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Remote Dianions in the Synthesis of Indolizidine Alkaloids

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Indolizidine alkaloids are an important class of compounds possessing diverse and potent biological activities. A novel synthetic route for the preparation of these alkaloids has been developed. The addition of the "remote" dianion of 4-(phenylsulfonyl)-butanoic acid (4-PSBA) to boron trifluoride etherate activated imines has been used to form 2-p[illegible]s. Extension of this methodology to the addition of the "remote" dianion of 4-PSBA to side-chain functionalized imines has provided 2-piperidones (lactams) that have been further manipulated to indolizidines. Further, the dianion addition-cyclization reaction sequence has been shown to proceed with diastereoselectivity. In the case of a chirally substituted imine, the reaction has been shown to proceed with enantioselectivity. This methodology has been employed in the synthesis of δ-coniceine and (+)-(1*S*, 8a*S*)-1-hydroxyindolizidine. The lactams synthesized are useful intermediates for elaboration to a wide variety of indolizidine alkaloid natural products.

LOYOLA UNIVERSITY OF CHICAGO

REMOTE DIANIONS IN THE SYNTHESIS OF INDOLIZIDINE ALKALOIDS

A DISSERTATION SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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LIST OF ABBREVIATIONS

[α]	optical rotation
anal	analysis
BOM	benzyloxymethyl
°C	degrees Celsius
calcd	calculated
cm	centimeter(s)
COSY	correlation spectroscopy
δ	chemical shift in parts per million
d	doublet
dt	doublet of triplets
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DME	dimethoxyethane
FID	flame ionization detection
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high-performance liquid chromatography
Hz	hertz
IR	infrared
J	coupling constant (in NMR)
μL	microliter(s)
mL	milliliter(s)
m	multiplet
M	moles per liter
m/z	mass to charge ratio (in mass spectrometry)
MHz	megahertz
min	minute(s)
mmol	millimole(s)

mp	melting point
Ms	methanesulfonyl (mesyl)
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
4-PSBA	4-(phenylsulfonyl)butanoic acid
q	quartet
Rf	retention factor
rt	room temperature
s	singlet
t	triplet
TBDMS	tert-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	p-toluenesulfonyl (tosyl)
UV	ultraviolet

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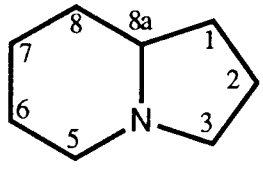
Chapter 1
Introduction

The Indolizidine Alkaloids

Indolizidine alkaloids possess the 1-azabicyclo[4.3.0]nonane skeletal structure **1**. The generally accepted numbering convention is also indicated. The simplest compound of this class is indolizidine itself, also known as δ-coniceine (**1**). In early literature references, this molecule also was referred to as octahydroindolizine, octahydropyrindole, piperolidine, and octahydropyrrocoline.



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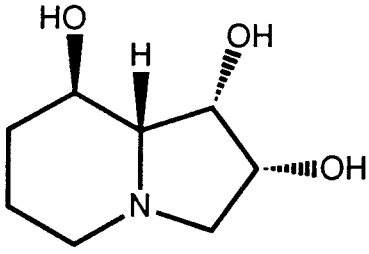
The indolizidine structure is found in a wide variety of natural products originating from plant, fungal, and animal sources. The more complex indolizidine natural products include (-)-swainsonine (**2**), (+)-castanospermine (**3**), (±)-slaframine (**4**), (-)-monomorine (**5**), and the gephyrotoxins **6**. These compounds are of great current interest due to very interesting and diverse biological properties.



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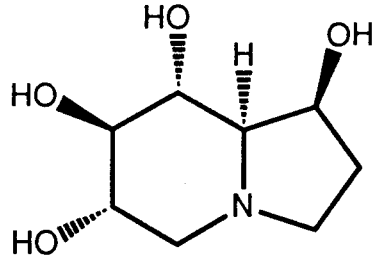

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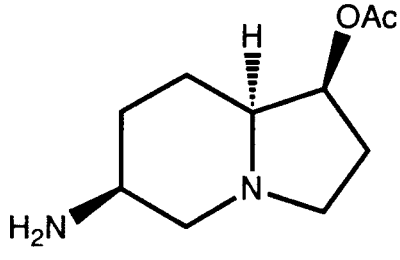

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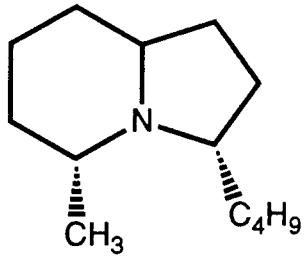

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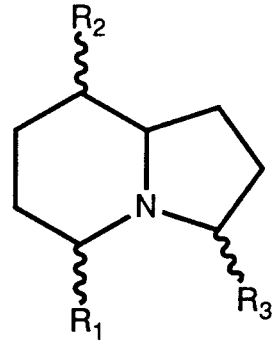


6 R_1= alkyl
R_2= H, alkyl
R_3= H, alkyl

Isolation and Biological Activities of Indolizidine Alkaloids

(-)-Swainsonine, (1*S*,2*R*,8*R*,8a*R*)-1,2,8-trihydroxyindolizidine (**2**), is isolable from the fungi *Rhizoctonia leguminicola* [1] and *Metarhizium anisopliae* F3622[2] as well as the plants *Swainsona canescens* ,[3] *Astragalus lentigenosus* (locoweed),[4] *Astragalus emoryanus* [5] and *Oxytropis sericea*.[4] Swainsonine is a potent inhibitor of mammalian lysosomal α-mannosidase, which functions in the degradation of the oligosaccharide portion of various glycoproteins.[6] **2** also has been shown to inhibit Golgi mannosidase II.[7] The inhibition of these mannosidases was determined to be very specific as swainsonine does not inhibit other glycosidases including other mannosidases, and the inhibition appears to be of the competitive type.[8] The inhibition of α-mannosidase indicates possible interference in the biosynthesis of N-linked glycoproteins. Experimental results showed that swainsonine altered the oligosaccharide structure of the glycoproteins studied although this change resulted in insignificant effects on the cellular secretion and routing of the glycoproteins.[9] **2** was found not to inhibit the degradation of non-glycoproteins.[10]

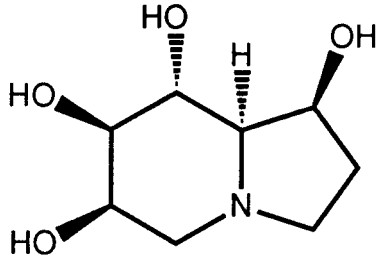
In mammals, swainsonine was found to be the causative agent of locoism from the ingestion of locoweed.[11] Abortion, birth defects and sometimes death can be caused by locoweed consumption. The effects are due to both the lysosomal α-mannosidase inhibition and the abnormal glycoprotein processing, which results in the storage of abnormally

processed asparagine-linked glycans.[12] Therapeutically, swainsonine has been shown to be an immunomodulator that could have possible applications in cancer chemotherapy.[13]

Castanospermine (**3**), (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine, has been isolated from *Castanospermum australe*,[14] a leguminous tree indigenous to Australia. These trees are also now found in southern California as ornamentals. **3** is found in the leaves, bark and seeds of the tree, with mature seeds containing the largest concentration (0.3%).[15] Consumption of the seeds results in severe gastroenteritis, which is often fatal in cattle. Human poisoning from raw seeds has also been reported.[16]

Castanospermine has been found to be a potent and specific inhibitor of β-glucosidase. In general, other glycosidases are not inhibited by **3**, one exception being fibroblast extracts that contain a lysosomal α-glucosidase, which is also susceptible to inhibition by this alkaloid.[15] At pH 6.5, castanospermine was determined to be a competitive inhibitor of β-glucosidase.[17] It has been determined that the sometimes fatal gastrointestinal disorder in animals which have ingested *Castanospermum australe* seeds is due to the presence of castanospermine.[18] In high doses, **3** also inhibits intestinal maltase and sucrase causing severe diarrhea. This effect has been overcome by inclusion of glucose in the diets of test animals.[19] Recent reports indicate that the glycoprotein processing inhibition may enable **3** to find applications as an antitumor agent,[20-24] antiviral,[25-29] and anti-AIDS agent.[30,31]

Also present in the seeds of the *Castanospermum australe* are small quantities of 6-*epi*-castanospermine (7). This compound is a very weak inhibitor of β-glucosidase, but a potent inhibitor of amyloglucosidase.[32] This specificity emphasizes the importance of the stereochemical arrangement in determining the inhibitory potency.



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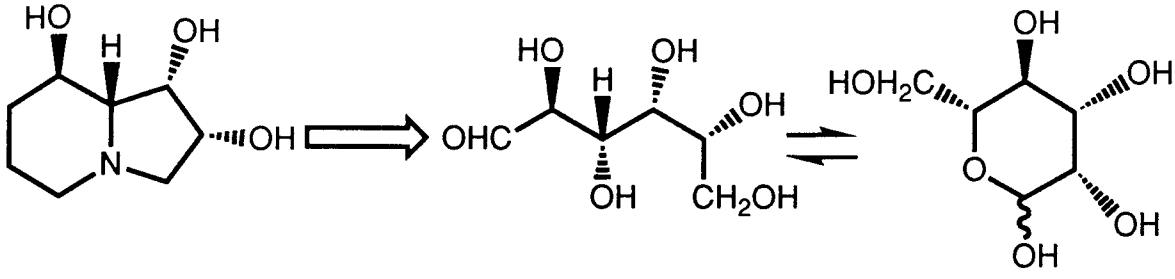
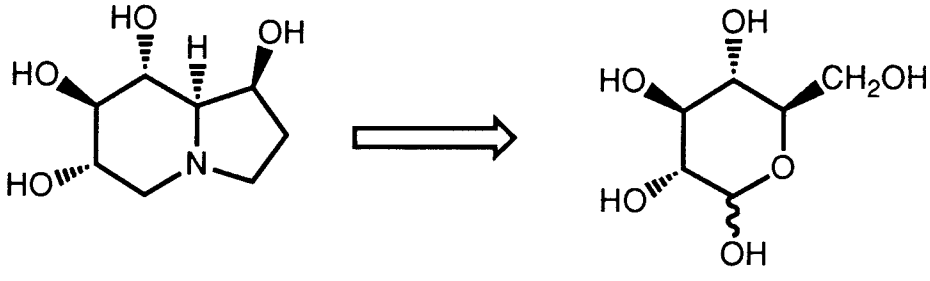
The specificity of these glycosidase inhibitors has been theorized to be due to the structural resemblance of the alkaloid to the specific sugar of which processing is inhibited (see Figure 1). The corresponding glycopyranosyl cations of the sugars are likely intermediates in reactions catalyzed by the glycolases, again structurally resembling the protonated form of the indolizidines, the predominant species at biological pH. Molecular modeling studies have been done to produce an inhibition model that fits the known data for these enzyme binding reactions and perhaps allows for the prediction of inhibition by new substrates.[33]

FIGURE 1



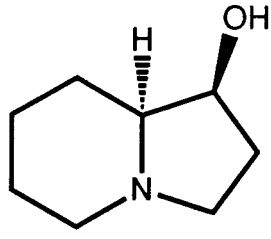
Structural similarity between swainsonine and D-mannose



Structural similarity between castanospermine and D-glucose

Slaframine (**4**), (1*S*,6*S*,8a*S*)-1-acetoxy-6-aminoindolizidine, is isolated from the fungus *Rhizoctonia leguminicola*.[34] This fungus is also a source of swainsonine (**2**), and both **2** and **4** are biosynthesized from the same intermediate- pipecolic acid via (1*S*,8a*S*)-1-hydroxyindolizidine (**8**).[35] Slaframine causes excessive salivation in cattle grazing on fungus-infected red clover hay.[36] **4** is not bioactive as shown, but is oxidized *in vivo* into a compound that associates with muscarinic acetylcholine receptors.[37] This interaction indicates the possible use of **4** to locate acetylcholine receptor

sites. Additionally, slaframine has been cited as a possible therapeutic for the relief of symptoms associated with cystic fibrosis.[38]



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Monomorine I (**5**) has been isolated from *Monomorium pharaonis L.*, the Pharaoh ant.[39] It is one of the more important trail hormones of this species.[40] Interest in this alkaloid arises due to the possibility of pheromonal control of Pharoah ants, common pests in European hospitals that carry harmful bacteria and often escape normal pesticidal control.

The gephyrotoxin alkaloids **6** consist of 22 natural products which have been isolated from the skin secretions of the neotropical poison-dart frogs belonging to the genus *Dendrobates*.[41] These alkaloids vary in substitution patterns from single substituents at C-5 to substitution at C-3 and C-5 or C-5 and C-8. Many of the structures of the bicyclic gephyrotoxins have not yet been completely elucidated. These alkaloids are potent competitive inhibitors of neuromuscular transmission.[42] Pharmacologically, these compounds are of interest in that the stereochemical requirements of the acetylcholine receptor complex binding site may be probed, providing for possible applications in neurotoxin and Alzheimer's research.

Previous Syntheses

Synthetic strategies for the preparation of the indolizidine alkaloids in both racemic and optically active forms have been the subject of many recent reports. Several excellent reviews covering the syntheses of compounds of this class are available, with updated reports appearing regularly in several sources.[43-45] This review is limited to those indolizidines that either have been prepared or can be easily accessed from the intermediates presented in this dissertation. δ-coniceine (**1**) was first synthesized in 1885 by Hofmann,[46]with the structure of the product yet unknown. The structure was later confirmed in an 1890 synthesis by Lellman.[47] Although this molecule is not a naturally occurring alkaloid, it provides an ideal model target molecule to show the viability of synthetic strategies directed toward the preparation of this class of compounds. In fact, synthetic interest in this simple bicyclic system has produced no fewer than 34 literature reports of the synthesis of δ-coniceine. Hofmann utilized the cyclization of N-bromoconiine with sulfuric acid for the first synthesis of **1** . This method has become known as the Hofmann-Löffler-Freytag reaction and has been employed and refined by several groups in the synthesis of (±)-δ-coniceine as well as optically active (+)-**1** (α_D=+9.3,c 1.77, ethanol) and (-)-**1** (α_D=-10.2,c 1.76, ethanol).[48-50] In addition, this method was extended to include the preparation of 3-methylindolizidine.[51] Schell et al. have obtained (±)-**1** via a silver induced rearrangement of N-

chlorogranatine.[52] Several groups have utilized a variety of cyclization conditions with 2-(3-hydroxypropyl)-piperidine to obtain (±)-δ-coniceine in varying yields (42-85%).[53-58] The distinguishing characteristics of the synthesis of **1** by Danishefsky and co-workers include hetero-mercuration followed by reductive coupling.[59] The synthesis of **1** by Branchaud effects one-step closure of both the five- and six-membered rings while exploring the use of the tritylsulfenyl nitrogen protecting group.[60] Meyers et al. have used the alkylation of α-metallo-formamidines in the development of a general route to 1-azabicyclic compounds, including **1**.[61] Hua and co-workers have utilized the annulation of an α-sulfinyl ketimine anion to 1,3-diiodopropane as a key step to produce **1**.[62,63] In a somewhat different approach, annulation of the six-membered ring onto the five-membered ring of chiral proline derivatives has provided (-)-1 as well as (+)-(1S,8aS)-1-hydroxyindolizidine.[64] Three groups have reported the synthesis of δ-coniceine employing transannular ring cyclizations.[65-67] Stevens et al. utilized a cyclopropylimine rearrangement as a key step in the synthesis of **1**.[68] Improvements on this synthesis have been reported recently by Pearson and coworkers.[69,70] The subsequent cyclization of the N-alkyl intermediate (at the α-position) represents a ring formation common to several subsequent syntheses. For example, Hart and Tsai utilized the cyclization of α-acylamino radicals;[71] Shono et al. employed a [3+3]-type annelation;[72] and Gmeiner and Lerche utilized an intramolecular cationic cyclization onto the 2-position of a pyrrole derivative.[73] Pizzorno and Albonico employed 1,3-dipolar cyclization as the key step in the

synthesis of **1** in a synthetic strategy which could be applied to a variety of octahydroindolizidines.[74] Weinreb's group utilized the intramolecular imino Diels-Alder reaction to produce **1** [75] while Gavina and co-workers employed the reaction of 2-aza-2,4-cyclopentadienone as a dienophile in the Diels-Alder process as a key step in the synthesis.[76,77] Radical additions to alkenes followed by cyclization steps similar to those of Danishefsky and co-workers have provided 1 as well as 1-hydroxyindolizidine.[78]

The conformation of **1** has been investigated. Although *cis* and *trans* fused isomers cannot be isolated due to rapid inversion at nitrogen, the presence of Bohlmann bands in the IR and calculations of the free energy differences of the conformers (+2.4 kcal/mol) indicate that the *trans* geometry predominates.[79] This conformation has been confirmed by ^{1}H NMR analysis of **1** and it's hydrobromide salt.[48] One additional report gives ^{13}C NMR data for **1**.[80]

Syntheses of **2** and **3** have mainly been accomplished utilizing carbohydrate derived starting materials, with only a few groups using non-carbohydrate based starting materials. The obvious advantage of carbohydrate precursors is the preset configurations of the chiral centers. The main drawback to these approaches lies in the difficulty of analogue preparation (especially deoxy analogues) as well as lack of versatility in the preparation of other non-oxygenated indolizidines such as **5** and **6**.

There have been eleven syntheses of swainsonine reported in the literature through 1990, of which only the methods of Sharpless et al.[81] and Hart et al.[82] use non-carbohydrate based starting materials. The

former method produced **2** in 6.6% overall yield from *N*-benzyl-p-toluenesulfonamide incorporating the well-known asymmetric epoxidations for the introduction of chiral centers. The latter strategy employed D-tartaric acid as the chiral precursor for the production of **2** via an α-acylamino radical cyclization. The syntheses of **2** by Richardson et al.[83] and Suami et al.[84] provided (-)-swainsonine in 3.3% and 4.0% yields, respectively, from similar mannose derived starting materials and following analogous routes. The synthetic method developed by Fleet and co-workers[85] yielded **2** in 21% yield, again from a mannose derived starting material with two consecutive reductive aminations effecting ring closure of both rings. The reported syntheses of **2** by Takaya et al[86] . and Hashimoto et al.[87] utilize D-mannose as the chiral precursor. The former process follows a similar route to that of Fleet's group, yet the differences result in very poor yields (0.3%). The latter method employs a one-step cyclization of an epoxy amine ester as the key step, but provides **2** in only 3% overall yield. A method for the preparation of swainsonine as well as several epimers was reported by Ikota and coworkers.[88] This synthesis exploits the chirality of an amino acid derivative to produce **2** and some epimers, although in somewhat poor overall yields. The biosynthesis of swainsonine by *Astragalus oxyphysus* has been studied and shown to proceed via a pathway similar to that of production of **2** in the fungus *Rhizoctonia leguminicola.* Both syntheses are accompanied by production of 1-hydroxyindolizidine as well as 1,2-dihydroxyindolizidine.[89] A recent report has included the syntheses of not only swainsonine, but also some

related ring contracted pyrrolizidines from mannose derived starting materials.[90] One additional report employs an intramolecular 1,3-dipolar cycloaddition of an olefinic azide as the key step in the preparation of **2** from an erythrose derivative.[91]

Several reports provide for syntheses of stereoisomers of swainsonine. Takaya et al.[92] report the syntheses of 2,8-di-*epi*-swainsonine and 8-*epi*-swainsonine from D-glucose, by a one-step double cyclization process similar to that devised by Hashimoto.[87] The yields of this route were very poor, however, producing the isomers in 1.5% and 0.2%, respectively. Suami et al.[93] synthesized 8-*epi*-swainsonine and 1,8-di-*epi*-swainsonine from glucose derivatives following an analogous route as that used in the swainsonine synthesis. The yields of these isomers were somewhat higher at 4.3% and 3.2%, respectively. The synthesis of 8a-*epi*-swainsonine by the same group via an azido-sugar prepared from glucose was reported shortly thereafter.[94] The 2,8a- and 8,8a-swainsonine epimers also have been synthesized by a similar route.[95] The synthesis of several polyhydroxy glycosidase inhibitors, including 8-*epi*-swainsonine, from a common glucose derived intermediate has appeared in a recent report.[96] In a similar pathway to that used in the synthesis of swainsonine, Ikota and Hanaki have prepared 1-*epi*-swainsonine and 1,8-di-*epi*-swainsonine from an amino acid derivative.[97] Finally, the 8-, 8a-, and 8,8a-di-epimers of swainsonine have been synthesized by Kim and Cha in divergent syntheses from the same erythrose derivative utilized in that group's synthesis of swainsonine.[98]

(+)-Castanospermine (**3**) has been the subject of a large body of synthetic work. Ganem and co-workers have reported two enantiospecific syntheses of **3** from glucose derivatives, the second of which provides (+)-castanospermine in a very efficient 19% overall yield.[99,100] Hashimoto et al. prepared **3** employing an analogous route as that utilized in their synthesis of swainsonine[92] starting with D-mannose.[101] In a very extensive study of the synthetic utility of "naked sugars", 7-oxanorborn-5-en-2-yl derivatives, Vogel and co-workers synthesized (±)-castanospermine,[102] 6-deoxy derivatives,[103] and several other biologically interesting molecules.[104] The enantiospecific syntheses of (-)-swainsonine (**2**) and (+)-castanospermine (**3**) have been effected via the corresponding hydroxylactams derived from monosaccharide lactones.[105] A relatively short (10 step) enantioselective synthesis of **3** from a glucuronolactone derivative has also been reported.[106] Finally, a chemoenzymatic route to **3** has been reported, employing microbial lipases in the preparation of a chiral pyrrolidine starting material.[107]

The syntheses of several analogues of **3** have been reported. 1-deoxy-castanospermine has been prepared.[108,109] The natural product that is present in smaller quantities in the natural source, 6-*epi*-castanospermine, has been synthesized along with 1,6-di-*epi*-castanospermine and their enantiomers, and the activity against amyloglucosidase studied.[110] The results show that only the natural product is active in inhibition of this enzyme, although other enzymes were not studied. The natural product has been isolated in sufficient quantity to

allow for studies on the selective acylation of (+)-castanospermine by enzymes,[111] as well as through traditional chemical transformations.[112] Finally, 6-acetamido-6-deoxy-**3** has been prepared and shown to be a potent inhibitor of β-N-acetylglucosaminidases, enzymes which have possible implications in tumor metastasis.[113]

Racemic slaframine (**4**) was first synthesized in 1970 from 2-bromo-5-nitropyridine.[114] This investigation also included the preparation of an isomeric compound, the structure of which had incorrectly been assigned to slaframine, synthetically establishing the true structure of **4**. Gensler and Hu effected stereoselective synthesis of **4** starting with a glutamic acid derivative.[115] Both of these synthetic strategies were highlighted by Dieckmann conditions to effect second ring cyclization. More recently, Weinreb and co-workers have utilized an intramolecular imino Diels-Alder approach in the preparation of slaframine, a method that simultaneously produced 1-*epi*-slaframine.[116] Harris and Schneider reported an efficient stereoselective synthesis of **4** providing an overall yield of 12% from a picolinic acid derivative.[117] The same group also later reported an extensive study of the biosynthesis of slaframine and swainsonine from 1-hydroxyindolizidine.[118] The reaction of potassium thalidomide and substituted cyclopropylphosphonium salts has been used as the key step in the preparation of racemic **4** as well as racemic 6-*epi*-slaframine.[119] Shono and co-workers have applied anodic oxidation to a lysine derivative[120] to supply an intermediate that appears in the aforementioned synthesis of slaframine by Schneider and Harris, providing a formal

synthesis of **4**. Finally, in a very recent report, the reductive cyclization of azido epoxides accomplished cyclization of both rings of the bicyclic system in one step, and was employed in the first preparation of optically pure (-)-slaframine and (-)-1,8a-di-*epi*-slaframine.[121]

Syntheses of hydroxyindolizidines related to **2**, **3**, and **4** also have been accomplished. The four possible stereoisomers of 1-hydroxyindolizidine have been synthesized in order to assist the study of the biosynthesis of swainsonine (**2**) and slaframine (**4**).[122] The preparation of *cis*-1-hydroxyindolizidine has been reported,[123] and the enantiospecific preparation of (+)-(1S,8aS)-1-hydroxyindolizidine as described previously.[63] Another biologically important analogue, 1,2-dihydroxyindolizidine, is cited as a precursor in the biosynthesis of swainsonine in the fungus *Rhizoctonia leguminicola*. This product has been synthesized, both chemically[124] and biologically,[125] and studied as a possible inhibitor of glucosidases. Although enzyme inhibition studies were not extensive, the data suggested that the weak inhibition of glucosidases by this compound indicated that the presence of a hydroxy-functionality at the 8-position was necessary for potent activity. In one final report, 6,7-dihydroxyindolizidine and 6,7,8-trihydroxyindolizidine were synthesized and tested for enzyme inhibition. The results showed both compounds to be very weak and non-selective inhibitors, also suggesting that substitution at the 1-position is necessary for potency and selectivity of these compounds in the inhibition of glucosidases.[126]

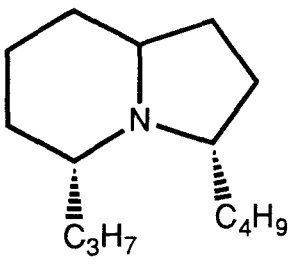
Some related polyhydroxy monocyclic heterocycles such as piperidines (nojirimycin and analogues)[127-130] and pyrrolidines,[131-133] and carbocycles[134] are potent anti-glycosidases. Polyhydroxypyrrolizidine alkaloids also have been the subject of recent investigations.[135,136] Studies have been undertaken to decipher the relationship between structure and biological activity of these compounds in order to design optimum therapeutic action.[137,138] Much work remains to be done in this area of research.

Monomorine (**5**) also has been the focus of a large amount of synthetic work. Oliver and Sonnet synthesized four possible stereoisomers of monomorine from 2,6-lutidine in order to unambiguously assign the structure of the natural product, (+)-monomorine, as 3R,5S,8aS.[139,140] This synthetic strategy also was used to decipher ^{13}C NMR assignments of indolizidines.[141] The stereoselective preparation of **5** from a substituted pyrroline and 1,4-dibromopentane has been reported by Macdonald.[142] Stevens and Lee have employed reductive amination conditions for the formation of (±)-monomorine.[143] The first enantiospecific preparation of (-)-**5** was conducted in 1985 establishing the configuration of the natural product as (+)-monomorine.[144] Further stereoselective routes to **5** have been effected from a hetero Diels-Alder intermediate[145] and through a-alkynylation of a 1-acylpyridinium salt.[146] Another enantioselective synthesis starting from a tartrate derivative has provided (+)-monomorine, the first enantiospecific preparation of the natural product.[147] Racemic **5** was prepared during the exploration of the utility of rhodium(II)-acetate

catalyzed decomposition of an intermediate diazo-compound,[148] and during method development for the preparation of ω-methyl lactams via reductive cyclizations of oxime intermediates.[149] Two very recent enantioselective syntheses were successful using asymmetric cleavage of a cyclic ketone[150] and asymmetric 1,3-dipolar nitrone cycloaddition.[151]

Far fewer syntheses of gephyrotoxin 223AB (**9**) have been completed, although the alkyl-indolizidines have received much synthetic interest. There are four stereoselective syntheses of **9** reported through 1990. Of these, the methods of Kibayashi and co-workers[152,153] and Stevens and Lee[154] parallel those reported for the synthesis of **5**. One additional synthesis of gephyrotoxin 223AB used a highly stereoselective radical cyclization.[155]

The pumiliotoxins are related dendrobatid alkaloids that consist of a large number of indolizidine structures. The indolizidines in this class are generally much more complex and will not be covered here. Other simple dendrobatid indolizidines have been isolated and the structures determined. These have been assigned numbers corresponding to their mass spectral parent ion peak and a few syntheses of these compounds have appeared in the recent literature. The 1,3-dipolar nitrone cycloaddition methodology has been applied to the preparation of indolizidines 167B (**10**), 205A (**11**), and 207A (**12**),[156] and the enantioselective synthesis of (-)-209B (**13**).[157] The alkylation of a common intermediate, an amino nitrile, was used to provide both indolizidine 167B and 209D (**14**).[158]



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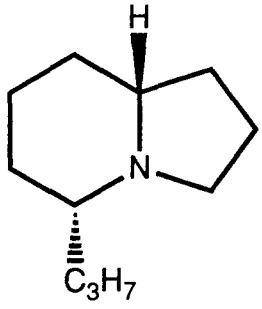

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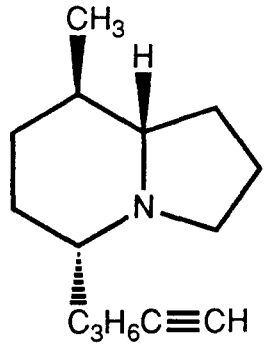

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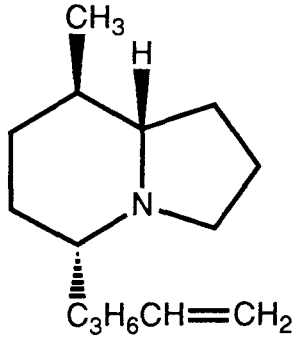

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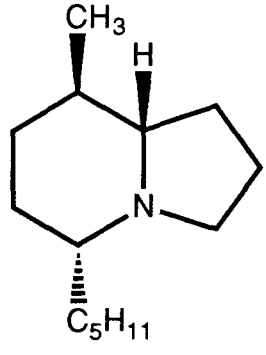

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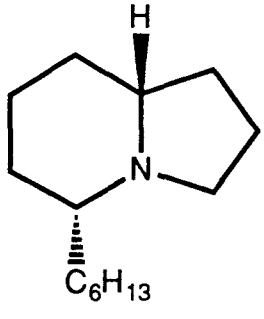
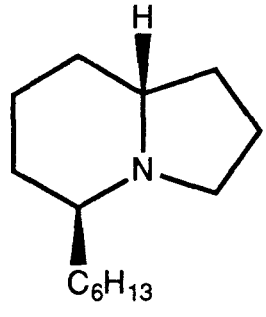


or

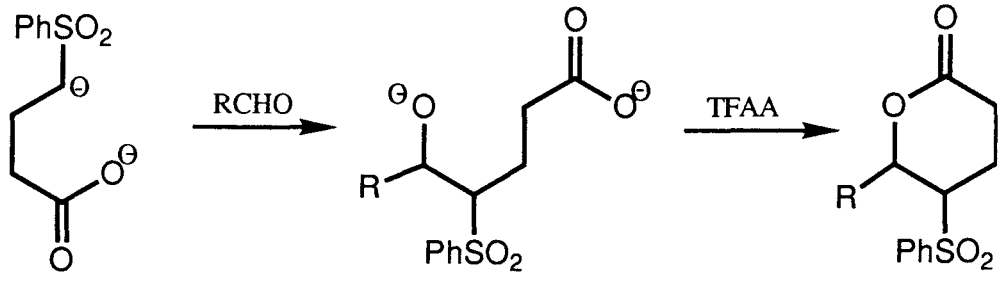


14

Synthetic Approach- Historical

Previous experimentation in our laboratory showed that the dianion of 4-(phenylsulfonyl)-butanoic acid (**4-PSBA**) (**15**) can be added to carbonyl compounds followed by subsequent cyclization to provide a very efficient one-pot procedure for the synthesis of lactones.[159] (Scheme I)

SCHEME I



15

R	YIELD(%)
n-C_3H_7-	77
CH_3CH=CH-	75
Ph	84
PhCH=CH-	72
n-C_7H_{15}-	65
tert-C_4H_9-	85

Extension of this methodology to the preparation of four-carbon homologated carbonyls provided an easily accessible alternative to Wittig

and Reformatsky transformations,[160] and has been incorporated into the synthesis of a pheromone natural product.[161]

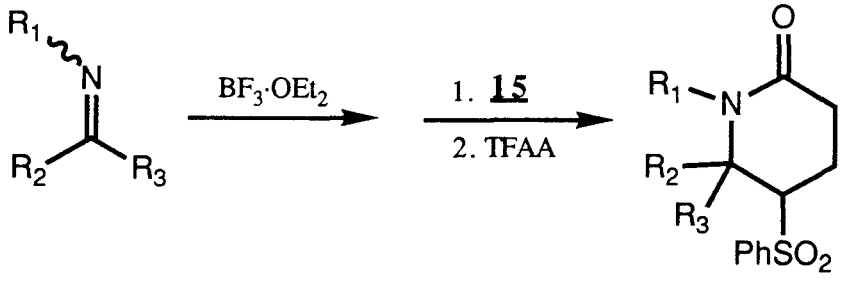
Broadening the scope of this synthetic strategy to the preparation of nitrogen heterocycles requires reaction with nitrogen-containing electrophiles isoelectronic with carbonyls, namely, imines.

The addition of carbon-based nucleophiles to imines has been well documented, yet underused in actual synthetic pathways. The chemistry of imines has been reviewed,[162] as has the most common nucleophilic addition reaction; lithium ester enolate-imine condensation (Reformatsky-type).[163] This condensation has been used in the preparation of a wide variety of β-lactams. Additional common reactions of imines with nucleophiles include reaction with Grignard reagents to give substituted amines[164,165] and Lewis acid-catalyzed addition of silyl ketene acetals to give β-lactams.[166] Other imine reactions of interest include the imino Diels-Alder reaction employing activated imines and dienes.[167] Lithiated nucleophiles other than an ester enolate also have been used to provide substituted amines that are often formed in asymmetric additions or with chiral auxiliaries.[168,169] Yamamoto and co-workers have conducted a great deal of research on the Cram selectivity of the additions of organometallic reagents to imines, and showed that the Lewis acid necessary for the activation of the imine must be *syn* to the side chain R group.[170-173] Examination of the possible transition states provides a rationale for the observed *erythro* predominance in the case of relatively unhindered nucleophiles and imines. However, the diastereoselectivity of imine

additions was determined to be very dependent upon both the nitrogen R group and the side chain substitution, in contrast to the corresponding carbonyl additions. Only one report of the addition of dianions to imines has appeared, again employing a lithium ester enolate to provide substituted amines.[174]

In preliminary investigations, a variety of imines were prepared through standard condensation reactions of aldehydes and ketones with primary amines, and purified by distillation. These imines were subjected to addition reactions with the dianion of 4-PSBA followed by cyclization with trifluoroacetic anhydride to provide 2-piperidones in an efficient two-step procedure.[175] (Scheme II)

SCHEME II



R_1	R_2	R_3	YIELD(%)
n-Pr	n-Pr	H	70
CH_3	PhCH=CH	H	82
CH_3	Ph	H	90
$PhCH_2$	n-Pr	H	66
$PhCH_2$	$-(CH_2)_5-$		78
CH_3	citryl	H	85

citryl=$(CH_3)_2C=CHCH_2CH_2(CH_3)C=CH$

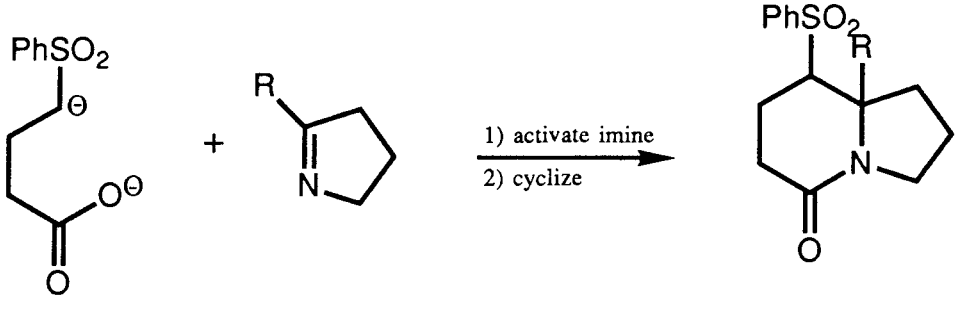
This investigation established the necessity of Lewis acid activation of the imines in order for addition to occur. Boron trifluoride etherate was chosen as the Lewis acid for this transformation over several other possibilities ($ZnBr_2$, $MgCl_2$, $AlCl_3$, $SnCl_4$, $Ti(O\text{-}ipr)_4$), all of which were shown to be inferior for obtaining the desired addition product. This synthetic method has broad application as there exists a multitude of biologically important piperidine-containing natural products.

Chapter 2

Results and Discussion

The initial approach to the construction of indolizidines envisioned the addition of the dianion of 4-(phenylsulfonyl)-butanoic acid (4-PSBA) (**15**) to appropriately activated cyclic imines (Scheme III). This strategy would effectively provide the indolizidine skeleton in one step from the imines.

Scheme III



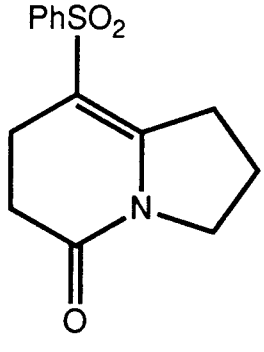
15

18 R= SCH_3

19 R=OCH_3

Our initial experiments concerned the addition of the dianion of 4-PSBA to cyclic imines with leaving groups (R) situated at the 2-position. This approach could provide, after subsequent structure manipulation, indolizidines that are unsubstituted at the 8a-position, the most common occurrence in simple natural products of this class. The two cyclic imines that were used in this study were the iminothioether **18** (R = SCH_3) and the

lactim ether **19** (R = OCH_3). The iminothioether was prepared via alkylation of the corresponding thioamide (2-pyrrolidone, Lawesson's reagent, toluene, reflux, 90%),[176] followed by free base liberation (50% KOH, diethyl ether extraction, 63%).[177] Boron trifluoride etherate activation of this product, followed by dianion addition-cyclization yielded primarily unreacted starting materials and a small amount of an addition product (<2%). This product exhibited spectra indicative of elimination product **20**. The major difficulties in the proper isolation of product most probably lies in the need for very pure starting materials (the iminothioether is very volatile and thus difficult to distill free from solvent) as well as problematic product purification. The crude reaction mixture was highly colored necessitating chromatographic purification. The very high polarity of the desired product causes some difficulties in elution with separation on silica columns. The enamine-type structure **20** would be expected to be sensitive to acids and nucleophiles complicating isolation.



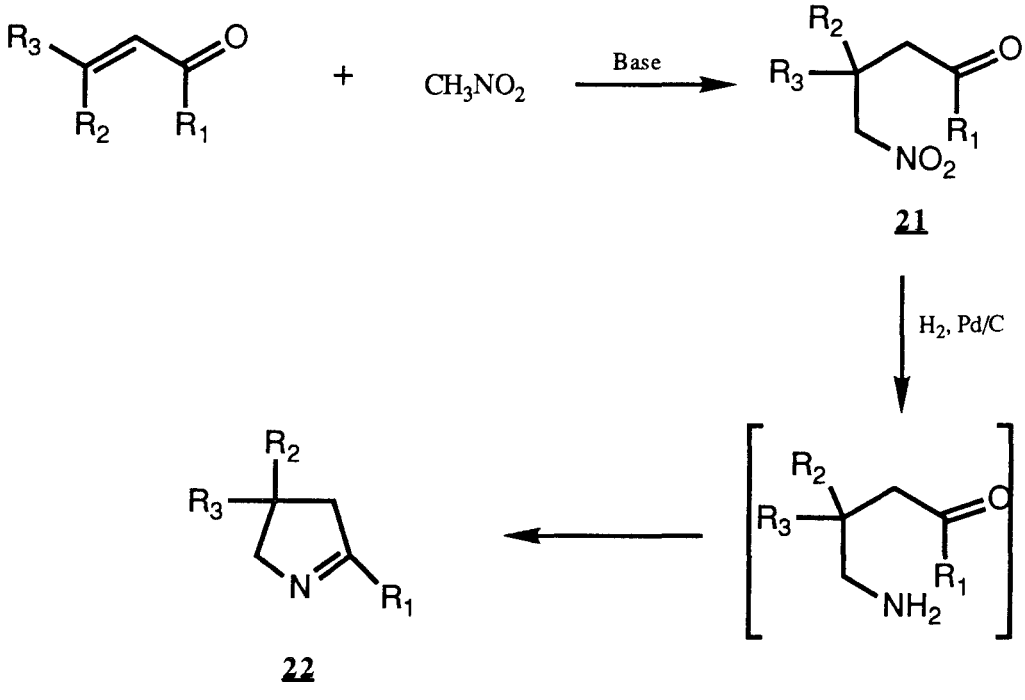
20

In 1984, Smith and co-workers reported the addition of organolithium nucleophiles to lactim ethers to provide 2-alkylated cyclic imines in moderate to good yields.[178] Thus, lactim ether **19** was prepared from 2-pyrrolidone (dimethyl sulfate, benzene).[179] In our hands, however, adequately pure lactim ether could not be isolated. Fractional distillation of the lactim ether (bp 118-120° C) from solvent was difficult. Additionally, it has recently been reported that upon heating, the lactim ether rearranges to N-methyl-2-pyrrolidinone.[180] Thus, we turned our attention to the addition of the dianion of 4-PSBA to alkyl-substituted cyclic imines (Scheme III, R=alkyl).

