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THE DEVELOPMENT OF STEREOCONTROLLED METHODS TO OBTAIN A DIVERSE SET OF TETRAHYDROQUINOLINE-BASED, NATURAL PRODUCT-INSPIRED COMPOUNDS

by

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Abbreviations and Acronyms

1D	1-dimensional
2D	2-dimensional
Å	angstrom(s)
Ac	acetyl
AD mix α	$(DHQ)_2PHAL$, $K_3Fe(CN)_6$, $K_2OsO_4 \cdot 2H_2O$
AD mix β	$(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2OsO_4 \cdot 2H_2O$
Alloc	allyloxycarbonyl
aq	aqueous
Ar	aryl
atm	atmosphere(s)
av	average
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn, Bzl	benzyl
BOC, Boc	*tert*-butoxycarbonyl
Br	bromine
br	broad (spectral)
bs	broad singlet
Bu, *n*-Bu	normal (primary) butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C	carbon
°C	degrees Celsius
calcd	calculated
CAN	ceric ammonium nitrate
cat	catalytic
CBZ, Cbz	benzyloxycarbonyl
CD	circular dichroism
c-Hex	$c\text{-}C_6H_{11}$, cyclohexyl
CI	chemical ionization; configuration interaction
Cl	chlorine
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
compd	compound
concd	concentrated
concn	concentration
COSY	correlation spectroscopy
Cp	cyclopentadienyl
m-CPBA	*meta*-chloroperoxybenzoic acid
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s); doublet (spectral); deci
DCC	*N,N¢*-dicyclohexylcarbodiimide
DCM	dichlorometheane (methylene chloride)

dd	Doublet of doublets
ddd	Doublet doublet of doublets
ddt	Doublet doublet of triplets
dt	Doublet of triplets
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOS	Diversity Oriented Synthesis
ED_{50}	dose that is effective in 50% of test subjects
ee	Enantiomeric excess
eq	equation
equiv	equivalent
ES+	Positive electrospray
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
F	fluoride
FT	Fourier transform
g	gram(s)
GC	gas chromatography
H	hydrogen, proton
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum correlation
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared
J	coupling constant (in NMR spectrometry)
LAH	lithium aluminum hydride
LD_{50}	dose that is lethal in 50% of test subjects
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl) amide
m	multiplet (spectral); milli
M	molar (moles per liter); mega
M^+	parent molecular ion
max	maximum
MCR	multicomponent reaction
Me	methyl
MEM	(2-methoxyethoxy)methyl

min	*minute(s); minimum*
mM	millimolar (millimoles per liter)
mol	mole(s); molecular (as in mol wt)
mp	melting point
*m*RNA	messenger ribonucleic acid
Ms	methylsulfonyl (mesyl)
MS	mass spectrometry
MW	mol wt molecular weight
m/z	mass-to-charge ratio
N	normal (equivalents per liter); nitrogen
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
O	oxygen
obsd	observed
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PHAL	phthalazine
piv	pivaloyl
ppm	part(s) per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
py	pyridine
q	quartet (spectral)
QSAR	Quantitative structure-activity relationship
RCM	ring-closure metathesis
rel	relative
R_f	retention factor
*r*RNA	ribosomal ribonucleic acid
rt	room temperature
S	sulfurs
s	singlet (spectral)
SN_1	unimolecular nucleophilic substitution
SN_2	bimolecular nucleophilic substitution
t	triplet (spectral)
TBAF	tetrabutylammonium Fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
Teoc	Trimethylsilylethoxycarbonyl
temp	temperature
Tf	trifluoromethanesulfonyl (triflyl)

TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TLC	thin-layer chromatography
TMS	trimethylsilyl; tetramethylsilane
*t*RNA	transfer ribonucleic acid
Ts	*para*-toluenesulfonyl (tosyl)
TS	transition state
UV	ultraviolet
vis	visible
vol	volume
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

Abstract

Over the years, it has been shown that natural products which are capable of acting as modulators (i.e., activators or inhibitors) of protein-protein interactions are highly complex and possess three-dimensional architectures with several chiral centers and a diverse range of protein-binding elements. These features appear to be required when it comes to dissecting protein functions with the help of small molecules. Therefore, it is not surprising that an interest in developing natural product-like small molecules, which could aid in understanding protein-protein interactions-based cellular signaling pathways, is growing. The success of the chemical genomics program that is aimed toward understanding complex protein networking and its roles in cellular signaling pathways depends on the availability of a diverse range of such chemical probes (Chapter 1).

Tetrahydroquinoline-derived natural products have long been utilized as modulators of protein functions and belong to an important family of bioactive compounds. We had developed a practical enantioselective synthesis of tetrahydroquinolione-based functionalized scaffold (Chapter 2). The bicyclic scaffold is highly versatile and contains four orthogonally protected functional groups that could further be utilized in obtaining polycyclic compounds. In one case, we successfully developed a solution phase synthesis of the tricyclic derivative having a bridged 10 membered ring (Chapter 3). In the other case, tetrahydroquinoline-based polycyclics containing α,β-unsaturated γ-lactam and δ-lactone were synthesized (Chapter 4). The stereoselective ring closing metathesis was the key reaction in those syntheses.

After the successful development of the methods in solution, some of the intramolecular and intermolecular stereoselective-based reactions had been tried on solid phase. Developing stereoselective reactions-based methods on solid phase is crucial for the rapid synthesis of analogs. Besides NMR, the

conformation of the bridged 10 and 5-membered ring derivatives were assigned by X-ray studies (Chapter 3 and 4).

In another study, a known polycyclic system containing tetrahydroquinoline was prepared using a tandem Povarov multi I component/cyclocondensation reaction. With our novel methodology, this complex system was constructed not only in one-pot, but also with high yield and complete stereo- and regio-selectivity (Chapter 5).

Finally, one of the several possible applications for our synthesized compounds was investigated. The aim was seeking for the small molecules capable of modulation of the Bcl-2 family proteins (Chapter 6). The observed preliminary results were found to be promising as the starting point on the general goal of 'Finding Small-Molecule Perturbators of Protein-Protein Interactions as the Possible Drug Targets in Cancer Therapy'.

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1: Introduction

1.1 Small Molecules or Smart Molecules?!

1.1.1 Drug Discovery Stages

Human diseases often need medical treatment. Despite the existence of many alternative treatments for some disorders, e.g. for psychological illnesses, medicines are the most effective remedies. Once the abnormality is properly identified, the drug discovery process begins. In many cases, various therapies, including drugs, have already been used; however, there is always an opportunity for improving medication, or for finding a method, or drug, that has fewer side effects.

With the help of synthetic and medicinal chemists, appropriate chemicals, in terms of their biological activity, are prepared by in vitro testing. The next step is to seek a derivative of the compound that has in vivo activity in a selected animal model, maximizing this activity normally by creating a synthesis of several analogs. This activity performs by synthesis of normally several analogs. The best compound for the desired activity is selected as the 'drug candidate', which should be toxicologically tested on animals. In order to ascertain acceptable safety results, all subsequent data are submitted for evaluation by the relevant government authority, such as the FDA, 'Health Canada', etc, and then, when approval is received, clinical trials may be initiated.

Depending on the satisfactory progress of these trials, which will contain several phases, healthy human volunteers may be recruited in order to evaluate tolerance to the drug (phase I). This will be followed by a trial on patients, in order to evaluate the drug's efficacy and dosage (phase II) and a complete database of drug safety and efficacy may be obtained through widespread trials on thousands of patients (phase III). Manufacturers will then submit all

documentation to the relevant authority in order for them to make a thorough assessment of the drug's safety, efficacy, and quality. Only a very few drug candidates survive this series of trials. On obtaining official approval, the supplier can then offer the new drug to doctors for treating the disease. These stages are illustrated in Figure 1.1.

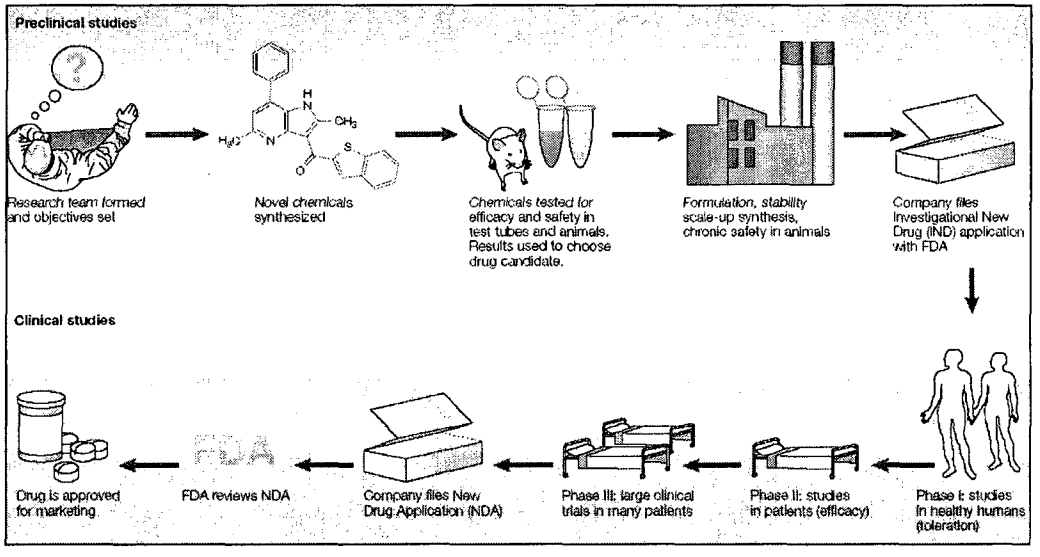


Figure 1.1 Stages in the Drug Discovery Process[1]

Dominant role in drug discovery is played by natural products and their derivatives/mimics[2,3]. Figure 1.2 shows the percentage of drug sources, which discovered for all diseases (left) and cancer (right). 58% of all drugs and 54% of cancer drugs are natural product related compounds [Natural (N), biologics (B), vaccines (V), synthetic (S), natural product-like or mimic (NM), natural product-derived (ND), made by total synthesis, but the pharmacophore is from a natural product (S*)].

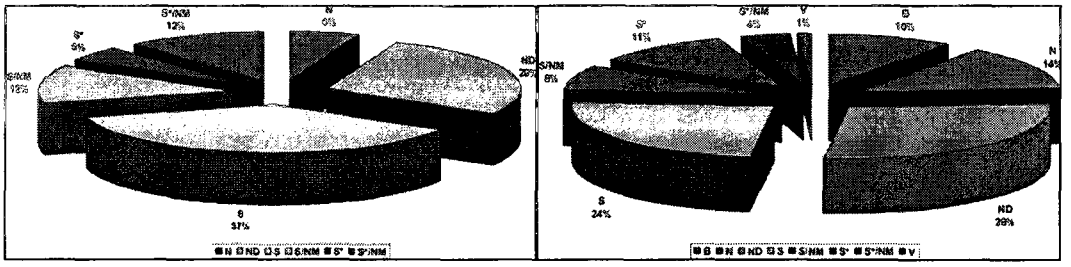


Figure 1.2 All small molecule new chemical entities-drugs [right, (1981-2006)] and all available anticancer drugs [left, (1940s-2006)][3]

1.1.2 Natural Products *vs.* Synthetic Drugs

There are several distinctions between synthetic drugs and natural products. Natural products normally have more chiral centres, thus they are more architecturally complex, however, some natural products, acting as protein receptors, have more simple structures. In addition, natural products often contain more carbon, oxygen, and hydrogen atoms and fewer other elements, including nitrogen, than do synthetic drugs. Many natural products have greater water solubility/polarity and possess molecular masses of over 500 daltons. Therefore, natural products violate Lipinski's 'rule of five'[4] where, according to research, 90% of orally absorbed drugs have fewer than 5 hydrogen-bond donors, fewer than 10 hydrogen-bond acceptors, molecular masses of below 500 daltons, and lipophilicity (measured by log P value-calculated octanol/water partition coefficient) of less than 5[5].

Although, in many cases, a similarity factor between natural products and synthetic material may result in similar actions, other cases do not follow this pattern, since similar biological activities are observed in totally different molecules. Some ligands for proteins, after minor structural modification, show unexpected binding patterns and different bioactivities have also been observed in even enantiomers[6]. Because of the lack of compatibility of natural product extract libraries with high-throughput screening, pharmaceutical companies have researched natural products during the last decade less frequently than had been

their previous practice. This decline, however, is now being reversed due to establishing advanced technologies[7].

1.1.3 Small Molecules as Chemical Probes- Modulators of Protein-Protein Interactions

There is a growing interest in the use of small molecules as chemical probes in parallel to classical genomic tools (i.e. gene expression, gene profiling, gene knockouts, and siRNA-based gene silencing etc.) to understand biological functions[8,9-12,13]. Small molecule probes have the ability to modulate macromolecules such as proteins, DNA, RNA, or carbohydrates in a controlled and selective manner; furthermore, some of the distinctive advantages of small molecules over the classical biological tools include the ability of the probes to function nondestructively to induce subtle and generally reversible changes in macromolecule dynamics[14,15]. In addition to using them as chemical probes to understand biological function, these small molecules offer an excellent starting point in launching drug discovery programs and could further be developed as therapeutic candidates.

In the past few years, an interest in this area has sparked because of the growing desire to modulate (and dissect through perturbation) intracellular signaling pathways[16]. The era of post-genomic chemical biology (also known as "Chemical Genomic Age") is challenging the chemistry and biology community to develop programs in which small molecules could be extensively used to enhance our current understanding of intracellular signaling pathways[13,17,18,19]. These pathways are fundamental to cellular functions, in both normal as well as deregulated cellular processes. Usually, these pathways involve multiple, highly complex, and dynamic protein-protein interactions, that are challenging to understand due to limited technology and tools available for studying signaling pathways[20,21]. A lack of a thorough understanding about their participation in various normal and deregulated processes combined with the formidable challenge to modulate protein-protein interactions in a controlled and in a

reversible manner, severely limits our ability to develop therapeutic approaches that exploit these pathways for beneficial outcomes. It is anticipated that the successful development of small molecule modulators of protein-protein interactions will create excellent opportunities for biomedical researchers to develop novel therapeutic strategies that would no longer be constrained by the limited set of proteins with enzymatic activity that are encoded in the genome[22,23].

In general, protein-protein interactions involve shallow surfaces and a comparatively large surface area. While there are certainly a few examples in the studies that support the use of "hot spots" in protein-protein interactions as small molecule targets, usually the lack of structural information about protein complexes, and the overall dynamic nature of protein complexes inside the cellular environment has limited success using designed molecules[24-26]. Thus, quick access to small molecules by high-throughput organic synthesis and screening (through dynamic assays) remains an attractive strategy for identifying small molecule modulators of protein-protein interactions. This leads to two main questions: (1) In the absence of any structural information, what types of small molecules are most likely to be successful for disrupting signaling pathways based on dynamic protein-protein interactions? (2) Can these molecules serve as generalized scaffolds for constructing libraries of compounds highly enriched in small molecules that are expected to disrupt protein-protein interactions? We will discuss 'Protein-Protein Interaction' subject with more details later in this chapter.

1.2 Combinatorial Chemistry- Some Aspects

To meet the growing challenges in search of functional small molecules, for more than two decades, the area of combinatorial chemistry is now much engaged in the drug discovery arena[27-29]. While taking an advantage of high-throughput access to DNAs/RNAs, peptides, and solid phase synthesis tools, the next challenge was to bring this and other related technologies to the small molecule arena. During this time, several outstanding reviews, book chapters and even books have been written on this topic. In general, as a community, we have

been very successful in embracing this area of high-throughput organic synthesis in producing rather simple compounds that are particularly rich in aromaticity and high sp^2 content; however, these compounds often lack the features that are frequently found in bioactive natural products.

1.2.1 Solution Phase *vs.* Solid Phase Combinatorial Synthesis

Selecting solution phase or solid phase combinatorial synthesis for a given application depends on a range of factors[30]. The advantages and limitations of these two basic methods are reviewed here:

i) Removal of excess reagents and reactants is simple in solid phase synthesis, but limited in solution phase synthesis.

ii) Purification after each step is possible for solution-phase, but not possible for solid phase synthesis.

iii) Convergent or linear synthesis can be conducted in solution-phase, but not for solid phase.

iv) Unlike solid-phase, solution-phase synthesis can perform in a mixture or in parallel fashion.

v) Split and mix synthesis is possible for solid-phase synthesis only.

vi) Unlike solution-phase, only limited amounts (scales) are available for solid phase synthesis.

vii) Reaction monitoring is easier in solution-phase, but more difficult in solid phase synthesis.

viii) Solid phase synthesis requires the additional steps for linking and cleavage, not needed in solution-phase synthesis.

ix) Solid phase synthesis is limited by the support or the linker. It should adapt chemistry to solid phase and develop linking as well as cleaving strategies.

x) Automation is straightforward for solid-phase synthesis. For solution phase synthesis, automation can be performed by liquid-liquid techniques.

xi) Pseudo-dilution effect is advantageous in solid-phase synthesis.

Due to limitations of both methods, one or the other may be chosen for each synthetic strategy. In fact, in many cases, these methods have completed each other. In our group, we have applied solution or solid phase library synthesis depending on the study required. For example, after finding a target 'hit' molecule using solid phase library synthesis, we have performed an additional larger scale, solution-phase synthesis. This approach enables diversification on the 'hit' using again solution-phase synthesis. As such, the best candidate for the desired bioactivity will be generated[31,32].

1.2.2 Parallel *vs.* Split-Pool Library Synthesis

In parallel library synthesis as shown in Figure 1.3-left, created compounds from the library are spatially separated. As such, this technique may be used for both solution and solid phase synthesis. As displayed in Figure 1.3, to create 9 compounds, 12 reactions are required. In split-pool synthesis (Figure 1.3-right), each library member is compartmentalized to allow mixing of the library. With this method, each compound is on its own solid support (bead). As a result, to create 9 compounds, only 6 reactions are required.

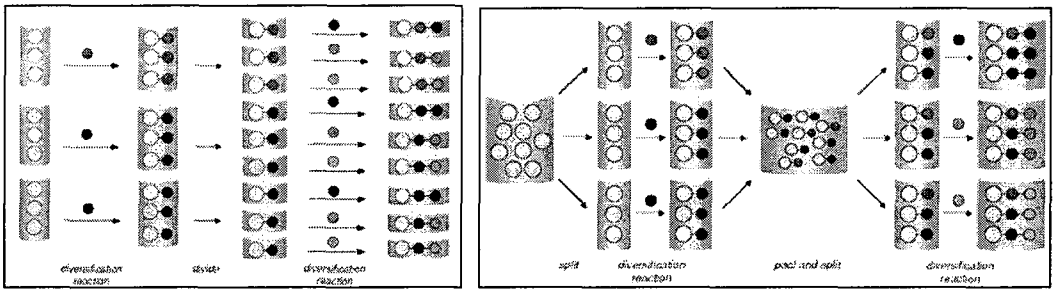


Figure 1.3 Parallel Library Synthesis (left) and Split-Pool Synthesis (right)[33]

1.2.3 Natural Products as "Role Models" for Combinatorial Chemistry

Over the years, architecturally complex natural products have been used as small-molecule probes for understanding protein function. The search for novel natural products with interesting biological properties is a continuing exercise[31,32,34]. Imbedded in these natural products are a number of highly diverse, chiral functional groups, which are potential sites for protein binding. Although natural products from different sources (i.e. plants, soil, sea, etc.) are useful candidates for identifying lead compounds, the major limit with natural products mostly is their follow-up organic synthesis/medicinal chemistry efforts. Often, the availability of the natural product is not sufficient for the various desired biological assays, thereby limiting the exploration of their full potential. Developing similar, relatively simple, structural analogs to natural products, with comparative biological responses often is a challenging and a highly time-consuming undertaking.

At this point, developing natural product-inspired, high-throughput organic synthesis programs could be extremely useful[34]. Some examples of generating natural product-like compound libraries that utilize the diversity-oriented synthesis (DOS) will be further discussed later in this chapter. DOS is aimed at populating the unexplored, natural products-based, chemical space that is currently unoccupied by conventional combinatorial chemistry[8,35-42] [*Chemical space*: Molecules are identified by several 'descriptors', e.g. molecular mass, structure. 'Chemical space' or is a region defined by a specific descriptor with particular limit placed on it. Mostly, however, chemical space is defined as the total descriptor space that includes all the molecules that could be prepared[43]].

Members of natural products including alkaloids[44-47], flavonoids[48] and several of their derivatives are known to possess a diverse range of biological properties. Most alkaloids and flavonoids are rich in nitrogen and oxygenated functional groups, and contain "sub-structures'" which are ideal for protein binding. Several

alkaloid and flavonoid natural products are known to interfere with protein surfaces and display a wide array of biological activities. Some of the bioactive alkaloids, oxygen-riched natural products and flavonoids are shown in Figure 1.4.

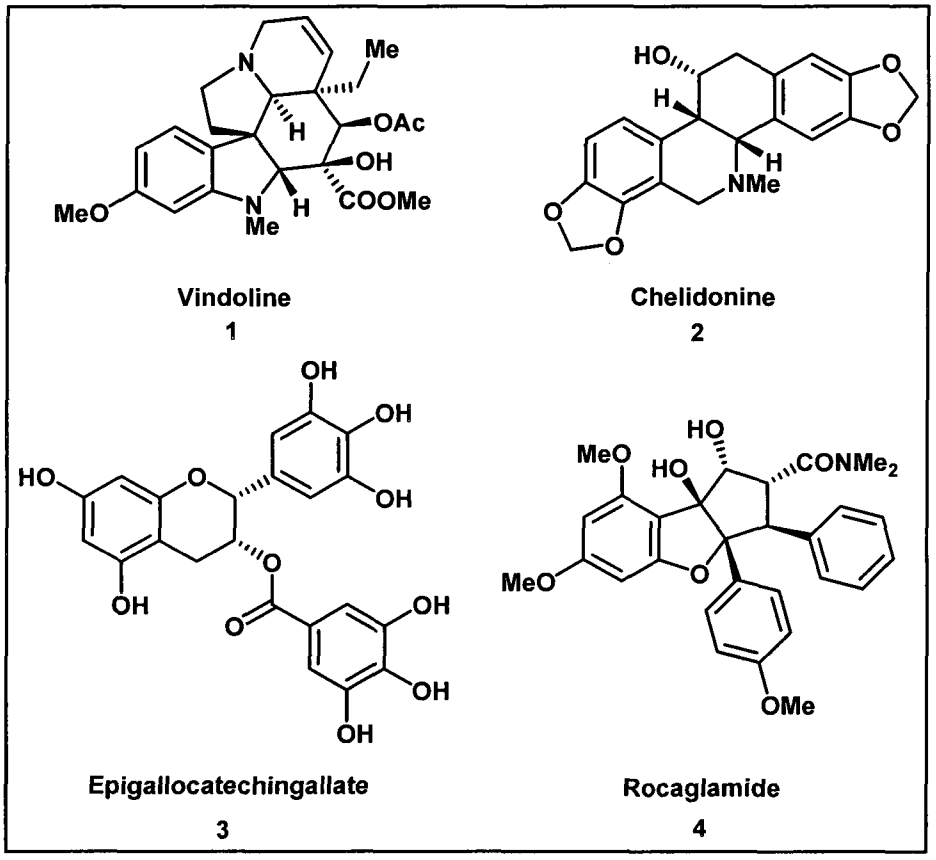


Figure 1.4 A few examples of alkaloids and oxygen-riched natural products

Belonging to the family of *Vinca* alkaloids, Vindoline **1** (Figure 1.4) and Vinblastine (not shown) contain indole/indoline moieties and act as antimitotic agent as they inhibit microtubule formation[49,50]. Chelidonine **2** is also an antimitotic alkaloid natural product and contains the tetrahydroisoquinoline moiety[51].

Flavonoids and several of their derivatives have been shown to exhibit a diverse

range of biological properties[48,52,53]. Most flavonoids are rich in oxygenated functional groups and contain polyphenolic moieties. These two features are ideal for protein binding, and several of these natural products are known to interfere with the protein surfaces and show a broad range of biological properties. The examples of bioactive polyphenolic natural products are also shown in Figure 1.4. During a high-throughput, in silico screening for small-molecule binders to the hydrophobic region of the Bcl-XL protein, epigallocatechingallate **3**[54] was identified in order to develop compounds that could promote apoptosis. This flavonoid natural product has been shown to interfere with the protein-protein interactions involving the Bcl-2 protein family and related proteins[55,56]. The ability to modulate these networks in a highly selective manner provides a means of obtaining a better understanding of these signaling pathways and their distinct roles in apoptosis[57,15]. The rocaglamides **4** are densely functionalized oxygen-enriched natural products and are shown to inhibit the NF-κB inhibitory activity at nanomolar concentrations in human T cells[58]. Several derivatives of this family are highly cytotoxic in human cancer cells with anti-cancer biological activities similar to Taxol[59,60].

These examples demonstrate that a variety of alkaloid and oxygenated natural products and their synthetic analogs are known to interact with protein surfaces and exhibit specific bindings. This information offers a valuable starting point for developing small-molecule chemical probes of biological pathways. These examples further validate the necessity for charting a chemical space that is currently occupied by bioactive natural products.

1.3 Diversity Oriented Synthesis

1.3.1 Diversity Oriented Synthesis *vs.* Target Oriented Synthesis

Diversity oriented synthesis aims to prepare natural product-like and/or drug-like compounds with collections of natural product/drug-like small molecules with

diverse structural features. In Target-oriented synthesis (TOS), one particular compound is synthesized using a series of reaction steps. These steps have already been designed by adjusting parameters including stereo/regio chemistry and yield. TOS is normally equivalent to 'Total Synthesis'. A comparison between DOS, TOS and also traditional combinatorial chemistry is illustrated in Figure 1.4[61].

A clear distinction can be made between DOS and TOS. DOS aims to synthesize as many compounds as possible, whereas the goal of TOS is to prepare compounds at specific points in chemical space. In (traditional) combinatorial chemistry, a discrete region of chemical space, normally around a lead molecule, is explored.

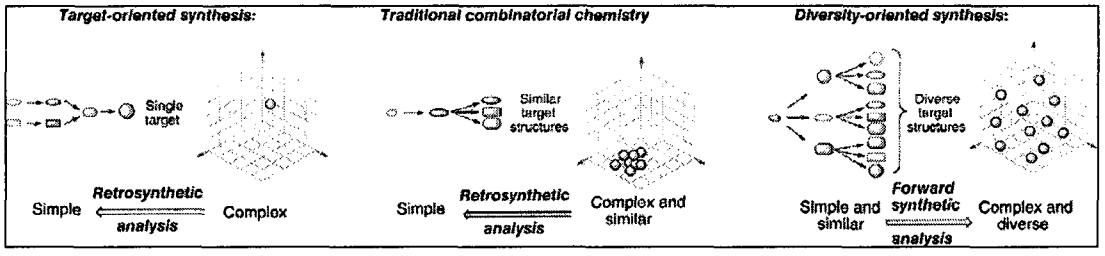


Figure 1.5 'DOS/TOS/Traditional Combinatorial Chemistry' Comparisons[61]

As shown in Figure 1.6, TOS locates in one extreme and synthesis of all compounds in the other. This "molecular diversity spectrum" also illustrates DOS, which theoretically should aim to synthesize molecules as close to the right as possible[62]. The combinatorial chemistry program in DOS utilizes stereo- and enantio-selective organic synthesis reactions and is designed to provide small molecules that are rich in (1) stereochemically-defined polyfunctional groups, and (2) conformationally diverse, natural product–like skeletons. On the contrary, with few exceptions, traditional combinatorial chemistry efforts have led to simple compounds. These simple compounds may not be able to populate the chemical space that is occupied by bioactive natural products, and may be less likely to be

useful as modulators of protein-protein interactions and as chemical probes for dissecting dynamic signaling pathways. With DOS, a synthetic platform is already established, re-synthesis at any stage is achievable, and second-generation compounds can be easily obtained.

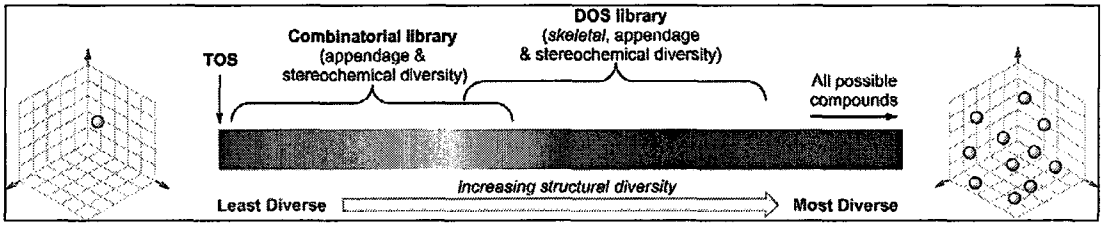


Figure 1.6 Molecular Diversity Spectrum[62]

1.3.2 Applications of DOS

In the following, we have provided some recent examples to demonstrate the capability of natural product–inspired DOS and, emphasize it as a tool in the quest for chemical probes.

Some representative compounds synthesized using DOS are presented in Figure 1.7. Secramine **7** (one member of 2,527 compounds) is found to be a specific modulator of protein trafficking out of the Golgi apparatus; haptamide **4** (one member of 4,320 compounds) is an inhibitor of Hap3p-mediated transcription; tetracycle **5** (one member of 2,500 compounds); tubacin **6** (one member of 7,200 compounds) is a tubulin deacetylase inhibitor; macrolide **8** (one member of 36 compounds); macrocyclic biaryl **9** (one member of 1,412 compounds) affects the cardiovascular system during zebrafish development (its enantiomer has no activity)[8].

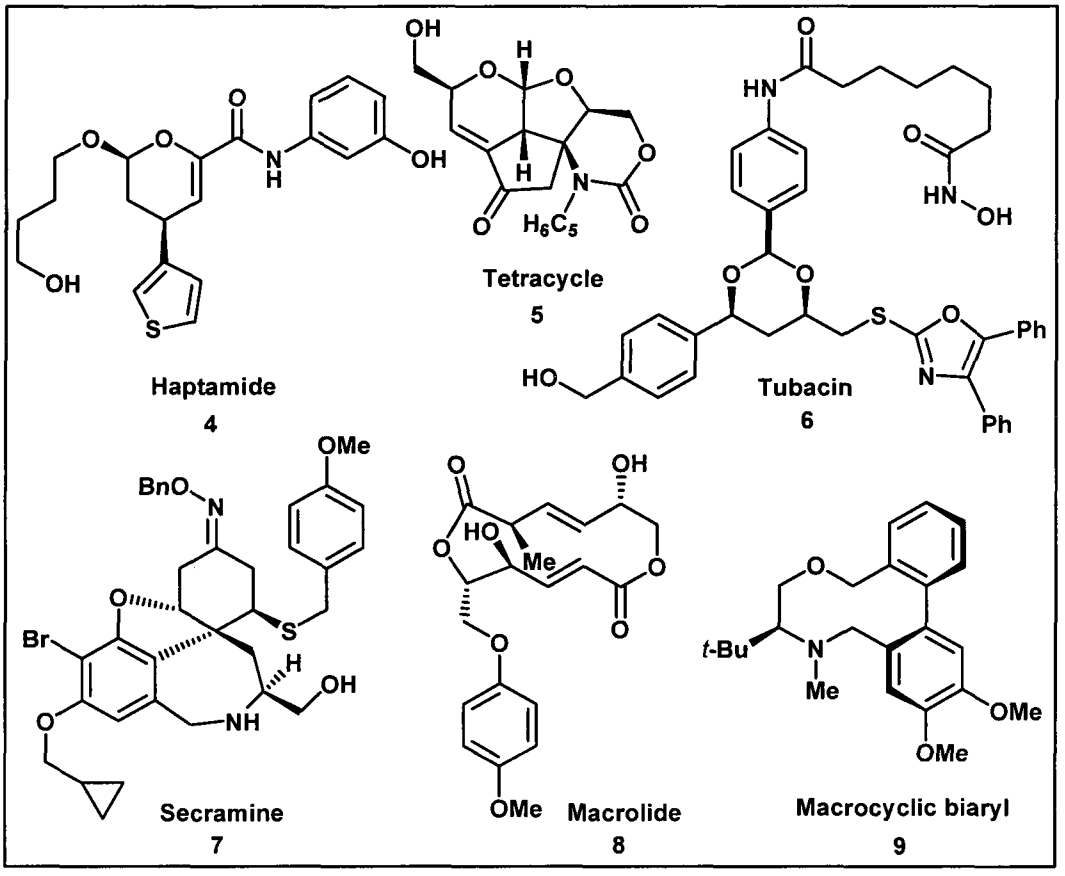
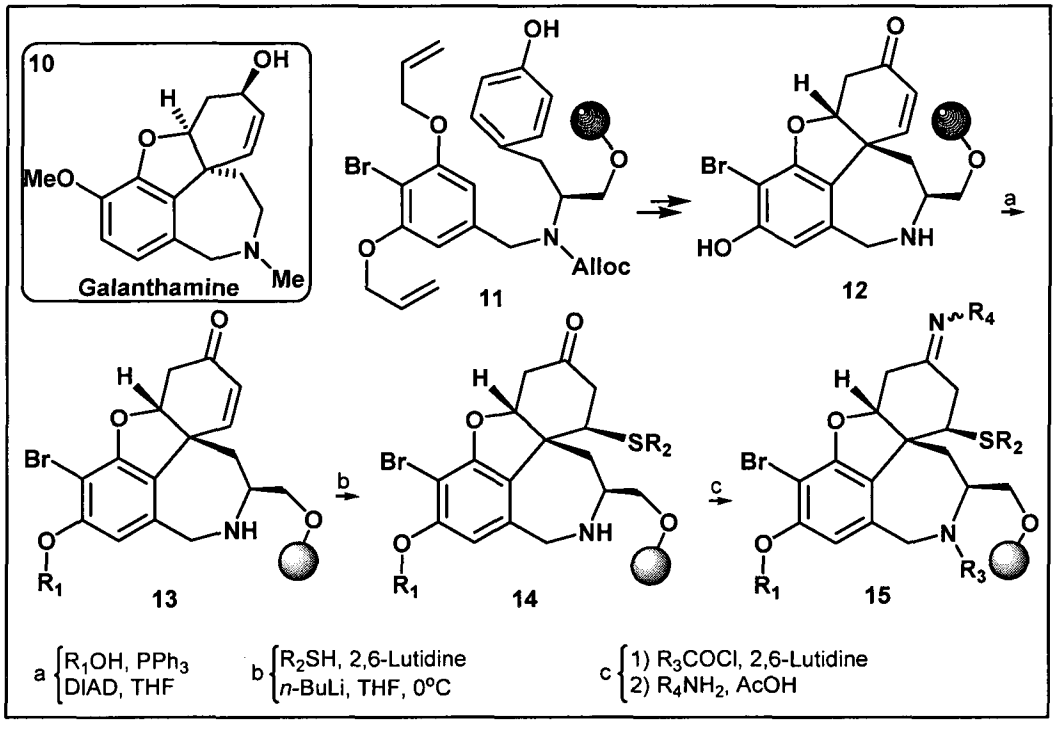


Figure 1.7 Representative Bioactive Molecules Synthesized using DOS

One of the objectives of high-throughput organic synthesis is to obtain small molecules, which are inspired by natural products but have biological properties beyond those found in naturally occurring molecules. Working with this goal, galanthamine **10**, a benzofuran based natural product, decorated with multiple functional groups in a rigid framework was chosen by Shair and co-workers in example of biomimetic synthetic strategy applied for library generation on solid support (Scheme 1.1)[63,64]. The Galanthamine framework **12** was obtained from the advanced solid supported intermediate **11** in the crucial hypervalent iodine mediated intramolecular oxidative coupling followed by Pd-catalyzed allyl deprotection and spontaneous facially selective cyclization. Four diversity points in **12** were then exploited to build a library of 2527 unique galanthamine-like

small molecules using split-pool technique. The phenolic hydroxy in **12** was treated with several alcohols under Mitsonobu conditions to obtain phenolic ethers, **13** as the first diversity, which was followed by diastereoselective 1,4 addition of thiols to give the adducts **14** with two diversities. The third and fourth diversities were introduced by manipulation of the ring nitrogen in **14** by acylation, followed by imine formation on the carbonyl group to obtain the resin-bound final derivatives **15**. The collection of 2527 molecules was cleaved from the silicon-based macrobeads by HF-py. treatment and subjected to phenotypic screening to identify a useful small molecule probe for understanding the mechanism of protein trafficking in secretory pathways (i.e. Secramine **7**, Figure 1.7).

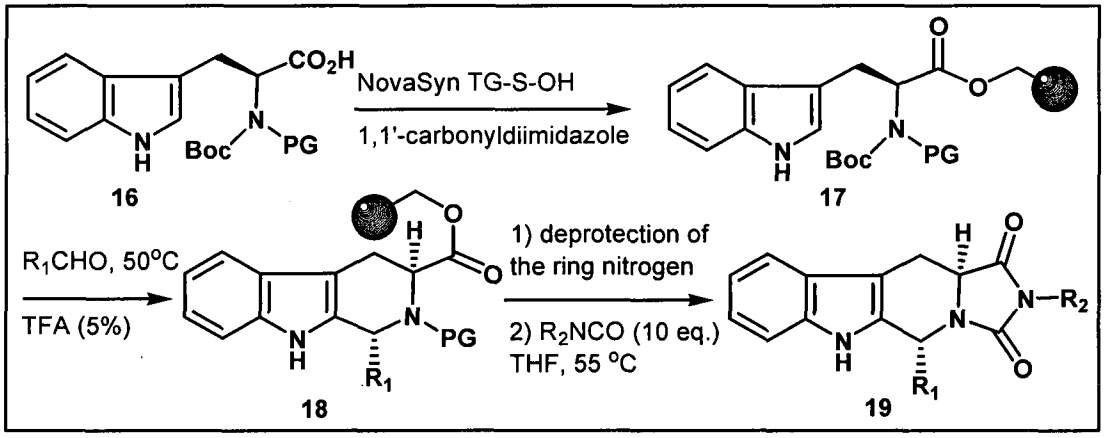
Scheme 1.1



Inspired by indole alkaloids, synthesis of a 50-compound library of HR22C16 analogs was achieved by Kapoor *et al.*[65]. HR22C16 is a cell-division inhibitor discovered from a forward-chemical-genetic screen[66].The resin-bound amino acid **17** (Scheme 1.2), which was obtained from the coupling of Nb-Boc-Nb-allyl-

L-tryptophan **16** with hydroxy-TentaGel resin, was subjected to Pictet–Spengler cyclization using various aldehydes. Following this, the protected cyclic amine **18** was deprotected, derivatized on reaction with different isocynates and then subjected to hydantoin-forming cleavage from the resin giving **19** as analogous to HR22C16. The overall yield of HR22C16 analogs was 46%, and the products were obtained in >90% purity as determined by HPLC analysis. These compounds were tested using in vitro assays with recombinant Eg5 and identified a lead compound [R_1 = *m*-phenol and R_2 = $(CH_2)_5NH_2$] with an IC_{50} value of 90±40 nM, thus making it the most potent inhibitor currently available for this key cell-division protein.

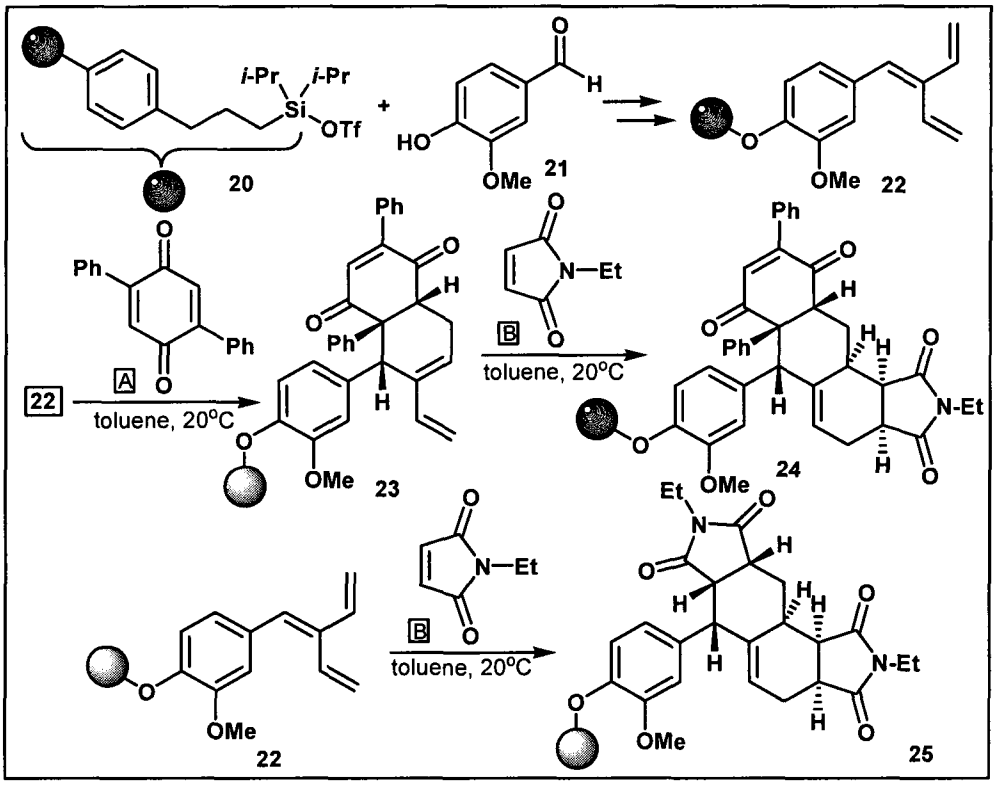
Scheme 1.2



Schreiber and co-workers[67] explored the use of a triene in cycloaddition reactions for the generation of structurally diverse complex, natural product-like small molecules (Scheme 1.3). Synthesis of the triene was carried out by a method, previously reported by Fallis *et al.*[68] in which indium-mediated alkylation was the key step. The substituted hydroxyl group could undergo elimination, leading to the desired triene. As exemplified with 4-hydroxy-3-methoxybenzaldehyde **21**, different aldehydes were immobilized on alkylsilyl macrobeads **20** and subsequently subjected to indium-mediated alkylation followed by hydroxyl elimination, giving the triene **22**. This triene was then subjected to two different cycloaddition conditions. In one case, it was treated with different tri/tetra-

substituted dienophiles that led to a single stereoselective Diels-Alder reaction affording only the bicyclic product **23** (explained with trisubstituted dienophile **A**). However, when **23** was subjected to another round of cycloaddition with different dienophiles, it afforded the tetracyclic product **24** in step-wise manner. In the second case, an interesting observation was made; the reaction of the triene **22** with a disubstituted dienophile (i.e. **B**) underwent two consecutive cycloaddition reactions resulting in the formation of *bis*-cycloadduct **25** with complete stereocontrol. This method is highly practical, and by using the split-and-mix synthesis protocol, an encoded library of 29,400 compounds was obtained from 40 different aldehydes and a series of di-, tri- and tetra-substituted dienophiles.

Scheme 1.3



Using natural product-inspired DOS and using modern organic chemistry, our group mainly synthesizes complex polycyclic natural product–like compounds having 3-dimensional skeletal and stereochemical architectures. Our three interested scaffolds are tetrahydroquinoline (**26-29**), indoline (**30-31**), and

benzofuran (**32**). As shown in Figure 1.8, several bicyclic compounds having the above-mentioned scaffolds were investigated. In each series, after completion of synthesis in the solution phase, a manual solid phase strategy is designed which allows us to develop library generation in a high-throughput manner. This trend can be performed for creating a tricyclic system as well[69].

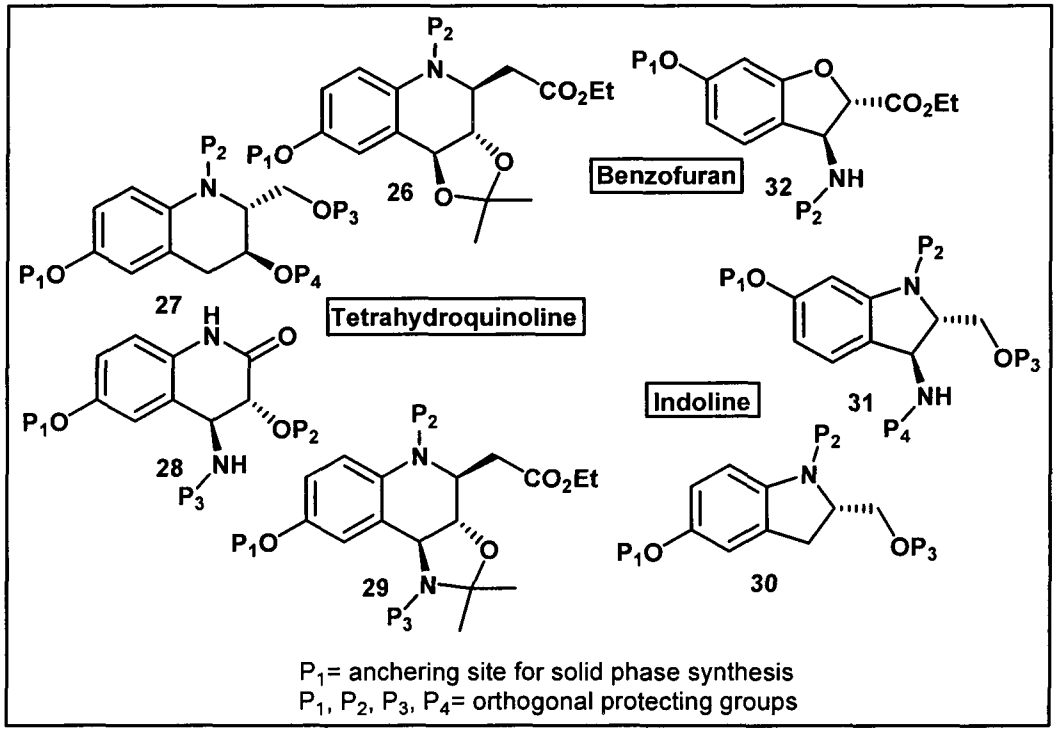
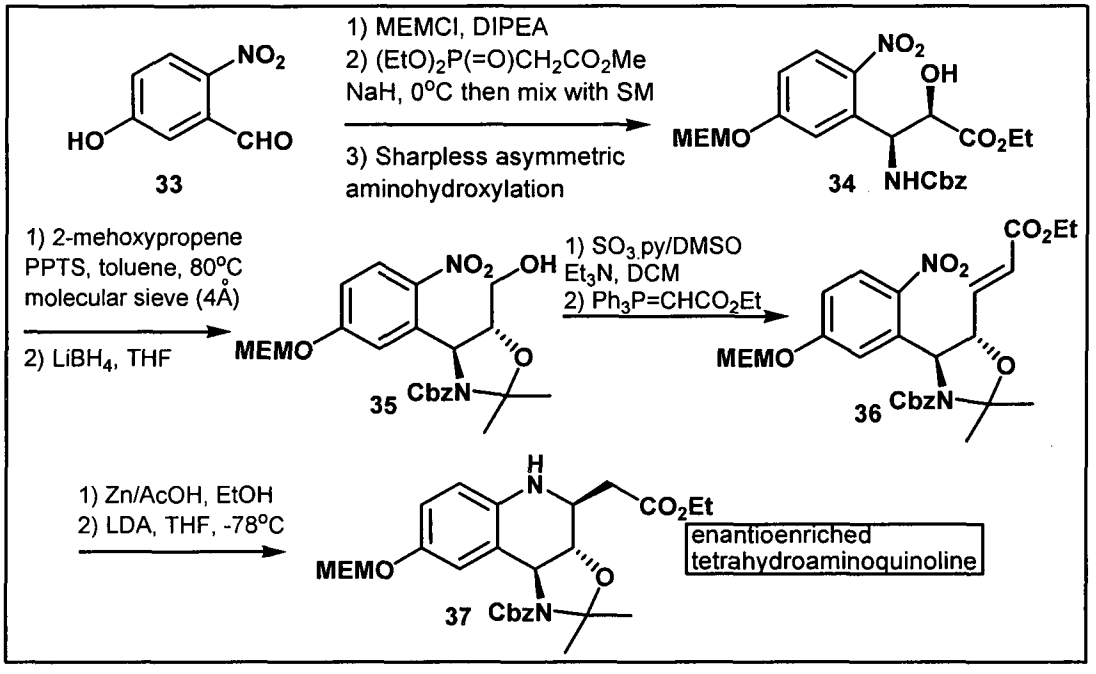


Figure 1.8 DOS Programs in Arya's Group

Arya and co-workers developed a highly practical, enantioselective synthesis of several tetrahydroquinoline scaffolds **26**, **27**, and **29** with an increase of complexity and the enantioselective synthesis of hydroquinoline-2-one scaffold **28** (Figure 1.8). Several features of the most complex **29** scaffold make it versatile and amenable to the production of a wide variety of very different polycyclic architectures. The key features include the presence of: (i) the β-amino acid moiety, (ii) the δ-amino acid moiety, (iii) the γ-hydroxy carboxyl ester

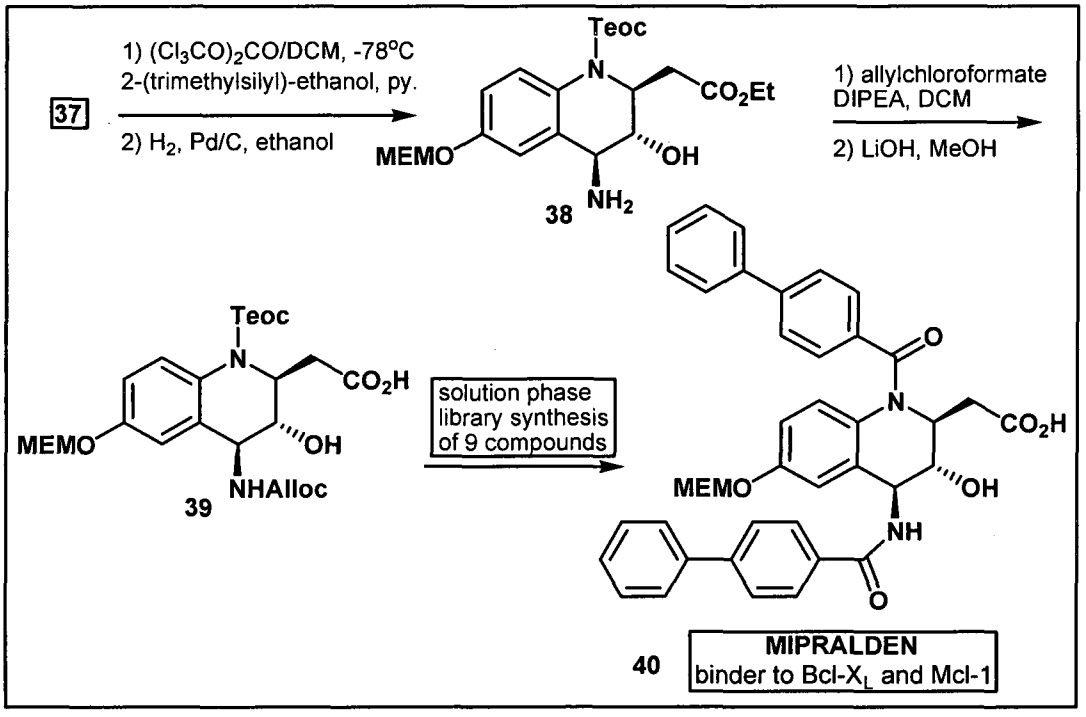
functionality, and (iv) the phenolic hydroxyl group that could be used as an anchoring site during solid-phase synthesis. For obtaining the enantioenriched, tetrahydroquinoline scaffold **29**, Arya and co-workers[70] used commercial available compound **33** as starting material (Scheme 1.4). As an extension to our early finding related to an aza Michael approach[71], this was the key reaction to obtain compound **37** from **36** in a stereocontrolled manner. Compound **36** was synthesized from **33** in several steps including (i) phenolic-hydroxy protection using methoxyethoxymethyl chloride (ii) carbon extension by Horner-Wittig-Emmons reaction (giving *E*-olefin), (iii) Sharpless enantioselective aminohydroxylation (>92% ee)[72] to give **34**, (iv) acetonide protection, (v) reduction of carboxylic ester to afford **35**, (vi) oxidation of alcohol **35** to generate aldehyde, and (vii) two carbon extension via a Wittig reaction forming **36**. After reducing of nitro group to amino, as observed in a former study from our group, the aza Michael reaction was clean and produced the cyclic β- and δ-amino acid derivative **37** in high diastereomeric purity.

Scheme 1.4



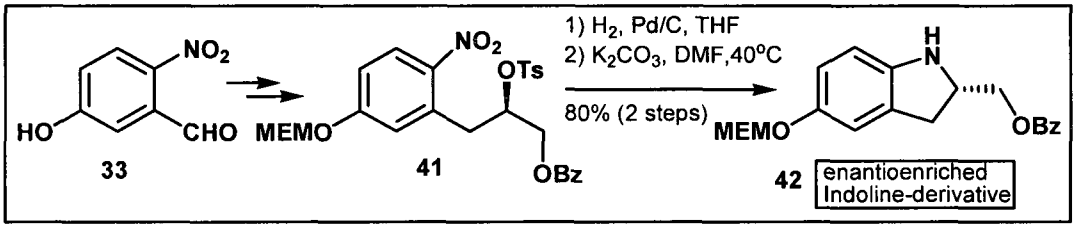
Arya and co-workers generated a library using **37** as the starting point with the goal of finding small molecule modulators of protein–protein interactions[73]. Nine created library members from compound **39** (Scheme 1.5) as well as other related intermediates were tested for their ability to bind to Bcl-X_L and Mcl-1 proteins by *in silico* and ^{15}N-NMR studies. This led to the discovery of a novel, small molecule [MIPRALDEN (named after two lead scientists; Drs. Michael Prakesch and Alexy Denisov), **40**] as a binder to both Mcl-1 and Bcl-X_L. Compound **39** was prepared from scaffold **37** by (i) *N*-Teoc protection, (ii) removing both acetonide and Cbz group using Paladium/carbon catalyzed hydrogenation to form **38**, (iii) Alloc protection of the primary amine group, and (iv) hydrolysis of carboxylic ester by Lithium hydroxide to afford acid **39**. Solution phase library generation on **39** afforded bis-(4-biphenyl) derivative **40** and 8 other compounds. Since there are currently not many small molecules capable to bind to Mcl-1, this finding is noteworthy.

Scheme 1.5



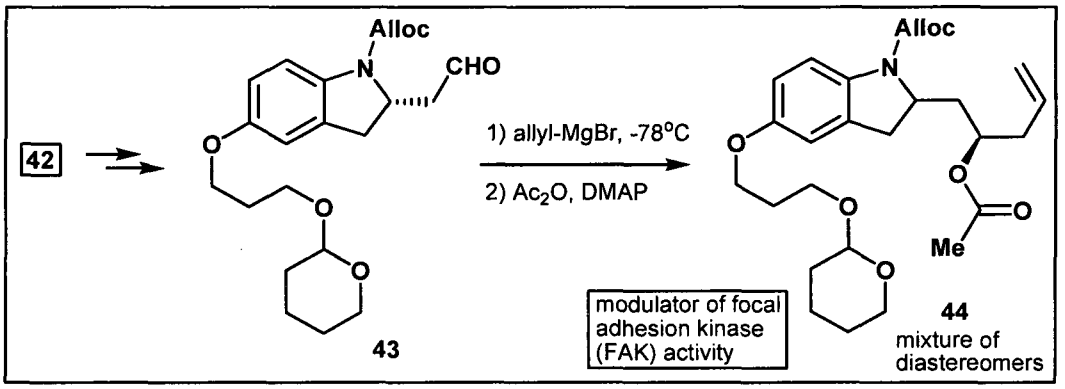
Arya and co-workers reported a different synthesis approach that led to skeletally diverse indoline alkaloid-inspired compounds[74]. As shown in Scheme 1.6, same starting material **33** was used. Similar transformations to tetrahydroquinoline system were performed but asymmetric Sharpless dihydroxylation instead of aminohydroxylation was used. Fully protected nitro compound **41** under hydrogenation followed by basic media/heating resulted in indoline-derivative **42** in 80% yield.

Scheme 1.6



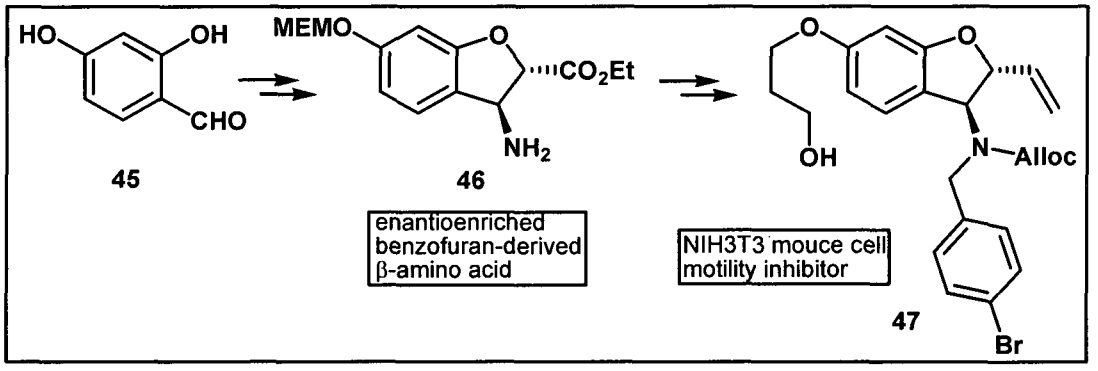
Several indoline-based bicyclic and tricyclic compounds were synthesized using scaffold **42**. Compounds obtained were next subjected to a series of *in vitro* and cellular assays to study their properties as modulators of focal adhesion kinase (FAK) activity. This analysis resulted in the identification of a lead inhibitor of FAK (**44**, Scheme 1.7), which was also active in a wound healing assay. In addition, this indoline-based compound was able to demonstrate its inhibitory activity in a cell invasion assay (Boyden chamber) which showed its ability to inhibit cell movement on a 3D scale and/or by reducing the cells' ability to form extracellular matrix degrading enzymes (such as matrix metalloproteinases). Compound **44** was synthesized in two steps from **43** by a Grignard reaction followed by acetylation of the generated secondary alcohol.

Scheme 1.7



Enantioselective synthesis of benzofuran-derived, cyclic trans-β-amino acid scaffold **46** (Scheme 1.8) was reported by Arya and co-workers[75]. Similar steps as the formation of the above-mentioned scaffolds were taken to create enantioriched benzofuran scaffold **46**. Many benzofuran-based bicyclic and tricyclic compounds were synthesized from **46**. To explore the biological applications, these compounds were subjected to cell-based assays, using NIH3T3 mouse cells to evaluate their potency as cell motility modulators. Compound **47** identified as a potent cell motility inhibitor (IC_{50} ≈ 40 μM in chamber cell migration assay).

Scheme 1.8



Inspired by bioactive natural products that have shown a proven track record in this arena, the need for developing methods for making natural product analogs

and natural product-like compounds with the goals of charting the natural product chemical territory has also grown. The examples covered here clearly demonstrate the growing research community that is committed to the young field of "exploring the natural product chemical territory". In many cases, the high-throughput synthesis methods have been successful in creating complex natural product-like architectures and, in few cases, their applications are emerging in the probe discovery research. Although the examples covered are taken from the recent literature and often, the mechanism of action of these chemical probes is not fully understood yet but this is an area that will be given a careful watch in the future.

1.4 Protein-Protein Interactions- Closer Look

Most drugs approved by FDA for human use are small molecules. More than 80% of the targets of these approved drugs are cell-surface receptors and enzymes[76]. Nuclear receptors, ion channels, and transporters are also considered important drug targets. These protein classes, therefore, are valuable in terms of drug discovery. For instance, drug candidates targeting protein kinases showed a great impact in cancer therapy. However, only 10–15% of human proteins are considered "druggable" (the feasibility with which a macromolecular/protein target can be modulated by a small molecule that has suitable properties to be developed into a drug[43]), meaning understanding the druggable proteins could have a substantial effect on drug discovery.

Most biological phenomena are performed by protein complexes consist of several proteins. Some limitations in the quest for modulation of protein–protein interactions are[77]:

1) protein ligands do not provide direct links in designing small molecules, and the key interacting residues are generally not completely known, 2) large interfacial areas involved in forming protein–protein interfaces generates difficulty

for small molecules to be competitive, 3) small synthetic peptides cannot mimic the binding region of protein complex because those binding regions are non-adjacent, 4) since many protein-protein interfaces do not exhibit clear pattern, selectivity in targeting a specific protein is difficult, 5) library screening for finding effective modulators of protein-protein interactions identified only few "drug-like" small molecules, and 6) more challenging techniques are needed for detecting direct binding because in many cases biological assays cannot follow enzyme activity.

Despite the above-mentioned limitations in this field, there are several known small molecules that modulate protein-protein interactions. Some examples of small molecules that have been discovered to purturbate protein-protein interactions have shown in Figure 1.9[22].

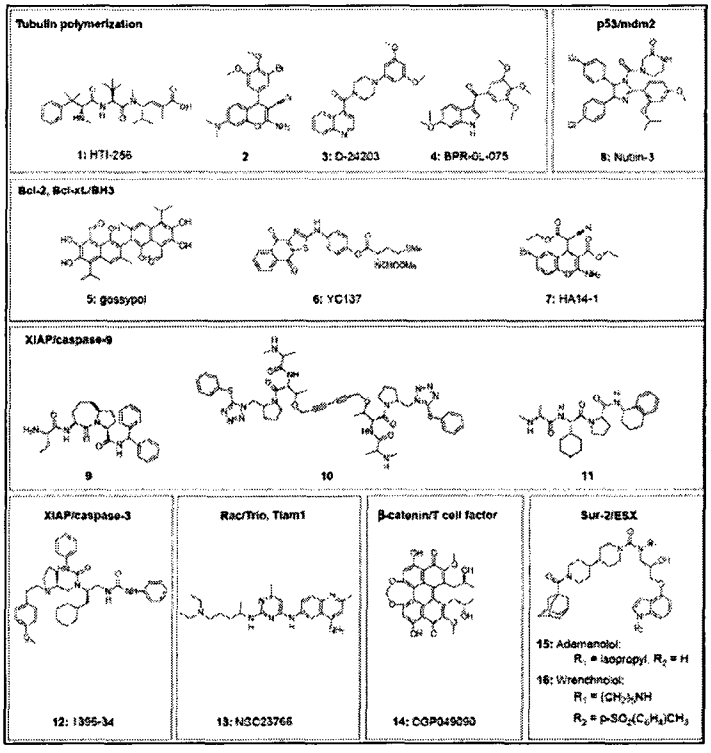


Figure 1.9 Structures of small-molecule inhibitors of protein–protein interactions [22]

As mentioned earlier, due to often unforeseen interactions between small molecules and their target proteins, the challenges in the high-throughput organic synthesis programs are to obtain natural product-inspired molecules with maximum skeletal, stereochemical, conformational and functional group diversities in order to maximize the possibility of finding a 'hit', that can modulate the biological activity of a distinct protein or a network of proteins involved in physiological processes. For more in-dept discussion about this exciting subject, we selected one family of proteins (*i.e.* Bcl-2) which has extensively studied in the field of 'cancer therapy'.

1.4.1 Small Molecule Inhibitors of Bcl-2 Family Proteins

Programmed cell death or 'Apoptosis' is a fundamental process in the development of organs. It is identified by several morphological and biological changes. There are diseases with inadequate apoptosis such as autoimmune diseases and cancer or excessive apoptosis such as Parkinson's diseases and Alzheimer's[78]. Apoptosis advances via one of the two major pathways; extrinsic and intrinsic[79]. The extrinsic pathway is initiated by ligation of cell-surface death receptors which, carry on the formation of a death-initiating signaling complex (DISC). The intrinsic pathway is activated via a substantial number of stimuli, and needs activation of the multi-domain pro-apoptotic Bcl-2 (B-cell lymphocyte/leukemia-2) family proteins (Bax or Bak) by BH-3 family members (a subgroup of Bcl-2). This activation results in releasing of apoptogenic molecules (cytochrome *c*, Smac/DIABLO) from mitochondria (Figure 1.10). The released cytochrome *c* protein binds to and activates a complex called the apoptosome. Both the assembled DISC and the apoptosome lead to the oligomerizating and activating a family of cysteine proteases known as pro-caspases. Caspase activation occurs via a cascade including initiator (DISC-activated caspase-8 and apoptosome-activated caspase-9) and effector (caspase-3) proteases that cause the cellular changes of apoptosis. An inhibitor of apoptosis proteins (IAPs), whose activity is stopped by Smac, can prevent activating caspases[80].

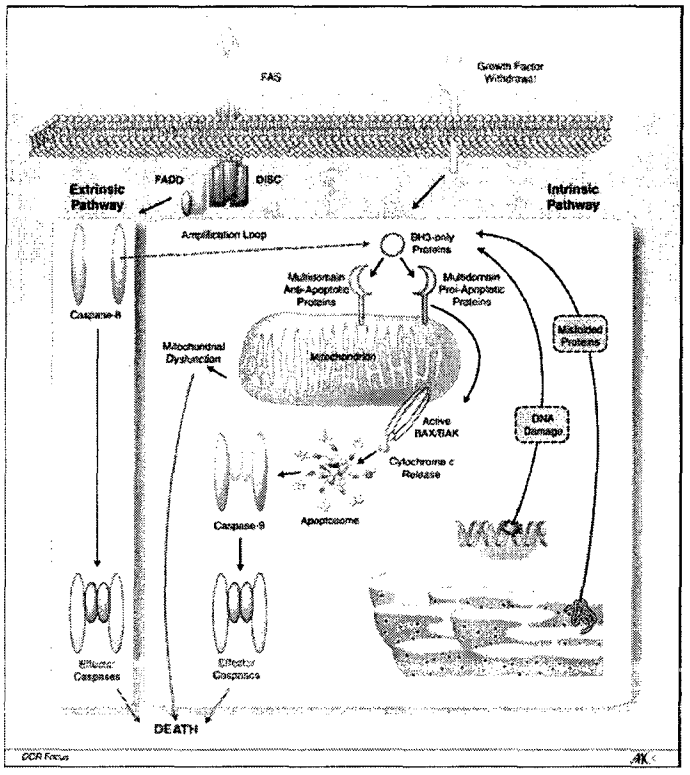


Figure 1.10 Apoptotic Pathways[81]

Several anticancer drugs can also promote apoptosis via upregulation of components of the FAS death-receptor pathway[82]. Some drug-candidates which target apoptosis, autophagy (process involving the degradation of a cell's own components through the lysosomal machinery), and necrosis (unnatural death of cells and living tissues) are introduced in Figure 1.11. Most of these compounds are currently (2007) at clinical trial stages[81].

Class	Examples	Current status of drug development
Apoptosis		
BH3 BAD mimetic	ABT 737	Phase I
Pan-BCL2 family inhibitor	GX15-070	Phase I
	TW-37	
Stapled peptide	BID $SAHB_A$	Preclinical
Death receptor ligand	Mapatumumab	Phase II
Caspase inhibitor	IDN-6556	Phase II
PARP inhibitor (activates apoptosis)	AG014699	Phase I
	KU59436	Phase II
	ABT-888	
	BSI-201	
	INO-1001	
	GPI-21016	
	AZD-2281	
BCl2 antisense	Oblimersen	Phase III
	SPC-2996	Phase I/II
MDM2 inhibitor	Nutlin-3	Preclinical
Autophagy		
Aminoquinoline	Chloroquine	Phase III
	Hydroxychloroquine	Phase I
Necrosis		
PARP inhibitor (inhibits necrosis)	AG014699	Phase I
	KU59436	Phase II
	ABT-888	
	BSI-201	
	INO-1001	
	GPI-21016	
	AZD 2281	
Death receptor ligand	Mapatumumab	Phase II

Figure 1.11 Therapeutics that target apoptosis, autophagy, and necrosis[81]

The Bcl-2 family proteins regulate the integrity of the mitochondrial outer membrane, which plays an undeniable role in the regulation of apoptotic cell death. Most human cancers possess over-expression of Bcl-2, Bcl-XL, or both. To date, more than 20 Bcl-2 family members have been characterized either which have anti or pro-apoptotic roles[83]. The Bcl-2 family proteins includes both anti-apoptotic (such as Bcl-2, Bcl-XL, Bcl-w, Bcl-B, Bfl-1 and Mcl-1) and pro-apoptotic (such as Bax, Bak, Bid, Bim and Bad). The main role of these family members is to control anti- and pro-apoptotic factors, release cytochrome *c* from the mitochondrial membrane, change mitochondrial permeability and prevent the polarization of the inner mitochondrial membrane[84].

As indicated above, anti-and pro-apoptotic Bcl-2 family members meet at the surface of mitochondria and compete to control the releasing of cytochrome *c*. It is believed that the relative balance of opposing Bcl-2 family members and their

mutual interactions controls the mitochondrial cell death pathway. Although not entirely clear, few theories exist for the mechanism by which the Bcl-2 family members control releasing of cytochrome *c*[85]:

i) form hetero-dimerization between pro- and anti-apoptotic family members,

ii) regulate caspases,

iii) interaction with other mitochondrial proteins, or

iv) form an ion channel by oligomerization.

Because of the size and complexity of the intracellular protein-binding interface, the creation of small molecules to target apoptotic protein interactions selectively and specifically manipulate their corresponding pathways *in vivo* has been challenging. Computational and NMR-based tactics, however, have introduced many compounds that target the Bcl-2 family.

A certain number of small molecules have been identified that are able to interrupt selectively the binding of Bcl-XL or Bcl-2 to the BH3 domains of pro-apoptotic proteins, and free them to induce cytochrome *c* release and apoptosis[86]. Natural products gossypol (isolated from cottonseeds), epigallecatechin gallate (from green tea), theaflavins (from black tea), chelerythrine (isolated from tropical plants) and antimycin A (produced by streptomyces bacteria), which bind Bcl-2 and Bcl-XL with affinities of between 0.1 and 10 μM, measured by competitive BH3 peptide displacement assays. Synthetic molecules that antagonize the BH3-binding site on Bcl-2 and other antiapoptotic family members include ABT-737, ABT-263, GX-15-070, as well as several other compounds identified (Figures 1.9 and 1.11).

1.4.2 Finding Hits Using Validation Tools

In an 'Apoptosis' project in our group, the generated libraries and collected intermediate compounds are screened by i) protein NMR (which can characterize the interactions between proteins and ligands/small molecules); ii) *in silico*

studies (using computer programs or computational chemistry to predict protein/small molecule interactions); iii) cell viability assays (instead of damaged or death cells, they are based on counting living active cells and normally can detect the process of programmed cell death and be used to distinguish between the mechanisms of cell-death apoptosis, necrosis or cell proliferation[87]); and iv) small molecules microarrays (molecules immobilized by chemical bonding on the solid surface with diverse linking techniques used for searching for proteins that bind with a specific small molecule)[88].

In a 'Kinase Signaling Networks' project and its function/structure characterization, Biacore© analysis is performed. In this method, surface plasmon resonance (SPR) is collected through the selected protein, which is bound on a gold sheet. This system is used in determining active concentration, screening and characterizing molecules in terms of their specificity, binding strength (affinity) and kinetics consequently measuring protein-protein interaction and binding affinity[89]. All the above-mentioned tools not only assist us to identify and modify promising hits, but also help us to further understand protein-protein interactions.

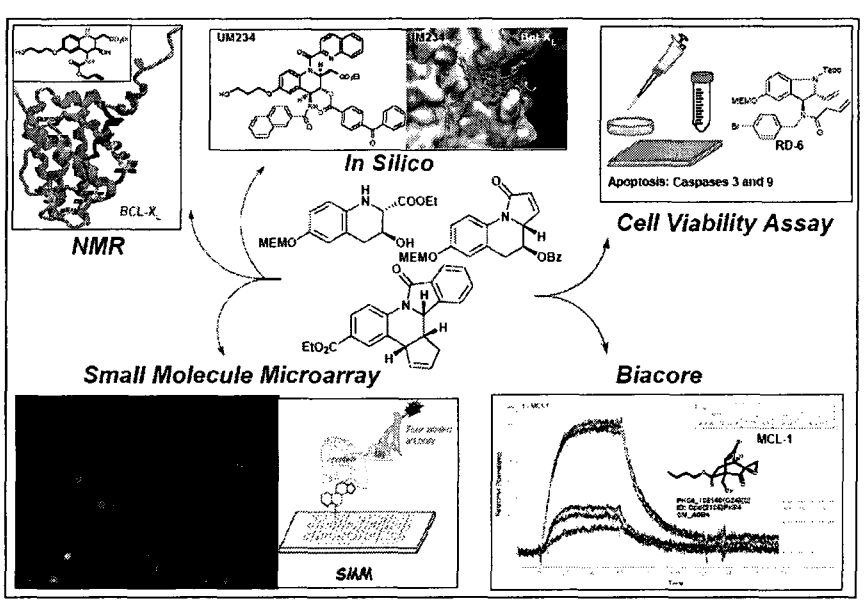


Figure 1.12 Validation Tools for DOS

1.5 Thesis Objectives

As indicated above, our group mainly synthesizes complex polycyclic natural product-like compounds that have three-dimensional skeletal and stereochemical architectures, using natural product-inspired DOS and modern organic chemistry. In this project, our scaffold of interest was 'Tetrahydroquinoline' (**49**, Figure 1.13). Starting materials for creating scaffold **49** were nitrogenated-aromatic compounds **48**. Ring **B**, and thus our tetrahydroquinoline system, was generated enantioselectively (in the key step, 'asymmetric Sharpless dihydroxylation' reaction used). Several tetrahydroquinoline-based tricyclic systems (**50**) were stereochemically synthesized using scaffold **49**. Ring **C** was formed in diverse positions involving N1 and C2 atoms, N1 and C3 atoms, and C2 and C3 atoms (skeletal diversity). Tricyclic systems **ABC** (**50**) would contain at least two diversity sites for further exploration.

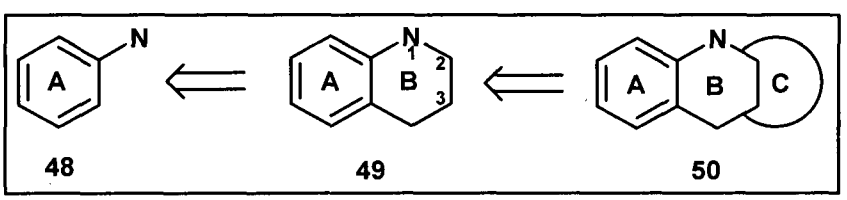


Figure 1.13 Schematic Project Goals

A clearer picture is presented in Figure 1.14 in which actual skeletons of tricylic compounds, such as **53-55**, are shown. For compatibility reasons, diversity sites in the tetrahydroquinoline system should be orthogonally protected (compound **52**). Preparation of all bicyclic and tricyclic compounds was initially performed in the solution phase. For extending this set of reactions in solid phase, we needed an anchoring site to enable immobilization of our bicyclic system onto a solid support (resin). This task was performed using protected phenolic oxygen that had already been installed on **52** (i.e., OP_4). Once P_4 was removed, the resulting free phenolic hydroxyl group could be directly attached to the selected resin.

Solid-phase syntheses of tricylic compounds were then performed using step-wise deprotection of the required arms (e.g., OP_2 and OP_3 to make **55**). The last step for tricyclic compound synthesis, in both solution and solid phases, was the 'Ring-Closing Metathesis (RCM)' reaction[90,91].

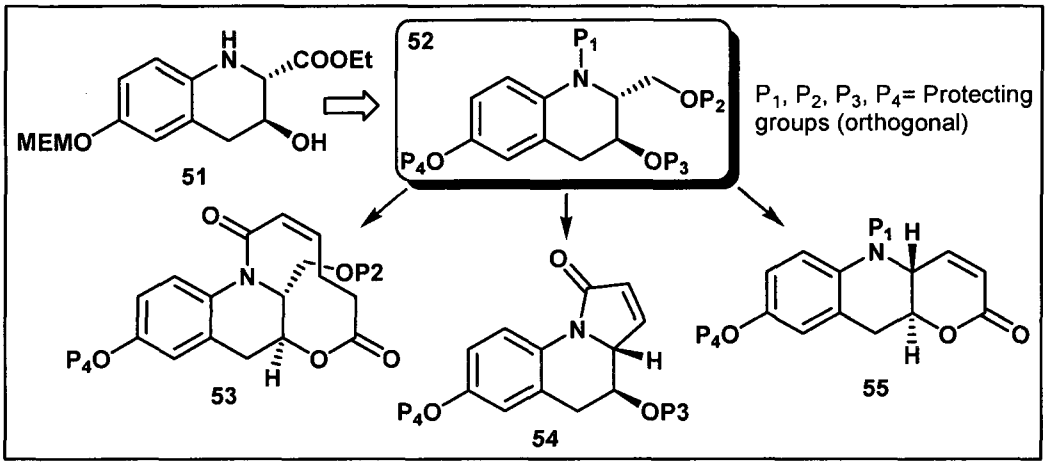


Figure 1.14 Target Molecules as Thesis Objectives

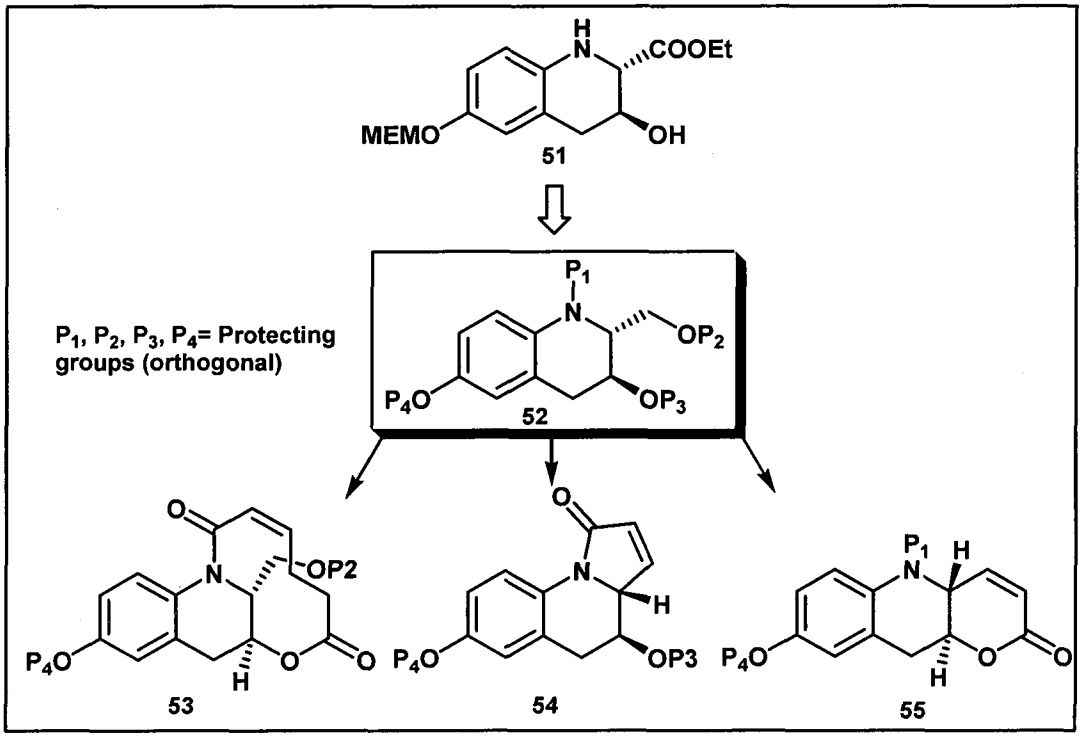
Synthesis of our tetrahydroquinoline scaffold (**51**) in the model as well as the precursor in solid phase is presented in Chapter 2. Chapter 3 discusses both solution and solid phase syntheses of tricyclic **53**. Preparation of **54** and **55** in solution and **54** in solid phase will be presented in Chapter 4. In Chapter 5, we will show another approach to create several complex polycyclic compounds using N-aromatic compounds as starting materials. Finally, in Chapter 6, the preliminary results from biological tests performed on our cyclic and intermediate compounds will be revealed.

2: Synthesis of Tetrahydroquinoline Scaffold

2.1 Design of Scaffold (51)

A tetrahydroquinoline core structure is the scaffold in this project. Due to the frequent occurrence of tetrahydroquinoline and related structures in nature, tetrahydroquinoline was chosen (section 2.2). Tetrahydroquinoline abundance has affected the evolutionary development of its diverse structures. Many of these compounds were proved to possess biological activity. The 'privileged structure' based approach discussed in Section 1.1, is the main approach in this thesis.

Scheme 2.1



Based on the tetrahydroquinoline core structure, the strategy was to develop the methodology needed to functionalize this scaffold and further extension to a

collection of compounds. Utilizing building block and stereochemical variety has resulted in obtaining the desired diversity. This strategy would lead to the solid-phase synthesis of several natural product-like compounds containing the tetrahydroquinoline-based structure. Consequently, having few diversity sites was the main intension for designing the scaffold. The presence of some orthogonally protected functional groups in compound **52** (Scheme 2.1) could further be utilized in building complexity and to explore the three-dimensional chemical space. Moreover, the phenolic hydroxyl group (after deprotection) in compound **52** provides a useful anchoring site in developing solid-phase synthesis. Compound **51** is a novel scaffold in the library generation of natural product-like polycyclics having functionalized rings for obtaining a new class of small molecules to be utilized as chemical probes. A functionalized 10-membered ring compound **53** (Chapter 3), polycyclics having α,β-unsaturated γ-lactam **54** and δ-lactone **55** functionalities (Chapter 4), and a pentacyclic complex system (Chapter 5) could be synthesized for example. This would result in the creation of novel compounds that should demonstrate the importance of creating such diverse polycyclic derivatives. This goal, accordingly, requires several models/solutions, solid-phase synthetic experiments, and optimizing diverse sets of reactions. Prior to the solid-phase synthesis (Chapters 3 and 4), a model study for the synthesis of the tetrahydroquinoline scaffold **50** was initiated.

2.2 Tetrahydroquinoline Core and Related Structures in Nature

The greatest interest in tetrahydroquinoline is due to its biological activities. Many of these compounds are found in nature. Few examples are provided in Figure 2.1. Galipinine and four tetrahydroquinoline alkaloids from *Galipea officinalis* trunk bark showed antimalarial activity[92]. Virantmycin an unusual chlorinated tetrahydroquinoline that was originally isolated from a strain of *Streptomyces nitrosporeus* possesses both strong inhibitory activity against RNA and DNA viruses, and antifungal activity[93]. Dynemicin A produced by cultured soil bacteria is an ene-diyne anticancer antibiotic[94]. An alkaloid called Isoschizogamine,

isolated from *Schizozygia caffaeoides*, shows antifungal property[95]. Martinelline is an isolate of *Martinella iquitosensis*, which exhibits activity as a bradykinin antagonist and with α-adrenergic, histaminergic, and muscarinic receptors[96]. Helquinoline isolated from the northern sea bacterium *Janibacter limosus* showed antimicrobial property[97]. Discorhabdin C (not shown), tetrahydro-quinoline-based compound, is a highly cytotoxic pigment from a marine sponge of the genus *Latrunculia*[98]. Poisoning effect of *Calycanthus floridus* is due to its toxic tetrahydroquinoline-based alkaloid constituent, Calycanthine[99] (not shown).

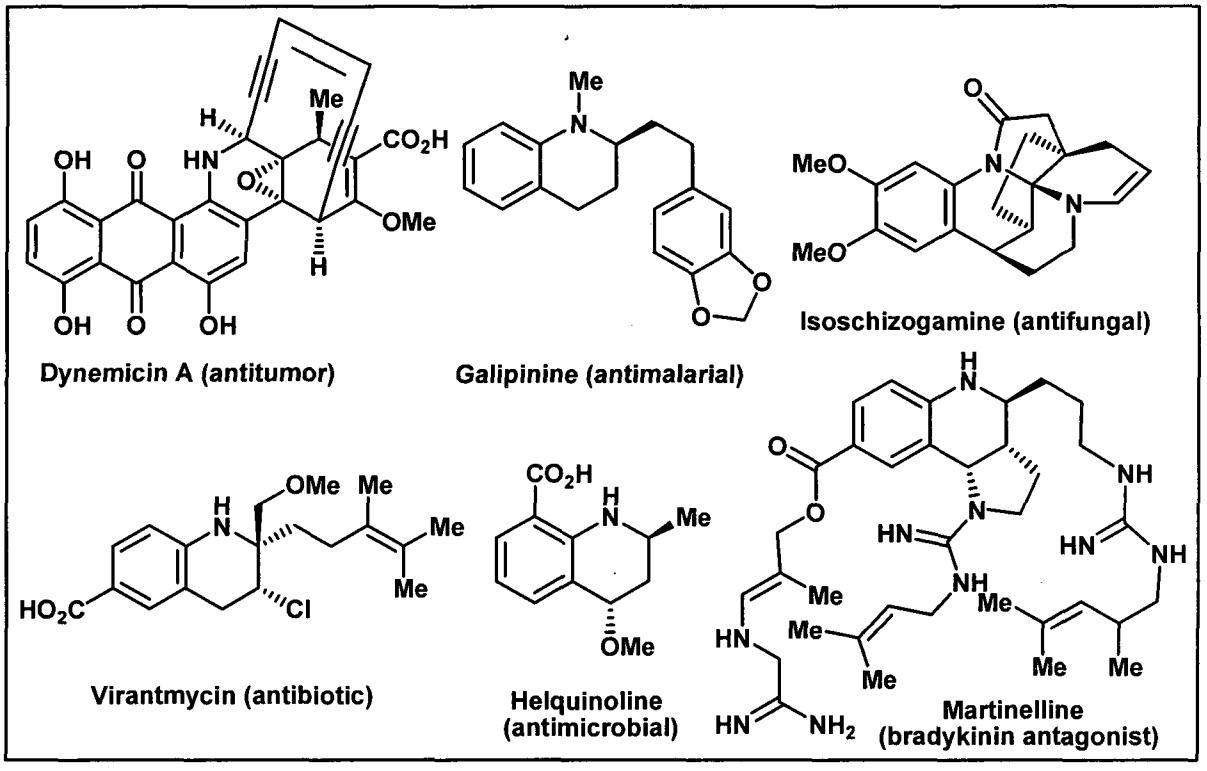


Figure 2.1 Natural Products with Tetrahydroquinoline Core

2.3 Tetrahydroquinolines as Pharmaceutical Products

Many synthetic tatrahydroquinolines are already used or have been tested as potential drugs. L-689, 560 (Figure 2.2) is a well-known NMDA antagonist[100].

IRA-378 showed antirheumatic activity[101]. Oxamniquine possesses the schistosomicide effect[102] and Nicainoprol has shown antiarrhythmics property[103]. Hundreds of tetrahydroquinoline derivatives have interesting bio-chemical activity and some are considered as potential pharmaceutical agents from analgesic to antidepressant[104].

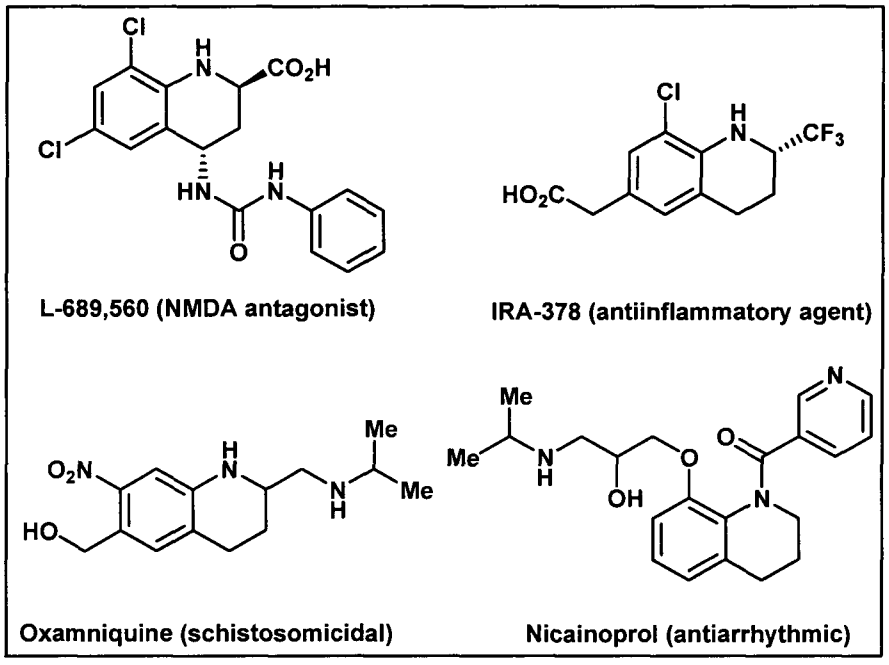


Figure 2.2 Tetrahydroquinoline Derivatives as Medicines

2.4 Synthetic Strategies in Literature

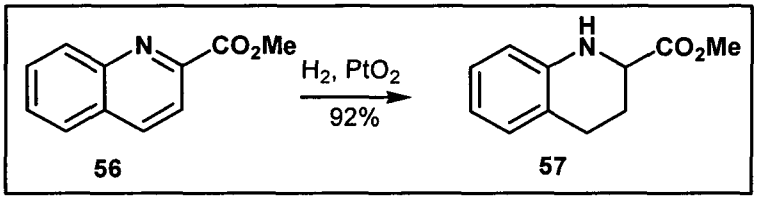
In this section, the major synthetic methods of tetrahydroquinolines currently in use will be reviewed. Due to the existence of many other related compounds with one or more sp^2 carbon, such as 2-oxo, 2,4-dioxo, etc., this review only restricts to 1,2,3,4-tetrahydroquinolines in which the C2, C3, and C4 are all sp^3 hybridized. In addition, in most examples, transformations between tetrahydroquinoline derivatives and other stages of the synthesis will not be covered. Moreover, it is mainly intended to review the literature in the period of 1986-2007. Major

methods have been classified for more clarity (Sections 2.4.1- 2.4.7) and a few examples in each section are presented. Despite the effort made to include most methods, this section is therefore not considered comprehensive.

2.4.1 Reduction of Unsaturated Heterocyclic Ring

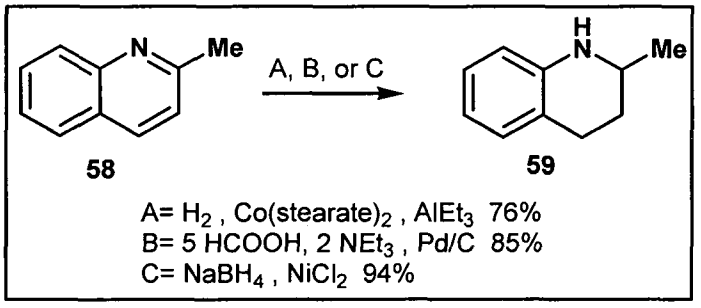
Direct reduction of the heterocyclic ring of quinolines is still considered as an attractive method. This is not only because of the existence of many suitable quinolines but also for introducing of many elegant techniques for asymmetric hydrogenation. High yield of tetrahydroquinolines are afforded under hydrogenation over platinum when there are electron-withdrawing substituents on the heterocyclic ring. Methyl quinoline-2-carboxylate **56** converts to tetrahydroquinoline **57** as shown in Scheme 2.2[105].

Scheme 2.2



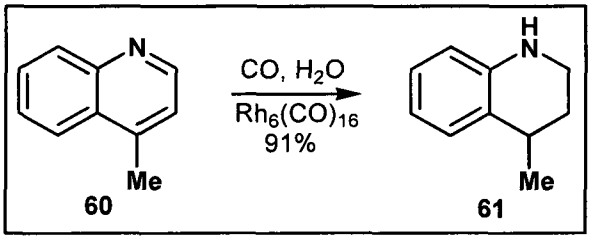
Other metal catalysts can also be used. For example cobalt stearate in the presence of triethylaluminum (Scheme 2.3) reduced 2-methylquinoline **58** into 2-methyl-1,2,3,4-tetrahydroquinoline **59**[106]. Same quinoline **58** is converted to the product with even better yield of 85% by mixing triethylamine and formic acid in the presence of a palladium catalyst[107]. Borohydride in the presence of nickel chloride can also be used giving the highest yield[108].

Scheme 2.3



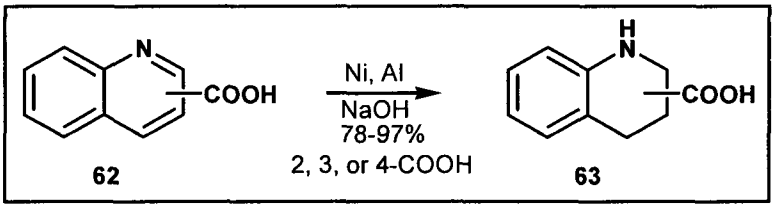
Using the mixture of carbon monoxide, water, and rhodium complex as catalyst gives a high yield of 4-methyl-tetrahydroquinoline **61** from its quinoline counterpart **60** (Scheme 2.4)[109].

Scheme 2.4



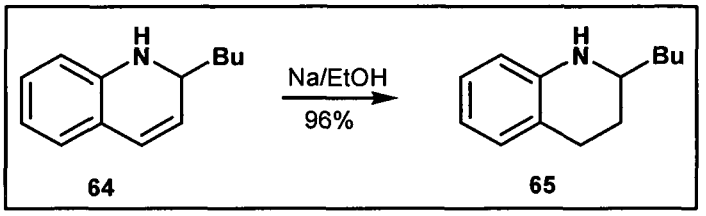
For reducing quinolinecarboxylic acids (Scheme 2.5), nickel-aluminum alloy is a convenient reagent[110]. Carboxylic acid moiety remains intact with this reagent.

Scheme 2.5



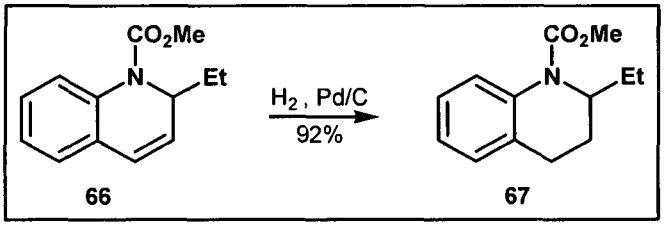
Quinolines convert to tetrahydroquinolines via 1,2-dihydroquinolines. Dihydroquinoline **64** (Scheme 2.6) is reduced to 2-butyl-tetrahydroquinoline **65** using ethanolic sodium in excellent yield[111].

Scheme 2.6



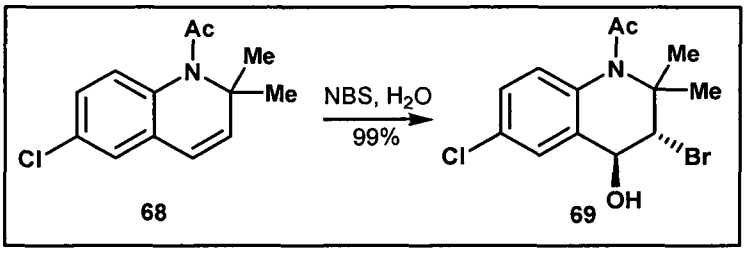
Tetrahydroquinoline **67** (Scheme 2.7) can be readily prepared by hydrogenation of **66** under palladium catalyst[112].

Scheme 2.7



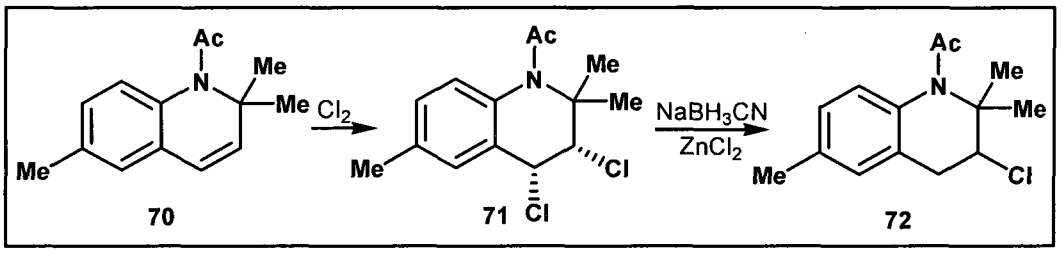
As a typical property of an electron rich double bond, wide range of addition reactions can be performed on the C3-C4 of 1,2-dihydroquinolines. Most of these additions are stereospecific. Bromination of **68** (Scheme 2.8) by NBS gives tetrahydroquinoline **69** regioselectively and almost quantitavely[113].

Scheme 2.8



Chlorination of dihydroquinoline **70** gives 3,4-dichlorotetrahydroquinoline **71** as shown in Scheme 2.9. Sodium cyanoborohydride in the presence of zinc chloride reduces this intermediate to tetrahydroquinoline **72** illustrating the lability of the substituent at C4[114].

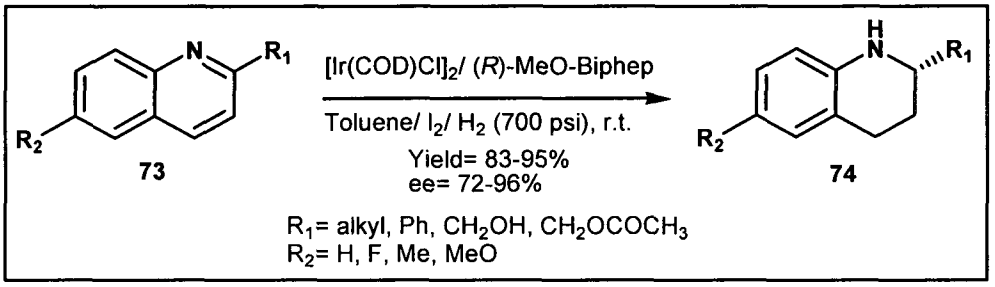
Scheme 2.9



Catalytic asymmetric reduction (hydrogenation) has been extensively studied and considered as a versatile method of creating chiral centers. Asymmetric hydrogenation of quinolines using iridium catalyst, iodine, and chiral ligand bisphosphine is an example showing high enantioselectivity (Scheme 2.10). In this reaction optical active tetrahydroquinolines **74** were prepared with high yield[115]. Several naturally occurring tetrahydroquinolines including angustrureine, galipinine, and cuspareine were prepared by methylation of the generated tetrahydroquinolines **74**. Hantzsch esters were used as a source of hydrogen with the same catalyst system[116]. In some cases, high enantioselectivity up to 88% was observed. The advantage of this method is the mild reaction conditions. Iridium complex-catalyzed asymmetric hydrogenation of same quinolines **73** in a

low molecular weight poly(ethyleneglycol) dimethyl ether/hexane biphasic system was studied[117]. Several C_2-symmetric ligands were used and high yield and enantioselectivity was observed. The advantage of this method is not only the ability for separation of catalysts and products by phase separation, but also retaining reactivity/stereoselectivity of the catalysts for at least three reaction cycles.

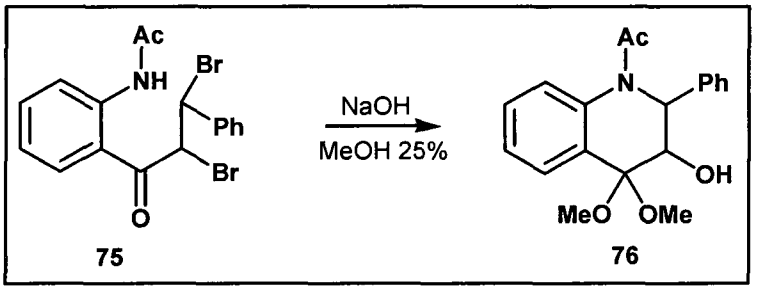
Scheme 2.10



2.4.2 Closure of One Bond

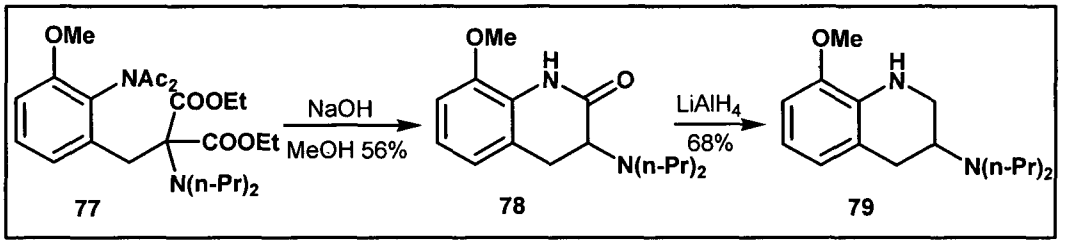
Tetrahydroquinolines can be synthesized from smaller fragments, namely by the formation of N-C1 or C4-C4a bonds. As an example for the transformation through N-C1, cyclocondensation of the bromo compound **75** (Scheme 2.11) in methanolic sodium hydroxide gives a tetrahydroquinoline (**76**) with an extra substitution on C3[118].

