INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

Université d'Ottawa · University of Ottawa

Table of Contents

List of Schemes

List of Figures

List of Tables

List of Abbreviations

aq	aqueous
Ac	acetyl
AIBN	azobis(isobutyro)nitrile
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
CAN	cerium ammonium nitrate
CSA	(S)-(+)-10-camphorsulfonic acid
Cy	cyclohexyl
DIBAL	diisobutyl aluminium hydride
DMAP	*N,N* – dimethylaminopyridine
DMF	*N,N* – dimethyl formamide
DMSO	dimethylsulfoxide
Et	ethyl
eq	equivalent
EWG	electron withdrawing group
GC	gas chromatography
HMPA	hexamethyl phosphorous triamide
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
*i*Pr	isopropyl
IR	infrared
LDA	lithium diisopropyl amide
Me	methyl
MOM	methoxymethyl
NBS	N-bromosuccinimide

NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
psi	pounds per square inch
ppm	parts per million
Pr	propyl
PTOC	*N*-hydroxypyridine-2-(1H)-thione acyl
py	pyridine
SAMP	*(S)*-amino-2-(methoxymethyl)pyrrolidine
RAMP	*(R)*-amino-2-(methoxymethyl)pyrrolidine
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosylate
TTMSS	tris(trimethylsilyl)silane

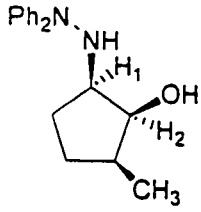
Abstract

Alkyl radicals, generated with tributyltin hydride from their haloprecursors, are trapped efficiently by carbon monoxide under pressure, and the resulting acyl radicals undergo rapid cyclization onto *N,N*-diphenylhydrazones to yield α-hydrazinocyclopentanones.

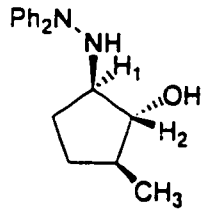
Selective reduction of the resulting ketones provided the corresponding *cis*- or *trans*-β-hydrazinoalcohols, such as **282a-283b**. A novel rearrangement was uncovered when the corresponding α-carbonyl hydrazine was treated with Lewis acids to afford product **292**. Attempted carbonylation of aminyl radicals failed to provide the expected products.

Tandem radical reactions were employed for the synthesis of the bicyclic ring system **359**. The monocyclized products **362** and **363** were also formed. Attempted synthesis of tropane analogs *via* tandem radical reactions resulted only in the formation of the 7-membered ring products, such as **406**.

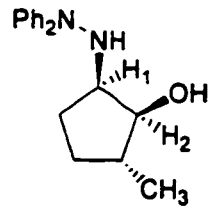
The level of asymmetric induction in radical carbocyclizations mediated by the presence of hydrazone chiral auxiliaries, such as **417** and **418** was examined.



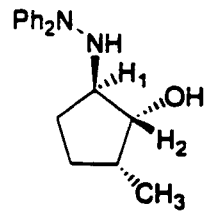
282a



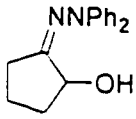
282b



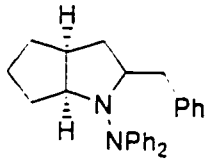
283a



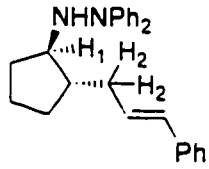
283b



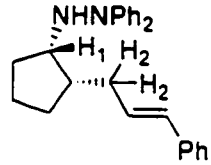
292



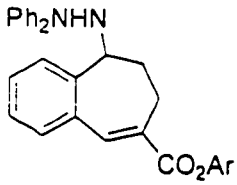
359



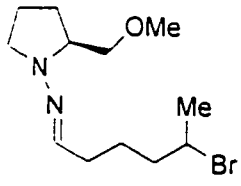
362



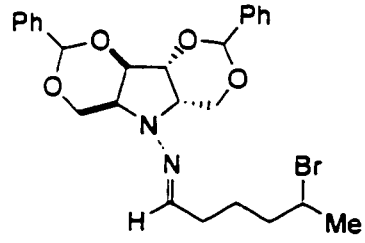
363



406



417



418

Acknowledgements

First and foremost, I would like to express my sincere gratitude to Professor Alex Fallis for giving me the chance to join his group. I enjoyed working under his supervision and appreciate his understanding and constant guidance and encouragement.

I would also like to thank the faculty members and the staff of the Department of Chemistry, University of Ottawa, in particular Professor Tony Durst, Professor Keith Ingold and Professor René Roy for their help and insightful discussions over the course of my studies.

I would like to thank Dr. Simon Woo for being a friend I could always rely upon and for his valuable advice on the preparation of this document. I am very grateful to Bogdan for helping me in the beginning of this journey, and for his friendship and support during all these years, and to Raluca for her encouragement during the more difficult times.

In Ottawa, a number of friends made life easier for me: Steph, Poonam, Pete, Claudio, Mike T., Martin, Curt, Stephanie L., Sandrine, Helene, Shawn, Tanya, Pat, Nicole, Kristian, Tham, Jodi, Mike B. I thank them for their help and inspiring discussions, and – most importantly – for creating a wonderful atmosphere. I feel very fortunate to have had the chance to meet and work with so many talented people.

Daniel, my husband, has been a constant source of love and support, and I am convinced that none of this work would have been finished without his help. Finally, I would not be where I am today without my parents: my Mom, who taught me to have patience and compassion for others, and my late Dad, who taught me to never stop learning and to have the courage to follow my own path in life. More than anyone, my Dad influenced and supported all the decisions I have made that ultimately led here.

In Loving Memory of My Dad

Chapter 1

Free Radical Cyclizations

1.1 Introduction

Free-radical reactions have received attention for nearly a century,[1] however, only recently have they been applied to a number of synthetic targets. This culminated in many elegant and novel approaches to natural products and other interesting compounds.[2] Some previous misconceptions that highly reactive radicals show low chemo-, regio-, and stereoselectivity were quickly dispelled by information on various kinds of radicals, their properties, chemistry and synthetic applications that appeared in numerous publications in the past two decades. Radical chemistry continues to be an important topic of research. The factors that control radical reactions, the characteristics of radical acceptors that determine regio- and chemoselectivities, and the features that direct the stereochemistry of products are still imperfectly understood. In many cases the ultimate goal is the application of radical chemistry to the synthesis of increasingly complex molecules.

Radicals are odd electron species without charge. Radical-radical reactions occur at the diffusion controlled limit ($k = 10^9$-10^{10} $M^{-1}s^{-1}$). Radical-molecule reactions occur with a large range of rate constants and may be both chemo- and regioselective. Radical concentrations control the rates of radical-radical reactions versus the rates of radical-molecule reactions, which can be further adjusted by the choice of reactive partners, concentration and temperature.

Radical reactions offer certain advantages over their ionic counterparts. They can be used for transformations that are quite often hard to accomplish by other means. Radicals themselves are very reactive species, but the reaction conditions are mild and tolerate various functional groups. Hence, hydroxyl and amino functional groups do not require the protection that is often essential for synthetic sequences using ionic reactions.

Most radical reactions show small solvent effects and inert solvents, like benzene or *tert*-butyl alcohol, are preferred.

Temperature has an important effect on the level of stereoselectivity of the reaction. Usually, radical reactions display increased stereoselectivity at lower temperatures. A drawback is the fact that radical chains are shorter at lower temperatures; hence, an increased amount of initiator is required.

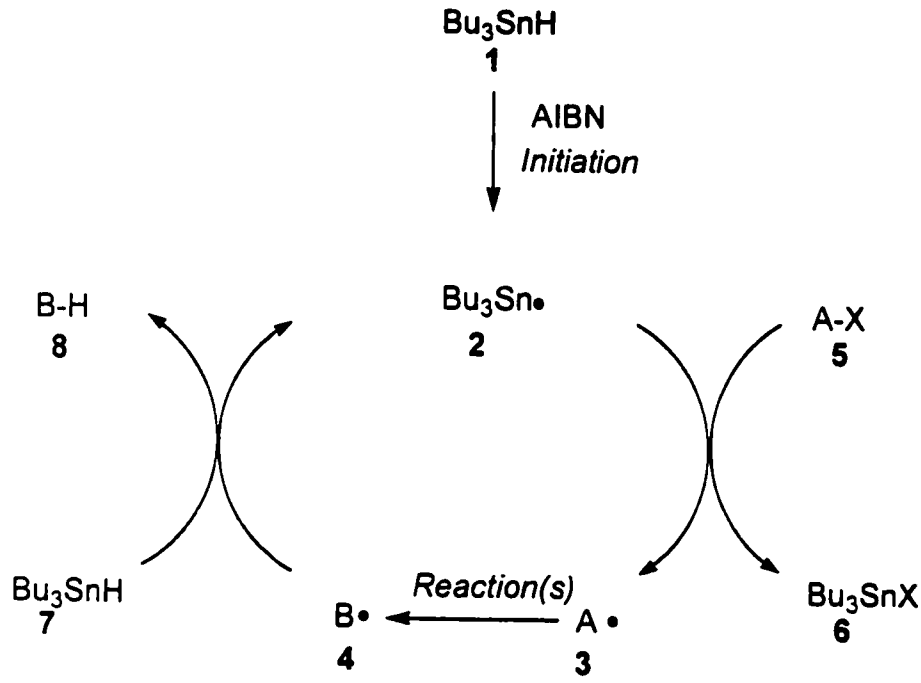
1.2 Methods for Radical Reactions

Radical reactions are chain reactions that consist of three stages: initiation, propagation and termination. Radical concentrations are limited by the rate of initiation, which is typically slow; therefore radical-radical reactions are uncommon.

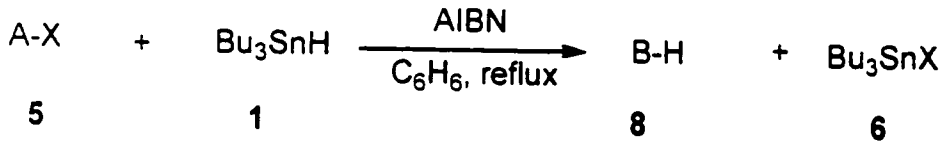
The most popular synthetic method for carrying out radical reactions is the "tin hydride method."[3] The mechanism for this reaction involves a chain process, as shown in Scheme 1.1.

The reaction is initiated by the thermal decomposition of AIBN (azobisisobutylnitrile) which generates the tributyltin radical **2**. Abstraction of a suitable radical precursor X from the substrate A-X **5** generates the initial radical A• **3**, which then suffers a transformation or a series of transformations to provide

a new radical B• **4**. Hydrogen atom transfer then forms the final product B-H **8** and regenerates the tributyltin radical **2** to continue the chain.



Overall Reaction:



Scheme 1.1. Mechanism of Tin Hydride Mediated Reaction

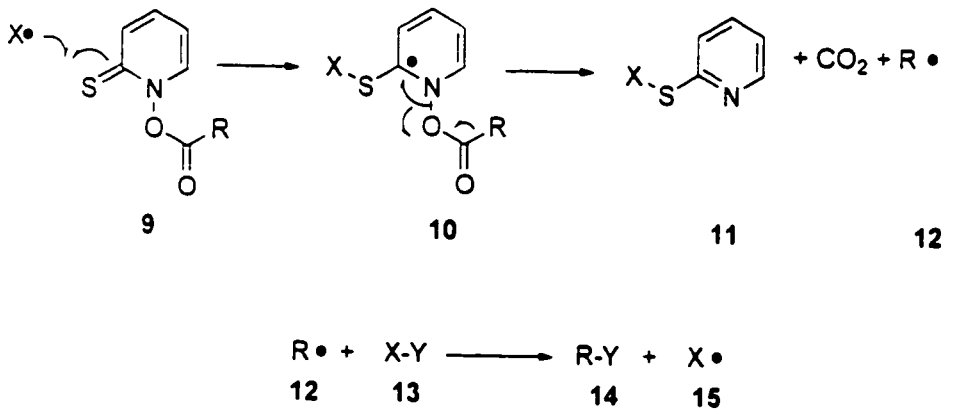
An analogous chain can be written for tris(trimethylsilyl)silane $(TMS)_3SiH$.[4]

The thermodynamic force that drives this process is the conversion of a C-X bond to a stronger C-H bond. In the Scheme 1.1 above, X can be a bromine, iodine, SePh, OC(S)SMe, SPh, etc.

One common problem in tin and silicon hydride reactions is the premature reduction of the radical A• **3** (or other intermediate radical) by the reagent. Tris(trimethylsilyl)silicon hydride is advantageous to use because it is a poorer

hydrogen donor than tributyltin hydride. The maintenance of low concentrations of the hydride reagent necessary to reduce the rate of the competing reduction is often facilitated by the use of a syringe pump.

The "thiohydroxamate method" (also called the "Barton method") uses the esters of *N*-hydroxypyridine-2-thione as a versatile source of radicals.[5] This method involves a thiopyridyl group transfer reaction, and it differs from the tin hydride method in that the group is transferred by an addition-elimination mechanism rather than a homolytic substitution. The generalized chain sequence is shown in Scheme 1.2.



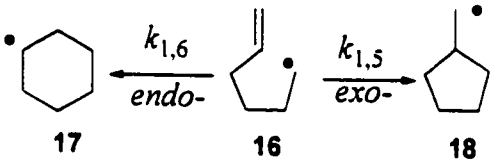
Scheme 1.2. Barton Method Chain Process

A decarboxylation occurs during the course of the reaction. The competing reaction of the initial radical R• **12** with the thiohydroxamate can be minimized by keeping a low concentration of the thiohydroxamate.

There are also non-chain methods for conducting radical reactions and these can involve radical-radical coupling, oxidation or reduction. Among these, reductive generation of radicals is usually followed by reductive trapping to form organometallic reagents. Samarium diiodide is a powerful one-electron reducing agent that generates alkyl radicals from halides and ketyl radicals from carbonyl substrates.[6]

1.3 Principles of Radical Cyclization

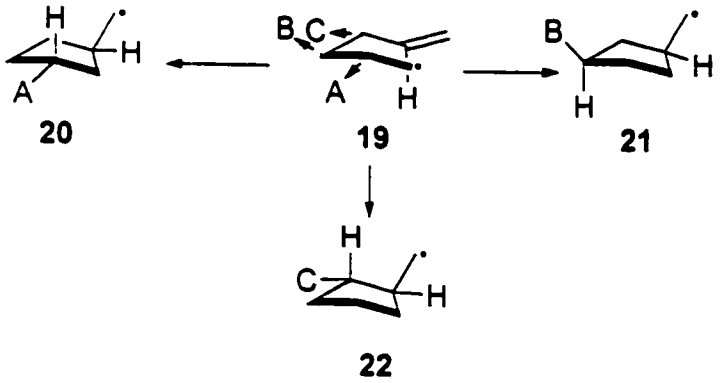
The 5-hexenyl radical cyclization is one of the most studied radical reactions. The reaction follows Baldwin's empirical rules of cyclization[7] with the 5-*exo* mode of ring closure favoured over the 6-*endo* mode of ring closure by a factor of 50 at 60 °C, as shown in Scheme 1.3.



at 60 °C $k_{1,6} / k_{1,5} = 50$

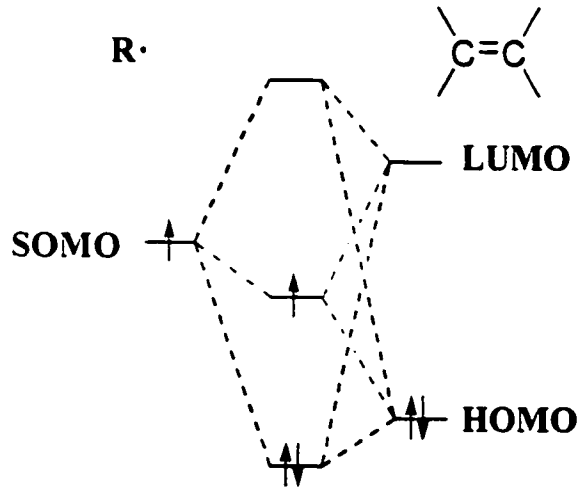
Scheme 1.3. 5-Hexenyl Radical Cyclization

Various studies[8] suggest a "chair-like" transition state. The stereochemical outcome of the products can be predicted based on this "chair-like" transition state, as demonstrated in Scheme 1.4. The presence of the substituents A, B or C can direct the reaction to yield products **20**, **21** or **22**, respectively.



Scheme 1.4. Stereochemical Outcome in a 5-exo trig Cyclization

In terms of Frontier Molecular Orbital (FMO) Theory, the frontier orbital of a free radical is the single occupied molecular orbital (SOMO). The FMO theory states that the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reacting species largely determines the rate of the reaction (Scheme 1.5).[9]



Scheme 1.5. Relative Energies of the SOMO and the π and π^* Orbitals of the Alkene

Radicals with high lying SOMO's, such as alkyl, alkoxyalkyl and aminoalkyl radicals, interact preferentially with the LUMO of the alkene. The rate of addition is further enhanced by placing electron-withdrawing substituents on the alkene, which lowers the energy of its LUMO. For example, the nucleophilic *tert*-butyl radical adds some 8500 times faster to 2-propenal than to 1-hexene.[10] However, in radicals with electron withdrawing groups the SOMO energy is lowered, and the SOMO-HOMO gap is reduced.

A variety of radical centers, from carbon radicals (*i.e.* alkyl, vinyl, aryl, allyl, acyl, imidoyl, etc.) to heteroatom radicals (*i.e.* aminyl, iminyl, alkoxy, sulfide) can be efficiently generated. They participate readily in radical cyclizations to yield

molecular structures of increased complexity. Also, heteroatom acceptors such as carbonyl groups, imines, nitriles and related systems are increasingly utilized in organic synthesis.

The participation of the nitrogen, both as a radical source and as an acceptor component, was reviewed.[11] The following section highlights examples from the recent literature of the use of carbon-nitrogen unsaturated systems in radical cyclizations.

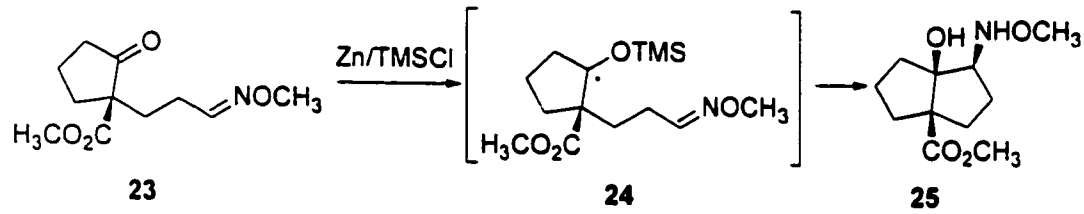
1.4 Cyclization onto Carbon – Nitrogen Unsaturated Systems

Oxime ethers, hydrazones and imines have been employed as radical acceptors in organic synthesis, and the study and application of these systems have expanded greatly in recent years. Nitriles also have been recognized and exploited as useful, but capricious radical acceptors. Additionally, a number of reports of azides and azo groups as radical acceptors have appeared.

1.4.1 Oxime Ethers Acceptors

Historically, oxime ethers were the first C=N π systems to be investigated as radical acceptors for either inter- or intramolecular reactions.

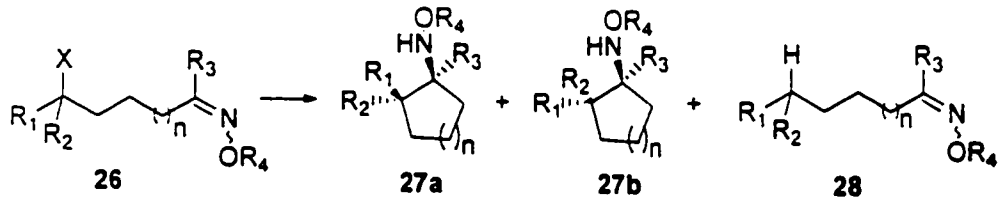
An early example[12] reported by Corey and Pyne in 1983 is the generation of the ketyl radical **24** from ketone **23** in the presence of trimethylsilyl chloride to afford the diquinane **25** in 84% yield as a single diastereomer (Scheme 1.6).



23 **24** **25**

Scheme 1.6. Oxime Ether as Radical Acceptor

In 1988 Bartlett[13] reported the first example of an alkyl radical cyclization onto an oxime ether. The general reaction, which explored variations in substitution at the radical center and at the oxime carbon, is illustrated in Scheme 1.7.

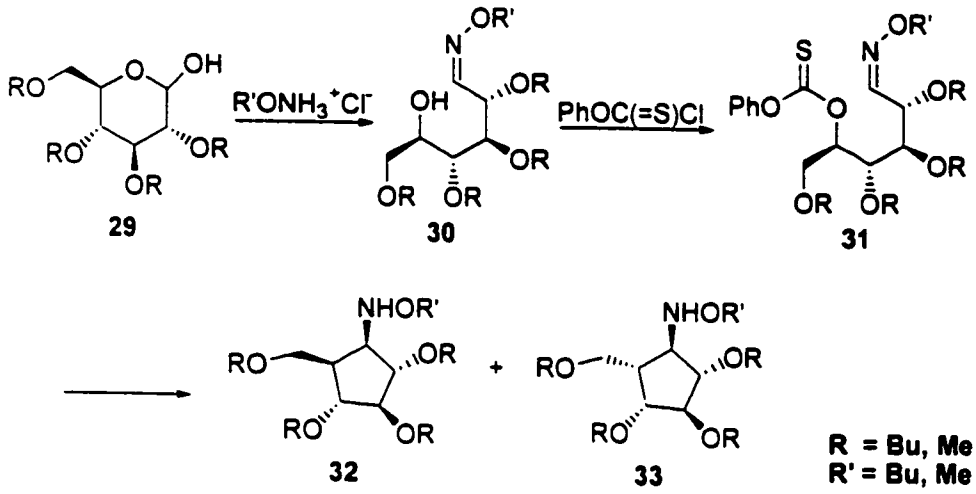


26 **27a** **27b** **28**

Scheme 1.7. Alkyl Radical Cyclization onto Oxime Ethers

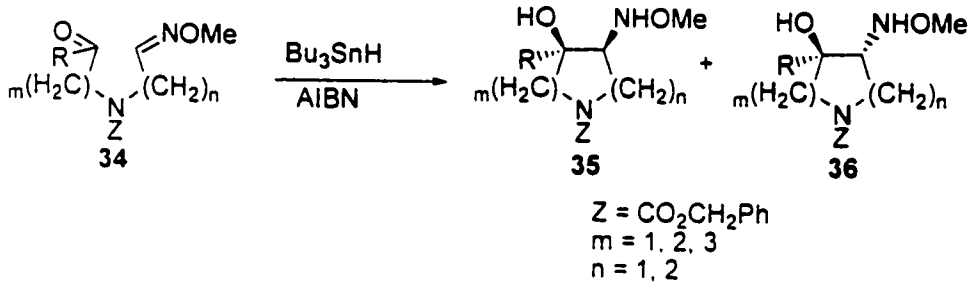
Thirteen different substrates were employed for this reaction and it was found that, while the stereoselectivity varied (*cis/trans* = **27a:27b** ratios between 51/49 and >98/2), the yields were good.

Bartlett also demonstrated the utility of this cyclization for the conversion of a carbohydrate **29** to a carbocycle (Scheme 1.8).



Scheme 1.8. Conversion of a Carbohydrate to a Carbocycle

The intramolecular cyclization of oxime ethers **34** with aldehydes or ketones was reported[14] by Naito and coworkers (Scheme 1.9).



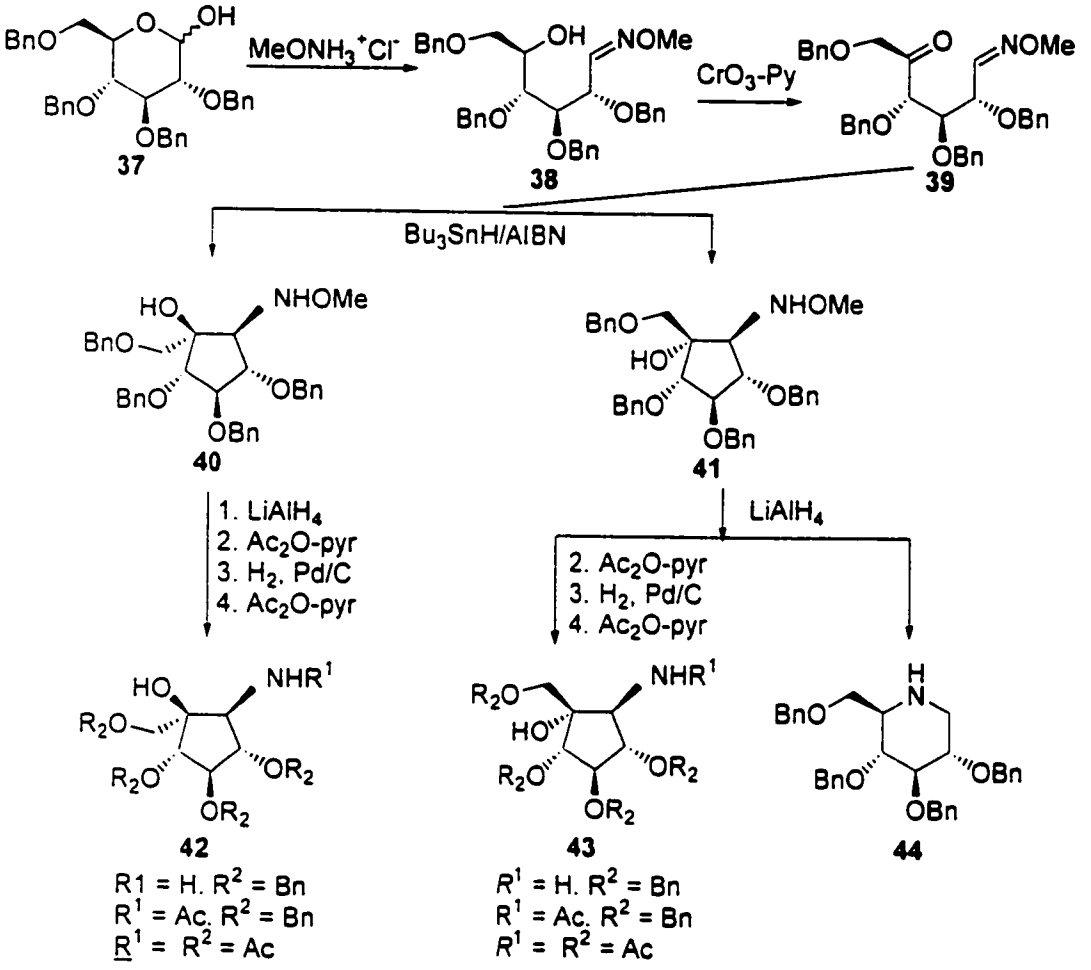
Scheme 1.9. Intramolecular Cyclization of Aldehydes or Ketones with Oxime Ethers

This method provides an interesting entry to cyclic amino alcohols **35** and **36** that are formed in 44-70% combined yield with ratios varying between 20:80 and 39:61.

In a related study, Fu and coworkers[15] also explored the Bu_3SnH-mediated reductive cyclization of carbonyi-oxime ethers to generate *trans*-amino alcohols with moderate to excellent levels of stereoselectivity.

Potent glycosidase inhibitors, such as aminocyclopentitols were found to have powerful and specific inhibitory activity against glycosidases.

Naito and his coworkers[16] reported the synthesis of the inhibitors aminocyclopentitols **42** and **43** and 1-deoxynojirimycin **44** *via* a route involving radical cyclization onto an oxime ether (Scheme 1.10).

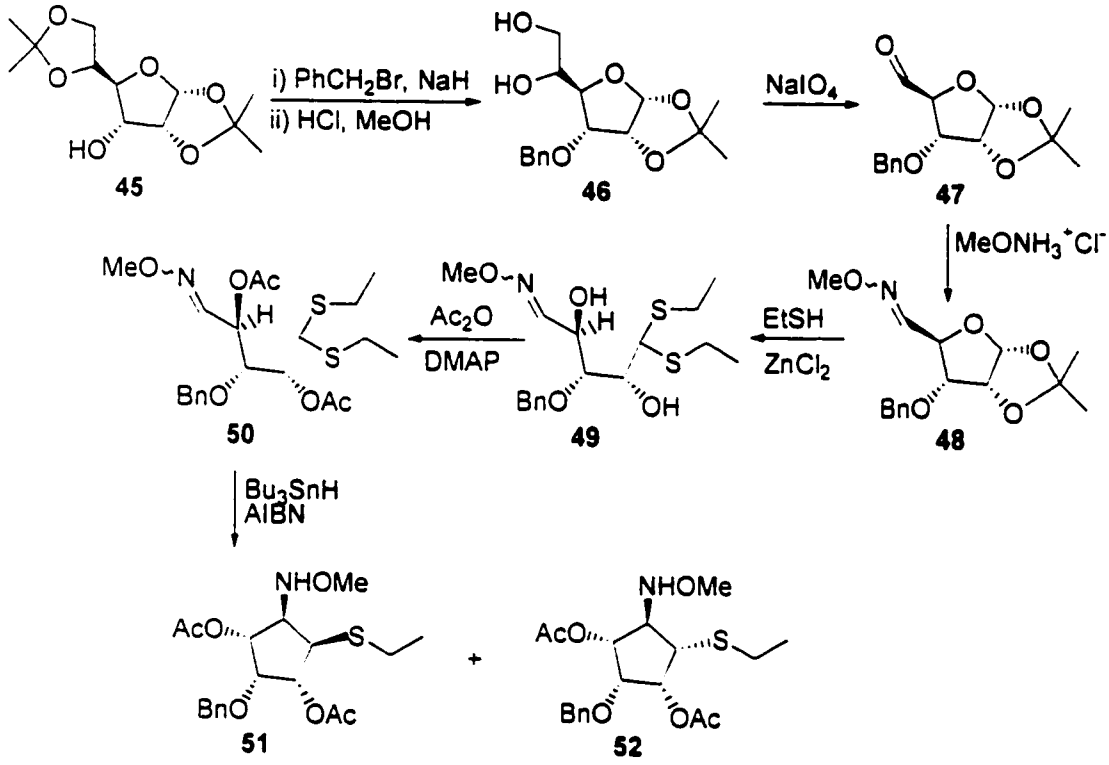


Scheme 1.10. Synthesis of Aminocyclopentitols and 1-Deoxynojirimycin

The tributyltin hydride-induced radical cyclization of the oxime ether **39** in the presence of AIBN afforded a 1.4:1 mixture of aminoalcohols **40** and **41** in 68% combined yield.

Naito and coworkers[17] also explored the radical addition-cyclization of oxime ethers tethered to an alkene group for the synthesis of functionalized cyclic compounds.

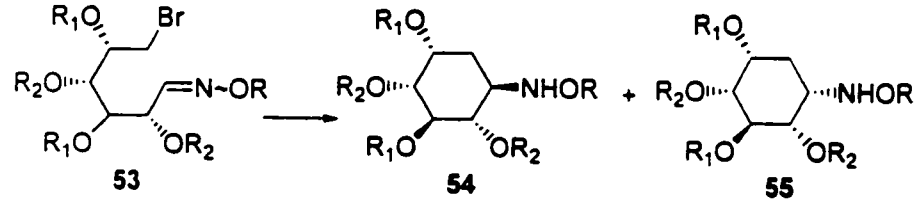
The synthesis of a carbocyclic compound related to the sugar hydrolase inhibitors mannostatin A and mannostatin B was accomplished by Moore *et. al.*[18] commencing with *D*-allofuranose **45** (Scheme 1.11).



Scheme 1.11. Synthesis of a Carbocyclic Compound Commencing with D-Allofuranose

The key carbon-carbon bond forming reaction was an intramolecular free radical cyclization of a radical derived from dithioacetal[19] **50** onto an oxime ether. The cyclized products **51** and **52** were formed in a ratio of 3:1, respectively, in 80% combined yield.

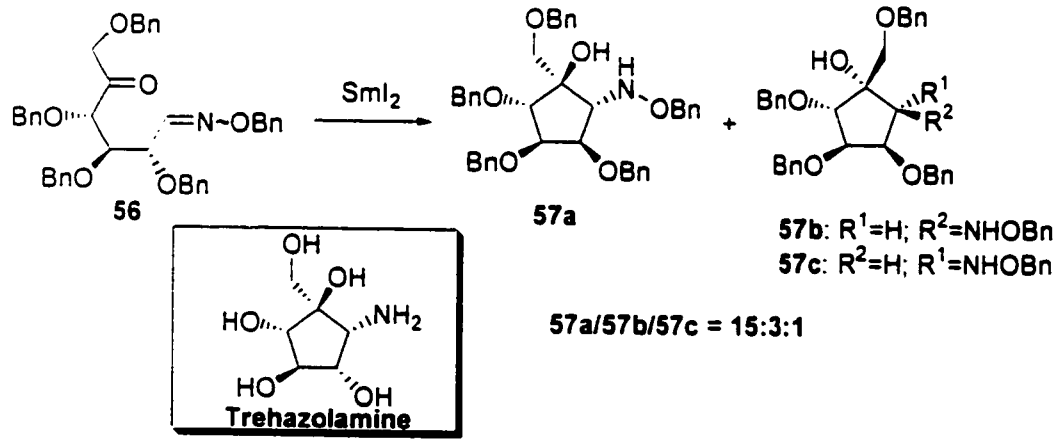
In 1991 Marco-Conteles and coworkers[20] used the 6-*exo* free radical cyclization of acyclic carbohydrate intermediates for the synthesis of carbocycles (Scheme 1.12).



Scheme 1.12. Synthesis of Carbocycles from Acyclic Carbohydrate Intermediates

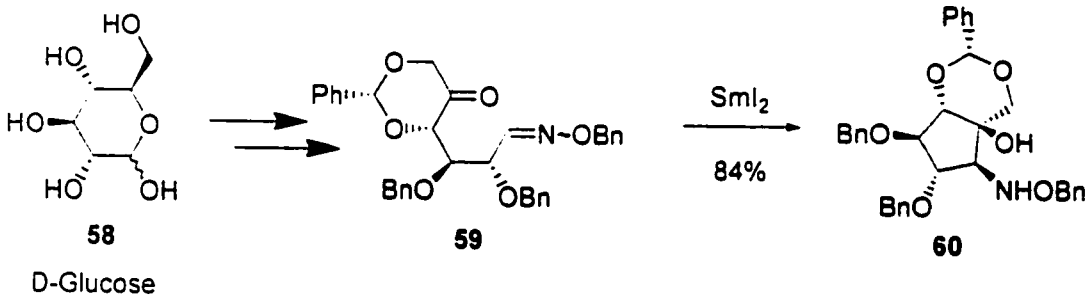
This cyclization gave compounds **54** and **55** in reasonable yields (40-55%) and good diastereoselectivity (75:25-83:17).

The same group have applied a similar method for the synthesis of enantiomerically pure carbocycles *via* a 5-*exo* radical cyclization[21] and demonstrated[22] that the intramolecular reductive coupling of carbonyl-tethered oxime ethers can be promoted by samarium diiodide. One example is shown in Scheme 1.13. It will be noted that compounds **57a-c** can be easily converted into epimers of trehazolamine, the aminocyclopentitol aglycon of the trehalaze inhibitor trehazoline[23].



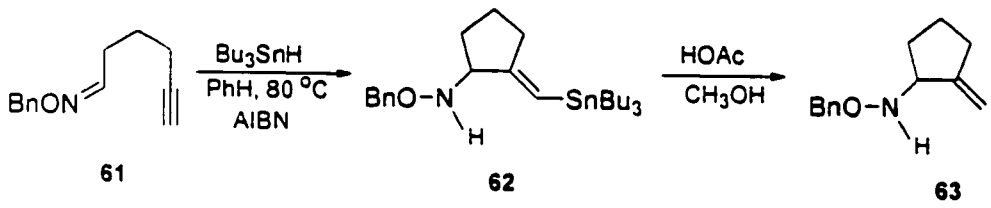
Scheme 1.13. Stereoselective Synthesis of Carbocycles

The synthesis of trehazolin and trehazolamine from D-glucose was recently described.[24] The presence of a six-membered cyclic acetal connecting C-4 and C-6 determined the exclusive formation of the desired diastereomer **60** during the intramolecular radical cyclization of a ketooxime ether **59** derived from D-glucose **58**, as shown in Scheme 1.14.



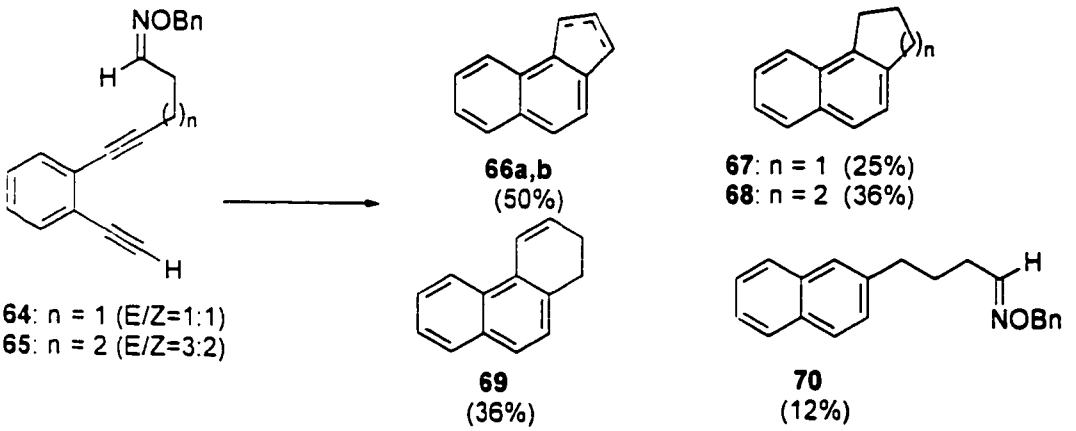
Scheme 1.14. Stereoselective Synthesis of Trehazolamine Precursor

Enholm[25] published the first report on the reaction between oxime ethers and alkynes in 1990 (Scheme 1.15). The reaction, which involves the intramolecular coupling of a terminal alkyne tethered to an oxime ether **61**, was promoted by tributyltin hydride to produce the cyclized product **62**. Subsequent protodestannylation afforded the desired cyclopentane ring bearing an *exo*-methylene unit and a benzyl-ether substituted amine in 56-90% yield.



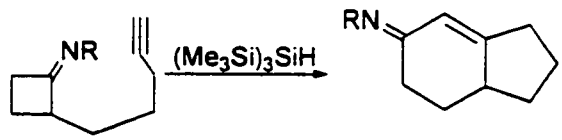
Scheme 1.15. Reaction between Oxime Ethers and Alkynes

In 1993 Grissom published a full report[26] on the possible use of the oxime ethers as traps for aryl radicals in an interesting intramolecular tandem enediyne-radical cyclization process. The aryl radicals were generated from a Bergman type cyclization of enediyne substrates. The oxime ethers **64, 65** were heated to 190 °C in chlorobenzene in the presence of 1,4-cyclohexadiene as a hydrogen atom source (Scheme 1.16). Thermolysis of oxime ether **64** (E/Z = 1:1) under these conditions formed only the products from tandem enediyne-radical cyclization. These were the hydrocarbons **66a,b** (50%) and O-benzylhydroxyl amine **67** (25%). Hydrocarbons **66a,b** were isolated as a mixture of double bond isomers in 1:1 ratio. Employing oxime ether **65** (E/Z = 3:2) as a substrate resulted in the formation of four products. In addition to the tricyclic products **68** and **69**, which were formed in 72% yield as a 1:1 mixture, the enediyne cyclization product oxime ether **70** was isolated in 12% yield as a 1:1 mixture of E/Z isomers.



Scheme 1.16. Intramolecular Tandem Enediyne-Radical Cyclization

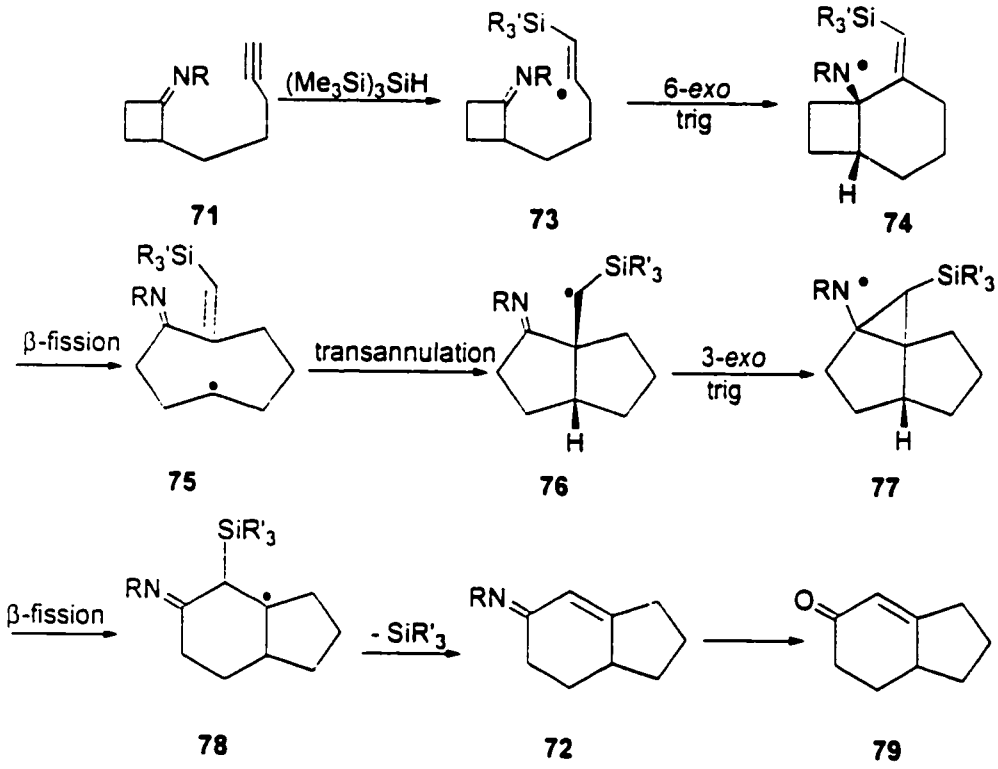
As part of his study of angular triquinane construction *via* consecutive ring forming reactions, Pattenden[27] examined the intramolecular free radical reactions of terminal acetylenes with cycloalkanone oxime ethers (Scheme 1.17).



71 72

Scheme 1.17. Free Radical Reactions Of Terminal Acetylenes With Cycloalkanone Oxime Ethers

The product of this interesting "one pot" transformation arises *via* a novel double ring expansion-cyclization process[28] involving aminyl radical intermediates (Scheme 1.18). The oxime **72** could be separated as Z- and E-isomers (93:7) in 70% yield. Hydrolysis of the oxime led to the bicyclic enone **79**.

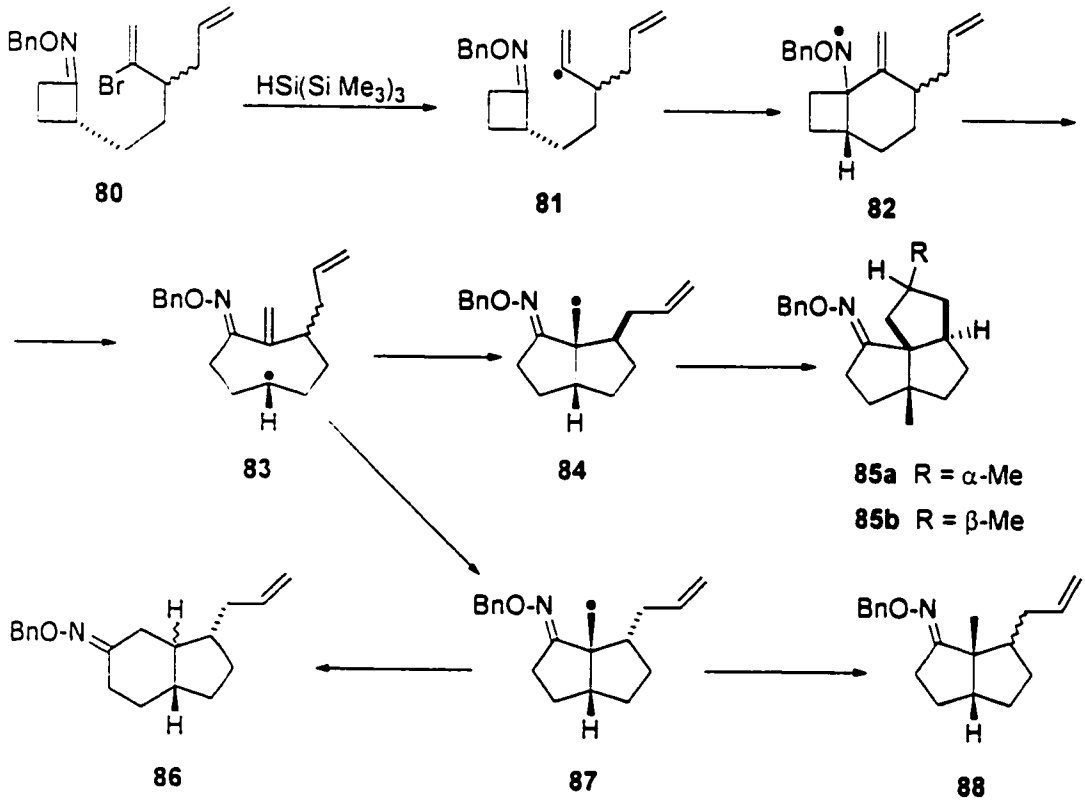


71 73 74 75 76 77 78 72 79

R = OCH_2Ph R' = Si Me_3

Scheme 1.18. Double Ring Expansion-Cyclization Process

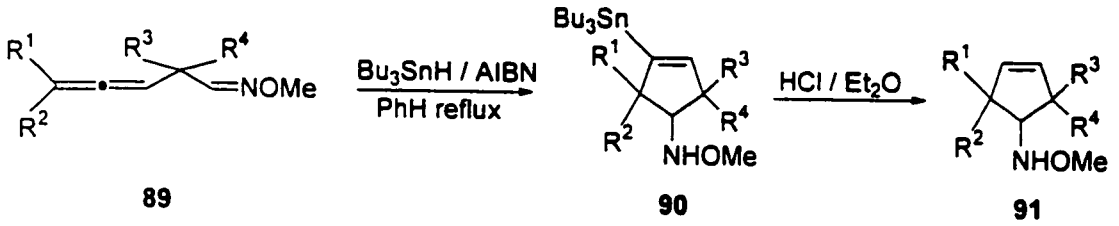
An extension of this study involved irradiation of the vinyl bromide cyclobutane oxime **80** (Scheme 1.19) in the presence of TTMSS. The main isolated product was the triquinane **85** as a 1:1 mixture of α- and β-methyl diastereoisomers in 38% yield. The product resulted from a cascade radical 6-*exo-trig* cyclization, aminyl radical fragmentation and 5-*exo-trig* radical transannulation. Interestingly, the initial functional group was not transformed into an O-alkylhydroxylamine, as was the case with other cyclizations. The oxime ether functionality was in fact regenerated in the process and was present in the final product.



Scheme 1.19. Cascade Radical Reactions

Hatem *et. al.*[29] have shown that β-allenic O-methyl oximes underwent a free radical hydrostannylation to afford cyclopentenes bearing a protected amine

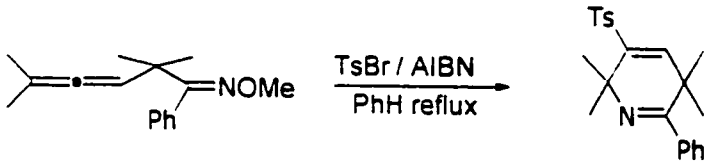
group and a vinyl stannyl functionality in 37-91% yield. These compounds were destannylated to yield the corresponding cyclopentenes (Scheme 1.20).



89 90 91

Scheme 1.20. Free Radical Hydrostannylation-Cyclization

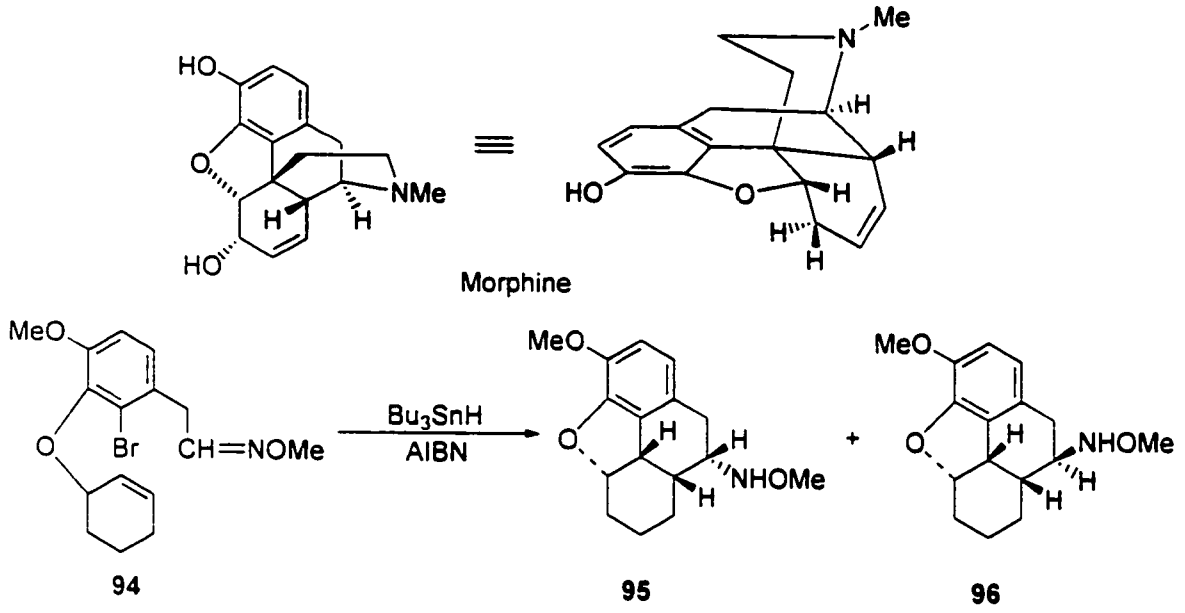
In a related study, the addition of tosyl bromide to β-allenyl-1-phenylketoximebenzoate **92** was explored (Scheme 1.21).[30] Under free radical conditions, the carbon-centered radical resulting from the addition of the tosyl radical on the sp carbon was formed. This carbon-centered radical underwent a 6-*endo* cyclization onto the nitrogen atom leading to the 3,6-dihydropyridine **93** in 94% yield.



92 93

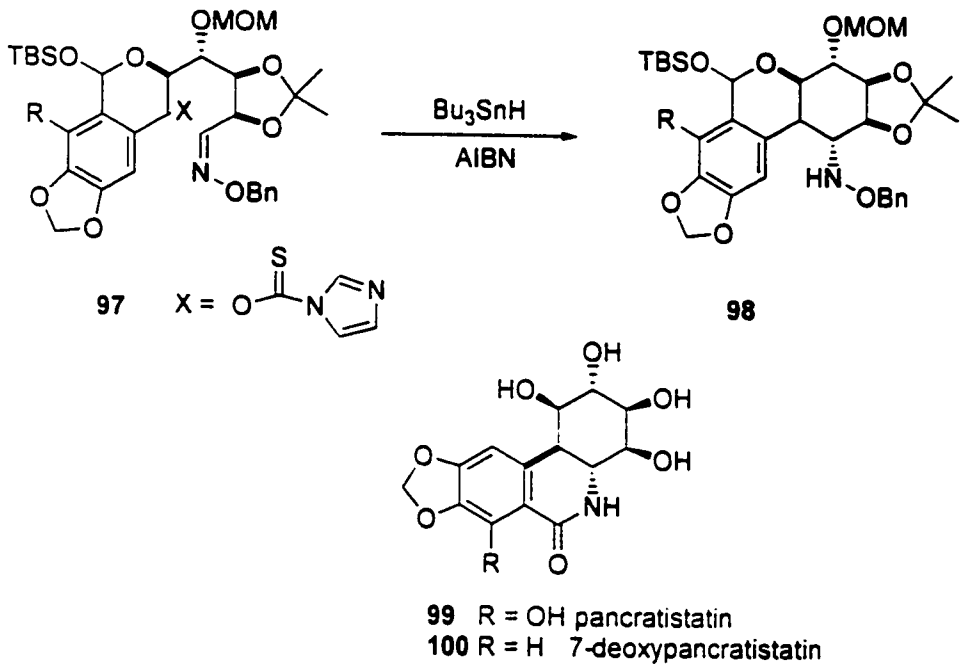
Scheme 1.21. 3,6-Dihydropyridine from 6-Endo Cyclization

In 1988 Parker and coworkers[31] used an oxime ether as radical trap in a tandem radical cyclization to generate a tetracyclic morphine model **95** in 31% yield, accompanied by its epimer **96** in 40% yield (Scheme 1.22).



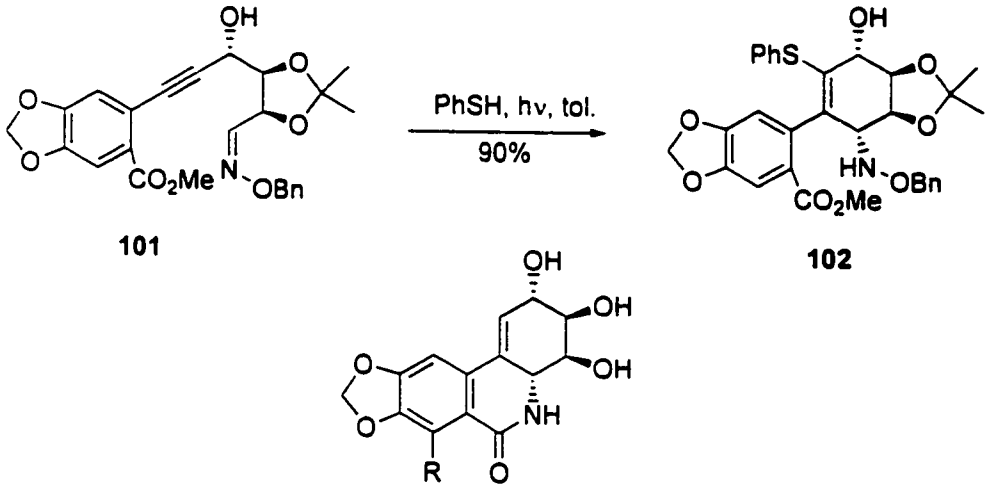
Scheme 1.22. Tetracyclic Morphine Model Synthesis

The alkaloid Pancratistatin **99** isolated from *Amaryllidaceous* plants displays promising antineoplastic and antiviral activity[32]. The 7-Deoxy compound **100** exhibits both better therapeutic properties and decreased toxicity[33]. The total synthesis of (+)-7-Deoxypancratistatin[34] involved a key 6-*exo* cyclization between a benzylic radical generated through a Barton deoxygenation of **97** to construct the highly functionalized cyclohexane nucleus found in the natural product (Scheme 1.23). The cyclization yielded the corresponding product in 70% isolated yield as a single stereoisomer.



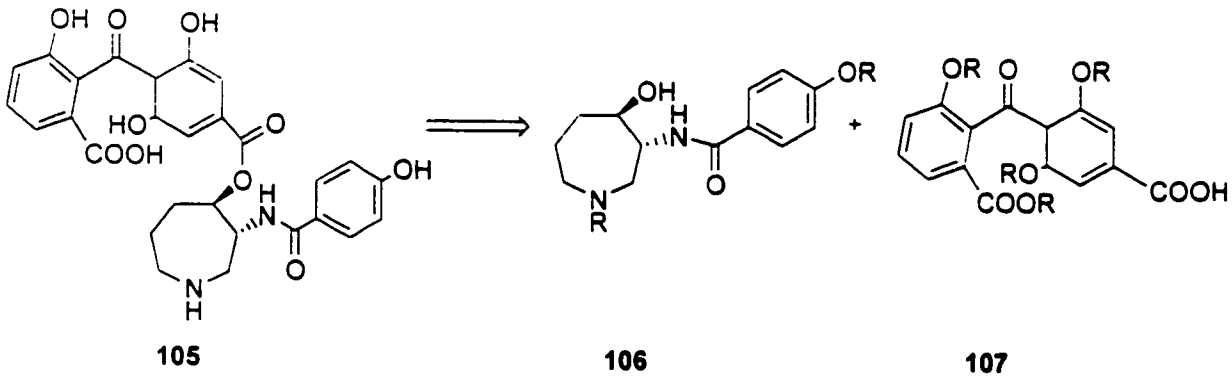
Scheme 1.23. Synthesis of (+)-7-Deoxypancratistatin Intermediate

The total synthesis of the pancratistatin-related alkaloids (-)-lycoricidine, its natural (+) enantiomer, and (+)-narciclasine *via* a stereoselective 6-*exo* radical cyclization of a vinyl radical to an *O*-benzyloxime radical acceptor group has been reported recently.[35] As seen in Scheme 1.24 below, the vinyl radical was itself generated by regioselective addition of phenylthiyl radical to a disubstituted alkyne **101**. The cyclization proceeded in 90% yield for the (+)-lycoricidine and 75% yield for the (+)-narciclasine to afford only the desired stereoisomer.



Scheme 1.24. Key Step in the Total Synthesis of (-)-lycoricidine and (+)-narciclasine

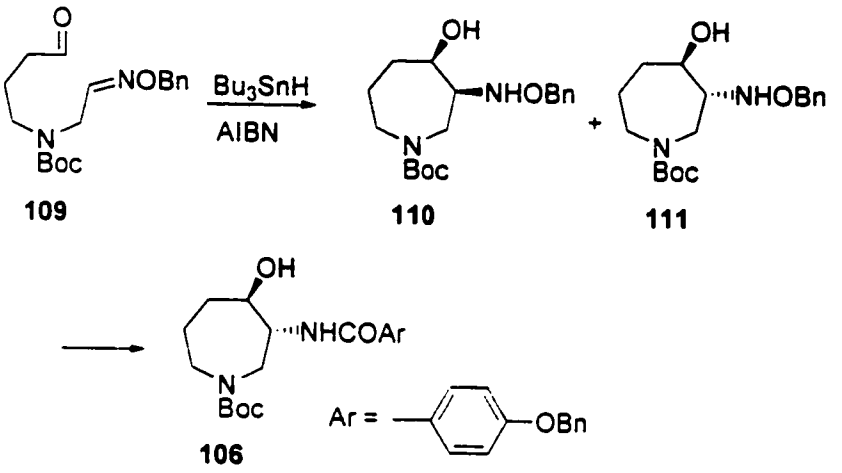
Both enantiomers of the hexahydroazepine **106** are key intermediates for the synthesis of (-)balanol **105** and its enantiomer, shown to be a potent inhibitor of protein kinase C enzymes (Scheme 1.25).



Scheme 1.25. Retrosynthetic Analysis of (-) Balanol

Both the *cis* and *trans* isomers of the hexahydroazepine were synthesized[36] in 58% yield as 2:3 mixture *via* stannyl radical cyclization of the

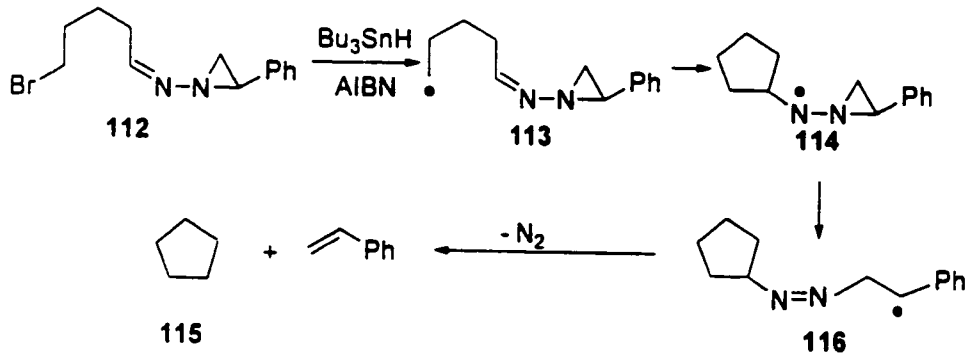
aldehyde **108** onto an oxime ether (Scheme 1.26). A more recent report[37] illustrated that changing the reaction conditions to samarium diiodide/HMPA led to the formation of the *trans* isomer in 48% yield, accompanied by the minor *cis* isomer formed in 7% yield.



Scheme 1.26. Ketyl Radicals Cyclizing onto Oxime Ether Systems

1.4.2 Hydrazone Acceptors

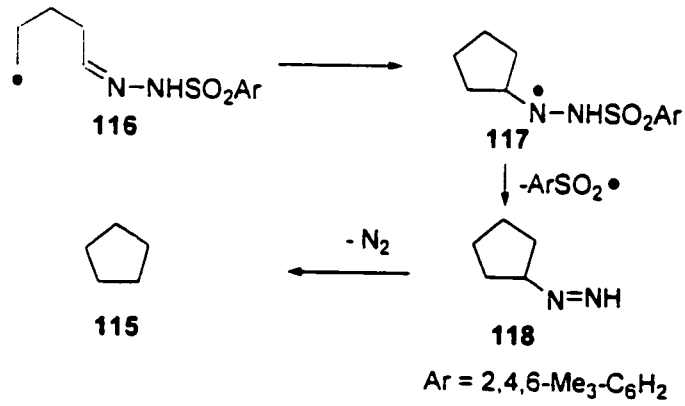
The first example of a radical hydrazone cyclization was published in 1991 by Kim and coworkers.[38] 2-Phenyl-*N*-aziridinyl imines were used as substrates and the proposed mechanism[39] for this specialized case is shown in Scheme 1.27.



Scheme 1.27. Mechanism for Cyclization onto Phenyl-N-Aziridinyl Imines

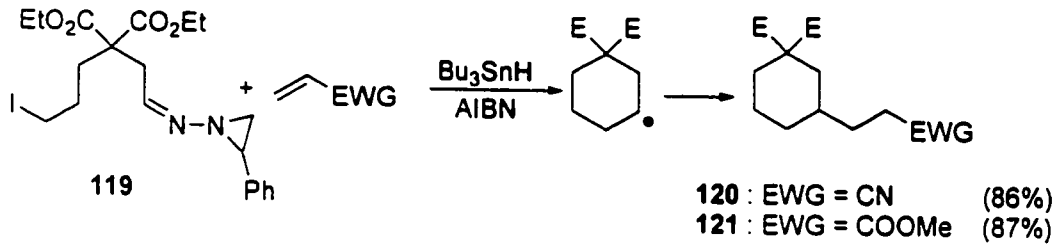
From substrate **112** generation of radical **113** was followed by cyclization to give the nitrogen centered radical **114**. This radical then underwent ring opening of the aziridine to form the benzylic radical **116** which extruded styrene and nitrogen to ultimately yield carbocycle **115** as the final product. The liberation of these neutral, stable molecules was clearly a driving force for this cyclization.

A conceptually similar approach[40] is the use of mesitylhydrazones (Scheme 1.28). The final product was formed by the decomposition of the diazene **118**.



Scheme 1.28. Cyclization onto Mesitylhydrazones

The feasibility of the cyclization-intermolecular addition sequence was also examined (Scheme 1.29).

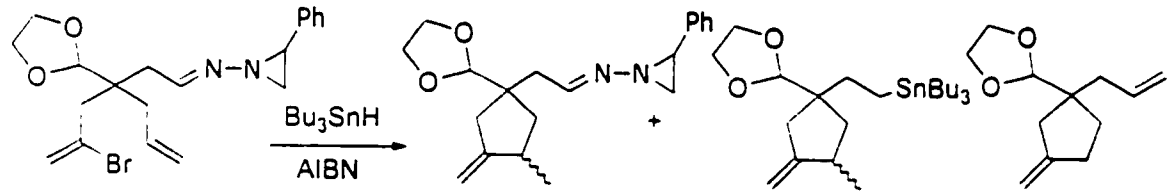


119

120 : EWG = CN (86%)
121 : EWG = COOMe (87%)

Scheme 1.29. Cyclization-Intermolecular Addition Sequence

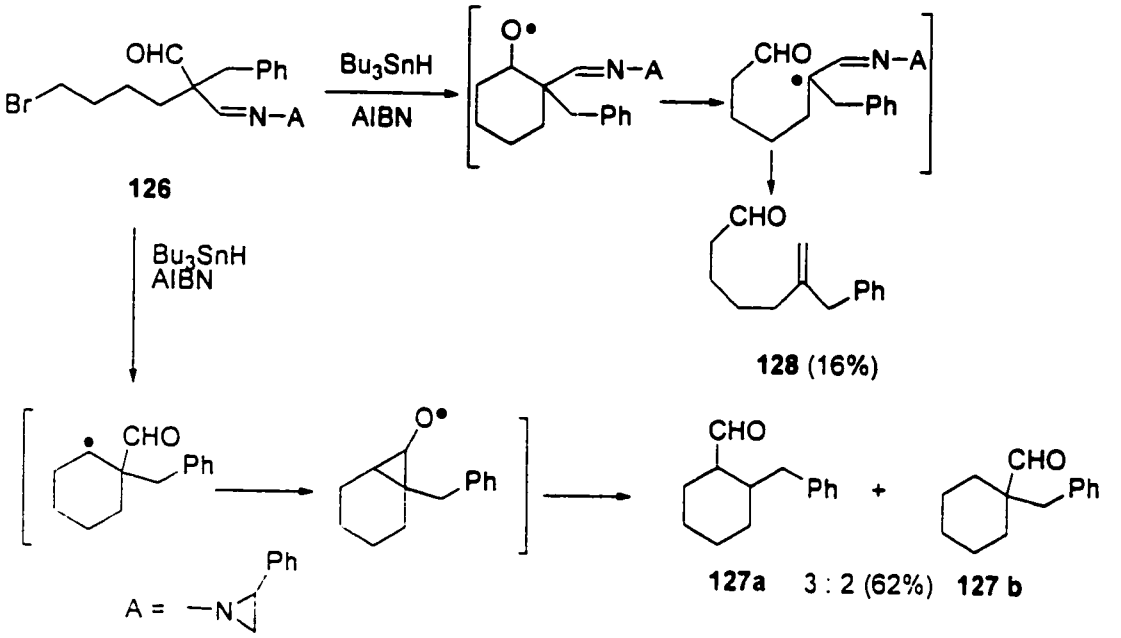
The same group[41] examined the competition between carbonyl and alkenyl group vs. N-aziridinyl imine as radical acceptors and concluded that the vinyl radical cyclizes onto the alkenyl group rather than onto *N*-aziridinyl imino group (Scheme 1.30). In this case **124** was derived from **123** by further tributyltin radical addition and there was no indication of the presence of **125**.



