Université d'Ottawa · University of Ottawa

Table of Contents

List of Schemes

List of Tables

List of Figures

List of Abbreviations:

AIBN	azobis(isobutyro)nitrile
cat.	catalytic
DIBAL-H	diisobutylaluminium hydride
DMSO	dimethylsufoxide
HMPA	hexamethylphosporaimide
HRMS	high resolution mass spectrometry
IR	infra red
LUMO	lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MHz	mega hertz
NMR	nuclear magnetic resonance
OEt	ethoxy
ppm	parts per million
S.M.	starting material
SOMO	single occupied molecular orbital
THF	tetrahydofuran
TIPSOTf	trisisopropysilyltriflate
TLC	thin layer chromatography
TMSI	trimethylsilyliodide
TTMSS	tris(trimethylsilyl)silane

Acknowledgments

I would like to thank Dr. Alex Fallis for his confidence in me. He has given me the chance to prove to myself and to others, that with a little bit of hard work and determination, anything is possible. Without his continuous support and leadership, this work would not be possible.

I would like to thank also Dr. Tony Durst and Dr. Howard Alper for their continuous support and encouragement as well as for the many interesting conversations we shared.

I would also like to thank the staff of the department (Lise, Annette, Mike O., Monique, Don, Lee, John, Mario...all the ones I forgot) since without their continuous hard work, no grad student would be able to finish what they started.

I would like to thank my colleagues (Mike T., Martin, Sandrine, Mike B., Claudio, Irina, Jodi, Hélène A., Jonathan, Simon, Poonam, Tham, Scott, Curt, Bogdan, Pete and Tim) for their continuous support, sense of humor, chemistry discussions and their immense patience. Thanks guys.

There are a few of my close friends I would like to thank for their help over the years, when I visited the various fine drinking establishments of this world, after many frustrating hours of lab work. Pete, Will, Chuck, Drew, Sue and Jeff..... thanks a bunch.

I would particularly like to thank someone who pushed me, and gave me a kick in the butt to finish when I wanted to give up. Cindy Jane Smith, thank you for everything. If it wasn't for you, this would never gotten done.

Jodi Lavers, thank you for your constant support, your wisdom and being a friend when times were hard. Thanks for listening to me bitch and complain about life and its many difficulties.

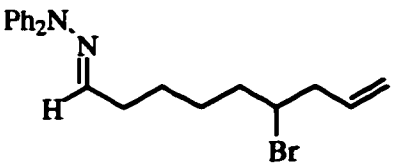
Il faut aussi que je remercie toute ma famille. Durant ces deux dernières années, ils m'ont encouragé, supporté et enduré. Merci

..... to those who have a dream.....

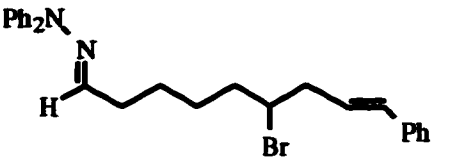
Abstract

The preparation of various hydrazones for use in radical cyclizations is described. The radical cyclization of (**A**) and (**B**) under various radical conditions lead to the tandem cyclization of octahydroindoles (**C**) and (**D**) under neutral conditions.

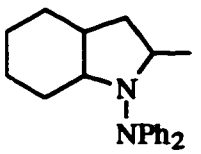
The reaction of (**E**) under various radical conditions lead to the first synthesis of a seven membered ring by attack of a carbon radical onto a carbon-nitrogen multiple bond, forming (**F**).



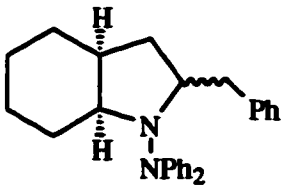
A



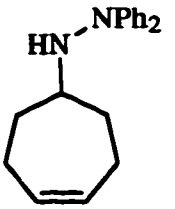
B



C



D



F

E

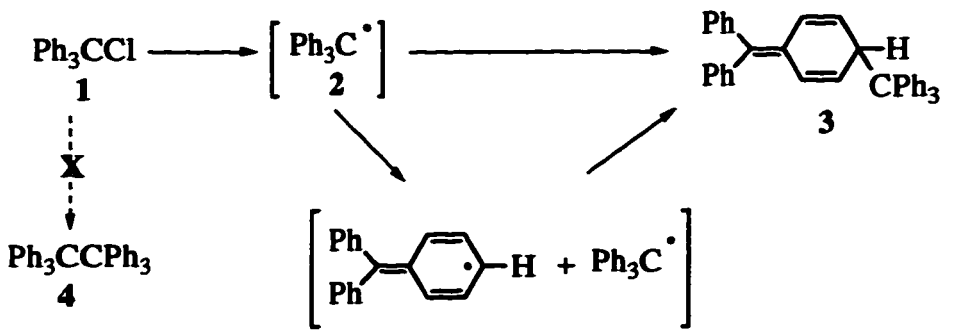
X= Br, I

Chapter 1: Introduction

General Introduction

One of the fastest growing fields in organic chemistry encompasses the use of free-radicals for the synthesis of target molecules[1]. It was Gomberg's[2] work on the preparation of the triphenylmethyl radical, who first discovered carbon centered free-radicals, in an attempted Wurtz coupling reaction. Treatment of Ph_3CCl with zinc generated the stable triphenylmethyl radical that underwent dimerization, as illustrated below (Scheme 1).

Scheme 1: Radicals Prepared by Gomberg

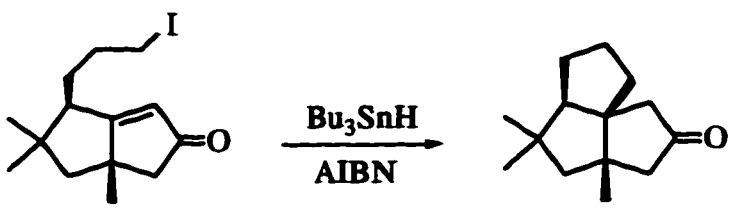


The methods of choice to make C-C bonds in organic synthesis are dominated by ionic reactions, but there are advantages to the use of radical methods over their corresponding ionic counterparts[3]. Radicals are by nature very reactive species, yet the conditions under which these reactions take place are usually neutral and mild. This is advantageous, in that functional groups such as NH or OH are commonly not affected by the conditions.

The addition of carbon centered radicals to C=C bonds are strongly exothermic and irreversible[4]. Radicals are not ionic in nature and hence do not have the burden of counter

ions or solvation shells which can be bulky. As such, they are very effective in that they react at congested sites[5]. An example of this is a 5-*exo* cyclization onto a sterically crowded double bond (Scheme 2) in the synthesis of silphinene by Nagarajan.

Scheme 2: Sterically Hindered Addition

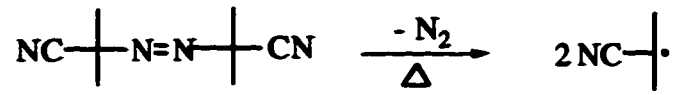


5 **6**

The most common procedure to carry out radical reactions is termed the "tin hydride method"[6]. There are three steps in a radical mediated process; initiation, propagation, and termination. The tin hydride method involves the treatment of a substrate (R-X, where X is usually a halogen) with Bu_3SnH and AIBN in benzene. The mechanism for this controlled chain reaction is depicted below (Scheme 3)

Scheme 3: Mechanism of The Tin Hydride Chain Reaction

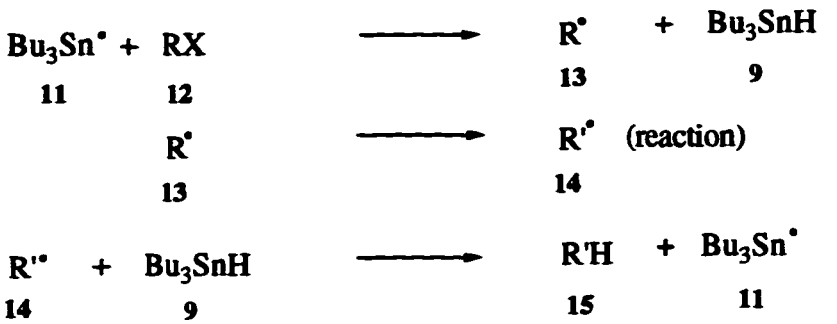
Initiation



7 8

8 9 10 11

Propagation



11 12 13 9

13 14

14 9 15 11

Termination

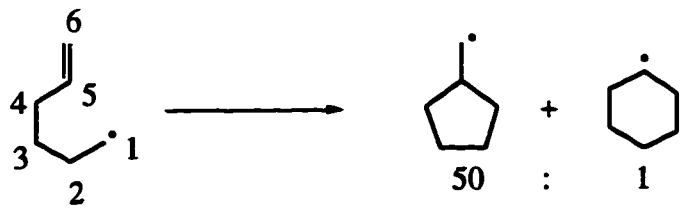
11 11 16

A radical initiator starts the chain process. Usually, AIBN is the reagent of choice since under thermal conditions, it decomposes to generate a *tert*-butyl radical. This radical then abstracts a hydride from the tin reagent generating a tin radical. The tin radical then attacks the carbon halogen bond giving the radical on the substrate. The substrate undergoes a reaction and the resulting radical can be quenched with a molecule of tin hydride. This regenerates the reactive tin radical and continues the chain process. The reaction stops when all the substrate has reacted and the tin radical recombines.

This general scheme also holds for other similar radical reagents such as Bu_3GeH and $(TMS)_3SiH$. AIBN thermally decomposes to generate the source of the initial radical. This leads to the formation of a tin radical which is also termed the chain transfer agent. The reaction is driven thermodynamically by the conversion of a weak C-X bond to a stronger C-H bond.

Intramolecular reactions are very useful in organic synthesis, particularly those which involve a cyclization process. The cyclization of the 5-hexenyl radical has been studied extensively, and is well understood[1]. The reaction follows Baldwin's rules of cyclization[7] where the 5-*exo* mode of closure is favored over the 6-*endo* by a factor of 50 at 25 °C as shown in the following scheme.

Scheme 4: 5-Hexenyl Cyclization



17 **18** **19**

The cyclization proceeds *via* a cyclic chair like transition state conformation as proposed by Beckwith[8] and shown below in Scheme 5. There are a few reasons why a 5-*exo* attack is preferred. The first is that the angle of attack for the 5-*exo* is 106 ° rather than 94 ° for the 6-*endo*. The 6-*endo* case would result in extra torsion strain compared to the 5-*endo*. Poor SOMO-LUMO interactions in the transition state also disfavor the 6-*endo* pathway. The 5-*exo* attack is also favored since entropically it retains a degree of freedom[4].

Scheme 5: Transition State of The 5-Hexenyl Cyclization

5-*exo* chair
favoured

20

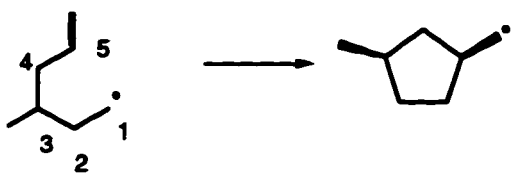
6-*eno* chair
disfavoured

21

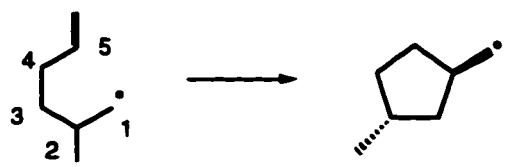
Relative Stereochemical Control

The relative stereochemistry of the 5-hexenyl cyclization can be predicted quite readily. The transition state resembles a cyclohexane ring in its chair conformation. Steric demand dictates that the substituents lie pseudo-equatorial rather than pseudo-axial[4,9]. Studies have shown that substitution at C1 and C3 result in *cis* disubstituted cyclopentanes, and substitution at C2 and C4 give *trans* disubstituted cyclopentanes as shown below (Scheme 6).

Scheme 6: Stereocontrol of Cyclizations



22 **23**



24 **25**

The high degree of relative stereocontrol found for the 5-*exo* hexenyl cyclization, does not follow for the 6-*exo* heptenyl case. The major product usually results from a chair conformation transition state with the substituents occupying the pseudo equatorial position[10] as shown in Scheme 7 below.

Scheme 7: Transition State of the 6-Heptenyl Cyclization

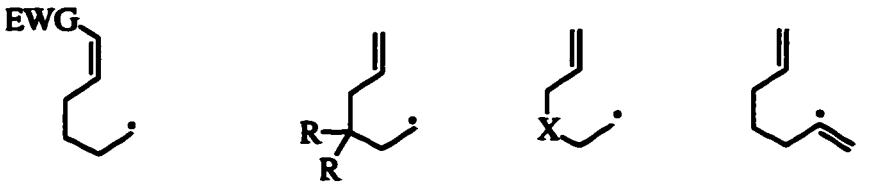
major **26**

minor **27**

Not only do the substituents play a significant role on the stereochemical outcome of a reaction, but they can also play an important role in the rate of cyclization. The following scheme summarizes briefly the accelerating and decelerating[1] effects of the substituents on simple cyclizations.

Scheme 8: Effects of Substitution on the Rate of Radical Cyclization

accelerating

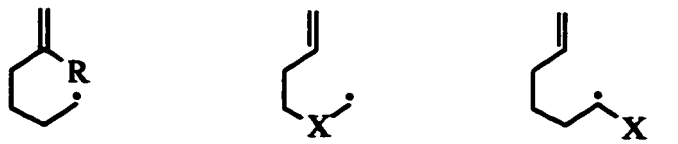


28a **28b** **28c** **28d**

EWG = electron-withdrawing group

X = O, NR

decelerating



29a **29b** **29c**

R ≠ H X = O, NR X = O, NR

The rate accelerating effect of the electron-withdrawing group (**28a**) can be explained by molecular orbital theory. The reactions of carbon centered radicals with C=C double bonds are dominated by SOMO-LUMO interactions. The electron-withdrawing group lowers the LUMO of the olefin and accelerates the rate of reaction[11]. The geminal alkyl groups (**28b**) and the heteroatom at C3 (**28c**) bring the radical and the C=C double bond closer in space and in turn increase the rate of reaction. This is known as the Thorpe-Ingold effect[1]. In the last example of accelerating substituents (**28d**), a vinyl radical is notably much more reactive (approx. 200X) than an alkyl radical.

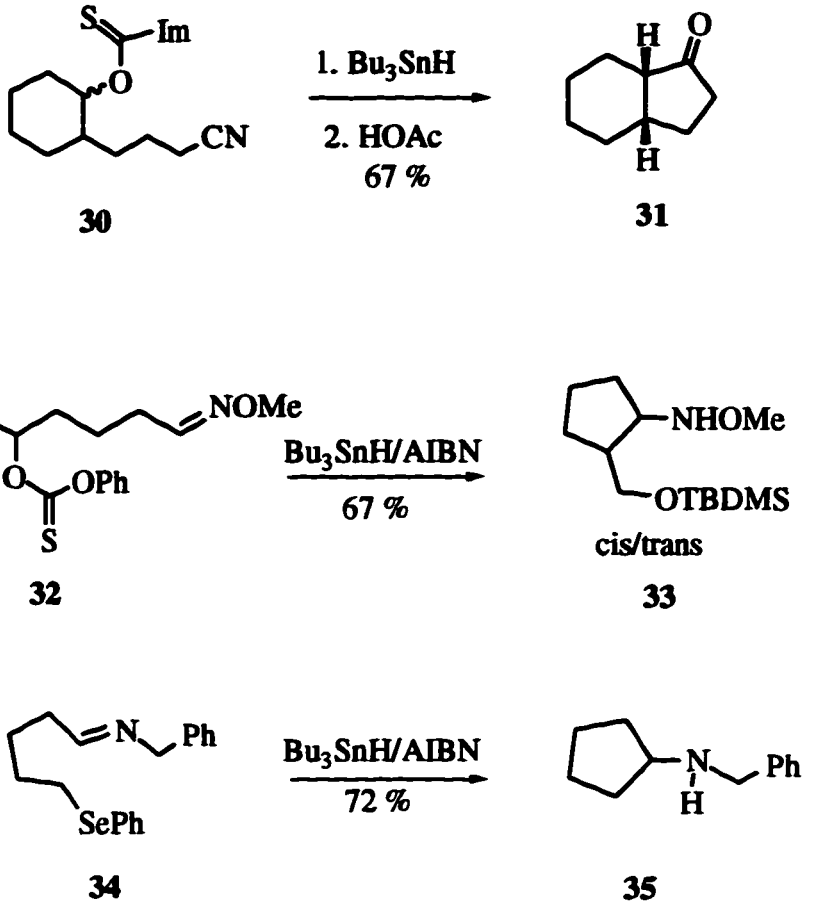
Increased substitution about the double bond (**29a**) decreases the rate of reaction. Replacement of R=H by R=Me, results in a 40 fold decrease in rate. The stabilizing effect by the oxygen or nitrogen α to the radical (**29b**, **29c**) also slows the rate of reaction[1].

Additions to C=N Double Bonds

Intramolecular radical cyclizations onto C=C have been examined extensively[1]. However, a problem of this process involves the net loss of two functional groups to construct a ring. This limits the use of classical radical reactions in the early stages of a synthetic route. An efficient alternative is to have a carbon centered radical attack a C=X (where X is a heteroatom) multiple bond. There is much literature covering the attack of radicals onto C=O double bonds[12]

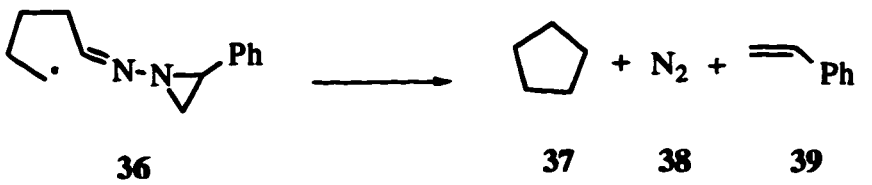
Much less interest has been directed towards C=N bonds but, nitriles[13] and oxime ethers[14] have been the most commonly used C=N acceptors. More recently, Bowman[15] has reviewed the extensive work on the utilization of imines as radical acceptors. Scheme 8 gives representative examples.

Scheme 9: Attack of Radicals onto C=N Systems



Hydrazones are equally good radical acceptors compared to the examples shown above. Indeed, Kim[16] has shown that his specialized hydrazones are very good radical acceptors as shown below (Scheme 10).

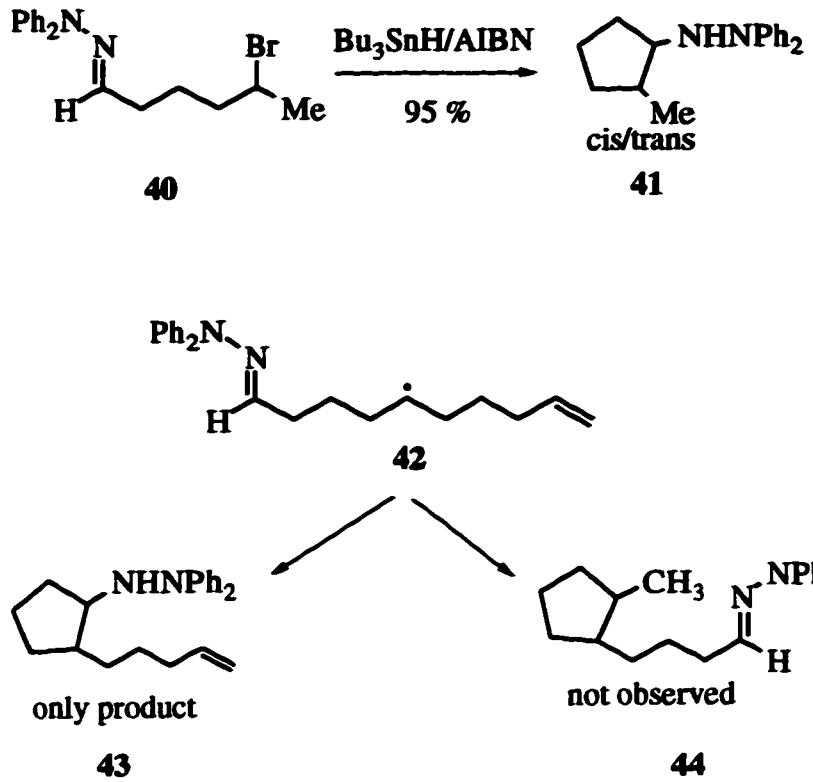
Scheme 10: Kim's Hydrazone



It is clear from Kim's work that the driving force of the reaction is the loss of nitrogen gas and the formation of styrene. When work in our laboratory started on the subject of radicals attacking C=N bonds, Kim's example of radical attack onto hydrazones, was the only example in the literature. It was decided to investigate whether these types of reactions were reserved for Kim' specialized hydrazone or whether a simple hydrazone was just as good a radical acceptor.

This reaction is interesting but not synthetically useful, as simple cyclic molecules are made at the expense of loss of functionality. Recently, studies from this laboratory[17,18] have shown that not only do *N,N*-diphenyl hydrazones prove to be good radical acceptors, but in a radical-clock experiment, covering competition for 5-*exo* cyclization onto the hydrazone *vs.* 5-*exo* cyclization onto C=C double bond, only the cyclized product form the 5-*exo* cyclization onto the hydrazone was observed.

Scheme 11: Radical Cyclization onto *N,N*-Diphenyl Hydrazones

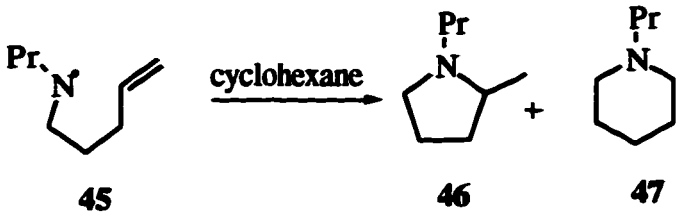


Rates calculated showed that the preferred hydrazone cyclization was >200 times faster than onto C=C double bonds. Concurrent results published by Bowman[19], showed that for a selection of hydrazones, the only product observed from the radical reaction was the 5-*exo* cyclization onto the hydrazones.

Attack of Nitrogen Radical onto C=C Double Bonds

One of the more interesting topics at the moment in radical chemistry involves the attack of aminyl radicals onto C=C double bonds. However, investigation of the literature reveals a number of discrepancies on this subject. The first work in this area was performed by Michejda[20] where it was shown that **45** cyclizes under both photolytic and thermolytic conditions to afford **46** and **47** in low yields as shown below (Scheme 12).

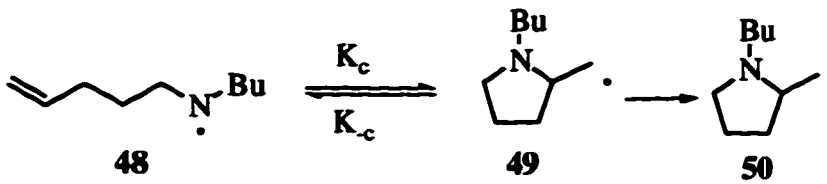
Scheme 12: Aminyl Radical Cyclizations



45 46 47

More recent examples include the work by Newcomb[21] where studies on compound **48** in the presence of Bu_3SnH show that the intermediate **49** can undergo reversible cyclization as shown in the scheme 13.

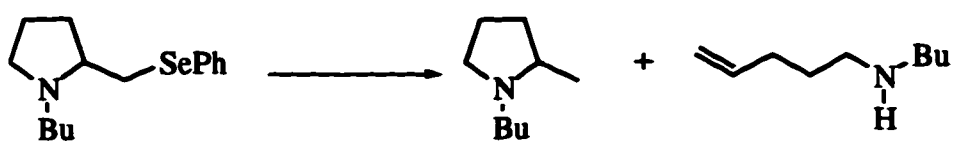
Scheme 13: Bowman's Reversible Cylization



48 49 50

Bowman[22] however was unable to isolate **50** at low concentrations of Bu_3SnH in boiling cyclohexane and this led him to believe that the cyclization was reversible. The latest report on this subject by Tsanaktsidis[23] has shown that upon treatment of **51** with Bu_3SnH/AIBN, no acyclic amine **52** was observed as shown in Scheme 14.

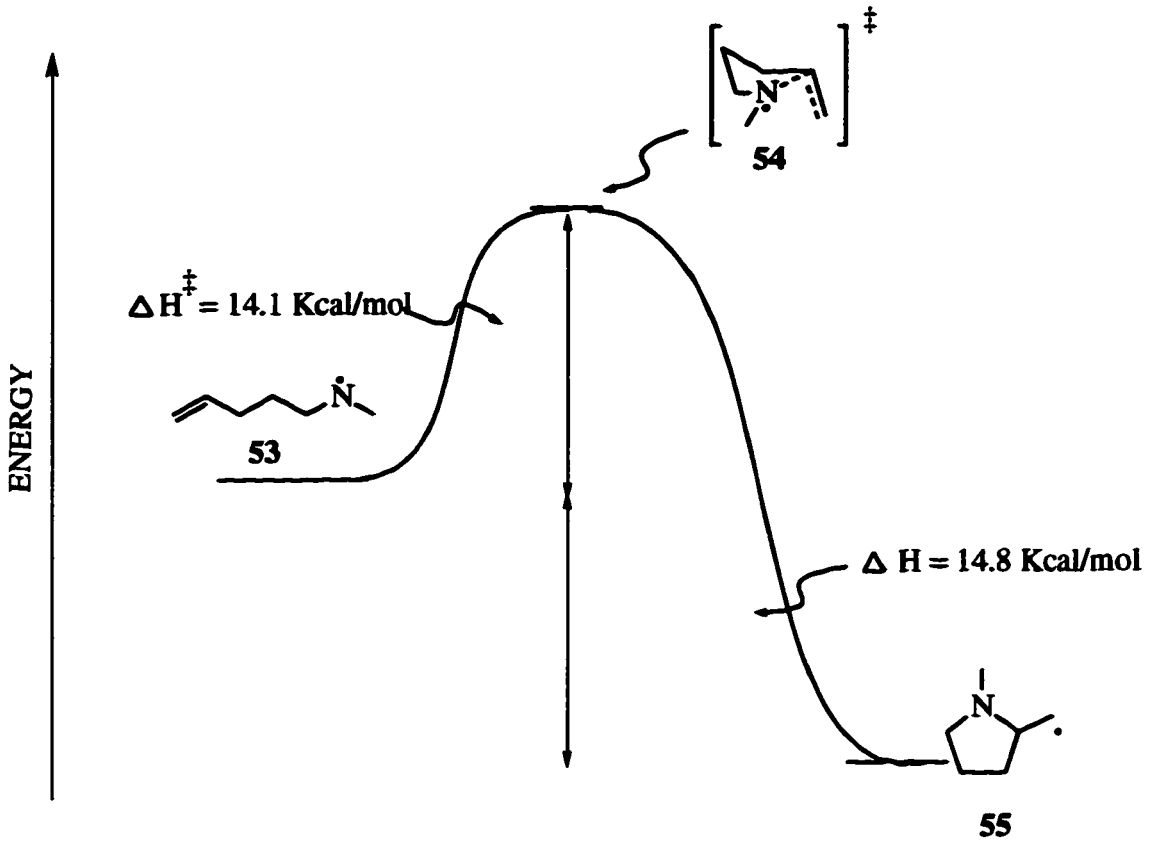
Scheme 14: Irreversible Cyclization



51 50 52

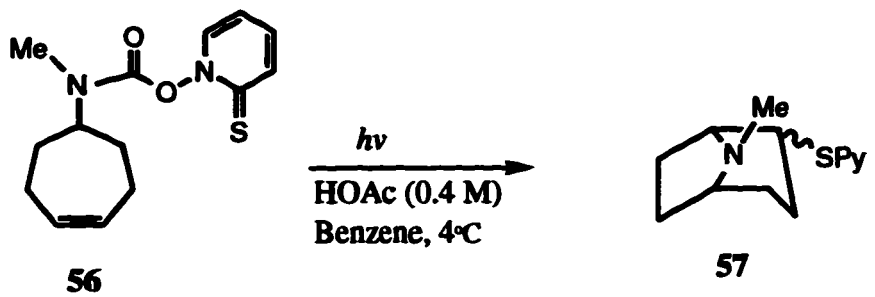
He also demonstrated with calculations that an *Ab initio* energy profile for the 5-*exo* ring closure to be highly exothermic as shown in the following figure 1.

