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PROGRESS TOWARDS A NEW SYNTHESIS OF LYSERGIC ACID

Cheryl A. Slessor B.Sc. Bio.Chem.

Thesis submitted to the
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à
L'Institut de Chimie d'Ottawa-Carleton

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To dream anything that you want to dream, that is the beauty of the human mind.

To do anything that you want to do, that is the strength of the human will.

To trust yourself, to test your limits, that is the courage to succeed.

- Bernard Edmonds

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I will never forget my experiences at the University of Ottawa during the work towards my Master's Degree. I look forward to having the opportunity to apply these lessons in my chosen career path of teaching.

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Abbreviations and Symbols

Ac	acetate
Ac_2O	acetic anhydride
BOC	*tert*-butoxycarbonyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
δ	chemical shift
d	doublet
dd	doublet of doublets
DEPT	distortionless enhancement polarization transfer
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
EI	electronic ionization
eq.	equivalents
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
^1H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectroscopy
Hz	hertz

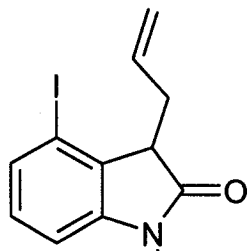
IR	infrared
J	coupling constant
LDA	lithium diisopropylamine
LG	leaving group
liq.	liquid
LTMP	lithium 2,2,6,6-tetramethyl piperidine
m	multiplet
M	molar
m/e	mass to charge ratio
Me	methyl
MeOH	methanol
min	minutes
m.p.	melting point
Ms	methanesulfonyl
MS	low resolution mass spectroscopy
MW	molecular weight
n	*normal*
NOE	nuclear overhausser effect
PG	protecting group
Ph	phenyl
Piv	pivalyl
ppm	parts per million
q	quartet

rt	room temperature
s	singlet
S_N2	bimolecular substitution
t	*tert*
t	triplet
td	triplet of doublets
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethyl piperidine
Ts	*p*-toluenesulfonyl

Abstract

This thesis describes the progress made towards the synthesis of the lysergine ring system **1**. Approaches based on benzyne, oxindole, and indole intermediates were explored. Results of these three central strategies are discussed.

The benzyne route as outlined in Chapter 2 illustrated the potential to synthesize a key bicyclic intermediate, 3-but-3-enyl-4-iodo-1-methyl-1,3-dihydro-indol-2-one **33**.

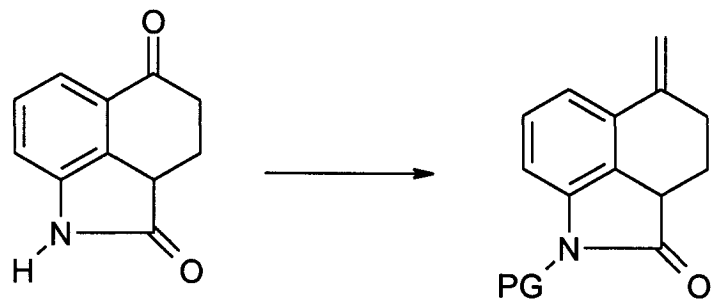


33

This approach utilized our existing results in benzyne chemistry to construct the lysergine AB ring system. Formation of **33** via a benzyne reaction would be followed by an intramolecular Heck cyclization reaction, resulting in formation of intermediate **34**. Due to low yields and difficulty in reproducing **33** in the benzyne reaction, this route was abandoned.

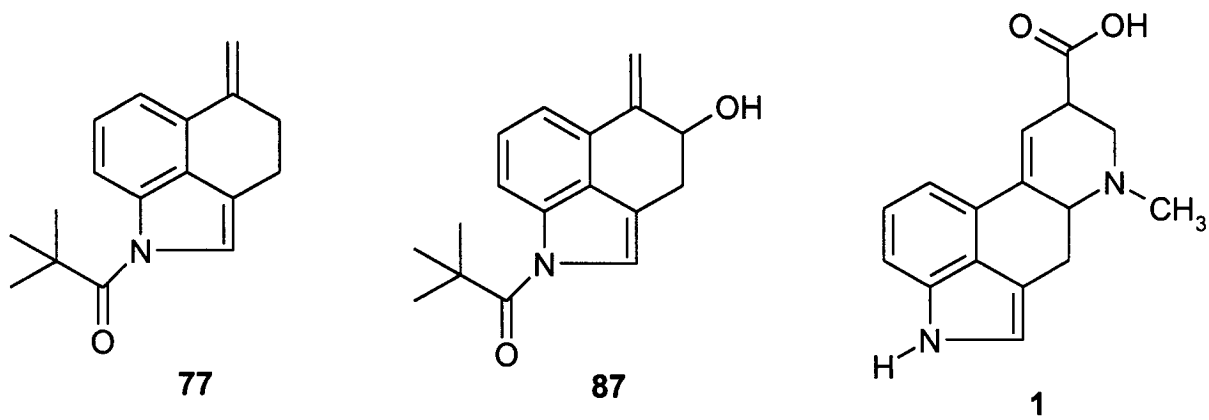
The oxindole route (Chapter 3) was an extension of the ideas developed during the exploration of the benzyne reaction. This approach examined the potential for an intramolecular Friedel Crafts reaction using oxindole-3-propionic acid as the starting material, followed by a Wittig olefination to yield the desired

tricyclic intermediate **34**. Unfortunately, the Friedel Craft product **70** was highly unstable therefore, this route was also abandoned.



70 **34**

The indole approach described in Chapter 4 combined the original ideas from both the benzyne and oxindole routes. Here, we demonstrated the ease of synthesis in obtaining 2,2-dimethyl-1-(5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-propan-1-one **77**, the *N*-pivalyl protected version of intermediate **34**. The success in forming **77** enabled us to proceed with the construction of Ring D using a selenium-dioxide allylic oxidation reaction to afford the α-alcohol **87**. In addition, the α,β-enone isomer **88** was obtained via modified Mannich reaction conditions. The successes realized with the indole approach presented a unique and promising synthetic approach to lysergine **1**.



77 **87** **1**

Chapter 1 – Introduction

1.1 Background and Biological Activity of Lysergic Acid

Ergot alkaloids are a group of fungal metabolites produced by members of the *Clavicipitaceae* family. The most commonly know fungi are the *Claviceps purpurea*, which are ubiquitous pathogens of cereals such as rye. The picture[1] on the left shows the schlerotia (black) amongst the grains of rye. These fungi were identified in 1676 as the causative agent of the medieval gangrenous scourge called St. Anthony's Fire. This was caused when infected rye was used to make bread.[2] Today, cereals are mechanically cleaned to reduce the contamination of the flours.

Many Ergot alkaloids and their derivatives have been reported to have diverse biological effects. In general, they are substitued indole derivatives, which have a tetracyclic ergoline ring structure as shown below (Figure 1.1).[3]

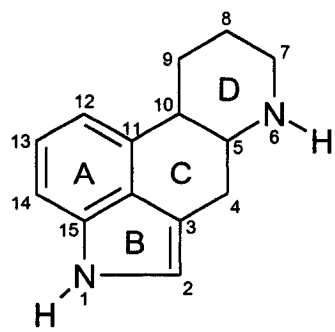


Figure 1.1 Ergoline ring system.

One of the most important compounds in this class is lysergic acid **1**. It was first isolated by the alkaline hydrolysis of Ergot alkaloids.[4,5] From it was produced the infamous hallucinogenic derivative, lysergic acid diethylamide (LSD) **2**. LSD has been a household word since the 1960's when it was popularized as a 'social drug' in North America.

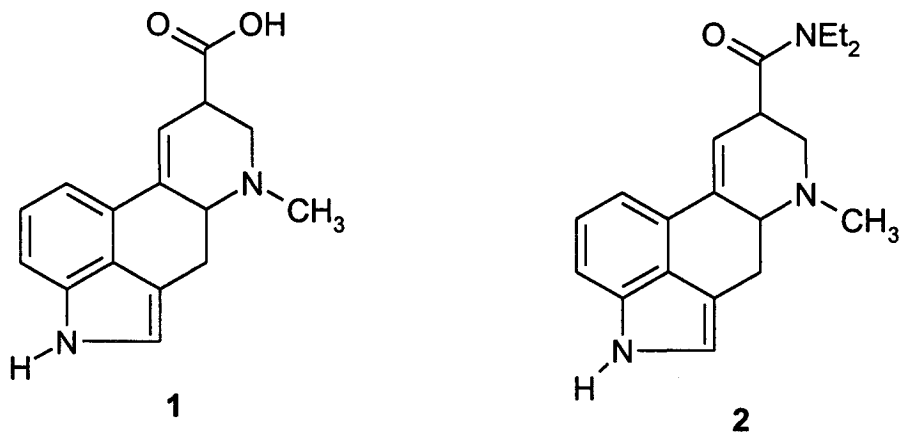


Figure 1.2 Structures of lysergic acid **1** and lysergic acid diethylamide **2**.

These alkaloids exhibit vasoconstrictive and sympatholytic-andrenolytic effects due to their affinitiy for the same andrenergic receptors for noradrenaline, dopamine and serotonin (Figure 1.3).[3] Many of the derivatives of ergot alkaloids have been applied in the clinical treatment of a variety of ailments. These include the treatment of: hypertension (nicergoline); migraine (methysergide), postpartum hemorrhage (ergonovine and methylergonovine); and prolactin-dependent disorders such as Parkinson's Disease (2-bromo-ergokryptine), (Figure 1.4).[3,5,6,7,8]

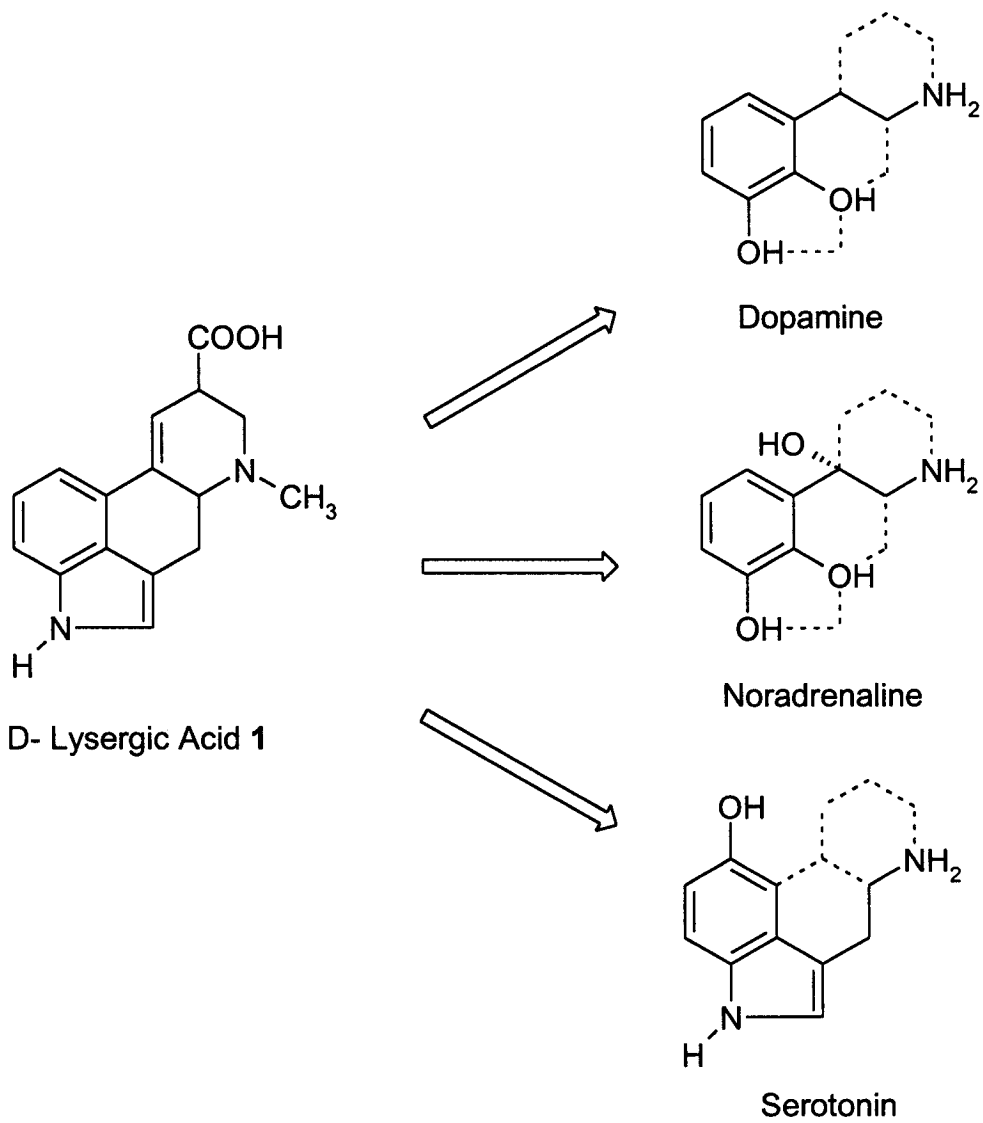
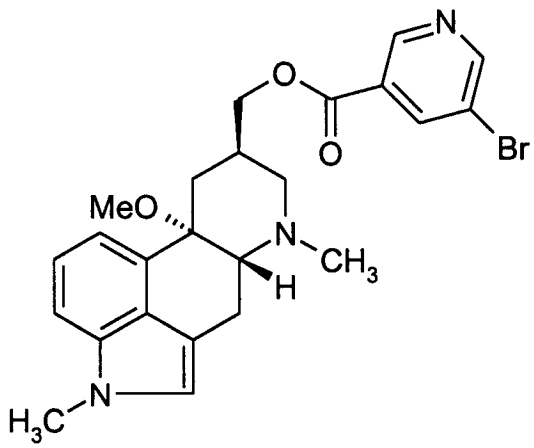
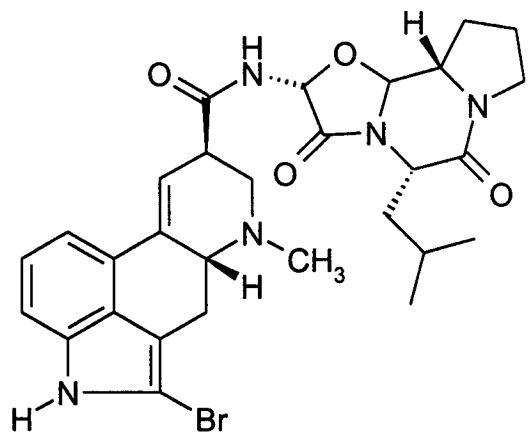


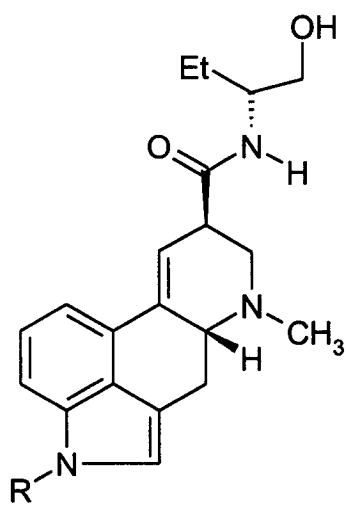
Figure 1.3 Structural similarities between **1** and andrenergic molecules.



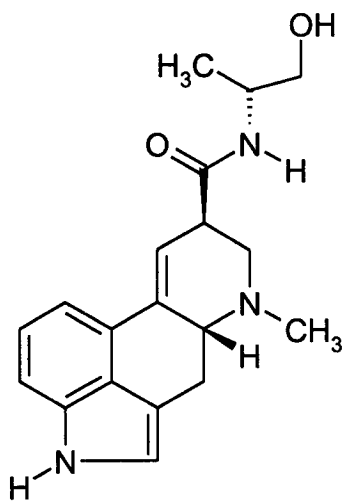
Nicergoline



2-Bromo-ergokryptine



R= H, Methylergonovine
R= CH_3, Methysergide



Ergonovine

Figure 1.4 Ergot alkaloid derivatives used in clinical treatment.[8]

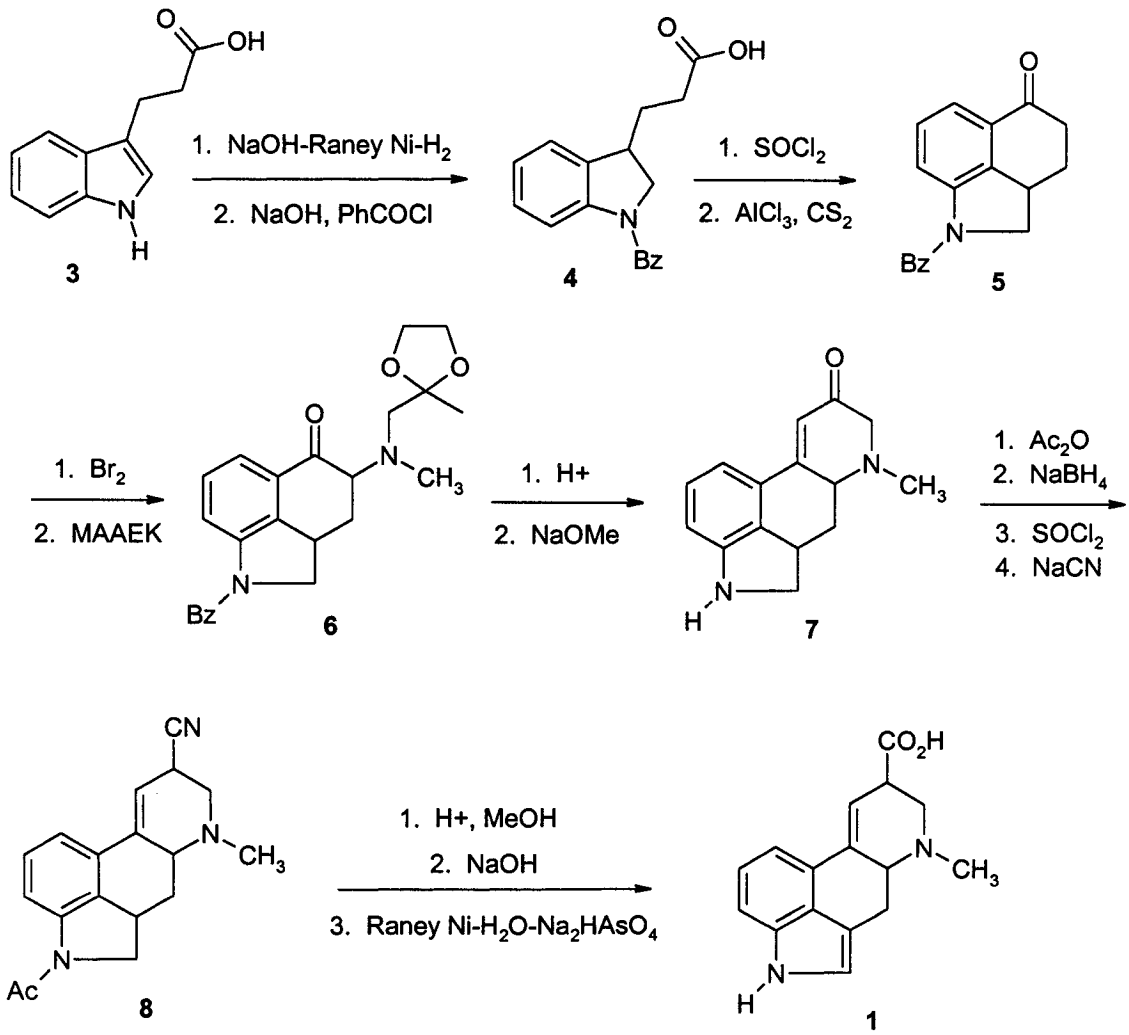
1.2 Previous Syntheses of Lysergic Acid

As a result of its position amongst the ergot alkaloids, lysergic acid has been a very important synthetic target. It provides the starting material for the formal syntheses of several other ergolines such as those mentioned in the previous section. Despite many attemts and partial syntheses, only 9 groups have reported the total synthesis[2,4,10-15] of **1**. The most recent publication was in 1994. These approaches have been reviewed extensively[16], with the general conclusion that chemical synthesis is not yet able to compete with fermentation processes for access to these substances.[12] This section reviews two of the published total syntheses: Kornfeld-Woodward[2] for it's historical significance, and that by Ortar[14] because it expands and improves upon the Woodward synthesis.

1.2.1 Kornfeld-Woodward Synthesis

The Kornfeld-Woodward group from the Eli Lilly Company and Harvard University reported the first total synthesis of racemic lysergic acid in 1954.[2] Their synthesis begins with 3-indole proprionic acid **3**, which is converted to *N*-benzoyl-3-(β-carboxyethyl)-dihydroindole **4** using Raney-Nickel conditions to reduce indole to indoline, followed by *N*-protection using a benzyl group. An intramolecular Friedel Crafts acylation reaction is used to convert **4** to **5**, the key central ketone known as *Kornfeld's Ketone*. Treatment of **5** with Br_2, followed by the addition of methylaminoacetone ethylene ketal (MAAEK) led to the formation

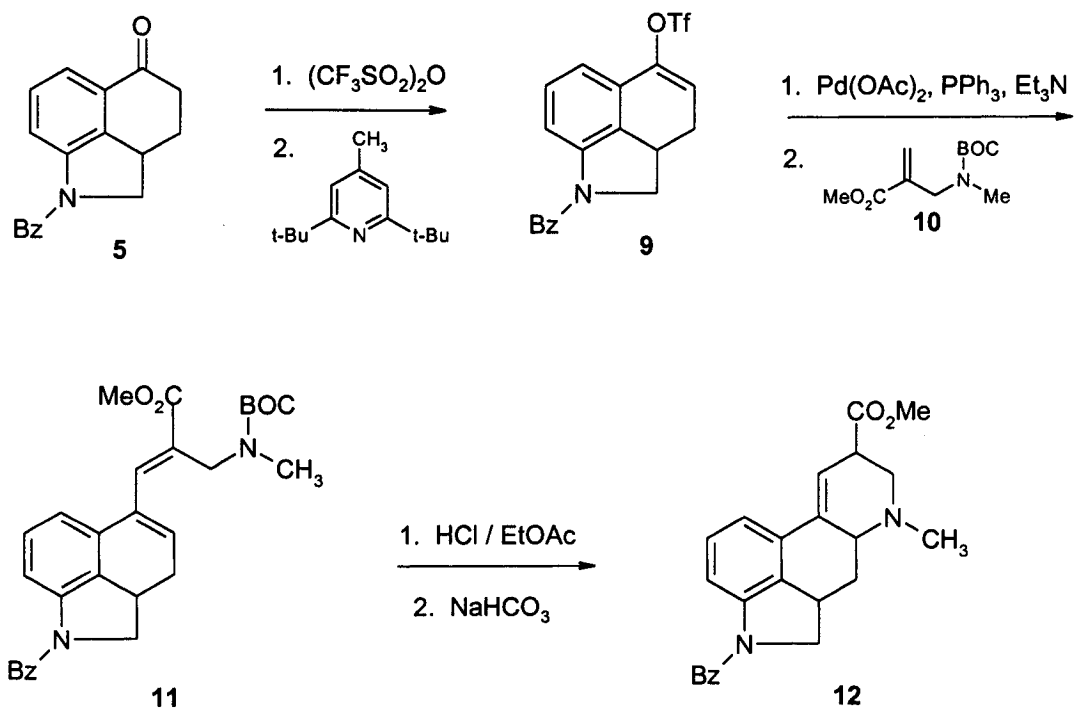
of ketal-ketone **6**. Treatment of **6** affords a diketone, which when treated with sodium methoxide, afforded the tetracyclic compound **7**. The free amine was protected by acetylation with Ac_2O, then the ketone reduced to the alcohol with $NaBH_4$, treated with $SOCl_2$ to generate the chloride, which was then displaced with NaCN in liquid HCN to give the nitrile **8**. Methanolysis of the nitrile to the methyl ester, followed by basic hydrolysis, and finally, dehydrogenation with Raney-Nickel afforded the final racemic product, lysergic acid **1**.



Scheme 1.1 Kornfeld-Woodward synthesis of lysergic acid **1**.

1.2.2 Ortar Synthesis

The synthesis by Ortar[14] and his group was published in 1988 as a concise, palladium-catalyzed approach. They begin with **5** (Kornfeld's Ketone) and convert it to the vinyl triflate **9** with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine. A palladium catalyzed reaction between **9** and **10** gave the desired aminodienoate **11** as the major coupling product. Cleavage of the BOC protecting group under acidic conditions followed by the treatment of sodium bicarbonate solution afforded the cyclized product **12** as a 1.7:1 mixture of diastereomers. The separation of the isomeric products was possible by crystallization from ethyl acetate. Since the final Raney-Ni dehydrogenation step had been described previously, they did not include it in their formal synthesis.

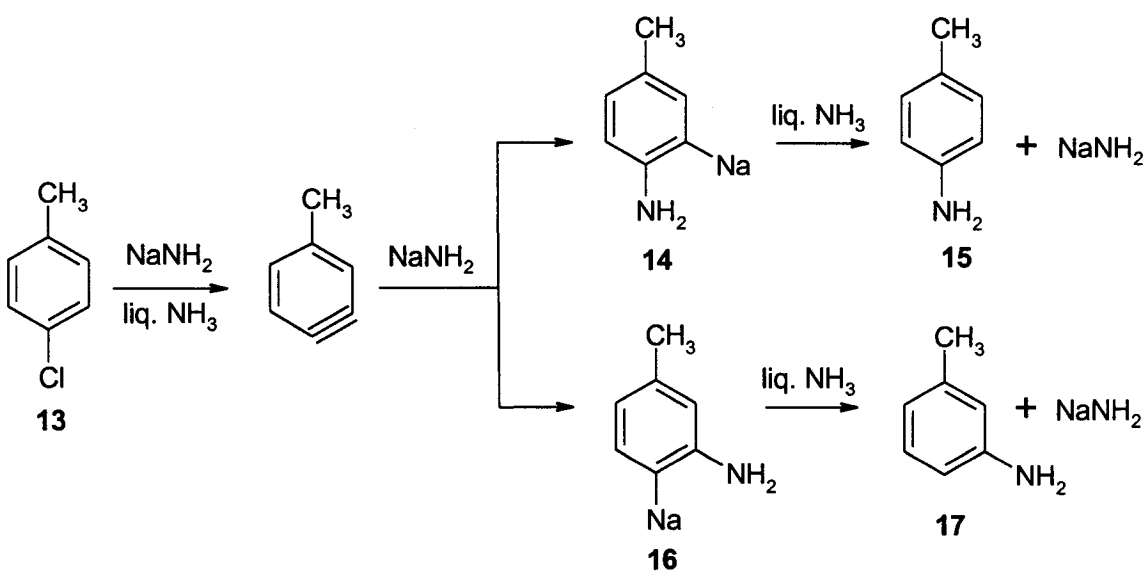


Scheme 1.2 Ortar synthesis of lysergic acid **1**.

Chapter 2 – The Benzyne Reaction

2.1 Background

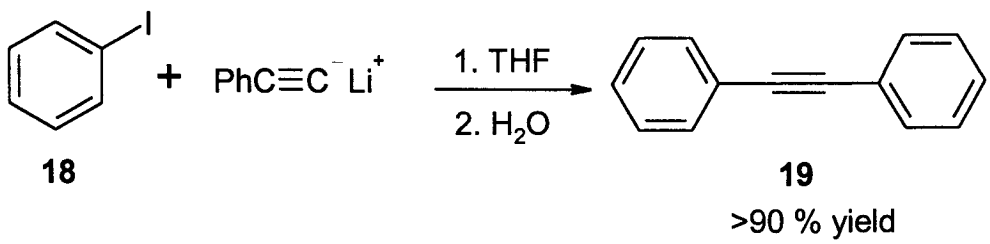
The reaction of chlorobenzene with sodium amide in liquid ammonia results in the formation of aniline.[17] The mechanism of this transformation was shown to involve elimination of HCl to form benzyne. This was followed by addition of ammonia ($NaNH_2$ and NH_3) to the short-lived, highly reactive benzyne. The mechanistic conclusions are best illustrated with 4-chlorotoluene (Scheme 2.1).[18]



Scheme 2.1 Nucleophilic aromatic substitution via a Benzyne intermediate.

In 1973, it was reported by Dougherty and Olofson that lithium tetramethylpiperidine (LTMP) was an excellent reagent for the generation of

benzyne from chlorobenzene.[19] The advantage of this reagent relative to lithium or sodium amide was that unlike the NH_2^- anion, it did not compete with other nucleophiles in the reaction system for addition to benzyne. Thus it became possible to trap benzyne selectively with a variety of desirable nucleophiles.

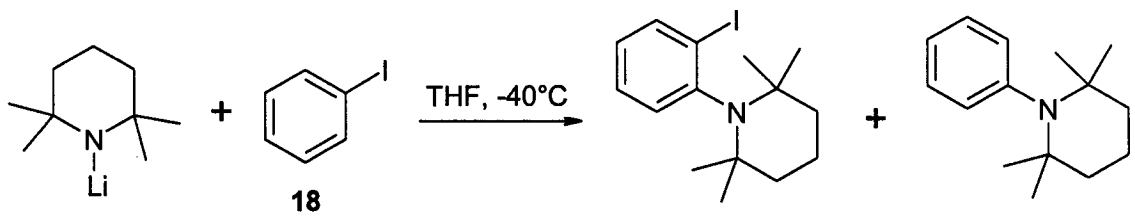


18 **19**

>90 % yield

Scheme 2.2 Trapping of benzyne with a nucleophile.

In 1999, our research group tested the use of iodobenzene **18** and LTMP as a source of benzyne.[19,20] As part of that study, **18** was reacted with LTMP in THF at -40°C in the absence of other nucleophiles. Two products were obtained: *N*-(2-iodophenyl)-2,2,6,6-tetramethylpiperidine **20** in 81% yield, and *N*-phenyl-2,2,6,6-tetramethylpiperidine **21** in 9 % yield.

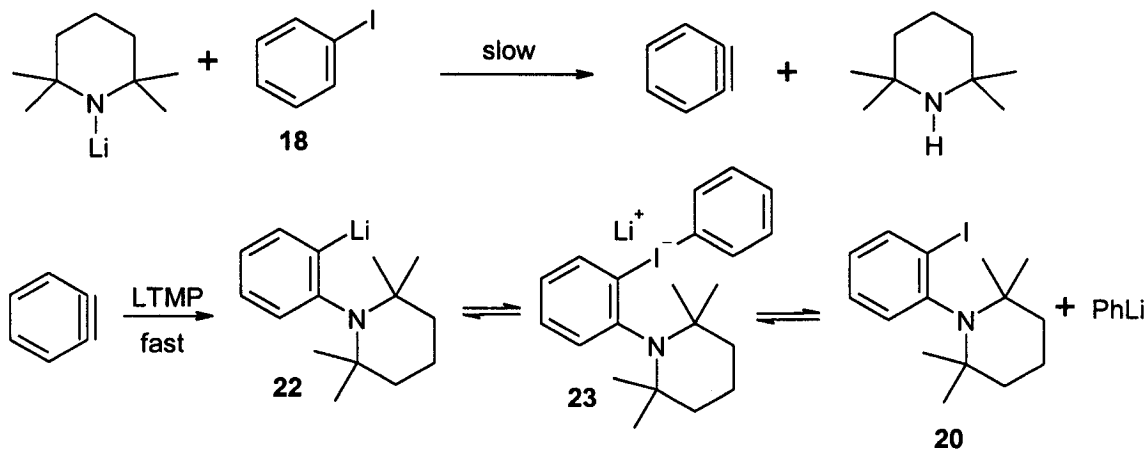


18 **20** **21**

81% yield 9% yield

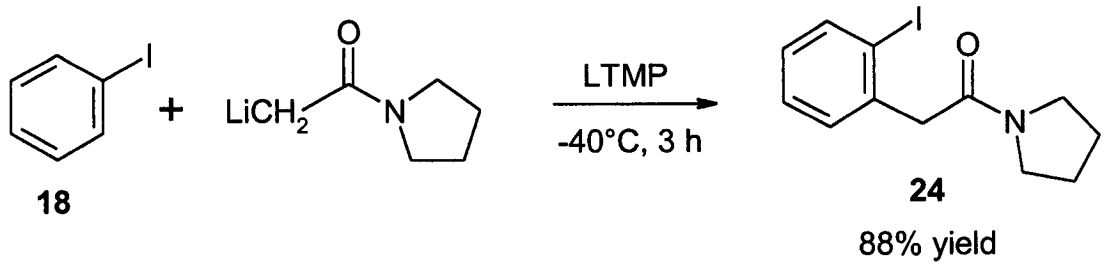
Scheme 2.3 Trapping of iodobenzene **18** with LTMP.

