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List of Abbreviations

Ac	acetyl
AIBN	azobis(isobutyronitrile)
Ar	aryl
BOC	butoxycarbonyl
Bn	benzyl
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
CSA	(*S*)-(+)-10-camphorsulphonic acid
DIBAL	diisobutylaluminium hydride
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
Ether	diethyl ether
GC	gas chromatography
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Im	imidazole
IR	infrared
LDA	lithium diisopropylamide
LRMS	low resolution mass spectrum
Me	methyl
nmr	nuclear magnetic resonance
Ph	phenyl
PPTS	pyridinium-*p*-toluenesulfonate

PTSA	*p*-toluenesufonic acid
Py	pyridine
rt	room temperature
TBDMS	*t*-butyl dimethylsilyl
TIPS	triisopropyl
TFA	trifluoroacetic acid
TMS	trimethylsilyl
TTMSS	tris(trimethylsilyl)silane

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I have been extremely fortunate in the amount of support I have received from my family members, especially my Mother-In-Law and for this I will always be grateful.

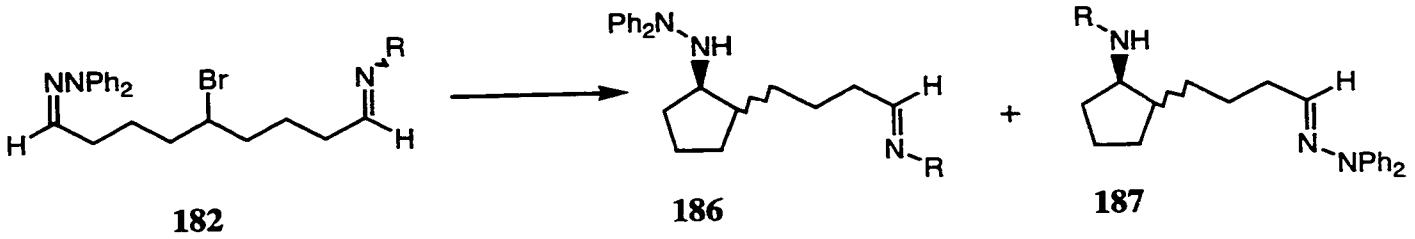
Abstract

The kinetics for the 5-*exo* cyclizations of secondary alkyl radicals onto various imine acceptors (alkyl-, aryl-, benzoylhydrazones, oxime ethers, etc) have been determined. The preparation of a series of halo C=N containing "bis imine" systems (**182 a-i**) for use in kinetic studies has been described. The rate constants have been established by competitive "internal radical clock" type cyclizations on the basis of the known rate constants for alkene and *N,N*-diphenylhydrazone systems. In refluxing benzene the rate constants for these 5-*exo* cyclizations fall within the range of 4×10^7 to 16×10^7 s^{-1} depending on the electron withdrawing capacity of the imine acceptor. These rate constants are approximately 200 times faster than those for the corresponding 5-*exo* cyclizations onto alkenes. The fastest rate constants were observed for the *N,N*-diphenylhydrazones and *N*-benzoylhydrazones.

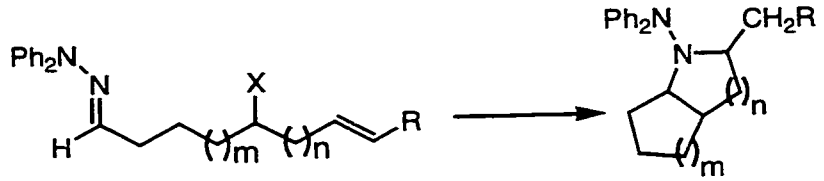
N,N-Diphenylhydrazones were further employed in the formation of nitrogen containing bicyclic systems via tandem radical cyclizations. Tandem products were obtained for 5,5- and 6,5- bicyclic systems. Attempted synthesis of 5,6- and 6,6- bicyclic systems via tandem cyclizations resulted only in the formation of monocylized products **284** and **285** respectively.

A new chiral auxiliary **327** was synthesized for use in the study of asymmetric induction in radical cyclizations in the presence of chiral auxiliaries in systems such as **328b**.

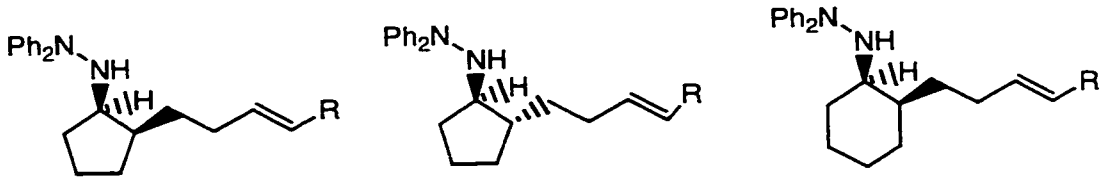
In search of "taxoid mimics" with less functionality and better therapeutic profile as compared to the anti cancer drug "Taxol", small taxol like compounds **350** and **351** were synthesized and their biological activity was evaluated.



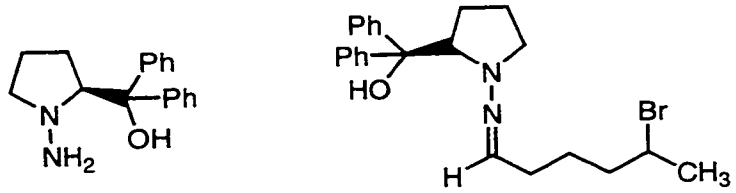
182 **186** **187**



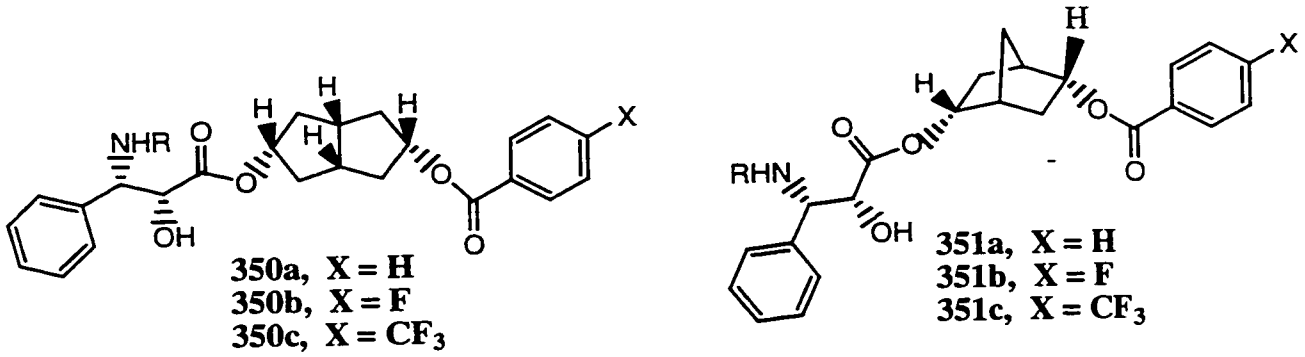
247 **248**



284i **284ii** **285i**



327 **328b**



350a, X = H
350b, X = F
350c, X = CF_3

351a, X = H
351b, X = F
351c, X = CF_3

Chapter One

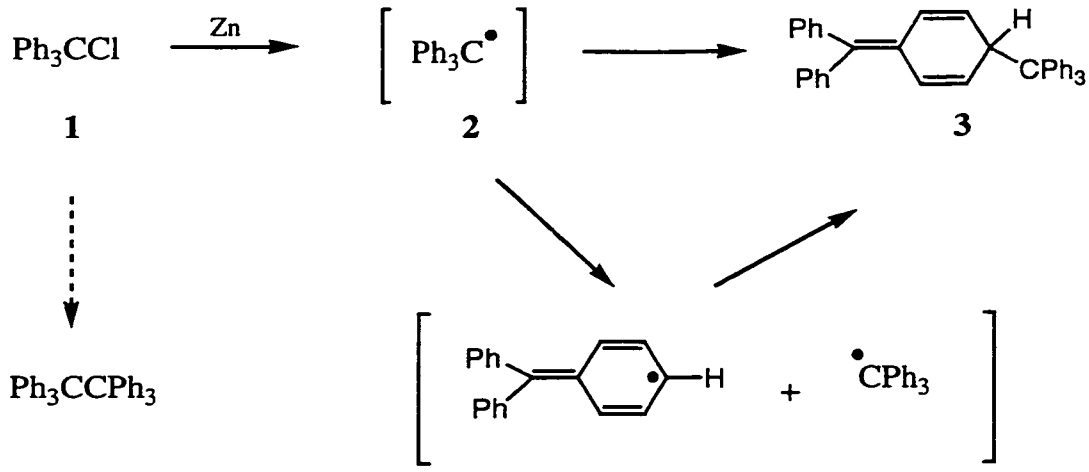
Free Radical Cyclizations

1.1 General Introduction

The interest in free radical reactions applied to synthetic problems continues to advance, and these reactions have been used successfully for a growing number of synthetic targets[1]. Until the early 1980's, the role of alkyl radical reactions in natural product total synthesis was limited to a few important functional transformations. However, during past two decades, radical reactions have grown in importance to the point, where they are now routinely considered in strategy level planning of complex targets.

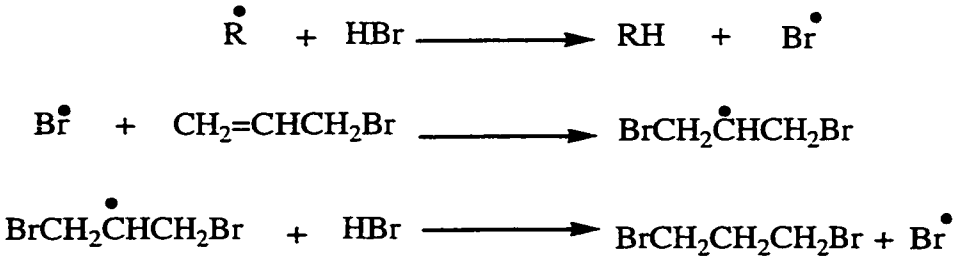
Historically, radical chemistry dates back to 1900, when Gomberg[2] investigated the formation and reaction of the triphenylmethyl radical (Scheme 1). In his attempt to generate hexaphenylethane by Wurtz coupling of triphenylmethyl chloride, he observed that treatment of Ph_3CCl with zinc, generated the stable triphenylmethyl radical, which slowly dimerized to **3**.

Scheme 1: Gomberg's Preparation of Triphenylmethyl Radical



Organic syntheses with radicals began in 1937, when Hey and Waters described the phenylation of aromatic compounds by benzoyl peroxide[3] as a radical reaction and Kharasch recognized that the anti-Markonikov's addition of HBr to alkene proceeds via a radical chain process[4] (Scheme **2**).

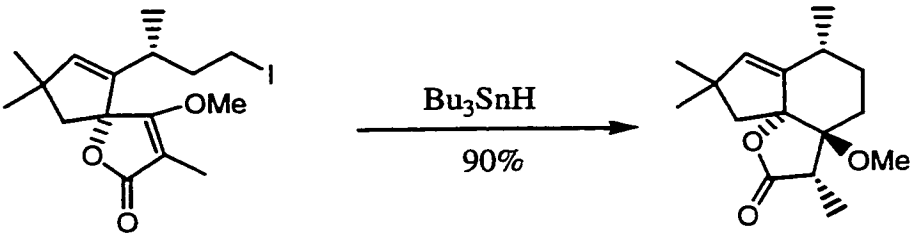
Scheme 2: Anti-Markonikov addition of HBr to Olefin



Radical reactions have a number of synthetic advantages over the corresponding ionic reactions[5]. Radicals are very reactive species; nevertheless radical reactions proceed under very mild and neutral conditions, leaving many functional groups intact including OH or NH groups. Hence these functional groups need not to be protected and removal of water is not necessary. The high reactivity of the radicals does not compromise the high level of chemo, regio and even stereoselectivities observed in radical-based reactions. Molecular complexity often increases the rates and intensifies the stereoselectivities of these reactions. In contrast, ionic reactions tend to diminish in efficiency with increased substrate complexity.

Radical reactions are usually free from the complications of ionic kinetics such as ion pairing, aggregation and large solvent effects and are not affected by remote substituent effects. Radicals being neutral species are not cluttered with bulky counterions or metal components or aggregation spheres and are highly suitable for the synthesis of crowded bonds, like quaternary and neopentyl centers[6]. As shown in Scheme **3**, a 6-*exo* cyclization proceeded efficiently, creating a quaternary center in **5** in 90% yield.

Scheme 3: Construction of a Quaternary Center

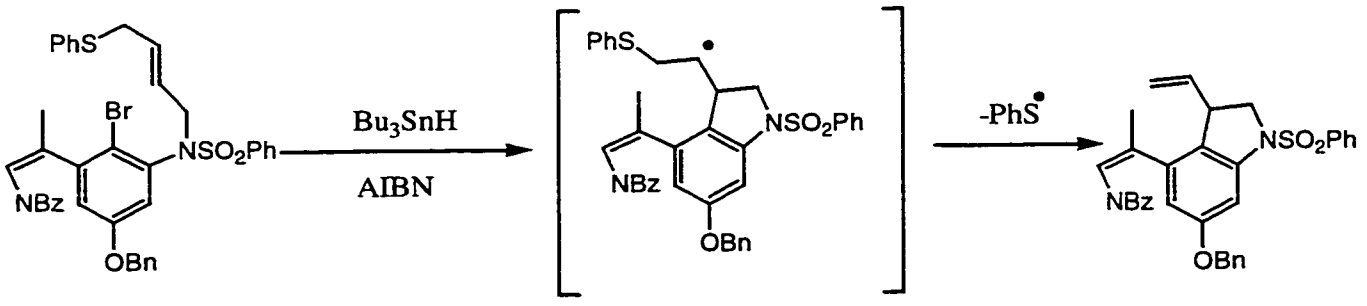


4 **5**

Absolute stereochemistry of the non-radical carbon center is usually retained in the radical reactions. However, most alkyl and alkenyl radicals have a negligible barrier of inversion, therefore the stereochemistry at these radical centers are usually not retained. This stereochemical liability actually simplifies the synthesis of radical precursors.

In carbanionic reactions, generation of an anion β to a leaving group results in elimination by-products. Reactions involving the formation of carbocations suffer from capture of β -OR or $-NR_2$ and migration or elimination of β-H or $-CF_3$ groups. These unwanted reactions are usually not observed under radical conditions. However, radicals are subject to β-elimination of stable radicals such as SR, SO_nR, or SnR_3. These eliminations are key steps in some useful radical transformations, as shown in the Scheme 4. Intermediate radical **7** not only gets reduced but is converted to a synthetically useful alkene **8,** which could be further manipulated to give the indoline portion of the antitumor-antibiotic (+)-CC-1065 and various analogues[7].

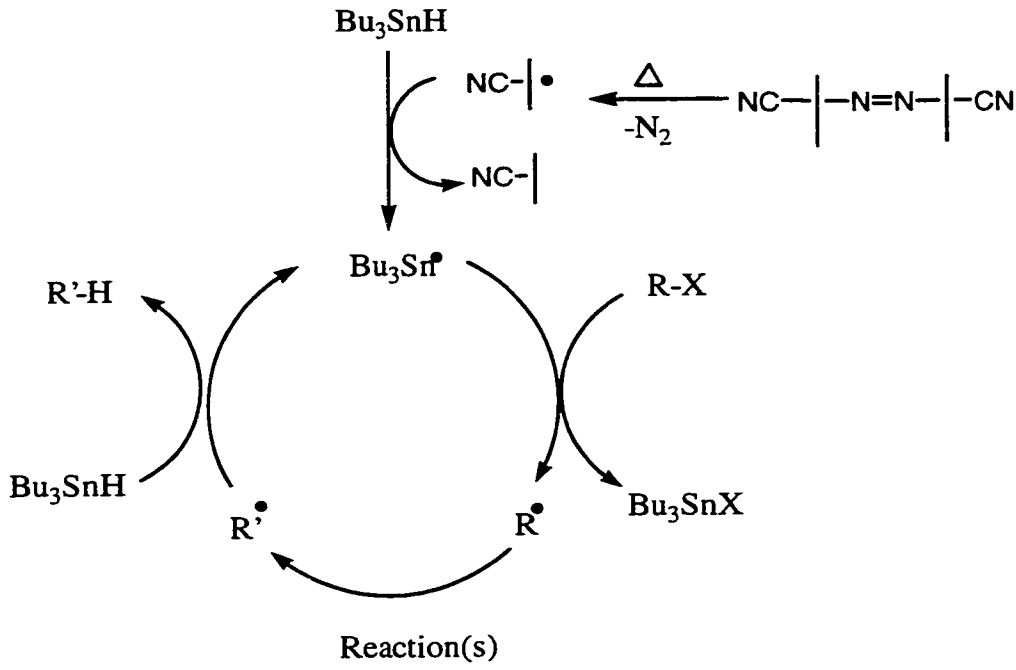
Scheme 4: β-Elimination of a Phenylthioxy Radical



6 **7** **8**

Tributyltin hydride is the most commonly used reagent to conduct free radical reactions by the "metal hydride method". The synthetic procedure involves treating the starting substrate (R-X) with Bu_3SnH and azobis(isobutyro)nitrile (AIBN) (as radical initiator) in benzene. The mechanism for the reaction[8] involves a chain reaction as shown in Scheme **5**. Abstraction of a suitable radical precursor X by tributyltin radical generates the initial radical $R^{\bullet}$, which then undergoes a transformation (or series of transformations) to generate a new radical $R'^{\bullet}$. Hydrogen transfer then forms the final product R'-H and regenerates the tributyltin radical to continue the chain.

Scheme 5: Mechanism of a Tin Hydride Mediated Chain Reaction



Competing Reaction

$$R^{\bullet} + Bu_3SnH \longrightarrow R\text{-}H + Bu_3Sn^{\bullet}$$

The reaction is thermodynamically driven by the conversion of a C-X bond to a stronger C-H bond. The standard problem in tin hydride reactions is the premature reduction of $R^{\bullet}$ (or another intermediate radical) by the reagent when the rate of

conversion of $R^{\bullet}$ to $R'^{\bullet}$ is slow[9]. This can be solved by using a low concentration (syringe pump techniques) of the hydride reagent to reduce the rate of the competing reduction.

This general scheme also holds for other similar reagents Bu_3GeH and $(TMS)_3SiH$. Various X groups used as radical precursors include: Cl, Br, I, SePh, OC(S)SMe, and SPh. The rate of transfer of these X groups to tin radical follows the general order as shown below. [10]

Order of Reactivity Towards Tin Hydride:

I > Br > SePh > -OC(S)SMe > Cl > SPh

The reactivity of various R radicals towards tin hydride is:

aryl ≈ vinyl > alkyl > allyl ≈ benzyl.

The reactivity of primary, secondary and tertiary radicals with tin hydride is approximately the same.[11]

Most of the useful free radical reactions can be grouped into two broad classes: atom (or group) abstraction and addition to multiple bonds. In the abstraction reactions, a radical abstracts an atom or a group from an organic molecule to produce a new radical located at the former site of the abstracted functionality (eq. 1). While formally reversible, the reaction usually not observed on the time scale of a radical chain reaction. The direction of the reaction is determined by the relative bond strength of the forming and breaking bond. The rate of the reaction is controlled largely by its exothermicity and the most commonly abstracted groups are : hydrogen, halogens, SeR and SR.

Eq. 1

In the second class, a radical adds to an unsaturated functional group (Eq. 2). This reaction is also reversible in principle, and the position of the equilibrium is controlled by the relative bond strengths and the stabilities of the radicals involved. The

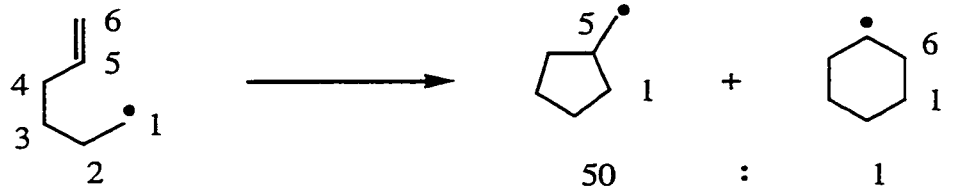
addition of carbon centered radicals to a C=C double bond is often particularly favorable, since a C-C σ bond is formed at the expense of a C-C π bond.

Eq. 2

1.2 Regiochemistry

Intramolecular radical addition reactions are very useful in organic synthesis for the construction of ring systems. There have been extensive mechanistic studies into the 5-hexenyl radical cyclization, which is a very well understood radical reaction. This reaction follows Baldwin's[12] rules of cyclization with the 5-*exo* mode of ring closure favored over the 6-*endo* mode by a factor of approximately 50 at 25 °C as shown in the equation 3.

5-Hexenyl Cyclization



50 : 1

Eq. 3

9 **10** **11**

The regiochemistry of this reaction can be explained by conformational and electronic effects in the transition state models proposed by Beckwith[13] and Houk and Spellmeyer[14]. According to their studies, three low energy transition states should be considered: (I) 5-*exo* chair, (ii) 5-*exo* boat, (iii) 6-*endo* chair (Table **1**). These models correctly predicted that the radical cyclizations have an early transition state with an incipient bond length of approximately 2.4 A°. This distance is similar to the distance between C1 and C3 of a cyclohexane ring. There are several reasons that the 5-*exo* cyclization is preferred. The angle of attack for this ring closure (106 °), is close to that

of unconstrained bimolecular addition (109 °). In contrast the predicted angle for a 6-*endo* attack (94 °) would result in a higher degree of torsional and/or bending strain than its 5-*exo* counterpart. This added strain might be due to the elongation of the forming bond, which stretches the cyclohexane ring away from its ideal geometry. This results in poor SOMO-LUMO interactions in the transition state, disfavoring the 6-*endo* pathway. Furthermore, the 5-*exo* transition state is entropically favored over the 6-*endo* as it retains a degree of freedom.

The *exo-endo* selectivities for the formation of 5, 6 and 7 membered rings are compared in Table **2.** As can be seen from this table, 5-hexenyl cyclization displays a high level of *exo/endo* selectivity (64) as compared to the corresponding 6-heptenyl cyclization (*exo/endo* = 6). The rate of cyclization of the 6-*exo* system is also slower than that of the 5-*exo* system. As a general rule, the degree of preference for *exo* ring closure depends upon the length of the carbon chain between the radical center and the alkene unit. When the chain is short the transition state for the endo attack would be highly strained, but when the chain is long and flexible, then the difference in strain energy

Table 1: Transition States for the 5-Hexenyl Radical Cyclization

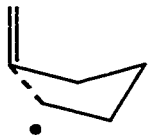
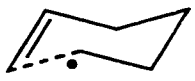
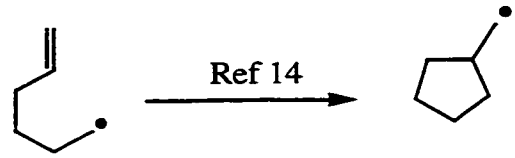
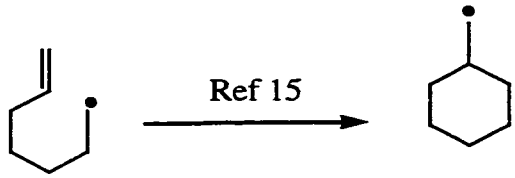
	Relative energy	Angle of attack	Bond distance
 5-*exo* chair	0 Kcal/mol	106 °	2.34
 5-*exo* boat	1 Kcal/mol	105 °	2.34
 6-*endo* chair	3 Kcal/mol	94 °	2.40

Table 2: Comparison of *Exo* and *Endo* Ring Closure at 25 °C



	$k_{exo} = 2.5X10^5 s^{-1}$	$k_{endo} = 3.9X10^3 s^{-1}$	64
12	**13**	**14**	
	$k_{exo} = 5.1X10^3 s^{-1}$	$k_{endo} = 8.8X10^2 s^{-1}$	6
15	**16**	**17**	

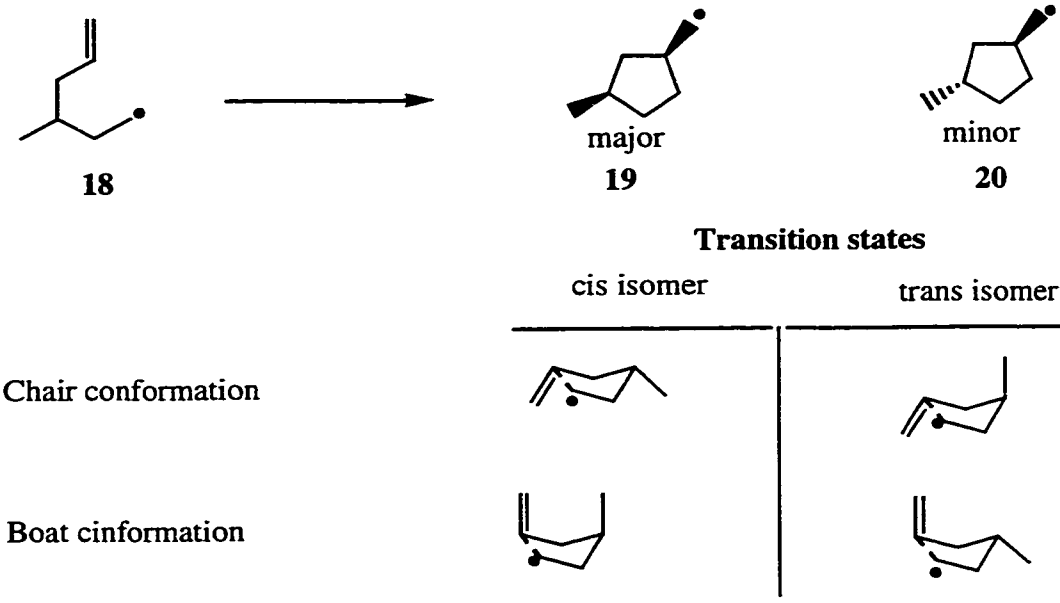


between two transition states is small, which leads to the lower *exo/endo* selectivities for the larger ring systems.

1.3 Relative Stereochemistry

Radical cyclizations have a reputation of exhibiting poor stereoselectivity, although currently there are many examples in the literature where highly stereoselective transformations have been achieved. The stereochemical outcome of a radical cyclization can be predicted by using the same Beckwith and Houk/Spellmeyer transition state models, which were used to explain the regiochemistry of the radical cyclizations. The major product can often be predicted by using the Beckwith chair conformation model and placing the larger substituent in a pseudo-equatorial position. For example, consider the cyclization of a 3-substituted hexenyl system as shown in the Scheme **6.** The major product **19** arises from the chair-equatorial transition state, while the minor *trans* product can arise from a boat-equatorial conformation, which has only 0.5 Kcal/mol higher energy than the lowest energy chair-equatorial conformation[14].

Scheme 6: Radical Cyclization of a 3-Substituted Hexenyl System



This model also provides a satisfactory rationale for the observed stereoselectivities in the cyclization of 1-, 2- and 4- substituted 5-hexenyl radicals. As a general rule: substitution at C1 or C3 position results in *cis* disubstituted cylopentanes and C2 or C4 substituted radicals give mainly *trans* disubstituted products.

The stereochemical outcome in 6-*exo* heptenyl cyclization can also be explained by Beckwith model. The major product usually results from a chair conformation with any substituent present occupying an equatorial position as shown in Scheme **7**. However stereoselectivities observed in this cyclization are lower than that of the 5-*exo* cyclizations[15].

Scheme 7: Transition States for the 6-Heptenyl Cyclization

major minor

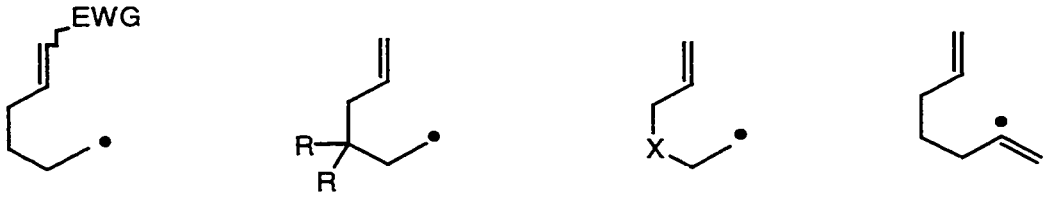
1.4 The Effect of Substituents

Substituents can also have a pronounced influence on both the rate and the regiochemistry of a radical cyclization. Substituent effects on the cyclization of hexenyl radicals have been studied extensively and quantitative data are available. The accelerating and decelerating[16] effects of certain substituents on simple 5-hexenyl cyclization are briefly summarized in Scheme **8**.

Substitution of olefin (C6) with an electron withdrawing group (**21a**) provides a large rate enhancement, which can be explained by molecular orbital theory. The electron-withdrawing group lowers the LUMO of the olefin and accelerates the rate of the reaction[17]. The presence of geminal alkyl group and (**21b**) a heteroatom at C3 (**21c**) brings the radical and the C=C double bond closer together and in turn increases the rate of the reaction. This is known as the Thorpe-Ingold effect. The last example in the accelerating section shows that vinyl radical is much more reactive than alkyl radicals with a rate enhancement of approximately 200 times (**21d**).

Radical cyclizations are generally sensitive to the steric effect at the olefin acceptor center. For example, the substitution of any group for H at the C5 (**22a**) slows down the 5-*exo* cyclization significantly and 6-*endo* products are observed. The introduction of radical stabilizing heteroatoms adjacent to the radical (**22b, 22c**) also results in slower cyclizations[18].

Scheme 8a: Accelerating Substituents

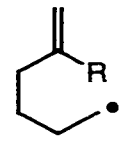


21a **21b** **21c** **21d**

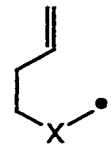
EWG = electron withdrawing group

X = O, NR

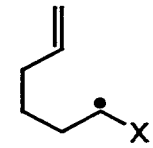
Scheme 8b: Decelerating Substituents



22a
R ≠ H



22b
X = O, NR



22c
X = O, NR

All the decelerating effects can be easily overridden by appropriate alkene substitution. Indeed any terminal alkene substitution decelerates the 6-*endo* cyclization. 5-*exo* cyclization can be further accelerated by placing an electronegative alkene substituent at C-6.

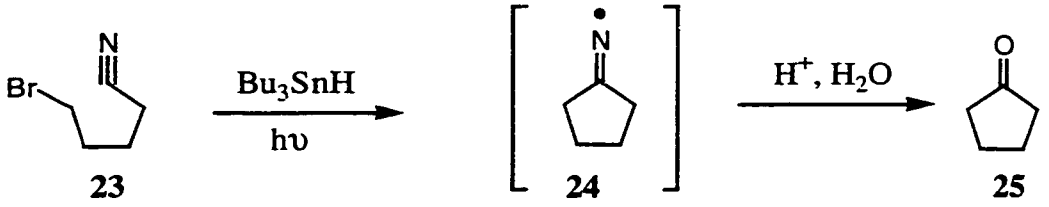
1.5 Radical Cyclizations onto C-N Multiple Bonds

The cyclization of a carbon-centered radicals onto C-N multiple bonds provide an attractive method for the preparation of nitrogen containing molecules. Radical cyclizations onto C=N bonds have received much less attention compared to radical cyclizations of alkyl radicals onto C=C and C=O bonds. Nitriles and oxime ethers are the most used acceptors in this class. Recently, radical cyclizations onto imines and hydrazones have also been reported and their synthetic usefulness seems to be increasingly important. More recently, reports of azides and azo groups as radical acceptors have also appeared. The following section reveals examples from the current literature[19] of the use of different C-N unsaturated systems as radicals acceptors and radical sources.

1.5.1 Nitrile Group as Radical Acceptors

The use of nitriles for intramolecular radical cyclizations has been known since 1975, when Ogibin *et al.* prepared cyclopentanone via cyclization of 5-bromocyanopentane **23** and subsequent acid hydrolysis of the generated iminyl radical intermediate[20] (Scheme **9**).

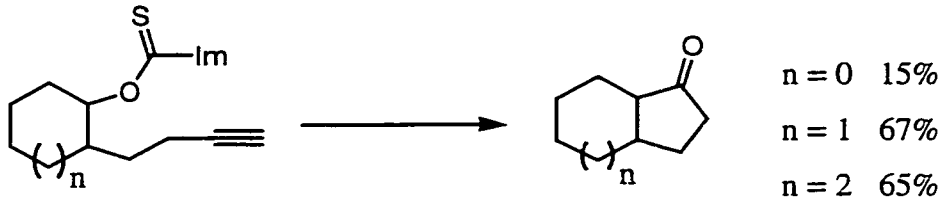
Scheme 9: Radical Cyclization onto Nitrile Group



23 **24** **25**

Clive and coworkers[21] have synthesized the fused ring systems **27**, using thiocarbamate precursors **26** to generate secondary alkyl radicals followed by cyclization onto the nitrile group (Scheme **10**).

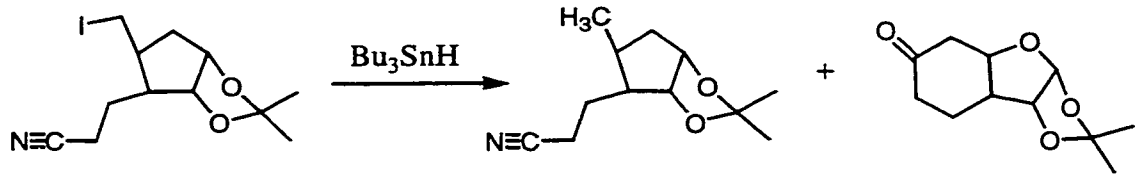
Scheme 10: Fused Ring Systems via Cyclization onto Nitrile



26 **27**

The rates of 6-*exo* cyclizations onto nitriles are slower than the competing reactions like 1,5-hydrogen transfer, thus simple reduction of the radical makes these reactions usually unsuccessful. For example, in an approach towards total synthesis of (+)-phenyllantocin via 6-*exo* cyclization of the ω-iodonotrile **28**, the desired product **30** was formed in only 2% yield and with 66% reduced material **29** [22] (Scheme **11**).

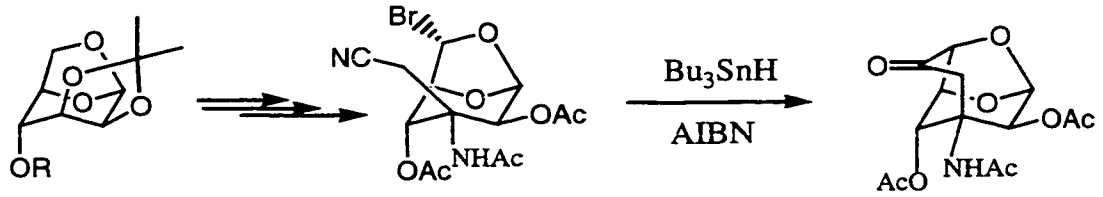
Scheme 11: 6-*Exo* Cyclization onto Nitrile Group



28 **29** **30**

Better results can be obtained when the reactive centers are part of a rigid system in which the unfavorable conformations are minimized. Scheme **12** represents an interesting example, where 6-*exo* cyclization[23] onto nitrile has been achieved successfully by making use of the constrained geometry of bromonitrile **32** to prepare a densely functionalized carbocyclic core **33** of the natural product tetrodotoxin.

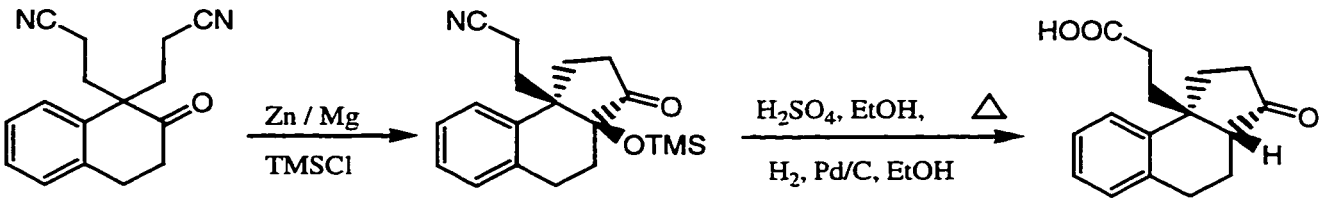
Scheme 12: 6-*Exo* Cyclization onto Nitrile towards Synthesis of Tetrodotoxin



31 **32** **33 77%**

Mann and Hegarty[24] have used ketyl radical cyclization onto a nitrile group as a key step in a general strategy for the synthesis of aphidicolin and stemodin diterpenoid skeletons (Scheme **13**). The treatment of dinitrile **34** with zinc and magnesium in the presence of trimethylsilyl chloride afforded compound **35** which, after further manipulation, generated the B-C rings of the diterpenoid skeleton with appropriate substitution and stereochemistry.

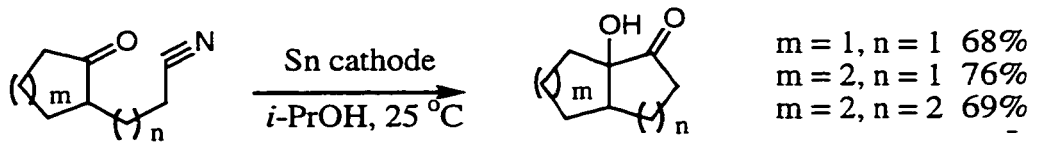
Scheme 13: Synthesis of Aphidicolin and Stemodin Diterpenoids Skeleton



34 **35** **36**

Shono and Kise[25] have used an electrochemical method to generate the ketyl radical from cyanoketones **37**, which cyclized onto a nitrile group to give a series of fused ring systems **38** in good yields (Scheme **14**).

Scheme 14: Ketyl Radical Cyclization onto Nitrile Group

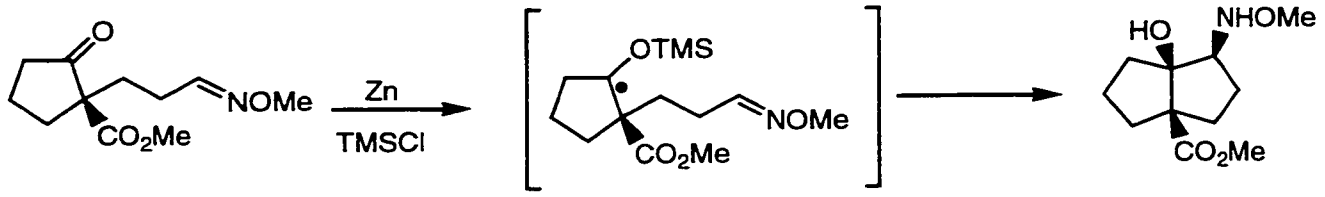


37 **38**

1.5.2 Oxime Ether Acceptors

The first example of a radical cyclization onto an oxime ether was reported by Corey and Pyne[26] and involves the addition of a trimethylsilyl protected ketyl radical **40** onto methyl oxime ether. This reaction proceeds to give the diquinane amino-alcohol **41** as a single diastereomer in 84% yield (Scheme **15**).

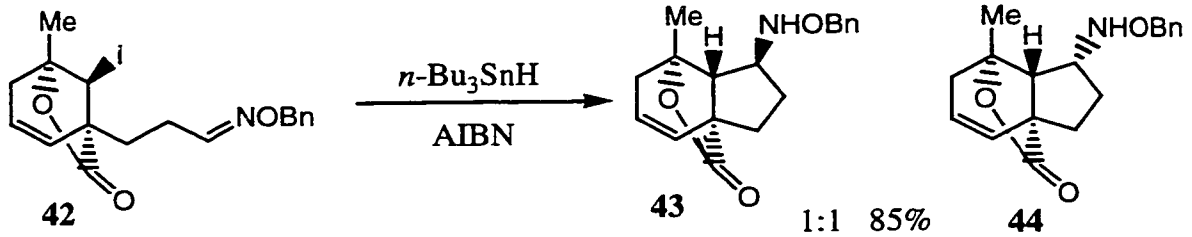
Scheme 15: Ketyl Radical cyclization onto an Oxime Ether



39 **40** **41** 84%

The first example of an alkyl radical cyclization onto an oxime ether was reported by Hart and Seely[27]. In their studies, bicyclo iodo-lactone **42** cyclized in the presence of Bu_3SnH to afford a 1:1 diastereomeric mixture of the perhydroindans (Scheme **16**).

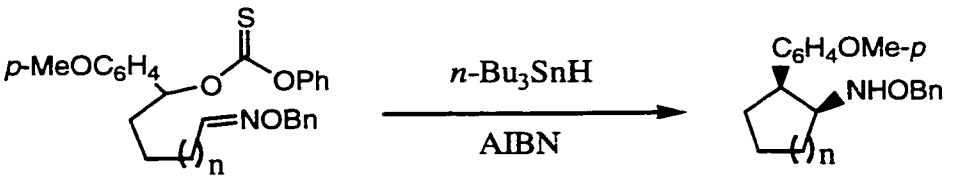
Scheme 16: Radical Cyclization onto Benzyloxime Ether



42 **43** 1:1 85% **44**

In the following article of the same journal, examples given by Bartlett and coworkers[28] described the synthesis of both cyclopentane and cyclohexanes, by employing *O*-benzyloxime ether acceptors for the capture of radicals generated from bromide or phenyl thionocarbonate precursors (Scheme **17**).

Scheme 17: Radical Generation from Thionocarbonate Precursor

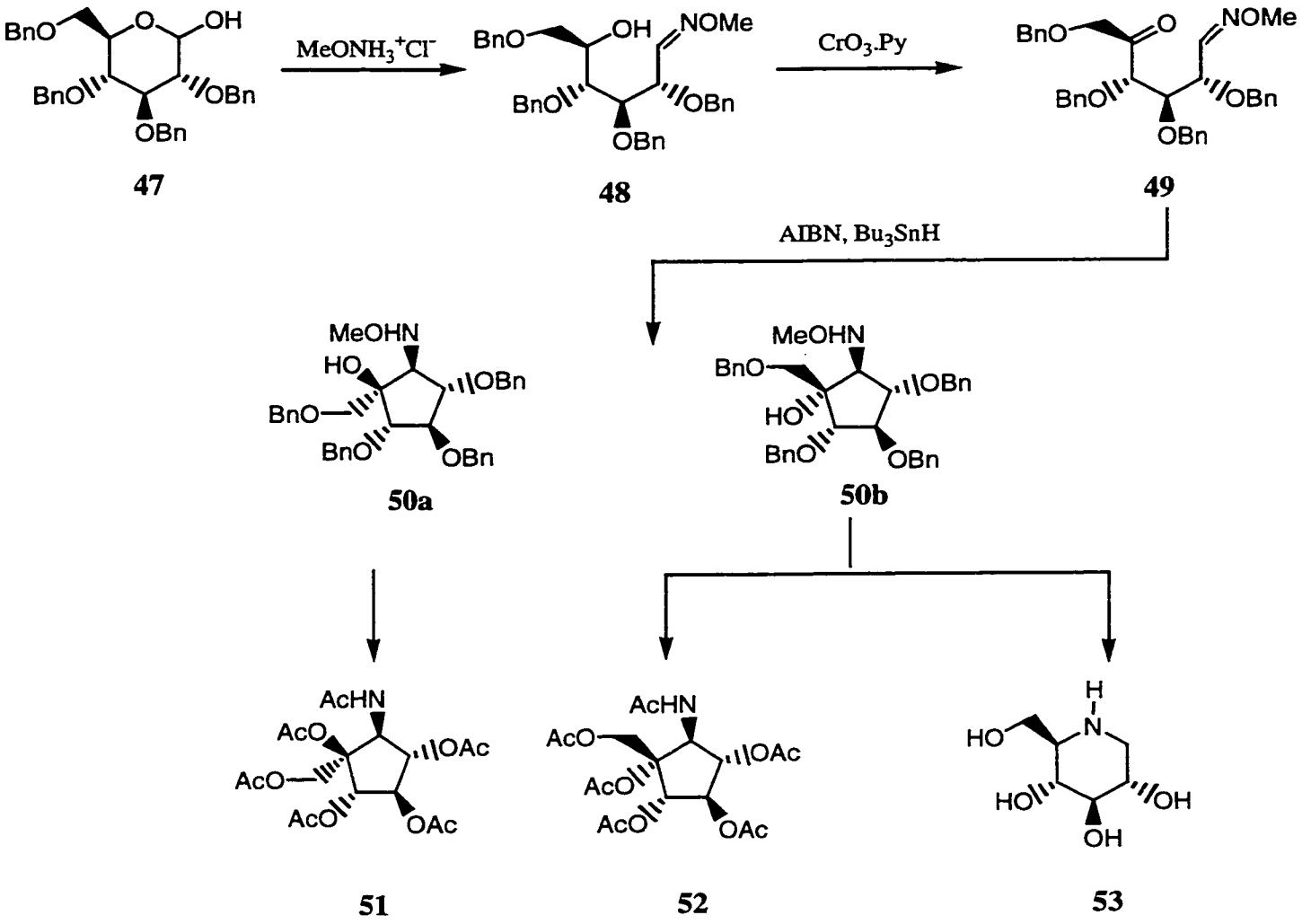


45
n = 1,2

46
n = 1 cis/trans >98/2
n =2 cis/trans 51/49

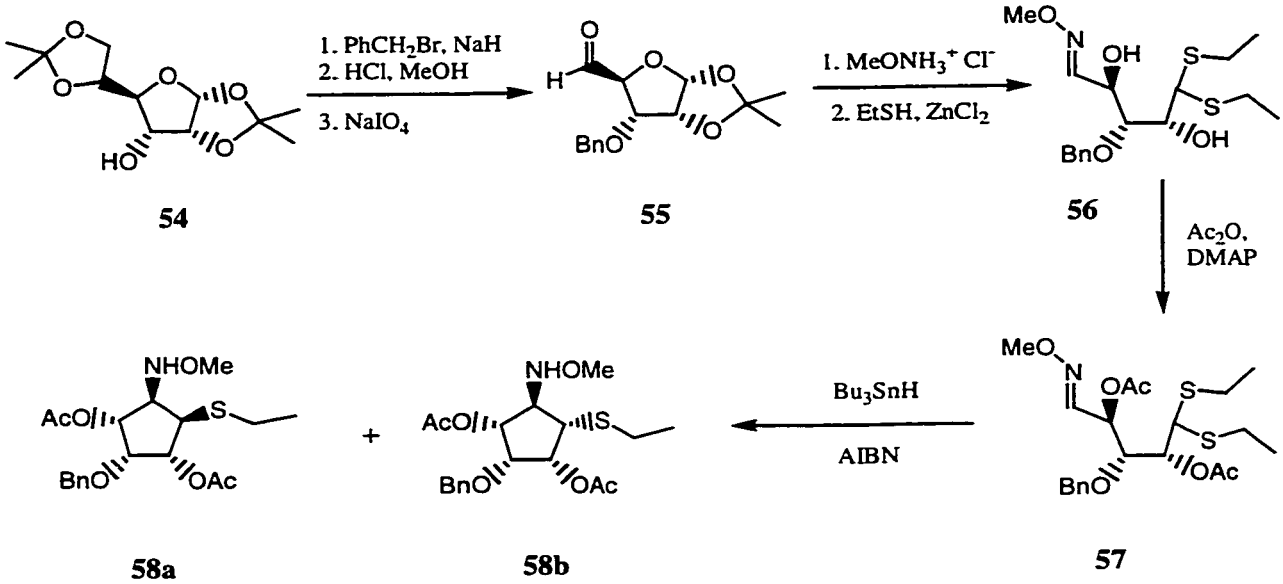
Radical cyclization of an alkyl radical onto an oxime ether has been successfully used as a key step in the synthesis of amonicyclopentitols **51** and **52** and 1-deoxynojirimycin **53**, which act as glycosidase and chitinase inhibitors[29]. As shown in the Scheme **18**, a keto-oxime **49** was obtained from tetrabenzyl hemi-acetal **47**, which cyclized to a *cis* and *trans* mixture of the aminoalcohols **50a** and **50b**. Further manipulation of these compounds afforded pentaacetates of aminocyclopentitols **51** and **52** and 1-deoxynojirimycin **53**.

Scheme 18: Synthesis of 1-Deoxynojirimycin via Radical Cyclization onto an Oxime Ether



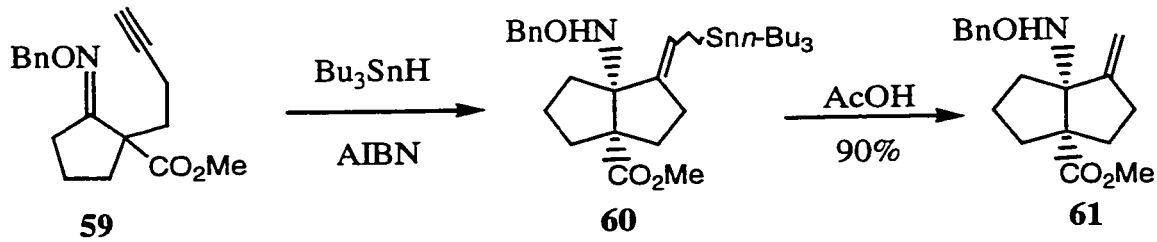
In a similar manner, Moore and coworkers[30] commenced with D-allofuranose to synthesize derivatives of the sugar hydrolase inhibitor mannostatin A and mannostatin B from the bisisopropylidene derivative **54**. The radical intermediate was derived from the dithiacetal **57**, which under tributytin hydride conditions cyclized onto methyl oxime ether to give a 3:1 mixture of the cyclic products **58a** and **58b** in 80% overall yields (Scheme **19**).

Scheme 19: Synthesis of Mannostatin A and Mannostatin B via Radical Cyclization



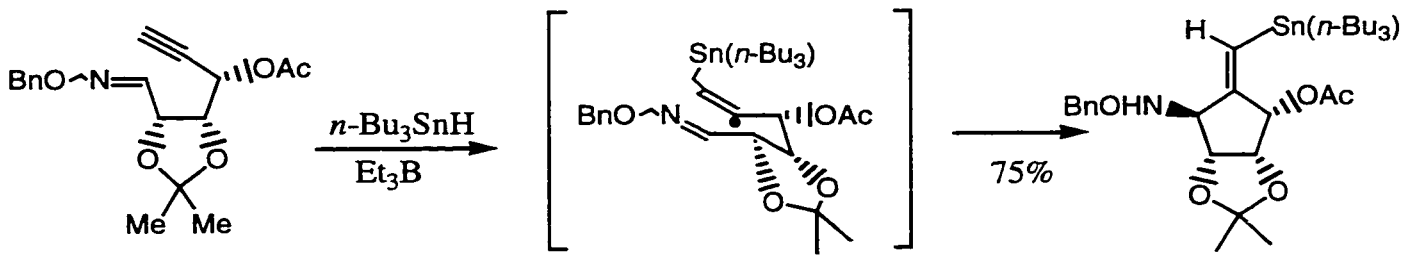
Vinyl radicals also add readily to oxime ethers in an intramolecular manner in both the 5-*exo* and 6-*exo* modes. The utility of the direct cyclization from a vinyl radical onto an oxime ether was investigated by Enholm's[31] group (Scheme **20**). A vinyl radical is generated by addition of tributyltin radical ($Bu_3Sn^{\bullet}$) to the terminal end of the alkyne **59**, followed by the cyclization of the vinyl radical onto the oxime ether to generate the fused ring system **61** with excellent stereocontrol. Subsequent removal of the vinyl stannane under acidic conditions yielded the final product in 90% isolated yield.

Scheme 20: Vinyl Radical cyclization onto an Oxime Ether



A more sophisticated example involving vinyl radical cyclization, based on a carbohydrate substrate has been reported by Marco-Contelles *et al.*[32] (Scheme **21**). The addition of tributyltin hydride to alkyne **62** in the presence of triethylborane initially afforded the vinyl radical intermediate **63**, which added to the oxime ether in a 5-*exo* manner to give **64** in 75% yield as the pure *Z*-isomer.

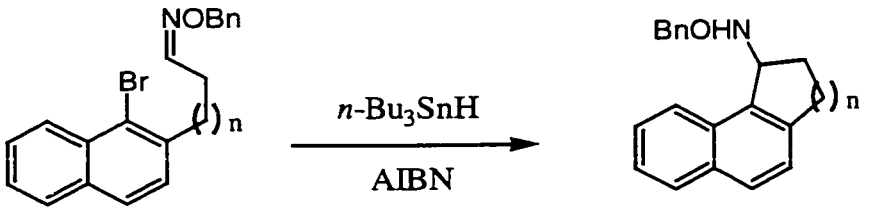
Scheme 21: Vinyl Radical Cyclization onto Carbohydrate Based Substrate



62 **63** **64**

Phenyl radicals have also been used for cyclization onto oxime ethers[33] to make 5- and 6- membered rings. The yields of these reactions varied with the size of the ring formed after cyclization (Scheme **22**).

Scheme 22: Phenyl Radical Cyclization onto Oxime Ether

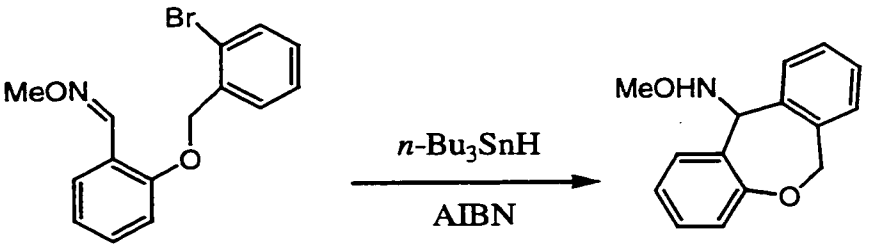


65

66 n = 1 72%
n = 2 21%

The formation of seven membered rings by cyclization of a phenyl radical onto an oxime ether has been achieved by Jenkins and coworkers[34]. Treatment of the bromide **67** with tributyltin hydride afforded the oxacycloheptane **68** in 49% yield, accompanied by 29% of the reduced starting material (Scheme **23**).

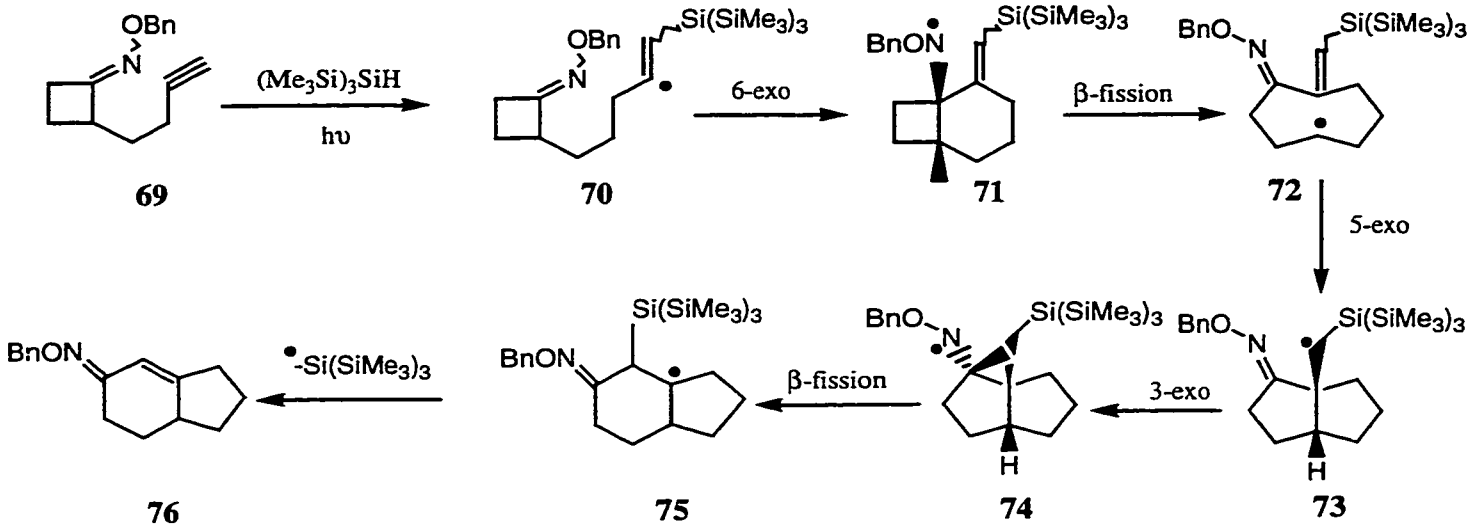
Scheme 23: Seven-membered Ring formation via Radical Cyclization Onto an Oxime Ether



67 **68**

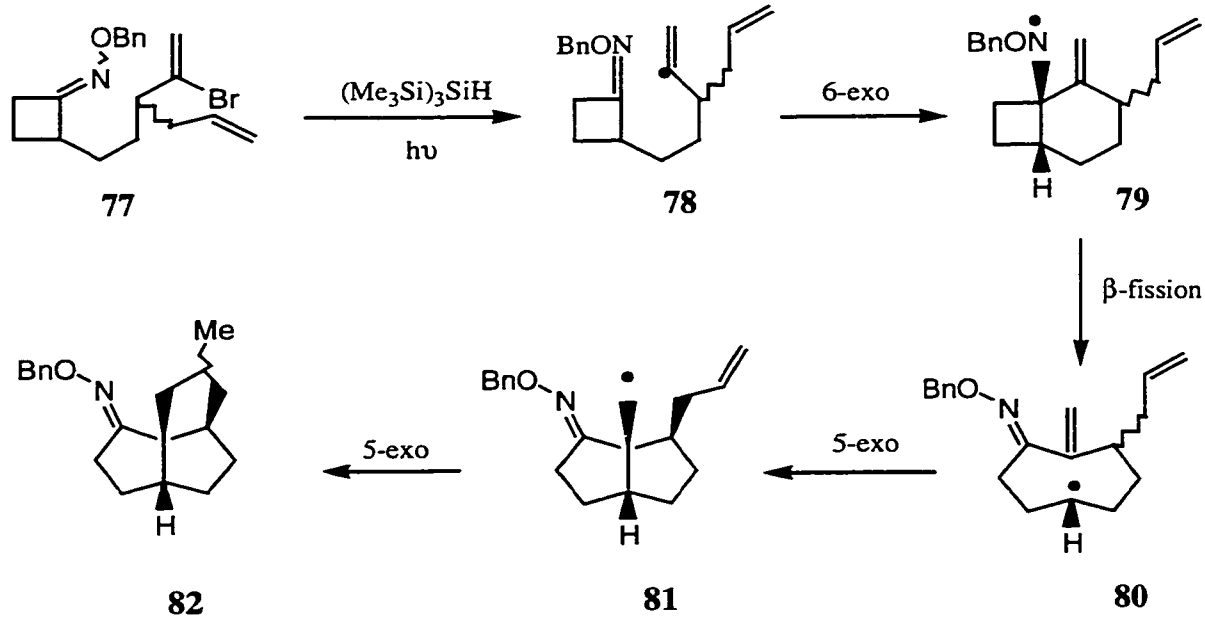
Cyclization onto an oxime ether has been used as a key step for the synthesis of bi and tricyclic ring systems via an interesting radical cascade sequence[35] (Schemes **24** and **25**). The cascade sequence leading towards the bicyclic ring commenced with the cyclobutanone oxime **69** in which the reaction was initiated by formation of the vinyl tris(trimethylsilyl)silyl radical. A 6-*exo* cyclization onto the oxime ether followed by a β-fission led to the intermediate **72** and then **73** from a second cyclization. A third ring closure afforded the α–cyclopropylaminyl radical **74**. Regeneration of the oxime from a second β-fission to afford **75** was followed by the final elimination of the tris(trimethylsilyl)silyl radical to give the final product. Thus the bicyclic product **76** of this novel "one pot" cascade arose via a double ring expansion-cyclization (Scheme **24**).

Scheme 24: Bicyclic System via Radical Cascade Reaction



The extension of this study to the vinyl bromide substituted cyclobutane oxime ether **77** resulted in triquinane **82** as 1:1 mixture of α– and β–methyl diastereomers in 38% yield (Scheme **25**).

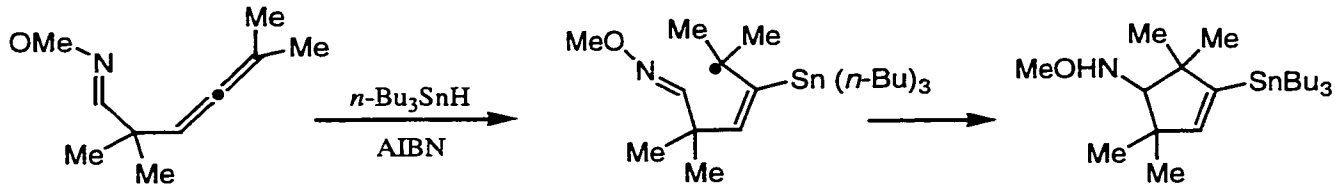
Scheme 25: Tricyclic System via Radical Cascade Reaction



In this case the product resulted from a cascade radical 6-*exo* cyclization, aminyl radical fragmentation and a 5-*exo* radical transannulation and finally a 5-*exo* ring closure to the tricyclic nucleus. In both examples given above, the initial functional group was not transformed into an *O*-alkylhydroxylamine. The retention of the oxime ether in the final product provides a synthetic bonus. The oxime can be hydrolyzed to a ketone, reduced to an amine or alcohol, or eliminated to form an olefin.

Allenes have received less attention than acetylenes as radical precursors, but Hatem and coworkers[36] showed that β-allenic *O*-methyloximes underwent a facile free radical hydrostannylation to afford cyclopentenes bearing a protected amine group and vinyl stannyl functionality in 37-91% yield. Tributyltin hydride added to the middle carbon of the allene **83** to form the allyl radical **84** which cyclized to the cyclopetenyl stannane **85**. Isolation of this material provided a vinyl tin species for further synthetic manipulation by exchange reactions (Scheme **26**).

Scheme 26: β-Allenic Oxime Ether Cyclization



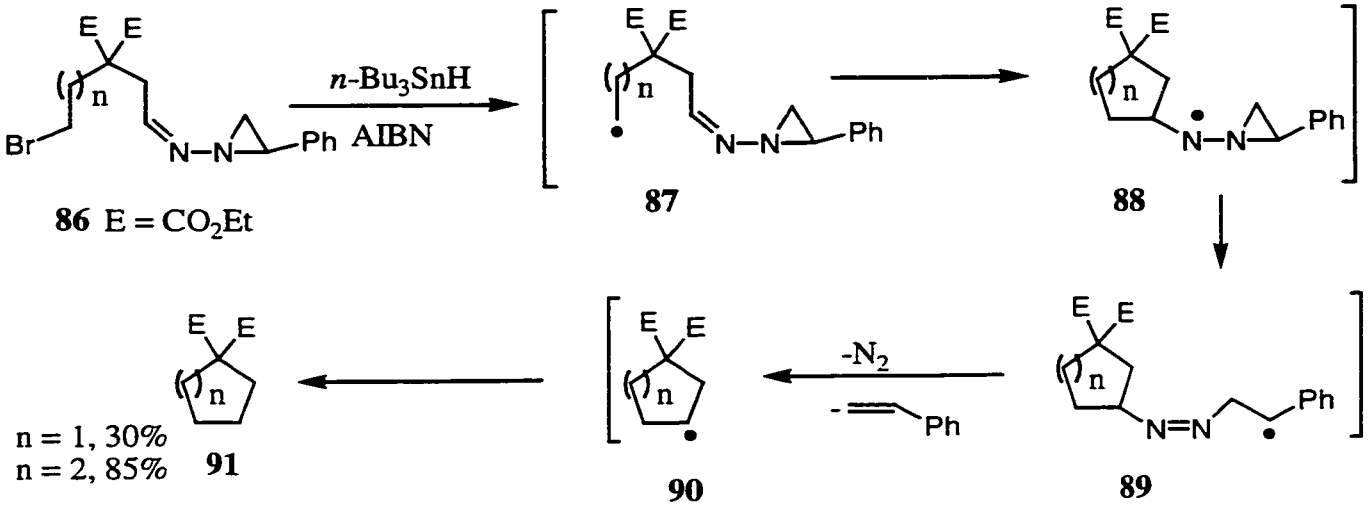
83 **84** **85**

1.5.3 Hydrazone Acceptors

Hydrazones are fairly new participants in radical reactions, but they are already emerging as useful radical acceptors. The first example of radical cyclization[37] onto hydrazones was reported by Kim's group in 1991 involving a unique hydrazone, 2-

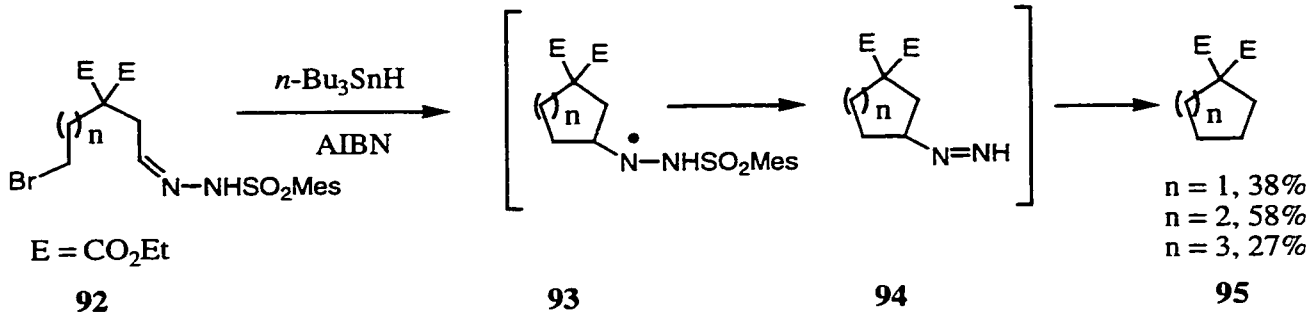
phenyl-*N*-aziridinyl imine (Scheme **27**). Under Bu_3SnH conditions, the initial radical, generated by abstraction of Br from precursor **86** cyclizes onto the C=N bond to generate an α-aziridinyl aminyl radical **88**. This radical undergoes rapid ring opening to the benzyl radical **89** with subsequent formation of styrene and expulsion of nitrogen to yield the final carbocyclic product **91** by quenching the intermediate radical **90**. The competition studies by the same group have proved that the *N*-aziridinyl imine is a better radical acceptor than the carbonyl group[38].

Scheme 27: Radical Cyclization onto 2-Phenyl-*N*-Aziridinylimine



Kim *et al.* further extended their investigations towards the use of arenesulfonylhydrazones as radical acceptors[39]. As shown in Scheme **28**, initial cyclization onto the hydrazone is followed by β-fragmentation of the arenesulfonyl radical **93** to form diazene **94**, and extrusion of nitrogen from the diazene to yield cyclic compounds **95**. Depending on the chain length, 5-, 6-, and 7- membered rings can be synthesized by this procedure.

Scheme 28: Arenesulfonyl Hydrazones as Radical Acceptors



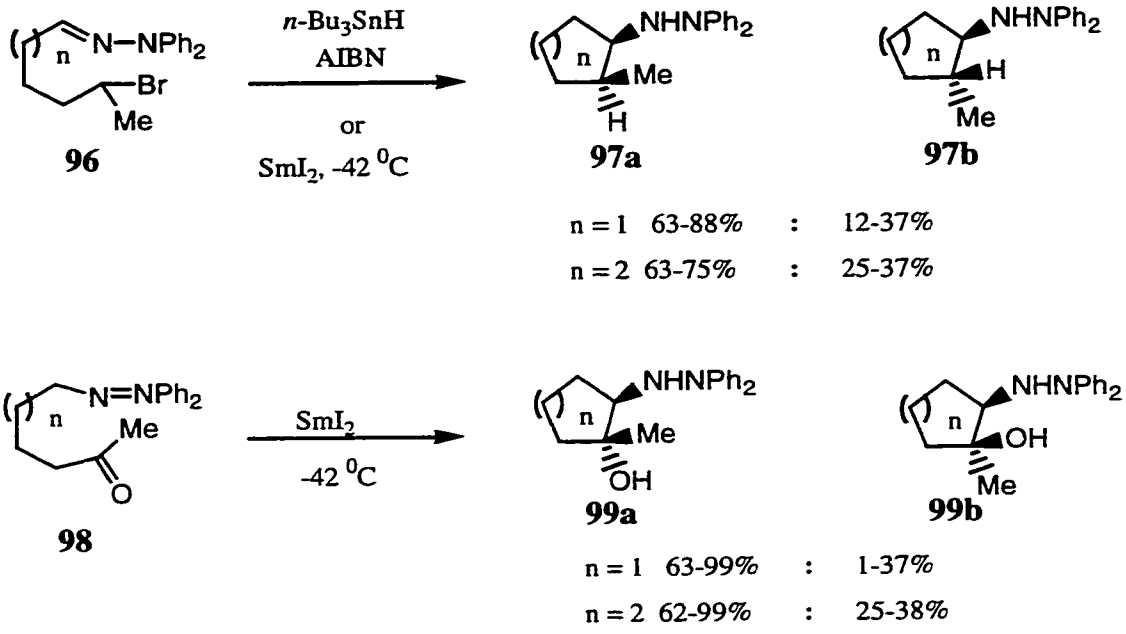
E = CO_2Et

92 **93** **94** **95**

As seen in the above examples, radical cyclizations onto *N*-aziridinyl imines and arensufonylhydrazones have introduced a versatile new approach for the formation of carbocycles. However, these reactions do not retain the nitrogen functionality in the final product. Therefore like simple alkenes, these cyclizations cannot be incorporated in the early stages of a multistep synthesis, where preservation of functionality is essential.

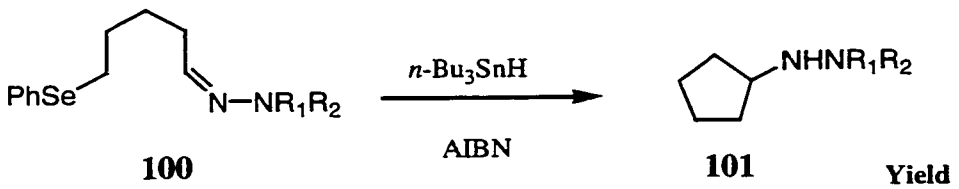
Recent studies in our laboratory have established that *N,N*-diphenylhydrazones[40] are excellent radical acceptors and can be used for the synthesis of nitrogen functionalized cyclopentanes and cyclohexanes. In contrast to the inseparable *syn/anti* mixture that usually results from oxime ethers, hydrazones can be prepared as (*E*)-isomers exclusively. As shown in Scheme **29**, treatment of bromo hydrazone **96** with Bu_3SnH at 80 °C or SmI_2 at 21 °C afforded **97a** and **97b** in 91-95% yield, in 67:33 ratio. The diastereoselectivity of the reaction could be improved for five membered rings to 88:12, by lowering the temperature (-42 °C) under SmI_2 conditions. For 6-*exo* cyclizations under the same conditions (-42 °C) the overall yield was 63% and the *cis:trans* ratio of **97a** to **97b** was 75:25. The related reaction with carbonylhydrazones **98** provided access to β-aminoalcohols after hydrazine cleavage, with a high level of diastereoselectivity.

Scheme 29: Radical Cyclizations onto *N,N*-Diphenylhydrazones



The substituent effects on the hydrazone acceptors have been studied by Bowman and coworkers[41] (Scheme **30**). An increase in yield was observed with increasing electron withdrawing groups on the hydrazone nitrogen, which must render the imine nitrogen more electropositive and raises the rate of the reaction.

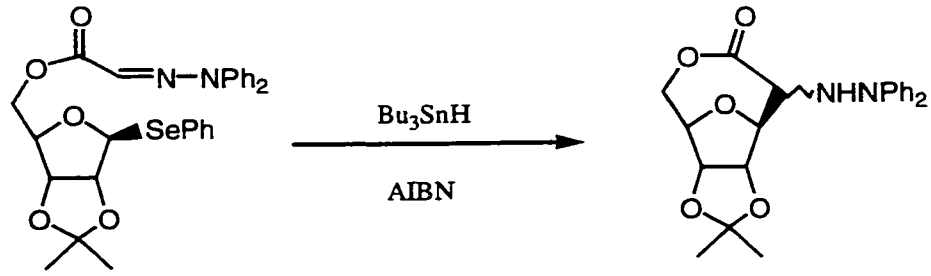
Scheme 30: Substituent Effects on Hydrazone Cyclizations



	Yield
$R_1 = H, R_2 = Ph$	18%
$R_1 = Ph, R_2 = Ph$	32%
$R_1 = H, R_2 = COPh$	50%
$R_1 = H, R_2 = CONH_2$	60%

Several other groups have also reported the successful use of *N,N*-diphenylhydrazones in radical cyclizations[42]. An interesting example involves the cyclization of the ribose derived selenide **102** in a 7-*exo* manner, to generate the tricyclic system **103** in 64% yield.[43] In this case the geometry constraints of trioxaquinane nucleus must have enhanced the facile ring closure (Scheme **31**).

Scheme 31: Radical Cyclization onto *N,N*-Diphenylhydrazones

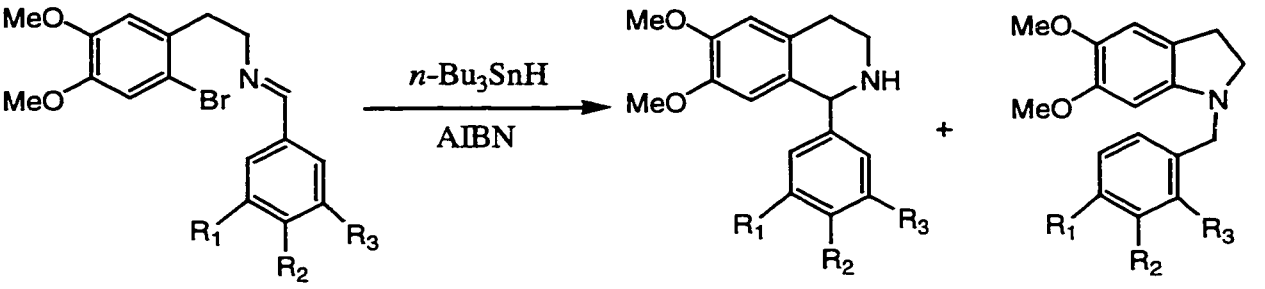


102 **103** 64%

1.5.4 Imine Acceptors

Like hydrazones, imines are also newcomers in the field of radical cyclizations. An early example of imines as a radical acceptor has been reported by Takano *et al.*[44] in 1990, as the key step in their synthesis of cryptostyline alkaloids (Scheme **32**). In this system, the aryl radical cyclizes onto the carbon atom of the imine bond in a 6-*endo* fashion to give **105** as a major product.

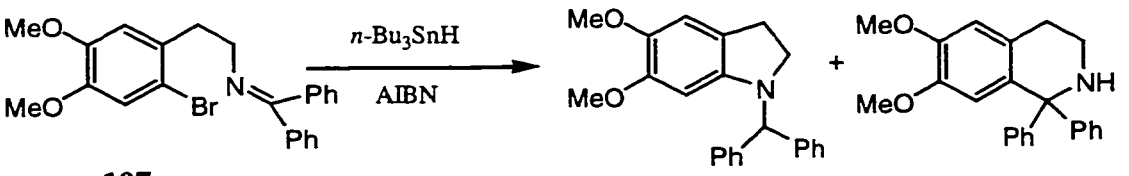
Scheme 32: Aryl Radical Cyclization onto Imines



104 **105** 6- endo **106** 5-exo

A similar pattern of reactivity has also been observed by other groups[45], using aldimines as radical acceptors. As seen in the above example, the cyclization onto the imine follows a route opposite to that followed by cyclization of an aryl radical onto alkene, where 5-*exo* cyclization is preferred over 6-*endo* cyclization. This was a consequence of the fact that formation of a C-C single bond is favored over the corresponding C-N bond formation by approximately 10 kcal/mol. The angle of attack in the endo transition state (109°) is closer to the tetrahedral angle, which results in better SOMO–LUMO interactions in the T.S. thus making the endo product the major product. This reaction was found to be sensitive to steric congestion at the acceptor. In the corresponding acetophenone- or benzophenone-derived ketimines, the radical center added exclusively to the nitrogen terminus of the azomethine bond in a 5-*exo* manner[46] (Scheme **33**).

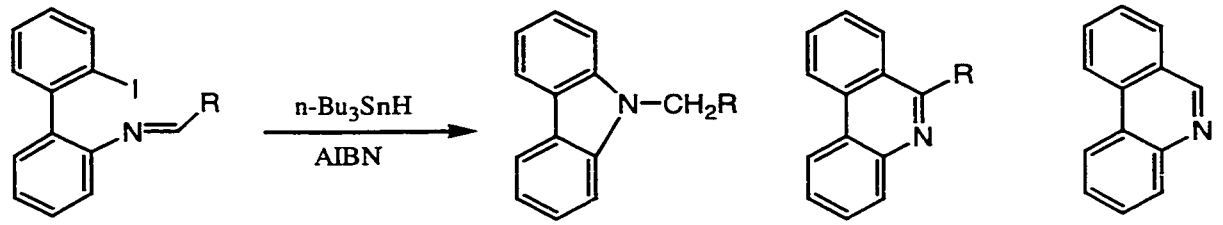
Scheme 33: Phenyl Radical Cyclization onto Ketimine



107 **108** 59% **109** 0%

In the systems studied by Leardini and Zanardi[47], a large 5-*exo* preference has been observed for the cyclization onto aldimines, which is in contrast with the result published by Warkentin *et al.*[45] As shown in Scheme **34**, aldimine **110** gave the 5-*exo* cyclized product predominantly. In the case of aldimine **110b**, the desired product was obtained in a moderate yield. The minor product **113** arises from rearrangement of the initial radical formed after 5-*exo* cyclization.

Scheme 34: Radical Cyclization onto Imines



110

a : R = *p*-ClPh
b : R = *t*-Bu

111

a : 71%
b : 45%

112

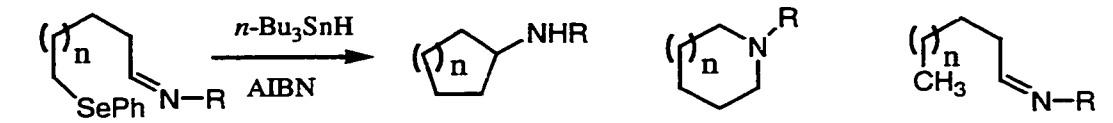
a : 9%

113

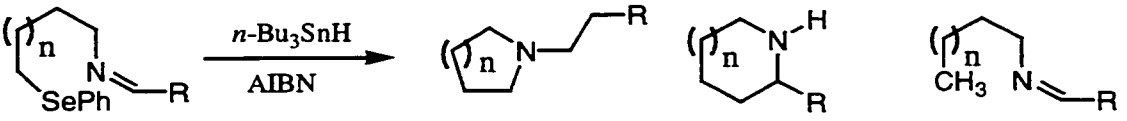
b : 19%

The cyclization of various primary radicals generated from phenylselenides onto diverse imines has been studied by Bowman and coworkers[41]. In their studies also, 5-*exo* mode of cyclizations dominated over the endo mode. Varying amounts of 5-*exo*, 6-*endo* and simple reduction products were isolated, depending on the size of the ring being formed, polarization of the imine bond and stability of the resulting radical (Scheme **35**).

Scheme 35: Primary Radical Cyclization onto Imines



	114	**115**	**116**	**117**
n = 1, R = *p*-Tolyl		39%	0%	0%
n = 1, R = CH_2Bn		47%	5%	0%
n = 2, R = *p*-Tolyl		0%	0%	35%
n = 2, R = CH_2Bn		43%	0%	0%

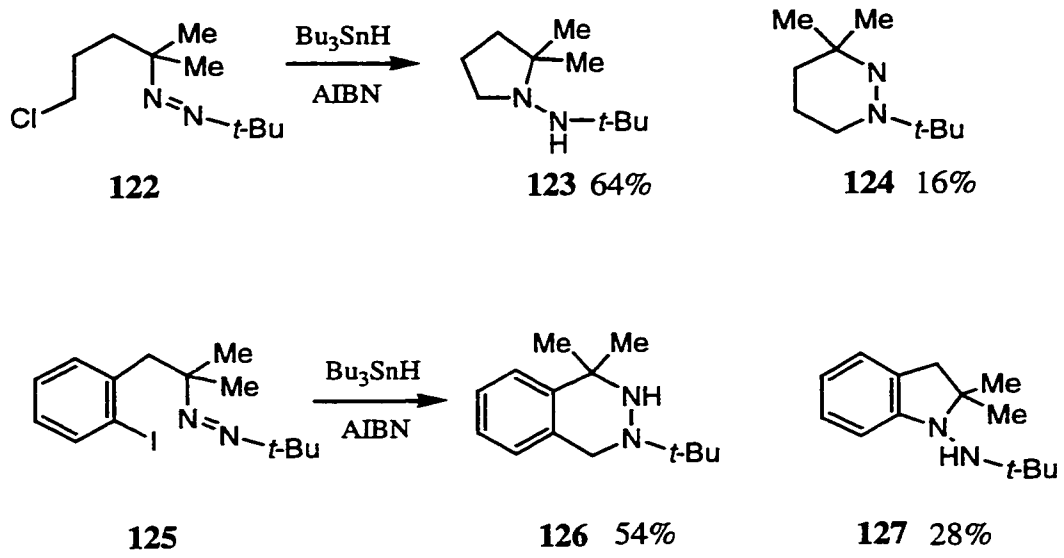


	118	**119**	**120**	**121**
n = 1, R = *p*-Tolyl		54%	6%	0%
n = 1, R = CH_2Bn		42%	18%	0%
n = 2, R = *p*-Tolyl		7%	0%	40%
n = 2, R = CH_2Bn		0%	0%	39%

1.5.5 Azo and Azide Acceptors

A limited number of examples are known where azides and azo compounds are used as radical acceptors. However, under appropriate conditions, these groups can also be employed successfully to prepare a variety of heterocyclic rings. Warkentin and coworkers have investigated the cyclizations of alkyl and aryl radicals onto azo acceptors and determined their rate constants[48]. They have found that alkyl radical **122** cyclizes in 5-*exo* manner predominantly to give the heterocycle as the major product, whereas related aryl radicals preferred the 6-*endo* pathway and product **126** was the major product from the cyclization of **125** (Scheme **36**).

Scheme 36: Radical Cyclization onto Azo Acceptors

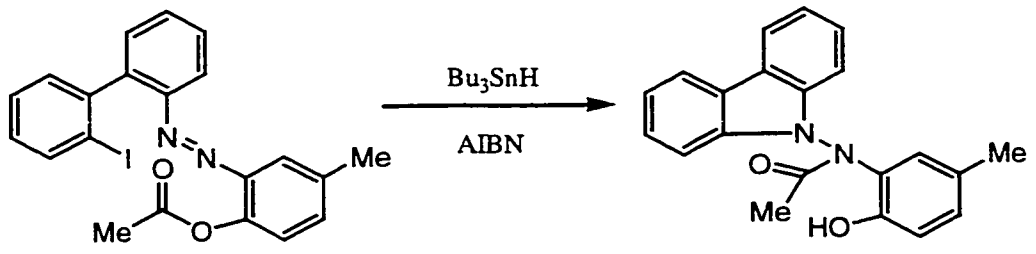


122 **123** 64% **124** 16%

125 **126** 54% **127** 28%

An interesting example of aryl radical cyclization onto azo acceptors has been reported by Zanardi, Leardini *et al.*[49] (Scheme **37**). In this instance the initial additions proceeded in a 5-*exo* manner to give an aminyl radical, which undergoes radical cyclization and rearrangement to generate the phenolic product in 50% yield.

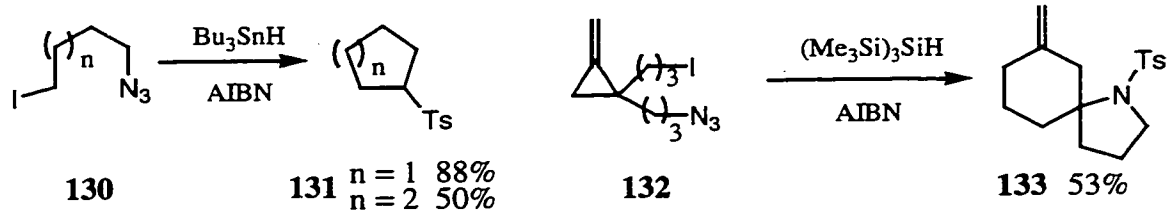
Scheme 37: Aryl Radical Cyclization onto Azo Acceptors



128 **129** 50%

Scheme **38** represents two examples where radical cyclization onto an azide group has been achieved to prepare heterocycles. Kim and coworkers have used tris(trimethylsilyl)silane with bromoalkanes and tributyltin hydride with more reactive iodo systems **130** to prepare 5 and 6 membered heterocycles **131** after tosylation on work up[50]. In a related study, Kilburn and Santogostino[51] have converted the methylene cyclopropane system **132** into a spiro-heterocycle **133** in moderate yield after tosylation.

