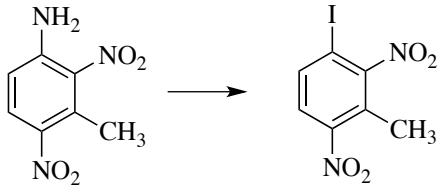
heated at 80 ºC (42 hours). The resulting brown solution was diluted with Et_2O (25 mL) and washed with 10% aq. NH_4OH (3 x 20 mL), H_2O (20 mL), and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed under reduced pressure. The resulting brown oil was purified using column chromatography (hexanes/EtOAc, 7:3) to afford **301** (101 mg, 0.29 mmol, 31%) as a yellow solid (mp= 132-134 ºC). ^{1}HNMR (400 MHz) 7.86 (d, *J*= 8.4 Hz, 1H), 7.37 (d, *J*= 8.4 Hz, 1H), 6.50 (q, *J*= 7.6 Hz, 1H), 3.69 (s, 3H), 2.30 (d, *J*= 7.6 Hz, 3H); ^{13}C 164.0, 147.0, 136.8, 136.6, 134.8, 134.2, 131.7, 128.3, 121.5, 114.3, 51.8, 16.4; IR (ATR) 3089, 2956, 1726, 1534, 1350, 1215 cm^{-1};



301 **302**

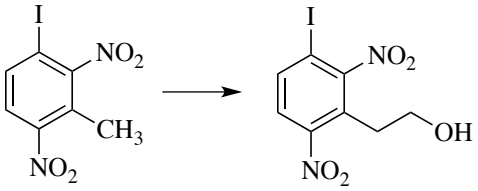
(*Z*)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate (302)

Reaction of **301** (99.0 mg, 0.29 mmol), tributyl(prop-1-en-2-yl)stannane (120 mg, 0.36 mmol), PPh_3 (15.8 mg, 0.06 mmol), and $Pd(dba)_2$ (8.8 mg, 0.15 mmol) in toluene (3 mL) at 110 ºC (24 hours) as described for **271** afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **302** (57.6 mg, 0.19 mmol, 66%) as a yellow oil. ^{1}H NMR (400 MHz) δ 7.54 (d, *J*= 8.0 Hz, 1H), 7.36 (d, *J*= 8.0 Hz, 1H), 7.34 (q, *J*= 7.2 Hz, 1H), 5.30 (s, 1H), 5.08 (s, 1H), 3.73 (s, 3H), 2.14 (s, 3H), 1.77 (d, *J*= 6.8 Hz, 3H); ^{13}C NMR (100 MHz) δ 164.9, 146.4, 144.1, 142.7, 139.0, 138.3, 133.7, 132.0, 129.9, 128.8, 118.4, 52.3, 23.1, 15.7; IR (ATR) 2952, 1726, 1552, 1354, 1205 cm^{-1};



307 **308**

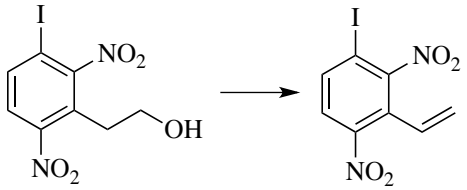
1-iodo-3-methyl-2,4-dinitrobenzene (308): To a solution of 2,4-dinitro-3-methylaniline **307**[156] (492 mg, 2.5 mmol) in AcOH (8 mL) cooled to 10 ºC, slowly added a solution of $NaNO_2$ (226 mg, 3.3 mmol) in H_2SO_4 (conc., 1.5 mL). Resulting red/brown solution stirred at 10 ºC for 1 hour before adding a solution of KI (600 mg, 3.6 mmol) in H_2O (5 mL). Resulting brown suspension heated at 50 ºC for 15 minutes. Suspension neutralized with $NaHCO_3$ (sat. aq.) and extracted with EtOAc (3x30 mL). Combined organic layers were washed with $NaHSO_3$ (sat. aq., 50 mL) and brine (50 mL), then organic layers dried ($MgSO_4$), filtered, and solvents removed under reduced pressure. The resulting red solid was purified using column chromatography (hexanes/EtOAc, 8:2) to afford **308** (647 mg, 2.10 mmol, 86%) as an orange solid (mp= 91-92 ºC) (Lit. 90ºC)[157] ^{1}HNMR (600 MHZ) δ 7.93 (d, *J*= 9.0 Hz, 1H), 7.71 (d, *J*= 9.0 Hz, 1H), 2.47 (s, 3H); ^{13}CNMR δ 157.1, 149.9, 138.5, 126.4, 126.2, 91.1, 14.9; IR (ATR) 1594, 1529, 1344, 902 cm^{-1};



308 **312**

2-(3-iodo-2,6-dinitrophenyl)ethanol (312): To a solution of **308** (221 mg, 0.71 mmol) in *N,N*-dimethylacetamide (5 mL) was added *para*-formaldehyde (30.0 mg, 1.00 mmol) and potassium hydroxide (10.2 mg, 0.18 mmol). The resulting brown solution was stirred at

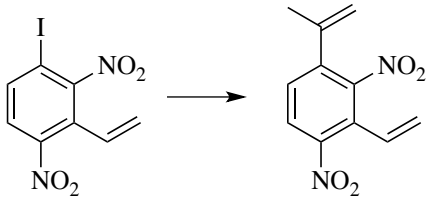
ambient temperature (5 hours). The resulting brown solution was diluted with EtOAc (20 mL) and washed with H_2O (4 x 25 mL) and brine (25 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed under reduced pressure. The resulting orange solid was purified using column chromatography (hexanes/EtOAc, 7:3) to afford **312** (176 mg, 0.52 mmol, 72%) as a light yellow solid (mp= 137-140 ºC). ^{1}H NMR (400 MHz) δ 7.98 (d, *J*= 8.4 Hz, 1H), 7.72 (d, *J*= 8.4 Hz, 1H), 3.87 (t, *J*= 6.4 Hz, 2H), 3.17 (t, *J*= 6.4 Hz, 2H), 2.10 (s, 1H); ^{13}C NMR (100 MHz) δ 157.1, 150.7, 139.2, 127.1, 126.5, 91.4, 61.8, 31.2; IR (ATR) 3391, 3083, 1531, 1357, 1031 cm^{-1};



312 **313**

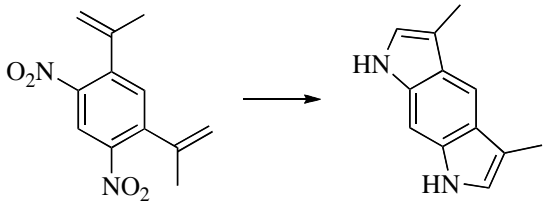
1-iodo-2,4-dinitro-3-ethenylbenzene (313): To an ice-cooled solution of **312** (164 mg, 0.48 mmol) in *N,N*-dimethylacetamide (5 mL) was added methanesulfonyl chloride (75 μL, 0.97 mmol) and triethylamine (200 μL, 1.43 mmol). The resulting cloudy solution was stirred while warming to ambient temperature (2 hours), then heated at 90 ºC (22 hours). The resulting light brown solution was diluted with EtOAc (15 mL) and washed with H_2O (5 x 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered, and solvents were removed under reduced pressure. The resulting brown oil was purified using column chromatography (hexanes/EtOAc, 7:3) to afford **313** (118 mg, 0.37 mmol, 77%) as a yellow solid (mp= 86-88 ºC). ^{1}H NMR (400 MHz) δ 8.02 (d, *J*= 8.8 Hz, 1H), 7.80 (d, *J*= 8.4 Hz, 1H), 6.85 (dd, *J*= 18.4, 11.6 Hz, 1H), 5.59 (d, *J*= 12 Hz, 1H),

5.49 (d, *J*= 18.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 148.2, 140.1, 139.7, 127.9, 126.8, 125.8, 123.4, 91.6; IR (ATR) 30.87, 2891, 1522, 1337, 837 cm^{-1};



313 **314**

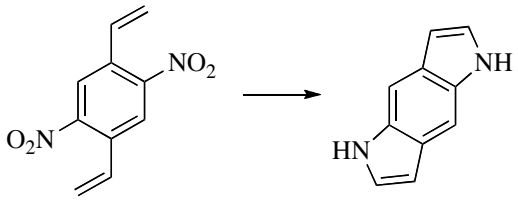
1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene (314): Reaction of **313** (109 mg, 0.34 mmol), tributyl(prop-1-en-2-yl)stannane (132 mg, 0.40 mmol), PPh_3 (18.2 mg, 0.07 mmol), $Pd(dba)_2$ (9.9 mg, 0.02 mmol), and BHT (2 pieces) in dioxane (3 mL) at 75 ºC (23 hours) as described for **271** afforded after purification using column chromatography (hexanes/EtOAc, 85:15) **314** (51.2 mg, 0.22 mmol, 64%) as a yellow solid (mp= 48-50 ºC). ^{1}H NMR (400 MHz) δ 8.04 (d, *J*= 8.4 Hz, 1H), 7.42 (d, *J*= 8.8 Hz, 1H), 6.90 (dd, *J*= 18.0, 12.0 Hz, 1H), 5.55 (d, *J*= 12.0 Hz, 1H), 5.45 (dd, *J*= 17.6, 0.8 Hz, 1H), 5.31 (m, 1H), 5.07 (m, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz) δ 149.8, 147.0, 140.9, 138.9, 128.7, 127.3, 127.2, 125.2, 122.4, 118.8, 23.3; IR (ATR) 3096, 2981, 1524, 1345, 918 cm^{-1};



260 **326**

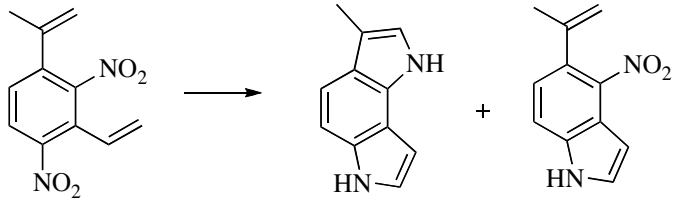
3,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole (326) In an oven-dried ACE glass pressure tube was mixed **260** (47.5 mg, 0.19 mmol), 1,10-phenanthroline (6.4 mg, 0.032 mmol), dppp (6.2 mg, 0.015 mmol), and $Pd(dba)_2$ (7.8 mg, 0.013 mmol) and dry DMF (2 mL). The tube was fitted with a pressure head, and the vessel was saturated with CO (three cycles, 6 atm). The tube was heated at 120 ^{0}C for 48 hours, then the solvent was

removed by bulb-to-bulb and the resulting dark brown crude mixture afforded after column chromatography (hexanes/EtOAc, 1:1) **326** (25.2 mg, 0.14 mmol, 73%) as a brown solid (mp= 195-200 ºC). ^{1}H NMR (600 MHz) δ 7.63 (s, 1H), 7.56 (s, 2H), 7.18 (s, 1H), 6.91 (s, 2H), 2.39 (s, 3H); ^{13}C NMR δ 135.3, 124.7, 121.1, 111.0, 106.7, 90.9, 10.1; IR (ATR) 3275, 2920, 1668, 1631, 1507, 1255 cm^{-1};



240 **239**

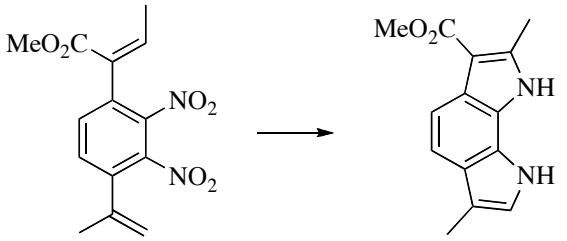
1,5-dihydropyrrolo[2,3-*f*]indole (**239**) Reaction of **240** (29.6 mg, 0.13 mmol), 1,10-phenanthroline (3.4 mg, 0.017 mmol), dppp (3.5 mg, 0.008 mmol), and Pd(dba)$_2$ (5.0 mg, 0.008 mmol) in DMF (2 mL) under carbon monoxide (3 cycles, 6 atm) for 87 hours as described for **326** afforded after column chromatography (hexanes/EtOAc, 85:15) **239** (15.9 mg, 0.10 mmol, 78%) as an off white solid. Spectral data were in accordance with literature values.[106]



314 **330** **329**

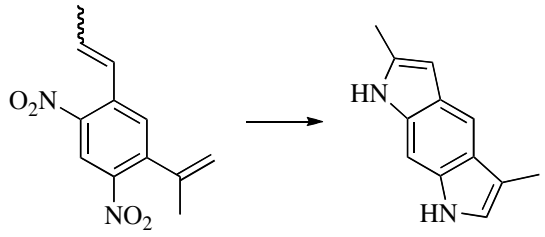
3-methyl-2,6-dihydropyrrolo[2,3-g]indole (330) Reaction of **314** (87.9 mg, 0.37 mmol), 1,10-phenanthroline (9.3 mg, 0.047 mmol), dppp (9.2 mg, 0.022 mmol), and Pd(dba)$_2$ (13.8 mg, 0.024 mmol) in DMF (3 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for **326** afforded after column chromatography (hexanes/EtOAc, 1:1) in order of elution **330** (19.4 mg, 0.11 mmol, 30%) as brown solid (mp= 89-91 ºC) and

329 (35.5 mg, 0.17 mmol, 47%) as a brown solid. Spectral data for **330** ^{1}H NMR (400 MHz) δ 8.24 (br s, 1H), 8.11 (br s, 1H), 7.39 (d, *J*= 8.4 Hz, 1H), 7.18 (dd, *J*= 8.8 Hz, 0.8 Hz, 1H), 7.14 (t, *J*= 2.8 Hz, 1H), 6.87 (m, 1H), 6.63 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz) δ 133.0, 128.9, 128.4, 121.9, 121.0, 117.8, 113.9, 112.7, 104.5, 98.5, 10.1; IR (ATR) 3398, 2924, 1632, 1402, 724 cm^{-1};



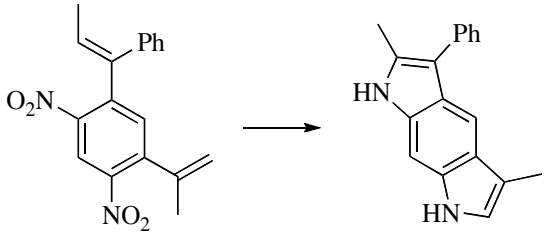
302 **331**

Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-*g*]indole-3-carboxylate (331): Reaction of **302** (46.9 mg, 0.15 mmol), 1,10-phenanthroline (3.8 mg, 0.019 mmol), dppp (4.1 mg, 0.010 mmol), and Pd(dba)$_2$ (5.6 mg, 0.010 mmol) in DMF (2 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for **326** afforded after column chromatography (hexanes/EtOAc, 1:1) **331** (28.6 mg, 0.12 mmol, 77%) as an off-white solid that turned green/brown upon dissolving in $CDCl_3$. ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 9.57 (s, 1H), 7.76 (d, *J*= 8.4 Hz, 1H), 7.32 (d, *J*=8.4 Hz, 1H), 3.92 (s, 3H), 2.75 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz) δ 166.6, 139.9, 123.5, 122.1, 121.8, 120.9, 118.3, 112.4, 112.2, 111.6, 104.3, 50.1, 113.9, 9.6; IR (ATR) 3381, 1655, 1446, 1419, 1198, 1109 cm^{-1};



274 **332**

2,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole (**332**)**:** Reaction of **274** (67.8 mg, 0.27 mmol), 1,10-phenanthroline (6.5 mg, 0.032 mmol), dppp (6.8 mg, 0.016 mmol), and $Pd(dba)_2$ (10.0 mg, 0.017 mmol) in DMF (2.5 mL) under carbon monoxide (3 cycles, 6 atm) for 110 hours as described for **326** afforded after column chromatography (hexanes/EtOAc, 1:1) **332** (12.3 mg, 0.07 mmol, 24%) as a brown solid (mp= 183-185 ^{o}C). ^{1}H NMR (600 MHz) δ 11.9 (br s, 1H), 8.76 (s, 1H), 8.50 (d, *J*= 1.8 Hz, 1H), 8.28 (br s, 1H), 8.12 (s, 1H), 6.25 (d, *J*= 1.2 Hz, 1H), 2.72 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (150 MHz) δ 159.8, 139.5, 137.5, 134.5, 128.9, 124.8, 124.4, 116.7, 102.8, 101.4, 14.1, 13.7; IR (ATR) 3197, 2924, 2857, 1677, 1625, 1504 cm^{-1};

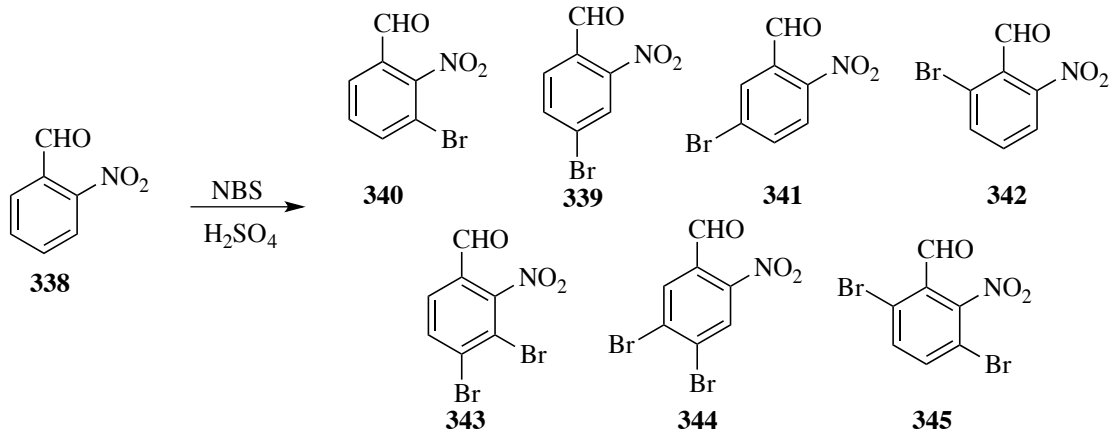


276 **333**

2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-*f*]indole (**333**): Reaction of **276** (25.6 mg, 0.079 mmol), $Pd(dba)_2$ (3.2 mg, 0.005 mmol), 1,10-phenanthroline (2.5 mg, 0.012 mmol), dppp (2.4 mg, 0.006 mmol), in DMF (1.5 mL) under carbon monoxide (3 cycles, 6 atm) for 120 hours as described for **326** afforded after column chromatography (hexanes: EtOAc, 1:1) **333** (4.8 mg, 0.02 mmol, 17%) as a brown residue. ^{1}H NMR (600 MHz) δ 11.95 (s, 1H), 8.78 (s, 1H), 8.49 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 7.53-7.45 (m,

5H), 3.28 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (150 MHz) δ 159.8, 134.3, 131.2, 130.0, 129.8, 129.3, 128.8, 128.5, 127.6, 127.1, 126.4, 125.3, 124.0, 122.1, 15.5, 12.5; IR (ATR) 3383, 2918, 2850, 1706, 1602, 1495 cm^{-1};

7.5 Supporting Information Chapter 6.1: 2-Nitrobenzaldehyde Brominations



Bromination of 2-nitrobenzaldehyde (338) using 0.75 equivalents of NBS. To a solution of **338** (986 mg, 6.53 mmol) in H_2SO_4 (conc. 5.0 mL) was added *N*-bromosuccinimide (NBS) (878 mg, 4.93 mmol). The resulting mixture was stirred at ambient temperature (3 h). The reaction was quenched with ice and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with saturated NaCl (aqueous, 30 mL), dried ($MgSO_4$), filtered through a silica gel plug, and the solvents were evaporated under reduced pressure. The resulting brown oil was purified by column chromatography (hexanes/EtOAc, 8:2) to afford the following fractions in order of elution: (I) 4-bromo-2-nitrobenzaldehyde (**339**)[158] (216 mg, 19%), 5-bromo-2-nitrobenzaldehyde (**341**)[159] (134 mg, 12%), and 4,5-dibromo-2-nitrobenzaldehyde (**344**) (18 mg, 1%) as a yellow solid; (II) 6-bromo-2-nitrobenzaldehyde (**342**) (268 mg, 24%),[160] 3,6-dibromo-2-nitrobenzaldehyde (**345**) (25 mg, 2%),[161] and **338** (409 mg, 41%) as a yellow oil; (III) 3-bromo-2-nitrobenzaldehyde (**340**)[162] as a yellow solid (60 mg, 0.26 mmol, 4%). **340**: mp = 73-74 ºC (Lit. mp = 75-77 ºC).

Bromination of 338 using 1.25 equivalents of NBS. Reaction of **338** (1.01 g, 6.71 mmol) and NBS (1.48 g, 8.32 mmol) in H_2SO_4 (5.0 mL) as described above afforded the

following fractions in order of elution: (I) **344** (28 mg, 0.09 mmol, 1%) as an off-white solid; (II) **339** (328 mg, 21%), **341** (140 mg, 9%), and 3,4-dibromo-2-nitrobenzaldehyde (**343**) (94 mg, 5%); (III) **342** (310 mg, 20%), **345** (65 mg, 3%), **338** (168 mg, 17%); (IV) **340** (54 mg, 0.23 mmol, 4%).

Data for **343**: mp = 105-106 ºC (Lit. mp = 105-107 ºC);[163] ^{1}H NMR δ 10.39 (s, 1H), 8.39 (s, 1H), 8.19 (s, 1H); ^{13}C NMR δ 185.9, 147.7, 134.3, 132.5, 130.8, 130.4, 129.6; IR (ATR) 3088, 2890, 1687, 1525, 1338, 1178 cm^{-1}

Bromination of 338 using 1.25 equivalents of NBS at 60 ºC. Reaction of **338** (459 mg, 3.03 mmol) and NBS (677 mg, 3.80 mmol) in H_2SO_4 (3.0 mL) at 60 ºC as described above afforded the following fractions in order of elution: (I) **344** (21 mg, 0.07 mmol, 2%); (II) **339** (66 mg, 9%) and **341** (24 mg, 3%); (III): **339** (5 mg, 0.7%) and **343** (85 mg, 9%); (IV) **342** (59 mg, 8%), **345** (13 mg, 1%),[162] and **338** (18 mg, 4%); (V) **340** (20 mg, 0.09 mmol, 3%).

Bromination of 338 using 2.5 equivalents of NBS. Reaction of **338** (504 mg, 3.33 mmol) and NBS (1.48 g, 8.30 mmol) in H_2SO_4 (3.0 mL) as described above provided after purification by chromatography (hexanes/EtOAc, 85:15) the following fractions in order of elution: (I) **344** (65 mg, 0.21 mmol, 9%); (II) **339** (58 mg, 8%), **341** (153 mg, 20%), and **343** (128 mg, 12%); (III) **342** (108 mg, 14%), **345** (129 mg, 13%), and **338** (17 mg, 3%); (IV) **340** (57 mg, 0.25 mmol, 8%).

Bromination of 338 using 5.0 equivalents of NBS. Reaction of **338** (504 mg, 3.33 mmol) and *N*-bromosuccinimide (2.94 g, 16.5 mmol) in H_2SO_4 (3.0 mL) as described above afforded the following in order of elution: (I) **344** (193 mg, 0.62 mmol, 19%); (II) **343** (247 mg, 24%) and **339** (32 mg, 4%); (III) **345** (174 mg, 0.56 mmol, 17%).

Data for **343**: mp = 98-99 ºC (white solid); ^{1}H NMR δ 10.21 (s, 1H), 7.94 (d, J= 9.0 Hz, 1H), 7.93 (d, J= 8.4 Hz, 1H); ^{13}C NMR δ 187.8, 146.2, 135.9, 135.5, 133.6, 123.9, 123.8; IR (ATR) 3112, 3075, 1702, 1522, 1342 cm^{-1}; HRMS (ESI) calcd for $C_7H_3Br_2NO_3$ ($M+H^+$) 307.8552; found 307.8556.

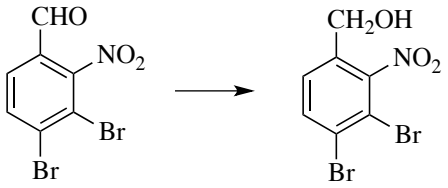
3-Bromo-2-nitrobenzylalcohol (346).[164] To a solution of **340** (105 mg, 0.46 mmol) in THF (3 mL) and H_2O (1 mL) was added sodium borohydride (37 mg, 0.98 mmol). The resulting solution was stirred at ambient temperature (20 min), water was added (20 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were evaporated under reduced pressure to give **346** (87 mg, 0.37 mmol, 81%) as a pale yellow oil. No further purification was required. Spectral data are in accordance with literature data.

4-Bromo-2-nitrobenzylalcohol (347)[165] and 5-bromo-2-nitrobenzylalcohol (348).[164] Reaction of a mixture of **339** and **341** (1.40 g, 64:36 ratio, 6.09 mmol) in dry THF (15 mL) and H_2O (5 mL) was added sodium borohydride (405 mg, 10.7 mmol), as described for **346**, afforded after work up and purification by chromatography (hexanes/EtOAc, 8:2) in order of elution 5-bromo-2-nitrobenzylalcohol **348** (476 mg, 2.04 mmol) and 4-bromo-2-nitrobenzylalcohol **347** (713 mg, 3.07 mmol) both as faint yellow solids. Spectral data were in accordance with literature data.

Fraction II:

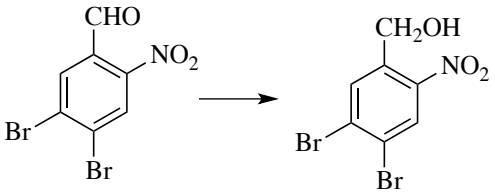
To a mixture of 6-bromo-2-nitrobenzaldehyde (**342**), 3,6-dibromo-2-nitrobenzaldehyde (**345**), and 2-nitrobenzaldehyde (**338**) (150 mg, 0.68 : 0.09 : 0.23) in THF (5 mL) and H_2O (3 mL) was added sodium borohydride (49.8 mg, 1.32 mmol) as described for **346** afforded after purification by chromatography (hexanes/EtOAc, 8:2) in order of elution: a

mixture of 6-bromo-2-nitrobenzyl alcohol[166] and 3,6-dibromo-2-nitrobenzyl alcohol (148 mg) followed by 2-nitrobenzyl alcohol[167] (36 mg, 0.23 mmol).



343 **349**

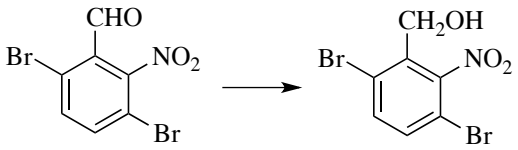
3,4-Dibromo-2-nitrobenzylalcohol (349). Reaction of **343** (101 mg, 0.33 mmol) with sodium borohydride (42.6 mg, 1.13 mmol) in THF (3 mL) and H_2O (1 mL) as described for **346** afforded after purification by chromatography (hexanes/EtOAc, 7:3) **349** (48 mg, 0.16 mmol, 47%) as an off-white solid. mp 76-78 ºC ^{1}H NMR δ 7.78 (d, J=9.0 Hz, 1H), 7.69 (d, J=8.4 Hz, 1H), 4.99 (s, 2H), 2.72 (br s, 1H); ^{13}C NMR δ 149.8, 136.2, 133.6, 132.2, 130.1, 124.0, 62.8; IR (ATR) 3554, 3073, 1518, 1339, 1028 cm^1; HRMS (ESI) calcd for $C_7H_5NO_3Br$ (M+Na$^+$) 333.8508; found 333.8508.



344 **350**

4,5-Dibromo-2-nitrobenzylalcohol (350). Reaction of **344** (292 mg, 0.94 mmol) with sodium borohydride (71.8 mg, 1.90 mmol) in THF (3 mL) and H_2O (1 mL) as described for **346** afforded after purification by chromatography (hexanes/EtOAc, 8:2) **350** (136 mg, 0.44 mmol, 46%) as an off-white solid. mp 112-113 ºC; ^{1}H NMR δ 8.36 (s, 1H), 8.11 (s, 1H), 4.98 (s, 2H), 2.41 (br s, 1H); ^{13}C NMR δ 145.8, 137.3, 134.1, 132.2, 129.7, 124.1,

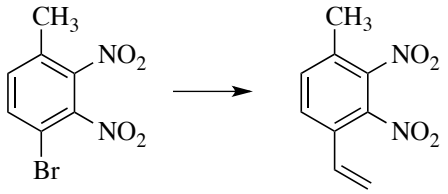
61.5; IR (ATR) 3225, 3089, 1505, 1336, 1035 cm^{1}; HRMS (ESI) calcd for $C_7H_5NO_3Br$ ($M+Na^+$) 333.8508; found 333.8509.



345 **351**

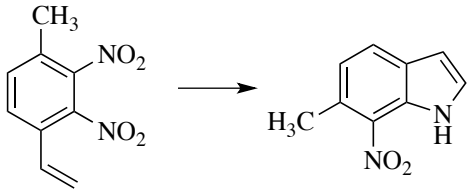
3,6-Dibromo-2-nitrobenzylalcohol (351). Reaction **345** (130 mg, 0.42 mmol) and sodium borohydride (30 mg, 0.79 mmol) in THF (3 mL) and H_2O (1 mL) as described for **346** afforded after purification by chromatography (hexanes/EtOAc, 7:3) **351** (99 mg, 0.32 mmol, 76%) as a white solid. mp 75-76 ºC; ^{1}H NMR δ 7.62 (d, J=9.0 Hz, 1H), 7.51 (d, J=9.0 Hz, 1H), 4.76 (d, J=6.6 Hz, 2H), 2.23 (t, J=7.2 Hz, 1H); ^{13}C NMR δ 152.0, 135.7, 134.3, 133.4, 124.5, 112.5, 61.6; IR (ATR) 3194, 1539, 1356, 1076, 1043 cm^{1}; HRMS (ESI) calcd for $C_7H_5NO_3Br$ ($M+Na^+$) 333.8508; found 333.8510.

7.6 Supporing Information for Chapter 6.2: Functionalized Indoles



352 **355**

2,3-dinitro-4-ethenyltoluene (355): To a solution of **352** (155 mg, 0.60 mmol) in toluene (5 mL) was added (ethenyl)tri-n-butylstannane (203 mg, 0.64 mmol), PPh_3 (62.9 mg, 0.24 mmol), $Pd(dba)_2$ (29.3 mg, 0.05 mmol) and the solution was heated at 110° C for 66 hours. The resulting brown solution was filtered through Celite, diluted with ethyl acetate (20 mL), washed with NH_4OH (10% aq, 3 x 30 mL), H_2O (30 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), filtered, then solvents removed under reduced pressure. Purification using column chromatography (hexanes/EtOAc, 8:2) afforded **355** (82.3 mg, 0.40 mmol, 66%) as a brown solid (mp= 68-71 °C) ^{1}H NMR (600 MHz) δ 7.70 (d, *J*= 8.4 Hz, 1H), 7.46 (d, *J*= 8.4 Hz, 1H), 6.73 (dd, *J*= 17.4, 11.4 Hz, 1H), 5.87 (d, *J*= 16.8 Hz, 1H), 5.60 (d, *J*= 11.4 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (150 MHz) δ 143.5, 142.1, 134.1, 132.2, 130.3, 129.1, 128.5, 121.5, 18.1; IR (ATR) 3031, 2963, 1612, 1558, 1341 cm^{-1}

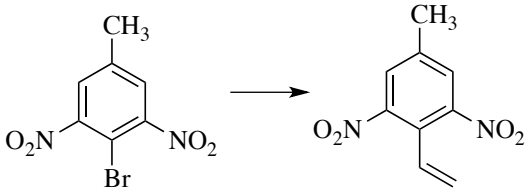


355 **356**

6-methyl-7-nitroindole (356): Reaction of **355** (82.3 mg, 0.40 mmol), PPh_3 (26.3 mg, 0.10 mmol), $Pd(OAc)_2$ (5.7 mg, 0.02 mmol) in MeCN (2 mL) under pressurized CO (g)

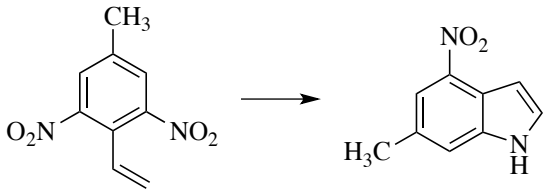
(3 cycles, 90 psi) at 70 ºC for 168 hours afforded after column chromatography (hexanes/EtOAc, 9:1) **356** (3.9 mg, 0.02 mmol, 6%) as a yellow solid.

HNMR (270 MHz) δ 9.97 (br s, 1H), 7.80 (d, *J*= 7.9 Hz, 1H), 7.33 (t, *J*= 2.8 Hz, 1H), 7.07 (d, *J*= 7.9 Hz, 1H), 6.65 (t, *J*= 2.8 Hz, 1H), 2.83 (s, 3H); IR (ATR) 3376, 2927, 1475, 1312, 1267 cm^{-1}



354 **357**

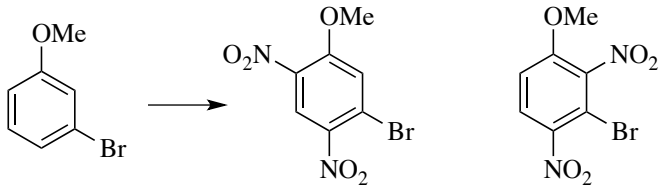
3,5-dinitro-4-ethenyltoluene (357): Reaction of **354** (148 mg, 0.57 mmol), (ethenyl)tri-n-butylstannane (206 mg, 0.65 mmol), PPh_3 (60.9 mg, 0.23 mmol), $Pd(dba)_2$ (26.0 mg, 0.04 mmol) in toluene (5 mL) at 110 ºC for 48 hours as described for 355 afforded after column chromatography (hexanes/EtOAc, 8:2) **357** (67.2 mg, 0.32 mmol, 57%) as a brown solid (mp= 59-61 ºC) ^{1}H NMR (600 MHz) δ 7.84 (s, 2H), 7.00 (dd, *J*= 17.4, 11.4 Hz, 1H), 5.49 (dd, *J*= 11.4, 0.6 Hz, 1H), 5.31 (dd, *J*= 18.0, 0.6 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (150 MHz) δ 149.9, 140.1, 128.1, 127.6, 125.8, 121.1, 20.9; IR (ATR) 3015, 2971, 1629, 1538, 1352 cm^{-1}



357 **358**

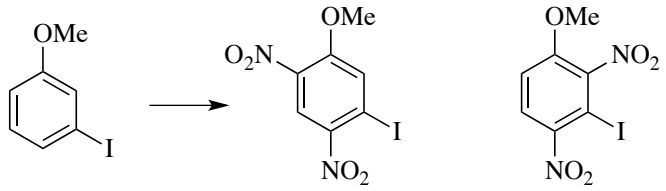
6-methyl-4-nitroindole (358): Reaction of **357** (67.2 mg, 0.32 mmol), PPh_3 (21.0 mg, 0.08 mmol), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol) in MeCN (2 mL) under pressurized CO (g) (3 cycles, 90 psi) at 70 ºC for 18 hours afforded after column chromatography

(hexanes/EtOAc, 9:1) **358** (34.0 mg, 0.19 mmol, 60%) as an orange solid (mp=169-171 °C); HNMR 8.52 (br s, 1H), 8.00 (s, 1H), 7.52 (s, 1H), 7.40 (t, *J*= 2.4 Hz, 1H), 7.24 (t, *J*= 2.4 Hz, 1H), 2.54 (s, 3H); CNMR 140.1, 138.2, 131.3, 127.8, 120.2, 119.0, 118.1, 103.2, 21.3; IR (ATR) 3364, 3115, 2915, 1504, 1346, 1277 cm^{-1};



359 **360** **361**

5-bromo-2,4-dinitroanisole (360)[168] **and 3-bromo-2,4-dinitroanisole (361)**: To fuming nitric acid (5 mL) cooled to -78° C was added **359** (309 mg, 1.7 mmol). Solution removed from cold bath upon addition of starting material and allowed to warm to ambient temperature over 30 minutes. Resulting yellow solution poured over 100 mL ice, causing off-white solid to form. Aqueous mixture extracted with ethyl acetate (3 x 40 mL), then combined organic layers washed with sodium carbonate (sat. aq, 50 mL), dried over $MgSO_4$, filtered, and solvents removed to give yellow solid. Purification via column chromatography (hexanes/EtOAc, 85:15) afforded in order of elution **361** (white solid, 26.1 mg, 6%) and **360** (off-white solid, 407 mg, 89%)[168]. Spectral data for **361**: ^{1}HNMR δ 7.97 (d, *J*= 8.9 Hz, 1H), 7.57 (d, *J*= 8.9 Hz, 1H), 4.04 (s, 3H);



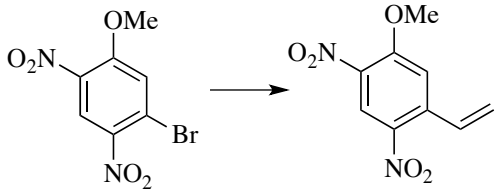
362 **363** **364**

5-iodo-2,4-dinitroanisole (363) 3-iodo-2,4-dinitroanisole (364): To a solution of fuming nitric acid (10 mL) cooled to -78° C was added **362** (3.02 g, 12.9 mmol). Solution removed from cold bath upon addition of starting material and allowed to warm

to ambient temperature over 30 minutes. Resulting brown solution poured over 100 mL ice, causing off-white solid to form. Aqueous mixture extracted with ethyl acetate (3 x 40 mL), then combined organic layers washed with sodium carbonate (sat. aq, 50 mL), dried over $MgSO_4$, filtered, and solvents removed to give yellow solid. Purification via column chromatography (hexanes/EtOAc ,7:3) afforded in order of elution **364** (yellow solid, 454.6 mg, 10.9%) and **363** (yellow solid, 742.6 mg, 17.7%)

Spectral data for **364**: mp= 154-157 ^{o}C, ^{1}HNMR δ 8.08 (d, *J*= 9.0 Hz, 1H), 7.13 (d, *J*= 9.6 Hz, 1H), 4.01 (s, 3H); ^{13}CNMR δ 154.0, 148.6, 146.3, 128.0, 112.5, 82.0, 57.6; IR (ATR) 1575, 1520, 1342, 1283, 1020 cm^{-1}

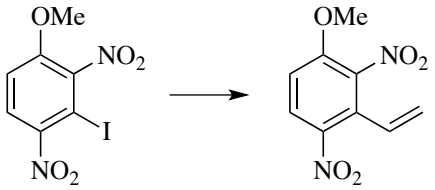
Spectral data for **363**: mp= 113-115 ^{o}C, ^{1}HNMR *δ 8.58 (s, 1H), 7.76 (s, 1H), 4.09 (s, 3H);* ^{13}C NMR *δ 155.0, 144.2, 138.2, 127.3, 123.4, 94.3, 57.9; IR (ATR) 1594, 1526, 1339, 1247, 987 cm^{-1}; HRMS (ESI) calc'd for $C_7H_5N_2O_5I$ (M+Na)= 346.9135, found 346.9139.*



360 **365**

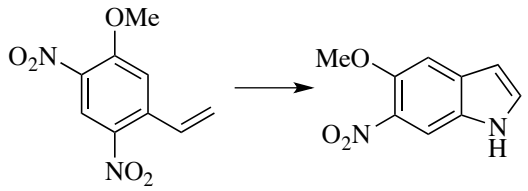
2,4-dinitro-5-ethenylanisole (365): Reaction of **360** (159 mg, 0.58 mmol), (ethenyl)tri-n-butylstannane (304 mg, 0.96 mmol), PPh_3 (68.6 mg, 0.26 mmol), and $Pd(dba)_2$ (27.4 mg, 0.05 mmol) in toluene (6 mL) for 48 hours as described for **355** afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **365** (55.8 mg, 38%) as a yellow solid (mp= 72-74 ^{o}C). ^{1}H NMR δ 8.69 (s, 1H), 7.36 (dd, *J*= 17.2, 10.8 Hz, 1H),

7.20 (s, 1H), 5.82 (d, *J*= 17.2 Hz, 1H), 5.68 (d, *J*= 10.9 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR *δ 156.0, 140.7, 132.5, 124.0, 123.7, 121.8, 115.3, 112.9, 57.3; IR (ATR)* 3108, 3060, 1607, 1579, 1516, 1338, 1277, 1249 cm^{-1} ;



364 **367**

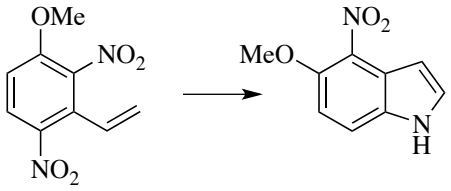
2,4-dinitro-3-ethenylanisole (367): To a solution of **364** (240.3 mg, 0.74 mmol) in toluene (10 mL) was added (ethenyl)tri-n-butylstannane (342.1 mg, 1.07 mmol), PPh_3 (85.3 mg, 0.32 mmol), and $Pd(dba)_2$ (35.2 mg, 0.06 mmol) and 2,6-di-*t*-butyl-4-methylphenol (18.7 mg, 0.08 mmol) for 48 hours as described for **355** afforded after purification using column chromatography (hexanes/EtOAc, 7:3) gave **367** (135.6 mg, 82%) as a brown solid. ^{1}HNMR *δ* 8.04 (d, *J*=8.4 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 1H), 6.60 (dd, *J*=17.4, 10.8 Hz, 1H), 6.00 (d, *J*=17.4 Hz, 1H), 5.69 (d, *J*= 11.4 Hz, 1H), 4.02 (s, 3H); ^{13}CNMR *δ 146.9*, *136.0*, *129.2, 128.6, 128.2, 127.1, 123.8, 121.5, 65.0; IR (ATR) 3109, 2958, 1672, 1577, 1519, 1340, 1286 cm^{-1} ;*



365 **366**

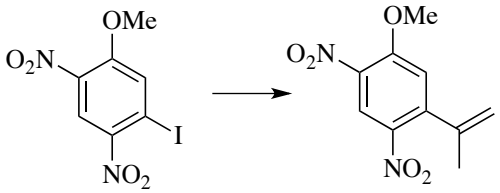
5-methoxy-6-nitroindole (366)[169]: In an oven-dried ACE glass pressure tube dissolved **365** (41.5 mg, 0.19 mmol), 1,10-phenanthroline (7.4 mg, 0.04 mmol), and $Pd(OAc)_2$ (4.1 mg, 0.02 mmol) in N,N-dimethylformamide (3 mL). Tube fitted with pressure head and

pressurized with carbon monoxide (4 cycles, 6 atm), then placed in aluminum heating block at heated at 120° C for 28 hours. Brown solution diluted with H_2O (25 mL), then extracted with ethyl acetate (4 x 40 mL). Combined organic layers dried over $MgSO_4$, filtered, then solvents removed under reduced pressure. Purification of crude brown residue via column chromatography (hexanes/EtOAc, 1:1) afforded **366** (10.3 mg, 28%) as a brown residue. Spectral data were in accordance with literature values.



367 **368**

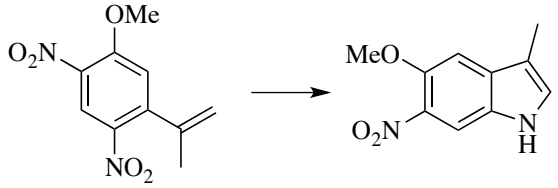
5-methoxy-4-nitroindole (368)[169]: In an oven-dried ACE glass pressure tube dissolved **367** (55.7 mg, 0.25 mmol), 1,10-phenanthroline (9.8 mg, 0.05 mmol), and $Pd(OAc)_2$ (5.3 mg, 0.024 mmol) in N,N-dimethylformamide (3 mL). Tube fitted with pressure head and pressurized with carbon monoxide (4 cycles, 6 atm), then placed in aluminum heating block at heated at 120° C for 24 hours. Solvent removed via bulb-to-bulb distillation. Purification of crude brown residue via column chromatography (hexanes/EtOAc afforded **368** (10.9 mg, 23%) as a yellow solid. Spectral data were in accordance with literature values.



363 **369**

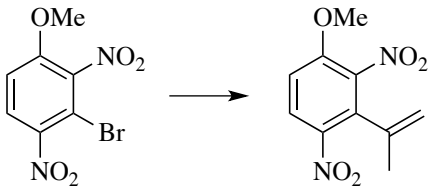
2,4-dinitro-5-(prop-1-en-2-yl)anisole (369): Reaction of **363** (257 mg, 0.79 mmol), tributyl(prop-1-en-2-yl)stannane (312 mg, 0.94 mmol), PPh_3 (57.0 mg, 0.22 mmol), and $Pd(dba)_2$ (35.4 mg, 0.06 mmol) in toluene (10 mL) for 41 hours as described for **355**

afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **369** (68.8 mg, 0.29 mmol, 37%) as a yellow oil. ^{1}HNMR δ 8.61 (s, 1H), 6.97 (s, 1H), 5.27 (s, 1H), 5.01 (s, 1H), 4.08 (s, 3H), 2.11 (s, 3H); ^{13}CNMR δ 156.0, 146.5, 142.5, 139.5, 137.4, 123.4, 226.4, 115.5, 57.5, 23.1; IR (ATR) 3114, 3045, 1615, 1579, 1516, 1338 cm^{-1}



369 **370**

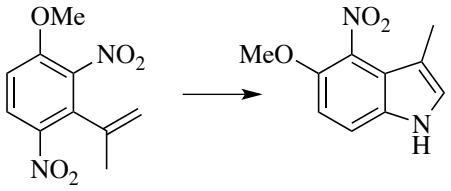
3-methyl-5-methoxy-6-nitroindole (370): Reaction of **369** (68.8 mg, 0.29 mmol), PPh_3 (33.2 mg, 0.13 mmol), and $Pd(OAc)_2$ (7.8 mg, 0.03 mmol) in MeCN (3 mL) under CO (g) (3 cycles, 90 psi) at 120 ºC (48 hrs) afforded after purification using column chromatography (hexanes/EtOAc, 8:2) **370** (4.3 mg, 0.02 mmol, 7%) as a yellow solid (mp= 127-129 ºC). ^{1}HNMR δ 8.11 (br s, 1H), 8.00 (s, 1H), 7.21 (t, *J*= 1.2 Hz, 1H), 7.10 (s, 1H), 4.01 (s, 3H), 2.32 (d, *J*= 1.2 Hz, 3H); ^{13}CNMR δ 148.1, 136.4, 132.6, 129.2, 128.1, 112.4, 109.8, 102.3, 57.4, 9.7; IR (ATR) 3289, 3098, 2945, 1524, 1340, 1271 cm$^{=1}$; HMRS (ESI) calc'd for $C_{10}H_{10}N_2O_3$ (M+Na) 229.0583, found 229.0583.



361 **371**

2,4-dinitro-3-(prop-1-en-2-yl)anisole (371): Reaction of **361** (204 mg, 0.74 mmol), tributyl(prop-1-en-2-yl)stannane (519 mg, 1.57 mmol), PPh_3 (79.9 mg, 0.30 mmol), and $Pd(dba)_2$ (34.6 mg, 0.06 mmol) in toluene (20 mL) for 47 hours as described for **355** afforded after purification using column chromatography (hexanes/EtOAc, 9:1) **371** (37.0

mg, 0.16 mmol, 21%) as a brown oil. ^{1}HNMR δ 8.25 (d, *J*= 9.6 Hz, 1H), 7.08 (d, *J*= 9.6 Hz, 1H), 5.30 (m, 1H), 4.98 (m, 1H), 4.01 (s, 3H), 2.11 (s, 3H); ^{13}CNMR δ 154.4, 141.4, 140.3, 137.2, 134.2, 128.2, 118.3, 111.1, 57.3, 23.3*; IR (ATR) 3113, 2954, 1662, 1581, 1345, 1275 cm^{-1};*



371 **372**

3-methyl-5-methoxy-4-nitroindole (372): Reaction of **371** (34.8 mg, 0.15 mmol), 1,10-phenanthroline (6.6 mg, 0.04 mmol), and $Pd(OAc)_2$ (3.1 mg, 0.01 mmol) in DMF (3 mL) under CO (g) (3 cycles, 90 psi) at 120 ºC (43 hrs) afforded after purification using column chromatography (hexanes/EtOAc, 7:3) **372** (16.5 mg, 0.08 mmol, 53%) as a brown solid (mp= 152-154 ºC). ^{1}HNMR δ 8.07 (br s, 1H), 7.39 (d, *J*=9.0 Hz, 1H), 7.06 (t, *J*= 0.6 Hz, 1H), 6.94 (d, *J*= 9.0 Hz, 1H), 3.93 (s, 3H), 2.18 (d, *J*= 1.2 Hz, 3H); ^{13}CNMR δ 145.6, 133.5, 133.0, 126.2, 120.1, 114.1, 109.9, 108.9, 58.2, 10.1; IR (ATR) 3348, 2984, 1521, 1322, 1242 cm^{-1}; HMRS (ESI) calc'd for $C_{10}H_{10}N_2O_3$ (M+Na) 229.0583, found 229.0583.

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Appendix

^{1}H and ^{13}C NMR Spectra

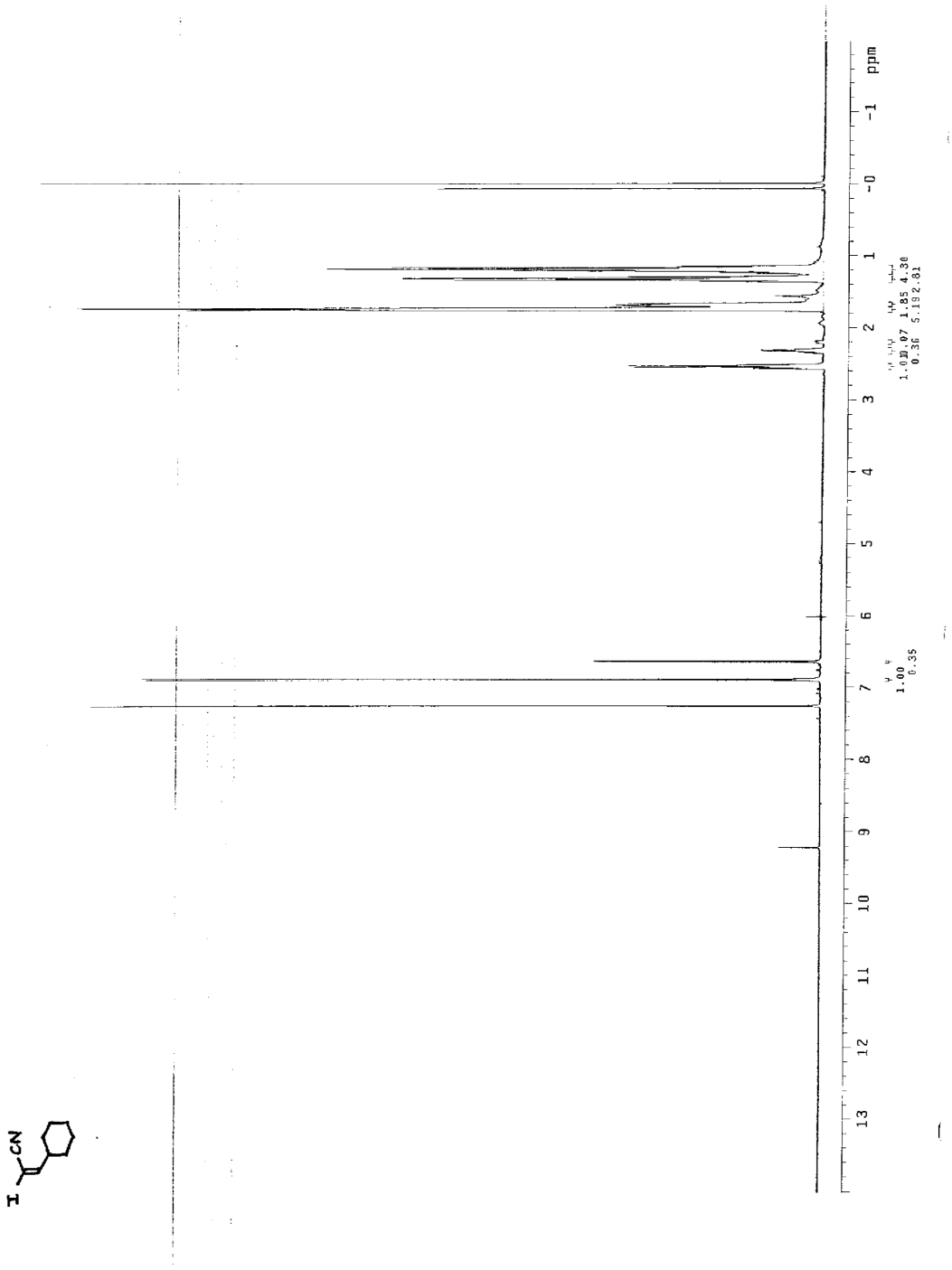

Figure 17: [1]H NMR of 3-Cyclohexyl-2-iodo-2-propenenitrile **(110)**

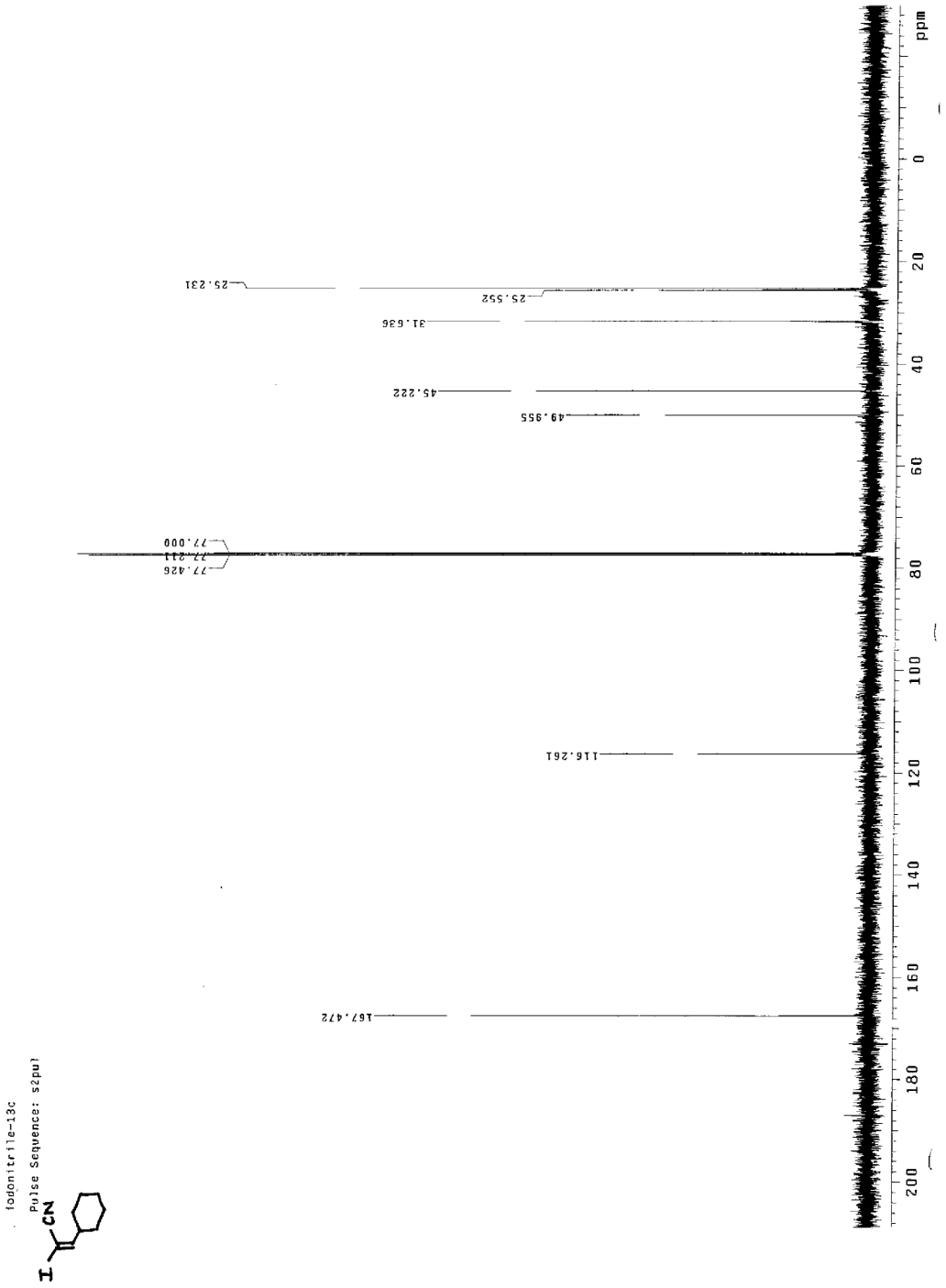

Figure 18: ^{13}C NMR of 3-Cyclohexyl-2-iodo-2-propenenitrile **(110)**

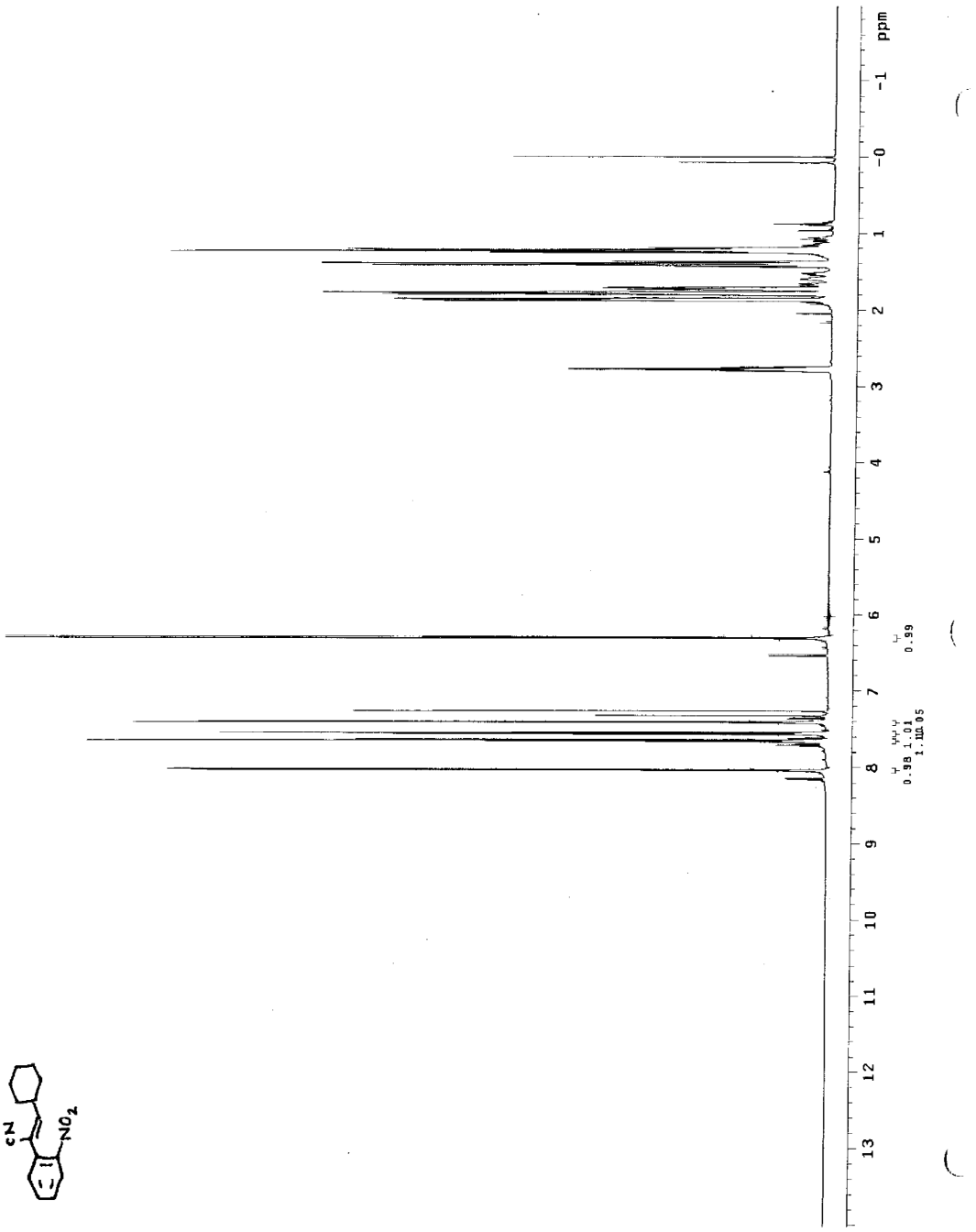

Figure 19: ^{1}H NMR of 3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile **(111)**

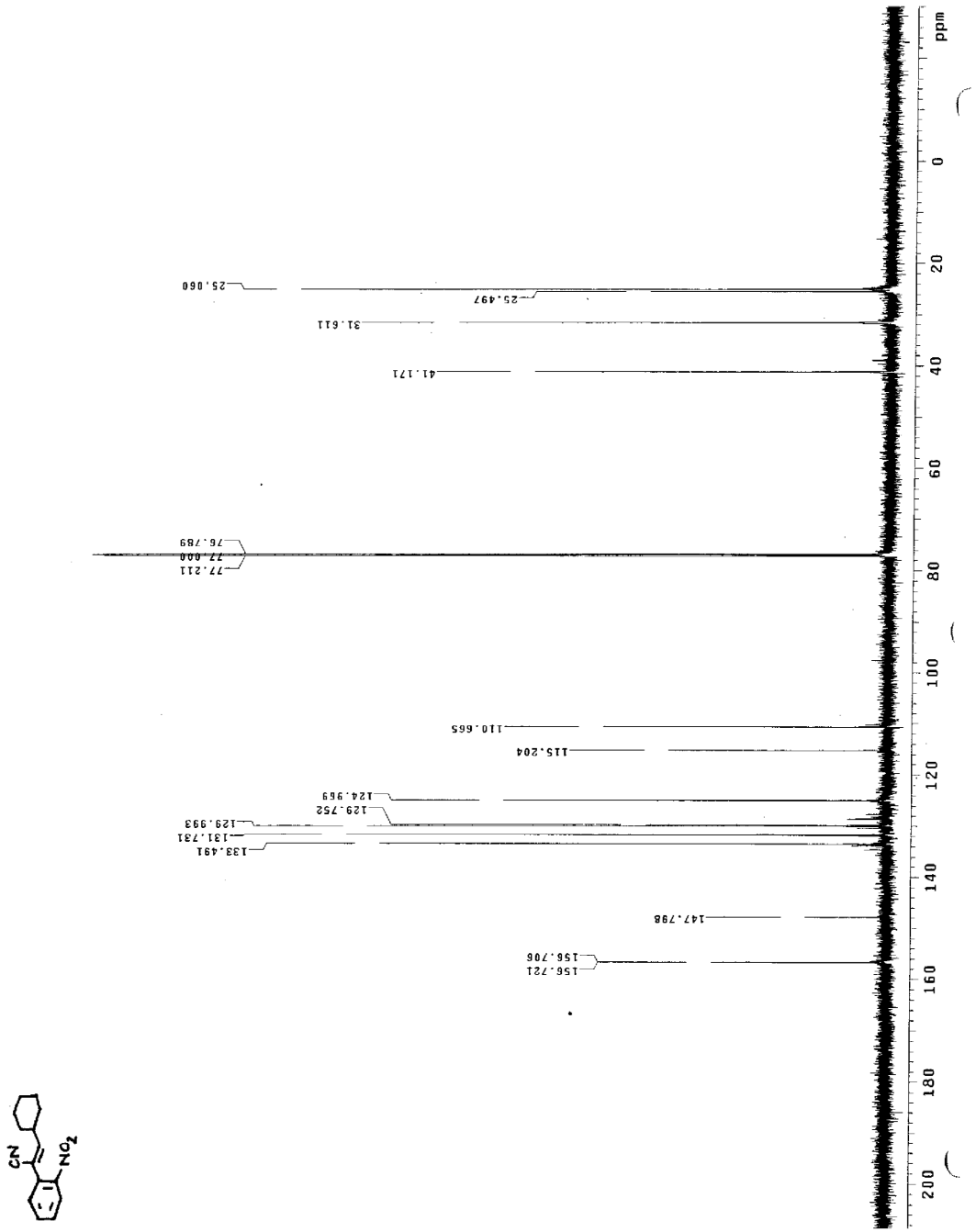

Figure 20: ^{13}C NMR of 3-Cyclohexyl-2-(2-nitrophenyl)-2-propenenitrile **(111)**

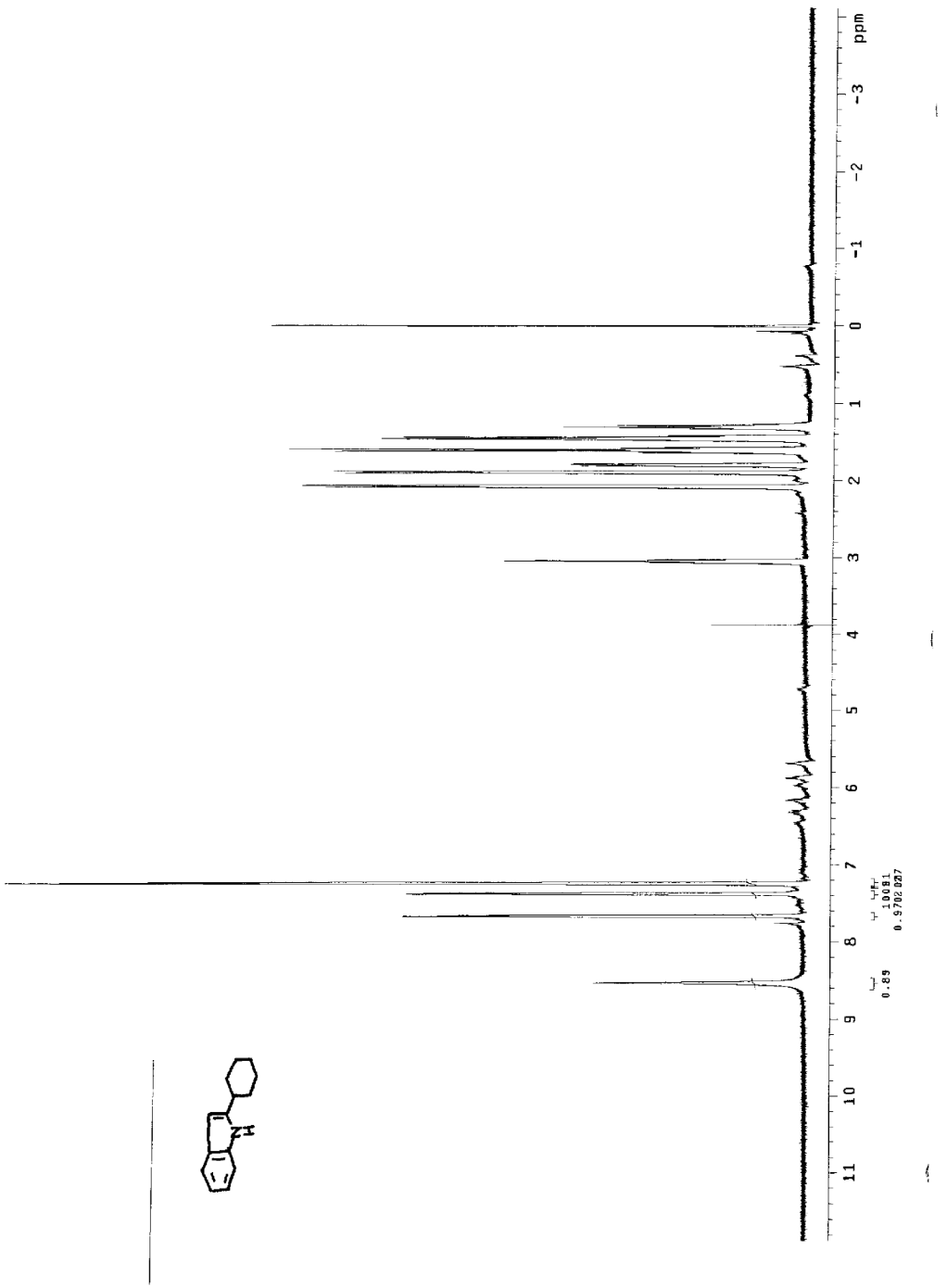

Figure 21: ^{1}H NMR of 3-Cyano-2-cyclohexylindole **(112)**

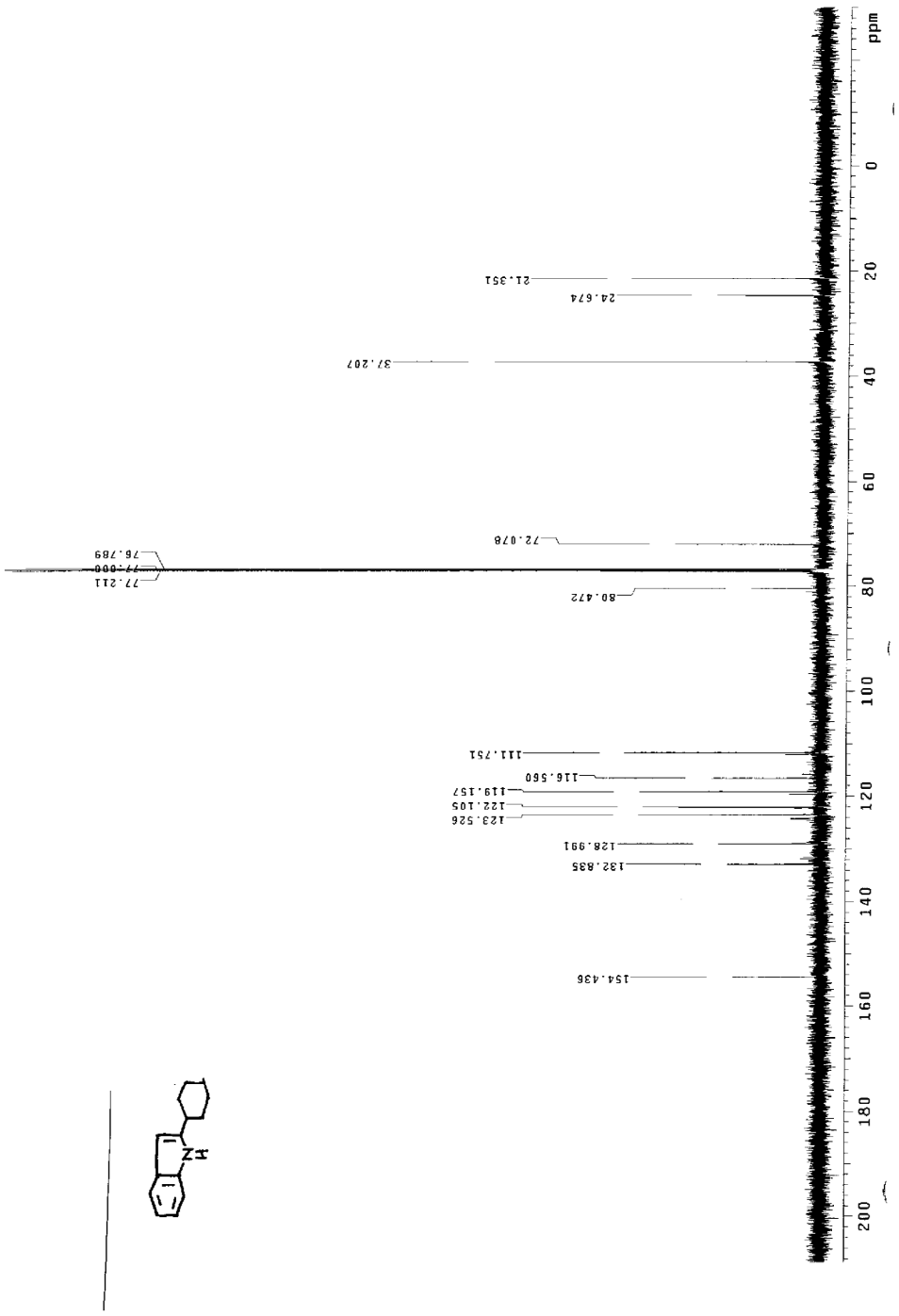

Figure 22: ^{13}C NMR of 3-Cyano-2-cyclohexylindole **(112)**

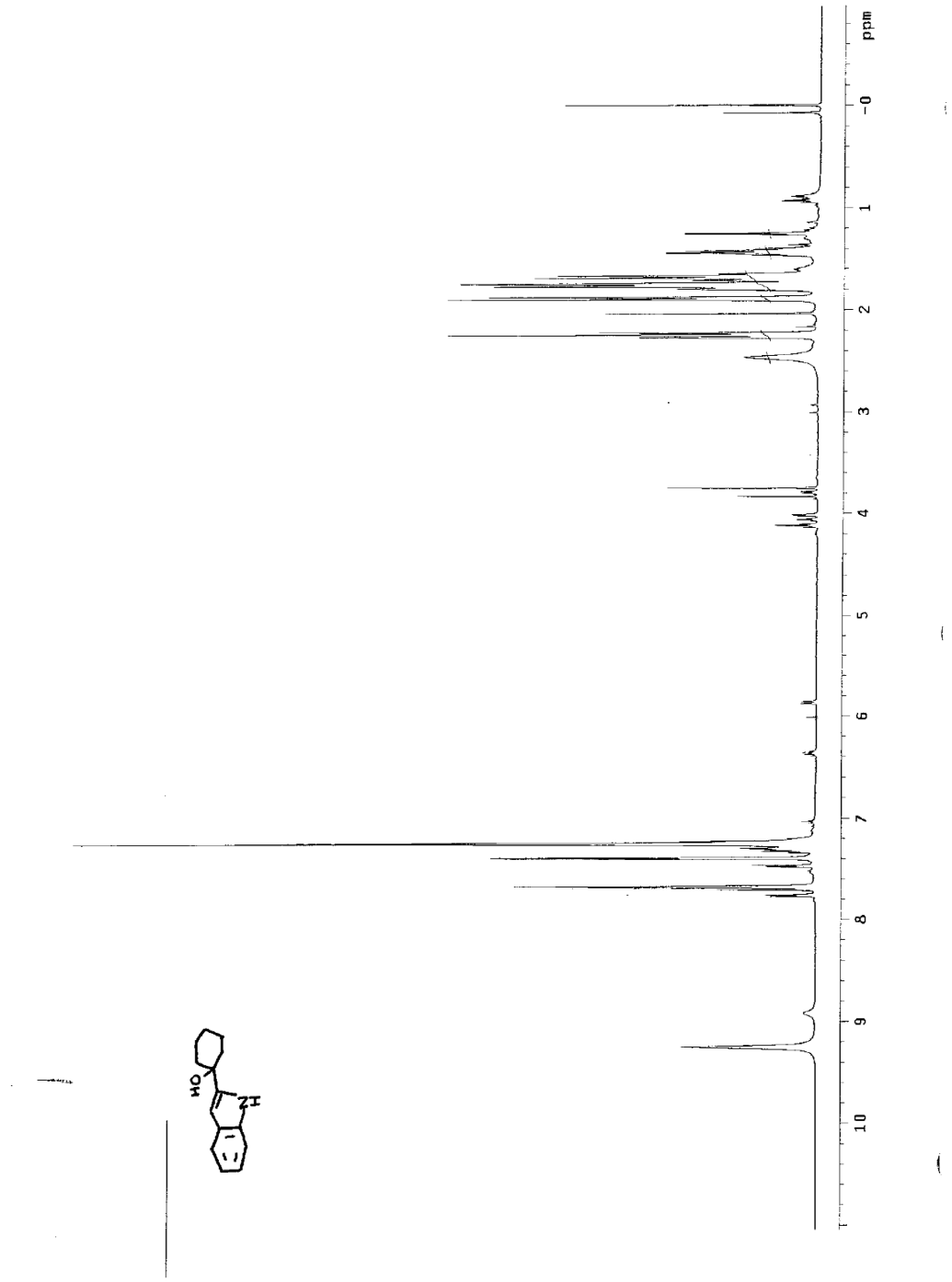

Figure 23: ^{1}H NMR of 3-cyano-2-(1-hydroxycyclohexyl)indole (**113**)

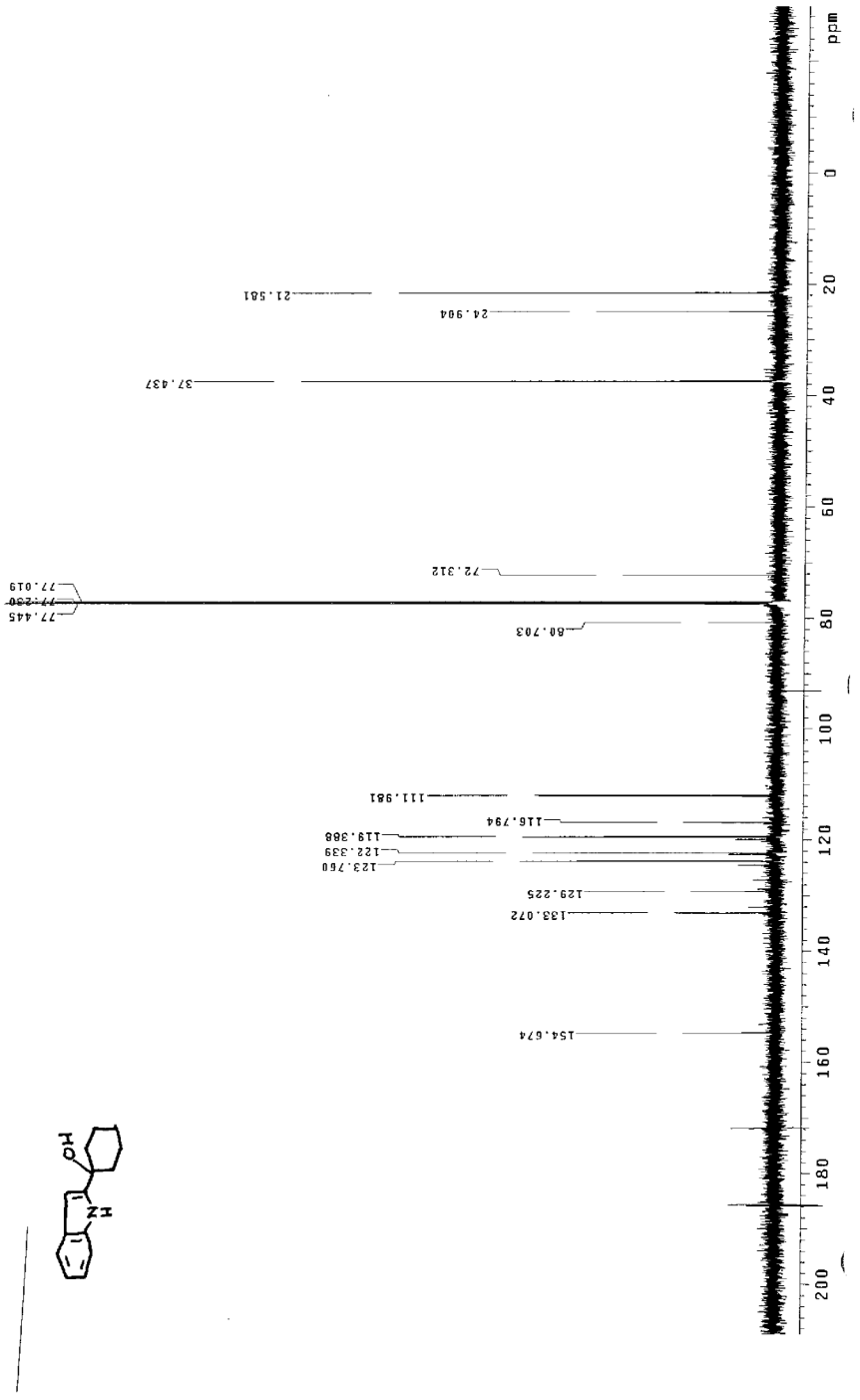

Figure 24: ^{13}C NMR of 3-cyano-2-(1-hydroxycyclohexyl)indole (**113**)