122 **123** (65%) **124** (21%) **125**

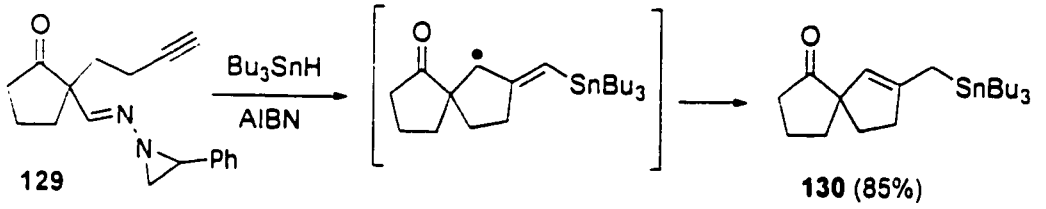
Scheme 1.30. Competition between Alkenyl Group Vs. N-Aziridinyl Imine as Radical Acceptors

The competition between a formyl and an imino group afforded a 16:62 mixture of **128** and **127** (Scheme 1.31) where **128** resulted from attack of the alkyl radical to the formyl group, whereas **127** was produced from initial attack of the alkyl radical to the imino group.



Scheme 1.31. Competition between a Formyl and an Imino Group

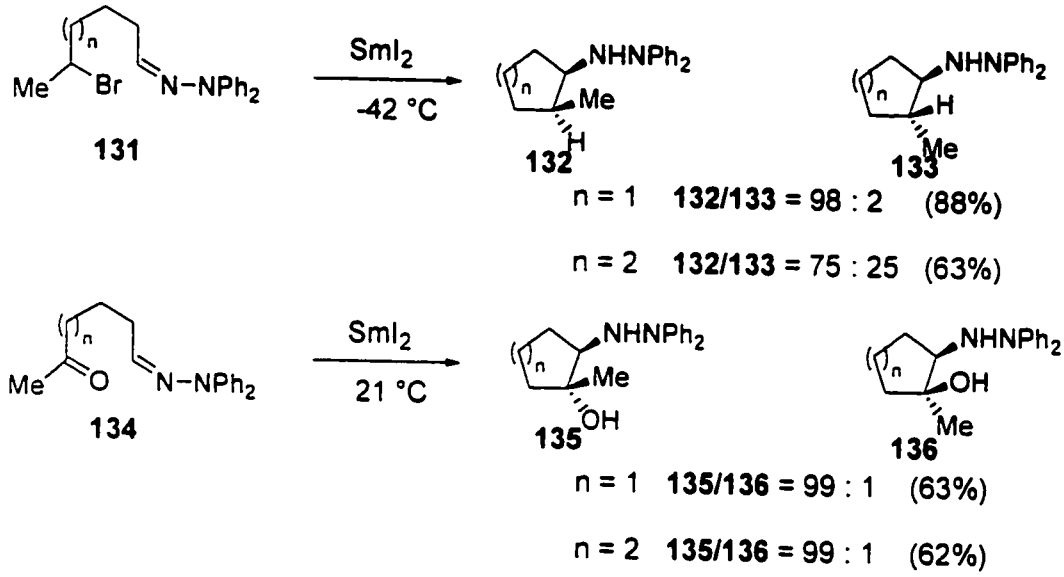
Furthermore, the competition between a keto and an *N*-aziridinyl imino group in **129** showed preferential attack of a vinyl radical to the imino group to afford **130** in 85% yield (Scheme 1.32).



Scheme 1.32. Competition between a Keto and an N-Aziridinyl Imino Group

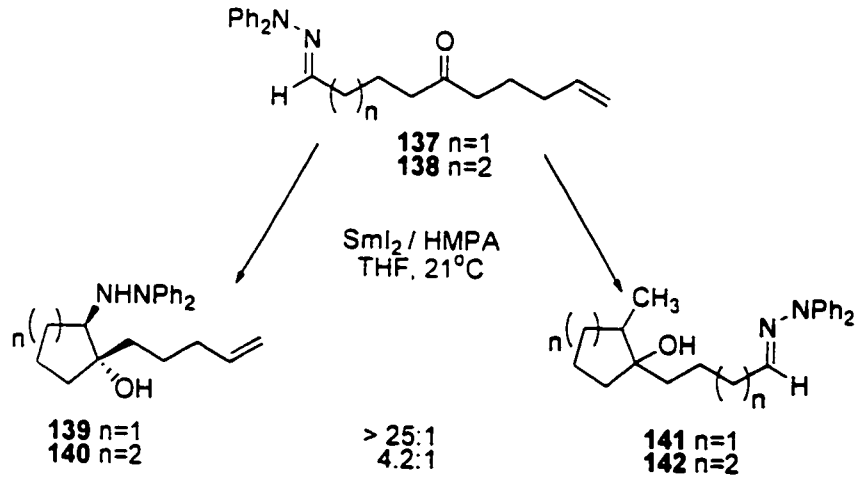
In our laboratory, it was established that both halo and carbonylhydrazones cyclize directly to hydrazines under either *n*-Bu_3SnH or SmI_2 mediated conditions (Scheme 1.33).[42] These reactions displayed a high level of diastereoselectivity. The carbonylhydrazones provided rapid access to *β*-

aminoalcohols after samarium diiodide mediated hydrazine reduction of the cyclic products.



Scheme 1.33. Cyclization onto N,N-Diphenylhydrazones

Kinetic studies, based on an intramolecular competition between alkene and hydrazone, revealed the hydrazone cyclization rates were quite rapid (Scheme 1.34).[43]

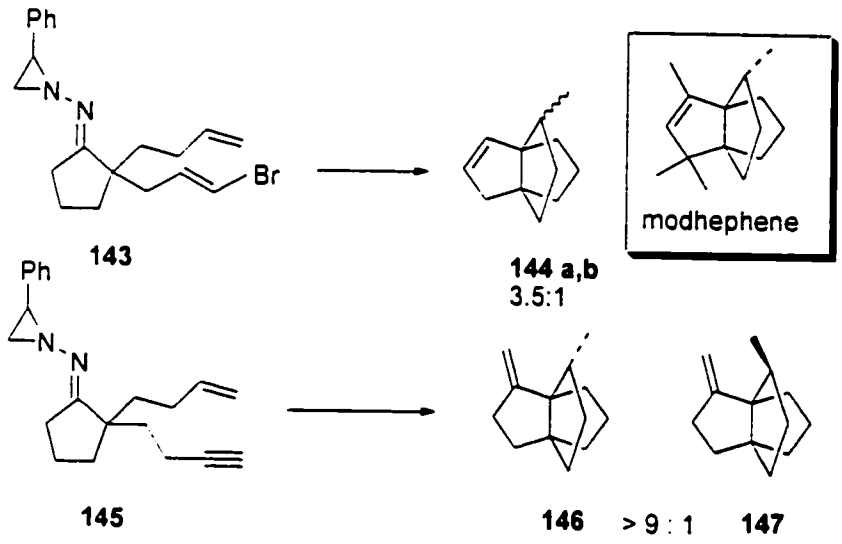


Scheme 1.34. Competitive "Radical Clock"-Type Cyclizations of Hydrazones and Alkenes

The 5-*exo* cyclization onto a *N,N*-diphenylhydrazone ($k = 1.1 \times 10^{-8}\ s^{-1}$) was determined by running the cyclization in concentrated Bu_3SnH and measuring the amounts of cyclized vs. reduced products. The cyclization is approximately 200 times faster than the intramolecular capture by an olefin. These studies have also established that with samarium diiodide these reactions were radical cyclizations and did not involve anionic organosamarium intermediates.

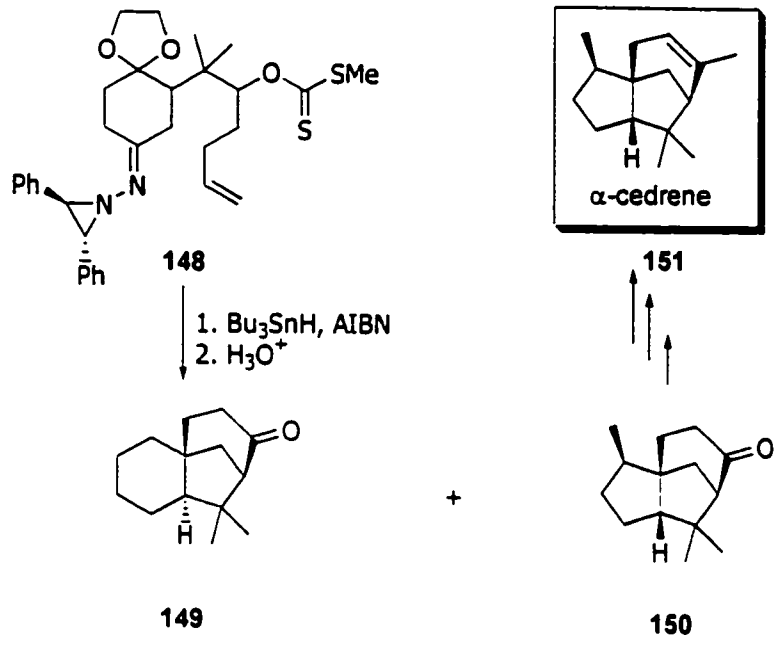
Kinetic and competition studies[44] have established that the rate constant for the 6-*exo* cyclizations of alkyl radicals to *N*-aziridinyl imines was approximately $4.7 \times 10^6\ s^{-1}$ at 80 °C. Further competition experiments indicated that the rate constant for the corresponding 5-*exo* cyclization onto the *N*-aziridinyl imines would be more than $2.5 \times 10^8\ s^{-1}$ at 20 °C.

N-aziridinyl imines were used in tandem radical cyclization to produce [3.3.3] propellanes (Scheme 1.35).[45] This strategy was applied to the synthesis of intermediates **146** and **147** that were further manipulated to give *dl*-modhephene.



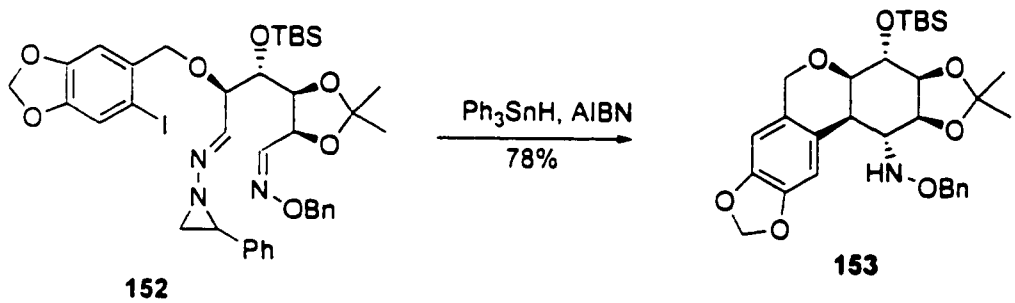
Scheme 1.35. Tandem Radical Cyclization onto N-Aziridinyl Imines

In a similar manner, *N*-aziridinyl imines were used in a tandem radical cyclization to produce the tricyclo[5.3.1.0]undecane skeleton **150** in 45% yield; this was further manipulated to give α-cedrene (Scheme 1.36).[46]



Scheme 1.36. Tricyclic Systems via Tandem Radical Cyclization onto N-Aziridinyl Imines

Keck and coworkers[47] employed a 6-*exo* cyclization of an aryl radical onto an *N*-aziridinylimine and, following the loss of nitrogen and styrene, the resulting radical cyclized to form the highly functionalized nucleus **153** in 78% yield (Scheme 1.37), which was further transformed to 7-deoxypancratistatin **100**.

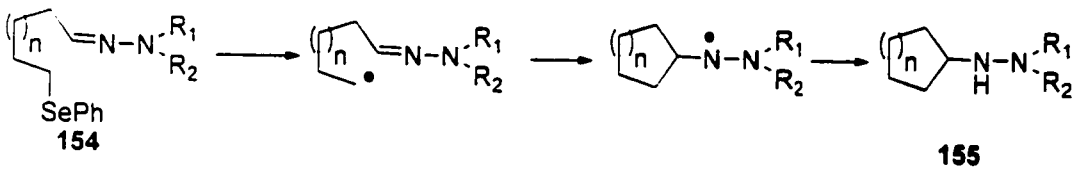


Scheme 1.37. Radical-Based Synthesis of (+)-7-Deoxypancratistatin Intermediate

Clearly, the radical cyclization of *N*-aziridinyl imines is a fundamentally new and important approach for the formation of five or six-membered rings.

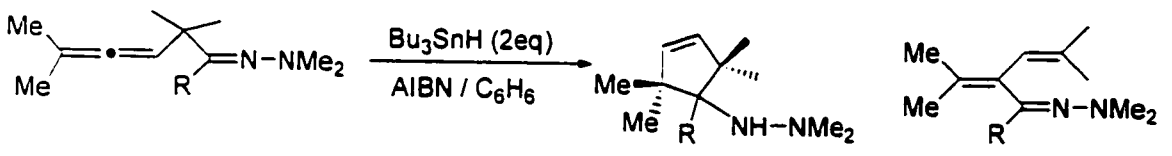
This strategy is limited by the fact that it does not retain the nitrogen functionality as this group present in the starting hydrazone is lost as nitrogen gas. In contrast, diphenylhydrazones are also good acceptors and can be converted easily to amines.

Bowman[48] has shown that 5-*exo* cyclization products were formed when several different hydrazones were used as substrates and no *endo*-cyclized or uncyclized products were detected (Scheme 1.38). The best yields were obtained for **155c** and **155d** in which the α-position of the hydrazone is more electropositive encouraging faster intramolecular addition by the nucleophilic alkyl radicals (Scheme 1.38).



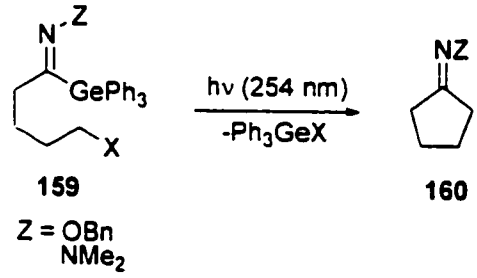
Scheme 1.38. 5-exo Cyclization onto Hydrazones

Hatem showed that β-allenic hydrazones undergo hydrostannylation[49] to afford cyclopentene derivatives **157** or linear rearrangement products **158** (Scheme 1.39) depending on the substitution of the allenic and hydrazone moieties.



Scheme 1.39. β-Allenic Hydrazones Cyclization

Curran and Iserloh[50] have studied the radical cyclizations of halo-, phenylseleno-, and vinylacylgermane hydrazones and oxime ethers (Scheme 1.40). They have also shown that acylgermane hydrazone and oxime ether radicals have cyclization rate constants of about 10^7 s^{-1}.



159

Z = OBn
NMe_2

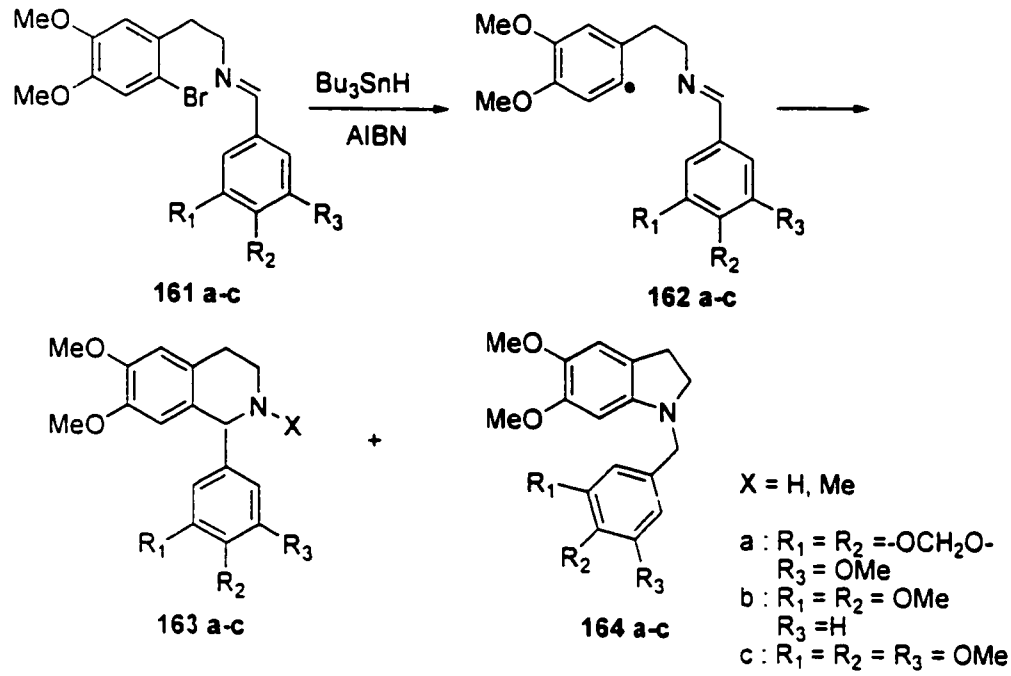
160

Scheme 1.40. Radical Cyclizations of Acylgermane Oxime Ethers and Hydrazones

For the radical cyclizations of acylgermane oxime ethers and hydrazones, a synthetically attractive feature is that cyclization products retain the C = N bond.

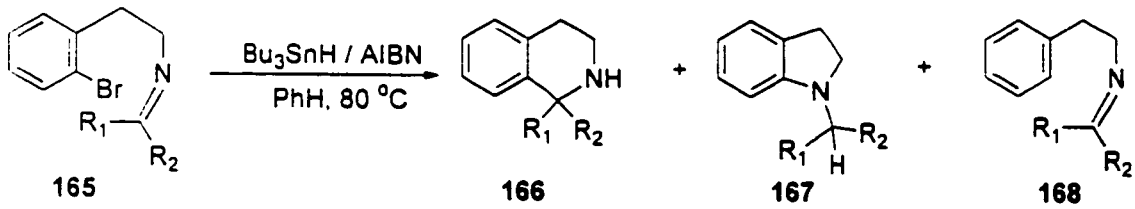
1.4.3 Imine Acceptors

Radical cyclization onto an imine bond was reported[51] by Takano in 1990. The racemic cryptostylines I, II, and III **163 a-c**, found in a family of *Orchidaceae* plants, were synthesized (Scheme 1.41) in 56%, 51.4% and 36.2% yields respectively. Products **164a-c** were formed in minor amounts demonstrating that the 6-*endo* cyclization mode onto the carbon atom of the imine bond was preferred.



Scheme 1.41. Synthesis of Cryptostylines I, II, and III

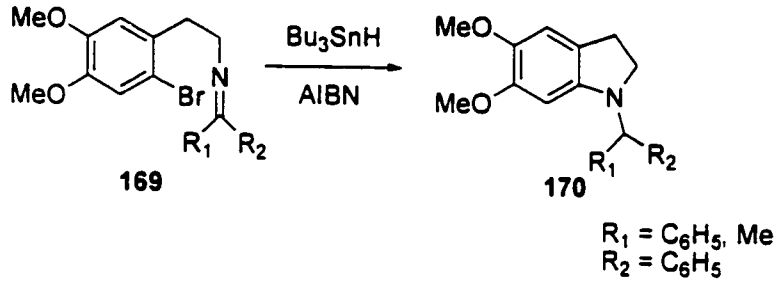
In 1992 Tomaszewski and Warkentin[52] found that there was a large 6-*endo* preference for an aryl radical to cyclize onto an aldimine (Scheme 1.42). The aryl radical can cyclize in either a 6-*endo* or 5-*exo* fashion to give **166** or **167** or can be reduced to **168**.



Scheme 1.42. Aryl Radical Cyclization onto an Aldimine

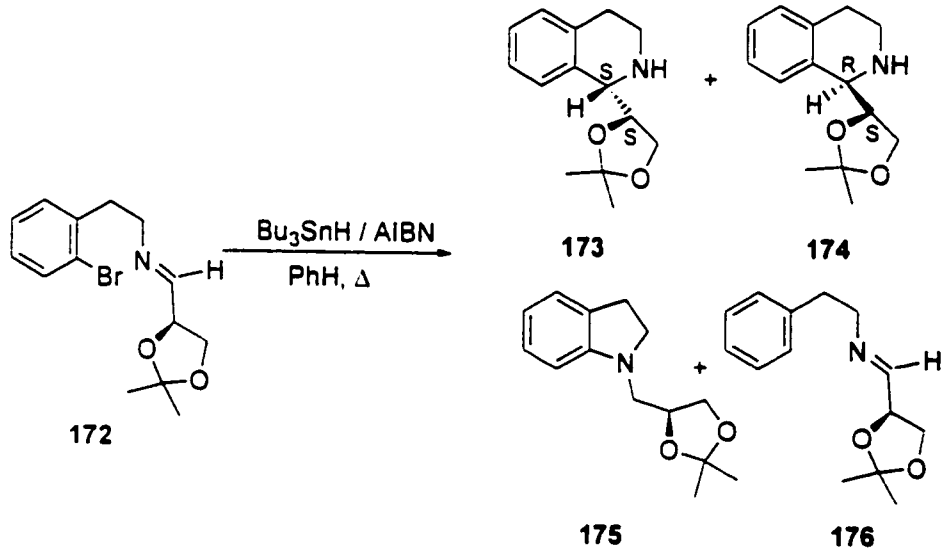
An exception to this general preference[53] involved aryl radical-initiated cyclization of the ketimines derived from acetophenone and benzophenone. These cyclized at the nitrogen end of the azomethine bond *via* an 5-*exo* mode to

yield the corresponding indoline derivatives in 10.5% and 58.7% yield respectively (Scheme 1.43). This is presumably due to the extra substituent on the azomethine bond.



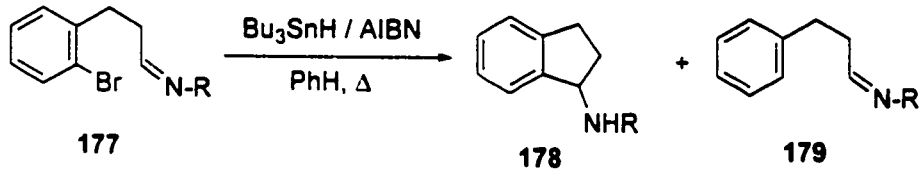
Scheme 1.43. Aryl Radical Cyclization of the Ketimines

Tomaszewski and Warkentin investigated the induction of asymmetry[54] in radical cyclization onto aldimines **172** bearing a chiral center close to the site of the attack (Scheme 1.44). These cyclizations provide four products **173**:**174**:**175**:**176** in the ratios 37:9.8:1:5.7 with 47:1 regioselectivity for 6-*endo* closure over 5-*exo* closure. The diastereomeric isoquinolines **173** and **174** were obtained in the ratio (S, S) / (R, S) = 3.8:1 and in 69% isolated yield.



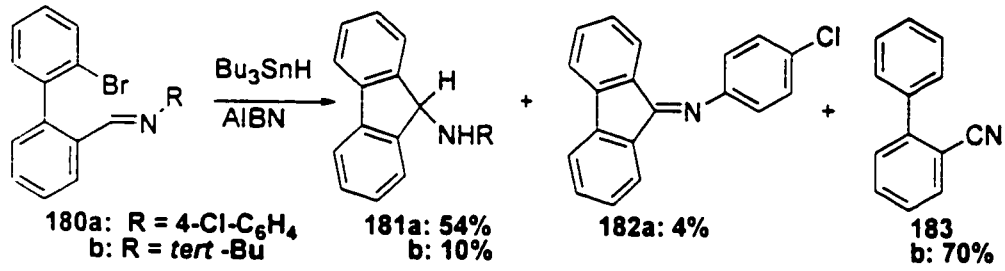
Scheme 1.44. Induction of Asymmetry in Radical Cyclization

The isomeric aldimines **177** cyclized exclusively[55] in a 5-*exo* sense (Scheme 1.45) forming the 1-indanamines **178** in good yields. The rate constant for this process was measured ($k = 3.9x10^8\ s^{-1}$ at 80 °C).



Scheme 1.45. Radical Cyclization onto Aldimines

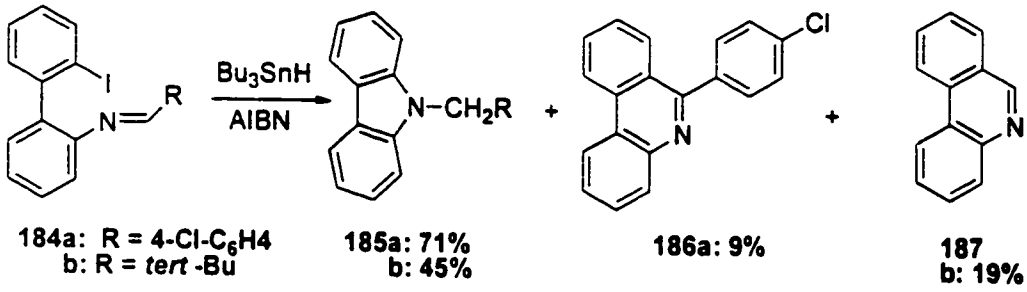
A similar result was obtained by Leardini and his coworkers[56] when imines **180** were allowed to react with tributyltin hydride in boiling benzene (Scheme 1.46).



Scheme 1.46. Radical Cyclization onto Imines

Imine **180a** yielded the 5-*exo* cyclization product predominantly, but under the same reaction conditions imine **180b** formed **183** and only a minor amount of the corresponding cyclization product. The presence of this product was explained by the β-fragmentation of the imidoyl radical resulting from a 1,5-H shift with loss of *t*-butyl radical. This kind of process is a peculiarity of *N*-alkyl substituted imidoyl radicals. [57]

In contrast with the results published by Warkentin *et. al.*, a large 5-*exo* preference was observed for the cyclization of imines **184** (Scheme 1.47).



184a: R = 4-Cl-C_6H_4
b: R = *tert*-Bu

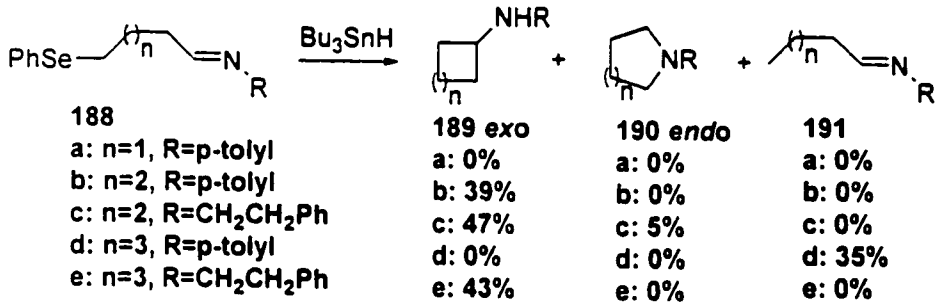
185a: 71%
b: 45%

186a: 9%

187
b: 19%

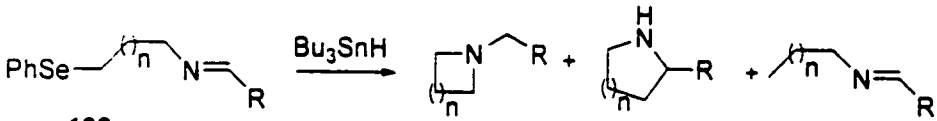
Scheme 1.47. 5-Exo Cyclization of Imines

In 1994 Bowman[58] *et. al.* showed that alkyl radicals can also cyclize onto various imines. Two types of isomeric imines **188** and **192** were used as substrates (Scheme 1.48). Depending on the ring size, stereoelectronic effects, polarization of the imine bond, stability of the resulting radical, varying amounts of *exo*, *endo* and simple reduction products were isolated.



188
a: n=1, R=p-tolyl
b: n=2, R=p-tolyl
c: n=2, R=CH_2CH_2Ph
d: n=3, R=p-tolyl
e: n=3, R=CH_2CH_2Ph

189 *exo*	**190 *endo***	**191**
a: 0%	a: 0%	a: 0%
b: 39%	b: 0%	b: 0%
c: 47%	c: 5%	c: 0%
d: 0%	d: 0%	d: 35%
e: 43%	e: 0%	e: 0%

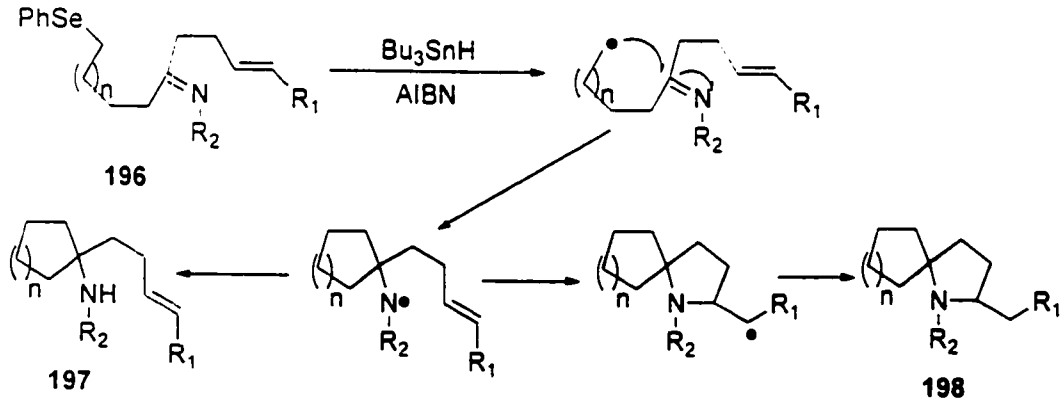


192
a: n=1, R=p-tolyl
b: n=2, R=p-tolyl
c: n=2, R=CH_2CH_2Ph
d: n=3, R=p-tolyl
e: n=3, R=CH_2CH_2Ph

193 *exo*	**194 *endo***	**195**
a: 0%	a: 0%	a: 71%
b: 54%	b:6%	b: 0%
c: 42%	c:18%	c: 0%
d: 7%	d: 0%	d: 40%
e: 0%	e: 0%	e: 39%

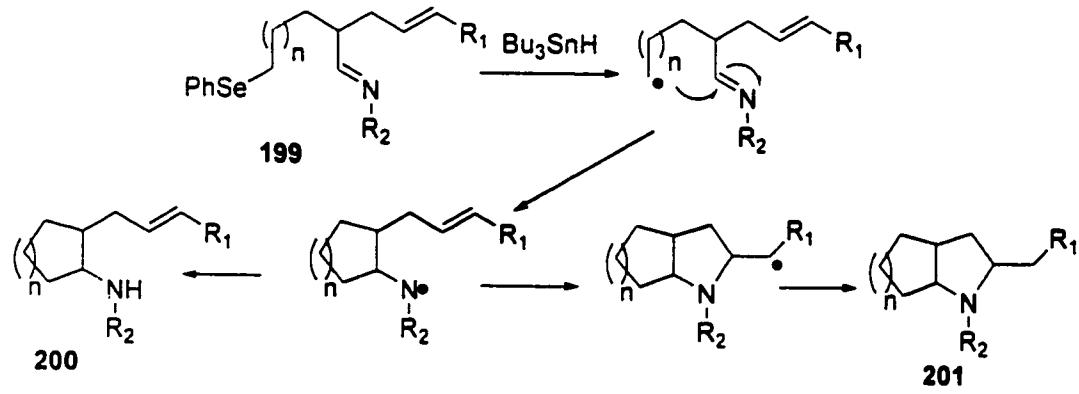
Scheme 1.48. Alkyl Radicals Cyclization onto Imines

Bowman synthesized three types of bicyclic nitrogen heterocycles using this strategy[59] (Scheme 1.49) and several imines were investigated as substrates for this process. However, intermediate radicals gave mainly monocyclic amines **197** with only traces of the tandem products, which reflects the reluctance of aminyls to undergo cyclization when the double bond is not activated. When R_1=Ph the tandem products are formed in moderate yields, with only traces of the monocyclized products. In this case, the use of $MgBr_2$-Et_2O[60] gave dramatically improved tandem yields as spiroamines **198** were isolated without any traces of monocylic products.



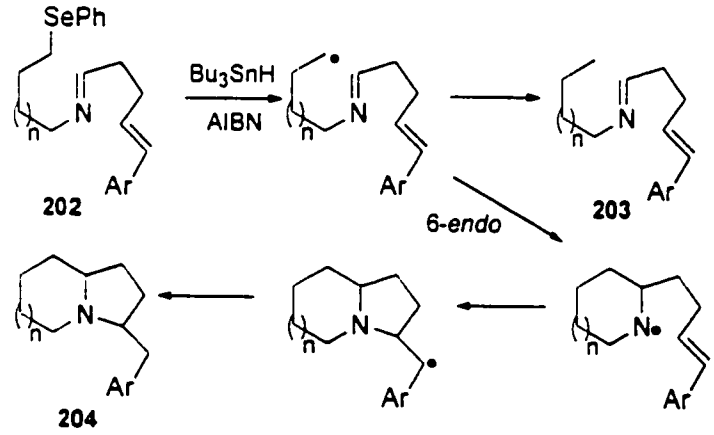
Scheme 1.49. Spiroamines Synthesis via Tandem Reactions

Similar results were obtained when this method was applied to the synthesis of the nitrogen bicycles **201** (Scheme 1.50). The formation of the tandem products is favored when the intermediate aminyl radicals is stabilized (R_2=Ph) and when Lewis acid ($MgBr_2$-Et_2O) is added to the reaction mixture.



Scheme 1.50. Bicyclic Nitrogen Heterocycle Synthesis

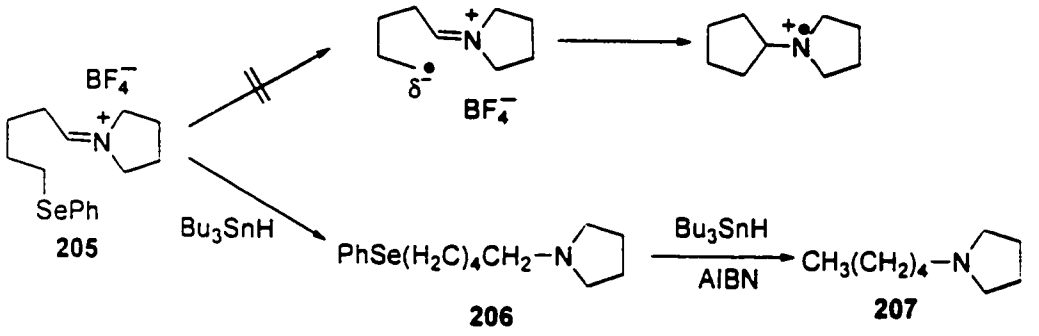
The synthesis of indolizidines and pyrrolizidines was also studied (Scheme 1.51). Imine **202a** (n=1) gave a moderate yield (26%) of the indolizidine **204**. Attempted tandem cyclization of the imine **202b** (n=0) which required an initial 5-*endo* cyclization was unsuccessful and only the reduced product was isolated.



Scheme 1.51. Synthesis of Indolizidines and Pyrrolizidines

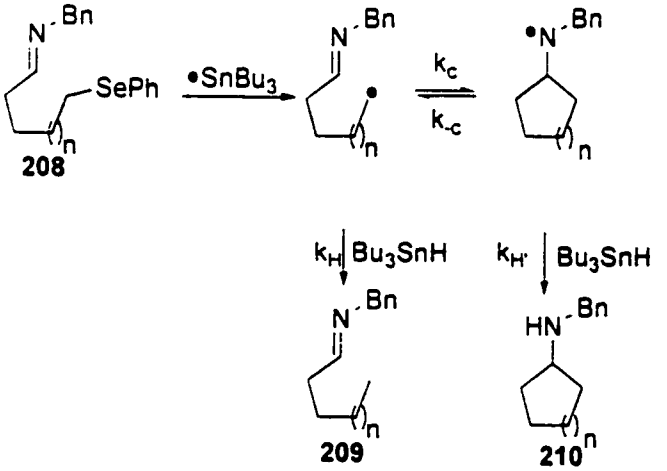
Cyclization onto iminium salts[61] (Scheme 1.52) was investigated as the intermediate aminium cation radical[62] could cyclize rapidly with alkenes for use in synthetic tandem reactions. Reaction between tributyltin hydride and the iminium

salt **205** gave the uncyclized *N*-pentylpyrrolidine **207** (75%) indicating that hydride addition to the iminium ion is faster than radical abstraction of the benzeneselenyl moiety.



Scheme 1.52. Cyclization onto Iminium Salts

The approximate rate constants for 5-*exo* and 6-*exo* cyclizations of alkyl radicals onto imines were determined to be 6.0×10^6 s^{-1} and 6.7×10^5 s^{-1}, respectively (Scheme 1.53).[63] Alkyl radical additions to imines were essentially irreversible and considerably slower than alkyl radical additions to hydrazones (see Section 1.4.3).



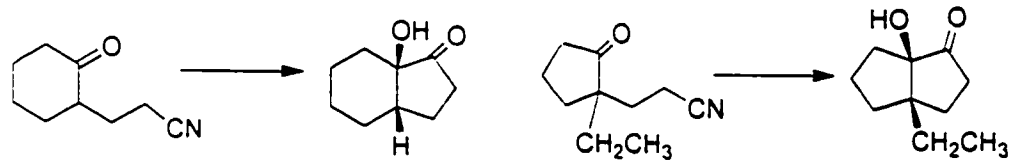
Scheme 1.53. Kinetic Considerations for Cyclization of Alkyl Radicals onto Imines

1.4.4 Nitrile Acceptors

The chemical versatility of the carbonyl group makes cyclic ketones a very common motif in organic synthesis. Radical cyclization onto a nitrile is interesting because it allows the initial formation of a cyclic imine that is subsequently hydrolized to a cyclic ketone.

A number of intramolecular free radical additions to nitriles had been reported[64], although it wasn't until 1979[65] that the rate constant for the irreversible cyclization of the 4 cyanobutyl radical to the cyclopentyiminyl radical was determined ($k=4.0x10^3$ s^{-1} at 25 °C and $k=4.0x10^4$ s^{-1} at 80 °C). For comparison the rate constant for the 5-hexenyl cyclization is $k=1.1x10^5$ at 25 °C and $k=5.5x10^5$ s^{-1} at 80 °C.

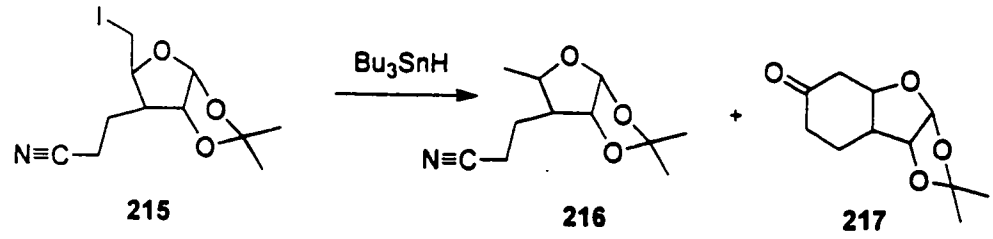
In 1983 Corey[66] reported the use of nitriles (as well as other functionalities) as radical acceptors in an intramolecular cyclization where the ketyl radical is generated from ketones by Zn-TMSCl (Scheme 1.54).



211 212 213 214

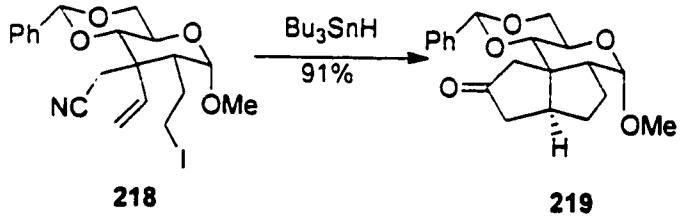
Scheme 1.54. Nitriles as Radical Acceptors in an Intramolecular Cyclization

The major problem associated with the radical cyclization onto a nitrile functionality is the simple reduction of the radical by tributyltin hydride to give the corresponding alkylnitrile. For example, when the radical cyclization of the ω-iodonitrile **215** was attempted[67] by Fraser-Reid *et. al.*, during the synthesis of (+)-Phenyllantocin, the desired product **217** was formed in only 2% yield and the major product was the reduced material **216** (66%).



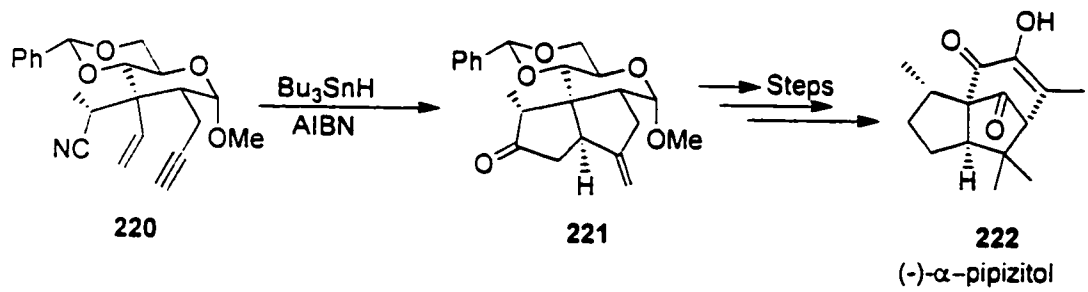
Scheme 1.55. Radical Cyclization as a Key Step Towards the Synthesis of (+)-Phenyllantocin

A much better result was achieved with a different carbohydrate framework in a tandem cyclization involving consecutive 5-*exo* additions[68] (Scheme 1.56).



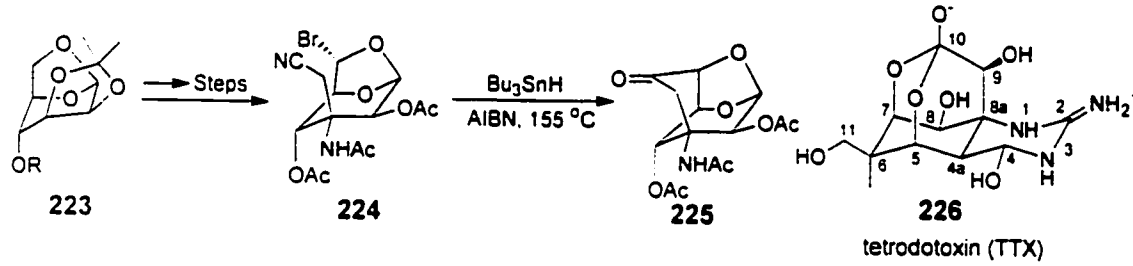
Scheme 1.56. Tandem Cyclization with Nitrile Participation

A related cyclization was employed[69] to achieve the stereospecific synthesis of (-) pipizitol. In this synthesis a key step was the formation of the core (5,5) bicyclic system **221** that became the B and C rings in the natural product **222** (Scheme 1.57).



Scheme 1.57. Stereospecific Synthesis of (-) Pipizitol

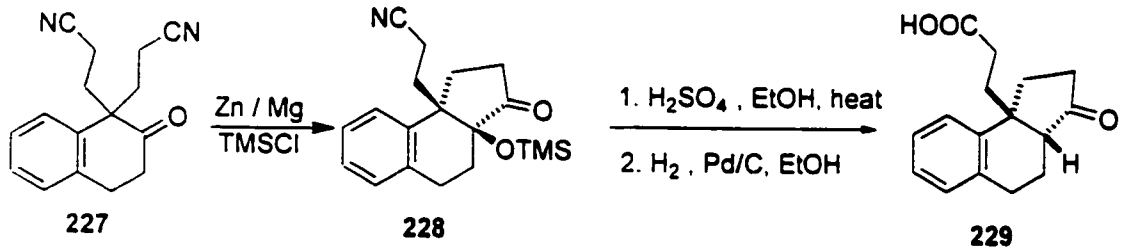
Another interesting example[70] by Fraser-Reid of a radical cyclization onto CN was applied in the total synthesis of the densely functionalized carbocyclic core of tetrodotoxin **226** (Scheme 1.58). The disconnection envisaged the annulated pyranose **225** as an interesting retron for the natural product. This precursor is synthesized over several steps from D-mannosan **223**; the last step in its synthesis is a radical ring closure onto a nitrile **224** in 77% yield.



Scheme 1.58. Radical Ring Closure onto a Nitrile in the Synthesis of the Tetrodotoxin

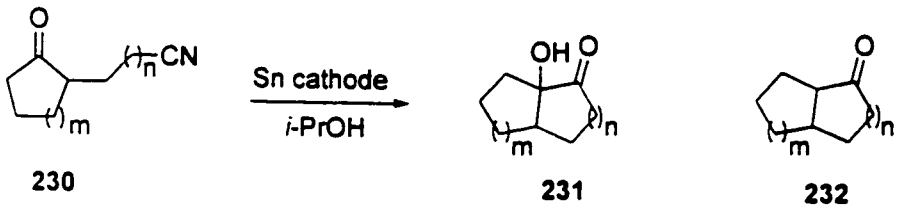
The formation of a six membered ring is facilitated by the rigidity of the 1,6-anhydro template that presents the nitrile to the radical in a highly ordered boatlike transition state.

A very interesting approach was taken[71] by Hegarty and Mann for the synthesis of the skeletons of both Aphidicolin and Stemodin diterpenoids. Corey's procedure for ketyl cyclization onto a nitrile was modified to generate the B-C ring system **228** with the appropriate substitution and stereochemistry (Scheme 1.59).



Scheme 1.59. Synthesis of the Skeletons of Aphidicolin and Stemodin Diterpenoids

The electroreductive intramolecular coupling by Shono and Kise[72] of δ and γ-cyanoketones affords cyclized α-hydroxyketones and the corresponding dehydroxylated ketones (Scheme 1.60).

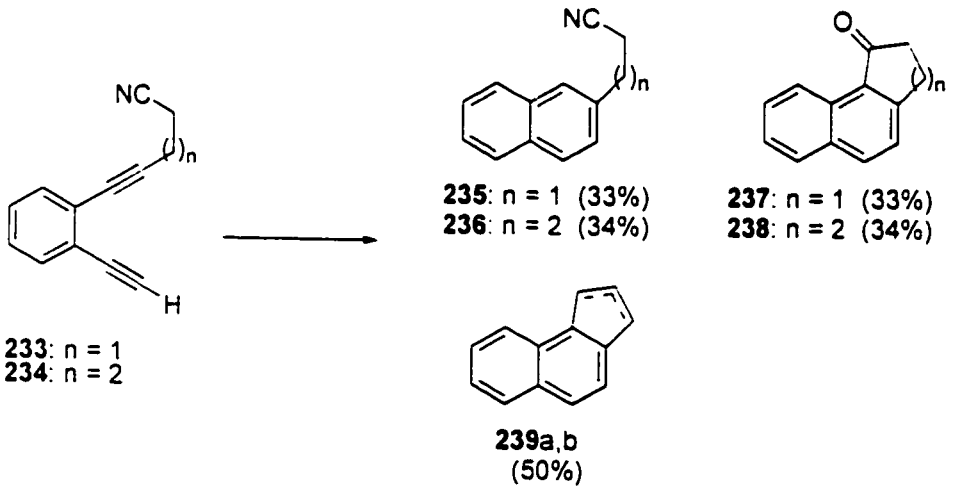


230 231 232

Scheme 1.60. Electroreductive Intramolecular Coupling

Molander and Wolfe[73] have reported the intramolecular ketone-nitrile reductive coupling reactions promoted by samarium(II) iodide. Monocyclic, fused bicyclic, and bridged bicyclic α-hydroxy ketones have been synthesized in moderate to excellent yield *via* this method.

Tandem enediyne-radical cyclizations were carried out by Grissom and coworkers [74] on substrates that contain nitrile radical acceptors (Scheme 1.61).



233: n = 1
234: n = 2

235: n = 1 (33%)
236: n = 2 (34%)

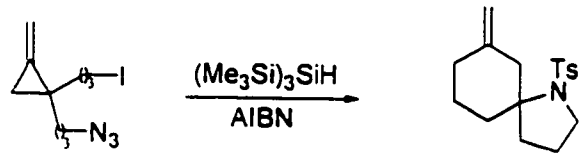
237: n = 1 (33%)
238: n = 2 (34%)

239a,b
(50%)

Scheme 1.61. Tandem Enediyne-Nitrile Radical Cyclizations

1.4.5 Azide Acceptors

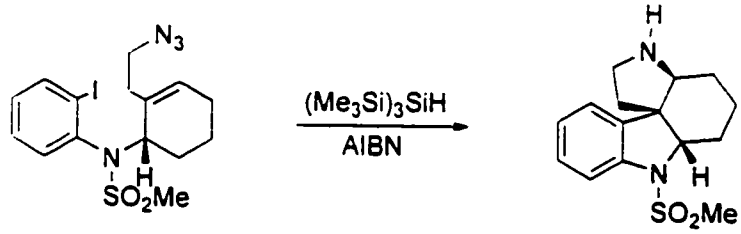
A limited number of reports of azides as radical acceptors have appeared. For example, Kilburn and Santagostino[75] converted the methylene cyclopropane system **240** into a spiro-heterocycle **241** in 53% yield after tosylation, as shown in Scheme 1.62.



240 **241**

Scheme 1.62. Cyclization onto Azide Acceptor

An interesting tandem approach to the pentacyclic ring system of aspidospermine was accomplished by Murphy and coworkers[76] (Scheme 1.63).



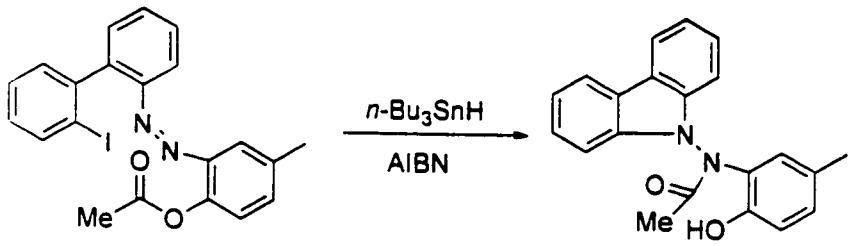
242 **243**

Scheme 1.63. Aspidospermine Ring System Synthesis.

The aryl radical generated from iodide **242** in the presence of tris(trimethylsilyl)silane and AIBN afforded **243** in 95% yield as a single stereoisomer.

1.4.6 Azo Acceptors

An interesting example of a cyclization of an aryl radical onto an azo acceptor was examined by Zanardi, Leardini and coworkers.[77] The phenolic product **245** was generated in 50% yield.



244 **245**

Scheme 1.64. Cyclization onto an Azo Acceptor

Warkentin and coworkers[78] have determined that the rate constants for the 5-*exo* and 6-*endo* cyclizations of aryl radicals onto azo acceptors are 1.5×10^9 s^{-1} and 2.3×10^9 s^{-1} respectively at 82 °C.

Chapter 1 References

1. Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 727.
2. For recent reviews, see: (a) Fossey, J.; Lefort, D.; Sorba, J. In *Free Radicals in Organic Chemistry*; Translated by Lomas, J.; John Wiley & Sons Inc.: New York, **1995**; pp 151 and pp 243. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (d) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* (N.Y.) **1996**, *48*, 301.
3. Neuman, W. P. *Synthesis* **1987**, 665.
4. Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188.
5. Barton, D. H. R.; Parekh, S. I. In *Half a Century of Radical Chemistry*; Cambridge University Press: Cambridge, 1993, pp164.
6. Molander, G. A. In *Organic Reaction*, Vol 46; L. A. Paquette, Ed.; Wiley: New York, **1994**; Vol. 46; pp 211.
7. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
8. (a) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (b) Little, R. D.; Masjedizadeh, M. R.; Moeller, K. D.; Dannecker-Doeih, I. *Synlett* **1992**, 107. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.
9. Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* **1972**, *94*, 9205.
10. Giese, B. *Angew. Chem. Int. Ed. Eng.* **1983**, *22*, 753, and references.
11. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.
12. Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
13. Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. See also Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631.

14. (a) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (b) Naito, T.; Nakagawa, K.; Nakamura, T.; Kasei, A.; Ninomiya, I.; Kiguchi, T. *J. Org. Chem.*, **1999**, *64*, 2003.
15. Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.*, **1998**, *63*, 201.
16. Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253.
17. Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271.
18. Ingall, H. A.; Moore, P. R.; Roberts, S. M. *Tetrahedron Asymmetry* **1994**, *5*, 2155.
19. (a) Yadav, V.; Fallis, A. G.*Tetrahedron Lett.* **1989**, *30*, 3283. (b) Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897.
20. (a) Marco-Contelles, J.; Martinez, L.; Martinez-Gram, A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1992**, *57*, 6437. (b) Marco-Contelles, J.; Martinez-Gram, A.; Bernabe, M.; Martin, N.; Seoane, C. *Synlett* **1991**, 165. (c) Marco Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Gram, A. *J. Org. Chem.* **1992**, *57*, 2625.
21. Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martinez, L.; Martinez-Gram, A. *Tetrahedron Asymmetry* **1991**, *2*, 961.
22. Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabe, M. *J. Org. Chem.* **1995**, *60*, 6010.
23. Knapp, S.; Purandare, A.; Rupitz, K.; Withers, S. G. *J. Am. Chem. Soc.* **1994**, *116*, 7461.
24. Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877.
25. Enholm, E. J.; Burroff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727.
26. Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6559.
27. Pattenden, G.; Schultz, D. J. *Tetrahedron Lett.* **1993**, *34*, 6787.
28. Hollingworth, G. J.; Pattenden, G.; Schuitz, D. J. *Aust. J. Chem.* **1995**, *48*, 381.
29. Hatem, J.; Henriet-Bernard, C.; Grimaldi, J.; Maurin, R. *Tetrahedron Lett.*

1992, *33*, 1057.

30. Depature, M.; Siri, D.; Grimaldi, J.; Hatem, J.; Faure, R. *Tetrahedron Lett.* **1999**, *40*, 4547.
31. Parker, K. A.; Spero, D. M.; Van Epp, J. *J. Org. Chem.* **1988**, *53*, 4628.
32. Pettit, G. R.; Gaddamidi, V.; Cragg, G. M. *J. Nat. Prod.* **1984**, *47*, 1018.
33. Ghosal, S.; Singh, S.; Kumar, Y.; Srivastava, R. S. *Phytochemistry* **1989**, *28*, 611.
34. (a) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (b) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Org. Chem.* **1999**, *64*, 4465.
35. Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.*, **1999**, *121*, 5176.
36. Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624.
37. Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T Naito, T. *J. Org. Chem.* **1998**, *63*, 4397.
38. Kim, S.; Kee, I. S.; Lee, S. *J. Am. Chem. Soc.* **1991**, *113*, 9882.
39. Kim, S. *Pure & Appl. Chem.* **1996**, *68*, 623.
40. Kim, S.; Cho, J. R. *Synlett* **1992**, 629.
41. Kim, S.; Kee, I. S. *Tetrahedron Lett.* **1993**, *34*, 4213.
42. Fallis, A. G.; Sturino, C. F. *J. Am. Chem. Soc.* **1994**, *116*, 7447.
43. Fallis, A. G.; Sturino, C. F. *J. Org. Chem.* **1994**, *59*, 6514.
44. Kim, S.; Cheong, J. H.; Yoon, K. S. *Tetrahedron Lett.* **1995**, *36*, 6069.
45. Lee, H.-Y.; Kim, D.-I.; Kim, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1539.
46. Lee, H.-Y.; Lee, S; Kim, D.; Kim, B. K.; Bahn, J. S.; Kim, S. *Tetrahedron Lett.* **1998**, *39*, 7713.
47. Keck, G. E.; Wager, T. E.; McHardy, S. F. *J. Org. Chem.* **1998**, *63*, 9164.
48. Bowman, W. R.; Stepheson, P. T.; Terett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369.

49. Bernard-Henriet, C. D.; Grimaldi, J. R.; Hatem, J. M. *Tetrahedron Lett.* **1994**, *35*, 3699.

50. Curran, D. P.; Iserloh, U. *J. Org. Chem.* **1998**, *63*, 4711.

51. Takano, S.; Suzuki, M.; Kijima, A.; Oasawara, K. *Chemistry Lett.* **1990**, 315.

52. Tomaszewski, M. T.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123.

53. Takano, S.; Suzuki, M.; Oasawara, K. *Heterocycles* **1994**, *37*, 149.

54. Tomaszewski, M. T.; Warkentin, J. *J. Chem. Soc., Chem. Commun.* **1993**, 966.

55. Tomaszewski, M. T.; Warkentin, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1407.

56. Gioanola, M.; Leardini, R.; Nanni, D., Pareschi, P.; Zanardi, G. *Tetrahedron* **1995**, *51*, 2039.

57. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765 and references cited therein.

58. Bowman, W. R., Stepheson, P. T.; Terett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369.

59. Bowman, W. R., Stepheson; Young, A. R. *Tetrahedron Lett.* **1995**, *36*, 5623.

60. Maxwell, B. J.; Tsanaksidis, J.*J. Chem. Soc., Chem. Commun.* **1994**, 533.

61. Bowman, W. R., Stepheson, P. T.; Terett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959.

62. Esker, J. L.; Newcomb, M. *Adv. Het. Chem.* **1993**, *58*, 1.

63. Kim, S.; Yoon, K. S.; Kim, Y. S. *Tetrahedron* **1997**, *53*, 73.

64. (a) Ogibin, Y. N.; Troyanskii, E. I.; Nikishin, G. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1975**, 1461. (b) Ogibin, Y. N.; Troyanskii, E. I.; Nikishin, G. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 843. (c) Hawthorne, D. G ; Jonhs, S. R.; Soloman, D. H.; Wiling, R. I. *J. Chem. Soc., Chem. Commun.* **1975**, 982. (d) Hawthorne, D. G.; Jonhs, S. R.; Soloman, D. H.; Wiling, R. I. *Aust. J. Chem.* **1976**, *29*, 315. (e) Roberts, B. P.; Winter, J. N.

J. Chem. Soc., Perkin Trans. 2 **1979**, 1353.

65. Griller, D.; Schmid, P.; Ingold, K. U. *Can. J. Chem.* **1979**, *57*, 831.
66. Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821.
67. Yeung, B. W. A.; Contelles, J. L. M.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1989,** 1160.
68. Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116.
69. Pak, H.; Canalda, I. I.; Fraser-Reid, B. *J. Org. Chem.* **1990**, *55*, 3009.
70. Alonso, R. A.; Burgey, C. S.; Rao, B. V.; Vite, G. D.; Vollerthun, R.; Zottola, M. A.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1993**, *115*, 6666.
71. Hegarty, P.; Mann, J. *Tetrahedron* **1995**, *51*, 9079.
72. Shono, T.; Kise, N. *Tetrahedron Lett.* **1990**, *31*, 1303.
73. Molander, G. A.; Wolfe, C. N. *J. Org. Chem.* **1998**, *63*, 9031.
74. Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876.
75. Santagostiono, M.; Kilburn, J. D. *Tetrahedron Lett.* **1995**, *36*, 1365.
76. (a) Kizil, M., Murphy J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409. (b) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy J. A. *Tetrahedron Lett.* **1999**, *40*, 161.
77. Leardini, R.; Lucarini, M.; Nanni, A.; Nanni, D.; Pedulli, G. F.;Tundo, A.; Zanardi, G. *J. Org. Chem.* **1993**, *58*, 2419.
78. Beckwith, A. L. J.; Wang, S.; Warkentin, J. *J. Am. Chem. Soc.* **1987**, *109*, 5289.

Chapter 2

Tandem Alkyl and Aminyl Radical Carbonylation - Radical Cyclization onto *N,N*-Diphenylhydrazones

2.1 Introduction

Free radical-mediated cyclizations have become a preeminent method for preparing diverse cyclic compounds. Most radical cyclizations employ methods utilizing conventional radical acceptors such as alkenes with typical radical precursors such as halides, selenides, and xanthates. One drawback in the traditional procedures using such radical acceptors and precursors is the loss of two inherent functional groups.

Solutions for this problem include α-heteroatom radical intermediates[1] and atom transfer reactions that place functional groups in predetermined positions.[2]

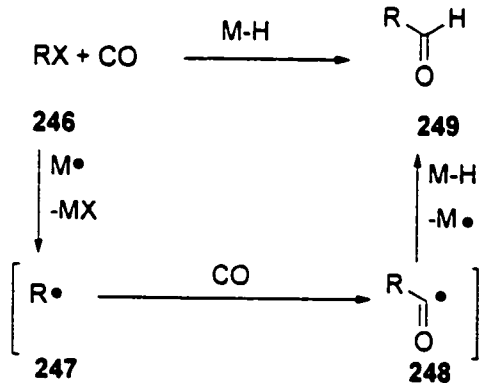
Alternatively, it is possible to have a heteroatom present in the addition terminus. As shown in Chapter 1, this usually leads to improved efficiency and retains useful functionality in the product.

Tandem radical reactions provide an elegant way to produce complex molecules in a radical process.[3] Indeed, radical reactions are ideally suited for sequencing since the product of every radical molecule with itself or with another closed shell molecule is a radical. This product radical then becomes the precursor for the subsequent step in a sequence of reactions. The major challenge in designing tandem radical reactions is one of selectivity.[4] The fate of individual radicals in a sequence must be strictly controlled. The short life time of radicals makes this especially challenging since the sequential addition of reagents to a reaction is generally not possible.

2.2 Free-Radical Carbonylation

The first free-radical carbonylation was reported almost half a century ago when Coffman *et al.* suggested the intermediacy of acyl radicals in the formation of polyketones by peroxide-initiated copolymerization.[5] Four years later, Foster *et al.* reported that the peroxide-initiated reaction of mercaptans with ethylene and carbon monoxide under 3000 atm at 130 °C gave 3-(alkylthio)propanal in 11-18% yields.[6] This reaction is noteworthy as a pioneering effort to effect trapping of acyl radicals by hydrogen abstraction, but the results were of limited utility because of the extremely high pressures of carbon monoxide required and the low yields of carbonylated products. Alternative ways for the generation of acyl radicals were developed in the following years, and these include hydrogen abstraction from aldehydes,[7] photochemical degradation with Norrish type I cleavage,[8] decomposition of acylmetals,[9] reaction of acyl chlorides with trialkyl tin hydrides,[10] radical addition to α-diketones and degradation,[11] and reaction of acyl selenides with trialkyl tin hydrides.[12]

In 1990, the efficient trapping of carbon monoxide by a variety of carbon radicals in a radical chain was demonstrated by Ryu et al.[13] Free-radical carbonylation was used for the introduction of a carbonyl group into organic molecules as shown in Scheme 2.1.



Scheme 2.1. Free Radical Carbonylation of Alkyl Halides

In this AIBN-induced radical reaction mediated by tributyltin hydride, an alkyl radical **247**, generated from an alkyl bromide or iodide **246** *via* abstraction of halogen by a tin radical, adds efficiently to carbon monoxide to form an acyl radical **248**. Subsequent hydrogen abstraction by the acyl radical from tin hydride produces an aldehyde **249** and at the same time regenerates the tin radical. Primary, secondary and tertiary alkyl radicals can be efficiently carbonylated by the tin hydride/carbon monoxide system to furnish one-carbon homologated aldehydes. These radical formylations are generally performed at substrate concentrations of 0.01-0.05 M with 70-90 atm of carbon monoxide at 80 °C for 2-4 hours. The reaction apparatus is an autoclave and AIBN is used as a radical initiator.

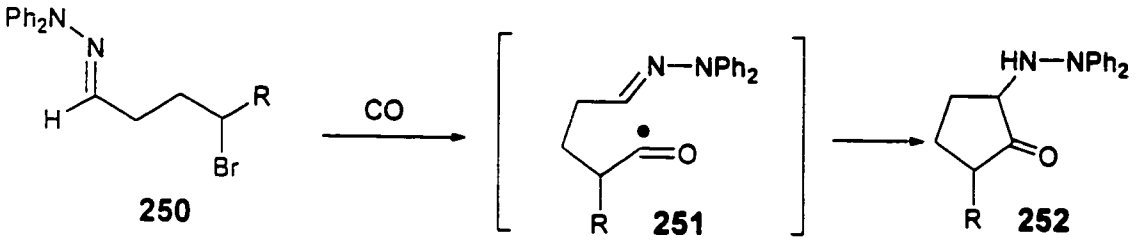
Aromatic or vinyl iodides can also be formylated to give the corresponding aldehydes.[14] Tris(trimethylsilyl)silane[15] (TTMSS) and triorganogermanes[16] can be used in place of tin hydride in the formylation reactions. These reagents are poorer hydrogen donors, so the formylation reaction proceeds at lower carbon monoxide pressures.

The inter- and intramolecular addition behavior of acyl radicals has been largely elucidated in the past decade.[17] In addition, the rate of decarbonylation can be obtained from the data reported by Chatgilialoglu and co-workers.[18]

2.3 Research Objectives

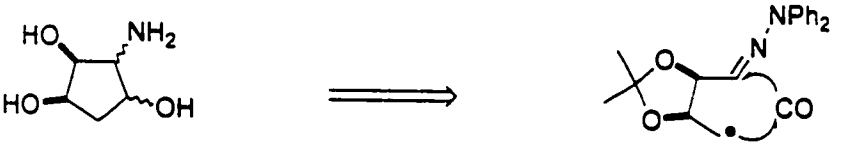
Stimulated by our own interest in understanding and expanding the scope of the radical cyclization onto hydrazones, coupled with the knowledge that free radical carbonylation is possible when the competing reaction of the alkyl radical is sluggish, a study was initiated to determine the feasibility of the tandem carbonylation – cyclization onto *N,N*-diphenylhydrazones. The proposed tandem process is outlined below in Scheme 2.2.

The alkyl radical generated from suitable alkyl halides **250** should be trapped by carbon monoxide. The resulting acyl radical **251** would then undergo a 5-*exo* radical cyclization onto the *N,N*-diphenylhydrazone bond. Subsequent cleavage of the hydrazine bond should provide cyclic α-amino ketones.



Scheme 2.2. Carbon Monoxide Trapping And Cyclization Onto Hydrazones

The utility of this method would be further expanded by the selective reduction of the ketone, leading to β-amino alcohols. Many of these are known as potential glycosidase and chitinase inhibitors.[19] Scheme 2.3 below depicts a potential route to a stereoselective synthesis of β-amino alcohols, which takes advantage of the tandem carbonylation-cyclization sequence followed by selective reduction.