Figure 1: Energy Requirements of N Radicals



This figure shows that the reaction is highly exothermic but a great amount of energy is required to overcome the transition state barrier. Most of the reported cyclizations occur under acidic conditions or with the addition of Lewis acids such as $(Bu_3Sn)_2O$ or $MgBr_2 \cdot Et_2O$. Newcomb[24] devised a very elegant method to tropane skeletons as shown in Scheme 15 below.

Scheme 15: Synthesis of the Tropane Skeleton

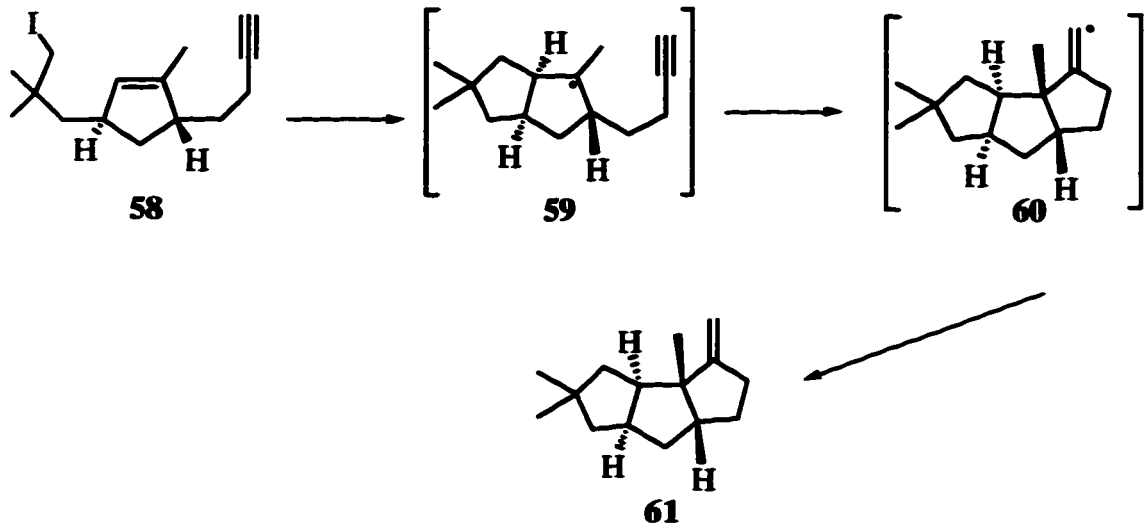


56 57

Tandem Radical Cyclization

One can postulate that the radical generated after one cyclization could continue in a second (or third, etc.) cyclization onto a suitable π system. This principle of tandem radical cyclization has been developed by Curran[1]. This powerful tool can create complex ring systems particularly if the regiochemistry and the absolute stereochemistry of the chain reaction can be controlled. There are a number of very interesting examples from Curran's[25] work, for example, the synthesis of Hirsutene.

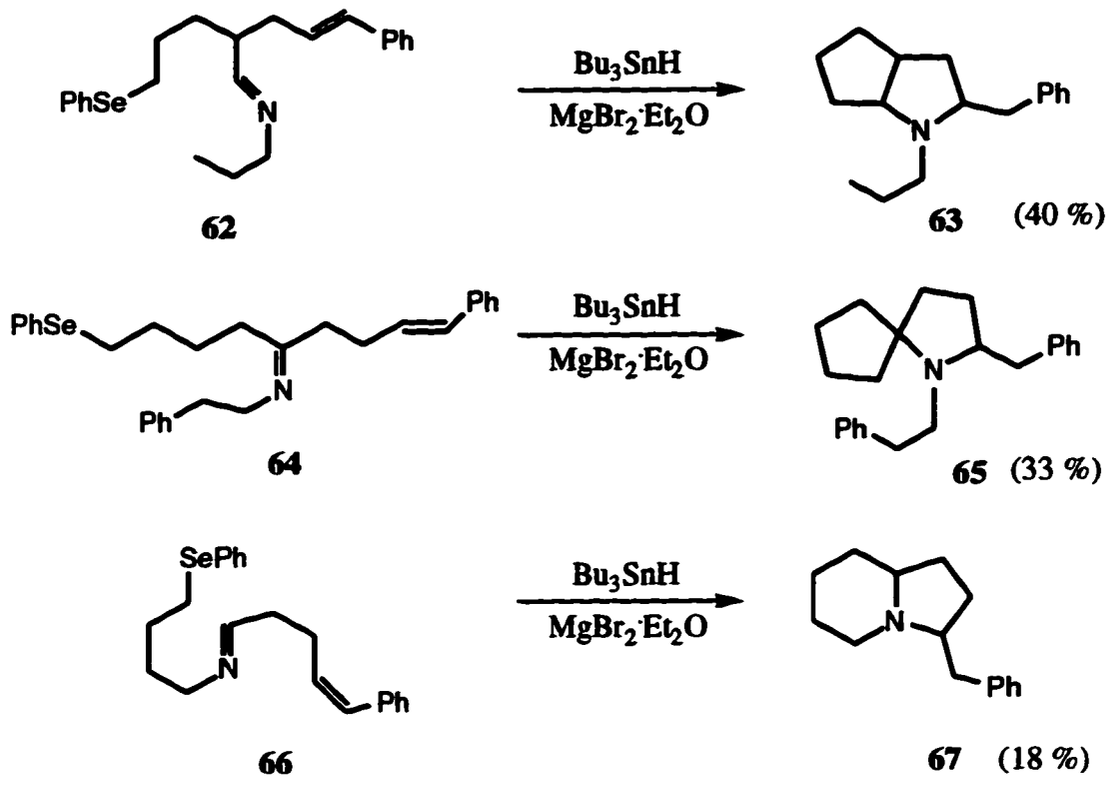
Scheme 16: Tandem Cyclization Leading to The Synthesis of Hirsutene



In this example, the first cyclization results in the generation of a 3° radical **59** which undergoes a second cyclization to give the tricyclic hirsutene **61** in 65 % yield.

The strategy of tandem cyclization has been utilized predominantly with the use of carbon centered radicals. However, recently Bowman[26] has reported the first example of a tandem cyclization that employs a nitrogen radical. Illustrations of his work are shown in the following scheme.

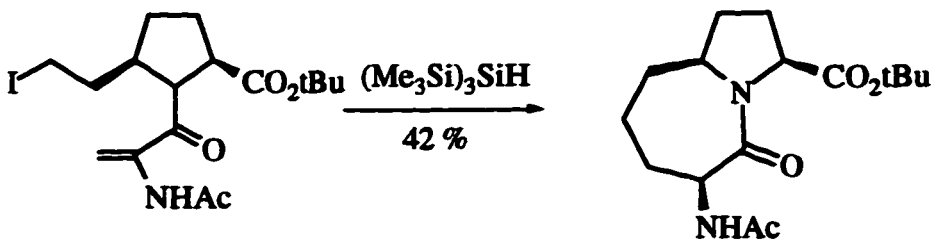
Scheme 17: Tandem Cyclizations With Nitrogen Radicals



Seven Membered Rings

The use of radicals to construct 5 and 6 membered rings is common in synthesis[1]. A new challenge arises when larger rings are desired. The synthesis of medium sized rings (7 or 8 carbons) under radical mediated conditions poses new problems. Here, two processes of ring closure are feasible[27] 7-*exo* trig and 6-*endo* trig. The entropic change for ring closure to 7 membered rings is unfavorable and to be successful, high dilutions are required[1] and thereby preclude intermolecular processes. As yet, there are no reports of a 7 membered ring being formed by an attack of radicals on a C=N system. The most recent example of a 7 membered ring closure by radicals was reported by Scolastico[28] where the synthesis of 7,5 and 7,6 fused lactams was achieved as shown below (scheme 18).

Scheme 18: Seven Membered Ring Lactam



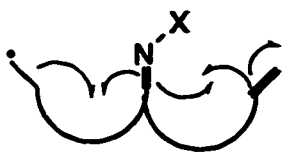
68 **69**

Chapter 2: Results and Discussion

Proposed Research:

At the commencement of this project, tandem cyclization utilizing a carbon centered radical followed by an aminyl radical had not been reported in the literature. There was increased interest in the carbon radical attack on C=N double bonds[21]. As previously mentioned, the common acceptors used are oxime ethers[29]. Only recently, have imines and hydrazones been identified as good radical acceptors[16,17,18,19].

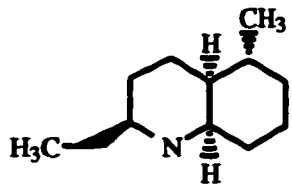
Scheme 19: Tandem Cyclization



70

Our objectives were simple. First we wanted to design a radical precursor which would be suitable for tandem cyclization where a C radical cyclization would be followed by a N radical cyclization as demonstrated above (Scheme 19). Secondly we wanted to investigate whether the second cyclization was reversible. The fused ring system resulting from such radical reactions would resemble naturally occurring alkaloids such as pumilotoxins and tropanes as shown below (Scheme 20).

Scheme 20: Natural Products



Pumilotoxin C

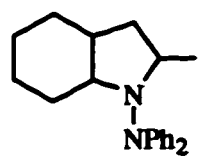
71

Cocaine

72

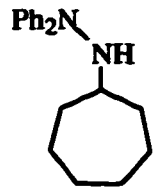
The carbon ring system in Pumilotoxin C is a 6,6 fused ring system, with the first ring having a nitrogen incorporated in the ring. The synthesis which we wanted to conduct was one where the system would be a 6,5 ring system with the nitrogen in the second ring, that is to say, in the ring containing the five atoms (Scheme 21).

Scheme 21: Proposed Targets



6,5 fused system

73



7 membered ring

74

In the design of the 6,5 fused system, it was important to ensure that the proper cascade of events would happen. From the work previously done in our laboratory, it was clearly demonstrated that the 6-*exo* cyclization was fast and would be the first to occur. This reaction proceeds cleanly and only the cyclized products can be isolated. This is important since it reduces the number of products in the reaction mixture. Furthermore,

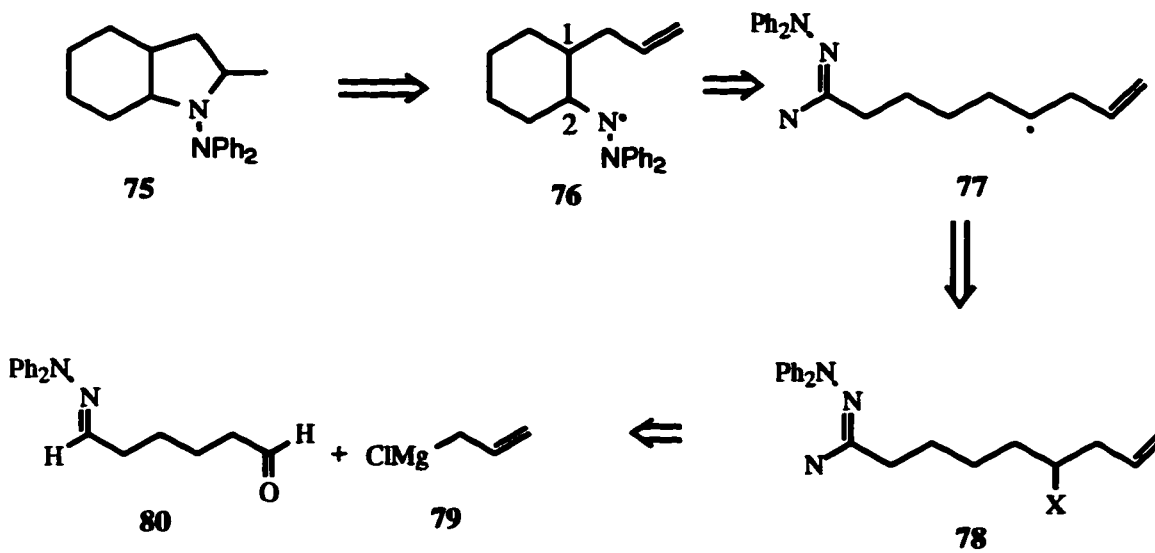
there has been no report in the literature of the construction of a 7-membered ring with a C centered radical attacking a C=N double bond. The hydrazones[17,18] investigated in our laboratory proved to be very successful for 5 and 6 carbocycles.

Synthesis of Tandem Precursors

The following scheme demonstrates the retrosynthetic analysis of a tandem reaction giving a 6,5 fused ring system.

Scheme 22: Retrosynthesis of 6,5 Fused Ring System

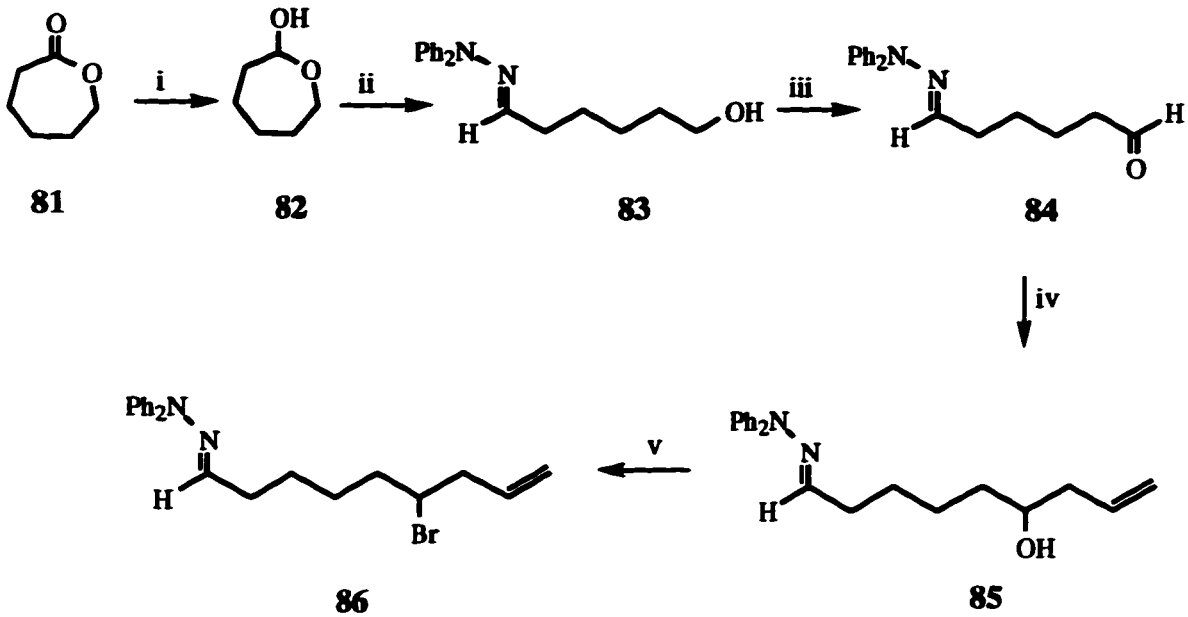
6,5 Fused System



The first disconnection is the second cyclization of the tandem cyclization; the N radical onto the carbon double bond. The next disconnection occurs between 1 and 2. This in turn is the first cyclization of the tandem process. This will bring us to the radical precursor **78** which is required for the tandem reaction giving the 6,5 ring system. The

precursor can be put together with a simple Grignard addition to aldehyde **80**. Aldehyde **80** had previously been synthesized in our laboratory[17,18].

Scheme 23: Synthesis of Radical Precursor



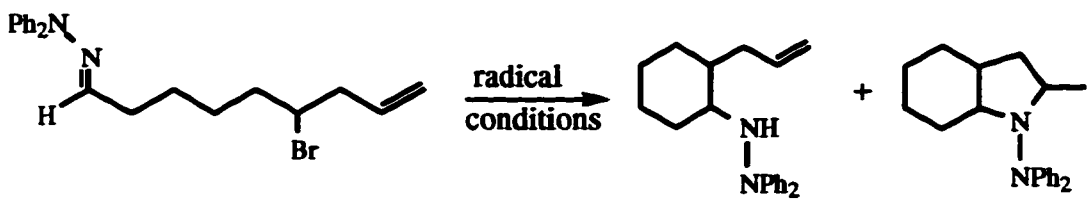
i) DIBAL-H, -78°C,toluene; ii) Ph_2NNH_2, room temp., MeOH; iii) SO_3·Py, DMSO, Et_3N, room temp.; iv) allyl magnesium bromide, -10°C, THF; v) PPh_3Br_2, Et_3N, room temp., DCM

Lactone **81** was reduced with DIBAL-H to afford lactol 82. Lactol 82 was then treated with *N,N*-diphenylhydrazine to afford exclusively the *E* hydrazone **83**. The product was clearly identified by the presence of the H at the hydrazone carbon δ 6.5 ppm in the proton NMR. The alcohol **83** was smoothly oxidized to the aldehyde using the sulfur trioxide pyridine complex, triethylamine method. The aldehyde **84** was identified by the presence of a peak at δ 9.74 ppm in the proton NMR. The addition of the Grignard reagent **79** showed the same chemoselectivity as reported by Sturino and Fallis[17,18] and

was identified by the appearance of characteristic vinylic signals and the disappearance of the aldehyde signal in the proton NMR. The bromination of the alcohol **85** was performed using bromine and trphenylphosphine and afforded the radical precursor. The precursor **86** was then treated under various radical conditions to afford the products as shown below (Scheme 24).

Attempted Tandem Cyclizations

Scheme 24: Radical Cyclization of 6-bromo-8-nonenal-*N,N*-diphenylhydrazone



cis/trans

86 **87** **75**

The result of the radical reactions are reported in the following table.

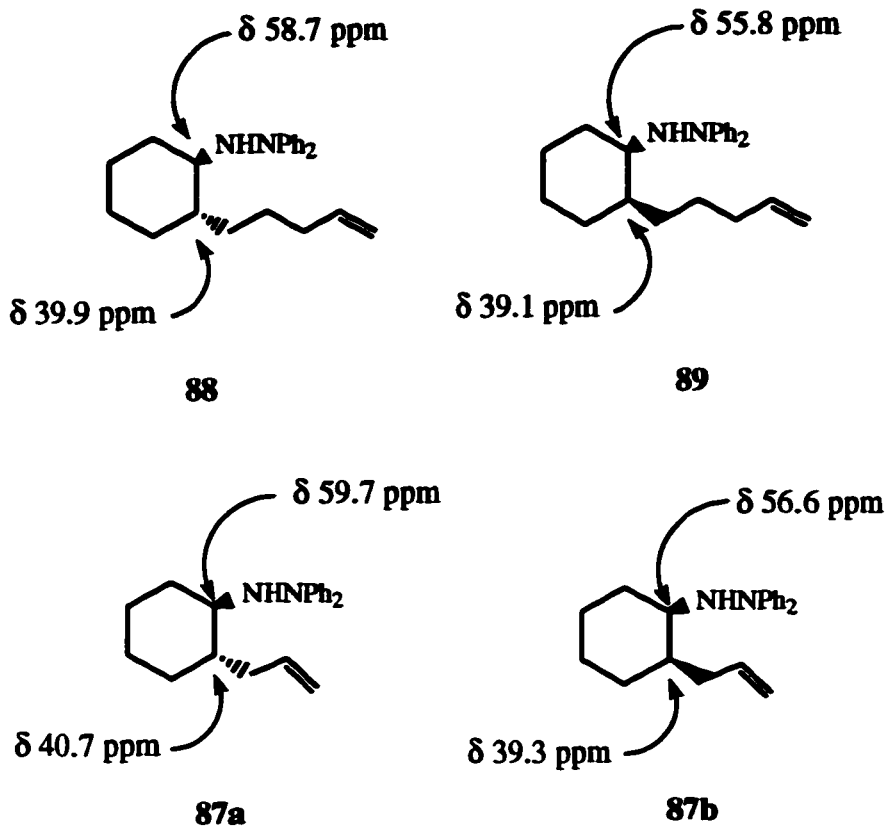
Table 1: Attempted Tandem Cyclization

Entry	Reaction Conditions	Tandem	Monocyclized	*cis/trans*
1	Bu_3SnH, 1.0 equiv.	trace	70%	1:1
2	Bu_3SnH, 1.0 equiv./ syringe pump	-	55%	6:1
3	SmI_2, 4.5 equiv.	-	55%	1:1
4	Bu_3SnH, 10.0 equiv.	-	-	
5	TTMSS, 10.0 equiv.	-	-	

The first radical experiment attempted on substrate **86** was a standard experiment using 1 equiv. of Bu_3SnH with a catalytic amount of AIBN refluxing in benzene. Monitoring the reaction by TLC analysis revealed that after 3 hours of reflux, all of the starting material had been consumed. After flash chromatography, ^1H NMR analysis of the least polar spot gave preliminary data showing trace amounts of tandem cyclization, product **75**. The evidence was the following: the triplet at 6.51 ppm had disappeared and so did the signals for the vinylic protons. The mass spectral data were consistent with that of a tandem product. However, the aliphatic region of the ^1H NMR was very complicated. This spectrum also showed that the sample was contaminated with organotin products. Attempts at further purification were futile and as a consequence, the product could not be fully characterized nor could we certify the findings of this first experiment.

The spectral data for the *cis* and *trans* products **87** *via* monocyclization were consistent with those previously reported by Sturino and Fallis[17]. The two isomers could easily be determined by their respective signals in both ^1H and ^{13}C NMR spectra in comparison with related compounds from the work of Sturino and Fallis as shown in the following scheme.

Scheme 25: Spectral Analysis of Monocyclized Products



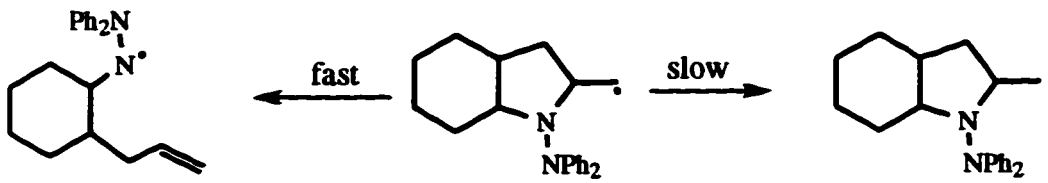
88 **89**

87a **87b**

It was suggested that the quenching of the N radical by the hydride source is faster than the rate of attack of the N radical on the C=C double bond. To prevent this from occurring, slow addition of hydride was utilized. The slow addition is performed by a method known as the syringe pump method. Small amounts of Bu_3SnH are present at one time and the resulting concentration of the hydride donor is much less than that of the substrate and hence it takes longer for the hydride to quench the radical. This would mean that the N radical has longer to react with the C=C double bond.

The results for the second entry were obtained by the slow addition of tin. The table indicates that only two products were formed and they were attributed to the two isomers of the monocyclized product. In this case, we do see a change in the *cis/trans* ratio. Here we report an increase in the *cis* product. It was puzzling to see that no tandem product was formed. At this point, we felt that the second cyclization was reversible as proposed by Bowman[22]. If the cyclization is reversible, this means that the rate of opening of the second ring is faster than the rate of quenching of the primary alkyl radical. We also believed that the quenching of the N radical was as well faster than the rate of formation of the second ring. This is demonstrated in the following scheme.

Scheme 26: Ring Opening VS Quenching



76 **90** **75**

The next trial with this substrate involved the use of SmI_2 at room temperature. This was used since SmI_2 would not only serve as a one electron donor to initiate the reaction, but as well, the resulting Sm(III) would serve as a mild Lewis acid which would complex with the N radical. This afforded a 1:1 mixture of the monocyclized products with a 55% yield.

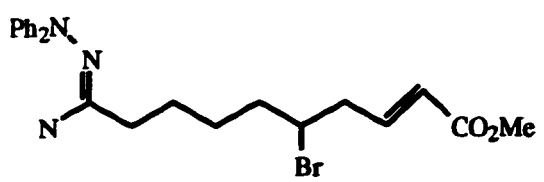
Due to these results, conditions reported by Tsanaktsidis[23] were attempted where 10 equiv. of Bu_3SnH with catalytic amounts of AIBN were required. Analysis by TLC of this reaction showed that all the starting material had been consumed and the products formed co-spotted with the monocyclized products. Isolation of these products proved

very difficult due to the presence of organo tin byproducts. A ^1H NMR spectrum of the crude mixture revealed that there were no more vinylic signals. The presence of the tin byproducts made the assignment of the aliphatic region impossible.

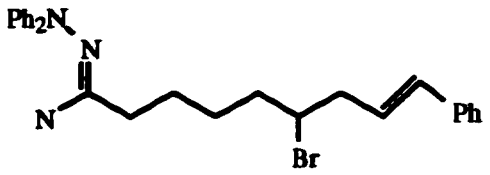
The last attempt was tried utilizing TTMSS as the radical and hydride source, which had two purposes. The first was to make the isolation of the products easier since the silicate byproducts would stay on the silica gel column. The second reason was the fact that this hydride donor has a much slower rate of quenching and should promote the tandem radical cyclization. Unfortunately only the monocyclized products **87a, 87b** could be identified by crude NMR.

It was then decided that perhaps a better radical acceptor would increase the chances for a tandem cyclization. Two functional groups were considered: an ester or a phenyl group on the double bond, since their electron withdrawing capabilities would provide the stability necessary to promote the tandem radical cyclization.

Scheme 27: Better Radical Acceptors



91



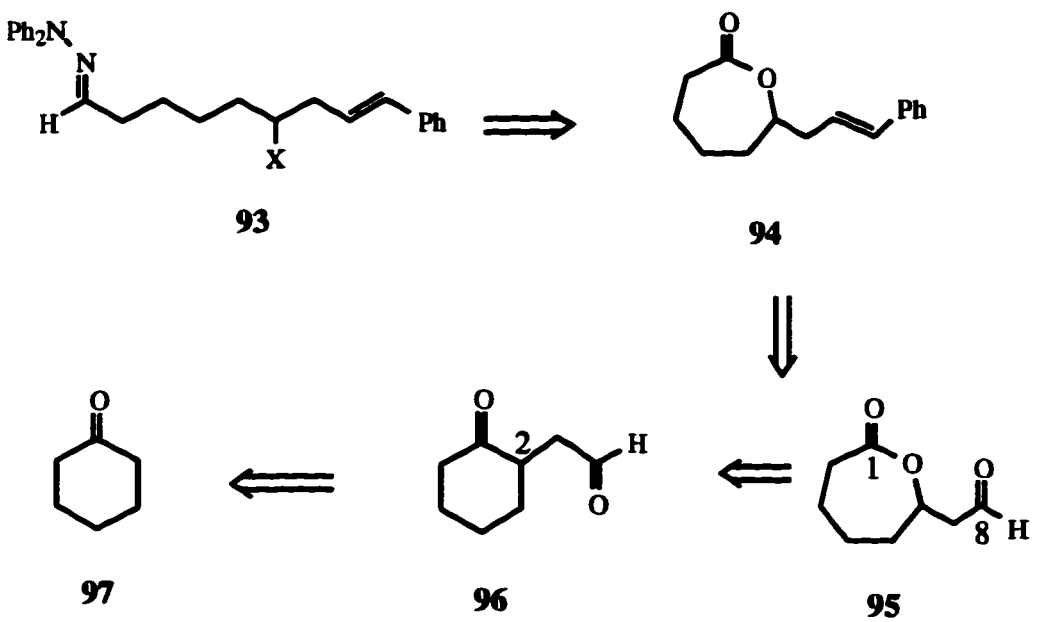
92

Preparation of E-6-Bromo-1(*N,N*-diphenylhydrazone)-9-phenylnon-8-enal

The following scheme shows the retro-synthetic analysis for the synthesis of a new tandem precursor. The hydrazone **93** can easily be obtained by condensation with

hydrazine and a lactol. The functionalized olefin **94** can be obtained *via* a Wittig reaction since the carbonyl of the aldehyde **98** is much more reactive than that of the ester, carbon 8 *versus* carbon 1. The lactone **95** can be formed by a Bayer-Villager oxidation at the most substituted carbon, carbon 2. Compound **96** can be obtained by alkylation of cyclohexanone.