^{1}H and ^{13}C NMR for Chapter 3: Salviadione

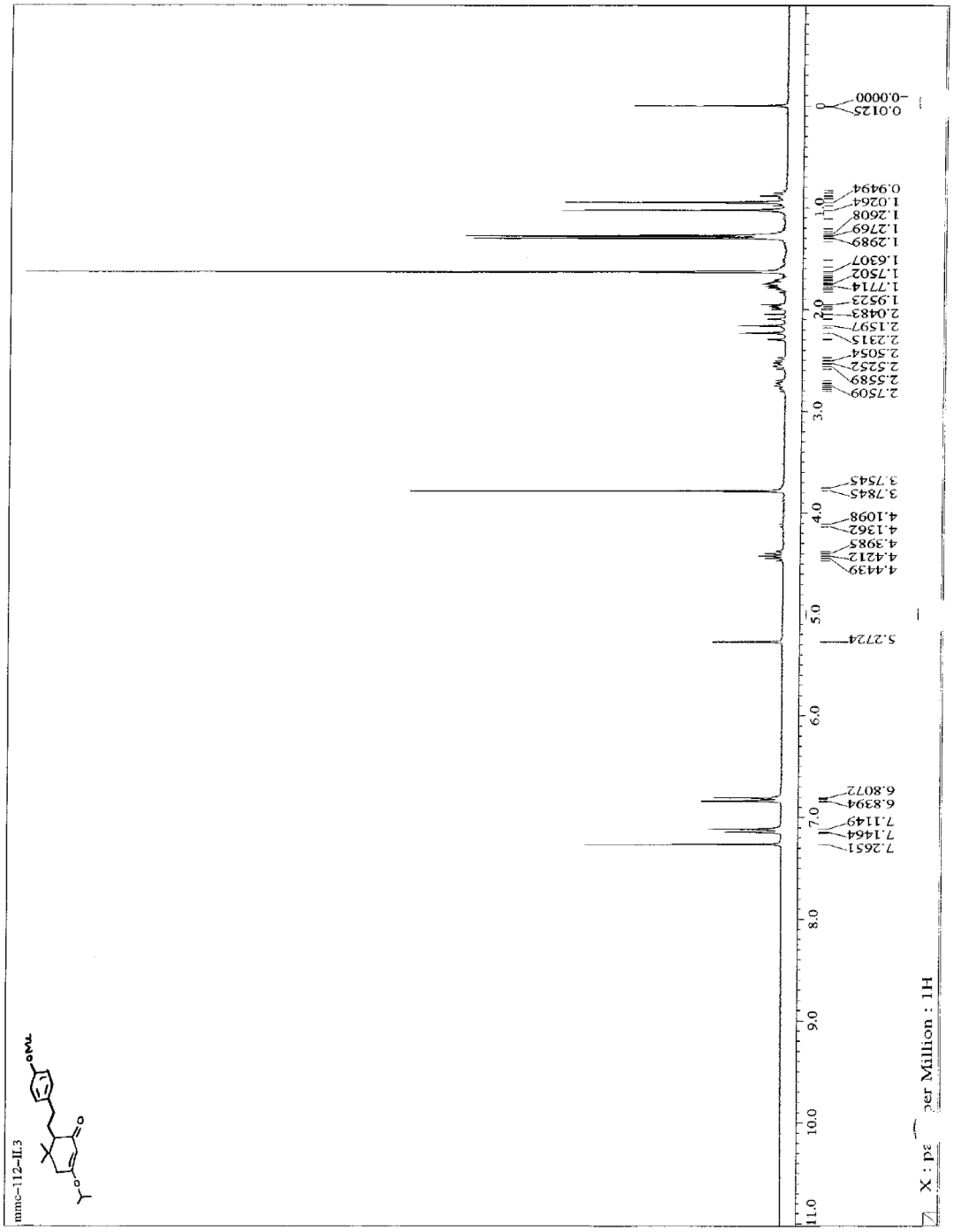

Figure 25: ^{1}H NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (**127**)

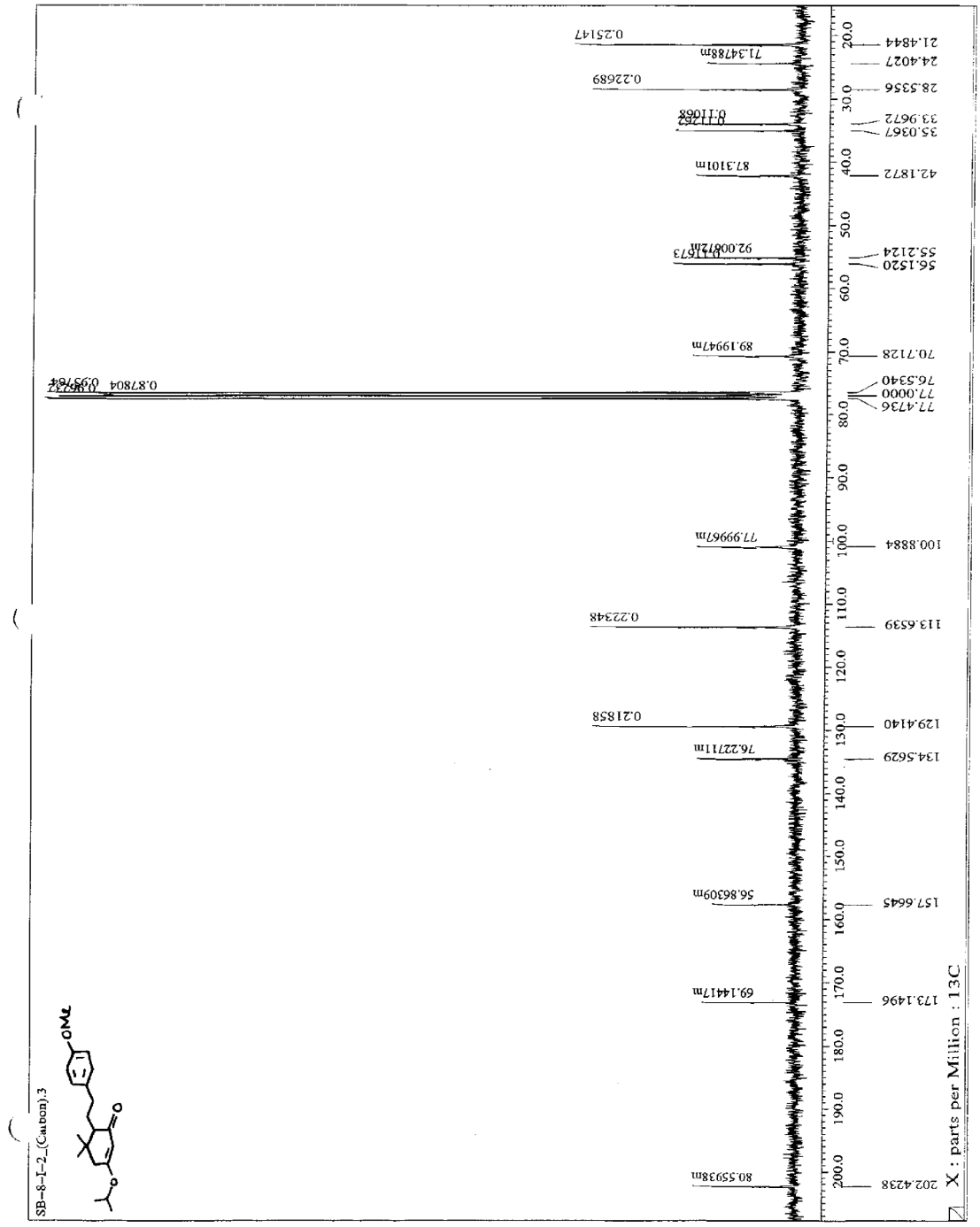

Figure 26: ^{13}C NMR of 5,5-Dimethyl-6-(4-methoxyphenylethyl)-3-(1-methylethoxy)-cyclohex-2-enone (**127**)

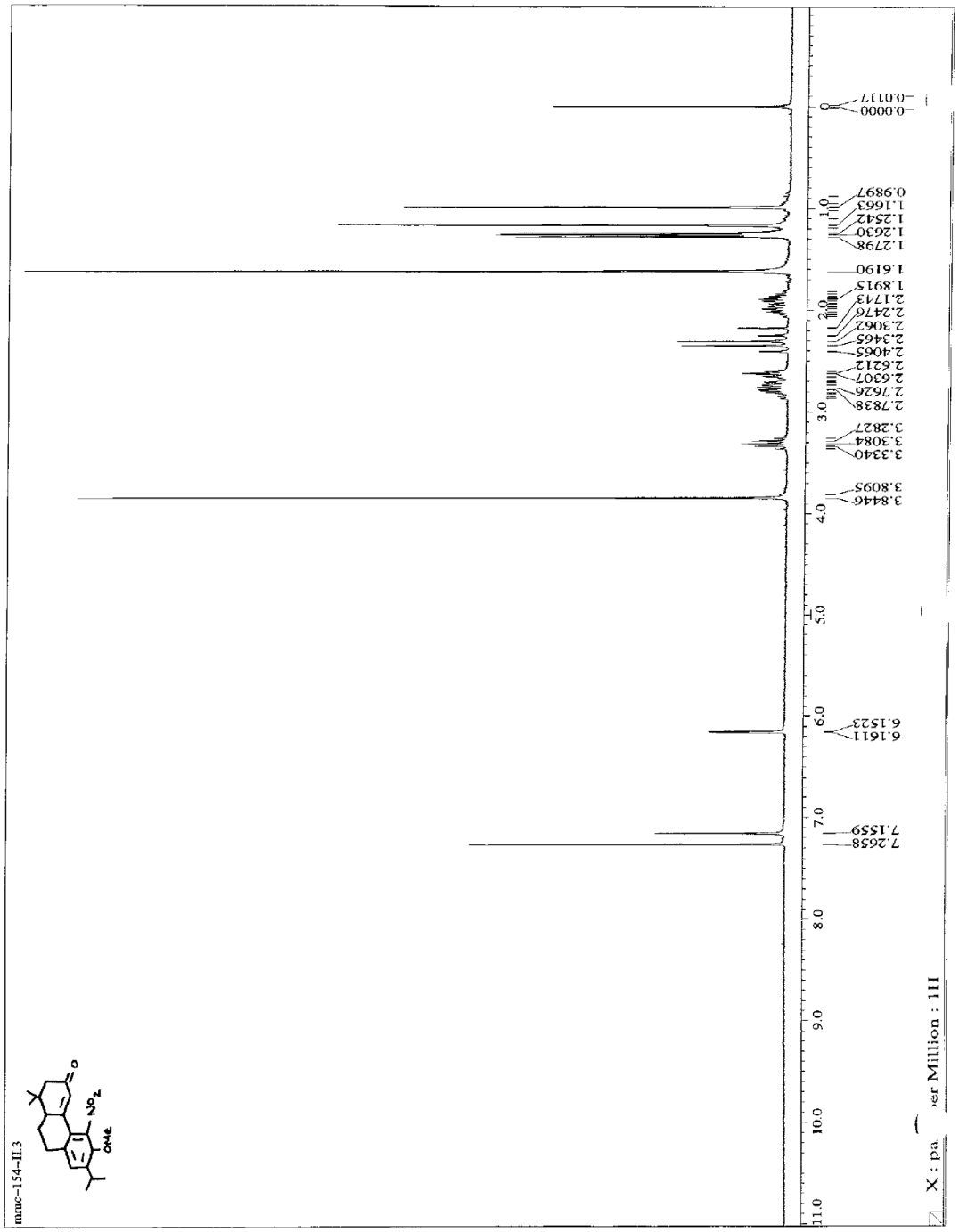

Figure 27: ^{1}H NMR of 10,10*a*-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1*H*,2*H*,9*H*)-one (**132)**

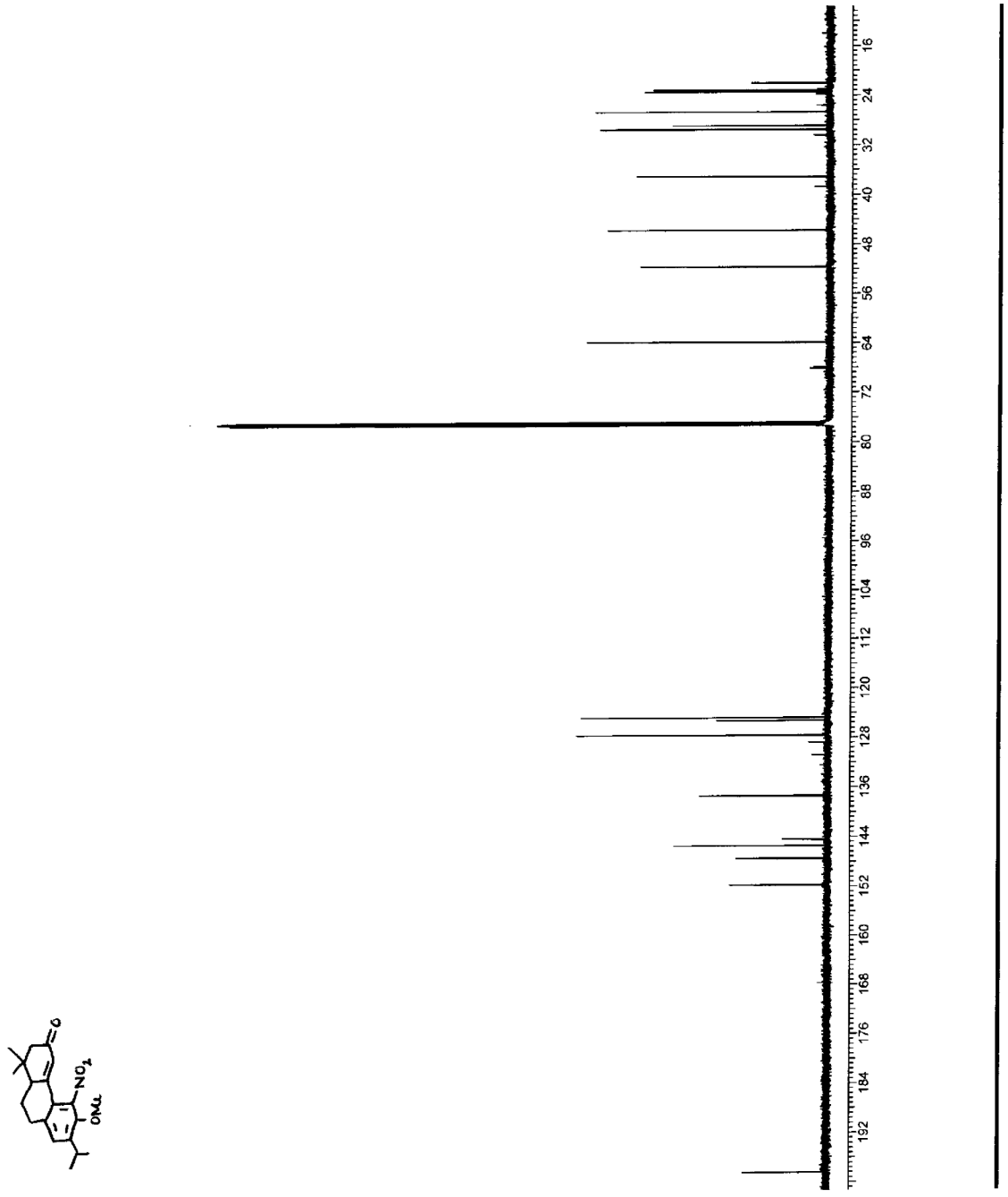

Figure 28: ^{13}C NMR of 10,10*a*-Dihydro-1,1-dimethyl-6-methoxy-7-(1-methylethyl)-5-nitrophenanthren-3(1*H*,2*H*,9*H*)-one (**132**)

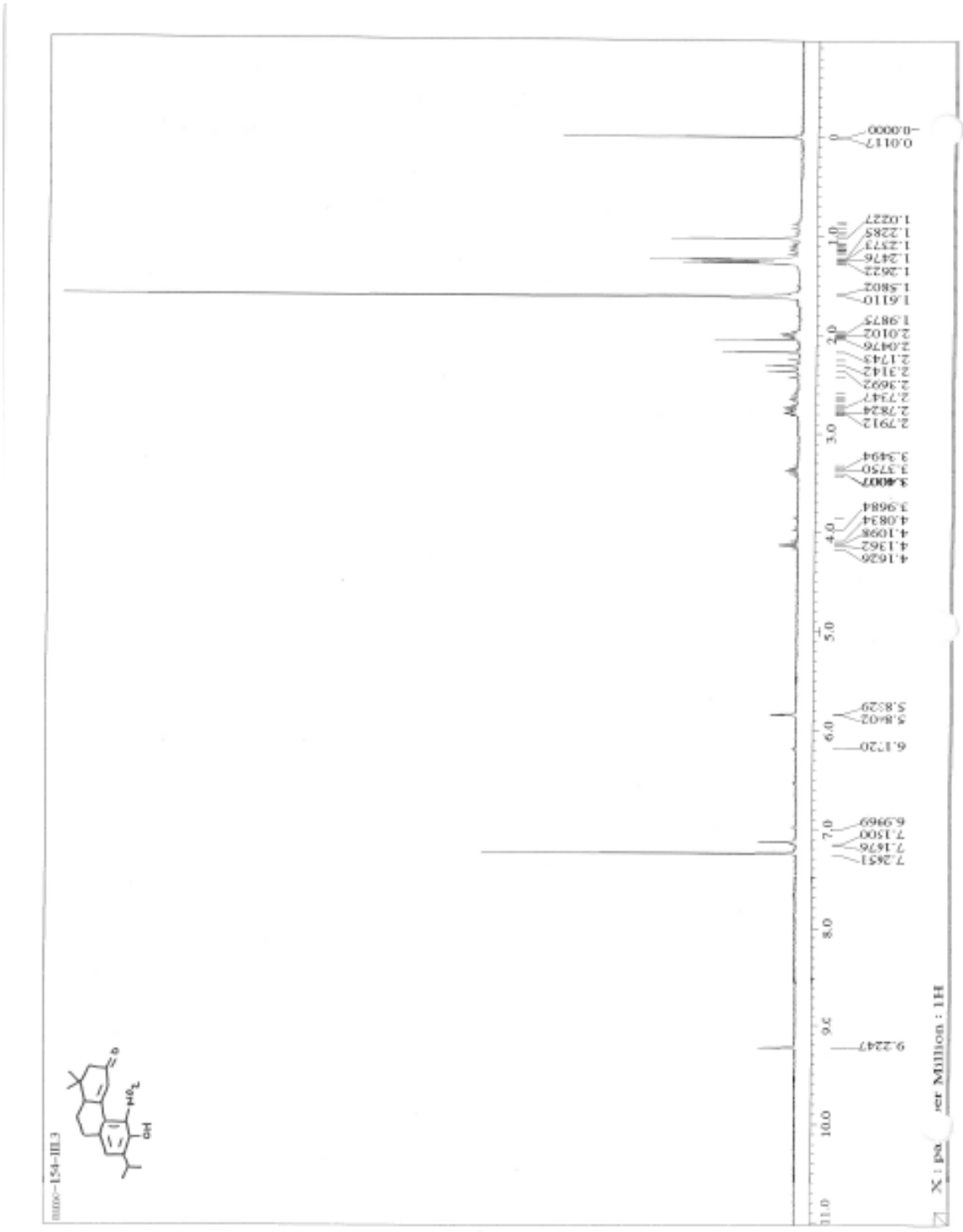

Figure 29: [1]H NMR of 10,10*a*-Dihydro-1,1-dimethyl-6-hydroxy-7-(1-methylethyl)-5-nitrophenanthren-3(1*H*,2*H*,9*H*)-one (**125**)

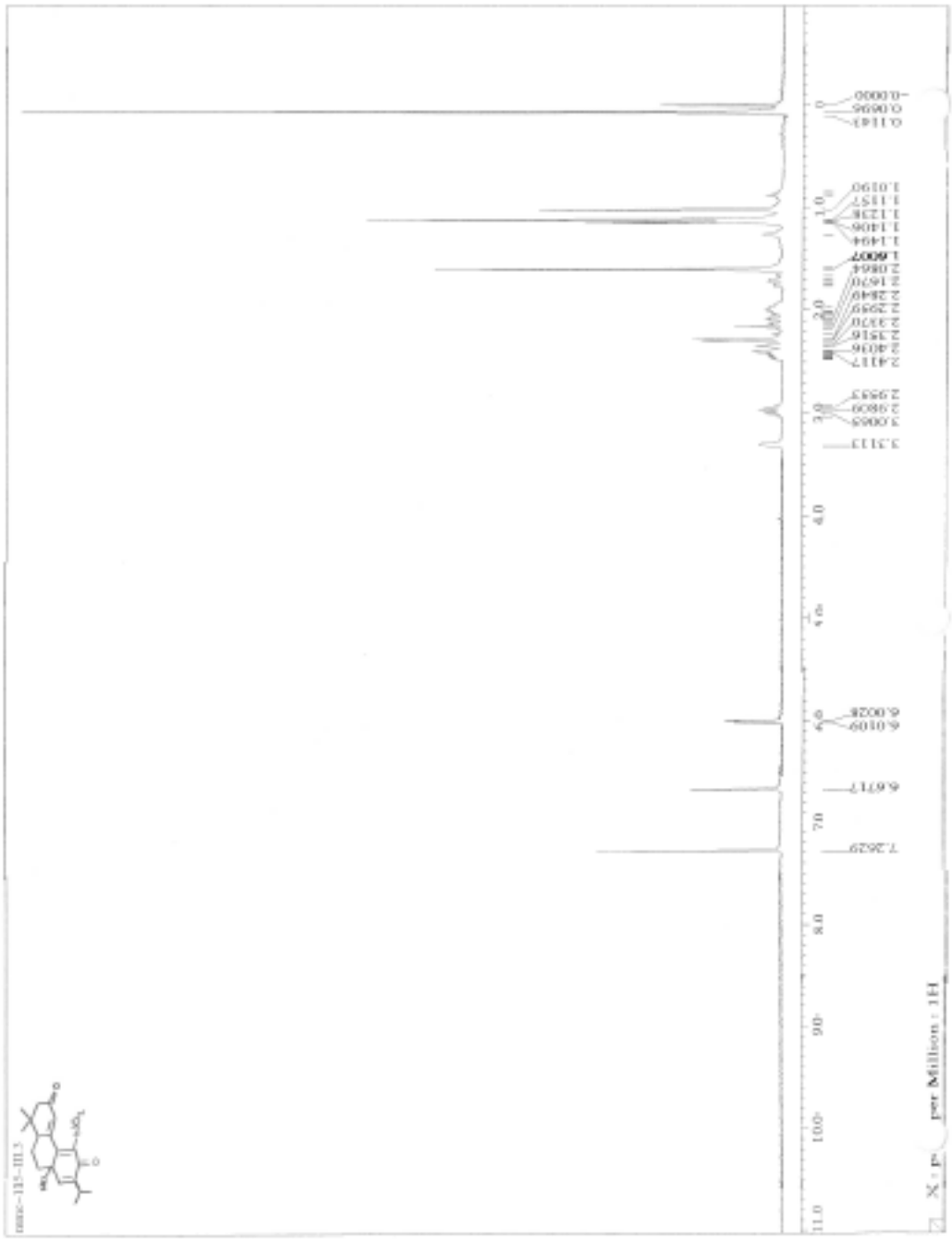

Figure 30: [1]H NMR of 8*a*,9,10,10*a*-Tetrahydro-1,1-dimethyl-8*a*-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1*H*,2*H*)-dione **(133)**

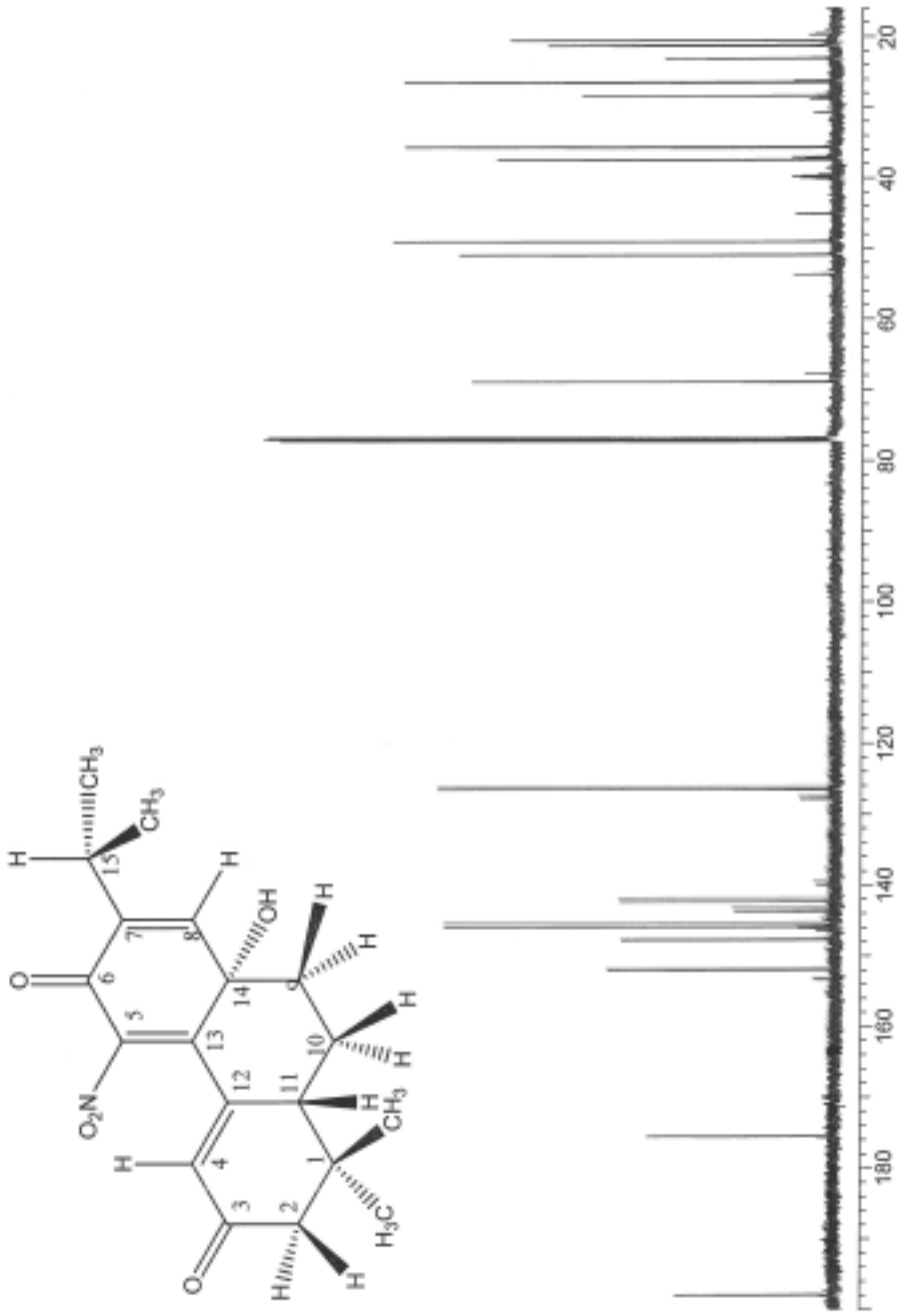

Figure 31: ^{13}C NMR of 8*a*,9,10,10*a*-Tetrahydro-1,1-dimethyl-8*a*-hydroxy-7-(1-methylethyl)-5-nitrophenanthrene-3,6(1*H*,2*H*)-dione **(133)**

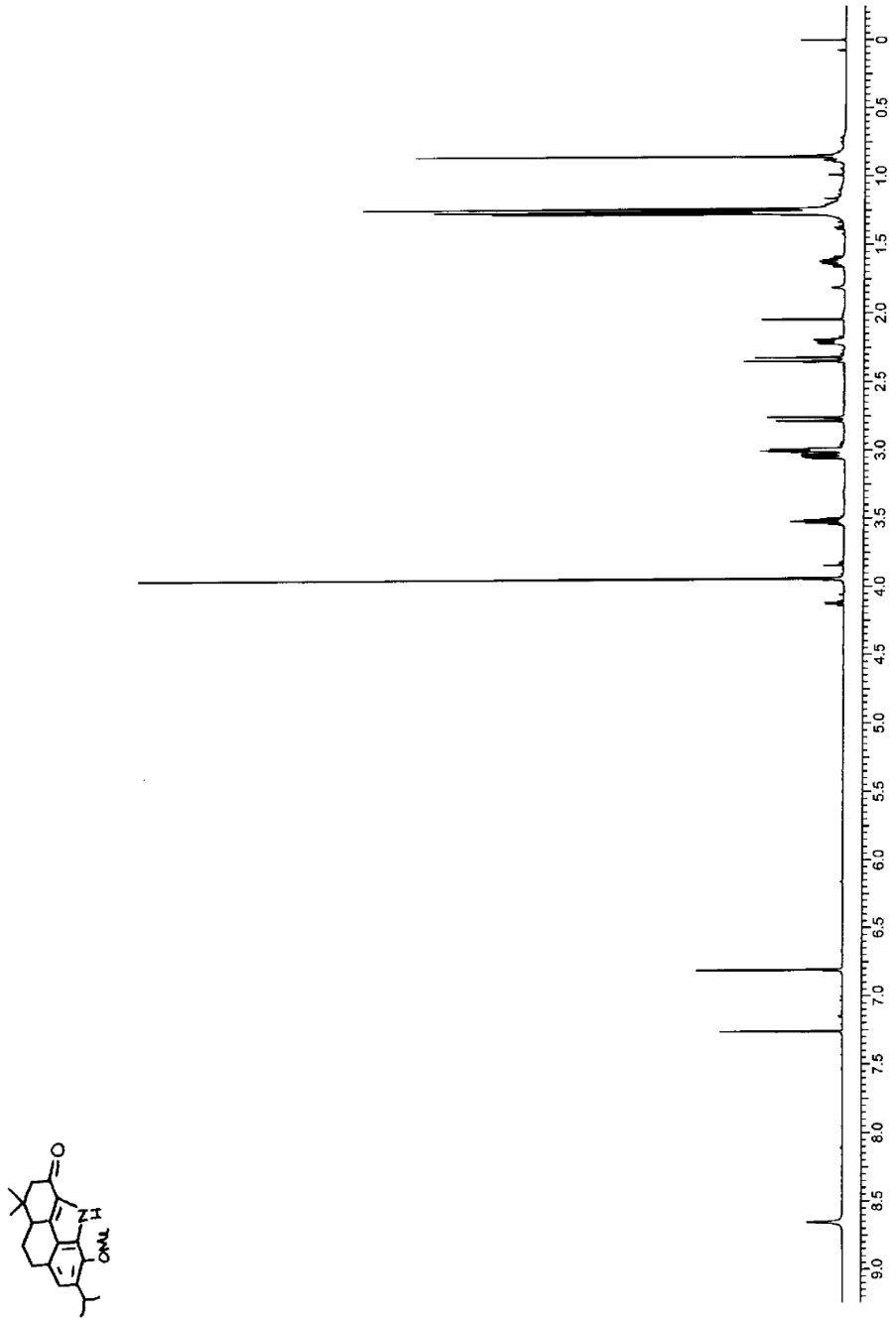

Figure 32: ^{1}H NMR of 1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one **(134)**

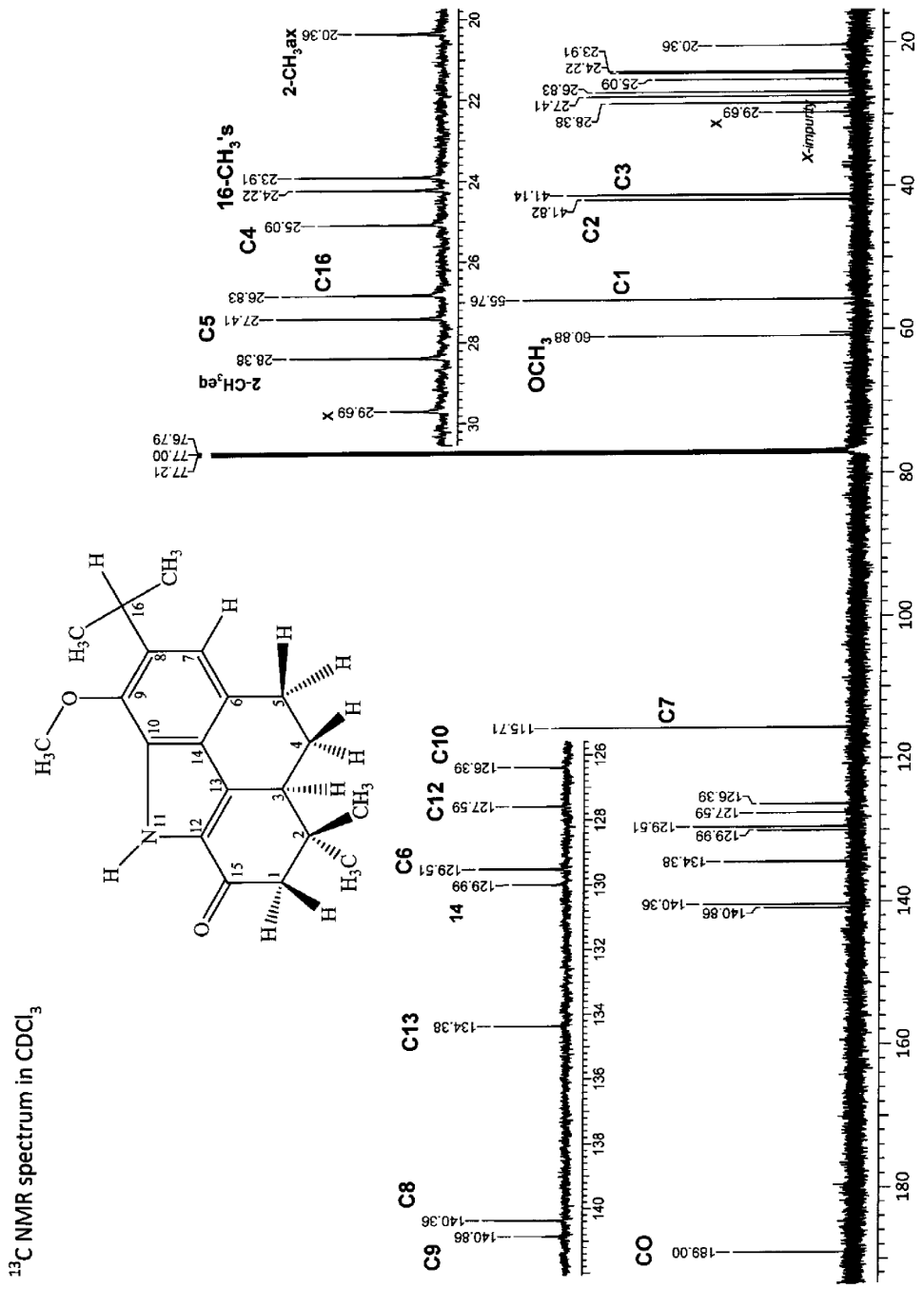

Figure 33: ^{13}C NMR of 1,8,9,9a-Dihydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one **(134)**

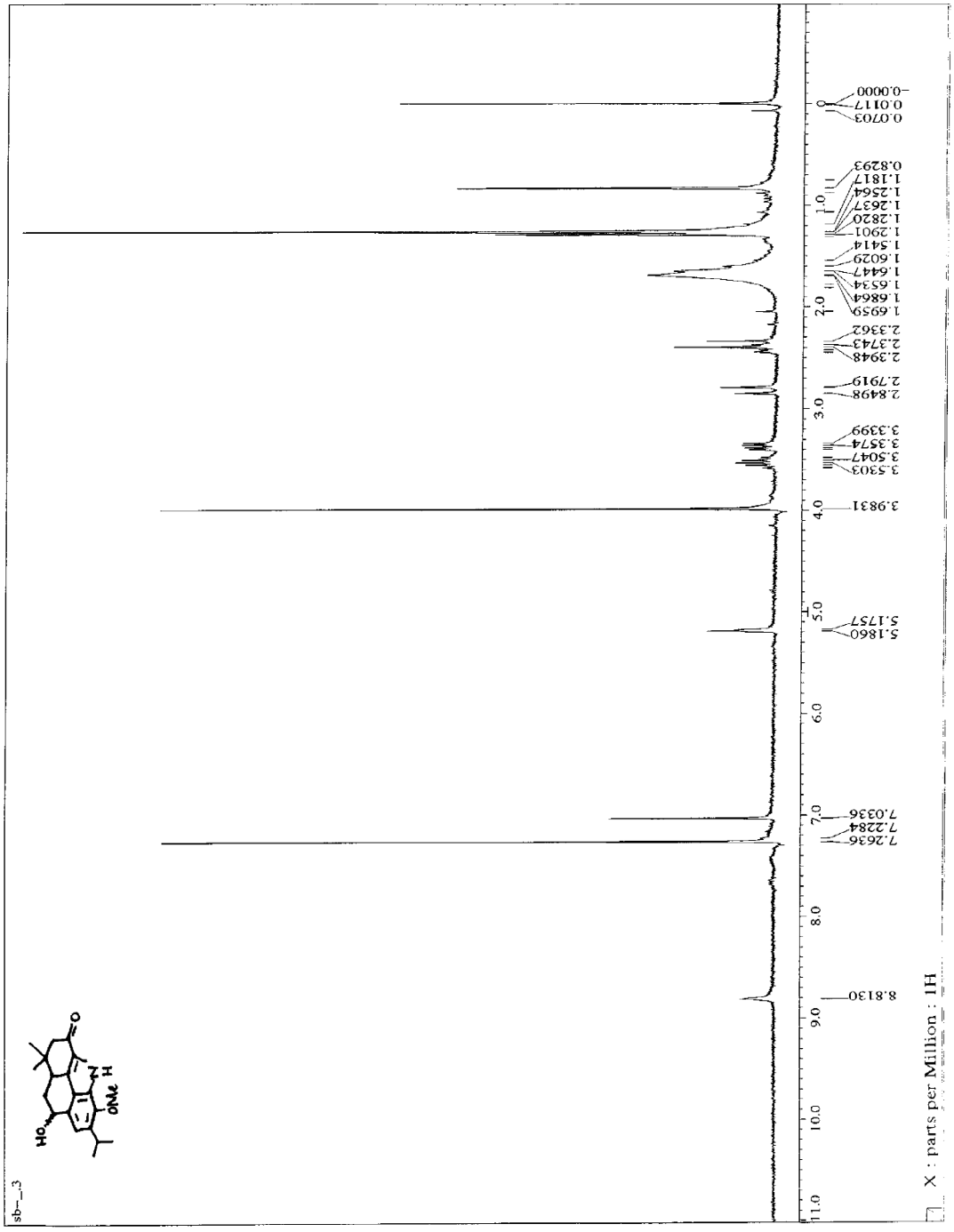

Figure 34: [1]H NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**136**)

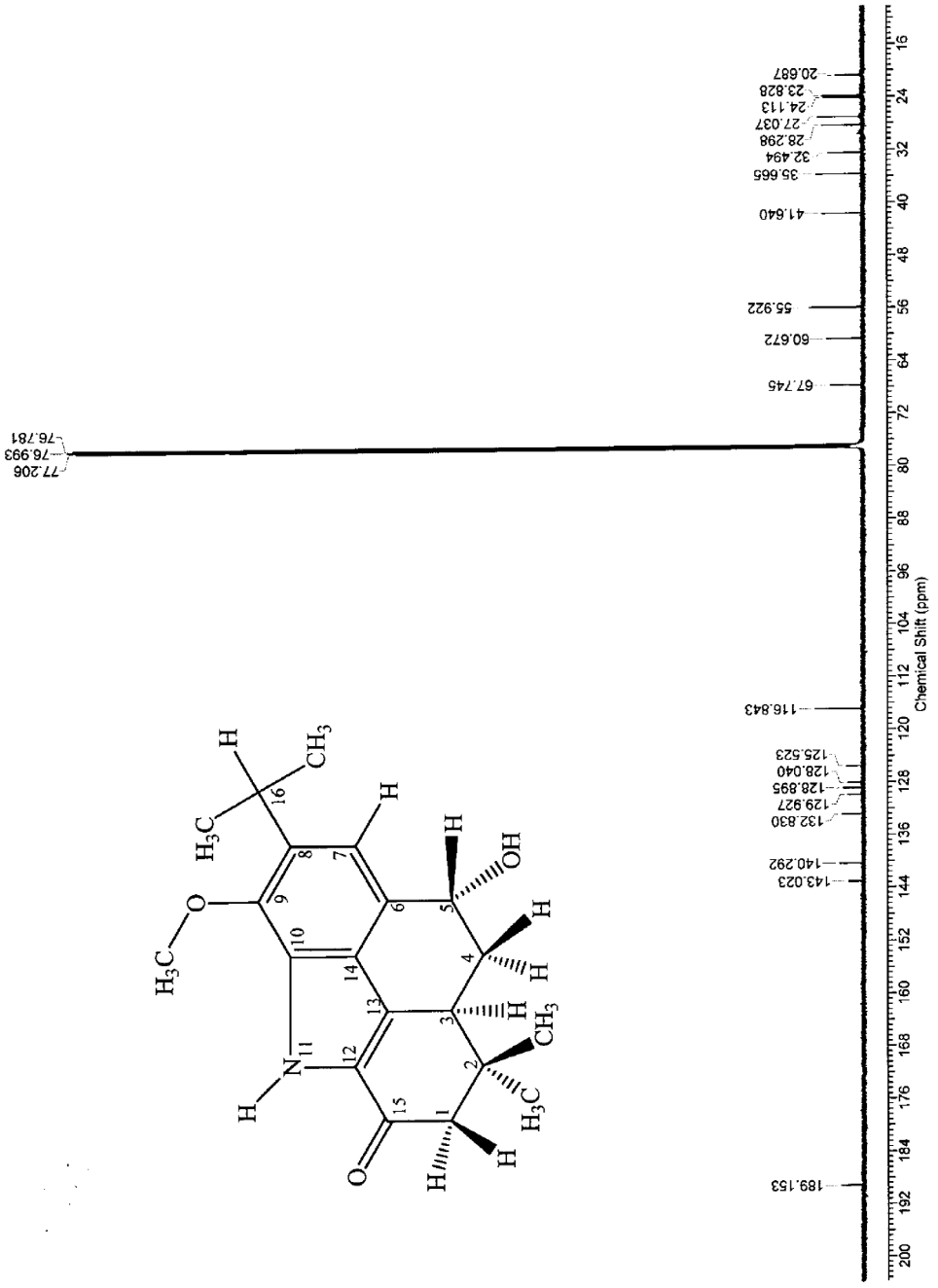

Figure 35: ^{13}C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-methoxy-6-(1-methylethyl)-8-hydroxy-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**136**)

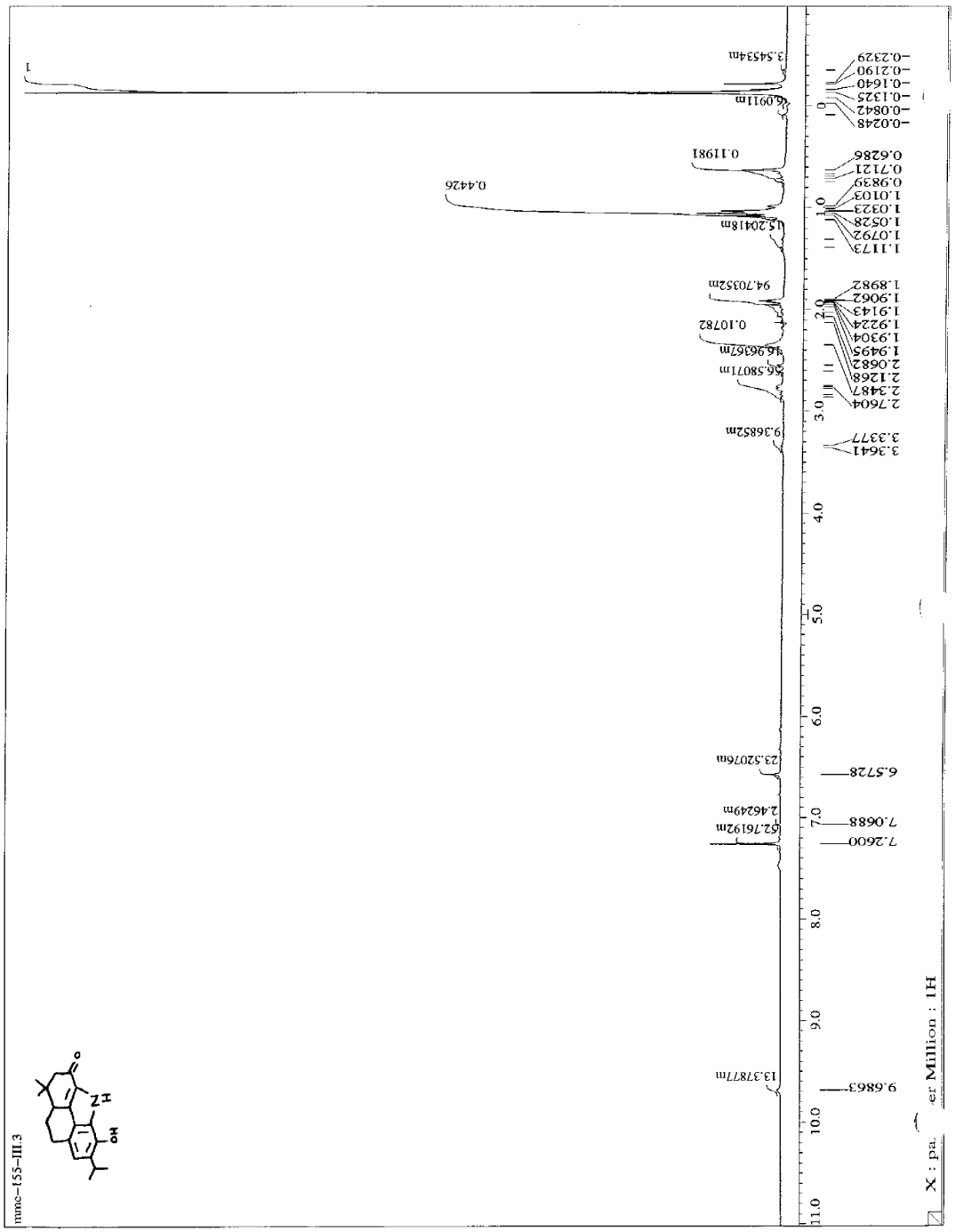

Figure 36: ^{1}H NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**124**)

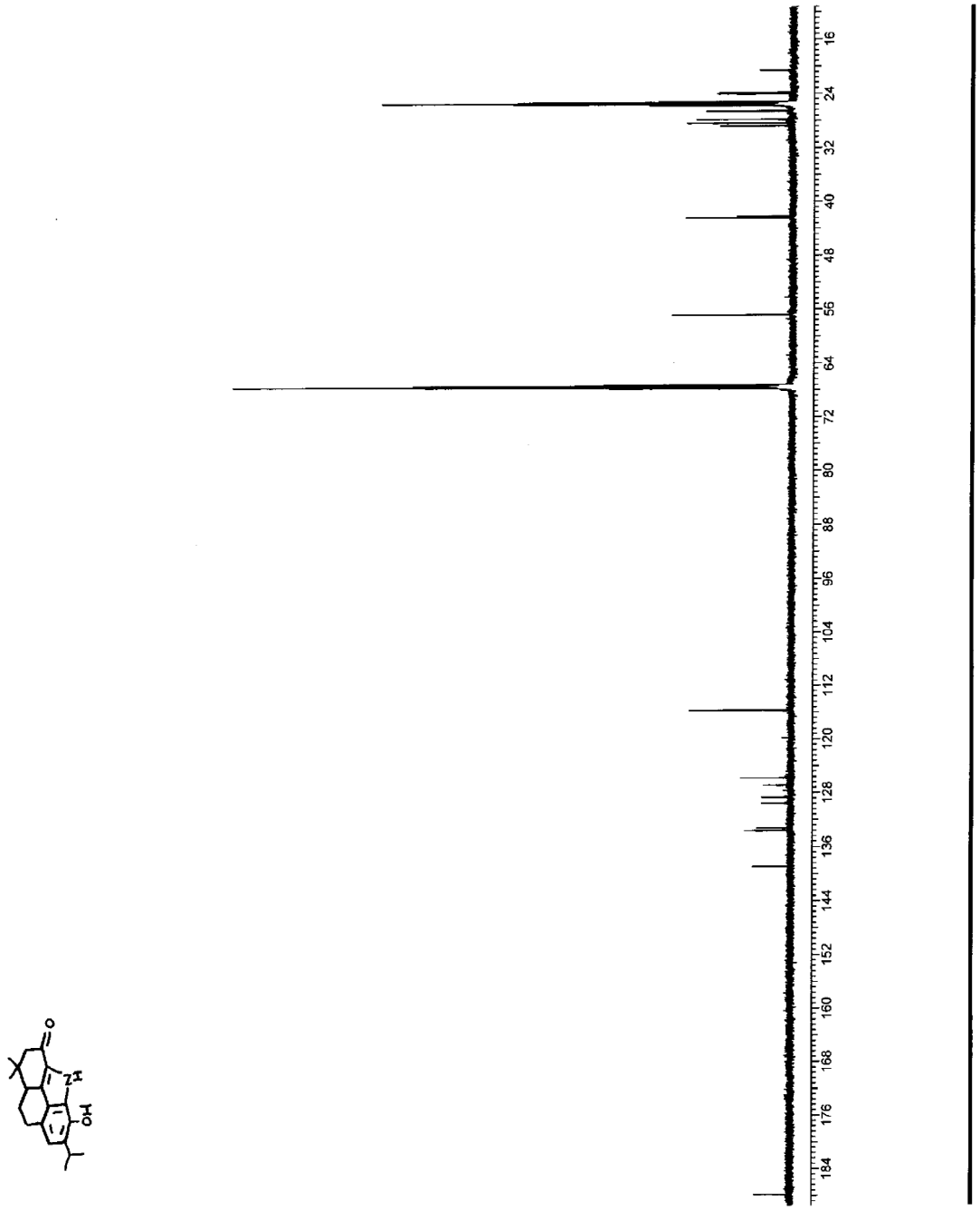

Figure 37: ^{13}C NMR of 1,8,9,9a-Tetrahydro-1,1-dimethyl-5-hydroxy-6-(1-methylethyl)-4*H*-benzo[*def*]carbazol-3(2*H*)-one (**124**)

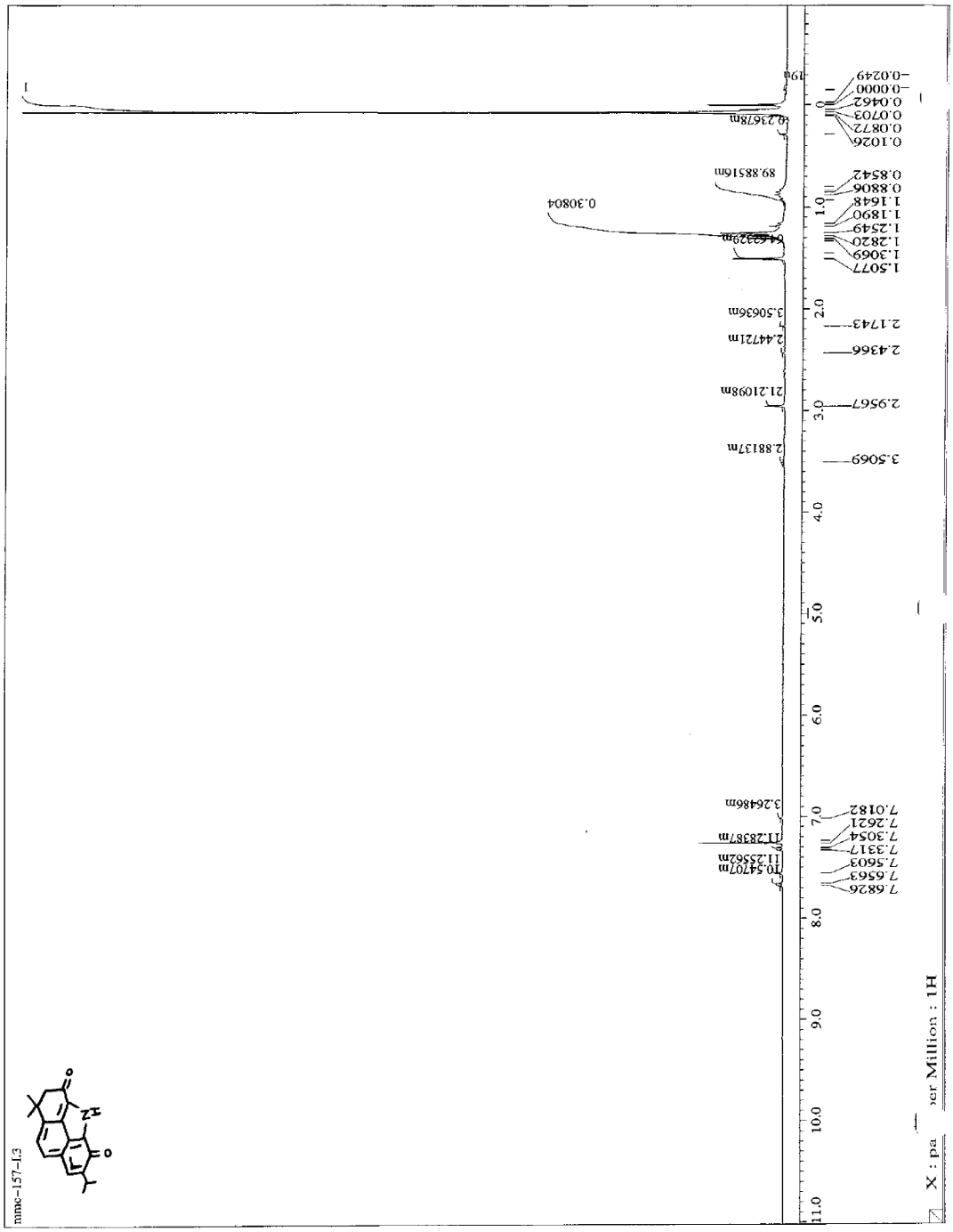

Figure 38: ^{1}H NMR of Salviadione **(123)**

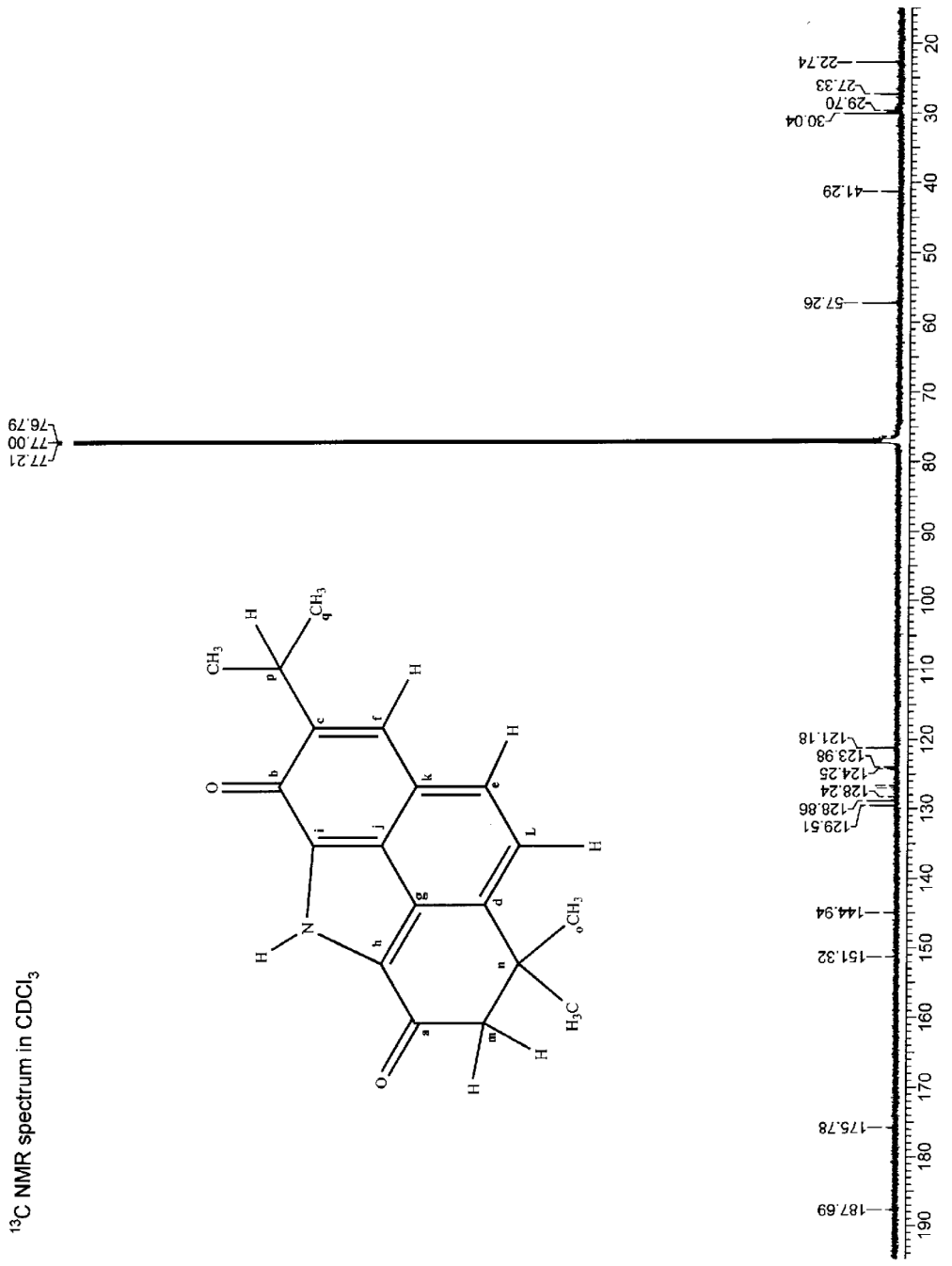

Figure 39: ^{13}C NMR of Salviadione **(123)**

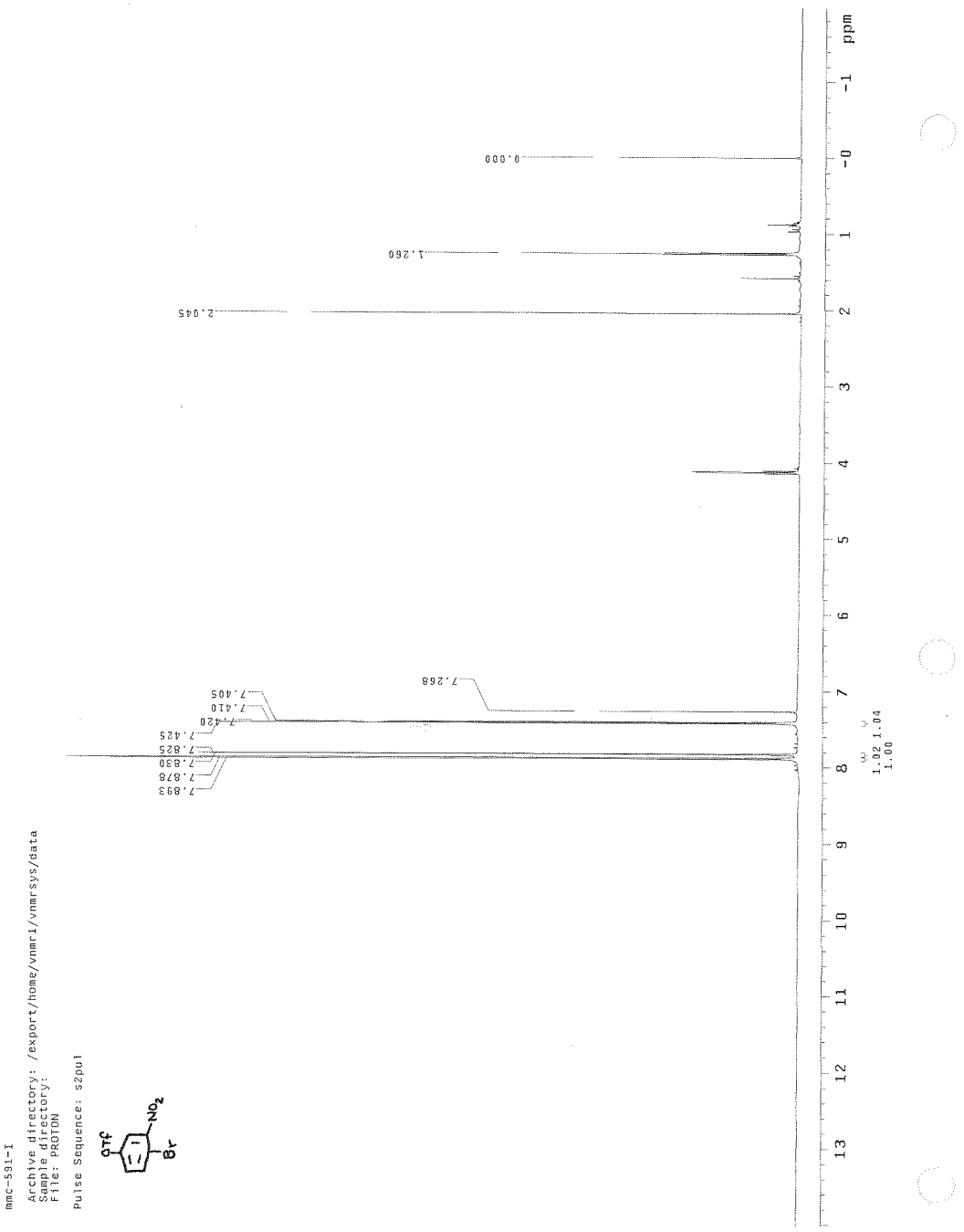

Figure 40: ^{1}H NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene **(163)**

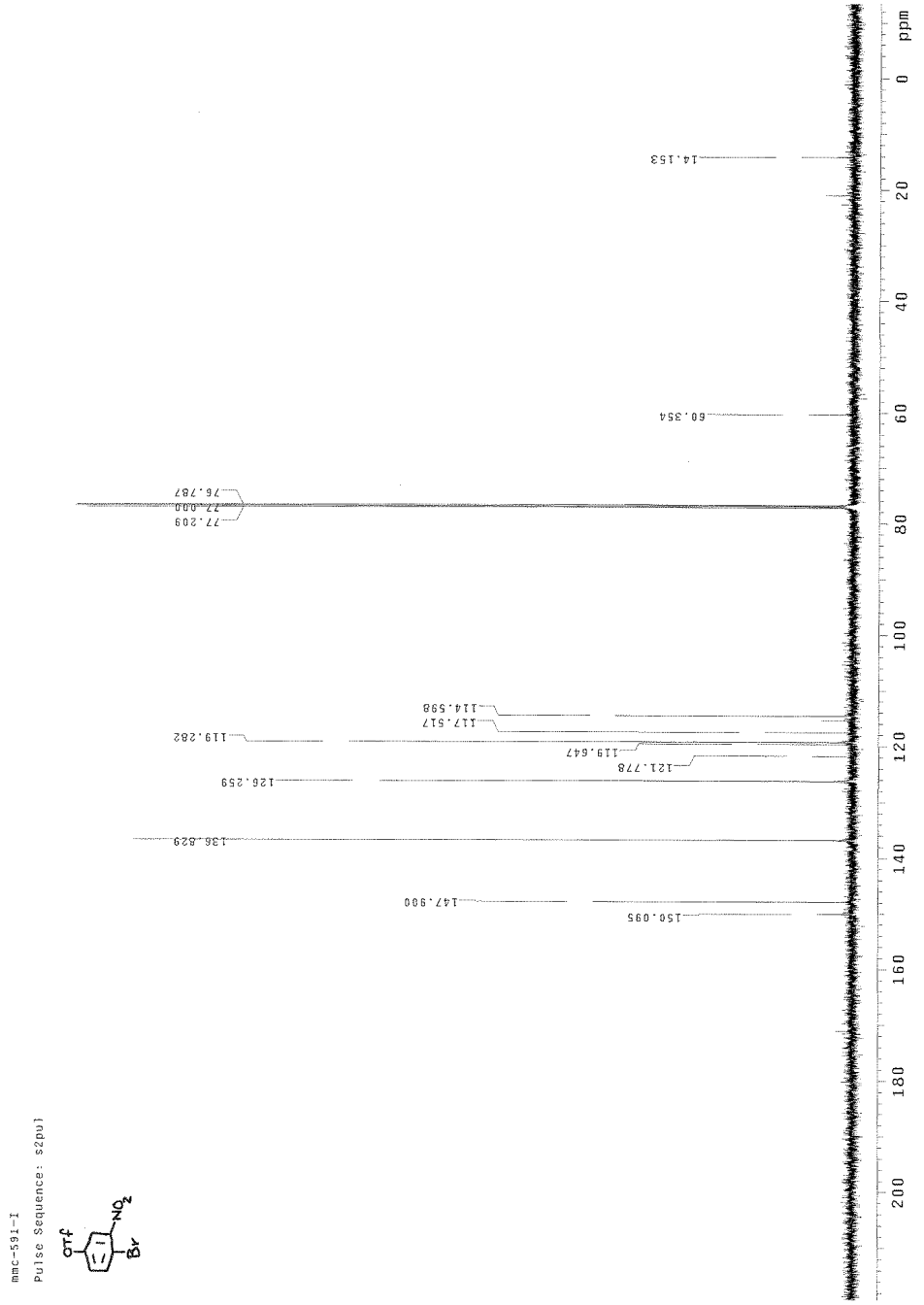

Figure 41: ^{13}C NMR of 2-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene **(163)**

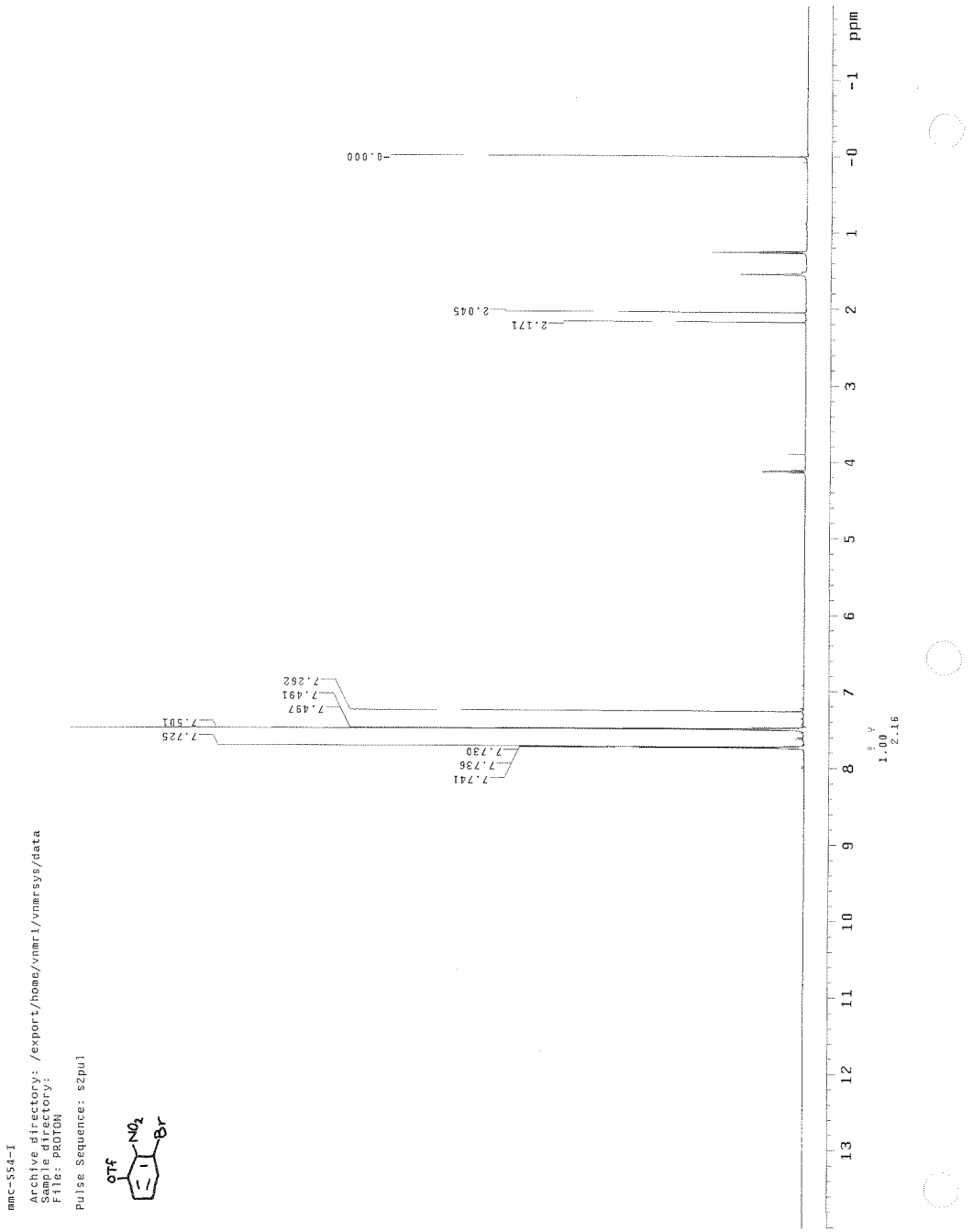

Figure 42: ^{1}H NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene **(166)**

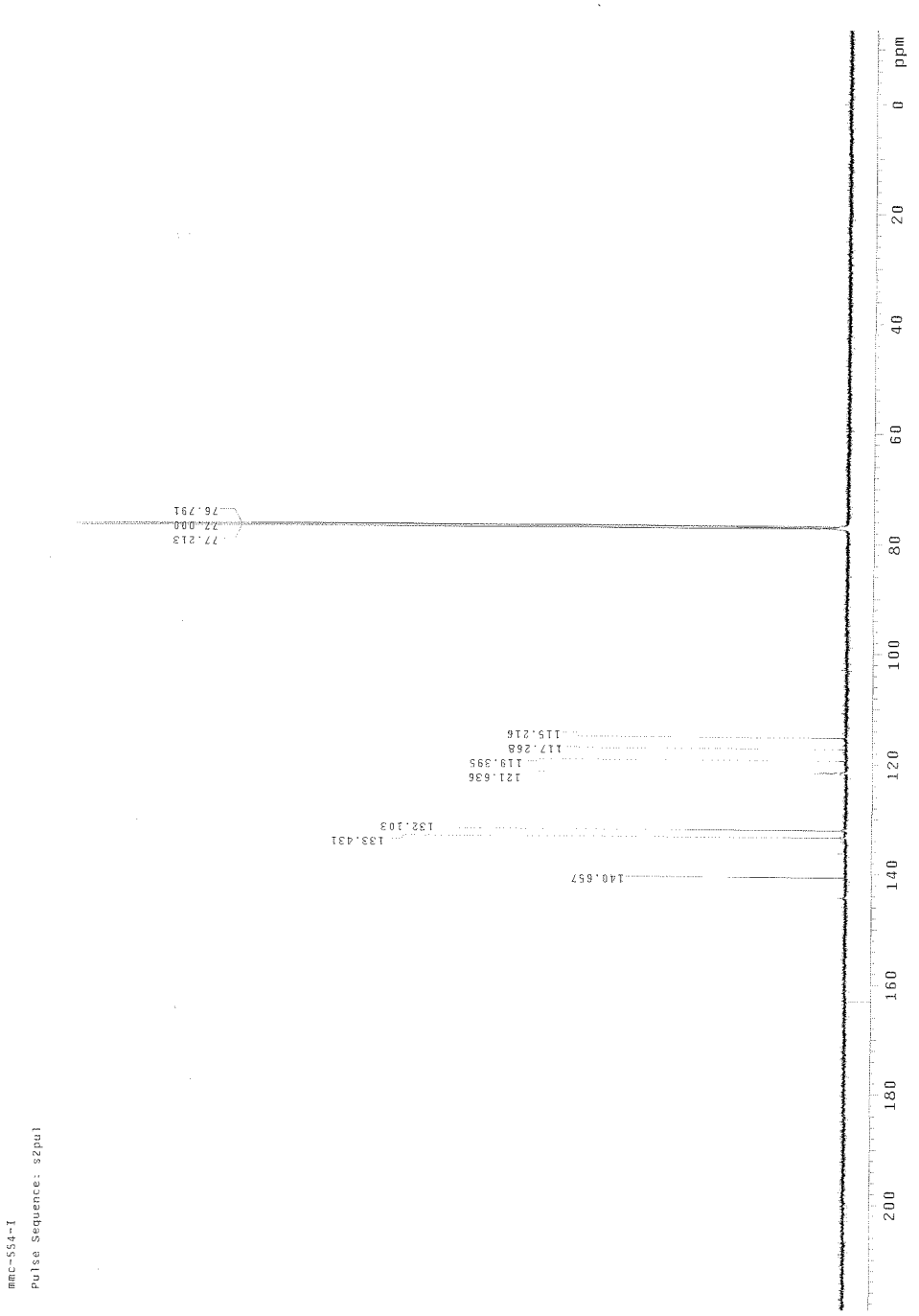

Figure 43: ^{13}C NMR of 2-Bromo-6-trifluoromethanesulfonyloxy-nitrobenzene **(166)**

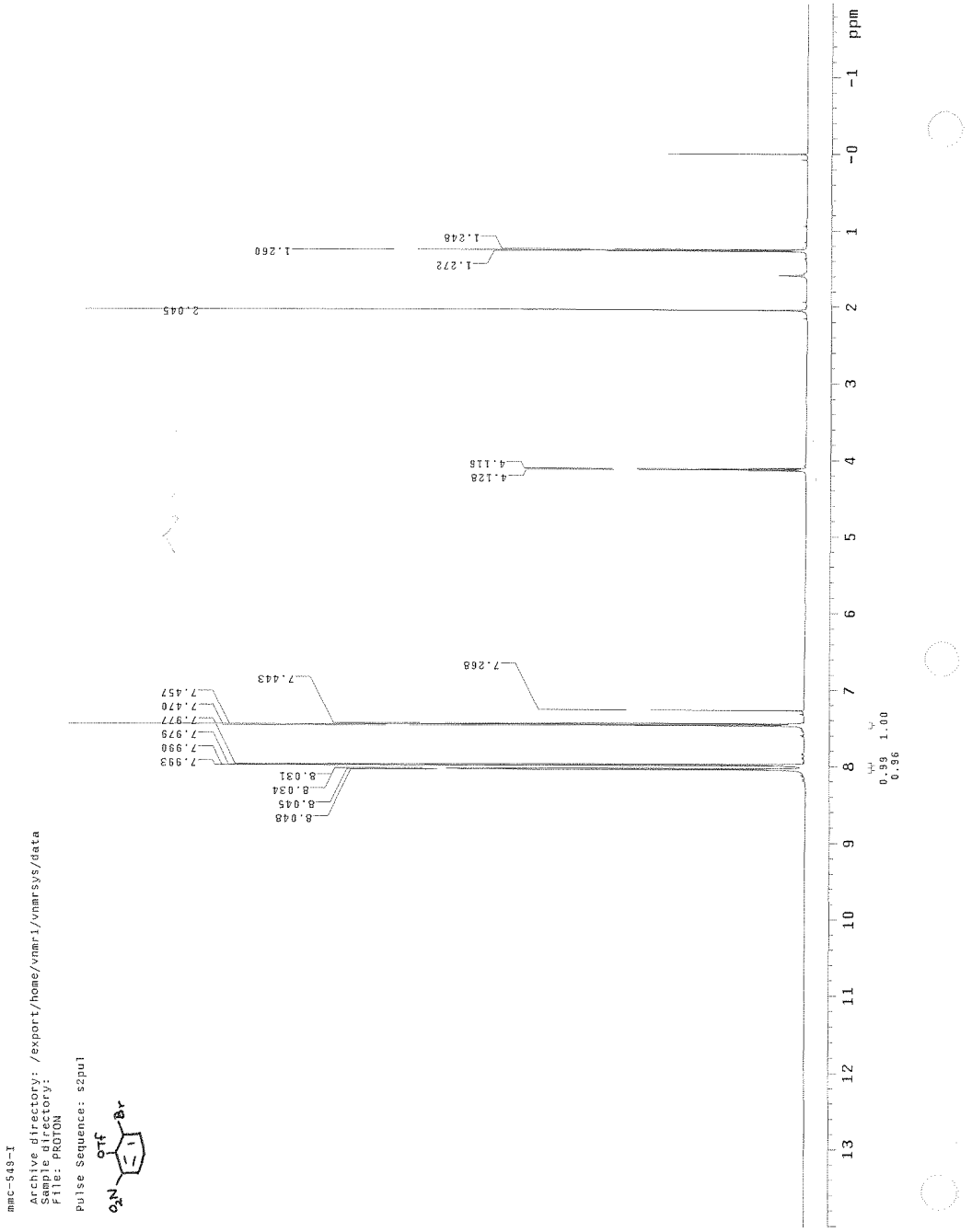

Figure 44: ^{1}H NMR of 3-Bromo-2-trifluoromethanesulfonyloxy-nitrobenzene **(151)**