253
β-Amino Alcohols
Glycosidase and Chitinase Inhibitors

254

Scheme 2.3. Retrosynthetic Analysis of β-Amino Alcohols

2.4 Kinetic Considerations

Kinetic information accumulated during the tin hydride mediated free radical formylation studies is useful to help design tandem radical reactions involving carbon monoxide. It has been demonstrated that high carbon monoxide pressures (concentrations) are necessary for efficient carbonylation. Otherwise, premature reduction of carbon radicals by tin hydride prior to carbon monoxide trapping, accompanied by decarbonylation (back reaction) of acyl radicals occurs. Kinetic data establish the relative efficiency of carbon radicals toward carbonylation. This efficiency depends largely on the structure of the starting radicals. For example, compared to primary and secondary alkyl radicals, higher carbon monoxide pressures are required for the carbonylation of sp^2 radicals such as phenyl and vinyl radicals. This is true even though the back reaction from the resulting acyl radicals is expected to be slow, judging from the strength of the newly formed sp^2 C-C bond and the instability of sp^2 radicals. The need for higher carbon monoxide pressures can be ascribed to the very rapid rate of hydrogen abstraction by sp^2 radicals.[20] The decarbonylation rate is in the order of primary acyl < secondary acyl < tertiary acyl < phenylacetyl.[21] This order explains why a primary radical can be carbonylated efficiently even at relatively low carbon monoxide pressures,[22] but carbonylation of benzyl radicals is difficult to achieve. In addition to benzyl radicals, carbon radicals substituted by other radical stabilizing groups (for example, cyano, carbonyl, vinyl, and alkoxy groups) do not add to carbon monoxide to a synthetically meaningful extent. Although the absolute rate constants for decarbonylation reactions of acyl radicals to give these stable radicals are not always available, rapid decarbonylation is probably the dominant factor causing these unsuccessful carbonylations. Some useful guidelines can be established to aid the design of efficient tandem radical reactions of carbon monoxide:

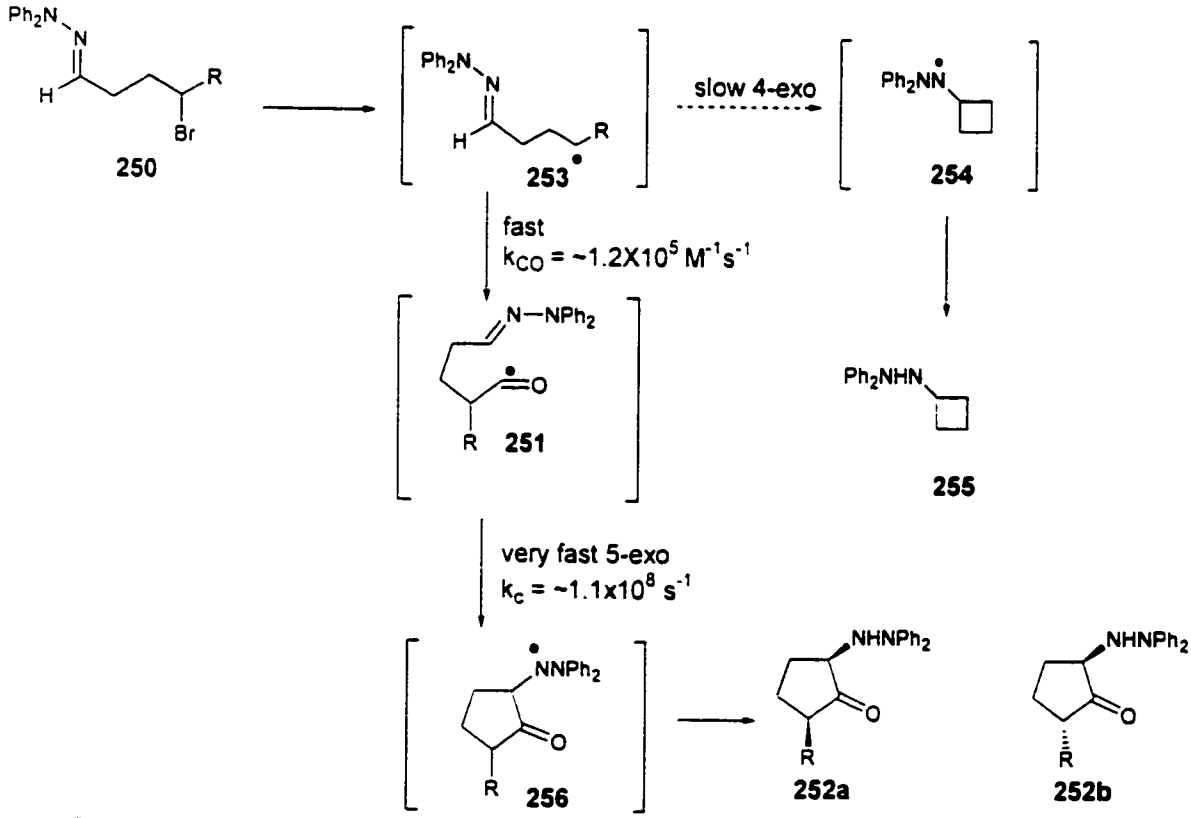
(i) The key radicals capable of adding to carbon monoxide should be alkyl, aryl, and vinyl.

(ii) Alkyl radicals should not have a radical-stabilizing substituent.

(iii) The product acyl radicals should be trapped rapidly by a subsequent C-C bond-forming reaction to lead to more stable radicals that are not prone to carbonylation.

(iv) The resulting radicals can be terminated by hydrogen atom abstraction or participate in additional C-C bond-forming reactions.

In principle, as shown in Scheme 2.4, if an alkyl radical **253** is generated from a corresponding alkyl bromide **250**, it should be possible to trap the radical with carbon monoxide prior to the 4-*exo* cyclization. The acyl radical **251** can then add to the hydrazone functionality in a very fast 5-*exo* cyclization to form the cyclic ketone **252**.



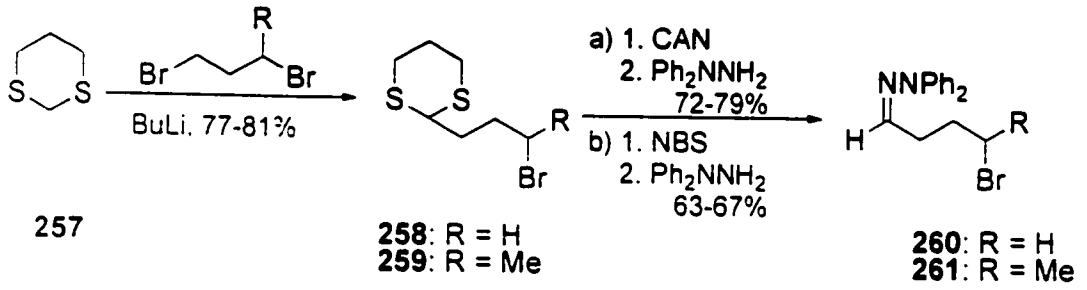
Scheme 2.4. Kinetic Considerations for the Tandem Carbonylation-Cyclization Reaction

It should be noted that the actual value for the rate constant for the carbonylation step was not available at the inception of this project. It has now been measured (k_{CO} = ~$1.2X10^5$ $M^{-1}s^{-1}$).[22a]

2.5 Substrate Synthesis

We devised two different approaches for the synthesis of the carbonylation reaction substrates.

Initially, in order to test the feasibility of the proposal, a couple of bromo-hydrazones were prepared in a very straightforward manner starting with dithiane **257** (Scheme 2.5).



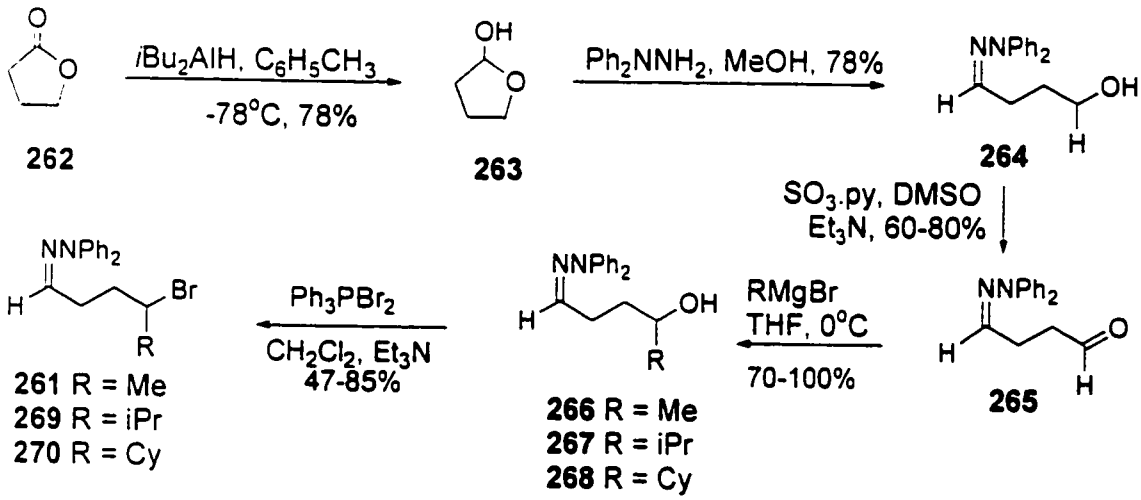
Scheme 2.5. Preparation of the Carbonylation Substrates

Dithiane **257** was subjected to deprotonation by *n*-buthyllithium at –10 °C. Displacement of the primary bromide of 1,3–dibromopropane or 1,4-dibromopentane by the resulting anion provided compound **258** in 77% and **259** in 81% yield. Hydrolysis of dithianes **258** and **259** was effected initially by treatment with NBS/H_2O/CH_3CN,[23] and the resulting aldehydes were condensed *in situ* with *N,N*-diphenylhydrazine to afford bromo-hydrazones **260** and **261** in 63% and 67% yields respectively. Higher yields of bromo-hydrazones **260** (72%)

and **261** (79%) were obtained when cerium ammonium nitrate (CAN)[24] was employed for the dithiane hydrolysis.

As previously observed[25], a key spectral feature of *N,N*-diphenylhydrazones is represented by the ^{1}H NMR signal the vinylic hydrogen (R_2N-N=C<u>H</u>CH_2R). This signal appears as a clean triplet at δ 6.59 (J = 4.7 Hz) in the ^{1}H NMR spectrum for the 4-bromobutenal-*N,N*-diphenylhydrazone **260** and at δ 6.55 (J = 4.7 Hz) for the 4-bromopentanal-*N,N*-diphenylhydrazone **261**. It can be deduced from the spectral data that a single geometric isomer resulted from the condensation of the intermediate aldehyde with *N,N*-diphenylhydrazine. Hydrazones are formed predominantly as the *E* geometric isomer.[26] Thus compound **260** was assigned as the *E* hydrazone (with the Ph_2N substituent *syn* to the hydrogen).

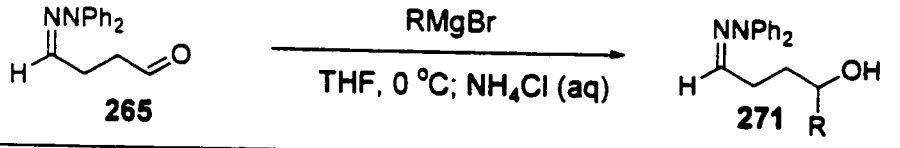
The synthetic pathway to substrates for the carbonylation experiments outlined above is simple and straightforward, but is limited by the commercial availability of the necessary dibromides. A more general method for the synthesis of hydrazones with various R groups was developed as follows (Scheme 2.6).



Scheme 2.6. General Route to Halo-Hydrazones

The synthesis of hydrazones **269** and **270** commenced with reduction of the commercially available γ-butyrolactone **262** in toluene at –78 °C to give the corresponding lactol **263** in 78% yield. Treatment of the γ-butyrolactol **263** with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature provided the *N,N*-diphenylhydrazone **264** in 78% yield. In this case, as with the other two hydrazones reported above, only a single geometric isomer was isolated from the reaction. The alcohol was oxidized to aldehyde **265**. Addition of Grignard reagents to aldehyde **265** generates the corresponding secondary alcohols.

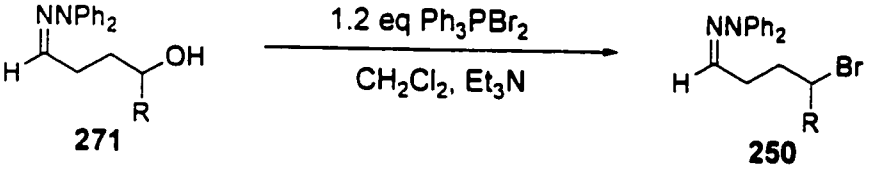
The addition of various Grignard reagents to the aldehyde functionality proceeded cleanly without any observed competitive addition to the hydrazone functionality, provided the reaction was conducted in THF. The chemospecificity of this reaction can be discerned by analysis of the ^{1}H NMR spectrum, as the signal for the vinyl hydrogen of the hydrazone remained in the spectrum of the product, while the aldehyde signal disappeared. The reactions were conducted THF (enough to make a 0.1–0.3 M solution) in a flame dried, round bottom flask maintained at 0 °C under argon. The required Grignard reagent (1-1.1 eq.) was added and the reaction was stirred at 0 °C until the starting material was consumed (typically 30 minutes, by TLC). The reaction was quenched with saturated ammonium chloride. Purification and spectral analysis of the reaction mixture confirmed the formation of the desired secondary alcohols. These results are summarized in Table 2.1.



Entry	Grignard	Alcohol	Yield (%)
1	MeMgCl	**266**	93
2	*i*PrMgCl	**267**	100
3	CyMgCl	**268**	87

Table 2.1. Chemoselective Grignard Addition to Aldehyde 265

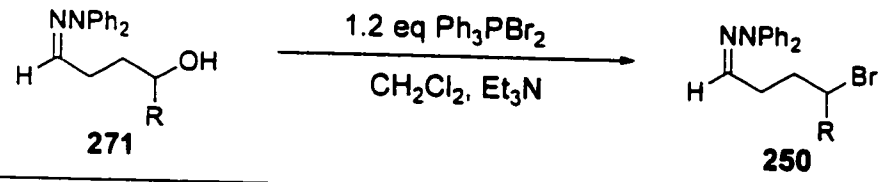
The last step required for the preparation of starting materials was the conversion of the secondary alcohols to bromides. The bromination was effected by $Ph_3P{\bullet}Br_2$,[27] as illustrated in Scheme 2.7 below.



Scheme 2.7. Bromination of the Hydroxy-Hydrazone Substrates

The use of triethylamine was found to be absolutely necessary for the formation of the desired bromohydrazones in high yields. Presumably, its role is to protect the hydrazone functionality from the hydrobromic acid released during the course of the bromination.

The yields for the conversion of the alcohols into the corresponding bromides are generally good, as summarized in Table 2.2 below.



Entry	R	Bromide	Yield (%)
1	H	**260**	73
2	Me	**261**	71
3	*i*Pr	**260**	47
4	Cy	**270**	67

Table 2.2. Bromination of the Primary and Secondary Alcohols

As can be observed from the above table, the yield decreases as the steric bulk of the substituent increases. Bromination of secondary alcohols containing a larger isopropyl or cyclohexyl substituent resulted in alkene formation. Attempts to alter the reaction conditions or use of alternative reagents did not change the relative yields.

2.6 Tandem Alkyl Radical Carbonylation-Cyclization onto *N,N*-diphenylhydrazones

With the bromo-hydrazones in hand, the tandem carbonylation-cyclization reactions under radical conditions were investigated.

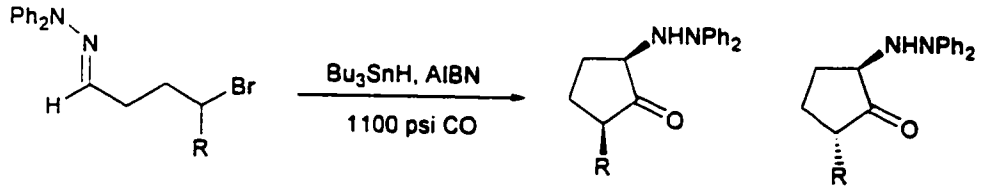
In these experiments, the starting hydrazone (0.5-0.6 mmol) dissolved in benzene (enough to make a 0.05 M solution, with respect to the hydrazone), AIBN (5-10 mol %) and tributyltin hydride (1.2 eq.) were added to a dry glass

tube inserted into a stainless steel autoclave (50 mL). The system was flushed three times, then pressurized with carbon monoxide. The reaction mixture was stirred under carbon monoxide pressure (usually 800-1100 psi) at 80 °C for five hours. The autoclave was cooled to room temperature and, after the release of excess carbon monoxide, benzene was removed under reduced pressure.

The ratio of stereoisomers was determined from the crude NMR data, thus it was necessary to separate the organostannane residue from the reaction mixture efficiently. There are several methods to address this problem, including partitioning between polar solvents such as acetonitrile or wet methanol and pentane[28] or treatment with 1,5-diazabicycloundecene followed by titration with iodine.[29] We discovered that dissolving the reaction mixture in diethyl ether and stirring it vigorously at room temperature for half an hour with a saturated aqueous solution of potassium fluoride[30] removes most of the organostannane residue.

Following this step, filtration, extraction with diethyl ether, drying on magnesium sulphate and concentration gave a crude mixture which was analyzed by ^{1}H NMR spectroscopy to determine the *cis*/*trans* ratios. This was followed by flash chromatography to separate the *cis*/*trans* isomers.

The results of the carbon monoxide trapping-cyclization studies are summarized in Table 2.3 below.



Entry	Substrate	R	Product	Yield (%)	Ratio *cis*/*trans*
1	**260**	H	**275**	69	-
2	**261**	Me	**276**	75	1:1
3	**269**	*i*Pr	**277**	71	1:1.1
4	**270**	Cy	**278**	67	1:1.2

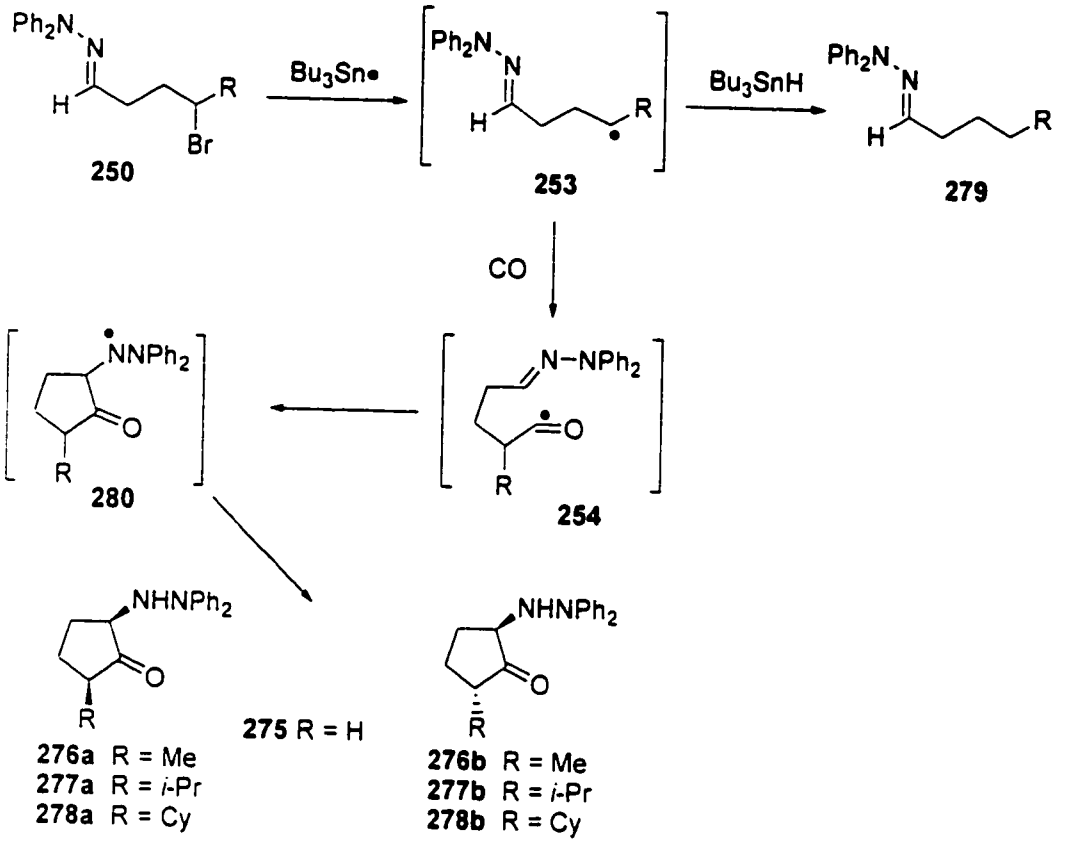
Table 2.3. Tandem Radical Carbonylation-Cyclization Results

As seen from the above table, the desired α-hydrazino ketones were produced in reasonable yields but with a disappointing level of stereoselectivity. Increasing the bulk of the R substituent favoured slightly the formation of the *trans* isomer. The *cis*/*trans* isomers can be separated readily by flash chromatography on silica gel.

In addition to the ketone products, 10-12% of reduced alkylhydrazone substrates were also isolated. Similar products were observed previously during carbon monoxide-trapping studies of cyclizations onto alkenes.[31] However, there was no evidence of any aldehyde that would have arisen from direct quenching of the intermediate acyl radical.

The products arise, presumably, from the pathway illustrated in Scheme 2.8. Abstraction of the bromide by the tributyltin radical ($Bu_3Sn\bullet$) generates the initial radical **253**, which adds to the carbon monoxide to provide the acyl radical **254**. This undergoes a 5-*exo* cyclization onto either face of the C=N double bond of the hydrazone to generate the radicals **280a**, where the R and the hydrazine substituents can be *cis* or *trans* to each other. Hydrogen transfer then forms the final products and regenerates the tributyltin radical to continue the chain.

Alternatively, the initial radical **253** can be reduced by tributyltin hydride to form reduced alkylhydrazone **279**.



Scheme 2.8. Mechanism for the Tandem Carbonylation-Cyclization Reaction

As would be expected, the alkylhydrazones **279** are formed in higher amounts at lower carbon monoxide pressure. The stereoselectivity of the formation of cyclic ketones was not altered significantly upon varying the pressure from 800-1100 psi.

The diastereoselectivity could be determined by examination of the ^{1}H NMR spectra, although the relative stereochemistries (i. e. *cis* or *trans*) were established by analyzing the ^{13}C NMR of the products.

As has been observed previously, the ^{13}C NMR resonances for both methine carbons in the *cis* isomer appeared at higher field than those for the *trans* isomer.[32] In order to be able to use this technique for the assignment of the relative stereochemistry, it is essential to have both isomers for comparison of the chemical shifts. Tandem carbonylation-cyclization gave an equimolar mixture of readily separable diastereomers, thus we were able to measure the ^{13}C NMR spectra of both. Figure 2.1 lists the key ^{13}C NMR signals that were used to assign the relative stereochemistry of the methyl substituted isomers.

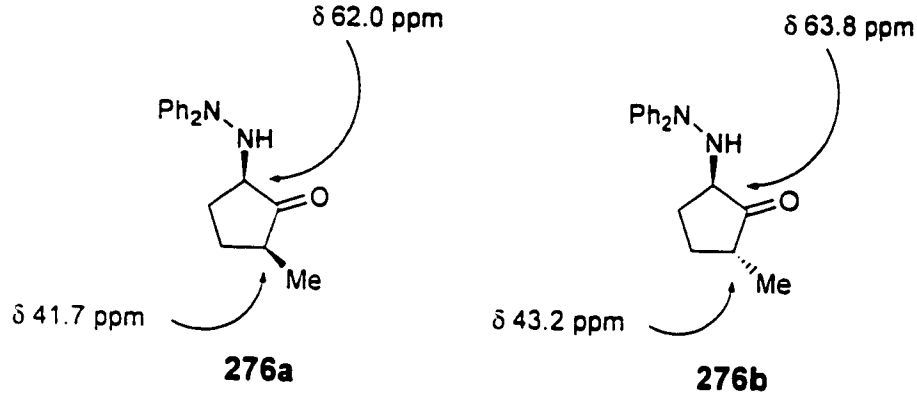
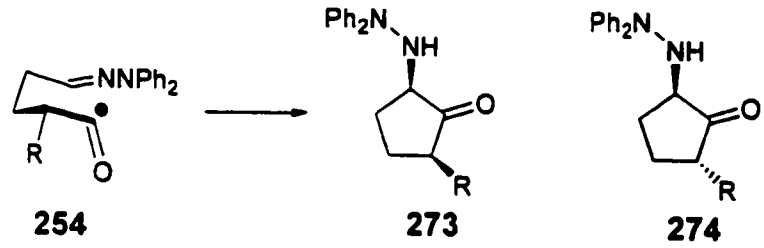


Figure 2.1. Assignment of Stereochemistry

The relative stereochemistry of the other products were determined in a similar fashion and for the cyclohexyl and isopropyl substituted isomers the major product from the cyclization was assigned as the *trans* isomer.

The formation of the major *trans* isomer could be predicted based on the Beckwith-Houk model (Scheme 2.9). For 2-substituted hexenyl radical-type systems it has been known that smaller substituents exhibit almost no selectivity,[33] whereas large alkyl or aryl substituents give increased selectivities.[34]



254 273 274

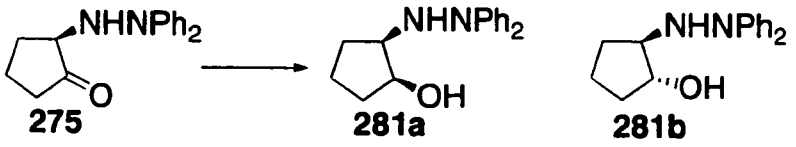
Scheme 2.9. Chair Transition State Diagram

The selectivity was increased at lower temperatures, depending on the type of the system studied.

2.7 Carbonyl Reduction

In view of the current interest in the synthesis of β-amino alcohols as potential glycosidase and chitinase inhibitors,[35] a series of carbonyl reductions to prepare the corresponding hydrazino-alcohols were performed.

As tabulated (Table 2.4), a series of common reduction reagents were employed for the reduction of the carbonyl group in ketone **275**. The reduction reactions proceeded generally in good to very good yields.



275 **281a** **281b**

Entry	Reagent	Product	Yield,[a] %	Ratio cis/trans[b]
1	$(i\text{-Bu})_2AlH$	**281a/281b**	87%	3:1
2	$Zn(BH_4)_2$	**281a/281b**	75%	2:1
3	$LiAlH_4$	**281a/281b**	72%	2.5:1
4	**$LiB(s\text{-}Bu_3)H$**	**281a/281b**	**93%**	**1:0**
5	H_2/PtO_2	**281a/281b**	82%	1:3
6	**$H_2/(Ph_3P)_3RuCl_2$**	**281a/281b**	**72%**	**0:1**

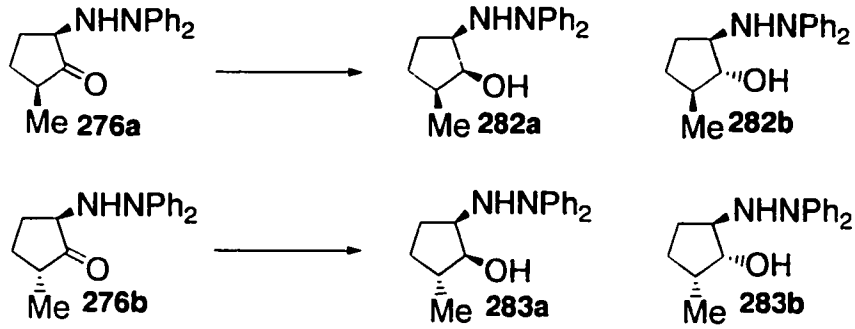
[a]Yields are for isolated chromatographically homogeneous material.
[b]Ratios were determined from ^1H NMR analysis of total product mixture.

Table 2.4. Reduction of the Carbonyl Group

Most reductions of carbonyl compounds are done with reagents that transfer a hydride from boron or aluminum and the numerous reagents of this type that are available provide a considerable degree of selectivity and stereochemical control.[36] As can be seen from Table 2.4, alkylated aluminium and borohydrides give the highest level of diastereocontrol in this reaction (compare entries 1 and 3 and 2 and 4). These reagents are more bulky than the parent hydrides and therefore are more stereoselective in situations where steric factors are important.[37] In these cases, the nucleophilic transfer of hydride to the carbonyl group takes place under steric approach control from the least hindered face of the C=O π bond to generate the *cis* hydrazino-alcohol as the major product of the reaction. The best result in this series was obtained with *L*-Selectride (entry 4), in which case the *cis* isomer was generated exclusively.

Another widely used method of reducing C=O double bonds is catalytic hydrogenation.[38] The stereochemistry of hydrogenation is affected by the presence of polar functional groups that can govern the mode of adsorption to the catalyst surface (the haptophilic effect). As can be seen from Table 2.4, when catalytic hydrogenations are employed (entries 5 and 6), the hydrogen is introduced from the side of the molecule occupied by the hydrazine substituent resulting in the predominant formation of the *trans* isomer. The *trans* isomer **281b** was generated exclusively (entry 6) upon hydrogenation of **275** in the presence of tris(triphenylphosphine)ruthenium(II) chloride catalyst.[39]

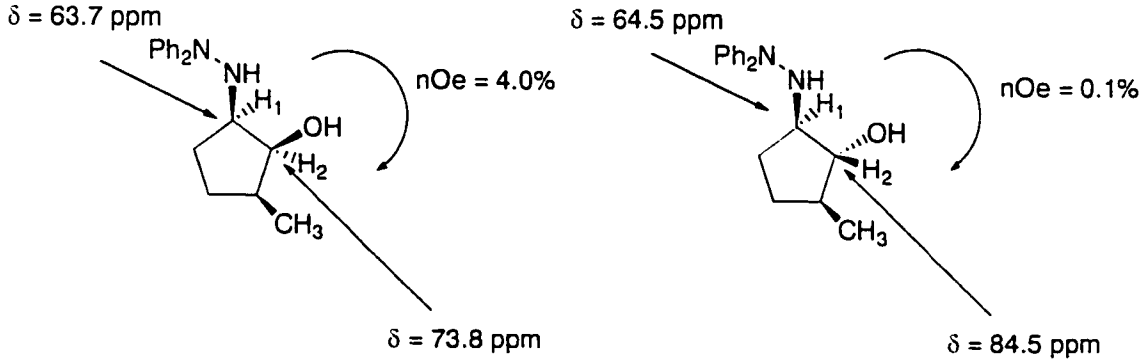
The selectivity of the reductions varied with the substitution pattern of the parent ketone. Thus the use of *L*-Selectride® also gave the *cis* isomer **282a** upon reduction of the ketone **276a** (Table 2.5). Mixtures were obtained in the other methyl substituted cyclopentanone examples, however, the alcohol products were separated cleanly by flash chromatography. Thus, all the possible diastereomers could be prepared depending upon the method selected.



Reagent	Product	Yield%	Ratio cis/trans
LiB(*s*-Bu_3)H	**282a/282b**	90%	1:0
	283a/283b	82%	1:3
H_2/$(Ph_3P)_3RuCl_2$	**282a/282b**	71%	1:1
	283a/283b	69%	1:4.5

Table 2.5. Reduction of the Carbonyl Group

As in the other cases, the compound with the higher field methine carbon signals in the ^{13}C NMR spectrum was assigned as the *cis* isomer **74**. The key spectral features used to assign the stereochemistry of the alkyl substituted hydroxy hydrazines **282a** and **282b** are shown below in Figure 2.2.



282a **282b**

Figure 2.2. Spectral Data for The Alkyl Substituted Hydroxy Hydrazines 282a and 282b

In a similar manner, the stereochemistries of the hydrazines **283a** and **283b** were determined based on nOe data shown in Figure 2.3.

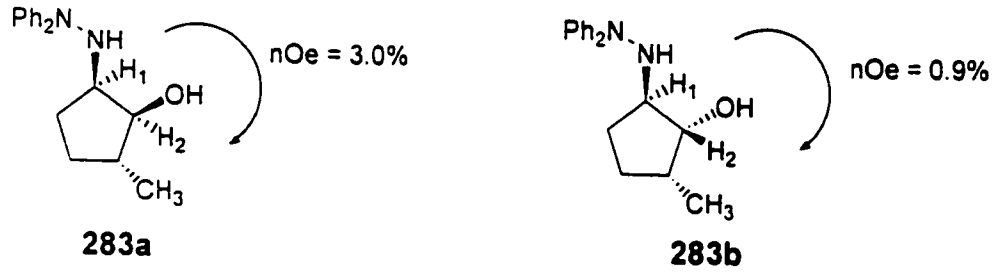


Figure 2.3. Spectral Data for The Alkyl Substituted Hydroxy Hydrazines 283a and 283b

2.8 Reductive Cleavage of the N-N bond

As mentioned before, one of the original goals of this project was to employ the tandem carbonylation-cyclization as a way to synthesize β-amino alcohols. To obtain β-amino alcohols from β-hydrazino alcohols an efficient method for the cleavage of the hydrazine N-N bond was required.

The N-N bond of the alcohol diphenylhydrazine product is doubly benzylic (Figure 2.4). It was shown previously in our laboratory,[25] based on the method of Burke,[40] that it is possible to cleave the N-N bond in diphenylhydrazine by hydrogenolysis with standard metal supported catalysts.

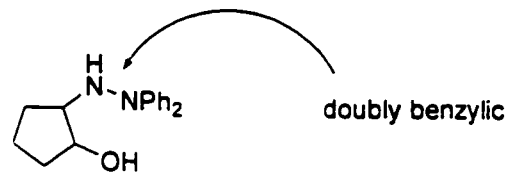
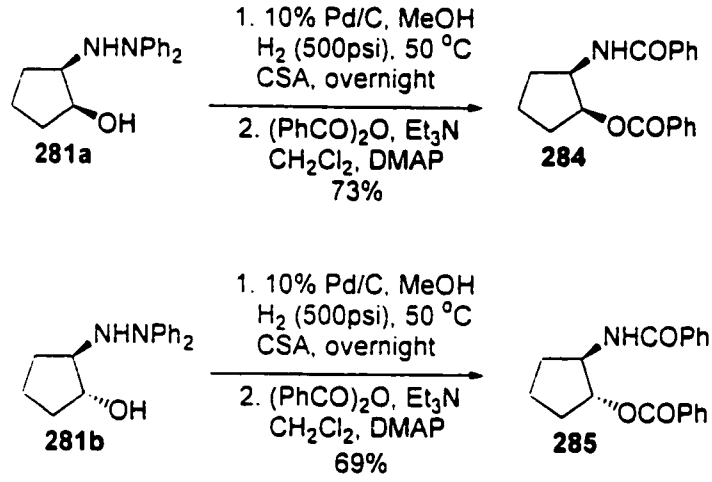


Figure 2.4. β-Hydroxy Hydrazine

Cleavage of the N-N bond in the β-hydroxy hydrazine was accomplished under typical hydrogenation condtions (10% Pd/C) with 500 psi of hydrogen in methanol (Scheme 2.10). Two equivalents of (S)-(+)-10-camphorsulphonic acid (CSA) were added to the reaction mixture. The reaction was heated to 50 °C and allowed to react overnight.



Scheme 2.10. Reductive Cleavage of the N-N bond

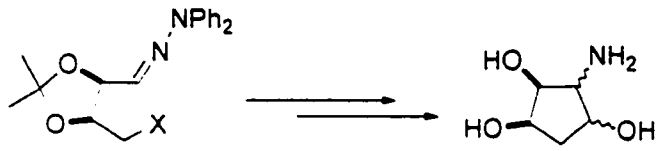
After hydrogenolysis, the resulting amine was not isolated as such, but benzoylated with benzoic anhydride in methylene chloride in the presence of triethylamine. Several DMAP crystals were added to the reaction mixture and this was allowed to stirr at room temperature for ten hours. Purification by flash chromatography afforded the *cis* isomer **284** in 73% yield and the *trans* **285** isomer in 69% yield over two steps.

2.9 Chiral Substrates

The tandem carbonylation-cyclization onto *N,N*-diphenylhydrazones is now a feasibile and reliable synthetic procedure. In addition, the reduction of the ketone functionality was accomplished in a selective manner, thus the development of a stereoselective synthesis of β-hydrazine alcohols, which could be converted to β-amino alcohols, was investigated.

One of the simplest ways to improve the diastereoselectivity of the cyclization reaction would be to use a chiral functionality positioned close to the site of radical attack. This stereodirecting group should also insure the proximity between the radical and the radical acceptor group.

A chiral isopropylidene acetal "tether control" group derived from tartaric acid seemed to be an appropriate choice, which could be easily incorporated into the appropriate starting material (Scheme 2.11).

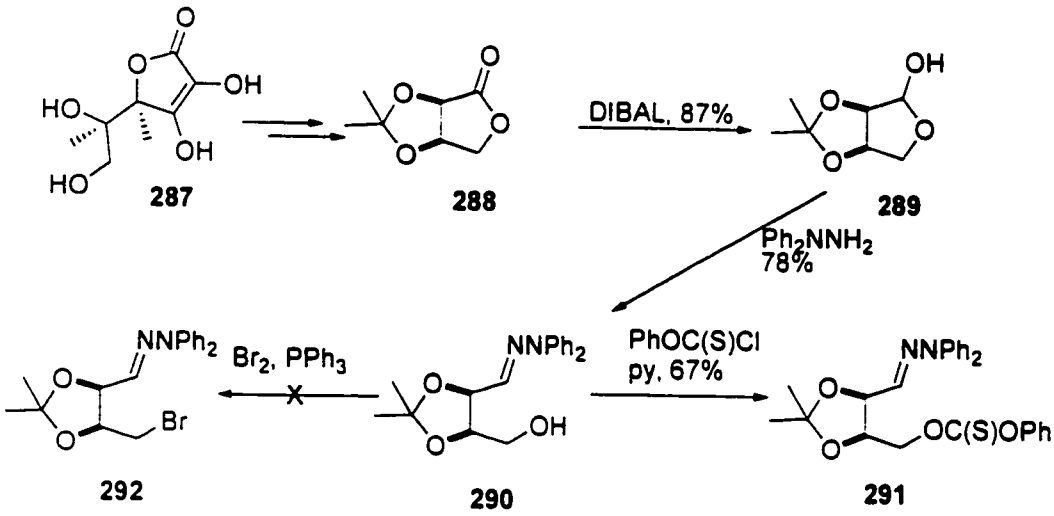


286 **253**

β-Amino Alcohols

Scheme 2.11. Stereoselective Synthesis of β-Amino Alcohols

The synthesis of the free radical precursor **286** is outlined below in Scheme 2.12.



Scheme 2.12. Synthesis of the Chiral Free Radical Precursor

D-Isoascorbic acid **287** was transformed into 2,2-O-isopropylidene-*D*-erythronolactone **288** in 71% yield by following Carozza's procedure.[41] Reduction of the erythronolactone **288** was accomplished with diisobutyl aluminium hydride in toluene at –78 °C to give the corresponding lactol **289** in 71% yield. Treatment of the erythronolactol **289** with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature provided the *N,N*-diphenylhydrazone **290** in 73% yield. As usual, only a single geometric isomer was isolated from the reaction. Extensive decomposition of this product was observed if the hydrazone was left at room temperature. The product was stored in the freezer.

The bromination of alcohol **290** proved to be a challenging step. Various experimental conditions were employed without success.

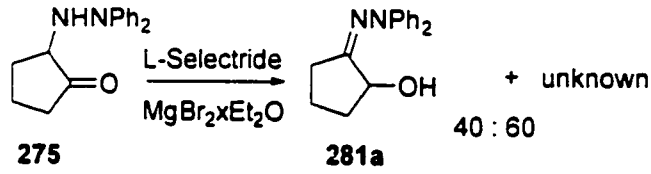
We decided to employ a radical deoxygenation procedure to generate a free radical from a substrate containing a primary hydroxyl group at the desired site. In order to accomplish this, alcohol **290** was transformed into phenoxythionocarbonate **291** in 67% yield upon treatment with phenyl chlorothionoformate and pyridine in methylene chloride.

With the substrate **291** in hand, the tandem carbonylation-cyclization reaction under radical conditions was attempted.

Using the standard procedure, a 0.05 M solution in benzene of the starting material, AIBN (5-10 mol %) and tributyltin hydride (1.2 eq.) were added to a dry glass tube inserted into a stainless steel autoclave (50 mL). The system was flushed three times, then pressurized with carbon monoxide. The reaction mixture was stirred under carbon monoxide pressure (1100 psi) at 80 °C for five hours. The autoclave was cooled to room temperature and, after the release of excess carbon monoxide, benzene was removed under reduced pressure. The reaction mixture was dissolved in diethyl ether and stirred vigorously at room temperature for half an hour with a saturated aqueous solution of potassium to remove most of the organostannane residue. Following this step, filtration, extraction with diethyl ether, drying over magnesium sulphate and concentration gave a crude mixture, which was analyzed by IR, ^{13}C NMR and ^{1}H NMR spectroscopy. The corresponding signals for the expected carbonyl stretch were visible in the IR and ^{13}C NMR spectra. Unfortunately, we were unable to obtain a clean sample of the desired product despite various attempts at purifying the reaction mixture (including flash chromatography with and without triethylamine present in the eluent, chromatography on neutral and basic alumina, preparative HPLC).

2.10 A Novel Rearrangement

As revealed in Section 2.8, in our quest to find selective reduction conditions for α-keto hydrazones, we explored a variety of reaction conditions. In one of the first experiments we employed *L*-Selectride as the main reduction agent along with two equivalents of magnesium dibromide etherate (Scheme 2.13).[42]



Scheme 2.13. Lewis Acid Reduction Conditions

We observed the formation of the expected *cis* hydroxy-hydrazine compound. At the same time, we were intrigued by the presence of an unknown compound, which was the major product in this reaction. A GCMS analysis of the reaction mixture indicated a 40:60 ratio between the two compounds.

Careful analysis of the IR, ^{1}H NMR and ^{13}C NMR spectra obtained, as well as the HRMS indicated the unexpected formation of the α-hydroxy hydrazone **292**. The key ^{1}H NMR and ^{13}C NMR spectral data are shown in Figure 2.5, below.

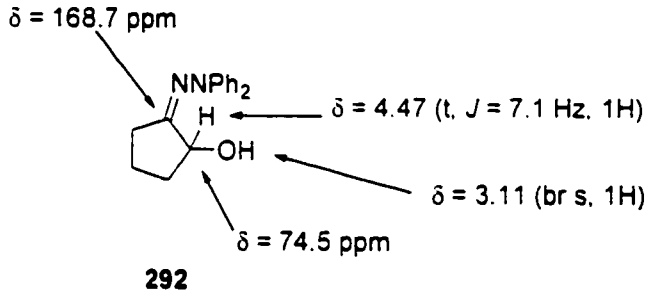
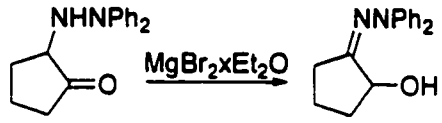


Figure 2.5. Spectral Data for the α-Hydroxy Hydrazone 292

We speculated that the formation of the α-hydroxy hydrazone **292** is the result of a rearrangement catalyzed by the presence of the magnesium dibromide etherate. In order to test this hypothesis, α-keto hydrazine **275** was treated with one equivalent of the Lewis acid in methylene chloride and the reaction stirred for two hours (Scheme 2.14). The reaction mixture was then

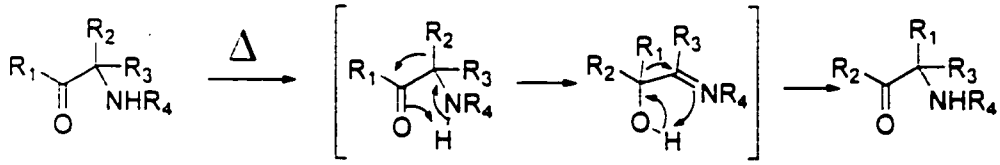
treated with methanol and extracted with diethyl ether to afford the α-hydroxy hydrazone **292** as the only product, formed in 97% yield.



275 **292**

Scheme 2.14. Lewis Acid Catalyzed Rearrangement

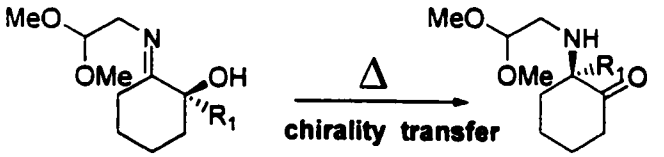
There are few literature precedents for this type of rearrangement. The rearrangement of α-hydroxy hydrazones may be related to the thermal rearrangement of α-hydroxy imines. Stevens et. al. have studied the thermal rearrangement α-amino ketones and to a lesser extent of α-hydroxy imines, essentially from a mechanistic point of view.[43] When heated, ketones containing an α secondary amino group undergo a rearrangement in which two R groups "change places", as shown in Scheme 2.15.



293 **294**

Scheme 2.15. Thermal Rearrangement of α-Amino Ketones

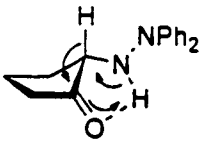
The benzilic-type mechanism of the thermal rearrangement of α-hydroxy imines involves a 1,2-carbon migration accompanied simultaneously by a 1,4-hydrogen migration to the termini of the double bond of the imine. A more recent study of this rearrangement shows that it occurs with complete 1,2 transfer of chirality, [44] as seen in Scheme 2.16.



295 296

Scheme 2.16. Chirality Transfer in the Thermal Rearrangement of α-Hydroxy Imines

No mechanistic studies of the rearrangement of α-keto hydrazine that we accidentally discovered have been conducted. We speculate that it proceeds through a transition state similar to the one represented in Figure 2.6.



297

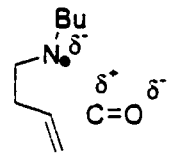
Figure 2.6. Transition State for the Thermal Rearrangement of α-Keto Hydrazine

2.11 Attempted Tandem Aminyl Radical Carbonylation – Cyclization onto *N,N*-diphenylhydrazones

Radical cyclization reactions have become part of the repertoire of the synthetic organic chemist, for the synthesis of both carbocyclic and nitrogen-containing heterocycles such as alkaloids.[45] In addition, recent contributions from the laboratories of Newcomb,[46] Suginome,[47] Kim,[48] and Bowman[49] on the cyclization reactions of alkenyl-aminyl radicals have focused considerable attention on the mechanistic features of these processes.

Aminyl radicals have been produced from a variety of sources: thermolysis and photolysis of symmetrical tetrazenes,[50] radical chain reactions of N-chloroamines,[51] PTOC carbamates[52] and other thiohydroxamate precursors,[53] and benzenesulfenamides[54] and related arenesulfenamides,[55] chemical[56] or electrochemical[57] oxidation of lithium amides; and ring openings of aziridines.[58]

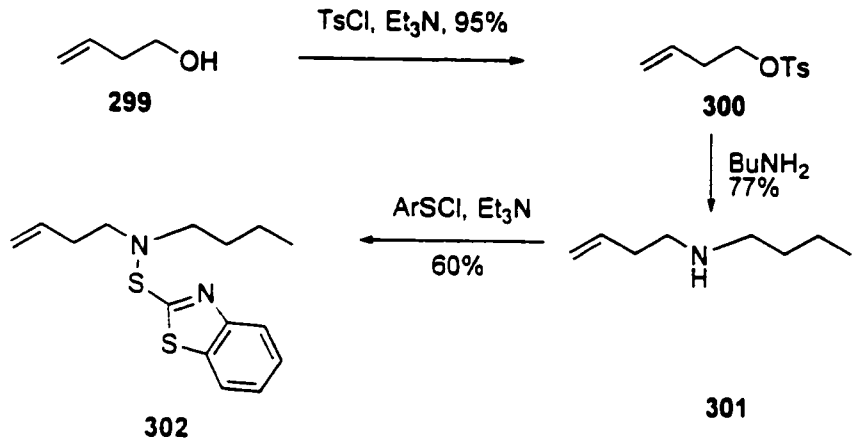
Encouraged by the results obtained in our carbonylation experiments, we anticipated that the introduction of another polar component into this radical reaction would create a new selective cyclization. The use of an aminyl radical which is δ^- polarized should increase the selectivity by matching with the $\delta^+/\ \delta^-$ character of the carbon monoxide (Figure 2.7). With this working hypothesis in mind, we set out to examine the tandem aminyl radical carbonylation - 5-*exo* cyclization reaction.



298

Figure 2.7. Polarization in the Aminyl Carbonylation System

The synthesis of the free radical precursor **302** for the aminyl carbonylation experiments is outlined below in Scheme 2.17.



Scheme 2.17. Synthesis of the Aminyl Carbonylation Precursor

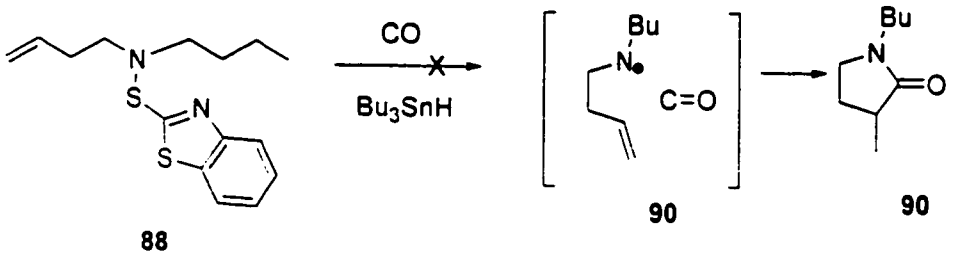
Butenyl alcohol **299** was tosylated following the standard procedure with *p*-toluenesulfonyl chloride and pyridine in methylene chloride to provide product **300** in 95% yield. Tosylate **300** was refluxed with butyl amine for two days to afford secondary amine **301** in 77% yield after distillation.

The precursor for the free radical reaction was prepared by a method described by Maxwell and Tsanaktsidis.[59] In this case, the benzolthiazolesulfenyl chloride was prepared from the corresponding 2,2'-dithiobis(benzothiazole), upon treatment with sulfuryl chloride in dichloromethane. The sulfenamide **302** was prepared from **301** upon treatment with the freshly prepared arenesulfenyl chloride in dry diethyl ether under nitrogen in the presence of triethylamine.[60] The formation of the desired compound was confirmed by ^{1}H NMR and ^{13}C NMR, as well as HRMS.

The major advantage offered by preparing benzolthiazolesulfenamide over other arenesulfenamide is the fact that the product can be purified by flash chromatography. Our previous attempts involving the preparation and study of benzenesulfenamide[61] failed as purification of the benzenesulfenamide by

chromatography on either silica or neutral alumina was complicated by competitive hydrolysis.

With the substrate **302** in hand, the tandem aminyl carbonylation-cyclization reaction under radical conditions was attempted (Scheme 2.18).



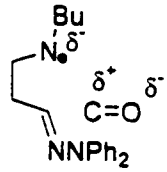
Scheme 2.18. Attempted Tandem Aminyl Radical Carbonylation – Cyclization

For the carbonylation experiment, we followed the same procedure as before: a 0.05 M solution in benzene of the starting material, AIBN (5-10 mol %) and tributyltin hydride (1.2 eq.) were added to a dry glass tube inserted into a stainless steel autoclave (50 mL) pressurized with carbon monoxide. The reaction mixture was stirred under carbon monoxide pressure (1100 psi) at 80 °C for five hours. The autoclave was cooled to room temperature and, after the release of excess carbon monoxide, benzene was removed under reduced pressure. The reaction mixture was worked-up as usual and concentration gave a crude mixture, which was analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy. Unfortunately, the only product clearly formed in this reaction was the secondary amine **301**.

Several possible reasons can account for this result: (a) CO trapping is reversible; (b) the rate of the reduction is faster than the trapping rate; or (c) the rate of the amidyl cyclization onto the unactivated alkene is too slow.

It is well known that acyl radicals are considered to be nucleophilic in the context of additions to C-C double bonds having electron-withdrawing groups.[62] Taking this consideration into account, as well as the results obtained with *N,N*-

diphenylhydrazones, we decided to take a different approach to the synthesis of precursor for the aminyl carbonylation-cyclization. It was reasoned that a precursor with a hydrazone functionality as a radical acceptor might be a better choice (Figure 2.8).



304

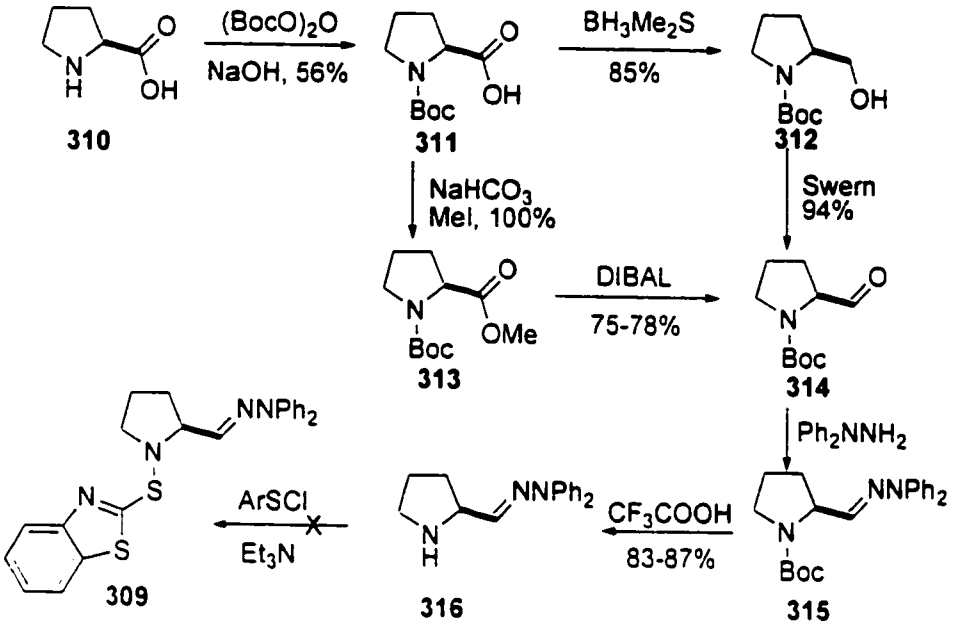
Figure 2.8. N,N-Diphenylhydrazone as Amidyl Acceptor

Cyclization of aminyl radicals derived from α-amino acids have been documented.[63] In our case, as shown in Scheme 2.19, employing α-amino acids **305** as starting materials would enable us to generate interesting β- and γ-lactones **307** and **308**.

305 **306** n = 0, 1 **307** **308**

Scheme 2.19. α-Amino Acids as Precursors for Aminyl Carbonylation

The attempted synthesis of the free radical precursor **309** for the tandem aminyl carbonylation-cyclization onto *N,N*-diphenylhydrazone reaction from commercially available *L*-proline is outlined below in Scheme 2.20.



Scheme 2.20. Synthesis of the Precursor for the Tandem Aminyl Carbonylation-Cyclization onto N,N-Diphenylhydrazone

The amine functionality in commercially available *L*-proline **310** is protected by *tert*-butoxycarbonyl group. The protecting group is introduced by reaction with di-*tert*-butyl dicarbonate in the presence of sodium hydroxide to yield Boc-proline **311** in 56% yield. In the next step, the acid functionality was reduced with borane-methyl sulfide complex to yield alcohol **312** in 85% yield. A Swern oxidation afforded the aldehyde **314** in 94% yield. Aldehyde **314** exists as a 3:2 mixture of isomers due to restricted rotation about the carbamate C-N bond.

An alternate way was also employed to arrive at the same aldehyde. In this case, the methyl ester of the Boc-proline **313** was obtained quantitatively upon treatment with methyl iodide and sodium bicarbonate in DMF.[64] Reduction of the ester was accomplished with DIBAL to afford aldehyde **314** in 76% yield.

Treatment of the aldehyde **314** with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature provided the *N,N*-diphenylhydrazone **315** in 75% yield. The compound was isolated as a faint

yellow oil, which later solidified in the freezer. As usual, only a single geometric isomer was isolated from the reaction. Some of the ^{1}H NMR signals are broadened presumably due to the restricted rotation around the C-N carbamate bond. Deprotection of the Boc group was effected with trifluoroacetic acid to afford amine **316** in 87% yield.

The synthesis of the precursor for the free radical reaction **309** proved to be especially frustrating. Several attempts to prepare the substrate **309** by the method described by Maxwell and Tsanaktsidis[65] were done under slightly different conditions. Various experimental conditions were employed for the synthesis of a different aminyl precursor without success.

Chapter 2 References

1. (a) Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1988**, *29*, 897. (b) Yadav, V.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 3283. (c) Yadav, V.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 779.
2. (a) Curran, D. P. In *Free Radicals in Synthesis and Biology*; Minisci, F., Ed.; Kluwer: Dordrecf, 1989, p. 37. (b) Curran, D. P. *J. Org. Chem.* **1991**, *56*, 2746.
3. Ho, T. L. *Tandem Reactions in Organic Synthesis*; Wiley-Inter-science: New York, 1992.
4. For recent reviews: (a) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983; p 359. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Oxford, 1986. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237-1286. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Ed.; Pergamon: Oxford, 1991; Vol. 4, p 779.
5. Coffman, D. D.; Pinkney, P. S.; Wall, F. T.; Wood, W. H.; Young, H. S. *J. Am. Chem. Soc.* **1952**, *74*, 3391.
6. Foster, R. E.; Larchar, A. W.; Lipscomb, R. D.; McKusick. B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5606.
7. (a) Kharasch, M. S.; Urry, W. H.; Kuderna, B. M. *J. Org. Chem.* **1949**, *14*, 248. (b) Harris, E. F. P.; Waters, W. A. Nature **1952**, *170*, 212. (c) Patric, T. M. *J. Org. Chem.* **1952**, *17*, 1009. (d) Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Chem. Commun.* **1979**, 473. (e) Chatgilialoglu, C.; Lunazzi, L.; Macciantelli, D.; Placicci, G. *J. Am. Chem. Soc.* **1984**, *106*, 5252. (f) Gottschalk, P.; Neckers, D. C. *J. Org. Chem.* **1985**, *50*, 3498. (g) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674.

8. (a) Urry, W. H.; Pai, M. H.; Chen, C. Y. *J. Am. Chem. Soc.* **1964**, *86*, 5342. (b) Fraser-Reid, B.; Anderson, R. C.; Hicks, D. R.; Walker, D. L. *Can. J. Chem.*, **1977**, *55*, 3986. (c) Druliner, J. D.; Wasserman, E. *J. Am. Chem. Soc.* **1988**, *110*, 5270. (d) Querin, B.; Johnston, L.J.; Quach, T. *J. Org. Chem.* **1988**, *53*, 2826.

9. Pattel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1988**, *29*, 707.

10. (a) Van der Kerk, G. J. M.; Noltes, G. J.; Luijten, J. G. A. *J. Appl. Chem*, **1957**, *7*, 356. (b) Kupchik, E. J.; Kiesel, R. J. *J. Org. Chem.* **1964**, *29*, (c) Kuivila, H. G.; Walsh, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 571. (d) Walsh, E. J.; Kuivila, H. G. *J. Am. Chem. Soc.* **1966**, *88*, 576. (e) Cekovic, Z. *Tetrahedron Lett.* **1972**, 749. (f) Walsh, E. J.; Messinger, J. M.; Grudoski, D. A.; Allcin, C. A. *Tetrahedron Lett.* **1980**, *21*, 4429.

11. (a) Urry, W. H.; Huyser, E. S. *J. Am. Chem. Soc.* **1953**, *75*, 4876. (b) Bentrude, W. G.; Darnall, K. R. *J. Am. Chem. Soc.* **1968**, *90*, 3588.

12. (a) Pfenninger, J.; Graff, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (b) Pfenninger, J.; Heuberger, C.; Graff, W. *Helv. Chim. Acta* **1980**, *63*, 2328. (c) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1986**, *27*, 641. (d) Bachi, M. D.; Bosch, E. *Tetrahedron Lett.* **1988**, *29*, 2581. (e) Crich, D.; Fort, S. *Tetrahedron Lett.* **1988**, *29*, 2585. (f) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377. (g) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1989**, *54*, 1234. (h) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *54*, 1777.

13. Ryu, I.; Kusano, K.; Ogawa, A.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 1295.

14. Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4; pp 779.

15. Ryu, I.; Hasegawa, M.; Kurihara, A.; Ogawa, A.; Tsunoi, S.; Sonoda, N. *Synlett* **1993**, 143.

16. Gupta, V.; Kahne, D. *Tetrahedron Lett.* **1993**, *34*, 591.

17. For recent reviews on acyl radicals, see: (a) Brown, C. E.; Neville, A. G.;

Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363. (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (c) Crich, D.; Yuan, H. In *Advances in Free Radical Chemistry*; Rawal, V. H., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

18. Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *Organometallics* **1995**, *14*, 2672.

19. For leading references see: (a) Trost, B. M.; VanVranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (b) Simpkins, N. S.; Stokes, S.; Whittle, A. J. *Tetrahedron Lett.* **1992**, *33*, 793. (c) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562. (d) Corbett, D. F.; Dean, D. K.; Robinson, S. R. *Tetrahedron Lett.* **1994**, *35*, 459. (e) Goering, B. K.; Li, J.; Ganem, B. *Tetrahedron Lett.* **1995**, *36*, 8905. (f) Nishimura, Y.; Umezawa, Y.; Adachi, H.; Kondo, S.; Takeuchi, T. *J. Org. Chem.* **1996**, *61*, 480.

20. Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

21. (a) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363. (b) Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* **1995**, *36*, 1299. (c) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *Organometallic* (d) Tsentalovich, Y. P.; Fischer, H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 729. (e) Lunazzi, L.; Ingold, K. U.; Scaiano, J. C. *J. Phys. Chem.* **1983**, *87*, 529. (f) Turro, N. J.; Gould, I. R.; Baretz, B. H. J. *Phys. Chem.* **1983**, *87*, 531.

22. Actually, there is no significant difference between the CO trapping rates of a primary alkyl radical (6×10^5 $M^{-1}s^{-1}$ at 80 °C in benzene)[a] and a secondary alkyl radical (1.2×10^5 M^{-1} s^{-1} at 50 °C in cyclohexane)[b]. (a) Nagahara, K.; Ryu, I.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org.* Chem. **1995**, 60, 7384. (b) Boese, W. T.; Goldman, A. S. *Tetrahedron Lett.* **1992**, *33*, 2119.

23. Cain, E. W.; Welling, L. L. *Tetrahedron Lett.* **1992**, *33*, 2119.

24. Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
25. Claudio Sturino, Ph.D. dissertation, University of Ottawa, 1994.
26. Enders, D. In *Asymmetric Synthesis*, Vol 3; Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**.
27. Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.
28. Berge, J. M.; Roberts, S. M. *Synthesis*, **1979**, 471.
29. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
30. Barton, D. H. R.; Motherwell, W. B.; Crich, D. *Tetrahedron*, **1985**, *41*, 3901.
31. Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, H. *J. Chem. Soc., Chem. Commun.* **1991**, 1018.
32. (a) Ley, G. C.; Lichter, R. L.; Nelson, A. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, 2nd ed.; J. Wiley and Sons; New York, 1980. (b) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.
33. Stork, G.; Mook, R.; Biller, S. A.; Rychnovski, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.
34. Srikrishna, A.; Krishnana, K. *J. Org. Chem.* **1989**, *54*, 3981.
35. For leading references see: (a) Trost, B. M.; VanVranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444. (b) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046. (c) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Reviews* **1999**, *99*, 779.
36. Hudlicky, M. *Reductions in Organic Chemistry*, Halstead Press, New York, 1984.
37. (a) Brown, H. C.: Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. (b) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1976**, *98*, 3383.
38. Rylander, P. N. *Hydrogenation Methods*, Academic Press, Orlando,

Florida, 1985.

39. (a) Devlin, J. A.; Robins, D. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1272. (b) Zonan, A.; Sasson, Y. *J. Org. Chem.* **1981**, *46*, 255.

40. Burke, M. J.; Feasta, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

41. Cohen, N.; Banner, B. L.; Laurenzano, A. J., Carozza, L. *Organic Synthesis*, vol. 63, **1984**, pp 127.

42. Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4930.

43. (a) Stevens, C. L.; Pillai, P. M; Munk, M. E.; Taylor, K. G. *Mech. Mol. Migr.* **1971**, 271. (b) Stevens, C. L.; Elliot, B.; Winch, B. L. *J. Am. Chem. Soc.* **1963**, *85*, 1464. (c) Stevens, C. L.; Hanson, H. T.; Taylor, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2769. (d) Stevens, C. L.; Ash, A. B.; Thuillier, A.; Amin, J. H.; Balys, A.; Dennis, W. E.; Dickerson, J. P.; Glinski, R. P.; Hanson, H. T.; Pillai, M. D.; Stoddart, J. W. *J. Org. Chem.* **1966**, *31*, 2593.

44. Compain, P.; Gore, J.; Vatele J. M. *Tetrahedron Lett.* **1995**, 36, 4059.

45. For recent reviews, see: (a) Sibi, M. P.; Ji, J. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Gribble, G. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 8. (b) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913. For selected recent examples on the synthesis of nitrogen heterocycles using radical cyclizations, see: (d) Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, 507. (e) Curran, D. P.; Josien, H.; Ko, S.-B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (f) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. (g) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801. (h) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430. (i) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 465. (j) Kizil, M.; Lampard, C.; Murphy, J. A. *Tetrahedron Lett.* **1996**, *37*, 2511. (k) Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193. (l) Clive, D. L. J.; Coltart, D. M. *Tetrahedron Lett.* **1998**, *39*, 2519. (m) Aurrecoechea, J. M.; Fernandez-

Acebes, A. *Synlett* **1996**, 39. (n) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529. (o) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825.

46. (a) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1. (b) Newcomb, M.; Horner, J. H.; Shahin, H. *Tetrahedron Lett.* **1993**, *34*, 5523. (c) Newcomb, M.; Ha, C. *Tetrahedron Lett.* **1991**, *32*, 6493. (d) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317. (e) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528. (f) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163. (g) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651. (h) Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329. (i) Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Heterocycles*. **1999**, *50*, 333.

47. (a) Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 777. (b) Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747. (c) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H. *Tetrahedron* **1987**, *43*, 281. (d) Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Suginome, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465.

48. (a) Kim, S.; Yoon, K. S.; Kim, S. S.; Seo, H. S. *Tetrahedron* **1995**, *51*, 8437. (b) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. (c) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328. (d) Kim, S.; Cheong, J. H. *Chemical Communications* **1998**, 1143.

49. (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275. (b) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295. (c) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* **1991**, *32*, 6441.

50. (a) Michejda, C. J.; Campbell, D. H.; Sieh, D. H.; Koepke, S. R. In *Organic Free Radicals*; Pryor, W. A., Ed.; American Chemical Society:

Washington, DC, 1978; chapter 18. (b) Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 7759.

51. Stein, J.-L.; Stella, L.; Surzur, J.-M. *Tetrahedron Lett.* **1980**, 21, 287 and references therein.

52. (a) Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163. (b) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317.

53. Newcomb, M.; Weber, K. A. *J. Org. Chem.* **1991**, *56*, 1309.

54. (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275 and references therein. (b) Beckwith, A. L. J.; Maxwell, B. J.; Tsanaktsidis, J. *Aust. J. Chem.* **1991**, *44*, 1809.

55. Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276.

56. Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 7759.

57. Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747-756, and references cited therein.

58. (a) Dickinson, J. M.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 1317. (b) Dickinson, J. M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun* **1990**, 434.

59. Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276.

60. (a) Craine, L.; Rabin, M. *Chem. ReV.* **1989**, *89*, 589. (b) Davis, F. A. Int. J. Sulfur Chem. **1973**, 8, 71.

61. (a) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275. (b) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295.