Scheme 38: Cyclization onto Azide Acceptors



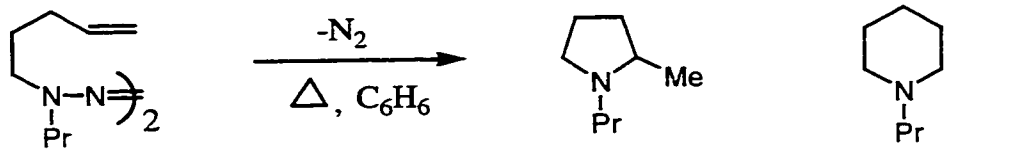
130 **131** n = 1 88%, n = 2 50% **132** **133** 53%

1.6 Cyclizations Involving Nitrogen Centered Radicals

The use of nitrogen-centered radicals in organic chemistry has increased in recent years. Nitrogen systems are very useful, as they incorporate a heteroatom in the cyclization step. Therefore, these systems can be used for the synthesis of alkaloids and the pyrrolidine nucleus. The electronic nature of the nitrogen-centered radicals is usually dictated by the reaction conditions or the radical precursor. Neutral aminyl radicals are neucleophilic species. Therefore radical cyclization of these nitrogen-centered radicals is usually slower than their carbon analogs[52]. Recent *ab initio calculations* by Tsanaktsidis[53] have shown that 5-*exo* ring closure of nitrogen centered radicals are highly exothermic, but a large amount of energy is required to overcome the transition state barrier. However, the rate of the reaction can be increased by using acidic conditions or Lewis acids such as $MgBr_2.Et_2O$ or $(Bu_3Sn)_2O$[54] which make these radicals electrophilic in nature.

Thermal extrusion of nitrogen from azene was one of the earlier methods to generate an aminyl radical[55]. As shown in Scheme **39**, under thermal conditions, the radical generated from **134** cyclizes predominantly in a 5-*exo* manner to afford pyrrolidine **135** as the major product.

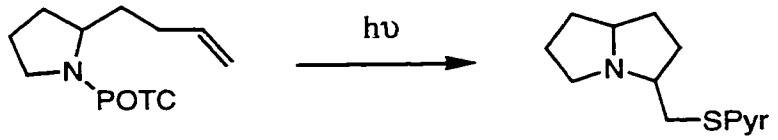
Scheme 39: Generation of Aminyl Radical by Thermal Method



134 **135** 42% **136** 18%

Another useful method for generation of the aminyl radical is the irradiation of the Barton esters (*N*-hydroxypyridine-2-(1H) thione acyl esters)[56] that has provided the bicyclic skeleton **138** in high yield (Scheme **40**).

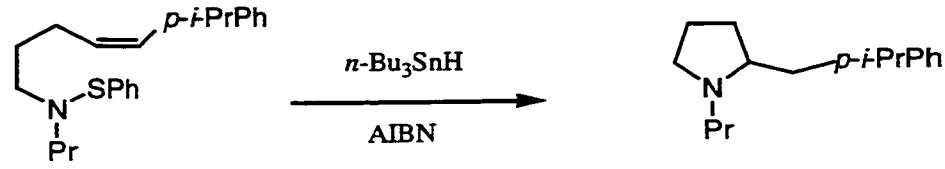
Scheme 40: Aminyl Radical Cyclization via Photochemical Method



137 **138** 96%

Bowman and coworkers have demonstrated the generality of arylsulfenamides for the generation of nitrogen centered radicals. Under standard tributyltin hydride conditions a variety of heterocyclic systems including bridged ring heterocycles have been synthesized[57] successfully (Scheme **41**).

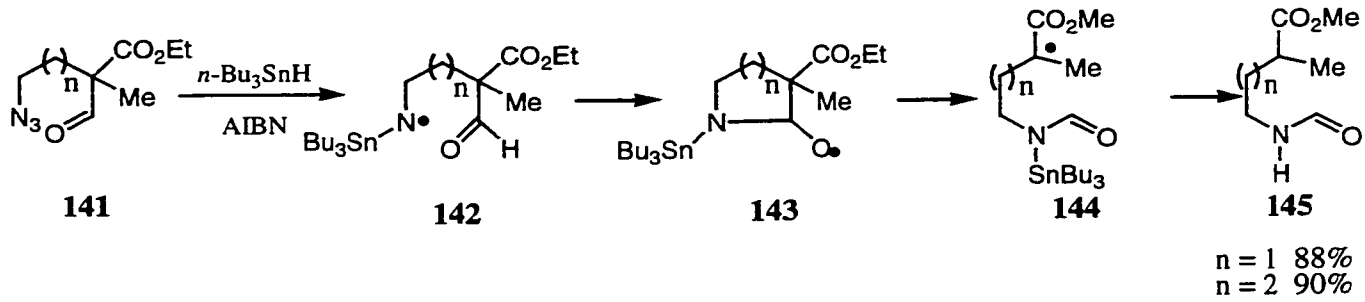
Scheme 41: Cyclization of Nitrogen Centered Radicals



139 **140**

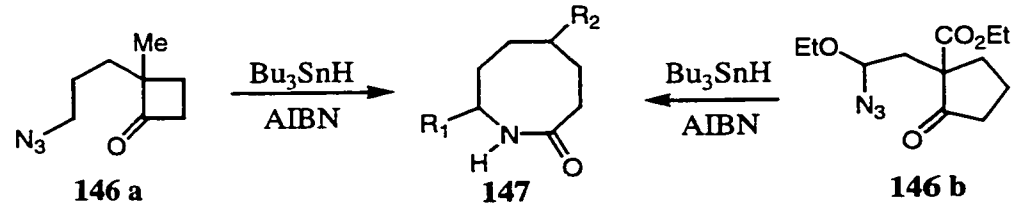
Kim and coworkers have used azides to generate aminyl radicals. These can be added onto carbonyl groups and hydrazones successfully. Scheme **42** shows an intramolecular addition of aminyl radical **142** to carbonyl groups to form amides **145** after rearrangement of the initial oxygen radical intermediate **143**[50]. The application of this chemistry to substituted cyclobutanone **146a** and substituted cyclopentanone **146b**, led directly to ring expanded lactams **147** in high yields.

Scheme 42: Aminyl Radical Cycization onto Carbonyl Group



141 **142** **143** **144** **145**

n = 1 88%
n = 2 90%

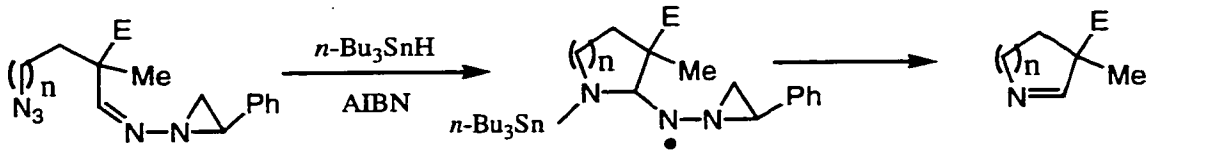


146 a **147** **146 b**

R_1 = H, R_2 = Me 96%
R_1 = OEt, R_2 = CO_2Et 83%

Scheme **43** represents cyclization of an aminyl radicals onto *N*-aziridinyl imines. An aminyl stannane radical can be generated from azide **148**, and the radical cyclizes onto the hydrazone[58] to give intermediate **149**. This species then provides the cyclic imines **150** in high yields after expulsion of nitrogen, styrene and elimination of the tin radical.

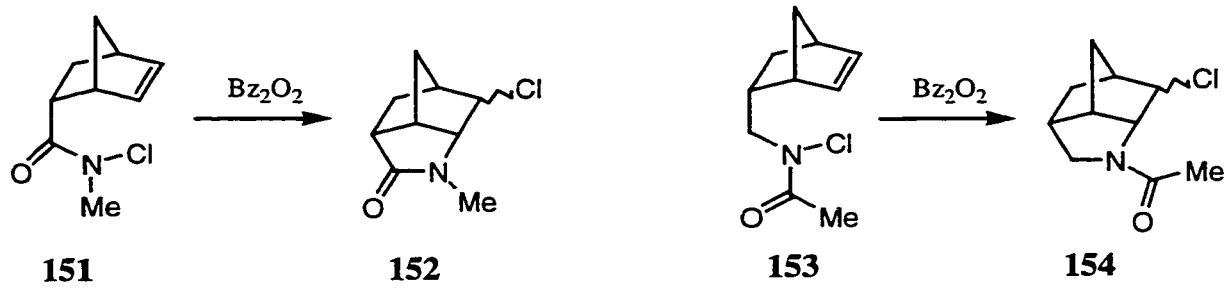
Scheme 43: Aminyl Radical Cyclization onto Hydrazone



148 **149** **150** n = 1. 81%
n = 2, 79%

Amidyl radicals are electropositive in nature and their cyclizations are faster than the neutral aminyl radicals. Amidyl radicals can be generated from N substituted amides in which the group cleaved is a halogen, a nitroso, a hydrazine, a benzoate, or a hydrazone or a *N*-hydroxypyridine-2-thione imidate. The first report of amidyl radical cyclization onto an unsaturated system came from Lessard and coworkers[59] (Scheme **44**). Tricyclic systems **152**, **154** were prepared using benzoylperoxide as a radical initiator. The placement of the carbonyl group outside the ring in compound **153** increased the flexibility of the system, thereby reducing the ease of cyclization.

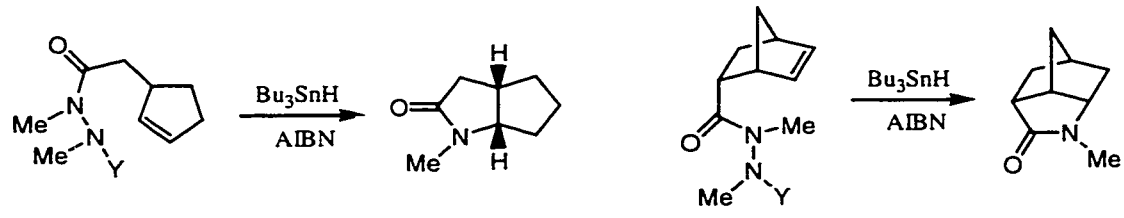
Scheme 44: Amidyl Radical Cyclizations



151 **152** **153** **154**

Xanthyl hydrazines have been used successfully to generate amidyl radicals by Callieer-Dublanchet and coworkers[60]. As shown in Scheme **45**, hydrazines, **155** and **157** afforded amidyl radicals upon treatment with tributyltin hydride from which the heterocyclic systems **156, 158** were isolated in high yields.

Scheme 45: Generation of Amidyl Radicals from Xanthyl Hydrazines

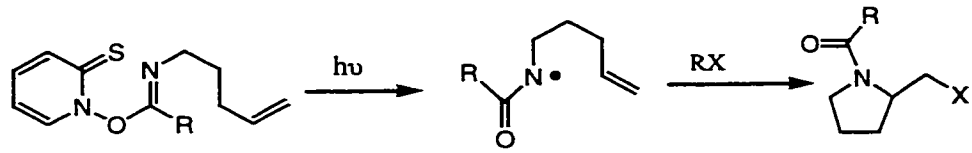


155 Y = CS(OMe)
Y = CS(SMe)

156 **157** **158**

Newcomb and Esker[61] have used the *N*-hydroxypyridine-2-thione unit **159** to generate amidyl radical **160**, which cyclizes and reacts with diphenyl diselenide to provide cyclic amide **161** in good yield (Scheme **46**).

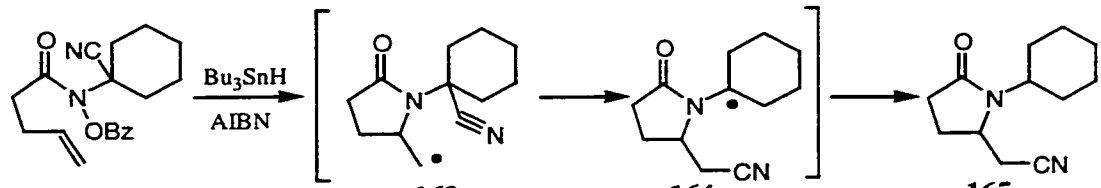
Scheme 46: Amidyl Radical from *N*-Hydroxypyridine-2-Thione Imidate Ester



159 **160** **161**

Scheme **47** represents an example where benzoate has been used to generate an amidyl radical intermediate[62]. Under tributytin hydride conditions, the radical **163** derived from **162** adds to the nitrile group and rearranges with concomitant ring cleavage resulting in nitrile transfer to give radical **164**. Subsequent hydrogen abstraction by this radical leads to the final product **165**.

Scheme 47: Amidyl Radicals from Benzoate Precursors



162 **163** **164** **165**

Chapter Two

Rate Constants for 5-*Exo* Secondary Alkyl Radical Cyclizations onto Hydrazones and Oxime Ethers

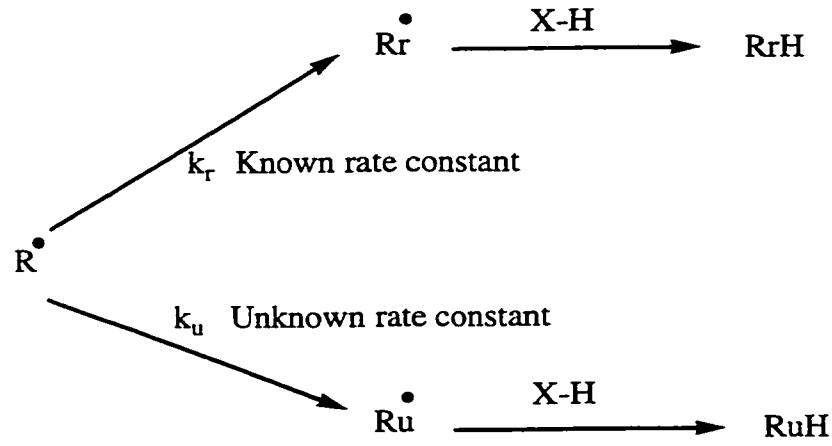
2.1 Introduction

The knowledge of rate constants of radical reactions is very important for their synthetic application and related mechanistic studies[63]. In mechanistic studies, it helps to establish the presence of possible radical intermediates in a radical pathway. The reactions of radicals with nonradicals (neutral organic molecules) have much greater use in synthesis. These reactions occur with a wide and predictable range of rate constants, and the concentration of a nonradical component is a readily controlled experimental variable that can greatly affect the chemoselectivity of a reaction. For radical–reagent reactions to be synthetically useful, they must be faster than radical-radical reactions and radical-solvent reactions. By estimating the rates of these destructive reactions, one can determine lower limits for synthetic procedures. Furthermore a qualitative understanding of radical kinetics of competing reactions helps in the selection of experimental conditions (reagents and concentrations) to make a particular radical reaction successful.

A considerable amount of work has been done in the past several years on the direct measurement of rates of radical reactions[64]. Extensive studies using laser flash photolysis or pulse radiolysis with time resolved UV-visible spectroscopy has allowed the measurements of many radical reactions. These rate constants can be used for reference in competitive systems (radical Clocks) to calculate rate constants for other reactions. For synthetic organic chemists, radical clock systems are convenient techniques for measuring rate constants[65]. This method involves partitioning of a radical

intermediate R$^{\bullet}$ between two reaction channels, the reaction of interest with an unknown rate constant and a basic reaction with a known rate constant (Scheme **48**).

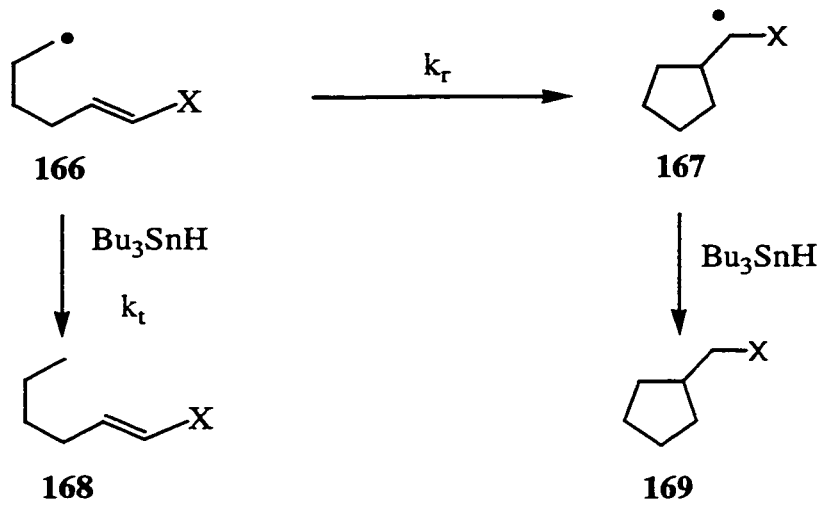
Scheme 48: Principles of Radical Clock Systems



Thus intermediate R$^{\bullet}$ can react to give Rr$^{\bullet}$, with some known rate constant k_r, or form Ru$^{\bullet}$ with some unknown rate constant k_u. From the measurement of the product ratios (RrH/RuH) the unknown rate constants can be determined. Two types of radical clock systems can be used: intermolecular and intramolecular.

The intermolecular system has been employed more frequently and involves the competition between a radical cyclization of unknown rate constant and the intermolecular quenching of the radical with tributyltin hydride (Scheme **49**). Thus the two competing reactions available to the radical **166** are cyclization to generate radical **167** or quenching of the starting radical with Bu_3SnH[66]. In this case, a bimolecular reaction competes with a unimolecular reaction under pseudo first order conditions and the ratio of the rate constants is found as the slope of a plot of the ratio of two products **168:169** as a function of the concentration of the trapping agent [Bu_3SnH].

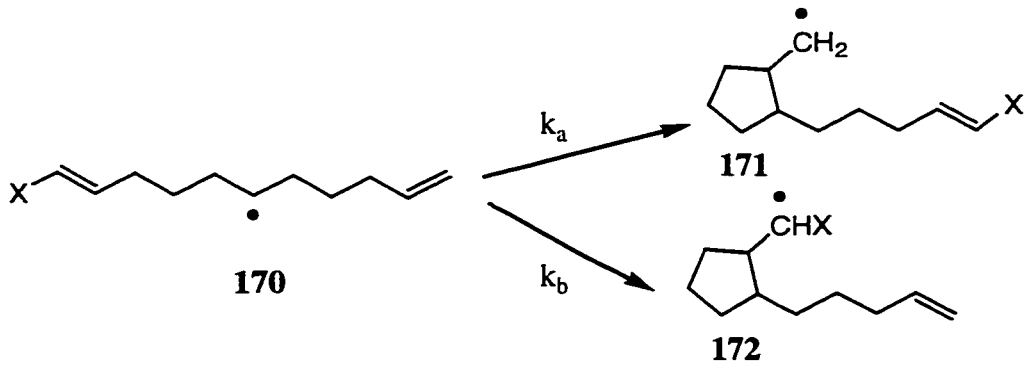
Scheme 49: Intermolecular Radical Clock System



Scheme **50** illustrates an intramolecular clock system. In this system, the competing reactions are a 5-*exo* cyclization onto a terminal alkene to generate P_a (**171**) with a known rate constant k_a and cyclization onto a substituted alkene to generate P_b (**172**) with an unknown rate constant. If the product ratio (P_b/P_a) can be measured analytically, then the unknown rate constant is given by the following equation.

$$k_b = k_a (P_b/P_a) \qquad \text{Eq.4}$$

Scheme 50: Intramolecular Radical Clock System



There are some implicit assumptions made for indirect kinetic studies that should be pointed out. The first assumption is that the rate constant for reaction of a given radical can be approximated accurately by that for another, structurally related radical. For example, for the intermolecular system, it has been assumed that the rate of quenching of the radical **166** (Scheme **49**) is equal to that for other primary alkyl radicals with Bu_3SnH, specifically the ethyl and butyl radicals, for which rate constants for reaction with Bu_3SnH are known[63].

For intramolecular systems, it is assumed that rate constants for the structurally related secondary alkyl 5-hexenyl type cyclization (shown below) is a good approximation for the cyclization of the secondary radical **171** shown in Scheme **50**. The intramolecular systems are generally considered to be irreversible and therefore the product ratios are assumed to result from the difference in reaction rates. Another important assumption is that the rate constants are relatively insensitive to solvent effects. The successful calibration of some unimolecular reactions on an absolute scale has proved the insensitivity to solvent polarity[67]. In most cases these assumptions are valid, in fact this makes the radical clock systems very useful.

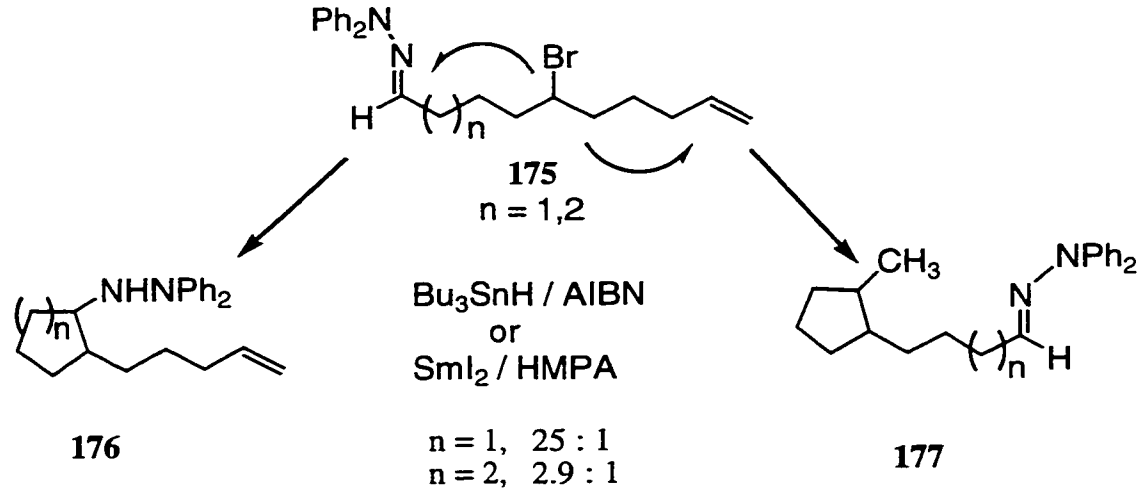
173 **174**

Organic synthesis involving radical cyclizations onto multiple bonds containing heteroatoms has been of increasing interest in recent years, but has developed more slowly than the synthetically important intramolecular addition of alkenes. As a result, in contrast to extensive literature containing kinetic information on free radical addition onto C-C double bonds, there is less kinetic data for C=O[68] and C=N-[38, 45] double bonds.

2.2 Comparison of Rate Constants for Alkene and Hydrazone Cyclizations

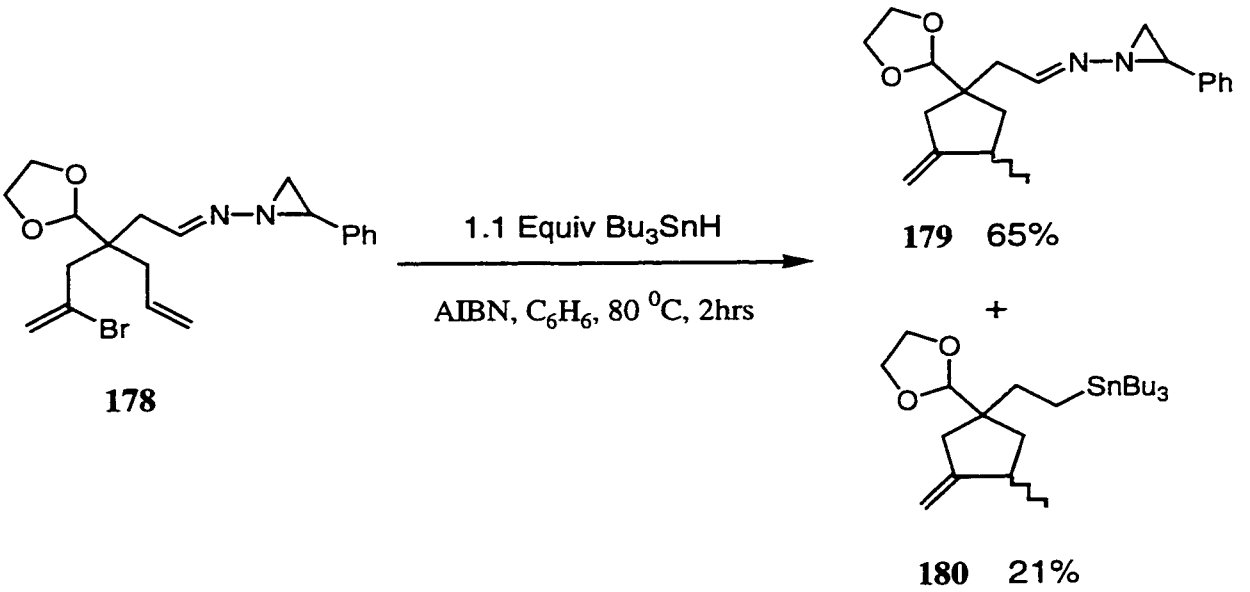
Recent studies in our laboratory have established that *N,N*-diphenylhydrazones are excellent radical acceptors and can be gainfully employed in the synthesis of nitrogen-containing cylopentanes and cyclohexanes[40]. These studies were extended to calculate the rate constant for the cyclization of an alkyl radical onto a hydrazone system for the first time. An intramolecular competitive "radical clock" system was designed to calculate the rate constants for 5-*exo* and 6-*exo* cyclization of alkyl radicals onto hydrazone systems[69].

Scheme 51: Competitive "Radical Clock" Systems for *N,N*-Diphenylhydrazones and Alkenes



Individual reactions conducted under standard conditions with tributyltin hydride or samarium diiodide/HMPA established that the rate constants for 5-*exo* cyclizations onto *N,N*-diphenylhydrazones were 1.1 X $10^8 s^{-1}$ and 4.6 X 10^7 s^{-1} at 80 °C for the *cis* and *trans* cyclopentylhydrazines respectively. The *6-exo* hydrazone rate constant was 9.4 X $10^5 s^{-1}$ at 80 °C for both *cis* and *trans* isomers. The important findings of this study were that 5-*exo* cyclization onto *N,N*-diphenyl hydrazone was approximately 200 times faster than the corresponding cyclization of an alkene, while the advantage for 6-*exo* cyclization onto *N,N*-diphenylhydrazone was ~100 fold. These studies also established that under samarium diiodide conditions, these reactions are radical cyclizations and excluded the involvement of anionic organosamarium intermediates. Surprisingly, these results were different than an earlier work by Kim *et al.* involving competition studies with *N*-aziridinyl imines and 5-hexenyl systems[70]. Their results are summarized in Scheme **52**.

Scheme 52: Competitive Vinyl Radical Cyclization between *N*-Aziridinyl Imine and Alkene



178

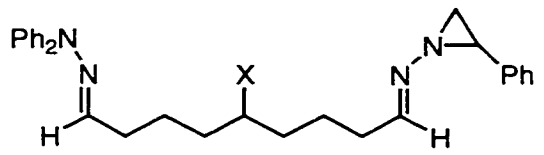
179 65%

+

180 21%

After generation of the vinyl radical from bromide **178**, only the cyclized product from the 5-*exo* cyclization onto the alkene was observed, with no evidence of cyclization onto the hydrazone. This was in stark contrast to our findings, where 5-*exo* cyclization of an alkyl radical proceeded exclusively onto the hydrazone with no evidence of cyclization onto the alkene. The minor product **180** most likely results from the addition of $Bu_3Sn^{\bullet}$ to C=N bond of the hydrazone **179**, which subsequently undergoes expulsion of styrene and nitrogen. In repeating the above reaction with 2.2 equivalents of Bu_3SnH, the organotin compound **180** was the only product of the reaction and again there was no evidence of hydrazone cyclization. These studies concluded that alkenes are better radical acceptors than hydrazones.

The reason for such a large difference between these two systems is not so clear. Given the amount of functionality present in compound **178**, conformational effects may play a significant role in the chemoselectivity observed. In order to understand these systems better, we thought of designing bis-hydrazone type internal competition clock systems **181**, which can allow a more direct comparison of our *N,N*-diphenylhydrazone with an *N*-aziridinyl imine.



181 a, X = Br
181 b, X = SePh

2.3 Research Objectives

At the commencement of this project rate constants for alkyl radical cyclizations onto other C=N bond systems (imines, oxime ethers etc.) were not available, a situation which resulted in limited information regarding the best acceptor in diverse imine systems in which two different substitution patterns are present. Therefore, we decided

to extend our kinetic studies to other C=N systems in different families. A diverse family of imines, oxime ethers and hydrazones were selected for investigation (Scheme **53**). These systems represent synthetically useful precursors. The oxime methyl ethers allow facile detection by ^{1}H NMR and can be converted to the parent oxime with trimethylsilyl iodide. In a related fashion the benzyl oxime can be cleaved by hydrogenolysis. *N*-benzoylhydrazones are synthetically versatile due to their ease of hydrolysis[41]. *N*-sulfonylhydrazones are also good radical acceptors, although the initial cyclization product is prone to fragmentation[39]. The different structures among imines, oxime ethers and hydrazones possess different electron density at the iminyl carbon. This influences the radical cyclizations and the rate constants due to nature of the –C=N bond. A comparison among these systems will help in establishing the dependence of the rate constant on stabilization of the initial nitrogen centered radical.

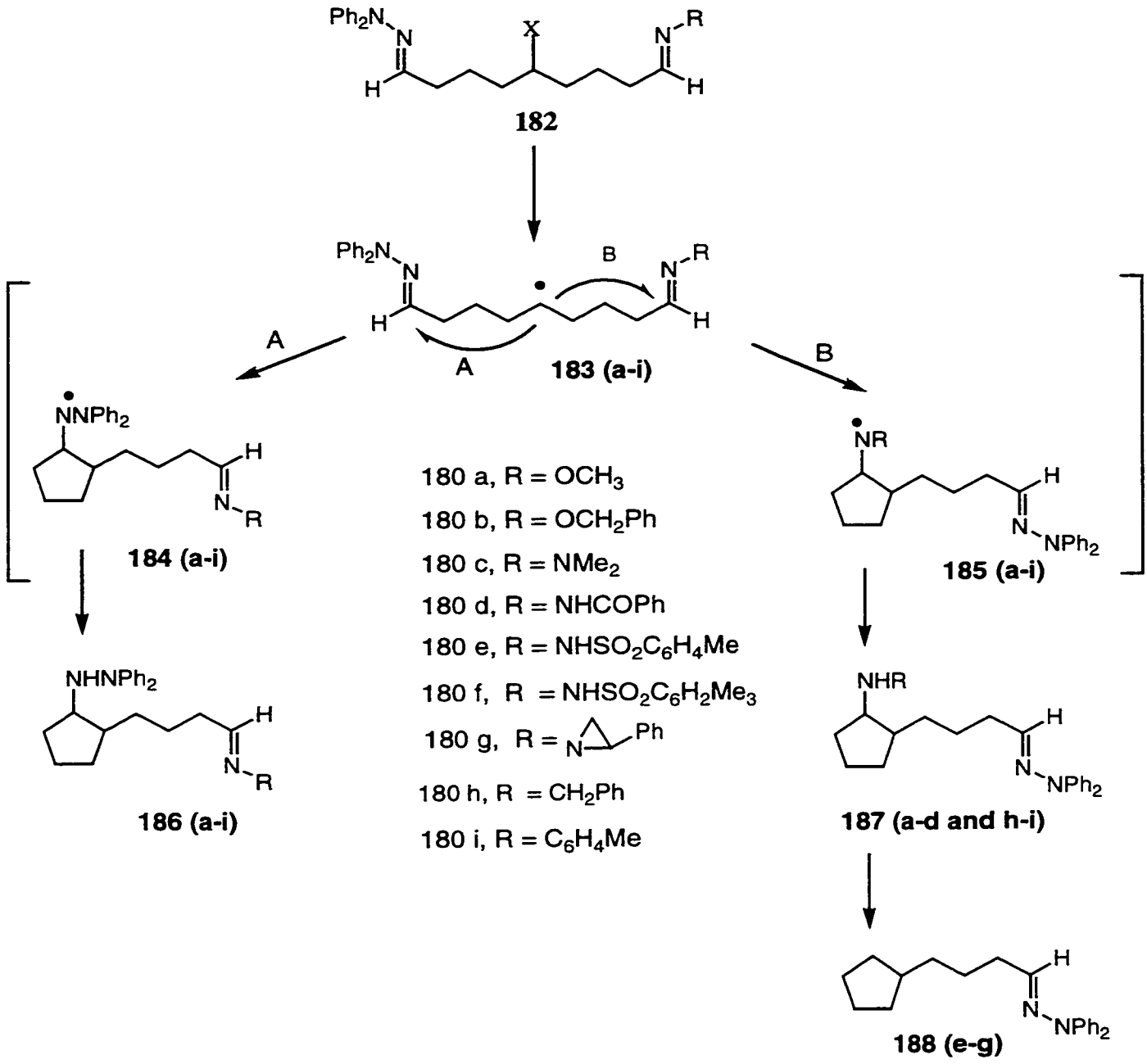
As seen in Scheme **53**, the initial radical generated from the precursor **182**, can partition between the 5-*exo* *N,N*-diphenylhydrazone (radical **184**) or 5-*exo* imine (imine, oxime, hydrazone, radical **185**) cyclization pathway with subsequent hydrogen abstraction to give final products **186** and **187**. In the case of the *N*-aziridinyl imine and mesitylenesulfonylhydrazone, radical **185** will undergo further expulsion of styrene or arylsulfonyl radical followed by nitrogen to give the monosubstituted cyclopentanes **188** as final products.

The rate constants can be calculated using the *N,N*-diphenylhydrazone rate constant (1.6×10^8 s^{-1}) based on the following equation.

$$k_b = k_a (P_b/P_a) \qquad \text{Eq.5}$$

Where $k_a = k_{cis} + k_{trans}$ (diphenylhydrazone) is the known rate constant and $k_b = k_{cis} + k_{trans}$ (oxime or other hydrazones) is the unknown rate constant for C=NR. P_b/P_a is the product ratio, which can be measured analytically.

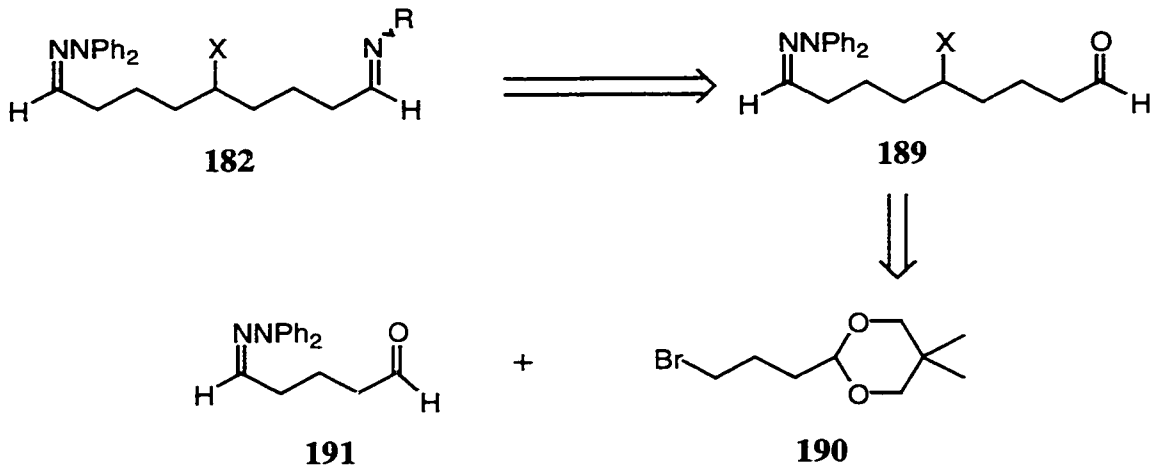
Scheme 53: Competitive *N,N*-Diphenylhydrazone-Imine Radical Cyclizations



2.4 Substrate Synthesis for Kinetic Studies

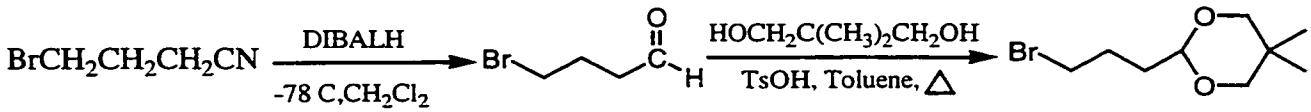
The retrosynthetic analysis of the required radical precursors is shown in Scheme **54**. As shown in the Scheme below, the synthesis of the intermediate **189** was required; this could be condensed with different H_2N-R to give the required "bisimine" systems of the internal clocks. The intermediate **189** can be prepared by Grignard addition of the precursor **190** to the aldehyde **191**.

Scheme 54: Retrosynthetic Analysis of the Radical Precursor.



The synthesis of the precursor **190** started with the diisobutylaluminium hydride (DIBALH) reduction of 4-bromobutyronitrile **192** at –78 °C to give 4-bromobutanal **193** in 80% yield[71]. Treatment of aldehyde **193** with neopentyl glycol and a crystal of *p*-toluenesulfonic acid in refluxing toluene overnight yielded the intermediate **190** in 82% yield[72] (Scheme **55**).

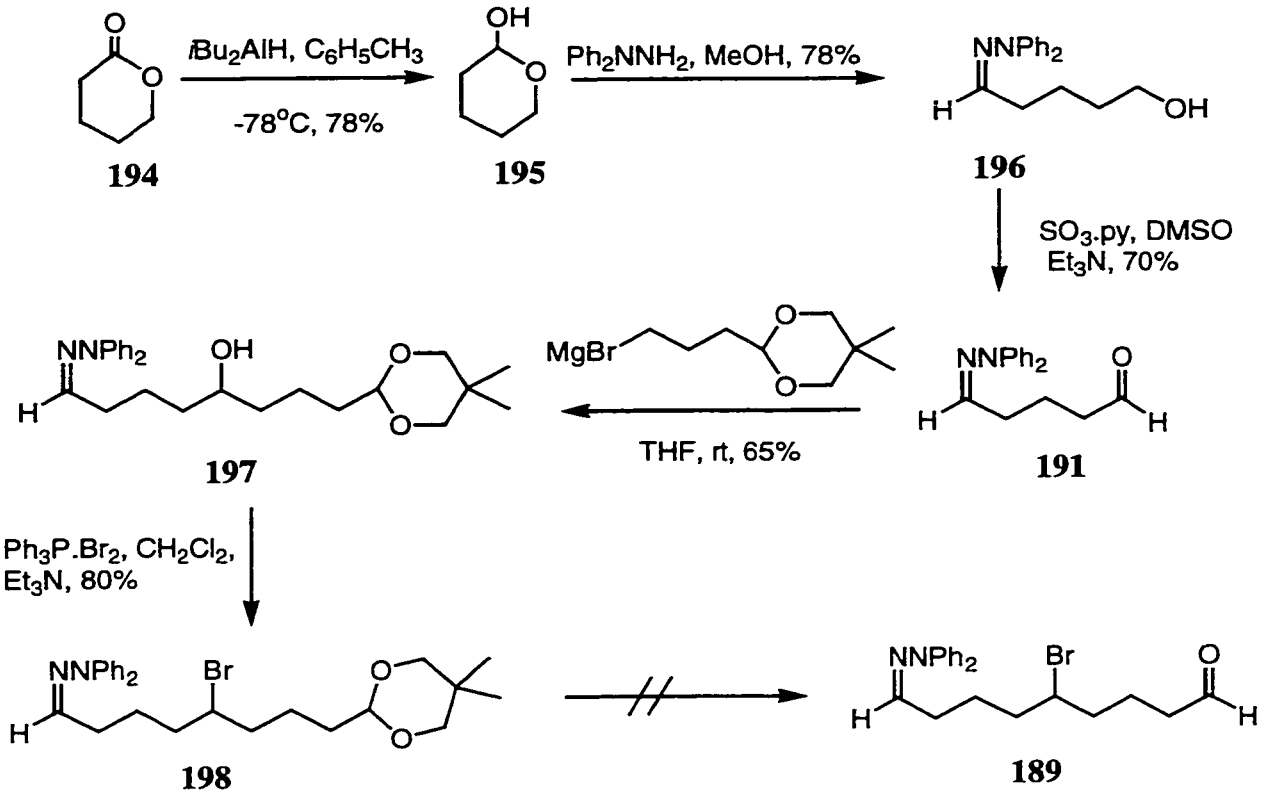
Scheme 55: Preparation of Precursor for Grignard Reagent



192 **193** **190**

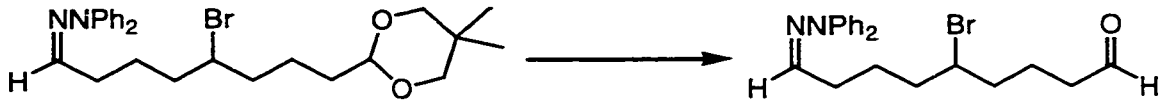
With one of the two major pieces in hand, we started our initial attempt to synthesize the aldehyde **189** as shown in Scheme **56**. The first step involved the reduction of commercially available δ-valerolactone **194** with DIBALH in toluene at –78 °C to give lactol **195** in 78% yield[73]. Treatment of the lactol **195** with one equivalent of Ph_2NNH_2 in MeOH at room temperature provided *N,N*-diphenylhydrazone **196** as a single geometric isomer in 80% isolated yield. A key spectral feature of this hydrazone is that the vinylic hydrogen (Ph_2N-N=<u>CH</u>CH_2R) appears as clean triplet at δ 6.5 ppm in ^1H NMR spectrum. Based on literature precedent[74] showing that hydrazones are formed predominantly as the *E* geometric isomer, compound **196** was assigned as the *E* hydrazone (with Ph_2N group *syn* to vinylic hydrogen). The oxidation of the resulting primary alcohol with SO_3.Py/DMSO/Et_3N as oxidizing agent provided the aldehyde **191** in 70-80% yield[75]. The *N,N*-diphenylhydrazone aldehyde **191** was treated with the Grignard reagent derived from compound **190** to afford secondary alcohol **197** in 65% yield. Treatment of alcohol **197** with triphenylphosphine dibromide in the presence of triethylamine gave the bromo compound **198** in 80% yield[76]. The use of Et_3N in this reaction was found to be necessary to ensure high yields. This is presumably to protect the hydrazone functionality from the HBr released during the course of bromination.

Scheme 56: Initial Synthetic Route for Radical Precursor



The next step in this synthesis involved the deprotection of the aldehyde, which proved to be quite challenging. As shown in the Table **2**, under milder conditions such as entries 1, 2 and 3, no reaction was observed. Increasing the strength of the acid (entries 4 and 5) did not improve the reaction. Harsher conditions such as in entry 6 and 7 resulted in decomposition of the starting material, indicating that under these conditions the *N,N*-diphenylhydrazone group was unstable. However, the reaction involving bromodimethylborane in CH_2Cl_2 at –78 °C (entry 8) gave the desired product in very low yield[77]. All the efforts to improve this yield were unsuccessful.

Table 3: Deprotection of 3,3-Dimethyl-1,2-Dioxane Group

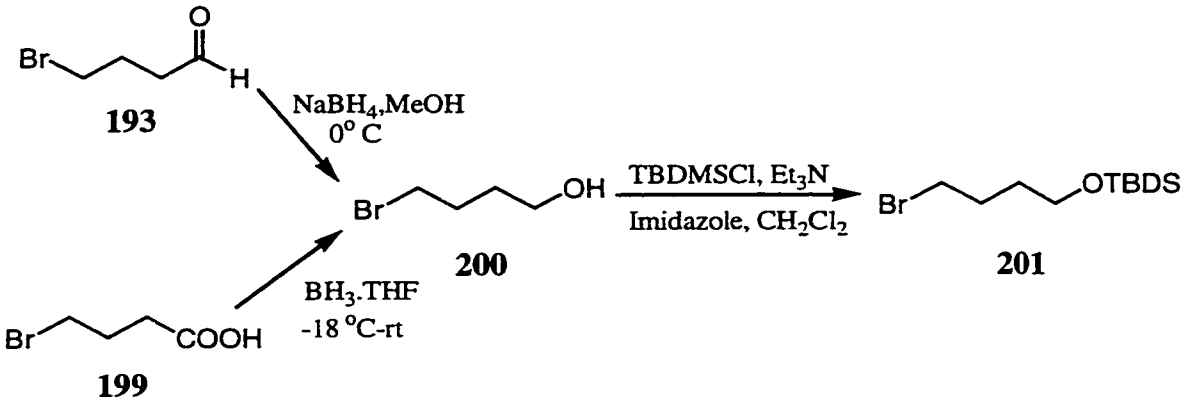


198 **189**

Entry	Conditions	Yield
1	PPTS, acetone,H_2O/rt-reflux	S.M.
2	AcOH/cat.-neat/rt	S.M.
3	10% HCl rt-reflux	S.M.-decomposition
4	TsOH/cat./rt.	S.M.
5	1M HCl, THF	S.M.
6	$TiCl_4$	Decomposition
7	$HClO_4$	Decomposition
8	Me_2BBr, -78° C, 4hr	10%
9	Me_2BBr, 0°C-rt.	Decomposition

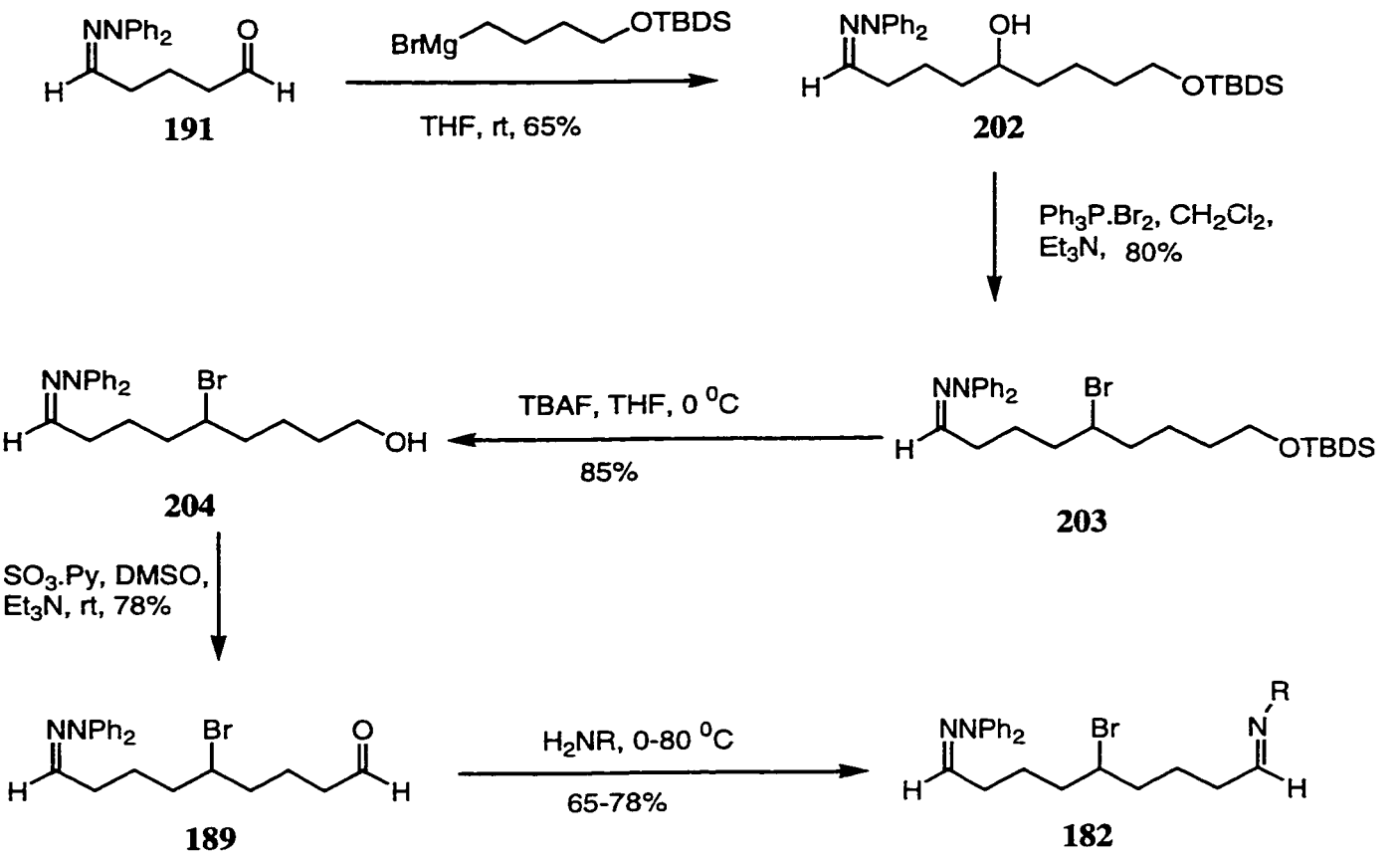
At this point we thought of modifying the precursor **189**, by oxidizing the aldehyde to alcohol and protecting the alcohol with TBDMS group, which would be easily removed without effecting the hydrazone. Reduction of the aldehyde **193** with sodium borohydride afforded the desired alcohol **200**, but the yield of the reaction dropped considerably on a large scale. Therefore, alcohol **200** was prepared by reduction of 4-bromobutyric acid **199** with borane[78] at –18 °C, in high yield (82%). This reaction could be repeated successfully on larger scales (25g of starting material). The alcohol **200** was protected with *t*-butyldimethylsilyl chloride in the presence of imidazole to give the protected bromo compound **201** in high yield[79] (Scheme **57**).

Scheme 57: Preparation of Modified Precursor for Grignard Reaction



Scheme **58** outlines the revised route to the aldehyde **189**, where precursor **190** was replaced with bromo compound **201**. The *N,N*-hydrazone aldehyde **191** prepared as in the previous procedure was treated with the Grignard reagent derived from 4-bromo-1-(*t*-butyldimethylsilyloxy)butane (**201**) to afford the secondary alcohol **202**. Treatment of the alcohol **202** with $PPh_3.Br_2$ gave the bromide **203**. The deprotection of the *t*-butyldimethylsilyl group was achieved with tetrabutylammonium fluoride[80] to give the primary alcohol **204**. Of several oxidants examined the sulfur trioxide-pyridine reagent was the only reagent that generated the aldehyde **189** cleanly without concomitant decomposition products. This oxidant was also required for the preparation of the aldehyde **191** from the corresponding primary alcohol. The last step required for the preparation of the radical precursor was the condensation of the bromoaldehyde **189** with appropriate amino derivatives to afford the desired bis-imine compounds (Scheme **58**).

Scheme 58: Revised Route to Substrate Synthesis



a. R = OMe
b. R = OBn
c. R = NMe_2
d. R = NHCOPh
e. R = $NHSO_2C_6H_4Me$
f. R = $NHSO_2C_6H_2$-2,4,6-Me_3
g. R = 

Table **4** summarizes the results of the condensation of different amino derivatives to give the corresponding bis imine compounds.

Table 4: Condensation of Aldehyde With Hydrazines, Oxime Ethers and Amines

189 **182**

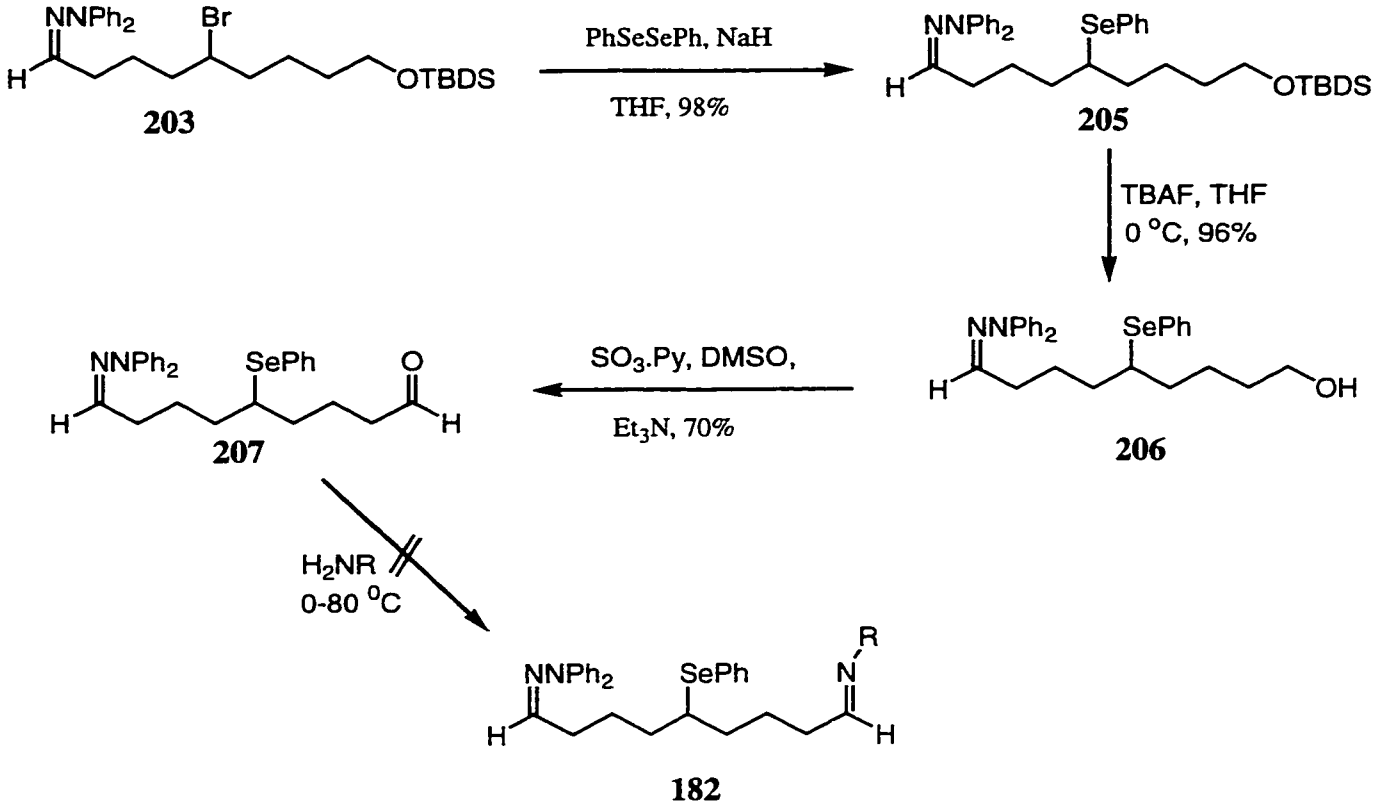
Entry	R	Compound	Yield (%)
1	$-OCH_3$	182 a	63
2	$-OCH_2Ph$	182 b	62
3	$-N(CH_3)_2$	182 c	75
4	-NHCOPh	182 d	71
5	$NHSO_2C_6H_4Me$	182 e	65
6	$NHSO_2C_6H_2Me_3$	182 f	50
7	2-Phenyl-*N*-aziridinyl	182 g	60
8	$-CH_2Ph$	182 h	Complex mixture
9	$-C_6H_4CH_3$	182 i	Complex mixture

Oxime ethers **182a** and **182b** were obtained in good yields by condensing aldehyde **189** with corresponding alkoxy amine hydrochloride salt in ethanol, using pyridine to get the free amine from the salt[81]. *N,N*-dimethylhydrazine was condensed in CH_2Cl_2 to give bis-hydrazone **182c**. Under similar reaction conditions benzoylhydrazine

reacted to give the desired product **182d** contaminated by some unidentified product, which could not be separated. However, changing the solvent from CH_2Cl_2 to toluene resulted in the precipitation of desired bis-hydrazone **182d** as sole product[41]. Arylsulfonylhydrazones **182e** and **182f** were prepared by condensing the corresponding hydrazine in methanol at room temperature. Bis-hydrazone **182g** was obtained by reacting aldehyde **189** with a pentane solution of 2-phenylaziridine[37] at 0 °C. Compounds **182a-d** were very stable and can be stored in freezer for a long time without any decomposition. Bis-hydrazones **182e and 182f** were relatively unstable and were used immediately after purification. However, the condensation of various amines with aldehyde **189** was not so clean and purification was not possible due to further decomposition.

A literature survey indicated that in the case of imine systems, phenylselenides have been preferred over bromides as radical precursors. This can be due to the reactivity of bromides towards the imino group present in the precursor and towards the amino group of the intermediate as well. Therefore to replace Br- with PhSe- group in bis-imine systems, compound **203** from Scheme **59** was treated with diphenyl diselenide and sodium hydride[82] to afford compound **205** in 96% yield. The resulting compound was treated with tetrabutylammonium fluoride to deprotect the *t*-butyldimethylsilyl group to yield the primary alcohol **206** in 96% of isolated yield. Oxidation of the free alcohol **206** was achieved with sulfur trioxide/pyridine complex in the presence of triethylamine in DMSO to afford aldehyde **207** in good yield (70%). Unfortunately the condensation of aldehyde **207** with different amines was also unsuccessful. Imines formed by condensation of *p*-toluidine and benzylamine were reported to be relatively stable and these have been purified also. In our case these imines were so unstable that they rapidly decomposed before use.

Scheme 59: Synthesis of Phenylselenide Precursor for Bis-Imine Systems

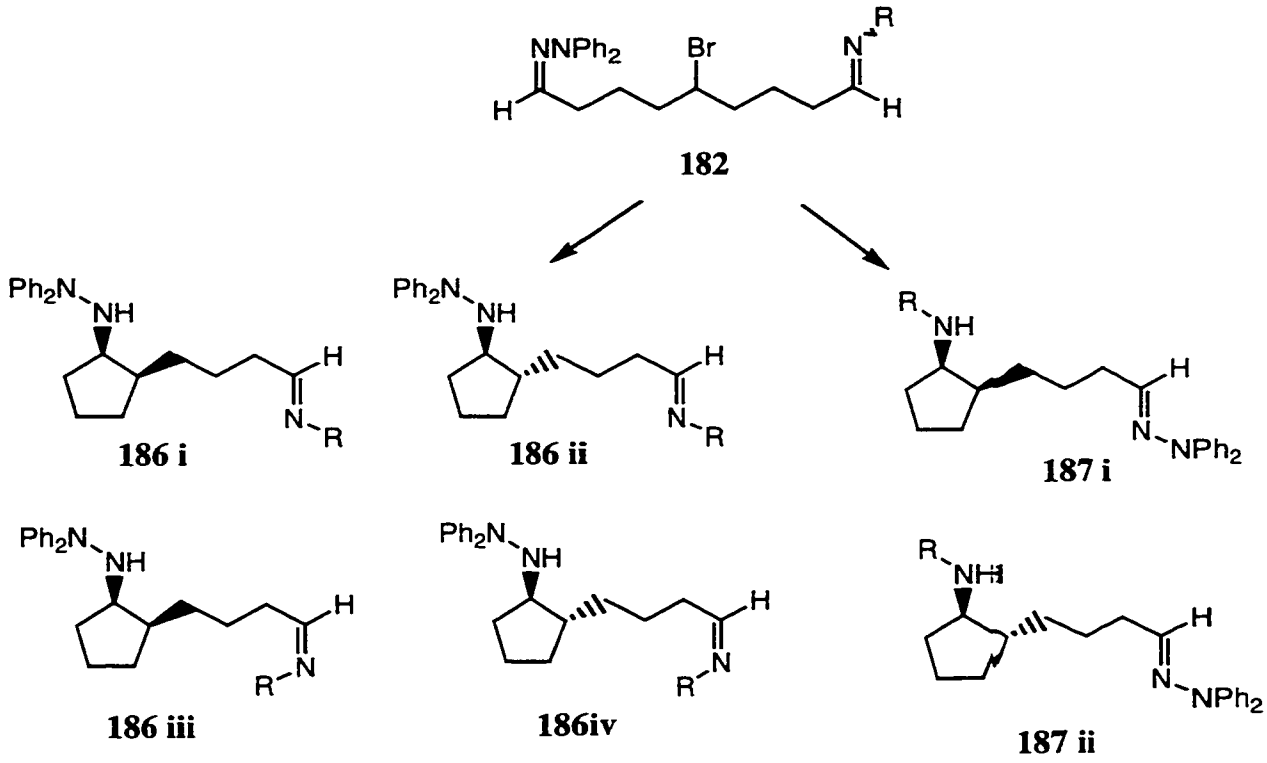


2.5 Result and Discussion

Faced with this problem, we turned our attention towards the cyclization studies of the prepared bis imine systems **182a-g**. Compounds **182a-g** were dissolved individually in refluxing benzene (0.05 M) and treated with tributytin hydride (1.1 eq.) and azobis(isobutyronitrile) (AIBN) (10-15 mol %) under syringe pump conditions (rate of addition was 1 mL per hour) and refluxed for 30 min. and then cooled to room temperature. TLC analysis of the crude reaction mixture revealed the complete consumption of the starting material with formation of some new products.

These compounds were expected to undergo 5-*exo* cyclizations to give products **186** and **187**, including *cis/trans* isomeric pairs. "Bis-imine" systems **182** b-g were obtained as inseparable mixtures of *syn* and anti isomers and these mixtures were used in cyclization studies. As a result, along with *cis/trans* isomeric pairs, *syn* and *anti* isomers were also expected for cyclopentanes **186** (Scheme **60**). Therefore four to six different products were expected from a single cyclization reaction.

Scheme 60: Expected Products from Competition Studies

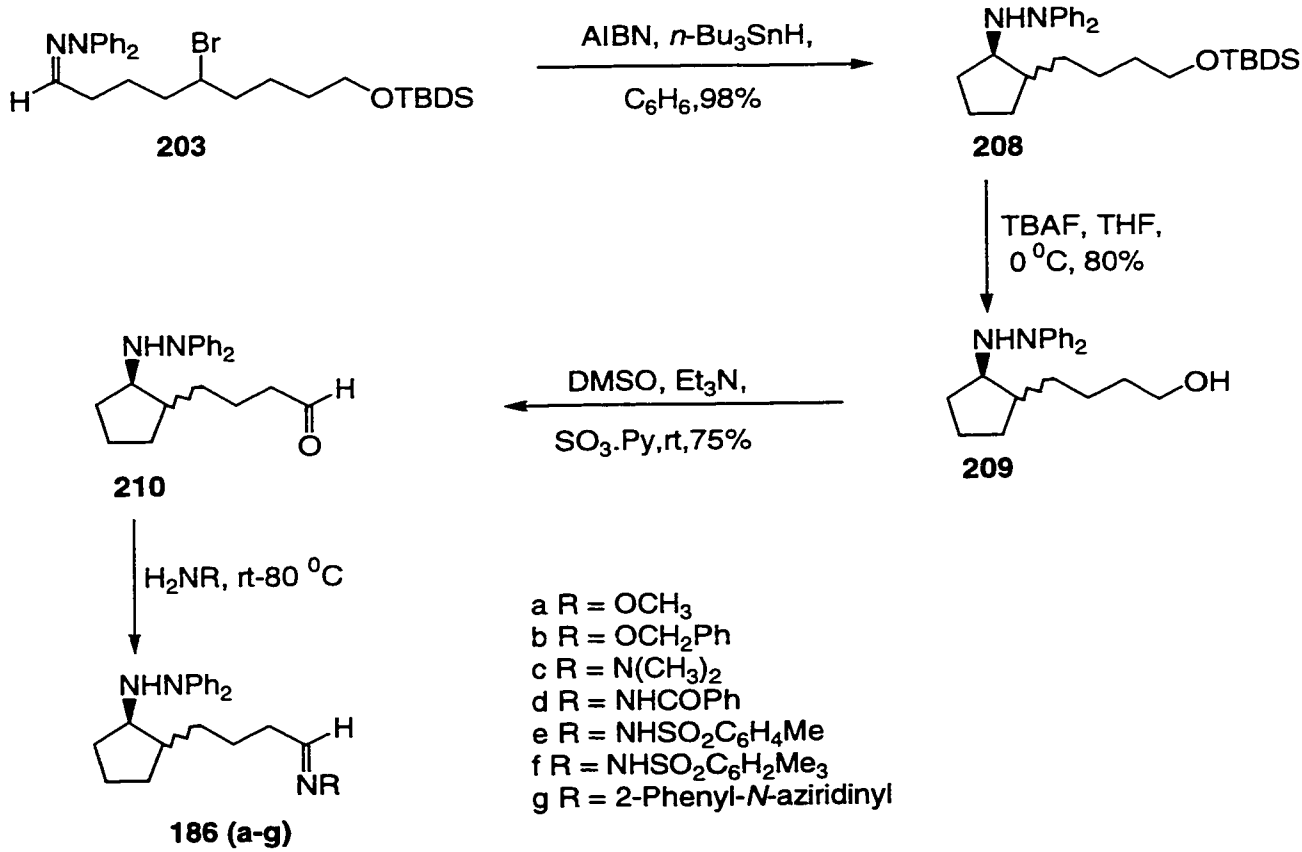


After completion of the reaction, the reaction mixture was dissolved in diethyl ether and stirred vigorously at room temperature for half an hour with a saturated aqueous solution of potassium fluoride to remove most of the organostannane residue.

2.6 Synthesis of Reference Compounds

^{1}H NMR analysis of these crude reaction mixtures was used to calculate the product ratios. Due to potential for *cis/trans* and *syn/anti* isomerism, the ^{1}H NMR of the crude mixtures were complex. In case of compounds **182a-c**, the anticipated signals for products **186** and **187** could be assigned easily, due to diagnostic signals of $-OCH_3$, $-OCH_2Ph$ and $-N(CH_3)_2$ groups respectively. However, the product assignment was relatively difficult for compounds **182d-g**, where no diagnostic signal was available. Therefore a series of authentic samples and closely related models of the expected products were prepared separately. These models were expected to provide accurate spectral details in various series for the direct comparison of the synthetic and cyclized samples.

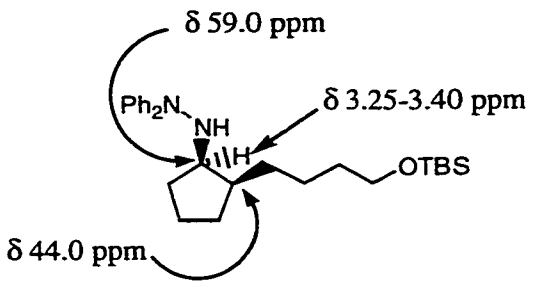
Scheme 61: Preparation of Reference Compounds 186 a-g



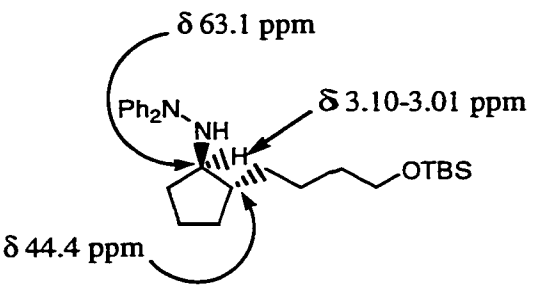
Our synthetic route to amino cyclopentanes **186 (a-g)** is shown in Scheme **61**. Compound **203**, prepared as shown in Scheme **58**, was subjected to tributyltin hydride conditions to give cyclic product **208** as a mixture of *cis* and *trans* isomers. The *t*-butyldimethylsilyl group was removed by treatment with tetrabutylammonium fluoride in THF to give the cyclic alcohols **209** in good yield. Oxidation of the resulting alcohols **209** with sulfur trioxide.pyridinium complex resulted in the aldehyde **210**, which decomposed on silica gel used for column chromatography. Therefore an ether solution of the aldehydes were filtered quickly through a silica gel pad and the crude product was used for the condensation with different amines, to give cyclopentanes **186 a-g** in good yields.

Relative stereochemistry (*cis* or *trans*) of the isomers was established by analyzing the ^{13}C NMR and ^{1}H NMR of the products. Based on previous observations in our laboratory and literature precedent[83], the isomer with the higher field methine signals in the ^{13}C NMR spectrum can be assigned as having the two substituents *cis* to each other. In order to utilize this technique to assign the stereochemistry, it is essential to have both isomers in order to compare the chemical shifts. The radical cyclization of the compound **203** gave a 2:1 mixture of readily separable diastereomers, thus we were able to measure the ^{13}C NMR and ^{1}H NMR spectra of both. In a similar manner the proton signal for hydrogen attached to carbon with the $-NHNPh_2$ group at lower field was assigned for *cis* isomer (**208 i**) and the higher field signal for *trans* isomer (**208 ii**). The positions of these diagnostic signals were retained in the final products **186 a-g**, formed after further manipulation of the side chain of compounds **208**. Figure **1** lists the key NMR signals that were used to assign the relative stereochemistry.

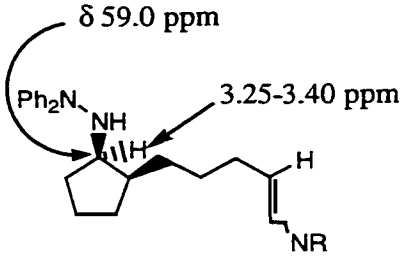
Figure 1: Assignment of Stereochemistry



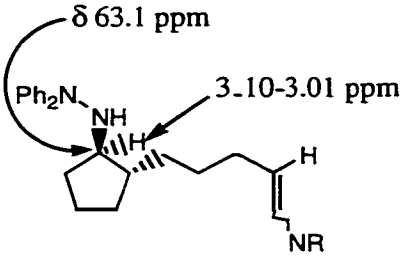
208 i



208 ii



186 i

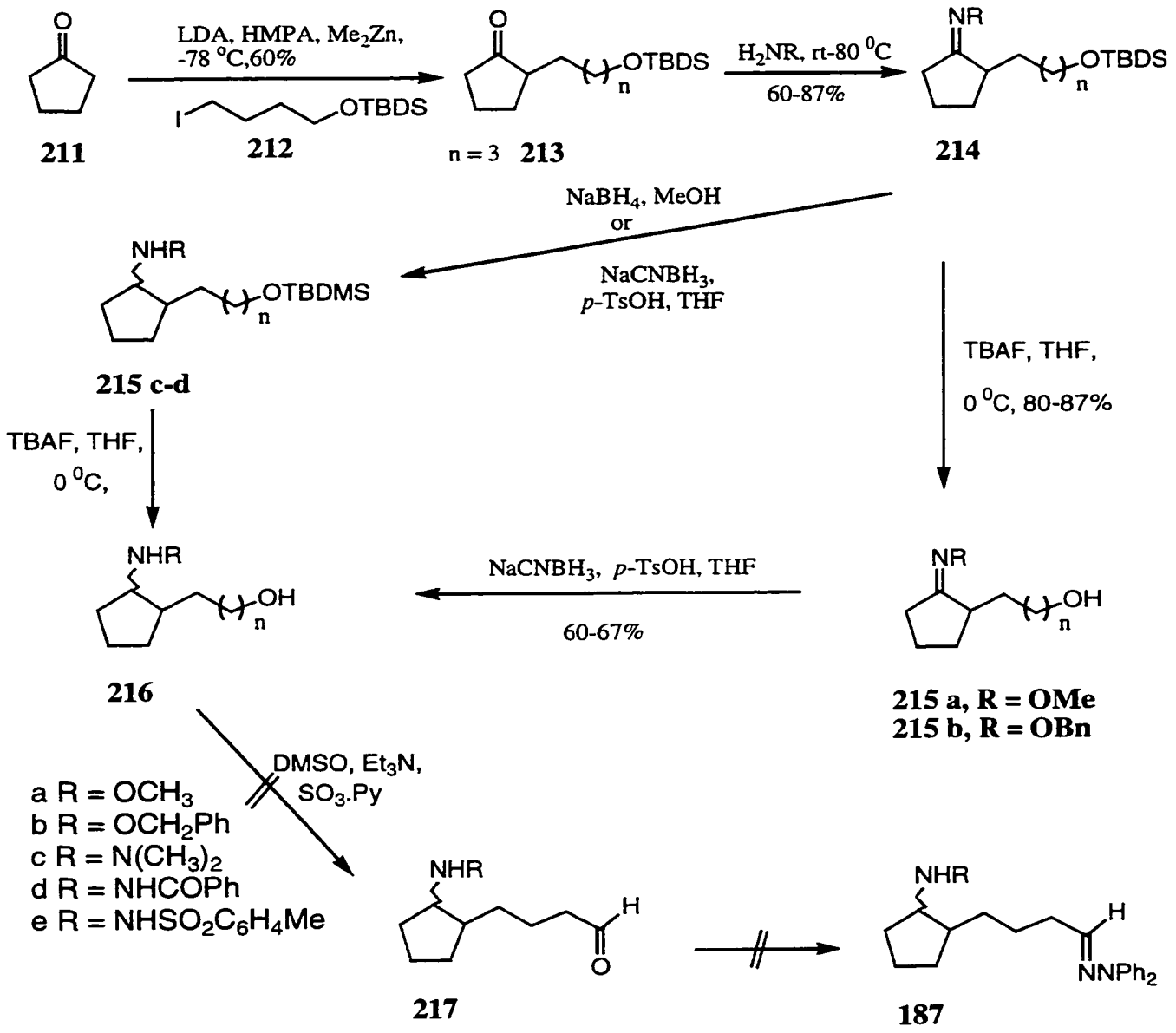


186 ii

Scheme **62** reveals the attempted synthetic route to compounds **187 a-g.** The lithium enolate generated from cyclopentanone **211** was alkylated with 4-iodo-1-(*t*-butyldimethylsilyloxy)butane **212** in the presence of dimethylzinc and HMPA to give compound **213**[84]. Condensation of the compound **213** with hydrazines and oximes gave the corresponding hydrazones and oxime ethers **214** respectively. Reduction of the compounds **214a-g** were achieved with sodium borohydride or sodium cyanoborohydride[85] to give the corresponding aminocyclopentanes **215** as mixture of *cis* and *trans* isomeric pairs in good yields. Removal of the *t*-butyldimethylsilyl group was achieved with tetrabutylammonium fluoride in THF to give the free alcohols **216.** In the case of compounds **214a** and **214b**, the deprotection was achieved before reduction of the imine bond. The oxidation of compounds **216** proved to be a challenging step. Various experimental conditions including the very mild SO_3.pyridinium complex were employed without success. As a result the condensation step leading to the compounds **187 a- g**

could not be achieved. However, the spectral data of the closely related compounds **216a-e** helped in the accurate assignment of the signals for the products **187 a-g** including their *cis* and *trans* isomers.

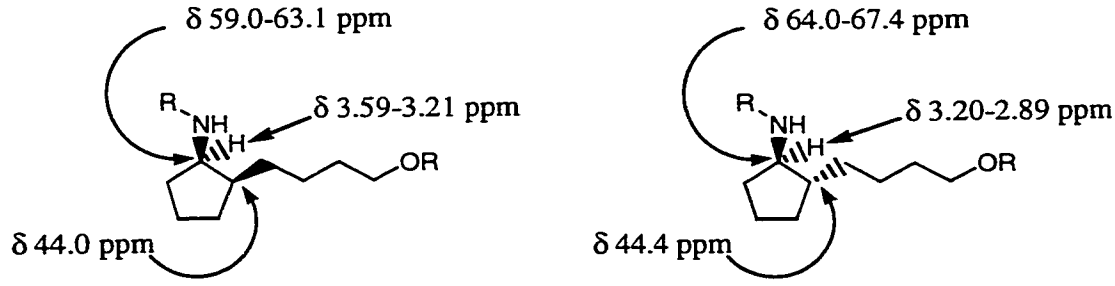
Scheme 62: Preparation of Reference Compounds 216 a-f



The cyclopentanes **215** formed by reduction of imines **214** a-g were obtained as separable mixture of *cis* and *trans* isomers. Thus relative stereochemistries of the cyclopentanes **215 a-g** were determined in a similar fashion as was achieved for compound **208** in Scheme **61.** The compounds with the higher field methine carbon signals in the ^{13}C NMR spectrum were assigned as the *cis* isomers. The lower field proton signals in the ^{1}H NMR spectra for hydrogen attached to methine carbon bearing – NHR group were assigned to the *cis* isomers. The shift differential of approximately 0.3 ppm in ^{1}H NMR and about 4.3 ppm in ^{13}C NMR spectrum was a consistent pattern among the isomeric pairs.

As seen in the case of compounds **186** and **208**, the side chains in the two compounds have different groups at the terminal end, yet the positions of the diagnostic signals for both compounds are the same in ^{13}C NMR and ^{1}H NMR spectra. In a similar manner, diagnostic signals for reference compounds **216 a-e** were expected to have the same positions as those for compounds **187 a-e**. Therefore data for reference compounds **216 a-e** were used to assign the spectra for compounds **187 a-e.**

Figure 2: Assignment of Stereochemistry for Aminocyclopentanes 216 a-e



216 i **216 ii**

These model systems provided spectral details in the various series for the direct comparison of the synthetic and the cyclized compounds. A comparison of ^{1}H NMR spectra of the cyclized crude product from compound **182** with these reference compounds provided accurate product ratios for the compounds **186** and **187**, necessary to calculate the rate constants (Fig **3**).

The first spectrum in Fig **3** is of the starting bis-imine system **182 b** and second is of the crude product from the tin hydride reaction (Fig. **3a**). The third spectrum is of the expected compound **186 b** from cyclization onto *N,N*-diphenyl hydrazone and the fourth spectrum is of the closely related model **216 b** of the expected product **187 b** from cyclization onto the oxime ether side (Fig **3b**). As can be seen from the crude spectrum, two $-OCH_2Ph$ signals are present. The signal at lower field (5.09-4.99 ppm) is due to product **186** and the signal at higher field (4.68-4.62) is due to product **187**. Additional confirmation of these signals was obtained by comparison with spectra 3 and 4 (Fig. **3b**). The ratio of *N,N*-diphenylhydrazone and *O*-benzyl oxime ether cyclized products was determined by integrating the two $-OCH_2Ph$ signals in the spectrum of the crude mixture. Product ratios for cyclization products from **182 a, c, d-g** were calculated in similar a manner. After calculating the product ratios, these crude products were purified using column chromatography to separate different compounds. Under these tin hydride formed conditions, uncyclized products from the direct quenching of the initial radical before cyclization were not detected. Thus these radicals were partitioned between the 5-*exo*-*N,N*-diphenylhydrazone or 5-*exo* imine cyclization pathways. The product ratios for the competitive 5-*exo* imine cyclizations, along with *cis/trans* ratio of the individual products are listed in the Table **5**.