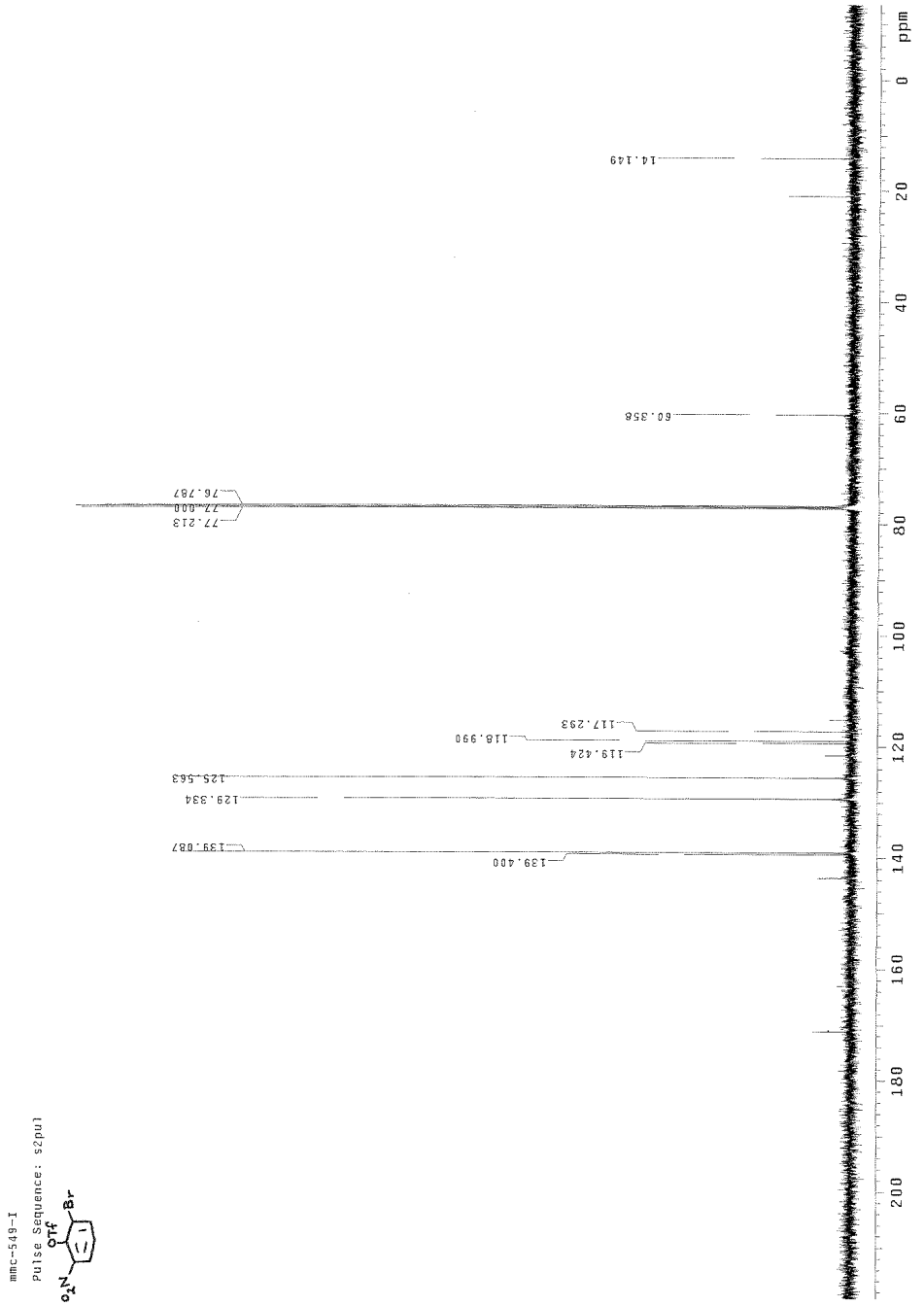

Figure 45: ^{13}C NMR of 3-bromo-2-trifluoromethanesulfonyloxy-nitrobenzene (**151**)

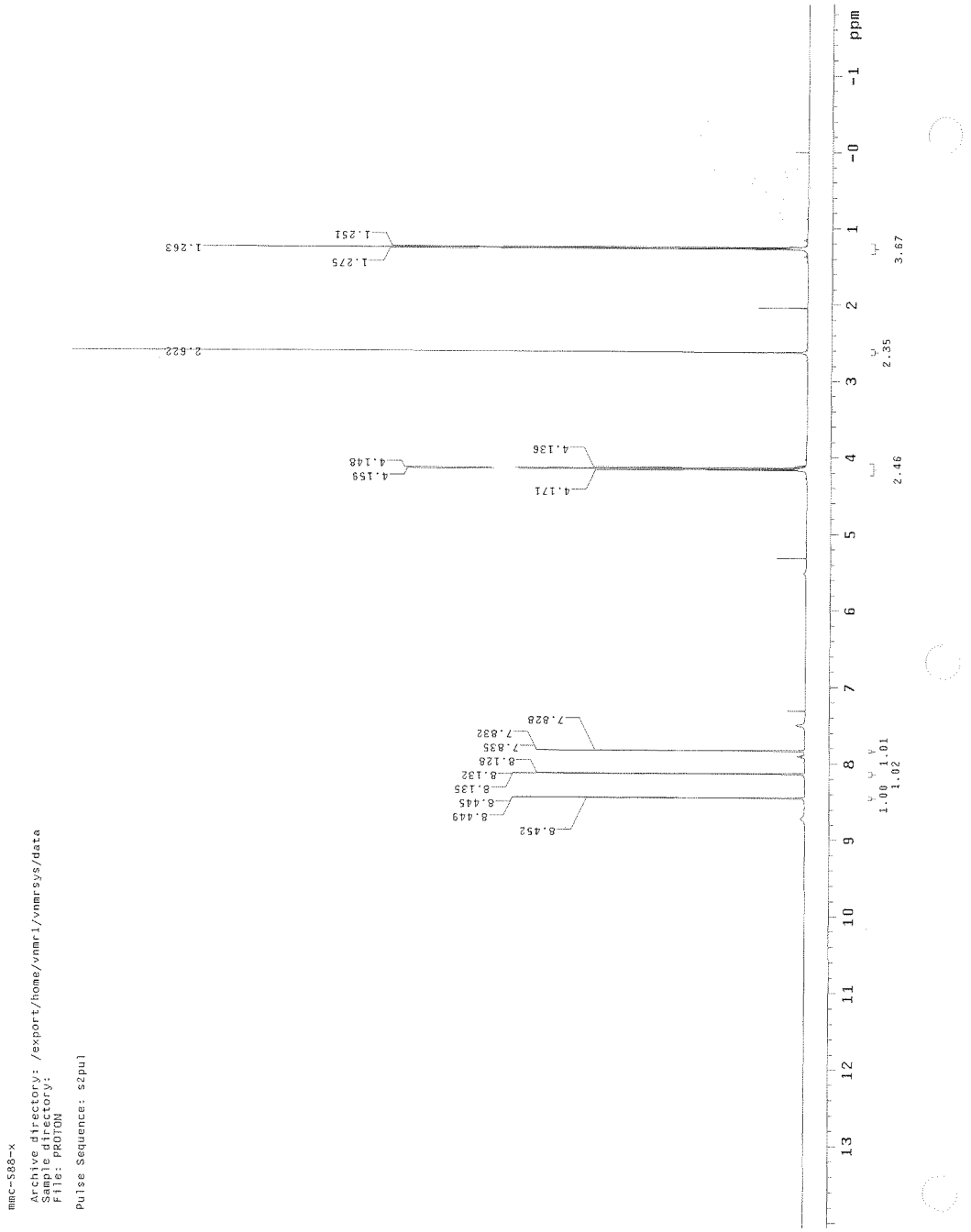

Figure 46: ^{1}H NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene **(157)**

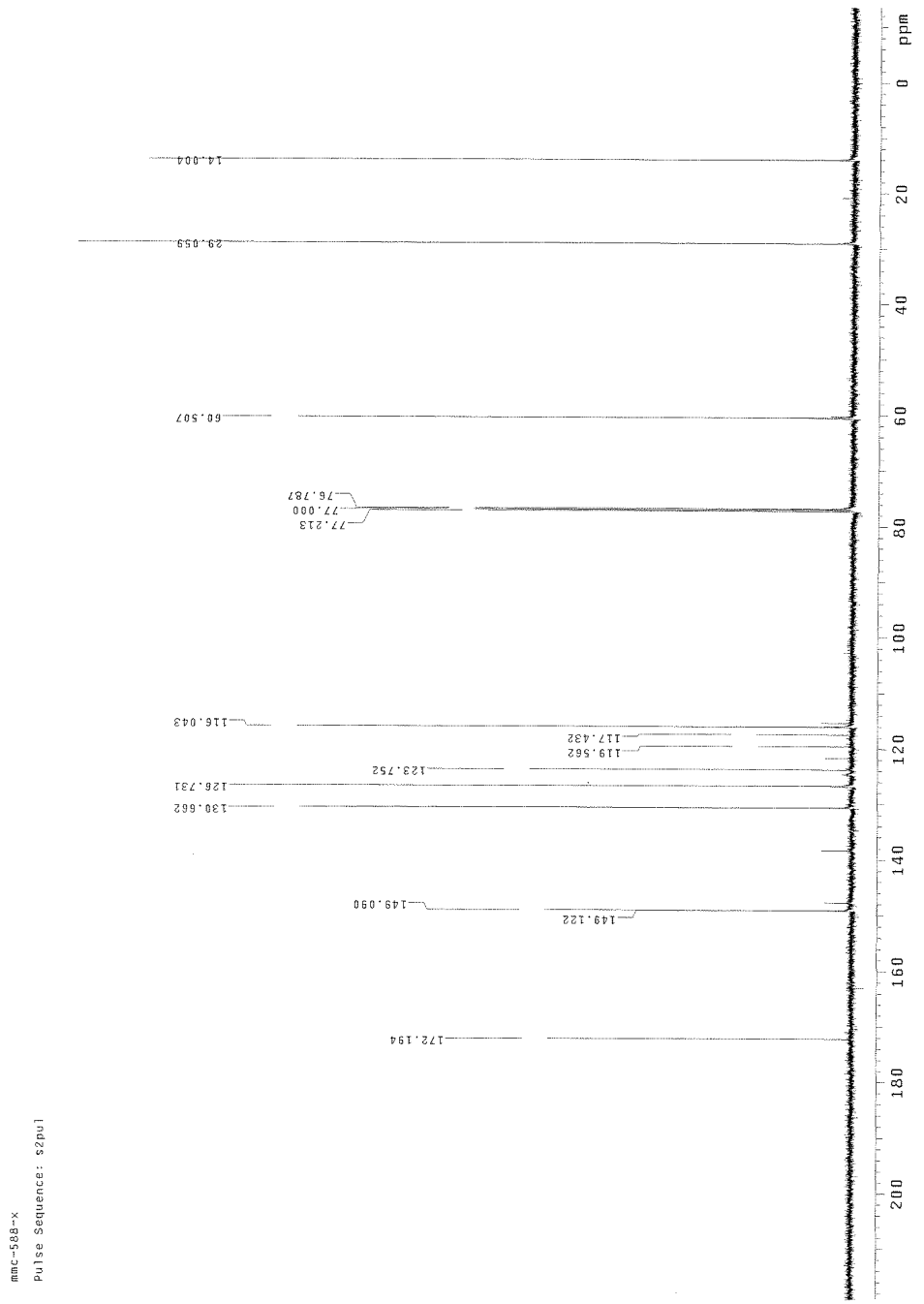

Figure 47: ^{13}C NMR of 3-Bromo-5-trifluoromethanesulfonyloxy-nitrobenzene **(157)**

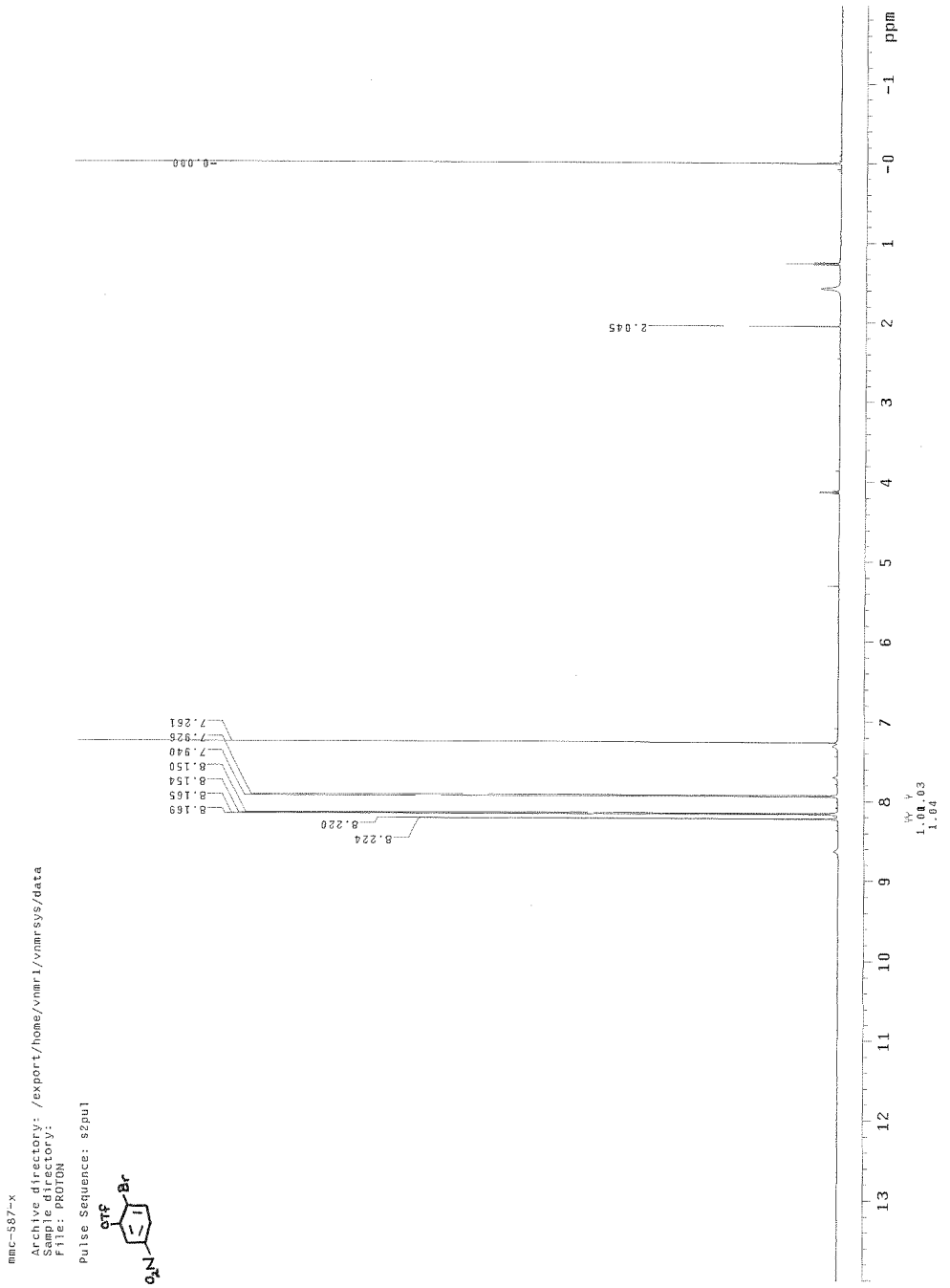

Figure 48: ^{1}H NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene **(159)**

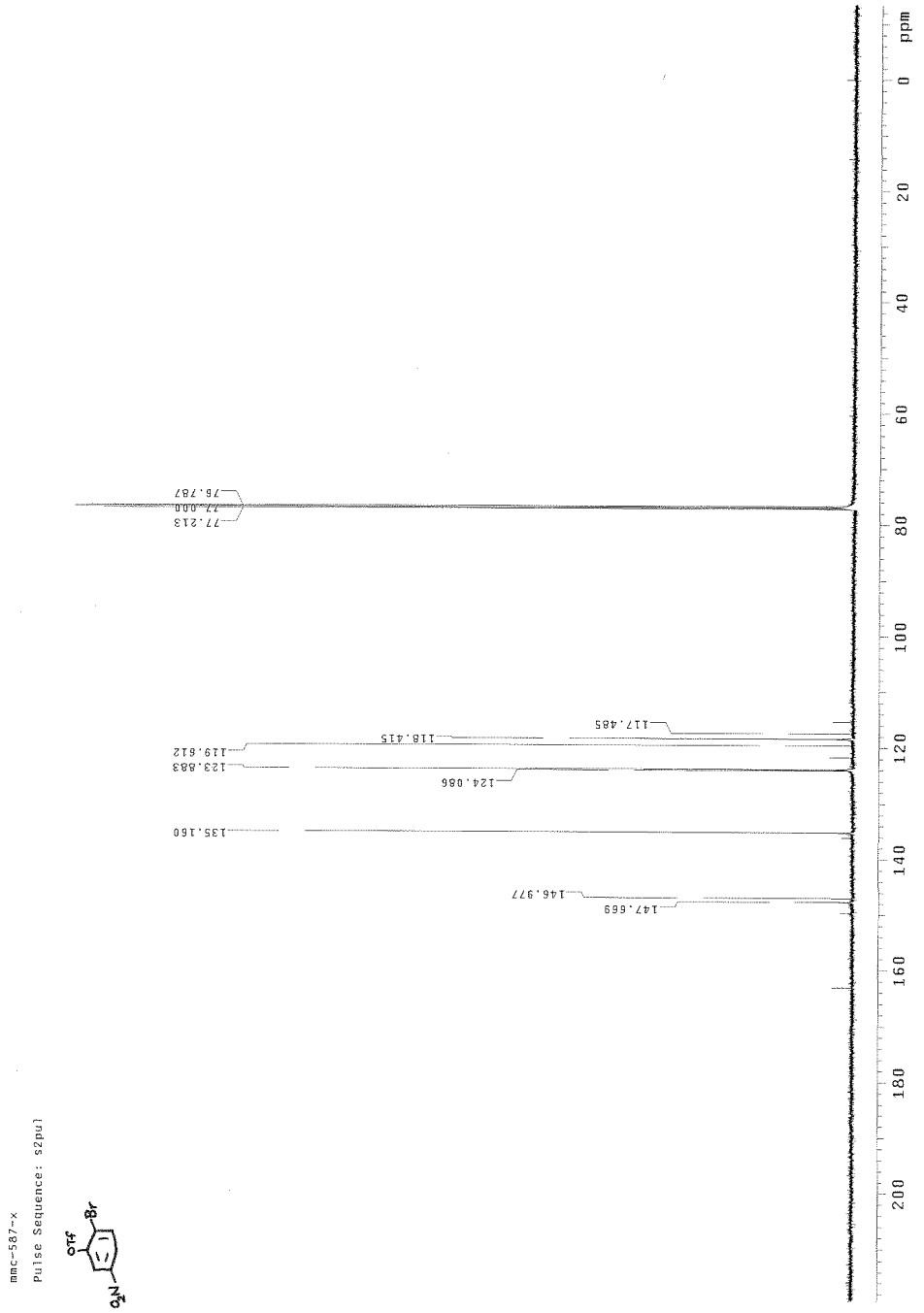

Figure 49: ^{13}C NMR of 4-Bromo-3-trifluoromethanesulfonyloxy-nitrobenzene **(159)**

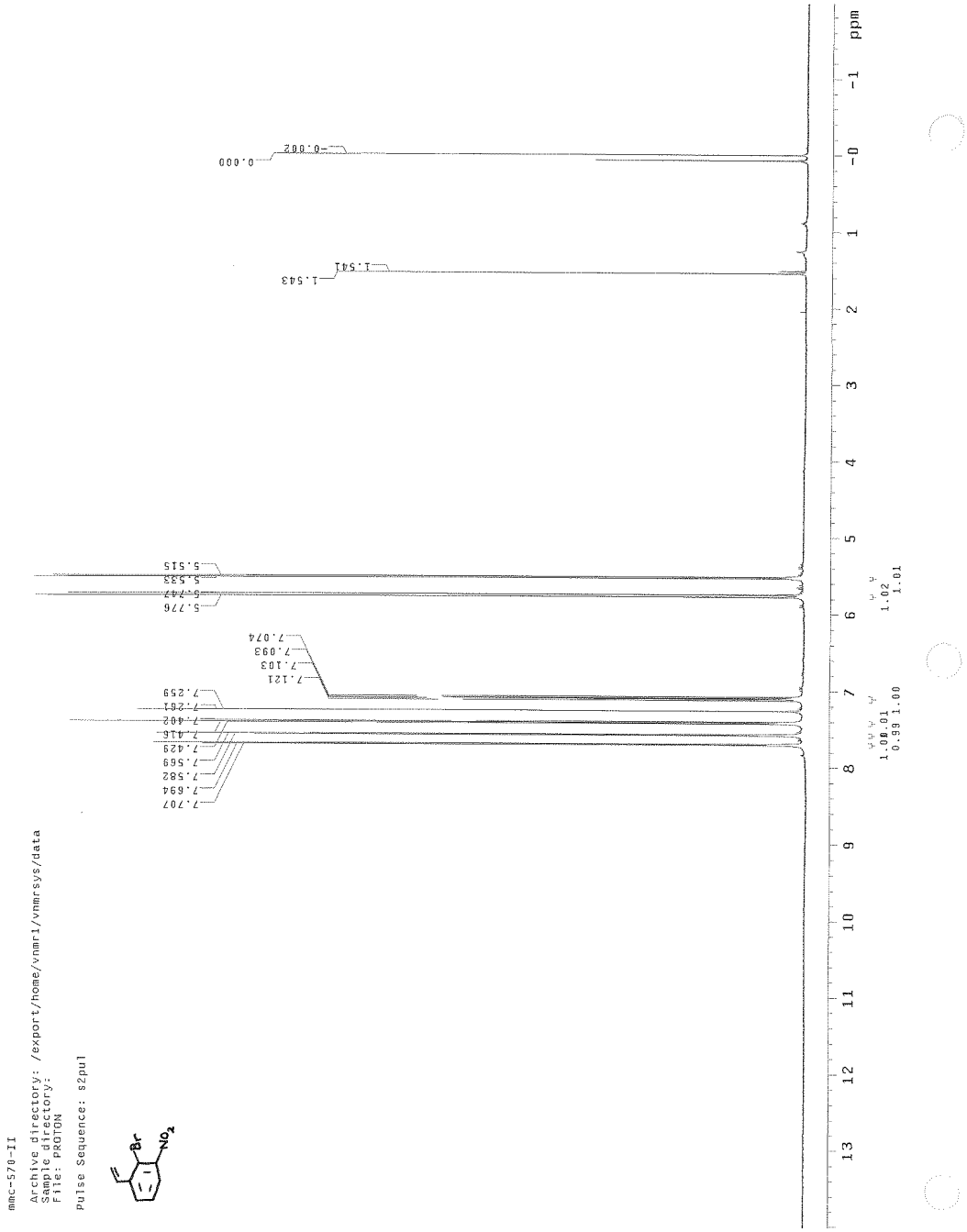

Figure 50: ^{1}H NMR of 2-Bromo-3-ethenyl-nitrobenzene **(170)**

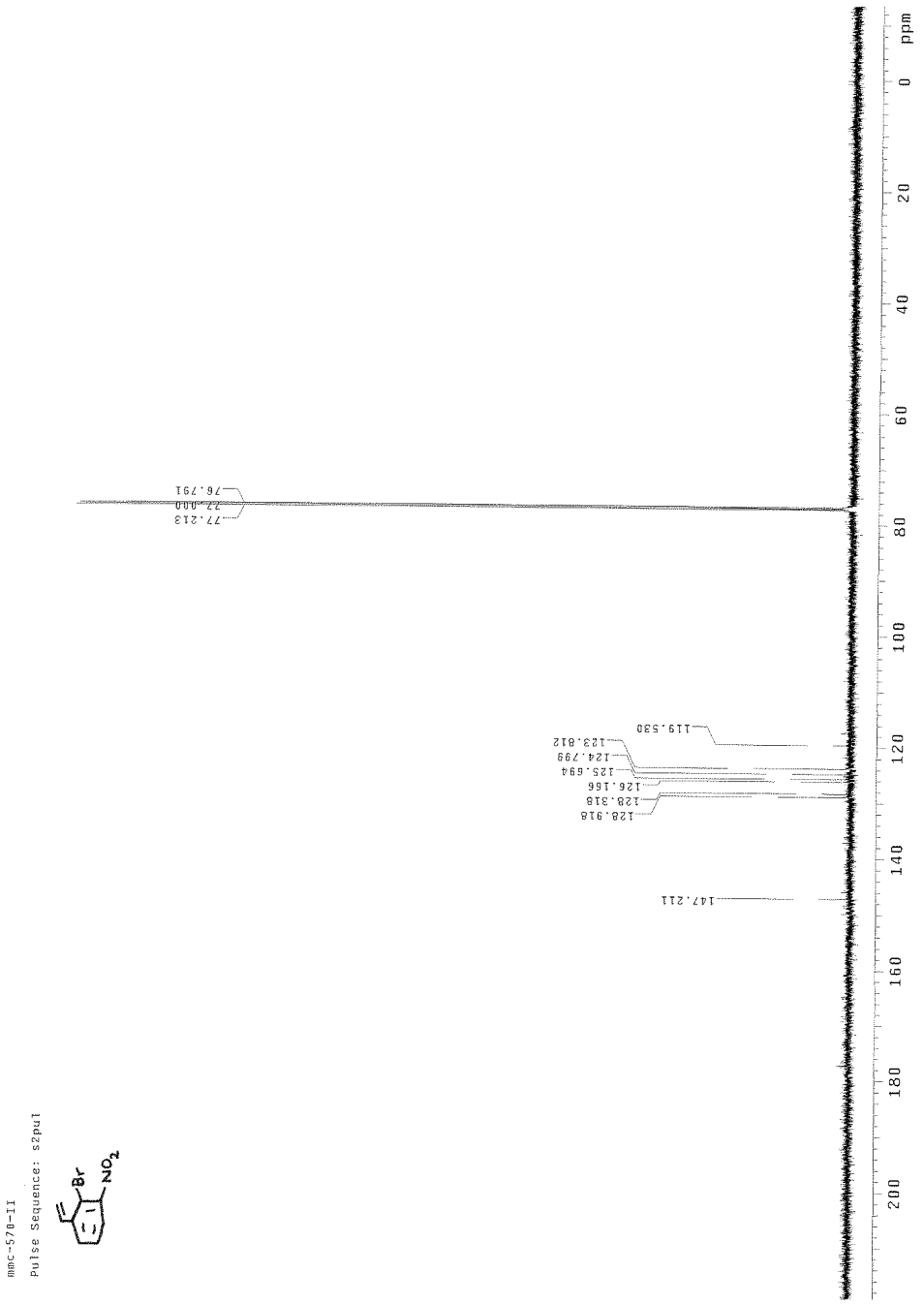

Figure 51: ^{13}C NMR of 2-Bromo-3-ethenyl-nitrobenzene **(170)**

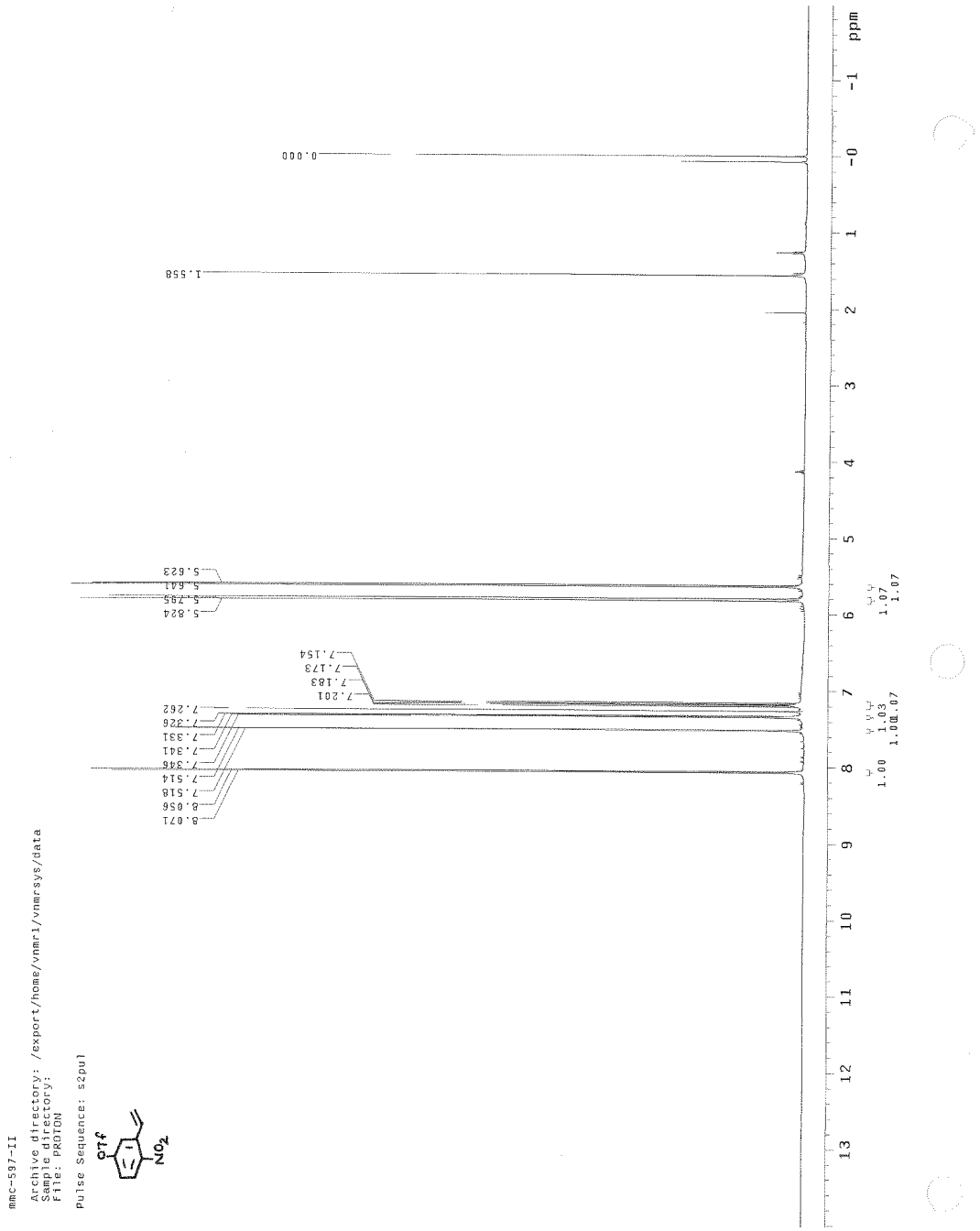

Figure 52: ^{1}H NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene **(171)**

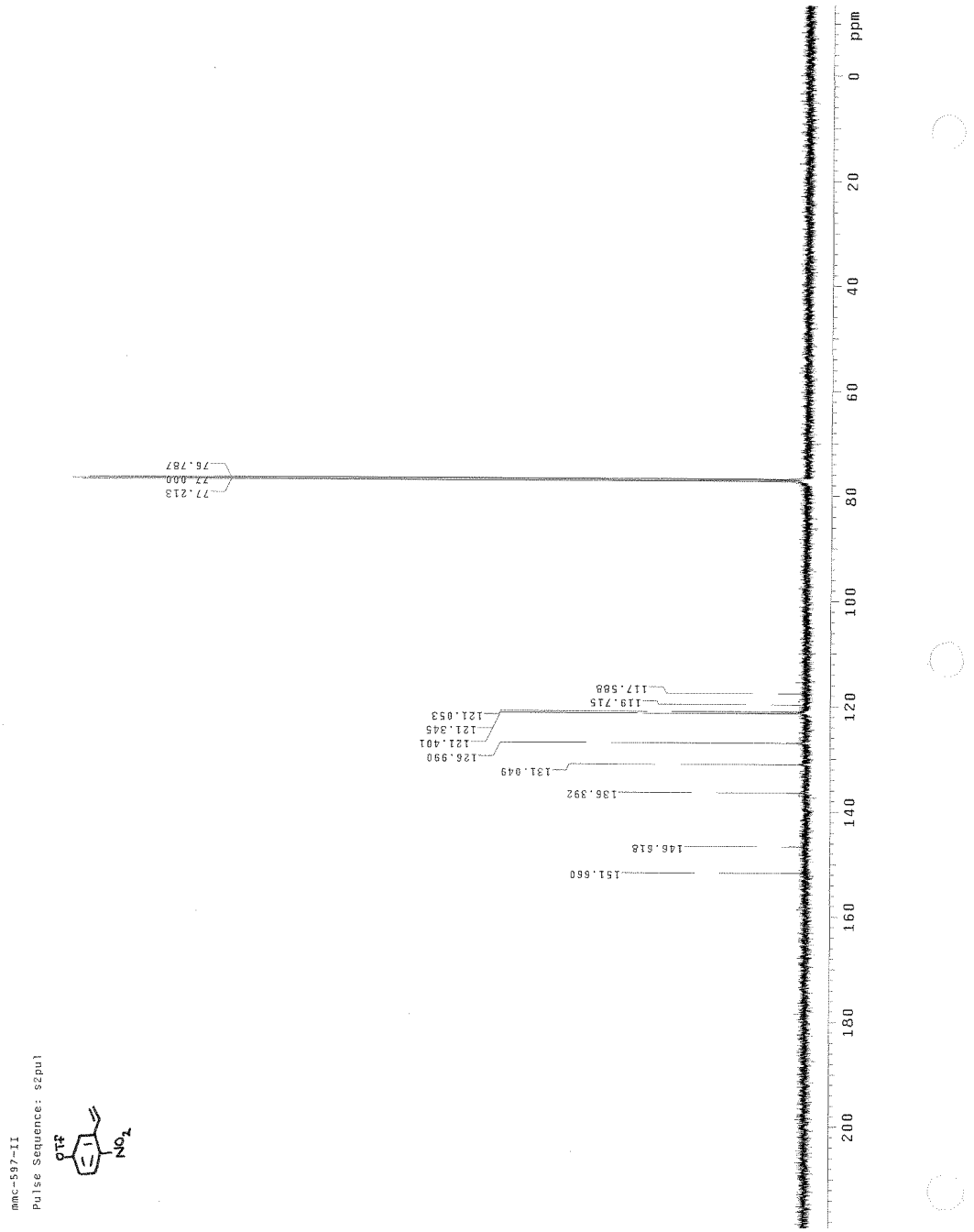

Figure 53: ^{13}C NMR of 2-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene **(171)**

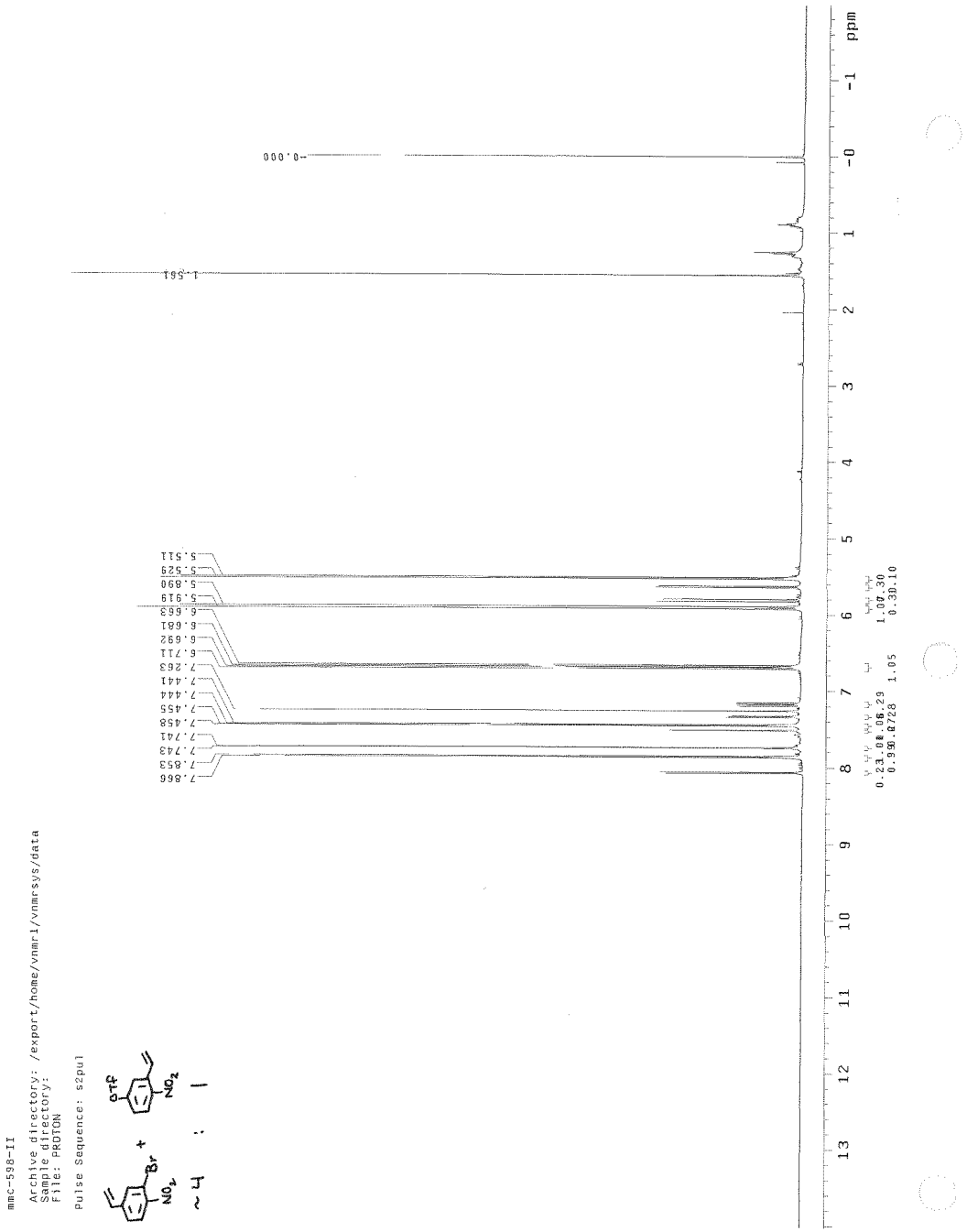

Figure 54: ^{1}H NMR of 2-Bromo-4-ethenyl-nitrobenzene **(172)**

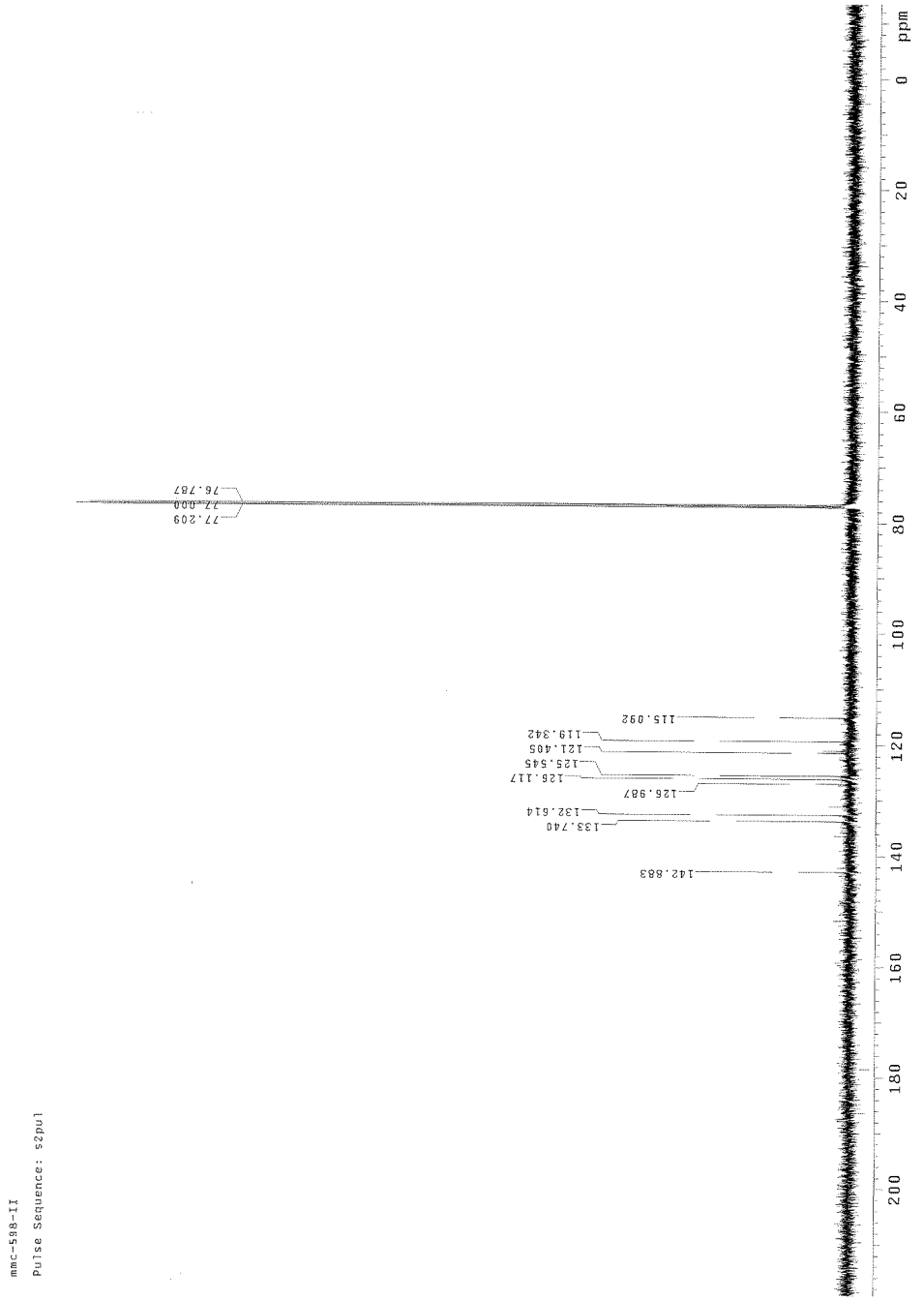

Figure 55: ^{13}C NMR of 2-Bromo-4-ethenyl-nitrobenzene **(172)**

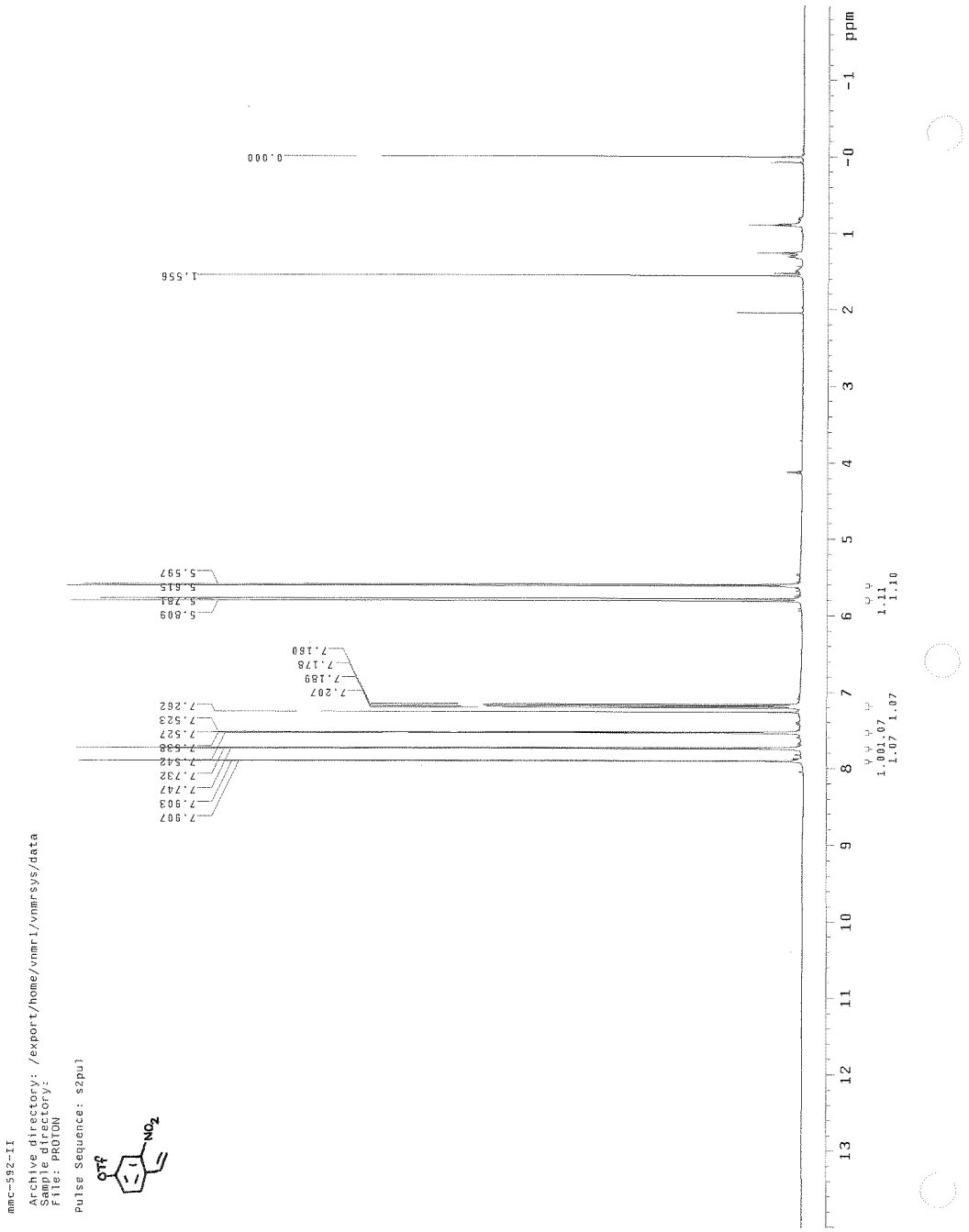

Figure 56: [1]H NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene **(173)**

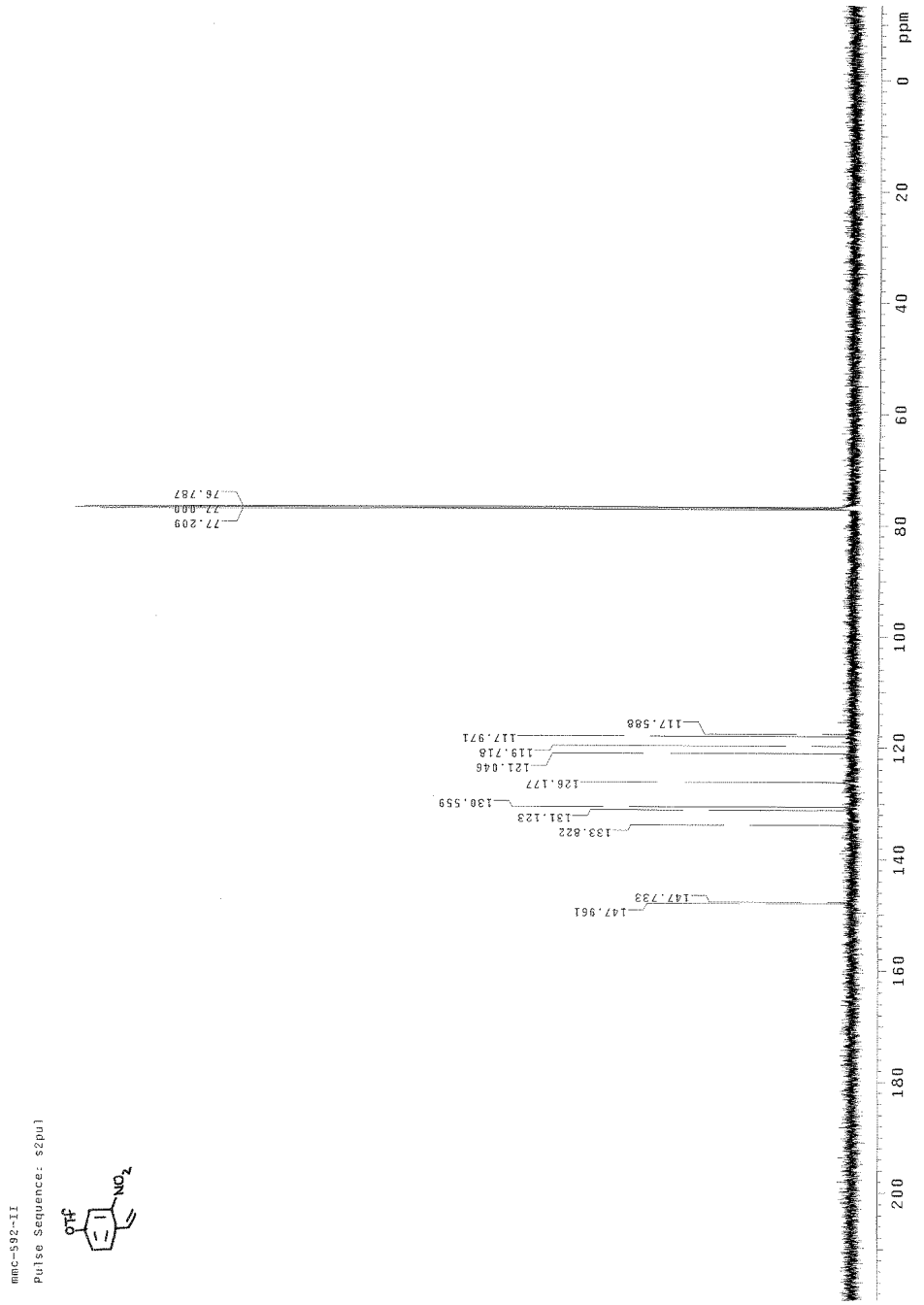

Figure 57: ^{13}C NMR of 2-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene **(173)**

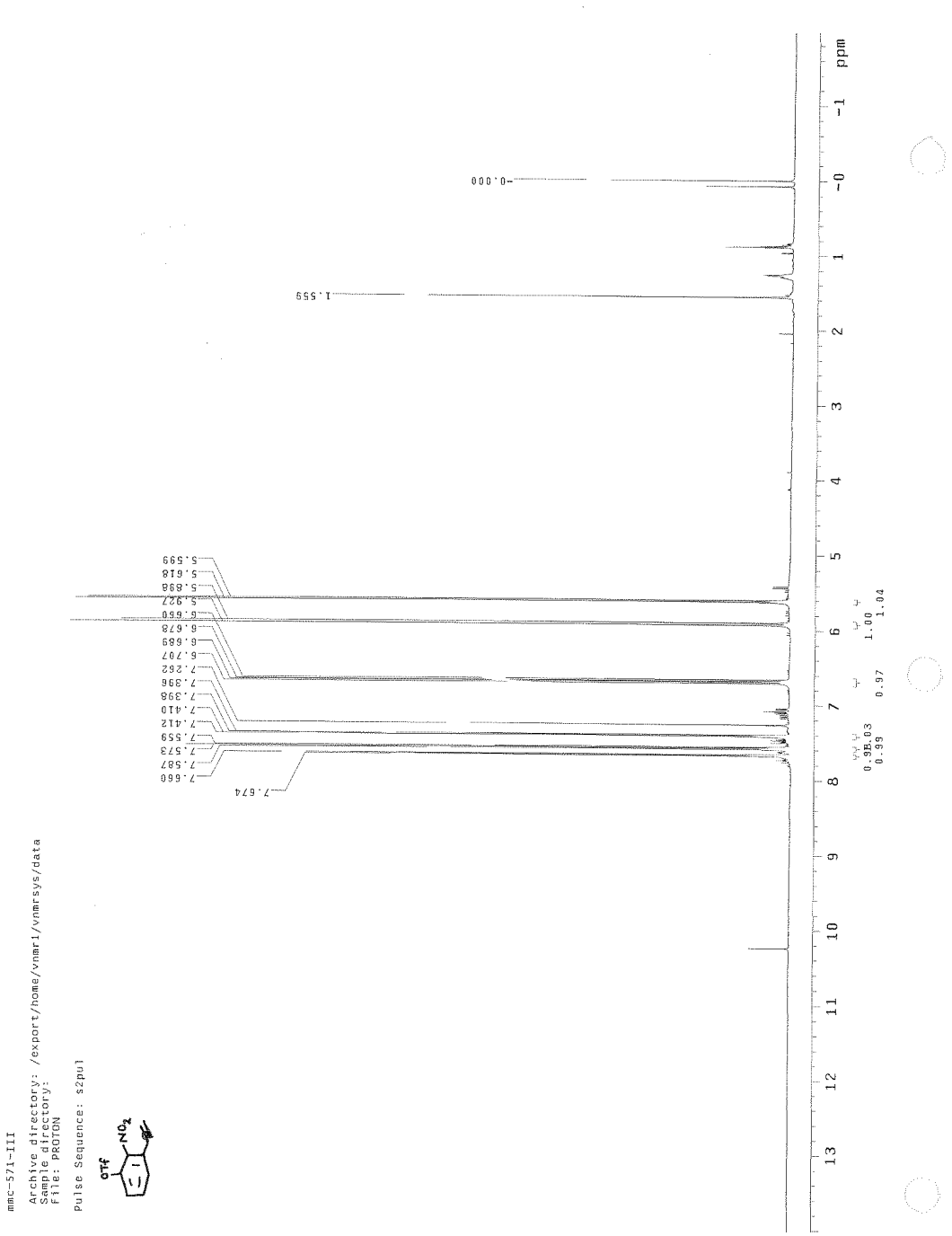

Figure 58: ^{1}H NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene **(175)**

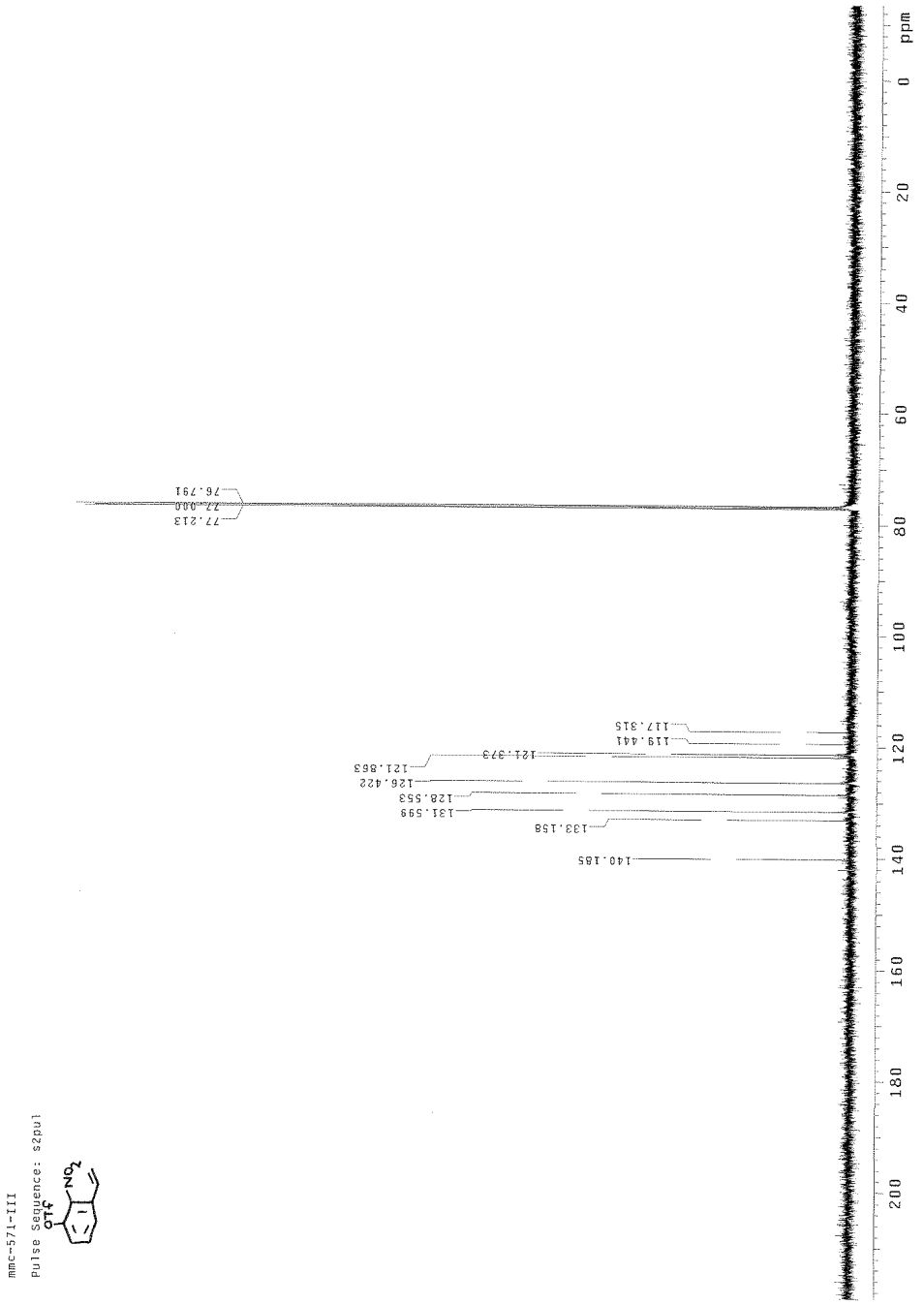

Figure 59: ^{13}C NMR of 2-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene **(175)**

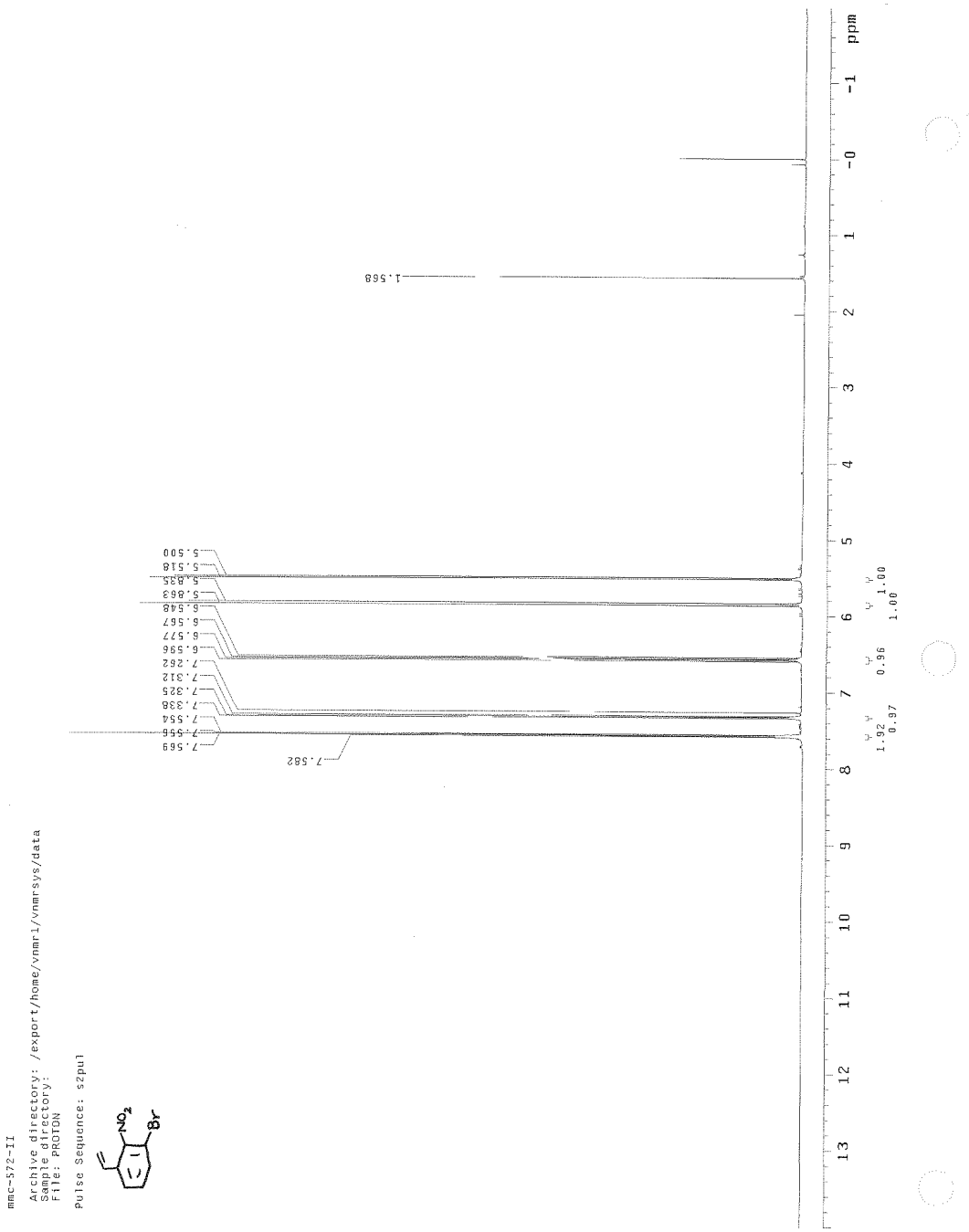

Figure 60: ^{1}H NMR of 2-Bromo-6-ethenyl-nitrobenzene **(176)**

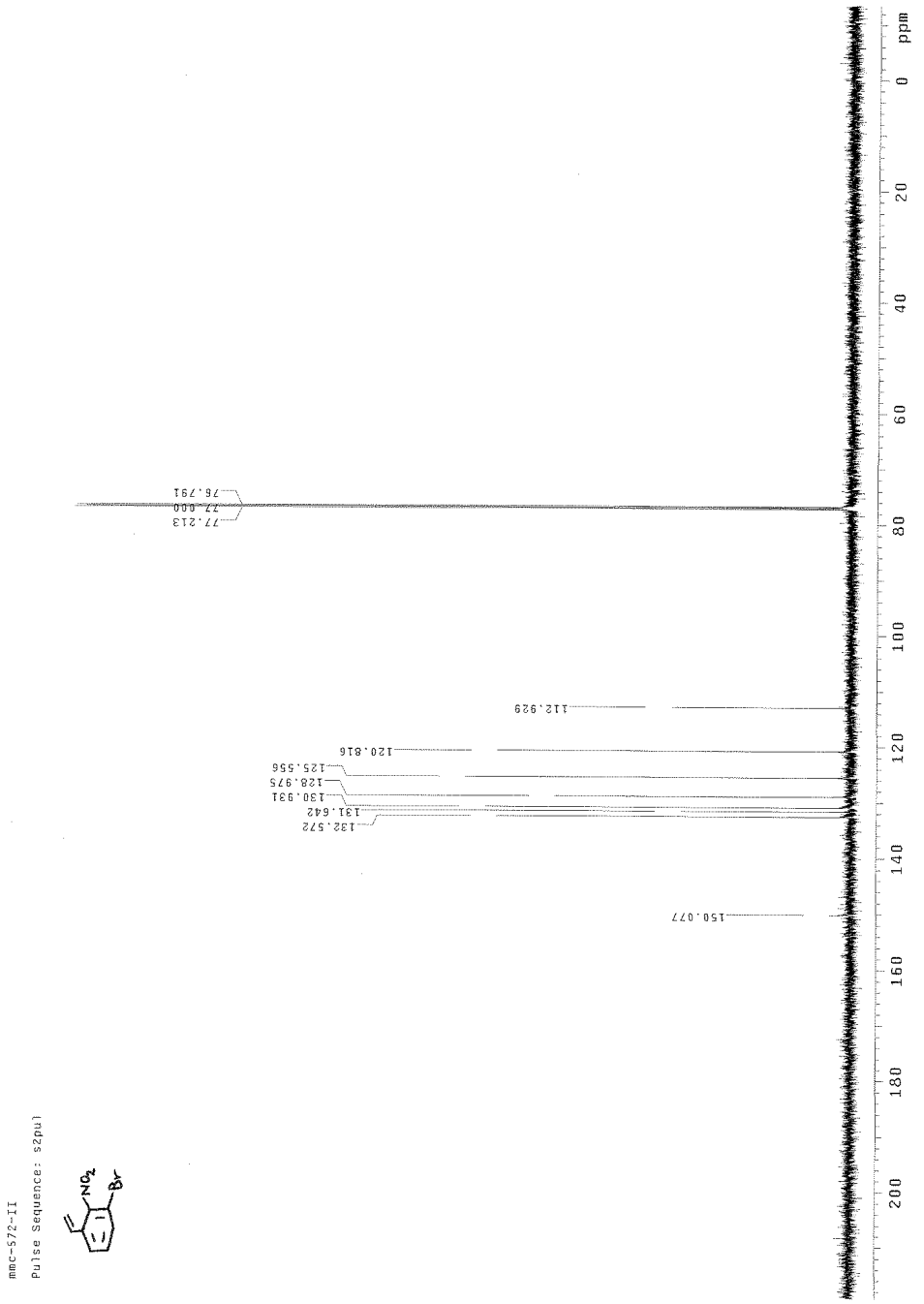

Figure 61: ^{13}C NMR of 2-Bromo-6-ethenyl-nitrobenzene **(176)**

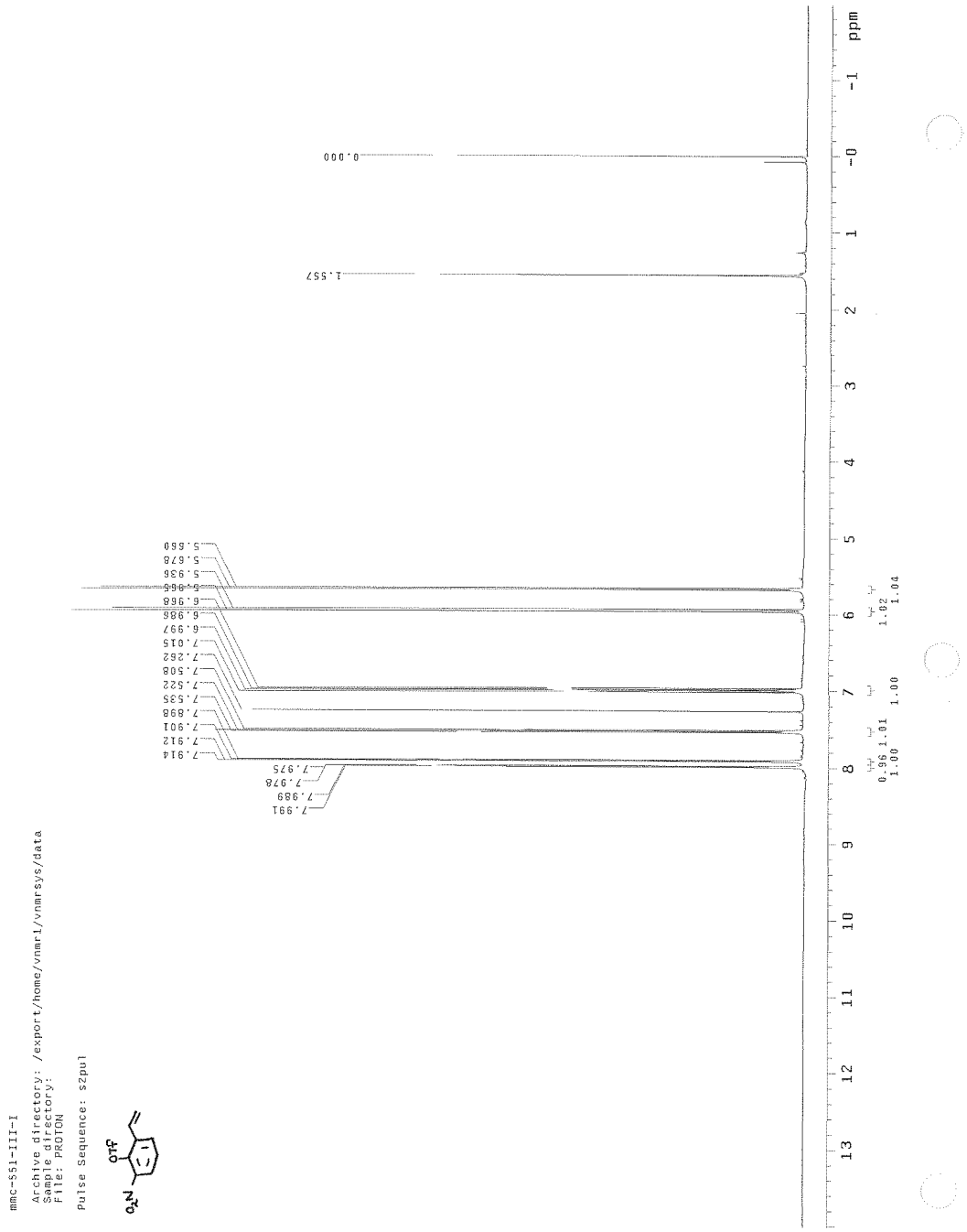

Figure 62: ^{1}H NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene **(177)**

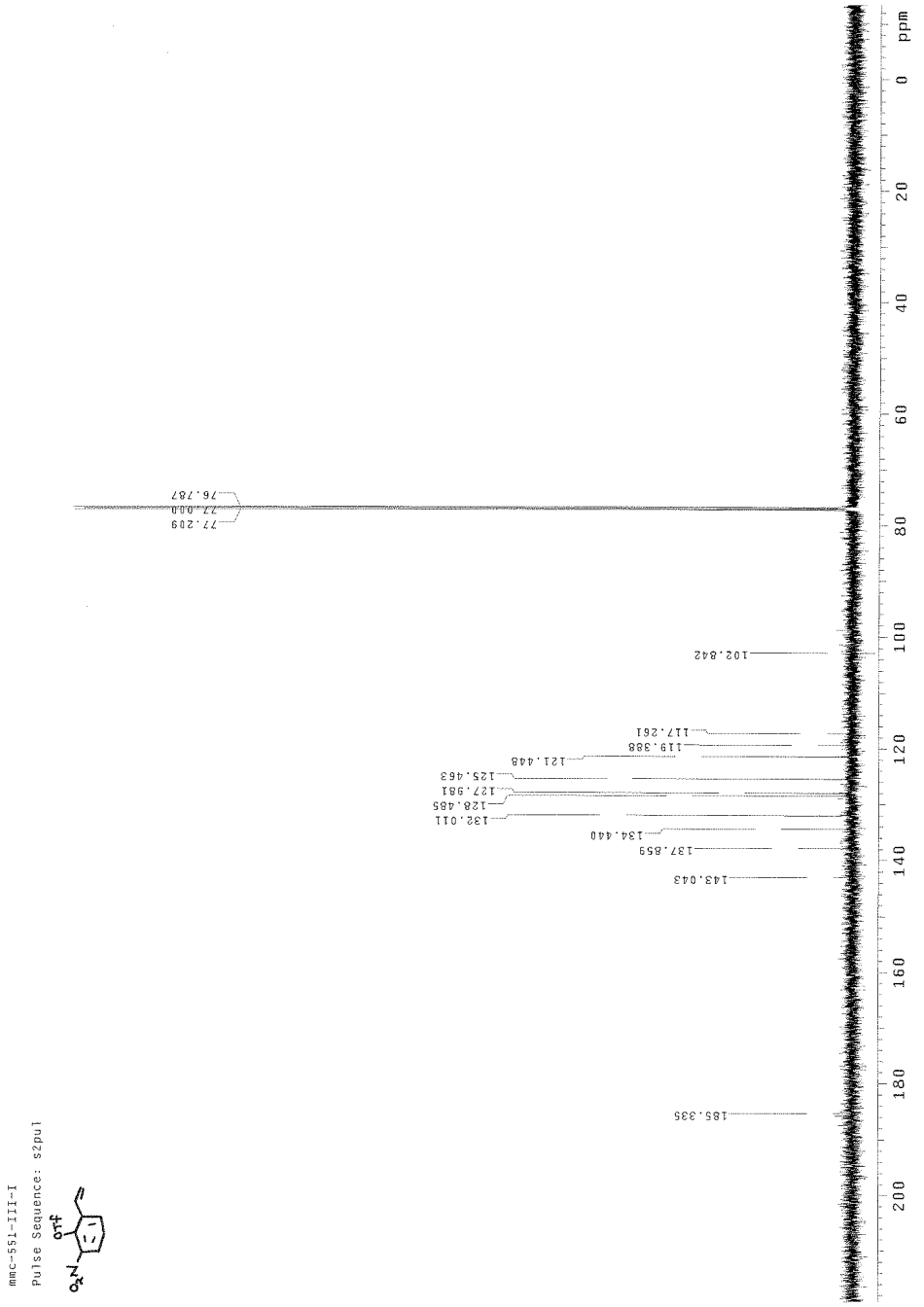

Figure 63: ^{13}C NMR of 3-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene **(177)**

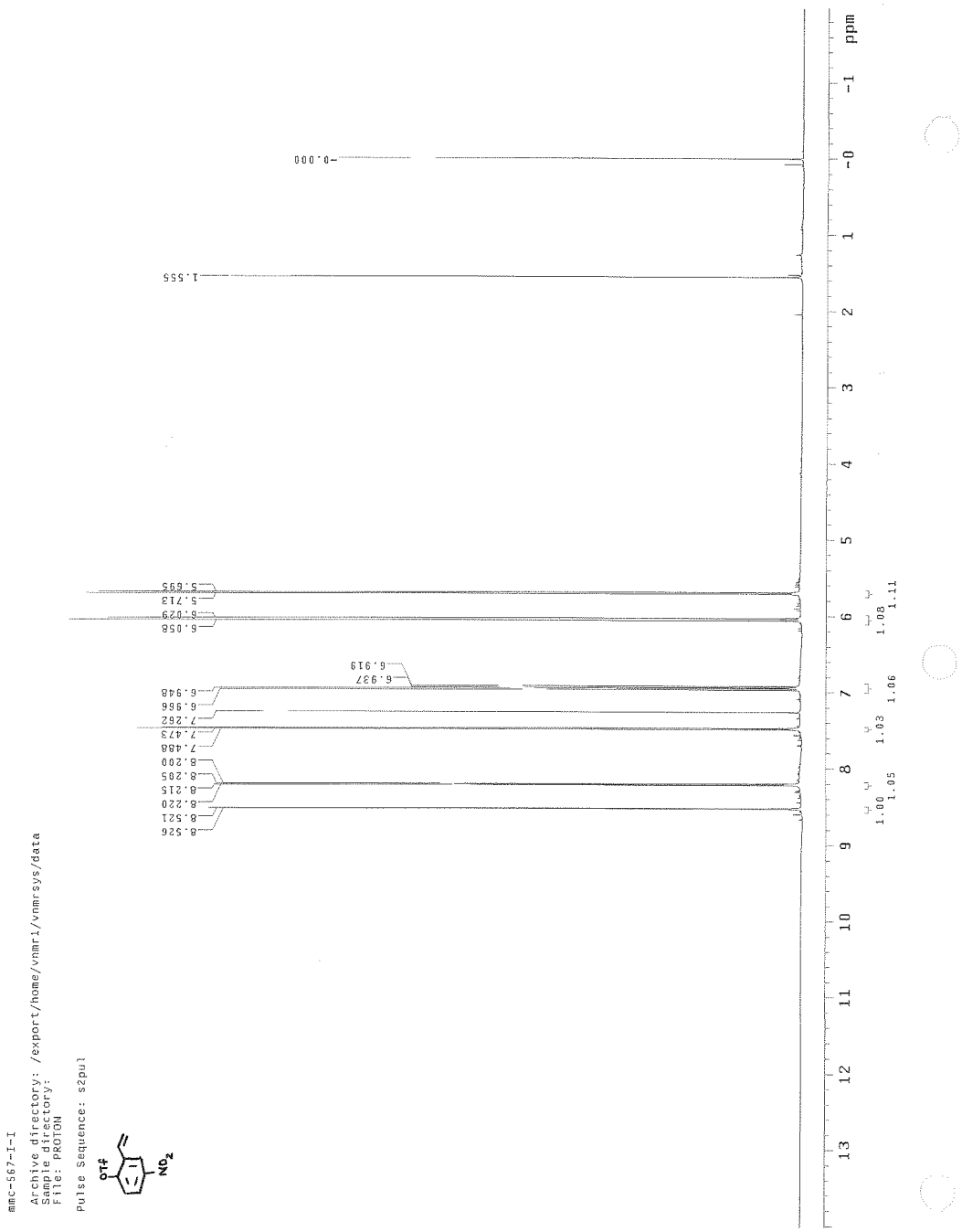

Figure 64: ^{1}H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene **(178)**

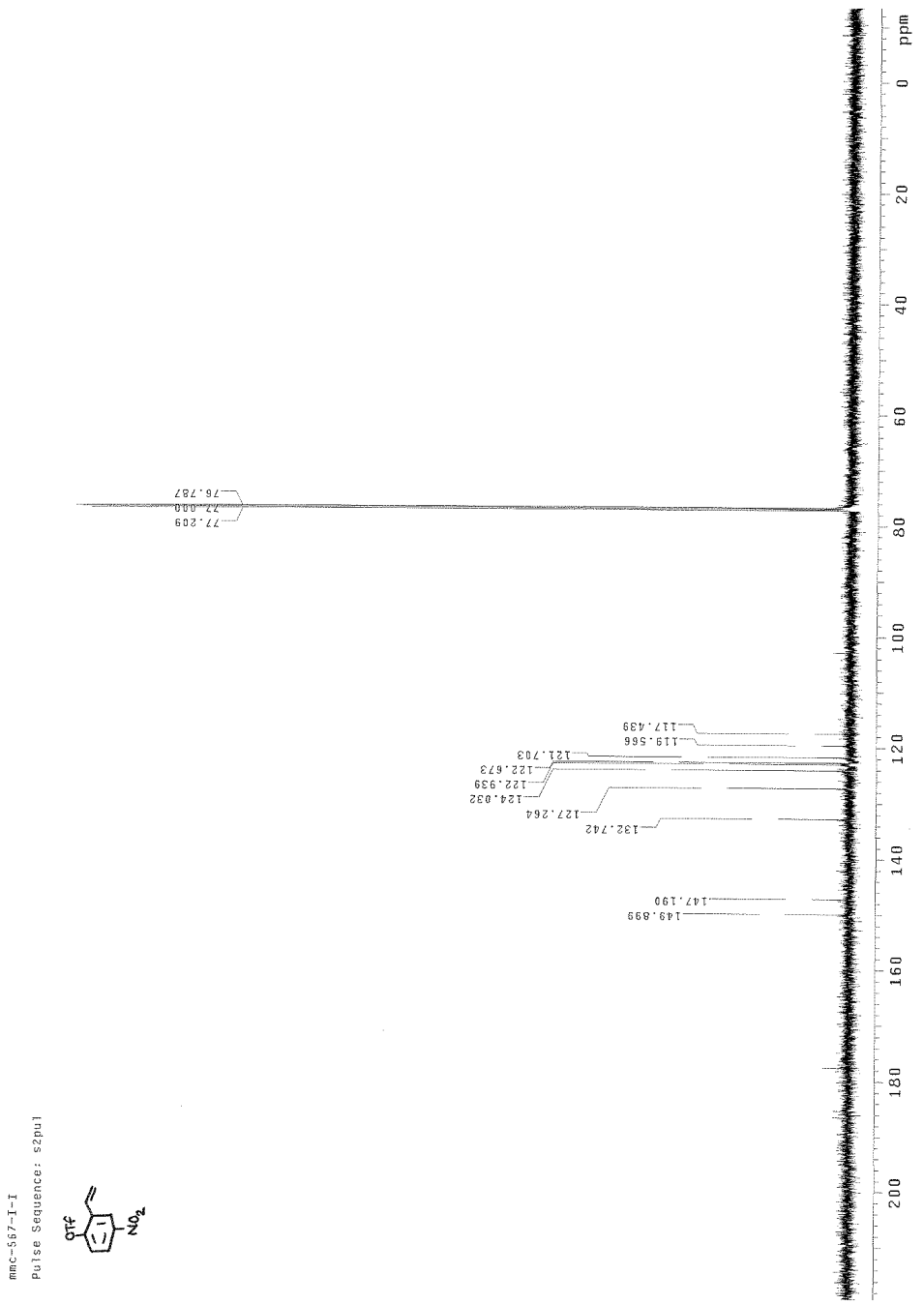

Figure 65: ^{13}C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy-nitrobenzene **(178)**