Scheme 28: Retro-Synthesis of E-6-Bromo-1(*N*,*N*-diphenylhydrazone)-9-phenylnon-8-enal

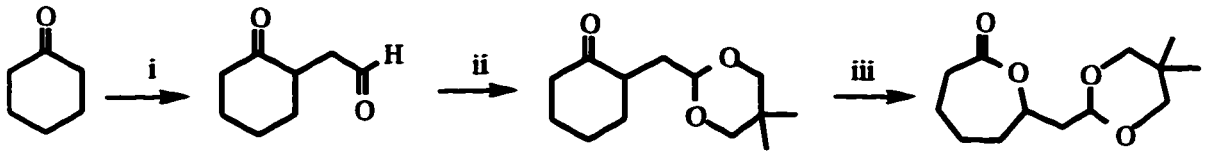


Scheme 29 shows the synthetic approach to the target molecule. Compound **96**, 2-(2-ethanal)-cyclohexanone was prepared according to Molander's[30] procedure. Protection of the aldehyde **96** was required since the following step was a Baeyer-Villiger oxidation, and there are two possible sites of oxidation. Protection the aldehyde **96** resulted in the removal of one of the two possible sites of oxidation. Treatment of **96** with neopentylidene glycol and a crystal of toluene sulfonic acid reflux in toluene overnight yielded the desired compound **98** in 38% yield. The low yield was a result of the reaction being stopped

before the total consumption of the starting material. This was done since analysis by TLC showed a second product being formed and it was suspected that this product was a result of diprotection.

The next step was the Baeyer-Villiger oxidation following Kohlenhydraten's[31] procedure. The mixture was heated to reflux in chloroform overnight, and analysis by TLC indicated that only one product **99** was formed. The NMR data showed that the signal at 2.5 ppm of the proton α to the ketone had shifted downfield to 4.45 ppm. This showed that the oxidation occurred on the proper side of the carbonyl group since the proton is now deshielded by the ester functionality.

Scheme 29: Synthetic Route to 6-(Ethanal)-neopentylacetal-ε-caprolactone



97 **96** **98** **99**

i) a)Me_2NNh_2, *n*-BuLi, allyl bromide, -78°C, THF, b)Amberlyst-15, room temp., acetone, c) O_3, -78°C, DCM; ii) Neopentylidene glycol, TsOH cat., toluene, reflux; iii) *m*-CPBA, chloroform, reflux

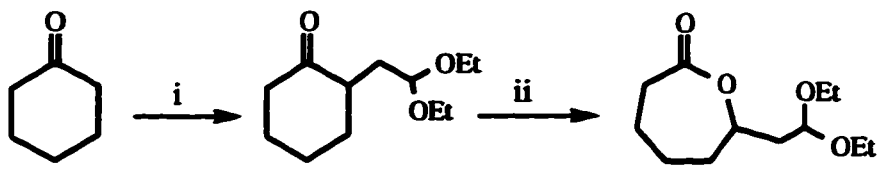
We now had a perfect opportunity to take advantage of the reactivity of the aldehyde *versus* that of the lactone carbonyl during the Wittig reaction of **95**. The deprotection of the aldehyde should have been straight forward but as shown the following table, the deprotection proved quite challenging.

Table 2: Deprotection of Neopentyl Glycol

Entry	Conditions	Yield
1	HOAc/cat.	S.M.
2	TsOH/cat	S.M.
3	HOAc/neat	Decomposition
4	4% HCl/THF	Decomposition

Mild conditions, cat. acetic acid in THF, were first tried. The substrate **99** was subjected to the conditions for three days and as reported in the table, no reaction had taken place. Increasing the strength of the acid such as TsOH did not improve the reaction. Harsher conditions such as entries 3 and 4 indicate that under these conditions, the lactone can open and undergo reactions which in turn decompose the substrate. The focus was now directed towards protection of the aldehyde with an acyclic acetal which would be easier to remove as shown in the following scheme (Scheme 30)..

Scheme 30: Synthesis of 6-Ethanal (diethoxyacetal)neopentyl acetal ε-Caprolactone



97 **100** **101**

i)a) Me_2NNH_2, *n*-BuLi, bromoacetaldehyde diethoxyacetal, -78°C, THF, b) O_3 , -78°C, DCM
ii) *m*CPBA, chloroform, reflux

Following the alkylation procedure for **96**, cyclohexanone **97** was treated with dimethylhydrazine followed by addition of *n*-BuLi and the alkylating agent. Unlike the synthesis of compound **96**, here an acidic removal of the hydrazone would most likely also result in the deprotection of our new acetal. This would lead to the same problem as before, where there would be two possible sites for the Baeyer-Villiger oxidation. A neutral and mild method of removal of hydrazones has been reported by Enders[32] where he treats hydrazones in the presence of ozone at low temperature. This method proved to be very good since a one pot synthesis of compound **100** was performed with a 38 % overall yield. The next step was the Baeyer-Villiger oxidation and the same conditions as for the synthesis of compound **98** afforded **101** in 80 % yield. Deprotection of the aldehyde was attempted under a variety of conditions and the results are summarized in the following table.

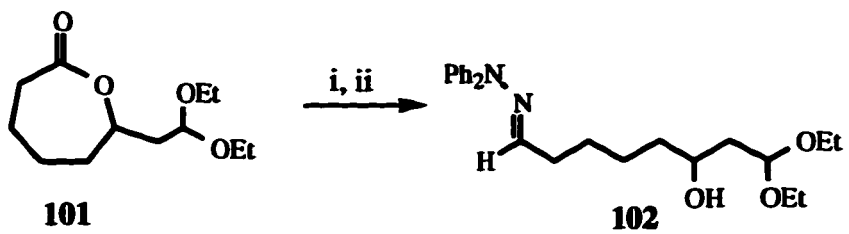
Table 3: Deprotection of Diethoxy Acetal

Entry	Conditions	Yield
1	HOAc/cat.	S.M.
2	TsOH/cat	S.M.
3	HOAc/neat	Decomposition
4	4% HCl/THF	Decomposition

The same difficulties as before were observed. Catalytic amounts of acid were not enough to initiate the deprotection, since only starting material was recovered. It was thought that perhaps the deprotection could be performed later in the synthesis, after the condensation with *N,N*-diphenyl hydrazine. In this case, chances for the opening of the lactone would be eliminated, although there is still a possibility that the hydrazone functionality might be

destroyed under acidic conditions. Work in our laboratory showed that this type of hydrazone is more stable to acidic conditions than other hydrazones, such as *N,N* dimethyl hydrazone. The following scheme shows the next steps in the synthesis.

Scheme 31: Synthesis of 6-Hydroxyocta-1-(*N,N*-diphenylhydrazone)-8-(diethoxyacetal)-dial



101 **102**

i) DIBAL-H, -78°C, toluene; ii) H_2NNPh_2, room temp.

Reduction of the lactone **101** was performed using the same conditions as described for the synthesis of compound **82**. Due to the high polarity of the product, purification was not performed and the crude product was treated with *N,N*-diphenyl hydrazine affording only the *anti* hydrazone **102** in a 70% overall yield. The results of the deprotection attempts are summarized in the following table.

Table 4: Deprotection of 6-Hydroxyocta-1-(*N,N*-diphenylhydrazone)-8-(diethoxyacetal)-dial

Entry	Conditions	Yield
1	TMSI	Decomposition
2	TFA cat./ rt 24 hr	Decomposition
3	4% HCl/ THF/ rt 24 hr	Decomposition
4	HOAc cat./ rt 1 week	S.M.
5	TsOH cat./ rt 1 week	S.M.
6	Oxalic Acid cat./ rt 1 week	S.M.
7	TsOH 2.5 equiv./ rt 1 week	S.M.
8	Oxalic Acid 2.5 equiv. / rt 1 week	S.M.
9	DMSO/ H_2O/ Dioxane	10 %

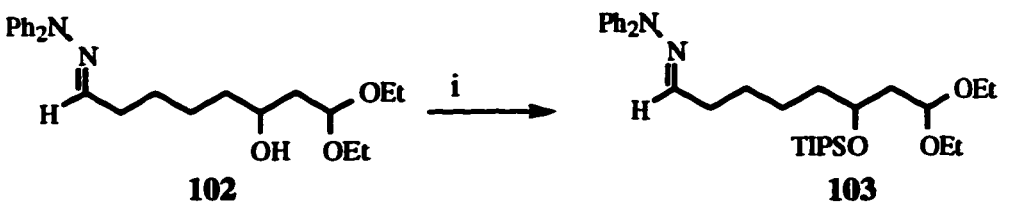
The first condition reported in the table was to directly convert the acetal to the aldehyde and convert the hydroxy group to an iodide. This reagent seemed too strong and in a matter of seconds, the reaction turned black and analysis by TLC showed total decomposition of the starting material. While the same holds true for the second entry, the reaction showed some signs of success since TLC analysis after 7 hours, showed that a faint new spot was observed and the reaction was allowed to stir overnight, resulting in decomposition of the starting material. The same was observed for the third entry. Milder conditions and longer reaction times, entries 4 through 8, showed no product formation. It was decided in entries 7 and 8 to increase the number of equivalents due to the fact that the presence of the nitrogens in the hydrazone functionality could act as bases and buffer the

system. Adding more than 2 equivalents would ensure that each nitrogen was protonated and the extra acid could initialize the deprotection, but no deprotection was observed.

Kametoni[33] has also observed difficulties with the deprotection of an aldehyde. They reported a new and mild method to successfully deprotect acyclic acetals in the presence of cyclic acetals and silyl ethers.

The last entry in the above table shows that we were able to isolate 10% of the desired compound with this method but the compound was very unstable and decomposed in the NMR tube possibly due to small amounts of acid in the deuterated chloroform. In order to increase the stability of the compound, it was decided to protect the secondary alcohol **102** since it was probably this functionality that rendered our compound unstable. The following scheme (Scheme 32) shows the protection of the hydroxyl group. The protection proceeded smoothly to give the silyl ether **103** in 92% yield.

Scheme 32: Protection of the Hydroxyl Group



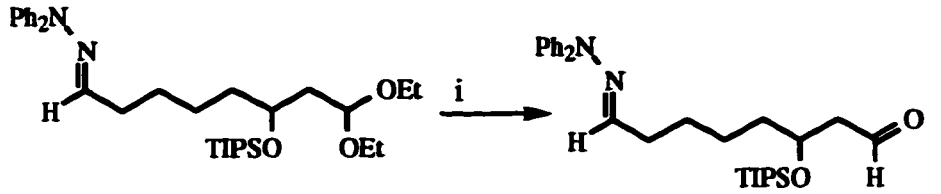
102 **103**

i) Imidazole, TIPSOTf

The deprotection was first carried out on a small scale. The desired compound **104** was isolated in 70% yield but proved to be just as unstable as the free hydroxy derivative. The yield for this deprotection varied dramatically, 0-70%. As the reaction was scaled up, it was observed that the yields were diminishing. In fact, the last attempted deprotection

was allowed to reflux for one week and only starting material could be recovered. The deprotection is demonstrated in the following scheme (Scheme 33).

Scheme 33: Deprotection of the Aldehyde

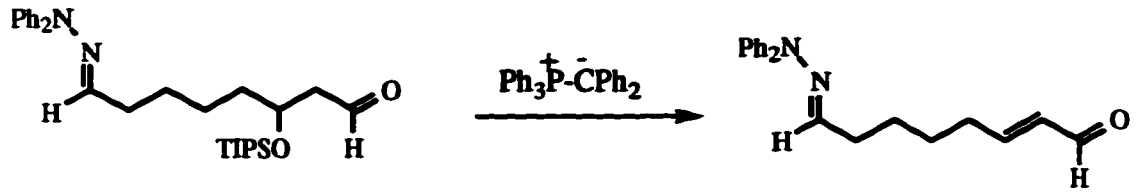


103 **104**

i) DMSO, Dioxane, H_2O, reflux

Kametani[33] *et al.* do not comment on a possible mechanism for this reaction, but report that this reaction is not acid mediated since the deprotection proceeds in the presence of pyridine. They also report that the reaction does not proceed if water or DMSO are absent from the reaction vessel. Transketalization will also occur if water is replaced by an alcohol. Some crude material was obtained and carried through to the next step (Scheme 34). The Wittig reaction was carried out in THF at -78°C. The reaction was clean but the only product resulting from the reaction was compound **105**. It is suspected that the ylide acted as a base and promoted the β elimination of the silyl ether functionality giving the α,β unsaturated aldehyde **105**.

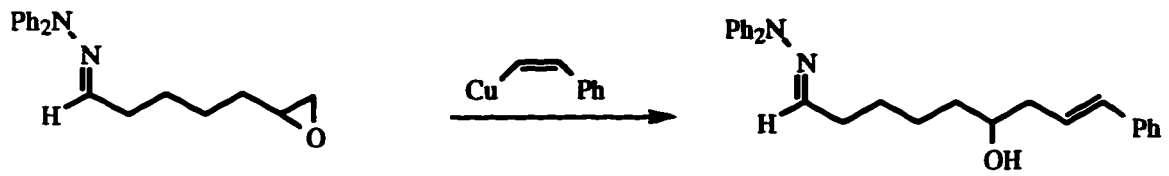
Scheme 34: Wittig Reaction



103 **105**

All attempts to obtain **92** were long and tedious. A new synthetic approach had to be designed in order to obtain the desired product in less steps. The new route involved opening an epoxide with a cuprate reagent and is shown in scheme 35 below.

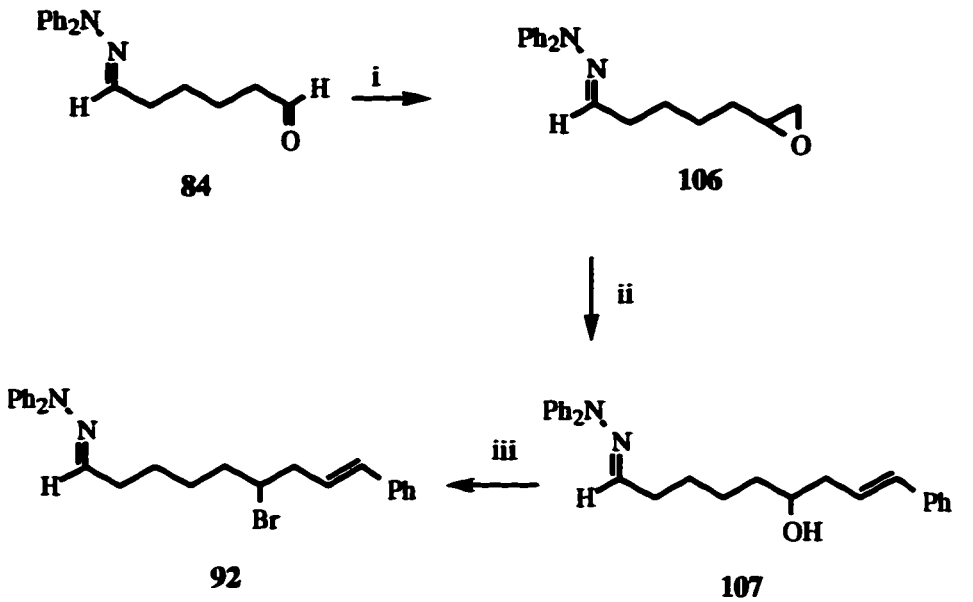
Scheme 35: New Synthetic Route to E-6-Bromo-1(*N,N*-diphenylhydrazone)-9-phenylnon-8-enal

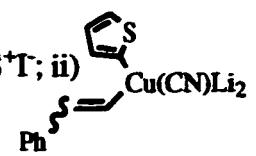


106 **107**

The first step in this new synthesis was the most important. As shown in scheme 36 below, treatment of **84** with dimethylsulfonium methylide derived from trimethylsulfonium iodide afforded the epoxide **105** cleanly. There was no formation of aziridine. This demonstrated the chemoselectivity of various nucleophiles for the aldehyde funtionality *versus* that of the hydrazone. The cuprate addition to the epoxide, using a higher order cuprate such as lithium-2-thienylcyano cuprate with β-bromostyrene, occured readily to afford alcohol **107**. The resulting alcohol was then brominated using the standard conditions and yielded the desired radical precursor **92**.

Scheme 36: Synthesis of E-6-Bromo-1(*N*,*N*-diphenylhydrazone)-9-phenylnon-8-enal



i) NaH, DMSO, 60°C, $Me_3S^+I^-$; ii)  , THF, *sec*-BuLi, -78°C; iii) Ph_3PBr_2, Et_3N, DCM
room temp.

Tandem Cyclization

The radical experiments performed on compound **92** are summarized in the following table.

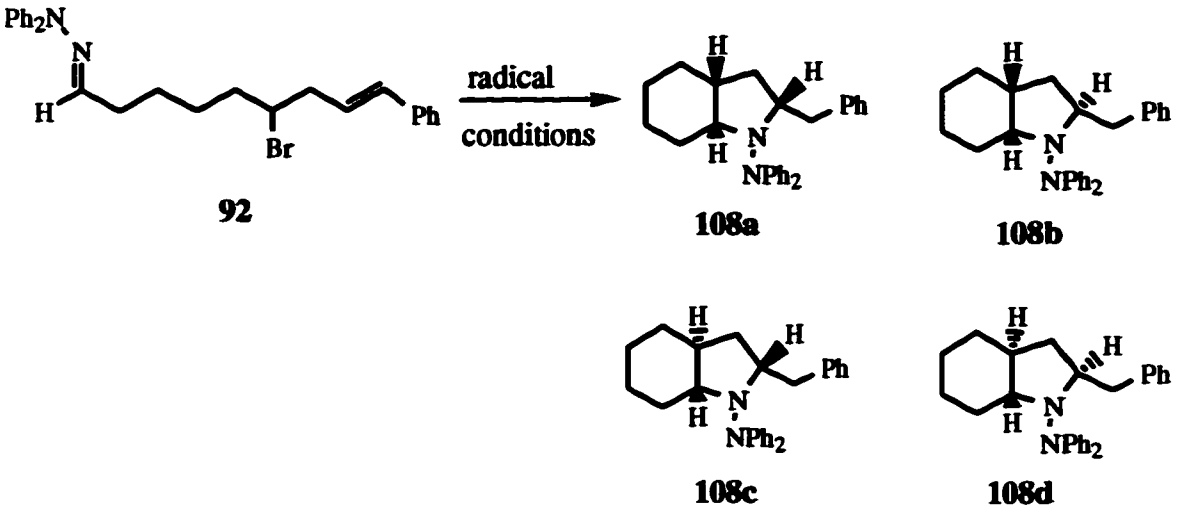
Table 5: Radical Cyclizations of E-6-Bromo-1(*N*,*N*-diphenylhydrazone)-9-phenylnon-8-enal

Entry	Conditions	Monocyclized	Tandem
1	Bu_3SnH 1 equiv.	0 %	30%
2	TTMSS 1 equiv.	0 %	28%

The first conditions studied were that of Bu_3SnH , 1 equiv. in benzene at reflux. TLC analysis revealed that only a single new spot, less polar than the one for the starting material had appeared. The second reaction was performed under the same conditions but changing the radical source with TTMSS. The reaction took considerably longer (approx. 7 hours) but the results were the same as for the tin reaction.

The ^1H NMR of the product isolated showed that the vinylic signals of the double bond had disappeared. The aliphatic region was complicated but had a distinct finger print region between 3.5 to 2.1 ppm. It was hoped that this region could help us to determine if the desired product had been isolated. As previously mentioned, there is a possibility of isolating four products from the tandem reaction and two formed by monocyclization. The four tandem products are shown in the following scheme.

Scheme 37: Radical Reactions of E-6-Bromo-1(*N*,*N*-diphenylhydrazone)-9-phenylnon-8-enal

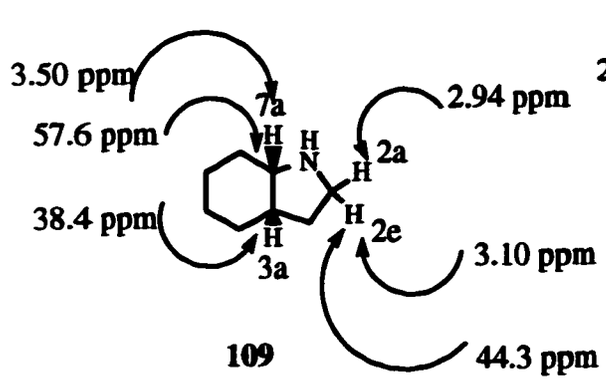


92 **108a** **108b**

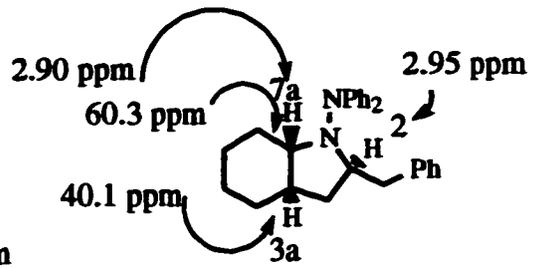
108c **108d**

The NMR spectra for both, *cis* and *trans*, isomers of octahydroindole have been studied carefully[34,35]. The following scheme shows the proton and carbon signal for both isomers and assigning them to the products synthesized.

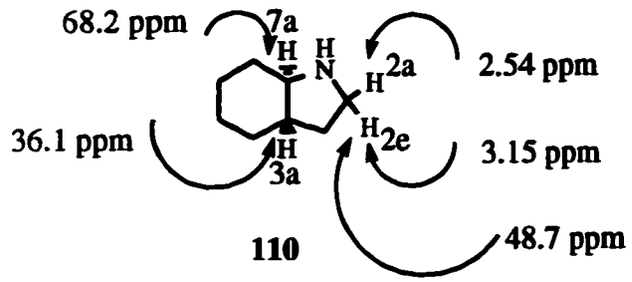
Scheme 38: Proton Signals for Octahydroindoles



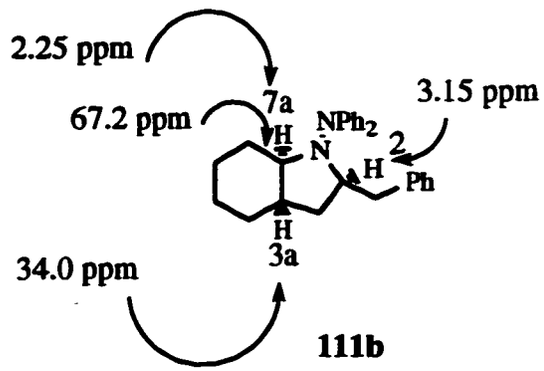
109



111a



110



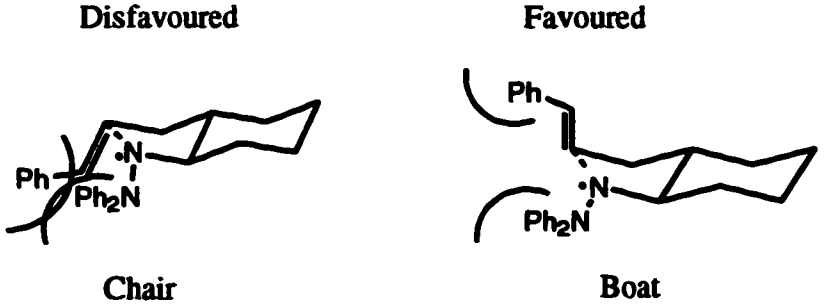
111b

Mokotoff[34] reports that for the *cis* isomer **109**, has a H7a at δ 3.05 ppm. The protons at C2 are unique so that one proton shows up at δ 3.10 ppm and the other at δ 2.94 ppm. Proton 7a is very characteristic since it has very little coupling. The carbon signal reported for C7a was at δ 57.6 ppm, for C2 at δ 44.3 ppm and for C3a at δ 38.4 ppm. For the *trans* isomer **110**, Vierhapper[35] reported that the proton H7a overlaps with the protons at 2. They were able to show with deuterated compounds that the axial proton shows up at δ 2.54 and the equatorial at δ 3.15. The carbon signal for C2 shows up at δ 48.7 ppm, the one for 7a at δ 68.2 ppm and for 3a at δ 38.4 ppm.

The NMR spectra of our compounds showed that we had a mixture of compounds **111a, 111b**. We expected a mixture but we were hoping to separate them. From the data available on octahydoindoles[34,35], we were able to assign the following signals. In the ^1H NMR, the signal at δ 3.15 ppm is that of the proton at 2. From the chemical shift and from constructed models, we determined that proton 2 is in the equatorial position. The signal at δ 2.25 ppm is due to the proton at 7a for the *trans* isomer. The carbon signal at δ 67.2 ppm is that of 7a and δ 34.0 ppm is that of 3a, both for the *trans* isomer. The proton signal for the *cis* isomer were determined to be the following. The proton for C2 comes up at δ 2.95 ppm and 7a at δ 2.90 ppm. The carbon signals assigned are δ 60.3 ppm for 7a and δ 40.1 ppm for 3a.

This implies that the second cyclization proceeds via a boat conformer as opposed to a chair conformer. The boat conformer is favored since in the chair conformer, the phenyl rings on the nitrogen interact with the phenyl ring on the double bond. The bulky nitrogen with the diphenyls will prefer to lie in the pseudo equatorial position thus pushing the double bond in the pseudo axial position leading to the more favored boat conformer. The hydrogen at position 2 will then be equatorial. This is shown in the following scheme.