62. For reviews involving acyl radicals, see: (a) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363. (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (c) Crich, D.; Yuan, H. In *AdVances in Free Radical Chemistry*; Rawal, V. H., Ed.: JAI Press: Greenwich, CT, 1998; Vol. 2, in press. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

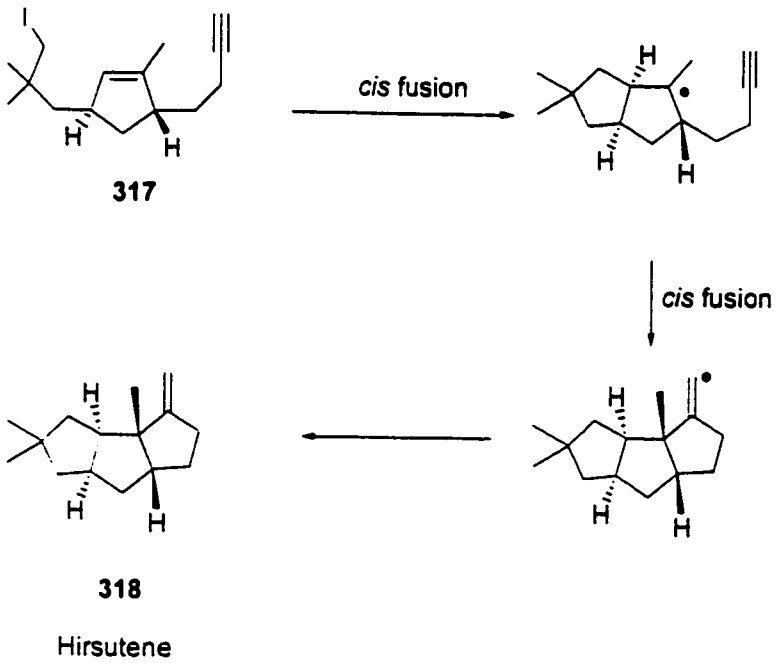
63. Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, K. A. *Tetrahedron Lett.* **1997**, *35*, 6301.
64. Ahmed-Schofield, R.; Mariano, P. S. *J. Org. Chem.* **1987**, *52*, 1478.
65. Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276.

Chapter 3

Bicyclic Ring Systems Synthesis *via* Tandem Radical Reactions

3.1 Tandem Radical Reactions

The radical generated after an initial cyclization may react with a suitably positioned π system to create an additional ring. This may lead to the formation of bicyclic or polycyclic products. The stereochemistry at the ring junction in the case of hydrindanes or decalins is predominantly or exclusively *cis*. This guideline holds independent of whether it is the radical or the alkene that is contained in the ring. An interesting example of a tandem cyclization that illustrates both possibilities was published by Curran and is shown in Scheme 3.1.[1]



317

318

Hirsutene

Scheme 3.1. Hirsutene Synthesis via Tandem Radical Reaction

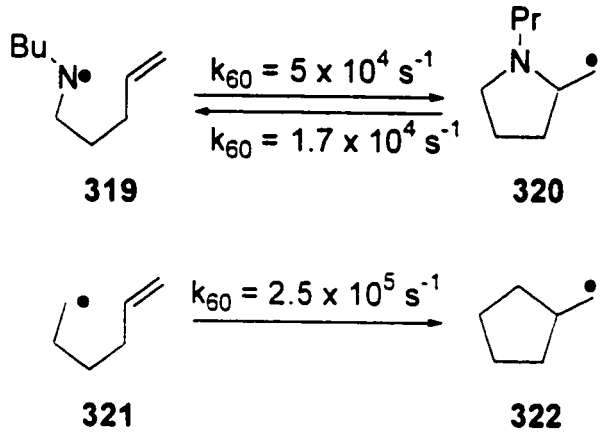
In the first cyclization, the acceptor is in the ring and the radical is on the chain, and in the second cyclization, the radical is in the ring and the alkyne is on the chain. Two new 5,5-*cis* ring fusions are formed in this process. The reason for the observed stereoselectivity is the presence of a short connecting chain between the cyclic alkene or radical and its partner. This permits the favoured geometry in the transition states for the *cis* isomers and avoids the ring strain for transition states leading to *trans* isomers.

3.2 Cyclizations of the Aminyl Radical

Cyclization of aminyl radicals is one of the most useful methods for the construction of pyrrolidine rings. These are important skeletons of some alkaloids and nitrogen heterocycles, particularly those with medicinal potential.

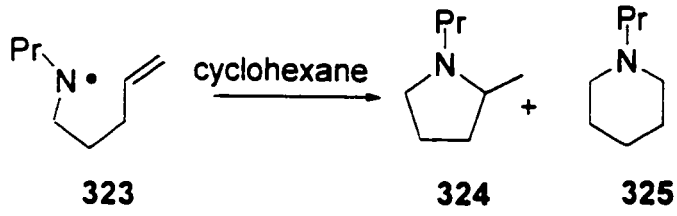
Neutral aminyl radicals are nucleophilic, in contrast to amidyl radicals, complexed aminyl, and aminium cation radicals, which are electrophilic in nature.

The rate of cyclization of nitrogen radicals[2] is slower than the cyclization of the corresponding carbon analog,[3] as shown in Scheme 3.2. An additional factor in the aminyl radical cyclization is the competing fragmentation process.



Scheme 3.2. Kinetics of the Aminyl Radical Cyclizations

Early investigations in the area of aminyl cyclizations were performed by Michejda;[4] it was shown that **323** cyclizes predominantly in a 5-*exo* manner under both photolytic and thermolytic conditions to afford **324** and **325** in 41% and 16% yield respectively (Scheme 3.3). Several other examples were published subsequently.[5]

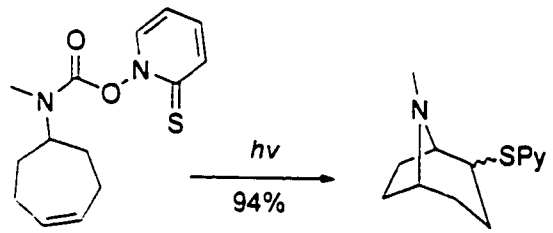


Scheme 3.3. Aminyl Radical Cyclizations

Neutral aminyl radicals from most nitrogen radical precursors are relatively unreactive. However, protonation of aminyl radicals gives aminium cation radicals that are much more reactive. Recent direct kinetic studies of analogous dialkylaminyl radicals and dialkylaminium cation radicals indicated that intramolecular reactions of the protonated species are several orders of magnitude faster than those of the neutral counterparts.[6]

Lewis acid catalysis of dialkylaminyl radical cyclization reactions has been known qualitatively for more than two decades.[7] More recently, Lewis acid activation and catalysis of dialkylaminyl radical reactions was demonstrated both qualitatively and quantitatively.[8] Cyclization of the *N*-butyl-4-pentenaminyl radical **319** in the presence of a wide range of Lewis acids such as $LiBF_4$, $MgBr_2$, and BF_3 gave good to excellent yields of cyclic products. Lewis acid or metal complexed aminyl radicals render the nitrogen center more electrophilic. Similar to the aminium cation radicals, these intermediates usually participate more readily in additions to unsaturated centers.

The use of PTOC carbamates for the generation and cyclization of aminium cation radicals in the presence of acid is a very efficient process. An interesting example is the synthesis of the tropane system **327** from **326**, as shown in Scheme 3.4 below.

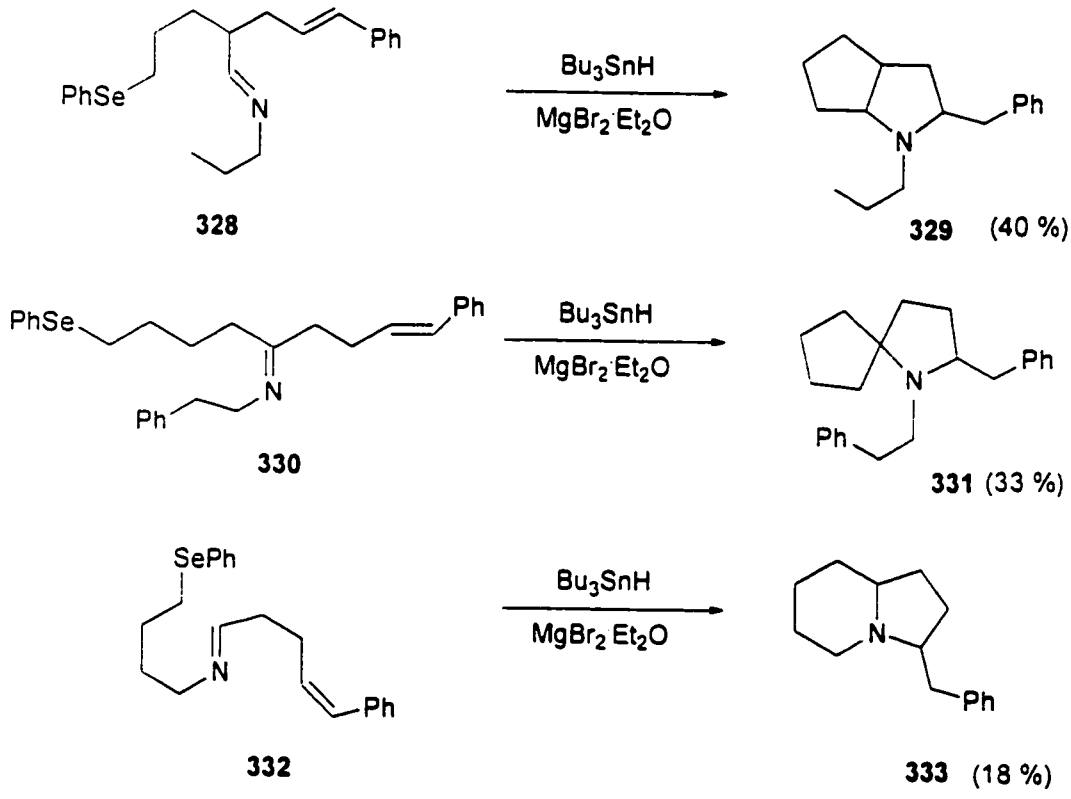


326 **327**

Scheme 3.4. Synthesis of the Tropane Skeleton

3.3 Tandem Cyclizations Involving Nitrogen Participation

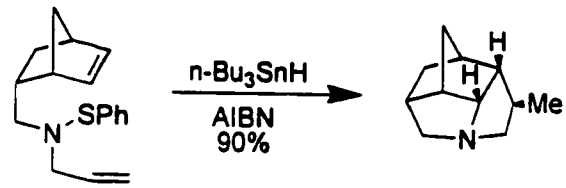
Bowman and coworkers[9] examined a series of tandem reactions in which the second step involved the addition of an aminyl radical to an alkene to provide various bicyclic systems, as demonstrated in Scheme 3.5. The addition of a Lewis acid, as well as the presence of the styryl group, was found necessary to insure a good yield of the desired product.



Scheme 3.5. Tandem Cyclizations with Nitrogen Radicals

Nitrogen centered radical generated directly from arylsulfenamides (as opposed to resulting from an initial cyclization onto a C=N bond) can also be

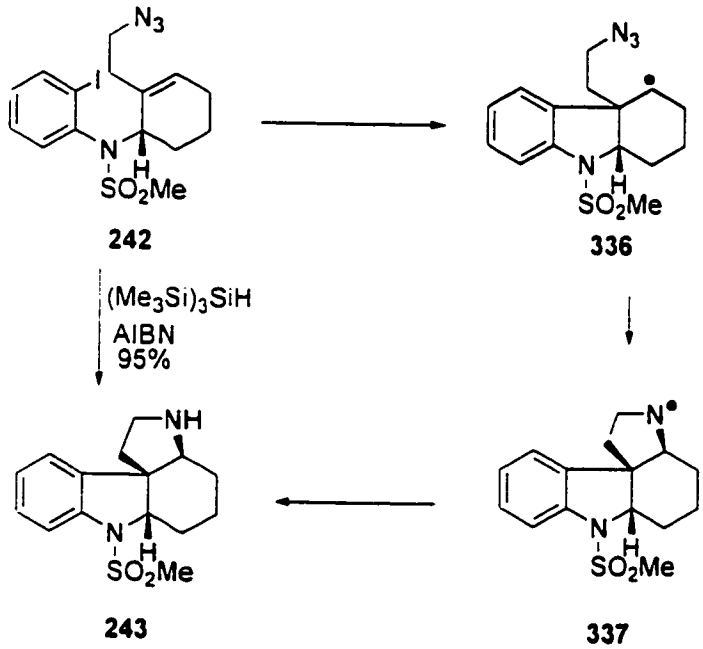
used for the synthesis of interesting polycyclic systems, as shown below in Scheme 3.6.



334 335

Scheme 3.6. Synthesis of Polycyclic Systems via Tandem Reactions

An aminyl radical is also involved in the interesting tandem approach to the pentacyclic ring system of aspidospermine **337** (Scheme 3.7).[10]



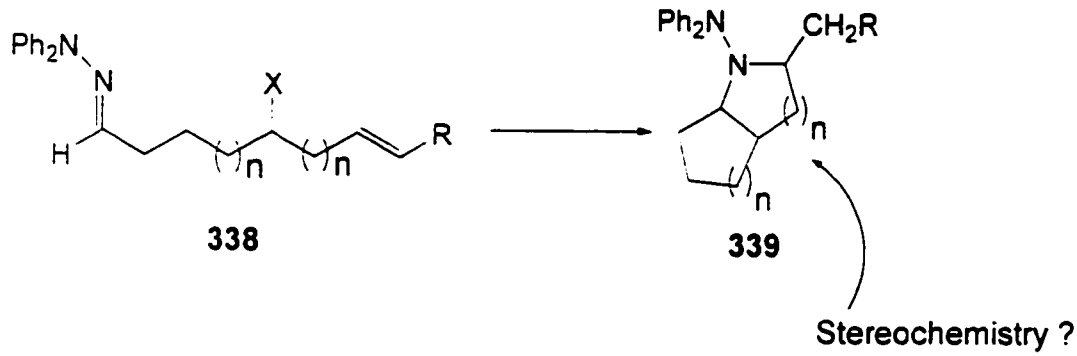
Scheme 3.7. Synthesis of Aspidospermine Ring System

3.4 Research Objectives

Modern synthetic design aims to incorporate high efficiency of synthetic steps together with maximization of complexity. The disconnection approach to synthesis design is used to analyze complex structures. The result of breaking one or more bonds assist in defining the shortest synthetic route.

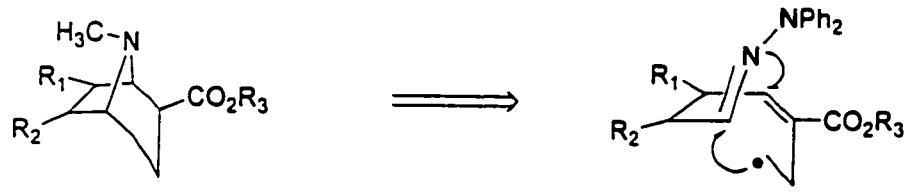
As demonstrated in the previous section, the aminyl radical generated after one cyclization could participate in a second cyclization step onto a suitable π system to create more complex ring systems.

As a continuation of previous studies done in our laboratory, we set out to explore the synthesis of a bicyclic aza quinane ring system through a tandem reaction under free radical conditions. The study of the influence of Lewis acids on this process (Scheme 3.8, n = 1) was also planned.



Scheme 3.8. Proposed Synthesis of a Bicyclic 5,5 System

In principle, tandem radical reactions with *N,N*-diphenylhydrazone acceptors can be employed for the synthesis of medicinally interesting products. Scheme 3.9 below shows a possible disconnection for the tropane system present in cocaine and cocaine analogs.



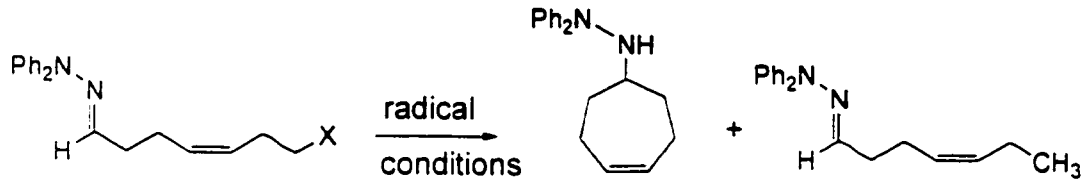
340

Cocaine Analogs
Dopamine Transporter Inhibitors

341

Scheme 3.9. Tropane System Disconnection

Previous attempts done in our laboratory to prepare the tropane nucleus using a tandem free radical cyclization strategy did not prove successful.[11] Subjecting the free radical precursors **342** and **343** to a number of free radical conditions only resulted in the formation of monocyclization **344** and reduction **345** products, as shown in Scheme 3.10.



342 X= Br
343 X= I

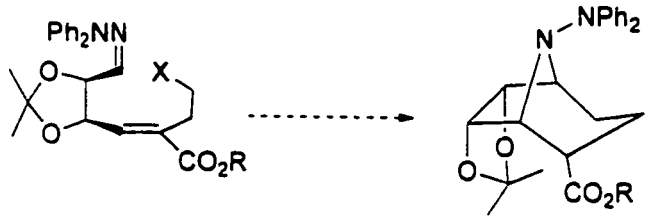
344

345

Scheme 3.10. Previous Attempt for the Tropane Nucleus Synthesis

In this case, X-ray data of the monocyclized product, obtained at –110 °C, shows that the cycloheptene ring exists in a chair like conformation; NMR data collected at room temperature suggests that this ring system fluctuates between chair like and boat like conformations. These findings are important because, if the second cyclization is to occur, the first cyclization intermediate must adopt a boat like conformation.

An alternative attempted way for the tropane nucleus synthesis included the presence of a chiral isopropylidene acetal group to ensure the proximity of the aminyl radical to the radical acceptor and an activating ester group on the double bond (Scheme 3.11). Unfortunately, the desired precursor for this experiment proved difficult to obtain.



346 **347**

Scheme 3.11. Second Attempt for the Tropane Nucleus Synthesis

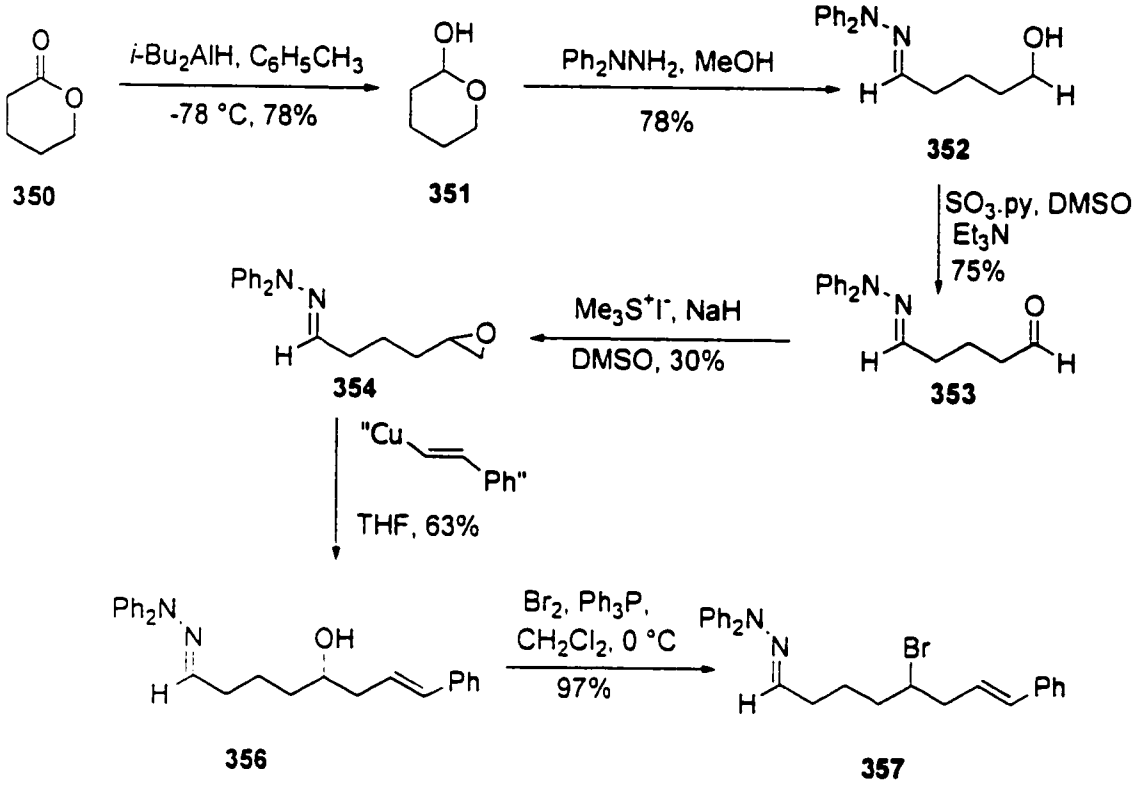
In view of the results obtained previously in our laboratory in the attempted generation of the tropane ring system, we decided to try and improve the possibility of the tandem reaction. The presence of a benzene ring in the precursor **349** should ensure the proximity between the radical and the radical acceptor (Scheme 3.12). In addition, an electron withdrawing group placed as a substituent on the alkene should encourage the second stage of the tandem process.

348 **349**

Scheme 3.12. Proposed Tropane System Synthesis

3.5 Substrates for the Synthesis of the 5,5 Bicyclic Ring System

The synthetic pathway to the substrate for the [3.3.0] octane ring system experiment is outlined in Scheme 3.13 below.



Scheme 3.13. Synthetic Route to the Substrate for the 5,5 Bicyclic Ring System

The synthesis of the substrate **357** commenced with reduction of the commercially available δ-valerolactone **350** in toluene at –78 °C to give the corresponding lactol **351** in 78% yield. Treatment of the δ-valerolactol **351** with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature provided the *N,N*-diphenylhydrazone **352** in 78% yield. The product was clearly

identified by the presence of the hydrazone proton at δ 6.52 ppm in the ^{1}H NMR. The oxidation of the resulting primary alcohol **352** with sulfur trioxide pyridinium complex in DMSO in the presence of triethylamine[12] afforded the aldehyde **353** in 75% isolated yield. The presence of a peak at δ 9.77 ppm in the ^{1}H NMR clearly indicated the formation of the aldehyde **353**.

As expected, treatment of aldehyde **353** with dimethylsulfonium methylide derived from trimethylsulfonium iodide[13] afforded the epoxide **354**, without any observed competitive reaction at the hydrazone functionality. The chemospecificity of this reaction was discerned by analysis of the H^1 NMR spectrum, as the vinyl hydrogen of the hydrazone remained in the product, while the aldehyde signal disappeared. This demonstrated, once again, the chemoselectivity of various nucleophiles for the aldehyde functionality *versus* the hydrazone. However, some problems were encountered during the course of the reaction. After approximately two hours of stirring at room temperature, TLC analysis revealed the consumption of the starting material, plus the formation of a new, more polar compound. A new TLC, taken after 30 more minutes of stirring, indicated the formation of a second, less polar product. The reaction was stopped at this stage. The major product was isolated and identified as epoxide **354** and starting material was recovered. The other, less polar product was not. Overall, the epoxide **354** was isolated in 30%, or 63% based on the recovered starting material. Attempts to modify the reaction time or alter the reaction conditions resulted in a lower overall yield for the desired product. The best results were therefore obtained at a conversion of 48% for the starting aldehyde.

The cuprate addition to the epoxide, using a higher order cuprate such as lithium-2-thienylcyano cuprate[14] with β-bromostyrene, occurred readily to afford alcohol **356**. Purification and spectral analysis of the reaction mixture confirmed the formation of the desired secondary alcohol.

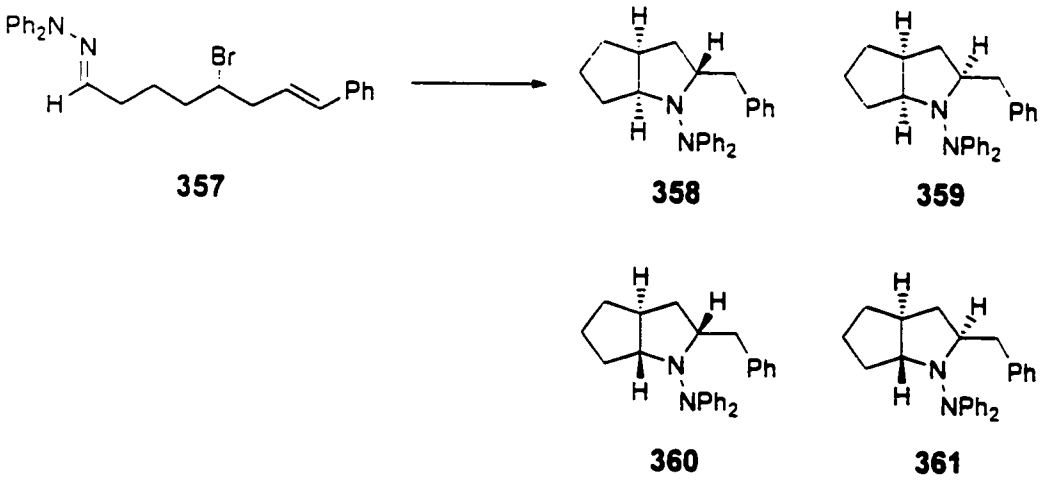
The last step required for the preparation of the starting material was the conversion of the secondary alcohol to bromide. The alcohol was converted to

the bromide using $Ph_3P{\bullet}Br_2$[15] in the presence of triethylamine and afforded the desired radical precursor **357** in 97% yield.

3.6 Tandem Radical Cyclization

Our first attempt at generating the bicyclic ring system followed the general procedure for the syringe pump radical reactions. Bromide **357** was dissolved in benzene, then treated with tributyltin hydride and AIBN. The reaction mixture was refluxed for two hours. TLC analysis of the reaction mixture revealed the presence of two new spots, both of them less polar than the starting material.

The ^1H NMR of the crude reaction mixture showed that the signal for the hydrazone proton had disappeared. In theory, there is a possibility of isolating four products from the tandem reaction and the two products from monocyclization. The four tandem products are shown in Scheme 3.14 below.



Scheme 3.14. Possible Products from the Tandem Reaction

In practice, however, we knew from previous studies done on our laboratory[16] that the 5-*exo* cyclization on *N,N*-diphenylhydrazones proceeds with the predominant formation of the *cis* isomer. Hence, the *cis* ring fusion is to be expected in the tandem product, along with the *cis* geometry of the monocyclized product. Moreover, any of the *trans* product formed in the first cyclization of the tandem process would likely fail to provide the tandem product. The formation of a tandem product with a *trans* ring junction would involve significant amount of strain present in the transition state leading to the *trans* isomer (Figure 3.1).

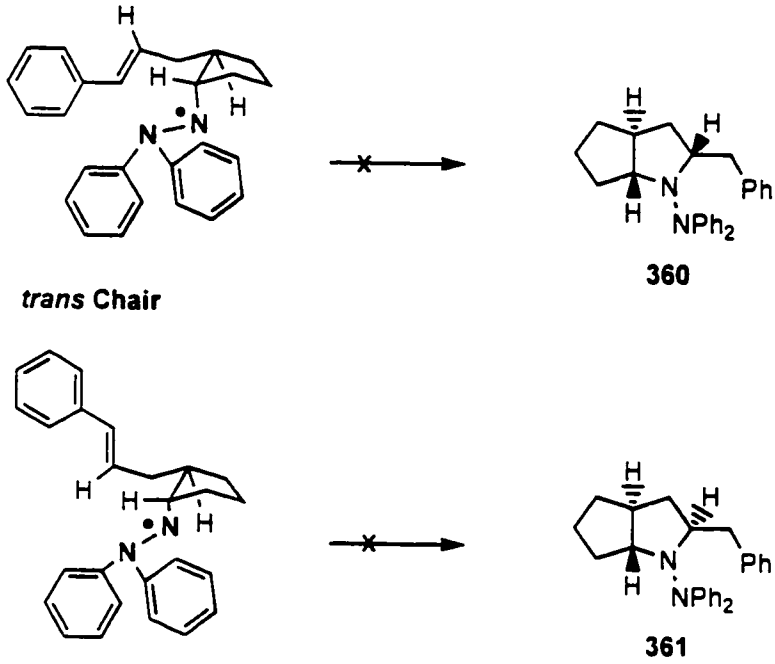


Figure 3.1. Transition States Leading to the trans Isomer

In addition, it can be safely assumed that the second cyclization proceeds *via* a boat conformation as opposed to a chair conformation. The boat conformation is favoured since in the chair conformation, the phenyl rings on the nitrogen interact with the phenyl ring on the double bond. The bulky nitrogen with the diphenyl substituents 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 conformation, as shown in the Figure 3.2.

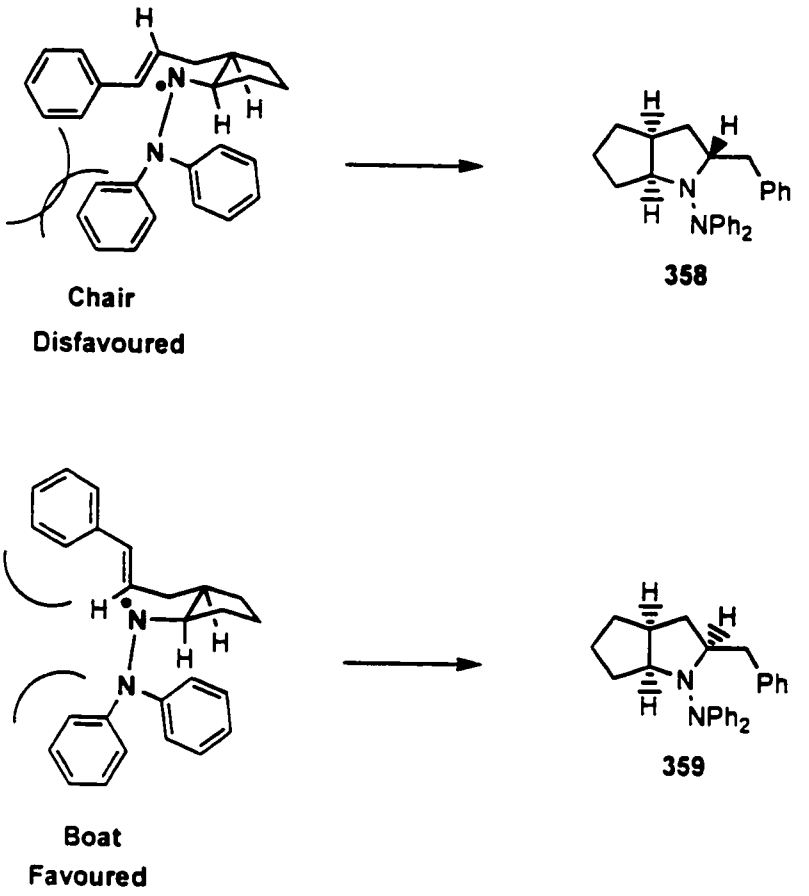
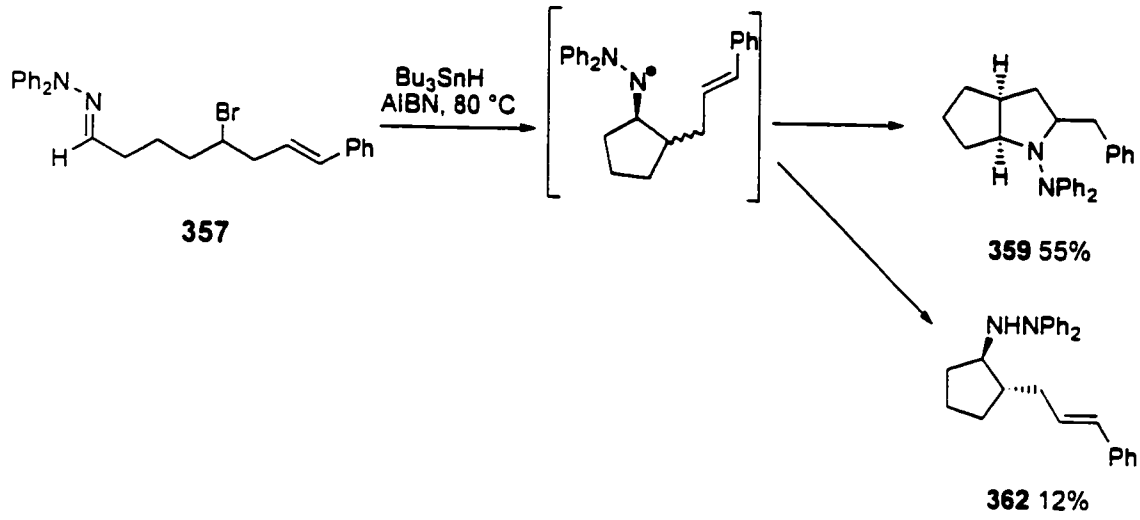


Figure 3.2. Proposed Transition State for the Tandem Cyclization

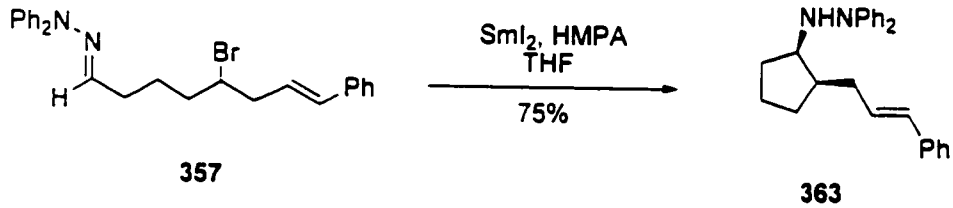
After subsequent purification of the reaction mixture and separation by flash cromatography, the two new products were isolated as clear oils in 55% and 12% yields, respectively (Scheme 3.15).



Scheme 3.15. Radical Reaction of Bromo-Hydrazone 357

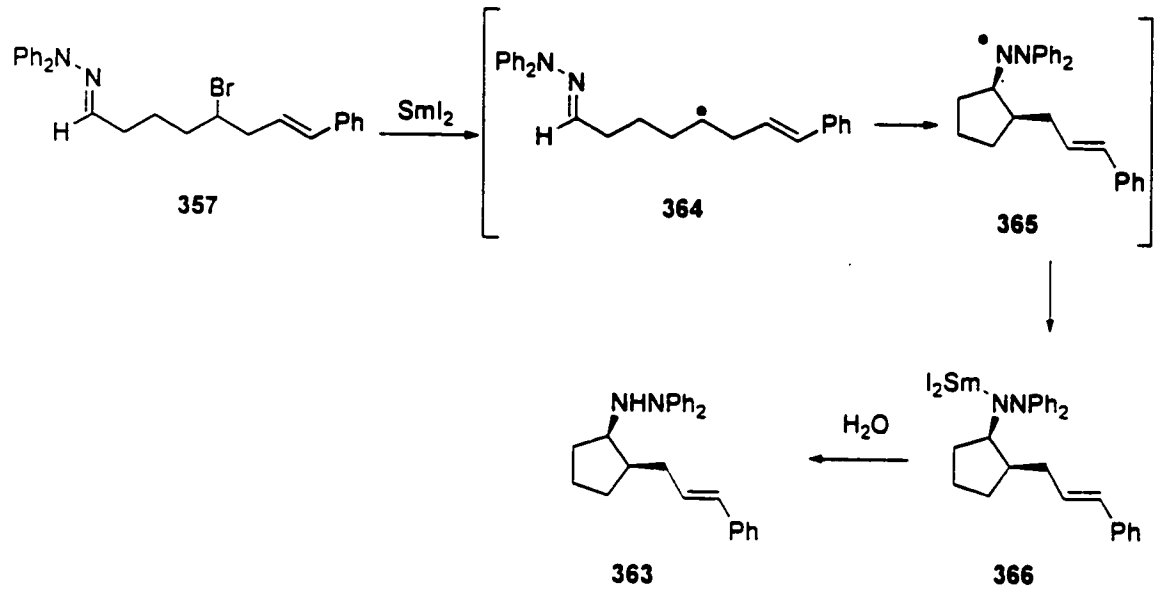
Experiments conducted earlier in our laboratory demonstrated an increase in the amount of the *cis* isomer formed as a result of the radical cyclization process onto *N,N*-diphenylhydrazones at lower temperature.[16] These reactions were conducted in the presence of samarium diiodide in THF at various temperatures.

In our case, the attempt to conduct the tandem radical reaction under samarium diiodide in THF conditions at room temperature failed to provide the expected 5,5 bicyclic system. The only product formed in this process was the monocyclized *cis* isomer **363** (Scheme 3.16).



Scheme 3.16. Samarium Diiodide Cyclization

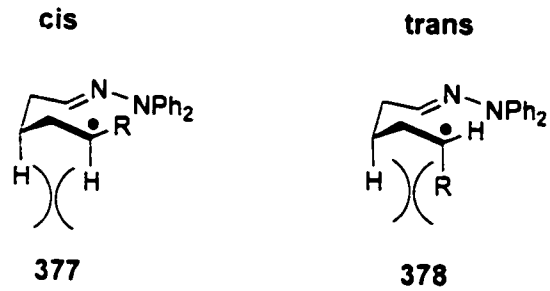
A likely mechanism is shown below in Scheme 3.17.



Scheme 3.17. Proposed Mechanism for the SmI_2 Mediated Hydrazone Cyclization

One equivalent of samarium diiodide generates the alkyl radical **364**, which subsequently cyclizes to generate the hydrazyl radical **365**. In the next step, a second electron transfer occurs to generate an N-SmI_2 species; this transfer likely occurs faster than the hydrazyl cyclization onto the substituted alkene bond. The N-SmI_2 bond is hydrolyzed on work-up to give the *cis* hydrazine **363**.

In order to explain the stereochemical outcome, a transition state based on Beckwith model is proposed (Figure 3.3).



377 **378**

Figure 3.3. Transition States for Radical Cyclization

The first cyclization of the tandem system proceeds through a chair conformation. The transition state that leads to the *cis* isomer is preferred because it minimizes the 1,3 diaxial interactions. It was observed previously that as the size of the R group increases, the steric interactions increase, which results in greater *cis/trans* selectivity.

As mentioned earlier, another factor that affects the *cis/trans* selectivity is temperature. The higher the reaction temperature, the higher the amount of the *trans* isomer obtained. Indeed, this seems to be the case as well in our system.

The *cis* and *trans* monocyclized products **363** and **362** were identified based on key spectral data. As has been observed previously, the ^{13}C NMR resonances for both methine carbons in the *cis* isomer appeared at higher field than those for the *trans* isomer.[17] In order to be able to use this technique for the assignment of the relative stereochemistry, it is essential to have both isomers in order to compare the chemical shifts. The attempted tandem experiments provided different isomers, thus we were able to measure the ^{13}C NMR spectra of both. Figure 3.4 lists the key ^{13}C NMR signals that were used to assign the relative stereochemistry of the methyl substituted isomers. In addition, NOESY spectra enabled us to unequivocally assign the stereochemistries of the two isomers.

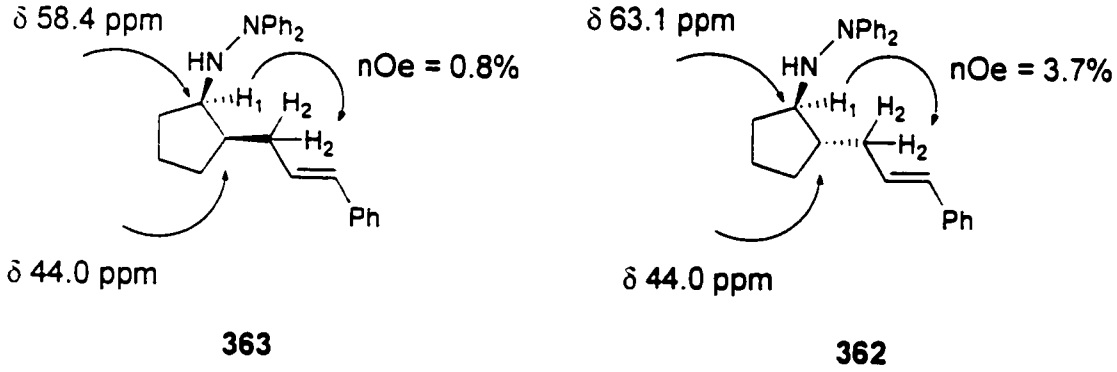
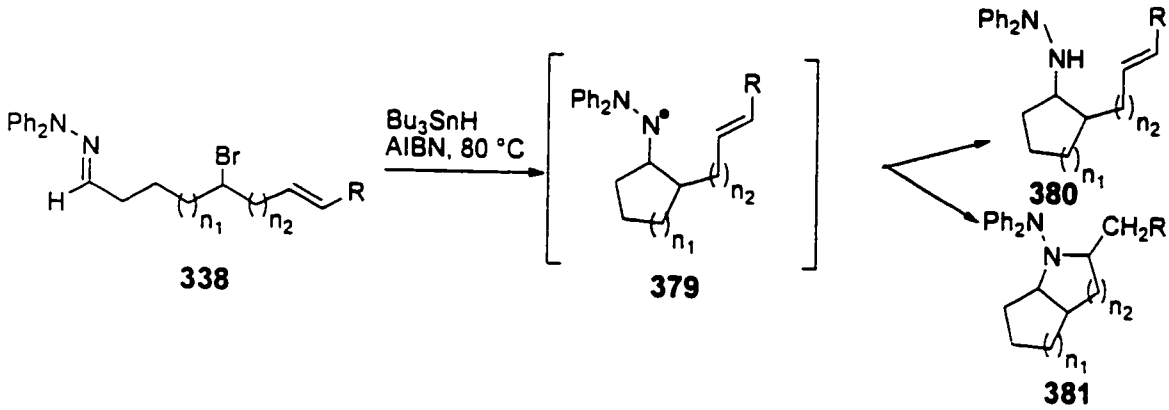


Figure 3.4. Assignment of Stereochemistry in the Monocyclized Products

Subsequent attempts of improving the yield of the tandem product by adding Lewis acids ($MgBr_2$ and BF_3) to the tributyltin hydride reaction system failed to provide the expected result. As a matter of fact, in these cases, addition of one equivalent of hydride did not affect the starting material. Adding more of the tin hydride and refluxing the reaction mixture for longer period of times caused extensive decomposition. We suspected that the quality of a recently purchased bottle of tributyltin hydride might be responsible for these undesired results. Consequently, we prepared a fresh batch of tributyltin hydride by reducing bistributyltin oxide with sodium borohydride in ethanol.[18] However, in spite of our efforts of employing freshly prepared tributyltin hydride along with Lewis acids, we did not isolate any of the tandem product in these experiments. Another unsuccessful attempt was conducted under tris(trimethylsilyl) hydride conditions.

As it was mentioned at the beginning of this chapter, our studies related to the synthesis of the bicyclic ring system are part of a larger set of experiments conducted in our laboratory to explore the feasibility of tandem reactions for the formation of various ring systems. Table 3.1 below illustrates all the results obtained so far.



Entry	R	n1	n2	Reaction Conditions	Monocycl. %	Tandem %	*cis*/trans
1	H	2	1	SmI_2, room temp.	55	-	1:1
2	H	2	1	Bu_3SnH, Benzene, reflux	70	11	1:1
3	Ph	2	1	Bu_3SnH, Benzene, reflux	-	30	1:1
4	Ph	2	1	TTMSS, Benzene, reflux	-	28	1:1
5	Ph	1	2	Bu_3SnH, Benzene, reflux	50	-	3:1
6	Ph	2	2	Bu_3SnH, Benzene, reflux	45	-	1:0
7	Ph	1	1	SmI_2, room temp	75	-	0:1
8	Ph	1	1	Bu_3SnH, Benzene, reflux	12	55	1:0

Table 3.1. Bicyclic Ring Systems Synthesis

Several conclusions can be drawn:

(a) The presence of an activating group on the double bond is necessary to ensure good yields of the tandem product.

(b) [4.3.0] Bicyclic ring systems are formed in reasonable yields.

(c) Best results are obtained in the synthesis of the [3.3.0] bicyclic ring system.

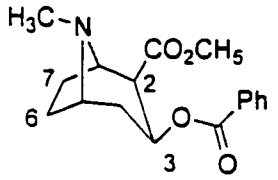
(d) [3.4.0] and [4.4.0] bicyclic ring systems cannot be obtained *via* this method.

3.7 Attempted Tropane Systems Synthesis

3.7.1 Introduction

In his work, "On Coca", published in 1884, Sigmund Freud warmly recommended cocaine as an antifatigue or aphrodisiac formula, and as potential treatment for alcohol and morphine addiction. On the other side of the Atlantic, his contemporary, John Pemberton, was marketing his new drink Coca Cola®, made from extract of coca leaves, as "intellectual beverage and temperance drink"!

Over the years, as use of the drug increased, the number of cocaine-related problems also increased. The need for the treatment of individuals who have become addicted to this powerful reinforcing drug has prompted a large amount of research aimed at the complete elucidation of its mode of action and development of new therapies.[19] It is believed that molecules that act as cocaine antagonists or partial agonists could help to identify drugs for addicted individuals, hence a great deal of research has focused on the preparation of cocaine related molecules.[20] For example, it was shown that replacement of the C-3 benzoate by phenyl leads to compounds of higher potency (these phenyl-bearing structures are often referred to as the WIN series compounds).[21]



382

Figure 3.5. Structure of Cocaine

In addition, major efforts are being expended to develop antibodies and vaccines.[22] For these purposes, a prodigious number of cocaine-related tropane analogues have been synthesized,[23] leading to high affinity and selective cocaine receptor ligands and providing information about the structure/activity relationship of cocaine-related tropane derivatives.

Cocaine contains an 8-azabicyclo[3.2.1]octane framework and is one of the eight possible stereoisomers of methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate.[24] In addition to construction of this azabicyclo ring system, the major hurdle to its synthesis has been control of stereochemistry, both of enantiomeric integrity and of the thermodynamically unstable axial carboxylate function. Most of the nonracemic cocaine analogues were synthesized by the derivatization of natural cocaine, while others were obtained by resolution or separation of racemic or diastereomeric reaction mixtures. The original and classical Mannich-type construct for the tropane skeleton was developed over half a century ago by Willstätter, Robinson, and Schöpf.[25] This first biomimetic synthesis, is still employed. Recent examples are the syntheses of 6- and 7-hydroxylated cocaine[26] and unnatural (+)-cocaine, *via* a chemical resolution.[27]

Several methods employ cycloaddition reactions, including the reaction of rhodium(II)-stabilized vinylcarbenoids with pyrroles,[28] [3 + 4] cycloaddition of iron oxyallyl cations to pyrrole,[29] nitrone cycloaddition,[30] nitroso cycloaddition,[31] and pyridinium betaine-based dipolar cycloaddition.[32] Recently, a number of methods for the enantiospecific synthesis of aza apical azabicyclos[33] related to the tropane framework were developed.

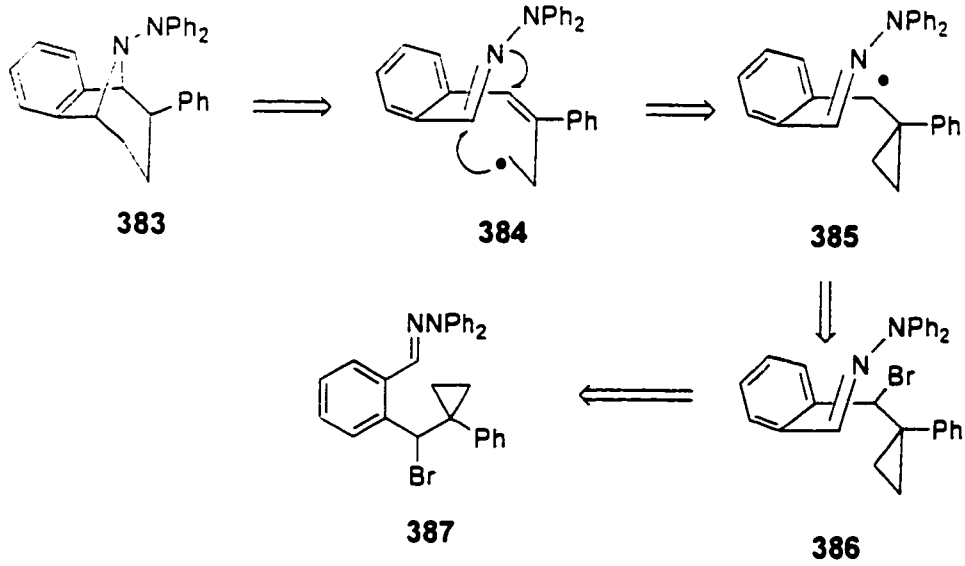
While previous synthetic methods have been directed primarily to alteration of substituents about the three-carbon bridge, no general strategy has allowed the introduction of diverse functionality into the 6- and 7-positions of the tropane skeleton. Interestingly, it was found that racemic two-carbon bridge methoxylated cocaines possessed interesting pharmacological properties; in

particular, some of these methoxylated derivatives were found to antagonize, albeit weakly, cocaine's ability to inhibit dopamine reuptake.[34]

3.7.2 Retrosynthetic Analysis

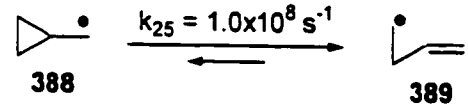
Based on the previous unsuccessful route, a benzene substituent at positions 7 and 8 of the tropane ring system was deemed necessary to ensure the proximity between the radical and the radical acceptor during the tandem process. In view of the results obtained during the study of the bicyclic ring systems synthesis *via* tandem radical reactions, we decided to introduce an activating substituent on the double bond to encourage the second cyclization step.

The tropane nucleus **383** could be generated from a cyclopropane bromide **387** through a series of steps. The retrosynthetic analysis is presented in Scheme 3.18.



Scheme 3.18. Rethrosynthetic Analysis of the Tropane Ring System

The ring opening of α-cyclopropyl radicals is a very fast process[35] (Scheme 3.19).



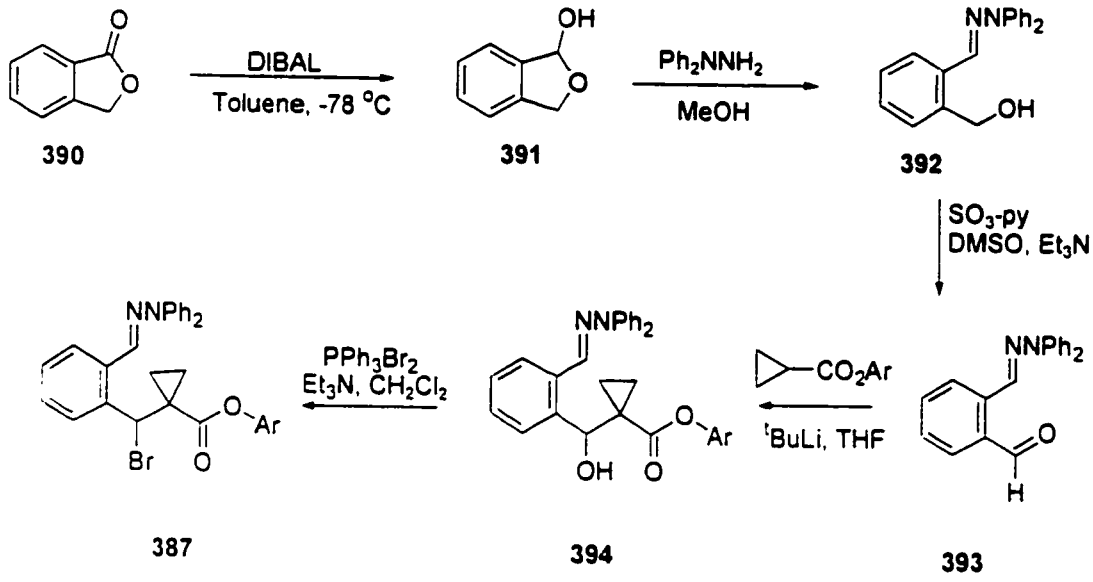
388 **389**

Scheme 3.19. Ring Opening of α-Cyclopropyl Radicals

The rate constants[36] for this type of system are known and some of the stereoelectronic[37] and conformational[38] characteristics have been established. Moreover, it is known that the rate of ring opening is faster than the rate of ring formation in systems of this type.[39]

3.7.3 Substrate Synthesis

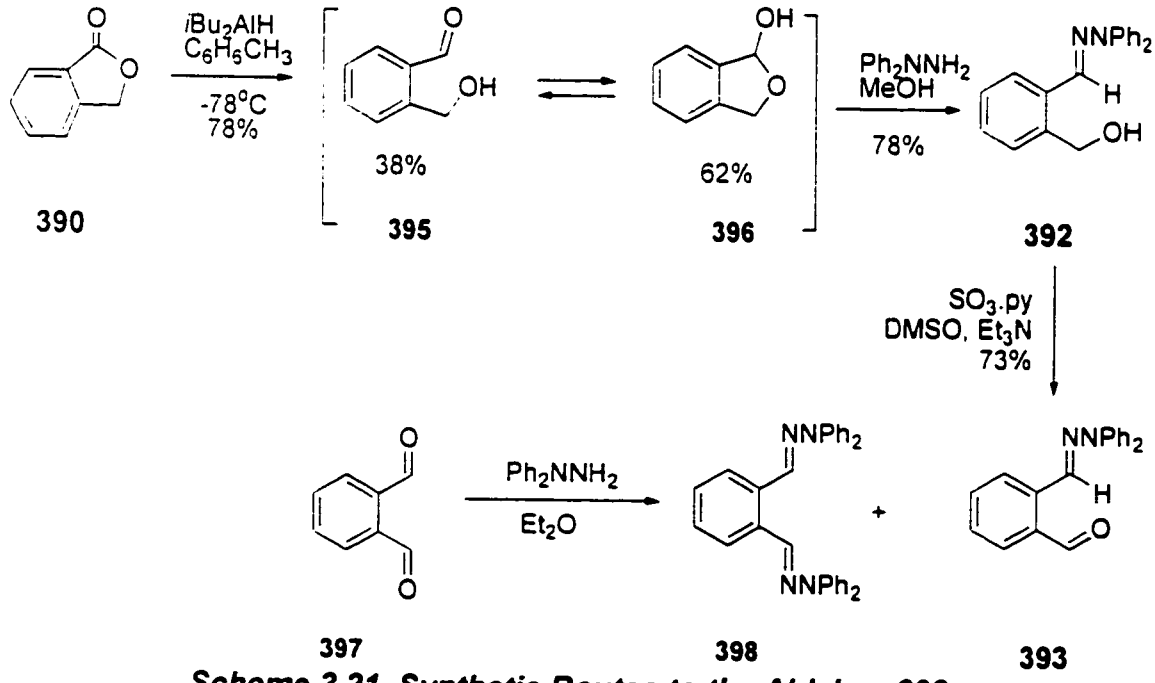
The proposed synthesis of the free radical precursor **387** is outlined in Scheme 3.20 below.



390 391 392 387 394 393

Scheme 3.20. Proposed Synthesis of the Free Radical Precursor

We devised two different route to arrive at the aldehyde **393**, as shown in Scheme 3.21.



390 395 396 392 397 398 393

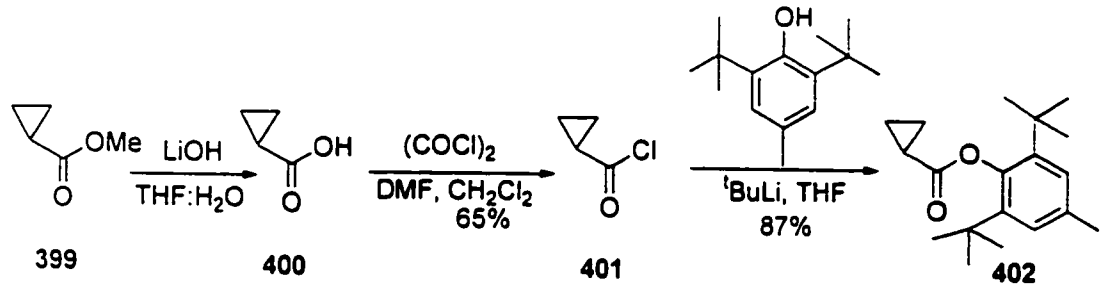
Scheme 3.21. Synthetic Routes to the Aldehye 393

The most straightforward pathway is the condensation of the phtalic dicarboxaldehyde **397** with one equivalent of *N,N*-diphenylhydrazine. For this reaction, the choice of solvent is critical. In methanol, the only product isolated is the dihydrazone **398**; this product is insoluble in methanol and precipitates quickly, shifting the equilibrium of the system towards its formation. A much better solvent choice is diethyl ether; in this case, the desired aldehyde was isolated in 23% yield, along with significant amounts of the dihydrazone **398**.

An alternative way for the synthesis of aldehyde **393** commences with reduction of the commercially available phtalide **390** in toluene at –78 °C to give the corresponding lactol **396** in 78% yield. This was isolated as an inseparable mixture of isomers **395** and **396** (38:62 by GCMS and ^{1}H NMR). Treatment of the lactol **396** with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature provided the *N,N*-diphenylhydrazone **392** in 78% yield as a single geometric isomer. The oxidation of the resulting primary alcohol **392** with sulfur trioxide pyridinium complex in DMSO in the presence of triethylamine afforded the aldehyde **393** in 73% isolated yield.

The proposed synthesis of the free radical precursor **387** features the addition of a lithium cyclopropanyl anion to an aldehyde **393**. An electron withdrawing substituent was required on the cyclopropane ring to facilitate its deprotonation and serve as an activating group on the resulting double bond. The presence of a bulky group on the ester functionality is absolutely necessary to prevent self condensation, which generates the trimerized product.[40] Seebach and coworkers determined the BHT ester does not undergo self condensation, presumably because of the steric hindrance of the carbonyl group.[41]

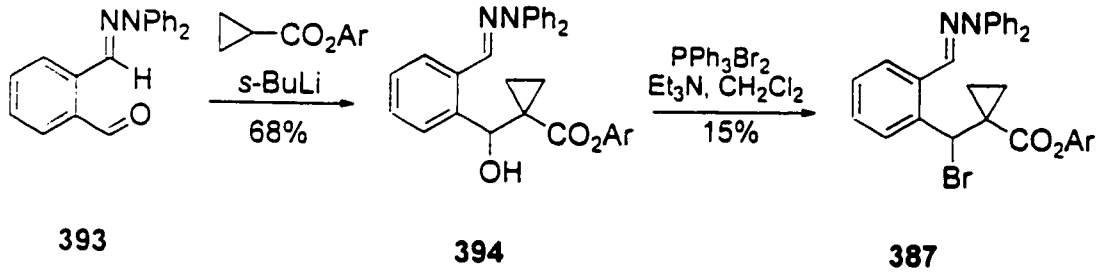
Due to its ease of use and high yields, Seebach's procedure was applied to our synthesis. Scheme 3.22 outlines the preparation of the BHT cyclopropanecarboxylate **402**.



Scheme 3.22. Preparation of the BHT Cyclopropanecarboxylate 402

Generation of the cyclopropanecarboxylic acid **400** from its methyl ester proceeds quantitatively under mild hydrolysis conditions. Formation of the acid chloride **401** using oxalyl chloride / DMF method proceeded in 65% yield. 2,6-Di(*tert*-butyl)-4-methylphenol was converted to the corresponding lithium phenoxide using *tert*-butyllithium. Addition of the acid chloride to a cold solution of the lithium phenoxide resulted in the formation of the desired product.

The final sequence required for the preparation of starting material **387** is shown in Scheme 3.23 below.

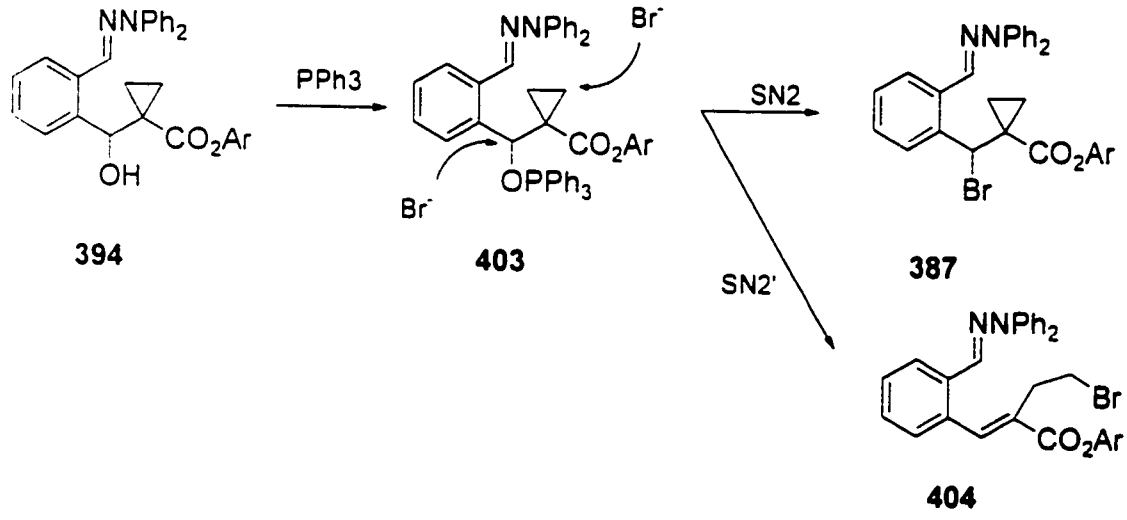


Scheme 3.23. Substrate Synthesis for the Tropane Ring System

The addition of the lithium cyclopropanyl anion to the aldehyde functionality proceeded cleanly without any observed competitive addition to the hydrazone functionality, to yield the corresponding β-hydroxy ester **394**. The chemospecificity of this reaction can be discerned by analysis of the H^1 NMR

spectrum, as the vinyl hydrogen of the hydrazone remained in the product, while the aldehyde signal disappeared.

The next step was the conversion of the secondary alcohol to a bromide. The bromination was effected with $Ph_3P{\bullet}Br_2$. The desired bromide was difficult to isolate. The ^1H NMR of the crude reaction mixture was very complex; interestingly, it indicated the presence of a vinyl proton. As we discovered previously (see Chapter 2), when bromination was effected on secondary alcohols containig a larger isopropyl or cyclohexyl substituent, a second compound was isolated and determined to be the corresponding alkene. Scheme 3.24 shows possible pathways for the generation of the bromide **387** along with the product **404** resulting *via* a SN2' nucleophilic attack on the cyclopropane carbon. Unfortunately, we were unable to isolate a clean sample of the alkene product **404** to confirm our hypothesis. A small sample of the bromide **387** was isolated and characterized.

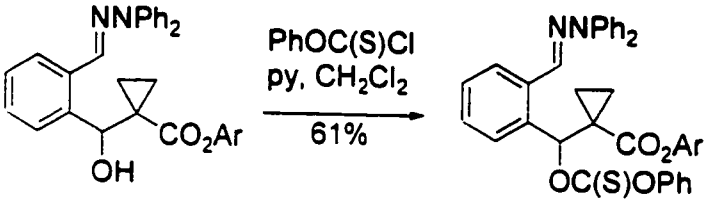


Scheme 3.24. Pathways for the Bromination of the Secondary Alcohol

According to literature reports, phenylselenides are good precursors for radical generation followed by cyclopropane ring opening. However attempted preparation of the corresponding starting material using several different

experimental conditions (Bu_3P, Ph_3P, various solvents etc.) did not provide the desired product.

An alternative substrate[42] for the corresponding free radical cyclization is the thionocarbonate **405** which was synthesized in 65% yield as shown in Scheme 3.25 below.



394 **405**

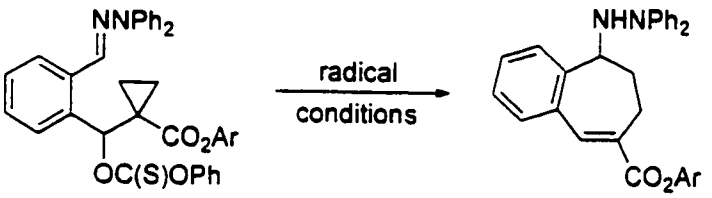
Scheme 3.25. Synthesis of the Thionocarbonate Precursor

3.7.4 Results and Discussion

We used the general procedure for the syringe pump radical reactions. Bromide **387** was dissolved in benzene, then treated with tributyltin hydride and AIBN. The reaction mixture was refluxed for two hours. TLC analysis of the reaction revealed the formation of a complex mixture of products. The ^1H NMR of the crude product showed that the signal for the hydrazone proton had disappeared. Attempts to purify the reaction mixture failed to provide any identifiable product.

Next, we subjected the thionocarbonate **405** to the same reaction conditions. In this case, TLC analysis of the reaction seemed promising, revealing the formation of one major, less polar spot.

Subsequent purification and characterization of the new product showed that the monocyclized product **406** was formed cleanly in 85% yield, as shown in Scheme 3.26.



405 **406**

Scheme 3.26. Radical Reaction of Thionocarbonate 405

We believe that the second cyclization of the aminyl radical onto the activated alkene bond to generate the tropane ring was prevented by both steric factors and the slow rate of the second cyclization. Geometry optimization calculations were carried out on the monocyclized product **406** using both molecular mechanics (MM2) and semi-empirical quantum mechanics (MOPAC). The MM2-optimized structure is shown below.

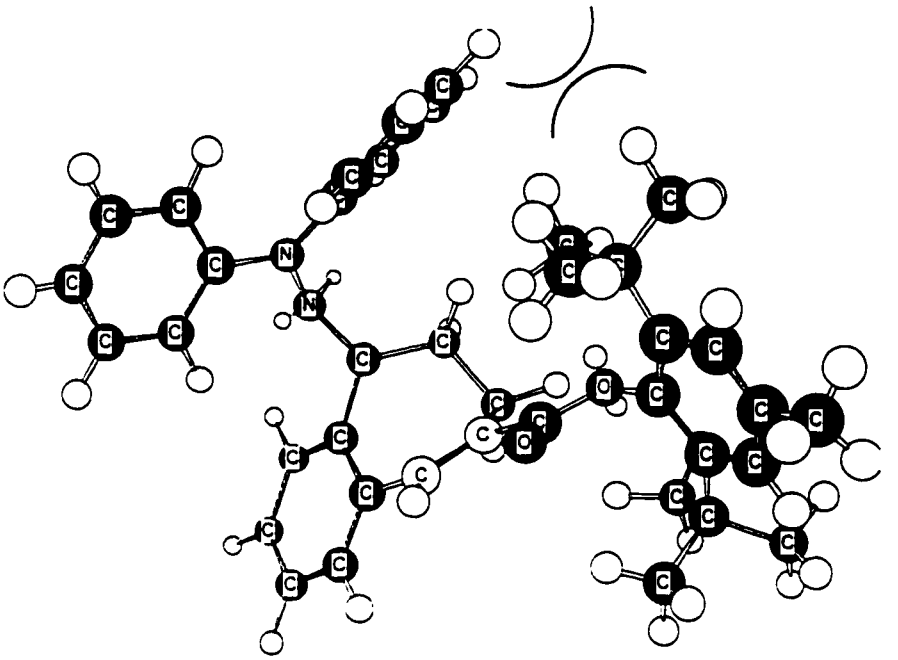


Figure 3.6. Optimized Structure of 406

It is likely that major steric interaction between one of the phenyl rings of the hydrazone and the *tert*-butyl group of the BHT ester prevented the formation of the desired bicyclic product.

Several attempts to hydrolyze or transesterify the ester functionality did not provide the expected products. The results are summarized in Table 3.2 below.