Scheme 2.11



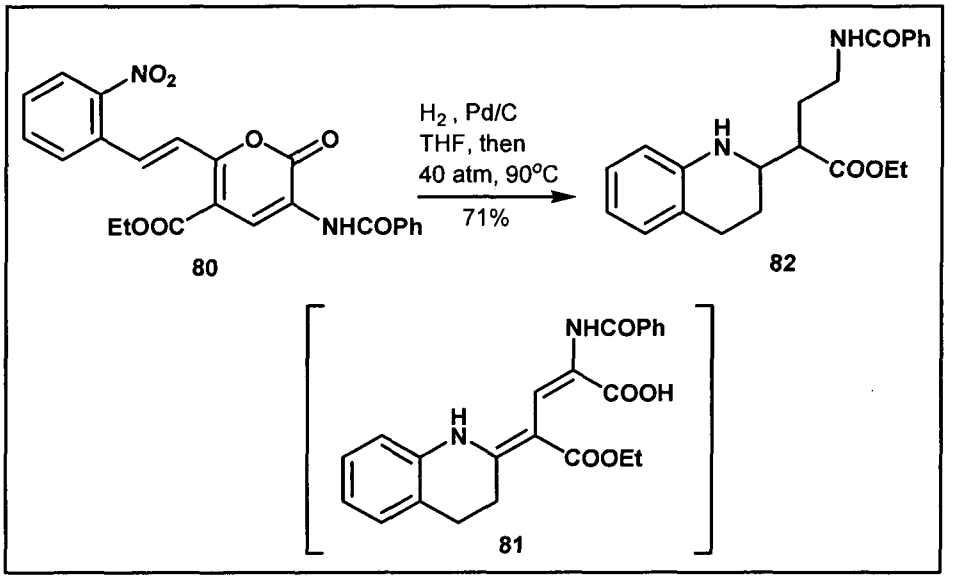
Compound **77** cyclized to 2-oxotetrahydroquinoline **78** by sodium hydroxide in ethanol (Scheme 2.12). Elimination of 2-oxo function occurred by reduction of this intermediate with lithium aluminum hydride affording 3-aminotetra-hydroquinoline **79**[119].

Scheme 2.12



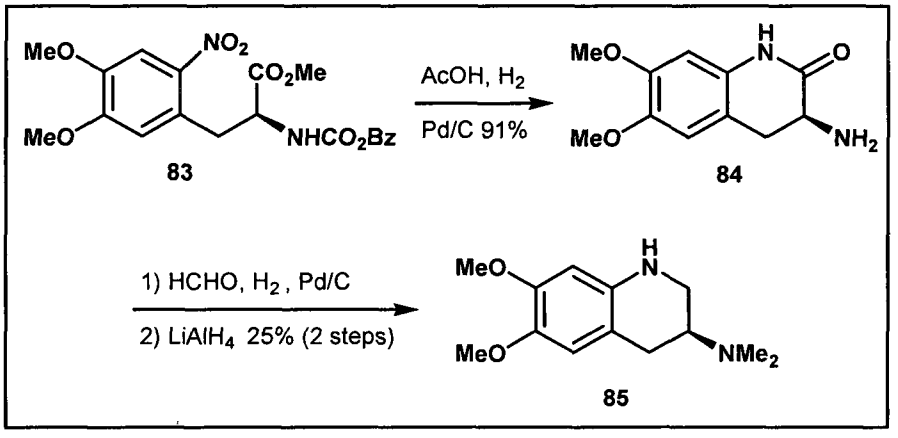
By catalytic reduction on palladium, the nitro group in **80** was converted to an amino group followed by cyclization to afford the intermediate **81** (Scheme 2.13). This intermediate can be isolated from the reaction mixture with 54% yield. By raising the temperature and pressure of hydrogen, the reaction is proceeded to decarboxylation and reduction of **81** to give tetrahydroquinoline **82**[120].

Scheme 2.13



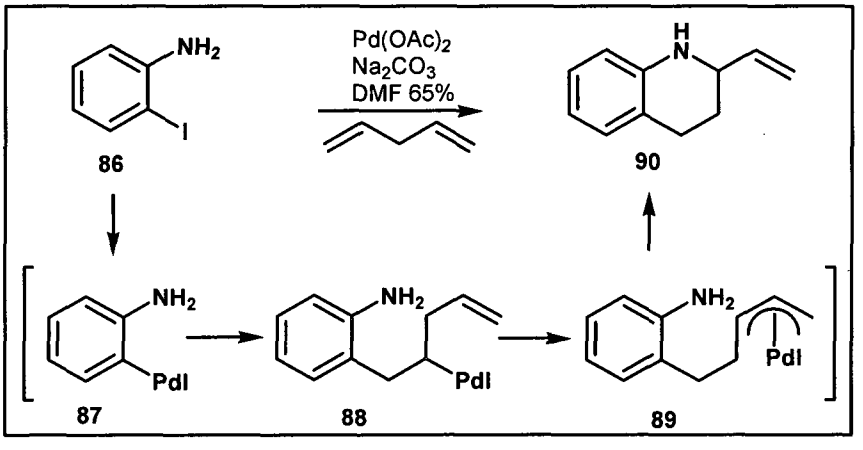
2-Oxotetetrahydroquinoline **84** (Scheme 2.14) was prepared using the reduction of the nitro group in **83** and then removal of the protecting group on the nitrogen. Amino group in **84** was methylated and subsequently reduced to 6,7-dimethoxy-3-(dimethylamino)-1,2,3,4-tetrahydroquinoline **85**[121]. The noted stereochemistry in **85** (at C3), however, inherited from the chiral starting material **83**.

Scheme 2.14



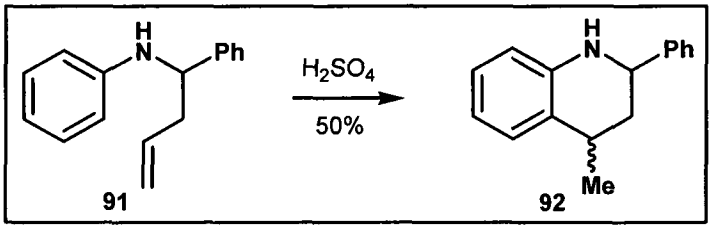
Palladium intermediate **87** prepared by treatment of 2-iodoaniline **86** with palladium acetate (Scheme 2.15) reacts with 1,4-pentadiene to produce 2-vinyl-1,2,3,4-tetrahydroquinoline **90**. This is an example for the formation of C3 bond using the palladium catalyzed annulation of 1,4-diene with *ortho* iodoaninines[122].

Scheme 2.15



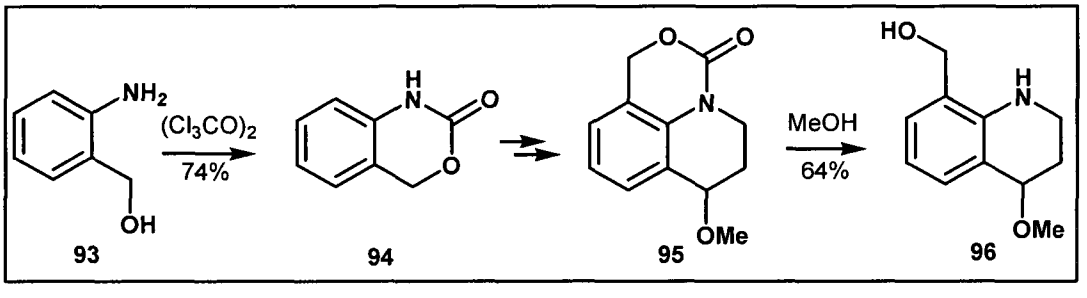
Sulfuric acid catalyzed cyclization of compound **91** (Scheme 2.16) gives a mixture of *cis* and *trans* 4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline **92**[123]. This is an example for the formation of tetrahydroquinolines via C4-C4a.

Scheme 2.16



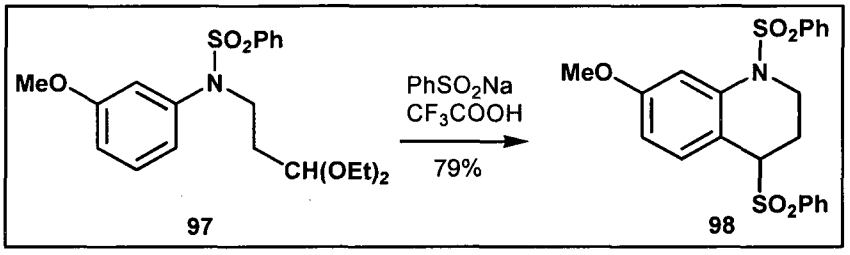
Compound **96** (Scheme 2.17) is a key intermediate in the synthesis of antiulcer agents[124]. For the synthesis of this intermediate, first functional groups in 2-(hydroxymethyl)-aniline **93** are protected as benzoxazine (**94**). After a few steps, compound **95** was treated with methanol for deprotecting its functional groups leading to tetrahydroquinoline **96**.

Scheme 2.17



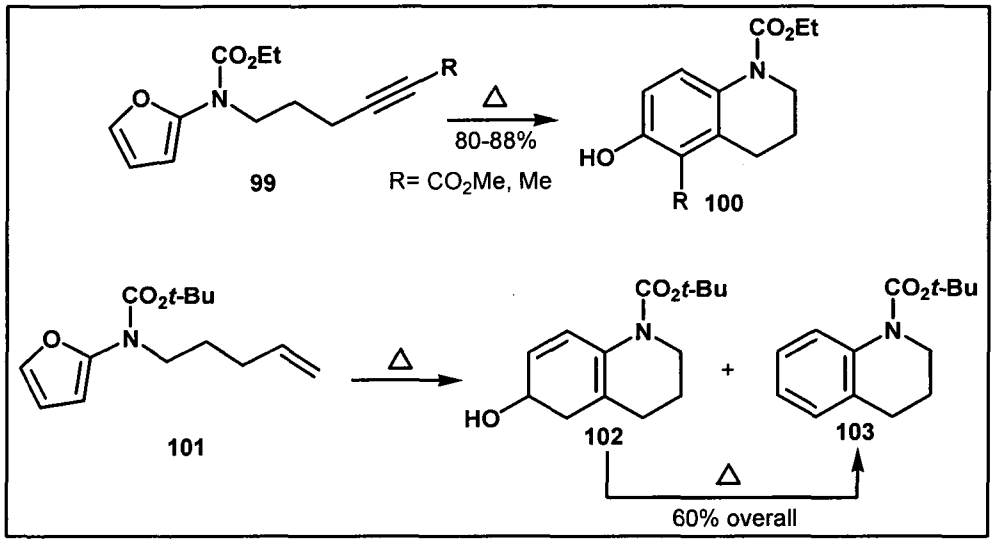
Compound **97** under cyclocondensation and a substitution reaction with the benzene-sulfonate anion (Scheme 2.18) gave tetrahydroquinoline **98** as the major compound[125].

Scheme 2.18



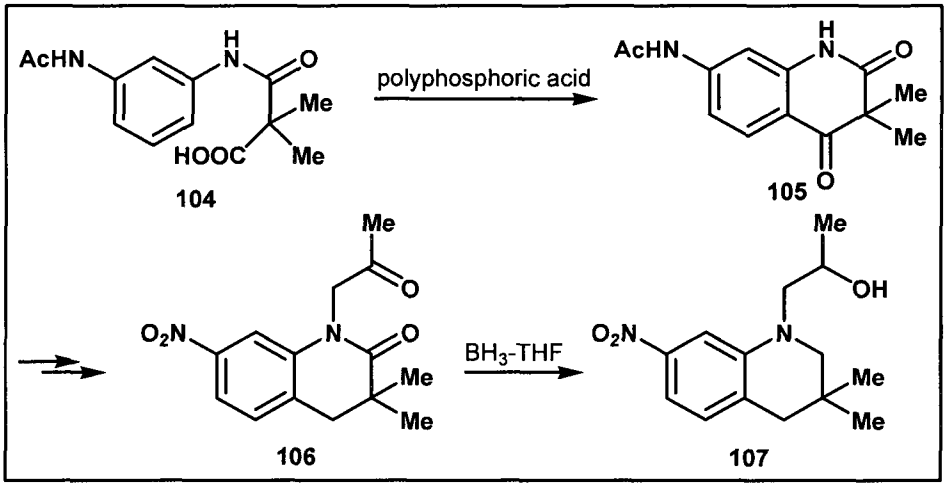
Various tetrahydroquinolines were prepared by an intramolecular Diels-Alder reaction of 2-substituted aminofurans[126]. These 2-aminofurans should contain a substituted alkyne **99** or a tethered olefin **101** (Scheme 2.19). It is believed that the initial cycloaddition reaction gives an oxa-bridge cycloadduct, which under nitrogen assisted ring opening followed by proton exchange and dehydration, forms the products (**100** or **103**).

Scheme 2.19



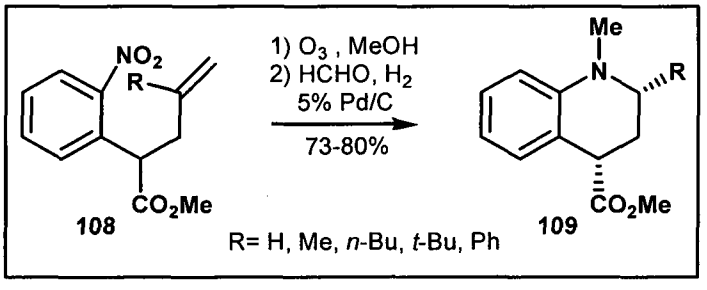
Ring closure of compound **104** (Scheme 2.20) with polyphosphoric acid gave 7-acetyl-amino-1,2,3,4-tetrahydroquinoline-2,4-dione **105**. After a few steps, the *N*-alkylated intermediate **106** under reduction with a BH_3-THF complex gave the tetrahydroquinline **107**[127].

Scheme 2.20



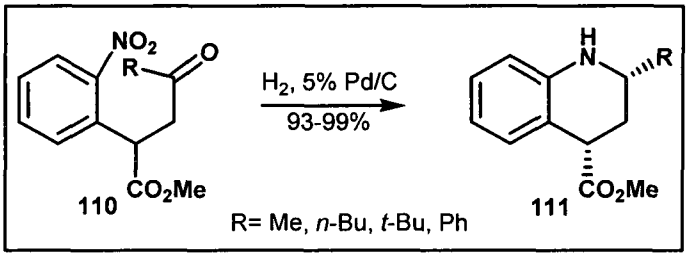
Diastereoselctive synthesis of 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters was studied[128]. This involves the ozonolysis of the double bond in compound **108** (Scheme 2.21) and catalytic hydrogenation. The hydrogenation stage involves a tandem sequence including a) reduction of the nitro group, b) condensation of the resulted amino group with the side chain carbonyl, c) reduction of the resulted nitrogen, and d) reductive amination of the tetrahydroquinoline with formaldehyde (formed at ozonolysis step). Reduction of the final iminium intermediate is diastereoselective; providing products derived from *syn* addition of hydrogen to the molecular face opposite the ester group. Final product is a 2,4-disubstituted tetrahydroquinoline **109** with *cis* relationship between C2 and C4.

Scheme 2.21



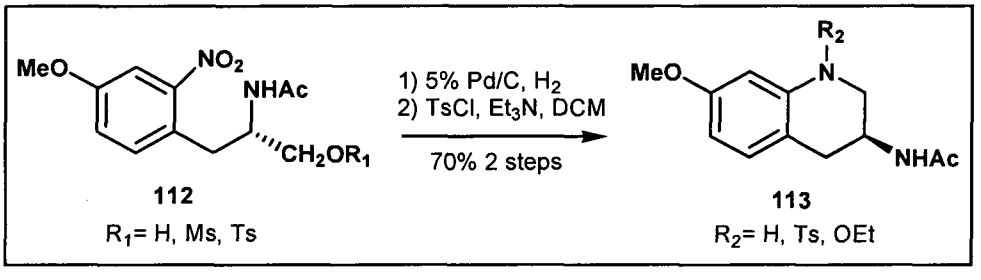
Same authors were able to prepare tetrahydroquinoline without alkyl substitution at nitrogen (Scheme 2.22). This was performed by the removal of the formaldehyde produced in ozonolysis step prior to reduction. Catalytic hydrogenation of **110** then afforded the *cis*-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylates **111** in excellent yields.

Scheme 2.22



Two independent routes to enatiomerically enriched 3-substituted tetrahydro-quinolines based on selective catalytic reaction were reported[129]. In asymmetric hydrogenation route, chirality in intermediate **112** (Scheme 2.23) is because of former rhodium-catalyzed asymmetric hydrogenation. Hydrogenation of this intermediate using palladium on carbon gave an unstable 3-acetamido-1,2,3,4-tetrahydroquinoline which protected as tosylamide **113**.

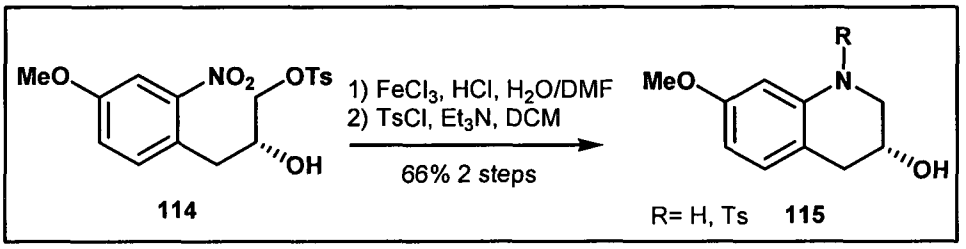
Scheme 2.23



On the other hand, in the asymmetric epoxidation route, chirality was created using epoxidation and consequent ring opening. Compound **112** (Scheme 2.24), was reduced with iron and hydrochloric acid. Neutralization of the reaction

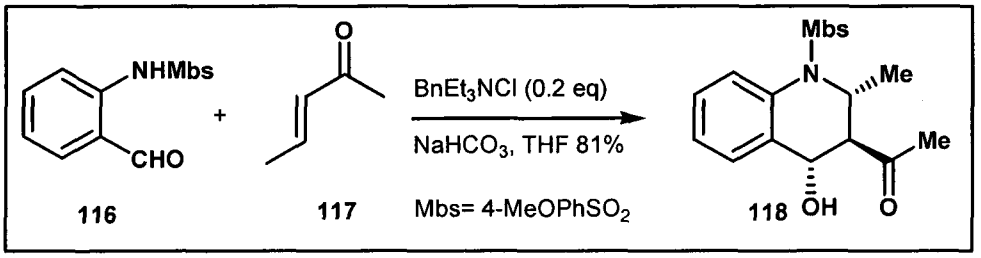
mixture by the addition of ammonia resulted in forming 3-hydroxy-1,2,3,4-tetrahydroquinoline which was protected as an *N*-tosylamide **115**.

Scheme 2.24



1,2,3,4-tetrahydroquinolines were made by a tandem Michael-aldol reaction[130]. As shown in Scheme 2.25, *N*-protected *o*-aminobenzaldehyde **116** and α,β-unsaturated carbonyl compound **117** in the presence of benzyltriethylammonium chloride, sodium bicarbonate as the base, and THF undergoes tandem Michael-aldol reaction leading to tetrahydroquinoline **118** in 81% yield. Interestingly, using potassium carbonate as the base and chloroform as solvent gave only 1,2-dihydroquinoline derivative probably by the subsequent base-catalyzed dehydration of the former product.

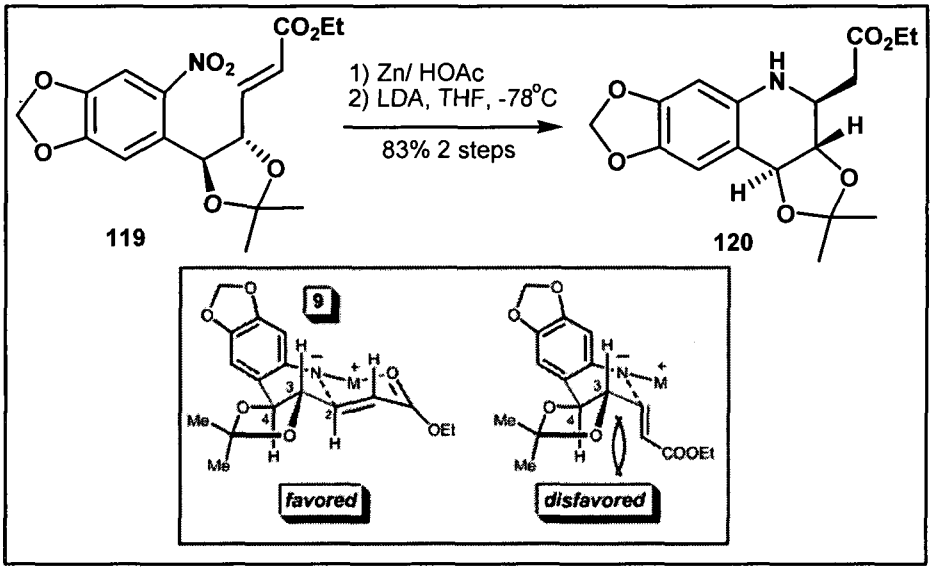
Scheme 2.25



In our group, tetrahydroquinoline was prepared through reduction of the nitro group in **119** (Scheme 2.26) and then treatment with LDA (or NaH) to obtain the tetrahydroquinoline derivative **120** as a single enantiomer with 3 stereogenic centres. The crucial ring-closure step includes an asymmetric hetero-Michael

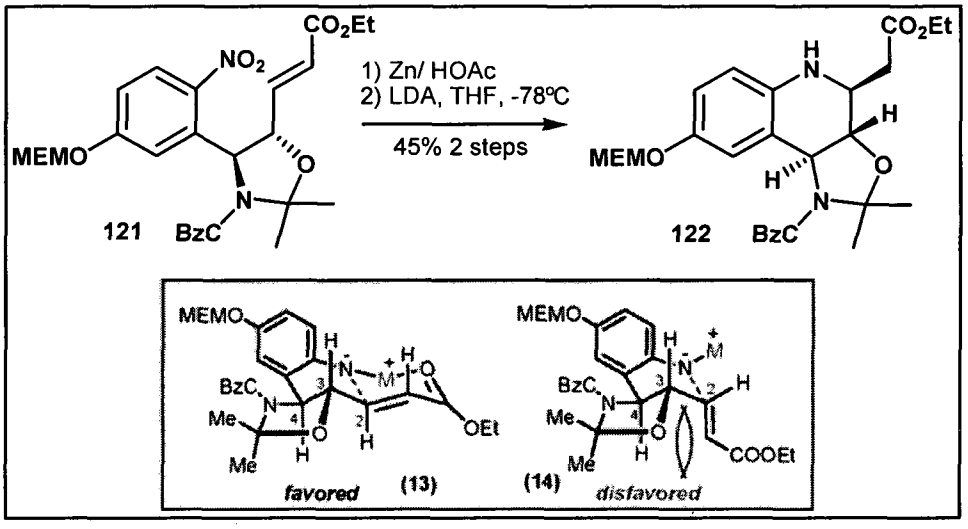
reaction. The stereochemistry of the new stereogenic center was assigned by nOe (observed between H-2 and H-4) and coupling constants (*J*) for adjacent protons. It appears that acetonide protection of vicinal hydroxyl at C3 and C4 is an influential factor in the observed stereoselectivity[71]. The proposed transition state contains a less-hindered environment and metal coordination in a chair-like fashion. The spatial interaction between the acetonide group and unsaturated ester gives disfavored transition state. Earlier Sharpless dihydroxylation reaction on the alkenes' site formed the enantiopure diol derivative (>90% ee, determined by chiral HPLC) which after a few steps led to compound **119**.

Scheme 2.26



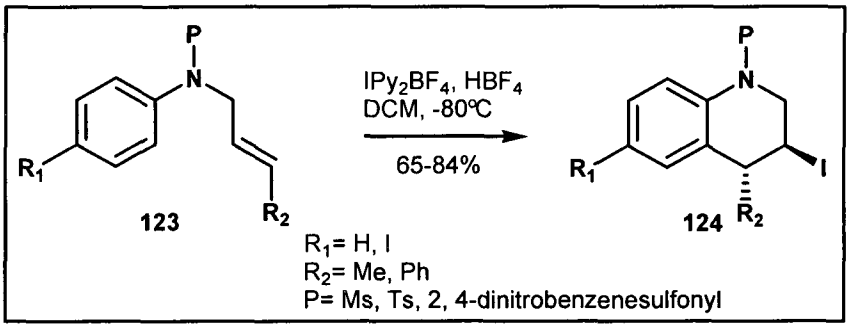
Similar approach was performed in compound **121** (Scheme 2.27) to prepare the enantiopure tetrahydroquinoline derivative **122**[70]. In this case, Sharpless aminohydroxylation reaction is responsible for the enantioselectivity (>92% ee). This reaction includes the favored chelation/less-hindered transition state accountable for the observed stereochemistry. Tetrahydroquinoline **122** features exceptional properties which allow it to be a base compound in multiple investigations in the group leading to several interesting findings [73,131,132].

Scheme 2.27



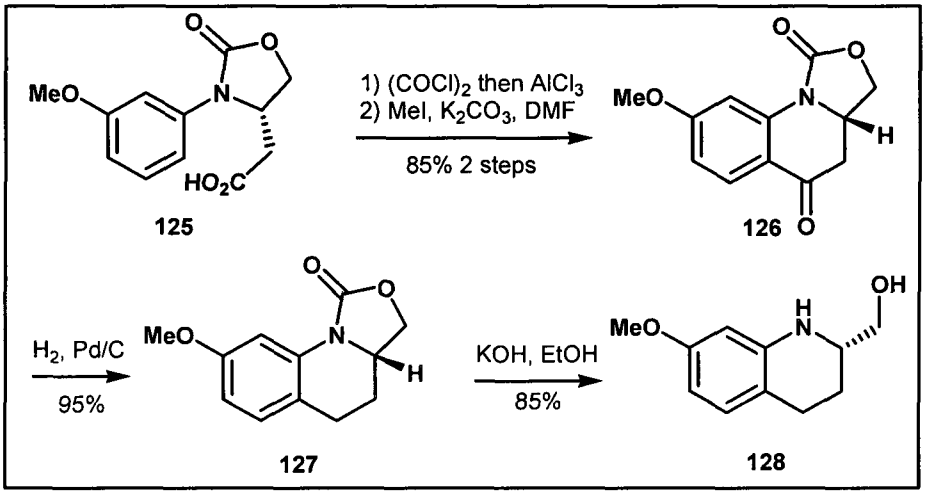
Chemistry of carbon-iodine bond was used for the diastereoselctive preparation of tetrahydroquinolines[133]. Compound **123** under treatment with IPy_2BF_4, as the source of iodonium ion, and with a variable amount of HBF_4, was cyclized to obtain the tetrahydroquinoline **124** (Scheme 2.28). The intramolecular arylation reaction of heteroatom-linked alkene promoted by iodonium ion in this method has found to be very effective in having high yield and obtaining no evidence for the formation of related heterocyclic structures involving additional rearrangement of the allyl moiety.

Scheme 2.28



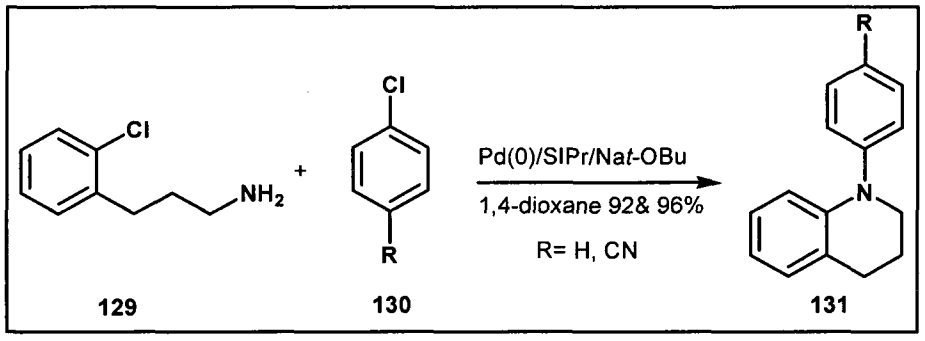
Optically pure 2-hydroxymethyl-1,2,3,4-tetrahydroquinoline **128** (Scheme 2.29) was prepared in a few steps[134]. Compound **125** cyclized to intermediate **126** by intramolecular acylation reaction. Reduction of carbonyl in C4 followed by deprotection led to the final product.

Scheme 2.29



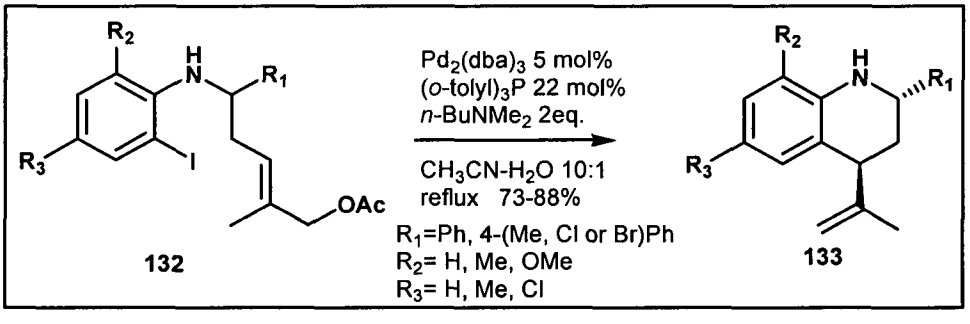
Cyclization of amino aryl chlorides which forms the *N*-arylated heterocycles can be performed via an intramolecular aryl amination followed by an intermolecular coupling reaction[135]. For this cycloamination reaction, an in situ formed Pd(0) catalyst associated to *N,N'*-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene (SIPr) as a ligand and sodium *t*-butoxide as the base for sequential aryl amination were used. *N*-arylated-1,2,3,4-tetrahydroquinoline **131** (Scheme 2.30) is prepared in excellent yield using this method.

Scheme 2.30



Palladium-catalyzed intramolecular direct cross-coupling reaction between an aryl iodine and an allyl moiety leads to 2,4-disubstituted 1,2,3,4-tetrahydro-quinoline[136]. As shown in Scheme 2.31, trans-2,4-disubstituted-tetrahydro-quinolines **133** were successfully synthesized with excellent diastereo-selectivity from allyl acetates **132**. It is believed the amine is responsible for reducing Pd(II) to Pd(0) after each catalytic cycle.

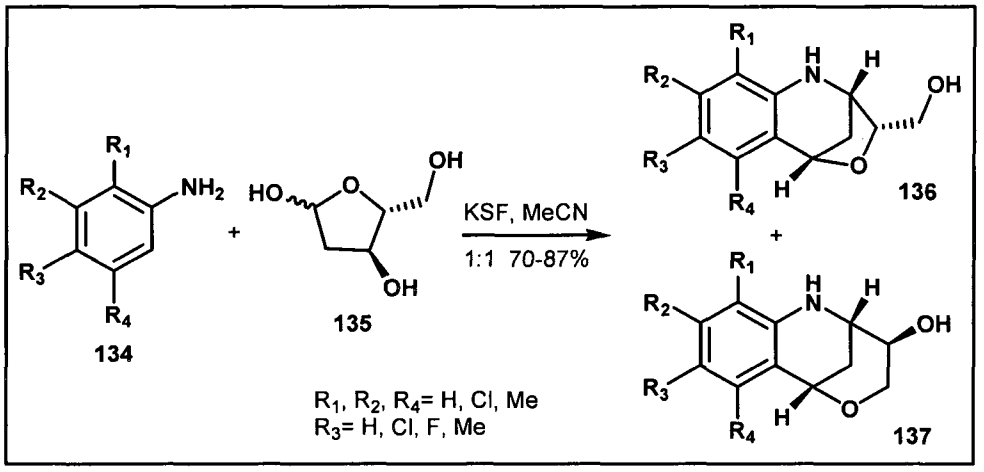
Scheme 2.31



Synthesis of sugar-derived chiral tetrahydroquinoline using montmorillonite clay was reported[137]. As shown in Scheme 2.32, 2-deoxy-D-ribose **135** and arylamines **134** in the presence of a solid acid (KFS) clay in acetonitrile reacted and generated the fused tetrahydropyranoquinoine **136** and hexahydrofuro[3,2-*c*]quinoline derivatives **137** in 1:1 ratio. It is believed the aldehyde formed *in-situ* from deoxyribose and acidic clay undergoes condensation with aniline followed a

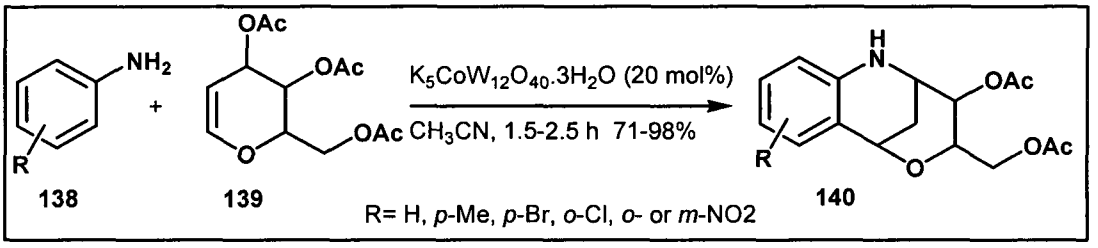
tandem Friedel-Crafts intramolecular cyclization giving the chiral tricyclic tetrahydroquinolines.

Scheme 2.32



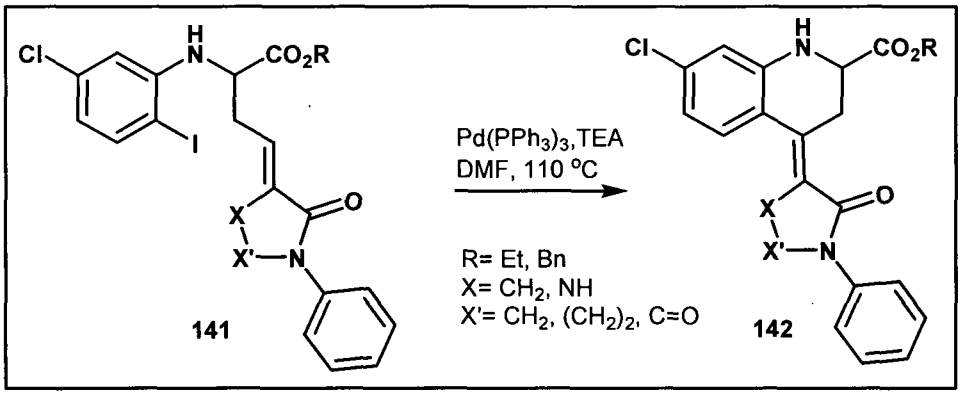
In a similar way, treatment of 3,4,6-tri-*O*-acetyl-D-glucal **139** (Scheme 2.33) with aryl amines (aniline derivatives) **138** in the presence of dodecatungstocobaltate gives fused tetrahydroquinolines **140**[138]. The mild reaction conditions, high regioselectivity, high yield in a short time, and reusable non-toxic catalyst are among the advantages for this method. However, stereochemistry was not assigned in final products.

Scheme 2.33



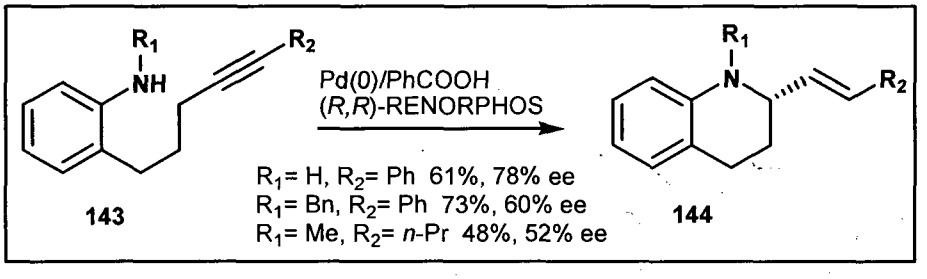
Tetrahydroquinolines **142** (Scheme 2.34) were prepared under the Heck-type cyclization reaction on α,β-unsaturated carbonyls **141** with complete control of the stereochemistry of the double bond[139].

Scheme 2.34



Enantiomerically enriched 2-substituted tetrahydroquinolines **144** shown on Scheme 2.35 were synthesized via the Pd(0)-catalyzed intramolecular hydroamination of aniline-alkynes **143**[140].

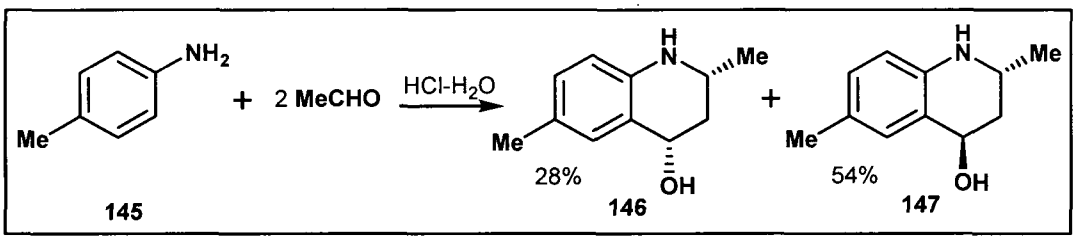
Scheme 2.35



2.4.3 Condensation of Anilines with Aldehyde

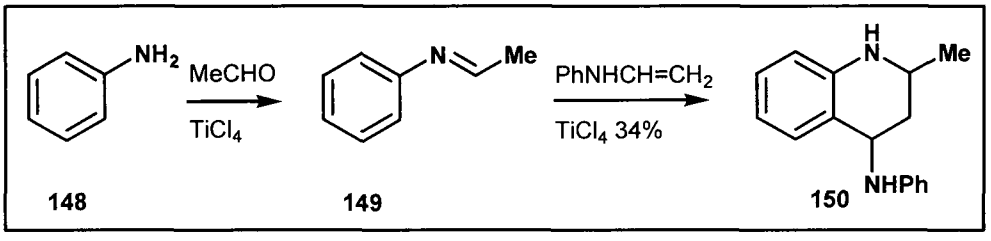
p-Toluidine **145** reacted with two molecules of acetaldehyde (Scheme 2.36). A mixture of *cis* **146** and *trans* **147** isomer of 2,6-dimethyl-4-hydroxy-1,2,3,4-tatra-hydroquinoline (1:2 ratio) were observed[141].

Scheme 2.36



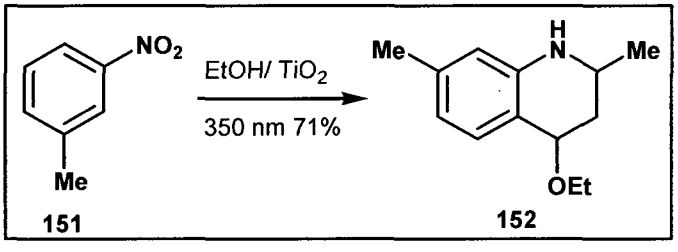
Condensation of aniline with acetaldehyde gives imine **149** (Scheme 2.37). A cycloaddition reaction between this imine and its enamine tautomer produces compound **150** with unknown stereochemistry[142].

Scheme 2.37



3-Methyl-nitrobenzene **151** in ethanol and in the presence of titanium dioxide and under irradiation gives 4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**152**, Scheme 2.38)[143]. This can be explained by reduction of the nitro group followed by oxidation of ethanol to acetaldehyde and finally condensation of these compounds.

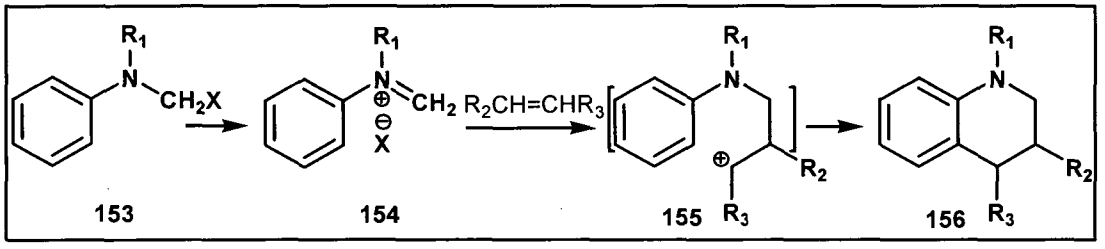
Scheme 2.38



2.4.4 Reaction of N-Aryl Methyleneiminiums with Alkenes

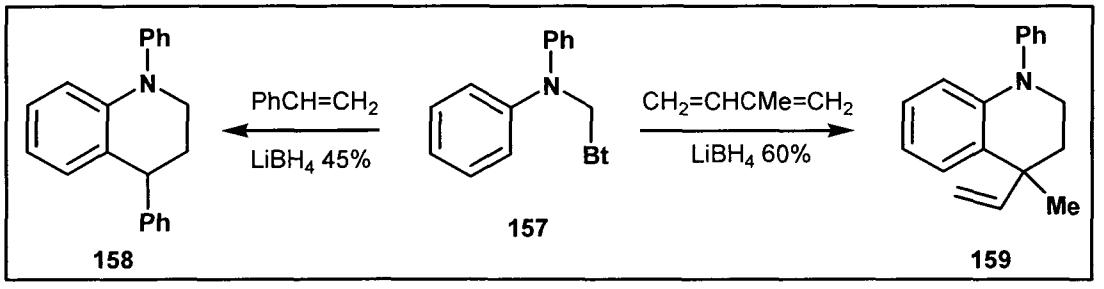
Reaction of *N*-aryl methyliminium cations with alkenes forms 3,4-disubstituted tetrahydroquinoline as shown in Scheme 2.39. Intermediate cation **155** is produced by an electrophilic attack of the methyliminium cation **154** on an alkene. Spontaneous cyclization leads to the formation of 3,4-disubstituted tetrahydroquinoline **156**. Regioselectivity can be observed if R_2 and R_3 are different in their electronic character.

Scheme 2.39



Benzotriazoyl substituent (Bt) can be used as the X group in **153**. For example diphenylamine compound **157** (Scheme 2.40) reacts with isoprene and styrene in the presence of lithium borohydride to give compound **159** and **158**, respectively[144].

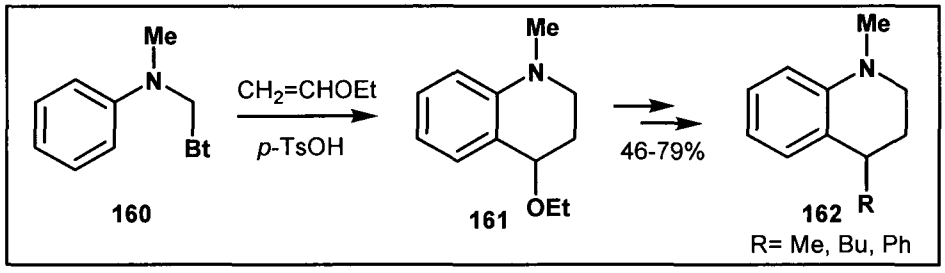
Scheme 2.40



Similar substrate **160** reacts with the ethyl vinyl ether (Scheme 2.41). The intermediate stabilized by the ethoxyl group (not shown), cyclized to 4-ethoxy-

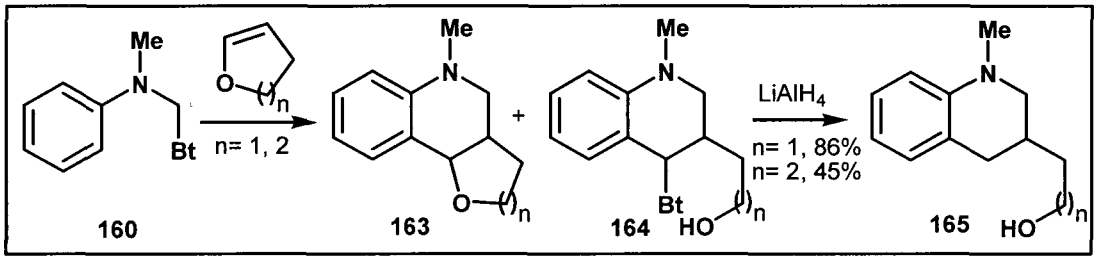
tetrahydroquinoline **161**. Other 4-substituted tetrahydroquinolines **162** are also prepared with this compound with average to good yield[145].

Scheme 2.41



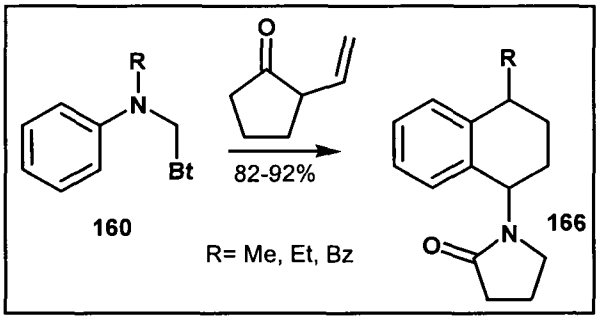
Same authors reported the reaction of this substrate **160** with 2,3-dihydrofuran and 3,4-dihydro-2H-pyran to first generate benzotriazolyl derivatives **164** mix with the tricyclic compounds **163** (Scheme 2.42) . Although these cyclic compounds can be separated from the reaction mixture, the treatment with lithium aluminum hydride converted both these compounds to 3-(3-hydroxypropyl) or 3-(3-hydroxybutyl)-1-methyl-1,2,3,4-tetrahydroquinoline **165**.

Scheme 2.42



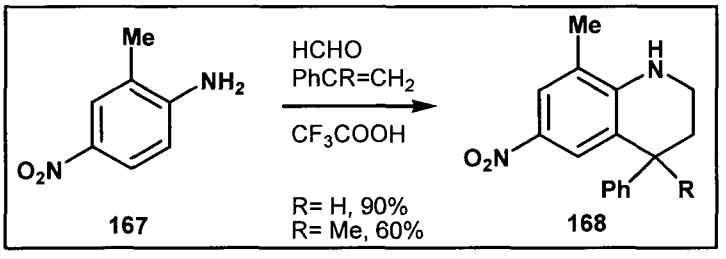
In another example of benzotriazole methodology, *N*-[(benzotriazol-1-yl)alkyl]-anilines **160** (Scheme 2.43) with 1-vinyl-2-pyrrolidinone afforded 4-(pyrrolidinon-1-yl)tetrahydroquinolines **166** in high yields[146].

Scheme 2.43



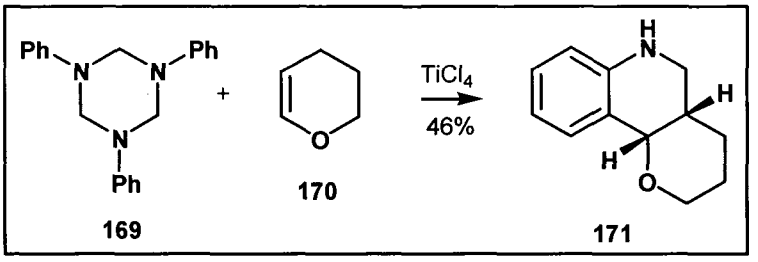
Nitrotoluidine **167** upon treatment with formaldehyde and styrene or its methyl derivative in the presence of trifluoroacetic acid converted to tetrahydroquinolines **168** (Scheme 2.44). In this case, the generated *N*-arylmethyleneiminium cation was trapped by the alkene[147].

Scheme 2.44



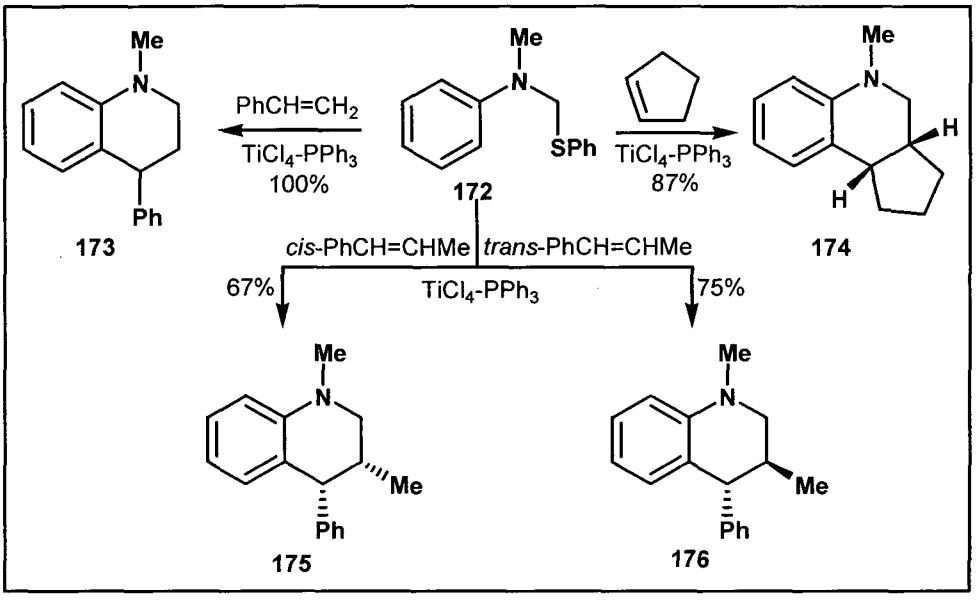
Triphenylhexahydro-1,3,5-triazine **169** (Scheme 2.45) which can easily be prepared by condensation of aniline with formaldehyde, under treatment with 3,4-dihydro-2*H*-pyran in the presence of titanium chloride afforded tetrahydroquinoline **171**[148]. This is an example of making methyleneiminium cation **154** (Scheme 2.39) by ionization of triazine.

Scheme 2.45



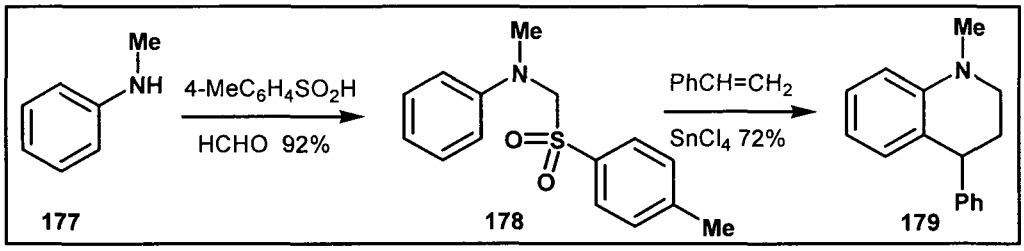
N-Methyl-*N*-(phenylthiomethyl)aniline **172** also showed very good results (Scheme 2.46). A series of tetrahydroquinoline (**173-176**) prepared using the reaction of compound **172** with styrene, cyclopentane, *cis*- and *transe*-1-phenyl-propane catalyzed by titanium chloride-triphenylphosphine[149].

Scheme 2.46



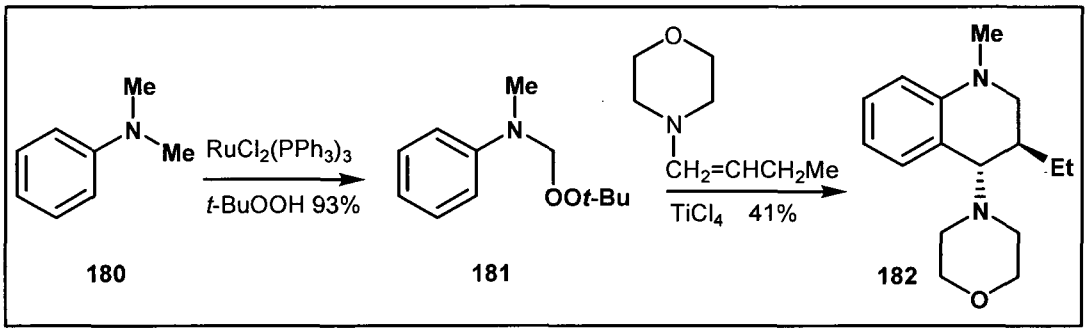
Condensation of *N*-methylaniline **177** with formaldehyde and arylsulfinic acid produced the α-arylaminomethyl sulfone **178** (Scheme 2.47) which upon treatment with styrene gave tetrahydroquinoline **179**[150].

Scheme 2.47



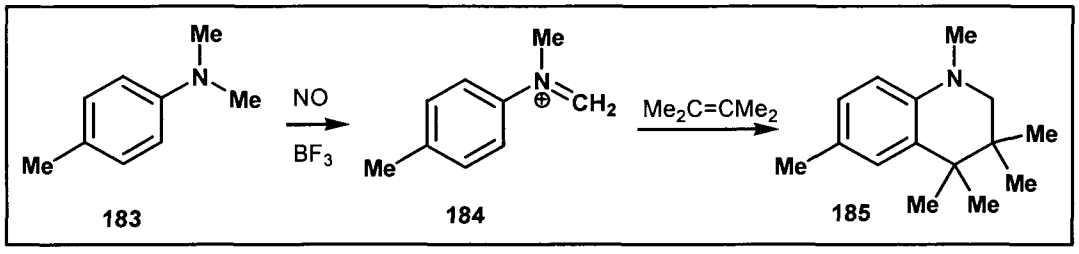
N,*N*-Dimethylaniline **180** (Scheme 2.48) is reacted with *tert*-butylhydroperoxide to create *N*-(*t*-butylperoxymethyl)-*N*-methylaniline **181** in excellent yield. This intermediate can react with olefins giving tetrahydroquinolines (for example **182**). This is due to the elimination of *t*-butoxide anion in the presence of a lewis acid providing *N*-methyl-*N*-phenylmethyleneiminium cation in performing the desired reaction[151].

Scheme 2.48



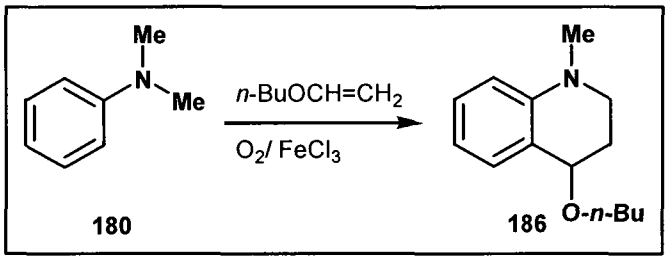
Oxidation of 4-methyl-*N*,*N*-dimethyl aniline **183** (Scheme 2.49) with nitric oxide in the presence of boron trifluoride as lewis acid leads to the formation of *N*-(arylamino)-*N*-methyleneiminium cation **184**. This cation trapped with tetramethylethylene to give tetrahydroquinoline **185**[152].

Scheme 2.49



N,N-Dimethyl aniline **180** (Scheme 2.50) similarly oxidized with oxygen/iron salt and trapped with vinyl *n*-butyl ether to afford 4-*n*-butoxytetrahydroquinoline **186**[153].

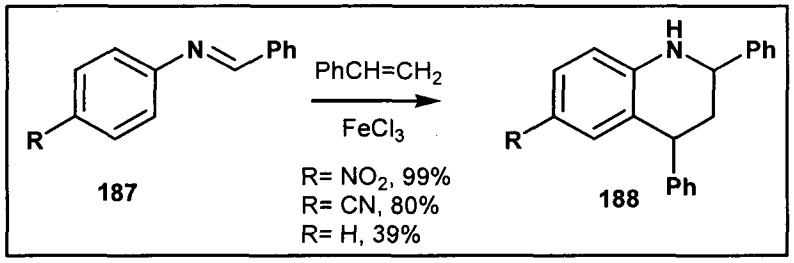
Scheme 2.50



2.4.5 From Aldimines (Aniline Imines)

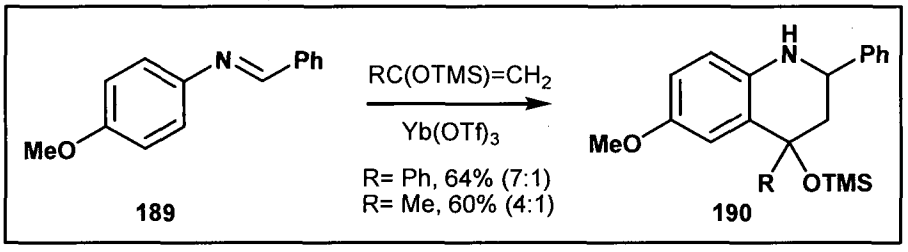
One of the most influential versions of this approach is the use of Schiff bases and their condensation with olefins in the presence of Lewis acids. Comparison of yields gained from the reaction of 4-substituent anilines **187** (Scheme 2.51) with styrene and ferric chloride as catalyst indicates that electron-withdrawing substituents on the aromatic ring prevent the formation of side products, such as quinolines[154].

Scheme 2.51



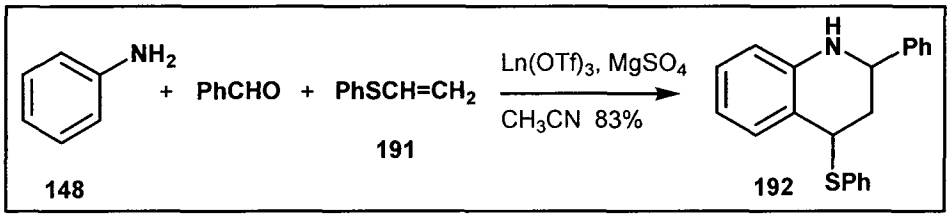
Ytterbium (III) triflate, as a milder Lewis acid, catalyzed the synthesis of 4-siloxytetrahydroquinolines **190** (Scheme 2.52) from Schiff base **189** and silyl enol ethers even with electron-donating groups[155].

Scheme 2.52



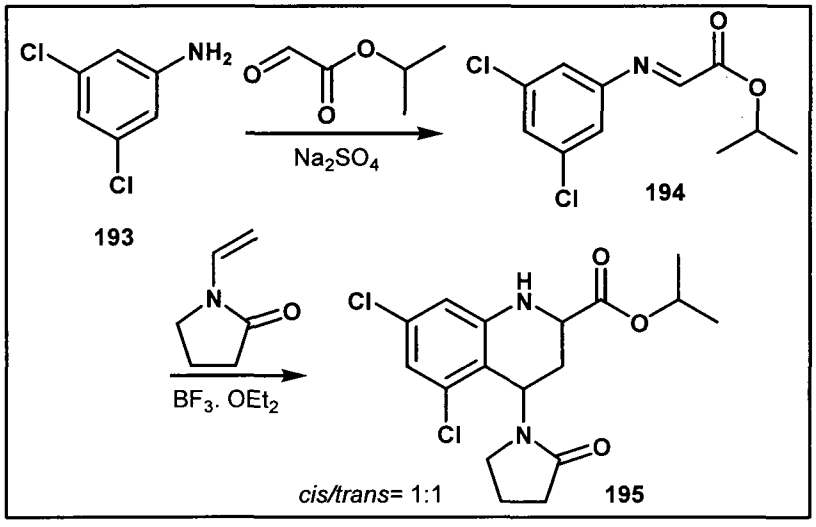
This reaction often performs in one pot without isolation of the Schiff base. For example tetrahydroquinoline **192** (Scheme 2.53) prepared in a very good yield with lanthanide triflate as the catalyst and aniline, benzaldehyde, and phenylvinyl sulfane as reagents[156]. This reaction will be discussed comprehensively in Chapter 5.

Scheme 2.53



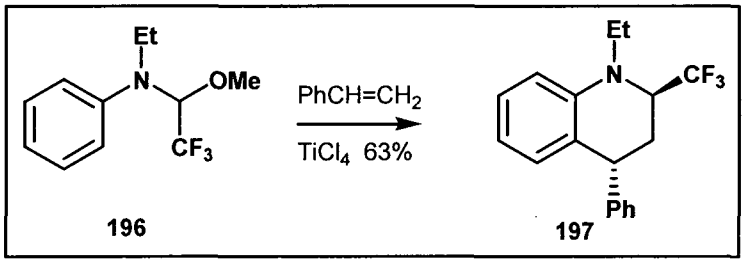
Alternatively, alkoxycarbonyl groups can be used in the synthesis of aniline alkylimines. In a structure-activity relationship for finding antagonists at the glycine site of the NMDA receptors, iminocaboxylic ester **194** (Scheme 2.54) was used to prepare tetrahydroquinoline **195**[157].

Scheme 2.54



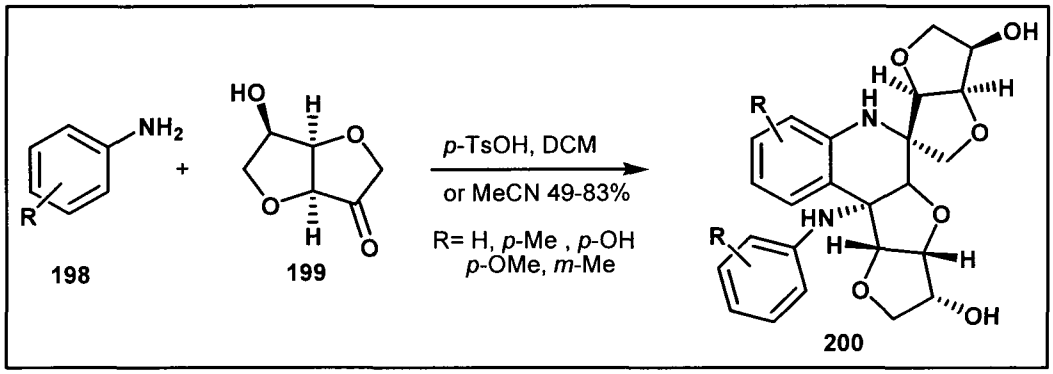
Electron withdrawing effect in trifluoromethyl group allowed forming stabilized *N*-(α-methoxyalkyl)aniline **196** (Scheme 2.55). In the presence of titanium tetrachloride, styrene reacts with this intermediate to give tetrahydroquinoline **197**[158].

Scheme 2.55



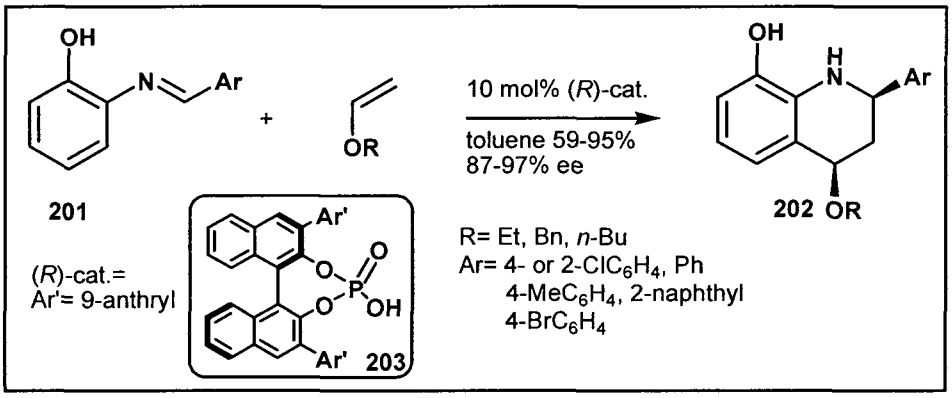
Spiro-tetrahydroquinolines **200** (Scheme 2.56) were stereoselectively prepared by using chiral keto-sugar **199** derived from sucrose[159]. It is believed that the reaction occurs via the inverse electron demand aza Diels-Alder reaction of the imine intermediate resulted from condensation of keto-sugar/aniline and its tautomer (self-cycloaddition).

Scheme 2.56



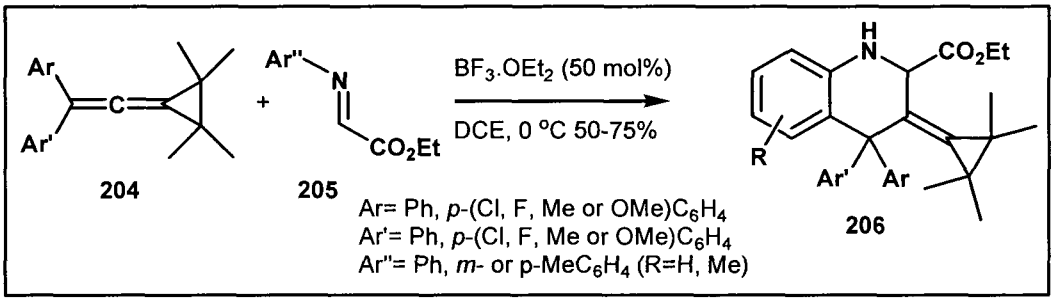
A chiral Brønsted acid-catalyzed inverse aza Diels-Alder reaction between aldimines **201** (Scheme 2.56) with electron-rich alkenes led to tetrahydro-quinolines **202** with high enantioselctively[160]. Chiral Brønsted acid [(*R*)-cat. **203**] is a phosphoric acid bearing 9-anthryl group on 3 and 3' position.

Scheme 2.56



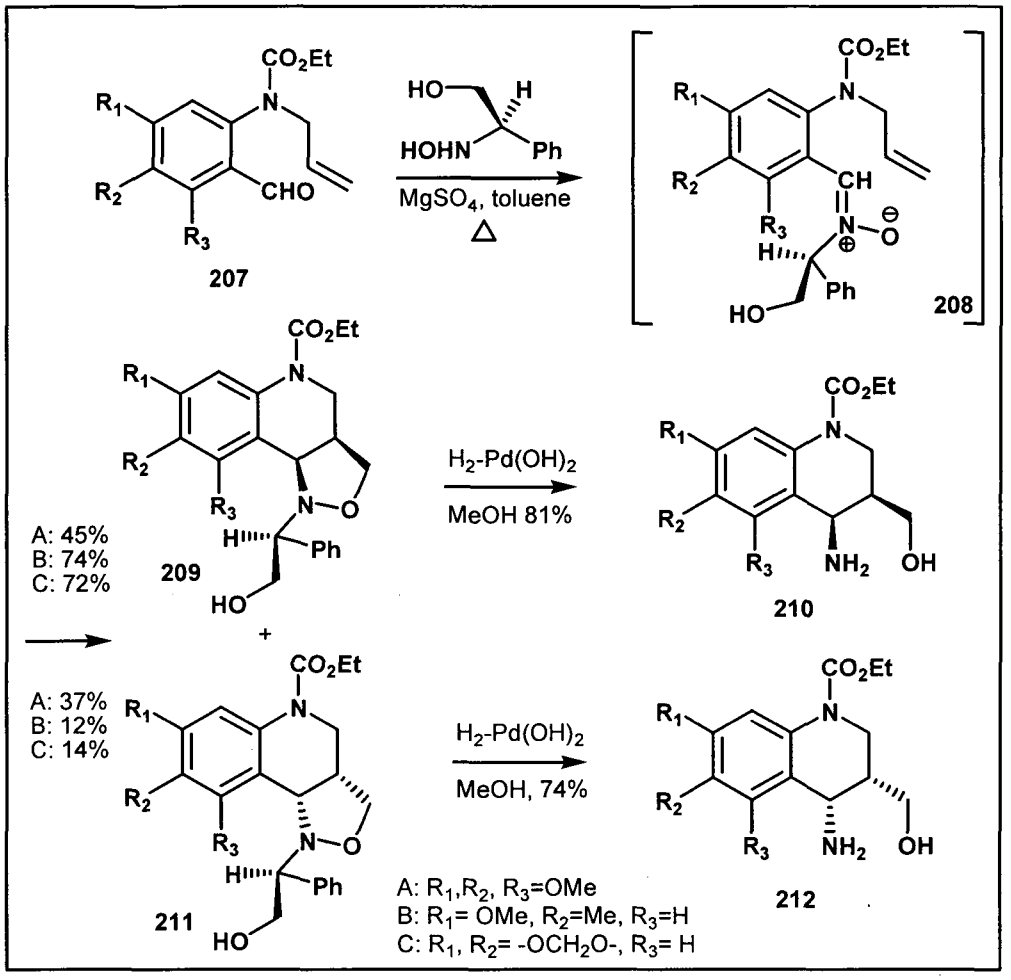
A recent interesting research reported the preparation of tetrahydroquinolines by the reaction of arylvinylidenecyclopropanes **204** (Scheme 2.57) with ethyl-(arylimino)acetates **205** in the presence of Lewis acid[161]. Depending on the electronic nature of **205** and Ar or Ar' groups of **204**, the final product would differ; for the synthesis of tetrahydroquinoline derivatives, electron-donating groups should be used. The reaction is believed to proceed via an intramolecular Friedel-Crafts pathway. In the case of using electron-poor aromatic groups, the mixture of tetrahydroquinoline and pyrrolidine (probably via [3+2] cycloaddition reaction pathway) was observed.

Scheme 2.57



An Intramolecular cycloaddition of chiral nitrone have shown to be useful in the synthesis of 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines[162]. As shown in Scheme 2.58, cycloaddition reaction on nitrone intermediates **208** prepared from aromatic aldehydes **207** and (*R*)-α-(hydroxymethyl)benzylhydoxylamine led to the separable diastereomic mixture of tricyclics **209** (major) and **211** (minor). These compounds were subjected to hydrogenation in methanol in the presence of $Pd(OH)_2$ affording corresponding 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydro-quinolines **210** and **212**, respectively.

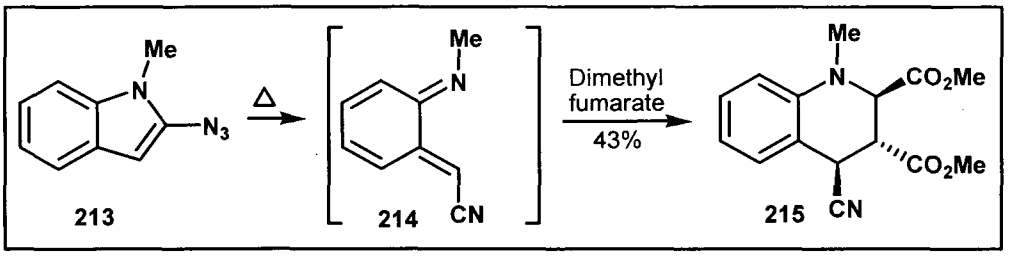
Scheme 2.58



2.4.6 By Insertion of C2-C3 Fragment

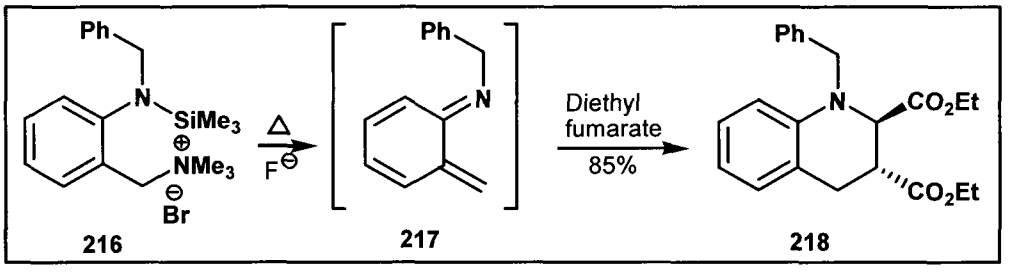
Cycloaddition reactions on *ortho*-methyleneiminoquinones produce C2 and C3 substituted 1,2,3,4-tetrahydroquinolines. As shown in Scheme 2.59, 2-azido-1-methylindole **213** under thermal cleavage gave **214** which trapped by dimethyl fumarate to afford tetrahydroquinoline **215**[163].

Scheme 2.59



In another study[164], silylated ammonium salt **216** (Scheme 2.60), under elimination catalyzed by fluoride, gives *ortho*-methyleneiminoquinone **217** which is trapped by diethyl fumarate to afford tetrahydroquinoline **218** in 85% yield.

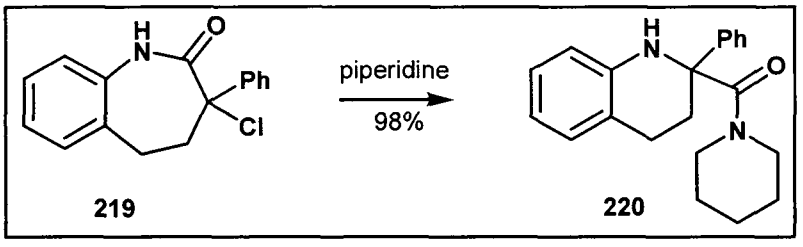
Scheme 2.60



2.4.7 Ring Contraction and Ring Expansion

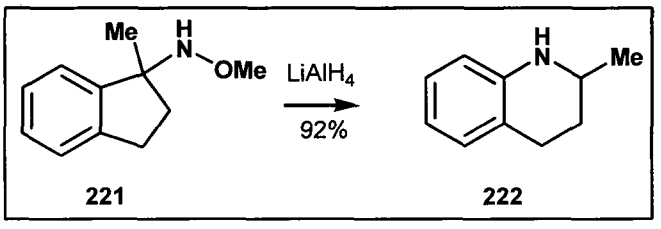
3-chloro-2,3,4,5-tetrahydro-1*H*-benazepin-2-ones react with amines leading to ring contraction and give 2-amino-1,2,3,4-tetrahydroquinolines[165]. For example, 3-chloro-3-phenyl-2,3,4,5-tetrahydro-1*H*-benazepin-2-one **219** (Scheme 2.61) upon reflux condition with piperidine converted to 2,2-disubstuted tetrahydro-quinoline **220** in excellent yield.

Scheme 2.61



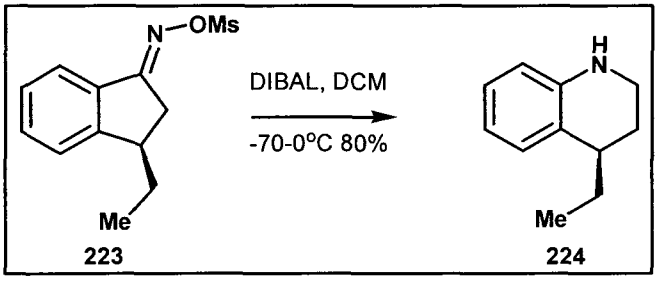
Reduction by lithium aluminum hydride on 1-(methoxyamino)-1-methylindane **221** (Scheme 2.62) leads to ring expansion and gives 2-methyl-1,2,3,4-tetra-hydroquinoline **222**[166].

Scheme 2.62



In the final stage of (*R*)-(+)-4-ethyl-1,2,3,4-tetrahydroquinoline **224** (Scheme 2.63) synthesis, the unstable mesylate compound **223** treated with excess DIBAL to provide the chiral tetrahydroquinoline **224** by ring expansion[167]. It is believed the reaction proceeds through the organoaluminum promoted Beckmann rearrangement of the oxime sulfonate; a method developed by Yamamoto[168]. This reaction will be revisited in Chapter 3.

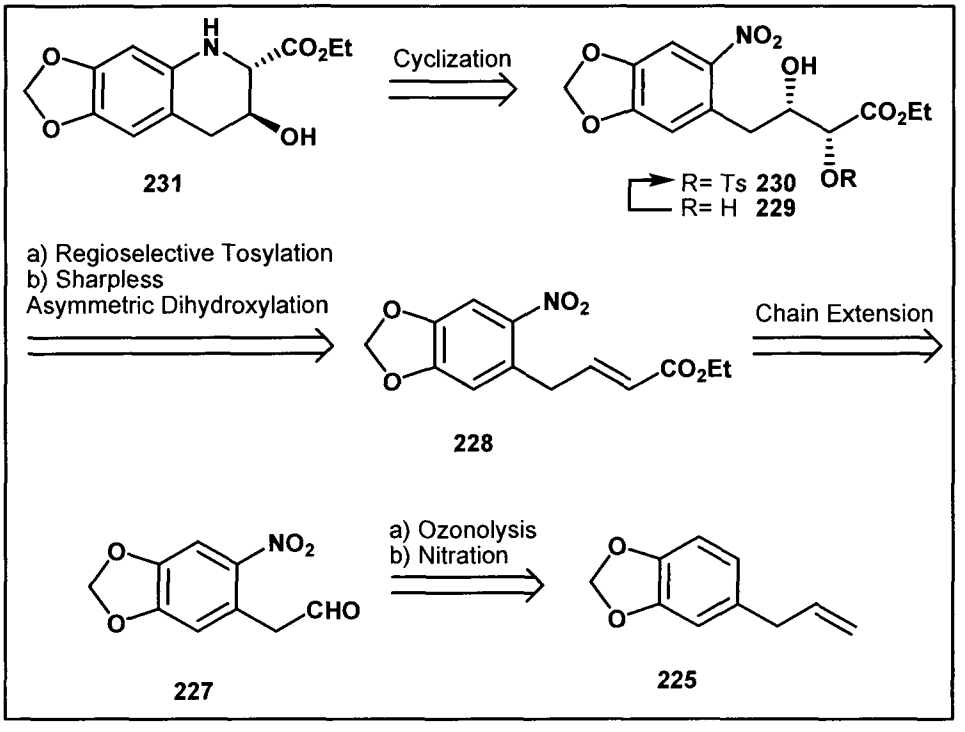
Scheme 2.63



2.5 Our Synthesis Approach

The retrosynthetic analysis of our approach is outlined in Scheme 2.64. Our approach to the enantioselective synthesis of tetrahydroquinoline core structure was achieved in three main stages: (1) synthesis of the aldehyde precursor **227** (2) chain extension followed by Sharpless asymmetric dihydroxylation to afford **230**, and (3) cyclization of **230** to the cyclic product **231** by a leaving group strategy via the regioselective tosylation of compound **230**. This method can be classified under section 2.4.2, i.e., synthesis of tetrahydroquinolines by the closure of one bond (namely N-C1).

Scheme 2.64



2.5.1 Model Study

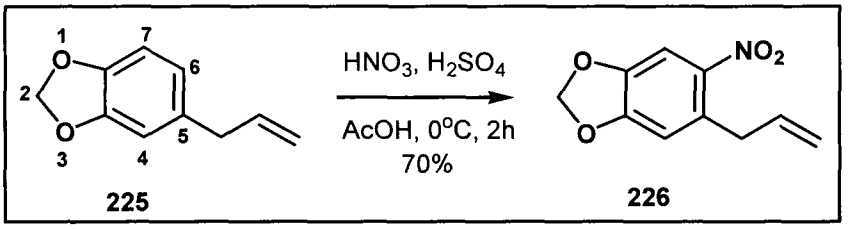
It was decided that preliminary synthesis steps were performed on the model system. This could offer the ability to explore various reactions and synthesis of

complex cyclic compounds and monitoring the feasibility for the expansion to solid-phase synthesis. For this aim, we were looking for the closest and preferably inexpensive starting material. Luckily, we found a suitable candidate for this important task. An inexpensive natural product named 'Safrole' was chosen. Safrole (**225**, Scheme 2.65) is a colorless oil extracted from sassafras or camphor oil and found naturally in several other plants such as basil, cinnamon, nutmeg, and pepper[169].

2.5.1.1 Synthesis of Aldehyde Precursor

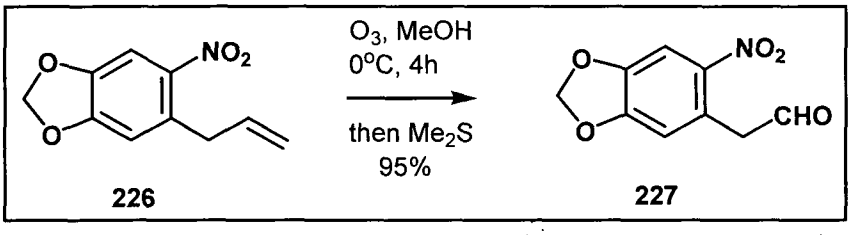
For the synthesis of the aldehyde precursor **227**, the first performed reaction was the nitration of safrole (Scheme 2.65). Nitration achieved using a mixture of nitric and sulfuric acid in glacial acetic acid as solvent. This reaction performed at 0°C for 2 hours and monitored by TLC. Although many side products, mainly dark oils, were also produced, the desired 6-nitrosafrole **226** was afforded in 70% yield after column chromatography. ^{1}H-NMR showed two singlet peaks of aromatic ring, i.e., at 7.51 and 6.78 ppm, expected for 6-nitrosafrole. Other possibilities namely nitration at C4 position which would show two doublets and nitration at C7 which would show two downfield peaks were most likely not the case. Moreover, due to electron-donating nature of oxygens in dioxolane ring and in allyl group (*ortho* and *para* directors), it is expected that nitration (electrophilic aromatic substitution) occurs in C7, C4 & C6, and C4 & C6 (for O_1, O_3 and allyl, respectively). Less steric hindrance at C6 (compared with C4) and more importantly, *p*-position (to O_3) likely resulted in the observed nitration. More accurately, this can be explained by *induction* (alkoxy more than allyl) and more importantly by *resonance* (oxygens' lone pair participation) effects.

Scheme 2.65



The desired aldehyde **227** prepared by ozonolysis of nitrosafrole **226** (Scheme 2.66). This reaction smoothly and effectively afforded the aldehyde needed for the next step in 95% yield. Peaks observed at 9.83 ppm and 197.3 ppm in ^{1}H-NMR and ^{13}C-NMR (respectively) are indicators for the existence of the aldehyde functionality.

Scheme 2.66

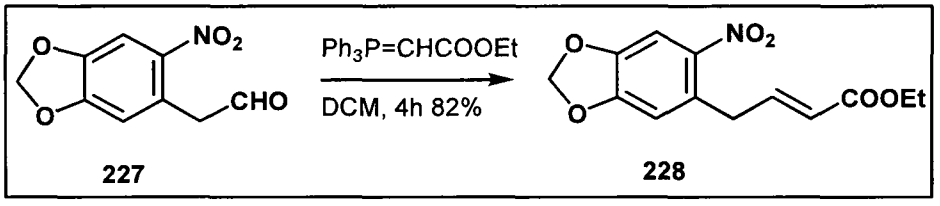


2.5.1.2 Chain Extension and Asymmetric Dihydroxylation

With aldehyde in hand, we performed the chain extension using Wittig reaction (Scheme 2.67). Aldehyde **227** was reacted with (carboxymethylene)-triphenyl-phosphorane in dichlormethane at room temperature. Reaction was monitored by TLC and finished in 4 hours. After purification by column chromatography, the desired (*E*) α,β-unsaturated ethylester **228** afforded in 82%. During the reaction, a second spot, with much lower concentration, noted in TLC plates. After separation, this portion was tested by mass spectroscopy; same peak (M+1) of 279.1 was found suggesting the minor amount of *Z* isomer was also produced. However, we expected to observe the *E* isomer as a major compound due to the use of the stabilized Wittig reagent. ^{1}H-NMR revealed the peaks for ethyl ester

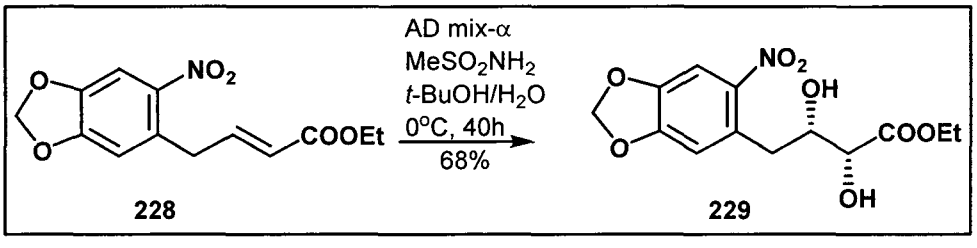
group and *trans* hydrogens by their coupling constant (J= 15.6 Hz). Moreover, existence of ^{13}C-NMR peaks for carbonyl group (in ethyl ester) and olefinic carbons proved the synthesis of the desired compound **228**.

Scheme 2.67



Enantioriched diol **229** (Scheme 2.68) was prepared by Sharpless asymmetric dihydroxylation of olefin **228**[170a] using commercially available 'AD-mix α' containing Potassium osmate $K_2OsO_2(OH)_4$ as the source of Osmium tetroxide, Potassium ferricyanide $K_3Fe(CN)_6$, which is the re-oxidant in the catalytic cycle, Potassium carbonate, and chiral ligand $(DHQ)_2PHAL$ (a phthalazine adduct with dihydroquinine) in *t*-Butanol/water mixture as the solvent and finally methane-sulfonamide (using as a reagent for better yield) at 0°C. Checking by TLC revealed the end of the reaction in 40 hours. Purification by column chromatography provided diol **229** in 68% yield. The complete structure elucidation was performed using 1D and 2D NMR. The enantiomeric excess of the product was 90% as determined by chiral HPLC. Therefore, this key reaction generates two chiral centres enantioselectively that remain in all subsequence products prepared in the synthesis of tetrahydroquinoline scaffold, its derivatives and cyclic complex compounds.

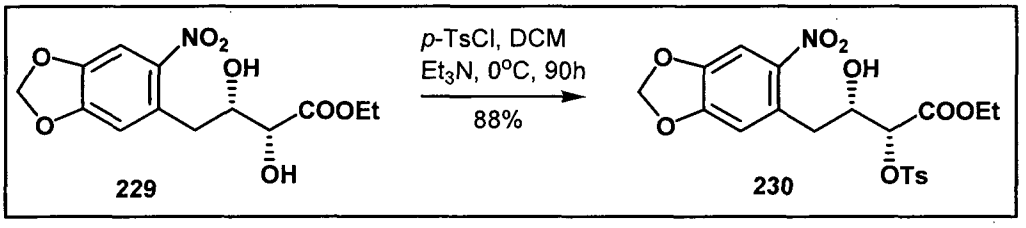
Scheme 2.68



2.5.1.3 Regioselective Tosylation and Cyclization

At this stage, one hydroxyl group in diol **229** selectively tosylated to form α-*O*-tosyl compound **230** (Scheme 2.69). This regioselective protection in α-hydroxyl group may be explained by the fact that hydrogen in α-hydroxy adjacent to carbonyl (ethylester) group is expected to be more acidic thus this hydroxy is more prone to be protected by tosyl chloride[170b, 170c]. However, other factors should also be considered. Nucleophilic attack of oxygen to quite bulky tosyl chloride is proved to be the rate determining step but deprotonation of the oxonium considered fast and normally not affected by type of the base used. That is the reason for the ability of weak bases such as triethylamine to facilitate the protection, as they are not capable of deprotonation of hydroxyl groups even adjacent to electron-withdrawing carbonyl group. Therefore, it is reasonable that the comparison between two hydroxyl groups in attacking to tosyl chloride is taking part considerably and leading to the product. From diol **229**, it seems that α-hydroxy is more available than β-hydroxy due to slight steric hindrance presented in β-hydroxyl group.

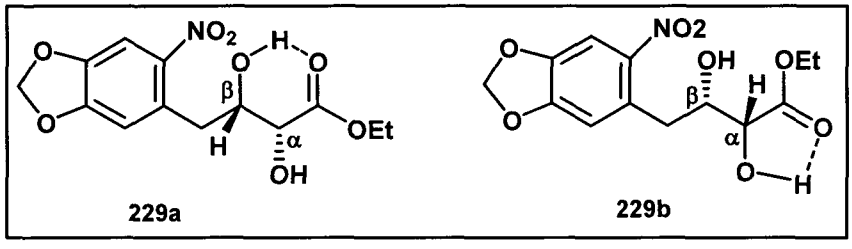
Scheme 2.69



In addition, we should not ignore the possibility of intramolecular hydrogen bonding between hydrogen at β-hydroxy group and carbonyl of ester functionality, which prevents the easy tosylation of β-hydroxyl group (**229a** in Scheme 2.70)[170d]. Although one can argue the possibility of an intramolecular hydrogen bonding between hydrogen at an α-hydroxy group and the carbonyl of ester (**229b**). Again, it seems the steric effect plays an important role in the observed regioselectivity, since the hydroxy group in **229a** is more accessible

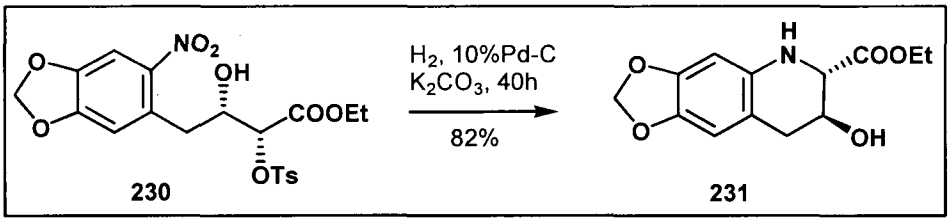
than the one on **229b**. For better regioselectivity, this reaction performed at 0°C and took 90 hours to complete. Although in higher temperature, starting material disappeared in a shorter time, a mixture of desired and undesired compounds, namely *bis*-tosyl and β-position tosyl (with different R_f value than α-isomer) were observed. Separation and characterization of these unwanted compounds were difficult despite observing their related mass peaks. ^{1}H-NMR revealed the existence of aromatic methyl (singlet at 2.46 ppm, 3H) and hydrogens (7.88 ppm, 2H and 7.37 ppm, 2H) within tosyl group.

Scheme 2.70



O-Tosyl compound **230** upon reduction conditions with hydrogen and palladium-carbon catalyst in the presence of a mild base, i.e., Potassium carbonate cyclized to give our tetrahydroquinoline scaffold **231** in 82% yield (Scheme 2.71). The acyclic amine intermediate was not isolated and the next step, i.e., cyclization, proceeded in the same pot. Structure elucidation performed using 1D and 2D NMR. As expected, aromatic hydrogens, which are now adjacent to a 6-membered ring, are more shielded resulting in an upfield shift (6.49 and 6.24 ppm compared to 7.51 and 6.82 ppm, respectively, in former acyclic tosylated compound **230**). The aromatic hydrogen adjacent to nitrogen was more affected (more than 1 ppm) due to reducing of nitro to the amine group.

Scheme 2.71

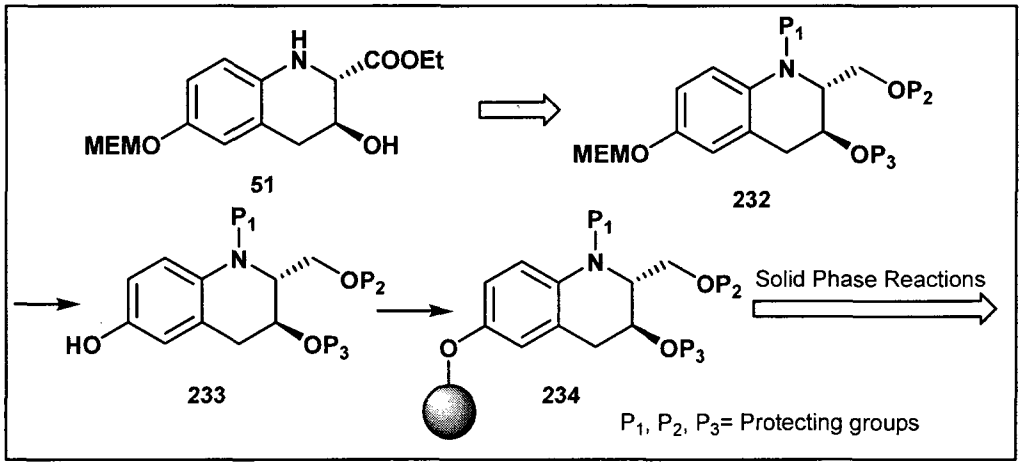


The overall yield for the synthesis of tetrahydroquinoline **231** from safrole was 27% (6 steps). For further projects in the model study, more than 4 grams of this compound was efficiently prepared and subjected to the next synthesis steps (Chapter 3).

2.5.2 Scaffold Required for Solid-Phase Synthesis

For developing a solid-phase synthesis project, we needed compound **232** (Scheme 2.72), in which the phenolic hydroxyl moiety easily could be obtained (compound **233**) and utilized as an anchoring site for the solid phase (solid supported compound **234**). Since all the three arms in tetrahydroquinoline **51** will be used in solid phase synthesis, there is a need for orthogonal protection of free amine, free hydroxyl, and also ester (reduced to alcohol) moiety. Therefore, fully protected tetrahydroquinoline **232** was prepared (Chapter 3 and Chapter 4).

Scheme 2.72

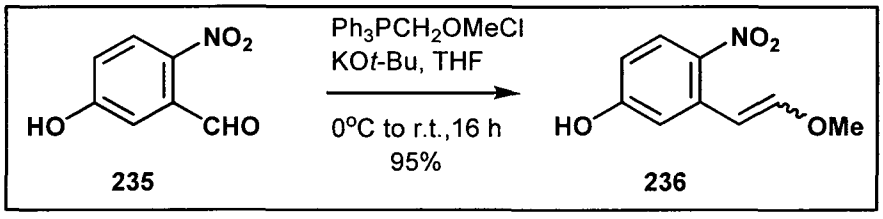


An enantioselective synthesis of compound **51** was developed with an approach similar to that discussed earlier in the model study (Section 2.5.1). The synthesis of **51** was achieved in a few steps from 5-hydroxy-2 nitrobenzaldehyde **235** (Scheme 2.73) in three major stages: (1) homologation and chain extension, (2) protection of phenolic hydroxyl group and Sharpless asymmetric dihydroxylation, and (3) regioselective tosylation and cyclization. This synthesis differs from model study in almost halfway through it.

2.5.2.1 Homologation and Chain Extension

Aldehyde homologation of compound **235** performed in two steps. Methoxymethylene-triphenylphosphonium as the Wittig reagent freshly prepared by the reaction of (methoxymethyl)triphenylphosphonium chloride and potassium *t*-butoxide. Wittig reaction of aldehyde **235** with the prepared Wittig reagent afforded a mixture of *E* and *Z* form of enol-ether **236** in 95% yield (Scheme 2.73). Although mostly *E* form was formed, since the next step, i.e., hydrolysis of this enol ether, would hydrolyze both *E* and *Z* form to the corresponding aldehyde **237**, no attempt was done for the complete separation of *E* and *Z* forms. Mass spectra showed M+1 peak for the product and ^{1}H-NMR revealed the absence of aldehyde hydrogen which replaced by olefinic (7.05 and 6.56 ppm) and methoxy (3.77 ppm, 3H) hydrogens.

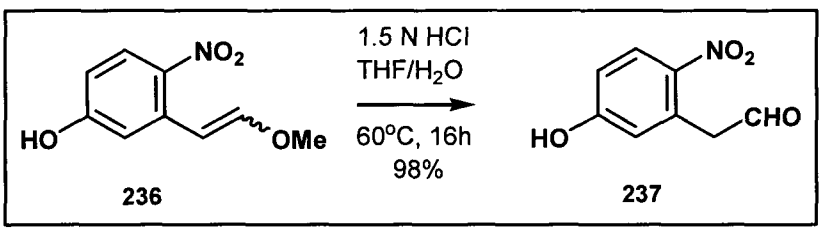
Scheme 2.73



Enol-ether **236** was hydrolyzed by hydrochloric acid in THF/water at 60°C during 16 hours to generate aldehyde **237** in 98% yield (Scheme 2.74). Replacement of hydrogens in enol-ether with aldehyde hydrogen (9.79 ppm) and benzylic

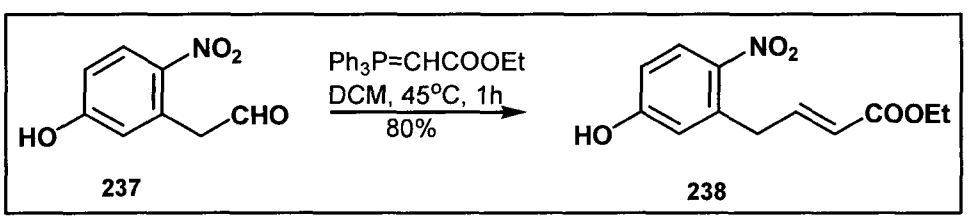
methylene (4.13-4.16 ppm, 2H) confirmed by ^{1}H-NMR. Moreover, ^{13}C-NMR showed the carbonyl peak (aldehyde) at 198.0 ppm.

Scheme 2.74



Another Wittig reaction, this time by (carboxymethylene)-triphenylphosphorane, converted aldehyde **237** to α,β–unsaturated ester **238** (Scheme 2.75). M+1 peak noted in the mass spectrum and ^{1}H-NMR showed the existence of olefinic (7.12 and 5.84 ppm) and ethyl ester hydrogens (4.24 ppm, 2H and 1.34 ppm, 3H). ^{13}C-NMR showed the carbonyl peak (ester) at 167.9 ppm. This product was afforded exclusively in *Z*-form confirmed by a coupling constant of *J*= 15.6 Hz between two olefinic hydrogens.

Scheme 2.75

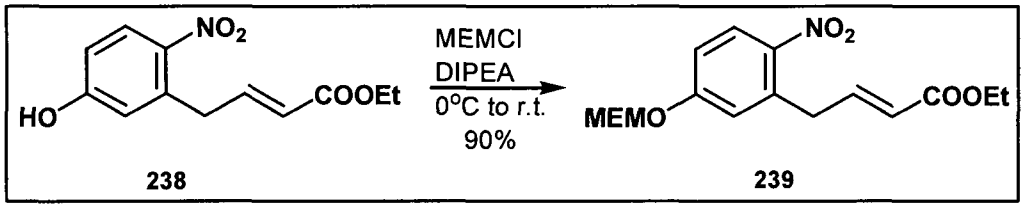


2.5.2.2 Protection of Phenolic Hydroxy and Asymmetric Dihydroxylation

Phenolic hydroxyl group in **238** was protected as MEM (methoxyethoxymethyl)-ether using MEMCl and *N,N*-diisopropylethylamine (DIPEA) as the base in dichloromethane in 90% yield (Scheme 2.76). Appearance of MEM hydrogen peaks in ^{1}H-NMR of the product **239** [i.e. 2 singlets at 5.36 ppm (2H, -OCH_2O-) and 3.39 ppm (3H, -OMe) and 2 multiplets at 3.57 and 3.84 ppm (-OCH_2CH_2O-)]

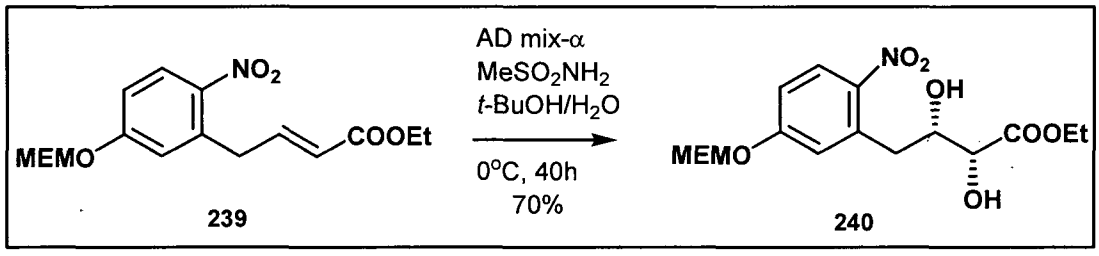
confirmed the synthesis. ^{13}C-NMR also revealed four additional peaks related to MEM group at 93.7, 71.8, 68.6, and 59.5 ppm.

Scheme 2.76



Sharpless asymmetric dihydroxylation of olefin **239** (Scheme 2.77) with the same conditions as the model study resulted in the formation of enantiorich diol **240** with 70% yield. Mass, 1D and 2D NMR confirmed the structure of diol **240**. As a practical guide, α,β-olefinic peaks in ^{13}C-NMR were not found.

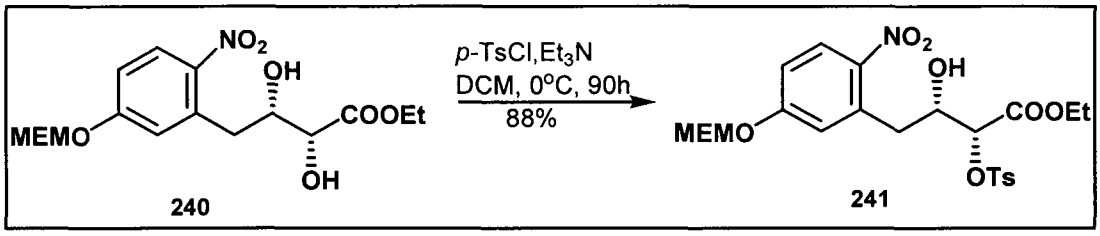
Scheme 2.77



2.5.2.3 Regioselective Tosylation and Cyclization

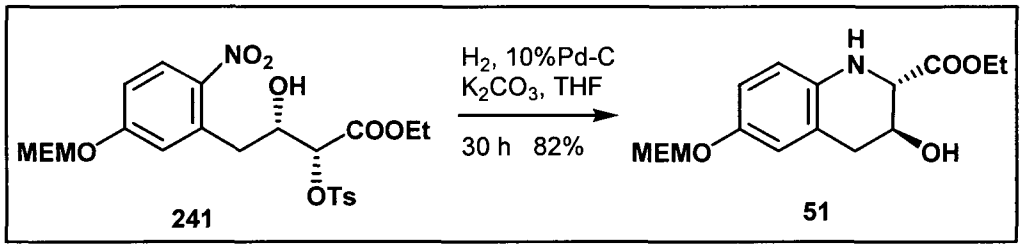
Regioselective tosylation of diol **240** performed with the similar conditions as the model study to afford α-*O*-tosyl compound **241** in 88% yield (Scheme 2.78). ^{1}H-NMR revealed the existence of aromatic methyl (singlet at 2.46 ppm, 3H) and hydrogens (two doublets at 7.89 ppm, 2H and 7.37 ppm, 2H) in tosyl group. ^{13}C-NMR showed carbonyl (ester) peak and 12 aromatic carbons.