Scheme 39: Proposed Transition State for the Tandem Cyclization



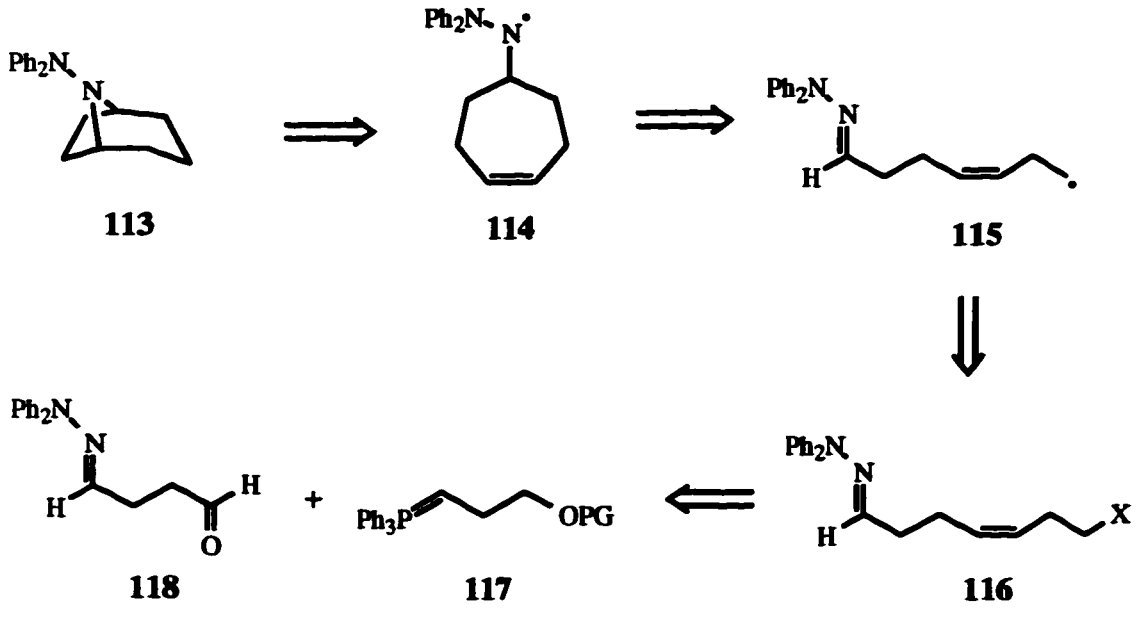
From the integration in the proton spectra, we find that there is a ratio of 1:1 for the *cis* **111a** and *trans* **111b** octahydroindole skeleton.

Synthesis of Tropane Radical Precursors

The retrosynthetic analysis is shown below (Scheme 40).

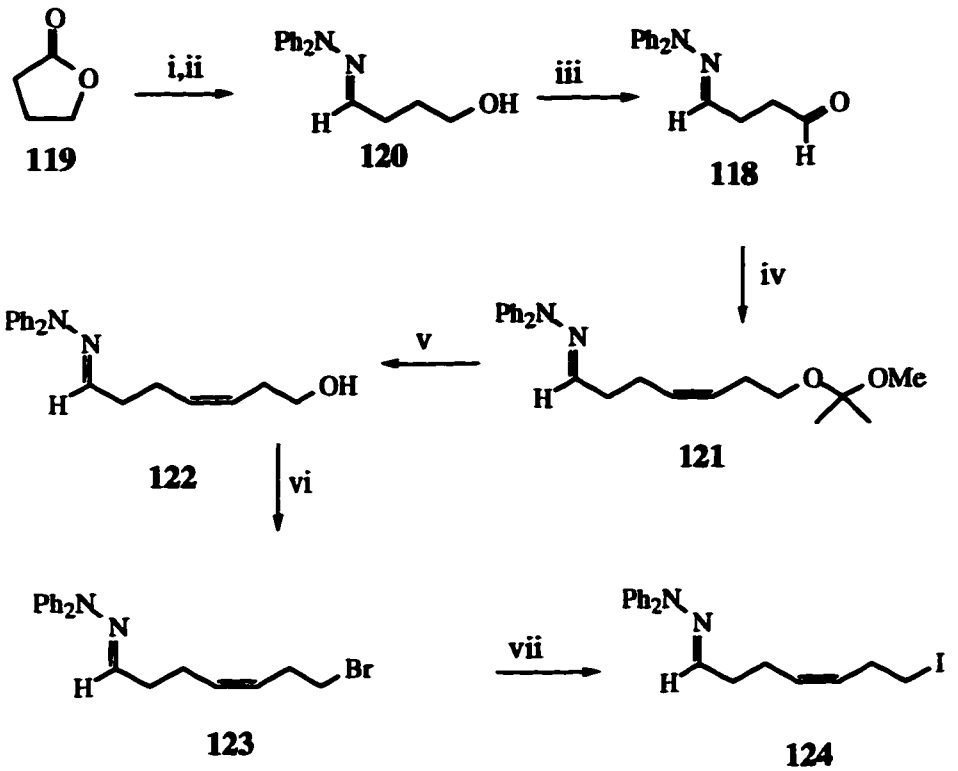
Scheme 40: Retrosynthesis of Tropane Skeleton

Tropane System



The two first disconnections are the result of the tandem cylization. The radical species **115** can be generated from the radical precursor **116**. This precursor can be disconnected between 4 and 5 giving and aldehyde **117** and ylide **117**. Hydrazone **118** can be synthesized in the same manner as described herein for compound **80**. The complete synthesis is shown below in Scheme 41.

Scheme 41: Synthesis of 4-Z-7-Bromo-4-heptenal-*N*,*N*-Diphenylhydrazone and 4-Z-7-Iodo-4-heptenal-*N*,*N*-Diphenylhydrazone



i) DIBAL-H, -30°C, toluene; ii) H_2NNPh_2, MeOH, room temp.; iii) $SO_3Py/DMSO/Et_3N$ room temp.; iv) $Ph_3P{=}CH(CH_2)_2OC(CH_3)_2OMe$, -78°C, THF; v) $HOAc/CH_3CN$, room temp.; vi) Ph_3PBr_2, Et_3N, DCM, room temp.; vii) NaI, acetone, room temp.

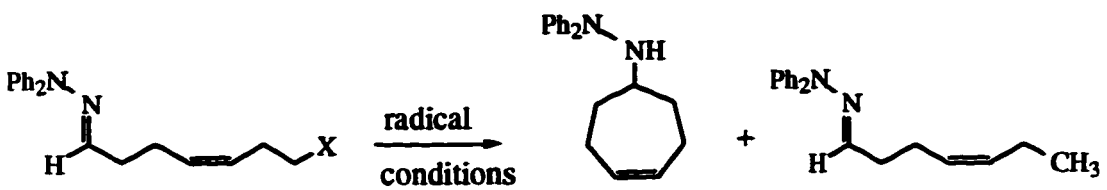
The synthesis of compound **118** follows the general approach used to obtain hydrazones from lactones. The Wittig salt was obtained following a procedure reported by Corey[36]. The Wittig reaction was performed in THF at -78°C and analysis by TLC indicated only one product was formed. Upon purification of **121**, new vinylic signals at δ 5.52-5.42 ppm were observed integrating for two protons. This indicates that only one isomer was formed, and, since both vinylic signals showed up at roughly the same field, it is safe to assume that the isomer is *cis*. Deprotection of the alcohol was performed under mild conditions using acetic acid in aqueous acetonitrile. The resulting alcohol **122** was

brominated under the usual conditions to afford the radical precursor **123**. Conversion of the bromide **123** to the iodode **124** was performed under Finkelstein[37] conditions.

Radical Reactions of Bromide 123 and Iodide 124

The radical reactions of **123** and **124** are shown below (Scheme 42).

Scheme 42: Radical reactions of 123 and 124



115 **125** **126**

X= Br, I

The results to the reactions of both precursors are shown in the following table.

Table 6: Radical Reactions of 4-Z-7-Bromo-4-heptenal-*N,N*-Diphenylhydrazone and 4-Z-7-Iodo-4-heptenal-*N,N*-Diphenylhydrazone

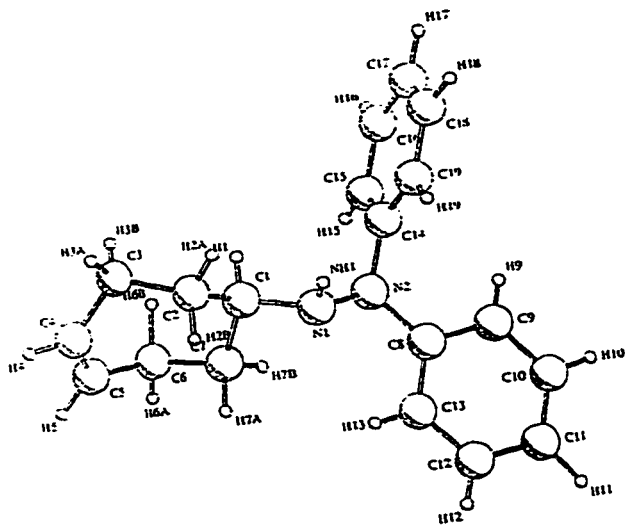
Entry	Reaction Conditions	Halide	% Reduced	% Cyclized
1	Bu_3SnH	Br	48	16
2	Bu_3SnH 1mL/hr	Br	22	33
3	SmI_2	Br	76	11
4	$Bu_3SnH + (Bu_3Sn)_2O$ 1 mL/hr	Br	35	30
5	TTMSS 1mL/hr	Br	20	16
6	TTMSS + $(Bu_3Sn)_2O$ 1 mL/hr	Br	35	32
7	TTMSS + $(Bu_3Sn)_2O$ 1 mL/hr	I	30	30

As seen in the table above, we report the first synthesis of a seven membered ring constructed by the use of a radical addition onto a C=N. An interesting point to make is the fact that also for the first time, we see that the rate of cyclization is comparable to the rate of reduction. The yield was low but promising. No tandem product was formed.

The first entry shows that the product formed in low yield. The reaction gave two spots, with very similar polarity. Isolation of the products revealed that the less polar product is the cyclized product **125**. The assignment of this compound was easy since the molecule is symmetrical and we also noticed the disappearance of the signal for the hydrazone proton δ 6.5 ppm. The NMR spectra, carbon and proton, of the cyclized product are very interesting. The spectra showed very broad peaks. This implies that

some dynamic processes are taking place. From the X-ray data, and the structure shown below, it seems that the angle C14, N2, C8 is approximately 120°. This implies rotation restrictions and as a result, the spectra show line broadening. The structure is shown below.

Figure 2: X-ray Structure



From this structure taken at -110°C, we see that the hydrazino group is in a pseudo equatorial position. The ring is in a chair like conformation. Therefore it should be not suprising that this large bulky group does not lie pseudo axial, the position required for the tandem reaction to take place. In order for the tandem reaction to occur, the ring must also adopt a boat like conformation. The NMR results at 21 °C, in contrast to the low temperature X-ray data, suggest that at an appropriate temperature the conformation for the second cyclization should be formed.

In order to maximize the yield in the reaction, and hopefully obtain some tandem product, we decided to do the next reaction using the syringe pump method. This has the advantage of prolonging the life of the radical and therefore reduce the amount of reduced product. We can see from the second entry that there was a 2 fold increase in the yield of the reaction for the cyclized product **125**.

We decided that perhaps in this case the use of SmI_2 would give the tandem product. The conversion of the starting material was very high, as shown in the third entry, but the yield of the cyclized product **125** was very low.

During this period of the work, Tsanatkis[23] reported the use of a mild Lewis acid to promote N radical attack onto C=C. The fourth entry shows the use of bis tributiltin oxide as the Lewis acid. The reaction was performed under syringe pump conditions since it showed the best yield and 1.5 equiv. of the tin oxide was employed. These conditions did not further improve the yield of the reaction.

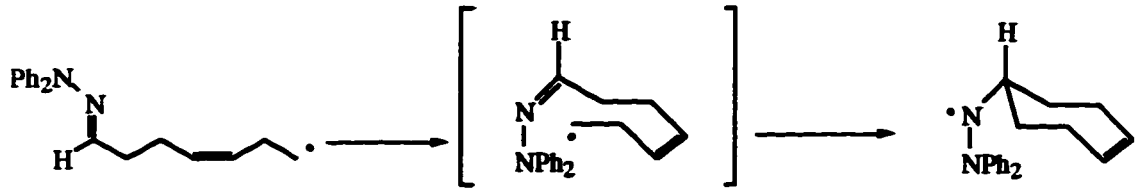
What we knew so far was that prolonging the life of the radical did improve the yields of cyclization and it was decided that a slower hydride donor would definitely increase the yield of the reaction. We used TTMSS and as demonstrated in the fifth entry, this did not prove successful. The reaction was very messy and it was difficult to isolate the desired products.

Entry six shows a second attempt using TTMSS in combination with tin oxide. The reason we pursued the reactions using TTMSS was that it was very difficult to remove the tin from the previous reactions. These reaction conditions showed no marked improvements in the yield of the reaction.

Based on our results, we decided that the conditions in entry 6 were the best ones. We decided then to try a different radical precursor. Iodides are generally much more reactive under radical conditions. From the seventh entry, we can see that the yields of this reaction are comparable to entries 2, 4, and 6.

We propose that this reaction proceeds via the transition state shown in Scheme 43 below.

Scheme 43:Transition State



114 127 128

We propose the reaction proceeds via a 7 membered chair transition state with the hydrazone pseudo equatorial. This leads to the 7-*exo* cyclization of the ring. The resulting N radical is too far from the double bond and the tandem reaction cannot take place.

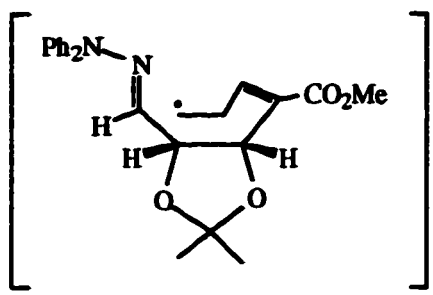
Proposed Future Work

The success of the tandem cyclization giving the octahydro indole is very exciting. This shows a facile route to fused ring systems having a N α to the ring junction. The 6,5 fused ring system described in this thesis was not synthesized with high yields or high level of diastereoselectivity. We propose that a 5,5 system similar to the one constructed in this work should be synthesized in better yields and higher diastereoselectivity. The reasoning behind this statement is that the first cyclization will happen faster and the levels of diastereoslectivity are much better according to Beckwith's rules.

The tandem approach to the tropane system did not prove as successful. We propose that since the energy requirements for the N radical attack onto a C=C are high[23] that a different solvent with a higher boiling point be utilized. This should not only

improve the chances for the tandem cyclization but should also increase the yield for the first cyclization. In **128** the geometry is not suitable for the required addition to the olefin. Consequently, a control group such as a *cis* acetal should encourage the conformation depicted in **129**. In addition, introduction of an electron withdrawing group should increase the chances for the second cyclization.

Scheme 44: Proposed Transition State



129

Conclusion

In conclusion, we were able to show that a tandem cyclization, where the second cyclization is performed by a nitrogen radical, can be achieved in moderate yields under neutral conditions. This leads to small alkaloid and octahydroindoles. We are also happy to report the first synthesis of a seven membered ring using a radical approach where a carbon centered radical adds to the imine bond of a diphelyhydrazone.

Chapter 3: Experimental

General Considerations

Melting points were determined in capillary tubes with a Thomas-Hoover Unit Melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bomem MB100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H NMR) were measured at 200 MHz with a Varian Gemini spectrometer or at 500 MHz with a Bruker AMX 500 in deuterochloroform unless otherwise stated. Carbon magnetic resonance spectra (^{13}C NMR) were measured at 50 MHz (Varian Gemini), at 75 MHz (Varian XL-300) or at 125 MHz (Bruker AMX 500). The residual signal was used as an internal lock, $CDCl_3$, ^{1}H: δ 7.24 ppm; ^{13}C: δ 77.0 ppm; chemical shifts reported in ppm downfield from tetramethylsilane (δ scale). The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad), coupling constants and number of protons are indicated in parentheses. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. Elemental analyses were conducted by M-H-W Laboratories, Pheonix, AZ, USA. Analytical thin layer chromatography (TLC) employed commercial aluminium sheets precoated (0.2 mm layer thickness) with silica gel $60F_{250}$ (E. Merck). Flash column chromatography utilised E. Merck silica gel (70-230 or 230-400 mesh) The purity of all title compounds was judged to be >95% as determined by ^{1}H NMR and ^{13}C NMR analyses.

Petroleum ether refers to the hydrocarbon fraction with boiling point range 30-60°C. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation from calcium hydride and stored over 4 Å molecular sieves. Anhydrous tetrahydrofuran (THF) and diethyl ether (ether) were obtained by distillation from sodium/benzophenone. Organic solvents collected from workup were dried over anhydrous magnesium sulfate and

concentrated by a Büchi rotary evaporator connected to a water aspirator. Unless otherwise stated, all reactions were conducted under an argon atmosphere inside flamed dried flasks equipped with a magnetic stirring bar and a rubber septum.

All commercially available starting materials were purchased from Aldrich Chemical Company unless otherwise stated. *N,N*-diphenylhydrazine was obtained by treating the commercially available *N,N*-diphenylhydrazine hydrochloride with 1.0 equivalents of sodium methoxide in methanol. The resulting solution was concentrated and filtered through a sintered glass funnel with a pad of silica gel eluting with 100% ether. The resulting *N,N*-diphenylhydrazine was used without further purification.

Compounds Prepared From Literature Procedures

2-(2-Ethanal)cyclohexanone was prepared according to the literature procedure, bp 36-40 °C /0.2 mmHg, [lit.[30] 34-40 (0.2 mmHg)].

3-Oxy(2-methoxypropane)propanetriphenylphosphonium bromide was prepared according to the literature procedure, mp 222-224 °C, [lit.[36] 222-224 °C].

General Procedure For Bu_3SnH and $(CH_3Si)_3SiH$ Radical Reactions

A round bottom flask, dried and cooled under argon, equipped with a reflux condenser, was charged with the appropriate substrates, and freshly distilled benzene, (0.02-0.05 M solution). To this was added Bu_3SnH or $(CH_3Si)_3SiH$ (1-2 equiv.) in one portion and AIBN (0.1-1 equiv.). Argon was then flushed through the solution for approximately 15 minutes. After this time the solution was heated at reflux for 2-4 hours until TLC analysis showed total consumption of starting material. After cooling to room

temperature, the solvent was removed and the resultant material was purified by flash chromatography on silica gel (3% ether, 97% petroleum ether).

General Procedure For The Bromination of Alcohols

A flamed dried round bottom flask was cooled under argon and charged with dichloromethane, (0.1-0.3 M solution). Triphenyl phosphine (1.2 equiv.) and Et_3N (4 equiv.) were added, followed by the dropwise addition of bromine (1.2 equiv., 3M solution in dichloromethane) until the reaction mixture turned faint yellow. The alcohol was added as a dichloromethane solution and allowed to stir at room temperature for 1 hour. After this time, the reaction mixture was poured into a separatory funnel containing water and ether. The aqueous layer was extracted three times with ether, and the combined organic extracts were dried and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (5% ether, 95% petroleum ether).

General Procedure -Radical Syringe Pump Reactions

A round bottom flask, dried and cooled under argon, equipped with a reflux condenser, was charged with benzene (1-3 mL) and Bu_3SnH or $(CH_3Si)_3SiH$ (1 equiv.). Argon was flushed through the solution for 30 minutes. After this time, the solution was taken up by syringe.

In a separate two-necked round bottom flask, dried and cooled under argon, equipped with a condenser and a rubber septum, was charged with the appropriate substrate followed by freshly distilled benzene (enough to make a 0.005 M solution). To this solution was added AIBN (0.25 equiv.), and argon was flushed through for 30 minutes. The needle of the syringe was then introduced into the system *via* the rubber

septum. The reaction mixture was heated to reflux and the contents of the syringe were added at a setting of 1 mL/hour. AIBN (0.25 equiv.) was added after each hour to maintain radical initiation. After the addition was completed, reflux was allowed to continue for an additional hour. The mixture was cooled to room temperature and concentrated *in vacuo* before being purified by flash column chromatography (3% ether, 97% petroleum ether).

General Procedure for SmI_2/HMPA Reactions

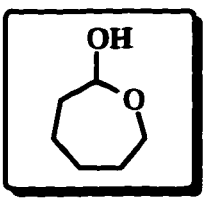
A round bottom flask, dried and cooled under argon, was charged with the appropriate substrate followed by THF (0.25M solution) and HMPA (1.0-2.0 mL per mmol of substrate). Argon was flushed through the system for 30 minutes. After this time, SmI_2 (4.5 equiv. 0.1M solution in THF) was then added and the solution was stirred at room temperature for 2 hours. The reaction was quenched with aqueous saturated sodium bicarbonate. The mixture was transferred into a separatory funnel and the aqueous layer was extracted with ether (3X 15 mL). The combined organic extracts were dried and concentrated *in vacuo* . The resulting oils were purified by flash chromatography (3% ether, 97% petroleum ether).

General Procedure For Wittig Reactions

A round bottom flask, dried and cooled under argon, was charged with the Wittig salt (1.1-1.5 equiv. based on starting aldehyde) followed by dry THF (0.2 M solution). The mixture was cooled to -78 °C and *n*-BuLi (1 equiv. based on the Wittig salt) was added dropwise. After stirring at -78 °C for 30 minutes, the aldehyde was added as a THF solution (1 mL) *via* cannula. The mixture was stirred at -78 °C for 30 minutes and then slowly warmed to room temperature where stirring was continued until analysis by TLC

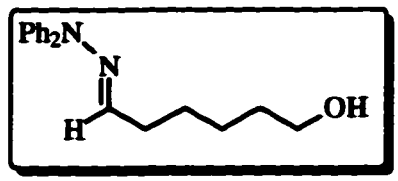
showed complete consumption of the starting aldehyde. The mixture was transferred into a separatory funnel containing water and ether. The aqueous phase was extracted with ether (3X 20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The resulting oils were purified by flash chromatography (30% ether, 70% petroleum ether)

Preparation of ε-Caprolactol (82)



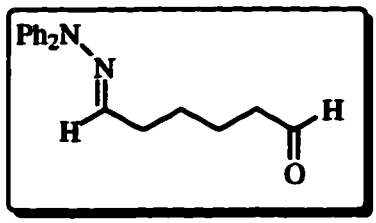
ε-Caprolactone (4.8 mL, 43.8 mmol) was added to a flamed dried flask (250 mL) containing toluene (50 mL) under argon. The solution was cooled to -78°C and DIBAL (49 mL of a 1.0 M solution in toluene, 49.0 mmol) was added and the mixture stirred at -78°C for 4 hours. Methanol was added to the reaction mixture at -78°C until the evolution of hydrogen gas stopped. The solution was warmed to room temperature, and diluted with ethyl acetate (50 mL) and saturated aqueous sodium potassium tartarate (100 mL). The mixture was stirred for 1 hour at room temperature. After this time, the mixture was poured into a separatory funnel and the aqueous layer was extracted with ether (3X 35 mL). The combined organic extracts were dried and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (70% ether, 30% petroleum ether) to afford 3.6 g (70%) of the title compound as a white solid. mp 82-84°C; IR (Nujol, cm^{-1}) 3409, 2906, 1725, 1458; ^1H NMR (200 MHz, $CDCl_3$) δ 9.64 (t, J = 1.6 Hz, 1H), 3.52 (t, J = 6.2 Hz, 2H), 2.37-2.29 (m, 2H), 1.97-1.23 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.7, 62.4, 43.8, 32.3, 25.3, 21.7 ppm; HRMS calcd. for $C_6H_{12}O_2$ (M^+): 116.0834. Found: 116.0809; Anal. calcd for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 62.20, H, 10.20.

Preparation of 6-hydroxyhexanal-*N,N*-diphenylhydrazone (83)



A solution of Ph_2NNH_2 (2.56 g in 10 mL of methanol) was added to a solution of lactol **82** (1.5g, 13 mmol) in methanol (30 mL) was . The mixture was stirred at room temperature for 10 minutes then concentrated and purified by flash chromatography (50% ether, 50% petroleum ether) to afford 2.86 g (80%) of the title compound as a clear oil. IR (neat, cm^{-1}) 3354, 3060, 2932, 2858, 1592, 1493, 1302, 1210, 749, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.14-7.04 (m, 6H), 6.52 (t, J = 5.3 Hz, 1H), 3.60 (t, J = 6.4 Hz, 2H), 2.32-2.22 (m, 2H), 1.60-1.36 (m, 6H) ppm (OH proton not observed); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 139.8, 129.5, 123.7, 122.2, 62.4, 32.5, 22.3, 26.6, 25.2, ppm; HRMS calcd. for $C_{18}H_{22}N_2O$ (M^+) : 282.1727. Found 282.1734; Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found C, 76.33; H, 8.14; N, 10.01.

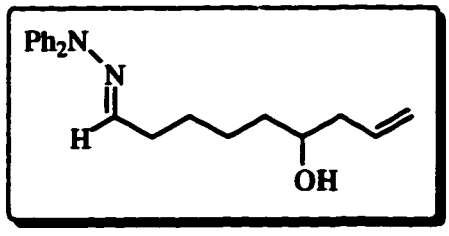
Preparation of Pentanal-(*N,N*-diphenylhydrazone)-5-carboxaldehyde (84)



Into a flamed dried flask, under argon was placed alcohol **83** (4.2 g, 15 mmol) DMSO (50 mL) and Et_3N (16.6 mL, 120 mmol). A suspension of SO_3/pyridine complex in DMSO (7.2 g, 45 mmol, in 10 mL DMSO) was added dropwise to the mixture. The

reaction mixture was stirred at room temperature until TLC analysis indicated that all the alcohol was consumed. The mixture was then poured into a separatory funnel containing water and ether. The organic phase was washed with water (2X 10 mL). The combined aqueous phases were then extracted with ether (3X 15 mL). The combined organic extracts were dried and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (25% ether, 75% petroleum ether) to afford the title compound as a yellow oil 2.93 g (70%). IR (neat, cm^{-1}) 3046, 2901, 2720, 1725, 1593, 1491, 1302, 1210, 748, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 9.74 (t, J = 1.8 Hz, 1H), 7.38-7.30 (m, 4H), 7.14-7.04 (m, 6H), 6.49 (t, J = 5.3 Hz), 2.44 (dt, J_1 = 7.0, J_2 =1.5 Hz, 2H), 2.33-2.23 (m, 2H), 1.70-1.52 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4, 144.2, 138.9, 129.6, 123.9, 122.3, 43.6, 32.3, 26.4, 21.6 HRMS calcd. for $C_{18}H_{20}N_2O$ (M^+) : 280.1571. Found: 280.1562.

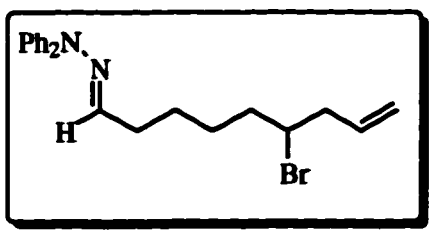
Preparation of 6-Hydroxy-8-nonenal-*N,N*-diphenylhydrazone (85)



A round bottom flask (100 mL), flame dried and cooled under argon was charged with aldehyde **84** (1.12 g, 4.11 mmol) followed by THF (40 mL). The solution was cooled to -10°C and allyl magnesium chloride (2.20 mL of a 2.0 M solution in THF) was added. The mixture was stirred at -10°C for 30 minutes, then the reaction mixture was brought to room temperature and quenched with water (15 mL). The mixture was poured into a separatory funnel and the aqueous phase was extracted with ether (3X 10 mL).The combined organic extracts were dried and concentrated *in vacuo*. The resulting oil was

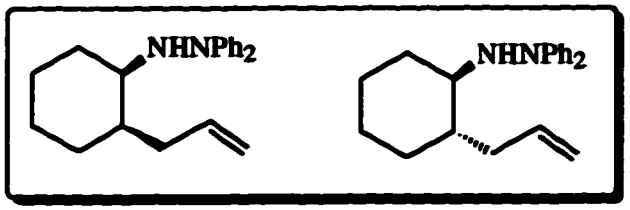
purified by flash chromatography (50% ether, 50% petroleum ether) to afford the title compound as a clear oil 1.02 g (75%). IR (neat, cm^{-1}) 3388, 3066, 2928, 2857, 1640, 1592, 1493, 1453, 1376, 1301, 1210, 1169, 1089, 1053, 995, 749, ^1H NMR (200 MHz, $CDCl_3$) δ 7.42-7.20 (m, 4H), 7.16-7.00 (m, 6H), 6.51 (t, *J* = 5.3 Hz, 1H), 5.92-5.78 (m, 1H), 5.20-5.04 (m, 2H), 3.70-3.52 (m, 1H), 2.38-2.00 (m, 4H), 1.70-1.10 (m, 7H) ppm ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.9, 140.4, 135.4, 130.2, 124.4, 122.9, 118.7, 71.1, 42.5, 37.1, 33.2, 27.6, 25.8 ppm; HRMS calcd. for $C_{21}H_{26}N_2O$ (M^+) : 322.2046. Found: 322.2039.