A search of the literature for methods for the preparation of cyclic imines revealed that rapid synthetic entry into these compounds needed augmentation. Bonnet et al.[181] reported the conversion of γ–nitrocarbonyls to cyclic alkyl imines. This strategy involves protection of the carbonyl as the cyclic ketal, followed by catalytic hydrogenation of the nitro group to the amine. Subsequent deprotection of the carbonyl results in spontaneous ring closure to provide the cyclic imines. Kloetzel[182] showed that direct hydrogenation of γ-nitrocarbonyls resulted in obtaining a mixture of both the desired cyclic imine and the overreduced cyclic amine, the latter being the predominant species. The conditions employed in this latter report were severe (very high H_2 pressures and temperatures). As the nitro group is especially susceptible to reduction by catalytic hydrogenation, we theorized that it might be possible to chemoselectively reduce the nitro-moiety in the presence of the unprotected carbonyl group.

We obtained the cyclic imines in good yields from γ-nitrocarbonyl compounds (obtained from a Michael addition of nitroalkanes to α,β-unsaturated ketones) using catalytic hydrogenation (H_2 pressures of less than 20 psi; Scheme IV). The imines were identified by a strong absorption in the IR at 1620 cm^{-1} (C=N). Further synthetic verification of the products included preparation of 2,4,4-trimethyl-Δ^1-pyrroline (**22**, R_1,R_2,R_3=CH_3) by the method of Bonnet et al., as well as reduction of the product with lithium aluminum hydride to yield 2,4,4-trimethylpyrrolidine (identified by NMR and IR).

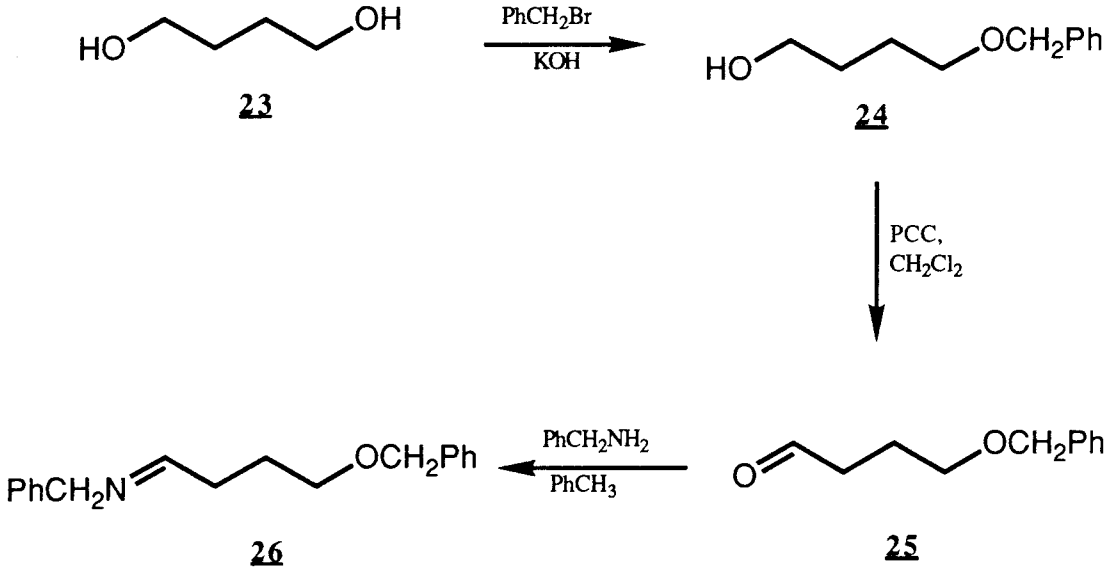
Scheme IV



The addition of the dianion of 4-PSBA to alkyl imines **22** was, unfortunately, largely unsuccessful. In only one instance, the case of 2,4,4-trimethyl-Δ^1-pyrroline, was a product obtained that provided reasonable spectral evidence of desired lactam formation, although in very poor yields (approx. 10%). Further analysis of the spectral and analytical data for this adduct show that it may be the uncyclized amino acid addition product. Possible reasons for the inability to obtain the desired bicyclic lactams from this reaction include the previously documented trimerization of the cyclic imines,[183] the potential enamine tautomerization, and the steric crowding that the presence of the alkyl substituent at the unsaturation site creates. Indolizidine natural products are primarily unsubstituted at the 8a position, requiring cyclic imine precursors that possess only a hydrogen at the 2-position. In light of the difficulties in obtaining cyclic imines that are unsubstituted at the 2-position due to the trimerization phenomena,[3] as well as the previously noted complications in obtaining these addition products, a different approach was devised to obtain the bicyclic indolizidine system.

This synthetic strategy takes advantage of the previously developed methodology of the addition of the dianion of 4-PSBA to Lewis acid activated acyclic imines (see Chapter 1, pages 15-17).[175] The six-membered ring of the bicyclic system is formed first through the dianion addition-cyclization procedure. Then closure of the five-membered ring follows facilitated by appropriate side chain substitution of the imine starting material. The requisite imine precursor for these transformations contains a four carbon side chain with a terminal protected alcohol. This imine was derived from 1,4-butanediol as shown in Scheme V.

Scheme V



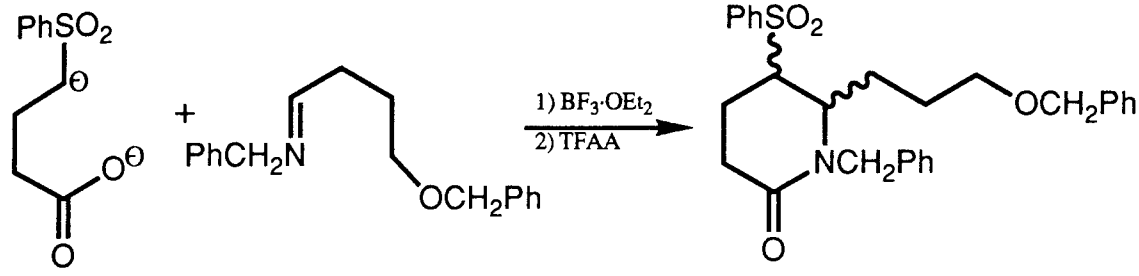
First, 1,4-butanediol was monoprotected as the benzyl ether. This was accomplished using a large excess (5-10x) of the diol in reaction with base and benzyl bromide.[184] The unreacted diol was removed in the aqueous extractions to provide clean monoprotected product **24** in very high yield (95% based on benzyl bromide). The use of a large excess of the diol is not a concern in this transformation due to the relative inexpense of this reagent as well as the ease of product purification. The unprotected terminal hydroxy functionality was oxidized to the aldehyde with pyridinium chlorochromate (PCC). This reaction proceeded in somewhat low yields, perhaps owing to the difficulties encountered in isolating **25**

from the "tar" produced in PCC oxidations. It was noted that distillation of the aldehyde **25** (80°C, 0.3mm) resulted in lower yields (57%) than did column purification (67-71%) presumably due to thermal degradation of the **25**. Swern[185] and Jones[186] oxidation conditions did not offer significantly better yields (50-70%). The aldehyde obtained is a known material,[187] although experimental procedures for the preparation of this compound have not yet been published. Finally, imine **26** was prepared by condensation of the aldehyde with benzylamine in very high yield (93-95%). Product **26** is relatively unstable, being readily hydrolyzed back to the aldehyde in the presence of water. Thus, the dianion addition reactions were generally performed within a few hours of imine formation.

The dianion addition-cyclization reaction (lactam formation) proved to be very sensitive to the conditions employed and required extensive experimentation. The instability of the imines necessitated distillation of boron trifluoride etherate immediately prior to use. It also was noted that the color of the dianion solution was discharged instantaneously upon addition of the imine complex. If reaction was allowed to continue for longer than 5 minutes before addition of trifluoroacetic anhydride (TFAA), the reaction yields were much lower. This is probably due to relocation of the resultant dianion to a more stable dianion wherein the second anionic site is alpha to the sulfonyl carbon as opposed to the initially generated nitrogen anion. The combination of these two precautions increased the yield of lactam formation from the initially obtained values of 20-40% to a consistent 76% (Scheme VI) . The major side-product

appears to be the N-benzyl amide of 4-PSBA. This product probably arises from unreacted benzylamine present in the imine solution.

Scheme VI

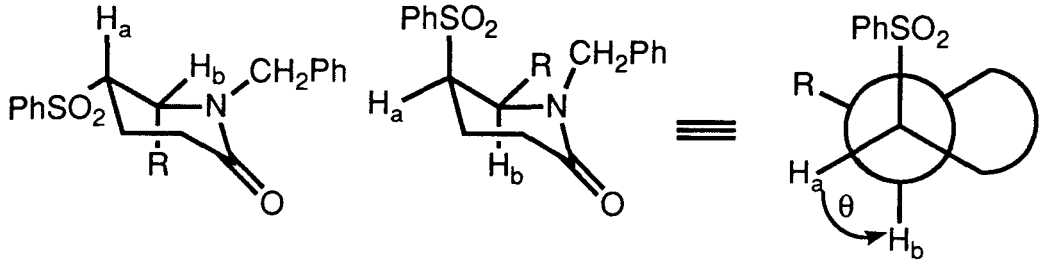


15 **26** **27a&b**

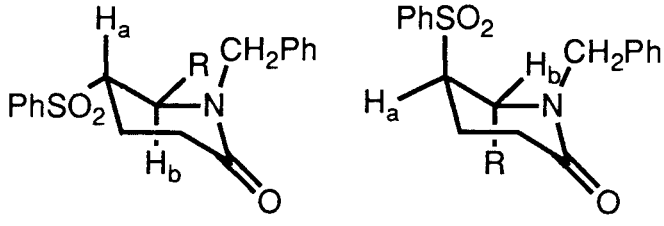
The lactam **27** possesses two chiral centers providing a mixture of two sets of enantiomers **27a** & **b**. These products are obtained in approximately 1:2 ratio (denoted fast **27a** and slow **27b**, respectively, due to their normal phase chromatographic elution order). The spectra of these products were extremely complex requiring ^{1}H-^{1}H COSY and ^{1}H-^{13}C COSY experiments to make spectral assignments. Deprotection of the terminal hydroxy functionality was carried out by hydrogenolysis under acidic conditions (10% Pd/C, trifluoroacetic acid) to provide **28a** & **b** whose NMR spectra were sufficiently simplified (although it is still essential that 2-D NMR experiments be done) to allow configurational assignments. The predominant isomeric mixture (slow band **28b**) has been assigned the conformations shown in Figure 2, where the phenylsulfonyl group and alkyl side-chain are in turn situated axial and equatorial (cis).

The other enantiomeric mixture (fast band **28a**) is then the configuration where these two groups are on opposite sides (diaxial and diequatorial) of the ring (trans).

Figure 2



28b, R= C_2H_4OH

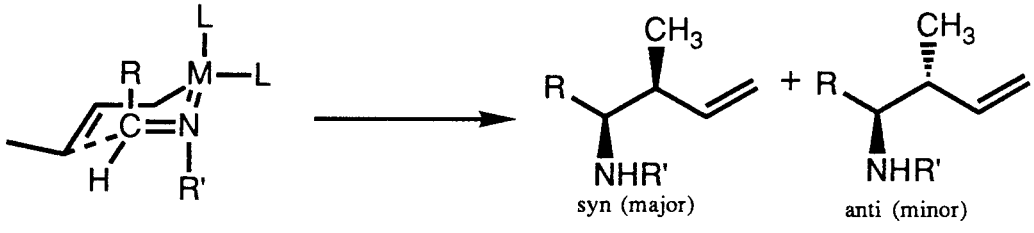


28a, R=CH_2OH

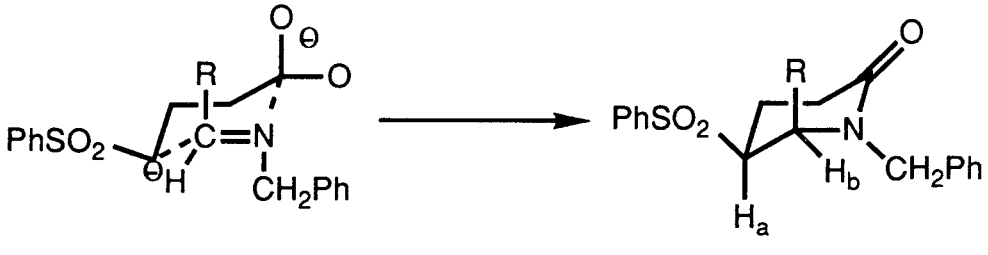
This assignment is based on the ^1H NMR coupling constants (J) of H_a and H_b and examination of models and molecular modelling calculations. These configurations are also in accordance with the facial selectivity observed by Yamamoto et al. in the addition of organometallics to imines[142] (Scheme VII). When the two R groups are cis, the angle θ between H_a and H_b is approximately 60° in both R,S and S,R enantiomers. Thus, the enantiomeric mix would exhibit a relatively simple spectrum with a $J_{H_aH_b}$ of approximately 2.0 Hz. This J value becomes 2.5 Hz for a

Karplus curve shifted for electronegative substituents(such as the phenylsulfonyl group).[188] In contrast, the diequatorial and diaxial enantiomeric mixture (S,S and R,R) provides two θ values of 60° and 180°, giving rise to two coupling constants of 2 Hz and 9.5 Hz, respectively, creating a much more complex spectrum. Indeed, in the slow lactam mix, a $J_{H_aH_b}$ of 2.5 Hz was observed, while the fast band spectrum was too complex to discern a single coupling constant for $J_{H_aH_b}$, and peak overlap led to difficulties in assignment. These correlations lead to the assignments of the enantiomeric mixes as shown above.

Scheme VII



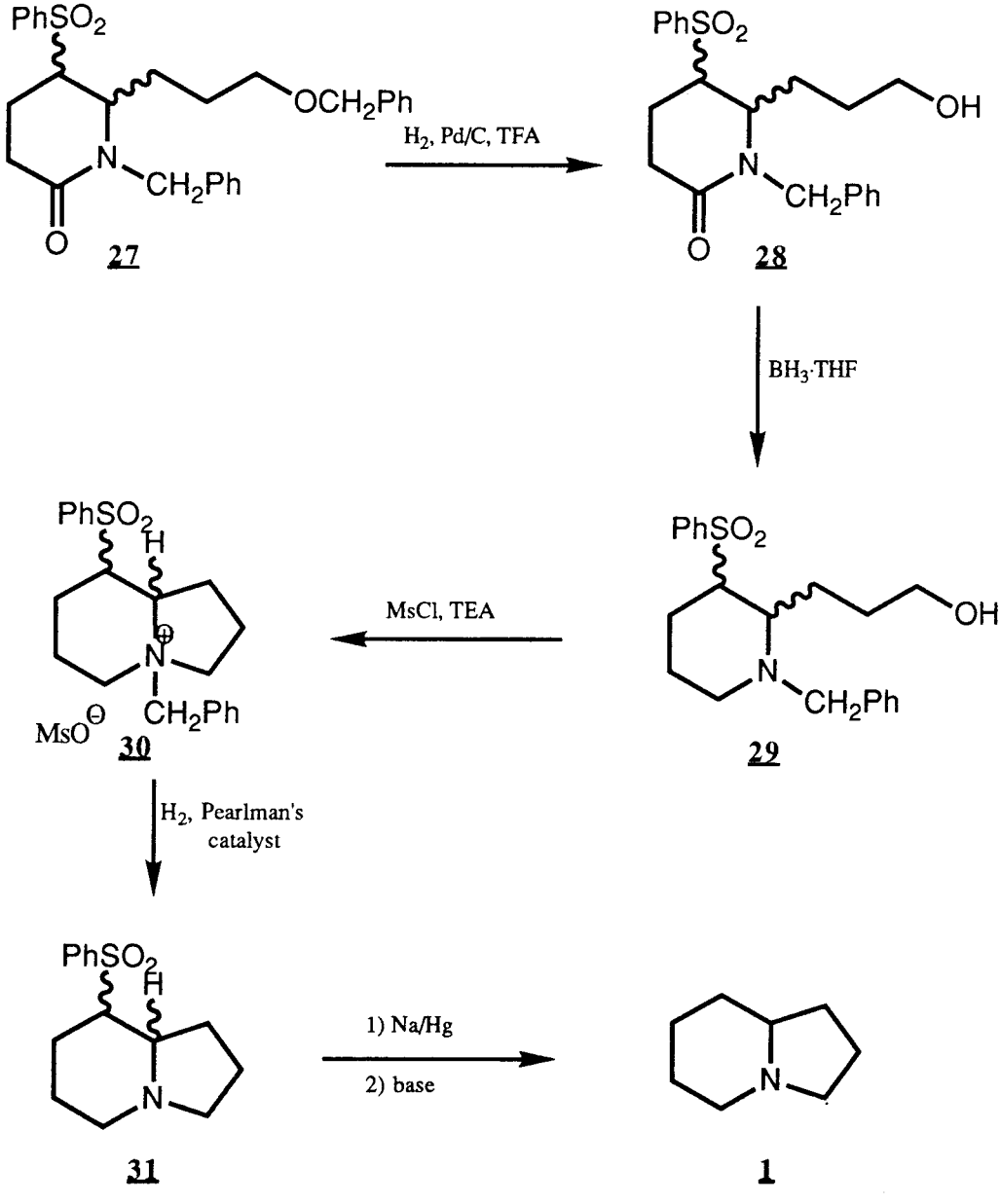
Yamamoto's model



Dianion addition model

The transformation of the diastereomeric lactams obtained from the dianion addition-cyclization sequence into the desired indolizidines is outlined in Scheme VIII. The de-O-benzylated lactam **28** was first reduced to the corresponding piperidine with three equivalents of borane-tetrahydrofuran complex (BH_3·THF). The terminal hydroxy group was then converted to a mesyl (methanesulfonyl) leaving group by reaction with either methanesulfonyl chloride (MsCl) or methanesulfonyl anhydride (Ms_2O). This reaction proceeded with immediate nucleophilic displacement of the mesyl group to give the quaternized ammonium salt **30**. This was liberated as the free base by removal of the N-benzyl group via hydrogenolysis over Pearlman's catalyst (20% palladium hydroxide on carbon).[189] The resulting 8-(phenylsulfonyl)-indolizidines **31** from both enantiomeric mixtures were white crystalline products. However, these products are rapidly oxidized in air to form N-oxides, which cause large errors in the combustion analyses. The presence of this impurity was, fortunately, small enough to allow verification of product formation via high resolution mass spectrometry (HRMS). Conversion to the well characterized δ-coniceine was effected by desulfonylation with sodium amalgam (Na/Hg)[190] to provide indistinguishable products from fast and slow bands.

Scheme VIII

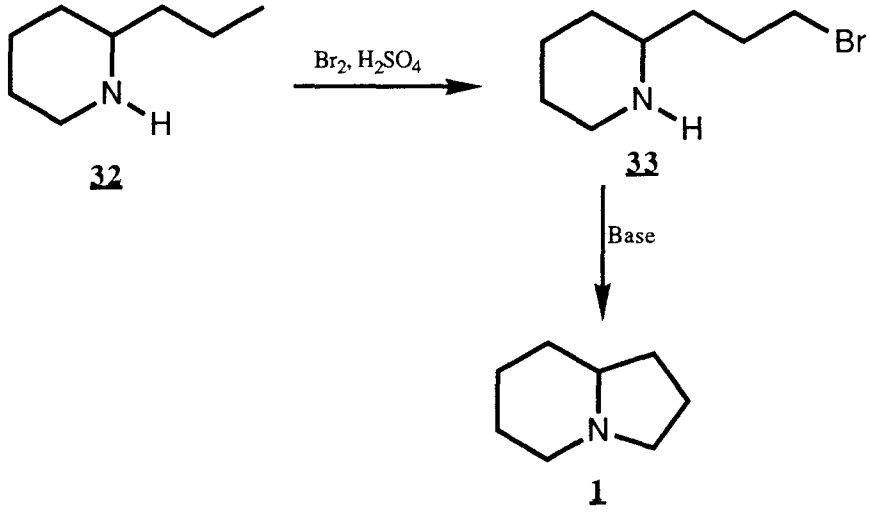


These products exhibited spectra (^{1}H and ^{13}C) that were identical to authentic δ-coniceine **1**. δ-Coniceine was prepared in an alternate route

employing the Hofmann-Löffler cyclization of bromoconiine **33** in order to compare and validate the physical properties and spectral data of our synthetic product (Scheme IX).

The sequence consists of nine steps and proceeds with an overall yield of 15.4%, comparing favorably with many of the synthetic methods previously reported for **1**.

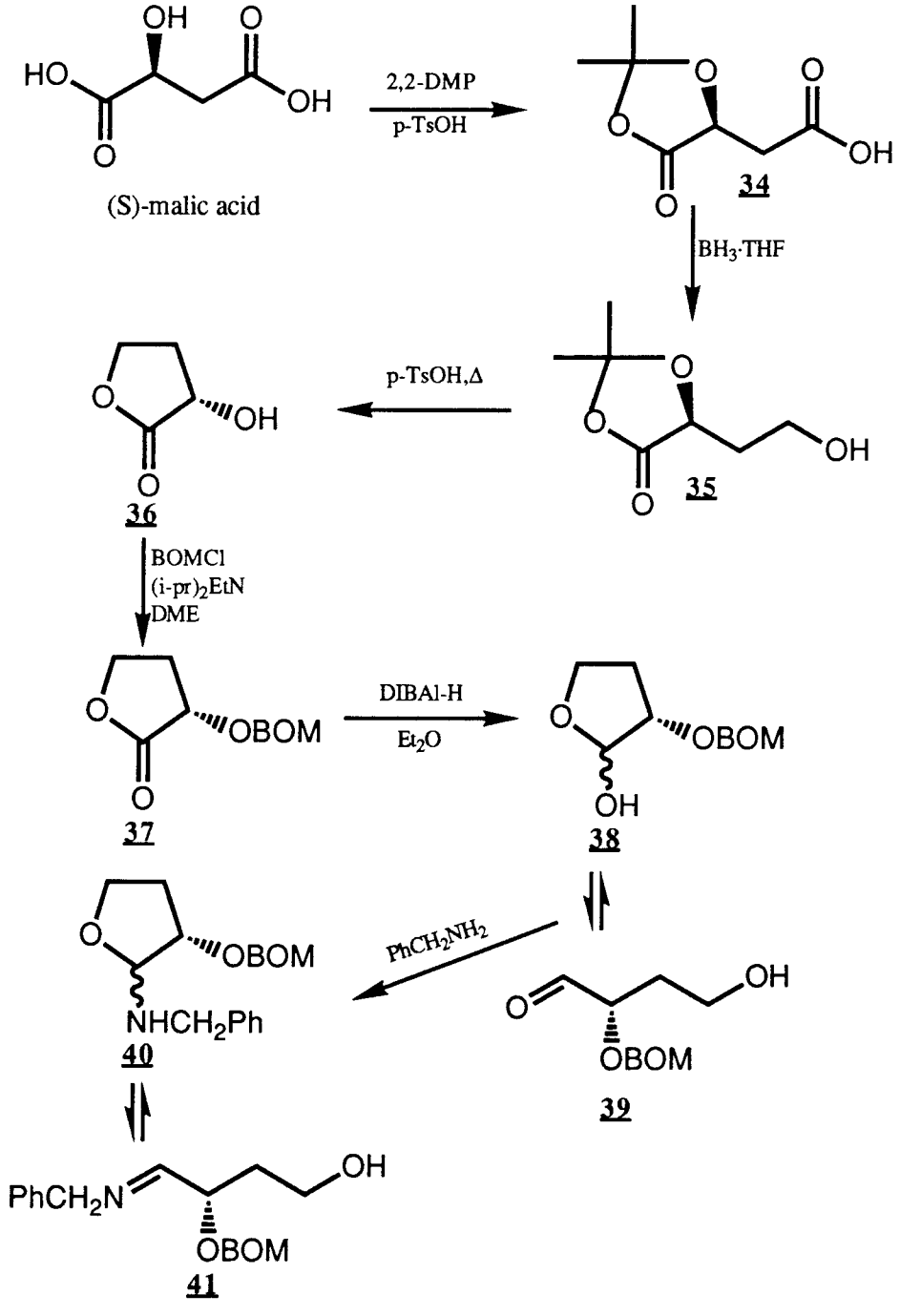
Scheme IX



32 33 1

With the methodology in hand to synthesize indolizidines from imines, we turned our attention to the preparation of a more complex indolizidine natural product. One of the lesser structurally demanding of these is 1-hydroxyindolizidine (**8**), which as mentioned previously, is an important intermediate in the biosynthesis of swainsonine and slaframine. The synthesis of this compound requires the availability of an imine with an alpha-hydroxy functionality. The synthesis of this imine from S-malic acid is outlined in Scheme X.

Scheme X

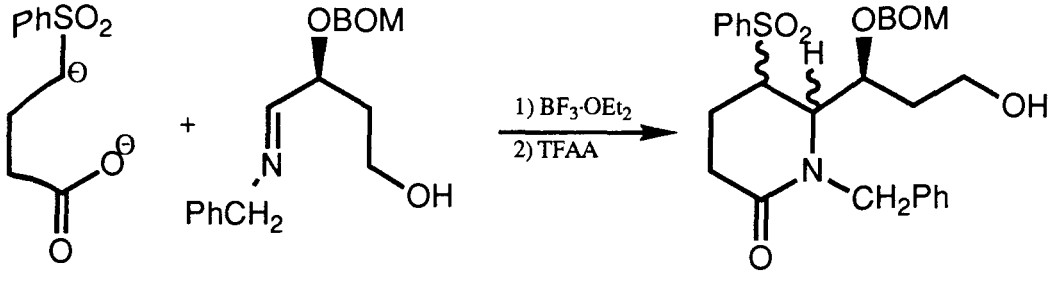

(S)-malic acid
2,2-DMP
p-TsOH
34
BH3·THF
35
p-TsOH,Δ
36
BOMCl
(i-pr)2EtN
DME
37
DIBAl-H
Et2O
38
PhCH2NH2
39
40
41

The synthesis of the benzyloxymethoxy lactone **37** is a procedure developed by Still et al. as part of a synthesis of monensin.[191] (*S*)-(–)-malic acid was first protected as the five-membered acetonide **34** (2,2-dimethoxypropane, *p*-toluenesulfonic acid). It should be noted here that this acetonide is the kinetic product and the thermodynamically more stable 6-membered ring was formed if the reaction was allowed to continue. The carboxylic acid was then reduced to the alcohol with BH_3·THF. This unstable product was rapidly converted to 3-hydroxybutyrolactone upon heating with acid (*p*-TsOH). In this process, deprotection of the acetonide led to intramolecular esterification (lactonization) to afford **36**. The remaining free hydroxy moiety was protected as the benzyloxymethyl (BOM) ether to provide the known lactone **37** in 33% overall yield (52% reported by Still et al.). Reduction of the ester with diisobutyl aluminum hydride (DIBAl-H) provided the lactol that exists in equilibrium with the open-chain hydroxy aldehyde form **39**. The NMR spectra of this compound is further complicated by the presence of two lactols (a second chiral center is created in the reduction) resembling the α and β anomers of the furanose forms of sugars. Indeed, the ^{13}C spectrum contains signals for 12 non-aromatic carbons, when only 6 signals for **38** are expected. This fits nicely with the model of ^{13}C spectra for sugars where the anomers can be distinguished.[192] A study of the ^{1}H NMR and IR spectra of **38** in several different solvents was undertaken in order to determine the optimum solvent for obtaining the desired aldehyde form. In all solvents tried (CD_3CN, diethyl ether, acetone, methanol, THF, $CDCl_3$) the lactol predominates, with only THF showing signs of the presence of aldehyde.

This information was used to advantage in an optimization of the yield for the DIBAl-H reduction. Using diethyl ether rather than THF as the solvent, the overreduction of the lactone to the diol was decreased. Next, protection of the terminal hydroxy functionality of the open-chain aldehyde form was attempted. Several selective protecting groups were examined. The tert-butyldimethylsilyl (TBDMS) ether was prepared, yet the lactol was preferentially protected to yield a 3:1 ratio of TBDMS-lactol and TBDMS-aldehyde, respectively. The diphenylmethylsilyl ether also was prepared, yielding only protected lactol. One final silyl ether, the tert-butyldiphenylsilyl (TBDPS) ether provided primarily the desired aldehyde. This aldehyde was converted to the imine by condensation with benzylamine. Reaction of the activated imine with the dianion of 4-PSBA followed by attempted cyclization resulted in an addition product that was uncyclized. This difficulty arises presumably because of the extreme bulkiness of the side chain with both BOM ether and TBDPS ether appendages. In continuation of the protecting group strategy, benzyl ether preparation yielded only protected lactol and the attempted protection as the triphenylmethyl(trityl) ether resulted in no reaction. At this juncture, it was decided that the direct condensation of the lactol **38** with benzylamine to effectively trap the aldehyde would provide the desired imine product, albeit with a terminal unprotected hydroxy functionality. This approach did provide the imine, although the product was very unstable and not amenable to subsequent alcohol protection steps. Attempted protection as the TBDMS and benzyl ethers resulted in some product formation although workup procedures were accompanied by

significant hydrolysis of the imine. The imine product **41** was not easily characterized, perhaps due to the presence of the hemi-aminal **40** formed from cyclization of the hydroxy group onto the imine. Since these products are in equilibrium favoring the cyclic hemi-aminal, they are not readily separated and characterized. Thus, the dianion addition reaction was performed directly on the **40/41** product mixture in hopes that deprotonation of **40** would lead to formation of the desired alkoxy-imine *in situ* (Scheme XI).

Scheme XI



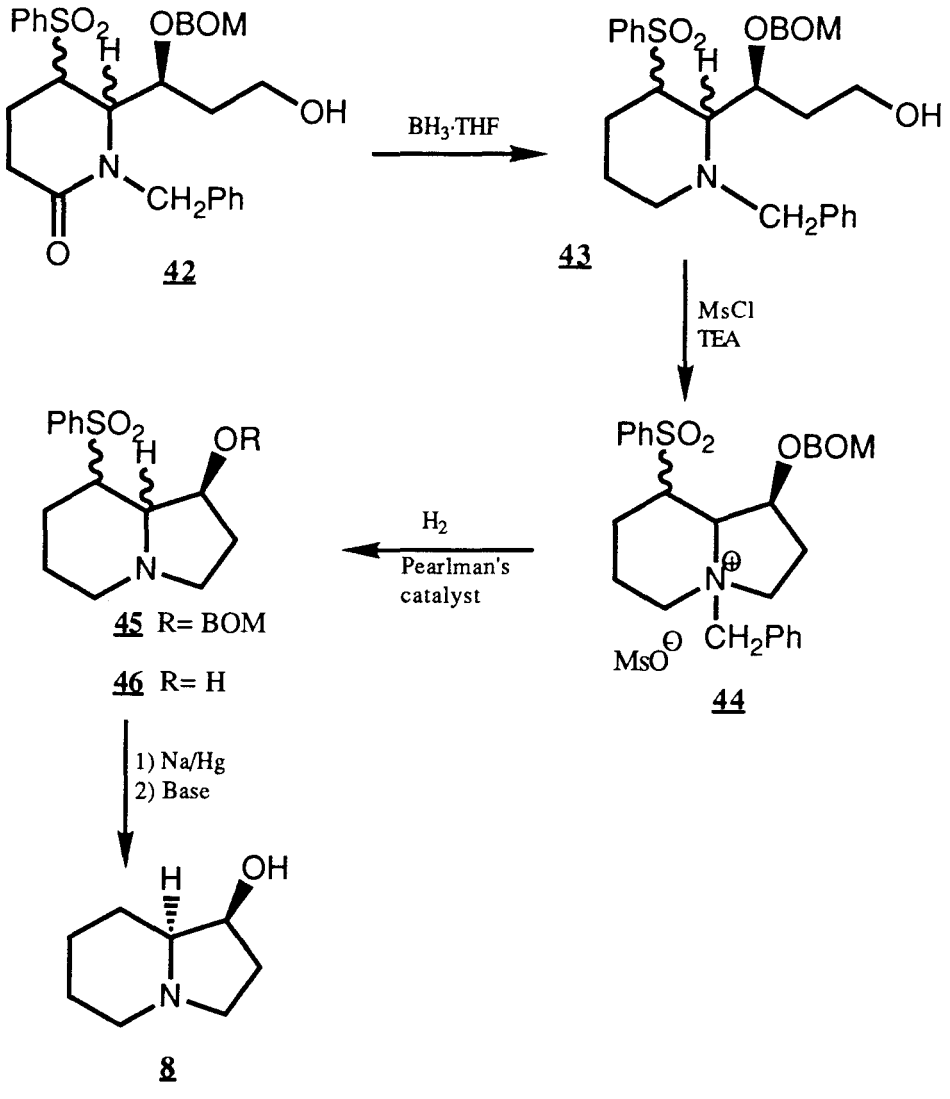
15 **41** **42**

The diastereomeric chiral lactams **42** (denoted as fast and slow based on their normal phase chromatographic behavior) were obtained in low yields (29% purified, 54% maximum based on 4-PSBA recovery) again in a 2:1 (slow/fast) ratio as in the case of the achiral lactam. The low yield is presumably due to impure starting imine, with the equilibrium still favoring the hemiaminal form. The addition-cyclization reaction required two equivalents of the dianion; one to deprotonate the unprotected terminal hydroxy functionality. The second equivalent of the dianion is delivered to the imine. The use of two equivalents of 4-PSBA was not of great concern

because greater than 95% of the unreacted acid could be recovered from the basic, aqueous washings performed in the normal workup procedure. The reaction products were carefully separated and analyzed to reveal that only two of the four possible diastereomers of the lactam were formed. The remainder of the reaction products appeared to correspond to the N-benzyl amide of 4-PSBA and the product of addition of the dianion of 4-PSBA to unreacted lactol (the lactone). The enhanced diastereoselection observed in this reaction (the isolation of only two of the four possible diastereomers) is presumably due to the additional bulk of the α-benzyloxymethoxy ether moiety. Invoking a six-membered transition state model as before, the steric bulk of the imine side-chain precludes it from being axial since 1,3-diaxial interactions would prohibit facile approach of the nucleophile. This model accounts for the observed products, although examination of Drieding stereomodels suggests that the opposite stereochemistry for the bridgehead proton would result from attack upon the imine at the face opposite the protected hydroxy group. The relative cis/trans orientation of the imine during attack is not known and is of importance in the inclusion of stereomodels.

Conversion of **42** into the desired 1-hydroxyindolizidine **8** is analogous to the achiral δ-coniceine synthesis (Scheme XII).

Scheme XII



The lactams were first reduced to the corresponding piperidines **43** with borane-THF. The piperidines were converted to the mesylates, resulting in spontaneous quaternization to the bicyclic indolizidine mesylate **44**. Hydrogenolysis with Pearlman's catalyst provided the BOM-protected

1-hydroxy-8-(phenylsulfonyl)-indolizidine **45**. It was noted that if the hydrogenolysis was carried out under slightly acidic conditions (10 μL TFA), cleavage of the BOM protecting group could be achieved concurrently with N-benzyl ether cleavage. This allows for the synthetic route to the chiral 1-hydroxyindolizidine to be shorter in actual number of steps than the achiral indolizidine. The final step in the synthesis was the desulfonylation with sodium amalgam to provide 1-hydroxyindolizidine (**8**) from both fast and slow bands. This sequence formally consists of seven steps (from Still's intermediate) and proceeds in approximately 3% overall yield. The two 1-hydroxyindolizidines obtained exhibited optical rotations that indicated they were the same product. The rotations are very close to that reported for (+)-(1S, 8aS)-1-hydroxyindolizidine, α_D^{22}=16.4(0.28, $CDCl_3$) and 18.1(0.42, $CDCl_3$), lit. α_D^{22}=20.2°(1.03, EtOH),[64] leading to the conclusion that this route is enantioselective. Throughout the synthetic transformations, the products from fast and slow bands have exhibited markedly different optical rotations and have been chromatographically separable. This indicates that the two predominant products are diastereomers at the phenylsulfonyl substituted carbon, and that upon desulfonylation, this difference is removed to provide the same 1-hydroxyindolizidine product. The slight variations in the rotation values can be accounted for in the concentration and solvent differences. There was insufficient material to obtain rotation data at higher concentrations and the volatility of the product precluded the use of ethanol. The enantioselectivity has been accounted for in the above representations of the facial selectivity of the addition reaction. Chiral resolution of the products

was facilitated by derivatization with (S)-1-napthylethyl isocyanate. HPLC analysis (D-phenylglycine, elution with 70:30 hexane/isopropanol) showed the 1-hydroxyindolizidines to be >99% optically pure and chromatographically identical.

Chapter 3

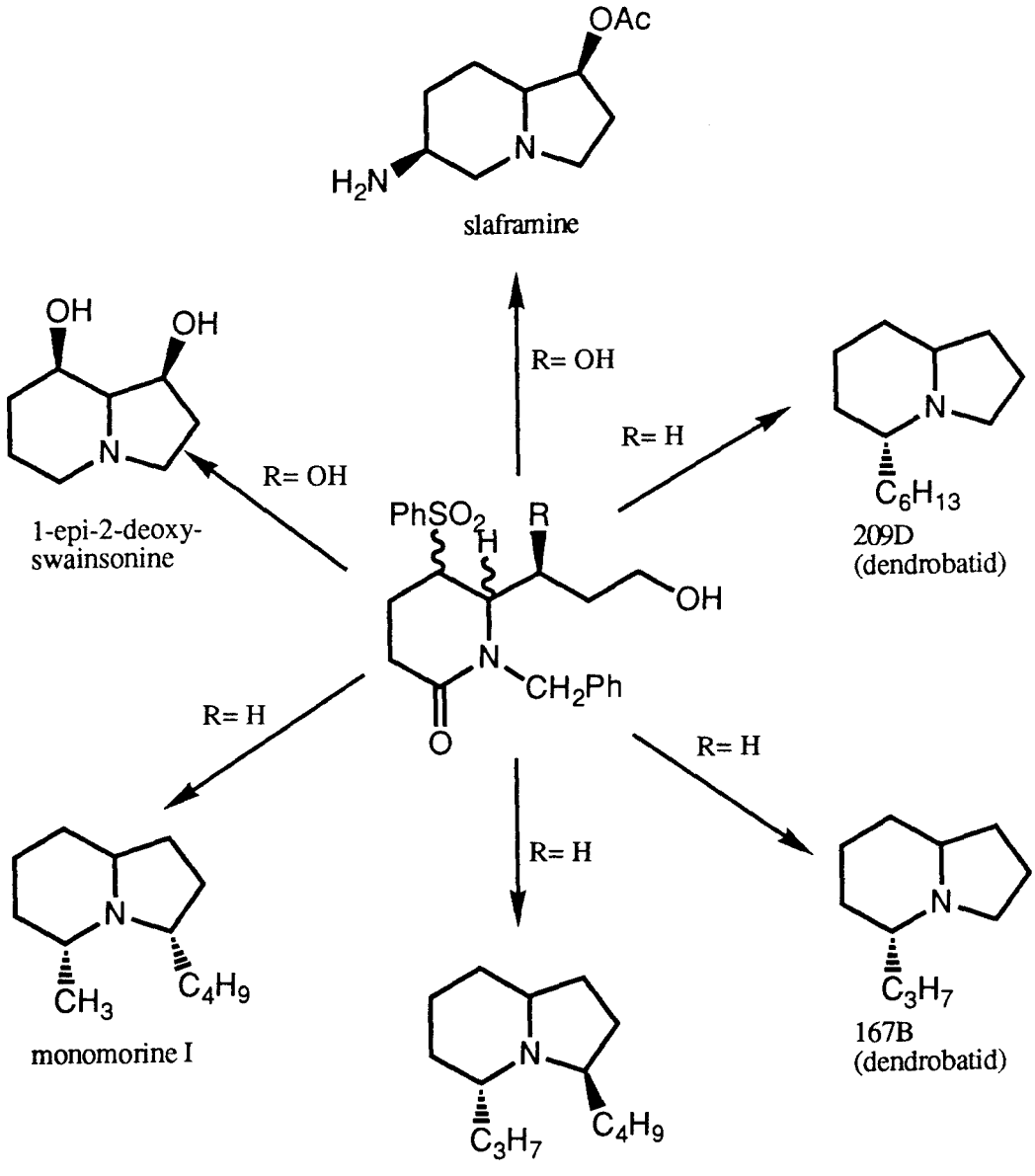
Conclusions

This investigation showed that the "remote" dianion addition-cyclization procedure can be extended to include the diastereoselective preparation of indolizidines from imines. Moreover, this synthetic route has proven to be an enantioselective method for the preparation of chiral indolizidine alkaloids when applied to imines with chiral appendages.