The formation of **21** was not unexpected since LTMP was the only nucleophile present in the reaction medium, but the formation of the major product **20** was surprising. Its formation was eventually rationalized as involving an iodine ate complex **22** intermediate in equilibrium with the initial adducts **22** and **20**. Work-up would eventually result in the isolation of **20** (Scheme 2.4).[19]



Scheme 2.4 Explanation of LTMP reaction with iodobenzene involving an iodine ate complex.

It was subsequently shown that when the generation of benzyne from iodobenzene **18** and LTMP was carried out in the presence of a variety of ester and amide enolates, a variety of 2-iodosubstituted benzenes such as **24** could be isolated, often in quite good yield.

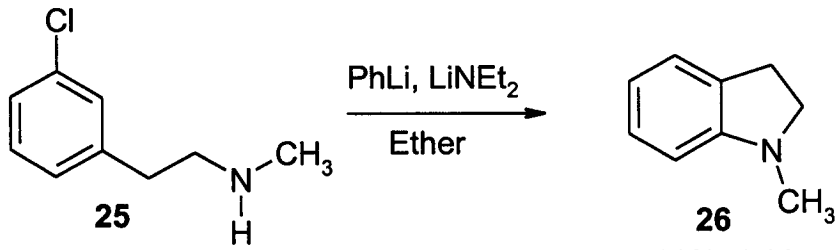


18 **24**

88% yield

Scheme 2.5 Preparation of 2-iodo-substituted benzenes via benzyne and iodine ate complex intermediates.

The intramolecular nucloephilic addition to a benzyne intermediate resulting in a ring closure reaction has also been reported.[17] The starting material most often an aryl halide that contains the nucleophilic species in the side chain. When this compound is treated with a strong base such as lithium diethylamide, the benzyne intermediate is generated, and the intramolecular nucleophilic addition can occur.[17] An example of this reaction is shown in Scheme 2.6.

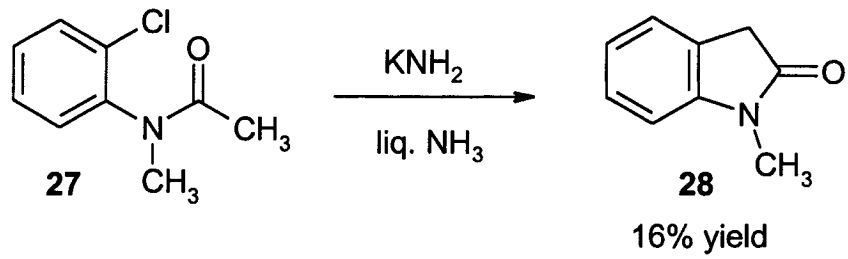


25 **26**

88% yield

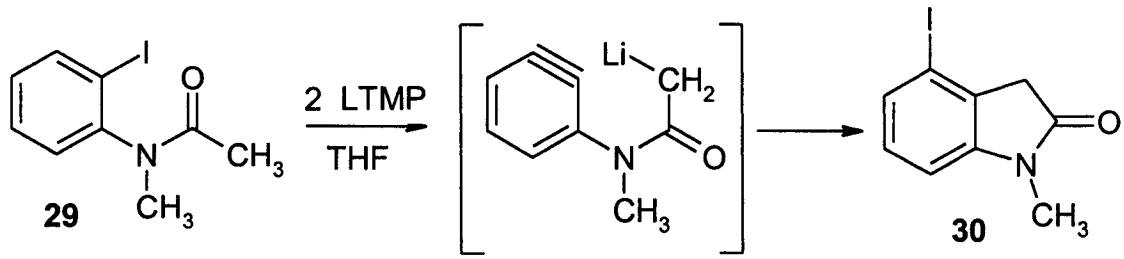
Scheme 2.6 Intramolecular trapping of a benzyne intermediate.[17]

A related example using potassium amide in liquid ammonia as the base to generate both the amide anion and the benzyne is shown below.[17]



Scheme 2.7 Intramolecular benzyne reaction using potassium amide in liquid ammonia as base.

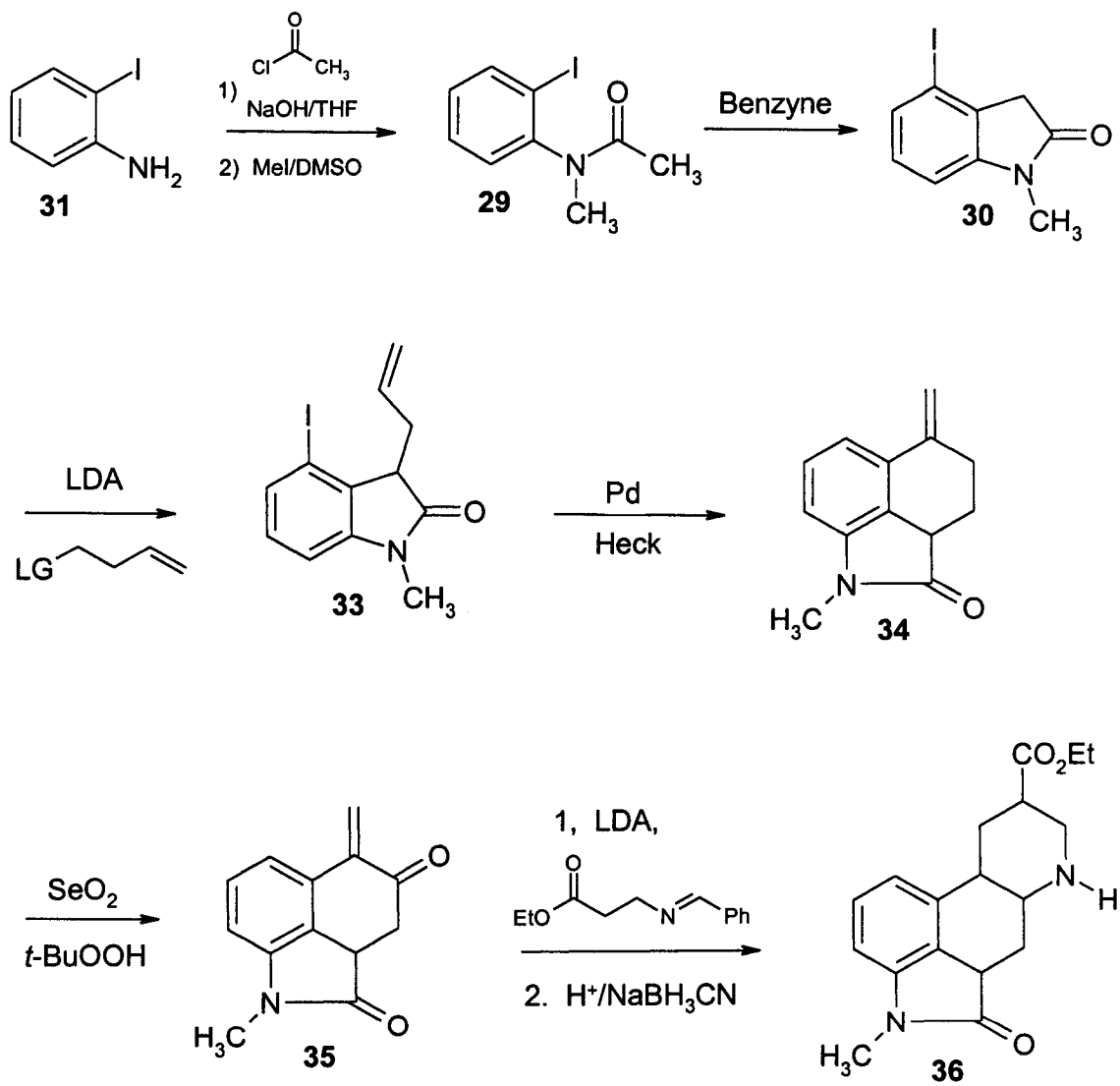
We used the above examples as models, and briefly studied the reaction of *N*-(2-iodophenyl)-*N*-methylamide **29** with LTMP at -40°C in THF. The major product, reported in unpublished results[21] was the tri-substituted benzene **30** in about 20-30% yield.



Scheme 2.8 Intramolecular benzyne reaction with LTMP.

2.2 Proposed Benzyne Route.

The formation of **30** suggested to us the possibility of a new and rather short synthesis of the tetracyclic lysergine ring core starting with **31**. This is outlined in Scheme 2.9.



Scheme 2.9 Proposed route to LSD derivative **36**.

Once the cyclized product **30** is formed, the addition of an olefinic tail, followed by an intramolecular palladium-catalyzed Heck cyclization would complete the synthesis of the desired core tricyclic structure **34**. Structure **34** differs from the Kornfeld Ketone **5** by the replacement of the ketone with a methylene group, and the indoline group is replaced by an oxindole ring. The proposed transformation of **34** into the lysergine ring system is discussed later in the thesis.

2.3 Results and Discussion.

2.3.1 Initial results of the benzyne reaction.

The first step towards our target **34** from commercially available starting materials was the acylation of the primary amine **31** with acetyl chloride. This reaction proceeded in 92% yield at 0°C in a 1:1 mixture of THF and water in the presence of excess NaOH. The product, *N*-(2-iodophenyl)-acetamide **32** was then treated with MeI in DMSO to yield **29**, an off-white solid in 77% overall yield. The readily identifiable acetyl peak at 1.53 ppm, a sharp N-methyl peak at 2.96 ppm, in addition to the clear aromatic proton pattern of a 1,2-disubstituted benzene were used to confirm structural identity.

It was then proposed that **30** be generated via the intramolecular benzyne reaction of **29**. Compound **29** was added to a solution of LTMP in THF at -40°C and was warmed slowly over 4 hours to room temperature. The TLC showed several spots, which after careful chromatograpy, **30** was isolated in 20%

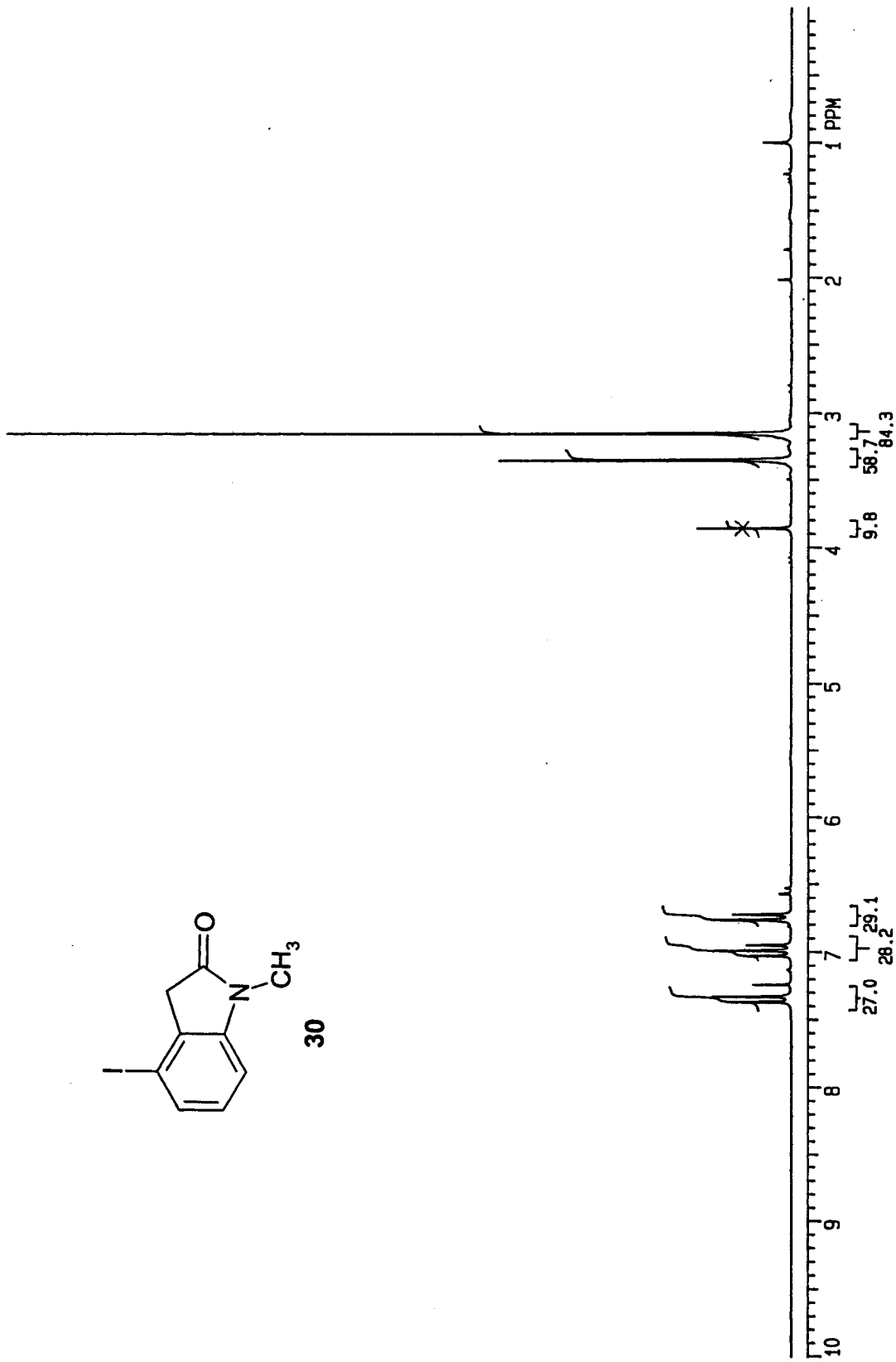
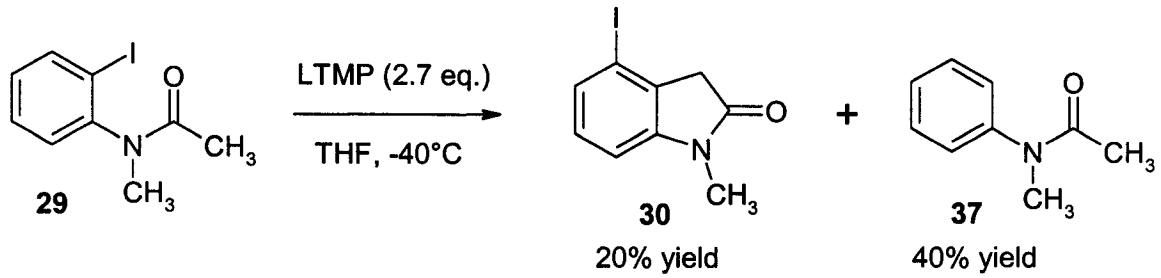


Figure 2.1 ^{1}H NMR spectrum of 4-ioco-1-methyl-1,3-dihydro-indol-2-one **30.**

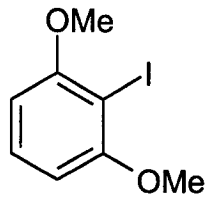
adjusted yield, along with 40% of dehalogenated starting material **37**. This reaction confirmed that **30** could be formed via the intramolecular benzyne reaction, however, yields were dissappointing.



Scheme 2.10 Preparation of 4-iodo-1-methyl-1,3-dihydro-indol-2-one **30**.

The ^{1}H NMR of **30** (Figure 2.1) indicated a loss of the acetyl singlet and a new singlet at 3.9 ppm with an integration value of 2 protons. This combined with a loss of one aromatic proton and a decrease in chemical shift of the hydrogen ortho to iodine provided the confirming evidence to support the formation of **30**.

The presence of a large amount of the non-halogenated starting material **37** suggested that the source of electrophilic iodine was **29** itself. This led us to propose that the yields of **30** could be improved upon the addition of an additional electrophilic iodine source. 2,6-Dimethoxyiodobenzene **38** was used as the iodine additive since it cannot participate in benzyne formation itself.[20] The use of 2,6-dimethoxyiodobenze as a source of positive iodine to trap the aryllithium species formed in the addition of an R-Li to benzyne was studied extensively by Dr. Helmi H. Hussain (a Post-Doctoral Fellow), while he was a member of our group.

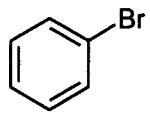
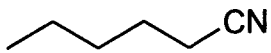
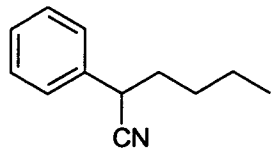
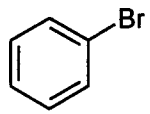
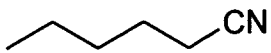
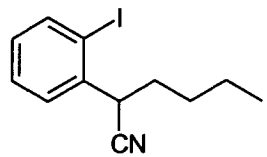
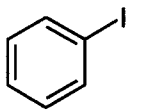
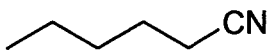
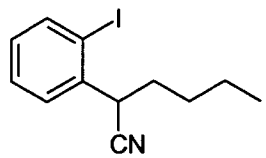
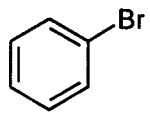
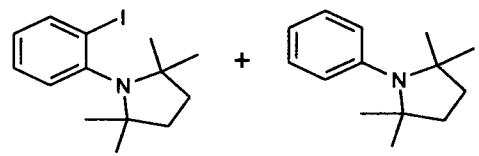
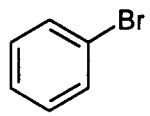
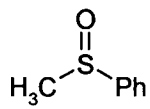
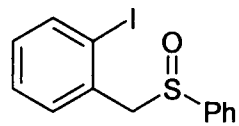
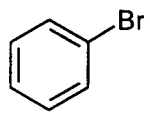
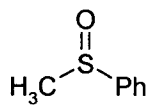
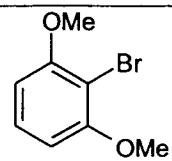
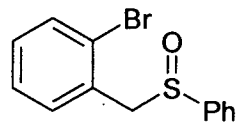


38

He found that when **38** was added to the reaction mixutre in small excess, the reaction products favoured 2-iodo substitution in increased yields. In each of the different reactions, LTMP was used as the base (2.5 eq.), and the reaction was warmed slowly from -40°C to room temperature over three hours. Table 2.1 includes a summary of the experiments completed by Dr. Hussain.

A comparison between entries 1 and 2 shows that in the presence of **38**, the 2-iodo-substituted product is formed in 51% yield, whereas without **38**, the expected nucleophilic reaction is the only product. Entry 3 demonstrates that when iodobenzene **18** is used as the source of electrophilic iodine, the 2-iodo-substitued product is formed, but in reduced yields of 37%. Confirming evidence to support the benefits of the addition of **38** as the electrophilic iodine source can be found in entry 4. Here, bromobenzene is used as the substrate in the presence of excess LTMP, which acts as both the nucleophile and the base. In this reaction, the benzyne is trapped by LTMP and forms the TMP-substituted product as before with iodobenzene (Scheme 2.3), but, in the presence of **38**, the 2-iodo-substituted product is the major reaction product in 71% yield. This evidence confirms that in the presence of **38**, 2-iodo-substituted benzyne products are the major products of the reaction.

Table 2.1 Results of Benzyne Reactions using LTMP as Base and 2,6-dimethoxybenzene **38** as the Iodine Source.

Entry	Substrate	Nucleophile	2,6-dimethyoxy-benzene **38**	Product(s) Identified	Yield (%)
1			No		56
2			Yes		51
3			No		37
4		LTMP	Yes		71, 11
5			Yes		76
6					45

It is interesting to note that in addition to 2,6-dimethoxyiodobenzene being an excellent source of electophilic iodine, the corresponding bromo-derivative was also successful. A comparison of entries 5 and 6 using the same substrate and nucleophile indicate that both the 2-iodo and 2-bromo products are formed in 76% and 45% yields respectively. The difference in yields can be attributed to the reactivity of the halogens themselves.

With the supporting evidence for **38** as the ideal electrophilic iodine source in hand, several reactions were attempted to improve the yield of the desired product **30** without success. Upon quenching of these reactions, the only products observed, were unreacted starting materials and dehalogenated starting material. A variety of modifications to the reaction conditions were attempted, but no significant quantities of the desired 4-iodo-oxindole **30** were formed.

In addition to the 2-iodo substituted starting material **32**, both the bromo- **39**, and the chloro- **41** compounds were prepared. We expected that the change of iodine to bromine to chlorine should facilitate benzyne formation, and possibly increase the yield of the cyclization reaction and subsequent trapping with positive iodine species.

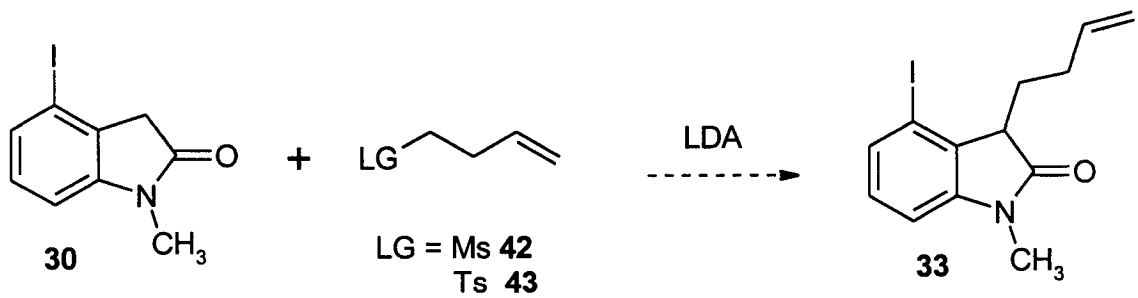
N-(2-bromo-phenyl)-*N*-methylacetamide **40** was isolated as a yellow oil in 74% yield giving an acetyl chemical shift of 1.06 ppm, and the N-methyl shift at 2.96 ppm. *N*-(2-chloro-phenyl)-*N*-methylacetamide **27**, also a yellow oil in 93% yield having an acetyl chemical shift of 1.73 ppm and the N-methyl shift at 3.12 ppm. Unfortunately when these compounds were treated with LTMP in THF at -40°C, the ^{1}H NMR of the crude reaction mixtures did not indicate cyclized

product. Other changes such as: temperature; time of reaction; order of addition of reagents; rate of addition of reagents; and temperature during quenching were also determined to have no positive effect on this reaction.

2.3.2 Alternate route in the prepararation 3-but-3-enyl-1-methyl-1,3-dihydro-indol-2-one 33.

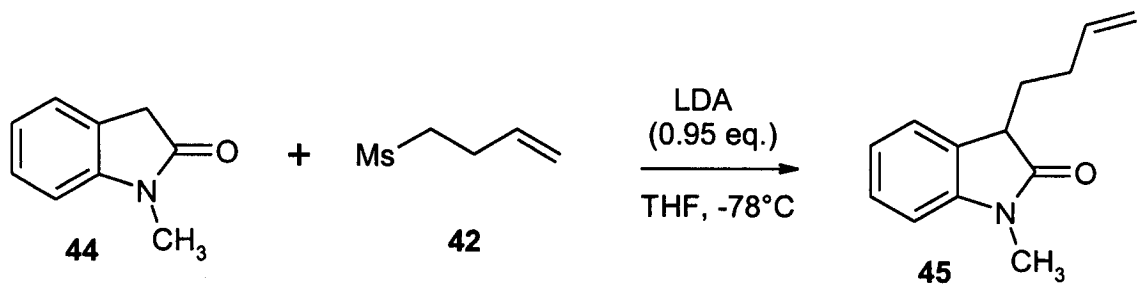
We were quite disappointed by our inability to improve on the initially reported yield of 4-iodo-oxindole **30**. This was only the first step in a series of reactions needed to reach the desired ring core **34**. If the benzyne cyclization reaction could be improved, the next step would be coupling with a 4-carbon unit containing a leaving group at C-1, and a C-3, C-4 double bond to obtain **33**. This could be accomplished in one of two ways.

The first method would be to attach the olefinic tail via an S_N2 reaction between either the mesylate **42** or tosylate **43** protected 3-buten-1-ol and the lithio enolate of **30**.



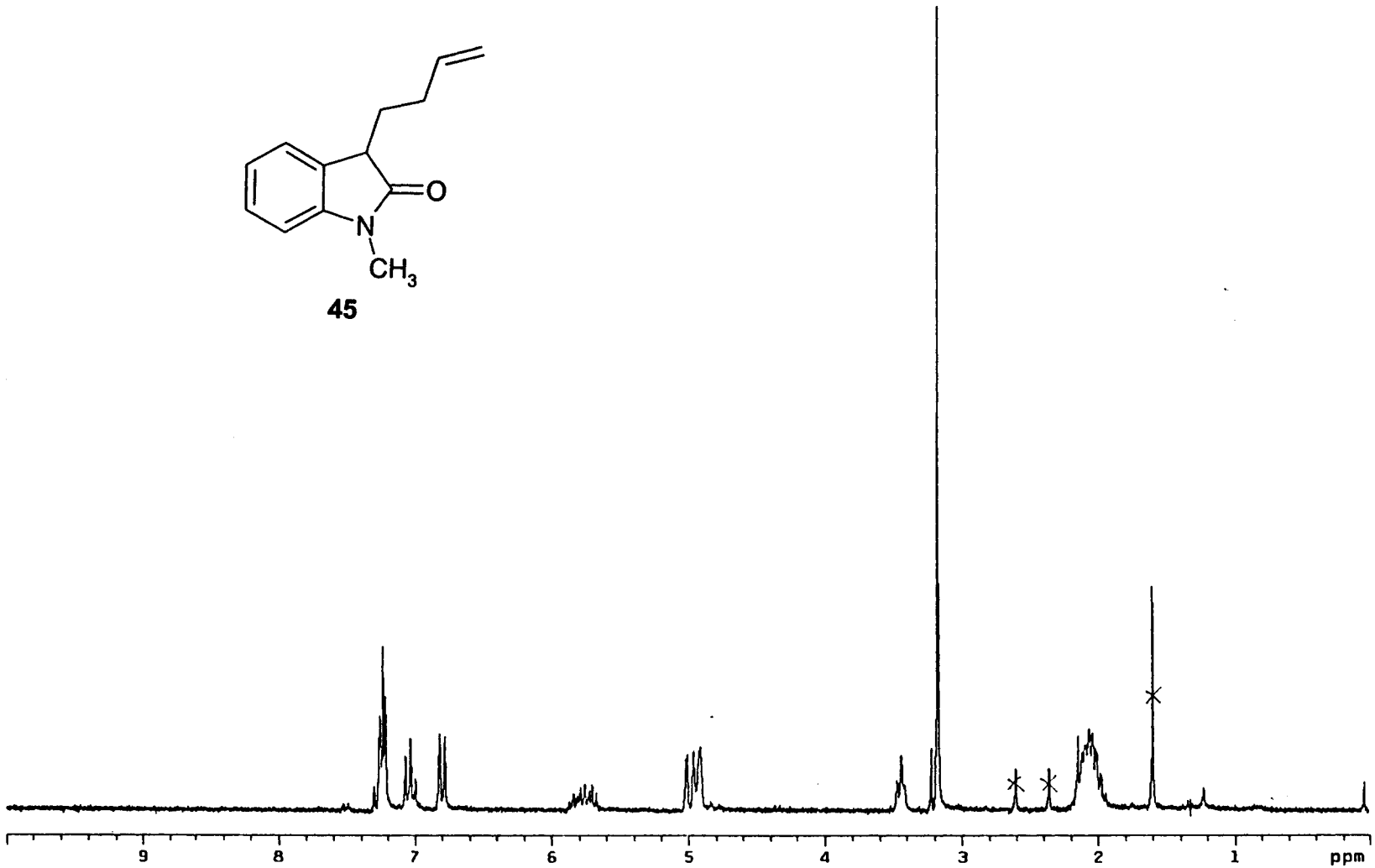
Scheme 2.11 Proposed S_N2 addition of olefinic tail to **30**.

Since the starting material **30** was not easily available via the benzyne route, the model reaction compound N-methyl oxindole **44** was used to determine the ideal conditions for the C-C coupling reaction.



Scheme 2.12 Preparation of 3-but-3-enyl-1-methyl-1,3-dihydro-indol-2-one **45**.

The above coupling reaction of the lithium enolate of **44** with mesolate **42** appeared to be successful as indicated by the ^{1}H NMR of the crude reaction mixture. The key spectroscopic evidence (Figure 2.2) to support the formation of **45** were the chemical shifts of the following protons: two terminal olefinic protons at 5.76 ppm and 5.02 ppm; a multiplet having integration of 4 for the alkyl chain hydrogens at 2.08 ppm; and the presence of a triplet at 3.44 ppm with an integration value of 1 representing the proton at position 3. Unfortunately, attempted purification of the reaction mixture did not yield a pure sample of **45**. Reaction of the enolate of **44** with the tosylate **43** in THF at -78°C to room temperature for 20 hours gave a crude reaction product whose ^{1}H NMR showed no evidence for the formation of **45**. This small success with **44** and **42** led us to believe that this addition would be possible with optimized conditions using halogenated **30** as the starting material.

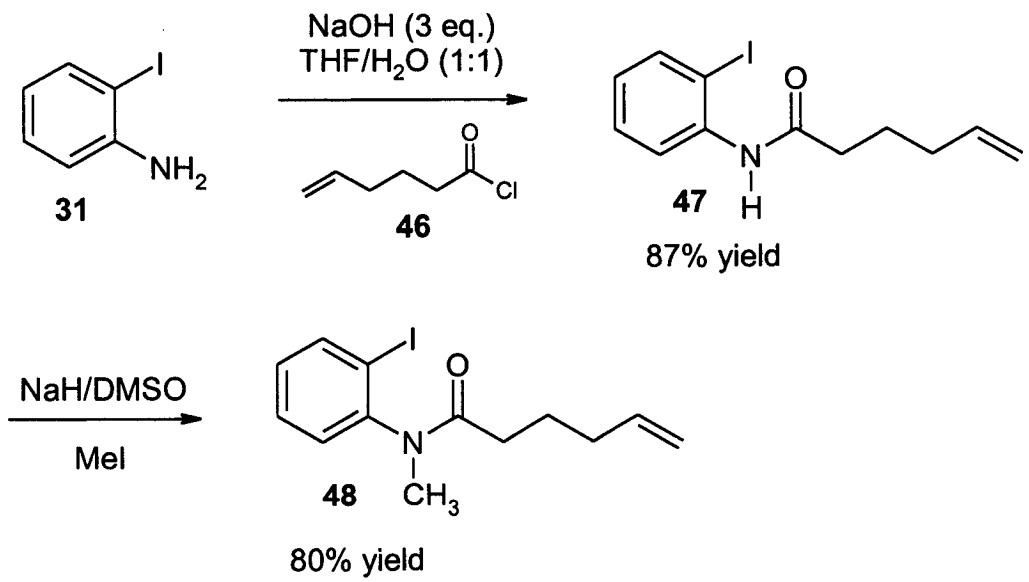


45

Figure 2.2 ^{1}H NMR spectrum of 3-but-3-enyl-1-methyl-1,3-dihydro-indol-2-one **45**.

2.3.3 Benzyne approach to prepare 3-but-3-enyl-1-methyl-1,3-dihydro-indol-2-one 33.

The second approach to **45** would be to assemble all of the required carbon atoms prior to the benzyne cyclization reaction. This could be accomplished by replacing acetyl chloride with the acid chloride of 5-hexenoic acid. The result would provide hex-5-enoic acid (2-iodophenyl)-methylamide **48** as the new benzyne precursor (Figure 2.3 and Figure 2.4). Hex-5-enoic acid (2-iodophenyl)-amide **47** was prepared in 87% yield by adding the acid chloride of hex-5-enoic acid **46** to a mixture of 2-iodoaniline and NaOH pellets in a 1:1 THF/H_2O solution. The methylation of **47** with MeI in a mixture of NaH in DMSO afforded **48** in 70% overall yield as orange oil.



Scheme 2.13 Preparation of hex-5-enoic acid (2-iodophenyl)-methylamide **48**.