Scheme 2.78



Finally, *O*-tosyl compound **241** under reduction conditions, i.e., hydrogen and palladium/carbon catalyst, gave the amine intermediate (not shown) and in the presence of potassium carbonate (as base) cyclized to tetrahydroquinoline derivative **51** in good yield (82%).

Scheme 2.79



The overall yield in the synthesis of this tetrahydroquinoline was 34% (7 steps). For further projects in solution and solid phase, more than 13.0 grams of this compound was efficiently prepared and subjected to the next solution and solid phase synthesis steps (Chapter 3 and Chapter 4).

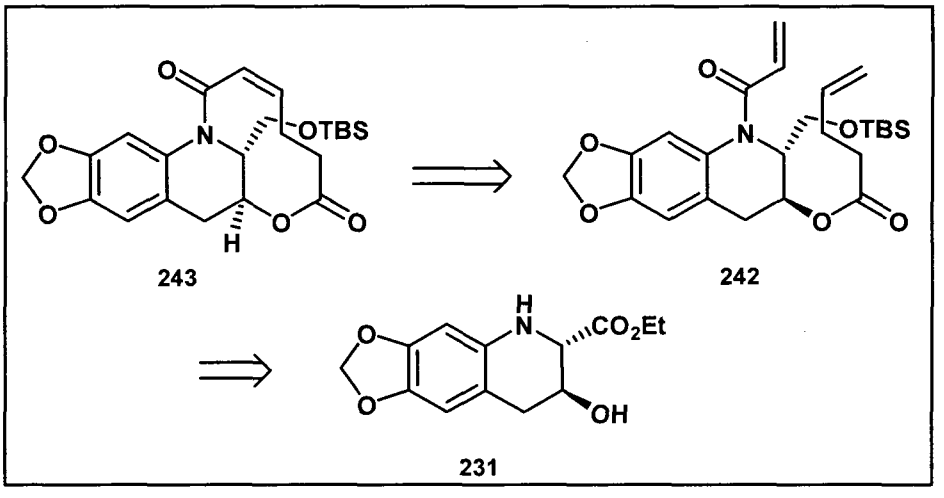
3: Solution and Solid Phase Synthesis of Tetrahydroquinoline Polycyclics. Part A: 10-membered Ring Unsaturated Lactam

3.1 Design Strategy

As described in Chapter 1, the primary objective of the project is to synthesize a diverse collection of compounds, using the tetrahydroquinoline scaffold. In this chapter, the solution and solid phase synthesis of a tetrahydroquinoline polycyclic having a ten-membered ring, unsaturated lactam will be presented[171]. Synthesis of other tetrahydroquinoline polycyclics will be discussed in Chapters 4 and 5.

As shown in Scheme 3.1, our target compound **243** was synthesized by the ring-closing metathesis (RCM) reaction of **242**. This reaction was performed using a second-generation Grubbs' catalyst. In this chapter, we prepare the required precursor **242** for the RCM reaction using simple transformations on our tetrahydroquinoline scaffold **231**.

Scheme 3.1



Successful results in this model study would encourage us to extend our synthesis to the solid phase (Section 3.4.2).

3.2 Ten-membered Rings Having Nitrogen (Lactam) as Natural and Pharmaceutical Products

Despite the existence of many ten-membered ring carbocycles and oxygenated cycles (such as lactones), ten-membered rings having nitrogen such as lactam are limited. However, this has not negatively affected the significance of this series of compounds and their synthesis thereafter. A few examples of natural products having ten-membered ring nitrogen/lactam are presented in Figure 3.1.

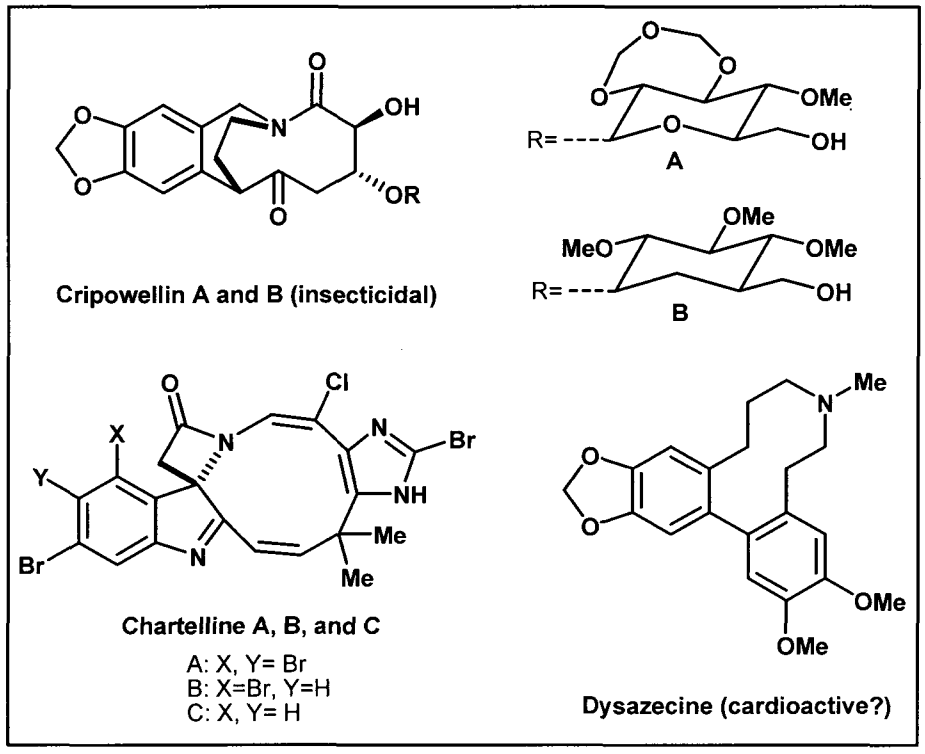


Figure 3.1 Natural Products Having a 10-membered Ring Nitrogen/Lactam

Cripowellin A and B, two *amaryllidaceae* alkaloids isolated from bulbs of *crinum powelii*[172] have shown strong insecticidal properties. A small group of halogenated indole-imidazole alkaloids, namely chartelline A, B, and C, were isolated from marine bryzoan *Chartella papyracea*[173]. Despite the lack of biological activity to date, their unique structural complexity make chartellines as valuable targets in total synthesis projects.

Dysazecine is the first alkaloid having a dibenz[*d*,*f*]azecine skeleton, which is found in leaves of *dysoxylum lenticellare*[174]. Although an extract of this plant including dysazecine showed strong cardioactivity, the responsible compound or compounds for the reactivity have not yet been identified[175]. LE-300 (Figure 3.2) is found to be one of the most potent D_5-selective dopamine-receptor antagonists known so far[176]. LE-300 is not a naturally occurring compound, but has the dibenz-azecine skeleton, similar to dysazecine, in its structure.

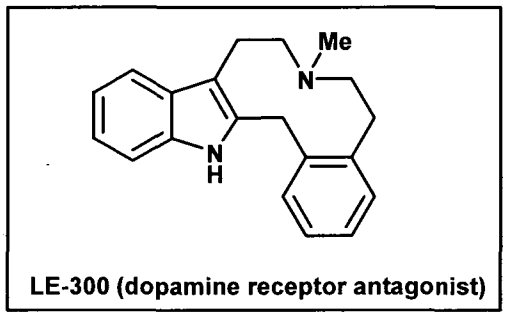


Figure 3.2 Structure of LE-300

Synthetic efforts for constructing these compounds will be discussed in Section 3.3.

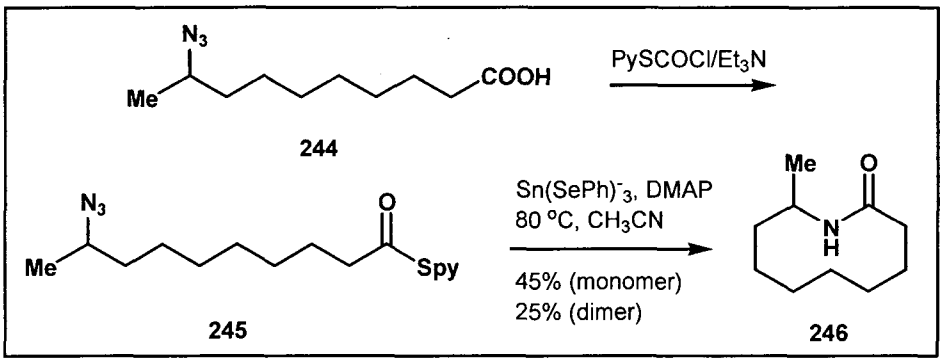
3.3 Synthesis of Ten-membered Rings Having Nitrogen (Lactam) in Literature

In the following section, a few synthetic methods for creating 10-membered-ring lactams and other nitrogenated compounds will be reviewed. Therefore, many other 10-memebered rings, such as carbocycles and oxygenated compounds like lactones and cyclic ethers, will not be discussed. Former stages of the synthesis will not be covered, but only the synthesis of the 10-membered-ring systems. In addition, I will review the literature from 1991-2006. Major methods have been classified for more clarity (Sections 3.3.1- 3.3.3) and a few examples in each section are presented. Despite the attempt made to include most methods, this section is not comprehensive.

3.3.1 Ring Closure and Ring Contraction

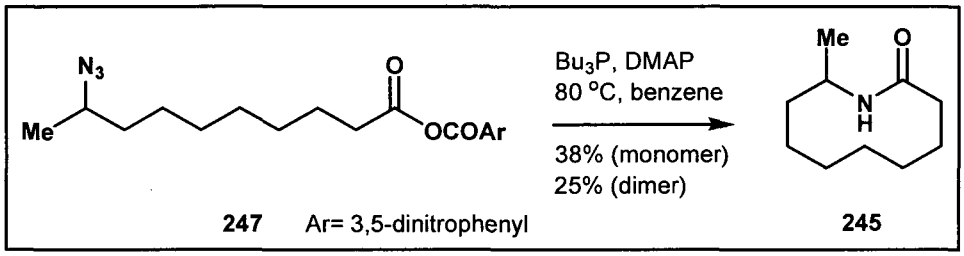
In their research, Bartra and Vilarrasa prepared 9-decanelactam by cyclization of decanoic acid derivatives[177]. As shown in Scheme 3.2, treatment of the more active 2-pyridyl 9-azidodecanethioate **245**, prepared from 9-azido carboxylic acid **244**, with tris(phenylselanyl)stannate in the presence of DMAP, gave 10-membered ring lactam **246** in 45% yield. The dimer as a side product (25% yield) was also observed.

Scheme 3.2



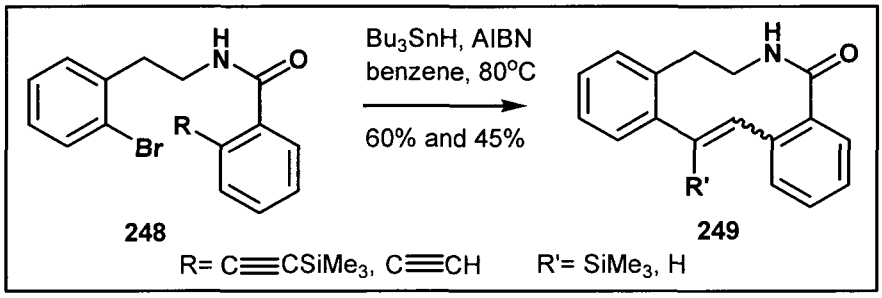
A similar approach was performed by Vilarrasa and co-workers using activated anhydride[178]. In Scheme 3.3, secondary azido compound **247,** under treatment with excess tributylphosphine and DMAP, (high-dilution) resulted in 10-membered ring lactam **245,** again with 25% undesired product. On the other hand, this method was found particularly effective in preparing amides and peptides. It was believed the reaction involves a direct aza-Wittig-like reaction.

Scheme 3.3



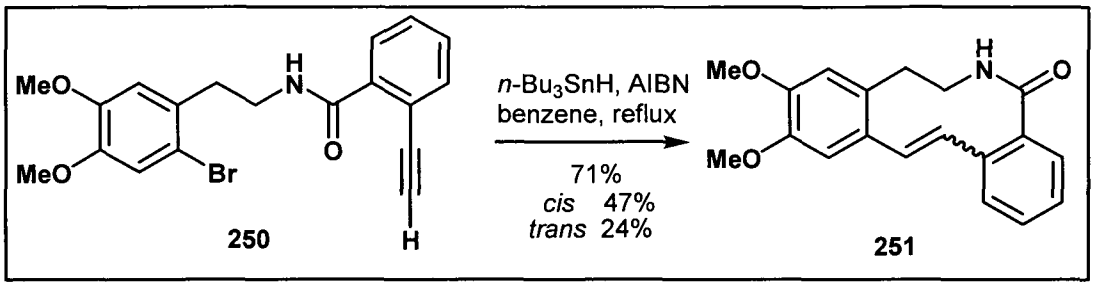
In Scheme 3.4, 10-membered ring lactams **249** were prepared by Castedo and co-workers using intramolecular addition of an aryl radical to acetylenes[179]. Intramolecular attack of the aryl radical, formed from bromoacetylene **248**, to the triple bond, afforded the lactam **249** in a mixture of *Z* and *E*-olefin. More reactive trimethylsilylacetylene resulted in better yield of 60%.

Scheme 3.4



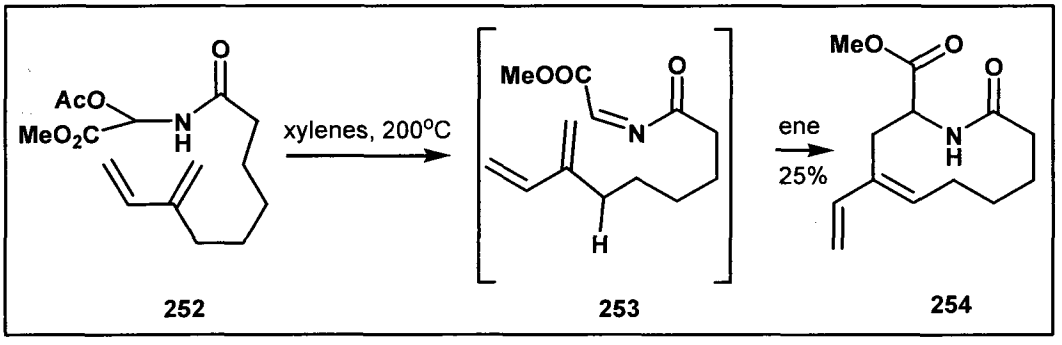
This reaction was repeated in a di-methoxy derivative of bromoacetylelne **250** by Saa and co-workers[180]. Yield of **251** in this case improved to 71%, shown in Scheme 3.5.

Scheme 3.5



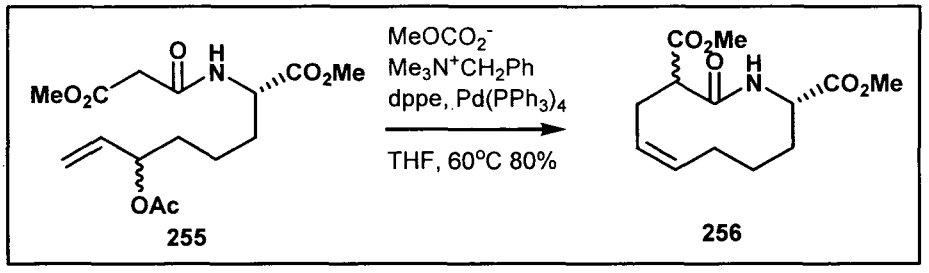
Shea and Lease observed an unprecedented reaction that resulted in the formation of a 10-membered-ring lactam[181]. Scheme 3.6 shows that thermolysis of acetate **252** gave 10-membered-ring lactam **254**. *N*-acyl imine **253** undergoes an intramolecular ene reaction. This is the first example of a type 3 intramolecular imino-ene rearrangement, which indicates the enophile is tethered to the 3-position of the ene.

Scheme 3.6



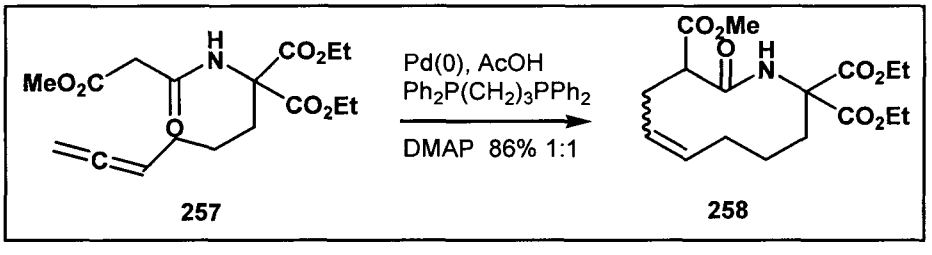
Macrolactamization via palladium π-allyl alkylation was studied by Johnson and co-workers[182a]. Benzyltrimethylammonium methyl carbonate is the source of slowly formed methoxide. Scheme 3.7 shows an example of this method giving 10-membered-ring lactam **256** from **255**. Synthesis of CGS25155, an inhibitor of neutral endopeptidase (NEP) 24.11, was performed using this method.

Scheme 3.7



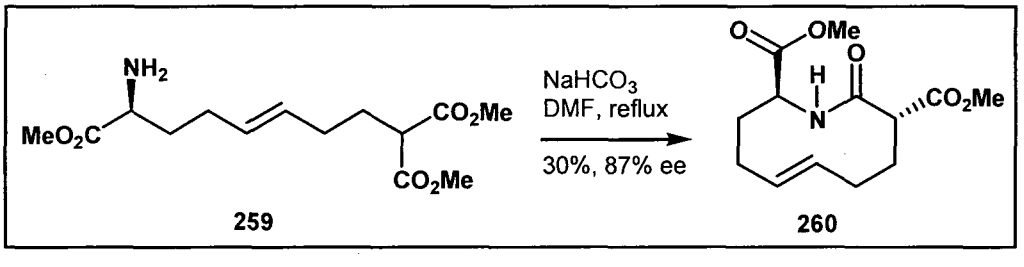
A novel cycloisomerization is used for the synthesis of medium and large rings via allenes by Trost and co-workers[182b]. 10-membered-ring lactam **258** in Scheme 3.8 was prepared using Pd(0)-catalyzed cyclization of allene **257**. Allen served as the precursor to the allyl ester.

Scheme 3.8



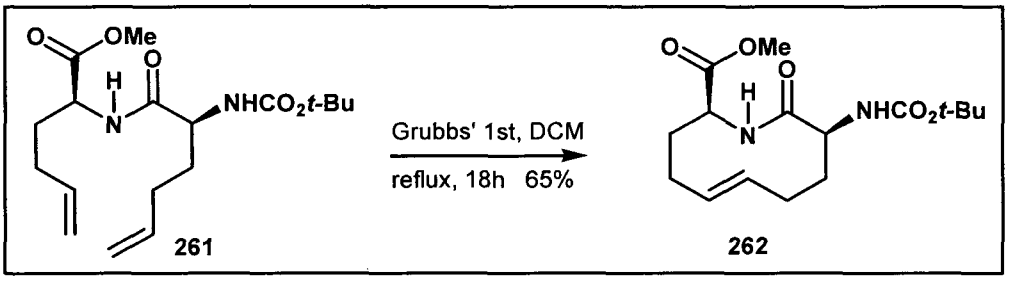
Katzenellenbogen and co-workers prepared ten-membered-ring lactam stereo-selectively with two methods[183]. In their macrolactamization route, cyclization of amino ester **259** (Scheme 3.9) in the presence of a base resulted in lactam **260** with 87% *ee*. However, the yield was poor.

Scheme 3.9



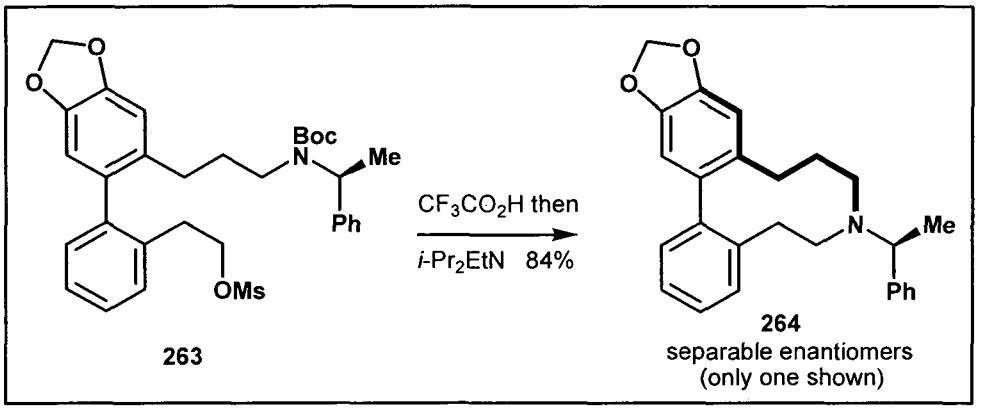
As shown in Scheme 3.10, the more efficient route used a ring-closing metathesis reaction with Grubbs' catalyst. This is the first example of cyclization using an RCM reaction to create a 10-membered-ring lactam. The reaction on **261** gave only one diastereomer (**262**) in 65% yield with a double bond in *E* form.

Scheme 3.10



In an effort to develop a method for the total synthesis of dysazecine, Mason and co-workers used *O*-mesylated compounds as a precursor for cyclization[184]. Intramolecular mesyloxy displacement of secondary amine, prepared from Boc deprotecion of compound **263** by trifluoroacetic acid (Scheme 3.11) generated the separable enantiomeric mixture of compound **264**.

Scheme 3.11

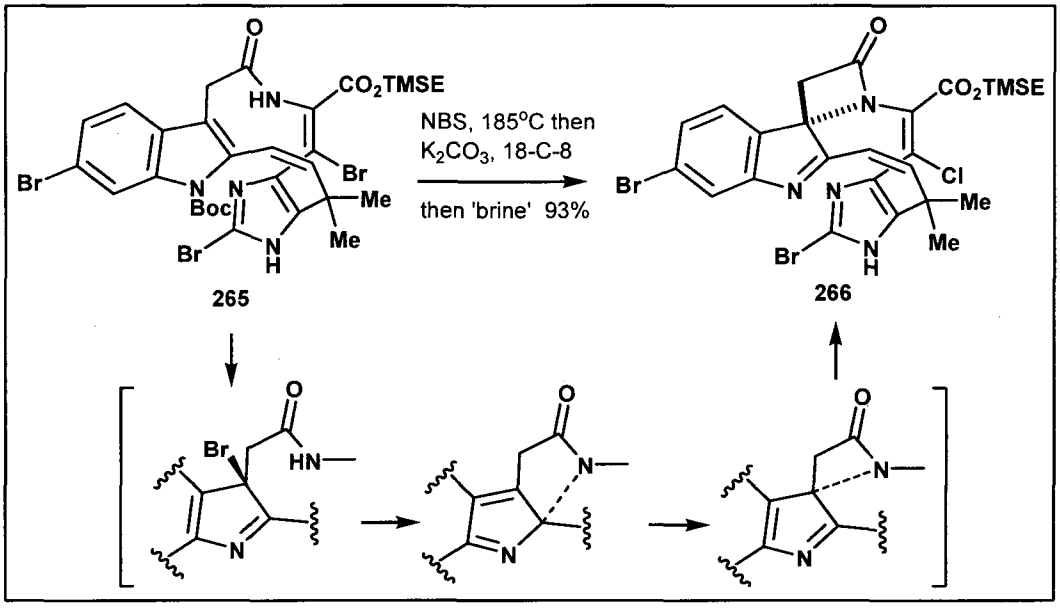


In the elegant synthesis of (±)-chatelline C by Baran and Shenvi, an inspired biosynthetic route was introduced for constructing the 10-membered-ring in the

chatelline molecule[185]. As shown in Scheme 3.12, compound **265** in one pot gave the necessary compound **266** containing a core of chatelline, a 10-membered nitrogen ring. It was believed the reaction involves:

- bromination at β-position of amide and Boc removal,
- nucleophilic attack of nitrogen to γ-position of carbonyl, resulting in debromination at β-position, aryl dearomtization, construction of a 9-membered nitrogen ring and γ-lactam (5-membered ring),
- a [1,5] N-shift leading to rearomatization, construction of β-lactam (ring contraction) and 10-membered ring core (ring expansion), and
- halogen substitution (with brine).

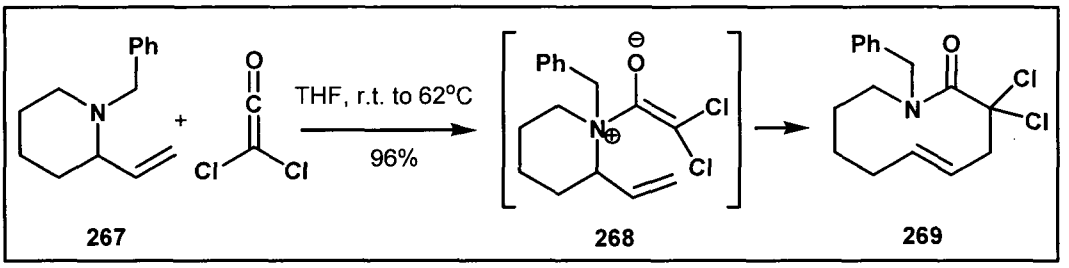
Scheme 3.12



3.3.2 Ring Expansion and Fragmentation

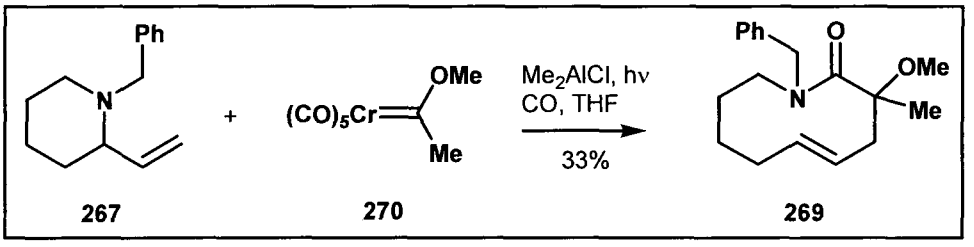
A notable reaction reported by Edstrom[186] involved the reaction of 2-vinyl-azacycles, such as **267** (Scheme 3.13), with the appropriate ketene creating zwitterionic intermediate **268,** which underwent [3,3] ring expansion to give lactam **269** in excellent yield.

Scheme 3.13



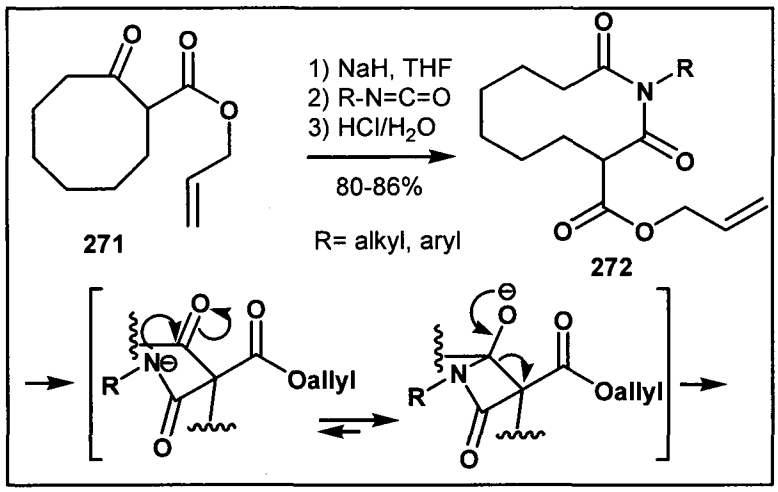
A photochemical variant of the reaction presented above was investigated by Hegedus and co-workers[187]. Chromium carbene complex **270** (Scheme 3.14) in the presence of tertiary allylic amine **267** under photolysis, generates a zwitterionic intermediate which by [3,3] sigmatropic rearrangement gave 10-membered-ring unsaturated lactam **269**. However, the yield was poor.

Scheme 3.14



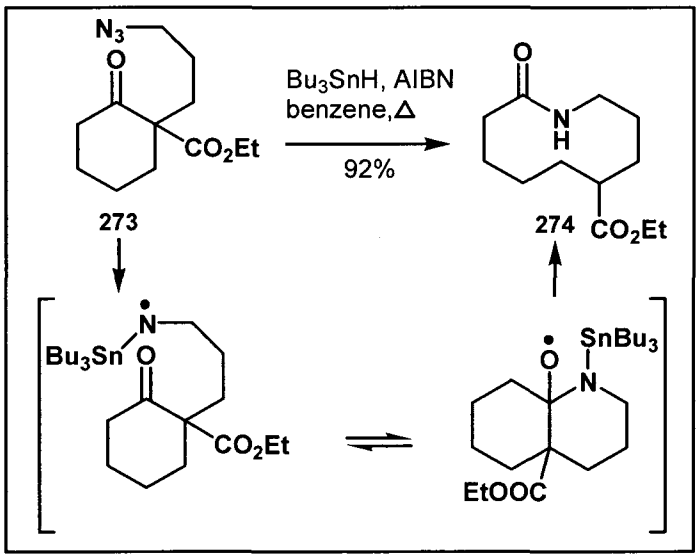
N-substituted cycloalkanedicarboxamides, including 10-membered rings, were successfully prepared from cycloalkanones by ring fragmentation[188]. As shown in Scheme 3.15, deprotonation of **271** with sodium hydride and subsequent addition to isocyanates gave the ring-expanded compounds **272** in very good yields. The provided intermediate from isocyanate underwent an intramolecular nucleophilic attack to the more active carbonyl, and the resulted β-lactam under fragmentation gave β-dicarboxylate anion, and then imide, in the acidic media. Several modifications have been performed on this method by Koch and Hesse to prepare various substituted cycloalkanedicarboxamides[189].

Scheme 3.15



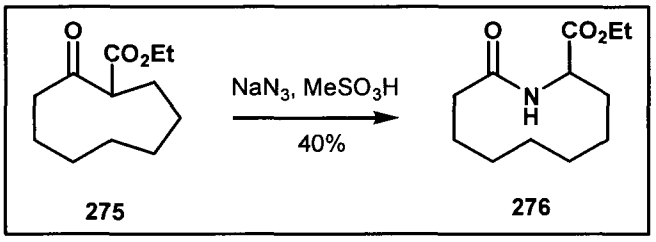
For construction of small to medium sized ring lactams, Kim *et al.* used an intramolecular addition of aminyl radicals to carbonyl groups[190]. Azido groups were used as precursors for aminal radicals, as shown in Scheme 3.16. Interamolecular addition of aminal radicals to a more reactive carbonyl group, and following ring expansion, resulted in 10-membered-ring lactam **274** in excellent yield.

Scheme 3.16



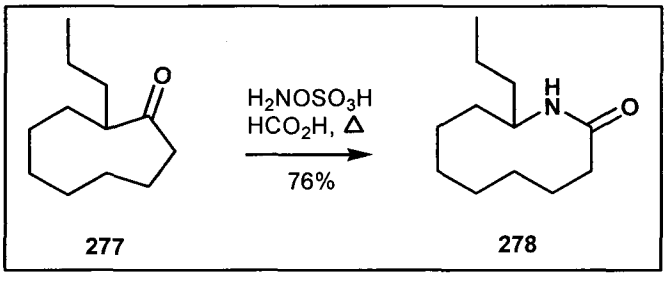
During the design and synthesis of active macrocyclic neutral endopeptidase (NEP) 24.11 inhibitors, MacPherson *et al.* used a simple ring expansion method for the synthesis of 10-membered ring lactams[191]. Treatment of 9-membered ring carbocycle **275** (Scheme 3.17) with sodium azide and methanesulfonic acid gave lactam **276**. This research led to several promising results including Johnson's work (explained in Section 3.3.1 above).

Scheme 3.17



In a report on the synthesis of Mexican bean beetles' defensive secretions, Gribble and Silva used a ring expansion method[192]. This reaction involves a hydroxylamine-*O*-sulfonic acid preparation from **277** in the presence of acetic acid (Scheme 3.18) followed by heating to afford lactam **278** in 76% yield. This is an example of the one-pot procedure reported by Olah in the late 1970s[193].

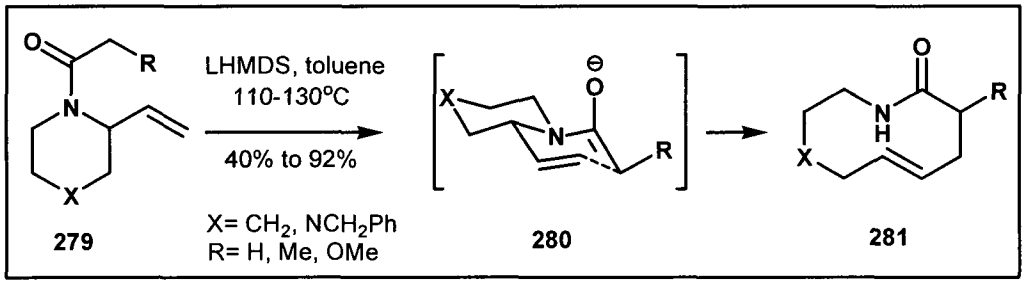
Scheme 3.18



Suh *et al.* in the synthesis of lactams with substitution at the α-position of the carbonyl used an Aza-Claisen rearrangement of amide enolate[194a]. As explained in Scheme 3.19, a ring expansion reaction of 1-acyl-2-vinylpiperidines or 1-acyl-

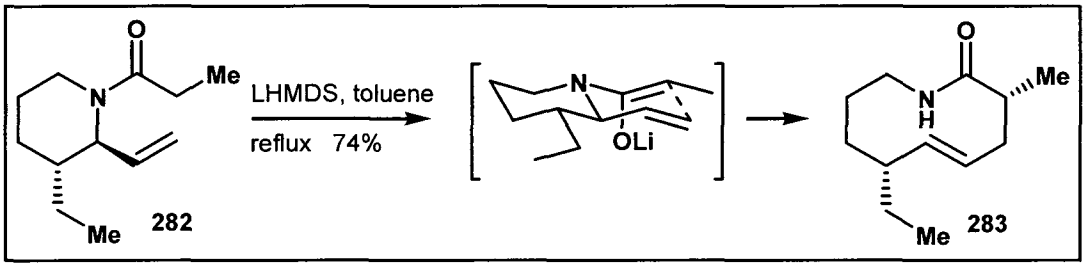
2-vinylpiperazines (**279**) occurred under heating with a strong base through aza-Claisen rearrangement of amide enolates **280**. The provided lactams **281** in moderate to excellent yield can introduce various substitutions at the α-position of the carbonyl moiety.

Scheme 3.19



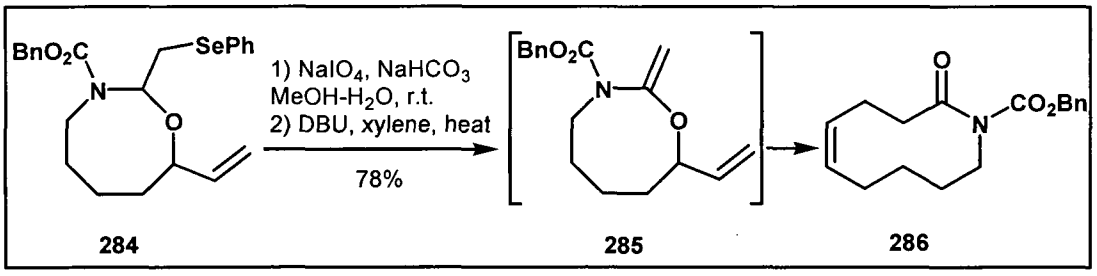
Suh *et al.* used this methodology in the total synthesis of fluvirucinine A_1[194b]. The identical conditions as described above afforded the desired lactam **283** (Scheme 3.20) from an aza-Claisen precursor **282** in 74% yield.

Scheme 3.20



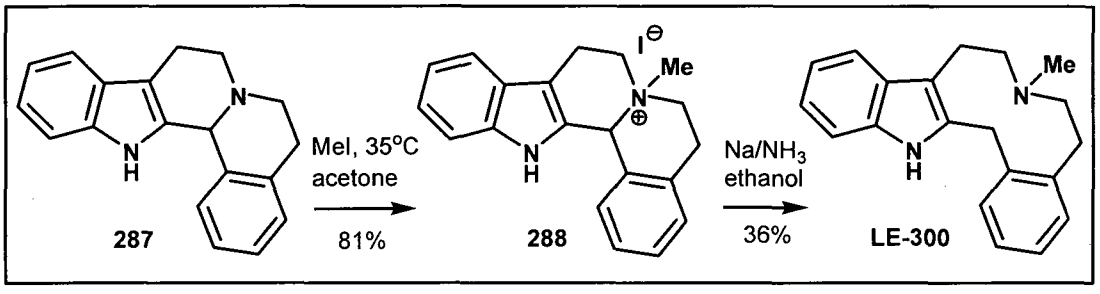
Evans and co-workers prepared an unsaturated 10-membered ring lactam by the Claisen rearrangement of the vinyl-substituted compounds and using 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU)[195]. Oxidation of selenide **284** (Scheme 3.21) with sodium periodate, followed by heating in the presence of DBU gave lactam **286** via a Claisen rearrangement of vinyl ketene aminal **285**.

Scheme 3.21



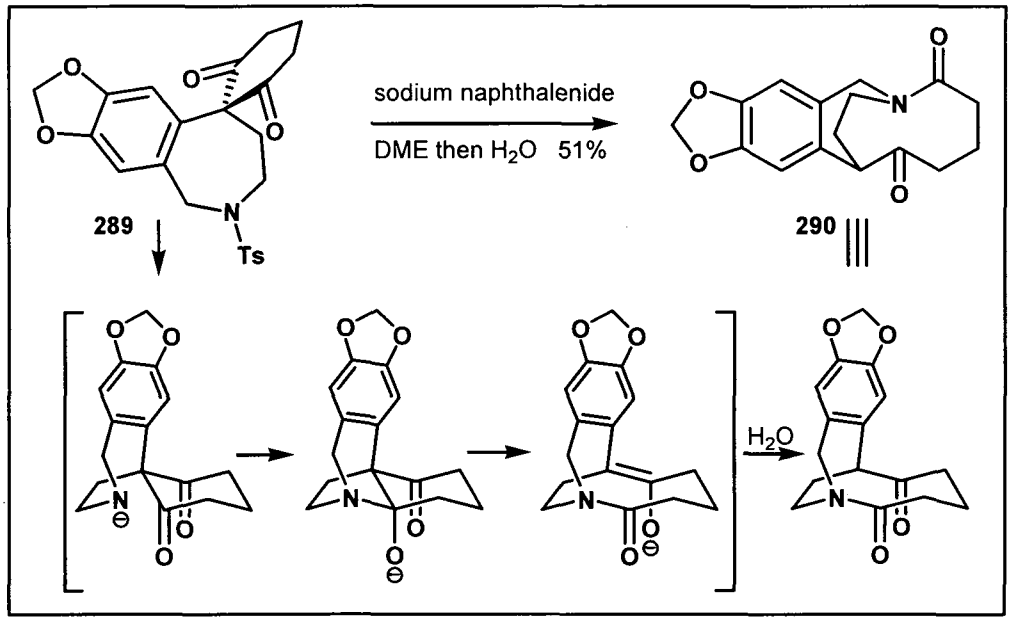
As pointed out in Section 3.2, LE-300 is found to be a dopamine antagonist. The strategy to synthesize this compound involves a ring expansion reaction[196]. *N*-methylation of pentacyclic **287** (Scheme 3.22) resulted in quaternary quinolizinium salt **288** with very good yield. Treatment of this intermediate with sodium in liquid ammonia induced ring expansion and afforded LE-300.

Scheme 3.22



An elegant synthesis of a cripowellin skeleton (see Section 3.2) by Moon and co-workers involved the construction of a 10-membered ring lactam as a key step[197]. Reaction of spiro(benzazepin-cyclohexadione)-*N*-tosyl amide **289** (Scheme 3.21) with sodium naphthalenide to remove the toluenesulfonyl group led to a ring expansion and observing the required unsaturated lactam **290**. Although it was expected the amine-form or hemiaminal-form observed in the reaction, the intermediate(s) underwent ring expansion, affording the desired ketolactam **290**.

Scheme 3.23



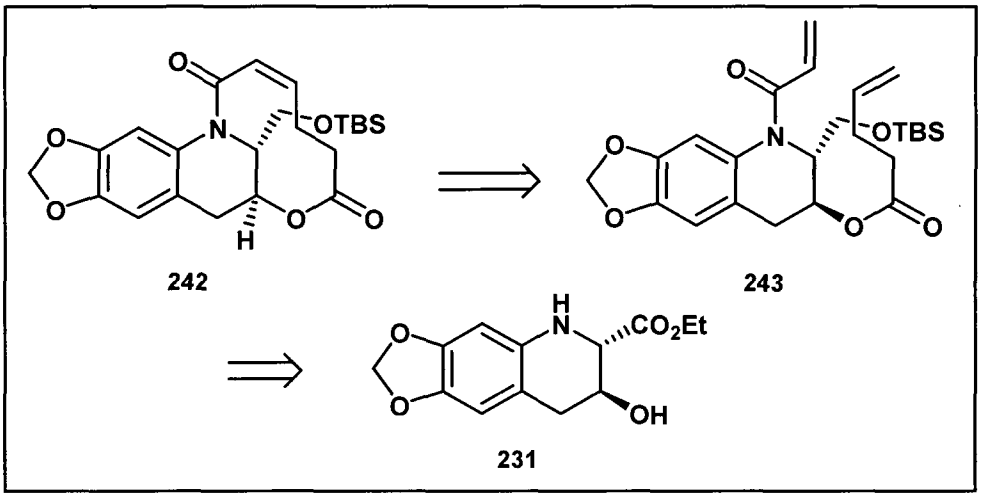
3.4 Our Synthesis Approach

As indicated in Section 3.1, both solution and solid phase synthesis of a tetrahydroquinoline polycyclic derivative with a ten-membered ring unsaturated lactam will be discussed here. Despite preceding the use of the RCM reaction in constructing 10-membered ring lactams by Katzenellenbogen (Scheme 3.10), our system is more complex; it is a tetracycle containing additional lactone functionality in its structure. Later Arya's group used this strategy to synthesize several 10-membered ring lactams in other systems[70,132]. Although the final key RCM reaction for both the solution and the solid phase synthesis is the same, different preparation steps were required. This is due to the fact that the necessary anchoring site for the solid phase exploration was not actually needed for the solution option and also the protection/deprotection steps were slightly different.

3.4.1 Model Study

Again, Scheme 3.24 outlined the strategy for this synthesis in the model study. It was expected that intermediate **243**, which could be prepared from our tetrahydroquinoline scaffold **231**, under RCM reaction would give the desired polycylic compound **242**. This polycyclic contains an α,β-unsaturated amide (lactam) moiety prone to Michael reaction. A hetero-Michael reaction performed on this Michael acceptor site; results are also provided here. Therefore, three subsections will present here: a) from tetrahydroquinoline scaffold to the precursor of RCM reaction, b) RCM reaction resulting in 10-membered ring lactam and c) hetero Michael reaction on this lactam.

Scheme 3.24

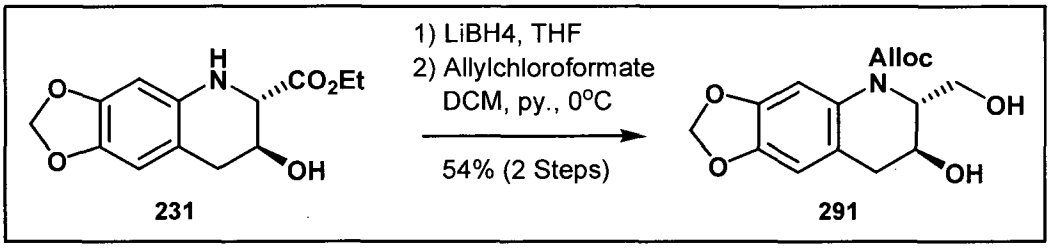


3.4.1.1 Synthesis of Precursor for RCM Reaction

For preparing the precursor needed for RCM reaction, secondary amine and alcohol in our tetrahydroquinoline scaffold should be modified considering the orthogonal nature of the protecting groups. On the other hand, if ethyl ester group reduces to primary alcohol, it will provide another active diversity site for further synthetic exploration. Therefore, this section contains the synthesis of the

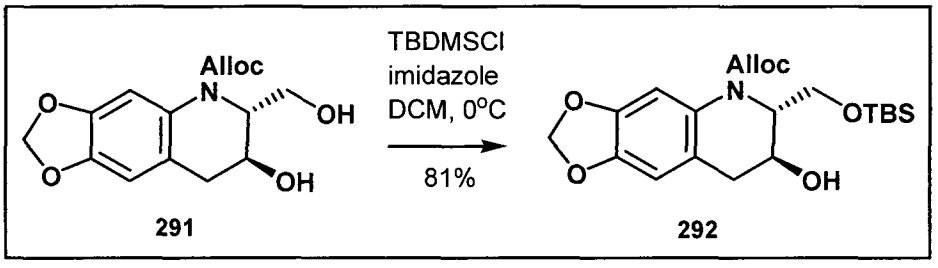
RCM precursor through manipulation of active sites. First, ethyl ester group in our scaffold **231** (Scheme 3.25) was reduced to primary alcohol (not shown) using lithium borohydride in THF. It was found that the provided amino diol was difficult for purification by column chromatography (very polar) and quite unstable. Therefore, it was decided that the next step would continue without complete purification of amino diol. Selective protection of the amino alcohol was performed using allylchloroformate in the presence of pyridine at 0°C to afford alloc-*N*-protected diol **291**. Purification by column chromatography was feasible then. Mass spectrum showed the peak 307.1 (M+1). The indicative peaks in ^{1}H and ^{13}C-NMR, such as olefinic protons [(5.95 ppm, m, 1H), (5.39 ppm, d, 1H), and (5.31 ppm, d, 1H)] and carbon in carbonyl position (155.5 ppm), also proved the correct synthesis.

Scheme 3.25



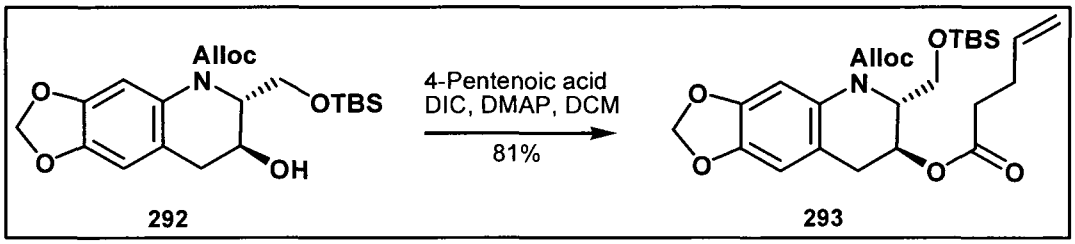
The primary hydroxyl group in diol **291** was selectively protected as *t*-butyl-dimethylsilyl **292** using TBDMSCl and imidazole at 0°C (Scheme 3.26). The reaction was clean and with high yield of 81%. Besides the precise mass of 422.2 (M+1), distinguishable peaks for TBS group in ^{1}H-NMR [(0.86 ppm, s, 9H), (0.05 ppm, d, 6H)] and ^{13}C-NMR (18.5 and -5.2 ppm) are the best proof of this transformation.

Scheme 3.26



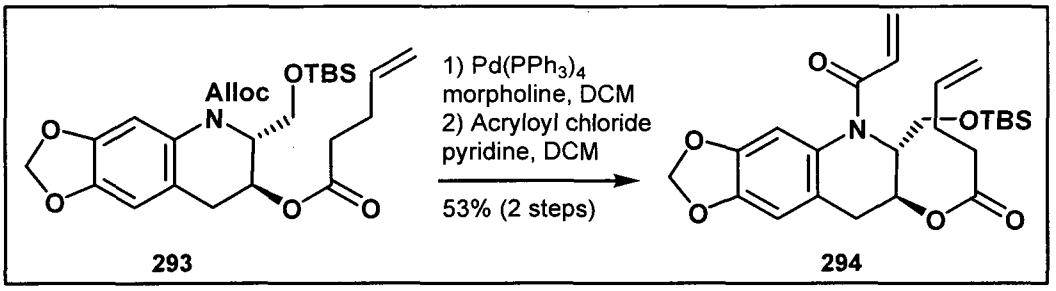
As the two terminal olefins (*i.e.* at position-1 and 3 of the tetrahydroquinoline) are needed for constructing the RCM precursor, secondary hydroxide at 3-position was first equipped with the required terminal olefin. This was performed by the coupling reaction between alcohol **292** (Scheme 3.27) and 4-pentenoic acid in the presence of DMAP and also *N,N'*-Diisopropylcarbodiimide (DIC) as carboxylic acid activator. High yield for **293** (81%) was observed in this reaction as well. Extra peaks for pentenoyl ester group in ^{1}H and ^{13}C-NMR (such as 172.6 ppm for carbonyl ester) showed the successful esterification.

Scheme 3.27



To install the second terminal olefin in nitrogen arm and synthesis of the desired precursor for RCM reaction, we had to replace *N*-alloc group with an acroyl group. For this aim, first the alloc group was removed by the treatment of compound **293** with Pd(0) catalyst in the presence of morpholine (Scheme 3.28). It was decided the next reaction would be performed without purification of the free amine. Therefore, the resulted free amine was subjected to acrylation with acryloyl chloride/py system in DCM to provide our required product **294** for the next step. Peak 474.2 (M+1) appeared in mass spectra and ^{1}H-NMR showed disappearance of methylene hydrogens in O-CH_2-vinyl (of alloc group) around 4.8 ppm

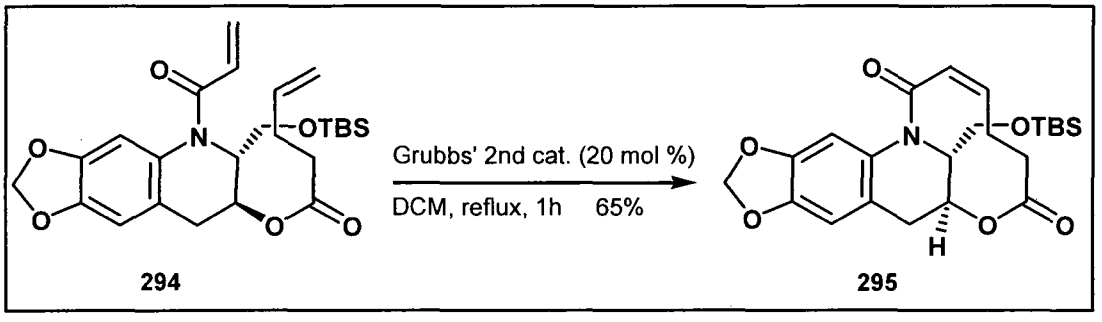
Scheme 3.28



3.4.1.2 RCM Reaction to 10-membered Ring Lactam

With RCM precursor **294** in hand, the first attempt was performed using Grubbs' 1st generation catalyst in DCM and reflux. No apparent progress in the reaction was noted after 1 hour and starting material stayed intact. However, with the same conditions and when Grubbs' 2nd generation catalyst was used instead, a considerable improvement including the appearance of a new spot in TLC was seen after one hour (Scheme 3.29). Work up and subsequent purification, resulted in the formation of a light green solid (**295**) and a small amount of recovered starting material. First sign of the successful reaction was proved by mass peak of 446.4 (M+1) which also showed M-28 from RCM precursor, meaning an ethylene molecule (a reliable indication in a successful RCM reaction) left the molecule.

Scheme 3.29



This product, found as our tetrahydroquinoline having 10-membered ring lactam, was extensively examined by 1D [^{1}H-NMR, ^{13}C-NMR (DEPT)], 2D NMR (COSY, HSQC) and X-ray crystallography. Figure 3.3 shows COSY and ^{1}H/^{1}H coupling. Hydrogen correlations in the right hemisphere of the molecule showed in RED and BLUE. Based on these correlations, possible location of each proton was identified (in numbers).

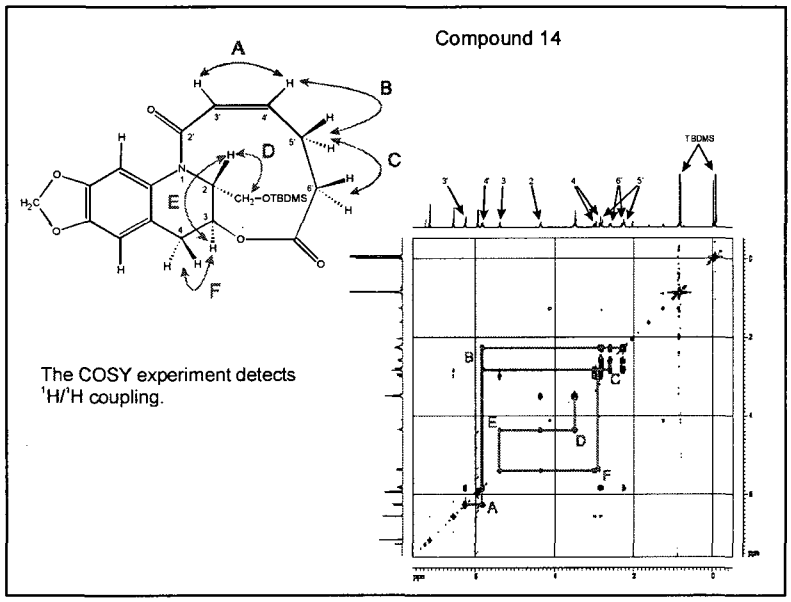


Figure 3.3 COSY of Compound **295** Showing H Correlations

With this information in hand, we were able to make initial assignment for proton signals (please see Figure 3.4).

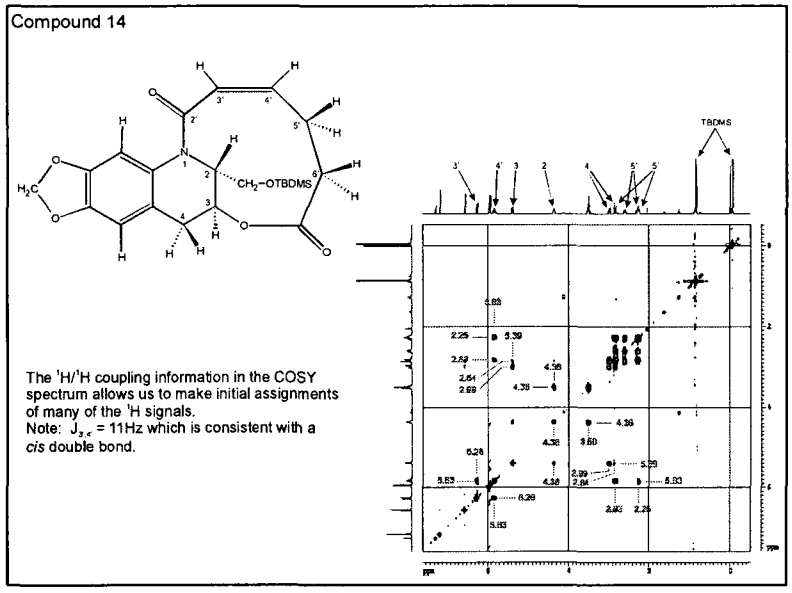


Figure 3.4 Proton Assignments for Compound **295** Using COSY

The information from ^{1}H-NMR and COSY allowed us to find ^{1}H chemical shifts. Chemical shifts are shown in Figure 3.5 in RED. Moreover, coupling constant of *J*= 11.5 Hz (found in ^{1}H-NMR) showed the *cis* proton relationship around the double bond.

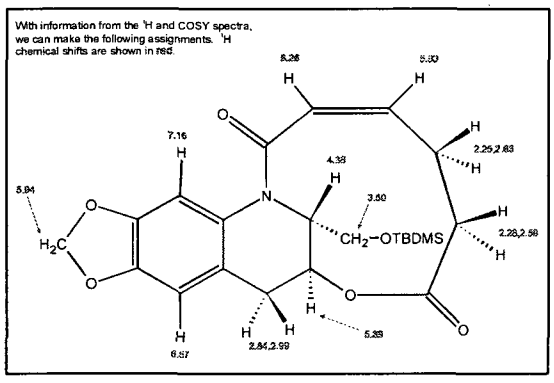


Figure 3.5 Chemical Shifts for Compound **295**

Another 2D experiment, i.e., HSQC provides $^{1}H/^{13}C$ correlations. It guides us to assign ^{13}C signals for all carbons, which have attached protons. Figure 3.6 shows ^{1}H chemical shifts in RED and ^{13}C chemical shifts in BLUE.

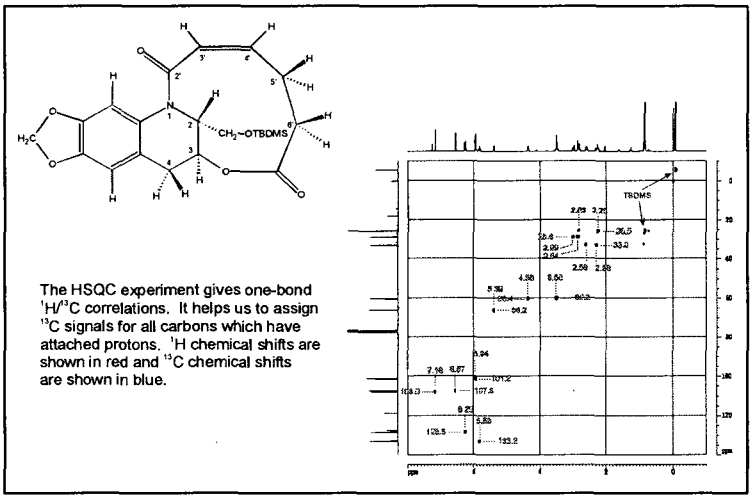


Figure 3.6 ^{1}H and ^{13}C Chemical Shifts Using HSQC

Finally, with information from all these experiments, we were able to assign all carbons that have attached protons. ^{1}H chemical shifts in RED and ^{13}C chemical shifts in BLUE are shown in Figure 3.7 (except in TBS group and for carbons having no attached hydrogen).

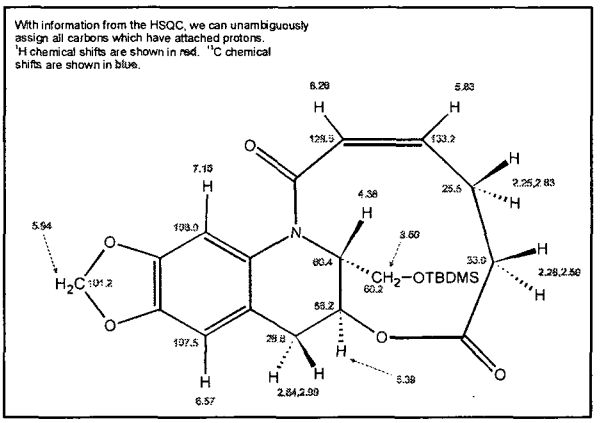


Figure 3.7 Final Assignment of Chemical Shifts Using all Experiments

Bright crystalline solid encouraged us to try recrystallization and a possible X-ray crystallography. After several attempts, and luckily enough, we were able to recover a crystal ideal for X-ray crystallography. X-ray structure of compound **295** is shown in Figure 3.8. From the X-ray structure, it appears the 10-membered ring is projected out of the tetrahydroquinoline plane and the double bond is not aligned with the amide functional group.

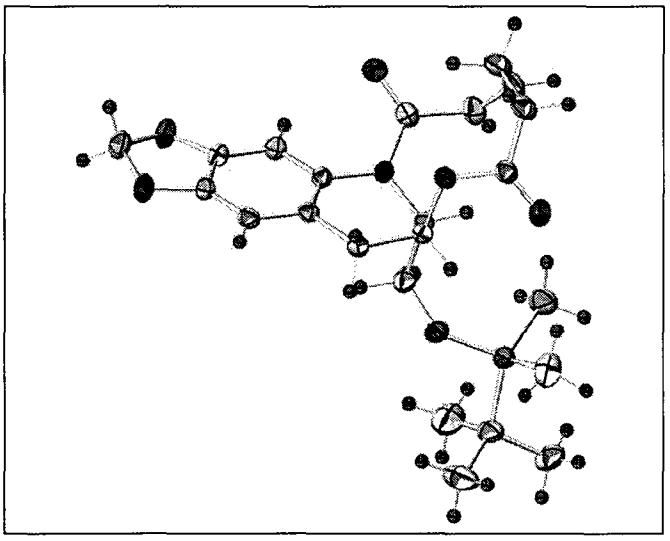


Figure 3.8 X-ray Structure of Compound **295**

Crystal data of compound **295** is presented in Table 3.1.

Table 3.1 Crystal Data for Compound **295**

Identification code	shah1
Empirical formula	$C_{23}H_{31}NO_6Si$
Formula weight	445.58
Temperature	173(2) K
Wavelength	0.71070 Å
Crystal system	Monoclinic
Space group	P2(1)

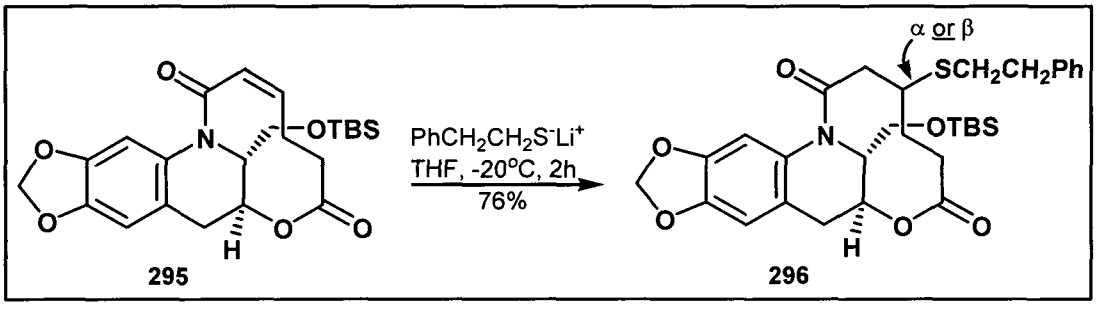
Unit cell dimensions	a = 7.1242(4) Å	α= 90°.
	b = 10.3236(5) Å	β= 99.4260(10)°
	c = 15.8881(8) Å	γ = 90°
Volume	1152.75(10) $Å^3$	
Z	2	
Density (calculated)	1.284 Mg/m^3	
Absorption coefficient	0.140 mm^{-1}	
F(000)	476	
Crystal size	0.5 x 0.4 x 0.15 mm^3	
Theta range for data collection	2.36 to 29.58°	
Index ranges	-9<=h<=9, -14<=k<=14, -21<=l<=22	
Reflections collected	14543	
Independent reflections	6357 [R(int) = 0.0165]	
Completeness to theta = 29.58°	99.5 %	
Absorption correction	Multiscan	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6357 / 1 / 280	
Goodness-of-fit on F^2	0.933	
Final R indices [I>2sigma(I)]	R1 = 0.0338, wR2 = 0.0901	
R indices (all data)	R1 = 0.0368, wR2 = 0.0925	
Absolute structure parameter	0.04(8)	
Largest diff. peak and hole	0.341 and -0.183 $e.Å^{-3}$	

3.4.1.3 Hetero Michael Reaction on Lactam

One of the reactions we tried on our polycyclic compound was Michael addition. In spite of milder activity of lactam (amide) functionality in Michael addition compared with other carbonyl compounds, this α,β-unsaturated lactam still should be active as Michael acceptor. Treatment of our lactam with benzenethiol, benzylthiol, and phenylethanethiol in the presence of triethylamine showed no progress as hetero(thio) Michael reaction. We believed if thiol was first deprotonated and then added to our lactam, the reaction may proceed better. Therefore, we treated phenylethanethiol with *n*-butyl lithium at -78°C in THF and then, while stirring, let it to get warm to room temperature during 16 hours. This

mixture containing lithium phenylethanethiolate (salt) then added to our lactam **295** (Scheme 3.30). After 2 hours, starting material disappeared and new spot completed (checking by TLC). Mass spectrum, as the primary sign of the successful reaction, showed us the peak of 584.2 (M+1 for **296**). It should be noted the same procedure with benzenethiol and benzylthiol had no reaction likely because of steric hindrance accompanying them.

Scheme 3.30



Similar to our polycyclic compound, we performed extensive characterization for this thio product including 1D and 2D NMR. Unfortunately, due to the possibility of multiple conformations that the product could adopt, we were not able to assign the stereochemistry for this addition reaction. We also observed many broad peaks in ^{1}H-NMR that made our assignment more difficult (Figure 3.9).

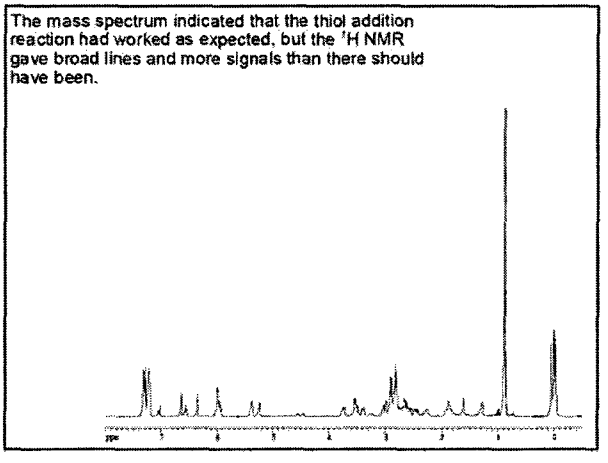


Figure 3.9 ^{1}H-NMR Spectrum for Thio Compound **296**

We also performed NOESY experiment. As shown in Figure 3.10, we highlighted some of the cross-peaks arise from chemical exchange as opposed to proximity through space (marked in RED).

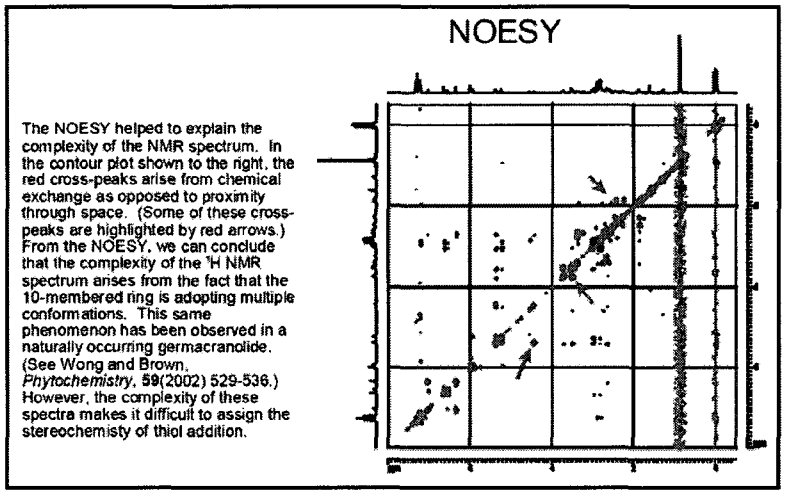


Figure 3.10 NOESY Spectrum for Thio Compound **296**

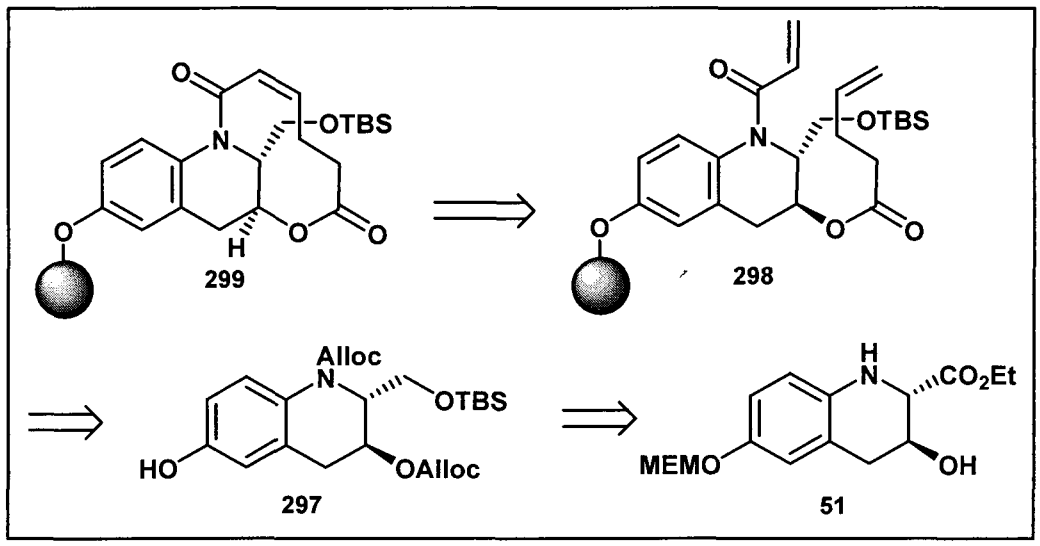
Although encountered problems made our assignment difficult, we were still able to characterize compound **296**. For instance, we found 41 protons in ^{1}H-NMR and 26 carbons in ^{13}C-NMR matching with our product. Moreover, carbonyls and aromatic carbons were shown clearly in ^{13}C-NMR. We should mention here that only one compound recovered from column chromatography, which previously noted in TLC during the course of the reaction. Therefore, attack of the thiol salt to the Michael acceptor site of the molecule occurred stereoselectively and only one product was prepared. It is also worthy to mention that several other researchers in Arya's group performed this methodology (addition of thiol salt) in their hetero Michael reaction[75,132,198].

3.4.2 Solid Phase Synthesis

To the best of our knowledge, the solid phase synthesis of a polycyclic compound containing a10-membered ring unsaturated lactam has never been reported. However, later, several other researchers in our group prepared

compounds with a variety of ring size (including 10-membered ring). For developing a solid-phase synthesis project, we needed compound **297** (Scheme 3.31), in which the phenolic hydroxyl moiety utilized as an anchoring site for the solid phase. Since all three arms in tetrahydroquinoline **51** will be used in solid phase stages, there is a need for orthogonal protection of free amine, free hydroxyl, and also ester (reduced to alcohol) moiety. Therefore, fully protected tetrahydroquinoline was prepared. An enantioselective solid phase synthesis of compound **299** was developed with an approach similar to that discussed earlier in the model study (section 3.4.1). The solid phase synthesis of compound **299** was achieved in a few steps from **51** in three main stages: (1) synthesis of the precursor **297** (2) loading and solid phase synthesis of compound **299**, and (3) cleavage from the solid support.

Scheme 3.31

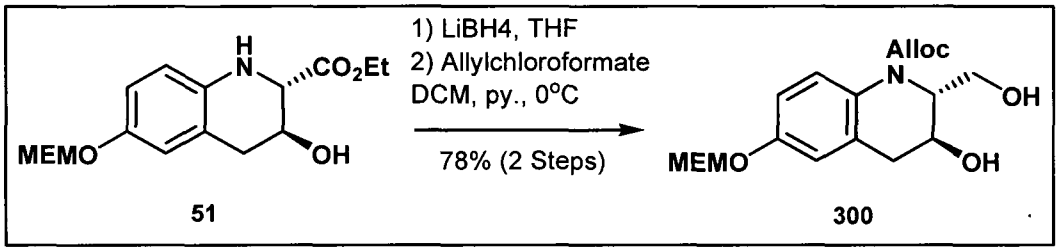


3.4.2.1 Synthesis of Precursor Having Anchoring Site

This series of reactions are similar to the previous ones in solution phase. Ethyl ester group in tetrahydroquinoline **51** (Scheme 3.32) reduced to primary alcohol using lithium borohydrate in THF. Next step proceeded without complete

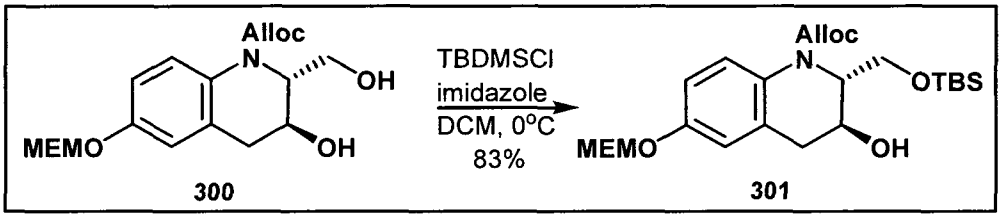
purification of amino diol. Selective protection of the amino alcohol performed using allylchloroformate in the presence of pyridine at 0°C to afford alloc-*N*-protected diol **300**. The indicative peaks in ^{1}H-NMR, such as olefinic protons [(5.91 ppm, m, 1H), (5.33 ppm, d, 1H), and (5.27 ppm, d, 1H)] proved the right reaction. Compared with the model study, yield was good (78%).

Scheme 3.32



Primary hydroxyl group in diol **300** selectively protected as *t*-butyl-dimethylsilyl using TBDMSCl and imidazole at 0°C (Scheme 3.33) to afford alcohol **301** in 83% yield. Again, besides the correct mass of 482.3 (M+1), TBS peaks in ^{1}H-NMR [(0.87 ppm, s, 9H), (0.06 ppm, d, 6H)] and ^{13}C-NMR (18.5 and -5.1 ppm) are the best proof for the correct synthesis.

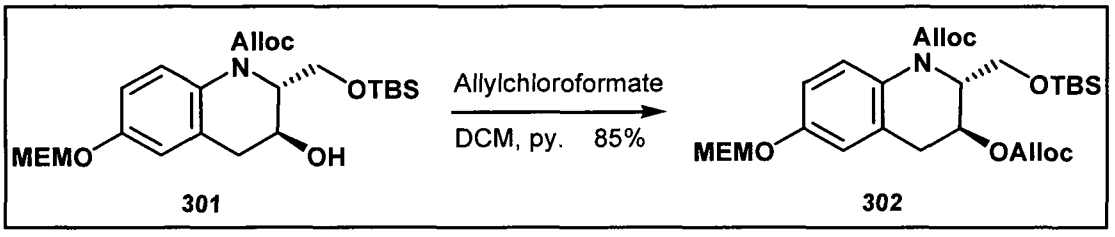
Scheme 3.33



Since the precursor for solid phase synthesis was better to have one free hydroxyl group for high yield loading, it was decided that the remaining secondary hydroxyl group in **301** would be also protected. Therefore, the remaining hydroxyl group was protected as alloc (Scheme 3.34). The reaction proceeded smoothly and gave the fully protected tetrahydroquinoline **302** in 85%

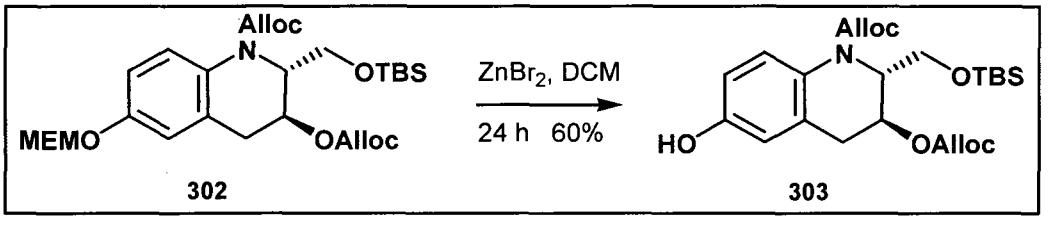
yield. It was quite straightforward to make sure we reached to the right compound by looking at ^{13}C-NMR spectrum. The noted peaks at 155.1 and 154.5 ppm suggested that two carbonyls (in alloc groups) existed.

Scheme 3.34



Last step in the preparation of the solid phase precursor was the MEM removal from **302** to afford the free phenolic hydroxyl (**303** in Scheme 3.35). Several reagents and conditions, including the routine method with *p*-TSA/ethanol, were used to deprotect the phenolic oxygen. Since TBS was also prone to removal in acidic media, the use of acids was performed with care. The best result we gained was MEM removal using zinc bromide (as Lewis acid) in DCM. Sluggish reaction and low yield, however, were considered drawbacks in this method.

Scheme 3.35

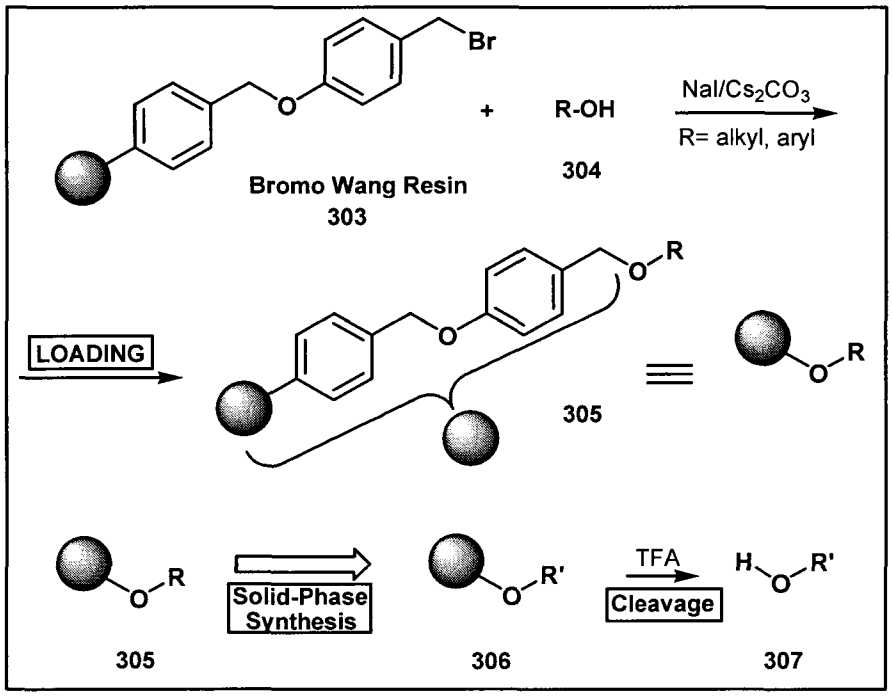


3.4.2.2 Loading and Solid Phase Synthesis of 10-membered Ring Lactam

With the precursor in hand, we were able to perform the loading. For loading, we used bromo Wang resin **303** (Scheme 3.36), in the solid phase synthesis[199a]. It is one of the commonly utilized solid supports for carboxylic acids and for alcohols (phenols). The linker is attached to the resin through a phenyl ether bond and the

phenolic substrate is bound to the linker by an ether bond. Loading can be achieved by treatment of the resin with phenolic compound **304** (or alcohol) in the presence of sodium iodide and cesium carbonate. The linkage is quite stable in a variety of reaction conditions but cleaves by the short treatment with an acid, normally TFA. Therefore, after solid phase reaction steps (**305** to **306**), the desired compound **307** will be formed by cleavage using TFA. It should be noted that between each step in solid phase reactions, several washing with different kind of solvents must be performed. Obviously, it removes all unused reagents and prepares the resin for the next reaction.

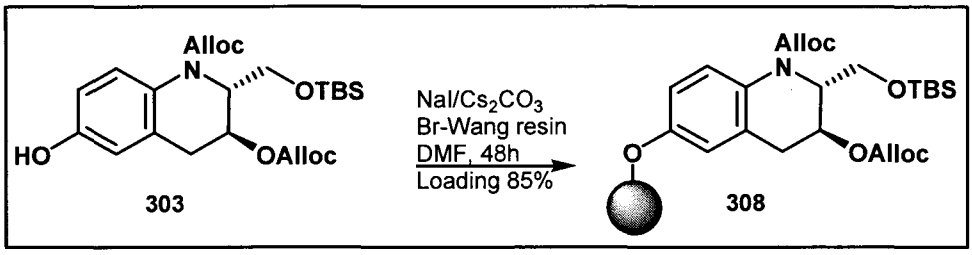
Scheme 3.36



Compound **303** (Scheme 3.37) was immobilized onto the solid support using the conditions mentioned above. For better loading, one equivalent of resin with two equivalents of the substrate was stirred for 48 hours. Remaining starting material (purified by column chromatography) pointed out the loading succeeded with 85% yield. The resin **308** was used as the starting material in our solid phase synthesis. It should be mentioned that products in each step were confirmed by

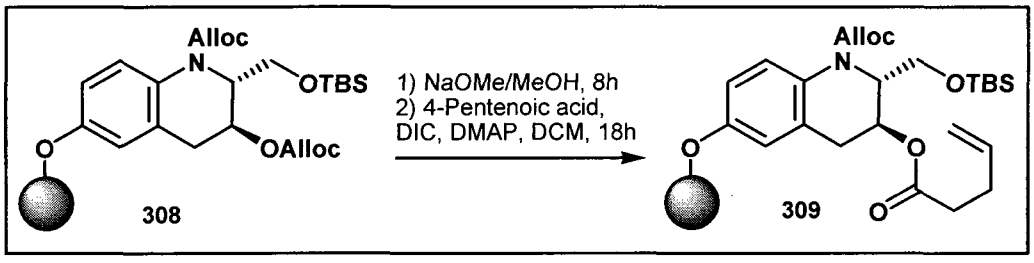
mass spectrum. This can be easily performed by quick cleavage of a small portion of the resin (around 1 mg).

Scheme 3.37



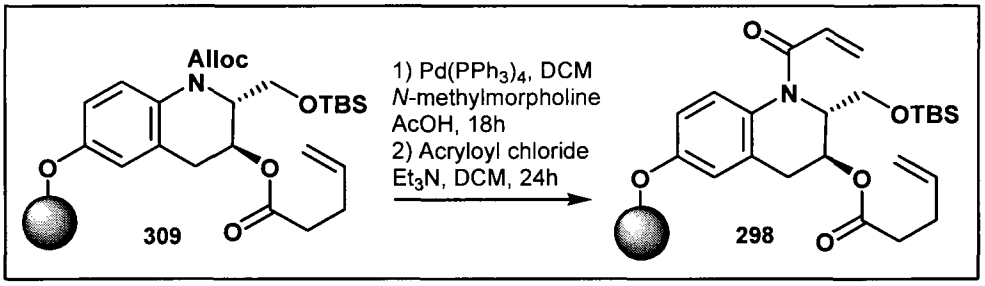
Few steps in solid phase were needed to supply our target **298** (Scheme 3.31). As showed in scheme 3.38, basic conditions were used for *O*-alloc removal from **308** giving free secondary hydroxyl group in the substrate (not shown). Coupling conditions were used for the attachment of one of our required arms for the RCM reaction (resin **309**).

Scheme 3.38



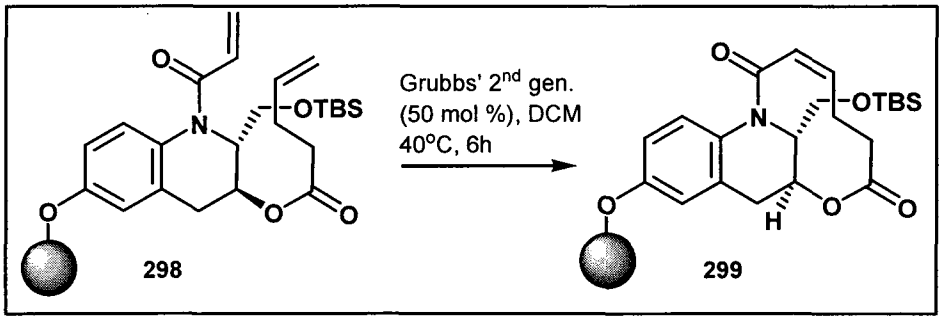
N-Alloc then removed from resin **309** (Scheme 3.39) by palladium(0) in the presence of *N*-methylmorpholine and the resulting free amine then acrylated to provide our second arm needed for RCM reaction (resin **298**).

Scheme 3.39



RCM reaction was performed using second-generation Grubbs' catalyst (Scheme 3.40) at 40°C and in 6 hours. We believed the reaction must be finished after 6 hours since the corresponding model study compound completed in 1 hour. However, mass spectrum revealed our correct guess. We were able to synthesize the tricyclic compound having 10-membered ring α,β-unsaturated lactam in solid phase for the first time (resin **299**). Despite this, we had to cleave the resin and characterize the final product.

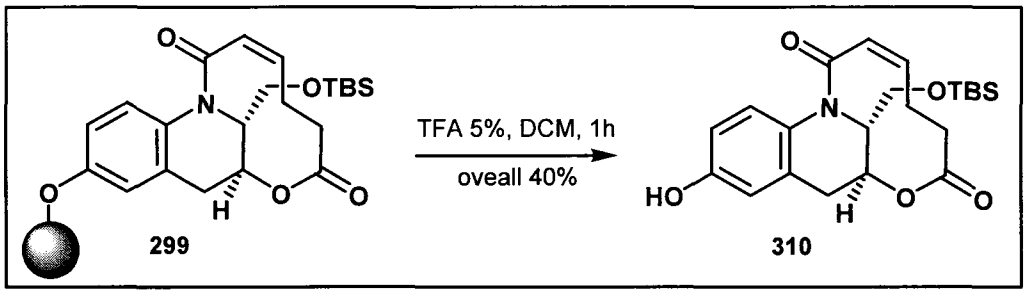
Scheme 3.40



3.4.2.3 Cleavage

Treatment of the resin **299** (Scheme 3.41) with 5% TFA for 1 hour was enough for cleavage. Purification of tricyclic **310** by flash column chromatography, although showed a blurred spot in TLC, provided the overall yield of 40% (5 steps). This meant average 83% for each step. For proper characterization, compound **310** was extensively studied by 1D and 2D NMR as follows.

Scheme 3.41



Using 2D NMR, i.e., COSY and HSQC, we were able to verify the presence of compound **310**. As shown in Figure 3.11, we assigned all the protons in the molecule (in RED). The *cis* relationship around the double bond confirmed by the coupling constant of J= 11.6 Hz.

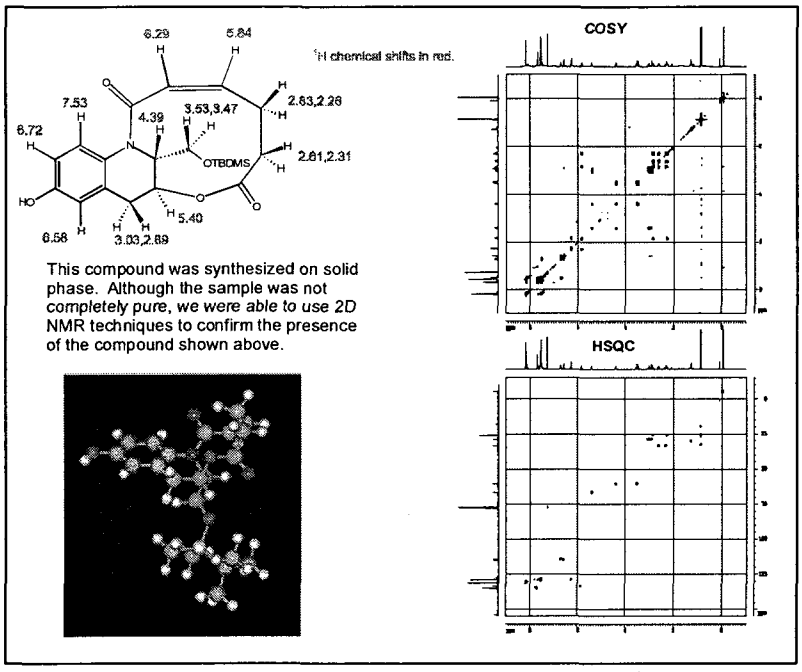


Figure 3.11 Proton Assignment for Compound **310** Using 2D NMR

Similar to model study, COSY enabled us to find the relationship between protons in RED and BLUE as shown in Figure 3.12.

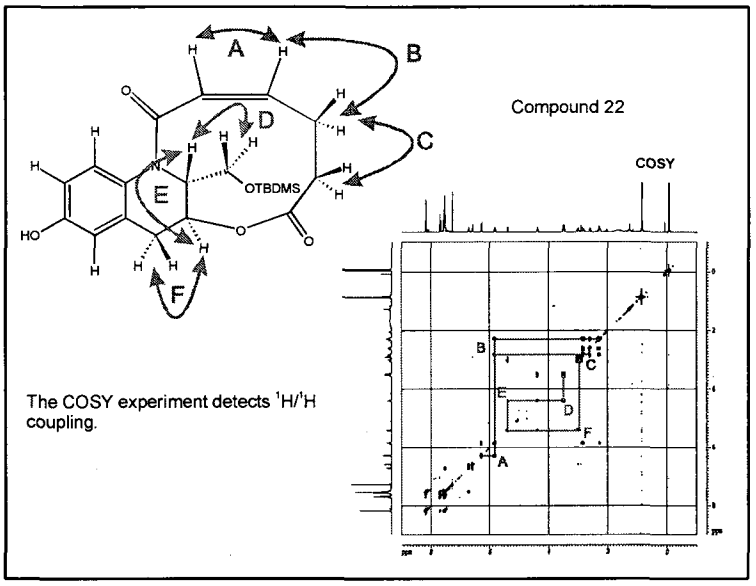


Figure 3.12 Revealing $^1H/^1H$ Coupling by COSY

Similarity of COSY spectrum with the one in model study (Figure 3.13) was also convincing enough for the successful solid phase synthesis.

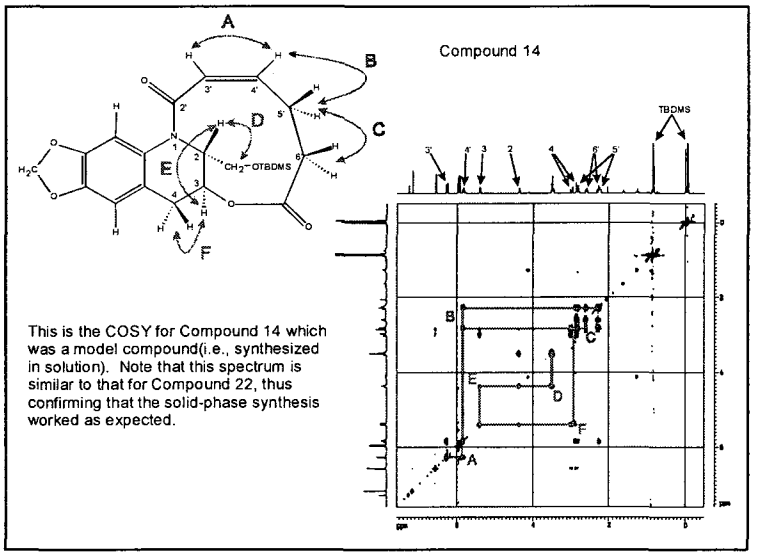


Figure 3.13 Pattern Likeness at Compound Made in Solution Phase

Finally, for better comparison between two COSY spectra, it is useful to show those results side-by-side (Figure 3.14) followed by their superimposed version (Figure 3.15).

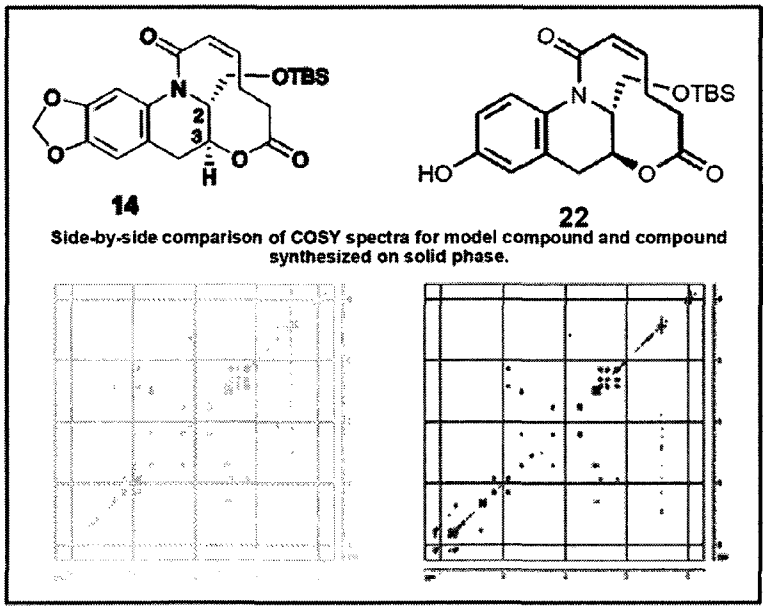


Figure 3.14 Side-by-Side Comparison of COSY Spectra

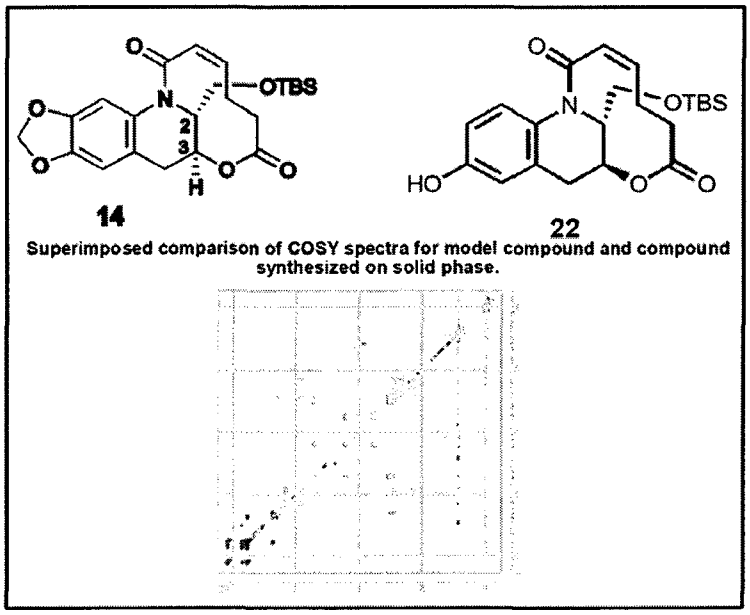


Figure 3.15 Superimposed Comparison of COSY Spectra

4: Solution and Solid Phase Synthesis of Tetrahydroquinoline Polycyclics. Part B: α,β-Unsaturated γ-Lactam and δ-Lactone

4.1 Design Strategy

As noted in Chapter 1, in addition to tetrahydroquinoline polycyclics (discussed in the previous chapter) we were also interested in developing a practical enantioselective synthesis of tetrahydroquinoline-based polycyclics containing α,β-unsaturated γ-lactam (**54**) and δ-lactone (**55**) (Scheme 2.1). These two building blocks have unique features: The presence of two orthogonal functional groups (i.e. hydroxyl or amine, and the α,β-unsaturated carbonyl) in γ-lactam **54** (*O*-3 position) and δ-lactone **55** (*N*-1 position) respectively, could also be utilized to build complexity by diversification. The particular polycyclics we are discussing in this chapter, the tricyclic compounds pyrrolo[1,2-*a*]quinoline (**311**) and pyrano[3,2-*b*]quinoline (**312**), are presented in Figure 4.1.

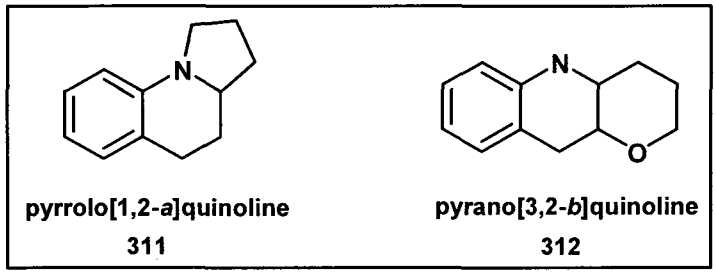
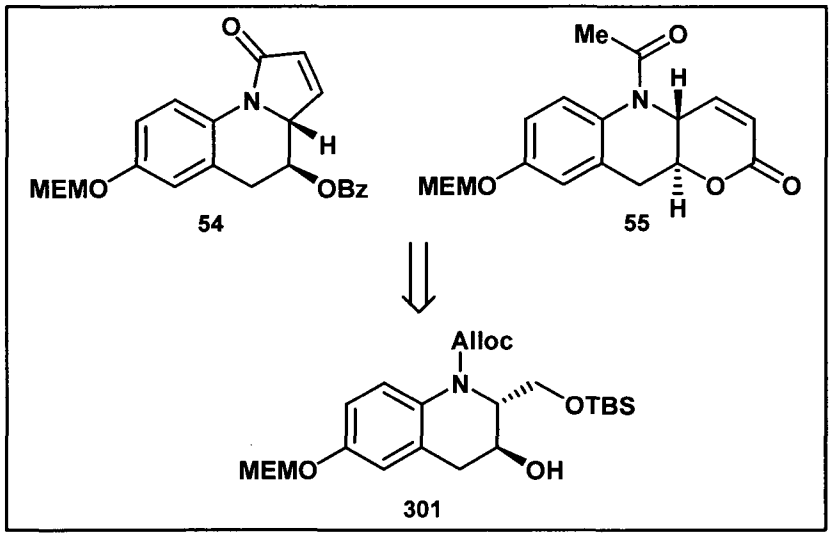


Figure 4.1 Tricyclic Systems Presenting in This Chapter

This chapter will discuss solution and solid phase synthesis of our pyrroloquinoline, and solution phase synthesis of pyranoquinoline[199b]. As illustrated in Scheme 4.1, tetrahydroquinoline-based tricyclic containing α,β-unsaturated γ-lactam (**54**) and δ-lactone (**55**) were prepared from our tetrahydroquinoline scaffold (**301**), the synthesis of which was explained in Section 3.4.2.1.

Scheme 4.1



4.2 Pyrrolo[1,2-*a*]quinolines as Natural and Pharmaceutical Products

Two schizozygane alkaloids, isoschizogaline and isoschizogamine (Figure 4.2), showed antibacterial and antifungal activities, respectively[200]. These compounds are extracts of the monotypic shrub *Schizozygia coffaeoides*, a plant used in traditional Kenyan medicine to treat skin diseases.

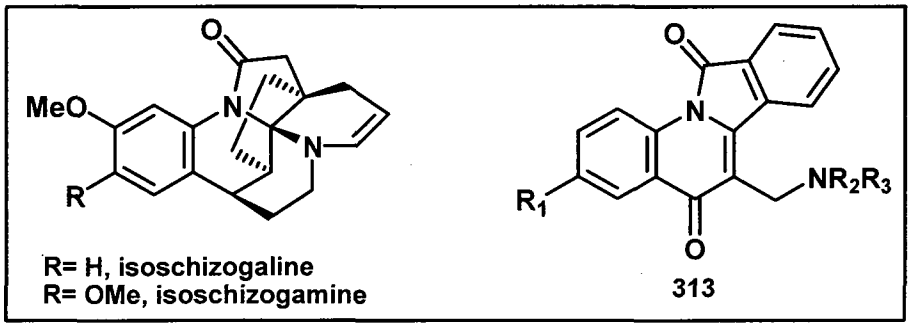


Figure 4.2 Interesting Compounds Having Pyrrolo-, Isoindoloquinoline Systems

Interestingly, synthetic compounds known as 5, 11-dioxosubstituted isoindolo-[2,1-*a*]quinolines **313** have protective effects against N_2-induced hypoxia[201]. We

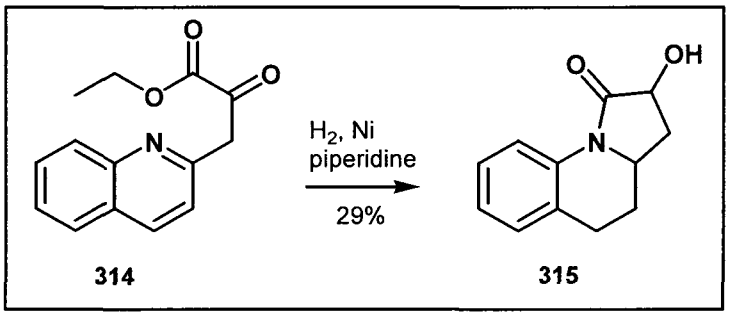
will re-examine the isoindolo[2,1-*a*]quinoline system in Chapter 5, and explore its chemistry more comprehensively.

4.3 Synthesis of Pyrrolo[1,2-*a*]quinolines and Pyrano[3,2-*b*]quinolines in Literature

In this section, few synthetic methods of pyrrolo[1,2-*a*]quinolines(and -1-one) will be reviewed. Former and later stages of the synthesis will not be covered but only the pyrroloquinoline system. It reviews the literature from 1960-2006. However, only few examples are provided. Unlike previous chapters, the methodologies will not be classified because of their limited instances. In spite of effort made to include most methods, this section is not considered comprehensive.

An early attempt for the synthesis of pyrroloquinoline-1-one was performed by Baumgarten and co-workers[202]. 2-hydroxy-3,3a,4,5-tetrahydropyrrolo[1,2-*a*]-quinoline-1(2*H*)one (**315**, Scheme 4.2) was prepared in one pot reaction from ethyl β-(2-quinolyl)-pyruvate **314** by the combined a) pyridine hydrogenation, b) keto carbonyl reductive amination by piperidine, and c) 5-membered ring closure.