One of the most important aspects of this research is the preparation of lactams from functionally substituted imines. A wide variety of indolizidine alkaloid natural products and analogues can be readily accessed from these intermediates (Scheme XIII).

Thus, the goal of providing a versatile synthetic strategy for the preparation of indolizidine alkaloids and analogues has been achieved. Additionally, we have provided one of the very few enantioselective routes for the formation of these compounds. Future studies in this project should include the re-analysis of the application of the dianion addition-cyclization methodology to cyclic imines, extension to alkyl substituted indolizidines (e.g. gephyrotoxins), and preparation of polyhydroxy indolizidines.

Scheme XIII


OAc
H_2N
N
slaframine
R= OH
R= H
OH
OH
N
1-epi-2-deoxy-swainsonine
R= OH
$PhSO_2$
H
R
OH
N
CH_2Ph
O
N
C_6H_{13}
209D
(dendrobatid)
R= H
R= H
R= H
N
CH_3
C_4H_9
monomorine I
N
C_3H_7
C_4H_9
gephyrotoxin 223AB
N
C_3H_7
167B
(dendrobatid)

Chapter 4

Experimental

General Methods. Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. NMR spectra were recorded emplo a Varian VXR-300 spectrometer. ^{1}H NMR spectra were taken in deuterated chloroform ($CDCl_3$) at 300 MHz. ^{13}C NMR spectra were taken at 75 MHz. ^{13}C assignments were made with the aid of DEPT experiments (see appendix). 2-D HOMCOR experimental results are also presented in the appendix. Infrared data were obtained in $CDCl_3$ on a Perkin Elmer 1400 spectrometer. Optical rotations were measured on a Perkin Elmer 241 Polarimeter using a 100 mm path length 1 mL quartz cell.

Analytical thin layer chromatography (TLC) was conducted with aluminum-backed silica plates (E. Merck). Visualization was accomplished with an ultraviolet lamp and/or anisaldehyde stain (2% o-anisaldehyde in 95:4:1 absolute ethanol-concentrated sulfuric acid-glacial acetic acid) with heating and/or iron(III) chloride-hydroxylamine stain and/or ninhydrin. Flash chromatography was done on Kieselgel 60, 230-400 mesh (E. Merck). Florisil (100-200 mesh; Fisher) was used where noted.

All solvents and reagents were purified when necessary according to standard literature methods. Air- or water-sensitive reactions were conducted under a positive argon atmosphere utilizing standard techniques. Hydrogenolyses were conducted either with doubled balloon pressures (10-

20 psi H_2) or in a Parr shaker (>20 psi H_2). Most reagents were purchased from Aldrich Chemical Co.(Milwaukee, WI); S-malic acid was obtained from Research Organics, Inc.(Cleveland, OH).

1. O-benzyl 1,4-butanediol, 24. 1,4-butanediol (20 g, 0.22 mol.) was stirred at ambient temperature with 12 g powdered KOH. Benzyl bromide (6.0 mL, 50.4 mmol) was added and after 2 h, 100 mL H_2O was added. The reaction mixture was cooled and extracted thrice with diethyl ether. The combined organic layers were were dried over Na_2SO_4 and the solvent was removed in vacuo. Column chromatography (4:1 diethyl ether/petroleum ether) yielded 8.62 g of a clear oil (95%). R_f = 0.34 (diethyl ether) IR 3430 cm^{-1} (OH, broad). Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.97; H, 9.08. ^1H NMR 1.68 (m, 4 H), 2.33 (s, 1 H), 3.51 (t, 2 H, J = 5.8 Hz), 3.63 (t, 2 H, J = 6.0 Hz), 4.51 (s, 2 H), 7.30 (m, 5 H). ^{13}C NMR 26.60, 30.06, 62.62, 70.31, 73.01, 127.59, 127.65, 128.36, 138.23.

2. 4-(benzyloxy)-butanal, 25. Alcohol **24** (2.0 g, 11.1 mmol) was dissolved in 2 mL CH_2Cl_2 and added to a stirred mixture of 3.0 g pyridinium chlorochromate (13.9 mmol, 1.25 eq) in 200 mL CH_2Cl_2. After 1 h, the mixture was filtered and the solvent was removed in vacuo. The residue was dissolved in diethyl ether and extracted with saturated Na_2CO_3. The organic phase was dried over Na_2SO_4 and the solvent was removed in vacuo. Column chromatography (1:1 CH_2Cl_2/petroleum ether) yielded 1.33 g (67%) as a colorless oil. R_f = 0.54 (diethyl ether). IR 1720

cm^{-1} (C=O, strong). ^1H NMR 1.87 (m, 2 H), 2.47 (dt, 2 H, J = 1.6, 7.1 Hz), 3.43 (t, 2 H, J = 6.1 Hz), 4.41 (s, 2 H), 7.20 (m, 5 H), 9.70 (t, 1 H, J = 1.5 Hz). ^{13}C NMR 22.57, 40.88, 69.12, 72.92, 127.56, 127.84, 128.28, 128.34, 138.28, 202.06.

3. N-benzylidene-4-(O-benzyl)-butanal, 26. Aldehyde **25** (1.33g, 7.5 mmol) was dissolved in approx. 1 mL toluene and was added to a stirring solution of benzylamine (0.80 g, 7.5 mmol) in 1 mL toluene. The mixture turned warm and became cloudy. After stirring at room temperature for 2 h, anhydrous diethyl ether (approx. 2 mL) was added and the organic phase was decanted and dried with BaO at 0 °C overnight. Following filtration and removal of solvent in vacuo, unreacted benzylamine and aldehyde were removed by heating at reduced pressure (50°C at 0.3mm) to yield 1.89 g (95%) of lightly yellow oil. This product was not stable and was used within hours of preparation without further purification. R_f = 0.45 (diethyl ether). IR 1660 cm^{-1} (C=N, strong). ^1H NMR 1.98 (quint, 2 H, J = 7.1 Hz), 2.47 (m, 2 H), 3.59 (t, 2 H, J = 6.4 Hz), 4.56 (s, 2 H), 4.62 (s, 2 H), 7.33 (m, 10 H), 7.88 (m, 1 H). ^{13}C NMR 26.16, 32.79, 65.02, 69.60, 72.86, 126.85, 127.51, 127.57, 127.86, 128.25, 128.33, 128.41, 165.61.

4. 1-benzyl-5-(phenylsulfonyl)-6-[3-benzyloxypropyl]-2-piperidinone, 27. Imine **26** (1.72 g, 6.4 mmol) was dissolved in 5 mL THF. The mixture was cooled to -78 °C under argon and 1.0 mL boron trifluoride etherate (1.25 eq) was added. Concurrently, the dianion of 4-

PSBA was generated: 4-PSBA (1.46 g, 6.4 mmol) was dissolved in 75 mL THF, cooled to -78 °C under argon, and 5.1 mL butyllithium (2.5 M in hexanes, 12.75 mmol) was added slowly. After 0.5 h, the activated imine solution was transferred via cannula to the dianion solution. The yellow color of the dianion solution quenched immediately, and within 5 minutes 1.7 mL trifluoroacetic anhydride (TFAA, 12.0 mmol) was added. The solution was allowed to equilibrate slowly to ambient temperature followed by the addition of 50 mL ethyl acetate. The reaction mixture was extracted twice with saturated Na_2CO_3 with a subsequent brine wash. The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. Flash chromatography (1:1 ethyl acetate/$CHCl_3$) yielded products **27a** and **27b** with R_f = 0.34, 0.28 (ethyl acetate) in approximately 1:2 ratio, respectively. 2.56 g recovered (75.6%). HRMS m/z calcd for $C_{28}H_{31}NO_4S$ 477.1974, found 477.1938.

27a Fast band (R_f = 0.34) IR 1635 cm^{-1} (C=O, strong). ^1H NMR 1.77 (m, 2 H), 2.09 (m, 2 H), 2.47 (m, 2 H), 2.66 (m, 1 H), 3.09 (m, 2 H), 3.48 (t, 2 H, J = 6.1 Hz), 3.67 (m, 2 H), 4.50 (s, 2 H), 5.47 (d, 1 H, J = 14.5 Hz), 7.46 (m, 15 H). ^{13}C NMR 16.85, 27.42, 27.85, 28.59, 50.73, 54.63, 63.25, 69.96, 73.13, 127.65, 127.75, 127.95, 128.13, 128.33, 128.44, 128.77, 129.34, 129.41, 133.94, 136.62, 169.04. (Some aromatic resonances unresolved).

27b Slow band (R_f = 0.28) IR 1638 cm^{-1} (C=O, strong). ^1H NMR 1.24 (m, 2 H), 1.57 (m, 1 H), 1.76 (m, 1 H), 2.27 (m, 3 H),

2.76 (m, 1 H), 3.19 (m, 3 H), 3.67 (dt, 1 H, J = 2.6, 9.7 Hz), 3.95 (d, 1 H, J = 14.8 Hz), 4.38 (s, 2 H), 5.27 (d, 1 H, J = 14.7 Hz), 7.43 (m, 15 H). ^{13}C NMR 18.74, 25.28, 28.86, 30.42, 48.08, 53.35, 60.66, 68.83, 73.04, 127.58, 127.64, 127.72, 128.10, 128.31, 128.43, 128.57, 128.74, 129.14, 129.20, 129.27, 129.39, 133.89, 136.60, 137.05, 138.12, 169.46. (Some aromatic resonances unresolved).

5. 1-benzyl-5-(phenylsulfonyl)-6-[3-hydroxypropyl]-2-piperidinone, 28. Lactam **27** (0.6 g, 1.26 mmol) was dissolved in approximately 2 mL THF and methanol was added until solution became just cloudy (approx. 4 mL). The reaction vessel (2-neck round bottom flask) was flushed with argon, 60 mg 10% Pd/C was added followed by 10 μL trifluroacetic acid. A doubled balloon charged with H_2 was connected to the reaction flask. Hydrogen was introduced by mild evacuation of the flask (aspirator vacuum) followed by opening of the H_2 balloon inlet. The mixture was stirred at ambient temperature under H_2 (<20 psi) overnight. Filtration and subsequent solvent removal in vacuo yielded 0.396 g (82%) as a clear oil. Anal. calcd for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.85; H, 6.39; N, 3.55.

28a Fast band R_f = 0.10 (ethyl acetate). IR 3400 cm^{-1} (OH), 1638 cm^{-1} (C=O). ^1H NMR 1.80 (m, 4 H), 2.05 (m, 1 H), 2.25 (m, 1 H), 2.54 (m, 2 H), 2.73 (m, 1 H), 3.13 (m, 1 H), 3.71 (t, 2 H, J = 5.7 Hz), 3.82 (m, 2 H), 5.49 (d, 1 H, J = 14.5 Hz), 7.20 (m, 2 H), 7.35 (m, 3 H), 7.55(m, 2 H), 7.70(m, 3 H). ^{13}C NMR 17.00, 27.58,

28.63, 30.13, 50.77, 54.47 (CH), 62.29, 63.12 (CH), 127.80, 128.25, 128.28, 128.75, 128.76, 129.40, 134.05, 136.50, 137.88, 169.05. (Some aromatic resonances unresolved).

28b Slow band Recrystallized in CH_2Cl_2/hexane to provide white crystals. mp. 136-137°C. R_f = 0.08 (ethyl acetate). IR 3400 cm^{-1} (OH), 1640 cm^{-1} (C=O). ^1H NMR 1.09 (m, 1 H), 1.24 (m, 1 H), 1.56 (m, 1 H), 1.73 (m, 1 H), 1.93 (s, 1 H), 2.26 (m, 3 H), 2.75 (m, 1 H), 3.21 (dt, 1 H, J = 2.3, 6.1 Hz), 3.35 (m, 2 H), 3.67 (dt, 1 H, J = 2.6, 9.4 Hz), 3.98 (d, 1 H, J = 14.7 Hz), 5.25 (d, 1 H, J = 14.7 Hz), 7.42 (m, 10 H). ^{13}C NMR 19.75, 27.79, 28.84, 30.13, 48.09, 53.29 (CH), 60.70 (CH), 61.26, 127.67, 128.68, 128.69, 129.14, 129.28, 133.95, 136.56, 169.55. (Some aromatic resonances unresolved).

6. 2-(3-hydroxypropyl)-3-phenylsulfonyl-N-benzyl piperidine, 29. Piperidinone **28** (0.255 g, 0.66 mmol) was dissolved in 2 mL THF. The mixture was cooled to 0 °C and 2.0 mL BH_3·THF (3.0 eq) was added. The reaction was allowed to equilibrate to ambient temperature and the excess borane was hydrolysed with 5 drops 5% NaOH. Subsequent partitioning between ethyl acetate and saturated Na_2CO_3 followed by drying the organic phase over Na_2SO_4 and removal of solvent in vacuo yielded a white foam, 0.212 g (86%). This product was purified by florisil chromatography (1:1 CH_2Cl_2/diethyl ether) to give 0.155 g of a clear oil (63%). HRMS m/z calcd for $C_{21}H_{27}NO_3S$ 373.1712, found 373.1723.

29a Fast band R_f = 0.44 (ethyl acetate). ^1H NMR 1.52 (m, 1 H), 1.79 (m, 4 H), 2.09 (m, 3 H), 2.60 (dd, 1 H, J = 4.3, 14.1 Hz), 2.90 (dt, 1 H, J = 3.5, 13.8 Hz), 3.34 (m, 1 H), 3.61 (m, 4 H), 3.74 (d, 1 H, J = 12.9 Hz), 3.84 (d, 1 H, J = 13.0 Hz), 7.33 (m, 5 H), 7.68 (m, 3 H), 7.94 (m, 2 H). ^{13}C NMR 20.02, 20.23, 23.45, 30.78, 41.97, 57.08, 57.47, 60.61, 62.73, 127.45, 128.36, 128.43, 128.95, 129.23, 133.62, 137.79, 138.63. (Some aromatic resonances unresolved).

29b Slow band R_f = 0.41 (ethyl acetate). ^1H NMR 1.75 (m, 8 H), 2.43 (m, 1 H), 2.65 (m, 1 H), 2.77 (s, 1 H), 3.23 (q, 1 H, J = 5.4 Hz), 3.37 (q, 1 H, J = 5.7 Hz), 3.65 (t, 2 H, J = 6.1 Hz), 3.67 (d, 1 H, J = 13.1 Hz), 3.90 (d, 1 H, J = 13.5 Hz), 7.34 (m, 5 H), 7.62 (m, 3 H), 7.92 (d, 2 H, J = 7.6 Hz). ^{13}C NMR 20.25, 22.33, 23.85, 29.07, 46.24, 56.71, 57.59, 62.08, 62.32, 127.02, 128.30, 128.66, 128.73, 129.05, 133.40, 138.60, 138.73.

7. 8-(phenylsulfonyl)-indolizidine, 31. Piperidine **29** (97.9 mg, 0.26 mmol) was dissolved in 3 mL CH_2Cl_2. Five drops of triethylamine were added to the mixture followed by 20 µL methanesulfonyl chloride (MsCl). The reaction appeared complete in 15 min. by TLC (the quaternized salt remains on the baseline, no starting material is observed). The solvent was removed in vacuo and the residue was dissolved in approximately 2 mL methanol. Palladium hydroxide on carbon (10-20 mg, 10%; Pearlman's catalyst) was added and the mixture was stirred under H_2 (<20 psi) overnight. The mixture was filtered and the solvent

was removed in vacuo. The residue was partitioned between 10% NaOH and CH_2Cl_2. The combined organic phases were dried and solvent was removed in vacuo. The product was purified by elution from florisil (ethyl acetate) to give 46.9 mg (67%) of a white solid. IR 2805 cm^{-1} (Bohlmann band).

31a Fast band R_f = 0.07 (ethyl acetate). mp 125-127 °C. HRMS m/z calcd for $C_{14}H_{19}NO_2S$ 265.1137, found 265.1120. ^1H NMR 1.49 (m, 1 H), 1.91 (m, 7 H), 2.45 (m, 2 H), 2.62 (dt, 1 H, J = 9.0, 11.5 Hz), 2.88 (m, 1 H), 3.09 (m, 1 H), 3.60 (quintet, 1 H, J = 4.8 Hz), 7.61 (m, 3 H), 7.90 (m, 2 H). ^{13}C NMR 20.53, 21.61, 22.51, 24.02, 48.34, 54.16, 59.19, 62.43, 128.36, 129.03, 133.46, 139.00.

31b Slow band R_f = 0.16 (ethyl acetate). mp 81-82 °C. HRMS m/z calcd for $C_{14}H_{19}NO_2S$ 265.1137, found 265.1124. ^1H NMR 1.60 (m, 6 H), 2.08 (m, 5 H), 3.00 (m, 3 H), 7.62 (m, 3 H), 7.87 (m, 2 H). ^{13}C NMR 20.76, 24.62, 25.67, 29.96, 51.64, 53.51, 62.49, 66.66, 128.76, 129.07, 133.65.

8. (±)-coniceine, 1. 8-(phenylsulfonyl)-indolizidine **31** (31.6 mg, 0.12 mmol) was dissolved in 1 mL methanol. An excess of 6% Na/Hg was added and the reaction was stirred at room temperature for 2 h. The mixture was filtered into 2 mL methanolic HCl to capture the volatile indolizidine as the hydrochloride salt. The solvent was removed in vacuo followed by partitioning between diethyl ether and 20% KOH to liberate

free base. Removal of solvent yielded 10.6 mg indolizidine (71%). R_f = 0.06 (ethyl acetate) visualized with ninhydrin stain. IR 2800 cm^{-1} (Bohlmann band). ^1H NMR 1.6 (m, 11 H), 2.0 (m, 2 H), 3.0 (m, 2 H). ^{13}C NMR 20.74 (CH_2), 24.66(CH_2), 25.65 (CH_2), 30.62 (CH_2), 31.24 (CH_2), 53.19 (CH_2-N), 54.40 (CH_2-N), 64.45 (CH).

9. (2,2-dimethyl-1,3-dioxolan-4-one)-5-ethanoic acid, 34. S-malic acid (10 g, 75 mmol) was suspended in 25 mL 2,2-dimethoxypropane. p-Toluenesulfonic acid monohydrate (p-TsOH; 200 mg, 1.05 mmol) was added and the mixture was stirred at ambient temperature for 30 min. The reaction mixture was partitioned between water and CH_2Cl_2. The aqueous was extracted two additional times and the combined organics were dried over Na_2SO_4. Removal of solvent yielded 7.47 g of a white solid (57%). Recrystallization from 1:1 $CHCl_3/CCl_4$ yielded 6.16 g (50%) colorless needles. R_f = 0.42 (ethyl acetate). mp 115-117 °C. $[\alpha]_D^{22}$ = +6.9° (0.94, $CHCl_3$). IR 1720 cm^{-1} (COOH), 1790 cm^{-1} (COOR) . ^1H NMR 1.58 (d, 6 H, J = 15.3 Hz), 2.91 (m, 2 H), 4.70 (m, 1 H), 9.98 (br s, 1 H). ^{13}C NMR 26.02, 26.96, 36.23, 70.62, 111.61, 172.11, 175.12.

10. (2,2-dimethyl-1,3-dioxolan-4-one)-5-ethanol, 35. Acid **34** (5.57g, 32 mmol) was dissolved in 32 mL THF. The solution was placed under Ar and cooled to -78 °C. BH_3·THF (35 mL, 1M in THF, 35 mmol) was added over 40 min. The reaction mixture was allowed to slowly equilibrate to ambient temperature and stirred until TLC showed

consumption of starting material (usually overnight reaction times were required). The solvent was removed in vacuo and the borate salts were removed by flash chromatography (60 g silica, acetone elution) to yield 5.49 g of a light yellow oil (>100%). This unstable material was subjected to reaction without further purification. R_f = 0.52 (ethyl acetate). $[\alpha]_D^{22}$ = +3.7 (0.76, $CHCl_3$). ^1H NMR 1.65 (d, 6 H, J = 15.3 Hz), 2.15 (m, 2 H), 3.20 (s, 1 H), 3.85 (t, 2 H, J = 6.0 Hz), 4.65 (m, 1 H). ^{13}C NMR 25.64, 27.08, 34.00, 58.72, 72.09, 110.98, 173.62.

11. 3-hydroxybutyrolactone, 36. Alcohol **35** (5.49 g, 34 mmol) was dissolved in 100 mL toluene. p-Toluenesulfonic acid monohydrate (50 mg) was added and the mixture was heated to 65 °C for 1 h. After cooling, the reaction was quenched with 75 mL pyridine. The solvent was removed in vacuo to yield 4.23 g of a yellow oil. The product was purified by flash chromatography (70 g silica, 40% acetone/petroleum ether elution) to provide 2.92 g of a colorless oil (83%). R_f = 0.31 (ethyl acetate). $[\alpha]_D^{22}$ = -20.3° (2.2, methanol). IR 1775 cm^{-1} (C=O). ^1H NMR 2.28 (m, 1 H), 2.58 (m, 1 H), 3.70 (bs, 1 H), 4.20 (m, 1 H), 4.42 (dt, 1 H, J = 2.0, 9.0 Hz), 4.51 (dd, 1 H, J = 8.4, 10.1 Hz). ^{13}C NMR 30.80, 65.19, 67.38 (CH), 178.10.

12. 3-(S)-hydroxybutyrolactone, benzyloxy methyl ether, 37. 3-hydroxybutyrolactone **36** (1.68 g, 16.4 mmol) was dissolved in 13 mL 1,2-dimethoxyethane (DME) under N_2, followed by sequential addition of diisopropyl ethyl amine (3.37 mL, 19.3 mmol) and benzyl chloromethyl

ether (3.6 mL, 25.9 mmol). The reaction mixture was heated at 65 °C for 2 h. The cooled mixture was diluted with water followed by three extractions with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. Removal of solvent provided a yellow oil which was chromatographed (60 g silica, 30% ethyl acetate/petroleum ether elution) to yield 2.87 g of a clear, colorless oil (79%). R_f = 0.42 (diethyl ether). $[\alpha]_D^{22}$ = -81.67° (1.86, $CHCl_3$). ^1H NMR 2.25 (m, 1 H), 2.51 (m, 1 H), 4.20 (td, 1 H, J = 6.5, 9.3 Hz), 4.40 (dt, 1 H, J = 3.0, 8.8 Hz), 4.47 (dd, 1 H, J = 8.1, 9.1 Hz), 4.68 (d, 2 H, J = 2.3 Hz), 4.87 (d, 1 H, J = 7.1 Hz), 5.07 (d, 1 H, J = 7.1 Hz), 7.32 (m, 5 H). ^{13}C NMR 29.86 (CH_2), 65.11 (CH_2), 70.15 (CH_2), 70.39 (CH), 94.02 (O-CH_2-O), 127.89, 127.99, 128.40, 128.51, 174.85.

13. 3-(S)-hydroxybutyrolactol, 3-benzyloxy methyl ether, 38. Lactone 37 (2.20 g, 9.9 mmol) was dissolved in 100 mL diethyl ether. The reaction mixture was cooled to -78 °C. 10.0 mL 1.0 M DIBAL-H was added and the mixture was allowed to slowly equilibrate to 0 °C. After 4 h, 100 mL 1% NaOH was added and the mixture was extracted thrice with diethyl ether. Removal of solvent followed by column purification (1:1 CH_2Cl_2/petroleum ether) yielded 1.61 g of a clear, colorless oil (73%). R_f = 0.34 (diethyl ether). $[\alpha]_D^{22}$ = +33.7° (2.3, $CHCl_3$). IR 3420 cm^{-1}(OH), 1785 cm^{-1} (C=O). Anal. calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.71; H, 7.35. ^1H NMR 2.10 (m, 2 H), 3.04 (s, 1 H), 4.07 (m, 2 H), 4.21 (m, 1 H), 4.63 (m, 2 H), 4.83 (m, 2 H), 5.36 (m, 1 H), 7.30 (m, 5 H). ^{13}C NMR 29.81, 29.86, 64.77, 66.88, 69.69, 70.08, 76.65, 81.33, 93.67,

94.32, 96.36, 101.05, 127.74, 127.83, 127.92, 128.43, 128.51, 137.57. (Mixture of α- and β- anomers).

14. N-benzylidene, 2-(S)-benzyloxymethylether-4-hydroxy-butanal, 41. A solution containing 0.625 g lactol **38** (2.8 mmol) in 1 mL toluene was added to a stirred solution of 0.38 g benzylamine (1.25 eq) in 2 mL toluene. The mixture was stirred at ambient temperature for greater than 10 h followed by removal of the solvent in vacuo. The residue was heated to 60-80 °C at 0.5 mm to remove unreacted benzylamine, yielding 0.869 g of a yellow oil (99.5%). This product was not stable and was submitted to further reaction without purification. R_f = 0.5 (diethyl ether). IR 1660 cm^{-1} (C=N). ^1H NMR (60 MHz) 1.6-2.3 (m, 2 H), 2.45 (s, 2 H), 3.5-4.2 (m, 4 H), 4.65 (s, 2 H), 4.85 (s, 2 H), 7.35 (d, 10 H).

15. 1-benzyl-5-(phenylsulfonyl)-6-[1-benzyloxymethoxy-3-hydroxypropyl]-2-piperidone, 42. Imine **41** (0.869 g, 2.8 mmol) was dissolved in 5 mL THF. The mixture was cooled to -78 °C and 1.0 mL boron trifluoride etherate (3.0 eq) was added. After 0.5 h, this mixture was added to a dianion solution prepared as follows: 4-PSBA (1.28 g, 5.6 mmol) was dissolved in 75 ml THF and cooled to -78 °C. Butyllithium (4.5 mL, 2.5 M, 11.2 mmol) was added dropwise to give a clear, yellow solution. Upon addition of the complexed imine to this dianion solution, the color was discharged. The mixture was allowed to slowly equilibrate to 0 °C whereupon 1.5 mL TFAA was added. After 0.5 h, the reaction was partitioned between ethyl acetate and saturated Na_2CO_3. A total of three

ethyl acetate extractions were performed and the combined organic phases were dried over Na_2SO_4. Removal of solvent yielded 1.543 g of a yellow oil (>100%). Column purification (ethyl acetate elution) provided two products of R_f = 0.21, 0.11 designated as fast and slow bands, respectively, in a total yield of 0.395 g (27%). Anal calcd. for $C_{29}H_{33}NO_6S \cdot 1/2\ H_2O$: C, 65.39; H, 6.43; N, 2.63. Found: C, 65.68; H, 6.29; N, 2.68.

42a Fast band $[\alpha]_D^{22}$ = -5.3° (0.34, $CHCl_3$). IR 3500 cm^{-1} (OH), 1640 cm^{-1} (C=O, strong). ^1H NMR 1.54 (m, 2 H), 2.13 (m, 2 H), 2.53 (m, 2 H), 3.53 (m, 3 H), 4.04 (d, 1 H, J = 14.8 Hz), 4.06 (m, 2 H), 4.52 (d, 2 H, J = 3.9 Hz), 4.56 (d, 1 H, J = 6.8 Hz), 4.73 (d, 1 H, J = 6.8 Hz), 5.30 (d, 1 H, J = 14.7 Hz), 7.29 (m, 10 H), 7.44 (m, 2 H), 7.58 (m, 3 H). ^{13}C NMR 21.06, 29.46, 33.78, 48.27, 56.48 (CH), 58.48 (CH), 58.77, 70.36, 76.47 (CH), 94.66, 127.52, 127.63, 127.69, 127.86, 128.42, 128.51, 128.56, 128.75, 128.89, 129.07, 129.19, 129.23, 133.92, 136.31, 136.67, 136.69, 136.95, 170.98. (Some aromatic resonances unresolved).

42b Slow band $[\alpha]_D^{22}$ = - 63.46° (0.26, $CHCl_3$). White crystals from $CHCl_3$/ diethyl ether, mp = 153.5-154.5 °C. IR 3500 cm^{-1} (OH), 1640 cm^{-1} (C=O, strong) ^1H NMR 1.52 (m, 1 H), 1.75 (m, 1 H), 2.18 (m, 2 H), 2.57 (m, 2 H), 2.93 (m, 1 H), 3.66 (m, 3 H), 3.94 (m, 3 H), 3.99 (d, 1 H, J = 14.9 Hz), 4.19 (m, 1 H), 4.40 (d, 1 H, J = 12.0 Hz), 4.58 (d, 1 H, J = 12.1 Hz), 5.61 (d, 1 H, J = 14.9 Hz), 7.44 (m, 15 H). ^{13}C NMR 18.86, 28.47, 32.51, 48.08, 53.93(CH),

56.52(CH), 58.75, 70.08, 72.83(CH), 93.17, 127.61, 127.81, 128.01, 128.53, 128.69, 128.83, 129.16, 129.29, 133.79, 136.19, 136.95, 137.05, 169.97. (Some aromatic resonances unresolved).

16. 2-(1-benzyloxymethoxy-3-hydroxypropyl)-3-(phenylsulfonyl)-N-benzyl-piperidine, 43. Piperidone **42** (0.105 g, 0.2 mmol) was dissolved in 5 mL THF. The mixture was cooled to 0° C and 0.6 mL of 1M BH_3·THF (3.0 eq) was added dropwise. The mixture was allowed to slowly warm to room temperature and stirred overnight. The reaction was quenched by addition of 5 drops 5% NaOH and partitioned between CH_2Cl_2 and saturated Na_2CO_3. A total of three extractions were performed. The combined organic phases were dried over Na_2SO_4. Removal of solvent in vacuo yielded 95.1 mg of a pale yellow oil. The product was purified on florisil (ethyl acetate with 1% TEA elution) to yield 84.5 mg of a clear, colorless oil (84%).

43a Fast band $R_f = 0.34$ (diethyl ether). $[\alpha]_D^{22} = +13.0°$ (0.52, $CHCl_3$). HRMS m/z calcd for $C_{29}H_{35}NO_5S$ 509.2236, found 509.2316. ^1H NMR 1.25 (m, 1 H), 1.98 (m, 5 H), 2.70 (m, 2 H), 2.82 (bs, 1 H), 3.65 (m, 4 H), 4.11 (s, 2 H), 4.17 (m, 1 H), 4.52 (d, 1 H, J =11.9 Hz), 4.56 (d, 1 H, J = 11.9 Hz), 4.82 (d, 1 H, J = 14.7 Hz), 4.84 (d, 1 H, J = 14.7 Hz), 7.19 (m, 2 H), 7.36 (m, 8 H), 7.62 (m, 3 H), 7.99 (d, 2 H, J = 7.1 Hz). ^{13}C NMR 16.62, 20.95, 35.34, 45.07, 46.25, 57.74(CH), 58.18(CH), 59.24, 70.39, 75.96, 94.52, 126.98, 127.44, 127.80, 128.19, 128.29, 128.42, 128.54, 128.69,

129.04, 129.08, 133.37, 137.14, 139.08, 139.25. (Some aromatic resonances unresolved).

43b Slow band R_f = 0.29 (diethyl ether). $[\alpha]_D^{22}$ = -46.5° (0.16, $CHCl_3$). ^1H NMR 1.50 (m, 1 H), 2.01 (m, 5 H), 2.74 (m, 1 H), 2.92 (m, 1 H), 3.50 (m, 2 H), 3.58 (t, 1 H, J = 4.2 Hz), 3.70 (m, 2 H), 3.98 (d, 1 H, J = 13.7 Hz), 4.09 (d, 1 H, J = 13.7 Hz), 4.18 (q, 1 H, J = 6.0 Hz), 4.53 (d, 1 H, J = 11.9 Hz), 4.58 (s, 2 H), 4.64 (d, 1 H, J = 11.9 Hz), 7.37 (m, 10 H), 7.53 (m, 2 H), 7.63 (m, 1 H), 7.89 (m, 2 H). ^{13}C NMR 17.64, 21.77, 35.03, 45.95, 57.25(CH), 58.51(CH), 58.56, 58.97, 70.27, 78.59(CH), 94.78, 127.11, 127.57, 127.77, 128.29, 128.43, 128.69, 129.01, 129.04, 133.37, 137.40, 138.35, 138.93. (Some aromatic resonances unresolved).

17. 8-(phenylsulfonyl)-1-benzyloxymethoxy-indolizidine, 45. A general procedure is presented: The piperidine was dissolved in CH_2Cl_2(approximately 25 mg/mL). Excess K_2CO_3, 5 drops TEA, and 1 eq. methanesulfonyl chloride were added sequentially. After 2 h, the mixture was filtered and the solvent was removed. The residue was dissolved in methanol (1-2 mL) and subjected to hydrogenolysis (100 mg Pearlman's catalyst, 39 psi H_2) for > 4 h. The solution was filtered and the solvent was removed in vacuo. Column purification (florisil, ethyl acetate with 1% TEA elution) provided the products as lightly yellow oils.

45a Fast band 85.4 mg piperidine reacted, 146.1 mg crude mesylate obtained, 69.1 mg crude indolizidine obtained (98%), 27.5 mg pure indolizidine recovered (40%). R_f = 0.31 (ethyl acetate). $[\alpha]_D^{23}$ = -65.8° (0.16, $CHCl_3$). HRMS m/z calcd for $C_{22}H_{27}NO_4S$ 401.1661, found 401.1608. ^1H NMR 1.32 (dq, 1 H, J = 4.5, 12.7 Hz), 1.64 (m, 2 H), 1.95 (m, 2 H), 2.16 (m, 2 H), 2.33 (dd, 1 H, J = 5.4, 9.9 Hz), 2.47 (m, 1 H), 3.03 (m, 3 H), 4.57 (dt, 1 H, J = 2.0, 6.0 Hz), 4.69 (d, 1 H, J = 11.8 Hz), 4.87 (d, 1 H, J = 11.9 Hz), 5.02 (d, 1 H, J = 7.0 Hz), 5.08 (d, 1 H, J = 7.0 Hz), 7.38 (m, 5 H), 7.65 (m, 3 H), 8.00 (m, 2 H). ^{13}C NMR 24.15, 27.10, 31.60, 51.46, 52.10, 64.72, 68.81, 70.11, 81.56, 96.30, 127.54, 127.74, 128.36, 128.93, 129.23, 129.34, 133.55, 137.57, 138.10. (Some aromatic resonances unresolved).

45b Slow band 171.1 mg piperidine reacted, 234.2 mg crude mesylate obtained, 141 mg crude indolizidine obtained (100%), 72.8 mg pure indolizidine recovered (52%). R_f = 0.29 (ethyl acetate). $[\alpha]_D^{23}$ = -5.1° (0.22, $CHCl_3$). HRMS m/z calcd for $C_{22}H_{27}NO_4S$ 401.1661, found 401.1663. ^1H NMR 1.30 (t, 1 H, J = 7.3 Hz), 1.77 (m, 5 H), 2.19 (m, 2 H), 3.11 (m, 3 H), 3.61 (m, 1 H), 4.67 (m, 1 H), 4.72 (d, 1 H, J = 11.8 Hz), 4.86 (d, 1 H, J = 11.8 Hz), 4.93 (d, 1 H, J = 7.1 Hz), 5.09 (d, 1 H, J = 7.1 Hz), 7.37 (m, 5 H), 7.62 (m, 3 H), 7.95 (m, 2 H). ^{13}C NMR 23.92, 25.29, 30.40, 51.64, 51.96, 60.06, 64.94, 70.02, 78.42, 95.81, 127.47, 127.63, 127.68, 128.15, 128.31, 128.67, 128.90, 129.05, 129.28, 133.60, 137.90, 138.18.

18. 1(S)-hydroxy-8-(phenylsulfonyl)-indolizidine, 46.

Indolizidine **45** (65.8 mg, 0.16 mmol) was dissolved in approximately 3 mL methanol. 20 mg of 10% Pd/C and 10 μL TFA were added. The mixture was stirred under 10-20 psi H_2 at ambient temperature for greater than 10 h. The solution was filtered and the solvent was removed in vacuo to yield 49.3 mg of a brown oil. The product was purified on florisil (ethyl acetate) to give 27.3 mg (54%) of a clear, colorless oil.

46a Fast band R_f = 0.21 (ethyl acetate). $[\alpha]_D^{23}$ = -13.7° (0.8, methanol). HRMS m/z calcd for $C_{14}H_{19}NO_3S$ 281.1086, found 281.1108. ^1H NMR 1.28 (dq, 1 H, J = 4.4, 12.8 Hz), 1.45 (m, 1 H), 1.69 (m, 2 H), 1.83 (m, 1 H), 1.97 (dt, 1 H, J = 2.9, 11.6 Hz), 2.11 (dd, 1 H, J = 6.6, 10.0 Hz), 2.31 (m, 1 H), 2.42 (q, 1 H, J = 8.9 Hz), 2.95 (m, 3 H), 4.09 (d, 1 H, J = 2.8 Hz), 4.39 (m, 1 H), 7.62 (m, 3 H), 7.90 (m, 2 H). ^{13}C NMR 24.29, 26.29, 30.29, 51.58, 52.15, 66.31, 69.22, 74.96, 129.12, 129.22, 134.05. (Some aromatic resonances unresolved).

46b Slow band R_f = 0.14 (ethyl acetate). $[\alpha]_D^{23}$ = +35.2° (1.1, methanol). HRMS m/z calcd for $C_{14}H_{19}NO_3S$ 281.1086, found 281.1097. ^1H NMR 1.82 (m, 10 H), 3.16 (dt, 1 H, J = 1.7, 8.9 Hz), 3.19 (m, 3 H), 7.60 (m, 3 H), 7.85 (m, 2 H). ^{13}C NMR 24.10, 25.57, 30.99, 51.87, 52.94, 61.23, 67.33, 71.29, 128.44, 128.83, 129.11, 129.22, 129.26, 134.05.

19. (+)-(1S, 8aS)-1-hydroxyindolizidine, 8. Indolizidine **46** (16.4 mg, 0.058 mmol) was dissolved in 2 mL methanol and excess Na/Hg was added. The mixture was stirred at room temperature for 2 h. The solution was filtered into a flask containing 1-2 mL acidic methanol(methanol saturated with HCl(g)). The solvent was removed in vacuo to provide a yellow solid. The residue was dissolved in 2 mL water and 3 pellets KOH were added, followed by three extractions with diethyl ether. The combined organics were dried over Na_2SO_4 and the solvent was removed in vacuo to yield 6.8 mg lightly yellow oil (83%). Filtration through florisil to remove the color provided 5.5 mg clear oil (67%). From fast $[\alpha]_D^{22} = +16.4°$ (0.28, $CDCl_3$). HRMS m/z calcd for $C_8H_{15}NO$ 141.1154, found 141.1157. From slow $[\alpha]_D^{22} = +18.1°$ (0.42, $CDCl_3$). HRMS m/z calcd for $C_8H_{15}NO$ 141.1154, found 141.1150. IR 2800 cm^{-1} (Bohlmann band). ^1H NMR 1.77 (m, 10 H), 3.00 (m, 2 H), 3.47 (s, 1 H), 4.00 (m, 1 H). ^{13}C NMR 24.08, 25.04, 28.79, 31.83, 52.54, 53.29, 71.11, 76.41.