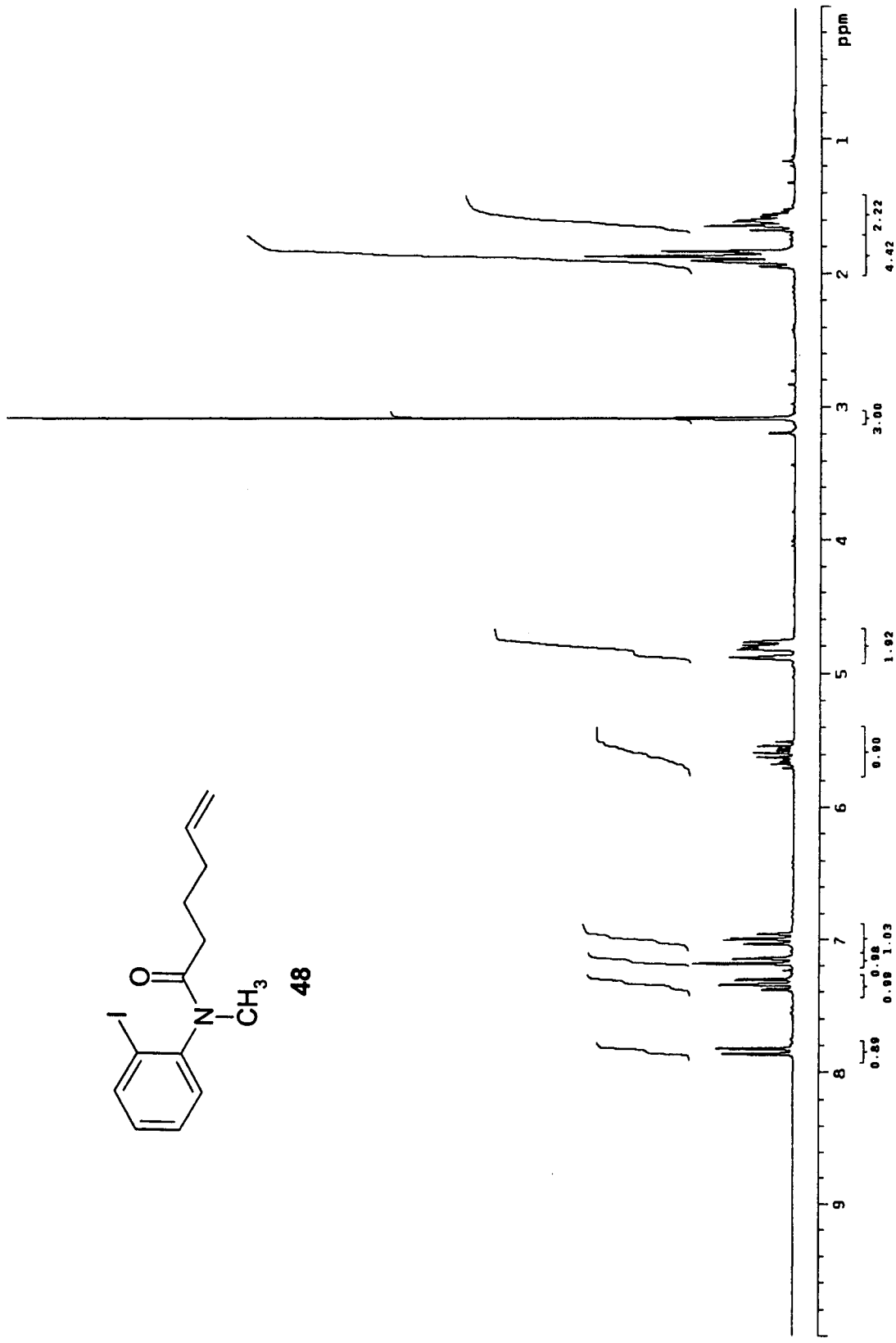


Figure 2.3 ^{1}H NMR spectrum of hex-5-enoic acid (2-iodophenyl)-methylamide **48**.

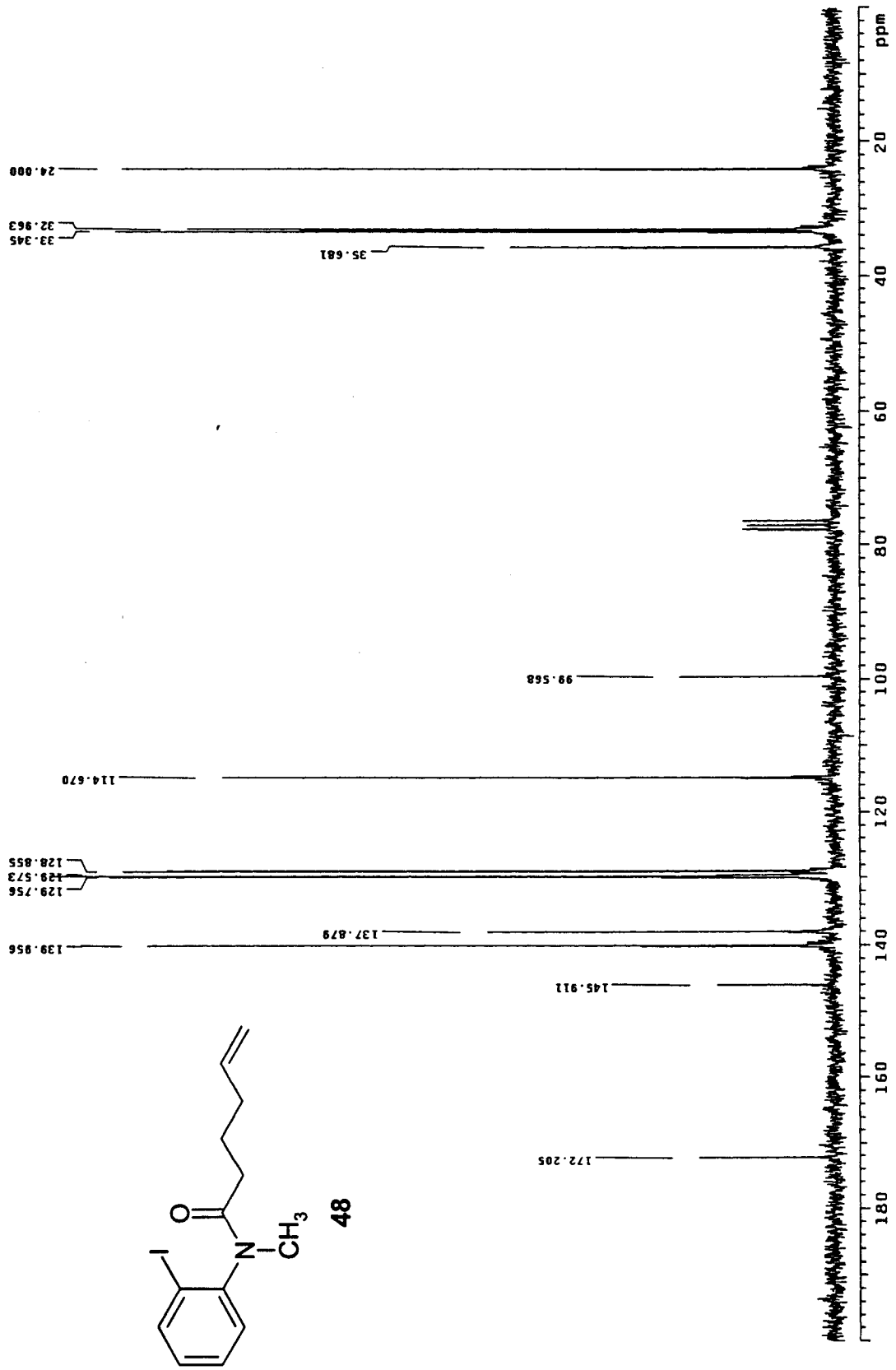
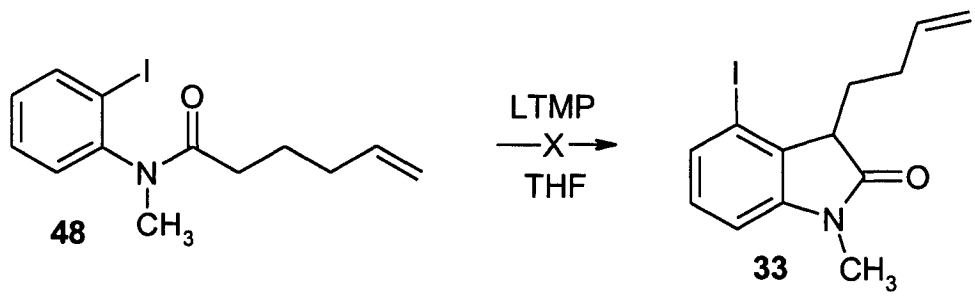


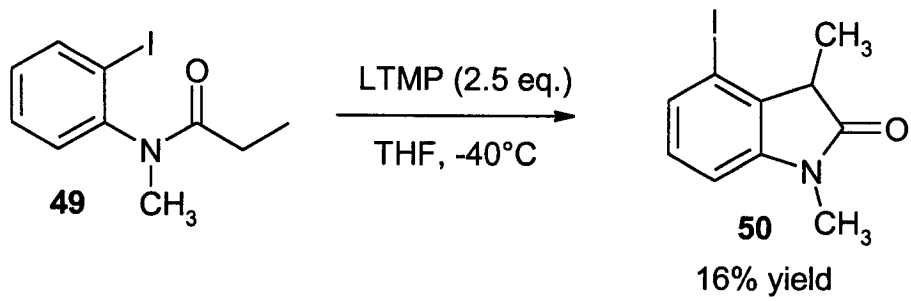
Figure 2.4 ^{13}C NMR spectrum of hex-5-enoic acid (2-iodophenyl)-methylamide **48**.

The generation of benzyne from **48** was attempted many times at -78°C, followed by different protocols of warming to 0°C. Upon quenching of the reaction with saturated ammonium chloride solution, only starting materials were identified in the ^{1}H NMR of the crude material. This indicates that the benzyne intermediate did not form in this case



Scheme 2.14 Attempted benzyne cyclization of hex-5-enoic acid (2-iodophenyl)-methylamide **48**.

These results were surprising, since earlier studies by Eva Puniani,[21] in which *N*-(2-iodophenyl)-*N*-methyl-ethylamide **49** was cyclized under essentially the same conditions. She obtained 4-iodo-1,3-dimethyl-2-methylene-2,3-dihydro-1H-indole **50** in 16% yield. It does not seem plausible that the longer alkyl chain of **48** compared to **49** should have a significant effect upon the progress of this reaction.

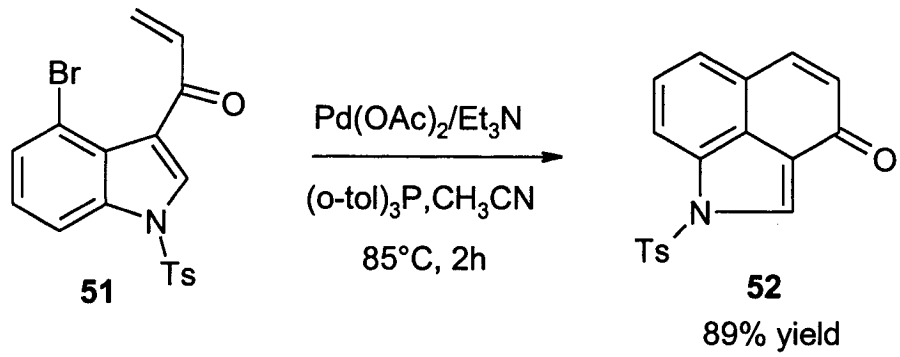


Scheme 2.15 Preparation of 3-but-3-enyl-1-methyl-1,3-dihydro-indol-2-one **50**.

As a result of the failure to complete the key benzyne cyclization step forming **33**, we did not proceed to the planned Heck cyclization. However, literature provides several examples[22-27] of compounds similar in structure to suggest that the intramolecular Heck cyclization of **33** to **34** would be successful.

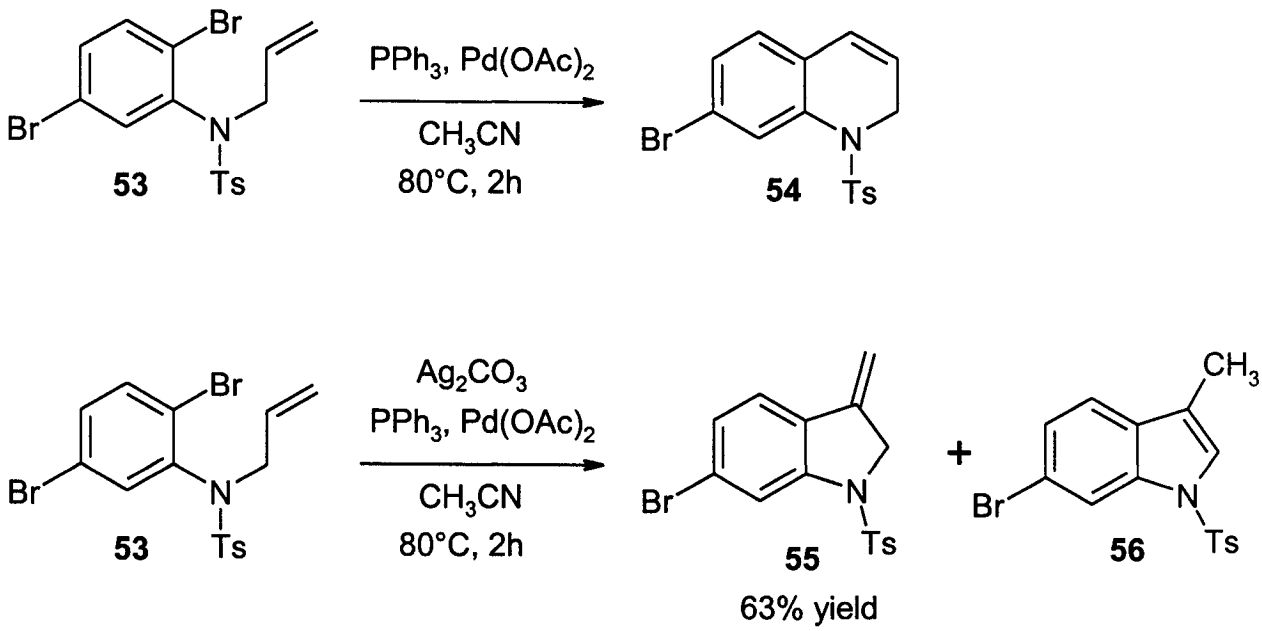
2.4 Literature Evidence to Complete Synthesis of Target 34.

Hegedus *et al.*,[22] published a series of palladium-catalyzed reactions specifically aimed at the synthesis of tricyclic indoles. A prime example of these studies is in the catalyzed cyclization of **51** to **52** in Scheme 2.17.[22] In this reaction, ring C is formed as the only product with an internal methylene bond.



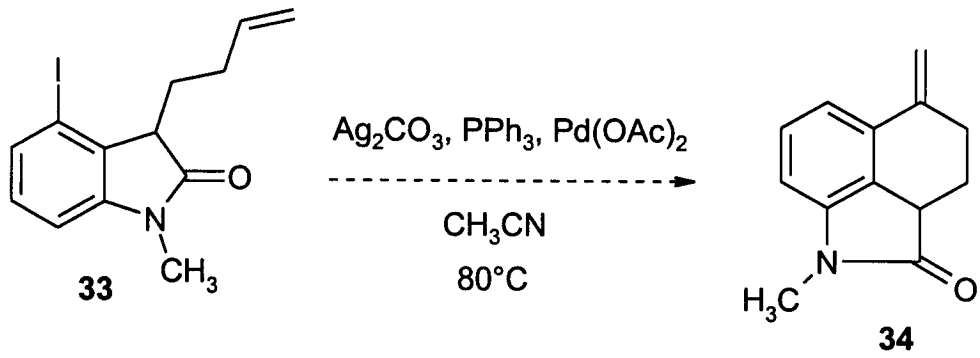
Scheme 2.16 Palladium-catalyzed intramolecular ring closing reaction.

However, for our purposes, we were more interested in obtaining an exo versus an endo methylene bond. This would provide us with an externally active site whereupon ring D could be built. One example that can be found illustrating the synthesis of an exocyclic methylene was published by A. Elder and D. Rich in 1999.[27] They demonstrated that in the absence of silver salt Ag_2CO_3, the product formed would be **54**, the endocyclic methylene product as expected. However, upon the addition of Ag_2CO_3, this reaction yielded a five-membered ring with an exo double bond **55** in moderate yields as the major product. Due to the reaction temperatures required for the bromide to be activated, a minor isomerization product **56** was also identified.



Scheme 2.17 Ring closure with an exo-cyclic methylene product.

In general, Heck-type cyclizations to form five-member rings are typically faster than the formation of six-member rings.[23] However, once the five-member ring is generated, there is migration of the exocyclic methylene resulting in the formation of the six-member ring as outlined in Scheme 2.16 and Scheme 2.17. However, Scheme 2.17 also illustrates that one can minimize this migration with the addition of silver salts[27] as illustrated in the reaction of **53** to **55**, thus enabling the exocyclic methylene to be isolated as the major product. Keeping these findings in mind, one could postulate the following reaction conditions to afford our desired product **34**.



Scheme 2.18 Proposed palladium-catalyzed ring closure of **33**.

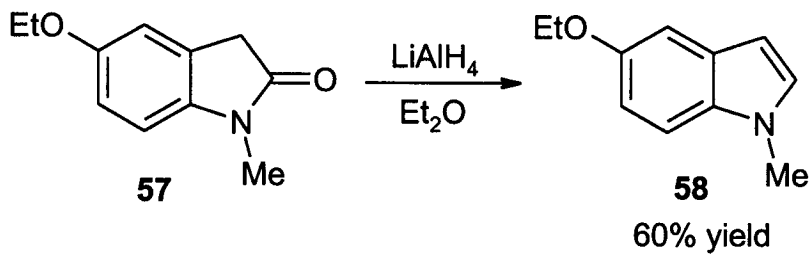
It is reasonable to expect that the six-member exocyclic methylene **34** would form faster than a seven-member ring. The addition of silver salts should minimize the rearrangement to the 7-membered ring.

2.5 Conclusions Regarding the Benzyne Route to Compound 34

The tricyclic compound **34** appeared to us as a key intermediate in a novel lysergine ring system synthesis. On paper, based on our preliminary benzyne chemistry results, it could be synthesized in two or three steps from the readily available amides **48** and **29** respectively. Unfortunately, we were not able to improve or duplicate the yields for the conversion of **29** to **30**, nor accomplish the conversion of **48** to **33**.

We were not overly concerned by the presence of the *N*-CH_3 group in our studies. Other nitrogen protecting groups such as benzyl or BOC could have been employed if **33** had been obtained. The oxidation state of ring B was not

expected to pose a problem since this can be corrected at a late stage in the synthesis by the reduction of the oxindole to the necessary indole oxidation state via lithium aluminum hydride.[28] This reduction is reported to proceed in good yields in the case of N-substituted oxindoles (Scheme 2.19).



57 **58**

60% yield

Scheme 2.19 Reduction of oxindole **57** to indole **58**.

2.6 Experimental

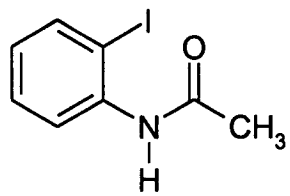
GENERAL: All reactions were carried out in oven-dried glassware that had been cooled in a dessicator. Melting points were determined by the use of a Thomas Hoover Capillary melting point apparatus and they were uncorrected. Infrared spectra were obtained by preparing compounds as thin films (chloroform, methylene chloride) on a sodium chloride plate, or as part of a KBr pellet. The data was recorded by a Bomem-Michelson MB-100 FT/IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained from either a Bruker AMX-300 spectrometer or a Varian Gemini-200 spectrometer, using the specified solvent. Spectra were referenced to residual protonated solvents, but are reported relative to TMS=0.00 ppm. The multiplicities of the NMR signals were reported with the following abbreviations: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of triplets (dt), triplet of doublets (td), quartet (q) and multiplet (m). Low and high resolution mass spectra were performed using EI technique.

All starting materials were used as received from commercial sources. Solvents used for reactions and chromatographic purifications were routinely distilled prior to use. Methylene chloride was dried by distillation from calcium hydride. THF was dried over sodium with benzophenone as an indicator. Triethylamine was distilled from CaH_2 and stored over KOH pellets. 2,2,6,6-Tetramethylpiperidine was used directly from commercial sources and KOH was added to keep the solution dry. Ethanol was distilled from calcium hydride and stored over molecular sieves. Hexanes and ethyl acetate was crudely distilled to

remove residual impurities using a rotoevaporator. BuLi solutions were routinely titrated at 0°C in dry THF with diphenyl acetic acid to a pale yellow end-point. Reactions were monitored by thin-layer chromatography (TLC) using Kieselgel 60 F_{254} pre-coated 0.25 mm thick alumina-backed plates. Visualization was facilitated by UV irradiation followed by charring the TLC plate in a molybdate solution. The molybdate solution was prepared by dissolving ammonium molybdate (25 g) and cerric (IV) sulfate (10 g) in distilled water (900 mL) and sulfuric acid (100 mL). The term chromatography refers to flash column chromatography performed using silica gel of 270-400 mesh .

PREPARATION OF *N*-(2-IODO-PHENYL)-ACETAMIDE 32

A mixture of 2-iodoaniline **31** (3.00 g, 13.8 mmol) and NaOH pellets (2.6 eq.) was stirred at 0°C in a 1:1 solution of THF/H_2O (10 mL) until the NaOH became soluble. Acetyl chloride (0.95 mL, 16.8 mmol) was added to the resulting solution at 0°C and the mixture was stirred while warming to room temperature for 2-3 hours. The reaction mixture was quenched by adding saturated ammonium chloride solution (10 mL) and extracted with ether (3 x 25 mL). The combined extracts were washed with saturated ammonium chloride solution (25 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording a light brown crystalline solid. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded unreacted 2-iodoaniline **31** (1.14 g), and **32** (2.05 g, 92% adjusted yield) as colourless needles.



32

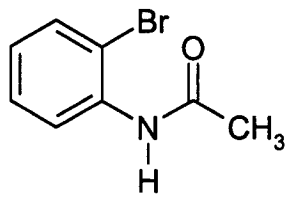
C_8H_8INO MW=261.06 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 8.06 (d, 1H), 7.72 (d, 1H), 7.30 (s, NH), 7.26 (t, 1H), 6.76 (t, 1H), 2.16 (s, 3H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ (ppm): 168.6, 138.8, 138.3, 129.0, 126.3, 123.2, 91.3, 24.6.

PREPARATION OF *N*-(2-BROMO-PHENYL)-ACETAMIDE 39

N-(2-bromo-phenyl)-acetamide **39** was prepared from 2-bromoaniline (3.2 mL, 29.4 mmol), using NaOH (2.6 eq), acetyl chloride (2.0 mL, 35.4 mmol) and 1:1 solution of THF/H_2O (30 mL) following the same procedure as **32**. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded starting material (1.40 g), and **39** (3.98g, 89% adjusted yield) as a white solid.



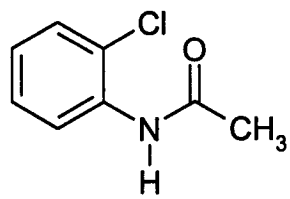
39

C_8H_8BrNO MW=214.07 g/mole)

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 8.31 (d, 1H), 7.42 (s, NH), 7.50 (d, 1H), 7.29 (t, 1H), 6.95 (t, 1H), 2.24 (s, 3H).

PREPARATION OF *N*-(2-CHLORO-PHENYL)-ACETAMIDE 41

N-(2-chloro-phenyl)-acetamide **41** was prepared from 2-chloroaniline (2.6 mL, 24.7 mmol), using NaOH (2.6 eq), acetyl chloride (1.8 mL, 35.4 mmol) and 1:1 solution of THF/H_2O (10 mL) following the same procedure as **32**. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **41** (3.86 g, 92% yield) as a white solid.



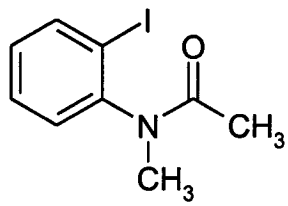
41

C_8H_8ClNO MW=169.61 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 8.18 (d, 1H), 7.80 (s, NH), 7.28 (d, 1H), 7.16 (t, 1H), 6.96 (t, 1H), 2.16 (s, 3H)

PREPARATION OF *N*-(2-IODO-PHENYL)-*N*-METHYL-ACETAMIDE 29

A suspension of sodium hydride (228 mg, 9.5 mmol) in DMSO (10 mL) was stirred under a nitrogen atmosphere at 0°C for 10 minutes. To this was added a solution of *N*-(2-iodo-phenyl)-acetamide **32** (2.07 g, 7.9 mmol) in DMSO (10 mL) dropwise followed by two DMSO washes (5 mL) to ensure complete addition. Methyl iodide (1.0 mL, 16.1 mmol) was added and the reaction was warmed to room temperature and stirred for 2-3 hours. The reaction was worked up by pouring into cold distilled water (150 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with saturated ammonium chloride solution (2 x 50 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording a brown solid. Chromatography of the crude (1:1 hexanes/ethyl acetate) yielded **29** (1.98 g, 91%) as an off-white solid.



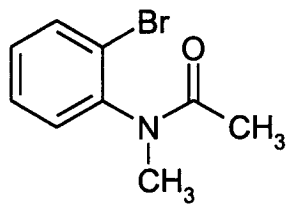
29

$C_9H_{10}INO$ MW=275.09 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.85 (dd, 1H), 7.37 (td, 1H), 7.20(dd, 1H), 7.01 (td, 1H), 3.07 (s, 3H), 1.71 (s, 3H).

PREPARATION OF *N*-(2-BROMO-PHENYL)-*N*-METHYL-ACETAMIDE 40

N-(2-bromo-phenyl)-*N*-methyl-acetamide **40** was prepared from *N*-(2-bromo-phenyl)-acetamide **39** (3.98 g, 18.6 mmol), using sodium hydride (2 eq.) and methyl iodide (2.3 mL, 36.9 mmol) in DMSO (40 mL) following the same procedure as **32**. The crude product was dissolved in ethyl acetate (50 mL) and washed with additional brine solution (3 x 50 mL) to ensure complete removal of DMSO, dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording **40** (3.13 g, 74% yield) of yellow oil as a pure product.



40

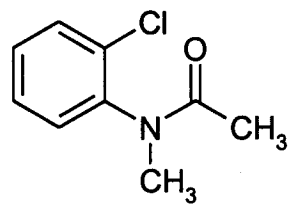
$C_9H_{10}BrNO$ MW=228.10 g/mole)

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.47 (dd, 1H), 7.13 (m, 3H), 2.96 (s, 3H), 1.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ (ppm): 170.0, 142.9, 133.7, 129.7, 129.5, 129.0, 123.1, 35.4, 21.9.

PREPARATION OF *N*-(2-CHLORO-PHENYL)-*N*-METHYL-ACETAMIDE 27

N-(2-chloro-phenyl)-*N*-methyl-acetamide **27** was prepared from *N*-(2-chloro-phenyl)-acetamide **41** (3.86 g, 22.7 mmol), using sodium hydride (1.2 eq.) and methyl iodide (1.8 mL, 28.9 mmol) in DMSO (100 mL) following the same procedure as **32** affording an orange oil. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **41** (1.17 g) unreacted starting material, and 1.53 g, 53% adjusted yield of **27** as pale yellow oil.



27

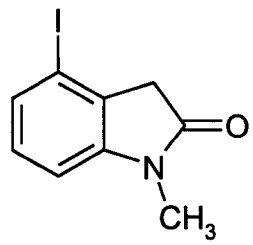
C_9H_9ClNO MW= 183.64 g/mole

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 7.44 (m 1H), 7.25 (m, 3H), 3.12 (s, 3H), 1.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 170.4, 141.4, 132.7, 130.5, 129.4 (2C), 128.8, 35.5, 21.7.

PREPARATION OF 4-IODO-1-METHYL-1,3-DIHYDRO-INDOL-2-ONE 30

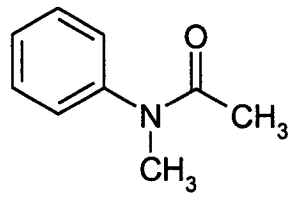
t-BuLi (1.70 mL, 2.9 mmol, 2.7 eq.) was added dropwise to a solution of tetramethylpiperidine (0.80 mL, 3.0 mmol, 2.8 eq) in dry THF (3 mL) under a nitrogen atmosphere at -40°C. This solution was stirred for 15 minutes. A solution of **29** (0.297 g, 1.08 mmol) in THF (10 mL) was added to the LTMP solution followed by two THF washes (5 mL) to ensure complete addition. The reaction was warmed to room temperature and stirred for 4 hours. The reaction mixture was cooled to -40°C, and quenched by the addition of saturated ammonium chloride solution (8 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated ammonium chloride solution (30 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording a brown crude oil. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **30** (0.032 g, 18%) as a pale yellow oil and *N*-methyl-*N*-phenyl acetamide **37** (0.064 g, 40%) as the major product. The ^{1}H NMR spectrum was identical to that obtained earlier by H.Hussain, R. Reddy and E. Puniani.



30

C_9H_8INO MW=273.07 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.36 (d, 1H), 7.00 (t, 1H), 6.74 (d, 1H), 3.38 (s, 2H), 3.16 (s, 3H).



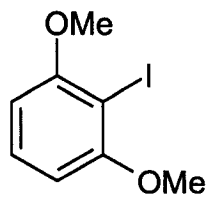
37

$C_9H_{11}NO$ MW=149.19 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.34 (m, 3H), 7.12 (d, 2H), 3.22 (s, 3H), 1.82 (s, 3H).

PREPARATION OF 2,6-DIMETHOXY-IODOBENZENE 38

t-BuLi (1.1 eq.) was added over 10 minutes to a stirred solution of 1,3-dimethoxyiodobenzene (2.0 mL, 15.3 mmol) in dry THF (8 mL) under a nitrogen atmosphere at -78°C. The solution was allowed to warm to 0°C and then recooled to -78°C prior to the addition of a solution of iodine (1.2 eq.) in THF (20 mL) via an addition funnel over 30 minutes. The solution was warmed slowly to 0°C, quenched with a solution of sodium thiosulfate (1 g in 25 mL water) and extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with saturated ammonium chloride solution (50 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording a yellow solid. The crude was recrystallized from benzene and yielded **38** (2.771 g, 69% yield) as a beige solid. The ^{1}H NMR spectrum was identical to that obtained earlier by H. Hussain.



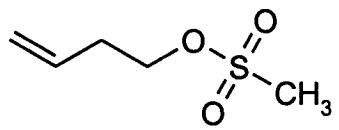
38

$C_8H_9IO_2$ MW=264.06 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.24 (t, 1H), 6.50 (d, 2H), 3.85 (s, 6H).

PREPARATION OF METHANESULFONIC ACID BUT-3-ENYL ESTER 42

Methanesulfunyl chloride (0.24 mL, 3.10 mmol) was added to a stirred solution of 3-buten-1-ol (0.24 mL, 2.79 mmol) in diethyl ether (1 mL) at room temperature. To this was added slowly triethylamine (1.16 mL, 8.32 mmol) and immediately the reaction turned yellow. After 5 minutes, the reaction mixture was quenched by pouring into distilled water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered through cotton, and concentrated *in vacuo* affording **42** (0.198 g, 47% yield) of orange oil as a pure product.



42

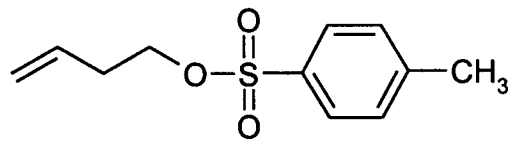
$C_3H_{10}SO_3$ MW=150.20 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 5.52 (m, 1H), 5.08 (d, 1H), 5.02 (s, 1H), 4.52 (t, 2H), 2.89 (s, 3H), 2.39 (q, 2H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ(ppm): 132.5, 118.3, 69.1, 37.2, 33.2.

PREPARATION OF TOLUENE-4-SULFONIC ACID BUT-3-ENYL ESTER 43

p-Toluenesulfonyl chloride (0.588g, 3.08 mmol) was added to a stirred solution of 3-buten-1-ol (0.24 mL, 2.79 mmol) in diethyl ether at room temperature. To this was added slowly pyridine (0.67 mL, 8.28 mmol) and immediately the reaction turned yellow. After 5 minutes, the reaction mixture was quenched by pouring into distilled water (20 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered through cotton, and concentrated *in vacuo* affording a white solid. The crude was dissolved in 30 mL of diethyl ether and washed with 10% hydrochloride solution (3 x 10 mL) to ensure complete removal of pyridine, dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording **43** (0.226 g, 36% yield) of pale yellow oil as a pure product.



43

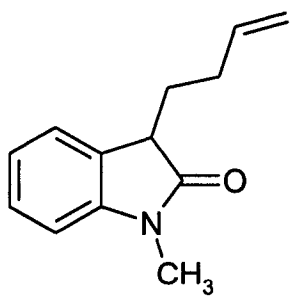
$C_{11}H_{14}SO_3$ MW=226.30 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.95 (d, 2H), 7.26 (d, 2H), 5.60 (m, 1H), 4.95 d(1H), 4.93 (s, 1H), 3.98 (t, 2H), 2.41 (s, 3H), 2.30 (q, 2H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ(ppm): 144.6, 132.6, 132.2, 129.6, 127.5, 117.8, 69.2, 32.8, 21.2.

PREPARATION OF 3-BUT-3-ENYL-1-METHYL-1,3-DIHYDRO-INDOL-2-ONE 45

n-BuLi (1.50 mL, 2.63 mmol) was added to a solution of diisopropylamine (360 μL, 2.57 mmol) in THF (5 mL) at –78°C. The resulting solution was stirred for 15 minutes at –78°C and a solution of amide **44** (0.403 g, 2.74 mmol) in THF (20 mL) was added dropwise. The resulting mixture was stirred for 30 minutes at –78°C and a solution of methanesulfonic acid but-3-enyl ester **42** (0.198 g, 2.74 mmol) in THF (5 mL) was added dropwise. After 1.5 hours at –78°C, the mixture was warmed to room temperature, and stirring was continued for 18 additional hours. The reaction mixture was quenched by addition of distilled water (20 mL). The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic extracts were washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo*. Chromatography of the crude (7:3 hexanes/ethyl acetate) yielded **45** as a partially pure product.