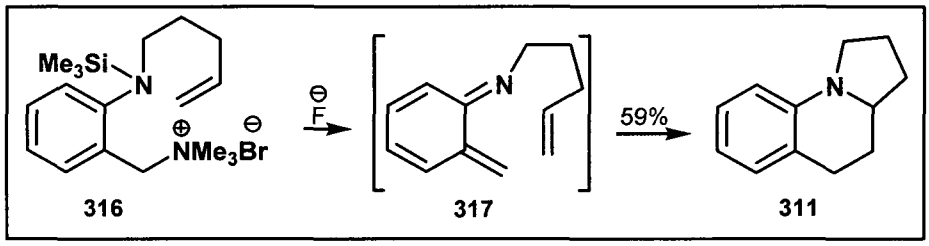
Scheme 4.2



Twenty years later and in a novel approach, Saegusa and co-workers synthesized pyrroloquinoline **311** (Scheme 4.3) by the fluoride anion induced intramolecular aza Diels-Alder reaction[203]. *Ortho*-quinone methide *N*-alkenylimine

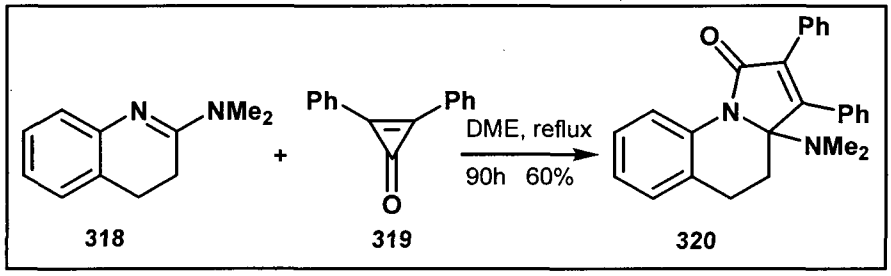
intermediate **317**, from fluoride induced 1,4-elimination of **316**, underwent the key Diels-Alder reaction to afford **311** in 59% yield. Later, Storr *et al.* performed this method by using 'flash vacuum pyrolysis' affording several other systems in moderate yields[204,205].

Scheme 4.3



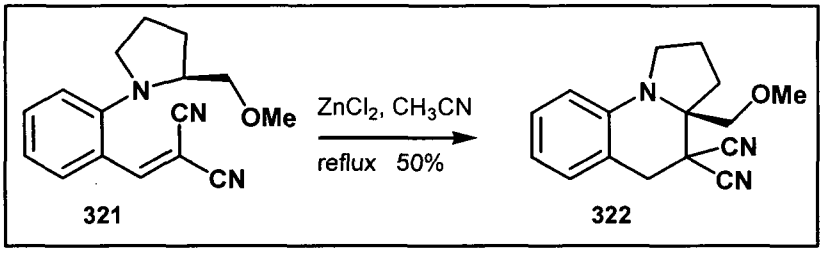
Rohde and Eicher used the [3+2] cycloaddition reaction of diphenylcyclopropenone **319** (Scheme 4.4) with cyclic amidine **318** for preparing pyrroloquinolone **320**[206]. Compound **320** shares its α,β-unsaturated γ-lactam moiety with our target (**54**).

Scheme 4.4



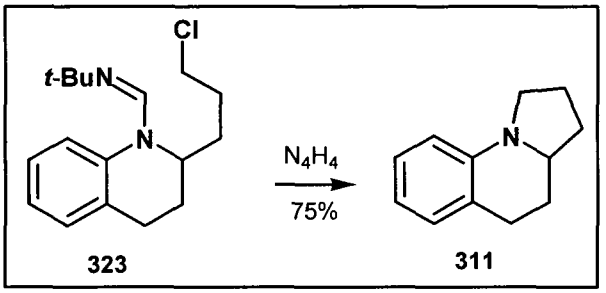
Reinhoudt *et al.* performed an interesting structural investigation in pyrrolo[1,2-*a*]quinolines[207-208]. They proved the long π-system (donor-π-acceptor) is inherently chiral and pyrrolidine ring is forced slightly (around 10°) out of plane. In cyclization reaction shown in Scheme 4.5, only one of the enantiomeric donor-π-acceptor systems of compound **322** was formed. This is due to asymmetric induction of the chiral atom in the pyrrolidine ring of **321**.

Scheme 4.5



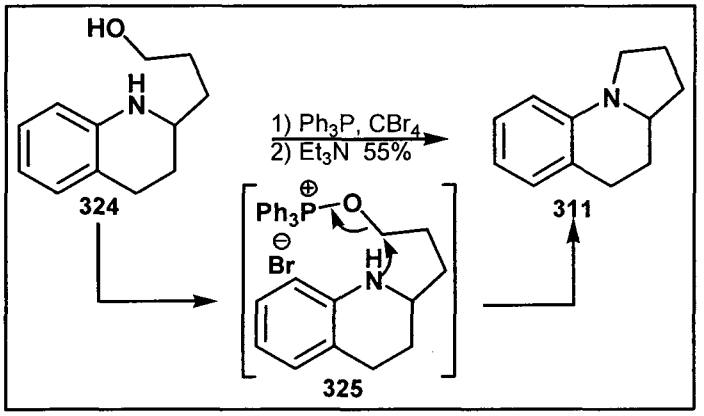
Meyers and Milot prepared scaffold **311** (Scheme 4.6) by hydrazinolysis of tetrahydroquinoline **323**[209]. Generated free amine intermediate is responsible for the observed cyclization.

Scheme 4.6



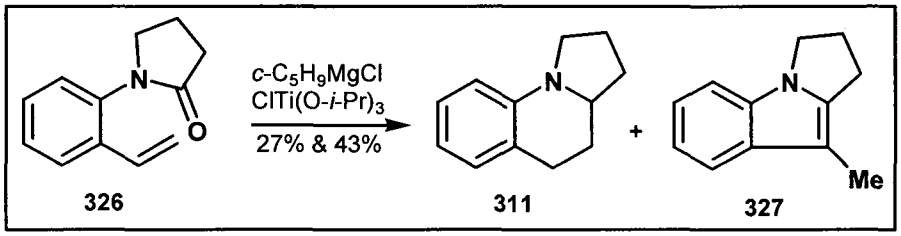
Compound **324** (Scheme 4.7) underwent intramolecular cyclodehydration via alkoxyphosphonium salt **325** to create compound **311**[210]. The observed yield (55%) was moderate compared to indole system (87%).

Scheme 4.7



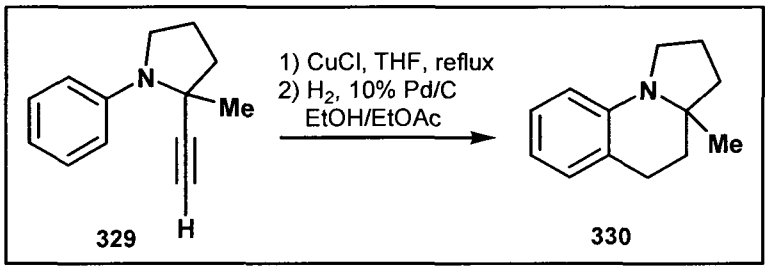
Cha *et al.* prepared **311** (Scheme 4.8) from titanium-mediated coupling of ω-vinyl lactam **326**[211]. Compound **326** upon reaction with cyclopentylmagnesium chloride in the presence of triisopropyltitanium (VI) chloride produced di-*i*-propoxytitana-cyclopentane intermediate which upon ring opening converted to **327** (43%) and **311** (27%). It was believed that the methyl group in **327** derived from reductive elimination of the hydridotitanate intermediate and not from hydrolysis of Ti-C bond.

Scheme 4.8



During research for finding nonsteroidal antiandrogenic pharmacophores (androgen receptor antagonists), Hamann *et al.* synthesized pyrroloquinoline **330** (Scheme 4.9) by copper-chloride cyclization of trisubstituted propargyl **329** (2-methyl-1-phenylpyrrolidine propargyl) following catalytic hydrogenation[212].

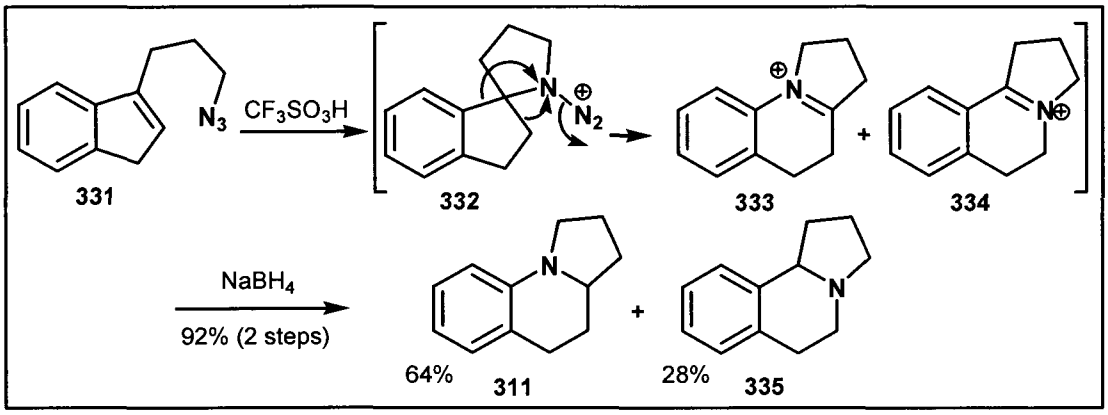
Scheme 4.9



Pearson and Fang reported the synthesis of pyrroloquinoline **311** along with pyrroloisoquinoline **335** with the method explained in Scheme 4.10[213]. Iminium ions **333** and **334**, prepared from treatment of azido compound **331** with trifluoromethanesulfonic acid, under *in situ* reduction with sodium borohydride

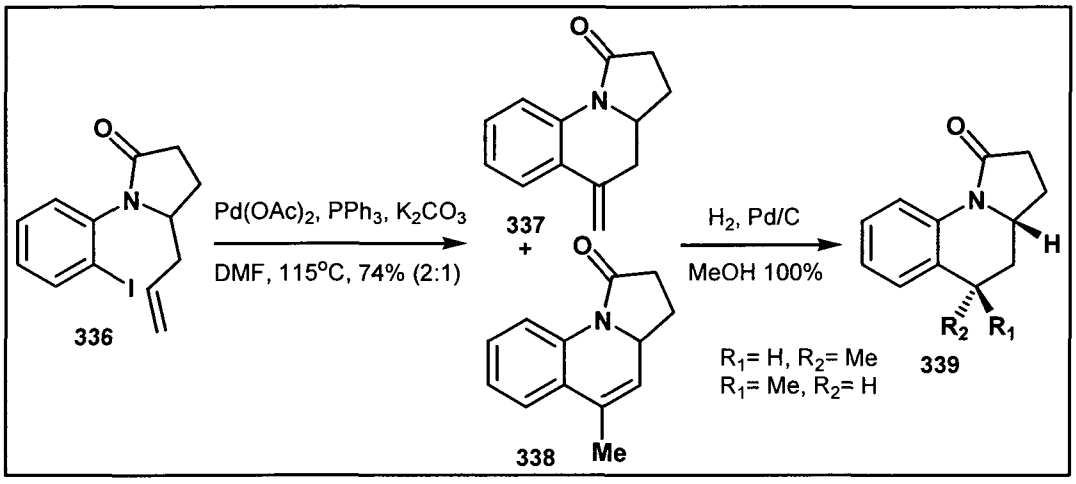
gave a mixture of **311** and **335**. Aryl migration occurred in the rearrangement of aminodiazonium **332** in an intramolecular Schmidt reaction[214].

Scheme 4.10



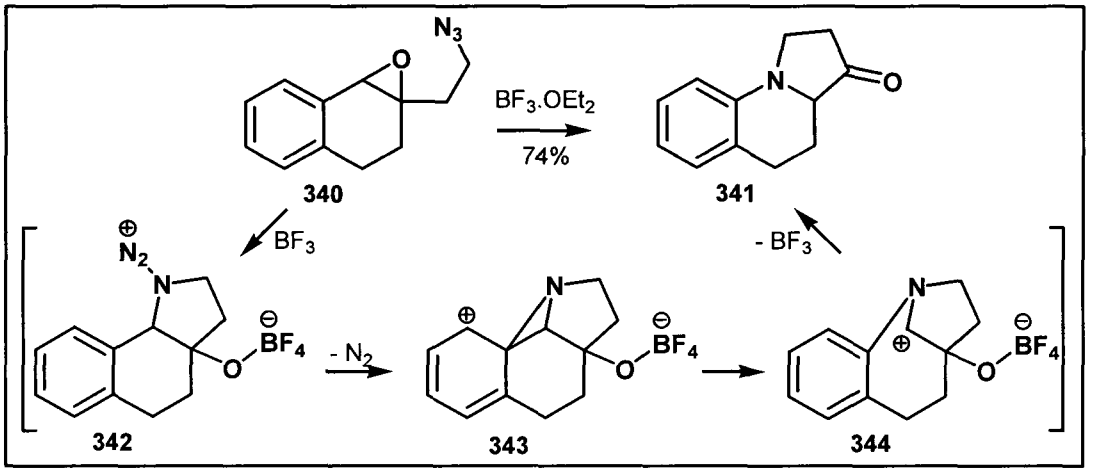
Pilli and co-workers used intramolecular Heck reaction in their synthesis[215]. Intramolecular cyclization of lactam **336** (Scheme 4.11) under palladium catalyst gave an inseparable mixture of pyrroloquinolones **337** and **338** (2:1). These two regio-isomers, however, after hydrogenation were perfectly separated.

Scheme 4.11



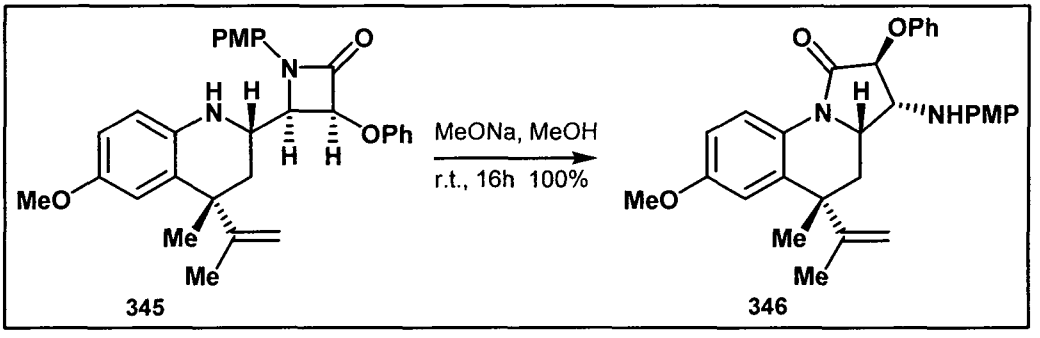
Payne *et al.* synthesized pyrroloquinoline-3-one from aryl epoxyazides[216]. As shown in Scheme 4.12, this occurred from cascades of electron-deficient reactions a) epoxide opening in **340**, b) electrophilic amination of the arene to give **343**, c) alkyl shift (cleavage of aziridine) to bridged compound **344**, and d) regiospecific ring-contraction (by assistance from oxygen) to pyrroloquinoline-3-one **341**.

Scheme 4.12



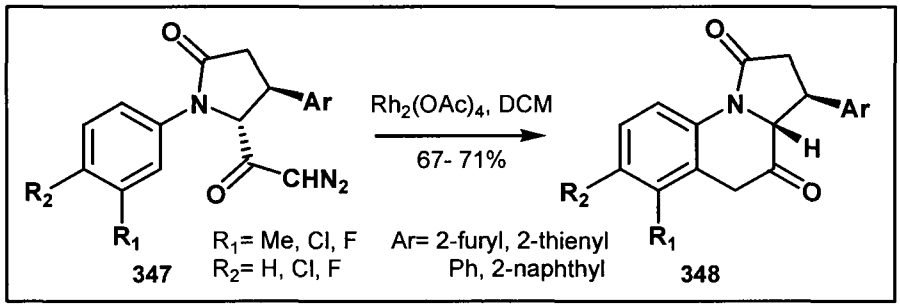
Alcaide and co-workers made pyrroloquinoline-2-one from β-lactams[217]. For example β-lactam **345** (Scheme 4.13) under treatment with sodium methoxide and amide bond cleavage (rearrangement) afforded tricyclic **346** quantitatively. Chirality transfer occurred when an enantiomericlly pure substrate was used.

Scheme 4.13



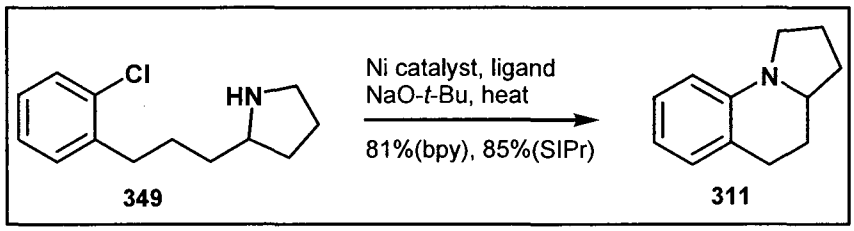
Intramolecular rhodium (II) catalyzed carbenoid insertion reaction into aromatic C-H bond was used by Ray *et al.* for preparing pyrroloquinoline-1,4-diones[218]. As shown in Scheme 4.14, diazoketones **347** in the presence of rhodium(II) acetate regioselectively converted to the substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-diones **348** in good yields.

Scheme 4.14



Although several methods for the preparation of compound **311** (Scheme 4.15) were indicated above, the work performed by Fort *et al.* is noteworthy due to its generality and high yield[219]. They synthesized pyrrolo[1,2-*a*]quinoline **311** by an intramolecular amination of aryl chloride **349** using Ni(0) catalyst in the presence of a ligand [2,2'-bipyridine (bpy) or *N*,*N*-bis(2,6-diisopropylphenyl)-dihydroimidazole-2-ylidene (SIPr)] and a base (NaO-*t*-Bu). The authors also used this method for preparing several five-, six-, and seven-membered rings.

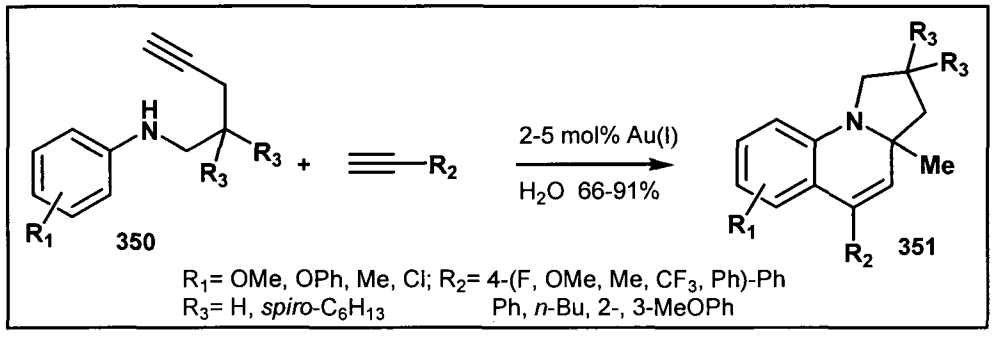
Scheme 4.15



Che and Liu recently displayed the synthesis of substituted pyrrolo[1,2-*a*]-quinolines using a gold-catalyzed tandem reaction in aqueous media[220]. 1,4-

aminoalkynes **350** (Scheme 4.16) with alkynes and an Au(I) catalyst in water underwent tandem cyclization to produce diversity substituted pyrroloquinolines **351** in good-to-excellent yields. Two new C-C bonds and one new N-C bond were formed in one pot. The proposed mechanism involves the generation of an enamine and the cyclization of the propargylamine, resulting from the attack of alkyne on the enamine.

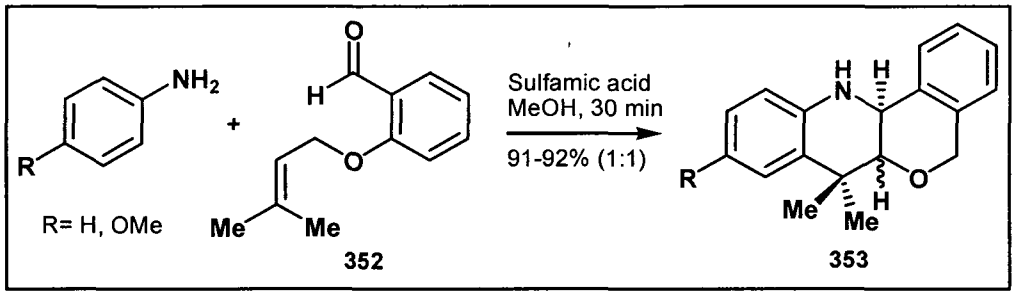
Scheme 4.16



In addition to search for the synthetic methods of pyrroloquinolines, possible methodologies for pyrano[3,2-*b*]quinolines were also researched. However, and surprisingly, apart from the method presented below, no other method—and even no natural or pharmaceutical products—with this system was found.

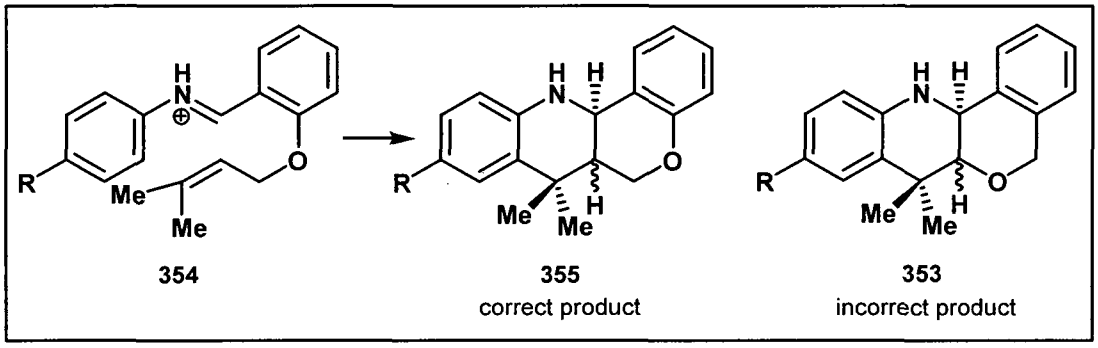
Perumal and co-workers claimed a synthetic method for pyrano[3,2-*b*]-quinoline[221a]. Treatment of aniline or *p*-methoxyaniline and O-prenylsalicylic aldehyde **352** (Scheme 4.17a) in the presence of sulfamic acid and in mild-reaction conditions yielded the 1:1 diastereoisomeric mixture of benzopyrano[3,2-*b*]quinolines **353**. Chapter 5 further discusses this type of intramolecular imino Diels-Alder reaction.

Scheme 4.17a



Interestingly, after a closer look at the above reaction, it appears that the product was not correctly identified. As shown in Scheme 4.17b, Schiff base **354** resulted from the reaction of anilines, and *O*-prenylsalicylic aldehyde (**352**) is expected to participate in a cycloaddition (imino Diels-Alder) reaction and form the chromeno[4,3-*b*]quinoline derivative **355**- not benzopyrano[3,2-*b*]quinolines **353**.

Scheme 4.17b

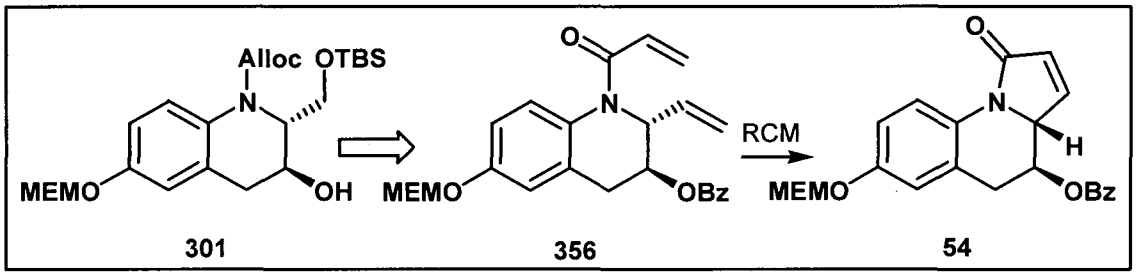


Since the preceding reaction was the only example found in the literature for the synthesis of pyrano[3,2-*b*]quinolines, and in fact, it was incorrectly presented, our synthetic method apparently can be considered the first successful method for the synthesis of this new system and, consequently, the first method to introduce a new system.

4.4 Our Synthesis Approach

Our approach for preparing two target systems is ring-closing metathesis (RCM) reaction, the method that apparently was never used for preparing these tricyclic systems. Precursor **356** (Scheme 4.18) which can be formed from **301** (Section 3.4.2.1) under RCM conditions afforded our tetrahydroquinoline tricyclic having an α,β-unsaturated γ-lactam moiety **54** (pyrrolo[1,2-*a*]quinoline)[199b].

Scheme 4.18

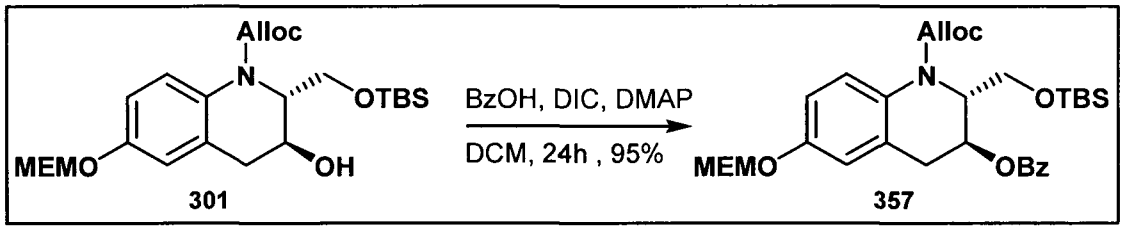


Similar methodology was used for the synthesis of pyrano[2,3-*b*]quinoline system. The solid phase synthesis of our pyrroloquinoline system will also be presented in this section.

4.4.1 Solution Phase Synthesis of Tetrahydroquinoline Tricyclic Having α,β-Unsaturated γ-Lactam

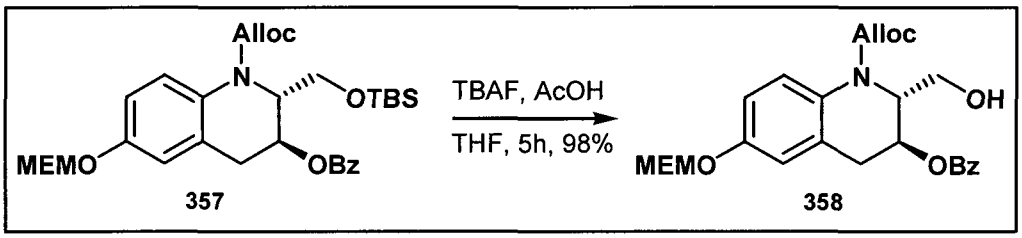
For the synthesis of the RCM precursor (**356**), we started from **301** (Scheme 4.19). Positions 1 and 2 in tetrahydroquinoline had to be modified to accommodate two terminal olefins. Before this task, the secondary hydroxyl group in **301** should be first blocked to minimize the formation of undesired side products. Benzoyl protection on **301** using coupling conditions resulted in fully protected tetrahydroquinoline **357** in an excellent yield. ^{1}H-NMR showed a doublet at 7.94 ppm (J = 7.3, 2H) suggesting two new aromatic protons close to carbonyl. This carbonyl in benzoyl group also showed a peak at 166.1 ppm in ^{13}C-NMR.

Scheme 4.19



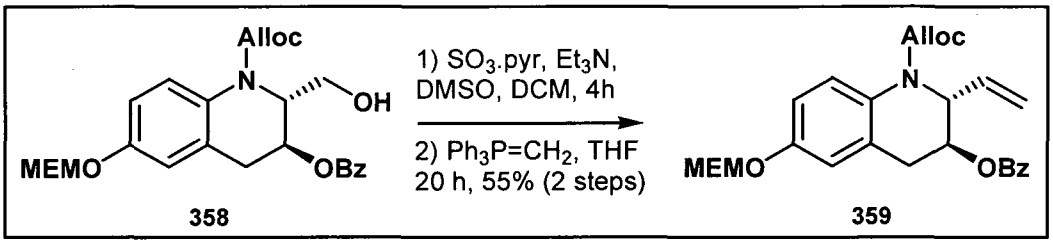
The next step was to prepare one terminal olefin at position 2 of our tetrahydroquinoline. In order to do so, the TBS group was first removed, at which point a fully protected compound **357** (Scheme 4.20) was treated with tetra-*n*-butylammonium fluoride (TBAF) in acetic acid, and cleanly gave compound **358** with a free, secondary alcohol moiety. Disappearance of TBS peaks in both ^{1}H-NMR [0.82 (9H) and -0.01 (6H) ppm], and ^{13}C-NMR [18.4 and -5.2 ppm] suggested that a successful deprotection reaction took place.

Scheme 4.20



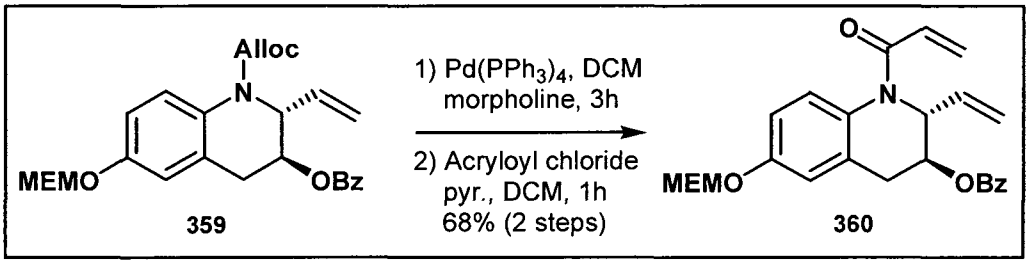
Oxidation of this alcohol (**358**), with a SO_3–pyridine system and a subsequent Wittig reaction, afforded compound **359** with the desired terminal olefin (Scheme 4.21). Due to the instability of the aldehyde, isolation at the oxidation stage was not efficient. Therefore, the next step was conducted (i.e. a Wittig reaction) without purification of the aldehyde intermediate. Although successful, the yield was slightly lower than expected (55% for two steps); mass spectrum showed peak 468.4 (M+1) and olefinic hydrogens and carbons appeared on ^{1}H-NMR and ^{13}C-NMR, respectively.

Scheme 4.21



Formation of the RCM precursor was achievd using the installation of the second terminal olefin. Similar to the procedure explained in chapter 3 (Section 3.4.1.1), alloc was replaced with an acryl group using a 2 step-reaction of *N*-deprotection, with Pd(0) in compound **359** proceeded by the installment of acryl in the nitrogen atom (Scheme 4.22), all without purifying the amine intermediate. This resulted in the formation of our desired compound **360**, with an average yield of 83% in each step. Although proven with all other methods (mass, ^{13}C-NMR, and 2D NMR), the disappearance of methylene hydrogens in "O-CH_2-olefin" of alloc group, in 4.50-4.60 ppm, was the easiest way verify the successful reaction. In addition, the presence of a carbonyl peak in ^{13}C-NMR for the acryl group (which appeared at 155.7 ppm) further validated the reaction.

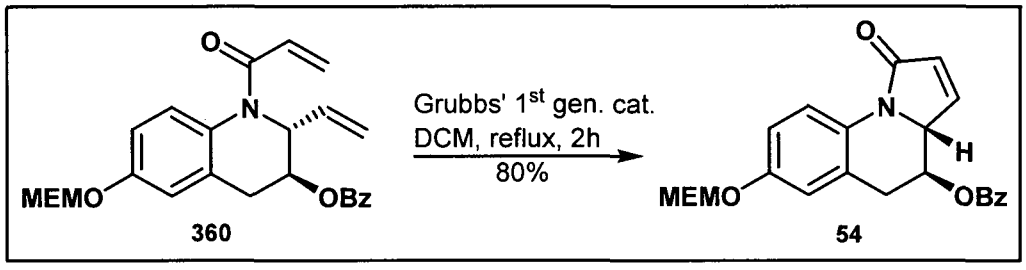
Scheme 4.22



In the final stage of our synthesis, RCM reaction using first generation Grubbs' catalyst on **360** (Scheme 4.23) cleanly afforded pyrrolo[1,2-*a*]quinoline **54** in 80% yield. Structure of this tricyclic compound containing α,β-unsaturated γ-lactam (5-membered ring lactam) was comprehensively studied by mass, 1D NMR, 2D NMR, and finally with X-ray crystallography. ^{1}H-NMR showed olefinic (α,β-

unsaturated) hydrogens at 6.38 and 7.28 ppm. However, best indication for RCM reaction is the expulsion of the ethylene molecule, which resulted in reducing the number of hydrogens and carbons by six and two, respectively. Counting H and C atoms in 1D-NMR spectra revealed this ethylene expulsion.

Scheme 4.23



NOESY spectrum for compound **54** (Figure 4.3) revealed that H(3a) and $H_\beta(5)$ are spatially close. Besides obvious H(4)-$H_\alpha(5)$, this close proximity also existed for H(3a) and H(2). On the other hand, no such this relationship was observed between H(3)-H(4) and even H(3)-H(3a). As explored by Reinhoudt (Section 4.3), pyrrolidine ring is forced slightly (around 10°) out of the quinoline plane.

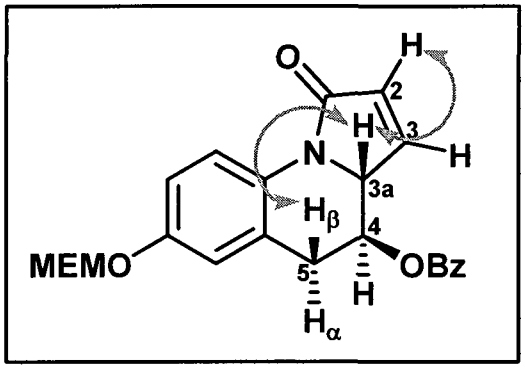


Figure 4.3 Spatially Close Hydrogens in Compound **54** Revealed by NOESY

Compound **54** under recrystallization using Ethyl acetate/DCM/Hexanes system gave a dark yellow crystal. X-ray crystallography enabled us for the ultimate

assignment (Figure 4.4). Crystal data for this compound is presented in Table 4.1.

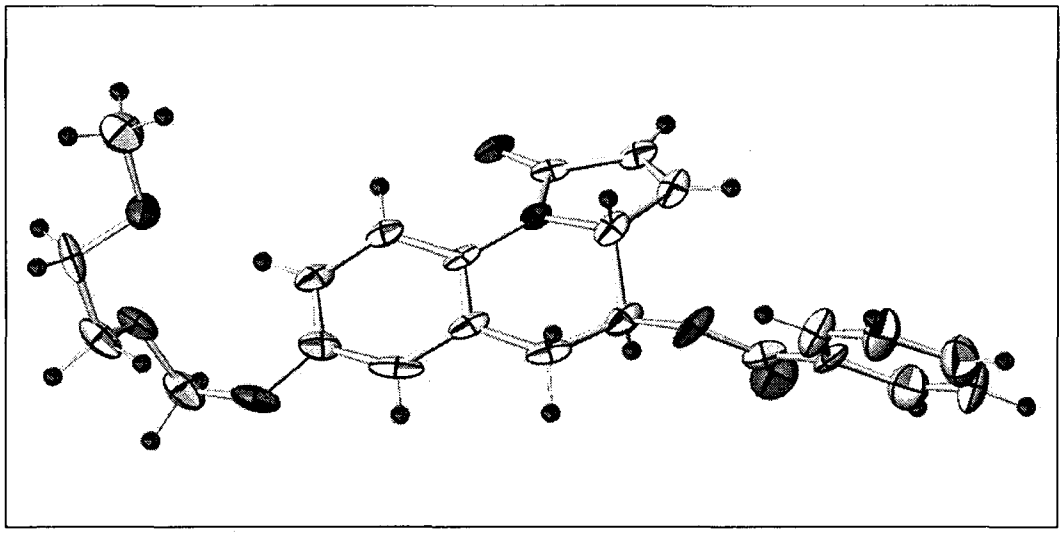


Figure 4.4 X-ray Structure of Compound **54**

Table 4.1 Crystal Data for Compound **54**

Empirical formula	$C_{23}H_{23}NO_6$
Formula mass	409.42
Wavelength (Å)	0.71070
Temperature (K)	150(2)
Crystal system	triclinic
Space group	P1
a (Å)	13.689(2)
b (Å)	16.580(3)
c (Å)	19.076(3)
α, β, γ (°)	102.68, 106.66, 90.12
Volume (Å^3)	4036.8(11)
Z (atoms/unit cell)	8
Calcd. density (gm/cm^3)	1.347
Reflections total	27110
unique	11489

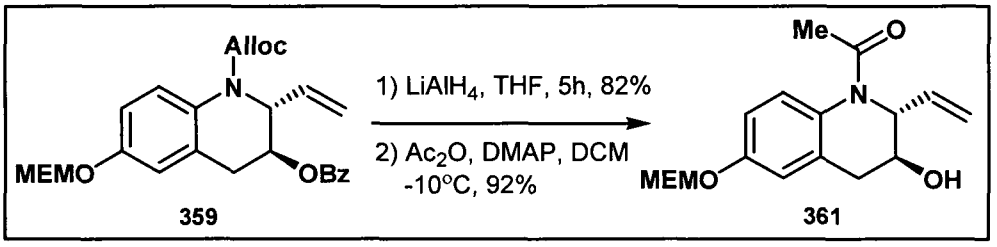
$F(000)$	1160
Crystal size	0.25 mm × 0.35 mm × 0.40 mm
θ range (°)	0.977-23.38
Index ranges	h (-15 to 15), k (-18 to 18), l (-21 to 21)
Goodness-of-fit on F^2	0.817
$> 2\sigma (I)$	5023
Final R indices [$I > 2\sigma (I)$]	R_1=0.099, wR_2=0.234
R indices (all data)	R_1=0.216, wR_2=0.281
Largest diff. Peak and hole (e Å^{-3})	0.43 and -0.41

4.4.2 Solution Phase Synthesis of Tetrahydroquinoline Tricyclic Having α,β-Unsaturated δ-Lactone

In section 4.1 (Scheme 4.1), the starting material **301** for both syntheses of tricyclics **54** and **55** is shown. However, for the synthesis of pyranoquinoline **55**, we are pleased that we were actually able to prepare our target using compound **359** (the synthesis is explained in Section 4.4.1) and save 4 steps. In this section, the stages required for the synthesis of our pyrano[3,2-*b*]quinolin-2-one **55** will be discussed. Our approach to the synthesis of this system again was RCM reaction although no other method was found. Since terminal olefin has already been installed in C-2 position of our tetrahydroquinoline compound **359** (Scheme 4.24), we needed to place an acryl group for proceeding by RCM reaction. Scheme 4.24 shows the first two steps for this synthesis. Reduction by lithium aluminum hydride on **359** successfully removed both alloc (amide) and benzoyl (ester) groups. The provided amino alcohol (not shown) isolated and fully characterized. Disappearance of two carbonyl peaks in ^{13}C-NMR indicated that -*N*alloc and benzoyl group had been removed. 1D DEPT-135 NMR also depicted -CH- (-CH_3-) and -CH_2- in the compound. The secondary amine in this amino alcohol was selectively acyl protected by acetic anhydride and 4-dimethylaminopyridine (DMAP) as the base to afford **361**. Temperature for this reaction was kept at -

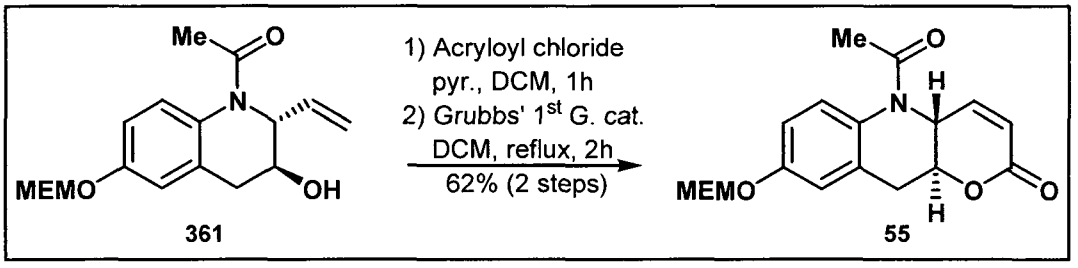
10°C for better selectivity. Peaks for acetyl group appeared in 1D NMR, i.e., 2.07 ppm (s, 3H) in ^{1}H-NMR for OC-CH_3 and 170.9 ppm in ^{13}C-NMR for carbonyl group. Moreover, DEPT-135 again showed all $CH_{1,2,\&3}$.

Scheme 4.24



The remaining steps including acryloylation of the secondary hydroxyl group in **361** and ring-closing metathesis reaction were performed without purification of the RCM precursor as intermediate. Therefore, alcohol **361** (Scheme 4.25) protected as acryl by acryloyl chloride/pyridine system to form second olefinic arm required in RCM reaction. Similar to our previous system, first generation Grubbs' catalyst was used for the cyclization reaction in refluxed DCM. After 2 hours (indicated by TLC) starting material completely converted to a new compound. 62% overall yield for these two steps showed an average of 80% for each step which is considered good. Appearance of M+1 (348.2 m/z) peak in the mass spectrum (348.2 m/z) gave us first approval. This tricyclic compound containing α,β-unsaturated δ-lactone (6-membered ring lactone) showed olefinic hydrogens at 6.36 ppm (1H) and 7.22 ppm (1H) in ^{1}H-NMR and lactone carbonyl at 170.1 ppm in ^{13}C-NMR.

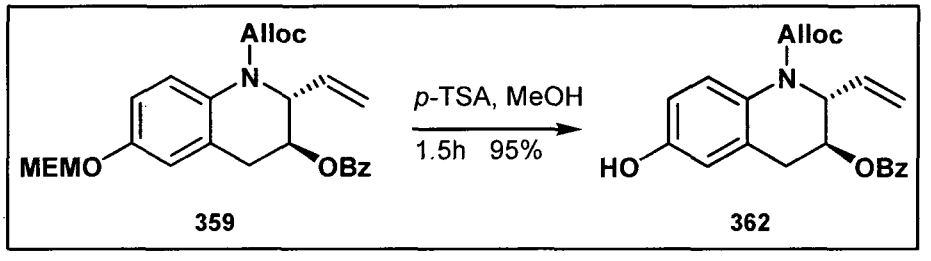
Scheme 4.25



4.4.3 Solid Phase Synthesis of Tetrahydroquinoline Tricyclic Having α,β-Unsaturated γ-Lactam

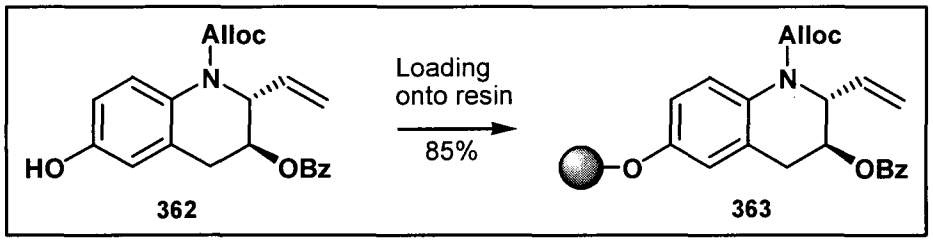
Ring-closing metathesis reaction was also the preferred method for our solid phase synthesis. In the previous section, we pointed out that for preparing our second tricyclic system, one of our intermediates from first synthesis was used (i.e. compound **359**). For the solid phase synthesis of pyrrolo[1,2-*a*]quinoline system we again started with the same intermediate **359** simply because it owned the all features we needed for a successful solid phase synthesis including orthogonally protecting groups and the potential anchoring site. Furthermore, it had one arm already equipped with olefin moiety suitable for the RCM reaction. Unlike the hardship we experienced for removal of MEM group in Section 3.4.2.1, treatment of tetrahydroquinoline **359** (Scheme 4.26) with *p*-TSA in methanol generated phenolic compound **362** in excellent yield. Comparison of ^{1}H-NMR spectra of **359** and **362** signalled the complete removal of MEM group (from CH_3-O-CH_2-CH_2-O-CH_2-OAr) which its protons used to be appeared around 3.4, 3.6, 3.8, and 5.2 ppm. However, other 1D and 2D NMR experiments were also performed.

Scheme 4.26



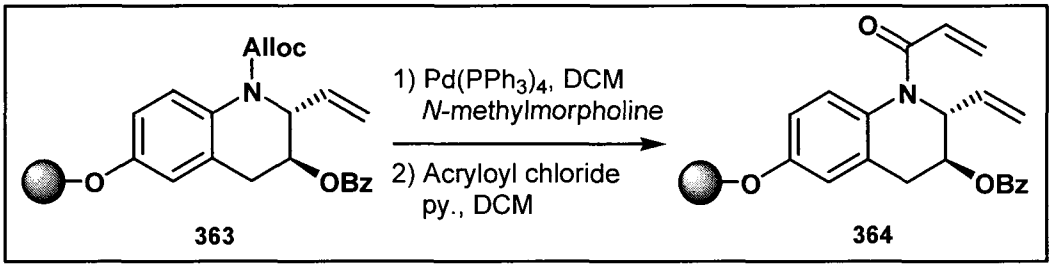
Loading was performed on **362** using the method explained in Section 3.4.2.2 (Scheme 4.27). Yield for loading was 85% and considered good. Resin loaded compound **363** was our starting material in solid phase. As shown above, formation of second olefinic arm at nitrogen position needed for RCM reaction can be achieved by replacement of -*N*alloc with acryloyl group.

Scheme 4.27



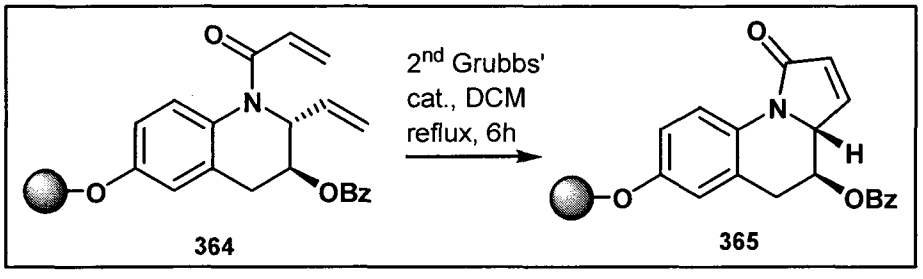
Alloc group removed using typical palladium(0)/methylmorpholine system and replaced by acryl using acroyl chloride/pyridine (Scheme 4.28). It should be reminded that each step was checked using mass spectroscopy. Resin **364** then was equipped with two arms needed for a metathesis reaction.

Scheme 4.28



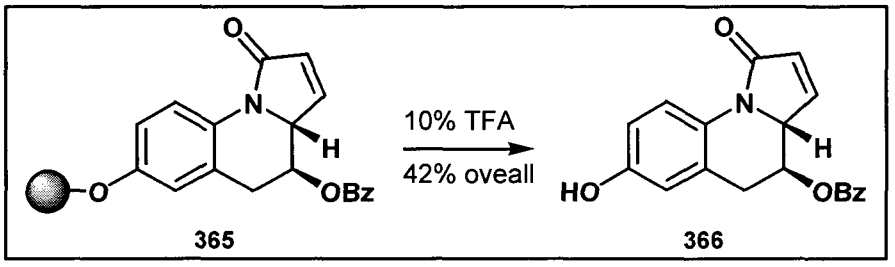
RCM reaction performed on **364** using second-generation Grubbs' catalyst in refluxed DCM for 6 hours (Scheme 4.29). Small amount of resin **365** was cleaved and submitted for mass analysis. M+1 peak (322.2) convinced us about our successful reaction.

Scheme 4.29



The remaining resin **365** under treatment with TFA was cleaved (Scheme 4.30) and purified by column chromatography. The overall yield was found to be 42% (four steps).

Scheme 4.30



In spite of the limited amount of pyrroloquinoline **365** formed, we were able to characterize it completely. Comparing with tricyclic compound **54**, complete sets of protons in NMR for **366** was observed. As expected, the difference was the disappearance of MEM protons and carbons in NMR spectra. 2D NMR spectra were also used for the final assignment. For instance, COSY spectrum showed the similar pattern as **54**. Comparison of the two COSY spectra presented in Figure 4.5.

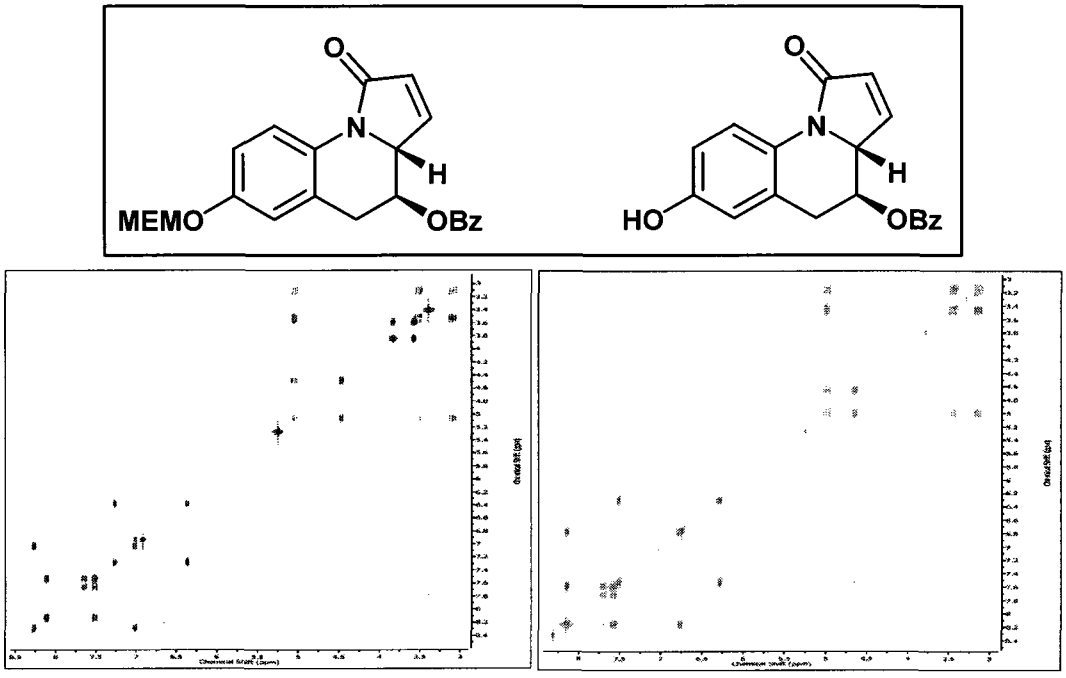


Figure 4.5 Comparison of COSY Spectra between Compounds **54** and **366**

In this chapter, we explained the solution and solid phase synthesis of tetrahydroquinoline system pyrrolo[1,2-*a*]quinoline and also solution phase synthesis of pyrano[3,2-*b*]quinoline. Unfortunately, any attempts for the solid phase synthesis of the later were not successful.

5: One-Pot Synthesis of Tetrahydroquinoline-Derived Polycyclics and Further Exploration

5.1 Design Strategy

In this chapter, as mentioned earlier, synthesis of some complex systems containing tetrahydroquinoline will be discussed. In particular, the centre of our interest is the synthesis of pentacyclic and hexacyclic compounds that carry the isoindolo[2,1-*a*]quinoline system. Isoindolo[2,1-*a*]quinoline system **367** and its 11-one derivative **368** are shown in Figure 5.1. Numbering shown for the latter derivative will be referred to throughout the chapter.

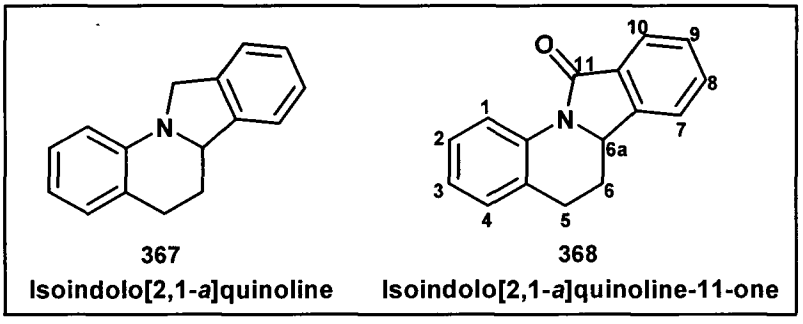


Figure 5.1 Isoindoloquinoline and Isoindoloquinolone

The synthesis of tetrahydroquinoline system **B** from *N*-aryl compound **A** (Figure 5.2) was explained in Chapter 2. Preparation of tricyclic system **C** from bicyclic **B** was detailed in Chapter 4. Although one can imagine synthesis of tetracyclic system **D** from **C**, we focused our efforts on the formation of **D** directly from **A** and were able to prepare complex systems such as **D** in one-pot from *N*-aryls **A**. This work will be presented in this chapter[221b].

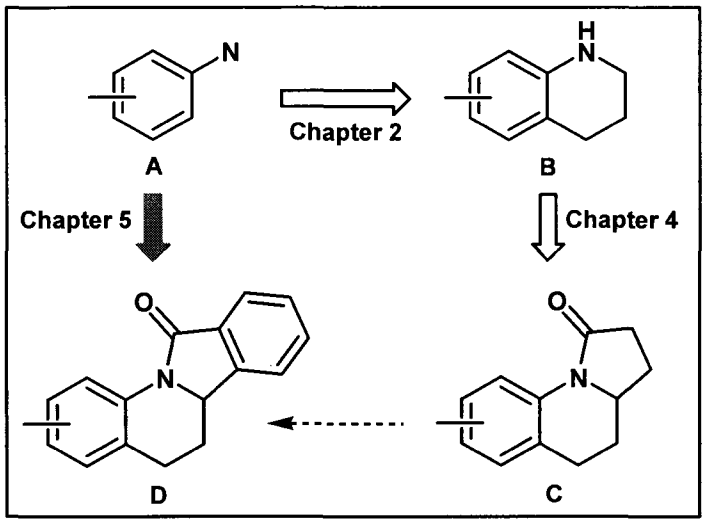


Figure 5.2 Synthetic Trends in Our Research

5.2 Isoindolo[2,1-*a*]quinolines as Biologically Active Targets

Isoindolo[2,1-*a*]quinolines possess an array of biological activities. For instance, 5,11-dioxosubstituted isoindolo[2,1-*a*]quinolines **369** (Figure 5.3) show protective effects against N_2-induced hypoxia[201] and trihydroxyisoindolo[2,1-*a*]quinolines **370** inhibit human topoisomerase II and bacterial DNA-gyrase[222].

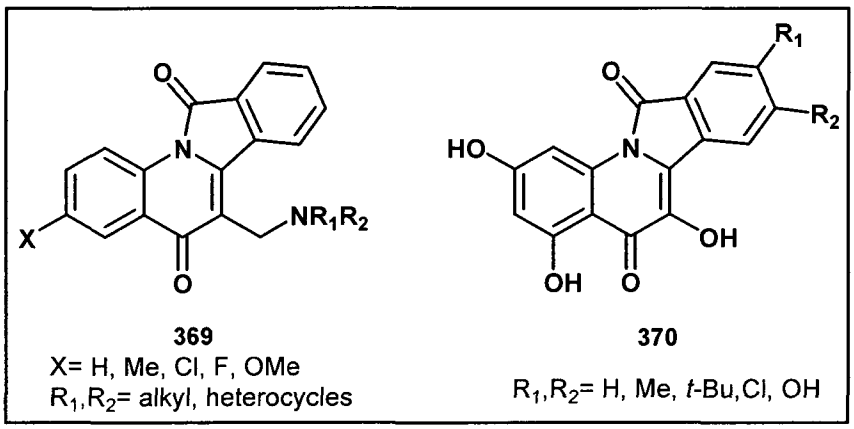


Figure 5.3 Bioactive Isoindoloquinolines

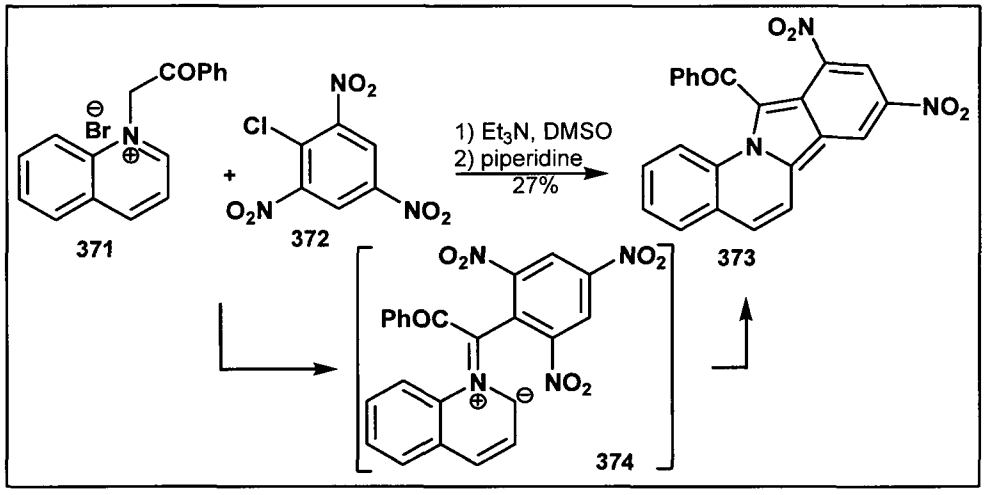
5.3 Synthesis of Isoindolo[2,1-*a*]quinoline System in Literature

Isoindolo[2,1-*a*]quinoline system is attractive not only as a potential bioactive target but as interesting synthetic compound. Few synthetic methods for preparation of isoindolo[2,1-*a*]quinolines have been reported. Methodologies for preparing isoindolo[2,1-*a*]quinolines often require several stages and are mostly not satisfactory either in generality or yield[223]. Moreover, these methods commonly lack the use of stereocontrolled reactions.

In this section, a brief review of certain synthetic efforts is chronologically presented. As isoindoloquinolines **367** (Figure 5.1) contain both quinoline and isoindole substructures potentially two methods, including installation of quinoline to isoindole and isoindole to quinoline, are considered the major synthetic methods. However, because of the better accessibility of isoindoles, the former approach is more often utilized.

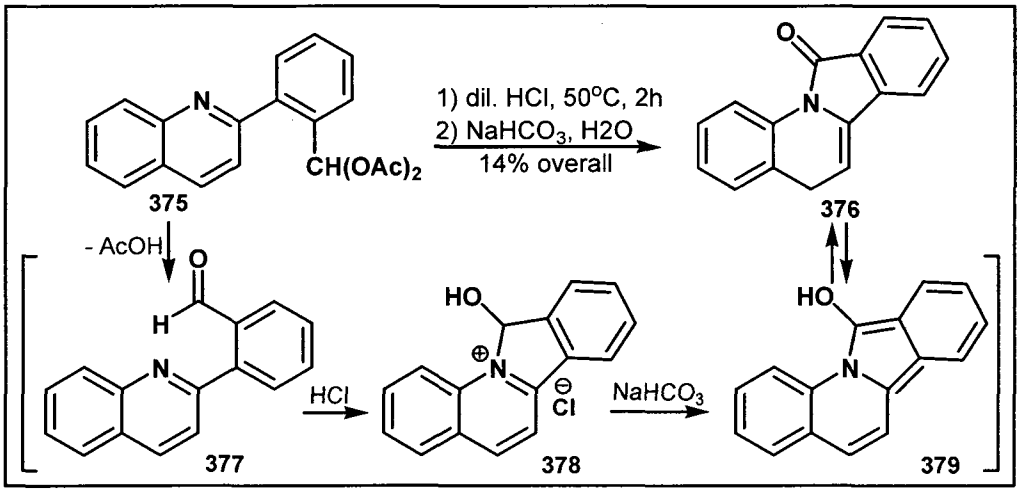
The earliest appearance of isoindoloquinoline system in literature goes back to 1971 when Reuschling and Krohnke introduced this system using cycloimmonium salts[224]. Activated cycloimmonium **371** (Scheme 5.1) reacted with picryl chloride **372** to afford 11-benzoyl-8,10-dinitroisoindolo[2,1-*a*]quinoline **373** presumably through intermediate **374**.

Scheme 5.1



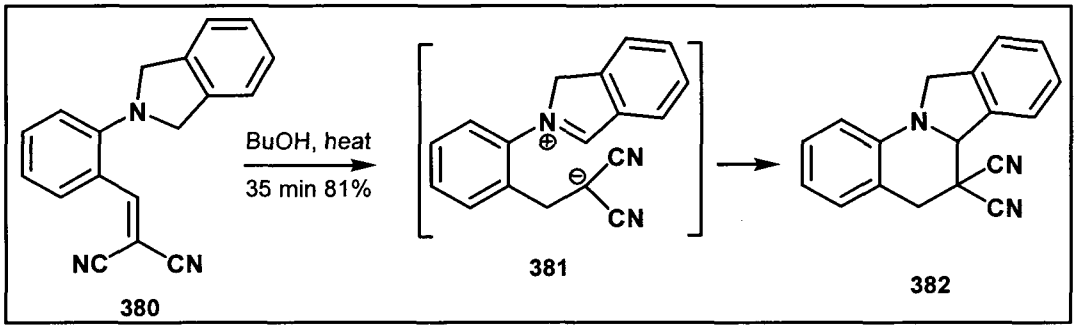
Ten years later Igeta and co-workers reported the synthesis of 5H-isoindolo[2,1-a]quinolin-11-one **376** (Scheme 5.2) by treatment of *o*-(α-quinolyl)benzylidene diacetae **375** with diluted hydrochloric acid followed by neutralization[225]. Aldehyde **377** formed by the acidic hydrolysis of **375**, cyclizes (nucleophilic attack of nitrogen to carbonyl) to give **378**. Neutralization by sodium bicarbonate leads to the formation of enol **379** which ketonized to afford the more stable isoindoloquinoline compound **376**. These two indicated syntheses which used isoindole attachment to quinolines, suffered from low yields.

Scheme 5.2



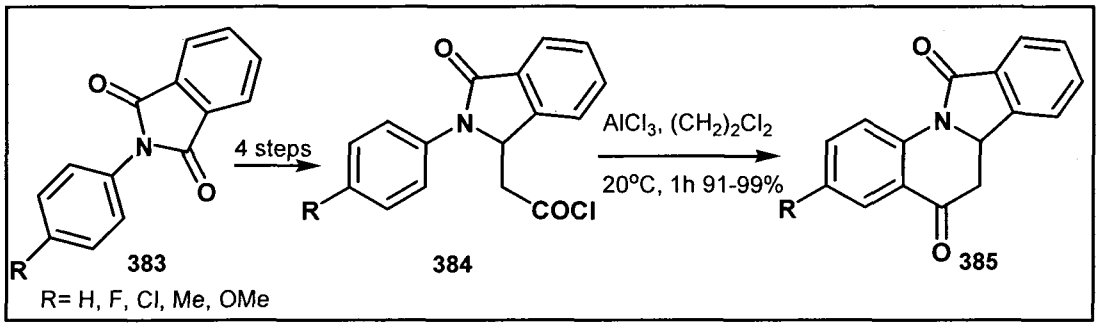
Reinhoudt *et al.* used dinitrile compound **380** (Scheme 5.3) in their synthesis of isoindoloquinoline **382**[226]. The reaction may proceed through a [1,5] hydrogen shift in **380** resulted in the formation of dipolar intermediate **381** which undergoes an intramolecular nucleophilic addition of carbanion to iminium forming **382**.

Scheme 5.3



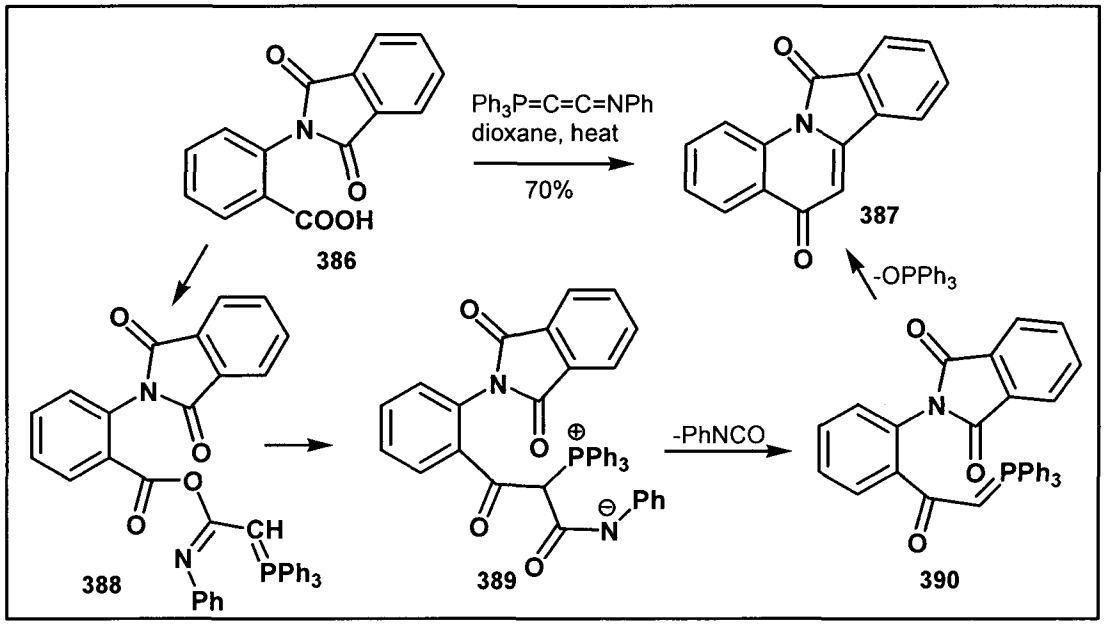
In the key cyclization step for the synthesis of bioactive compounds **369** (Figure 5.3), Ishihara and co-workers used intramolecular Friedel-Crafts acylation reaction[201]. Acyl chlorides **384** (Scheme 5.4) which can be formed in 4 steps from 2-arylisoindol-1,3(2*H*)-diones **383** under Friedel-Crafts condition (aluminum chloride) gave 6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11(5*H*)-diones **385** in excellent yields. Former steps of the synthesis were revisited and expanded for the formation of other cyclic systems[227].

Scheme 5.4



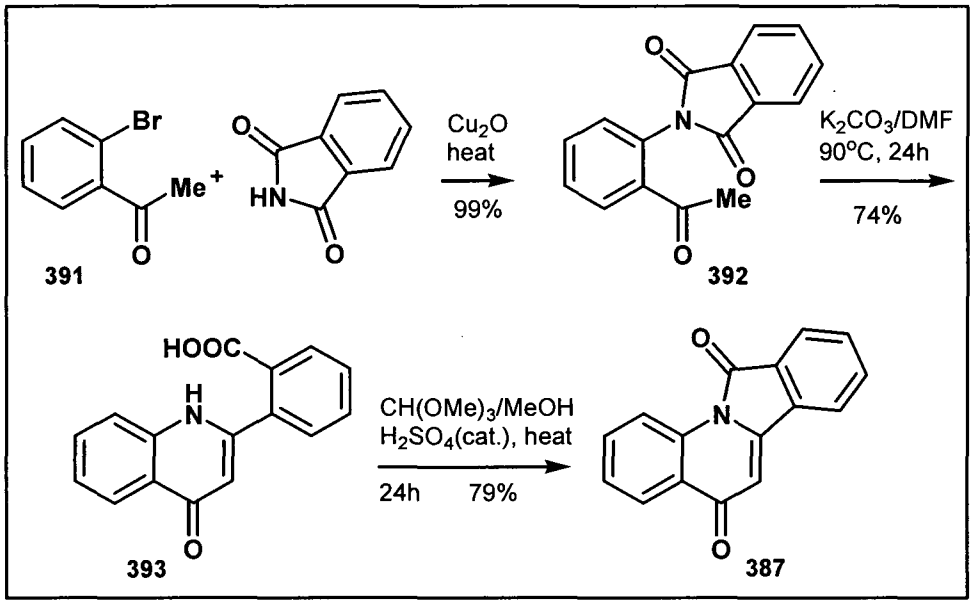
In Kumar *et al.* methodology, *N*-phenyl-(triphenylphosphoranylidene)ethenimine was used[228]. *N*-phthaloylanthranilic acid **386** was treated in the conditions shown in Scheme 5.5 and converted to isoindolo[2,1-*a*]quinoline-5,11-dione **387** in 70% yield. The proposed mechanism involves a carboxyl group addition of **386** to the C=C bond of the ylide resulted in the formation of *O*-acylimidate **388**. Phenyl isocyanate elimination from 389 leads to acylphosphorane **390**, which undergoes an intramolecular Wittig reaction to afford **387**. Formation of **389** from ester carbonyl migration in **388** was proven by isolation and characterization of **389** at milder conditions. Vorbruggen and co-workers earlier reported cyclization of **386** by triphenylphosphine/CCl_4 in dichloromethane[229]. However, the product was found to be 6-chloroisoindolo[2,1-*a*]quinoline-5,11-dione.

Scheme 5.5



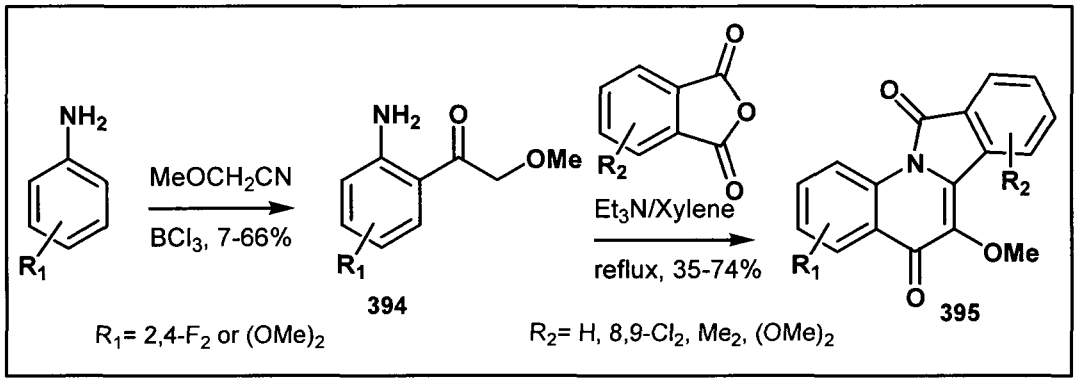
Kim and Keum reported the synthesis of **387** using quinolonecarboxylic acids[230]. *o*-Amidoacetophenone **392** (Scheme 5.6) which can be prepared from phthalimide and *o*-bromoacetophenone **391** using Copper(I)oxide, cyclized to quinolonecarboxylic acid **393** in alkaline medium. Orthoester and a catalytic amount of sulfuric acid then afforded isoindolo[2,1-*a*]quinoline-5,11-dione **387**.

Scheme 5.6



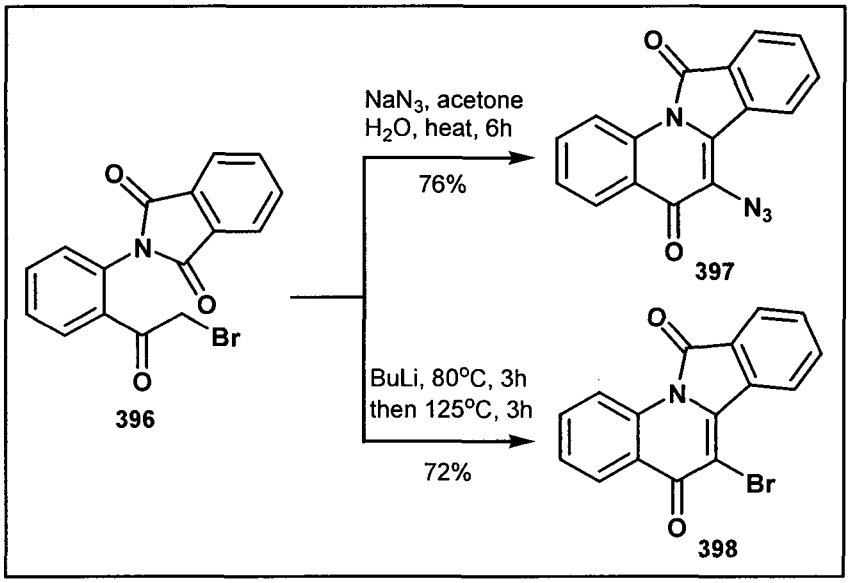
Sui *et al.* who successfully prepared bioactive isoindoloquinolines **369** (Figure 5.3), synthesized isoindoloquinoline-diones **395** by treatment of 2-aminoacetophenones **394** (Scheme 5.7) with phthalic anhydrides in basic medium[222]. Intermediate **394** was prepared from acylation of anilines with methoxyacetonitrile in the presence of trichloroborane. However, yields in both reactions vary from low to moderate. Mechanism contains an initial formation of amide by nucleophilic attack of nitrogen to phthalic anhydride followed by cyclization of the resulted amide. The reaction proceeded in basic/heat condition to form compound **395**.

Scheme 5.7



o-Phthalimidobromoacetophenone **396** (Scheme 5.8) was converted to the corresponding isoindolo[2,1-*a*]quinolines **397** and **398** under treatment with sodium azide and butyl lithium, respectively[231].

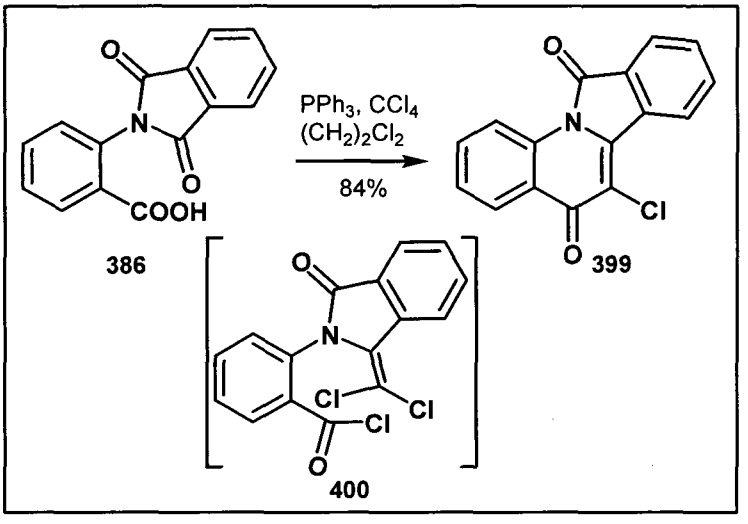
Scheme 5.8



Vorbruggen *et al.* reported cyclization of **386** (Scheme 5.9) by triphenylphosphine/CCl_4 in dichloromethane[229]. However, product was found to be 6-chloroisoindolo[2,1-*a*]quinoline-5,11-dione **399**. Proposed mechanism involves the initial formation of intermediate 2-[1-(dichloromethylene)-3-

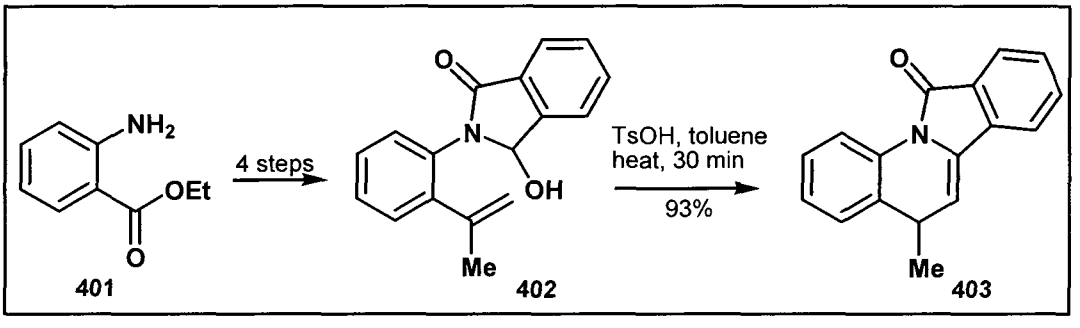
oxoisoindolin-2-yl]benzoyl chloride **400** which under Wittig-type reaction converts to **399**.

Scheme 5.9



Hydroxylactams such as **402** (Scheme 5.10) under acidic conditions in boiling toluene cyclized to 5-alkylisoindolo[2,1-*a*]quinolin-11(5*H*)-ones like **403**, the 5-methyl derivative[232]. Although the yield is excellent, hydroxylactam **402** needs to be prepared first in 4 steps from ethyl 2-aminobenzoate **401**.

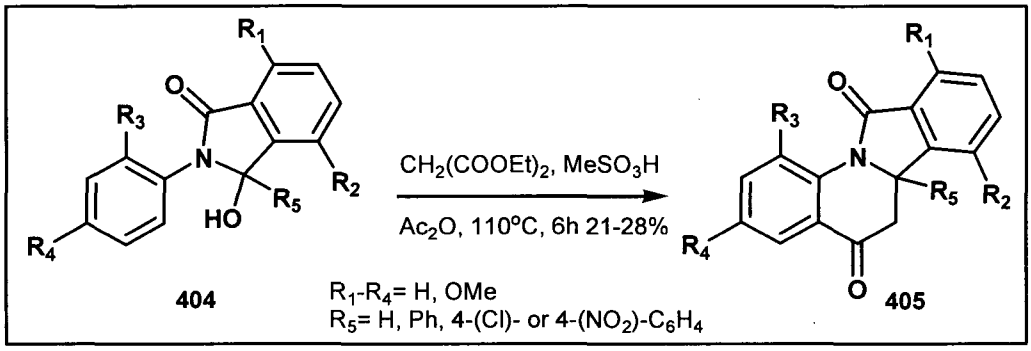
Scheme 5.10



Epsztajn *et al.* prepared isoindoloquinolones from hydroxyisoindolinones[233]. 2-aryl-3-hydroxyisoindol-1-one **404** (Scheme 5.11) treated with diethyl malonate in

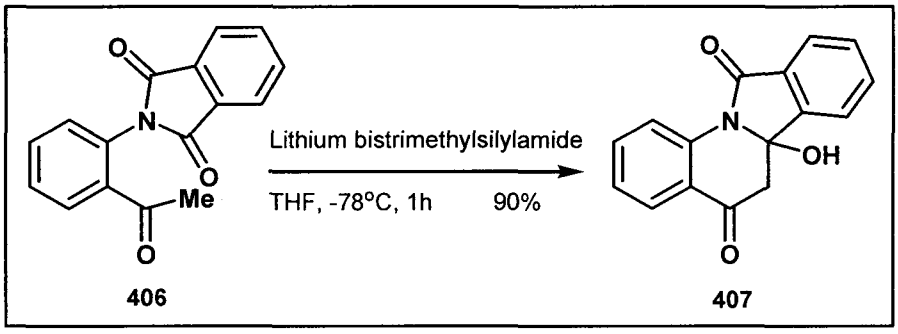
acetic anhydride in the presence of methanesulfonic acid to form isoindolo[2,1-*a*]quinoline-5,11-dione **405**. Yields were poor despite the acceptable generality.

Scheme 5.11



Sunjic *et al.* used 2-phthalimidoacetophenone **406** (Scheme 5.12) and converted it to 6a-hydroxy-6,6a-dihydroisoindolo[2,1-*a*]quinoline-5,11-dione **407** under deprotonation by LBTSA-lithium bistrimethylsilylamide[234]. Weaker bases showed to be less effective. Thermal dehydration of **407** formed **387** (Scheme 5.5 and 5.6).

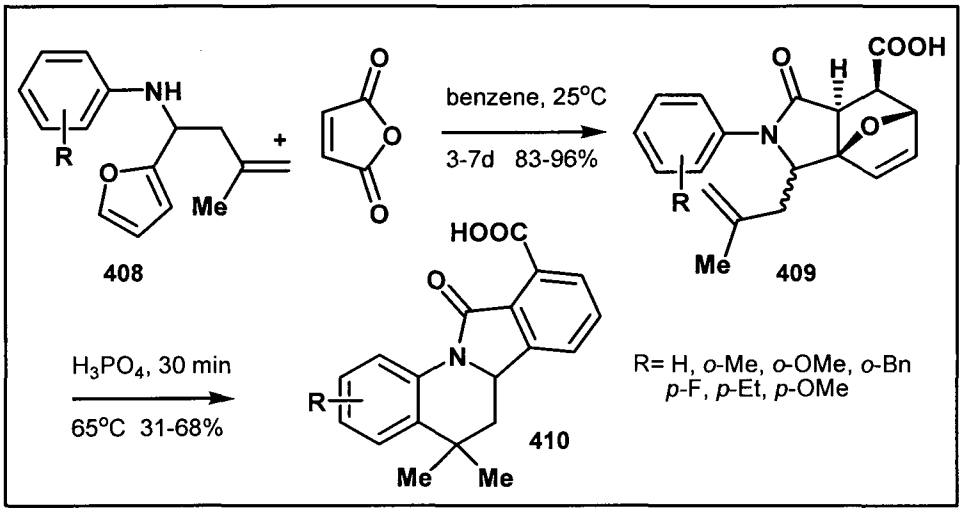
Scheme 5.12



Russian chemists in recent years seriously worked on the synthetic methods of isoindoloquinoline system. Zubkov and his colleagues used 3-aryl-2-methallyl-3-aza-10-oxatricyclo[5.2.1.01,5]dec-8-ene-6-carboxylic acids **409** (Scheme 5.13) as precursor for the synthesis of isoindoloquinolines **410**[235]. 4-α-Furyl-4-*N*-

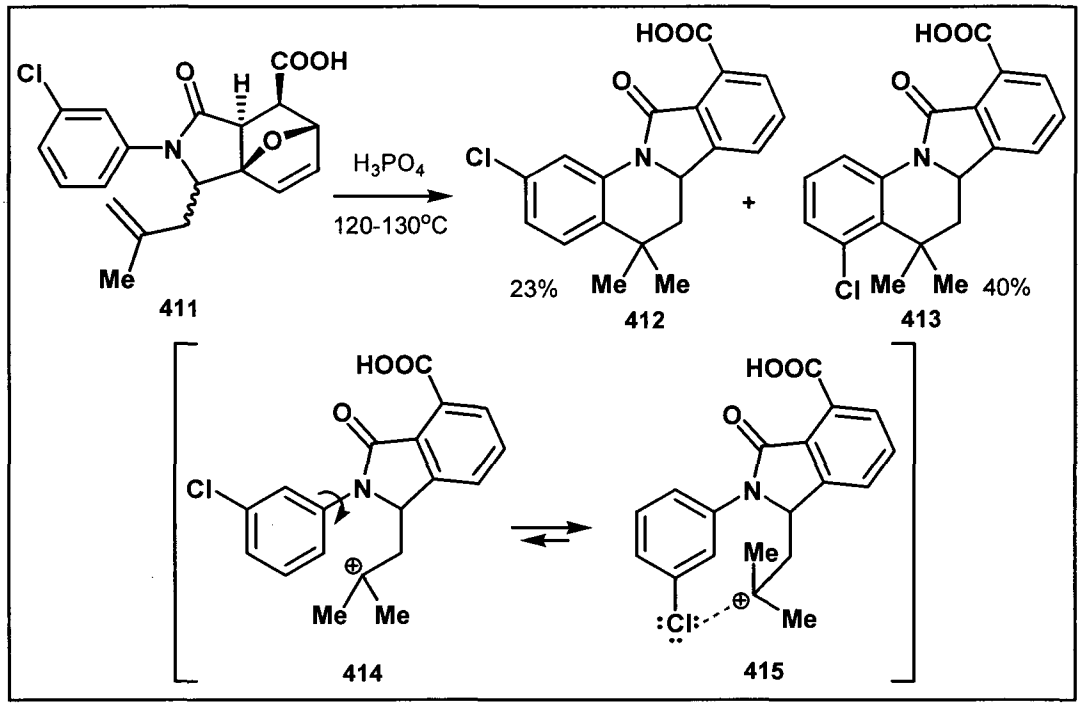
arylaminobut-1-enes **408** and maleic anhydride underwent the N-acylation/intramolecular [4+2] cycloaddition reaction to form **409**. Dehydration/aromatization of the oxabicyclic fragment of **409** using phosphoric acid followed by an intramolecular cyclization of the methallyl [$-CH_2CH(Me)=CH_2$] group resulted in **410**.

Scheme 5.13



Zubkov and co-workers later reported a similar reaction with many other systems and conditions[236,237]. In an interesting observation[238], they used *m*-chloroaryl derivative **411** (Scheme 5.14) and got two cyclic compounds **412** (minor) and **413** (major). This may be explained by involving carbocation **414**, which upon free *N*-Ar bond rotation converts to the relatively more stable carbocation **415**. The higher stability of **415** is due to the interaction between carbocation and non-bonding pair electrons of chloride, which consequently resulted in the major formation of **413**. We will be back to the mechanistic features of the reaction later in this chapter.

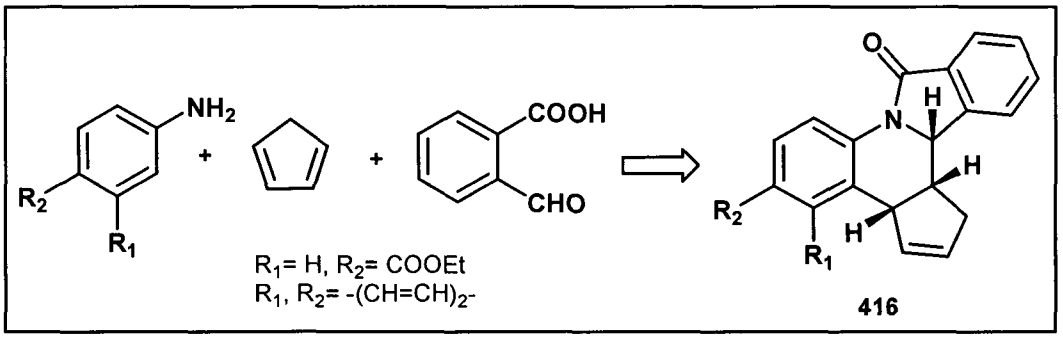
Scheme 5.14



5.4 Our Synthesis Approach

As mentioned in section 5.1, the main purpose of this work is the preparation of isoindolo[2,1-*a*]quinoline system directly from *N*-aryl compounds. This interest fortunately led us to the novel synthesis of cyclopenta[*c*]-isoindolo[2,1-*a*]-quinoline-11-one derivatives **416** (Scheme 5.15) using simple and commercially available starting materials[221b]. We are also pleased that the presenting reaction was performed in one-pot (tandem type). Consequently, it is considered a multicomponent reaction.

Scheme 5.15



This complex pentacyclic system (hexacyclic system when aminonaphthalene used) contains three stereogenic centres and a few sites for further exploration. In the remaining section of this chapter, we will discuss many aspects of the mechanism, characterization of polycyclics, further reactions in the system, etc. Since the key step for the above transformation is multicomponent 'Povarov' reaction, we will begin with this subject.

5.4.1 Povarov Reaction: An Extension

Utilizing multi-component reactions (MCR) is a well-recognized approach to obtain heterocyclic compounds[239,240]. Povarov reported an interesting multi-component reaction using amines, aldehydes, electron-rich olefins and an acid (or Lewis acid) as the catalyst to prepare substituted tetrahydroquinolines[241]. During past 40 years, many scientists continue to explore this reaction[242]. The great interest in making tetrahydroquinoline scaffold using this method and the promising biological activities associated with this scaffold were also acknowledged in many patents. Compounds presented in Figure 5.4 are only two examples of bioactive molecules, which were prepared using Povarov reaction. G-protein-coupled receptor (GPR-30) is a cell surface receptor, which with high affinity binds estrogen. The first GPR-30 specific agonist **417** which is capable of activating GPR-30 in complex environments was identified by the teams of Oprea and Prossnitz[243]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a

bacterium responsible for infections difficult to treat. Antibacterial agents **418** with potent *in vitro* activity versus MSRA discovered by Hoemann and his team[244].

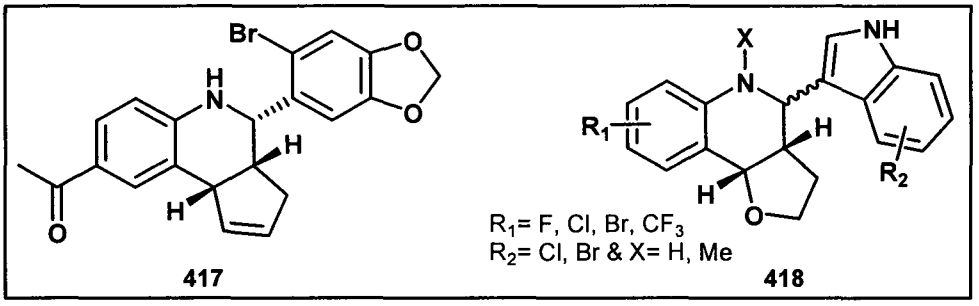
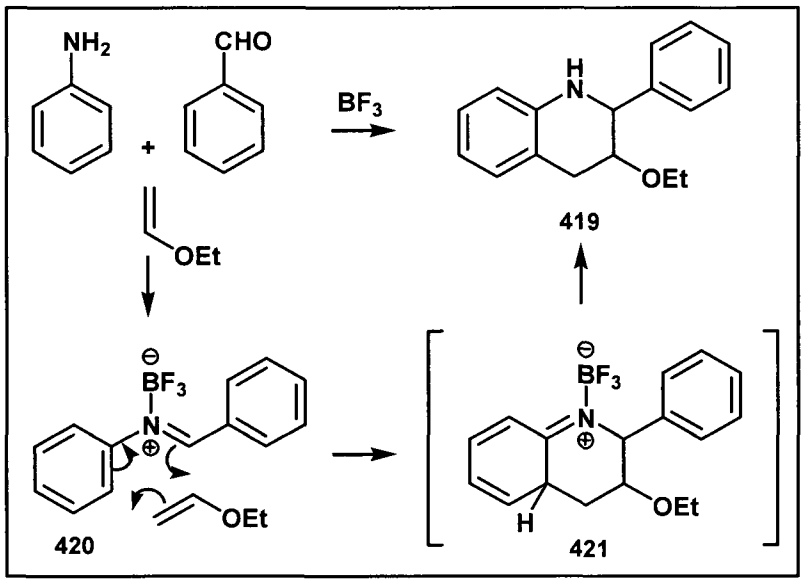


Figure 5.4 Bioactive Compounds Synthesized by Povarov Reaction

This MCR allows tetrahydroquinoline to be obtained in one single step and with only one stereoisomer. This reaction is also regioselective. In Scheme 5.16 the original reaction performed by Povarov and the proposed mechanism were illustrated. 3-ethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline **419** was prepared from aniline, benzaldehyde, and ethyl vinyl ether in the presence of the Lewis acid trifluoroborane in high yield. The mechanism proposed by Povarov includes intermediacy of **421** and involvement of a [4+2] cycloaddition reaction on the activated Schiff base **420** (an aza Diels-Alder reaction). Re-aromatization on **421** would afford the tetrahydroquinoline **419**.

Scheme 5.16

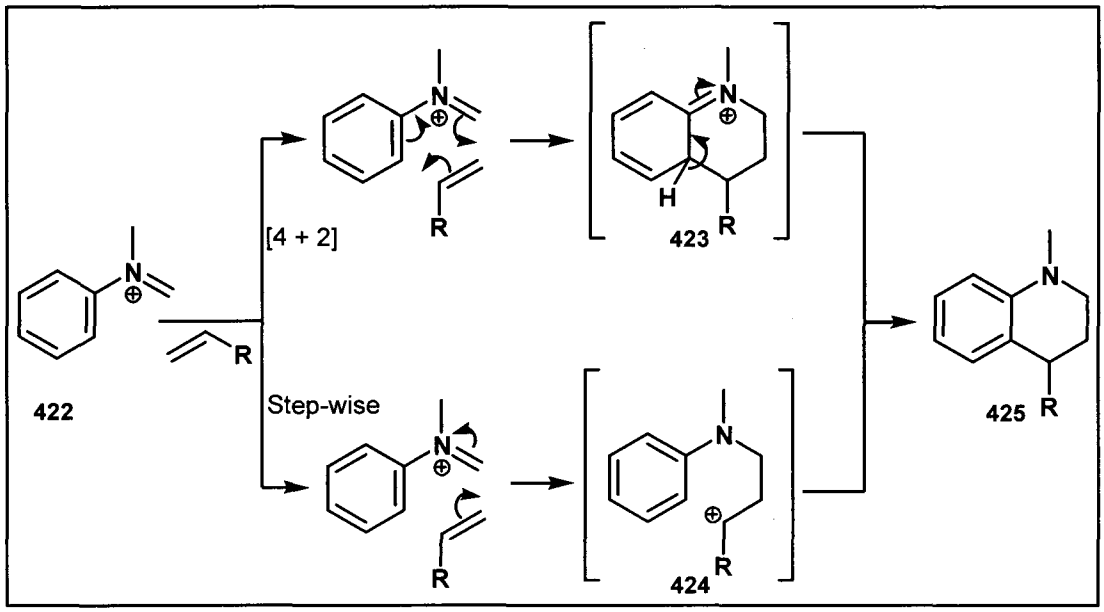


5.4.1.1 Mechanism

Aza Diels-Alder reaction between electron-deficient Schiff base and electron-rich alkene is one of the most convenient routes to the synthesis of *N*-heterocycles[245]. The tetrahydroquinoline obtained through Povarov type reaction can be viewed as being formed through either a concerted inverse electron demand hetero Diels-Alder reaction with intermediacy of **423** (Scheme 5.17-simplified) or via a step-wise process beginning from the addition of an olefin to an iminium ion forming carbocation **424** as an intermediate followed by an intramolecular electrophilic aromatic substitution (Friedel-Crafts) reaction to create tetrahydro-quinoline **425**. Despite initial proposed mechanism by Povarov and a few groups in favor of the cycloaddition route[245,246], many other chemists found the step-wise route more complying with their observed results[148,151,247-250]. Both mechanisms, however, can appropriately explain the regio- and stereo-selective nature of the reaction[242]. Almost all the reported works on the mechanism of this reaction have stressed their approach on the olefin and/or the azabutadiene fragment but rarely on the aromatic ring. Our approach to the mechanism of Povarov reaction and to

further synthesis of complex polycylics has also considered the role of the aromatic substitutions (Sections 5.4.1.3 and 5.4.2.2 below).

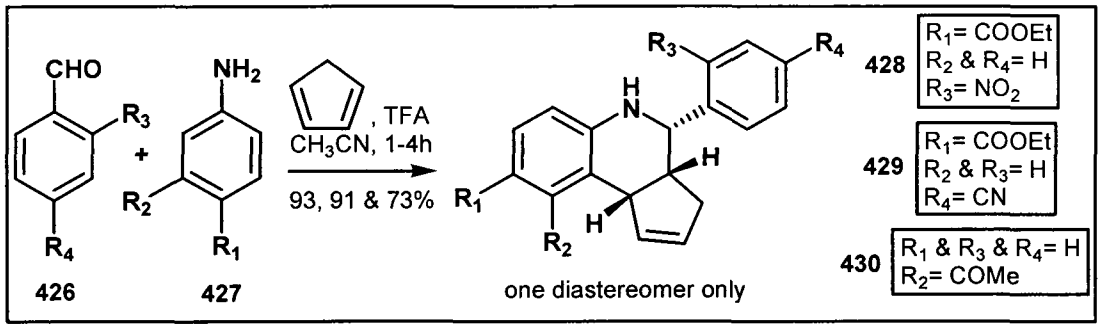
Scheme 5.17



5.4.1.2 Synthesis of Tetrahydroquinoline Tricycles

For a better understanding of stereo- and regio-selective nature of Povarov reaction, we performed this reaction three times using two different aldehydes **426** and amines **427**, cyclopentadiene as dienophile, trifluoroacetic acid as the acid in acetonitrile (Scheme 5.18). Reactions were performed at room temperature and were completed between one and four hours. Tetrahydro-quinoline tricycles **428-430** formed only in one of their diastereomeric forms. Yields varied from 73 to 93%. These compounds completely characterized by mass, 1D and 2D NMR, and finally by X-ray crystallography.

Scheme 5.18



Since the synthesized compounds are similar, we only indicate some aspects of 1D and 2D NMR. For more clarity, only hydrogens on cyclopenta[*c*]pyridine fragment of **428-430** are presented here (Figure 5.5).

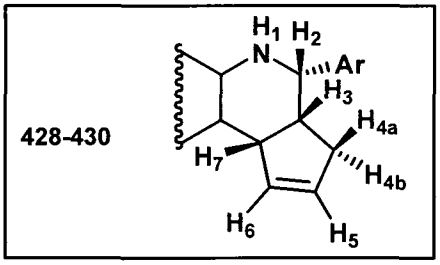


Figure 5.5 Protons in Cyclopenta[*c*]pyridine Fragment

Extracted from ^{1}H-NMR spectra, chemical shifts (in ppm, first number), multiplicities (second part), and coupling constants [*J* in Hz, last number(s)] are presented for all H_1 to H_7 of **428-430** at Table 5.1. For H_{4a} and H_{4b}, the exact α or β position could not be defined.

Table 5.1 ^{1}H-NMR Data (In Part) for Tetrahydroquinolines Tricycles **428** to **430**

	H_1	H_2	H_3	H_{4a}	H_{4b}	H_5	H_6	H_7
428	3.98, bs	5.24, d 3.0	3.33, qd 3.0, 9.0	1.84, dd 8.5, 15.5	2.65, m	5.69, m	5.99, m	4.19, d 9.0
429	4.66, bs	4.75, d 3.0	3.0, qd 3.5, 9.0	1.74, dd 8.5, 15.5	2.49, m	5.64, m	5.92, m	4.12, m
430	not found	4.64, d 3.0	3.10, qd 3.0, 9.0	1.85, dd 8.7, 16.1	2.68, m	5.64, m	5.64, m	4.91, d 9.0

Tetrahydroquinoline **430** was afforded not only stereoselectively but also regioselectively. 1D and 2D NMR confirmed the synthesized product is in fact **430** and not **431** (Figure 5.6). The explanation for this noted regio-selectivity will be discussed in the next section (Section 5.4.1.3).

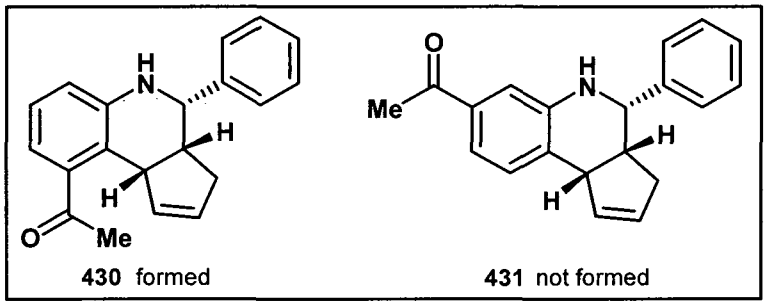


Figure 5.6 Regioselective Formation of **430**

As sample, COSY spectrum of tetrahydrouinoline tricyclic compound **429** is shown in Figure 5.7. Each color represents the correlation between marked couple protons. H_{4a} and H_{4b} are diastereomeric protons, therefore; we expected to see not only two different chemical shifts but also two different correlation patterns. Interestingly, each olefinic proton, i.e., H_5 and H_6, also showed a relationship with either H_{4a} or H_{4b}.

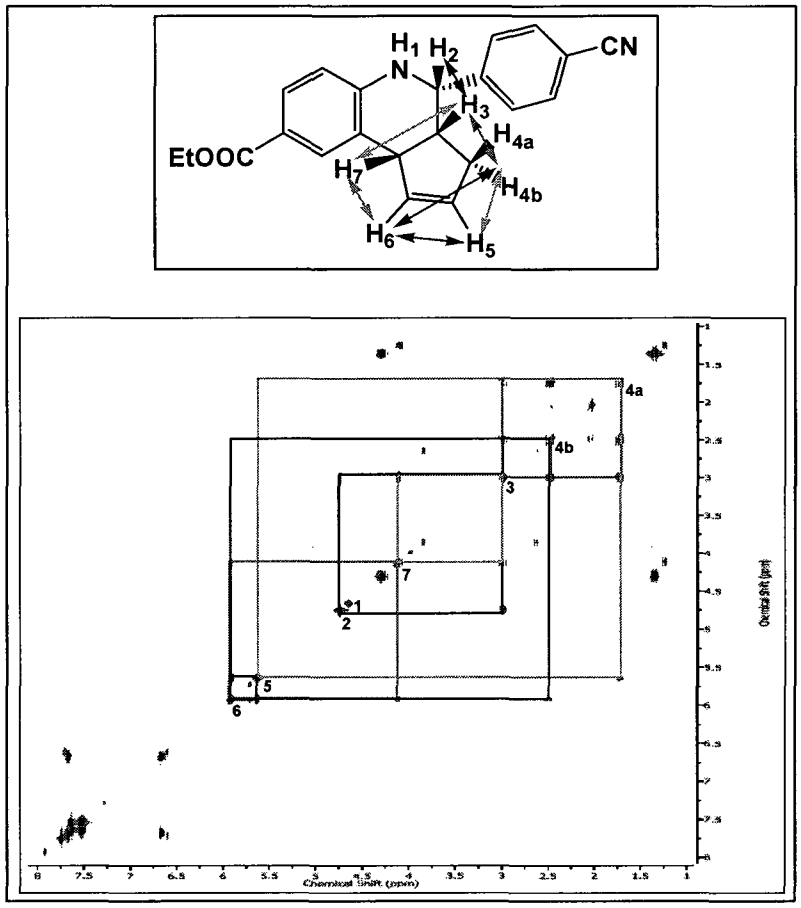


Figure 5.7 Proton Correlations and COSY Spectrum for Compound **429**

Finally, by recrystallization of all three prepared tetrahydroquinoline tricycles and taking X-ray, the entire characterization package completed. In Figure 5.8, the X-ray structure for each compound (**428** to **430**) was presented. Note the stereoselectivity for all compounds (only one diastereomer) and regioselectivity (for **430**).