Chapter 5

References

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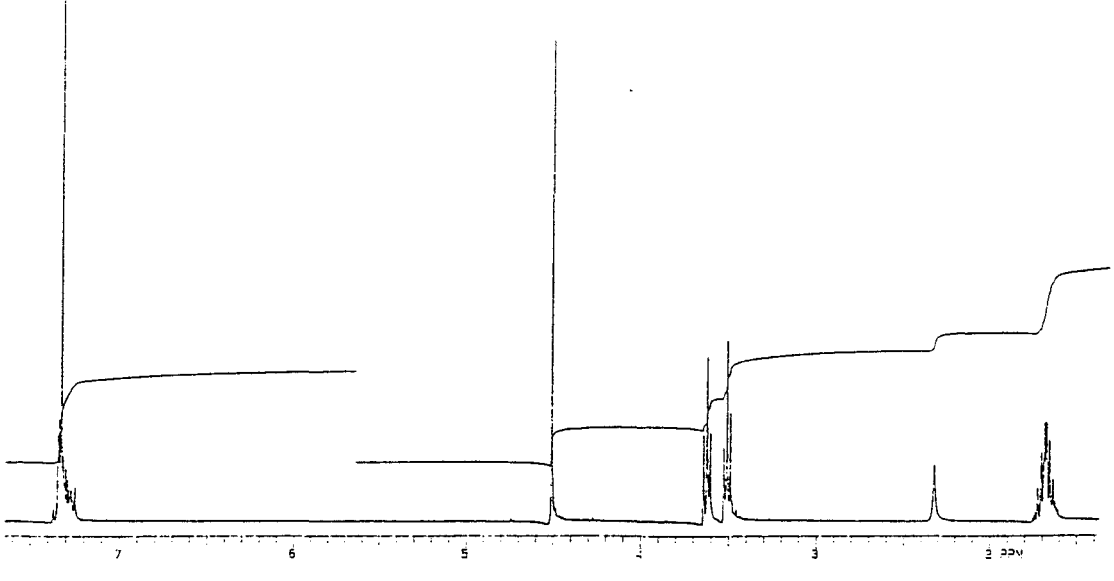
Chapter 6

Sample Spectra

24



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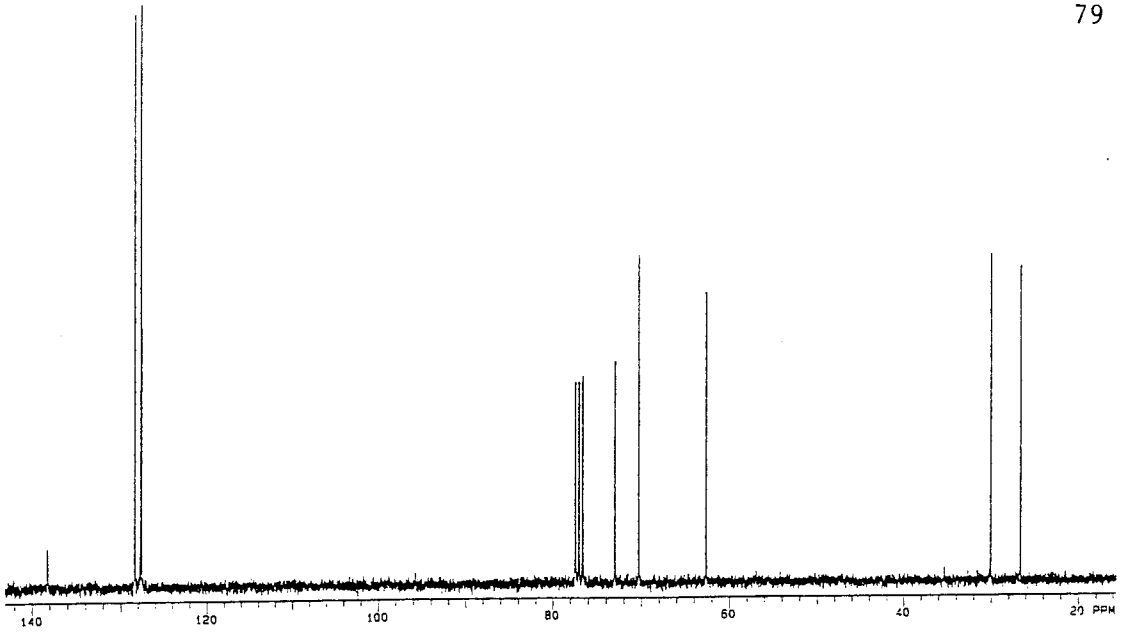

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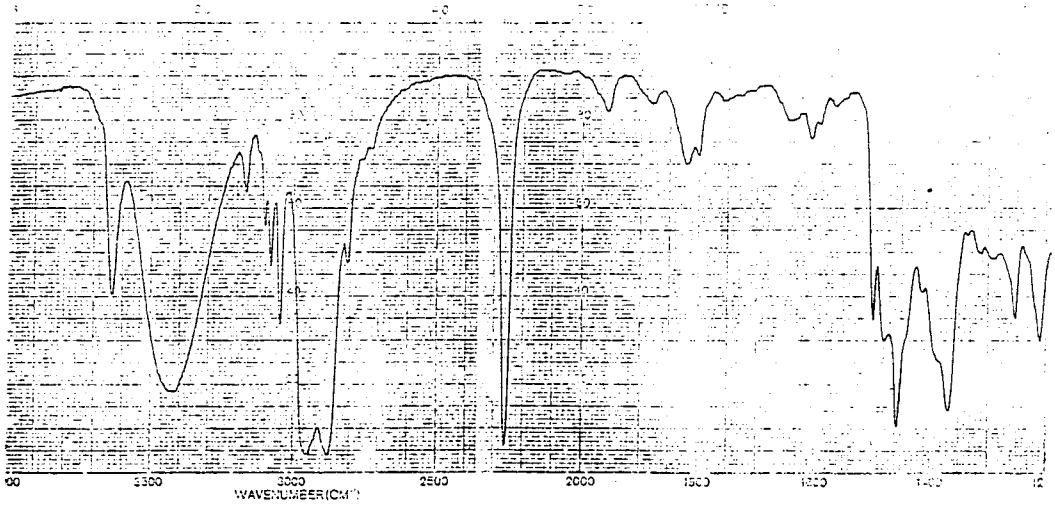

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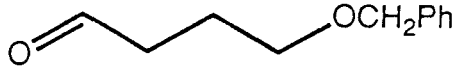

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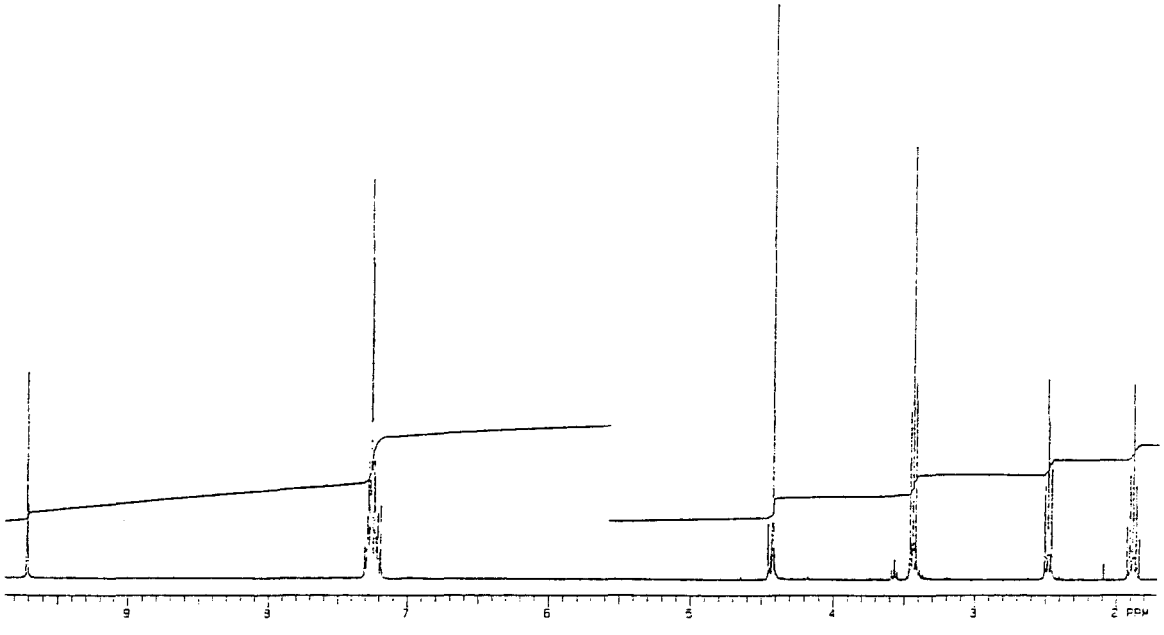

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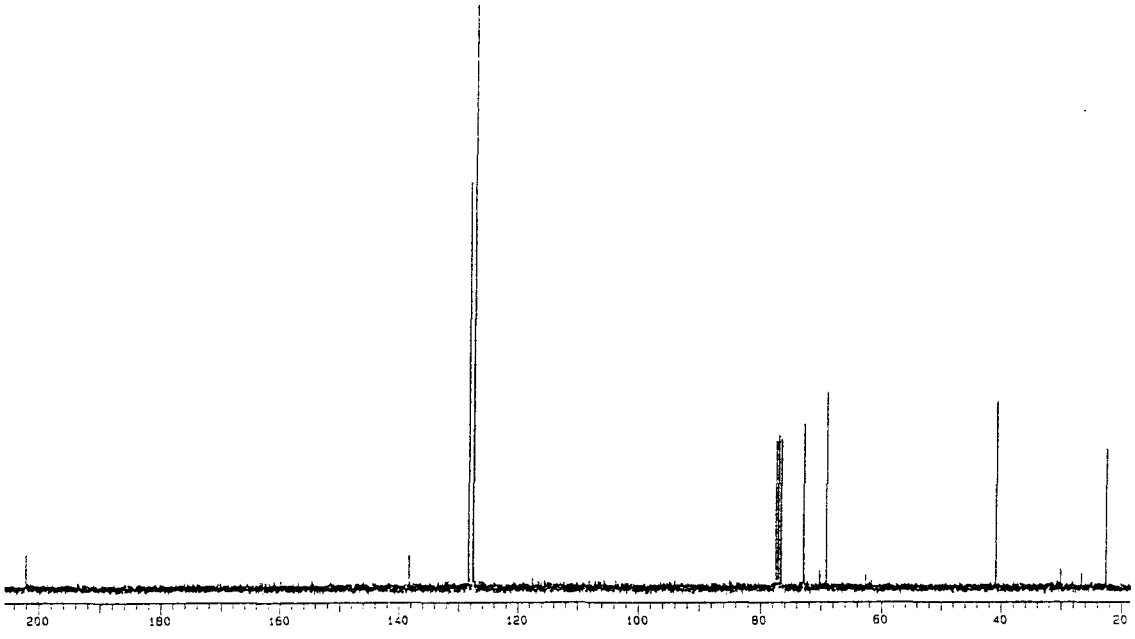

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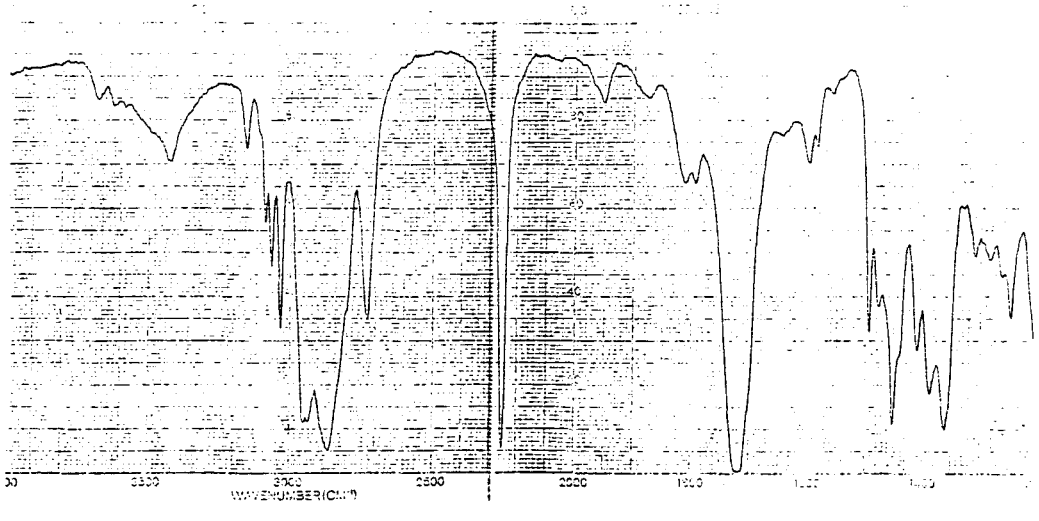

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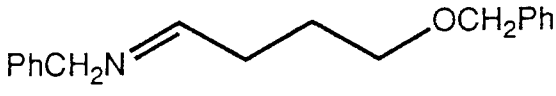

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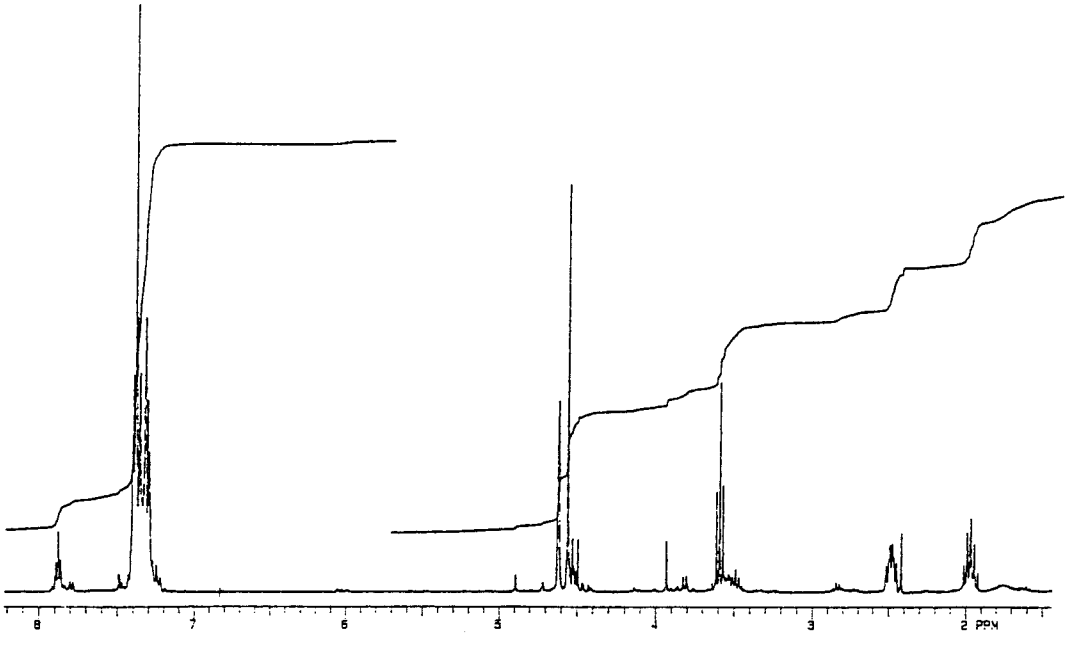

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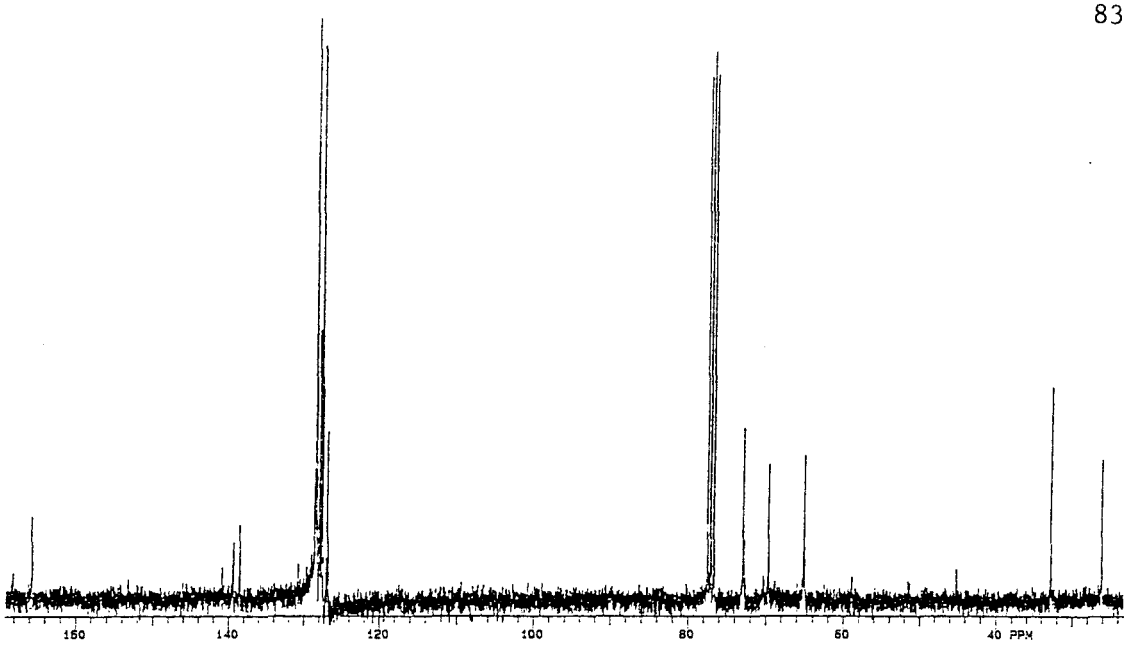

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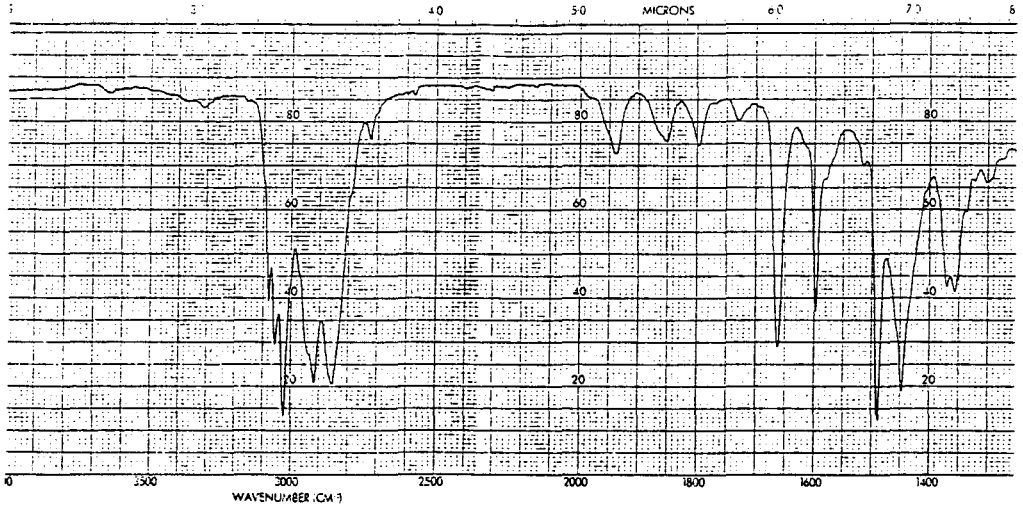

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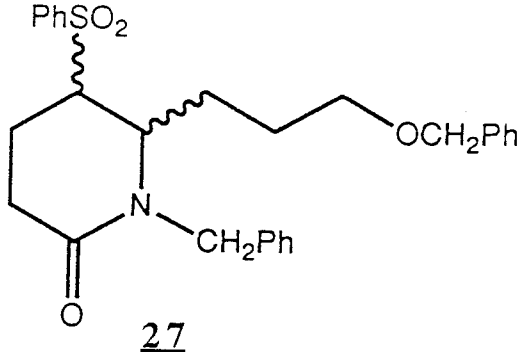

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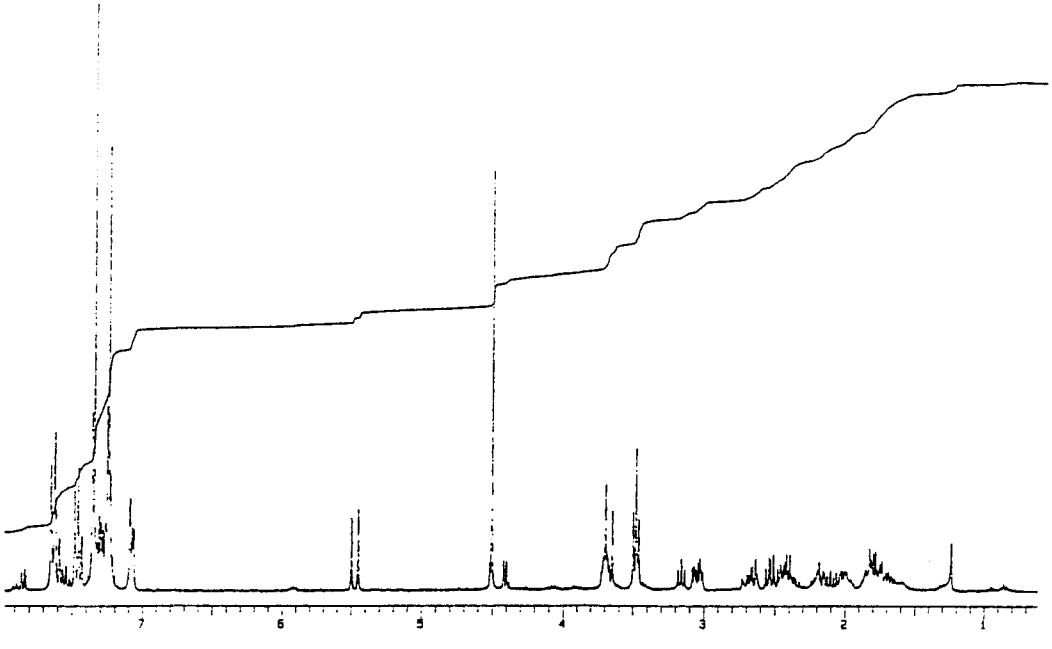

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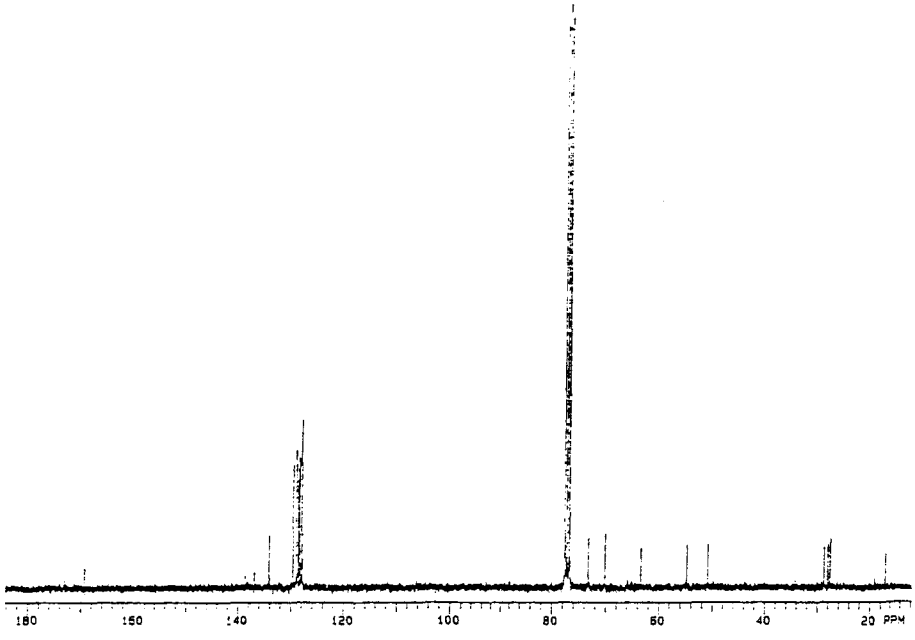

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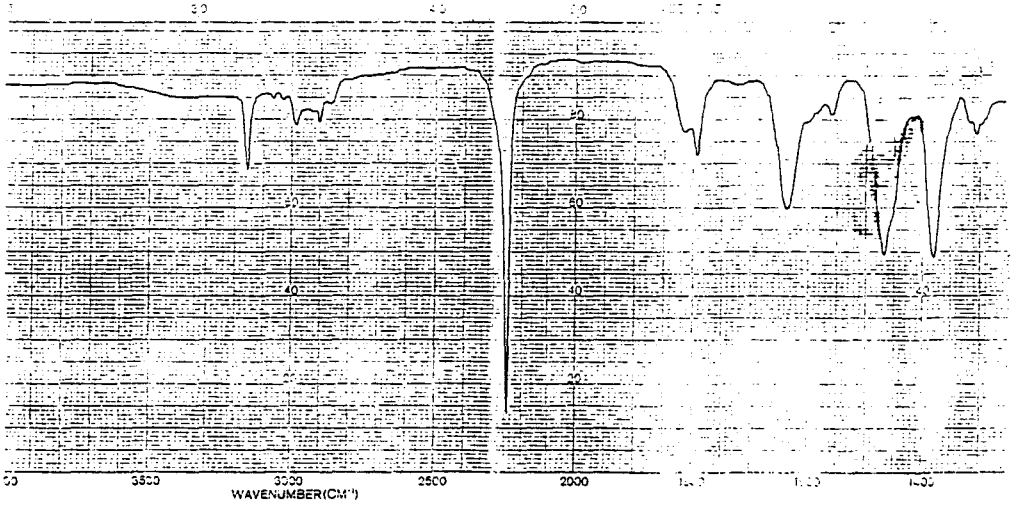

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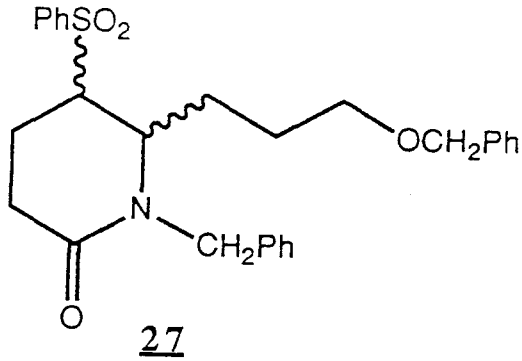

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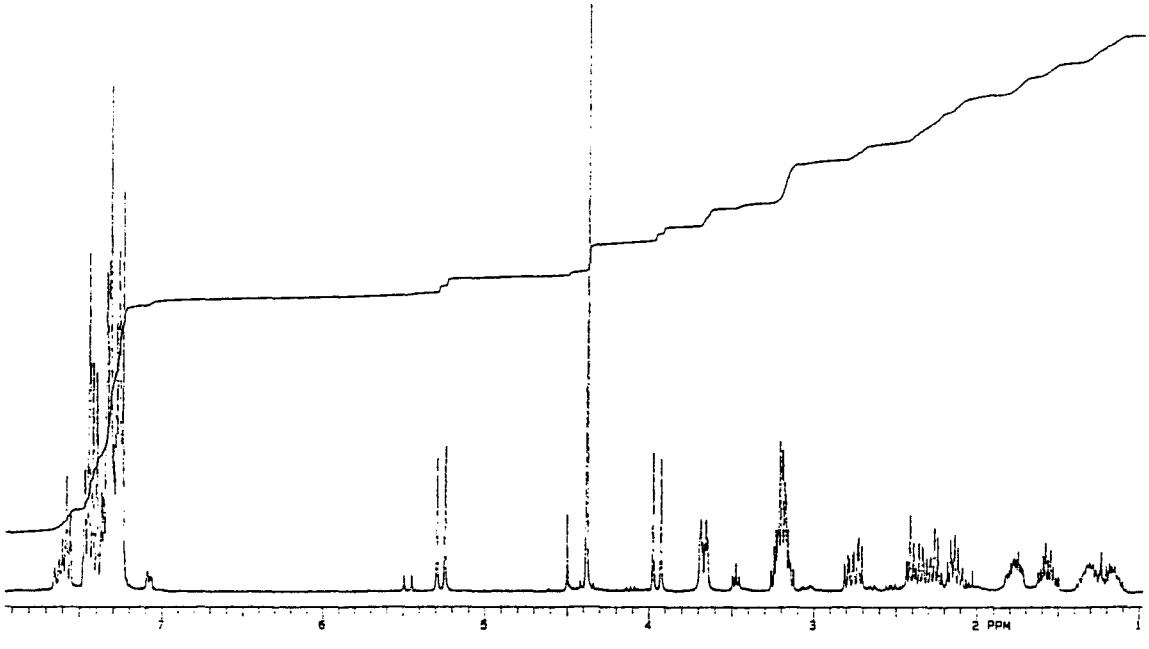

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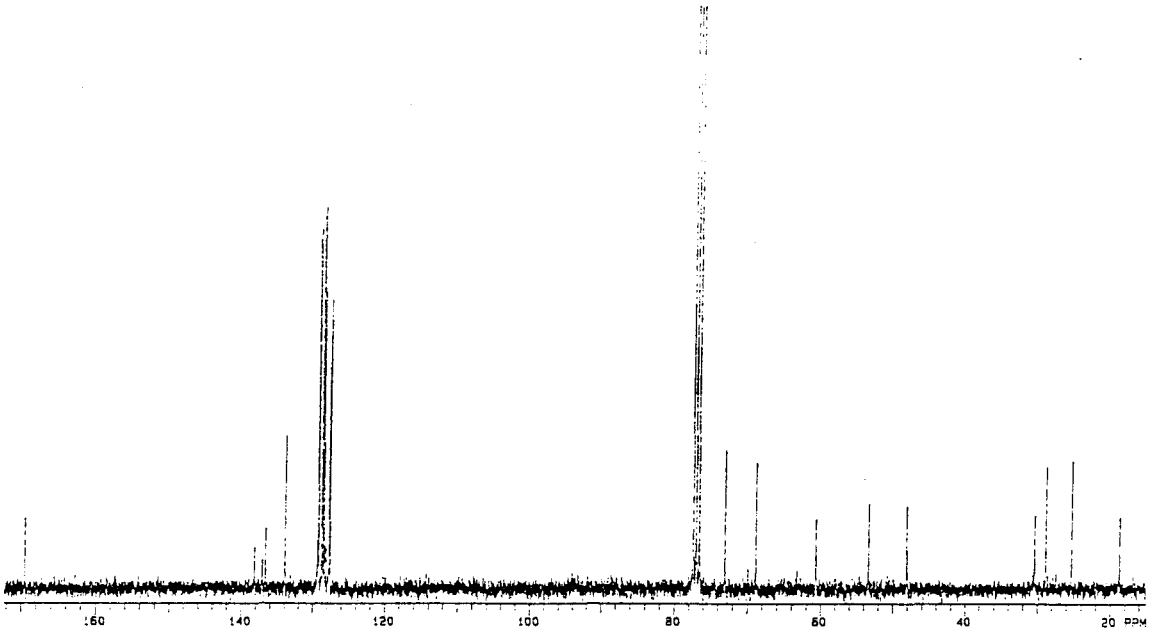

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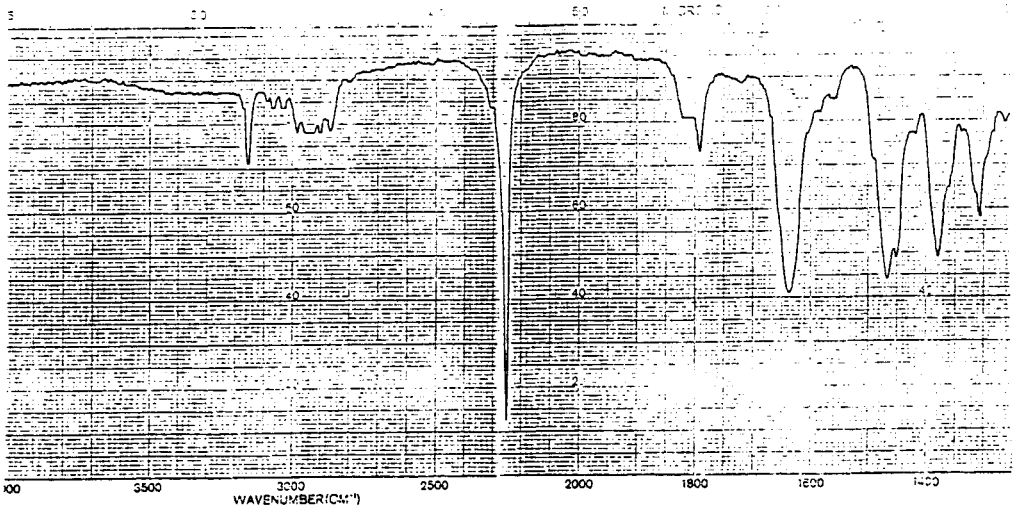

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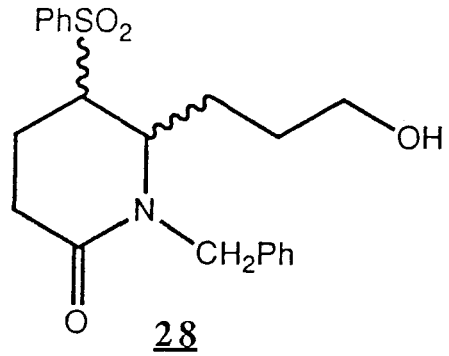
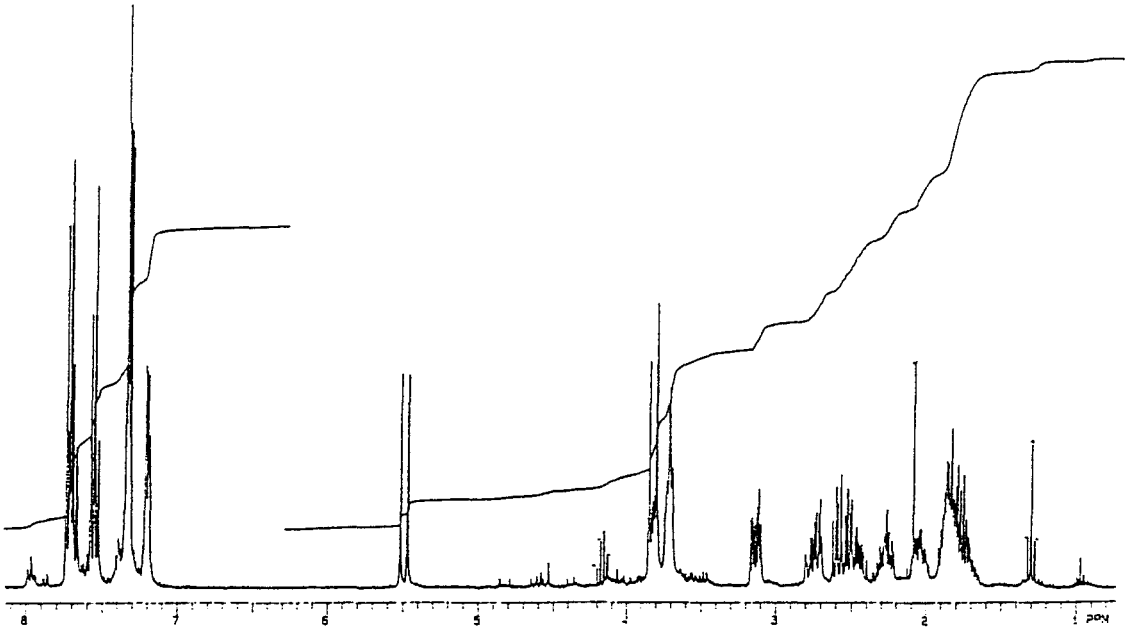
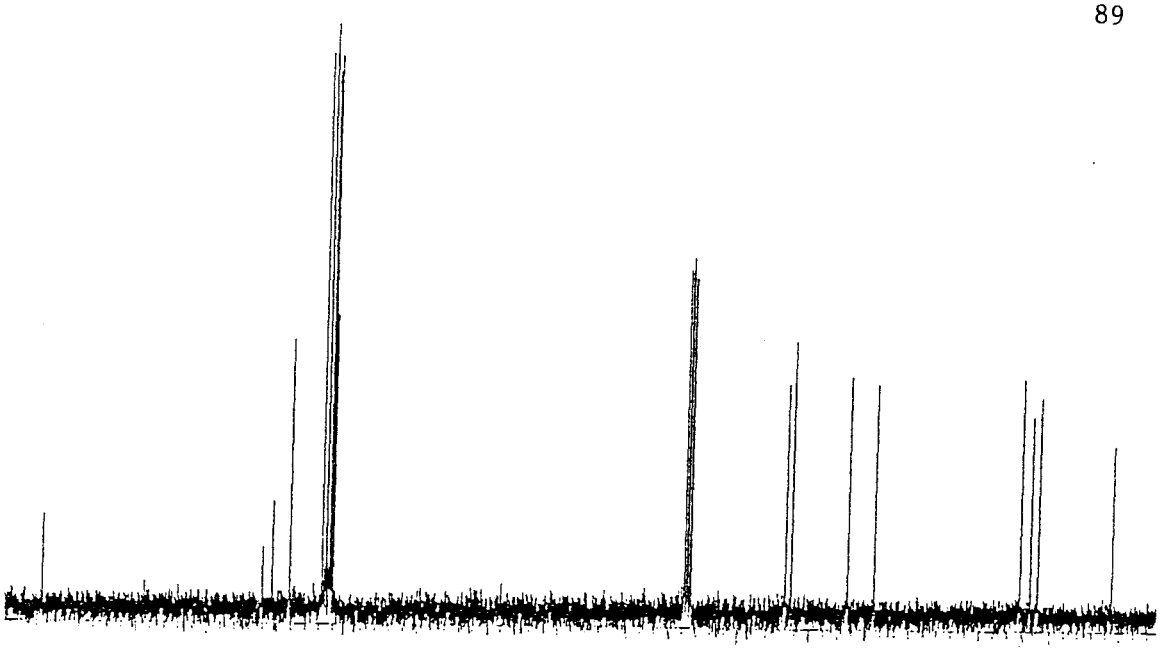