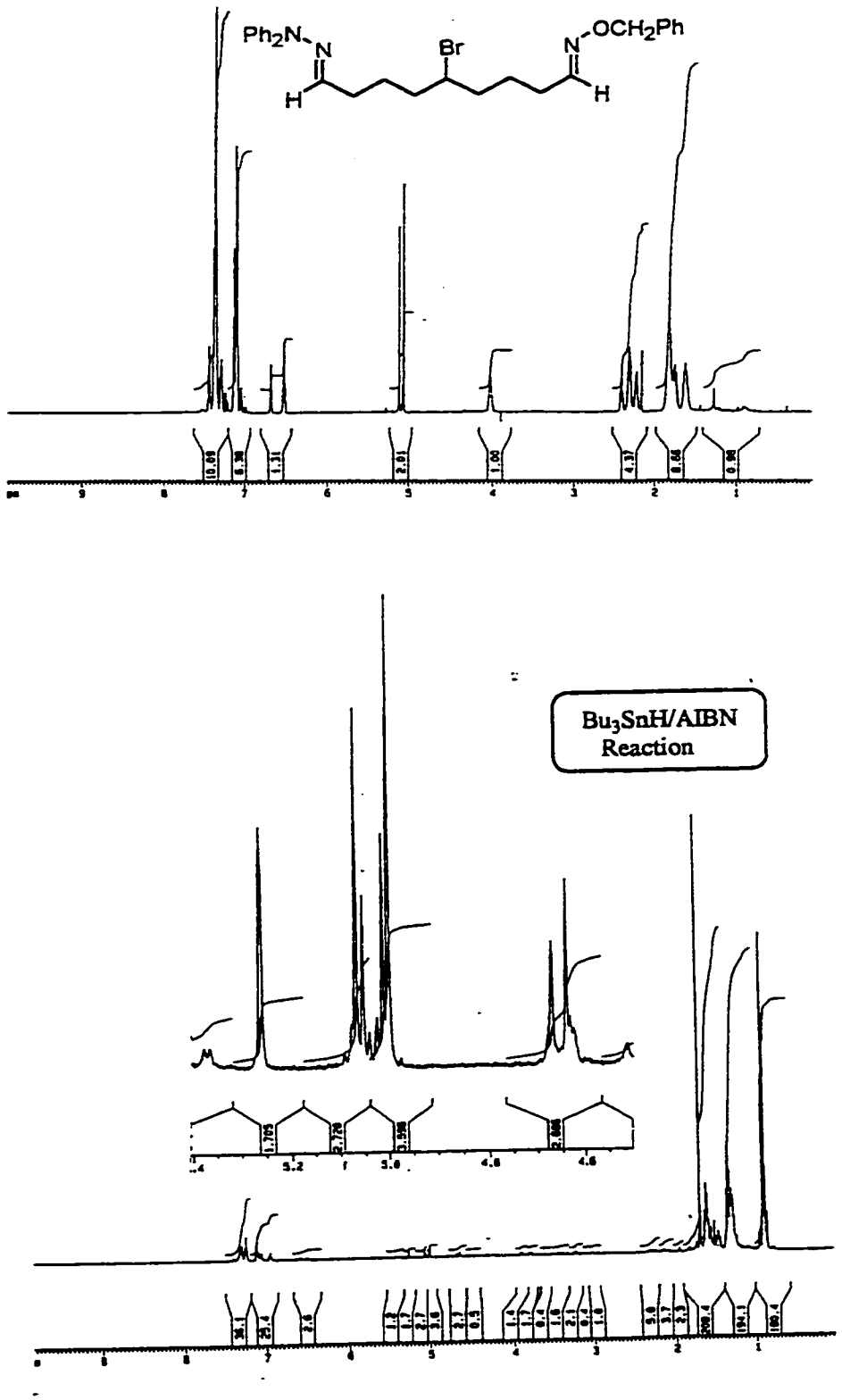


Figure 3 (a): Competition Cyclization of Substrate 186b under Free-Radical Conditions

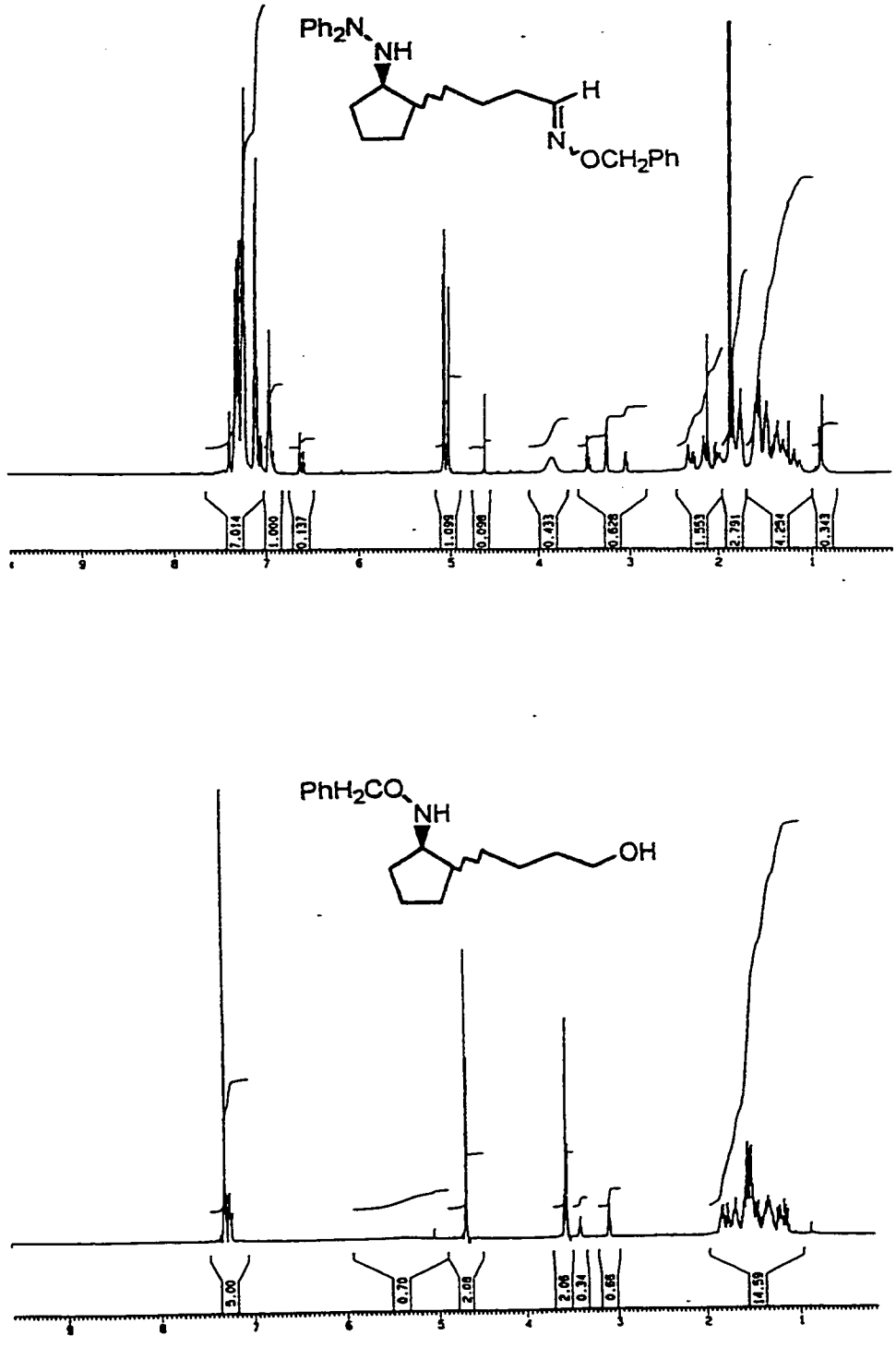
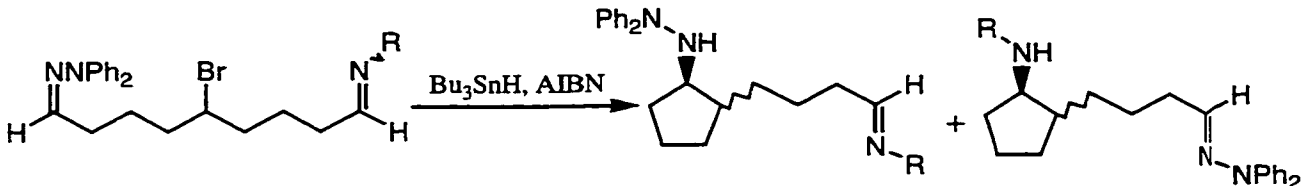


Figure 3 (b): Reference Compounds for Cyclization of Substrate 186b under Free-Radical Conditions

Table 5: Product Ratios for 5-*Exo* Imine Cyclizations

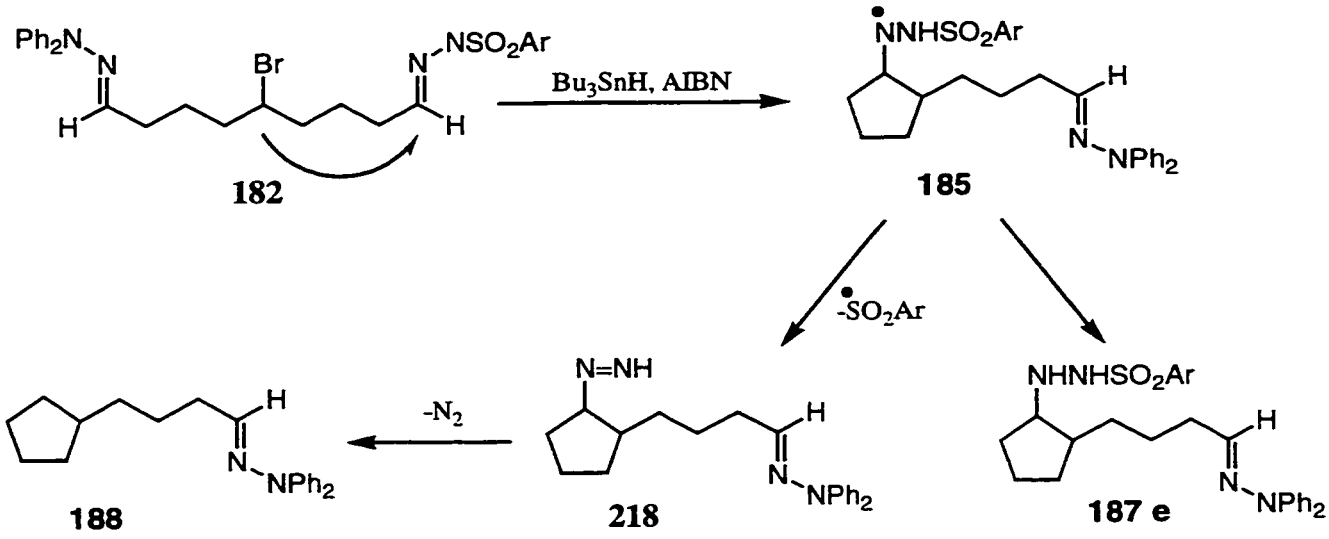


182 a-g **186 a-g** **187 a-e**

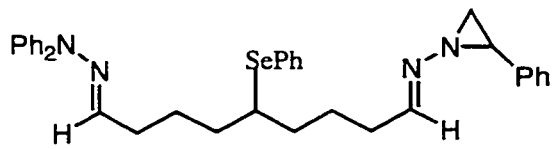
Entry	**Compound** 182	**Ratio** 186:187	***Cis/trans* Ratio for** 187
1	a. R = OMe	4:1	1.6:1
2	b. R = OBn	2.5:1	1.7:1
3	c. R = NMe_2	3:1	2:1
4	d. R = NHCOPh	1:1	3.4:1
5	e. R = $NHSO_2C_6H_4Me$	1:0	
6	f. R = $NHSO_2C_6H_2Me_3$	1:0	
7	g. R = 2-Phenyl-*N*-aziridinyl	Complex MIxture	

In the case of entries 5 and 6, the only product obtained was the one from cyclization onto the *N,N*-diphenylhydrazone side. Based on previous observations by Kim *et al.*[39] for both of these systems, it was expected that product **185** formed after cyclization onto the arylsulfonylhydrazone side would expel the arylsufonyl radical ($^{\bullet}SO_2Ar$) to give the azo compound **218.** Subsequent loss of nitrogen will generate the cyclopentenyl radical, and ultimately a monosubstituted cyclopentane **188** will be the final product. An independent experiment in our laboratory has shown that the rate of expulsion of the arylsulfonyl radical is much slower in the case of entry 5 and product resulting from quenching of the radical was also expected. Careful analysis of all the compounds obtained after column chromatography showed no indication of either of the expected compounds (**187 e and 188 e-f**).

Scheme 63: Decomposition Pathway for Arylsulfonylhydrazones



In a similar manner, the radical formed after cyclization onto an *N*-aziridinyl imine can expel styrene and nitrogen to give a substituted cyclopentane as one of the two expected products. The competition between *N,N*-diphenylhydrazone and *N*-aziridinyl imine gave a complex mixture and the ^{1}H NMR spectrum of the crude mixture was very hard to interpret. Initially, failure of this experiment was attributed to the presence of the bromine substituent in radical precursor **182g**, which can undergo thermal *N*-alkylation and other reactions under thermal conditions. However, reliable data could not be obtained even when the same reaction was performed under photochemical conditions or when a selenide radical precursor **181b** was employed.

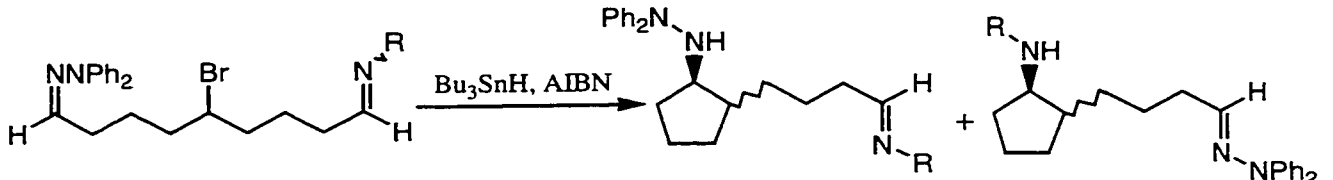


181b

2.7 Calculation of Rate Constants

After determining the product ratios, the rate constants for different imine systems were calculated using the equation **5** shown on page **44**. We were able to measure product ratios from *N,N*-diphenylhydrazone and other imine cyclizations as well as the *cis* and *trans* product ratios from the ^{1}H NMR spectra of the crude reaction mixtures. Therefore, we could then calculate the *cis* and *trans* 5-*exo* cyclization rate constants for different imines (other hydrazones and oxime ethers). These data are given in the Table below. In the case of arylsufonylhydrazones the rate constants are estimated, because compounds expected from sulfonylhydrazones were not detected and the only products isolated were the cyclic hydrazines from *N,N*-diphenylhydrazones.

Table 6: Determination of 5-*Exo* Hydrazone and Oxime Ether Cyclizations Rate Constants



182 a-g **186 a-g** **187 a-e**

Entry	**Compound**	$k_{C=NR}$ s^{-1}	$k^{cis}_{C=NR}$ s^{-1}	$k^{trans}_{C=NR}$ s^{-1}
1	R = OMe	4.0×10^7	2.4×10^7	1.5×10^7
2	R = OBn	6.4×10^7	4.0×10^7	2.4×10^7
3	R = NMe_2	5.3×10^7	3.5×10^7	1.8×10^7
4	R = NHCOPh	1.6×10^8	1.2×10^8	$0.4 \times 10^{8-}$
5	R = $NHSO_2C_6H_4Me$	$<1.0 \times 10^7$		
6	R = $NHSO_2C_6H_2Me_3$	$<1.0 \times 10^7$		

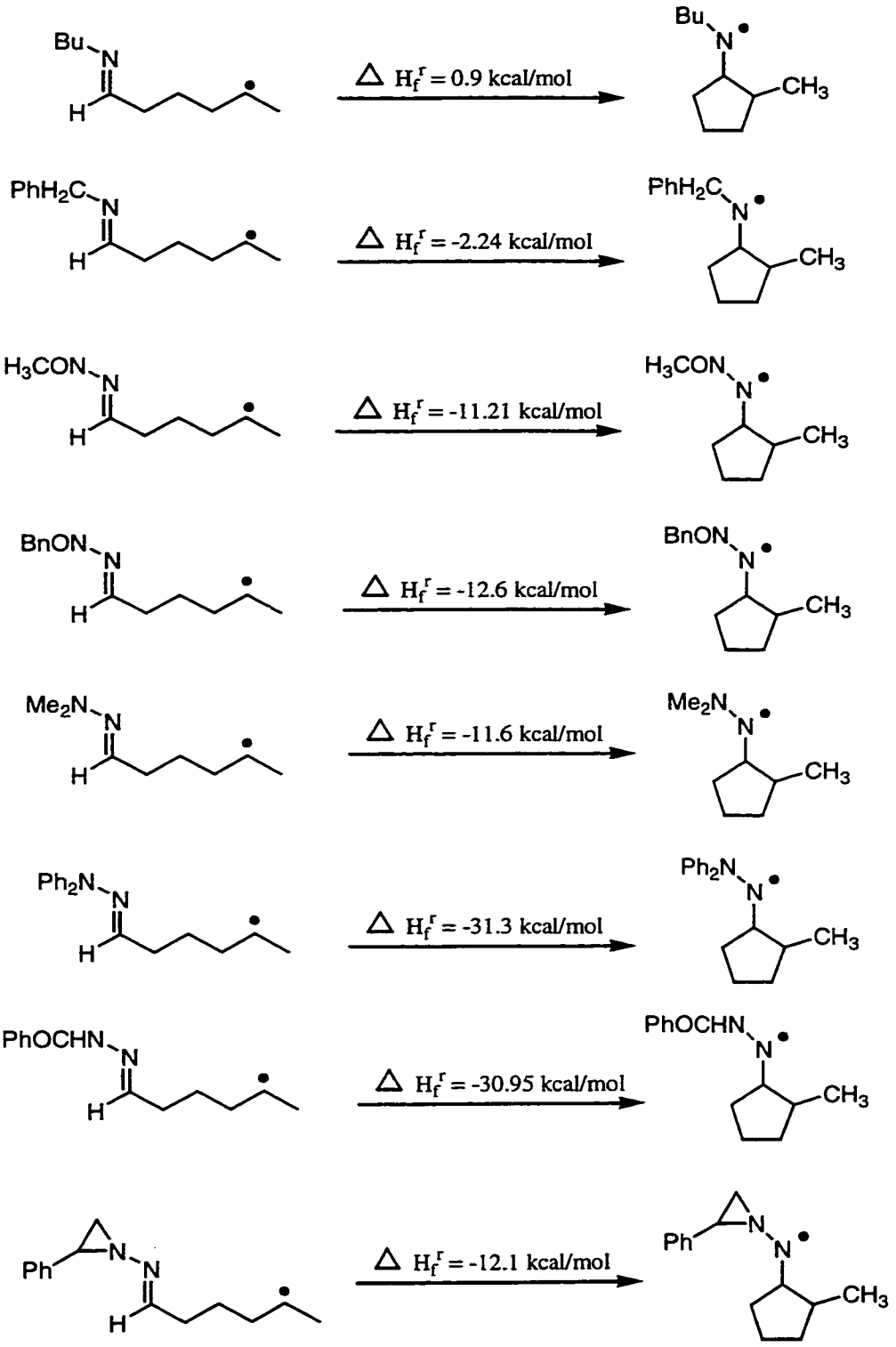
2.8 Calculations of ΔHf° for Radical Cyclizations onto C=N Systems

As seen in Table **6** the rate constants for secondary radical cyclization onto –C=NR bonds of different hydrazones and oxime ethers are approximately 200 times faster than those for corresponding 5-*exo* cyclization onto alkenes. Unfortunately the exact rate constants for cyclization onto *N*-aziridinyl imine and other simple imines could not be calculated due to the complex mixture obtained from our bis-imine system. Yet we expected, that due to the presence of C=NR bond in these systems, the rate of cyclizations should not be less than that of simple alkenes. To further explore the reactivities of these systems, we performed calculations at the AM1-UHF level[86]. The results of these calculations on the heat of formation for radical cyclizations onto various C=N containing systems are shown in Table **7**.

As shown in the first entry, radical cyclization onto a simple butyl imine was found to be approximately thermoneutral (0.9 kcal/mol). This was somewhat surprising since the corresponding alkene cyclizations are approximately 10 kcal/mol exothermic. The reason for this can be due to the fact that the C=N bond is believed to be ca. 10 kcal/mol stronger than the C=C bond. The cyclization onto a benzyl imine was found to be slightly exothermic (-2.24 kcal/mol), whereas the cyclizations onto hydrazones are strongly exothermic (-11.6 to –31.3 kcal/mol). Similar exothermicity was noted for the oxime ether substrates shown in entries 4 and 5 of the Table **7**. These calculations demonstrate the beneficial influence of R_2N and RO substituents on reaction exothermicity for radical cyclizations.

In fact the results from these calculations correspond to the rate constants calculated in our studies. For example, the cyclizations onto *N,N*-diphenylhydrazone (-31.3 kcal/mol) and *N*-benzoylhydrazone (-30.95 kcal/mol) were found to be highly exothermic reactions and the rate constants for these systems were determined to be the highest ($1.6 \times 10^8 s^{-1}$). Similarly the heat of formation for methyl oxime, benzyl oxime and *N,N*–dimethylhydrazone cyclizations are very close (-11.2, -12.6 and –11.6 respectively),

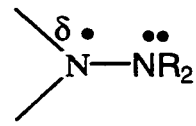
Table 7: Heat of Formation Calculations for Radical Cyclizations onto C=N Containing Systems



and this is also reflected in the relatively small difference in the rate of cyclization for these systems ($4.0x10^7$, $6.4x10^7$, $5.3x10^7$ s^{-1}, respectively). Based on these observations, we expected that the rate constant for imines should be slightly lower than those of oximes or hydrazones, whereas the rates for *N*-phenylaziridine hydrazone should be close to that for *N,N*-dimethylhydrazone. The cyclization onto an *N*-phenylaziridine hydrazone was found to be less exothermic than onto the *N,N*-diphenylhydrazone.

While our research was in progress, Kim *et al.* determined rate constants[87] for primary alkyl radical cyclization onto *N*-aziridinyl imines at 25 °C ($2.5 \times 10^8 s^{-1}$), which was slightly higher than that of *N,N*-diphenyl hydrazone (1.6×10^8 s^{-1}) established from our research. As mentioned earlier, in the phenylaziridine system, initial cyclization onto hydrazone is followed by further extrusion of nitrogen and styrene to form the cyclopentane. In view of the high rate constant for phenylaziridine system, initial cyclization, followed by ring opening may mimic a "concerted process", to be the key driving force to make this cyclization much more faster than the calculated value. The same group measured the rate of primary radical cyclization onto the C=NR bond of a benzyl imine[88](6×10^6 s^{-1}). These results also correspond to the results from heat of formation calculations performed in our laboratory.

The following section compares 5-*exo* hydrazone and oxime ether cyclization rate constants determined in this study with those reported for imines and other systems at 80 °C. As seen in the Table **8**, the increased cyclization rate of all the imine systems compared to unsubstituted alkenes is a consequence of the polarization of the –C=NR bond and the increased stability of the substituted nitrogen radical. Naturally, the nitrogen stability varies with the attached group. The second nitrogen present in the hydrazone and the oxygen in oximes are likely involved in a two center three electron bond with the developing nitrogen center radical during cyclization.

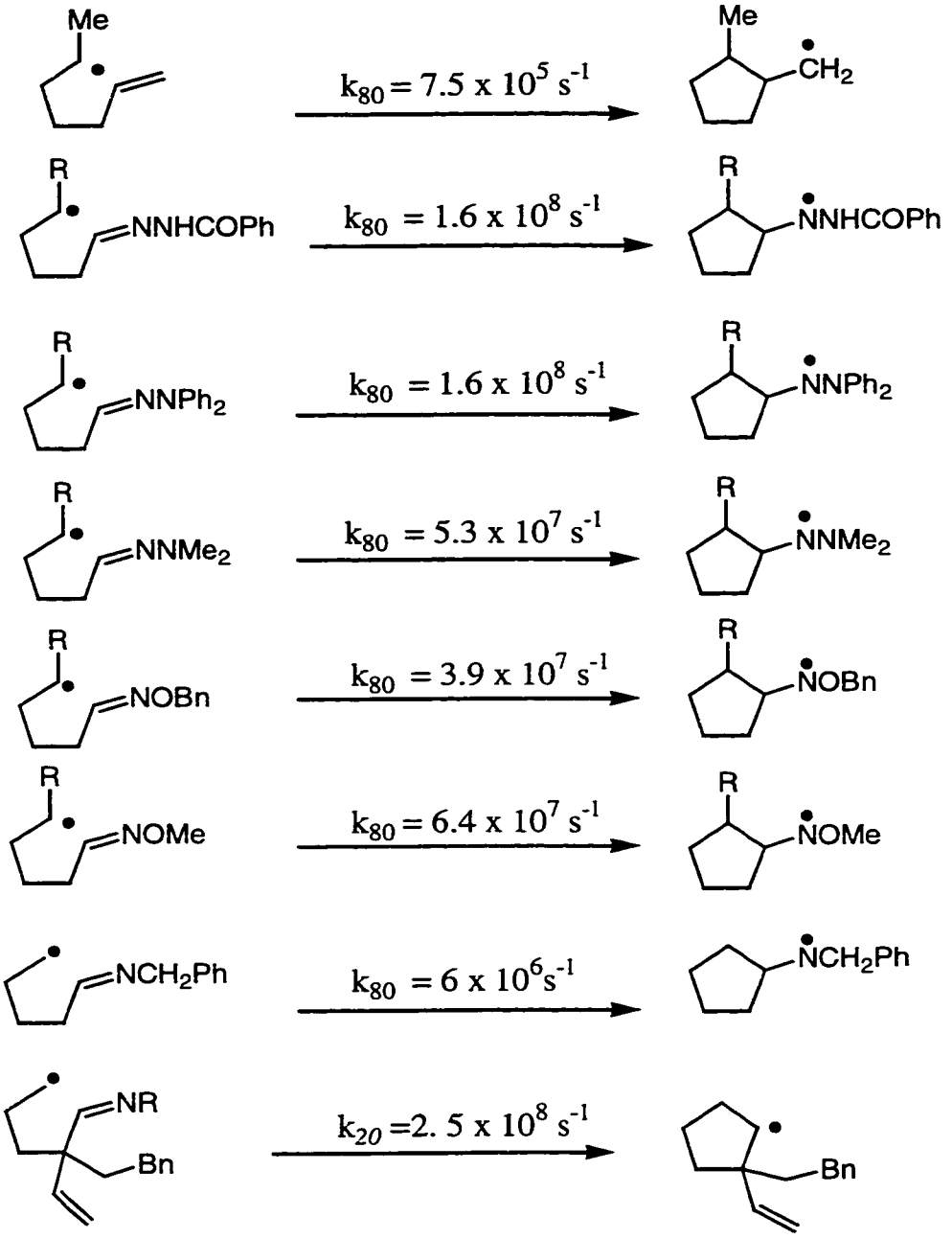


This three-electron bond helps stabilize the developing nitrogen radical during cyclization and this may be the reason for the increased exothermicity of the hydrazones and oxime ethers as compared to simple imines. This is reflected in the 200 fold increase in the rate of cyclization in the case of hydrazones and oxime ethers. On the other hand in simple imines such as C=N-CH_3 or C=N-CH_2Ph a two center three electron bond is not formed. Consequently the increase in the rate for this system is approximately 90 times, which must be due to the polarization of the C=N bond only.

The nature of the group attached to the second nitrogen of the hydrazone and oxygen of oxime ether is also an important factor in affecting the rates. For example, as a general rule it was predicted that hydrazones are better radical acceptors than oximes ethers, which in turn are better than imines. However in our studies it was established that the rate of cyclization onto an *O*-benzyl oxime is higher than for an *N,N*-dimethyl hydrazone, which in turn is higher than for an *O*-methyl oxime. The presence of the phenyl group must provide extra stabilization to the developing nitrogen radical.

The high exothermicity of the hydrazones and oxime ether cyclizations implies that these reactions proceed via early transition states. It is generally true that the product stabilities are not as important as the transition states of the exothermic reactions compared to endothermic reactions. Nevertheless, there will be some radical character on nitrogen at the transition state of the hydrazone cyclization. The R_2N substituent would then be expected to interact with this radical and help stabilize the system.

Table 8: Rate Constants for 5-*Exo*-Cyclizations to Cyclopentanes



Chapter Three

Synthetic Studies of Bicyclic Systems via Tandem Cyclizations of Aminyl Radicals

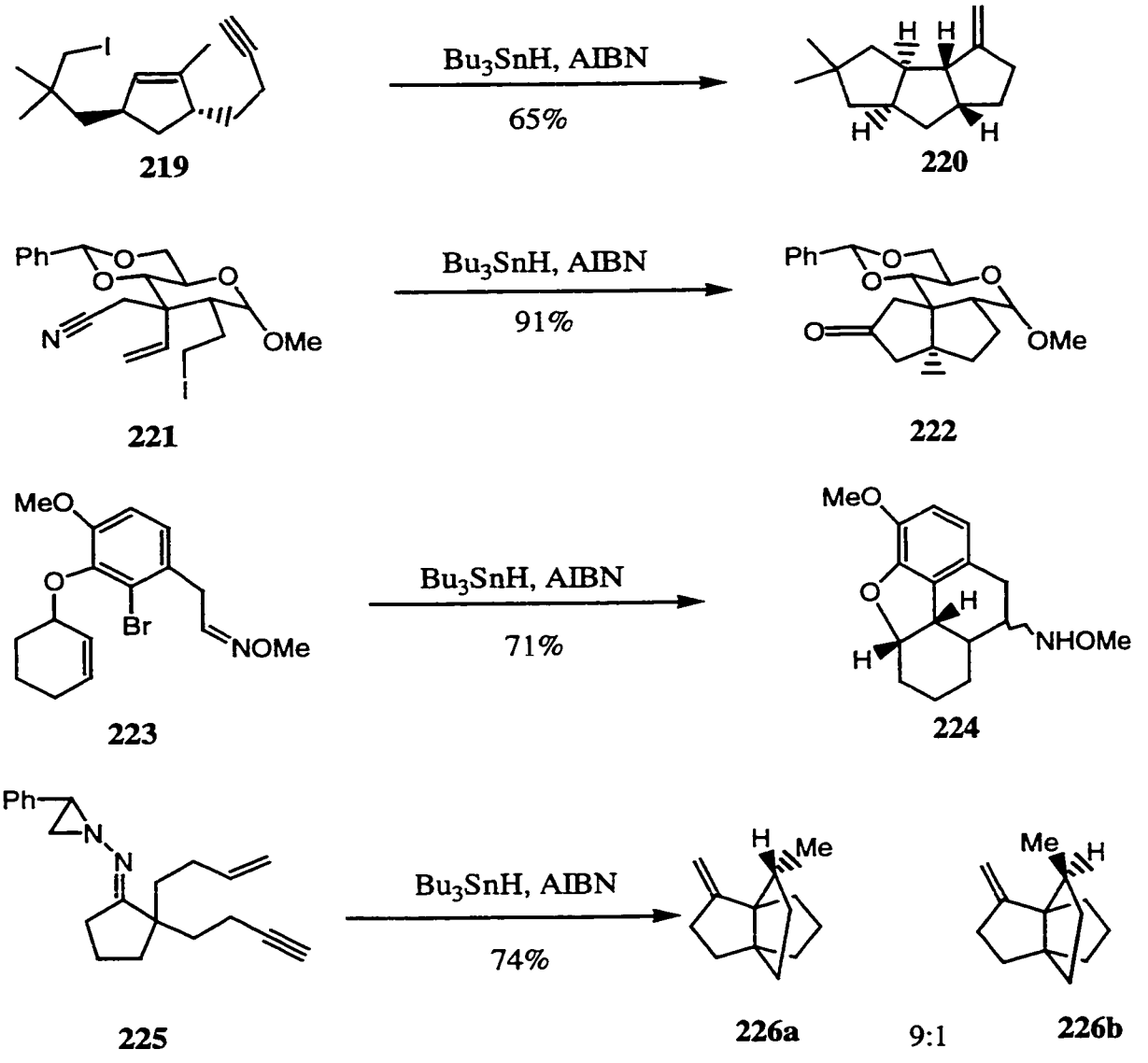
3.1 Tandem Radical Cyclizations

In a tandem radical reaction, the radical formed after the first transformation can undergo further reaction for a second or third time (even more) with the strategically positioned acceptor in the same molecule or with the other compounds in the reaction mixture before the radical is quenched. In principle many reactions can be conducted between radical generation and radical removal. The sequencing of two or more cyclizations is a simple and very powerful strategy for the construction of polycyclic compounds by a single experimental manipulation. In recent years, impressive strides have been made in the use of tandem radical reactions in organic synthesis.

Scheme **64** includes some of the representative examples from the literature, where carbon centered radicals have been used in tandem cyclizations onto different types of acceptors to synthesize complex molecular structures. These examples illustrate the power of this method for the regio and stereochemical formation of functionalized polycyclic systems, useful in the total synthesis of natural products. In the first example[89], generation of the initial radical is followed by cyclization to generate a 3° radical. This 3° radical undergoes a second cyclization to give the tricyclic compound hirustene in 65% yield with very high stereocontrol. The reason for the observed stereoselectivity is the presence of a short connecting chain between the cyclic alkene or radical and its partners. Similarly a diquinane system has been obtained in the second example[90], in very high yield via tandem cyclization involving consecutive 5-*exo* additions. In this case the 2° radical formed after the first cyclization adds onto a nitrile group to give compound **222** in very high yield. The next two examples illustrate how quickly molecular complexity can be achieved through the use of tandem sequences. In

the third example[91], on oxime ether has been employed as the final radical acceptor in a tandem 5-*exo* aryl radical, 6-*exo* alkyl radical cyclization. In the last example[92], vinyl radical addition to the *N*-aziridinyl imine, followed by expulsion of styrene and nitrogen, generates a secondary radical on the same carbon center. The secondary radical then adds onto the alkene to give the [3.3.3] propellene skeleton **226a** of the natural product modhephene.

Scheme 64: Tandem Cyclizations of Carbon-Centered Radicals

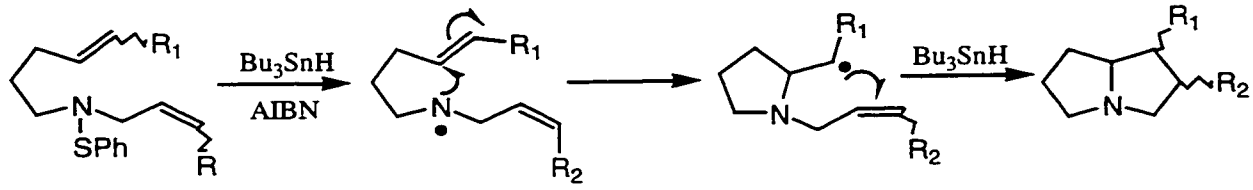


219 **220** **221** **222** **223** **224** **225** **226a** **226b**

3.2 Tandem Cyclizations Involving Nitrogen

Tandem cyclization involving nitrogen-centered radicals is potentially a powerful method of synthesizing complicated nitrogen heterocycles in a one-pot reaction. These reactions have received less attention than the reactions involving carbon-centered radicals. A pioneering study by Bowman and coworkers has established that tandem cyclization of nitrogen centered (aminyl) radicals can be achieved successfully. Their protocol can be divided into two parts. In the first method [93] (Scheme **65**), the aminyl radical is generated from a sulfenamide precursor, and it then undergoes cyclization onto an alkene to form a carbon centered radical, which in turn adds onto another alkene (or any other radical acceptor) to complete the tandem process.

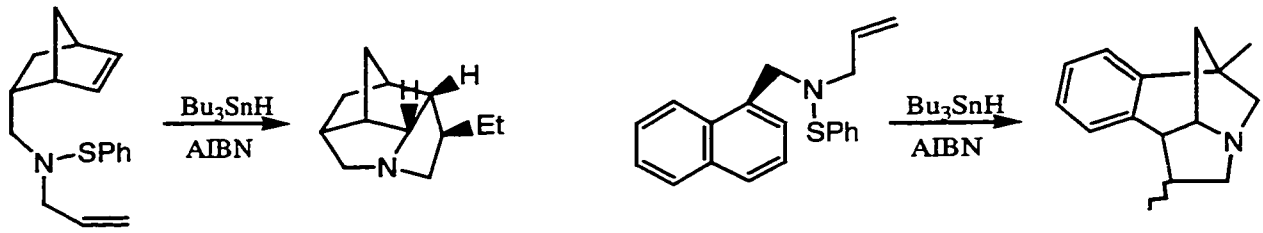
Scheme 65: Tandem Cyclization with Nitrogen Radicals



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

Citing previous examples, the authors have pointed out that this type of multiple cyclizations gave better results than the monocyclization. The 5-*exo* cyclizations of neutral aminyl radicals are believed to be usually reversible, but trapping the initial radical in a second ring forming prevents the ring-opening step, thereby increasing the rate of the reaction. This protocol has been used for the synthesis of the interesting polycyclic systems **232** and **234** shown in Scheme **66**. However, in a recent paper, Tsanaktsidis *et al.*[142] have established that contrary to an earlier suggestion by Newcomb *et al.*[106], *N*-methylpent-4-enylaminyl radical undergoes a relatively slow, but irreversible 5-*exo* cyclization.

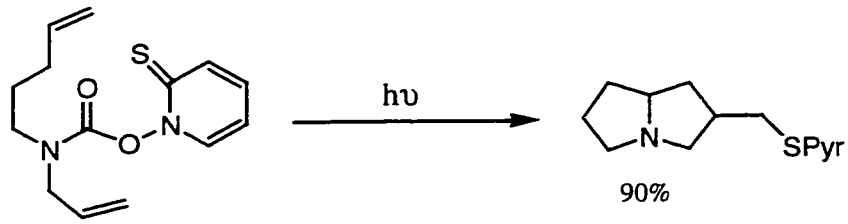
Scheme 66: Synthesis of Polycyclic Systems via Tandem Cyclizations



231 **232** **233** **234**

Newcomb and coworkers[56] have earlier used this protocol. They have used the *N*-hydroxypyrdine-2-thione carbamates as the radical precursor to generate the nitrogen-centered radical. The tandem cyclization of **235** afforded the bicyclic skeleton in which the final primary radical was trapped as the sulfide to furnish the product **236** in 90% yield (Scheme **67**).

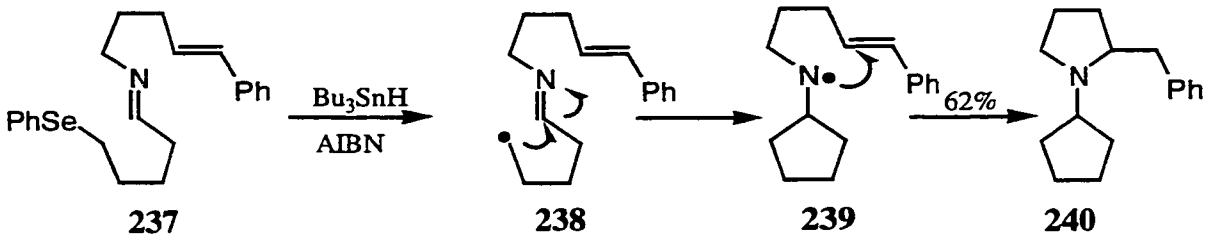
Scheme 67: Tandem Cyclization of Aminyl Radical Generated from Barton Ester



235 **236**

In the second protocol[94], aminyl radicals are generated by radical cyclizations of carbon centered radicals onto C=N double bond of imines. These aminyl radicals then undergo tandem cyclizations onto suitably positioned alkenes (Scheme **68**). These cyclizations are facilitated by the use of Lewis acid ($MgBr_2$-Et_2O), which binds to the nitrogen atom, thereby making both imine and the intermediate aminyl radical more electrophilic and increasing the rate of cyclization and preventing side reactions.

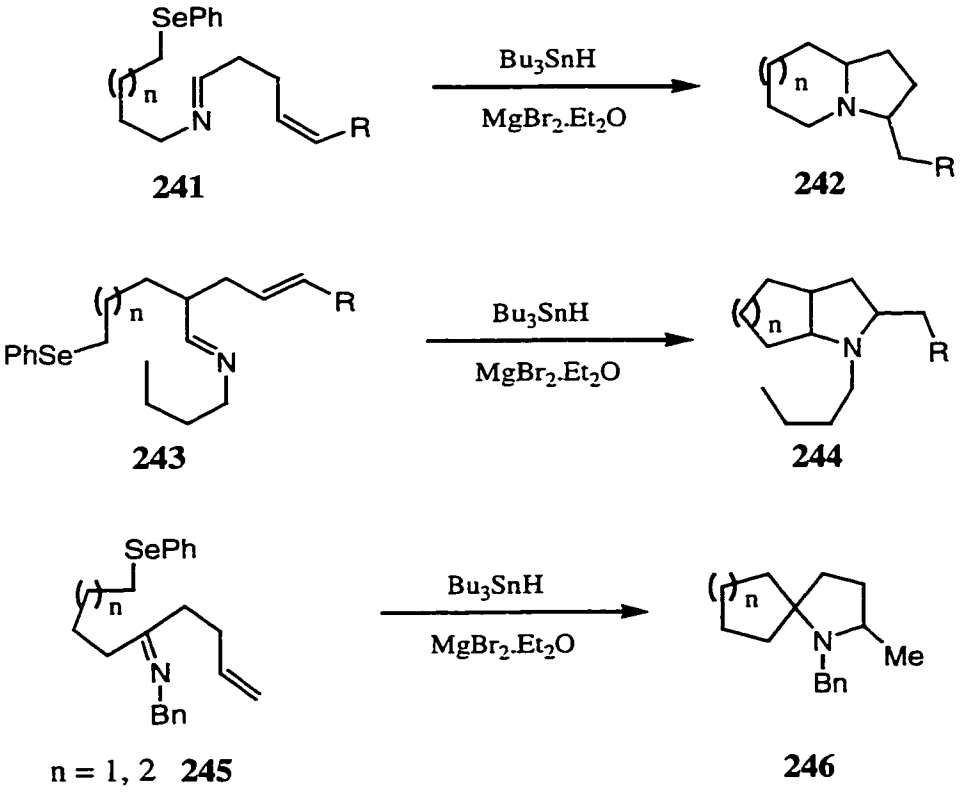
Scheme 68: Tandem Cyclizations of Aminyl Radicals



237 **238** **239** **240**

As seen in Scheme **69**, a wide range of bicyclic nitrogen heterocycles, including pyrolidizidines and indolizidines have been synthesized by using this method.

Scheme 69: Bicyclic Systems via Tandem Cyclizations with Aminyl Radicals



241 **242**

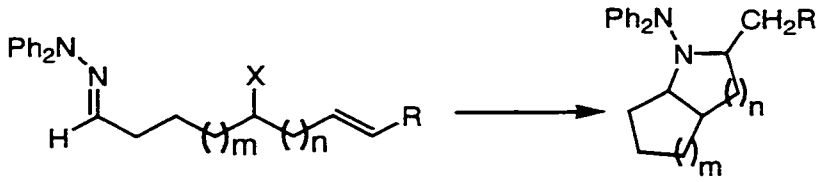
243 **244**

n = 1, 2 **245** **246**

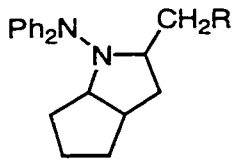
3.3 Research Objectives

In the previous chapter, we established the superiority of *N,N*-diphenylhydrazones as radical acceptors. As seen earlier, the radical cyclization onto the sp^2 carbon atom of *N,N*-diphenylhydrazone generates an intermediate aminyl radical, which provides the potential for tandem cyclization. The tandem cyclization of this type of aminyl radical on a suitable π system can create complex ring systems, including bicyclic nitrogen heterocycles as shown in Scheme **70**.

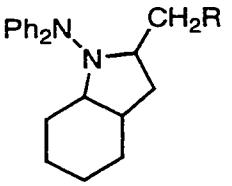
Scheme 70: Bicyclic Systems via Tandem Cyclization of Aminyl Radicals Generated on *N,N*-Diphenylhydrazones



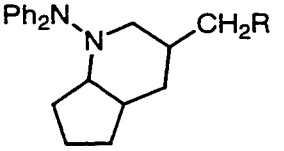
247 **248**



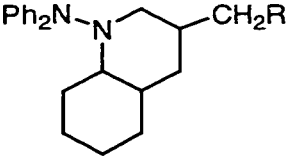
248(i)



248(ii)



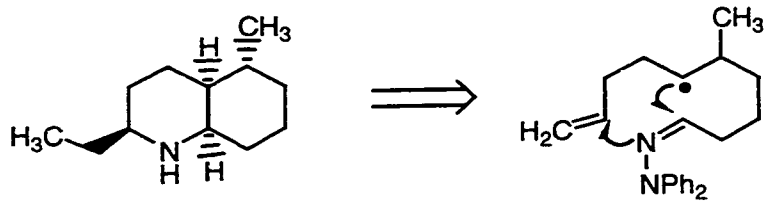
248 (iii)



248(iv)

The bicyclic system **248(iv)** resulting from 6,6 tandem cyclization would resemble a natural product called Pumilotoxin C. This comprises part of an interesting family of physiologically active alkaloids found in the skin secretion of frogs of the family Dendrobatidae. In principle, these studies can be further extended for the total synthesis of Pumilotoxin C and a possible disconnection for this system is show in Scheme **71**.

Scheme 71: Retrosynthetic Analysis for Pumilotoxin C Synthesis

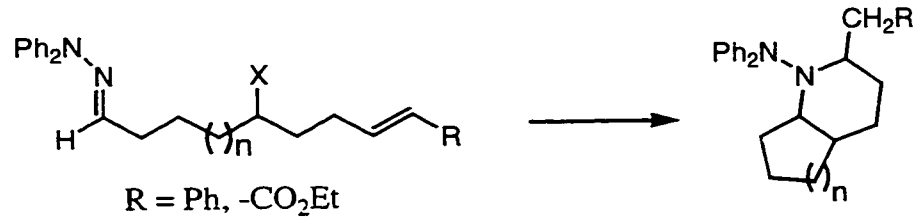


Pumilotoxin C
249

250

As a continuation of previous studies in our laboratory, we set out to explore the synthesis of bicyclic 5,6- and 6,6- ring systems, through tandem reactions under radical conditions as well as the influence of Lewis acids on this process. The results obtained in preliminary studies in our laboratory and Bowman's study of tandem aminyl radical cyclizations, indicated that the presence of an electron withdrawing group as a substituent on the alkene is important for the second stage of the tandem process. Two functional groups namely an ester and a phenyl group were selected as substituents. Due to their electron withdrawing capabilities, these groups were expected to provide the stability necessary to promote the tandem cyclization. The following bicyclic ring systems were chosen as targets for the study of the tandem cyclization of the aminyl radicals from *N,N*-diphenylhydrazones (**Scheme 72**).

Scheme 72: Proposed Synthesis of Bicyclic 5,6-and 6,6-Systems



R = Ph, -CO_2Et

251 n = 1
252 n = 2

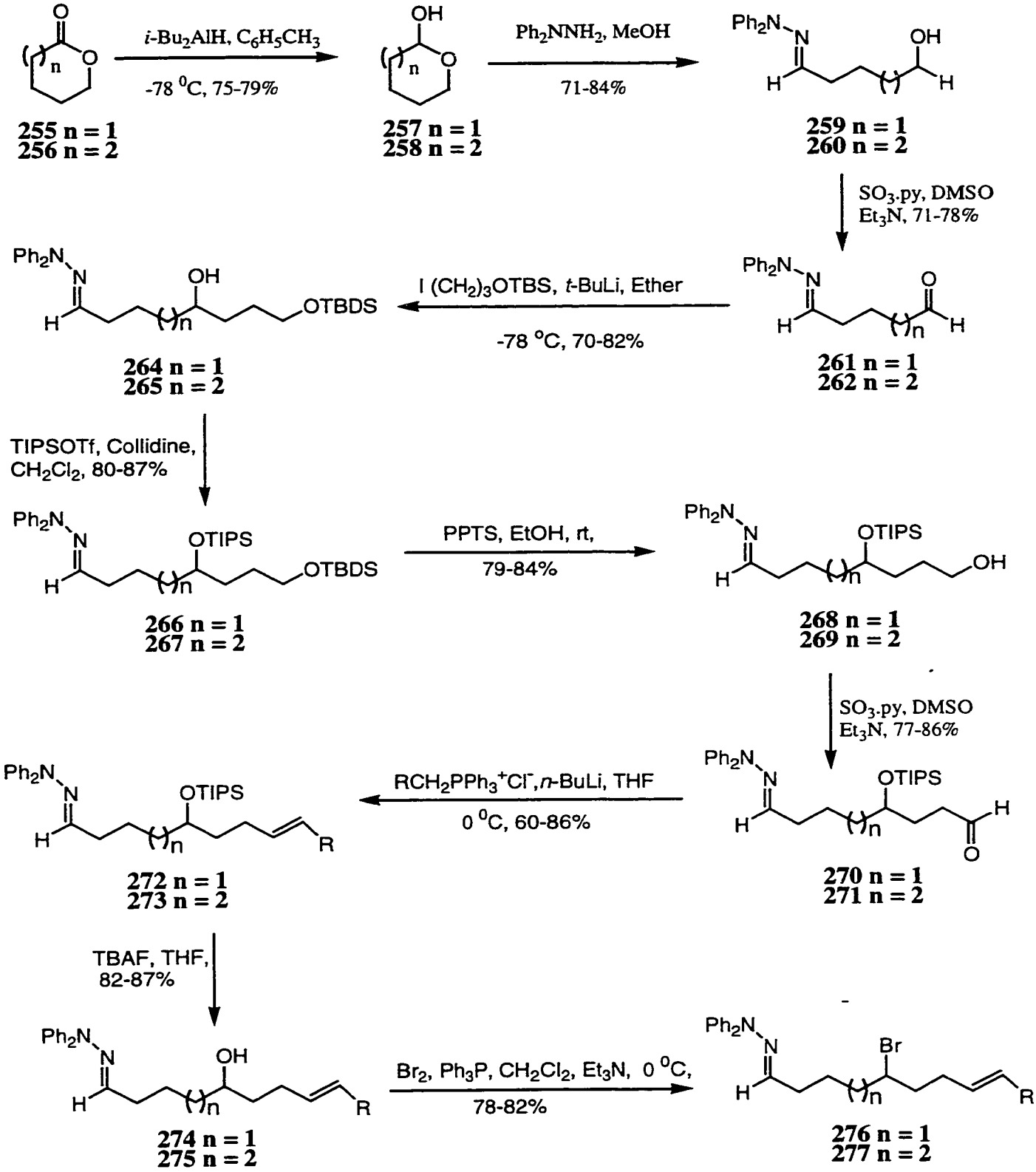
253 n = 1
254 n = 2

3.4 Substrate Syntheses for the 5,6-and 6,6-Bicyclic Ring Systems

The syntheses of the cyclization substrates **276** and **277** commenced with reduction of the commercially available lactones (δ-valerolactone **255** or ε-caprolacone **256**) with diisobutylaluminium hydride[73] (DIBALH), in dry toluene at -78 °C to give the corresponding alcohols **257** and **258** in good yields (75-79%) (Scheme **73**). δ-Valerolactol[95] **257** exists predominately in the ring closed form as no aldehyde hydrogen could be observed in ^{1}H NMR spectrum, whereas ε–caprolacol **258** exists primarily as the ring opened form. Treatment of these alcohols with one equivalent of Ph_2NNH_2 in MeOH at room temperature provided the *N,N*-diphenylhydrazones **259** and **260** in 78-85% isolated yields. The products were clearly identified by the presence of the hydrazone proton at δ 6.50 ppm in ^{1}H NMR spectra. As reported earlier, only a single geometric isomer (*E* isomer) was isolated from the reaction. Oxidation of the resulting primary alcohols **259** and **260** with sulfur trioxide pyridinium complex in DMSO in the presence of triethylamine afforded the aldehydes **261** and **262** in good yields (71-78%).

The next step in the sequence was the chemoselective addition of the appropriate nucleophile to the aldehydes. The chemoselective addition of various Grignard reagents [CH_3MgBr, *i*-PrMgBr, CyMgBr, $BrMg(CH_2)_4OTBDS$] to the aldehyde side without competitive addition to the hydrazone functionality has been achieved successfully in our laboratory[96]. In this case, the reaction of aldehydes **261** and **262** with $BrMg(CH_2)_3OTBDS$ gave only starting materials with some decomposition products. However, replacement of $BrMg(CH_2)_3OTBDS$ with $Li(CH_2)_3OTBDS$ was successful. Treatment of the aldehydes **261** and **262** with $I(CH_2)_3OTBDS$ **263** in the presence of *t*-BuLi at –78 °C afforded the desired compounds **264** and **265** in 70-82% isolated yields[97]. The chemospecificity of this reaction can be discerned by analysis of ^{1}H NMR spectra, since the vinyl hydrogen of the hydrazone remained in the product, and the signal due to aldehyde had disappeared. However some problems were encountered with the reaction

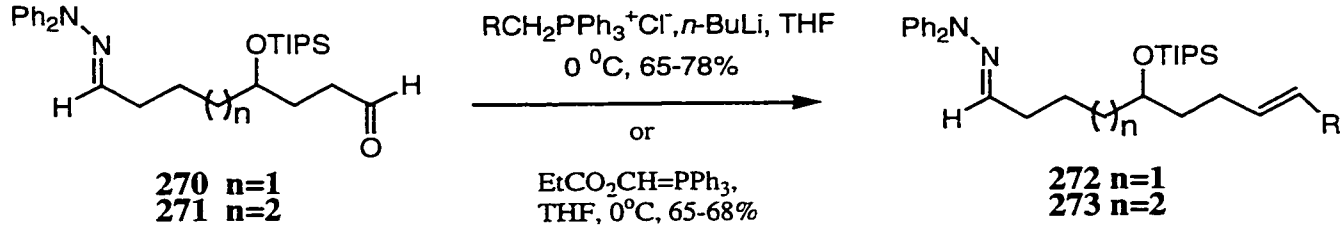
Scheme 73: Synthetic Route to the Substrates for the 5,6- and 6,6-Bicyclic Systems



of aldehyde **261** with $I(CH_2)_3OTBDS$. This reaction was unsuccessful at scales larger than 2 g for aldehyde **261**. The alcohols **264** and **265** were treated with triisopropyl trifluoromethanesulfonate (TIPSOTf) in the presence of collidine in CH_2Cl_2 to yield the protected compounds **266** and **267** in high yields (80-85%)[98]. Removal of the *t*-butyldimethylsilyl group was achieved by treating these compounds with pyridinium *p*-toluene sulfonate (PPTS) in ethanol at room temperature[99], to give the desired primary alcohols **268** and **269** in good yields (77-78%). The resulting alcohols were oxidized with sulfur trioxide pyridinium complex in DMSO in the presence of triethylamine to afford aldehydes **270** and **271** in 77-86% isolated yields.

The next step at this point was the conversion of the aldehyde group to the activated alkene. This was achieved by treating the aldehydes **270** and **271** with appropriate Wittig salts[100] to give compounds **272a**, **272b**, **273a** and **273b** in good yields (Table **9**).

Table 9: Wittig Reactions of Aldehydes



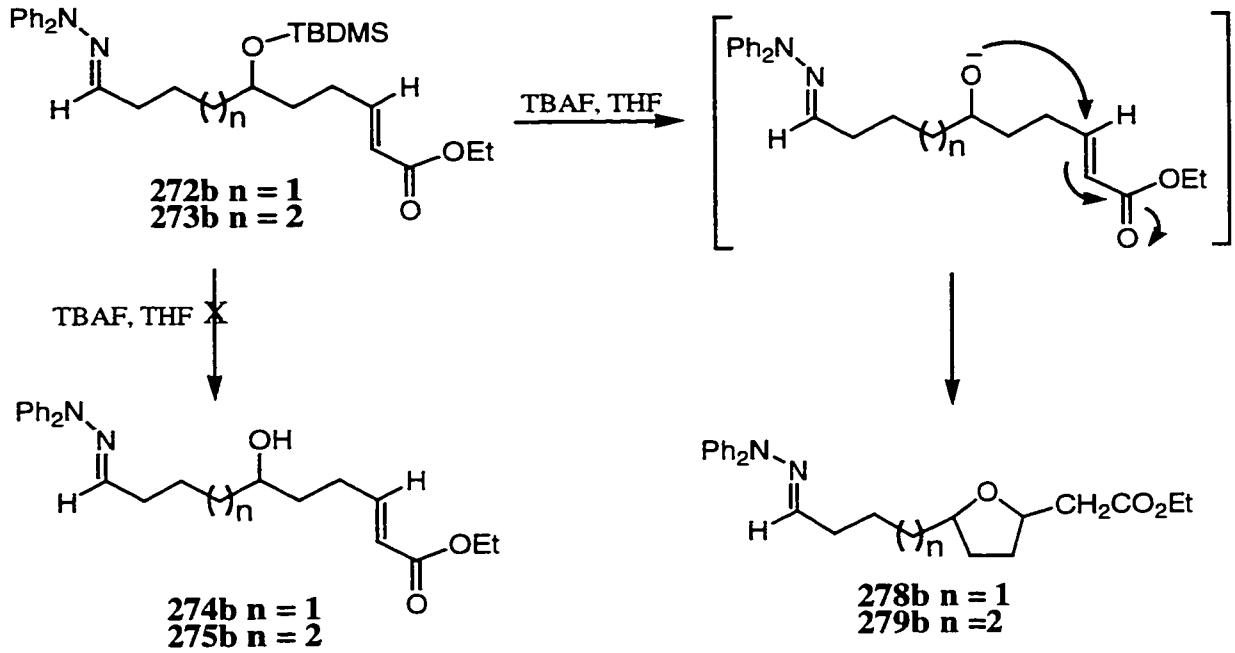
270 n=1
271 n=2

272 n=1
273 n=2

Entry	n	Wittig Salt	R	Alkene	Yield
A	1	$PhCH_2PPh_3^+Cl^-$	Ph	**272a**	86%
B	1	$EtCO_2CH{=}PPh_3$	$CHCO_2Et$	**272b**	77%
C	2	$PhCH_2PPh_3^+Cl^-$	Ph	**273a**	65%
D	2	$EtCO_2CH{=}PPh_3$	$CHCO_2Et$	**273b**	60%

Deprotection of the secondary alcohol group in compounds **272a** and **273a** with tetrabutylammonium fluoride in THF afforded the corresponding free alcohols **274a** and **276a** in 80-90% isolated yields. However, the reaction of compounds **272b** and **273b** under similar conditions did not afford the desired products. ^{1}H NMR analysis of the products indicated the absence of vinylic hydrogen signal (-C<u>H</u>-CHCO$_2$Et). This must be due to the Michael type addition of the alkoxy anion forming under these conditions to give products **278b** and **279b** (Scheme **74**).

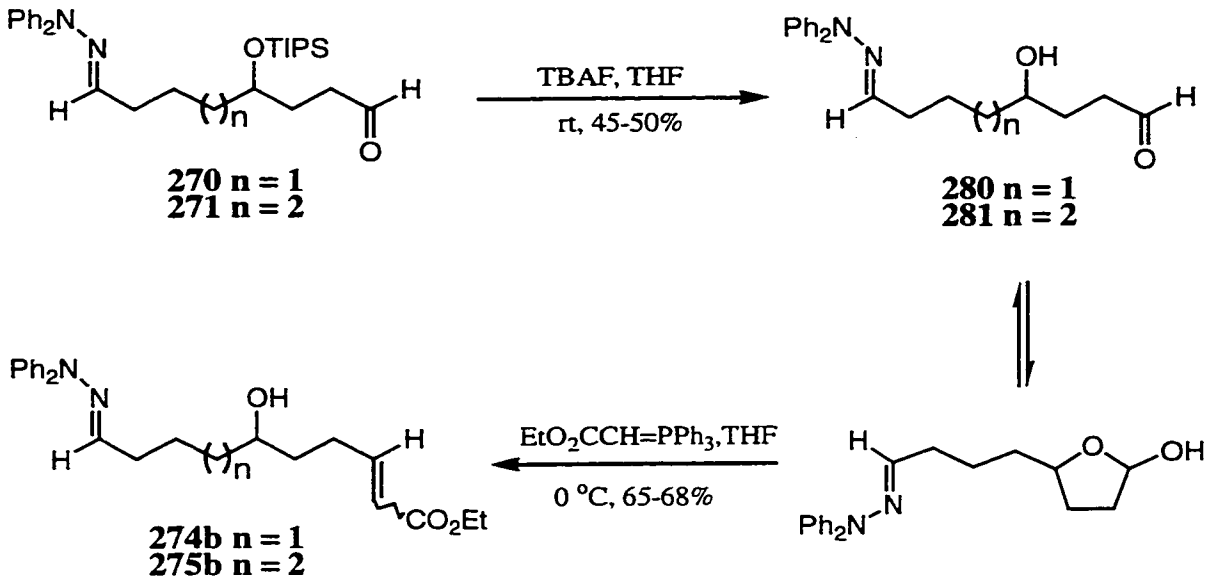
Scheme 74: Formation of Cyclic Product via Michael Addition



Wittig reaction of lactols with carbalkoxytriphenylphosphoranes[101] is a well-known reaction in carbohydrate chemistry to give products similar to our desired compounds **274b** and **275b**, without any trace of the Michael addition products. Thus compounds **270** and **271** were first treated with tetrabutylammonium fluoride to give compounds **280** and **281** in moderate yields (45-50%), which exist predominately in the

ring closed form (Scheme **75**). Treatment of compounds **280** and **281** with (carbethoxymethylene)triphenylphosphorane in the presence of a catalytic amount of benzoic acid, provided the desired alcohols **274b** and **275b** in 60-68% isolated yields.

Scheme 75: Preparation of Radical Precursors via Alternative Route

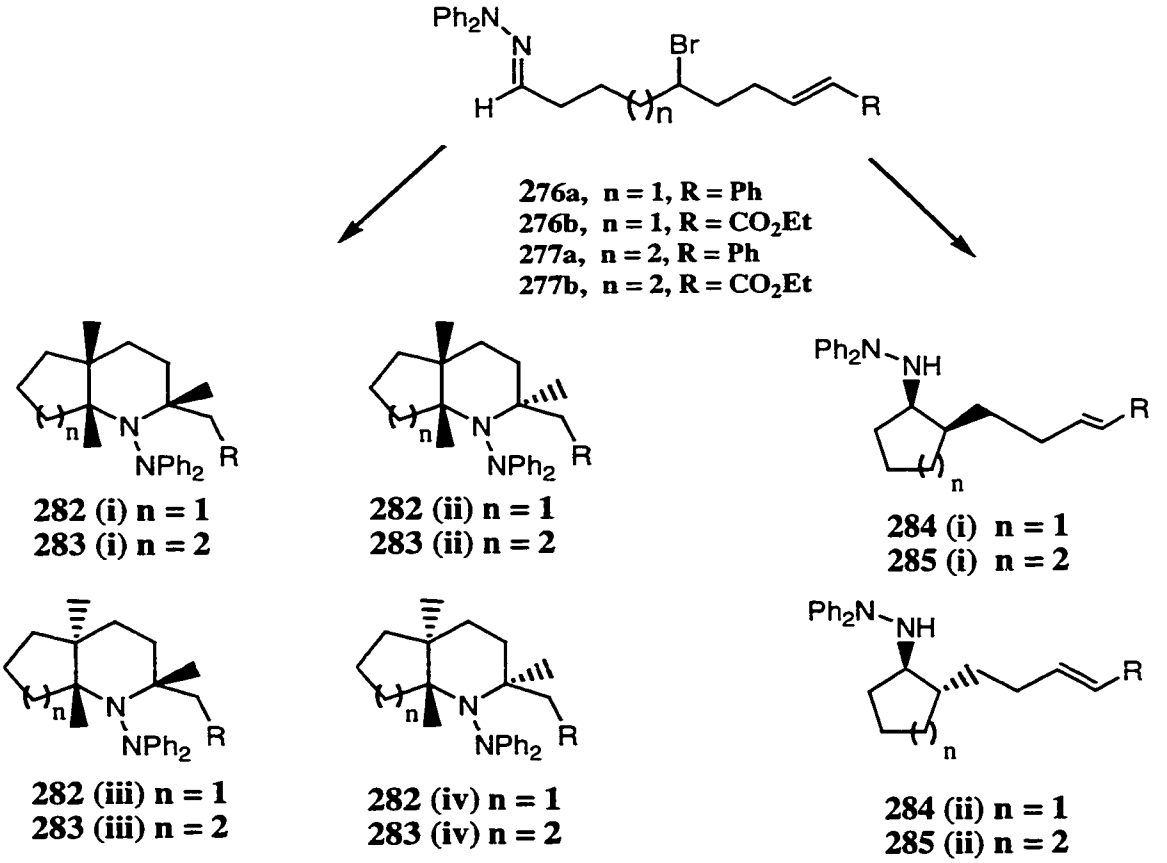


The free alcohol group in these compounds does not undergo Michael addition onto the activated alkene. The last step required for the preparation of the starting materials was the conversion of the secondary alcohols **274** and **275** to bromides or iodides. The alcohols **274a**, **274b**, **275a** and **275b** were brominated using $Ph_3P.Br_2$ in the presence of triethylamine and the desired radical precursors **276a**, **276b**, **277a** and **277b** were obtained in 78-82% isolated yields.

3.5 Results and Discussion

Our first attempt at generating the bicyclic 5,6 and 6,6 ring systems followed the general procedure for the syringe pump controlled radical reaction. The bromides **276a**, **276b**, **277a** and **277b** were dissolved in benzene and then treated with tributyltin hydride and AIBN. The reaction mixture was refluxed for two hours and then cooled to room temperature. TLC analysis of the reaction mixture revealed the presence of two new spots, both of them less polar than the starting material. The ^{1}H NMR of the crude reaction mixtures 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 two formed by monocyclization. The four tandem products and two monocylized products are shown in Scheme **76**.

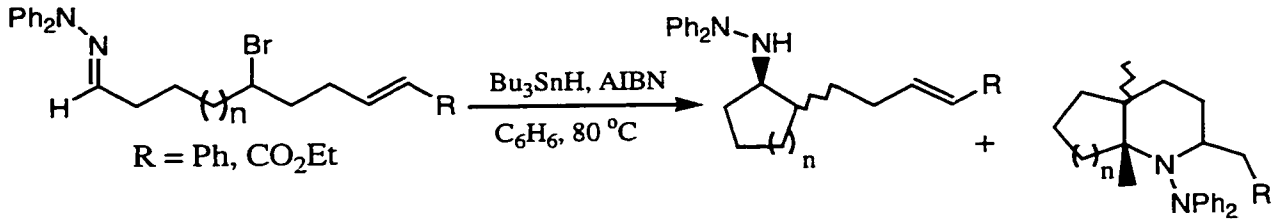
Scheme 76: Possible Products from the Tandem Reaction



Previous studies done in our laboratory have shown that 5-*exo* cyclization of *N,N*-diphenylhydrazones proceeds with the predominant formation of the *cis* isomer, whereas for 6-*exo* cyclizations onto *N,N*-diphenylhydrazones the *cis/trans* selectivity is relatively poor. Hence, the *cis* ring fusion was expected in the tandem products for the 5,6-bicyclic systems, along with the *cis* geometry of the monocylized product. For 6,6-bicyclic systems a mixture of *cis* and *trans* isomers were expected.

The NMR analyses of the products obtained after purification by flash chromatography indicated the formation of only monocyclized products with no trace of bicyclic systems resulting from tandem cyclizations. The results of these radical reactions are reported in table **10**.

Table 10: Tandem Radical Cyclizations



276 n = 1
277 n = 2

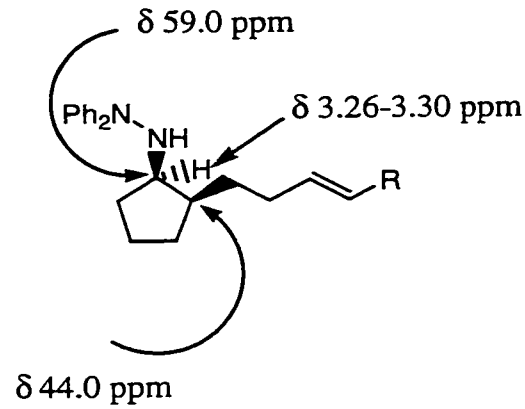
284 n = 1
285 n = 2

282 n = 1
283 n = 2

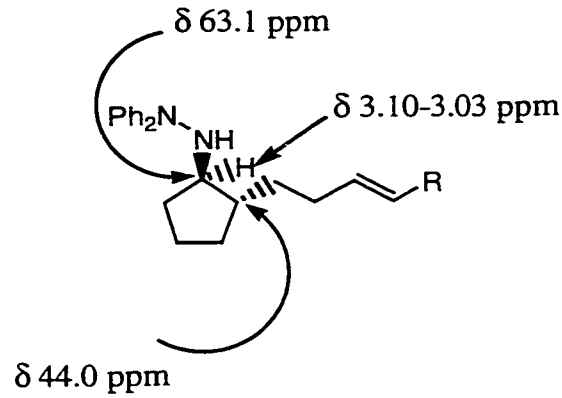
Entry	H	N	Compound	Monocycl.%	Tandem %	*cis/trans*
1	Ph	1	**276a**	54	-	3:1
2	CO_2Et	1	**276b**	46	-	3:1
3	Ph	2	**277a**	60	-	1:0
4	CO_2Et	2	**277b**	51	-	1:0

In the case of 5,6 bicyclic systems the monocyclized products were obtained as a 3:1 mixture of *cis* and *trans* isomers. The two isomers could easily be identified by their respective signals in both ^{1}H and ^{13}C NMR spectra. As has been observed previously the ^{13}C resonances for both methine carbons in the *cis* isomers appeared at higher field than those for the *trans* isomers. Whereas the ^{1}H signal for the protons attached to the carbon with $-NHNPh_2$ group appeared at lower field as compared to the *trans* isomers. Figure **4** lists the key ^{13}C NMR signals that were used to assign the relative stereochemistry of the substituted isomers.

Figure 4: Assignment of Stereochemistry for Monocyclized Products of 5,6-Bicyclic Systems



284a (i), R = Ph
284b (i), R = CO_2Et

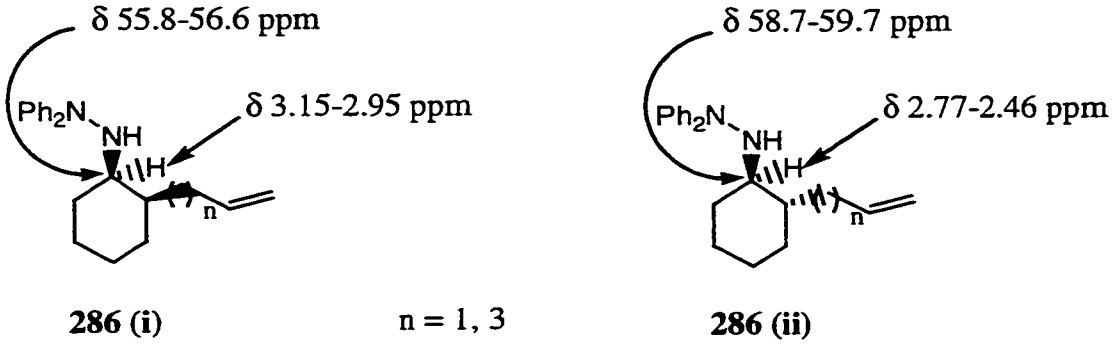


284a (ii), R = Ph
284b (ii), R = CO_2Et

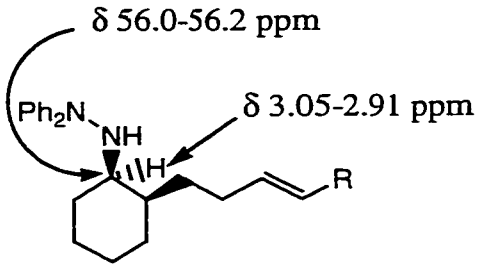
In the case of 6,6 systems only one isomer of the monocyclized product was obtained. The stereochemistry of these products **285** has been assigned as *cis* by comparing both ^{1}H and ^{13}C NMR spectra of the related compounds **286 (i)** and **286 (ii)** from previous studies

in our laboratory [95, 102]. Figure **5** lists the key NMR signals used to assign the stereochemistry.

Figure 5: Spectral Analysis of Monocyclized Products of 6,6-Bicyclic Systems



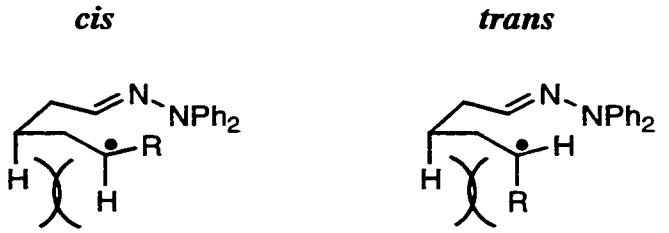
286 (i) n = 1, 3 **286 (ii)**



285a (i), R = Ph
285b (i), R = CO_2Et

The stereochemical outcome observed for the monocyclized products in 5,6-systems was as expected on the basis of previous results obtained for the 5-*exo* radical cyclizations. These cyclizations proceed through a chair conformation following Beckwith's model, as shown in Fig **6**. The transition state **287**, which leads to the *cis* isomer is preferred over the structure **288**, since it minimizes the 1,3 diaxial interactions.

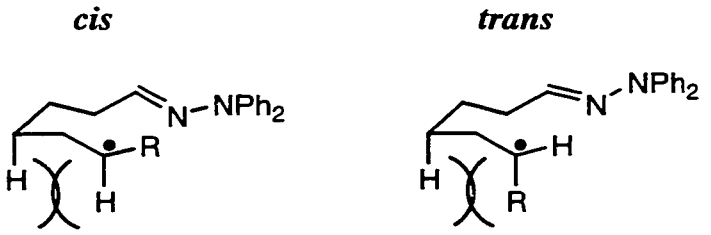
Figure 6: Transition States for 5-*Exo* Radical Cyclizations



287 **288**

6-*Exo* radical cyclizations are known to be less stereoselective compared to 5-*exo* cyclizations. In this case also, the major product usually results from a chair conformation with any substituent present occupying the equatorial position (Fig 7). However, the very high level of stereocontrol observed in the monocyclized products of 6,6-systems suggests that the orientation of the diphenylamine substituent may exert a subtle influence.

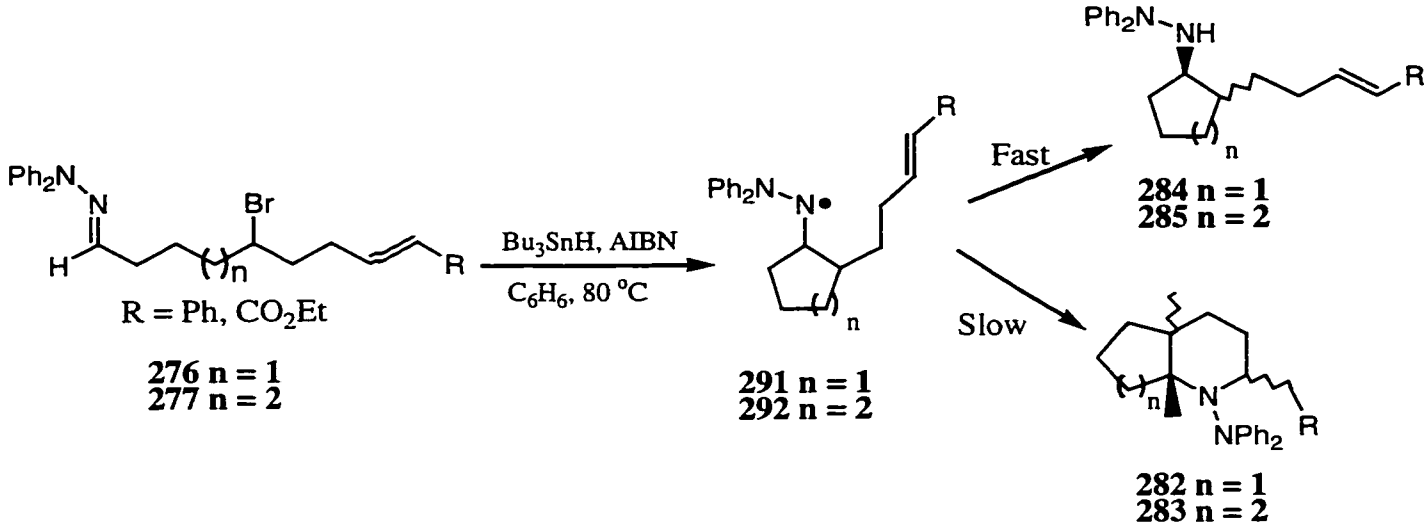
Figure 7: Transition States for 6-*Exo* Radical Cyclizations



289 **290**

The absence of the tandem cyclization products in the above reactions can be attributed to the faster rate of quenching ($k_{21} = 4.3x10^5 s^{-1}$) of the nitrogen centered radical by the hydride source (Bu_3SnH) than the rate of attack of this aminyl radical on the activated double bond (Scheme **77**). In the presence of other hydride sources with lower rate of quenching, the aminyl radical would have longer time to react with the double bond and tandem radical cyclization should be facilitated.

Scheme 77: Quenching VS Tandem Cyclization



Metal hydrides such as tris(trimethylsilyl)silane, phenylsilane and tributylgermanium hydride are known to have lower rates of H-atom transfer to carbon- and oxygen- centered radicals as compared to tributyltin hydride (Table **11**)[103]. Therefore, the cyclizations of the compounds **276,** and **277** were performed in the presence of these hydride sources. However, the products isolated under these conditions were only monocyclized products, indicating that the rate of cyclization of the aminyl radical is also slower than the rate of hydrogen atom transfer by these hydride sources.

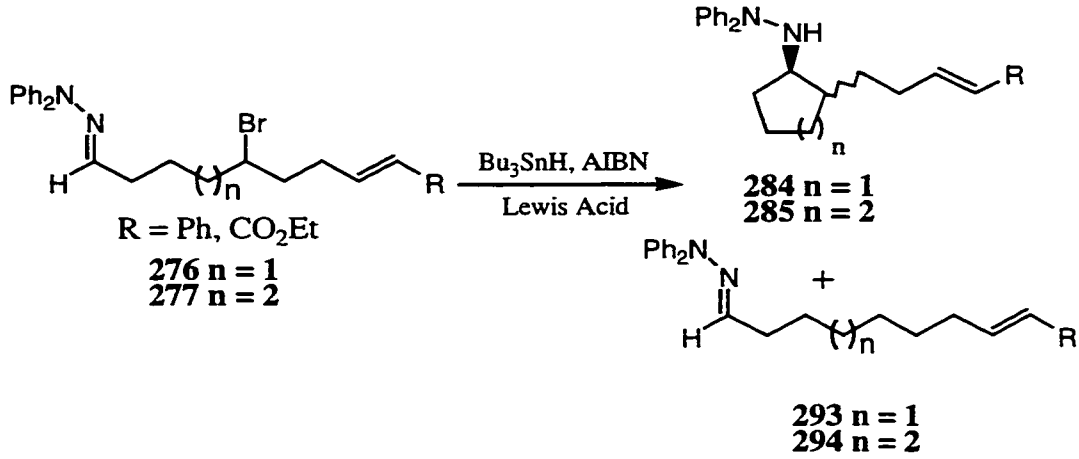
Table 11: Kinetics of Hydrogen Atom Transfer to Alkyl, alkoxy and Dialkylaminyl Radicals at 25 °C

H-Atom Donor	$RCH_2^{\bullet}$ ($M^{-1}S^{-1}$)	$RO^{\bullet}$ ($M^{-1}S^{-1}$)	$R_2N^{\bullet}$ ($M^{-1}S^{-1}$)
Bu_3SnH	2.4×10^6	2.2×10^8	4.3×10^5
$(Me_3Si)_3SiH$	3.8×10^5	1.1×10^8	-
$PhSiH_3$	2.9×10^4	7.5×10^6	-
Bu_3GeH	9.3×10^4	-	-

Lewis acid activation and catalysis of dialkylaminyl radical cyclization reactions has been known qualitatively for more than two decades[104]. In a recent study by Newcomb *et al.*, cyclization of the *N*-butyl-4-pentenaminyl radical in the presence of a wide range of Lewis acids such as $LiBF_4$, $MgBr_2$ and BF_3 was shown to be efficient with good to excellent yields of cyclic products[105]. Bowman and coworkers have also proved that tandem cyclizations of aminyl radicals are facilitated by the use of Lewis acids ($MgBr_2$, $CuCl_2$)[93]. Lewis acids 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.

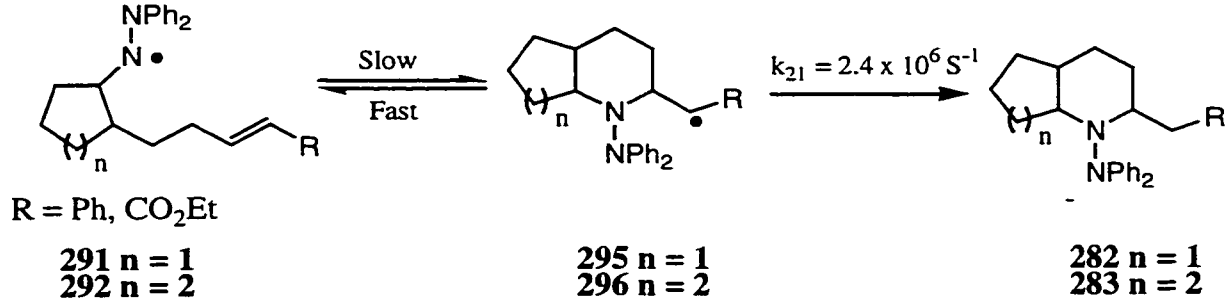
All our attempts to obtain tandem cyclization products by adding Lewis acids such as $MgBr_2.OEt_2$, BF_3 and $CuCl_2$ were unsuccessful. In these cases, addition of one equivalent of hydride did not affect the starting material. Upon adding more of the tin hydride and refluxing the reaction mixture for longer periods of time, extensive decomposition of the starting material was observed. In spite of our efforts employing freshly prepared tributyltin hydride along with Lewis acids, we did not isolate any of the tandem products in these experiments. As a matter of fact, in these cases the reduced products **293** and **294** after quenching of initial radical formed from the precursors **276** and **277** were obtained along with the monocyclized products (Scheme **78**).

Scheme 78: Quenching of Initial Radical before Cyclization



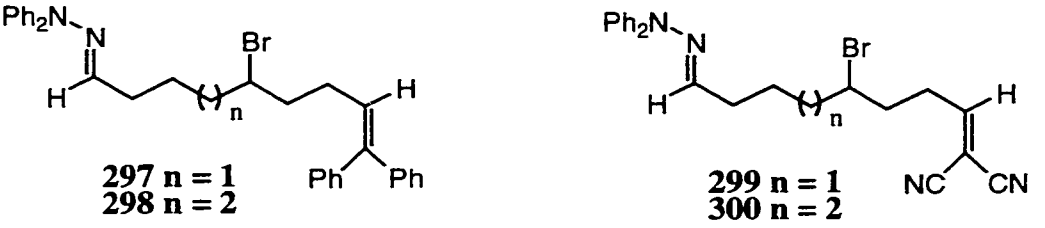
Another reason for the failure of tandem cyclization reaction can be the reversibility of the second cyclization, as shown by Newcomb *et al.* for the radical cyclization of *n*-butyl-4-pentenaminyl radical during the course of this work[106]. If the cyclization is reversible, this means that the rate of opening of the second ring is close to the rate of quenching of the secondary alkyl radical by the hydride source (Scheme **79**).

Scheme 79: Quenching Vs Ring Opening



In order to overcome all the above-mentioned limitations, it was decided to activate the double bond fully by substituting two phenyl or two cyano groups on the olefin. Activation of the double bond by two electron withdrawing groups should increase the rate of the forward reaction in the second cyclization in comparison with the rate of quenching of the aminyl radical. Furthermore, the presence of two electron withdrawing groups should stabilize the secondary alkyl radicals **295** and **296** formed after the second cyclization. This should decrease the rate of ring opening and should facilitate the forward reaction thereby increasing the chance of formation of tandem cyclization products.

Scheme 80: Activation of Double Bond with two Electron Withdrawing Groups

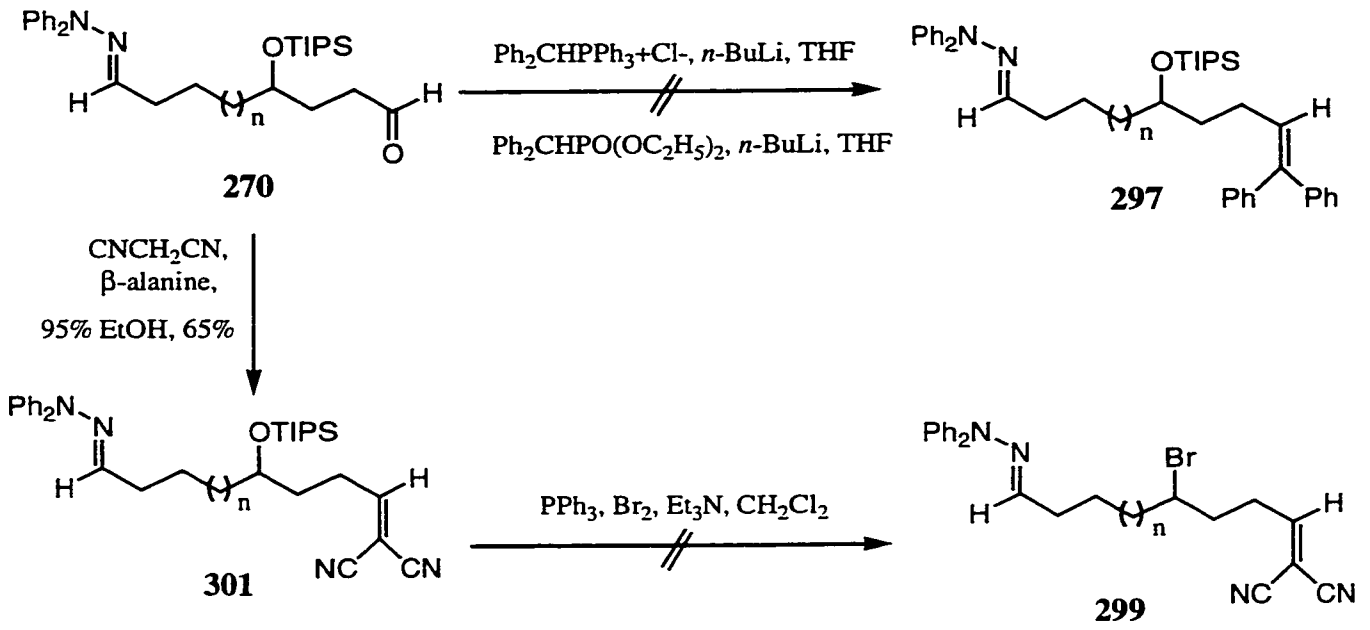


As shown in the Scheme **81**, all the efforts at synthesizing the activated compounds **297** and **299** were unsuccessful. In the reaction of aldehyde **270** with benzyl-triphenylphosphonium chloride and *n*-butyllithium in presence of THF at –78 °C to rt, only starting material was recovered[107]. However, treatment of aldehyde **270** with $Ph_2CHPO(OC_2H_5)_2$ in the presence of *n*-BuLi and THF gave the desired compounds **297** in 15% isolated yield. All the efforts to improve this yield were unsuccessful.

Reaction of aldehyde **270** with malonitrile in the presence of β-alanine in ethanol[108] afforded compound **301** in 65% yield. Compound **301** was treated with

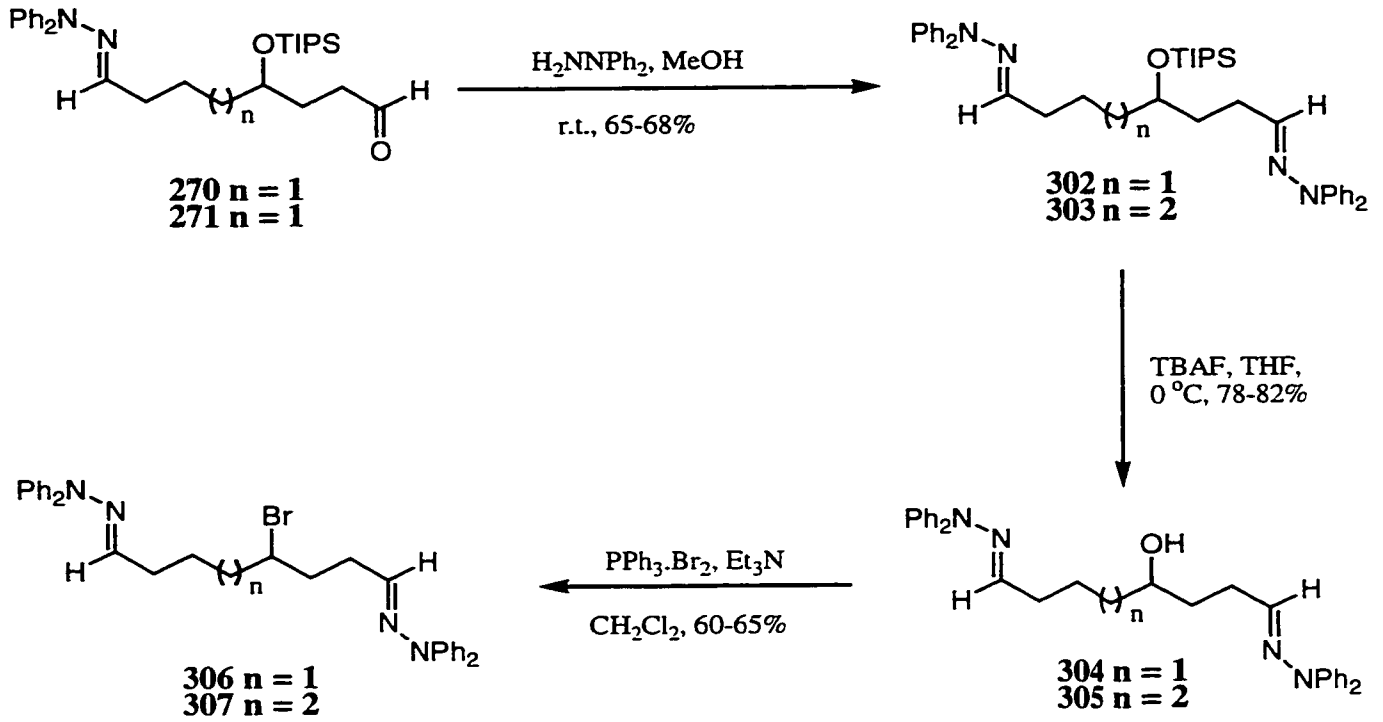
$Ph_3P.Br_2$ in the presence of Et_3N to convert –OTIPS group directly to Br to give compound **299**. However, these reaction conditions resulted in decomposition of the starting material.