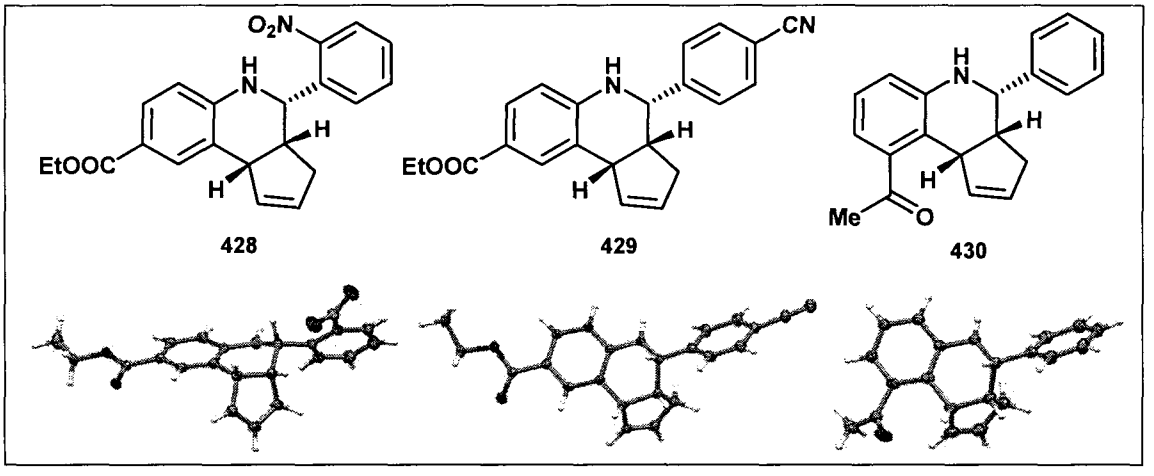


Figure 5.8 X-ray Structures for Tetrahydroquinolines Tricycles **428-430**

Crystal data for these compounds are presented in Table 5.2.

Table 5.2 Crystal Data for Tetrahydroquinoline Tricycles **428-430**

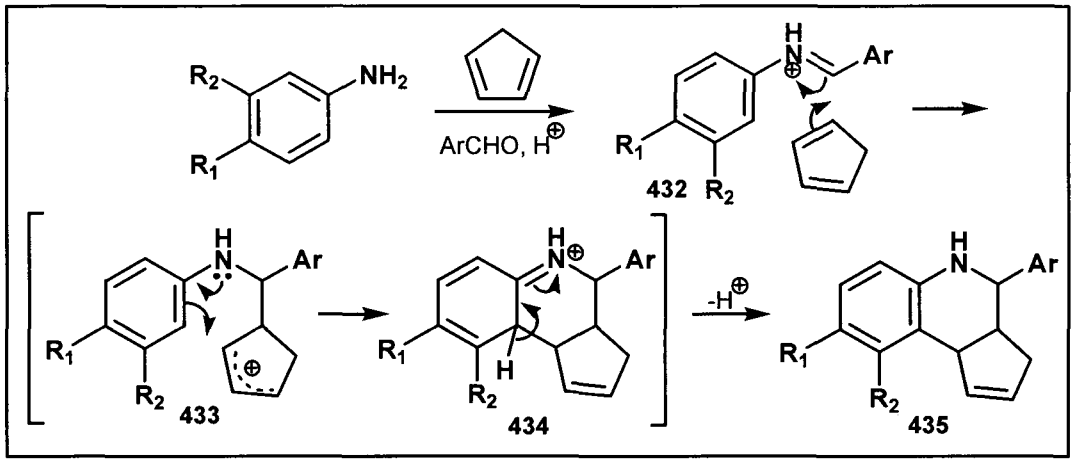
	Compound 428	**Compound 429**	**Compound 430**
Identification code	Shah 8	SH 4	SH 12
Empirical formula	$C_{21}H_{20}N_2O_4$	$C_{22}H_{20}N_2O_2$	$C_{20}H_{19}NO$
Formula weight	364.39	344.40	289.36
Temperature	125(2) K	125(2) K	125(1) K
Wavelength	0.71070 Å	0.71070 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	P2(1)/n	P-1	P2(1)/c
Unit cell dimensions	a = 9.943(13) Å, α= 90°	a = 8.669(8) Å, α= 111.56°	a = 15.283(3) Å, α= 90°
	b = 12.796(17) Å, β= 108.48(2)°	b = 9.146(8) Å, β= 100.92°	b = 7.373(15) Å, β=117.81(3)°
	c = 15.293(2) Å, γ = 90°	c = 12.287(11) Å, γ = 94.73°	c = 15.427(3) Å, γ = 90°
Volume	1845.4(4) $Å^3$	877.22(14) $Å^3$	1537.6(5) $Å^3$
Z	4	2	4
Density (calculated)	1.304 Mg/m^3	1.304 Mg/m^3	1.250 Mg/m^3
Absorption coefficient	0.090 mm^{-1}	0.084 mm^{-1}	0.076 mm^{-1}
F(000)	764	364	616
Crystal size	0.5 × 0.5 × 0.15 mm^3	0.5 × 0.25 × 0.5 mm^3	0.35 × 0.20 × 0.08 mm^3
θ range for data collection	2.12 to 28.25°	1.83 to 29.55°	1.49 to 29.53°
Index ranges	$-13 \le h \le 13$	$-12 \le h \le 11$	$-21 \le h \le 21$
	$-16 \le k \le 17$	$-12 \le k \le 12$	$-10 \le k \le 10$
	$-20 \le l \le 20$	$-17 \le l \le 16$	$-21 \le k \le 21$
Reflections collected	20761	10945	18429

Independent reflections	4569 [R(int) = 0.0247]	4808[R(int) = 0.0160]	4260[R(int) = 0.0311]
Absorption correction	multiscan	multiscan	multiscan
Data / restraints / parameters	4569 / 12 / 331	4808 / 0 / 315	4260/ 0 / 276
Goodness-of-fit on F^2	1.027	1.039	1.031
Final R indices [I>2σ(I)]	R1 = 0.0479, wR2 = 0.1400	R1 = 0.0390, wR2 = 0.1105	R1 = 0.0613, wR2 = 0.1489
R indices (all data)	R1 = 0.0521, wR2 = 0.1456	R1 = 0.0428, wR2 = 0.1154	R1 = 0.0833, wR2 = 0.1605
Largest diff. peak and hole	0.693 and -0.323 e.Å^{-3}	0.370 and -0.231 e.Å^{-3}	0.339 and -0.269 e.Å^{-3}

5.4.1.3 Closer Look at the Mechanism: More Evidence for Step-Wise Route

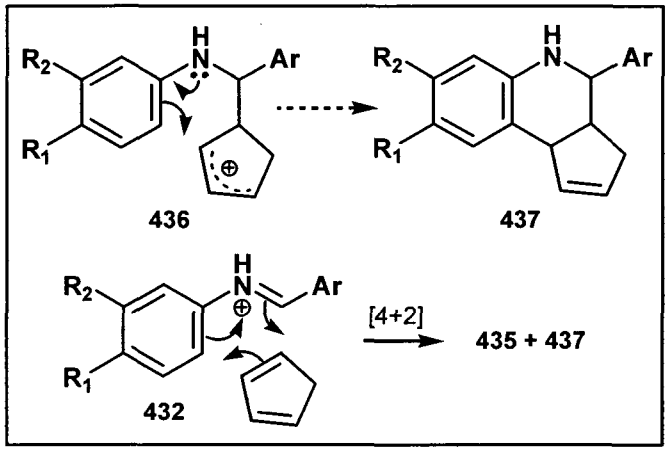
In Section 5.3 (Scheme 5.14) based on the work by Zubkov and co-workers, the chloro compound **413** was the major product. We suggested this result might be due to more stability of the carbocation intermediate **415** (compared to **414**). If a [4+2] cycloaddition mechanism predominantly occurs, compound **412** will be expected to be the major product because of its less steric hindrance. However, this example cannot resolve all the issues about the mechanism simply because both products were observed. As seen above, although compounds **428** and **429** were formed with complete diastereoselection, compound **430** was afforded with complete regio- and diastereoselectivity. This regioselectivity cannot be explained by the concerted hetero Diels-Alder reaction as both **430** and **431** expected to be observed. As a matter of fact, due to steric hindrance, compound **431** is expected to be the major product. For a better explanation for this observation, a more detailed step-wise mechanism is presented in Scheme 5.19. Intermediate **433** was initially formed from Schiff base **432** and cyclopentadiene. The electron demanding allylic carbocation **433** is stabilized by neighboring group R_2 on the aromatic ring affording **434**. Re-aromatization on **434** gives the product **435**. Carbocation **433** should not be predominate intermediate unless by assistance from R_2.

Scheme 5.19



On the other hand, less crowded allylic carbocation **436** (Scheme 5.20) would generate tetrahydroquinoline **437** exclusively. Concerted [4+2] cycloaddition route would afford a mixture of regioisomeric products due to free *N*-Ar bond rotation prior to addition. Observation by other chemists such as Zubkov, showed mixtures of products were formed which overweighs neither of the explained mechanisms.

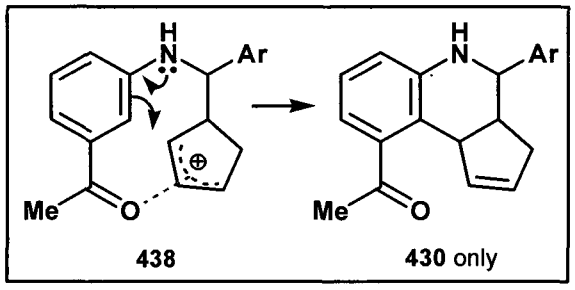
Scheme 5.20



The only remaining possibility for the unique formation of **430** is the step-wise route through carbocation **438** illustrated in Scheme 5.21. Non-bonding pairs of

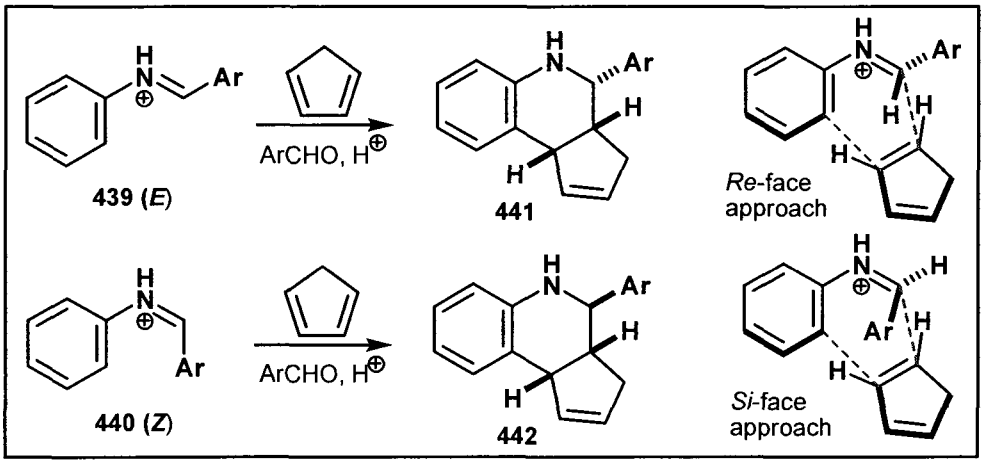
electrons in Oxygen in keto group theoretically can stabilize **438** and make it the predominant carbocation intermediate. In our performed reaction, in fact, **438** must be the only generated carbocation. Electron rich neighboring groups orient in close proximity with allylic carbocation. Another evidence for this conclusion will be presented in Section 5.4.2.2.

Scheme 5.21



The complete diastereoselectivity in the preparation of tetrahydroquinoline tricycles can be explained by the exclusive formation of Schiff base in its *E* form (**439**, Scheme 5.22) which produces **441** through *Re*-face approach of dienophile (cyclopentadiene). Similarly, less stable Schiff base **440** (*Z* form) affords **442**. Both mechanisms explained above do not affect the stereoselectivity of the reaction.

Scheme 5.22



5.4.2 Synthesis of Tetrahydroquinoline-Derived Penta- and Hexacycles

In section 5.3 we reviewed the methodologies for the preparation of isoindolo[2,1-*a*]quinolines. Most of them needed several stages and were not satisfactory either in generality or in yield. Moreover, they generally suffered from lack of stereochemistry. We were particularly successful for the synthesis of the cyclopenta[*c*]isoindolo[2,1-*a*]quinoline-11-one system (compounds **443** and **444**) in one-pot through a tandem type reaction (Figure 5.9). When 2-aminonaphthalene was used as the starting material, the hexacyclic compound **444** was formed regioselecetively. Besides synthesis, this section will present several aspects of this reaction including mechanism, characterization of polycyclics, further reactions in the system, and future works.

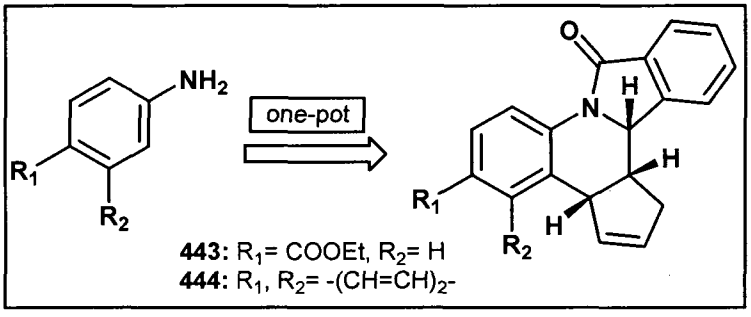
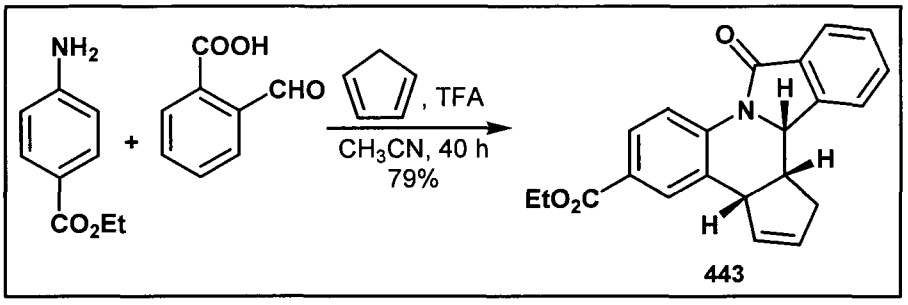


Figure 5.9 One-pot Synthesis of Cyclopenta[*c*]isoindolo[2,1-*a*]quinoline System

5.4.2.1 One-Pot Synthesis of Isoindolo[2,1-*a*]quinoline System

3-Ethyl-11-oxo-cyclopenta[c]isoindolo[2,1-a]quinoline-carboxylate **443** (Scheme 5.23) was synthesized by a multicomponent reaction using ethyl-4-aminobenzoate, 2-carboxybenzaldehyde, and cyclopentadiene in the presence of trifluoroacetic acid. Acetonitrile as the solvent and other conditions are similar for preparing tricyclic compounds in Section 5.4.1.2. Although the reaction took 40 hours to complete, only one product was observed by TLC.

Scheme 5.23



Crude mass spectrum showed a distinct peak at 346.3 corresponding to M+1. After purification, structural elucidation of this compound was performed using 1D NMR (^{1}H and ^{13}C), 2D NMR (COSY, HSQC), and finally by X-ray crystallography. The pattern observed in 1D and 2D spectra were similar to those for compound **428-430** (Figure 5.5 and 5.7). However, the difference appeared in ^{13}C-NMR by finding an extra peak for carbonyl group (in γ-lactam) around 166.8 ppm. Product itself was in a form of crystalline solid (white in color). We recrystallized compound **443** and took its X-ray diffraction. X-ray structure of our pentacyclic compound presents in Figure 5.10.

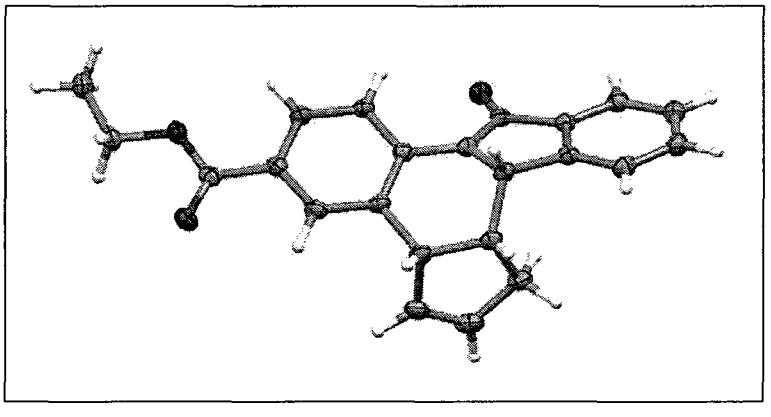


Figure 5.10 X-ray Structure of Compound **443**

Crystal data for this compound is provided in Table 5.3.

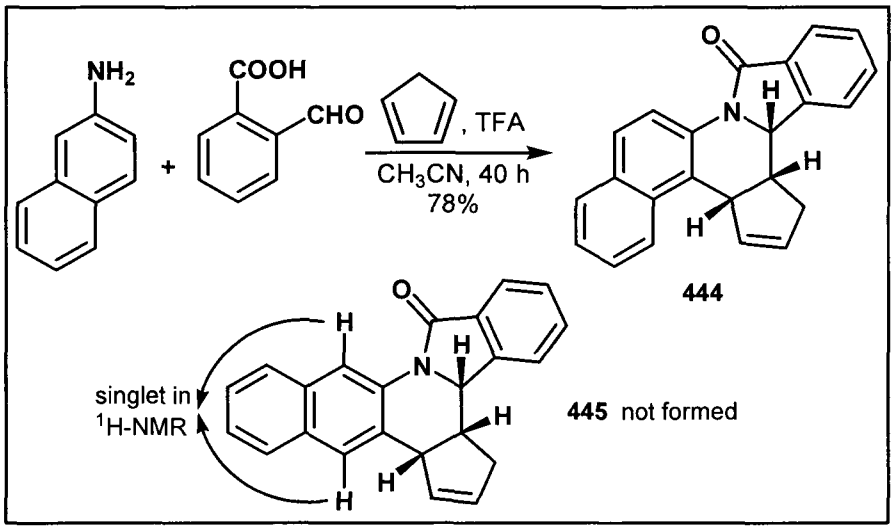
Table 5.3 Crystal Data for Compound **443**

Identification code	sadf
Empirical formula	$C_{22}H_{19}NO_3$
Formula weight	345.38
Temperature	125(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 13.299(5) Å α= 90°
	b = 8.521(3) Å β= 94.04(3)°
	c = 14.969(5) Å γ = 90°
Volume	1692.0(11) $Å^3$
Z	4
Density (calculated)	1.356 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	728
Crystal size	0.45 x 0.15 x 0.15 mm^3
θ range for data collection	1.54 to 29.05°.
Index ranges	-18≤h≤18, -11≤k≤11, -20≤l≤20
Reflections collected	19839
Independent reflections	4514 [R(int) = 0.0258]
Completeness to theta = 29.05°	99.6 %
Absorption correction	Multiscan
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4514 / 0 / 311
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.1038
R indices (all data)	R1 = 0.0490, wR2 = 0.1106
Largest diff. peak and hole	0.371 and -0.225 e.$Å^{-3}$

Exploring the regioselectivity of this reaction and comparing the outcome with the previous Pavarov reaction in the synthesis of compound **430** was our next stage. As shown in Figure 5.6, complete regioselectivity on the aromatic ring of **430** was observed. This time we used 2-aminonaphthalene instead as our amine but the

same reagents and conditions (Scheme 5.24). TLC showed an appearance of just one product. After purification, complete data analysis was performed using mass spectra, 1D NMR (^{1}H, ^{13}C, DEPT), 2D NMR (COSY, HSQC, HMBC), and finally by X-ray crystallography which confirmed our synthesis (**444**). The full name of this hexacyclic compound which its commercial form has no defined stereochemistry, found to be '4c,7,7a,7b-tetrahydro-12H-benzo[*f*]cyclopenta[*c*]-isoindolo[2,1-*a*]quinoline-12-one'. No reported synthesis of this commercial compound was found.

Scheme 5.24



The non-aromatic hydrogens in NMR spectra showed similarity. Distinguish between **444** and **445** were not difficult; aromatic hydrogens in **445** should show 2 singlets and no such this was observed in the product. This aromatic region was selected for some more in-depth analysis. In Figure 5.11 structure, ^{1}H-NMR, and COSY spectra (for aromatic hydrogens) for compound **444** were showed. Aromatic hydrogens were numbered and correlations between them showed in different colors for better clarity.

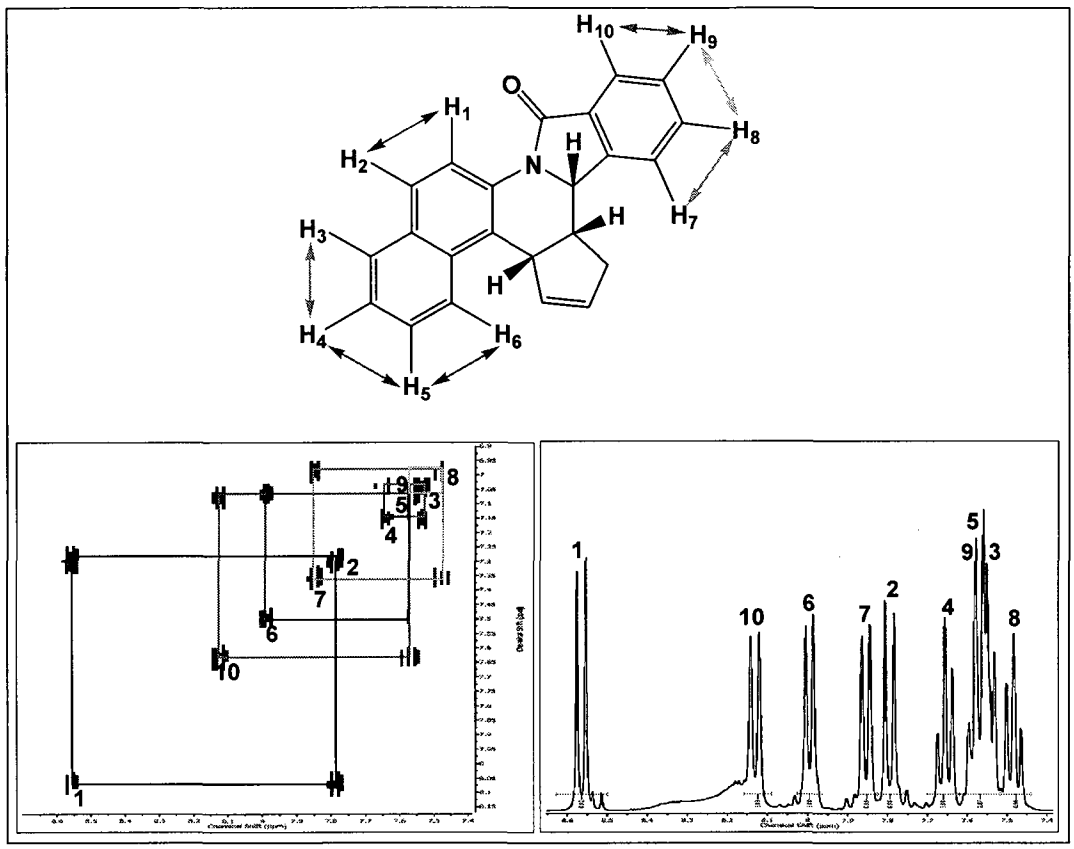


Figure 5.11 Proton Assignment/ Correlations and Using COSY/ ^{1}H-NMR Spectra for Compound **444**

This compound was re-crystallized for the purpose of providing suitable crystal form for the X-ray diffraction. X-ray structure and crystal data of this hexacyclic compound presents in Figure 5.12 and Table 5.4, respectively.

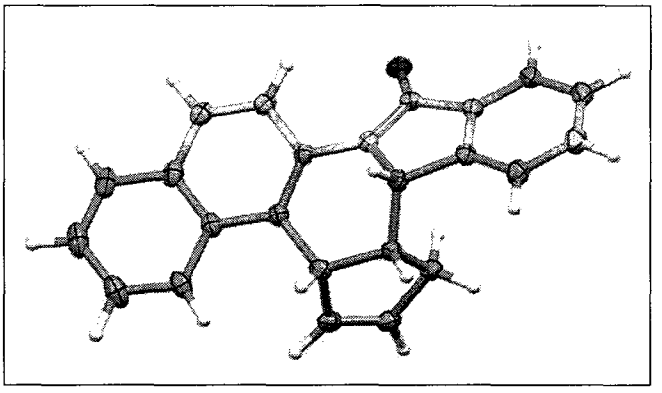


Figure 5.12 X-ray Structure of Compound **444**

Table 5.4 Crystal Data for Compound **444**

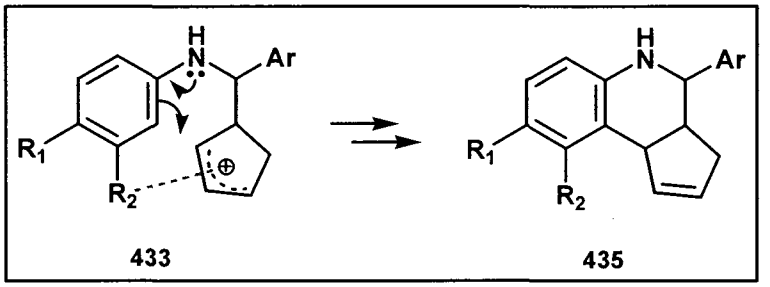
Identification code	SH 10
Empirical formula	$C_{23}H_{17}NO$
Formula weight	323.38
Temperature	125(2) K
Wavelength	0.71070 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 8.847(11) Å, α= 90°
	b = 12.554(16) Å, β= 90°
	c = 14.410(18) Å, γ = 90°
Volume	1600.4(3) $Å^3$
Z	4
Density (calculated)	1.342 Mg/m^3
Absorption coefficient	0.082 mm^{-1}
F(000)	680
Crystal size	0.5 × 0.2 × 0.2 mm^3
θ range for data collection	0.997 to 29.53°
Index ranges	$-12 \leq h \leq 12$
	$-17 \leq k \leq 17$
	$-19 \leq l \leq 19$
Reflections collected	20029

Independent reflections	4430[R(int) = 0.0213]
Absorption correction	multiscan
Data / restraints / parameters	4430 / 0 / 294
Goodness-of-fit on F^2	1.039
Final R indices [I>2σ(I)]	R1 = 0.0332, wR2 = 0.0903
R indices (all data)	R1 = 0.0345, wR2 = 0.0922
Largest diff. peak and hole	0.277 and -0.263 e.Å^{-3}

5.4.2.2 Mechanistic View

It seems reasonable if we assume this tandem reaction contains; a) Schiff base preparation from nucleophilic attack of amine to more reactive carbonyl function of 2-carboxybenzaldehyde, i.e., aldehyde, b) reaction of Schiff base with cyclopentadiene, and c) intramolecular condensation (dehydration) of the formed secondary amine (located at tetrahydroquinoline core) to *o*-carboxylic acid function resulted in the formation of a γ-lactam ring meaning the construction of whole polycyclic system. This mechanism, however, may simply be explained by a Povarov/cyclocondensation tandem reaction. In Section 5.4.1.3, we provided an evidence for a step-wise route through a stabilized carbocation **433**. If R_2 could stabilize **433** by keeping allylic carbocation in close proximity to itself, we would expect to observe **435** exclusively.

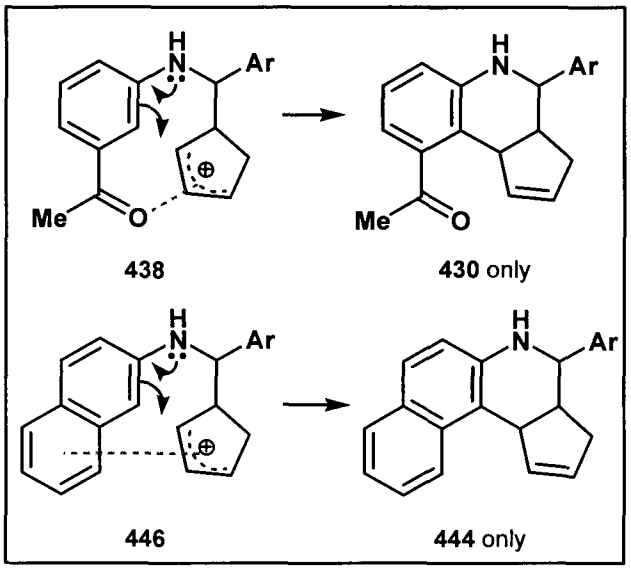
Scheme 5.25



As we explained before, carbocation **438** will afford **430** (only) by its ability to self-stabilizing (Scheme 5.26). The similar approach may apply for product **444**

by forming self-stabilized carbocation **446**. However, in this case there is no non-bonding pair(s) of the electron but only the electron-rich environment within naphthalene's second ring. This complete regioselectivity cannot be rationalized by a concerted cycloaddition mechanism.

Scheme 5.26



5.4.2.3 Further Exploration: Stereoselective Reactions

Pentacyclic compound **443** is a valuable scaffold in diversity-oriented synthesis (Chapter 1), not just because it can be prepared in only one-pot, but because of its several diversity sites (Figure 5.13). Moreover, it potentially contains an anchoring site needed for solid phase synthesis, i.e. the carboxyl ester. One can imagine the possible diversification in both aromatic rings. Since we have already made the compound, we decided to explore some extra reactions on the double bond.

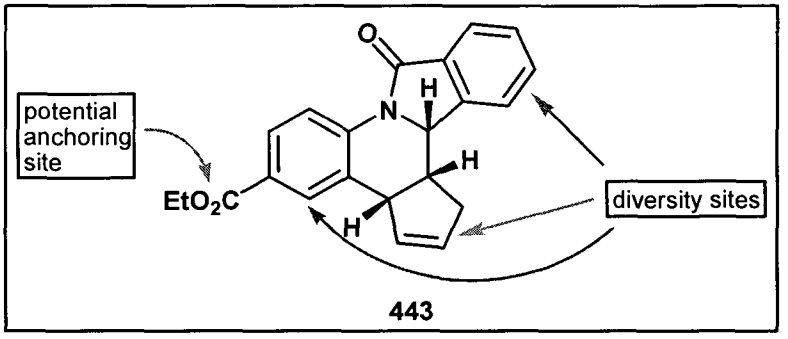


Figure 5.13 Compound **443**; a Valuable Scaffold in DOS

Typical for cycloalkenes, an addition reaction had to be designed. Chirality and specific shape of **443** (see its X-ray in Figure 5.10) enticed us to explore a stereoselective reaction. We decided to try epoxidation using *m*-CPBA on the double bond with hope to see some stereoselectivity. Because of difference between the two faces of **443**, *i.e.*, concave and convex (Figure 5.14), our expectation was valid.

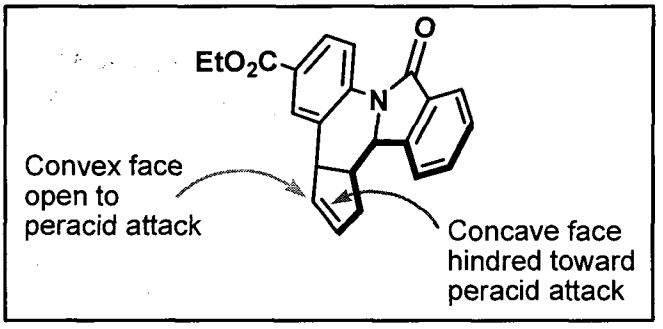
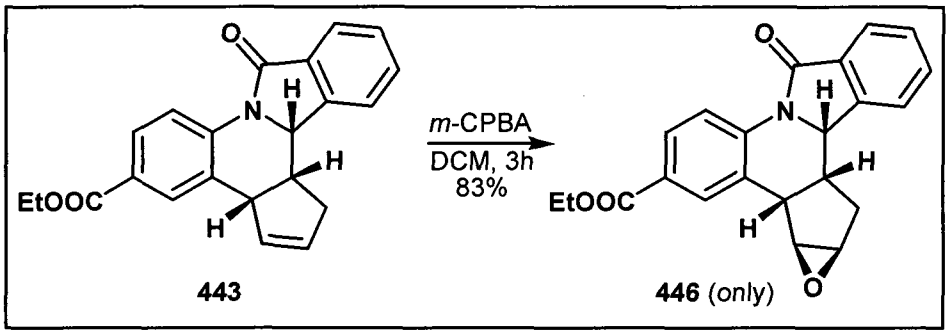


Figure 5.14 Concave and Convex faces in **443**

Epoxidation by *m*-CPBA smoothly proceeded in dichloromethane at room temperature (20°C) and ended in three hours (Scheme 5.27). Although mass spectrum confirmed the transformation, *i.e.*, (M+1) of compound **443** + 16, we purified epoxide **446** and found a yield of 83%. Expecting some degree of stereoselectivity, we observed only one compound. We believed the epoxide ring

is in β-position (as shown). However, confirmation by data analysis was necessary.

Scheme 5.27



NMR data analysis and X-ray crystallography confirmed our proposed structure. Since the proton pattern in **446** is quite different from previous compounds, especially on cyclopenta[*c*] ring, we look at the aliphatic protons of the molecule more closely. As shown in Figure 5.15, aliphatic protons are numbered and COSY spectrum showing the hydrogen's relationships (in different colors), is provided. Finally, the assignment for the aliphatic protons is presented in ^{1}H-NMR. Correlations between H_6-H_5 and also H_6-H_{3a} appeared weakly (showed in dotted lines).

This reaction was highly facial selective since only β-epoxide was observed. The epoxide ring added two more stereogenic centres to **443**, so this number for hexacyclic **446** has now reached to five.

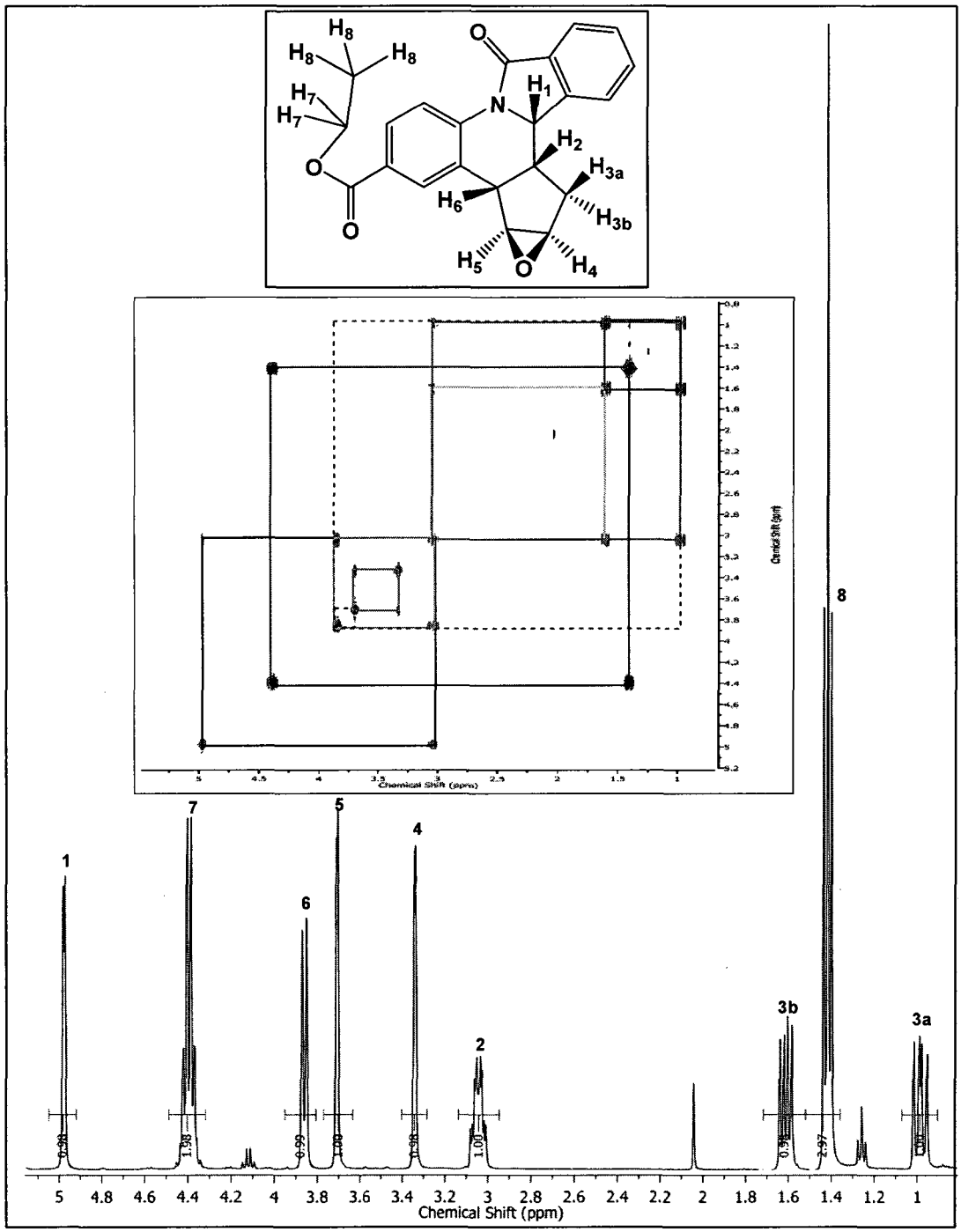


Figure 5.15 Aliphatic Protons Assignment for **446** Using ^{1}H-NMR and COSY

As the most reliable and precise structure determination, X-ray crystallography was performed on this compound. X-ray structure of polycyclic **446** as well as X-ray data have provided in Figure 5.15 and Table 5.5, respectively.

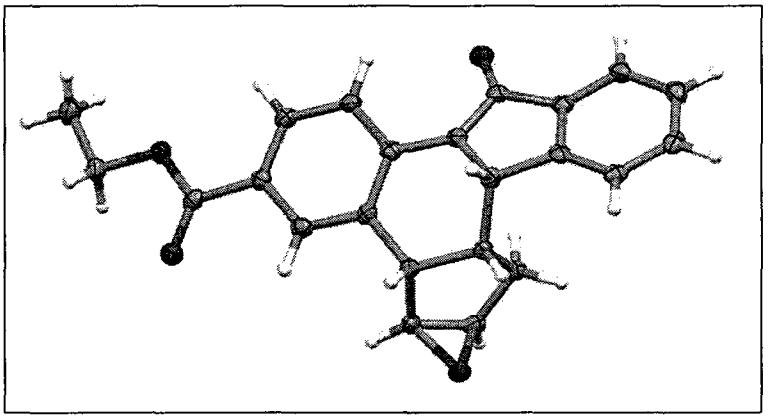


Figure 5.15 X-ray Structure of Compound **446**

Table 5.5 X-ray Data for Compound **446**

Identification code	Sh9	
Empirical formula	$C_{22}H_{19}NO_4$	
Formula weight	361.38	
Temperature	125(2) K	
Wavelength	0.71070 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 20.128(3) Å	α= 90°
	b = 13.147(2) Å	β= 92.227(3)°
	c = 12.929(2) Å	γ = 90°
Volume	3418.7(10) $Å^3$	
Z	8	
Density (calculated)	1.404 Mg/m^3	
Absorption coefficient	0.097 mm^{-1}	
F(000)	1520	
Crystal size	0.50 x 0.10 x 0.05 mm^3	

θ range for data collection	1.01 to 28.33°.
Index ranges	-26<=h<=26, -17<=k<=17, -17<=l<=17
Reflections collected	38298
Independent reflections	8474 [R(int) = 0.0541]
Completeness to theta = 28.33°	99.4 %
Absorption correction	Multiscan
Max. and min. transmission	0.9952 and 0.9531
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8474 / 3 / 646
Goodness-of-fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1033
R indices (all data)	R1 = 0.0886, wR2 = 0.1217
Largest diff. peak and hole	0.369 and -0.285 e.Å^{-3}

Since epoxide-opening reaction provides, at least two diversity sites, any nucleophile capable of the reaction can be considered. For ring opening, we decided to use *p*-bromoaniline; it is a good nucleophile having a symmetrical structure (easier for NMR assignment) which provides an additional secondary amine for diversification purpose. However, we did not know about the regioselective nature of this reaction. By looking at the structure of epoxide **446**, especially its X-ray (Figure 5.15), it seems there is a difference for α-nucleophilic attack between two side of the epoxide ring. However, the size of the nucleophile also plays an influential role in the regioselectivity. As showed in Scheme 5.28, nucleophilic attack from the right side of the epoxide (green arrow) would give **447** and from the left (red arrow) would afford its regioisomer (**448**). Without any further guess, we performed the reaction using *p*-bromoaniline in the presence of the Lewis acid (boron trifluoride). One single compound appeared as the product meaning the complete regioselectivity was achieved.

Compound **447**, the most complex cyclic compound in our research, has some interesting features:

a) it has 5 stereogenic centres,

b) it has several diversity sites; i) first diversification may come from aromatic rings **A** and/or **B**, ii) nucleophile itself is a choice, in this situation **C** ring with bromine,

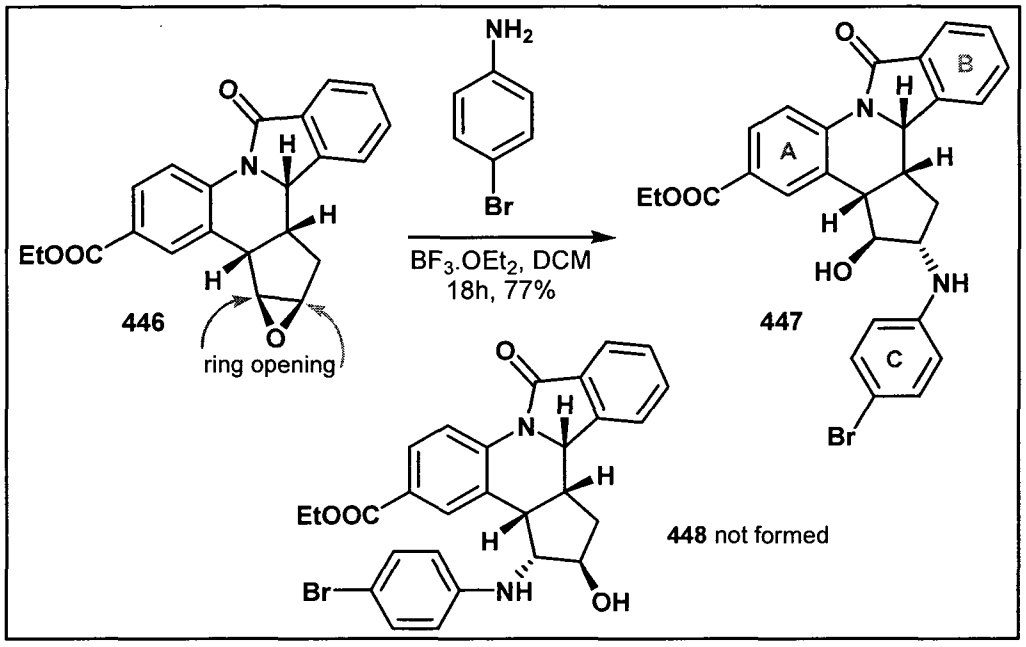
c) it created further reaction possibilities; in this case hydroxyl, bromine, and secondary amine,

d) it has a potential anchoring site for solid phase exploration, i.e., carboxy-ester group which can easily be modified to become active on loading process,

e) reaction performed in only 3 stages, and finally

f) reaction advanced with complete stereo- and regio-selectivity.

Scheme 5.28



Since in this case we were not able to get the X-ray structure, we should assign the molecule using NMR. For this task, we used ^{1}H-NMR, ^{13}C-NMR, COSY, and HSQC. For the complete structure determination, we worked on aromatic and aliphatic protons separately similar to the previous compounds. Then, combination of those provided us the complete assignment. Interesting 'problem solving' was performed but this stage will not be fully explained with details because of prevention from repeating. Final ^{1}H-NMR with integration is presented in Figure 5.16 (NMR spectrum has moved up slightly for more clarity). All hydrogens were numbered except OH and NH, which could not accurately find. On the other hand, peaks corresponded to solvents (chloroform, ethyl acetate, and hexane) did not integrate. Based on full information we gathered, we can now claim the epoxide ring opening reaction on **446** proceeded regioselectively (and stereospecific) since pure product contains only **447**.

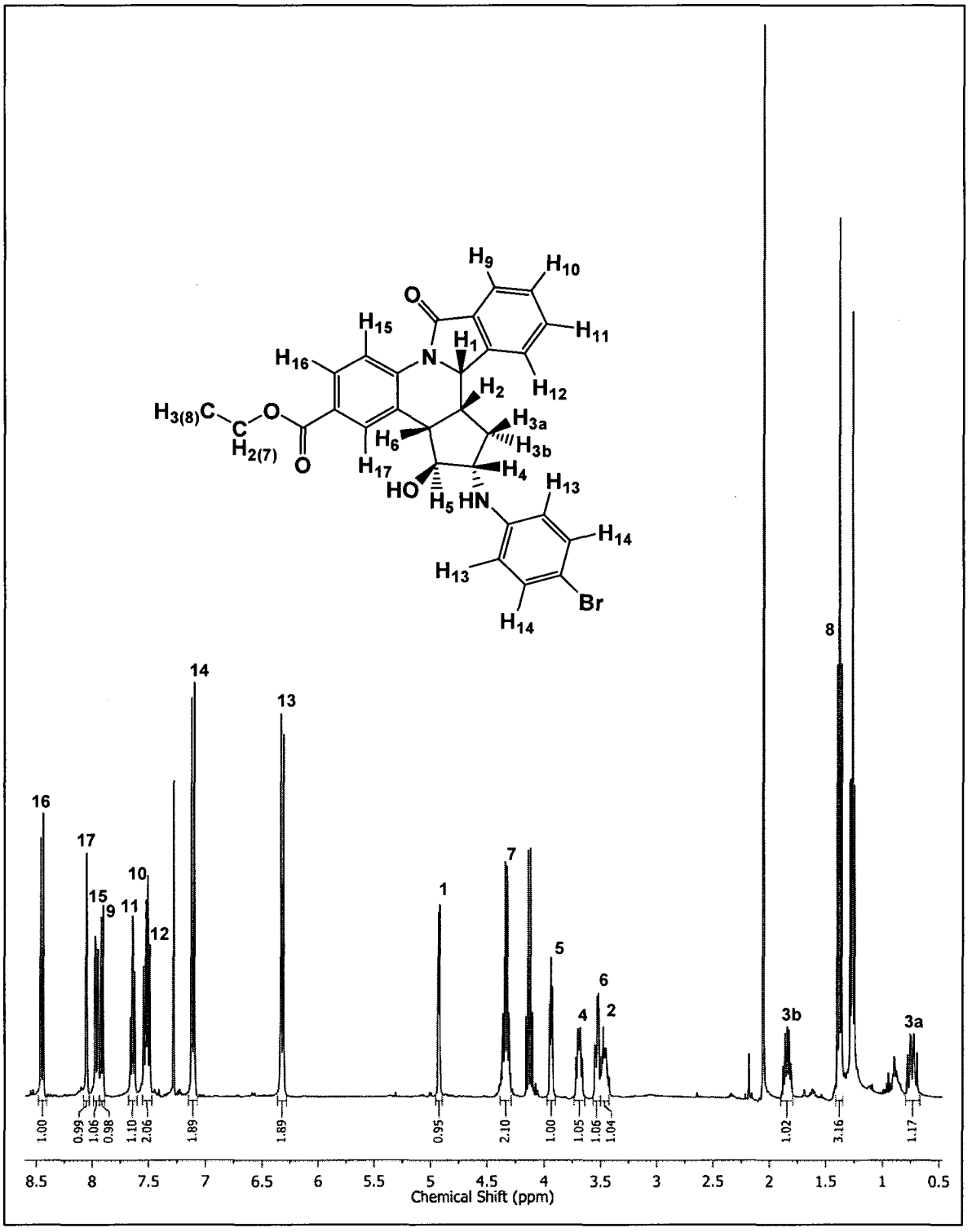
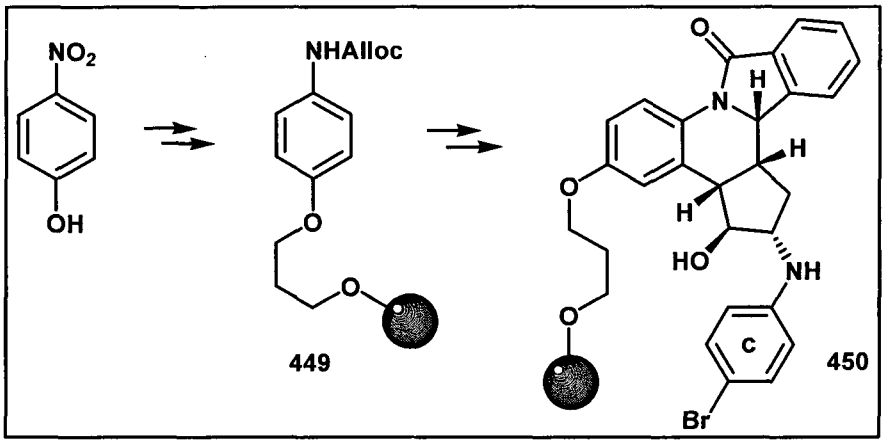


Figure 5.16 Protons Assignment and ^{1}H-NMR Spectrum for Compound **447**

5.5 Future Work

As pointed out in section 5.4.2.3 (Figure 5.13), compound **443** is a suitable scaffold for DOS. For proving this idea, we should explore if performing these sequences in solid-phase is possible. One of our post-doc colleagues performed the solid-phase synthesis of this complex system. Summary of this work is presented in scheme 5.29. *p*-Nitrophenol was selected as the starting material which underwent few steps to afford loaded compound **449**. Functionalized pentacyclic compound **450** was then successfully prepared in solid phase and fully characterized after cleavage. Compound **450** (in solid support), as indicated above, has 1+3 diversity sites (ring **C** + NH, OH, and Br) ideal for library generation.

Scheme 5.29



Library designation has already been performed. The above solid phase synthesis and any successful results on library generation are expected to communicate as soon as they are available.

6: Natural Product-inspired, Small Molecule Modulators of Protein-Protein Interactions Involved in Cell Death Pathways

6.1 From 'Small Molecules' to 'Cancer Drugs'

Apoptosis maintains tissue homeostasis by balancing cellular life and death. Deregulated apoptotic pathways disrupt the balance, resulting in diseases of premature cell loss or continuous cell survival (Figure 6.1)[251]. Little is known to date about the signals that are sent to cells to induce apoptosis. However, we know that due to protein-protein and lipid-protein interactions (signal transduction) these signals from the outside of a cell are mediated to the inside it. Different cellular functional pathways then execute these environmental stimuli. Signal transduction has gained so much attention because protein complexes (which considered as part of the undruggable genome) are now being seen as possible drug targets to treat various human diseases. It must be noted that proteins rarely function in isolation. In a given cell, all proteins are somewhat connected through non-covalent interactions in constant formation and disassociation. Much research has now been driven towards the how, when and where of proteins interacting with one another to better explain certain biological processes.

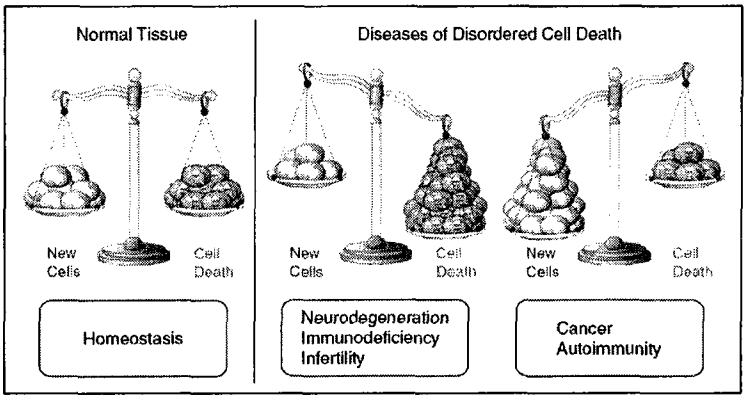


Figure 6.1 Disordered Cell Death Causes Abnormality[251]

Due to the importance of protein-protein interactions, the ability to interfere with these processes is means for therapeutic intervention because then it becomes possible to modify protein functioning within the cell. To affect the function of selected proteins, small organic modulators of protein-protein interactions can be utilized. In addition to drug development and validation, these cell permeable molecules will allow further research into the physiological cellular processes (such as abnormal signal transduction). Numerous successes have come from the discovery of these protein-protein interaction modulators, most importantly in the field of cancer. As indicated in Chapter 1, several protein-protein interactions involved with apoptosis are subjected to inhibition by small organic molecules and have helped define proteins such as the Bcl-2 family as possible drug targets. More specifically, the mitochondria appear to be a great target for small compounds that interfere with apoptosis.

Many challenges arise when discovering small molecules to target protein-protein interaction-based signaling pathways such as apoptosis. These protein-protein interactions cover large yet shallow surfaces and due to the lack of structural knowledge regarding these proteins, the success behind the design of small modulators is somewhat limited. In addition, a major limitation is the dynamic nature and complexity of proteins within their natural cellular environment; their reactivity will be quite different if taken out from their cellular milieu. The many aspects of a potential organic modulator with a specific protein target are often unpredictable. If a specified compound has been tested and it targets a certain protein, it might once in the body, the biochemical interaction between these two will not occur because of the cell's environment, specifically the presence of all enzymes, salts, nucleotides etc. Moreover, biological processes, such as apoptosis, are not generally easy to comprehend.

In apoptosis, the design of small organic compounds that interfere with the interactions between the Bcl-2 family proteins will guide on the ways in which cells function and may actually lead to new successful drug therapies. Chemists

have developed several novel techniques to identify such modulators: high throughput techniques to obtain bioactive natural product-inspired small molecules (or diversity-oriented synthesis- see Chapter 1) and high throughput screening (HTS). In general, HTS uses automation and allows researchers to screen for biological responses in a high-throughput manner for specific activity, against libraries of molecules in a timely fashion. In other words, HTS is valuable to identify rapidly any active compounds, "hits", which modulate a specific cellular process in which case can be used as a starting point to understand protein-protein interactions. Both these tools as well as a combination of rational design have used to create modulators of protein-protein interaction. It is worth noting, however, that even though HTS has been very beneficial for such screenings, the fact still remains that this approach is distinct from the activity in a living organism, and conclusions about the reactivity of a specific small molecule may be incomplete. In addition, as discussed above, many challenges still remain for researchers to get a better picture of the whole process.

As apoptosis is regulated by dynamic protein-protein interactions, it has generally been difficult to target with small molecules using conventional approaches. Screening natural product-inspired compounds made by high-throughput organic synthesis to identify small molecule inhibitors of Bcl-2 is the key step for overcome of this obstacle. Taking compounds that score as positive "hits" from this screen and testing their activity to prevent the same interactions in the more physiologic context of "addicted" mitochondria from cancer cell lines and patient cells are two main stages. The long-term goal is to identify lead compounds for drug development that selectively kill tumor cells by interfering with the critical membrane-associated function of Bcl-2.

6.2 Binding Bcl-2 Proteins to Membranes as the Key Process

For a tumor to arise, apoptosis must be inhibited. In many cancers, this inhibition results in the cells being addicted to one or more anti-apoptotic proteins.

Frequently those proteins are anti-apoptotic members of the Bcl-2 family (see Section 1.4.1). Inhibition of these proteins with small molecules should selectively kill addicted cancer cells. Small molecules such as the Bcl-2/Bcl-XL and Mcl-1 inhibitors that are currently undergoing clinical trials, are directed against the cytoplasmic functions of these proteins. Bcl-2 and Bcl-XL adopt a different conformation when they embed into the membrane and that these conformers bind to activated Bax. In cancer cells addicted to anti-apoptosis proteins, Bcl-XL is embedded into the membrane. Inhibitors of the membrane embedded form of Bcl-XL are therefore, expected to selectively kill addicted cancer cells.

Although drug companies have made molecules that target Bcl-2 family proteins that are undergoing clinical trials, those compounds were made to inhibit only one form of the proteins. It has been shown that Bcl-2 family proteins change their shape and their function when they bind to membranes[252]. Other researches have shown that cancer cells are addicted to membrane bound Bcl-2 proteins[252 253,254]. There is good evidence that compounds that prevent the membrane bound forms of Bcl-2 proteins will either kill or make cancer cells more sensitive to chemotherapy. Compounds that increase hole formation by Bcl-2 family proteins will be examined further in the lab for their effectiveness in living cancer cells compared with normal cells isolated from patients. The promising compounds will serve as leads for the development of pharmaceuticals aimed at the effective treatment of cancer.

6.3 Quest for Small Molecules as Modulators of Protein-Protein Interactions- Past and Current Approaches

Having some structural information available for soluble Bcl-2, Bcl-XL, Mcl-1 by NMR and X-ray and knowing the protein-protein interactions with pro-apoptotic proteins (e.g. Bak, Bax and Bad) has provided a starting point in developing approaches to obtain small molecules. Using structural information for Bcl-2 and Bcl-XL, Fesik's team at Abbott has been working for several years in developing

small molecules using the NMR fragment-based[25]. Different binding domains of a protein target are individually screened by NMR to identify weak binders, called "active fragments". Using these fragments, various stitching approaches link them to get more potent lead compounds. Fesik's team successfully developed the synthesis of a lead compound, ABT 737 by first identifying two active fragments.

Other small molecules for Bcl-2 and Bcl-XL have been developed using cell free assays and purified proteins. However, no study published to date explores the use of more complex and dynamic assays that model the Bcl-2 protein family activation in membranes. This approach includes the 'embedding together model' to emphasize the significance of Bcl-2 family protein interactions with and within membranes. The embedding together model proposes that both pro- and anti-apoptotic Bcl-2 family proteins engage in similar dynamic interactions that are governed by membrane dependent conformational changes and culminate in either aborted or productive membrane permeabilization depending on the final oligomeric state of pro-apoptotic Bax and/or Bak[252].

6.4 Role of Bcl-2 Family Proteins in the 'Membrane Permeabilization'

As indicated above, Bcl-2 proteins interact with membranes (Figure 6.2). In fact, Bcl-2 family proteins are able to regulate the membrane permeabilization. The compounds synthesized from DOS or HTS will be screened to determine if they interfere with Bcl-2 proteins within a cell free membrane permeabilization assay. Any "hits" will then be further analyzed to identify possible modulators of apoptosis.

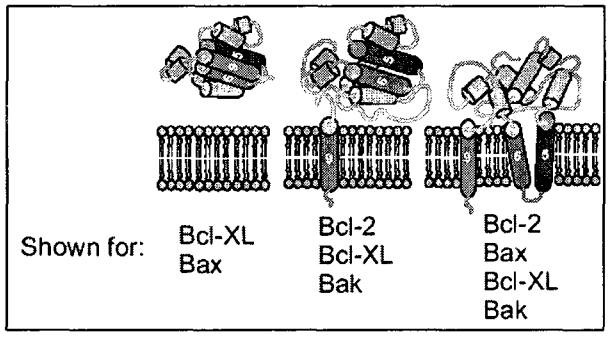


Figure 6.2 Interactions of Bcl-2 Proteins with Membranes[255]

A summary of this process is illustrated in Figure 6.3[255]. At stage-1, Capsase 8 cleaves Bid to cBid, cBid dissociates into p7 and p15 (tBid), and tBid binds to membranes. Stage-2 involves binding of Bax to tBid. Bax inserts helices 5,6,9 into the membrane at stage-3. Finally, at stage-4, Bax oligomerizes releasing contents from liposomes. Alternative route includes competing Bcl-XL with Bax for tBid, inserting Bcl-XL into membrane, recruiting other Bcl-XL, and inhibition of Bax in cytosol as well as membrane (Stage-2'). At stage-3', Bax and Bcl-XL release tBid and Bad respectively, and tBid recruits Bax into membranes.

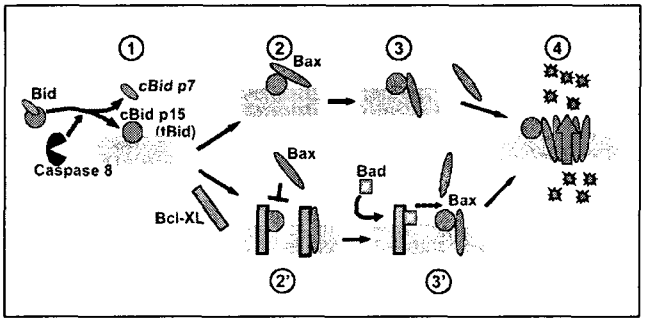


Figure 6.3 Regulation of Membrane Permeabilization by Bcl-2 Family Proteins[255]

During the initial evaluation stage of this assay, a tetrahydroquinoline-based compound (in our lab), B2P199F1, was found to be an inhibitor of membrane permeabilization. Its activity was quite significant compared to compound NJ-307

(also from our lab), which displayed no considerable modulator activity (Figure 6.4). This natural product-inspired compound B2P199F1, inhibits tBid-Bax which mediates pore formation. Although this is the opposite effect of what we actually would like to induce cell death in cancer cells, it is quite an interesting molecule for other fields such as neural degeneration.

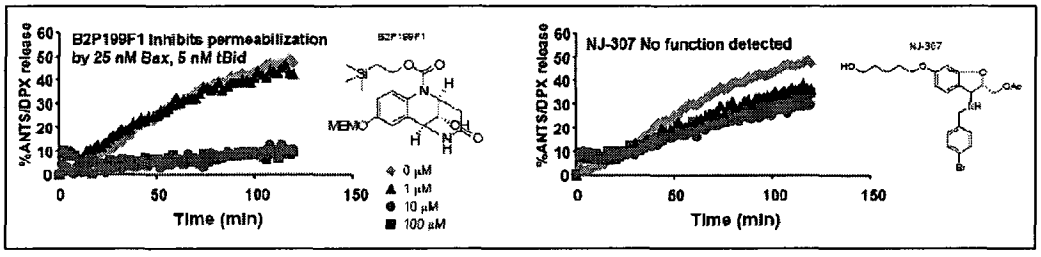


Figure 6.4 Identification of a small molecule inhibitor of membrane permeabilization

In collaboration with McMaster University, all compounds will be screened using the HTS tools available at the McMaster Bio-photonics Facility. All compounds will also be screened using a liposome based dye release assay (Figure 6.5) to see whether they modulate the function of tBid or Bax. This dye release assay will determine if these small organic modulators will inhibit or activate these Bcl-2 families of proteins. In this assay, a fluorophore, ANTS (8-aminonapthalene-1,3,6-trisulfonic acid) and a quencher, DPX (*p*-xylene-bis-pyridinium bromide) are submitted within a liposome. DPX acts to quench the fluorescence of ANTS but because of permeabilization of the mitochondrial membrane, these molecules are subsequently released and separated to allow dye fluorescence. This assay will permit measuring interactions between proteins within the membrane.

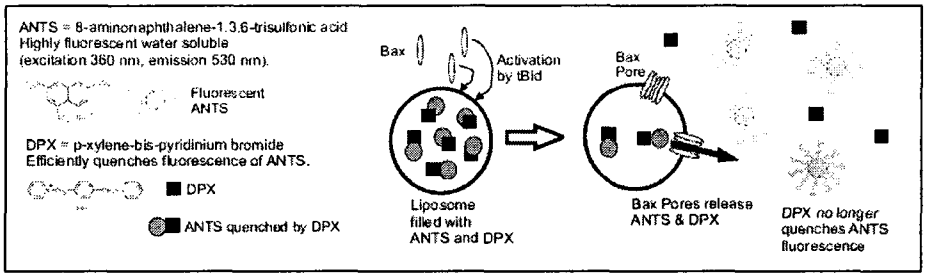


Figure 6.5 ANTS release assay for pore formation by Bax[255]

6.5 Biological Evaluation of Tetrahydroquinoline-based Compounds (In Progress)

As indicated above, assessment of membrane destabilizing property by small molecules would achieve by monitoring the release of liposomal inner content and typically, fluorescent dyes such as ANTS/DPX, are used as markers of inner content release. Most tetrahydroquinoline-based compounds prepared in this project and several other structurally similar compounds synthesized in other unfinished/unsuccessful studies were being tested with the methodology explained above to find the promising 'hits' as modulators of Bcl-2-membrane interactions. Structures of 52 compounds submitted for this assay have shown in Figure 6.6.

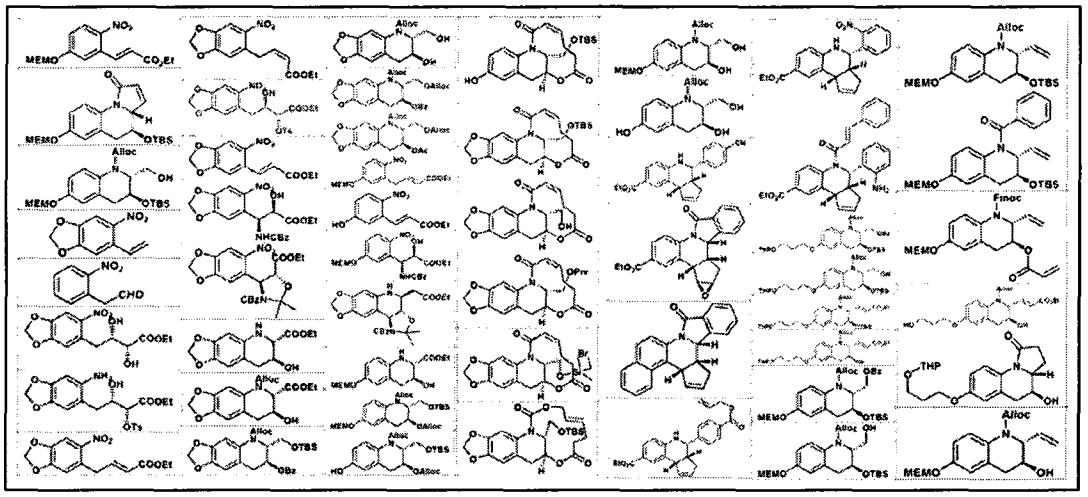


Figure 6.6 Small Molecules Tested for Finding Modulators of Protein-Protein Interaction

Several tetrahydroquinoline-based small molecules showed inhibitor activity against Bax. Although a number of stages should perform in order to attain a reliable 'hit', these preliminary results have demonstrated the potential capability of this kind of small molecules as modulators of protein-protein interactions. The diagrams illustrated in Figure 6.7 show the initial testing results obtained from four different tetrahydroquinoline-based compounds. The IC_{50} [*i.e.*, the half-maximal inhibitory concentration; the concentration of a substance that is required for 50% inhibition of a biological or biochemical function (in this case, 'protein binding') *in vitro*] for compounds B4P050brut and SSB321A (diagram A and C in Figure 6.7, respectively) reported as around 10 μM and for compound SSB326A (diagram B) in a range of 5-10 μM, whereas for compound B4P017brut (diagram D) was not assessable yet. Large error bars generally indicate solubility problems.

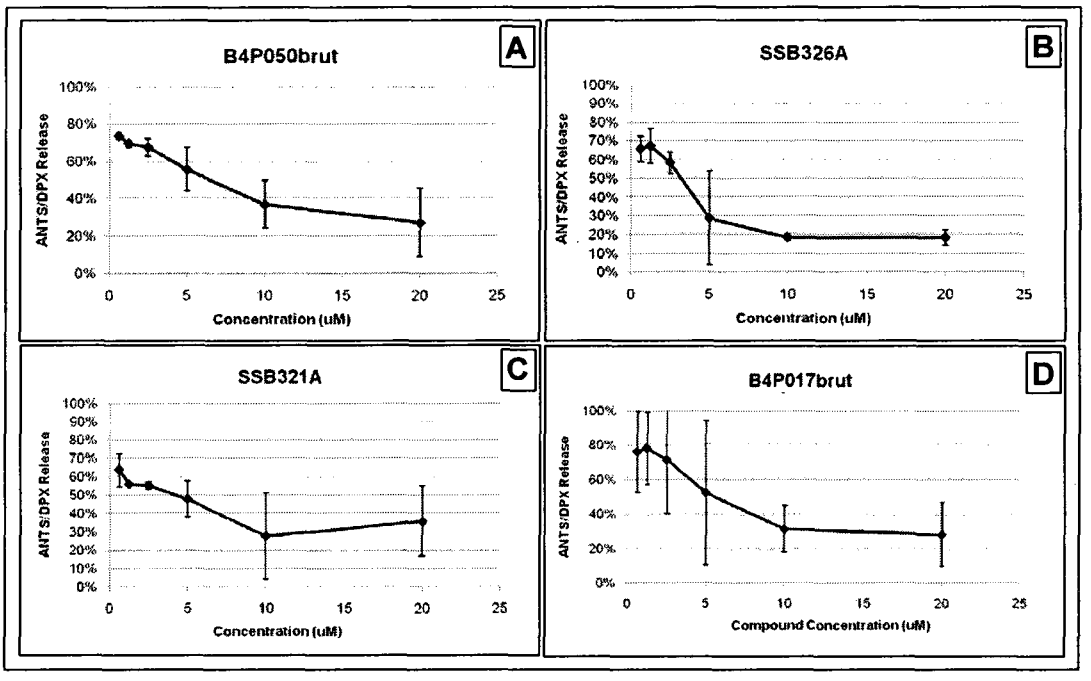


Figure 6.7 Tetrahydroquinoline-based Compounds as Bax Inhibitors

6.6 Closing Remarks

There is absolutely no doubt that natural products have shown tremendous effects on drug discovery. However, their limited accessibility and somehow challenging synthetic methods make them only one of the valuable sources for scientists and pharmaceutical companies in the quest for identifying druggable hits. Despite the existence of many successful stories in the area of drug design using diversity-oriented synthesis approach, chemical biologist still need preferably small-molecules to demonstrate some degree of perturbation effects on biological processes. This is now up to chemists to construct small-molecules having some features that are generally known as hints in finding bioactive compounds. One of the most reliable guidance is our mother nature; synthesis of natural product-inspired compounds. Knowledge of natural products enables us to identify some structural features, which may have been responsible for certain biological activities. Although considering these molecular level features is

crucial, rapid access to the target molecules using modern organic chemistry is the ultimate key in this journey. Borrowing the concept from natural products, these targets preferably have three-dimensional complex structures.

In the presented thesis, we showed how we have achieved in making several natural product-inspired molecules and systems on the basis of tetrahydro-quinoline structure or sub-structure. Some of the complex tricyclic systems were synthesized in solid as well as solution phase and two of these systems were introduced for the first time. In addition, some complex polycyclic systems were obtained in only one-pot using a tandem reaction. Many of these compounds have been tested in 'Bcl-2/membrane permeabilization' assay in collaboration with Professor David Andrews (Mc Master University) to find promising hits. Although preliminary results are encouraging, further investigation is required in order to identifying the 'Smart Molecules'!

7. Experimental

7.1 General Methods

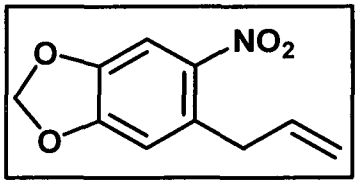
The materials were obtained from commercial suppliers and used without purification. THF and CH_2Cl_2 were distilled under N_2 over sodium/benzophenone and CaH_2 respectively. All NMR experiments were recorded on an AC-BRÜKER instrument (400 MHz). Unless otherwise noted, proton and carbon chemical shifts are reported in ppm using residual $CHCl_3$ as an internal standard at 7.26 and 77.0 ppm respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with pneumatically-assisted electrospray ionization source, operating in positive mode. The enantiomeric excess was determined by chiral HPLC, Hewlett-Packard (Agilent) 1090 LC equipped with Diode Array Detector and CHIRACEL-OD column. The HPLC spectra were recorded on a Gilson Combinatorial Chromatography System with 215 Liquid Handler / Injector and equipped with a Vydac C-18 Monomeric column and a Diode Array Detector.

7.2 X-ray crystallography

The diffraction data was collected with Mo K_α radiation, ω scan mode, and a graphite monochromator on a Bruker Smart diffractometer equipped with a CCD detector. The structure was solved by direct method using the SHELXTL suite of programs (a). Multiscan absorption correction was made with program sadabs (b). All hydrogen atoms were put in calculated positions. (a) Sheldrick, G. M. SHELXTL, version 6.10; Brucker AXS Inc.: Madison, WI, 2000. (b) Sheldrick, G. M. SADABS, version 2.03; University of Gottingen, Germany, 2002.

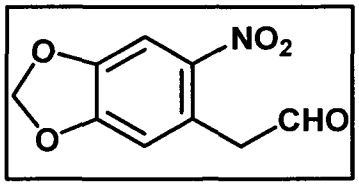
7.3 Procedures

Compound 226: 5-allyl-6-nitrobenzo[d][1,3]dioxole



To a solution of safrole (10 g, 61.73 mmol) in glacial acetic acid (40 mL) at 0°C, a solution (10:1 ratio) of nitric acid and sulfuric acid (10 mL) was added drop wise. After 2 hours at 0°C, ethyl acetate (350 mL) was added and the layers were separated. The combined organic layer was washed with water (4 x 250 mL) and saturated sodium bicarbonate solution (2 x 250 mL), dried over magnesium sulphate and then concentrated after filtration. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 8.93 g (70%) of nitrosafrole (**226**) as a yellow solid. R_f: 0.53 (4:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 208.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 6.76 (s, 1H), 6.09 (s, 2H), 5.97 (ddt, J = 13.5, 6.5, 6.4 Hz, 1H), 5.12 (dd, J = 6.5, 1.4 Hz, 1H), 5.08 (dd, J = 13.5, 1.4 Hz, 1H), 3.65 (d, J = 6.4 Hz, 2H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 152.5, 146.0, 144.0, 132.0, 117.5, 111.0, 106.0, 103.0, 70.0, 38.0 ppm

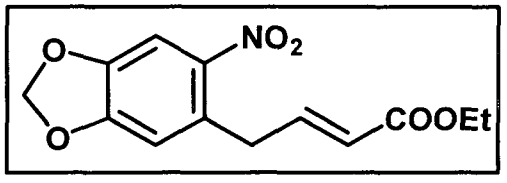
Compound 227: 2-(6-nitrobenzo[d][1,3]dioxol-5-yl)acetaldehyde



A solution of 8.93 g (43.14 mmol) of **226** in 100 mL methanol was treated at 0°C with a stream of ozone via a sintered diffuser until the TLC showed disappearance of the starting material (~4 hours). Excess ozone was then removed under a positive flow of nitrogen. This was then followed by the addition of dimethylsulfide (9 mL, 118.0 mmol) and the mixture kept at room

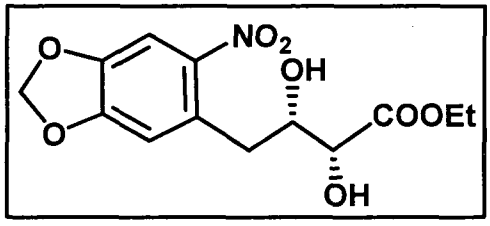
temperature for one hour. After being stored in the freezer for overnight, the pale yellow crystals appeared. The solid was then filtered and washed with cold methanol. Recrystalization from methanol afforded pure product, **227** (8.56 g, 95%). R_f: 0.21 (4:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 280.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 9.83 (s, 1H), 7.68 (s, 1H), 6.72 (s, 1H), 6.16 (s, 2H) and 4.06 (s, 2H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ = 197.3, 152.7, 148.1, 143.2, 125.9, 112.3, 106.5, 103.6, 49.2 ppm.

Compound 228: (E)-ethyl 4-(6-nitrobenzo[d][1,3]dioxol-5-yl)but-2-enoate



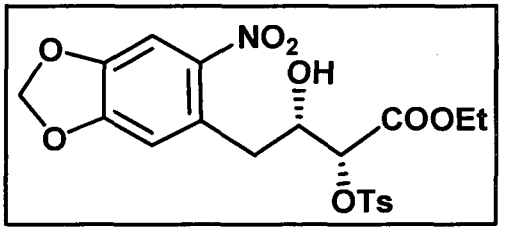
To a solution of **227** (8.56 g, 40.98 mmol) in dried dichloromethane (100 mL) was added (carboxymethelene)triphenylphosphorane (18.56 g, 53.27mmol) at room temperature. The reaction mixture was stirred until the starting material disappeared (4 h). The reaction was quenched with saturated ammonium chloride solution, washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) giving compound **228** as a yellow solid (82% *trans*, 16% *cis*, 9.38 g *trans* product). R_f: 0.81 (1:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 279.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.50 (s, 1H), 7.04 (d, *J*= 15.6 Hz, 1H), 7.01 (s, 1H), 6.21 (dt, *J*= 7, 15.6 Hz, 1H), 6.13 (s, 2H), 4.21 (q, *J*= 7 Hz, 2H), 3.31 (dd, *J*= 1.5, 7 Hz, 2H), 1.31 (t, *J*= 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ = 166.5, 152.3, 145.4, 130.3, 129.5, 123.5, 111.1, 106.3, 105.5, 103.4, 60.8, 36.6 and 14.6 ppm.

Compound 229: (2R,3S)-ethyl 2,3-dihydroxy-4-(6-nitrobenzo[d][1,3]dioxol-5-yl)butanoate



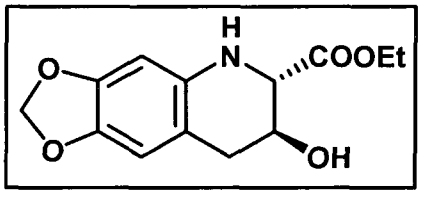
To a 1 L round-bottomed flask equipped with a magnetic stirrer, were added *t*-BuOH (170 mL), water (170 mL) and AD mix-α (47.27 g). To this mixture, methanesulfunamide (3.19 g, 33.62 mmol) was then added. The mixture is stirred at room temperature until both phases are clear and cooled to 0 °C. Compound **228** (9.37 g, 33.62 mmol) was then added to this mixture and further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time: approx. 40h). The reaction was quenched at 0°C by the addition of sodium sulfite (50.0 g), warmed to room temperature and further stirred for 1 hour. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2*N* KOH, dried over magnesium sulfate and then concentrated. Purification by flash chromatography (silica gel, 50% ethyl acetate in hexanes) gave pure diol **229** as a yellow oil (7.15 g, 68%). R_f: 0.19 (1:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 313.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.88 (s, 1H), 6.12 (s, 2H), 4.32 (q, *J* = 7 Hz, 2H), 4.18 (dd, *J* = 2.5 Hz, 1H), 3.51 (s, 1H), 3.23 (d, *J* =1 Hz, 1H), 3.20 (dd, *J* = 5.5 & 9 Hz, 2H), 2.35 (d, *J* = 9.1 Hz, 1H) and 1.33 (t, *J* = 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ = 173.5, 152.2, 147.4, 143.7, 130.9, 112.2, 106.1, 103.6, 73.2, 73.0, 62.8, 38.4 and 14.6 ppm.

Compound 230: (2R,3S) ethyl-3-hydroxy-4-(6-nitrobenzo[d][1,3]dioxol-5-yl)-2-(tosyloxy)butanoate



To a stirred solution of diol **229** (7.15 g, 22.84 mmol) in dichloromethane (200 mL) at 0 °C under nitrogen was added triethylamine (4.17 mL, 29.69 mmol) followed by *p*-toluenesulfonyl chloride (4.35 g, 22.84 mmol). The solution was then stirred for 90 hours at 0°C, the reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the tosyl derivative **230** (9.38 g, 88 %) as an oil. R_f: 0.67 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 467.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.4 Hz, 2H), 7.51 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 6.11 (d, J = 2.8 Hz, 2H), 4.99 (d, J = 3.3 Hz, 1H), 4.34 (bs, 1H), 4.13 (q, J = 7 Hz, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.60 (s, 1H), 2.46 (s, 3H) and 1.21 (t, J = 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ =167.3, 152.3, 147.6, 145.9, 143.5, 133.3, 130.1, 128.7, 128.2, 112.3, 106.3, 103.4, 79.9, 72.3, 62.7, 37.7, 22.1 and 14.4 ppm.

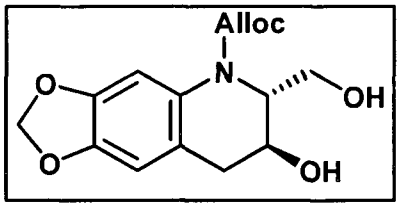
Compound 231: (6S,7S)-ethyl 7-hydroxy-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]-quinoline-6-carboxylate



To a solution of **230** (9.38 g, 20.08 mmol) in dry THF (250 mL), added oven dried potassium carbonate (5.54 g, 40.16 mmol) and Pd-C (1.87 g, 20% w/w - added under nitrogen). The mixture was then hydrogenated for 40 h (monitored by TLC). After completion of the reaction, the mixture filtered, washed several times with ethyl acetate and then concentrated. Column chromatography on silica gel (20% to 50% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative **231** as a yellow oil (4.35 g, 82%). R_f: 0.53 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 265.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.49 (s,1H), 6.24 (s,1H), 5.85 (s, 2H), 4.35 (q, J = 5.7 Hz, 1H), 4.27 (dq, J = 2.3 & 7 Hz, 2H), 3.89 (d, J = 6 Hz, 1H), 3.51 (s, 1H), 2.83 (dd, J = 4.8 and 15.3 Hz, 2H),

1.49 (m, 1H) and 1.32 (t, J = 7 Hz, 3H) ppm. ^{13}C-NMR-DEPT-135: (100 MHz, $CDCl_3$) δ = 109.8, 101.0, 97.1, 65.2, 62.1, 59.8, 33.8, and 14.6 ppm.

Compound 291: (6R,7S)-allyl7-hydroxy-6-(hydroxymethyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-5(6H)-carboxylate

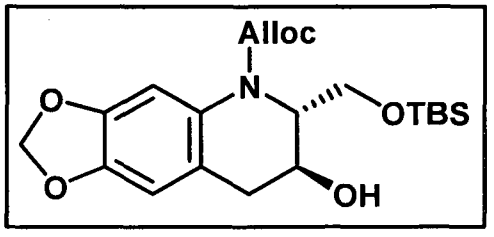


To a stirred solution of **231** (1.0 g, 3.77 mmol) in anhydrous THF (40 mL) at 0°C under nitrogen was added lithium borohydride (2M in THF, 3.77 mL, 7.54 mmol). After stirring for 1.5 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous ammonium chloride. Following evaporation of THF, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. After evaporation of the solvent, the residue was used directly for the next step without further purification.

To a stirred solution of the amino alcohol obtained from the above reaction in anhydrous dichloromethane (40 mL) at 0°C, was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34mL, 3.14mmol). After stirring for 45 minutes at 0°C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate giving product **291** (630 mg, 54% over two steps) as a yellow oil. R_f: 0.09 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 307.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 6.48 (s, 1H), 6.16 (s, 1H), 5.95 (m, 1H), 5.83 (s, 2H), 5.39 (d, J = 17.7 Hz, 1H), 5.31 (d, J = 10.2 Hz, 1H), 4.65 (dt, J = 5.7, 1.3 Hz, 2H), 4.32 (m, 1H), 4.20 (m, 1H), 3.97 (q, J = 6.5 Hz, 1H), 3.46 (s, 1H), 2.89 (m, 1H) and 2.74 (m, 1H) ppm. ^{13}C-NMR: (100 MHz,

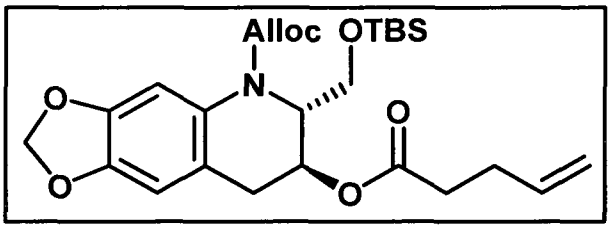
$CDCl_3$) δ= 155.5, 147.2, 140.8, 136.9, 131.7, 119.8, 110.2, 109.7, 100.9, 97.1, 69.2, 68.7, 64.9, 56.6 and 34.6 ppm.

Compound 292: (6R,7S)-allyl 6-((tert-butyldimethylsilyloxy)methyl)-7-hydroxy-7,8-dihydro[1,3]dioxolo[4,5-g]quinoline-5(6H)-carboxylate



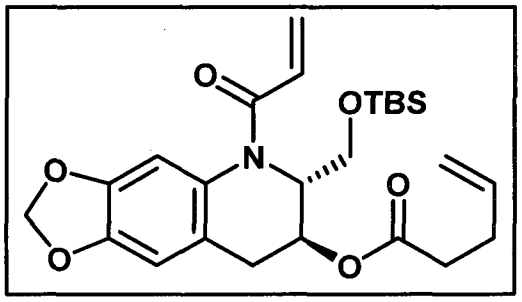
To a stirred solution of **291** (630 mg, 2.05 mmol) in dichloromethane (10 mL) at 0°C was added imidazole (280.0 mg, 4.1 mmol) followed by TBDMSCl (370 mg, 2.46 mmol). The mixture was stirred at 0°C for additional 75 minutes. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with 10-20% ethyl acetate in hexanes afforded 700 mg (81%) of **292** as a yellow oil. R_f: 0.57 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 421.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.97 (s, 1H), 6.59 (s, 1H), 5.96 (m, 1H), 5.92 (d, *J*= 7.5 Hz, 2H), 5.32 (d, *J*= 17 Hz, 1H), 5.24 (d, *J*= 10.6 Hz, 1H), 4.68 (m, 2H), 4.26 (m,1H), 3.96 (m,1H), 3.88 (m,1H), 3.46 (t, *J*= 9 Hz, 1H), 2.82 (d, *J*= 3 Hz, 1H), 2.79 (dd, *J*= 4.5, 14 Hz, 1H), 2.62 (m, 1H), 0.86 (s, 9H), 0.05 (d, *J*= 8.5 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) DEPT-135: δ= 118.4, 101.5, 67.1, 64.6, 34.9 ppm (methelenes) and 155.1, 146.4, 145.1, 132.8, 130.4, 122.8, 107.8, 107.1, 71.9, 62.0, 26.2, 18.5, - 5.2 ppm

Compound 293: (6R,7S)-allyl 6-((tert-butyldimethylsilyloxy)methyl)-7-(pent-4-enoyloxy)-7,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-5(6H)-carboxylate



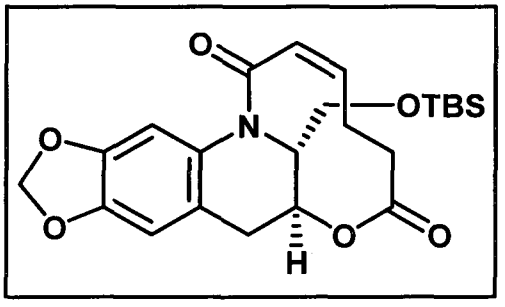
To a stirred solution of **292** (690 mg, 1.65 mmol) in dichloromethane (50 mL) were added DIC (0.53 mL, 3.32 mmol), DMAP (20 mg, 0.166 mmol) and 4-pentenoic acid (0.26 mL, 2.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24h. After quenching the reaction with saturated ammonium chloride, the aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo.* Purification by flash chromatography using 10% ethyl acetate in hexanes afforded compound **293** (680 mg, 81%). R_f: 0.76 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 503.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.06 (s, 1H), 6.57 (s, 1H), 5.98 (m, 1H), 5.93 (d, J = 7 Hz, 2H), 5.81 (m, 1H), 5.34 (d, J = 17 Hz, 1H), 5.25 (d, J = 10.6 Hz, 1H), 5.16 (q, J = 5.5 Hz, 1H), 5.05 (d, J = 17 Hz, 1H), 5.00 (d, J = 10.6 Hz, 1H), 4.64-4.73 (m, 3H), 5.58 (d, J = 6.5 Hz, 2H), 2.96 (dd, J = 5.6, 15.6 Hz, 1H), 2.69 (dd, J = 6 & 16 Hz, 1H), 2.34-2.43 (m, 4H), 0.82 (s, 9H) and 0.01 (d, J = 10.6 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 172.6, 155.2, 146.5, 145.1, 136.9, 132.8, 130.7, 118.4, 115.9, 107.9, 106.9, 101.5, 70.0, 67.1, 62.3, 58.6, 34.0, 31.4, 29.2, 26.1, 18.4 and - 5.2 ppm

Compound 294



To a solution of **293** (670 mg, 1.33 mmol) in dichloromethane (25 mL) at 0°C under nitrogen were added tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.08 mmol) and morpholine (0.235 mL, 2.7 mmol). After stirring for 40 minutes at room temperature, dichloromethane was evaporated. The crude residue obtained was utilized in next reaction without purification. To a solution of above amine residue in dry dichloromethane (10 mL) at 0°C under nitrogen were added pyridine (0.22 mL, 2.7 mmol) and acryloyl chloride (0.137 mL, 1.62 mmol). After stirring at room temperature for 70 minutes, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted two times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded 340 mg compound **294** as an oil (53% for two steps). R_f: 0.28 (4:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 474.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.67 (s, 1H), 6.53 (m, 2H), 6.47 (s, 1H), 5.99 (s, 1H), 5.94 (s, 1H), 5.82 (m, 1H), 5.71 (d, J = 12.1 Hz, 1H), 5.03-5.12 (m, 3H), 4.80 (s, 1H), 3.67 (d, J = 4Hz, 2H), 2.97 (dd, J = 5.5, 14.1 Hz, 1H), 2.58 (t, J = 11.3 Hz, 1H), 2.36-2.46 (m, 4H), 0.76 (s, 9H) and - 0.03 (d, J = 4.5 Hz, 6H) ppm.

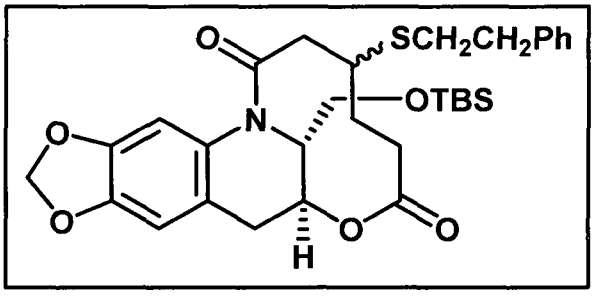
Compound 295



To a solution of **294** (340 mg, 0.72 mmol) of in dry dichloromethane (340 mL) at room temperature under nitrogen was added 2nd generation of Grubbs catalyst (122 mg, 0.144 mmole, 0.2 equiv). After refluxing at 45°C for 1 hour under nitrogen, the reaction mixture was cooled to room temperature and the solvent

evaporated. Purification of the residue by flash chromatography over silica gel using 20% ethyl acetate in hexanes afforded the 10-membered macrocycle derivative **295** (210 mg, 65%) of as a light green crystalline solid. R_f: 0.35 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 446.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.18 (s, 1H), 6.57 (s, 1H), 6.28 (d, J = 11.5 Hz, 1H), 5.96 (d, J = 11.5 Hz, 2H), 5.85 (td, J= 11.6 & 4.5 Hz, 1H), 5.41 (m, 1H), 4.38 (td, J= 8.2 & 2.6 Hz, 1H), 3.49-3.55 (m, 2H), 3.00 (m, 1H), 2.82-2.87 (m, 2H), 2.61 (m, 1H), 2.17-2.23 (m, 2H), 0.87 (s, 9H), -0.03 (d, J = 4 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$); DEPT-135: δ= 101.6, 60.6, 33.4, 29.0, 25.9 ppm (methylenes) and 172.4, 169.7, 146.1, 133.6, 128.9, 119.5, 66.6, 60.8, 32.0, 26.2, 26.1, 26.0, 25.7, 18.5, 5.2 ppm.

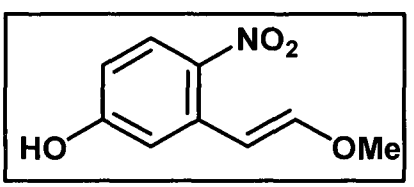
Compound 296



To a solution of benzene ethanethiol (0.336 mL, 2.5 mmol) in freshly distilled THF (9.0 mL) slowly at -78 °C was added *n*-butyl lithium (1.0 mL, 2.5 mmol). The mixture was stirred over night (16 hours) at ambient temperature. To a stirred solution of **295** (20.0 mg, 0.045 mmol) in dry THF (10 mL) at -20 °C under nitrogen was added the lithium salt solution (0.36 mL, 0.09 mmol, 2 equiv) of the freshly prepared solution. After stirring at this temperature for 2 hours, a solution of saturated ammonium chloride was added and the aqueous layer extracted by dichloromethane. The combined organic layer was dried by magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography over silica gel using 10% ethyl acetate in hexanes afforded the hetero Michael product **296** (20 mg, 76 %) as a yellow oil. R_f: 0.60 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 584.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.29-7.33 (m, 2H), 7.21-

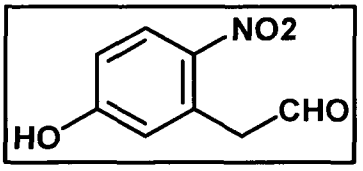
7.25 (m, 3H), 6.65 (s, 1H), 6.35 (s, 1H), 5.97 (s, 2H), 5.26-5.30 (m, 1H), 3.71 (m, 1H), 3.50-3.55 (m, 2H), 3.39 (m, 1H), 2.99-3.05 (m, 1H), 2.90-2.93 (m, 2H), 2.84-2.86 (m, 1H), 2.80-2.83 (m, 2H), 2.60-2.69 (m, 2H), 2.56 (m, 1H), 2.38-2.43 (m, 1H), 1.85-1.94 (m, 2H), 0.89 (s, 9H), 0.03 (d, *J*= 11.3 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 177.0, 170.6, 146.6, 140.6, 130.7, 128.9, 126.8, 120.1, 109.7, 109.2, 107.6, 107.1, 101.7, 68.0, 61.0, 58.1, 44.3, 42.6, 36.3, 33.5, 32.2, 29.2, 26.1, 18.5, 14.5 and -5.1 ppm.

Compound 236: (*E*)-3-(2-methoxyvinyl)-4-nitrophenol



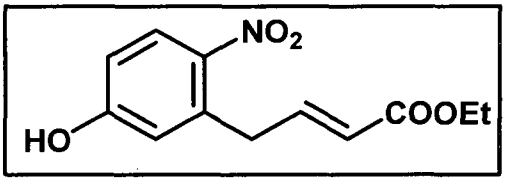
To a suspension of (methoxymethyl)-triphenylphosphonium chloride (25.5 g, 72 mmol) in THF (175 mL) at 0°C was added dropwise potassium *tert*-butoxide (1.0M in THF, 150 mL, 150 mmol). The resulting mixture was stirred at 0 °C for 1 hour. A solution of 5- hydroxy-2-nitrobenzaldehyde (10.0 g, 60 mmol) in THF (100 mL) was added drop wise at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding water (200 mL) at 0°C. After removal of THF, the aqueous layer was acidified to pH 6 by adding a 2*N* HCl solution at 0°C and then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated. Purification by column chromatography (25% ethyl acetate in hexanes) afforded **236** (11.2 g, 95%) as a yellow oil. R_f: 0.68 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 196.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 8.02 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 12.8 Hz, 1H), 6.86 (s, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.56 (d, *J* = 12.8 Hz, 1H), 5.47 (bs, 1H), 3.77 (s, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 159.9, 152.9, 141.2, 135.9, 128.6, 113.8, 113.4, 101.7, 57.1 ppm.

Compound 237: 2-(5-hydroxy-2-nitrophenyl)acetaldehyde



To a solution of **236** (11.2 g, 57.5 mmol) in THF (150 mL) was added 1.5*N* HCl solution (300 mL). The mixture was then heated to 60°C and stirred overnight. The reaction mixture cooled to 0°C and neutralized with saturated sodium carbonate solution. After the THF removal, the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to afford 10.15 g (98%) of the crude aldehyde **237** as a solid (mp 101.8-103.0 °C). R_f: 0.53 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 180.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 9.78 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 6.97 (dd, J = 2.4 & 9.0 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 4.15 (s, 2H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 198.0, 163.5, 142.1, 128.9, 120.9, 115.8, 49.5 ppm.

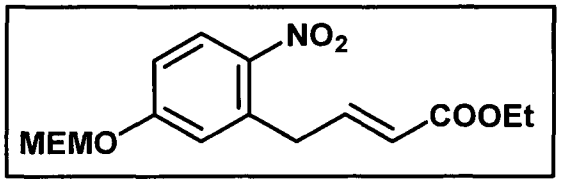
Compound 238: (*E*)-ethyl 4-(5-hydroxy-2-nitrophenyl)but-2-enoate



To a solution of **237** (10.15g, 56.0 mmol) in dry dichloromethane (200mL) was added (carboxymethelene)triphenylphosphorane (23.4g, 67.0 mmol) at room temperature. The reaction mixture was refluxed at 45°C until the starting material disappeared (TLC ~1h). The reaction was quenched with saturated ammonium chloride solution at room temperature, washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (10-30% ethyl acetate in hexanes). The product **238** was obtained as a yellow solid (80% *trans*, 10% *cis*; 11.25 g *trans* product). R_f: 0.68 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 252.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.97 (d,

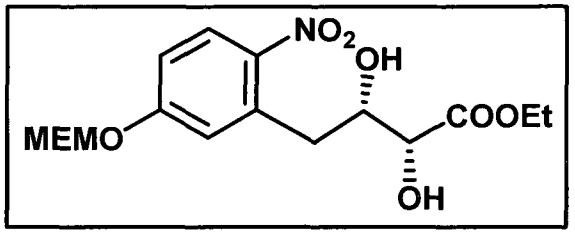
J= 9 Hz, 1H), 7.12 (m,1H), 6.99 (m, 1H), 6.74 (d, J= 2.8 Hz, 1H), 6.22 (m, 1H), 5.84 (d, J= 15.6 Hz, 1H), 4.24 (q, J= 7 Hz, 2H), 3.86 (d, J= 6.5 Hz, 1H), 3.37(d, J= 7 Hz, 1H), 1.33 (t, J= 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.9, 161.1, 146.4, 142.0, 136.5, 128.4, 123.1, 118.9, 115.4, 61.7, 37.6, 14.5 ppm.

Compound 239: (E)-ethyl 4-(5-((2-methoxyethoxy)methoxy)-2-nitrophenyl)but-2-enoate



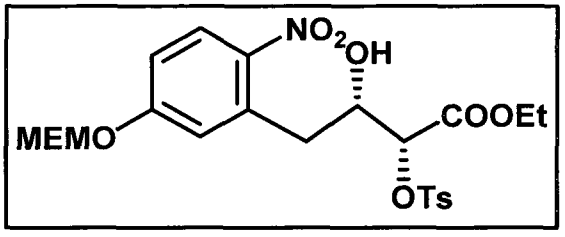
To a solution of **238** (11.25 g, 44.8 mmol) in dry dichloromethane (150 mL) at 0°C under nitrogen were added DIPEA (11.7 mL, 67 mmol) and MEMCl (10.4 mL, 67 mmol). After stirring for 2 hours at ambient temperature, the reaction mixture was quenched by a solution of saturated ammonium chloride. The aqueous layer extracted by dichloromethane and the combined organic layer dried over magnesium sulfate, filtered and concentrated *in vacuo*. Flash column chromatography with silica gel using 30% ethyl acetate in hexanes afforded 13.65 g (90%) of **239** as an oil. R_f: 0.69 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 340.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 8.02 (d, J = 9 Hz, 1H), 7.20 (m, 1H), 7.06 (m, 1H), 6.29 (m, 1H), 5.80 (d, J = 16 Hz, 1H), 5.36 (m, 2H), 4.20 (q, J = 7 Hz, 2H), 3.88 (d, J = 6.5 Hz, 1H), 3.82-3.86 (m, 2H), 3.55-3.59 (m, 2H), 3.39 (s, 3H), 3.32 (d, J = 7 Hz, 1H) and 1.30 (t, J= 7.5 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 171.4, 161.3, 145.3, 136.3, 127.9, 123.7, 119.7, 116.3, 115.3, 93.7, 71.8, 68.6, 61.1, 59.5, 37.6, 14.6 ppm.