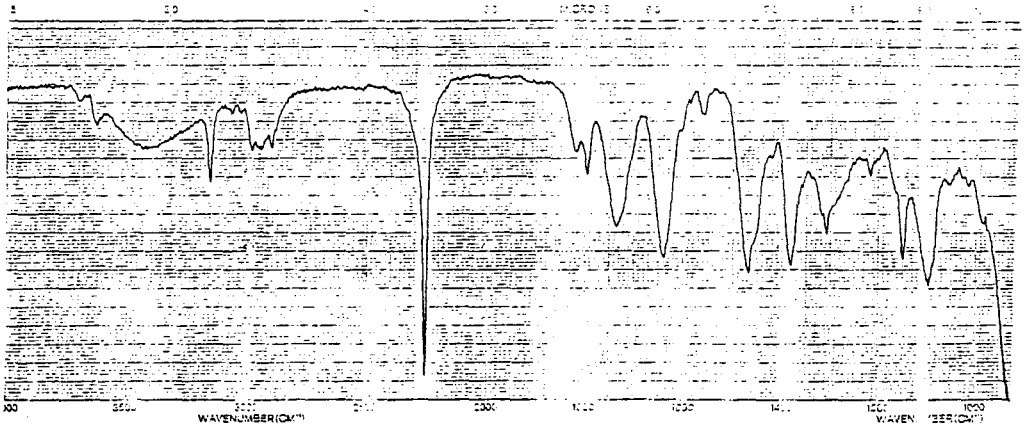
28



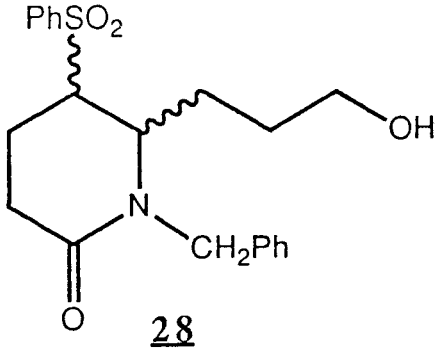
^{1}H NMR for **28a**



^{13}C NMR for **28a**



IR for **28a**



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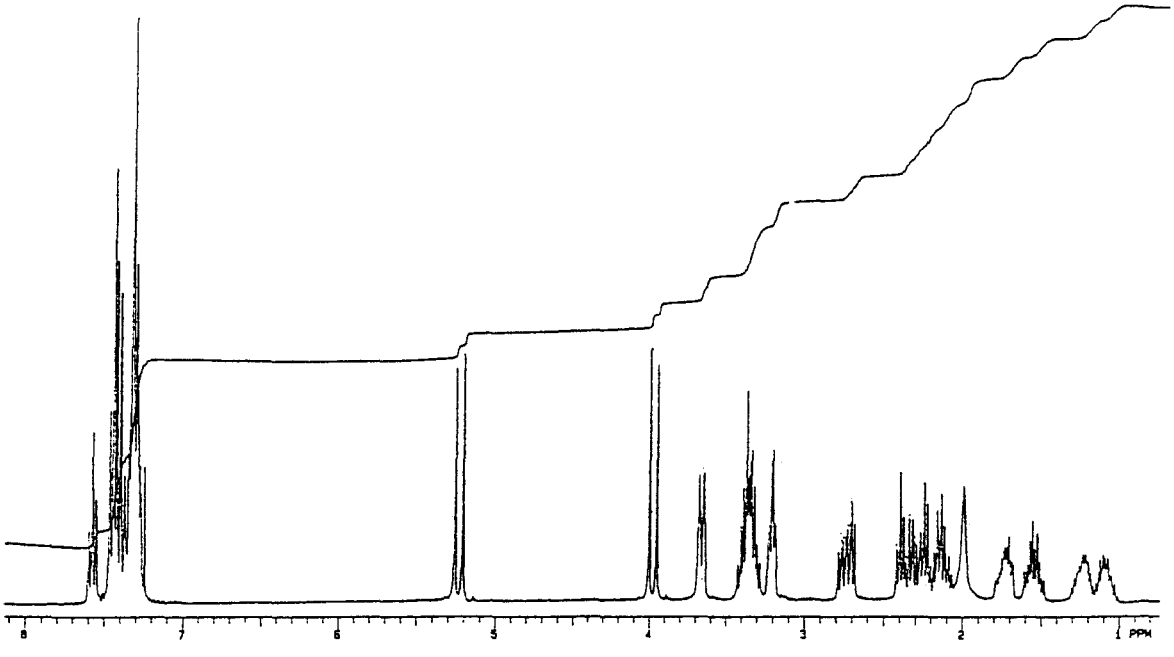
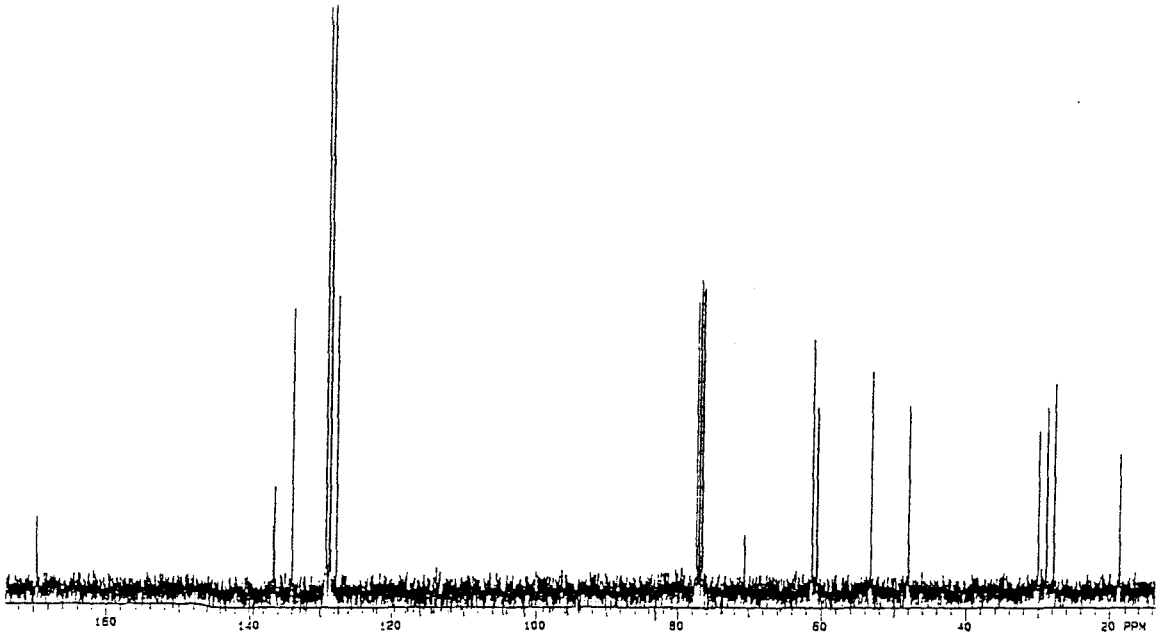
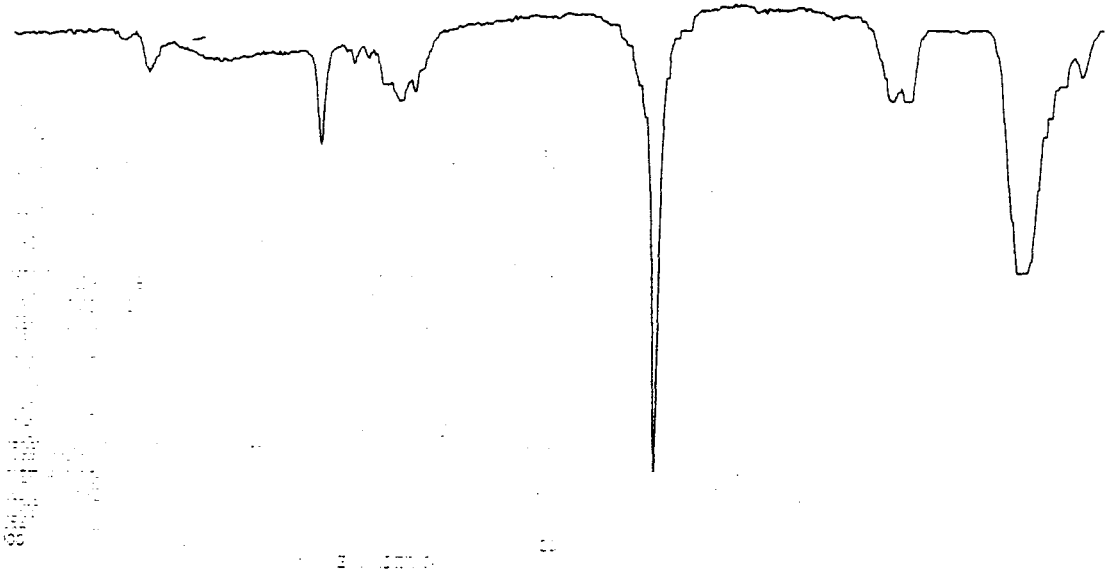


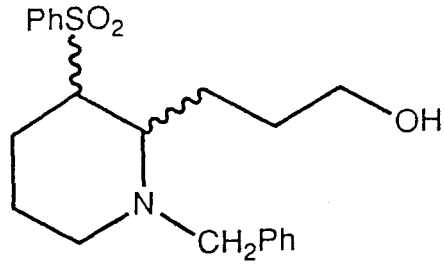
^{1}H NMR for **28b**



^{13}C NMR for **28b**



IR for **28b**



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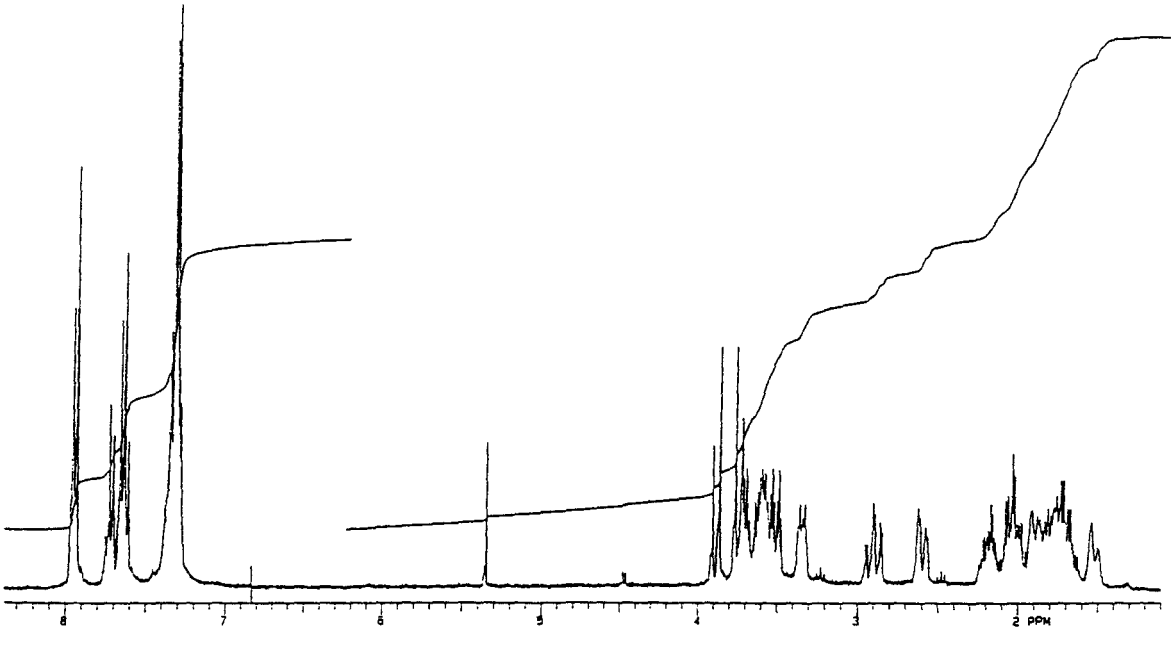
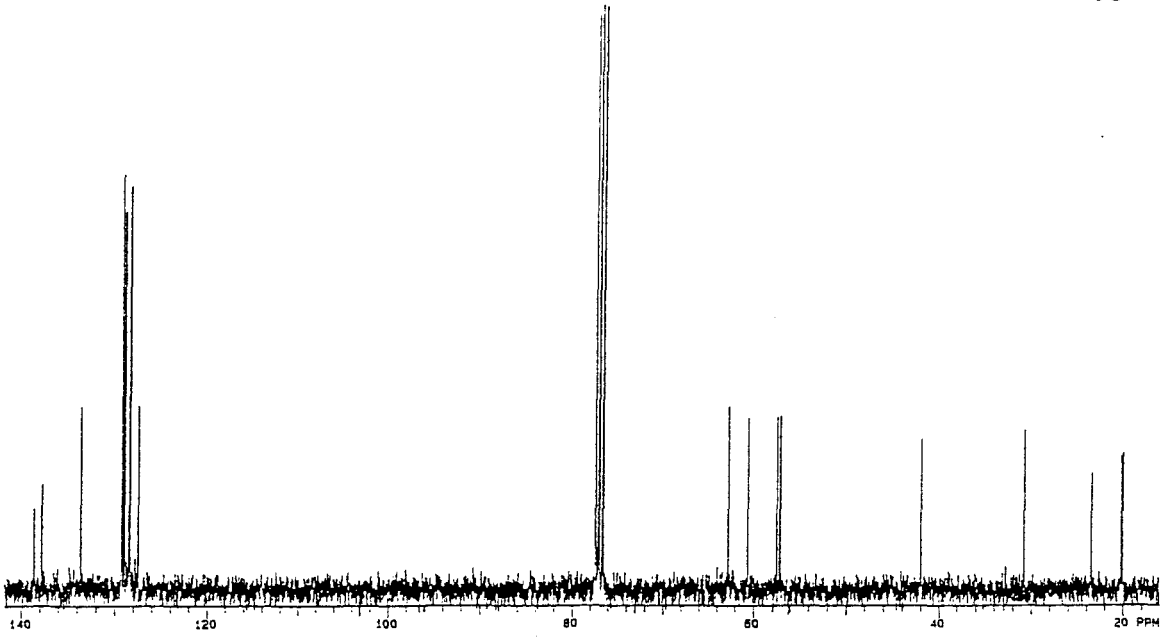
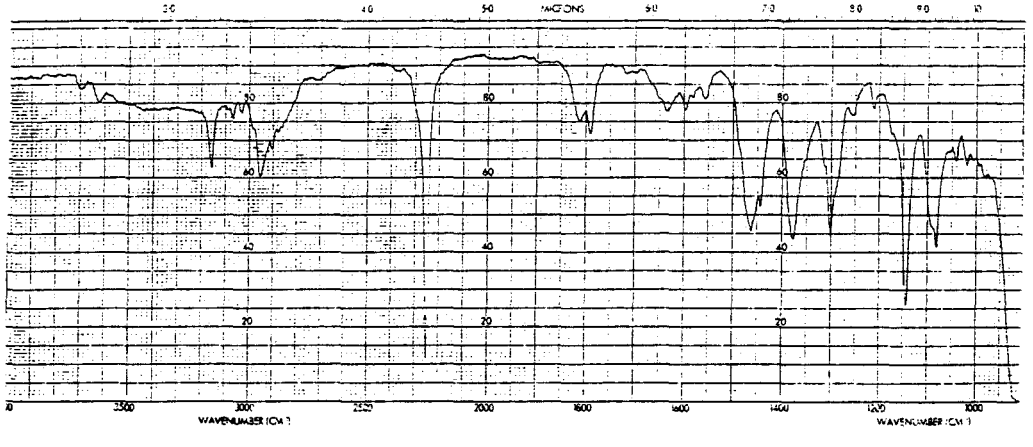


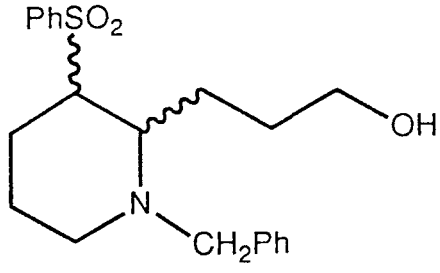
^{1}H NMR for **29a**



^{13}C NMR for **29a**



IR for **29a**



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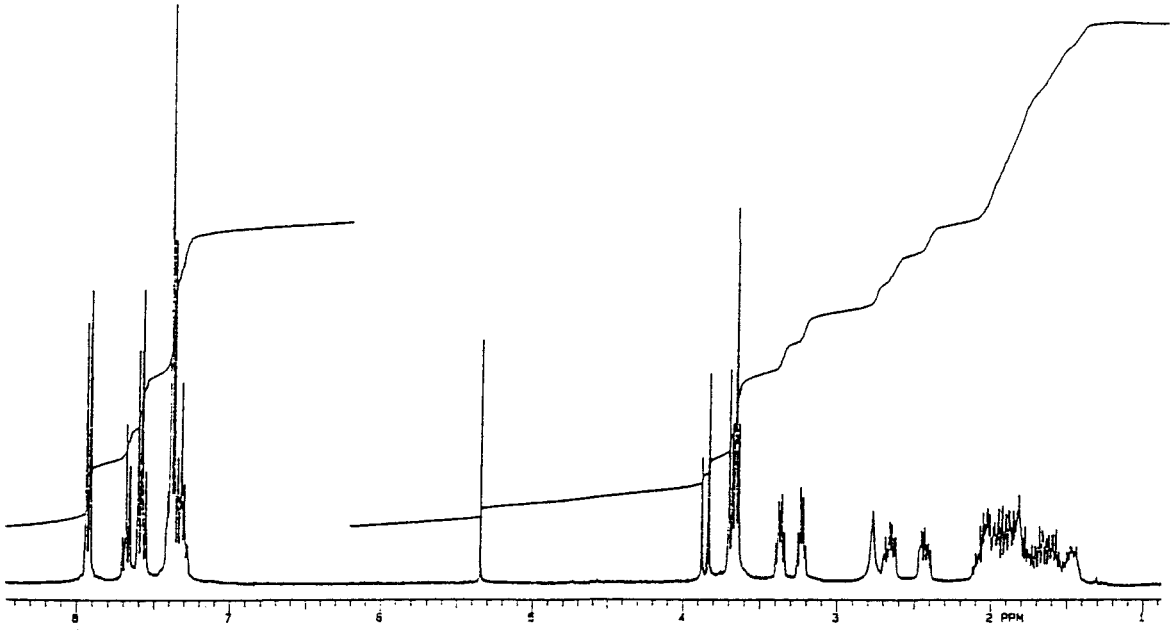
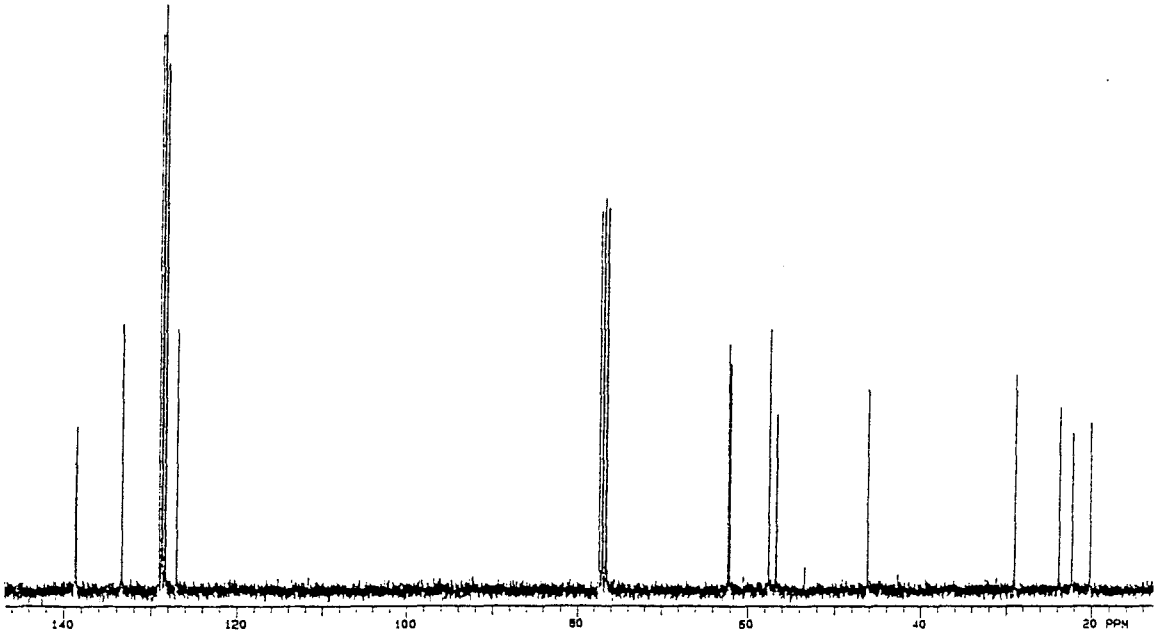
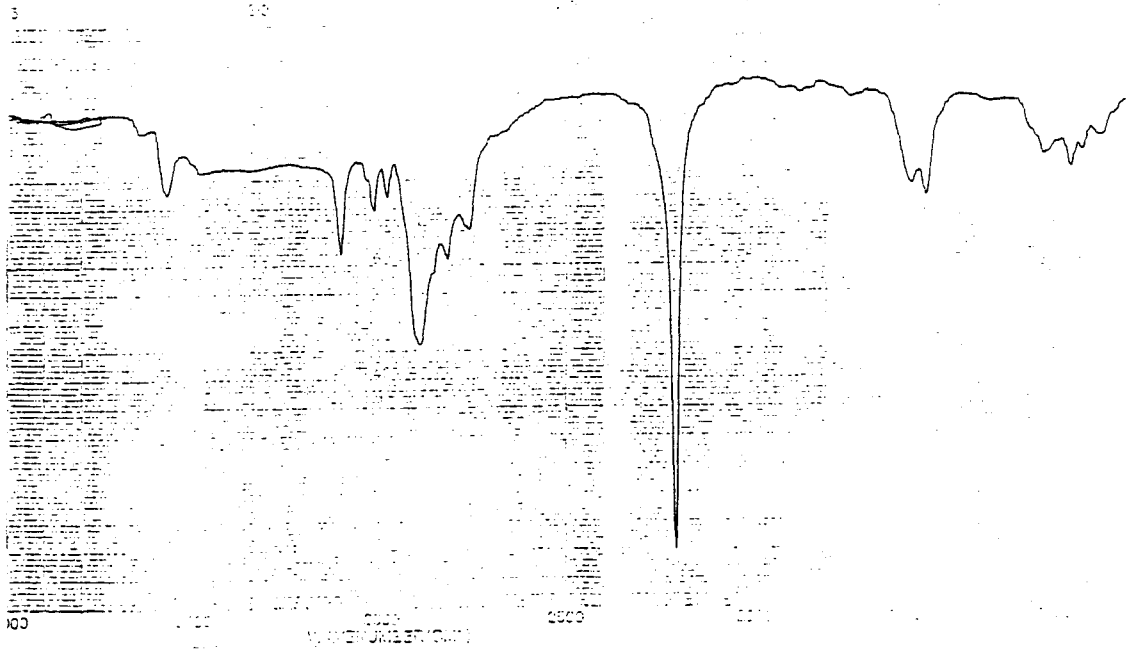


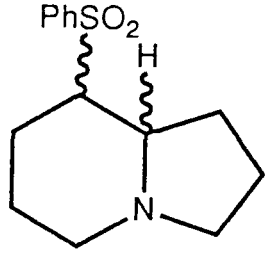
^{1}H NMR for **29b**



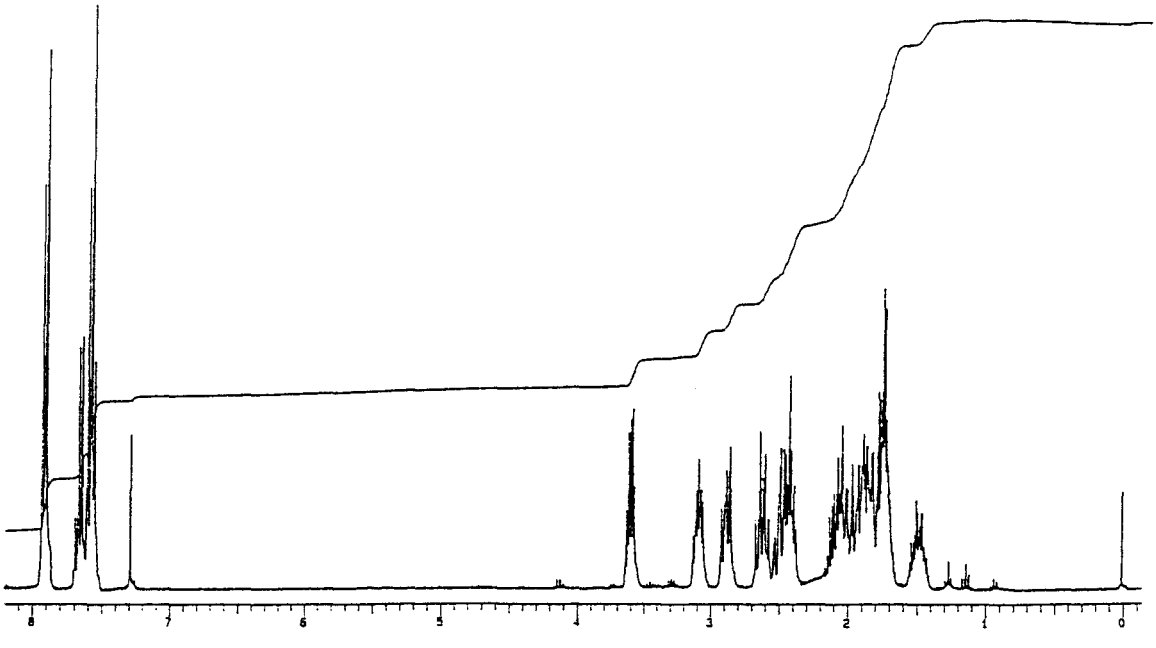
^{13}C NMR for **29b**



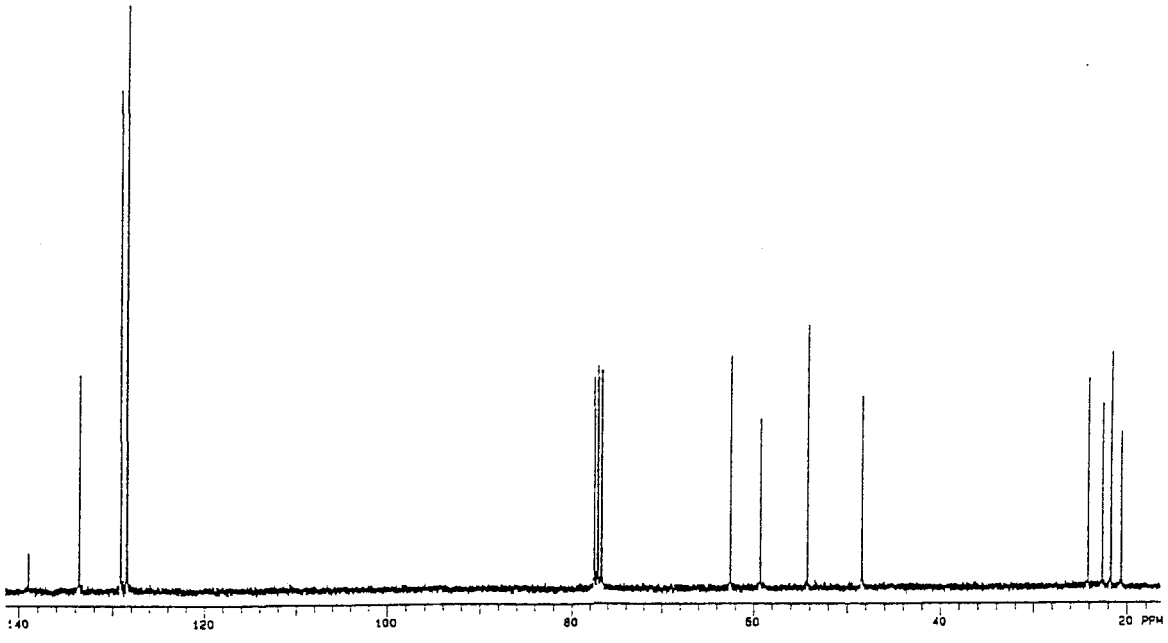
IR for 29b



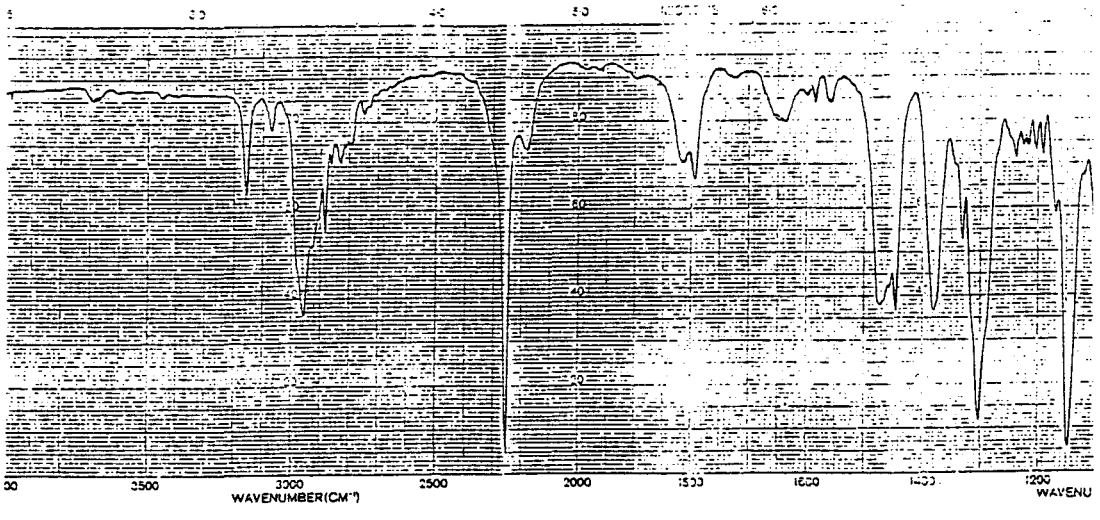
31



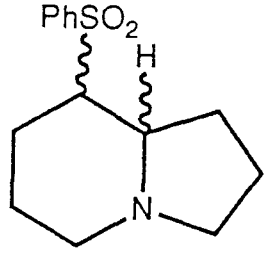
^{1}H NMR for **31a**



^{13}C NMR for **31a**



IR for **31a**



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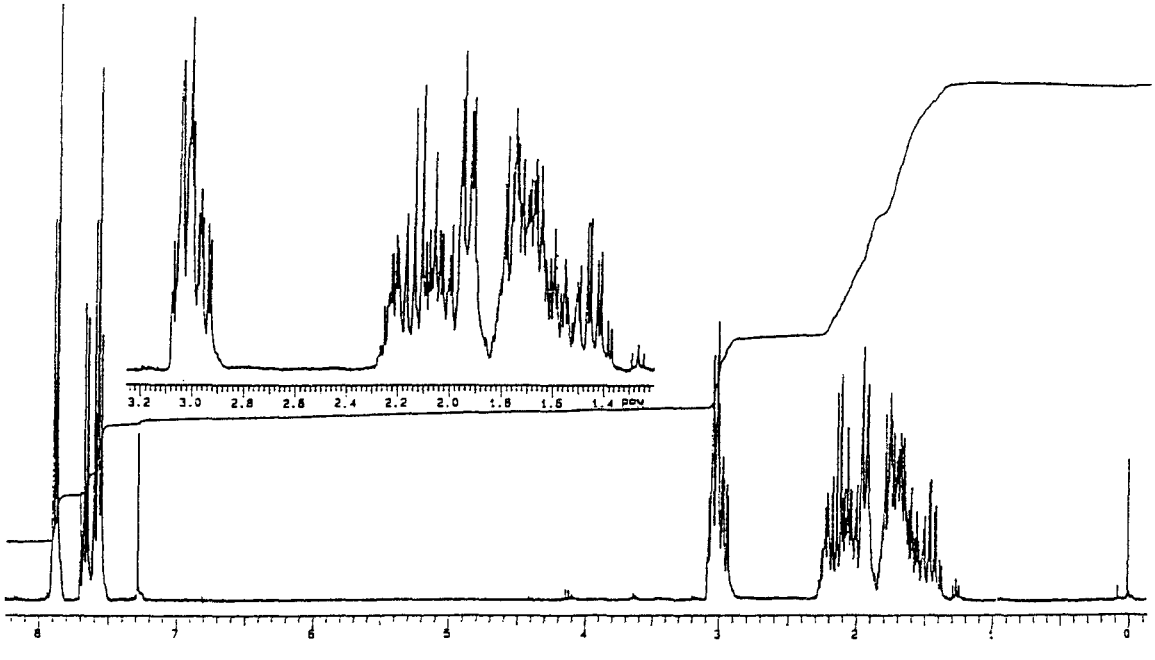
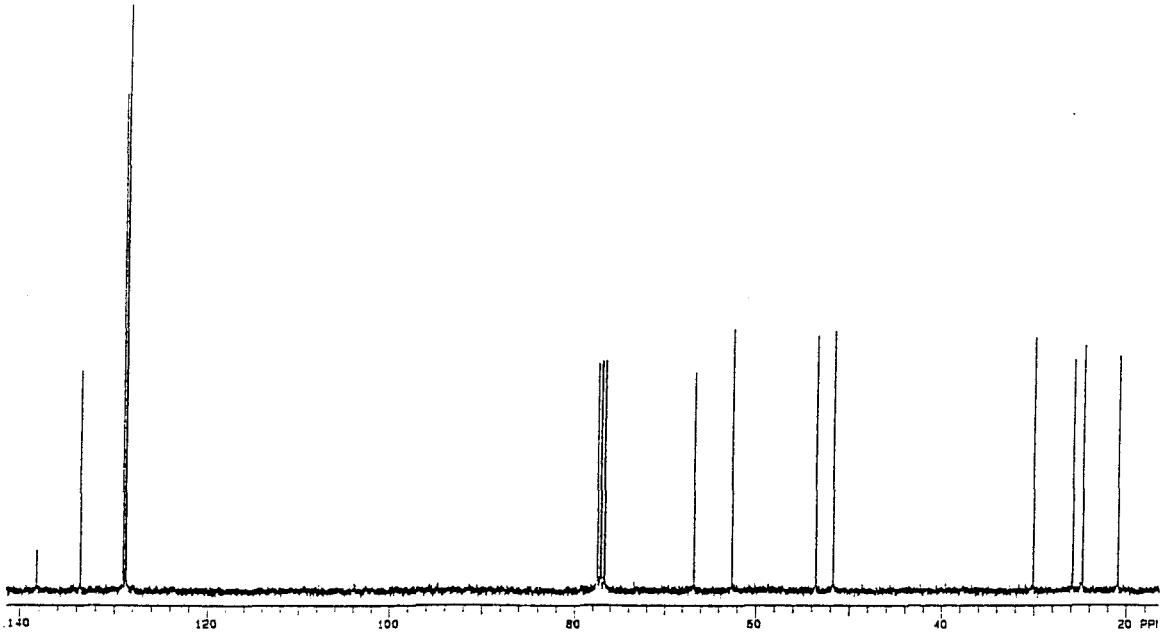
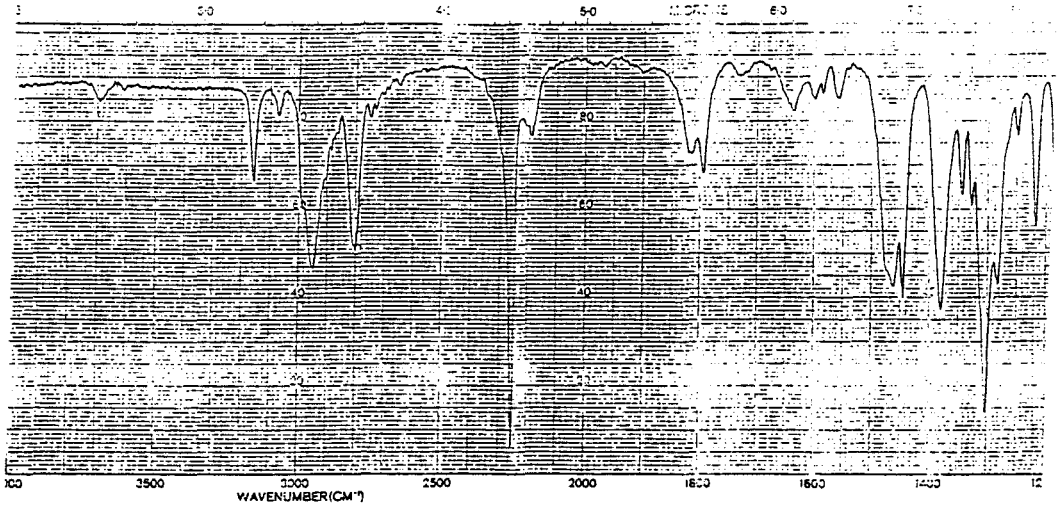


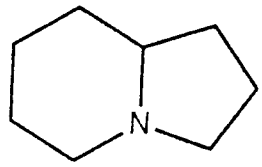
^{1}H NMR for **31b**



^{13}C NMR for **31b**



IR for **31b**



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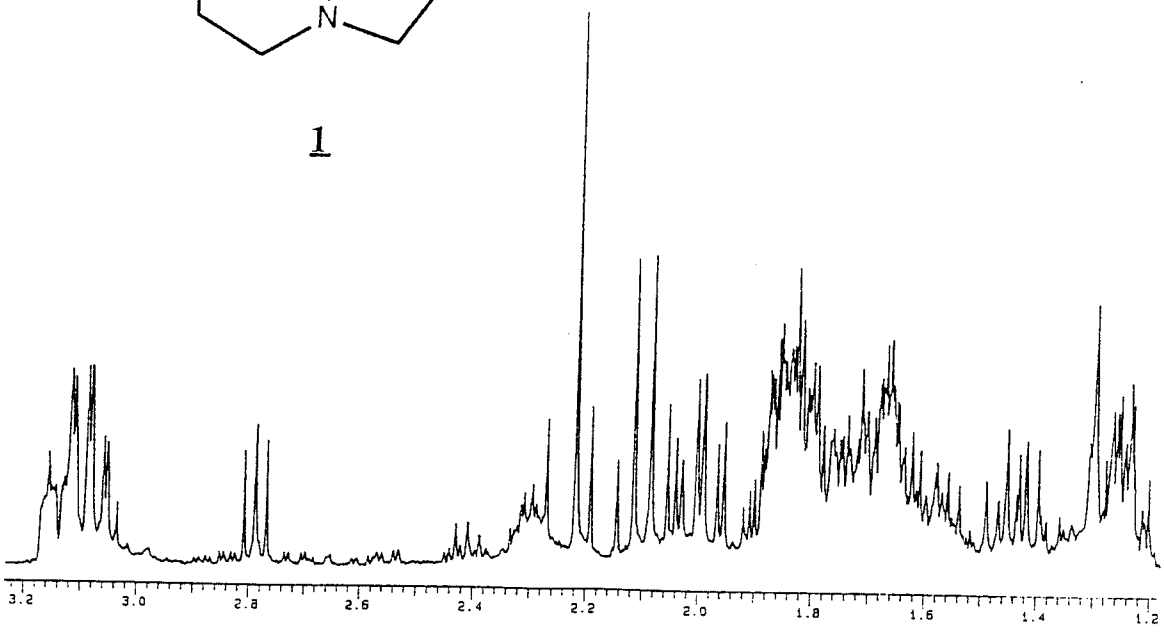
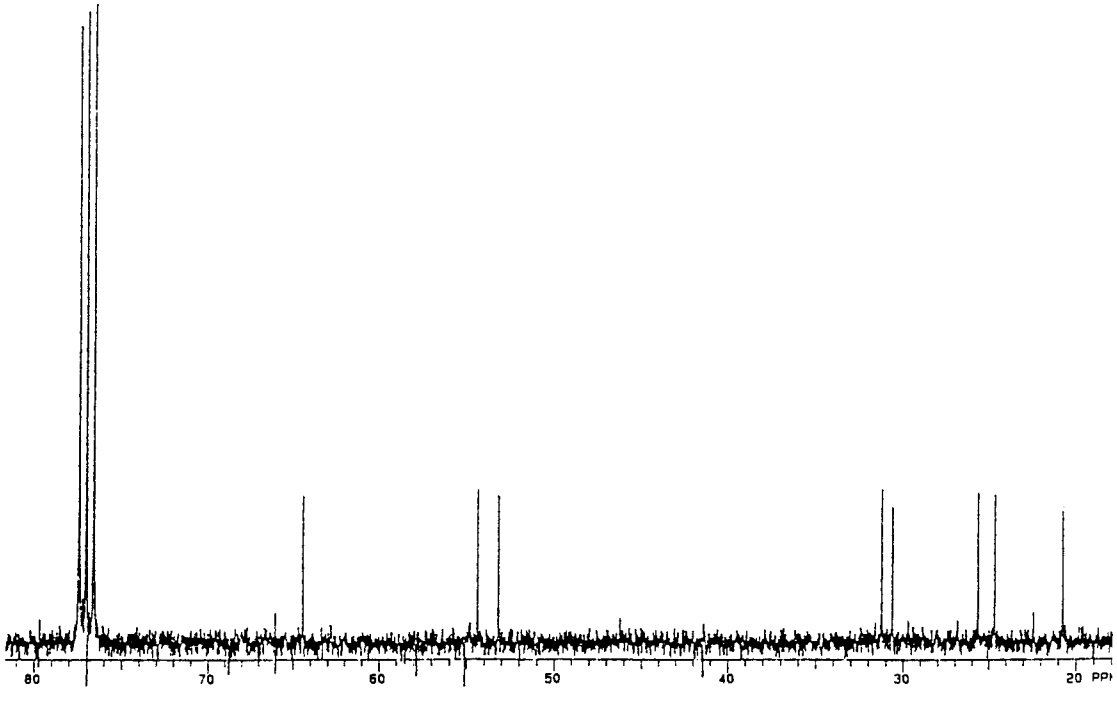
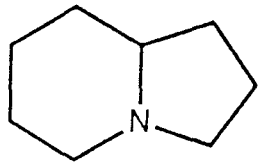
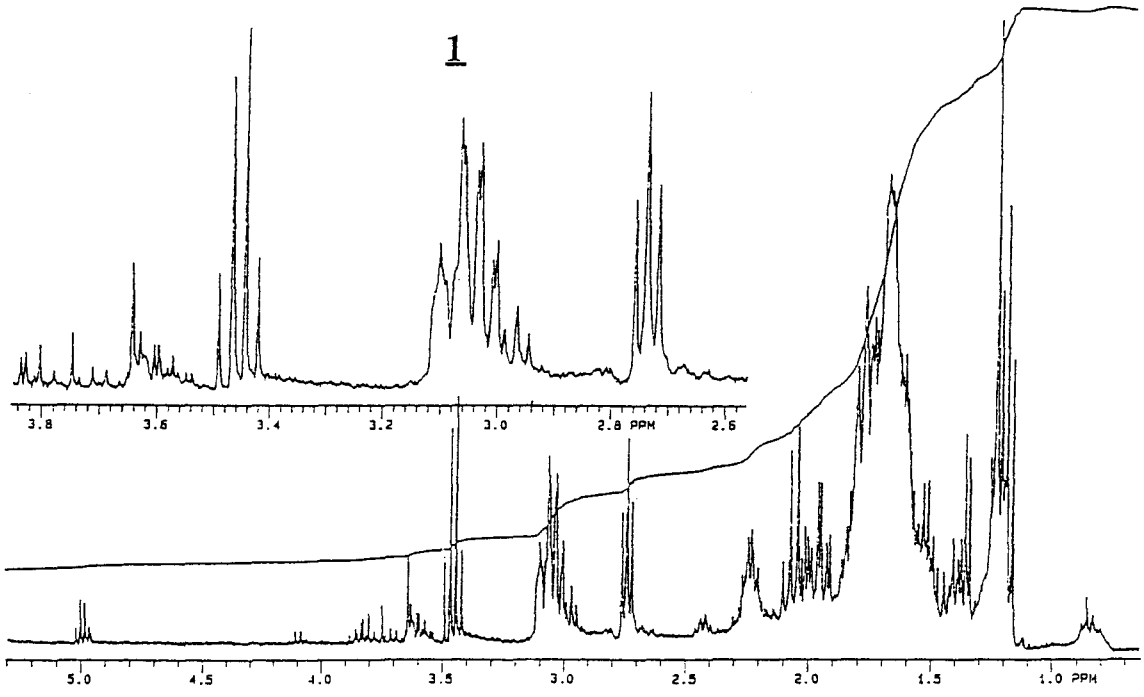