Scheme 81: Attempted Activation of Double Bond



In our comparative study, we found that *N,N*-diphenylhydrazones are the best radical acceptors among different –C=N-R acceptors. At this stage, we decided to use *N,N*-diphenylhydrazone group for the activation of the double bond. In this case the radicals formed after the first and second cyclization are going to be equally stabilized. Scheme **82** depicts the synthetic route to the new radical precursors **306, 307**.

Scheme 82: Synthesis of Bis-Hydrazone Radical Precursors

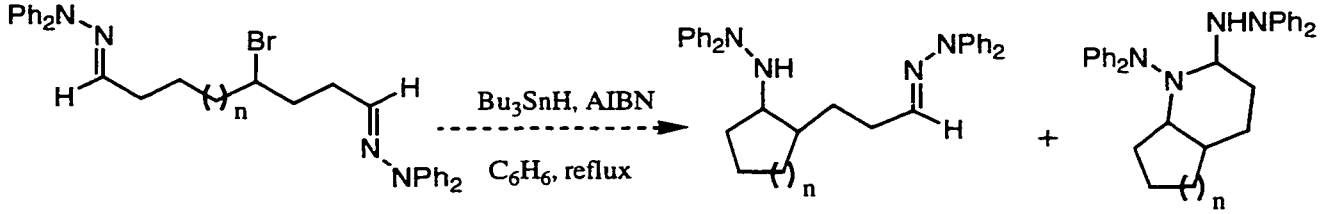


The aldehydes **270** and **271** were prepared as shown in Scheme **73**, were treated with one equivalent of *N,N*-diphenylhydrazine in methanol at room temperature to yield bis-hydrazones **302** and **303** in good yields (86-90%). Deprotection of the resulting compounds **302** and **303** was achieved with tetrabutylammonium fluoride in THF at 0 °C to give free alcohols **304** and **305** in 78-95% isolated yields. Subsequent bromination of the free alcohols with $PPh_3.Br_2$ in the presence of triethyl amine afforded the desired radical precursors **306** and **307** in 50-62% isolated yields.

With the new radical precursors in hand, the tandem radical reactions were performed under standard syringe pump conditions. The bromides **306** and **307** were dissolved in dry benzene and treated with tributyltin hydride and azoisobutyronitrile. The reaction mixture was refluxed for two hours and then allowed to cool to room temperature. TLC analysis of the reaction mixtures revealed the consumption of the

starting material and formation of three new products. The ^{1}H NMR analysis of the crude products indicated the formation of tandem products **310** and **311** along with monocyclized products **308** and **309**. Unfortunately, these products were very unstable and could not be isolated. All the purification efforts using neutralized silica gel, neutral alumina and preparative HPLC were unsuccessful.

Scheme 83: Tandem Radical Cyclizations of Bis-Hydrazone Precursors



306 n = 1
307 n = 2

308 n = 1
309 n = 2

310 n = 1
311 n = 2

As mentioned at the beginning of this chapter our studies related to the synthesis of 5,6-and 6,6-bicyclic ring systems are part of a larger set of experiments conducted in our laboratory to explore the feasibility of tandem reactions of aminyl radicals for the formation of various ring systems. Table **12** illustrates all the results obtained in this study.

The following conclusion can be drawn from these results:

(a) Tandem Cyclizations involving aminyl radicals generated from *N,N*-diphenylhydrazones are feasible only when the second ring formed is a five membered ring.

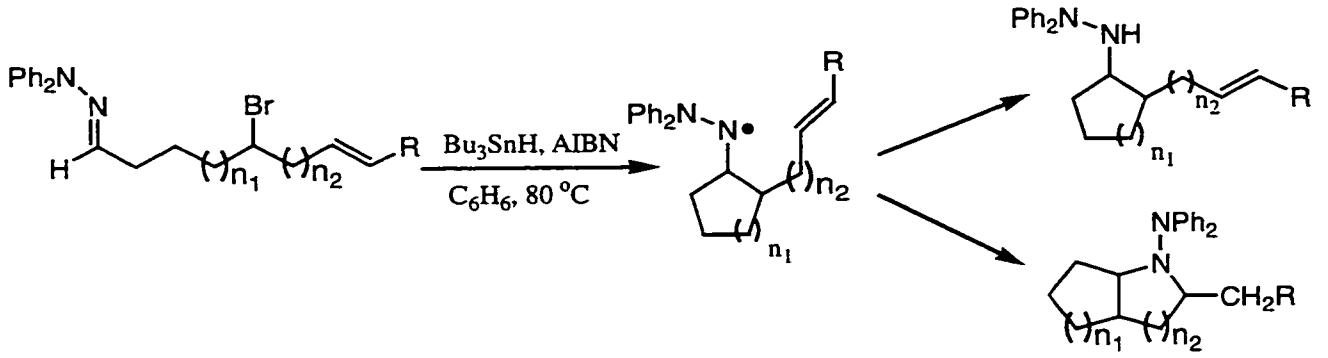
(b) The presence of an activating group on the double bond is necessary to ensure good yields of the tandem products.

(b) Best results are obtained in the synthesis of 5,5-bicyclic systems.

(c) 6,5-bicyclic ring systems are formed in reasonable yields.

(c) 5,6-and 6,6-bicyclic ring systems cannot be obtained via this method.

Table 12: Bicyclic Ring Systems via Tandem Radical Cyclizations



Entry	R	n_1	n_2	Reaction Conditions	Monocycl %	Tandem %	*Cis/trans*
1	H	2	1	Bu_3SnH, Benzene, reflux	-	11	1:1
2	Ph	2	1	Bu_3SnH, Benzene, reflux	-	30	1:1
3	Ph	2	1	TTMSS, Benzene, reflux	-	28	1:1
4	Ph	1	1	Bu_3SnH, Benzene, reflux	12	55	1:0
5	Ph	1	2	Bu_3SnH, Benzene, reflux	50	-	3:1
6	Ph	2	2	Bu_3SnH, Benzene, reflux	45	-	1:0

Chapter Four

Alkyl Radical Cyclizations onto Chiral Hydrazones

4.1 General Introduction

The synthesis of chiral compounds in enantiomerically pure form has become a virtual necessity. This is primarily due to the decreasing usefulness of the racemic products in the pharmaceutical, agrochemical and food industries. A racemic compound behaves as a mixture of two different products, of which only one has the desired properties, while the other is potentially harmful and at least undesirable. Significant efforts have been made in the past few decades to develop efficient synthetic pathways leading to enantiomerically pure compounds.

There are four general approaches commonly used to obtain enantiomerically pure compounds, each having its own advantages and disadvantages. The first approach involves incorporation of resolution step in the synthetic plan[109]. This method is only efficient if the undesired enantiomer can be recycled and for practical reasons resolution has to occur early in the synthetic plan. The second approach[110] involves the use of chiral substrates, which are usually chiral natural products such as carbohydrates, aminoacids and terpenes, etc. The third method is to use a chiral catalysts such as enzymes and bases to direct the conversion. In the fourth method a chiral group (chiral auxiliary) is deliberately attached to an achiral substrate in order to direct the reaction[111]. It can be removed once it has served its purpose. Thus, a chiral auxiliary 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.

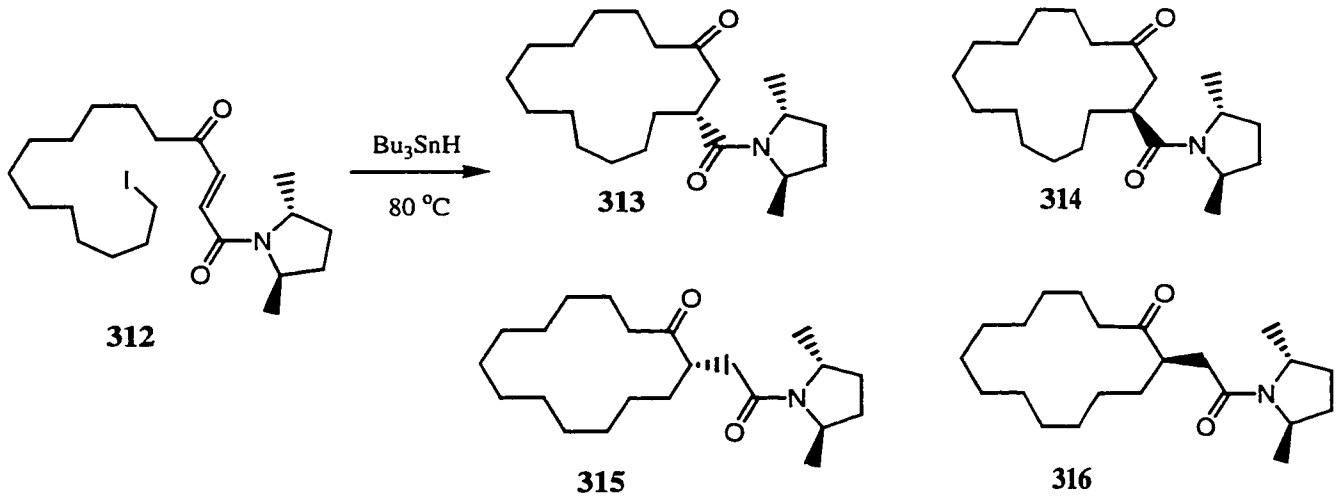
The reactions involving chiral auxiliaries are often predictable and reliable and this approach usually offers significant advantages, provided chiral auxiliaries fulfill the necessary conditions. These are, the chiral auxiliaries should be inexpensive and readily available and if used in stoichiometric amounts, should be recycled without loss of

enantioselectivity. Chiral auxiliaries have been very successfully used in enolate alkylation and aldol chemistry.

4.2 Chiral Auxiliary Induced Stereochemistry in Radical Reactions

Recent advances in radical chemistry have shown that in radical additions to alkenes, the configuration of the resulting stereogenic centers can be controlled by chiral auxiliaries attached to the radical acceptor (alkene). The requirements for control of configuration in these reactions are based on the concepts developed in carbanion and enamine chemistry[112]. That means, that the orientation of the chiral group intended to control the configuration of new stereogenic center formed must be fixed and the chiral group must shield differentially the diastereotopic faces of the radical acceptor.

Scheme 84: Free Radical Macrocyclization of Alkene bearing Chiral Auxiliary

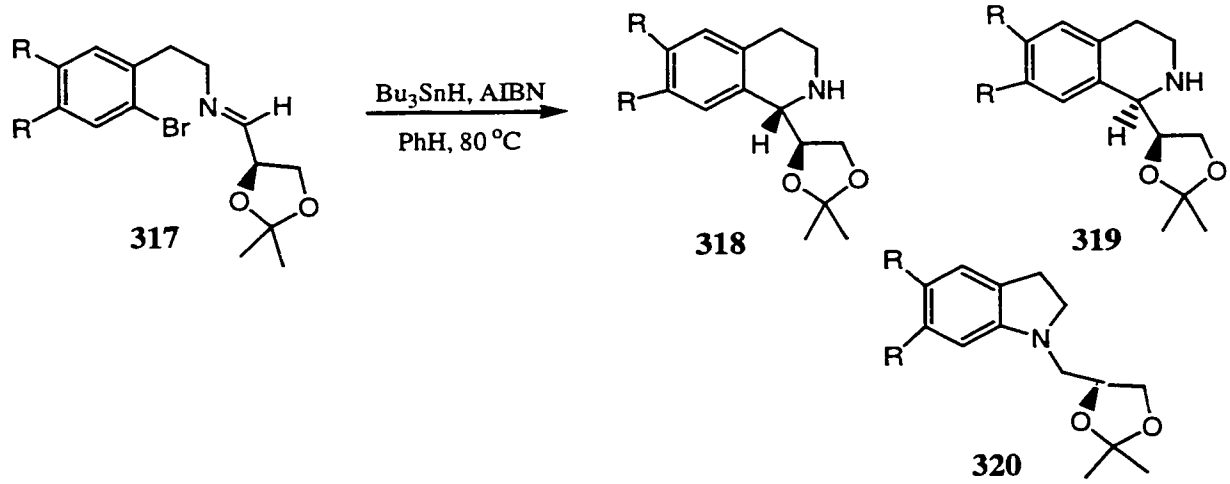


Porter and coworkers[113] have reported the high diastereoselective free radical macrocyclization of the olefin **312** bearing the dimethylpyrrolidine amide group as the chiral auxiliary leading to four diastereomeric products in 65-75% yield (Scheme **84**).

Two diastereomeric products **313** and **314** result from *endo*-cyclization via addition of the primary radical to the end of the alkene nearest to the amide. At 80 °C these two fifteen-membered ring products were formed with a selectivity of approximately 14/1, **313** being the major product. Two diastereomeric *exo* products **315** and **316** are formed as a 1/1 mixture. The ratio of regioisomers (*endo*/*exo*) is approximately 8:1 in this macrocyclization.

Diastereoselectivity induced by a chiral auxiliary has also been observed in the aryl radical cyclization onto imines[45]. As shown in Scheme **85**, the 6-*endo* cyclization of aryl radical to the carbon of the aldimino double bond in the imine **317**, afforded 1,2,3,4-tetrahydroisoquinolines **318** and **319** in 62-69% isolated yields, along with small amount of 5-*exo* product **320**. At 80 °C, compound **318** was obtained as the major product with a diastereomeric excess of 53-58%, which could be improved moderately (to 65% d.e.) by running this reaction at low temperature (60 °C). The enantiomeric excess of the major product is found to be 97%.

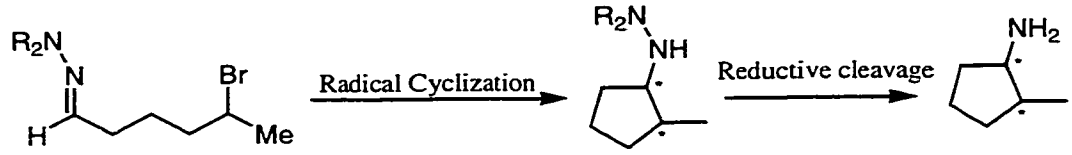
Scheme 85: Radical Cyclizations onto Imine bearing Chiral Auxiliary



4.3 Research Objectives

Encouraged by the successful cyclizations onto *N,N*-diphenyl- and other hydrazones, we decided to study the radical cyclizations of aldehyde hydrazones bearing chiral auxiliaries. Ideally the presence of the chiral auxiliary should influence the diastereoselectivity level of the radical reactions onto the chiral hydrazones. The employment of the chiral hydrazones could lead to cyclic chiral amines **323** by subsequent cleavage of the N-N bond of the chiral trisubstituted hydrazine **322** formed by the radical cyclization process (Scheme **86**). The reductive cleavage could be affected by hydrogenolysis or by employing samarium diiodide conditions, which have been successfully used in the reductive cleavage of the N-N bond of *N,N*-diphenyl hydrazines[114].

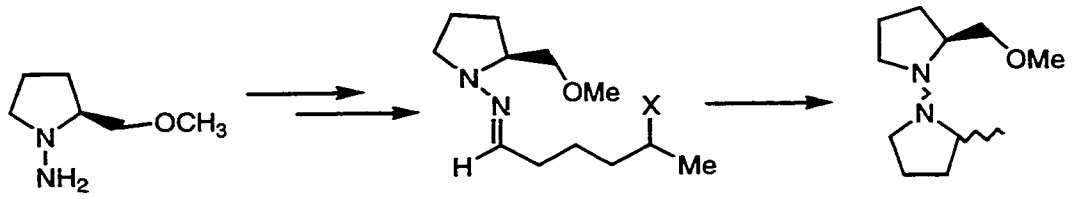
Scheme 86: Chiral Amines via Radical Cyclization



321 **322** **323**

(*S*) and (*R*) -1-Aminomethoxymethyl pyrrolidines (SAMP and RAMP) have been extensively used as chiral auxiliaries in α-alkylations of aldehydes and ketones, yielding excellent enantioselectivities and good overall chemical yields[115]. In fact, in the course of the development of modern synthetic methods in the field of asymmetric synthesis the SAMP-RAMP hydrazone methods opened a highly diastereo- and enantioselective route to a great variety of carbonyl compounds, alcohols, amines and heterocycles. Therefore, in our studies of radical cyclizations onto chiral hydrazones, commercially available SAMP hydrazine **324,** having the requisite chiral element, was chosen as a suitable starting material to prepare chiral hydrazones **325** as the radical precursors.

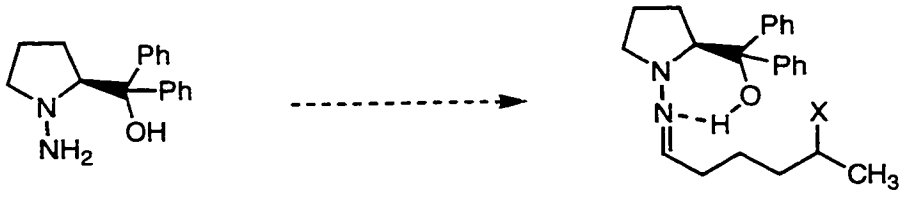
Scheme 87: Chiral Hydrazones containing Chiral Auxiliary Employed in Diastereoselective Radical Cyclizations



324 **325a, X = CSOMe** **325b, X = Br** **326**

Under Bu_3SnH/AIBN radical conditions compound **325** afforded a mixture of *cis* and *trans* cyclic hydrazines with the *cis* isomer being the major product. The diastereomeric excess was found to be 30% for compound **325a**. The bromo compound **325b** was found to be unstable for higher temperature experiments, as extensive decomposition was observed under Bu_3SnH/AIBN conditions at 80°C. However, when the cyclization reaction was carried out at lower temp (-78°C) using SmI_2/HMPA conditions, the only product obtained was the *cis* isomer with diastereoisomeric excess of 56%[116].

These results obtained with hydrazones bearing SAMP as the chiral auxiliary were encouraging. The diastereomeric excess was less than desired; yet these values are comparable to current literature methods. In order to have a better chance of success, we decided to replace the present chiral auxiliary with a modified one having structure **327**.



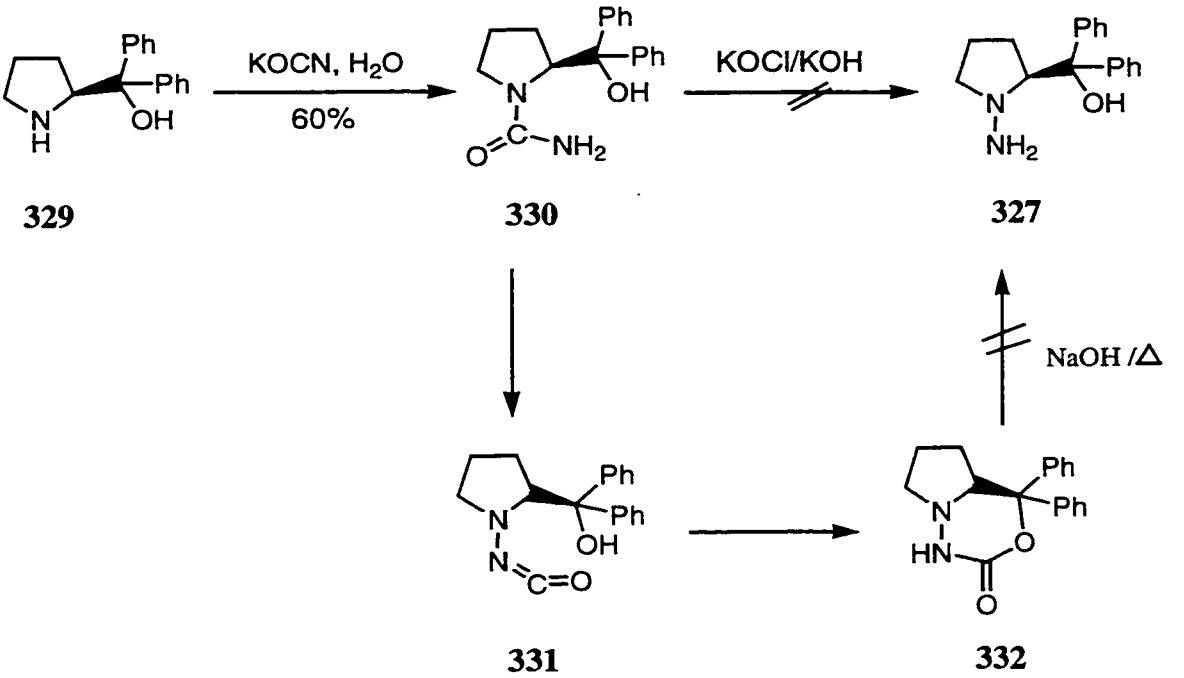
327 **328a, X = CSOMe** **328b, X = Br**

4.4 Synthesis of Chiral Auxiliary

In the new chiral auxiliary, the steric bulk of the side chain has been increased and the –OH group can be involved in hydrogen bonding with the hydrazone nitrogen. The presence of hydrogen bonding should provide a geometric bias to system **328** and the radical attack from one side should be preferred.

Scheme **88** reveals our initial attempts to prepare the desired chiral hydrazine **327** from α,α-diphenyl-L-prolinol **329**, via Enders and Kipphardts' protocol for *N*-amination[117], used in the latest synthesis of SAMP/RAMP hydrazines.

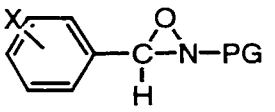
Scheme 88: Attempted Synthesis of *N*-Amino-α,α-Diphenyl-2-Pyrrolidine Methanol via Ender's Method



α,α-Diphenyl-L-prolinol **329** was treated with potassium cyanate in aqueous solution to give the urea derivative **330** in 60% yield. Compound **330** was treated with potassium hypochlorite in the presence of potassium hydroxide. Under these conditions, this compound should undergo Hoffman degradation leading to formation of hydrazine **327**. However, the compound isolated after completion of the reaction was not the desired hydrazine **327**. IR and ^{13}C NMR of the isolated compound showed the presence of a –C(O)- group in the compound, and the product was confirmed to be the cyclic compound **332**. This must arise from the intramolecular attack of the hydroxyl group on the carbon center of the isocyanate type compound **331**, which is formed as an intermediate in the expected rearrangement. Treatment of the cyclic compound **331** with NaOH under reflux resulted in the starting compound **329**, instead of the desired hydrazine **327**. The unsuccessful attempts to convert compound **332** to the desired product lead to the search of an alternate route to the chiral auxiliary **327**.

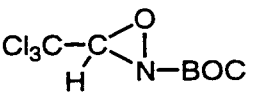
Electrophilic amination is an important synthetic reaction in which an electron poor nitrogen carried by the reagent is transferred to a nucleophilic center of the substrate to form a Nu-N bond in the product[118]. Inspired by earlier work by Schmitz and coworkers, Vidal *et al.* have shown that this process can be achieved by the means of *N*-alkoxycarbonyl–3–aryloxaziridines such as **333** and *N*-*t*-butoxycarbonyl–3 trichloromethyloxaziridine **334** (Fig. **8**). These reagents deliver their N-CO_2R fragment to nitrogen, carbon, sulphur and phosphorus nucleophiles to give under mild conditions the respective amination product in N-protected form[119].

Figure 8: Reagents for Electrophilic Amination Reaction



333

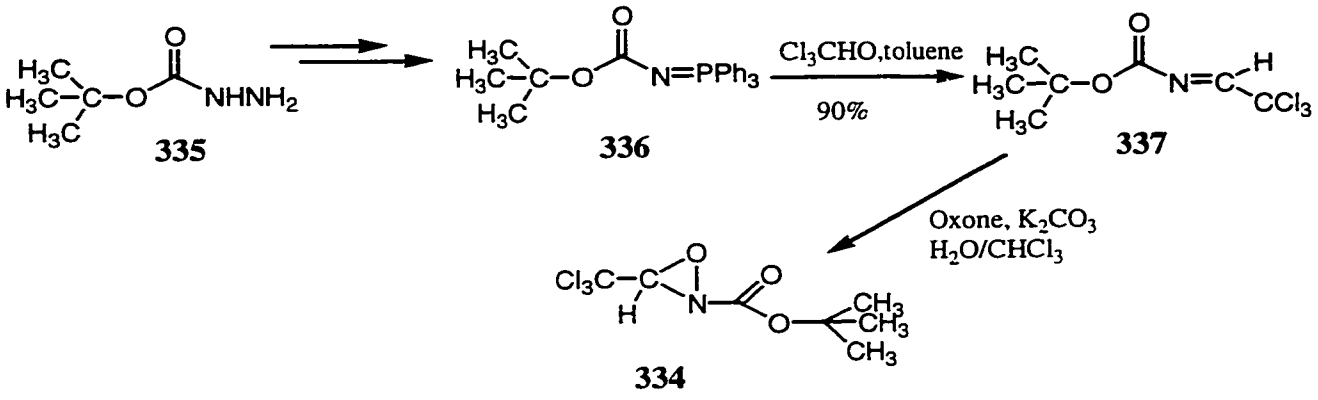
PG = BOC or MOC



334

Compound **334** has proved to be the most powerful electrophilic amination reagent, therefore this reagent was selected for the electrophilic amination of the starting α,α-diphenyl prolinol **329** (Scheme **89**). This reagent can be prepared in high yield via aza-Wittig reaction of Ph_3P=N-BOC **336** with chloral followed by oxone oxidation of the resulting imine **337** (Scheme **89**)[119]. Compound **336** can in turn be prepared from *t*-butylcarbazate **335** following the literature procedures[120].

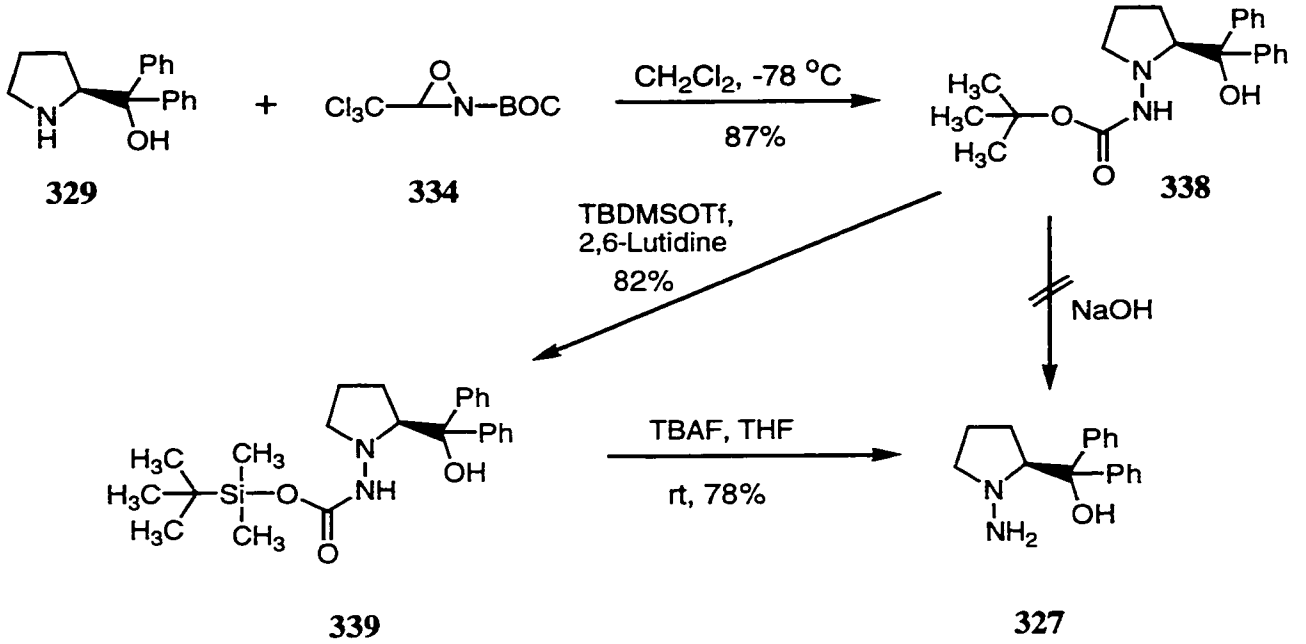
Scheme 89: Preparation of *N*-Butoxycarbonyl-3-Trichloromethyloxaziridine



Scheme **90** shows an alternative route for the synthesis of the desired chiral hydrazine **327**. The treatment of α,α-diphenyl prolinol **339** with oxaziridine **334** in dichloromethane at –78 °C afforded the aminated product **338** in 87% isolated yield. Initial attempts to deprotect **338** via refluxing in aqueous NaOH did not afford the desired product **327**[121]. Alternately, compound **338** was treated with *t*-butyldimethylsilyl trifuloromethanesulfonate in the presence of 2,6-lutidine in CH_2Cl_2 to afford compound **339** in 80% yield[122]. The desired product **339** has the same RF value as the starting compound **338**. Therefore purification by column chromatography was not very clean. However, compound **339** can be recrystalized from petroleum ether to give the pure compound in good yield. The *t*-butydimethylsilyl group of compound **339** was removed

by treatment with tetrabutylammonium fluoride in the THF at room temperature to afford the desired product **327** in 78%-isolated yield. The compound **327** proved to be unstable. Attempts to purify it by column chromatography failed, regardless of the packing material used. A small amount of the pure compound could be isolated by recrystalization from ether. Consequently compound **327** was prepared and used in the next step immediately after the first recrystalization.

Scheme 90: Preparation of *N*-Amino-α,α-Diphenyl-2-Pyrrolidine Methanol via Electrophilic Amination



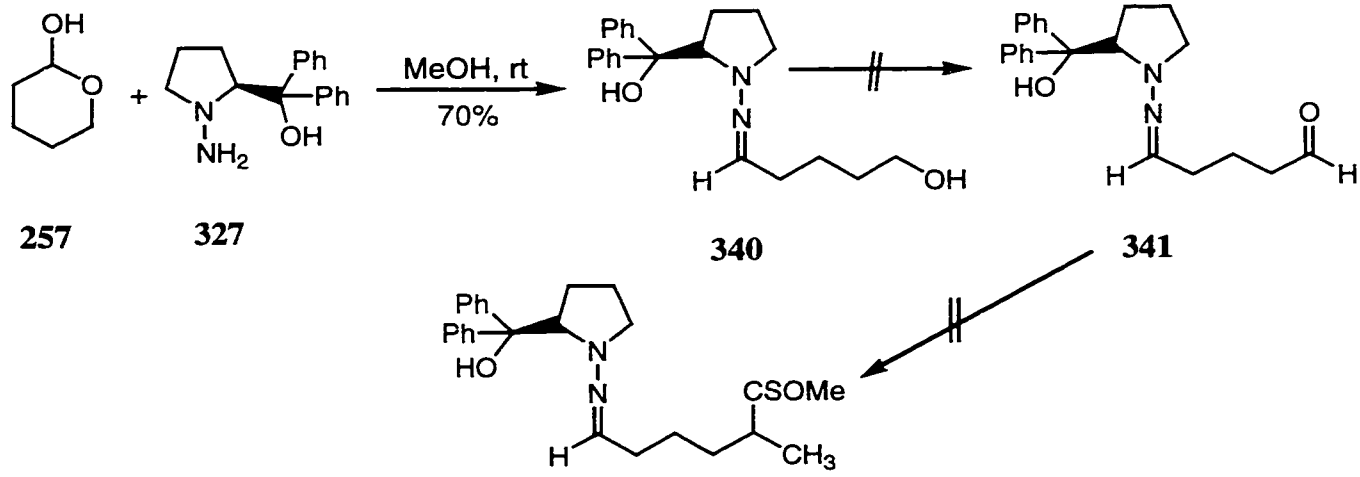
4.5 Substrate Synthesis for Radical Cyclizations

Having prepared the desired chiral hydrazine, the time came to use this compound in the synthesis of the hydrazone **328** required for the cyclization studies. As mentioned earlier, in our previous studies involving SAMP hydrazine as the chiral auxiliary, the bromo hydrazone was found to be unstable for high temperature reactions. Therefore

hydrazone **325a** was prepared for the cyclization carried out under Bu_3SnH/AIBN conditions at 80°C.

Keeping these results in mind, we set out to synthesize chiral hydrazone **328a** as shown in Scheme **91**. δ-Valerolactol **257**, obtained by reduction of the commercially available δ-valerolactone, was treated with one equivalent of the hydrazine **327** in methanol at room temperature to provide the desired hydrazone **340** in 80% isolated yield. As with the other hydrazones reported above, only the *E* geometric isomer was isolated from the reaction. Oxidation of alcohol **340** proved to be the challenging step. Under milder conditions involving SO_3/pyridine/Et_3N, starting material was recovered, along with only 10% of the desired product. All efforts to improve the yield of the desired product were unsuccessful. Stronger conditions involving the use of Dess Martin reagent as oxidant resulted in decomposition of the starting material. At this stage we decided to synthesize the hydrazone **328b** with Br as the radical precursor.

Scheme 91: Attempted Synthesis of Hydrazone 328a



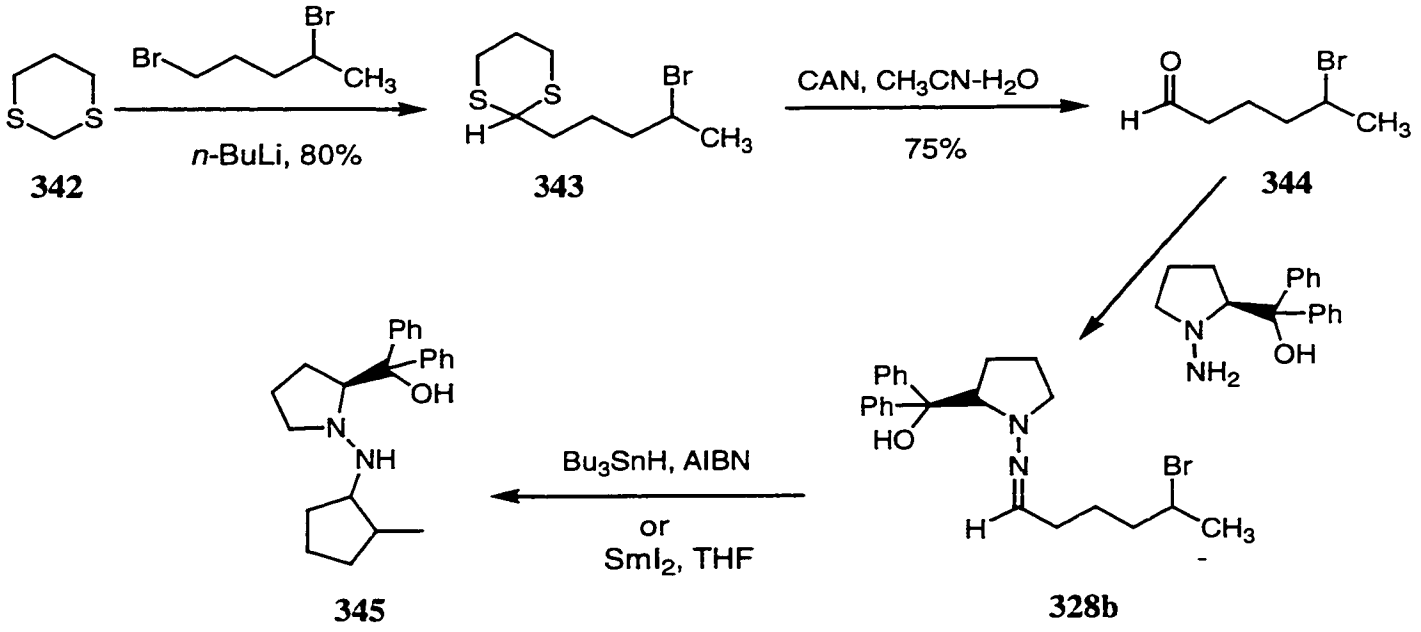
257 **327** **340** **341** **328a**

Scheme **92** outlines the synthesis of chiral hydrazine **328b**. Dithiane **342** was subjected to deprotection by *n*-butyl lithium at -10°C. Displacement of the primary

bromide of 1,4-dibromopentane by the resulting anion provided compound **343** in 80% yield[123]. Hydrolysis of dithiane-protected compound **343** to the corresponding aldehyde was affected by treatment with ceric ammonium nitrate (CAN)[124]. The resulting aldehyde **344** was not purified, but treated directly with the chiral hydrazine **327** to yield the bromohydrazone **328b** in 60% yield over these two steps.

As was found to be the case with other hydrazones, a key spectral feature of this hydrazone is also represented by the vinylic hydrogen (R_2N-N=$CHCH_2R$). This appears as a clear triplet at 56.51 ($J = 5.5H_2$) in the ^1H NMR spectrum. It can be deduced from the spectral data that a single geometric isomer resulted from the condensation of the intermediate aldehyde with the hydrazine **327**. Based on the literature precedent and our previous experience showing that hydrazones are formed predominantly as the *E* geometric isomer, compound **328b** was assigned as the *E* hydrazone (with the pyrrolidine substituent *syn* to the hydrogen).

Scheme 92: Synthesis of Chiral Hydrazone 328b

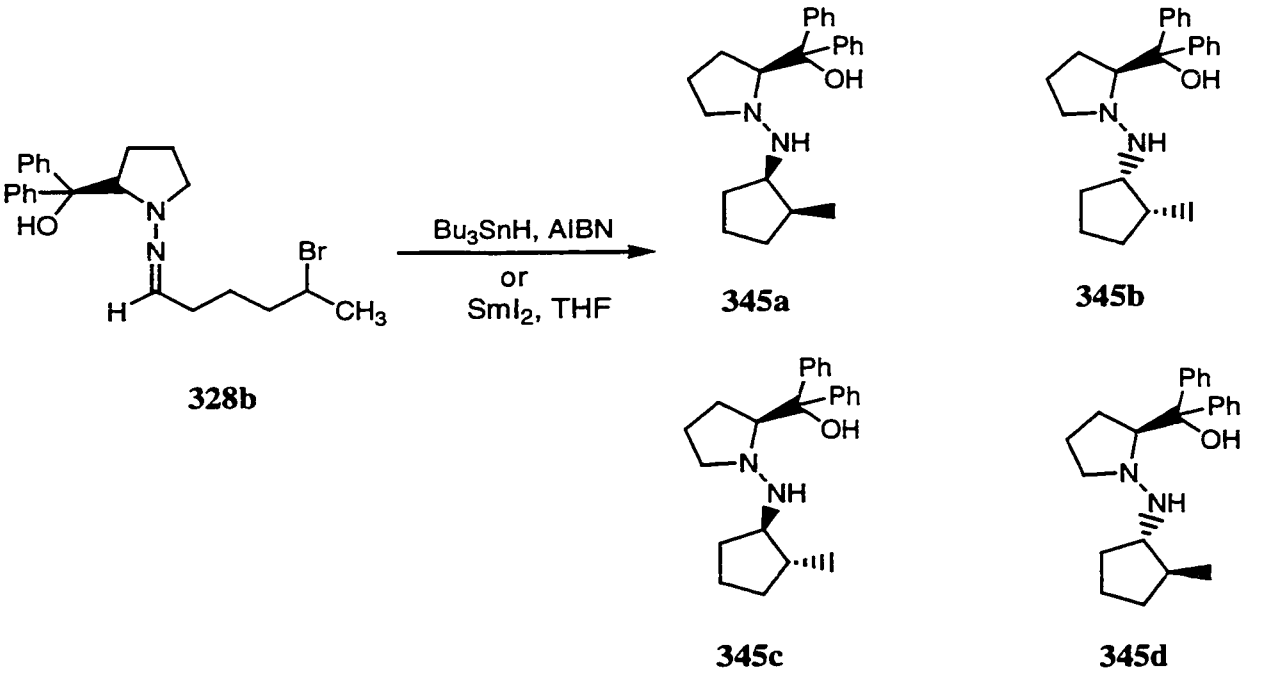


4.6 Results and Discussion

With the desired hydrazone in hand, the next step was to carry out the free radical cyclization. Hydrazone **328b**, was treated with a 0.02 M tributyltin hydride and AIBN in benzene and heated to reflux. TLC analysis of the reaction mixture indicated complete consumption of the starting material with the formation of two new more polar compounds.

There are three different stereogenic centers in the expected product, thus $2^3 = 8$ possible stereoisomers could be formed as a result of the cyclization process. As one of the stereogenic centers has a fixed configuration, in practice, only four different stereoisomers could be produced. Two *cis* and two *trans* stereoisomers are expected as shown in Scheme **93**.

Scheme 93: Possible Stereoisomers from the Radical Cyclization of Hydrazone 328b

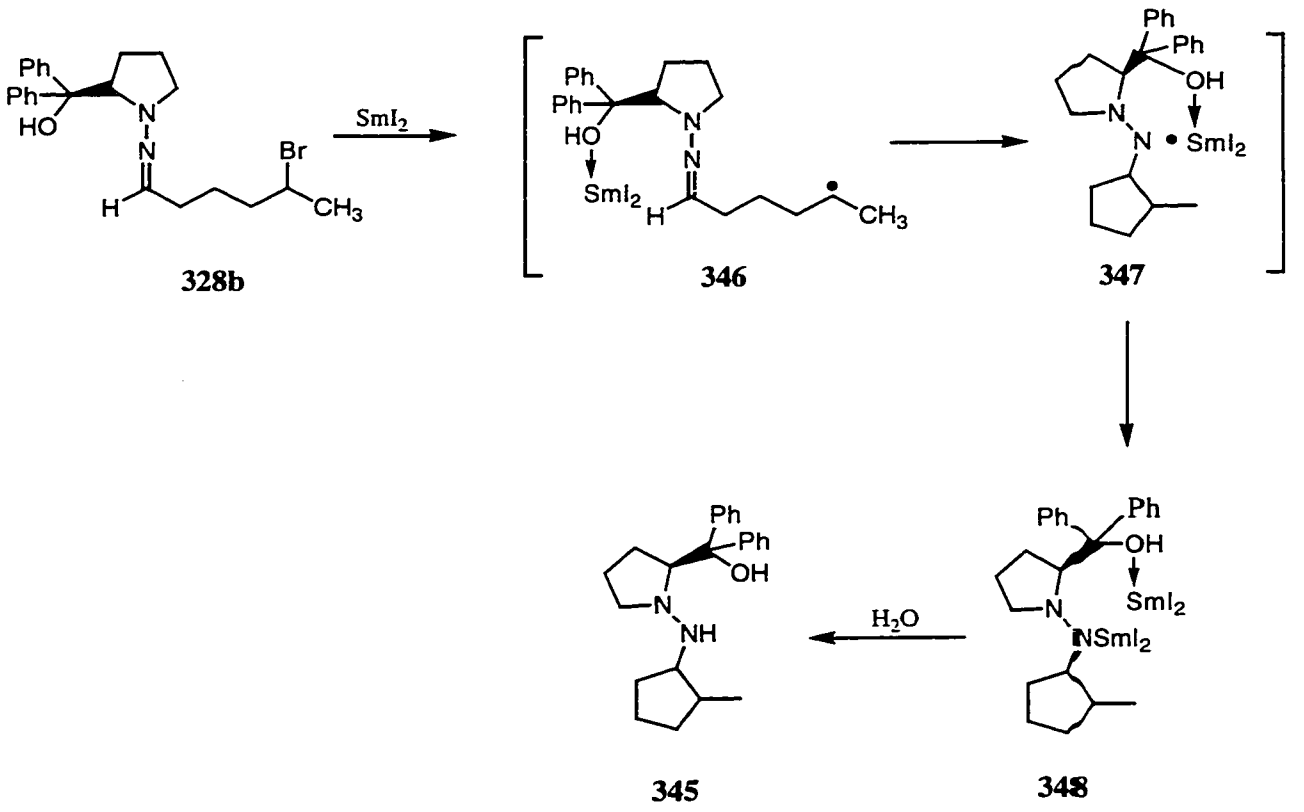


328b

The ^{1}H NMR spectrum of the crude reaction mixture revealed that both *cis* and *trans* geometric isomers were formed in a ratio of 2:1, *cis* being the major one. The *cis* and *trans* isomers could not be separated. Despite considerable effort the diastereomeric ratio could not be determined.

The diastereomeric ratio is a function of temperature. Higher temperature leads to lower *cis/trans* ratio (more *trans* formed). Previous studies in our laboratory have shown that high *cis/trans* selectivity can be achieved for 5-*exo* alkyl radical cyclizations, through the use of SmI_2 in the presence of HMPA. Therefore we decided to conduct the reaction at lower temperature and to minimize potential side reactions. The bromide **328b** was found to be unreactive towards SmI_2/HMPA at –78 °C to 0 °C in the presence of 1-4.5 equivalents of SmI_2. Repeating the reaction with 8 equivalents of SmI_2 and slowly warming the reaction mixture to 0 °C resulted in complete consumption of the starting material.

Scheme 94: Proposed Mechanism for the SmI_2 Mediated Hydrazone Cyclization



It is not clear why more than 8 equivalents of SmI_2 were required to complete the reaction, since only three equivalents should in theory be sufficient. A likely mechanism for this reaction is given in Scheme **94**. This process involves the initial association of samarium with the free alcohol. The second equivalent of samarium iodide is consumed in generating the alkyl radical **346**. This subsequently cyclizes to generate the hydrazine radical **347**. A third transfer then occurs from samarium to the nitrogen radical generating an N-SmI_2 species **348** and consuming the third equivalent of samarium iodide. The N-SmI_2 and O-SmI_2 bonds are hydrolyzed on work-up conditions to give the observed hydrazine **345**.

TLC analysis of the reaction mixture indicated the formation of three new more polar compounds. ^1H NMR analysis of the crude product indicated that a 4:1 mixture of the *cis* and *trans* isomers was formed. However, this reaction was not very clean and other decomposition products were also formed. Flash chromatography was used to separate the *cis* and *trans* isomers. The *cis* and *trans* isomers were separated, yet both of the isomers were contaminated with some unidentified compounds. Further attempts at purification of these compounds were unsuccessful.

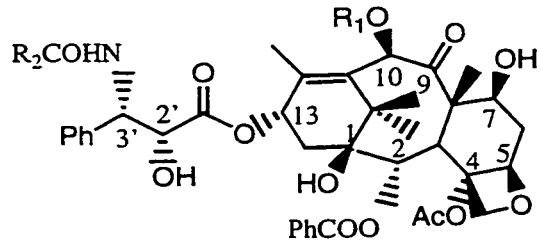
In view of these complications this research was terminated at this stage and, for the future, a different strategy will be required if significant induction is to be achieved.

Chapter Five

Synthesis of Taxol/Taxotere Mimics

5.1 General Introduction

The anticancer taxanes, Taxol® (Paclitaxel) and Taxotere® (Docetaxel) are the most promising new chemotherapeutic agents developed for cancer treatment in the past decade[125]. Taxol is a natural product isolated from the bark of the yew tree and taxotere is the semisynthetic non-natural compound. These compounds have attracted the attention of scientists throughout the world due to their unusual bridgehead double bond structure, potent antitumor[126] (active against poorly responsive solid tumors) and antileukemic activities and the novel mode of action.



Taxole R_1 = Ac, R_2 = Ph

Taxotere R_1 = H, R_2 = *t*-Bu-O

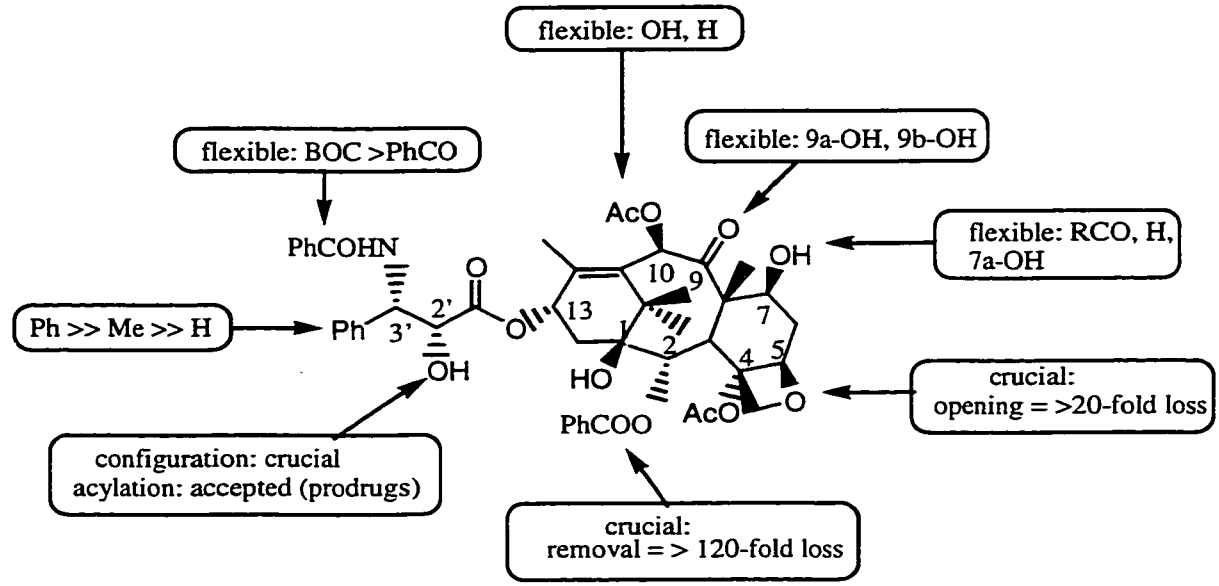
Current antitumor drugs such as Vincristine and Vinblastine interact with tubulin by preventing the assembly of tubulin into microtubules. In contrast, taxol and taxotere act as promoters of tubulin assembly as well as inhibitosr of the disassembly process[127]. They reduce the critical concentration of tubulin for assembly *in vitro*, and enhance and

stabilize microtubules against depolymerizarion. They bind to these rod like structures that form the cytoskeleton and thus inhibit cell division. In *vivo* in interphase cells these drugs promote the assembly of stable microtubules, which then associate laterally to form bundles. Such cells may progress through the cell cycle, but when they enter mitosis, multiple asters are formed instead of normal mitotic spindles and the cells are arrested in the M phase. This novel mode of action led to the selection of taxol as a new lead structure for further pharmacological studies.

A principal initial obstacle to the wider therapeutic use of taxol was the limited supply. Taxol was isolated only in low yields (40-165 mg/Kg bark) from very slowly growing Pacific yew trees that are sparsely distributed in the Northern Hemisphere[128]. Therefore alternative approaches for obtaining taxol have been explored. These include isolation of taxol from renewable foliage[129] and other tissues of taxol species, production in tissue culture of taxus plant cells[130], production by culture of taxol producing endophytic fungus and semisynthesis of the drug or its analogues such as taxotere from baccatin III or related taxoid metabolites that are readily available from renewable sources[125]. In fact taxotere was found to be more active than taxol. Although four groups in the United States and two in Japan have achieved the total synthesis of taxol, these routes are not yet commercially viable owing to the multiple synthetic processes involved.

Recent reports on clinical trials of taxol and taxotere have disclosed that these highly effective drugs have some undesired side effects as well as multidrug resistance. This simply emphasizes the need for new therapeutics with a better risk/reward profile. In a broader sense, better understanding of the structure activity relationship (SARs) of taxol and its derivatives will be pivotal in the design and synthesis of a new generation of taxol based antitumor agents with improved physical, chemical and biological activities. An improved understanding in this field can lead to the rational design and synthesis of simple "taxoid mimics' with less functionality and better therapeutic profile.

Figure 9: Structure-Activity Relationships of Taxol



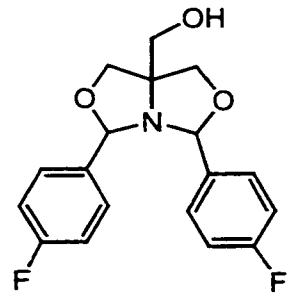
Intense studies on the taxoid framework and its diterpenoid moiety have been performed in attempts to identify the paclitaxel pharmacophore[131]. A broad summary of these SAR studies is shown in the figure **9**, and can be stated as follows: 1) SIDE CHAIN: the presence of the C-13 side chain is an absolute requirement for activity and the length, hydroxyl substituent at C-2´ and the phenyl group at C-3´ are all needed for the activity. Variation of substituents on the nitrogen at C-3´ is tolerated including aromatic or aliphatic groups as amides or carbamates. The natural taxol stereochemistry of 2´*R*, 3´*S* is markedly more active than the other possibilities. Minor changes in the side chain can have profound effects on activity; therefore the side chain is a key recognition element; 2) POSITIONS 7, 8, 9 and 10: variations in these positions across the top of the molecule can be made without destroying activity and even fairly large substituents are tolerated. Moderate enhancements of activity have been achieved by modifications at these positions, and the 7- and 10- positions are used as handles to attach polar groups in attempts to enhance solubility. These positions do not appear to be

critical for receptor binding; 3) POSITIONS 2, and 4: removal of either the 2-benzoate or the 4-acetate causes dramatic loss of activity and these positions appear necessary for interaction with the binding site; the presence of the 4,5-oxetane is necessary for activity but it is not clear whether it is involved in binding or serves as a "conformational lock" on the preferred binding conformation. Most of the compounds prepared for analysis of structure activity relationships were deliberately modified at a single position to obtain baseline data and the next step will be to combine multiple favorable changes to create more advanced analogues.

5.2 New Taxol Mimic

Recently Tanaka and Nozaki[132] have found that a small synthetic compound designated as GS-164 (**349**) (Fig.**10**) interferes with the assembly of porcine microtubule proteins and has cytotoxicity against a wide range of human tumor cell lines. The *in vitro* microtubule polymerization of the drug was found to be one tenth that of taxol. In this study, microtubule polymerization assay and flow cytometric measurement techniques were used to investigate the mode of action of GS-164 in comparison with taxol. The results from these studies indicated that GS-164 stimulates microtubule assembly by a similar mechanism to that of taxol.

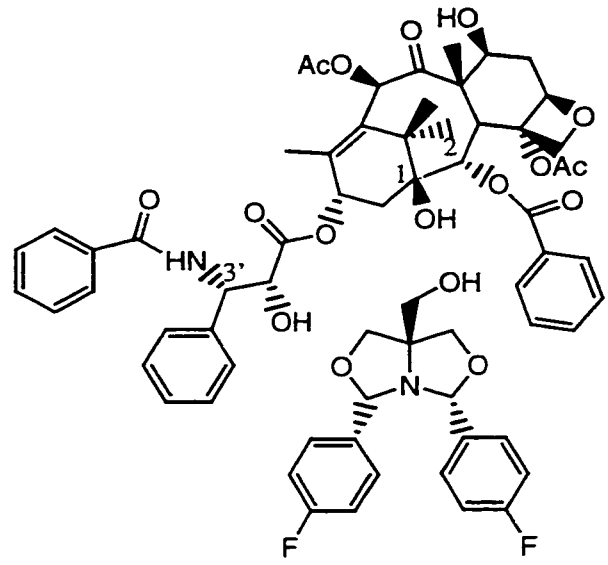
Figure 10: Taxol Mimic GS-164



349

To understand the structural elements of GS-164 responsible for its tubulin polymerizing activity, the stable conformations of GS-164 and taxol (generated by molecular mechanics calculations) were analyzed. It was suggested that one of the two phenyl groups of GS-164 was homologous to the phenyl group in the benzoyloxy side chain at position 2 of taxol and other phenyl group of GS-164 was homologous to the side chain phenyl ring at position 3' of taxol. Furthermore the –OH group and one ring oxygen of GS-164 may correspond to the –OH group at position 1 and the ester oxygen at position 2 of taxol respectively (Fig **11**).

Figure 11: Comparative Conformational Analysis of GS-164 and Taxol



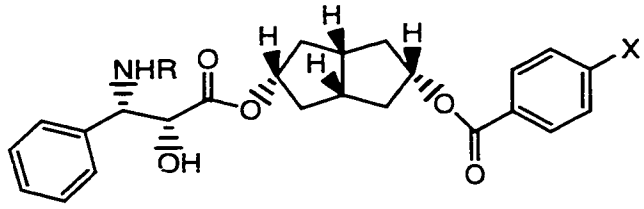
The comparative conformational analysis suggested that GS-164 mimics the minimum essential structural elements of taxol responsible for its tubulin polymerization stimulatory activity and further substantiates the importance of the two phenyl groups at position 2 and position 3' of taxol. However, the cytotoxicity of GS-164 against human tumor cells was 1000-fold lower than that of taxol, whereas when assayed *in vitro*,

microtubule polymerization stimulatory activity of the drug was one tenth that of taxol. This discrepancy between *in vitro* and *in vivo* activities of GS-164 and taxol might be a consequence of insufficient uptake of GS-164 through the cellular membrane of the animal cells. This suggests that by introducing hydrophobic side chains into GS-164, its *in vivo* activity could be improved up to *in vitro* level.

5.3 Research Objectives

Encouraged by the interesting results from the above studies, we decided to evaluate other simplified compounds as taxol/taxotere mimics. Two series of compounds **350** and **351** having minimum essential sites of taxol/taxotere were chosen as synthetic targets for biological evaluation as taxol analogues. As seen in the figures **12** and **13**, these compounds have simplified structures as compared to taxol, but they retain critical shapes and groups required for its interesting activity.

Figure 12: Bicyclo[3.3.0]octane Compounds as Taxol Mimics



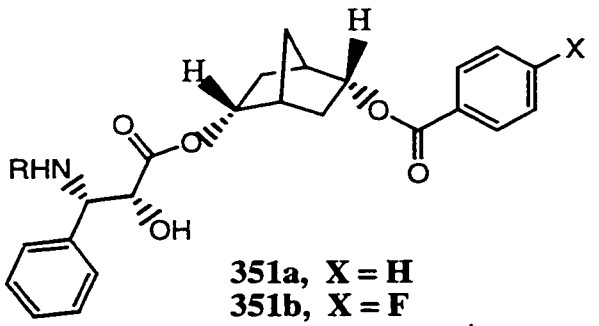
350a, X = H
350b, X = F
350c, X = CF_3

Compounds **350a**, **b** and **c** have structural similarity with GS-164 with some modifications. These compounds have a bent conformation with two *cis* fused five-membered rings as in GS-164, whereas, the CH_2OH group, the center nitrogen atom and the ring oxygen atoms are absent. The comparative conformational studies of GS-164 and taxol have indicated that one of the ring oxygens of the GS-164 is homologous to the

ester oxygen of the C-2 benzoate group of the taxol. In our target compound, we have replaced one ring oxygen and one phenyl group with the C-2 benzoate group of the taxane structure. Results from recent SAR study on taxol have indicated that the C-1 hydroxyl group is not required for its biological activity[133]. Furthermore in the above-discussed studies of GS-164, the ring nitrogen, and the other ring oxygen were found not to be so critical. Therefore these groups have been removed from the target compounds **350a, b** and **c**.

The presence of the –OH group at position 2' of taxol has been shown to increase the affinity of taxol for tubulin[134]. The cytotoxicity of GS-164 *in vivo* experiments has been found to be 100 times less than in the *in vitro* studies. This decrease in cytotoxicity has been explained as a consequence of decreased uptake of GS-164 through the cellular membrane of the animal cells, thereby emphasizing the importance of C-2' –OH group and entire hydrophobic chain. Therefore, in order to have cytotoxicity comparable to taxol and more than GS-164 the entire hydrophobic side chain has been installed in the compound **350.** In SAR studies of taxol the substitution of the phenyl group of the C-2 benzoate group has been found to affect the cytotoxicity[135]. Furthermore, considering the presence of *p*-fluoro substituted phenyl rings in GS-164, we decided to synthesize compounds **350b** and **350c** as well. A comparison among these compounds will establish if the presence of an electron-withdrawing group at the para position is really important for the biological activity of these simplified compounds.

Figure 13: Bicyclo[2.2.1]heptane Compounds as Taxol Mimics



351a, X = H
351b, X = F
351c, X = CF_3

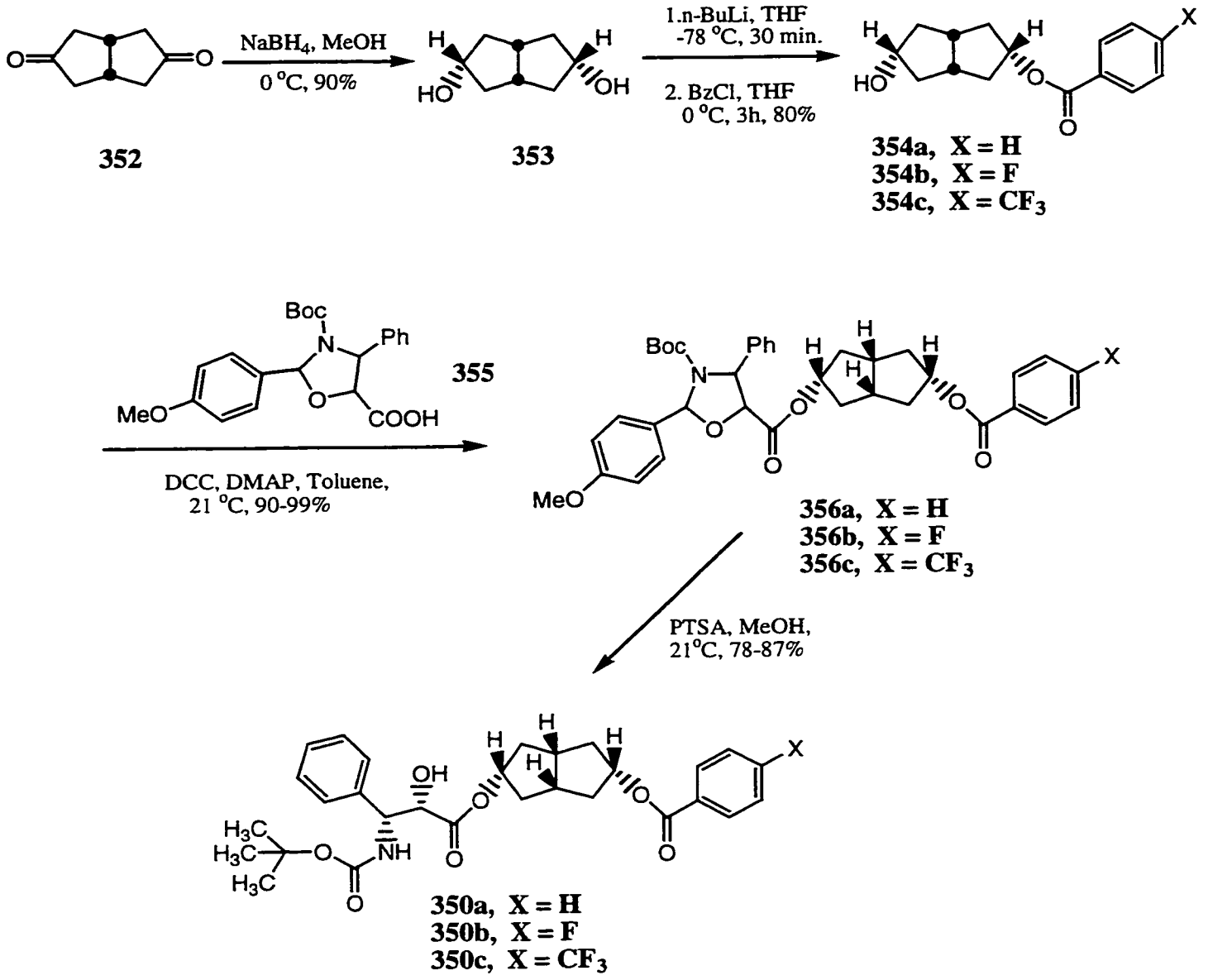
Compounds **351a, b** and **c** (Fig **13**) are markedly simplified analogues of taxol/taxotere. These compounds have a bent conformation same as in the A and B rings of the Southern Hemisphere of the taxane skeleton, with essential requirements for taxol type activity. These features include the presence of C-13 side chain and C-2 benzoyloxy group and these two hydrophobic groups are two carbon atoms away, having 1,4 relationship same as in taxol/taxotere.

Gueard *et al.*[125c] have postulated that during the binding of taxol to tubulin, the benzoate group at position 2 could locate in the core region of the protein and the phenyl group at 3' and the –OH at position 2' could stabilize the drug protein complex through direct interaction. Mastropoalo and coworkers[136] have reported crystal structure data on taxol indicating that the benzoate group at position 2 and the phenyl at C-3' are close to each other and possibly influence each other's orientation in a polar environment. Compounds **351b** and **c** were also synthesized to evaluate the presence of electron withdrawing group at the para position of the phenyl ring of benzoate group.

5.4 Synthesis of Taxol Mimics

Scheme **95** outlines the synthetic process leading to the target compounds **350a, b** and **c**. The synthesis of the compounds **350a, b** and **c** commenced with the reduction of commercially available *cis*-bicyclo[3.3.0]octane-3,7-dione **352** with sodium borohydride[137] in methanol at 0 °C to give selective formation of the desired diol **353** in 90% isolated yield. The presence of only five signals in the ^{13}C NMR spectrum established the plane of symmetry in the diol. The structure was confirmed as the endo-*endo* isomer by noe experiments. The irradiation of the bridgehead proton H-1 resulted in 1.2% enhancement in the signal for H-3. Had this compound been the *exo-exo* isomer, then there should be no enhancement in the signal. Molecular modeling calculations have shown that H-1, H-3 interproton distance for the *endo-endo* isomer is 2.9Å while this distance is 4Å for the *exo-exo* isomer. Nuclear overhauser effects can be observed for interproton distance up-to 3.5Å. Therefore the presence of a 1.2% noe enhancement confirmed the compound **353** to be the 3-*endo*-7-*endo* diol.

Scheme 95: Synthesis of Bicyclo Compounds 350a, b and c



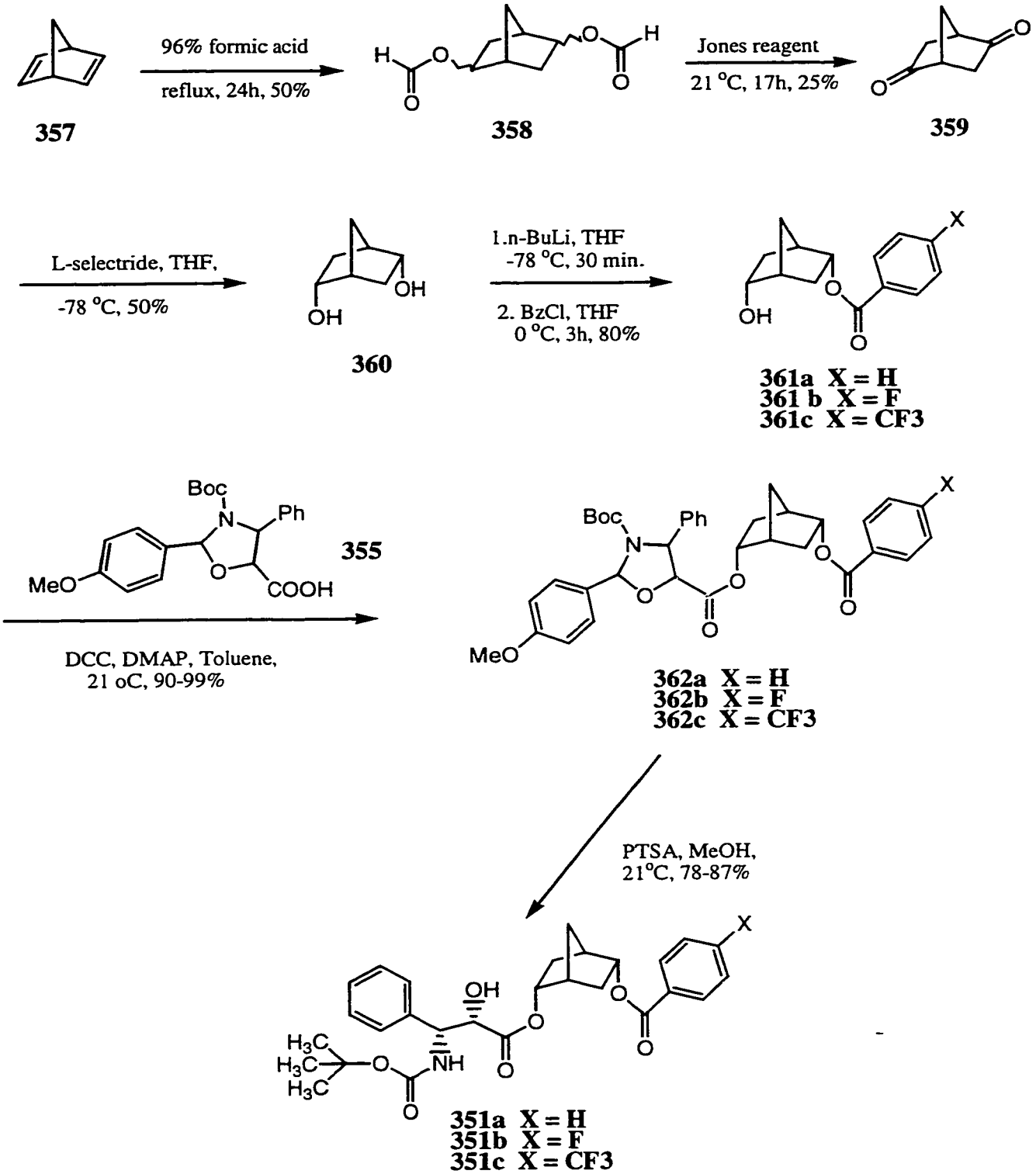
Treatment of diol **353** with one equivalent of benzoyl chloride in the presence of *n*-BuLi in THF at –78 °C afforded 80% of the monobenzoate **354a**[138]. Compound **354a** was coupled with (2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-(*t*-butoxycarbonyl)-oxazolidine-5-carboxylic acid **355** (protected form of taxotere side chain)[139] in the

presence of 1, 3-dicyclo carbodimide and 4-dimethylaminopyridine at 21 °C to yield 99% of the esterification compound **356b.** Acid mediated oxazoline cleavage of the ester was conducted with *p*-toluenesulfonic acid (PTSA)[138] in methanol without removal of the Boc group to give the desired compound **350a** in 87% of isolated yield. Compounds **350b** and **350c** were also obtained in good overall yields from 3-*endo*,5-*endo* diol **353**, via treatment with one equivalent of *p*-fluorobenzoyl chloride and *p*-(trifluoromethyl) benzoyl chloride respectively, followed by coupling and deprotection reactions as for compound **350a**.

Synthesis of compounds **351a**, **351b** and **351c** commenced with formylation-oxidation of the commercially available norbornadiene **357** via a known procedure, but with some modifications[140] (Scheme **96**). A solution of diene **357** and 96% formic acid was gradually warmed to reflux for 24 h and subsequent distillation of the crude product afforded the diformylated compound **358** in 50% isolated yield. The resulting compound **358** was oxidized with Jones reagent (CrO_3/H_2SO_4/acetone) at room temperature for 17 h to afford 24% of the desired bicyclo[2.2.1]heptane-2,5-dione **359**. Reduction of compound **359** with sodium borohydride gave a 3:1 mixture of the 2-*endo*, 5-*endo* and 2-*exo*, 5-*exo* diols, confirmed by ^{1}H NMR analysis. However, the use of lithium tri-*sec*-butylborohydride (L-selectride)[141] as reducing agent resulted in the selective formation of the 2-*endo*, 5-*endo* diol **360** as the sole product. No other isomers were detected by ^{1}H and ^{13}C NMR analysis. The presence of only four resonances in the ^{13}C NMR spectrum established the C_2 symmetry of the diol. A comparison of the ^{1}H NMR spectrum of the compound **360** with the spectrum of the known 2-*exo*,5-*exo* diol confirmed that compound **360** was the *endo-endo* diol.

Treatment of the diol **360** with one equivalent of benzoyl chloride in the presence of *n*-butyllithium in tetrahydrofuran at –78 °C afforded the monobenzoylated compound **361a** in 75% isolated yield. After monobenzoylation, the C_2 symmetry of the diol is lost and compound **361a** was expected to be a mixture of positional isomers. However, the ^{1}H and ^{13}C NMR analysis indicated the presence of only one compound. The isomeric mixture of compounds **361a** was coupled with (2*R*,4*S*,5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-(*t*-butoxycarbonyl)oxazolidine-5-

Scheme 96: Synthesis of Bicyclo Compounds 351a, b and c



carboxylic acid **355** in the presence of 1,3-dicyclohexylcarbodimide and 4-dimethylaminopyridine at 21 °C to yield 99% of the esterification compound **362a.** The doubling of important signals in ^{1}H and ^{13}C NMR spectra confirmed the presence of a diastereomeric mixture. However the separation of the mixture was unsuccessful at this stage.

Therefore the isomeric mixture of esters **362a** was treated with *p*-toluenesulfonic acid (PTSA) in methanol to achieve the oxazolidine cleavage without removal of the *t*-butoxycarbonyl group to give the desired compound **351a** in 87% of isolated yield. The isomeric mixture was separated via reverse phase HPLC. The absolute configurations of the separated products have not been assigned. The compounds **351b** and **351c** were also obtained in good overall yields from 2-*endo*,5-*endo* diol **360**, via treatment with one equivalent of *p*-fluorobenzoyl chloride and *p*-(trifluoromethyl)benzoyl chloride respectively, followed by the coupling and deprotection reactions same as compound **351a.**

5.5 Biological Evaluations

All the above-synthesized compounds (**350a**, **b**, **c** and the separated isomers of **351a**, **b**, and **c**) were evaluated for their ability to promote assembly of tubulin into microtubules. Unfortunately these compounds failed to polymerize tubulin under standard conditions. The absence of biological activity in these compounds indicates that the presence of the diterpenoid moiety and some additional functionality of the taxanes is an absolute necessity for taxol-like tubule polymerization activity. Furthermore, an improved knowledge of SAR of taxol and analogues is required to design simplified compounds with taxol-like activity. Our compounds contain the minimum essential sites of taxol equivalent to the above-discussed GS-164 and these compounds were expected to show at least GS-164 like activity. However, the biological activity of GS-164 may result in part from the central nitrogen. This atom may be important in small taxol like mimics. No biological activity in our compounds may also indicate that the compound GS-164 has a different mode of action as compared to taxol and may bind at a different site.

Chapter Six: Experimental

General Considerations

Melting points were determined in capillary tubes with a Thomas-Hoover Unit-melt apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bomem Michelson 100 FTIR spectrometer. Proton magnetic resonance spectra (^{1}H 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 AMX500 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). The residual $CHCl_3$ signal was used as an internal reference, $CDCl_3$ ^{1}H; δ 7.24 ppm; ^{13}C: δ 77.0 ppm. Chemical shifts are reported in ppm downfield from trimethylsilane (δ scale). The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (J = Hz) and number of protons are indicated in parentheses. Mass spectra (MS) were determined on a V. G. micromass 7070 HS instrument using an ionization energy of 70 eV. Elemental analyses were conducted by M-H-W Laboratories, Phoenix, Az, USA. 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.

Unless otherwise stated, all nonaqueous reactions were performed under an atmosphere of nitrogen in flame-dried glassware equipped with stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Reactions were monitored by analytical thin layer chromatography (TLC) using commercial aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Visualization of the TLC spots was accomplished with ultraviolet light, iodine vapor, treatment with 2.5% ethanolic solution of *p*-anisaldehyde containing 3% aqueous H_2SO_4 (w/v) or by treatment with ammonium molibdate in 10% aqueous H_2SO_4 (w/v) and subsequent heating. Product purification by conventional and flash column chromatography was performed using E. Merck Silica Gel 60 (70-230 or

230-400 mesh). Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvents with a Büchi rotatory evaporator connected to water aspirator. Trace solvents were removed on a vacuum pump. All compounds were stored at -15 °C in vials flushed with nitrogen.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60 °C. Anhydrous diethyl ether (ether) and anhydrous tetrahydrofuran (THF) were distilled from benzophenone/sodium. Dry benzene, toluene, dichloromethane (CH_2Cl_2), triethylamine, ethanol and diisopropylamine were distilled from calcium hydride. Anhydrous hexamethylphosphoramide (HMPA) was obtained by distillation under a reduced pressure from calcium hydride and stored under 4 Å molecular sieves. All commercial starting materials were purchased from Aldrich Chemical Company unless otherwise stated.

General Procedure for Radical Cyclizations under Bu_3SnH/AIBN Conditions

The hydrazone or oxime (1 eq) was dissolved in dry benzene (0.007 M soln), nitrogen was bubbled through the solution for 30 min., and the solution was heated to a steady reflux. Tributyltin hydride (1.2 eq), and AIBN (0.34 eq) were dissolved in dry benzene (0.02 M soln) and the solution was purged with nitrogen for 20 min. The latter solution was then added to the refluxing hydrazone or oxime solution at a rate of 5.0 ml/hr using a syringe pump. After addition of the tin hydride was complete, the reaction mixture was refluxed for another 30 min. before cooling to room temperature. The resulting solution was concentrated and purified by flash chromatography on deactivated silica gel (pet ether, to remove Bu_3SnH and Bu_3SnBr; followed by 50% CH_2Cl_2/pet ether). All the fractions not containing tin compounds were collected along with approximately 100 mL of additional eluent. ^1H NMR analysis of the 'semi-crude' mixture indicated the ratio of different cyclized products formed. Authentic samples and closely related models of the possible products were prepared separately for comparison.

General Procedure for the Bromination of Alcohols:

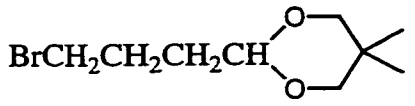
Triethylamine (1.2 equiv) was added to a solution of triphenylphosphine (1.2 equiv) in dry dichloromethane (generally enough to prepare a 01-0.1M solution) at 0 °C. A solution of bromine (1.2 equiv) in dichloromethane (3M) was added dropwise until the reaction mixture turned faint yellow and the mixture was stirred at this temperature for 15 min followed by addition of the alcohol (1 equiv) as a solution in dichloromethane. The reaction mixture was stirred at 0 °C for 30 min and at 21 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried and concentrated. The resulting oils were purified by flash column chromatography.

4-Bromo-1-butanal (193)

$BrCH_2CH_2CH_2CHO$

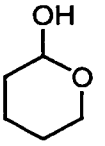
DIBALH (170 mL of 1M soln., 170 mmol) was added, in portions, to a solution of 4-bromobutyronitrile (20 g, 1.25 mmol) in dry ether at 0 °C. The reaction was stirred at 0 °C for 2h and then at 23 °C for 1h. The reaction was quenched by adding the reaction mixture to 10% H_2SO_4 (100 mL) solution in water at 0° C and extracted with ethyl acetate (3 x 250 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution, dried over anhydrous $MgSO_4$ and concentrated under water aspirator with temperature < than 30 °C; IR (neat) 3008, 1718, 1250, 1129, 922, 778 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.70 (t, J = 0.94 Hz, 1H), 3.36 (t, J = 6.4 Hz, 2H), 2.57 (t, J = 7.0 Hz, 2H), 2.14-2.0 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 200.7, 41.8, 32.6, 24.71ppm; FAB accurate mass calcd. for C_4H_8OBr (M^+ + 1): 150.9758, found; 150.9975.

2-(3-Bromopropyl) -5, 5-dimethyl-3,3-dioxane (190)



2,2-Dimethylpropanediol (1.37 g, 6.6 mmol) was added to a solution of 4-bromobutanal **193** (1.0 g, 3.3 mmol) in benzene (6.6 mL), followed by addition of oxalic acid (80 mg, 0.670 mmol) as a catalyst. The reaction mixture was refluxed overnight under azeotropic distillation conditions. After completion the reaction was quenched with saturated $NaHCO_3$ solution (3.0 mL), and extracted with ether (3 x 100 mL). The combined organic extracts were washed with aqueous NaCl solution (3 x 50 mL), dried, over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by flash chromatography (30% pet ether/ CH_2Cl_2) to afford 1.25 g (80%) of the title compound as a clear colorless oil; IR (neat) 2951, 2848, 1462, 1395, 1154, 1168, 1128, 1028 cm^{-1}; ^{1}HNMR (200 MHz, $CDCl_3$) δ 4.39 (t, J = 4.7, Hz, 1H), 4.54-3.30 (m, 6H), 1.97-1.90 (m, 2H), 1.74-1.70 (m, 2H), 1.10 (s, 3H), 0.64 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 100.9, 77.0, 33.6, 29.9, 27.1, 22.8, 21.7 ppm; HRMS calculated for $C_9H_{17}BrO_2$ (M^+): 236.0412. Found: 236.0353.

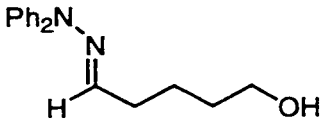
δ-Valerolactol (195)



δ-Valerolactone (6.0 mL, 6.5 g, 64.6 mmol) was added to a flame dried flask (500 mL) containing freshly distilled toluene (100mL) under argon. The solution was cooled to -78 °C and DIBALH in toluene (44.5 mL, 1.5 M solution, 66.7 mmol, Aldrich) was added and the reaction mixture allowed to stir at this temperature for 4 h. The reaction was quenched at –78 °C with methanol 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. The aqueous layer was extracted 3 times with ethyl acetate, 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 with 50% ethyl acetate/petroleum ether under aspirator vacuum to afford 4.9 g (75%) of **195** as a faint yellow oil; IR (neat) 3375, 2912, 1449 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.80-4.90 (m, 1H), 4.70-4.50 (br s, 1H), 3.95-3.88 (m, 1H), 3.52-3.38 (m, 1H), 1.85-1.62 (m, 2H), 1.56.132 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 94.2, 63.6, 31.7, 25.0, 20.1 ppm.

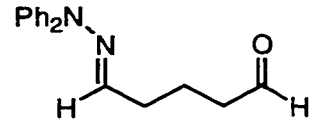
5-Hydroxpentanal-*N,N*-diphenylhydrazone (196)



Lactol **195** (2.59 g, 25.4 mmol) in methanol (30 mL) was added to a flame dried round bottom flask (100 mL). To this solution was added dropwise a solution of Ph_2NNH_2 (4.65 g in 15 mL of methanol). The reaction mixture was allowed to stir at room temperature overnight. Concentration gave a purple oil, which was purified by flash chromatography. The silica gel was deactivated by washing first with a 1% solution of Et_3N added to the eluting solution 30% ethyl acetate/petroleum ether. After packing the column, fresh eluting solvent was used that did not contain Et_3N. (N.B. all hydrazones and hydrazines were purified on silica gel deactivated in this manner.) Concentration of the appropriate fractions yielded 5.28 g (78%) of the title alcohol as a faint yellow oil; IR (neat) 3380, 3044, 2917, 1592, 1492, 1303, 1090, 1066 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46-7.30 (m, 4H), 7.21-6.99 (m, 6H), 6.52 (t, J = 6.7 Hz, 1H), 3.72-3.58 (m, 2H), 2.42-2.35 (m, 2H), 1.70-1.52 (m, 4H), 1.40 (br s, 1H) ppm; ^{13}C

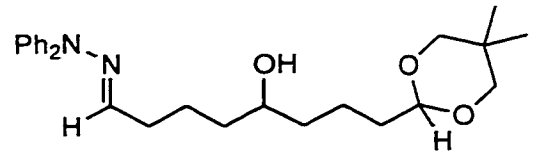
NMR (50 MHz, $CDCl_3$) δ 144.2, 139.6, 129.6, 123.8, 122.2, 62.3 32.2, 32.0, 23.0 ppm; HRMS calcd. For $C_{17}H_{20}N_2O$ (M^+): 268.1571. Found: 268.1569.