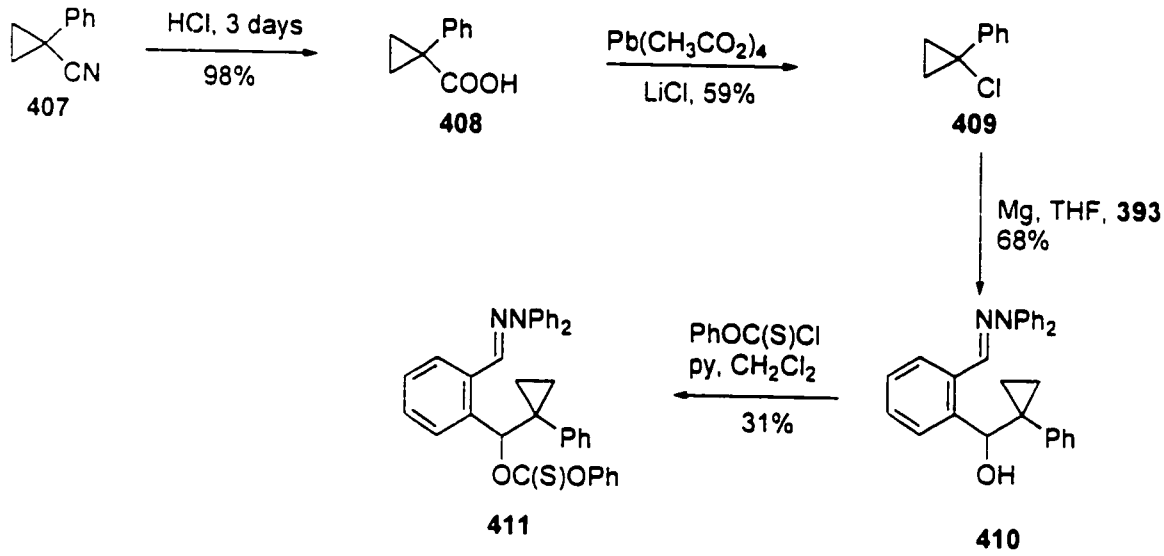
Ester Hydrolysis		**Transesterification**	
Reaction Conditions	**Results**	**Reaction Conditions**	**Results**
tBuOK, THF, H_2O, reflux	Extensive decomposition	BBr_3, MeOH	No reaction
tBuOK, THF, H_2O	No desired product	TsOH, MeOH	No reaction
BBr_3, CH_2Cl_2	No reaction	MeONa, MeOH	No reaction
H_2O_2, H_2O, DMF	No reaction	DMAP, MeOH	No reaction

Table 3.2. Attempts to Hydrolyze or Transesterify the BHT Ester

3.7.5 Modified Approach

In view of the results obtained up to this point, a modified approach was designed. We decided to replace the activating BHT ester substituent of the alkene bond with a much smaller phenyl substituent.

Scheme 3.27 below outlines the synthesis of the free radical precursor **411**.



Scheme 3.27. Synthesis of the Phenyl Substituted Radical Precursor

The synthesis commenced with the hydrolysis of the nitrile **407** to afford phenylcyclopropanecarboxylic acid **408** in 98% yield upon refluxing with concentrated HCl for three days. Phenylcyclopropanecarboxylic acid **408** was chlorodecarboxylated[43] with lead tetraacetate to yield phenylcyclopropylchloride **409** in 59% yield. This reaction must be thoroughly degassed, otherwise the major product formed is 1-phenylcyclopropyl acetate.

The Grignard reagent of the phenylcyclopropylchloride **409** was prepared and allowed to react with aldehyde **393**. The corresponding secondary alcohol **410** was formed in 68% yield. Following this step, thionocarbonate **411** was

prepared in 31% yield. This material was difficult to isolate and attempted purification by flash chromatography led to some decomposition.

The thionocarbonate was subjected to our standard syringe pump radical reaction conditions. TLC analysis revealed a complex reaction mixture. In spite of repeated attempts, we failed to isolate any of the desired product.

Chapter 3 References

1. Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.*, **1985**, *107*, 1448.
2. Newcomb, M.; Musa, O. M.; Martinez, F. N.; Horner, G. H. *J. Am. Chem. Soc.* **1997**, *119*, 4569.
3. (a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T. Saelis, A. K. *Aust. J. Chem.* **1983**, *36*, 535. (b) Beckwith, A. L. J.; Schiessser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373.
4. 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.
5. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.
6. (a) Horner, J. H.; Martinez, F. N.; Musa, O. M.; Newcomb, M.; Shahin, H. E. *J. Am. Chem. Soc.* **1995**, *117*, 11124. (b) Musa, O. M.; Horner, J. H.; Shahin, H.; Newcomb, M. *J. Am. Chem. Soc.* **1996**, *118*, 3862.
7. (a) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241. (b) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. (c) Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1993; Vol. 58, pp 1.
8. Ha, C.; Musa, O. M.; Martinez, F. N.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 2704.
9. Bowman, W. R., Stepheson; Young, A. R. *Tetrahedron Lett.* **1995**, 36, 5623.
10. Kizil, M., Murphy J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409.
11. Gravelle, Kristian M.Sc. dissertation, University of Ottawa, 1997.
12. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
13. Corey, E. J., Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
14. (a) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R.S. *J. Am. Chem. Soc.* **1982**,

104, 2305. (b) Lipshutz, B. H.; Korner, M.; Parker, D.A. *Tetrahedron Lett.* **1987**, *28*, 945.

15. Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964.
16. Sturino, Claudio Ph.D. dissertation, University of Ottawa, 1994.
17. (a) Ley, G. C.; Lichter, R. L.; Nelson, A. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, 2nd ed.; J. Wiley and Sons; New York, 1980. (b) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* 1981. **1988**, *110*, 1633.
18. Doe, J. *Chem. Ind.* **1988**, 764, pp 43.
19. W. L. Woolverton and K. M. Johnson, *Trends Pharmacol. Sci.*, 1992, **13**, 193; W. L. Woolverton and M. S. Kleven, *NIDA Research Monograph*, 1988, **88**, 160.
20. (a) Carroll, F. I.; Gray, J. L.; Abraham, P.; Kuzemko, M. A.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1993**, *36*, 2886. (b) Davies, H. M. L.; Saikali, E.; Huby, N. J. S.; Gilliatt, V. J.; Matasi, J. J.; Sexton, T.; Childers, S. R. *J. Med. Chem.* **1994**, *37*, 1262. (c) Kelkar, S. V.; Izenwasser, S.; Katz, J. L.; Klein, C. L.; Zhu, N.; Trudell, M. L. *J. Med. Chem.* **1994**, *37*, 3875. (d) Kozikowski, A. P.; Saiah, M. K. E.; Johnson, K. M.; Bergmann, J. S. *J. Med. Chem.* **1995**, *38*, 3086. (e) Carroll, F. I.; Kotian, P.; Dehghani, A.; Gray, J. L.; Kuzemko, M. A.; Parham, K. A.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1995**, *38*, 379. (f) Neumeyer, J. L.; Tamagnan, G.; Wang, S.; Gao, Y.; Milius, R. A.; Kula, N. S.; Baldessarini, R. J. *J. Med. Chem.* **1996**, *39*, 543.
21. (a) R. L. Clarke, S. J. Daum, A. J. Gambino, M. D. Aceto, J. Pearl, M. LevSitt, W. R. Cumiskey and E. F. Bogado, *J. Med. Chem.*, 1973, **16**, 1260. (b) F. I. Carroll, Y. Gao, M. A. Rahman, P. Abraham, K. Parham, A. H. Lewin, J. W. Boja and M. J. Kuhar, *J. Med. Chem.*, 1991, **34**, 2719. (c) F. I. Carroll, A. H. Lewin, J. W. Boja and M. J. Kuhar, in *Drug Design for Neuroscience*, ed. A. P. Kozikowski, Raven Press, New York, 1993, pp.

149–166.

22. (a) Landry, D. W.; Zhao, K.; Yang, G. X.-Q.; Glickman, M.; Georgiadis, T. M. *Science* **1993**, *259*, 1899. (b) Carrera, M. R. A.; Ashley, J. A.; Parsons, L. H.; Wirsching, P.; Koob, G. F.; Janda, K. D. *Nature* **1995**, *378*, 727. (c) Sakurai, M.; Wirsching, P.; Janda, K. D. *Tetrahedron Lett.* **1996**, *37*, 5479. (d) Berkman, C. E.; Underiner, G. E.; Cashman, J. R. *J. Org. Chem.* **1996**, *61*, 5686.

23. (a) Kline, R. H., Jr.; Wright, J.; Fox, K. M.; Eldefrawi, M. E. *J. Med. Chem.* **1990**, *33*, 2024. (b) Kozikowski, A. P.; Xiang, L.; Tanaka, J.; Bergmann, J. S.; Johnson, K. M. *Med. Chem. Res.* **1991**, *1*, 312. (c) Milius, R. A.; Saha, J. K.; Madras, B. K.; Neumeyer, J. L. *J. Med. Chem.* **1991**, *34*, 1728. (d) Carroll, F. I.; Lewin, A. H.; Abraham, P.; Parham, K.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 883. (e) Carroll, F. I.; Gao, Y.; Rahman, M. A.; Abraham, P.; Parham, K.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1991**, *34*, 2719. (f) Carroll, F. I.; Gao, Y.; Abraham, P.; Lewin, A. H.; Lew, R.; Patel, A.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 1813. (g) Kozikowski, A. P.; Roberti, M.; Xiang, L.; Bergmann, J. S.; Callahan, P. M.; Cunningham, K. A.; Johnson, K. M. *J. Med. Chem.* **1992**, *35*, 4764. (h) Wang, S.; Gao, Y.; Laruelle, M.; Baldwin, R. M.; Scanley, B. E.; Innis, R. B.; Neumeyer, J. L. *J. Med. Chem.* **1993**, *36*, 1914. (i) Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *J. Med. Chem.* **1993**, *36*, 3975. (j) Carroll, F. I.; Abraham, P.; Kuzemko, M. A.; Gray, J. L.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Chem. Soc., Chem. Commun.* **1993**, 44. (k) Carroll, F. I.; Mascarella, S. W.; Kuzemko, M. A.; Gao, Y.; Abraham, P.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1994**, *37*, 2865. (l) Meltzer, P. C.; Liang, A. Y.; Madras, B. K. *J. Med. Chem.* **1994**, *37*, 2001. (m) Aronson, B.; Enmon, J. L.; Izenwasser, S.; Katz, J. L.; Kelkar, S. V.; Luo, L.; Nolan, S. P.; Trudell, M. L. *J. Med. Chem.* **1996**, *39*, 1560. (n) Chen, Z.; Izenwasser, S.; Katz, J. L.; Zhu, N.; Klein, C. L.; Trudell, M. L. *J. Med. Chem.* **1996**, *39*, 4744.

(o) Chang, A.-C.; Burgess, J. P.; Mascarella, S. W.; Abraham, P.; Kuhar, M. J.; Carroll, F. I. *J. Med. Chem.* **1997**, *40*, 1247. (p) Thiruvazhi, M.; Abraham, P.; Kuhar, M. J.; Carroll, F. I. *Chem. Commun.* **1997**, 555. (q) Kozikowski, A. P.; Simoni, D.; Baraldi, P. G.; Lampronti, I.; Manfredini, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 441.

24. Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. *J. Med. Chem.* **1992**, *35*, 969.

25. (a) Willstätter, R. *Ber.* **1896**, *29*, 936. (b) Willstätter, R. *Liebigs Ann. Chem.* **1903**, *326*, 23. (c) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762. (d) Schöpf, C.; Lehman, G. *Liebigs Ann.* **1935**, *518*, 1.

26. Kozikowski, A. P.; Simoni, D.; Manfredini, S.; Roberti, M.; Stoelwinder, J. *Tetrahedron Lett.* **1996**, *37*, 5333.

27. Lewin, A. H.; Naseree, T.; Carroll, F. I. *J. Heterocycl. Chem.* **1987**, *24*, 19.

28. Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095 and references therein.

29. Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786.

30. Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786.

31. Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Org. Chem.* **1985**, *50*, 1818.

32. (a) Pham, V. C.; Charlton, J. L. *J. Org. Chem.* **1995**, *60*, 8051. (b) Lomenzo, S. A.; Enmon, J. L.; Troyer, M. C.; Trudell, M. L. *Synth. Commun.* **1995**, *25*, 3681. (c) Rumbo, A.; Mouriño, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1996**, *61*, 6114. (d) Kozikowski, A. P.; Araldi, G. L.; Ball, R. G. *J. Org. Chem.* **1997**, *62*, 503.

33. (a) Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 314. (b) Hernández, A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 1058. (c) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683. (d) Sardina, F.; J.; Howard, M. H.; Koskinen, A. M. P.;

Rapoport, H. *J. Org. Chem.* **1989**, *54*, 4654. (e) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539 and the related references therein. (f) Koskinen, A. M. P.; Rapoport, H. *J. Med. Chem.* **1985**, *28*, 1301. (g) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313. (h) Lin, R.; Castells, J.; Rapoport, H. *J. Org. Chem.*, **1998**, *63*, 4069.

34. Simoni, D.; Stoelwinder, J.; Kozikowski, A. P.; Johnson, K. M.; Bergmann, J. S.; Ball, R. G. *J. Med. Chem.* **1993**, *36*, 3975.

35. Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 4132

36. (a) Ash, C. E.; Hurd, P. W.; Darensbourg, M. Y.; Newcomb, M. *J. Am. Chem. Soc.* **1987**, *109*, 3313; (b) Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1989**, *111*, 275; (c) Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* **1986**, *108*, 7981; (d) Griller, D.: Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

37. (a) Beckwith, A. L. J.; Phillipou, G. *Aust. J. Chem.* **1976**, *29*, 123. (b) Pereyre, M.; Quintard, J.-P. *Pure Appl. Chem.* **1981**, *53*, 2401.

38. Mariano, P. S.; Bay, E. *J. Org. Chem.* **1980**, *45*, 1763.

39. Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

40. Pinnick, H. W.; Chang, Y.-H.; Foster, S. C. Govindan, M. *J. Org. Chem.* **1980**, *45*, 4505.

41. Seebach, D.; Haner, R.; Maetzke, T. *Helv. Chim. Acta* **1986**, *69*, 1655.

42. Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

43. (a) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, 279. (b) Ogle, C. A.; Riley, P. A.; Dorchak, J. J.; Hubbard, J. L. *J. Org. Chem.* **1988**, *53*, 4409.

Chapter 4

Chiral Hydrazones

4.1 General Considerations

The difference in biological activity of most enantiomers requires the synthesis of pharmaceuticals, pesticides, food additives, pheromones, *etc.*, in high enantiomeric purity. The last few decades have seen a tremendous surge of interest in asymmetric synthesis, as organic chemists struggle to develop more efficient synthetic pathways to enantiomerically pure compounds.

There are four general approaches that are commonly used to obtain enantiomerically pure material by synthesis. One approach involves incorporating a resolution into the synthetic plan.[1] A second general approach is to use a starting material that is enantiomerically pure.[2] A third way is to use a chiral catalyst in a reaction that creates one or more chiral centres. Finally, a fourth method for enantioselective synthesis involves the use of a chiral auxiliary. This is an enantiomerically pure material that can control the stereochemistry of one or more reaction steps in order to give a product with the desired configuration. Once the chiral auxiliary has achieved its purpose, it can be removed from the molecule and recycled.

Chiral auxiliaries have been extensively used in enolate alkylation and aldol chemistry.[3] The requirements for control of configuration of new stereogenic centers are based on concepts developed initially in carbanion and enamine chemistry.[4]

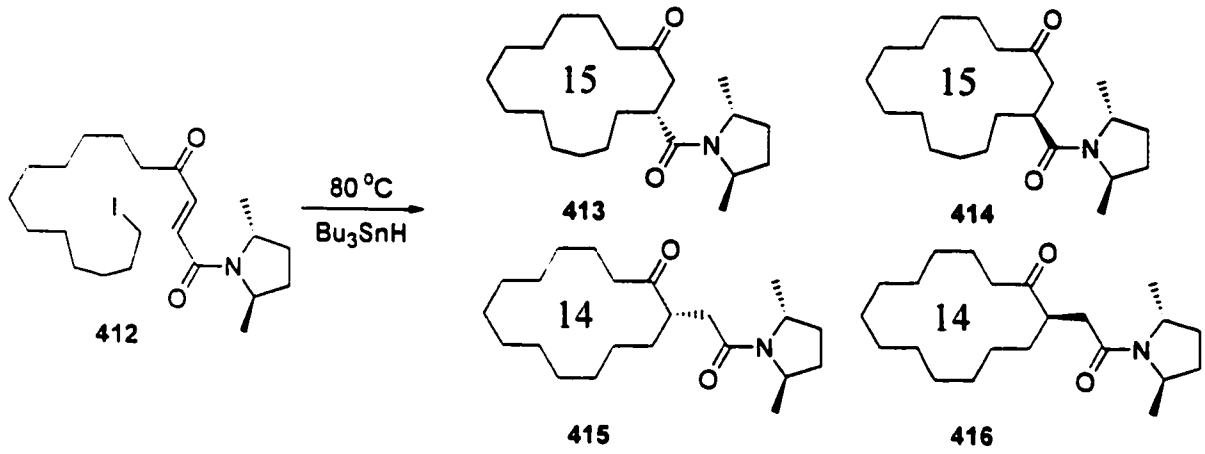
It should also be noted that a basic requirement for a practicable asymmetric synthesis using stoichiometric amounts of a chiral auxiliary is that this reagent be inexpensive and easily available in large amounts.

Among the many examples of chiral auxiliaries used in stereoselective synthesis, chiral hydrazones have played an important role. In the course of the development of modern synthetic methods in the field of asymmetric synthesis the SAMP-/RAMP-hydrazone method opened a highly diastereo- and enantioselective route to a great variety of carbonyl compounds, alcohols, amines and heterocycles.[5]

4.1.1 Stereoselectivity In Radical Reactions

In a radical cyclization process, the configuration of the resulting stereogenic centers can be controlled by chiral auxiliaries attached to the radical acceptor. For this, the chiral group must differentially shield the diastereotopic faces of the radical trap.

For example, as shown in Scheme 4.1, free radical macrocyclization of the alkene **412** bearing the dimethyl-pyrrolidine amide gave rise to four diastereomeric products in 65-70% yield.[6] Two diastereomeric products, **413** and **414**, result from an *endo* cyclization, addition of the primary radical to the end of the alkene nearest to the amide. At 80 °C, these two fifteen-membered ring products are formed with a selectivity of approximately 14/1, **413** being the major product formed. Two diastereomeric *exo* cyclization products, **415** and **416**, are formed as a 1/1 mixture. The ratio of regioisomers is also 1/1 on this macrocyclization.



Scheme 4.1. Free Radical Macrocyclization of the Alkene 412

4.1.2 Research Objectives

As part of our continuing interest in the use of hydrazones as radicals acceptors, the following chapter describes the preparation and use in radical cyclizations of aldehyde hydrazones such as **417** and **418** that contain chiral auxiliaries adjacent to the C=N double bond (Figure 4.1).

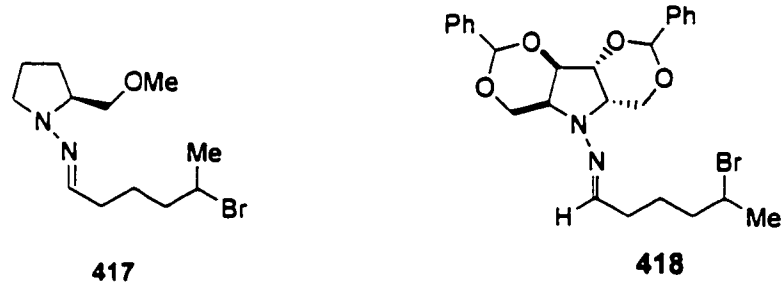
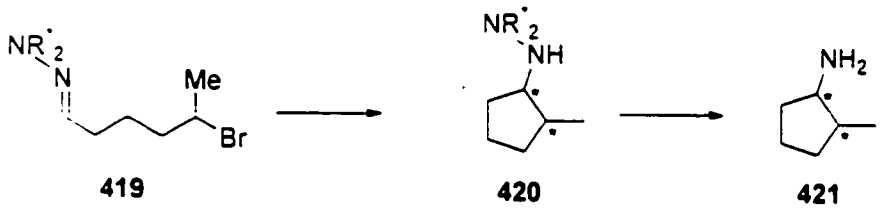


Figure 4.1. Chiral Auxiliaries Containing Hydrazones Employed in Diasteroselectivities in Radical Cyclizations Studies

Ideally, the presence of the chiral auxiliary will influence the diastereoselectivity level of the radical cyclization reaction onto this special class of hydrazones. This level could be dependent on the reaction conditions such as temperature or reagents employed.

The employment of chiral hydrazones could lead to cyclic chiral amines in the radical cyclization process followed by subsequent cleavage of the N-N bond of chiral trisubstituted hydrazines **420**, as shown in Scheme 4.2. The reductive cleavage could be effected by hydrogenolysis or by employing samarium diiodide.[7]



419 **420** **421**

Scheme 4.2. Chiral Amines via Radical Cyclization

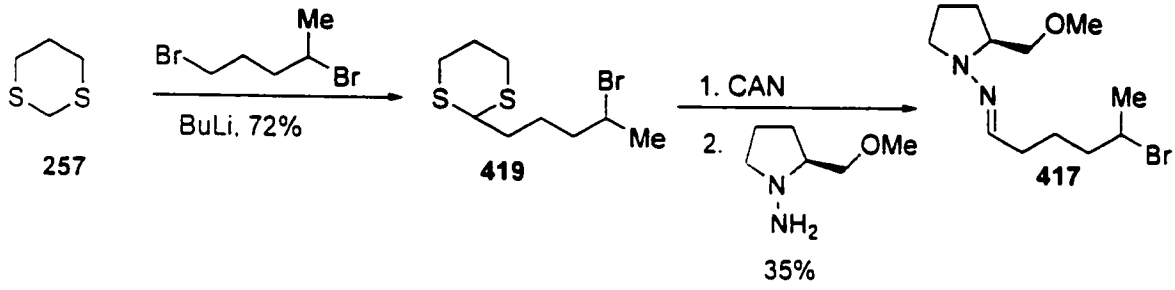
In addition, a recent report describes the mild, racemization free cleavage of ketone SAMP-hydrazones with oxalic acid; it is possible for the chiral auxiliary to be isolated and reused.[3]

4.2 Results and Discussion

4.2.1 SAMP Hydrazones

The commercially available SAMP hydrazine was considered to be a suitable starting material. This not only contains the requisite chiral element, but

a straightforward synthetic sequence would allow for its conversion to a suitable hydrazone. It was also hoped that any cyclization products would lend themselves to analysis by NMR. The synthesis of hydrazone **417** is outlined below (Scheme 4.3).



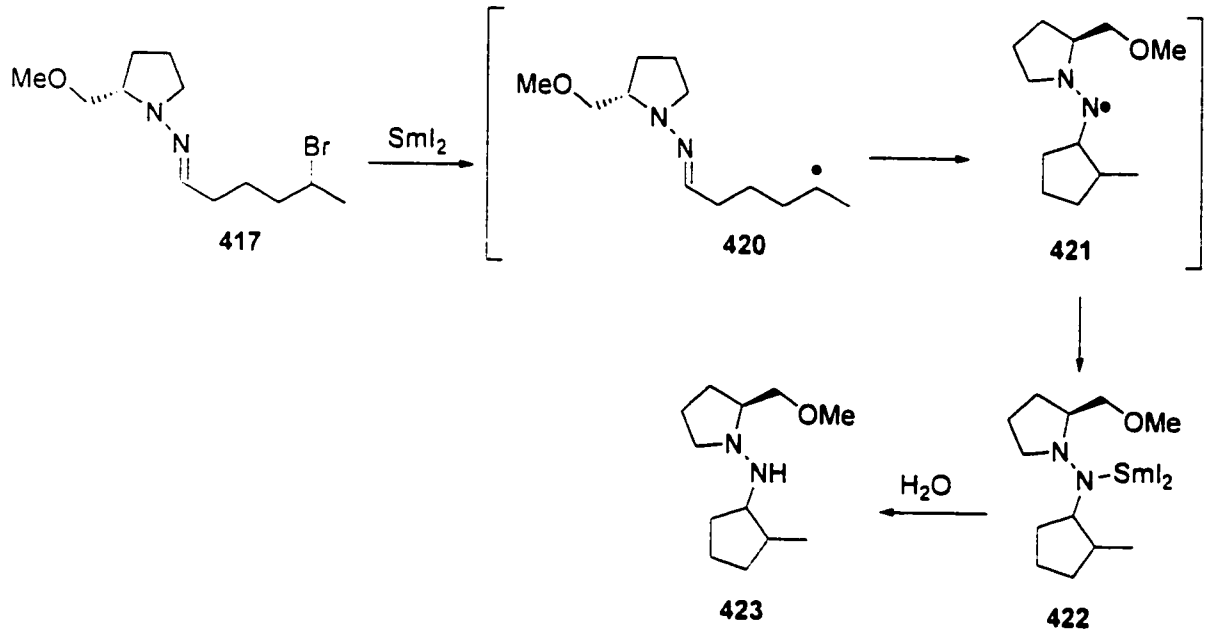
Scheme 4.3. Synthesis of hydrazone 417

Dithiane **257** was subjected to deprotonation by *n*-butyllithium at –10 °C. Dispalcement of the primary bromide of the 1,4-dibromopentane by the resulting anion provided compound **419** in 72% yield. Hydrolysis of dithiane **419** to the corresponding aldehyde was effected by treatment with cerium ammonium nitrate (CAN). The resulting aldehyde was not purified, but treated directly with the commercially available SAMP to yield bromo-hydrazone **417** in 35% total yield over these two steps.

As it was found to be the case with *N,N*-diphenylhydrazones, a key spectral feature of this hydrazone is also represented by the vinylic hydrogen (R_2N-N=C<u>H</u>CH_2R). This appears as a clean triplet at δ 6.51 (J = 5.5 Hz) in the ^{1}H NMR spectrum. It can be deducted from the spectral data that a single geometric isomer resulted from the condensation of the intermediate aldehyde with SAMP hydrazine. Based on our previous experience and on literature precedence[9] showing that hydrazones are formed predominantly as the *E* geometric isomer, compound **417** was assigned as the *E* hydrazone (with the pyrrolidine substituent *syn* to the hydrogen).

The next step in our investigation was the free-radical cyclization which was conducted under samarium diiodide conditions. The bromo-hydrazone **417** was dissolved in THF containing HMPA in a Schlenk flask. The system was degassed using three freeze pump thaw cycles, introducing argon after the last cycle. The solution was then warmed to the desired temperature and samarium diiodide was added dropwise.

A likely mechanism for this reaction is shown in Scheme 4.4.

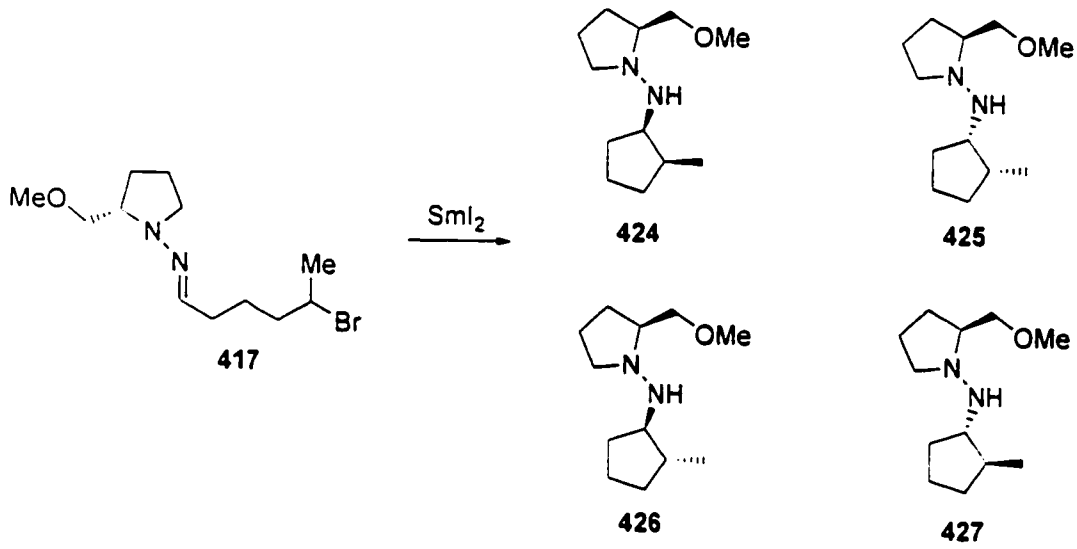


Scheme 4.4. Proposed Mechanism for the SmI_2 Mediated Hydrazone Cyclization

In this process, one equivalent of samarium diiodide is consumed in generating the alkyl radical **420**. This subsequently cyclizes to generate the hydrazine radical **421**. A second electron transfer then occurs from samarium to the nitrogen radical generating an N-SmI_2 species **422** and consuming the second equivalent of samarium diiodide. The N-SmI_2 bond is hydrolyzed on work-up to give the observed hydrazine **423**.

4.2.2. Chiral Induction Investigation

In theory, there are three different stereogenic centers in the product, thus 2^3 = 8 possible stereoisomers could be formed as a result of the cyclization process; however, only four different stereoisomers could be produced in practice, as one of the stereogenic centers has a fixed configuration. As shown in Scheme 4.5, two *cis* and two *trans* stereoisomers could be expected.



Scheme 4.5. Possible Stereoisomers from the Radical Cyclization

When the radical cyclization reaction was conducted at room temperature under samarium diiodide conditions, it appears by TLC and crude NMR analysis that a mixture of *cis* and *trans* geometric isomers were formed, *cis* being the major one. The ^{1}H NMR spectrum of the mixture of the diastereomers obtained is so complex that we did not succeed in analyzing it completely. Furthermore, the reaction mixture proved to be difficult to purify, so no conclusive data were obtained from this first experiment.

We decided to conduct the reaction at a lower temperature, to minimize the potential side reactions. A radical cyclization reaction under samarium diiodide conditions was conducted at –78 °C. In this case, TLC analysis indicates the formation of one geometric isomer only. Upon purification of the reaction mixture and separation by flash chromatography, we were able to isolate the two *cis* diastereoisomers **424** and **425** in 31% yield. Unfortunately, we were unable to determine the diastereomeric ratio directly from the ^{1}H NMR spectrum of the mixture, as there was a great deal of overlapping.

In theory, it is possible to resolve enantiomers on analytical scale high-performance liquid chromatography. In this case the preferential interaction between one enantiomer and the chiral stationary phase is of fundamental importance. We tried to determine the diastereomeric excess using Chiralcel-OJ chiral column without success.

The common NMR methods used to determine %ee involve chiral derivatizing reagents,[10] chiral solvating agents,[11] or chiral lanthanide shift reagents.[12]

There are certain advantages in employing a chiral solvating agent: this approach is very direct requiring only the mixing of the solute, the chiral solvating agent and an achiral cosolvent (such as benzene d^6 or deuterochloroform), and recording the NMR spectrum. The chiral solvating agent employed was (R)-(-)-2,2,2-Trifluoro-1-(9-anthryl)ethanol[13], available from Aldrich. For this method it is, however, important to keep in mind that a prerequisite for peak separation to occur is the existence of an enantioselective interaction with the chiral solvent. Unfortunately, in our case this effect was too small to be of practical use. We were able to recover the solute from the chiral solvating agent by flash chromatography.

The common shift reagents are β-diketones complexes with metal ions of the lanthanide series, such as europium, praseodymium or ytterbium. Such paramagnetic complexes can combine or interact with compounds containing electron-donating groups, such as amines, amino-acids, alcohols, ketones and

esters, resulting in a considerable downfield shift for nuclei which are not too far from the site of interaction. The example given in Figure 4.2 is based on (+)-camphor.

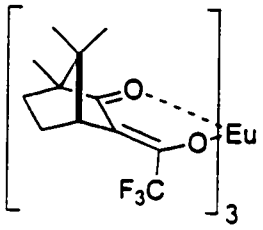


Figure 4.2. Structure of [tris(3-trifluoromethylhydroxymethylene-(+)-camphorato]-europium (III) (Eu[(+)(tfc)]$_3$)

The reagents are readily soluble in typical NMR solvents such as carbon tetrachloride or deuterated chloroform and the spectral shifts produced are often studied as a function of the amount added. A substantial increase in spectral resolution may be achieved when chiral lanthanide-shift reagents are used and consequently resonance lines corresponding to two enantiomers are better separated and the enantiomer composition can be accurately determined by integration. Results obtained from NMR methods by peak integration give the concentration ratio (r) of the enantiomers, and the enantiomeric purity or enantiomeric excess (e.e.) is calculated as:

$$\text{e.e.} = \frac{(1-r)}{(1+r)} \times 100\%$$

The diastereomeric ratio was determined by ^{1}H NMR analysis with chiral shift reagent Eu(tfc)$_3$ in which the methyl ether group that appears at 3.30 was split into two peaks: one enantiomer at 3.59 and the other at 3.53 when 0.8 equivalents of the shift reagent was added (Figure 4.3). The absolute configuration of the major diastereomer has not been assigned.

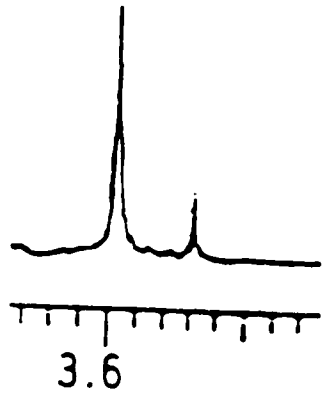


Figure 4.3. ^1H NMR Spectra of Enantiomers 424 and 425 in the Presence of Chiral Shift Reagent $Eu(Tfc)_3$

From the ratio of the peak heights in the ^1H NMR the diastereomeric ratio is *ca.* 0.28, therefore the diastereomeric excess (%de) is 56%.

At this point, a rationale based on transition state models is proposed to account for the stereochemical outcome of the radical cyclization. The cyclization proceeds through a chair conformation following Beckwith's model and the transition state that leads to the *cis* isomer is preferred because it minimizes the 1,3 diaxial interactions (Figure 4.4). It is difficult to explain the level of enantiocontrol achieved, unless a more elaborate transition state that involves the chelation of the SmI_2•HMPA complex to effectively shield one of the faces of the hydrazone π bond is taken into consideration.

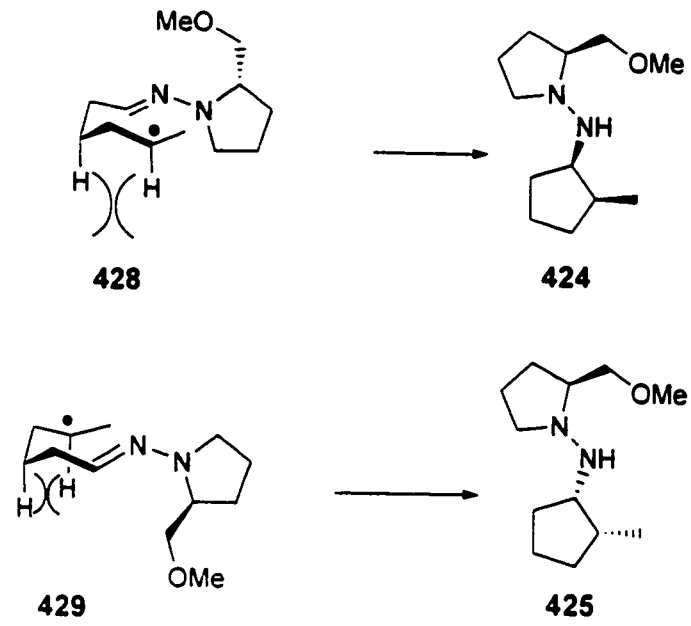
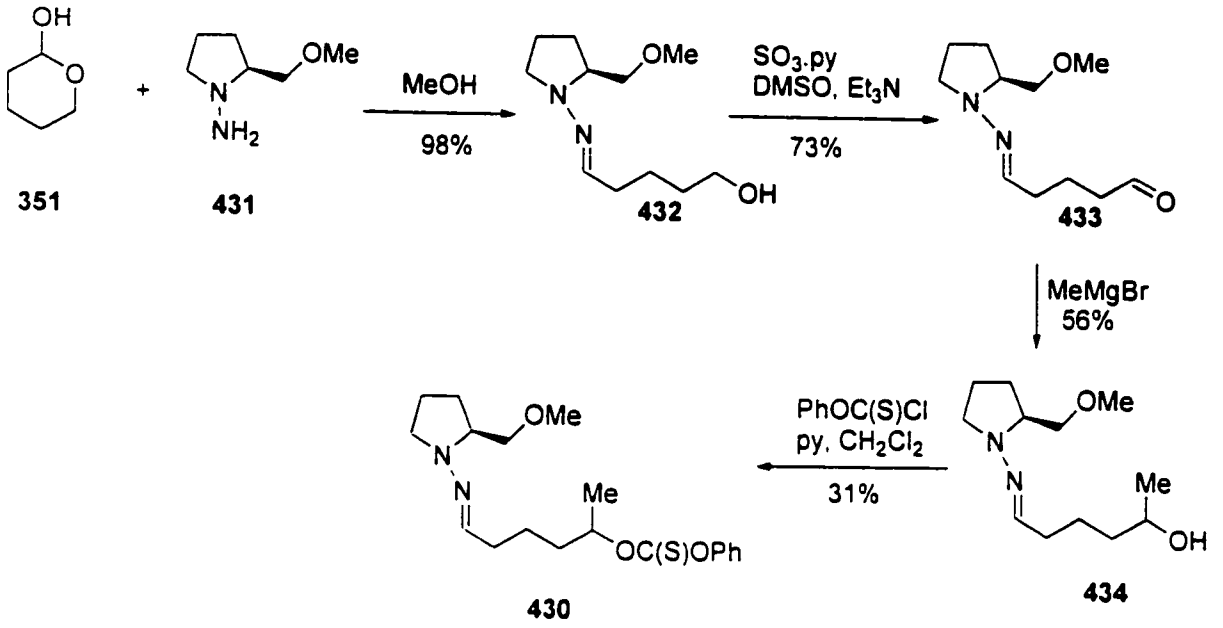


Figure 4.4. Proposed Transition State Structures

The diastereomeric ratio is a function of temperature. Higher temperature leads to lower *cis*/*trans* ratio (more *trans* formed). As the bromide substrate was found to be unsuitable for higher temperature experiments, we decided to take an alternate approach whereby the thionocarbonate would be used as substrate.

The synthesis of the **430** is shown in Scheme 4.6 below.



351 431 432 433 434 430

Scheme 4.6. Synthesis of Hydrazone 430

Valerolactol **351**, obtained by the reduction of the commercially available lactone, was treated with one equivalent of SAMP in methanol at room temperature to provide the desired hydrazone **432** in 98% isolated yield. As with the other hydrazone reported above, only the E geometric isomer was isolated from the reaction. The primary alcohol **432** was oxidized by a SO_3•py/DMSO/Et_3N system[14] to provide the aldehyde **433** in 73% yield. The chemoselective addition of the methylmagnesium bromide to the aldehyde functionality provided the secondary alcohol **434** in 56% yield. Finally, the last step required for the preparation of the starting material was the conversion of the secondary alcohol to the corresponding thionocarbonate ester. Treatment of the alcohol with phenyl chlorothionoformate provided hydrazone **430** in 31% yield.

Having prepared the desired hydrazone, the time came to carry out a free-radical cyclization. Thus, hydrazone **430** was treated with a 0.02M tributyltin hydride solution in benzene with AIBN and heated to reflux. TLC analysis of the

resulting mixture indicated the complete consumption of the starting material with the formation of two new less polar compounds.

The analysis of the ^{1}H NMR spectra of the crude reaction mixture revealed that the *cis* isomer is formed predominantly. Although some of the *trans* isomer was also obtained, this proved too difficult to purify for a complete characterization.

The diastereomeric ratio for the *cis* geometric isomer was determined by ^{1}H NMR analysis with chiral shift reagent Eu(tfc)$_3$. From the ratio of the peak heights in the ^{1}H NMR diastereomeric excess (%de) was determined to be about 30%, lower than in the previous experiment.

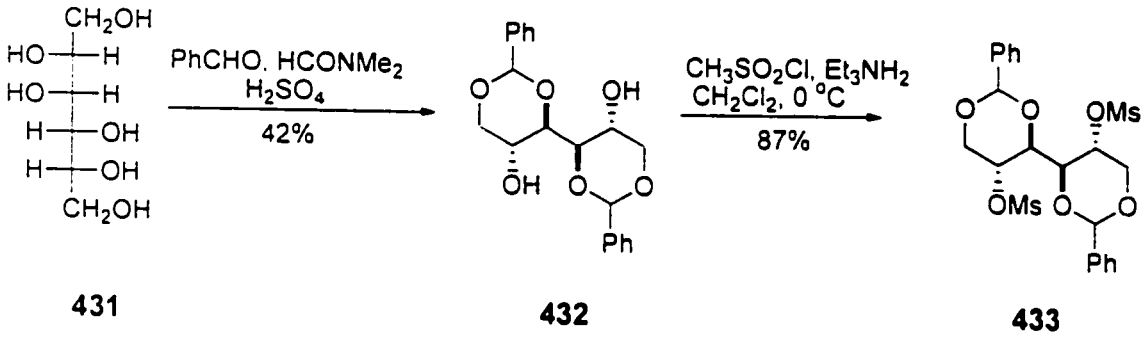
4.2.3 C_2 Chiral Hydrazone

The results obtained with hydrazones that bear SAMP as a chiral auxiliary, were encouraging. It was decided that, in order to have the best chance of success, a more carefully considered chiral auxiliary should be developed. The compound to be prepared should be capable of inducing high levels of enantioselectivity and should be convenient to use. It was implied that, in order to avoid the need for a resolution, the auxiliary should be prepared from inexpensive materials that are already chiral. Ideally, the auxiliary would be a solid.

Some of the more successful reagents developed for asymmetric transformations have used C_2 symmetry as a control element.[15] In a molecule with C_2 symmetry the two chiral centers reinforce each other; the molecule can in effect present identical faces to the incoming reactant (or radical) no matter which way they approach each other. This mode of addition is also valid when the π bond has a C_2 chiral auxiliary present; however, in this case, both sides of

the bond are identical, so the incoming radical "sees" only one face. This should facilitate the prediction of the reaction outcome and simplify mechanistic investigations and calculations.

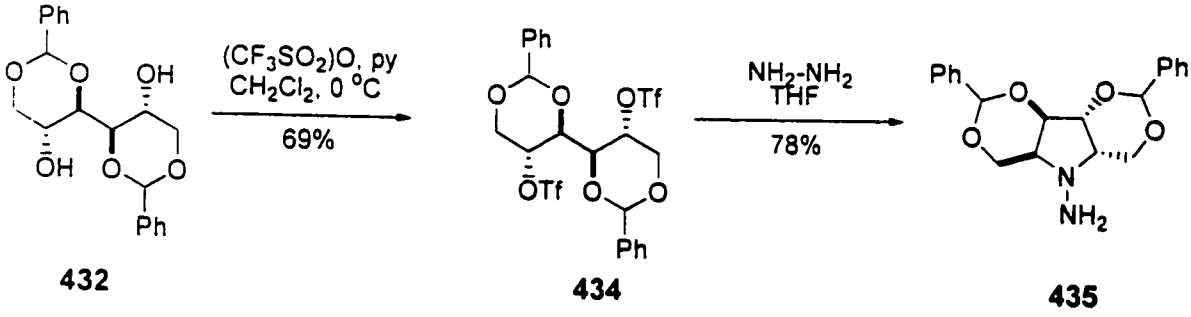
An interesting class of chiral auxiliaries is represented by 1,3:4,6-diacetals of D-mannitol, which proved their potential in asymmetric synthesis.[16] Mannitol **431** is an inexpensive sugar alcohol which is readily available in large quantities. Because of its ease of preparation,[17] the dibenzylidene acetal **432** was chosen. This compound was prepared in 42% yield by treatment of D-mannitol with benzaldehyde in *N,N*-dimethylformamide (Scheme 4.7).



431 **432** **433**

Scheme 4.7. Synthesis of the Dimesylate 433

The resulting diol **432** was converted to dimesylate[18] **433** upon treatment with methanesulfonyl chloride and triethylamine in methylene chloride. Several attempts to convert dimesylate **433** into the corresponding *N*-amino pyrrolidine **435** (Scheme 4.8) were not successful. These included boiling dimesylate **433** with hydrazine, neat or in various solvents, as well as control experiments with benzylamine.[19]

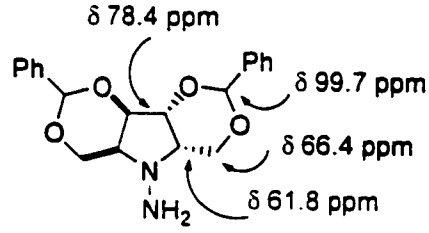


432 **434** **435**

Scheme 4.8. Synthesis of the N-Amino Pyrrolidine 435

The unsuccesful attempts to convert the dimesylate **433** to the desired product dictated that an alternate route involving ditriflate **434** would have been preferable.[20] Consequenly, diol **432** was converted to ditriflate **434** in 69% yield in the presence of triflic anhydride and pyridine in methylene chloride at 0 °C. This compound proved to be quite unstable. Attempts to purify it by column chromatography failed, regardless of the packing material used (silica gel neutralized with triethylamine, neutral or basic alumina). We attempted to recrystalize the ditriflate **434** from several different solvent systems and were succesful when a mixture of diethylether / petroleum ether was used, but only a relatively small yield of the pure ditriflate was isolated (*ca.* 35%). When ^{1}H NMR spectra were compared, it was found that the crude material was almost identical to the recrystallized product. Consequently, ditriflate **434** was prepared and used immediately in the next step, without further purification.

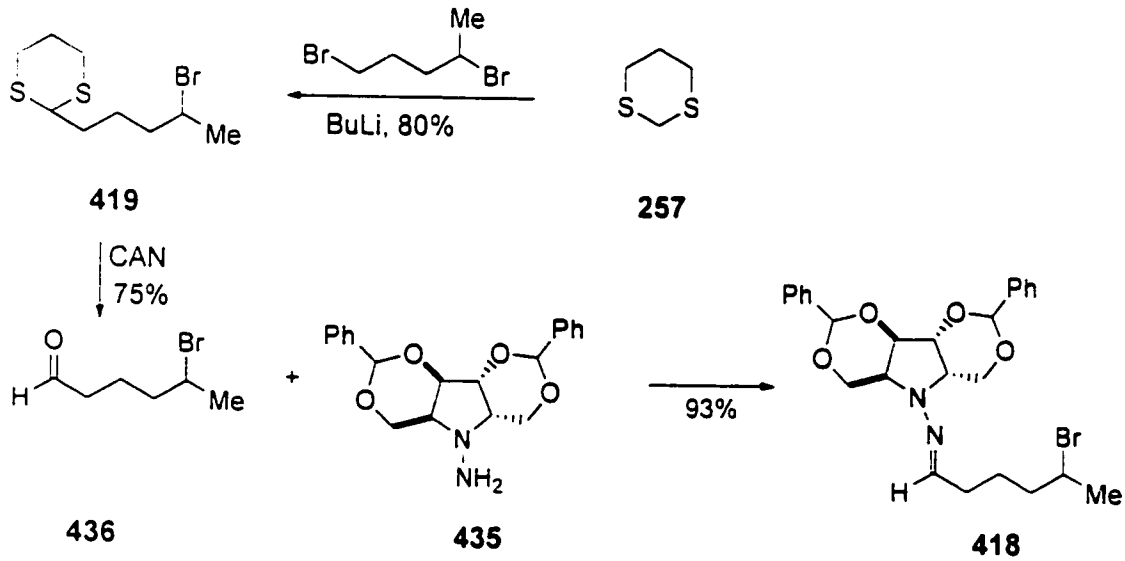
In order to obtain the amino-pyrrolidine **435**, a solution of the ditriflate **434** in dry THF containing anhydrous hydrazine was stirred at room temperature for 20 hours. Nucleophilic substitution of the ditriflate **434** with hydrazine afforded the pyrrolidine framework in 78% yield. Formation of the alternative six-membered heterocycle was not observed since the rate of ring closure is faster for five-membered rings.[21] As evidenced by both ^{1}H and ^{13}C NMR, the product retained C_2 symmetry (Figure 4.5). The ^{13}C NMR spectrum was most informative showing an acetal carbon resonance at δ 99.7, a methylene at δ 66.4 and two methines at δ 78.4 and δ 61.8, in addition to four aromatic signals.



435

Figure 4.5. Spectral Data of N-amino pyrrolidine 435

The synthesis of the desired hydrazone **418** posed no problems (Scheme 4.9). Dithiane **257** was subjected to deprotonation by *n*-buthyllithium at –10 °C. Displacement of the primary bromide of the 1,4-dibromopentane by the resulting anion provided compound **419** in 80% yield. Hydrolysis of dithiane **419** was effected by treatment with cerium ammonium nitrate to afford aldehyde **436** in 75 % yield. Aldehyde **436** was condensed with hydrazine **435** in methanol to produce bromo-hydrazone **418** in 71% yield. The ^{1}H NMR displays the typical vinylic signal at δ 6.67 ppm for the hydrazone proton.

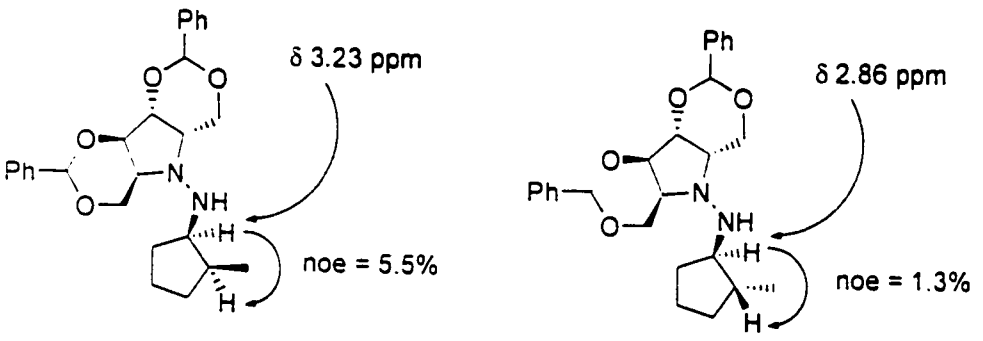


Scheme 4.9. Synthesis of the Hydrazone 418

The next step in our investigation was the free-radical cyclization which was conducted under samarium diiodide conditions. The bromo-hydrazone **418** was dissolved in THF containing HMPA in a Schlenk flask. The system was degassed using three freeze pump thaw cycles, introducing argon after the last cycle. The solution was then warmed to –78 °C and samarium diiodide was added dropwise.

Similarly to the SAMP hydrazone cyclization, it appears by TLC and crude NMR analysis that a mixture of *cis* and *trans* geometric isomers were formed, *cis* being the major one.

Flash chromatography was used to separate the *cis/trans* isomers. The diastereoselectivity and the relative stereochemistries (i. e. *cis* or *trans*) were established by analyzing both the ^{1}H NMR and ^{13}C NMR spectra of the products. Figure 4.6 lists the key spectral data that were used to assign the relative stereochemistry of the two diastereoisomers.



437a **437b**

Figure 4.6. Assignment of Stereochemistry

For the *cis* geometric isomer, the diastereomeric ratio was determined by ^{1}H NMR analysis with chiral shift reagent $Eu(tfc)_3$ in which the methylene proton that appears at 3.23 was split into two peaks: one enantiomer at 3.59 and the

other at 3.53 when one equivalent of the shift reagent was added. The absolute configuration of the major diastereomer has not been assigned.

From the ratio of the peak heights in the ^{1}H NMR the diastereomeric ratio is *ca.* 0.14, therefore the diastereomeric excess (%de) is 75%.

Unfortunately, the amount of the *trans* isomer obtained was too small, with the ^{1}H NMR spectra complicated by the presence of impurities, to enable us to determine the diastereomeric ratio between the other two diasteroisomers.

4.3 Conclusion

In conclusion, we have examined the level of asymmetric induction in radical carbocyclizations mediated by the presence of a hydrazone chiral auxiliary.

We have investigated two chiral auxiliaries. In both systems studied, we observed high levels of diastereoselectivity, the *cis* isomer being formed predominantly.

The level of asymmetric induction was modest under thermal conditions. Better results were obtained at lower temperatures, under samarium diiodide conditions.

Of the two systems studied, the C_2 symmetric chiral auxiliary displayed a higher level of asymmetric induction. In both cases, transition states probably involve some chelation of the SmI_2•HMPA complex to effectively shield one of the faces of the hydrazone π bond.

The diastereomeric excess is less than desired but at a useful level and comparable to current literature methods.

The results should be improved by choosing auxiliaries that have chiral centres located as close as possible to the reaction centre to avoid attenuation of the chiral information.

Chapter 4 References

1. Wilen, D. *Top. Stereochem.* **1971**, *6*, 107.
2. Hanessian, S. *Total synthesis of Natural Products, the Chiron Approach*, Pergamon Press, New York, **1983**.
3. (a) Evans, D. A. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**, p. 2. (b) Heathcock, C. H. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**, p. 111. (c) Lutomski, K. A.; Meyers, A. I. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**, p. 213.
4. (a) Whitesell. J. K., *Chem. Rev.* **1989**, *89*, 1581. (b) Whitesell. J. K., *Acc. Chem. Res.* **1991**, *24*, 296.
5. Enders, D. In *Asymmetric Synthesis*, Vol 3; Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**.
6. Porter, N. A.; Scott, D. M.; Lacher, B.; Giese, B.; Zeitz, H.-G.; Lindner, H. J. *J. Am. Chem. Soc.* **1989**, *111*, 8311.
7. Burke, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.
8. Enders, D.; Hundertmark, T.; Lazny, R. *Synlett* **1998**, 721.
9. Enders, D. In *Asymmetric Synthesis*, Vol 3; Morrison, J. D. Ed.; Academic Press; Orlando, Fl., **1984**.
10. Yamaguchi, S. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press: New York, Vol. 1, **1983**, p. 125.
11. Weisman, G. R. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press: New York, Vol. 1, **1983**, p. 153.
12. Fraser, R. R. In *Asymmetric Synthesis*, Morrison, J. D. Ed.; Academic Press: New York, Vol. 1, **1983**, p. 173.
13. (a) Pirkle, W. H.: Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436. (b) Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 3217.

14. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
15. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
16. Morrison, J. D.; Mosher, H. S. Asymmetric Organic Reactions, Prentice-Hall, New Jersey, **1971**; Inch, T. D., *Adv. Carbohydrate Chem.* **1972**, *27*, 191.
17. Baggett, N.; Stribblehill, P. *J. Chem. Soc., Perkin I* **1977**, 1123.
18. Sinclair, H. B. *Carbohydr. Res.* **1970**, *12*, 150.
19. Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089.
20. Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1987**, 262.
21. Capon, B. *Quart. Rev.* **1964**, *18*, 45.

CHAPTER 5

Experimental

Maistryefull merveylous and Archimastrye
Is the tincture of holy Alkimy;
A wonderful Science, secrete Philosophie,
A singular grace and gift of th'Almightie:
Which never was found by labour of Mann,
But it by teaching, or by Revalacion begann.
(THOMAS NORTON, *The Ordinall of Alchemy, c.* 1477)

General Considerations

Melting points were determined in capillary tubes with a Thomas-Hoover Unit Melt apparatus and are uncorrected. Infrared (IR) spectra were obtained either as neat films on sodium chloride discs, carbon tetrachloride solutions in potassium bromide cells or as potassium bromide pellets. All IR spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR) and the data are reported in reciprocal centimeters (cm^{-1}). Proton magnetic resonance spectra (^1H NMR) were measured at 200 MHz with a Varian Gemini spectrometer, at 300 MHz with a Varian XL-300 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; $CDCl_3$, ^1H: δ 7.24 ppm; ^{13}C: δ 77.0 ppm. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). The multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants (*J*) 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. Gas chromatography-mass spectrometry (GC-MS) was performed with a Hewlett Packard 5890 Series II gas chromatograph using a Hewlett Packard HP-1

(crosslinked methyl silicon gum, 12 m x 0.2 mm x 0.33 μm film thickness) capillary column connected to a Hewlett Packard 5971A mass selective detector. Low resolution mass spectroscopy (LRMS) was performed on a V.G. Micromass 7070 HS mass spectrometer with an electron beam energy of 70 eV (electron impact ionization). High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-IIA mass spectrometer with an electron beam energy of 70 eV. Elemental analyses were conducted by M-H-W Laboratories, Pheonix, AZ, USA or were performed in house. The purity of all title compounds was judged to be >95% as determined by a combination of GC-MS, ^{1}H NMR and ^{13}C NMR analyses.

All commercially available starting materials were purchased from Aldrich Chemical Company unless otherwise stated. All reactions were carried out under an atmosphere of dry nitrogen or argon, unless otherwise stated, in oven-dried or flame-dried glassware equipped with a magnetic stirring bar and rubber septa. Standard inert atmosphere techniques were used in handling all air and/or moisture-sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC). TLC was performed on commercial aluminium sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Visualisation of the TLC spots was accomplished with ultraviolet light, iodine vapour, treatment with 2.5% ethanolic solution of *p*-anisaldehyde containing 3% aqueous H_2SO_4 (w/v) or a 5% solution of ammonium molibdate in 10% aqueous H_2SO_4 (w/v) and subsequent heating. Flash column chromatography using E. Merck silica gel 60 (70-230 or 230-400 mesh) or E. Merck neutral alumina was employed for all column chromatography. 'Concentration' during the work-up refers to concentration *in vacuo* using a Buchi R110 Rotovapour connected to a water or air aspirator, unless otherwise stated. Trace solvents were removed on a vacuum pump. All compounds were stored at –15 °C.

Petroleum ether refers to the hydrocarbon fraction with boiling point range 30-60 °C. Anhydrous tetrahydrofuran (THF) and diethyl ether (ether) were obtained by distillation under an atmosphere of dry nitrogen from

sodium/benzophenone. Benzene, toluene, dichloromethane (CH_2Cl_2), dimethylformamide (DMF), triethylamine, diisopropylamine were dried over calcium hydride and distilled under an atmosphere of dry nitrogen. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation under an atmosphere of dry nitrogen from calcium hydride and stored over 4 Å molecular sieves.

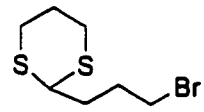
N,N-diphenylhydrazine was obtained by treating the commercially available *N,N*-diphenylhydrazine hydrochloride with 1.0 equivalents of sodium methoxide in methanol. The resulting solution was concentrated and filtered through a sintered glass funnel with a pad of silica gel eluting with 100% ether. The resulting *N,N*-diphenylhydrazine was used without further purification.

n-, *sec*- and *tert*-Buthyllithium were used as received from Aldrich after titration with diphenylacetic acid at 0 °C. Lithium diisopropylamide (LDA) was prepared by adding a solution of *n*-buthyllithium in hexanes to a cooled solution (-78 °C) of dry diisopropylamine (1.05 eq.) in freshly distilled THF. The resulting colourless or slightly yellow solution was stirred at 0 °C for 15 minutes before use. Dess-Martin periodinane was prepared according to the reported literature procedure.[§]

---

§ Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

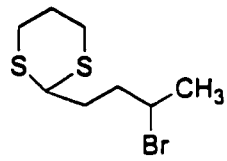
2-(3-Bromopropyl)-1,3-dithiane



258

Dithiane (1.76 g, 14.7 mmol) was placed in a round bottom flask (250 mL) and dissolved in THF (20.0 mL). The resulting solution was cooled to –10 °C, treated with *n*–BuLi (7.0 mL of a 2.5 M solution in hexanes, 17.7 mmol), then stirred at –10 °C for 45 minutes. 1, 3–Dibromopropane (1.48 mL, 14.7 mmol) was added to this solution and stirred at –10 °C for an additional 2 hours. The reaction was quenched with brine (10 mL) and the resulting mixture was poured into a separatory funnel containing ethyl acetate (30 mL) and brine (10 mL). The aqueous layer was extracted with ethyl acetate (3x10 mL), dried and concentrated. The resulting oil was purified by flash chromatography (2:98, diethyl ether / petroleum ether) to give 2.71 g (77%) of the title compound as a light yellow oil; IR (neat, cm^{-1}) 2914, 1429, 1275, 908, 779; ^1H NMR (200 MHz, $CDCl_3$) δ 4.00 (t, J = 6.6 Hz, 1H), 3.41-3.32 (m, 2H), 2.84-2.73 (m, 4H), 2.12-1.78 (m, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.3, 33.6, 32.8, 30.1, 29.4, 25.6 ppm; HRMS *m / z* calcd. for $C_7H_{13}S_2Br$ (M^+): 239.9642, found: 239.9656.

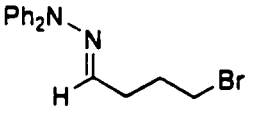
2-(4-Bromobutyl)-1,3-dithiane



259

Dithiane (5.00 g, 41.6 mmol) was placed in a round bottom flask (500 mL) and dissolved in THF (200 mL). The resulting solution was cooled to –10 °C, treated with *n*–BuLi (18.3 mL of a 2.5 M solution, 45.7 mmol) and stirred at –10 °C for 45 minutes. 1, 3–Dibromobutane (5.5 mL, 45.7 mmol) was added and stirring continued at –10 °C for 2 hours. The reaction was quenched with brine (10 mL) and poured into a separatory funnel containing ethyl acetate (100 mL) and brine (50 mL). The aqueous layer was extracted with ethyl acetate (3x150 mL), dried, concentrated and purified by flash chromatography (2:98, diethyl ether / petroleum ether) to yield 8.55 g (81%) of the title compound as a light yellow oil; IR (neat, cm^{-1}) 2919, 1431, 1378, 1275; ^1H NMR (200 MHz, $CDCl_3$) δ 4.13-3.98 (m, 2H), 2.84-2.76 (m, 4H), 2.14-1.74 (m, 6H), 1.71 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.6, 46.6, 37.7, 33.5, 30.2, 26.4, 25.8 ppm; HRMS *m / z* calcd. for $C_8H_{15}S_2Br$ (M^+) : 253.9798, found: 253.9805.

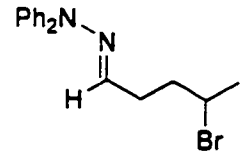
4-Bromobutenal-*N,N*-diphenylhydrazone



260

2-(3-Bromopropyl)-1,3-dithiane **258** (0.686 g, 2.8 mmol) was added to a round bottom flask (50 mL) containing CAN (6.24g, 11.4 mmol) dissolved in an aqueous solution of 75% acetonitrile (8 mL). The solution was stirred at room temperature for 5 minutes and poured into a separatory funnel containing water (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3X 10 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was further purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, ethyl acetate / petroleum ether) under aspirator vacuum, then concentrated. The resulting aldehyde was then mixed with *N,N*-diphenylhydrazine (0.515 g, 2.8 mmol) in MeOH (50 mL). The reaction mixture was stirred at room temperature for 2 hours. The resulting solution was filtered through a sintered glass funnel with a pad of silica gel and washed with EtOAc, concentrated and chromatographed (2:98, diethyl ether / petroleum ether) to afford 0.668 g (75%) of the title compound as a yellowish oil; IR (neat, cm^{-1}) 3047, 2942, 1592, 1492, 1300, 1210; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.38 (m, 4H),7.23-7.12 (m, 6H), 6.59 (t, J = 4.7 Hz, 1H), 3.53 (t, J = 6.6 Hz, 2H), 2.53-2.44 (m, 2H), 2.25-2.15 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 136.7, 129.4, 123.7, 121.9, 32.9, 30.7, 29.5 ppm; HRMS *m / z* calcd. for $C_{16}H_{17}N_2Br$ (M^+): 318.0556, found: 318.0563. Anal. Calcd. for $C_{16}H_{17}N_2Br$: C, 60.58, H, 5.40; N, 8.83. Found: C, 60.56, H, 5.37; N, 9.23.

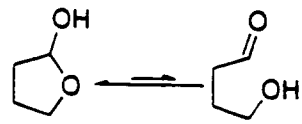
4-Bromopentanal-*N,N*-diphenylhydrazone



261

2-(4-Bromobutyl)-1,3-dithiane **259** (5.08 g, 20 mmol) was added to a round bottom flask (250 mL) containing CAN (44.57 g, 81.3 mmol) dissolved in an aqueous solution of 75% acetonitrile (60 mL). Following the same procedure as above, 5.24 g (79%) of the title compound was isolated as a faint yellow oil; IR (neat, cm^{-1}) 3060, 2963, 1592, 1491, 1210, 748, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.35 (m, 4H), 7.18-7.07 (m, 6H), 6.55 (t, J = 4.7 Hz, 1H), 4.28-4.18 (m, 1H), 2.51-2.41 (m, 2H), 2.13-2.12 (m, 2H), 1.72 (d, J = 6.4 Hz, 3 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.0, 137.4 129.6, 123.9, 122.5, 50.9, 37.9, 30.8, 26.4 ppm; HRMS *m / z* calcd. for $C_{17}H_{19}N_2Br$ (M^+) : 332.0712, found: 332.0698.

4-Hydroxy Butanal

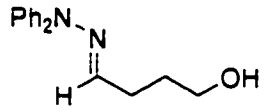


263a **263b**

γ-Butyrolactone (4.96 mL, 5.56 g, 64.6 mmol) was added to a flame dried flask (500 mL) containing freshly distilled toluene (100 mL) under argon. The solution was cooled to -34°C and DIBALH (64.6 mL, 1 M solution in toluene) was added and the reaction mixture stirred at this temperature for 4 hours. The

reaction was quenched with methanol at -34 °C until gas evolution ceased. The solution was warmed to room temperature (21 °C) and saturated aqueous sodium potassium tartrate solution (100 mL) was added. This mixture was poured into a separatory funnel containing water and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (3 X 100 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, ethyl acetate / petroleum ether) under aspirator vacuum to afford 4.12 g (76%) of the corresponding lactol as a colourless oil which was used in the next step without further purification; *for the lactol form*: IR (neat, cm^{-1}) 3360, 2933, 1441, 1215, 747, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 5.09-5.07 (m, 1H), 4.65 (br s, 1H), 3.88-3.83 (t, J = 6.0 Hz, 1H), 3.73-3.65 (m, 2H), 2.01-1.80 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 97.7, 66.7, 32.7, 23.1 ppm; HRMS m / z calcd. for $C_4H_8O_2$ (M^+) : 88.0524, found: 88.0254; *for the aldehyde form*: ^1H NMR (200 MHz, $CDCl_3$) δ 9.77 (s, 1H), 3.46-3.38 (m, 2H), 2.52-2.46 (m, 2H), 2.01-1.80 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.1, 61.5, 40.1, 28.5 ppm.

4-Hydroxybutanal-*N,N*-diphenylhydrazone

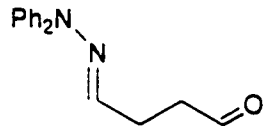


264

4-Hydroxy butanal **263** (4.12 g, 49.0 mmol) in methanol (200 mL) was added to a round bottom flask (500 mL). A solution of Ph_2NNH_2 (10.32 g, 56.0 mmol) in methanol (150 mL) was added dropwise to this solution and the reaction was stirred at 21 °C overnight. Concentration gave a purple oil which

was purified by chromatography (50:50, diethyl ether / petroleum ether) to yield 8.3 g (53% over 2 steps) of the title alcohol as a faint yellow 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), 6.57 (t, *J* = 6.7 Hz, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.98 (br 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 *m / z* calcd. for $C_{16}H_{18}N_2O$ (M^+): 254.1412, found: 254.1407.