^{1}H NMR for 1 from fast band



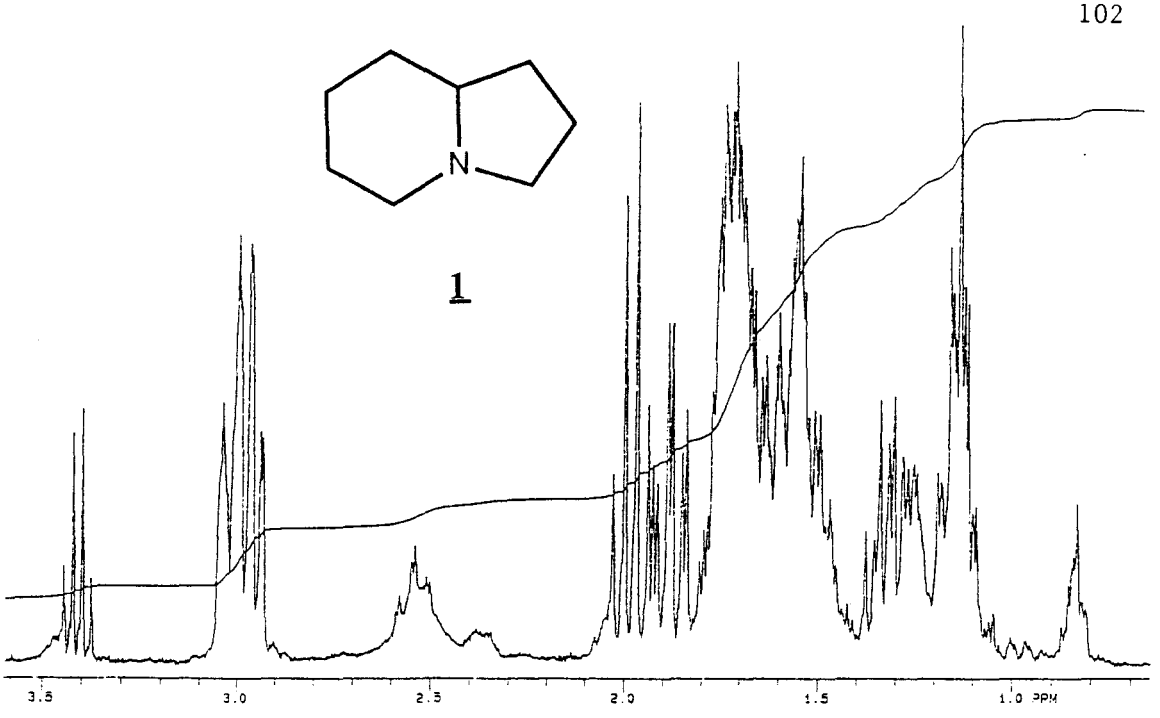
^{13}C NMR for 1 from fast band



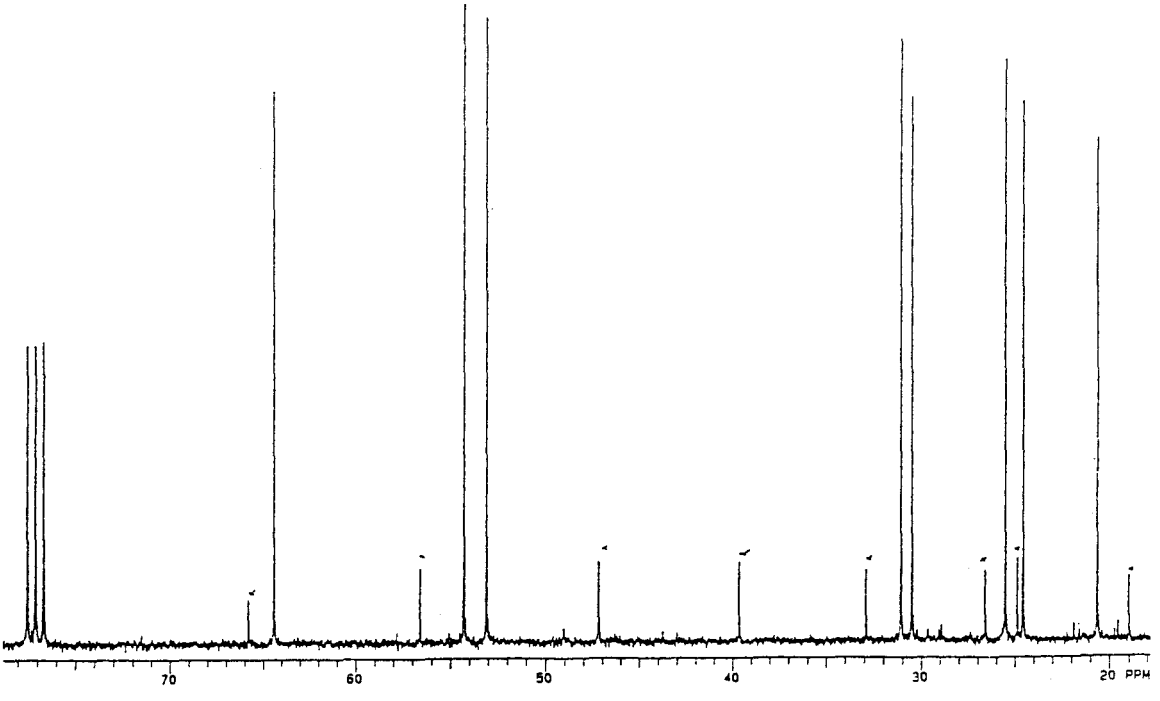


^{1}H NMR for 1 from slow band

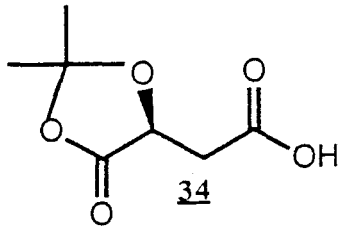
^{13}C NMR for 1 from slow band



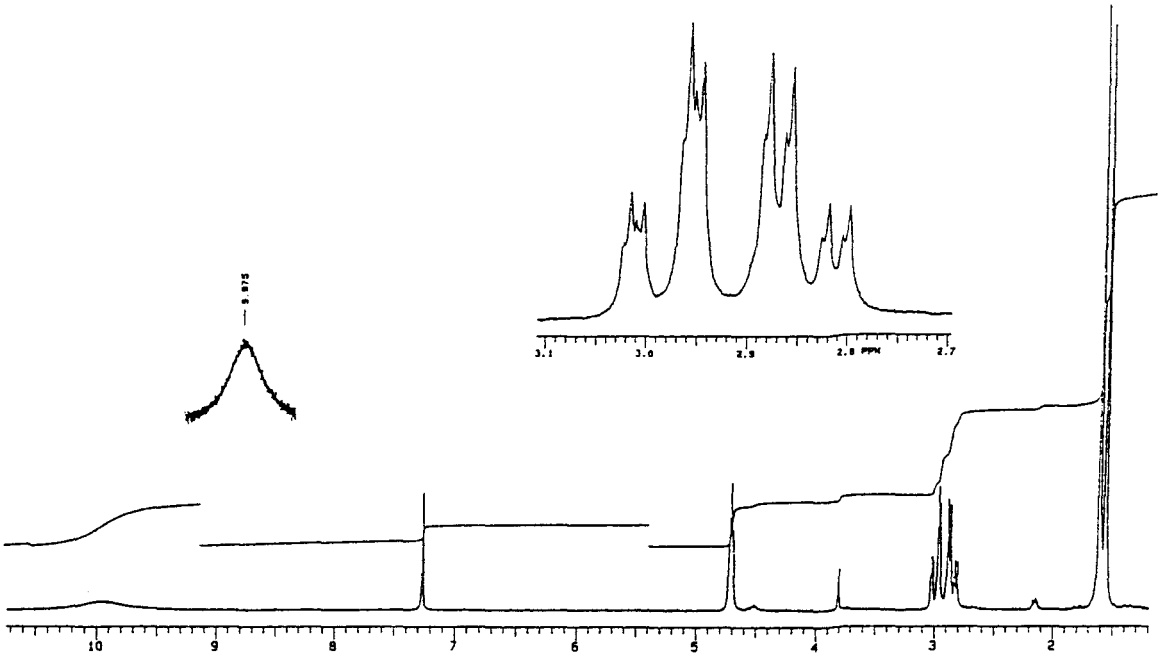
^{1}H NMR for 1 from Hofmann-Loffler preparation



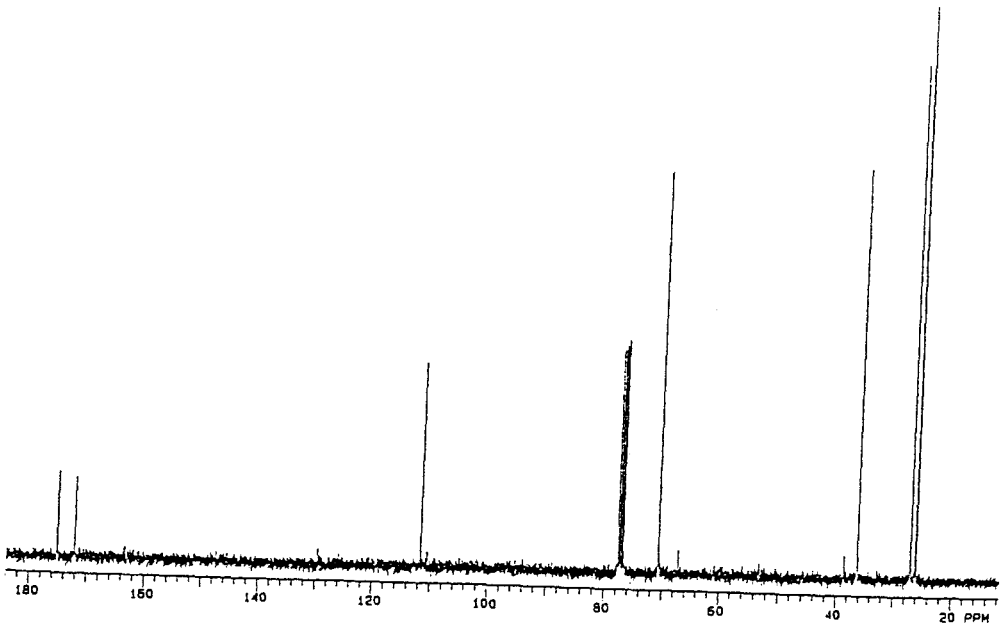
^{13}C NMR for 1 from Hofmann-Loffler preparation



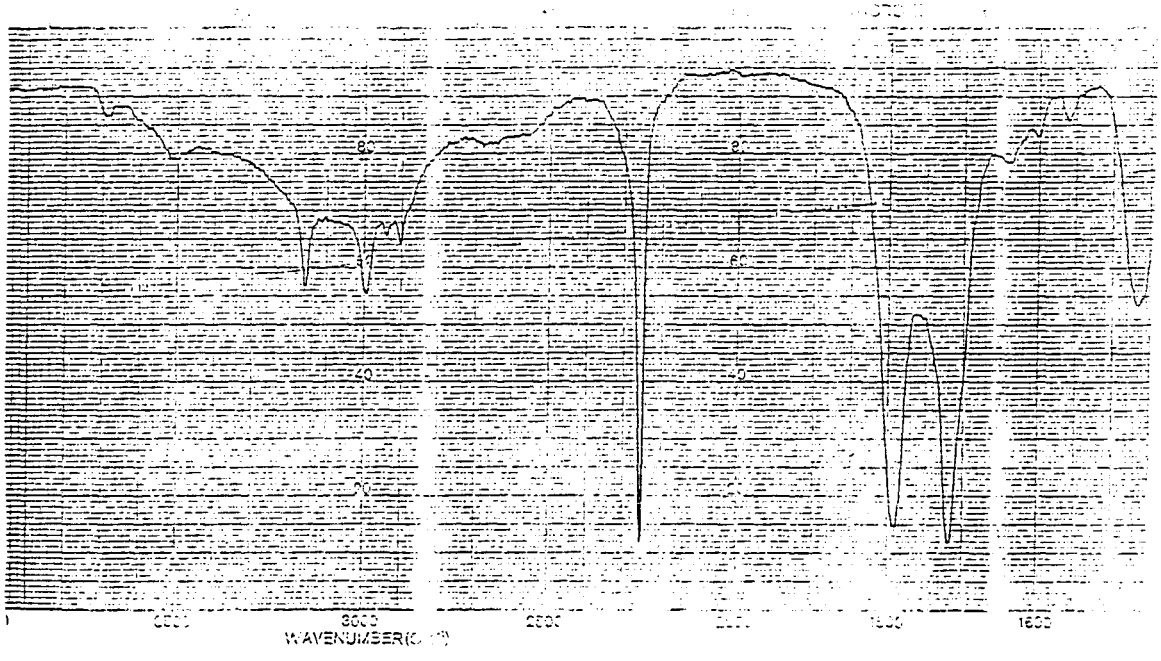
34



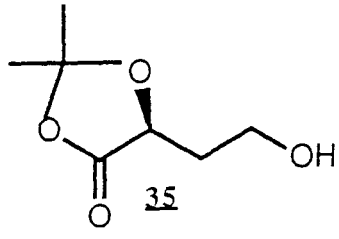
^{1}H NMR for 34



^{13}C NMR for <u>34</u>



IR for <u>34</u>



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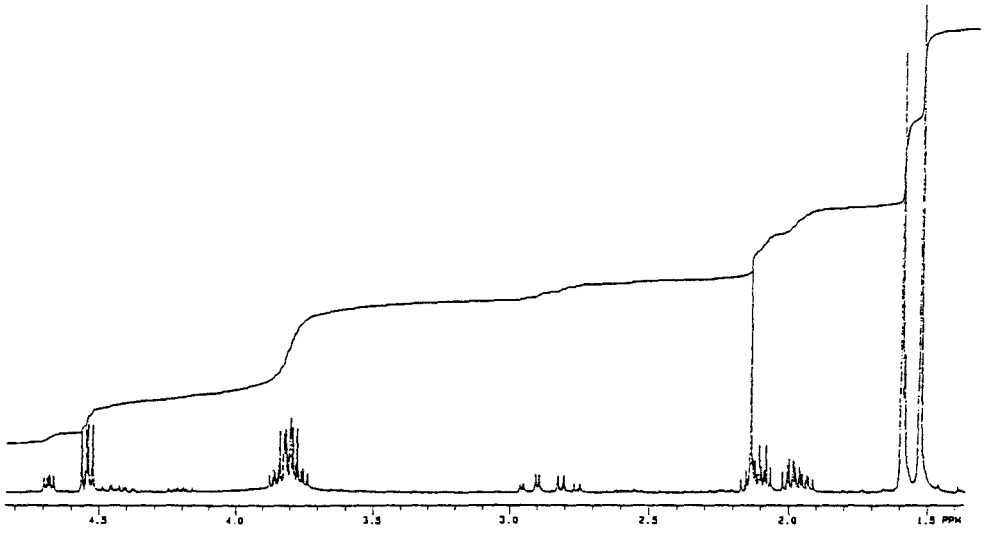
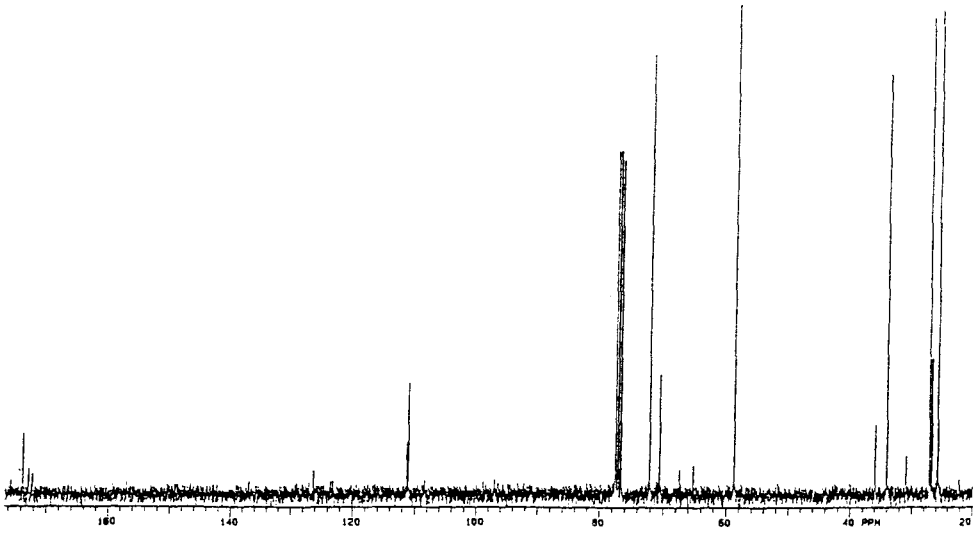
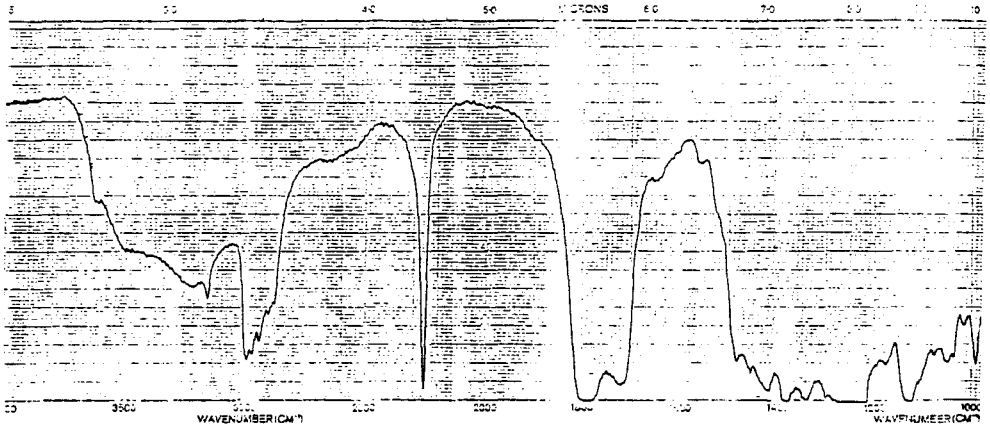


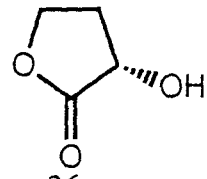
^{1}H NMR for 35



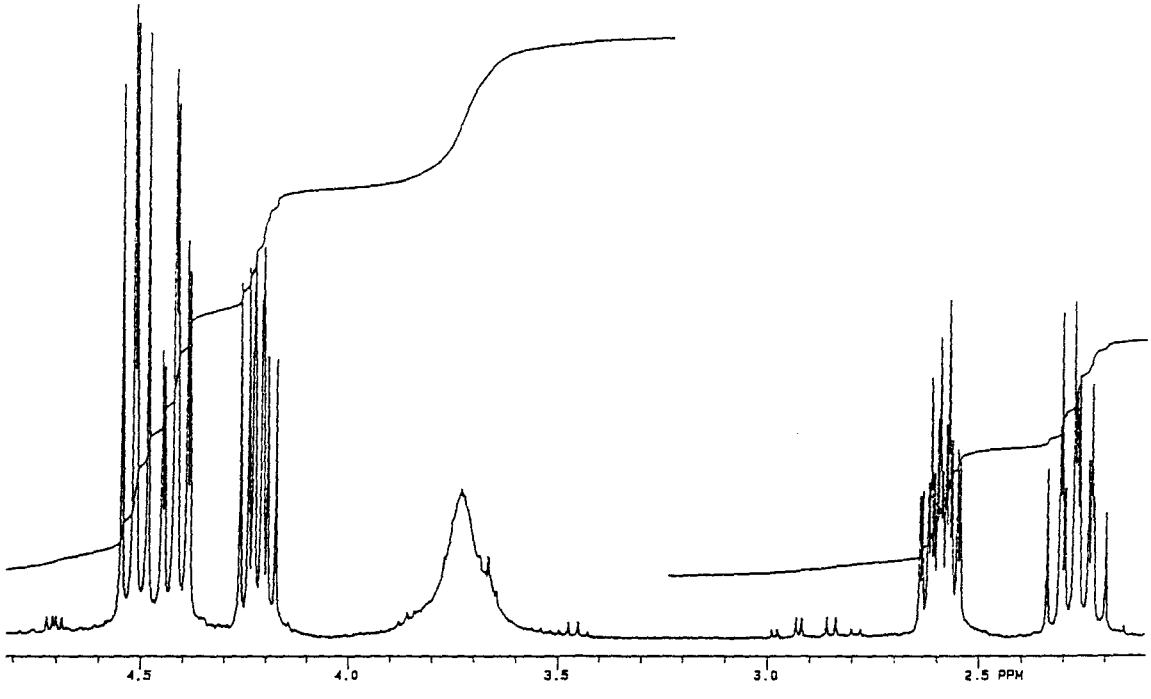
^{13}C NMR for **35**



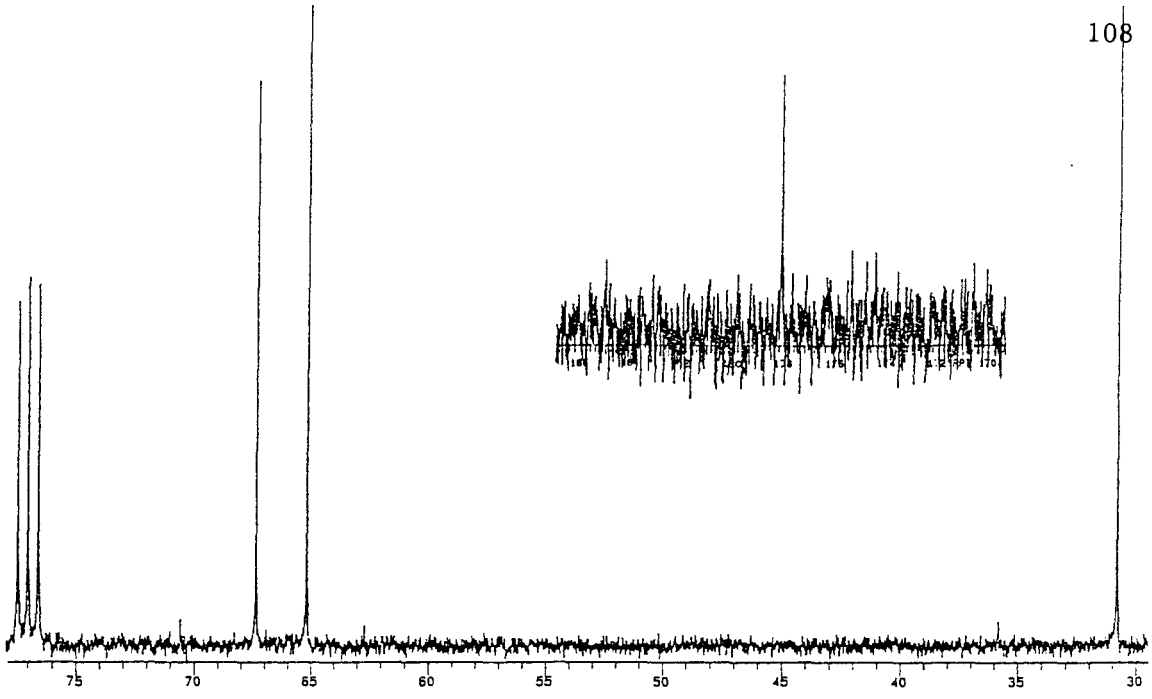
IR for **35**



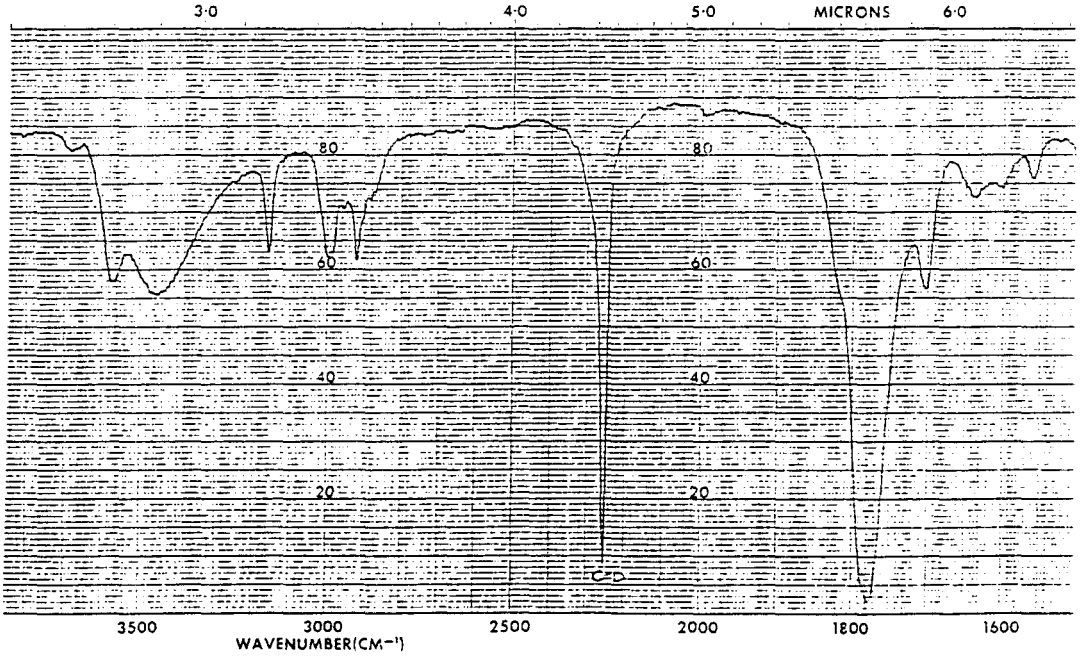
36



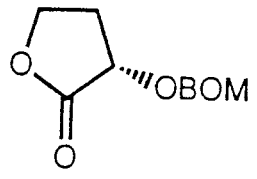
^{1}H NMR for **36**



^{13}C NMR for **36**



IR for **36**



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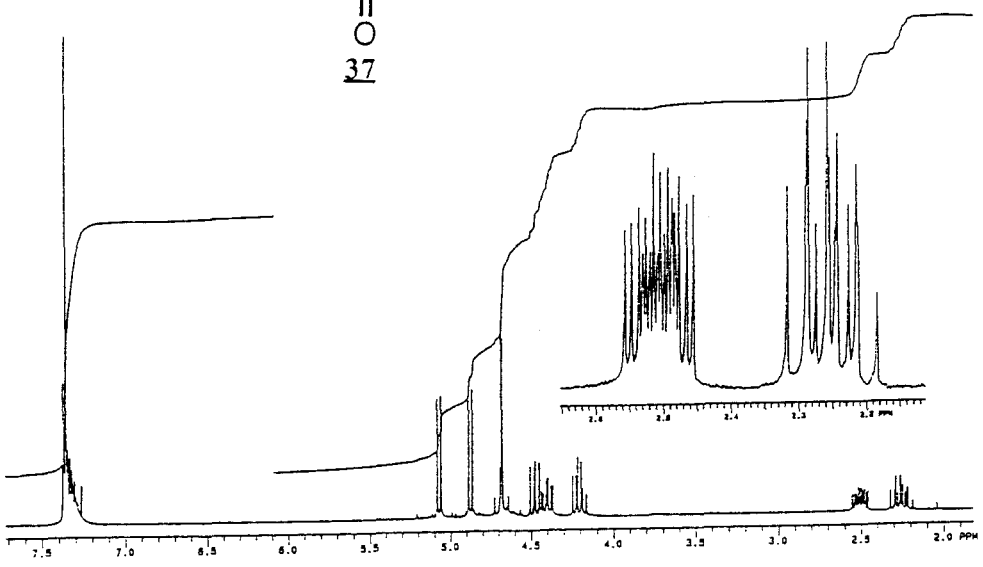
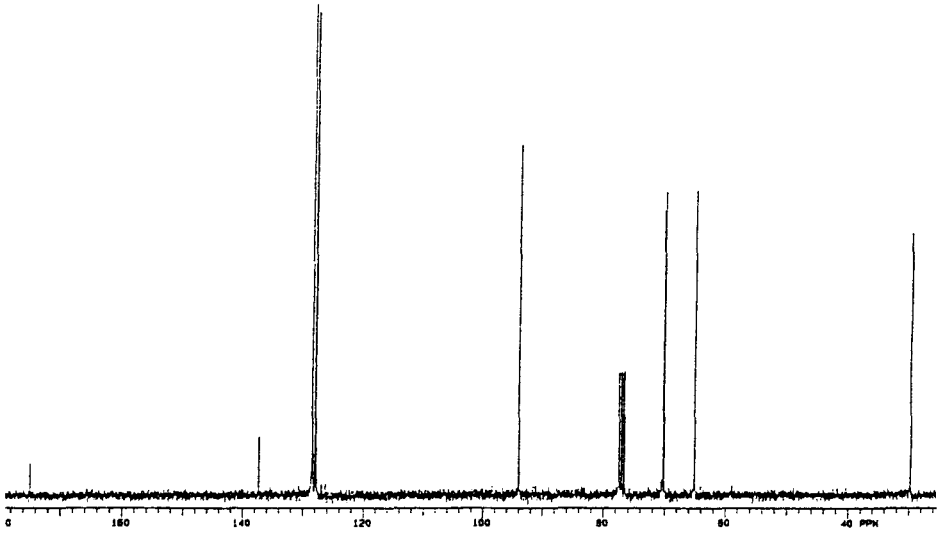
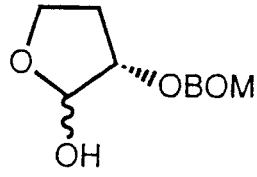


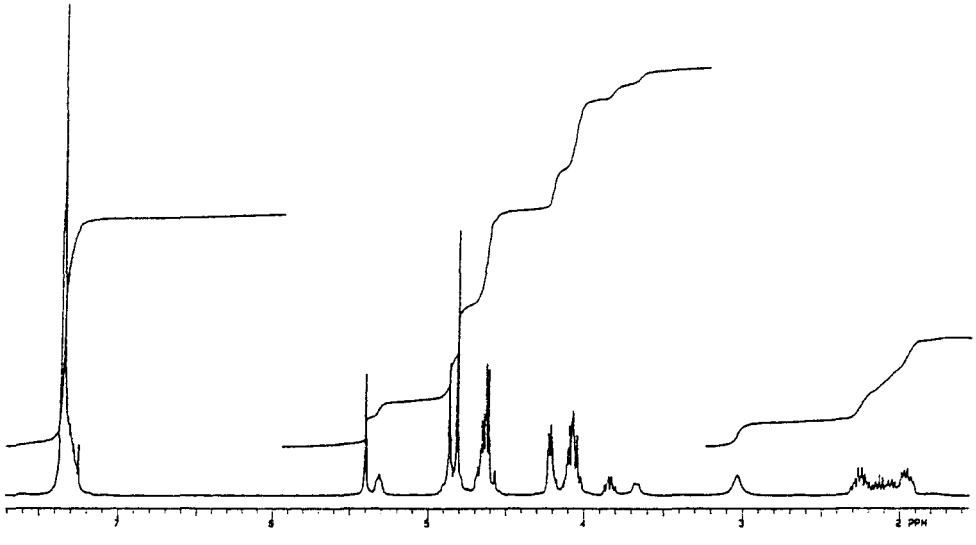
^{1}H NMR for 37



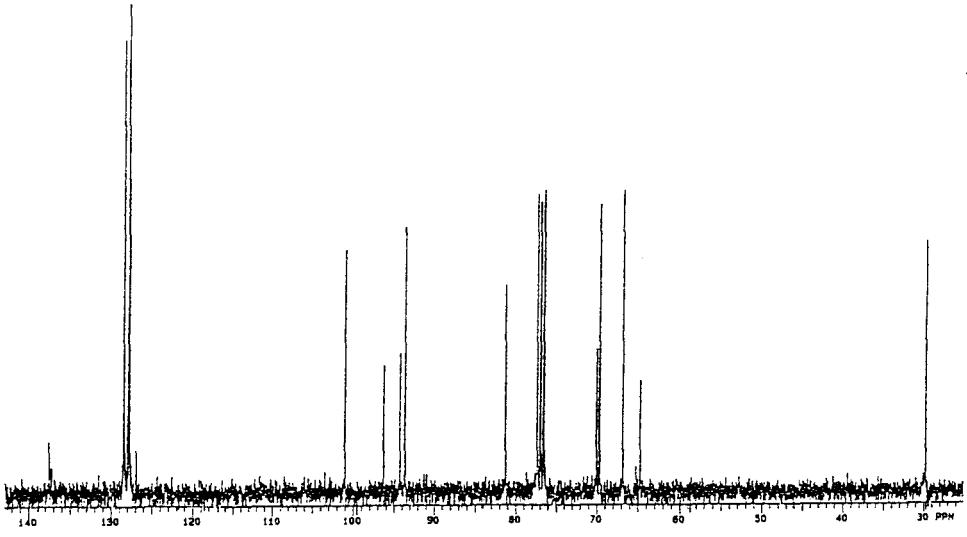
^{13}C NMR for 37



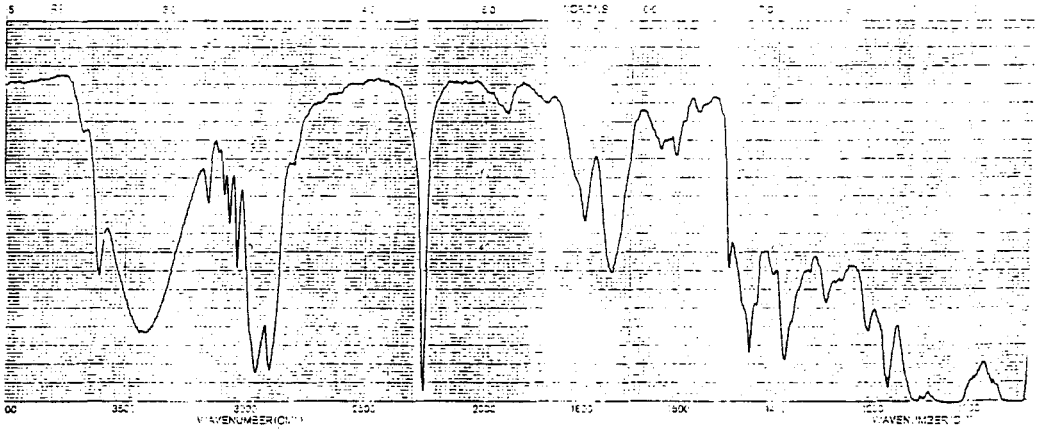
38



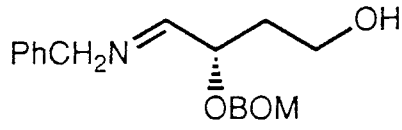
^{1}H NMR for 38



^{13}C NMR for **38**



IR for **38**



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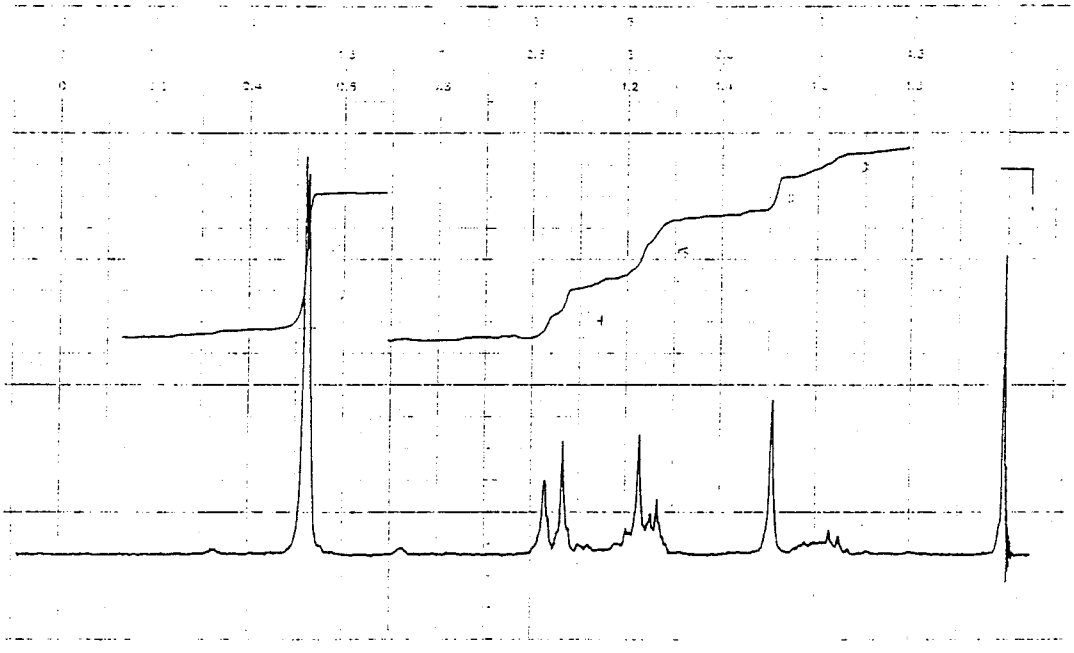
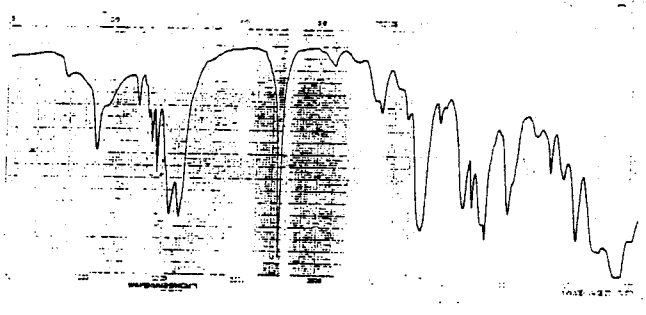
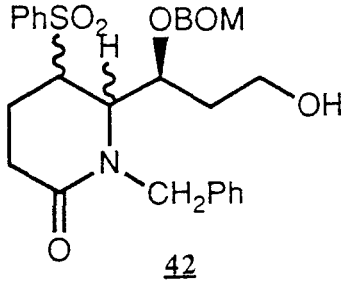