Preparation of 6-Bromo-8-nonenal-*N*,*N*-diphenylhydrazone (86)



Following the general procedure for the bromination of alcohols, alcohol **85** (0.5 g, 1.5 mmol) was treated with Ph_3P (448 mg, 1.65 mmol), Et_3N (0.25 mL, 1.65 mmol) and titrated with a bromine solution as described above. After purification, 331 mg (65%) of the title compound was obtained as a clear oil. IR (neat, cm^{-1}) 3065, 3031, 2936, 1592, 1453, 1431, 1376, 1091, 798, 697; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.20 (m, 4H), 7.12-7.03 (m, 6H), 6.51 (t, *J* = 4.8 Hz, 1H), 5086-5.79 (m, 1H). 5.12-5.08 (m, 2H), 4.50 (p, *J* = 2.1 Hz, 1H), 2.61-2.55 (m, 2H), 2.28-2.22 (m, 2H), 1.81-1.76 (m, 2H), 1.61-1.36 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 139.4, 134.8, 129.0, 122.3, 120.4, 117.7, 56.1, 43.2, 38.1, 32.4, 27.0, 24.3 ppm; HRMS calcd. for $C_{21}H_{25}N_2Br$ (M^+) : 384.1202. Found: 384.1192.

Preparation of 1-Allyl-2-(*N,N*-diphenylhydrazino)-cyclohexanes *cis* (87b) and *trans* (87z)

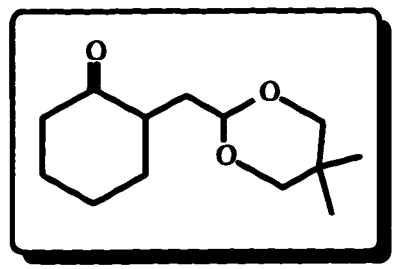


A) Following the general procedure for radical reactions, bromide **86** (150 mg, 0.39 mmol) was placed in a round bottom flask (50 mL) followed by benzene (20 mL), and was treated with Bu_3SnH (127 μL, 0.42 mmol) and AIBN (25 mg). After concentration and purification of the reaction mixture, the *cis* and *trans* isomers were isolated as clear oils. IR (neat, cm^{-1}) 3028, 2927, 1590, 1495, 1285, 1028; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-6.92 (m, 20H), 5.75-5.62 (m, 2H), 5.02-4.88 (m, 4H), 3.17-2.95 (m, 1H), 2.2.65-2.51 (m, 1H), 2.2.32-2.24 (m, 2H), 2.17-21.95 (m, 2H), 1.75-1.11 (m, 18H), NH not observed; ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.4, 137.6, 130.2, 129.6, 129.6, 122.9, 122.8, 122.6, 121.2, 120.9, 116.7, 116.1, 59.7, 56.6, 40.7, 39.3, 38.1, 34.5, 31.0, 27.8, 27.7, 25.9, 24.8, 24.0, 23.4; HRMS calcd. for $C_{21}H_{26}N_2$ (M^+) : 306.2097. Found: 306.2120.

B) Following the general procedure for the syringe pump radical reactions, bromide **86** (36 mg, 0.09 mmol) was placed in a round bottom flask (50 mL) followed by benzene (20 mL), and was treated with Bu_3SnH (29 μL, 0.1 mmol) and AIBN (5 mg). After concentration and purification of the reaction mixture, the *cis* and *trans* isomers were isolated as clear oils.

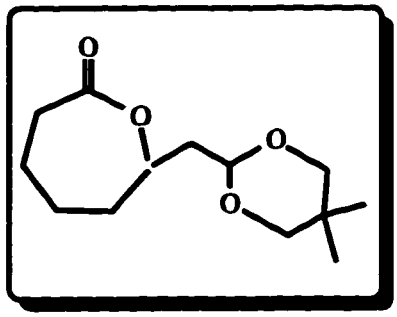
C) Following the general procedure for SmI_2/HMPA, bromide **86** (68 mg, 0.18 mmol) was placed in a dry round bottom flask (50 mL) followed by THF (7 mL). The mixture was treated with HMPA (0.3 mL) and SmI_2 (8 mL as a 0.1 M solution in THF). After work-up and purification, the *cis* and *trans* isomers were isolated as clear oils.

Preparation of Cyclohexanone-2-[(2-carboxaldehyde)-neopentylidene acetal] (98)



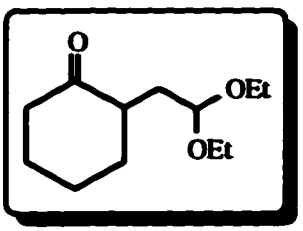
A round bottom flask (100 mL) fitted with a Dean-Stark condenser was charged with compound **96** (3.8 g, 25 mmol) followed by neopentylidene glycol (2.87 g, 25 mmol) and a crystal of TsOH. The mixture was heated and allowed to reflux over night. The mixture was then concentrated *in vacuo* and purified by flash column chromatography (50% ether, 50% petroleum ether). Concentration of the appropriate fractions gave 2.0 g (30%) of the title compound as a clear oil. IR (neat, cm^{-1}) 2941, 2858, 1710, 1460, 1394, 1363, 1311, 1239, 1145, 1122, 1041, 1018, 985, 910, 845, 792, 666; ^1H NMR (200 MHz, $CDCl_3$) δ 4.51 (dd, J_1 = 4.4 Hz, J_2 = 7.4 Hz, 1H), 3.58-3.50 (m, 2H), 3.43-3.32 (m, 2H), 2.65-2.49 (m, 1H), 2.41-2.29 (m, 1H), 2.23-2.02 (m, 4H), 1.81-1.71 (m, 1H), 1.70-1.61 (m, 2H), 1.47-1.34 (m, 2H), 1.14 (s, 3H), 0.67 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.3, 101.0, 77.7, 77.6, 46.6, 42.8, 35.6, 35.3, 30.8, 28.9, 25.8, 23.6, 22.4 ppm; HRMS calcd. for $C_{13}H_{22}O_3$ (M^+) : 226.1569. Found: 226.1531.

Preparation of 6-[(2-Carboxaldehyde) neopentylidene acetal) ε-Caprolactone (99)



A round bottom flask (250 mL), flamed dried and cooled under argon, was fitted with a condenser, charged with lactone **98** (1.83 g, 8.1 mmol) and chloroform (155 mL) followed by (2.6 g, 9.2 mmol, 57% *m*-CPBA) and heterogeneous sodium bicarbonate (2.0 g). The mixture was heated and allowed to reflux over night. After this time, the mixture was cooled to room temperature and poured into a separatory funnel with ether and aqueous saturated sodium bicarbonate. The aqueous layer was extracted with ether (3X 50 mL) and the combined organic extracts were washed with water, dried and concentrated *in vacuo*. Purification by flash chromatography (100% ether) gave the title compound 1.8g (90%) as a clear oil. IR (neat, cm^{-1}) 2943, 2862, 1730, 1454, 1395, 1329, 1269, 1218, 1170, 1140, 1094, 1016, 998, 927, 845; ^1H NMR (500 MHz, $CDCl_3$) δ 4.59 (dd, J_1 = 3Hz, J_2 = 8.6Hz, 1H), 4.44 (dt, J_1 = 3.7 Hz, J_2 = 9.4 Hz, 1H), 3.57-3.51 (m, 2H), 3.44-3.38 (m, 2H), 2.63-2.53 (m, 2H), 2.26-2.23 (m, 2H), 2.05-2.00 (m, 1H), 1.93-1.83 (m, 2H), 1.74-1.70 (m, 1H), 1.64-1.49 (m, 2H), 1.12 (s, 3H), 0.67 (s, 3H), ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 98.8, 77.3, 77.1, 76.3, 63.8, 34.9, 34.8, 34.2, 30.2, 28.1, 22.9, 22.8, 21.7 ppm; HRMS calcd. for $C_{13}H_{22}O_4$ (M^+) : 242.1519. Found: 242.1506.

Preparation of Cyclohexane-2-[(2-carboxaldehyde)-diethoxy acetal] (100)

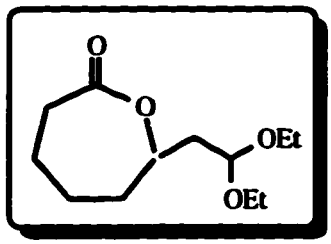


A round bottom flask (250 mL) was charged with cyclohexanone (10 g, 102 mmol) and methanol (100 mL) followed by *N,N*--dimethylhydrazine (6 g, 102 mmol). The mixture was allowed to stir at room temperature for 4 hours. After this time, the solvent was evaporated *in vacuo*. Dry THF (100 mL) was added, the flask was fitted with a rubber septum, and argon introduced before the solution was cooled to 0 °C. *n*-BuLi (45 mL of a 2.5 M solution in hexanes) was added dropwise and the mixture was allowed to stir at 0 °C for 30 minutes after which bromoacetaldehyde diethoxy acetal (22.4 g, 102 mmol) was added. The reaction mixture was slowly warmed to room temperature and allowed to stir for 4 hours. The mixture was quenched with water (50 mL) and poured into a separatory funnel. The aqueous layer was extracted with ether (3X 25 mL). The combined ogranic extracts were dried and concentrated *in vacuo*.

The resulting yellow liquid was transferred to a three neck round bottom flask (250 mL) equipped with a drying tube, a stopcock and a stopper with a hollow glass tube. The flask was charged with dichloromethane (100 mL) and the solution was cooled to -78 °C. Ozone was then bubbled through the solution for 6.5 hours; the solution turned bright red. After this time, the reaction was flushed with oxygen. The solution was then warmed to room temperature and the colour changed to yellow. The solution was concentrated *in vacuo* and purified by flash chromatography (70% ether, 30% petroleum ether). Concentration of the appropriate fractions gave 8.2 g (38%) of the title compound as a

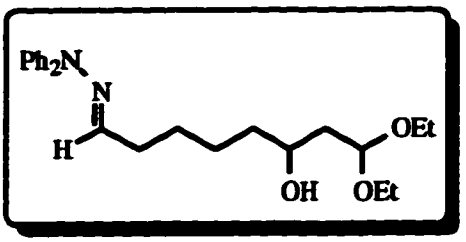
yellow oil. IR (neat, cm^{-1}) 2935, 2864, 1711, 1448, 1374, 1346, 1225, 1124, 1060, 1005; ^1H NMR (200 MHz, $CDCl_3$) δ 4.57 (dd, J_1 = 5 Hz, J_2 = 6.6 Hz, 1H), 3.63-3.36 (m, 4H), 2.52-2.23 (m, 2H), 2.19-1.95 (m, 2H), 1.93-1.54 (m, 4H), 1.42-1.29 (m, 3H), 1.14 (t, J = 7 Hz, 3H), 1.12 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.7, 100.9, 61.0, 41.7, 34.6, 33.4, 28.6, 24.7, 14.9, 14.7 ppm; HRMS calcd. for (M^+ - C_2H_5O) 169.1223. Found: 169.1233.

Preparation of 6-[(2-Carboxaldehyde) diethoxy acetal] ε-Caprolactone (101)



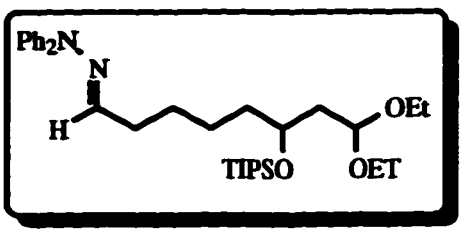
Following the procedure for compound **99**, ketone **100** (2.67 g, 12.5 mmol) was treated with *m*-CPBA (3.3 g, 57% pure, remainder being 3-chlorobenzoic acid) and sodium bicarbonate (4 g). After workup and purification by flash chromatography (80% ether, 20% petroleum ether), concentration of the appropriate fractions yielded 2.23 g (80%) of the title compound as a light yellow oil. IR (neat, cm^{-1}) 2974, 2833, 1729, 1444, 1375, 1348, 1272, 1222, 1173, 1125, 1060, 1013, 960, 846; ^1H NMR (200 MHz, $CDCl_3$) δ 4.64 (dd, J_1 = 3.5 Hz, J_2 = 8.2 Hz, 1H), 4.40 (dt, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 4.21-4.10 (m, 2H), 3.74-3.44 (m, 4H), 2.64-2.56 (m, 4H), 2.08-1.54 (m, 4H), 1.16 (t, J = 7.1Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 99.8, 62.3, 61.9, 40.4, 34.4, 34.2, 27.7, 22.5, 15.0 ppm; HRMS calcd. for (M^+ - C_2H_5O) 185.1183. Found: 185.1178.

Preparation of 6-Hydroxyocta-1-(*N,N*-diphenylhydrazone)-8-(diethoxy acetal)-dial (102)



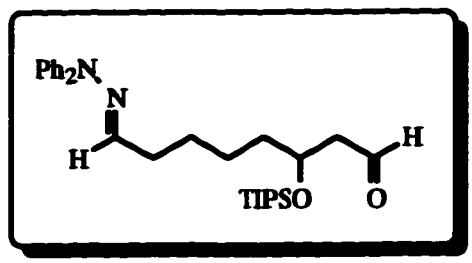
Following the procedure for compound **83**, lactone **99** (1 g, 4.3 mmol) was treated with DIBAL (4.8 mL of a 1.0 M solution in toluene). After quenching and concentration, the crude oil was diluted with MeOH and treated with *N,N*-diphenylhydrazine (0.8 g, 4.3 mmol). The mixture was allowed to stir at room temperature for 15 minutes, after which the mixture was concentrated *in vacuo* and purified by flash column chromatography (70% ether, 30% petroleum ether). Concentration of the appropriate fractions yielded 1.2 g (70%) of the title compound as a yellow oil. IR (neat, cm^{-1}) 3446, 2924, 1592, 1493, 1452, 1375, 1301, 1210, 1080, 749, 698, 639; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.13-7.03 (m, 6H), 6.51 (t, J = 5.3 Hz, 1H) 4.67 (t, J = 5.7 Hz, 1H), 3.76-3.45 (m, 4H), 3.16 (d, J = 2.2 Hz, 1H), 2.30-2.25 (m, 2H), 1.75-1.69 (m, 2H), 1.56-1.22 (m, 7H), 1.16 (t, J = 2.8 Hz, 6H) ppm ;^{13}C NMR (50 MHz, $CDCl_3$) δ 145.5, 140.5, 130.2, 124.4, 122.9, 103.1, 68.9, 63.0, 40.8, 37.8, 33.3, 27.6, 25.7, 15.9 ppm; HRMS calcd. for $C_{24}H_{34}N_2O_3$ (M^+) : 398.2571. Found: 398.2579.

Preparation of 6-Triisopropylsilyloxyocta-1(*N*,*N*-diphenylhydrazone)-8-(diethoxy acetal)-dial (103)



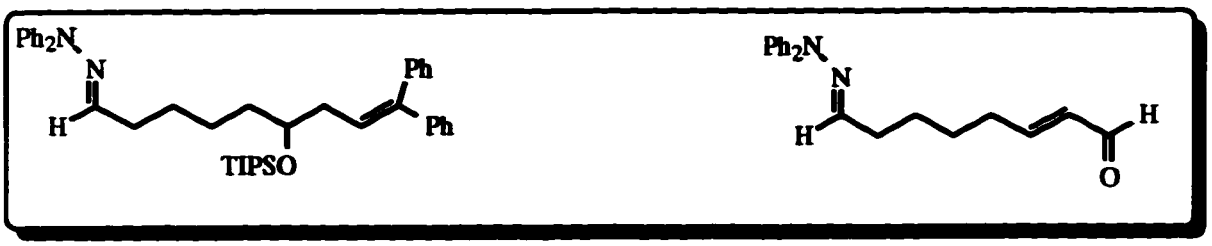
A round bottom flask (25 mL), dried and cooled under argon, was charged with alcohol **102** (1.13 g, 2.8 mmol) and freshly distilled dichloromethane (10 mL). To this solution was added TIPSOTf (1.15 mL, 4.3 mmol) and collidine (0.6 mL, 4.3 mmol). The mixture was allowed to stir at room temperature overnight. The reaction was quenched with aqueous saturated sodium bicarbonate and poured into a separatory funnel. The aqueous layer was extracted with ether (3X 5 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification by flash chromatography (30% ether, 70% petroleum ether) yielded the title compound, 1.44 g (91.5%) as a clear oil. IR (neat, cm^{-1}) 2938, 2868, 1593, 1495, 1211, 1092, 747; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.21 (m, 4H), 7.13-7.03 (m, 6H), 6.51 (t, J = 5.3 Hz, 1H), 4.64 (t, J = 6.5 Hz, 1H), 3.98-3.93 (m, 1H), 3.67-3.38 (m, 4H), 2.31-2.22 (m, 2H), 1.78-7.71 (m, 2H), 1.62-1.22 (m, 6H), 1.17 (t, J = 5.7 Hz, 6H), 1.08-0.82 (br s, 21H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 139.5, 129.3, 123.4, 121.9, 100.4, 68.8, 60.7, 40.3, 36.9, 32.3, 27.0, 23.7, 17.8, 15.0, 12.4 ppm; HRMS calcd. for $C_{33}H_{54}N_2O_3Si$ (M^+) : 554.3905. Found: 554.3884.

Preparation of 6-Triisopropysilyloxyocta-1(*N,N*-diphenylhydrazone)-8-dial (104)



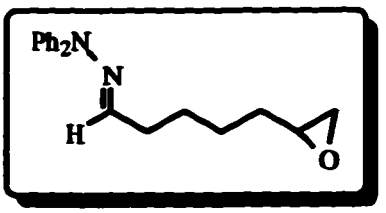
A round bottom flask (10 mL) equipped with a condenser was charged with acetal **103** (0.5 g, .95 mmol) followed by a mixture of DMSO/Dioxane, (1:1, 3 mL) and water (0.1 mL). The mixture was heated and allowed to reflux over night. The mixture was cooled to room temperature, diluted with ether and poured into a separatory funnel containing water and ether. The organic phase was washed with water (3X 5 mL) and the combined aqueous phases were extracted with ether (3X 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by flash chromatography (20% ether, 80% petroleum ether) yielded the title compound, 0.3 g (70%) as an orange oil. The ^{1}H NMR indicated that the silyl group had been removed and a new signal downfield, integrating for one proton had appeared. The compound was unstable and could not be further characterized. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.84-9.83 (m, 1H);

Attempted Preparation of 6-Triisopropylsilyloxy-1(*N,N*-diphenylhydrazone)-9,9-diphenyl-8-nonene Resulting in *trans*-1-(*N,N*-diphenylhydrazone)octa-6-ene-8-dial (105)



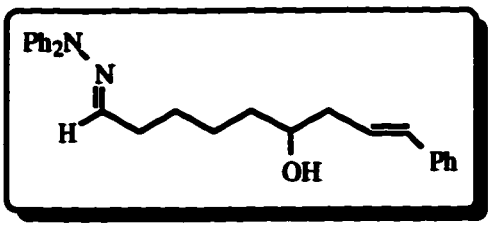
Following the general procedure for Wittig reactions, aldehyde **104** (48 mg, 0.13 mmol) was treated with benzhydryltriphenylphosphonium chloride (92.5 mg, 0.2 mmol) and *n*-BuLi (80 μL as a 2.5 M solution in hexanes). After workup and purification by flash chromatography (20% ether, 80% petroleum ether), compound XXX was isolated, 41 mg (98%) as a yellow oil. IR (neat, cm^{-1}) 3034, 2946, 1705, 1492, 1301, 1209, 749; ^1H NMR (200 MHz, $CDCl_3$) δ 9.47 (d, J = 7.9 Hz, 1H), 7.40-7.24 (m, 4H), 7.16-7.01 (m, 6H), 6.87 (dt, J_1 = 6.7 Hz, J_2 = 16 Hz, 1H), 6.51 (t, J =5.3 Hz, 1H), 6.10 (dd, J_1 = 7.9 Hz, J_2 = 16 Hz, 1H), 2.37-2.24 (m, 3H), 1.65-1.49 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 158.1, 143.8, 138.5, 132.7, 129.3, 121.9, 32.1, 31.9, 26.9, 26.0 ppm; HRMS calcd. for $C_{20}H_{22}N_2O$ (M^+) : 306.1733. Found: 306.1742.

Preparation of 6,7-Epoxyheptanal-*N*,*N*-diphenylhydrazone (106)



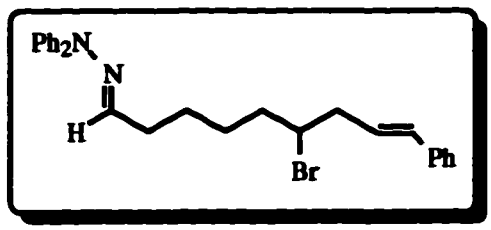
A three-necked round bottom flask (50 mL), dried and cooled under argon, was charged with NaH (258 mg as a 60% dispersion in mineral oil) and dry DMSO (5 mL). The mixture was stirred at 70°C for 1 hour. The mixture was cooled to room temperature and diluted with THF (15 mL) and recooled to -10°C. Trimethyl sulfonium iodide (1.31 g, 6.4 mmol) was added and the mixture stirred. After 2 minutes, a solution of aldehyde **84**, (91.5 g) in THF (2 mL) was added and allowed to stir at -10°C for an additional 30 minutes. After this time, the mixture was poured into a separatory funnel with water and ether. The aqueous layer was extracted with ether (3X 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Further purification by flash chromatography (20% ether, 80% petroleum ether) gave the title compound, 966 mg (61%) as a clear oil. IR (neat, cm^{-1}) 3046, 2930, 2858, 1592, 1492, 1454, 1376, 1301, 1210, 1172, 1062, 912, 836, 749; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.26 (m, 4H), 7.24-7.03 (m, 6H), 6.52 (t, J = 2.7 Hz, 1H), 2.95-2.88 (m, 1H), 2.75-2.70 (m, 1H), 2.46-2.42 (m, 1H), 2.39-2.26 (m, 2H), 1.57-1.37 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 139.1, 129.3, 123.5, 121.9, 46.7, 32.2, 31.9, 26, 25.2; HRMS calcd. for $C_{19}H_{22}N_2O$ (M^+) : 294.1733. Found: 294.1733.

Preparation of *trans*-6-Hydroxy-9-phenylnon-8-eneal-(*N,N*-diphenylhydrazone) (107)



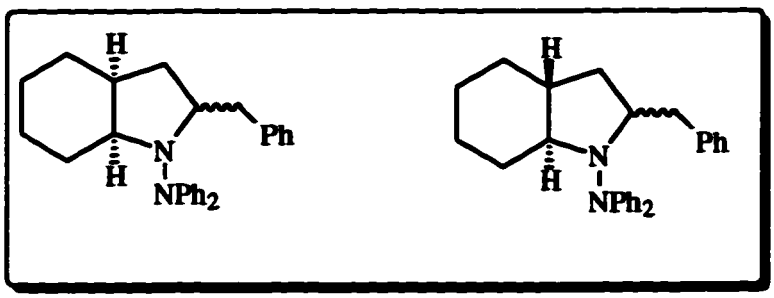
A round bottom flask (50 mL), dried and cooled under argon, was charged with THF (10 mL) and *trans*-β-bromostyrene (240 μL, 1.9 mmol). The solution was cooled to -78 °C and *sec*-BuLi (2.8 mL as a 1.3 M solution in hexanes) was added dropwise and the mixture was allowed to stir at -78°C for 30 minutes. Lithium 2-thienylcyanocuprate (7.6 mL of a 0.25M solution in THF) was added dropwise and the mixture was allowed to stir for an additional 15 minutes at -78°C. After this time, epoxide **106** (0.5 g, 1.7 mmol) was added as a THF solution (1 mL) and the mixture was warmed slowly to room temperature. The mixture was allowed to stir at room temperature over night. After this time, the reaction was quenched with a 9:1 solution of saturated ammonium chloride and ammonium hydroxide (10 mL). The mixture was allowed to stir for 8 hours and then transferred to a separatory funnel. The aqueous layer was extracted with ether (3X 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification by flash column chromatography (50% ether, 50% petroleum ether) gave 175 mg (69% based on recovered starting material) of an orange oil. IR (neat, cm^{-1}) 3411, 3022, 2911, 1606, 1493, 1451, 1301, 1206, 1090, 967, 908, 740; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.19 (m, 9H), 7.13-7.02 (m, 6H), 6.54-6.42 (m, 2H), 6.27-6.21 (m, 1H), 3.79-3.67 (m, 1H), 2.54-2.24 (m, 4H), 1.59-1.40 (m, 6H), OH proton not observed, ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 132.6, 129.03, 128.2, 126.9, 125.7, 123.5, 121.9, 70.6, 40.8, 36.3, 32.3, 26.6, 24.9 ppm; HRMS calcd. for $C_{27}H_{30}N_2O$ (M^+) : 398.2360. Found: 398.2385.

Preparation of *trans*-6-Bromo-1(*N*,*N*-diphenylhydrazone)-9-phenylnon-8-enal (108)



Following the general procedure for the bromination of alcohols, alcohol **107** (140 mg, 0.35 mmol) was treated with Ph_3P (101 mg, 0.4 mmol), Et_3N (0.2 mL, 1.2 mmol) and titrated with a bromine solution as described above. Purification yielded 86 mg (55%) of the title compound as a clear oil. IR (neat, cm^{-1}) 3028, 2931, 1592, 1492, 1452, 1302, 1209, 1170, 1066, 966, 746; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.20 (m, 9H), 7.13-7.02 (m, 6H), 6.53-6.48 (m, 2H), 6.41-6.18 (m, 1H), 4.07 (p, J = 6.3 Hz, 1H), 2.75 (t, J = 3.7 Hz, 2H), 2.33-2.23 (m, 2H), 1.93-1.79 (m, 2H), 1.58-1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 133.2, 129.8, 128.3, 127.0, 125.8, 123.5, 121.9, 56.2, 42.1, 37.8, 32.1, 26.7; HRMS calcd. for $C_{27}H_{29}N_2Br$ (M^+) : 460.1515. Found: 460.1527.

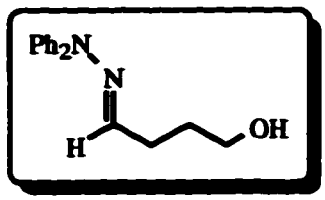
Preparation of *cis* *N*-Diphenylamino-2-benzyloctahydro Indole (111a) and *trans* *N*-Diphenylamino-2-benzyloctahydro Indole (111b)



A) Following the general procedure for radical reactions, bromide **108** (86 mg, 0.18 mmol) was placed in a round bottom flask (50 mL) followed by benzene (10 mL), and was treated with Bu_3SnH (75 μL, 0.20 mmol) and AIBN (5 mg). After concentration and purification of the reaction mixture, the *cis* and *trans* isomers were isolated as colorless solids (19 mg) 30% yield. IR (neat, cm^{-1}) 3028, 2931, 1592, 1492, 1452, 1318, 1164; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-6.96 (m, 30H), 3.35-3.32 (m, 1H), 3.22-3.13 (m, 2H), 2.97-2.89 (m, 2H), 2.64-2.57 (m, 2H), 2.27-2.23 (m, 1H), 2.09-2.04 (m, 2H), 1.87-1.57 (m, 10H), 1.51-1.12 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 139.9, 129.0, 128.8, 128.1, 125.8, 125.7, 67.2, 60.3, 41.6, 41.3, 40.1, 34.1, 34.0, 32.6, 31.7, 30.4, 30.3, 26.2, 25.4, 25.3, 24.4, 21.9; HRMS calcd. for $C_{27}H_{30}N_2$ (M^+) : 382.2410. Found: 382.2422.