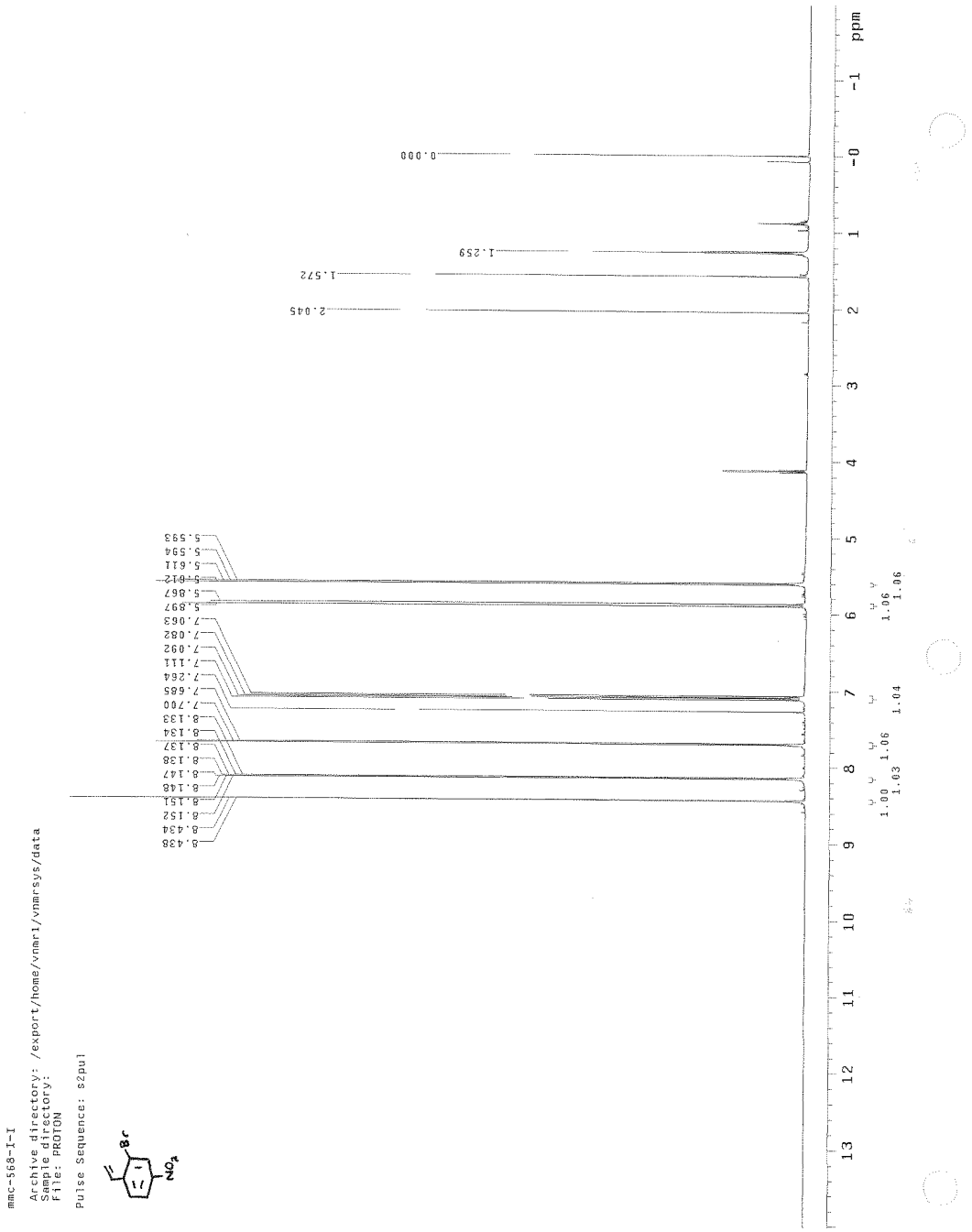

Figure 66: ^{1}H NMR of 3-Bromo-4-ethenyl-nitrobenzene **(179)**

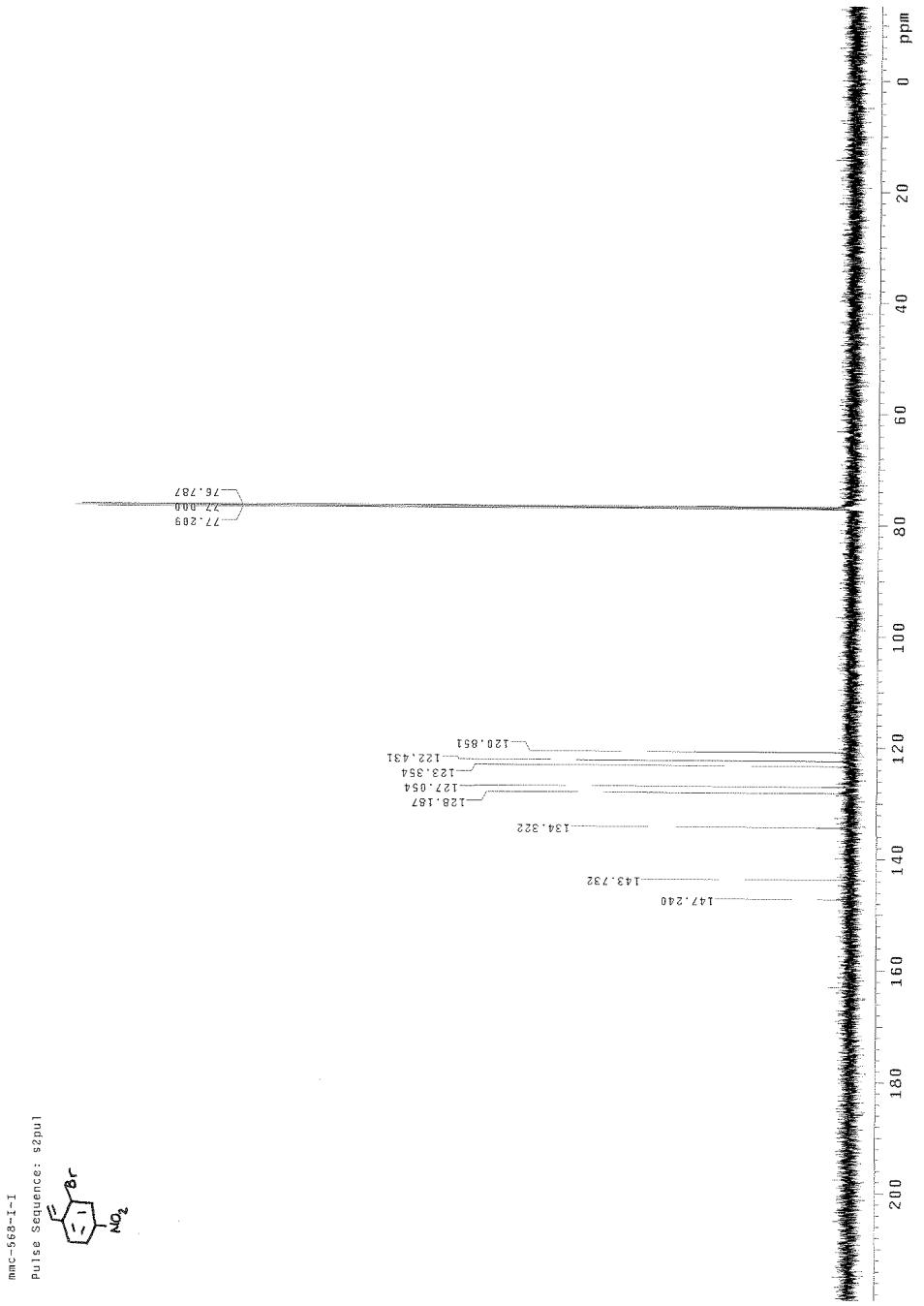

Figure 67: ^{13}C NMR of 3-Bromo-4-ethenyl-nitrobenzene **(179)**

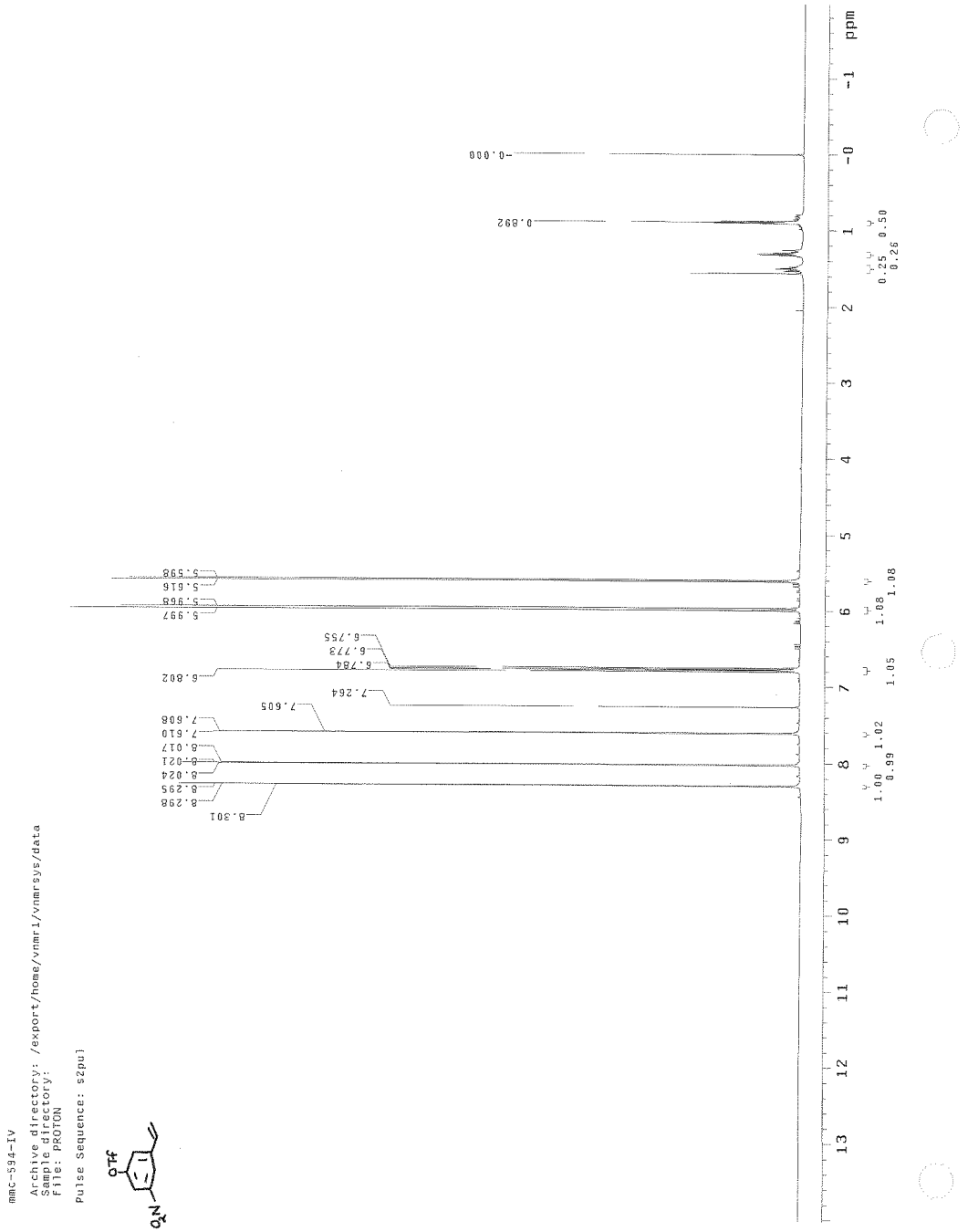

Figure 68: ^{1}H NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene **(180)**

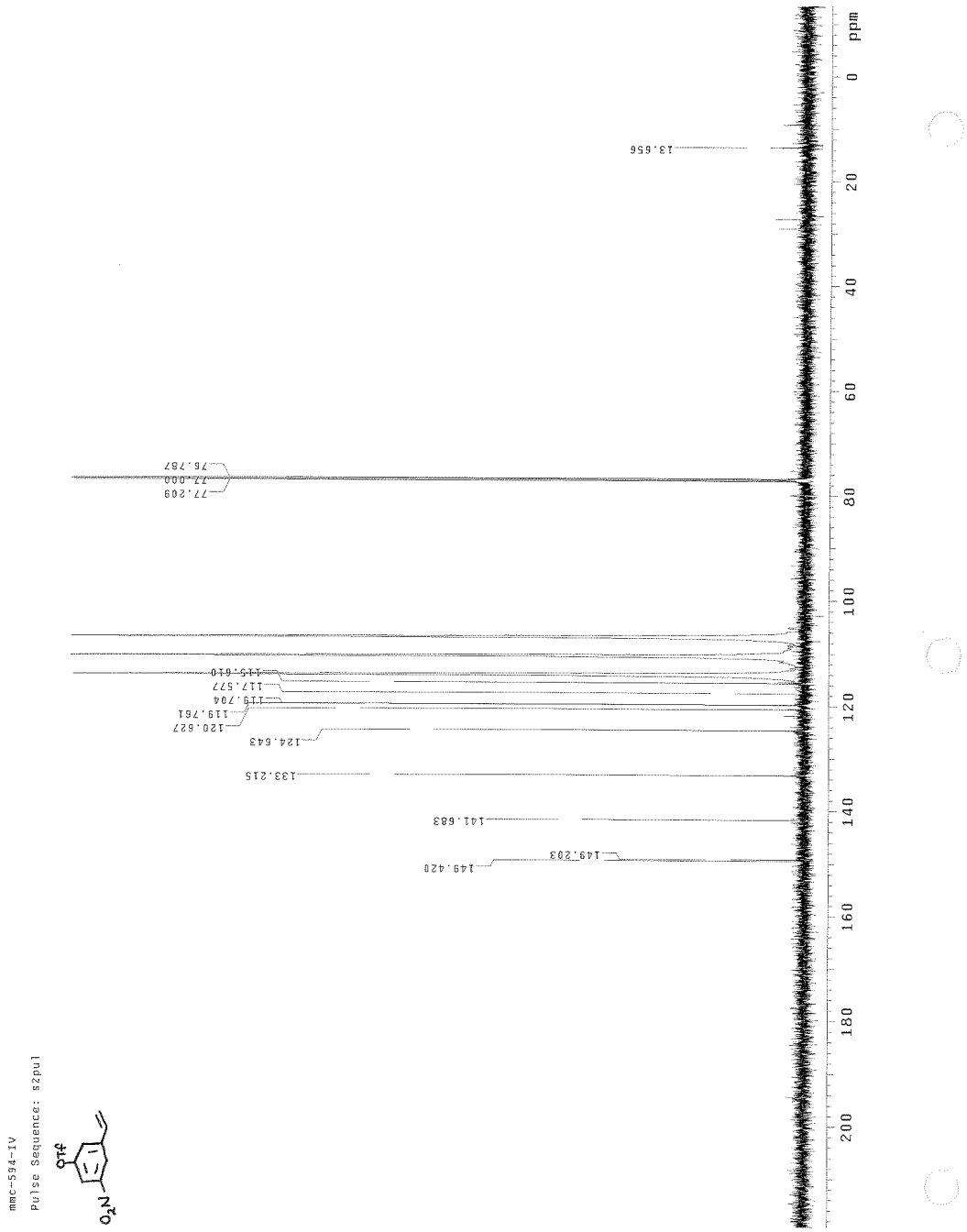

Figure 69: ^{13}C NMR of 3-Ethenyl-5-trifluoromethanesulfonyloxy-nitrobenzene **(180)**

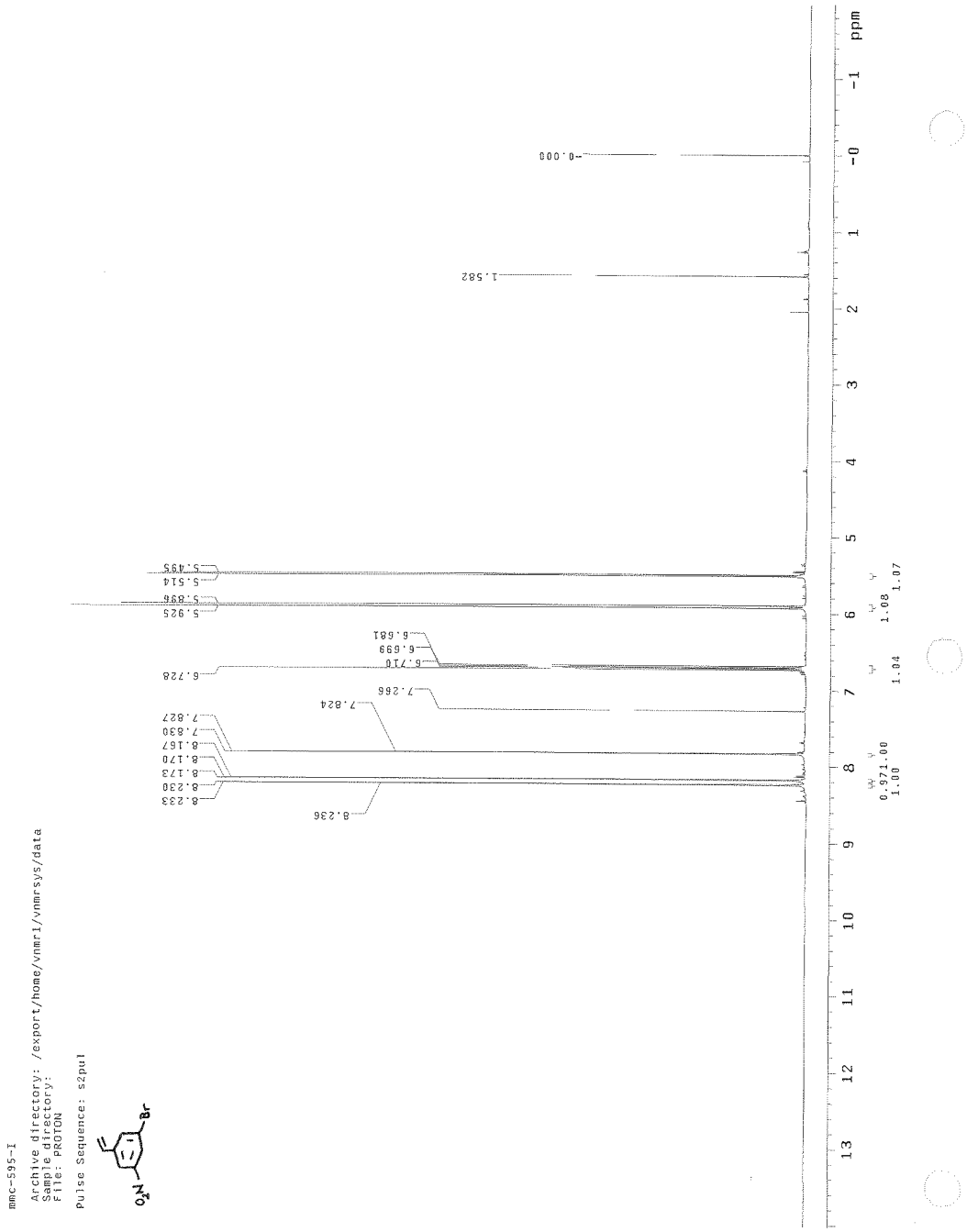

Figure 70: [1]H NMR of 3-Bromo-5-ethenyl-nitrobenzene **(181)**

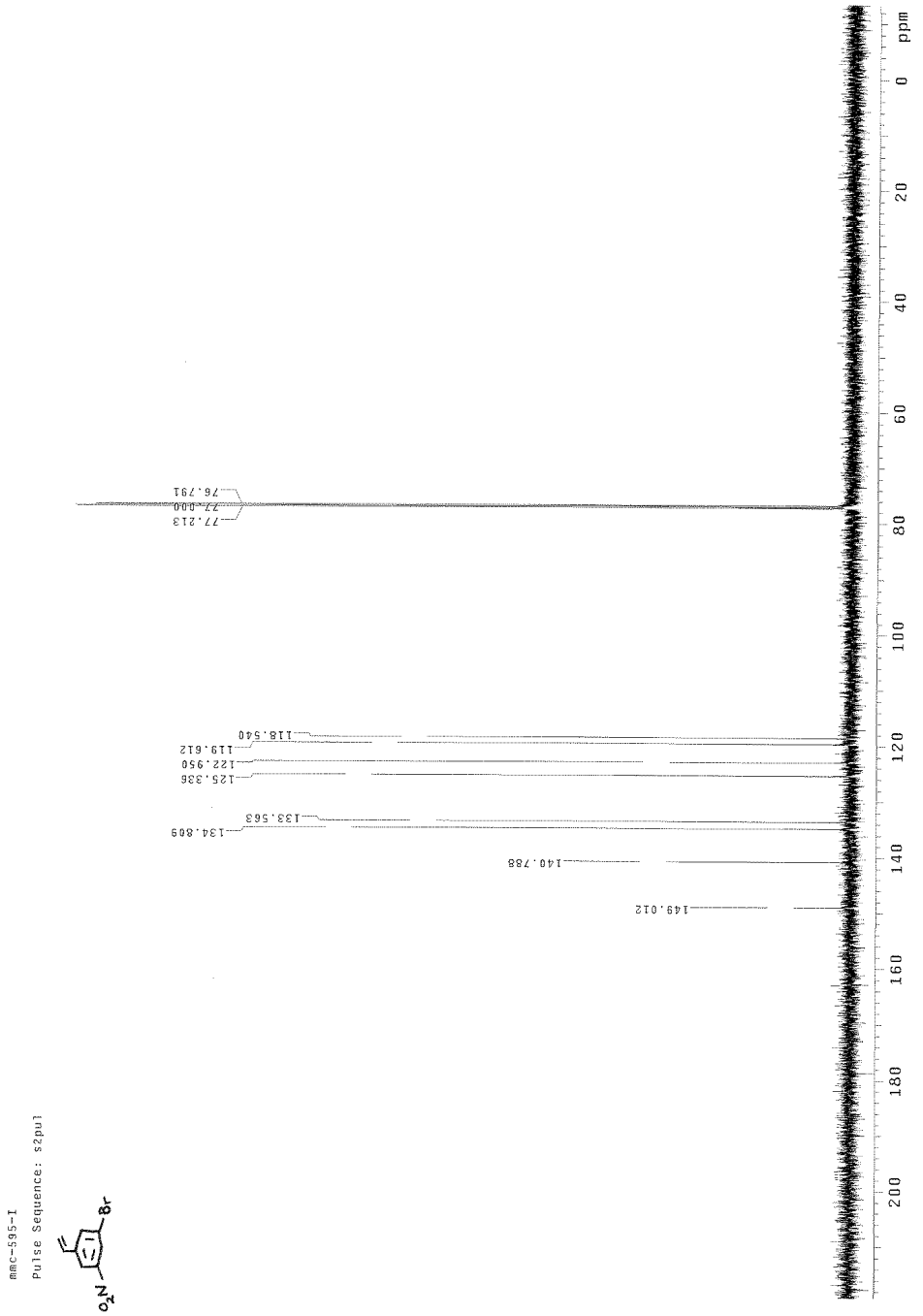

Figure 71: ^{13}C NMR of 3-Bromo-5-ethenyl-nitrobenzene **(181)**

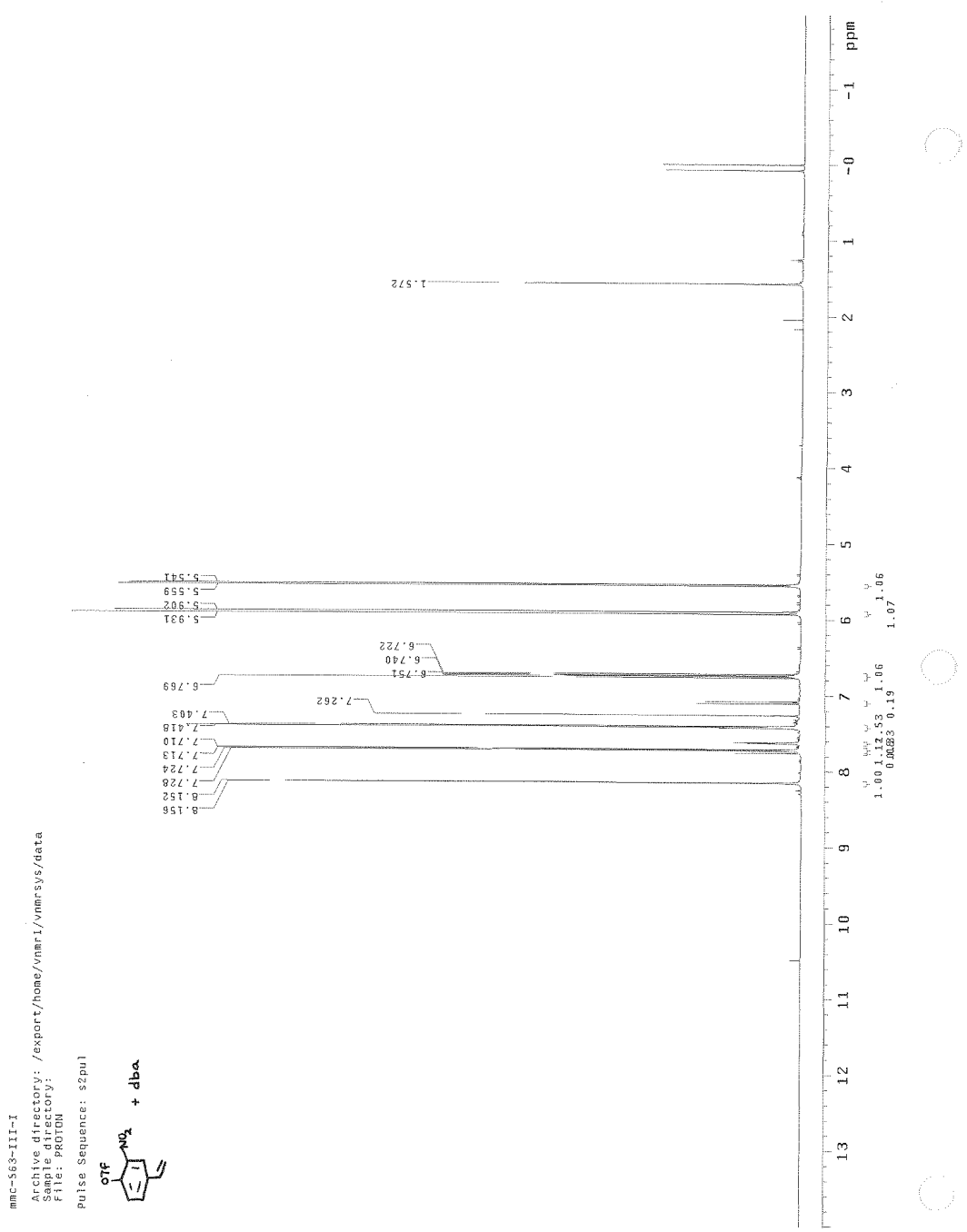

Figure 72: [1]H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene **(182)**

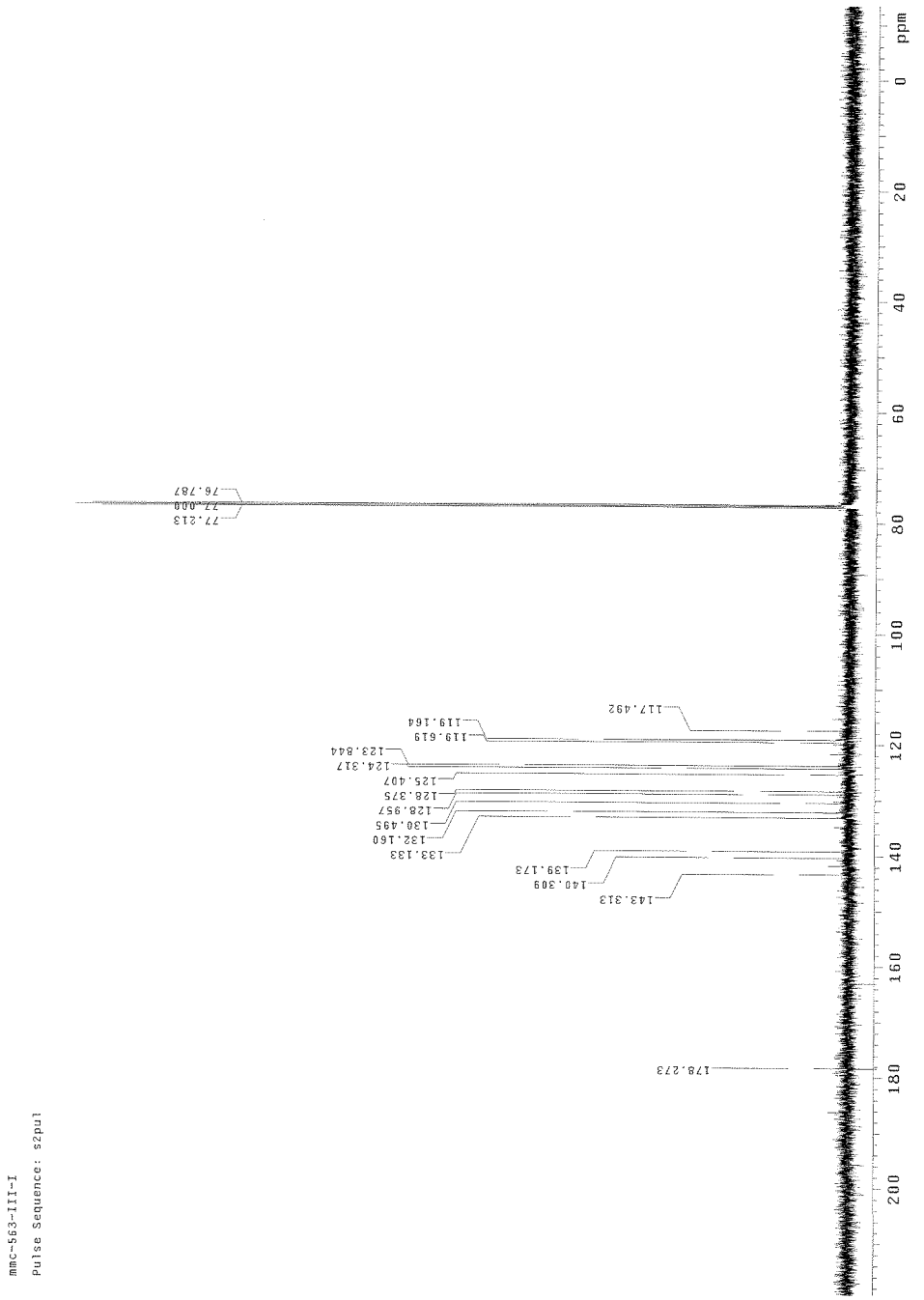

Figure 73: ^{13}C NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy-nitrobenzene **(182)**

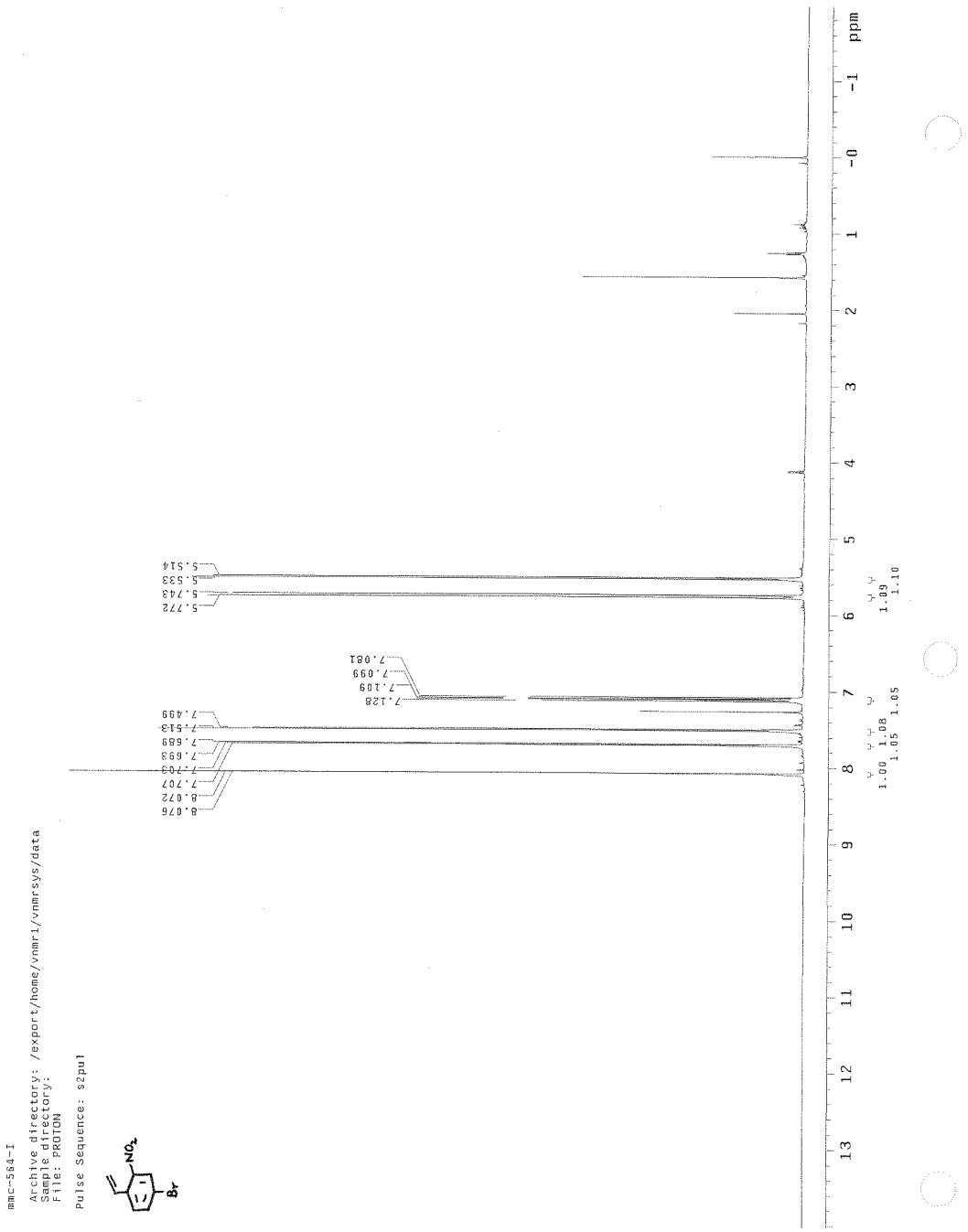

Figure 74: ^{1}H NMR of 5-Bromo-2-ethenyl-nitrobenzene **(183)**

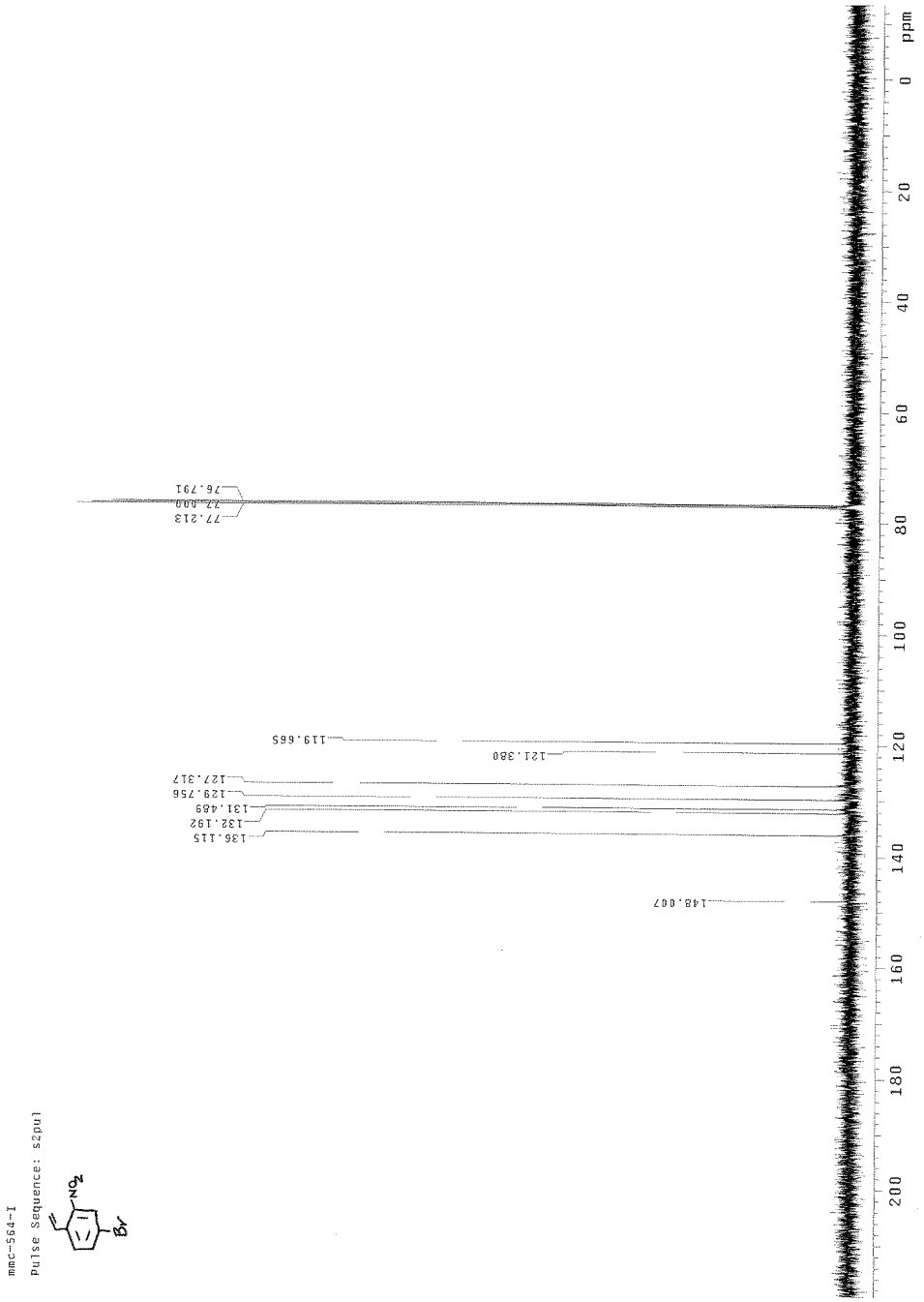

Figure 75: ^{13}C NMR of 5-Bromo-2-ethenyl-nitrobenzene **(183)**

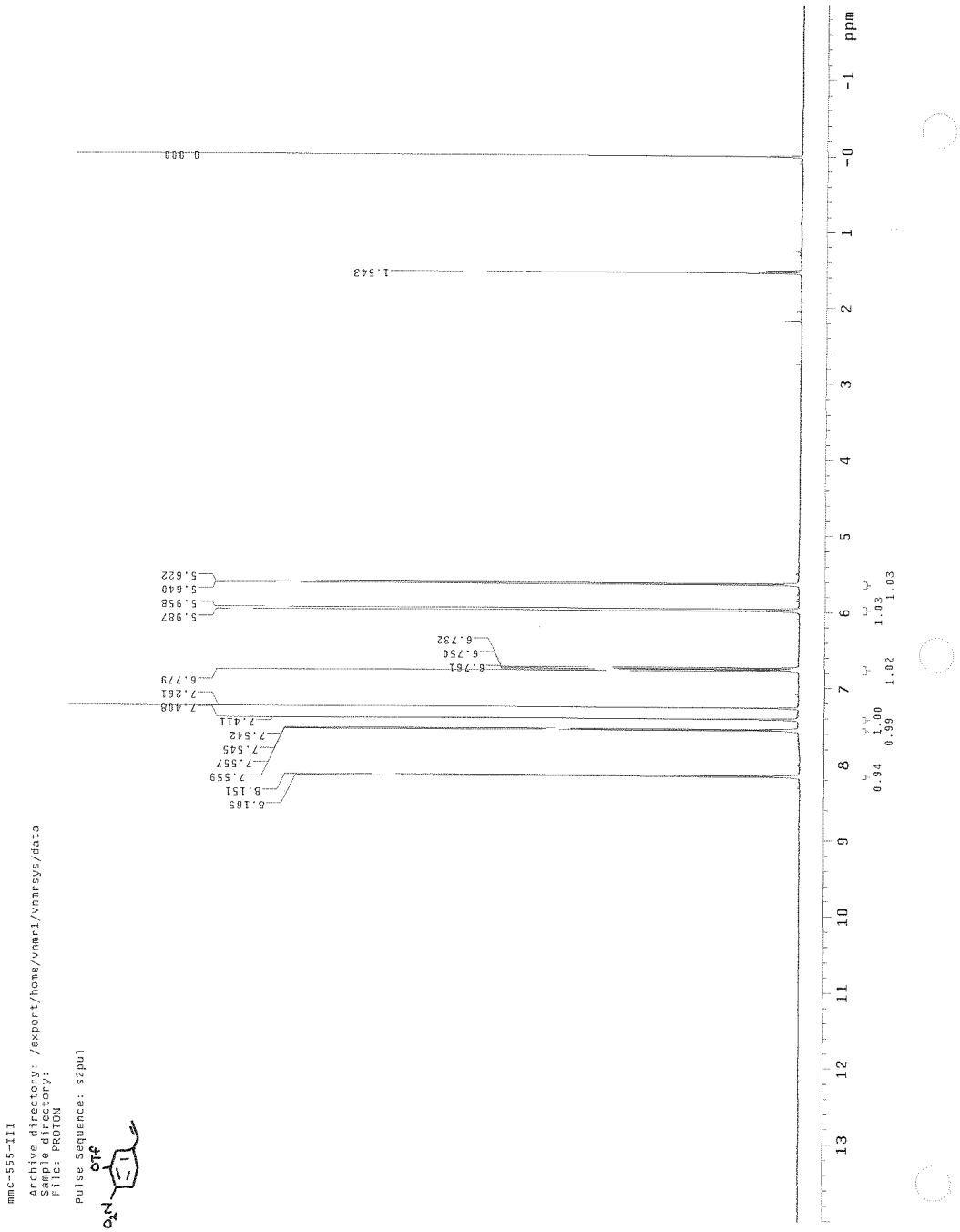

Figure 76: ^{1}H NMR of 4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene **(184)**

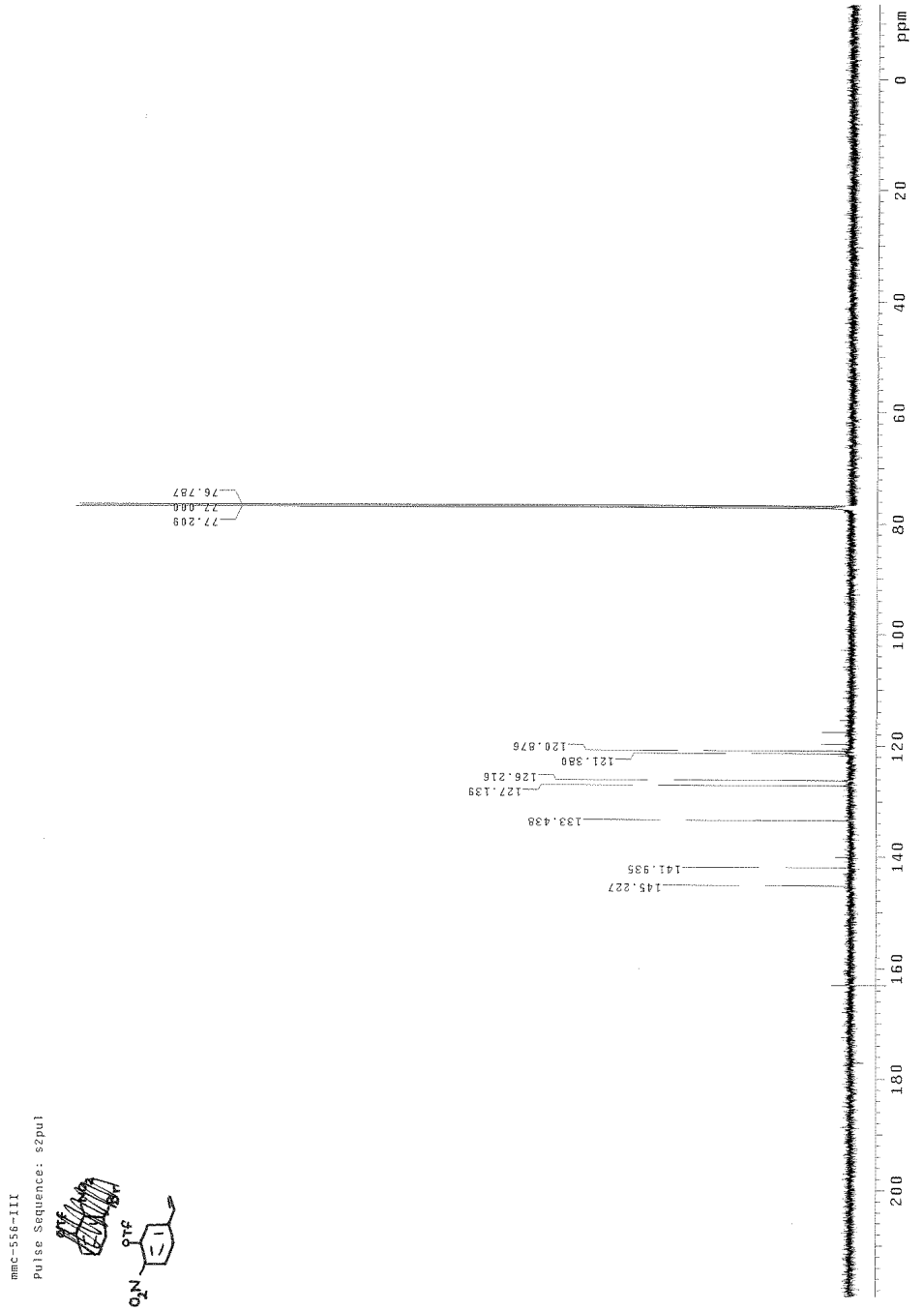

Figure 77: ^{13}C NMR of 4-Ethenyl-2-trifluoromethanesulfonyloxy-nitrobenzene **(184)**

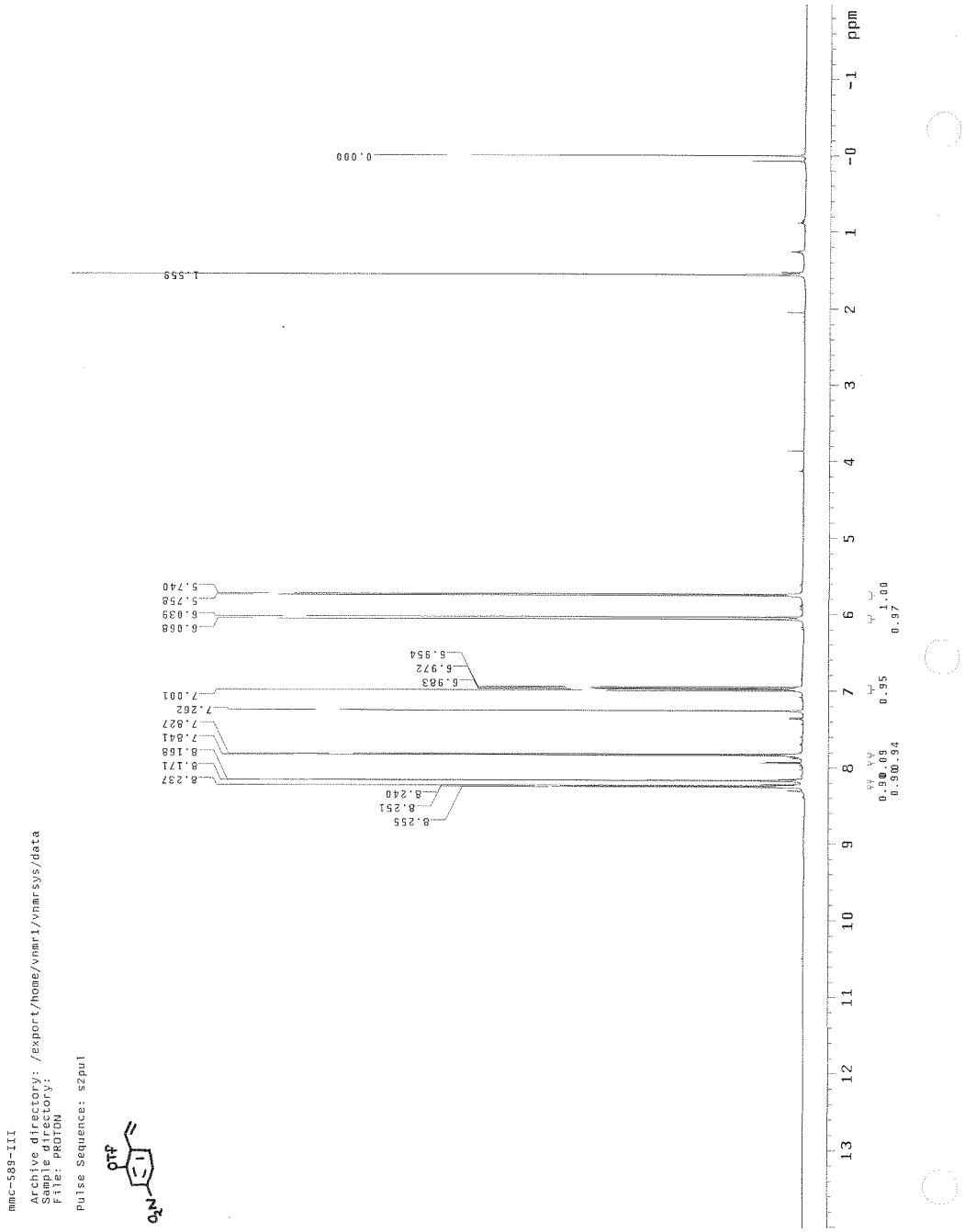

Figure 78: [1]H NMR of 4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene **(186)**

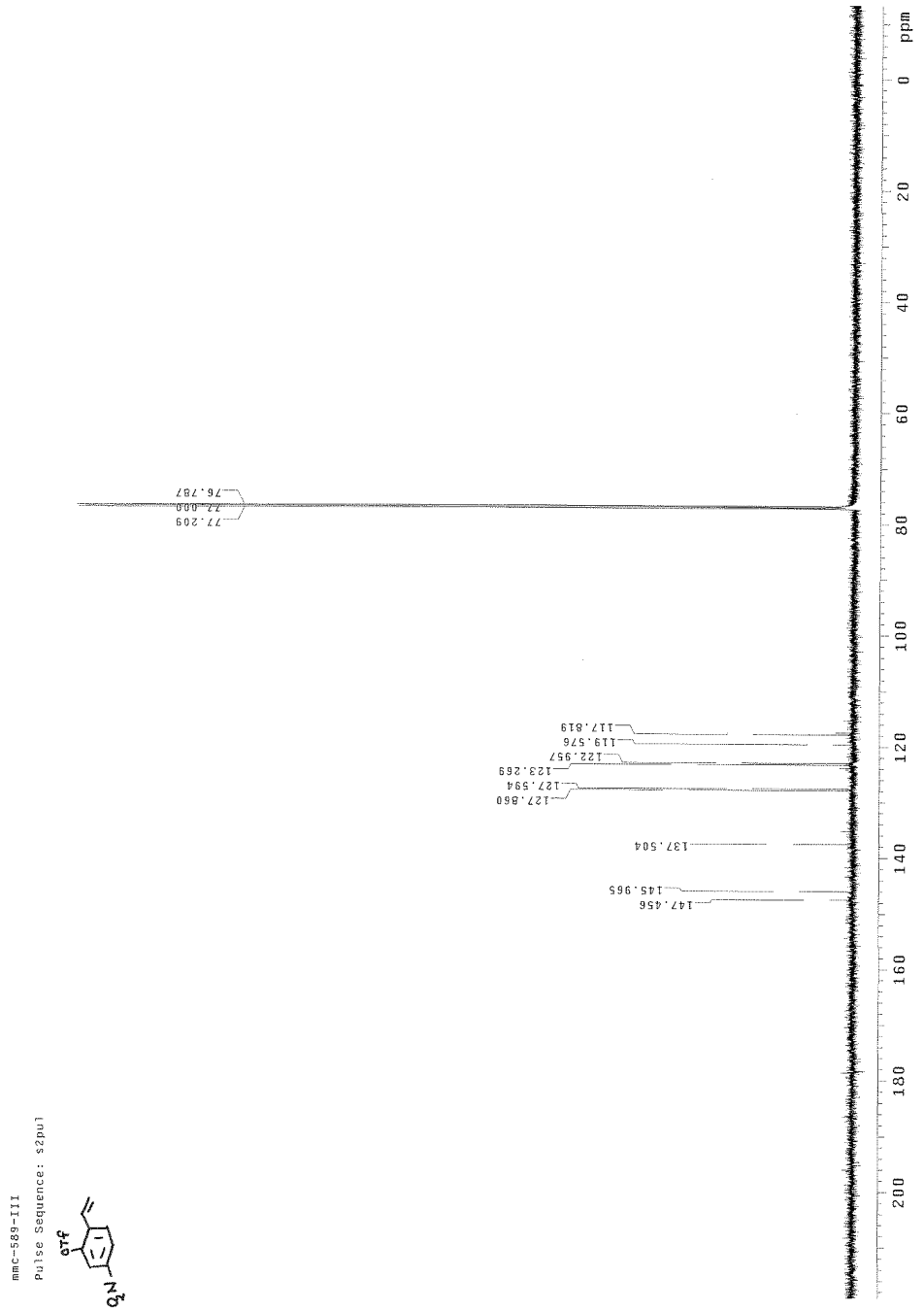

Figure 79: ^{13}C NMR of 4-Ethenyl-3-trifluoromethanesulfonyloxy-nitrobenzene **(186)**

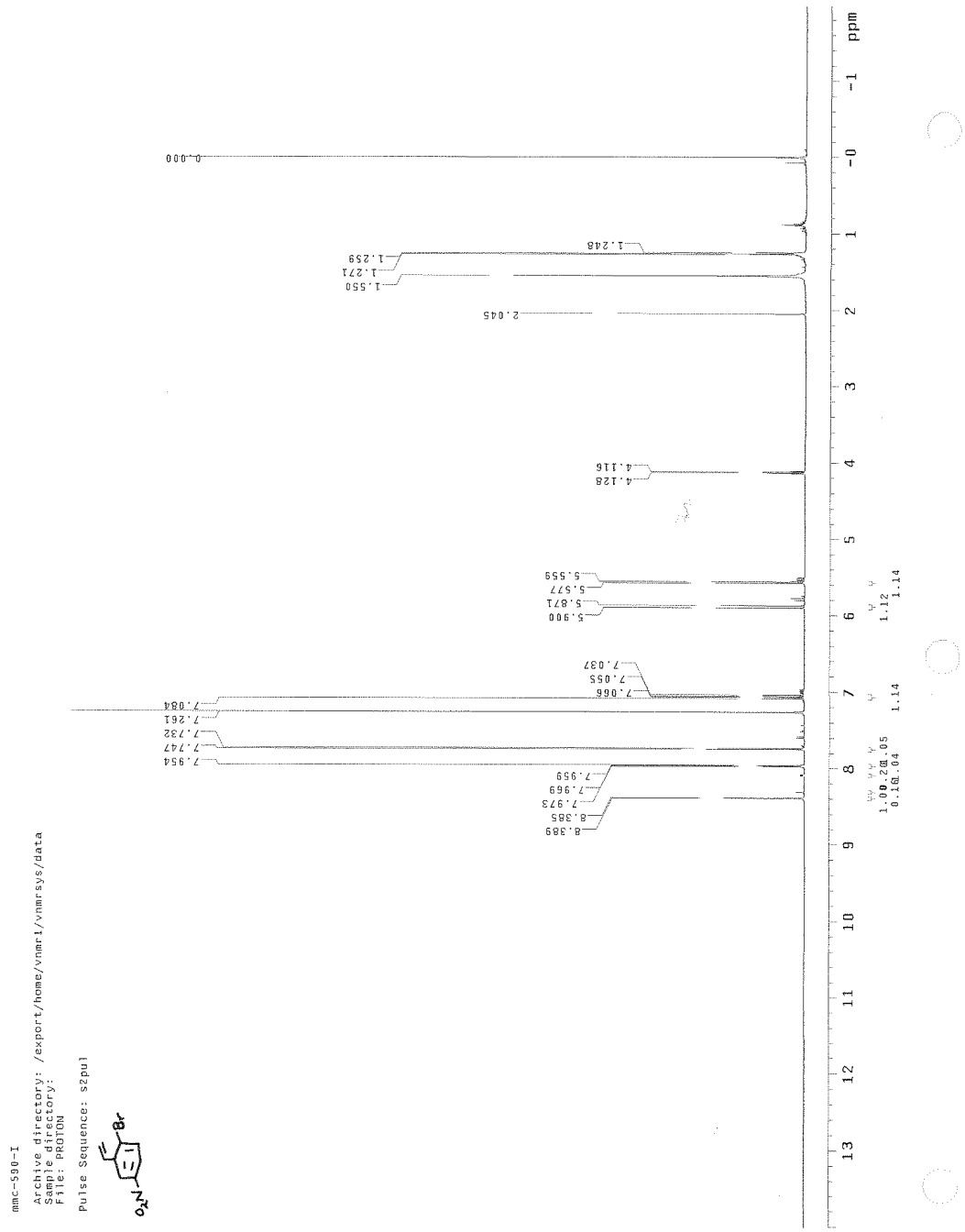

Figure 80: ^{1}H NMR of 4-Bromo-3-ethenyl-nitrobenzene **(187)**

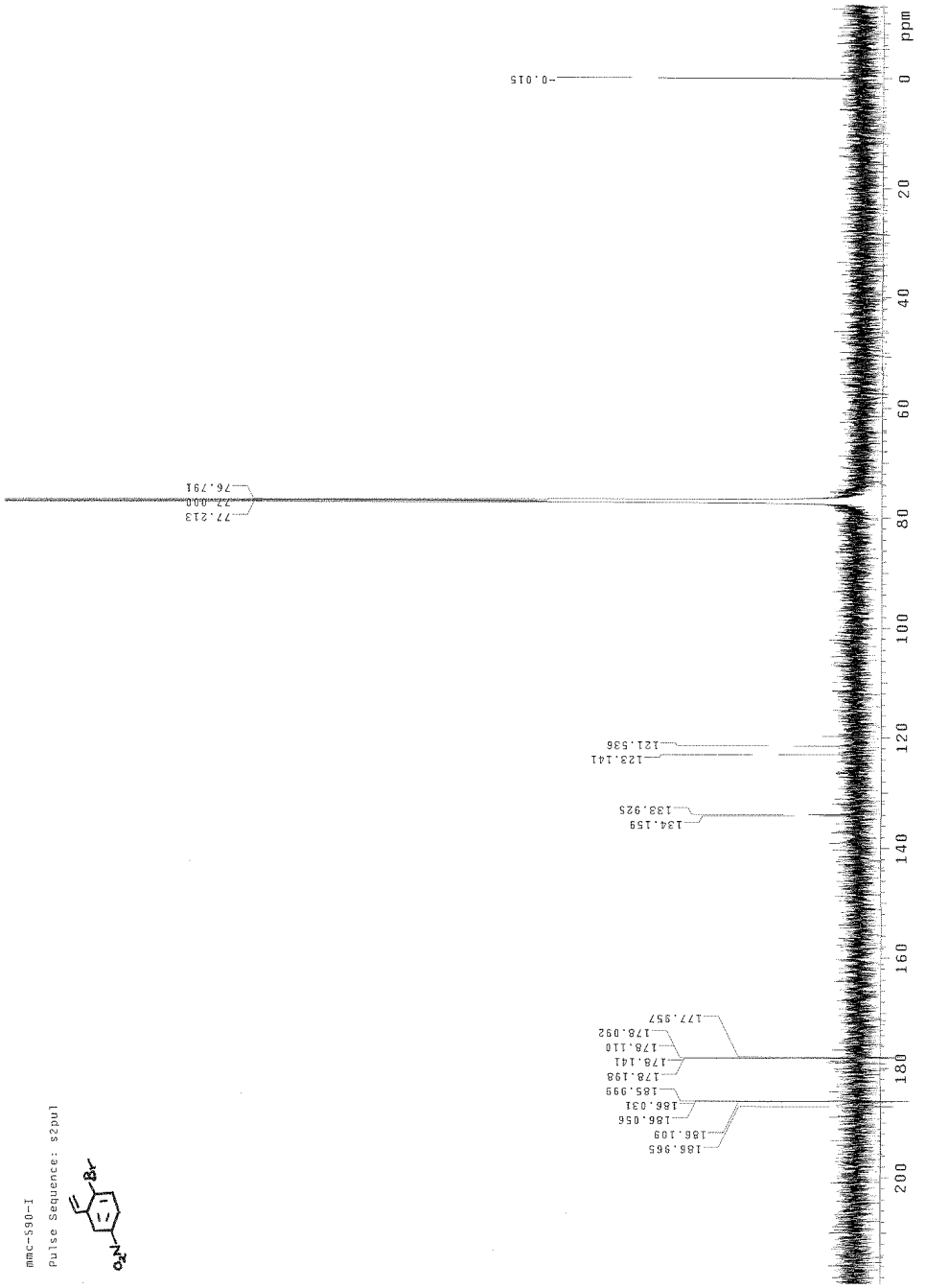

Figure 81: ^{13}C NMR of 4-Bromo-3-ethenyl-nitrobenzene **(187)**

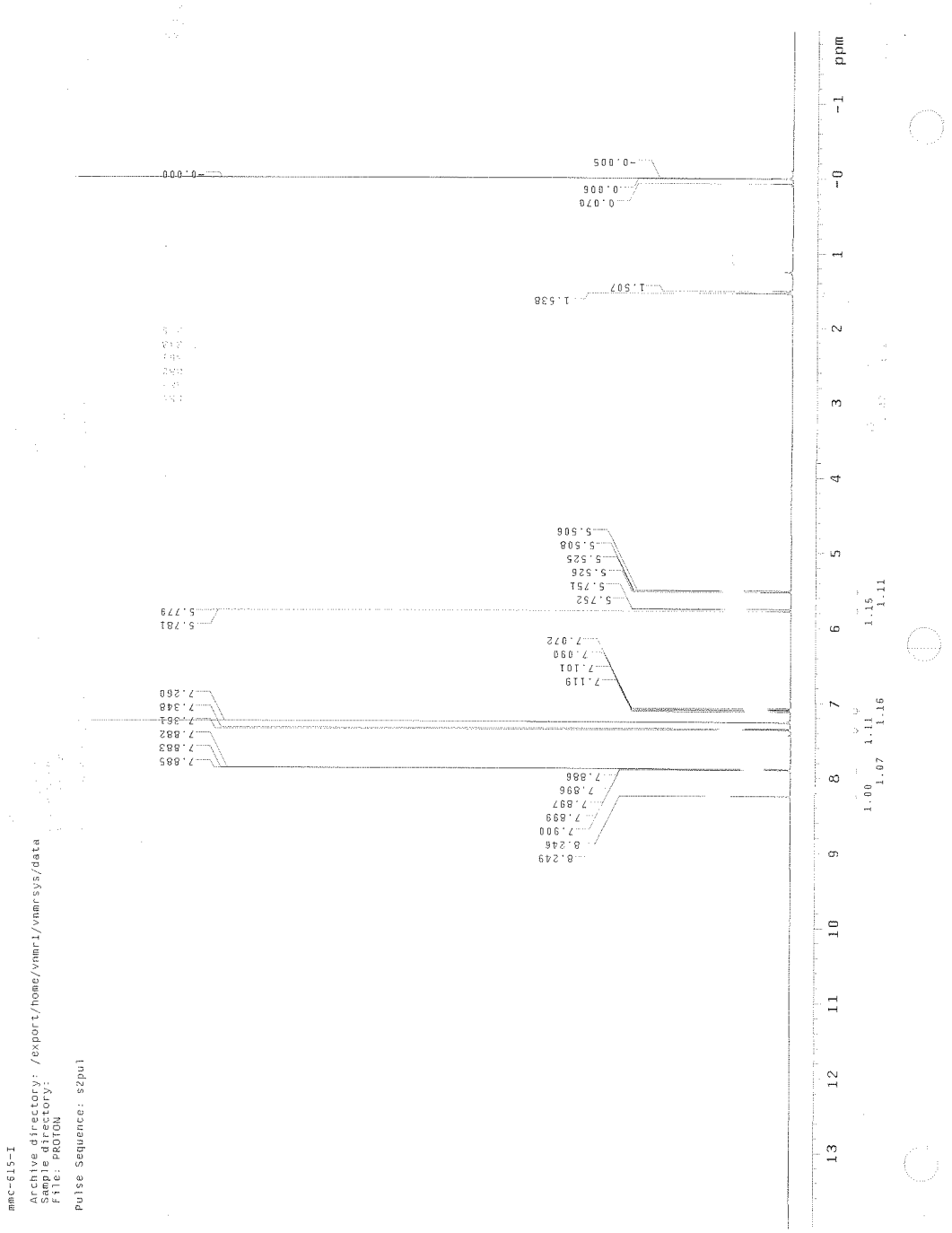

Figure 82: ^{1}H NMR of 3-Iodo-6-ethenyl-nitrobenzene **(198)**

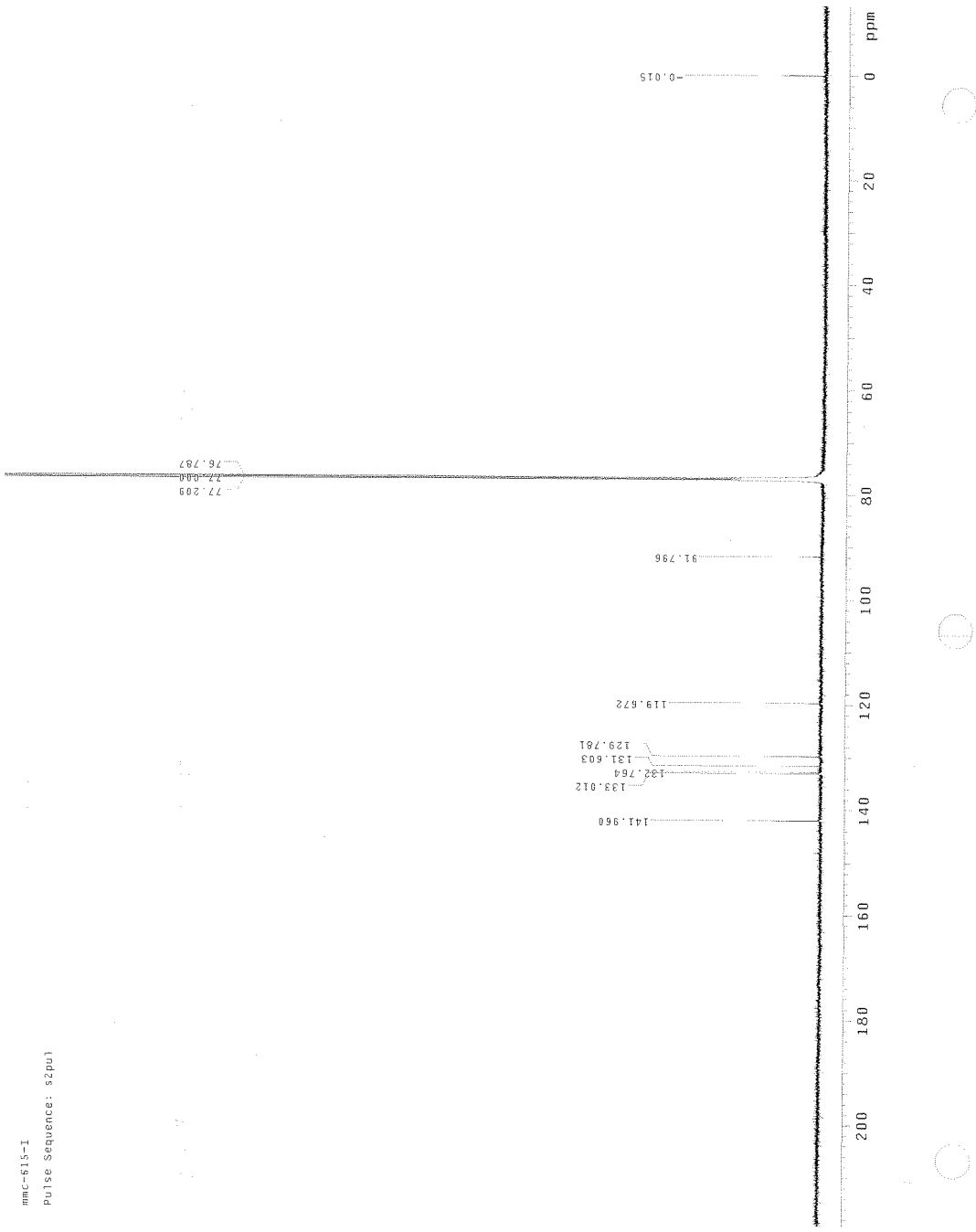

Figure 83: ^{13}C NMR of 3-Iodo-6-ethenyl-nitrobenzene **(198)**

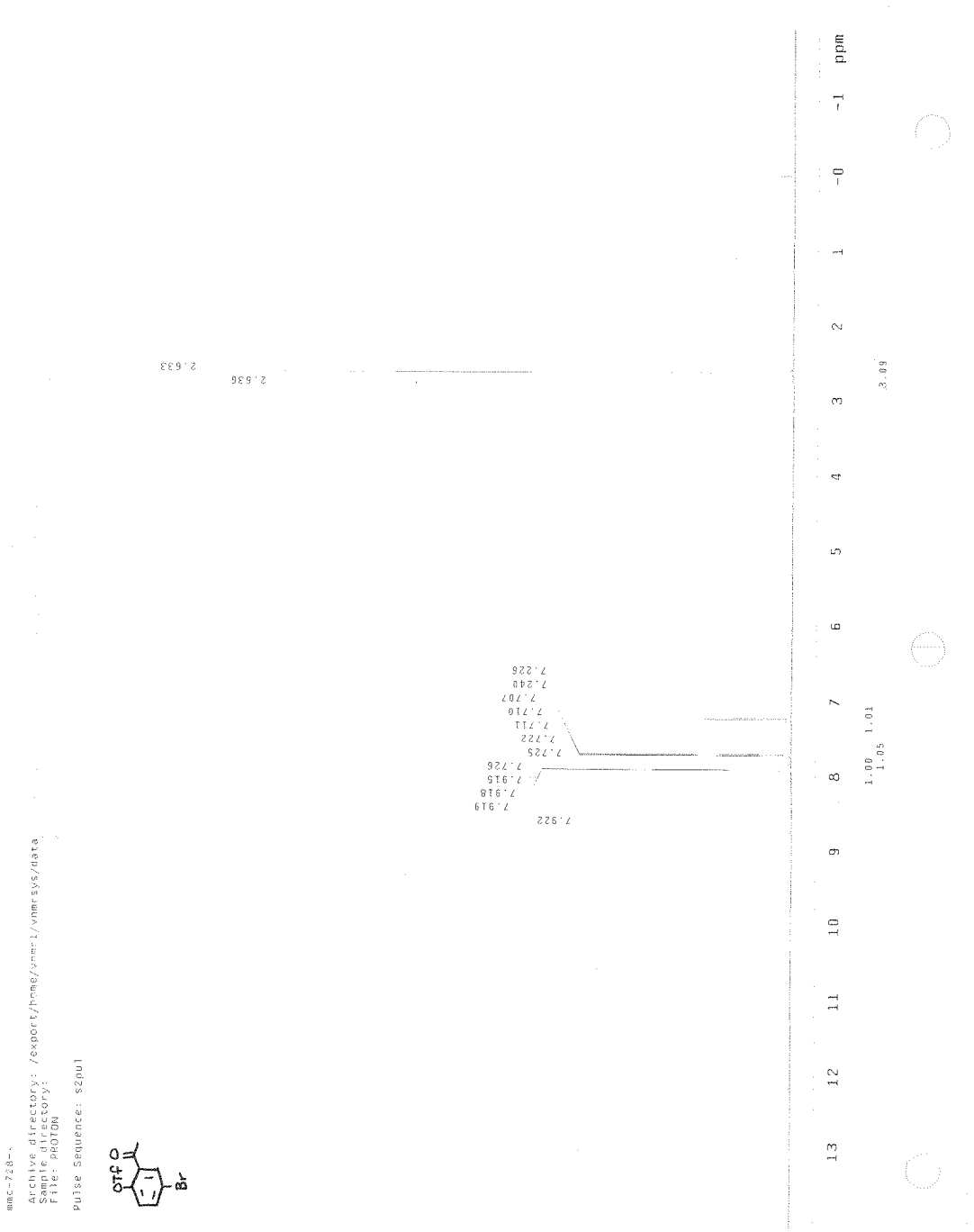

Figure 84: ^{1}H NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone **(201)**

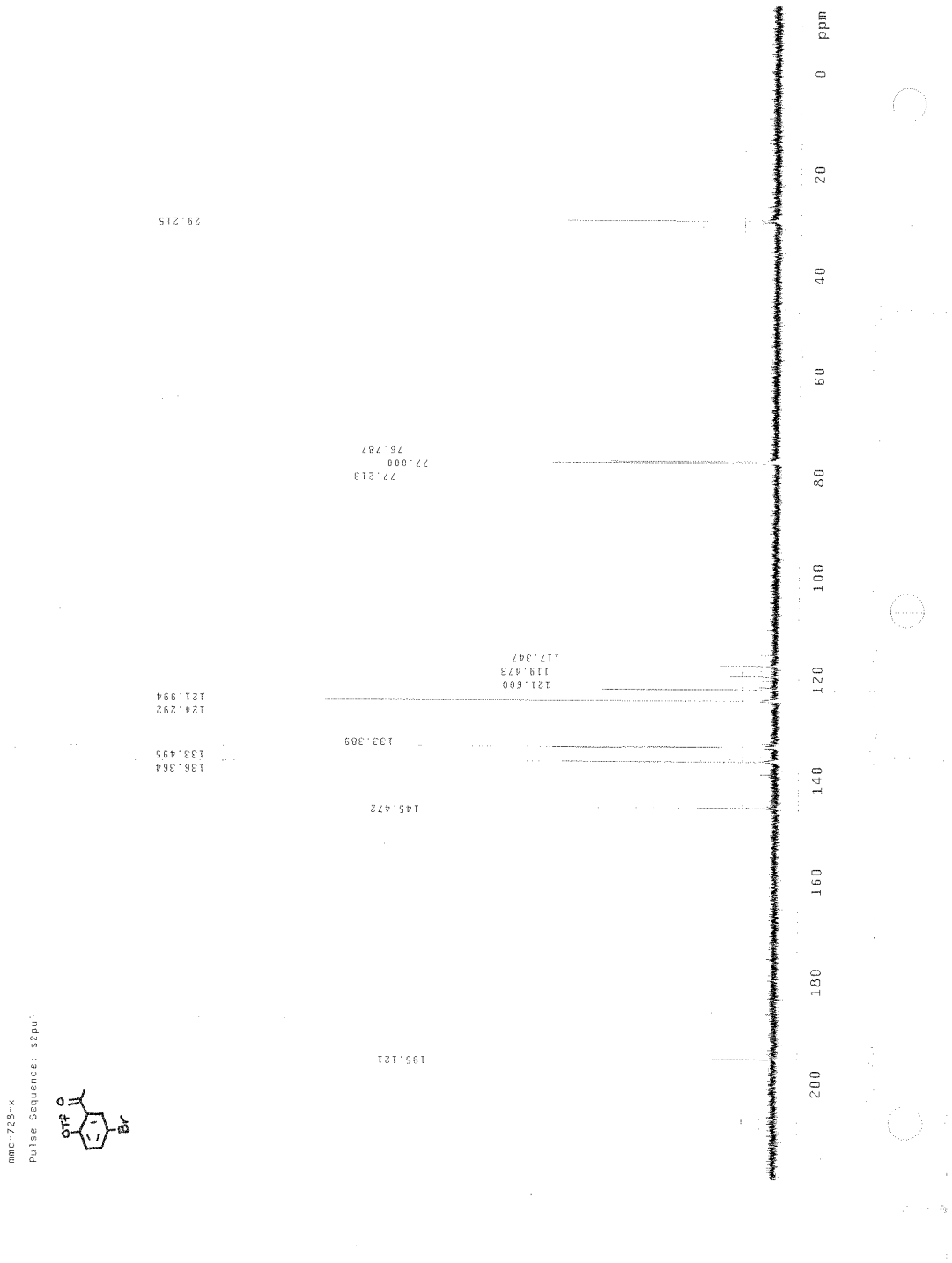

Figure 85: ^{13}C NMR of 3-Bromo-6-trifluoromethanesulfonyloxy acetophenone **(201)**

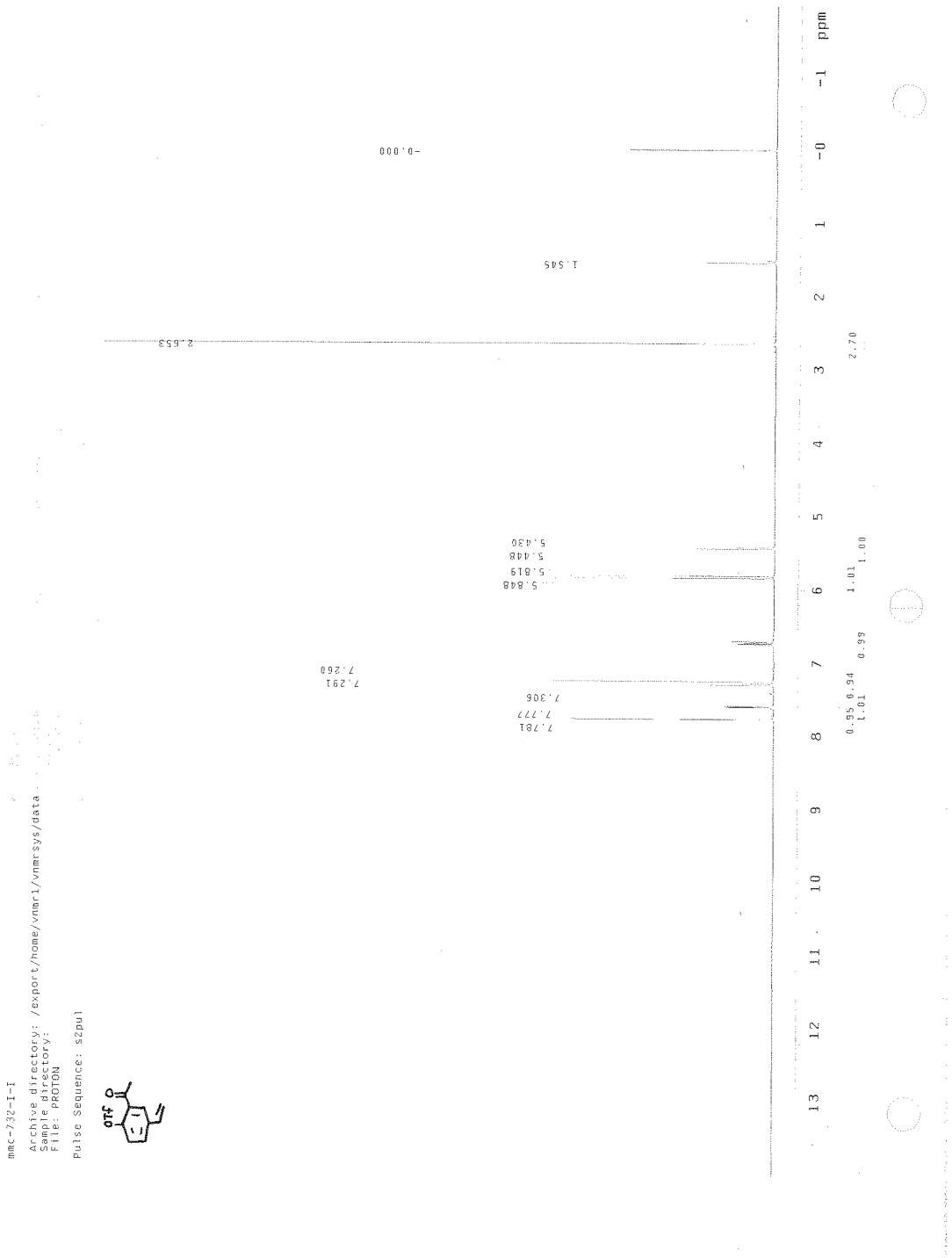

Figure 86: ^{1}H NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone **(202)**