Propanal-(*N,N*-diphenylhydrazone)-3carboxaldehyde



265

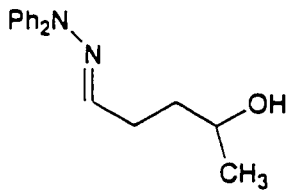
4-Hydroxybutanal-*N,N*-diphenylhydrazone **264** (486 mg, 1.9 mmol) was added to a round bottom flask (250 mL), along with methylene chloride (20 mL) and Dess-Martin reagent (1.05 g, 2.47 mmol). The mixture was stirred for 5 minutes at 21 °C, then ether (50 mL), saturated aqueous sodium bicarbonate solution (20 mL) and aqueos sodium thiosulphate solution (25 mL) were added to the flask. The resulting mixture was stirred until two clear layers were formed (*ca.* 30 minutes) then poured into a separatory funnel containing water (30 mL) and diethyl ether (100 mL). The aqueous layer was extracted with diethyl ether (3X 20 mL), and the combined organic layers were washed with brine, dried and concentrated *in vacuo*. Flash chromatography (25:75, diethyl ether / petroleum ether) afforded 407 mg (85%) of the title compound as a faint yellow oil; IR (neat, cm^{-1}) 3048, 2904, 2828, 1723, 1592, 1491, 1300, 1211, 1068; ^1H NMR (200 MHz, $CDCl_3$) δ 9.87 (br 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 *m / z* calcd. for $C_{16}H_{16}N_2O$ (M^+): 252.1263, found: 252.1277.

General Procedure for Grignard Additions:

The appropriate aldehyde plus enough THF to make a 0.1–0.3 M solution was added to a flame dried, round bottom flask maintained at 0 °C under argon. The required Grignard reagent (1-1.1 eq.) was added at 0 °C and the reaction was stirred at 0 °C until the starting material was consumed (typically 30 minutes, by TLC). The reaction was quenched with saturated ammonium chloride and poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3X) and the combined organic layers were washed with brine, dried, concentrated and chromatographed.

4-Methyl-4-Hydroxybutanal-*N,N*-diphenylhydrazone

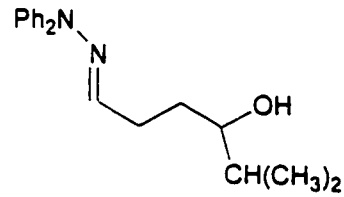


266

Following the general procedure, propanal-(*N,N*-diphenylhydrazone)-3carboxaldehyde **265** (0.46 g, 1.84 mmol) was treated with MeMgCl (0.70 mL, 3.0 M solution in THF, 2.11 mmol) to afford 0.45 g (93%) of the title compound as

a faint yellow oil; IR (neat, cm^{-1}) 3378, 3061, 2925, 1592, 1487, 1302, 1210, 741, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.29 (m, 4H), 7.19-7.07 (m, 6H), 6.57 (t, *J* = 5.2 Hz, 1H), 3.81-3.77 (m, 1H), 2.39-2.29 (m, 2H), 2.01 (br s, 1H), 1.64-1.43 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 139.7, 129.5, 123.7, 122.2, 71.0, 36.5, 31.8, 26.3 ppm; HRMS *m / z* calcd. for $C_{17}H_{20}N_2O$ (M^+): 268.1018, found: 268.1026.

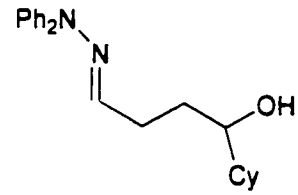
4-Hydroxy-5-methylhexanal-*N,N*-diphenylhydrazone



267

Following the general procedure, propanal-(*N,N*-diphenylhydrazone)-3carboxaldehyde **265** (0.56 g, 2.21 mmol) was treated with *i*–PrMgCl (1.22 mL, 2.0 M solution in THF, 2.44 mmol) to afford 0.65 g (100%) of the title compound as a faint yellow oil; IR (neat, cm^{-1}) 3393, 3061, 2928, 1592, 1483, 1302, 1210, 741, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 7.23-7.07 (m, 6H), 6.60 (t, *J* = 5.1 Hz, 1H), 3.41-3.35 (m, 1H), 2.46-2.36 (m, 2H), 2.11 (br s, 1H), 1.74-1.65 (m, 2H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 139.7, 129.6, 123.8, 122.2, 76.0, 33.5, 30.8, 29.3, 18.6, 17.3 ppm; HRMS *m / z* calcd. for $C_{19}H_{24}N_2O$ (M^+): 296.1890, found: 296.1895.

4-Cyclohexyl-4-Hydroxybutanal-*N,N*-diphenylhydrazone



268

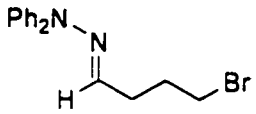
Following the general procedure, propanal-(*N,N*-diphenylhydrazone)-3carboxaldehyde **265** (0.17 g, 0.67 mmol) was treated with CyMgCl (0.4 mL as a 2.0 M solution in THF, 0.8 mmol) at 0 °C to yield 0.195 g (87%) of the title compound ; IR (neat, cm^{-1}) 3392, 2923, 2852, 1592, 1493, 1450, 1301, 1210; ^1H NMR (200 MHz, CDCl3) δ 7.39-7.24 (m, 4H), 7.14-7.04 (m, 6H), 6.57 (t, *J* = 5.0 Hz, 1H), 3.42-3.31 (m, 1H), 2.47-2.32 (m, 2H), 1.85-1.45 (m, 6H), 1.37-0.65 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 139.8, 129.6, 123.9, 122.3, 75.6, 43.7, 30.9, 29.3, 29.1, 27.9, 26.5, 26.3, 26.1 ppm; HRMS *m / z* calcd. for $C_{22}H_{28}N_2O$ (M^+): 336.2203, found: 336.2202.

General Procedure for the Bromination of Alcohols:

Triphenylphosphine (1.2 eq.) and Et_3N (1.2 eq.) in dichloromethane (generally enough to prepare a 0.1–0.3 M solution) was added to a flame dried, round bottom flask maintained at 0 °C under argon. Bromine (1.2 eq.) was added dropwise as a 3 M solution in dichloromethane until the reaction mixture turned a faint yellow colour. This mixture was cooled to 0 °C and the alcohol was added dropwise as a dichloromethane solution. The solution was allowed to stirr

at 0 °C for 30 minutes and at 21 °C for 30 minutes. After this time, the reaction mixture was poured into a separatory funnel containing saturated sodium bicarbonate solution and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3X), and the combined organic layers were washed with brine, dried and concentrated and further purified by flash chromatography.

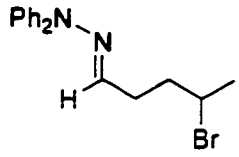
4-Bromobutenal-*N,N*-diphenylhydrazone



260

Following the general procedure, 4-hydroxybutanal-*N,N*-diphenylhydrazone **264** (332 mg, 1.31 mmol) was dissolved in dichloromethane (15 mL) and treated with triphenylphosphine (413 mg, 1.57 mmol), Et_3N (0.21 mL, 1.57 mmol) and titrated with bromine solution as described above. After purification, 304 mg (73%) of the title compound was obtained of the title compound as a yellowish oil; IR (neat, cm^{-1}) 3047, 2942, 1592, 1492, 1300, 1210; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.38 (m, 4H),7.23-7.12 (m, 6H), 6.59 (t, J = 4.7 Hz, 1H), 3.53 (t, J = 6.6 Hz, 2H), 2.53-2.44 (m, 2H), 2.25-2.15 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 136.7, 129.4, 123.7, 121.9, 32.9, 30.7, 29.5 ppm; HRMS *m / z* calcd. for $C_{16}H_{17}N_2Br$ (M^+): 318.0556, found: 318.0563. Anal. Calcd. for $C_{16}H_{17}N_2Br$: C, 60.58, H, 5.40; N, 8.83. Found: C, 60.56, H, 5.37; N, 9.23.

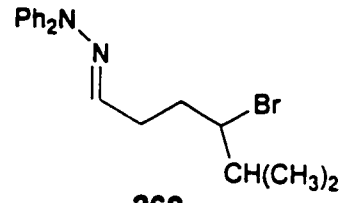
4-Bromopentanal-*N,N*-diphenylhydrazone



261

Following the general procedure, 4-methyl-4-hydroxybutanal-*N,N*-diphenylhydrazone **266** (351 mg, 1.31 mmol) was dissolved in dichloromethane (15 mL) and treated with triphenylphosphine (413 mg, 1.57 mmol), Et_3N (0.21 mL, 1.57 mmol) and titrated with bromine solution as described above. After purification, 323 mg (71%) of the title compound was obtained as a clear colourless oil; IR (neat, cm^{-1}) 3060, 2963, 1592, 1491, 1210, 748, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-7.35 (m, 4H), 7.18-7.07 (m, 6H), 6.55 (t, *J* = 4.7 Hz, 1H), 4.28-4.18 (m, 1H), 2.51-2.41 (m, 2H), 2.13-2.12 (m, 2H), 1.72 (d, *J* = 6.4 Hz, 3 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.0, 137.4 129.6, 123.9, 122.5, 50.9, 37.9, 30.8, 26.4 ppm; HRMS *m / z* calcd. for $C_{17}H_{19}N_2Br$ (M^+) : 332.0712, found: 332.0698.

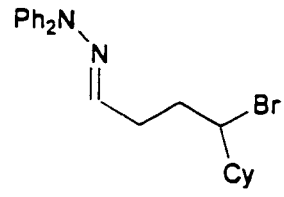
4-Bromo-5-methylhexanal-*N,N*-diphenylhydrazone



269

Following the general procedure, 4-hydroxy-5-methylhexanal-*N,N*-diphenylhydrazone **267** (700 mg, 2 mmol) was treated with triphenylphosphine (630 mg, 2.4 mmol), Et_3N (0.33 mL, 2.4 mmol) and titrated with bromine solution as described above. After purification, 337 mg (47%) of the title compound was obtained as a clear colourless oil; IR (neat, cm^{-1}) 2953 1592, 1492, 1302, 1211, 748, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.35 (m, 4H), 7.15-7.08 (m, 6H), 6.56 (t, *J* = 4.8 Hz, 1H), 4.12-4.09 (m, 1H), 2.60-2.53 (m, 1H), 2.46-2.39 (m, 1H), 2.20-1.95 (m, 1H), 1.94-1.89 (m, 1H), 1.07 (d, *J* = 6.7 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 137.7, 129.6, 124.0, 122.3, 66.1, 34.6, 33.7, 31.2, 21.0, 18.2 ppm; HRMS *m / z* calcd. for $C_{19}H_{23}N_2O$ (M^+): 358.1598, found: 358.1059.

4-Bromo-4-cyclohexylbutanal-*N,N*-diphenylhydrazone



270

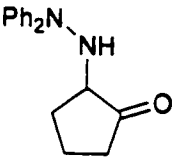
Following the general procedure, 4-cyclohexyl-4-Hydroxybutanal-*N,N*-diphenylhydrazone **268** (444 mg, 1.31 mmol) was dissolved in dichloromethane (15 mL) and treated with triphenylphosphine (413 mg, 1.57 mmol), Et_3N (0.21 mL, 1.57 mmol) and titrated with bromine solution as described above. After purification, 349 mg (67%) of the title compound was obtained as a clear colourless oil; IR (neat, cm^{-1}) 2927, 2852, 1591, 1490, 1301, 1211; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41-7.32 (m, 4H), 7.17-7.04 (m, 6H), 6.54 (t, *J* = 4.8 Hz, 1H), 4.09-4.01 (m, 1H), 2.57-2.39 (m, 2H), 2.12-2.03 (m, 3H), 2.00-1.54 (m, 6H), 1.33-1.16 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 137.8, 129.6, 123.9, 122.2, 64.8, 44.5, 33.2, 31.1, 30.9, 29.2, 26.2, 26.1, 26.0 ppm; HRMS *m / z* calcd. for $C_{22}H_{27}N_2Br$ (M^+): 398.1358, found: 398.1342. Anal. Calcd for $C_{22}H_{27}N_2Br$: C, 66.16; H, 6.81; N, 7.01. Found: C, 66.15; H, 6.96; N, 7.02.

General Procedure for the Carbonylation/Cyclization Reactions:

The starting hydrazone (0.5-0.6 mmol) plus benzene (enough to make a 0.05 M solution, with respect to the hydrazone), AIBN (5-10 mol %) and tributyltin hydride (1.2 eq.) were added to a dry glass tube inserted into a stainless steel autoclave (50 mL). The reaction mixture was stirred under carbon monoxide pressure (usually 800-1100 psi) at 80 °C for 5 hours. The autoclave was cooled to 21 °C and, after the release of excess carbon monoxide, benzene was removed under reduced pressure. The residue was dissolved in diethyl ether (4 mL) and stirred at 21 °C with saturated aqueous potassium fluoride solution (4 mL). Filtration, extraction with diethyl ether, drying over magnesium sulfate and concentration gave a crude mixture which was analyzed by ^1H NMR

spectroscopy to determine the cis/trans ratios. This was followed by chromatography to separate the cis/trans isomers.

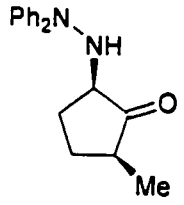
2-(*N,N* -diphenylhydrazino) cyclopentanone



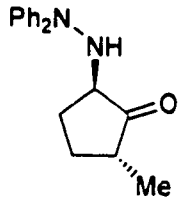
275

Following the general carbonylation/cyclization procedure, 4-bromobutenal-*N,N*-diphenylhydrazone **260** (190 mg, 0.57 mmol) was dissolved in benzene (15 mL) and treated with AIBN (22 mg), Bu_3SnH (0.2 mL, 0.68 mmol) and stirred under CO atmosphere. After workup and purification, 104 mg (69%) of the cyclized product was obtained; IR (neat, cm^{-1}) 2964, 1739, 1591, 1483, 1291; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.12 (m, 6H), 7.01-6.94 (m, 4H), 4.71 (br s, 1H), 3.42 (t, *J* = 6.2 Hz, 1H), 2.37-1.57 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.5, 147.0, 129.1, 122.4, 120.2, 63.9, 36.7, 30.3, 18.4 ppm; HRMS *m / z* calcd. for $C_{17}H_{18}N_2O(M^+)$: 266.1415, found: 266.1404.

2-Methyl-5-(*N,N*-diphenylhydrazino)-cyclopentanones



276a



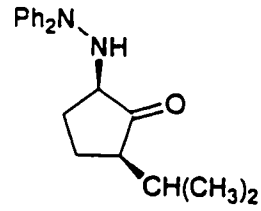
276b

Following the general carbonylation/cyclization procedure, 4-bromopentanal-*N,N*-diphenylhydrazone **261** (214 mg, 0.59 mmol) was dissolved in benzene (13 mL) and treated with AIBN (19 mg), *n*-Bu_3SnH (0.21 mL, 0.70 mmol) and stirred under CO atmosphere. After workup and purification, 117 mg (71%) of the cyclized product as a 1/1.1 = cis/trans mixture was obtained;

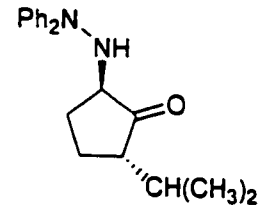
Cis isomer 276a: IR (neat, cm^{-1}) 2952, 2872, 1735, 1590, 1494, 1285; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 4H), 7.16-7.12 (m, 4H), 6.99-6.96 (m, 2H), 4.46 (br s, 1H), 3.49-3.45 (m, 1H), 2.34-2.29 (m, 1H), 2.10-1.98 (m, 2H), 1.77-1.17(m, 2H), 1.13 (d, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.3, 146.6, 128.8, 122.0, 119.8, 62.0, 41.7, 27.3, 26.6, 14.6 ppm; HRMS *m / z* calcd. for $C_{18}H_{20}N_2O(M^+)$: 280.15764, found: 280.15697.

Trans isomer 276b: IR (neat, cm^{-1}) 2961, 2872, 2361, 1738, 1589, 1495, 1280; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.14 (m, 8H), 7.02-6.94 (m, 2H), 4.75 (br s, 1H), 3.46-3.37 (m, 1H), 2.34-2.17 (m, 2H), 1.85-1.60 (m, 1H), 1.44-1.16 (m, 2H), 1.11 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.4, 146.8, 129.1, 122.3, 120.1, 63.8, 43.2, 28.9, 27.3, 14.6 ppm; HRMS *m / z* calcd. for $C_{18}H_{20}N_2O(M^+)$: 280.1576, found: 280.1576. Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.22; H, 6.98; N, 9.74.

2-Isopropyl-5-(*N,N*-diphenylhydrazino)cyclopentanone



277a



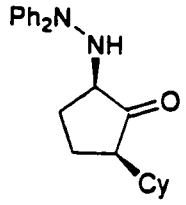
277b

Following the general carbonylation/cyclization procedure, 4-bromo-5-methylhexanal-*N,N*-diphenylhydrazone **269** (152 mg (0.42 mmol) was dissolved in benzene (13 mL) and treated with AIBN (14 mg), Bu_3SnH (0.14 mL, 0.50 mmol) and stirred under CO atmosphere. After workup and purification, 92 mg (71%) of the cyclized product as a 1/1.1 = cis/trans mixture was obtained;

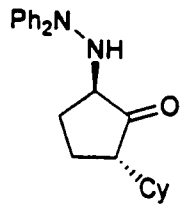
Cis isomer 277a: IR (neat, cm^{-1}) 2925, 1731, 1591, 1481, 1300; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.22 (m, 4H), 7.15-7.11 (m, 4H), 7.08-6.94 (m, 2H), 4.39 (br s, 1H), 3.43-3.39 (m, 1H), 2.21-2.12 (m, 2H), 2.04-1.89 (m, 3H), 1.24-1.21 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 217.8, 147.0, 129.1, 122.3, 120.2, 62.5, 53.5, 28.3, 27.5, 21.3, 21.1, 18.8 ppm; HRMS *m / z* calcd. for $C_{20}H_{24}N_2O(M^+)$: 308.1890, found: 308.1895.

Trans isomer 277b: IR (neat, cm^{-1}) 2951, 2872, 1736, 1591, 1495, 1287; ^1H NMR (200 MHz, $CDCl_3$) δ 7.31-7.10 (m, 8H), 7.01-6.94 (m, 2H), 4.80 (br s, 1H), 3.36-3.27 (m, 1H), 2.38-2.28 (m, 2H), 2.18-1.92 (m, 2H), 1.78-1.70 (m, 1H), 1.66-1.40 (m, 1H), 1.24-1.15 (m, 1H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 217.6, 146.8, 129.1, 122.2, 120.0, 65.2, 54.2, 28.4, 28.0, 20.6, 20.3, 18.7 ppm; HRMS *m / z* calcd. for $C_{20}H_{24}N_2O(M^+)$: 308.1890, found: 308.1866.

2-Cyclohexyl-5-(*N,N*-diphenylhydrazino)-cyclopentanones



278a



278b

Following the general carbonylation/cyclization procedure, 4-bromo-4-cyclohexylbutanal-*N,N*-diphenylhydrazone **270** (210 mg (0.52 mmol) was dissolved in benzene (12 mL) and treated with AIBN (12 mg), *n*-Bu_3SnH (0.18 mL, 0.62 mmol) and stirred under CO atmosphere. After workup and purification 121.2 mg (67%) of the cyclized product as a 1/1.2 = cis/trans mixture was obtained;

Cis isomer 278a: IR (neat, cm^{-1}) 2923, 2851, 1735, 1591, 1494; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.31 (m, 4H), 7.27-7.09 (m, 4H), 7.05-6.94 (m, 2H), 4.41 (br s, 1H), 3.45-3.35 (m, 1H), 2.25-0.88 (m, 16H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.0, 147.0, 129.1, 122.3, 120.2, 62.7, 53.0, 38.6, 31.6, 29.1, 27.8, 26.5, 26.3, 26.2, 21.9 ppm; HRMS *m / z* calcd. for $C_{23}H_{28}N_2O(M^+)$: 348.2203, found: 348.2211.

Trans isomer 278b: IR (neat, cm^{-1}) 2925, 2853, 1735, 1591, 1495, 1450; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.30 (m, 4H), 7.26-7.11 (m, 4H), 7.09-6.93 (m, 2H), 4.80 (br s, 1H), 3.35-3.26 (m, 1H), 2.36-2.27 (m, 1H), 2.18-1.92 (m, 2H), 1.83-1.00 (m, 13H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.7, 146.9, 129.1, 122.2, 120.0, 65.3, 53.7, 38.1, 31.1, 29.0, 28.6, 26.5, 26.3, 26.1, 21.0 ppm; HRMS *m / z* calcd. for $C_{23}H_{28}N_2O(M^+)$: 348.2203, found: 348.2224. Anal. Calcd for $C_{23}H_{28}N_2O$: C, 79.27; H, 8.09; N, 8.04. Found: C, 79.94; H, 8.39; N, 8.39.

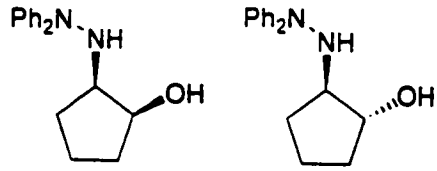
General Procedure for L-Selectride® Reductions:

The ketone was dissolved in methylene chloride to make a 0.1 M solution and added to a flame dried, round bottom flask maintained at -78 °C under argon. The L-Selectride® (2 eq.) was added to the stirred solution at -78 °C and the reaction continued until the starting material was consumed (typically 30 minutes, by TLC). The reaction was warmed to 21 °C, methanol, aqueous sodium hydroxide (25%) and hydrogen peroxide were added and the mixture stirred for 45 minutes. Water and diethyl ether were added and the aqueous layer extracted with diethyl ether (3X). The combined organic layers were washed with saturated ammonium chloride, brine, dried, concentrated and chromatographed.

General Procedure for Catalytic Hydrogenations:

The ketone was dissolved in methanol to make a 0.1 M solution, mixed with tris(triphenylphosphine)ruthenium(II) chloride (10%) and added to a dry glass tube which was inserted into a stainless steel autoclave (50 mL). The reaction mixture was stirred under hydrogen pressure (500 psi) at 21 °C overnight. After the release of excess hydrogen, the solid residue was filtered and methanol was removed under reduced pressure. The crude mixture was analyzed by ^{1}H NMR spectroscopy to determine the *cis/trans* ratios. This was followed by chromatography to separate the *cis/trans* isomers.

1-Hydroxy-2-(*N,N*-diphenylhydrazino)cyclopentane

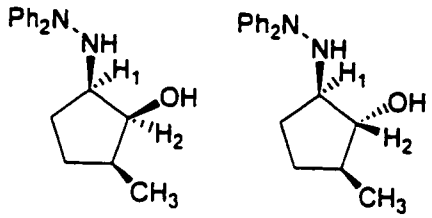


281a **281b**

Cis isomer 281a: IR (neat, cm^{-1}) 3472, 2936, 1590, 1494, 909; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34-7.23 (m, 4H), 7.12-6.99 (m, 6H), 4.35-4.20 (m, 1H), 4.19-4.05 (m, 1H), 3.38-3.30 (m, 1H), 2.77-2.74 (m, 1H), 1.94-1.52 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 129.3, 122.7, 120.2, 71.8, 63.2, 31.7, 26.4, 20.3 ppm; HRMS *m / z* calculated for $C_{17}H_{20}N_2O$ (M^+): 268.1571, found: 268.1600.

Trans isomer 281b: IR (neat, cm^{-1}) 3395, 2930, 1591, 1489, 1373, 1057; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.24 (m, 4H), 7.18-7.05 (m, 4H), 7.02-6.98 (m, 2H), 4.18-4.11 (m, 1H), 4.05-3.80 (br s, 1H), 3.35-3.22 (m, 1H), 2.17-2.04 (m, 1H), 1.97-1.43 (m, 5H) ppm (either O<u>H</u> or N<u>H</u> not observed); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 129.2, 122.5, 120.5, 77.4, 65.6, 33.4, 28.6, 21.6 ppm HRMS *m / z* calcd. for $C_{17}H_{20}N_2O$ (M^+): 268.1571, found: 268.1592. Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.09; H, 7.51; N, 10.38.

2-Hydroxy-3-Methyl-1-(*N,N*-diphenylhydrazino) cyclopentane

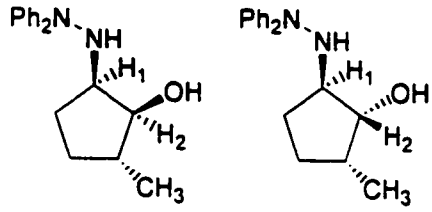


282a **282b**

282a: IR (neat, cm^{-1}) 3375, 2920, 1590, 1494, 1279, 1058; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.23 (m, 4H), 7.16-7.10 (m, 4H), 7.06-6.97 (m, 2H), 3.57-3.54 (m, 1H), 3.38-3.25 (m, 1H), 1.84-1,75 (m, 2H), 1.53-1.47 (m, 1H), 1.40-1.32 (m, 2H), 1.06 (d, *J* = 7.1 Hz, 3H) ppm (O<u>H</u> and N<u>H</u> not observed); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 129.2, 122.6, 120.6, 84.5, 64.5, 40.9, 29.3, 26.9, 17.9 ppm; nOe of the two methine hydrogens (H_1, H_2) = 0.1%; HRMS *m / z* calcd. for $C_{18}H_{22}N_2O$ (M^+): 282.1733, found: 282.1756;

282b: IR (neat, cm^{-1}) 3451, 3060, 2921, 1591, 1494, 1291, 1073; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.28 (m, 4H), 7.27-7.06 (m, 4H), 7.02-6.99 (m, 2H), 4.15 (br s, 1H), 3.81-3.79 (m, 1H), 2.70 (br.s, 1H), 1.90-1.83 (m, 2H), 1.73-1.67 (m, 1H), 1.58-1.49 (m, 2H), 1.05 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 129.3, 122.7, 120.2, 73.8, 63.7, 38.0, 28.8, 26.5, 14.2 ppm; nOe of the two methine hydrogens (H_1, H_2) = 4.0%; HRMS *m / z* calculated for $C_{18}H_{22}N_2O$ (M^+): 282.1733, found: 282.1728.

2-Hydroxy-3-methyl-1-(*N,N* -diphenylhydrazino)cyclopentane

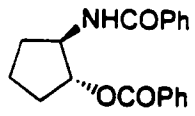


283a **283b**

283a: IR (neat, cm^{-1}) 3406, 3051, 2948, 2870, 1591, 1494, 1276, 1069; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.23 (m, 4H), 7.11-7.07 (m, 4H), 7.02-6.99 (m, 2H), 4.15 (br s, 1H), 3.62-3.60 (m, 1H), 3.49-3.40 (m, 1H), 2.67 (br.s, 1H), 2.20-2.15 (m, 1H), 2.09-2.02 (m, 1H), 1.81-1.75 (m, 1H), 1.66-1.58 (m, 1H), 1.21-1.10 (m, 1H), 0.96 (d, *J* = 7.1 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 129.3, 122.7, 120.2, 73.8, 63.7, 38.0, 28.8, 26.5, 14.2 ppm; nOe of the two methine hydrogens (H_1, H_2) = 0.9%; HRMS *m / z* calculated for $C_{18}H_{22}N_2O$ (M^+): 282.1733, found: 282.1736.

283b: IR (neat. cm^{-1}) 3451, 2916, 1591, 1494, 1286, 1140, 1027; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.23 (m, 4H), 7.08-7.04 (m, 4H), 7.02-6.99 (m, 2H), 4.07 (br s, 1H), 3.80-3.79 (m, 1H), 3.48-3.41 (m, 1H), 2.69 (br.s, 1H), 1.90-1.83 (m, 2H), 1.75-1.67 (m, 1H), 1.57-1.48 (m, 2H), 1.04 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 129.3, 122.7, 120.2, 73.8, 63.7, 38.1, 28.8, 26.5, 14.3 ppm; nOe of the two methine hydrogens (H_1, H_2) = 3.0%; HRMS *m /z* calculated for $C_{18}H_{22}N_2O$ (M^+): 282.1733, found: 282.1756.

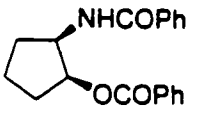
trans (2-Benzoyloxy)-*N*-cyclopentyl benzamide



285

Trans 1-hydroxy-2-(*N*,*N*-diphenylhydrazino)cyclopentane **281b** (67 mg, 0.25 mmol) was placed in the glass liner of a stainless steel autoclave along with methanol (5.0 mL), (S)-(+)-10-camphor sulfonic acid (116.3 mg, 0.50 mmol) and 10% Pd/C (7.0 mg). The glass liner was then placed in the autoclave and the gauge block assembly attached. The hydrogen line and the system was flushed three times before pressurizing to 500 psi. The autoclave was heated to 50 °C and the reaction mixture was stirred overnight. After this time the excess gas was discharged and the reaction mixture filtered through a sintered glass funnel to remove the Pd/C. The solid residue of Pd/C was then rinsed with ethyl acetate and the volatiles removed *in vacuo*. To the resulting yellow foam was added dichloromethane (10.0 mL), triethylamine (0.2 mL, 1.30 mmol), and benzoic anhydride (120.1 mg. 3.00 mmol) along with several crystals of DMAP and allowed to stir at 21 °C overnight. The resulting oil was purified by flash chromatography (40:60, ethyl acetate / petroleum ether) to afford 57 mg (74%) of the title compound as a white solid; m.p. 175-178 °C; IR (neat, cm^{-1}) 1705, 1635, 1544, 1456, 1027; ^1H NMR (200 MHz, $CDCl_3$) δ 8.02-7.98 (m, 2H), 7.65-7.60 (m, 2H), 7.52-7.25 (m, 8H), 6.67 (br s, 1H), 5.63 (m, 1H), 4.84 (m, 1H), 2.31 (m, 1H), 2.17-1.62 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.8, 167.1, 134.2, 133.1, 131.3, 129.9, 129.6, 128.4, 128.3, 126.5, 78.4, 57.7, 31.9, 30.5, 21.5 ppm; nOe of the two methine hydrogens = 4.3%; HRMS *m /z* calculated for $C_{19}H_{19}NO_3$ (M^+): 309.1365, found: 309.1355.

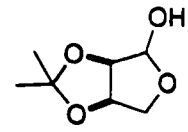
cis (2-Benzoyloxy)-*N*-cyclopentyl benzamide



284

Following the procedure for the hydrogenolysis of hydrazine **281a**, *cis* 1-hydroxy-2-(*N,N*-diphenylhydrazino)cyclopentane **aa1** (222.4 mg, 0.83 mmol) was placed in the glass liner of a steel autoclave along with methanol (10 mL), (S)-(+)-10-camphor sulfonic acid (385.2 mg, 1.67 mmol) and 10% Pd/C (25.0 mg) and pressurized to 500 psi. The crude reaction mixture was then treated with methylene chloride (20 mL),triethylamine (0.58 mL), benzoic anhydride (393.1 mg) and several crystals of DMAP and allowed to stirr overnight. Work-up and purification by flash cromatography (40:60, ethyl acetate / petroleum ether) yielded 210.1 mg (82%) of the title compound as a white solid; m.p. 169-172 °C; IR (neat, cm^{-1}) 1705, 1624, 1544, 1426, 1027; ^1H NMR (200 MHz, $CDCl_3$) δ 8.01-7.97 (m, 2H), 7.60-7.27 (m, 10H), 6.71 (br s, 1H), 5.72 (m, 1H), 4.89 (m, 1H), 2.90 (m, 1H), 2.14-1.72 (m, 5H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 167.2. 134.3, 132.9, 131.2, 129.9, 129.7, 128.4, 128.3, 126.3, 72.8, 55.5, 30.2, 28.3, 20.2 ppm; nOe of the two methine hydrogens = 6.8%; HRMS *m /z* calculated for $C_{19}H_{19}NO_3$ (M^+): 309.1365, found: 309.1367.

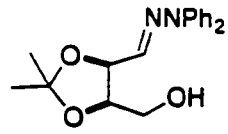
2,3-O-Isopropylidene-D-Erythronolactol



289

2,3-O-Isopropylidene-D-Erythronolactone **288** (9.56 g, 60.5 mmol) was added to a flame dried flask (500 mL) along with freshly distilled toluene (100 mL) under argon. The solution was cooled to –78 °C and DIBALH (60.5 mL, 1 M solution in toluene) was added and the reaction mixture stirred at this temperature for 4 hours. The reaction was quenched with methanol at -78 °C until gas evolution ceased. The solution was warmed to room temperature (21 °C) and saturated aqueous sodium potassium tartrate solution (100 mL) was added. This mixture was poured into a separatory funnel containing water and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (3 X 100 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was purified by flash chromatography (50:50, diethyl ether / petroleum ether) to afford 6.87 g (71%) of the title compound as a white solid; IR (neat, cm^{-1}) 3356, 2950, 1590, 1498, 1284; ^1H NMR (200 MHz, $CDCl_3$) δ 5.39 (d, *J* = 1.6 Hz, 1H), 4.80 (dd, *J* = 1.6 Hz, *J* = 2.9 Hz, 1H), 4.54 (dt, *J* = 2.9 Hz, *J* = 4.9 Hz, 1H), 4.01 (br s, 2H), 2.25 (br s, 1H), 1.44 (s, 3H), 1.29 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 112.3, 101.8, 85.1, 79.9, 71.9, 26.1, 24.7 ppm; HRMS *m / z* calcd. for $C_7H_{12}O_4$ (M^+): 160.0735, found: 160.0738.

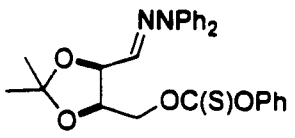
2,3-O-Isopropylidene-4-*N,N*- diphenylhydrazone-1-butanol



290

2,3-O-Isopropylidene-D-Erythronolactol **289** (4.57 g, 28.5 mmol) in methanol (200 mL) was added to a round bottom flask (500 mL). A solution of Ph_2NNH_2 (5.26 g, 28.5 mmol) in methanol (100 mL) was added dropwise to this solution and the reaction was stirred at 21 °C for 4 hours. Concentration gave a slightly purple coloured oil which was purified by flash chromatography (5:95, diethyl ether / methylene chloride) to yield 6.78 g (73%) of the title alcohol as a faint yellow oil; IR (neat, cm^{-1}) 3349, 3048, 2917, 1592, 1491, 1298, 1056, 745, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41-7.32 (m, 4H), 7.18-7.06 (m, 6H), 6.41 (d, J = 7.3 Hz, 1H), 4.91 (dd, J = 7.3 Hz, J = 6.4 Hz, 1H), 4.37 (m, 1H), 3.53-3.39 (m, 2H), 2.09 (br s, 1H), 1.41 (s, 3H), 1.36 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 133.8, 129.8, 124.6, 122.2, 78.6, 77.6, 61.5, 27.3, 24.9 ppm; HRMS *m / z* calcd. for $C_{19}H_{22}N_2O_3$ (M^+): 326.1631, found: 326.1611.

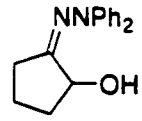
Preparation of2,3-O-Isopropylidene-4-*N,N*- diphenylhydrazone-1-butanol-thionocarbonate phenyl ester



291

2,3-O-Isopropylidene-4-carboxaldehyde-*N,N*- diphenylhydrazone-1-butanol **290** (2.22 g, 6.8 mmol) was added to a round bottom flask (25 mL) along with CH_2Cl_2 (40 mL) and pyridine (2.0 g, 2.03 mL, 25.2 mmol) the solution was cooled to -78 °C. Phenyl chlorothionoformate (1.29 g, 1.03 mL, 7.5 mmol) was added and the solution was stirred at room temperature (*ca.* 22 °C) for four hours. The resulting mixture was poured into a separatory funnel containing dilute aqueous HCl (50 mL) and ethyl acetate (100 mL). The aqueous layer was extracted with ethyl acetate (2x100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, 20:80, diethyl ether / petroleum ether) to afford the title compound (67%) as a yellow oil; IR (neat, cm^{-1}) 3367, 3053, 2871, 1703, 1592, 1491, 1275, 1056, 743, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.27 (m, 7H), 7.11-7.01 (m, 8H), 6.45 (d, *J* = 7.2 Hz, 1H), 4.87 (dd, *J* = 7.3 Hz, *J* = 6.2 Hz, 1H), 4.39 (m, 1H), 3.69-3.51 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.4, 153.3, 144.0, 133.7, 129.8, 129.4, 126.6, 124.5, 122.1, 121.7, 88.7, 78.9, 63.8, 28.1, 24.3 ppm; HRMS *m / z* calcd. for $C_{26}H_{26}N_2O_4S$ (M^+): 462.1990, found: 462.1990.

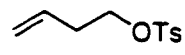
2-Hydroxy-Cyclopentanone-(*N,N*-diphenylhydrazone)



292

2-(*N,N* -diphenylhydrazino) cyclopentanone **275** (57 mg, 0.21 mmol) was added to a round bottom flask (10 mL) and dissolved in methylene chloride (4 mL). Magnesium dibromide etherate (56 g, 0.21 mmol) was added and the reaction mixture was stirred at 21 °C for 2 hours. The resulting cloudy yellow solution became clear when methanol (5 mL) was added over. The resulting mixture was poured into a separatory funnel containing water (5 mL) and diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (3X 5 mL), and the combined organic layers were washed with brine, dried and concentrated *in vacuo* to afford 54 mg (97%) of the title compound as a yellow oil; IR (neat, cm^{-1}) 3366, 2950, 1590, 1498, 1284; ^1H NMR (200 MHz, $CDCl_3$) δ 7.34-7.25 (m, 4H), 7.09-7.03 (m, 6H), 4.47 (t, *J* = 7.1 Hz, 1H), 3.11 (br s, 1H), 2.13-2.11 (m, 1H), 1.86-1.66 (m, 3H), 1.57-1.46 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.7, 147.5, 129.1, 123.5, 121.9, 74.5, 32.6, 29.1, 19.8 ppm; HRMS *m / z* calcd. for $C_{17}H_{18}N_2O$ (M^+): 266.1419, found: 266.1390.

3-Butenyl-1-Tosylate

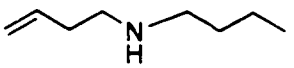


300

3-Buten-1-ol **299** (1.47 g, 20.4 mmol) was added to a flame dried flask (100 mL) along with freshly distilled methylene chloride (50 mL) and pyridine

(1.74 g, 22.0 mmol). The solution was cooled to 0 °C and *p*-toluenesulfonyl chloride (4.19 g, 22.1 mmol) was added and the reaction mixture stirred at room temperature for 12 hours. The reaction was quenched with aqueous HCl (30 mL). This mixture was poured into a separatory funnel containing water and methylene chloride (100 mL). The aqueous layer was extracted with methylene chloride (2 X 100 mL), dried over anhydrous magnesium sulfate and concentrated. The resulting oil was purified by flash chromatography (50:50, diethyl ether / petroleum ether) to afford 4.38 g (95%) of the title compound as a colourless oil; IR (neat, cm^{-1}) 3033, 2850, 1845, 1644, 1478, 1420, 1355, 1188, 910, 723; ^1H NMR (200 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 5.69-5.63 (m, 1H), 5.11-5.04 (m, 1H), 4.06 (t, *J* = 6.8 Hz, 2H), 2.44 (s, 3H), 2.38 (dt, *J* = 6.8 Hz, *J* = 2.9 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.9, 144.8, 134.6, 130.1, 128.1, 117.5, 58.3, 33.0, 21.7 ppm; HRMS *m / z* calcd. for $C_{11}H_{14}O_3S$ (M^+): 226.0664, found: 226.0659.

But-3-enyl-butyl-amine

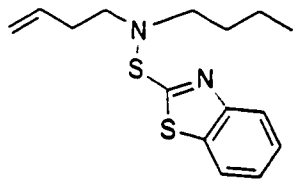


301

3-Butenyl-1-tosylate **300** (3.61 g, 16 mmol) was added to a round bottom flask (100 mL) equipped with a reflux condenser along with butylamine (20 mL). The mixture was heated to reflux for *ca.* 2 days. The excess butylamine was removed by rotary evaporation and the residue diluted with 10% NaOH (400 mL) and extracted with diethyl ether (3X20 mL). The combined organic layers were then washed with brine (2X 20 mL), dried over anhydrous magnesium sulfate

and to yield a yellow oil. Distillation (Kugelrohr, 76-80 °C, 10 mmHg) afforded 1.56 g (77%) of the title compound as a colourless liquid; IR ($CHCl_3$, cm^{-1}) 3325, 2544, 1645, 1515, 1418, 1156, 1078, 911, 890, 688; ^1H NMR (200 MHz, $CDCl_3$) δ 5.82-5.59 (m, 1H), 5.10-4.91 (m, 2H), 2.67-2.49 (m, 4H), 2.25-2.15 (m, 2H), 1.80 (br s, 1H), 1.49-1.20 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.5, 116.0, 49.3, 48.6, 34.0, 31.9, 20.2, 13.7 ppm; HRMS *m / z* calcd. for $C_8H_{17}N$ (M^+): 127.1362, found: 127.1355.

_N_-Butyl-_N_-3-butenyl-2-benzothiazolesulfenamide

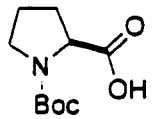


302

2,2'-Dithiobis(benzothiazole) (2.09 g, 6.3 mmol) was added to a pear-shaped bottom flask (100 mL) along with freshly distilled methylene chloride (15 mL) and one drop of pyridine. The solution was heated to reflux, sulfuryl chloride (864 mg, 514 μL, 6.4 mmol) was added and the reaction mixture stirred for *ca.* 10 min. The resultant sulfenyl chloride solution was added dropwise by syringe to a round bottom flask (250 mL) containing but-3-enyl-butyl-amine **301** (2.91g, 12.9 mmol) and triethylamine (. 5 equiv) in diethyl ether (40 mL) maintained at 0 °C. The mixture was allowed to warm to room temperature and left to stir for an additional 1-2 h, at which time the mixture was diluted with diethyl ether (50 mL). This mixture was poured into a separatory funnel the layers were separated. The aqueous layer was extracted with diethyl ether(2 X 50 mL), and the organic layers were combined and washed with brine (50 mL), dried over anhydrous

magnesium sulfate and concentrated. The resulting oil was purified by flash chromatography (20:80, ethyl acetate / petroleum ether) to afford 2.26 g (60%) of the title compound as a pale yellow oil; IR ($CHCl_3$, cm^{-1}) 3423, 2749, 2247, 1218, 1167, 1091, 913, 732; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 5.59-5.81 (m, 1H), 4.93-5.08 (m, 2H), 3.03-3.12 (m, 4H), 2.04-2.20 (m, 2H), 1.20-1.44 (m, 4H), 0.93 (t, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 154.9, 137.9, 136.0, 125.7, 123.5, 121.5, 120.8, 116.0, 58.5, 57.9, 32.0, 31.5, 20.3, 13.9 ppm; HRMS m/z calcd. for $C_{15}H_{20}N_2S_2$ (M^+): 292.1068, found: 292.1074.

***N*-(*tert*-Butoxycarbonyl)-L-proline**

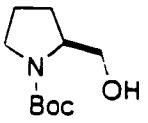


311

L-proline **310** (1.15 g, 10.0 mmol) was added to a flame dried flask (50 mL) along with *tert*-butanol (8 mL), water (10 mL) and sodium hydroxide (0.44 g, 10.1 mmol). Di-*tert*-butyl dicarbonate (2.29 mL, 10 mmol) was added and the reaction mixture stirred at room temperature for 12 hours. This mixture was poured into a separatory funnel containing water (10 mL) and ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (3 X 25 mL), dried over anhydrous magnesium sulfate and concentrated. The product was recrystalized from diethyl ether to afford 1.20 g (56%) of the title compound as a white powder, mp = 132-134 °C; IR ($CHCl_3$, cm^{-1}) 3423, 2949, 2247, 1644, 1418, 1167, 1091, 913, 732; ^1H NMR (200 MHz, $CDCl_3$) δ 10.3 (br s, 1H), 4.38-4.18 (m, 1H), 3.52-3.29 (m, 2H), 2.39-2.20 (m, 1H), 2.06-1.82 (m, 3H), 1.48 (s, 9H) ppm; ^{13}C NMR

(50 MHz, $CDCl_3$) δ 180.01, 155.3, 79.9, 60.9, 46.9, 29.5, 28.4, 24.4 ppm; HRMS *m / z* calcd. for $C_{10}H_{17}NO_4$ (M^+): 215.1158, found: 215.1164. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.91; H, 8.02; N, 6.62.

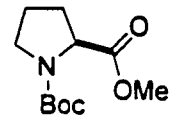
***(S)-N-(tert*-Butoxycarbonyl)-2-(hydroxymethyl)-pyrrolidine**



312

Boc-L-proline **311** (10.1 g, 47.1 mmol) was added to a round bottom flask (500 mL) along with freshly distilled THF (250 mL). Borane-methyl sulfide complex (26 mL of a 2M THF solution, 52 mmol) was added dropwise to this solution over the course of 45 minutes with stirring. The reaction mixture was heated to reflux for 45 minutes, then cooled to room temperature. The reaction concentrated, then dissolved in a mixture of methylene chloride (300 mL) and water (100 mL). This mixture was poured into a separatory funnel. The organic layer was isolated, washed with aqueous saturated sodium bicarbonate (50 mL), then brine (50 mL), dried over anhydrous magnesium sulfate and concentrated to afford 8.04 g (85%) of the title compound as a a white solid, mp 56-58 °C; IR ($CHCl_3$, cm^{-1}) 3373, 2979, 1667, 1369, 1206, 1167, 1045; ^1H NMR (200 MHz, $CDCl_3$) δ 3.98-3.93 (m, 1H), 3.62-3.57 (m, 2H), 3.48-3.44 (m, 1H), 3.37-3.33 (m, 1H), 2.04-2.01 (m, 1H), 1.85-1.81 (m, 2H), 1.59-1.56 (m, 1H) 1.47 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.6, 80.0, 67.1, 60.0, 47.4, 28.5, 28.4, 23.9 ppm; HRMS *m / z* calcd. for $C_{10}H_{19}NO_3$ (M^+): 201.1365, found: 201.1369. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.48; H, 9.34; N, 6.95.

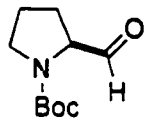
N-(*tert*-Butoxycarbonyl)-L-proline methyl ester



313

Boc-L-proline **311** (0.72 g, 3.38 mmol) was added to a round bottom flask (50 mL) along with freshly distilled DMF (15 mL) and sodium bicarbonate (0.85g, 10 mmol). Methyl iodide (0.23 mL, 3.72 mmol) was injected into the flask and the reaction mixture was stirred at room temperature for five days. This mixture was poured into a separatory funnel containing water (10 mL) and ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (3 X 25 mL), dried over anhydrous magnesium sulfate and concentrated. The product was recrystalized from diethyl ether to afford 0.77 g (100%) of the title compound as a white solid, mp = 78-79 °C; IR ($CHCl_3$, cm^{-1}) 3422, 2934, 2233, 1697, 1427, 1165, 1123, 1091, 911, 722; ^1H NMR (200 MHz, $CDCl_3$) δ 4.15 and 4.08 (m, 1H), 3.57 (s, 3H), 3.48-3.25 (m, 2H), 2.15-1.97 (m, 1H), 1.87-1.71 (m, 3H), 1.29 and 1.25 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 154.3, 80.1, 59.9, 46.1, 43.2, 31.5, 29.5, 22.0 ppm; HRMS *m / z* calcd. for $C_{11}H_{19}NO_4$ (M^+): 229.1314, found: 229.1323.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-2carboxaldehyde

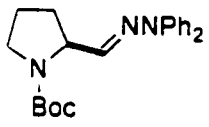


313

Method A. *N*-Boc-proline methyl ester **313** (4.3 g, 18.8 mmol) was added to a round bottom flask (100 mL) along with toluene (10 mL). The solution was cooled to –78 °C, DIBALH (25 mL, 1.5 M solution in toluene, 37.6 mmol) was added and the reaction mixture stirred at this temperature for 1 hour. An additional 15 mL of DIBAL was added and reaction mixture was stirred for another 2 hours. The reaction was quenched with methanol (15 mL) at -78 °C until gas evolution ceased. The solution was warmed to room temperature (21 °C) and saturated aqueous sodium potassium tartrate solution (20 mL) was added. This mixture was poured into a separatory funnel containing water and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3 X 20 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, ethyl acetate / petroleum ether) under aspirator vacuum to afford 2.84 g (76%) of the corresponding aldehyde as a colourless oil which was used in the next step without further purification. Distillation (165 °C (0.6 Torr)) of a small portion provided analytically pure product; IR ($CHCl_3$, cm^{-1}) 2982, 2870, 2805, 2710, 1734, 1686, 1402, 1369, 1165; ^1H NMR (200 MHz, $CDCl_3$) δ 9.54 and 9.45 (d, J = 1.2 and 8 Hz, 1H), 4.20 and 4.04 (m, 1H), 3.50 (m, 1H), 2.11 and 1.97 (m, 2H), 1.83 (m, 2H), 1.46 and 1.42 (s, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.5, 155.5. 80.1, 58.4, 46.4, 29.7, 28.4, 23.6 ppm; HRMS *m / z* calcd. for $C_{10}H_{17}NO_3$ (M^+): 199.1208, found: 199.1215. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.27; H, 8.69; N, 6.99.

Method B. Oxalyl chloride (5.3 mL, 61 mmol) was added to a round bottom flask (500 mL) along with methylene chloride (125 mL). The solution was cooled to –63 °C and DMSO (7.9 mL, 111 mmol) dissolved in methylene chloride (25 mL) was added dropwise over a 10 minutes period. After 10 minutes, a solution of *(S)-N-(tert*-butoxycarbonyl)-2-(hydroxymethyl)-pyrrolidine **312** (10.16 g, 50.5 mmol) dissolved in methylene chloride (50 mL)) was added dropwise over a 15 minutes period. The reaction mixture was stirred for 30 minutes. Diisopropylethylamine (35 mL, 202 mmol) was added and the mixture was allowed to warm to room temperature over a 30-minutes period. This mixture was poured into a separatory funnel and washed with aqueous 5% HCl (3x50 mL), water (3x 50 mL), then brine (50 mL), dried over anhydrous magnesium sulfate and concentrated to afford 9.45 g (94%) of the title compound as an oil that was stored in a freezer and used without further purification. The product coeluted on TLC and was spectroscopically identic with a product sample prepared by method A.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-2carboxaldehyde *N,N*-diphenylhydrazone

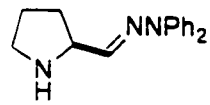


315

(2*S*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-2carboxaldehyde **314** (3.98 g, 20.0 mmol) in methanol (200 mL) was added to a round bottom flask (500 mL). A solution of Ph_2NNH_2 (3.69 g, 20.0 mmol) in methanol (50 mL) was added dropwise to this solution and the reaction was stirred at 21 °C for 2 hours.

Concentration gave a slightly purple coloured oil which was purified by flash chromatography (10:90, diethyl ether / petroleum ether) to yield 5.47 g (75%) of the title alcohol as a faint yellow oil; IR (neat, cm^{-1}) 2963, 2877, 2245, 1689, 1592, 1488, 1356, 1155, 915; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 4H), 7.24-7.05 (m, 6H), 6.41 (br s, 1H), 4.39 (br s, 1H), 3.46-3.35 (m, 2H), 2.13-2.05 (m, 2H), 1.83-1.77 (m, 2H), 1.34 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 143.9, 138.7, 129.7, 124.1, 122.3, 79.3, 58.4, 46.4, 30.7, 28.4, 23.6; HRMS *m / z* calcd. for $C_{22}H_{27}N_3O_2$ (M^+): 365.2104, found: 365.2092. Anal. Calcd for $C_{22}H_{27}N_3O_2$: C, 72.30; H, 7.44; N, 11.49. Found: C, 72.45; H, 7.42; N, 11.66.

(2*S*)- pyrrolidine-2carboxaldehyde *N,N*-diphenylhydrazone

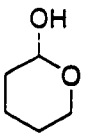


316

(2*S*)-*N*-(*tert*-Butoxycarbonyl)pyrrolidine-2carboxaldehyde *N,N*-diphenylhydrazone **315** (1.61 g, 4.43 mmol) was added to a round bottom flask (100 mL) along methylene chloride (45 mL) and trifluoroacetic acid (3.42 mL, 44.3 mmol). The reaction mixture was heated was stirred at room temperature for *ca.* 30 minutes. The reaction mixture was concentrated, then dissolved in diethyl ether (30 mL). This mixture was poured into a separatory funnel containing 5% aqueous sodium hydroxide (10mL). The organic layer was isolated, washed with aqueous saturated sodium bicarbonate (5 mL), then brine (5 mL), dried over anhydrous magnesium sulfate and concentrated. The resulting oil was purified by

flash chromatography (30:70, diethyl ether / petroleum ether) to to afford 1.02 g (87%) of the title compound as a yellow oil; IR (neat, cm^{-1}) 2919, 1715, 1591, 1491, 1296, 1155, 1019, 911; ^1H NMR (200 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 7.41-7.29 (m, 4H), 7.21-6.99 (m, 6H), 6.35 (d, *J* = 4.4 Hz, 1H), 4.37-4.27 (m, 1H), 3.36-3.19 (m, 2H), 2.19-1.85 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.2, 142.7, 129.8, 124.9, 122.1, 59.7, 44.8, 29.0, 23.4; HRMS *m / z* calcd. for $C_{17}H_{19}N_3$ (M^+): 265.1579, found: 265.1559. Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.83. Found: C, 76.65; H, 7.11; N, 16.01.

δ-**Valerolactol**

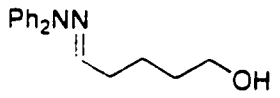


351

δ-Valerolactone **350** (3 mL, 32.3 mmol) was added to a round bottom flask (250 mL) flame dried under argon, along with freshly distilled toluene (50 mL). The solution was cooled to -78 °C and DIBAL (23 mL, 1.5 M solution in toluene, 34.5 mmol) was added. After four hours of stirring at -78 °C the reaction was quenched with methanol until gas evolution ceased. The solution was warmed to room temperature and aqueous sodium potassium tartrate solution (50 mL) was added. The mixture was stirred vigurously at room temperature until two clear layers were formed (*ca.* 30 min.). The resulting mixture was poured into a separartory funnel containing water (50 mL) and ethyl acetate (60 mL). The aqueous layer was extracted with ethyl acetate (2X 50 mL) and the combined organic layers were washed brine, dried over magnesium sulfate, filtered through a pad of silicagel and concentrated *in vacuo* to afford the title compound (2.59 g,

78%) as a faint yellow oil. IR (neat) 3374, 2911, 1449, 911, 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.90-4.81 (m, 1H), 4.65 (br s, 1H), 3.95-3.88 (m, 1H), 3.50-3.40 (m, 1H), 1.85-1.62 (m, 2H), 1.56-1.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 94.2, 63.6, 31.7, 25.0, 20.1; HRMS *m / z* calcd. for $C_5H_{10}O_2$ (M^+) 102.0681, found: 102.0683.

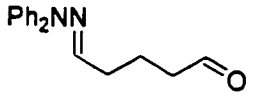
5-Hydroxypentanal-*N,N*-diphenylhydrazone



352

δ-Valerolactol **351** (2.58 g, 25.3 mmol) was added to a round bottom flask (100 mL) along with methanol (30 mL). A solution of diphenylhydrazine (4.65 g, 25.3 mmol) in methanol (15 mL) was added and the reaction mixture was stirred at room temperature (*ca.* 22 °C) overnight. Concentration *in vacuo* gave a purple oil which was purified by flash cromatography (50:50, diethyl ether / petroleum ether) to afford 5.28 g of the title compound (78%) as a light yellow oil; IR (neat) 3380, 3044, 2917, 1592, 1492, 1303, 1090, 1066 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.45-7.29 (m, 4H), 7.20-6.98 (m, 6H), 6.52 (t, *J* = 6.7 Hz, 1H), 3.72-3.61 (m, 2H), 2.42-2.33 (m, 2H), 1.71-1.53 (m, 4H), 1.45 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 139.6, 129.6, 123.8, 122.2, 62.3, 32.2, 32.0, 23.0; HRMS *m / z* calcd. for $C_{17}H_{20}N_2O$ (M^+) 268.1571, found: 268.1568.

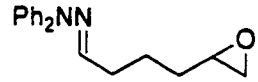
Butanal-(*N,N*-diphenylhydrazone)-4-carboxaldehyde



353

5-Hydroxypentanal-*N,N*-diphenylhydrazone **352** (3.09 g, 11.5 mmol) was added to a round bottom flask (50 mL) flame dried under argon along with DMSO (20 mL) and Et_3N (12.9 mL, 92.8 mmol). A SO_3-pyridine/DMSO suspension (5.4 g of SO_3-pyridine, 34.5 mmol in 6 mL DMSO stirred separately until they form a homogenous mixture) was added dropwise to this mixture with stirring. After 15 min. at room temperature (*ca.* 22 °C), TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separartory funnel containing water (100 mL) and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (2x100 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash cromatography (silica gel, 30:70, diethyl ether / petroleum ether) to afford the title compound (2.32 g, 75%) as a light yellow oil; IR (neat) 3046, 2896, 1723, 1595, 1491, 1303, 1209, 1069 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5 Hz, 1H), 7.40-7.29 (m, 4H), 7.16-7.04 (m, 6H), 6.49 (t, J = 5.1 Hz, 1H), 2.51 (dt, J_1 = 7.3, J_2 = 1.5 Hz, 2H), 2.36-2.27 (m, 2H), 1.86 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 144.0, 137.9, 129.6, 123.9, 122.2, 43.1, 31.8, 19.2; HRMS *m / z* calcd. for $C_{17}H_{18}N_2O$ (M^+) 266.1415, found: 266.1411.

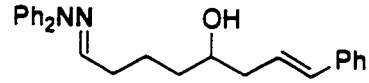
5,6-Epoxyhexanal-*N,N* Diphenylhydrazone



354

DMSO (7 mL) was added to a three neck round bottom flask (100 mL) equipped with a magnetic stirring bar, flame dried and cooled under argon followed by sodium hydride (293 mg, as a 60% dispersion in oil, 7.32 mmol). The mixture was stirred at room temperature (*ca.* 22 °C) until the gas evolution stopped (*ca.* 5-10 min.), heated (60 °C) for one hour then cooled to room temperature. Dry THF (17 mL) was added to the grey solution which was then cooled to -10 °C. Trimethylsulfonium iodide (1.59 g, 7.32 mmol) was added followed by aldehyde **353** (1.624 g, 6.10 mmol) dissolved in THF (2 mL). The cloudy orange solution was stirred at -10 °C for 30 min. The reaction was quenched with water (2 mL) and the mixture poured into a separatory funnel over water (100 mL) and dietyl ether (100 mL). The aqueous layer was extracted with diethyl ether (3x25 mL): the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, then filtered and concentrated; the resulting oil was purified by flash chromatography (silica gel, 20:80, diethyl ether / petroleum ether) to afford 0.51 g (30%) of the title compound as a light yellow oil, along with 0.85 g (52%) recovered starting material. IR (neat) 3046, 2935, 1594, 1490, 1454, 1302, 1210, 1172, 1092, 911, 837, 742 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41-7.33 (m, 4H), 7.17-7.07 (m, 6H), 6.53 (t, 1H, J = 5.15 Hz), 2.94-2.91 (m, 1H), 2.77-2.73 (m, 1H), 2.49-2.45 (m, 1H), 2.40-2.30 (m, 2H), 1.74-1.56 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 138.8, 129.6, 123.8, 122.2, 51.9, 47.0, 32.2, 31.8, 23.2; HRMS *m / z* calcd. for $C_{18}H_{20}N_2O$ (M^+) 280.1576, found: 280.1585.

***trans* 5-Hydroxy-8-phenyloct-7-eneal-(*N,N* Diphenylhydrazone)**

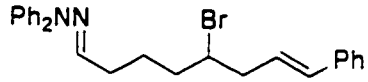


356

β-Bromostyrene (227 μl, 1.77 mmol) was added to a round bottom flask (50 mL) equipped with a magnetic stirring bar, flame dried and cooled under argon along with THF (8 mL). The mixture was cooled to -78 °C and *sec*-BuLi (2.6 mL of a 1.24 M solution in cyclohexane, 3.21 mmol) was added dropwise and the mixture was allowed to stir at -78 °C for 30 minutes. Lithium 2-thienylcyanocuprate (7.1 mL of a 0.25M solution in THF, 1.77 mmol) was added dropwise and the colour changed from yellow to dark purple. After 30 min. 5,6-epoxyhexanal-*N,N* diphenylhydrazone **354** (452 mg, 1.61 mmol) was added as a solution in THF (1 mL) with a subsequent wash of THF (2 mL). The mixture was allowed to warm to room temperature (*ca.* 22 °C) and the colour changed gradually to dark, cloudy green. After 2:30 min of stirring at room temperature the reaction was quenched with a solution of 90% NH_4Cl / 10% NH_4OH (10 mL). The mixture was stirred vigurously for *ca.* 30 min. and then transferred to a separatory funnel. Brine (10 mL) was added and the blue aqueous layer was extracted with diethyl ether (3x25 mL); the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, then filtered and concentrated *in vacuo*; the resulting oil was purified by flash chromatography (silica gel, 50:50, diethyl ether / petroleum ether) to afford 385 mg (63%) of product as a light yellow oil. IR (neat) 3395, 2932, 1593, 1493, 1301, 1210, 748, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-7.18 (m, 9H), 7.15-7.02 (m, 6H), 6.55-6.40 (m, 2H), 6.28-6.12 (m, 1H), 3.79-3.67 (m, 1H), 2.48-2.18 (m, 4H), 1.79-1.41 (m, 4H), O<u>H</u> proton not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 139.5, 133.1, 129.6, 128.5, 127.3, 127.2, 126.2, 126.1, 123.8, 122.3, 70.8, 41.1, 36.2, 32.5, 23.1; HRMS *m /*

z calcd. for $C_{26}H_{28}N_2O$ (M^+) 384.2203, found: 384.2221. Anal. Calcd for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34; N, 7.28. Found: C, 81.32; H, 7.50; N, 7.06.

trans 5-Bromo-8-phenyloct-7-eneal-(*N,N* Diphenylhydrazone)



357

Triphenylphosphine (41 mg, 0.15 mmol) was added to a round bottom flask (25 mL) flame dried under argon along with methylenechloride (1.5 mL) and Et_3N (60 μL, 0.45 mmol). The solution was cooled to 0 °C and bromine (8 μL 0.5 mL methylenechloride, 0.15 mmol) was added to this mixture with stirring. *trans* 5-hydroxy-8-phenyloct-7-eneal-(*N,N* diphenylhydrazone) **356** (60 mg, 0.15 mmol) was added and the solution warmed to room temperature (*ca.* 22 °C). After 15 min. of stirring at this temperature, TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separatory funnel containing aqueous $NaHCO_3$ (10 mL) and methylenechloride (10 mL). The aqueous layer was extracted with methylenechloride (3x10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash cromatography (silica gel, 3:97, diethyl ether / petroleum ether) to afford the title compound (68 mg, 97%) as a brown oil; IR (neat) 3046, 2896, 1723, 1595, 1491, 1303, 1209, 1069 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5 Hz, 1H), 7.40-7.29 (m, 4H), 7.16-7.04 (m, 6H), 6.49 (t, J = 5.1 Hz, 1H), 2.51 (dt, J_1 = 7.3, J_2 = 1.5 Hz, 2H), 2.36-2.27 (m, 2H), 1.86 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 144.0, 137.9, 129.6, 123.9, 122.2, 43.1, 31.8, 19.2; HRMS *m / z* calcd. for $C_{17}H_{18}N_2O$ (M^+) 266.1415, found: 266.1411.

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), Bu_3SnH (1 equiv.) and AIBN (0.25 equiv.). Argon was flushed through the solution for 30 minutes. After this time, the solution was taken up by syringe.

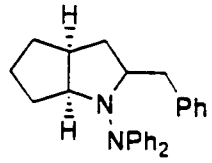
In a separate two-necked round bottom flask, dried and cooled under argon, equipped with a condenser and a rubber septum, was charged with the appropriate substrate followed by freshly distilled benzene (enough to make a 0.005 M solution). To this solution was added AIBN (0.10 equiv.), and argon was 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. After the addition was completed, the reaction mixture was refluxed for an additional hour. The mixture was cooled to room temperature and concentrated *in vacuo* before being purified by flash column chromatography.

General Procedure for SmI_2/HMPA Reactions:

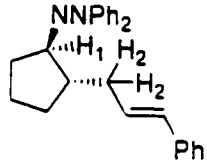
A Schlenk flask, flame dried and cooled under argon, was charged with the appropriate substrate followed by THF (enough to make a 0.025M solution) and HMPA (1.0-2.0 mL per mmol of substrate). The system was degassed using three freeze pump thaw cycles, introducing argon after the last cycle. After this

time, SmI_2 (4.5 equiv. as a 0.1M solution in THF) was then added yielding a deep purple solution. 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 containing water and diethyl ether. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. The resulting oils were purified by flash chromatography.

cis *N*-Diphenylamino-2-benzyl-hexahydro-cyclopenta[*b*]pyrrole 359 and _trans_ 1-(_trans_ 3-phenyl-2-propenyl)-2-(*N*,*N*-diphenylhydrazino)-cyclopentane 362



359



362

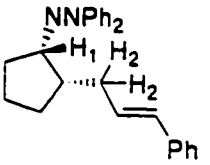
Following the general procedure for the syringe pump radical reactions, bromide **357** (72 mg, 0.17 mmol) was placed in a three neck round bottom flask (25 mL) equipped with a reflux condenser, followed by benzene (8 mL), and was treated with Bu_3SnH (55 μL, 0.18 mmol) and AIBN (7 mg). The reaction mixture was refluxed for two hours then concentrated under reduced pressure. The residue was dissolved in diethyl ether (4 mL) and stirred at 21 °C with saturated aqueous potassium fluoride solution (4 mL). Filtration, extraction with diethyl ether, drying over magnesium sulfate and concentration gave a crude mixture which was analyzed by ^1H NMR spectroscopy to determine the isomers ratios. Following this, the resulting oil was purified by flash cromatography (silica gel,

3:97, diethyl ether / petroleum ether) to afford the tandem (35 mg, 55%) and the *cis* monocyclized (8 mg, 12%) isomers as clear oils.

Isomer **359**: IR (neat) 2952, 2862, 1593, 1492, 1117, 1072, 909, 763 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.49-7.19 (m, 8H), 7.17-6.96 (m, 7H), 3.29-3.22 (m, 2H), 2.98-2.92 (m, 1H), 2.53-2.48 (m, 2H), 2.15-2.09 (m, 1H), 1.95-1.85 (m, 3H), 1.61-1.49 (m, 3H), 1.25-1.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.9, 129.0, 128.9, 128.8, 128.4, 128.2, 126.0, 125.8, 65.0, 64.9, 39.6, 37.5, 36.6, 33.9, 31.2, 24.1; HRMS *m / z* calcd. for $C_{26}H_{28}N_2$ (M^+) 368.2254, found: 368.2263.