Pentanedial-5-(*N,N*-diphenylhydrazone) (191)



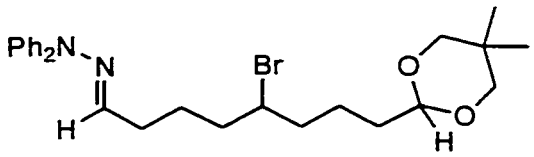
A round bottom flask (100 mL) flame dried under argon was charged with alcohol **196** (3.09 g, 11.5 mmol) along with DMSO (20 mL) and Et_3N (12.9 mL, 92.8 mmol). A SO•pyridine/DMSO suspension (5.4 g of SO_3•pyridine, 34.5 mmol in 5 mL DMSO) was added dropwise to this mixture with stirring. After 30 minute at room temperature, TLC analysis indicated the consumption of the alcohol. The resulting mixture was poured into a separatory funnel containing water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine, dried and concentrated *in vacuo*. The resulting oil was purified by flash chromatography on deactivated silica gel eluting with 10% ethyl acetate/petroleum ether. Concentration of the appropriate fractions yielded 2.17 g (71%) of the title compound as faint yellow oil; IR (neat, cm^{-1}) 3045, 2896, 1723, 1595, 1491, 1303, 1209, 1069 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.77 (t, J = 1.5 Hz, 1H), 7.40-7.32 (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) ppm; ^{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 ppm; HRMS calcd. for $C_{17}H_{18}N_2O$ (M^+): 266.1415. Found: 266.1408.

5-Hydroxynonanedial-[1-(5,5-dimethyl-1,3-dioxanyl)]-9-*N*,*N*-diphenylhydrazone (197)



The aldehyde **191** (2 g, 7.8 mmol) was dissolved in dry THF (5 mL) in a two necked flame dried flask and the resulting solution was cooled to 0 °C. The Grignard reagent (prepared from bromo compound **190** (3 g, 12.6 mmol), by refluxing with a suspension of Mg (450 mg) in THF (5 mL), was added slowly at 0° C and the reaction was monitored by TLC until the starting material was consumed. The reaction was quenched by saturated aqueous NH_4Cl (30 mL) solution. The resulting mixture was poured into a separatory funnel containing water and ethyl acetate (300 mL). The aqueous layer was extracted with ethyl acetate (3 x 250 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by flash chromatography (1:4, ether/pet ether) to obtain 1.9 g (60%) of the title compound; IR (neat) 3428, 2936, 2855, 2243, 1592, 1479, 1387, 1210, 1110, 913 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31 (m, 4H), 7.09-7.05 (m, 6H), 6.52 (t, J = 5.7 Hz, 1H), 4.38 (t, J = 7.2 Hz, 1H), 3.57-3.55 (m, 3H), 3.39-3.36 (m, 2H), 2.26 (q, J = 7.0 Hz, 2H), 2.22-2.17 (Br S, OH), 1.64-1.39 (m, 10 H), 1.16 (s, 3H), 0.68 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ 144.3, 139.8, 126.6, 123.3, 122.3, 102.0, 77.1, 71.1, 37.1, 36.7, 34.6, 32.5, 30.0,23.1, 23.0, 21.8, 19.9 ppm; HRMS calcd. for $C_{26}H_{36}N_2O_3$ (M^+): 424.2727. Found: 424.27463.

5-Bromononanedial-[1-(5,5-dimethyl-1,3-dioxanyl)]-9-*N,N*-diphenylhydrazone (198)



Triethylamine (78 μL, 0.56 mmol) was added to a cold solution (0 °C) of triphenylphosphine (0.148 g, 0.56 mmol) in dry CH_2Cl_2 (6.5 mL). Bromine (28 μL, 0.56 mmol) was added dropwise until the reaction mixture turned a faint yellow in colour. The mixture was stirred at this temperature for 10 min., then alcohol **197** (0.2 g, 0.47 mmol) was added dropwise as a solution in dry CH_2Cl_2 (1.0 mL). The reaction mixture was stirred at 0 °C for 30 min. and then at 22 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) solution. The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (4:1, hexane/ether) to afford 240 mg (75%) of the title compound as a clear colorless oil; IR (neat) 3060, 2945, 2853, 1582, 1493, 1455, 1302, 1210, 1129, 915 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37-7.31 (m, 4H), 7.12-7.06 (m, 6H), 6.50 (t, J = 5.2 Hz , 1H), 4.39 (t, J = 4.7 Hz, 1H), 4.04-4.01 (m, 1H), 3.57 (d, J = 11.1 Hz, 2H), 3.39 (d, J = 11.8 Hz, 2H), 2.31-2.26 (m, 2H), 1.86-1.51 (m, 10H), 1.17 (s, 3H), 0.70 (s, 3H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ 144.2, 138.8, 129.6, 123.8, 122.3, 101.8, 77.1, 76.7, 57.7, 38.9, 38.3, 31.9, 30.0, 24.8, 22.9, 22.1, 21.8 ppm; HRMS Calcd. for $C_{26}H_{35}N_2O_2Br$ (M^+): 486.1883. Found: 486.1886.

4-Bromo-1-butanol (200)

$BrCH_2CH_2CH_2CH_2OH$

Borane-THF complex (1.25 mL of 1M soln., 1.25 mmol) was added, in portions, to a solution of bromobutyric acid (210 mg, 1.25 mmol) in dry THF at -18 °C. The reaction was stirred overnight and allowed to warm up to 21 °C. The reaction was quenched with an aqueous solution of K_2CO_3 (1.5 mL) at 0 °C and extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution, and concentrated *in vacuo.* Purification by flash chromatography (4:1, hexane/ether) provided 161 mg (83%) of the title compound; IR (neat) 3337, 2918, 1648, 1435, 1051 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.61 (t, J = 6.4 Hz, 1H), 3.40 (t, J = 6.6 Hz, 2H), 2.80 (s, 1H), 1.93-1.83 (m, 2H), 1.71-1.61 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 61.6, 33.7, 31.0, 29.1 ppm; HRMS calcd. for C_4H_7Br (M^+-H_2O): 133.9731, found; 133.9742.

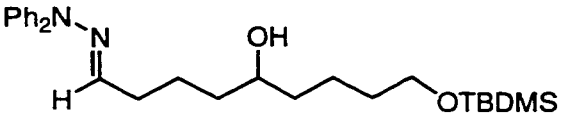
4-Bromo-1-(*t*-butyldimethylsilyloxy)butane (201)

$BrCH_2CH_2CH_2CH_2OTBDMS$

TBDMSCl (148 mg, 0.979 mmol), was added to a solution of 4-bromobutanol **200** (100 mg, 0.653 mmol), imidazole (89 mg, 1.307 mmol) and 4-dimethylaminopyridine (40 mg, 0.326 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C. The solution was stirred overnight and warmed to 21 °C, quenched with aqueous NH_4Cl solution (2.5 mL), and extracted with ether (3 x 10 mL). The combined organic extracts were washed with aqueous NaCl solution (3 x 3 mL), dried filtered and concentrated. The resultant oil was purified by flash chromatography (pet ether) to afford 140 mg (80%) of the title compound as a clear colorless oil; IR (neat) 2994, 2858, 2361, 1468, 839, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.61 (t, J = 6.0 Hz, 2H), 3.41 (t, J = 6.7 Hz, 2H), 1.95-1.87

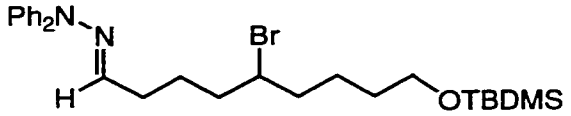
(m, 2H), 1.66-1.58 (m, 2H), 0.86 (s, 9H), 0.02 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 62.1, 33.8, 31.2, 29.4, 25.9, 25.7, -5.3 ppm; HRMS calculated for $C_6H_{14}BrOSi(M^+$-*t*-Butyl): 208.9998. Found: 209.0.

5-Hydroxy-9-(*tert*-butyldimethylsilyloxy)nonanal-*N*,*N*-diphenylhydrazone (202)



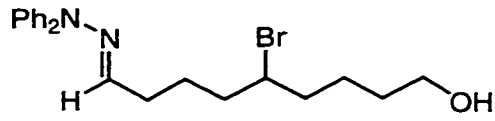
The aldehyde **191** (425 mg, 1.5 mmol) was dissolved in dry THF (2 mL) in a two necked flame dried flask and the resulting solution was cooled to 0 °C. The Grignard reagent $BrMgCH_2CH_2CH_2CH_2OTBDMS$ [prepared from bromocompound **201** (1.5 g, 5.6 mmol), by refluxing with a suspension of Mg (225 mg) in THF (2.5 mL)], was added slowly at 0 °C and the reaction was monitored by TLC until the starting material was consumed. The reaction was quenched by saturated aqueous NH_4CI (15 mL) solution. The resulting mixture was poured into a separatory funnel containing water and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by flash chromatography (1:4, ether/pet ether) to obtain 525 mg (60%) of the title compound; IR (neat) 3396, 3061, 2906, 1592, 1479, 1302, 1210, 910, 744, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39–7.21 (m, 4H), 7.14-7.06 (m, 6H), 6.54 (t, J = 5.2 Hz, 1H), 3.64-3.56 (m, 3H), 2.31-2.28 (m, 2H), 1.80 (br s, 1H), 1.62-1.45 (m, 10H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ 144.3, 139.7, 129.6, 123.8, 122.3, 71.5, 63.1, 37.1, 36.9, 32.7, 32.6, 25.9, 23.0, 21.9, 18.3, -5.3 ppm; calcd. for $C_{27}H_{42}N_2O_2Si$ (M^+): 454.3096. Found: 454.3052.

5-Bromo-9-(*tert*-butyldimethylsilyloxy)nonanal-*N*,*N*-diphenylhydrazone (203)



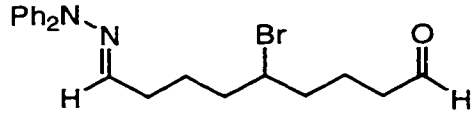
Triethylamine (1.2 mL, 0.79 mmol) was added to a cold solution (0 °C) of dry CH_2Cl_2 (8 mL) containing triphenylphosphine (0.207 g, 0.79 mmol). Bromine (45 mL, 0.79 mmol) was added dropwise until the reaction mixture turned a faint yellow in colour. The mixture was stirred at this temperature for 10 min., then alcohol **202** (0.3 g, 0.66 mmol) was added dropwise as a dichloromethane solution (0.7 mL). The reaction mixture was stirred at 0 °C for 30 min. and then at 22 °C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL) solution. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (4:1, hexane/ether) to afford 240 mg (75%) of the title compound as a clear colorless oil; IR (neat) 2940, 2858, 2351, 1593, 1494, 749, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.41-7.32 (m, 4H), 7.16-7.06 (m, 6H), 6.52 (t, J = 5.17 Hz , 1H), 4.05 (m, 1H), 3.62 (t, J = 5.86 Hz, 2H), 2.36-2.26 (m, 2H), 1.88-1.50 (m, 10H), 0.91 (s, 9H), 0.06. (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 138.7, 129.6, 123.8, 122.2, 62.8, 58.0, 38.8, 38.4, 32.1, 31.9, 25.9, 24.8, 23.9, 18.2, -5.2 ppm; HRMS calcd. for $C_{27}H_{41}N_2SiBrO$ (M^+): 516.2173. Found: 516.2221. Anal. Calcd. for $C_{27}H_{41}N_2SiBrO$: C, 62.95; H, 7.98; N, 5.41. Found: C, 62.75; H, 7.83; N, 5.49.

5-Bromo-9-hydroxynonanal-*N,N*-diphenylhydrazone (204)



Tetrabutylammonium fluoride (0.490 mL of 1M soln. in THF, 0.49 mmol) was added to the solution of compound **203** (210 mg, 0.41 mmol) in dry THF (3.5 mL), at 0 °C and the resulting mixture was stirred overnight. The reaction was quenched with water (2 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (1:1 ether/hexanes) afforded 130 mg (80%), of the title compound as a faint yellow oil; IR (neat) 3360, 3060, 2916, 1592, 1210, 1091, 1062, 749, 689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.32 (m, 4H), 7.14-7.03 (m, 6H), 6.50 (t, J = 5.2 Hz, 1H), 4.07-4.01 (t, J = 6.2 Hz, 1H), 3.65-3.59 (t, J = 6.0 Hz, 2H), 2.34-2.24 (m, 2H), 1.90-1.42 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 144.1, 138.8, 129.6, 123.8, 122.2, 62.5, 57.9, 38.8, 38.3, 31.9, 31.8, 24.8, 23.8 ppm; HRMS calcd. for $C_{21}H_{27}N_2OBr$ (M^+): 402.1297. Found: 402.1293.

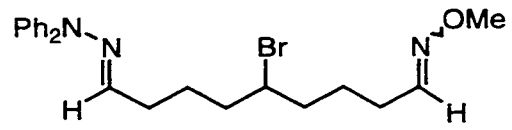
5-Bromononanedial-9-(*N,N*-diphenylhydrazone) (189)



A suspension of pyridine.SO_3 complex (1.51 g, 3.23 mmol) in DMSO (3.6 mL) was added to a solution of the alcohol **204** (1.3 g, 3.23 mmol), and Et_3N (3.6 mL, 25.8 mmol) in DMSO (5.6 mL) at room temperature. After consumption of the alcohol the reaction was poured into a separatory funnel containing water and ethyl acetate (3x50

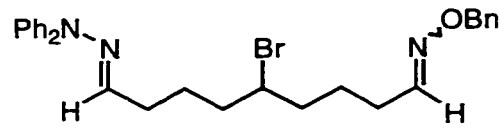
mL) and the combined organic extracts were washed with brine (2 x 25 mL), dried and concentrated *in vacuo*. The purification by flash chromatography (4:1 hexanes/ether) yielded 967 mg (75%) of the title compound as a faint yellow oil; IR (neat) 3059, 2933, 1723, 1592, 1492, 1301, 1210, 1062 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.73 (t, J = 1.5 Hz, 1H), 7.39-7.24 (m, 4H), 7.2-7.03 (m, 6H), 6.49 (t, J = 5.2 Hz, 1H), 4.05-4.02 (m, 1H), 2.48-2.24 (m, 4H), 1.90-1.60 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.7, 144.0, 138.6, 129.6, 123.8, 122.5, 57.1, 43.0, 38.3, 38.2, 31.8, 24.7, 20.1 ppm; HRMS calcd. for $C_{21}H_{25}N_2OBr$ (M^+): 400.1151. Found: 400.1161.

5-Bromooctanedial-(1-*O*-methyloxime)-9-*N*,*N*-diphenylhydrazone (182a)



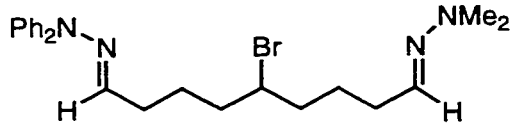
Methoxyamine hydrochloride (417 mg, 0.50 mmol) was added to the solution of aldehyde **189** (200 mg, 0.50 mmol) and pyridine (42 μL, 0.52 mmol) in dry ethanol (3 mL) at 0 °C. The solution was stirred at this temperature until the reaction was complete. The resulting solution was concentrated and purification by flash chromatography (1:20, ether/pet ether) yielded 135 mg (63%) of the title compound as a clear colorless oil; IR (neat); 3060, 2933, 2351, 1592, 1492, 1454, 1301, 1210, 1054, 883, 749, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36-7.24 (m, 4H), 7.13-7.07 (m, 6H), 7.37, 6.61 [t, J = 5.5 Hz, 1H (*syn*, *anti*)], 6.50 (t, J = 5.1 Hz, 1H), 4.06-4.00 (m, 1H), 3.83, 3.80[s, 3H (*syn*, *anti*)], 2.35-2.17 (m, 4H), 1.88-1.59 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ {150.9, 150.0 (*syn*, *anti*), 144.2, 138.7, 129.6, 123.9, 122.3, [61.6, 61.2 (*syn*, *anti*)], 57.2, [38.6, 38.5 (*syn*, *anti*)], [38.4, 38.3 (*syn*, *anti*)], 31.9, 28.8, [24.8, 24.6 (*syn*, *anti*)], 24.2 ppm; HRMS calcd. for $C_{22}H_{28}N_3OBr$ (M^+): 429.1417. Found: 429.1433.

5-Bromooctanedial-(1-*O*-benzyloxime)-9-*N,N*-diphenylhydrazone (182b)



Benzyloxyamine hydrochloride (86 mg, 0.53 mmol) was added to the stirred solution of aldehyde **189** (179 mg, 0.45 mmol) and pyridine (48 μL, 0.57 mmol) in dry ethanol (1 mL) at 0 °C. After completion of the reaction, the solution was concentrated and the residue purified using flash chromatography (1:20, ether/pet ether). Concentration of the appropriate fractions afforded 140 mg (62.2%) of the title compound as faint yellow oil; IR (neat): 3031, 2933, 1592, 1453, 1301, 1210, 917, 748, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44, 6.68 [t, (*syn*, J = 6.1 Hz, *anti*, J = 5.5 Hz) 1H], 7.41-7.34 (m, 9H), 7.14-7.05 (m, 6H), 6.52 (dt, J = 2.3 Hz, 5.2 Hz, 1H), 5.11, 5.05 [s, 2H, (*syn*, *anti*), 4.04-4.01 (m, 1H), 2.41-2.24 (m, 4H), 1.86-1.59 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ [151.5, 150.6 (*syn*, *anti*)], 144.2, [138.8, 138.7 (*syn, anti*), [138.0, 137.7 (*syn*, *anti*)], 129.7, [128.3, 128.2 (*syn*, *anti*)], 127.9, [127.8, 127.7 (*syn*, *anti*)], 123.9, 122.3, [75.8, 75.5 (*syn*, *anti*)], 57.3, [38.6, 38.5 (*syn*, *anti*)], 38.2, 31.9, 28.8, [25.1, 24.8 (*syn*, *anti*)], [24.5, 24.2 (*syn*, *anti*)] ppm; HRMS calcd. for $C_{28}H_{32}N_3OBr$ (M^+): 505.1729. Found: 505.1739.

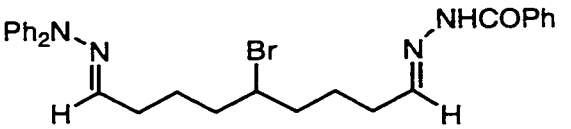
5-Bromooctanedial-(1-*N,N*-dimethyl-9-*N,N*-diphenyldihydrazone) (182c)



N,N-dimethylhydrazine (54 mg, 0.897 mmol) was added to the solution of aldehyde **189** (120 mg, 0.299 mmol) in dry CH_2Cl_2 (2 mL). The resulting solution was

stirred overnight at 40 °C. After the completion of the reaction, the solvent was evaporated to provide the crude product. Purification by flash chromatography (2:5 ether/pet ether) afforded 100 mg (75%) of the title compound as a faint yellow oil; IR (neat) 2920, 2781, 1593, 1494, 1300, 1210, 749, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.13-7.04 (m, 6H), 6.59 (t, J = 5.42 Hz, 1H), 6.49 (t, J = 5.4 Hz, 1H), 4.05 (br q, J = 6.05 Hz, 1H), 2.70 (s, 6H), 2.33-2.19 (m, 4H), 1.90-1.59 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.1, 138.7, 138.0, 129.6, 123.8, 122.2, 57.7, 43.2, 38.3, 38.3, 32.3, 31.9, 25.6, 24.8 ppm; HRMS calcd. for $C_{23}H_{31}N_4Br$ (M^+): 442.1733. Found: 442.1723.

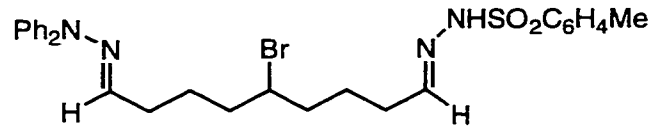
5-Bromooctadianal-(1-*N*-Benzoylhydrazone)-9-*N*,*N*-diphenylhydrazone (182d)



Benzoylhydrazine (106 mg, 0.78 mmol) and aldehyde **189** (250 mg, 0.625 mmol) were stirred in dry toluene (6.6 ml) at 21 °C for 24 h. The resulting mixture was evaporated to dryness and purified by flash chromatography (1:24, ether/CH_2Cl_2). Concentration of appropriate fractions yielded 230 mg (71%) of a viscous oil, which was crystallized from toluene and pet ether to obtain a white solid; mp 110-112 °C; IR (neat): 3221, 3052, 2935, 1736, 1648, 1492, 1210, 749, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.10 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.60 (br s, 1H), 7.43 (t, J = 7.4 Hz, 1H), 7.40-7.10 (m, 6H), 7.08-7.04 (m, 6H), 6.48 (t, J = 5.16 Hz, 1H), 3.99-3.94 (m, 1H), 2.30-2.23 (m, 4H), 1.84-1.57 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.4, 152.3, 144.2, 138.9, [133.1, 132.9 (*syn*, *anti*)], 131.9, 129.7, [128.5, 128.4 (*syn*, *anti*)], [127.7, 127.5 (*syn*, *anti*)], 123.9, 122.3, [57.7, 57.4 (*syn*, *anti*)], 38.5, [38.4, 38.3 (*syn*, *anti*)], 32.0, 31.9,

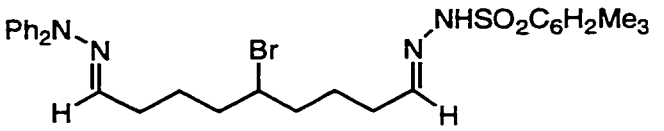
[24.9, 24.6 (*syn*, *anti*)], 24.8 ppm; FAB acc. mass calcd for $C_{28}H_{32}N_4OBr$ (M^+ + 1): 519.17604. Found: 519.2069.

5-Bromononanedial-[1-*N*-(*p*-toluene)sulfonyl hydrazone]- 9-*N*, *N*-diphenylhydrazone (182e)



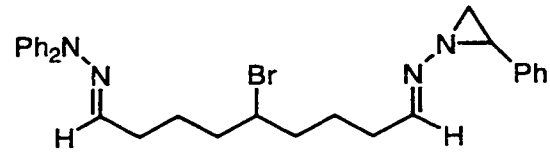
p-Toluene sulfonylhydrazine (134 mg, 0.625 mmol) and aldehyde **189** (200 mg, 0.50 mmol) were stirred in ethanol (1 ml) at 21 °C for one h. The resulting solution was evaporated to dryness and purification by flash chromatography (2:5 ether/pet ether) afforded 170 mg of the title compound (60%) as faint yellow oil; IR (neat): 3204, 2936, 1592, 1493, 1452, 1210, 1164, 1092, 902 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.84, 7.82 [d, 2H, (*syn anti*), J = 8.3 Hz, J = 8.2 Hz], 7.36-7.27 (m, 6H), 7.23-7.05 (m, 6H), 6.68 [t, J = 5.2 Hz, (*anti*), (*syn* hidden under 7.23-7.05), 1H], 6.50 (t, J = 5.0 Hz, 1H), 3.95-3.92 (m, 1H), 2.19-2.39 (s, 3H), 2.30-2.24 (m, 2H), 2.19-2.12 (m, 2H), 1.82-1.50 (m, 8H) ppm; ^{13}C NMR (125 Hz, $CDCl_3$) δ [151.9, 150.8 (*syn*, *anti*)], 144.2, 144.1, 138.8, 135.2, 129.7, 129.6, [127.9, 127.8 (*syn*, *anti*)], 123.9, 122.3, [57.3, 57.0 (*syn*, *anti*)], [38.4, 38.3 (*syn anti*)], [38.2, 38.1 (*syn anti*)], 31.8, 31.5, [26.4, 24.7(*syn*, *anti*)], [24.0, 23.8 (*syn*, *anti*)], 21.6 ppm; FAB accurate Mass calcd for $C_{28}H_{34}N_4O_2SBr$ (M^++1):569.1586. Found: 569.1845.

5-Bromononanedial-[1-*N*-(2,4,6-trimethylbenzene)sulfonylhydrazone]-9-*N*,*N*-diphenylhydrazone (182f)



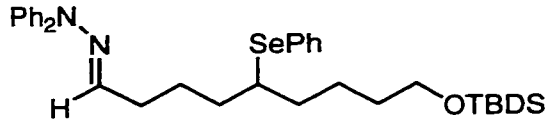
2,4,6-Trimethylbenzensulfonyl hydrazide (67 mg, 0.312 mmol) and aldehyde **189** (100 mg, 0.25 mmol) were stirred in ethanol (1 ml) at 21 °C for one h. The resulting solution was evaporated to dryness and purification by flash chromatography (2:5 ether/pet ether) afforded 67 mg of the title compound (50%) as faint yellow oil; IR (neat) 3267, 2937, 1597, 1494, 1453, 1371, 1210, 1153, 851, 749, 659 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.38-7.27 (m, 4H), 7.14-7.06 (m, 6H), 6.96-6.93 [overlapping s, 2H, (*syn anti*)], 6.63[t, *J* = 5.2 Hz, (*anti*), (*syn* hidden under, 7.14-7.06) 1H], 6.48 (t, *J* = 5.2 Hz, 1H), 3.97-3.90 (m, 1H), 2.67-2.60 [overlapping s, 6H, (*syn*, *anti*)], 2.28-2.27 [overlapping s, 3H (*syn*, *anti*)], 2.24-2.15 (m, 2H), 1.76-1.51 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ [150.2, 149.0 (*syn*, *anti*)], 144.2, 142.8, [140.2, 140.1 (*syn*, *anti*)], [138.7, 138.6 (*syn*, *anti*)], [132.3, 132.0 (*syn anti*)], [131.9, 131.8 (*syn*, *anti*)], 129.9, 123.9, 122.3, [57.2, 56.8 (*syn*, *anti*)], [38.5, 38.4 (*syn*, *anti*)], [38.2, 38.0 (*syn*, *anti*)], 31.8, 31.4, [25.9, 24.8 (*syn*, *anti*)], [23.8, 23.7 (*syn*, *anti*)], [23.1, 23.0 (*syn*, *anti*)], 20.9 ppm; FAB Accurate Mass calcd for $C_{30}H_{38}N_4O_2BrS$ (M^+ + 1): 597.1984. Found: 597.1899.

5-Bromononanedial-[1-*N*-(2-phenyl-*N*-aziridinyl)hydrazone]-9-*N*,*N*-diphenylhydrazone (182g)



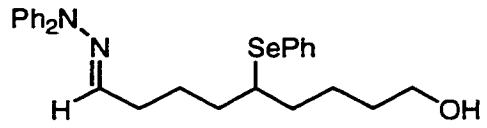
Phenyl aziridine (557 mg, 4.1 mmol) dissolved in pentane (15 mL), was added to a cold solution (0° C) of the aldehyde **189** (1.5 g, 3.75 mmol) in ethanol (15 mL). The resulting solution was stirred at this temperature for 4 h. The reaction was quenched with water (10 mL) and extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 25 mL) and dried over anhydrous $MgSO_4$ and dried *in vacuo*. Purification by column chromatography (2:3 ether/pet ether) afforded 1.2 g (61%) of the desired compound as a faint yellow oil; IR (neat) 3031, 2035, 1593, 1492, 1454, 1301, 1210, 1090, 748, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, J = 5.4 Hz, 1H), 7.39-7.24 (m, 9H), 7.16-7.10 (m, 6H), 6.53 (t, J = 5.1 Hz, 1H), 4.07-4.04 (m, 1H), [3.03-3.00 (m, *syn*), 2.95-2.85 (m, *anti*), 1H], 2.46-2.41 (m, 1H), 2.34-2.25 (m, 5H), 1.89-1.75 (m, 6H), 1.68-1.64 (m, 2H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ [162.3, 162.2 (*syn*, *anti*)], 144.2,144.2, [138.7, 138.6 (*syn*, *anti*)], 129.7, 128.4, [127.2, 126.2 (*syn*, *anti*)], 126.4, 123.9, 122.3, 57.3, 43.6, 40.18, 38.6, 38.4, 31.9, 31.7, 24.8, 24.2 ppm; FAB accurate mass calcd. for $C_{29}H_{34}N_4Br$ (M^+ + 1): 517.1967. Found: 517 .1799.

5-Phenylseleno-9-(*tert*-butyldimethylsilyloxy)nonanal-*N,N*-diphenylhydrazone (205)



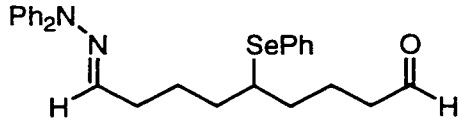
Diphenyl diselenide (359 mg, 1.16 mmol) and sodium hydride (92 mg, 2.08 mmol, 60% dispersion in mineral oil) were placed in an oven dried, two necked flask. The flask and its contents were evacuated (oil pump) and flushed with nitrogen five times. Dry THF (6 mL) was added to the contents of the flask using a syringe the mixture was refluxed for 45-60 min. To the resulting light yellow suspension of the sodium phenylselenide, compound **203** was added slowly (270 mg, 0.523 mmol) and refluxed for 3 h. The reaction was quenched by methanol (5 mL) and extracted with ether (3 x 30 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 10 mL) and dried over anhydrous $MgSO_4$ and dried *in vacuo*. Purification by column chromatography (2% ether/pet ether) afforded 675 mg (98 %) of the desired compound as a faint yellow oil; IR (neat) 3062, 2937, 2837, 1592, 1494, 1436, 1300, 1258, 1211, 1098, 1023, 838, 776, 743, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.57-7.53 (m, 2H), 7.42-7.34 (m, 4H), 7.26-7.21 (m, 3H), 7.17-7.08 (m, 6H), 6.52 (t, J = 5.2 Hz, 1H), 3.78-3.61 (m, 2H), 3.39-3.09 (m, 1H), 2.30-2.28 (m, 2H), 1.71-1.53 (m, 10H), 0.93 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ 144.1, 139.1, 134.7, 129.5, 129.3, 128.7, 127.1, 123.7, 122.2, 62.3, 46.3, 35.0, 34.8, 32.5, 32.3, 25.9, 24.9, 23.8, 18.2, -5.2 ppm; HRMS calcd. for $C_{33}H_{46}N_2OSeSi$ (M^+): 594.2497. Found: 594.2512.

5-Phenylseleno-9-hydroxynonanal-*N,N*-diphenylhydrazone (206)



Tetrabutylammonium fluoride (1.03 mL of 1 M sol. In THF, 1.03 mmol) was added to the solution of compound **205** (650 mg, 0.943 mmol) in dry THF (10 mL) at 0 °C, and the resulting solution was stirred for 4 h. The reaction was quenched with water (6 mL) and extracted with ether, and the combined organic extracts were washed with saturated NaCl (2 x 20 mL), dried and concentrated.. Purification by flash chromatography (2:3, ether/pet ether) afforded 435 mg (96%) of the title compound as faint yellow oil; IR (neat) 3369, 3058, 2928, 1591, 1493, 1301, 1210, 1090, 1022, 744, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.37-7.33 (m, 4H), 7.26-7.20 (m, 3H), 7.12-7.05 (m, 6H), 6.49 (t, J = 5.3 Hz, 1H), 3.59-3.56 (m, 2H), 3.17-3.15 (m, 1H), 2.27-2.25 (m, 2H), 1.71-1.61 (m, 6H), 1.57-1.42 (m, 4H) ppm, OH proton not observed; ^{13}C (50 MHz, $CDCl_3$) δ 144.0, 139.2, 134.7, 129.5,129.2, 128.8, 127.2, 123.7, 122.2, 62.5, 46.2, 35.0, 34.7, 32.3, 32.2, 24.9, 23.7 ppm; HRMS calcd. for $C_{27}H_{32}N_2OSe$ (M^+): 480.1681. Found: 480.1647.

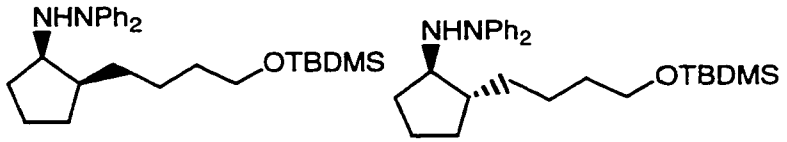
5-Phenylselenononanedial-9-(*N,N*-diphenylhydrazone) (207)



A suspension of pyridine.SO_3 complex (397 mg, 2.50 mmol) in DMSO (3.5 mL) was added to a solution of the alcohol **206** (400 mg, 0.836 mmol), and triethylamine (0.916 mL) in DMSO (4 mL) at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were

washed with brine (2 x 10 mL), dried and concentrated. The purification by flash chromatography (1:9 ether/pet ether) yielded 278 mg (70%) of the title compound as a faint yellow oil; IR (neat) 2923, 1724, 1592, 1493, 1453, 1299, 1210, 1091, 749, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.70 (s, 1H), 7.54-7.50 (m, 2H), 7.47-7.39 (m, 4H), 7.36-7.20 (m, 3H), 7.15-7.02 (m, 6H), 6.49 (t, J = 5.1 Hz, 1H), 3.22-3.11 (m, 1H), 2.42-2.23 (m, 4H), 1.86-1.57 (m, 8H) ppm; ^{13}C (50 MHz, $CDCl_3$) δ 202.1, 144.1, 139.0, 134.8, 129.5,129.2, 128.9, 127.4, 123.8, 122.2, 45.9, 43.4, 34.7, 34.7, 32.2, 24.9, 20.1 ppm; HRMS calcd. for $C_{27}H_{30}N_2OSe$ (M^+): 478.1524. Found: 478.1570.

cis- and *trans*-2-(4-*t*-Butyldimethylsilyloxybutyl)-1-(*N*,*N*-diphenylhydrazino)cyclopentane (208)

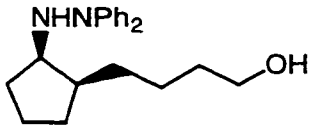


208i **208ii**

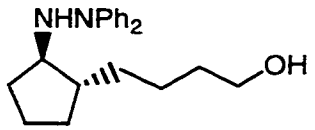
Following the general procedure for the radical cyclization, tributyltin hydride (0.390 mL, 1.45 mmol) and AIBN (53 mg, 0.33 mmol) were added to the solution of hydrazone **203** (500 mg, 0.96 mmol) in dry benzene (15.6 mL). The product mixture was purified by flash chromatography (3:1 ether/pet ether) to obtain 424 mg 96%, 3:1 mixture of *cis* and *trans* of the title compound as a faint yellow oil; ***Cis* Isomer (208i)**: IR (neat) 3061, 2939, 2858, 1591, 1495, 1467, 1259, 1099, 838, 748, 695 cm^{-1}; ^1H NMR, (200 MHz, $CDCl_3$) δ 7.32–7.20(m, 4H), 7.16-7.10 (m, 4H), 6.97 (t, J = 6.9 Hz, 2H), 3.89 (br s, 1H), 3.58 (t, J = 6.3 Hz, 2H), 3.31-3.27 (m, 1H), 1.88-1.70 (m, 4H), 1.69-1.25 (m, 9H), 0.90 (s, 9H), 0.05 (s, 6) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.0, 129.0, 121.9, 120.2, 63.1, 59.0, 44.3, 33.0, 29.9, 29.5, 28.8, 25.9, 25.1, 22.2, 18.3, –5.1 . ***Trans* Isomer**

(208ii): ^{1}H NMR (By subtracting the signals due to *cis* isomer), (500 MHz, $CDCl_3$) δ 7.25 (t, J = 7.8 Hz, 4H), 7.1 (d, J = 8.2 Hz, 4H), 6.97 (t, J = 7.2 Hz, 2H), 3.86 (br s, 1H), 3.55 (t, J = 6.5 Hz, 2H), 3.06-3.02, (m, 1H), 2.13-1.2 (m, 13 H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) 147.9, 128.9, 121.9, 120.1, 63.7, 63.1, 44.0, 34.4, 32.9, 31.4, 30.6, 25.9, 24.4, 23.6, 18.3, -5.1 ppm; HRMS calcd for $C_{27}H_{42}N_2OSi$ (M^+);438.3068. Found: 438.3061. Anal. calcd. for $C_{27}H_{42}N_2OSi$: C, 73.86; H, 9.67; N, 6.3. Found: C, 73.68; H, 9.77; N, 6.48.

cis- and *trans*-2-(4-Hydroxybutyl)-1-(*N,N*-diphenylhydrazino) Cyclopentane (209)



209i



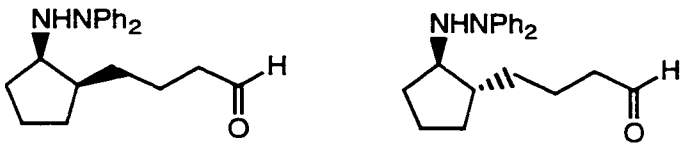
209ii

Tetrabutylammonium fluoride (1.12 mL of 1M soln. in THF, 1.12 mmol) was added to a solution of compound **208** (408 mg, 0.931 mmol) in dry THF (7.5 mL) at 0 °C, and the resulting solution was stirred overnight. The reaction was quenched with water (5 mL) and extracted with ether. The combined organic extracts were washed with brine (2x10 mL) and concentrated. Purification by flash chromatography (1:2.5 ether/pet ether) afforded 258 mg (86%) of the title compound as a faint yellow oil; ***Cis* Isomer (209i)**: IR (neat) 3348, 2937, 2865, 1590, 1495, 1290, 1052, 748, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34–7.23 (m, 4H), 7.19–7.15 (m, 4H), 6.99–6.96 (m, 2H), 3.92 s, 1H), 3.58 (q, 2H), 3.30–3.26 (m, 1H), 1.91–1.30 (m, 13H) ; ^{13}C NMR (50 MHz,

$CDCl_3$) δ 148.0, 128.9, 121.8, 120.1, 62.5, 58.9, 44.2, 32.7, 29.8, 29.5, 28.6, 24.8, 22.2.

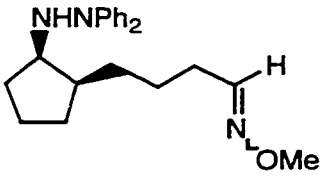
***Trans* Isomer (209ii)**: ^1H NMR (by subtracting signals due to *cis* isomer) (500 MHz, $CDCl_3$) δ 7.30-7.20 (m, 4H), 7.16-7.13 (m, 4H), 6.99-6.95 (m, 2H), 3.80 (br s, 1H), 3.55 (t, J = 6.6 Hz, 2H), 3.08-3.07 (m, 1H), 1.89-1.76 (m, 3H), 1.65-1.28 (m, 10H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) 147.7, 128.8, 121.7, 120.0, 63.5, 62.4, 43.8, 34.2, 32.6, 31.3, 30.5, 24.2, 23.5 ppm; HRMS calcd for $C_{21}H_{28}N_2O$ (M^+): 324.2202. Found: 324.2219.

cis- and *trans*-4-[2-(*N,N*-Diphenylhydrazino)cyclopentyl]butanal (210)

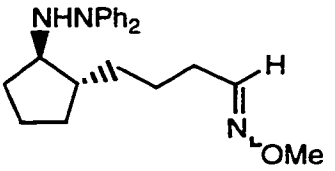


A suspension of pyridine.SO_3 complex (380 mg, 0.81 mmol) in DMSO (3 mL) was added to a solution of the alcohol **209** (258 mg, 0.79 mmol) and triethylamine (0.90 mL, 6.45 mmol) in DMSO (5.6 mL) at room temperature. After complete consumption of the alcohol the reaction was poured into a separatory funnel containing water and extracted with ethyl acetate (3 x 20 mL), and the combined organic extracts were washed with brine (2 x 10 mL), dried and concentrated *in vacuo.* to give 250 mg (97%) of the title compound as a faint yellow oil. The title compound could not be purified due to its instability to silica gel; IR (neat); 2915, 2351, 1723, 1590, 1493, 1292, 749, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.48–6.92 (m, 10 H), 3.96 (br s, 1H), 3.35-3.21 (m, 1H), 2.48-2.39 (m, 2H), 1.99-1.45 (m, 11H).

cis- and _trans_-4-[2-(_N,N_-Diphenylhydrazino)cyclopentyl]butanal (_O_-methyloxime) (186a)



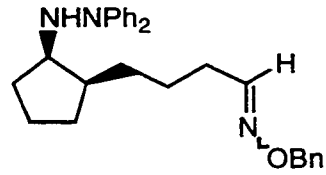
186ai



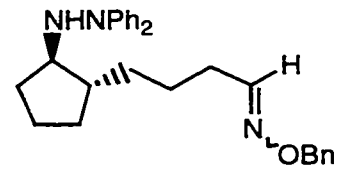
186aii

Methoxyamine hydrochloride (27 mg, 0.32 mmol) was added to a solution of aldehyde **210** (65 mg, 0.20 mmol) and pyridine (33 μL, 0.40 mmol) in dry ethanol (1 mL) at 0 °C. The solution was stirred at this temperature until the reaction was complete. The resulting solution was concentrated, and purification by flash chromatography (1:20, ether/pet ether) yielded 52 mg (73.4%) of the title compound as a clear colorless oil; ***Cis* Isomer**; IR (neat); 2918, 1590, 1494, 1279, 1053, 802, 749, 696 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.23 (m, 4H), 7.16-7.10 (m, 4H), 6.99-6.92 (m, 2H), 6.57 [t, J = 5.5 Hz (*anti*, *syn* hidden under 7.13-7.10), 1H], 3.92-3.87 (br s, 1H), 3.84, 3.77 [s, 3H (*syn*, *anti*)], 3.27-3.25 (m, 1H), 2.28-2.12 (m, 2H), 1.86-1.30 (m, 11H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ [151.5, 150.5 (*syn*, *anti*)], 148.0, 129.0, 122.0, 120.2, 61.1, [59.1, 58.9 (*syn*, *anti*)], [44.0, 43.9 (*syn*, *anti*)], [29.9, 29.7 (*syn*, *anti*)], [29.6, 29.5 (*syn*, *anti*)], [29.5, 29.4 (*syn*, *anti*)], [28.7, 28.4 (*syn*, *anti*)], [25.7, 25.6 (*syn*, *anti*)], [22.2, 22.1 (*syn*, *anti*)] ppm; HRMS calcd for $C_{22}H_{29}N_3O$ (M^+): 315.2319. Found: 315.2321. ***Trans Isomer***: ^{1}H NMR (by subtracting the signals due to *cis* isomer) (500 MHz, $CDCl_3$) δ 7.33-7.23 (m, 4H), 7.14-7.10 (m, 4H), 6.98-6.94 (m, 2H), 6.52 (t, J = 5.2 Hz, 1H), 3.92-3.87 (br s, 1H), 3.82, 3.79 [s, 3H (*syn*, *anti*)], 3.05-3.04 (m, 1H), 2.27-1.50 (m, 13 H).

cis- and _trans_-4-[2-(_N,N_-Diphenylhydrazino)cyclopentyl]butanal (_O_-benzyloxime) (186b)



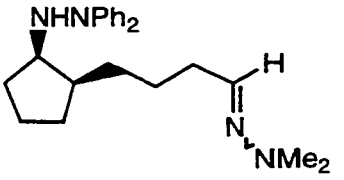
186bi



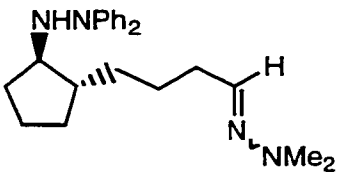
186bii

Benzyloxyamine hydrochloride (40 mg, 0.25 mmol) was added to a stirred solution of aldehyde **210** (50 mg, 0.15 mmol) and pyridine (28 μL, 0.34 mmol) at 0 °C. After completion of the reaction, the solution was concentrated and the residue purified using flash chromatography (1:10, ether/pet ether). Concentration of the appropriate fractions afforded 51 mg (79.7%) of the title compound as a faint yellow oil; ***Cis* Isomer**: IR (neat): 3030, 2933, 1590, 1495, 1454, 1283, 1029, 912, 814, 748, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.21 (m, 9H), 7.16-6.93 (m, 6H), 6.63 [t, J = 5.4 Hz (*anti*) (*syn* hidden under 7.45-7.21), 1H], 5.09, 5.02 [s, 2H (*syn*, *anti*)], 3.91 (br s, 1H), 3.28-3.21 (m, 1H), 2.18-2.13 (m, 2H), 1.87-1.38 (m, 11H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ [152.1, 151.1 (*syn*, *anti*)], [148.1, 148.0 (*syn*, *anti*)], [138.3,138.0 (syn, anti)], 129.0, 129.0, [128.3, 128.1 (*syn*, *anti*)], [127.8, 127.7 (*syn*, *anti*)], [122.0, 121.9 (*syn*, *anti*)], 120.2, 120.0, [75.6, 75.5 (*syn*, *anti*)], [59.2, 58.9 (*syn*, *anti*)], [44.1, 43.9 (*syn*, *anti*)], [29.9, 29.7 (*syn*, *anti*)], [28.7, 28.4 (*syn*, *anti*)], 26.0, [25.5, 25.4 (*syn*, *anti*)], 22.2 ppm; HRMS calcd. for $C_{28}H_{33}N_3O$ (M^+): 427.2625. Found: 427.2606. ***Trans* Isomer**: ^{1}H NMR (by subtracting the signals due to *cis* isomer) (500 MHz, $CDCl_3$) δ 7.42-7.21 (m, 9H), 7.13-7.05 (m, 4H), 7.07-6.91 (m, 2H), {6.62[t, J = 5.5 Hz (*cis*)], 6.58 [t, J = 5.62 Hz (*trans*)], 1H(*syn*) (*anti* hidden under 7.42-7.21)}, 5.08-5.01 [s, 2H (*syn*, *anti*)], 3.85 (br s, 1H), 3.07-3.04 (m, 1H), 2.17-2.12 (m, 2H), 1.88-1.35 (m, 11H).

cis- and *trans*-4-[2-(*N,N*-Diphenylhydrazino)cyclopentyl]butanal (*N,N*-dimethylhydrazone) (186c)



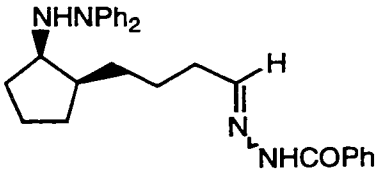
186ci



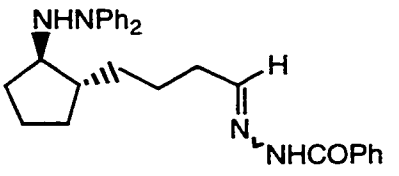
186cii

N,N-Dimethylhydrazine (34 mg, 0.564 mmol) was added to a solution of aldehyde **210** (50 mg, 0.153 mmol) in dry CH_2Cl_2 (1.5 mL). The resulting solution was stirred overnight at 40 °C. The solvent was evaporated to provide the crude product. Purification by flash chromatography (2:5 ether/pet ether) afforded 45 mg (80%) of the title compound as a faint yellow oil; ***Cis* Isomer**: IR (neat): 2909, 1591, 1482, 1029, 748, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30-7.22 (m, 4H), 7.23-7.11 (m, 4H), 6.98-6.91 (m, 2H), 6.66-6.65 (m, 1H), 3.99-3.98 (br s, 1H), 3.27-3.23 (m, 1H), 2.68 (s, 6H), 2.24-2.16 (m, 2H), 1.85-1.39 (m, 11H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.0, 138.9, 128.9, 121.8, 120.2, 58.8, 44.2, 43.4, 33.1, [29.9, 29.6 (*syn*, *anti*)], 29.5, 28.5, 26.5, 22.2 ppm; FAB acc. mass calcd. for $C_{23}H_{33}N_4$ (M^++1): 365.2706. Found: 365.3281. Anal. calcd. for $C_{23}H_{32}N_4$: C, 75.78; H, 8.84; N, 15.36. Found: C, 75.59; H, 8.90; N, 15.23. ***Trans* Isomer:** ^1H NMR (500 MHz, $CDCl_3$) (by subtracting signals due to *cis* isomer) δ 7.35-7.23 (m, 4H), 7.19-7.11 (m, 4H), 6.97-6.93 (m, 2H), 6.55 (t, J = 5.5 Hz, 1H), 3.98-3.96 (br s, 1H), 3.05-3.03 (m, 1H), 2.67 (s, 6H), 2.20-2.17 (m, 2H), 2.16-1.34 (m, 11H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 139.2, 128.7, 121.9, 120.3, 63.8, 43.9, 43.4, 34.1, 31.4, 30.7, 28.5, 26.4, 23.6 ppm.

cis-and _trans_-4-[2-(_N,N_-Diphenylhydrazino)cyclopentyl]butanal (_N_-benzoylhydrazone) (186d)



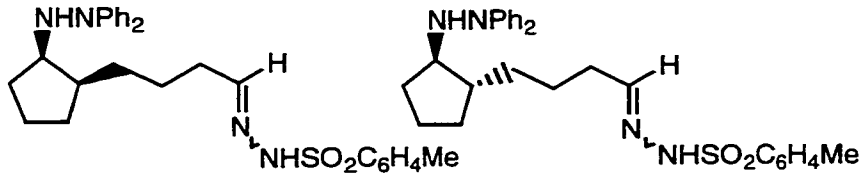
186di



186dii

Benzoylhydrazine (33.7 mg, 0.248 mmol) and aldehyde **210** (50 mg, 0.155 mmol) were stirred in dry CH_2Cl_2 (1 mL) at 21 °C for 4 h. The resulting mixture was evaporated to dryness and purified by flash chromatography (1:24, ether/CH_2Cl_2). Concentration of the appropriate fractions yielded 55 mg (80%) of viscous oil; ***Cis* Isomer:** IR (neat): 3226, 3052, 2937, 2865, 1648, 1586, 1494, 1289, 1075, 1028, 909, 748, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.1 (br s, 1H), 7.77-7.73 (m, 2H), 7.48-7.31 (m, 4H), 7.28-7.16 (m 4H), 7.12-7.02 (m, 4H), 6.99-6.90 (m, 2H), 3.80-3.79 (br s, 1H), 3.28-3.25 (m, 1H), 2.31-2.27 (m, 2H), 1.88-1.35 (m, 11H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 162.2, 152.2, 148.0, 148.0, 131.8, 129.0, 128.6, 127.3, 122.1, 120.3, 59.1, 44.1, 32.1, 29.6, 28.5,28.5, 25.8, 22.1 ppm; HRMS calcd. for $C_{28}H_{32}N_4O$ (M^+): 440.2577. Found: 440.2578. ***Trans* Isomer**: ^1H NMR (500 MHz, $CDCl_3$) (by subtracting signals due to *cis* isomer), δ 8.96 (br s, 1H), 7.75-7.74 (m, 2H), 7.49-7.39 (m, 4H), 7.27-7.22 (m, 4H), 7.19-7.09 (m, 4H), 6.97-6.92 (m, 2H), 3.70 (br s, 1H), 3.07-3.05 (m, 1H), 2.48-2.34 (m, 2H), 1.86-1.40 (m, 11H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 152.2, 147.1, 147.1, 131.8, 129.0, 128.7, 127.2, 122.2, 120.2, 59.5, 44.1, 33.9, 31.2, 30.7, 30.6, 25.2, 23.4 ppm.

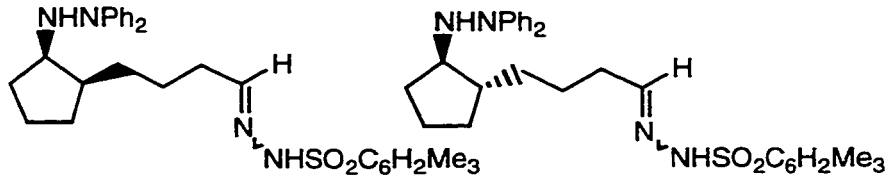
cis-and _trans_-4-[2-(_N,N_-Diphenylhydrazino)cyclopentyl]butanal [_N_-(_p_-toluenesulfonyl)hydrazone] (186e)



186ei **186eii**

_p_-Toluene sulfonylhydrazide (32 mg, 0.175 mmol) and aldehyde **210** (47 mg, 0.146 mmol) were stirred in ethanol (1 mL) at 21 °C for 1 h. The resulting solution was evaporated to dryness, and purification by flash chromatography (2:5 ether/pet ether) afforded 45 mg (63.3%) of the title compound as a faint yellow viscous oil; IR (neat) 3207, 3092, 2914, 1591, 1479, 1320, 1165, 1059, 909, 813, 748, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84-7.75 (m, 2H), 7.29-7.22 (m, 6H), 7.15-7.08 (m, 4H), 7.07-6.94 (m, 3H), 6.63 [t, J = 5.2 Hz (*anti*) (*syn* hidden under 7.07-6.94), 1H], 3.74 (br s, 1H), [3.23-3.21 (m, *cis*), 2.99-2.96 (m, *trans*), 1H], 2.45-2.36 [overlapping s (*cis*, *trans*, *syn*, *anti*), 3H], 2.21-2.10 (m, 2H), 1.91-1.25 (m, 11H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): ***Cis* Isomer**: [152.7, 152.2 (*syn*, *anti*)], 148.1, 143.9, 135.3, 129.5, 129.0, 127.9, 122.0, 120.3, [59.4, 59.1 (*syn*, *anti*)], 44.1, [33.7, 32.3 (*syn*, *anti*)], 29.7, 29.6, [28.5, 28.3 (*syn*, *anti*)], 25.2, [22.1, 22.0 (*syn*, *anti*)], 21.5 ppm. ***Trans* Isomer**: [152.7, 151.2 (*syn*, *anti*)], 147.9, 143.9, 135.3, 129.6, 129.0, 128.0, 122.0, 120.1, 63.6, 43.7, 33.7, 31.3, 30.6, 29.6, [24.8, 24.7 (*syn*, *anti*)], 23.4, 21.5 ppm; HRMS calcd. for $C_{28}H_{34}N_4O_2S$ (M^+): 490.2405. Found: 490.2445.

***cis*-and *trans*-4-[2-(*N,N*-Diphenylhydrazino)cyclopentyl]butanal [*N*-(2,4,6-trimethylbenzenesulfonyl)hydrazone] (186f)**



186fi **186fii**

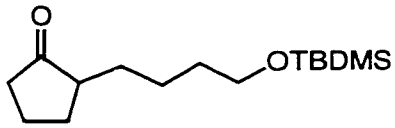
2, 4, 6-Trimethylbenzenesulfonyl hydrazide (37 mg, 0.175 mmol) and aldehyde **210** (47 mg, 0.146 mmol) were stirred in ethanol (1 mL) at 21 °C for 1h. The resulting solution was evaporated to dryness, and purification by flash chromatography (2:5 ether/pet ether) afforded 42 mg (55%) of the title compound as a faint yellow oil; IR (neat) 3214, 2916, 1591, 1474, 1314, 1159, 1046, 852, 660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.22 (m, 4H), 7.11-7.05 (m, 4H), 7.01-6.95 (m, 2H), 6.93-6.90 [overlapping s, 2H, (*syn*, *anti*)], 6.57 [t, *J* = (*anti*), (*syn* hidden under 7.01-6.95), 1H], 3.82-3.74 (br s, 1H), [3.22-3.20 (m, *cis*), 2.98-2.96 (m, *trans*) 1H], 2.67-2.60 [overlapping s, 6H], 2.30-2.25 (s, 3H), 2.22-2.08 (m, 2H), 1.88-1.70 (m, 4H), 1.67-1.66 (m, 3H), 1.59-1.30 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: ***Cis* Isomer**: 151.1, 148.1, 142.7, 140.6, 132.3, 131.8, 129.0, 122.1, 120.2, 59.2, 44.0, [32.3, 32.2 (*syn*, *anti*)], 29.6, 29.5, 28.2, 25.1, 23.0, 22.0, 20.9 ppm. ***Trans* Isomer**: 151.0, 147.9, 142.7, 140.0, 132.3, 131.8, 129.0, 122.0, 120.1, 63.6, 43.8, 33.7, 31.3, 30.6, 24.5, 23.4, 23.0, 22.0, 20.9 ppm; HRMS calcd. for $C_{30}H_{38}N_4O_2S$ (M^+): 518.2717. Found: 518.2725.

4-Iodo-1- (*tert*-Butyldimethylsilyloxy)butane (212)

$ICH_2CH_2CH_2CH_2OTBDMS$

4-Bromobutanol (2 g, 7.52 mmol) was refluxed with sodium iodide (5.62 g, 37.6 mmol) in acetone (30 mL) for 24 h. Precipitated salt (NaBr) was filtered off and washed with ether and the filtrate was concentrated. Purification by column chromatography (1:9, CH_2Cl_2/pet ether) afforded 2.16 g (92%) of the title compound as faint yellow oil; IR (neat) 2941, 2858, 1468, 1254, 1224, 1099, 838, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.60 (t, $J = 6.1$ Hz, 2H), 3.18 (t, $J = 6.9$ Hz, 2H), 1.99-1.83 (m, 2H), 1.61-1.54 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 61.8, 33.4, 30.1, 25.9, 18.2, 7.0, -5.3; HRMS calcd for $C_6H_{14}IOSi$ (M^+-*t*-Bu): 256.9859. Found: 256.9840.

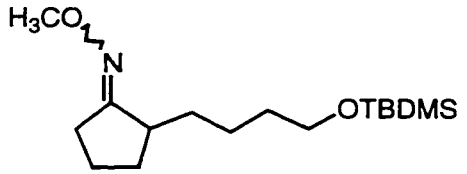
2-(4-*t*-Butyldimethylsilyloxybutyl)cyclopentanone (213)



n-Butyllithium (14.35 mL of 2.5 M soln., 35.8 mmol) was added dropwise to a cold solution (-78 °C) of diisopropylamine (4.16 g, 41.11 mmol) in dry THF (42.6 mL).This solution was stirred for 15 min., and then cyclopentanone (2.7 g, 33.12 mmol) was added as a solution in THF (21.2 mL) and stirred for 20 min. To this solution , HMPA (27.73 mL, 163.8 mmol) was added, followed by dimethyl zinc (16.3 mL of 1M soln, 16.3 mmol) and compound **212** (2.6 g, 8.28 mmol) as a solution in THF (32.2 mL). The reaction mixture was stirred at -78 °C for 4 h and then warmed to room temperature. The reaction was quenched with aqueous NH_4Cl solution (50 mL) and extracted with ether (3x150 mL). The combined organic extracts were washed with brine (3 x 50 mL), dried and concentrated *in vacuo*. The resultant oil was purified by flash chromatography (6% ether/ pet ether) to afford 1.34 g (60%) of the title compound as a clear colorless oil; IR (neat) 2942, 2859, 1740, 1465, 1360, 1253, 1152, 1100, 1006, 840, 776 cm^{-1}; ^1H NMR

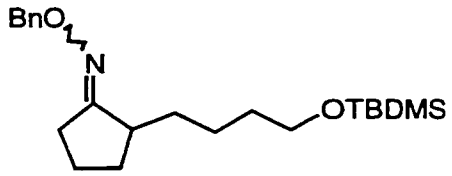
(500 MHz, $CDCl_3$) δ 3.57 (t, J = 6.45 Hz, 2H), 2.29-2.16 (m, 2H), 2.10-1.94 (m, 3H), 1.78-1.72 (m, 2H), 1.54-1.50 (m, 3H), 1.45-1.31 (m, 2H), 1.26-1.20 (m, 1H), 0.85 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.3, 62.9, 49.1, 38.1, 32.7, 29.5, 29.4, 25.9, 23.8, 20.7, 18.3, -5.3 ppm; HRMS calcd for $C_{11}H_{21}O_2Si$ (M^+-*t*-Bu): 213.1312. Found: 213.1315. Anal. calcd. for $C_{15}H_{30}O_2Si$: C, 66.68; H, 11.17. Found: C, 66.65; H, 10.94.

2-(4-*t*-Butyldimethylsilyloxybutyl)cyclopentanone-*O*-methyloxime (214a)



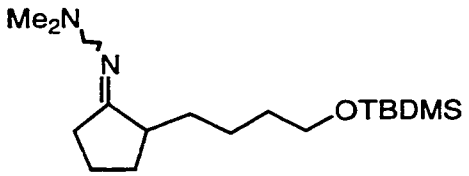
Methoxyamine hydrochloride (102 mg, 1.22 mmol) was added to a solution of ketone **213** (300 mg, 1.11 mmol) and pyridine (107 μL, 1.33 mmol) in dry ethanol (5 mL) at 0 °C. The solution was stirred at this temperature until the reaction was complete. The resulting solution was concentrated, and purification by flash chromatography (1:20, ether/pet ether) yielded 290 mg (87%) of the title compound as a clear colorless oil; IR (neat) 2942, 2859, 1486, 1387, 1361, 1253, 1100, 1052, 1006, 841, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.54 (t, J = 6.4 Hz, 2H), 2.46-2.35 (m, 2H), 2.28-2.21 (m, 1H), 1.92-1.86 (m, 1H), 1.77-1.64 (m, 2H), 1.57-1.41 (m, 3H), 1.39-1.24 (m, 4H), 0.83 (s, 9H), -0.01 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, [62.9, 62.8, (*syn*, *anti*)], 61.1, [43.1, 39.7 (*syn*, *anti*)], 32.8, 32.3, 31.4, 27.5, 25.8, 23.9, 22.5, 18.2, -5.3 ppm; HRMS calcd. for $C_{16}H_{33}NO_2Si$ (M^+): 299.2282. Found: 299.2286.

2-[4-(*t*-Butyldimethylsilyloxy)butyl]cyclopentanone-*O*-benzyloxime (214b)



Benzyloxyamine hydrochloride (150 mg, 0.937 mmol) was added to a stirred solution of ketone **213** (230 mg, 0.852 mmol) and pyridine (83μL, 1.02 mmol) at 0 °C. After completion of the reaction, the solution was concentrated and the residue purified using flash chromatography (1:10, ether/pet ether). Concentration of the appropriate fractions afforded 275 mg (86%) of the title compound as a faint yellow oil; IR (neat):2941, 2858, 2362, 1462, 1253, 1049, 1036, 839, 776, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 5.07 (s, 2H), 3.5 (t, J = 6.4 Hz, 2H), 2.57-2.34 (m, 3H), 1.97-1.70 (m, 3H), 1.62-1.45 (m, 3H), 1.39-1.29 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 130.4, 128.1, 127.9, 127.4, 75.4, [63.1, 62.9 (*syn*, *anti*)], [43.2, 40.1 (*syn*, *anti*)], [32.8, 32.7 (*syn*, *anti*)], [32.7, 31.0 (*syn*, *anti*)], [31.5, 30.6 (*syn*, *anti*)], 28.0, 25.9, [23.8, 23.6 (*syn*, *anti*)], [23.0, 22.5 (*syn*, *anti*)], 18.3, -5.3 ppm; HRMS calcd for $C_{22}H_{37}NO_2Si$ (M^+): 375.2595. Found: 375.2586.

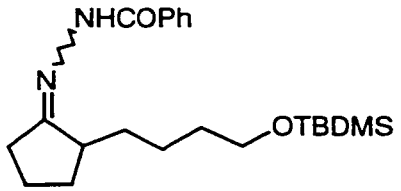
2-[4-(*t*-Butyldimethylsilyloxy)butyl]cyclopentanone-*N*-*N*-dimethylhydrazone (214c)



N,N-Dimethylhydrazine (77 μL, 1.02 mmol) was added to a solution of ketone **213** (250 mg, 926 mmol) in dry CH_2Cl_2 (1.5 mL). The resulting solution was stirred

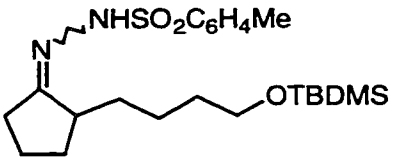
overnight at 40 °C. The solvent was evaporated to provide the crude product. Purification by flash chromatography 1:1 ether/pet ether) afforded 121 mg (42%) of the title compound as a faint yellow oil; IR (neat) 2943, 2858, 1654, 1468, 1387, 1253, 1100, 975, 840, 776; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.51 (t, J = 6.5 Hz, 2H), 2.47-2.41 (m, 1H), 2.38 (s, 6H), 2.35-2.20 (m, 2H), 1.88-1.61 (m, 3H), 1.55-1.17 (m, 7H), 0.80 (s, 9H), -0.04 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 63.0, 46.9, 44.4, 33.0, 32.9, 30.2, 29.3, 25.8, 23.8, 22.7, 18.1, -5.38 ppm; HRMS calcd for $C_{17}H_{36}N_2OSi$ (M^+): 312.2598. Found: 312.2600.

2-[4-(*t*-Butyldimethylsilyloxy)butyl]cyclopentanone-*N*-benzoylhydrazone (214d)



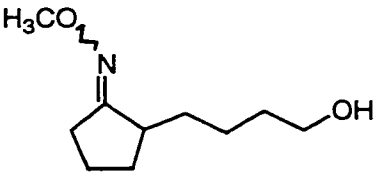
Benzoylhydrazine (122 mg, 0.88 mmol) and ketone **213** (200 mg, 0.74 mmol) were stirred in dry toluene (8 mL) at 21 °C for 4 h. The resulting mixture was concentrated and purified by flash chromatography (1:24, ether/CH_2Cl_2). Concentration of the appropriate fractions yielded 178 mg (62%) of a viscous oil; IR: (CCl_4) 3180, 3069, 2913, 1657, 1577, 1463, 1383, 1254, 1102 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (br s, 1H), 7.85-7.65 (m, 2H), 7.43-7.34 (m, 3H), 3.54 (m, 2H), 2.52-2.17 (m, 3H), 2.02-1.67 (m, 4H), 1.59-1.19 (m, 6H), 0.83 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.9, 163.3, 133.5, [131.4, 131.2 (*syn*, *anti*)], [128.1, 128.0 (*syn*, *anti*)], [127.3, 127.0 (*syn*, *anti*)], 62.9, 44.7, 32.7, 32.1, 30.6, 27.6, 25.8, 23.8, 22.4, 18.1, -0.05 ppm; HRMS calcd. for $C_{22}H_{36}N_2O_2Si$ (M^+): 388.2547. Found: 388.2517.

2-[4-(*t*-Butyldimethylsilyloxy)butyl]cyclopentanone-*N*-(*p*-toluenesufonyl)hydrazone (214e)



p-Toluene sulfonylhydrazide (163 mg, 0.88 mmol) and ketone **213** (200 mg, 0.74 mmol) were stirred in ethanol (3 ml) at 21 °C for 1 h. The resulting solution was evaporated to dryness, and purification by flash chromatography (2:5 ether/pet ether) afforded 213 mg (66%) of the title compound as a faint yellow viscous oil; IR (neat) 3212, 2911, 1660, 1597, 1461, 1398, 1369, 1254, 1166, 1096, 924, 829, 776, 679 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 6.9 Hz, 2H), 7.39 (br s, 1H), 7.26 (d, J = 10.9 Hz, 2H), 3.55-3.51 (m, 2H), 2.39 (s, 3H), 2.36-2.20 (m, 2H), 2.09-2.03 (m, 2H), 1.93-1.79 (m, 2H), 1.66-1.39 (m, 2H), 1.27-1.11 (m, 4H), 0.86 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 143.7, 135.9, 129.3, 128.0, 63.0, 44.7, 32.8, 31.6, 31.1, 28.0, 25.9, 23.5, 22.5, 21.5, 18.3, -5.2 ppm; HRMS calcd for $C_{18}H_{29}N_2O_3SSi$ (M^+-*t*-Butyl): 381.1669. Found: 381.1655.

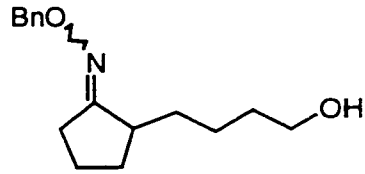
2-(4-Hydroxybutyl)cyclopentanone-*O*-methyloxime (215a)



Tetrabutylammonium fluoride (0.609 mL of 1M soln. in THF, 0.609 mmol) was added to a solution of oxime ether **214a** (190 mg, 0.609 mmol) in dry THF (4.2 mL) at 0 °C, and the resulting mixture was stirred overnight. The reaction was quenched with water (2 mL) and extracted with ether. The combined organic extracts were washed with

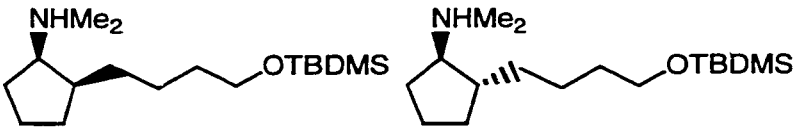
brine (2 x 10 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:3, ether/hexanes) afforded 150 mg (80%) of the title compound as a faint yellow oil; IR (neat) 3369, 2914, 2363, 1652, 1450, 1176, 1053, 873, 847 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.79-3.60 [overlapping s, 3H (*syn*, *anti*)], 3.56-3.44 (m, 2H), 3.06 (br s, 1H), 2.44-2.10 (m, 2H), 1.89-1.10 (m, 11H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.2, [62.0, 61.9 (*syn*, *anti*)], [42.9, 39.6 (*syn*, *anti*)], [32.3, 31.8 (*syn*, *anti*)], [31.2, 30.4 (*syn*, *anti*)], [30.7, 30.6 (*syn*, *anti*)], 27.4, 23.5, 22.7, 22.3 ppm; HRMS calcd for $C_{10}H_{19}NO_2$ (M^+): 185.1416. Found: 185.1397.

2-(4-Hydroxybutyl)cyclopentanone-*O*-benzyloxime (215b)



Tetrabutylammonium fluoride (0.806 mL of 1M soln. in THF, 0.806 mmol) was added to a solution of oxime ether **214b** (275 mg, 0.733 mmol) in dry THF (5 mL) at 0 °C, and the resulting solution was stirred overnight. The reaction was quenched with water (2 mL) and extracted with ether. The combined organic extracts were washed with brine (2 x 10 mL) and concentrated. Purification by flash chromatography (1:1, ether/pet ether) afforded 133 mg (86.9%) of the title compound as a faint yellow oil; IR (neat) 3365, 2936, 2863, 1496, 1454, 1365, 1037, 906, 737, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 5.03 (s, 2H), [3.56 (t, J = 6.4 Hz), 3.52 (t, J = 6.5 Hz) 2H (*syn*, *anti*)], 2.56-2.31 (m, 4H), 1.84-1.66 (m, 3H), 1.61-1.51 (m, 3H), 1.49-1.30 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ [169.0, 168.8 (*syn*, *anti*)], [138.3, 138.2 (*syn*, *anti*)], [128.2, 128.1 (*syn anti*)], [127.9, 127.8 (*syn*, *anti*)], [127.5, 127.4 (*syn*, *anti*)], 75.4, [65.7, 62.4 (*syn*, *anti*)], [41.1, 39.9 (*syn*, *anti*)], [32.5, 30.1 (*syn*, *anti*)], [31.9, 30.6 (*syn*, *anti*)], [31.5, 30.6 (*syn*, *anti*)], 28.0, [23.5, 22.9 (*syn*, *anti*)], 22.5 ppm; HRMS calcd for: $C_{16}H_{23}NO_2$: 261.1729. Found: 261.1751.

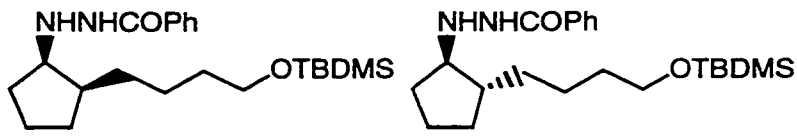
cis-and _trans_-2-[4-(_t_-Butyldimethylsilyloxy)butyl]-1-(_N,N_-dimethylhydrazino)cyclopentane (215c)



215ci **215cii**

A suspension of sodium cyanoborohydride (12.6 mg, 0.199 mmol) and dimethylhydrazone **214c** (50 mg, 0.166 mmol) and a few milligrams of Bromocresol Green in dry MeOH (1 mL) were stirred under nitrogen in a round bottom flask. A solution of _p_-toluenesulfonic acid (190 mg, 1 mmol) in MeOH (1 mL) was then slowly added at 0 °C to maintain the pH at 3.5, indicated by a tan colour of the indicator. The reaction mixture was stirred at 0°C for 1 h, quenched with water, extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (2 x 3 mL), dried with anhydrous $MgSO_4$, filtered and concentrated _in vacuo_. Purification by flash chromatography (1:1, ether/ pet ether) afforded 25 mg (50%) of the title compound as a faint yellow viscous oil; IR (neat) 3395, 2909, 2361, 1464, 1253, 1100, 839, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59-3.55 [overlapping t, 2H (_cis_, _trans_)], [3.22-3.20 (m, _cis_), 2.93-2.89 (m, _trans_), 1H], [2.40, 2.41, s (_cis_, _trans_), 6H], 1.87-1.20 (m, 13 H), 0.86 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ [64.0, 59.6 (_cis_, _trans_)], [63.2, 63.0 (_cis_, _trans_)], [47.6, 46.9 (_cis_, _trans_)], [44.2, 43.4 (_cis_, _trans_)], [34.5, 33.5 (_cis_, _trans_)], [33.0, 31.3 (_cis_, _trans_)], [32.1, 31.1 (_cis_, _trans_)], [29.5, 28.5 (_cis_, _trans_)], 25.9, [24.8, 24.5 (_cis_, _trans_)], [22.5, 21.8 (_cis_, _trans_)], 18.2, -5.3 ppm; FAB acc. mass calcd for $C_{17}H_{39}N_2OSi$ (M^++1): 315.2833. Found: 315.3075.

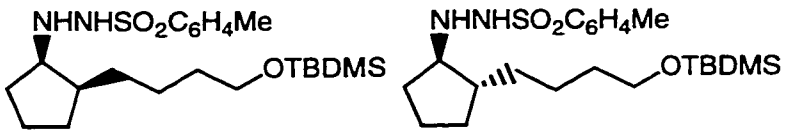
cis-and _trans_-2-[4-(t-Butyldimethylsilyloxy)butyl]-1-(_N_-benzoylhydrazino)cyclopentane (215d)



215di **215dii**

Sodium borohydride (40 mg, 1.12 mmol) was added to a solution of benzoyl hydrazone **214d** (220 mg, 0.563 mmol) in dry methanol (4 mL), and the resulting mixture was stirred overnight at 21 °C. The reaction was quenched with acetone (3 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine, dried and concentrated *in vacuo*. Purification by flash chromatography (2% $MeOH/CH_2Cl_2$) afforded 124 mg (56%) (1:1.2 mix of *cis* and *trans*) of the title compound as a faint yellow oil; IR (neat) 3277, 2911, 2352, 1638, 1577, 1457, 1253, 1097, 817 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75-7.71 (m, 2H), 7.49-7.23 (m, 3H), [3.59, t, J = 6.4 Hz (*cis*), 3.54, t, J = 6.5 Hz (*trans*), 2H], [3.51-3.43, m (*cis*), 3.17-3.10, m, (*trans*) 1H], 1.89-1.15 (m, 13H), [0.86, 0.85 overlapping s (*cis*, *trans*) 9H], [0.25, 0.00 overlapping s (*cis*, *trans*) 6H] ppm, two NH protons not observed; ^{13}C NMR (125 MHz, $CDCl_3$); ***Cis* Isomer:** δ 167.2, 133.0, 131.6, 128.5, 126.7, 63.3, 63.1, 43.9, 33.0, 30.3, 29.3, 29.1, 25.9, 24.9, 21.8, 15.1, -5.3 ppm. ***Trans* isomer:** δ 167.1, 132.9, 131.6, 128.5, 128.5, 67.3, 63.0, 44.2, 34.5, 32.9, 31.2, 31.0, 25.9, 24.4, 23.1, 15.1, -5.3 ppm; HRMS calcd for $C_{22}H_{38}N_2O_2Si$ (M^+): 390.2704. Found: 390.2685.

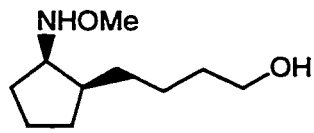
cis-and _trans_-2-[4-(_t_-Butyldimethylsilyloxy)butyl]-1-[_N_-(_p_-toluenesulfonylhydrazino)]cyclopentane (215e)



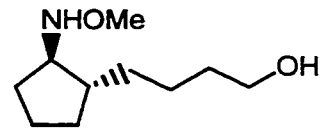
215ei **215eii**

A suspension of sodium cyanoborohydride (34 mg, 0.545 mmol) and _p_-toluenesulfonylhydrazone **214e** (200 mg, 0.448 mmol) and a few milligrams of Bromocresol Green in dry THF (10 mL) were stirred under nitrogen in a round bottom flask. A solution of _p_-toluenesulfonic acid (190 mg, 1.0 mmol) in THF (1 mL) was then slowly added at 0 °C to maintain the pH at 3.5, indicated by a tan colour of the indicator. The reaction mixture was stirred at 21°C for 18 h, quenched with water, and extracted with ether (3 x 10 mL). The combined organic extracts were washed with brine (2 x 10 mL), dried with anhydrous $MgSO_4$, filtered and concentrated _in vacuo_. Purification by flash chromatography (1:1, ether/ pet ether) afforded 100 mg (50%) of the title compound as a faint yellow viscous oil; IR (neat) 3245, 2940, 2859, 1598, 1466, 1321, 1251, 1160, 1097, 838, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.27-7.26 (m, 2H), 3.58-3.52 (overlapping t, 2H), [3.12-3.11, m (_cis_), 2.78-2.76, m (_trans_), 1H], [2.39, 2.36, overlapping s, (_cis_, _trans_), 3H], 1.73-1.01 (m, 13H), 0.85 (s, 9H), 0.01 (s, 6H), ppm, two NH protons were not observed; ^{13}C NMR (125 MHz, $CDCl_3$); ***Cis* Isomer**: δ 143.8, 135.6, 129.4, 128.1, 63.1, 62.6, 43.3, 33.0, 30.7, 29.5, 28.6, 25.9, 24.9, 21.5, 21.3, 18.3, -5.27 ppm. ***Trans* Isomer**: δ 143.7, 135.6, 129.2, 128.1, 63.3, 62.2, 43.8, 34.1, 33.0, 30.5, 29.2, 25.9, 24.3, 22.7, 21.3, 18.3, -5.3 ppm.

***cis*-and *trans*-4-[2-(*N*-Methoxylamino)cyclopentyl]-1-butanol (216a)**



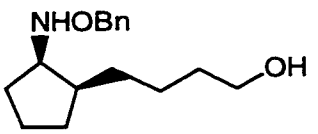
216ai



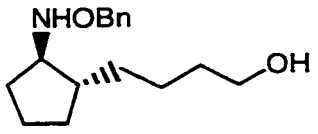
216aii

A suspension of sodium cyanoborohydride (76 mg, 1.216 mmol), *O*-methyloxime **215a** (150 mg, 0.811 mmol) and a few milligrams of Bromocresol Green in methanol (5 mL) were stirred under nitrogen in a round bottom flask. A solution of *p*-toluenesulfonic acid (190 mg, 1 mmol) in methanol (1 mL) was then slowly added at 20 °C to maintain the pH at 3.5, indicated by a tan colour of the indicator. The reaction mixture was stirred at this temperature for 3 h, quenched with water, and extracted with ether (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:20, ether/ pet ether) afforded 90 mg (60%) of the title compound as a clear colorless oil; IR (neat) 3342, 2909, 1453, 1360, 1034, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58-3.55 [overlapping t, (*cis*, *trans*) 2H], 3.47, 3.45 [overlapping s, (*cis*, *trans*) 3H], 3.36-3.35, 3.04-3.01 [m, 1H (*cis*, *trans*)], 1.82-1.64 (m, 3H), 1.58-1.29 (m, 8H), 1.22-1.10 (m, 2H) ppm, NH and OH protons were not observed; ^{13}C NMR (125 MHz, $CDCl_3$): ***Cis* Isomer**: δ 67.3, 62.6, 61.9, 43.0, 34.5, 32.8, 31.4, 30.4, 24.7, 23.3. ***Trans* Isomer**: 62.9, 62.5, 61.6, 43.0, 32.7, 29.8, 29.4, 28.4, 24.7, 21.8 ppm; HRMS calcd for $C_{10}H_{21}NO_2(M^+)$: 187.1533. Found: 187.1557.

cis-and _trans_-4-[2-(_n_-Benzyloxyamino)cyclopentyl]-1-butanol (216b)



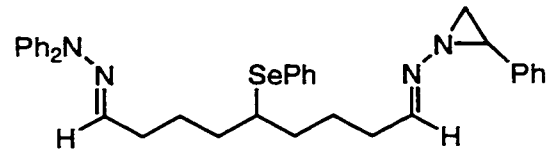
216bi



216bii

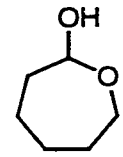
A suspension of sodium cyanoborohydride (32 mg, 0.509 mmol), *O*-benzyloxime **215b** (133 mg, 0.509 mmol) and a few milligrams of Bromocresol Green in methanol (5 mL) were stirred under nitrogen in a round bottom flask. A solution of *p*-toluenesulfonic acid (190 mg, 1 mmol) in methanol (1 mL) was then slowly added at 20 °C to maintain the pH at 3.5, indicated by a tan colour of the indicator. The reaction mixture was stirred at this temperature for 3 h, quenched with water, and extracted with ether (3 x 5 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:20, ether/ pet ether) afforded 90 mg (67%) of the title compound as a clear colorless oil; IR (neat) 3353, 2910, 2361, 1453, 1361, 1035, 742, 6987 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 4.69, 4.67 [s, 2H (*cis*, *trans*)], 3.60-3.56 [overlapping s, 2H (*cis*, *trans*, *syn*, *anti*)], [3.43-3.42 (m, *cis*), 3.12-3.09 (m, *trans*) 1H], 1.85-1.13 (m, 14H) ppm, NH proton not observed; ^{13}C NMR (125 MHz, $CDCl_3$): ***Cis* Isomer**: δ 137.9, 128.3, 128.1, 127.6, 76.3, 67.5, 62.7, 43.0, 34.5, 32.8, 31.4, 30.6, 24.3, 23.4 ppm; ***trans* Isomer:** δ 137.9, 128.3, 128.2, 127.6, 75.4, 63.0, 62.6, 43.1, 34.5, 29.8, 29.5, 28.5, 24.7, 21.8 ppm; HRMS calcd for $C_{16}H_{25}NO_2(M^+)$: 263.1886. Found: 263.1861.

5-Phenylselenononanedial-[1-*N*-(2-phenyl-*N*-aziridinyl)hydrazone]-9-*N*,*N*-diphenylhydrazone (181b)



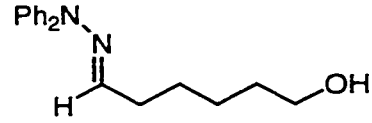
Diphenyl diselenide (122 mg, 0.392 mmol) and sodium hydride (34 mg, 0.82 mmol, 60% dispersion in mineral oil) were placed in an oven dried, two necked flask. The flask and its contents were evacuated (oil pump) and flushed with nitrogen five times. Dry THF (1.5 mL) was added to the contents of the flask using a syringe the mixture was refluxed for 45-60 min. To the resulting light yellow suspension of the sodium phenylselenide, compound **182g** was added slowly (270 mg, 0.523 mmol) and refluxed for 3 h. The reaction was quenched by methanol (2 mL) and extracted with ether (3 x 20 mL). The combined organic extracts were washed with saturated NaCl solution (2 x 5 mL) and dried over anhydrous $MgSO_4$ and dried *in vacuo*. Purification by column chromatography (2:3 ether/pet ether) afforded 186 mg (65%) of the desired compound as a faint yellow oil; IR (neat) 3059, 3033, 2937, 1596, 1495, 1455, 1299, 1210, 1066, 747, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, J = 5.6 Hz, 1H), 7.48-7.45 (m, 2H), 7.33-7.13 (m, 12H), 7.08-7.01 (m, 6H), 6.45 (t, J = 5.2 Hz, 1H), 3.11-3.10(m, 1H), 2.92 (d , J = 4.89 Hz, 1H), 2.38-2.32 (m, 1H), 2.25-2.11 (m, 5H), 1.70-1.52 (m, 8H) ppm; ^{13}C (125 MHz, $CDCl_3$) δ 162.5, 144.2,139.1, 138.5, 134.8, 129.6, 129.1, 128.9, 128.3, 127.3, 127.1, 126.3, 123.8, 122.3, 45.9, 43.6, 40.0, 34.8, 34.8, 32.3, 32.2, 25.6, 24.3; FAB accurate mass calcd. for $C_{35}H_{39}N_4Se$ (M^+ + 1): 595.2340. Found: 595.2680.