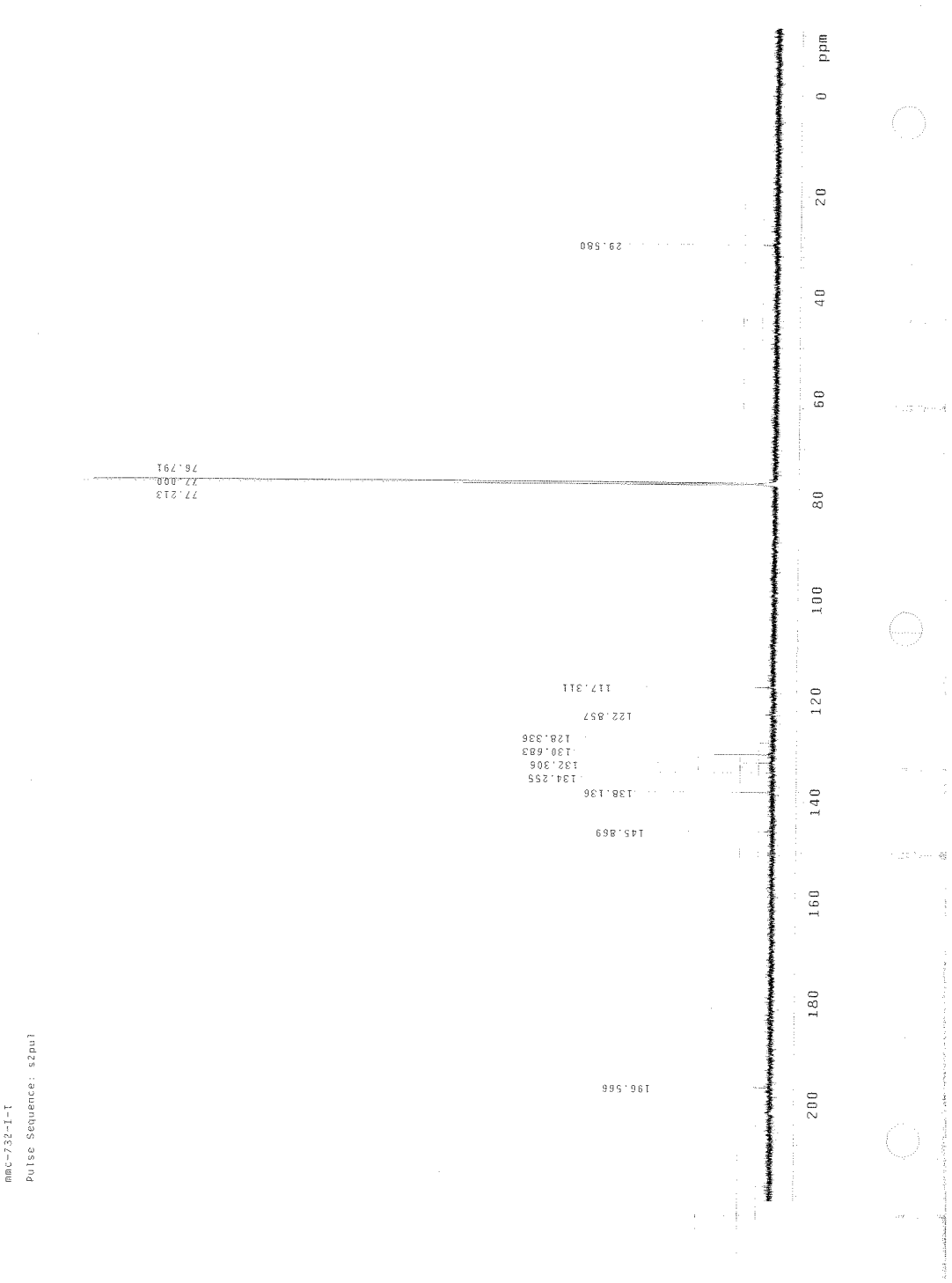

Figure 87: ^{13}C NMR of 3-Ethenyl-6-trifluoromethanesulfonyloxy acetophenone **(202)**

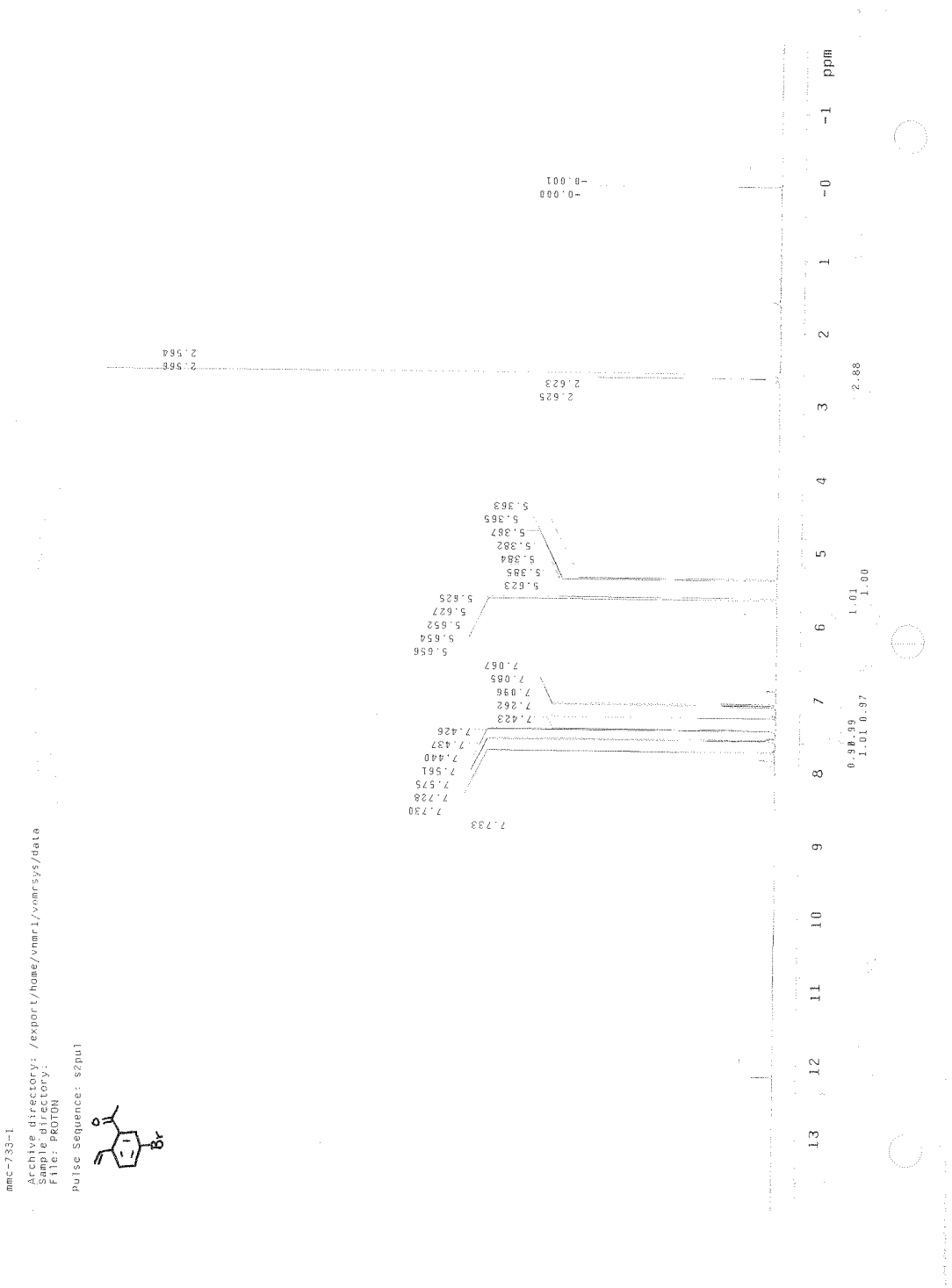

Figure 88: ^{1}H NMR of 6-Ethenyl-3-bromoacetophenone **(203)**

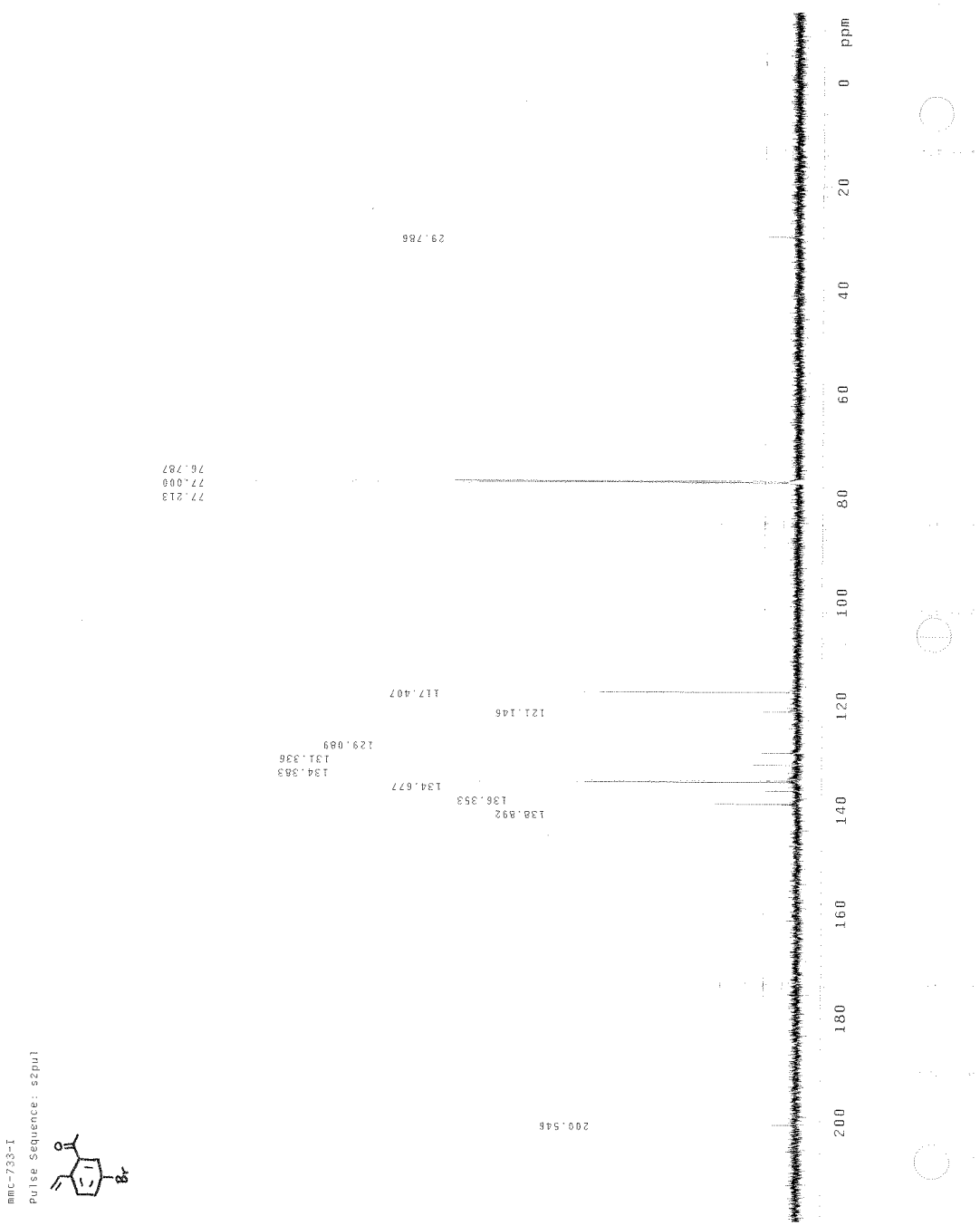

Figure 89: ^{13}C NMR of 6-Ethenyl-3-bromoacetophenone **(203)**

Figure 90: ^{1}H NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole **(209)**

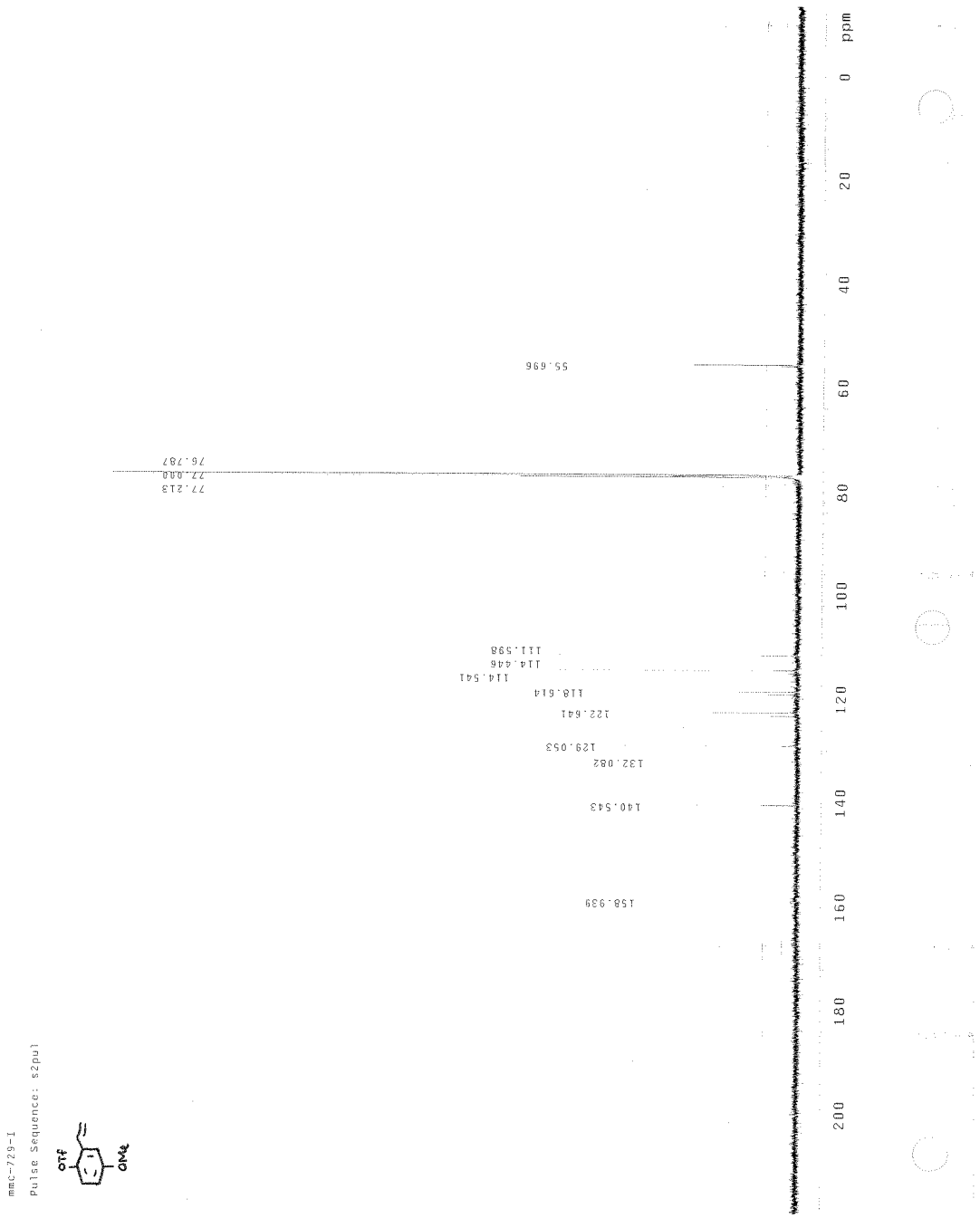

Figure 91: ^{13}C NMR of 3-Ethenyl-4-trifluoromethanesulfonyloxy anisole **(209)**

^{1}H and ^{13}C NMR for Chapter 5: Pyrroloindoles

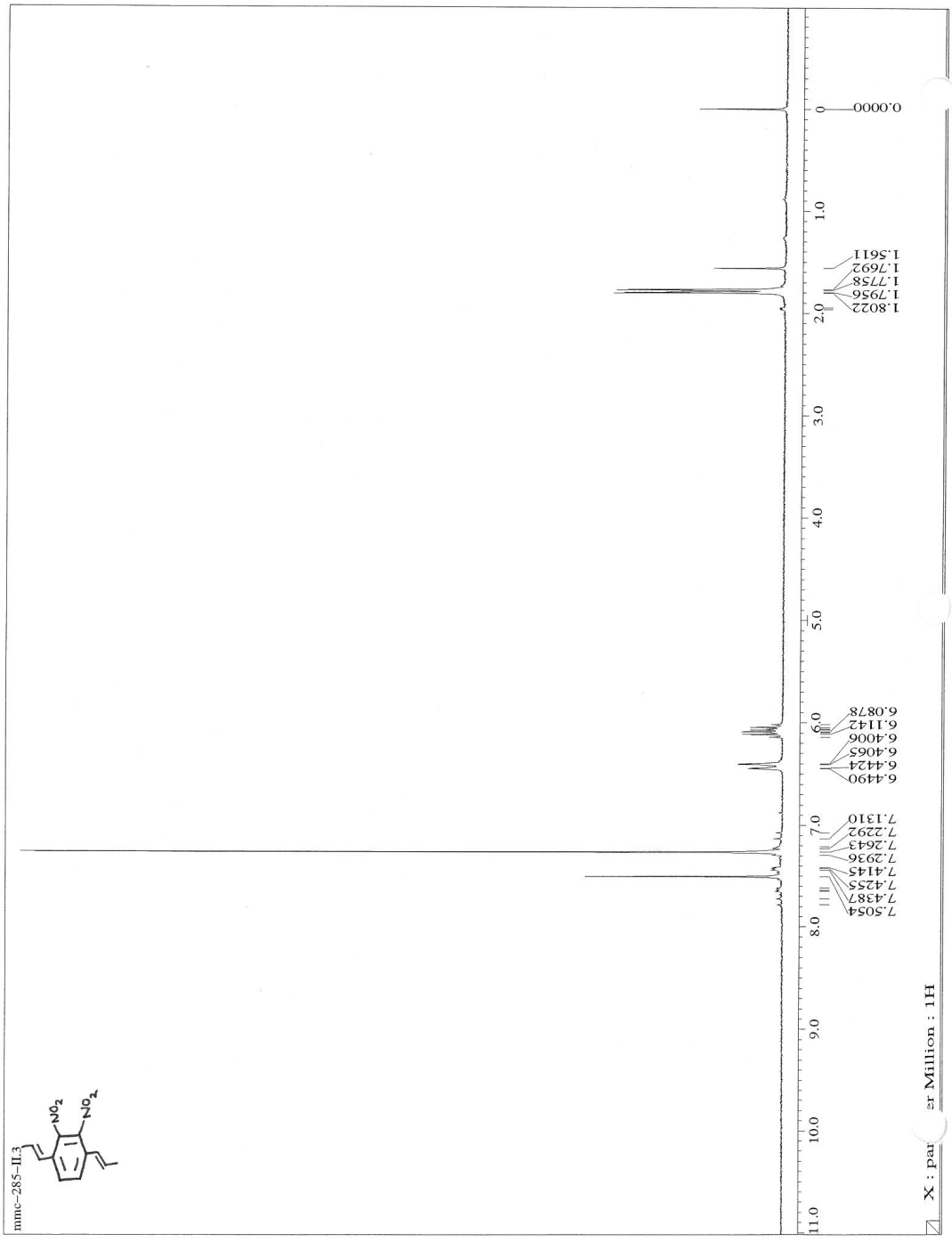

Figure 92: ^{1}H NMR of 2,3-dinitro-1,4-ethenylbenzene **(241)**

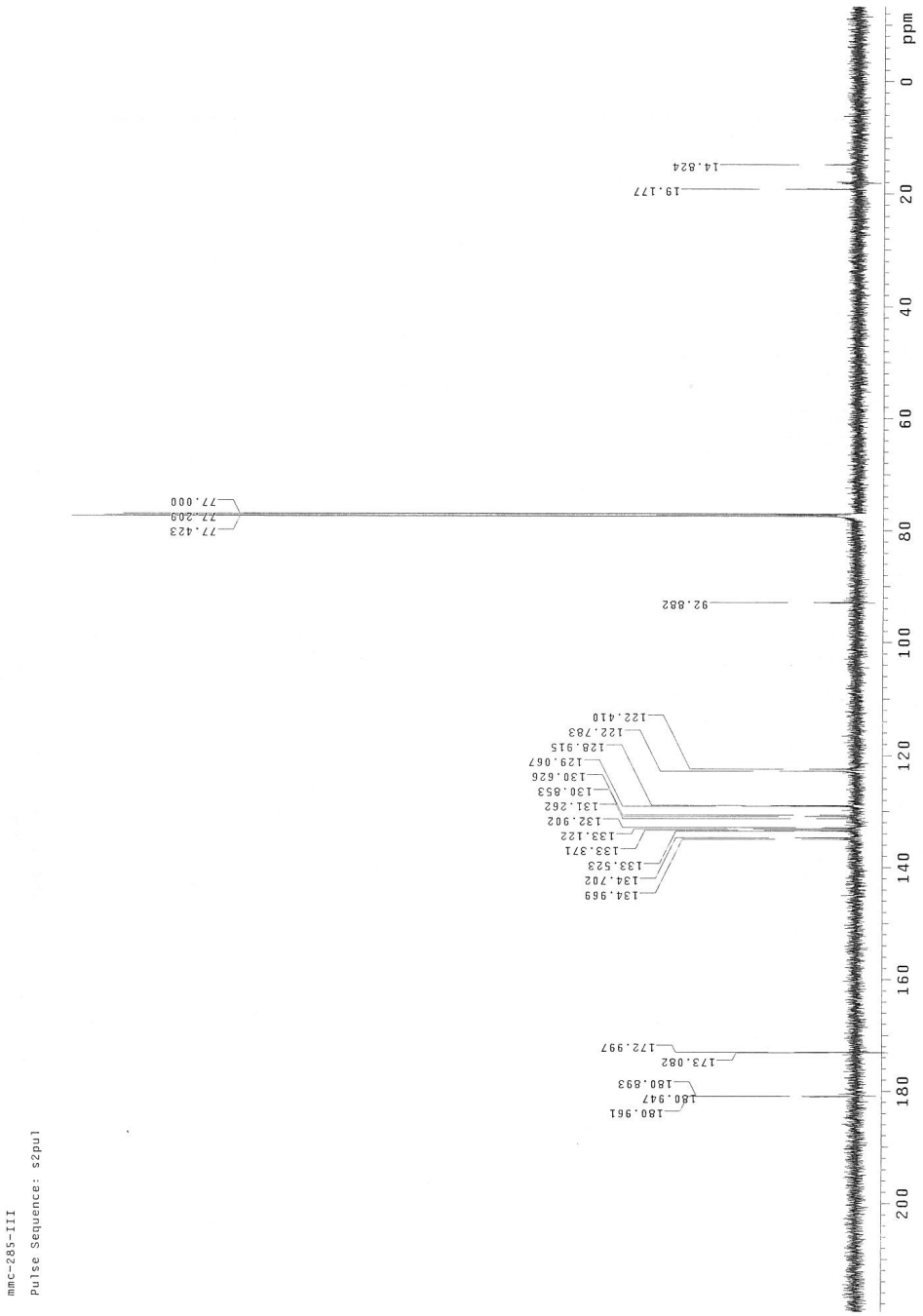

Figure 93: ^{13}C NMR of 2,3-dinitro-1,4-ethenylbenzene **(241)**

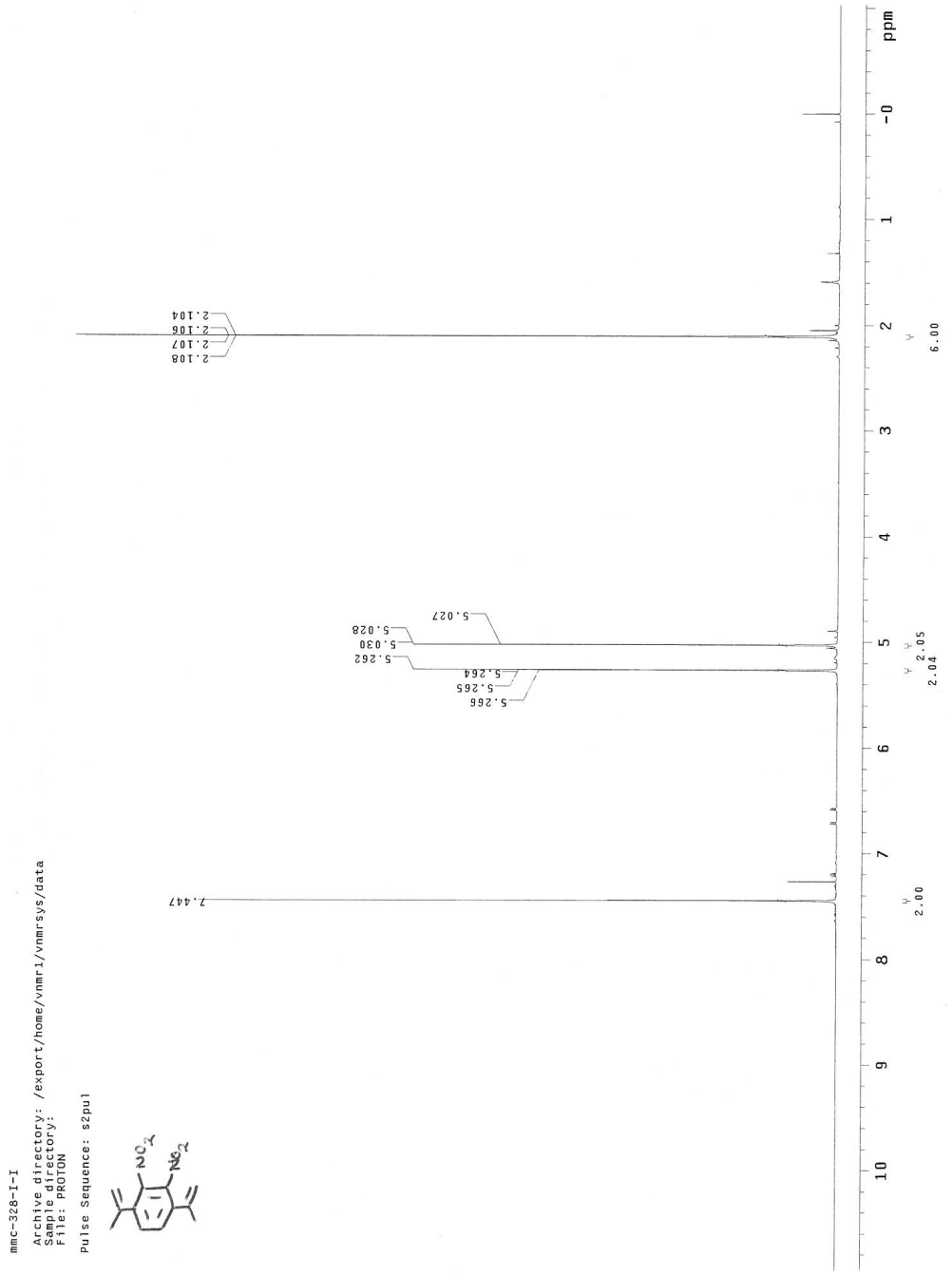

Figure 94: ^{1}H NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene **(257)**

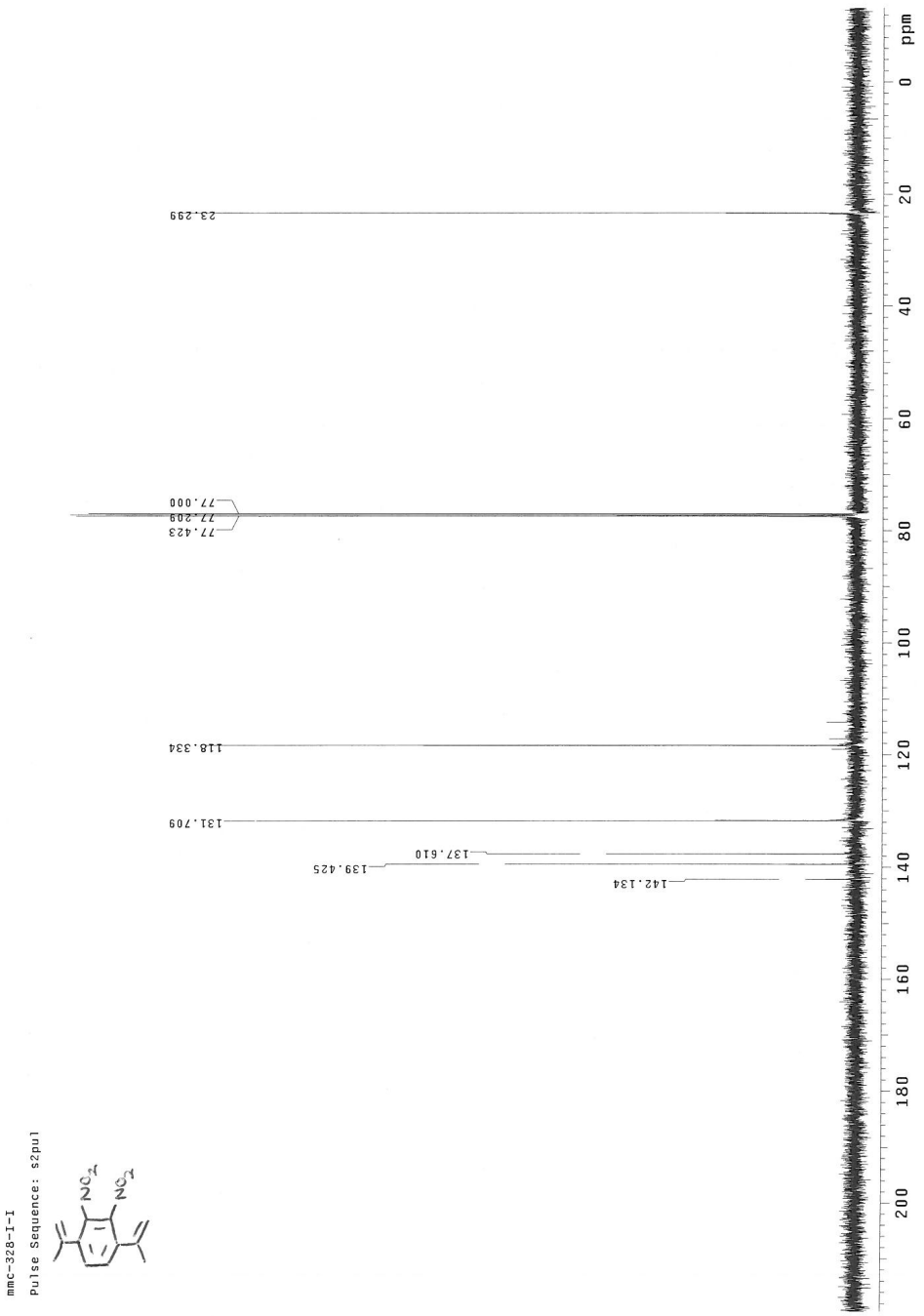

Figure 95: ^{13}C NMR of 2,3-dinitro-1,4-di(prop-1-en-2-yl)benzene **(257)**

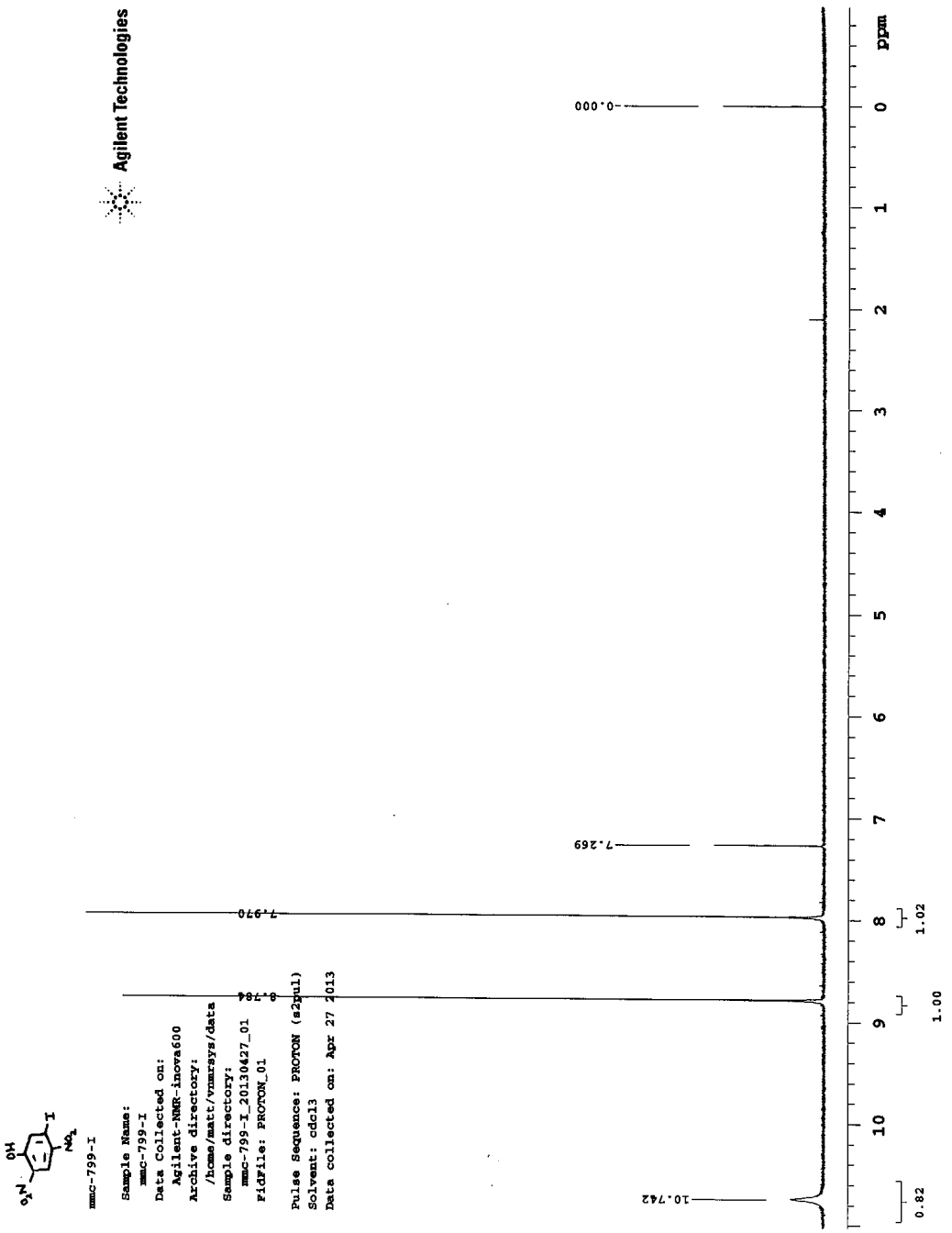

Figure 96: ^{1}H NMR of 5-iodo-2,4-dinitrophenol (**263**)

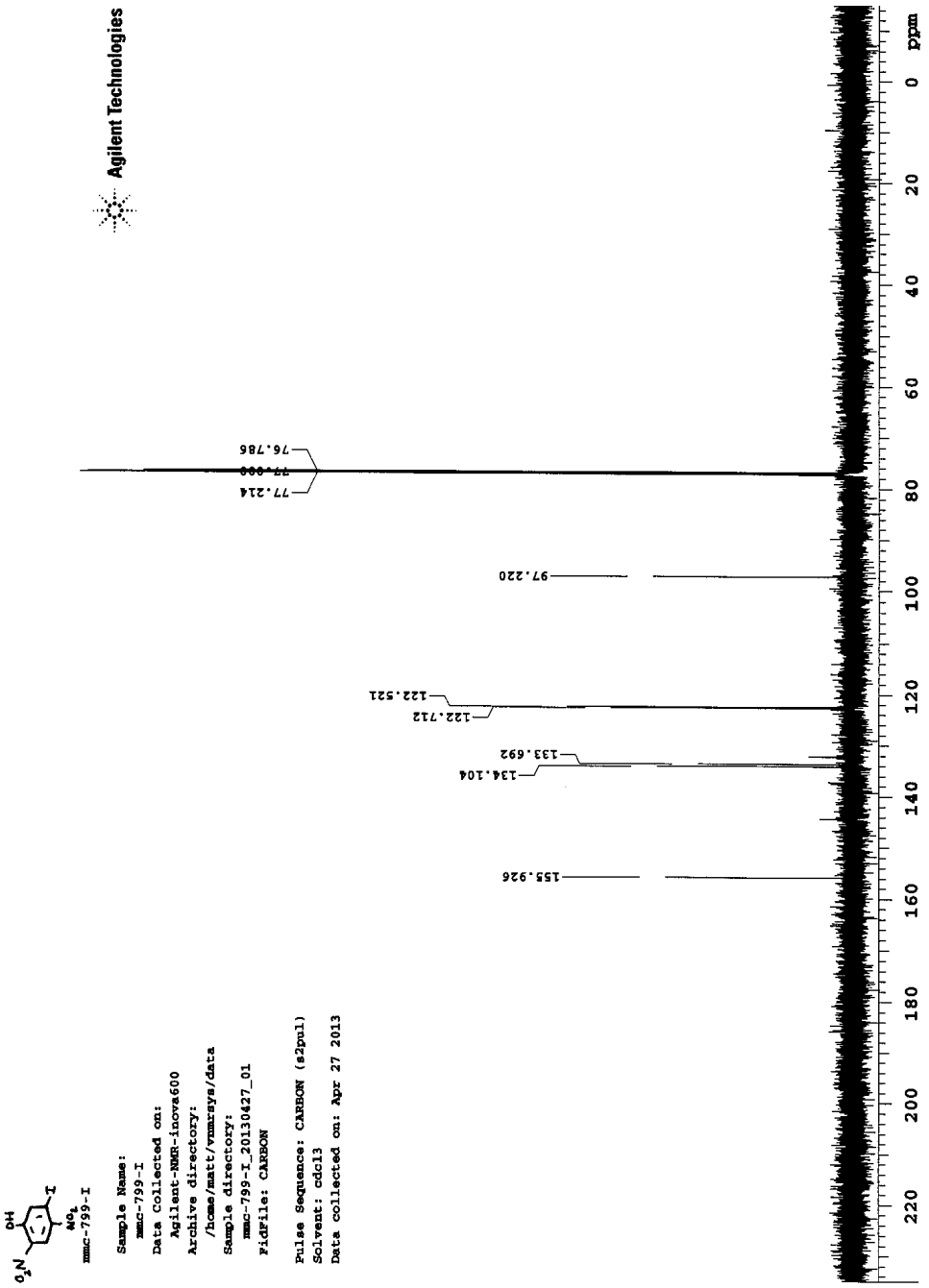

Figure 97: ^{13}C NMR of 5-iodo-2,4-dinitrophenol (**263**)

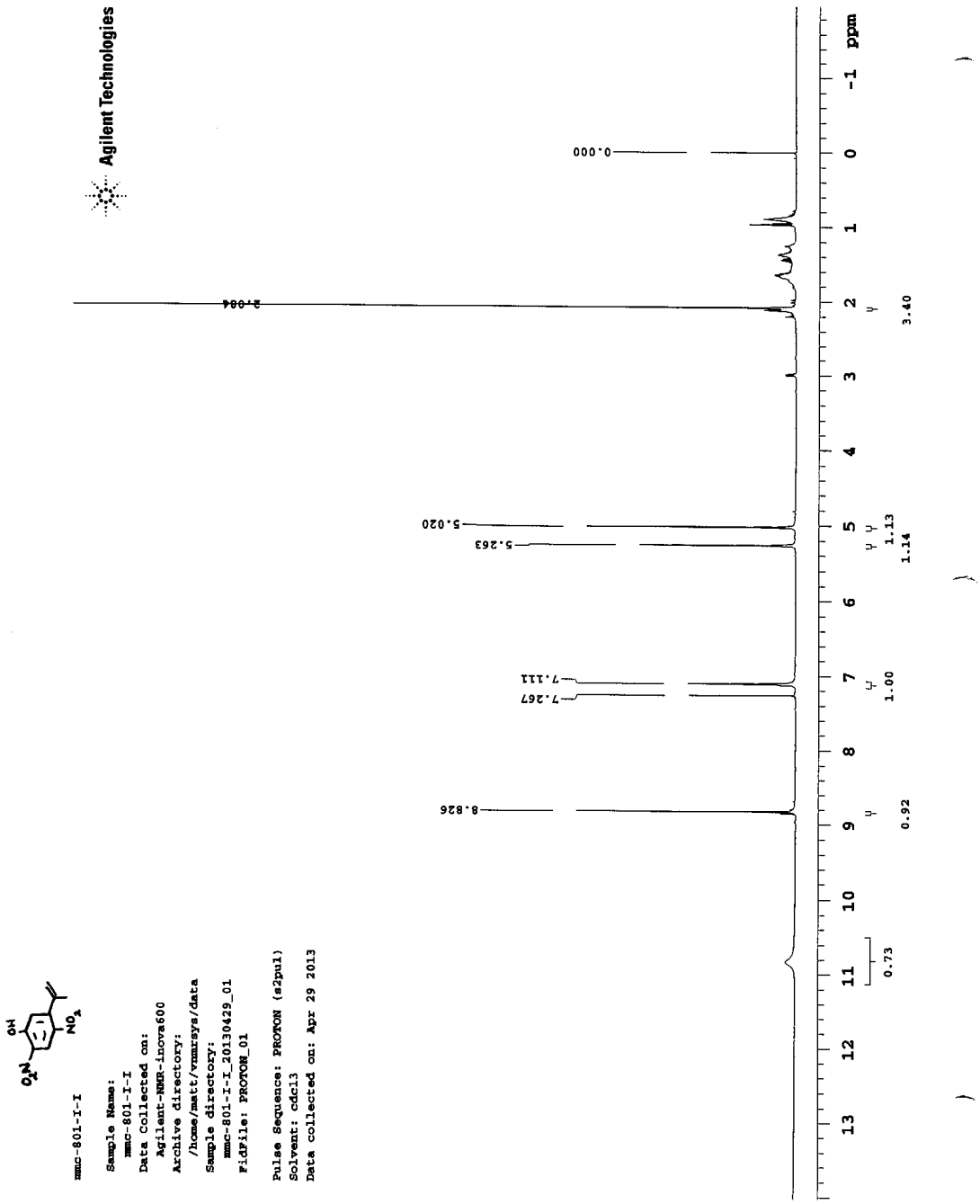

Figure 98: ^{1}H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol **(271)**

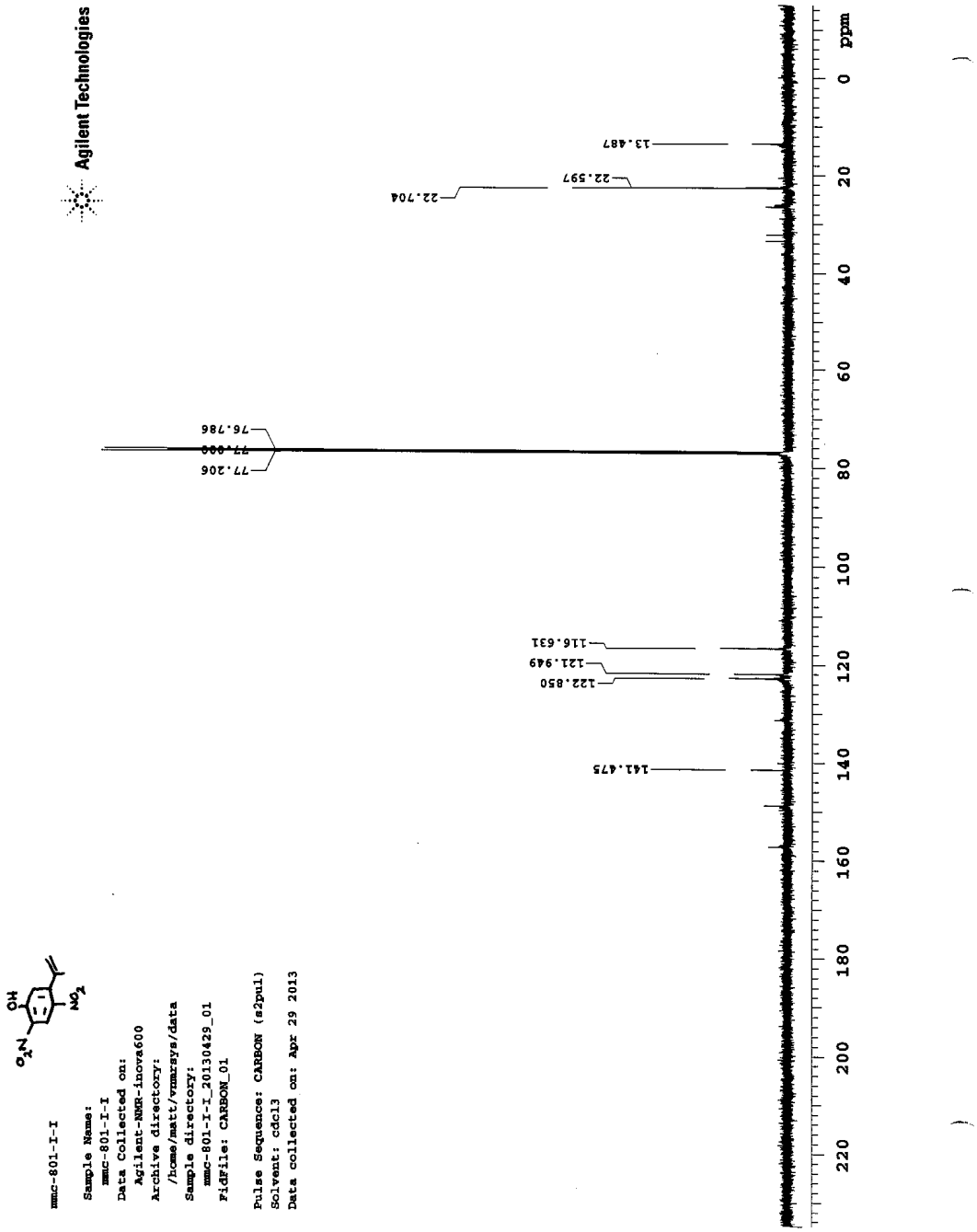

Figure 99: ^{13}C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenol **(271)**

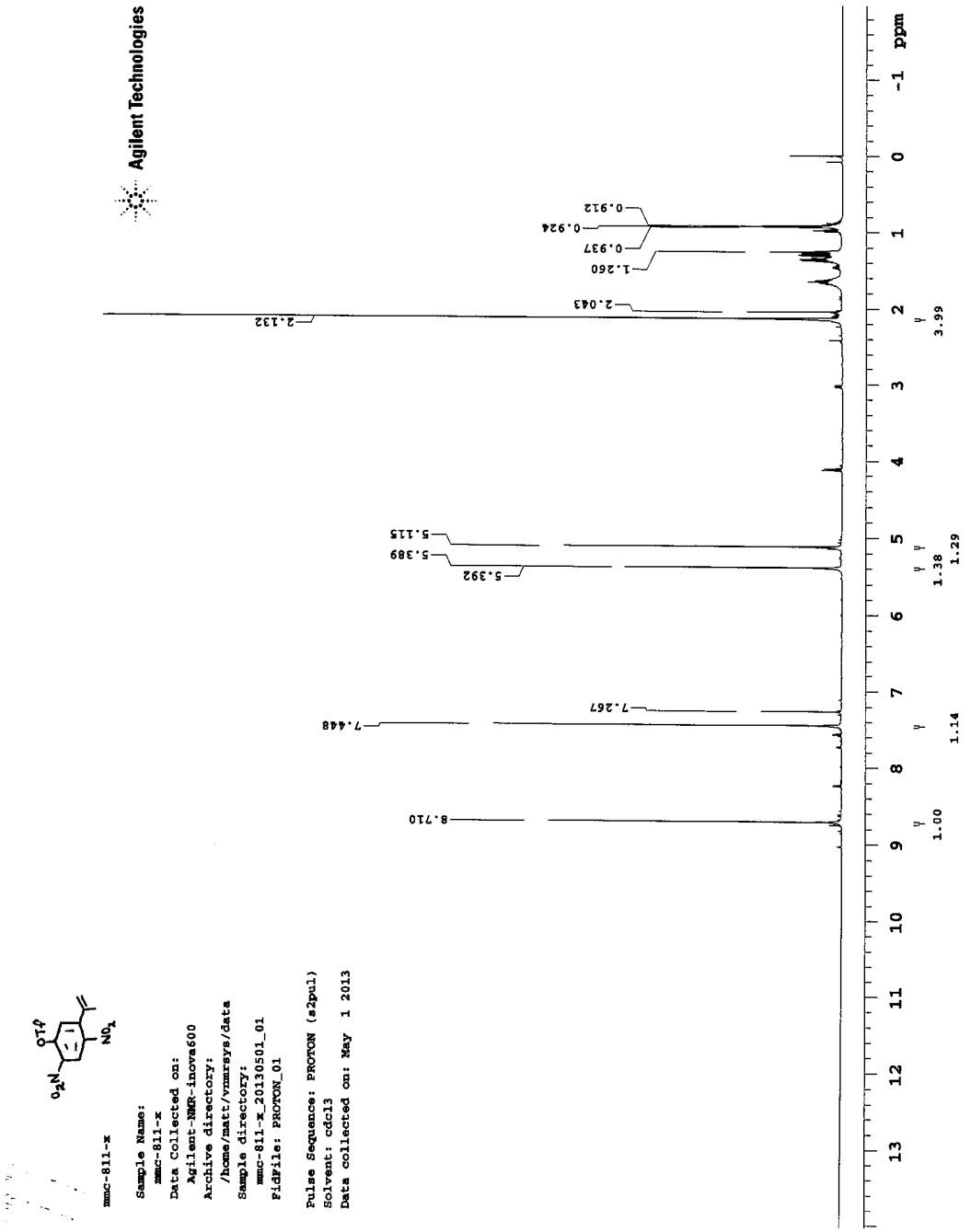

Figure 100: ^{1}H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate **(261)**

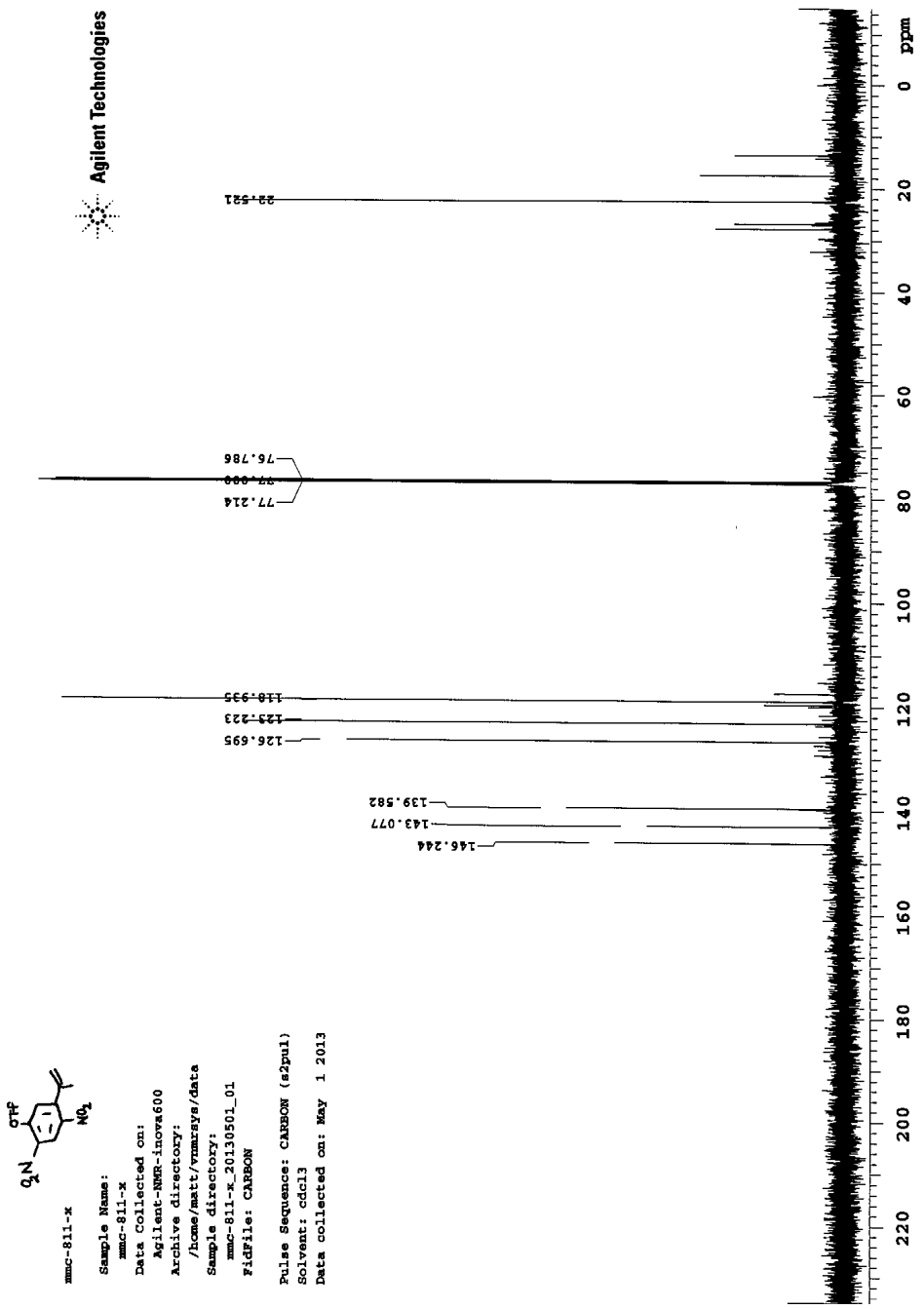

Figure 101: ^{13}C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)phenyl trifluoromethanesulfonate (**261**)

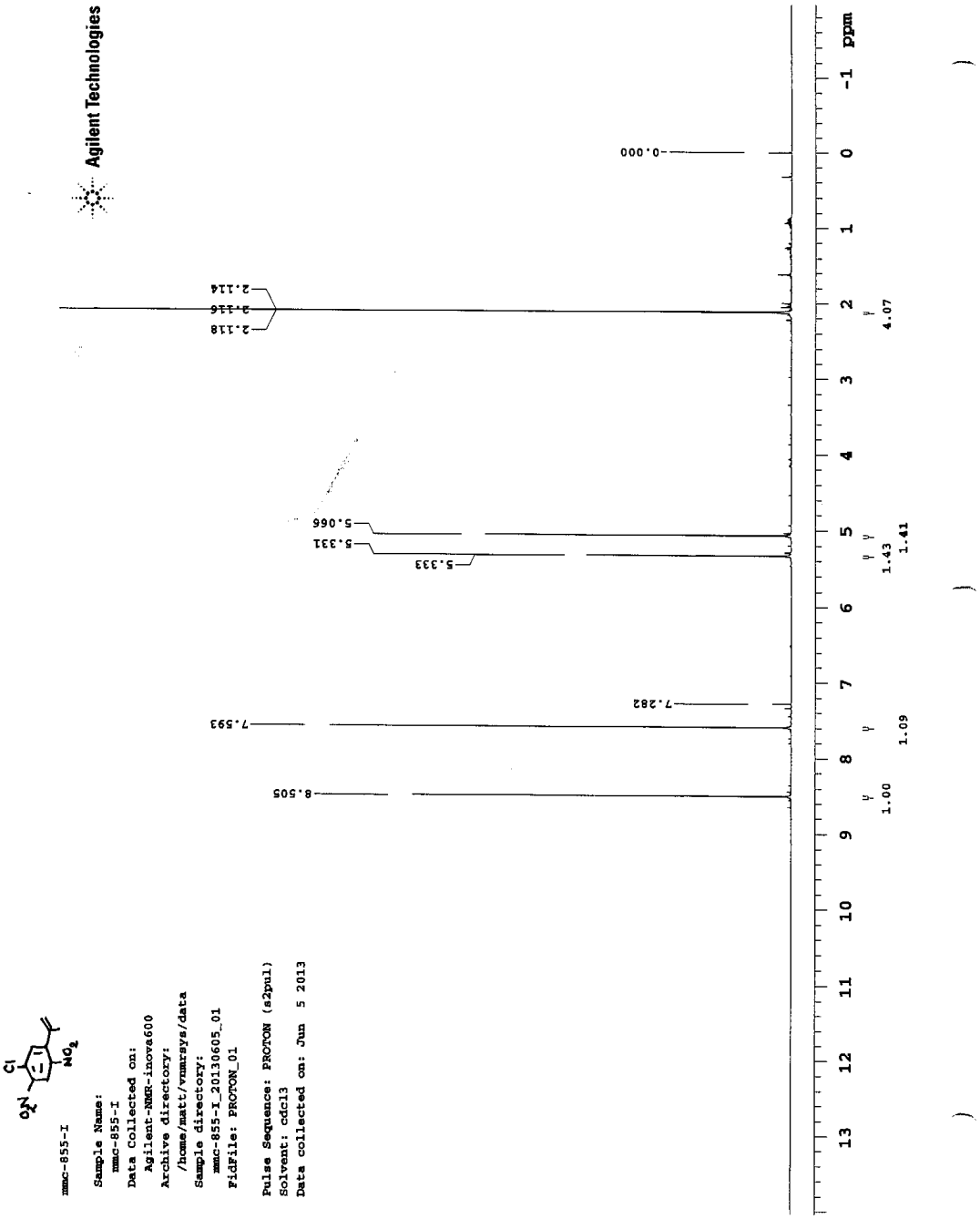

Figure 102: ^{1}H NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene **(273)**

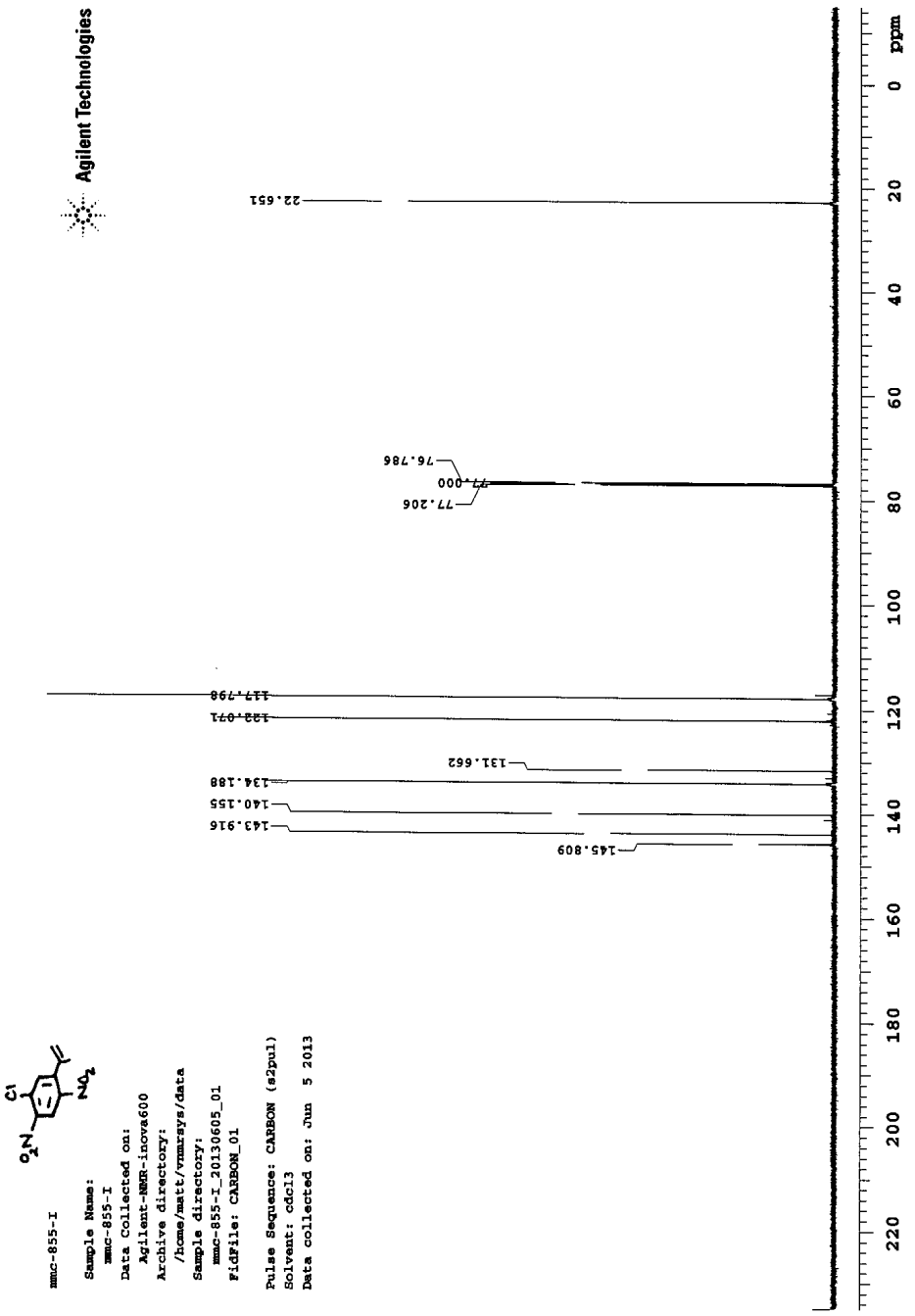

Figure 103: ^{13}C NMR of 1-chloro-2,4-dinitro-5-(prop-1-en-2-yl)benzene **(273)**

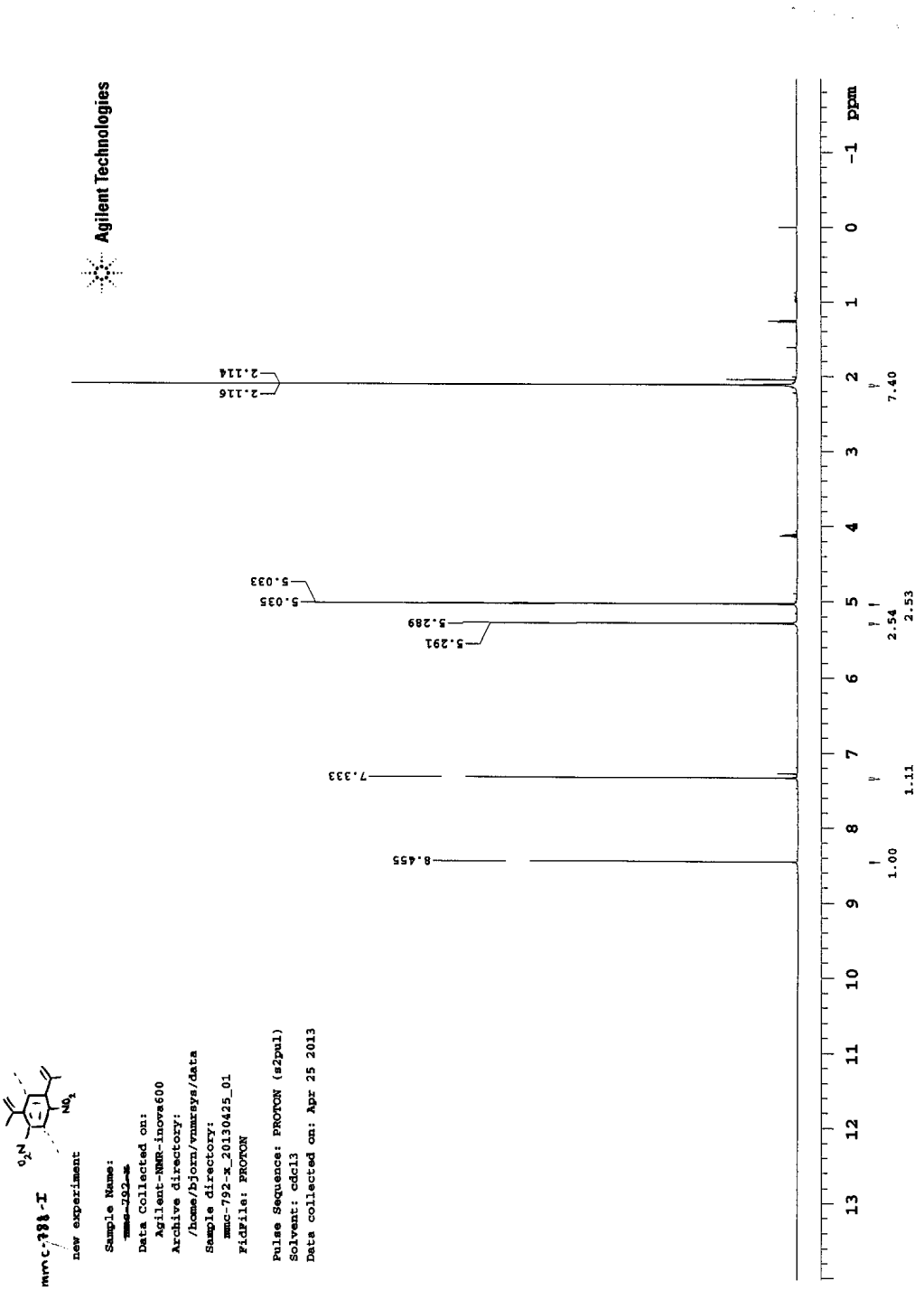

Figure 104: ^{1}H NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene (**260**)

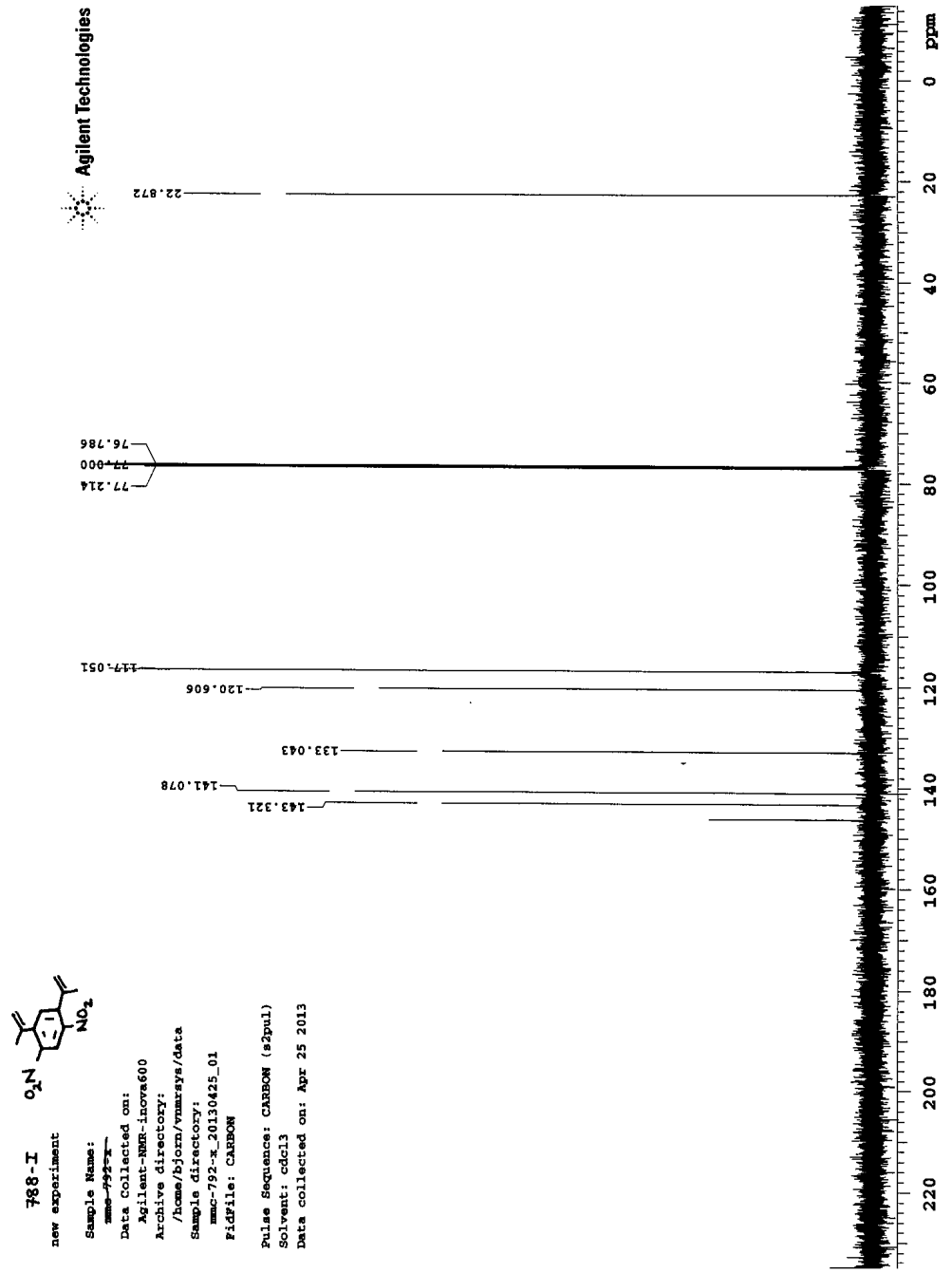

Figure 105: ^{13}C NMR of 1,5-dinitro-2,4-di(prop-1-en-2-yl)benzene **(260)**

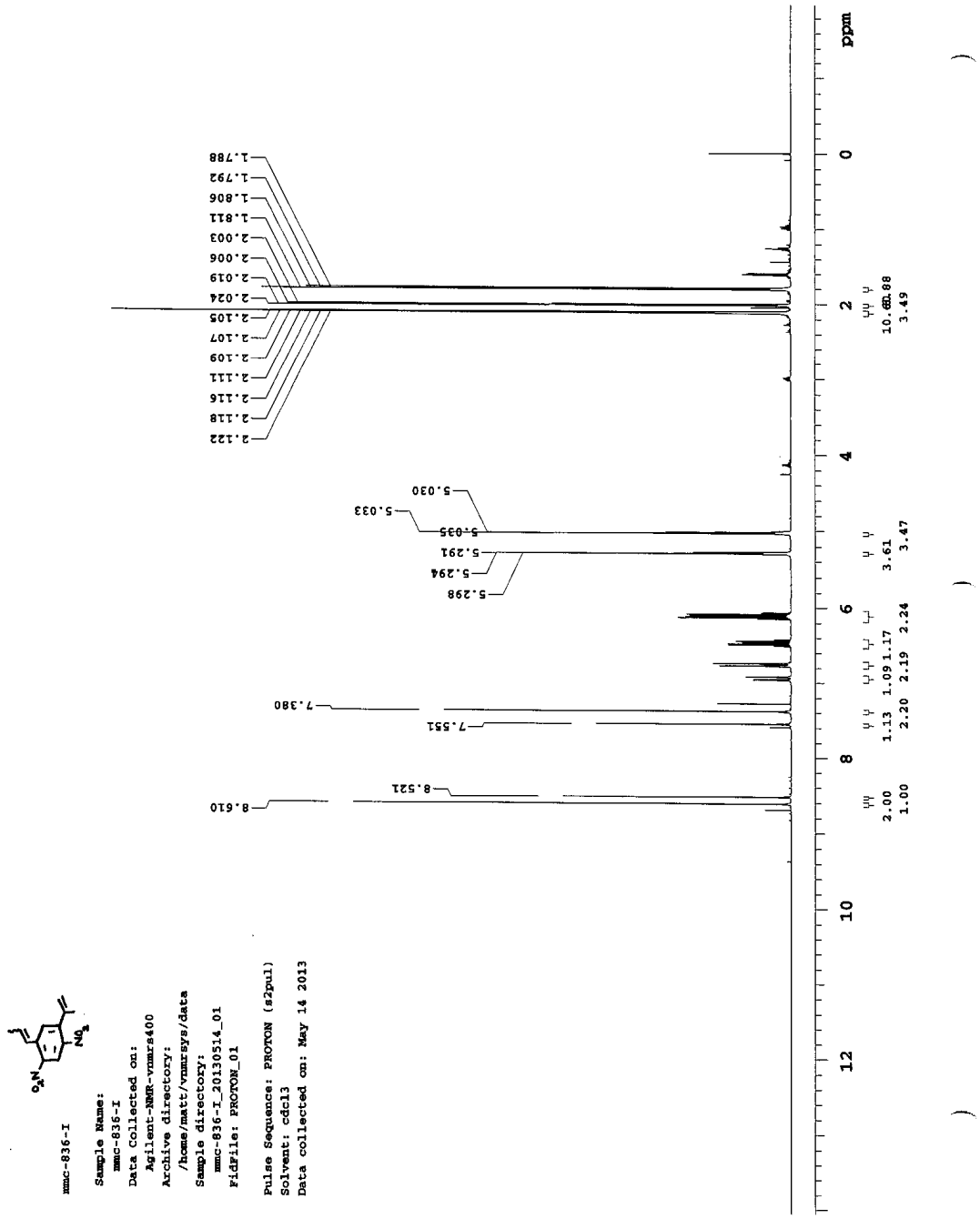

Figure 106: ^{1}H NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene **(274)**

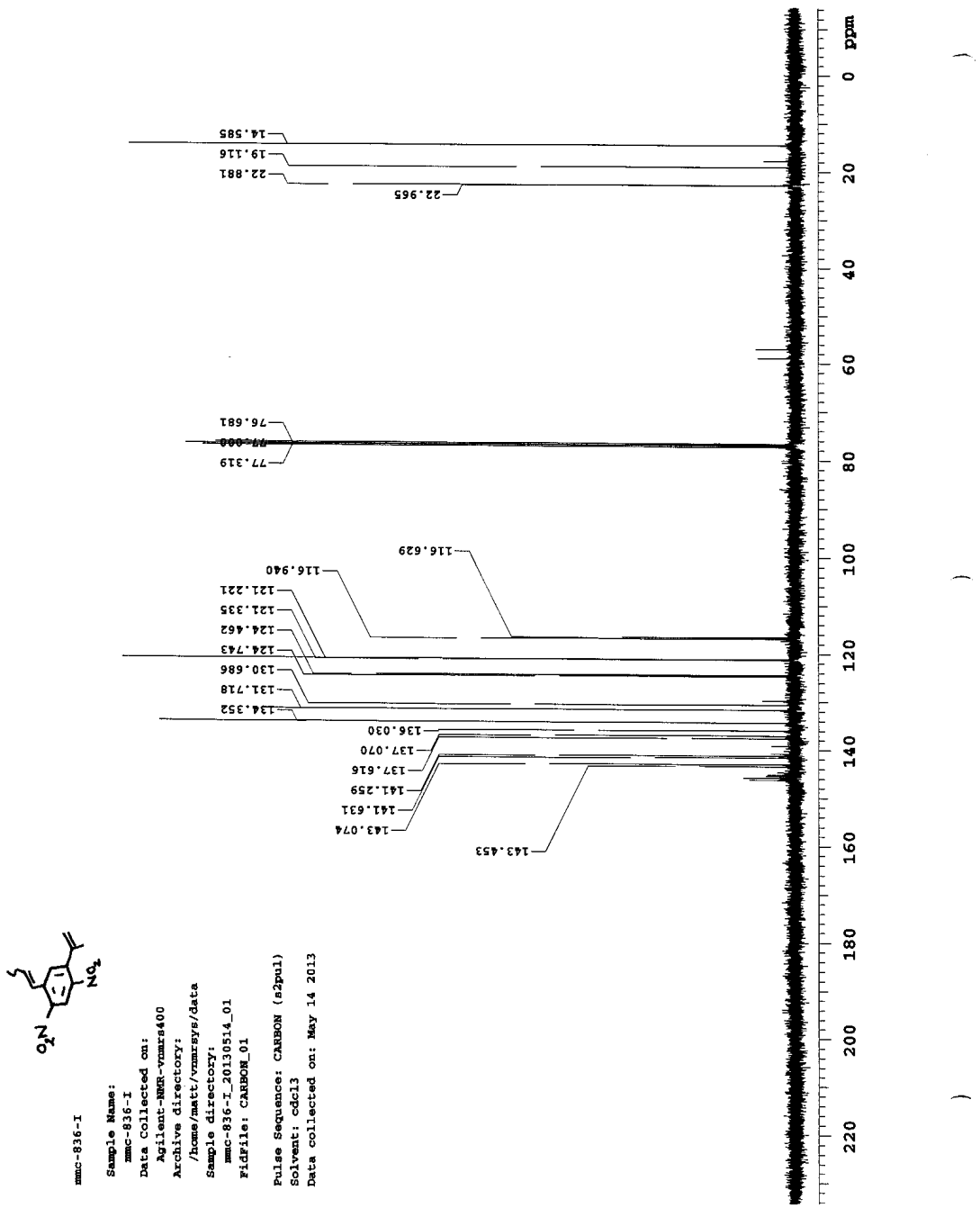

Figure 107: ^{13}C NMR of 1,5-dinitro-2-(prop-1-en-2-yl)-4-(prop-1-enyl)benzene **(274)**