Compound 240: (2R,3S)-ethyl 2,3-dihydroxy-4-(5-((2-methoxyethoxy)methoxy)-2-nitrophenyl)butanoate



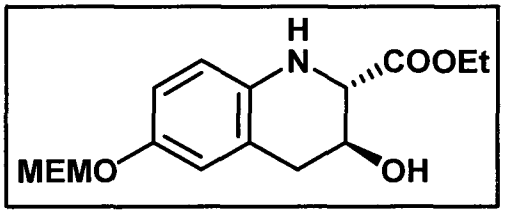
To a 1 L round-bottomed flask equipped with a magnetic stirrer, were added *t*-BuOH (200 mL), water (200 mL) and AD mix-α (56.4 g). To this mixture, methanesulfunamide (3.83 g, 40.27 mmol) was then added. The mixture is stirred at room temperature until both phases are clear and cooled to 0 °C. Compound **239** (13.65 g, 40.27 mmol) was then added to this mixture and further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time: approx. 40h). The reaction was quenched at 0 °C by the addition of sodium sulfite (60.0 g), warmed to room temperature and further stirred for 1 hour. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2*N* KOH, dried over magnesium sulfate and then concentrated. Purification by flash chromatography (silica gel, 25-8% ethyl acetate in hexanes) gave pure diol as a yellow oil (**240**, 10.5 g, 70%; 90% ee determined by chiral HPLC OD column). R_f: 0.29 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 374.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 9.1 Hz, 1H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.20 (dd, *J* = 2.5 and 9.1 Hz, 1H), 6.17 (d, *J* = 4Hz, 1H), 5.42 (m, 1H), 5.37 (m, 2H), 5.15 (s, b, 1H), 3.86 (m, 1H), 3.83 (t, *J* = 4.6Hz, 2H), 3.55-3.59 (m, 2H), 3.36-3.40 (m, 1H), 3.36 (s, 3H), 3.03 (dd, *J* = 6.1 & 17.5 Hz, 1H), 2.74 (dd, *J* = 1.5 & 18 Hz, 1H), 1.94 (bs, 1H) and 1.32 (m, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 174.9, 162.1, 133.4, 128.3, 117.5, 116.1, 93.7, 82.6, 71.8, 69.8, 68.6, 59.4, 38.7, 14.5 ppm.

Compound 241: (2R,3S)-ethyl 3-hydroxy-4-(5-((2-methoxyethoxy)methoxy)-2-nitrophenyl)-2-(tosyloxy)butanoate



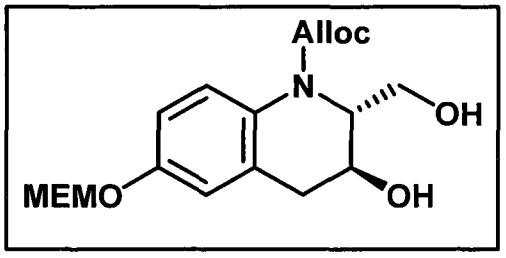
To a stirred solution of diol **240** (10.5 g, 28.15 mmol) in dichloromethane (100 mL) at 0 °C under nitrogen was added triethylamine (5.9 mL, 42.2 mmol) followed by *p*-toluenesulfonyl chloride (5.37 g, 28.14 mmol). The solution was then stirred for 90 hours at 0°C, the reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the tosyl derivative **241** (13.0 g, 88 %) as an oil. R_f: 0.37 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 528.3.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 8.05 (d, *J*= 9.1 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.01-7.06 (m, 2H), 5.33 (q, *J*= 7.1 Hz, 2H), 5.02 (d, *J* = 3 Hz, 1H), 4.37 (bs, 1H), 4.12-4.18 (m, 2H), 3.81 (t, *J* = 4.5 Hz, 2H), 3.54 (t, *J* = 4.5 Hz, 2H), 3.34 (s, 3H), 3.21 (m, 1H), 3.05 (m, 1H), 2.73 (d, *J* = 8.1 Hz, 1H), 2.46 (s, 3H) and 1.20 (t, *J* = 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.3, 161.1, 145.8, 143.4, 136.0, 133.6, 130.1, 128.5, 128.1, 120.6, 118.4, 116.9, 115.5, 93.6, 80.1, 72.0, 68.6, 62.6, 60.8, 59.4, 38.2, 21.7, 14.3 ppm.

Compound 51: (2S,3S)-ethyl 3-hydroxy-6-((2-methoxyethoxy)methoxy)-1,2,3,4-tetrahydroquinoline-2-carboxylate



To a solution of **241** (13.0 g, 24.77 mmol) in dry THF (250 mL), were added oven dried potassium carbonate (6.84 g, 49.5 mmol) and 10% Pd-C (1.87 g, 20% w/w, added under nitrogen). The mixture was then hydrogenated for 30 h (monitored by TLC). After completion of the reaction, the mixture was filtered, washed several times with ethyl acetate and then concentrated. Column chromatography on silica gel (20%-70% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative **51** as an oil (6.8 g, 84%). R_f: 0.56 (1:3, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 326.3 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.58 (d, *J*= 8.5 Hz, 1H), 7.00 (dd, *J*= 2.5, 8.5 Hz, 1H), 6.94 (s, 1H), 5.31 (d, *J*= 2.5 Hz, 2H), 5.17 (m, 1H), 4.83 (t, *J*= 6.5 Hz, 1H), 4.47 (dq, *J*= 1.8, 7.2 Hz, 2H), 3.85 (t, *J*= 4.8 Hz, 2H), 3.58 (t, *J*= 4.8 Hz, 2H), 3.40 (s, 3H), 3.05-3.09 (m, 2H), 1.63 (bs, 1H), 1.46 (t, *J*= 7 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 165.8, 158.9, 155.9, 136.9, 131.5, 128.5, 116.5, 115.6, 93.7, 72.0, 68.3, 62.8, 62.2, 59.5, 32.9, 14.7 ppm.

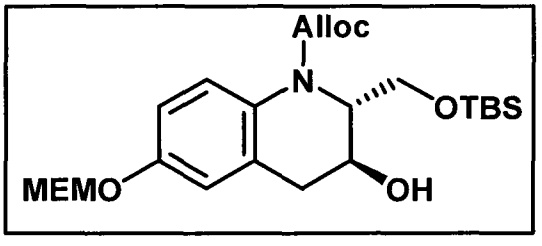
Compound 300: (2R,3S)-allyl 3-hydroxy-2-(hydroxymethyl)-6-((2-methoxyethoxy)-methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate



To a stirred solution of **51** (1.0 g, 3.08 mmol) of in anhydrous THF (30 mL) at 0°C under nitrogen was added lithium borohydride (2 M in THF, 3.08 mL, 6.16 mmol). After stirring for 1.0 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous ammonium chloride. Following evaporation of THF, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. After evaporation of the solvent, the residue was used directly for the next step without further purification. To a stirred solution of the amino alcohol

obtained from the above reaction in anhydrous dichloromethane (20 mL) at 0°C, was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34 mL, 3.14 mmol). After stirring for 40 minutes at 0°C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate giving product **300** (880 mg, 78% over two steps) as a yellow oil. R_f: 0.48 (1:4, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 368.1 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.34-7.50 (m, 1H), 6.90 (d, J = 9.5 Hz, 1H), 6.84 (s, 1H), 5.84-6.01 (m, 1H), 5.33 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 5.24 (s, 2H), 4.71 (td, J= 5.1 and 13.6 Hz, 1H), 4.62-4.67 (m, 1H), 4.59 (d, J = 5.5 Hz, 1H), 4.24-4.32 (m, 1H), 4.11-4.19 (m, 1H), 3.94-4.02 (m, 1H), 3.83 (t, J = 5.1 Hz, 2H), 3.58 (t, J = 4.3 Hz, 2H), 3.39 (s, 3H), 2.85-2.93 (m, 1H) and 2.72-2.80 (m, 1H) ppm.

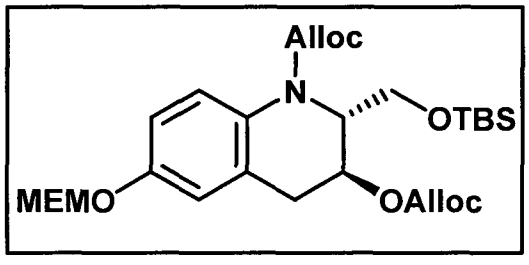
Compound 301: (2R,3S)-allyl 2-((tert-butyldimethylsilyloxy)methyl)-3-hydroxy-6-((2-methoxyethoxy)methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate



To a stirred solution of **300** (880.0 mg, 2.4 mmol) in dichloromethane (20 mL) at 0°C was added imidazole (326.0 mg, 4.8 mmol) and TBDMSCl (370 mg, 2.46 mmol). The mixture was stirred at 0°C for additional 25 minutes. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with 20% ethyl acetate in hexanes afforded 960 mg (83%) of **301** as a yellow oil. R_f: 0.84 (1:4,

hexane: ethyl acetate). LRMS: MS (ES+) m/z = 482.3 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.38 (d, *J*= 8 Hz, 1H), 6.90 (dd, *J* = 2.8 and 9 Hz, 1H), 6.87 (s, 1H), 5.96 (m, 1H), 5.33 (d, *J* = 17.5 Hz, 1H), 5.25 (s, 2H), 5.23 (m, 1H), 4.69 (qd, *J* = 5.5 Hz, 2H), 4.29 (m, 1H), 4.01 (m, 1H), 3.94 (m, 1H), 3.84 (t, *J* = 4.5 Hz, 2H), 3.58 (t, *J* = 4.5 Hz, 2H), 3.46 (t, *J* = 9.3 Hz, 1H), 3.40 (s, 3H), 2.88 (m, 1H), 2.78 (bs, 1H), 2.71 (m, 1H), 0.87 (s, 9H) and 0.06 (d, *J* = 11.3 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ = 155.1, 154.7, 132.8, 131.0, 130.7, 126.4, 118.3, 115.9, 115.1, 94.1, 72.0, 71.7, 68.0, 67.0, 64.8, 61.9, 59.4, 34.9, 26.2, 18.5, -5.1 ppm.

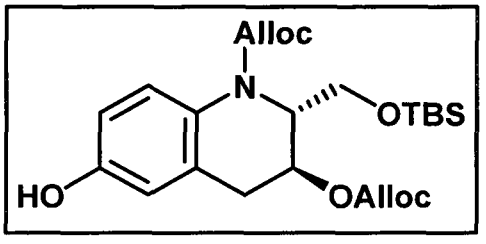
Compound 302: (2R,3S)-allyl 3-(allyloxycarbonyloxy)-2-((tert-butyldimethyl-silyloxy)-methyl)-6-((2-methoxyethoxy)methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate



To a stirred solution of **301** (960 mg, 2.0 mmol) in anhydrous dichloromethane (30 mL) at room temperature was added pyridine (0.323 mL, 4.0 mmol) and allylchloroformate (0.437 mL, 4.0 mmol). After stirring for 48 hours at room temperature, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with hexanes and ethyl acetate and afforded 960 mg (85%) of the product **302** as a yellow oil. R_f: 0.74 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 566.3 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.47 (s, 1H), 6.91 (dd, *J*= 2.5, 9 Hz, 1H), 6.84 (d, *J*= 2.5 Hz, 1H), 5.93-5.98 (m, 2H), 5.35 (m, 1H), 5.30 (m, 1H), 5.24 (s, 2H), 5.20-5.25 (m, 2H), 5.08 (m, 1H), 4.79 (q, *J*= 5 Hz, 1H), 4.68 (qd, *J*= 5.5 Hz, 2H), 4.63 (d, *J*= 5.5 Hz, 2H), 3.83 (t, *J*= 4.5 Hz, 2H),

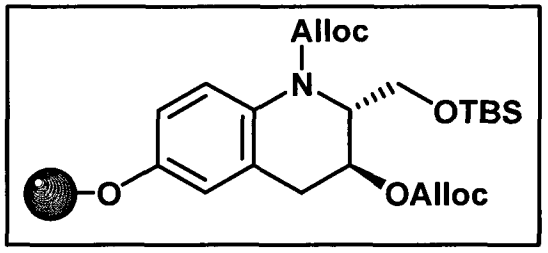
3.65 (m, 1H), 3.60 (m, 1H), 3.58 (t, J= 4.5 Hz, 2H), 3.40 (s, 3H), 3.08 (m, 1H), 2.88 (m, 1H), 0.81 (s, 9H), -0.01 (d, J= 8.5 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 155.1, 154.5, 132.9, 131.9, 131.3, 126.4, 119.3, 118.2, 116.0, 115.4, 94.1, 73.7, 72.0, 70.1, 68.9, 68.0, 67.0, 62.4, 59.4, 58.2, 31.4, 26.1, 18.4, 10.6, -5.2 ppm.

Compound 303: (2R,3S)-allyl 3-(allyloxycarbonyloxy)-2-((tert-butyldimethyl-silyloxy)-methyl)-6-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate



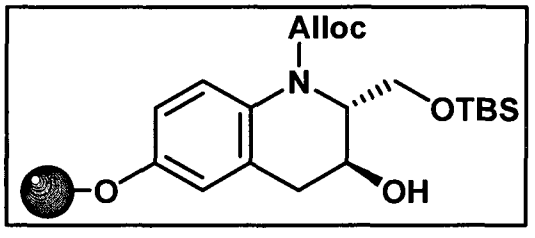
To a stirred solution of **302** (960 mg, 1.7 mmol) and zinc bromide (1.9 g, 8.5 mmol) in dichloromethane (50 mL) under nitrogen was stirred at room temperature for 24 hours. After filtration and evaporation of the solvent, purification was carried out by column chromatography over silica gel using 20-50% ethyl acetate in hexanes giving the free phenol **303** (480 mg, 60%). R_f: 0.24 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 478.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.41 (s, 1H), 6.68 (dd, J= 2.8 and 8.8 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.91-6.02 (m, 2H), 5.33-5.41 (m, 2H), 5.32 (m, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.05 (q, J = 5.5 Hz, 1H), 4.78 (q, J = 4.0 Hz, 1H), 4.69 (qd, J = 5.5, 13.5 Hz, 2H), 4.64 (d, J = 5.5 Hz, 2H), 3.59-3.64 (m, 2H), 3.04 (m, 1H), 2.84 (m, 1H), 0.82 (s, 9H) and -0.01 (d, J= 7 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 155.3, 154.7, 153.2, 132.8, 131.8, 129.9, 126.6, 119.4, 118.2, 115.0, 114.4, 73.9, 68.9, 67.1, 62.4, 58.3, 31.3, 26.1, 18.4, -5.2 ppm.

Compound 308



BromoWang resin (1.7 mmol/g; 62 mg, 0.105 mmol) was washed several times with dichloromethane, DMF and then suspended in DMF for 30 min in DMF. To this mixture was added a solution of compound **303** in anhydrous DMF (1.0 mL), sodium iodide (32.0 mg, 0.21 mmol, oven dry) and cesium carbonate (69.0 mg, 0.21 mmol, oven dry). The mixture was bubbled vigorously with nitrogen for 48 hours. The resin was successively washed with Methanol (x 2), DMF (x 2), water (x 2), Methanol (x 2) and dichloromethane (x 3) and then dried under vacuum for a few hours. The mother liquor containing the starting material in DMF was evaporated and the residue was re-dissolved in DCM. The organic layer was washed with water and brine, dried over magnesium sulfate, filtered and then evaporated to dryness. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in hexanes) giving the recovered starting material **303** (61.0 mg, 0.128 mmol) of was obtained. The loading of the compound was determined to be 78% after cleavage from the support.

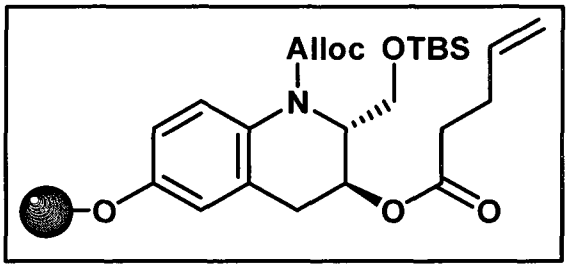
Compound 308'



To a suspension of resin **308** (61.0 mg) in methanol (2.5 mL) was added NaOMe (0.4 mL, 0.2 mmol, 0.5 M in methanol) at room temperature. The mixture was stirred gently for 8 hours. Following this, the resin was filtered and then washed

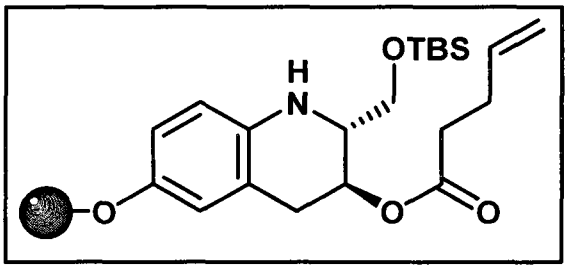
with methanol (x 3), DMF (x 3), water (x 3), methanol (x 3), dichloromethane (x 3) and dried under vacuum.

Compound 309



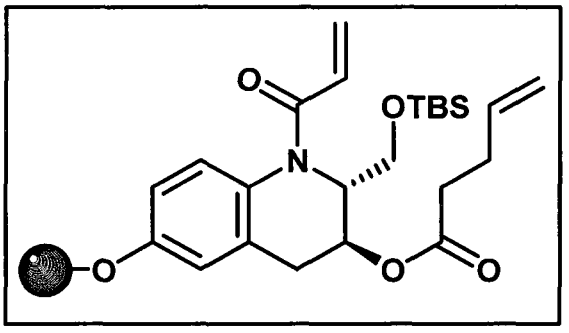
To a suspension of resin **308'** (61.0 mg) in dry dichloromethane (3.0 mL) were added DIC (0.6 mL, 0.095 mmol), 4-pentenoic acid (0.5 mL, 0.43 mmol) and DMAP (30 mg, 0.25 mmol). The mixture was stirred for 18 hours at room temperature and then filtered. The resin was washed with methanol, DMF, water, methanol, dichloromethane (3 times each) and then dried under vacuum.

Compound 309'



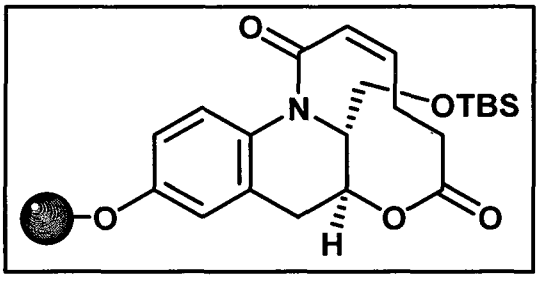
To a suspension of resin **309** obtained from the previous reaction in DCM (3.0 mL) was added tetrakis(triphenylphosphine) palladium(0) (33.0 mg, 0.03 mmol) dissolved in dry dichloromethane (3.0 mL). To this mixture were added a mixture of *N*-methylmorpholine (0.12 mL) and acetic anhydride (0.12 mL). The reaction mixture was bubbled under nitrogen for 18 hours. The resin was washed consecutively with DMF, water, methanol and dichloromethane (two times each) and then dried on a vacuum pump for overnight.

Compound 298



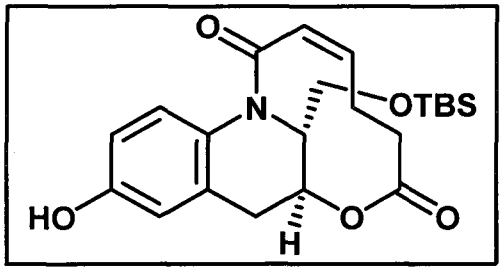
The resin **309'** obtained from the previous reaction was suspended in dichloromethane (3.0 mL) and to this were added triethylamine (0.38 mL, 2.7 mmol) and acryloyl chloride (0.17 mL, 2.0 mmol). The mixture was bubbled with nitrogen flow for 24 hours. The resin was washed with DMF (x 2), methanol (x 2) and dichloromethane (x 3) and then dried over high vacuum pump.

Compound 299



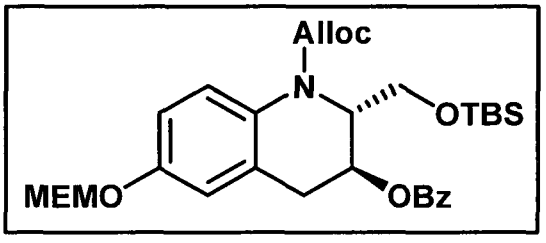
In a RB flask, the above resin **298** was suspended in dichloromethane (5.0 mL) under nitrogen. To this solution, was added a 2nd generation Grubbs catalyst (51 mg, 0.06 mmol) dissolved in dichloromethane (4.0 mL). The reaction mixture was warmed to 40 °C and stirred for 6 hours. The mixture was brought to room temperature and then the resin was washed with dichloromethane, methanol and dichloromethane (3 times each) and finally was dried over high vacuum pump.

Compound 310



The resin **299** was treated with 5% TFA in anhydrous dichloromethane (10 mL) at room temperature for 1 hour. Following this, it was washed twice with dichloromethane, filtered and the solvent evaporated. The residue was then purified by flash column chromatography over silica gel using 10% ethyl acetate and hexanes giving 12.0 mg of the final product **310** in overall 40% for 5 steps. R_f: 0.28 (2:1, hexane: ethyl acetate). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ = 7.56 (m, 1H), 6.73 (dd, *J*= 2.8 & 8.8 Hz, 1H), 6.59 (d, *J* = 3 Hz, 1H), 6.30 (d, *J* = 11.6 Hz, 1H), 5.85 (td, *J* = 4 & 11.8 Hz, 1H), 5.41 (m, 1H), 4.40 (m, 1H), 3.46-3.56 (m, 2H), 3.04 (m, 1H), 2.92 (m, 1H), 2.84 (m, 1H), 2.61 (m, 1H), 2.32 (m, 1H), 2.29 (m, 1H), 0.87 (s, 9H) and -0.05 (d, *J*= 4 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ = 172.5, 169.8, 162.8, 153.8, 134.9, 133.7, 130.6, 129.4, 128.9, 127.5, 115.2, 114.3, 66.7, 60.8, 33.4, 28.9, 26.1, 18.5, -5.2 ppm.

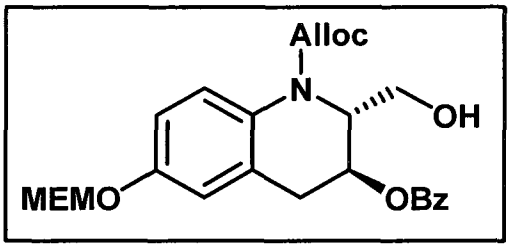
Compound 357: (2R,3S)-allyl 3-(benzoyloxy)-2-((tert-butyldimethyl-silyloxy)methyl)-6-((2-methoxyethoxy)methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate



To a stirred solution of 301 (1.2 g, 2.5 mmole) in 100mL dried dichloromethane at 0°C were added 0.8 mL (5 mmole) of DIC and 0.3 g (2.5 mmole) of DMAP followed by benzoic acid (0.457 g, 3.75 mmole). After being stirred for 24 hours

at room temperature, the reaction mixture was processed with dichloromethane and ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded 357 as a dark brown solid; 1.38 g (95%). Rf: 0.62 in 35% Ethyl acetate/Hexanes. Molecular Weight and Formula: 585.3, C31H43NO8Si. LRMS: MS (ES+) m/z = 586.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.94 (d, J=7.3 Hz, 2H), 7.52 (s, 1H), 7.51 (m, 1H), 7.38-7.45 (m, 2H), 6.93 (dd, J= 3.0 & 9.0 Hz, 1H), 6.85 (m,1H), 5.80-5.90 (m, 1H), 5.51 (m, 1H), 5.24 (m, 3H), 5.12 (d, J= 10.3 Hz, 1H), 4.92 (m, 1H), 4.58 (s, 2H), 3.83 (m, 2H), 3.60-3.70 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H), 3.15 (m,1H), 2.97 (m,1H), 0.82 (s, 9H), -0.01 (d, J= 6.0 Hz, 6H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 172.7, 166.1, 155.5, 154.5, 137.6, 133.5, 132.7, 131.0, 130.3, 128.9, 126.7, 118.4, 116,1, 115,3, 94.1, 72.0, 68.0, 67.0, 62.2, 59.4, 58.1, 50.6, 43.1, 26.1, 18.4, -5.2 ppm.

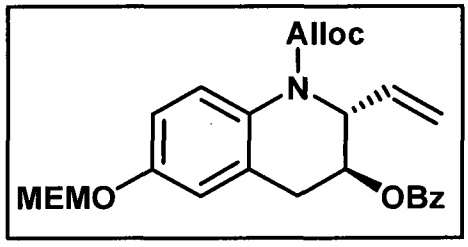
Compound 358: (2R,3S)-allyl 3-(benzoyloxy)-2-(hydroxymethyl)-6-((2-methoxy-ethoxy)-methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate



To a solution of compound **357** (1.2 g, 2.5 mmole) in 100mL dried dichloromethane at 0°C while stirring were added 0.8 mL (5 mmole) of DIC and 0.3 g (2.5 mmole) of DMAP followed by benzoic acid (0.457 g, 3.75 mmole). After stirring for 24 hours at room temperature, the reaction mixture was processed with dichloromethane and ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded a dark brown solid; 1.38 g (95%). A solution of TBAF (2.5 mL, 2.5 mmole) and Acetic acid (0.15 mL) in THF was added to the solution of the ester compound (1.3 g, 2.2 mmole) in THF at 0°C. The reaction

mixture was stirred for 5 hours. The reaction was processed with ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacum. Column chromatography on silica gel (50% ethyl acetate in hexanes) afforded compound **358** as a dark yellow oil; 1.02 g (98%). R_f: 0.13 in 35% Ethyl acetate/Hexanes. Molecular Weight and Formula: 471.4, $C_{25}H_{29}NO_8$ LRMS: MS (ES+) m/z = 472.4 (M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.01 (d, *J*= 7.0 Hz, 2H), 7.58 (t, *J*= 7.8 Hz, 1H), 7.48 (m, 1H), 7.43 (t, *J*= 7.8 Hz, 2H), 6.97 (dd, *J*= 2.8 & 9.0 Hz, 1H), 6.89 (m,1H), 5.81-5.91 (m, 1H), 5.37 (m,1H), 5.27 (s, 2H), 5.23 (m,1H), 5.15 (d, *J*= 10.3 Hz, 1H), 4.96 (m,1H), 4.60 (d, *J*= 4.8 Hz, 2H), 3.85 (m, 2H), 3.73 (m, 1H), 3.63 (m, 1H), 3.60 (m, 2H), 3.40 (s, 3H), 3.13 (m,1H), 2.99 (m,1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.2, 154.9, 133.7, 132.5, 130.4, 130.2, 130.1, 129.1, 128.8, 127.1, 126.8, 118.7, 116.1, 115.7, 94.1, 72.0, 68.1, 67.3, 62.3, 59.4, 23.9, 22.7, 21.3 ppm.

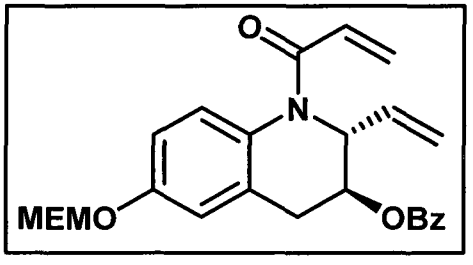
Compound 359: (2R,3S)-allyl 3-(benzoyloxy)-6-((2-methoxyethoxy)methoxy)-2-vinyl-3,4-dihydroquinoline-1(2H)-carboxylate



To a solution of the alcohol **358** (1 g, 2.1 mmol) in 100 mL DCM was added triethylamine (0.87 mL, 6.3 mmol) at 0°C. To the above solution, 875 mg SO_3.Py (6.3 mmol) in 6 mL DMSO was added over 10 min. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated ammonium chloride solution, extracted with DCM, and dried over anhydrous magnesium sulfate. The organic solvent was concentrated, and the crude aldehyde derivative was then directly subjected to the Wittig reaction. For making the Wittig reagent, to a solution of methyltriphenylphosphonium bromide (2 g, 4.76 mmol) in 20 mL of THF was added NaHMDS (3.5 mL, 3.5 mmol) at -78 °C. The reaction mixture was stirred for 1 h at 0°C and the solution turned to

yellow color. To this solution was added the former crude aldehyde (0.98 g, 2.09 mmol) in THF (50 mL) at -78 °C. The reaction mixture was warmed to 0°C and then stirred at this temperature for 20 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate, dried over magnesium sulfate, and concentrated. The crude residue was purified by column chromatography using 20% EtOAc in hexanes to obtain 540 mg (1.16 mmole) of compound **359** as a brown oil (55% for 2 steps). R_f: 0.69 in 50% Ethyl acetate/Hexanes Molecular Weight and Formula: 467.4, $C_{26}H_{29}NO_7$ LRMS: MS (ES+) m/z = 468.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.96 (d, *J*= 7.1 Hz, 2H), 7.61 (m, 1H), 7.55 (t, *J*= 7.5 Hz, 1H), 7.40 (t, *J*= 7.5 Hz, 2H), 6.96 (dd, *J*= 2.5 & 9.0 Hz, 1H), 6.83 (d, *J*= 2.5 Hz, 1H), 5.70-5.81 (m, 2H), 5.45-5.50 (m, 2H), 5.30 (m, 1H), 5.28 (s, 2H), 5.17-5.23 (m, 2H), 5.09 (d, *J*= 10.0 Hz, 1H), 4.53 (m, 2H), 3.85 (t, *J*= 4.5 Hz, 2H), 3.59 (t, *J*= 4.5 Hz, 2H), 3.40 (s, 3H), 3.16 (m,1H), 3.01 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.2, 155.7, 154.3, 133.6, 132.8, 132.6, 130.7, 130.2, 130.1, 128.7, 127.0, 126.8, 118.7, 118.5, 116.1, 115.4, 94.1, 72.0, 7.0.4, 68.0, 67.1, 59.4, 57.9, 30.1 ppm.

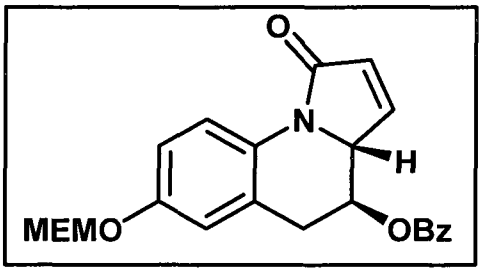
Compound 360: (2R,3S)-1-acryloyl-6-((2-methoxyethoxy)methoxy)-2-vinyl-1,2,3,4-tetrahydroquinolin-3-yl benzoate



To a solution of 530 mg (1.13 mmole) of compound 359 in 25 mL dichloromethane at 0°C under nitrogen were added tetrakis-(triphenylphosphine)palladium(0) (76 mg, 0.07 mmole) and morpholine (0.2 mL, 2.26 mmole). After stirring for 3 hours at room temperature, dichloromethane was evaporated. The crude amine obtained was utilized in next reaction without

purification. To a solution of the provided amine in 10 mL dry dichloromethane at 0°C under nitrogen were added pyridine (0.18 mL, 2.26 mmole) and acryloyl chloride (0.14 mL, 1.69 mmole). After stirring at room temperature for 1 hour, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded 336 mg (0.77 mmole, 68% over 2 steps) of compound 360 as a dark brown oil. R_f: 0.43 in 50% Ethyl acetate/Hexanes. Molecular Weight and Formula: 437.4, $C_{25}H_{27}NO_6$ LRMS: MS (ES+) m/z = 438.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.95 (d, *J*= 7.0 Hz, 2H), 7.54 (m,1H), 7.45 (m, 1H), 7.40 (t, *J*= 7.5 Hz, 2H), 6.95 (dd, *J*= 2.8 & 8.8 Hz, 1H), 6.91 (m, 1H), 6.55-6.62 (m, 1H), 6.40-6.49 (m, 1H), 5.78 (q, *J*= 5.0 Hz, 1H), 5.74 (m, 2H), 5.41 (m, 1H), 5.30 (m, 1H), 5.27 (s, 2H), 5.21 (d, *J*= 10.0 Hz, 1H), 3.85 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H), 3.18 (dd, *J*= 5.0 & 17.1 Hz, 1H), 3.00 (dd, *J*= 4.3 & 17.1 Hz, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.1, 155.5, 137.6, 133.6, 133.2, 131.0, 130.9, 130.1, 129.7, 129.0, 128.8, 127.1, 126.8, 118.6, 116.8, 115.3, 94.1, 72.0, 68.2, 59.5, 31.2, 22.7, 21.3 ppm.

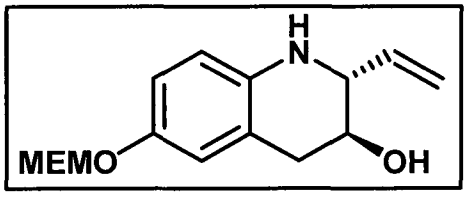
Compound 54



To a solution of 300 mg (0.73 mmole) of compound **308** in 300 mL anhydrous dichloromethane at room temperature under nitrogen was added 120 mg (0.146 mmole, 0.2 eq) of 1st generation of Grubbs catalyst. After refluxing at 45°C for 2 hours under nitrogen, the solvent evaporated. Purification of the residue by flash chromatography over silica gel using 20% ethyl acetate in hexanes afforded 238

mg (0.58 mmole, 80%) of compound **54** as a brown oil. R_f: 0.58 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 409.4, $C_{23}H_{23}NO_6$ LRMS: MS (ES+) m/z = 410.4 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.28 (d, *J*= 9.0 Hz, 1H), 8.12 (d, *J*= 7.3 Hz, 2H), 7.66 (t, *J*= 7.5 Hz, 1H), 7.53 (t, *J*= 7.5 Hz, 2H), 7.28 (m,1H), 7.03 (dd, *J*= 2.5 & 9.3 Hz, 1H), 6.93 (d, *J*= 2.5 Hz, 1H), 6.38 (dd, *J*= 1.8 & 6.0 Hz, 1H), 5.27 (s, 2H), 5.06 (td, *J*= 5.8 & 10.5 Hz, 1H), 4.48 (dt, *J*= 1.8 & 10.5 Hz, 1H), 3.84 (m, 2H), 3.58 (m, 2H), 3.53 (m, 1H), 3.40 (s, 3H), 3.11 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 168.9, 165.8, 154.0, 144.1, 134.1, 130.4, 130.2, 129.8, 129.1, 128.8, 125.1, 120.9, 116.9, 116.2, 94.1, 72.0, 71.3, 68.0, 64.0, 59.5, 34.8 ppm. X-Ray within supplementary data.

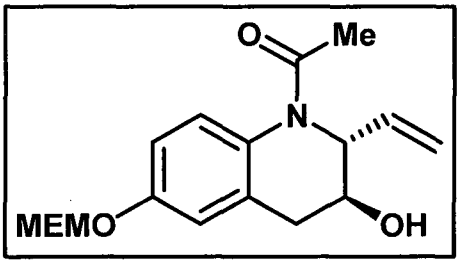
Compound 359': (2R,3S)-6-((2-methoxyethoxy)methoxy)-2-vinyl-1,2,3,4-tetrahydroquinolin-3-ol



To a stirred solution of 100 mg (0.21 mmole) **359** in 10 mL THF was added 0.21 mL (0.21 mmole) of a 1M $LiAlH_4$ solution at 0°C under nitrogen. After stirring for 5 hours at room temperature, the reaction was quenched with methanol and ammonium chloride solution, extracted with DCM, and dried over anhydrous magnesium sulfate. The organic solvent was concentrated and the residue was purified by column chromatography using 50% ethyl acetate in hexanes to obtain 48 mg (1.16 mmole) of compound **359'** as a dark brown oil (82%). R_f: 0.18 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 279.3, $C_{15}H_{21}NO_4$ LRMS: MS (ES+) m/z = 280.3 (M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.78 (m, 2H), 6.51 (d, *J*= 8.5 Hz, 1H), 5.80-5.88 (m, 1H), 5.34 (dt, *J*= 1.3 & 17.0 Hz, 1H), 5.26 (dt, *J*= 1.3 & 10.3 Hz, 1H), 5.17 (s, 2H), 3.93 (q, *J*= 6.0 Hz, 1H), 3.84 (m, 2H), 3.71 (m, 1H), 3.59 (m, 2H), 3.40 (s, 3H), 2.99 (m, 1H), 2.78 (m, 1H) ppm^{13}C-

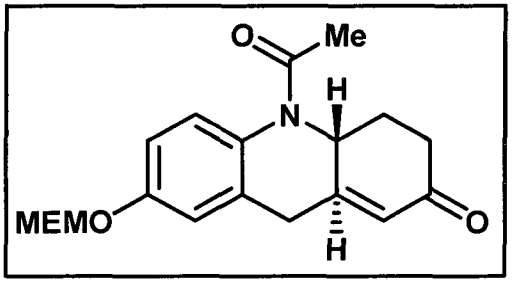
NMR: (100 MHz, $CDCl_3$) δ= 150.2, 138.0, 120.1, 118.7, 118.5, 116.7, 115.6, 115.2, 95.0, 72.1, 67.8, 67.2, 60.9, 59.4, 33.7 ppm.

Compound 361: 1-((2R,3S)-3-hydroxy-6-((2-methoxyethoxy)methoxy)-2-vinyl-3,4-dihydroquinolin-1(2H)-yl)ethanone



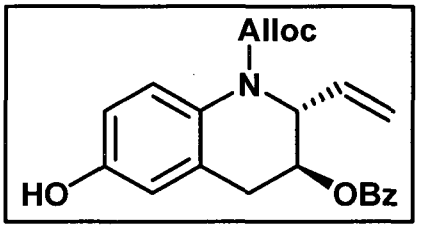
To a stirred solution of 40 mg (0.143 mmole) amino alcohol **359'** in 5 mL, 0.15 mL (0.15 mmole) anhydride acetic and 19 mg (0.15 mmole) DMAP were added at -10°C and stirred for 3 hours. The reaction was processed with ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography over silica gel (10% ethyl acetate in hexanes) afforded compound **361** as a dark oil; 42 mg (92%). R_f: 0.52 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 321.2, $C_{17}H_{23}NO_5$ LRMS: MS (ES+) m/z = 322.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 6.79 (m, 1H), 6.73 (s, 1H), 6.52 (d, *J*= 8.5 Hz, 1H), 5.80-5.89 (m, 1H), 5.32 (dt, *J*= 1.3, 17.0 Hz, 1H), 5.22 (d, *J*= 10.3 Hz, 1H), 5.17 (s, 2H), 5.10 (m, 1H), 3.87 (m, 1H), 3.84 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H), 3.04 (m, 1H), 2.81 (m, 1H), 2.07 (s, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 170.9, 150.0, 137.5, 119.4, 118.3, 118.1, 116.8, 115.7, 115.2, 95.0, 72.1, 69.4, 67.8, 59.4, 57.9, 30.9, 21.7 ppm.

Compound 55



To a stirring solution of compound **361** (30 mg, 0.093 mmole) in 10mL dried dichloromethane at 0°C were added pyridine (0.016 mL, 0.186 mmole) and acryloyl chloride (0.017 mL, 0.186 mmole). After stirring at room temperature for 1 hour, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted with dichloromethane (2 × 2 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was utilized in the next reaction without purification. To the above crude compound in 50 mL anhydrous dichloromethane at room temperature under nitrogen was added 16 mg (0.019 mmole, 0.2 eq) of 1st generation of Grubbs catalyst. After refluxing at 45°C for 2 hours under nitrogen, the solvent evaporated. Purification of the residue by flash chromatography over silica gel using 50% ethyl acetate in hexanes afforded 20 mg (62% in 2 steps) of compound **55** as a dark brown oil. R_f: 0.31 (in 50% Ethyl acetate/Hexanes running 2 times). Molecular Weight and Formula: 347.2, $C_{18}H_{21}NO_6$ LRMS: MS (ES+) m/z = 348.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.24 (d, *J*= 9.0 Hz, 1H), 7.22 (m, 1H), 7.00 (m, 1H), 6.90 (s, 1H), 6.36 (m, 1H), 5.25 (s, 2H), 4.75-4.82 (m, 1H), 4.31 (m, 1H), 3.83 (m, 2H), 3.58 (m, 2H), 3.48 (m, 1H), 3.40 (s, 3H), 2.94 (m, 1H), 2.19 (s, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 170.1, 168.8, 154.0, 144.1, 130.4, 128.9, 125.1, 120.9, 116.8, 116.1, 94.0, 72.0, 70.9, 68.0, 63.7, 59.5, 34.7, 21.4 ppm.

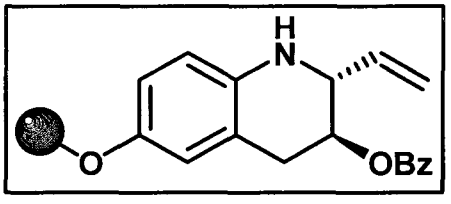
Compound 362: (2R,3S)-allyl 3-(benzoyloxy)-6-hydroxy-2-vinyl-3,4-dihydro-quinoline-1(2H)-carboxylate



To a solution of compound **359** (25 mg, 0.053 mmol) in 10 mL of anhydrous CH_2Cl_2/methanol (9:1) solution was added p-toluenesulfonic acid monohydrate (10 mg, 0.053 mmol), and the mixture was refluxed for 1.5 h. The reaction

mixture was cooled and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and washed with water (2 x 10 mL), and the organic layer was dried over anhydrous magnesium sulfate. Purification of the residue by flash chromatography over silica gel using 50% ethyl acetate in hexanes afforded 19 mg (95%) of compound **362** as a brown oil. R_f: 0.7 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 379.2, $C_{22}H_{21}NO_5$ LRMS: MS (ES+) m/z = 380.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.92 (m, 2H), 7.80 (m, 2H), 7.63 (t, *J*= 7.5 Hz, 1H), 7.40-7.50 (m, 2H), 6.74 (dd, *J*= 3.0 & 8.8 Hz, 1H), 6.64 (m, 1H), 5.81-5.90 (m, 2H), 5.52 (m, 1H), 5.49 (m, 1H), 5.29 (m, 1H), 5.21 (m, 1H), 5.18 (m, 1H), 5.08 (d, *J*= 10.8 Hz, 1H), 4.51 (m, 2H), 3.16 (m, 1H), 3.00 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.6, 165.6, 154.2, 143.8, 133.5, 133.3, 130.6, 129.9 129.8, 128.8, 127.1, 127.0, 117.5, 117.3, 114.9, 113.9, 70.4, 66.5, 57.7, 20.9 ppm.

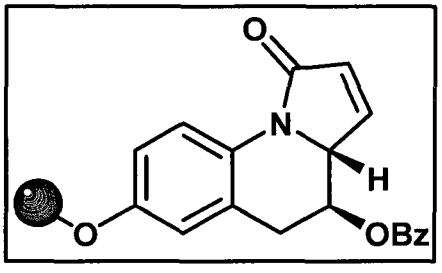
Compound 363'



22 mg (0.04 mmole) of bromo wang resin (1.7 mmole/g) was preliminary washed several times with dichloromethane and DMF, then swollen 30 min in DMF. Onto the resin in 1mL of anhydrous DMF, 30 mg (0.08 mmole) of compound **362**, pre-dissolved in 1mL of anhydrous DMF was added. 12 mg (0.08 mmole) of sodium iodide and 26 mg (0.08 mmole) of cesium carbonate, both beforehand dried over night in the oven, were added to the solution. The mixture was bubbled vigorously by nitrogen while stirring for 48 hours. The resin was successively washed with Methanol (2 × 2 mL), DMF (2 × 2 mL), water (2 × 2 mL), Methanol (2 × 2 mL) and dichloromethane (3 × 2 mL) and then dried under vacuum for a few hours. The filtrates containing starting material in DMF were evaporated and the residue was dissolved in DCM. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in

hexanes). 16 mg (0.044 mmole) of recovered starting material was obtained, giving an indirect yield for the loading step of 90%. The loading was found as 1.53 mmole/g of resin. 1mg of the resin was subjected to cleavage in 5% TFA in dichloromethane for 1 hour. The resin was then filtered and washed several times with dichloromethane. The solvent was evaporated and dried under vacuum. ESI-MS showed only the expected compound and the TLC showed one major spot. Molecular Weight and Formula: 379.2, $C_{22}H_{21}NO_5$ LRMS: MS (ES+) m/z = 380.2 (M+1). To 12 mg (0.032 mmole) of compound-resin, 6 mg (0.006 mmole) of tetrakis-(triphenylphosphine)palladium(0) dissolved in 2 mL of dry dichloromethane was added. To this mixture, 0.02 mL of *N*-methylmorpholine and 0.02 mL of anhydride acetic were added. The reaction mixture was bubbled under nitrogen for 15 hours and then was washed consecutively with DMF, water, methanol and dichloromethane (two times each with 2 mL). The resin was dried on vacuum pump over night to afford compound 13. No further purification was performed.

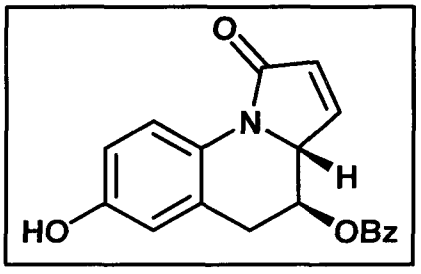
Compound 365



To a suspension of 8 mg (0.028 mmole) of resin compound 363' in dichloromethane (2 mL) were added 0.08 mL (0.54 mmole) of triethylamine and 0.034 mL (0.4 mmole) ofacryloyl chloride. The mixture was bubbled by a flow of nitrogen for 24 hours. The resin was washed with DMF(2 × 2 mL), methanol (2 × 2 mL) and dichloromethane (3 × 2 mL) and then dried over high vacuum pump. Molecular Weight and Formula: 349.4, $C_{21}H_{19}NO_4$ LRMS: MS (ES+) m/z = 350.4 (M+1).

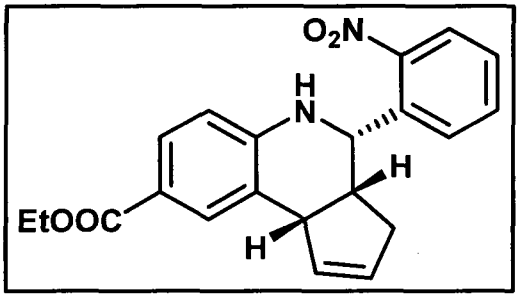
To 8 mg (0.022 mmole) of the above resulted diene under nitrogen was added 4 mL of dichloromethane. To this, a solution of 10 mg (0.012 mmole) of 2nd Grubbs catalyst in 2 mL dichloromethane was added. The reaction mixture was warmed to 40°C and stirred for 6 hours. The mixture was cooled to room temperature and the resin was washed with dichloromethane, methanol and dichloromethane (3 times each with 2 mL) and finally was dried over high vacuum pump to afford compound **365**. Molecular Weight and Formula: 321.3, $C_{19}H_{15}NO_4$. LRMS: MS (ES+) m/z = 322.3 (M+1)

Compound 366



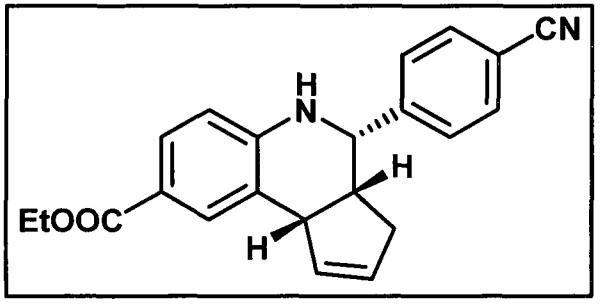
Resin compound **365** was treated with 2 mL solution of 5% TFA in anhydrous dichloromethane at room temperature for 1 hour. Following this, the resin was washed two times with dichloromethane, filtered and the solvent was evaporated. The residue was then purified by flash column chromatography over silica gel using 10% ethyl acetate and hexanes. 4 mg (0.012 mmole, 42% over 3 steps) of compound **366** as a dark brown oil was afforded. Molecular Weight and Formula: 321.3, $C_{19}H_{15}NO_4$. LRMS: MS (ES+) m/z = 322.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.34 (s, 1H), 8.15 (m, 3H), 7.72 (t, *J*= 7.5 Hz, 1H), 7.59 (t, *J*= 7.5 Hz, 2H), 7.52 (m, 1H), 6.77 (m, 2H), 6.30 (dd, *J*= 1.8 & 6.0 Hz, 1H), 5.00 (td, *J*= 5.8 & 10.5 Hz, 1H), 4.66 (dt, *J*= 1.5 & 10.5 Hz, 1H), 3.46 (m, 1H), 3.16 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 170.4, 168.4, 154.0, 145.2, 133.9, 130.2, 130.0, 129.4, 129.0, 125.6, 120.5, 115.7, 115.6, 114.3, 71.6, 63.7, 34.3 ppm.

Compound 428: (3aR,4S,9bS)-ethyl 4-(2-nitrophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylate



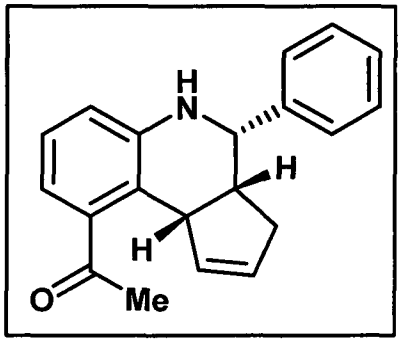
To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-nitrobenzaldehyde (362 mg, 2.4 mmol) was added. After stirring for 4.5 hours (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.81 g of orange solid was afforded (93%). R_f: 0.56 (65:35, Hex.:ethyl acetate) Molecular Weight and Formula: 364.4, $C_{21}H_{20}N_2O_4$ LRMS: MS (ES+) m/z = 365.2 (M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.95 (d, *J*= 8.0 Hz, 2H), 7.79 (s, 1H), 7.66-7.73 (m, 2H), 7.50 (t, *J*= 8.0 Hz, 1H), 6.62 (d, *J*= 8.5 Hz, 1H), 5.97- 6.01 (m,1H), 5.67- 5.71 (m, 1H), 5.24 (d, *J*= 3 Hz, 1H), 4.35 (qd, *J*= 2.5 & 7.0 Hz, 2H), 4.19 (d, *J*= 9.0 Hz, 1H), 3.98 (bs, 1H), 3.33 (qd, *J*= 3.0 & 9.0 Hz, 1H), 2.61- 2.70 (m, 1H), 1.84 (dd, *J*= 8.5 & 15.5 Hz, 1H), 1.39 (t, *J*= 7.0 Hz, 3H) ppm ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.1, 149.6, 137.1, 134.4, 134.1, 133.5, 131.6, 130.5, 130.1, 128.8, 125.5, 125.1, 124.9, 121.8, 115.8, 60.8, 53.1, 46.1, 43.9, 30.1, 14.7 ppm.

Compound 429: (3aR,4S,9bS)-ethyl 4-(4-cyanophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylate



To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 4-cyanobenzaldehyde (314 mg, 2.4 mmol) was added. After stirring for 2 hours (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.75 g of white solid was afforded (91%). R_f: 0.58 (65:35, Hex.:ethyl acetate) Molecular Weight and Formula:
344.4, $C_{22}H_{20}N_2O_2$ LRMS: MS (ES+) m/z = 345.3(M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.75 (s, 1H), 7.62-7.69 (m, 3H), 7.54 (d, *J*= 8.3 Hz, 2H), 6.67 (d, *J*= 8.5 Hz, 1H), 5.89- 5.95 (m, 1H), 5.62- 5.66 (m, 1H), 4.75 (d, *J*= 3.0 Hz, 1H), 4.66 (bs, 1H), 4.30 (qd, *J*= 2.3 & 7.0 Hz, 2H), 4.10- 4.15 (m, 1H), 3.00 (qd, *J*= 3.5 & 9.0 Hz, 1H), 2.44- 2.54 (m, 1H), 1.74 (dd, *J*= 8.5 & 15.5 Hz, 1H), 1.36 (t, *J*= 7.0 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.3, 149.6, 148.1, 136.5, 134.3, 132.8, 131.5, 130.6, 129.3, 128.5, 127.6, 125.2, 121.4, 119.1, 115.8, 111.6, 60.9, 57.7, 45.9, 31.8, 21.5, 14.7 ppm.

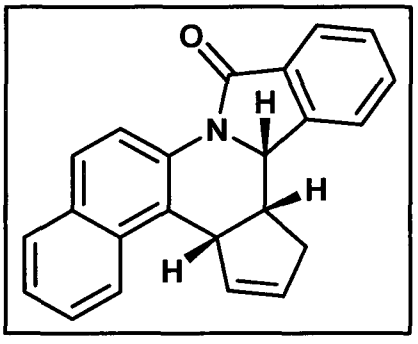
Compound 430: (3aR,4S,9bS)-9-methyl-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta-[c]quinoline



To a mixture of 3'-aminoacetophenone (324 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), benzaldehyde (0.24 mL, 2.4 mmol) was added. After stirring for 1 hour (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.51 g of bright yellow solid was afforded (79%). R_f: 0.59 (65:35, Hex.:ethyl acetate).

$C_{20}H_{19}NO$ LRMS: MS (ES+) m/z = 290.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 7.38-7.46 (m, 5H), 7.30-7.34 (m, 1H), 7.06-7.12 (m, 1H), 6.79 (d, *J*= 7.0 Hz, 1H), 5.62- 5.65 (m, 2H), 4.91 (d, *J*= 9.0 Hz, 1H), 4.64 (d, *J*= 3.0 Hz, 1H), 3.10 (qd, *J*= 3.0 & 9.0 Hz, 1H), 2.65- 2.72 (m, 1H), 2.62 (s, 3H), 1.85 (dd, *J*= 9.0 & 16.1 Hz, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 203.7, 142.8, 139.3, 134.3, 130.9, 129.0, 128.9, 127.7, 126.8, 126.3, 120.8, 120.0, 118.5, 58.3, 46.3, 44.9, 32.3, 30.5 ppm.

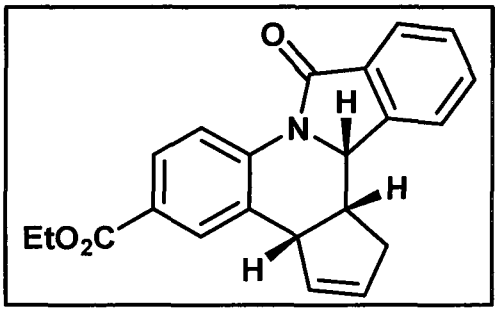
Compound 444



To a mixture of 2-aminonaphthalene (343 mg, 2.4 mmol), trifluoroacetic acid (0.37 mL, 4.8 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-carboxybenzaldehyde (360 mg, 2.4 mmol) was added. After stirring for 40 hours (TLC monitoring), the solvent was evaporated, the crude was dissolved in dichloromethane, washed with dilute sodium bicarbonate solution, dried over magnesium sulfate and subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.60 g of white solid was afforded (78%). R_f: 0.53 (65:35, Hex.:ethyl acetate). $C_{23}H_{27}NO$ LRMS: MS (ES+) m/z = 324.3(M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.56 (d, *J*= 9.0 Hz, 1H), 8.13 (d, *J*= 8.5 Hz, 1H), 7.99 (d, *J*= 7.5 Hz, 1H), 7.85 (d, *J*= 8.0 Hz, 1H), 7.79 (d, *J*= 9.0 Hz, 1H), 7.66 (t, *J*= 7.0 Hz, 1H), 7.53-7.60 (m, 3H), 7.48 (t, *J*= 7.5, 1H), 6.04-6.08 (m,1H), 5.52-5.56 (m, 1H), 5.08 (d, *J*= 3.5 Hz, 1H), 4.82 (d, *J*= 9.0 Hz, 1H), 3.76 (qd, *J*= 4.0 & 9.0 Hz, 1H), 2.03 (dd, *J*= 9.0 & 16.6 Hz, 1H), 1.75-1.83 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.7, 143.8, 133.4, 133.3, 133.0, 132.8, 131.9, 131.7, 130.6, 129.4,

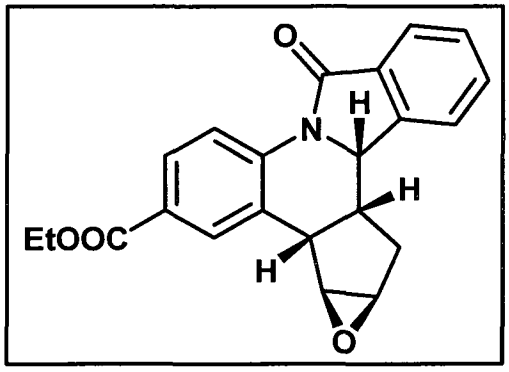
129.2, 127.9, 127.0, 125.5, 125.4, 124.7, 124.0, 122.5, 120.4, 60.8, 44.5, 40.7, 32.6 ppm.

Compound 443 : Cyclopenta[c]- ethyl 11-oxo-5,6,6a,11-tetrahydroisoindolo[2,1-a]-quinoline-3-carboxylate



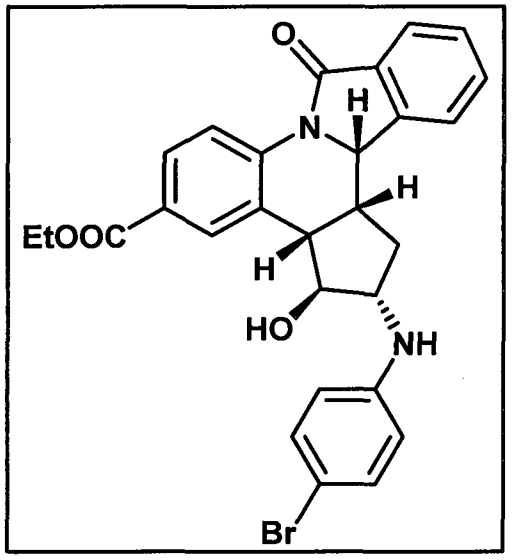
To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.37 mL, 4.8 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-carboxybenzaldehyde (360 mg, 2.4 mmol) was added. After stirring for 40 hours (TLC monitoring), the solvent was evaporated, the crude was dissolved in dichloromethane, washed with dilute sodium bicarbonate solution, dried over magnesium sulfate, filtered and subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.65 g of white solid was afforded (79%). R_f: 0.55 (65:35, Hex.:ethyl acetate) $C_{22}H_{19}NO_3$ LRMS: MS (ES+) m/z = 346.3 (M+1) ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.44 (d, *J*= 9.0 Hz, 1H), 7.90-7.95 (m, 3H), 7.63 (t, *J*= 8.0 Hz, 1H), 7.53 (t, *J*= 7.0 Hz, 2H), 5.84-5.89 (m, 1H), 5.53-5.57 (m, 1H), 5.09 (d, *J*= 4.0 Hz, 1H), 4.38 (qd, *J*= 1.5 & 7.0 Hz, 2H), 4.26 (d, *J*= 8.5 Hz, 1H), 3.55 (qd, *J*= 4.0 & 9.0 Hz, 1H), 1.94 (dd, *J*= 9.0 & 16.6 Hz, 1H), 1.60-1.70 (m, 1H), 1.41 (t, *J*= 7.0 Hz, 3H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.8, 166.2, 143.3, 139.0, 133.5, 132.6, 132.5, 130.2, 130.1, 130.0, 128.7, 128.0, 126.2, 124.3, 122.0, 120.1, 60.9, 59.5, 46.0, 39.9, 31.3, 14.3 ppm.

Compound 446



To a solution of **443** (450 mg, 1.3mmol) in dichloromethane (10 mL) was added 3-chloroperoxybenzoic acid (380 mg, 1.43 mmol). The reaction mixture was stirred for 3 hours (TLC monitoring). After quenching with saturated sodium bicarbonate solution, the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and purified by column chromatography (hexanes:ethyl acetate; 5:1). A white solid as major compound **446** was afforded; 300 mg (83%). R_f: 0.40 (65:35, Hex.:ethyl acetate). $C_{22}H_{19}NO_4$ LRMS: MS (ES+) m/z = 362.2 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.56 (d, *J*= 9.0 Hz, 1H), 8.08 (s, 1H), 8.00 (dd, *J*= 1.5 & 15.6 Hz, 1H), 7.93 (d, *J*= 7.5 Hz, 1H), 7.64 (t, *J*= 7.5 Hz, 1H), 7.53 (t, *J*= 7.5 Hz, 1H), 7.48 (d, *J*= 7.5 Hz, 1H), 4.98 (d, *J*= 3.5 Hz, 1H), 4.40 (qd, *J*= 1.5 & 7.5 Hz, 2H), 3.86 (d, *J*= 7.5 Hz, 1H), 3.71 (d, *J*= 2.5 Hz, 1H), 3.34 (bs, 1H), 3.04 (qd, *J*= 3.5, 10 Hz, 1H), 1.61 (dd, *J* = 7.5, 14.6 Hz, 1H), 1.42 (t, *J*= 7.5 Hz, 3H), 0.99 (dd, *J*= 10.0, 14.1 Hz, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 166.5, 165.9, 142.6, 139.7, 132.8, 132.4, 130.8, 128.9, 128.8, 126.1, 124.3, 124.2, 121.9, 120.1, 61.5, 61.0, 58.2, 56.6, 40.9, 35.3, 26.0, 14.3 ppm.

Compound 447



To a solution of 446 (155 mg, 0.45 mmol) and boron trifluoride diethyl etherate (0.057 mL, 0.45 mmol) in dichloromethane (10 mL), 4-bromoaniline (160 mg, 0.9 mmol) was added. After completion of the reaction (5 hours, TLC), the reaction was quenched by ammonium chloride solution. The aqueous layer was extracted by dichloromethane. Combined organic layer was dried over magnesium sulfate and filtered. Column chromatography (hexanes:ethyl acetate; 4:1) was afforded a white solid 447; 185mg (77%). R_f: 0.37 (65:35, Hex.:ethyl acetate). $C_{28}H_{25}BrN_2O_4$ LRMS: MS (ES+) m/z = 533.3, 535.3 (M+1). ^{1}H-NMR: (400 MHz, $CDCl_3$) δ= 8.45 (d, *J*= 8.5 Hz, 1H), 8.05 (s, 1H), 7.96 (dd, *J*= 1.8 & 8.5 Hz, 1H), 7.92 (d, *J*= 7.5 Hz, 1H), 7.64 (td, *J*= 1.0 & 7.5 Hz, 1H), 7.49-7.55 (m, 2H), 7.11 (d, *J*= 9.0 Hz, 2H), 6.33 (d, *J*= 8.8 Hz, 2H), 4.93 (d, *J*= 4.0 Hz, 1H), 4.34 (qd, *J*= 1.5, 7.0 Hz, 2H), 3.94 (t, *J*= 4.5 Hz, 1H), 3.69 (m, 1H), 3.49-3.56 (m, 1H), 3.43-3.49 (m, 1H), 1.81-1.89 (m, 1H), 1.38 (t, *J*= 7.0 Hz, 3H), 0.79-0.89 (m, 1H) ppm. ^{13}C-NMR: (100 MHz, $CDCl_3$) δ= 167.3, 166.7, 146.5, 143.1, 139.5, 133.2, 132.8, 132.3, 130.8, 129.4, 129.2, 129.1, 126.8, 124.9, 122.6, 120.5, 115.5, 109.8, 86.2, 61.5, 60.9, 59.7, 47.3, 37.5, 30.3, 14.7 ppm.

8. Claims to Original Research

1. A practical enantioselective synthesis of a tetrahydroquinolione scaffold in solution phase (model and real systems).

2. Enantioselective syntheses of tetrahydroquinolione-based functionalized tricyclic compounds in solution phase (3 systems). One of these systems has introduced for the first time. X-ray crystallography was performed on two other systems.

3. Enantioselective syntheses of tetrahydroquinolione-based functionalized tricyclic compounds in solid phase (2 systems).

4. One-pot diastereo- and regioselective syntheses of polycyclic compounds using a multi-component/cyclocondensation (tandem) reaction and the mechanistic studies. X-ray crystallography was performed on six polycyclic compounds.

8.1 Publications

1. **Shahriar Khadem**, Reni Joseph, Majid Rastegar, Donald M. Leek, Konstantin Udachin and Prabhat Arya. "A Solution and Solid Phase Approach to Tetrahydroquinoline Derived Polycyclics Having a Ten-Membered Ring" *Journal of Combinatorial Chemistry*, 6, 724-734 (**2004**).

2. P. Arya, S. Quevillon, R. Joseph, CQ. Wei, Z. Gan, M. Parisien, E. Sesmilo, P. Reddy, ZX. Chen, P. Durieux, D. Laforce, LC. Campeau, S. **Khadem, S.** Couve-Bonnaire, R. Kumar, U. Sharma, D. M. Leek, M. Daroszewska and M. Barnes. "Towards the Library Generation of Natural Product-like Polycyclic Derivatives by

Stereocontrolled Diversity-Oriented Synthesis" *Pure & Applied Chemistry*, 77, 163-178 (**2005**).

3. Michael Prakesch, Utpal Sharma, Maya Sharma, **Shahriar Khadem**, Donald M. Leek and Prabhat Arya. "A Modular Approach to Obtaining Diverse Tetrahydroquinoline-derived, Polycyclic Skeletons for use in High-throughput Generation of Natural Product-like Chemical Probes" *Journal of Combinatorial Chemistry*, 8, 715-734 (**2006**).

4. Jyoti P. Nandy, Michael Prakesch, **Shahriar Khadem**, P. Thirupathi Reddy, Utpal Sharma and Prabhat Arya. "Advances in Solution and Solid Phase Synthesis of Natural Product-like Libraries" *Chemical Rev*eiws, 109, 1999-2060 (**2009**).

5. **Shahriar Khadem**, Konstantin Udachin, Gary D. Enright, Michael Prakesch, and Prabhat Arya. "One-Pot Construction of Isoindolo[2,1-a]quinoline system" *Tetrahedron Letters,* 50, 6661-6664 (**2009**).

6. **Shahriar Khadem**, Konstantin Udachin, and Prabhat Arya. "Solution- and Solid-Phase Synthesis of Tetrahydroquinoline-Based Polycyclics Having α,β-Unsaturated γ-Lactam and δ-Lactone Functionalities" *SYNLETT*, 2, 199-202 (**2010**).

8.2 Presentations

1. 13th Quebec-Ontario Minisymposium in Organic and Bioorganic Chemistry, poster presentation, November 2002, Kingston, Ontario.

2. 39th IUPAC Congress and 86th Conference of the Canadian Society for Chemistry, poster presentation, August 2003, Ottawa, Ontario.

3. 14th Quebec-Ontario Minisymposium in Organic and Bioorganic Chemistry, poster presentation, December 2003, Montreal, Quebec.

4. Synthesis day, poster presentation, May 2004, University of Ottawa, Ottawa, Ontario.

5. 15th Quebec-Ontario Minisymposium in Organic and Bioorganic Chemistry, poster presentation, November 2004, Gatineau, Quebec.

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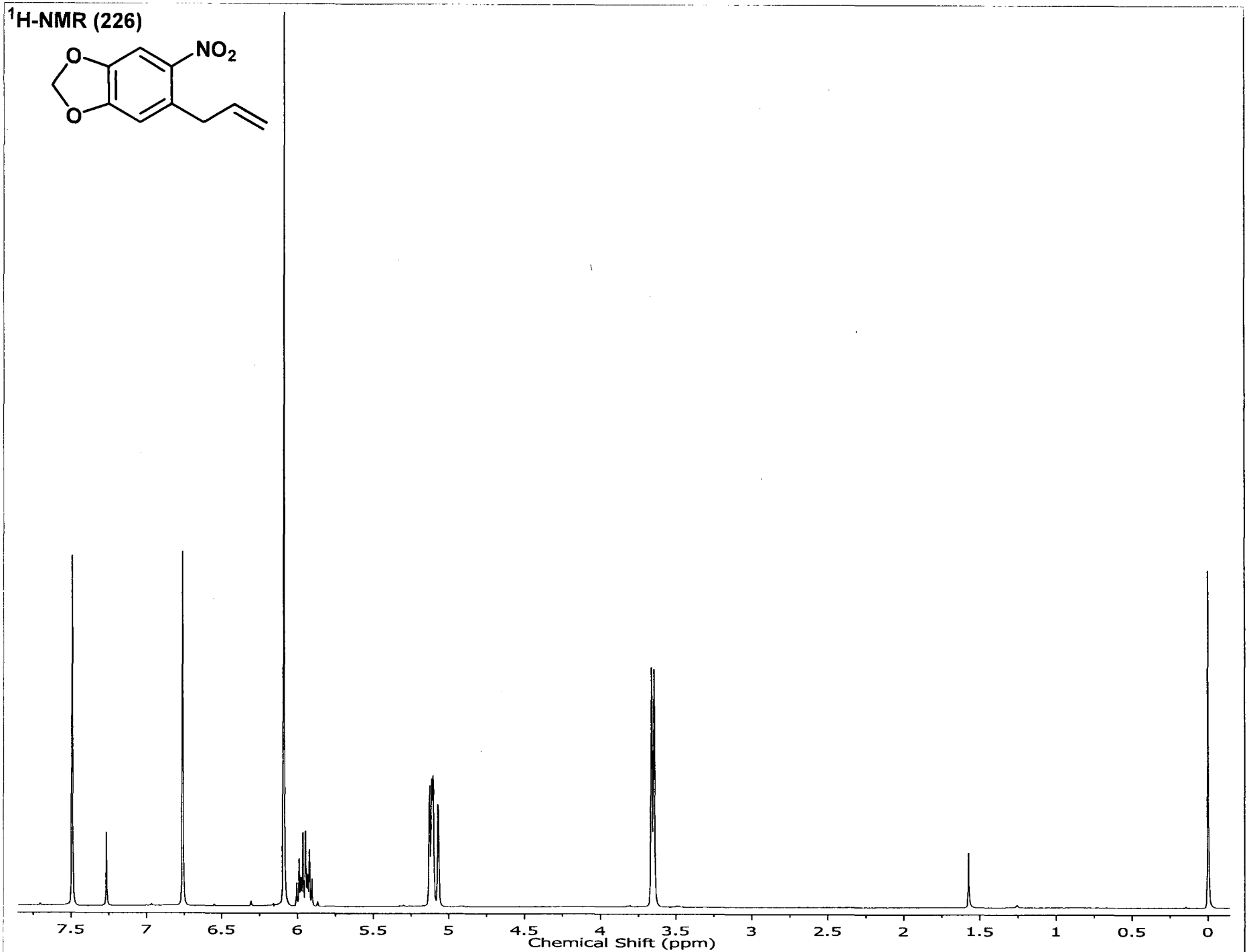
10: Appendix

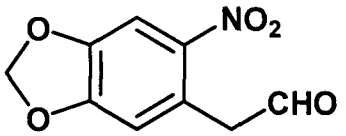
Spectroscopy data for the synthesized compounds are presented in this section (in order) as follow:

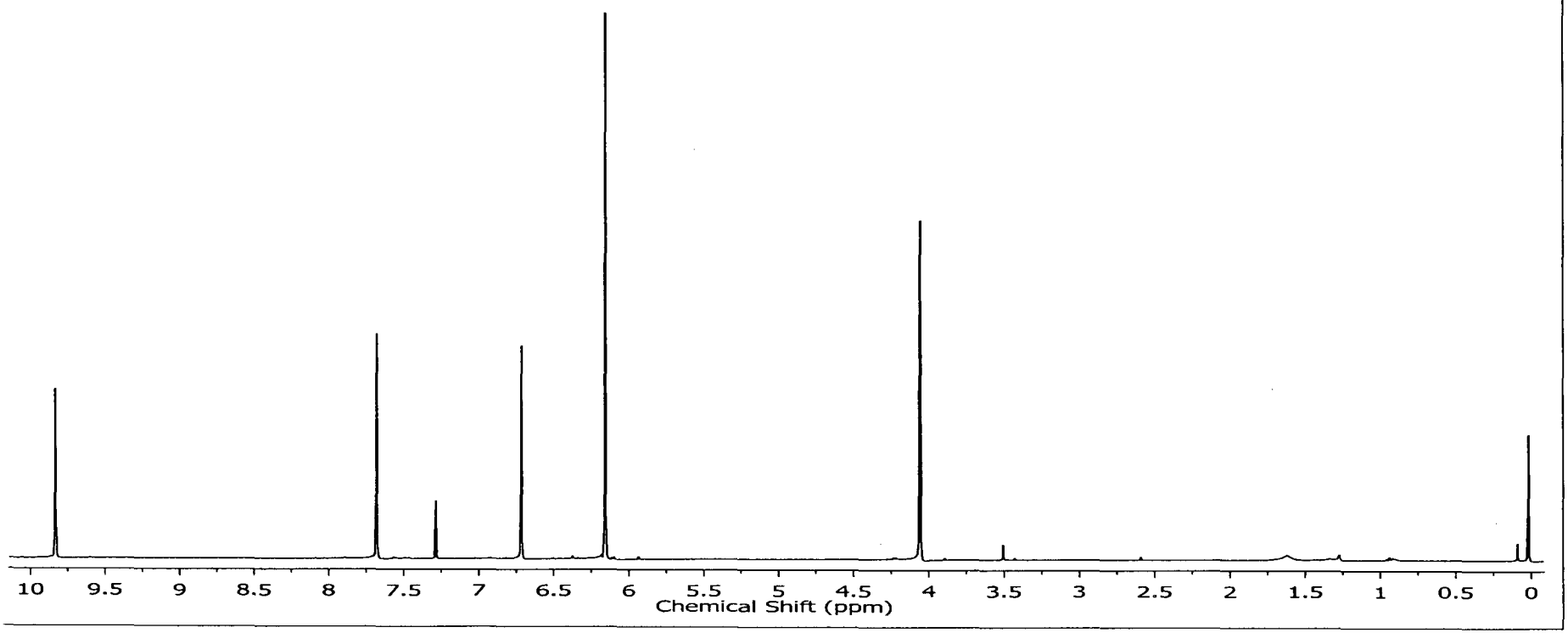
1. ^{1}H-NMR
2. ^{13}C-NMR
3. Chiral HPLC (if applicable)

^{1}H-NMR (226)

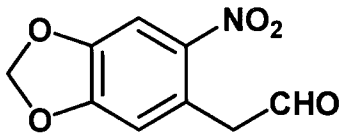


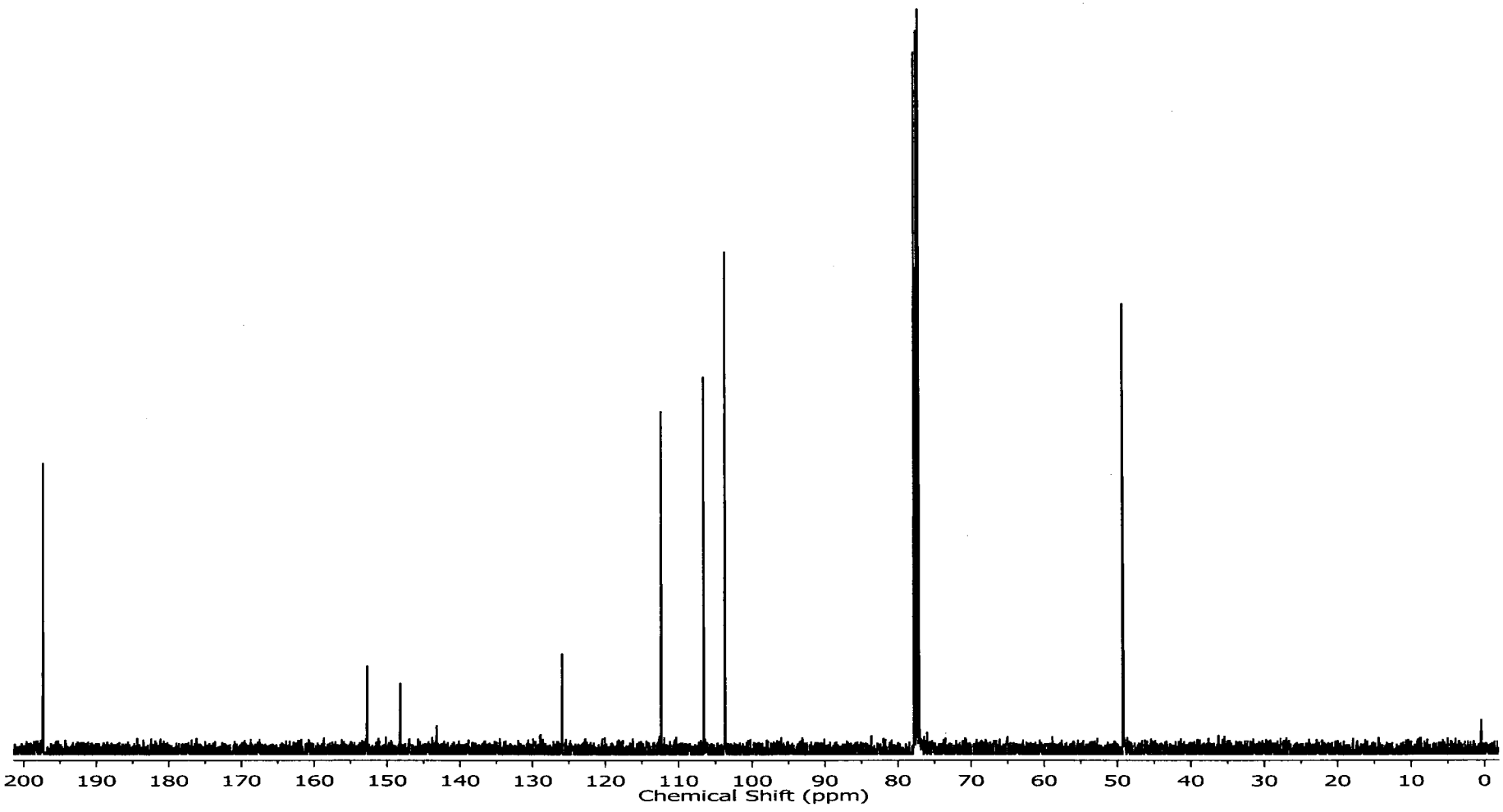
^{1}H-NMR (227)


O
O
NO2
CHO

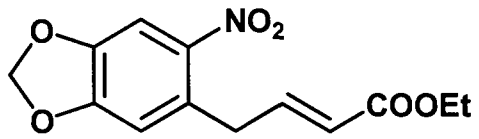

10
9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

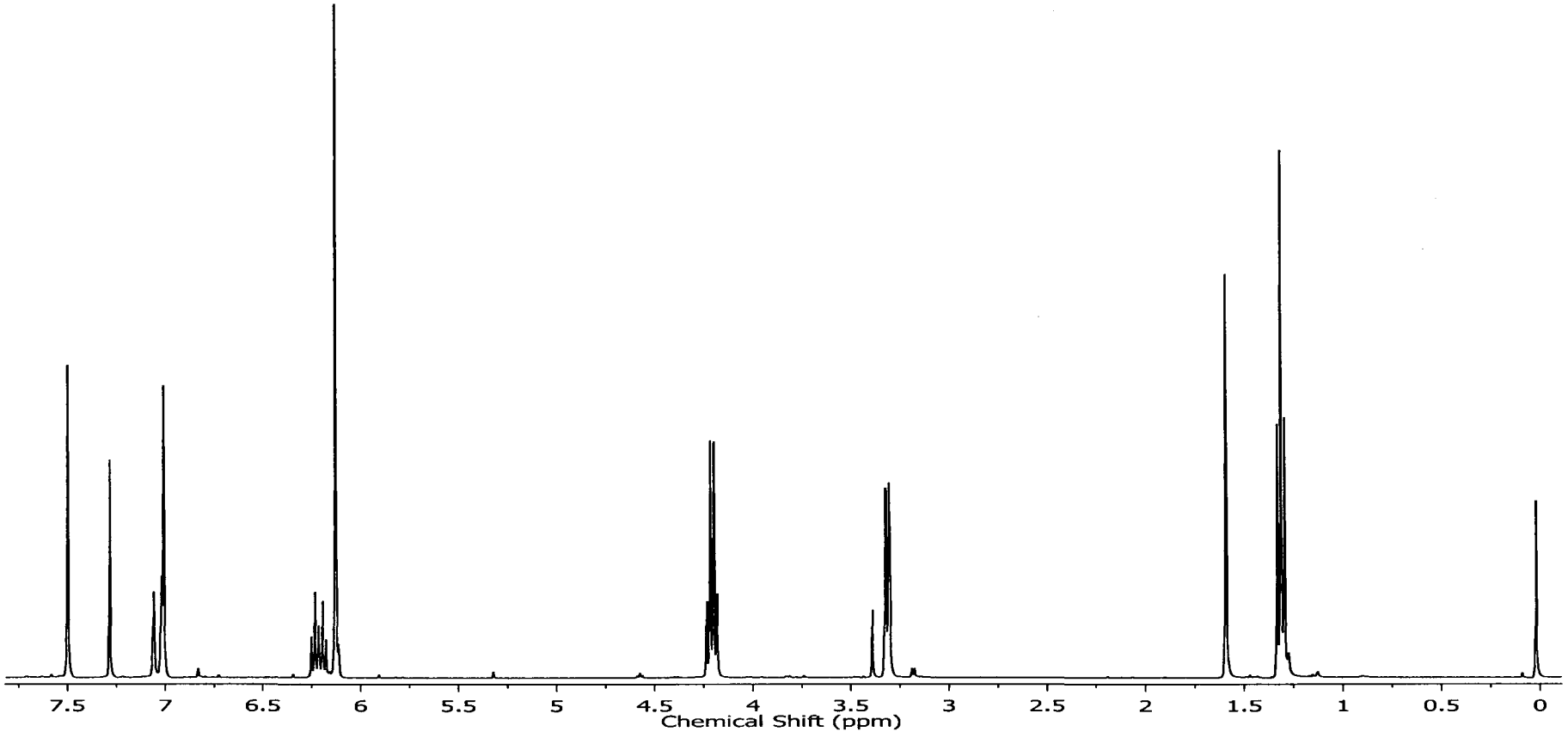
^{13}C-NMR (227)


O
O
NO2
CHO

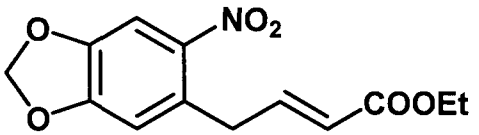

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)

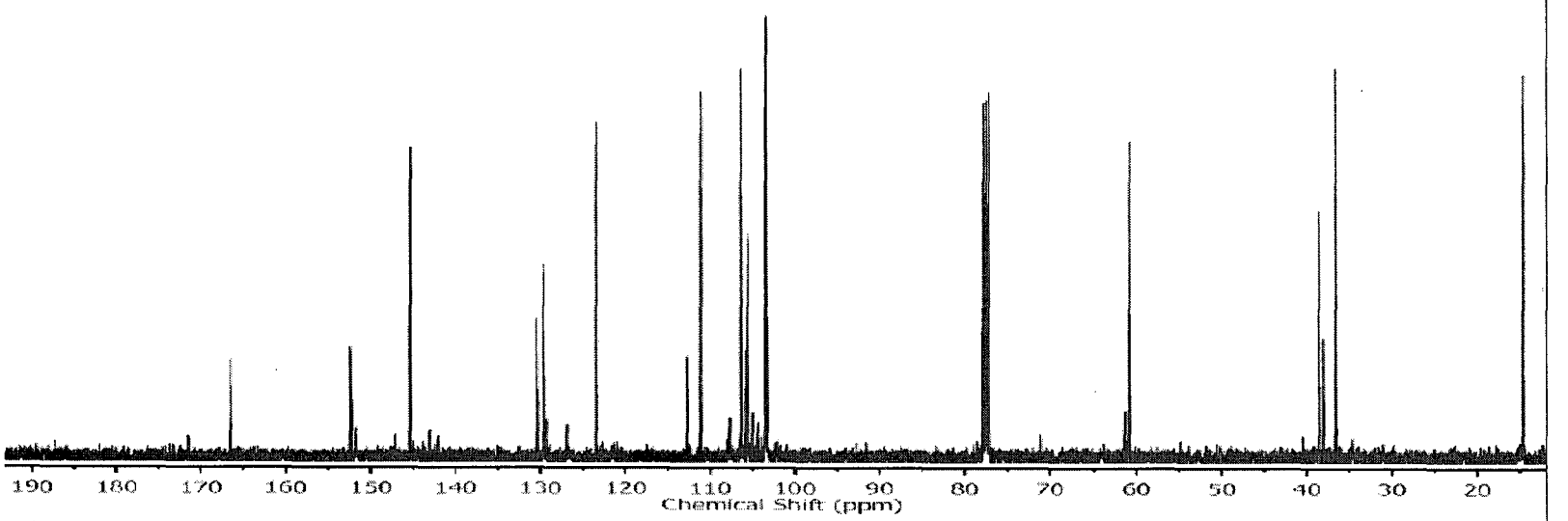
^{1}H-NMR (228)


O
O
NO2
COOEt


7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

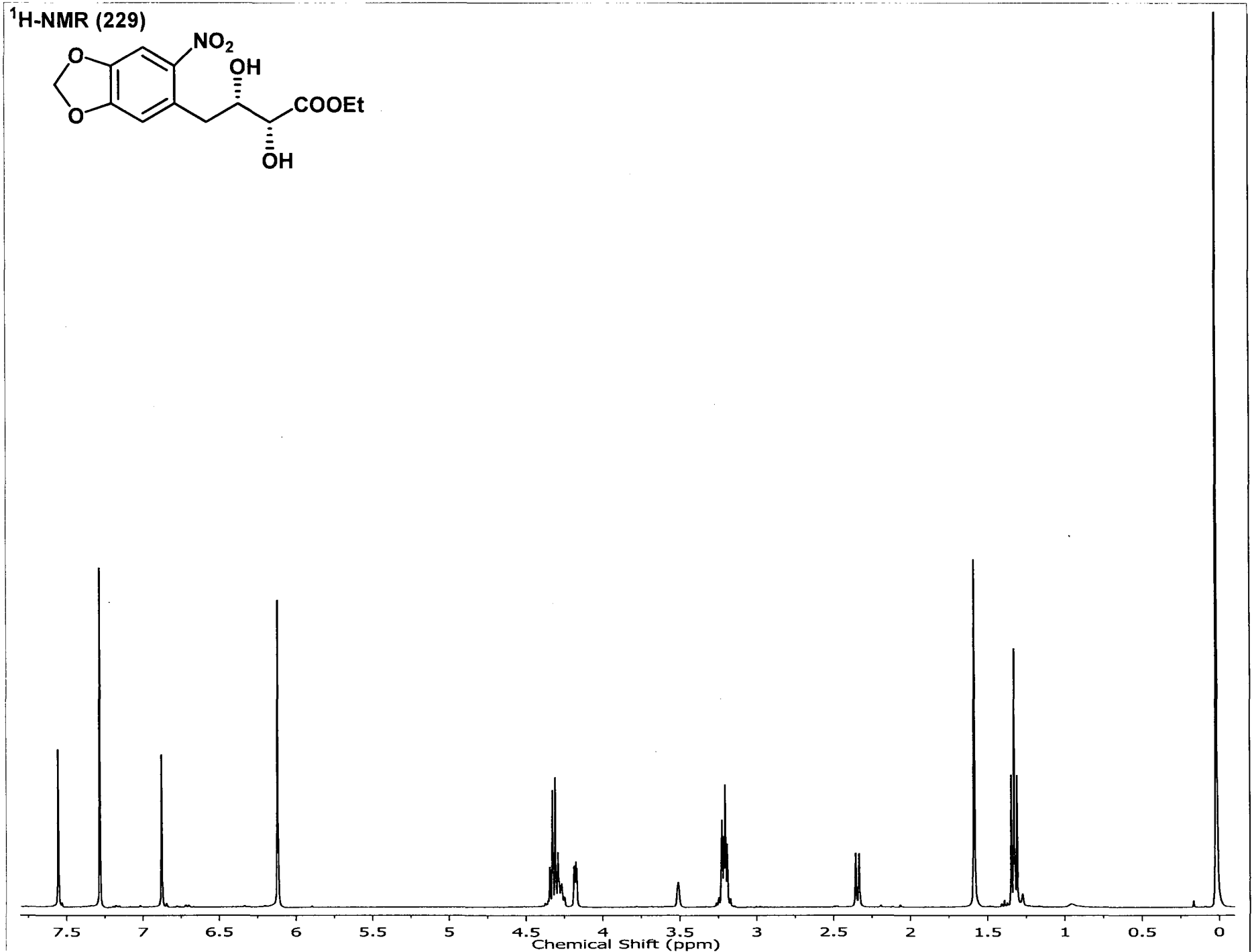
^{13}C-NMR (228)


O
O
NO2
COOEt

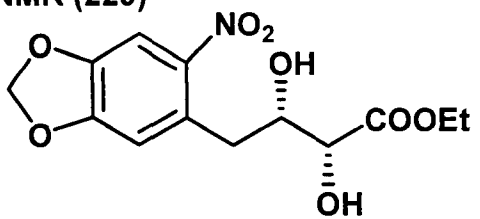

190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

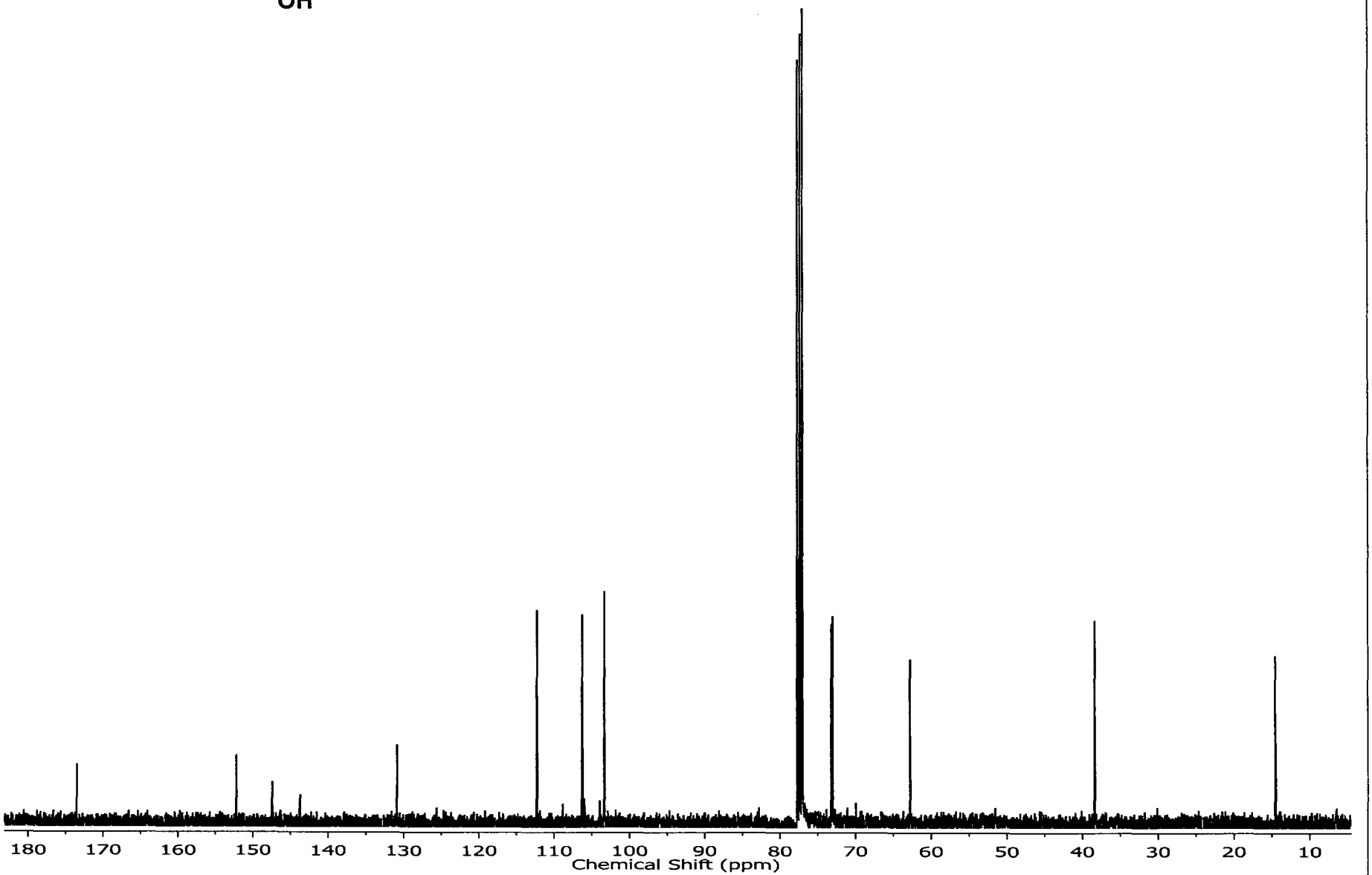
^{1}H-NMR (229)

NO2
OH
COOEt
OH
O
O


7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

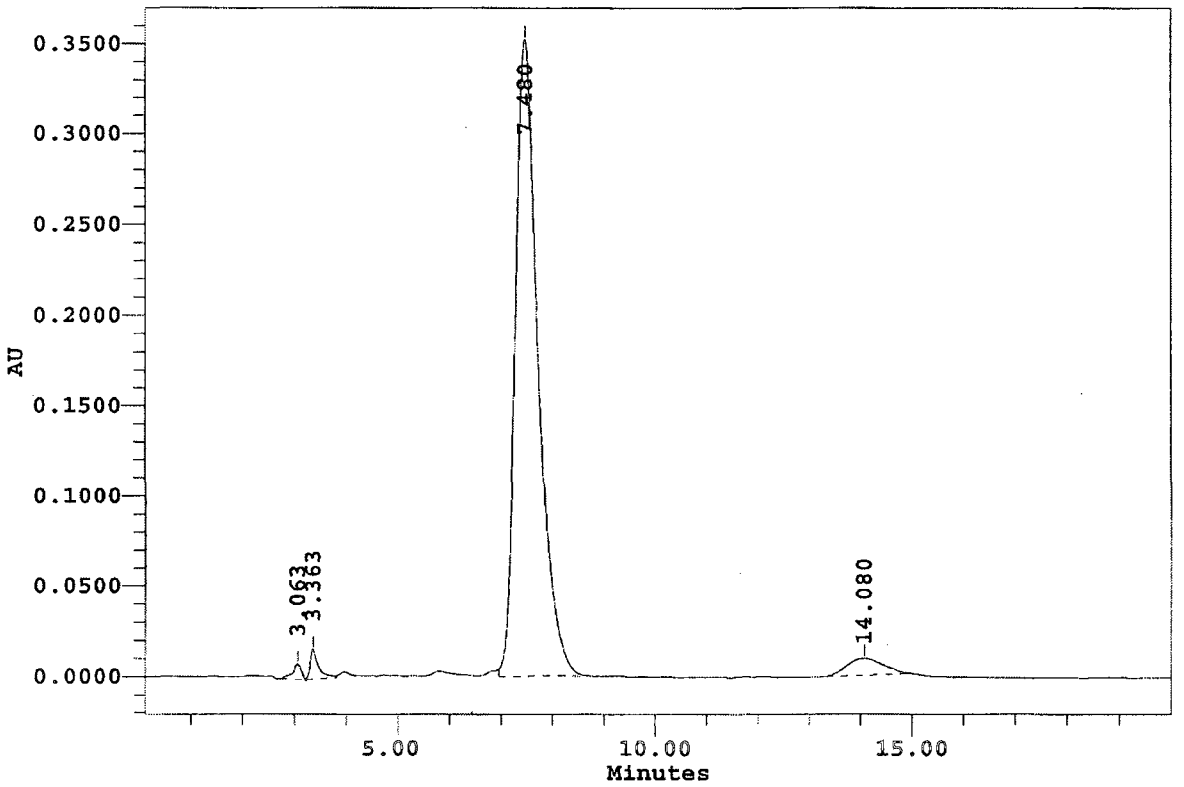
^{13}C-NMR (229)


NO2
OH
COOEt
OH
O
O


180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

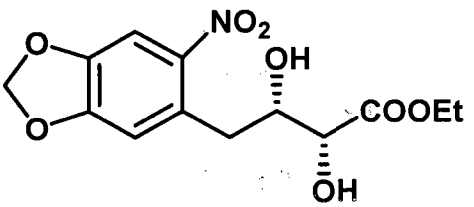
Millennium Results Report April 16, 2003 Page: 1 of 1
For Sample: SH 3.3 Report Method: NP_1
Inj. volume: 30.00 ul Vial: 1 Injection: 2
Comments: 70/30 hexane/ethanol

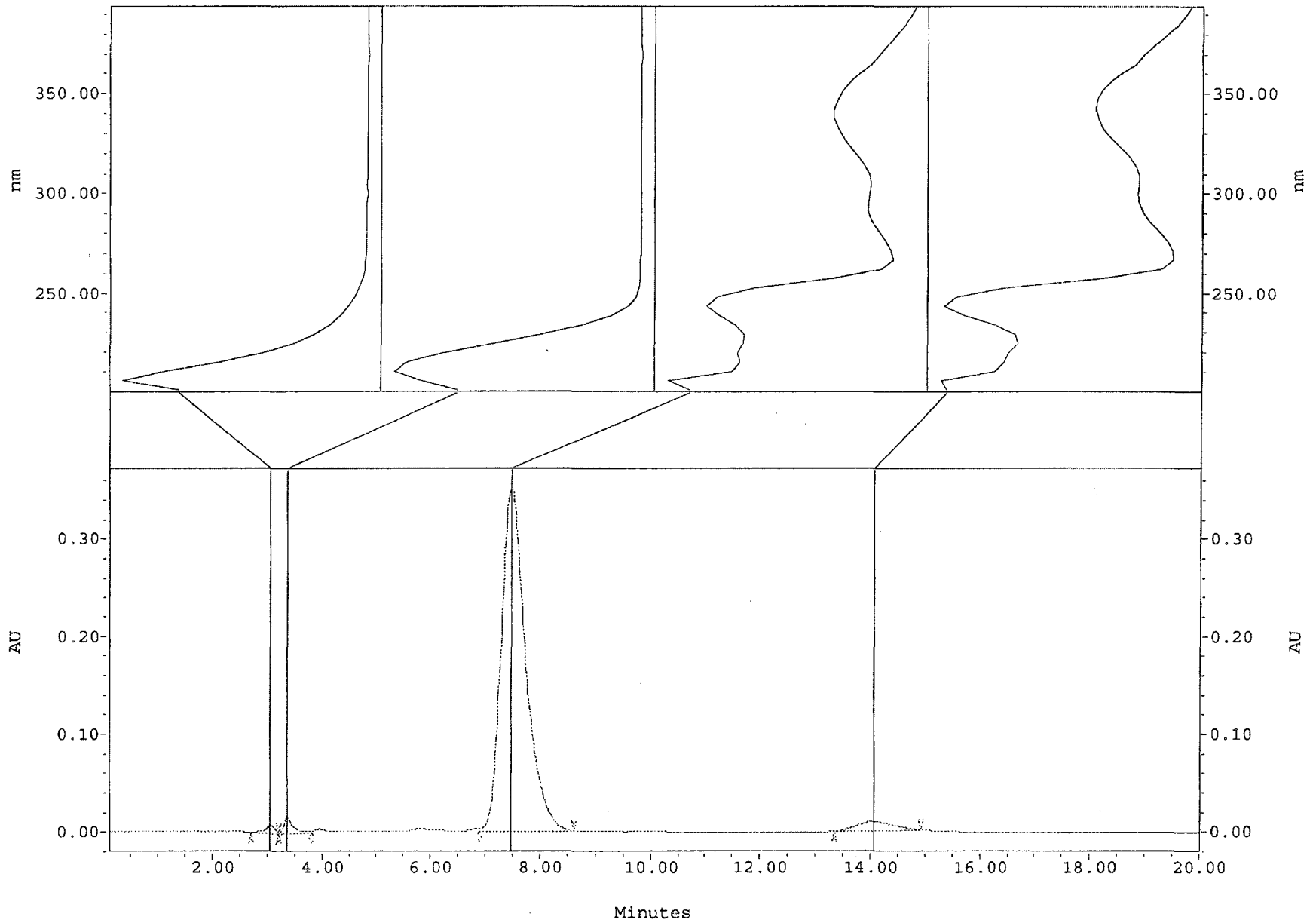
Column Name: CHIRALCEL OD Acq Meth Set: NP_30A_70C
Flow: 1.0 ml/min Processing Method: NP_1
Instrument Method: 30A_70C Proc Chan: 240nm
Date Acquired: 04/16/03 12:57:57 PM Date Processed: 04/16/03 01:24:45 PM