ε–Caprolactol (258)



Following the procedure for the preparation of lactol **195,** ε-Caprolactone (5.0 mL, 5.2 g, 45.3 mmol) in toluene (50 mL) was treated at –78 °C with DIBALH (36.5 mL, 1.5 M solution in toluene, 54.8 mmol). Workup and purification as described for lactol **195,** gave **258** (4.2 g, 79%) as a faint yellow oil; IR (neat, cm^{-1}) 3409, 2906, 1725, 1458; ^1H NMR (200 MHz, $CDCl_3$) δ 9.64 (t, J = 1.6 Hz, 1H), 4.65 (br s, 1H), 3.52 (t, J = 6.2 Hz, 2H)), 2.37-2.29 (m, 2H), 1.97-1.23 (m, 7H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.2, 62.4, 43.8, 32.3, 25.3, 21.7 ppm; HRMS calcd. For $C_6H_{12}O_2$ (M^+): 116.0834. Found: 116.0809.

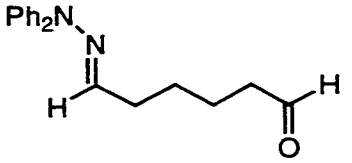
6-Hydroxyhexanal-*N,N*-diphenylhydrazone (260)



Lactol **258** (10.0 g, 86.2 mmol) in methanol (500 mL) was added dropwise to a solution of Ph_2NNH_2 (14 g, 76.3 mmol) in methanol (500 mL) and the reaction was stirred at 21 °C overnight. Concentration gave a purple oil, which was purified by flash chromatography. The silica gel was deactivated by washing first with a 1 % solution of Et_3N added to the eluting solution 50% ethyl acetate/petroleum ether. After packing the column, fresh eluting solvent was used that did not contain Et_3N. Concentration of the appropriate fractions yielded 20.3 g (94 %) of the title alcohol as a faint yellow oil;
IR (neat, cm^{-1}) 3354, 3060, 2932, 2858, 1592, 1493, 1302, 1210, 749, 698; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.31 (m, 4H), 7.14-7.06 (m, 6H), 6.52 (t, J = 5.3 Hz, 1H), 3.60 (t, J = 6.4 Hz, 2H), 2.98 (br s, 1H), 2.32-2.22 (m, 2H), 1.60-1 .36 (m, 6H), ppm; ^{13}C NMR (50

MHz, $CDCl_3$) δ 144.1, 139.8, 129.5, 123.7, 122.2, 62.4, 32.5, 32.3, 26.6, 25.2 ppm; HRMS calcd. For $C_{18}H_{22}N_2O$ (M^+): 282.1727. Found: 282.1734.

Hexanedial-6(*N,N*-diphenylhydrazone) (262)



Following the procedure for the preparation of aldehyde **191**, alcohol **260** (6.78 g, 2.4 mmol) was dissolved in DMSO (30 mL) and Et_3N (2.7 mL). The mixture was then treated with SO_3.Py (1.14 g, 7.2 mmol) in DMSO (10 mL). After purification, 5.57 g (83 %) of the title compound was obtained as light yellow oil; IR (neat, cm^{-1}) 3426, 3046, 2901, 2720, 1725, 1593, 1491, 1302, 1210, 748, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.74 (t, J = 1.8 Hz, 1H), 7.38-7.30 (m, 4H), 7.15-7.03 (m, 6H), 6.49 (t, J = 5.3 Hz, 1H), 2.44 (dt, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 2H), 2.33-2.23 (m, 2H), 1.70-1.52 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.4, 144.2, 138.9, 129.6, 123.9, 122.3, 43.6, 32.3, 26.4, 21.6 ppm; HRMS calcd. for $C_{18}H_{20}N_2O$ (M^+): 280.1571. Found: 280.1562.

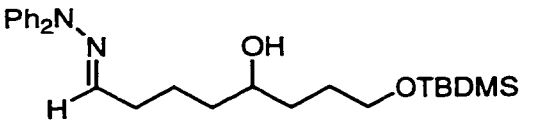
3-Iodo-1- (*tert*-butyldimethylsilyloxy)propane (263)

$ICH_2CH_2CH_2OTBDMS$

3-Bromopropanol (10 g, 71.9 mmol) was refluxed with sodium iodide (42 g, 280 mmol) in acetone (300 mL) for 24 h. Precipitated salt (NaBr) was filtered off and washed with ether and the filtrate was concentrated. The resulting 3-iodopropane (14.5 g, 78.3 mmol) was then treated with imidazole (10.6 g, 155 mmol) followed by *t*-butyldimethylsilyl chloride (17.7 g, 117 mmol) in dry CH_2Cl_2 (400 mL). The reaction mixture was stirred at 21 °C for 5 h and then quenched with aqueous NH_4Cl solution

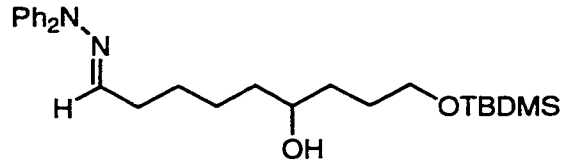
(100 mL) and extracted with ether (3x300 mL). The combined organic extracts were washed with brine (3 x 75 mL), dried and concentrated. Purification by column chromatography (petroleum ether) afforded 18 g (72%) of the title compound as faint yellow oil; IR (neat) 2943, 2858, 1468, 1361, 1253, 1181, 1137, 1101, 1052, 835, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.63 (t, J = 5.6 Hz, 2H), 3.24 (t, J = 6.6 Hz, 2H), 1.98-1.92 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 62.2, 36.0, 32.0, 18.2, 3.6, -5.3; HRMS calcd for $C_5H_{12}IOSi$ (M^+-*t*-Bu): 242.9360. Found: 242.9524.

5-Hydroxy-8-(*tert*-butyldimethylsilyloxy)octanal-*N,N*-diphenylhydrazone (264)



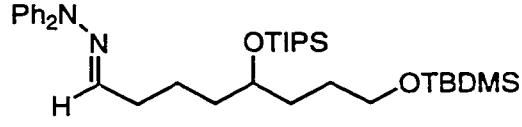
$ICH_2CH_2CH_2OTBS$ (2.35 g, 7.14 mmol) in dry ether (30 mL) was added to a cold solution (-78 °C) of *t*-BuLi (11.78 mL of 1.33 M soln, 15.70 mmol) in ether (90 mL). The resulting solution was stirred for 30 min then aldehyde **191** (1.9 g, 7.14 mmol) was added as a solution in ether (30 mL). The reaction was stirred at -78 °C for 20 min. and then warmed to room temperature. The reaction was quenched by saturated aqueous NH_4Cl (25 mL) solution and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The resultant oil was purified by flash chromatography (1:3, ether/pet ether) to obtain 2.2 g (70%) of the title compound as a faint yellow oil; IR (neat) 3392, 3061, 2907, 1593, 1482, 1383, 1301, 1253, 1210, 1065, 836, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ7.47–7.32 (m, 4H), 7.13-7.05 (m, 6H), 6.52 (t, J = 5.3 Hz, 1H), 3.67-3.59 (m, 3H), 2.61 (br s, 1H), 2.30-2.26 (m, 2H), 1.67-1.40 (m, 8H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C (125MHz, $CDCl_3$) δ 144.3, 139.8, 129.6, 123.7, 122.2, 71.1, 63.4, 36.8, 34.6, 32.6, 29.1, 25.9, 23.3, 18.2, –5 .4; Fab acc. mass calcd. for $C_{26}H_{41}N_2O_2Si$ (M^+ + 1): 441.2939. Found: 441.2977.

6-Hydroxy-9-(*tert*-butyldimethylsilyloxy)nonanal-*N*,*N*-diphenylhydrazone (265)



$ICH_2CH_2CH_2OTBS$ (2.34 g, 7.80 mmol) in dry ether (30 mL) was added to a cold solution (-78 °C) of *t*-BuLi (11.30 mL, 15.62 mmol) in ether (90 mL). The resulting solution was stirred for 30 min. then aldehyde **262** (2 g, 7.09 mmol) was added as a solution in ether (30 mL). The reaction was stirred at -78 °C for 20 min. and then warmed to room temperature. The reaction was quenched by saturated aqueous NH_4Cl (25 mL) solution and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant oil was purified by flash chromatography (1:3, ether/pet ether) to obtain 2.65 g (82%) of the title compound as a faint yellow oil; IR (neat) 3393, 3061, 2909, 1593, 1478, 1382, 1302, 1253, 1210, 1065, 836 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ7.38–7.29 (m, 4H), 7.13-7.05 (m, 6H), 6.52 (t, J = 5.3 Hz, 1H), 3.67-3.56 (m, 3H), 2.71 (br s, 1H), 2.29-2.26 (m, 2H), 1.63-1.37 (m, 10H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C (50 MHz, $CDCl_3$) δ 144.2, 139.8, 129.5, 123.6, 122.2, 71.1, 63.4, 37.1, 34.5, 32.6, 29.0, 27.0, 25.8, 25.3, 18.2, –5.4; Fab acc. mass calcd. for $C_{27}H_{43}N_2O_2Si$ (M^+ + 1): 455.3085. Found: 455.3314.

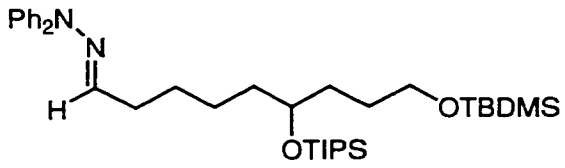
8-(*tert*-Butyldimethylsilyloxy)-5-(triisopropylsyliloxy)octanal-*N*,*N*-diphenylhydrazone (266)



TIPSOTf (10.06 mL, 38.0 mmol) and collidine (5.3 mL, 38.0 mmol) were added to the solution of alcohol **264** (10.9 g, 24.77 mmol) in dry CH_2Cl_2 (145 mL) at room

temperature. The resulting mixture was allowed to stir at this temperature overnight. The reaction was quenched with aqueous NH_4CI (150 mL) solution and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:49 ether/pet ether) yielded 11.8 g (80%) of the title compound as faint yellow oil; IR (neat) 2942, 2164, 1594, 1495, 1465, 10867 837, 747, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37-7.34 (m, 4H), 7.13-7.08 (m, 6H), 6.53 (t, J = 5.3 Hz , 1H), 3.87-3.83 (m, 1H), 3.63-3.58 (m, 2H), 2.29-2.28 (m, 2H), 1.55-1.48 (m, 8H), 1.06 (s, 21H), 0.91 (s, 9H), 0.05. (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.3, 139.7, 129.5, 123.7, 122.3, 71.8, 63.9, 35.9, 32.8, 32.6, 28.1, 25.9, 22.4, 18.2, 18.1, 12.6, -5.3; HRMS calcd. for $C_{35}H_{60}N_2O_2Si$ (M^+): 596.4196; found: 596.4192. Anal. calcd. for $C_{35}H_{60}N_2O_2Si$: C, 70.41; H, 10.13; N, 4.69. Found: C, 70.58; H, 9.97; N, 4.75.

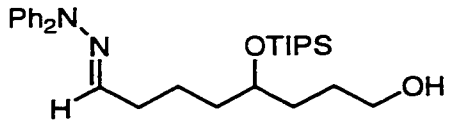
9-(*tert*-Butyldimethylsilyloxy)-6-(triisopropylsyliloxy)nonanal-*N,N*-diphenylhydrazone (267)



TIPSOTf (7.6 mL, 28.68 mmol) and collidine (4 mL, 28.68 mmol) were added to the solution of alcohol **265** in dry CH_2Cl_2 (110 mL) at room temperature. The resulting mixture was allowed to stir at this temperature overnight. The reaction was quenched with aqueous NH_4CI (150 mL) solution and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:49 ether/pet ether) yielded 9.7 g (85%) of the title compound as faint yellow oil; IR (neat) 2940, 2863, 1594, 1495, 1464, 1301, 1252, 1211, 1086, 882, 776, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.36-7.32 (m, 4H), 7.12-

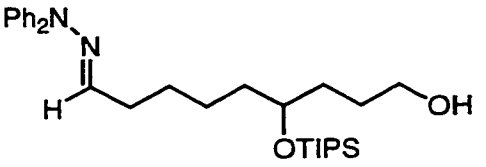
7.06 (m, 6H), 6.52 (t, J = 5.3 Hz , 1H), 3.83 (m, 1H), 3.61-3.55 (m, 2H), 2.29-2.25 (m, 2H), 1.55-1.44 (m, 8H), 1.36-1.32 (m, 2H), 1.04 (s, 21H), 0.88 (s, 9H), 0.03. (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.3, 139.9, 129.5, 123.7, 122.3, 71.9, 63.4, 36.2, 32.7, 32.6, 28.1, 27.3, 25.9, 24.4, 182, 18.1, 12.6, -5.3; HRMS calcd. for $C_{36}H_{62}N_2O_2Si$ (M^+): 610.4353; found: 610.4369. Anal. calcd. for $C_{36}H_{62}N_2O_2Si$: C, 70.76; H, 10.23; N, 4.50. Found: C, 71.0; H, 10.31; N, 4.61.

8-Hydroxy -5-(triisopropylsilyloxy)-octanal-*N,N*-diphenylhydrazone (268)



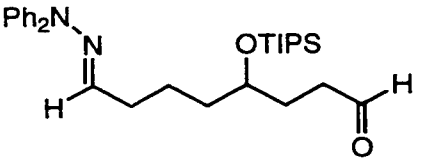
. Pyridinium *p*-toluene sulfonate (3.8 g, 14.76 mmol) was added to the solution of the compound **266** (11.0 g, 18.45 mmol) in ethanol (99%, 145 mL) at room temperature, and the resulting mixture was stirred at 21 °C overnight. The reaction was quenched with aqueous $NaHCO_3$ (50 mL) solution and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 ether/pet ether) yielded 7.5 g (84.3%) of the title compound as a clear colorless oil; IR (neat) 3359, 2909, 1593, 1478, 1378, 1301, 1210, 1060, 883, 748, 677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.46-7.29 (m, 4H), 7.14-7.03 (m, 6H), 6.50 (t, J = 5.2 Hz, 1H), 3.89-3.72 (m 1H), 3.64-3.59 (m, 2H), 2.27-2.24 (m, 2H), 2.07-2.01 (br s 1H), 1.64-1.46 (m, 8H), 1.03 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) 144.2, 139.4, 129.6, 123.8, 122.3, 71.3, 63.2, 35.5, 32.7, 32.6, 27.6, 22.6, 18.1, 12.5; HRMS calcd. for $C_{29}H_{46}N_2O_2Si$ (M^+): 482.3331. Anal. calcd. for $C_{29}H_{46}N_2O_2Si$: C, 72.15; H, 9.60; N, 5.80. Found: C, 72.38; H, 9.54; N, 5.64.

9-Hydroxy -5-(triisopropylsilyloxy)nonanal-*N,N*-diphenylhydrazone (269)



Pyridinium *p*-toluene sulfonate (3.28 g, 12.72 mmol) was added to the solution of the compound alcohol **267** (9.70 g, 15.9 mmol) in ethanol (99%, 135 mL) at room temperature, the resulting mixture was stirred at 21°C overnight. The reaction was quenched with aqueous $NaHCO_3$ (50 mL) solution and the aqueous layer was extracted with ether (3 x 200 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (3:7 ether/pet ether) yielded 6.2 g (79%) of the title compound as a clear colorless oil; IR (neat) 3361, 2939, 2865, 1593, 1494, 1461, 1060, 883, 747, 689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.30 (m, 4H), 7.14-7.04 (m, 6H), 6.52 (t, J = 5.2 Hz, 1H), 3.89-3.86 (m 1H), 3.59-3.56 (m, 2H), 2.32-2.22 (m, 3H), 1.65-1.41 (m, 8H), 1.36-1.20 (m, 2H), 1.03 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) 144.2, 139.7, 129.6, 123.7, 122.2, 71.8, 63.2, 35.8, 32.6, 32.6, 27.5, 27.1, 24.6, 18.1, 12.5; HRMS calcd. for $C_{30}H_{48}N_2O_2Si$ (M^+): 496.3487. Found: 496.3509. Anal. calcd. for $C_{30}H_{48}N_2O_2Si$: C, 72.53; H, 9.74; N, 5.60. Found: C, 72.34; H, 9.87; N, 5.71.

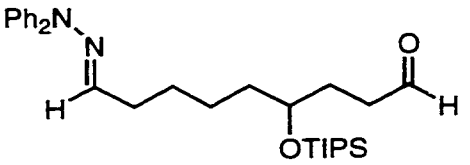
4-(Triisopropylsilyloxy)octanedial-8-(*N,N*-diphenylhydrazone) (270)



A suspension of pyridine.SO3 complex (6.9 g, 43.6 mmol) in DMSO (40 mL) was added to a solution of alcohol **268** (5.8 g, 11.71 mmol), and triethylamine (13.14 mL, 94.17 mmol) in DMSO (10 mL) at room temperature. After consumption of the alcohol

the reaction was poured into a separatory funnel containing water and ethyl acetate (3 x 150 mL) and the combined organic extracts were washed with brine (2 x 50 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:9 ether/pet ether) yielded 4.5 g (78.9%) of the title compound as a faint yellow oil; IR (neat) 2908, 2718, 1725, 1592, 1481, 1379, 1301, 1061, 883, 748, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.49-7.32 (m, 4H), 7.23-7.07 (m, 6H), 6.54 (t, J = 5.1 Hz, 1H), 3.96-3.93 (m, 1H), 2.59-2.45 (m, 2H), 2.32-2.29 (m, 2H), 1.96-1.75 (m, 2H), 1.59-1.51 (m, 4H), 1.05 (s, 21 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 144.3, 139.0, 129.6, 123.8, 122.3, 70.9, 39.1, 35.9, 32.6, 28.1,22.5, 18.2, 12.7; HRMS calcd. for $C_{29}H_{44}N_2O_2Si$ (M^+): 480.3173. Found; 480.3190.

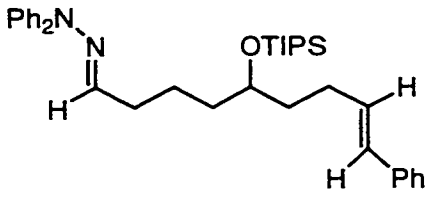
4-(Triisopropylsilyloxy)nonanedial-9-(*N,N*-diphenylhydrazone) (271)

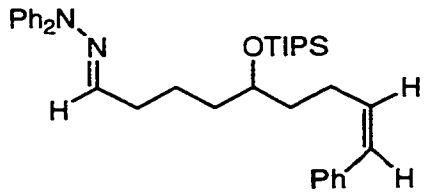


A suspension of pyridine.SO_3 complex (5.65 g, 11.71 mmol) in DMSO (40 mL) was added to a solution of the alcohol **269** (5.8 g, 11.71 mmol), and triethylamine (13.14 mL, 94.17 mmol) in DMSO (10 mL) at room temperature. After consumption of the alcohol the reaction was poured into a separatory funnel containing water and ethyl acetate (3 x 150 mL) and the combined organic extracts were washed with brine (2 x 50 mL) dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:9 ether/pet ether) yielded 4.5 g (78.9%) of the title compound as a faint yellow oil; IR (neat) 2939, 2865, 1725, 1593, 1494, 1461, 1379, 1301, 1210, 1093, 1060, 883, 748, 689 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.39-7.32 (m, 4H), 7.14-7.05 (m, 6H), 6.52 (t, J = 5.1 Hz, 1H), 3.92-3.87 (m, 1H), 2.54-2.46 (m, 2H), 2.33-2.23 (m, 2H), 1.89-1.71 (m, 2H), 1.57-1.17 (m, 6H), 1.05 (s, 21 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 202.5, 144.1, 139.5, 129.6, 123.7, 122.2, 70.9, 39.0, 36.1, 32.5, 28.0,

27.0, 24.5, 18.1, 12.5; HRMS calcd. for $C_{30}H_{46}N_2O_2Si$ (M^+): 494.3330. Found; 494.3344. Anal. calcd. for $C_{30}H_{46}N_2O_2Si$: C, 72.82; H, 9.37; N, 5.66. Found: C, 73.0; H, 9.29; N, 5.47.

cis/trans-5-Triisopropylsilyloxy-9-phenylnon-8-eneal-(_N,N_-diphenylhydrazone) (272a)

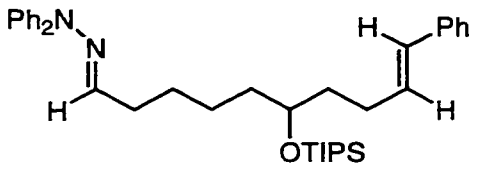


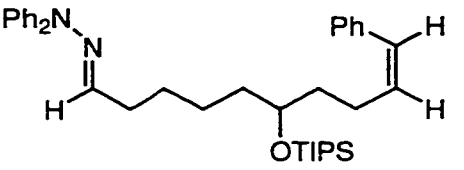


n-Butyllithium (867 μL of 2.41 M soln., 2.09 mmol) was added to the solution benzyltriphenylphosphonium chloride (907 mg, 2.29 mmol) in dry THF (20 mL) at 0 °C. The resulting solution stirred at this temperature for 1 h., followed by the addition of aldehyde **270** (1 g, 2.09 mmol) as a soln. in dry THF (10 mL). The resulting solution was stirred at 22 °C overnight. The reaction was quenched with aqueous NH_4Cl soln. (25 mL), extracted with ether (3 x 50 mL) and combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (1%, ether/pet ether) to afford 1.16 g (86%) of the title compound as a faint yellow oil; IR (neat); 2940 2865, 15943 1494, 1301 1211, 1083, 964,883, 749, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (m, 9H), 7.25-7.05 (m, 6H), 6.52, 6.49 [overlapping t, J = 5.1 Hz, 1H (*cis, trans*)], 6.38, 6.28 [overlapping d, J = 11.8 Hz, 15.9 Hz (*cis, trans*) 1H], {6.21, 6.18 [dt, J = 15.8, 6.8 Hz] (*trans*), 5.63, 5.61 [dt, J = 11.5 Hz, 7.3 Hz] (*cis*), 1H}, 3.91-3.83 (m, 1H), 2.38-2.18 (m, 4H), 1.70-1.47 (m, 6H), 1.04, 1.01 [s, 21H (*cis, trans*)]; ^{13}C NMR (125 MHz, $CDCl_3$): *Trans Isomer* δ 144.0, 139.6, 137.8, 130.8, 129.7, 129.6, 128.4, 126.7, 125.8, 123.7, 122.3, 71.5, 36.0, 35.9, 32.8, 28.3, 22.3, 18.1, 12.6; *Cis* Isomer δ 144.3, 139.6, 137.6, 132.7, 129.6, 128.9, 128.6, 128.4, 126.4,123.7, 122.3, 71.6, 36.5, 35.9, 32.8, 28.3, 24.1, 18.1, 12.6; HRMS calcd. for $C_{36}H_{50}N_2OSi$ (M^+): 554.3695

Found: 554.3737. Anal. calcd for $C_{36}H_{50}N_2OSi$: C, 77.92; H, 9.08; N, 5.05. Found: C, 77.99; H, 9.00; N, 4.96.

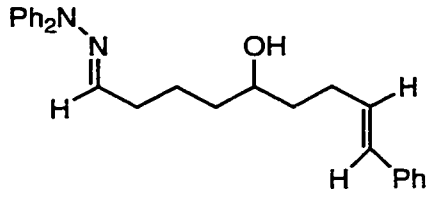
cis/trans-6-Triisopropylsilyloxy-10-phenyldec-9-eneal-(_N,N_-diphenylhydrazone) (273a)

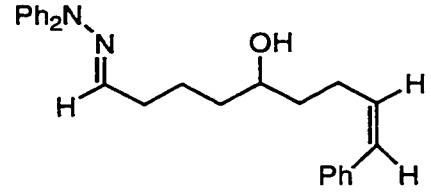




n-Butyllithium (842 μL of 2.41 M soln., 2.03 mmol) was added to the solution benzyltriphenylphosphonium chloride (879 mg, 2.22 mmol) in dry THF (20 mL) at 0 °C. The resulting solution stirred at this temp. for 1 h., followed by the addition of aldehyde **271** (1 g, 2.02 mmol) as a soln. in dry THF (10 mL).The resulting solution was stirred at 22 °C overnight. The reaction was quenched with aqueous NH_4Cl soln. (25 mL), extracted with ether (3 x 50 mL) and combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (1%, ether/pet ether) to afford 885 mg (77%) of the title compound as a faint yellow oil; IR (neat); 2937, 2864, 2351, 1594, 1494, 1210, 1075, 882, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 9H), 7.20-7.02 (m, 6H), 6.52, 6.50 [overlapping t, J = 5.2 Hz, 1H (*cis, trans*)], 6.38, 6.28 [overlapping d, J = 11.6 Hz, 15.8 Hz (*cis, trans*) 1H], {6.21, 6.17 [dt, J = 15.8, 6.8 Hz (*trans*)] 5.64 5.61 [dt, J = 11.8 Hz, 7.3 Hz (*cis*)], 1H}, 3.89-3.73 (m, 1H), 2.42-2.20 (m, 4H), 1.69-1.30 (m, 8H), 1.05, 1.03 [s, 21H (*cis, trans*)]; ^{13}C NMR (125 MHz, $CDCl_3$) *Trans Isomer* δ 144.3, 139.9, 137.8, 132.8, 130.9, 129.6, 128.4, 126.7, 125.8, 123.7, 122.3, 71.7, 36.3, 35.9, 32.6, 28.3, 27.3, 24.4, 18.1, 12.6; *cis* Isomer δ 144.3, 139.6, 137.6, 129.6, 128.9, 128.6, 128.2, 128.0, 126.4, 123.7, 122.3, 71.8, 36.5, 36.4, 32.6, 28.3, 27.3, 24.2, 18.1, 12.6; HRMS calcd. for $C_{36}H_{52}N_2OSi$ (M^+): 568.3851. Found: 568.3835.

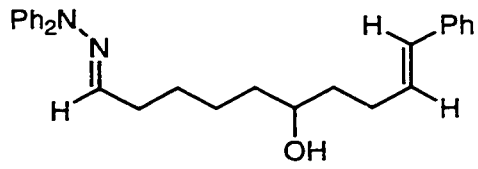
***cis/trans* 5-Hydroxy-8-phenylnon-7-eneal-(*N,N*-diphenylhydrazone) (274a)**

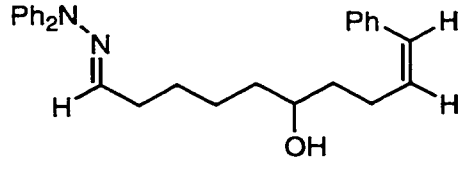




Tetrabutylammonium fluoride (2 mL of 1M solution in THF, 2.09 mmol) was added to the solution of compound **272a** (965 mg, 1.44 mmol) in dry THF (25 mL) at 0 °C and the resulting mixture was stirred overnight. The reaction was quenched with water (10 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:3, ether/pet ether) afforded 600 mg (86.7%) of the title compound as a faint yellow oil; IR (neat); 3026, 2933, 1592, 1492, 1300 1210, 747, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 9H), 7.21-7.05 (m, 6H), 6.52, (t, J = 5.1 Hz, 1H), 6.39, (d, J = 16.1 Hz, 1H), {6.23, 6.20 [d t, J = 15.8, 6.8 Hz, 1H), 3.68-3.65 (m, 1H), 2.37-2.25 (m, 4H), 1.67-1.42 (m, 6H), OH proton not observed; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 139.5 137.6, 130.3, 130.2, 129.6, 128.4, 126.8, 125.9, 123.8, 122.3, 71.1, 36.9, 36.8, 32.5, 29.4, 22.9; HRMS calcd. for $C_{27}H_{30}N_2O$ (M^+): 398.2359. Found: 398.2360.

***cis/trans*-6-Hydroxy-10-phenyldec-9-eneal-(*N,N*-diphenylhydrazone) (275a)**

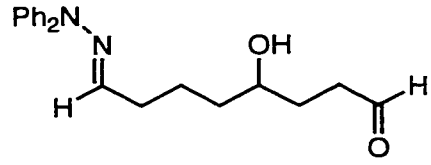




Tetrabutylammonium fluoride (1.65 mL of 1M solution in THF, 1.65 mmol) was added to the solution of compound **273a** (771 mg, 1.36 mmol) in dry THF (20 mL) at 0 °C and the resulting mixture was stirred for 4 h. The reaction was quenched with water (5

mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:3, ether/pet ether) afforded 458 mg (82%) of the title compound as a faint yellow oil; IR (neat); 3386, 3826, 2927, 1593, 1493, 1301, 1210, 1074, 747, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.25 (m, 9H), 7.21-7.01 (m, 6H), 6.51,6.50 [overlapping t, J = 5.2 Hz (*cis, trans*) 1H], 6.42, 6.39 [overlapping d, J = 15.9 Hz, 11.8 Hz (*cis, trans*) 1H], {6.22, 6.19 [dt, J = 15.8, 6.8 Hz (*trans*)] 5.67. 5.63 [dt, J = 7.3 Hz, 11.6 Hz (*cis*)] 1H}, 3.64-3.36 (m, 1H), 2.49-2.21 (m, 4H), 1.67-1.24 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) *Trans Isomer* δ 144.3, 139.8, 137.6, 130.3, 130.2, 129.6, 128.4, 126.9, 125.9, 123.8, 122.3, 71.3, 37.3, 36.9, 32.6, 29.2, 27.0, 25.1; *Cis Isomer* δ 144.3, 139.8, 137.6, 132.2, 129.3, 128.7, 128.1, 126.6, 123.8, 122.3, 71.3, 37.4, 37.2, 32.6, 29.2, 26.9, 25.2; HRMS calcd. for $C_{27}H_{32}N_2O$ (M^+): 412.2516. Found: 412.2521.

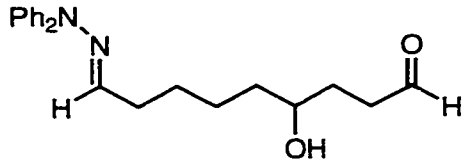
4-Hydroxyoctanedial-8-(*N,N*-diphenylhydrazone) (280)



Tetrabutylammonium fluoride (4.86 mL of 1M soln. in THF, 4.86 mmol) was added to the solution of compound **270** (2 g, 4.05 mmol) in dry THF (40 mL), at 0 °C and the resulting mixture was stirred overnight. The reaction was quenched with water (20 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:3 ether/hexanes) afforded 476 mg (40%), of the title compound as a faint yellow oil; IR (neat) 3385, 2923, 1592, 1493, 1456, 1301, 1209, 1040, 749 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48-7.27 (m, 4H), 7.21-7.09 (m, 6H), 6.50 (t, J = 5.2 Hz, 1H), 5.53-5.42 (m, 1H), 4.23-3.95 (m, 1H), 2.92-2.85 (br s, 1H), 2.37-1.35 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, [138.7, 139.4], 129.6,

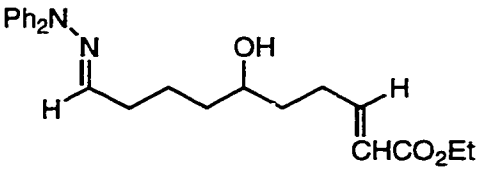
123.8, 122.2, [98.8, 98.2], [80.7, 78.1], [36.9-35.0], [33.9, 32.6], [32.9, 32.6], [29.3, 29.4],[23.7, 23.5]; HRMS calcd. for $C_{20}H_{24}N_2O_2$ (M^+) : 324.1839. Found: 324.1820.

4-Hydroxynonanedial-9-(*N,N*-diphenylhydrazone) (281)



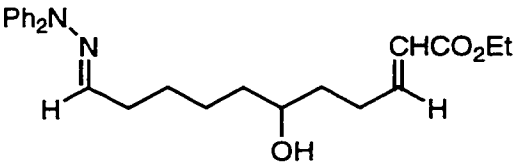
Tetrabutylammonium fluoride (4.86 mL of 1M soln. in THF, 4.86 mmol) was added to the solution of compound **271** (2 g, 4.05 mmol) in dry THF (40 mL), at 0 °C and the resulting mixture was stirred overnight. The reaction was quenched with water (20 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (2:3 ether/hexanes) afforded 820 mg (45%), of the title compound as a faint yellow oil; IR (neat) 3382, 2912, 1593, 1478, 1300, 1208, 1034, 747 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.49-7.31 (m, 4H), 7.19-7.04 (m, 6H), 6.51 (t, J = 5.42 Hz, 1H), 4.61-3.91 (m, 1H), 2.28-1.80 (m, 6H), 1.70-1.21 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 139.9, 129.6, 123.8, 122.3, [98.8, 98.2], [80.7, 78.3], 35.2, 32.6, 29.3, 27.0, 25.8, 25.6; HRMS calcd. for $C_{21}H_{26}N_2O_2$ (M^+): 338.1995. Found: 338.1972.

***cis/trans*-5-Hydroxy-9-carbethoxynon-8-eneal-(*N,N*-diphenylhydrazone) (274b)**



(Carbethoxymethylene)-triphenylphosphorane (642 mg, 1.85 mmol) and benzoic acid (14 mg, 0.14 mmol) were added to a solution of aldehyde **280** (476 mg, 1.47 mmol) in dry toluene (13 mL)at 22 °C. The reaction mixture was stirred at 22 °C overnight. The reaction was quenched with H_2O (3 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (2:3, ether/pet ether) to afford 394 mg (68%) of the title compound as a faint yellow oil; IR (neat); 3442, 2929, 1712, 1593, 1494, 1296, 1207, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.22 (m, 4H), 7.19-7.04 (m, 6H), 6.96(dt, J = 15.6 Hz, 6.9 Hz, 1H), 6.51 (t, J = 5.2 Hz, 1H), 5.82 (dt, J = 15.6 Hz, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.61-3.60 (m, 1H), 2.34-2.24 (m, 3H), 1.59-1.37 (m, 7H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, [149.1, 148.8], 144.2, 139.3, [129.6, 128.8], [123.8, 122.0], [122.3, 120.1], [121.2, 120.4], [89.9, 70.1], [75.1, 60.1], 36.9, 35.5, 32.4, 29.4, 22.8, 14.2; HRMS calcd. for $C_{24}H_{30}N_2O_3$ (M^+): 394.2257. Found: 394.2253.

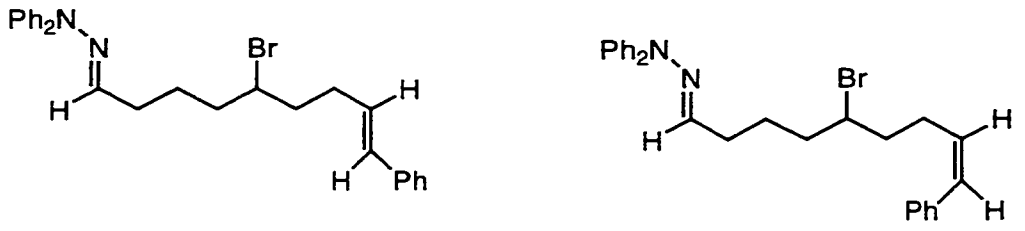
***cis/trans*-6-Hydroxy-10-carbethoxydec-9-eneal-(*N,N*-diphenylhydrazone) (275b)**



(Carbethoxymethylene)-triphenylphosphorane (905 mg, 2.6 mmol) and benzoic acid (20 mg, 0.16 mmol) were added to a solution of aldehyde **281** (700 mg, 2.07 mmol)

in dry toluene (18 mL) at 22 °C. The reaction mixture was stirred at 22 °C overnight. The reaction was quenched with aqueous H_2O (3 mL). The aqueous layer was extracted with ether (3 x 20 mL) and the combined organic extracts were washed with brine, dried and concentrated. The resultant oil was purified by flash chromatography (2:3, ether/pet ether) to afford 506 mg (60%) of the title compound as a faint yellow oil; IR (neat); 3435, 2928, 1712, 1593, 1494, 1298, 1208, 749, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.31 (m, 4H), 7.09-7.00 (m, 6H), 6.96 (dt, J = 15.6 Hz, 7.0 Hz, 1H), 6.52 (t, J = 5.3 Hz, 1H), 5.82 (dt, J = 15.6 Hz, 1.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.56-3.52 (m, 1H), 2.36-2.12 (m, 4H), 1.59-1.37 (m, 8H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$)δ 166.6, 149.0, 144.3, 139.8, 129.6, 123.8, 122.3, 121.4, 70.7, 60.1, 37.2, 35.3, 32.5, 28.4, 26.9, 25.1, 14.2; HRMS calcd. for $C_{25}H_{32}N_2O_3$ (M^+): 408.2414. Found: 408.2420. Anal. calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.29; H, 7.92; N, 6.89.

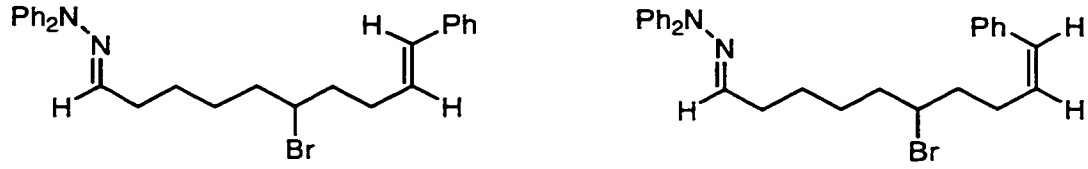
***cis/trans* 5-Bromo-9-phenylnon-8-eneal-1-(*N,N*-diphenylhydrazone) (276a)**



Following the general procedure for bromination of alcohol, bromine (86 μL, 1.728 mmol) and triethylamine (237 μL, 1.73 mmol) were added to a solution of triphenylphosphine (448 mg, 1.73 mmol) in dry CH_2Cl_2 (20 mL), followed by the addition of alcohol **274a** (567 mg, 1.44 mmol) in dry CH_2Cl_2 (6.5 mL). Purification by flash chromatography (4%, ether/pet ether) afforded 545 mg (82%) of the title compound as a clear colorless oil; IR (neat); 3026, 2933, 1592, 1494, 1300 1210, 1083, 747, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.26 (m, 9H), 7.23-7.05 (m, 6H), 6.52, 6.49

[overlapping t, J = 5.2 Hz, 1H (*cis, trans*) 1H], 6.44, 6.43 [overlapping d, J = 11.6 Hz, 15.8 Hz (*cis, trans*)], {6.18, 6.14 [dt, J = 15.7, 7.0 Hz] (*trans*), 5.62, 5.59 [dt, J = 11.5 Hz, 7.3 Hz] (*cis*), 1H}, 4.10-4.01 (m, 1H), 2.48-2.25 (m, 4H), 2.0-1.61 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) *Trans* Isomer δ 144.2, 138.8, 137.3, 131.0, 129.6, 128.7, 128.4, 127.0, 125.9, 123.9, 122.3, 57.2, 38.6, 38.5, 31.9, 30.9, 24.8 *Cis* Isomer δ 144.2, 138.7, 137.3, 130.7, 129.9, 129.6, 128.6, 128.1, 126.6, 123.9, 122.3, 57.2, 39.2, 38.4, 31.9, 30.9, 26.7; HRMS calcd. for $C_{27}H_{29}N_2Br$ (M^+): 460.1495. Found: 460.1518.

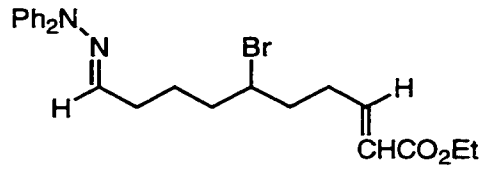
cis/trans-6-Bromo-10-phenyldec-9-eneal-(_N,N_-diphenylhydrazone) (277a)



Following the general procedure for bromination of alcohol, bromine (57 μL, 1.14 mmol) and triethylamine (156 μL, 1.73 mmol) were added to a solution of triphenylphosphine (295 mg, 1.14 mmol) in dry CH_2Cl_2 (15 mL), followed by the addition of alcohol **275a** (390 mg, 0.95 mmoi) in dry CH_2Cl_2 (5 mL). Purification by flash chromatography (4%, ether/pet ether) afforded 360 mg (80%) of the title compound as a clear colorless oil; IR (neat); 3026, 29311, 1593, 1493, 1450, 1301, 1210, 1090, 965, 747, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.21 (m, 9H), 7.16-7.11 (m, 6H), 6.57-6.56 (m, 1H), 6.52, 6.46 [overlapping d, J = 11.9 Hz, 15.8 Hz (*cis, trans*) 1H], {6.21, 6.18 [dt, J = 15.7, 7.0 Hz] (*trans*), 5.66, 5.63 [dt, J = 11.6 Hz, 7.3 Hz] (*cis*), 1H}, 4.09-4.05 (m, 1H), 2.50-2.30 (m, 4H), 2.04-1.84 (m, 4H), 1.63-1.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) *Trans* Isomer δ 144.3, 139.4, 137.5, 131.0, 129.6, 128.9, 128.5, 127.0,

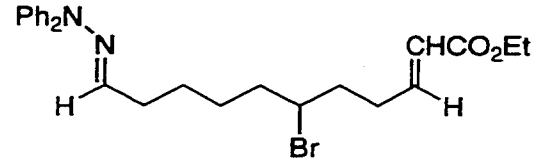
126.0, 123.8, 122.3, 57.4, 38.9, 38.6, 32.4, 31.0, 27.0, 26.4; *Cis* Isomer δ 144.3, 139.4, 137.3, 130.8, 130.0, 129.6, 128.7, 128.3, 128.2, 126.7, 122.3, 57.4, 39.2, 38.8, 32.4, 31.0, 26.7, 26.3; HRMS calcd. for $C_{28}H_{31}N_2Br$ (M^+): 474.1651. Found: 474.1700. Anal. calcd for $C_{28}H_{31}N_2Br$: C, 63.69; H, 6.62; N, 5.94. Found: C, 64.37; H, 6.86; N, 5.69.

cis/trans-5-Bromo-9-carbethoxydec-8-eneal-(_N,N_-diphenylhydrazone) (276b)



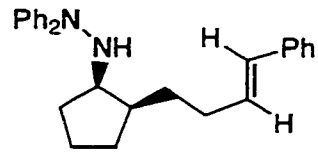
Following the general procedure for bromination of alcohol, bromine (51 μL, 1.02 mmol) and triethylamine (140 μL, 1.02 mmol) were added to the solution of triphenylphosphine (265 mg, 1.02 mmol) in dry CH_2Cl_2 (12 mL), followed by the addition of alcohol **274b** (335 mg, 0.85 mmol) in dry CH_2Cl_2 (4 mL). Purification by flash chromatography (1:9, ether/pet ether) to afford 290 mg (75%) of the title compound as faint yellow oil; IR (neat); 2938, 1718, 15943 1493, 1293, 1203, 1092, 1047, 964,883, 749, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.32 (m, 4H), 7.12-7.04 (m, 6H), 6.89 (d t, J = 15.6 Hz, 7.1 Hz, 1H), 6.48 (t, J = 5.1 Hz, 1H), 5.84 (dt, J = 15.6 Hz, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.00-3.96 (m, 1H), 2.46-2.26 (m, 4H), 1.95-1.62 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 147.0, 144.1, 138.5, 129.6, 123.9, 122.3, 122.2, 60.2, 56.6, 38.4, 37.1, 31.8, 30.1, 2.7, 14.2; HRMS calcd. for $C_{24}H_{29}N_2O_2Br$ (M^+): 456.1413. Found: 456.1419

***cis/trans*-6-Bromo-10-carbethoxydec-9-eneal-(*N,N*-diphenylhydrazone) (277b)**

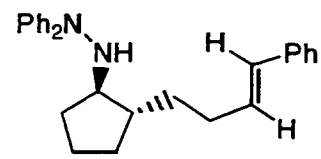


Following the general procedure for bromination of alcohol, bromine (67 μL, 1.34 mmol) and triethylamine (184 μL, 1.34 mmol) were added to the solution of triphenylphosphine (347 mg, 1.34 mmol) in dry CH_2Cl_2 (15 mL), followed by the addition of alcohol **275b** (455 mg, 1.12 mmol) in dry CH_2Cl_2 (5 mL). Purification by flash chromatography (1:9, ether/pet ether) to afford 367 mg (70%) of the title compound as a faint yellow oil; IR (neat); 2931, 2352, 1718, 1593, 1495, 1302, 1209, 1092, 749, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) d 7.36-7.32 (m, 4H), 7.11-7.04 (m, 6H), 6.89 (dt, J = 15.6 Hz, 7.1 Hz, 1H), 6.51 (t, J = 4.9 Hz, 1H), 5.84 (dt, J = 15.5 Hz, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.97-3.94 (m, 1H), 2.46-2.25 (m, 4H), 1.95-1.78 (m, 4H), 1.57-1.44 (m, 4H), 1.26 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 147.1, 144.2, 139.3, 129.6, 123.8, 122.3, 122.3, 60.2, 56.7, 38.8, 37.1, 32.3, 30.1, 27.0, 26.3, 14.2; HRMS calcd. for $C_{25}H_{31}N_2O_2Br$ (M^+): 470.1570. Found: 470.1544.

***cis/trans* -2-(4-Phenyl-3-butenyl)-1-(*N,N*-diphenylhydrazino)-cyclopentane (284a)**



284ai

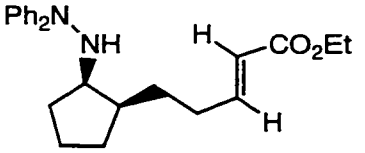


284aii

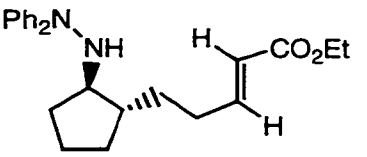
Following the general procedure for the syringe pump radical reactions, bromide **276a** z(100 mg, 0.21 mmol) was dissolved in dry benzene (15 mL) and then treated with Bu_3SnH (79.4 μL, 0,26 mmol) and AIBN (9 mg). The reaction mixture was then

refluxed for two h, cooled to 21 °C and then concentrated under reduced pressure. The residue was dissolved in diethyl ether (5 mL) and stirred with saturated aqueous potassium fluoride solution (4 mL) at 21 °C. Filtration and extraction with diethyl ether followed by drying over anhydrous $MgSO_4$ and concentration gave a crude mixture, which was analyzed by ^1H NMR spectroscopy to determine the isomer ratios. Purification by flash chromatography (3:97 ether/pet ether) afforded 45 mg (54 %) of the title compound as faint yellow oil; IR (neat); 3025, 2955, 2351, 1592, 1494, 1291, 1028, 747, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-6.99 (m, 15H), 6.34, 6.28 (overlapping d, J = 6.9 Hz, 9.1 Hz, 1H), [6.17, 6.15 (dt, J = 16.0 Hz, 6.9 Hz), 1H], 3.95-3.85 (br s, 1H), [3.31-3.29, 3.12-3.02 m (*cis, trans*) 1H], 2.26-2.0 (m, 2H), 1.96-1.79 (m, 2H), 1.68-1.40 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [148.2, 148.0 (*cis, trans*)], [137.8, 137.7 (*cis, trans*)], [130.7, 130.6 (*cis, trans*)], [130.0, 129.7 (*cis, trans*)], [129.8, 129.7 (*cis, trans*)], 129.0, [128.6, 128.5 (*cis, trans*)], 128.4, [126.9, 126.8 (*cis, trans*)], 125.9, [63.8, 59.2 (*cis, trans*)], [43.7, 43.6 (*cis, trans*)], [34.3, 32.1 (*cis, trans*)], [31.6, 31.5 (*cis, trans*)], [30.7, 29.8 (*cis, trans*)], [29.6, 28.8 (*cis, trans*)], [23.6, 22.2 (*cis, trans*)]; HRMS calcd. for $C_{27}H_{30}N_2$ (M^+): 382.2410. Found: 382.2423.

cis/trans -2-(4-Carbethoxy-3-butenyl)-1-(*N,N*-diphenylhydrazino)-cyclopentane (284b)



284bi

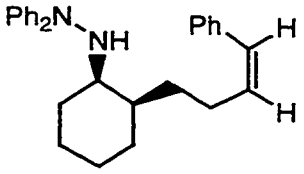


284bii

Following the general procedure for the syringe pump radical reactions, bromide **276b** (90 mg, 0.19 mmol) was dissolved in dry benzene (25 mL) and then treated with Bu_3SnH (62.4 μL, 0,24 mmol) and AIBN (9 mg). The reaction mixture was then refluxed for two h, cooled to 21 °C and then concentrated under reduced pressure. The residue was dissolved in diethyl ether (5 mL) and stirred with saturated aqueous

potassium fluoride solution (4 mL) at 21 °C. Filtration and extraction with diethyl ether followed by drying over anhydrous $MgSO_4$ and concentration gave a crude mixture, which was analyzed by ^1H NMR spectroscopy to determine the isomer ratios. Purification by flash chromatography (3:97 ether/pet ether) afforded 35 mg (46 %) of the title compound as faint yellow oil; IR (neat): 2925, 2351, 1716, 1652, 1590, 1494, 1368, 1280, 1178, 1040, 749, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (*cis isomer*) 7.36-7.32 (m, 4H), 7.28-7.23 (m, 4H), 7.11-7.10 (m, 2H), 6.89 (d t, J = 15.6 Hz, 6.9 Hz, 1H), 5.73 (dt, J = 16.0 Hz, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.90-3.80 (br s, 1H), 3.27-3.26 (m, 1H), 2.19-2.07 (m, 2H), 1.86-1.75 (m, 4H), 1.65-1.50 (m, 5H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 148.8, 148.1, 129.0, 122.1, 121.4, 120.3, 60.1, 59.2, 43.5, 31.2, 29.8, 29.6, 27.4, 22.0, 14.2; ^1H NMR (500 MHz, $CDCl_3$) δ (*trans isomer*) 7.35-7.320 (m, 4H), 7.18-7.03 (m, 4H), 7.11-7.10 (m, 2H), 6.83(d t, J = 15.6 Hz, 6.9 Hz, 1H), 5.70 (dt, J = 16.0 Hz, 1.5 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.90-3.79 (br s, 1H), 3.09-3.03 (m, 1H), 2.19-1.92 (m, 2H), 1.89-1.75 (m, 4H), 1.65-1.51 (m, 5H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 148.5, 148.0, 129.5, 122.1, 121.4, 120.3, 63.9, 60.1, 43.8, 33.2, 31.1, 30.9, 30.8, 22.8, 14.2; HRMS calcd. for $C_{24}H_{30}N_2O_2$ (M^+): 378.2307. Found: 378.2290.

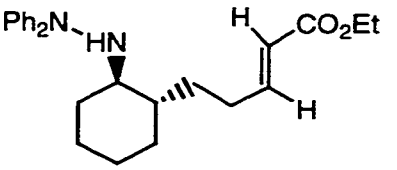
trans-2-(4-Phenyl-3-butenyl)-1-(_N,N_-diphenylhydrazino)-cyclohexane (285a)



Following the general procedure for the radical cyclization, bromide **277a** (75 mg, 158 mmol) was dissolved in benzene (15 mL) and, was treated with Bu_3SnH (53 μL, 174 mmol) and AIBN (4 mg). After concentration and purification of the reaction mixture, 38 mg (60%) of the title compounds were isolated as clear colorless oil; IR (neat) 3026, 2927, 2854, 2351, 1592, 1494, 1452, 1290, 747, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.20 (m, 7H), 7.18-7.14 (m, 6H), 7.13-7.08 (m, 2H), 6.36, 6.24 [overlapping d, J

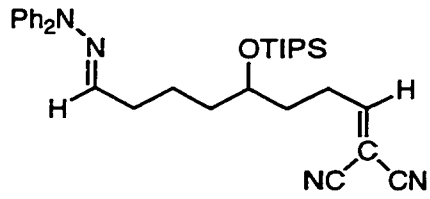
= 11.9 Hz, 15.8 Hz (*cis, trans*) 1H], {6.11, 6.08 [dt, J = 15.8, 7.0 Hz] (*trans*), 5.57, 5.53 [dt, J = 15.8 Hz, 7.3 Hz] (*cis*), 1H}, 3.71 (br s, 1H), 3.05-2.97 (m, 1H), 2.45-1.93 (m, 2H), 1.74-1.24 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, [137.7, 132.2 (*cis, trans*)], 130.9, 129.8, 129.0, [128.6, 128.4 (*cis, trans*)], [128.0, 126.7 (*cis, trans*)], [126.3, 125.8 (*cis, trans*)], 122.1, 120.5, 56.0, 38.2, 30.9, [29.6, 28.8 (*cis, trans*)], 27.4, 27.1, 23.7, 22.7; HRMS calcd. for $C_{28}H_{33}N_2$ (M^+ + 1): 397.2645. Found: 397.3123.

trans-2-(4-Carbethoxy-3-butenyl)-1-(_N,N_-diphenylhydrazino)-cyclohexane (285b)



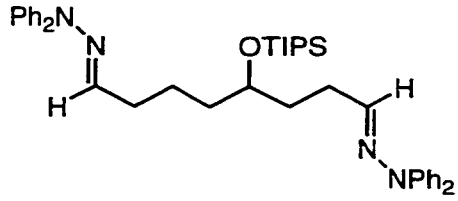
Following the general procedure for the radical cyclization, bromide **277b** (100 mg, 212 mmol) was dissolved in benzene (25 mL) and, was treated with Bu_3SnH (63 μL, 233 mmol) and AIBN (8 mg). After concentration and purification of the reaction mixture, 42 mg (51%) of the title compounds were isolated as clear colorless oil; IR (neat) 2926, 2349, 1716, 1652, 1591, 1492, 1366, 1278, 1176, 1040, 749, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) d 7.31-7.25 (m, 4H), 7.11-7.09 (m, 4H), 7.03-6.94 (m, 2H), 6.84 (dt, J = 15.6 Hz, 6.9 Hz, 1H), 5.69 (dt, J = 15.6 Hz, 1.5 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.79-3.61 (br s, 1H), 3.05-2.91 (m, 1H), 2.25-1.85 (m, 2H), 1.75-1.55 (m, 5H), 1.45-1.30 (m, 6H), 1.26 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 149.2, 148.5, 129.0, 122.3, 122.1, 120.3, 68.1, 60.1, 56.2, 38.3, 30.1, 28.9, 27.3, 23.7, 22.8, 14.2; HRMS calcd. for $C_{25}H_{32}N_2O_2$ (M^+): 392.2465. Found: 392.2454.

4-(Triisopropylsilyloxy)octanedial-1-dicyano-8-*N,N*-diphenylhydrazone (301)



β-alanine (7.4 mg, 0.82 mmol) followed by malonitrile (41 mg, 0.625 mmol) were added to a solution of the aldehyde **270** (250 mg, 0.52 mmol) in 95% ethanol (2.5 mL), at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then at 20 °C for 30 min. The reaction was quenched with aqueous NH_4Cl (5 mL) solution and the aqueous layer was extracted with ether (3x20 mL). The combined organic extracts were washed with saturated aqueous NaCl solution (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash chromatography (1:10 ether/pet ether) yielded 137 mg (50%) of the title compound as a faint yellow oil; IR (neat) 3033, 2942, 2866, 2235, 1594, 1494, 1460, 1301, 1210, 1093, 1061, 883, 749, 690 cm^{-1}; ^1H NMR (125 MHz, $CDCl_3$) δ 7.42-7.30 (m, 4 H, and hidden t, 1H), 7.15-7.04 (m, 6H), 6.50 (t J = 5.1 Hz, 1H), 3.94-3.93 (m, 1H), 2.67-2.59 (m, 2H), 2.33-2.23 (m, 2H), 1.76-1.46 (m, 6H), 1.04 (s, 21H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.2, 144.2, 139.6, 129.6, 123.8, 122.3, 112.1, 89.2, 70.9, 35.5, 33.5, 32.5, 28.0, 22.5, 18.1, 12.5; FAB accurate mass calcd. for C_{32} H_{45} N_4 O Si (M^+ + 1): 529.3354. Found: 529.2506.

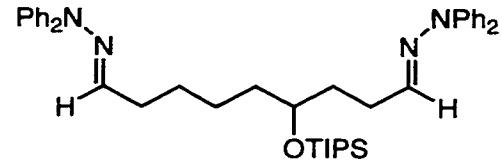
4-(Triisopropylsilyloxy)octanedial-1,8-bis(*N,N*-diphenylhydrazone) (302)



A solution of Ph_2NNH_2 (183 mg, 1.1 mmol) was added to a stirred solution of the aldehyde **270** (480 mg, 1.0 mmol) in MeOH (2 mL) at 20 °C. The resulting mixture was

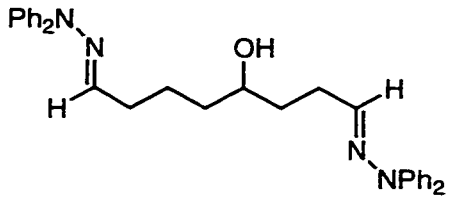
stirred at this temperature for 2 h. After the completion of the reaction the solvent was evaporated and purification of the crude product with column chromatography (1:49 ether/pet ether) afforded 581 mg (90%) of the desired compound as a faint yellow oil; IR (neat) 3081, 2741, 2805, 1502, 1498, 1457, 1301, 1210, 1091, 883, 748, 688 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.38-7.29 (m, 8H), 7.14-7.02 (m, 12H), 6.51 (t, J = 5.0 Hz, 1H), 6.50 (t, J = 5.2 Hz, 1H), 3.86-3.84 (m, 1H), 2.36-2.22 (m, 4H), 1.74-1.50 (m, 6H), 1.02 (s, 21H); ^{13}C (50 MHz, $CDCl_3$) δ 144.2, 144.2, 139.6, 139.5, 129.6, 129.6, 123.8, 123.8, 122.3, 122.3, 71.3, 36.0, 33.3, 32.8, 28.2, 22.3, 18.2, 12.6; HRMS calcd. for $C_{41}H_{54}N_4OSi$ (M^+): 646.4068. Found: 646.4085.

4-(Triisopropylsilyloxy)nonanedial-1,9-bis(*N,N*-diphenylhydrazone) (303)



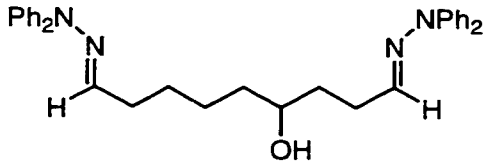
A solution of Ph_2NNH_2 (245 mg, 1.33 mmol) in dry MeOH (2 mL), was added to a stirred solution of the aldehyde **271** (550 mg, 1.1 mmol) in dry MeOH (3 mL) at 20 °C. The resulting mixture was stirred at this temperature for 2 h. After the completion of the reaction the solvent was evaporated and purification of the crude product with column chromatography (1:49 ether/pet ether) afforded 632 mg (86 %) of the desired compound as faint yellow oil; IR (neat) 3060, 2938, 2864, 1593, 1494, 13775, 302, 1210, 1090, 1058, 748, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.32 (m, 8H), 7.11-7.05 (m, 12H), 6.51 (two overlapping t, J = 5.0 Hz, 2H), 3.90-3.82 (m, 1H), 2.36-2.24 (m, 4H), 1.79-1.61 (m, 2H), 1.59-1.44 (m, 4H), 1,42-1.25 (m, 2H), 1.02 (s, 21H); ^{13}C (125 MHz, $CDCl_3$) δ 144.4 144.3, 139.9, 139.6, 129.6, 129.6, 123.7, 123.7, 122.4, 122.3, 71.3, 36.4, 33.4, 32.7, 28.2, 27.3, 24.2, 18.2, 12.6; HRMS calcd. for $C_{42}H_{56}N_4O$ Si (M^+): 660.4225. Found: 660.4218.

4-Hydroxyoctanedial-1,8-bis(*N,N*-diphenylhydrazone) (304)



Tetrabutylammonium fluoride (1.08 mL, 1.08 mmol) was added to a solution of compound **302** (560 mg, 0.867 mmol) in dry THF (12.5 mL) at 0 °C and the resulting mixture was stirred for 4 h. The reaction was quenched with water (5 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 50 mL), dried over anhydrous $MgSO_4$ and concentrated. Purification by flash chromatography (2:3, ether/pet ether) afforded 402 mg (95%) of the title compound as faint yellow oil; IR (neat) 3388, 3080, 2837, 2884, 1582, 1488, 1455, 1378, 11301, 1210, 1080, 749, 897 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.26 (m, 8H), 7.20-7.0 (m, 12H), 6.58 (t, J = 5.0 Hz, 1H), 6.57 (t, J = 5.3 Hz, 1H), 3.69-3.4 (m, 1H), 2.45-2.26 (m, 4H), 2.11-2.09 (br s, H), 1.74-1.45 (m, 6H); ^{13}C (50 MHz, $CDCl_3$) δ 144.2, 144.0, 139.6, 139.4, 129.6, 129.6, 123.9,123.8, 122.2, 122.2, 71.0, 36.8, 34.0, 32.5, 29.0, 23.06; HRMS calcd. for $C_{32}H_{34}N_4O$ (M^+): 4902734. Found: 490.2705.

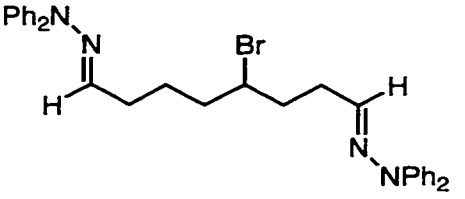
4-Hydroxynonanedial-1,9-bis(*N,N*-diphenylhydrazone) (305)



Tetrabutylammonium fluoride (1.01 mL of 1M soln. in THF, 1.01 mmol) was added to a solution of compound **303** (560 mg, 0.846 mmol) in dry THF (12 mL), at 0 °C and the resulting mixture was stirred overnight. The reaction was quenched with water (5 mL) and extracted with ether. The combined organic extracts were washed with saturated NaCl solution (2 x 5 mL), dried over anhydrous $MgSO_4$ and concentrated.

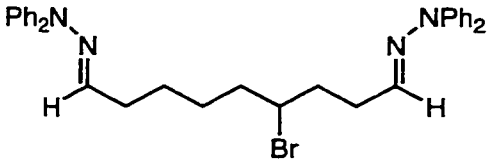
Purification by flash chromatography (2:3 ether/hexanes) afforded 327 mg (78%), of the title compound as a faint yellow oil; IR (neat) 3394, 3047, 2926, 1592, 1491, 1301, 1090, 748, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47-7.31 (m, 8H), 7.19-7.04 (m, 12H), 6.57 (t, J = 4.9 Hz, 1H), 6.52 (t, J = 5.3 Hz, 1H), 3.63-3.60 (m, 1H), 2.44-2.24 (m, 4H), 1.93-1.92 (br s, H), 1.74-1.40 (m, 8H); ^{13}C (50 MHz, $CDCl_3$) δ 144.2, 144.1 139.8, 139.4, 129.6, 129.6, 123.9,123.8, 122.3, 122.3, 71.2, 37.2, 34.0, 32.5, 29.0, 26.9, 25.2; HRMS calcd. for $C_{33}H_{36}N_4O$ (M^+): 504.2891. Found: 504.2904.

4-Bromooctanedial-1,8-bis(*N,N*-diphenylhydrazone) (306)



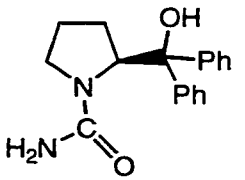
Following the general procedure for bromination of alcohol, bromine (50 μL, 0.816 mmol) and triethylamine (135 μL, 0.816 mmol) were added to the solution of triphenylphosphine (257 mg, 0.816 mmol) in dry CH_2Cl_2 (13 mL), followed by the addition of the alcohol **304** (400 mg, 0.816 mmol) in dry CH_2Cl_2 (4 mL). Purification by flash chromatography (2%, ether/pet ether) afforded 360 mg (82%) of the title compound as a clear colorless oil; IR (neat) 3046, 2934, 1592, 1492, 1300, 1210, 1063, 748, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.33 (m, 8H), 7.19-7.05 (m, 12H), 6.52 (two overlapping t, J = 5.0 Hz, 2H), 4.14-4.09 (m, 1H), 2.55-2.50 (m, 1H), 2.49-2.40 (m, 1H), 2.39-2.25 (m, 2H), 2.19-2.00 (m, 2H), 1.93-1.86 (m, 2H), 1.84-1.74 (m, 1H), 1.72-1.68 (m, 1H); ^{13}C (125 MHz, $CDCl_3$) δ 144.2, 144.1, 138.8, 137.5, 129.6,129.6,124.0, 123.9, 122.4, 122.3, 57.2, 38.5, 36.0, 32.0, 30.7, 24.9; FAB accurate mass calcd. for $C_{32}H_{34}N_4Br$ (M^+ + 1): 553.1968. Found: 553.2763.

4-Bromononanedial-1,9-bis(*N,N*-diphenylhydrazone) (307)



Following the general procedure for bromination of alcohol, bromine (18 μL, 0.357 mmol) and triethylamine (48 μL, 0.357 mmol) were added to the solution of triphenylphosphine (92 mg, 0.357 mmol) in dry CH_2Cl_2 (5 mL), followed by the addition of alcohol **305** (180 mg, 0.357 mmol) in dry CH_2Cl_2 (1.5 mL). Purification by flash chromatography (2%, ether/pet ether) afforded 101 mg (50%) of the title compound as a clear colorless oil; IR (neat) 3058, 3032, 2856, 1596, 1495, 1455, 1376, 1299, 1210, 1173, 1090, 748, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 8H), 7.18-7.04(m, 12H), 6.51 (two overlapping t, J = 5.1 Hz, 2H), 4.09-4.05 (m, 1H), 2.49-2.37 (m, 2H), 2.30-2.26 (m, 2H),2.13-1.98 (m, 2H), 1.88-1.82 (m, 2H), 1.61-1.41 (m, 6H); ^{13}C (125 MHz, $CDCl_3$) δ 144.3, 144.1, 139.4, 137.6, 129.7,129.6,123.9, 123.8, 122.4, 122.3, 57.2, 38.9, 36.0, 32.4, 30.7, 27.1, 26.3; HRMS calcd. for $C_{33}H_{36}N_4Br$ (M^+ + 1): 566.20463. Found: 566.2085.

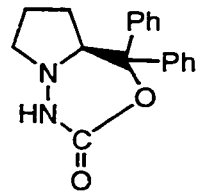
***N*-(Formamidyl)-2-(hydroxydiphenyl)-pyrrolidine (330)**



A solution of potassium cyanate (234 mg, 2.9 mmol) in water (2 mL) was added to a solution of α,α-diphenyl-L-prolinol (100 mg, 0.385 mmol) in 1:1 H_2O/MeOH (2 mL). The reaction mixture was stirred at 21 °C for 12 h and extracted with 1:1 $CHCl_3$/

EtOH solution (3 x 10 mL). The combined organic extracts were washed with brine (2 x 5 mL), dried over anhydrous $MgSO_4$ and concentrated. Purification by column chromatography (2:98, $MeOH/CH_2Cl_2$) yielded 70 mg (60%) of the title compound as a white paste; IR (neat) 3477, 3341, 3203, 2873, 1643, 1588, 1489, 1450, 1305, 1266, 1185, 1032, 765, 701 cm^{-1}.^1H NMR ($CDCl_3$, 200 MHz) δ 7.39-7.21-2 (m, 10H), 6.87-6.70 (m, 1H), 5.20-5.17 (m, 2H), 5.08-5.03 (m, 1H), 3.15-3.03 (m, 1H), 2.81-2.72 (m, 1H), 2.15-1.86 (m, 2H), 1.49-1.35 (m, 1H), 0.56-0.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.1, 146.5, 143.8, 128.4, 127.8, 127.6, 127.2, 127.1, 127.0, 81.4, 65.3, 47.5, 29.2, 22.9; FAB accurate mass calcd. for $C_{18}H_{21}N_2O_2$ (M^+ + 1): 297.1603. Found: 297.1498.

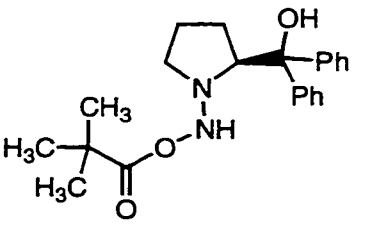
6(*R*)-1,2-Aza-4-oxa-5,5-diphenylbicyclo[4.3.0]nonan-3-one (332)



A solution of compound **330** (180 mg, 0.61 mmol) in 1:1 mixture of 5N KOH/MeOH (1mL) was treated with potassium hypochlorite (1 mL of 0.875 M solution) at 0 °C. The reaction mixture was stirred at 21 °C for 12 h. Saturated aqueous solution of sodium bisulfate (1 mL) was added to destroyed excess of KOCl and the mixture was acidified (pH 2) with minimum amount of 12 N HCl at 0 °C. The reaction mixture was stirred at 21 °C for 20 minutes and then aqueous potassium hydroxide solution (50%) was added slowly to make the reaction mixture alkaline (pH 9) and saturated potassium carbonate (300 mg). Precipitated salts were filtered off and washed with ethanol. The filtrate was extracted with 1:1 $CHCl_3$/EtOH mixture (3 x 10 mL). The organic extracts were dried over anhydrous $MgSO_4$ and concentrated. Purification by column chromatography (2:3, ether/pet ether) afforded 125 mg (70%) of the title compound as white solid; IR (neat) 2965, 2871, 1751, 1494, 1477, 1447, 1355, 1052,

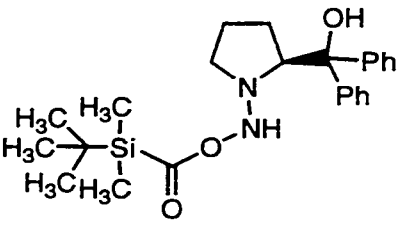
1199, 1052, 992, 961, 763, 694' cm^{-1}.^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.52-7.41 (m, 2H), 7.39-7.19 (m, 8H), 4.60-4.48 (m, 1H), 3.0-4.62 (m, 1H), 3.32-3.15 (m, 1H), 2.18-1.51 (m, 3H), 1.2-1.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.3, 1443.2, 140.1, 128.4, 128.2, 127.6, 125.8, 125.3, 125.3, 85.7, 69.1, 45.9, 28.9, 24.8.

_N_-(_t_-Butoxycarbonylaminyl)-2-hydroxydiphenylmethylpyrrolidine(338)



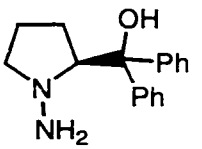
A solution Of _N_-butoxycarbonyl-3-trichloromethyloxazirine **334** (2.27g, 9.5 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise, to a cold solution (-78 °C) of α,α-diphenyl-L-prolinol (2 g mg, 7.92 mmol) in CH_2Cl_2 (40 mL). The reaction was stirred at this temp. for 30 min. and slowly allowed to warm up to 21 °C. After the completion of the reaction, solvent was evaporated. Purification with column chromatography (2% MeOH/CH_2Cl_2) afforded 2.4 g (83%) of the title compound as white solid; mp: 238-240 °C; IR (neat) 3347, 3309, 2952, 2856, 2455, 1414, 1347, 12998, 1084 cm^{-1}.^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62-7.60 (m, 2H), 7.51-7.49 (m, 2H), 7.26-7.21 (m, 4H), 7.11-7.08 (m, 2H), 5.24 (s, 1H), 4.66 (br s, 1H), 4.35 (s, 1H), 3.30-3.27 (m, 1H), 3.08-3.03 (m, 1H), 1.81-1.62 (m, 4H), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.4, 147.2, 146.1, 128.0, 127.9, 126.1, 126.0, 125.4, 125.2, 79.9, 76.8, 68.7, 56.4, 28.1, 27.1, 21.5; FAB accurate mass calcd. for $C_{22}H_{29}N_2O_3$ (M^+ + 1): 369.2179. Found: 369.1972. Ana. Calcd for $C_{22}H_{28}N_2O_3$: C, 71.71; H, 7.67; N, 7.65. Found: C, 71.91; H, 7.61; N, 7.66.

N-(t-Butyldimethylsilyloxycarbonylaminyl)-2-hydroxydiphenylmethylpyrrolidine (339)



t-Butydimethylsilyl trifluoromethanesulfonate (1.63 mL, 7.14 mmol) was added to a stirred solution of the compound **338** (2.19 g, 5.95 mmol) and 2,6-lutidine (1.1 mL, 9.54 mmol) in dry CH_2Cl_2 (15 mL). The reaction mixture was stirred at 21 °C for 12 h, quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ether several times. The combined organic extracts were washed with water and then with brine (3 x 10 mL), dried and concentrated. The crude product was recrystalized from pet ether to afford 1.8 g (74%) of the title compound as white solid; mp: 206-208 °C; IR (KBr) 3329, 3267, 2928, 2856, 1678, 1527, 1451, 1271, 1189, 1067, 838, 791, 740, 665 cm^{-1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, J = 7.5 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H), 7.23-7.19 (m, 4H), 7.11-7.05 (m, 2H), 5.24 (s, 1H), 4.40-4.30 (m, 2H), 3.28-3.25 (m, 1H), 3.13-3.08 (m, 1H), 1.88-1.81 (m, 1H), 1.74-1.63 (m, 3H), 0.77 (s, 9H), 0.18 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 147.4, 145.9, 128.0, 127.9, 126.2, 126.1, 125.3, 125.2, 68.5, 55.8, 27.1, 25.6, 25.3, 21.8, 17.3, -4.7; HRMS calcd. for $C_{20}H_{26}N_2O_3Si$ (M^+ - *t*-Bu): 369.1634. Found: 369.1639.

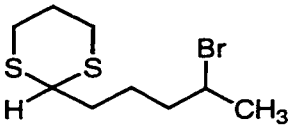
N-Amino-α,α-diphenyl-2-pyrrolidine methanol (327)



Following the general procedure for TBAF deprotection, tetrabutylammonium fluoride (3.6 mL of 1M solution, 3.6 mmol) was added to the solution of compound **339**

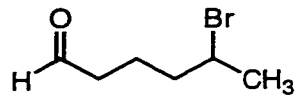
(1.4 g, 3.2 mmol) in dry THF (20 mL). Recrystalization from ether afforded 770 mg (75%) of the title compound as white solid; mp: 110-112 °C; IR (KBr) 3335, 2955, 2807, 1492, 1306m 1171, 944, 859, 773, 641 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.72-7.49 (m, 4H), 7.47-7.09 (m, 6H), 4.71 (br s, 1H), 3.71-3.53 (m, 1H), 3.33-3.20 (m, 1H), 2.67-2.51 (m, 2H, br s 2H), 2.14-1.93 (m, 1H), 1.63-1.51 (m, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.2, 140.2, 128.2, 127.9, 126.6, 126.4, 125.7, 125.5, 77.9, 76.0, 59.9, 27.7, 21.8; HRMS calcd. for $C_{17}H_{20}N_2O$ (M^+): 268.1576. Found: 268.1598.

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



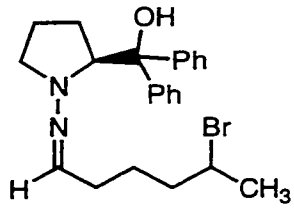
n-Butyllithium (21.1 mL of a 2.5 m solution, 53.0 mmol) was added to a cold solution (-10 °C) of dithiane **343** (5.28 g, 43.9 mmol) in dry THF (50 mL). The reaction mixture was stirred at this temperature for 45 minutes, followed by the addition of 1,3-dibromopentane (6.0 mL, 44.0 mmol) and the stirring was continued at –10 C for 2 h. The reaction was quenched with brine (10 mL) and poured into a separatory funnel containing ethyl acetate (3x150 mL), dried, concentrated and purified by flash chromatography (2:98, ether/pet ether) to yield 8.55 g (72%) of the title compound as a light yellow oil: IR (neat) 2914, 1435, 1378, 1275 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) d 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 calcd. for $C_9H_{17}S_2Br$ (M^+): 367.9950. Found: 367.9939.

5-Bromohexanal (344)



Ceric ammonium nitrate (6.24 g, 11.4 mmol) was added to a solution of 2-(4-bromopentyl)-1,3-dithiane **343** (751 mg, 2.8 mmol) in 3:1 mixture of CH_3CN/H_2O (8 mL). The reaction mixture was stirred at 21 °C for 30 minutes and poured into a separatory funnel containing water (5 mL) and ethyl acetate (10 mL). The aqueous layer was extracted with ethyl acetate (3 x 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 (1:1, ethyl acetate/pet ether) under aspirator vacuum and then concentrated and used for the next reaction without further purification.

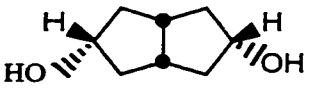
5-Bromohexanal-(*S*)-(-)-Amino-2-(diphenylhydroxy methyl)pyrrolidine-hydrazone (328)



Aldehyde **344** (476 mg, 2.66 mmol) was added to a solution of hydrazine **327** (650 mg, 2,42 mmol) inn dry methanol at 0 °C. The reaction mixture was stirred at this temperature for 2 h and then concentrated to give the crude compound. Purification by column chromatography afforded 375 mg (34%) of the title compound as faint yellow oil; IR (neat) 3352, 3057, 2942, 1598, 1492, 1448, 1169, 1033, 747, 701 cm^{-1}.^1H NMR ($CDCl_3$, 200 MHz) δ 7.48-7.44 (m, 2H), 7.39-7.31 (m, 2H), 7.28-7.19 (m, 4H), 7.11-7.05 (m, 2H), 6.58 (t, J = 5.0 Hz, 1H), 5.61 (s, 1H), 4.35-3.28 (m, 1H), 4.18-4.03 (m, 1H), 3.24-3.18 (m, 1H), 2.79-2.66 (m, 1H), 2.16-2.06 (m, 2H), 1.88-1.42 (m, 11H); ^{13}C NMR

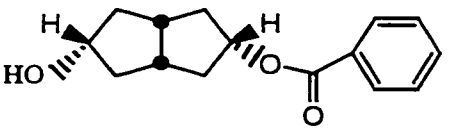
($CDCl_3$, 50 MHz) δ 146.8, 145.1, 138.9, 127.6, 127.4, 127.3, 127.2, 126.8, 126.3, 80.4, 68.8, 51.4, 50.4, 40.3, 32.0, 31.9, 26.8, 26.4, 25.0, 22.1; FAB accurate mass calcd. for $C_{23}H_{30}N_2OBr(M^+ + 1)$: 429.1542. Found: 429.1102.

Bicyclo[3.3.0]octane-3,7-diol (353)



Sodium borohydride (122 mg, 3.22 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-dione **352** (200 mg, 1.61 mmol) in methanol (2 mL) at 0 °C. The reaction mixture was stirred for 1 h preceding the addition of acetone (1 mL). Removal of solvent *in vacuo* afforded pale yellow oil. Flash chromatography (neutral alumina, 19:1 chloroform/methanol) afforded **2** (103 mg, 50%) as a white solid. mp: 82-84 °C (sublimed); IR (neat) 3347, 3309, 2952, 2856, 2455, 1414, 1347, 12998, 1084, 1039, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.62-4.58 (m, 1H), 4.19-4.16 (m, 1H), 2.46-2.45 (m, 1H), 2.05-2.00 (m, 2H), 1.66-1.27 (m, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 75.9, 44.2, 40.9; HRMS calcd for $C_8H_{14}O_2$ (M^+): 142.09942. Found: 142.09761.

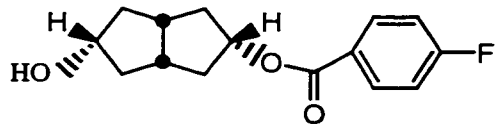
7-Benzoyloxybicyclo[3.3.0]octane-3-ol (354a)



n-butyllithium (0.347 ml of 2.03 M soln. in hexanes, 0.704 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-diol **353** (100 mg, 0.704 mmol) in dry tetrahydrofuran (5.5 mL) at -78 °C and the reaction mixture was stirred for 30 min. The reaction mixture was added to a solution of benzoyl chloride (0.176 mL, 1.408 mmol) in

dry tetrahydrofuran (7 mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (8 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded title compound (135 mg, 78%) as a white solid. mp 59-60° C; IR (neat) 3251, 3162, 2956, 2861, 2354, 1717, 1268, 1100, 1068, 710 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.02-7.98 (m, 2H), 7.53-7.33 (m, 3H), 5.37-5.29 (m, 1H), 4.22-4.11 (m, 1H), 3.10 (br s, 1H), 2.51-2.39 (m, 2H), 2.19-2.06 (m, 4H), 1.87-1.76 (m, 2H), 1.63-1.50 (m, 2H); ^{13}C NMR, CDCl3,50 MHz) δ 166.2, 132.7, 130.4, 129.4, 128.2, 78.6, 79.8, 38.9, 42.3, 38.7;HRMS calcd. for $C_{15}H_{18}O_3$ (M^+) : 246.1256. Found: 246.1280.

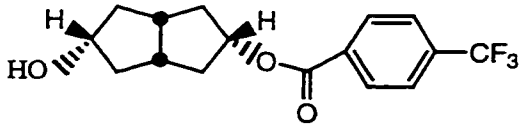
7-(*p*-Flourobenzoyloxy)bicyclo[3.3.0]octane-3-ol (354b)



n-butyllithium (0.475 ml of 2.03 M soln. in hexanes, 0.976 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-diol **353** (137 mg, 0.964 mmol) in dry tetrahydrofuran (7.5 mL) at -78 °C and the reaction mixture was stirred for 30 min. The reaction mixture was added to a solution of *p*-fluoro benzoyl chloride (0.228 mL, 0.1.93 mmol) in dry tetrahydrofuran (9.8 mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (5 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded title compound (200 mg, 79%) as white solid; mp. 56-58° C. IR (neat) 3409, 2952, 2868, 1715, 1604, 1507, 1279, 1236, 1153, 1015, 855, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.02-7.98 (m, 2H), 7.07-7.00 (m, 2H), 5.32 (q, J = 5.6 Hz, 1H), 4.23-4.17 (m, 1H), 2.51-2.42 (m, 2H), 2.26-2.09 (m, 4H, 1 OH), 1.84-1.79 (m, 2H),

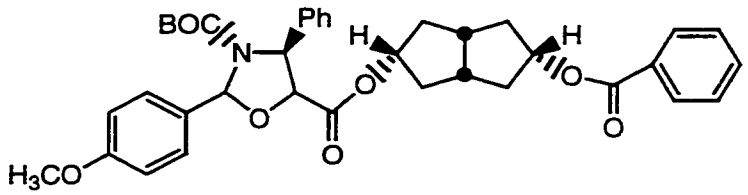
1.60-1.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.6 (d, CF coupling, J = 253 MHz), 165.3, 132.0 (d, J = 9.35 MHz), 126.7 (d, J = 2.79 MHz), 115.4, (d, J = 21.96 Hz), 78.8, 74.9, 42.5, 39.0, 38.9; HRMS calcd for $C_{15}H_{17}O_3F$ (M^+): 263.1093. Found: 263.1083.