Isomer **362**: IR (neat) 3024, 2952, 1588, 1495, 1272, 966, 748, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31-7.05 (m, 13 H), 6.93 (m, 2H), 6.27 (d, J = 15.8 Hz, 1H), 6.10 (dt, J = 15.8 Hz, J = 7.2 Hz, 1H), 3.92 (br s, 1H), 3.16-3.14 (m, 1H), 2.16-2.13 (dd, J = 7.3 Hz, J = 7.3 Hz, 2H), 2.04-1.95 (m, 2H), 1.81-1.75 (m, 1H), 1.68-1.59 (m, 2H), 1.35-1.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 147.8, 137.5, 131.7, 129.2, 128.9, 128.4, 126.9, 125.9, 122.0, 120.3, 63.0, 44.0, 37.9, 31.6, 30.7, 23.6; nOe of the two hydrogens (H_1, H_2) = 0.8%; HRMS *m / z* calcd. for $C_{26}H_{28}N_2$ (M^+) 368.2254, found: 368.2268.

1-(trans 3-phenyl-2-propenyl)-2-(*N,N*-diphenylhydrazino)-cyclopentane *cis*



363

Following the general procedure for SmI_2/HMPA, bromide **357** (72 mg, 0.17 mmol) was placed in a dry round bottom flask (25 mL) followed by THF (5

mL). The mixture was treated with HMPA (0.3 mL) and SmI_2 (3.5 mL as a 0.1 M solution in THF). After work-up and purification of the reaction mixture, compound T9 (47 mg, 75%) was isolated as a pale yellow oil; IR (neat) 3054, 2972, 1578, 1497, 1252, 988, 738, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.31-7.19 (m, 10 H), 7.12-7.05 (m, 3H), 6.93 (m, 2H), 6.43 (d, *J* = 15.8 Hz, 1H), 6.18 (dt, *J* = 15.8 Hz, *J* = 7.9 Hz, 1H), 4.09 (br s, 1H), 3.34-3.31 (m, 1H), 2.40-2.37 (dd, *J* = 7.9 Hz, *J* = 6.6 Hz, 2H), 2.04-1.97 (m, 1H), 1.96-1.68 (m, 4H), 1.66-1.60 (m, 1H), 1.59-1.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 147.8, 137.5, 130.5, 129.8, 128.9, 128.4, 127.0, 125.9, 121.9, 120.2, 58.4, 44.0, 32.8, 30.2, 29.5, 22.3; nOe of the two hydrogens (H_1, H_2) = 0.8%; HRMS *m / z* calcd. for $C_{26}H_{28}N_2$ (M^+) 368.2254, found: 368.2262.

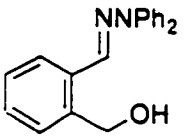
2-(Hydroxymethyl)benzaldehyde

395 **396**

Phtalide **390** (2.68 g, 20 mmol) was added to a round bottom flask (250 mL) along with freshly distilled toluene (50 mL). The solution was cooled to -78 °C and DIBAL (21 mL of a 1.0 M solution in toluene, 21 mmol) was added. After two hours of stirring at -78 °C the reaction was quenched with methanol until gas evolution ceased. The solution was warmed to room temperature and aqueous sodium potassium tartrate solution (50 mL) was added. The mixture was stirred vigurously at room temperature until two clear layers were formed (*ca.* 30 min.). The resulting mixture was poured into a separartory funnel containing water (50 mL) and ethyl acetate (60 mL). The aqueous layer was extracted with ethyl

acetate (2x50 mL) and the combined organic layers were washed brine, dried over $MgSO_4$, filtered through a pad of silicagel and concentrated *in vacuo* to afford an inseparable mixture (38:62 by GCMS and ^1H NMR) of isomers **395** and **396** (2.12 g, 78%) as a faint yellow oil. IR (neat) 3611, 3381, 2978, 1700, 1449, 1105, 911, 766 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.5 (s, 1H), 7.99-7.79 (m, 4H), 5.06 (s, 2H), O<u>H</u> not observed for isomer **395**) δ 7.99-7.79 (m, 4H), 6.50 (d, *J* = 8.4 Hz, 1H), 5.33 (br s, 2H), 3.19 (d, *J* = 8.4 Hz, 1H) for isomer **396**; ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.0, 141.8, 137.6, 134.7, 129.9, 129.8, 129.1, 127.7, 105.8, 65.1; HRMS *m / z* calcd. for $C_8H_8O_2$ (M^+) 136.0524, found: 136.0519.

2-(Hydroxymethyl)benzaldehyde *N,N*-Diphenylhydrazone

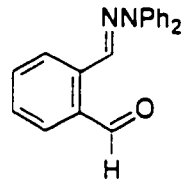


392

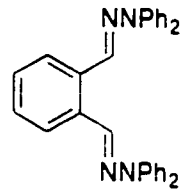
2-(Hydroxymethyl)benzaldehyde **395** (2.00 g, 14.7 mmol) was added to a round bottom flask (100 mL) along with methanol (15 mL). A solution of diphenylhydrazine (2.70 g, 14.7 mmol) in methanol (10 mL) was added and the reaction mixture was stirred at room temperature (*ca.* 22 °C) for four hours. Concentration *in vacuo* gave a purple oil which was purified by flash chromatography (silica gel, 50:50, diethyl ether / petroleum ether) to afford the title compound (5.28 g, 78%) as a light yellow oil; IR (neat) 3397,3053, 2917, 2246, 1590, 1490, 1205, 1067, 910, 739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45-7.35 (m, 6H), 7.27-7.14 (m, 9H), 4.83 (s, 2H), O<u>H</u> not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.3, 138.2, 133.5, 130.4, 129.9, 129.7, 128.3, 127.8,

124.9, 122.7, 64.7; HRMS *m / z* calcd. for $C_{20}H_{18}N_2O$ (M^+) 302.1420, found: 302.1410.

2-(*N,N*-Diphenyl-hydrazonomethyl)-benzaldehyde 393 and Phtalic dicarboxaldehyde bis(*N,N*-diphenylhydrazone) 398



393



398

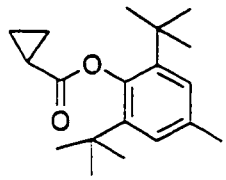
Method A. Into a dry round bottom flask (100 mL) equipped with a magnetic stirring bar was added dicarboxaldehyde **397** (1.34 g, 10 mmol) followed by diethyl ether (60 mL) and *N,N*-diphenylhydrazine (1.84g, 10 mmol). A yellow precipitate was formed quickly. The mixture was stirred at room temperature (*ca.* 22 °C) for approximately two hours.

Phtalic dicarboxaldehyde bis(*N,N*-diphenylhydrazone) **398** was obtained by filtration from the reaction mixture (3.47 g, 75% based on hydrazine consumption) as a fine yellow powder, mp 162-163 °C; IR (CCl_4) 3053, 1586, 1491, 1376, 1215, 1061, 951, 561; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92-7.82 (m, 2H), 7.37-7.22 (m, 12H), 7.18-7.12 (m, 4H), 7.10-7.01 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.5, 133.5, 129.7, 127.9, 126.6, 124.4, 122.4, 112.3; HRMS *m / z* calcd. for $C_{32}H_{26}N_4$ (M^+) 466.2158, found: 466.2155. Anal. Calcd for $C_{32}H_{26}N_4$: C, 82.37; H, 5.62; N, 12.01. Found: C, 82.53; H, 5.69; N, 12.13.

2-(*N,N*-Diphenyl-hydrazonomethyl)-benzaldehyde **393** was recrystalized from diethylether (690 mg, 23%) as small orange needles, mp 118-120 °C; IR (CCl_4) 3051, 2836, 2734, 1697, 1586, 1550, 1489, 1228, 1197, 1069, 911, 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.00-7.92 (m, 2H), 7.77-7.73 (m, 1H), 7.55-7.38 (m, 6H), 7.26-7.18 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 192.2, 143.2, 133.3, 133.0, 132.4, 131.7, 129.9, 127.7, 127.2, 125.0, 122.4, 119.7; HRMS *m / z* calcd. for $C_{20}H_{16}N_2O$ (M^+) 300.1263, found: 300.1247. Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.96; H, 5.37; N, 9.33. Found: C, 80.05; H, 5.42; N, 9.50.

Method B. 2-(Hydroxymethyl)benzaldehyde *N,N*-Diphenylhydrazone **392** (350 mg, 1.16 mmol) was added to a round bottom flask (50 mL) flame dried under argon along with DMSO (2mL) and Et_3N (1.29 mL, 9.28 mmol). A SO_3-pyridine/DMSO suspension (0.54 g of SO_3•pyridine, 3.45 mmol in 1mL DMSO) was added dropwise to this mixture with stirring. After 15 min. at room temperature (*ca.* 22 °C), TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separatory funnel containing water (20 mL) and ethyl acetate (30 mL). The aqueous layer was extracted with ethyl acetate (2x20 mL) and the combined organic layers were washed brine, dried over $MgSO_4$, filtered through a pad of silicagel and concentrated *in vacuo*. 2-(*N,N*-Diphenyl-hydrazonomethyl)-benzaldehyde **393** was recrystalized from ether (254 mg, 73%) as small orange needles. The product coeluted on TLC and was spectroscopically identic with a product sample prepared by method A.

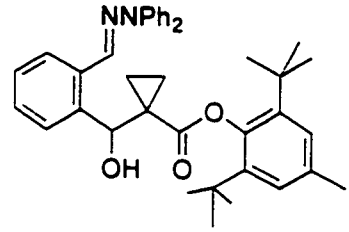
2,6-Bis(1,1-methylethyl)4-methylphenyl cyclopropanecarboxylate



402

2,6-Di-*tert*-butyl-4-methylphenol (11 g, 50 mmol) was added to a round bottom flask (500 mL) flame dried under argon along with THF (60 mL) and the solution was cooled to 0 °C. BuLi (20 mL of a 2.50 M solution in hexanes, 50 mmol) was added dropwise with stirring as the solution turned cloudy pale yellow. After 15 min. at 0 °C the cyclopropanecarbonyl chloride (6.4 g, 53 mmol) was added in one portion. The solution was warmed and stirred at room temperature (*ca.* 22 °C) overnight. The resulting mixture was poured into a separatory funnel containing aqueous NH_4Cl (70 mL) and diethyl ether (70 mL). The aqueous layer was extracted with diethyl ether (2x70 mL) and the combined organic layers were washed with aqueous NaHCO3 (40 mL), brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield an yellow oil. The product was obtained by recrystalization from methanol (12.5 g, 87%) as a white solid, mp 66-67 °C. IR (CCl_4) 2945, 1748, 1598, 1379, 1211, 1144, 1107, 1032, 931, 668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.10 (s, 2H), 2.31 (s, 3H), 1.96-1.88 (m, 1H), 1.34 (s, 18H), 1.19-1.11 (m, 2H), 1.07-0.99 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.9, 142.7, 134.9, 132.5, 127.5, 35.9, 32.1, 22.1, 14.7, 9.5; HRMS *m / z* calcd. for $C_{19}H_{28}O_2$ (M^+) 288.2090, found: 288.2101. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 79.31; H, 9.78.

2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-hydroxy(2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate

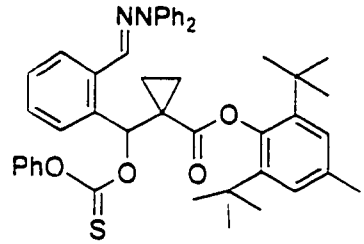


394

2,6-Bis(1,1-methylethyl)4-methylphenyl cyclopropanecarboxylate **402** (1.5 g, 5.20 mmol) was added to a round bottom flask (50 mL) flame dried under argon along with THF (30 mL) and the solution was cooled to -78 °C. *t*-BuLi (3.60 mL of a 1.55 M solution in THF, 5.58 mmol) was added dropwise with stirring as the solution turned bright yellow. After 30 min. at -78 °C the aldehyde **393** (1.3g, 4.33mmol) was injected as a solution in THF (3 mL). The solution was stirred at –78 °C for another hour then warmed to room temperature (*ca.* 22 °C). The resulting mixture was poured into a separatory funnel containing aqueous NH_4Cl (30 mL) and diethyl ether (40 mL). The aqueous layer was extracted with diethyl ether (2x25 mL) and the combined organic layers were washed brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, 15:85, diethyl ether / petroleum ether) to afford the title compound (1.66 g, 68%) as a yellow solid, mp 84-85 °C; IR (neat) 3497, 2950, 1730, 1591, 1492, 1364, 1108, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.61-7.51 (m, 2H), 7.45-7.36 (m, 4H), 7.32-7.26 (m, 2H), 7.19-7.15 (m, 6H), 7.09 (s, 2H), 5.75 (s, 1H), 2.31 (s, 3H), 1.64-1.59 (m, 1H), 1.57-1.52 (m, 1H), 1.26 (s, 9H), 1.23 (s, 9H), 0.90-0.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 145.7, 143.7, 142.0, 141.9, 136.8, 134.6, 134.0, 129.8, 129.4, 128.0, 127.8, 126.9, 126.8, 124.6, 122.4, 68.7, 35.1, 35.0, 31.3, 31.2, 29.6, 21.4, 13.7, 11.4; HRMS *m / z* calcd. for $C_{39}H_{44}N_2O_3$ (M^+) 588.3354, found: 588.3313. Anal.

Calcd for $C_{39}H_{44}N_2O_3$: C, 79.56; H, 7.53; N, 4.76. Found: C, 79.65; H, 7.47; N, 4.57.

2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-hydroxy- thionocarbonate phenyl ester (2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate

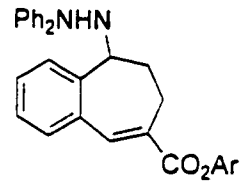


405

2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-hydroxy- (2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate **394** (382 mg, 0.68 mmol) was added to a round bottom flask (25 mL) flame dried under argon along with methylene chloride (4 mL) and pyridine (199 mg, 203 μL, 2.52 mmol). The solution was cooled to -78 °C. Phenyl chlorothionoformate (129 mg, 103 μL, 0.75 mmol) was added and the solution was stirred at room temperature (*ca.* 22°C) for four hours. The resulting mixture was poured into a separatory funnel containing dilute aqueous HCl (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2x10 mL) and the combined organic layers were washed brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, 10:90, diethyl ether / petroleum ether) to afford the title compound (61% based on the recovered starting material) as a yellow solid, mp 96-97 °C; IR (neat) 2950, 2248, 1739, 1591, 1490, 1364, 1242, 1107, 1007, 909, 739, 696, 569 cm^{-1}; ^1H NMR (500

MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.73 (s, 1H), 7.42-7.28 (m, 9H), 7.25-7.18 (m, 5H), 7.15-7.12 (m, 3H), 7.09-7.06 (m, 1H), 6.97-6.93 (m, 2H), 2.33 (s, 3H), 1.76-1.74 (m, 1H), 1.52-1.50 (m, 1H), 1.36 (s, 9H), 1.24 (s, 9H), 0.92-0.84 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.8, 172.5, 153.5, 145.9, 143.5, 142.2, 141.9, 134.9, 134.6, 133.2, 132.4, 129.8, 129.3, 128.6, 127.7, 127.5, 127.2, 126.7, 126.5, 126.3, 124.6, 122.4, 121.9, 80.8, 35.1, 35.0, 31.6, 31.3, 27.9, 21.4, 13.3, 10.4; FAB HRMS *m / z* calcd. for $C_{46}H_{48}N_2O_4S$ (M^+) 724.3336, found: 724.3335. Anal. Calcd for $C_{46}H_{46}N_2O_4S$: C, 76.42; H, 6.41; N, 3.87. Found: C, 76.18; H, 6.51; N, 3.92.

1-*N,N* diphenylhydrazine-4-carboxylic acid [2,6-di(*tert*-butyl)4-methylphenyl ester] 6,7-benzocyclohept-4-ene

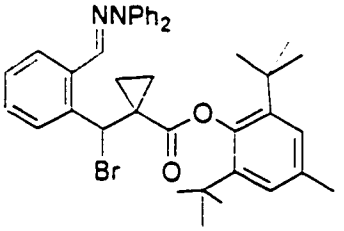


406

2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-hydroxy- thionocarbonate phenyl ester (2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate **405** (163 mg, 0.23 mmol) was added under argon to a dry round bottom flask (25 mL) equipped with a reflux condenser followed by freshly distilled benzene (11 mL). Argon was then bubbled through the solution for approximately 15 min. After this time the solution was heated at reflux and Bu_3SnH (75 μL, 0.28 mmol) and AIBN (10 mg, 0.05 mmol) were added as a solution in benzene (2 mL) via syringe pump technique over one hour. The solution was then refluxed for another two hours then cooled to room temperature. The solvent was removed and the resulting material was purified

by flash chromatography (silica gel, 10:90, diethyl ether / petroleum ether) to afford the title compound (113 mg, 85%). An analytical sample was recrystalized from diethyl ether as a pale yellow solid, mp 210-211 °C; IR (neat) 2946, 2362, 1718, 1591, 1493, 1278, 1186, 1108, 909, 736, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96-7.95 (m, 1H), 7.46-7.41 (m, 1H), 7.30-7.21 (m, 7H), 7.17-7.08 (m, 6H), 7.03-6.98 (m, 2H), 4.25-4.17 (m, 1H), 4.01 (br s, 1H), 2.95-2.91 (m, 1H), 2.86-2.78 (m, 1H), 2.34 (s, 3H), 2.37-2.33 (m, 1H), 2.23-2.15 (m, 1H), 1.35 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 148.1, 146.2, 142.1 (d), 140.9, 134.3, 133.9, 133.7, 133.3, 129.1, 128.9, 127.4, 126.9 (d), 122.6, 120.6, 59.1, 35.2 (d), 31.6 (d), 29.7, 25.7, 21.5; HRMS *m / z* calcd. for $C_{39}H_{44}N_2O_2$ (M^+) 572.3405, found: 572.3370. Anal. Calcd for $C_{39}H_{44}N_2O_2$: C, 81.78; H, 7.74; N, 4.89. Found: C, 81.60; H, 7.85; N, 4.78.

2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-bromo(2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate

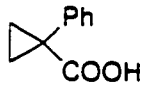


387

Triphenylphosphine (41 mg, 0.15 mmol) was added to a round bottom flask (25 mL) flame dried under argon along with methylenechloride (1.5 mL) and Et_3N (60 μL, 0.45 mmol). The solution was cooled to -10 °C and bromine (8 μL in 0.5 mL methylenechloride, 0.15 mmol) was added to this mixture with stirring. 2,6-Di(*tert*-butyl)4-methylphenyl 1-[α-hydroxy(2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] cyclopropanecarboxylate **394** (88 mg, 0.15 mmol) was added

and the solution warmed slowly to room temperature (*ca.* 22 °C). After 15 min. of stirring at this temperature, TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separatory funnel containing aqueous $NaHCO_3$ (10 mL) and methylenechloride (10 mL). The aqueous layer was extracted with methylenechloride (3x10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (silica gel, 3:97, diethyl ether / petroleum ether) to afford the title compound (68 mg, 97%) as a brown oil; IR (neat) 3497, 2950, 1730, 1591, 1492, 1364, 1108, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.61-7.51 (m, 2H), 7.45-7.36 (m, 4H), 7.32-7.26 (m, 2H), 7.19-7.15 (m, 6H), 7.09 (s, 2H), 5.75 (s, 1H), 2.31 (s, 3H), 1.64-1.59 (m, 1H), 1.57-1.52 (m, 1H), 1.26 (s, 9H), 1.23 (s, 9H), 0.90-0.77 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 145.7, 143.7, 142.0, 141.9, 136.8, 134.6, 134.0, 129.8, 129.4, 128.0, 127.8, 126.9, 126.8, 124.6, 122.4, 68.7, 35.1, 35.0, 31.3, 31.2, 29.6, 21.4, 13.7, 11.4. Anal. Calcd for $C_{39}H_{43}BrN_2O_2$: C, 71.88; H, 6.65; N, 4.29. Found: C, 72.03; H, 6.31; N, 4.59.

1-Phenylcyclopropane carboxylic acid



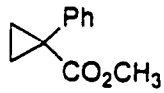
408

1-phenyl-1-cyclopropanecarbonitrile **407** (5 mL, 29.8 mmol) was added to a round bottom flask (50 mL) equipped with a reflux condenser and magnetic stirring bar along with concentrated hydrochloric acid (20 mL). The colourless solution was refluxed for 3 days. The reaction mixture was extracted with ether

(3x30mL) and the combined organic phase was poured into a separatory funnel and washed with saturated aqueous $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound (4.73 g, 98%) as a colourless liquid; IR (neat) 3479, 2833, 1682, 1308, 1204, 951, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 1.65 (dd, *J* = 4.2 Hz, *J* = 7.3 Hz, 2H), 1.25 (dd, *J* = 4.2 Hz, *J* = 7.3 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.1, 138.7, 130.5, 128.2, 127.4, 28.8, 17.3; HRMS *m / z* calcd. for $C_{10}H_{10}O_2$ (M^+) 161.9763, found: 162.0664. Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.05; H, 6.21. Found: C, 74.06; H, 5.99.

1-Phenylchlorocyclopropane 409 and 1-Phenylcyclopropyl acetate 409a

409



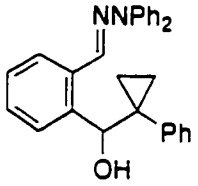
409a

A three-neck round bottom flask (250 mL) flame dried under argon, equipped with a reflux condenser and magnetic stirring bar was charged with 1-phenylcyclopropanecarboxylic acid **408** (5 g, 30.9 mmol) along with dry benzene (100 mL) and lithium chloride (1.3 g, 30.6 mmol). The pale yellow solution was degassed with argon for 30 min. Lead tetraacetate (14 g, 31.6 mmol) was added as the solution turned bright yellow and the mixture was stirred until it became nearly homogenous. The flask was then placed in an oil bath at 100 °C and the mixture stirred until gas evolution ceased (*ca.* 1 hour). The reaction mixture was filtered, the solids were washed with ether and the combined organic phase was poured into a separatory funnel and washed with saturated aqueous $NaHCO_3$ (3x30 mL), dried over $MgSO_4$ and concentrated *in vacuo*.

The product **409** was purified by bulb-to-bulb distillation to afford the title compound (2.76 g, 59%) as a colourless liquid; an analytical sample was obtained by flash chromatography (silica gel, 10:90, diethyl ether / petroleum ether); IR (neat) 3047, 1448, 1180, 753, 617 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.55-7.49 (m, 2H), 7.43-7.31 (m, 3H), 1.53 (m, 2H), 1.34 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.9, 128.4, 127.7, 127.5, 43.2, 17.5; HRMS *m / z* calcd. for C_9H_9Cl (M^+) 152.0394, found: 152.0392. Anal. Calcd for C_9H_9Cl: C, 70.83; H, 5.94. Found: C, 70.76; H, 5.98.

1-Phenylcyclopropyl acetate **409a** was obtained from the reaction mixture by bulb-to-bulb distillation as a colourless liquid (1.68 g, 31%); IR (neat) 3047, 1710, 1454, 1125, 783, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 2.10 (s, 3H), 1.29 (m, 2H), 1.22 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.4, 139.9, 128.2, 127.0, 125.9, 59.8, 21.2, 14.8; HRMS m / z calcd. for $C_{11}H_{12}O_2$ (M^+) 176.0837, found: 176.0845.

1-[α-hydroxy(2carboxaldehyde *N,N*-diphenyl-hydrazone)phenyl] phenylcyclopropane

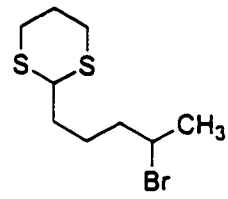


410

Magnesium (68 mg, 2.80 mmol), a crystal of iodine and THF (4mL) were added to a three-neck round bottom flask (50 mL) flame dried under argon, equipped with a reflux condenser and magnetic stirring bar. 1-Phenylchlorocyclopropane **409** (426 mg, 2.80 mmol) in dry THF (1 mL) was

added dropwise with stirring. Upon completion of the addition, the mixture was heated at reflux for 1 hour under argon and the colour of the solution changed from yellow to grey. After cooling to room temperature, the Grignard reagent was taken up by syringe and added slowly to aldehyde **393** (841 mg, 2.80 mmol) in THF (4 mL) at –10 °C, as the colourchanged from bright yellow to orange. The reaction mixture was stirred for 3 hours then warmed to room temperature (*ca.* 22 °C). The resulting mixture was poured into a separatory funnel containing aqueous NH_4Cl (5 mL) and diethyl ether (10 mL). The aqueous layer was extracted with diethyl ether (2x5 mL) and the combined organic layers were washed brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, 20:80, diethyl ether / petroleum ether) to afford the title compound (795 mg, 68%) as a white solid, mp 60-61 °C; IR (neat) 3342, 2352, 1588, 1493, 1205, 751, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08-8.06 (m, 1H), 7.57 (s, 1H), 7.50-7.47 (m, 4H), 7.38-7.20 (m, 12H), 6.96 (m, 2H), 5.12 (s, 1H), 2.06 (br s, 1H), 0.76-0.70 (m, 2H), 0.64-0.61 (m, 1H), 0.54-0.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 143.3, 137.9, 133.4, 133.3, 130.0, 129.8, 127.6, 127.4, 126.9, 126.5, 125.4, 124.6, 122.5, 73.8, 31.2, 11.4, 7.2; HRMS *m / z* calcd. for $C_{29}H_{26}N_2O$ (M^+) 418.2046, found: 418.2024.

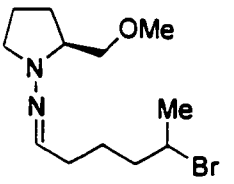
2-(4-Bromopentyl)-1,3-dithiane



419

Dithiane (5.28 g, 43.9 mmol) was placed in a round bottom flask (500 mL) and dissolved in THF (50 mL). The resulting solution was cooled to –10 °C, treated with *n*–BuLi (21.1 mL of a 2.5 M solution, 53.0 mmol) and stirred at –10 °C for 45 minutes. 1, 3–Dibromopentane (6.0 mL, 44.0 mmol) was added and the stirring continued at –10 °C for 2 hours. The reaction was quenched with brine (10 mL) and poured into a separatory funnel containing ethyl acetate (100 mL) and brine (50 mL). The aqueous layer was extracted with ethyl acetate (3x150 mL), dried, concentrated and purified by flash chromatography (2:98, diethyl ether / petroleum ether) to yield 8.55 g (72%) of the title compound as a light yellow oil; IR (neat, cm^{-1}) 2914, 1435, 1378, 1275; ^1H NMR (200 MHz, $CDCl_3$) δ 4.11-3.97 (m, 2H), 2.84-2.76 (m, 4H), 2.10-2.03 (m, 1H), 1.90-1.64 (m, 7H), 1.71 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 50.8, 47.0, 40.2, 34.4, 30.1, 26.1, 25.7, 24.7 ppm; HRMS *m / z* calcd. for $C_9H_{17}S_2Br$ (M^+) : 267.9950, found: 267.9939.

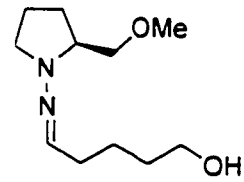
5-Bromohexanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine -hydrazone



417

2-(4-Bromopentyl)-1,3-dithiane **419** (0.751 g, 2.8 mmol) was added to a round bottom flask (50 mL) containing CAN (6.24g, 11.4 mmol) dissolved in an aqueous solution of 75% acetonitrile (8 mL). The solution was stirred at room temperature for 5 minutes and poured into a separatory funnel containing water (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3X 10 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was further purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, ethyl acetate / petroleum ether) under aspirator vacuum, then concentrated. The resulting aldehyde was then mixed with *(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine (0.375 mL, 2.8 mmol) in THF (50 mL). The reaction mixture was stirred at 0 °C for 5 hours. The resulting solution was filtered through a sintered glass funnel with a pad of silica gel and washed with diethyl ether, concentrated and chromatographed (30:70, diethyl ether / petroleum ether) to afford 284 mg (35%) of the title compound as a yellowish oil; IR (neat, cm^{-1}) 2931, 1604, 1455, 1342, 1031, 749, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 6.51 (t, J = 5.5 Hz, 1H), 4.11-3.95 (m, 1H), 3.49-3.22 (m, 4H), 3.27 (s, 3H), 2.68-2.54 (m, 1H), 2.20-2.15 (m, 2H), 1.87-1.42 (m, 8H), 1.60 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 74.6, 63.2, 58.9, 51.2, 50.1, 40.3, 32.0, 26.3, 26.2, 25.6, 21.9 ppm; HRMS *m / z* calcd. for $C_{12}H_{23}N_2OBr$ (M^+): 290.0994, found: 290.0982.

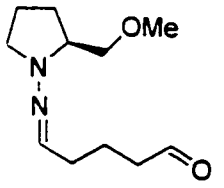
5-Hydroxypentanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone



432

δ-Valerolactol **351** (0.545 g, 5.34 mmol) was added to a round bottom flask (100 mL) along with methanol (40 mL). A solution of *(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine (aa1) (0.715 mL, 5.34 mmol) in methanol (15 mL) was added and the reaction mixture was stirred at room temperature (*ca.* 22 °C) overnight. Concentration *in vacuo* gave a brown oil which was purified by flash cromatography (50:50, diethyl ether / petroleum ether) to afford 1.05 g of the title compound (92%) as a light yellow oil; IR (neat) 3402, 2931, 1604, 1458, 1341, 1196, 1117, 972 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.60 (t, *J* = 5.3 Hz, 1H), 3.61-3.42 (m, 3H), 3.39-3.25 (m, 3H), 3.30 (s, 3H), 2.71-2.59 (m, 1H), 2.49 (br s, 1H), 2.25-2.12 (m, 2H), 1.95-1.65 (m, 4H), 1.60-1.43 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 74.7, 63.3, 62.1, 59.0, 50.4, 32.4, 31.9, 26.4, 23.6, 22.0; HRMS *m / z* calcd. for $C_{11}H_{22}N_2O_2$ (M^+) 214.1682, found: 214.1679.

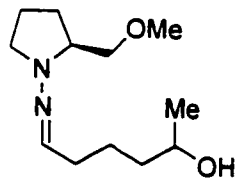
Butanal-[*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone]-4-carboxaldehyde



433

5-Hydroxypentanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone **432** (0.778 g, 3.64 mmol) was added to a round bottom flask (50 mL) flame dried under argon along with DMSO (15 mL) and Et_3N (4.0 mL, 29.4 mmol). A SO_3-pyridine/DMSO suspension (1.71 g of SO_3-pyridine, 10.9 mmol in 2 mL DMSO stirred separately until they form a homogenous mixture) was added dropwise to this mixture with stirring. After 15 min. at room temperature (*ca.* 22 °C), TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separartory funnel containing water (30 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2x30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by flash cromatography (silica gel, 40:60, diethyl ether / petroleum ether) to afford 0.502 g of the title compound (65%) as a light yellow oil; IR (neat) 2932, 1723, 1604, 1435, 1348, 1197, 1121, 972 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.4 Hz, 1H), 6.58 (t, *J* = 4.8 Hz, 1H), 3.50-3.25 (m, 4H), 3.31 (s, 3H), 2.69-2.57 (m, 1H), 2.50 (dt, *J* = 7.3 Hz, *J* = 1.4 Hz, 2H), 2.23-2.13 (m, 2H), 1.87-1.43 (m, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.1, 138.0, 74.7, 63.2, 58.9, 50.2, 43.1, 32.2, 26.5, 23.5, 21.1; HRMS *m / z* calcd. for $C_{11}H_{20}N_2O_2$ (M^+) 212.1525, found: 212.1538.

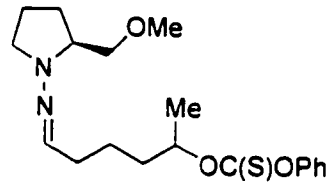
5-Hydroxyhexanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone



434

Following the general procedure, butanal-[*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone]-4-carboxaldehyde **433** (0.411 g, 1.94 mmol) was treated with methylmagnesium chloride (724 μL, 3.0 M solution in THF, 2.17 mmol) to afford 0.398 g (90%) of the title compound as a faint yellow oil; IR (neat, cm^{-1}) 3381, 2931, 1604, 1435, 1347, 1121, 972; ^1H NMR (200 MHz, $CDCl_3$) δ 6.61 (t, *J* = 5.2 Hz, 1H), 3.81-3.78 (m, 1H), 3.51-3.25 (m, 4H), 3.30 (s, 3H), 2.70-2.55 (m, 1H), 2.19-2.09 (m, 2H), 1.92 (br s, 1H), 1.82-1.41 (m, 8H), 1.20 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 74.7, 67.5, 63.3, 59.0, 50.3, 38.6, 32.4, 26.6, 23.5, 23.3, 23.0 ppm; HRMS *m / z* calcd. for $C_{12}H_{24}N_2O_2$ (M^+): 228.1838, found: 228.1837.

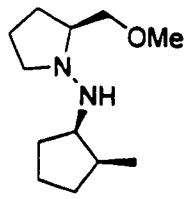
5-Hydroxy-(thionocarbonate phenyl ester)-hexanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone



430

5-Hydroxyhexanal-*(S)*-(-)-Amino-2-(methoxymethyl)pyrrolidine-hydrazone **434** (0.198 g, 0.87 mmol) was added to a round bottom flask (25 mL) flame dried under argon along with CH_2Cl_2 (5 mL) and pyridine (254 mg, 260 μL, 3.22 mmol) the solution was cooled to -78 °C. Phenyl chlorothionoformate (166 mg, 133 μL, 0.96 mmol) was added and the solution was stirred at room temperature (*ca.* 22°C) for four hours. The resulting mixture was poured into a separatory funnel containing dilute aqueous HCl (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (2x10 mL) and the combined organic layers were washed brine, dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by flash chromatography (silica gel, 20:80, diethyl ether / petroleum ether) to afford 98 mg of the title compound (31%) as a faint yellow oil; IR (neat, cm^{-1}) 3393, 3061, 2928, 1592, 1483, 1302, 1210, 741, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.41-7.11 (m, 5H), 6.61 (t, *J* = 5.1 Hz, 1H), 5.39-5.36 (m, 1H), 3.50-3.23 (m, 4H), 3.31 (s, 3H), 2.71-2.57 (m, 1H), 2.15-2.03 (m, 2H), 1.82-1.22 (m, 8H), 1.19 (d, *J* = 6.4 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.4, 153.2, 139.1, 132.4, 127.5, 121.9, 87.3, 67.1, 63.2, 59.1, 50.2, 38.7, 32.1, 26.9, 23.7, 23.4, 23.1 ppm; HRMS *m / z* calcd. for $C_{19}H_{28}N_2O_3S$ (M^+): 364.1821, found: 364.1835.

2 Methyl cyclopentyl [*N*-(S)-2-(methoxymethyl) pyrrolidine] amine

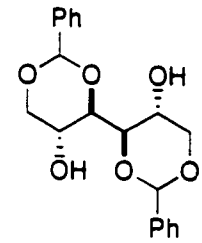


424

Following the general procedure for the SmI_2/HMPA reactions 5-hydroxy-(thionocarbonate phenyl ester)-hexanal-*(S)*-(-)-amino-2-(methoxymethyl-)pyrrolidine-hydrazone **430** (0.081 g, 0.22 mmol) was added, under argon, to a dry Schlenk flask (50 mL), followed by THF (10 mL) and HMPA (0.3 mL). The system was degassed using three freeze pump thaw cycles, introducing argon after the last cycle. The solution was then warmed to –78 °C and SmI_2 was added (10.1 mL as a 0.1M solution in THF, 1.01 mmol) yielding a deep purple solution. The reaction mixture was stirred at room temperature for 2 hours, then quenched with aqueous sodium bicarbonate (3 mL). The resulting mixture was poured into a separatory funnel containing water (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3X 5 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous magnesium sulfate and concentrated. Residual HMPA had to be removed from the crude reaction mixture since it interfered with the determination of the cis/trans ratios by ^1H NMR spectroscopy. For this purpose, the resulting oil was further purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, dichloromethane / petroleum ether) under aspirator vacuum. The solvent was removed and the resulting material was purified by flash chromatography (silica gel, 10:90, diethyl ether / petroleum ether) to afford 15 mg (33%) of the cis isomer as a pale yellow oil and traces of the trans isomer as a pale yellow oil.

Cis isomer: IR (KBr, cm^{-1}) 2952, 2872, 1590, 1494, 1285, 690; ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (br s, 1H), 3.50-3.25 (m, 4H), 3.31 (s, 3H), 3.24-3.21 (m, 1H), 2.69-2.57 (m, 1H), 2.05-1.43 (m, 10H) 1.02 (d, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 74.7, 65.2, 63.2, 58.9, 50.2, 38.3, 33.3, 30.5, 26.5, 23.5, 23.2, 19.3; HRMS *m / z* calcd. for $C_{12}H_{24}N_2O$ (M^+): 212.1985, found: 212.1988.

1,3:4,6-Di-O-benzylidene-D-mannitol

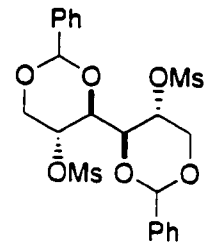


432

D-mannitol **431** (10 g, 54.9 mmol) was added to a round bottom flask (250 mL) containing *N,N*-dimethylformamide (30 mL) and benzaldehyde (12.1 mL, 109.8 mmol). Concentrated sulfuric acid (2 mL) was added and the mixture was stirred for three days at room temperature (*ca.* 22 °C). The mixture was poured into ice-water (300 mL) containing potassium carbonate (*ca.* 3g) and petroleum ether (50 mL). The mixture was stirred vigorously and a white precipitate was formed as the ice melted. The solid was filtered off and washed with petroleum ether, then recrystallized from methanol to afford 8.58 g (42%) of the title compound as a white solid, mp = 192 °C (lit.[aa1] mp = 192-193 °C); IR (neat, cm^{-1}) 3547, 3031, 1625, 1478, 1310, 1120, 690; ^1H NMR (200 MHz, $(CD_3)_2SO$) δ 7.48-7.40 (m, 4H), 7.38-7.23 (m, 6H), 5.60 (s, 2H), 5.34 (d, *J* = 5.4 Hz, 2H), 4.46 (dd, *J* = 5.4 Hz, *J* = 9.0 Hz, 2H), 4.18-3.90 (m, 4H) 3.85 (t, *J* = 10.5 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.9, 129.8, 128.5, 123.2, 100.1, 79.3, 76.7, 67.3

ppm; HRMS *m / z* calcd. for $C_{20}H_{22}O_6$ (M^+): 313.7971, found: 313.7969. Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.05, H, 6.20. Found: C, 67.02, H, 5.97.

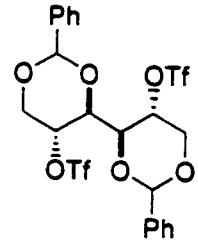
1,3:4,6-Di-O-benzylidene-D-mannitol-2,5-di-O-methanesulfonate



433

1,3:4,6-Di-O-benzylidene-D-mannitol **432** (4 g, 11.2 mmol) was added to a round bottom flask (50 mL) containing triethylamine (3.2 mL, 24.6 mmol) and dry methylene chloride (15 mL) at 0 °C. A solution of methanesulfonyl chloride (1.72 mL, 24.6 mmol) dissolved in methylene chloride (5 mL) was added dropwise. The solution was stirred at 0 °C for one hour, then poured into a separatory funnel containing 10% chlorhydric acid (7 mL). The organic layer was subsequently washed with 5% sodium bicarbonate (10 mL), dried over anhydrous sodium sulfate and concentrated to afford 5.0 g (87%) of the title compound as a white foam which was used without further purification, mp = 187 °C (lit. mp = 187-189 °C); IR (neat, cm^{-1}) 3047, 1615, 1473, 1347, 1187, 1120, 977, 750; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-7.44 (m, 4H),7.38-7.32 (m, 6H), 5.51 (s, 2H), 5.29 (ddd, *J* = 5.5 Hz, *J* = 9.2 Hz, *J* = 10.8 Hz, 2H), 4.55 (dd, *J* = 5.5 Hz, *J* = 10.8 Hz, 2H), 4.13 (d, *J* = 9.2 Hz, 2H), 3.85 (t, *J* = 10.8 Hz, 2H), 3.02 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.3, 129.5, 128.2, 126.2, 99.9, 88.3, 78.7, 66.8, 37.8 ppm: HRMS *m / z* calcd. for $C_{22}H_{26}O_{10}S_2$ (M^+): 514.0967, found: 514.0979.

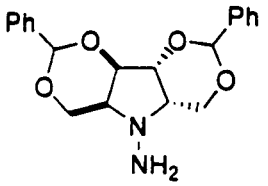
1,3:4,6-Di-O-benzylidene-D-mannitol-2,5-di-O-trifluoromethanesulfonate



434

1,3:4,6-Di-O-benzylidene-D-mannitol **432** (1 g, 2.8 mmol) was added to a round bottom flask (25 mL) containing pyridine (0.50 mL, 5.80 mmol) and dry methylene chloride (10 mL) at 0 °C. A solution of triflic anhydride (1.0 mL, 5.6 mmol) dissolved in methylene chloride (5 mL) was added dropwise. The solution was stirred at 0 °C for 20 minutes, then poured into a separatory funnel containing ice cold water (7 mL). The organic layer was subsequently washed with cold 10% chlorhydric acid (3 mL), 5% sodium bicarbonate (10 mL), dried over anhydrous sodium sulfate and concentrated to afford 1.23 g (69%) of the title compound as a pale yellow foam which was used without further purification. A small analytical sample was recrystallized from ether / petroleum ether, mp = 74 °C (lit. mp = 74-75 °C); IR (neat, cm^{-1}) 3032, 1627, 1475, 1332, 1225, 1189, 963, 761; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-7.38 (m, 10H, Ph), 5.54 (s, 2H, PhC*H*), 5.31 (ddd, *J* = 5.5 Hz, *J* = 9.1 Hz, *J* = 10.5 Hz, 2H, 2- and 5-H), 4.56 (dd, *J* = 5.5 Hz, *J* = 10.5 Hz, 2H, 1- and 6-H), 4.18 (d, *J* = 9.1 Hz, 2H, 3- and 4-H) 3.97 (t, *J* = 10.5 Hz, 2H, 1'- and 6'-H) ppm.

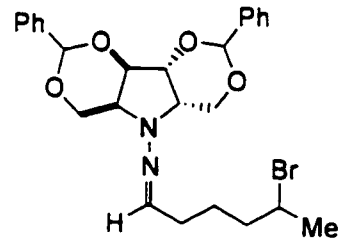
N-Amino-1,3:4,6-Di-O-benzylidene-2,5-dideoxy-2,5-imino-L-iditol



435

1,3:4,6-Di-*O*-benzylidene-*D*-mannitol-2,5-di-*O*-trifluoromethanesulfonate **434** (3.12 g, 5.0 mmol) was added to a round bottom flask (100 mL) containing anhydrous hydrazine (10.0 mL, 24.6 mmol) and dry THF (40 mL) at room temperature (*ca.* 22 °C) for 20 hours. The solvent was removed *in vacuo* and the resulting syrup was dissolved in ethyl acetate (200 mL), then poured into a separatory funnel containing cold aqueous sodium hydroxide (1M, 30 mL). The organic layer was washed again with cold aqueous sodium hydroxide (2 X 20 mL), dried over anhydrous sodium sulfate, filtered through a pad of silicagel and concentrated. The residue was recrystallized from diethyl ether to afford 1.38 g (78%) of the title compound as white plates, mp = 136 °C (lit. mp = 136-138 °C); IR (neat, cm^{-1}) 3510, 3375, 3037, 1591, 1473, 1277, 1120, 875, 690; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.38 (m, 4H, Ph), 7.35-7.25 (m, 6H, Ph), 5.54 (s, 2H, PhC*H*). 4.63 (d, *J* = 12.6 Hz, 2H, 1- and 6-H), 4.43 (d, *J* = 2.3 Hz, 2H, 3- and 4-H), 4.17 (dd, *J* = 2.3 Hz, *J* = 12.6 Hz, 2H, 1'- and 6'-H), 3.51 (br s, 2H, N*H*), 3.42 (br s, 2H, 2- and 5-H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.7, 129.1, 128.3, 126.1, 99.7, 78.4, 66.4, 61.8 ppm; HRMS *m / z* calcd. for $C_{20}H_{22}N_2O_4$ (M^+): 354.1580, found: 354.1584. Anal. Calcd. for $C_{20}H_{22}N_2O_4$: C, 67.78, H, 6.25; N, 7.90. Found: C, 67.97, H, 6.17; N, 8.01.

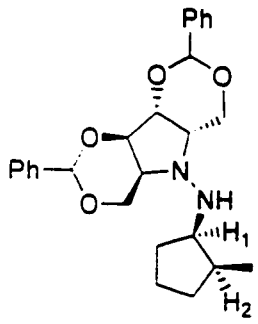
5-Bromohexanal-(*N*-Amino-1,3:4,6-Di-*O*-benzylidene-2,5-dideoxy-2,5-imino-*L*-iditol)-hydrazone



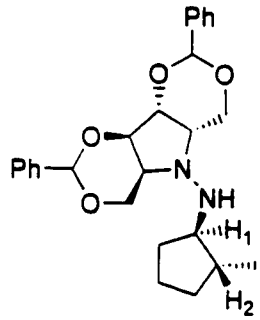
418

2-(4-Bromopentyl)-1,3-dithiane **419** (0.751 g, 2.8 mmol) was added to a round bottom flask (50 mL) containing CAN (6.24g, 11.4 mmol) dissolved in an aqueous solution of 75% acetonitrile (8 mL). The solution was stirred at room temperature for 5 minutes and poured into a separatory funnel containing water (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3X 10 mL), dried over anhydrous sodium sulfate and concentrated. The resulting oil was further purified by passage through a sintered glass funnel filled with silica gel and eluted (50:50, ethyl acetate / petroleum ether) under aspirator vacuum, then concentrated. The resulting aldehyde was then mixed with *N*-Amino-1,3:4,6-Di-*O*-benzylidene-2,5-dideoxy-2,5-imino-*L*-iditol **435** (0.991 g, 2.8 mmol) in MeOH (50 mL). The reaction mixture was stirred at room temperature for 4 hours. The resulting solution was filtered through a sintered glass funnel with a pad of silica gel and washed with EtOAc, concentrated and chromatographed (20:80, diethyl ether / petroleum ether) to afford 1.02 g (71%) of the title compound as a yellowish oil; IR (neat, cm^{-1}) 3061, 2968, 1592, 1491, 1210, 748, 697; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.29 (m, 10H, Ph), 6.67 (m, 1H), 5.49 (s, 2H, PhC*H*), 4.75 (d, *J* = 12.5 Hz, 2H), 4.45 (d, *J* = 2.5 Hz, 2H), 4.15-4.05 (m, 3H), 3.81 (br s, 2H), 2.32-2.25 (m, 2H), 1.85-1.55 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.5, 137.5, 128.9, 128.2, 126.0, 99.5, 77.4, 64.4, 60.8, 51.3, 40.7, 31.2, 26.4, 25.5 ppm; HRMS *m / z* calcd. for $C_{26}H_{31}N_2O_4Br$ (M^+): 514.1467, found: 514.1468.

(2-methyl-cyclopentyl)-(*N*-1,3:4,6-Di-*O*-benzylidene-2,5-dideoxy-2,5-imino-*L*-iditol) Amine



437a



437b

5-Bromohexanal-(*N*-Amino-1,3:4,6-Di-*O*-benzylidene-2,5-dideoxy-2,5-imino-*L*-iditol)-hydrazone **418** (0.576 g, 1.12 mmol) was added, under argon, to a dry Schlenk flask (250 mL), followed by THF (45 mL) and HMPA (1.6 mL). The system was degassed using three freeze pump thaw cycles, introducing argon after the last cycle. The solution was then warmed to the room temperature and SmI_2 was added (50.4 mL as a 0.1M solution in THF, 5.04 mmol) yielding a deep purple solution. The reaction mixture was stirred at room temperature for 2 hours, then quenched with aqueous sodium bicarbonate (15 mL). The resulting mixture was poured into a separatory funnel containing water (15 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (3X 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous magnesium sulfate and concentrated. Residual HMPA had to be removed from the crude reaction mixture since it interfered with the determination of the cis/trans ratios by ^1H NMR spectroscopy. For this purpose, the resulting oil was further purified by passage through a sintered glass funnel filled with silica

gel and eluted (50:50, dichloromethane / petroleum ether) under aspirator vacuum. The solvent was removed and the resulting material was purified by flash chromatography (silica gel, 30:70, diethyl ether / petroleum ether) to afford 176 mg (36%) of the cis isomer as a white solid and 15 mg (3%) of the trans isomer as a pale yellow oil.

Cis isomer 437a: white solid, m.p. 89-91 °C; IR (KBr, cm^{-1}) 3497, 2951, 2873, 1590, 1494, 1285; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.19 (m, 10H, Ph), 5.53 (s, 2H, PhC*H*), 4.68 (d, *J* = 12.5 Hz, 2H), 4.42 (d, *J* = 2.5 Hz, 2H), 4.18 (dd, *J* = 2.3 Hz, *J* = 12.5 Hz, 2H), 3.93 (br s, 1H), 3.41 (br s, 2H), 3.24-3.19 (m, 1H), 2.03-1.58 (m, 6H), 1.34-1.25 (m, 1H), 1.02 (d, *J* = 7.0 Hz, 3H) ppm; nOe of the two hydrogens (H_1, H_2) = 5.5%; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.6, 129.1, 128.2, 126.1, 99.7, 78.3, 63.7, 61.3, 60.8, 38.4, 32.4, 29.6, 22.3, 14.5 ppm; HRMS *m / z* calcd. for $C_{26}H_{32}N_2O_4$ (M^+): 436.2363, found: 436.2383. Anal. Calcd for $C_{26}H_{32}N_2O_4$: C, 71.53; H, 7.39; N, 6.42. Found: C, 71.82; H, 7.28; N, 6.55.

Trans isomer 437b: IR (neat, cm^{-1}) 3486, 2966, 2876, 2359, 1589, 1495, 1280; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.21 (m, 10H, Ph), 5.53 (s, 2H, PhC*H*), 4.63 (d, *J* = 12.5 Hz, 2H), 4.42 (d, *J* = 2.5 Hz, 2H), 4.19 (dd, *J* = 2.3 Hz, *J* = 12.5 Hz, 2H), 3.83 (br s, 1H), 3.39 (br s, 2H), 2.90-2.83 (m, 1H), 2.03-1.48 (m, 6H), 1.24-1.15 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H) ppm; nOe of the two hydrogens (H_1, H_2) = 1.3%; ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.6, 129.1, 128.2, 126.1, 99.7, 78.3, 65.8, 63.7, 61.3, 39.0, 33.6, 30.9, 23.7, 21.1 ppm; HRMS *m / z* calcd. for $C_{26}H_{32}N_2O_4$ (M^+): 436.2363, found: 436.2367.

Claims to Original Research

1. Alkyl radicals, generated with tributyltin hydride from their haloprecursors, are trapped efficiently by carbon monoxide under pressure. The resulting acyl radicals undergo rapid cyclization onto *N,N*-diphenylhydrazones to yield α-hydrazinocyclopentanones.

2. Selective reduction of the resulting ketones provided the corresponding *cis*- or *trans*-β-hydrazinoalcohols.

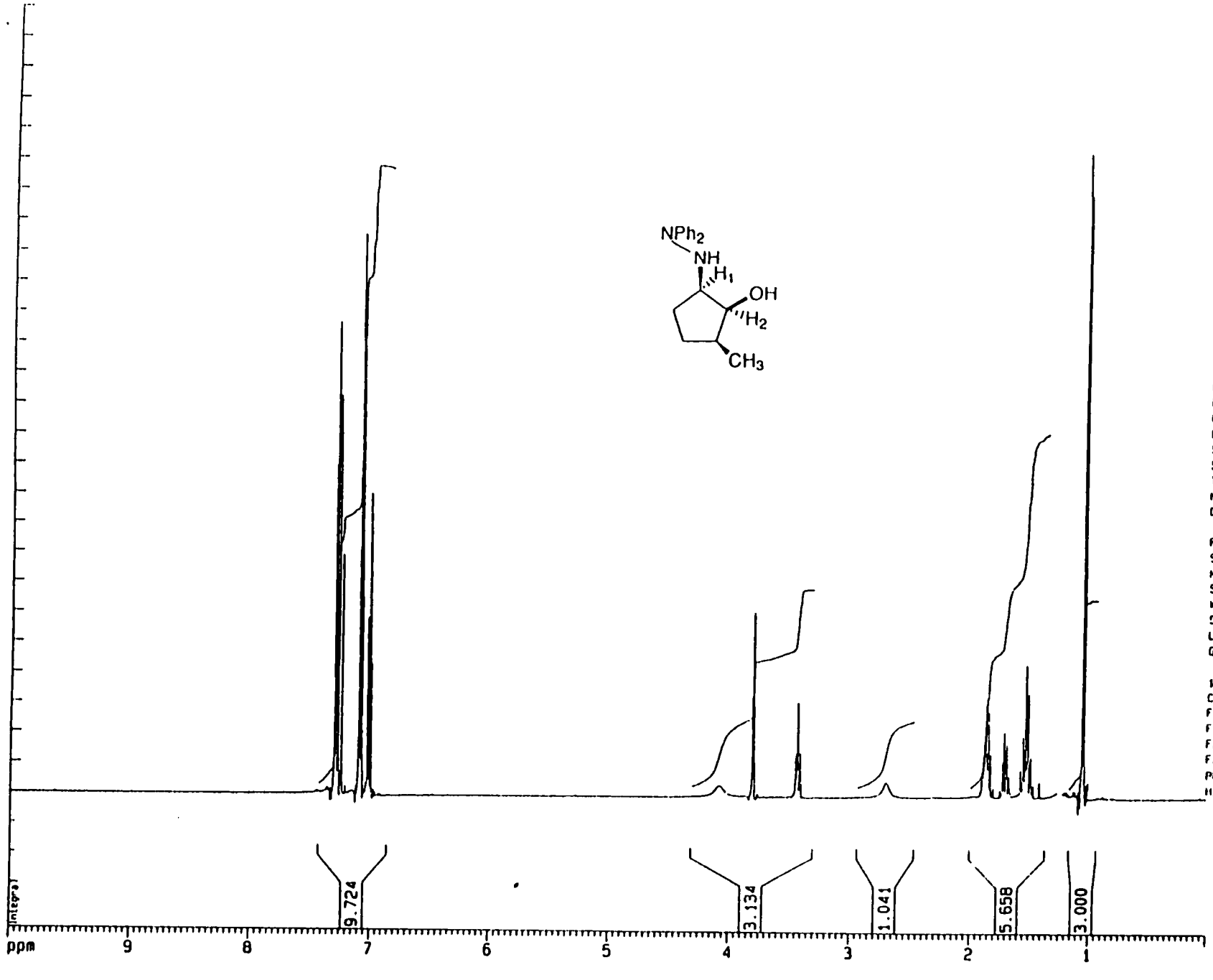
3. 7-Membered rings and a bicyclic ring systems were synthesized *via* tandem radical reactions.

4. The level of asymmetric induction in radical carbocyclizations mediated by the presence of a hydrazone chiral auxiliary was examined.

5. A novel rearrangement was uncovered when α-carbonyl hydrazine **275** was treated with Lewis acids to afford product **292**.

6. a) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580.
   b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

Appendix: Selected Spectra



Current Data Parameters

NAME	irina_:0276
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

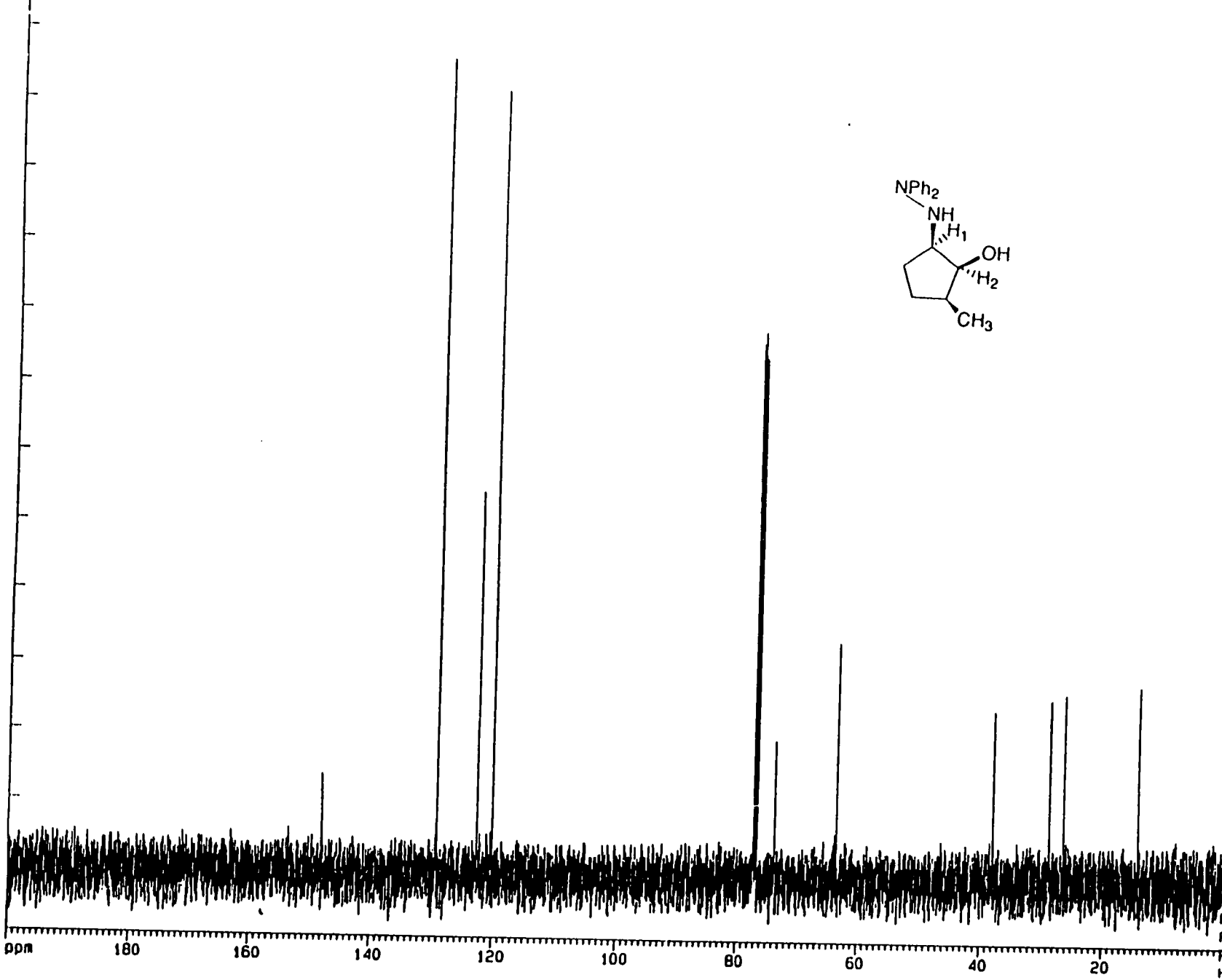
Date	960212
Time	21 37
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	512
NUCLEUS	1H
TE	300.0 K
ML1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
WC2	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/cm
HZCM	227.33429 Hz/cm



Current Data Parameters

NAME	irina_ib276
EXPNO	4
PROCNO	1

F2 - Acquisition Paramet

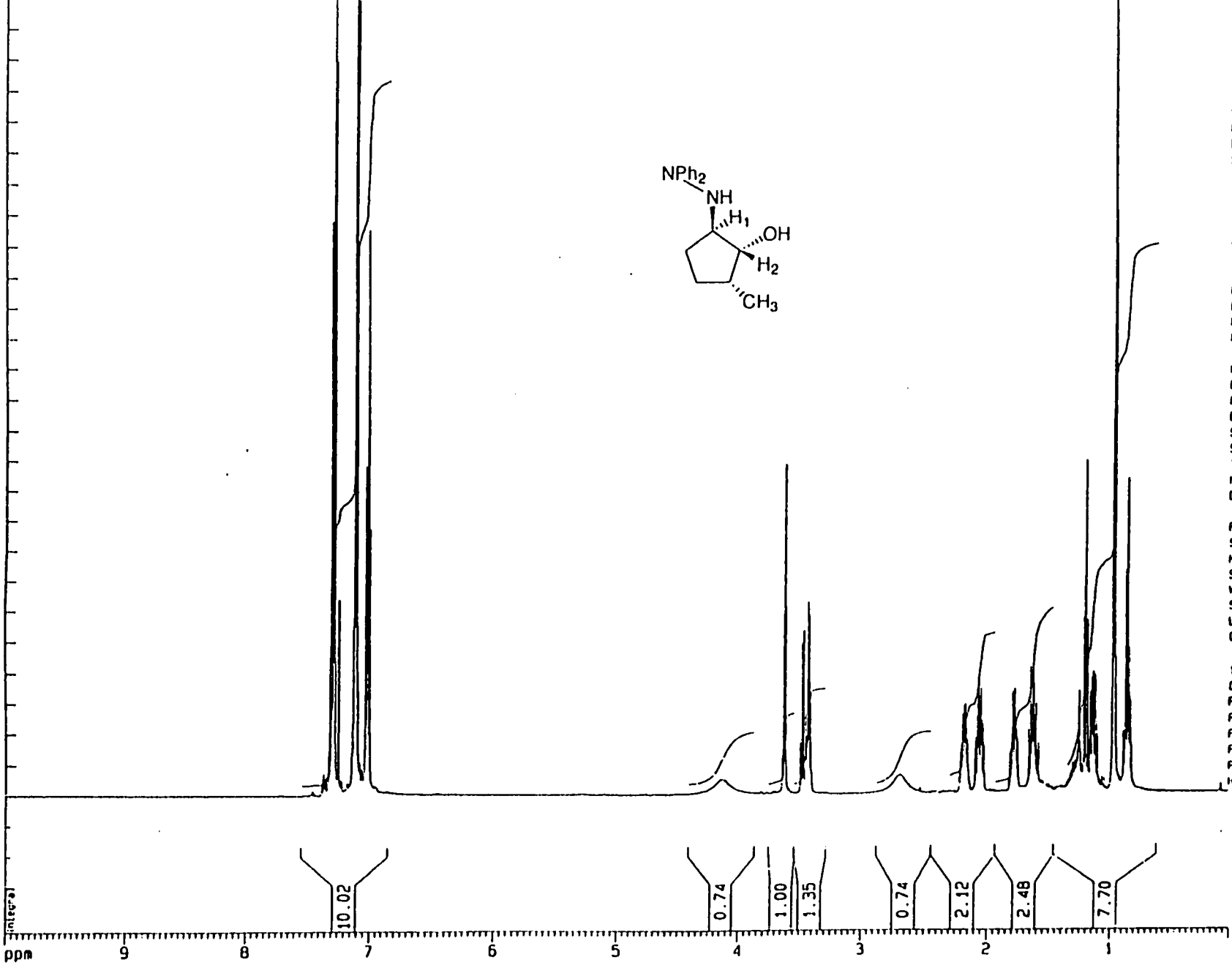
Date	960212
Time	22.39
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
TE	300.0
D11	0.0300000
P31	70.0
S2	22
ML1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	4096
DS	0

F1 - Processing paramete

SI	32768
WC2	QF
SF	125.7591523
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501



Current Data Parameters

NAME	irina_102772
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

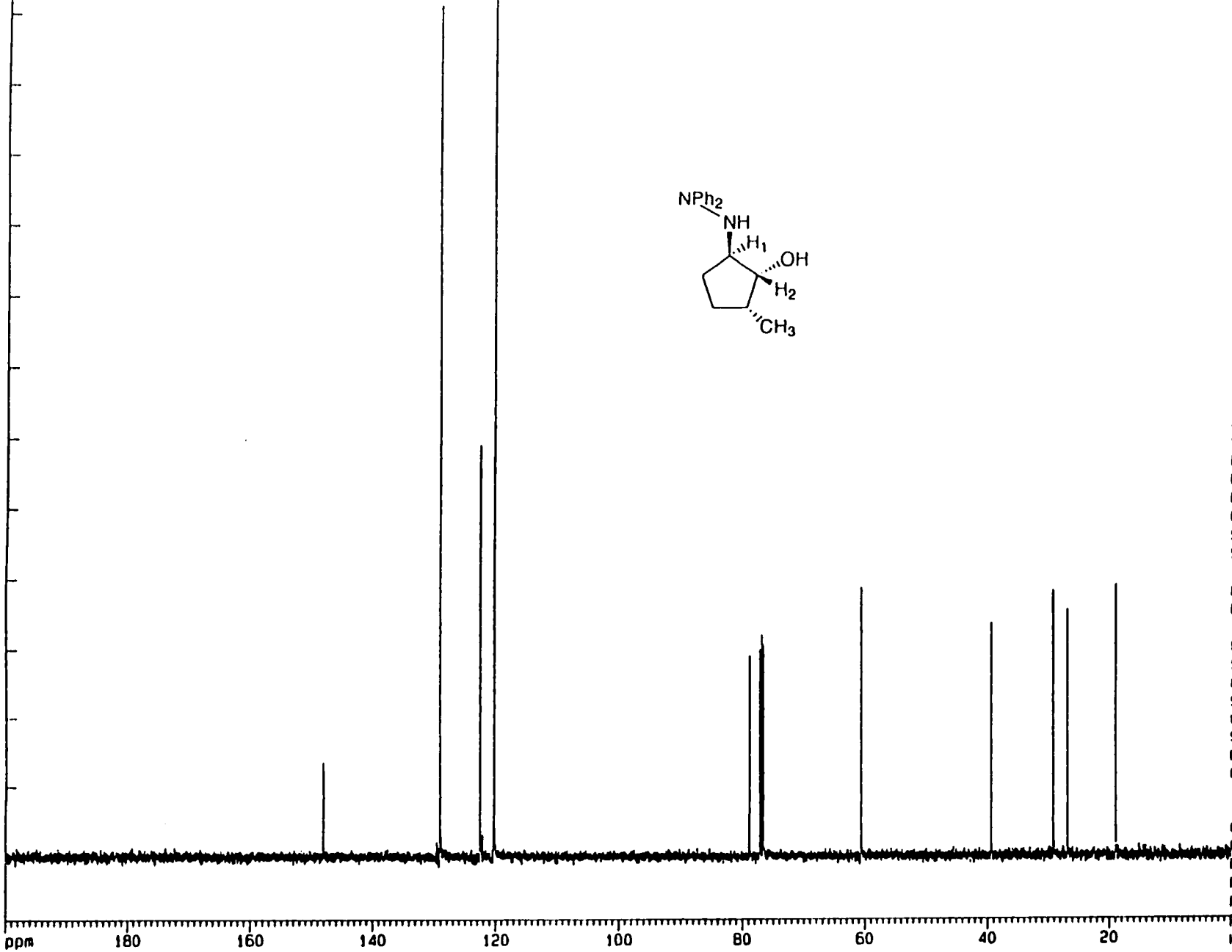
Date	960212
Time	19.50
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	256
NUCLEUS	1H
TE	300.0 K
ML1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	4.630 ppm
F1	2315.66 Hz
F2P	0.453 ppm
F2	226.79 Hz
PPMCM	0.18595 ppm/
HZCM	94.94669 Hz/