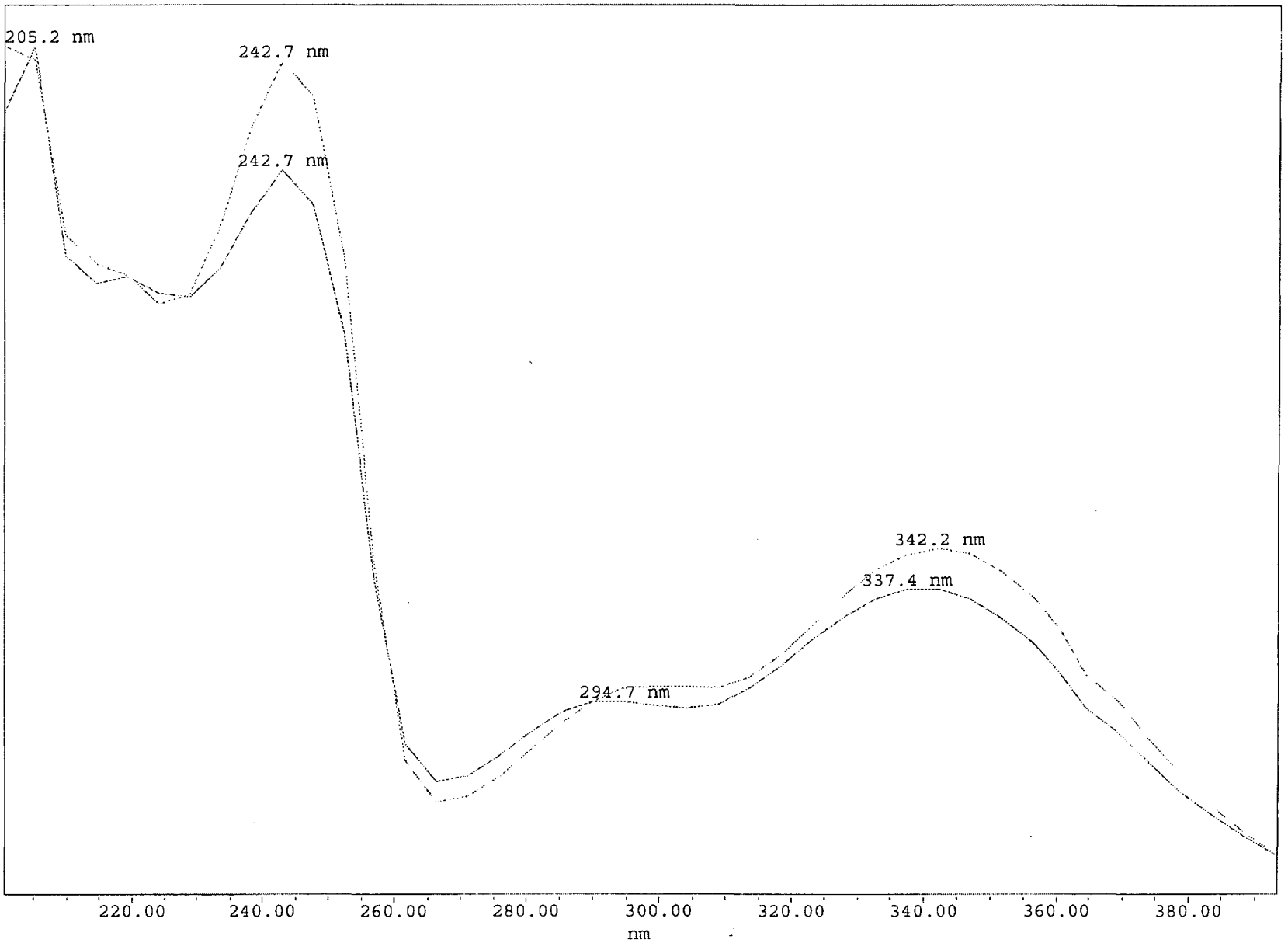
Peak Results

#	Ret Time (min)	Area (uV*sec)	Height (uV)	% Area	% Ht	Int Type	Start Time (min)	End Time (min)
1	3.063	101006	8632	0.87	2.23	BB	2.713	3.213
2	3.363	185823	16537	1.60	4.28	BV	3.213	3.813
3	7.480	10922016	351919	93.78	91.10	VB	6.947	8.680
4	14.080	436978	9207	3.75	2.38	BB	13.330	14.947



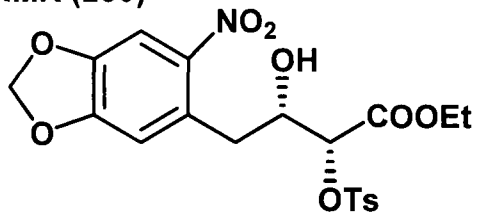


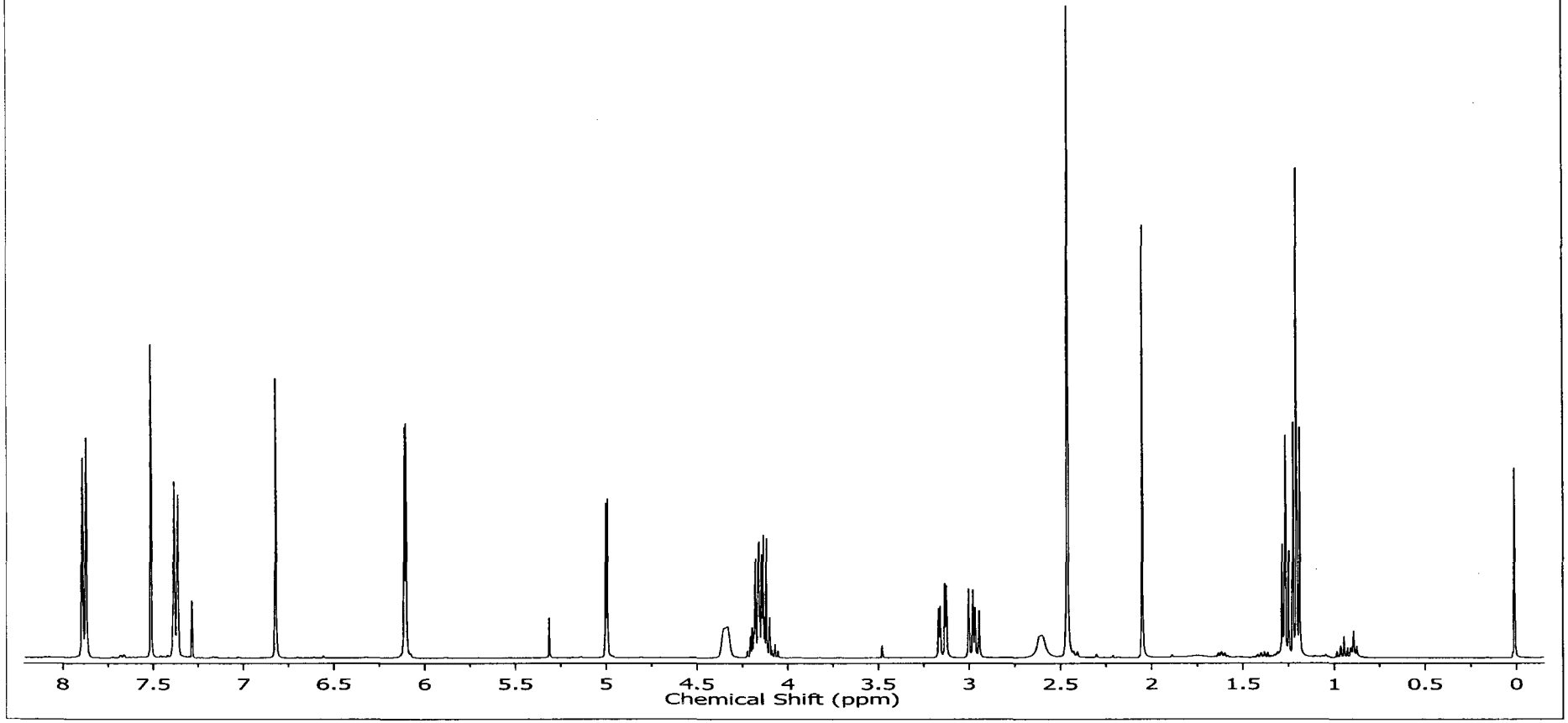
Millennium PDA Spectrum Index Plot - SampleName SH 3.3, Wvln Ch1 - PDA 240.0 nm



Millennium PDA Spectrum Plot - SampleName SH 3.3, Vial 1, Inj. 2

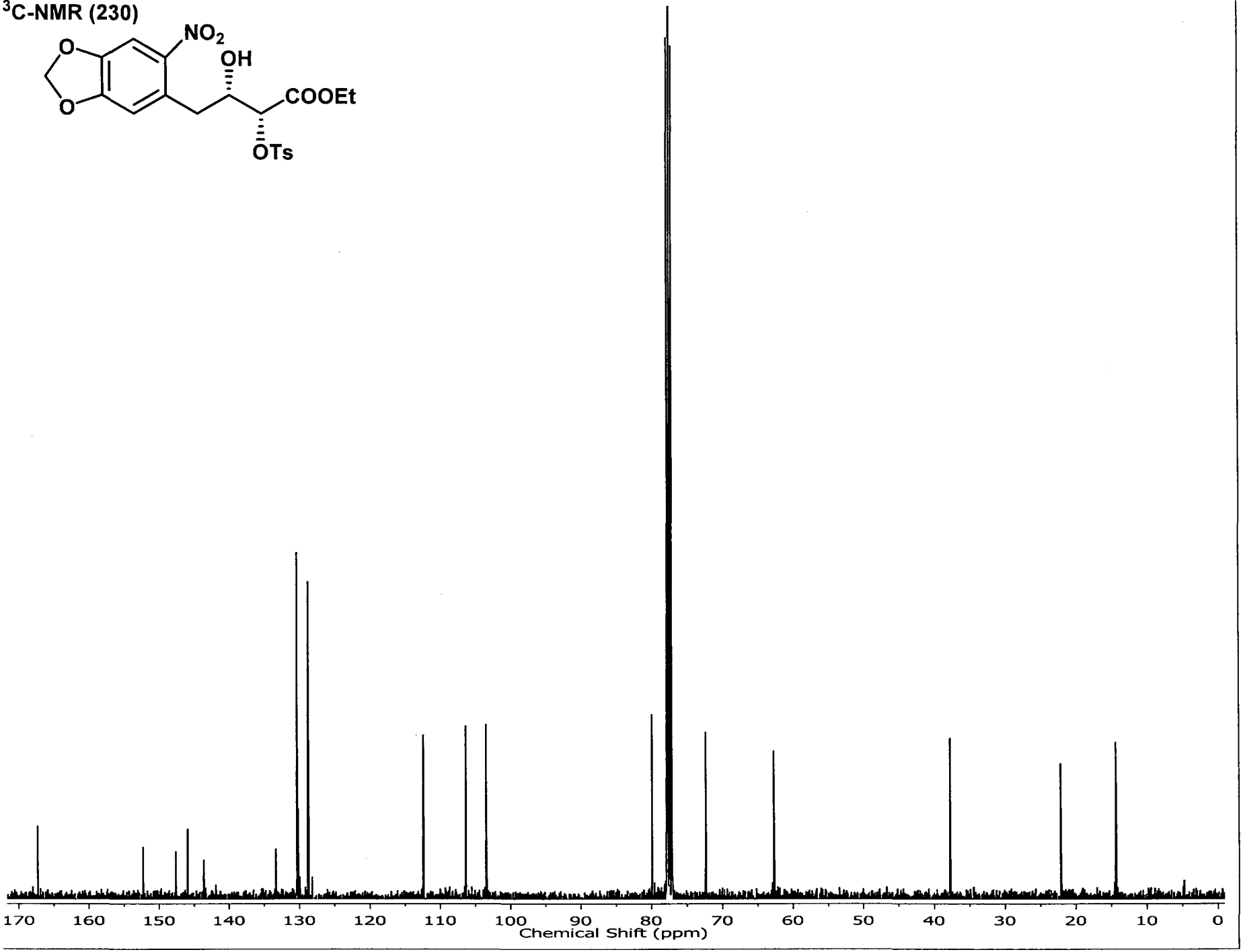
^{1}H-NMR (230)


NO2
OH
COOEt
OTs
O
O

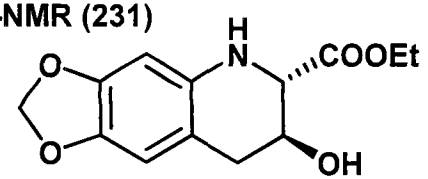

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

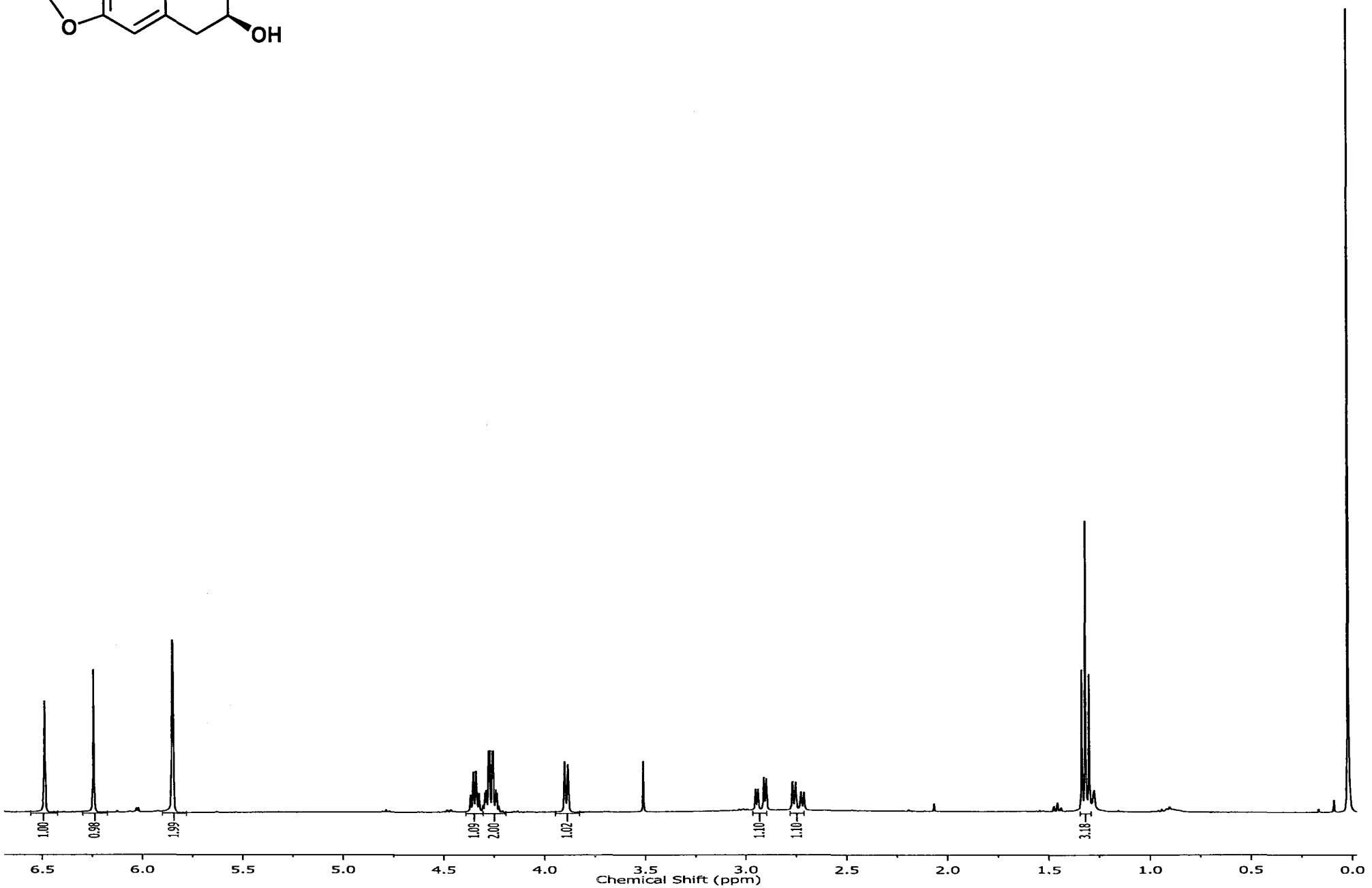
^{13}C-NMR (230)

NO2
OH
COOEt
OTs
O
O

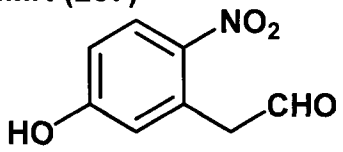

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

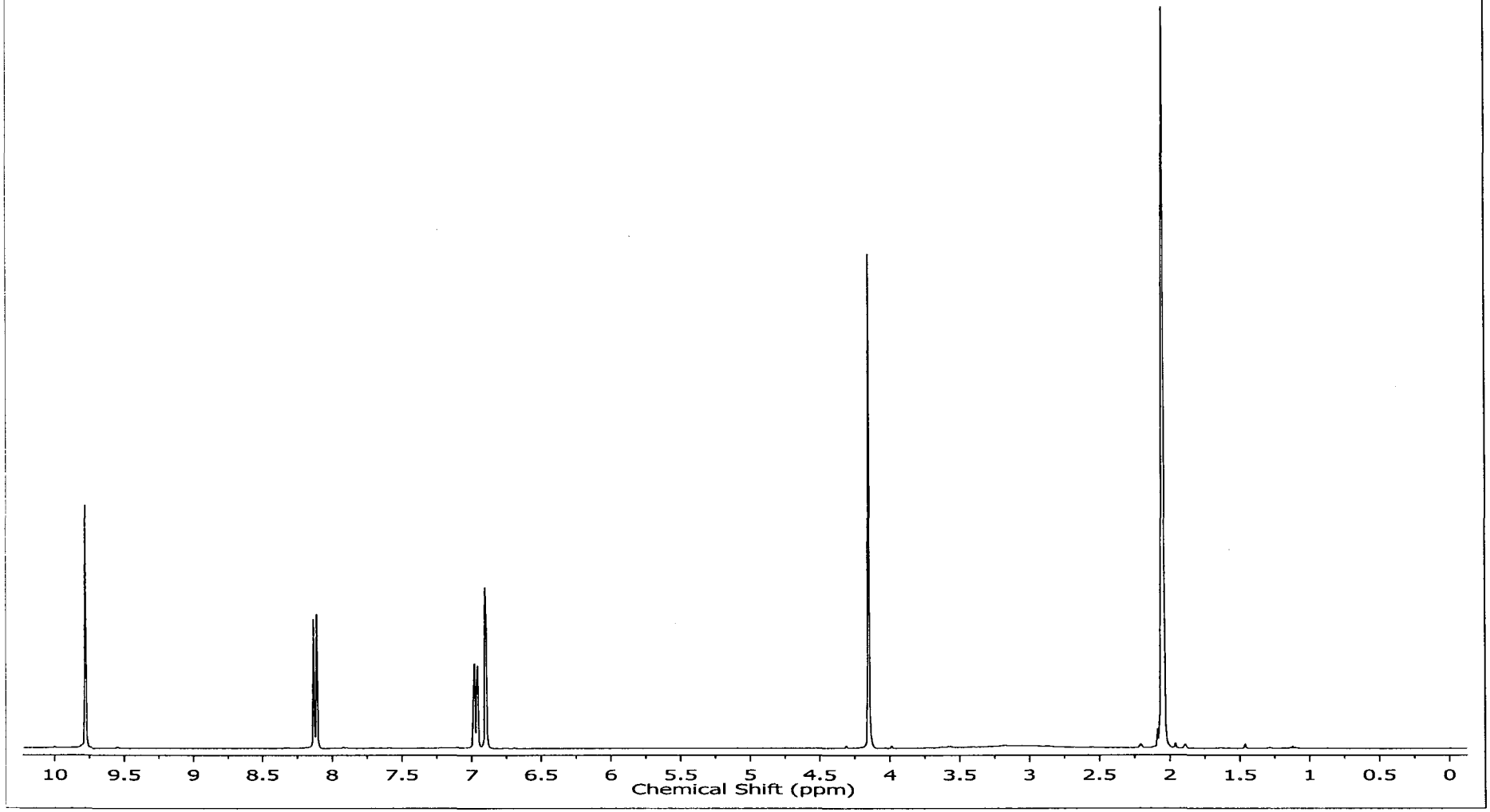
^{1}H-NMR (231)

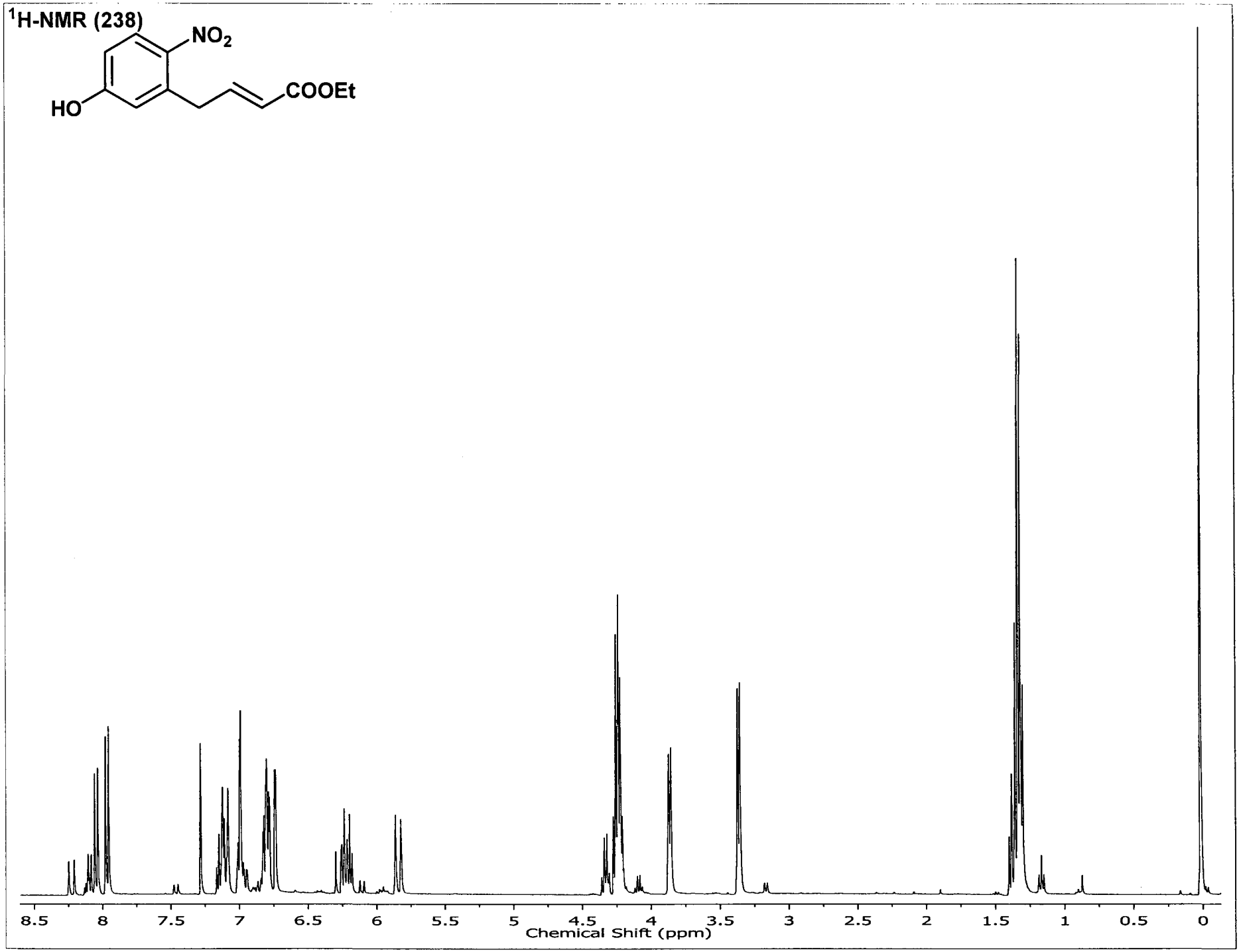

H
N
COOEt
O
O
OH


1.00
0.98
1.99
1.09
2.00
1.02
1.10
1.10
3.18
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

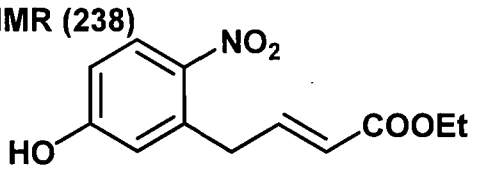
^{1}H-NMR (237)

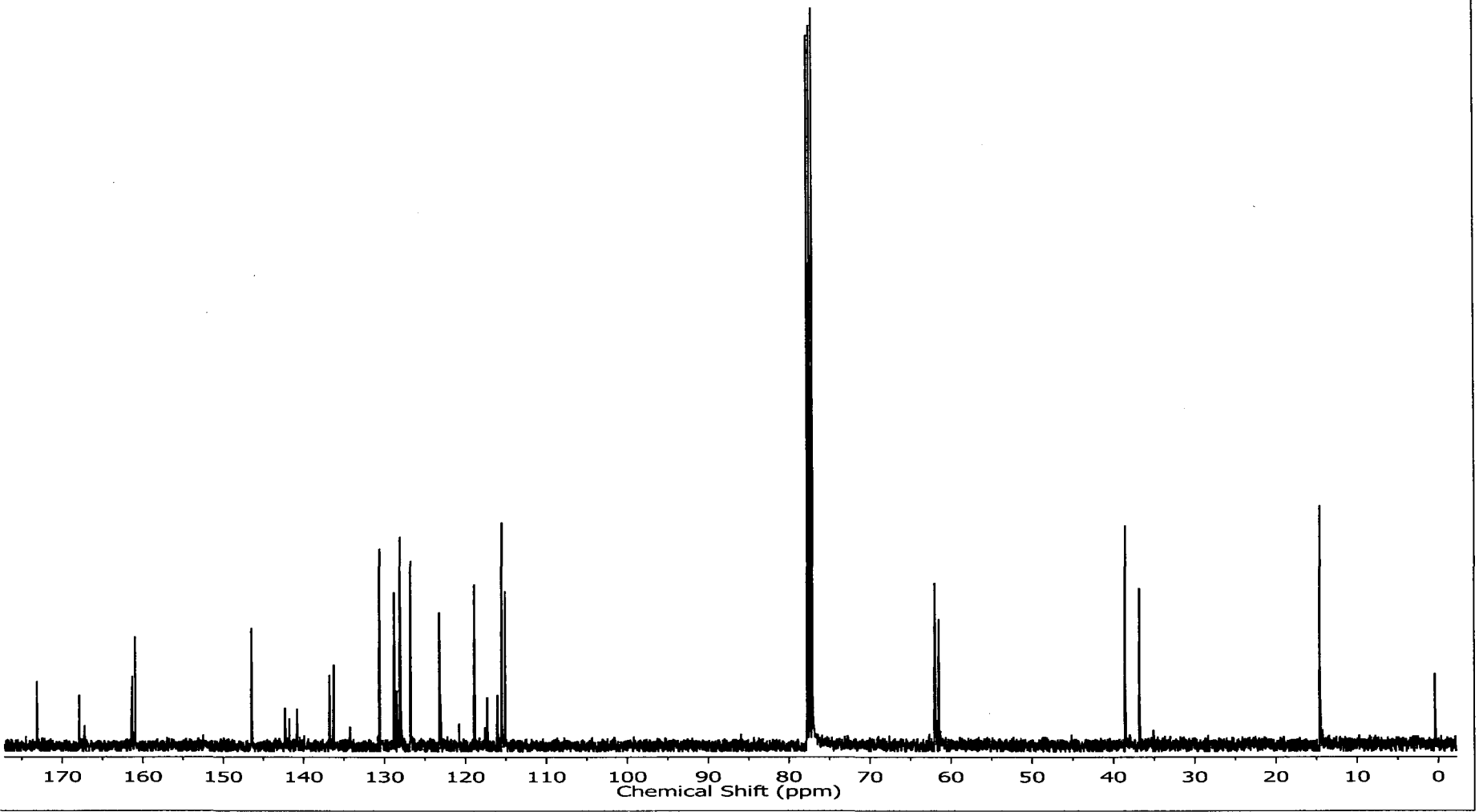

NO2
CHO
HO


10
9.5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

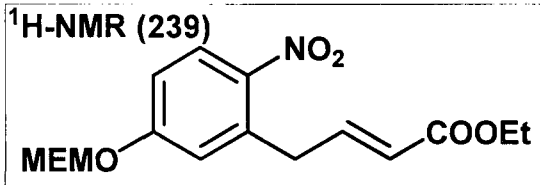

1H-NMR (238)
NO2
COOEt
HO
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

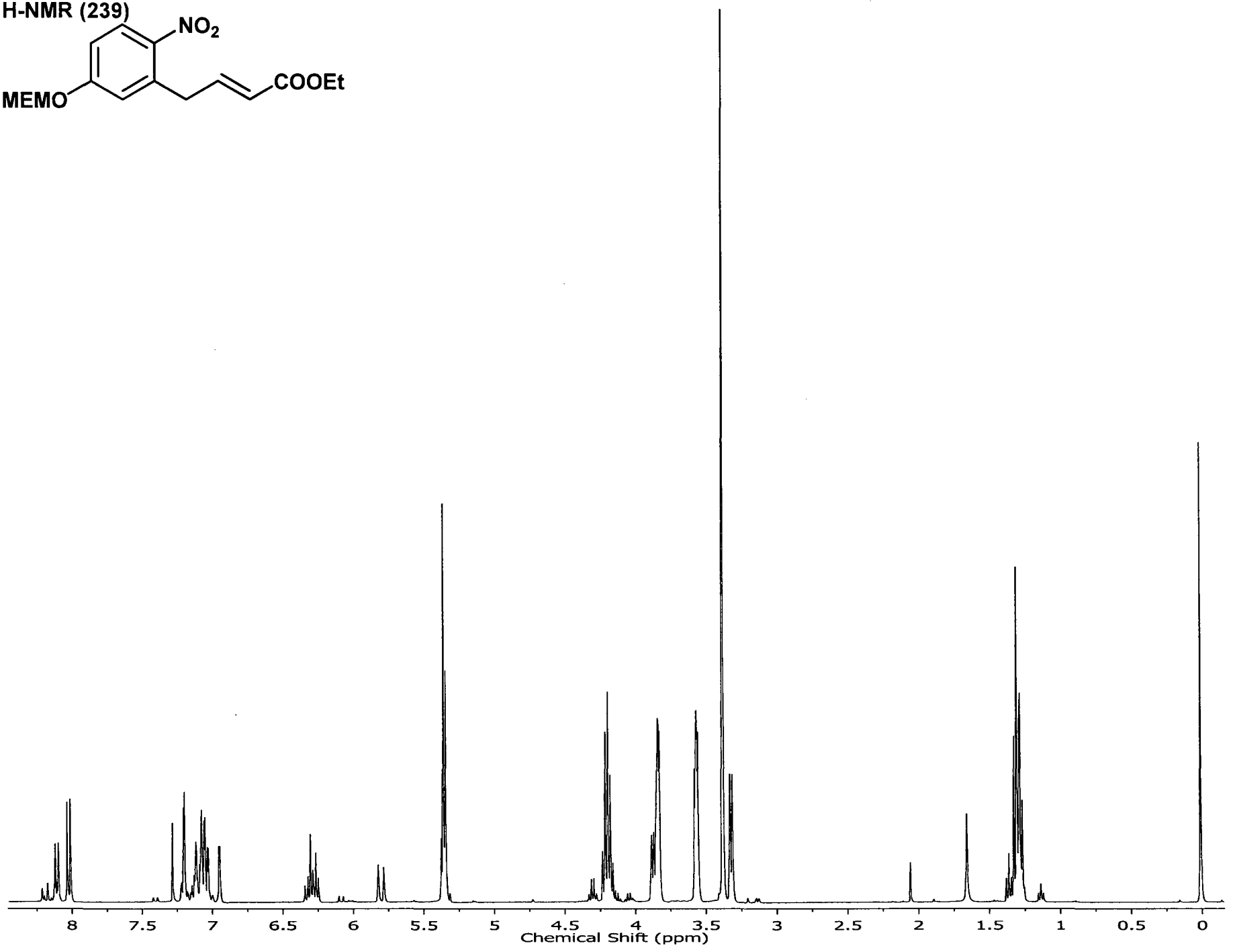
^{13}C-NMR (238)


NO2
COOEt
HO

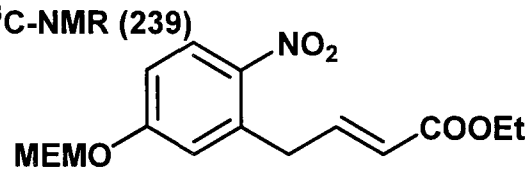

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

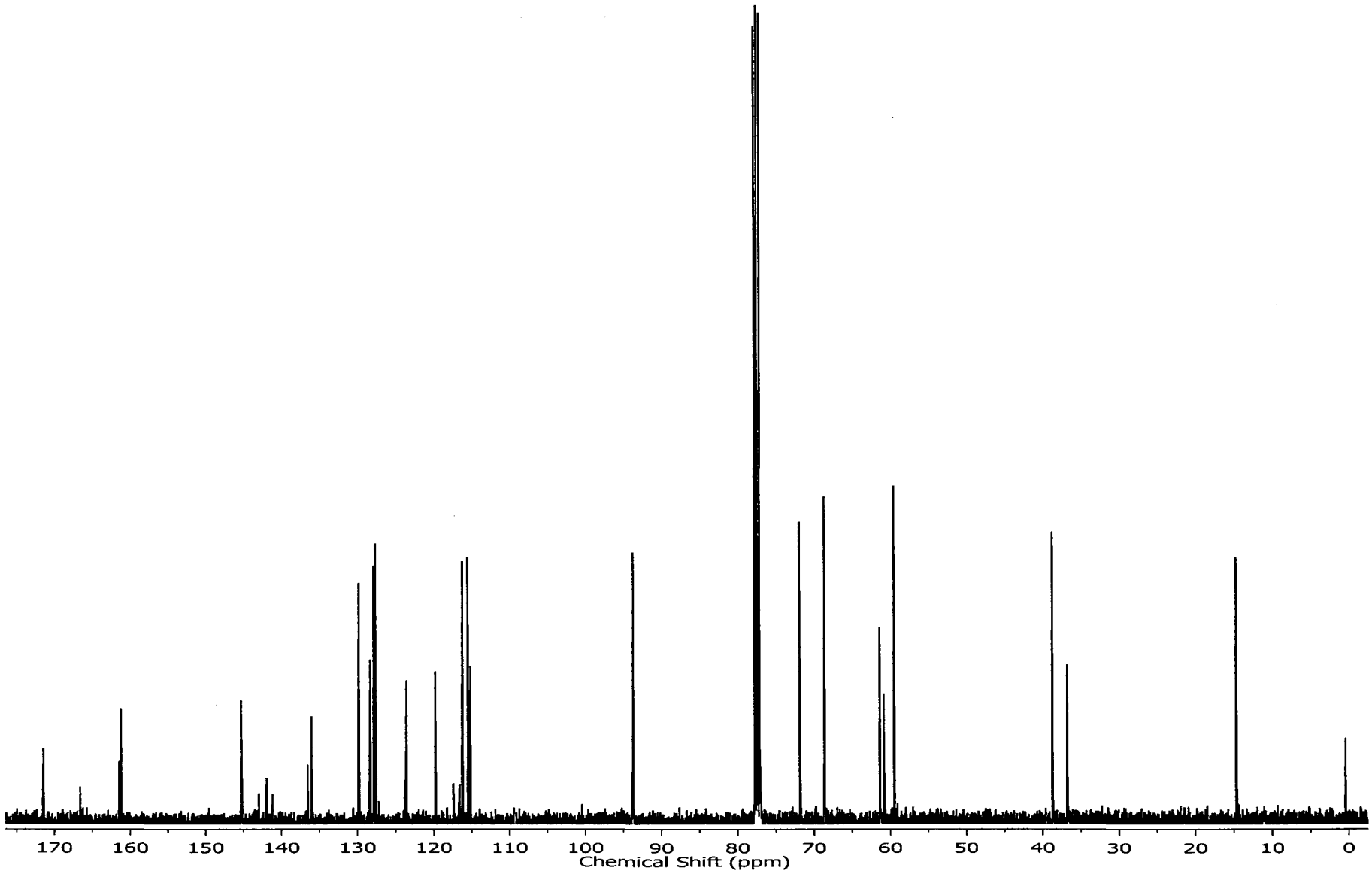
^{1}H-NMR (239)

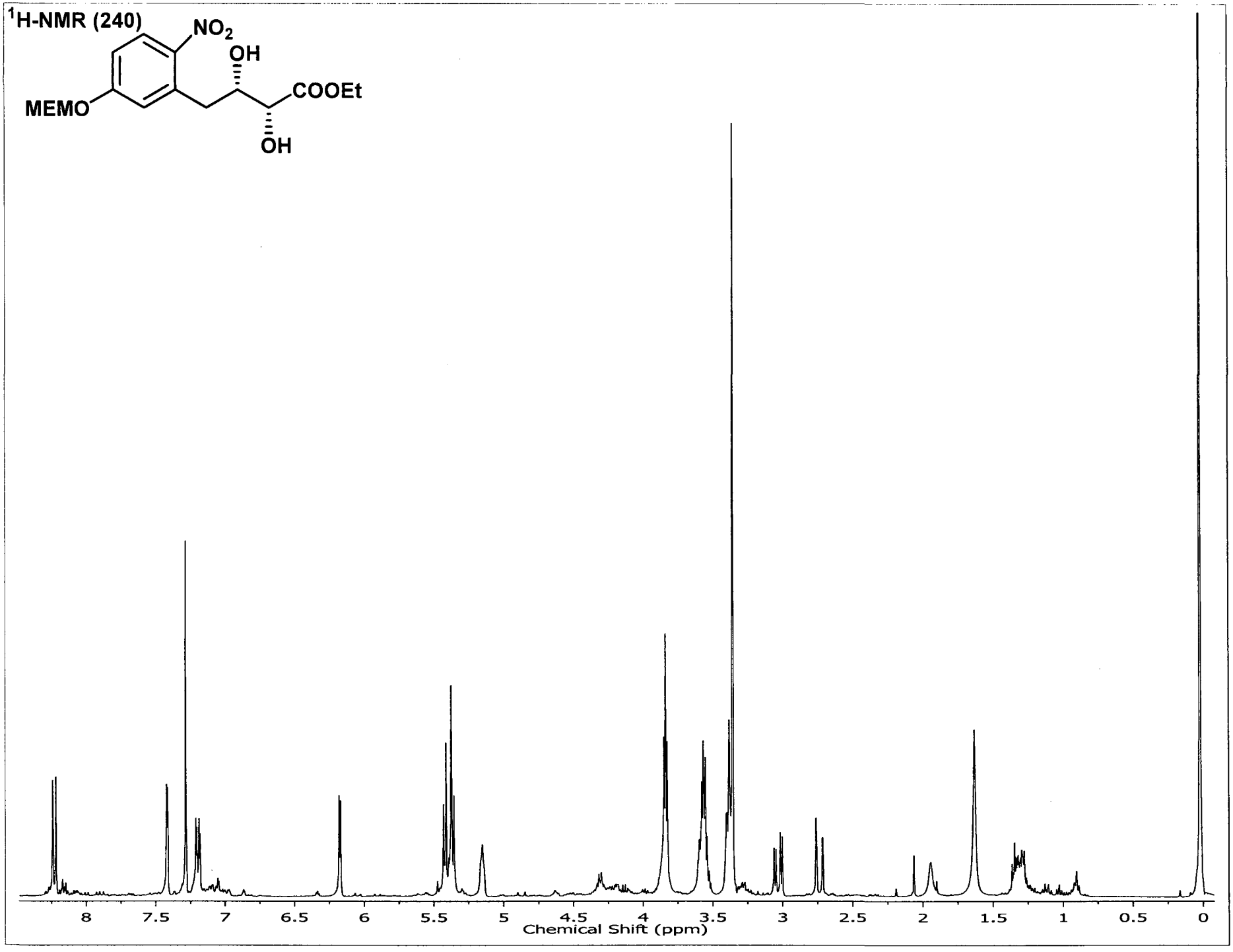

NO2
COOEt
MEMO

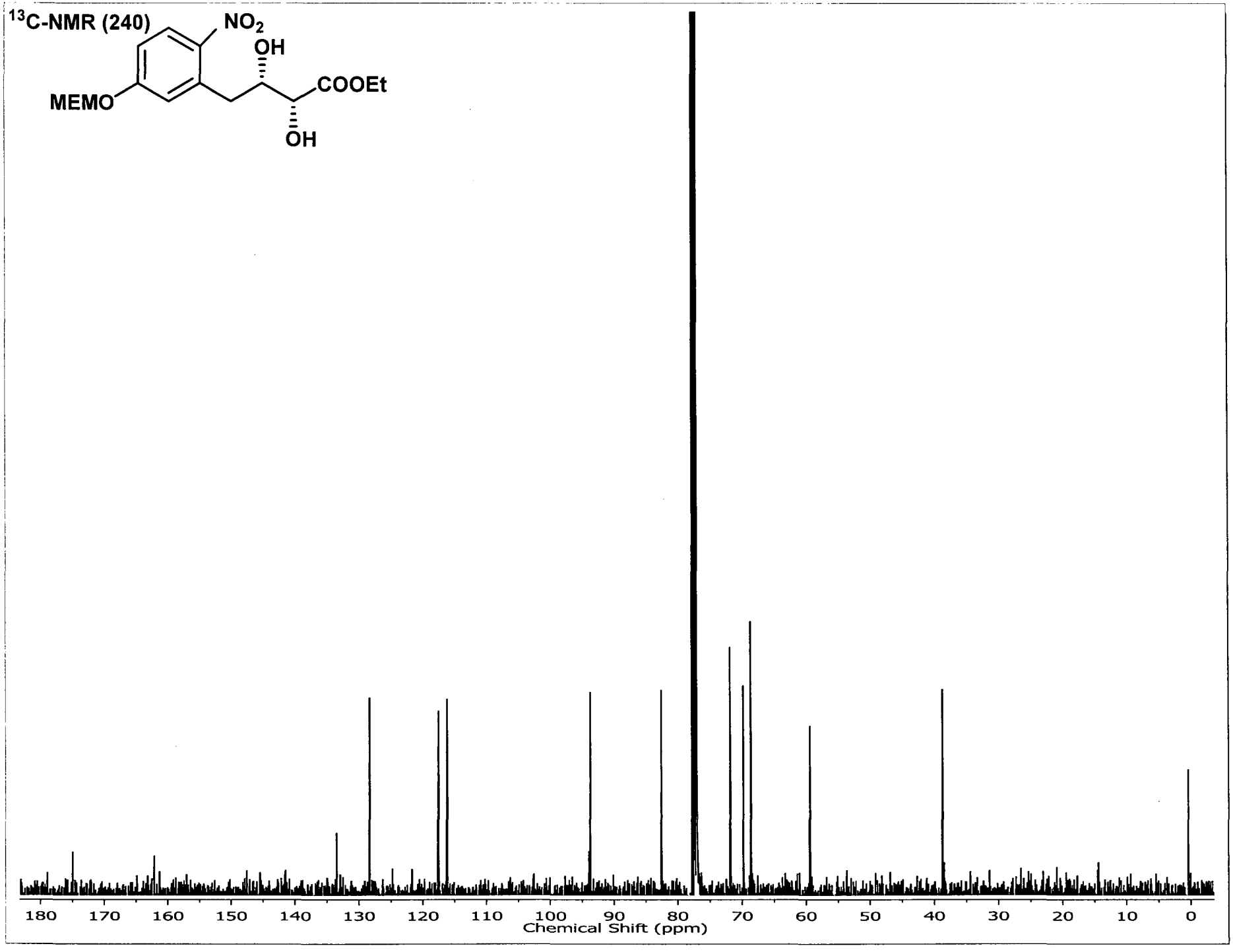

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

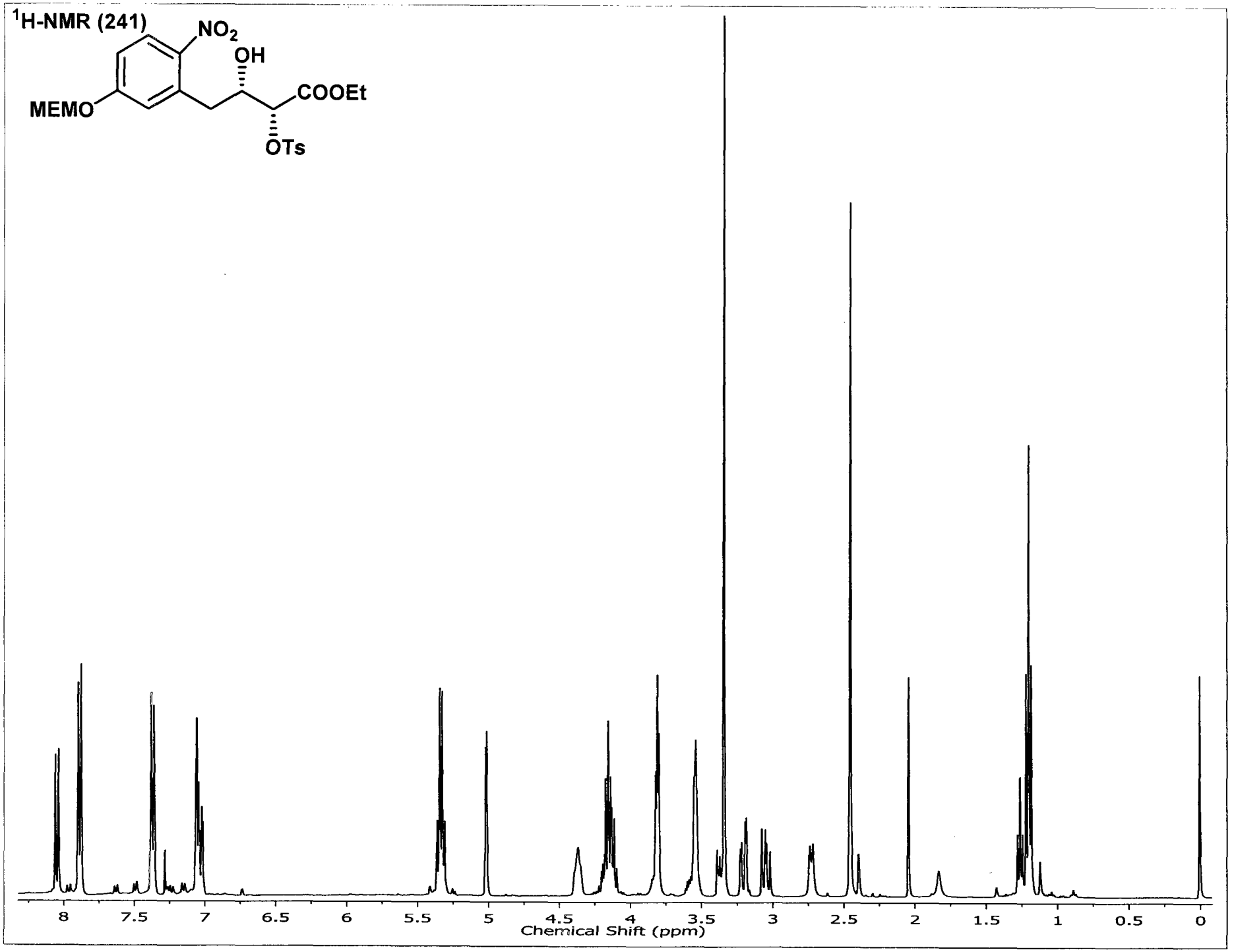
^{13}C-NMR (239)


NO2
COOEt
MEMO

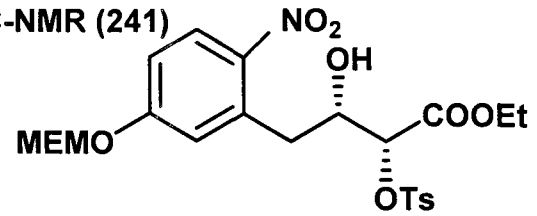

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

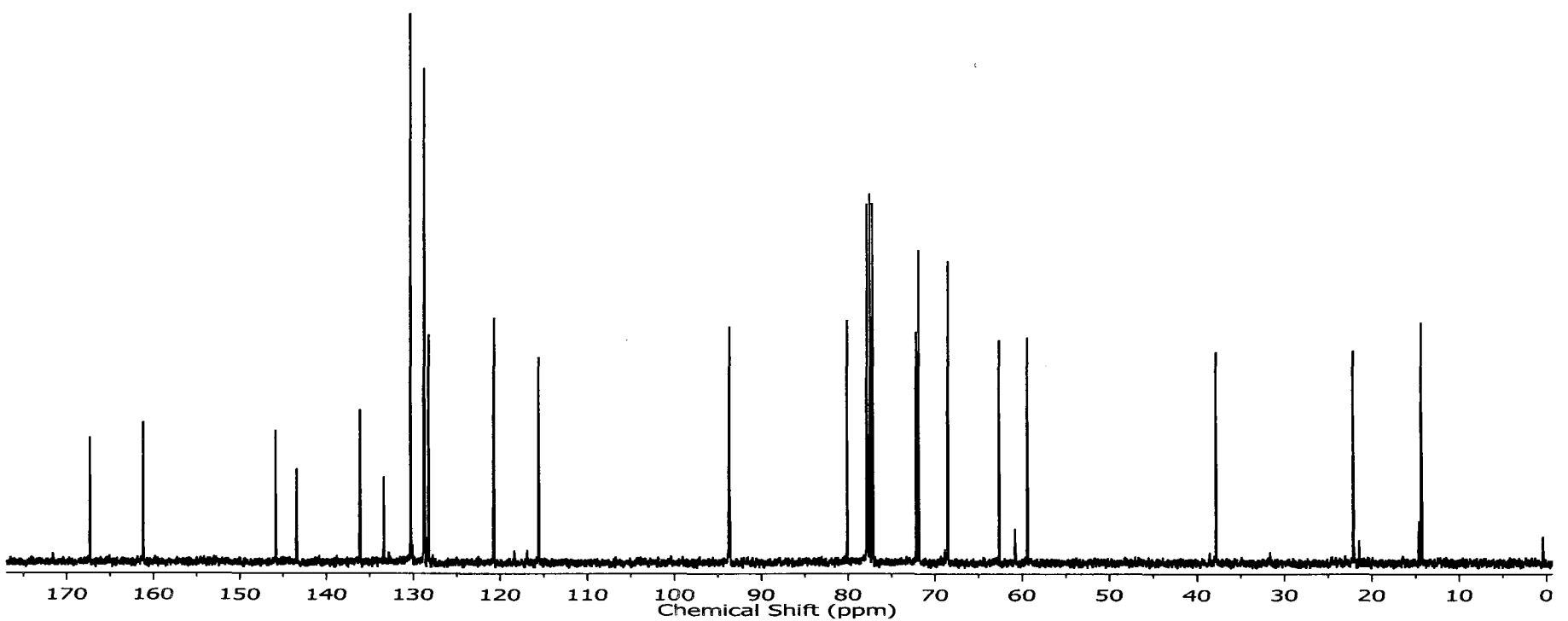

1H-NMR (240)
NO2
OH
COOEt
MEMO
OH
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)


13C-NMR (240)
NO2
OH
COOEt
MEMO
OH
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

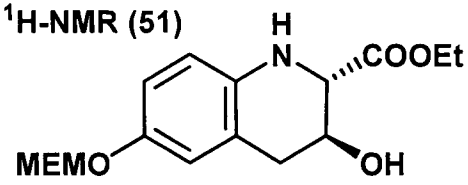

1H-NMR (241)
NO2
OH
COOEt
MEMO
OTs
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

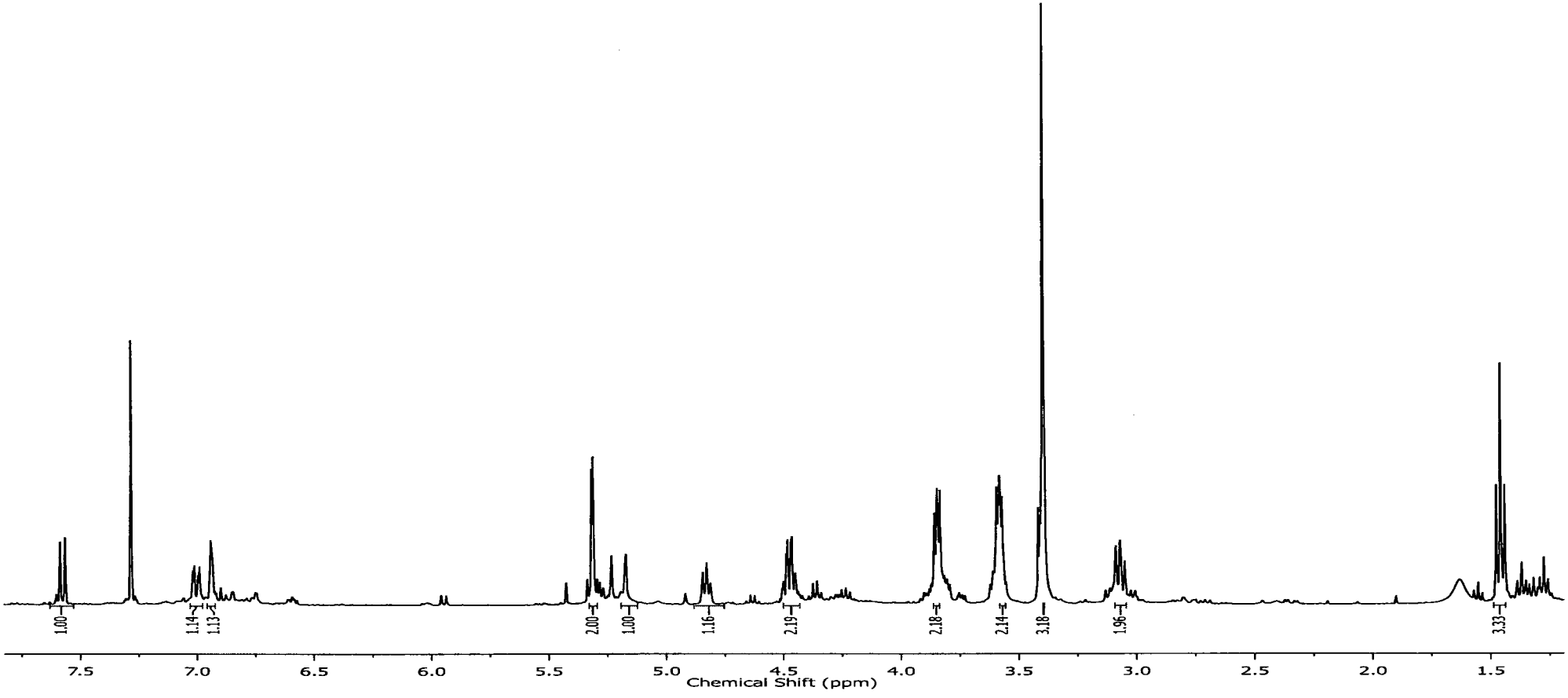
^{13}C-NMR (241)


NO2
OH
COOEt
MEMO
OTs


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

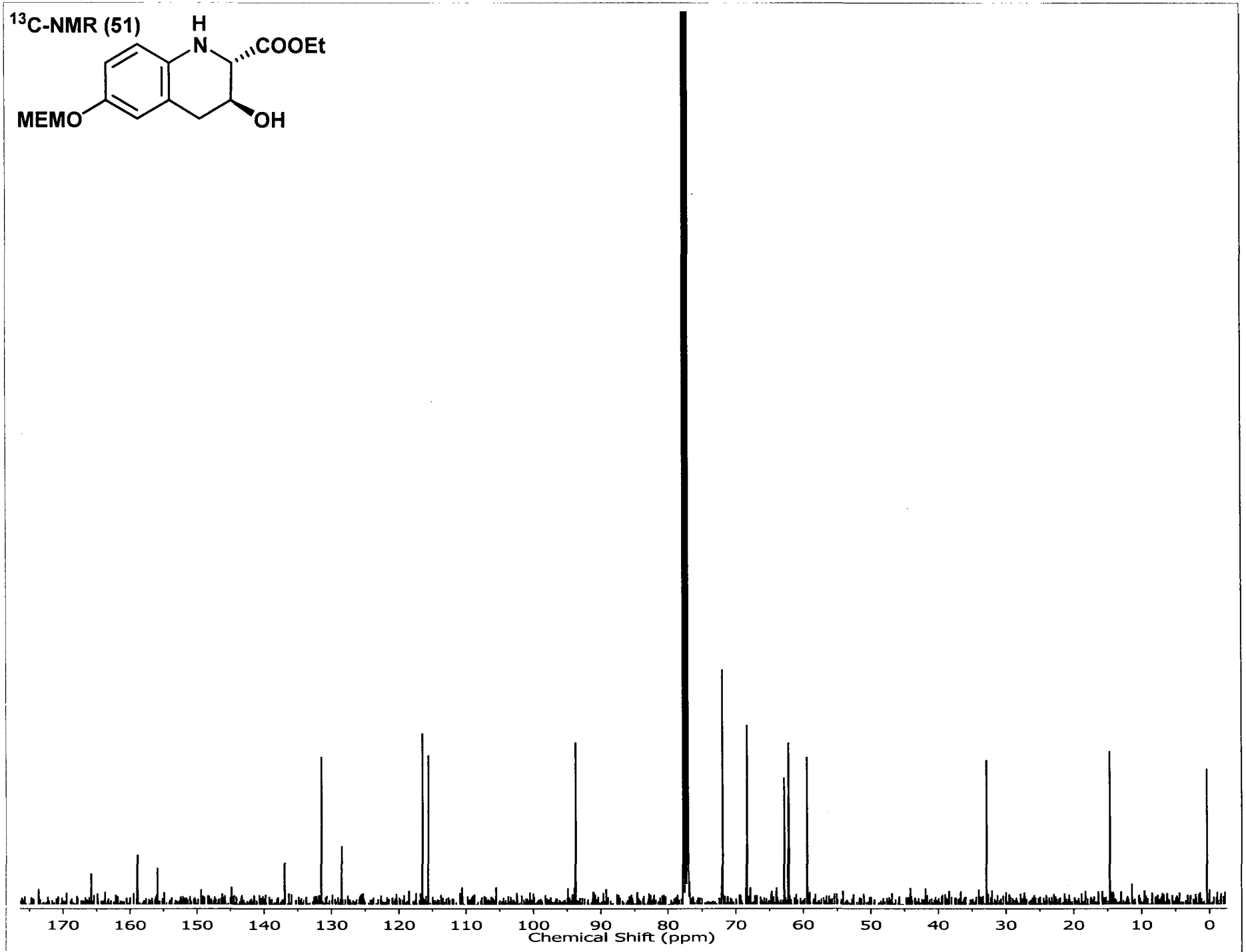
^{1}H-NMR (51)

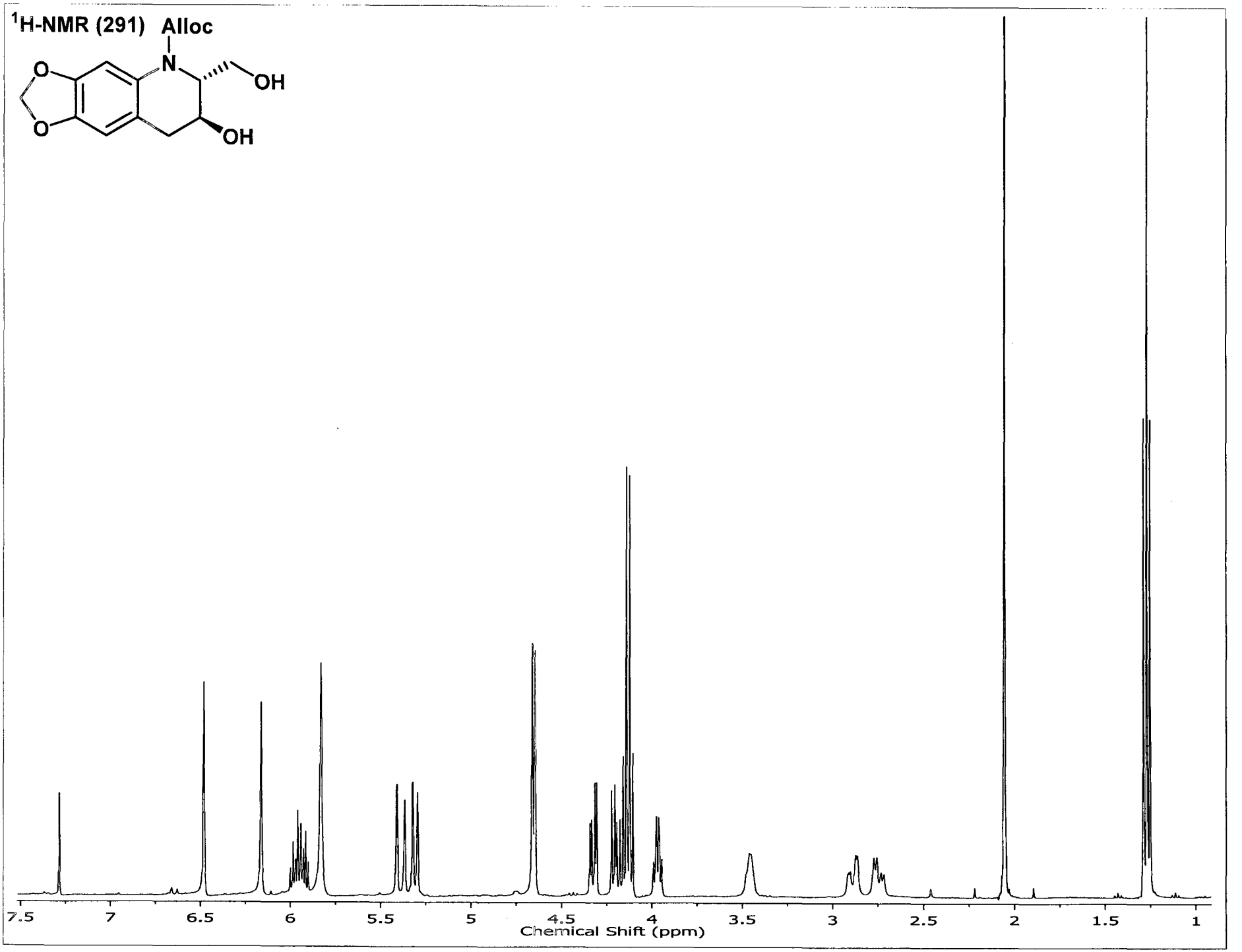

H
N
COOEt
MEMO
OH


1.00
1.14
1.13
2.00
1.00
1.16
2.19
2.18
2.14
3.18
1.96
3.33
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

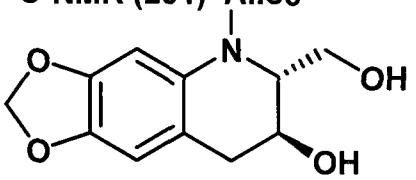
^{13}C-NMR (51)

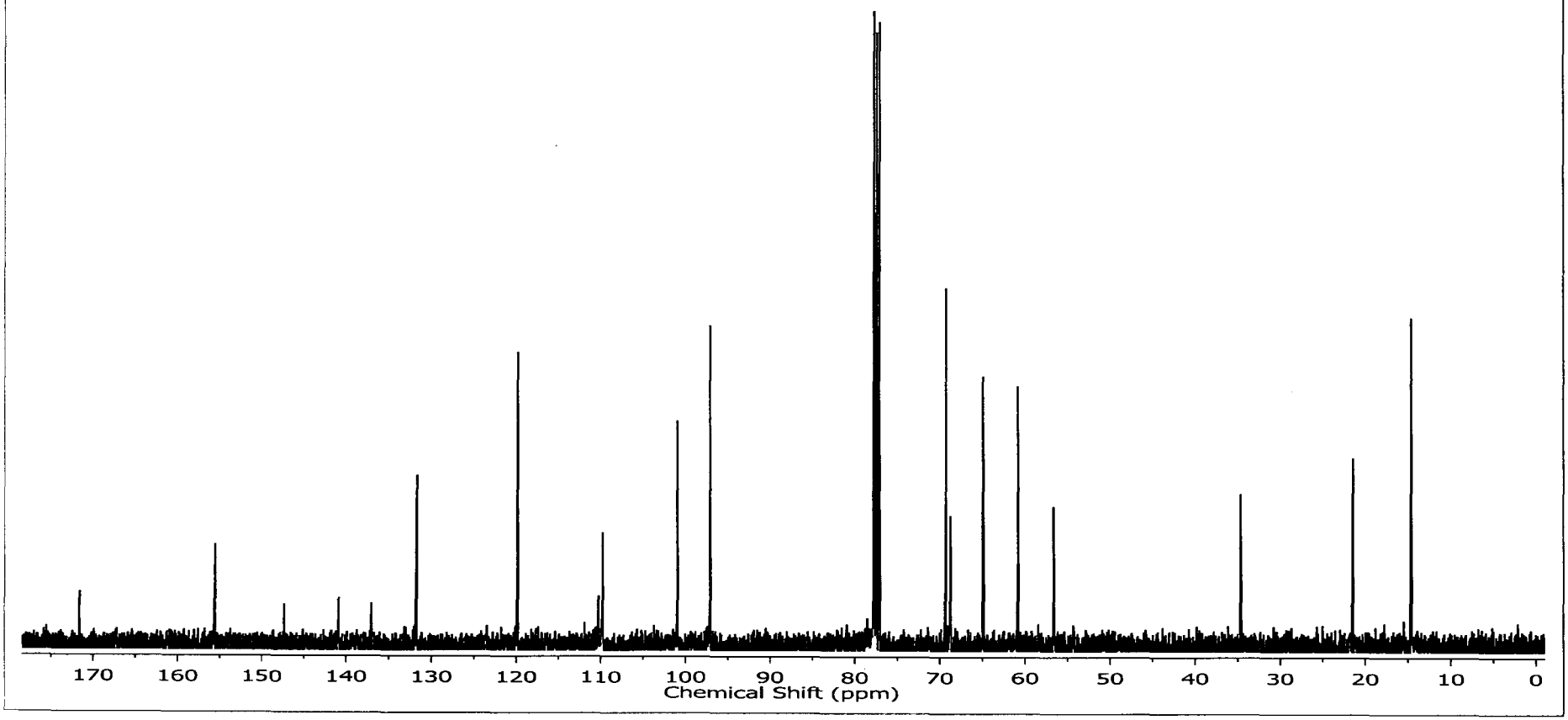
H
N
COOEt
MEMO
OH


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


1H-NMR (291)
Alloc
N
O
O
OH
OH
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
Chemical Shift (ppm)

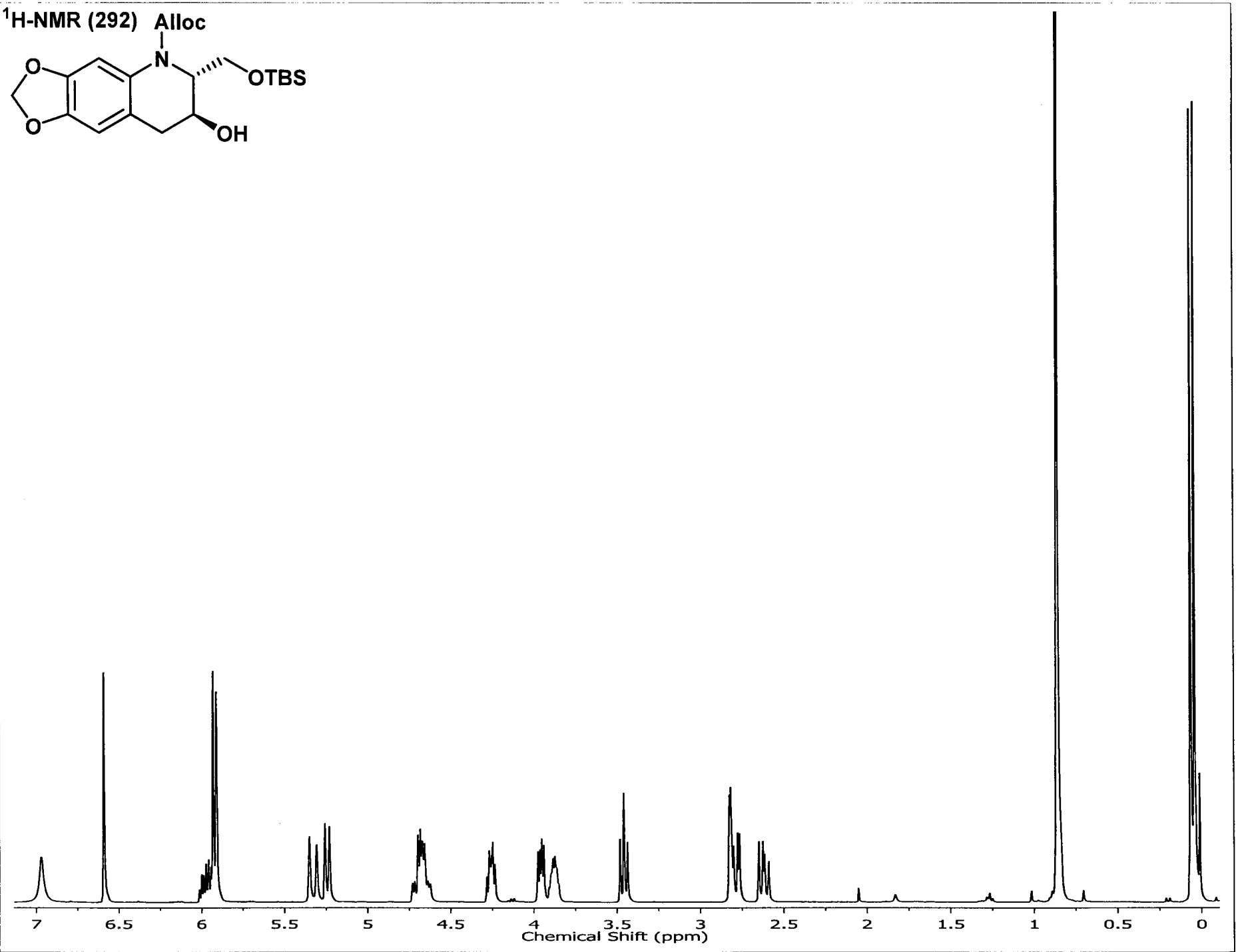
^{13}C-NMR (291)


Alloc
N
O
O
OH
OH


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

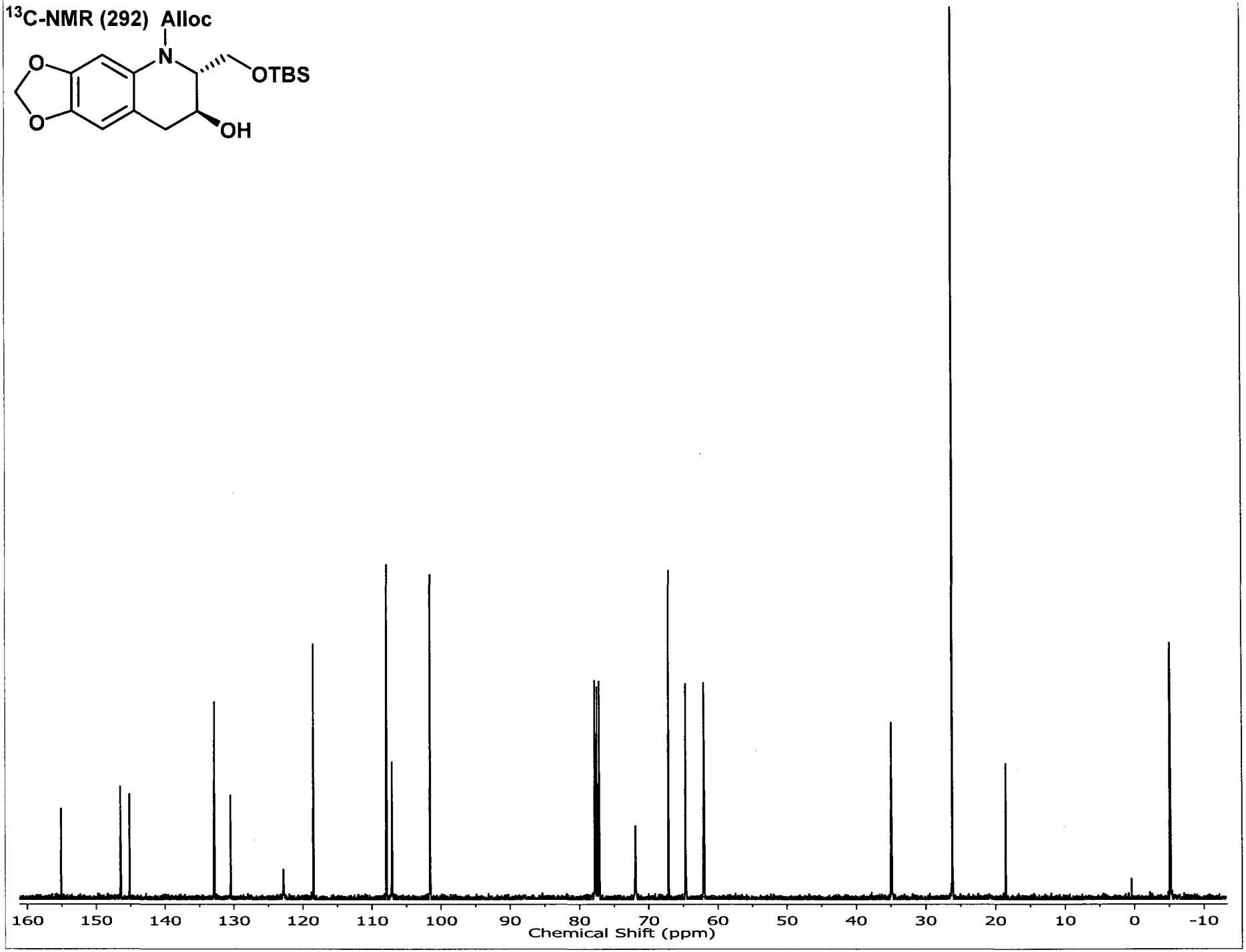
^{1}H-NMR (292)

Alloc
N
OTBS
O
O
OH


7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

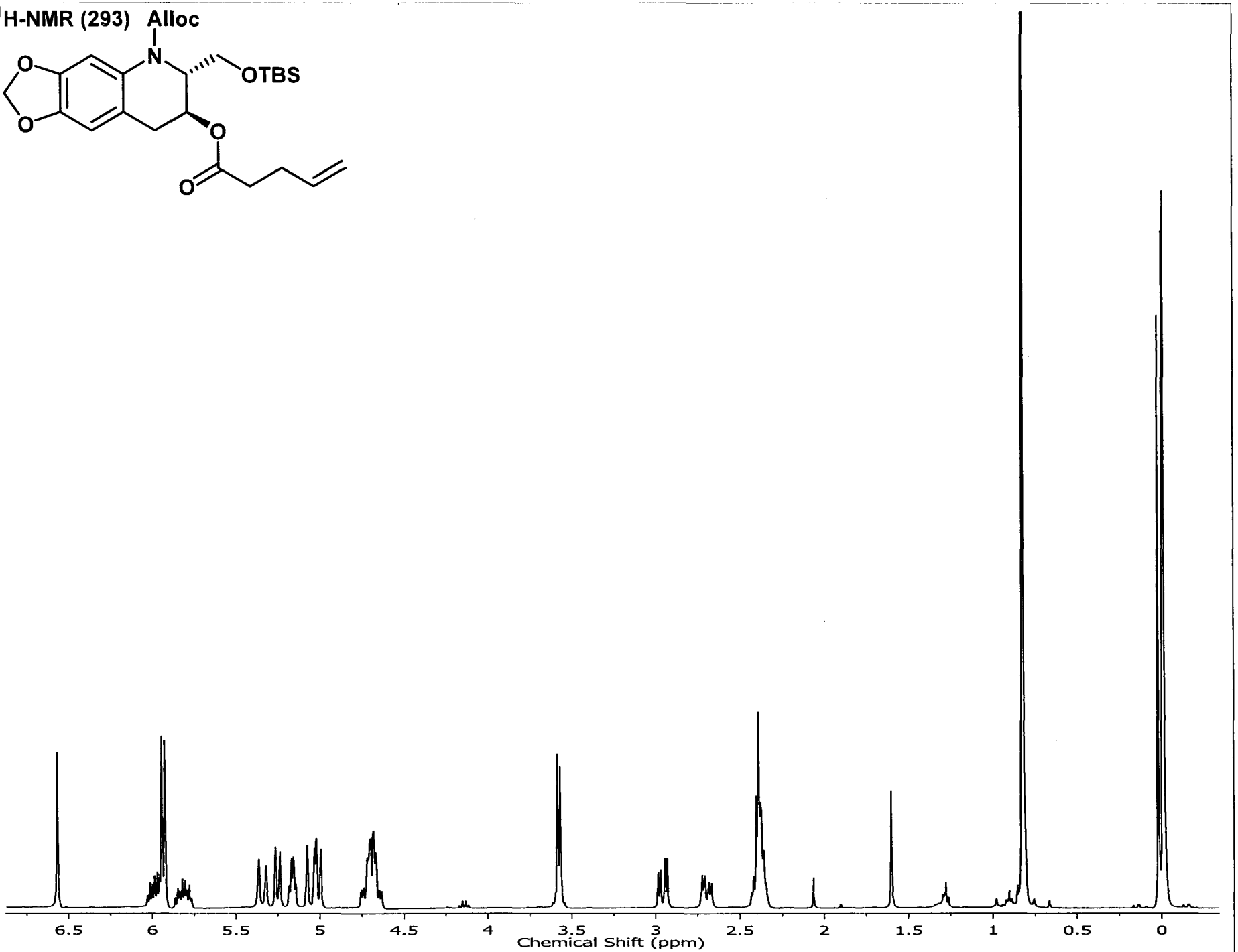
^{13}C-NMR (292)

Alloc
N
OTBS
O
O
OH

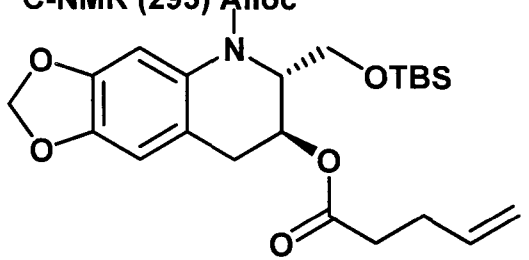

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

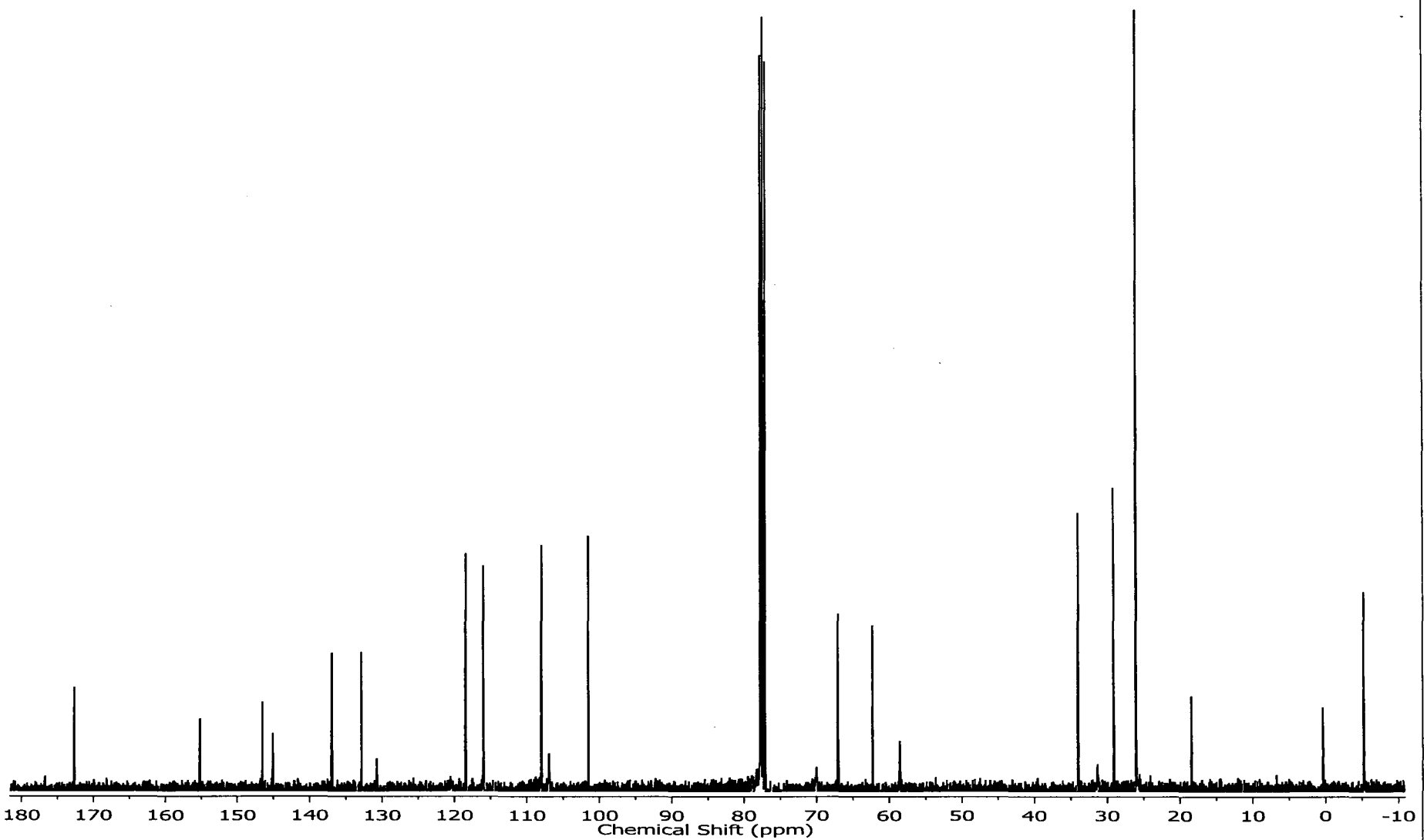
^{1}H-NMR (293)

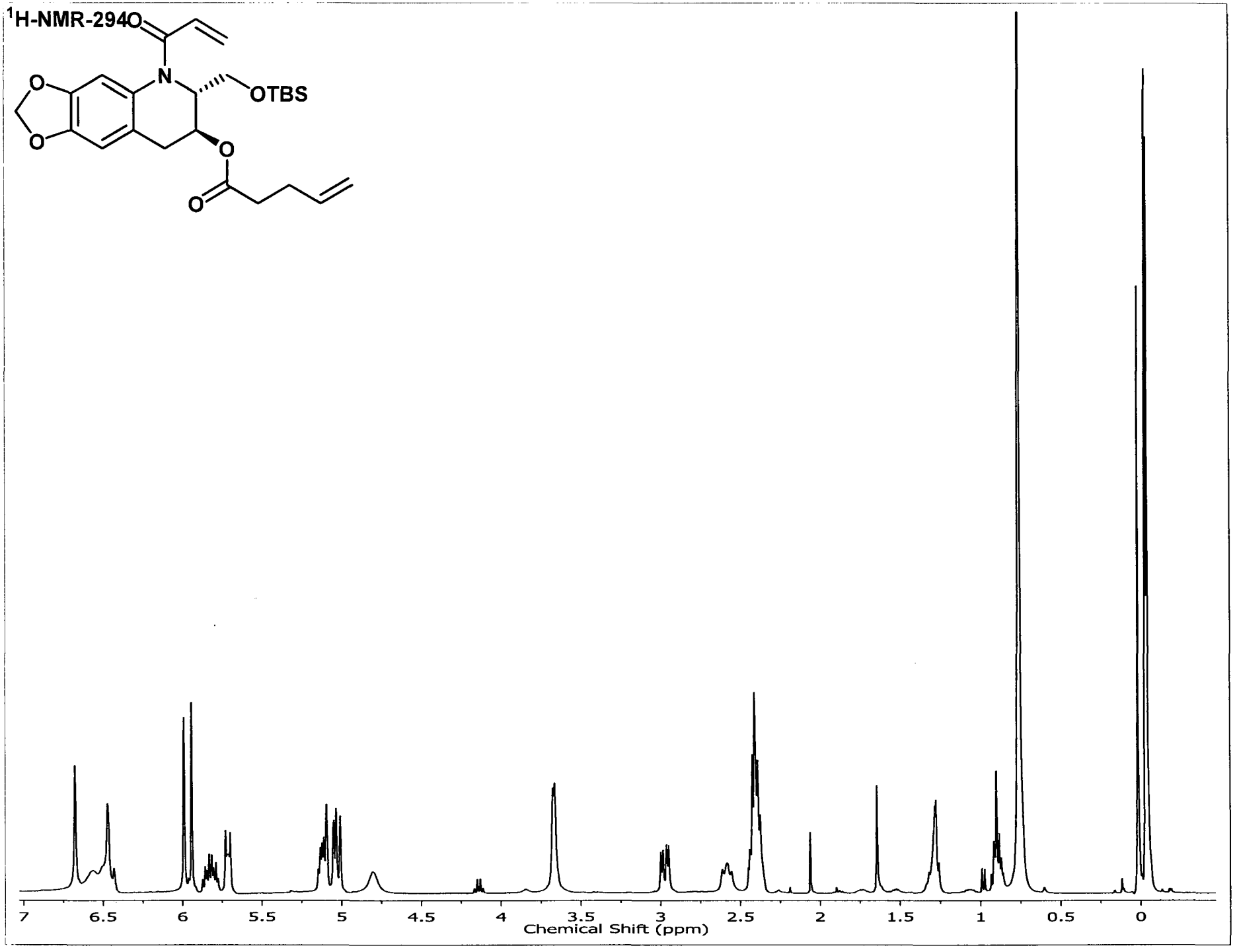
Alloc
N
OTBS
O
O
O
O


6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

^{13}C-NMR (293) Alloc

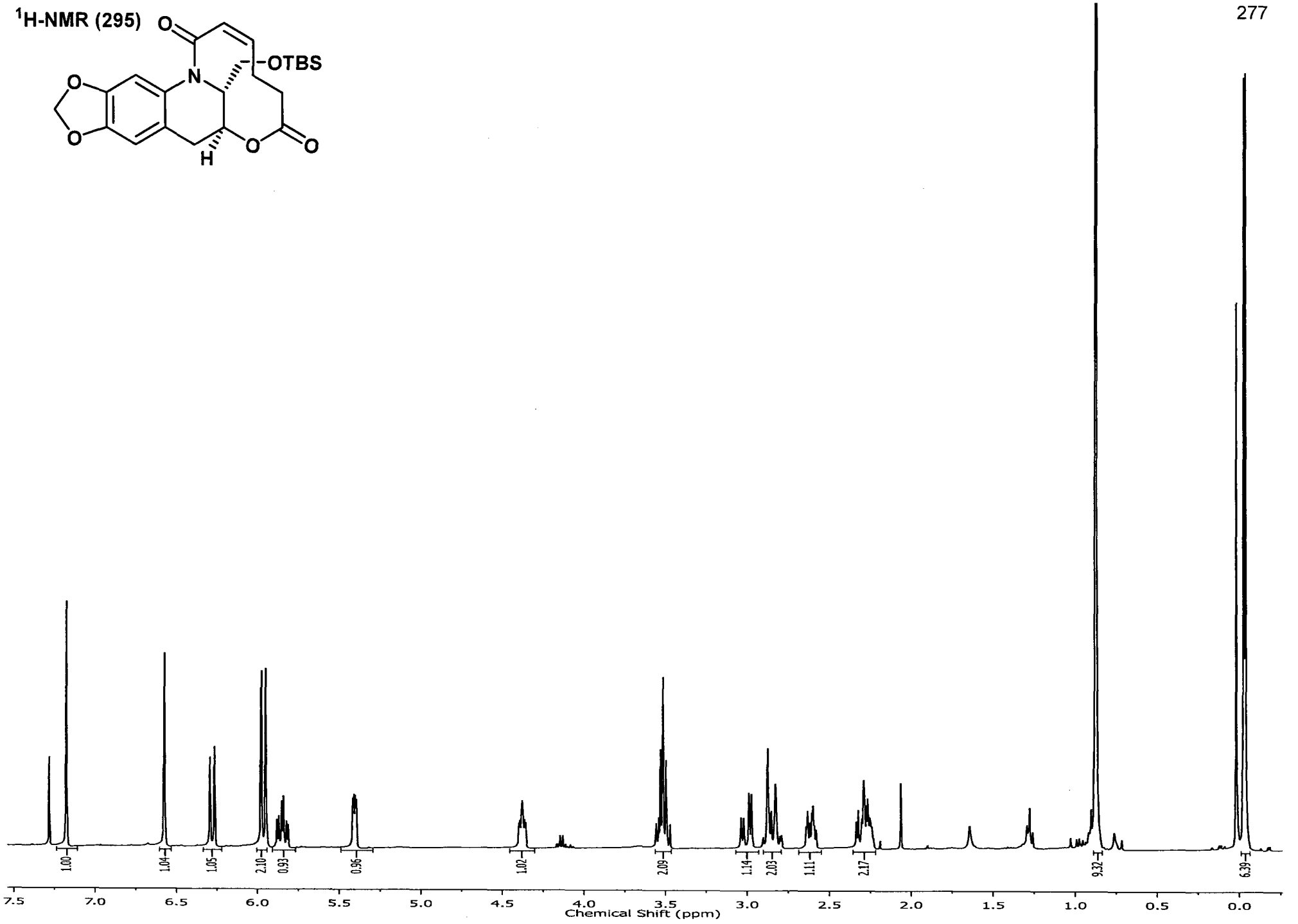


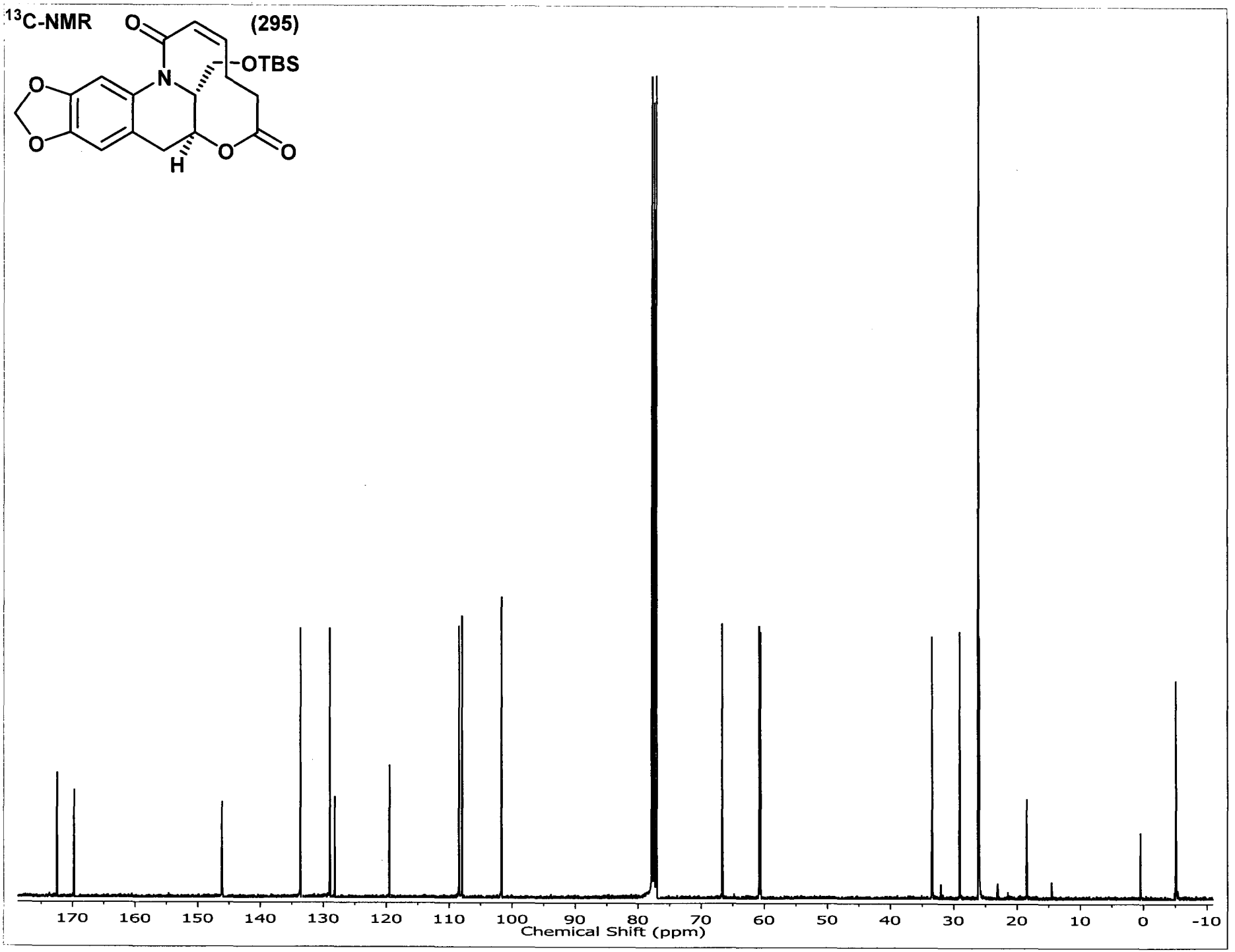


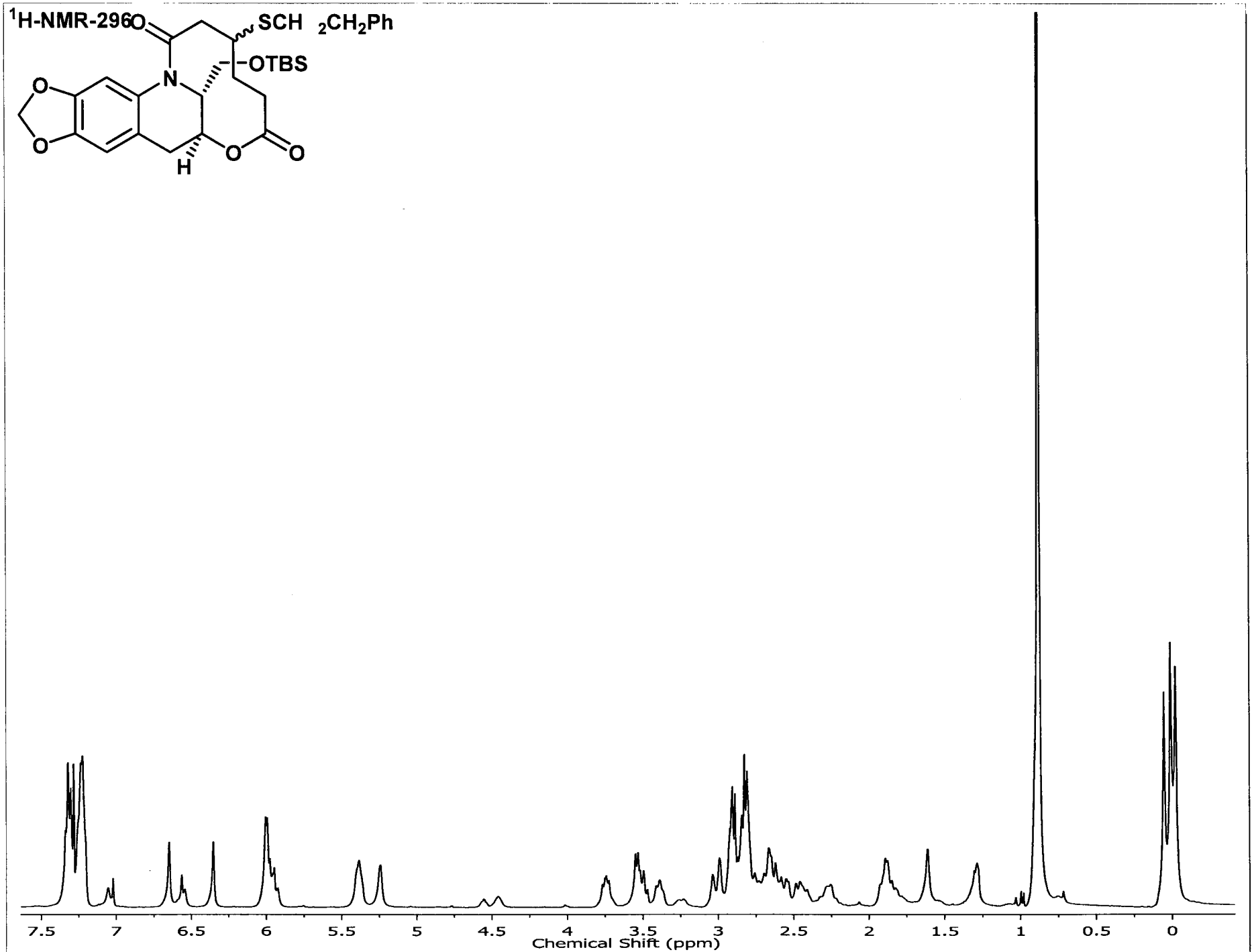

1H-NMR-294O
N
OTBS
O
O
O
O
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

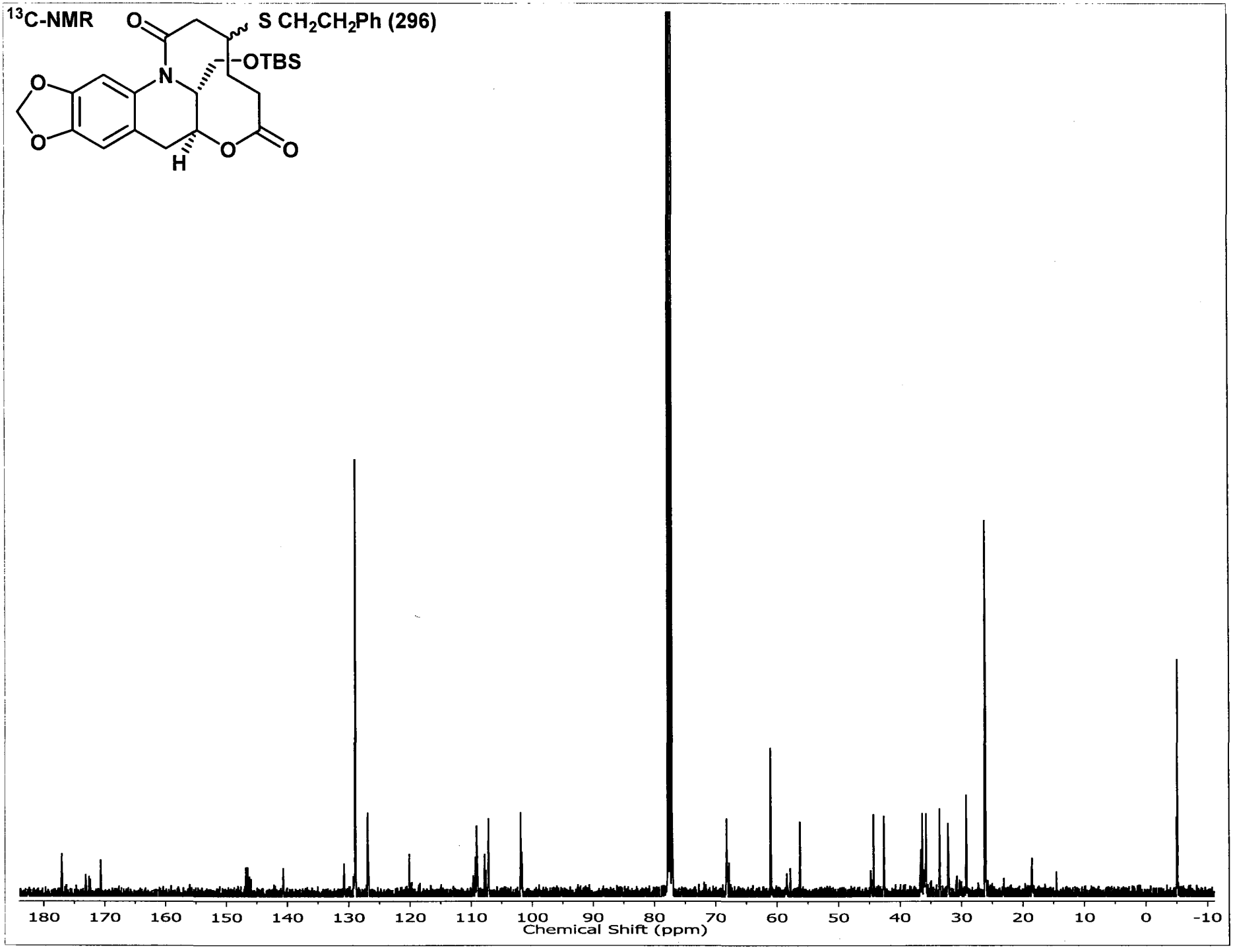
^{1}H-NMR (295)

O
N
OTBS
O
O
H
O
O

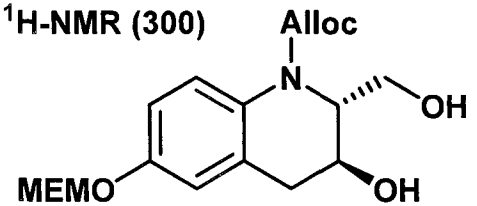

1.00
1.04
1.05
2.10
0.93
0.96
1.02
2.09
1.14
2.03
1.11
2.17
9.32
6.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)