7-[4-(Trifluoromethyl)benzoyloxy]bicyclo[3.3.0]octane-3-ol (354c)



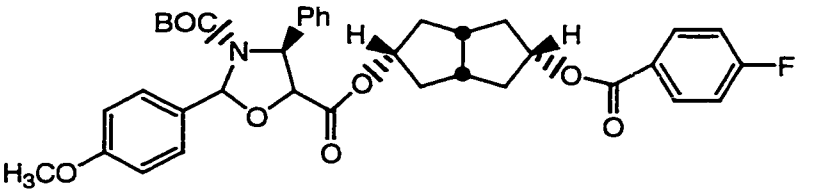
n-butyllithium (0.374 ml of 2.03 M soln. in hexanes, 0.704 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-diol **353** (100 mg, 0.704 mmol) in dry tetrahydrofuran (5.5 mL) at -78 °C and the reaction mixture was stirred for 30 min. The reaction mixture was added to a solution of *p*-(trifluoromethyl)benzoyl chloride (0.209 mL, 1.41 mmol) in dry tetrahydrofuran (7 mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (4 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded title compound (160 mg, 72%) as a clear colourless oil; IR (neat) 3542, 2934, 2861, 1704, 1585, 1326, 1099, 1074, 864, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13-8.11 (m, 2H), 7.67-7.23 (m, 2H), 5.39-5.26 (m, 1H), 4.25-4.20 (m, 1H), 2.52-2.47 (m, 2H), 2.22-2.12 (m, 4H,), 1.87-1.82 (m, 2H), 1.78-1.74 (br s, IH), 1.60-1.54(m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) 165.0, 132.0 (q, J = 42.3 Hz), 133.7, 19.8, 125.3, 123.5 (q, J = 272.7 Hz), 79.2, 75.0, 42.5, 39.0, 38.9; HRMS calcd for $C_{16}H_{17}O_3F_3$ (M^+): 314.1130. Found: 314.1197.

3-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-7-benzoyloxybicyclo[3.3.0]octane(356a)



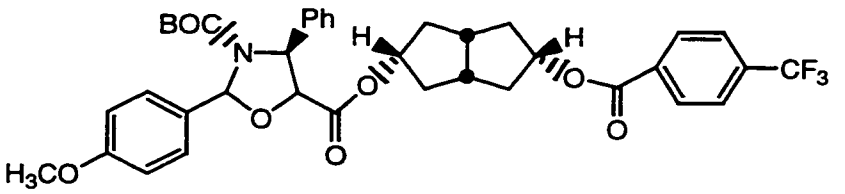
1,3-Dicyclohexylcarbodiimide (210 mg, 1.05 mmol) was added to a solution of compound **354a** (127 mg, 0.516 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (306 mg, 0.765 mmol) in dry toluene (25 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (12 mg, 0.099 mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (25 mL). The aqueous phase was extracted with ether (3 x 30 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 291 mg (90%) of the tile compound as a white foam; IR (neat) 2965, 2927, 1711, 1613, 1515, 1391, 1173, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96-9.94 (m, 2H), 7.50-7.22 (m, 10H), 681-6.78 (m, 2H), 6.45-6.25 (br s, 1H), 5.45-5.35 (br s, 1H), 5.28-5.26 (m, 1H), 5.05-5.01 (m, 1H), 4.49 (m, 1H), 3.73 (s, 3H), 2.47-2.42 (m, 2H), 2.20-2.08 (m, 3H). 2.06-1.90 (m, 1H), 1.67-1.57 (m, 3H), 1.39-1.30 (m, 1H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 169.3, 166.0, 160.0, 152.0, 132.7,132.7, 130.5, 129.5, 128.6, 128.4, 128.3, 127.8, 126.2, 113.5, 91.9, 83.3, 80.5, 78.2, 77.9, 63.1, 55.2, 38.7, 38.6, 38.5,38.4, 27.8; HRMS calcd for $C_{37}H_{41}O_8$ (M^+): 627.2833. Found: 627.2738.

3-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-7-(4-flourobenzoyloxy)bicyclo[3.3.0]octane (356b)



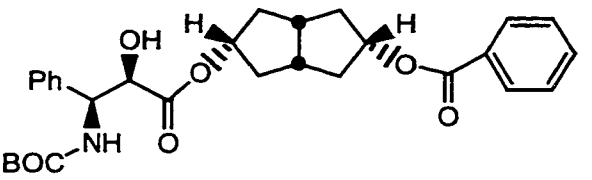
1,3-Dicyclohexylcarbodiimide (223 mg, 1.08 mmol) was added to a solution of compound **354b** (145 mg, 0.549 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (325 mg, 0.813 mmol) in dry toluene (25 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (13 mg, 0.107 mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (25 mL). The aqueous phase was extracted with ether (3 x 35 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 312 mg (88%) of the title compound as a white foam; IR (neat) 2973, 1712, 1605, 1506, 1392, 1281, 1092, 1032, 769, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95-7.92 (m, 2H), 7.35-7.23(m, 7H), 7.03-6.99 (m, 2H), 6.81-6.78 (m, 2H), 6.49-6.15 (br s, 1H), 5.45-5.30 (br s, 1H), 5.27-5.265 (m, 1H), 5.09-5.01 (m, 1H), 4.48-4.47 (m, 1H), 3.74 (s, 3H), 2.48-2.43 (m, 2H), 2.19-2.10 (m, 4H), 1.66-1.58 (m, 3H), 1.34-1.20 (m, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 169.3, 165.6 (d, J = 254 Hz), 165.0, 160.0, 151.6, 131.9, (d, J = 9.3 Hz), 128.6, 128.6, 128.4, 127.8, 126.7, 126.7, 126.2, 115.4, (d, J = 22.0 Hz), 113.5, 91.9, 80.5, 78.2, 78.1, 63.1, 55.1, 38.7, 38.6, 38.5, 38.4, 27.7; HRMS calcd for $C_{37}H_{41}NO_8F(M^+ + 1)$: 646.2817. Found: 646.3819.

3-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-7-[4-(triflouromethyl)benzoyloxy]bicyclo[3.3.0]octane (356c)



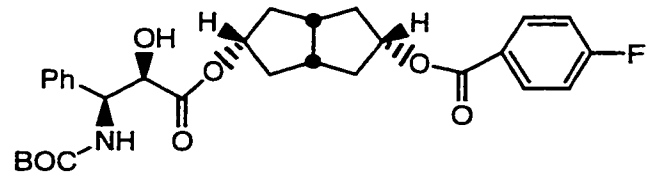
1,3-Dicyclohexylcarbodiimide (162 mg, 0.782 mmol) was added to a solution of compound **354c** (124 mg, 0.398 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (236 mg, 0.59 mmol) in dry toluene (18 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (9 mg, 0.0775 mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 247 mg (90%) of the title compound as a white foam; IR (neat) 2974, 2929, 1712, 1613, 1515, 1325, 1171, 1131, 918, 863, 776, 731 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, J = 8.2 Hz 1H), 7.63-7.61 (d, J = 8.1 Hz, 2H), 7.36-7.22 (m, 7H), 6.88-6.76 (d, J = 12.3 Hz, 2H), 6.49-6.25 (m, 1H), 5.45-5.32 (m, 1H), 5.30-5.25 (m, 1H), 5.15-5.00 (m, 1H), 4.48-4.47 (m, 1H), 3.74 (s, 3H), 2.50-2.47 (m, 2H), 2.18-2.10 (m, 4H), 1.75-1.60 (m, 3H), 1.34-1.20 (m, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 169.3, 164.8, 160.0, 151.0, 134.2 (q, J = 32.3), 133.6, 129.8, 128.6,128.4, 127.8, 127.6, 1262., 125.4, 125.3, 123.0 (q, J = 350 Hz), 113.5, 92.0, 80.5, 79.4, 78.5, 63.1, 56.7, 38.7, 38.6, 38.5, 38.4, 27.8 ; HRMS calcd for $C_{38}H_{41}N_1O_8F_3(M^+ + 1)$: 696.2784. Found: 696.3204.

3-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-7-benzoyloxybicyclo[3.3.0]octane (350a)



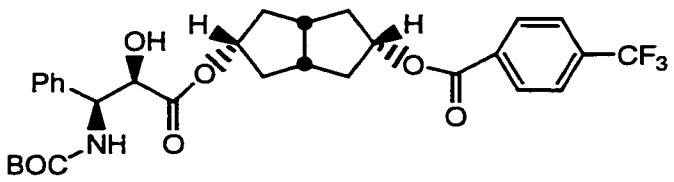
p-Toluenesulfonic acid monohydrate (30 mg, 0.156 mmol) was added to a solution of the oxazolidine **356a** (100 mg, 0.158 mmol) in methanol (6.5 mL). The reaction was stirred for 90 min and then concentrated *in vacuo*. The resulting residue was diluted with ether (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 73 mg (90%) of the title compound as a white solid; mp. 48-50 °C; IR (neat) 3451, 3386, 2969, 2349, 1715, 1495, 1366, 1277, 1168, 1096, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, J = 7.44 Hz 2H), 7.52-7.49 (m, 1H), 7.41-7.38 (m, 2H), 7.31-7.22 (m, 5H), 5.40-5.33 (m, 2H), 5.22-5.20 (m, 2H), 4.99-4.98 (m, 1H), 3.17-3.16 (m, 1H), 2.59-2.51 (m, 2H), 2.26-2.20 (m, 4H), 1.88-1.72 (m, 4H), 1.17 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 172.4, 166.2, 154.8, 139.3, 132.8, 130.4, 129.6, 128.5, 128.3, 127.6, 126.6, 79.6, 79.1, 78.1, 73.7, 55.9, 38.9, 38.8, 38.6, 28.2 ; FAB accurate mass calcd for $C_{29}H_{36}NO_7$ (M^+ + 1): 510.2482. Found: 510.2844. Anal. calcd. for $C_{29}H_{35}NO_7$: C, 68.34; H, 6.94; N, 2.75. Found: C, 68.31; H, 7.10; N, 2.78.

3-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-7-(4-fluorobenzoyloxy)bicyclo[3.3.0]octane (350b)



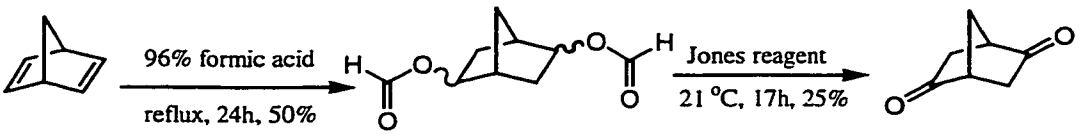
p-Toluenesulfonic acid monohydrate (47 mg, 0.25 mmol) was added to a solution of the oxazolidine **356b** (162 mg, 0.25 mmol) in methanol (10 mL). The reaction was stirred for 90 min and then concentrated *in vacuo*. The resulting residue was diluted with ether (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 116 mg (88%) of title compound as a white solid; mp 52-54 °C; IR (neat) 3444, 2972, 1719, 1604, 1505, 1366, 1274, 1158, 1094, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.07-8.05 (m, 2H), 7.33-7.23 (m, 5H), 7.07-7.03 (m, 2H), 5.41 (d, J = 9.7 Hz, 1H), 5.33 (q, J = 5.8 Hz, 1H), 5.22-5.20 (m, 2H), 4.42-4.35 (m, 1H), 3.29-3.17 (m, 1H), 2.561-2.51 (m, 2H), 2.26-2.17 (m, 4H), 1.81-1.70 (m, 4H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 172.4, 165.6 (d, J = 253.9 Hz), 165.3, 154.4, 139.3, 132.8 (d, J = 9.26 Hz), 128.5, 127.6, 126.7, 126.6, 115.5 (d, J = 21.9 Hz), 79.6, 79.0, 78.2, 73.7, 55.8, 38.9, 38.7, 38.5, 28.2 ; FAB accurate mass calcd for $C_{29}H_{35}NO_7F$ (M^+ + 1): 528.2398. Found: 528.1889. Anal. calcd. for $C_{29}H_{34}NO_7F$: C, 68.34; H, 6.94; N, 2.75. Found: C, 66.01; H, 6.51; N, 2.66. Found: C, 65.86; H, 6.52; N, 2.61.

3-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-7-[4-(trifluoromethyl)benzoyloxy]bicyclo[3.3.0]octane (350c)



p-Toluenesulfonic acid monohydrate (45 mg, 0.23 mmol) was added to a solution of the oxazolidine **356a** (165 mg, 0.24 mmol) in methanol (10 mL). The reaction was stirred for 90 min and then concentrated *in vacuo*. The resulting residue was diluted with ether (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 126 mg (92%) of the title compound as a white solid; mp 54-56 °C; IR (neat) 3451, 3380, 2971, 1363, 1716, 1496, 1325, 1279, 11667, 1120, 109, 864, 777, 702, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.17 (d, J = 7.88 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.31-7.21 (m, 5H), 5.41-5.36 (m, 2H), 5.26-5.21 (m, 2H), 4.40 (s, 1H), 3.22 (s, 1H), 2.61-2.53 (m, 2H), 2.29-2.21 (m, 4H), 1.91-1.72 (m, 4H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) 172.4, 165.0, 154.8, 139.3, 134.2 (d, J = 32.3 Hz), 133.6, 130.1, 128.5, 127.7, 126.6, 125.4 (q, J = 3.6 Hz), 123.6 (q, J = 272.4 Hz), 79.6, 79.0, 78.7, 73.6, 55.8, 38.9, 38.7, 38.6, 28.1 ; FAB accurate mass calcd for $C_{30}H_{35}NO_7F_3$ (M^+ + 1): 578.2366. Found: 578.3180. Anal. calcd. for $C_{30}H_{34}NO_7F$: C, 68.34; H, 6.94; N, 2.75. Found: C, 60.29; H, 5.95; N, 2.44. Found: C, 60.40; H, 5.70; N, 2.42.

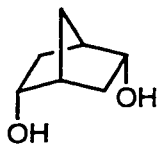
Bicyclo[2.2.1]octane-2,5-dione (359).



357 **358** **359**

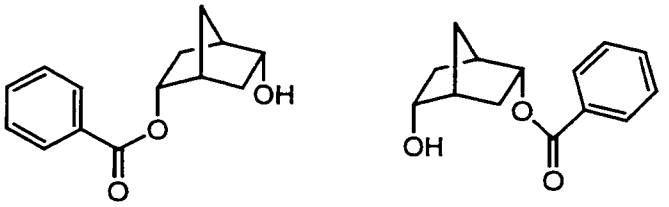
A solution of 96% formic acid (80 g, 170 mol) and bicyclo[2.2.1]octane-2,5-diene (20 g,0.22 mol) **343** was heated at reflux for 24 h (see note below). The reaction mixture was cooled to 21 °C and excess formic acid was removed by distillation (26-30 °C, 15 torr). Fractional distillation through a 5 cm vigreaux column afforded two fractions **A** (bp: 70-90 °C, 15 torr, 11.4 g) and **B** (bp: 110-140 °C, 15 torr, (lit: 124 °C, 10 torr), 20.4 g, 50%). Jones reagent (120 mL) was added dropwise to a solution of the crude mixture of bicyclo[2.2.1]octane-2,5-diformate esters **B** (20.4 g, 0.11 mol) in acetone (100 mL) keeping the temperature between 20-30 °C by using an ice water bath. The reaction mixture was stirred at 21 °C for 17 h at which time the solution was orange brown. The mixture was decanted into a 1L erlenmeyer flask and the chromium salts were rinsed with acetone (5 x 50 mL). Excess oxidant was reduced with sodium hydrosulfite (the solution turned light green) and the mixture was neutralized by the addition of solid sodium bicarbonate. The solvent was removed *in vacuo* and the resulting residue was partitioned between ethyl acetate (100 mL) and brine (100 mL) and the layers were separated. The organic phase was extracted with ethyl acetate (3 x 100 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 4:1 then 1:1 hexanes/ethyl acetate) afforded the title compound (3.2 g, 24%) as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.00-2.90 (m, 2H), 2.45-2.05 (m, 6H).

endo,endo-Bicyclo[2.2.1]octane-2,5-diol (360)



A 1.0 M solution of L-selectride in tetrahydrofuran (3.54 mL, 3.54 mmol) was added dropwise to a solution of bicyclo[2.2.1]octane-2,5-dione **359** (200 mg, 1.61 mmol) in dry tetrahydrofuran (5 mL) at -78 °C. The reaction mixture was stirred for 3 h followed by the addition of pH 7.0 phosphate buffer (1 mL) and 30 % hydrogen peroxide (1 mL). The mixture was allowed to stir for 1 h while warming to 21 °C. The mixture was filtered through celite, transferred to a separatory funnel and extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (neutral alumina, 19:1 chloroform/methanol) afforded 103 mg (50%) of the title compound as a white solid. mp: 210 °C (sublimed); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.28 (dt, J = 8.5, 3.8 Hz, 2H), 2.30-2.05 (m, 4H), 1.90-1.20 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 72.44, 43.04, 36.82, 30.35. HRMS calcd. For $C_7H_{12}O_2$ (M^+): 128.0838. Found: 128.0837.

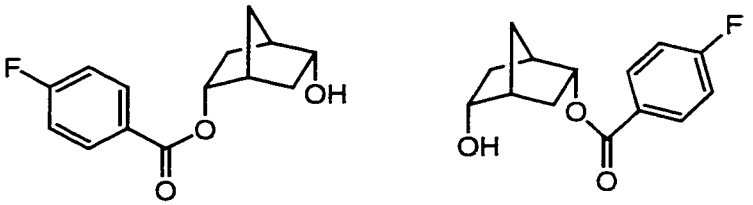
5-Benzoyloxybicyclo[2.2.1]octan-2-ol (361a).



A 0.5 M solution of *n*-butyllithium in hexane (0.78 mL, 0.39 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-diol **360** (50 mg, 0.39 mmol) in dry tetrahydrofuran (3 mL) at -78 °C and the reaction mixture was stirred for 30 min. The

reaction mixture was added to a solution of benzoyl chloride (0.098 mL, 0.78 mmol) in dry tetrahydrofuran (4 mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (4 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 68 mg (75%) of the title compound as a clear colourless oil; IR (neat) 3396, 2958, 2877, 1714, 1601, 1451, 1179, 1119, 996, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.05-8.02 (m, 2H), 7.54-7.50 (m, 1H), 7.42-7.23 (m, 2H), 5.26-5.22 (m, 1H), 4.35-4.31 (m, 1H), 2.55-2.53 (m, 1H), 2.30-2.28 (m 1H), 1.99-1.83 (m, 3H), 1.75-1.65 (br s, 1H), 1.62-1.58 (m, 1H), 1.55-1.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.5, 132.7, 130.5, 129.5, 128.2, 75.8, 72.3, 42.6, 41.0, 36.1, 30.9, 27.1. HRMS calcd. For $C_{14}H_{16}O_3$ (M^+): 232.1099. Found: 232.1097.

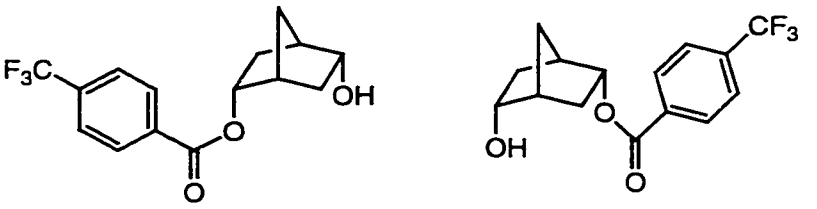
5-(*p*-Fluoro)benzoyloxybicyclo[2.2.1]octan-2-ol (361b).



n-Butyllithium (0.287 mL of 2.04 M solution, 0.59 mmol) was added to a solution of bicyclo[2.2.1]octane-2,5-diol **360** (75 mg, 0.58 mmol) in dry tetrahydrofuran (4.5 mL) at -78 °C and the reaction mixture was stirred for 30 min. The reaction mixture was added to a solution of *p*-fluoro benzoyl chloride (0.138 mL, 1.17 mmol) in dry tetrahydrofuran (6 mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (6 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 114 mg (80%) of the title compound as a clear colourless oil; IR (neat)

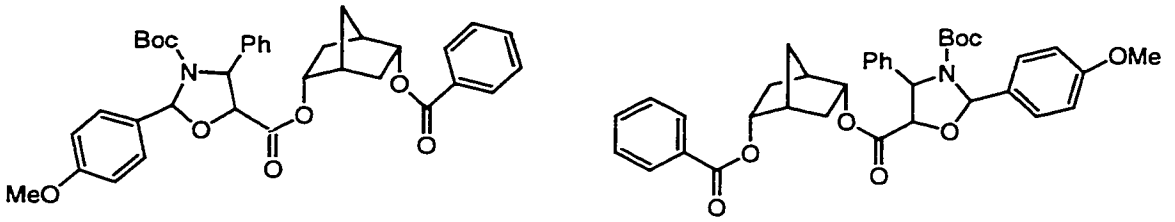
3419, 2959, 1725, 1604, 1507, 1412, 1238, 1154, 1120, 1091, 1040, 855, 769 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.07-8.02 (m, 2H), 7.10-6.98 (m, 2H), 5.25-5.14 (m, 1H), 4.35-4.26 (m, 1H), 2.51-2.50 (br s, 1H), 2.48-2.25 (m, 2H), 1.94-1.75 (m, 3H), 1.60-1.48 (m, 3H); ^{13}C NMR (CDCl3, 50 MHz) δ 168.3, 164.3, 132.0, 126.6, 115.3, 76.1, 72.2, 42.5, 40.9, 35.9, 30.6, 27.0. HRMS calcd. for $C_{14}H_{15}O_3F$ (M+): 250.1005. Found: 250.1038.

5-(*p*-Trifluoromethyl)benzoyloxybicyclo[2.2.1]octan-2-ol (361c).



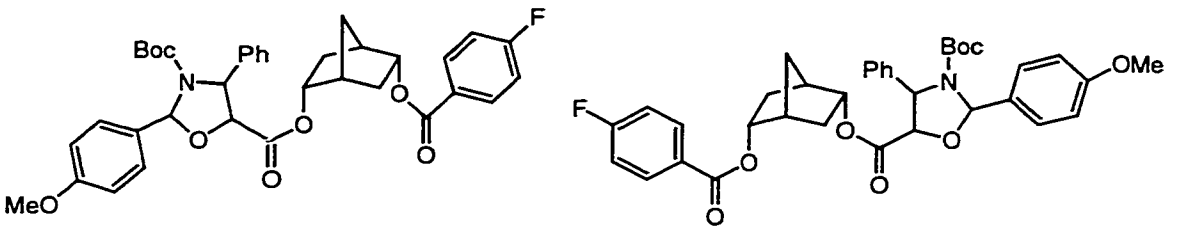
n-Butyllithium (0.39 mL of 2.0 M solution, 0.78 mmol) was added to a solution of compound **360** (100 mg, 0.78 mmol) in dry tetrahydrofuran (6 mL) at -78 °C and the reaction mixture was stirred for 30 min. The reaction mixture was added to a solution of *p*-(trifluoromethyl)benzoyl chloride (0.232 mL, 1.56 mmol) in dry tetrahydrofuran (mL) at 0 °C and stirred for 3 h. A saturated aqueous solution of sodium bicarbonate (10 mL) was added. The reaction mixture was stirred for 1 h and then extracted with ether (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 164 mg (70%) of the title compound as a clear colourless oil; IR (neat) 3351, 2966, 2880, 1721, 1412, 1326, 1284, 1168, 1129, 1065, 1039, 863, 776, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.14-8.12 (m, 2H), 7.66-7.23 (m, 2H), 5.26-5.22 (m, 1H), 4.35-4.32 (m, 1H), 2.54-2.53 (m, 1H), 2.28-2.24 (m, 1H), 1.99-1.91 (m, 2H), 1.89-1.83 (m, 1H), 1.78-1.76 (br s, 1H), 1.59-1.49 (m, 3H); ^{13}C NMR (CDCl3, 125 MHz) δ 166.3, 134.3 (q, CF_3), 133.7, 129.8, 125.2, 123.5 (q, C-CF_3), 76.6, 72.1, 42.6, 41.0, 36.0, 30.7, 27.0. HRMS calcd. For $C_{15}H_{15}O_3F_3$ (M^+): 300.0973. Found: 300.1010.

2-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-5-benzoyloxybicyclo[2.2.1]octane (362a)



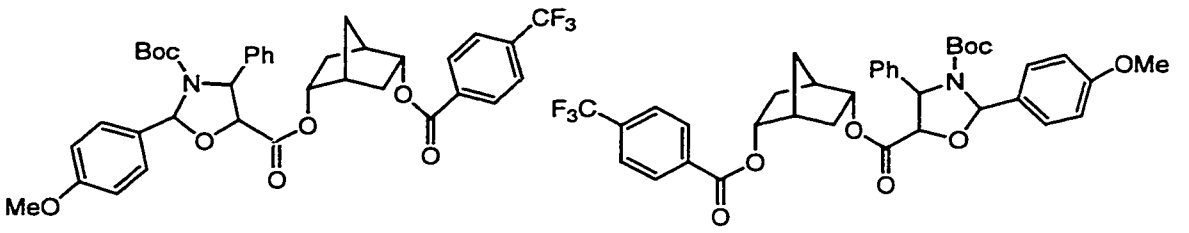
1,3-Dicyclohexylcarbodiimide (118 mg, 0.57 mmol) was added to a solution of 5-benzoyloxybicyclo[2.2.1]octan-2-ol **361a** (68 mg, 0.29 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (172 mg, 0.43 mmol) in dry toluene (15 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (7 mg, 0.058 mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (15 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 176 mg (99%) of the title compound as a white foam; IR (neat) 2974, 1713, 1613, 1515, 1452, 1392, 1281, 1171, 1115, 1028, 831 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.96-7.94 (m, 2H), 7.58-7.51 (m, 1H), 7.49-7.25 (m, 10H), 6.84-6.81 (m, 2H), 6.45-6.25 (br s, 1H), 5.41-5.19 (m, 2H), 5.09-4.95 (m, 1H), 4.54-4.52 (m, 1H), 3.77 (s, 3H), 2.56-2.52 (m, 1H), 2.45-1.23 (m, 6H), 1,01 (s, 9H); ^{13}C NMR (CDCl3, 125 MHz) δ [169.8, 169.4], 166.4, [160.1, 160.0], 132.0, [132.8, 132.7], 130.3, 130.3, [129.5, 129.4], 128.4, 128.4, 128.3, [127.9, 127.8], 126.6, 113.5, 92.0, 80.5, [76.1, 76.0], [75.0, 74.8], [63.6, 63.3], 55.2, [40.4, 40.3], 40.2, [35.9, 35.6], 28.3, 28.1, 28.0, 27.9, 27.7. FAB acc. mass calcd. For $C_{36}H_{40}N_3O_8$ (M^++ 1): 614.2754. Found: 614.2921.

2-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-5-(*p*-fluoro)benzoyloxybicyclo[2.2.1]octane (362b)



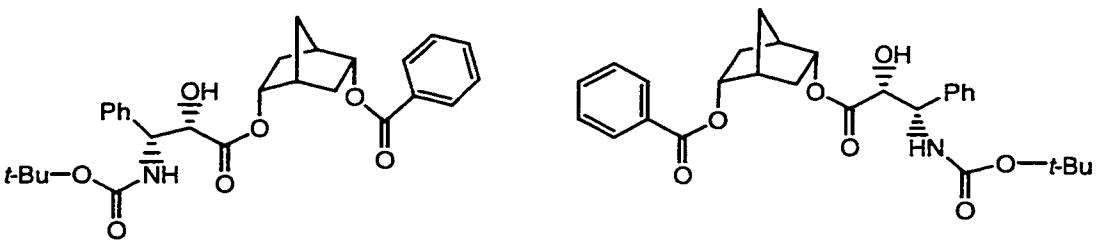
1,3-Dicyclohexylcarbodiimide (130 mg, 0.62 mmol) was added to a solution of compound **361b** (80 mg, 0.32 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (180 mg, 0.47 mmol) in dry toluene (15 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (8 mg, 0.063 mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (15 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 165 mg, (82%) of the title compound as a white foam; IR: (neat) 2974, 1712, 1605, 1393, 1275, 1243, 1162, 1112, 1032, 915, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.95-7.92 (m, 2H), 7.34-7.30 (m, 8H), 7.00-6.97 (m, 2H), 6.83-6.81 (m, 2H), 6.45-6.25 (br s, 1H), 5.45-5.25 (m, 1H), 5.24-5.12 (m, 1H), 5.16-4.98 (m, 1H), 4.53-4.52 (m, 1H), 3.77 (s, 3H), 2.55-2.51 (m, 1H), 1.99-1.51 (m, 6H), 1,01 (s, 9H); ^{13}C NMR (CDCl3, 125 MHz) δ [169.7, 169.4], [165.7, 165.6], [165.4, 165.3], [160.1, 160.0], 151.5, 132.0, [131.9, 131.8], 128.6, [128.5, 128.3], [127.9, 127.8], 127.6, 126.6, [126.3, 126.2], [115.5, 115.3], 113.5, [92.0, 91.6], 80.5, [76.1, 75.9], [75.1, 74.9], [63.6, 63.3], 55.2, 40.0, [40.3, 40.2], [36.0, 35.7], [28.3, 28.2], [28.1, 28.0], 27.8, 27.7. FAB acc. mass calcd. For $C_{36}H_{39}NO_8F$ (M^++1): 632.2660. Found: 632.3136.

2-[(2*R*, 4*S*, 5*R*)-3-*tert*-Butoxycarbonylamino-2-(4-methoxyphenyl)-4-phenyl-oxazolidine-5-carboxy]-5-(*p*-trifluoromethyl)benzoyloxybicyclo[2.2.1]octane (362c)



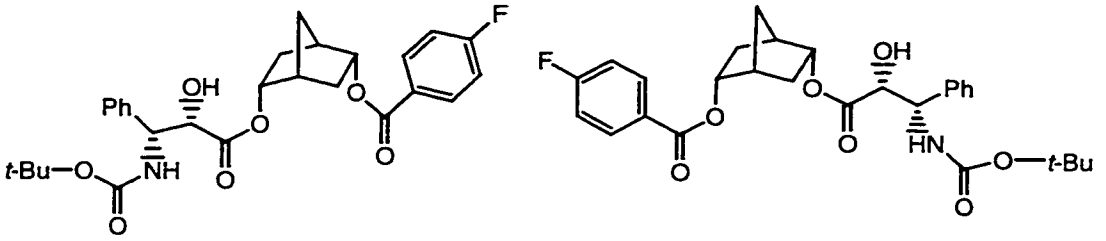
1,3-Dicyclohexylcarbodiimide (199 mg, 0.96 mmol) was added to a solution of compound **361c** (147 mg, 0.49 mmol) and (2*R*, 4*S*, 5*R*)-2-(4-methoxyphenyl)-4-phenyl-3-*tert*-butoxycarbonyl-oxazolidine-5-carboxylic acid **355** (290 mg, 0.73 mmol) in dry toluene (25 mL). The reaction mixture was stirred at 21 °C for 10 min and 4-dimethylaminopyridine (12 mg, 0.087mmol) was added. The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous phase was extracted with ether (3 x 35 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 233 mg (70%) of the title compound as a white foam; IR (neat) 2971, 2358, 1714, 1613, 1444, 1387, 1275, 1171, 1066, 915, 863, 776 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.03-8.00 (m, 2H), 7.59-7.56 (m, 2H), 7.36-7.19 (m, 8H), 6.88-6.80 (m, 2H), 6.31 (br s, 1H), 5.45-5.24 (m, 2H), 5.22-5.20 (m, 1H), 4.54-4.53 (m, 1H), 3.75 (s, 3H), 2.58-2.56 (m, 1H), 1.96-1.53 (m, 6H), 1,01 (s, 9H); ^{13}C NMR (CDCl3, 125 MHz) δ [169.6, 169.4], [165.2, 165.1], [160.2, 160.1], 153.2, 151.5, 134.1(q, CF_3), [133.5, 133.4], [129.8, 129.7], [128.7, 128.6], [128.5, 128.4], 127.8, [126.3, 126.2], [125.4, 125.3], 125.2 (q, C-CF_3), 113.5, [92.1, 92.0], 80.6, [75.9, 75.8], [75.5, 75.4], [63.6, 63.4], 61.7, 55.2, [40.4, 40.3], 40.2, [36.0, 35.8], [28.4, 28.3], [28.2, 28.1], 27.8, 27.7. FAB acc. mass calcd. For $C_{37}H_{39}NO_8F_3$ (M^++1): 682.2628. Found: 682.2643.

2-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-5-benzoyloxybicyclo[2.2.1]octane (351a).



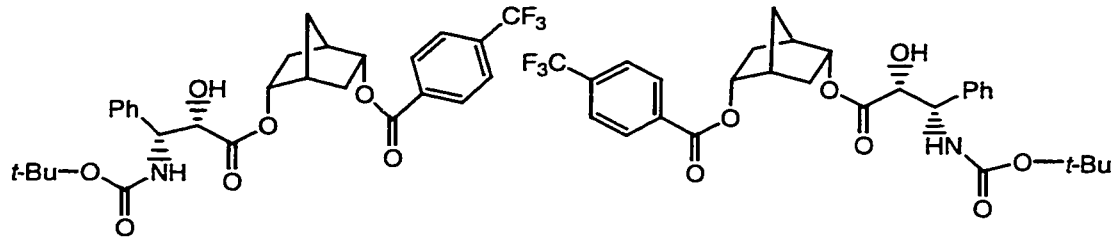
p-Toluenesulfonic acid monohydrate (46 mg, 0.24 mmol) was added to a solution of the oxazolidine **362a** (149 mg, 0.24 mmol) in methanol (10 mL). The reaction was stirred for 90 min and then concentrated *in vacuo*. The resulting residue was diluted with ether (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 103 mg (87%) of the title compound as a white solid; IR (neat) 3411, 2962, 1716, 1497, 1366, 1318, 1168, 1113, 1026, 710 cm^{-1}; (**compound a**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.05 (d, J = 9.2 Hz, 2H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 2H), 7.30-7.22 (m, 5H), 5.38 (d, J = 9.3 Hz, 1H), 5.36-5.30 (m, 1H), 5.27-5.18 (m, 2H), 4.42 (br s, 1H), 3.16 (br s, 1H), 2.67-2.58 (m, 2H), 2.06-1.95 (m, 2H), 1.86-1.56 (m, 2H), 1.49-1.43 (m, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 166.4, 154.9, 139.3, 132.8, 130.4, 129.4, 128.5, 128.3, 127.6, 126.6, 79.9, 76.8, 74.2, 73.6, 56.1, 40.5, 40.3, 36.0, 28.4, 28.4, 28.2. (**Compound b**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.12 (d, J = 6.4 Hz, 2H), 7.55-7.59 (m, 1H), 7.43-7.38 (m, 2H), 7.24-7.20 (m, 5H), 5.38-5.36 (m, 1H), 5.31-5.27 (m, 1H), 5.24-5.22 (m, 1H), 5.22-5.26 (M, 1H), 4.41 (br s, 1H), 2.62 (d, J = 14.2 Hz, 2H), 2.08-1.90 (m, 3H), 1.66-1.57 (m, 3H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 166.3, 154.8, 139.2, 132.8, 130.3, 129.6, 128.5, 128.4, 127.6, 126.7, 79.6, 77.1, 74.8, 73.4, 56.0, 40.5, 40.3, 36.1, 28.6, 28.1, 27.9. Anal. calcd. for $C_{28}H_{33}NO_7$: C, 67.82; H, 6.71; N, 2.83. Found: C, 67.74; H, 6.80; N, 2.78.

2-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-5-(p-trifluoro)benzoyloxybicyclo[2.2.1]octane (351b).



p-Toluenesulfonic acid monohydrate (54 mg, 0.29 mmol) was added to a solution of the oxazolidine **362b** (180 mg, 0.28 mmol) in methanol (10 mL). The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous phase was extracted with ether (3x25 mL) and the combined organic extracts were washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 130 mg (90%) of the title compound as a white solid; IR (neat) 3418, 2977, 2369, 1719, 1603, 1515, 1274, 1165, 1113, 1017 cm^{-1}; (**compound a**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.09–8.05 (m, 2H), 7.36-7.26 (m, 5H), 7.09-7.06 (m, 2H), 5.35-5.33 (m, 1H), 5.27-5.24 (m, 1H), 5.18-5.12 (m, 2H), 4.42 (br s, 1H), 2.68 (t, J = 4.1 Hz, 1H), 2.65 (t, J = 4.0 Hz, 1H), 2.01-1.94 (m, 2H), 1.83-1.75 (m, 2H), 1.62-1.56 (m, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 165.7, 165.4, 154.9, 139.3, 132.0, 131.9, 128.5, 127.7, 126.6, 115.5, 79.7, 77.0, 75.1,73.6, 56.0, 40.4, 40.3, 36.0, 28.4, 28.3, 28.1; (**Compound b**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16–8.02 (m, 2H), 7.28-7.21 (m, 5H), 7.09-7.03 (m, 2H), 5.35-5.33 (m, 1H), 5.31-5.27 (m, 2H), 5.17-5.16 (m, 1H), 4.42 (br s, 1H), 2.62 2.58 (m, 2H), 2.06-1.93 (m, 3H), 1.74-1.57 (m, 3H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 165.7, 165.6, 154.8, 139.1, 132.3, 132.2, 128.4, 127.6, 126.6, 115.5, 79.6, 76.5, 74.9, 73.4, 55.9, 40.5, 40.3, 36.1, 28.6, 28.31 27.9. Fab accurate mass calcd. for $C_{28}H_{33}NO_7F$: (M^++1): 514.2241. Found: 514.2209

2-[(2*R*, 3*S*)-3-*tert*-Butoxycarbonylamino-)-2-hydroxy-3-phenyl-propanecarboxy]-5-(*p*-trifluoromethyl)benzoyloxybicyclo[2.2.1]octane (351c).



p-Toluenesulfonic acid monohydrate (50 mg, 0.264 mmol) was added to a solution of the oxazolidine **362c** (180 mg, 0.264 mmol) in methanol (10 mL). The reaction mixture was stirred for 20 min and then diluted with a saturated aqueous solution of sodium bicarbonate (20 mL). The aqueous phase was extracted with ether (3 x 25 mL) and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Rapid flash chromatography (silica gel, 1:1 ether/petroleum ether) afforded 119 mg (80%) of the title compound as a white solid; IR (neat) 3412, 2961, 2358, 1712, 1612, 1510, 1275, 1171, 863, 776 cm^{-1}; (**Compound a**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.27–8.26 (m, 2H), 7.68-7.66 (m, 2H), 7.58-7.21 (m, 5H), 5.40-5.38 (m, 1H), 5.29-5.28 (m, 1H), 5.18-5.17 (m, 2H), 4.42 (br s, 1H), 3.01 (br s, 1H), 2.68-2.64 (m, 2H), 2.01-1.94 (m, 2H), 1.85-1.72 (m, 2H), 1.63-1.52 (m, 2H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 165.4, 154.9, 139.4, 134.3 (q, CF_3), 133.7, 130.1, 128.5, 127.7, 126.6, 125.4, 123.5 (q, C-CF_3), 79.6, 77.0, 75.6, 73.6, 56.1, 40.5, 40.4, 36.1, 28.6, 28.3, 28.1; (**Compound b**) ^1H NMR ($CDCl_3$, 500 MHz) δ 8.19–8.14 (m, 2H), 7.64-7.63 (m, 2H), 7.56-7.19 (m, 5H), 5.39-5.38 (m, 1H), 5.30-5.27 (m, 2H), 5.18-5.17 (m, 1H), 4.42 (br s, 1H), 2.62-2.58 (m, 2H), 2.06-1.92 (m, 3H), 1.76-1.53 (m, 3H), 1.37 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8, 165.2, 154.9, 139.2, 134.3 (q, CF_3), 133.5, 129.9, 128.5, 127.7, 126.6, 125.4, 123.5 (q, C-CF_3), 79.6, 76.5, 75.5, 73.4, 55.9, 40.4, 40.4, 36.1, 28.6, 28.1, 27.9; Fab accurate mass calcd. for $C_{29}H_{33}NO_7F_3$: (M^++1): 564.2209. Found: 564.216

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Claims to Original Research

1. We have developed intramolecular radical clock system to determine the rate constants for the cyclization of secondary alkyl radicals onto various hydrazones and oxime ethers. In refluxing benzene the rate constants for these 5-*exo* cyclizations fall within the range of 4×10^7 to 16×10^7 s^{-1} depending on the electron withdrawing capacity of the imine acceptor.

2. We have shown through calculations at the AM1 level that the hydrazone cyclizations are highly exothermic reactions, as are the related oxime ether cyclizations.

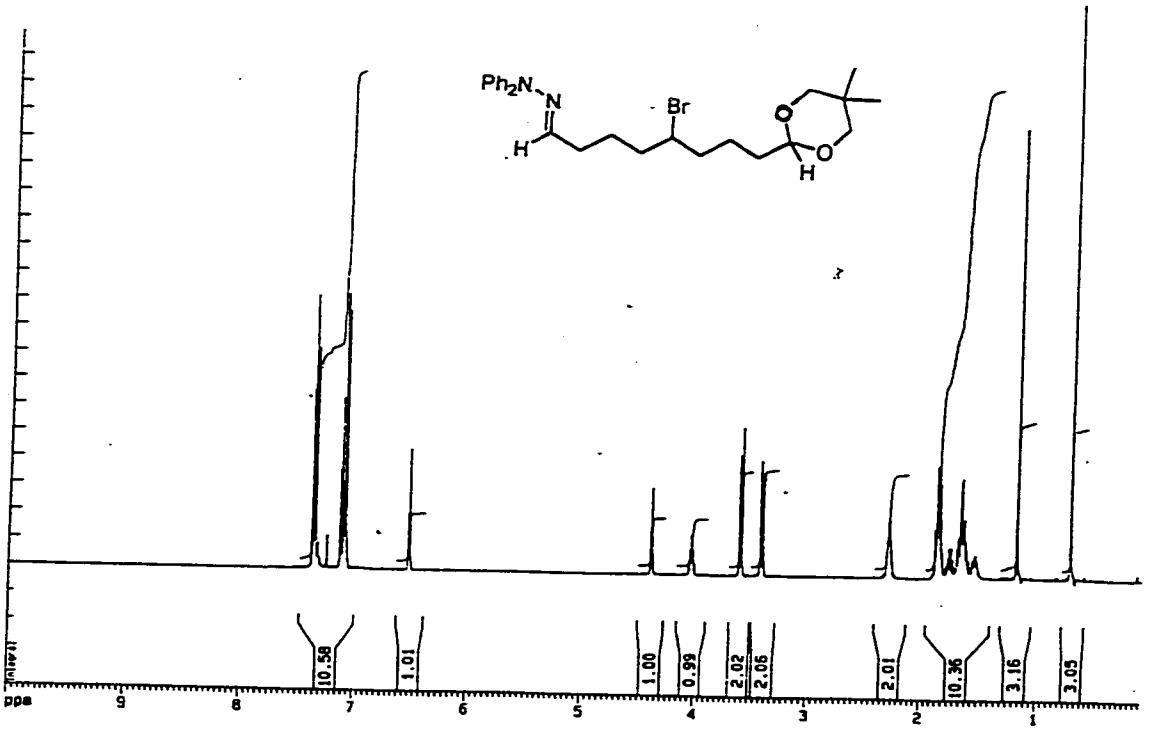
3. Tandem radical cyclizations involving aminyl radical generated by cyclization onto *N,N*-diphenylhydrazone were studied in attempted synthesis of 5,6- and 6,6-bicyclic systems.

4. A new chiral auxiliary **327** was synthesized, for use in the study of asymmetric induction in radical cyclizations in the presence of chiral auxiliaries.

5. Novel taxoid mimics **350** and **351** were synthesized and their biological activity was evaluated.

A portion of this research has been published.
Tauh, P.; Fallis, A. G. *J. Org. Chem.* **1999**, *64*, 6960-6968.

Appendix: Selected Spectra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H
Br
O
O
H
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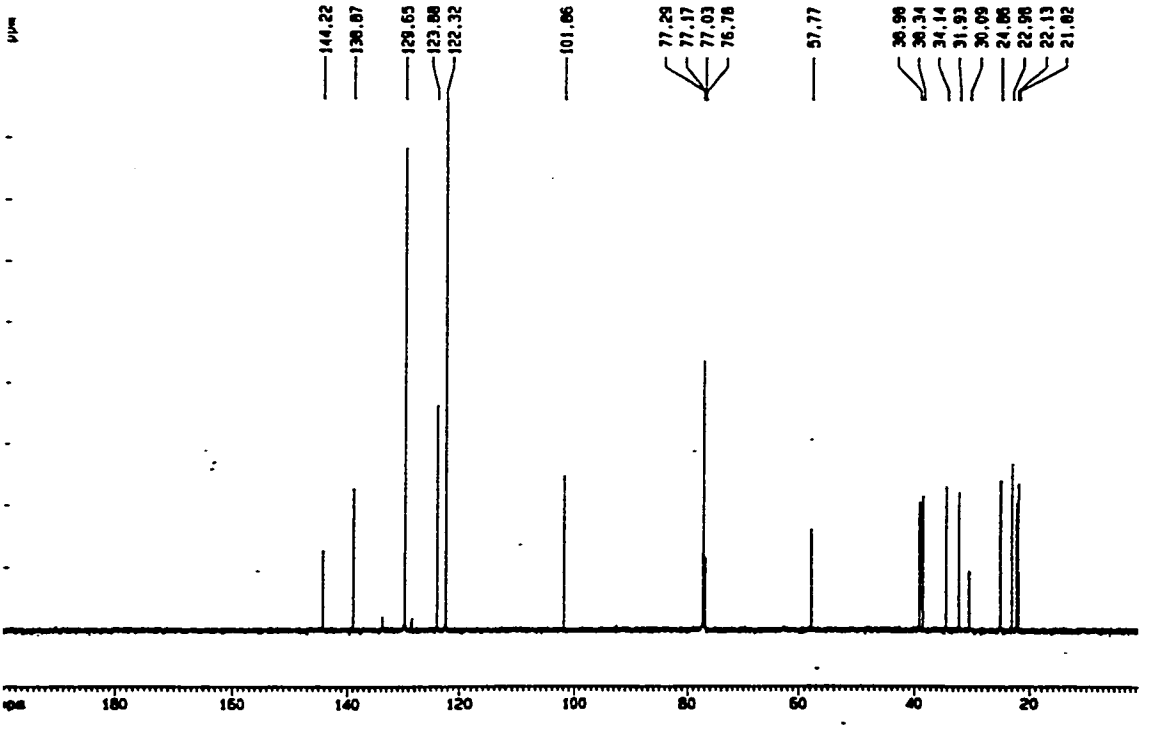
1.00
0.99
2.02
2.06
2.01
10.36
3.16
3.05
ppm
9
8
7
6
5
4
3
2
1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123.88
122.32
101.86
77.29
77.17
77.03
76.78
57.77
38.98
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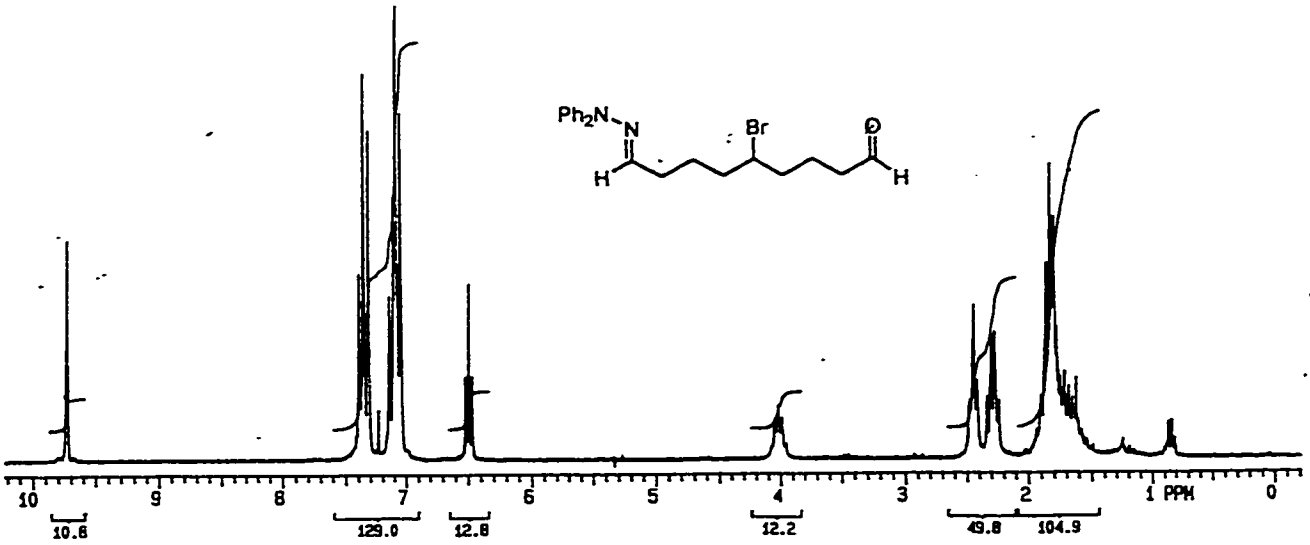
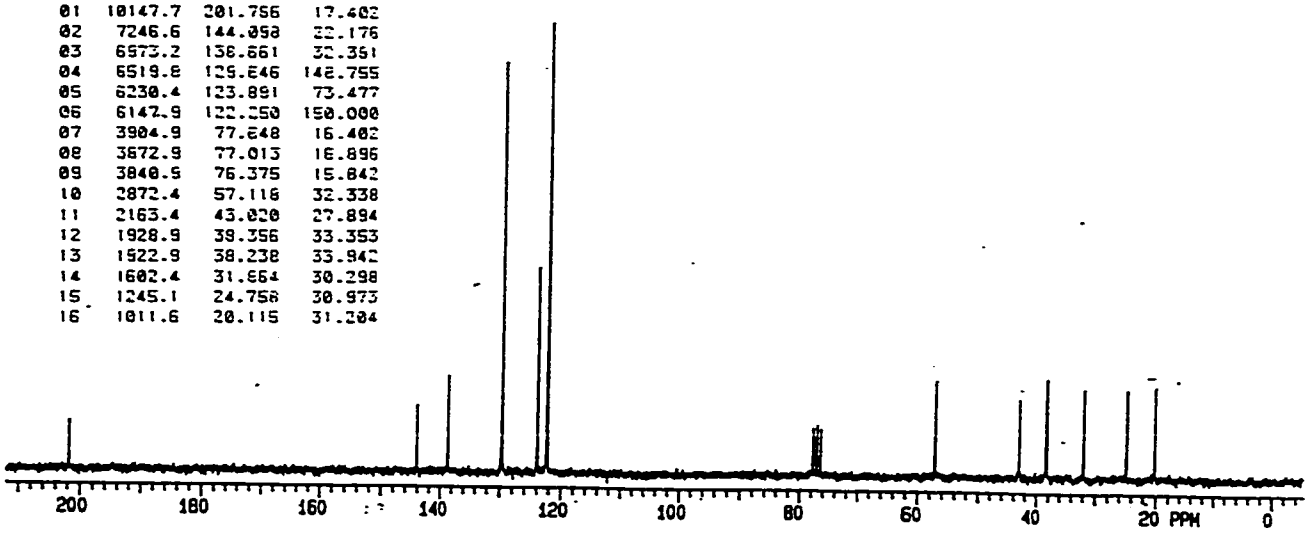
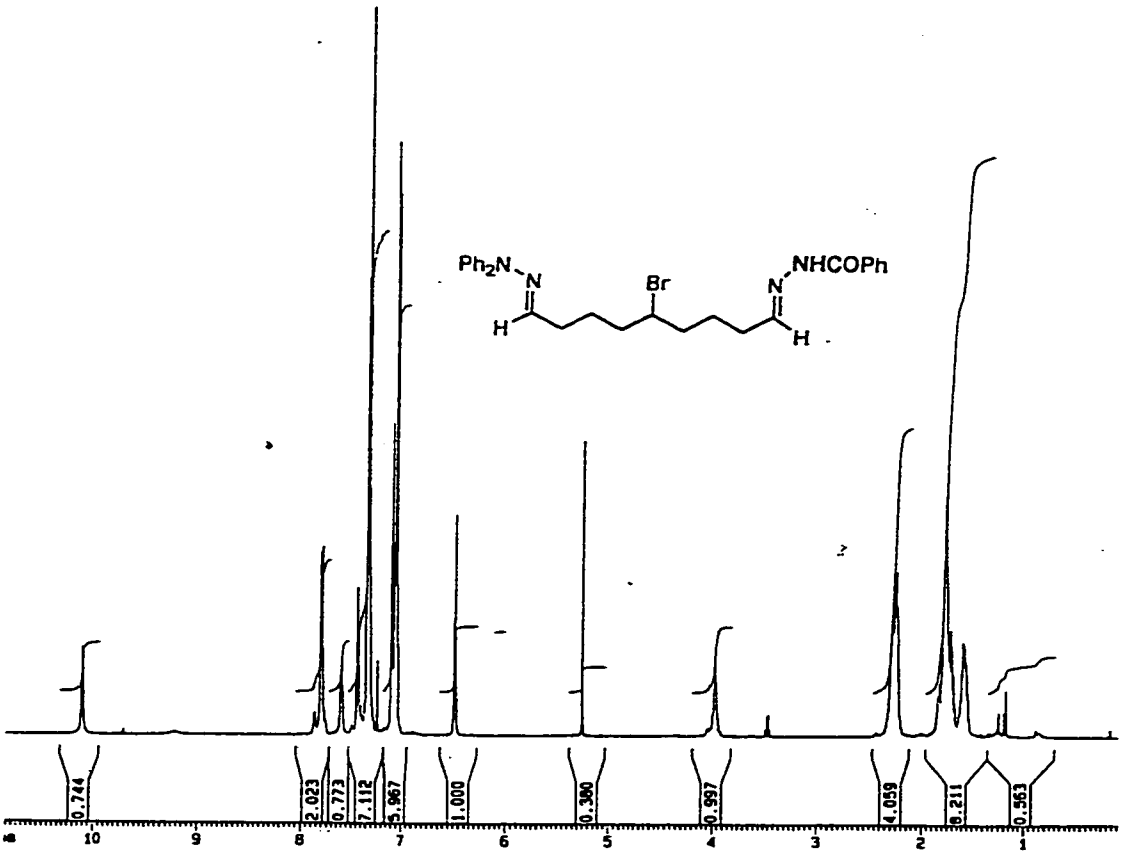
34.14
31.93
30.09
24.86
22.98
22.13
21.82
ppm
180
160
140
120
100
80
60
40
20



INDEX	FREQ	PPM	INTENSITY
01	10147.7	201.756	17.402
02	7246.6	144.098	22.176
03	6973.2	138.661	32.351
04	6519.8	129.646	142.755
05	6230.4	123.891	73.477
06	6142.9	122.150	150.000
07	3904.9	77.648	16.402
08	3872.9	77.013	16.896
09	3840.9	76.375	15.842
10	2872.4	57.116	32.338
11	2163.4	43.020	27.894
12	1928.9	38.356	33.353
13	1922.9	38.238	33.942
14	1602.4	31.864	30.298
15	1245.1	24.758	30.973
16	1011.6	20.115	31.284

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N
H
Br
N
NHCOPh
H
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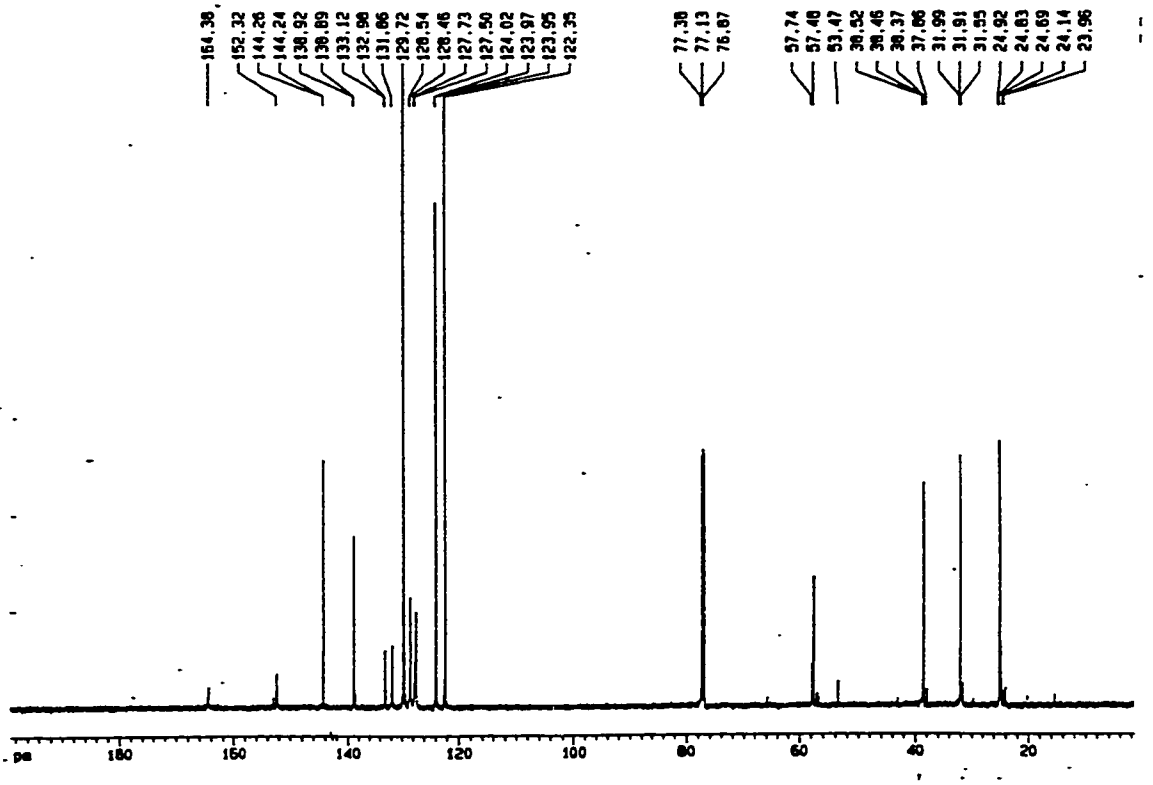
2.023
0.773
7.112
5.967
1.000
0.300
0.997
4.059
8.211
0.963
10
9
8
7
6
5
4
3
2
1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127.73
127.50
124.02
123.97
123.95
122.35
77.38
77.13
76.87
57.74
57.48
53.47
38.52
38.46
38.37
37.86
31.99
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24.83
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24.14
23.96
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160
140
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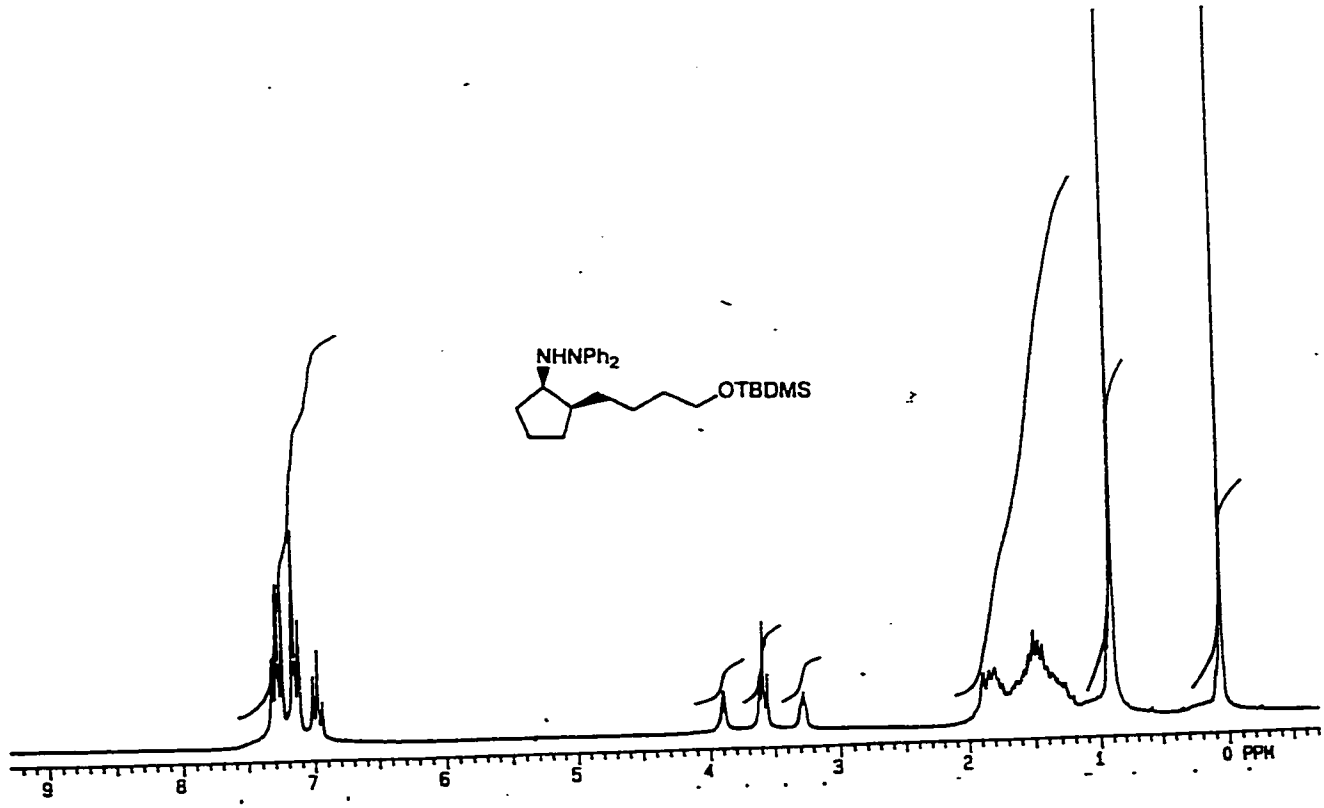
100
80
60
40
20



SPECTRAL LINES FOR TH= 7.27
RFL= 4515.6 RFP= 3672.3

INDEX	FREQ	PPM	INTENSITY
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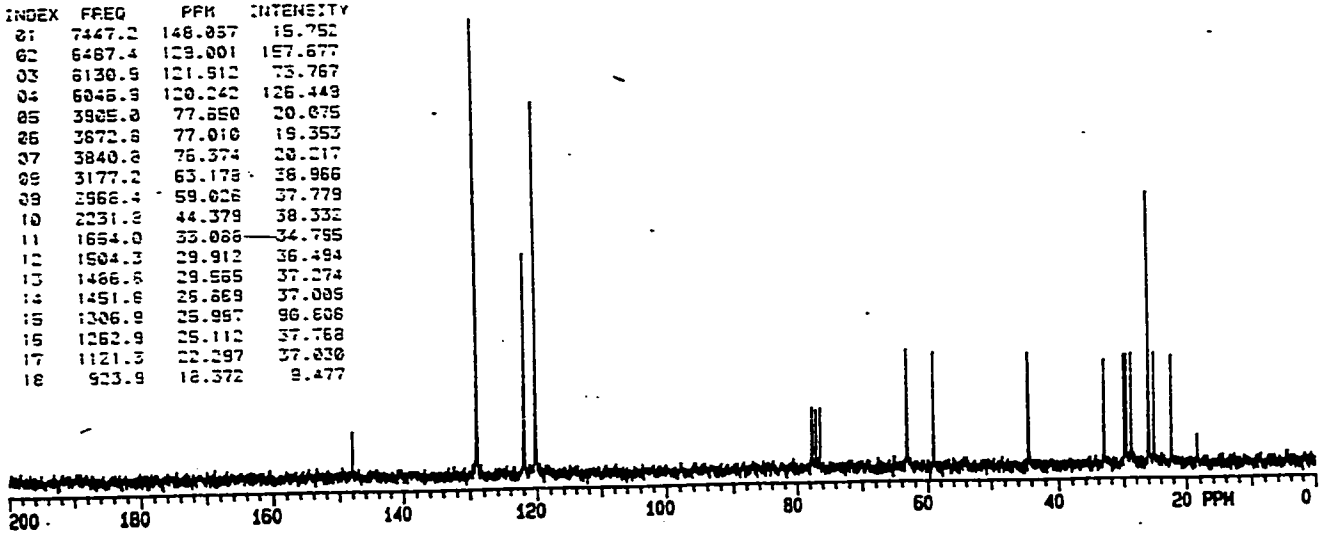
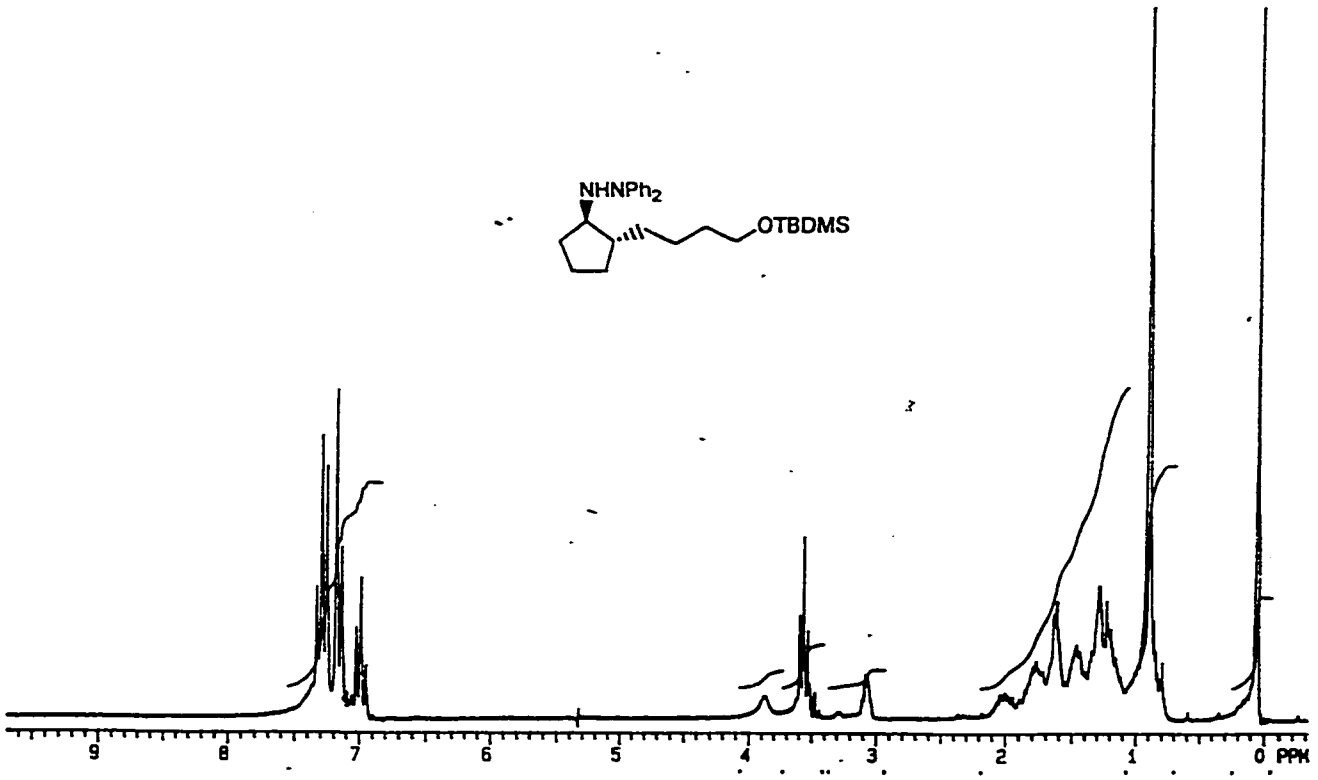
02	6487.4	128.001	157.677
03	6130.9	121.912	73.767
04	6046.9	120.242	126.449
05	3905.0	77.650	20.675
06	3872.8	77.010	19.353
07	3840.6	76.374	28.217
08	3177.2	63.178	36.966
09	2966.4	59.026	37.779
10	2231.8	44.379	38.332
11	1654.0	33.006	34.795
12	1504.3	29.912	36.494
13	1466.6	29.565	37.274
14	1451.6	28.869	37.005
15	1306.9	25.997	96.606
16	1262.9	25.112	37.768
17	1121.3	22.297	37.030
18	923.9	18.372	8.477





INDEX	FREQ	PPM	INTENSITY
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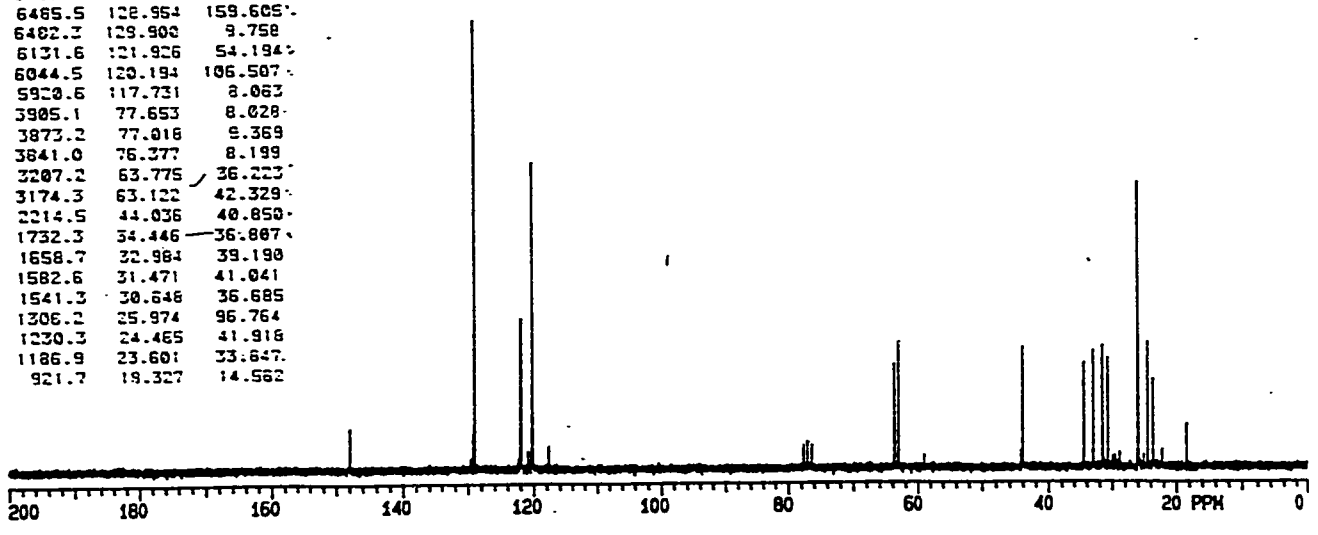
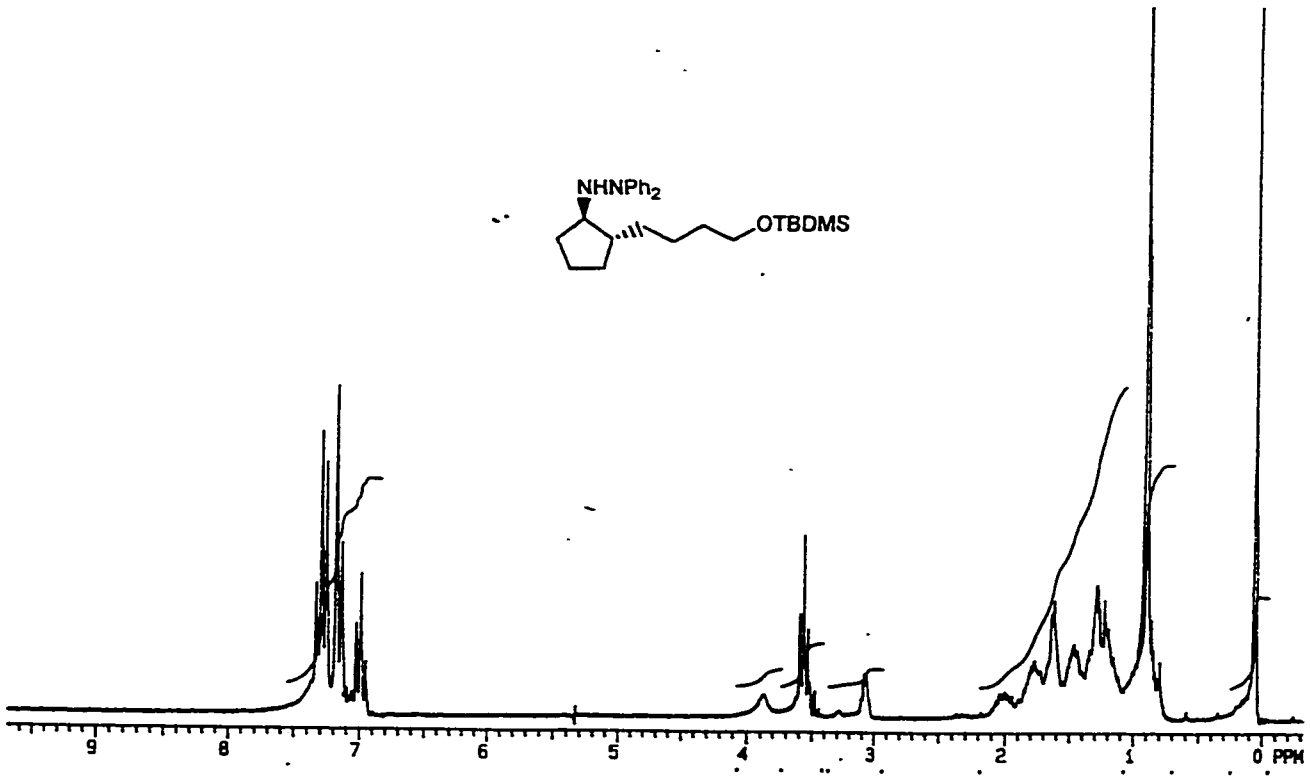
02	6500.4	129.260	11.570
03	6488.7	129.027	15.398
04	6485.5	128.964	159.605
05	6482.3	128.900	9.758
06	6131.6	121.926	54.194
07	6044.5	120.194	106.507
08	5920.6	117.731	8.063
09	3905.1	77.653	8.028
10	3873.2	77.018	8.369
11	3841.0	76.377	8.199
12	3207.2	63.775	36.223
13	3174.3	63.122	42.329
14	2214.5	44.036	40.850
15	1732.3	34.446	36.807
16	1658.7	32.984	39.190
17	1582.6	31.471	41.041
18	1541.3	30.648	36.685
19	1306.2	25.974	96.764
20	1230.3	24.465	41.918
21	1186.9	23.601	33.647
22	921.7	18.327	14.562





INDEX	FREQ	PPM	INTENSITY
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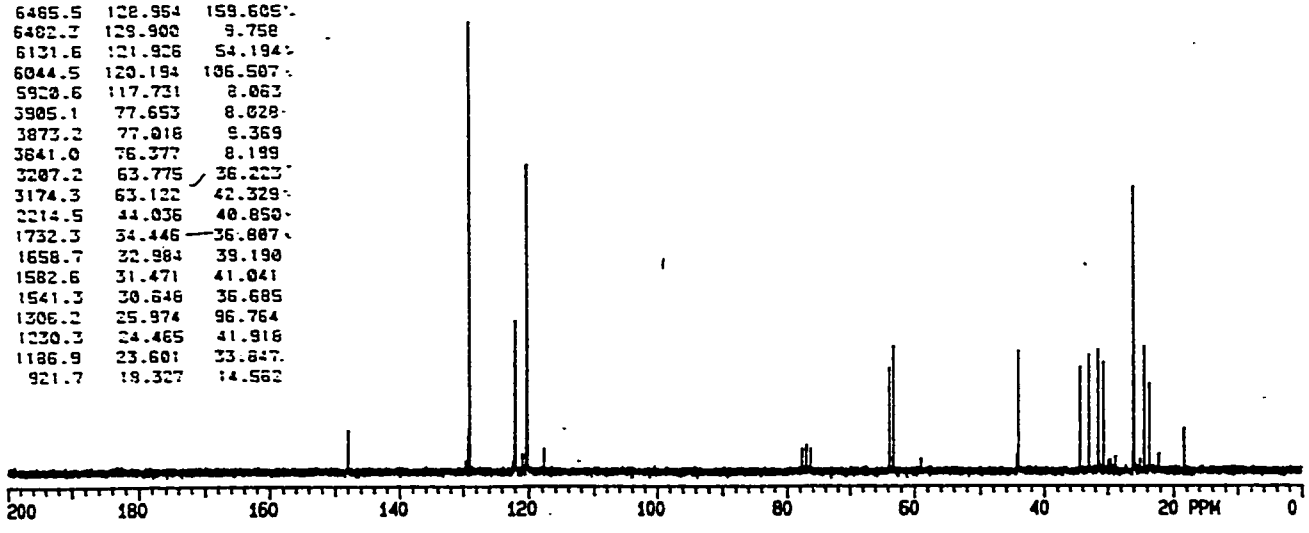
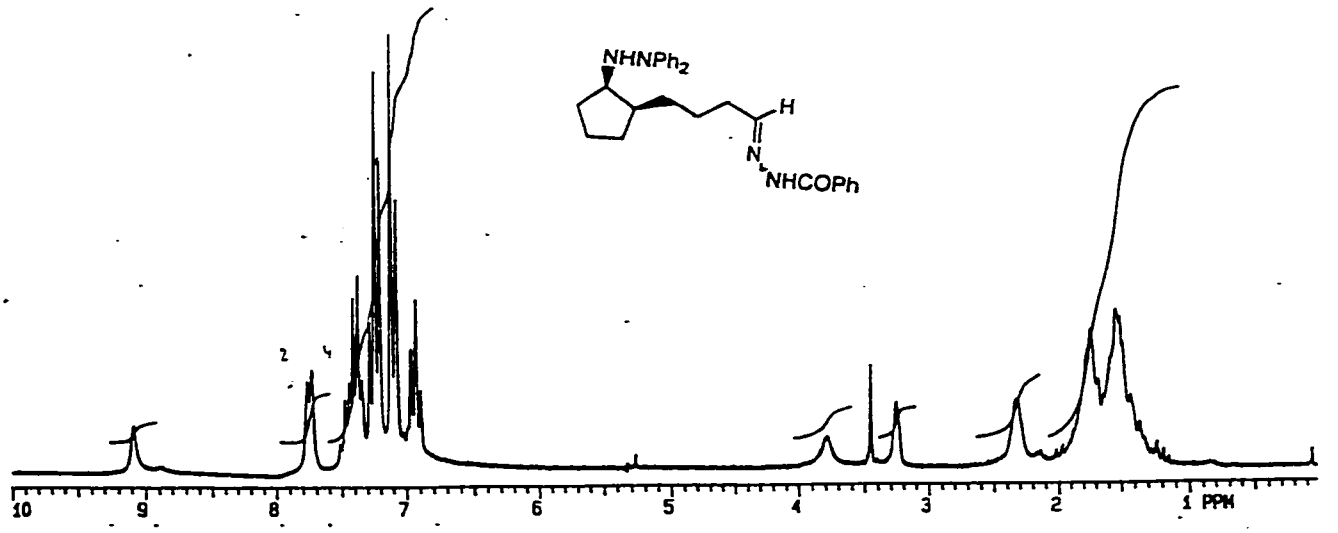
03	6486.7	129.027	15.398
04	6485.5	128.954	159.605
05	6482.3	128.900	9.758
06	6131.6	121.926	54.194
07	6044.5	120.194	186.507
08	5920.6	117.731	8.063
09	3905.1	77.653	8.028
10	3873.2	77.018	9.369
11	3841.0	76.377	8.199
12	3207.2	63.775	36.223
13	3174.3	63.122	42.329
14	2214.5	44.036	40.850
15	1732.3	34.446	36.887
16	1658.7	32.984	39.190
17	1582.6	31.471	41.041
18	1541.3	30.646	36.685
19	1306.2	25.974	96.764
20	1230.3	24.465	41.918
21	1186.9	23.601	33.647
22	921.7	18.327	14.562