Current Data Parameters

NAME	irina_ib2772
EXPNO	4
PROCNO	1

F2 - Acquisition Paramet

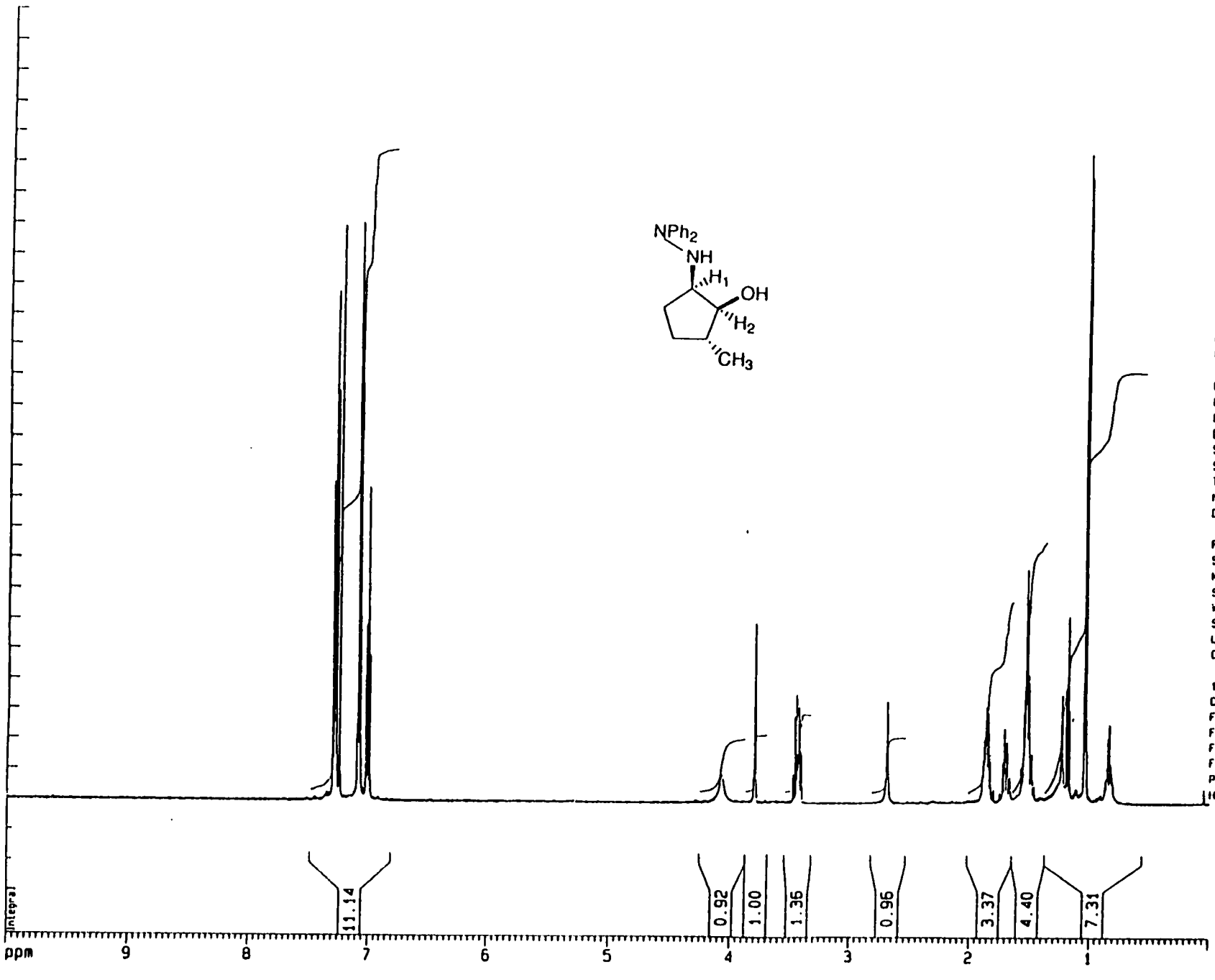
Date	960212
Time	20.53
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIORES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
TE	300.0
D11	0.0300000
P31	70.0
S2	22
ML1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	777
DS	0

F1 - Processing paramete

SI	32768
WC2	QF
SF	125.7591523
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501

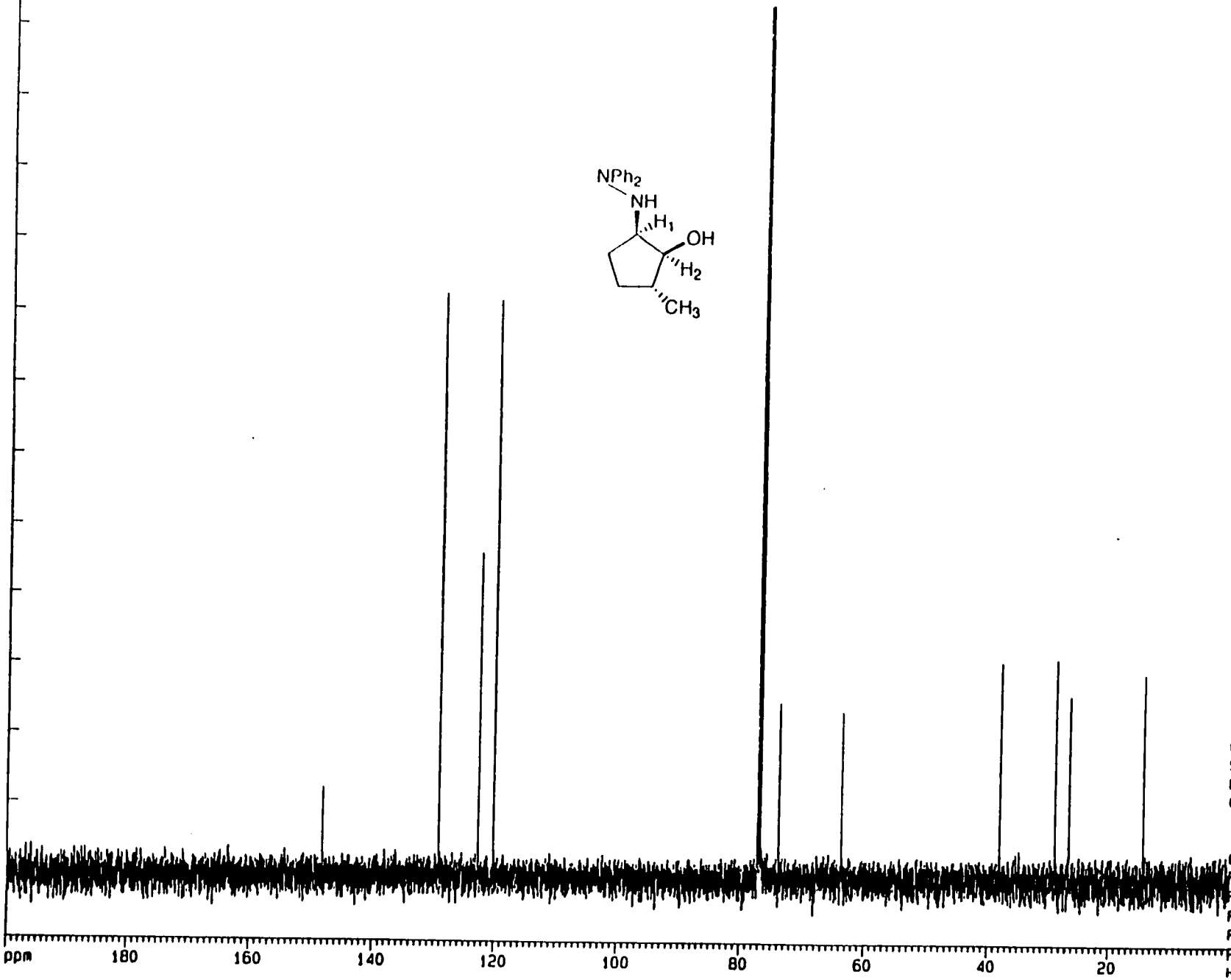


Current Data Parameters
NAME irina_102771
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 960212
Time 15.59
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 use
RG 2048
NUCLEUS 1H
TE 300.0 K
NL1 0 dB
D1 0.0100000 sec
P1 3.0 use
DE 88.8 use
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 8
DS 0

F1 - Processing parameters
SI 32768
WC2 DF
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/



Current Data Parameters

NAME	irina_ib2771
EXPNO	2
PROCNO	1

F2 - Acquisition Paramet

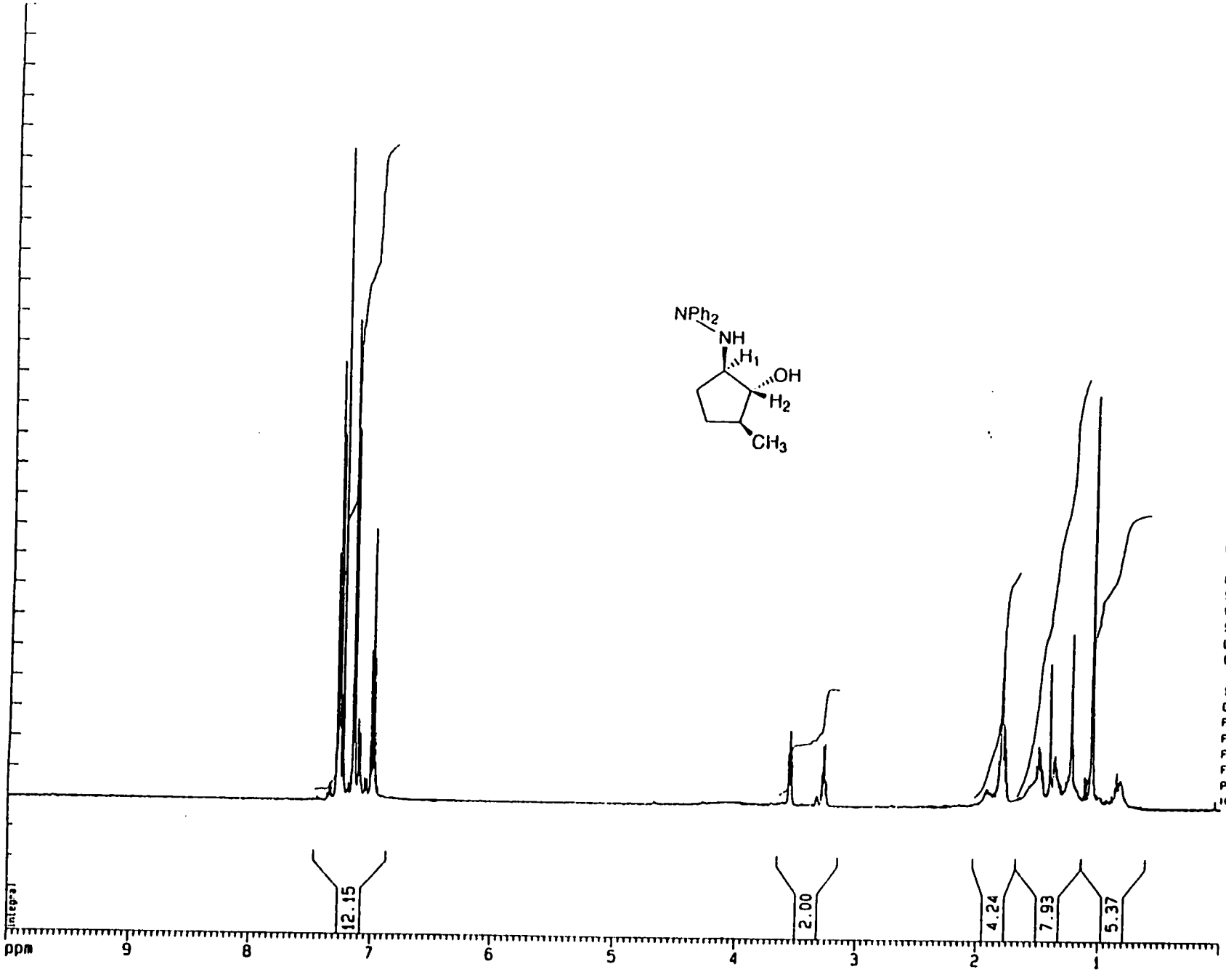
Date	960212
Time	16.15
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
TE	300.0
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	771
DS	0

F1 - Processing paramete

SI	32768
WC2	QF
SF	125.7591523
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501



Current Data Parameters

NAME	Irina_10278
EXPNO	4
PROCNO	1

F2 - Acquisition Parameters

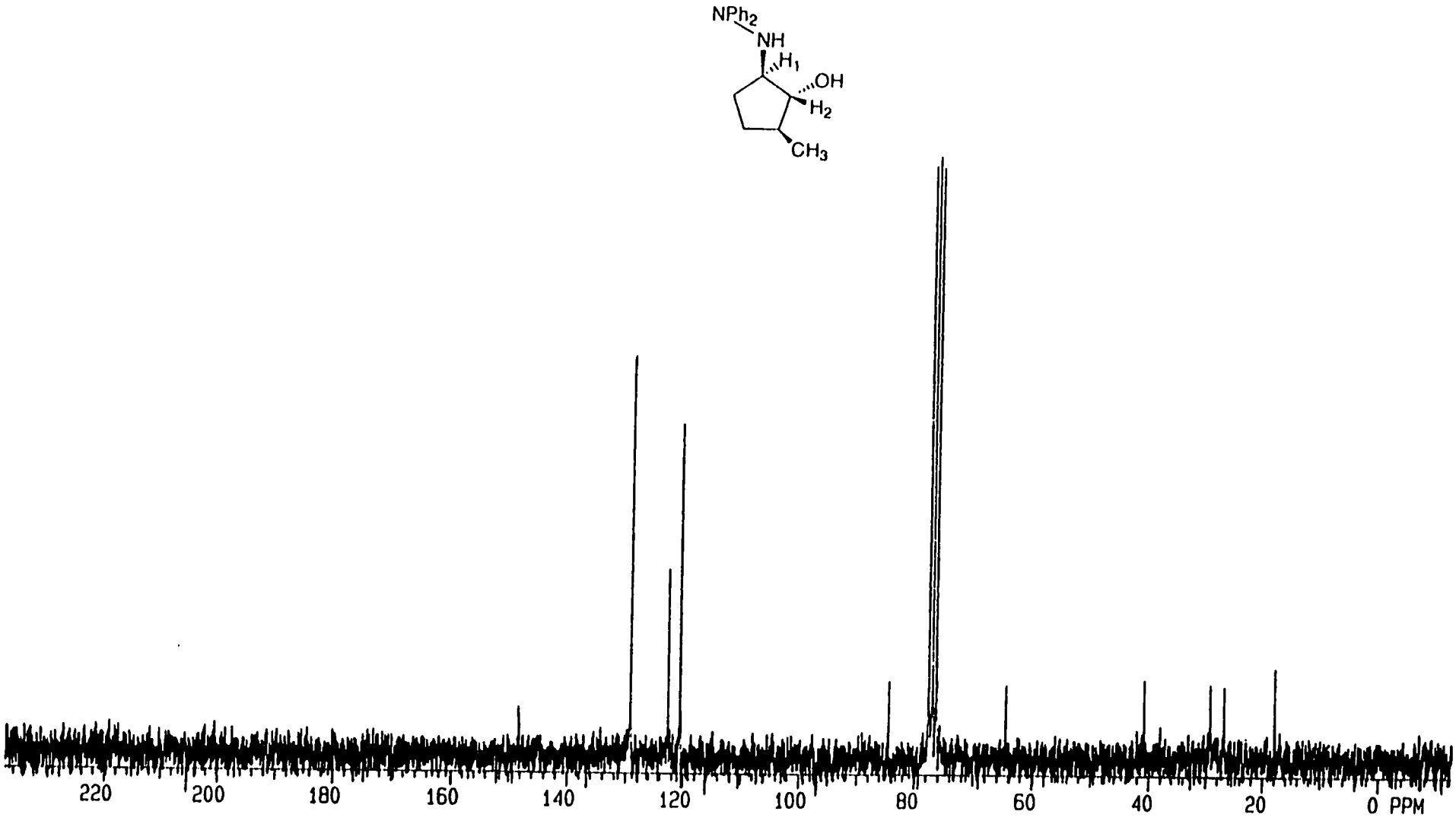
Date	960216
Time	17.48
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	2049
NUCLEUS	1H
TE	300.0 K
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1301707 MHz
SWH	7042.253 Hz
TD	65536
NS	8
DS	0

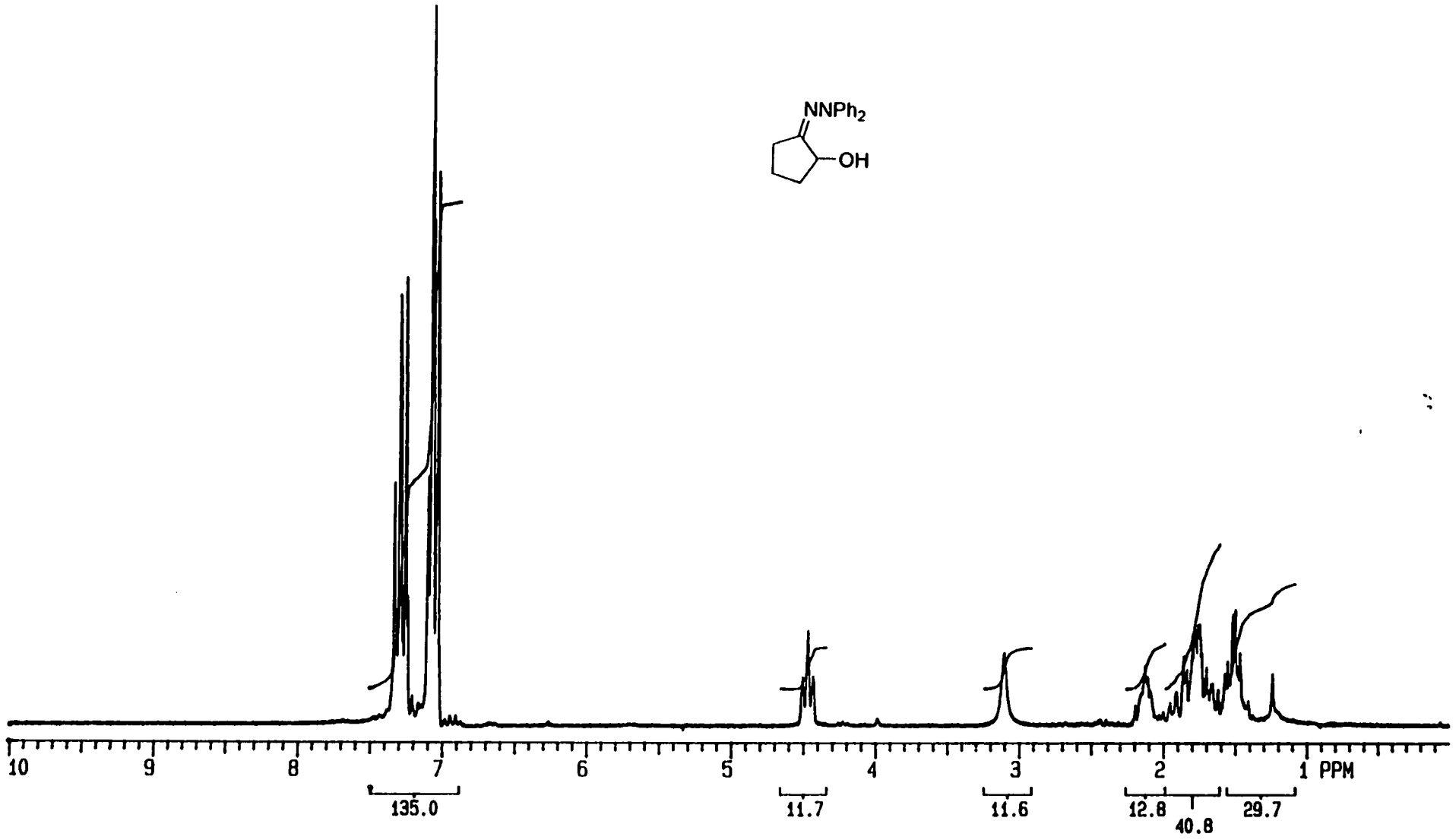
F1 - Processing parameters

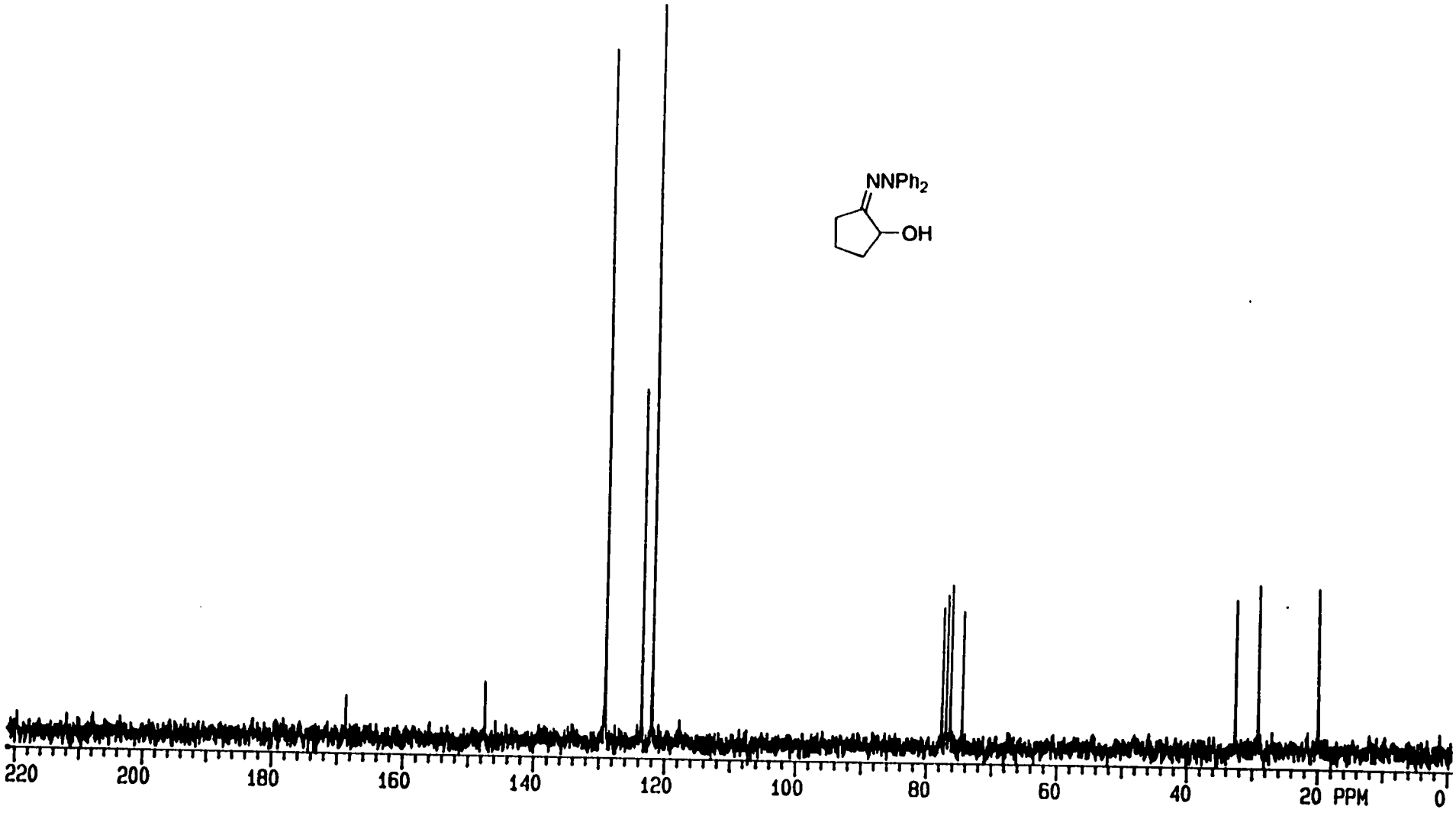
SI	32768
WC2	DF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

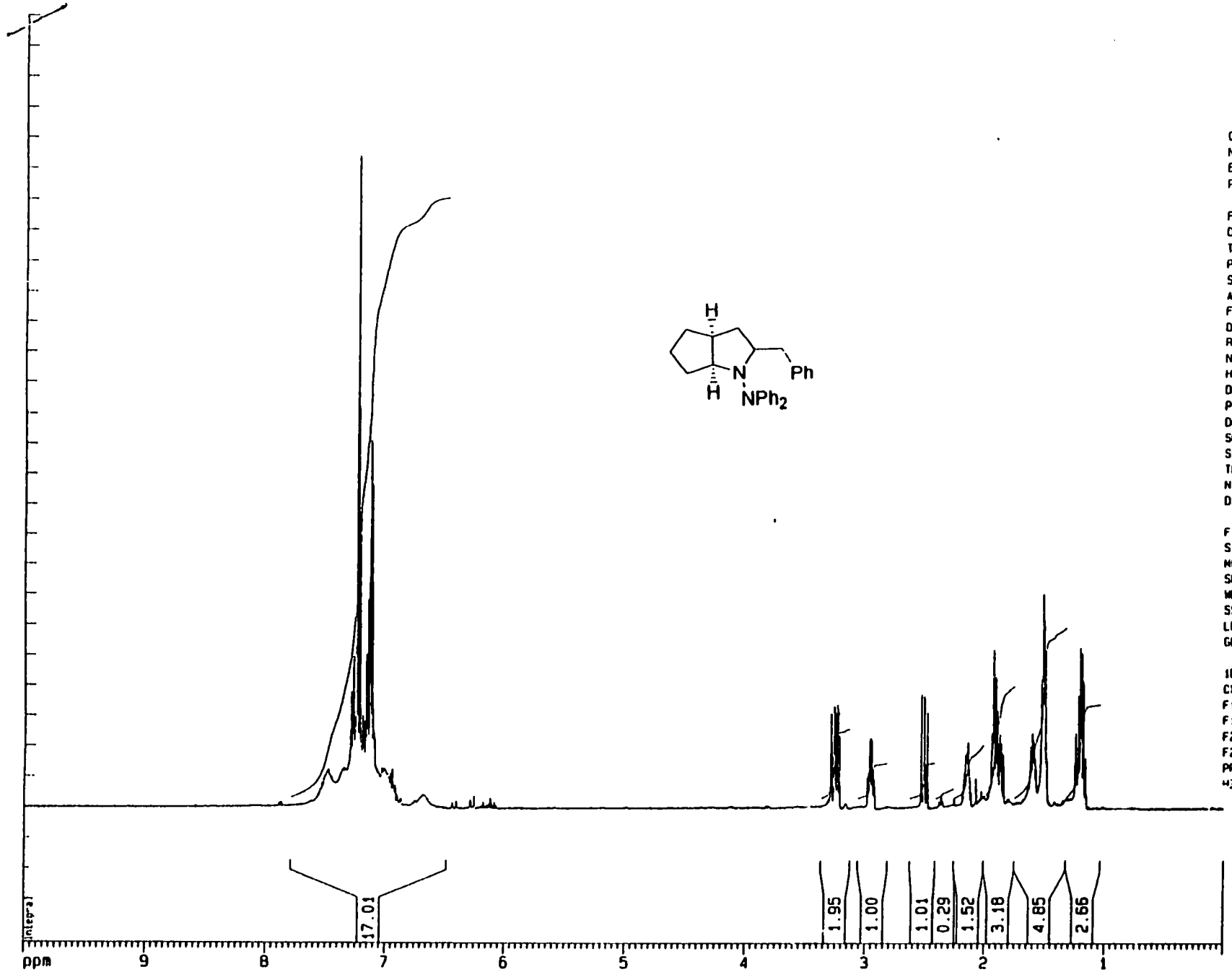
1D NMR plot parameters

CX	22.00 cm
F1P	4.797 ppm
F1	2399.22 Hz
F2P	0.453 ppm
F2	226.79 Hz
PPMCM	0.19744 ppm/cm
HZCM	98.73663 Hz/cm


NPh2
NH
H1
OH
H2
CH3
220
200
180
160
140
120
100
80
60
40
20
0 PPM


NNPh2
OH
10
9
8
7
6
5
4
3
2
1 PPM
135.0
11.7
11.6
12.8
40.8
29.7


NNPh2
OH
220
200
180
160
140
120
100
80
60
40
20
PPM
0



Current Data Parameters

NAME	irina_ib334
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

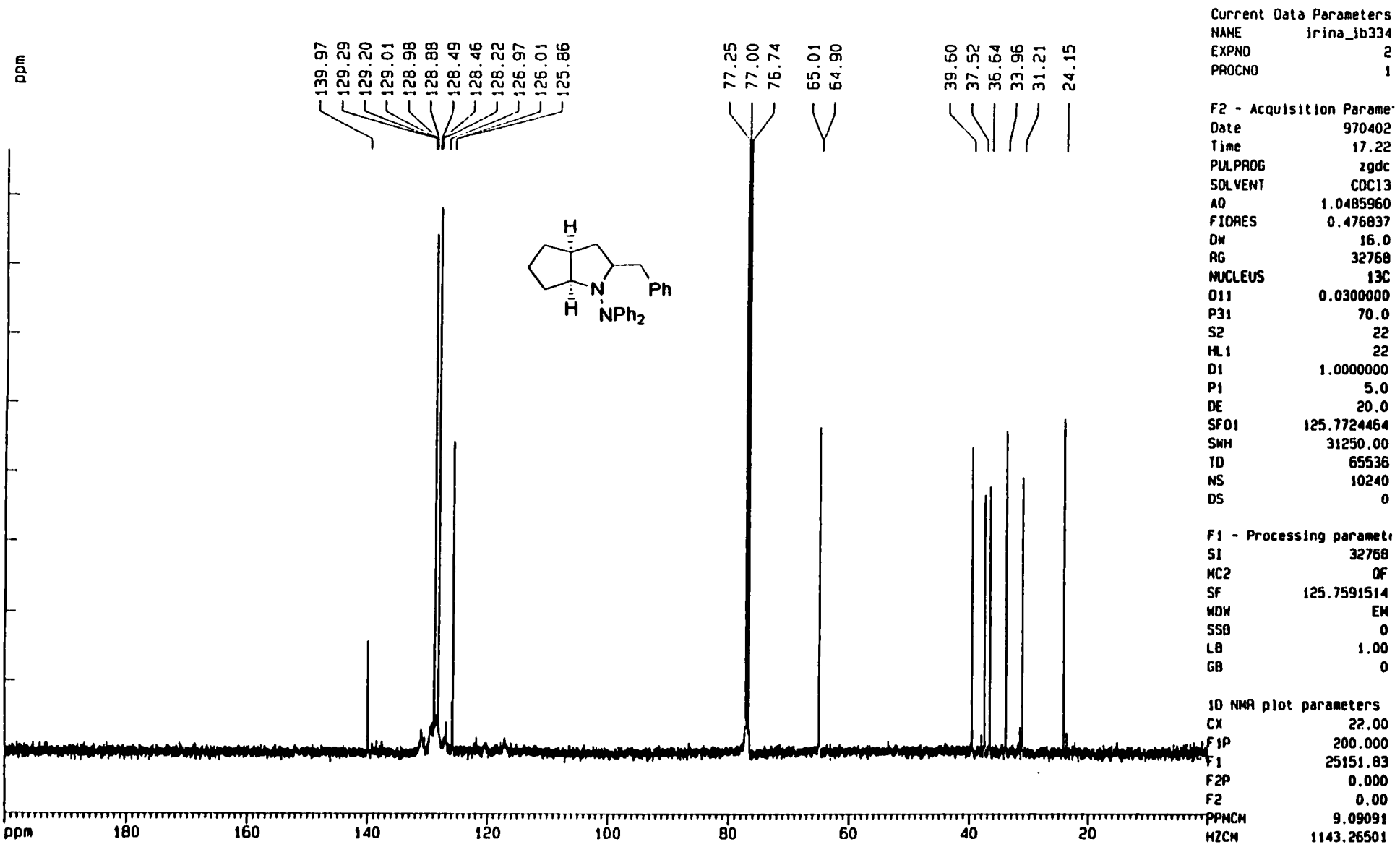
Date	970402
Time	17.16
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	2048
NUCLEUS	1H
NL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
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/



Current Data Parameters

NAME	irina_ib334
EXPNO	2
PROCNO	1

F2 - Acquisition Parame

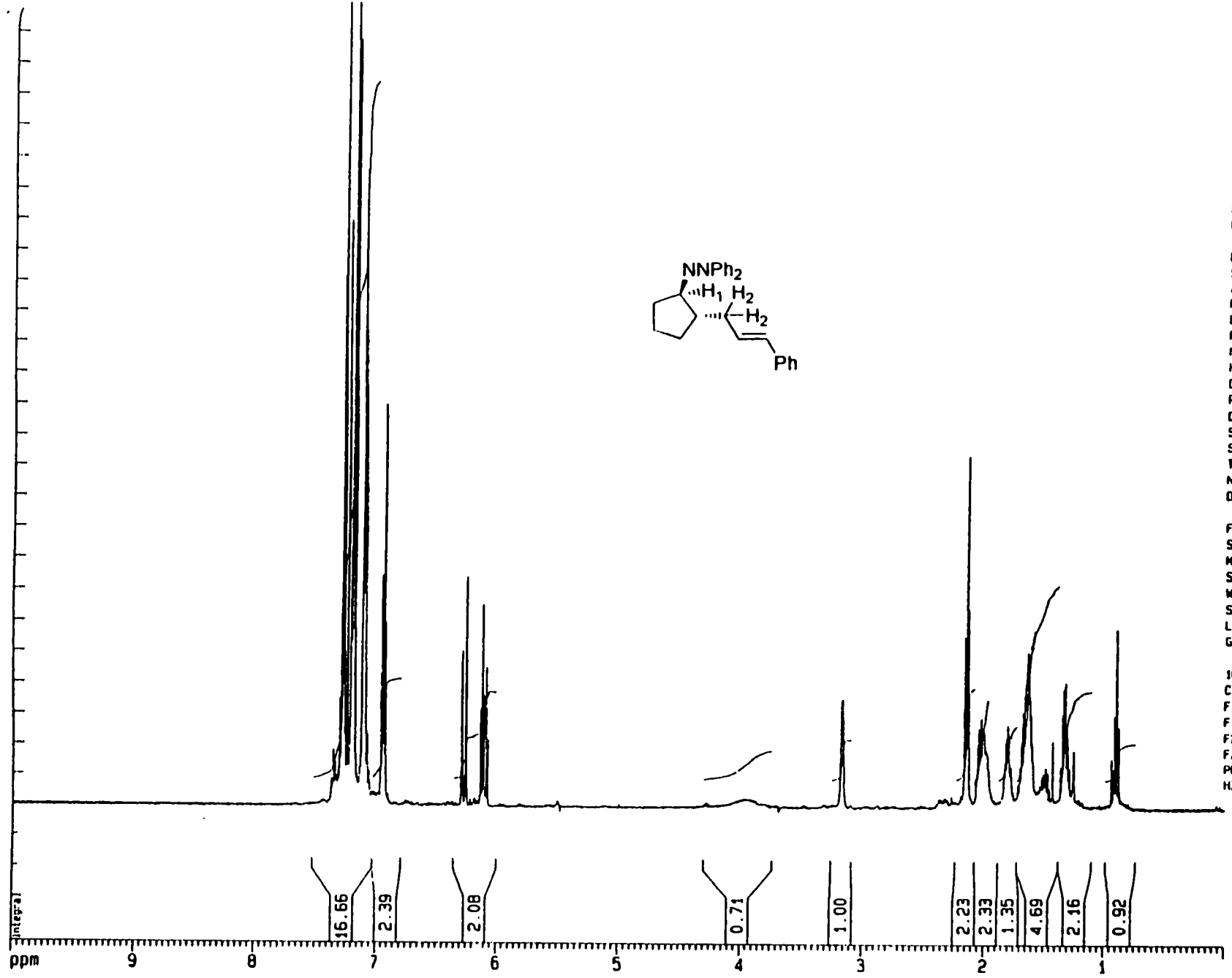
Date	970402
Time	17.22
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	10240
DS	0

F1 - Processing paramet

SI	32768
MC2	QF
SF	125.7591514
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501



Current Data Parameters

NAME	irina_1bmono
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

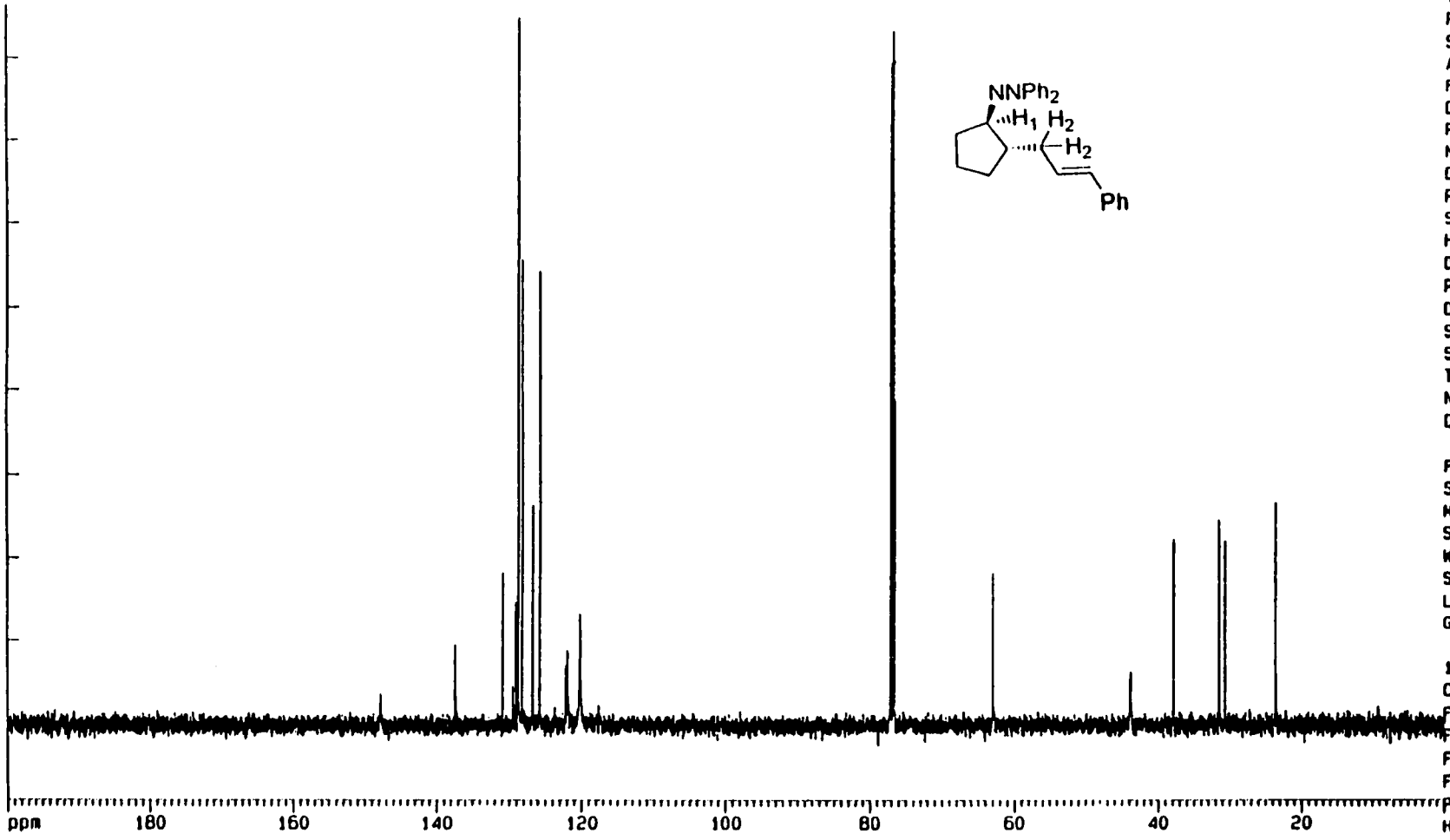
Date	970630
Time	12.49
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 use
RG	1024
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 use
DE	88.8 use
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	4
DS	0

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/



Current Data Parameters

NAME	irina_1bmono
EXPNO	2
PROCNO	1

F2 - Acquisition Parame

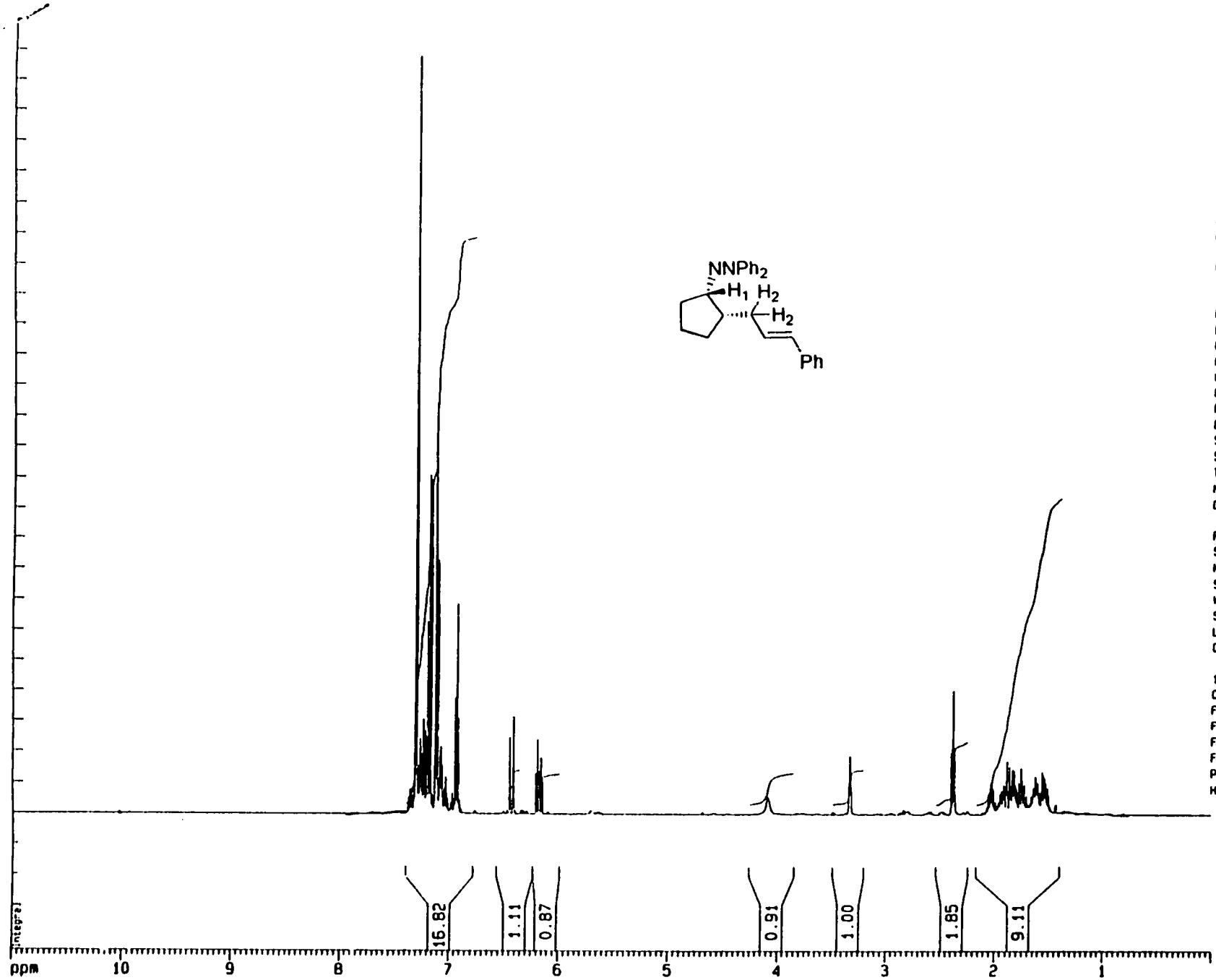
Date	970630
Time	13.11
PULPROG	zgdc
SOLVENT	COC13
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	1024
DS	0

F1 - Processing paramet

SI	32768
WC2	QF
SF	125.7591571
WDW	EM
SSB	0
LB	1.00
GB	0

1D NMR plot parameters

CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501



Current Data Parameters

NAME	irina_10351
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

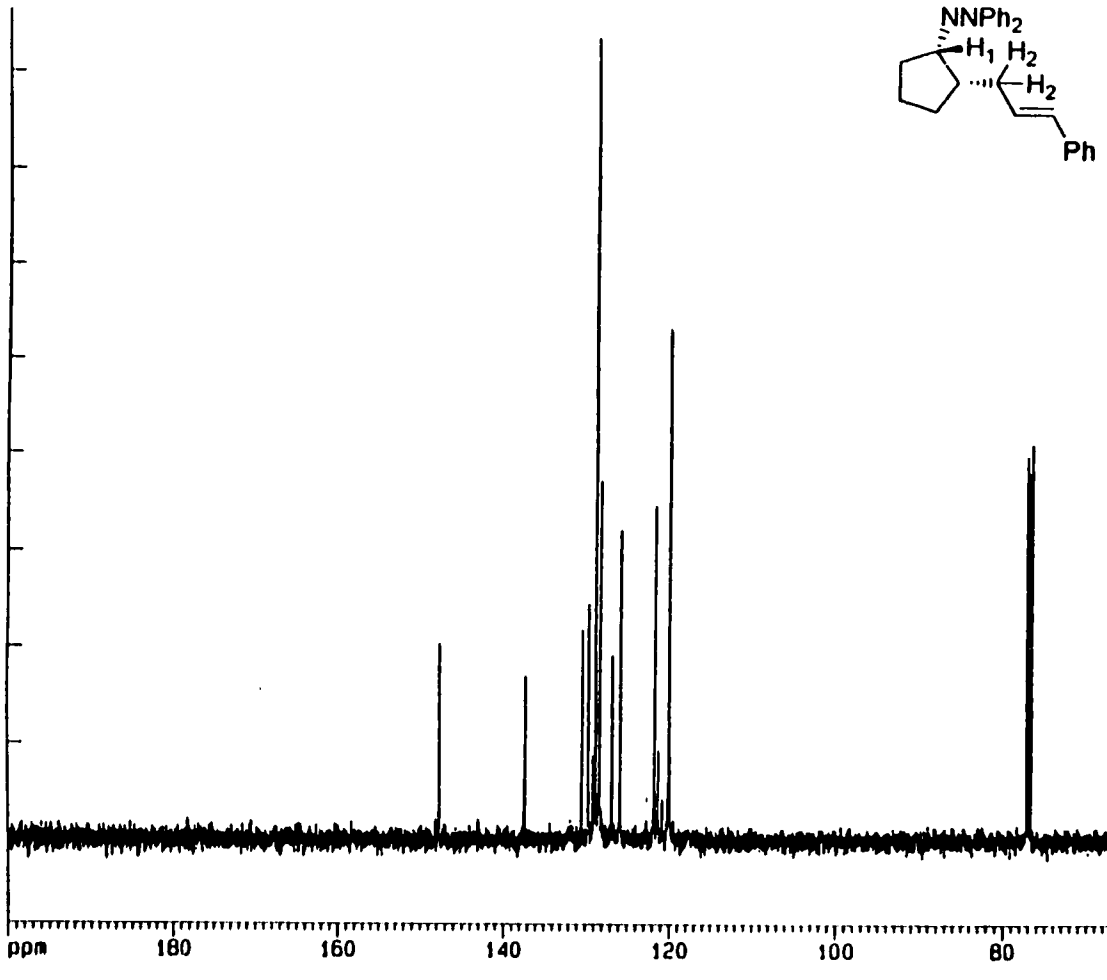
Date	970718
Time	13.53
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	256
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	88.8 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
WC2	QF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	11.000 ppm
F1	5501.49 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.50000 ppm/
HZCM	250.06772 Hz/



Current Data Parameters

NAME	irina_1b351
EXPNO	3
PROCNO	1

F2 - Acquisition Parame

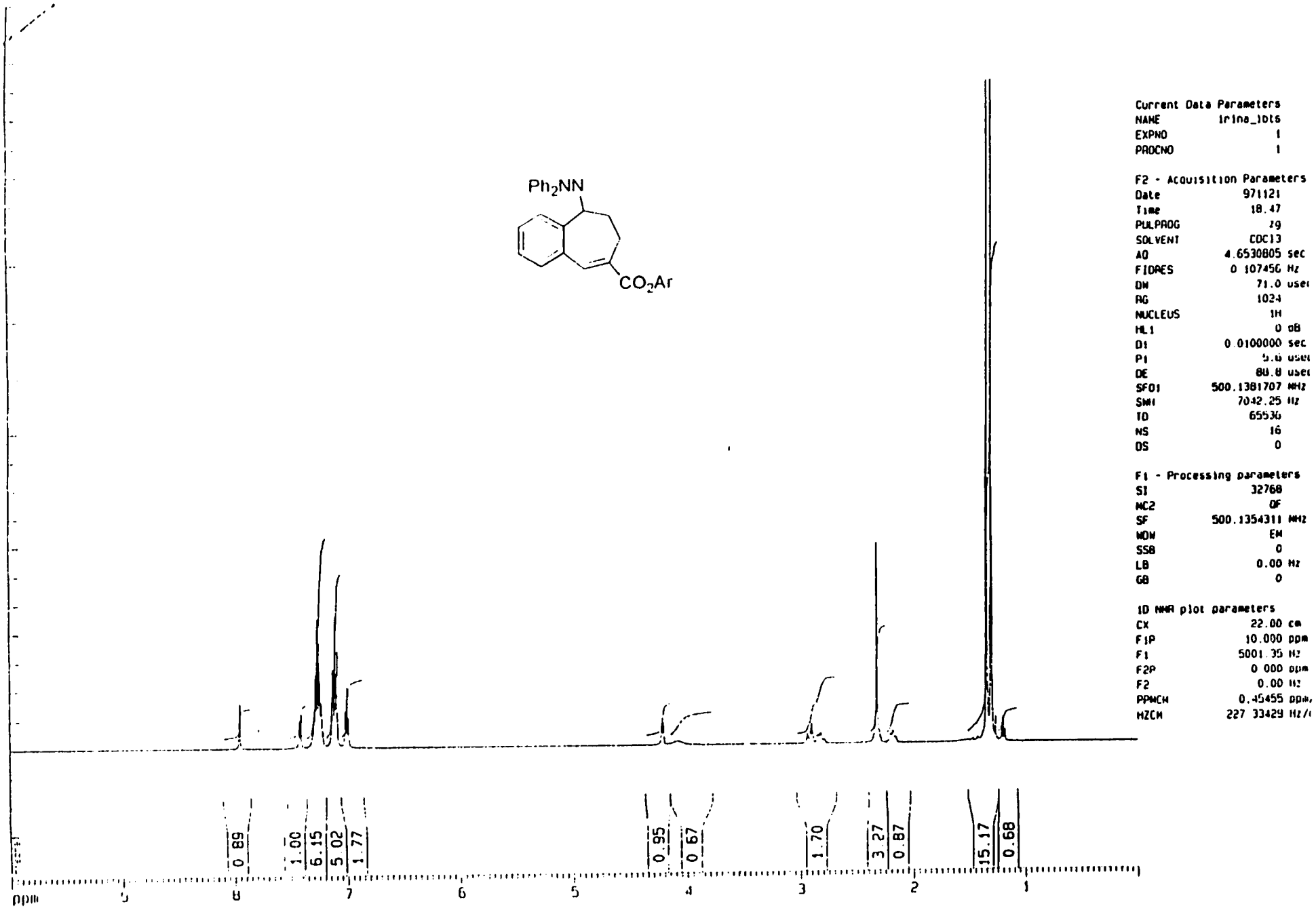
Date	970718
Time	15.03
PULPROG	zgdc
SOLVENT	CDCl3
AQ	1.0485960
FIDRES	0.476837
DW	16.0
RG	32768
NUCLEUS	13C
D11	0.0300000
P31	70.0
S2	22
HL1	22
D1	1.0000000
P1	5.0
DE	20.0
SFO1	125.7724464
SWH	31250.00
TD	65536
NS	650
DS	0

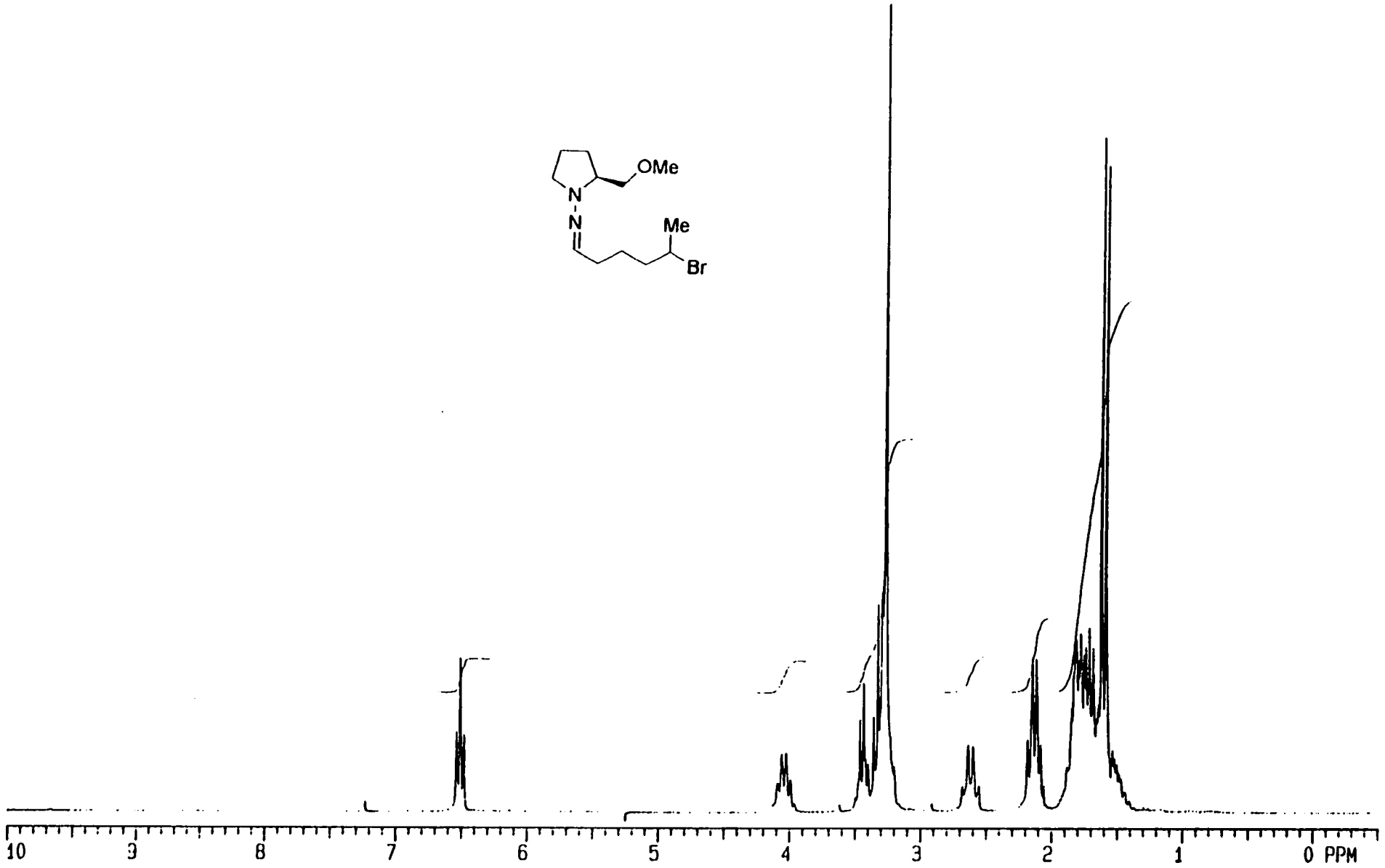
F1 - Processing paramet

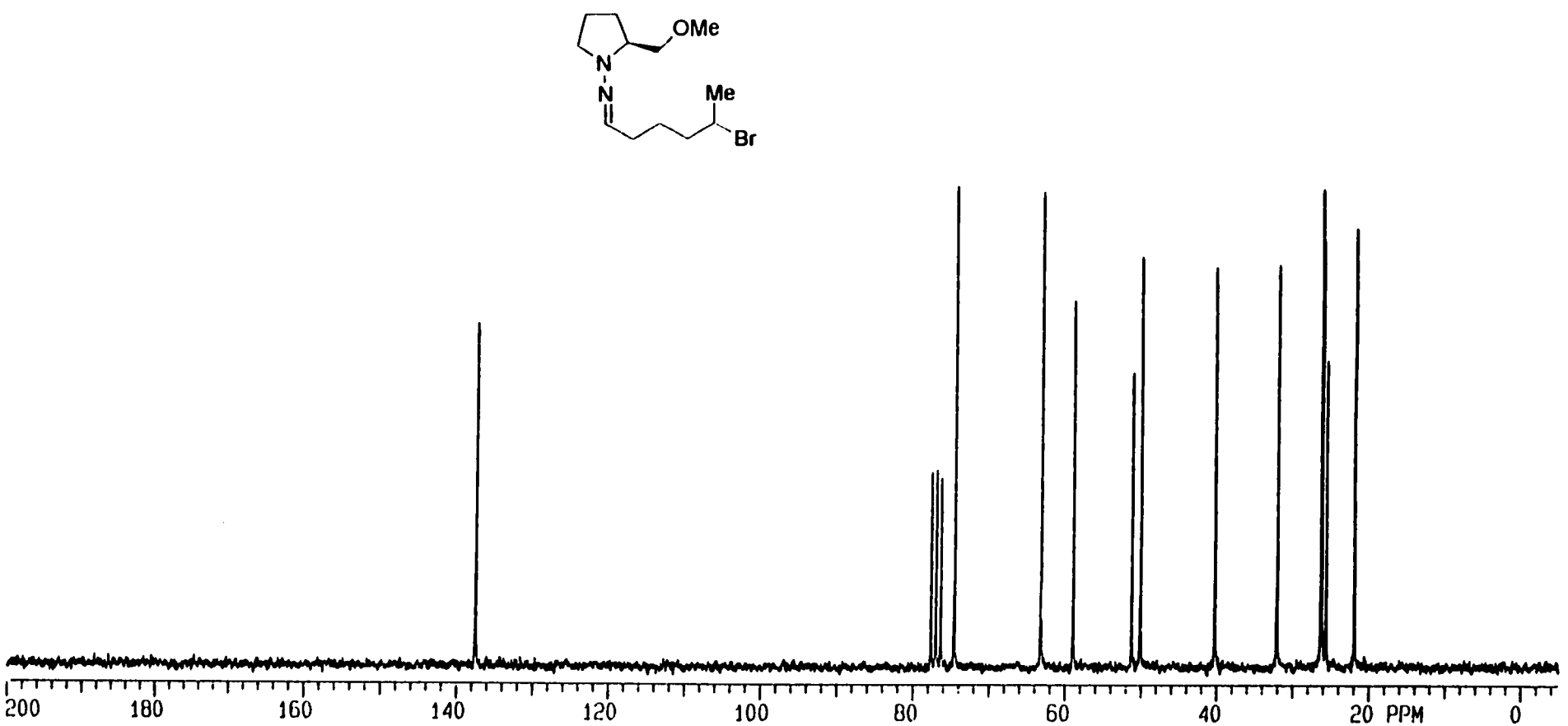
SI	32768
MC2	QF
SF	125.7591552
WDW	EM
SSB	0
LB	1.00
GB	0

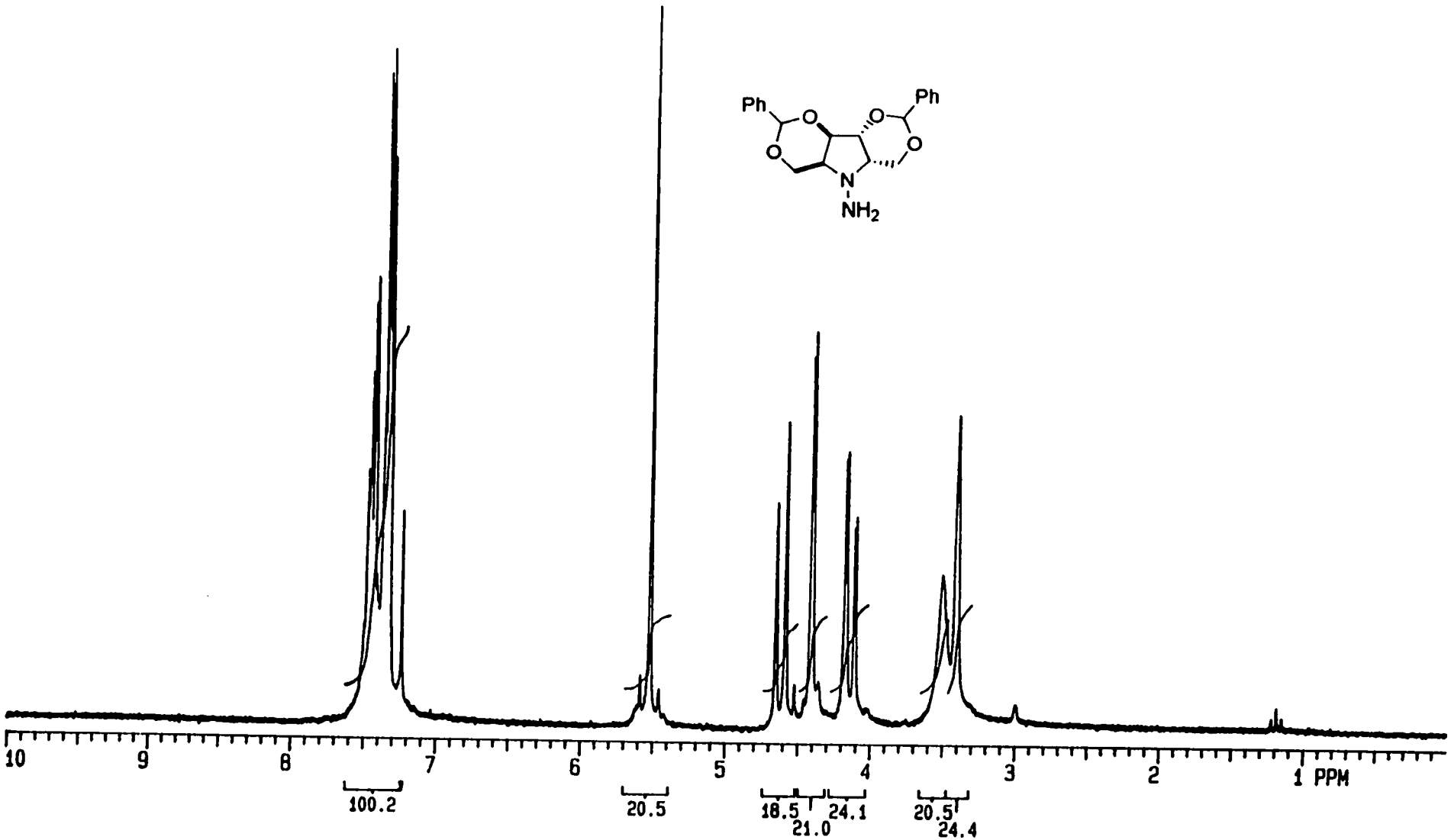
1D NMR plot parameters

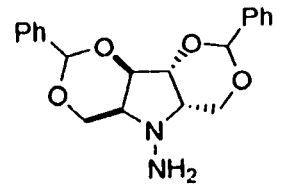
CX	22.00
F1P	200.000
F1	25151.83
F2P	0.000
F2	0.00
PPMCM	9.09091
HZCM	1143.26501

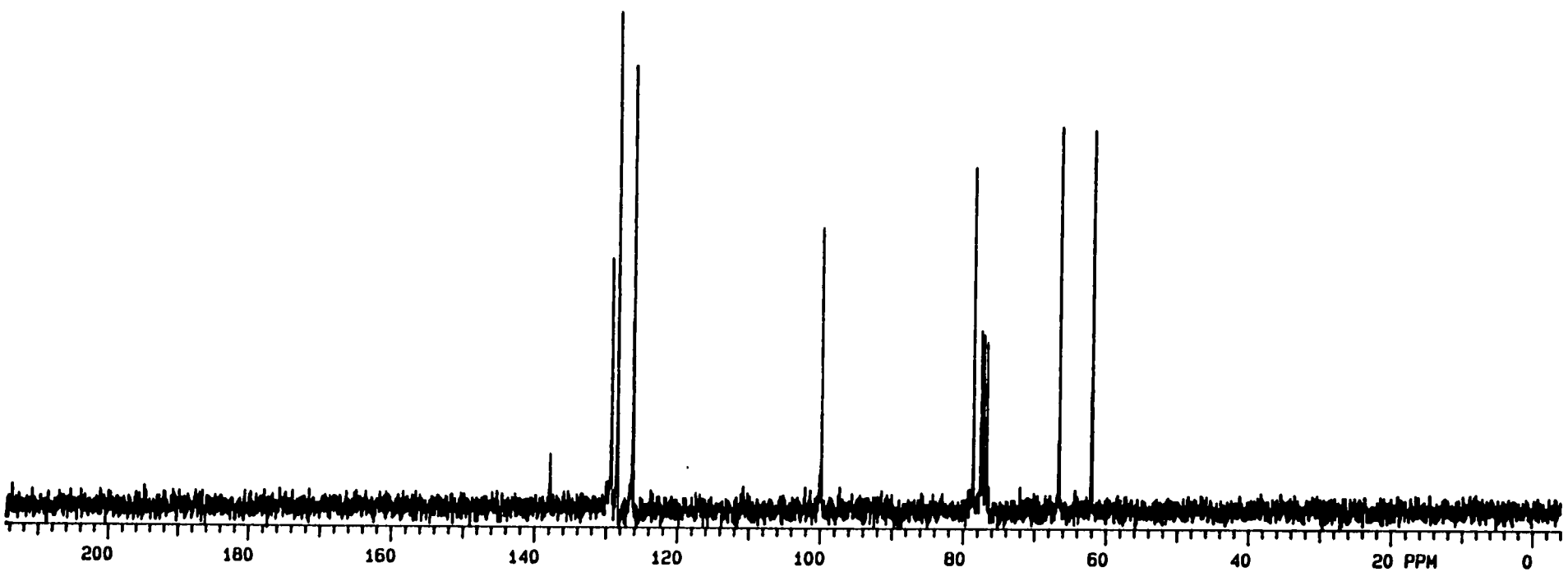

Ph2NN
CO2Ar
0.89
1.00
6.15
5.02
1.77
0.95
0.67
1.70
3.27
0.87
15.17
0.68
ppm
8
7
6
5
4
3
2
1
Current Data Parameters
NAME Irina_1Dt6
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date 971121
Time 18.47
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 use
RG 1024
NUCLEUS 1H
ML1 0 dB
D1 0.0100000 sec
P1 5.6 use
DE 88.8 use
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0
F1 - Processing parameters
SI 32768
WC2 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/


OMe
N
N
Me
Br
10
9
8
7
6
5
4
3
2
1
0 PPM


OMe
N
N
Me
Br
200
180
160
140
120
100
80
60
40
20
PPM
0


Ph
Ph
O
O
O
O
N
NH2
10
9
8
7
6
5
4
3
2
1 PPM
100.2
20.5
18.5
21.0
24.1
20.5
24.4


Ph
O
O
Ph
O
O
N
NH2


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