45

$C_{13}H_{15}NO$ MW=201.29 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.24 (t, 2H), 7.04 (t, 1H), 6.80 (d, 1H), 5.76 (m, 1H), 5.02 (s, 1H), 4.92 (m, 1H), 3.44 (t, 1H), 3.18 (s, 3H), 2.08 (m, 4H).

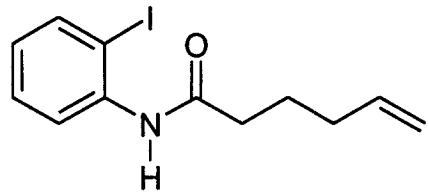
PREPARATION OF HEX-5-ENOIC ACID CHLORIDE 46

Oxalyl chloride (5.5 mL, 63.0 mmol) was added dropwise to a solution of hex-5-enoic acid (2.00 mL, 16.8 mmol) in methylene chloride (3 mL) under a nitrogen atmosphere. This was followed by the addition of 1 drop of DMF while stirring at room temperature for 2 hours. Benzene (3 mL) was added and the solvents were removed *in vacuo* affording a brown oil used immediately in the preparation of hex-5-enoic acid (2-iodophenyl)-amide **47**.

PREPARATION OF HEX-5-ENOIC ACID (2-IODOPHENYL)-AMIDE 47

A 1:1 solution of THF/H_2O (22 mL) was added to a mixture of 2-iodoaniline **31** (3.10 g, 14.1 mmol) and NaOH pellets (3.1 eq.) and stirred at 0°C until all the NaOH dissolved. To this was added a solution of **46** in THF (5 mL) at 0°C the mixture was stirred while warming to room temperature for 2-3 hours. The reaction was quenched by adding saturated ammonium chloride solution (10 mL) and extracted with ether (3 x 30 mL). The combined extracts were washed with saturated ammonium chloride solution (30 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo*. The crude light brown crystalline solid was dissolved in 60 mL of methylene chloride and extracted with 10% sodium carbonate solution (3 x 25 mL) and 10% HCl solution (3 x 25 mL). The neutral organic extract was dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording **47** (3.28 g, 87% adjusted yield) as pure product. The acidic aqueous extracts were

neutralized and extracted with methylene chloride (3 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated *in vacuo* to afford 0.467 g of unreacted starting material **31**.



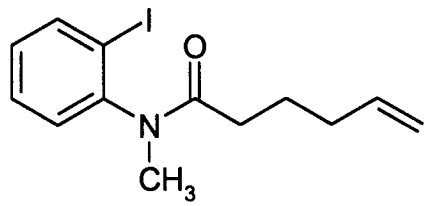
47

$C_{12}H_{14}INO$ MW=315.15 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 8.19 (d, 1H), 7.74 (d, 1H), 7.42 (s, NH), 7.30 (t, 1H), 6.81 (t, 1H), 5.78 (m, 1H), 5.04 (d, 1H), 5.02 (s, 1H), 2.42 (t, 2H), 2.14 (q, 2H), 1.84 (m, 2H).

PREPARATION OF HEX-5-ENOIC ACID (2-IODOPHENYL)-METHYLAMIDE 48

A suspension of 60% dispersion sodium hydride (0.268 g, 6.70 mmol) in DMSO (10 mL) was stirred under a nitrogen atmosphere at 0°C for 10 minutes. To this was added a solution of **47** (1.53 g, 4.86 mmol) in DMSO (10 mL) dropwise followed by two DMSO washes (5 mL) to ensure complete addition. Methyl iodide (0.40 mL, 6.4 mmol) was added and the reaction was warmed to room temperature and stirred for 2-3 hours. The reaction mixture was quenched by pouring into cold distilled water (150 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic extracts were washed with saturated ammonium chloride solution (2 x 50 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording an oily crude mixture. Chromatography of the crude (1:1 hexanes/ethyl acetate) yielded **48** (1.28 g, 80%) as an orange oil.



48

$C_{13}H_{15}INO$ MW=328.18 g/mole

MS m/e (% rel. int.): 329 (1.4), 275 (6.5), 233 (83.4), 202 (100), 148 (20.5), 77 (12.8).

HRMS Calculated: 329.0278 g/mole

Found: 329.0237 g/mole

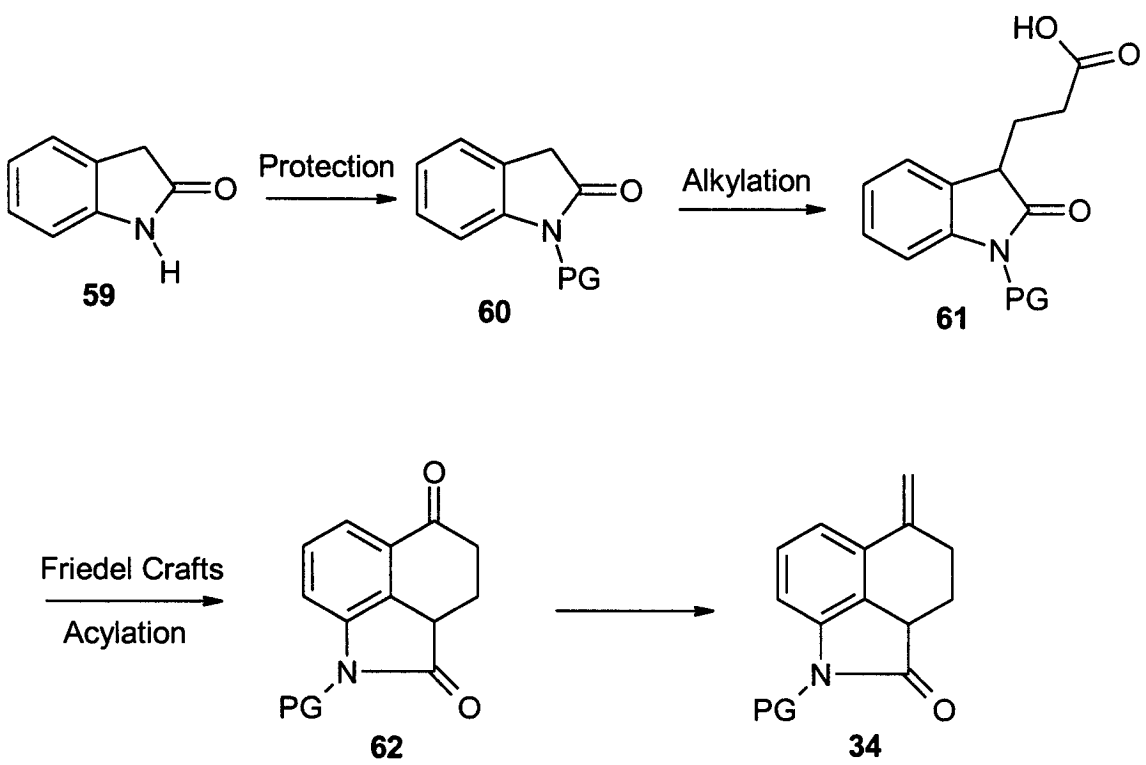
^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.85 (dd, 1H), 7.35 (td, 1H), 7.17 (dd, 1H), 6.09 (td, 1H), 5.60 (m, 1H), 4.89 (s, 1H), 4.79 (m, 1H), 3.09 (s, 3H), 1.93 (m, 4H), 1.61 (m, 2H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ(ppm): 145.9, 140.0, 137.9, 129.8, 129.6, 128.9, 114.7, 99.6, 35.7, 33.3, 33.0, 24.0.

Chapter 3 – The Oxindole Approach

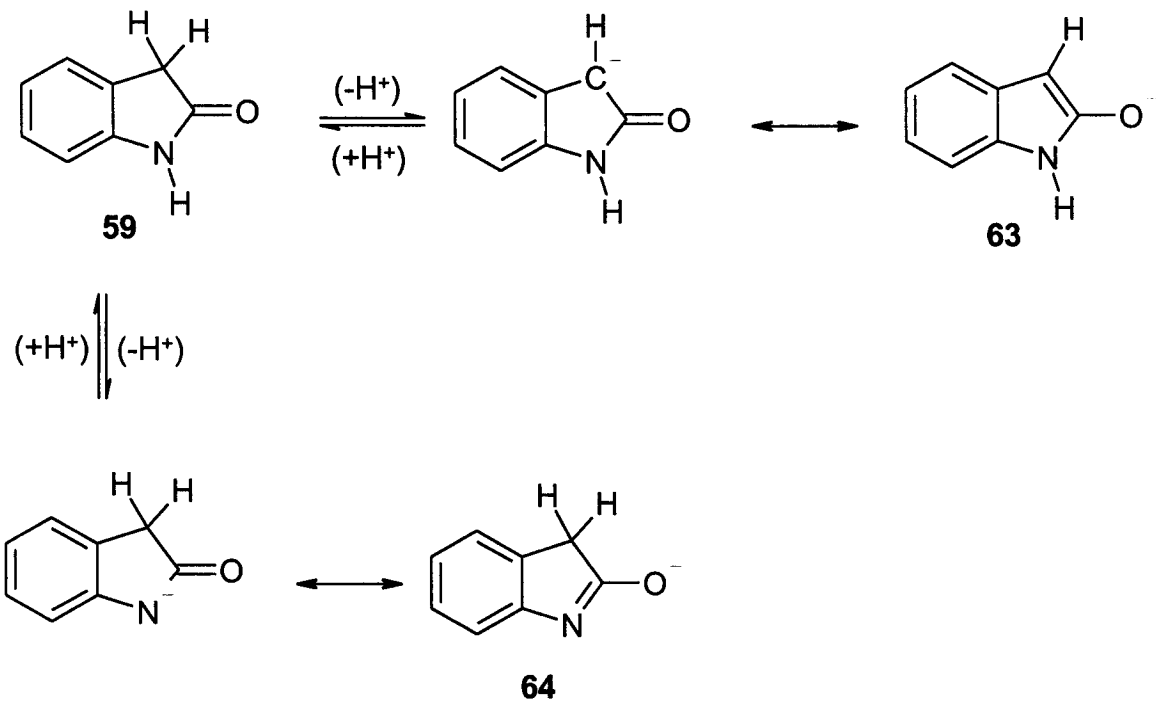
3.1 Background and Proposed Synthetic Approach

Based on the results of the previous section, we decided to explore the possibility of synthesizing the key intermediate **34** via an alternate route starting with oxindole. The proposed scheme is shown below in Scheme 3.1.



Scheme 3.1 Propsed route to **34** via oxindole **59**.

The protection of the amide is necessary before the alkylation step due to the similarities in pKa of the amide and the protons in position 3.[29] In a 1991 study of anion stabilization energies, F.G. Bordwell and H.E. Fried reported that the deprotonation of **59** in DMSO could give either a carbanion-enolate ion **63**, or a nitranion **64**, as illustrated in Scheme 3.2.[29] The pKa value reported for oxindole was 18.2, however, under the same conditions, pKa for *N*-methyl oxindole was 18.5.[29] This small difference in pKa between position 3 and the amide provides evidence that protection of the amide is necessary such that selective alkylation can occur at position 3.



59 **63** **64**

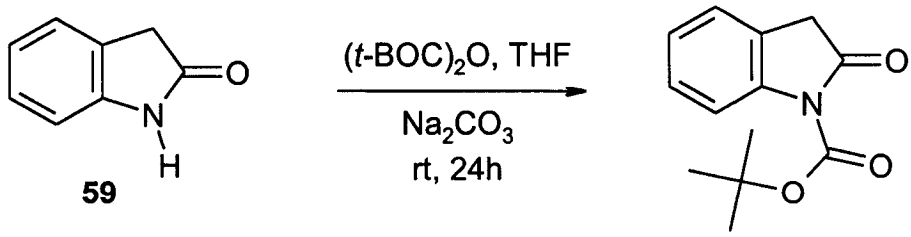
Scheme 3.2 Deprotonation of oxindole **59** in DMSO.

A review of the literature provides several possibilities for the protection of the secondary amides in general,[30] but the information for oxindoles was limited.[31] The successful protection of oxindoles is possible by treating with Na_2CO_3 in THF at room temperature and acetic anhydride, benzyloxocarbonyl anhydride, or BOC-anhydride affording 74%, 67% and 76% yields respectively.[31] Under LDA alkylation conditions, the BOC protection group would be moderately stable in comparison with the other protecting groups.

3.2 Results and Discussion

3.2.1 Initial results using oxindole 59 as starting material.

In our hands, we used BOC-anhydride to effectively protect the amide of oxindole in 73% isolated yield of pure product **65**. Purification was accomplished by column chromatography using 2% ethyl acetate in hexane to first elute the unreacted BOC-anhydride, followed by increasing the polarity to 20% ethyl acetate in hexanes to afford **65** as a pale pink solid.

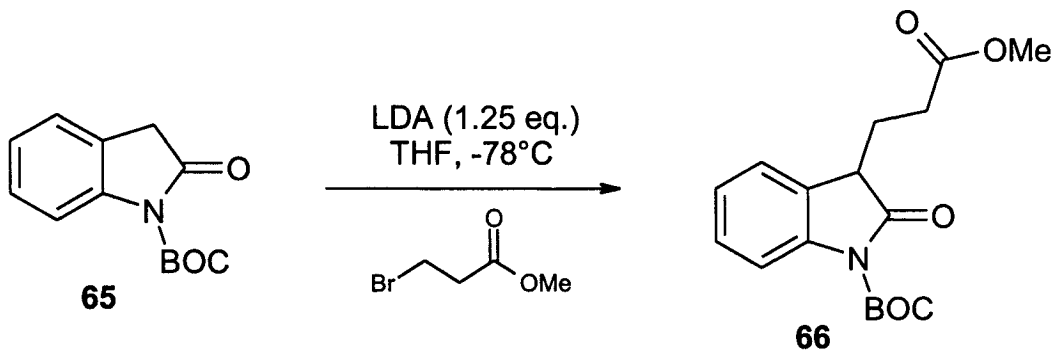


59 **65**
73% yield

Scheme 3.3 BOC-protection of oxindole **59**.

The ^{1}H NMR spectrum confirmed the disappearance of the NH proton at 10.25 ppm, with the addition of a strong singlet at 1.62 ppm having an integration value of 9 for the *t*-butyl group. The chemical shifts of the protons at position C-2 were unchanged at 3.44 ppm.

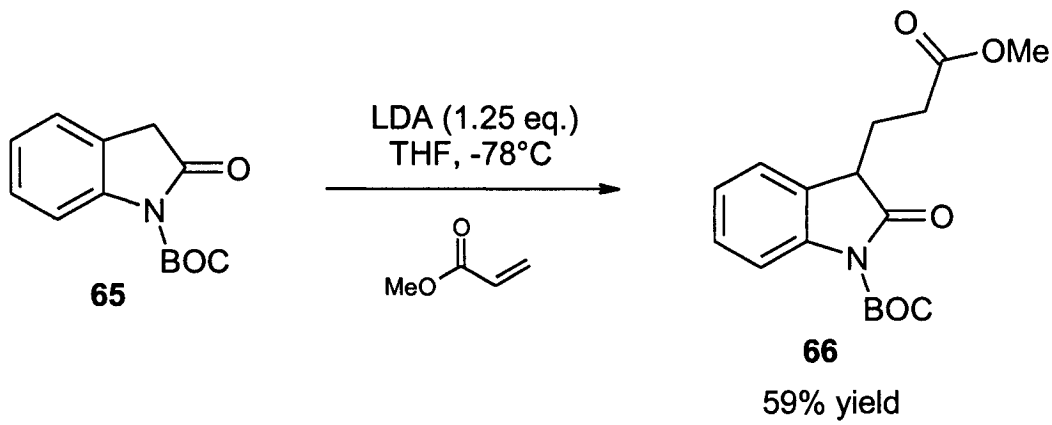
Once **65** was in hand, we attempted to alkylate position 3 via two different reactions. The first being a S_N2 reaction with methyl-3-bromopropionate, and the second a Michael Addition with methyl acrylate.



Scheme 3.4 First alkylation attempt of BOC-oxindole **65** via S_N2.

The lithio derivative of **65** was generated in THF at -78°C. Methyl-3-bromoproprionate was added and the reaction mixture was warmed from -78°C to room temperature after 2 hours. Stirring was continued for an 18 additional hours. TLC evidence showed the development of a new spot in addition to unreacted starting material. Column chromatography did not yield pure **66**, but the NMR of the partially purified sample showed peaks at 1.60 ppm (*t*-butyl), 3.48 ppm (OMe), a multiplet at 7.30 ppm and a doublet at 7.77 ppm. These peaks are consistent with the desired product, but yields were not determined.

An alternate route involving a Michael Addition of the lithio salt of **65** to methyl acrylate was successful. In the Michael reaction, the mixture was warmed from -78°C to room temperature after 1 hour. Stirring was continued for an additional 20 hours. Chromatography of the crude mixture afforded the desired product **66** in 59% yield based on 45% of recovered BOC-oxindole.



Scheme 3.5 Michael addition to BOC-oxindole **65**.

The structure of **66** was confirmed using both proton (Figure 3.1) and carbon (Figure 3.2) NMR data. The proton spectrum showed peaks as follows: *t*-butyl group at 1.60 ppm; a multiplet with an integrated value of 4 representing the 2-carbon chain at 2.72 ppm; the methoxy peak at 3.58 ppm; a very small triplet at 3.60 ppm for the CH proton at position 3; a mutliplet in the aromatic region at 7.19 ppm; and a doublet at 7.64 ppm representing the proton in position 7. The carbon spectrum confirmed the presence of two carbonl carbons at 172.8 ppm from the BOC ester, and the oxindole carbonyl at 148.9 ppm.

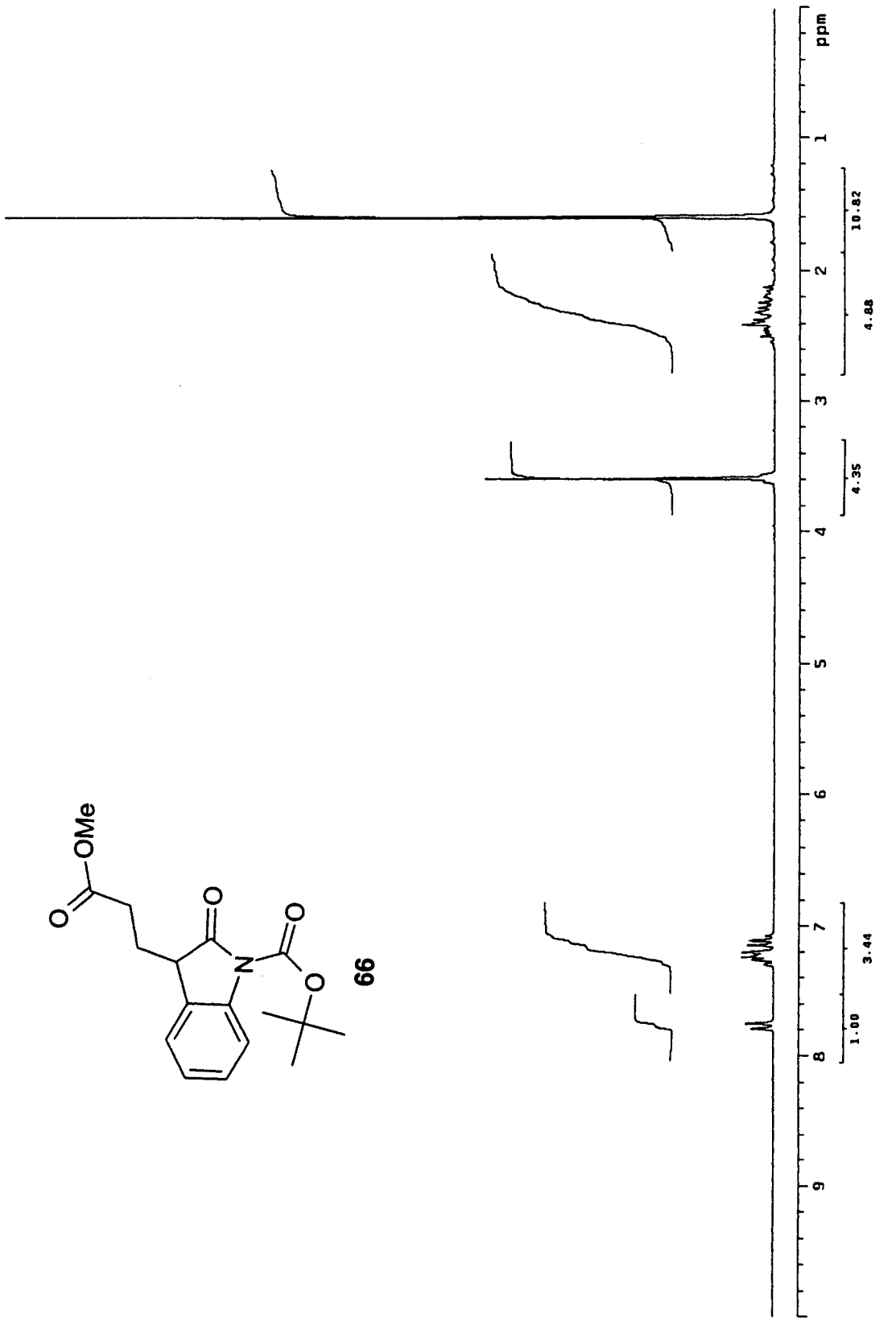


Figure 3.1 ^{1}H NMR spectrum of 3-(2-methoxycarbonyl-ethyl)-*N*-(*tert*-butoxycarbonyl)indol-2-one **66**.

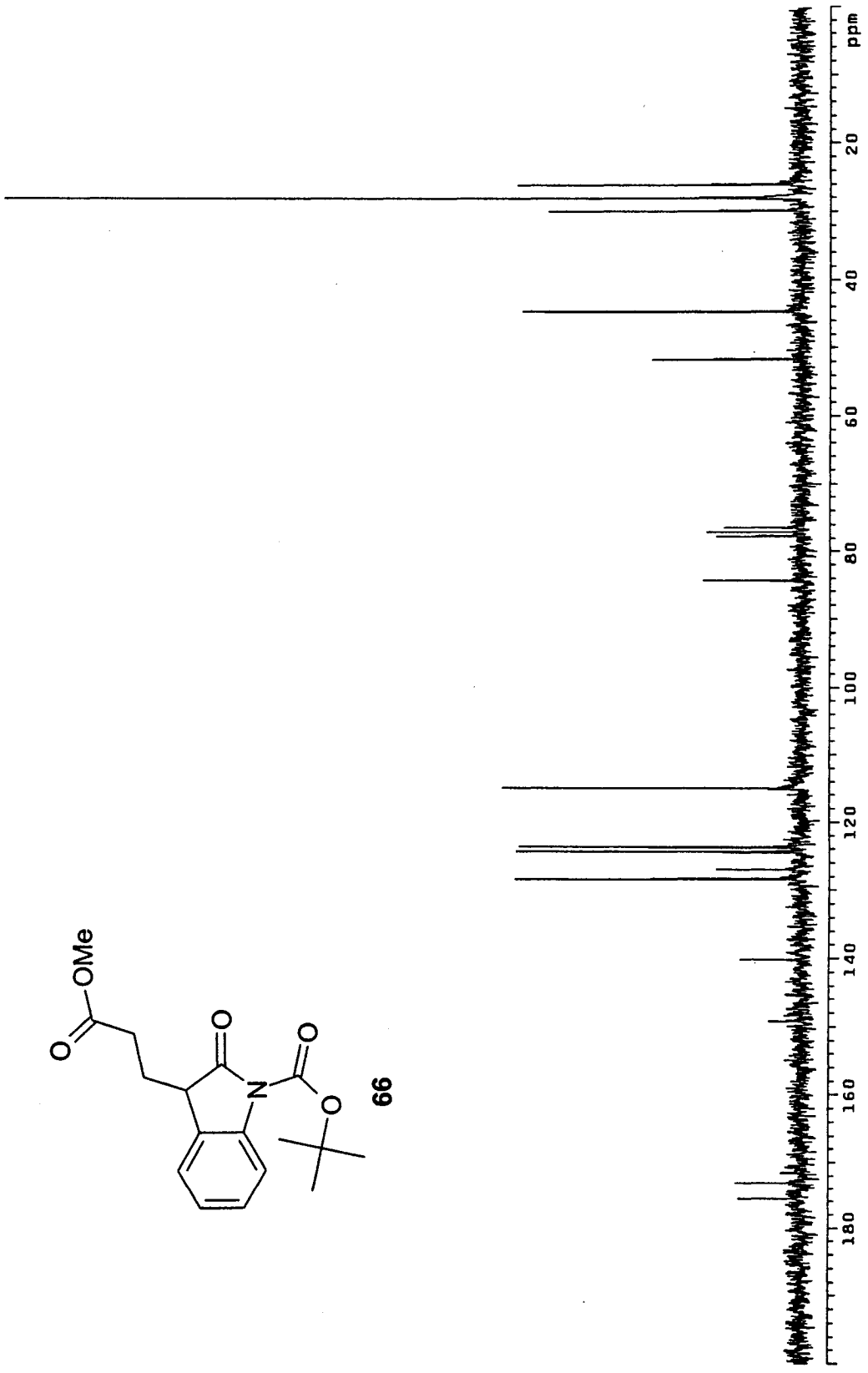
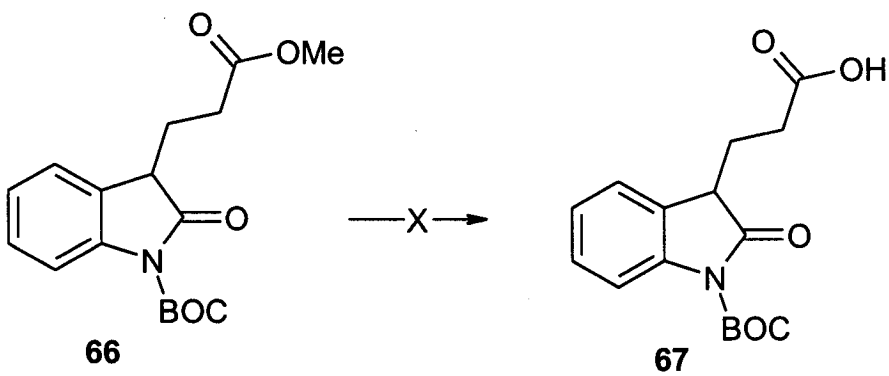


Figure 3.2 ^{13}C NMR spectrum of 3-(2-methoxycarbonyl-ethyl)-*N*-(*tert*-butoxycarbonyl)indol-2-one **66**.

3.2.2 Efforts in the preparation of acid of BOC-oxindole 67.

The de-esterification reaction of the methyl ester proved to be extremely difficult, in fact, not possible for us. Many reaction conditions were attempted to convert the ester to its corresponding acid **67**, with the hopes that a Friedel Crafts cyclization could be attempted. These are summarized in Table 3.1.



Scheme 3.6 Hydrolysis of ester **66** to acid **67**.

Table 3.1 Attempted reaction conditions to hydrolyze ester **66**.

Entry	Reagent	Solvent	Time and Temperature	Product[a]
1	LiOH (1.0 eq.)	MeOH/THF/H_2O (1:4:1)	rt, 24 h	**66**
2	MeOH/KOH (1 M)		Reflux, 24 h	**66**
3	LiCl (4.3 eq.)	DMF	90-100°C, 52 h	N/A
4	*t*-BuOK (12 e.q)	H_2O	rt, 52 h	N/A
5	NaCN (4.7 eq.)	DMSO	90-100°C, 52 h	N/A
6	$MgBr_2$ (11 eq.) $(Bu_3)_3NHI$ (cat.)	Et_2O	rt, 24 h	**66**
7	HCl (3 M)	THF	90°C, 24 h	N/A
8	10% H_2SO_4	THF	90°C, 24 h	N/A

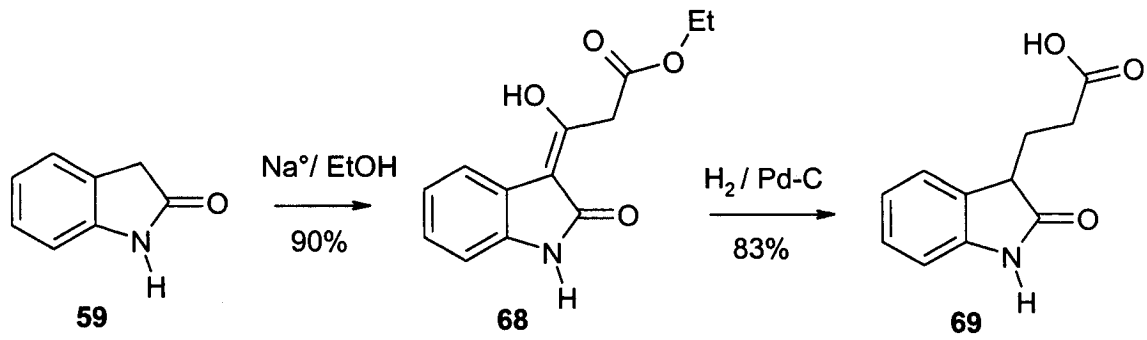
[a] Determined by ^1H NMR, N/A unidentified starting material or products

Since all of these reactions resulted in re-isolation of unreacted starting material, or untraceable mixtures, the ester **66** was clearly not suitable as an intermediate for the preparation of **62** and **34**..

3.2.3 An alternate route to oxindole-3-propionic acid 66.

This led us to another review of the published literature in search of an alternate route to **69**. In 1991, it was shown that indole-3-propionic acid **3** could be converted to oxindole-3-propionic acid **69** in DMSO/HCl with phenol in 30% yield.[32] Further research identified another procedure from different starting

materials in 1953.[33] Julian and Printy demonstrated the conversion of oxindole to oxindole-3-propionic acid in 75% overall yield as follows:



59 68 69

Scheme 3.7 Julian and Printy's route to oxindole-3-propionic acid **69**.

In our hands, the conversion of **59** to **68** was a smooth reaction occurring in 92% yield using freshly distilled anhydrous ethanol. The ester **68** is a fine beige powder with a melting point range of 152-156°C (literature[33] m.p. 155-156°C). Since no spectral data was published we confirmed the structure via NMR and MS. The MS data confirmed the molecular weight of **68** to be 247.08 g/mole. The chemical shifts in the proton spectrum of interest include: the signature ethyl peaks of a triplet at 1.25 ppm and quartet at 4.22 ppm; a singlet for the CH_2 α to the carbonyl at 3.76 ppm; and the NH peak at 8.59 ppm. The OH peak was not visible. The carbon spectrum confirmed the presence of the ethyl ester carbonyl peak at 172.7 ppm, and the oxindole carbonyl peak at 136.4 ppm.

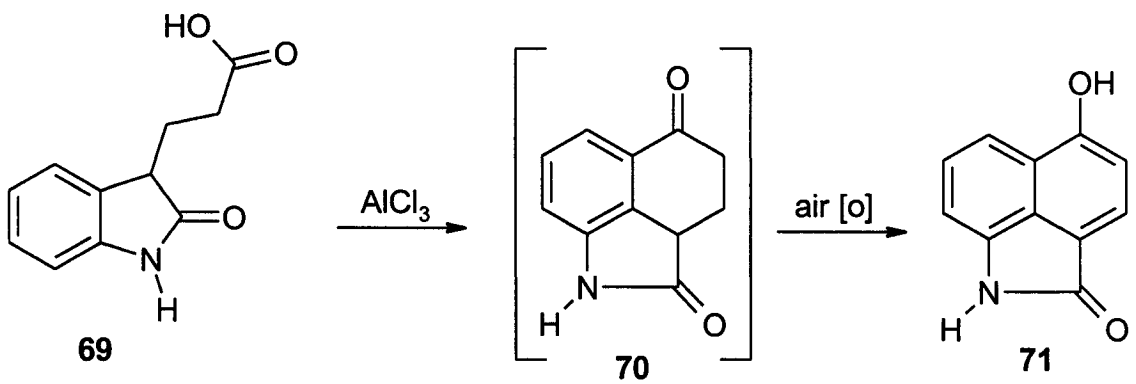
According to the published procedure, **68** was shaken in an atmosphere of hydrogen until two moles was absorbed with palladium-on-charcoal as the catalyst in glacial acetic acid containing a catalytic amount of concentrated sulfuric acid.[33] We followed the procedure with respect to the solvents and the palladium, however, we placed **68** in a Fisher-Porter Apparatus to monitor the uptake of hydrogen. The reaction was placed under pressure to 50psi (3.4 atm), and heated to 70°C for up to 24 hours. We obtained **69** as a white powder-like solid in 36% yield after recrystallization from water. Once again, no spectral data was given in the literature, so a comparison of melting points was the only evidence to confirm the published structure with our own. The reported melting point was 164-168°C, compared to our own of 164-165°C.