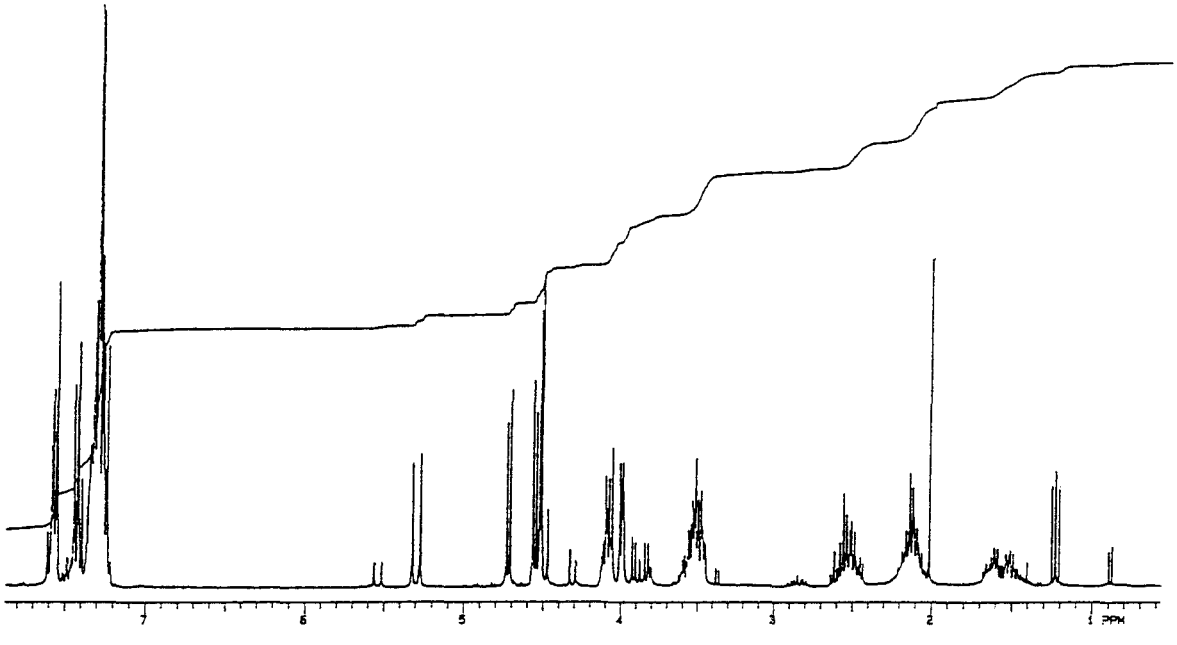
^{1}H NMR for **41**



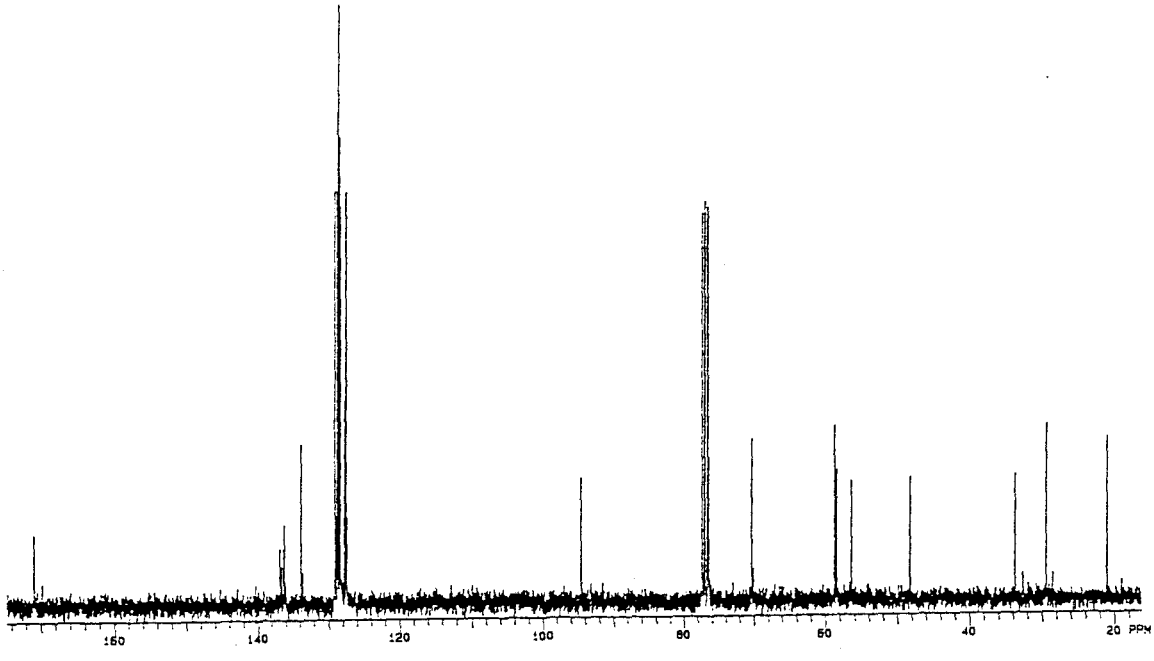
IR for **41**



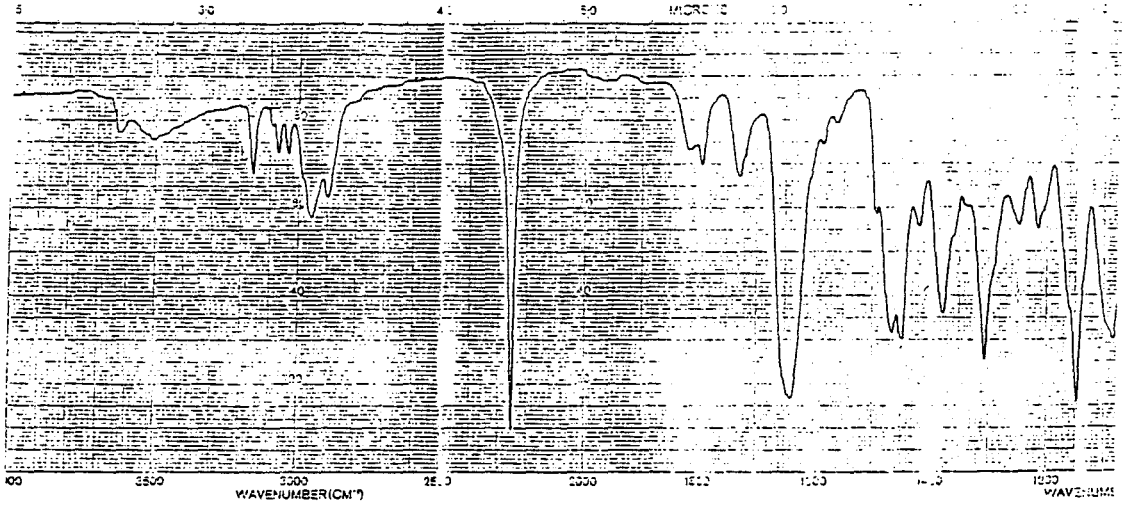
42



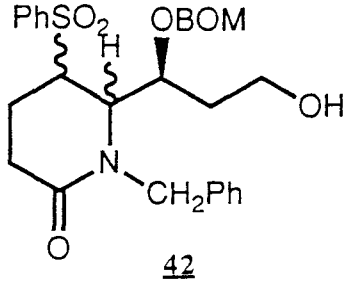
^{1}H NMR for 42a



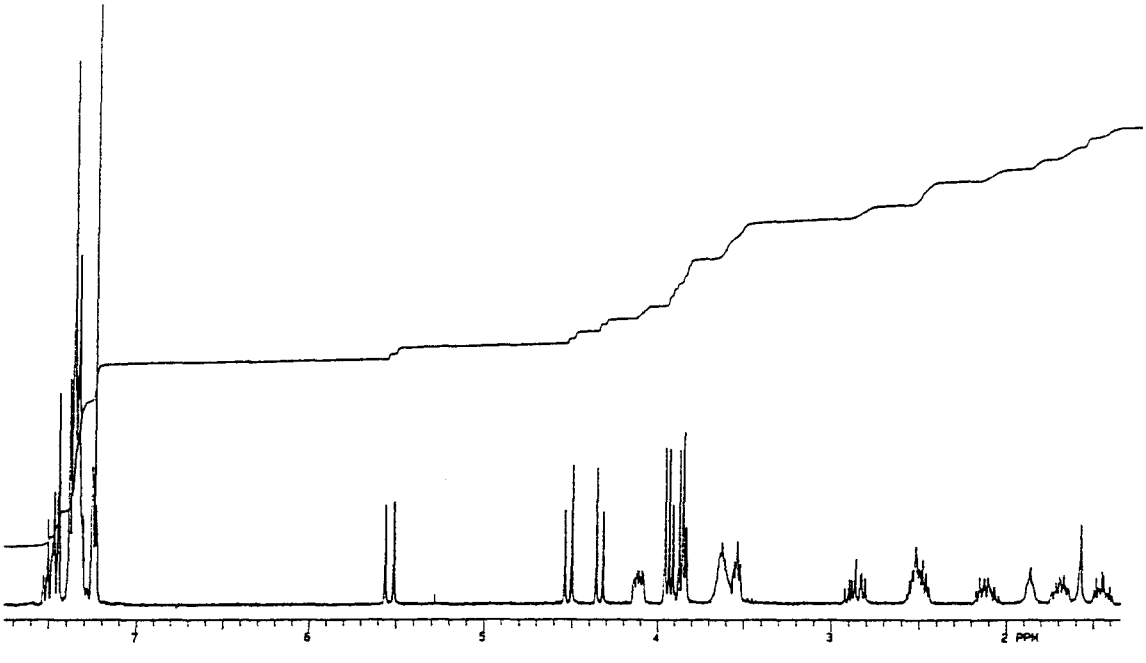
^{13}C NMR for <u>42a</u>



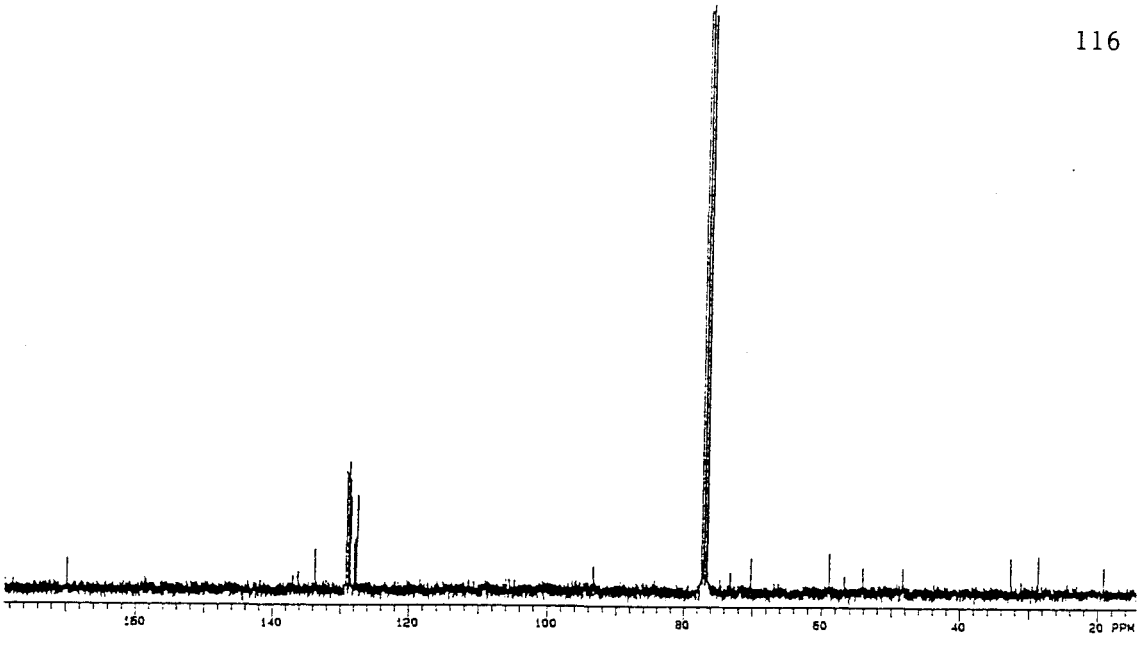
IR for <u>42a</u>



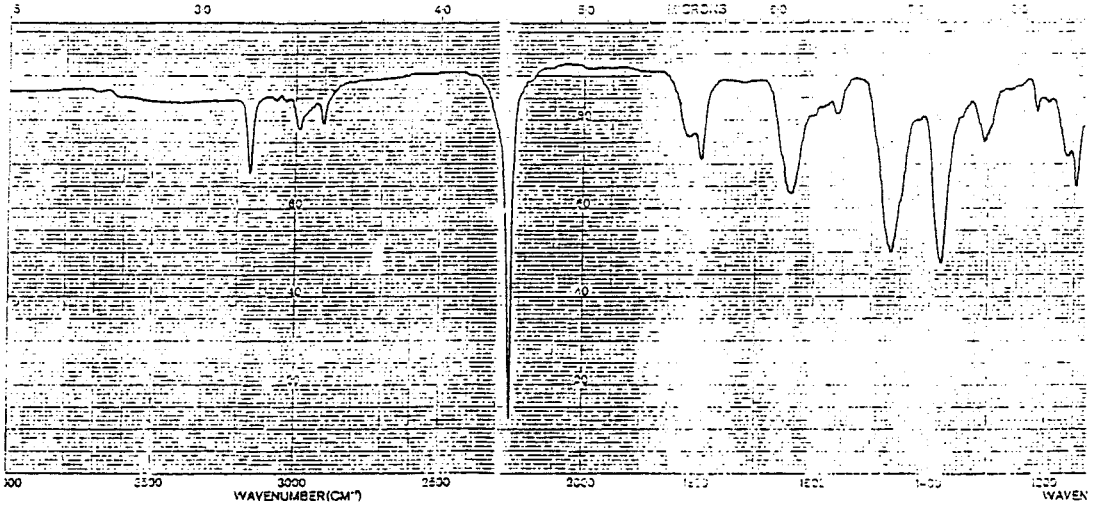
42



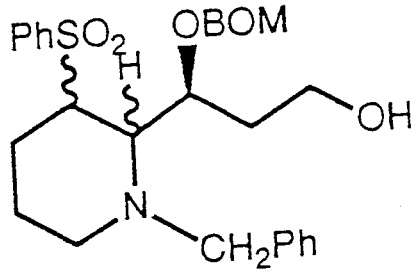
^{1}H NMR for 42b



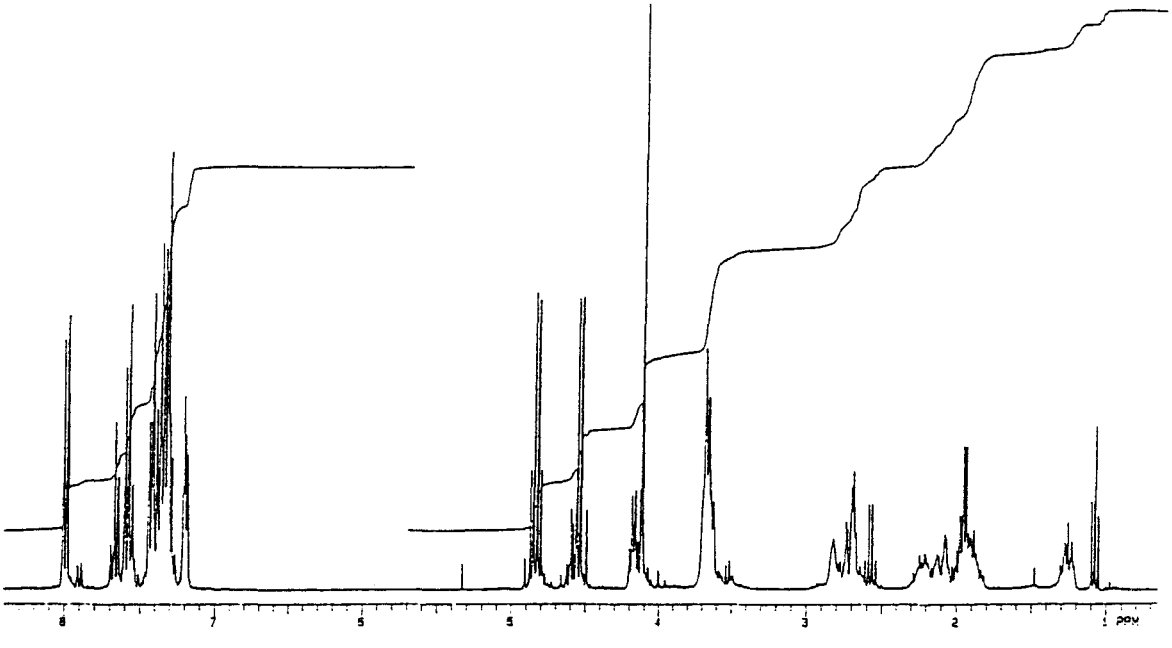
^{13}C NMR for **42b**



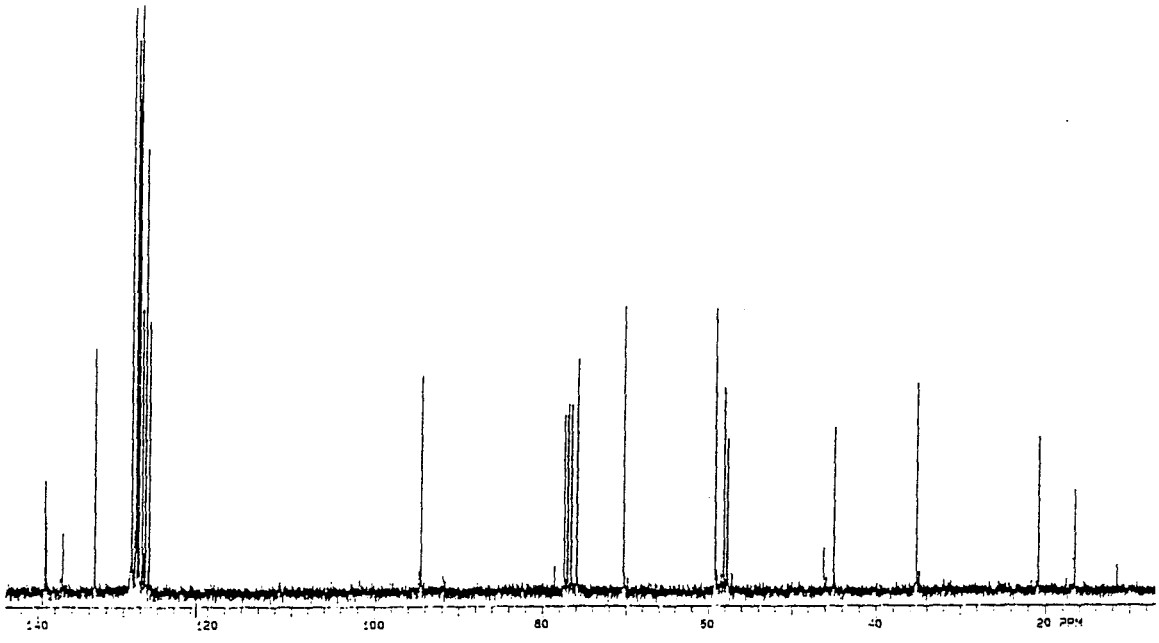
IR for **42b**



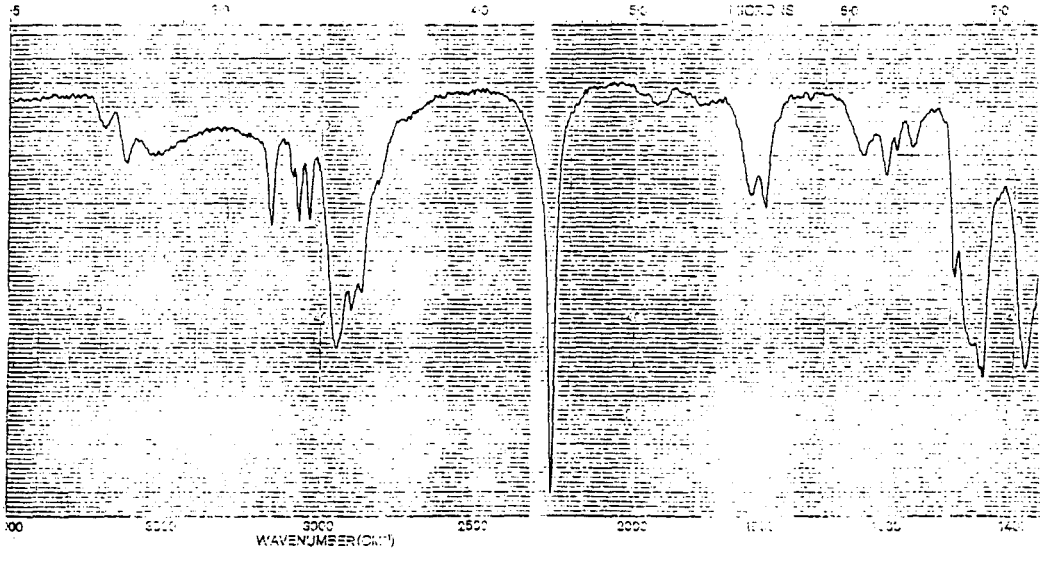
43



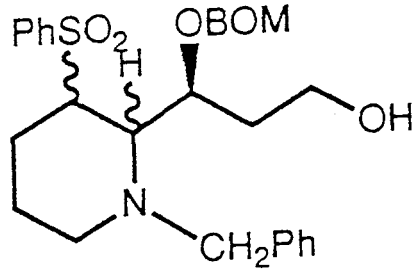
^{1}H NMR for 43a



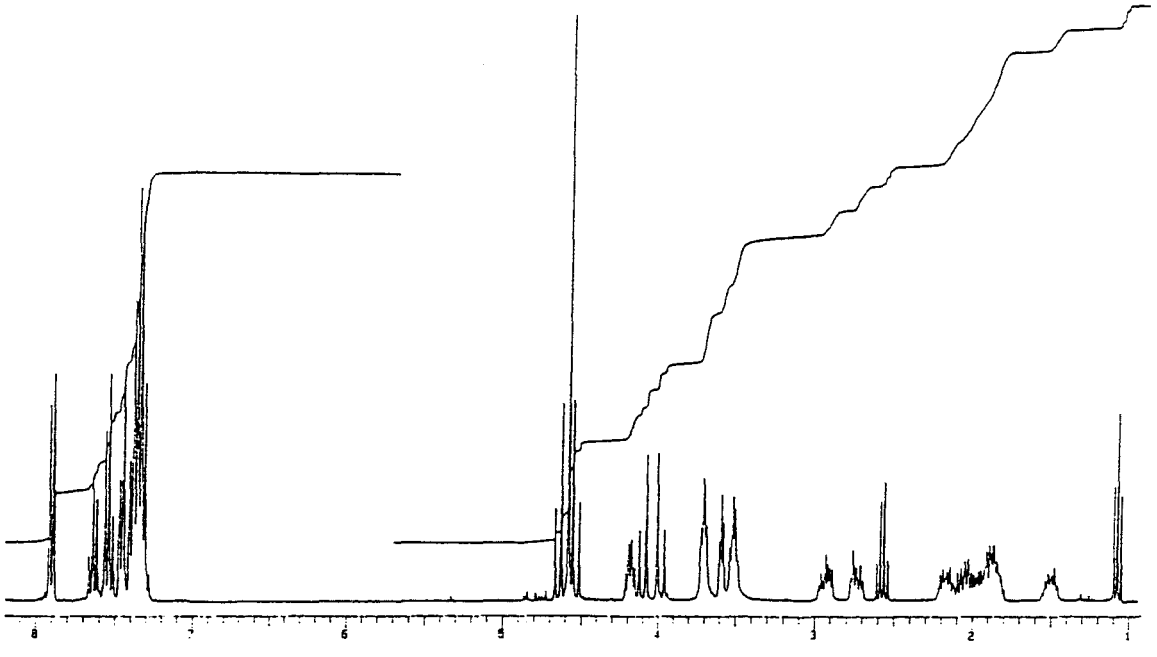
^{13}C NMR for **43a**



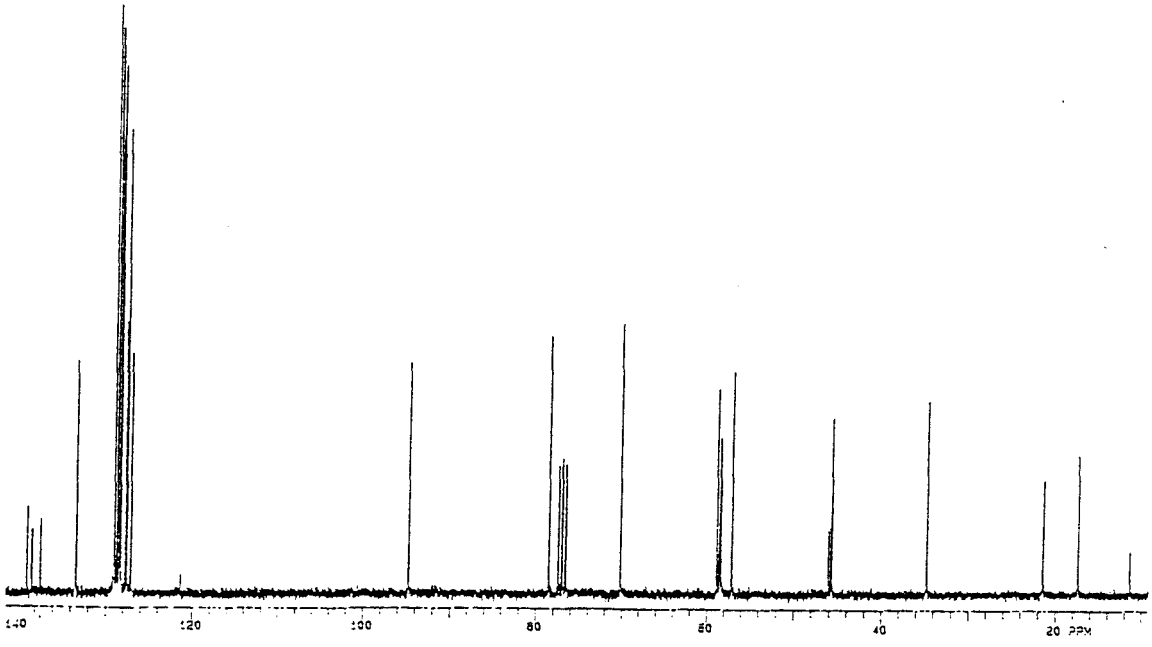
IR for **43a**



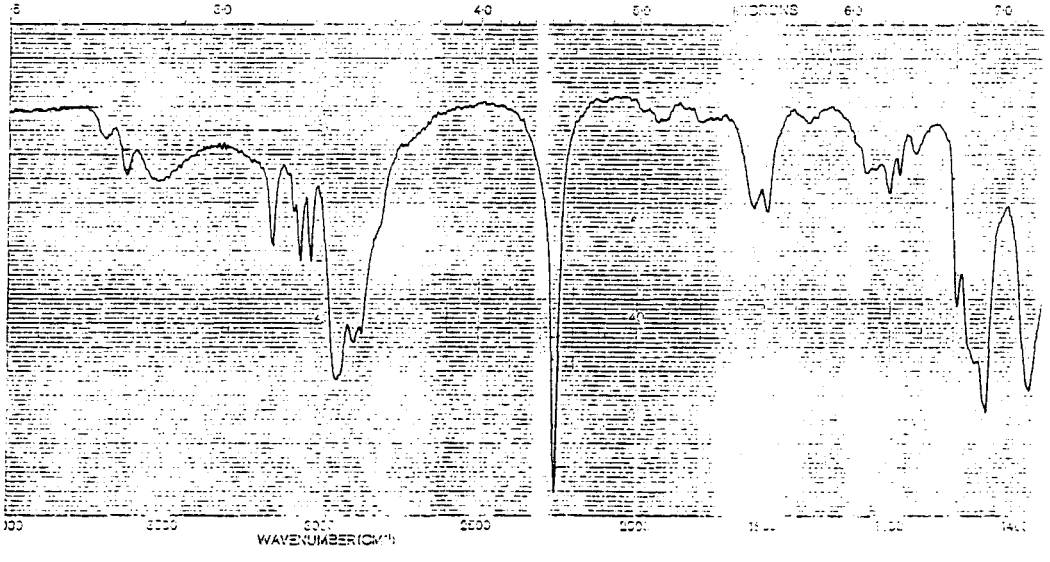
43



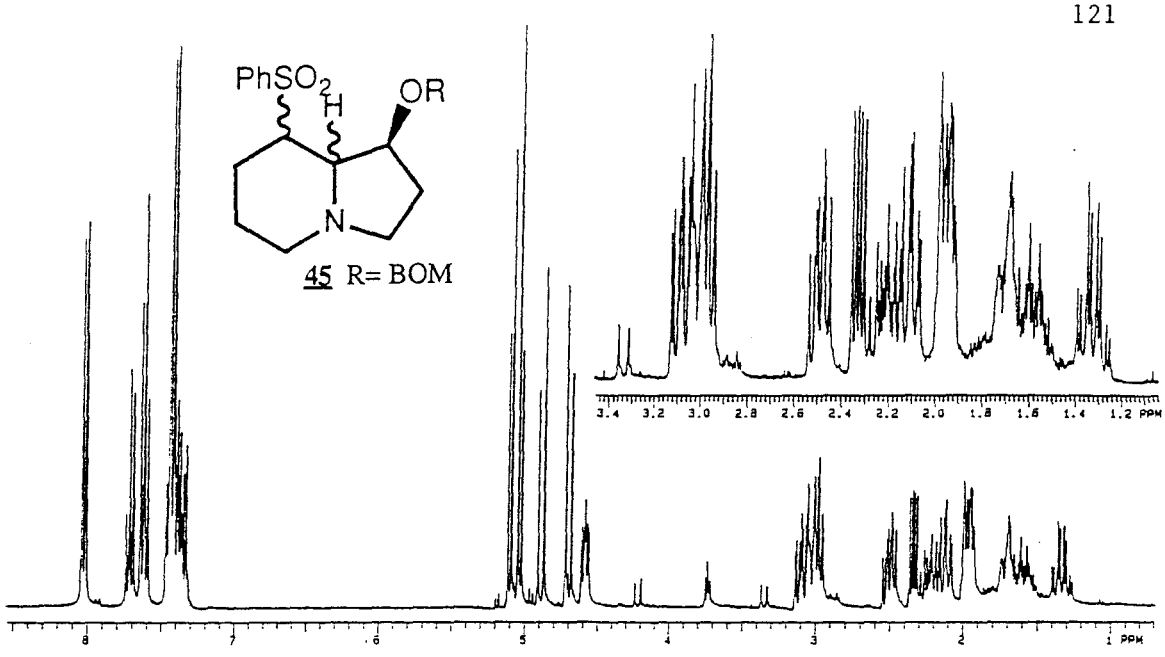
^{1}H NMR for 43b



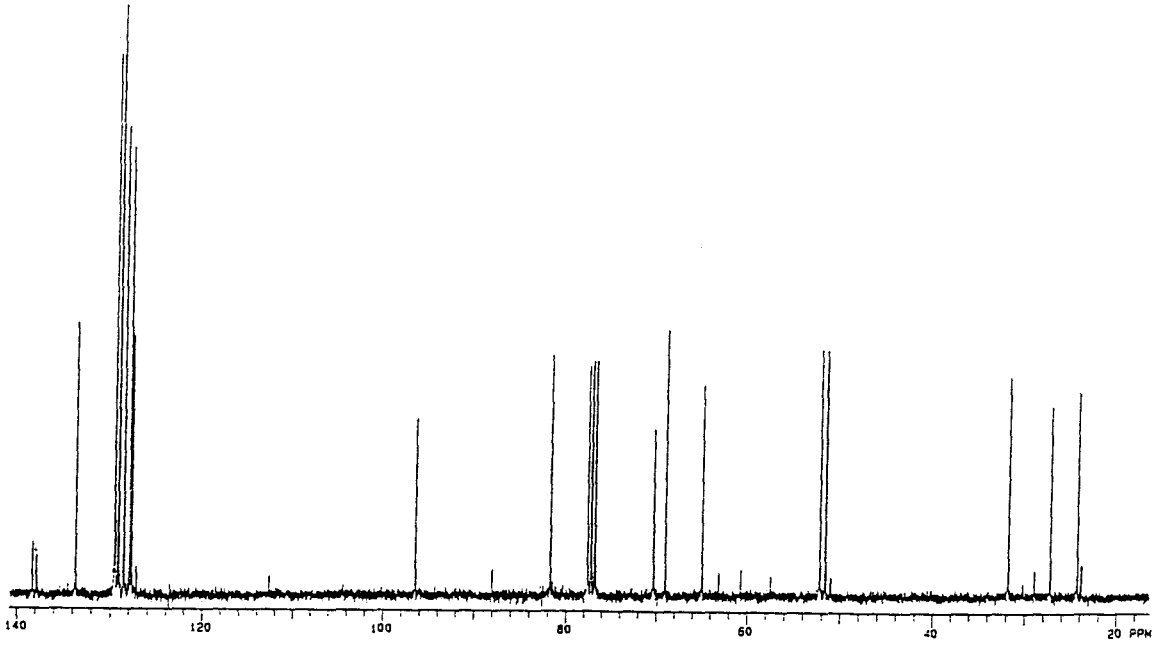
^{13}C NMR for **43b**



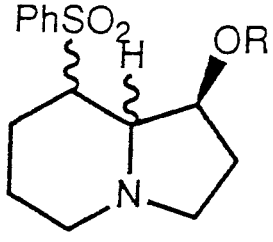
IR for **43b**



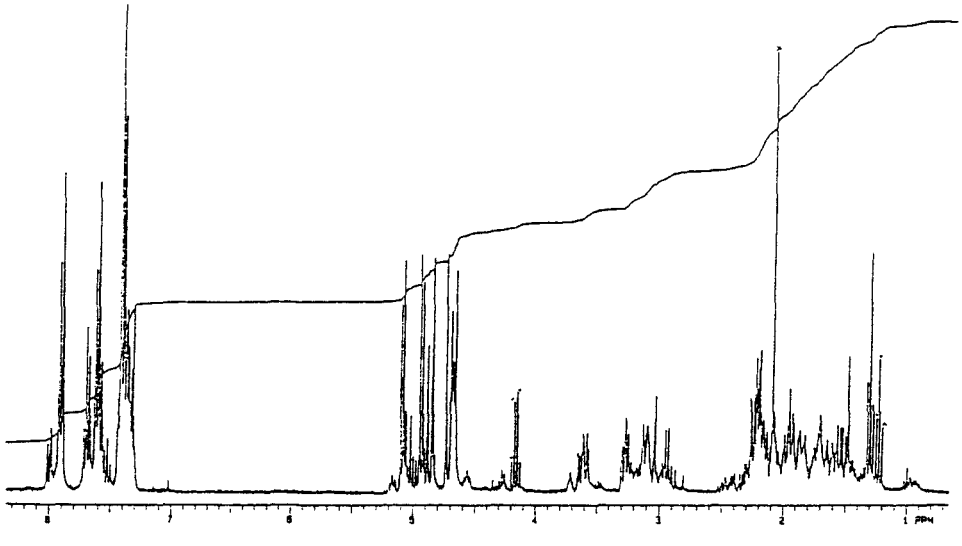
^{1}H NMR for **45a**



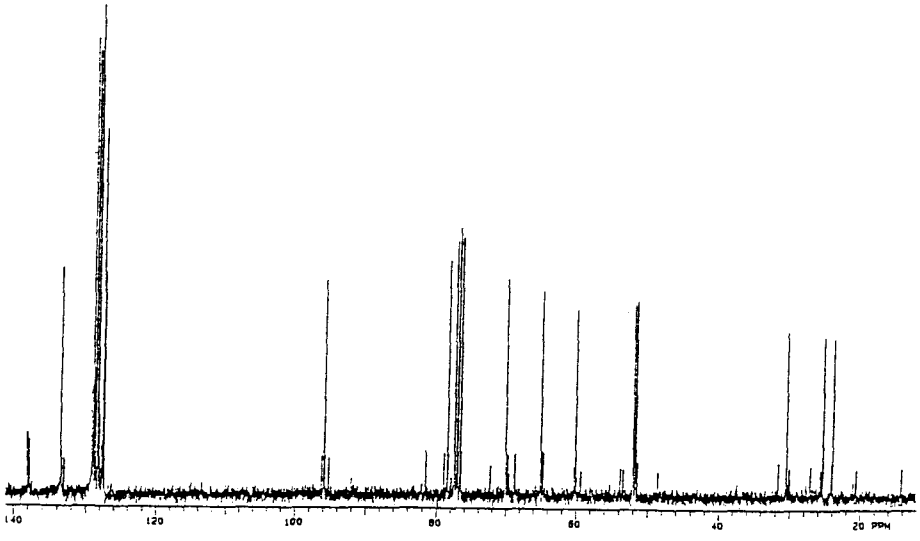
^{13}C NMR for **45a**



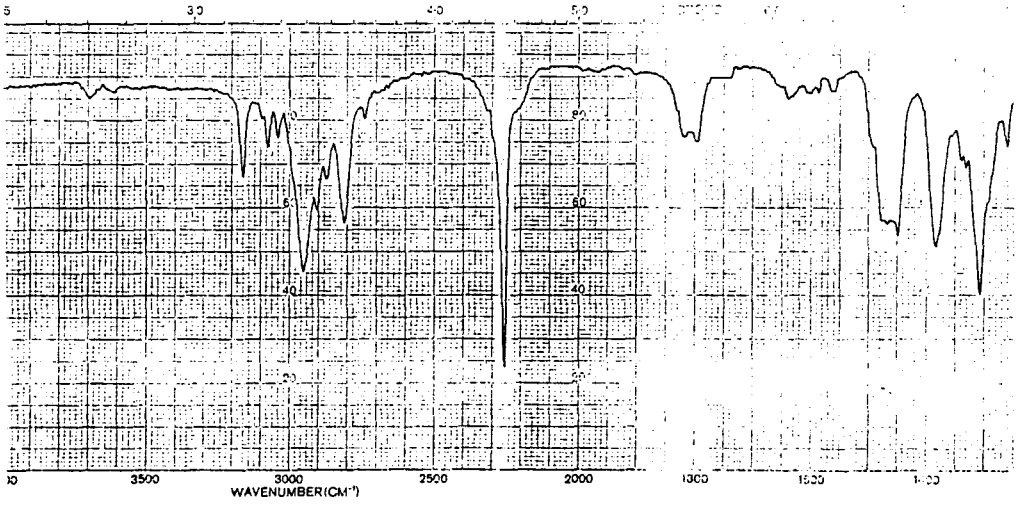
45 R= BOM



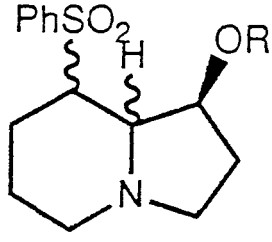
^{1}H NMR for **45b**



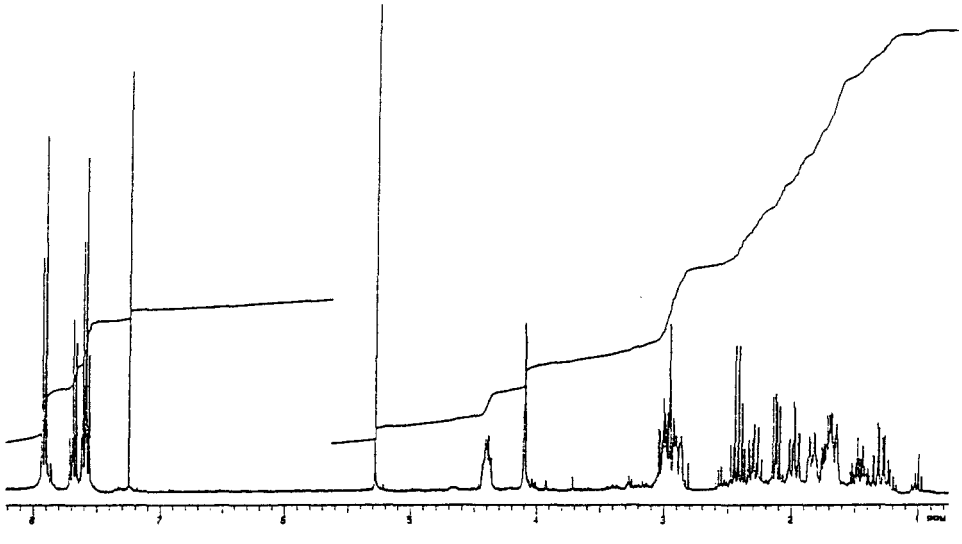
^{13}C NMR for **45b**



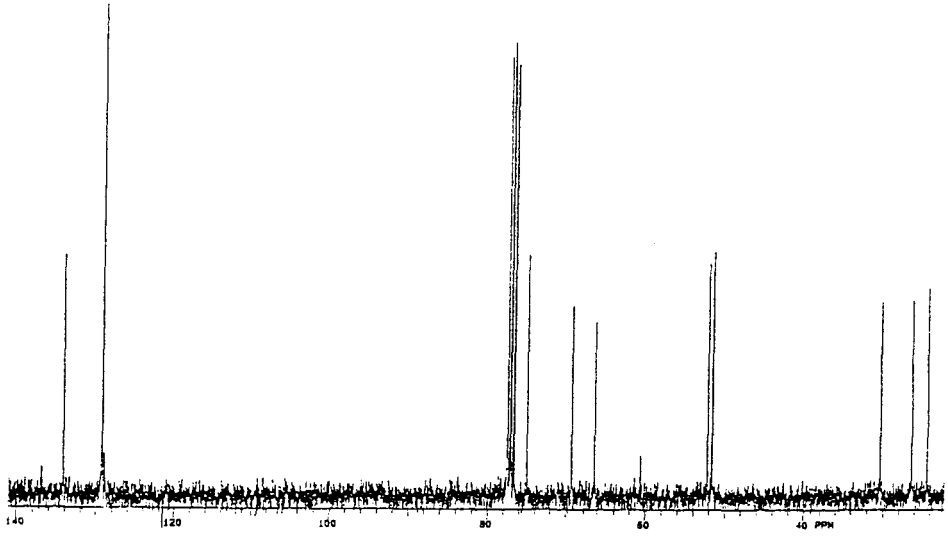
IR for **45b**



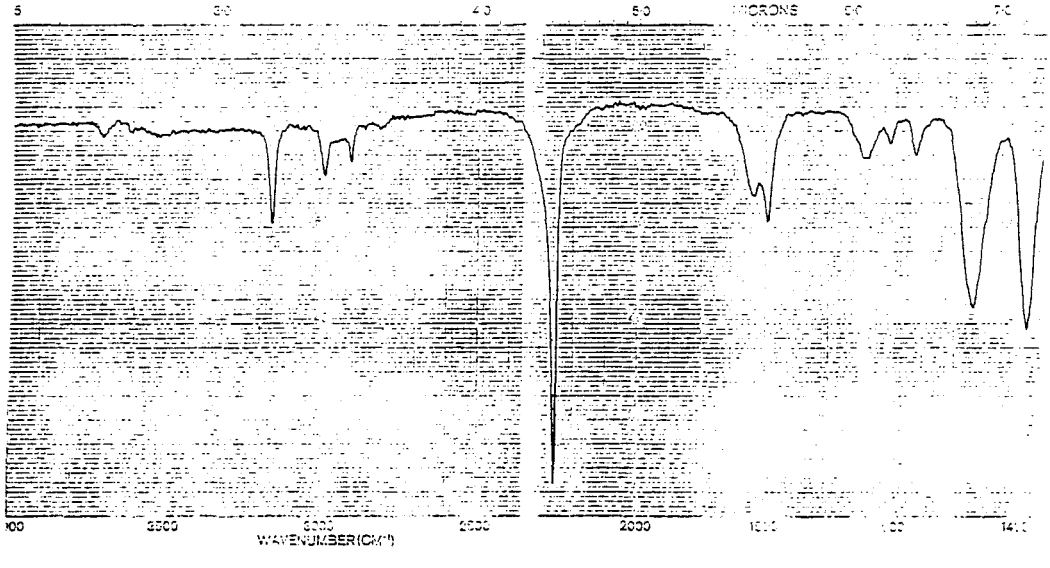
46 R= H



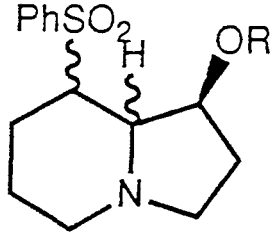
^{1}H NMR for 46a



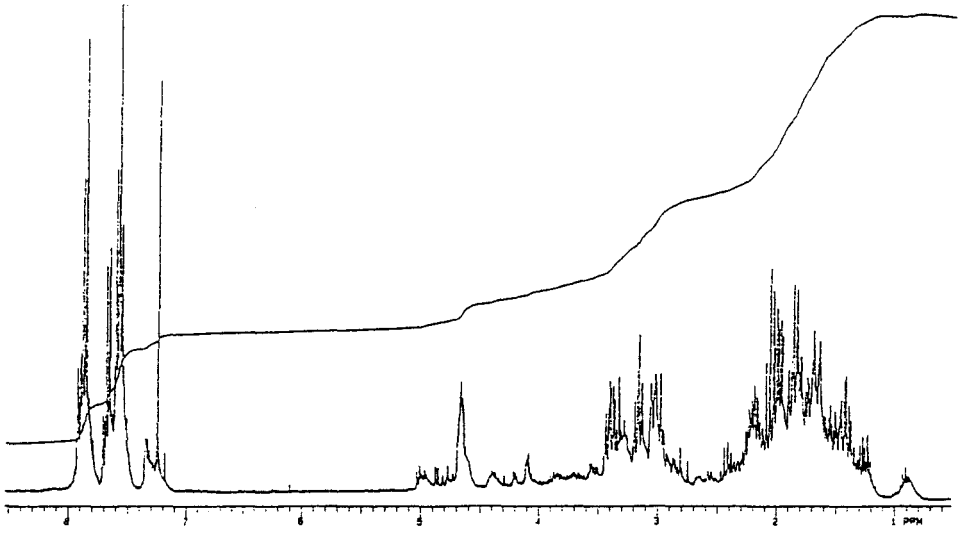
^{13}C NMR for **46a**



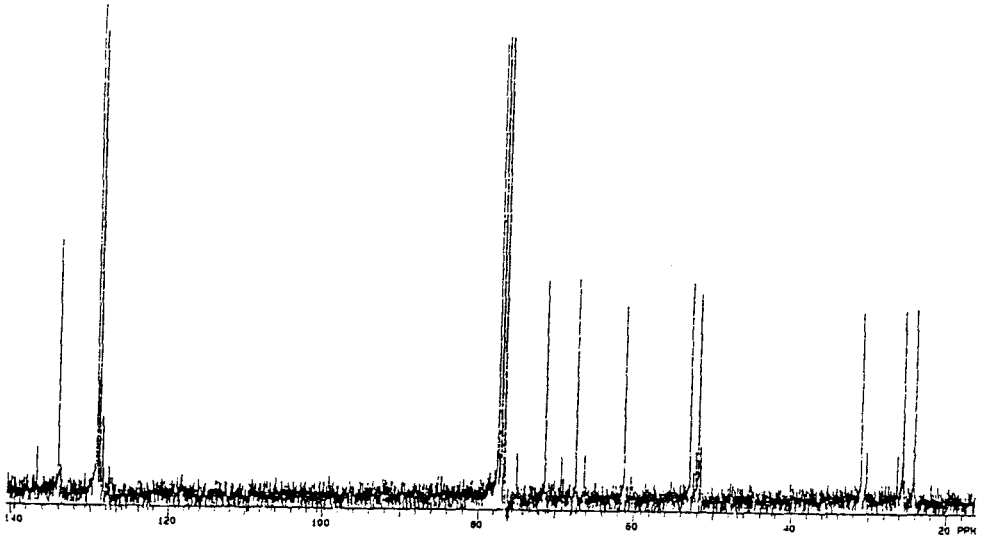
IR for **46a**



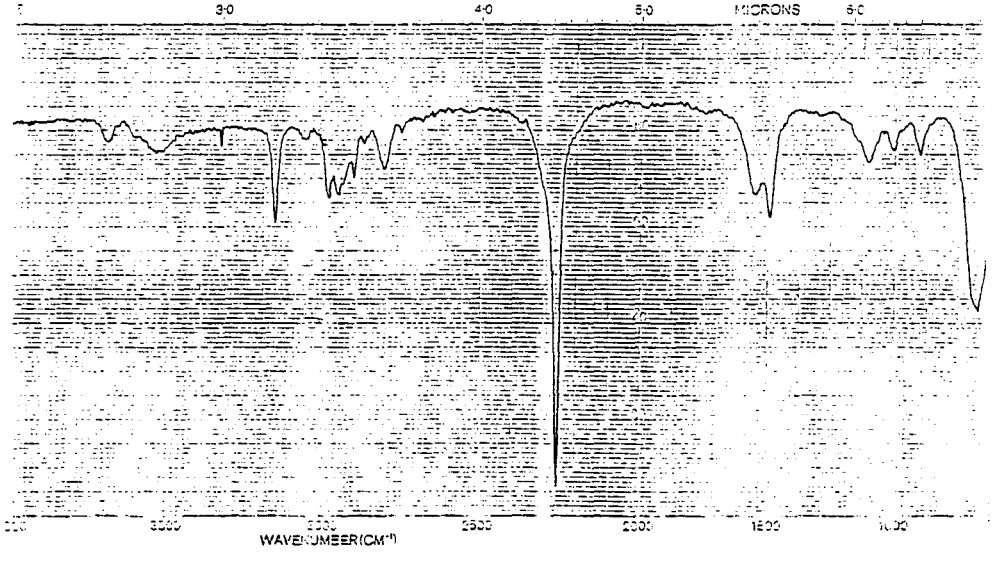
<u>46</u> R= H



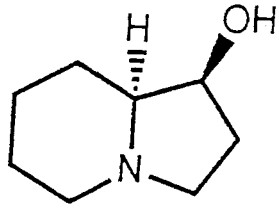
^{1}H NMR for <u>46b</u>



^{13}C NMR for **46b**



IR for **46b**



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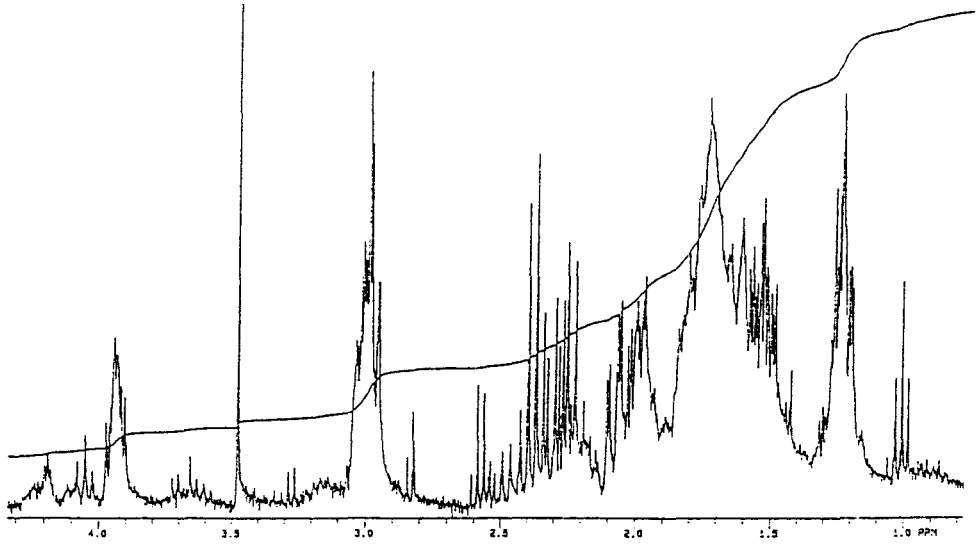
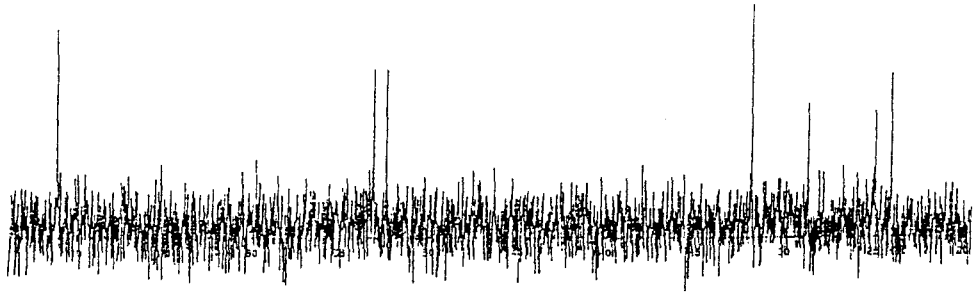
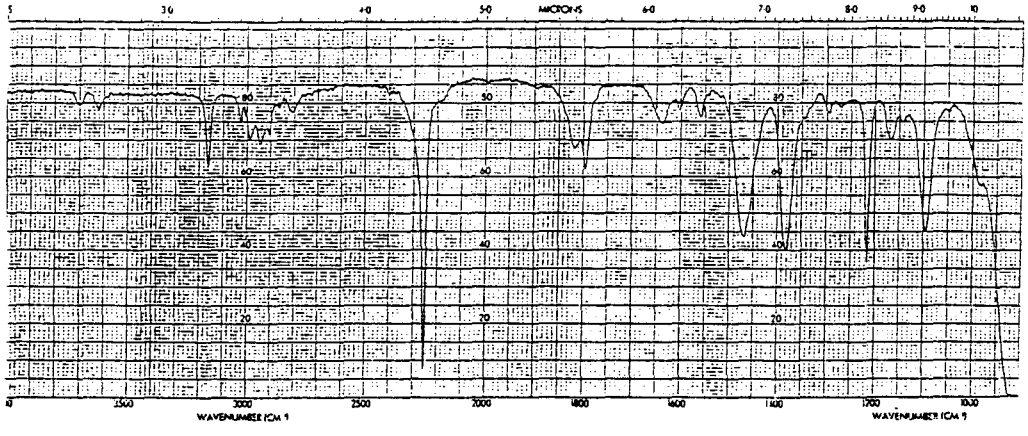


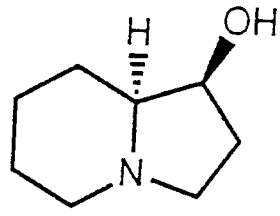
^{1}H NMR for 8 from fast



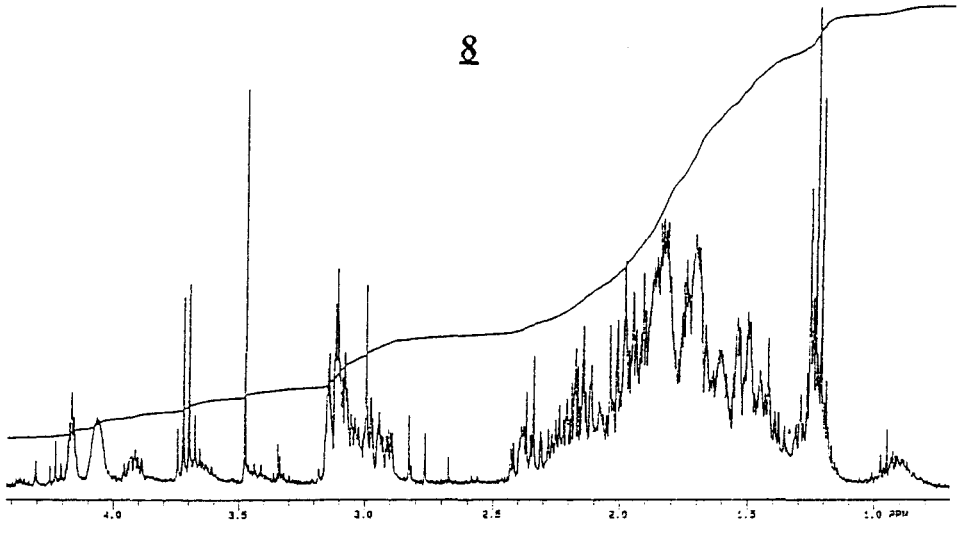
^{13}C NMR for 8 from fast



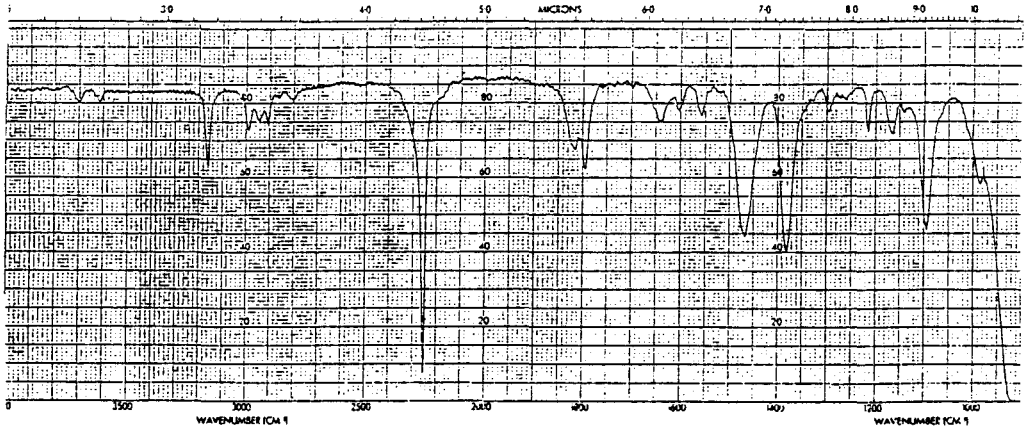
IR for 8 from fast



8



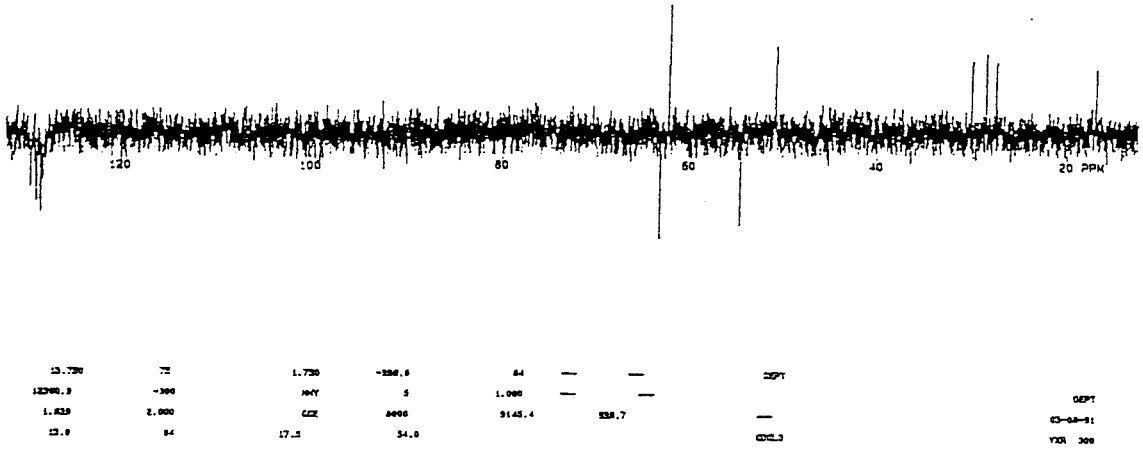
^{1}H NMR for 8 from slow



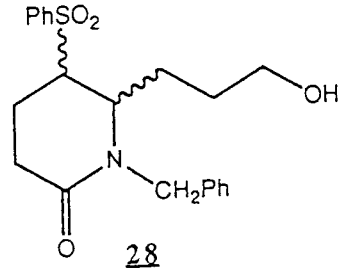
IR for 8 from slow

Chapter 7

Selected DEPT experiments.


120
100
80
60
40
20 PPM

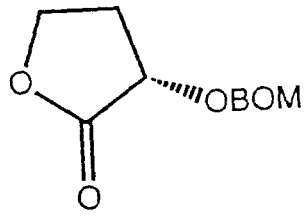
28a


PhSO2
OH
N
CH2Ph
O

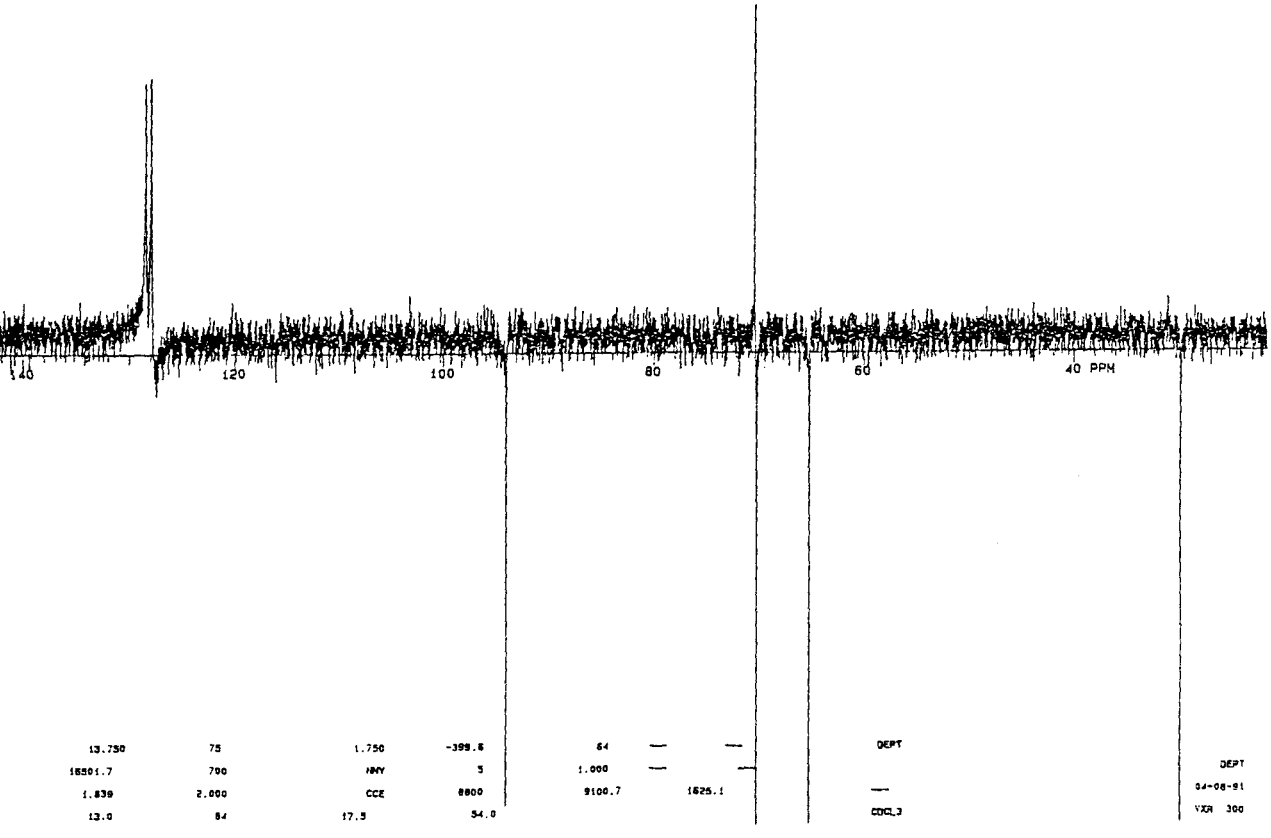
28

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

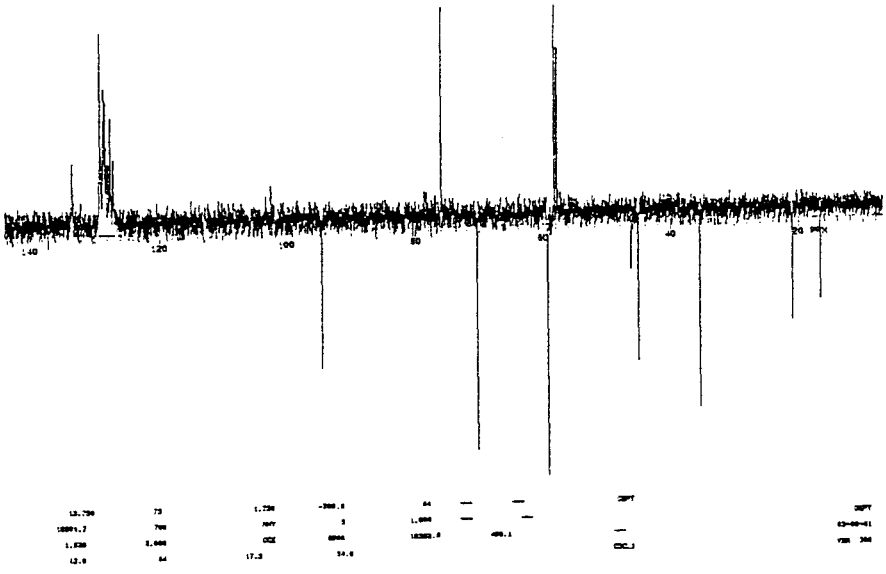
28b


OBOM
O
O

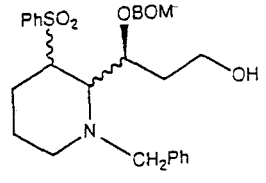
37


140
120
100
80
60
40 PPM
13.750
75
1.750
-399.6
64
DEPT
16501.7
700
NNY
5
1.000
1.839
2.000
CCE
8800
9100.7
1625.1
DEPT
13.0
84
17.5
54.0
CDCL3
04-08-91
VXR 300

37



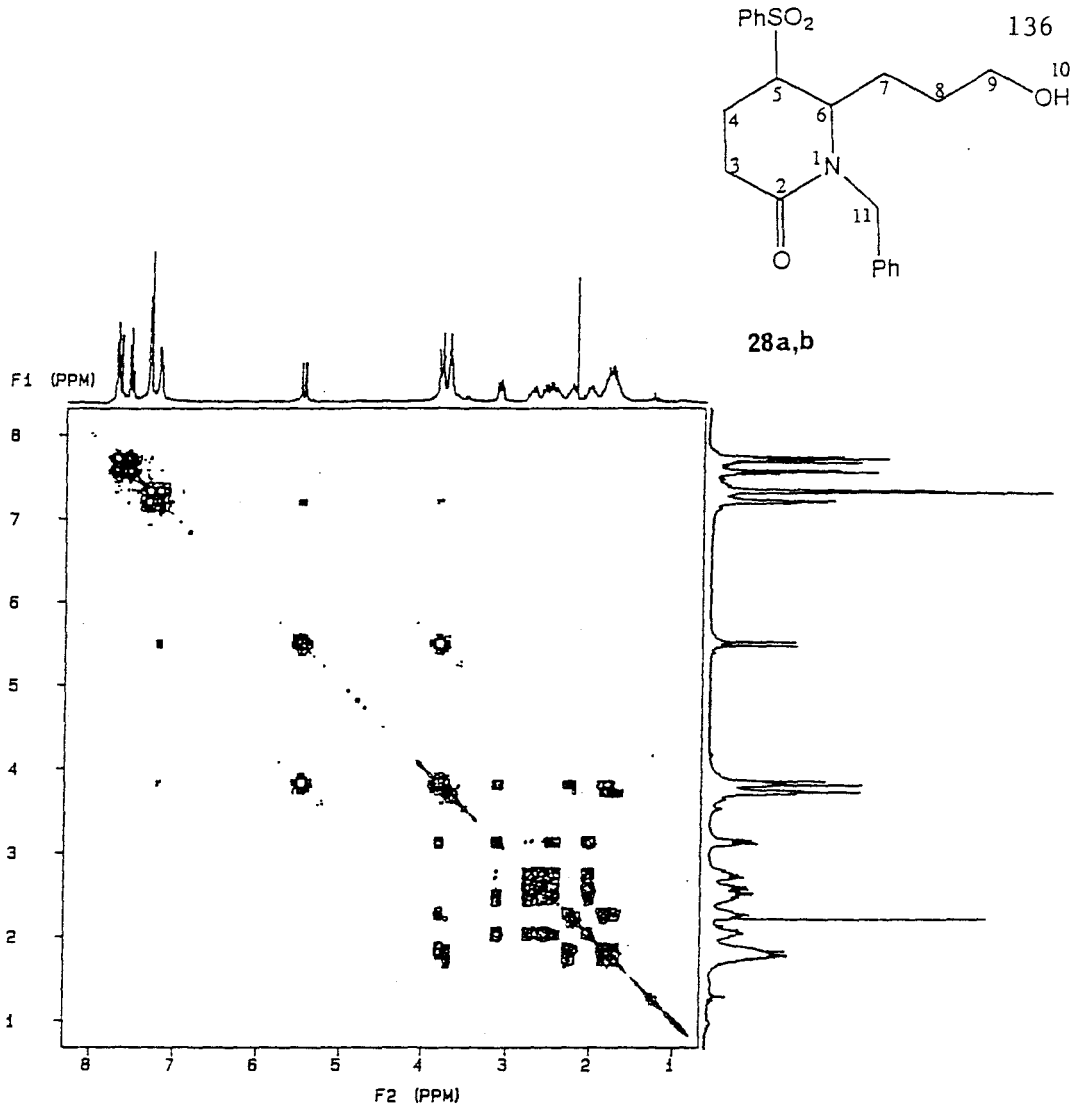
43a



43b