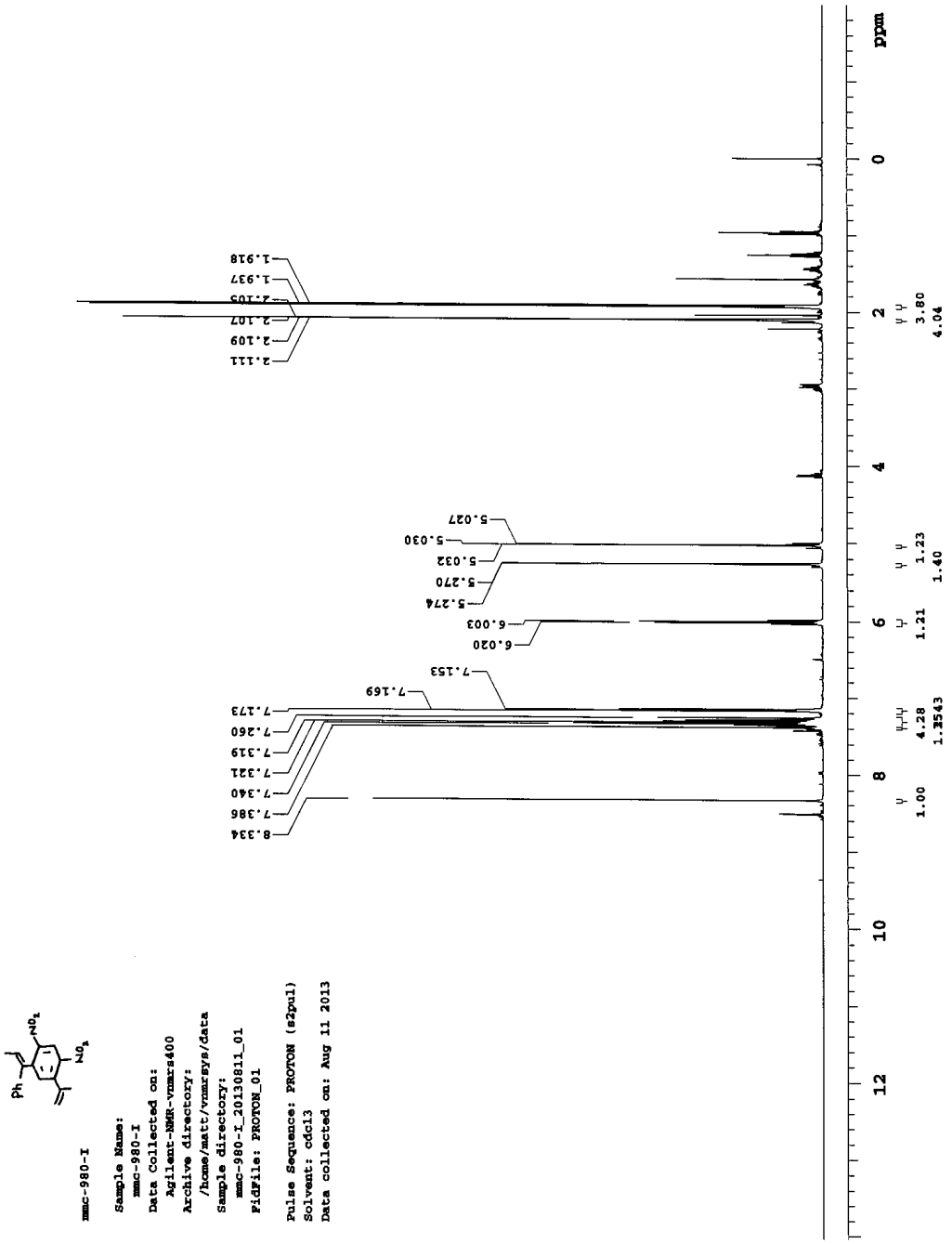

Figure 108: [1]H NMR of (*E*)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene **(276)**

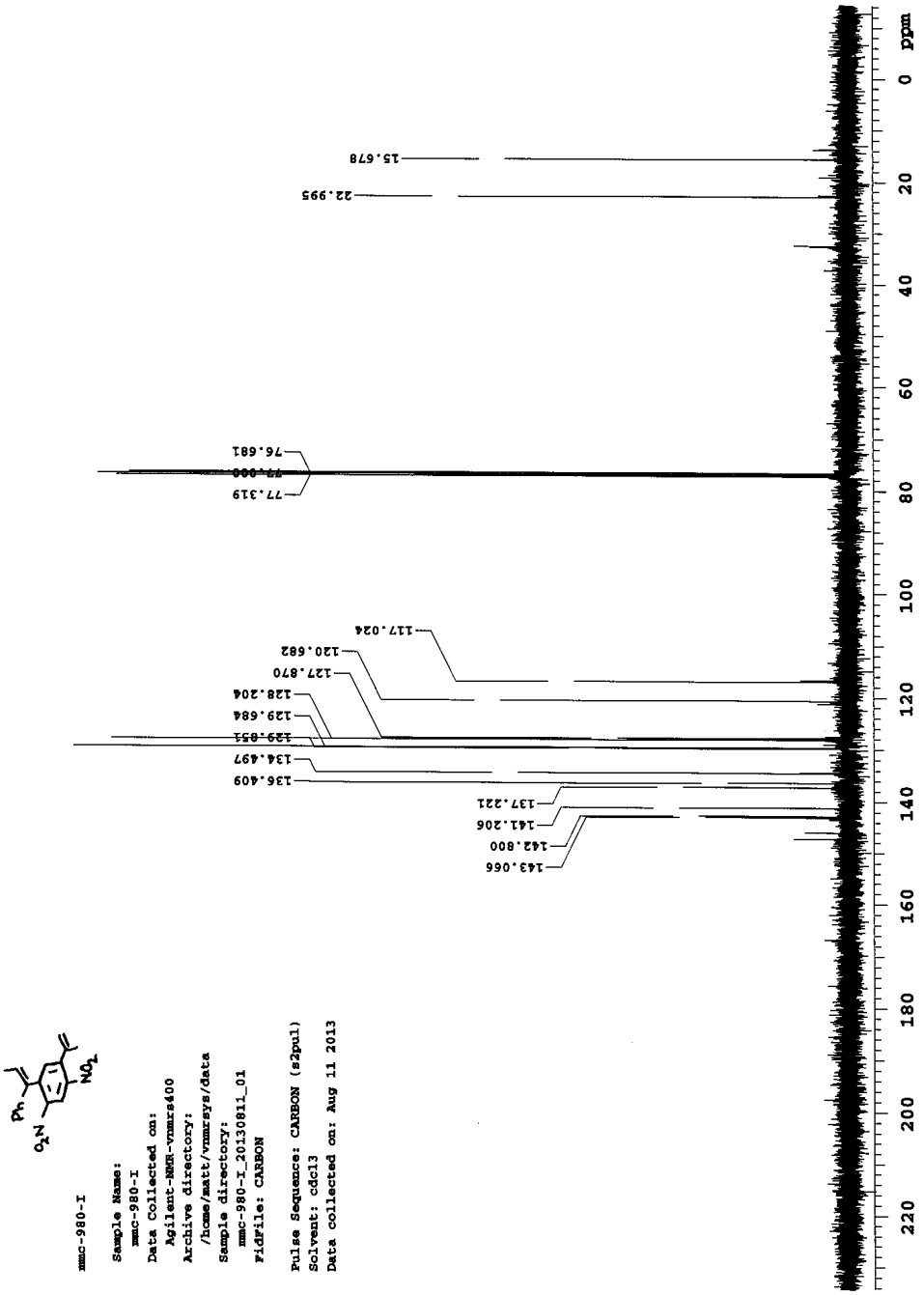

Figure 109: ^{13}C NMR of (*E*)-1,5-dinitro-2-(1-phenylprop-1-enyl)-4-(prop-1-en-2-yl)benzene **(276)**

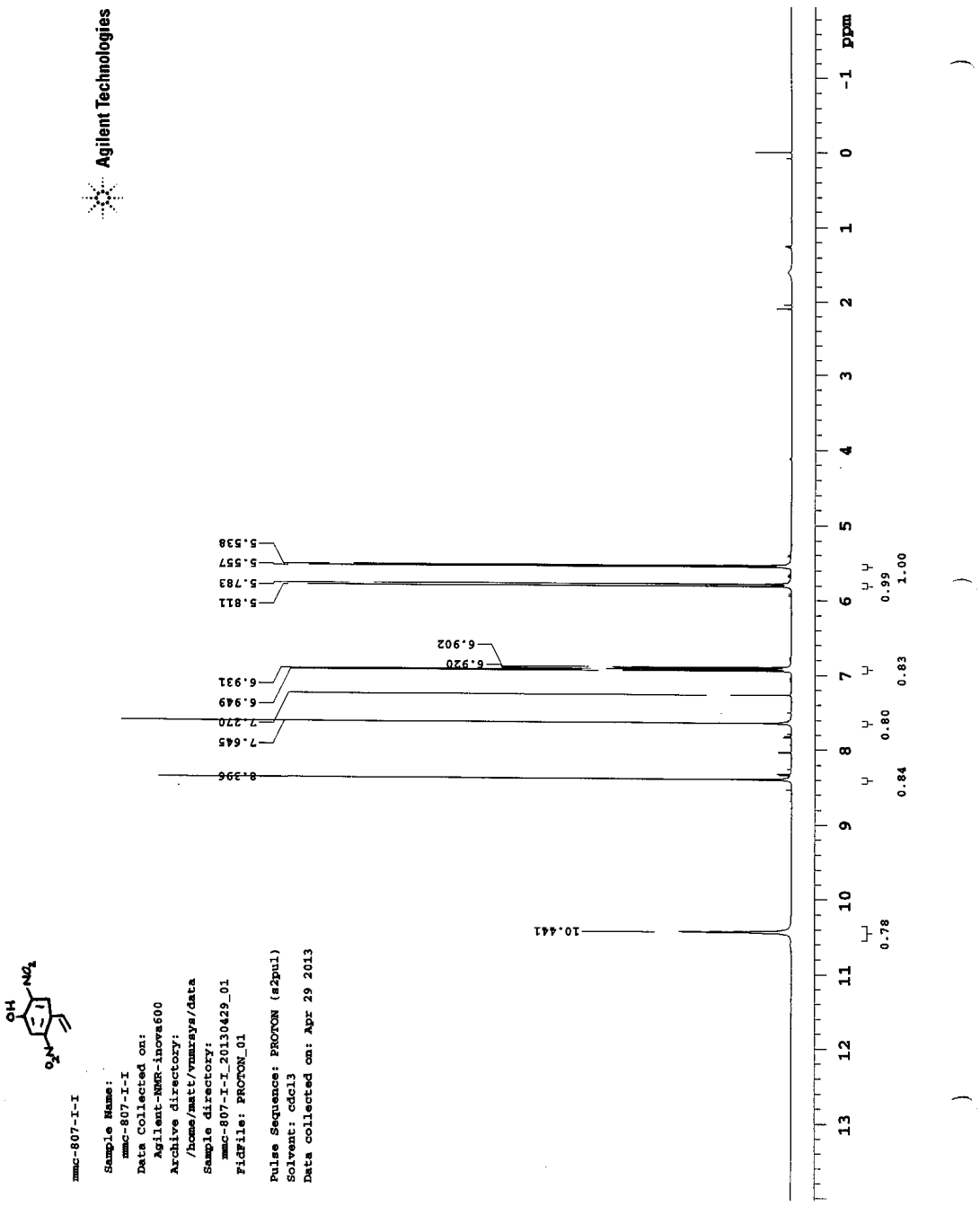

Figure 110: [1]H NMR of 2,5-dinitro-4-ethenylphenol **(278)**

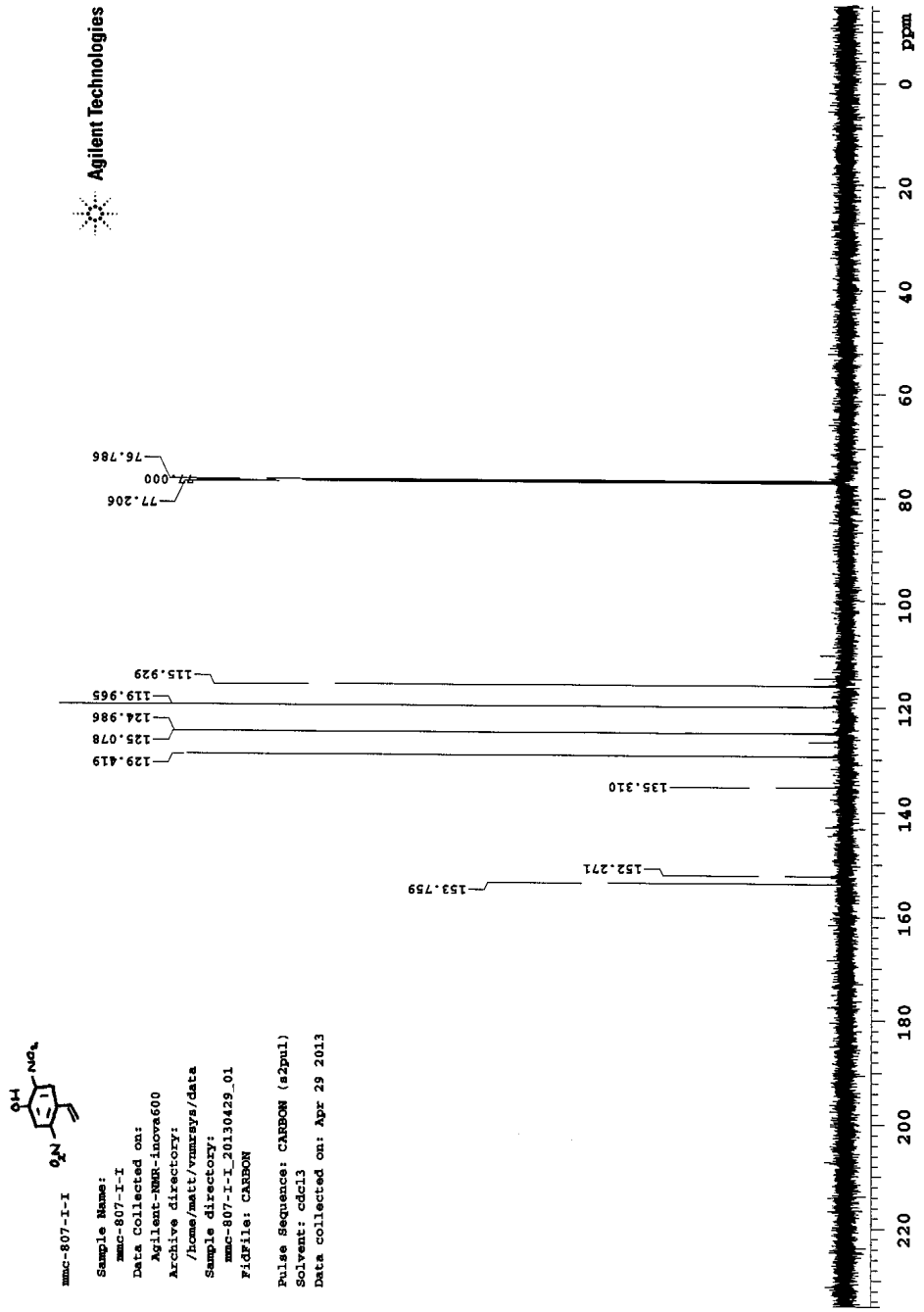

Figure 111: ^{13}C NMR of 2,5-dinitro-4-ethenylphenol **(278)**

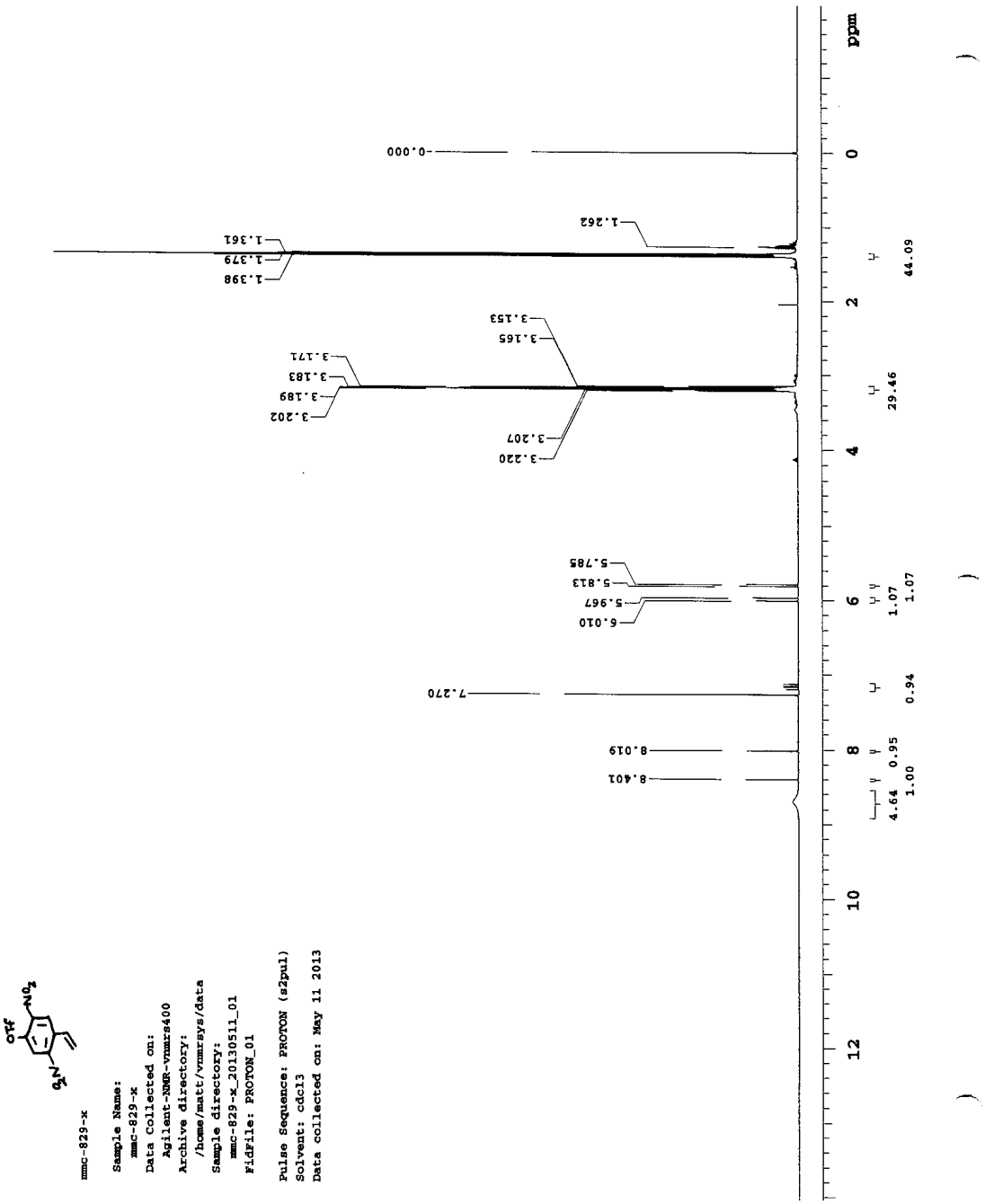

Figure 112: ^{1}H NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate **(277)**

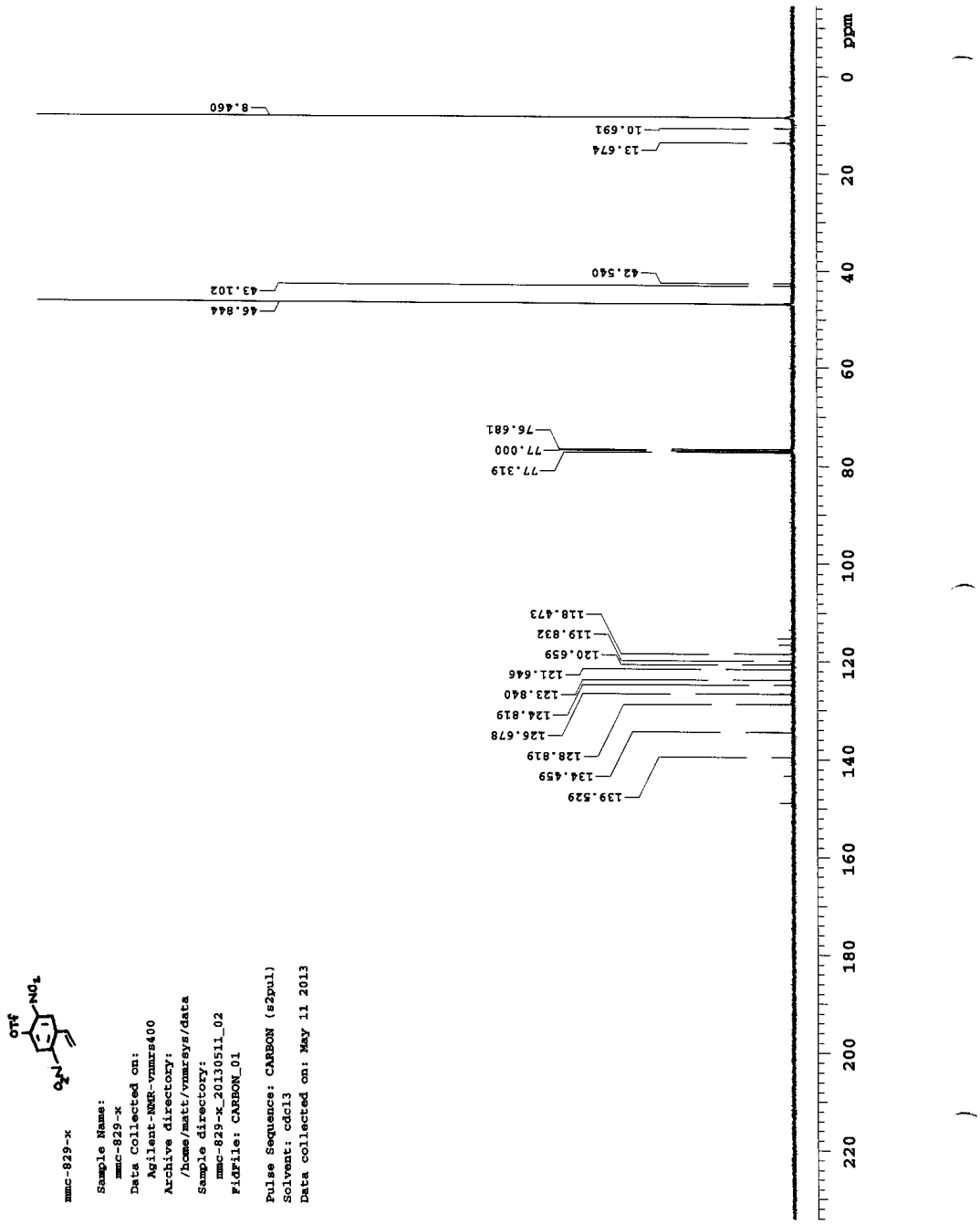

Figure 113: ^{13}C NMR of 2,5-dinitro-4-ethenylphenyl trifluoromethanesulfonate (**277**)

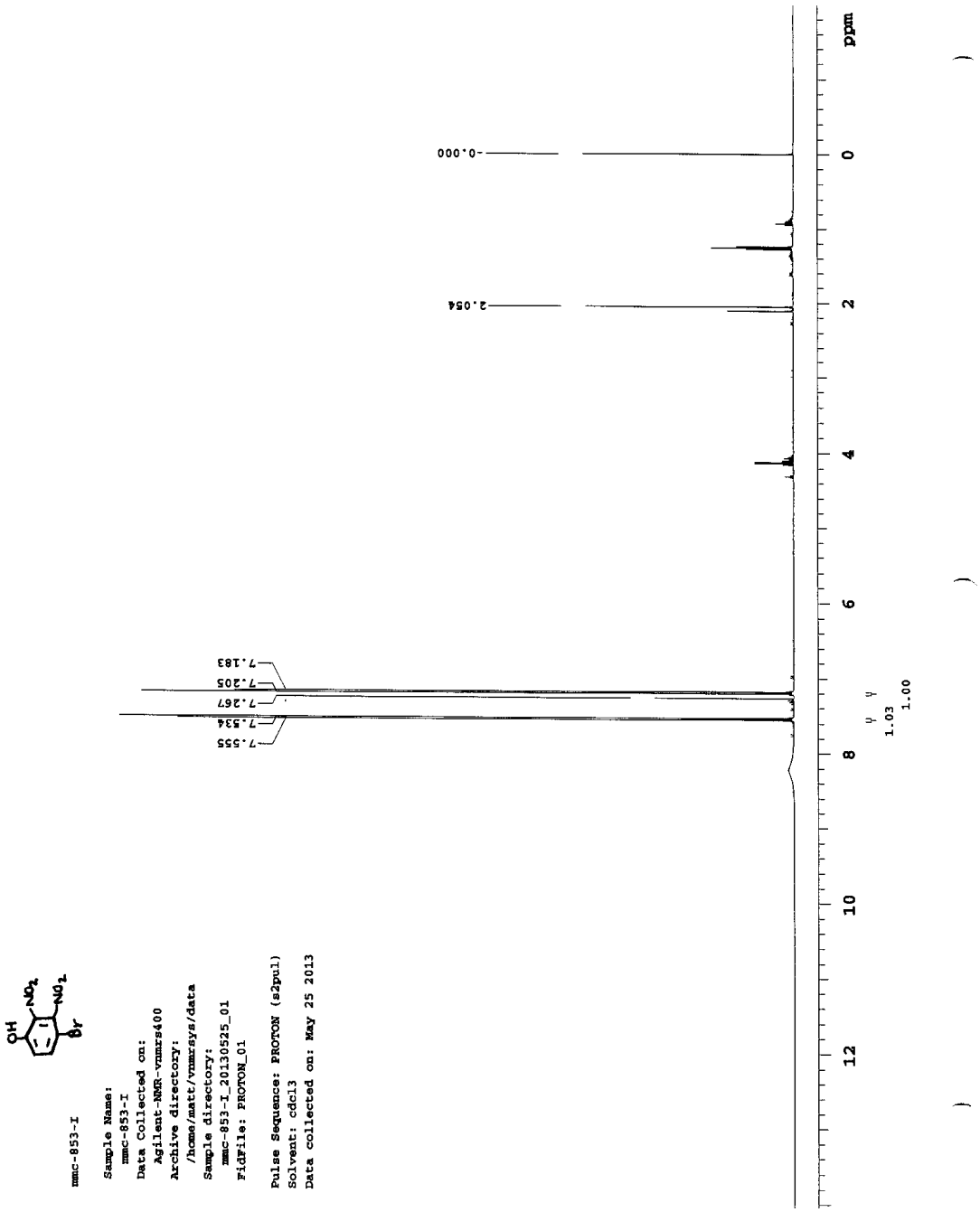

Figure 114: ^{1}H NMR of 4-bromo-2,3-dinitrophenol (**292**)

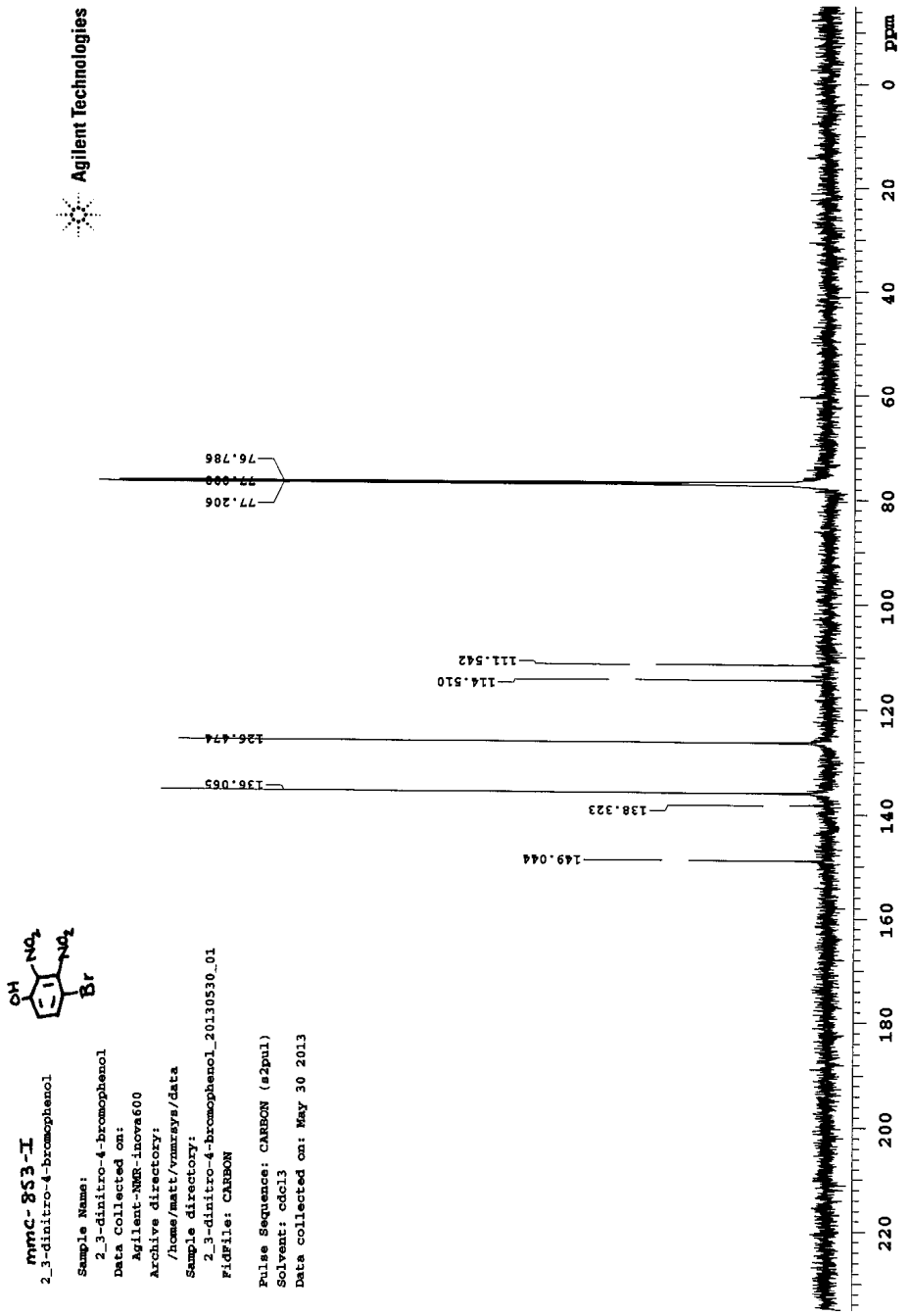

Figure 115: ^{13}C NMR of 4-bromo-2,3-dinitrophenol (**292**)

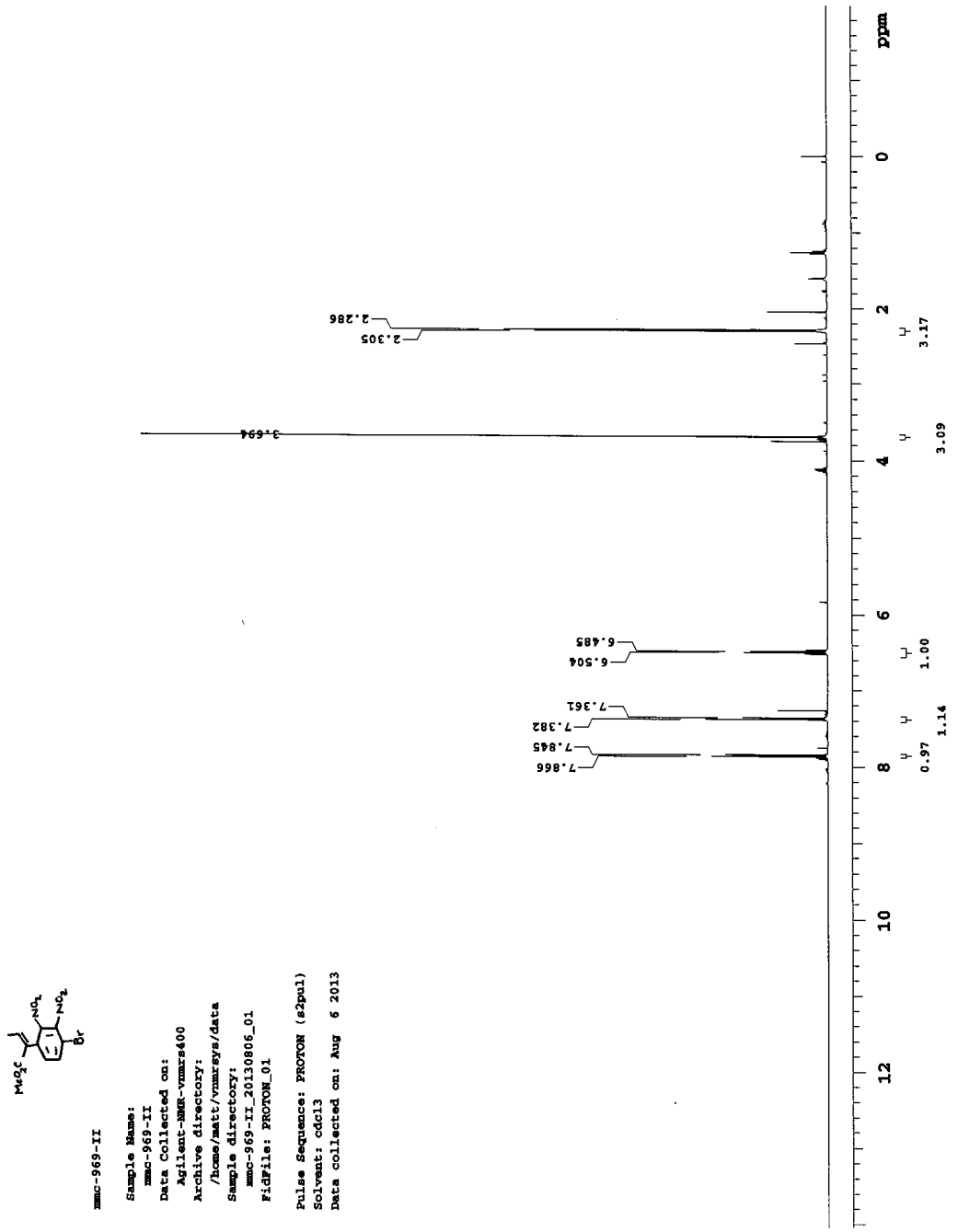

Figure 116: ^{1}H NMR of (*Z*)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate **(301)**

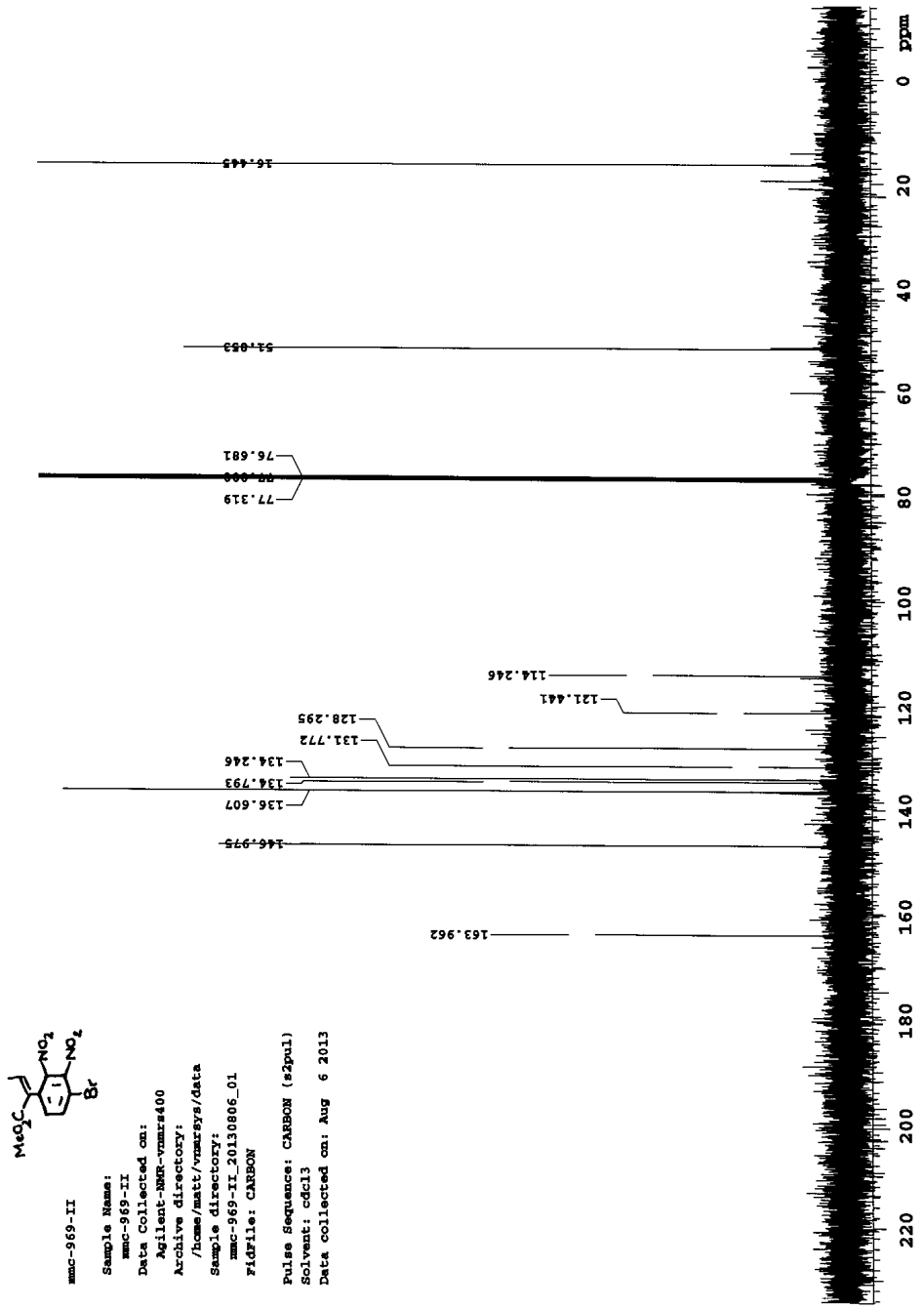

Figure 117: ^{13}C NMR of (*Z*)-methyl 2-(4-bromo-2,3-dinitrophenyl)but-2-enoate **(301)**

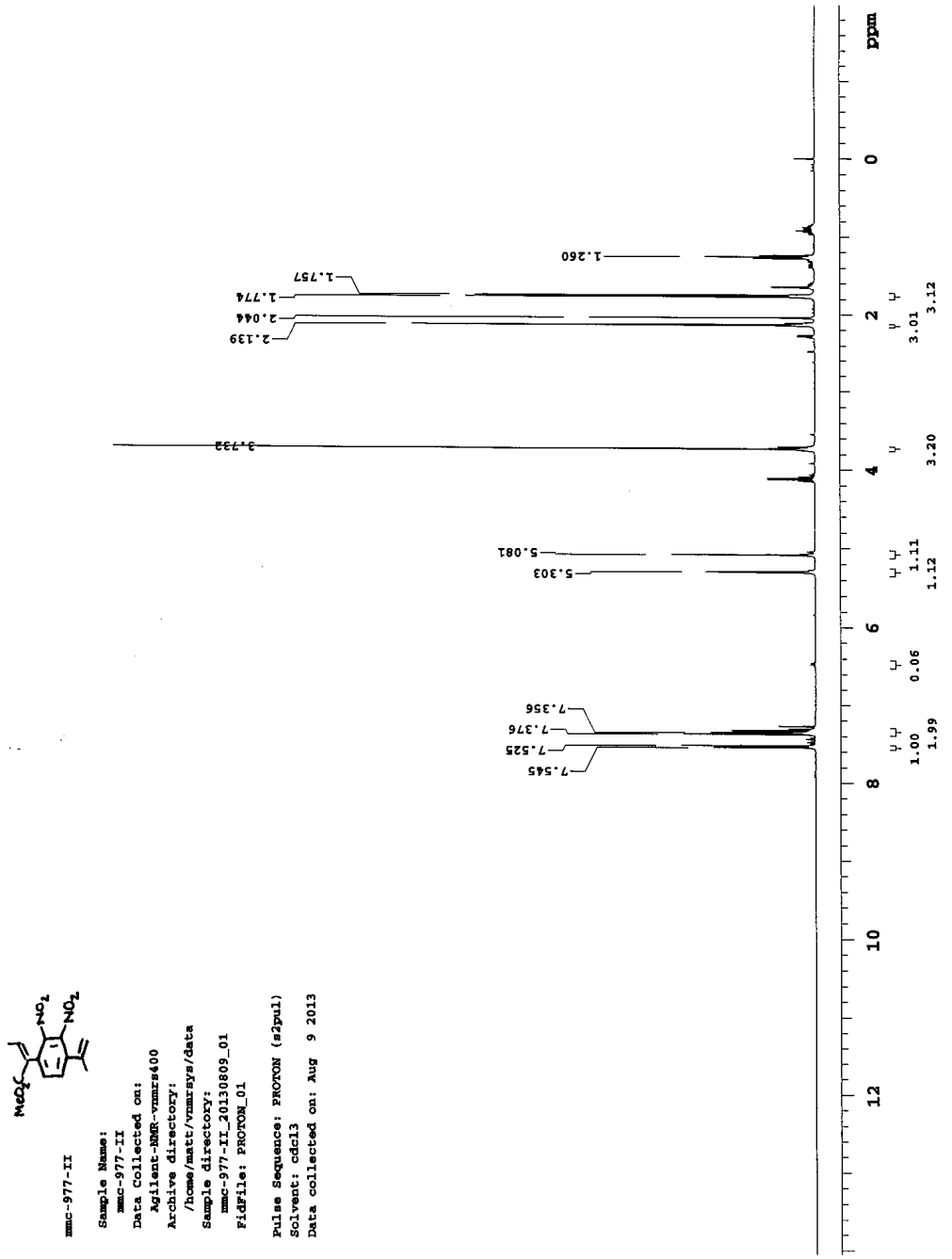

Figure 118: ^{1}H NMR of (*Z*)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate

(302)

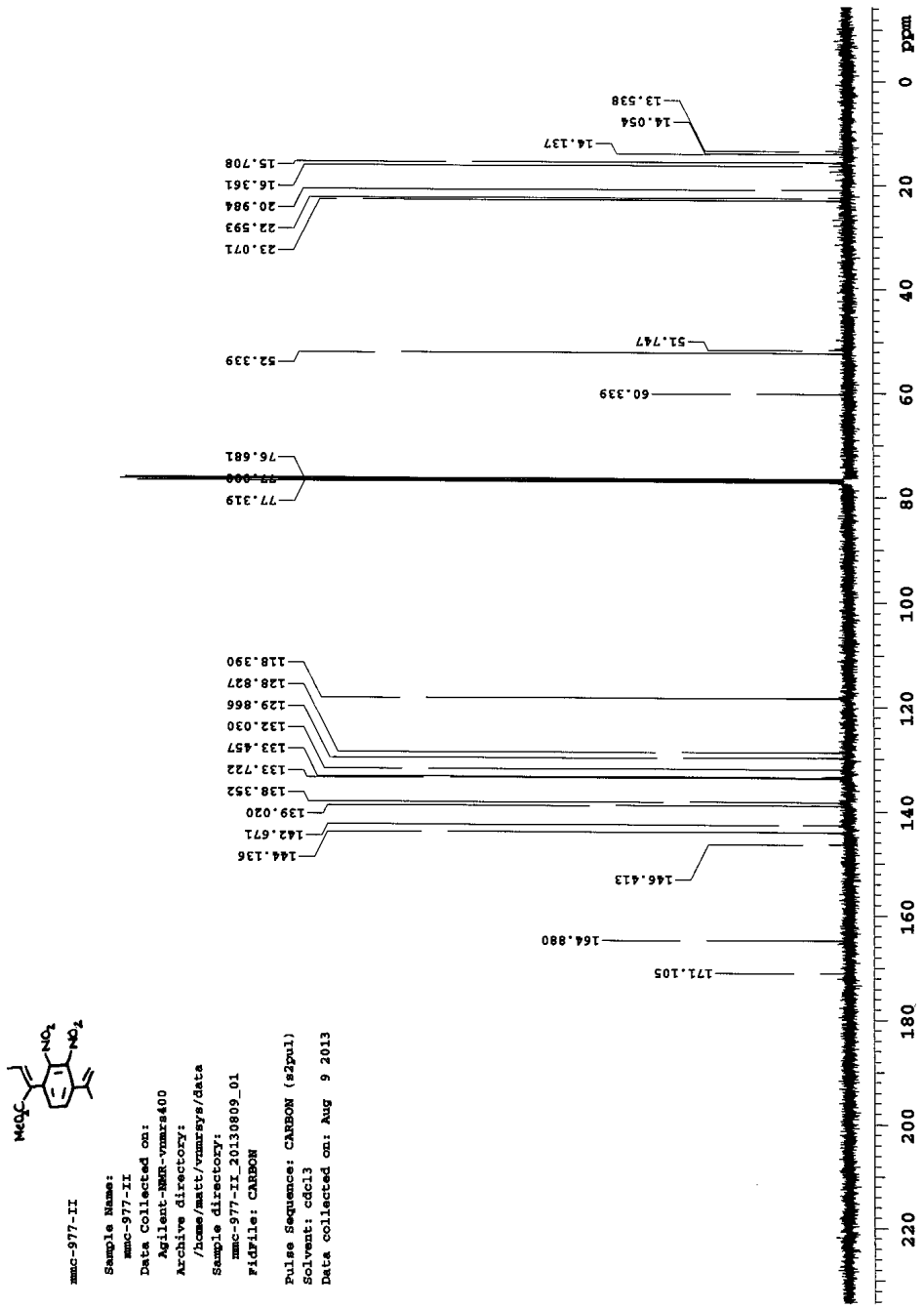

Figure 119: ^{13}C NMR of (*Z*)-methyl 2-(2,3-dinitro-4-(prop-1-en-2-yl)phenyl)but-2-enoate **(302)**

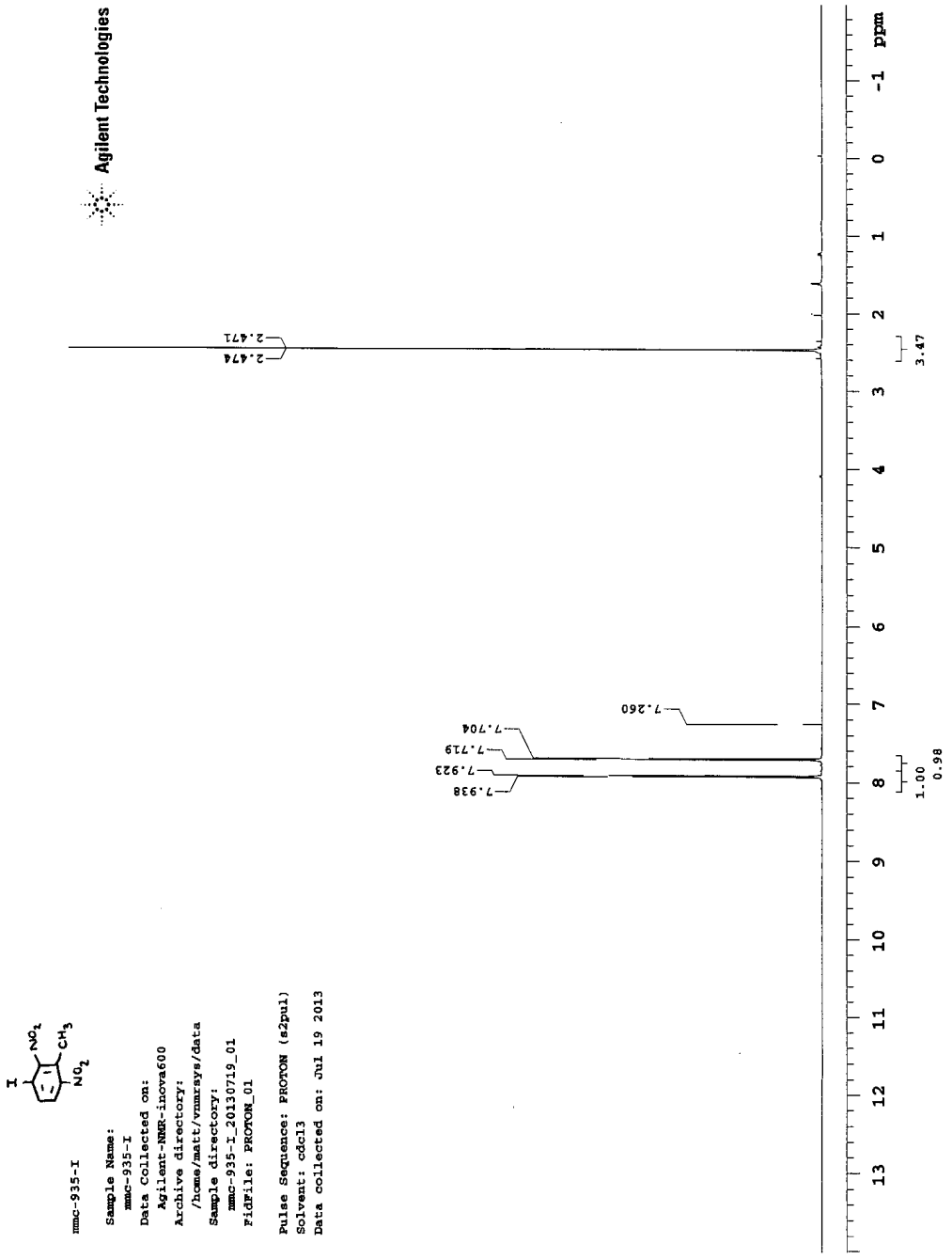

Figure 120: ^{1}H NMR of 1-iodo-3-methyl-2,4-dinitrobenzene **(308)**

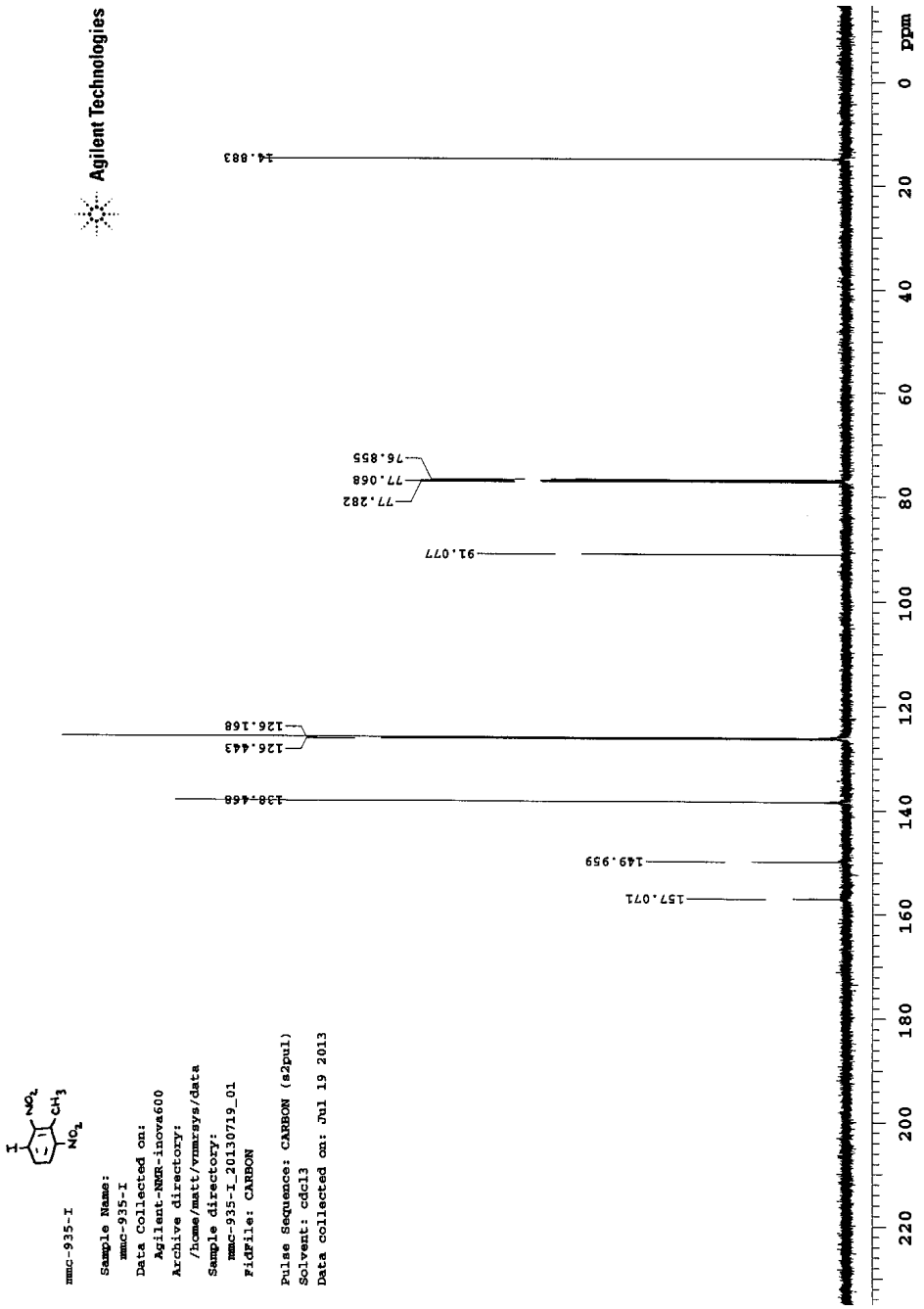

Figure 121: ^{13}C NMR of 1-iodo-3-methyl-2,4-dinitrobenzene **(308)**

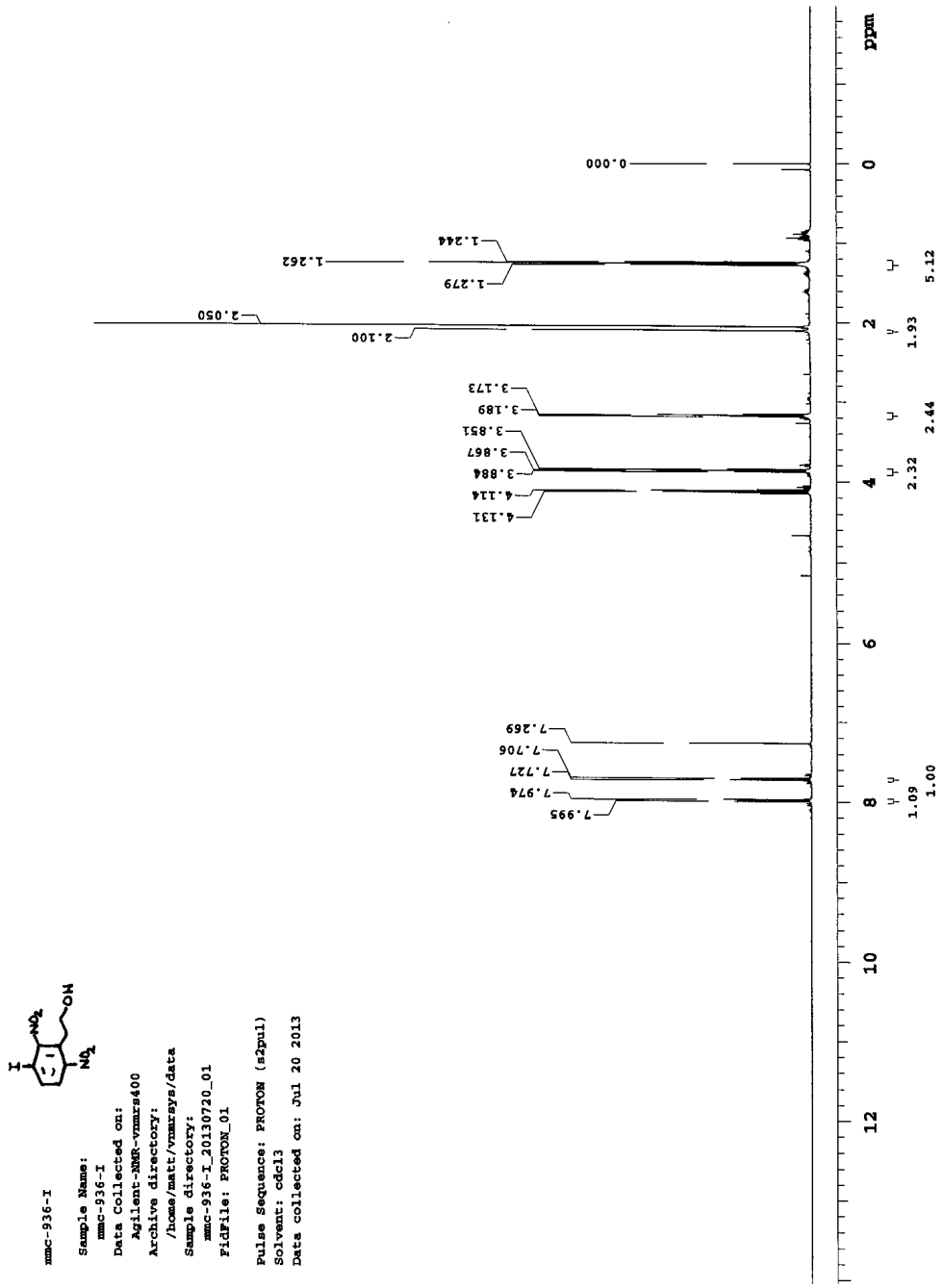

Figure 122: ^{1}H NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol **(312)**

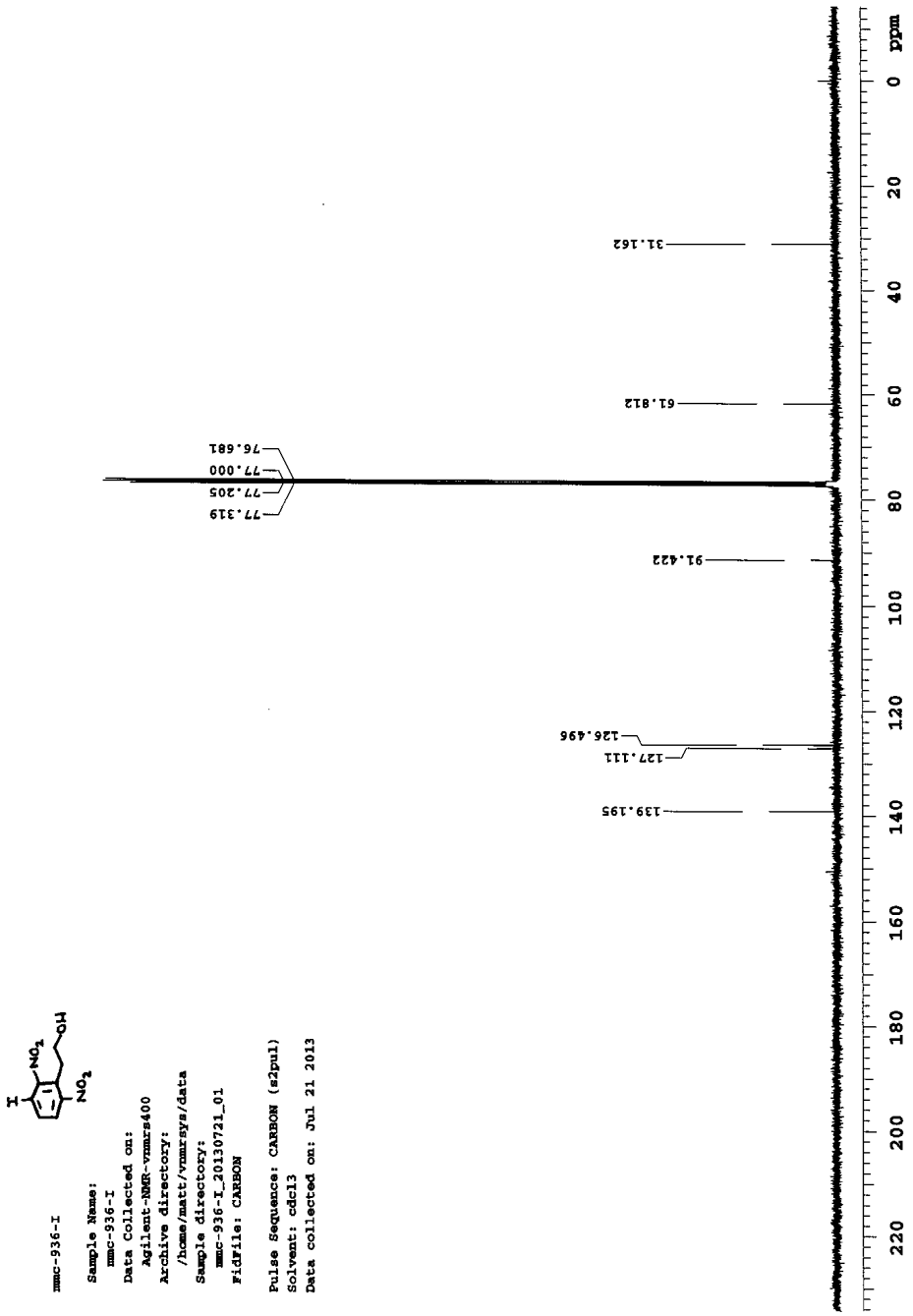

Figure 123: ^{13}C NMR of 2-(3-iodo-2,6-dinitrophenyl)ethanol **(312)**

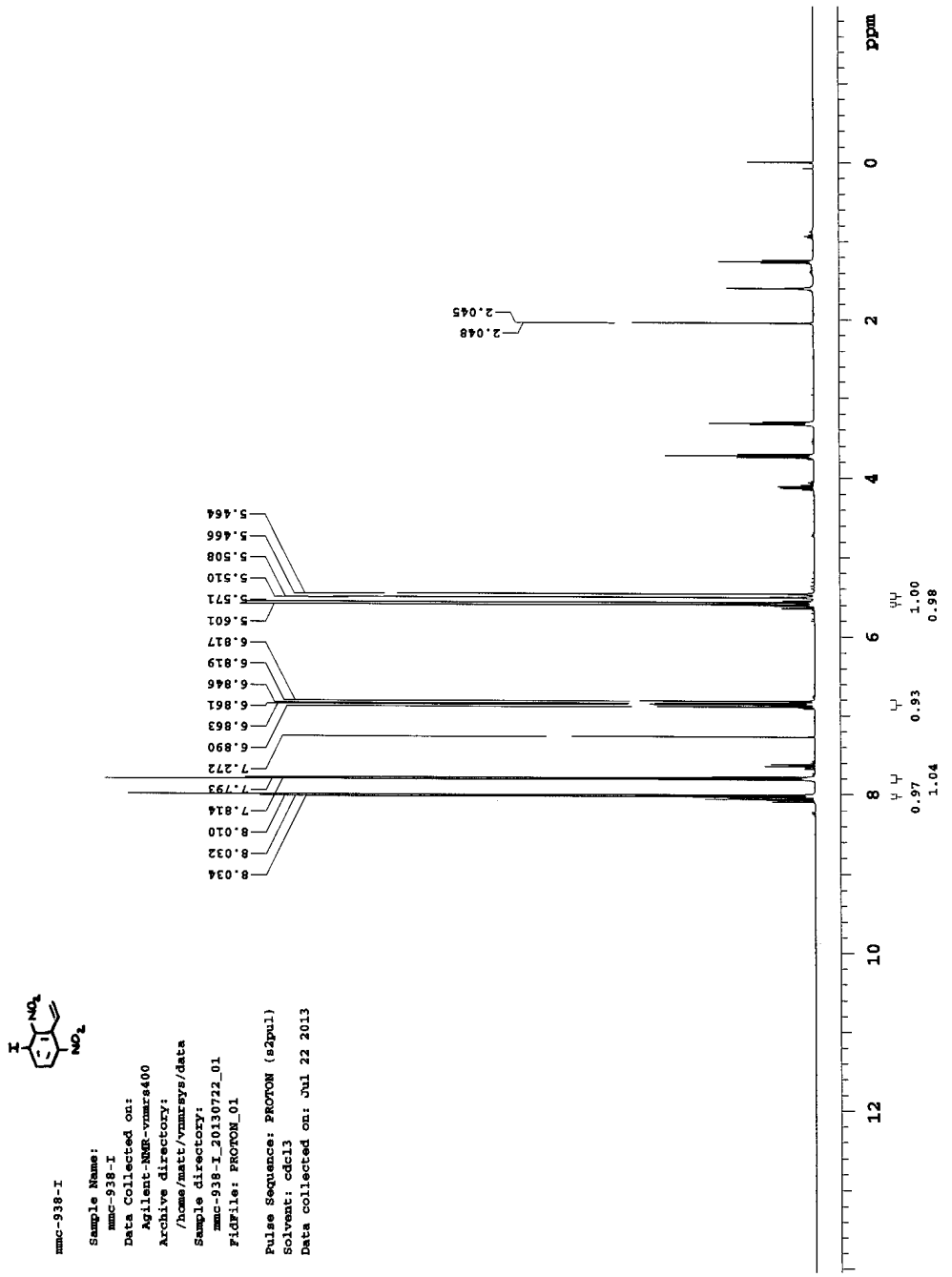

Figure 124: ^{1}H NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene **(313)**

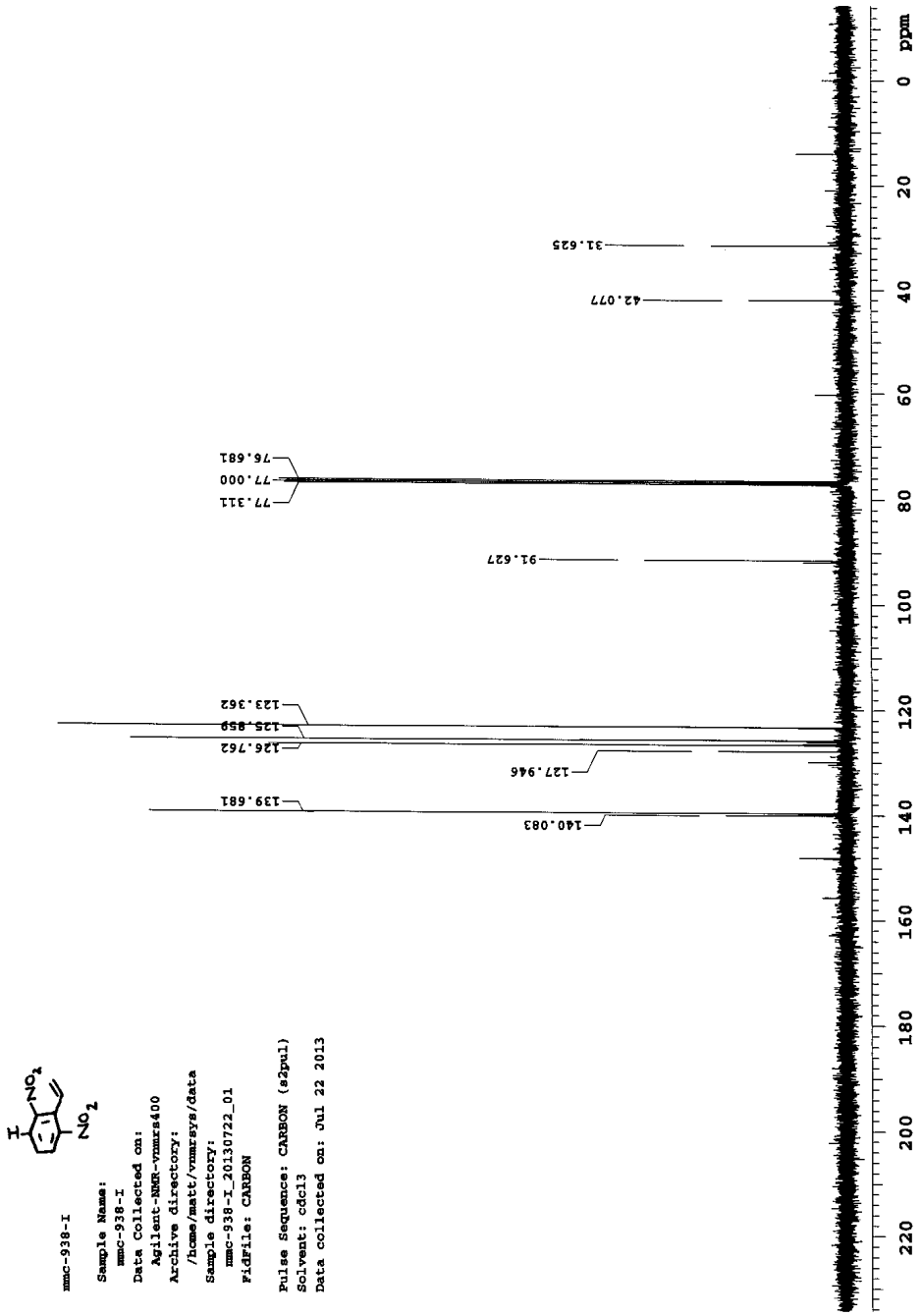

Figure 125: ^{13}C NMR of 1-iodo-2,4-dinitro-3-ethenylbenzene **(313)**

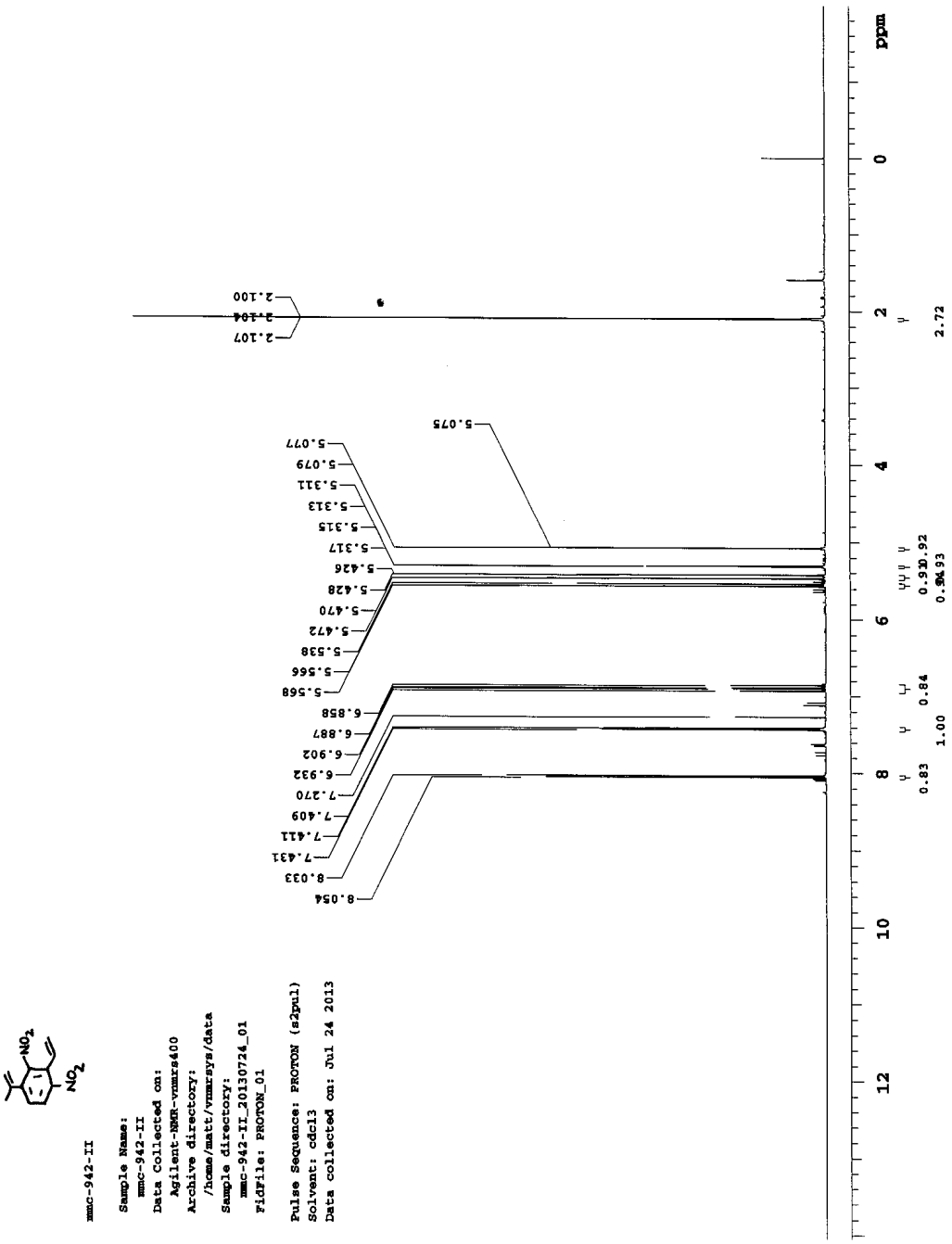

Figure 126: ^{1}H NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene **(314)**

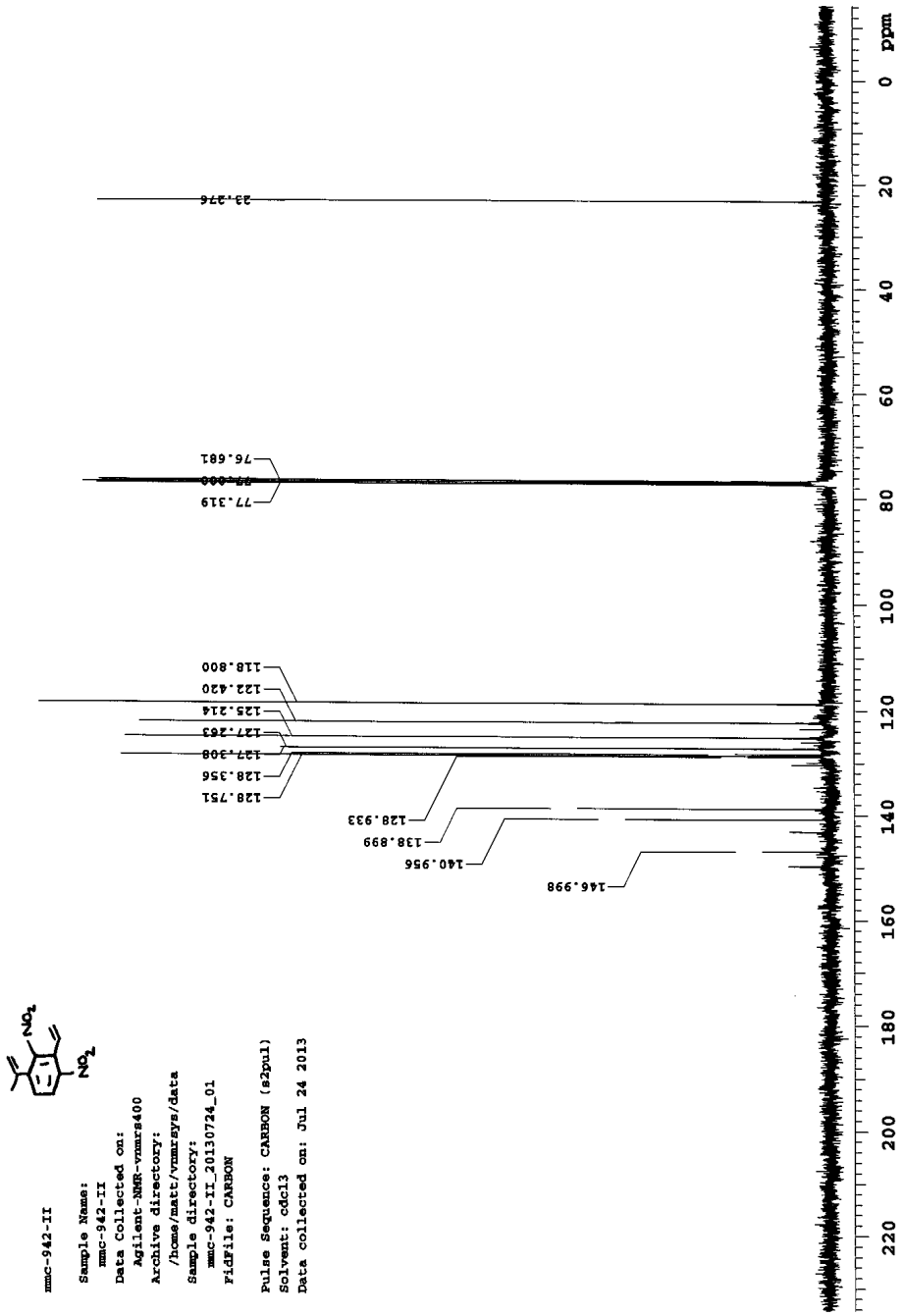

Figure 127: ^{13}C NMR of 1,3-dinitro-4-(prop-1-en-2-yl)-2-ethenylbenzene **(314)**

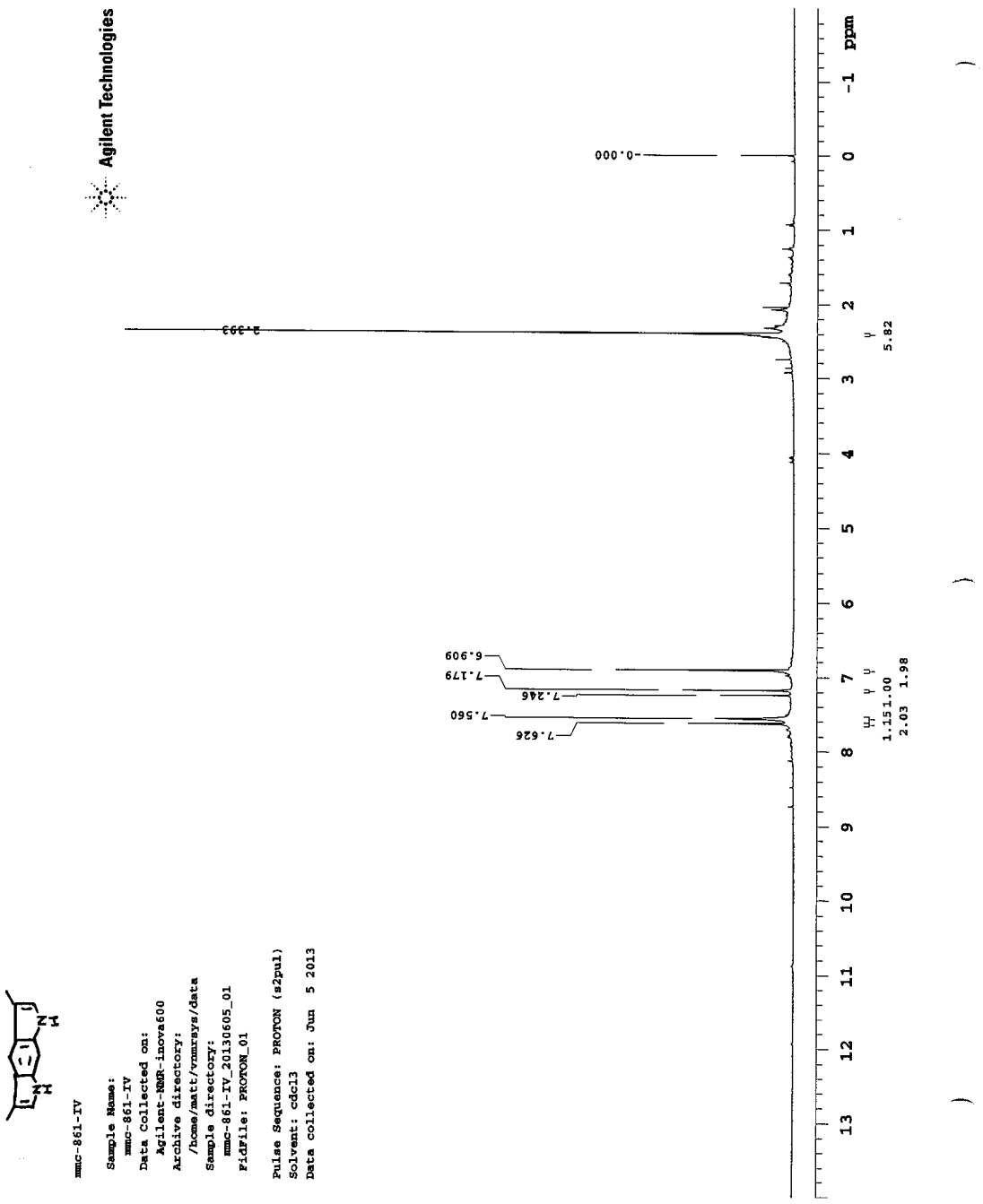

Figure 128: ^{1}H NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole **(326)**