Since **69** was to be used as the starting material for the Friedel Crafts reaction, it was important to us to confirm the structure through other experiments. The accurate mass was calculated to be 205.0739 g/mole, and was found to be 205.0726 g/mole. Both ^{1}H and ^{13}C NMR data was gathered, in addition to IR information. The functionalities present were identified in the IR spectrum as follows: the NH band at 3287 cm^{-1}; broad OH at 2933 cm^{-1}; and two carbonyl bands at 1722 cm^{-1} (amide) and 1679 cm^{-1} (acid).

3.3 The Intramolecular Friedel Crafts Reaction.

3.3.1 Background

During a literature search for an intramolecular Friedel Crafts procedure, I was fortunate enough to stumble across some very important references that would change the course of our synthetic focus.[16,34,35] Under the proposed Friedel Crafts conditions, the cyclized product **70** , is rapidly oxidized by air to give a more stable compound **71**. This stability is recognizable since it's structure resembles α-naphthol.



Scheme 3.8 Friedel Crafts cyclization of oxindole-3-propionic acid **69**.

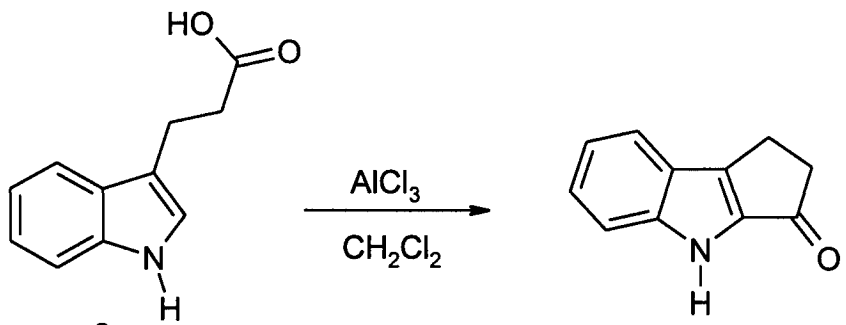
This dead end so to speak, led to the investigation of the two main alternatives found at length in literature.[16] The options would be to complete the desired chemistry at either the indole or indoline oxidation level.

Indole Indoline

Figure 3.3 Structures of Indole and Indoline

3.3.2 Indole oxidation level.

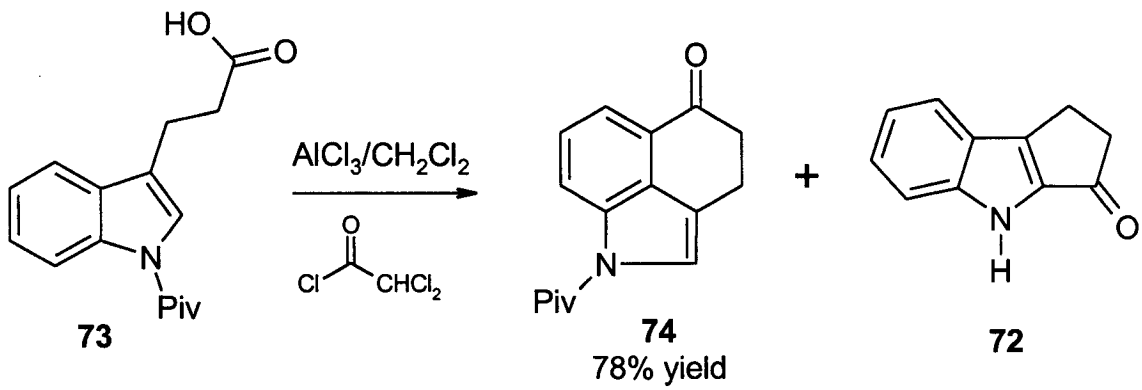
Several attempts to cyclize indole-3-propionic **3** acid via the Friedel Crafts route were reported to be unsuccessful prior to 1994.[16,34,35] In these attempts, substitution occurred at the 2-position rather than the desired 4-position affording **69**, an amorphous white solid as the only product.



3 **72**

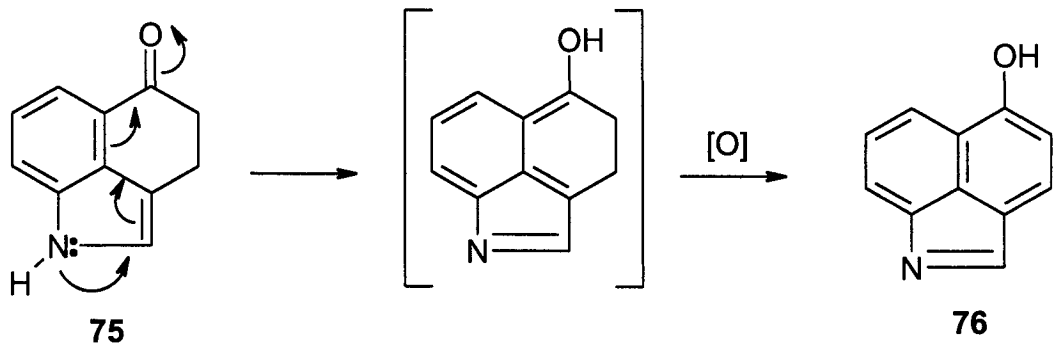
Scheme 3.9 Friedel Crafts cyclization of indole-3-propionic acid **3**.

Thus, it was postulated that by blocking the 2-position, cyclization should occur in the desired 4-position. Attempts to block with a Me group,[16] were moderately successful, however, in 1994 and 1995, Nakatsuka *et al.*[36,37] proposed a viable solution. They found that by protecting the nitrogen with trimethylacetyl chloride, Friedel Crafts cyclization to the desired **74** was possible. Furthermore, the addition of a Lewis Acid complexing agent such as chloroacetyl chloride increased the product ratio of **74**:**72** to 94:6 with an overall 78% yield of **74**.



Scheme 3.10 Nakatsuka's Friedel Crafts cyclization of **73**.

The protection of the nitrogen here serves a two-fold purpose. Firstly, it reduces the likelihood of aromatization of ring C **76** as illistrated in Scheme 3.11, and secondly, it reduces the possibility of electrophilic substitution in the 2-position.[37]

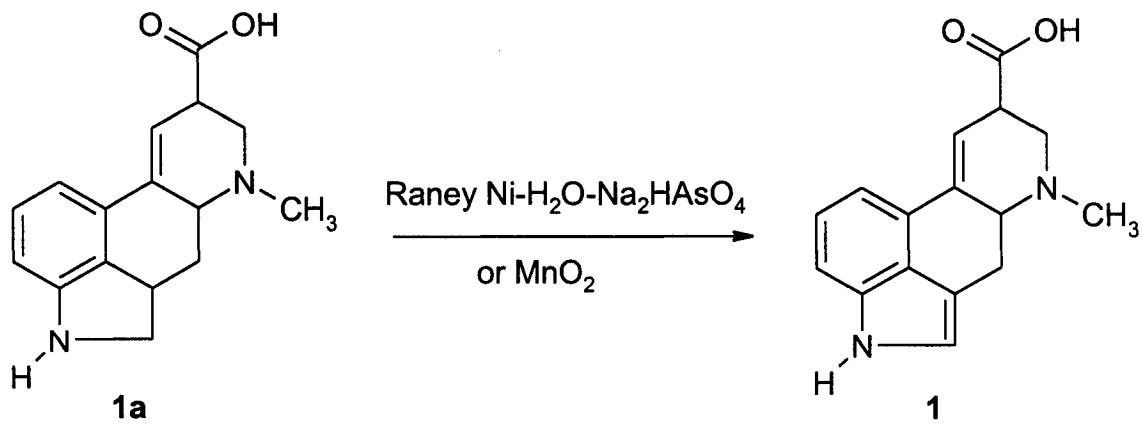


75 **76**

Scheme 3.11 Potential aromatization of Uhle's Ketone[38] **75**.

3.3.3 Indoline oxidation level.

A viable alternative would be to work at the indoline level, similar to Woodward.[2] His synthesis was successful, including the necessary reduction of ring B to the indole level as his final step. The most common methods for the dehydrogenation of ring B are Raney-Nickel or manganese dioxide. These conversions are often in low yields, and with variable results.[39]



1a **1**

Scheme 3.12 Reduction of indoline ring B to lysergic acid **1**.

3.4 Conclusions of the Oxindole Approach

In consideration of the two alternatives presented above, indole and indoline, we favoured the indole approach for the following reasons:

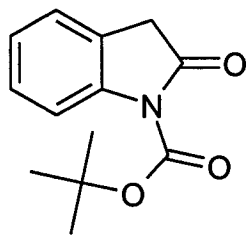
i. Indole-3-propionic acid **3** as the starting material is commercially available.
ii. Conversion to central ketone **74** is short, and reported yields are good.
iii. This route allows for a short synthetic design, potentially without loss of product in the final step.
iv. Woodward[2] and others[9,10,16] have already completed the synthesis at the indoline level.

The details of our approach at the indole level can be found in the next chapter.

3.5 Experimental

PREPARATION OF *N*-(*TERT*-BUTOXYCARBONYL) INDOL-2-ONE 65

THF (250 mL) was added to a mixture of oxindole (5.03 g, 37.8 mmol), sodium carbonate (28.7 g), and BOC-anhydride (25 g, 108.8 mmol, 2.9 eq.). The resulting mixture was stirred under a nitrogen atmosphere for 48 hours. The mixture was filtered through cotton to remove sodium carbonate, and the cotton was rinsed with THF (25 mL). The resulting solution was concentrated *in vacuo* to afford pink oil. The crude products were left open to the air for 24 hours to aid in the isolation of pure products. Chromatography of the crude (98:2 hexanes/ethyl acetate) afforded unreacted BOC-anhydride followed by increased polarity of elution solvent (8:2 hexanes/ethyl acetate) to yield **65** (6.42 g, 73% yield) as a pale pink solid.



65

$C_{13}H_{15}NO_3$ MW=233.27 g/mole

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.52 (d, 1H), 7.18 (m, 3H), 3.44 (s, 2H), 1.62 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 172.8, 148.9, 140.7, 127.8, 123.9, 123.0, 114.7, 84.0, 36.2, 27.8 (3C).

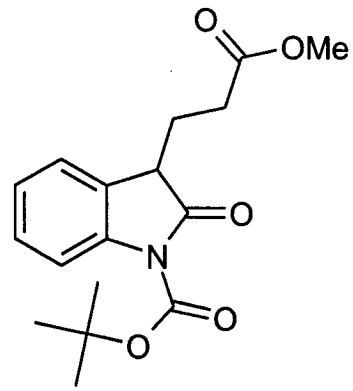
PREPARATION OF 3-(2- METHOXYCARBONYL-ETHYL)-*N*-(*TERT*-BUTOXYCARBONYL) INDOL-2-ONE 66

Method A:

n-BuLi (0.78 mL, 1.25 mmol) was added dropwise to a stirred solution of diisopropylamine (0.18 mL, 1.28 mmol) in THF (10 mL) under a nitrogen atmosphere at –78°C. This solution was stirred for 10 minutes at –78°C followed by cannulation to a solution of **65** (0.255 g, 1.09 mmol) in THF (10 mL) at –78°C. The flask was rinsed with additional THF (2 mL). The resulting mixture was stirred for 10 minutes at –78°C, and methyl-3-bromopropionate (140 μL, 1.28 mmol) was added dropwise. The reaction mixture was warmed from –78°C to room temperature slowly while stirring was continued for 20 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (25 mL), and subsequently diluted with distilled water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording dark red oil. Column chromatography of the crude using graduated solvent polarity from pure hexanes to 8:2 (hexanes/ethyl acetate) yielded **66** as a partially purified product.

Method B:

n-BuLi (0.78 mL, 1.25 mmol) was added to a stirred solution of diisopropylamine (0.18 mL, 1.28 mmol) in THF (10 mL) under a nitrogen atmosphere at –78°C. The resulting solution was stirred for 10 minutes followed by cannulation to a solution of **65** (0.256 g, 1.09 mmol) in THF (10 mL) at –78°C. The flask was rinsed with additional THF (2 mL). The resulting mixture was stirred for 10 minutes at –78°C, and methyl acrylate (120 μL, 1.33 mmol) was added dropwise. The reaction mixture was warmed slowly from –78°C to room temperature. Stirring was continued for 20 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (25 mL), and subsequently diluted with distilled water (20 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* to dark red oil. Column chromatography of the crude using graduated solvent polarity from pure hexanes to 8:2 (hexanes/ethyl acetate) yielded unreacted starting material **65** (0.113 g), and **66** (0.114 g, 59% yield) as a viscous yellow oil.



66

$C_{17}H_{21}NO_5$ MW=319.14 g/mole

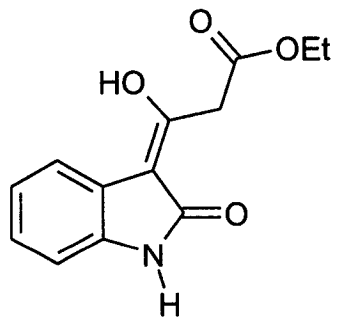
MS m/e (% rel. int.): 263 (2.9), 219 (20.4), 187 (54.2), 145 (100), 41 (41.2).

^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm): 7.64 (d, 1H), 7.19 (m, 3H), 3.60 (t, 2H), 3.58 (s, 3H), 2.72 (m, 4H), 1.60 (s, 9H).

^{13}C NMR ($CDCl_3$, 200 MHz) δ(ppm): 176.0, 173.4, 149.2, 140.0, 128.4, 126.4, 124.4, 123.8, 115.2, 84.8, 48.0, 44.8 30.0, 28.0 (3C), 26.4.

PREPARATION OF 3-HYDROXY-3-(2-OXO-1,2-DIHYDRO-INDO-1,3-YLIDINE)-PROPIONIC ACID ETHYL ESTER 68

Sodium metal (1.72 g, 74.25 mmol) was added very slowly to absolute ethanol (25 mL) and stirred at room temperature until all metal had reacted. To this mixture was added diethyl malonate (10.90 mL, 72.0 mmol) dropwise and stirred for 10 minutes. A solution of oxindole **59** (3.04 g, 22.5 mmol) in absolute ethanol (20 mL) was added dropwise to the sodium/ethanol mixture over 2 hours at room temperature. The resulting mixture was refluxed for 18 hours, cooled to room temperature and diluted with distilled water (50 mL). The solvents were removed *in vacuo* affording thick beige oil. The crude residue was dissolved in cold water (100 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with cold water (50 mL). The combined aqueous extracts were acidified with concentrated hydrochloric acid until a white precipitate formed. The product was filtered by aspiration and rinsed with cold water to yield **68** (5.21 g, 92% yield) as a fine beige powder.



68

$C_{13}H_{13}NO_4$ MW=247.08 g/mole

m.p. 152-156°C

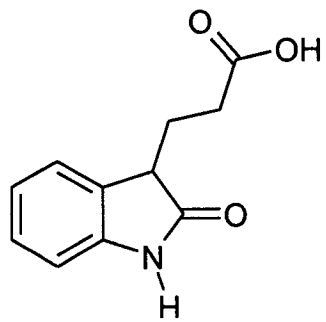
MS m/e (% rel. int.): 247 (7.3), 224 (100), 178 (96.3), 159 (59.9), 133 (38.7), 105 (30.1), 87 (37.5)

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.59 (s, NH), 7.33 (d, 1H, J=7.6 Hz), 7.18 (t, 1H, J=7.6 Hz), 7.07 (t, 1H, J=7.5 Hz), 6.99 (d, 1H, J=7,7 Hz), 4.22 (q, J=14.2, 7.1 Hz), 3.76 (s, 2H), 1.25 (t, 3H, J=7.1 Hz).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 172.7, 167.5, 167.0, 136.4, 126.1, 122.4, 121.7, 120.1, 110.5, 103.8, 61.9, 40.3, 14.1.

PREPARATION OF 3-(2-OXO-2,3-DIHYDRO-1H-INDOL-3-YL)-PROPIONIC ACID 69

A mixture of **68** (1.32 g, 5.3 mmol), 10% palladium on charcoal (0.21 g), glacial acetic acid (25 mL) and concentrated sulfuric acid (1 mL) were added to a Fischer-Porter Bottle. The apparatus was sealed and purged with hydrogen gas three times. The apparatus was then filled with pressurized hydrogen (50 psi, 3.4 atm), heated to 70°C, and stirred vigorously for 19 hours. The pressure was released slowly; the mixture was filtered through a 1 cm pad of celite on a sintered glass funnel, and rinsed with glacial acetic acid (15 mL). The resulting pale yellow solution was concentrated *in vacuo* to afford the crude as pale yellow oil. The crude was dissolved in water (10 mL), and heated to reflux for 1 hour. The hot solution was treated with activated charcoal, filtered, and cooled to yield a beige precipitate. Filtration yielded **69** (0.408 g, 36% yield) as a white powder-like solid.



69

$C_{11}H_{11}NO_3$ MW=205.18 g/mole

m.p. 164-165°C

MS m/e (% rel. int.): 205 (10.0), 187 (27.9), 145 (100), 132 (25.9), 117 (24.2), 77 (14.7)

HRMS Calculated 205.0739 g/mole

Found 205.0726 g/mole

^{1}H NMR (Acetone D_6, 200 MHz) δ(ppm): 9.42 (s, NH), 7.30 (d, 1H), 7.09 (dt, 2H), 6.89 (d, 1H), 3.50 (t, 1H), 2.97 (s, OH), 2.35 (t, 2H), 2.17 (t, 2H).

Chapter 4 – The Indole Approach

4.1 Background

The preferential ratio of **74** to **72** during the Friedel Crafts cyclization reaction is due to the combined effects of the pivalyl protecting group in conjunction with the additive, chloro-acetyl chloride. Nakatsuka *et al.*[37] published a viable explanation for these results. They used NOE experiments to confirm the structural conformation of the pivalyl-protected 3-indole-pripionic acid. Their results shown in structure **A** below demonstrate the relative position of the pivalyl group. The NOE relationship between the *t*-butyl group and the proton at position 2 calculated at 10% compared with the NOE of 0% with proton in position 7 confirms that the orientation of the pivalyl group is as shown (Figure 4.1).

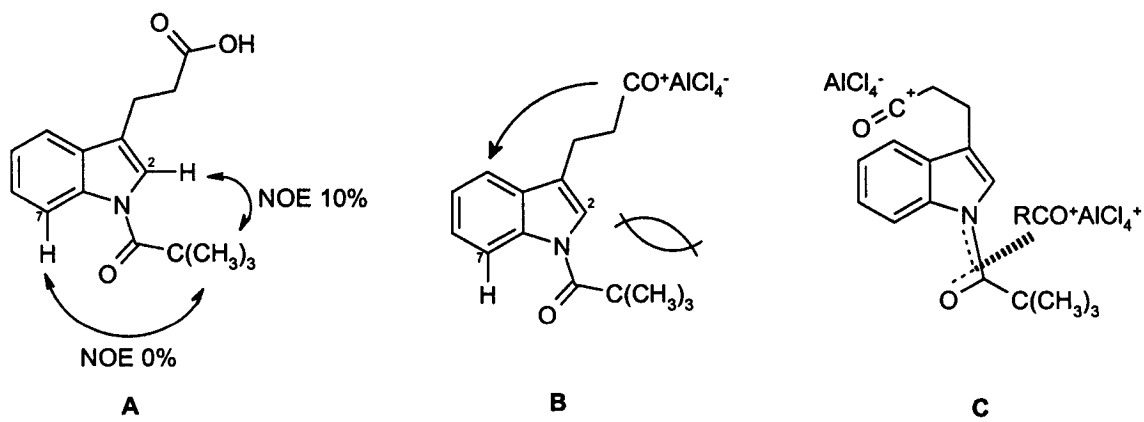
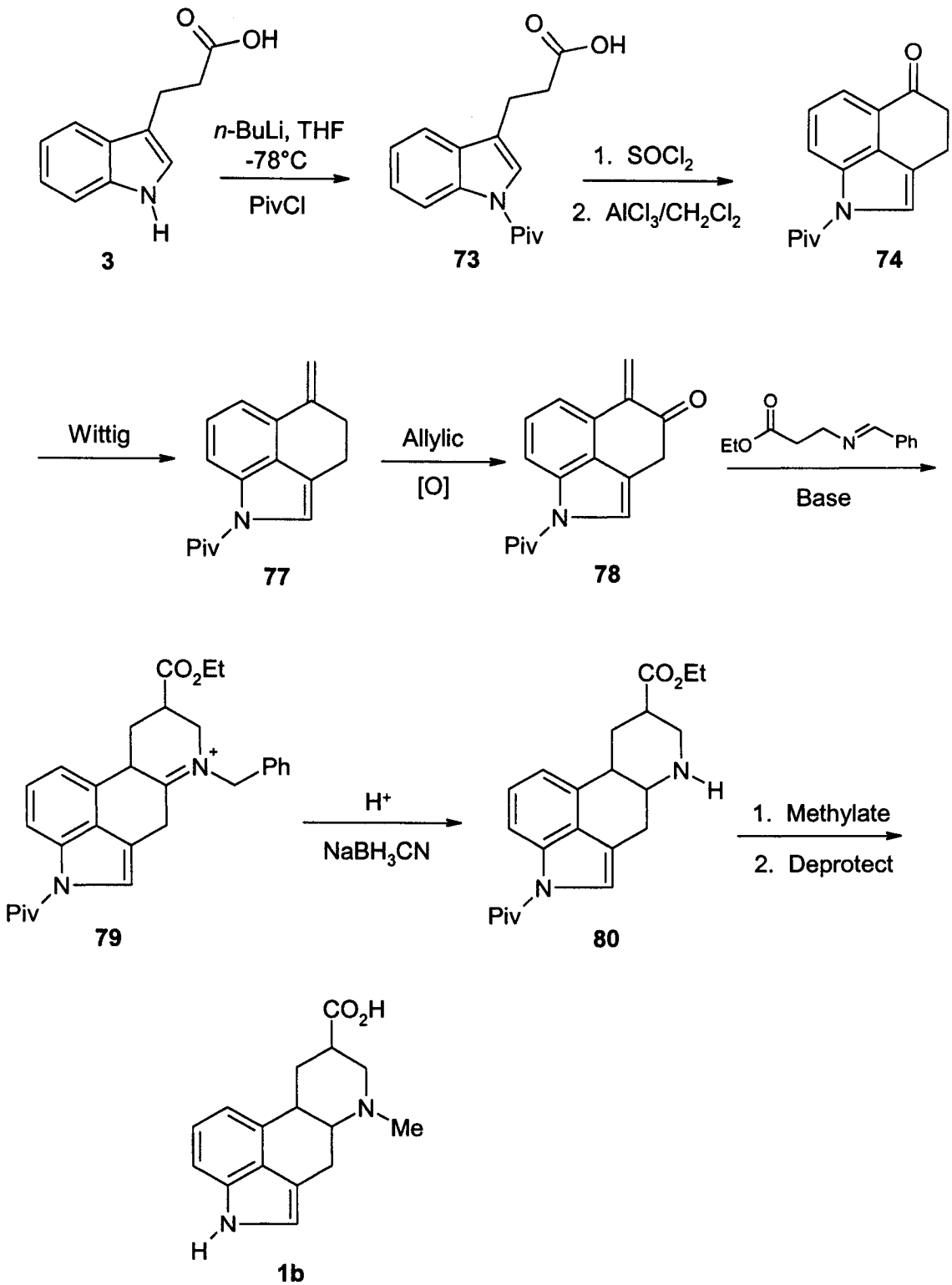


Figure 4.1 Structural effects of Piv-protecting group and chloroacetyl chloride.

This particular orientation supports their results for the regioselective formation of **74** since the pivalyl group has the desired effect of partially blocking the 2-position as the electron-acceptor for a Friedel Crafts reaction. This is illustrated in structure **B**. It is believed that upon the addition of the chloro-acetyl chloride, the reaction proceeds via intermediate **C**. Chloro-acetyl chloride is believed to complex with the carbonyl of the pivalyl group forming an acyl chloride-aluminum chloride complex[36] called an *oxocarbonium ion*. The oxocarbonium ion, in conjunction with the pivalyl group, are sufficiently bulky to block the 2-position of the indole ring, thus allowing for the 4-position to be the major electron acceptor.

4.2 Proposed Synthetic Route to Lysergic Acid 1 via Indole

The availablility of the protected Uhle's Ketone **75** in gram quantities via the modified Friedel Crafts reaction,[36,37] presented the opportunity to explore a concise synthesis from this key intermediate to lysergic acid ring system. The proposed route to lysergic acid **1** is outlined in Scheme 4.1.

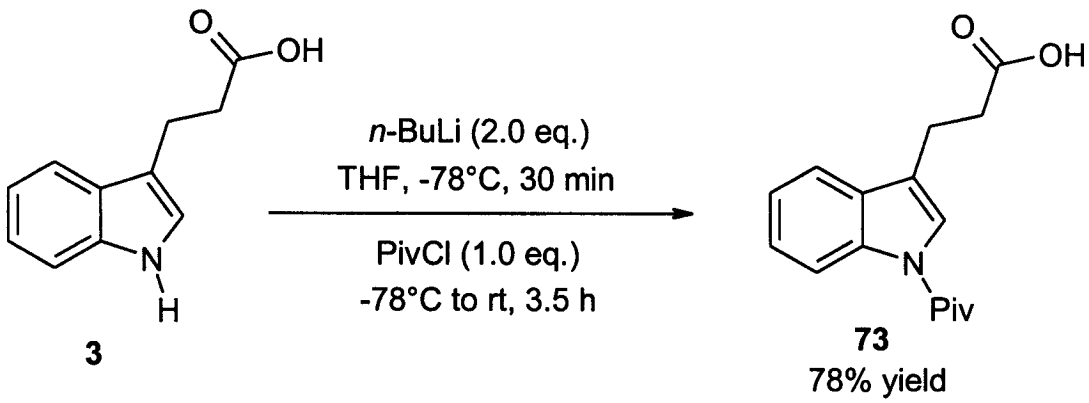


Scheme 4.1 Proposed indole approach to dihydrolysergic acid **1b**.

4.3 Results and Discussion

4.3.1 Preparation of protected Uhle's Ketone 74.

The commercially available indole-3-propionic acid **3** was treated in THF at -78°C with 2 equivalents of *n*-BuLi followed by the addition of 1 equivalent of trimethylacetyl chloride (PivCl). This resulted in the selective *N*-protection after workup generating **73** as the major product in 78% yield.

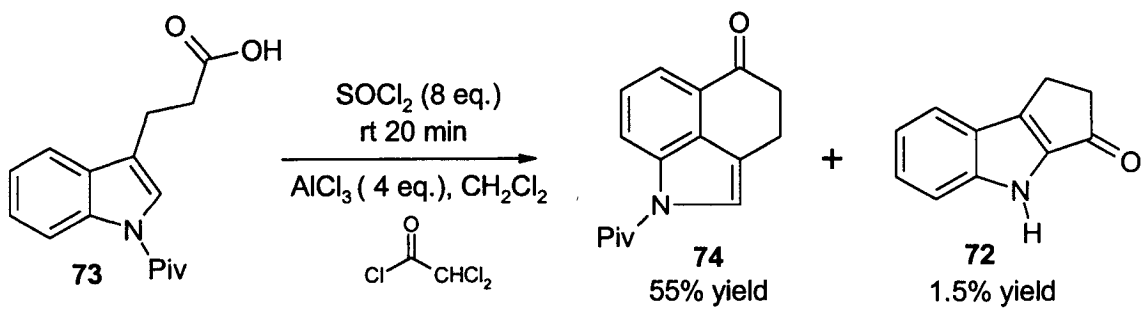


Scheme 4.2 Pivalyl-protection of indole-3-propionic acid **3**.

The acid **73**, a pale peach solid with a melting point of 128-130°C (literature[35] m.p. 126-127°C.) was isolated by column chromatography and its structure confirmed by comparison with previously published analytical data.[36,37] The key spectroscopic data included the disappearance of the NH peak in ^{1}H NMR at 12.3 ppm and the appearance of the *t*-butyl singlet at 1.48 ppm while maintaining

an OH peak of about 10.6 ppm. A new carbonyl peak in the ^{13}C spectrum for the Piv-group at 179.1 ppm was also identified.

The acid **73** was converted into the protected ketone **74** following a specific literature procedure,[36] which was designed to minimize electrophilic attack at C-2 of the indole ring, and thus favour formation of the desired compound **74**. The generation of the acid chloride **81** was obtained by treating **73** with excess $SOCl_2$ at room temperature followed by evaporation of the excess *in vacuo* afforded a dark brown oil. The acid chloride was not purified, but dissolved in methylene chloride and used immediately. $AlCl_3$ and chloro-acetylchloride, both in 4 equivalent excess, were stirred in methylene chloride at room temperature under a nitrogen atmosphere. The acid chloride solution was added slowly to this mixture and the reaction was quenched after 1 hour by pouring into ice water. The product **74** was obtained via column chromatography as white needles in 55% yield having a melting point of 161-162°C (literature m.p. 168-169°C). A beige solid byproduct identified as **72** was isolated in 1.5% yield.



Scheme 4.3 Results of Nakatsuka's Friedel Crafts reaction.

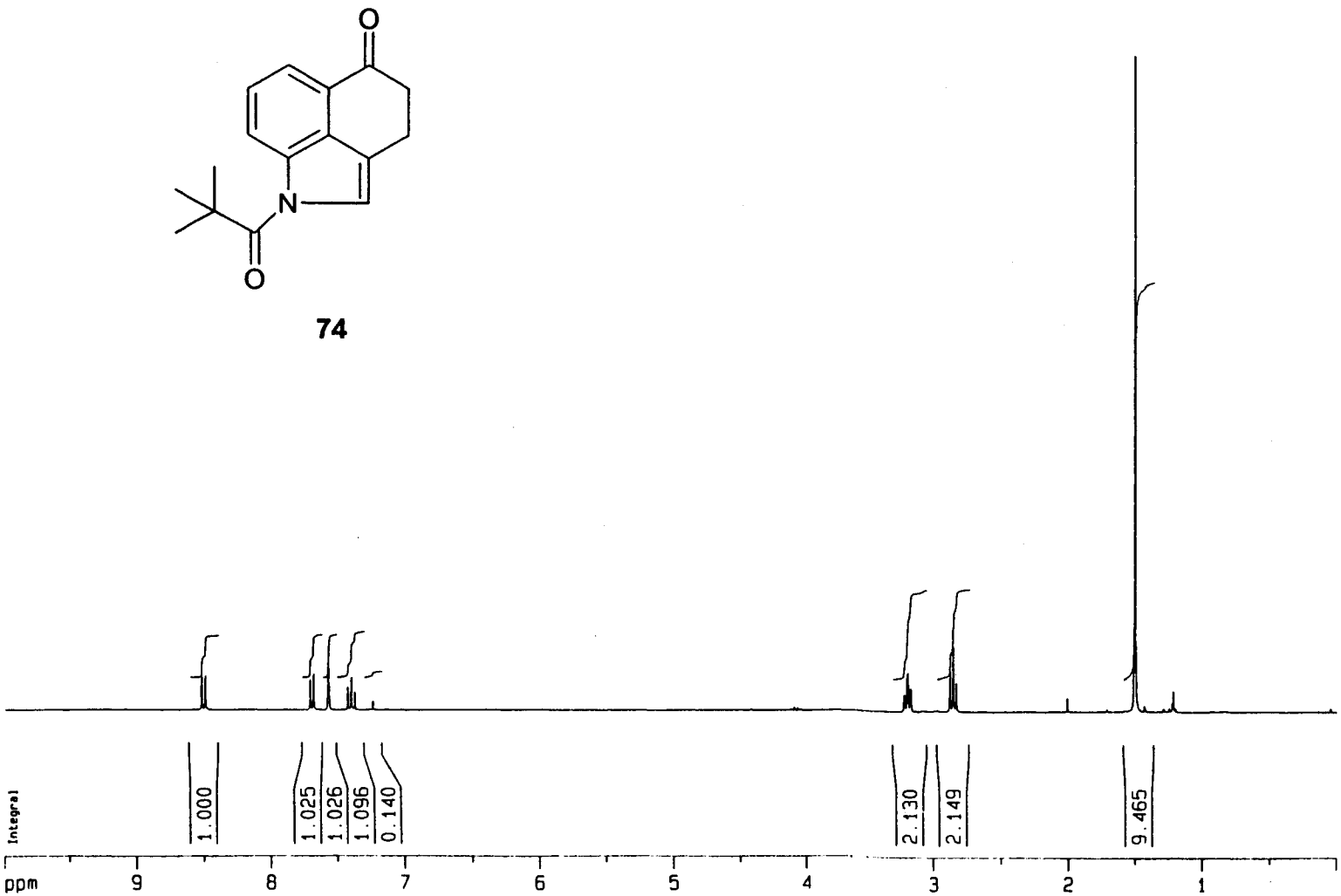


Figure 4.2 ^{1}H NMR spectrum of 1-(2,2-dimethylpropionyl)-3,4-dihydro-1H-benzo[c,d]indol-5-one **74**.