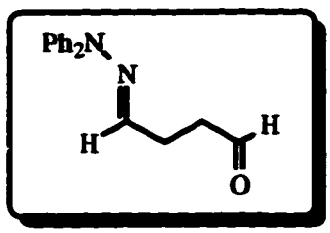
B) Following the general procedure for the syringe pump radical reactions, bromide **108** (54 mg, 0.11 mmol) was placed in a round bottom flask (50 mL) followed by benzene (10 mL), and was treated with $(CH_3Si)Si_3H$ (54 μL, 0.14 mmol), and AIBN (5 mg). After concentration and purification of the reaction mixture, the *cis* and *trans* isomers were isolated as colorless solids (9 mg) 28% yield.

Preparation of 4-Hydroxybutanal-*N,N*-diphenylhydrazone (120)



Following the procedure for compound **83**, γ-butyrolactone (5 g, 58 mmol) was treated with DIBAL (64 mL of a 1 M solution in toluene) and *N,N*-diphenyl hydrazine (10.7g, 58 mmol). After purification by flash chromatography (60% ether, 40% petroleum ether), yielded the title compound, 8.8 g (60%) as a red oil. IR (neat, cm^{-1}) 3352. 3048, 2917, 1592, 1491, 1298, 1056, 745, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.14-7.06 (m, 6H), 5.67 (t, *J* =6.7 Hz, 1H), 3.63 (t, *J* = 6,4 Hz, 2H), 2.98 (bd s, 1H), 2.40-2.30 (m, 2H), 1.83-1.73 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 140.0, 130.3, 124.6, 122.9, 62.8, 30.2, 28.9 ppm; HRMS calcd. for $C_{16}H_{18}N_2O$ (M^+) : 254.1420. Found: 254.1407.

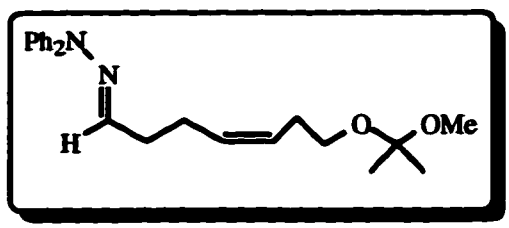
Preparation of Propanal-(*N,N*-diphenylhydrazone)-3-carboxaldehyde (118)



Following the procedure for compound **84**, alcohol **120** (1 g, 3.9 mmol) was treated with SO_3/pyridine complex (1.9 g, 12 mmol) and Et_3N (4.4 mL, 24 mmol). After purification by flash chromatography (30% ether, 70% petroleum ether), the title compound was isolated 900 mg (90%) as a yellow oil. IR (neat, cm^{-1}) 3048, 2904, 2828,

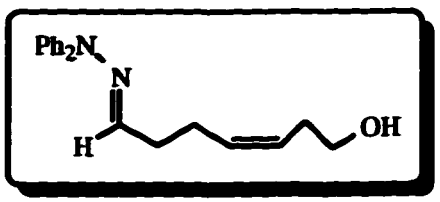
1723, 1592, 1491, 1300, 1211, 1068; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.87 (bd s, 1H), 7.39-7.32 (m, 4H), 7.15-7.01 (m, 6H), 6.56 (t, *J* = 4.0 Hz, 1H), 2.80-2.73 (m, 2H), 2.63-2.49 (m, 2H), ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.5, 143.7, 136.0, 129.5, 123.8, 122.0, 39.7, 25.2 ppm; HRMS calcd. for $C_{16}H_{16}N_2O$ (M^+) : 252.1263. Found: 252.1276.

Preparation of (4Z)-7(oxy(2-methoxypropane))-4-heptenal-*N,N*-diphenylhydrazone (121)



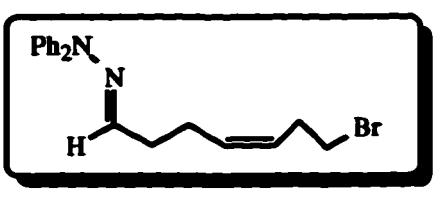
Following the general procedure for Wittig reactions, aldehyde **118** (1.33 g, 5.3 mmol) was treated with 3-Oxy(2-methoxypropane)propanetriphenylphosphonium bromide (2.48 g, 5.4 mmol), and *n*-BuLi (2.6 mL of a 2.5 M solution in hexanes). After workup and purification by flash chromatography (30% ether, 70% petroleum ether), the title compound was isolated, 1.5 g (79%) as a clear oil. IR (neat, cm^{-1}) 3020, 2954, 1590, 1495, 1370, 1305, 1210, 1080, 747; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38-7.29 (m, 4H), 7.13-7.03 (m, 6H), 6.51 (t, *J* = 5 Hz, 1H), 5.52-5.42 (m, 2H), 3.36 (t, *J* = 7.1 Hz, 2H), 3.17 (s, 3H), 2.54-2.20 (m, 6H), 1.34 (s, 6H), ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 138.5, 131.6, 129.3, 125.5, 123.5, 121.9, 80.3, 61.8, 32.3, 30.5, 30.4, 24.5 ppm; HRMS calcd for $C_{23}H_{30}N_2O_2$ (M^+) : 366.2308. Found: 366.2279.

Preparation of (4Z)-7-Hydroxy-4-heptenal-*N,N*-diphenylhydrazone (122)



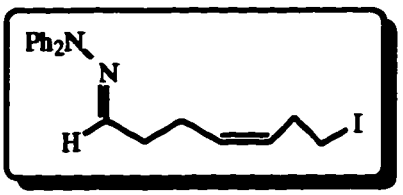
Compound **121** (2.7 g, 7.3 mmol) was placed in a round bottom flask with CH_3CN (40 mL), water (10 mL) and glacial acetic acid (0.3 mL). The mixture was allowed to stir at room temperature for 3 hours. The reaction was quenched with aqueous saturated sodium bicarbonate and taken up in ether. The mixture was poured into a separatory funnel and the aqueous phase was extracted with ether (3X 10 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification by flash chromatography (30% ether, 70% petroleum ether) yielded 1.9 g (86%) of the title compound as a yellow oil. IR (neat, cm^{-1}) 3359, 3060, 2916, 1592, 1491, 1172, 1054, 749; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.14-7.04 (m, 6H), 6.50 (t, J = 4.9 Hz, 1H), 5.53-5.33 (m, 2H), 3.60 (t, J = 6.4 Hz, 2H), 2.34-2.22 (m, 6H), OH proton not observed; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 138.9, 131.9, 129.6, 125.9, 123.9, 122.3, 62.2, 32.6, 30.8, 24.9 ppm; HRMS calcd. for $C_{19}H_{22}N_2O$ (M^+) : 294.1733. Found: 294.1734.

Preparation of (4Z)-7-Bromo-4-heptenal-*N,N*-diphenylhydrazone (123)



Following the general procedure for the bromination of alcohols, alcohol **122** (0.6 g, 2 mmol) was treated with Ph_3P (590 mg, 2.2 mmol), Et_3N (0.4 mL, 2.4 mmol) and titrated with a bromine solution as described above. After purification, 501 mg (70%) of the title compound was obtained as a clear oil. IR (neat, cm^{-1}) 3059, 2938, 1590, 1453, 1431, 1375, 1093, 790, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.15-7.04 (m, 6H), 6.51 (t, *J* = 2.5 Hz, 1H), 5.50-5.39 (m, 2H), 3.32 (t, *J* = 7.1 Hz, 2H), 2.63-2.52 (m, 2H), 2.36-2.24 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 138.6, 131.7, 129.7, 126.6, 123.9, 122.3, 32.5, 32.4, 30.8, 25 ppm; HRMS calcd. for $C_{19}H_{21}N_2Br$ (M^+) : 356.0888. Found: 356.0892.

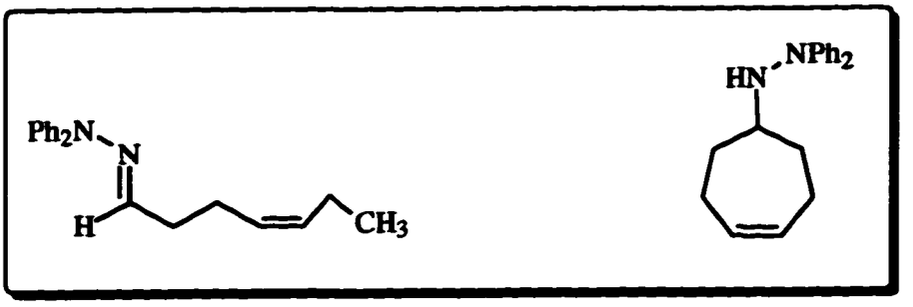
Preparation of (4Z)-7-Iodo-4-heptenal-*N*,*N*-diphenylhydrazone (124)



A round bottom flask (50 mL), dried and cooled under argon, fitted with a condenser, was charged with bromide **123** (120 mg, 0.33 mmol), sodium iodide (200 mg, 1.34 mmol) and dry acetone (25 mL). The mixture was heated and allowed to reflux overnight. After this time, the mixture was cooled to room temperature and diluted with ether. The mixture was poured into a separatory funnel and the organic phase was washed with water (10 mL) and saturated aqueous sodium chloride (10 mL). The organic phase was then dried and concentrated to yield 107 mg (79%) of the title compound as a clear oil. No further purification was required. IR (neat, cm^{-1}) 3016, 2930, 1592, 1492, 1301, 1210, 748; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.14-7.04 (m, 6H), 6.50 (t, *J* = 4.6 Hz, 1H), 5.62-5.25 (m, 2H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.64-2.53 (m, 2H), 2.36-2.21 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 139.2, 131.8, 130.2,

129.2, 124.5, 122.9, 33.1, 32.1, 25.6, 5.93 ppm; HRMS calcd. for $C_{19}H_{21}N_2I$ (M^+) : 404.0751. Found: 404.0734.

Preparation of (4Z)-Heptenal-*N,N*-diphehylhydrazone (126) and 1-*N,N*-diphenylhydrazino-4-cycloheptene (125)



A) Following the general procedure for radical reactions, bromide **123** (160 mg, 0.47 mmol) was dissolved in benzene (22 mL) and treated with Bu_3SnH (132 μL, 0.47 mmol) and AIBN (25 mg). After concentration and purification of the reaction mixture, compound **125**, 25 mg (16%) was isolated as clear crystals IR (neat, cm^{-1}) 3007, 2927, 1589, 1496; ^1H NMR (200 MHz, $CDCl_3$) δ7.39-7.00 (m, 9H), 6.98-6.94 (m, 1H), 5.77-5.73 (m, 2H), 3.83 (bd, 1H), 3.02-3.00 (m, 1H), 2.34-2.03 (m, 2H), 1.98-1.77 (m, 4H), 1.57-1.45 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 132.4, 130.6, 129.8, 124.5, 123.5, 122.9, 121.2, 59.6, 31.7, 24.4 ppm; HRMS calcd. for $C_{19}H_{22}N_2$ 278.1784 (M^+) found 278.1810, and compound **126**, 68 mg (48%) was isolated as a clear oil. IR (neat, cm^{-1}) 3007, 2938, 1592, 1493; ^1H NMR (200 MHz, $CDCl_3$) δ7.3-7.30 (m, 6H), 7.13-7.04 (m, 4H) 6.54-6.48 (m, 1H), 5.43-5.36 (m, 2H),2.37-2.30 (m, 2H), 2.19-2.14 (m, 2H), 2.05-1.90 (m, 2H), 0.92 (t, *J*= 6.3 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.4, 140.3 133.8, 130.1, 128.5, 124.4, 122.9, 33.3, 30.9, 26.2, 14.5 ppm; HRMS calcd. for $C_{19}H_{22}N_2$ 278.1784 (M^+) found 278.1782.

B) Following the general procedure for the syringe pump radical reactions, bromide **123** (230 mg, 0.68 mmol) was placed in a round bottom flask (250 mL) followed by benzene (120 mL), and was treated with Bu_3SnH (190 μL, 0.75 mmol) and AIBN (25 mg). After concentration and purification of the reaction mixture, compound **125**, 43 mg (33%) was isolated as clear crystals and compound **126**, 31 mg (22%) was isolated as a clear oil.

C) Following the general procedure for SmI_2/HMPA, bromide **123** (230 mg, 0.68 mmol) was placed in a dry round bottom flask (50 mL) followed by THF (25 mL). The mixture was treated with HMPA (1.3 mL) and SmI_2 (12.8 mL as a 0.1 M solution in THF). After work-up and purification of the reaction mixture, compound **125**, 43 mg (33%) was isolated as clear crystals and compound **126**, 31 mg (22%) was isolated as a clear oil.

D) Following the general procedure for the syringe pump radical reactions, bromide **123** (100 mg, 0.30 mmol) was placed in a round bottom flask (50 mL) followed by benzene (14 mL), and was treated with Bu_3SnH (98 μL, 0.33 mmol), $(Bu_3Sn)_2O$ (142 μL, 0.33 mmol) and AIBN (25 mg). After concentration and purification of the reaction mixture, compound **125**, 23 mg (30%) was isolated as clear crystals and compound **126**, 27 mg (35%) was isolated as a clear oil.

E) Following the general procedure for the syringe pump radical reactions, bromide **123** (80 mg, 0.22 mmol) was placed in a round bottom flask (50 mL) followed by benzene (14 mL), and was treated with $(CH_3Si)Si_3H$ (120 μL, 0.33 mmol), $(Bu_3Sn)_2O$ (284 μL, 0.66 mmol) and AIBN (25 mg). After concentration and purification of the reaction

mixture, compound **125**, 20 mg (32%) was isolated as clear crystals and compound **126**, 22 mg (35%) was isolated as a clear oil.

F) Following the general procedure for the syringe pump radical reactions, bromide **123** (200 mg, 0.55 mmol) was placed in a round bottom flask (50 mL) followed by benzene (28 mL), and was treated with $(CH_3Si)Si_3H$ (207 μL, 0.66 mmol), and AIBN (25 mg). After concentration and purification of the reaction mixture, compound **125**, 25 mg (16%) was isolated as clear crystals and compound **126**, 31 mg (20%) was isolated as a clear oil.

G) Following the general procedure for the syringe pump radical reactions, iodide **124** (107 mg, 0.26 mmol) was placed in a round bottom flask (50 mL) followed by benzene (18 mL), and was treated with $(CH_3Si)Si_3H$ (120 μL, 0.32 mmol), $(Bu_3Sn)_2O$ (0.4 mL, 0.91 mmol) and AIBN (25 mg). After concentration and purification of the reaction mixture, compound **125**, 25 mg (30%) was isolated as clear crystals and compound **126**, 25 mg (30%) was isolated as a clear oil.

References

1. For leading reviews see (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, **1986**. (b) Curran, D.P. *Synthesis* **1988**, 417. (c) Curran, D. P. *Synthesis* **1988**, 489. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.*, **1991**, *91*, 1237. (e) Curran, D. P.*Comprehensive Organic Synthesis*, Vol. 4; pp 715-777, Trost, B. M., Semmelhack, M. F., Pergamon Press; New york, **1991**.

2. Gomberg, M. *J. Am. Chem. Soc.*, **1900**, *22*, 757.

3. Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.*, **1991**, *22*, 1237.

4. Spellemeyer, D. C.; Houk, K. N. *J. Org. Chem.*, **1987**, *52*, 959.

5. a) Rao, Y. K.; Nagarajan, M. J. *J. Org. Chem.*, **1989**, *54*, 5678. b) Rao, Y. K.; Nagarajan, M. J. *Tetrahedron Lett.* **1988**, *29*, 107.

6. Newman, W. P. *Synyhesis* **1987**, 665.

7. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

8. Beckwith, A. L.; Scheisser, C. H. *Tet.* **1985**, *41*, 3925.

9. Beckwith, A. L.; Scheisser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.

10. Hanessian, S.; Dhava, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859.

11. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1983**, *23*, 753.

12. a)Dowd, P.; Choi, S. C. *J. Am. Chem. Soc.* **1987**, *107*, 6548. b) Motherwell, W. B.; Crich, D. In *Best Synthetic Methods: Free Radical Chain Reactions in Organic Synthesis*; Academic Press; New York, **1992**, chapter 5. c) Dowd, P.; Choi, S. C. *Tetrahedron* **1989**, *45*, 77. d) Bowman, W. R.; Westlake, P. J. *Tetrahedron* **1992**, *48*, 4027.

13. Clive, D. C. J.; Beaulieu P. L.; Set, L., *J. Org. Chem.*, **1984**, *49*, 1313

14. (a)Bartlett, P. A.; McLaren, K. L.; Tury, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 163.

15 Bowman, W. R.; Terret, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959.

16 Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882.

17 Sturino, C. F.; Fallis, A. G. *J. Am. Chem. Soc.* **1994**, *116*, 7447.

18 Sturino, C. F.; Fallis, A. G. *J. Org. Chem. Soc.* **1994**, *59*, 6514.

19. Bowman, W. R.; Stephenson, P. T.; Nicholas, K. T.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369.

20. Michejda, C. J.; Campbell, D. H.; Koepke, S. R., In *Organic Free Radicals*, Pryor, W. A., Ed.; ACS Symposium Series 69, ACS: Washington, D.C., 1978; p 292.

21. Newcomb, M.; Burchill, M. T.; Deeb, T. M., *J. Am. Chem. Soc.* **1988**, *110*, 6528.

22. Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.*, **1991**,*32*, 6441

23. Tsanaktsidis, J.; Maswell, B. J. *J. Am. Chem. Soc.*, **1996**, *118*, 4276

24. Newcomb, M. *Heterocycles*, **1989**,*28*, 129

25. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.*, **1985**, *107*, 1448

26. Bowman, W. R.; Stephenson, P. T.; young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623.

27. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734.

28. Scolastico, C.; Manzoni, L.; Belvisi, L.; Molteni, V. *Tetrahedron Lett.* **1995**, *36*, 1995.

29. a) Simpkins, N. S.; Stokes, S.; Whittle A. J. *Tetrahedron Lett.* **1992**, *33*, 793. b) Grissom, J. W.; Klimberg, D. J *J. Org. Chem.*, **1993**, *58*, 6559. c) Macro-Contelles, J.; Pozuelo, C.; Jineneo, M. L.; Maritng, L.; Martinez-Grau, A. *J. Org. Chem.* **1992**, *57*, 2655. d) Enholm, E. J.; Pourroff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727. e) Maro-Contelles, J.; Martinez, J.; Martinez-Grau, A.; Jaramillo, L. M. *Tetrahedron Lett.* **1991**, *32*, 6437.

30. Molander, G.A., and Cameron, K.O. *J. Org. Chem.* **1993**, *58*, 5931-5943.

31. Kohlenhydraten, A. ; Onsave, D. *Tetrahedron Lett.* **1972**, *50*, 5081.

32. Enders, D.; Fey, P.; Kippahardt, H. *Org. Synth.* **1987** *65*, 173.

33. Kametoni, T.; Kendoh, H.; Honda, T.; Ishizone, H.; Suzuki, Y; Mori W. *Chem. Lett.* **1989**, 901.

34. Mokotoff, M; Hill, S.T. *J. Het. Chem.* **1988**, *25*, 65.

35. Vierhapper, F.W.; Eliel, E.L. *J. Org. Chem.* **1979**, *44*, 1081.

36. Corey, E.J., Marafat, A., Munroe, J. E., Kim, K. S., Hopkins, P. B., Brion, F. *Tetrahedron Lett.* **1981**,*21*, 1077-1080.

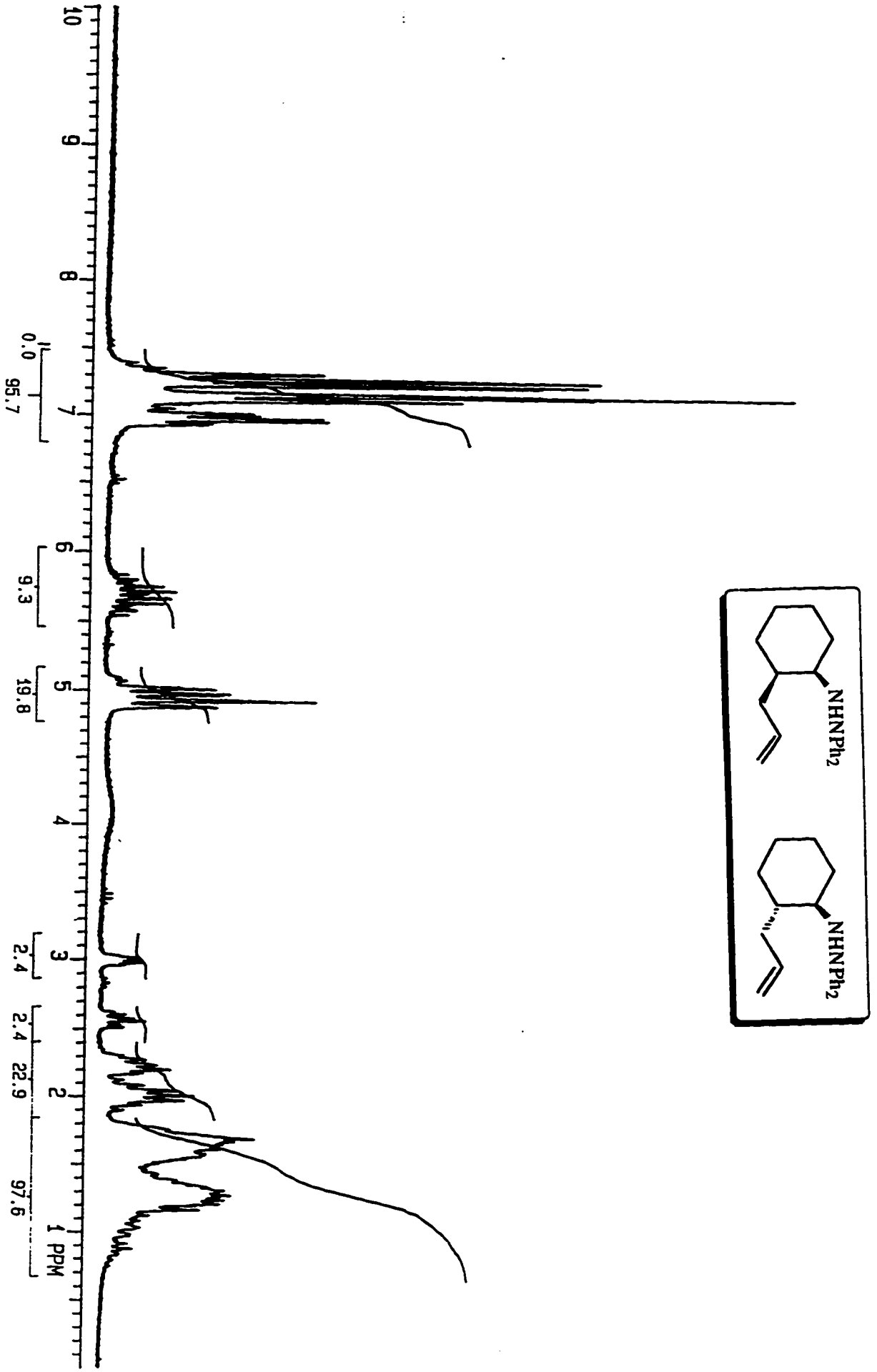
37. Finkelstein, H. *Chem. Ber*, **1910**, *43*, 1528.

Claims to Original Research

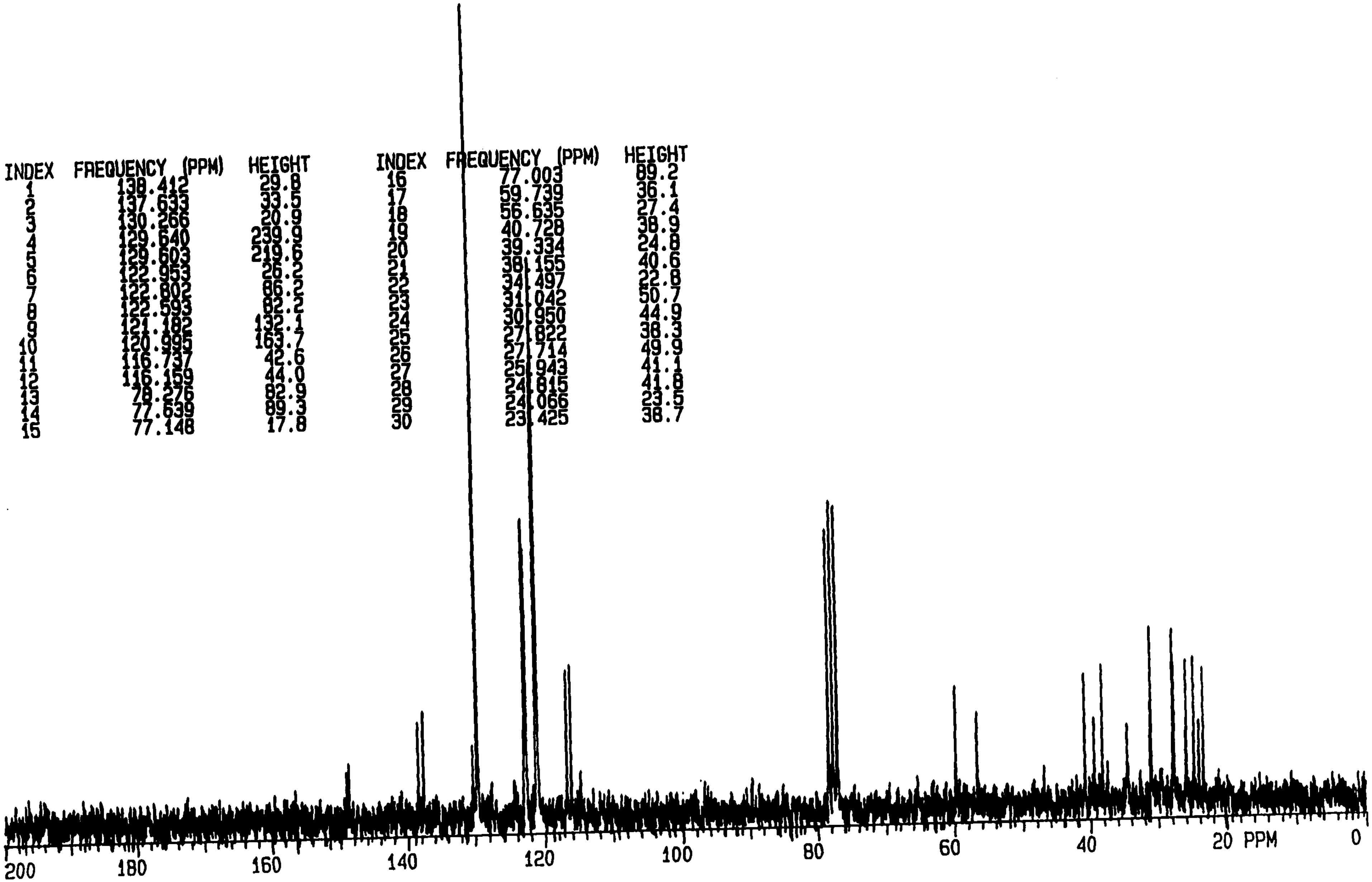
1) We have reported the successful tandem cyclization under radical condition of octahydroindoles. This reaction can be useful in the synthesis of small alkaloids.