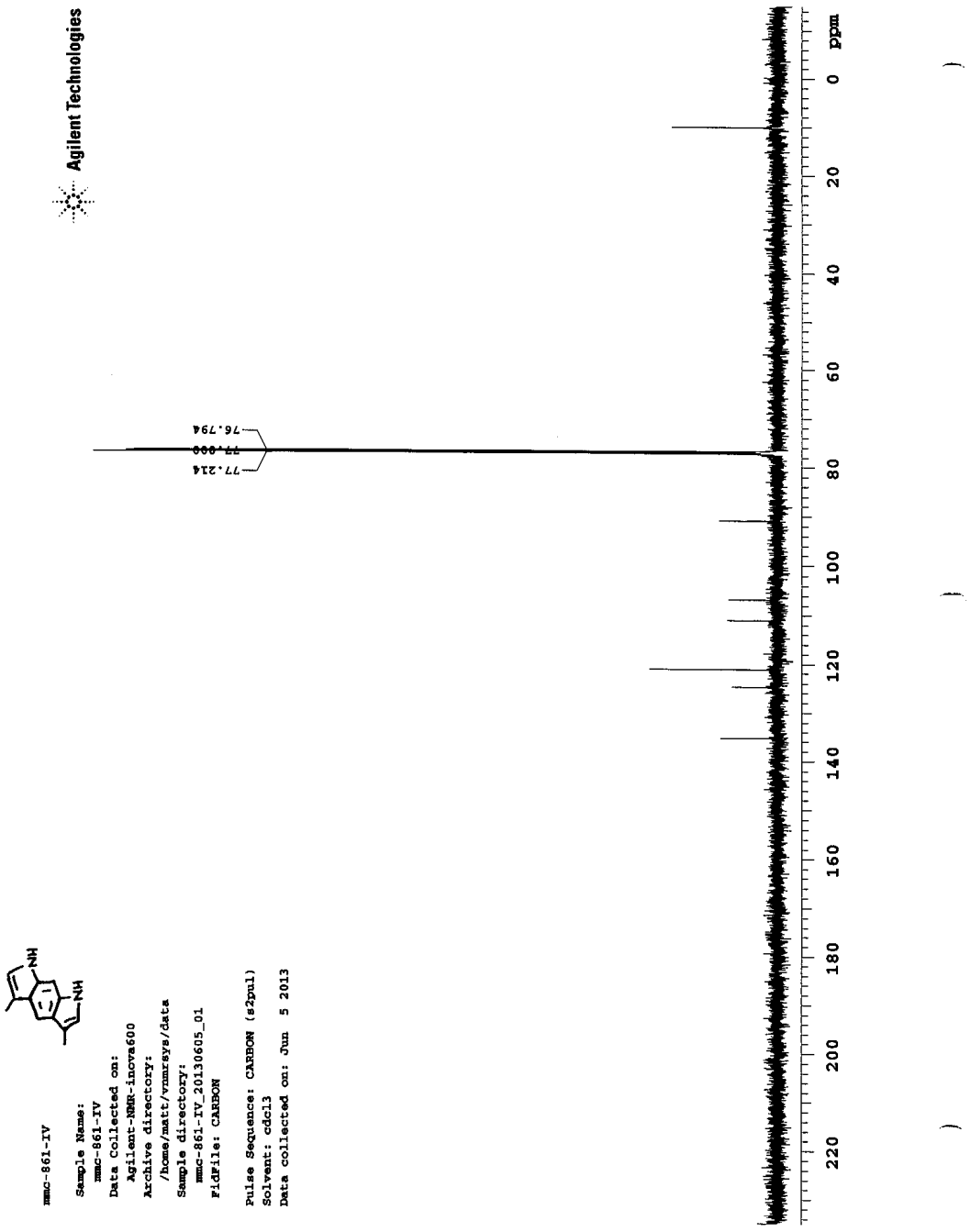

Figure 129: ^{13}C NMR of 3,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole **(326)**

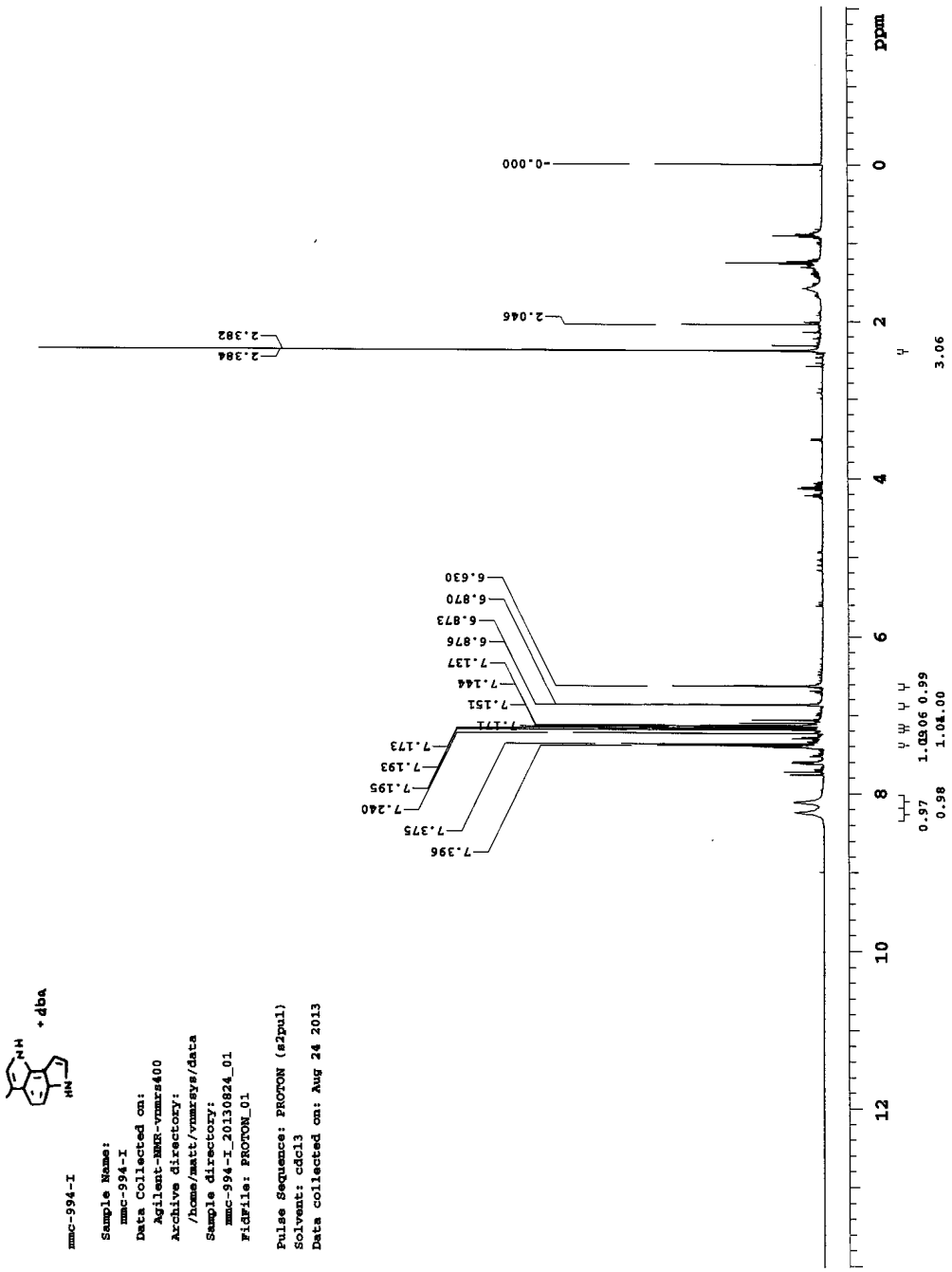

Figure 130: ^{1}H NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole **(330)**

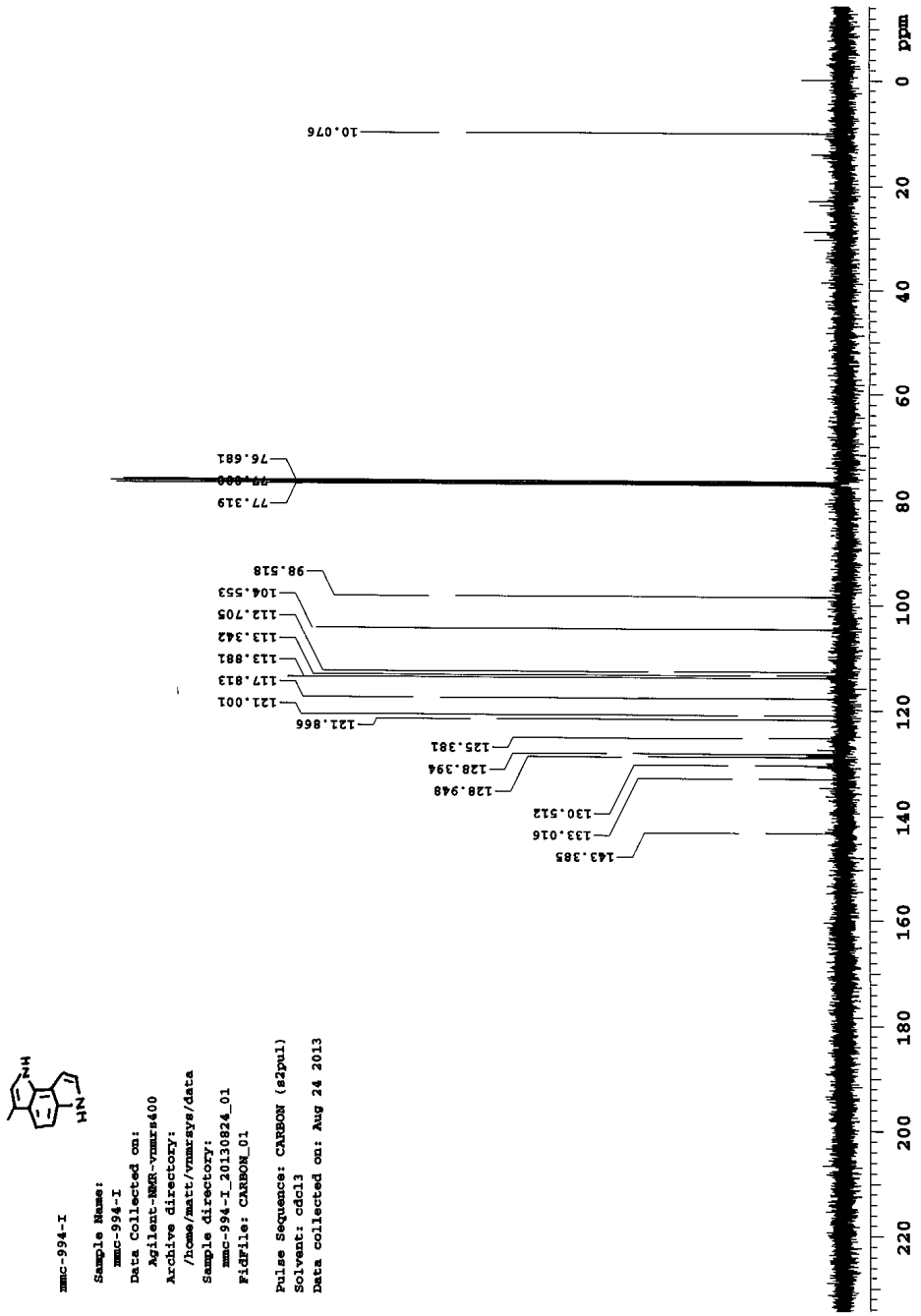

Figure 131: ^{13}C NMR of 3-methyl-2,6-dihydropyrrolo[2,3-g]indole **(330)**

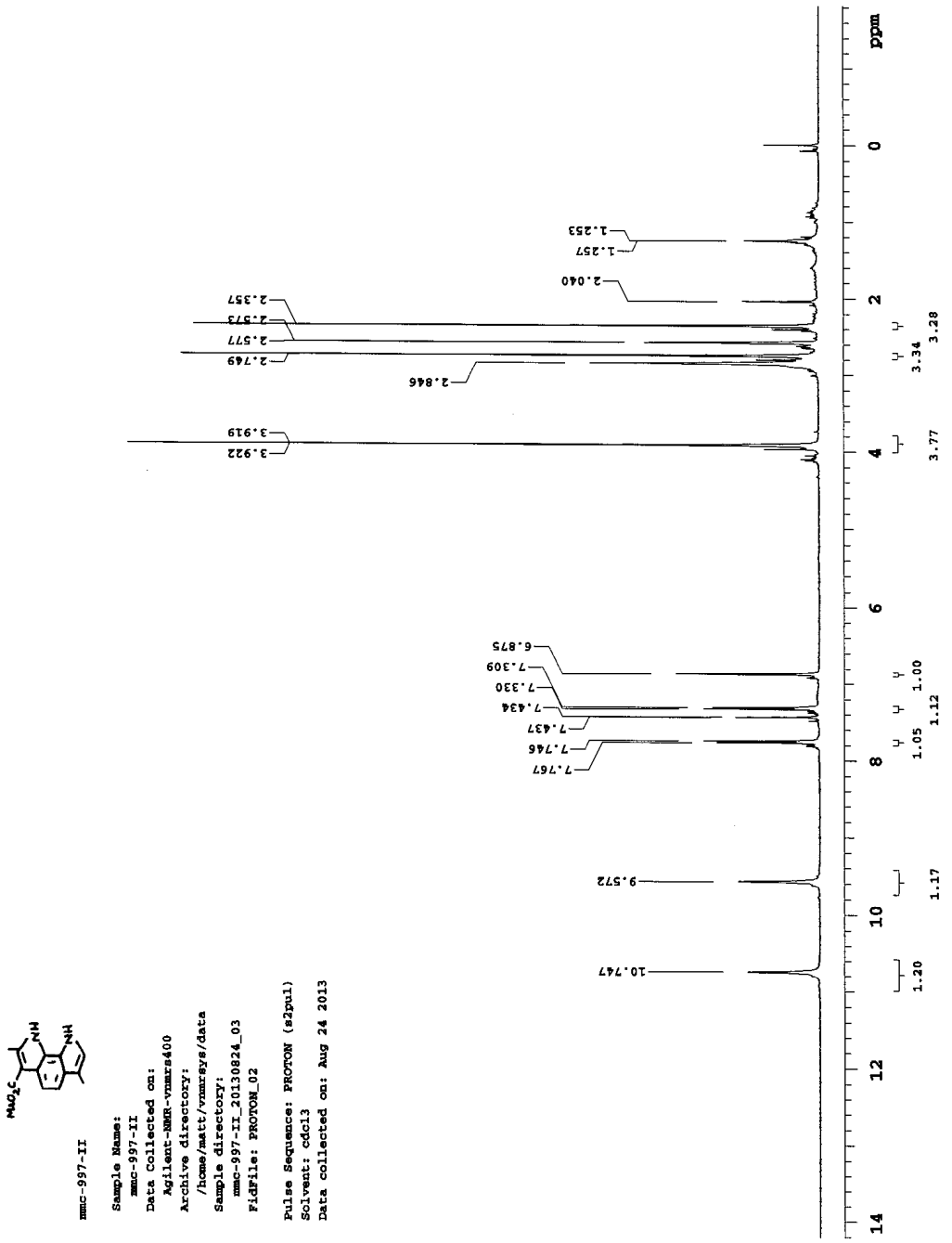

Figure 132: [1]H NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-*g*]indole-3-carboxylate **(331):**

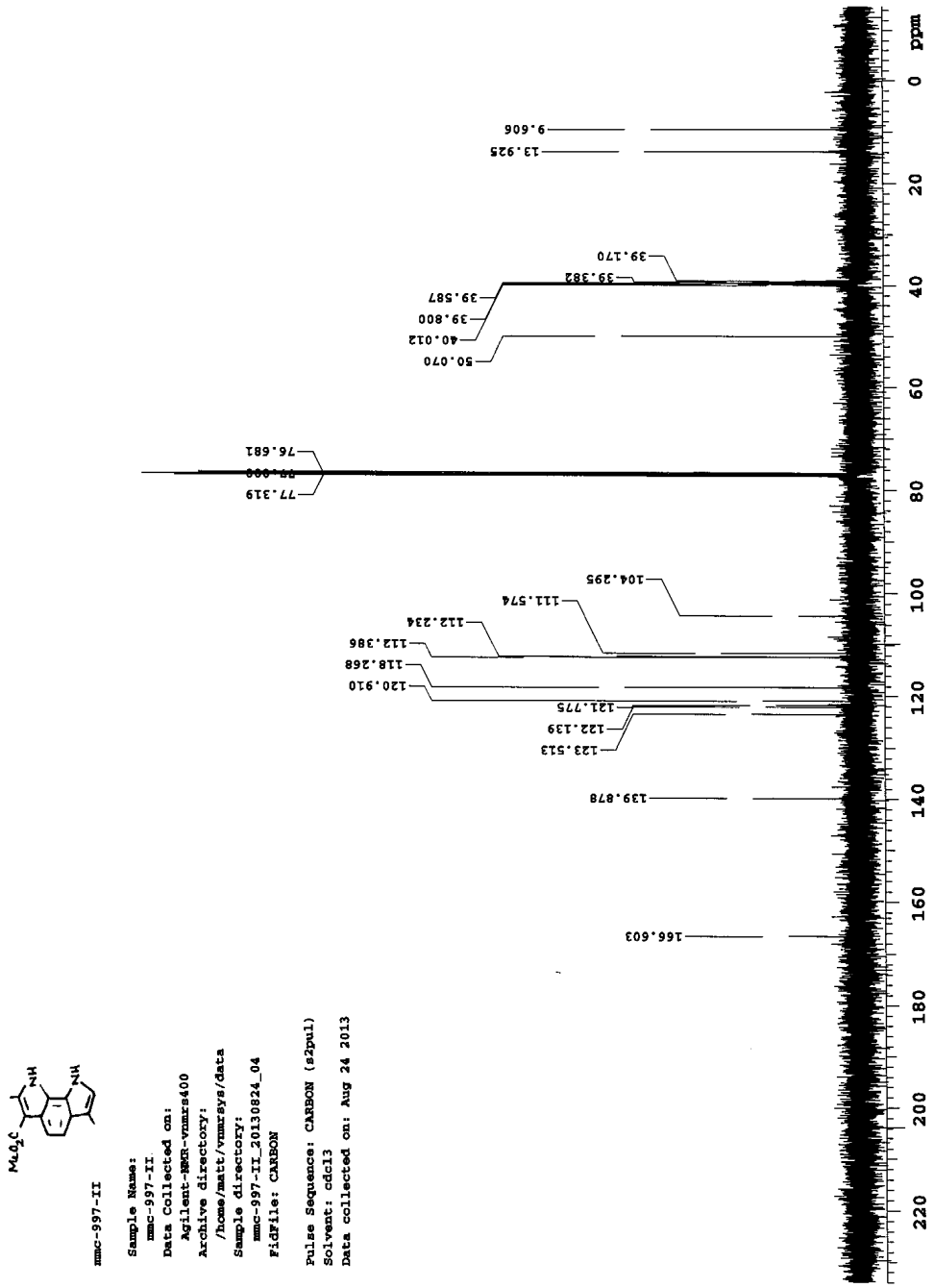

Figure 133: ^{13}C NMR of Methyl 2,6-dimethyl-1,8-dihydropyrrolo[3,2-*g*]indole-3-carboxylate **(331):**

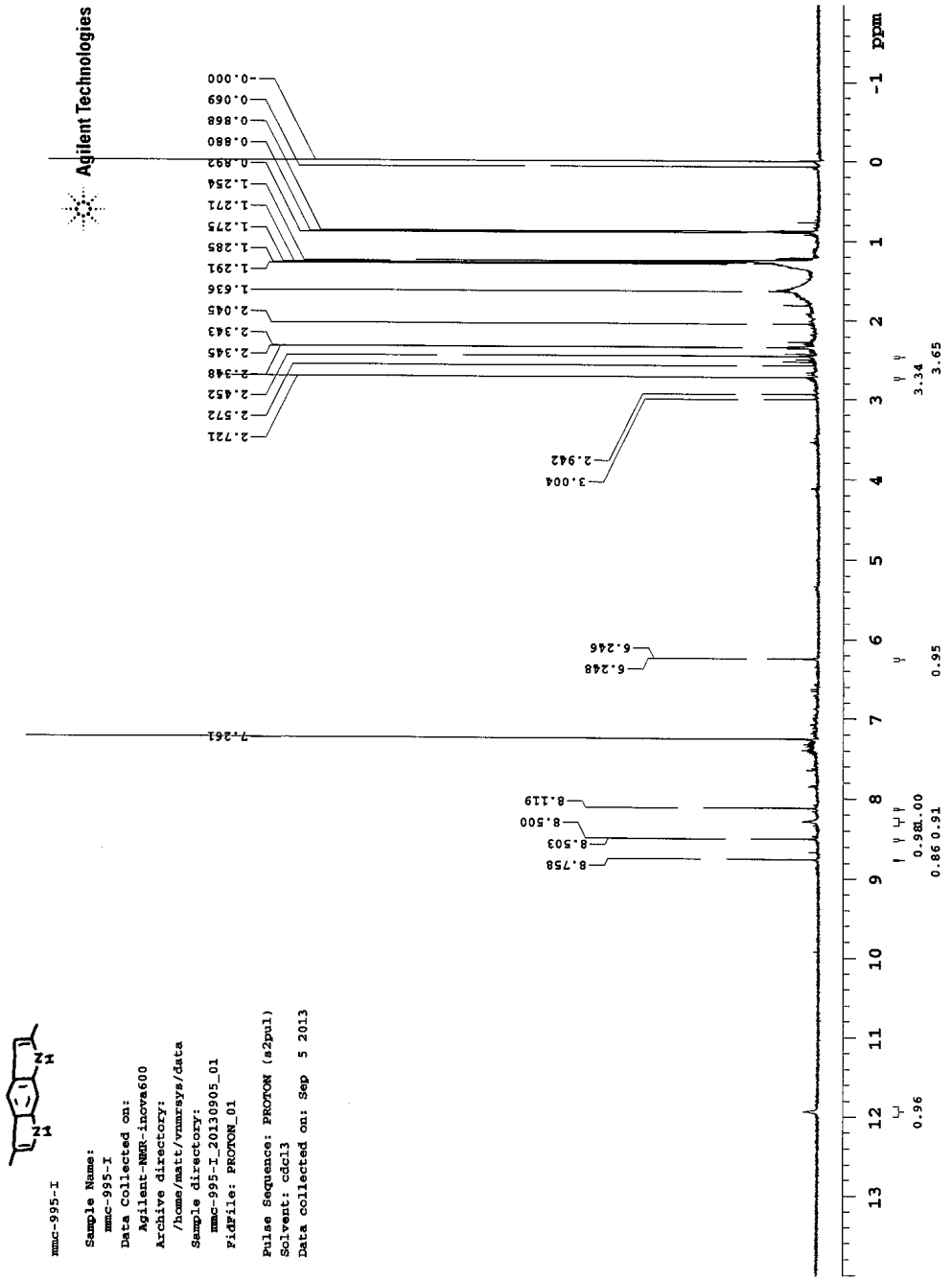

Figure 134: ^{1}H NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole **(332)**

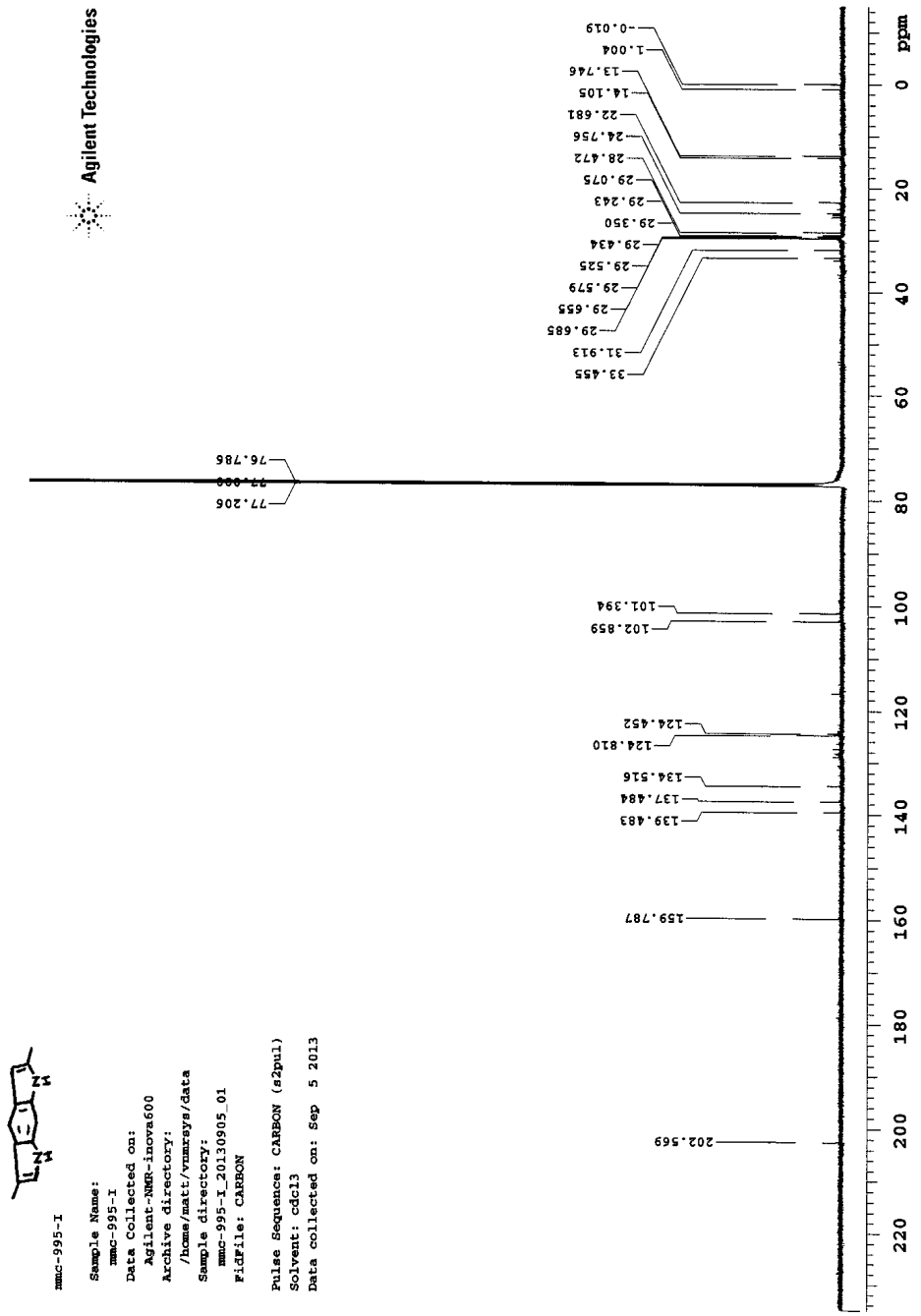

Figure 135: ^{13}C NMR of 2,5-dimethyl-1,7-dihydropyrrolo[3,2-*f*]indole **(332)**

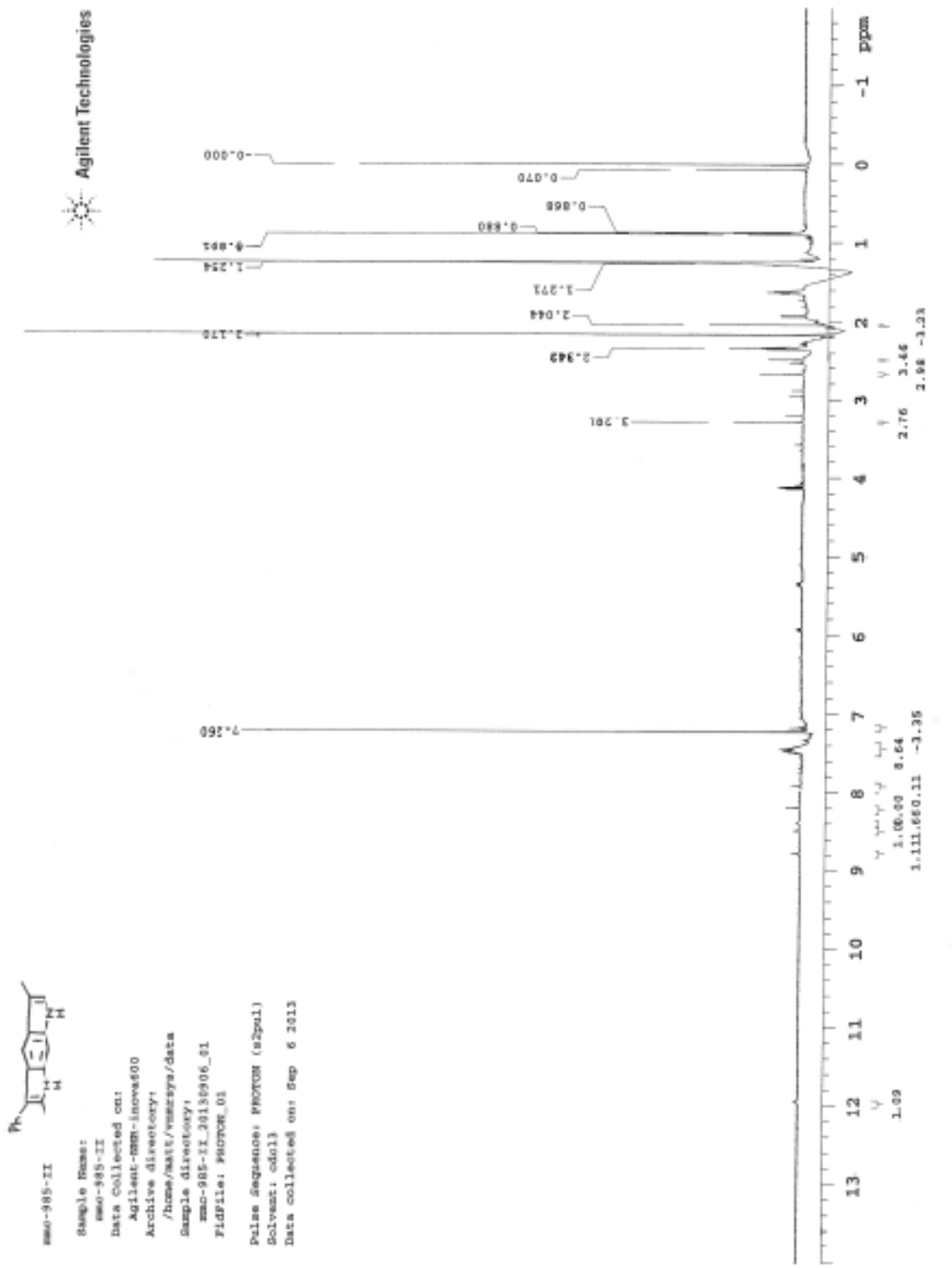

Figure 136: ^{1}H NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-*f*]indole (**333**)

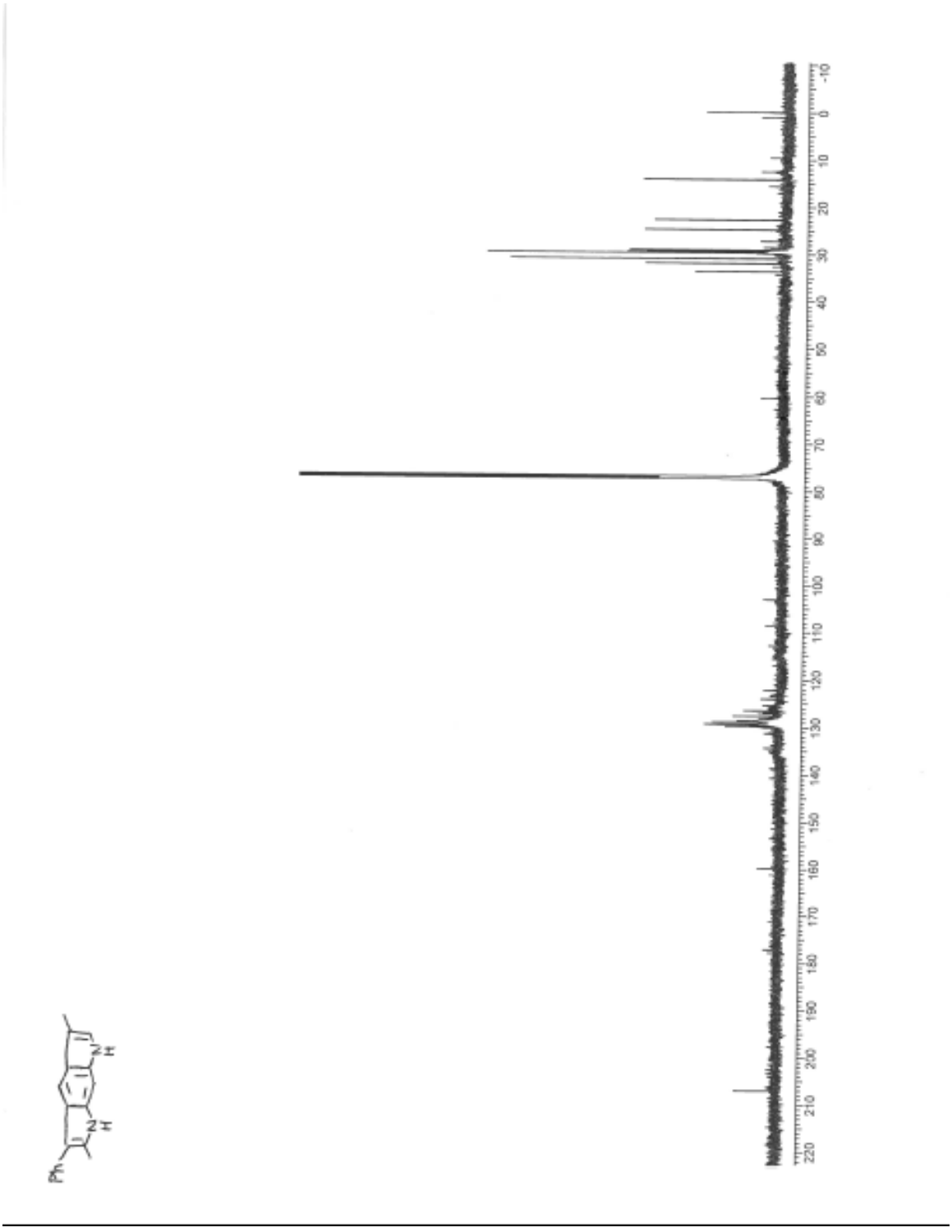

Figure 137: ^{13}C NMR of 2,5-dimethyl-3-phenyl-1,7-dihydropyrrolo[3,2-*f*]indole (**333**)

^{1}H and ^{13}C NMR for Chapter 6.1: Bromination

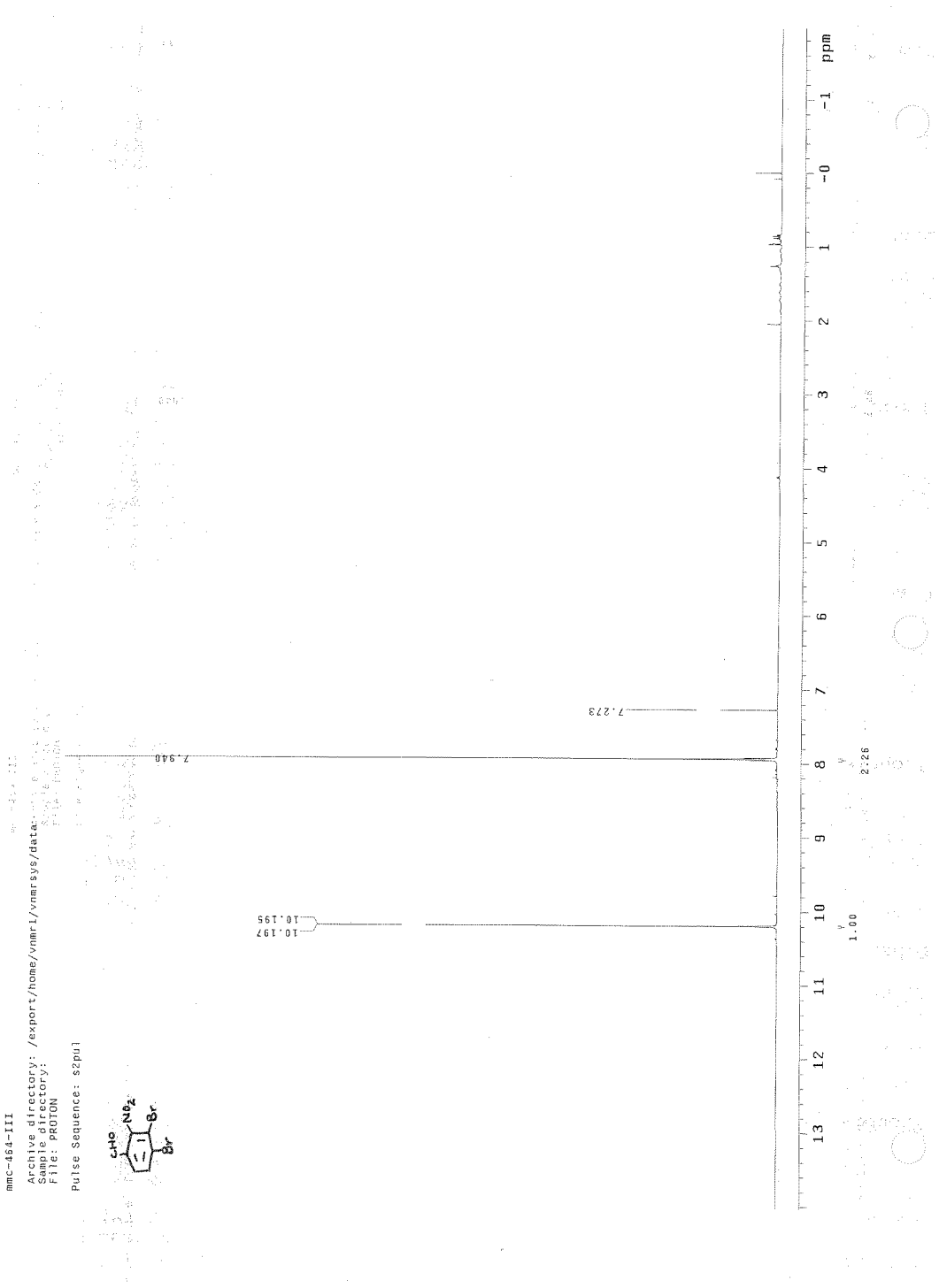

Figure 138: ^{1}H NMR of 3,4-dibromo-2-nitrobenzaldehyde (**343**)

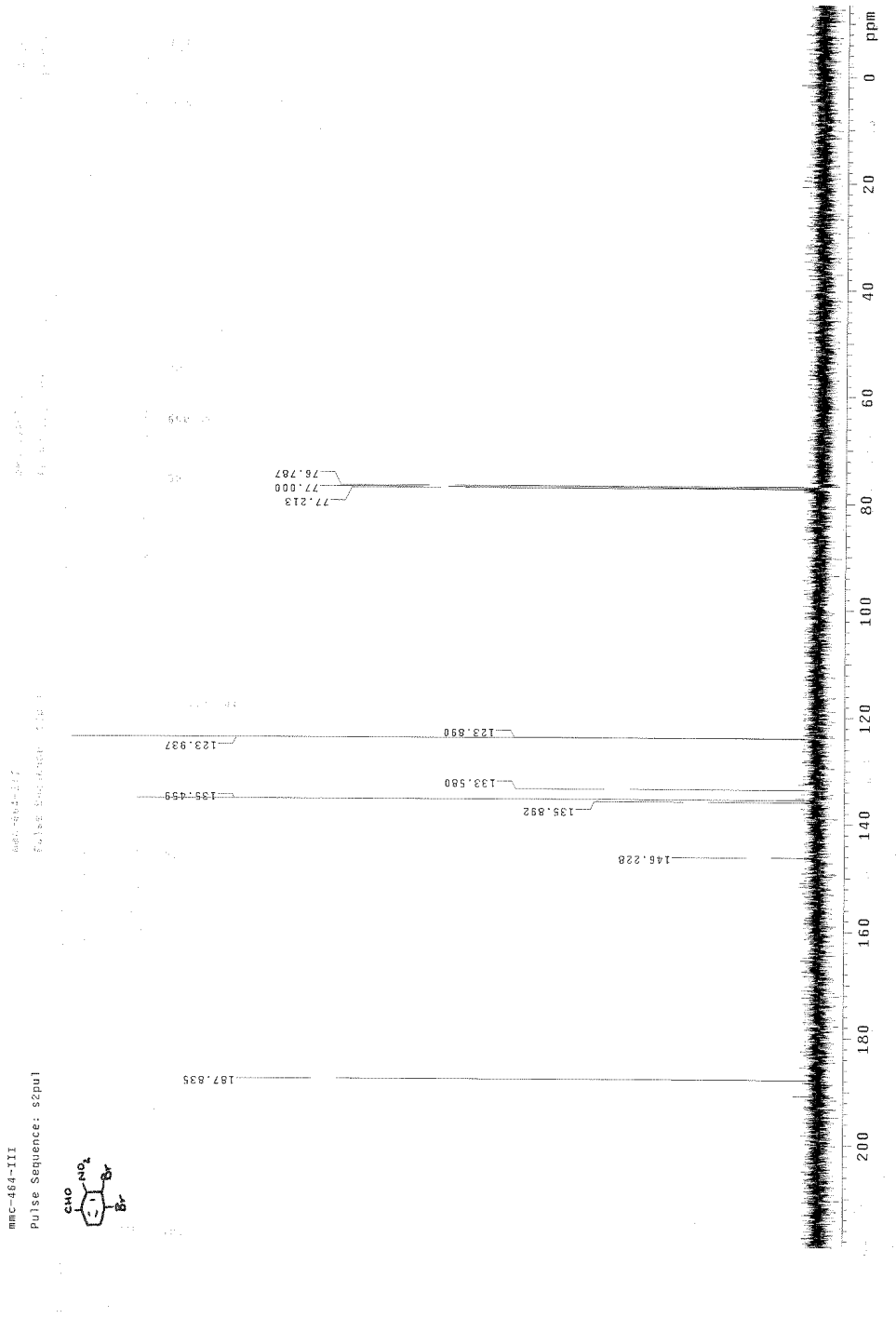

Figure 139: ^{13}C NMR of 3,4-dibromo-2-nitrobenzaldehyde (**343**)

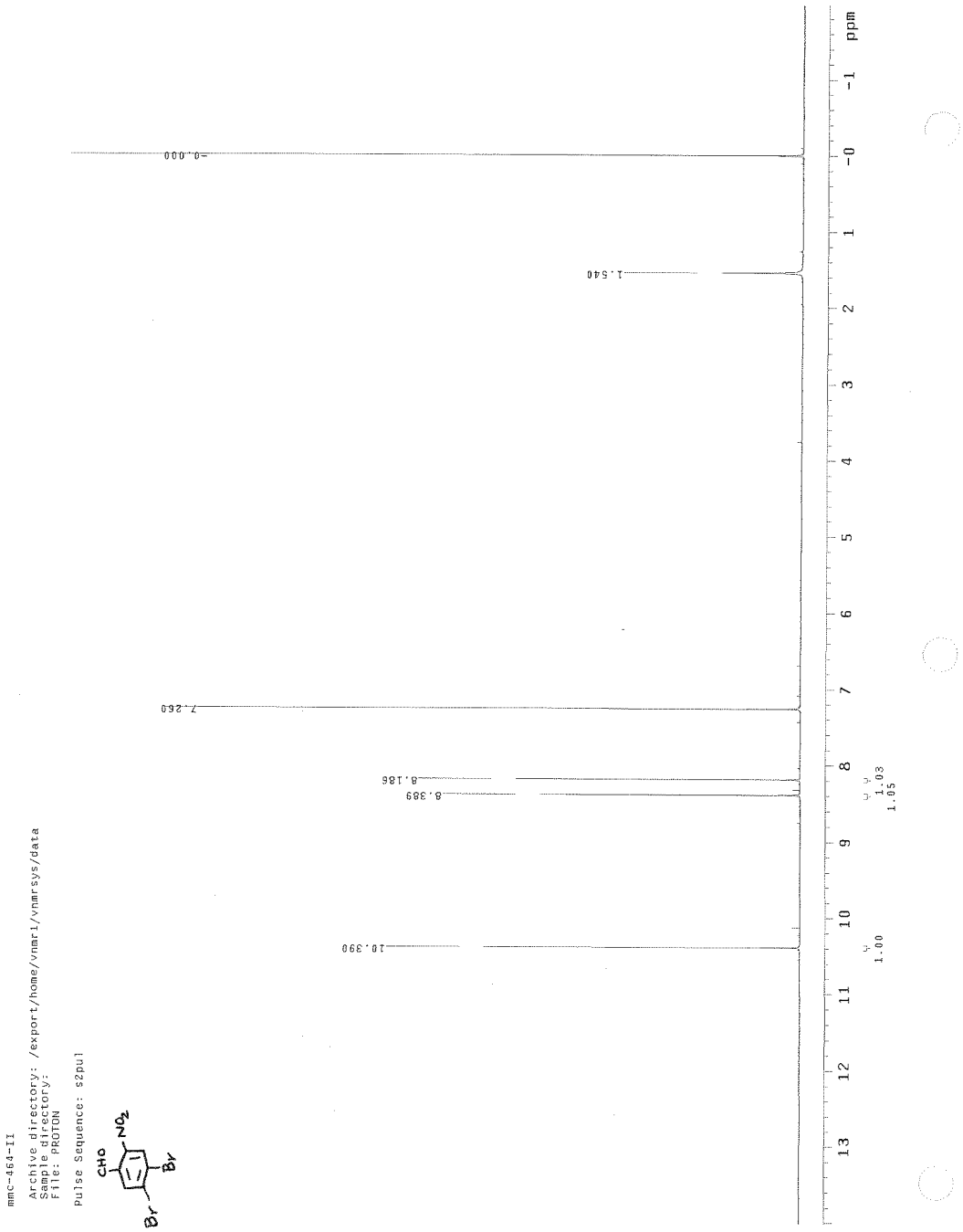

Figure 140: ^{1}H NMR of 4,5-dibromo-2-nitrobenzaldehyde (**344**)

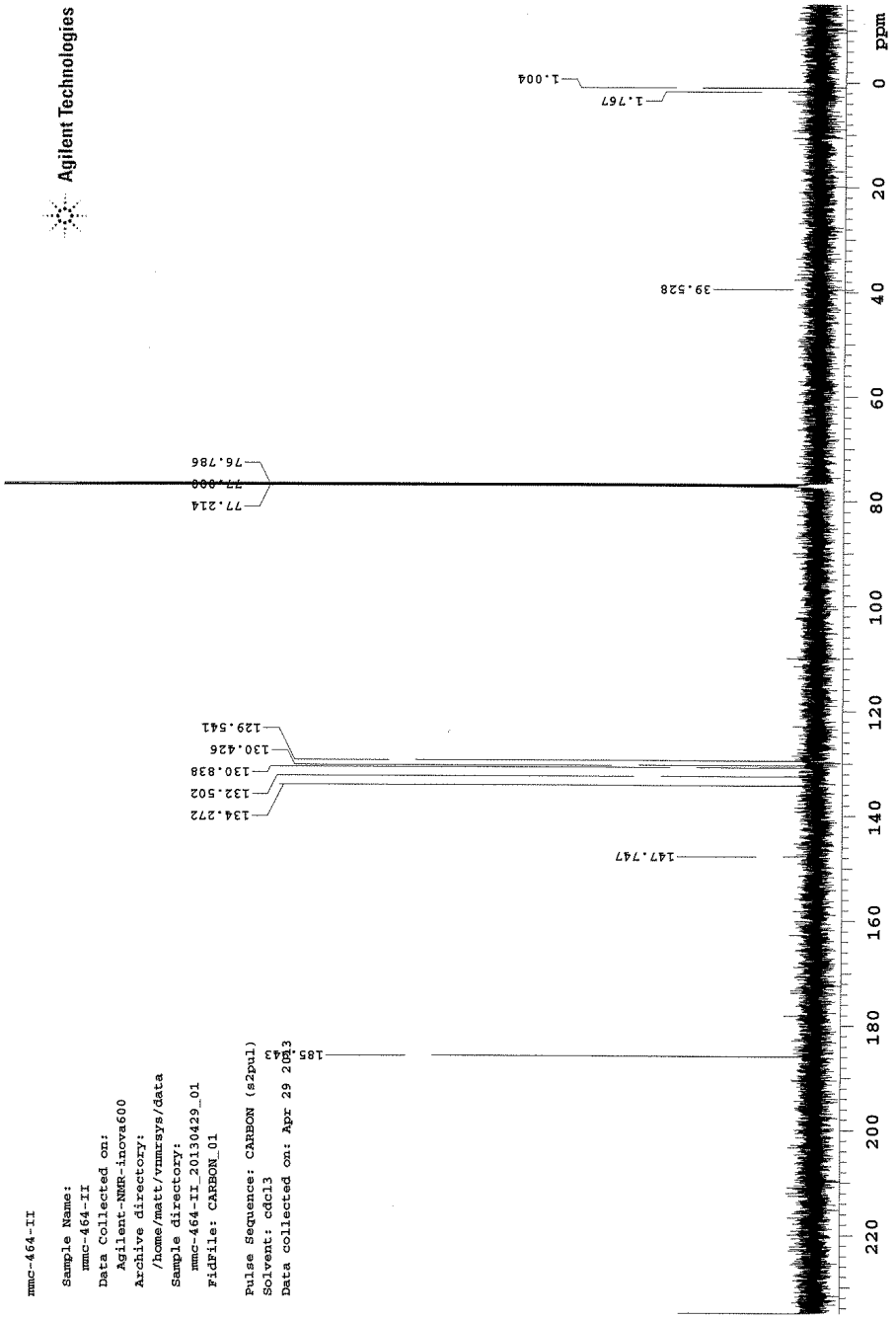

Figure 141: ^{13}C NMR of 4,5-dibromo-2-nitrobenzaldehyde (**344**)

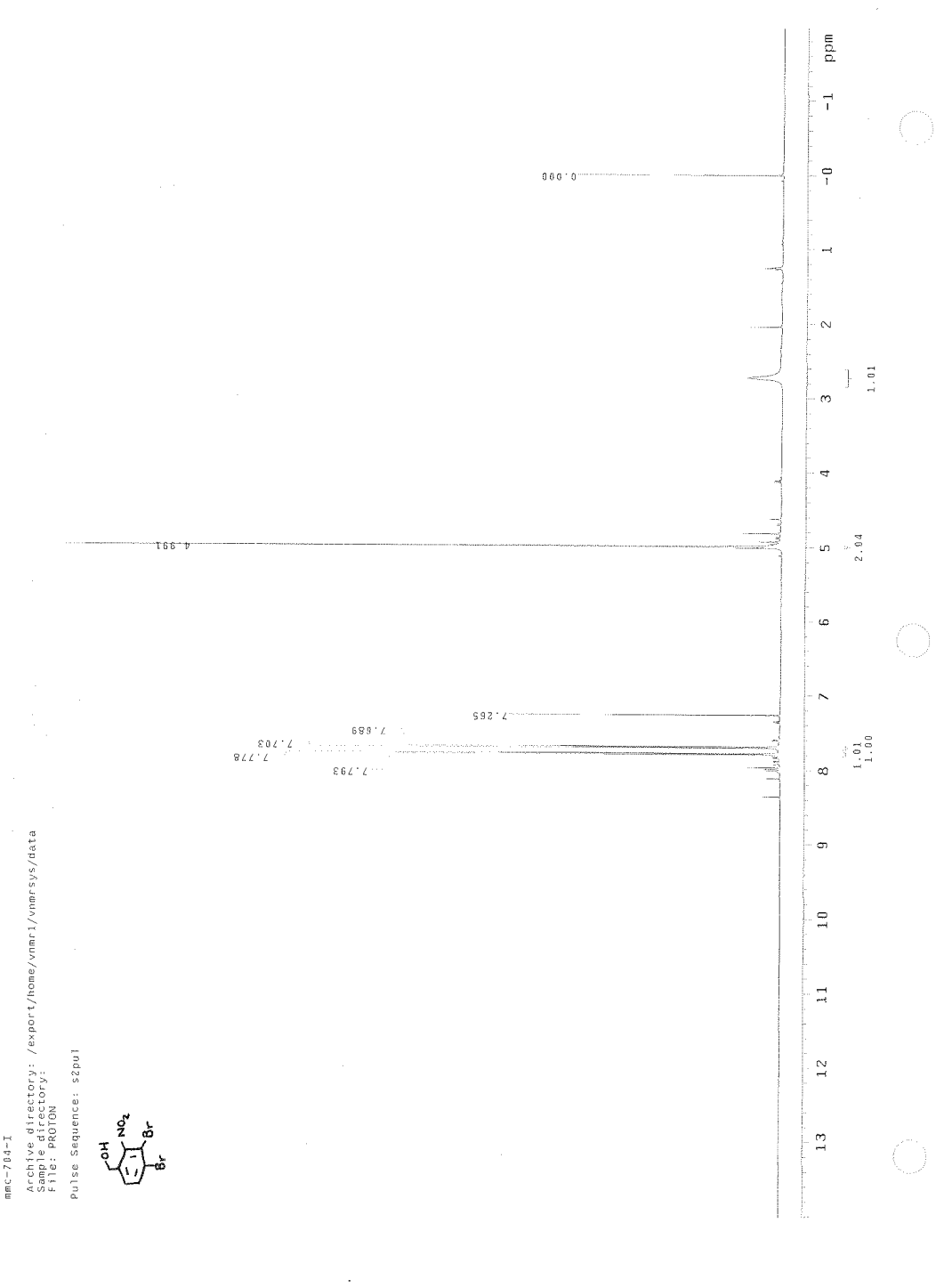

Figure 142: ^{1}H NMR of 3,4-dibromo-2-nitrobenzylalcohol (**349**)

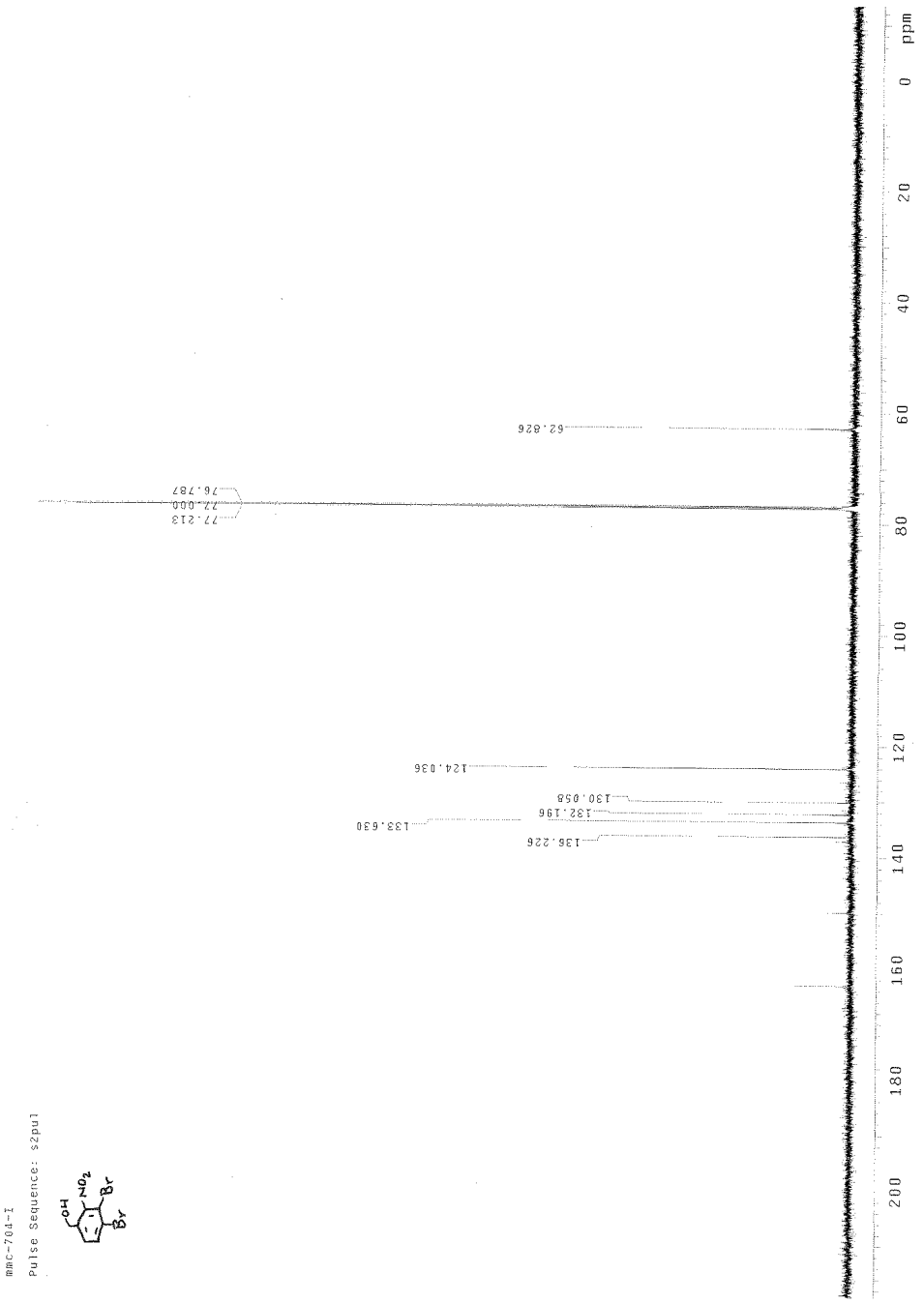

Figure 143: ^{13}C NMR of 3,4-dibromo-2-nitrobenzylalcohol (**349**)

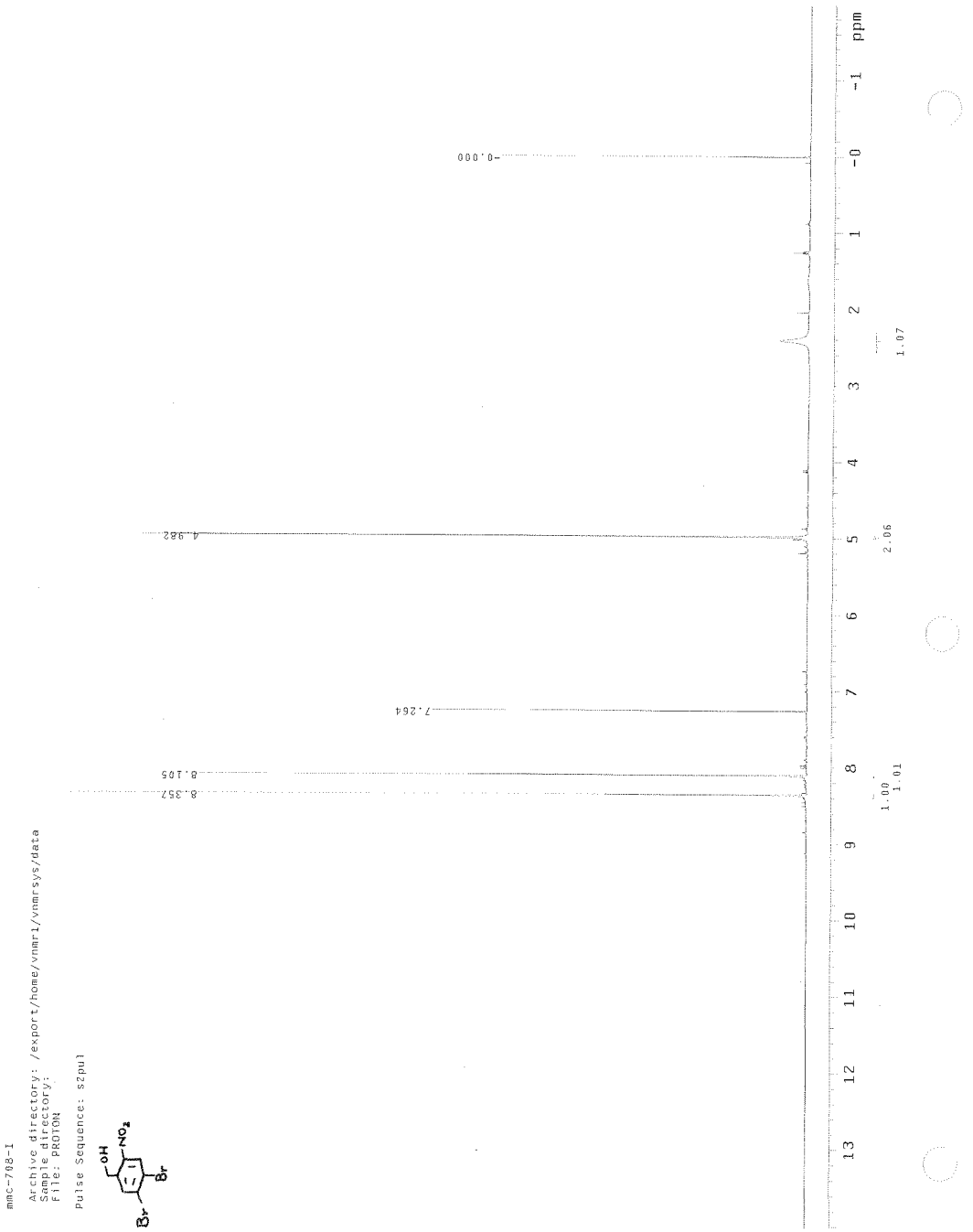

Figure 144: ^{1}H NMR of 4,5-dibromo-2-nitrobenzylalcohol (**350**)

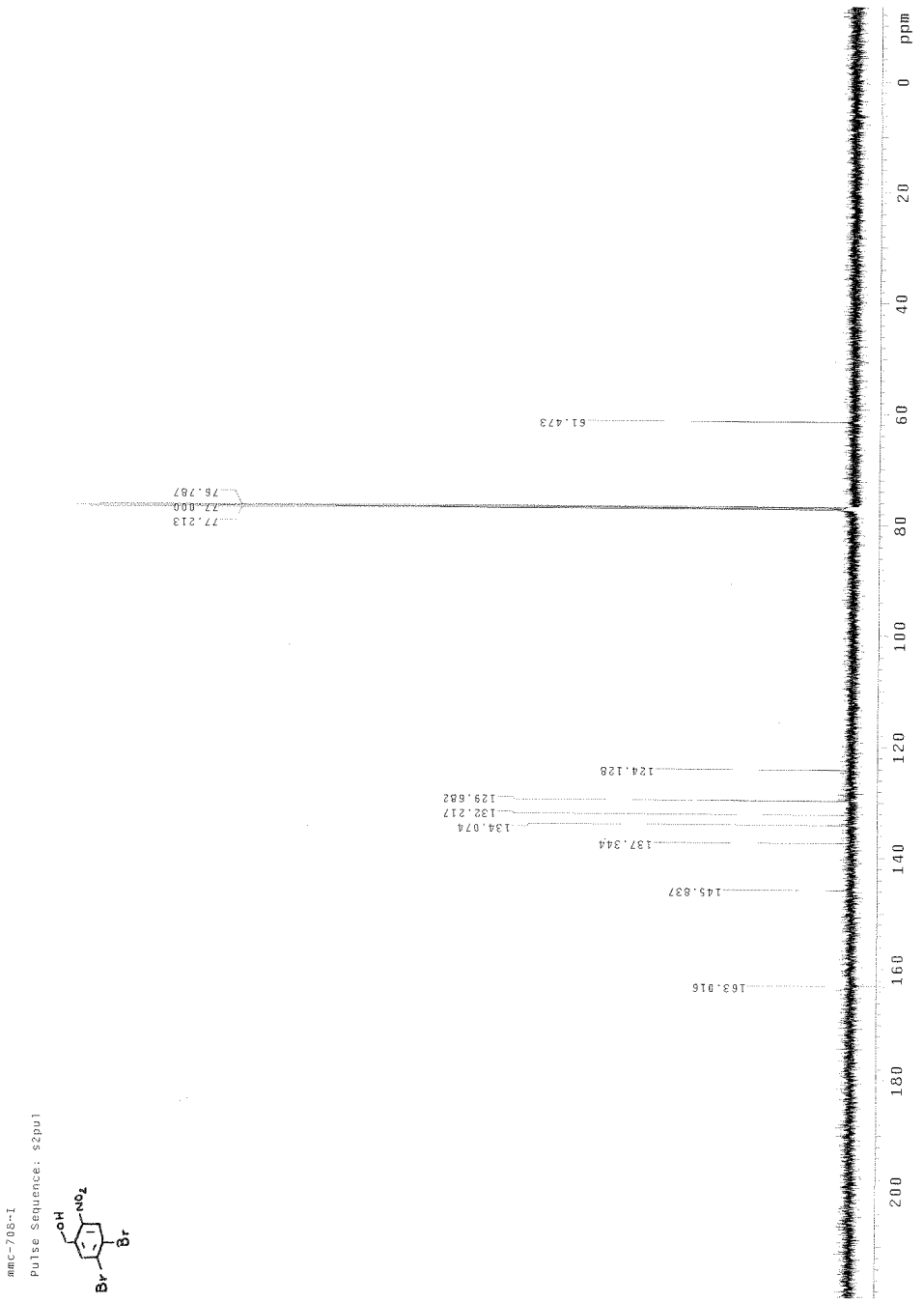

Figure 145: ^{13}C NMR of 4,5-dibromo-2-nitrobenzylalcohol (**350**)

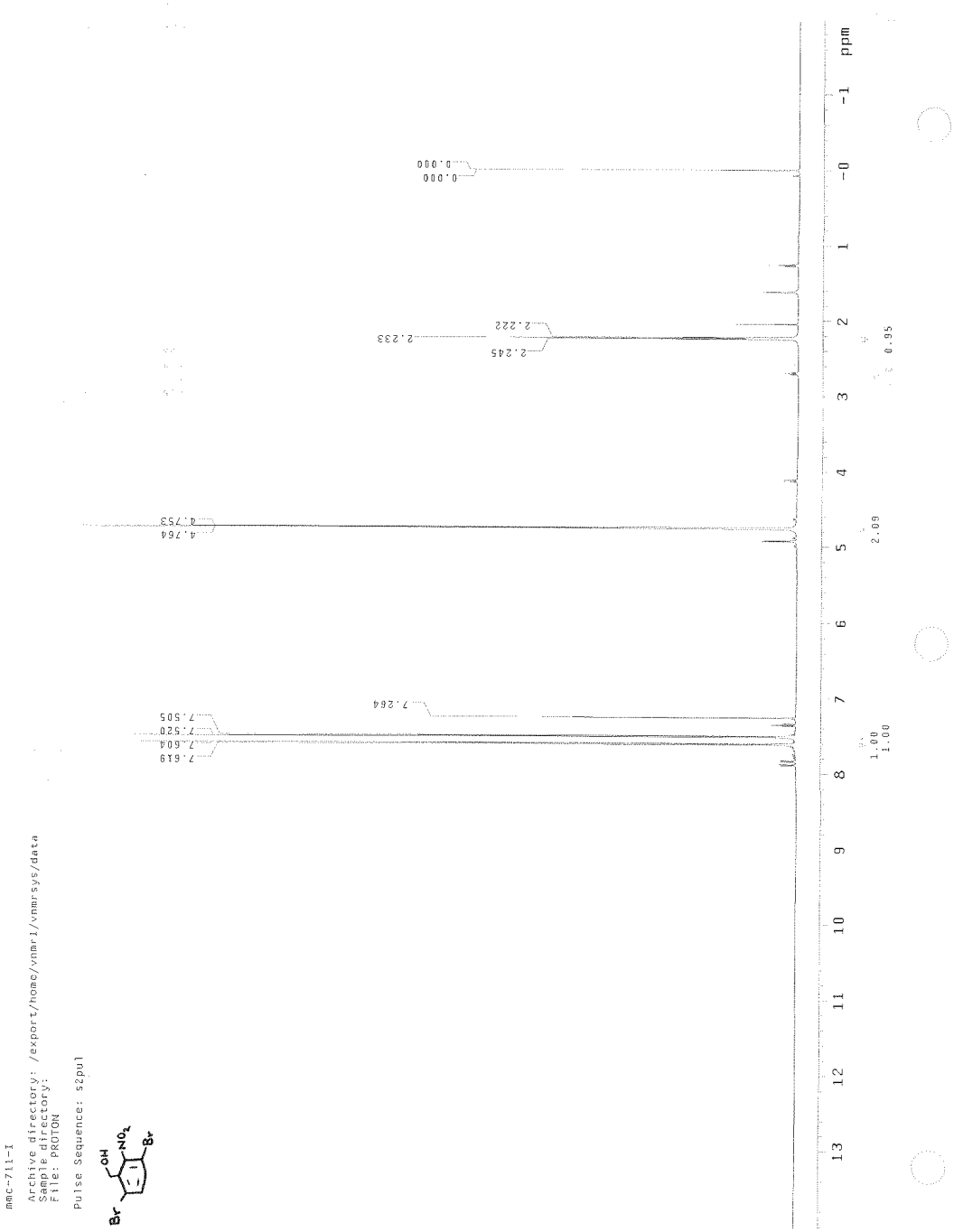

Figure 146: ^{1}H NMR of 3,6-dibromo-2-nitrobenzylalcohol (**351**)

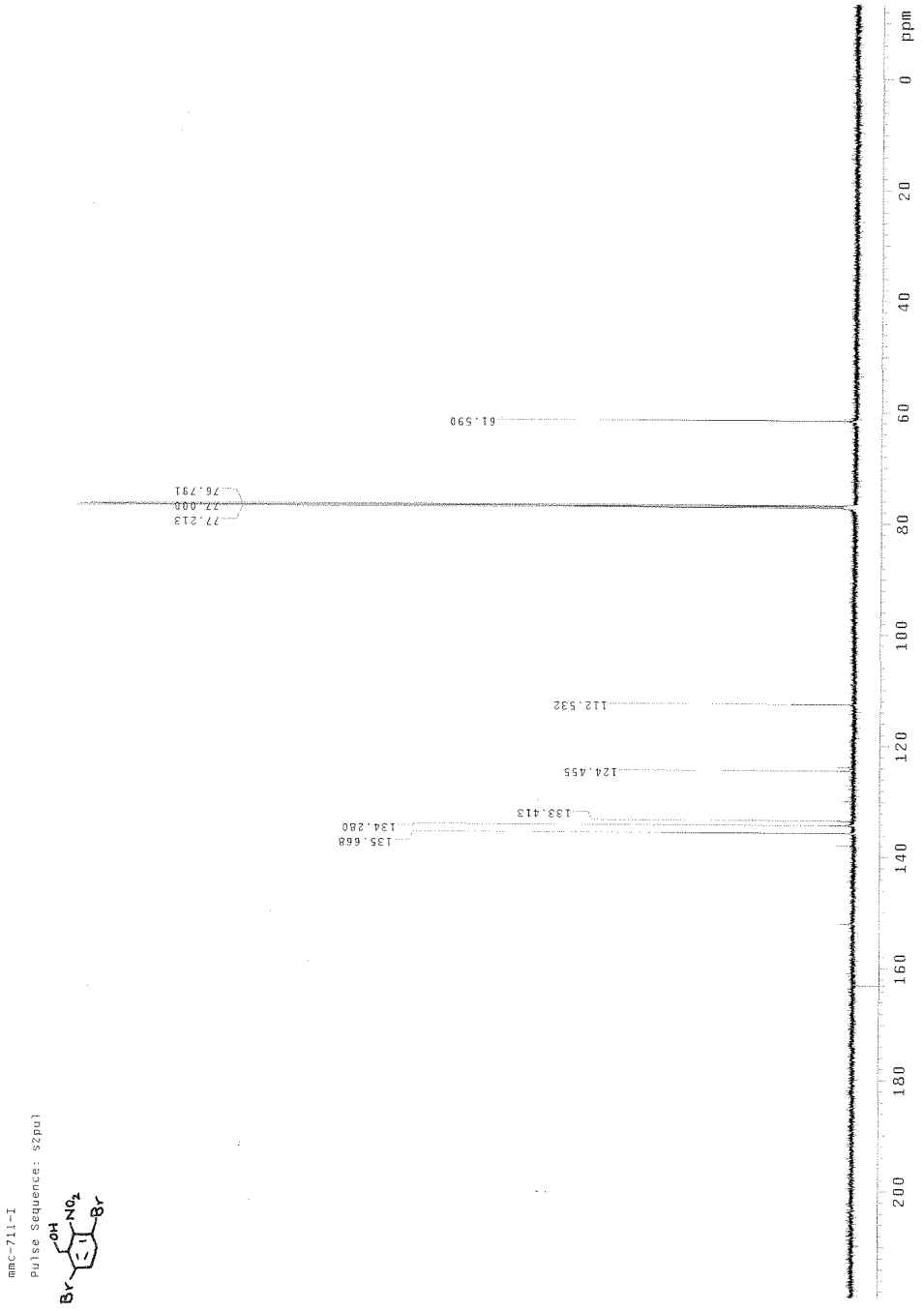

Figure 147: ^{13}C NMR of 3,6-dibromo-2-nitrobenzylalcohol (**351**)

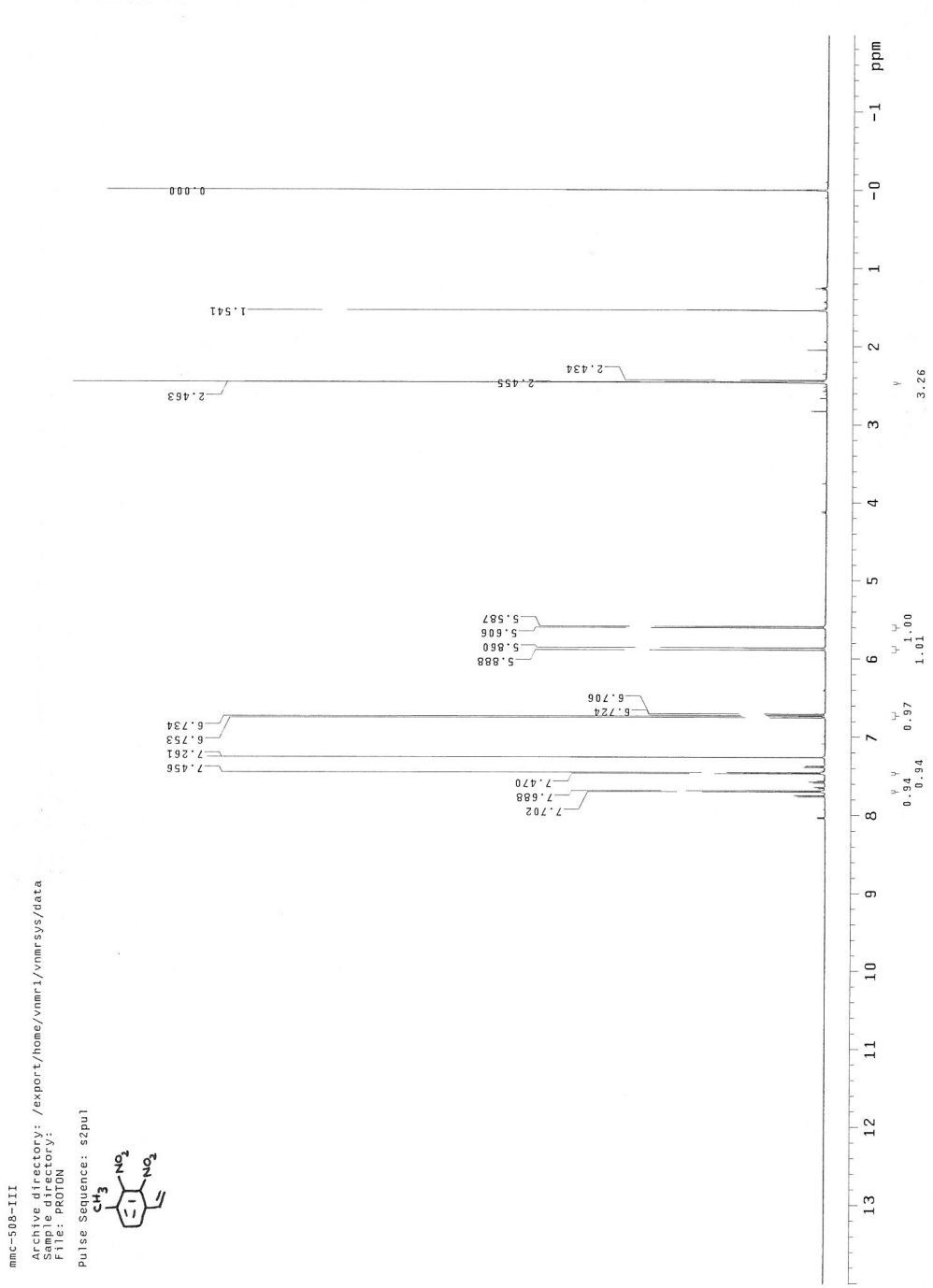

Figure 148: ^{1}H NMR of 2,3-dinitro-4-ethenyltoluene (**355**)