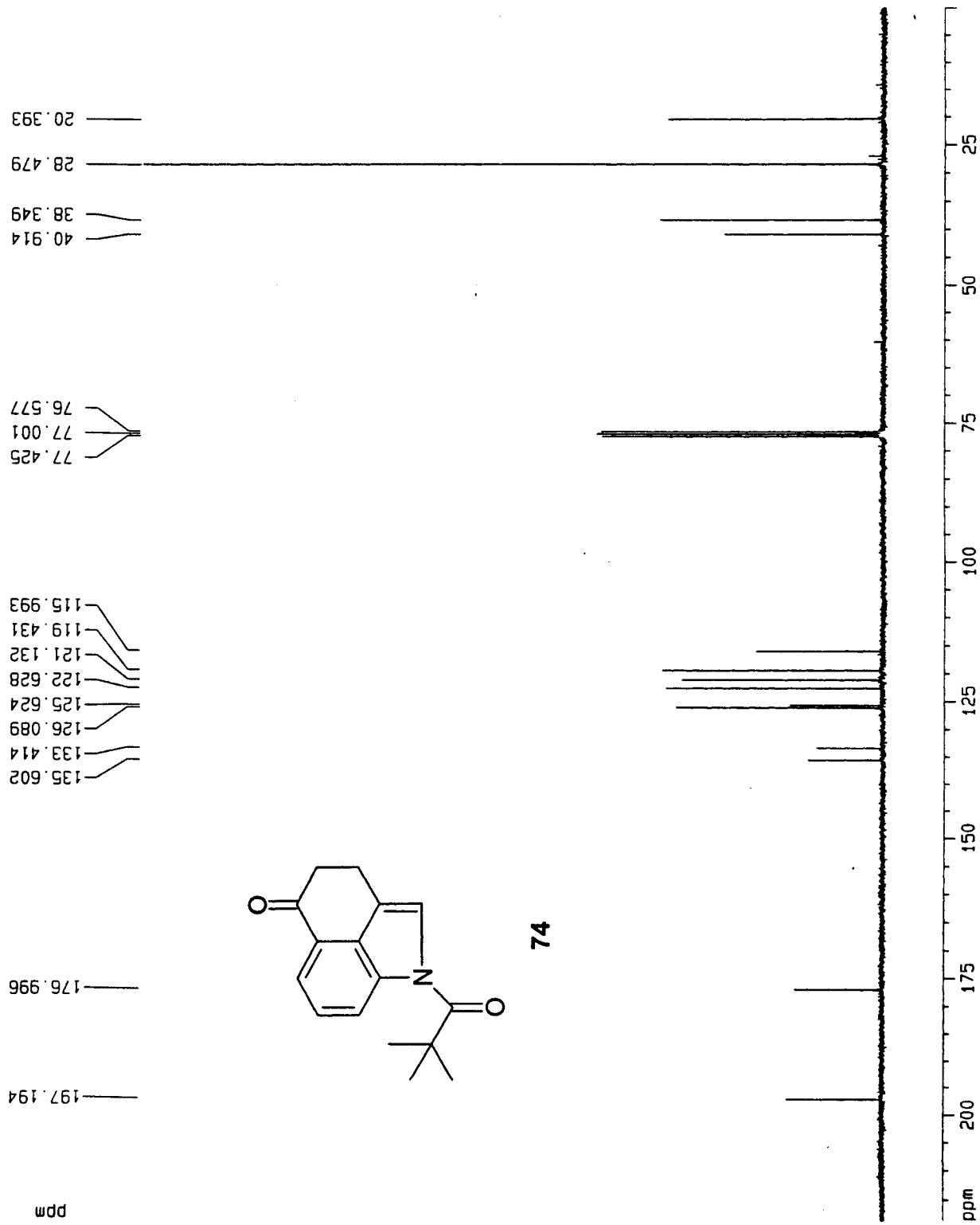


Figure 4.3 ^{13}C NMR spectrum of 1-(2,2-dimethylpropionyl)-3,4-dihydro-1H-benzo[c,d]indol-5-one **74**.

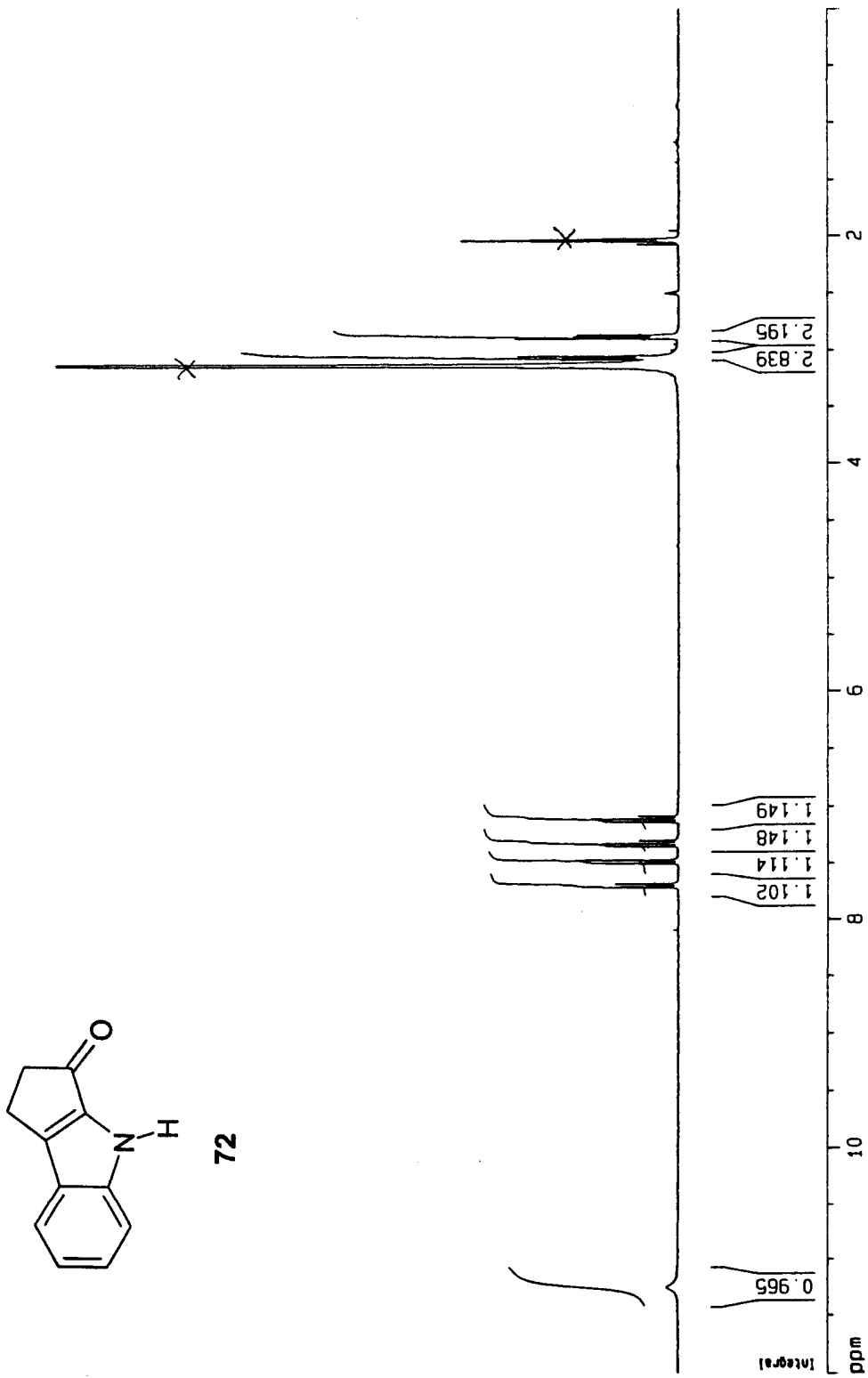


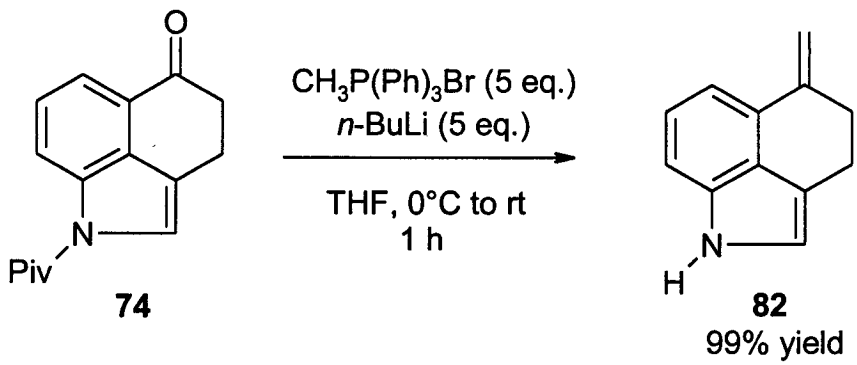
Figure 4.4 ^{1}H NMR spectrum of 1,4-dihydro-2H-cyclopenta[b]indol-3-one **72**.

The structures of both **74** and **72** were confirmed by a comparison of spectroscopic information previously published[36,37] with our own findings. The keys to distinguishing between the starting material **73** and the cyclized product **74** were: distinct changes in the ^{1}H NMR (Figure 4.2) aromatic pattern, and a shift from 179.1 ppm to 197.2 ppm in the ^{13}C spectrum (Figure 4.3) for the carbonyl carbons. The byproduct **72** was readily identified by the ^{1}H NMR (Figure 4.4) by the disappearance of the C-2 proton, a sharp singlet found at 7.58 ppm for both the starting material **73** and desired product **74**.

This brought us to the point where most literature references finished their efforts towards the synthesis of lysergic acid derivatives. For many,[5,8,39-41] the challenge lay in obtaining Uhle's Ketone **75** in good yield, and not necessarily in completing the entire synthesis. For us however, the exciting part was just beginning, for the remaining steps would be to put into practice the route to the lysergine ring skeleton, which grew out of our benzyne work.

4.3.2 New results using a Wittig Reaction.

The first step was to convert the ketone function of **74** into a methylene group via a Wittig reaction. Using standard conditions of a 5-fold excess of triphenylphosphonium bromide and *n*-BuLi in THF to generate the ylide *in-situ*, followed by the addition of ketone **74**, quantitative yields of **82**, the *N*-unprotected methylene derivative was produced. We presume that the deprtoection of the indole nitrogen resulted from the use of excess of the very basic methylene ylide in the reaction.



Scheme 4.4 First Wittig reaction of ketone **74**.

The presence of two distinct methylene protons at 5.15 ppm and 5.63 ppm in the ^{1}H NMR (Figure 4.5), the broad NH singlet at 7.82 ppm, as well as the loss of *t*-butyl confirmed the structure of **82** as illustrated. The ^{13}C spectrum (Figure 4.6) showed a loss of both carbonyl carbons, and a new methylene carbon at 142.7 ppm. The final evidence for confirmation of **82**, was the accurate mass analysis calculated to be 169.0892, and found at 169.0900.

The characterization of **82** proved to be quite challenging since exposure to air caused the pure yellow oil to turn dark indigo blue within about 30 minutes. This required us to work quickly in order to obtain structural proof. Also, this product would need to be transformed further vial allylic oxidation before decomposition could occur. Decomposition was also observed while obtaining NMR data upon the immediate addition of deuterated chloroform. Attempts to identify the decomposed products were unsuccessful. By TLC, there were 8-10 spots, and both ^{1}H and ^{13}C NMR spectrum became very cluttered with peaks.

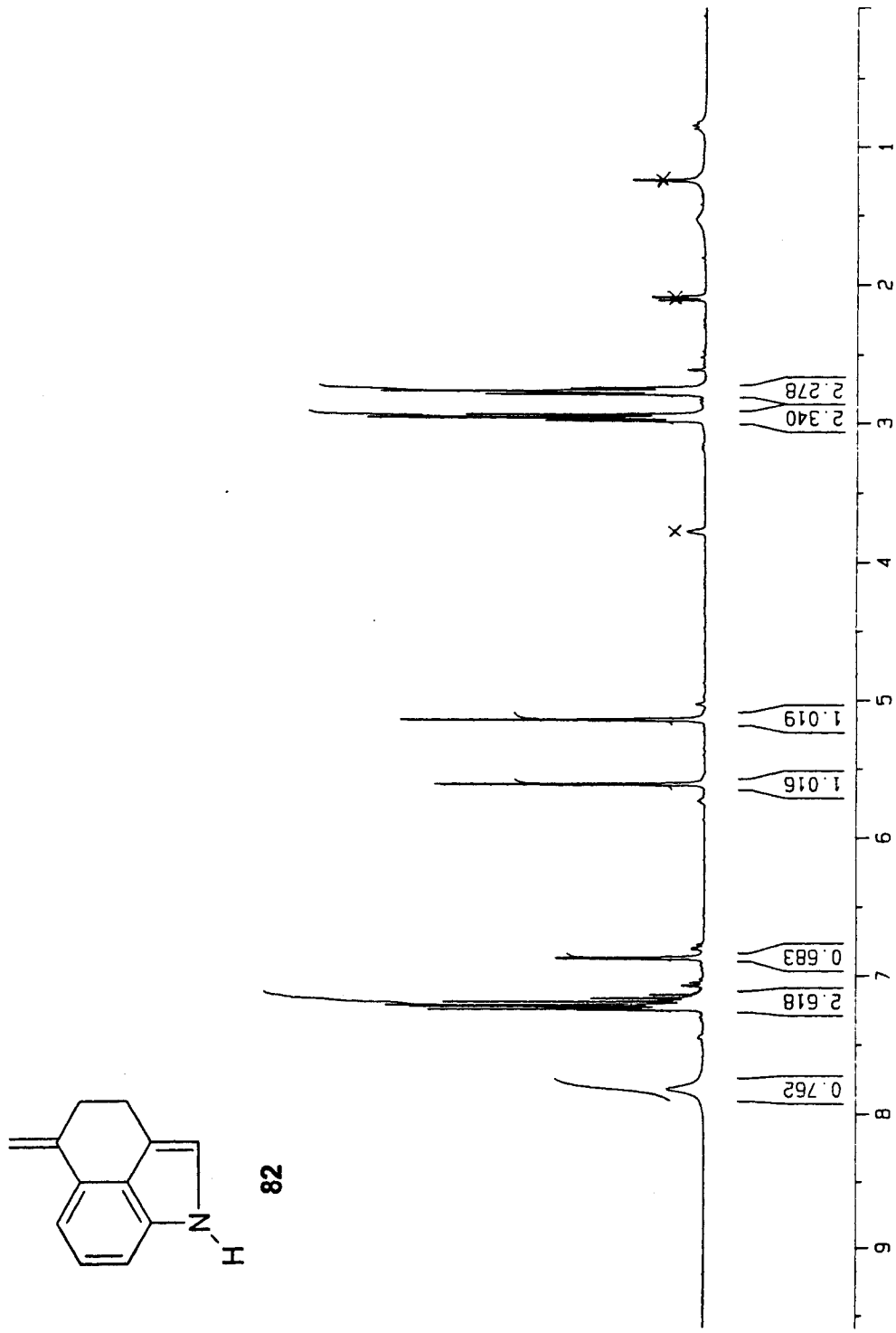


Figure 4.5 ^{1}H NMR spectrum of 5-methylene-1,3,4,5-tetrahydro-benzo[c,d]indole **82.**

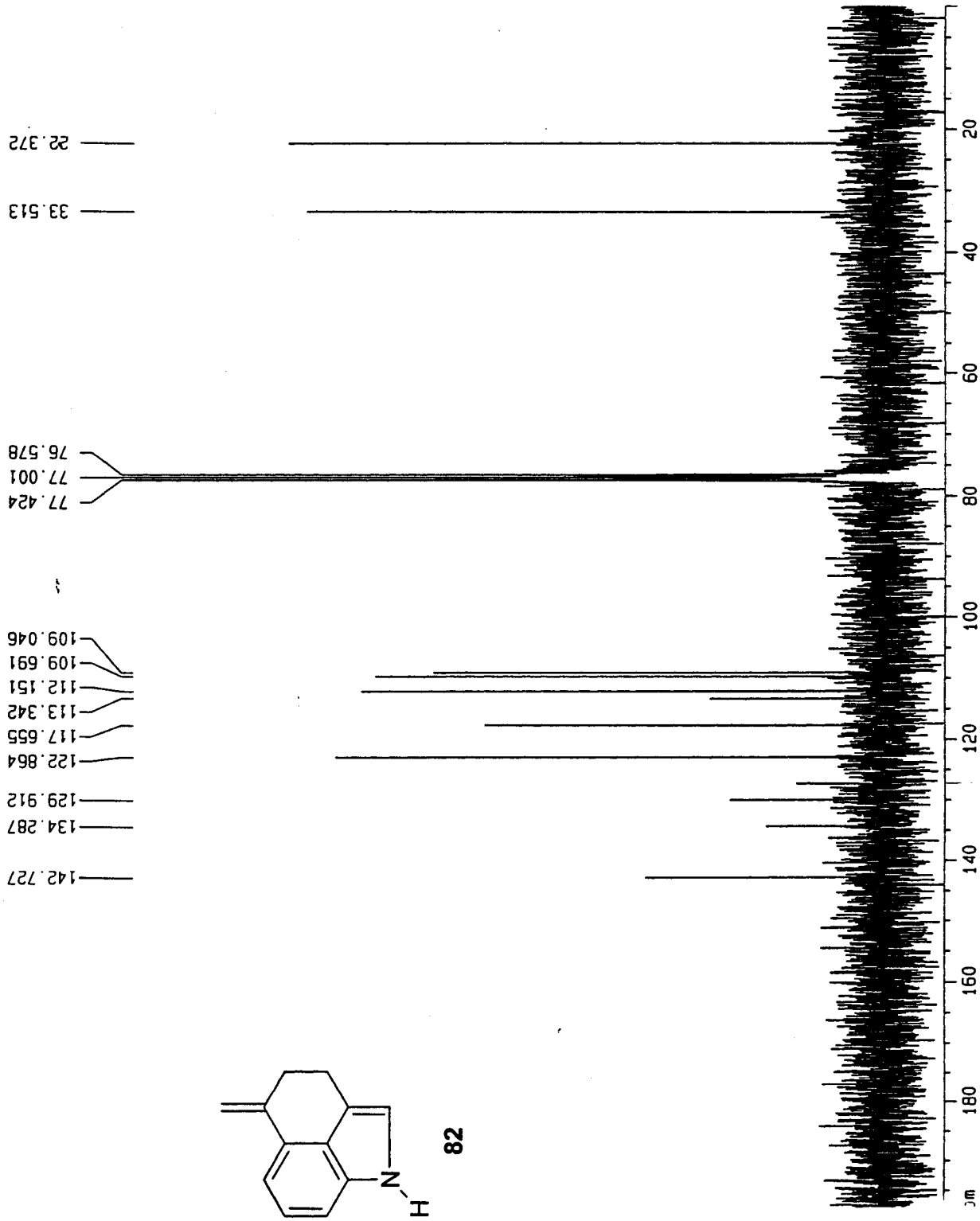
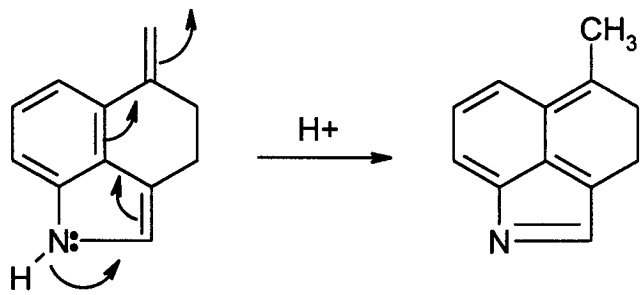


Figure 4.6 ^{1}H NMR spectrum of 5-methylene-1,3,4,5-tetrahydro-benzo[c,d]indole **82.**

Although we did not identify the decomposition products of **82**, we presume that the high instability to acids can be appreciated by considering the intermediate obtaind by reactions with acids.



82 **83**

Scheme 4.5 Proposed acid instability of Wittig product **82**.

Protonation at the methylene carbon of **82** would be accomplished by loss of the hydrogen on nitrogen to generate the ortho-quinodine intermediate **83**. The intermediate can now undergo a variety of cycloadditions, nucleophilic additions, and oxidation reactions to generate the many products visible on TLC. The formation of an anionic equivalent of **83** under basic conditions is also plausible.

Fortunately, during the remaking of **82** from **74**, the quality of *n*-BuLi was not good, and thus a smaller excess of Wittig reagent was generated under these conditions. Therefore, a second product was isolated in addition to **82**.

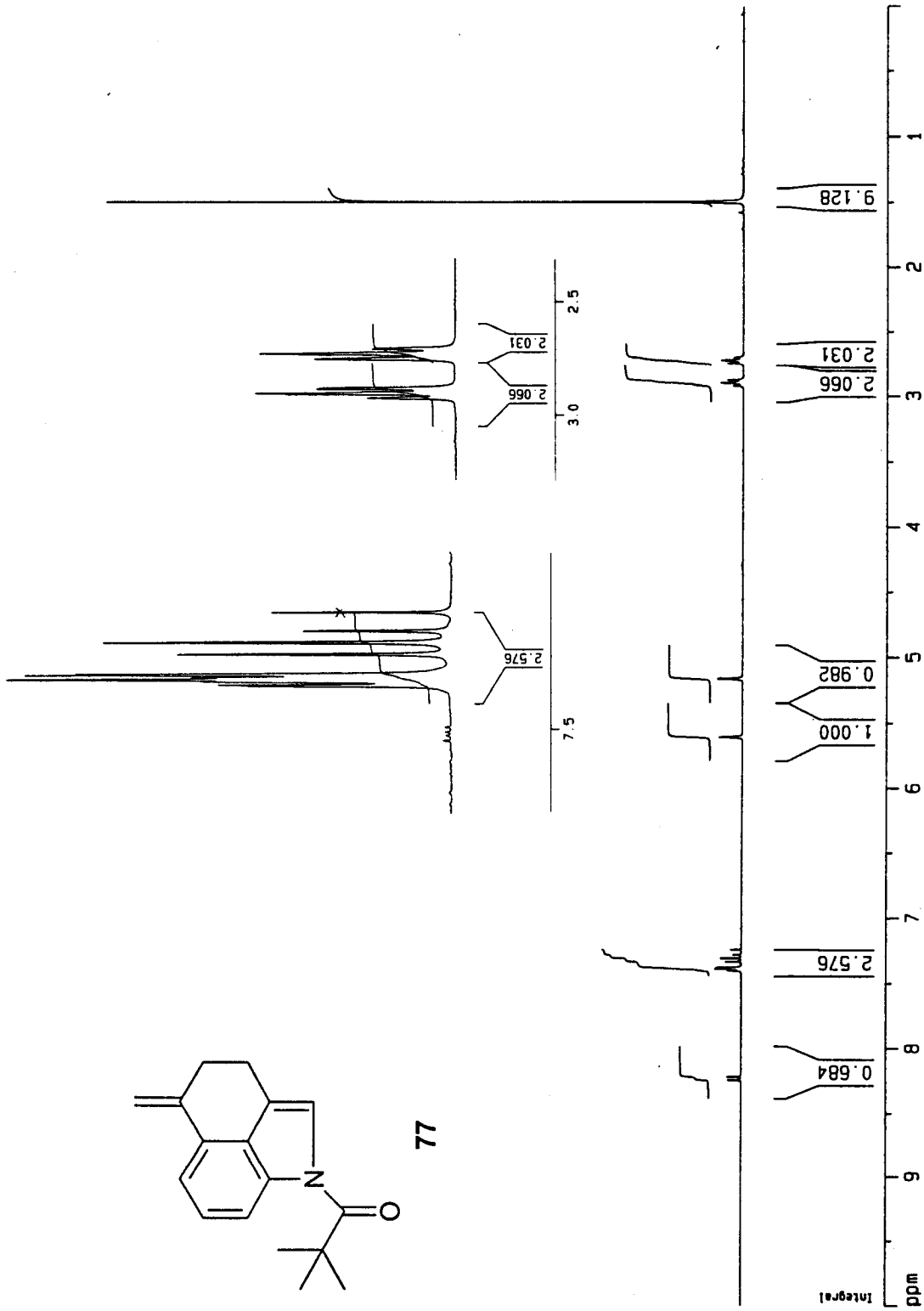
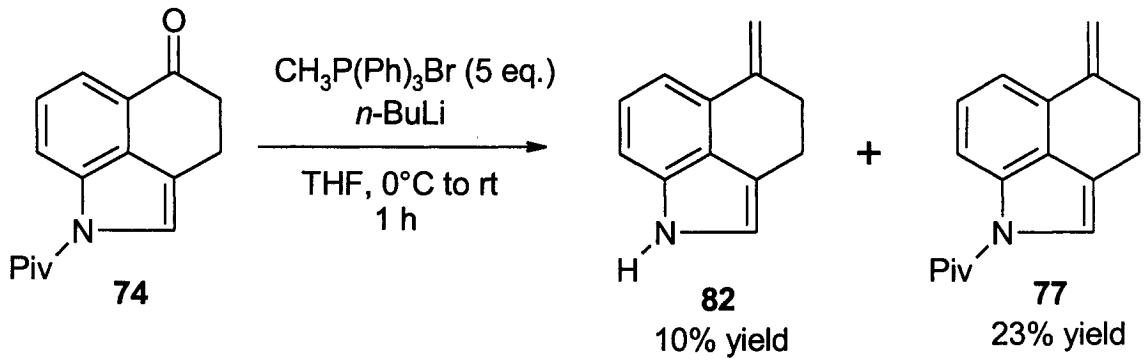


Figure 4.7 ^{1}H NMR spectrum of 2,2-dimethyl-1-(5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-propan-1-one **77**.



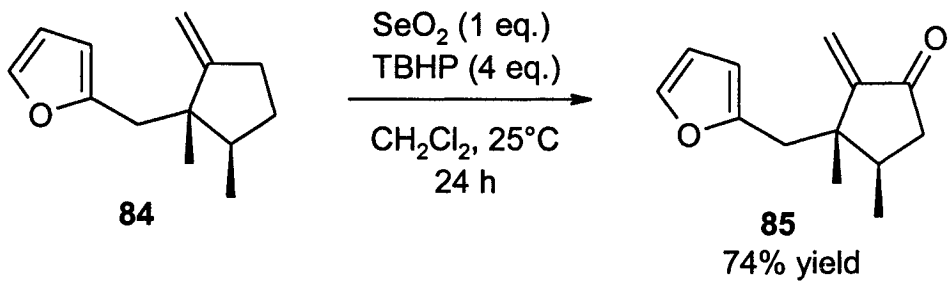
Scheme 4.6 Modified conditions of Wittig Reaction of ketone **74**.

The second Wittig product **77** was obtained as a pale yellow solid with a melting point of 133-135°C. The ^{1}H NMR (Figure 4.7) showed the desired ketone to $=CH_2$ conversion with the presence of two singlets at 5.16 and 5.61 ppm. The appearance of a peak at 1.50 ppm indicated that the pivalyl-protecting group on the nitrogen had been retained. In contrast to **82**, this compound was quite stable and could be stored at room temperature for days without obvious decomposition. A future approach to improve the yield of **77** would be to make **82** as described earlier in Scheme 4.4, then re-protect the nitrogen immediately with pivalyl or another group.

4.3.3 Allylic oxidation of Wittig products using SeO_2.

The next step involved the oxidation of the allylic carbon-hydrogen bonds to afford the α,β-unsaturated enone **78**. The most reliable and predictable reagent for the direct insertion of oxygen into an allylic carbon-hydrogen bond is

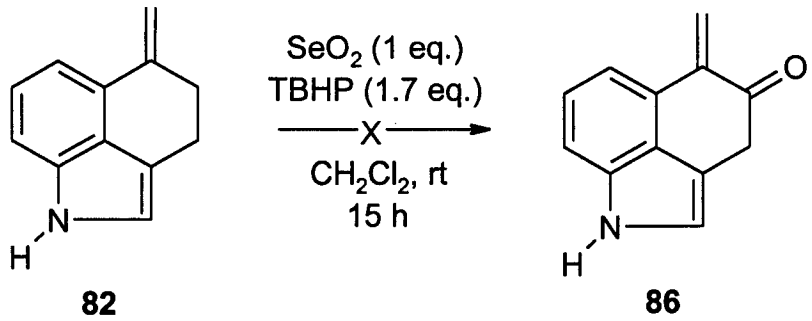
selenium dioxide.[42] Umbreit and Sharpless[42] improved this reaction with the addition of *t*-butyl hydroperoxide (TBHP). They reasoned that an oxidant which would rapidly and selectively re-oxidixe the reduced selenium species to SeO_2 would prevent reported problems such as the difficult removal of colloidal selenium from the products. In one example, allyic oxidation of the exocyclic double bond using SeO_2 in the presence of TBHP afforded the enone product **85** in 74% yield.[43]



84 **85** 74% yield

Scheme 4.7 Example of SeO_2 allylic oxidation to afford an enone product.

Despite the instability of the methylene derivative **82**, we decided to attempt its conversion to the α,β-unsaturated enone **86**. The SeO_2/*t*-BuOOH oxidation was carried out following literature procedure.[42] Unfortunately, neither TLC monitoring of the reaction mixture or NMR evaluation of the crude reaction products indicated the successful formation of the desired product. ^1H NMR confirmed only the presence of starting materials.



82 **86**

Scheme 4.8 Attempt to oxidize Wittig product **82** to enone **86**.

Since we had the *N*-pivalyl protected Wittig product **74** in our hands, we carried out the selenium dioxide oxidation reaction on this compound as well. Silica gel chromatography of the crude reaction mixture yielded yellow oil, which was identified as the allylic alcohol **87**. The formation of this product was not altogether surprising since allylic alcohols represent the intermediate stages in the allylic oxidation to enones. Several NMR experiments were carried out to ensure the allylic alcohol as indicated was the product and not the enone. The key evidence in the ^{1}H NMR spectrum (Figure 4.8) was the presence of a quartet of doublets for the adjacent CH_2 confirming that there must be one adjacent hydrogen influencing their spin environment. Furthermore, a broad OH peak was located at 1.93 ppm. The ^{13}C NMR spectrum (Figure 4.9) confirmed that the α-CH_2, originally at 22.1 ppm had relocated to 71.5 ppm and had become a CH proton confirmed using DEPT 135 and DEPT 90 experiments.

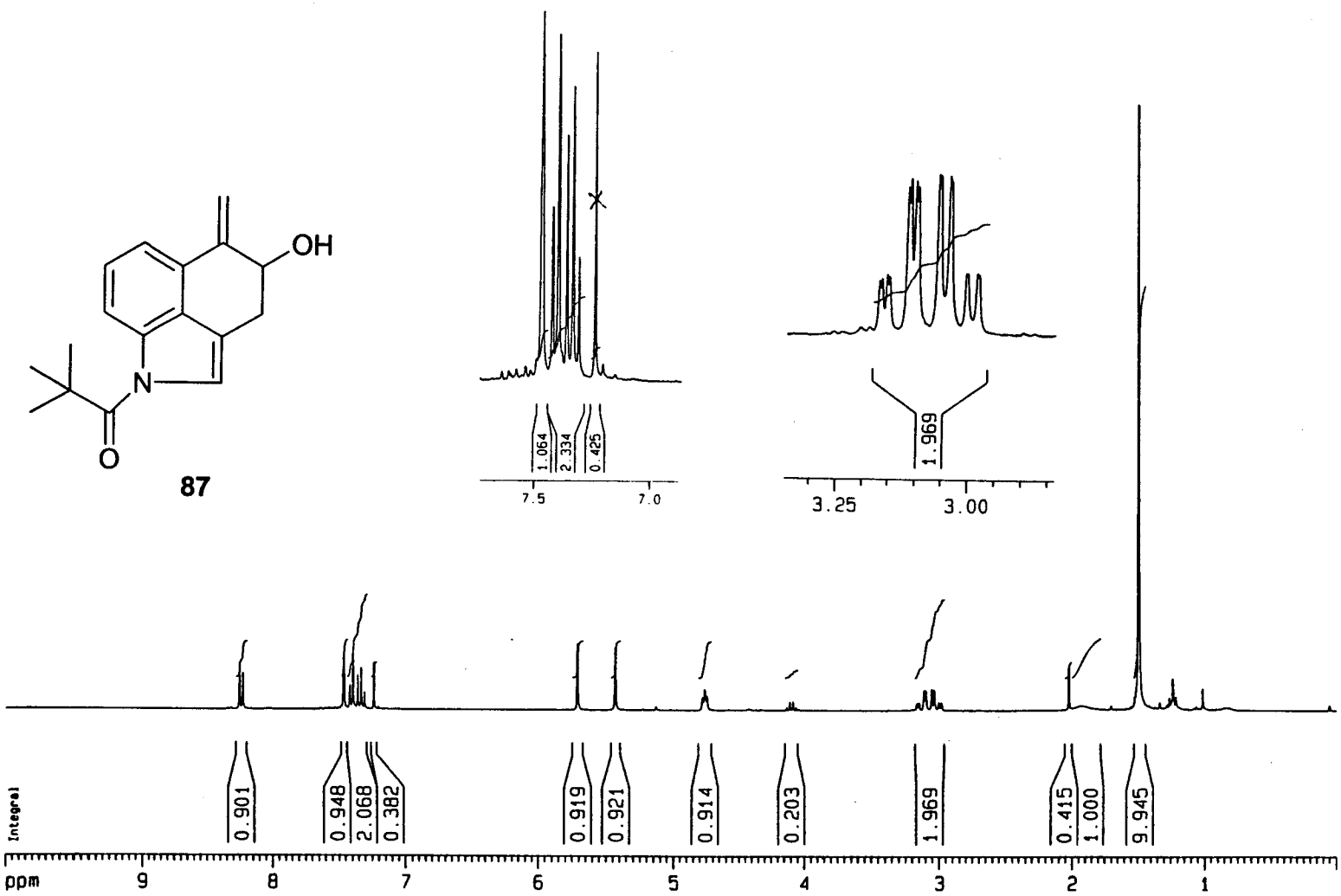


Figure 4.8 ^{1}H NMR spectrum of 1-(4-hydroxy-5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-2,2-dimethyl-propan-1-one **87**.