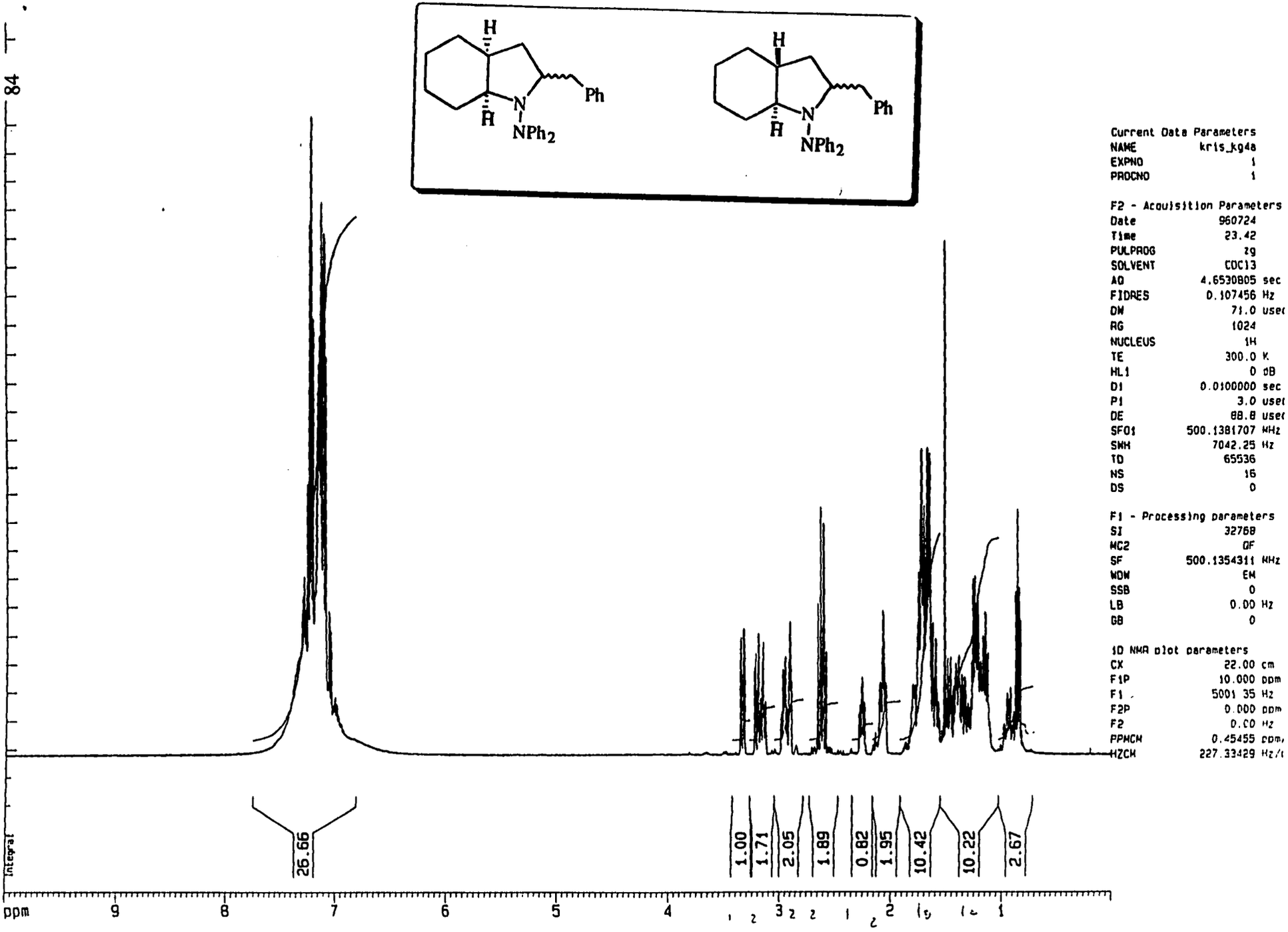
2) We report the first evidence of the synthesis of a 7-membered ring under radical conditions in which an imine bond of a diphenylhydrazone acts as an acceptor for a carbon radical.

Appendix: Selected Spectra


NHNPh2
NHNPh2
10
9
8
7
6
5
4
3
2
1 PPM
0.0
95.7
9.3
19.8
2.4
2.4
22.9
97.6

INDEX	FREQUENCY (PPM)	HEIGHT
1	138.412	29.8
2	137.633	33.5
3	130.266	20.9
4	129.640	239.9
5	129.603	219.6
6	122.953	26.2
7	122.802	86.2
8	122.593	82.2
9	121.182	132.1
10	120.995	163.7
11	116.737	42.6
12	116.159	44.0
13	78.276	82.9
14	77.639	89.3
15	77.148	17.8
16	77.003	89.2
17	59.739	36.1
18	56.635	27.4
19	40.728	38.9
20	39.334	24.8
21	38.155	40.6
22	34.497	22.8
23	31.042	50.7
24	30.950	44.9
25	27.822	38.3
26	27.714	49.9
27	25.943	41.1
28	24.815	41.8
29	24.066	23.5
30	23.425	38.7



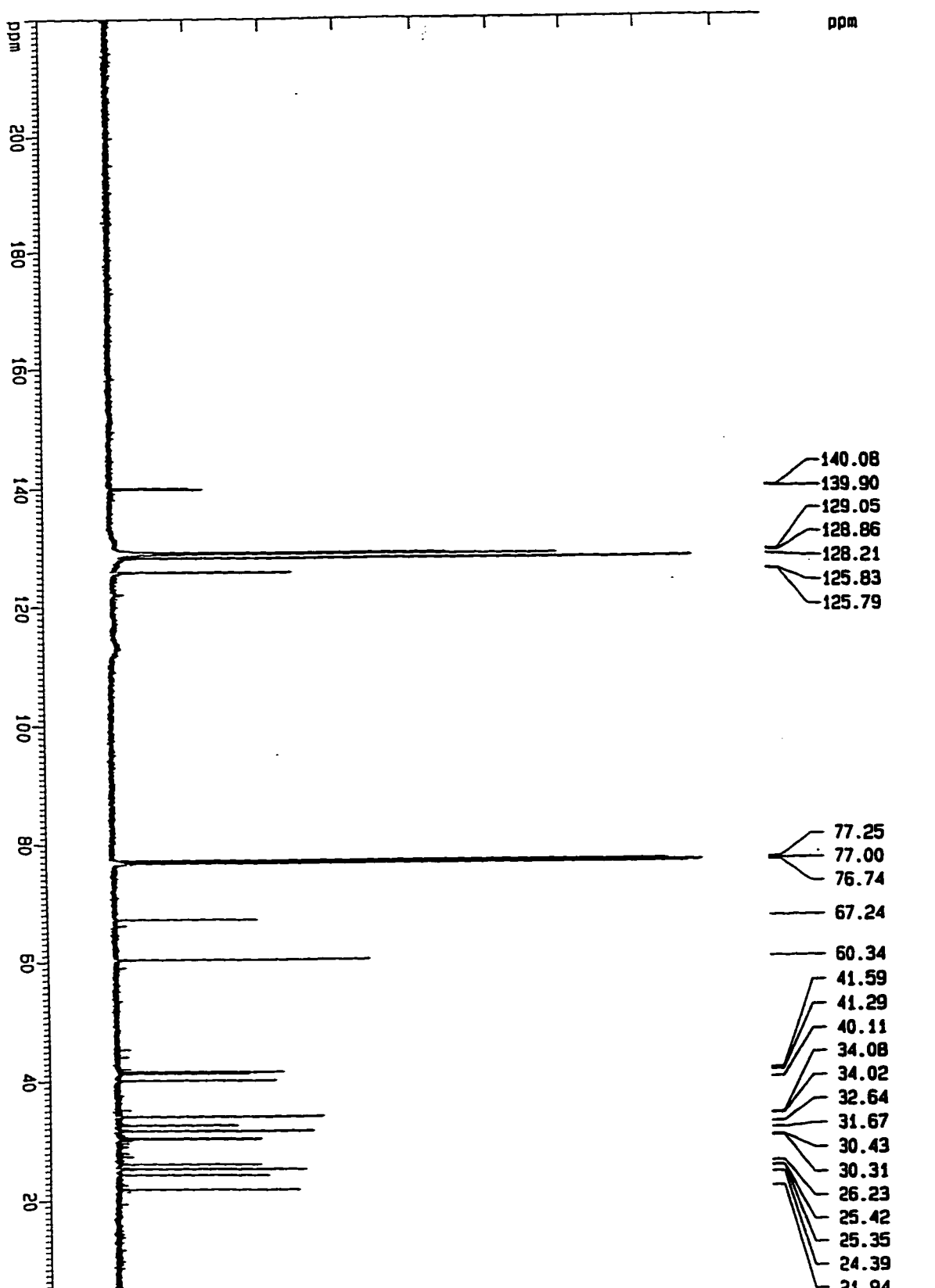


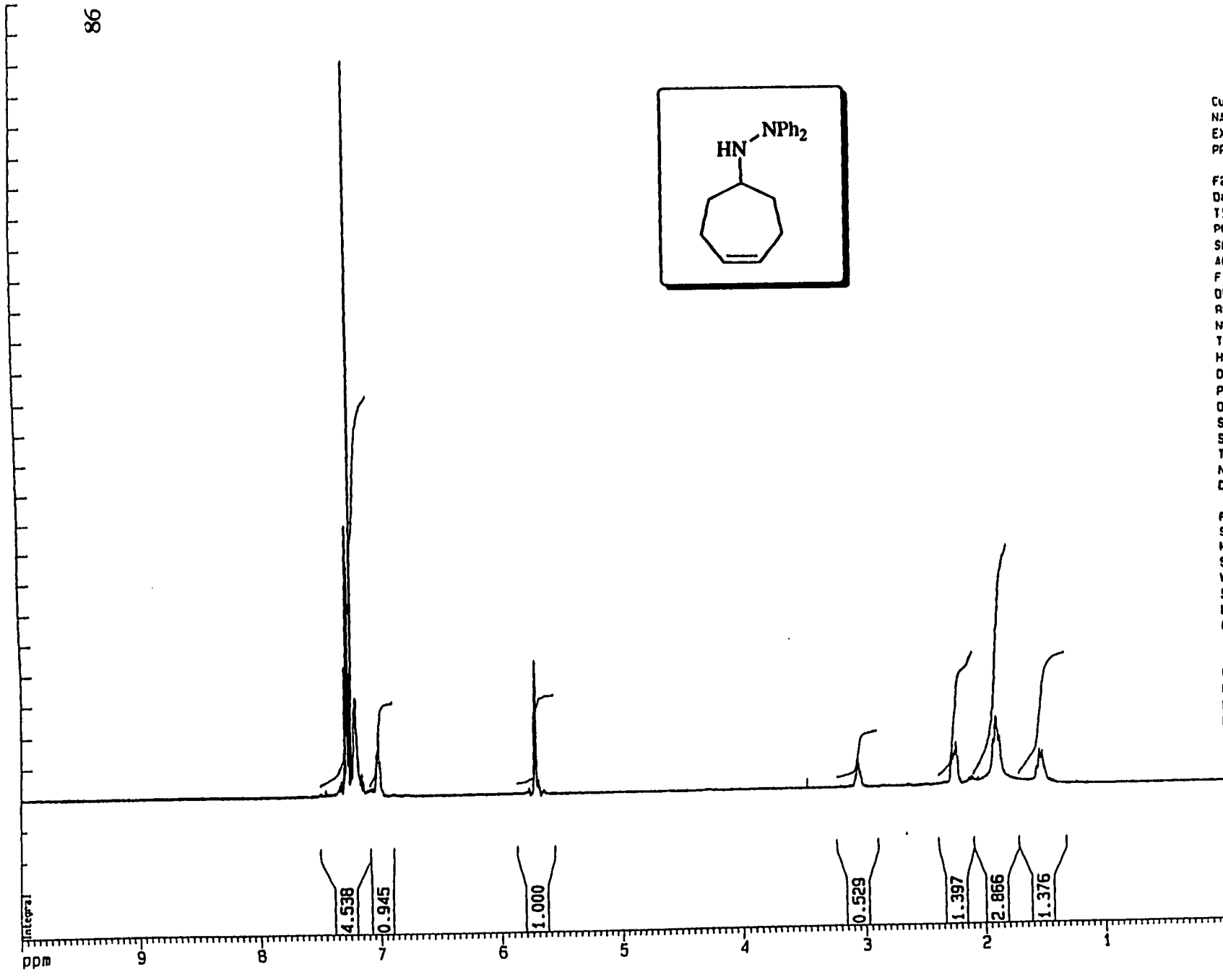
Current Data Parameters
NAME kris_kg4a
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 960724
Time 23.42
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 1024
NUCLEUS 1H
TE 300.0 K
HL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 88.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354311 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/


ppm
200
180
160
140
120
100
80
60
40
20
ppm
140.08
139.90
129.05
128.86
128.21
125.83
125.79
77.25
77.00
76.74
67.24
60.34
41.59
41.29
40.11
34.08
34.02
32.64
31.67
30.43
30.31
26.23
25.42
25.35
24.39
21.94
Current Data Parameters
NAME kris_kg4a
EXPNO 4
PROCNO 1
F2 - Acquisition Paramet
Date 960725
Time 3.17
PULPROG zgdc
SOLVENT CDCl3
AD 1.0485960
FIORES 0.476837
DW 16.0
RG 32768
NUCLEUS 13C
TE 300.0
D11 0.0300000
P31 70.0
S2 22
HL1 22
D1 1.0000000
P1 5.0
OE 20.0
SFO1 125.7724464
SWH 31250.00
TD 65536
NS 12288
DS 0
F1 - Processing paramete
SI 32768
MC2 0F
SF 125.7591523
WDW EM
SSB 0
LB 1.00
GB 0
1D NMR plot parameters
CX 22.00
F1P 220.000
F1 27667.01
F2P 0.000
F2 0.00
PPMCM 10.00000
HZCM 1257.59155



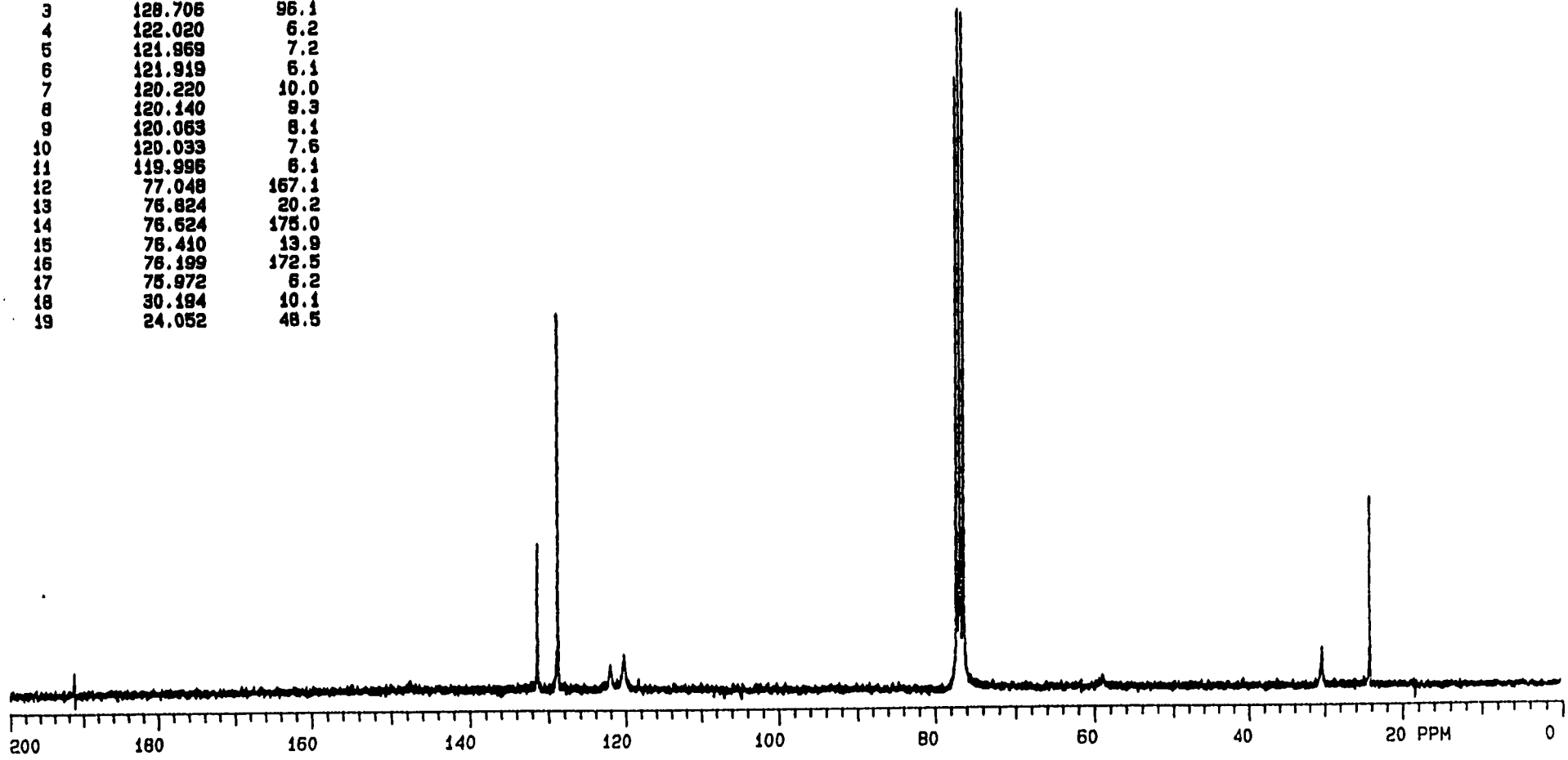
Current Data Parameters
NAME kris_kg67
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 960808
Time 15.03
PULPROG 19
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 4096
NUCLEUS 1H
TE 300.0 K
HL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 68.8 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

F1 - Processing parameters
SI 32768
MC2 GF
SF 500.1354311 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/

INDEX	FREQUENCY (PPM)	HEIGHT
1	131.255	37.6
2	128.906	8.9
3	128.706	96.1
4	122.020	6.2
5	121.969	7.2
6	121.919	6.1
7	120.220	10.0
8	120.140	9.3
9	120.063	8.1
10	120.033	7.6
11	119.996	6.1
12	77.048	167.1
13	76.824	20.2
14	76.624	175.0
15	76.410	13.9
16	76.199	172.5
17	75.972	6.2
18	30.194	10.1
19	24.052	48.5



10
9
8
7
6
5
4
3
2
1 PPM
119.5
8.6
17.3
53.3
26.6

Ph2N
N
H
CH3

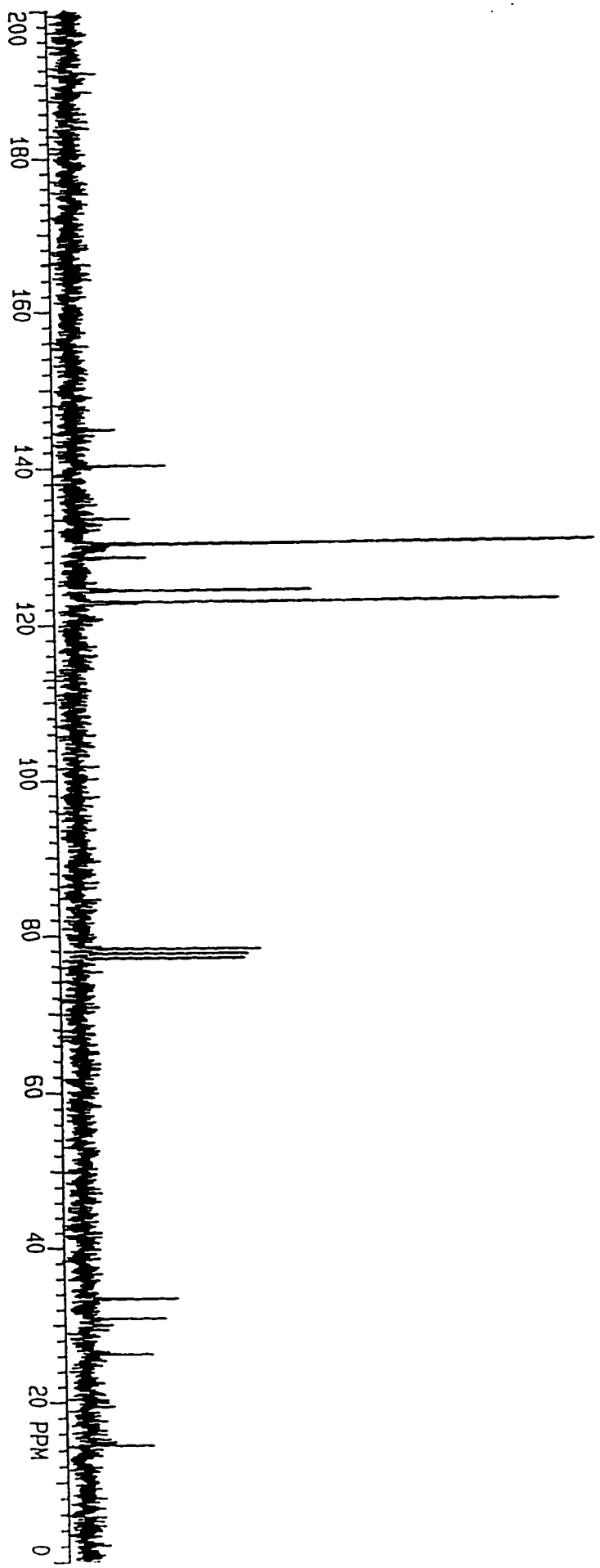

200
180
160
140
120
100
80
60
40
20 PPM
0

Table of Contents

EXPERIMENTAL

1. Data Collection

A crystal of N2C19H22 having approximate dimensions of .2,.2,.2 mm was mounted on a glass capillary. All the measurements were made on a Rigaku diffractometer with Cu Kalpha radiation.

Cell constants and an orientation matrix for data collection, were obtained from least-squares refinement using the setting angles of 25 reflections in the range 80<2theta<100 corresponded to a monoclinic cell with dimensions:

a = 9.5840(13)
b = 15.272(3)
c = 10.9367(17)
beta= 91.761(12)

For Z=4 and FW=278.39, the calculated density is 1.156 g/cm3. Based on the systematic absences, the space group was determined to be P 21/c.

The data was collected at a temperature of -110 degrees using the omega-2theta scan technique to a maximum 2theta value of 99.9 degrees.

2. Data reduction

A total of 1770 reflections was collected. The unique set contains only 1649 reflections. The standards were measured after every 150 reflections. No crystal decay was noticed. The data were corrected for Lorentz and polarisation effects (1). No absorption correction was made.

3. Solution and refinement:

The structure was solved by direct methods. All the atoms were refined anisotropically except the hydrogen. The hydrogen atoms were found by differences fourier map. The final cycle of full matrix least-squares refinement

was based on 1429 observed reflections (I>2.5 sigma(I)) and 279 variable parameters. Weights based on counting statistics were used. The maximum and minimum peaks on the final differences Fourier map corresponded to .270 and -.180 e/a3, respectively.

All the calculations were performed using the NRCVAX crystallographic software package (2).

EXPERIMENTAL DETAILS

Empirical formula	N2C19H22
Formula weight	278.39
Crystal shape	cube
Crystal dimensions (mm)	.2,.2,.2
Crystal system	monoclinic
No. Reflection used for unit cell dimension (2theta range)	25 80-100
Lattice parameters	a=9.5840(13) b=15.272(3) c=10.9367(17) beta=91.761(12)
Space group	P 21/c
Z value	4
Dcalc (g.cm-3)	1.156
F(000)	601.32
mu (mm-1)	1.16
No of reflection measured	1770
No of reflection unique	1649
No of reflection observed	1429
No of atoms	43
No of variables	279
Rf (sign refl)	.037
Rw (sign refl)	.045
Rf (all refl)	.045
Rw (all refl)	.046
Goodness of fit	2.86
Last difference fourier map	
max peak	.270
min peak	-.180

References

1. D.F. Grant and E.J. Gabe
   J. Appl. Crystallogr., 11, 114 (1978)
2. E.J. Gabe, F.L. Lee and Y. Lepage
   J. Appl. Crystallogr., 22, 384 (1989)

Space Group and Cell Dimensions Monoclinic, P 21/c
a 9.5840(13) b 15.272(3) c 10.9367(17)
beta 91.761(12)
Volume 1600.0(4)A**3

Empirical formula : N2 C19 H22

Cell dimensions were obtained from 24 reflections with 2Theta angle
in the range 80.00 - 100.00 degrees.

Crystal dimensions : 0.20 X 0.20 X 0.20 mm

FW = 278.39 Z = 4 F(000) = 601.52

Dcalc 1.156Mg.m-3, mu 1.16mm-1, lambda 1.54056A, 2Theta(max) 99.9

The intensity data were collected on a Rigaku diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -9 9; Kmin,max 0 15; Lmin,max 0 10
No. of reflections measured 1770
No. of unique reflections 1649
No. of reflections with Inet > 2.5sigma(Inet) 1429
Merging R-value on intensities 0.020
No correction was made for absorption

The last least squares cycle was calculated with
43 atoms, 279 parameters and 1429 out of 1649 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.037, Rw 0.045 GoF 2.86
For all reflections, RF 0.045, Rw 0.046.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.156.

In the last D-map, the deepest hole was -0.180e/A**3,
and the highest peak 0.270e/A**3.

Secondary ext. coeff. 1.242823 sigma 0.049613

The following references are relevant to the NRCVAX System.

1. Full System Reference :
Gabe, E.J., Le Page, Y., Charland,.J.-P., Lee, F.L. and White, P.S.
(1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :

International Tables for X-ray Crystallography, Vol. IV, (1974) Kynoch Press, Birmingham, England.

The following references may also be relevant.