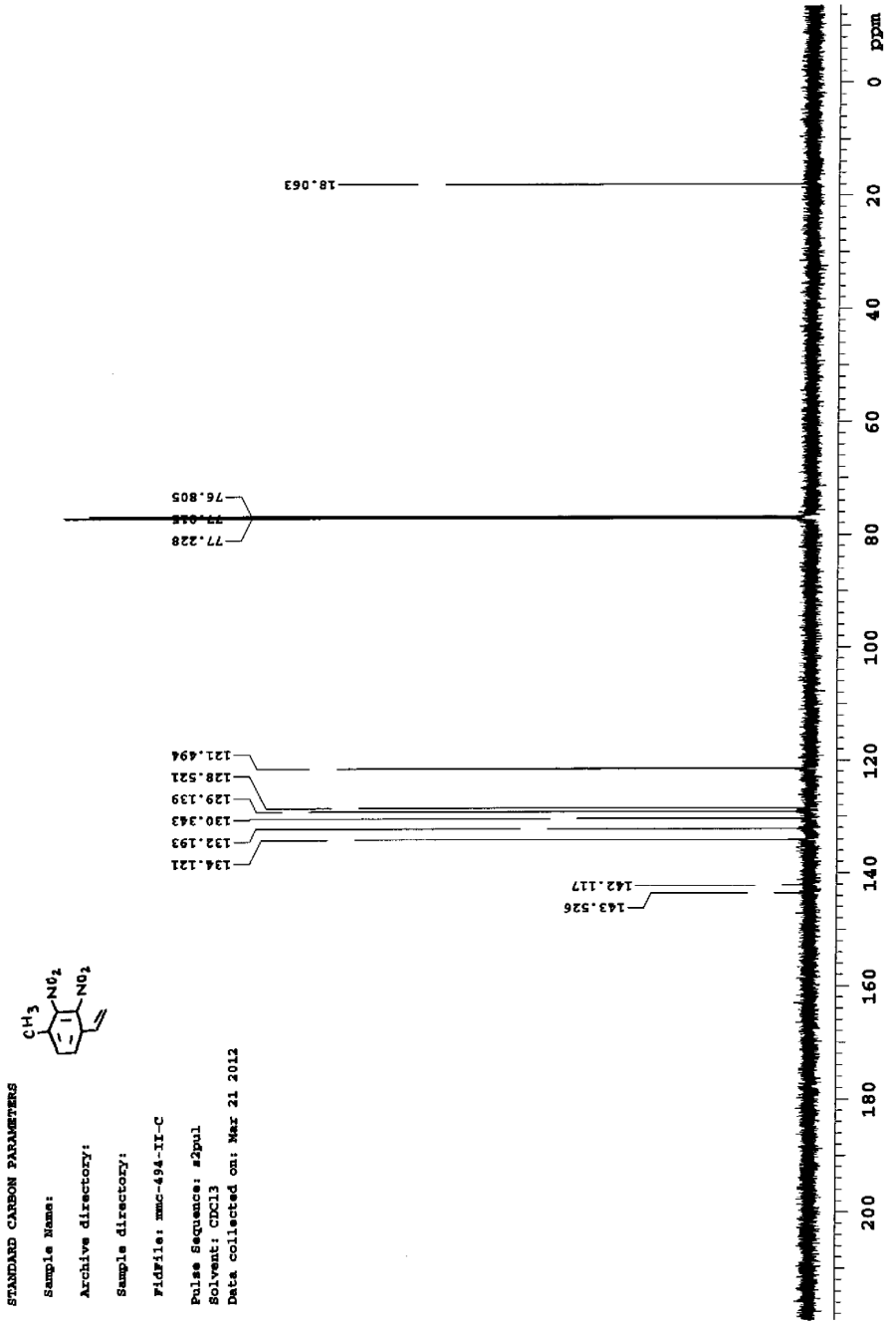

Figure 149: ^{13}C NMR of 2,3-dinitro-4-ethenyltoluene (**355**)

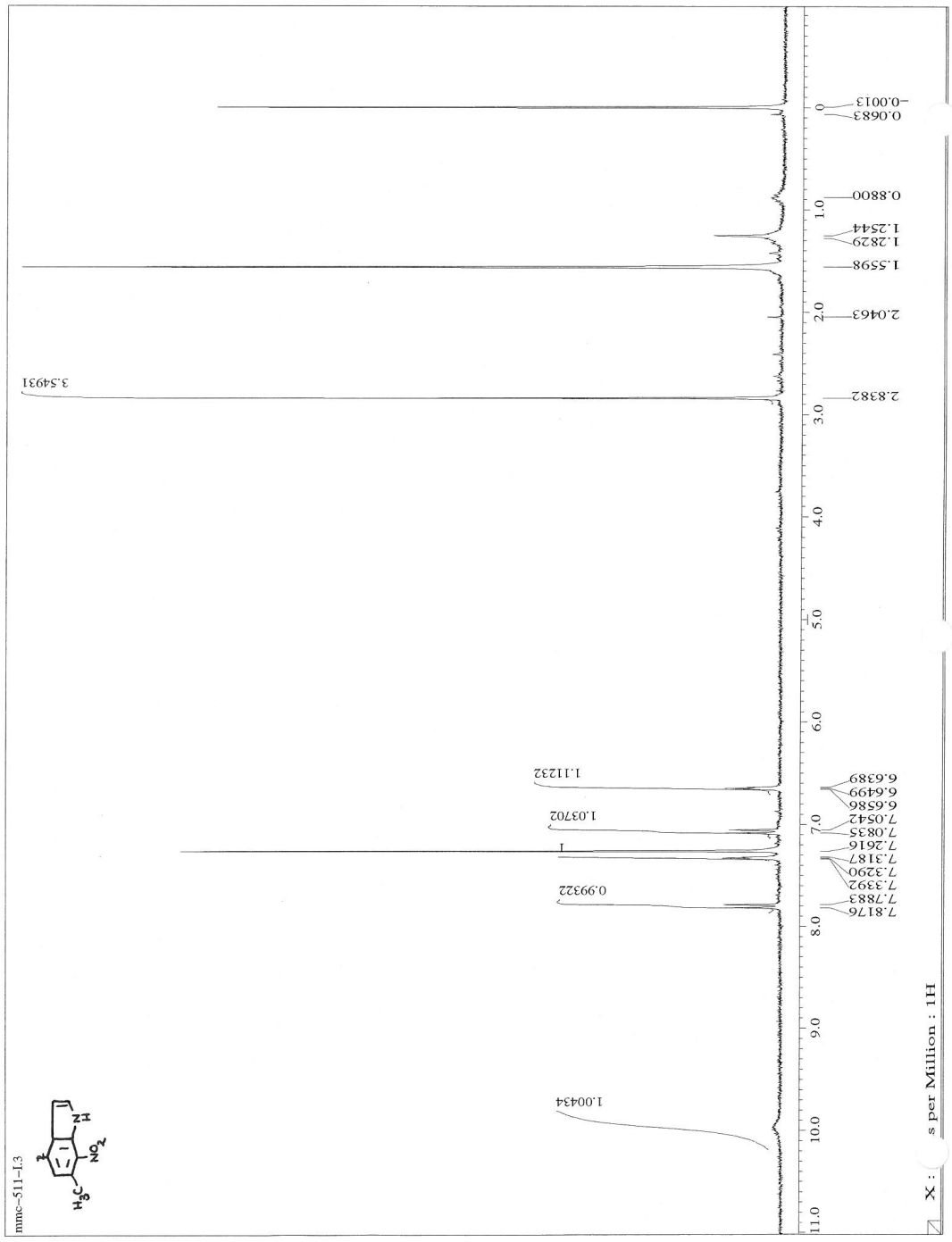

Figure 150: ^{1}H NMR of 6-methyl-7-nitroindole (**356**)

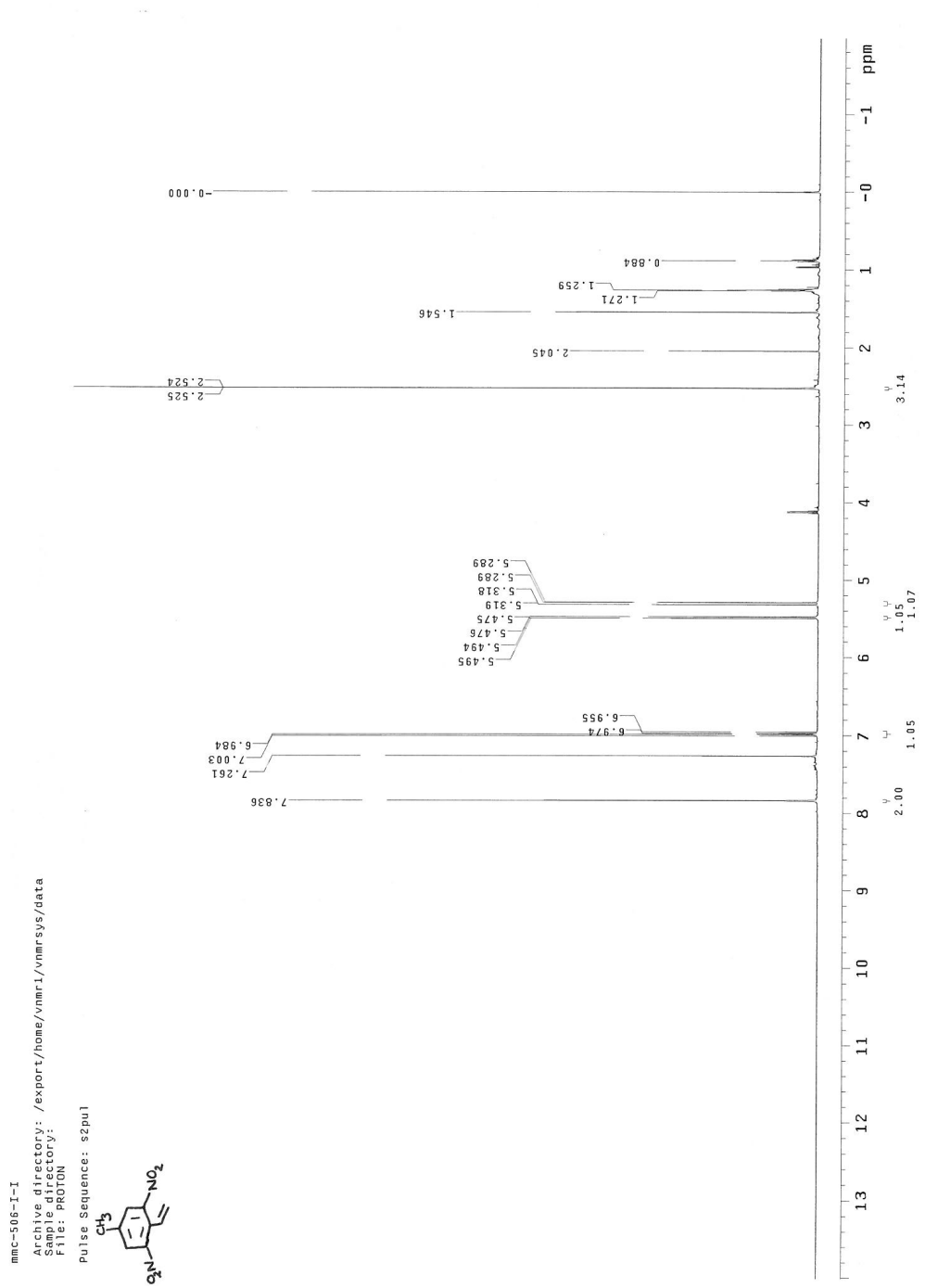

Figure 151: ^{1}H NMR of 3,5-dinitro-4-ethenyltoluene (**355**)

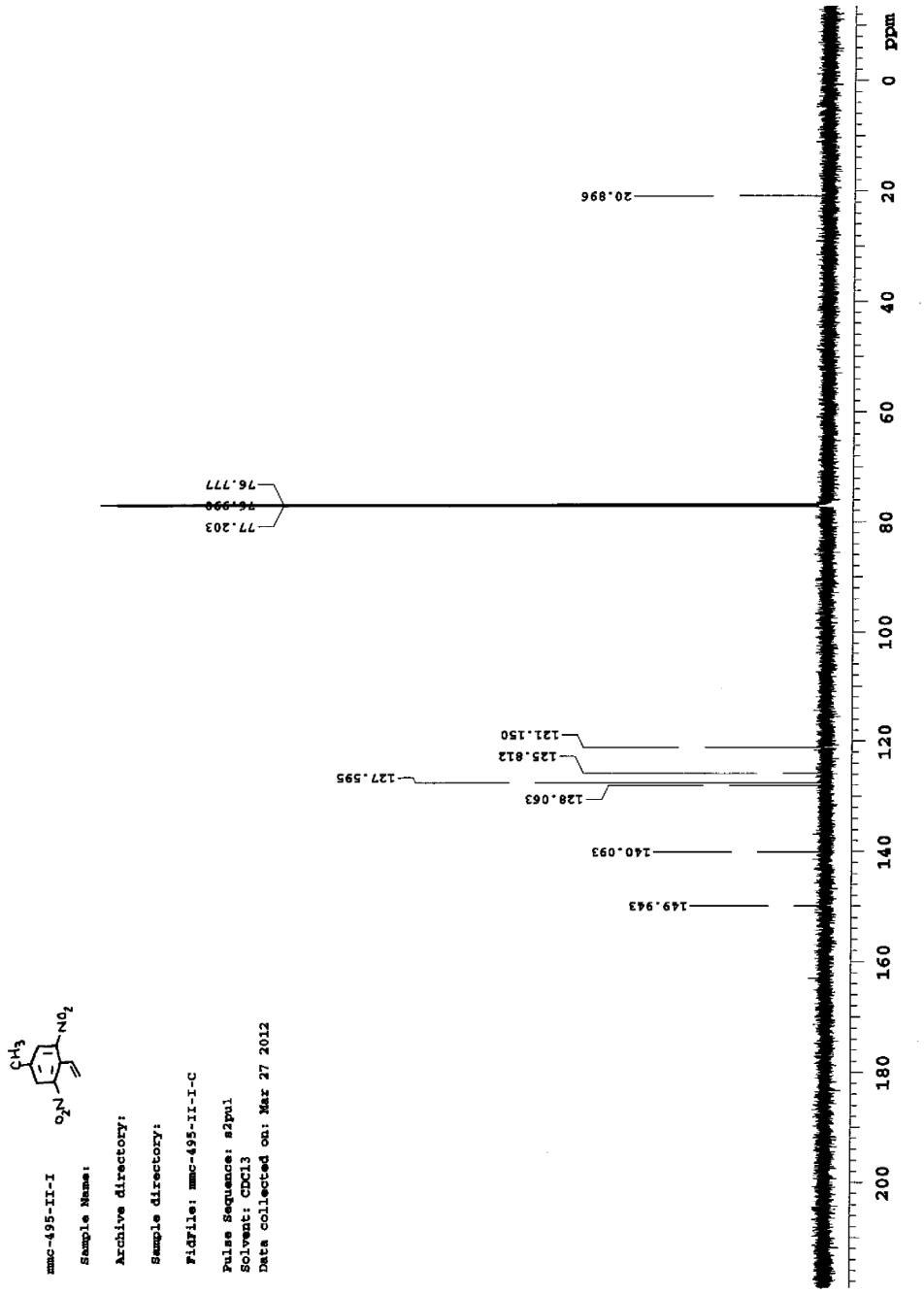

Figure 152: ^{13}C NMR of 3,5-dinitro-4-ethenyltoluene (**355**)

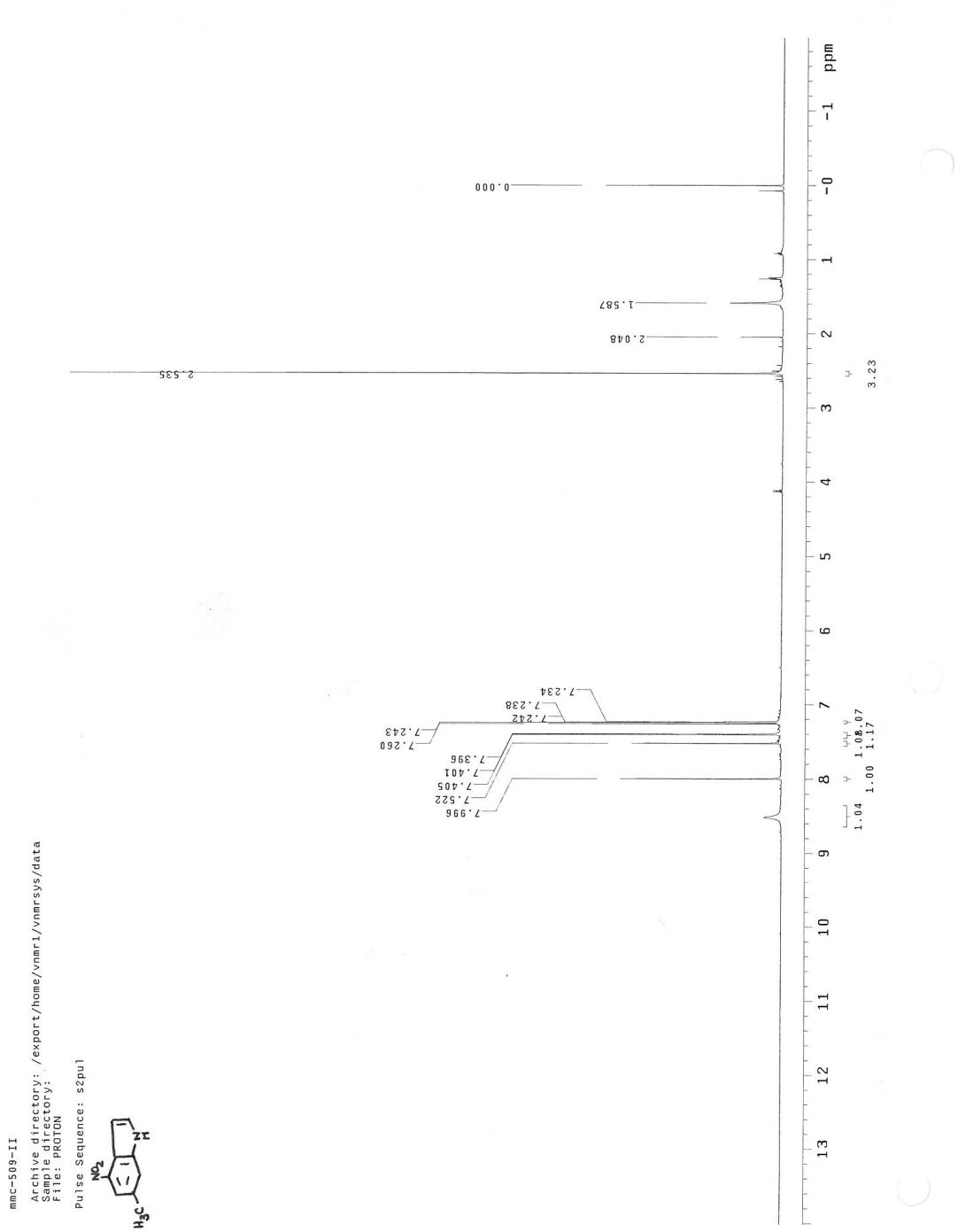

Figure 153: ^{1}H NMR of 6-methyl-4-nitroindole (**356**)

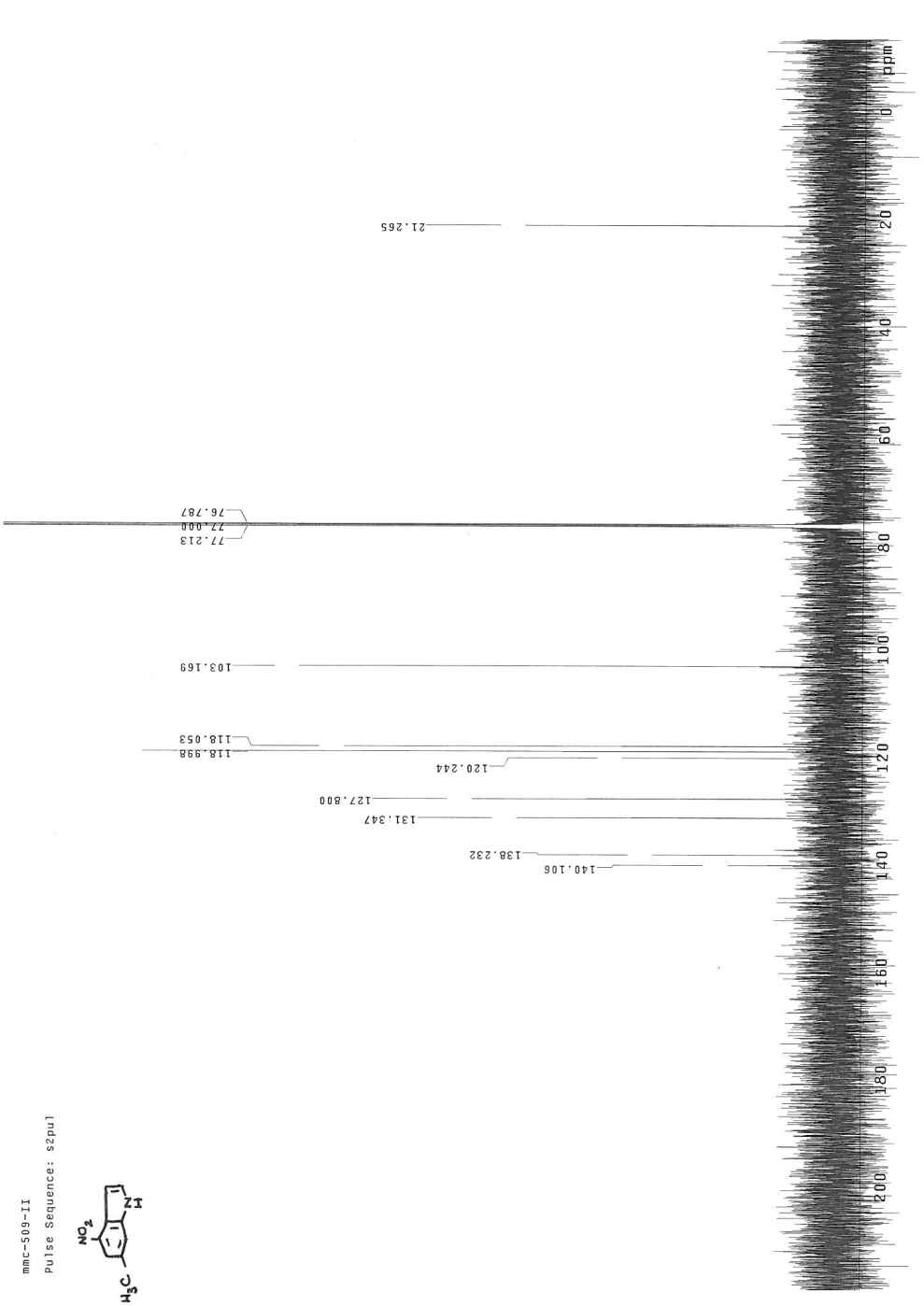

Figure 154: ^{13}C NMR of 6-methyl-4-nitroindole (**356**)

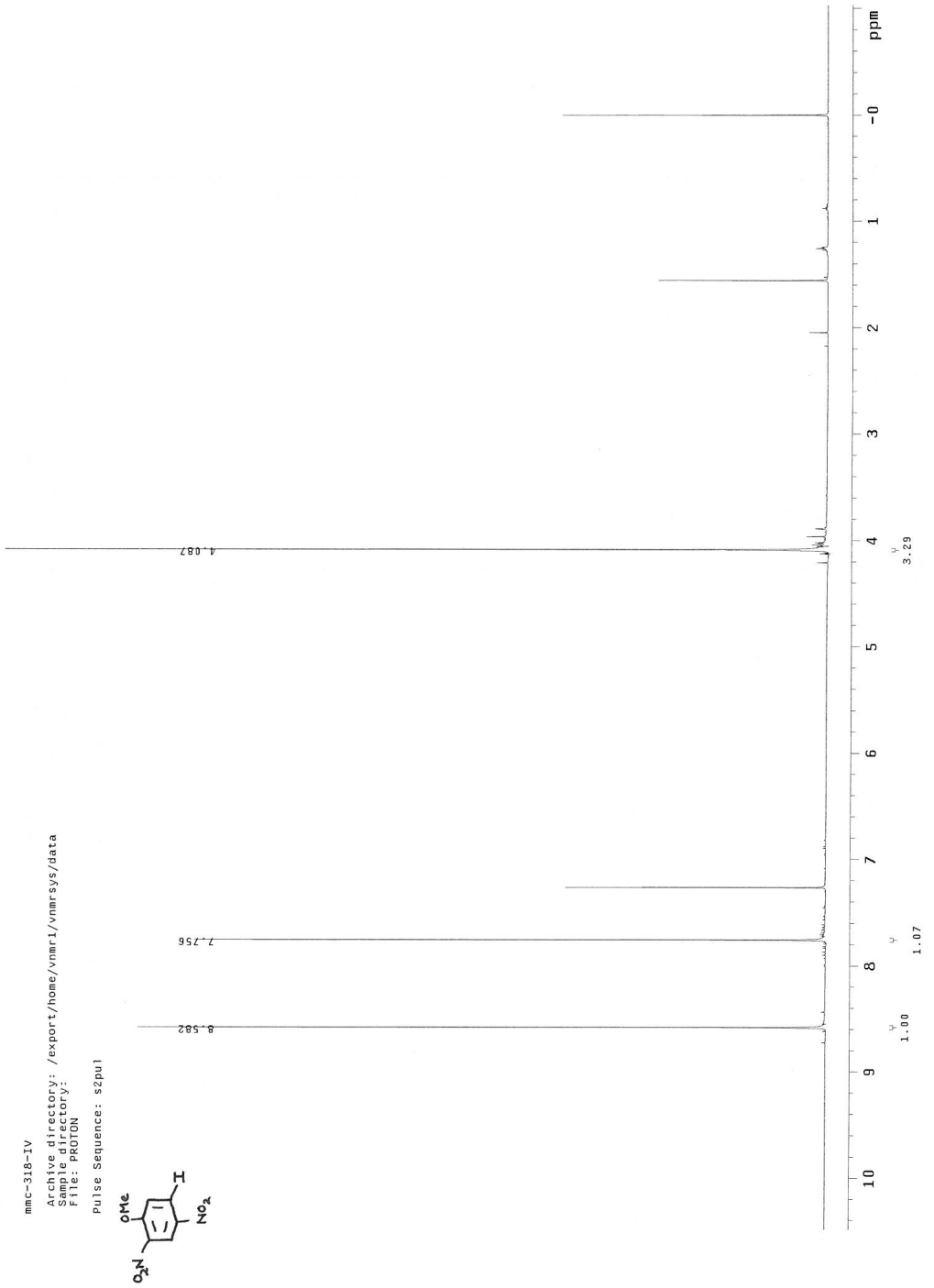

Figure 155: ^{1}H NMR of 5-iodo-2,4-dinitroanisole (**363**)

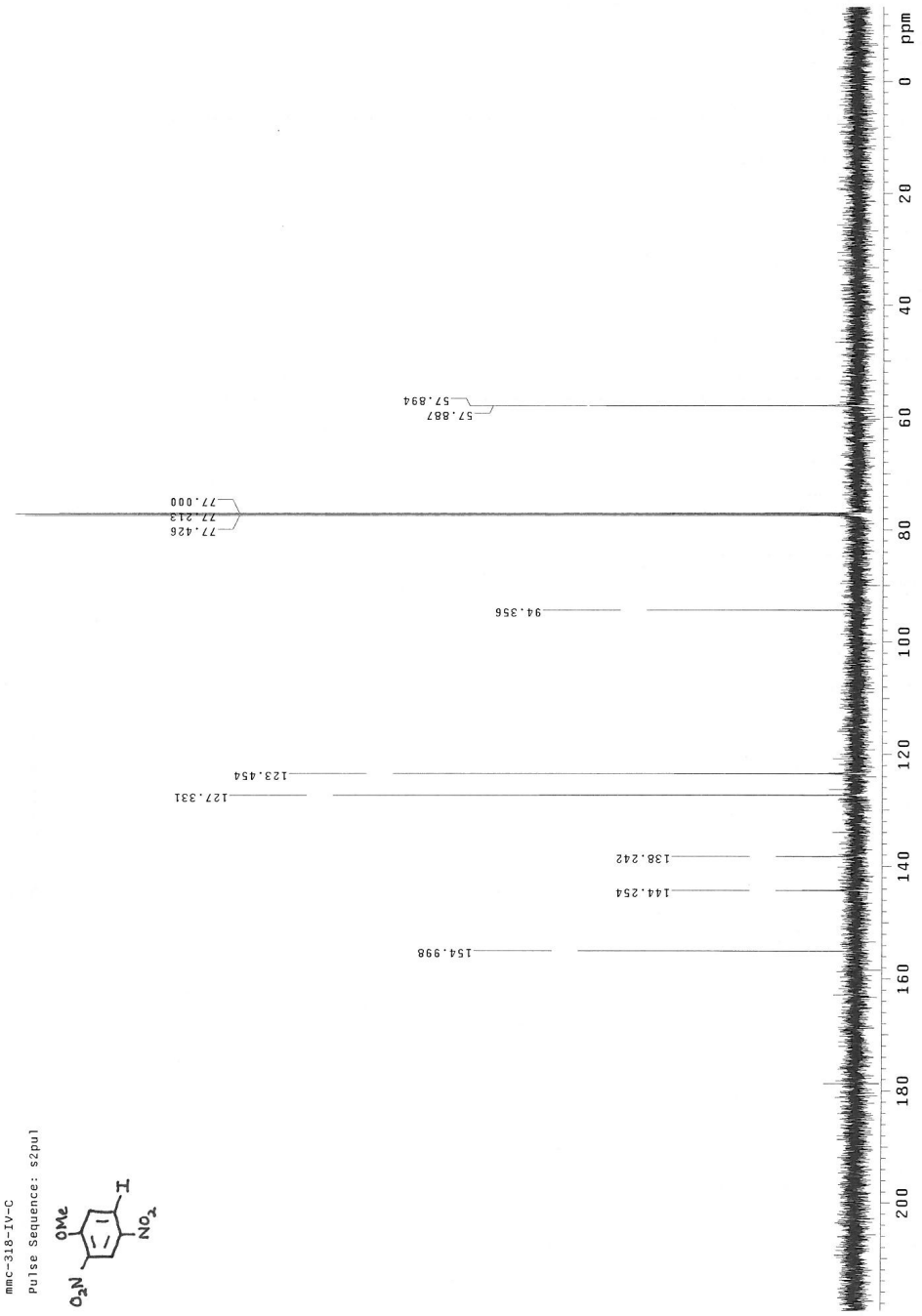

Figure 156: ^{13}C NMR of 5-iodo-2,4-dinitroanisole (**363**)

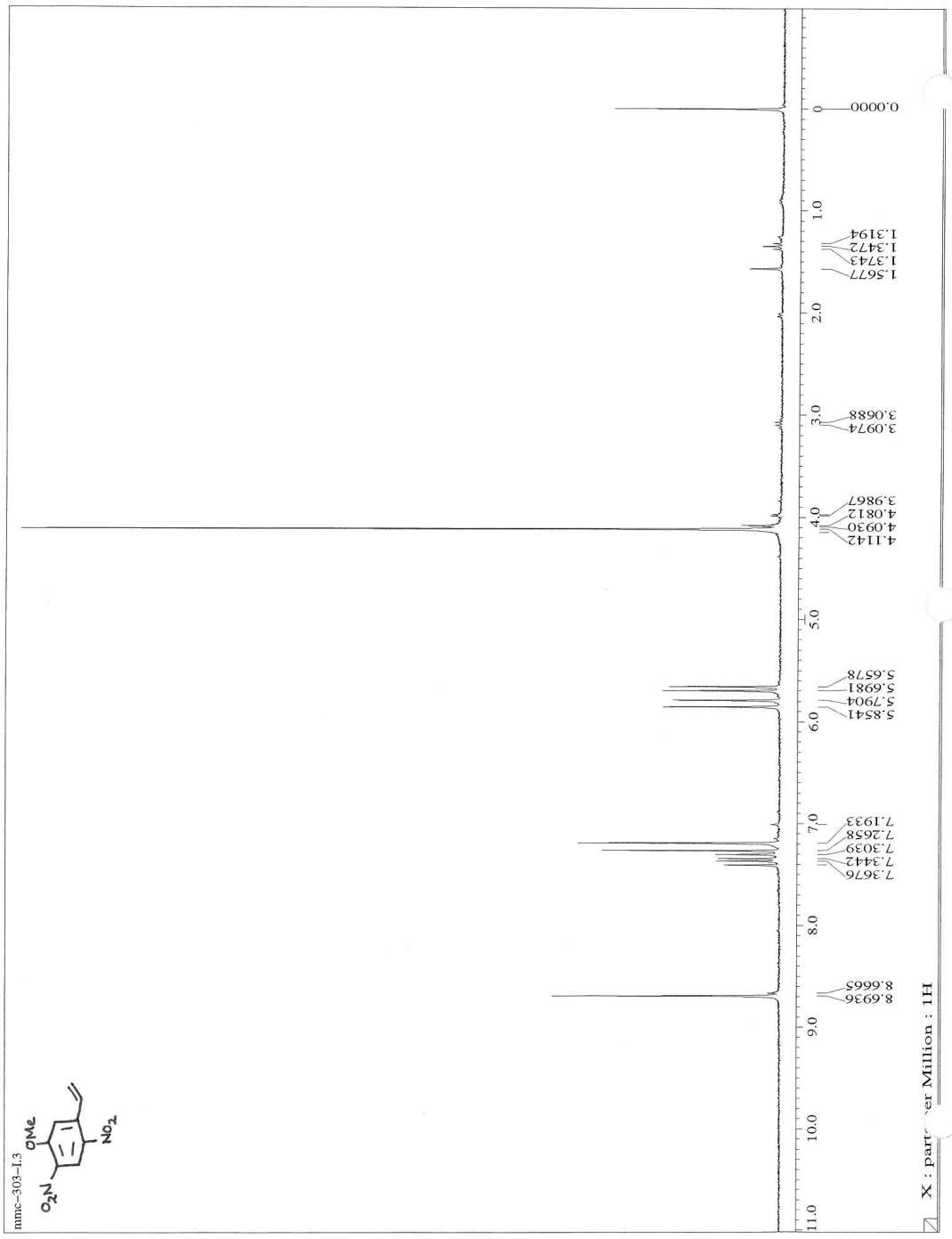

Figure 157: ^{1}H NMR of 5-ethenyl-2,4-dinitroanisole (**365**)

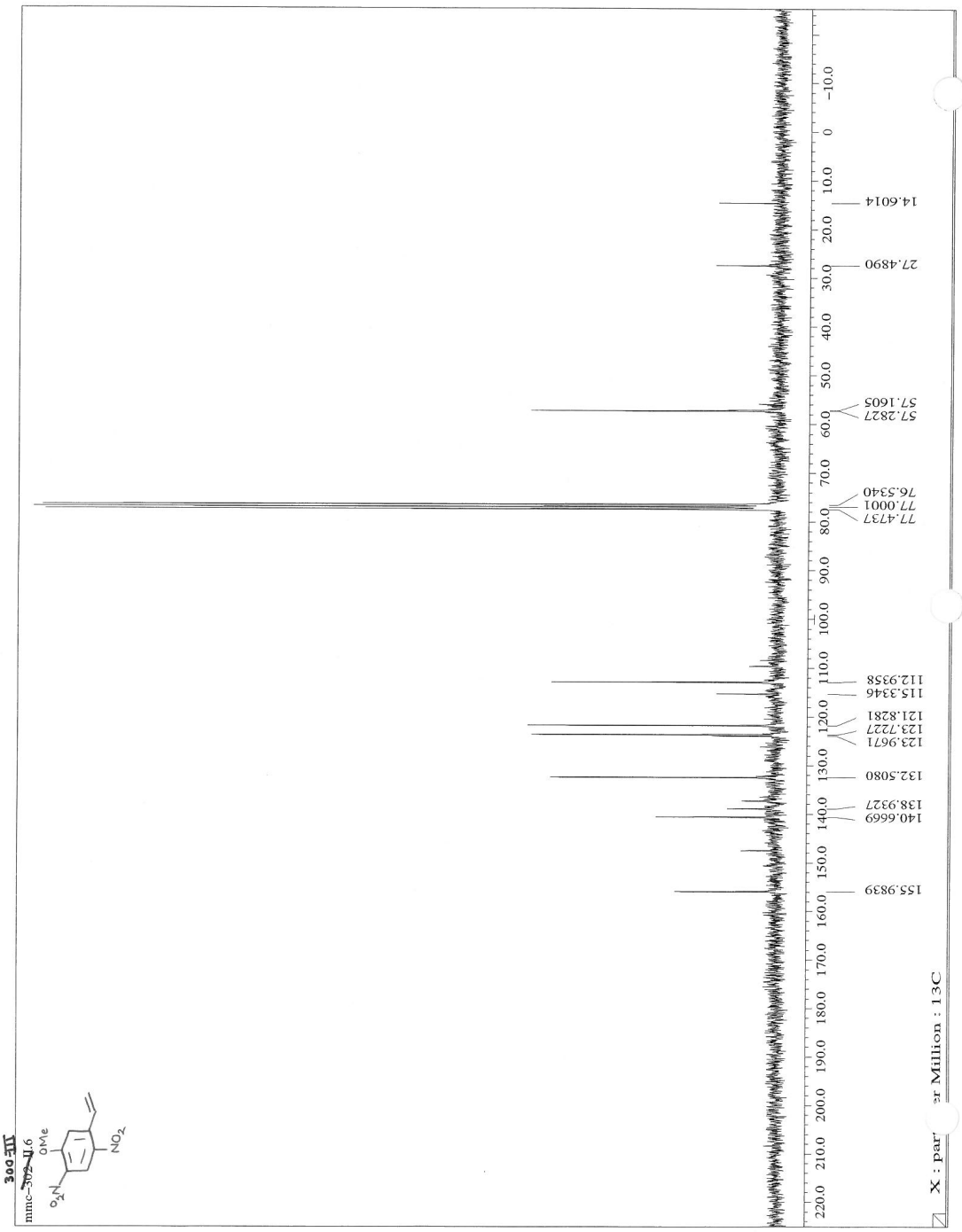

Figure 158: ^{13}C NMR of 5-ethenyl-2,4-dinitroanisole (**365**)

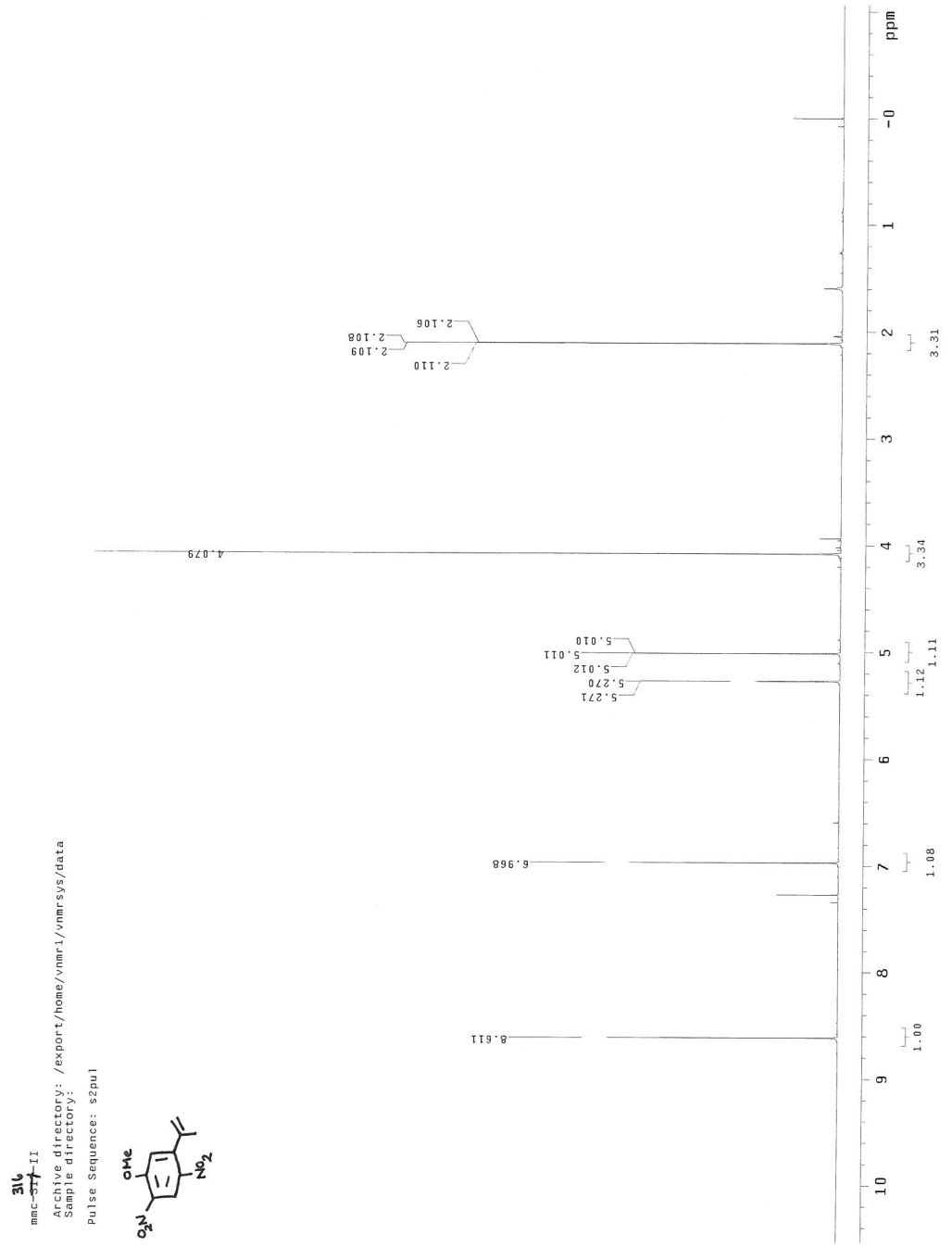

Figure 159: ^{1}H NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole **(369)**

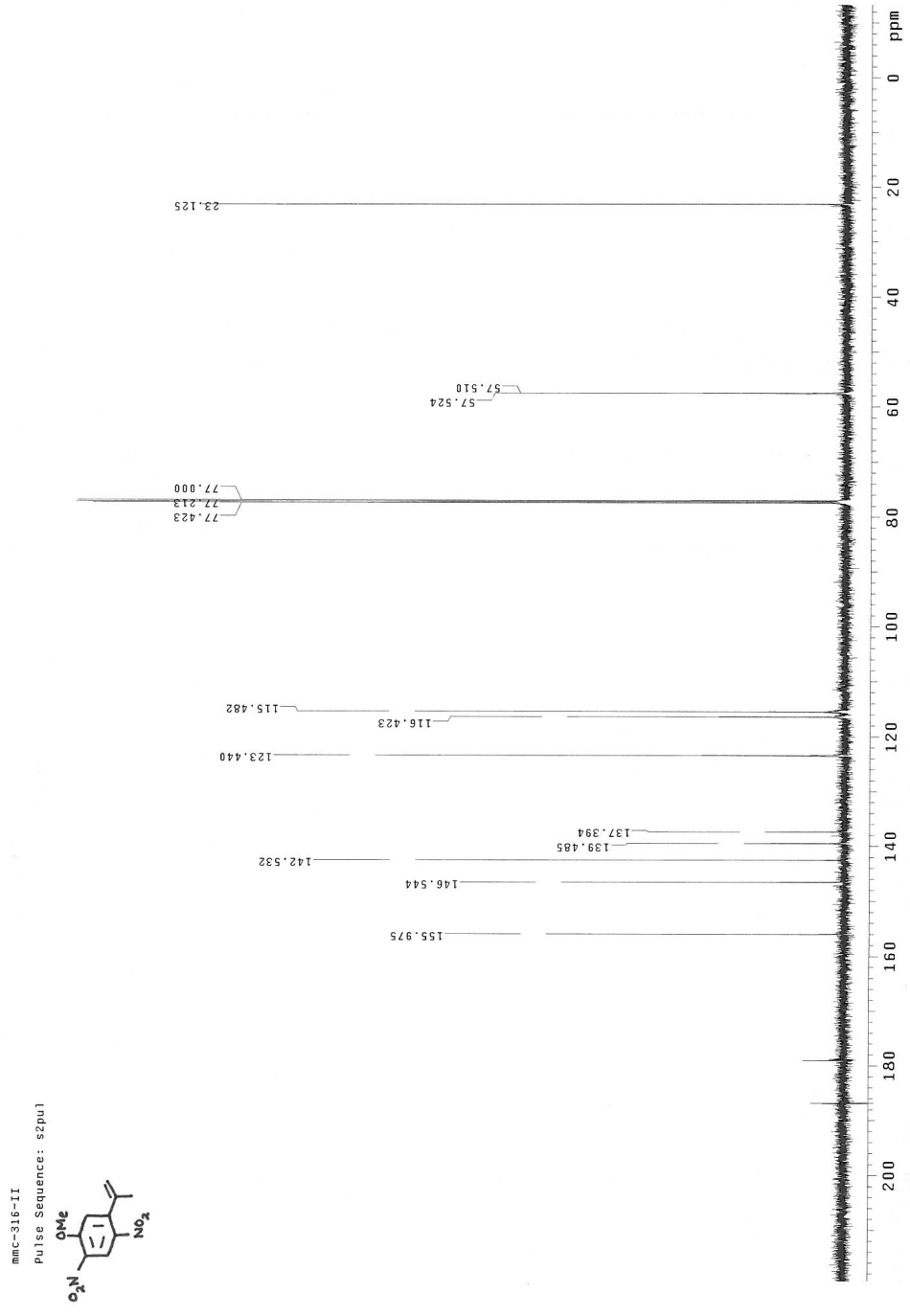

Figure 160: ^{13}C NMR of 2,4-dinitro-5-(prop-1-en-2-yl)anisole **(369)**

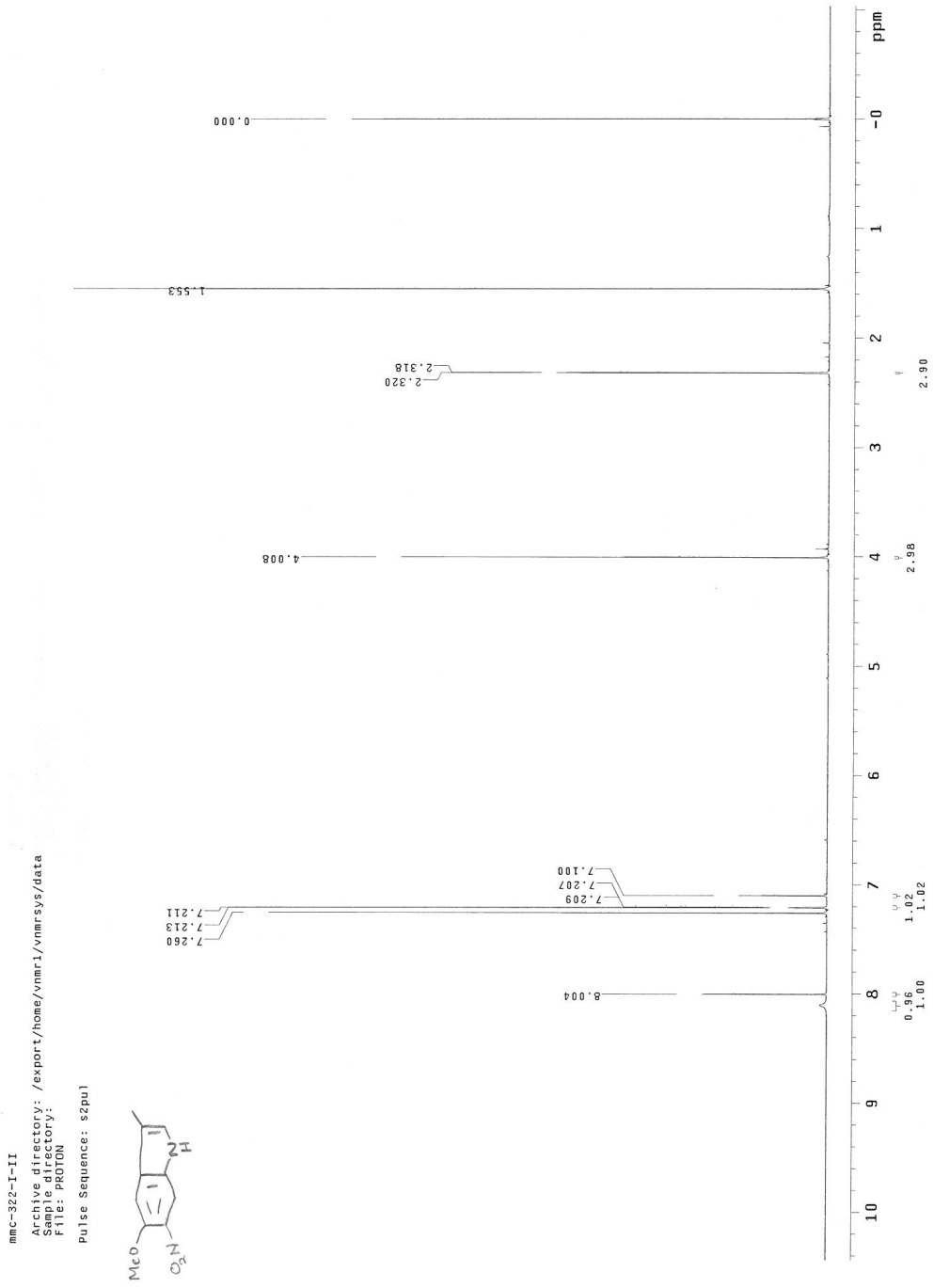

Figure 161: ^{1}H NMR of 3-methyl-5-methoxy-6-nitroindole (**370**)

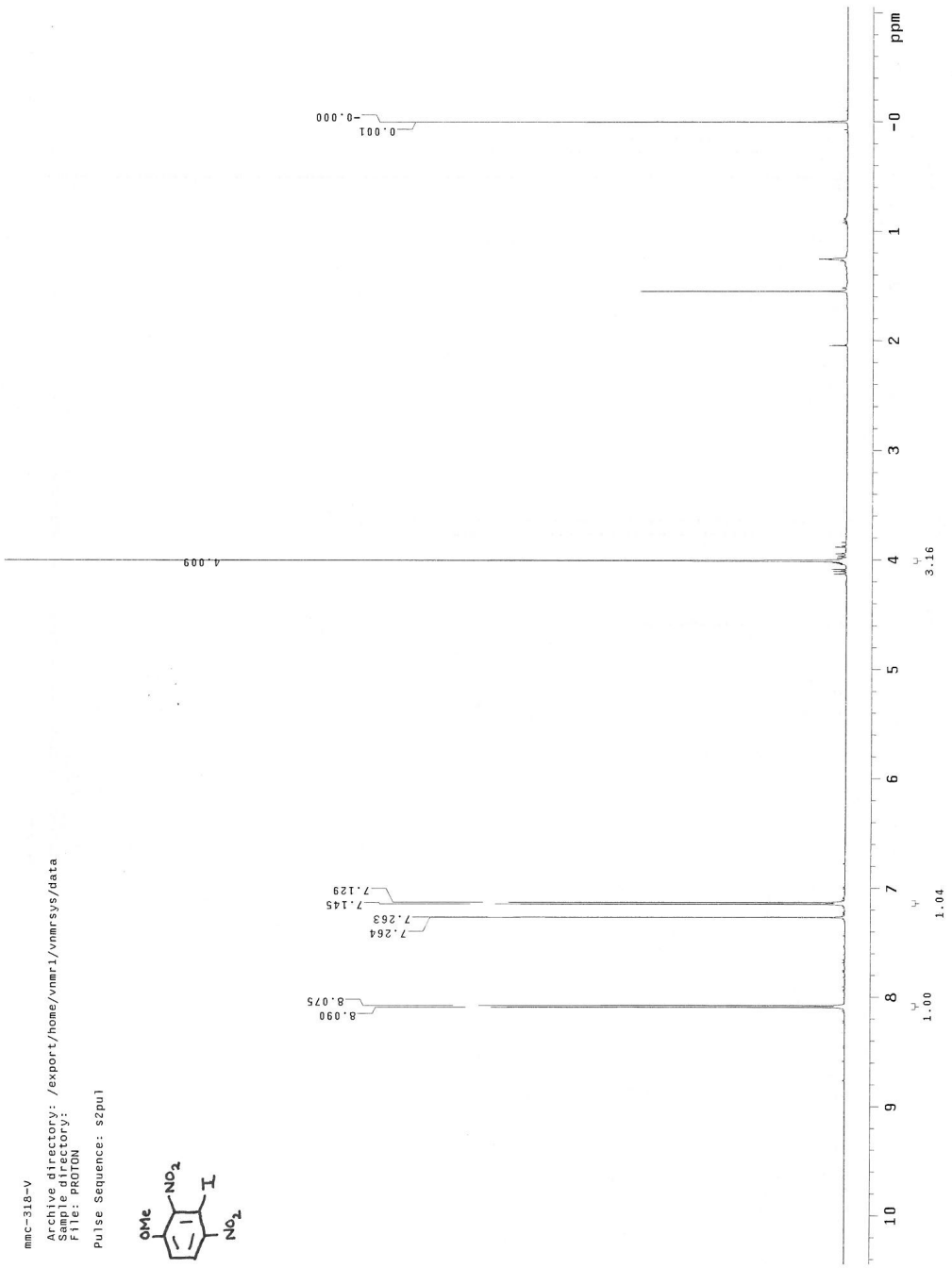

Figure 162: ^{1}H NMR of 3-iodo-2,4-dinitroanisole (**364**)

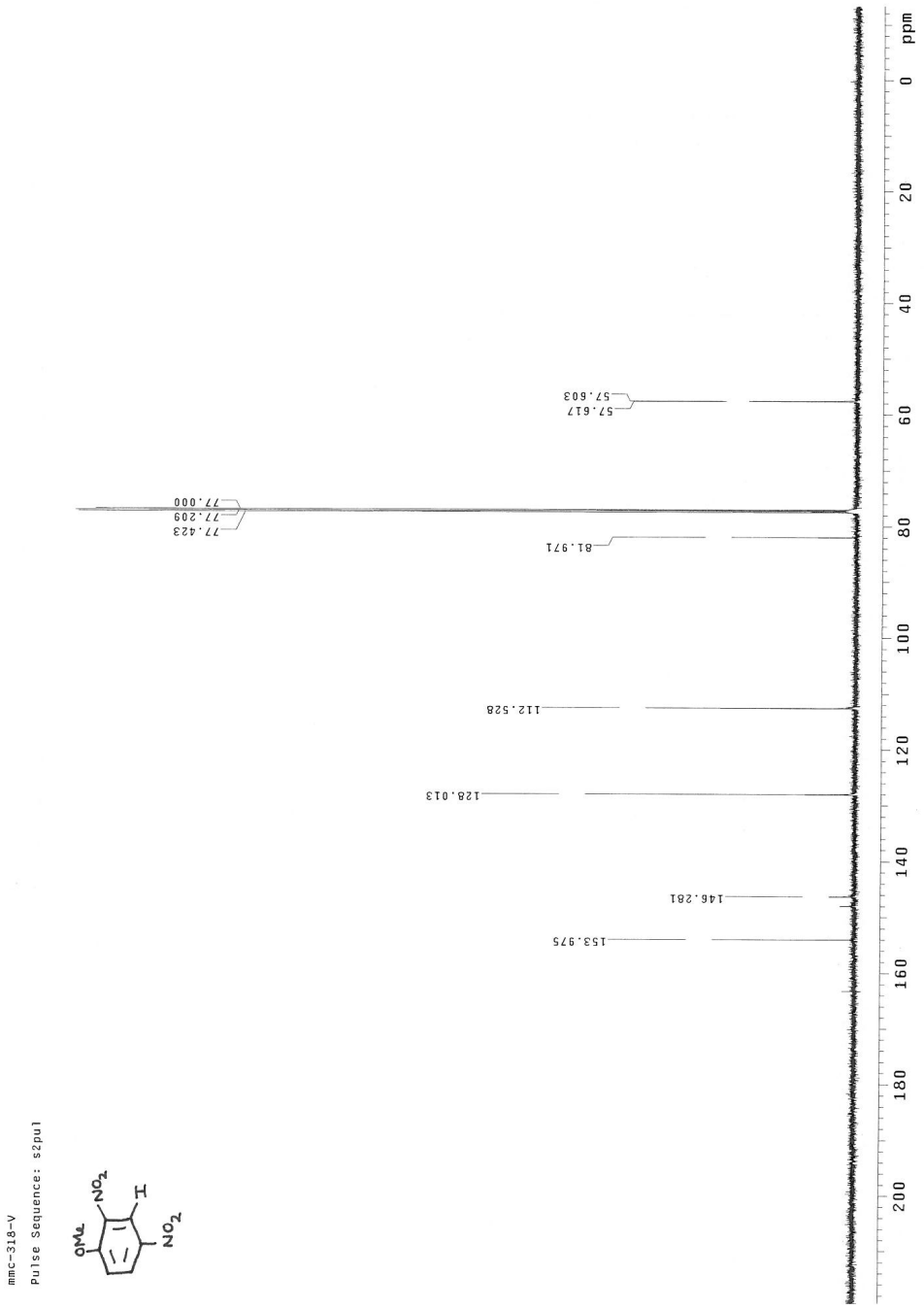

Figure 163: ^{13}C NMR of 3-iodo-2,4-dinitroanisole (**364**)

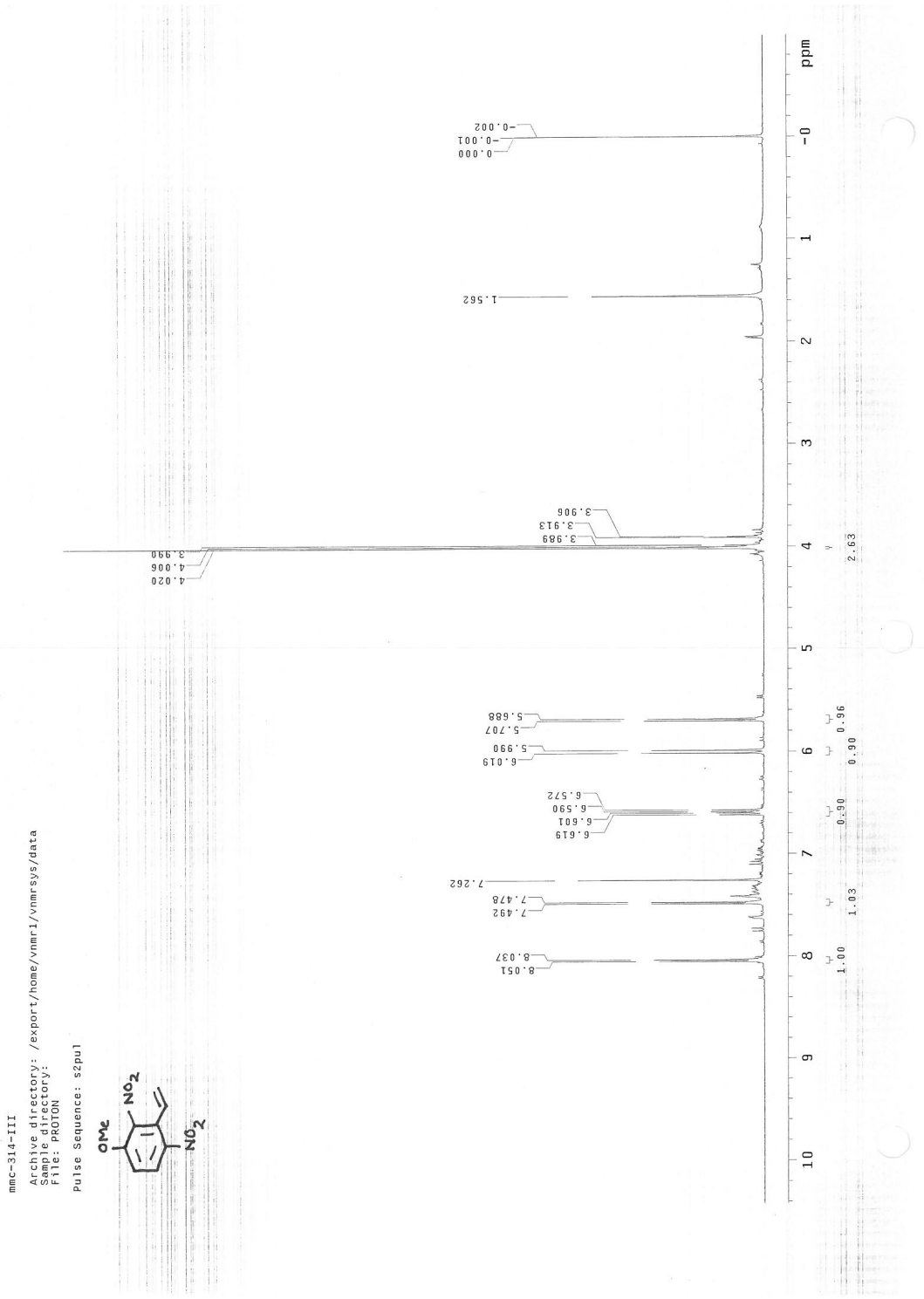

Figure 164: ^{1}H NMR of 3-ethenyl-2,4-dinitroanisole (**367**)

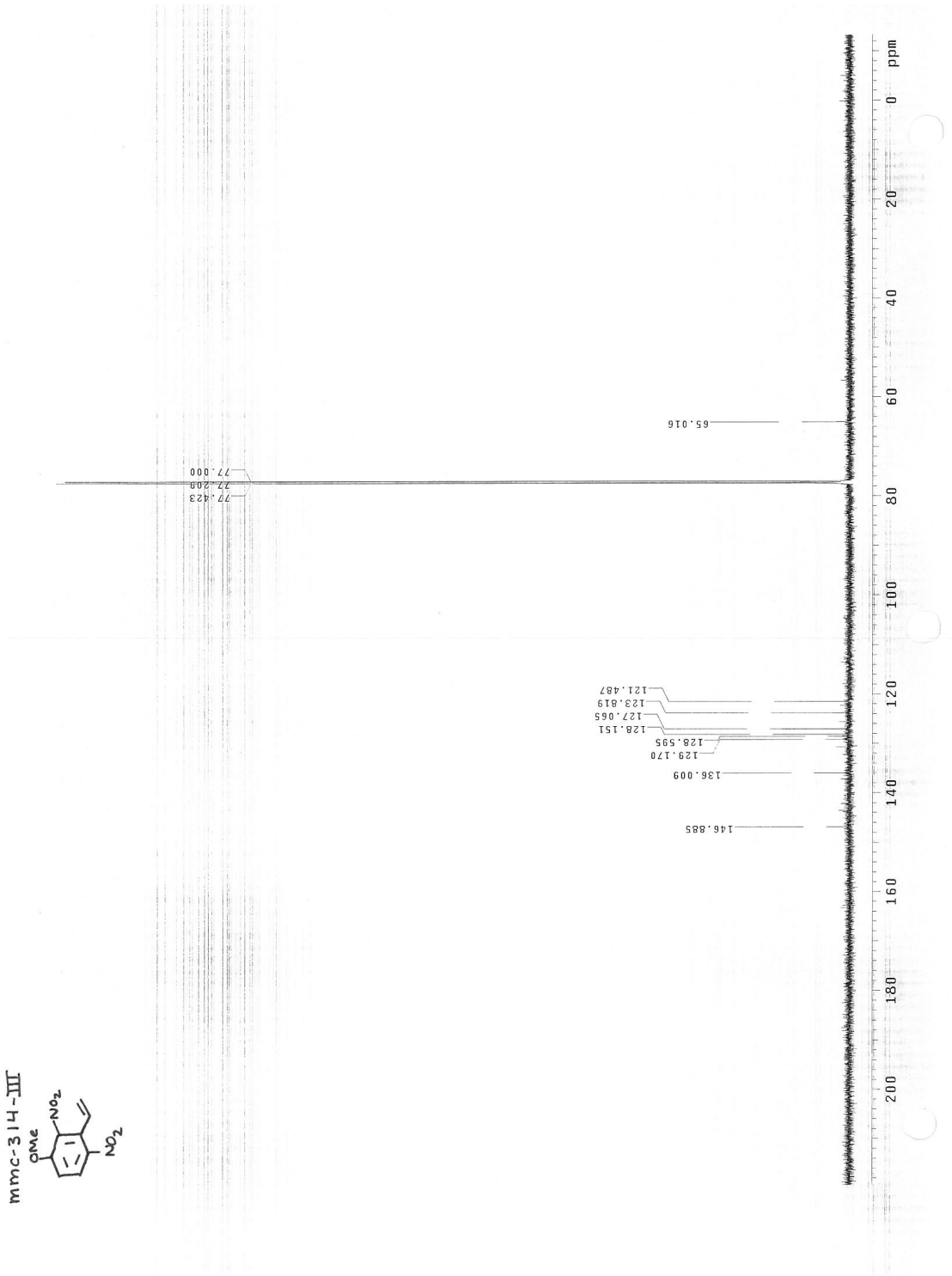

Figure 165: ^{13}C NMR of 3-ethenyl-2,4-dinitroanisole (**367**)

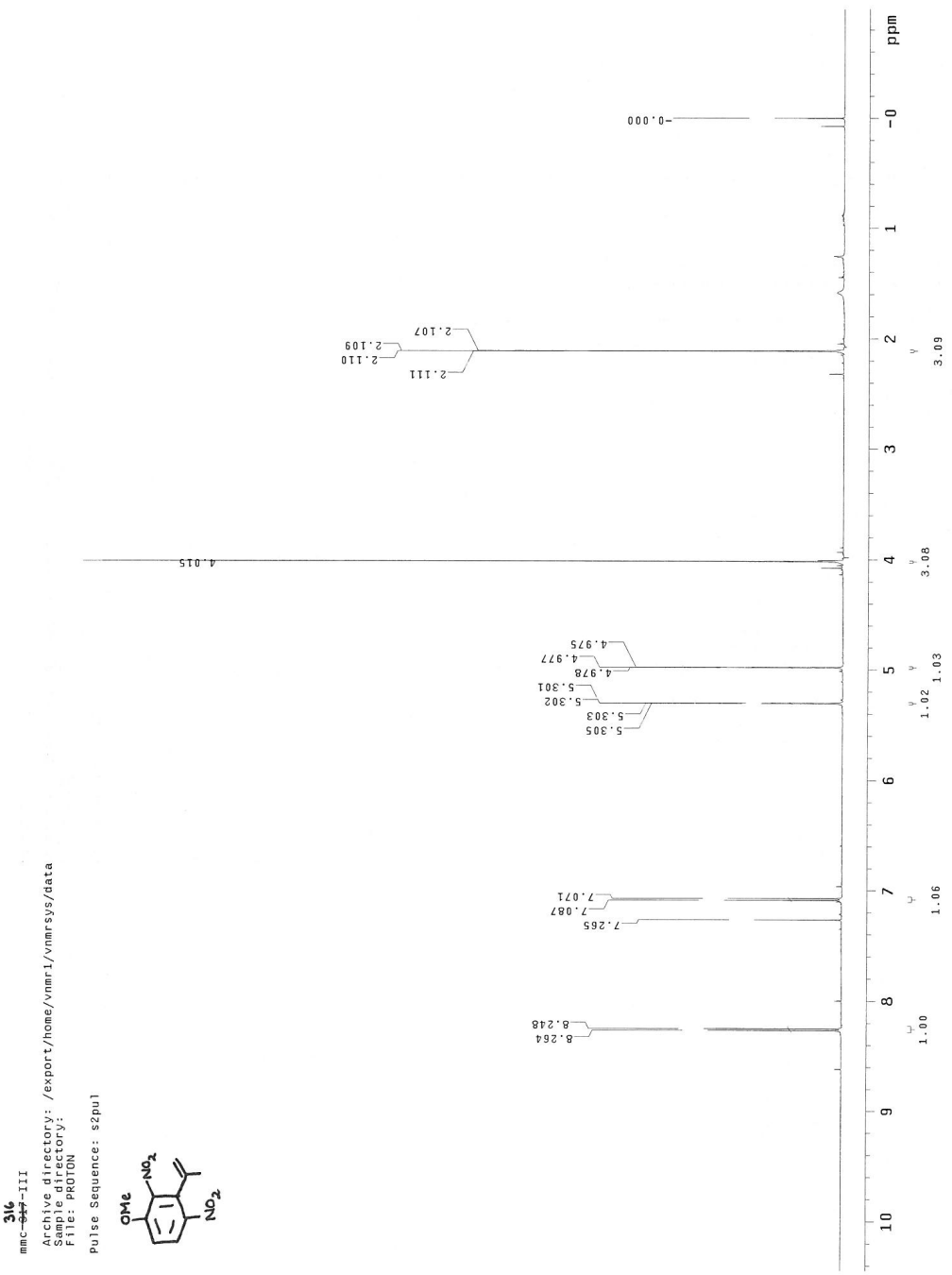

Figure 166: ^{1}H NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (**371**)

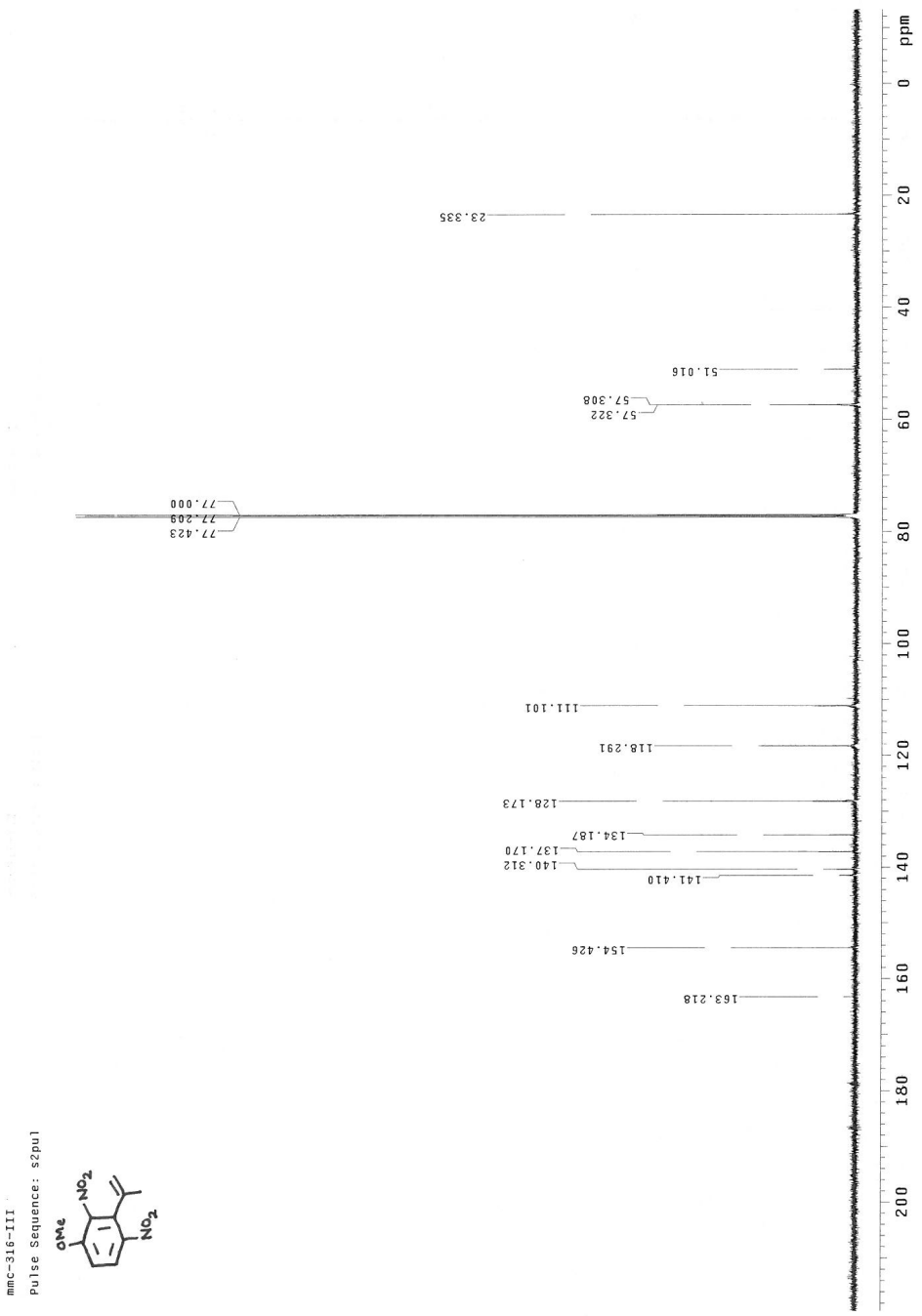

Figure 167: ^{13}C NMR of 3-(prop-1-en-2-yl)-2,4-dinitroanisole (**371**)

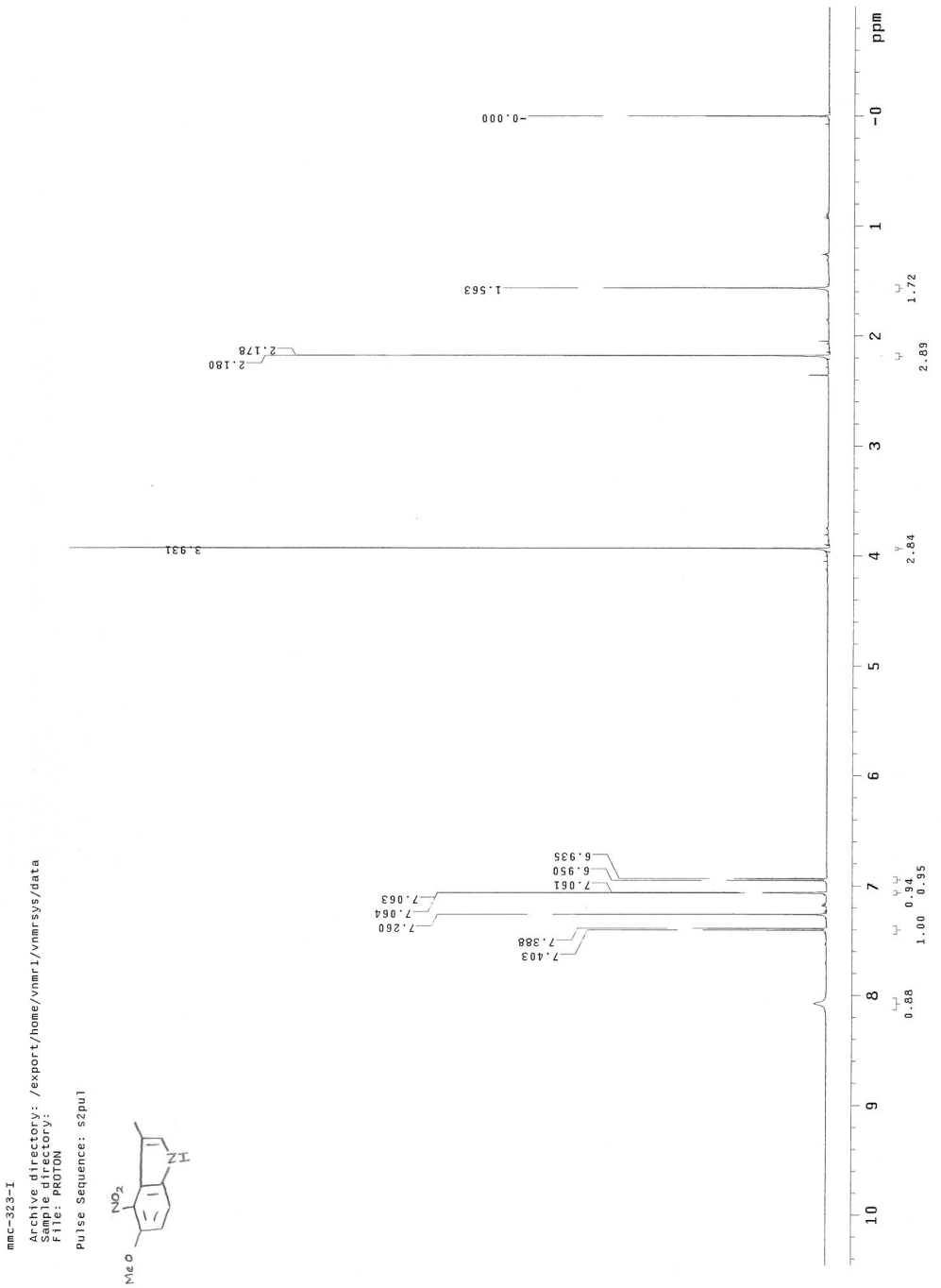

Figure 168: ^{1}H NMR of 3-methyl-5-methoxy-4-nitroindole (**372**)

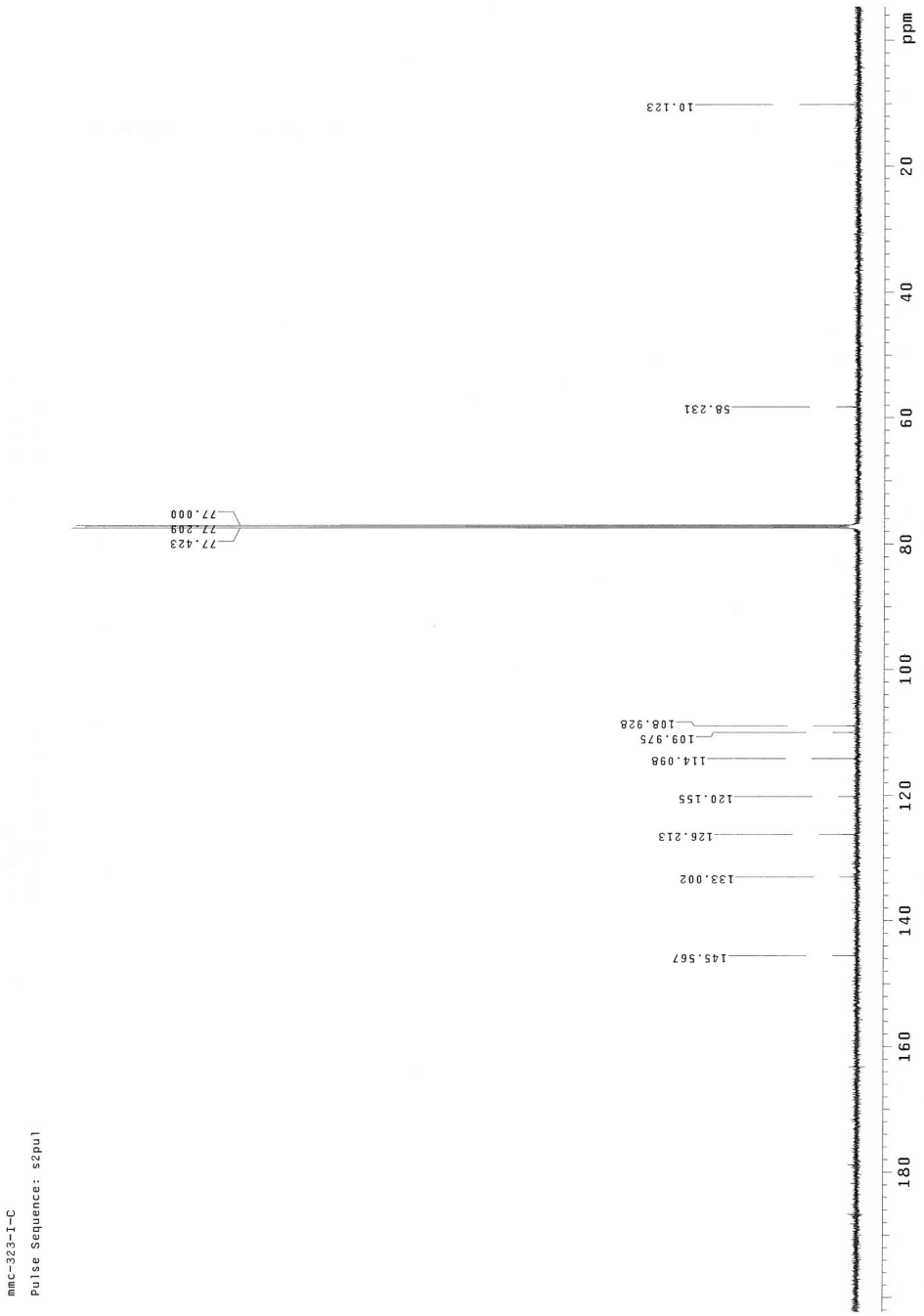

Figure 169: ^{13}C NMR of 3-methyl-5-methoxy-4-nitroindole (**372**)