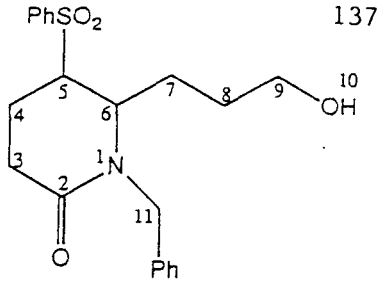
Chapter 8

Selected 2-D HOMCOR assignments.

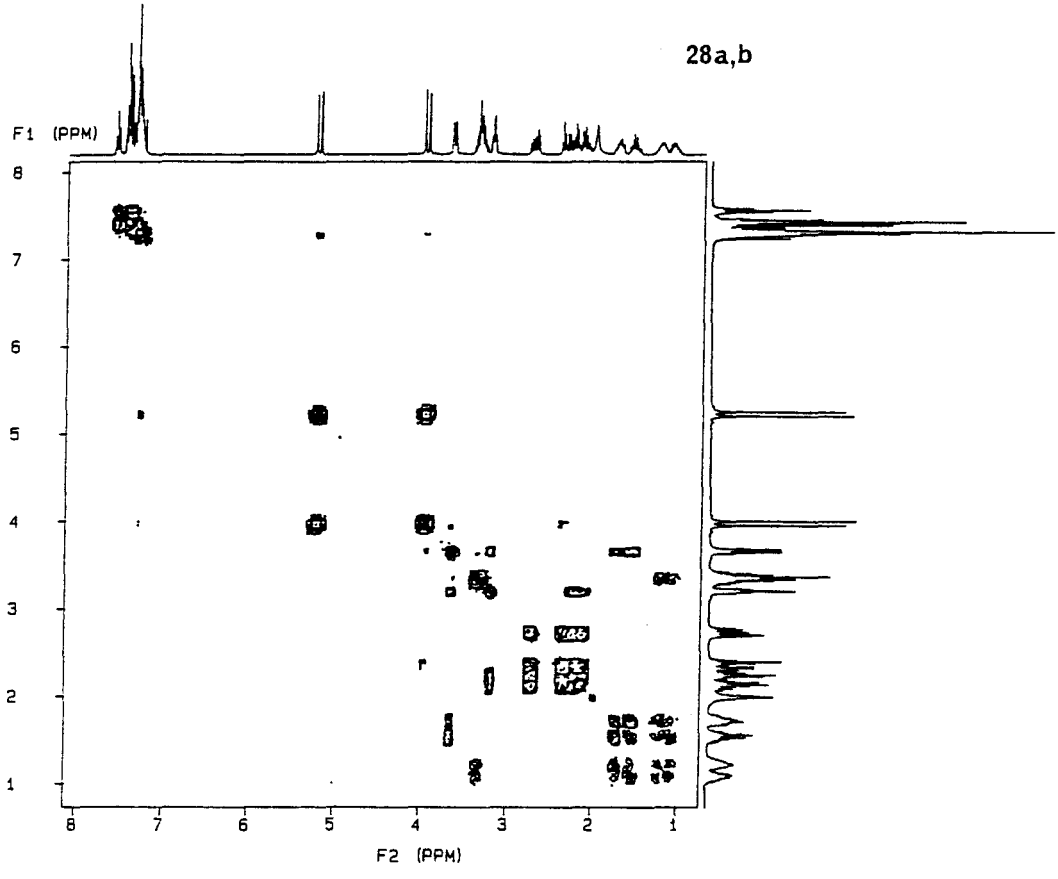


^{1}H assignments for <u>28a</u>:

δ	proton assignment
1.80 (m, 4H)	H-7, H-8(1) and H-10
2.05 (m, 1H)	H-4
2.25 (m, 1H)	H-8
2.54 (m, 2H)	H-3 and H-4
2.73 (m, 1H)	H-3
3.13 (m, 1H)	H-5
3.71 (t, 2H)	H-9
3.82 (m, 2H)	H-6 and H-11
5.49 (d, 1H)	H-11

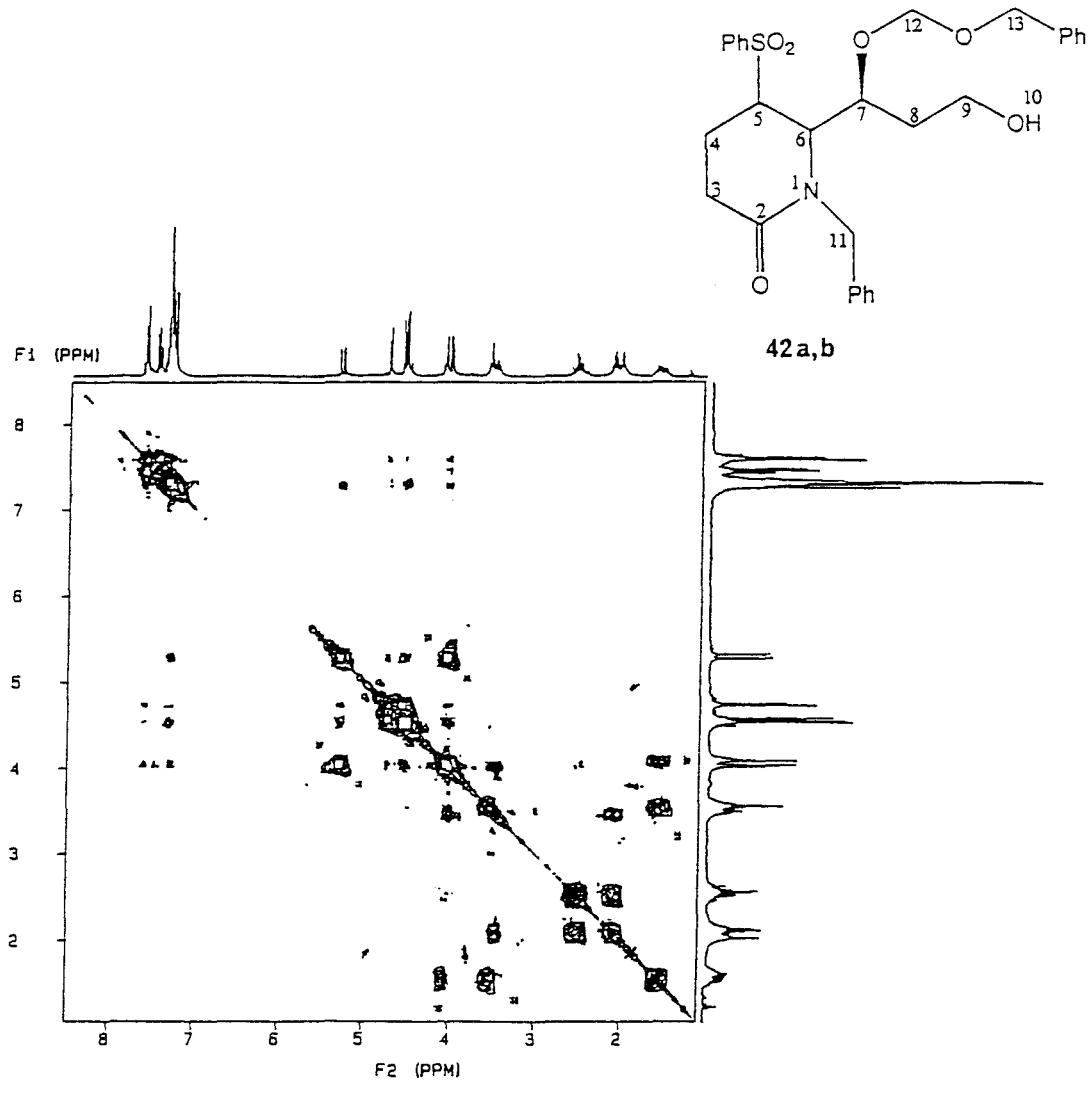


28a,b



^{1}H assignments for **28b**:

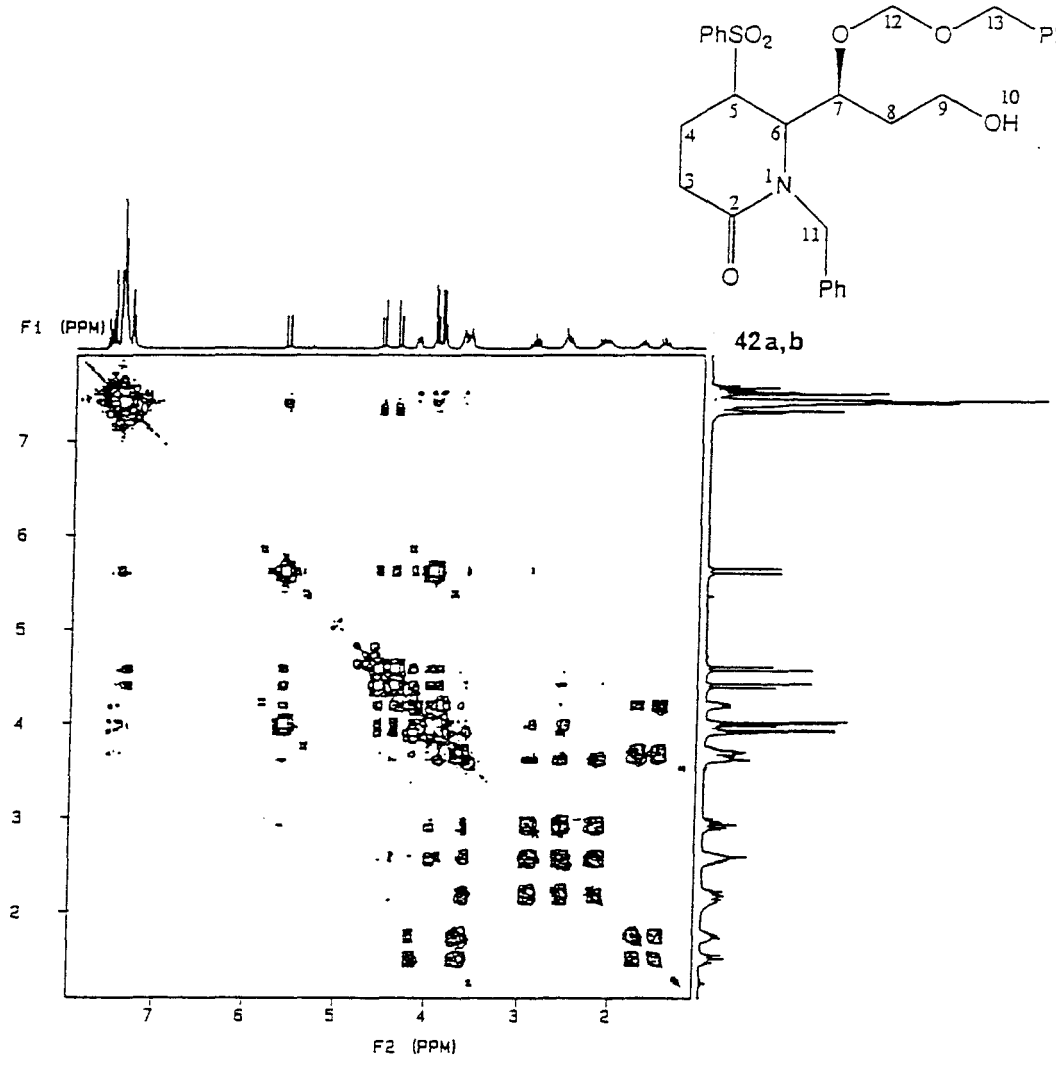
δ	proton assignment
1.09 (m, 1H)	H-8
1.24 (m, 1H)	H-8
1.56 (m, 1H)	H-7
1.73 (m, 1H)	H-7
1.93 (s, 1H)	H-10
2.26 (m, 3H)	H-3(1) and H-4
2.75 (m, 1H)	H-3
3.21 (dt, 1H)	H-5
3.35 (m, 2H)	H-9
3.67 (dt, 2H)	H-6
3.98 (d, 1H)	H-11
5.25 (d, 1H)	H-11



42a,b

^{1}H assignments for <u>42a</u>:

δ	proton assignment
1.54 (m, 2H)	H-8
2.13 (m, 3H)	H-10 and H-4
2.53 (m, 2H)	H-3
3.53 (m, 3H)	H-9 and H-5
4.04 (d, 1H)	H-11
4.06 (m, 2H)	H-7 and H-6
4.52 (d, 2H)	H-12
4.56 (d, 1H)	H-13
4.73 (d, 1H)	H-13
5.30 (d, 1H)	H-11



^{1}H assignments for <u>42b</u>:

δ	proton assignment
1.52 (m, 1H)	H-8
1.75 (m, 1H)	H-8
2.18 (m, 2H)	H-10 and H-3
2.57 (m, 2H)	H-4
2.93 (m, 1H)	H-3
3.66 (m, 3H)	H-9 and H-5
3.94 (m, 3H)	H-6 and H-12
3.99 (d, 1H)	H-11
4.19 (m, 1H)	H-7
4.40 (d, 1H)	H-13
4.58 (d, 1H)	H-13
5.61 (d, 1H)	H-11

VITA

The Author of this dissertation, Diana Lee Conway Green, was born on July 27, 1961 in Miami, Florida.

She received her Bachelor of Science Degree in Chemistry in 1982 from Indiana University, Bloomington, IN. She completed her Doctorate of Philosophy in Chemistry at Loyola University of Chicago in 1991.

During her tenure in graduate school, Ms. Green was supported through Teaching Fellowships from the Graduate School of Loyola University of Chicago, research assistantships funded by the National Institute of Environmental Health, and a dissertation fellowship from the Arthur J. Schmidt Foundation.

Ms. Green is a member of the American Chemical Society and the Organic Division of this society.

The dissertation submitted by Diana L. C. Green has been read and approved by the following committee:

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Loyola University of Chicago

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Professor, Chemistry
Loyola University of Chicago

Dr. Daniel J. Graham
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Loyola University of Chicago

Dr. David S. Crumrine
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Loyola University of Chicago

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Professor, Chemistry
University of Wisconsin-Milwaukee

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated and that the dissertation is now given final approval by the Committee with reference to content and form.

The dissertation is, therefore, accepted in partial fulfillment of the requirements for the degree of Ph.D.

8/23/91
Date

Chuck Thompson
Signature of Director