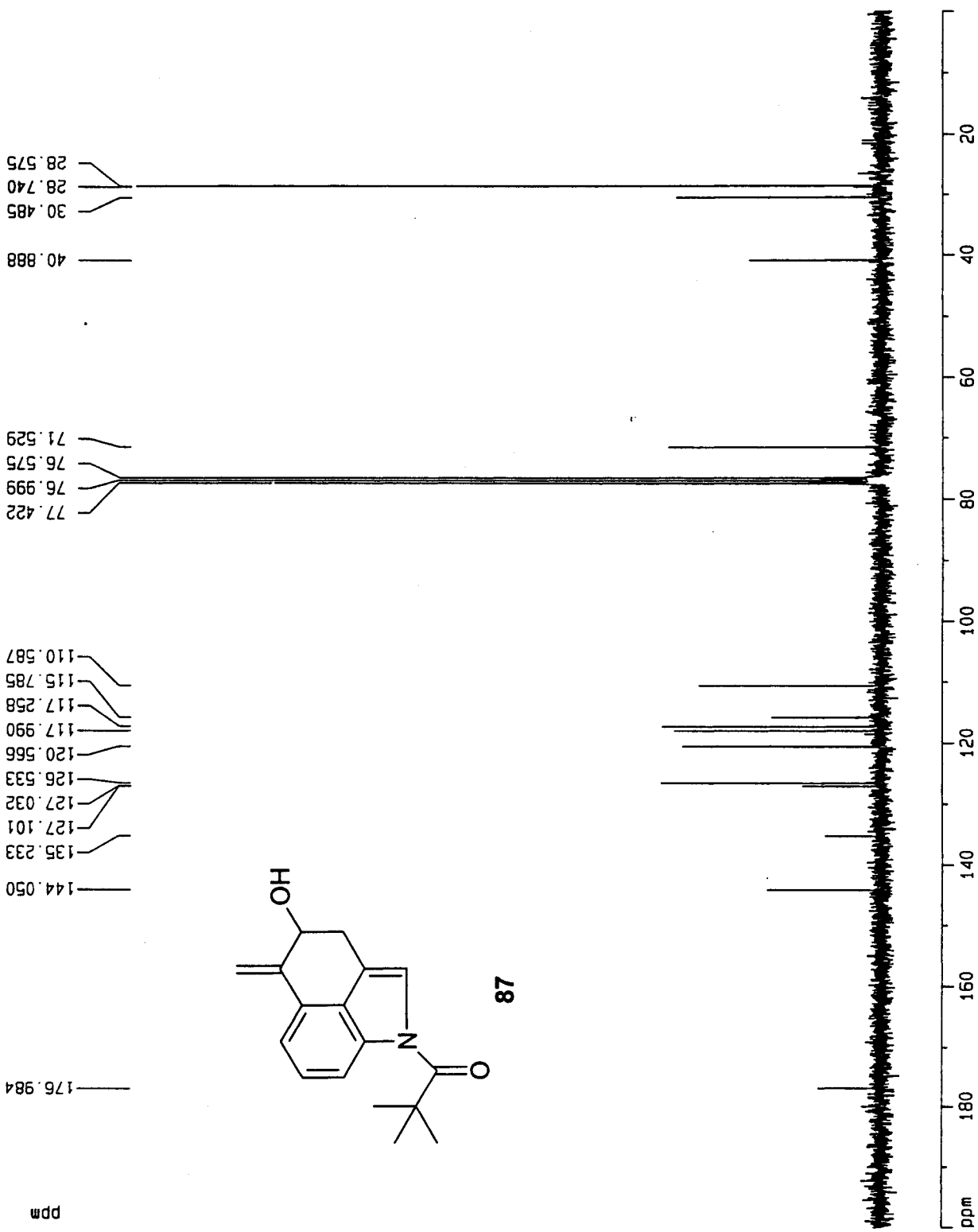
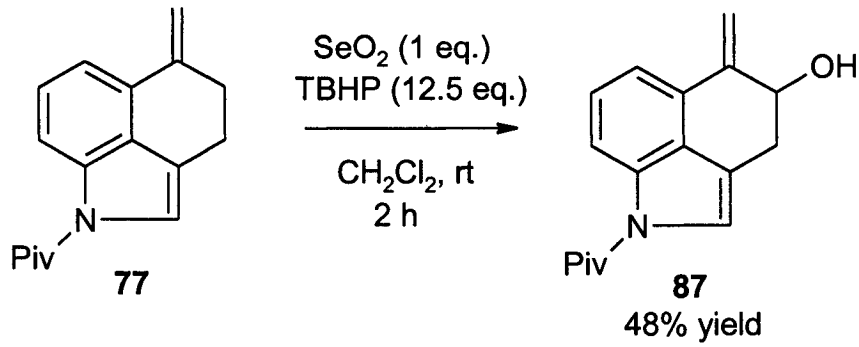
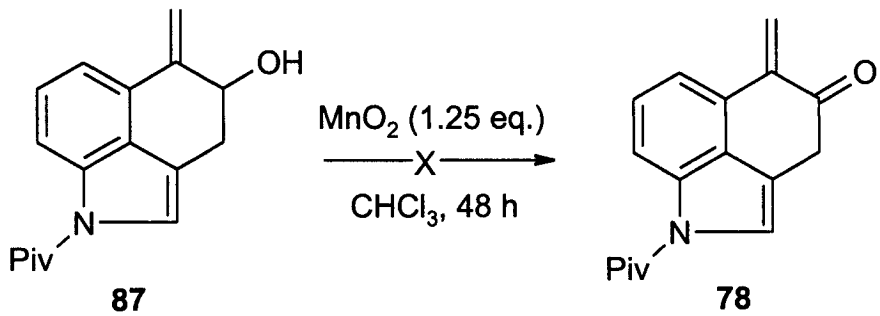


Figure 4.9 ^{13}C NMR spectrum of 1-(4-hydroxy-5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-2,2-dimethyl-propan-1-one **87**.



Scheme 4.9 Actual SeO_2 oxidation result of Wittig product **77**.

We believed that it would be possible to further oxidize the allylic alcohol to the enone using manganese dioxide[44] as the oxidizing agent in chloroform at room temperature. **87** was allowed to react in the presence of 1.25 equivalent excess of MnO_2 for 48 hours. The ^1H NMR of the crude material indicated the presence of starting material amongst other unidentified peaks. It is well known that the quality of the MnO_2 is important in these oxidation reactions. Unfortunately, the lack of time and material did not permit the repeat of these oxidation experiments.



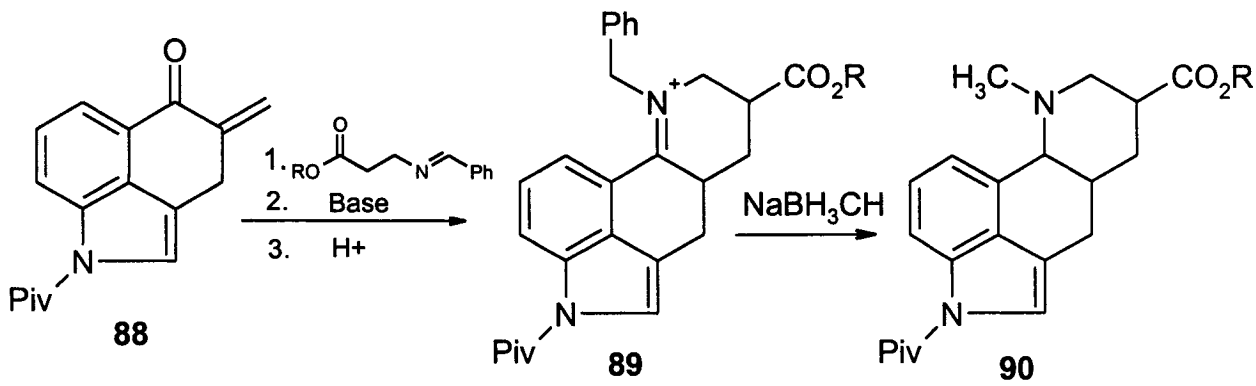
Scheme 4.10 Attempted oxidation of alcohol **87** to enone **78**.

We are currently in the process of making more starting material **87** to attempt other oxidative conditions. The ones favoured for consideration are the Swern, or Jones oxidations.

4.4 Isomeric Lysergine Compounds

4.4.1 Background and proposed synthetic route.

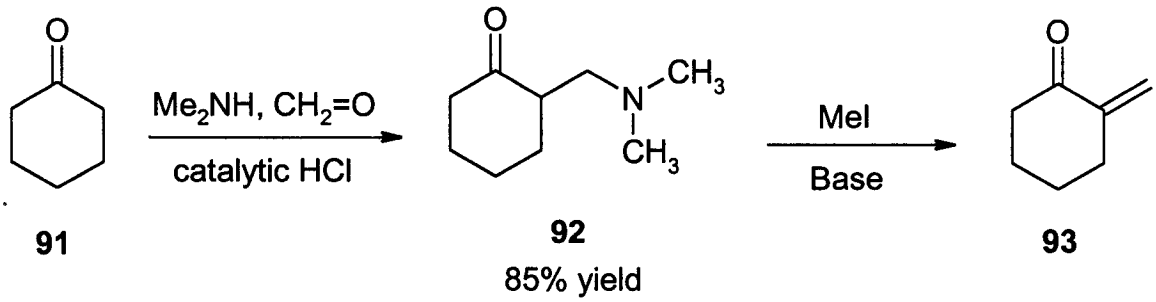
The enone **78** has been proposed as the key intermediate in a new lysergic acid synthesis in Scheme 4.1. It occurred to us that the compound **88** would be a viable intermediate leading to the isomeric lysergines such as **90** as shown in Scheme 4.11.



Scheme 4.11 Proposed route to isomeric lysergine compound **90**.

The enone **88** should arise from **74** under Mannich reaction conditions. In general, the Mannich reaction[45] involves the formation of an imine salt from the

secondary amine and formaldehyde. The imine salt adds to the enol of the ketone formed under acidic conditions, resulting in an amine called a Mannich base, often in good yields. A generalized example of this reaction is as follows:

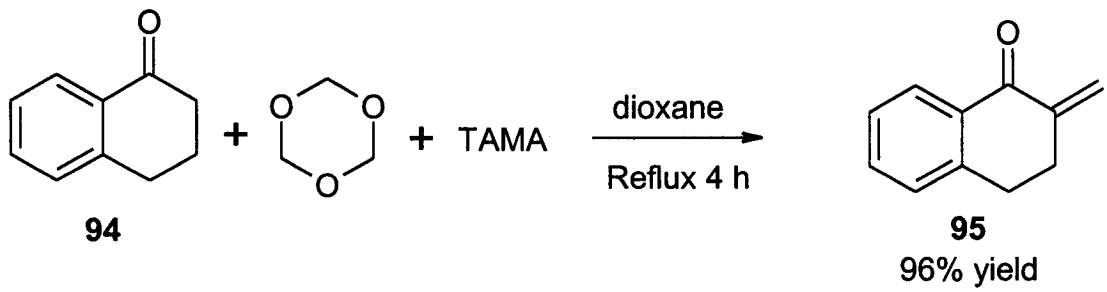


91 **92** 85% yield **93**

Scheme 4.12 General Mannich Reaction.

The Mannich base can then be reliably converted to enones by alkylating with MeI followed by treating the ammonium salt with base.

A search of the published literature identified a modified Mannich reaction that enabled a direct synthesis of α-methylene ketones.[46] The approach presented by Jean-Louis Gras is analogous to the classical Mannich reaction, but by the choice of appropriate reagents, he was able to obtain directly the α-methylene ketone for many ketones. The key aspect of the Gras procedure are the use of the amine salt *N*-methylanilinium trifluoroacetate (TAMA), and the use of an aprotic solvent such as dioxane or THF. The example which most closely resembles the ring structure of our starting material **74** is as follows:



94 **95**
96% yield

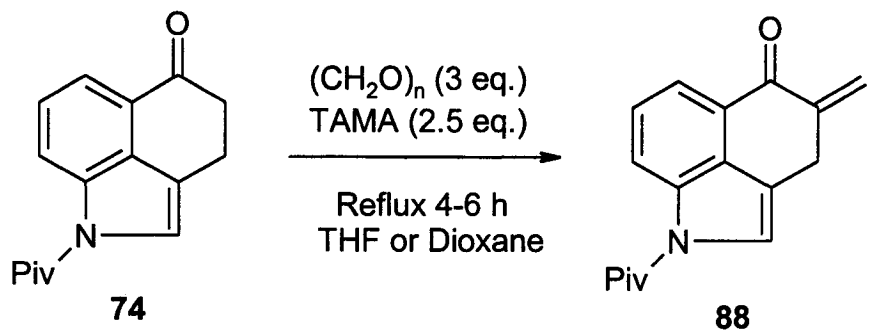
Scheme 4.13 Direct reaction conditions to α-methylene ketones.

We quickly confirmed the above reaction using both dioxane and THF as the solvents. A TLC of the reaction of **94** with paraformaldehyde and TAMA in refluxing dioxane or THF after 4 hours showed no remaining starting materials, and one major new product had been formed. The ^{1}H NMR of the crude reaction was obtained for both mixtures indicated the presence of two singlets at 5.2 and 6.1 ppm. These test reaction mixtures were not purified further, since we wanted only to confirm the quality of the TAMA reagent, and determine if this procedure worked in our hands.

4.4.2 Results of Mannich Reaction

The α-methylation of ketone **74** was carried out as above, both in THF and dioxane. In each reaction, **74**, paraformaldehyde (3 equivalents), and TAMA (2.5 equivalents) were dissolved in 10 mL of solvent. Both reactions were brought to reflux temperature. The reactions were monitored by TLC analysis at 4 and 6 hours of reflux time. The TLC indicated a new spot had formed, however starting

material was still very evident. The reactions were cooled to room temperature and stirred overnight with no change in appearance of TLC. The crude mixtures were diluted with diethyl ether and extracted with distilled water followed by saturated sodium carbonate solution. The organic extract was concentrated *in vacuo*, and a crude ^{1}H NMR was obtained. The desired methylene peaks near 5.5 ppm and 6.4 ppm expected for **88** were present in both cases.



Scheme 4.14 Mannich reaction using ketone **74** as starting material.

We attempted to purify the THF reaction product via column chromatography. The R_f difference between the **74** and product **88**, was very small so a careful chromatography was needed. The tubes containing the expected product were combined and concentrated to afford yellow oil. The ^{1}H NMR spectrum indicated the necessary methylene peaks at about 5.5 ppm and 6.4 ppm, in addition to only one CH_2 peak at about 4.1 ppm. This indicated that **88** had indeed formed via this reaction. However, in addition to these peaks, the spectrum also indicated a very large number of other peaks that were unidentifiable. A TLC sample was taken of the material in the NMR tube showed

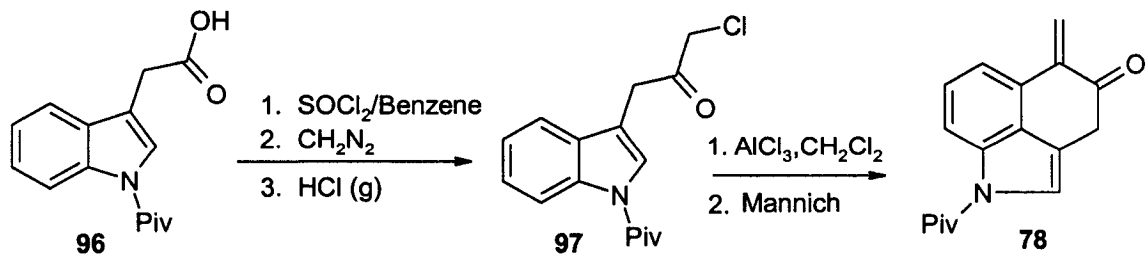
five new components. It appears that either the acid present in the slightly acidic silica gel, or the NMR solvent $CDCl_3$ may have caused the decomposition of the product.

At this time, the isolation of products from the dioxane reaction have not been completed. However, in future, a small amount of triethylamine should be added to the elution solvents in hopes of avoiding this problem.

4.5 Alternate Route to Enone 78

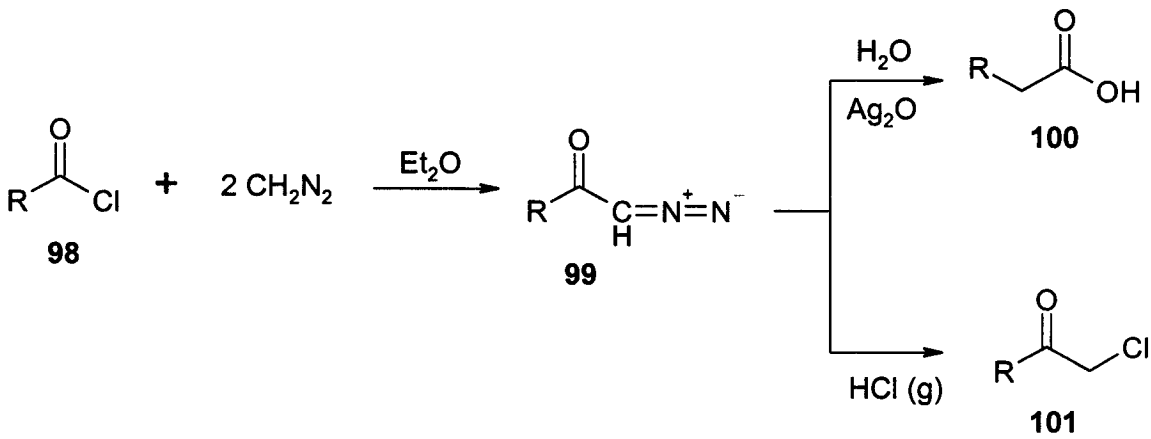
4.5.1 Background and proposed alternate route.

We also envisioned a second approach to **78** beginning with commercially available indole-3-acetic acid. In this approach, protection of the amine as its pivalyl amide was carried out in exactly the same manner as for indole-3-propionic acid. The yield of **96** was 62%. From here, an addition of one more carbon to the chain would be required to effect a 6-membered ring C after cyclization via a Friedel Crafts alkylation reaction.



Scheme 4.15 Proposed alternate route to enone **78**.

The conversion of of **96** to **97** is an example of the first step of the Arndt-Eistert synthesis. In the Arndt-Eistert synthesis, the addition of an acid chloride to an ethereal solution of diazomethane results in the formation of a diazo ketone with one additional carbon.[47] The treatment of ketone **99** with water and silver oxide results in the formation of the carboxylic acid product **100**, but, can be converted to the haloakane product **101** as illustrated in Scheme 4.16 in the presence of HCl gas.

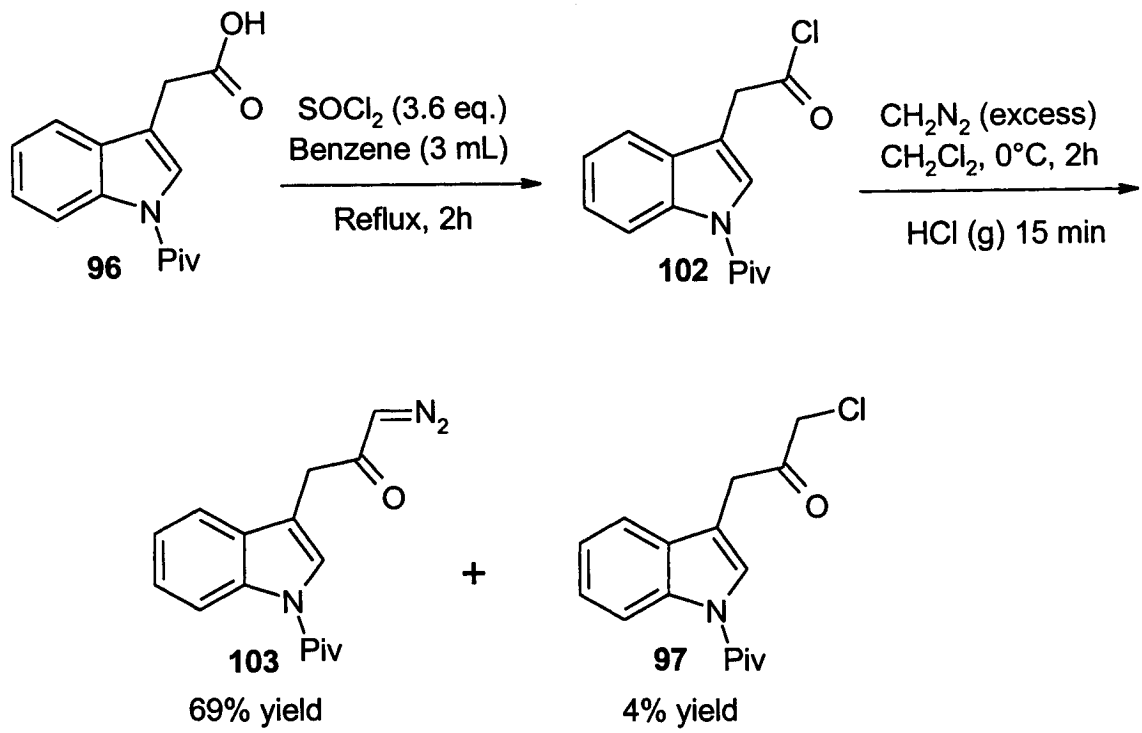


Scheme 4.16 General Arndt-Eistert synthesis.

4.5.2 Results and discussion.

For the conversion of **96** to **97**, we followed the procedure of Heathcook *et al.*[48] wherein they reported the conversion of 3-chlorphenylacetic acid to 1-chloro-3-(3'-chlorophenyl)-2-propanone in 89% yield. We did not have access to HCl gas and thus it was generated *in situ* by the addition of concentrated sulfuric acid

to sodium chloride and bubbled into the reaction mixture separately (Scheme 4.17).



Scheme 4.17 Results of the diazomethane chain extension reaction.

In our hands, this reaction did not proceed to completion as expected. The most plausible reason is due to inefficient HCl bubbling. We expected **97** as the only product, however, it was formed in very small quantities. This structure was confirmed using ^{1}H NMR (Figure 4.10) by the presence of two sharp singlets, each with an integration value of 2 at 4.01 and 4.16 ppm representing the two unique CH_2 groups on either side of the carbonyl. The ^{13}C spectrum (Figure 4.11) clearly identified 14 unique carbons for this 16-carbon molecule.

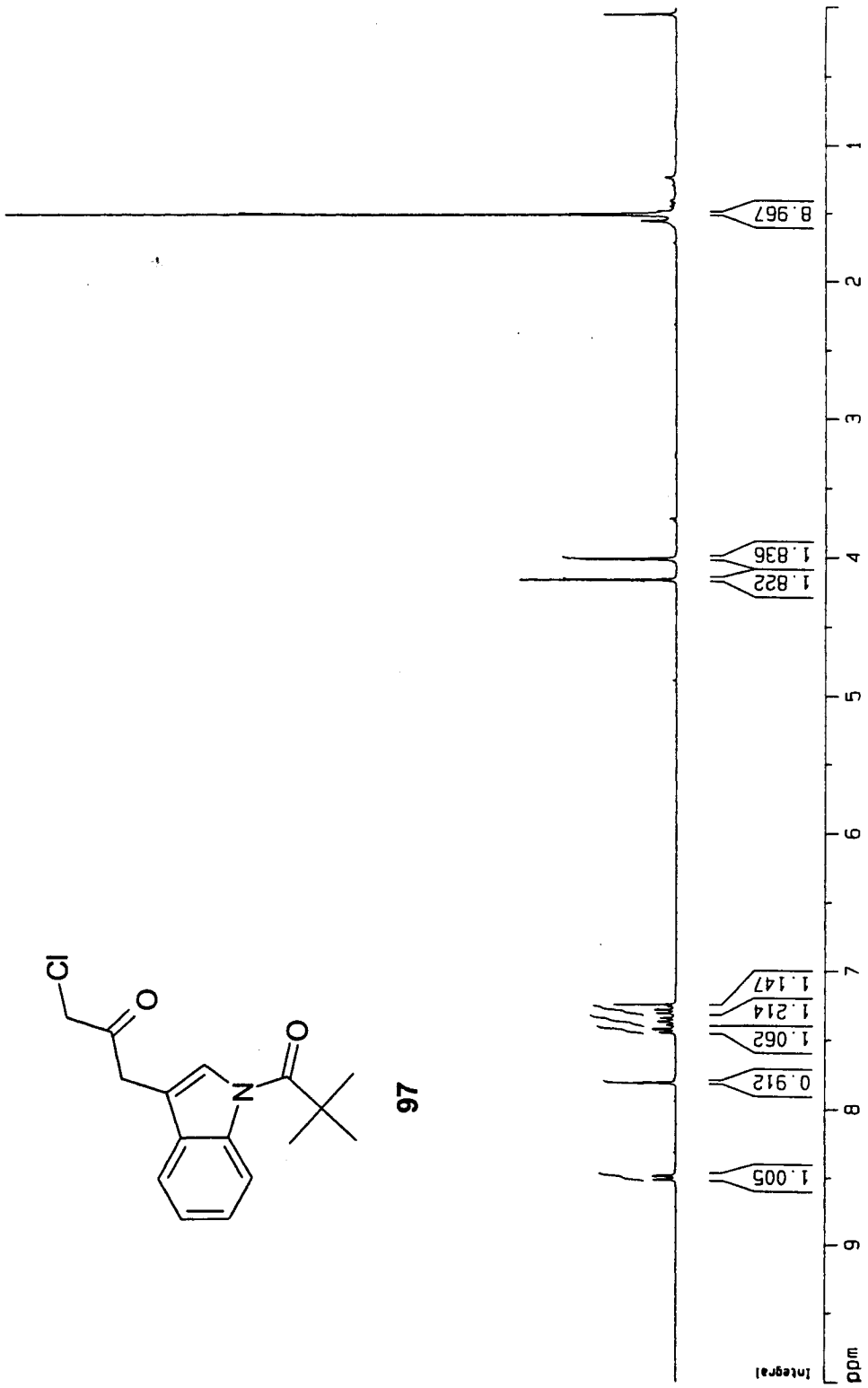


Figure 4.10 ^{1}H NMR spectrum of 1-[3-(3-chloro-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **97**.

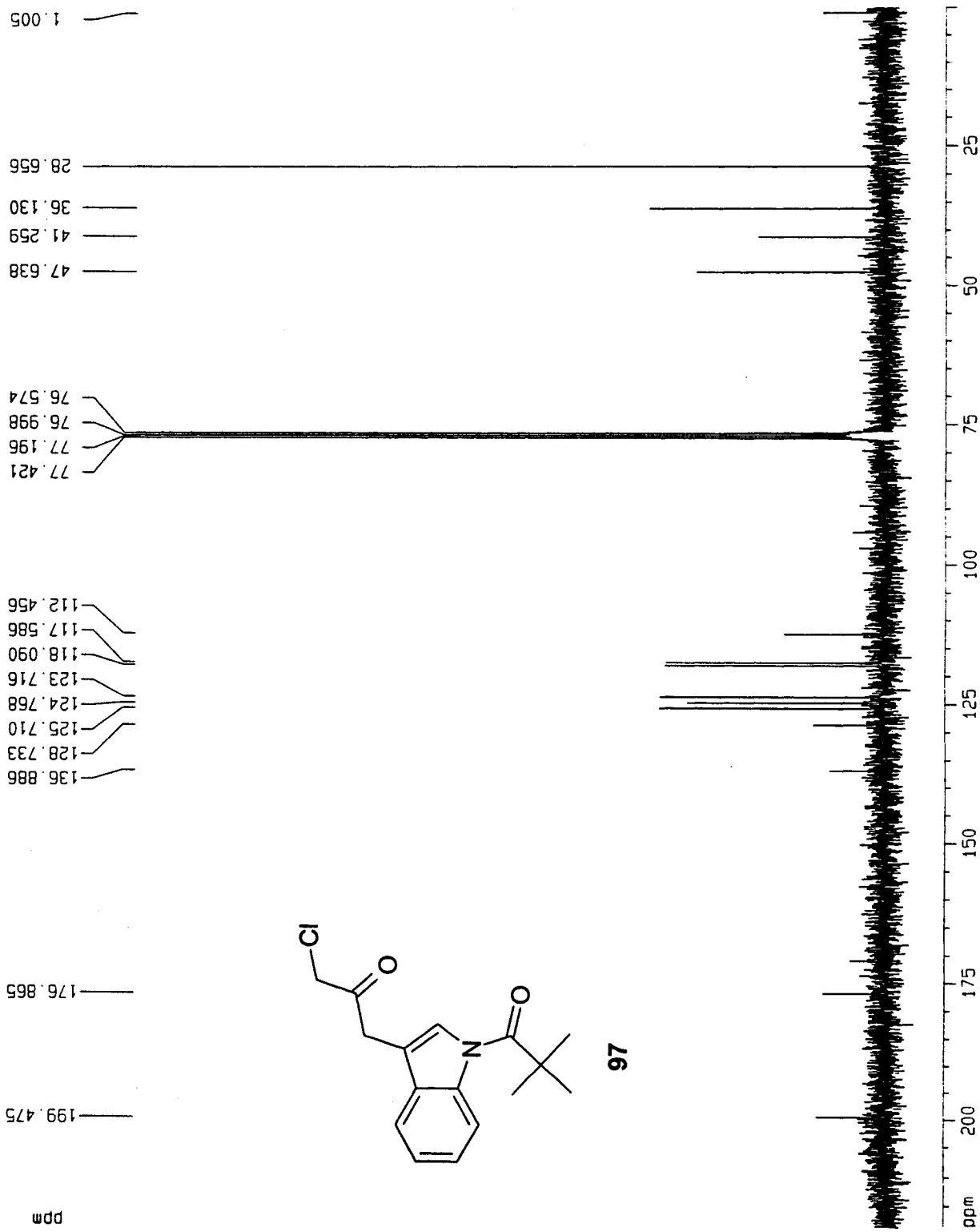


Figure 4.11 ^{13}C NMR spectrum of 1-[3-(3-chloro-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **97**.

The remaining two carbons are part of the *t*-butyl moiety of the protecting group. Mass spectral analysis confirmed the presence of one chlorine and one nitrogen atom in the molecular formula. Since only a very small amount of **97** was isolated, the Friedel Crafts alkylation reaction was not attempted.

The diazo reaction intermediate **103** was isolated as the major product in 69% yield as a yellow crystalline solid having a melting point of 130-136°C. These results were confirmed when the ^{1}H NMR spectrum (Figure 4.12) showed the expected H-2 singlet at 7.71 ppm in addition to a new methylene proton singlet at 5.25 ppm corresponding to the new α-proton. The $C=N_2$ carbon could be found at 141.4 ppm in the ^{13}C NMR spectrum (Figure 4.13) with all other carbons maintaining closely their original chemical shifts.