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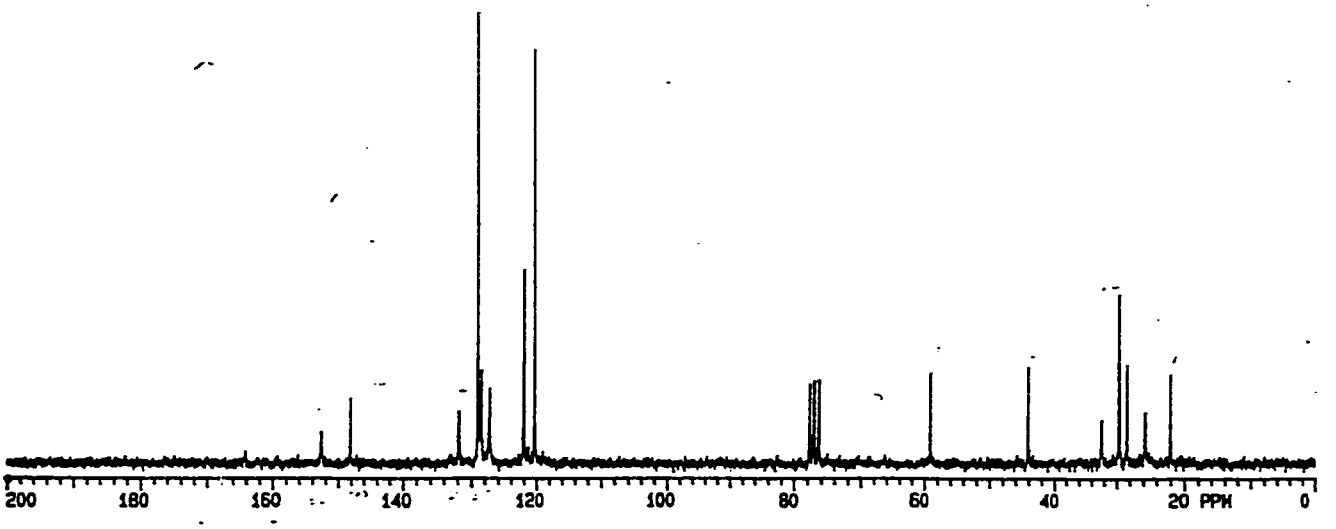
9
8
7
6
5
4
3
2
1 PPM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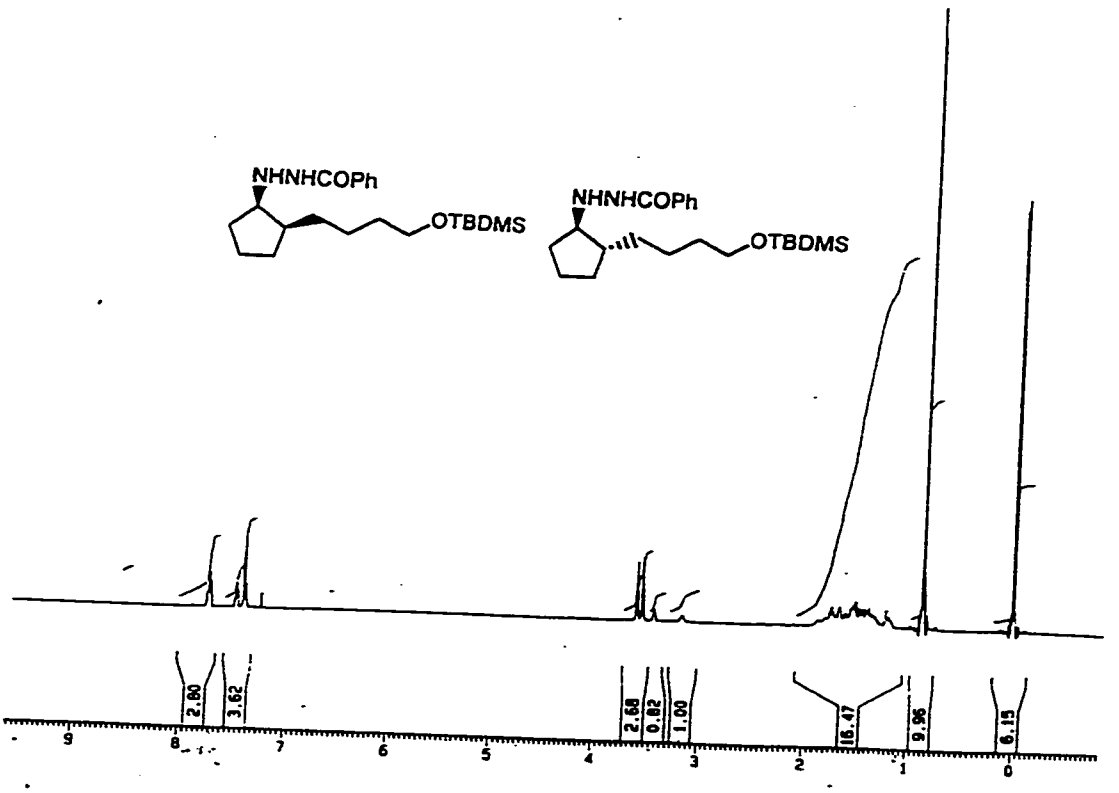
160
140
120
100
80
60
40
20 PPM
0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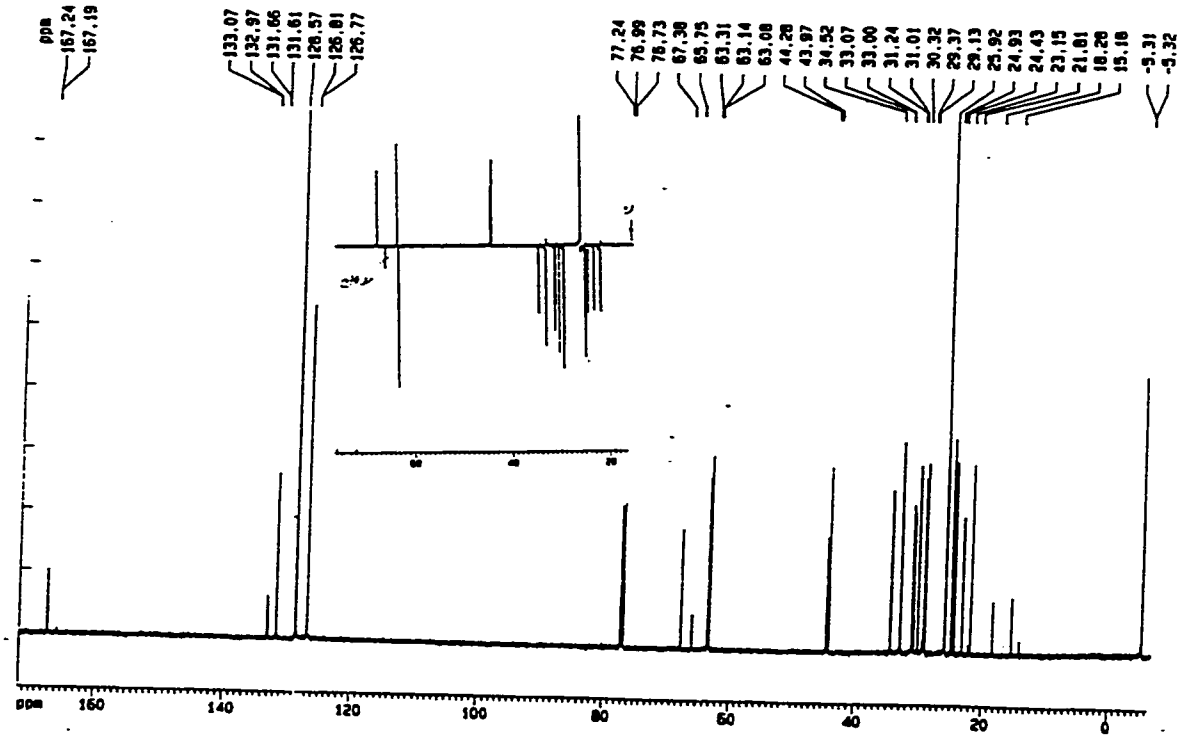
6.15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63.31
63.14
63.08
44.28
43.97
34.52
33.07
33.00
31.24
31.01
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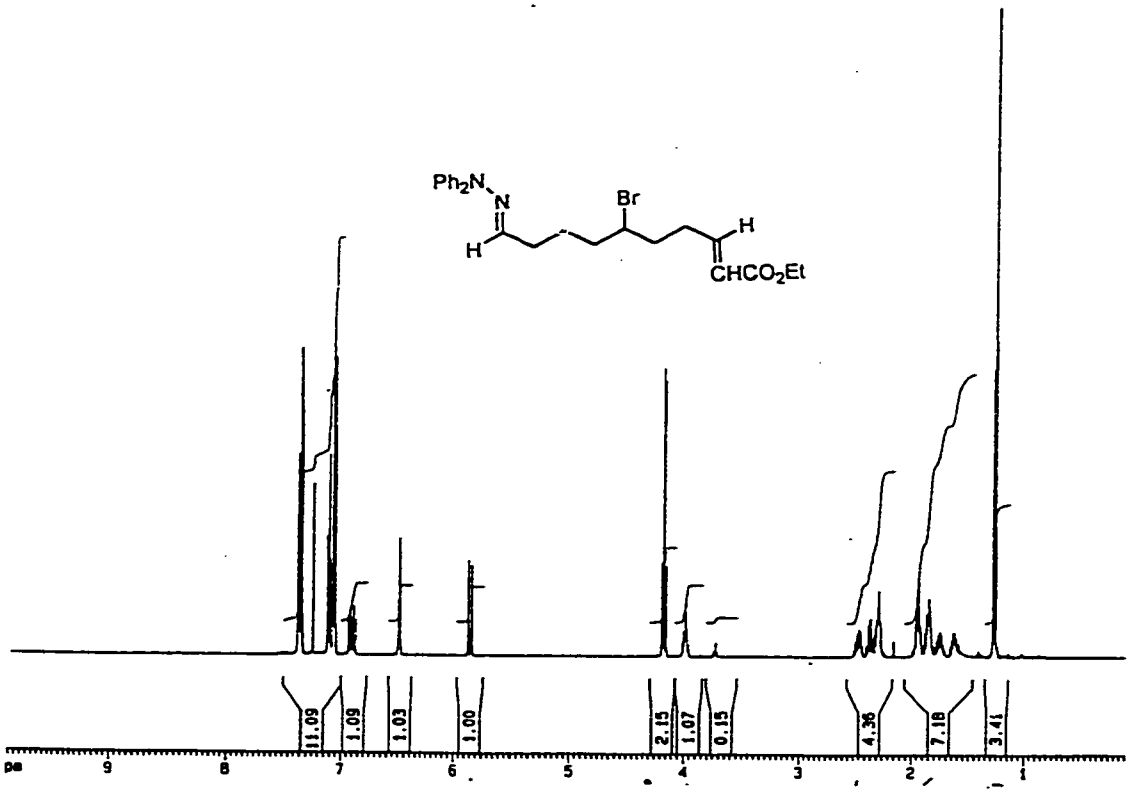
-5.32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H
Br
H
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1.03
1.00
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4.36
7.18
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ppm
9
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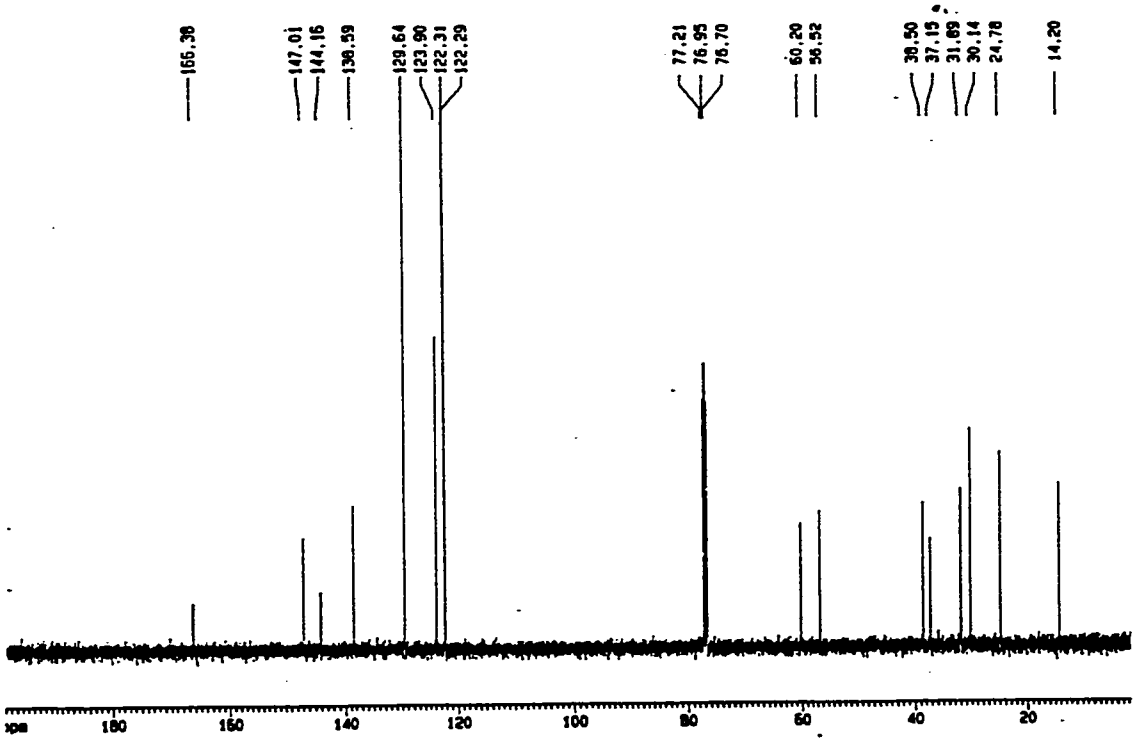
7
6
5
4
3
2
1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31.69
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ppm
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80
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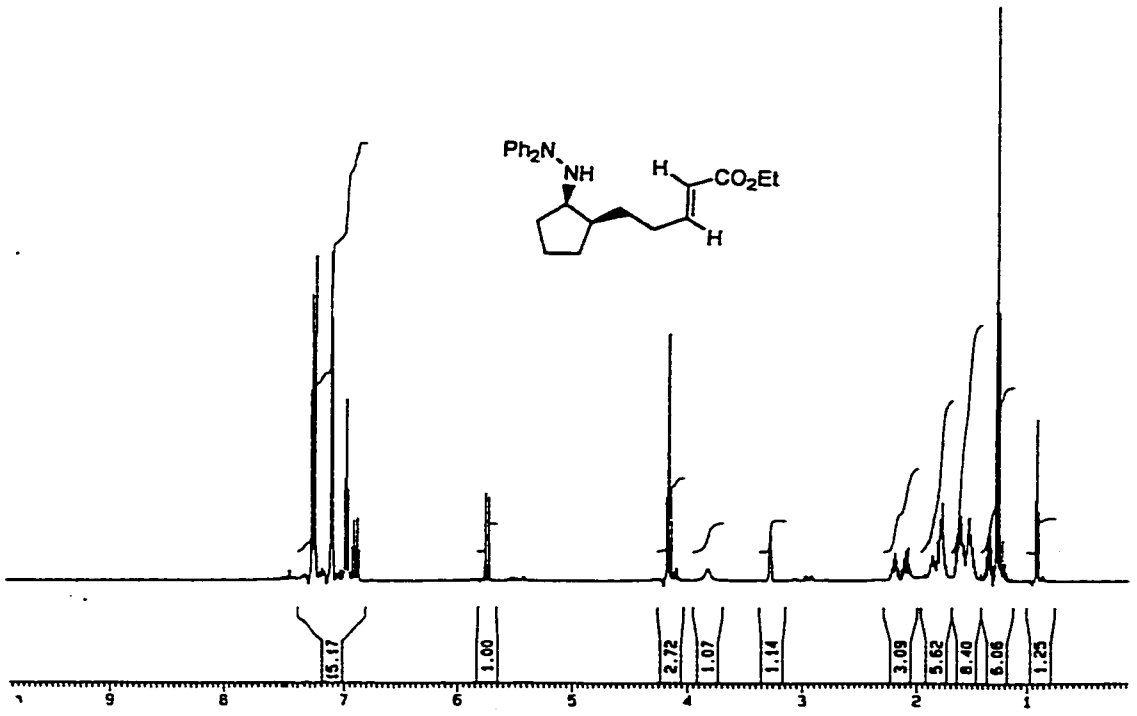
40
20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H
CO2Et
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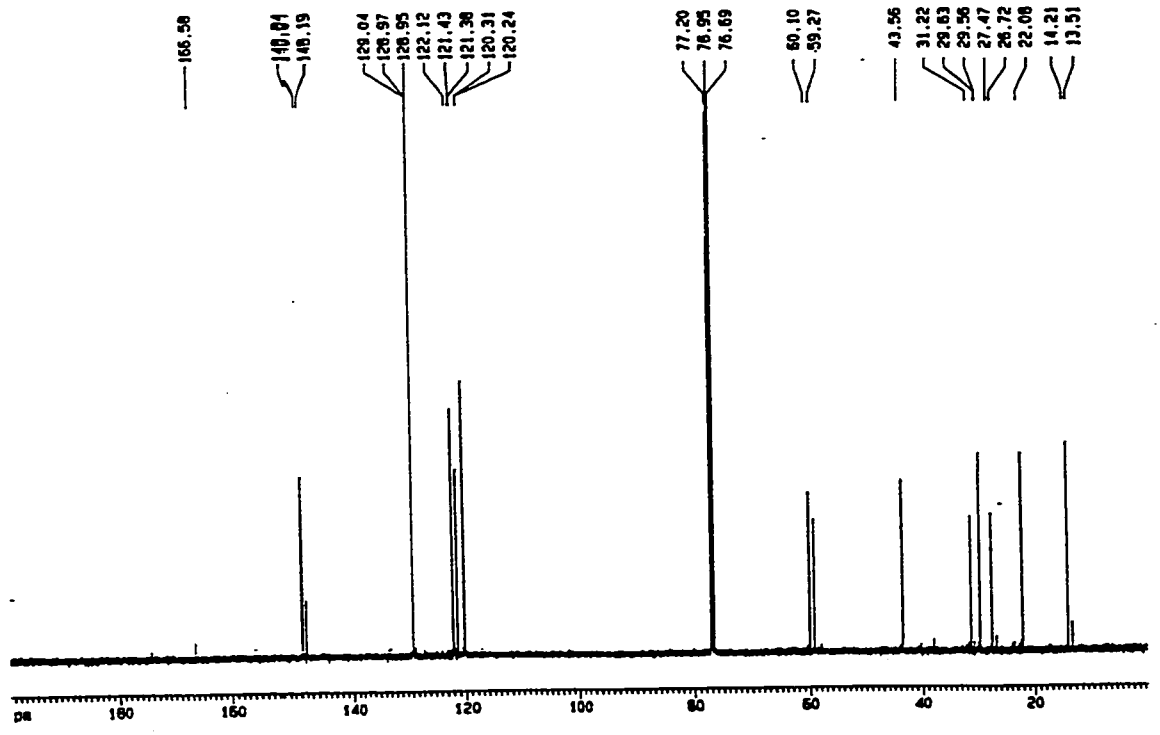
6.06
1.25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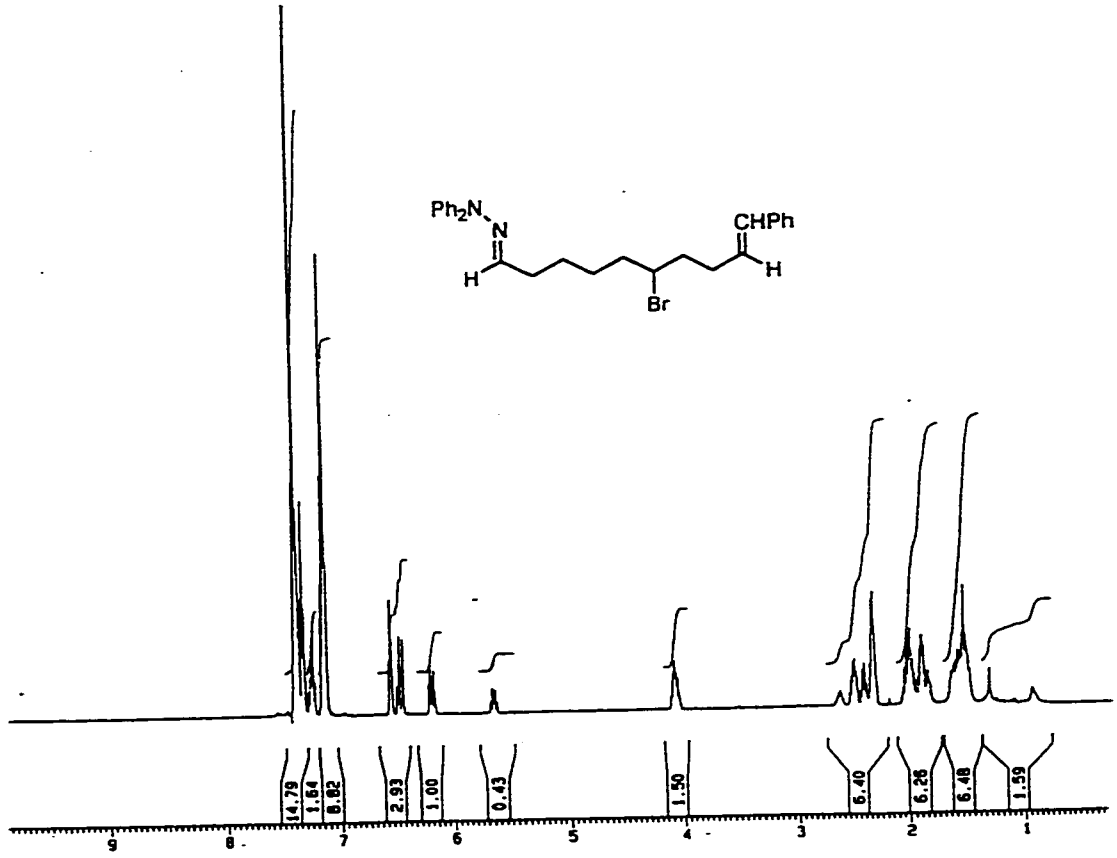
14.21
13.51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CHPh
H
Br
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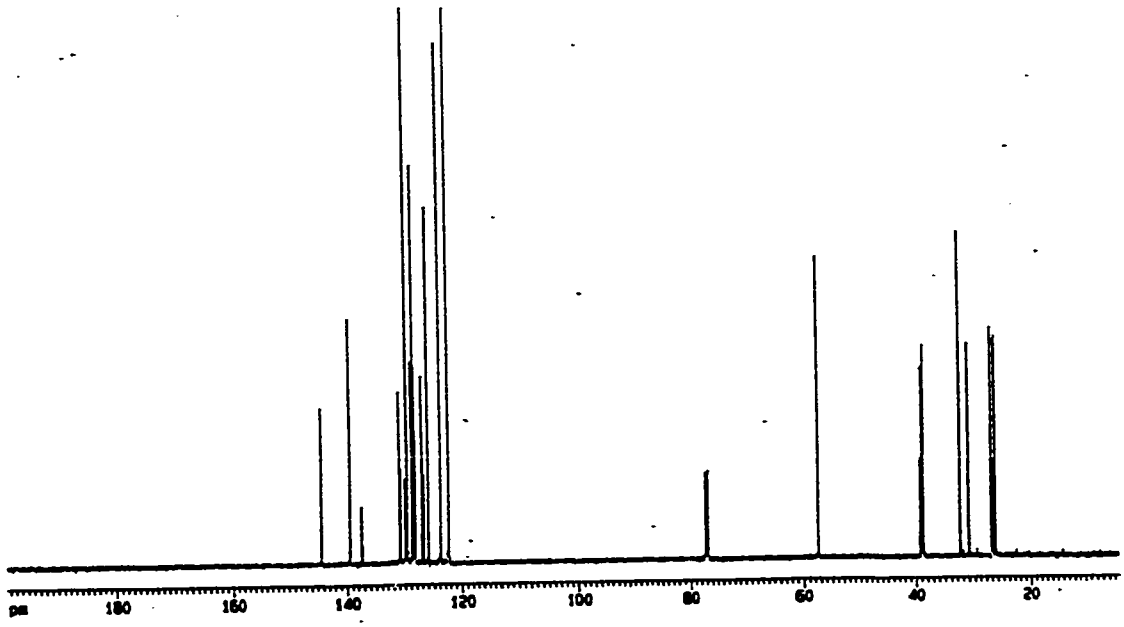
8
7
6
5
4
3
2
1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140
120
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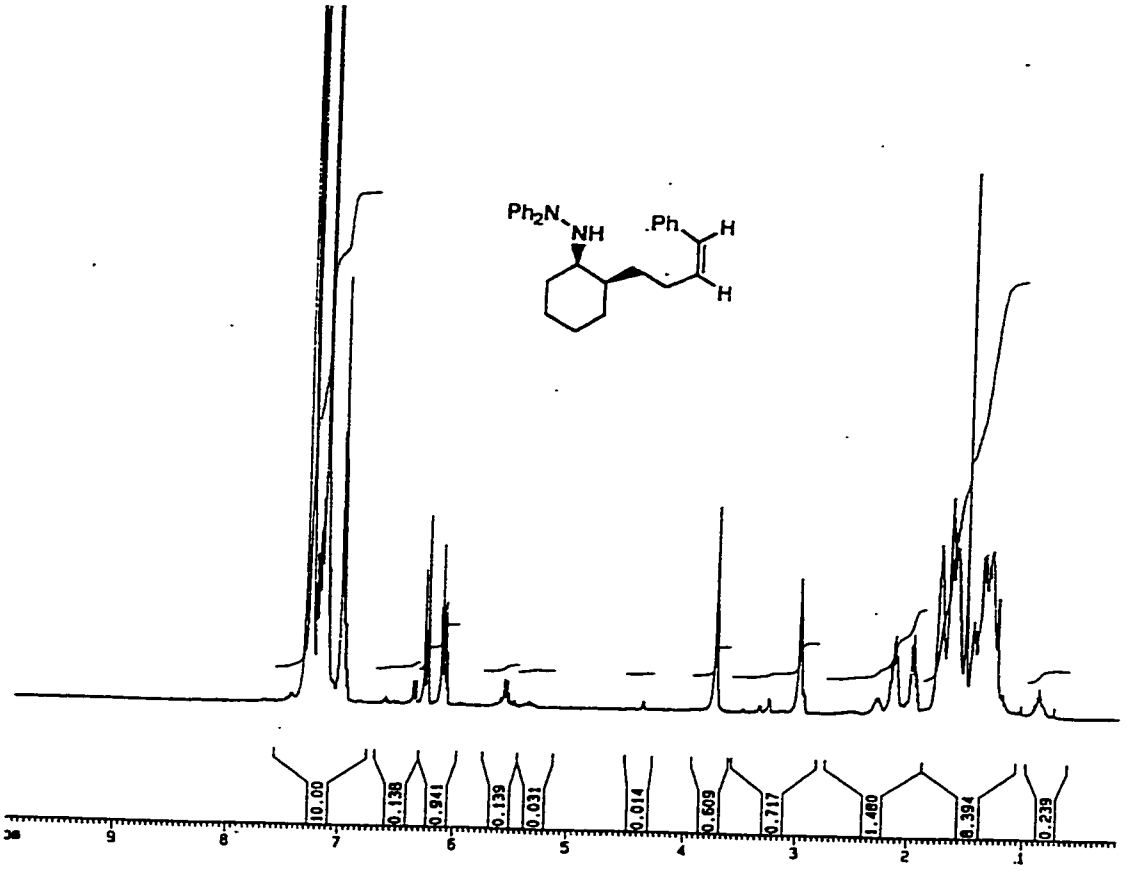
80
60
40
20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Ph
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5
4
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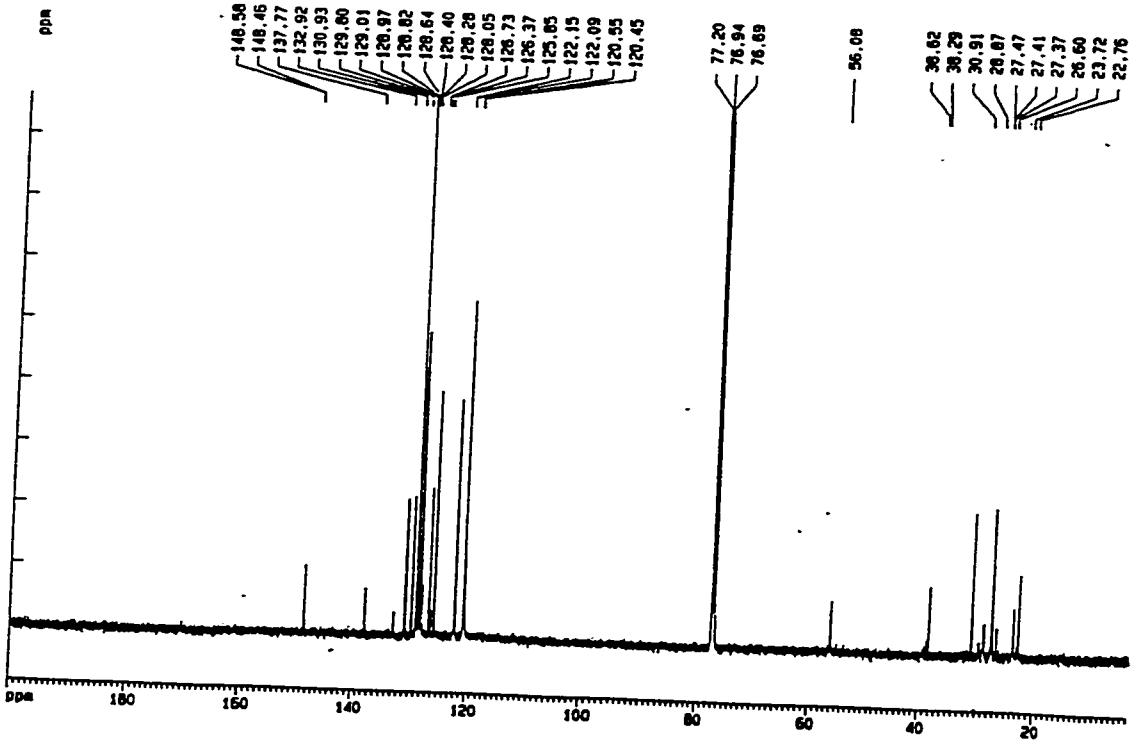
2
1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128.64
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128.28
128.05
126.73
126.37
125.85
122.15
122.09
120.55
120.45
77.20
76.94
76.69
56.08
38.62
38.29
30.91
28.87
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26.60
23.72
22.76
180
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140
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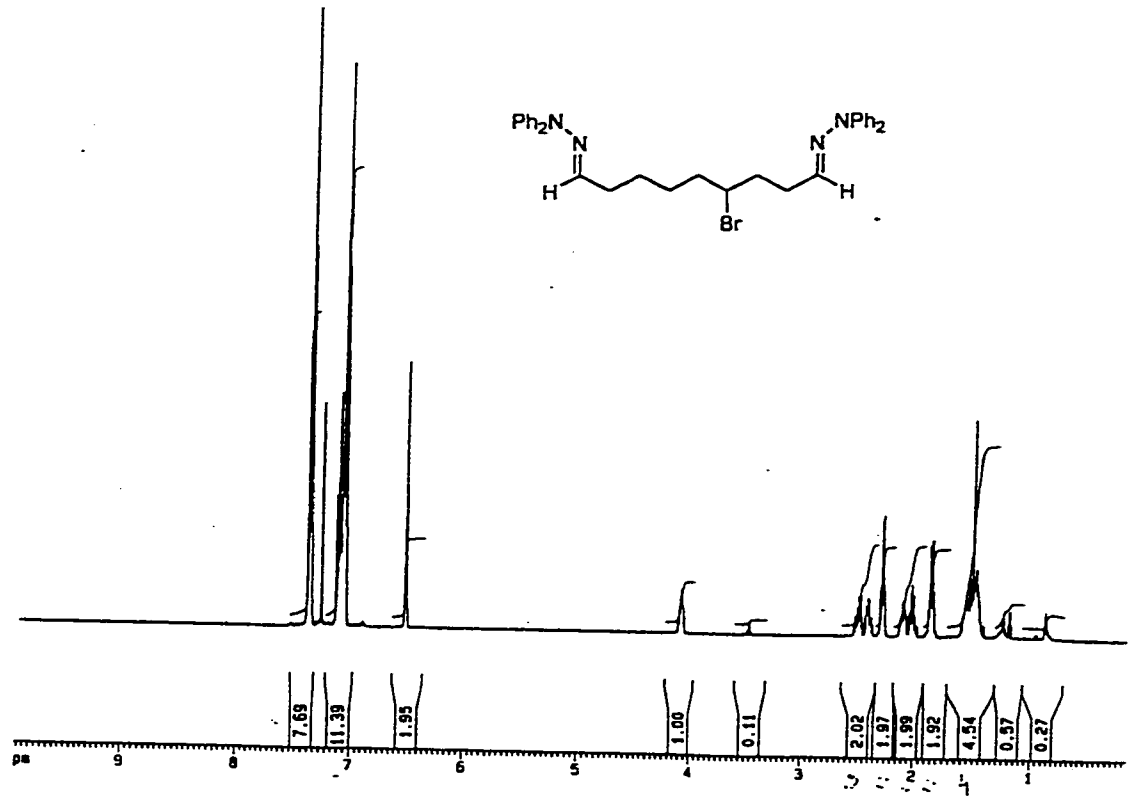
100
80
60
40
20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H
Br
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2.02
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ppm
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8
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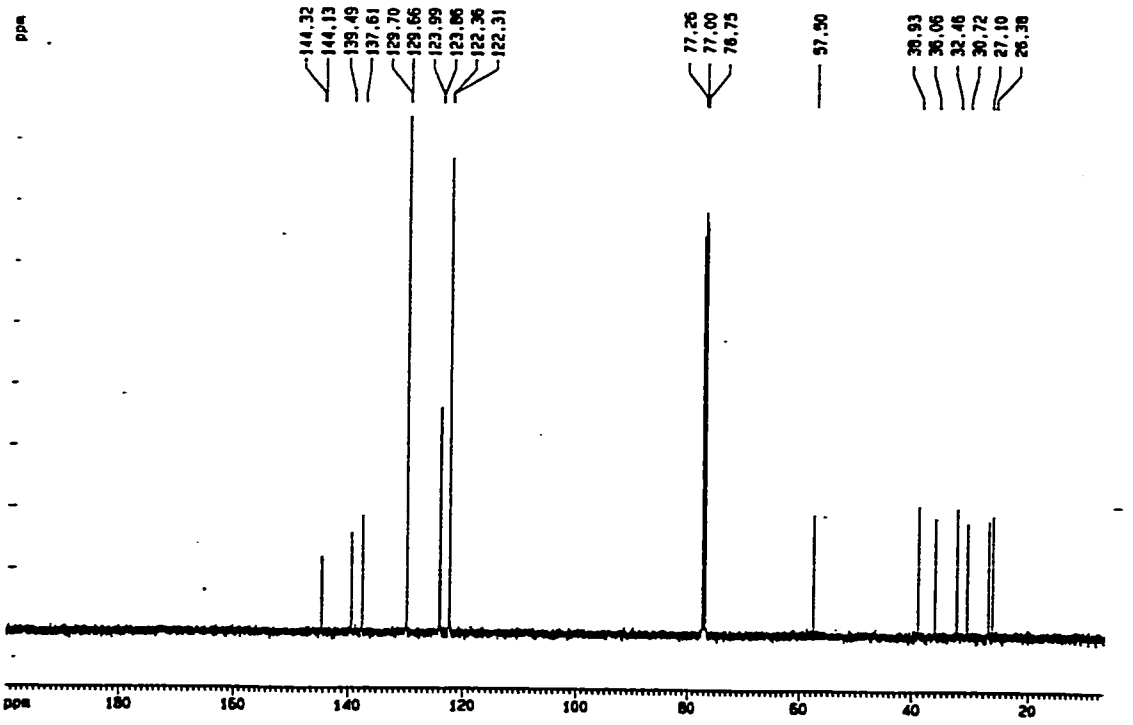
4
3
2
1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122.36
122.31
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57.90
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30.72
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26.38
ppm
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160
140
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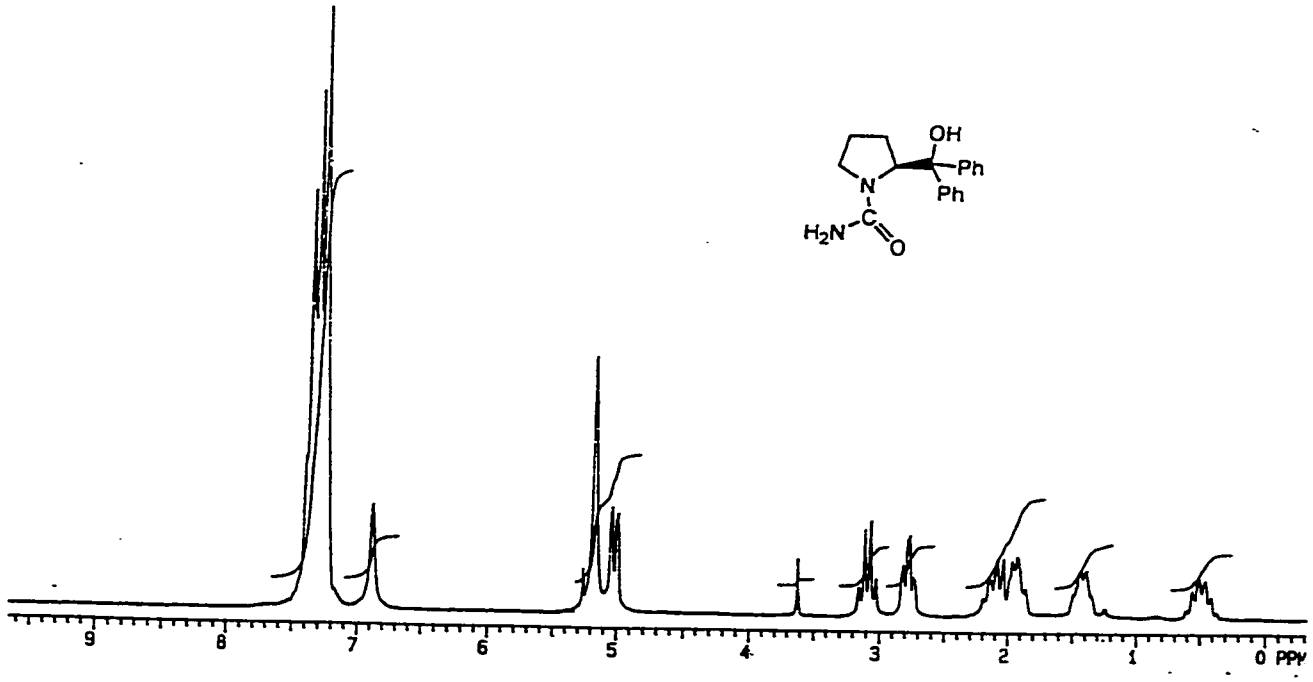
40
20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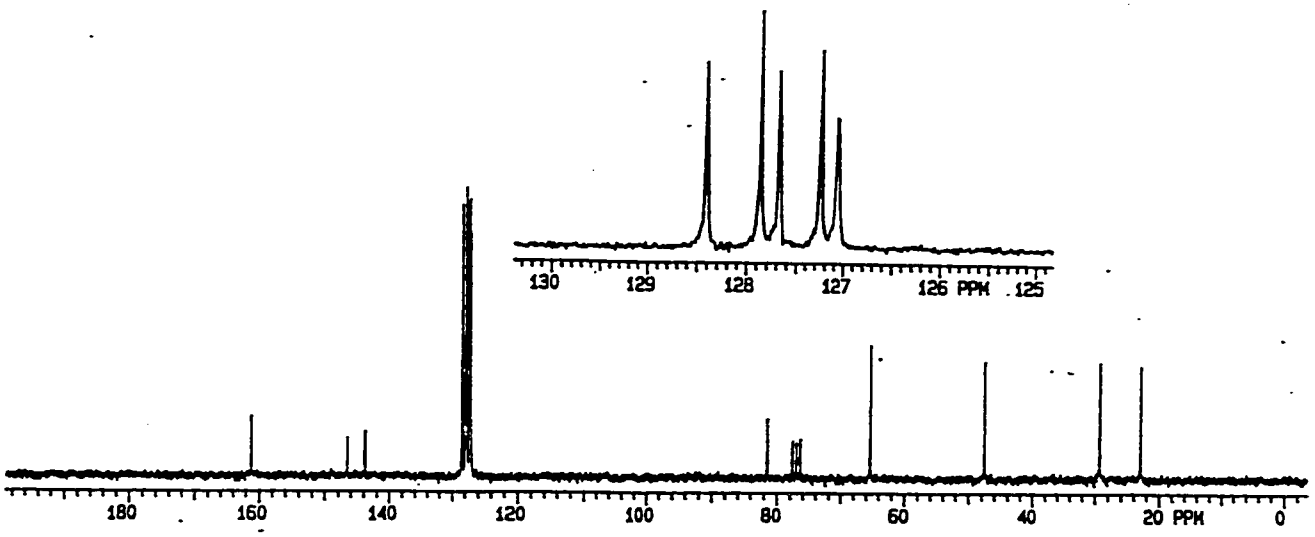
Ph
N
C
O
H_2N
9
8
7
6
5
4
3
2
1
0 PPM


130
129
128
127
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125
180
160
140
120
100
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60
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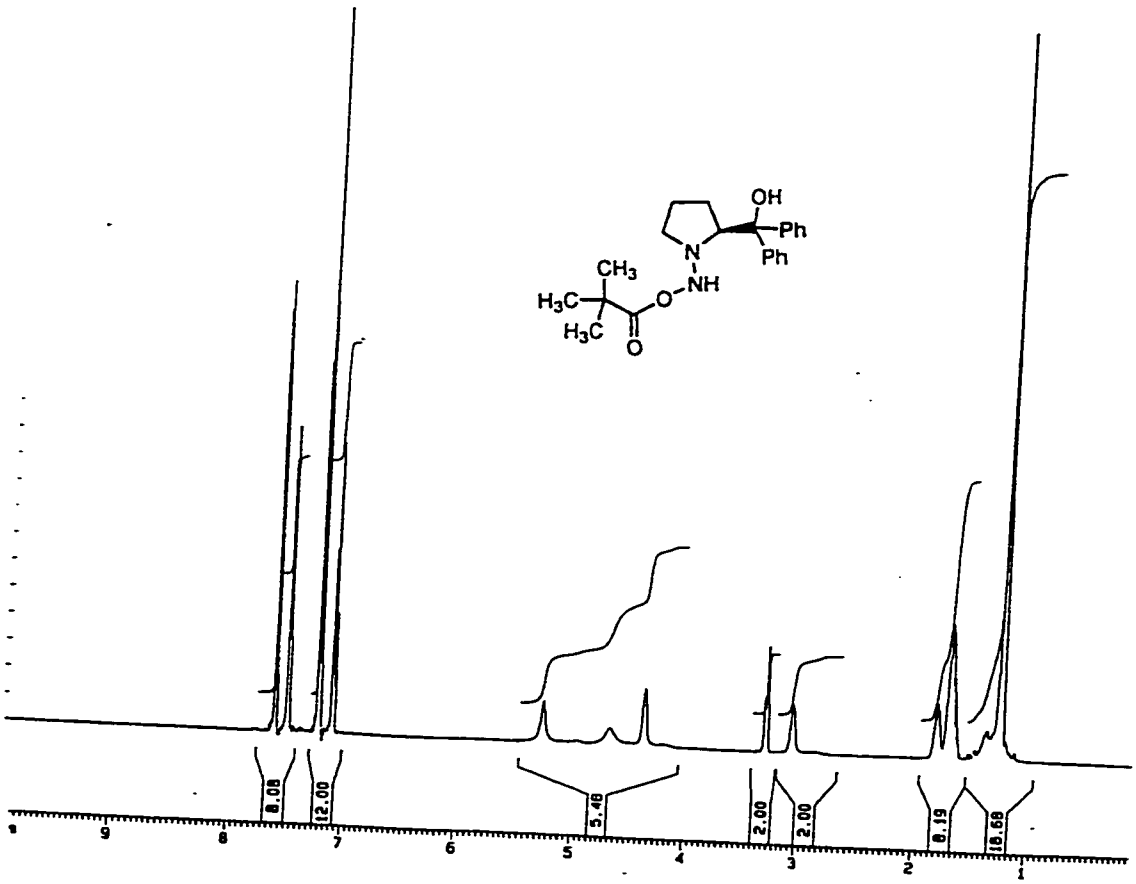
20 PPM
0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Ph
N
NH
O
O
H_3C
CH_3
H_3C
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2.00
8.19
18.68
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8
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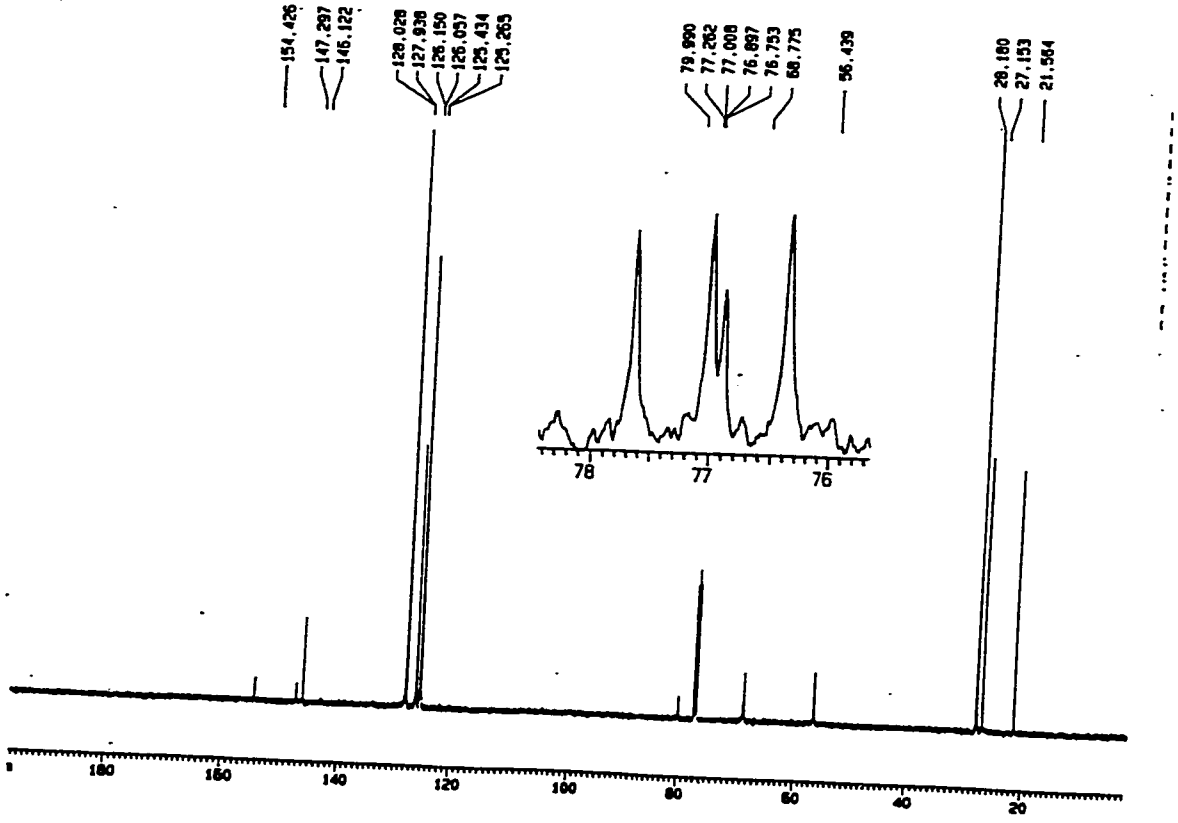
2
1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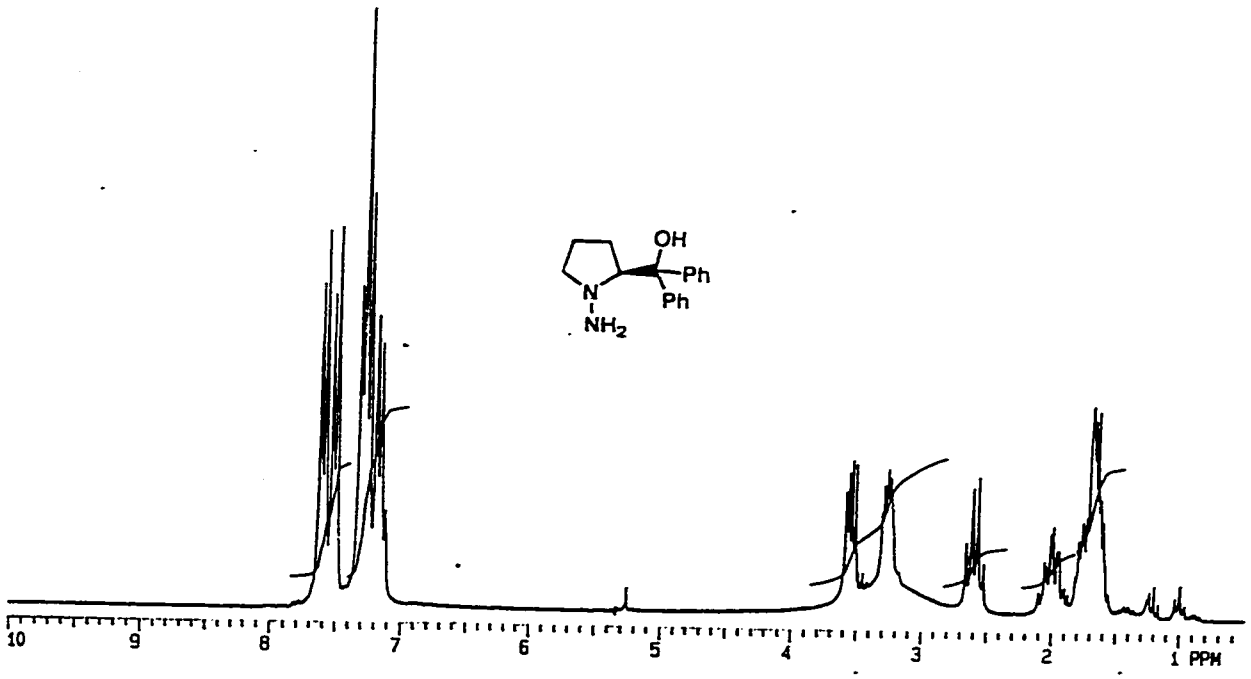
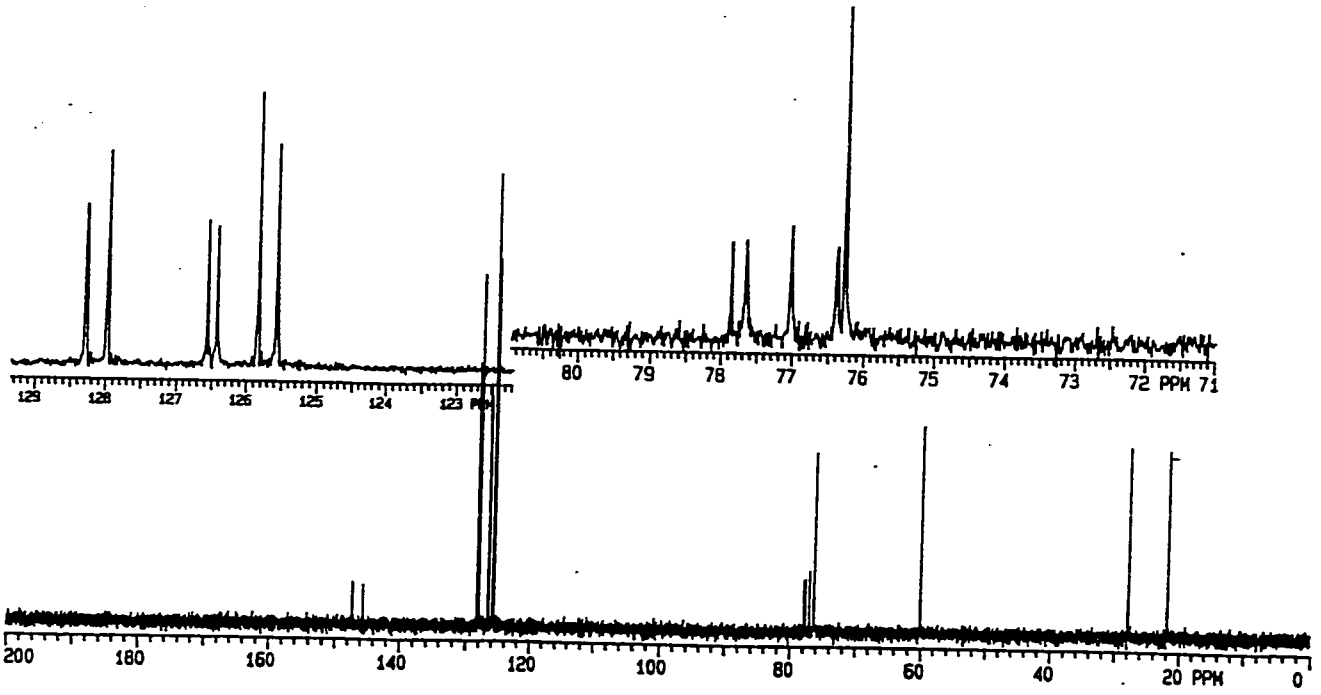
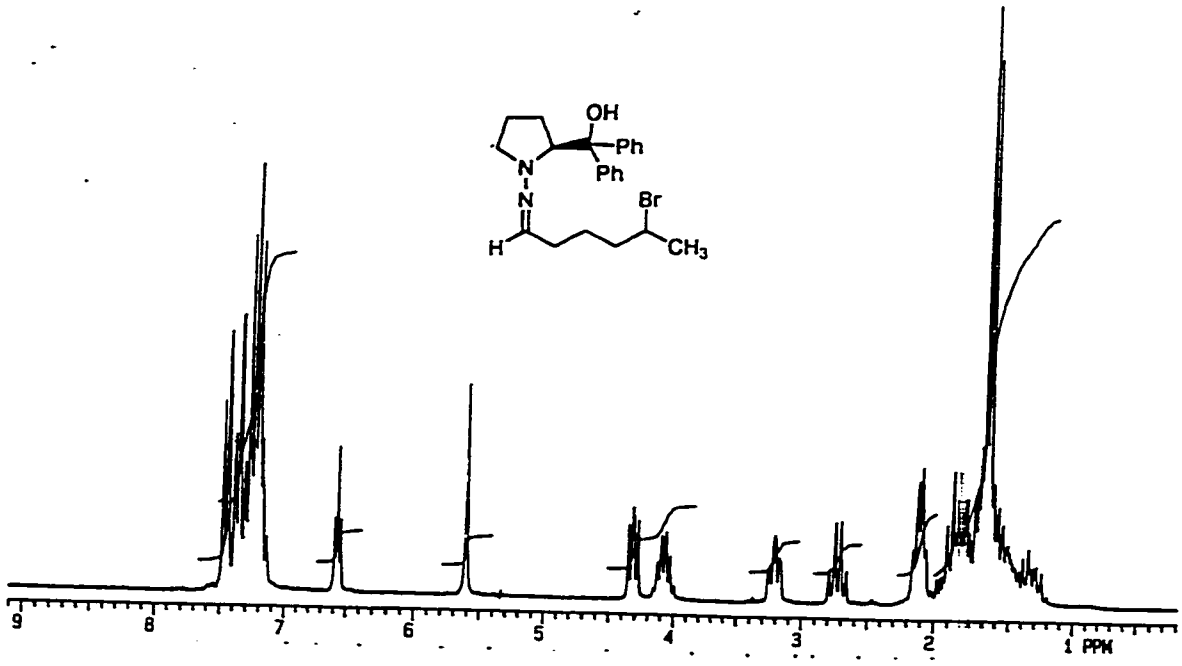
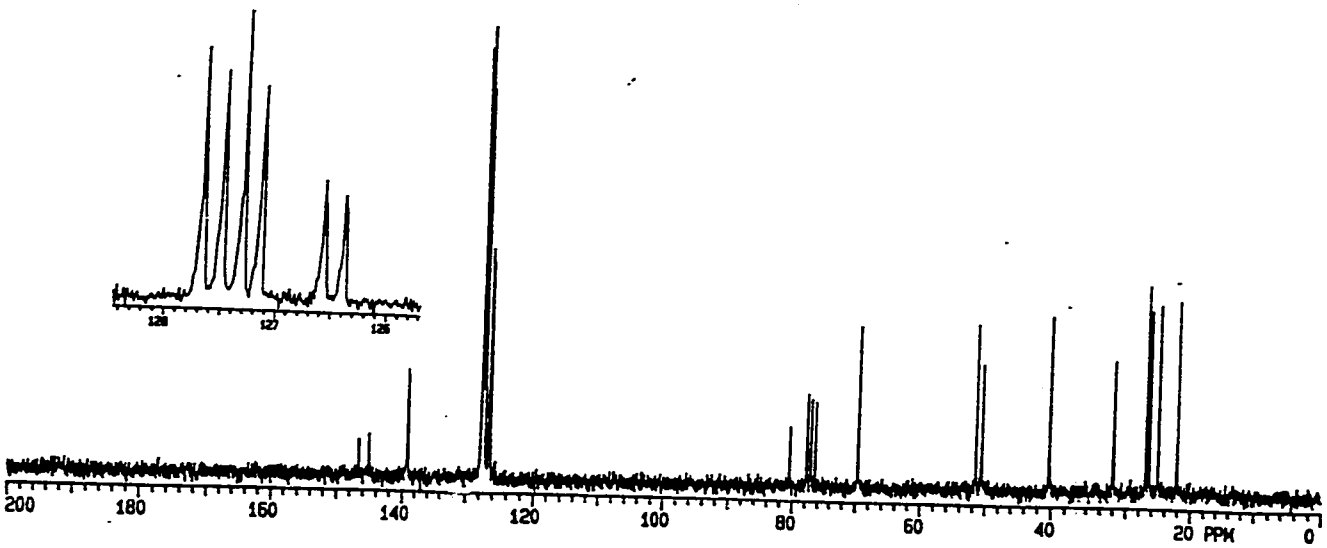
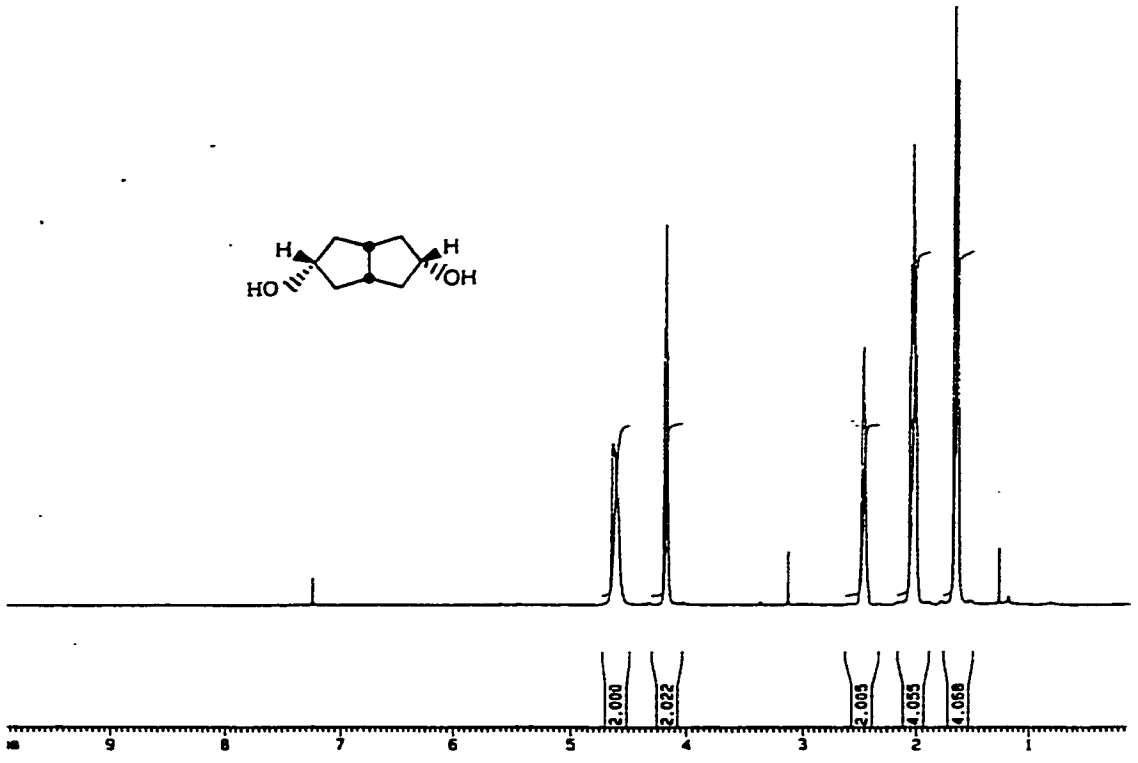
76.897
76.753
56.439
28.180
27.153
21.564
78
77
76
180
160
140
120
100
80
60
40
20

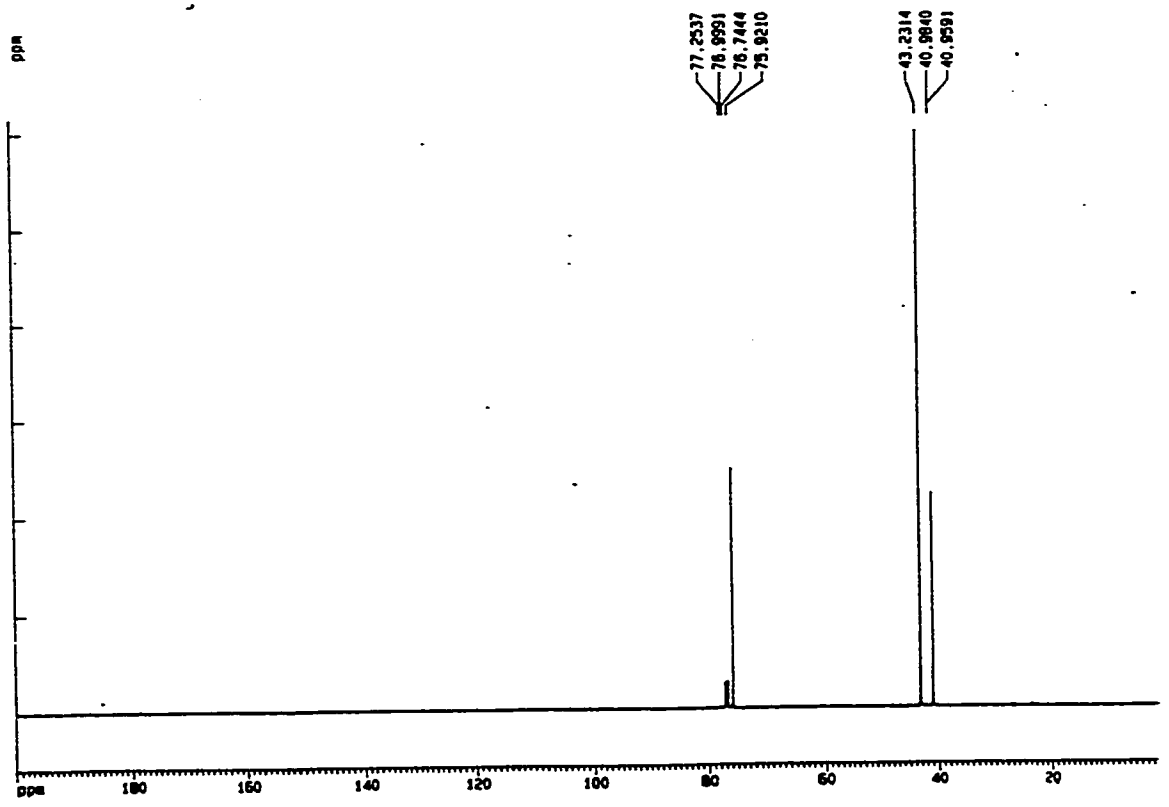

OH
Ph
Ph
N
NH2
10
9
8
7
6
5
4
3
2
1 PPM

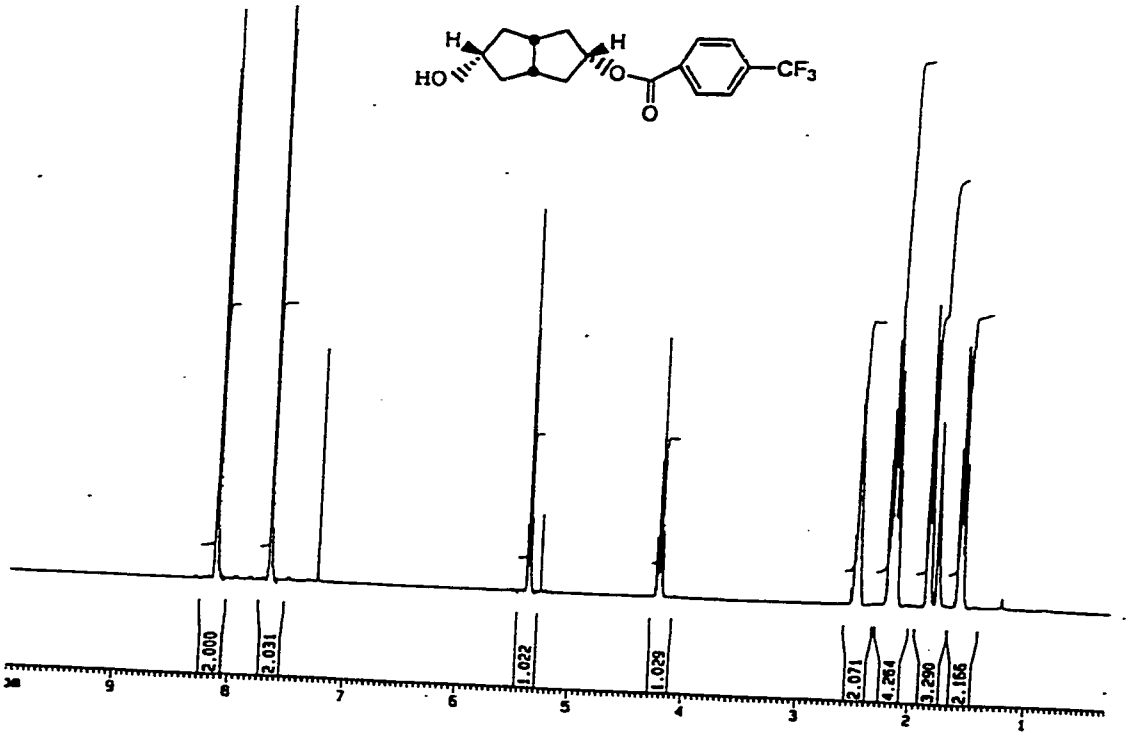

80
79
78
77
76
75
74
73
72 PPM 71
200
180
160
140
120
100
80
60
40
20 PPM
0

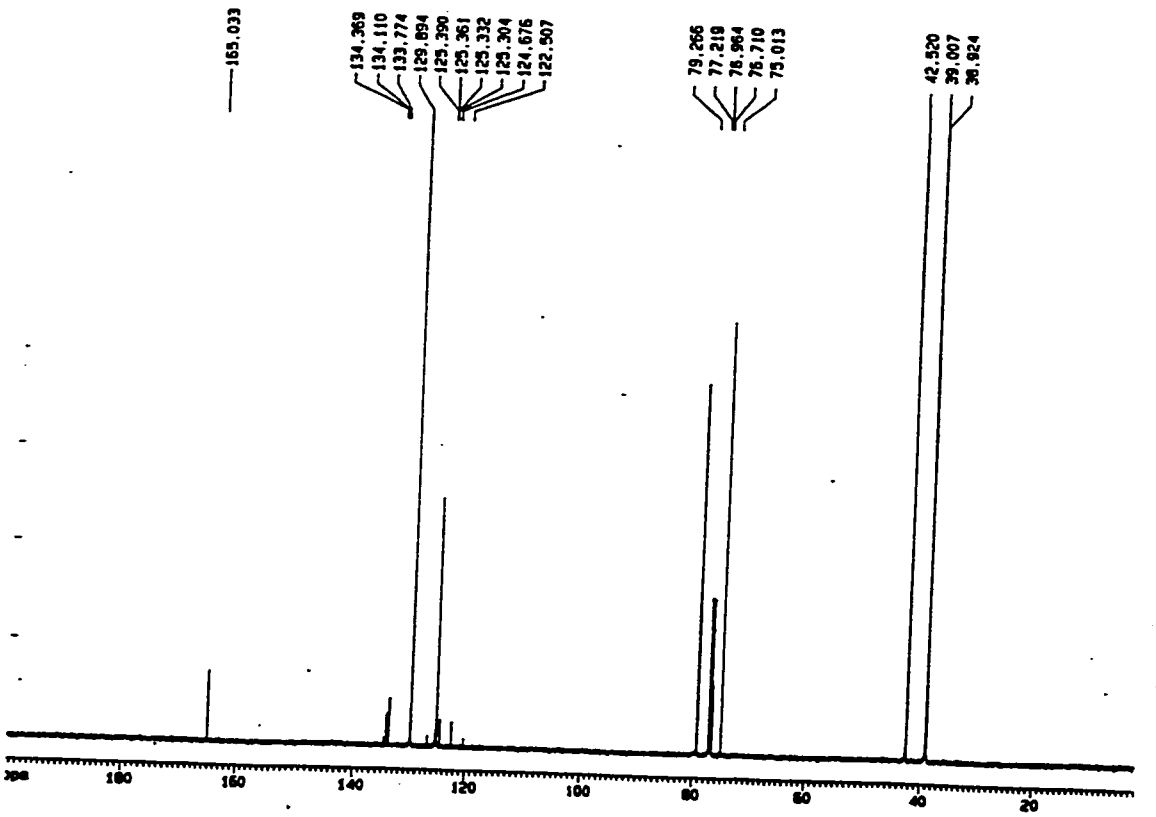

OH
Ph
Ph
N
N
H
Br
CH3
9
8
7
6
5
4
3
2
1 PPM

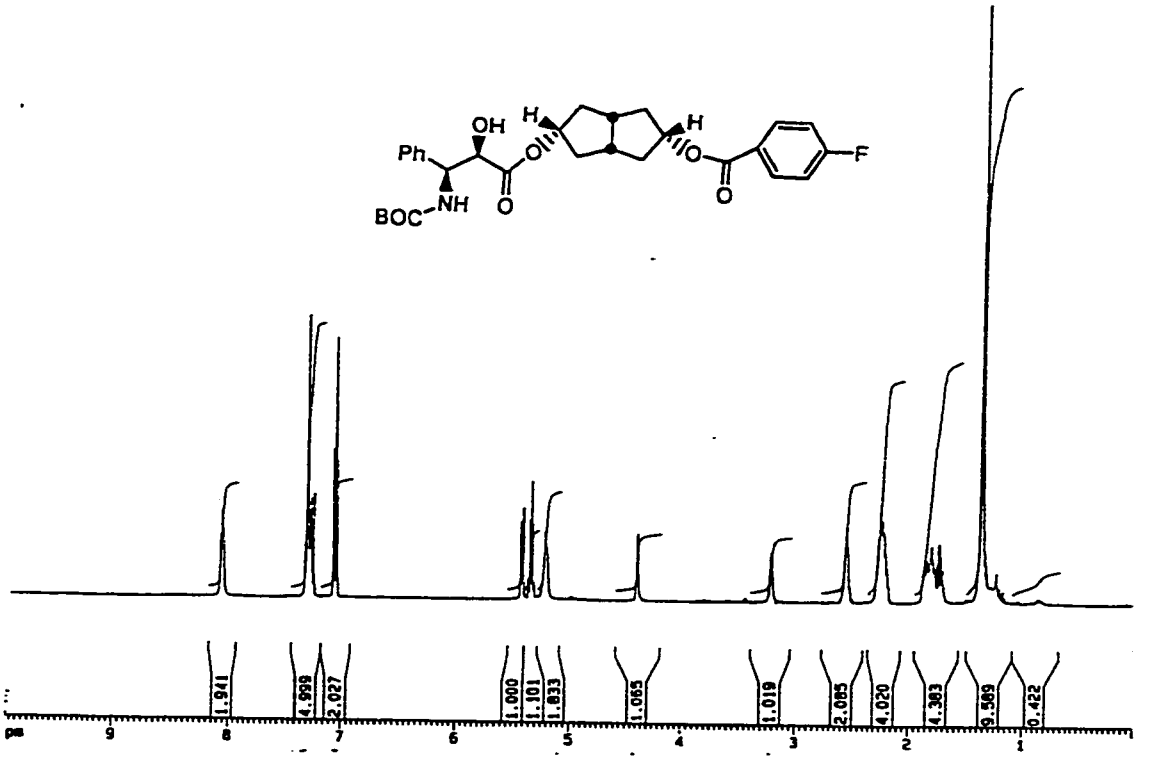

200
180
160
140
120
100
80
60
40
20 PPM
0

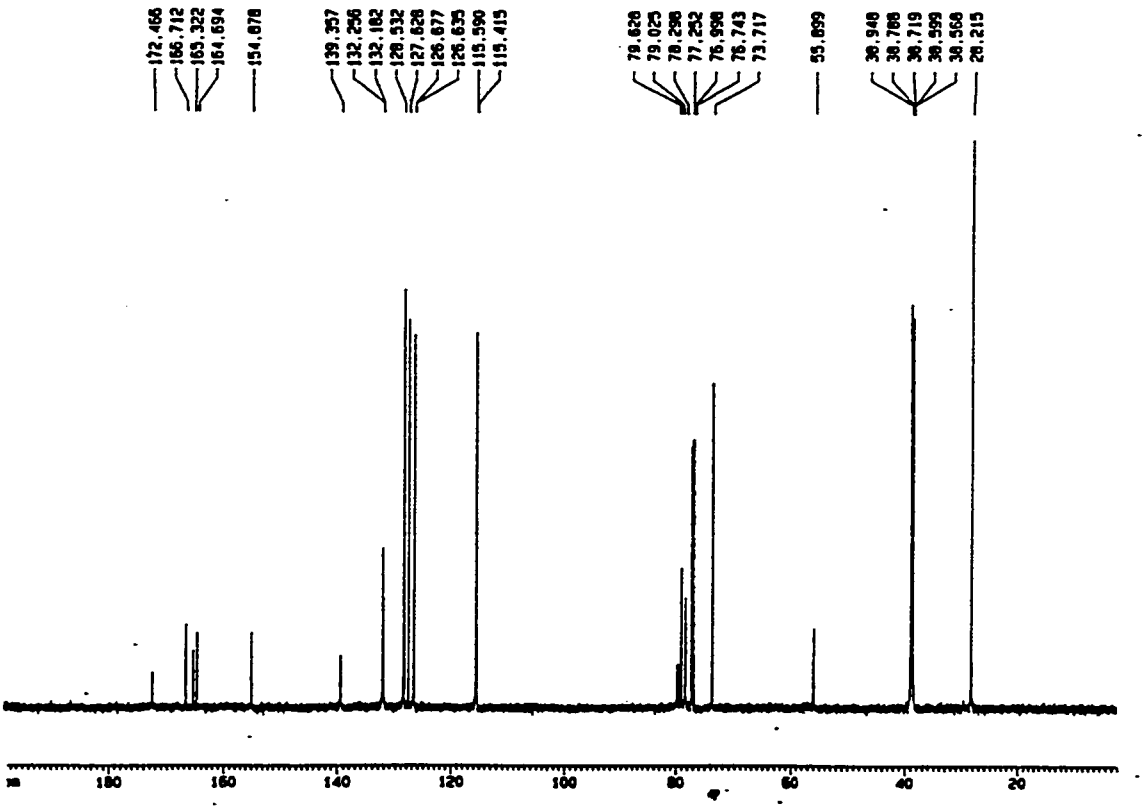

H
HO
H
OH
2.000
2.022
2.005
4.055
4.058
9
8
7
6
5
4
3
2
1

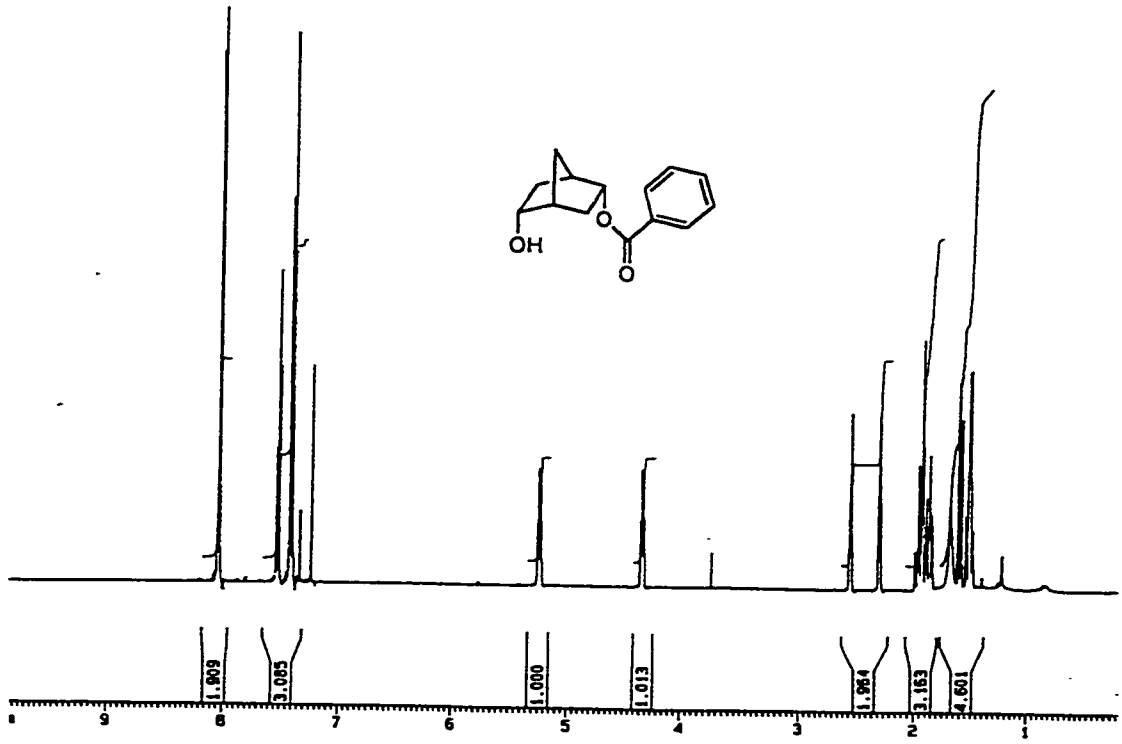

ppm
77.2537
76.9991
76.7444
75.9210
43.2314
40.9840
40.9591
ppm
180
160
140
120
100
80
60
40
20

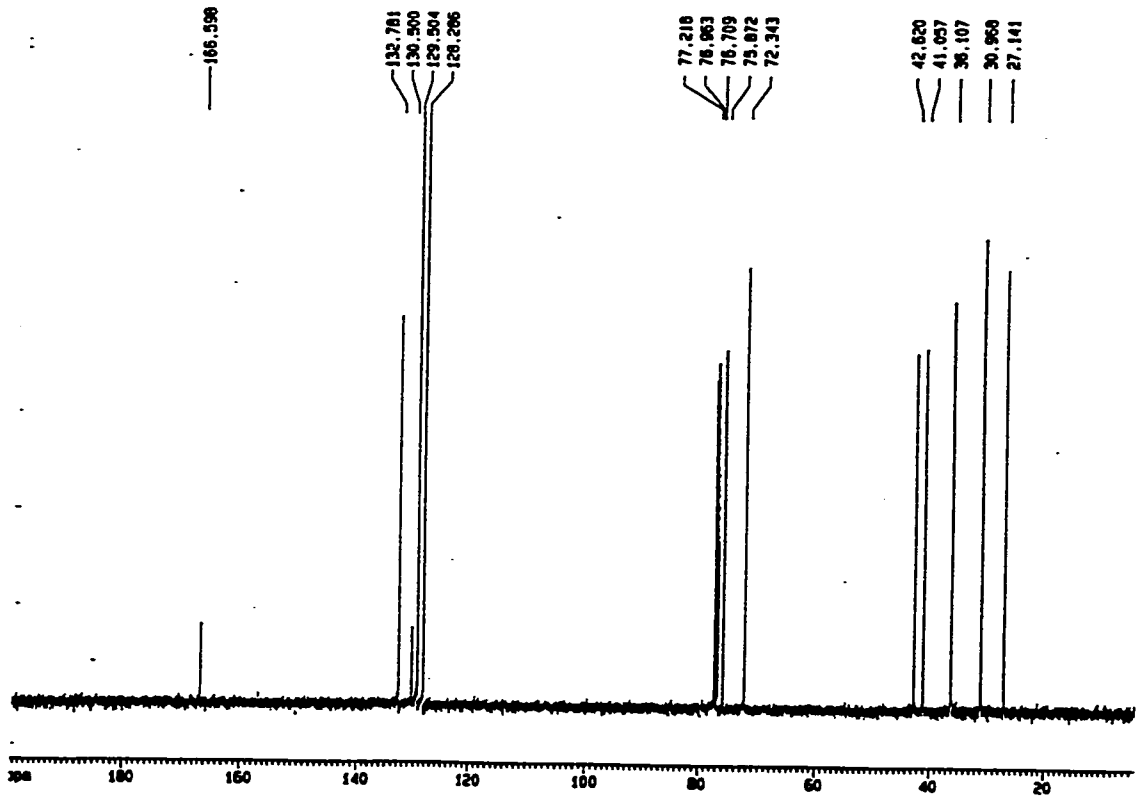

H
HO
H
O
O
CF3
2.000
2.031
1.022
1.029
2.071
4.264
3.290
2.166
9
8
7
6
5
4
3
2
1

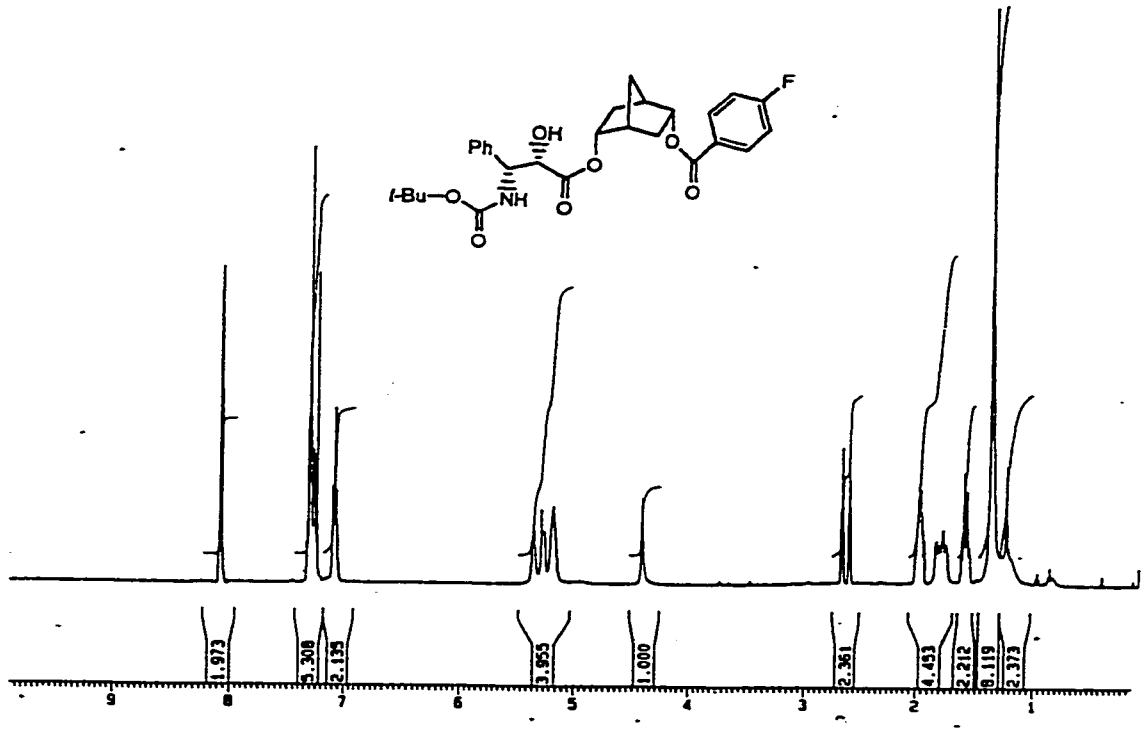

165.033
134.369
134.110
133.774
129.894
125.390
125.361
125.332
125.304
124.676
122.507
79.266
77.219
76.964
76.710
73.013
42.520
39.007
38.924
160
150
140
120
100
80
60
40
20

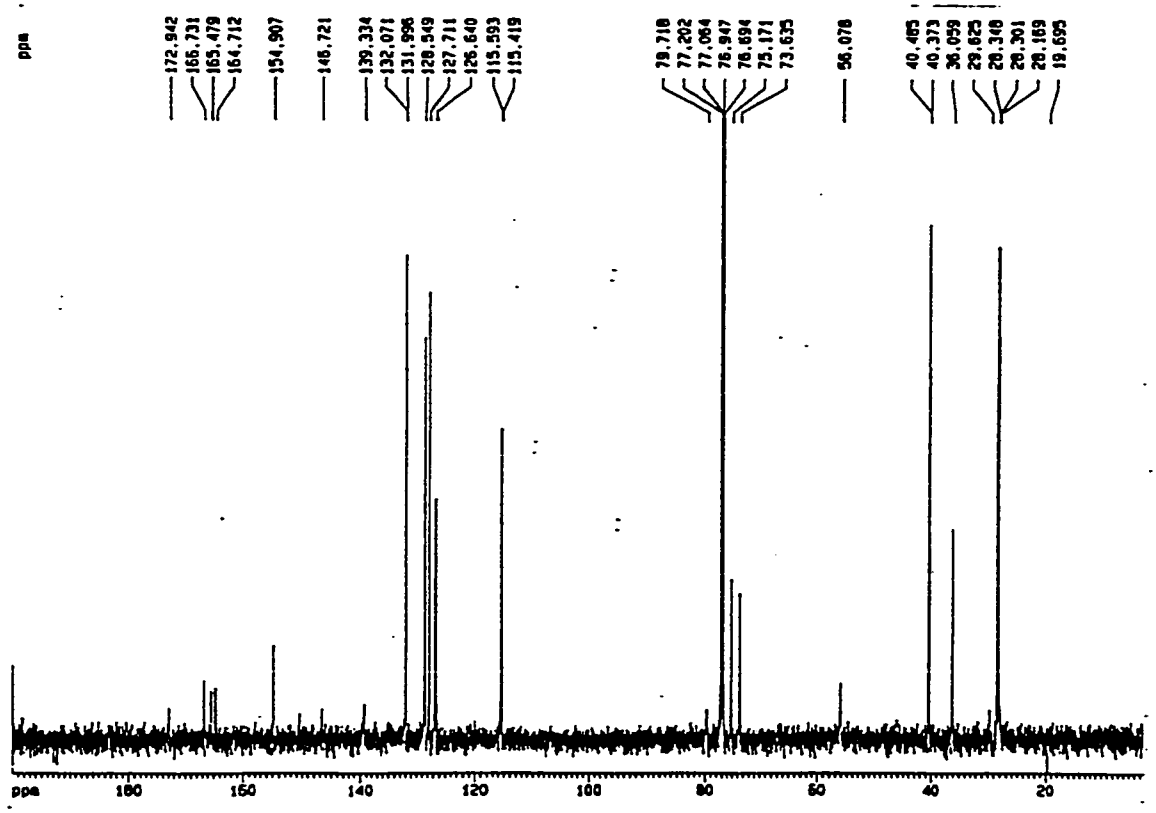

OH
H
H
Ph
O
O
F
NH
O
O
BOC
1.941
4.999
2.027
1.000
1.101
1.833
1.065
1.019
2.085
4.020
4.303
9.569
0.422
9
8
7
6
5
4
3
2
1


172.466
166.712
165.322
164.694
154.878
139.357
132.256
132.182
128.532
127.828
126.877
126.635
115.590
115.415
78.826
79.025
78.298
77.252
76.998
76.743
73.717
55.899
30.946
30.788
30.719
30.599
30.566
28.215
180
160
140
120
100
80
60
40
20


OH
O
O
1.909
3.085
1.000
1.013
1.964
3.163
4.601
9
8
7
6
5
4
3
2
1


166.590
132.781
130.500
129.504
128.286
77.218
76.963
76.709
75.872
72.343
42.620
41.057
36.107
30.958
27.141
180
160
140
120
100
80
60
40
20


Ph
OH
t-Bu—O
NH
O
O
O
O
F
11.973
5.308
2.135
3.955
1.000
2.361
4.453
2.212
6.119
2.373
9
8
7
6
5
4
3
2
1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165.479
164.712
154.907
146.721
139.334
132.071
131.996
128.549
127.711
126.640
115.593
115.419
79.718
77.202
77.064
76.947
76.694
75.171
73.635
56.078
40.485
40.373
36.059
29.625
28.348
28.301
28.169
19.695
ppm
180
160
140
120
100
80
60
40
20