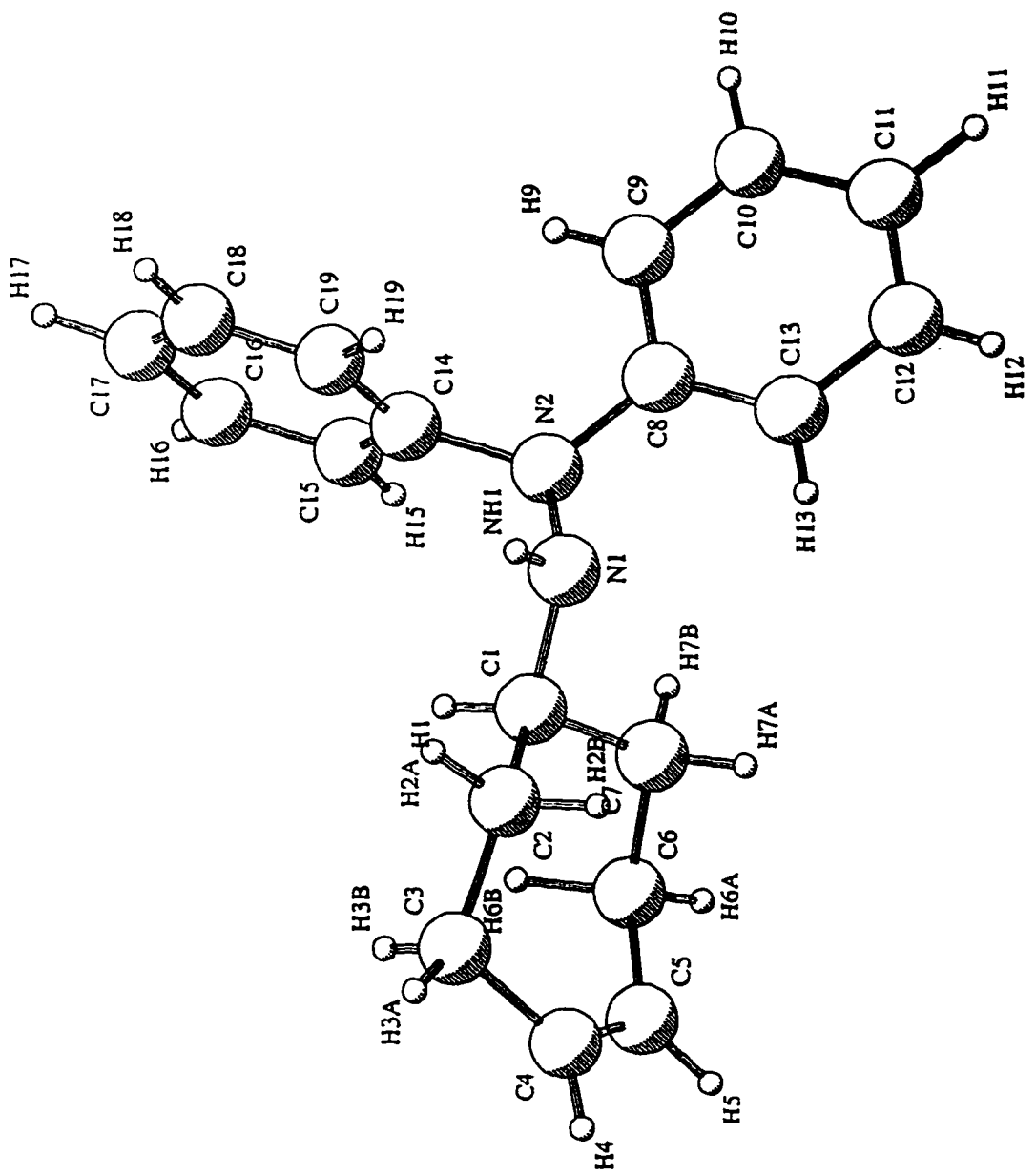
3. ORTEP Plotting :
Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, Oak Ridge

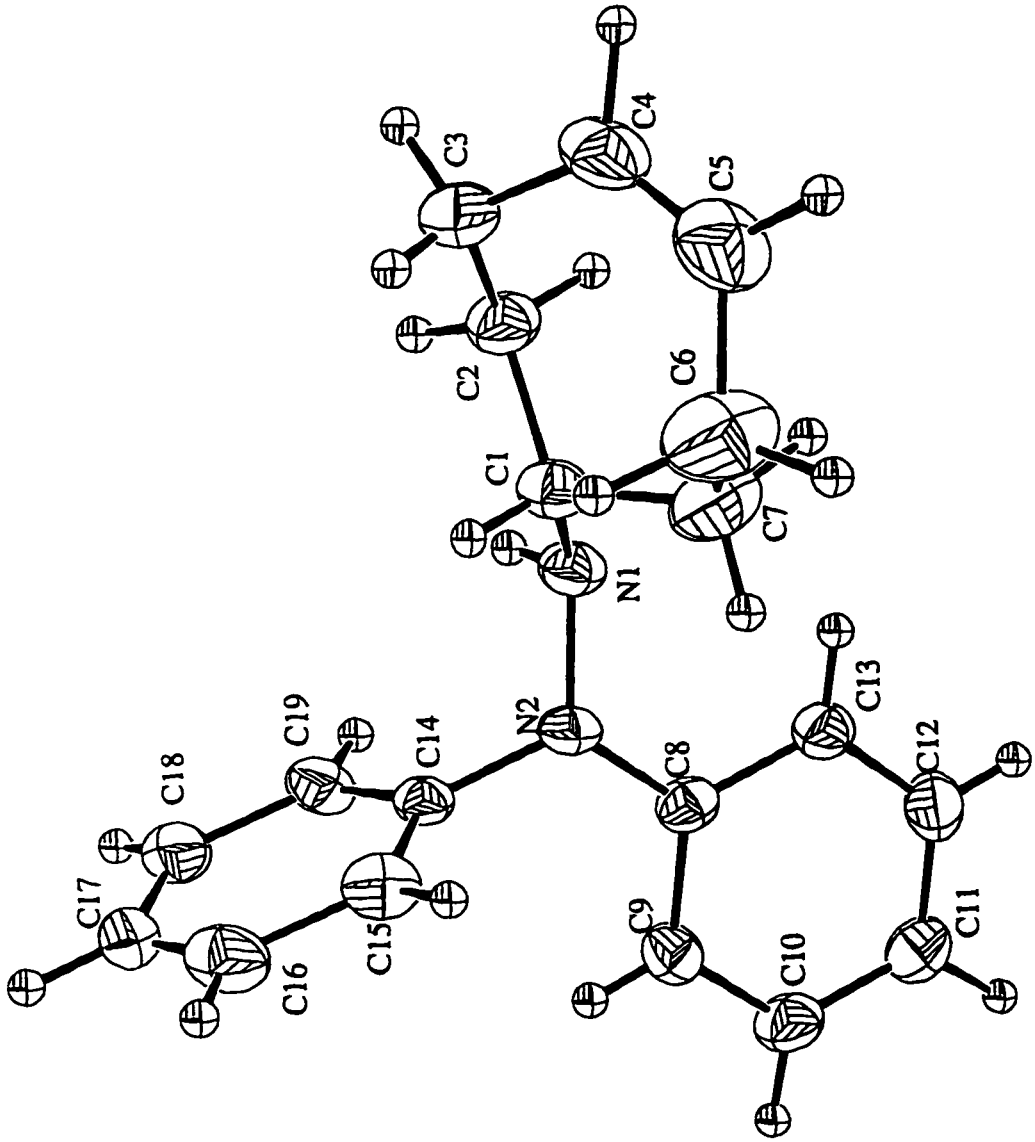
4. Pluto Plotting :
S. Motherwell, University Chemical Laboratory, Cambridge, 1978

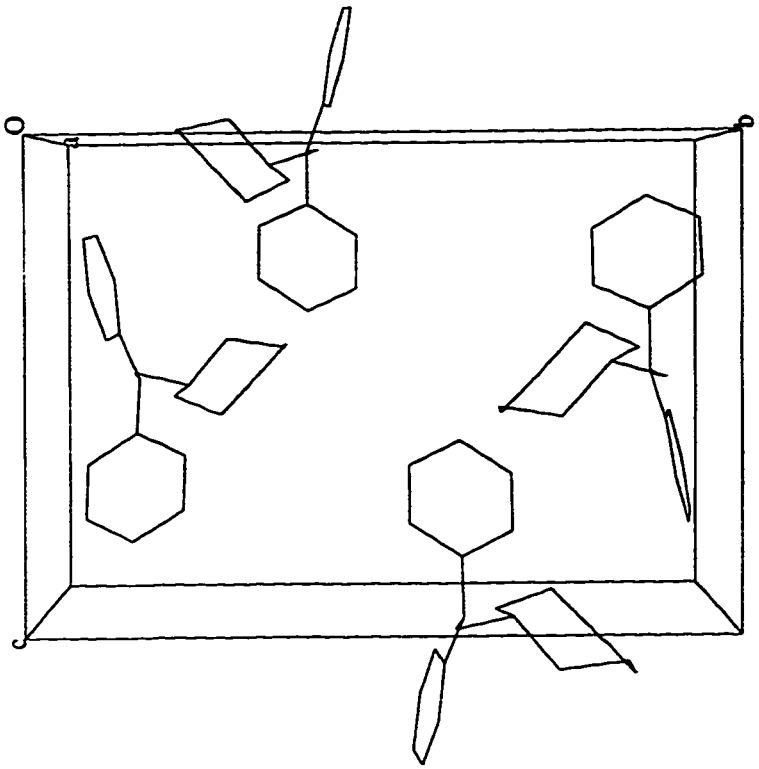
5. Missing Symmetry Treatment by MISSYM :
Le Page, Y., (1988) J. Appl. Cryst., 21, 983-984.

6. Grouping of Equivalent Reflections in DATRD2 :
Le Page, Y. and Gabe, E.J., (1979) J. Appl. Cryst., 12, 464-466.

7. Extinction Treatment :
Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.


H17
H18
C18
C19
H19
C17
C16
C14
H16
C15
H15
N2
NH1
N1
C1
H1
H2A
H2B
C7
C2
C3
H3B
H6B
H3A
C4
H4
C5
H5
C6
H6A
H7B
H7A
C8
C13
H13
C9
H9
C10
H10
C11
H11
C12
H12


C3
C4
C5
C2
C6
C1
C7
N1
N2
C13
C19
C14
C8
C12
C18
C17
C15
C9
C11
C16
C10



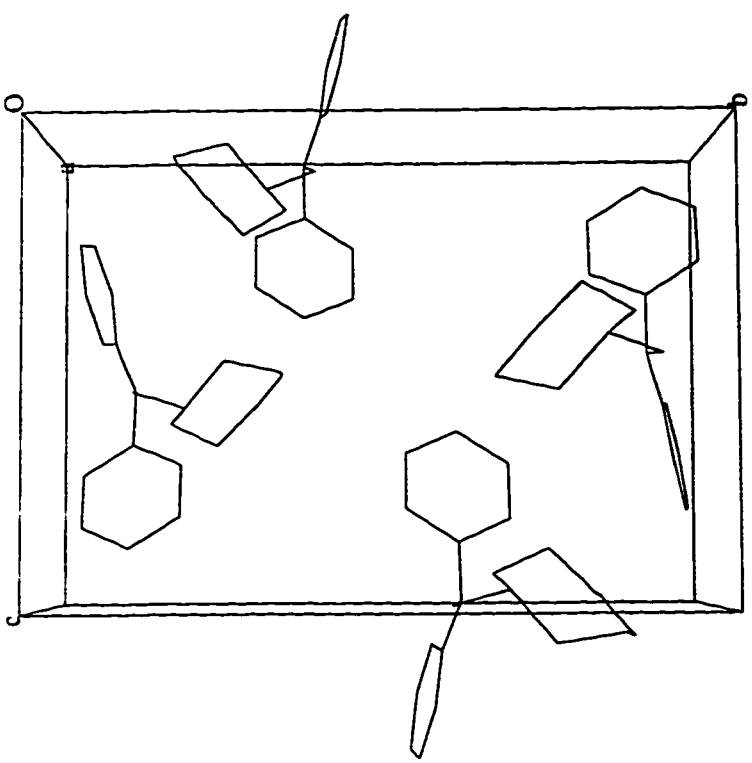


Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
N1	1.01038(19)	0.39462(12)	0.01559(16)	2.54(8)
N2	0.86299(17)	0.38074(12)	0.02131(15)	2.38(9)
C1	1.09036(23)	0.31624(15)	0.04925(20)	2.61(10)
C2	1.23873(23)	0.34440(16)	0.08198(21)	3.17(11)
C3	1.33403(25)	0.27172(18)	0.13102(22)	3.84(13)
C4	1.3797 (3)	0.20797(17)	0.03629(22)	3.73(12)
C5	1.2977 (3)	0.16234(18)	-0.03574(23)	4.32(13)
C6	1.1411 (3)	0.16290(19)	-0.0344 (3)	5.17(15)
C7	1.0773 (3)	0.25216(17)	-0.05774(23)	3.88(12)
C8	0.78242(22)	0.40750(14)	-0.08075(19)	2.11(9)
C9	0.63856(23)	0.41995(15)	-0.07212(19)	2.55(10)
C10	0.55836(23)	0.44182(16)	-0.17404(20)	2.91(11)
C11	0.61663(24)	0.45260(16)	-0.28655(20)	3.12(11)
C12	0.75862(25)	0.44057(16)	-0.29514(20)	3.03(11)
C13	0.84116(22)	0.41758(15)	-0.19419(19)	2.42(10)
C14	0.80606(21)	0.38249(14)	0.14107(19)	1.98(9)
C15	0.74852(23)	0.30792(15)	0.18799(20)	2.80(11)
C16	0.69272(24)	0.30825(16)	0.30311(21)	3.31(11)
C17	0.69628(24)	0.38361(17)	0.37136(20)	3.31(12)
C18	0.75453(24)	0.45838(17)	0.32538(20)	3.35(12)
C19	0.80897(23)	0.45829(15)	0.21008(19)	2.69(10)
H1	1.0536 (16)	0.2903 (11)	0.1220 (13)	0.8 (3)
H2A	1.2304 (21)	0.3917 (12)	0.1438 (17)	3.1 (5)
H2B	1.2821 (21)	0.3730 (13)	0.0041 (17)	3.6 (5)
H3A	1.4141 (21)	0.2967 (14)	0.1715 (18)	4.0 (5)
H3B	1.2886 (23)	0.2351 (15)	0.1897 (18)	5.0 (6)
H4	1.4852 (23)	0.2042 (15)	0.0282 (19)	5.1 (6)
H5	1.3352 (25)	0.1234 (15)	-0.0933 (21)	5.5 (6)
H6A	1.106 (3)	0.1220 (18)	-0.1000 (23)	7.3 (7)
H6B	1.099 (3)	0.1441 (17)	0.0612 (21)	6.5 (7)
H7A	1.129 (3)	0.2821 (16)	-0.1365 (21)	5.8 (6)
H7B	0.9825 (22)	0.2449 (14)	-0.0773 (17)	4.3 (5)
H9	0.6022 (18)	0.4129 (11)	-0.0022 (15)	1.6 (4)
H10	0.4617 (20)	0.4495 (13)	-0.1629 (15)	2.7 (4)
H11	0.5597 (23)	0.4717 (15)	-0.3658 (19)	4.9 (6)
H12	0.7974 (19)	0.4441 (12)	-0.3653 (16)	2.3 (4)
H13	0.9372 (19)	0.4084 (12)	-0.2008 (16)	2.4 (4)
H15	0.7459 (18)	0.2584 (12)	0.1463 (15)	2.1 (4)
H16	0.6565 (20)	0.2595 (13)	0.3294 (16)	3.0 (5)
H17	0.6571 (22)	0.3852 (13)	0.4513 (17)	3.5 (5)
H18	0.7526 (21)	0.5099 (13)	0.3710 (17)	3.6 (5)
H19	0.8454 (19)	0.5076 (12)	0.1737 (15)	2.7 (4)
NH1	1.0279 (20)	0.4309 (12)	0.0591 (15)	2.5 (4)

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
N1	2.41(11)	3.42(12)	3.84(11)	0.31(9)	0.34(9)	-0.32(9)
N2	1.82(10)	4.06(13)	3.19(11)	0.32(9)	0.12(9)	0.11(9)
C1	2.61(14)	3.41(15)	3.91(14)	0.35(11)	0.11(11)	0.35(12)
C2	2.86(14)	4.41(16)	4.77(15)	0.82(13)	-0.30(12)	-1.03(13)
C3	3.04(15)	6.59(20)	4.93(16)	1.15(14)	-0.31(13)	-0.40(14)
C4	3.71(16)	5.21(18)	5.29(16)	1.86(14)	0.89(13)	0.66(14)
C5	5.73(18)	4.89(18)	5.84(18)	2.10(15)	0.94(15)	-0.66(14)
C6	5.39(19)	4.81(19)	9.38(23)	1.40(15)	-0.97(17)	-1.88(17)
C7	3.82(16)	4.57(17)	6.29(18)	0.49(13)	-1.13(14)	-1.52(14)
C8	2.46(13)	2.51(13)	3.04(13)	0.16(10)	-0.22(10)	-0.13(10)
C9	3.14(14)	3.49(15)	3.09(13)	0.31(12)	0.47(11)	-0.30(11)
C10	2.58(13)	4.31(16)	4.14(15)	0.57(12)	-0.43(11)	-0.38(12)
C11	3.69(15)	4.30(16)	3.80(14)	0.15(13)	-0.77(12)	0.23(13)
C12	4.47(16)	4.03(16)	3.04(13)	-0.50(13)	0.41(12)	-0.26(12)
C13	2.68(13)	3.20(14)	3.30(14)	0.19(11)	0.03(11)	-0.47(11)
C14	1.73(12)	2.98(14)	2.83(13)	0.35(10)	0.04(10)	0.44(11)
C15	3.31(14)	2.87(14)	4.48(15)	0.22(12)	0.12(12)	0.05(12)
C16	3.46(15)	4.27(16)	4.86(16)	-0.18(13)	0.37(12)	1.87(13)
C17	3.00(15)	6.68(19)	2.91(14)	-0.28(13)	0.10(12)	0.55(13)
C18	3.28(15)	5.38(17)	4.09(15)	-0.76(13)	0.41(12)	-1.16(13)
C19	2.90(13)	3.60(15)	3.78(14)	-0.55(12)	0.80(11)	0.21(12)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table of Atomic Bond Distances in Angstroms

N1-N2	1.4317(25)	C8-C9	1.398(3)
N1-C1	1.462(3)	C8-C13	1.387(3)
N1-NH1	0.746(18)	C9-C10	1.376(3)
N2-C8	1.399(3)	C9-H9	0.857(16)
N2-C14	1.434(3)	C10-C11	1.377(3)
C1-C2	1.518(3)	C10-H10	0.945(19)
C1-C7	1.528(3)	C11-C12	1.379(3)
C1-H1	0.965(15)	C11-H11	1.051(21)
C2-C3	1.524(3)	C12-C13	1.384(3)
C2-H2A	0.994(19)	C12-H12	0.864(18)
C2-H2B	1.054(20)	C13-H13	0.936(19)
C3-C4	1.497(4)	C14-C15	1.372(3)
C3-H3A	0.954(20)	C14-C19	1.382(3)
C3-H3B	0.965(21)	C15-C16	1.383(3)
C4-C5	1.298(4)	C15-H15	0.883(18)
C4-H4	1.019(23)	C16-C17	1.372(4)
C5-C6	1.501(4)	C16-H16	0.873(20)
C5-H5	0.945(24)	C17-C18	1.373(4)
C6-C7	1.513(4)	C17-H17	0.962(20)
C6-H6A	1.00(3)	C18-C19	1.379(3)
C6-H6B	1.169(24)	C18-H18	0.932(20)
C7-H7A	1.106(24)	C19-H19	0.926(19)
C7-H7B	0.933(22)		

Table of Atomic Bond Angles in Degrees

N2-N1-C1	112.21(16)	C6-C7-H7B	108.5(14)
N2-N1-NH1	106.6(15)	H7A-C7-H7B	109.1(17)
C1-N1-NH1	110.0(14)	N2-C8-C9	120.49(18)
N1-N2-C8	116.30(16)	N2-C8-C13	121.14(19)
N1-N2-C14	116.15(16)	C9-C8-C13	118.27(19)
C8-N2-C14	120.47(17)	C8-C9-C10	120.40(20)
N1-C1-C2	107.91(18)	C8-C9-H9	118.2(11)
N1-C1-C7	107.54(18)	C10-C9-H9	121.4(12)
N1-C1-H1	110.0(10)	C9-C10-C11	121.42(21)
C2-C1-C7	114.61(19)	C9-C10-H10	116.8(10)
C2-C1-H1	106.6(9)	C11-C10-H10	121.7(10)
C7-C1-H1	110.2(10)	C10-C11-C12	118.24(20)
C1-C2-C3	115.06(21)	C10-C11-H11	123.8(12)
C1-C2-H2A	105.8(12)	C12-C11-H11	118.0(12)
C1-C2-H2B	108.5(11)	C11-C12-C13	121.37(20)
C3-C2-H2A	110.5(11)	C11-C12-H12	120.3(12)
C3-C2-H2B	109.8(11)	C13-C12-H12	118.2(12)
H2A-C2-H2B	106.9(16)	C8-C13-C12	120.28(20)
C2-C3-C4	114.51(20)	C8-C13-H13	118.7(11)
C2-C3-H3A	109.7(13)	C12-C13-H13	121.0(11)
C2-C3-H3B	112.2(13)	N2-C14-C15	119.65(19)
C4-C3-H3A	109.5(13)	N2-C14-C19	120.83(19)
C4-C3-H3B	103.3(13)	C15-C14-C19	119.52(20)
H3A-C3-H3B	107.3(18)	C14-C15-C16	120.58(21)
C3-C4-C5	125.78(22)	C14-C15-H15	121.5(11)
C3-C4-H4	114.1(13)	C16-C15-H15	117.9(11)
C5-C4-H4	120.1(13)	C15-C16-C17	119.65(21)
C4-C5-C6	125.28(23)	C15-C16-H16	117.7(12)
C4-C5-H5	120.4(14)	C17-C16-H16	122.6(12)
C6-C5-H5	114.3(14)	C16-C17-C18	120.14(21)
C5-C6-C7	113.76(24)	C16-C17-H17	120.8(12)
C5-C6-H6A	107.7(16)	C18-C17-H17	119.1(12)
C5-C6-H6B	112.6(12)	C17-C18-C19	120.22(22)
C7-C6-H6A	108.4(15)	C17-C18-H18	119.4(12)
C7-C6-H6B	102.8(13)	C19-C18-H18	120.3(12)
H6A-C6-H6B	111.6(20)	C14-C19-C18	119.89(21)
C1-C7-C6	115.12(21)	C14-C19-H19	116.7(11)
C1-C7-H7A	107.7(13)	C18-C19-H19	123.4(11)
C1-C7-H7B	107.9(13)		
C6-C7-H7A	108.4(13)		

Torsion angles

C1	N1	N2	C8	-131.0(2)	C1	N1	N2	C14	78.2(2)
NH1	N1	N2	C8	108.5(14)	NH1	N1	N2	C14	-42.2(14)
N2	N1	C1	C2	-161.2(2)	N2	N1	C1	C7	74.7(2)
N2	N1	C1	H1	-45.3(9)	NH1	N1	C1	C2	-42.7(14)
NH1	N1	C1	C7	-166.9(14)	NH1	N1	C1	H1	73.1(17)
N1	N2	C8	C9	-162.0(2)	N1	N2	C8	C13	21.7(1)
C14	N2	C8	C9	-12.5(1)	C14	N2	C8	C13	171.1(2)
N1	N2	C14	C15	-115.0(2)	N1	N2	C14	C19	64.7(2)
C8	N2	C14	C15	95.5(2)	C8	N2	C14	C19	-84.8(2)
N1	C1	C2	C3	174.5(3)	N1	C1	C2	H2A	52.3(11)
N1	C1	C2	H2B	-62.1(11)	C7	C1	C2	C3	-65.7(2)
C7	C1	C2	H2A	172.1(11)	C7	C1	C2	H2B	57.7(11)
H1	C1	C2	C3	56.5(9)	H1	C1	C2	H2A	-65.7(14)
H1	C1	C2	H2B	179.9(15)	N1	C1	C7	C6	-173.9(3)
N1	C1	C7	H7A	65.1(12)	N1	C1	C7	H7B	-52.5(13)
C2	C1	C7	C6	66.2(2)	C2	C1	C7	H7A	-54.8(12)
C2	C1	C7	H7B	-172.4(13)	H1	C1	C7	C6	-54.0(9)
H1	C1	C7	H7A	-175.0(16)	H1	C1	C7	H7B	67.4(16)
C1	C2	C3	C4	73.7(2)	C1	C2	C3	H3A	-162.8(13)
C1	C2	C3	H3B	-43.7(13)	H2A	C2	C3	C4	-166.6(11)
H2A	C2	C3	H3A	-43.1(16)	H2A	C2	C3	H3B	76.0(17)
H2B	C2	C3	C4	-49.0(11)	H2B	C2	C3	H3A	74.5(16)
H2B	C2	C3	H3B	-166.4(17)	C2	C3	C4	C5	-56.2(2)
C2	C3	C4	H4	120.9(13)	H3A	C3	C4	C5	-179.9(13)
H3A	C3	C4	H4	-2.7(17)	H3B	C3	C4	C5	66.1(13)
H3B	C3	C4	H4	-116.8(18)	C2	C3	H3A	H3B	122.1(16)
C4	C3	H3A	H3B	-111.5(15)	H3B	C3	H3A	H3B	0.0(16)
C2	C3	H3B	H3A	-120.5(16)	C4	C3	H3B	H3A	115.6(16)
H3A	C3	H3B	H3A	0.0(15)	C3	C4	C5	C6	-2.2(1)
C3	C4	C5	H5	180.0(14)	H4	C4	C5	C6	-179.1(13)
H4	C4	C5	H5	3.0(19)	C4	C5	C6	C7	59.5(2)
C4	C5	C6	H6A	179.6(16)	C4	C5	C6	H6B	-57.0(12)
H5	C5	C6	C7	-122.6(14)	H5	C5	C6	H6A	-2.4(20)
H5	C5	C6	H6B	121.0(19)	C5	C6	C7	C1	-74.7(2)
C5	C6	C7	H7A	45.9(12)	C5	C6	C7	H7B	164.2(13)
H6A	C6	C7	C1	165.6(15)	H6A	C6	C7	H7A	-73.8(20)
H6A	C6	C7	H7B	44.5(20)	H6B	C6	C7	C1	47.3(12)
H6B	C6	C7	H7A	167.9(18)	H6B	C6	C7	H7B	-73.8(18)
N2	C8	C9	C10	-176.6(3)	N2	C8	C9	H9	2.6(11)
C13	C8	C9	C10	-0.2(1)	C13	C8	C9	H9	179.0(12)
N2	C8	C13	C12	177.3(3)	N2	C8	C13	H13	-2.6(11)
C9	C8	C13	C12	0.9(1)	C9	C8	C13	H13	-179.0(11)
C8	C9	C10	C11	-0.4(1)	C8	C9	C10	H10	-179.9(12)
H9	C9	C10	C11	-179.6(12)	H9	C9	C10	H10	0.9(16)
C9	C10	C11	C12	0.2(1)	C9	C10	C11	H11	-177.5(12)
H10	C10	C11	C12	179.7(12)	H10	C10	C11	H11	1.9(16)
C10	C11	C12	C13	0.5(1)	C10	C11	C12	H12	176.6(12)
H11	C11	C12	C13	178.4(12)	H11	C11	C12	H12	-5.5(17)
C11	C12	C13	C8	-1.1(1)	C11	C12	C13	H13	178.8(11)

H12	C12	C13	C8	-177.3(12)	H12	C12	C13	H13	2.6(16)
N2	C14	C15	C16	-179.8(3)	N2	C14	C15	H15	0.3(11)
C19	C14	C15	C16	0.5(1)	C19	C14	C15	H15	-179.4(12)
N2	C14	C19	C18	-179.5(3)	N2	C14	C19	H19	2.7(11)
C15	C14	C19	C18	0.2(1)	C15	C14	C19	H19	-177.6(11)
C14	C15	C16	C17	-0.7(1)	C14	C15	C16	H16	179.6(13)
H15	C15	C16	C17	179.2(12)	H15	C15	C16	H16	-0.6(17)
C15	C16	C17	C18	0.2(1)	C15	C16	C17	H17	179.4(12)
H16	C16	C17	C18	180.0(13)	H16	C16	C17	H17	-0.9(17)
C16	C17	C18	C19	0.4(1)	C16	C17	C18	H18	177.1(13)
H17	C17	C18	C19	-178.7(12)	H17	C17	C18	H18	-2.0(17)
C17	C18	C19	C14	-0.6(1)	C17	C18	C19	H19	177.0(12)
H18	C18	C19	C14	-177.3(13)	H18	C18	C19	H19	0.3(16)
C3	H3A	H3B	C3	0.0(2)					