Interestingly, the reaction intermediate **103**, the diazo product presented an unforeseen opportunity to continue the synthetic route using a rhodium acetate catalyst. There are many examples of intramolecular carbenoid insertions which use rhodium to promote the formation of the carbene.[49,50] One particular example I found to be very interesting was from a research group at Brock University in St. Catherines, Ontario, Canada. Mohamed Salim and Alfredo Capretta[50] looked at the intramolecular reactions of α-diazoketones derived from indolyl-carboxylic acids, in which the α-diazoketone is linked at the C-3 position. Their results can be summarized as follows in Scheme 4.18:

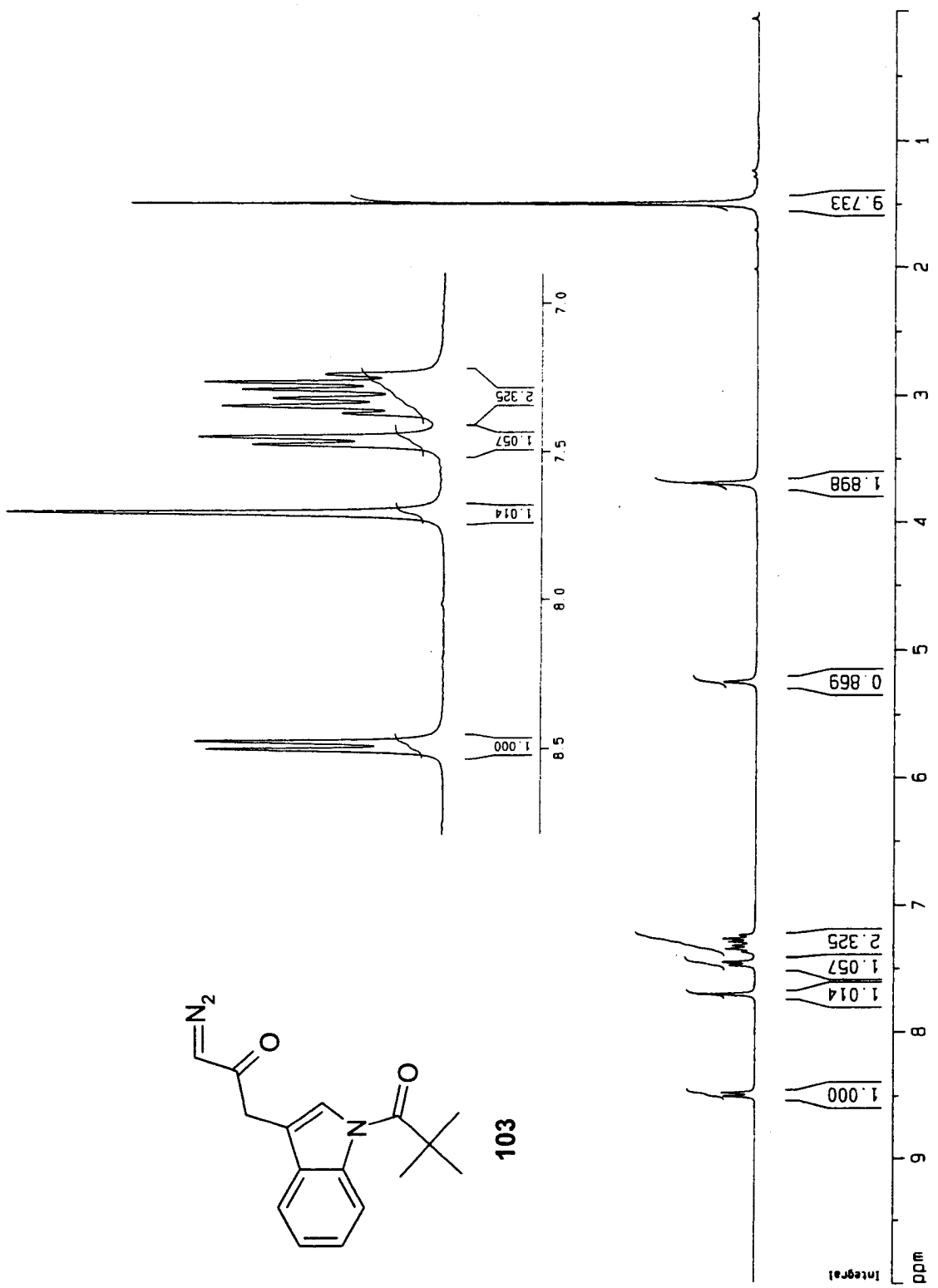


Figure 4.12 ^{1}H NMR spectrum of 1-[3-(3-diazo-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **103**.

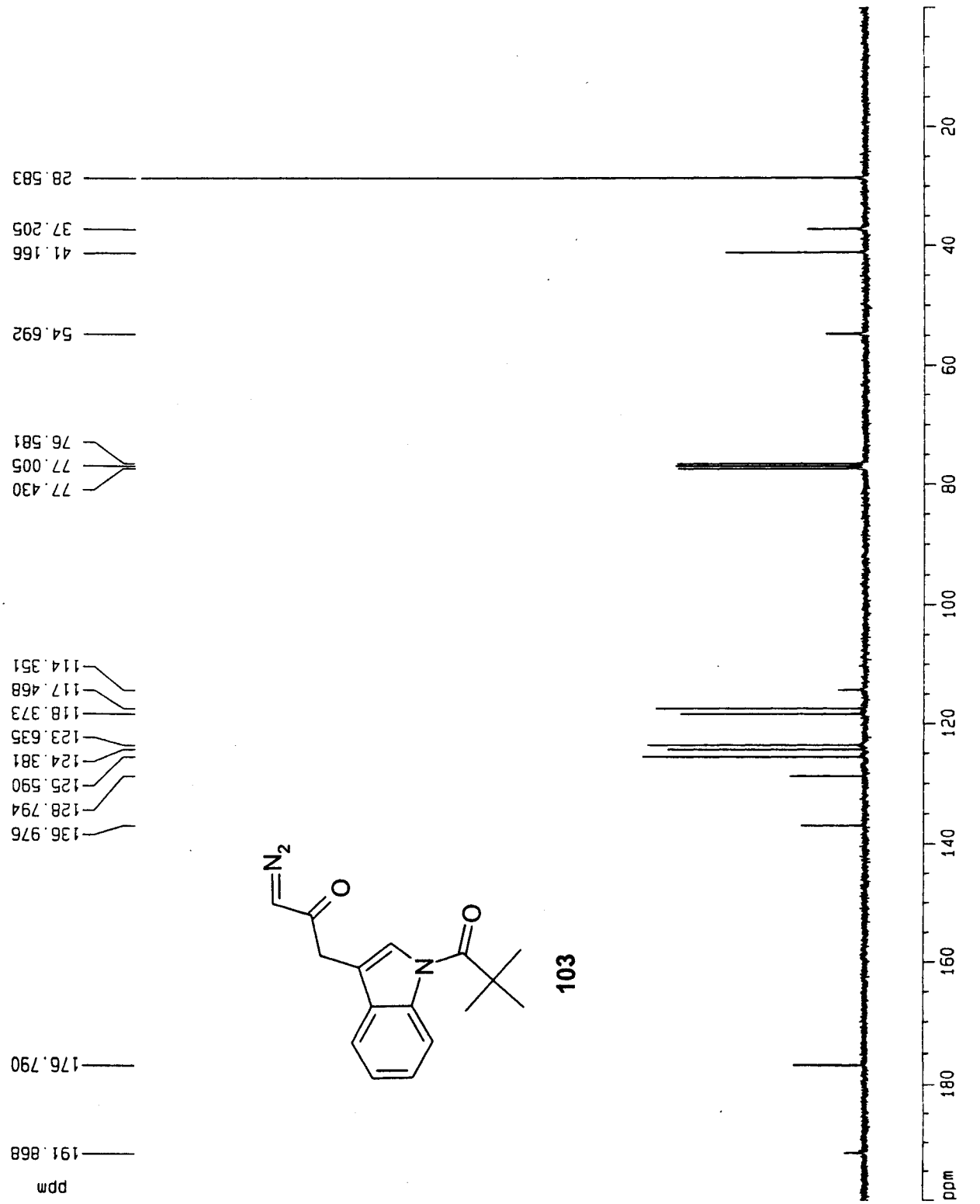
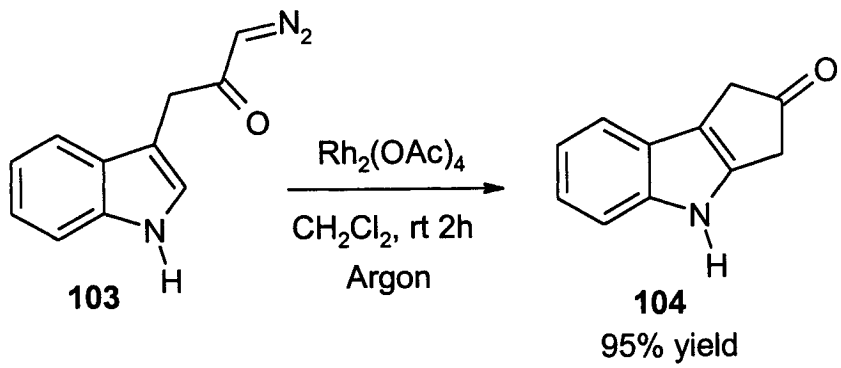


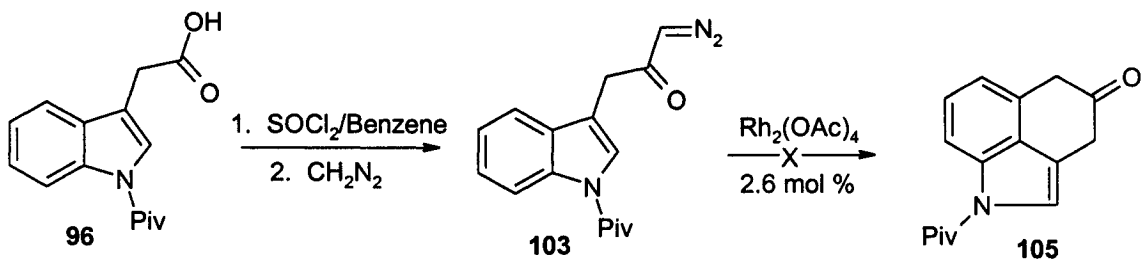
Figure 4.13 ^{13}C NMR spectrum of 1-[3-(3-diazo-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **103**.



103 **104**
95% yield

Scheme 4.18 Rhodium catalyzed ring closing reaction.

In this example, the cyclization occurs at the C-2 position. This is very reminiscent of the results of the previously described Friedel Crafts reaction before the modified conditions were used to block position 2. Therefore, we concluded that if position 2 were effectively blocked using the same pivalyl-protecting group, cyclization would once again occur in the desired position.



96 **103** **105**

Scheme 4.19 Attempt to use Rhodium catalyst to prepare ketone **105**.

A solution of **103** in methylene chloride was stirred at room temperature with 2.6 mol % of rhodium(II) acetate. Immediately after addition of the rhodium

species, the reaction bubbled vigorously and a green precipitate began to form. This evolution of gas confirmed that the starting material **103** was indeed a diazo compound. After 30 minutes, the evolution of gas had stopped and the reaction appeared to be complete. A TLC sample taken at this time showed many reaction products, so the mixture was stirred overnight at room temperature. The TLC once again showed many spots, and a crude NMR showed no identifiable compounds. No further purification was done at this time.

4.6 Conclusions of the Indole Apprach

The indole approach afforded many new synthetic ideas, all of which have potential to afford both the desired lysergic acid product **1**, and a variety of its isomers. Some of the key highlights to this approach are:

i. Starting materials are commercially available and are inexpensive.
ii. Reactions are well known and straight forward.
iii. Progress to the β-alcohol product **87** was short (4 steps), with only one additional oxidation step necessary to realize key intermediate, enone **78**.
iv. Opportunity exists to incorporate structural diversity into ring D.
v. To complete the synthesis of lysergic acid **1**, would require 4-5 additional steps for a total of 9-10 steps.

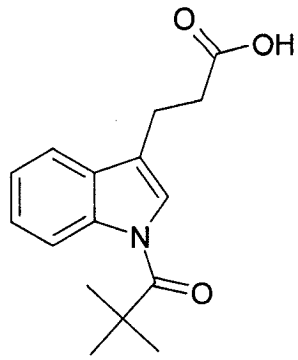
Therefore, we found the successes of this approach very exciting. Unfortunately, many of these results were only obtained during the last month of

experimentation, and further experiments were not able to be completed due to time restraints. However, the potential for the indole approach appears to be very promising indeed.

4.7 Experimental

PREPARATION OF 3-[1-(2,2-DIMETHYL-PROPIONYL)-1H-INDOL-3-YL]-PROPIONIC ACID 73

n-BuLi (20.2 mL, 34.3 mmol) was added dropwise to a stirred solution of 3-indole propionic acid **3** (3.25 g, 17.2 mmol) in THF (100 mL) under a nitrogen atmosphere at –78°C. The reaction mixture was stirred for 15 minutes followed by the dropwise addition of pivalyl chloride (2.12 mL, 17.2 mmol). The reaction was warmed slowly from –78°C to room temperature over 4 hours. The reaction mixture was quenched with saturated ammonium chloride solution (30 mL). The mixture was diluted with ethyl acetate (100 mL) and distilled water (100 mL). The layers were separated and the aqueous layer acidified to pH 5. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with water (2 x 50 mL) and brine (100 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo*. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **73** (3.64 g, 78% yield) as a fine white needle.



73

$C_{16}H_{19}NO_3$ MW=273.33 g/mole

m.p. 128-130°C

MS m/e (% rel. int.): 273 (43.6), 189 (20.9), 130 (100), 57 (82.1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 10.60 (s, OH), 8.51 (d, 1H, J=8.1 Hz), 7.58 (s, 1H), 7.50 (d, 1H, J=7.0 Hz), 7.36 (td, 1H, J=7.2, 1.1 Hz), 7.29 (td, 1H, J=7.2, 1.1 Hz), 3.06 (t, 2H, J=7.3 Hz), 2.78 (t, 2H, J=7.3 Hz), 1.48 (s, 9H).

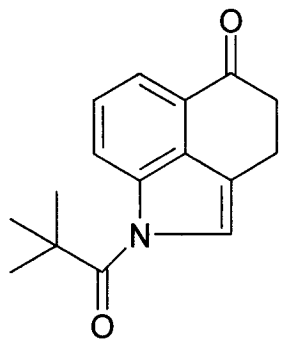
^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 179.1, 176.8, 137.1, 129.0, 125.4, 123.4, 122.7, 119.7, 118.1, 117.5, 41.4, 33.6, 28.5 (3C), 20.0.

PREPARATION OF 3-[1-(2,2-DIMETHYL-PROPIONYL)-1H-INDOL-3-YL]-PROPIONYL CHLORIDE 81

Thionyl chloride (4.7 mL, 18.1 eq.) was added **73** (0.9737 g, 3.56 mmol) and stirred at room temperature for 30 minutes. The excess thionyl chloride was removed *in vacuo*, and used immediately in the preparation of **74**.

PREPARATION OF 1-(2,2-DIMETHYLPROPIONYL)-3,4-DIHYDRO-1H-BENZO[C,D]INDOL-5-ONE 74

The solution of **81** in methylene chloride (20 mL) was added dropwise to a stirred mixture of aluminum chloride (1.89 g, 14.2 mmol) and chloroacetyl chloride (1.20 mL, 15.1 eq.) in methylene chloride (40 mL) at room temperature. The resulting mixture was stirred for 1 hour at room temperature before pouring into a beaker of ice and methylene chloride (50 mL). The layers were separated and the aqueous layer extracted with methylene chloride (3 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* to a dark solid. Column chromatography using a dry-loading method for the crude (8:2 hexanes/ethyl acetate) yielded **74** (0.56 g, 62% adjusted yield) as a white solid, and 1,4-dihydro-2H-cyclopenta[b]indol-3-one **72** (0.016 g, 1.5% yield).



74

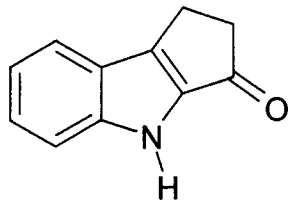
$C_{16}H_{17}NO_2$ MW=255.32 g/mole

m.p. 161-162 °C

MS m/e (% rel. int.): 255 (14.9), 171 (23.8), 143 (20.1), 115 (18.3), 85 (7.1), 57 (100), 41 (16.2).

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.51 (d, 1H, J=8.2 Hz), 7.70 (d, 1H, J=7.0 Hz), 7.58 (s, 1H), 7.40 (t, 1H, J=7.8 Hz), 3.20 (td, 2H, J=7.1, 1.1 Hz), 2.86 (t, 2H, J=7.1 Hz), 1.50 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 197.2, 177.0, 135.6, 133.4, 126.1, 125.6, 122.6, 121.1, 119.4, 116.0, 40.9, 38.8, 28.5 (3C), 20.4.



72

$C_{11}H_9NO$ MW=171.20 g/mole

m.p. > 250 °C

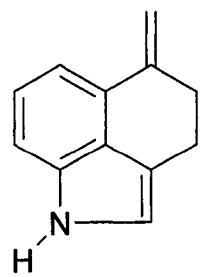
MS m/e (% rel. int.): 171 (100), 143 (74.8), 115(17.3), 40 (7.1).

^{1}H NMR (Acetone D_6, 300 MHz) δ(ppm): 11.31 (s, 1H), 7.71 (dd, 1H), 7.50 (dt, 1H), 7.34 (td, 1H), 7.12 (td, 1H), 3.07 (m, 3H), 2.88 (m, 2H).

^{13}C NMR (Acetone D_6, 300 MHz) δ(ppm): 194.1, 146.0, 144.9, 140.0, 127.1, 124.2, 121.9, 120.7, 114.4, 41.2, 20.2.

PREPARATION OF 5-METHYLENE-1,3,4,5-TETRAHYDRO-BENZO[C,D]INDOLE 82

n-BuLi (2.05 mL, 5 eq.) was added dropwise to a stirred suspension of methyl triphenylphosphonium bromide (1.45 g, 4.06 mmol, 5 eq.) in THF (20 mL) at 0°C. The reaction mixture was stirred for 1 hour at 0°C. To the resulting clear yellow solution was added a solution of **74** (0.207 g, 0.81 mmol, 1 eq.) in THF (15 mL) dropwise followed by three THF washes (6 mL). The ice bath was removed and the reaction mixture stirred at room temperature for 1 hour. The addition of saturated ammonium chloride solution (20 mL) and a 1:1 solution of hexanes/diethyl ether (25 mL) quenched the reaction mixture. The layers were separated and the aqueous layer extracted with 1:1 hexanes/diethyl ether (2 x 25 mL). The combined organic extracts were washed with distilled water (3 x 20 mL), and filtered through a 1 inch thick pad of silica wet with hexanes in a sintered glass funnel, then rinsed with 1:1 hexanes/diethyl ether (100 mL). The filtrate was dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* to afford pure **82** (0.135 g, 99% yield) as a pale yellow oil.



82

$C_{12}H_{11}N$ MW=169.23 g/mole

IR (CH_2Cl_2 thin film) $\nu(cm^{-1})$: 3417, 1631, 1594.

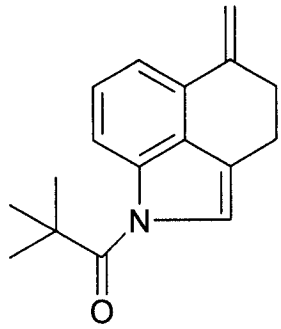
MS m/e (% rel. int.): 169.1 (100), 154.0 (33.1), 139.0 (18.2), 115.1 (13.5), 83.5 (12.1).

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 7.82 (s, 1H), 7.21 (m, 3H), 6.87 (s, 1H), 5.63 (dd, 1H), 5.15 (dd, 1H), 2.96 (t, 2H), 2.77 (t, 2H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 142.7, 134.3, 129.9, 123.5, 122.9, 117.7, 113.3, 112.2, 110.0, 109.0, 33.5, 22.4.

PREPARATION OF 2,2-DIMETHYL-1-(5-METHYLENE-4,5-DIHYDRO-3H-BENZO[C,D]INDOL-1-YL)-PROPAN-1-ONE 77

n-BuLi (0.60 mL, 1.2 eq.) was added dropwise to a stirred suspension of methyl triphenylphosphonium bromide (0.304 g, 0.85 mmol) in THF (20 mL) at 0°C. The reaction mixture was stirred for 1 hour at 0°C. To the resulting clear yellow solution was added a solution of **74** (0.217 g, 0.85 mmol) in THF (5 mL) dropwise followed by three THF washes (6 mL). The ice bath was removed and the reaction mixture stirred at room temperature for 1 hour. The reaction mixture was quenched with the addition of saturated sodium chloride solution (20 mL), distilled water (20 mL) and 1:1 hexanes/diethyl ether (50 mL). The layers were separated and the aqueous layer was extracted with 1:1 hexanes/diethyl ether (3 x 20 mL). The combined organic extracts were washed with brine (3 x 20 mL), then filtered through a 1 inch thick pad of hexane-wet silica on a sintered glass funnel, and rinsed with 1:1 hexanes/diethyl ether (100 mL). The filtrate was dried over anhydrous magnesium sulfate, filtered with cotton and concentrated *in vacuo*, and adsorbed to silica for purification. Column chromatography using a dry-load column yielded **77** (0.115 g, 69 % adjusted yield) as a white solid, and recovered starting material **74** (0.047 g).



77

$C_{17}H_{19}NO$ MW=253.35 g/mole

m.p. 133-135 °C

MS m/e (% rel. int.): 253 (76.3), 169 (100), 154 (19.6), 115 (14.1) 57 (100), 41 (19.4).

HRMS calculated 253.1467 g/mole

Found 253.1468 g/mole

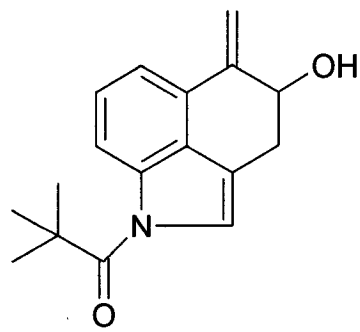
IR (KBr pellet) $\nu(cm^{-1})$: 1676, 1589, 1575.

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.23 (dd, 1H, J=7.3, 0.8 Hz), 7.39 (m, 2H), 7.31 (t, 1H, J=7.8 Hz), 5.61 (d, 1H, J=0.5 Hz), 5.16 (d, 1H, J=0.7 Hz), 2.90 (td, 2H, J=7.0, 1.1 Hz), 2.73 (td, 2H, J=6.9, 1.1 Hz), 1.50 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 177.0, 141.4, 135.5, 129.6, 128.1, 126.0, 118.8, 118.7, 116.9, 116.7, 109.9, 40.9, 32.7, 28.6 (3C), 22.1.

PREPARATION OF 1-(4-HYDROXY-5-METHYLENE-4,5-DIHYDRO-3H-BENZO[C,D]INDOL-1-YL)-2,2-DIMETHYL-PROPAN-1-ONE 87

tert-Butylhydroperoxide (TBHP) (200 μL, 2.06 mmol) was added to a stirred suspension of selenium dioxide (0.017 g, 0.15 mmol) in methylene chloride (5 mL) at room temperature. The reaction mixture was stirred for 30 minutes. To this suspension was added a solution of **77** (0.041 g, 0.16 mmol) in methylene chloride (5 mL) dropwise followed by one methylene chloride wash (3 mL). The resulting solution was clear yellow. After 2 hours at room temperature, benzene (5 mL) was added and the solvents were removed *in vacuo* to afford yellow oil. The crude oil was dissolved in diethyl ether (10 mL) and washed with 10% potassium hydroxide solution (4 x 1 mL) followed by brine (2 mL). The organic extracts were passed through a pipette filled with anhydrous magnesium sulfate and concentrated *in vacuo*. Chromatography of the crude product (8:2 hexanes/ethyl acetate) yielded **87** (0.021 g, 48 % yield) as a yellow oil.



87

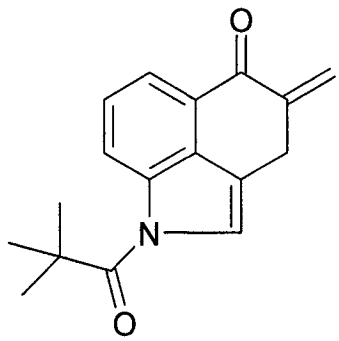
$C_{17}H_{19}NO_2$ MW=269.35 g/mole

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.25 (d, 1H, J=8.0 Hz), 7.49 (s, 1H), 7.45 (d, 1H, J=14 Hz), 7.36 (t, 1H, J=9.5 Hz), 5.71 (s, 1H), 5.44 (s, 1H), 4.77 (t, 1H, J=5.2 Hz), 3.08 (qd, 2H, J=16.6, 1.2 Hz), 1.98 (s, OH), 1.49 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 177.0, 144.0, 135.2, 127.1, 127.0, 126.5, 120.6, 118.0, 117.3, 115.8, 110.6, 71.5, 40.9, 30.5, 28.7 (3C).

PREPARATION OF 1-(2,2-DIMETHYL-PROPIONYL-4-METHYLENE-3,4-DIHYDRO-1H-BENZO[C,D]INDOL-5-ONE 88

A mixture of **77** (0.251 g, 0.98 mmol), paraformaldehyde (0.267 g, 2.96 mmol, 3 eq.), TAMA (0.546 g, 2.46 mmol, 2.5 eq.) in THF (50 mL) was refluxed for 6 hours, then cooled to room temperature while stirring was continued for an additional 18 hours. The reaction mixture was diluted with diethyl ether (50 mL) and distilled water (25 mL). The layers were separated, and the organic layer washed with distilled water (2 x 10 mL), and saturated sodium bicarbonate solution (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered through cotton, and concentrated *in vacuo* to a purple solid. Chromatography of the crude (8:2 hexanes/ethyl acetate) resulted in the partially purified product **88**. Yield was not determined.



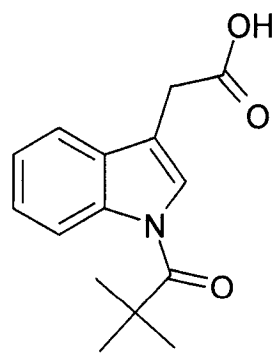
88

$C_{17}H_{17}NO_2$ MW=267.33 g/mole

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 6.38 (s, 1H), 5.55 (s, 1H).

PREPARATION OF [1-(2,2-DIMETHYL-PROPIONYL)-1H-INDOL-3-YL]-ACETIC ACID 96

n-BuLi (17.4 mL, 2 eq.) was added dropwise to a stirred solution of 3-indole acetic acid (3.04 g, 17.4 mmol) in THF (200 mL) at -78°C. The reaction mixture was stirred for 15 minutes. To the resulting solution, pivalyl-chloride (2.10 mL, 17.9 mmol, 1.03 eq.) was added at -78°C. The reaction mixture was warmed slowly from -78°C to room temperature over 3 hours. The reaction mixture was quenched by the addition of saturated ammonium chloride solution (50 mL) at room temperature. The resulting mixture was acidified to pH 5, extracted with ethyl acetate (3 x 100 mL), and the combined organic extracts washed with brine (100 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo*. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **96** (2.75 g, 62 % yield) as a hard caramel-like solid.



96

$C_{15}H_{17}NO_3$ MW=259.31 g/mole

MS m/e (% rel. int.): 259.1 (16.4), 175.1 (25.8), 130.1 (86.9), 77.0 (15.7), 57.1 (100).

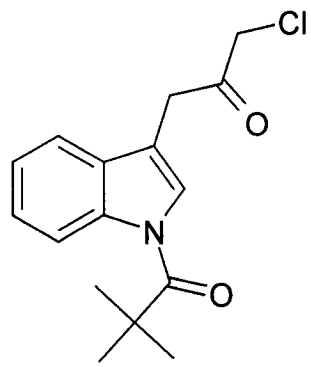
IR (KBr pellet) $\nu(cm^{-1})$: 2983, 1717, 1692, 1609.

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 10.24 (s, 1H), 8.52 (d, 1H, J=8.3 Hz), 7.67 (s, 1H), 7.53 (d, 1H, J=7.3 Hz), 7.33 (dt, 2H, J=12, 7.3 Hz), 3.78 (s, 2H), 1.50 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 177.0, 176.9, 137.0, 128.8, 125.5, 124.4, 123.5, 118.4, 117.5, 113.2, 41.2, 30.7, 28.6 (3C).

PREPARATION OF 1-[3-(3-CHLORO-2-OXO-PROPYL)-INDOL-1-YL]-2,2-DIMETHYL-PROPAN-1-ONE 97

Thionyl chloride (0.20 mL, 3.6 eq.) was added to a stirred a mixture of **96** (0.199 g, 0.77 mmol) in benzene (3 mL) at room temperature. The resulting dark red solution was refluxed for 2 hours. The reaction mixture became brown during the refluxing process. Once cooled, the reaction mixture was concentrated *in vacuo*, then dissolved in methylene chloride (5 mL) and cooled further to 0°C. To this solution was added dropwise ethereal diazomethane solution (0.32-0.35 g CH_2N_2) 0°C. The resulting mixture was stirred at 0°C for one hour followed by one hour at room temperature. Hydrochloric acid gas (NaCl pellets and concentrated sulfuric acid) was bubbled through the reaction mixture for 15 minutes followed by the slow addition of distilled water (15 mL). The layers were separated and the aqueous layer extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (20 mL), dried over anhydrous magnesium sulfate, filtered through cotton and concentrated *in vacuo* affording a brown oil. Chromatography of the crude (8:2 hexanes/ethyl acetate) yielded **97** (0.009 g, 4% yield) as a pale yellow oil, and 1-[3-(3-diazo-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **103** (0.151 g, 69% yield), a yellow crystalline solid as the major product.



97

$C_{16}H_{18}NO_2Cl$ MW=291.78 g/mole

IR (neat) $\nu(cm^{-1})$: 1737, 1693, 1320, 756.

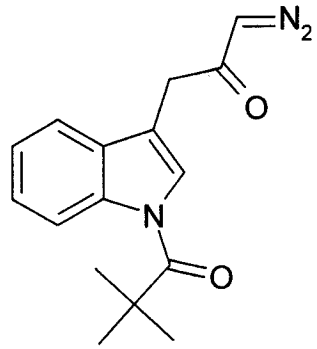
MS m/e (% rel. int.): 291 (7.1), 130 (82.1), 84 (59), 57 (100), 47(22.3), 35 (10.5).

HRMS calculated 291.1027 g/mole

found 291.1046 g/mole

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.50 (d, 1H, J=8.3 Hz), 7.81 (s, 1H), 7.43 (d, 1H, J=7.8 Hz), 7.37 (td, 1H, J=7.7, 1.3 Hz), 7.28 (td, 1H, J=7.2, 0.9 Hz), 4.16 (s, 2H), 4.01 (s, 2H), 1.51 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 199.5, 176.9, 136.9, 128.7, 125.7, 124.8, 123.7, 118.1, 117.6, 112.5, 47.6, 41.3, 36.1, 28.7 (3C).



103

$C_{16}H_{17}N_3O_2$ MW=283.33 g/mole

m.p. 130-136°C

IR (KBr pellet) $\nu(cm^{-1})$: 3129, 2113, 1687, 1628.

MS m/e (% rel. int.): 283 (1.4), 255 (20.1), 170 (11.5), 143 (29.8), 130 (22.2), 57 (100), 41 (25.7).

^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm): 8.50 (d, 1H, J=8.2 Hz), 7.71 (s, 1H), 7.47 (d, 1H, J=7.5 Hz), 7.35 (t, 1H, J=7.6 Hz), 7.27 (t, 1H, J=7.7 Hz), 5.25 (s, 1H), 3.70 (s, 2H), 1.50 (s, 9H).

^{13}C NMR ($CDCl_3$, 300 MHz) δ(ppm): 191.9, 176.8, 137.0, 128.8, 125.6, 124.4, 123.6, 118.4, 117.5, 114.4, 54.7, 41.7, 37.2, 28.6 (3C).

Claims to Original Research

1. A new route to the lysergine ring system was proposed via the Benzyne route.
2. A number of synthetic routes to the Heck cylclization precursor 3-but-3-enyl-4-iodo-1-methyl-1,3-dihydro-indol-2-one **33**.
3. The preparation of the following key intermediates for our proposed Indole route to lysergic acid **1** and some isomers of **1**:
    a) 5-Methylene-1,3,4,5-tetrahydro-benzo[c,d]indole **82**.
    b) 2,2-Dimethyl-1-(5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-propan-1-one **77**.
    c) 1-(4-Hydroxy-5-methylene-4,5-dihydro-3H-benzo[c,d]indol-1-yl)-2,2-dimethyl-propan-1-one **87**.
    d) 1-(2,2-Dimethyl-propionyl-4-methylene-3,4-dihydro-1H-benzo[c,d]indol-5-one **88**.
    e) 1-[3-(3-Chloro-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **97**.
    f) 1-[3-(3-Diazo-2-oxo-propyl)-indol-1-yl]-2,2-dimethyl-propan-1-one **103**.

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