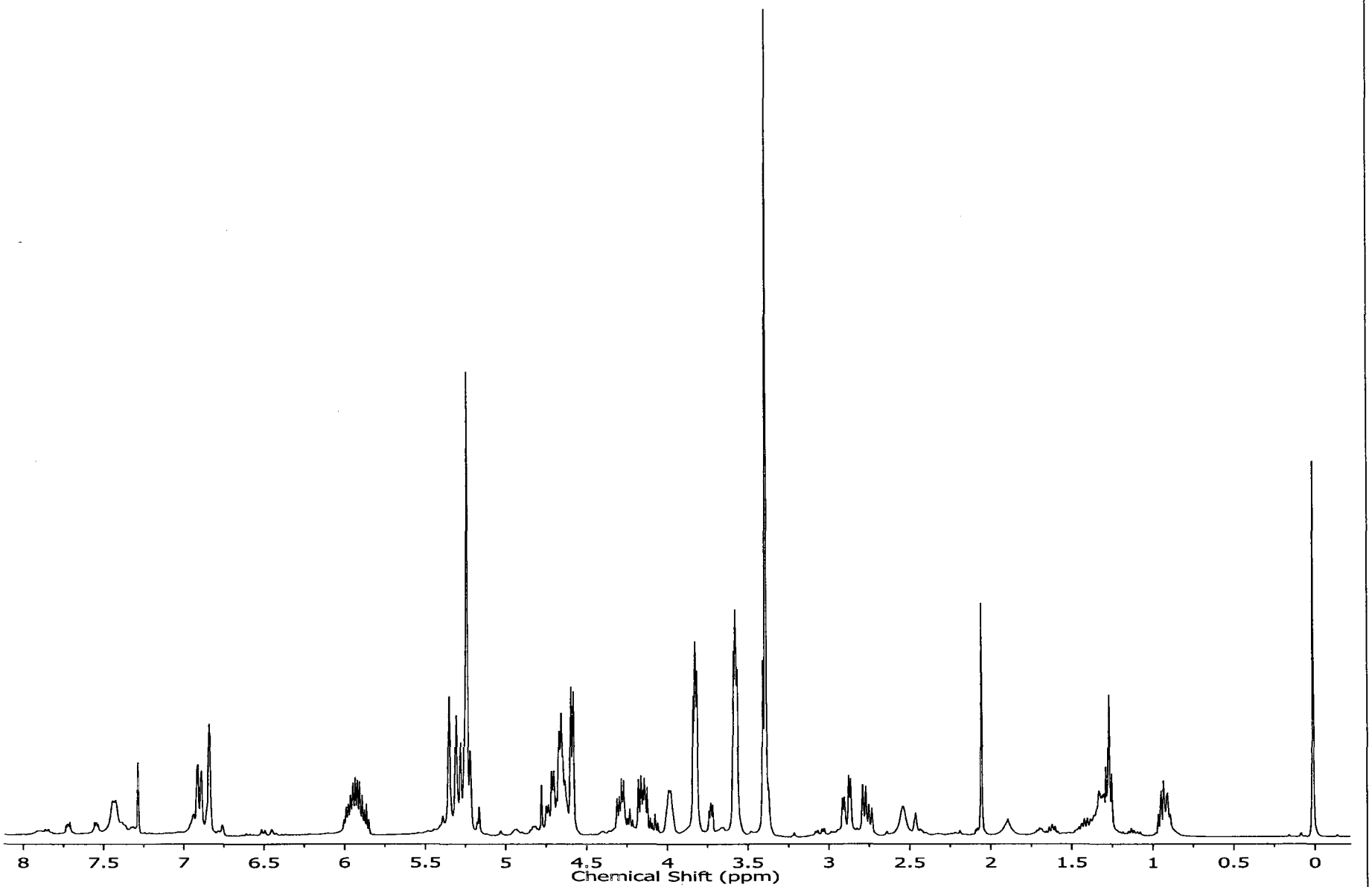

13C-NMR
(295)
OTBS
Chemical Shift (ppm)

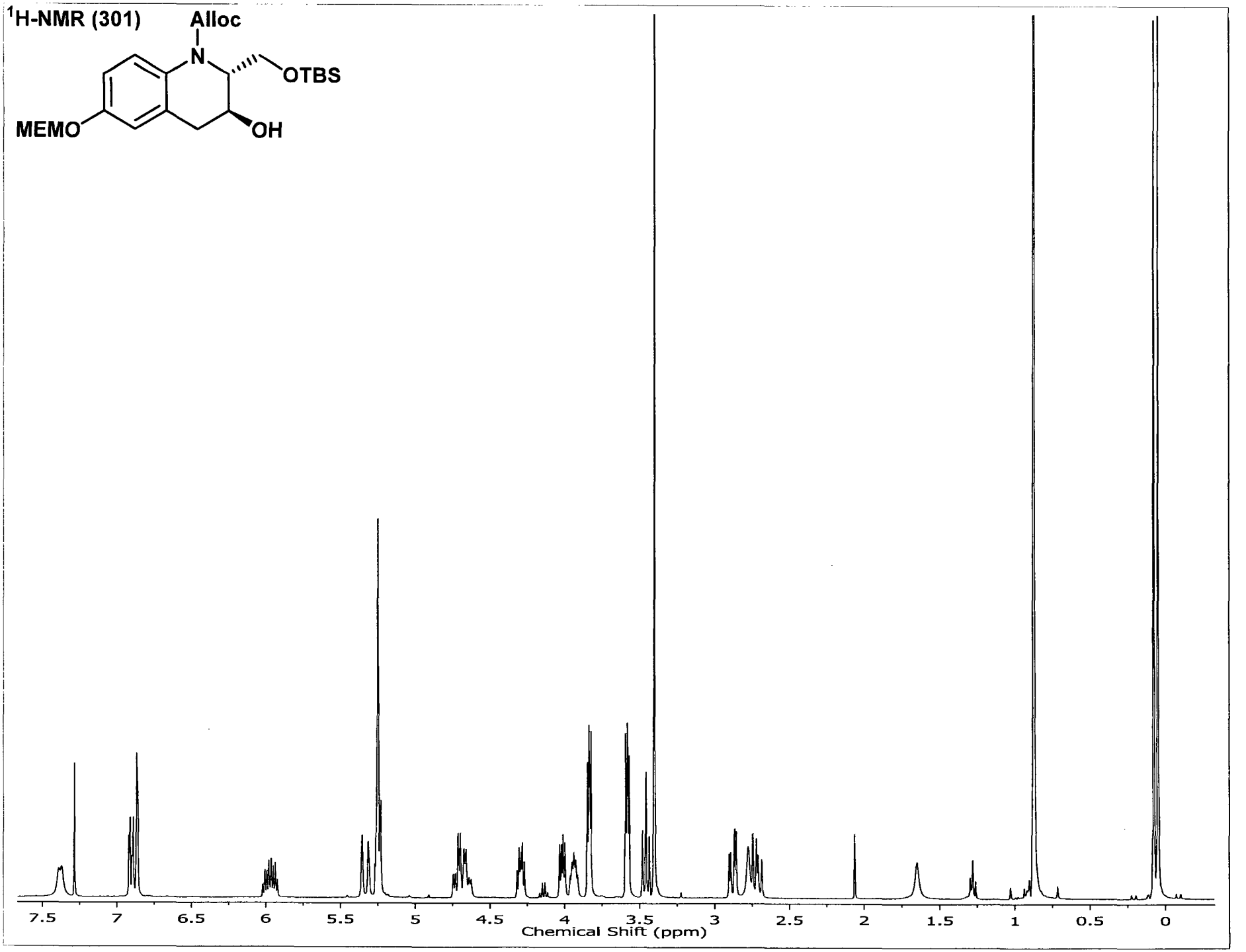

1H-NMR-296
SCH 2CH2Ph
OTBS
N
O
O
O
O
H
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)


13C-NMR
S CH2CH2Ph (296)
OTBS
Chemical Shift (ppm)

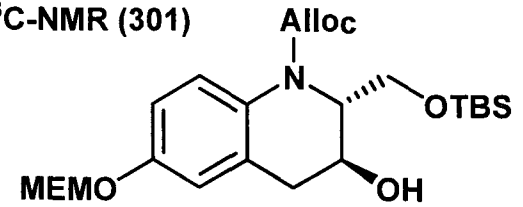
^{1}H-NMR (300)

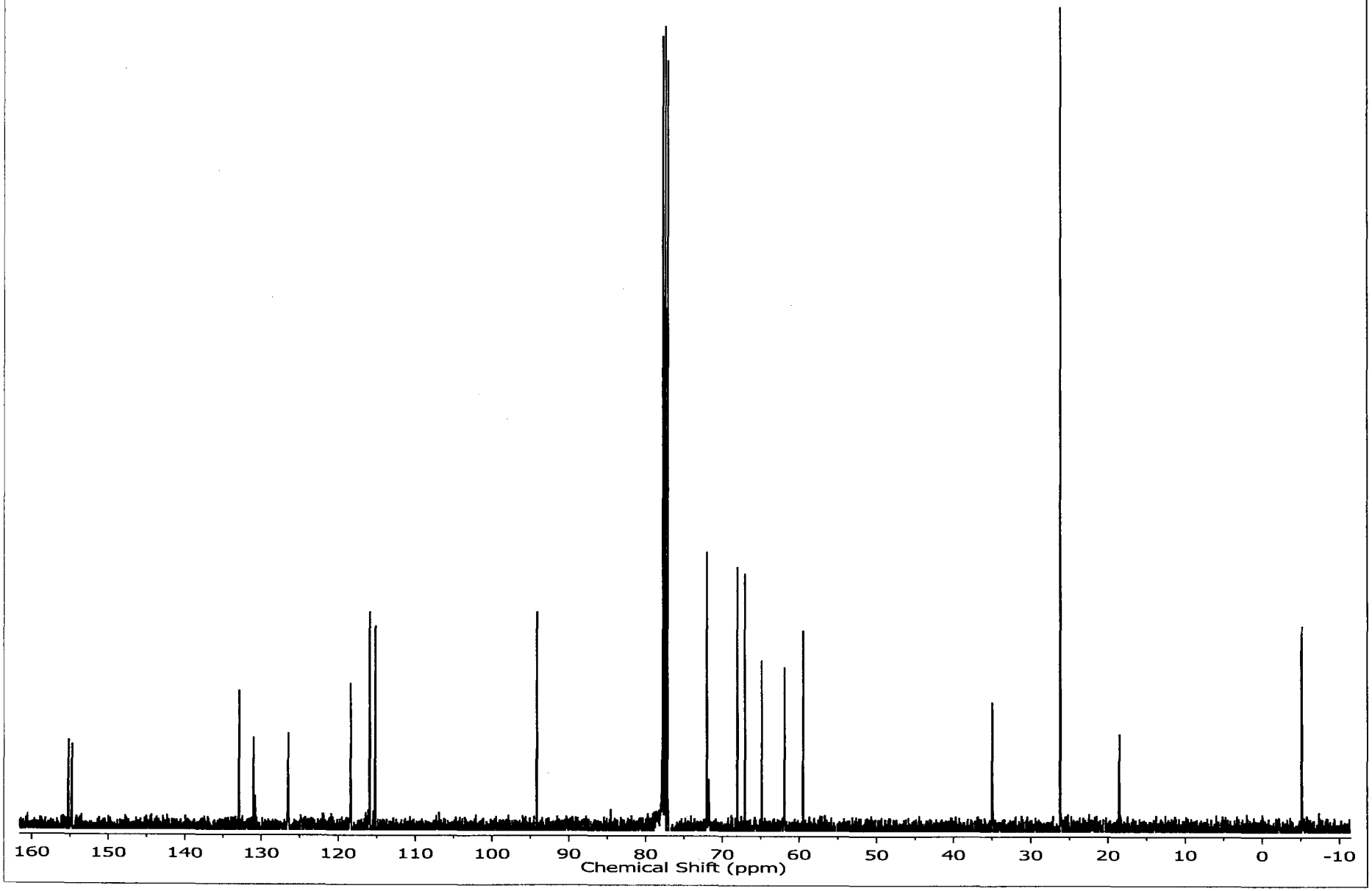

Alloc
N
OH
MEMO
OH

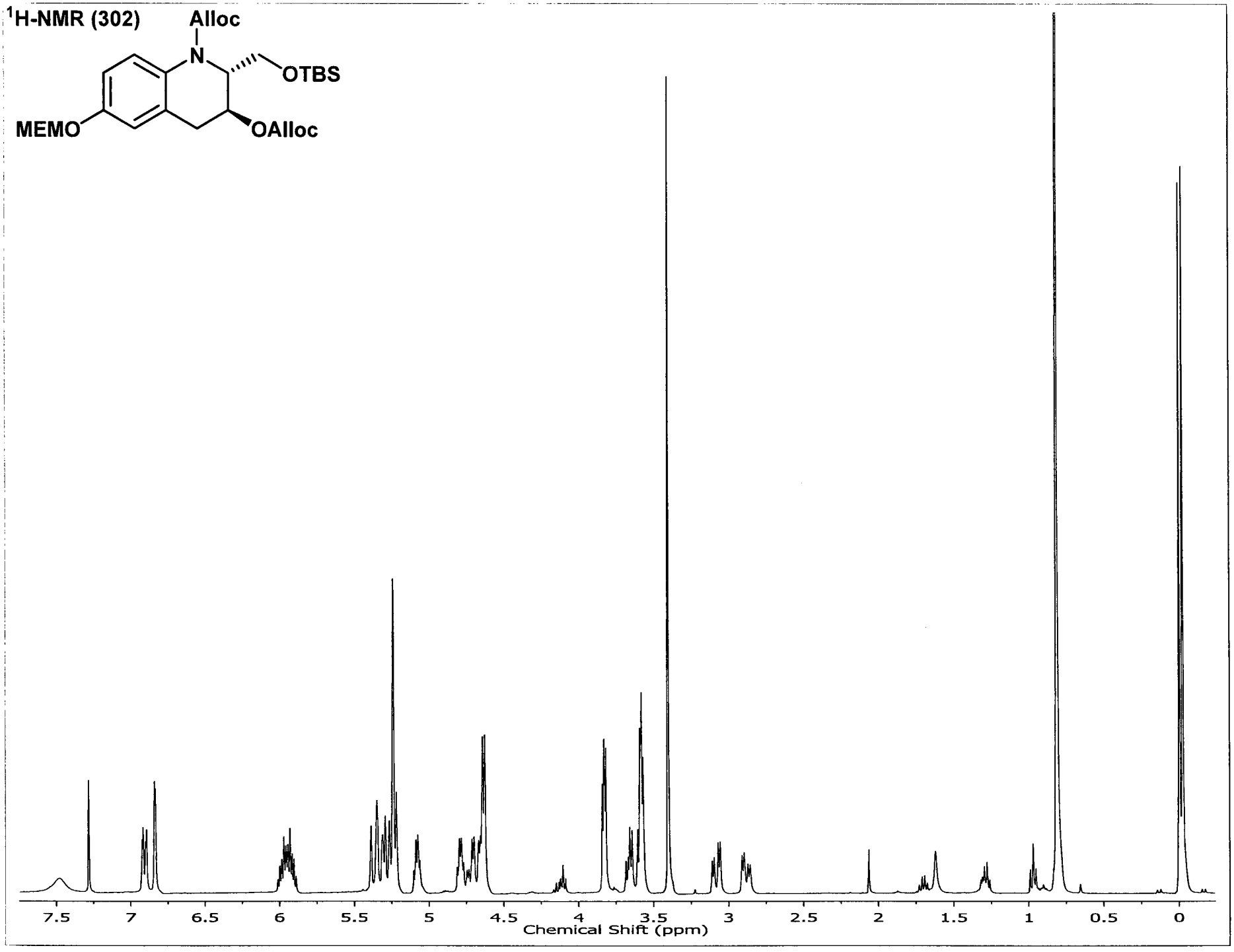

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

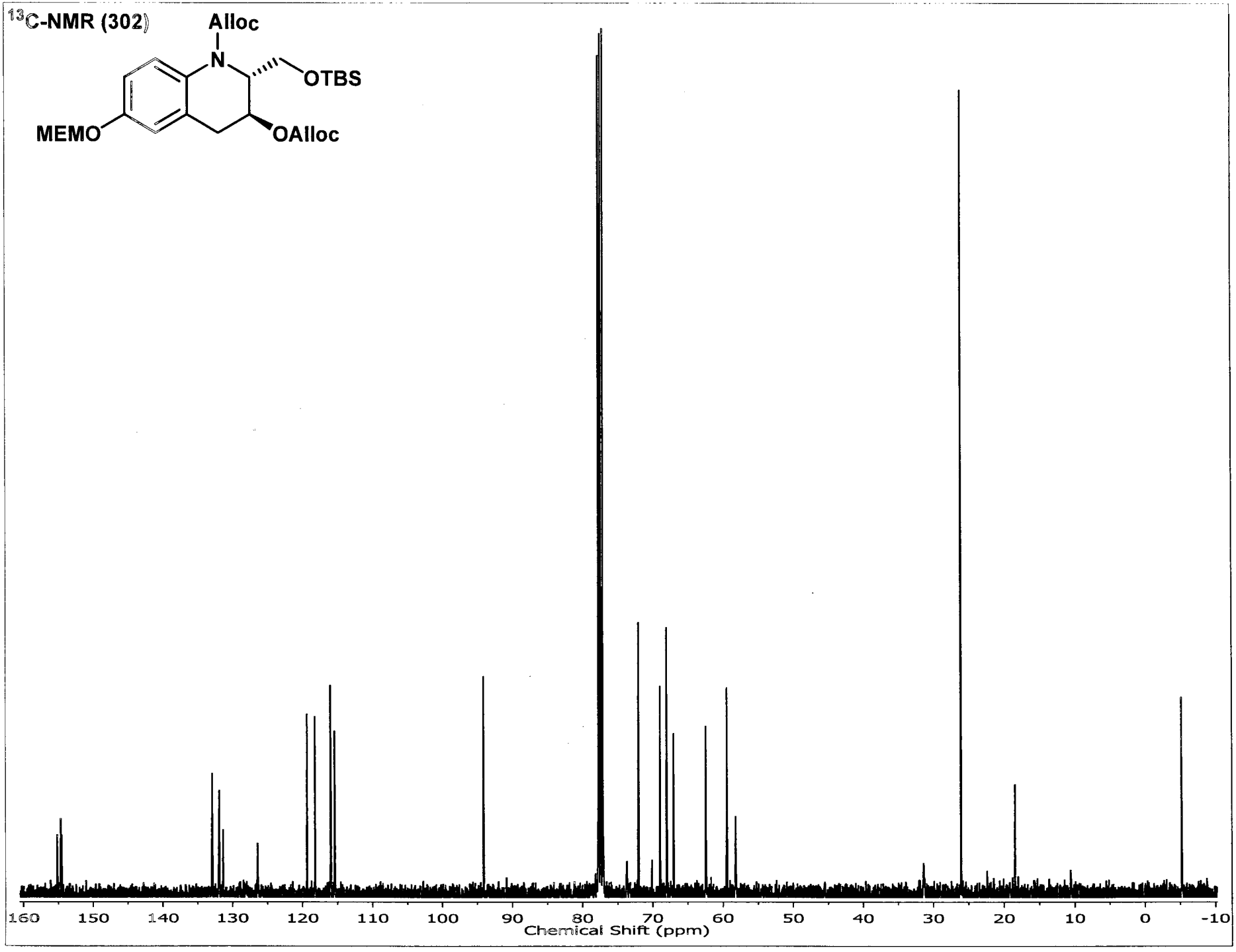

1H-NMR (301)
Alloc
N
OTBS
MEMO
OH
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

^{13}C-NMR (301)


Alloc
N
OTBS
MEMO
OH

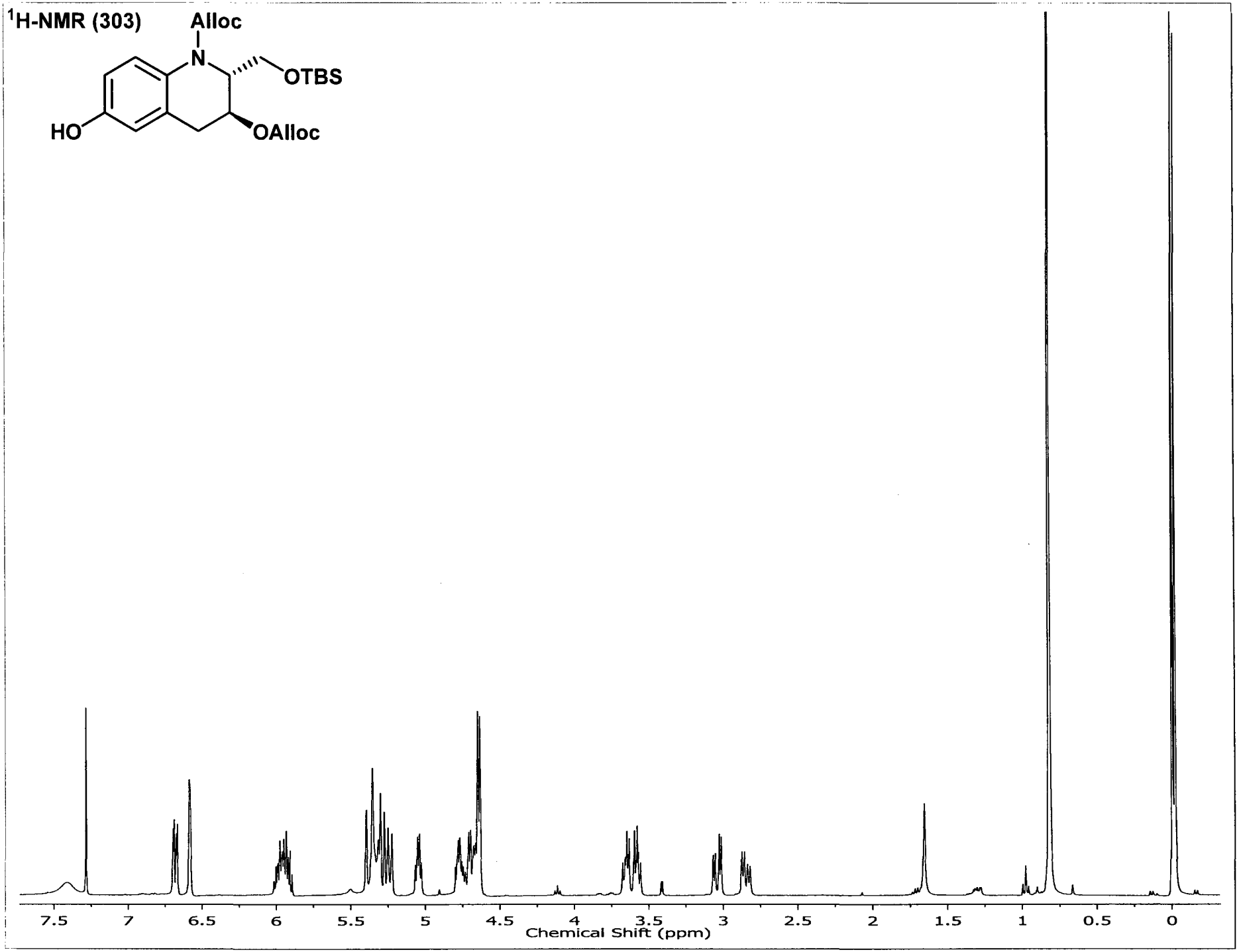

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

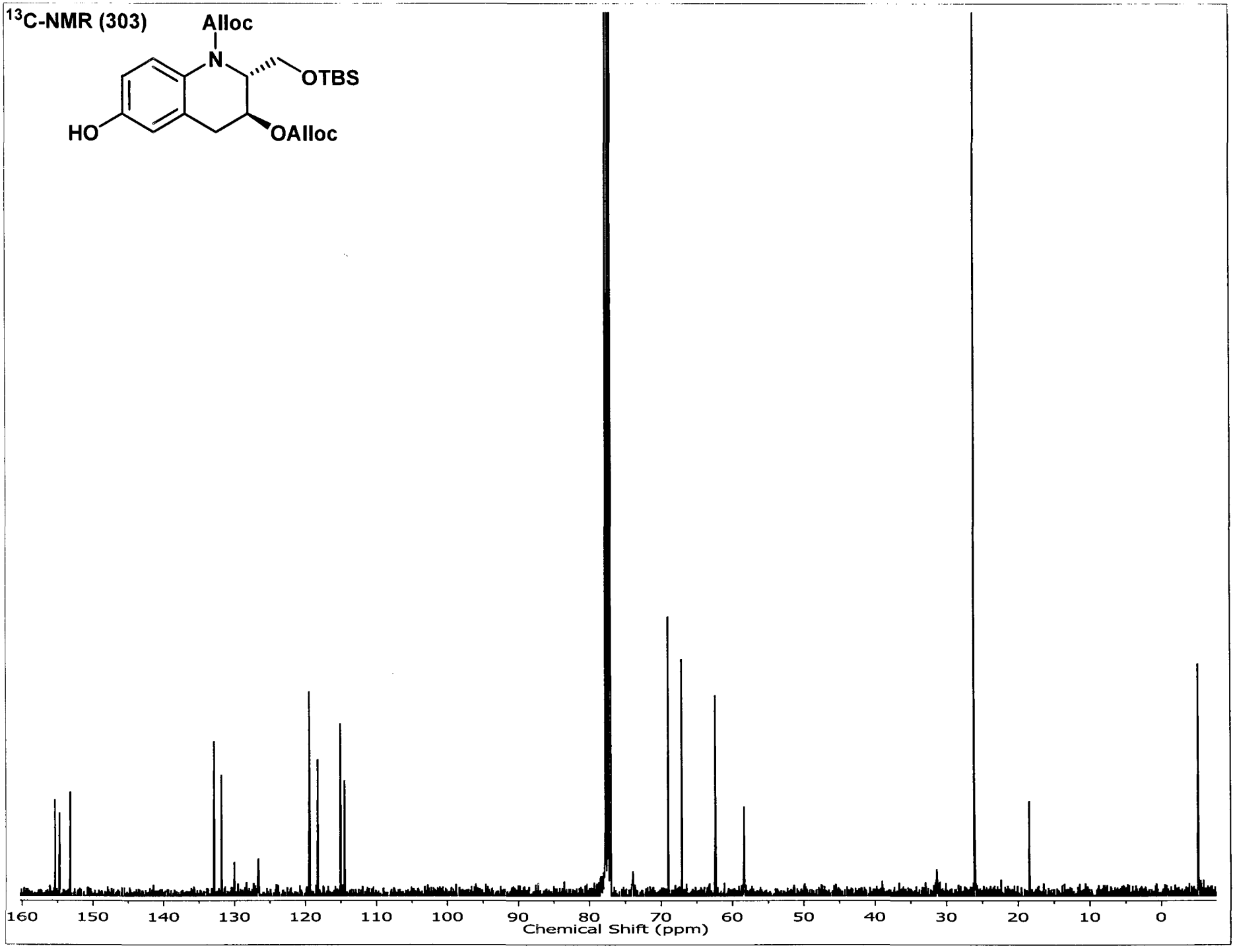

1H-NMR (302)
Alloc
N
OTBS
MEMO
OAlloc
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)


13C-NMR (302)
Alloc
N
OTBS
MEMO
OAlloc
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)

^{1}H-NMR (303)

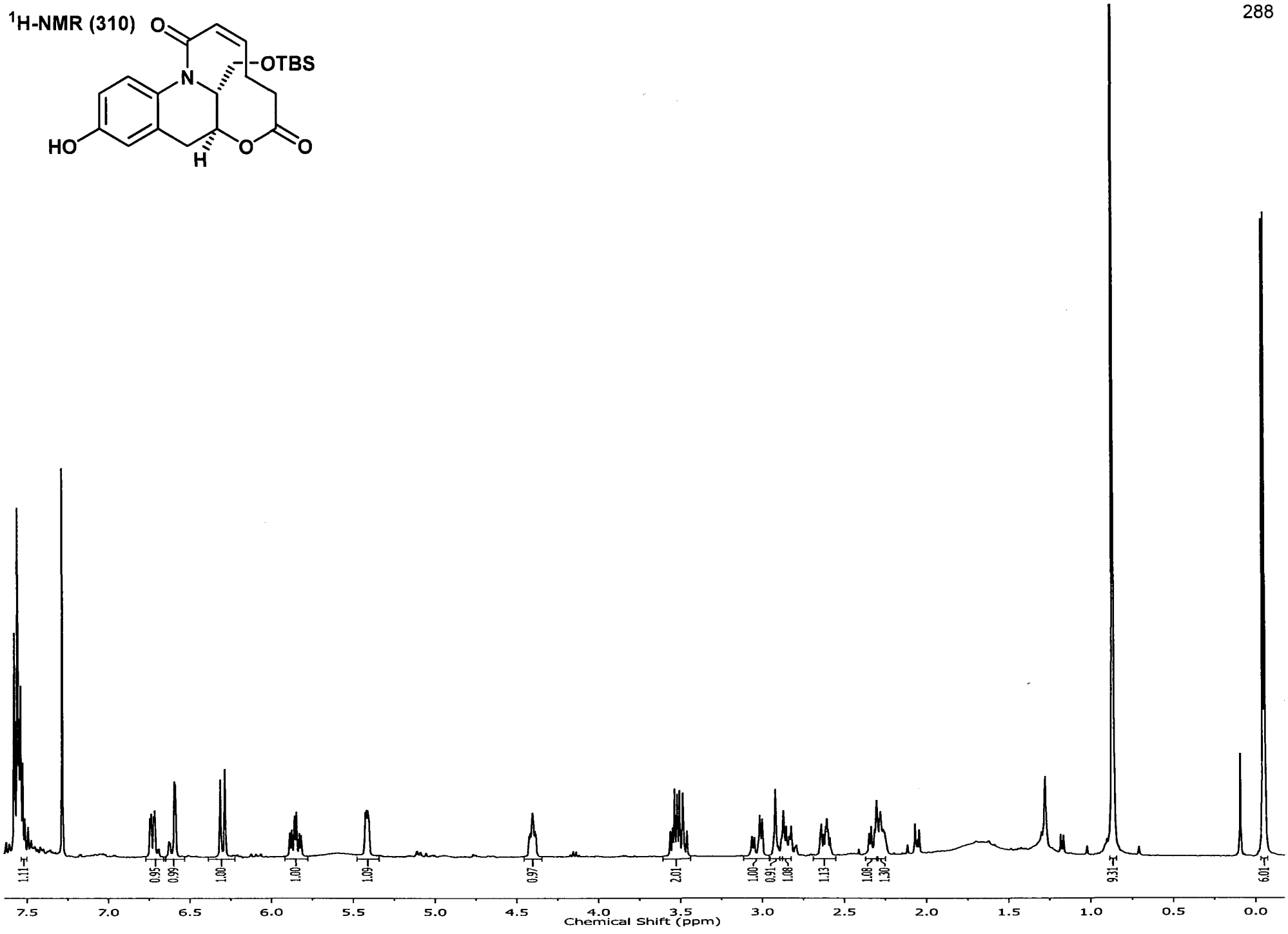
Alloc
N
OTBS
HO
OAlloc

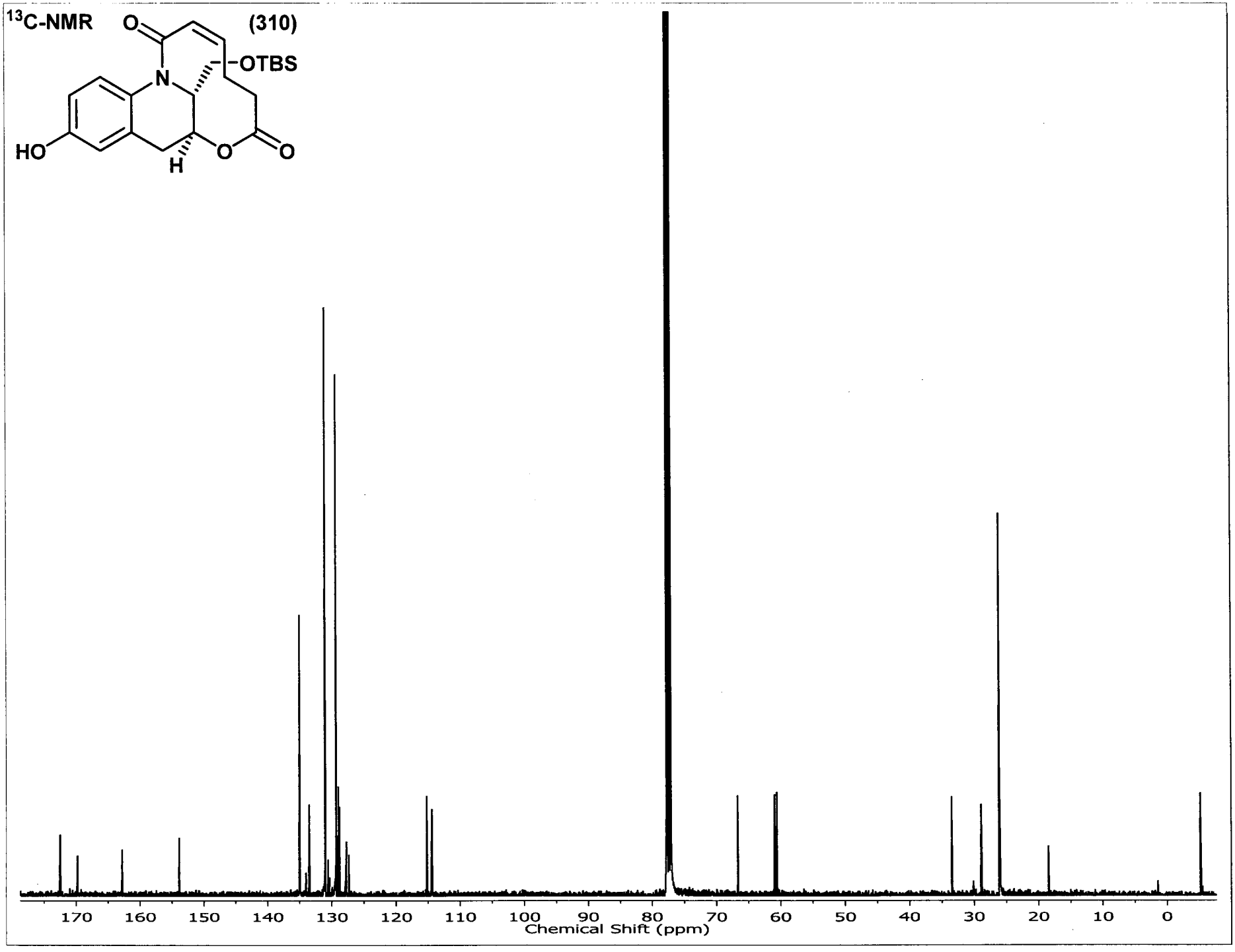

7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

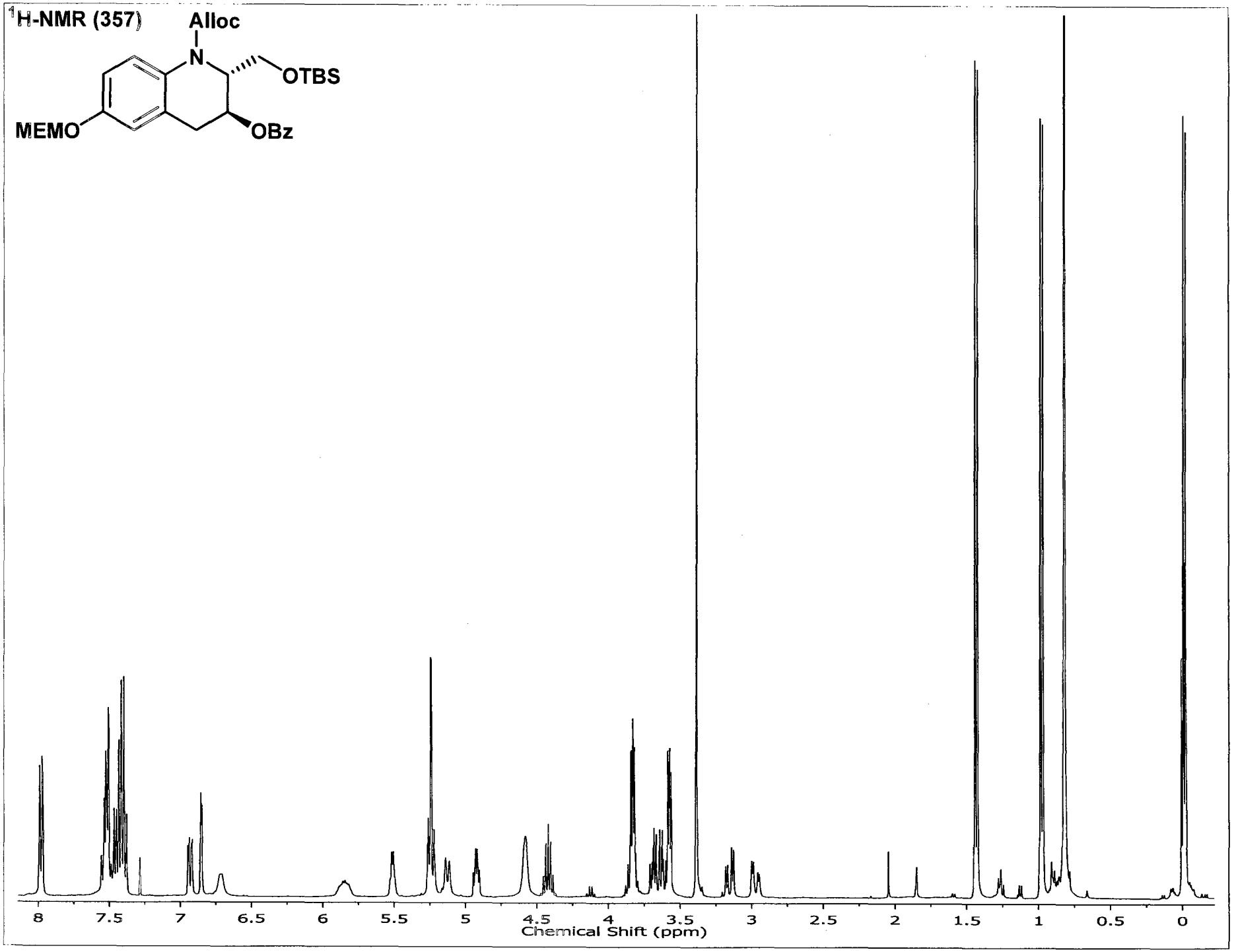

13C-NMR (303)
Alloc
N
OTBS
HO
OAlloc
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

^{1}H-NMR (310)

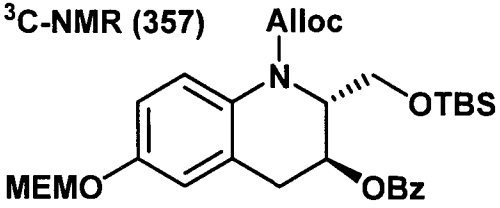
O
OTBS
N
HO
H
O
O

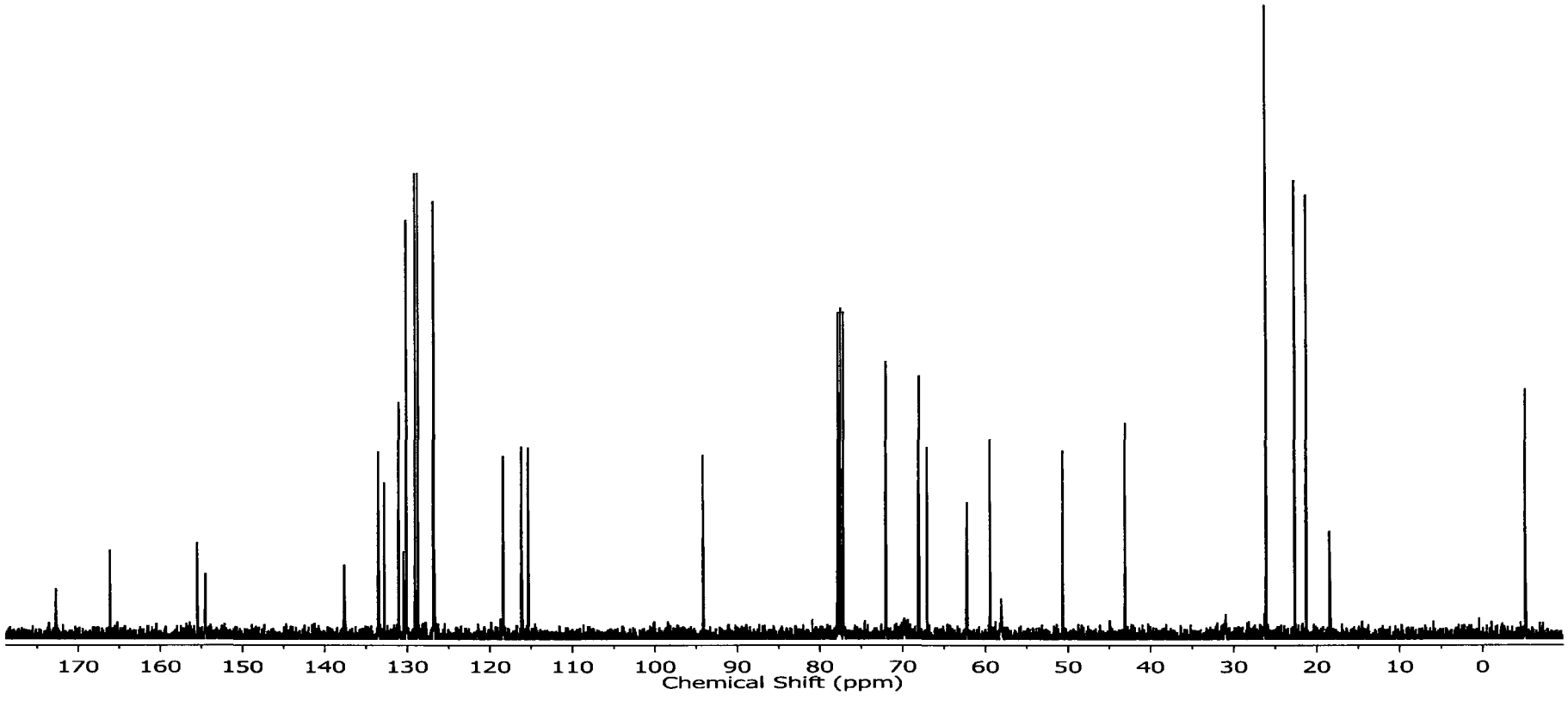

1.11
0.95
0.99
1.00
1.00
1.09
0.97
2.01
1.00
0.91
1.08
1.13
1.08
1.30
9.31
6.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chemical Shift (ppm)


13C-NMR
(310)
OTBS
HO
Chemical Shift (ppm)


1H-NMR (357)
Alloc
N
OTBS
MEMO
OBz
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Chemical Shift (ppm)

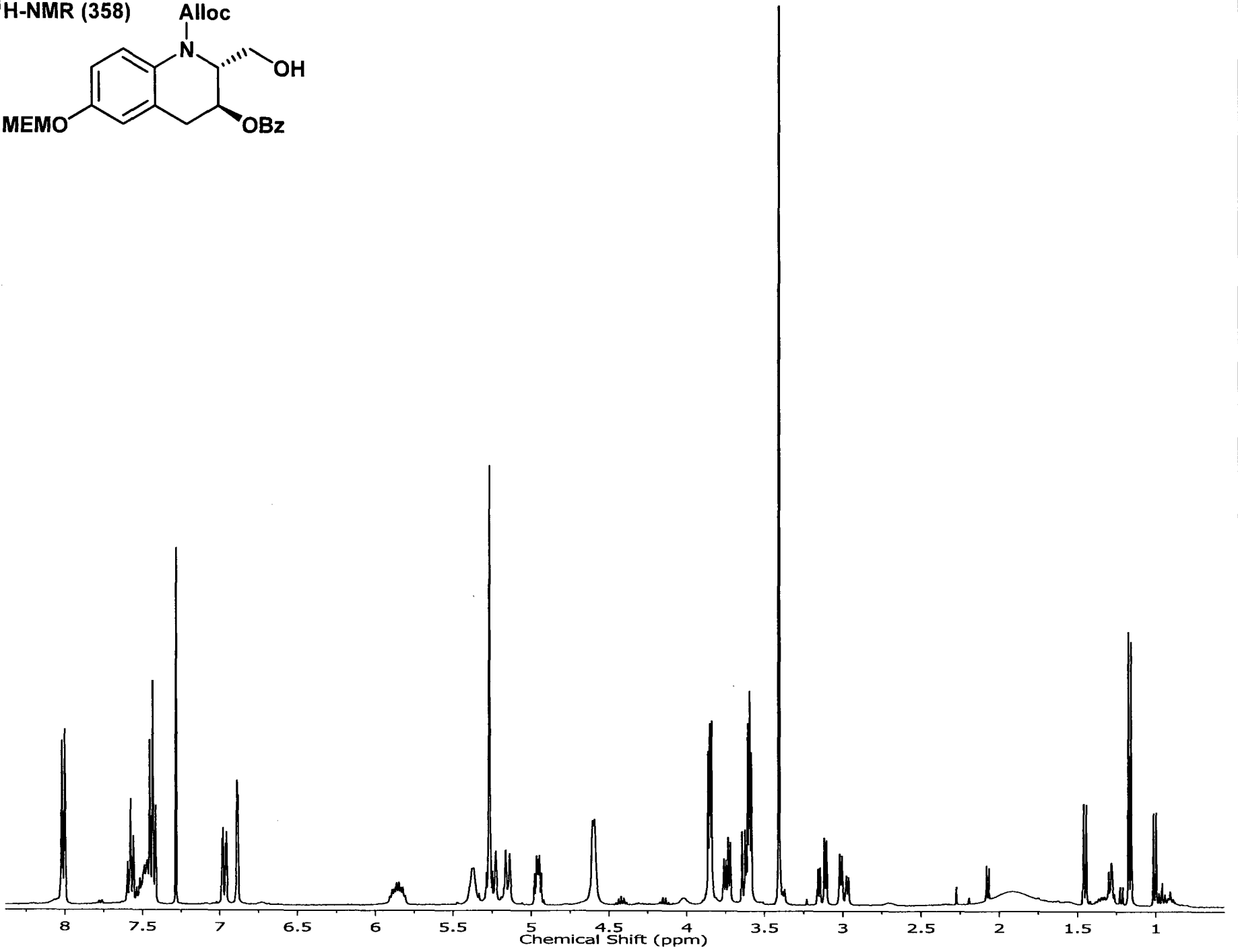
^{13}C-NMR (357)

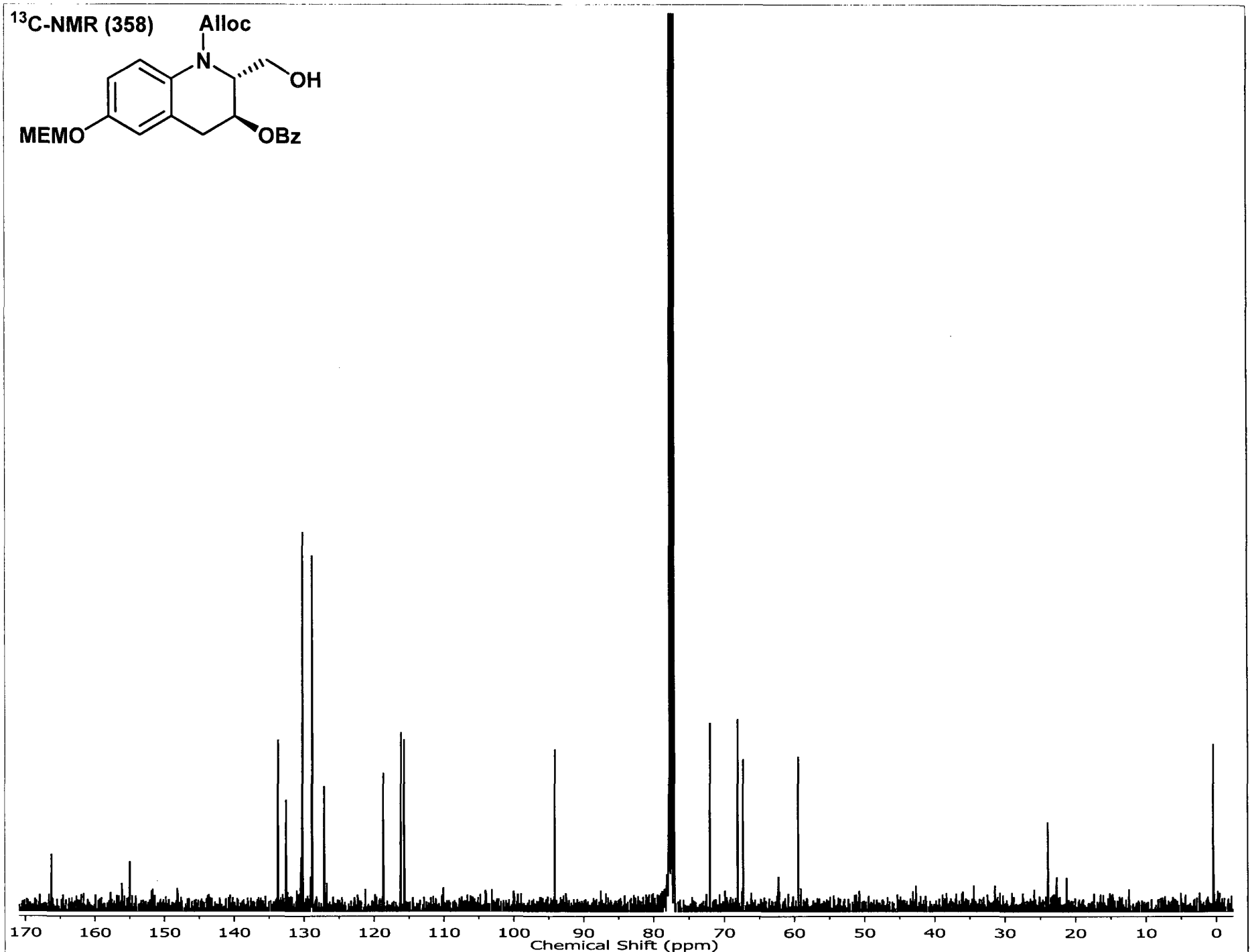

Alloc
N
OTBS
MEMO
OBz

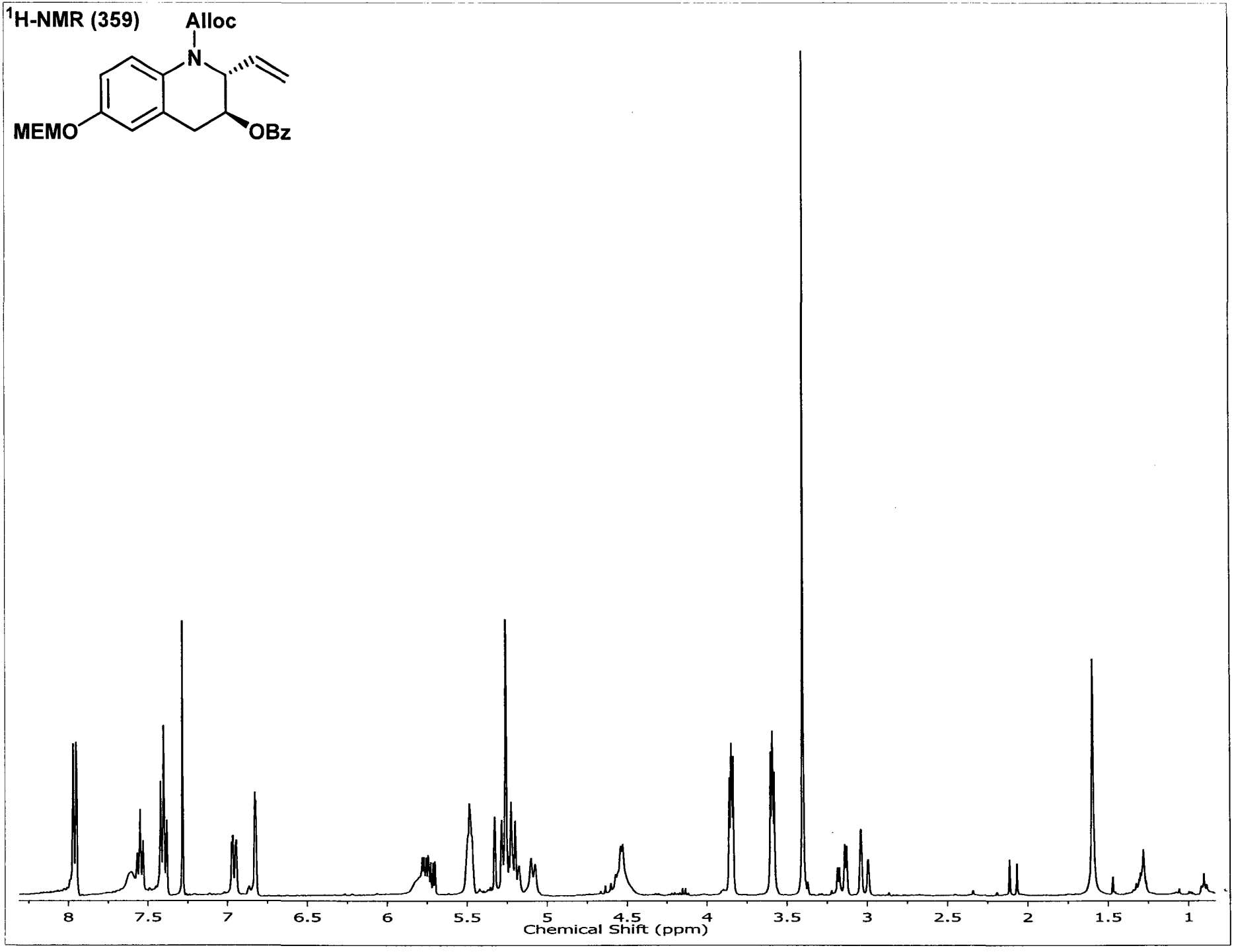

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

^{1}H-NMR (358)

Alloc
N
OH
MEMO
OBz

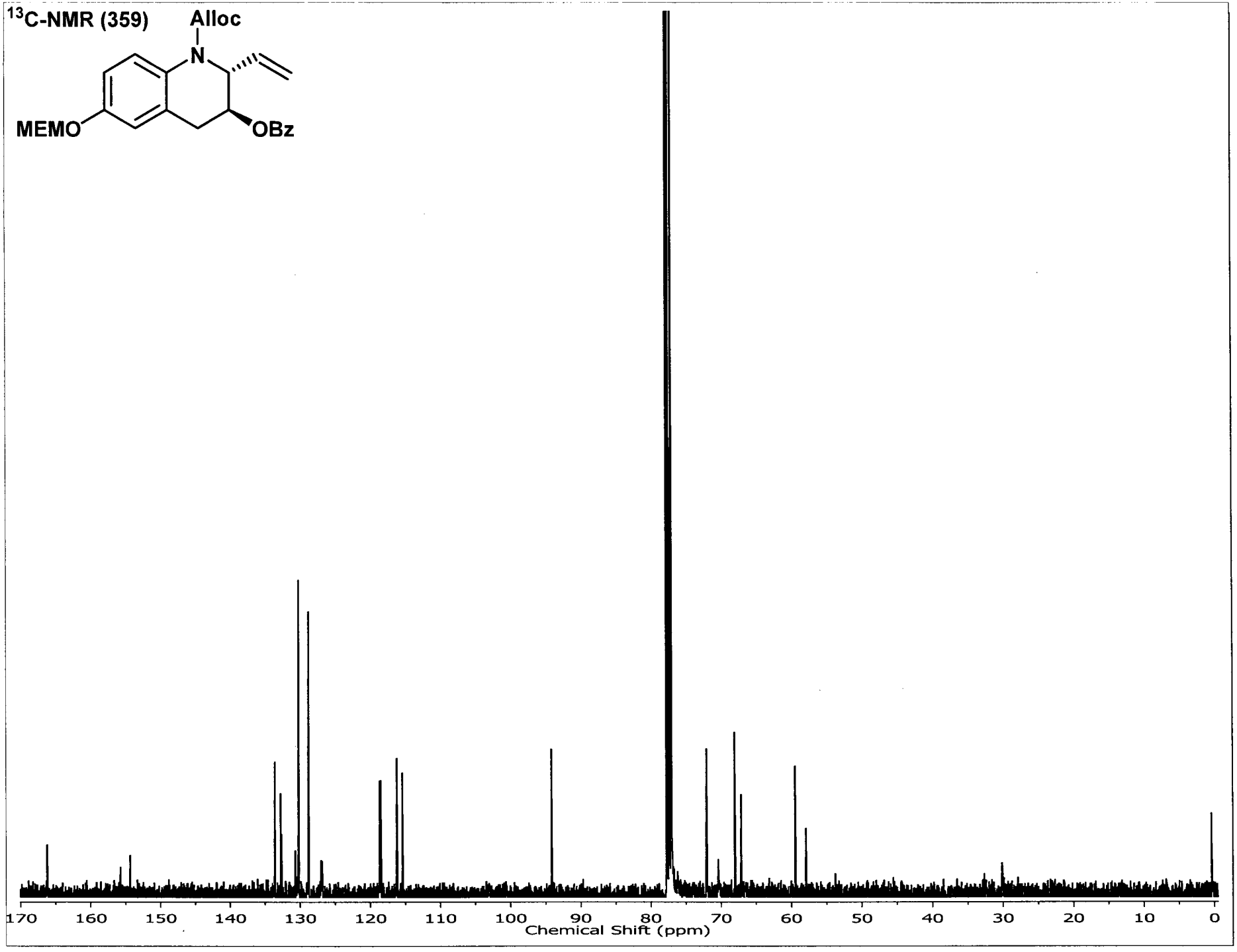

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
Chemical Shift (ppm)

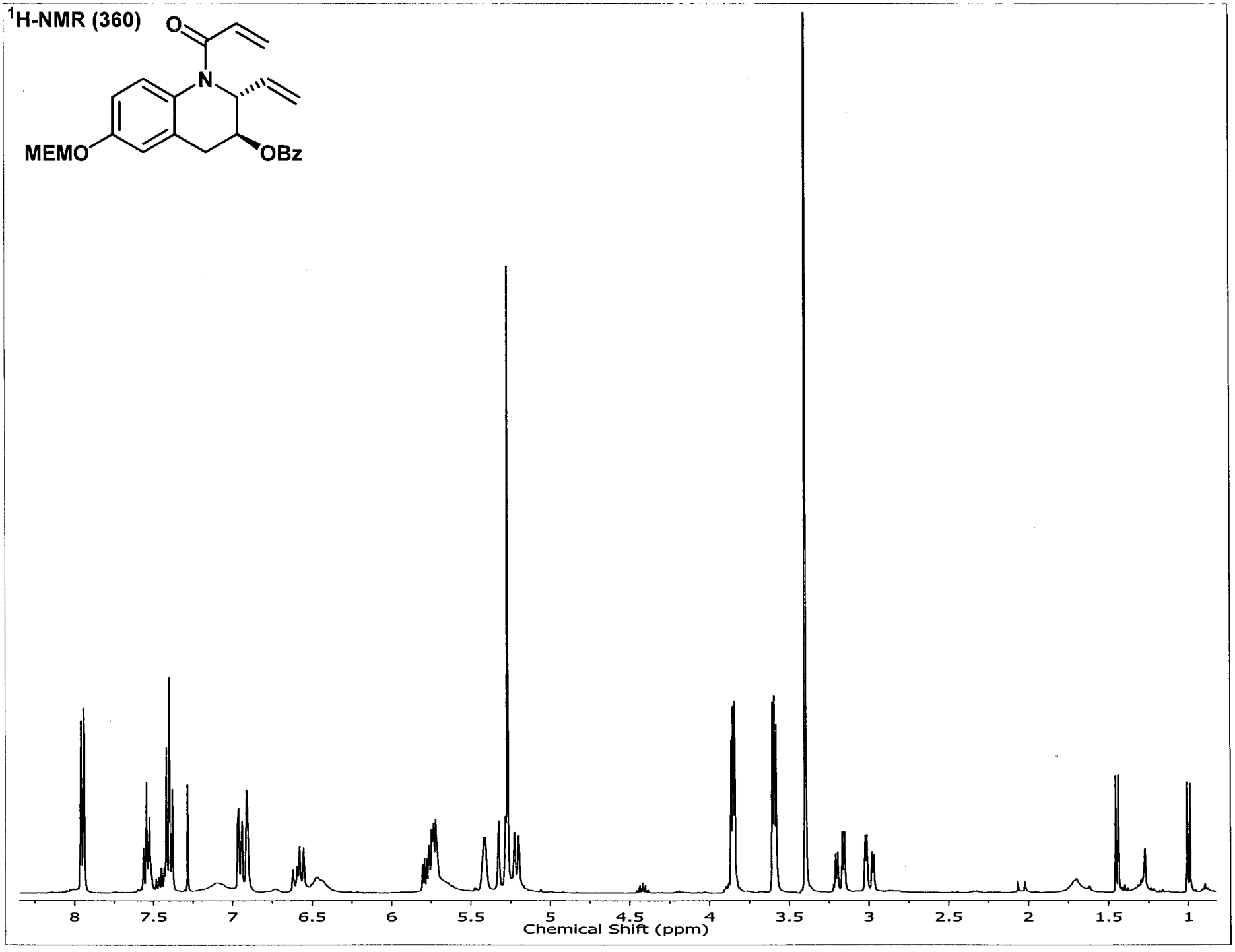

13C-NMR (358)
Alloc
N
OH
MEMO
OBz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

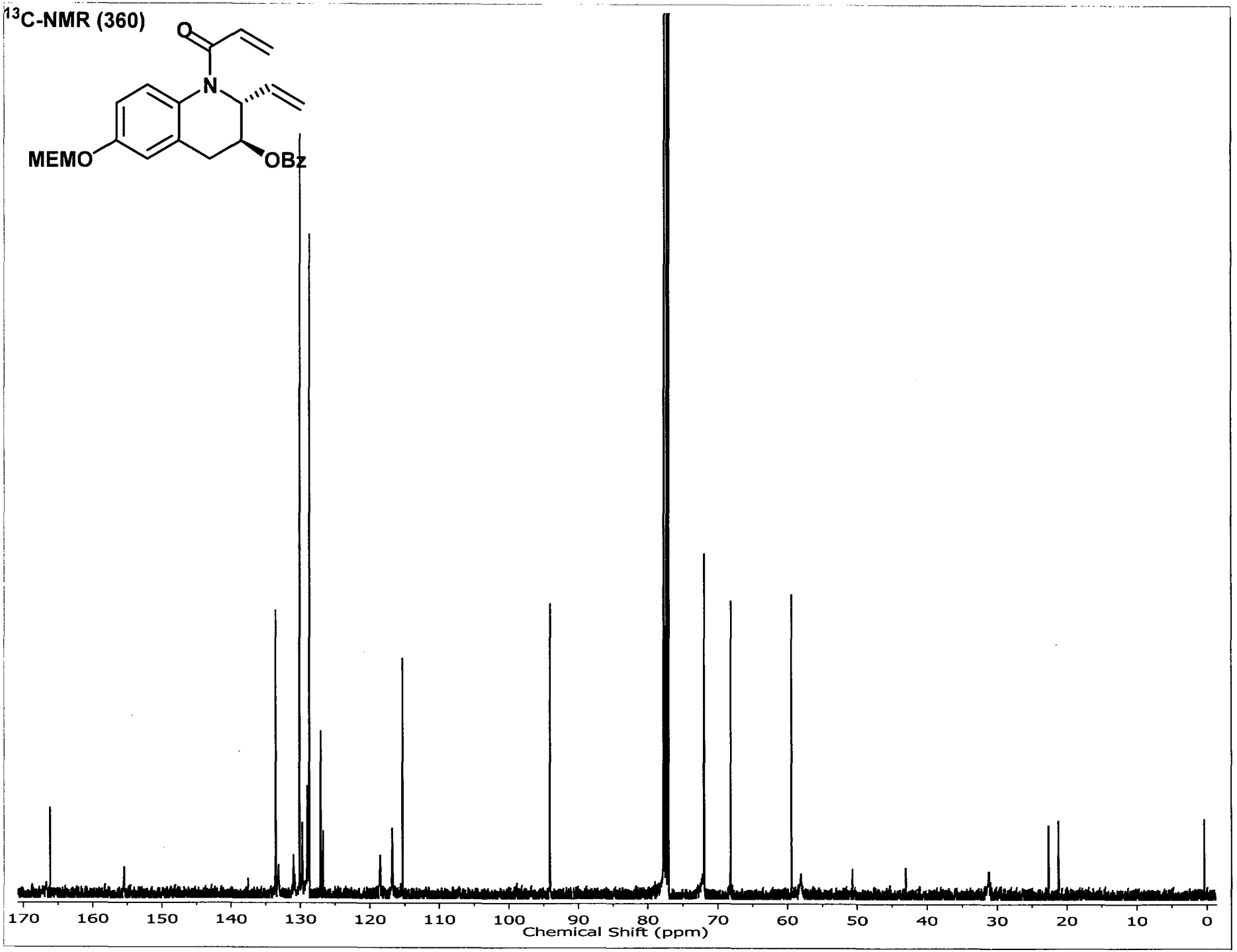

1H-NMR (359)
Alloc
N
MEMO
OBz
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
Chemical Shift (ppm)

^{13}C-NMR (359)

Alloc
N
MEMO
OBz

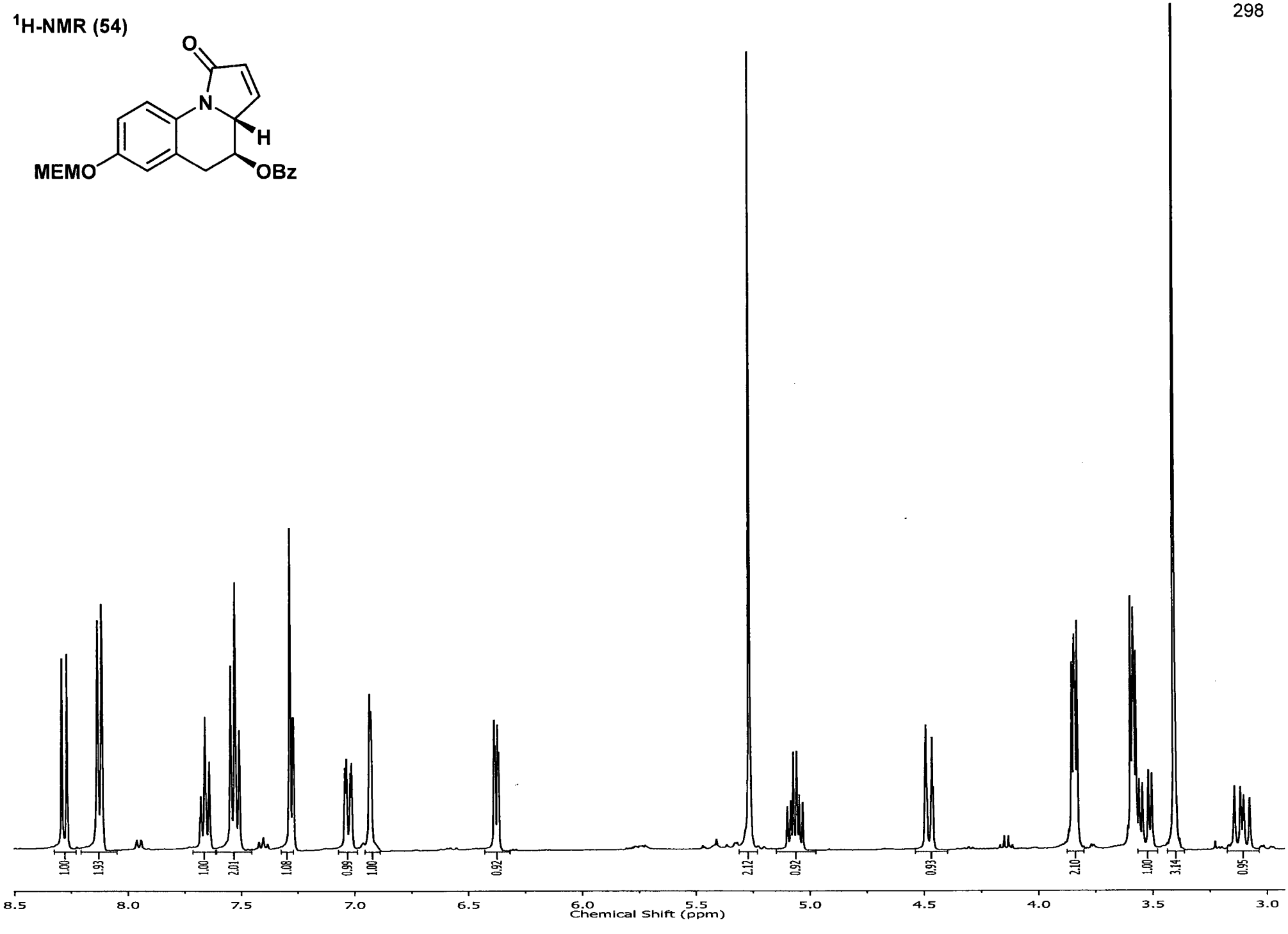

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


1H-NMR (360)
O
N
MEMO
OBz
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
Chemical Shift (ppm)

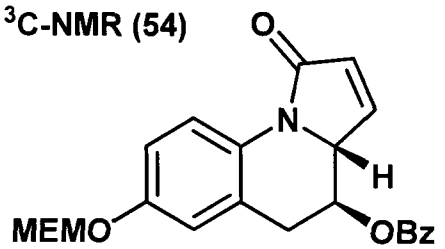

13C-NMR (360)
O
N
MEMO
OBz
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

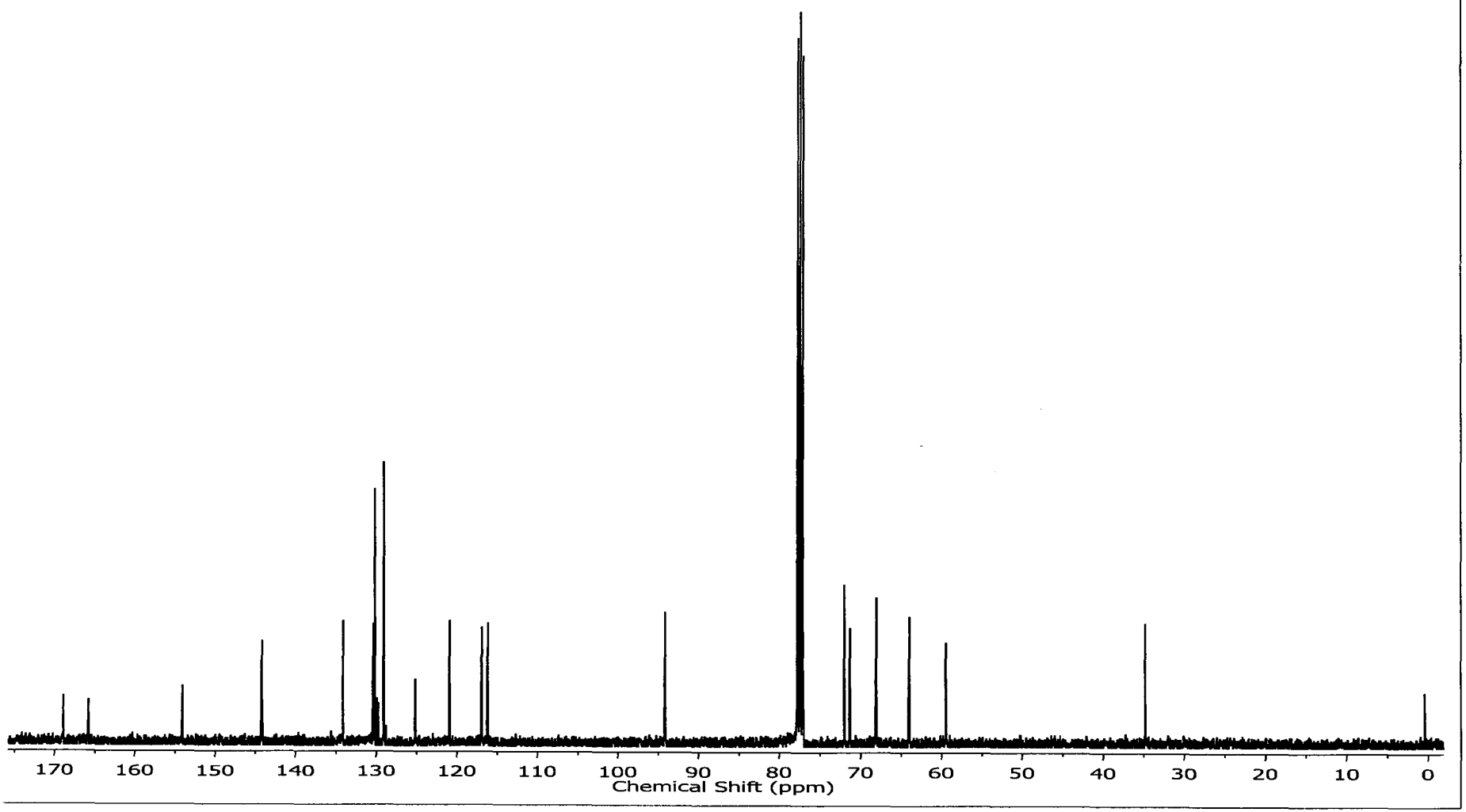
^{1}H-NMR (54)

O
N
H
MEMO
OBz

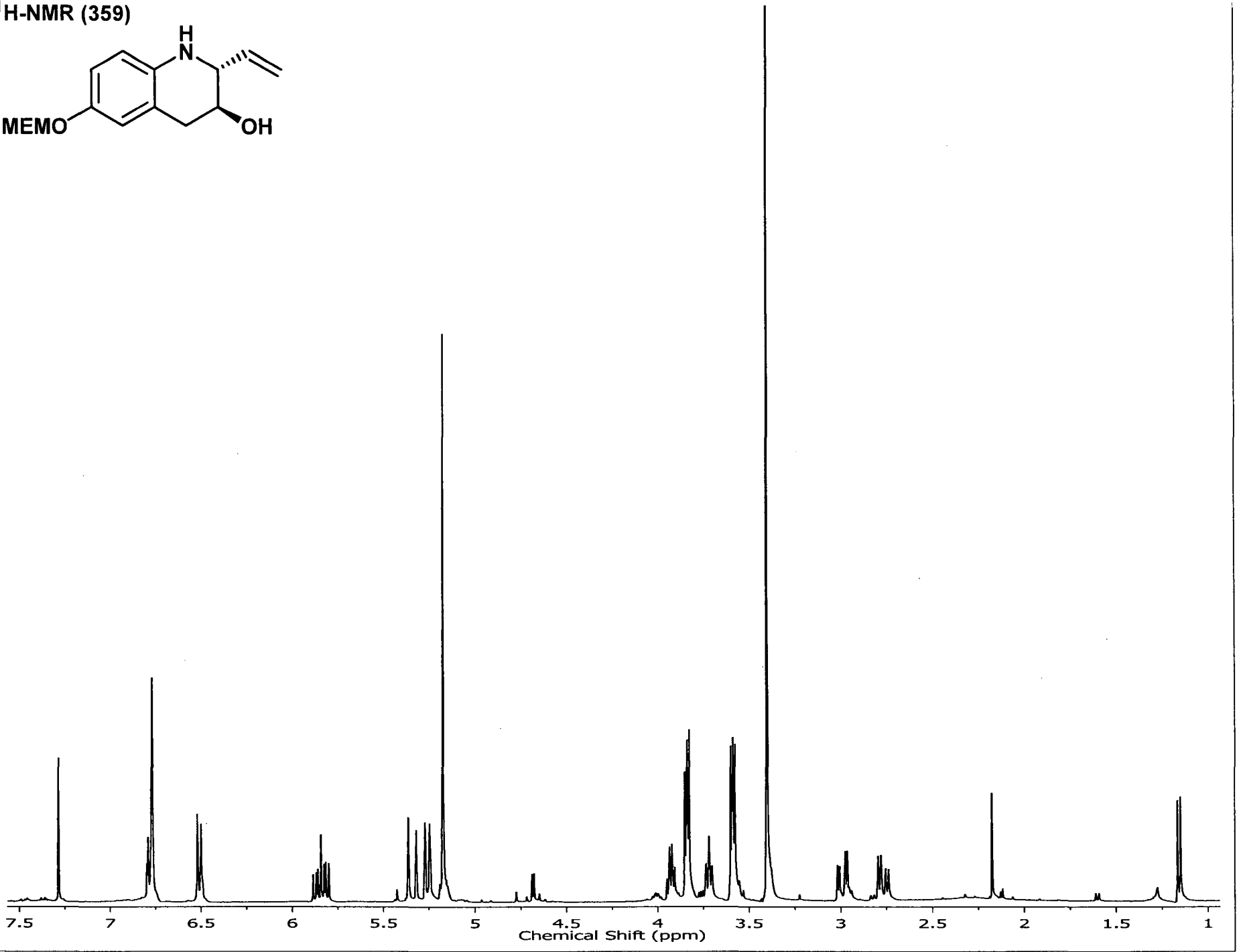

1.00
1.93
1.00
2.01
1.08
0.99
1.00
0.92
2.12
0.92
0.93
2.10
1.00
3.14
0.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Chemical Shift (ppm)

^{13}C-NMR (54)

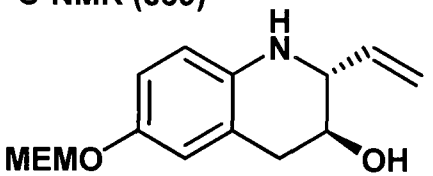

O
N
H
MEMO
OBz

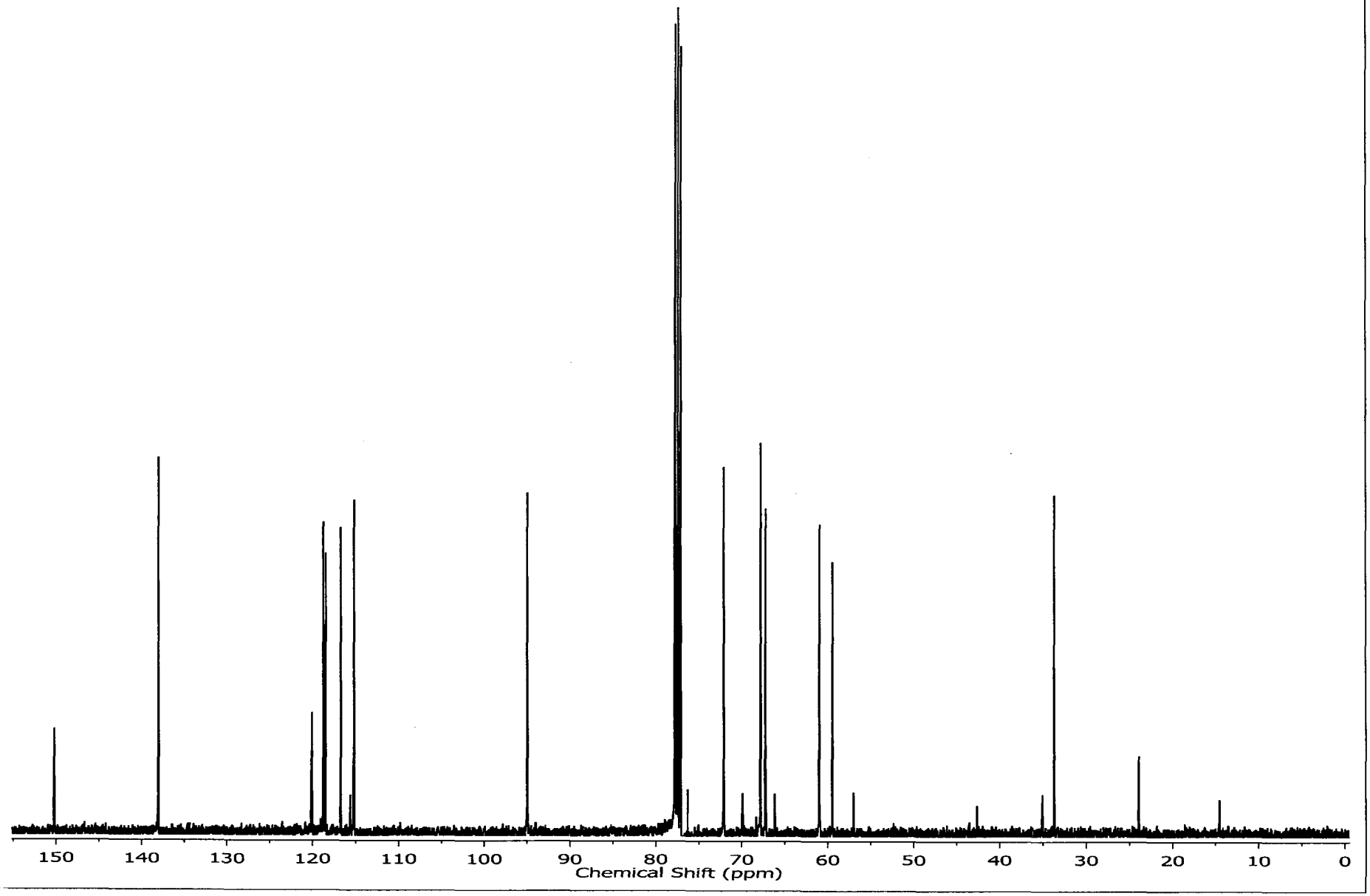

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

^{1}H-NMR (359)

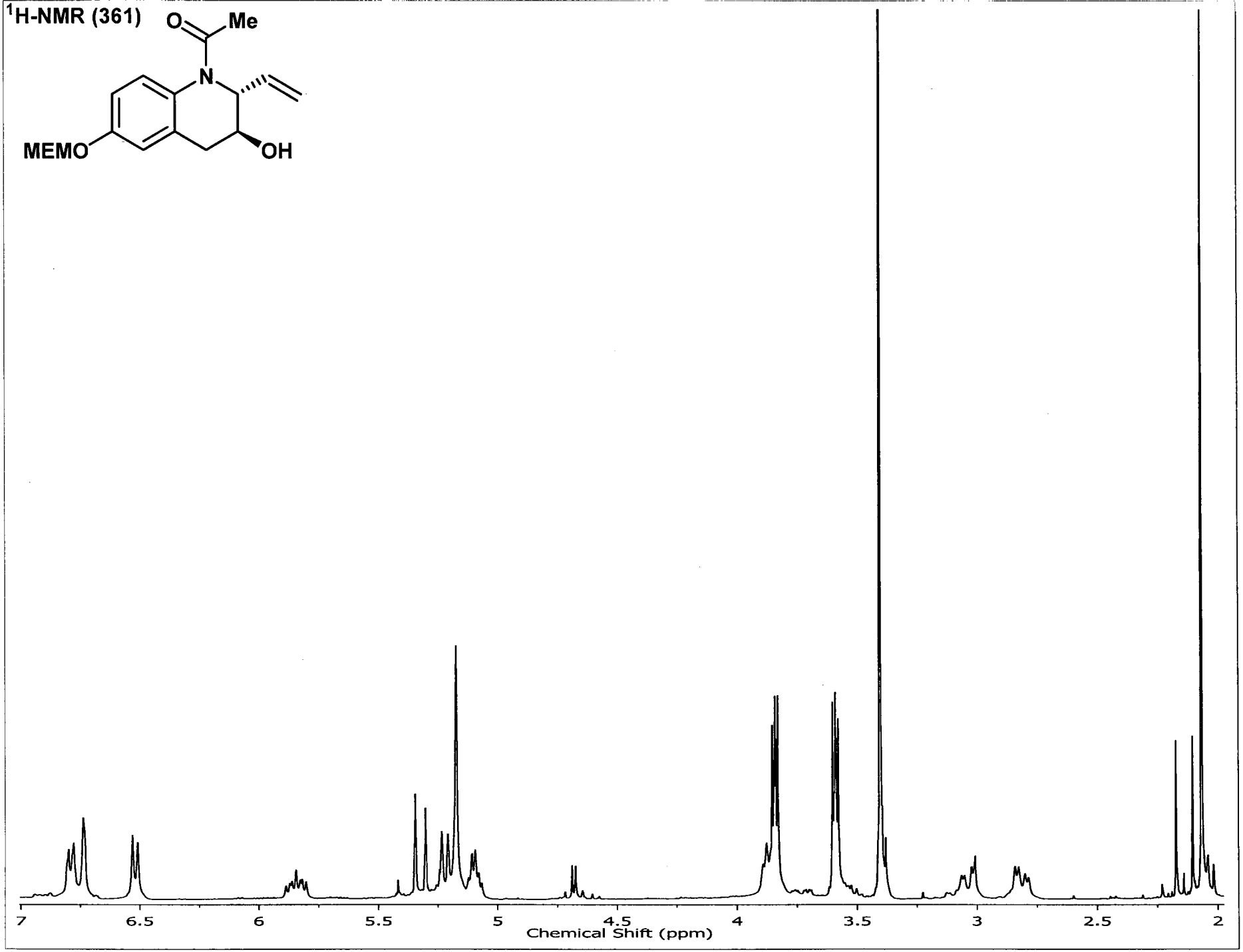


^{13}C-NMR (359)

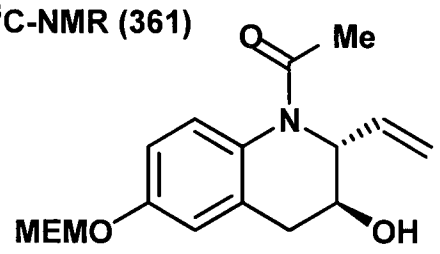

H
N
MEMO
OH

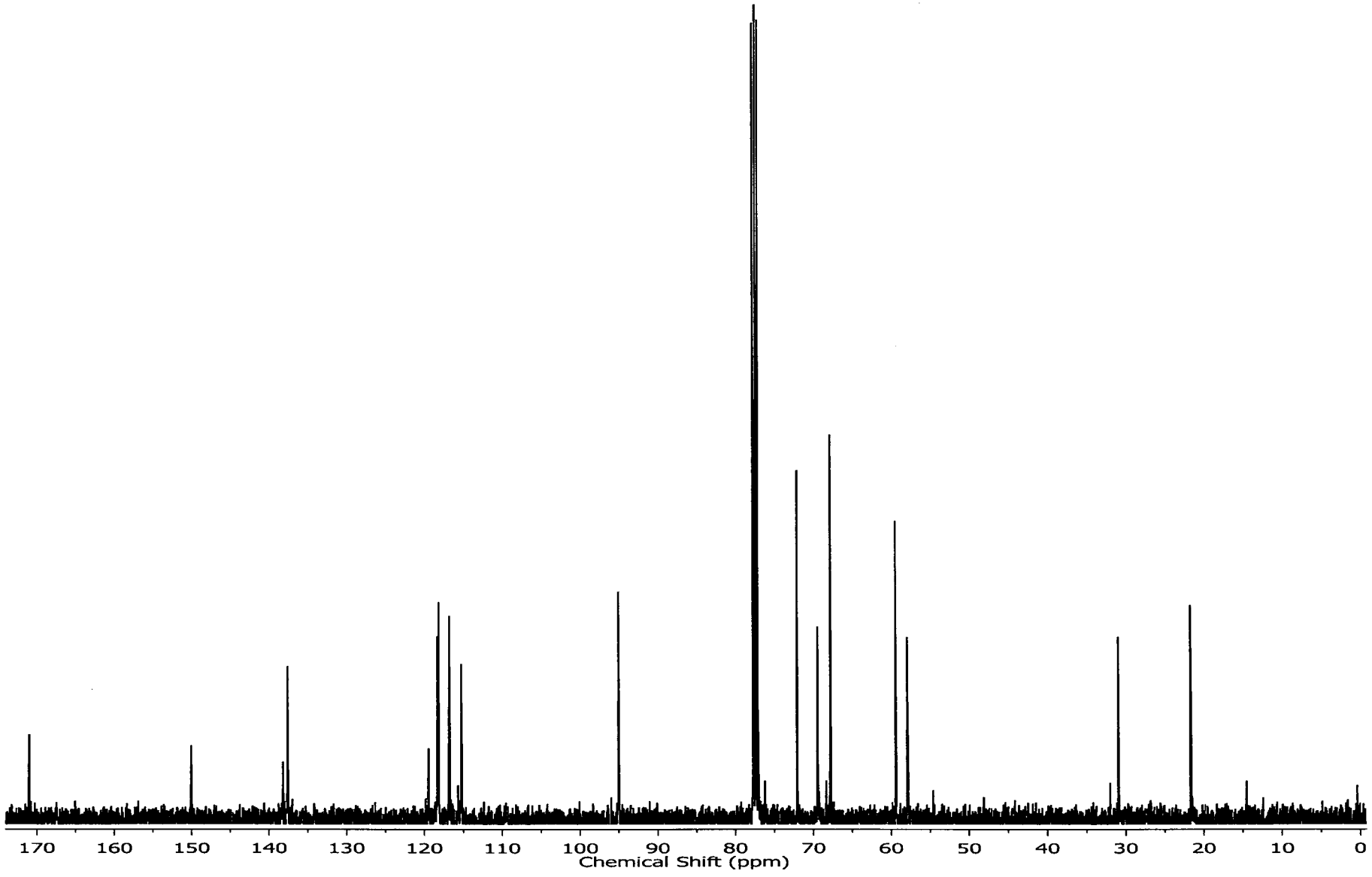

150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

^{1}H-NMR (361)



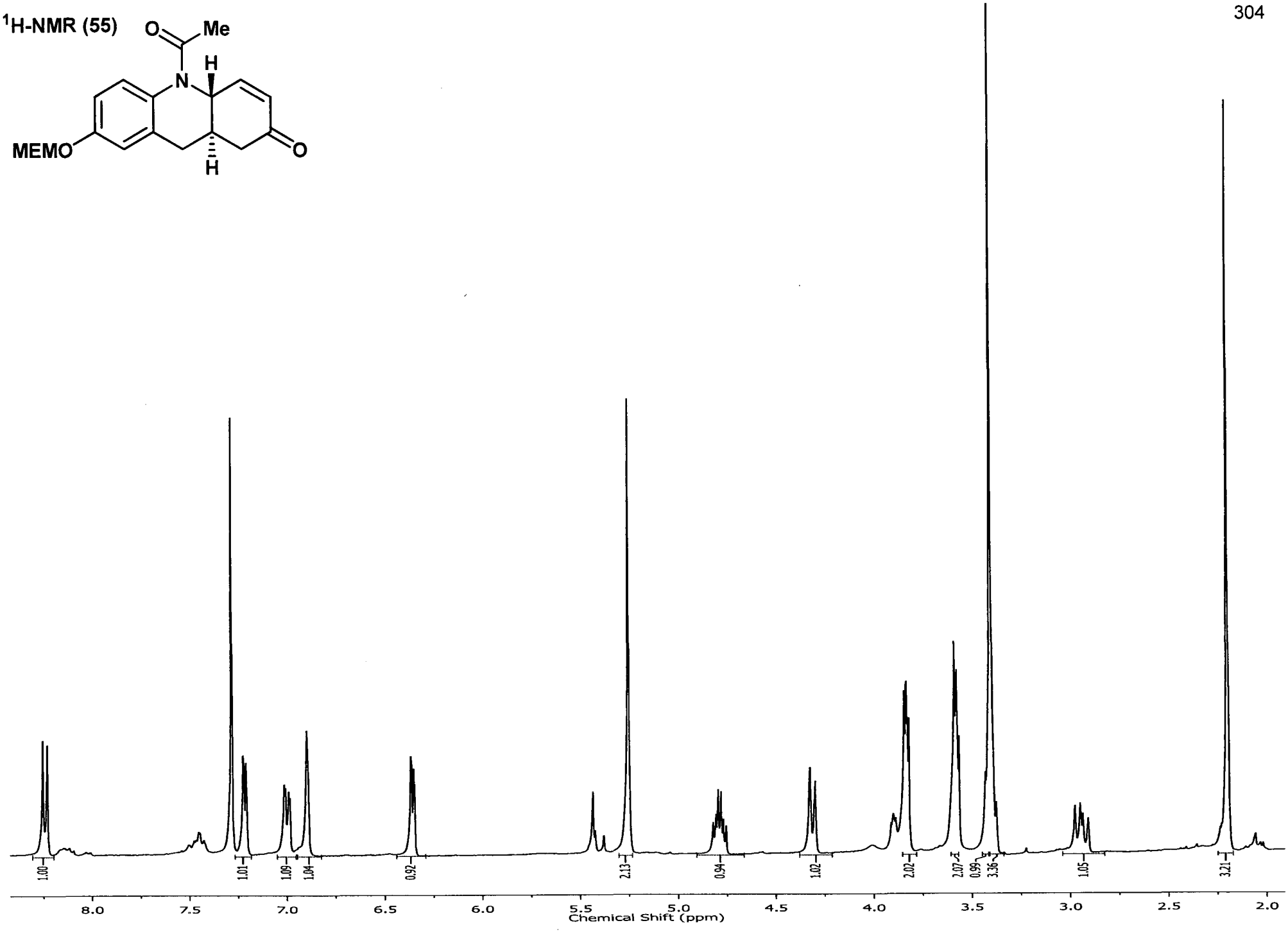
^{13}C-NMR (361)


O
Me
N
MEMO
OH


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

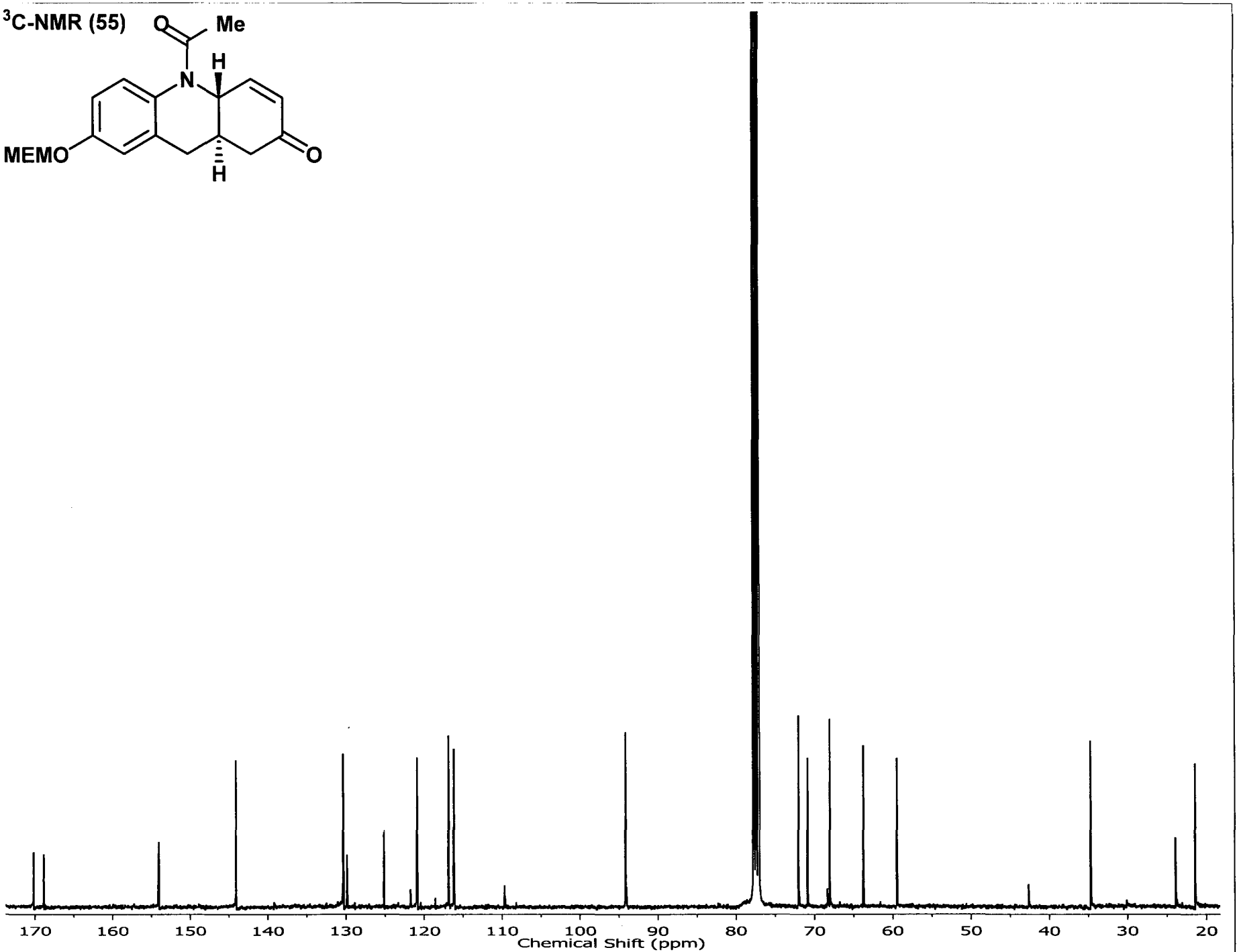
^{1}H-NMR (55)

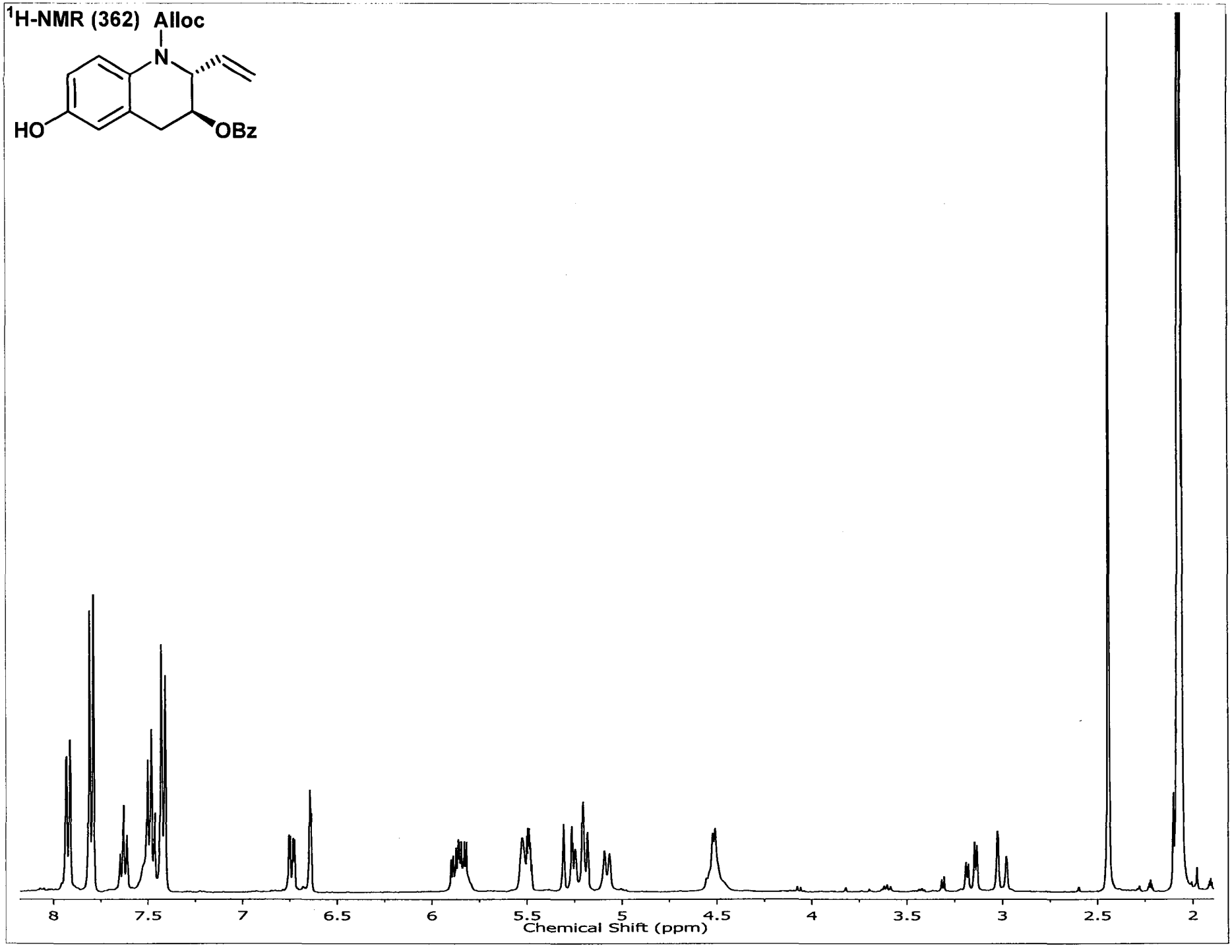
O
Me
H
N
MEMO
O
H


1.00
1.01
1.09
1.04
0.92
2.13
0.94
1.02
2.02
2.07
0.99
3.36
1.05
3.21
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

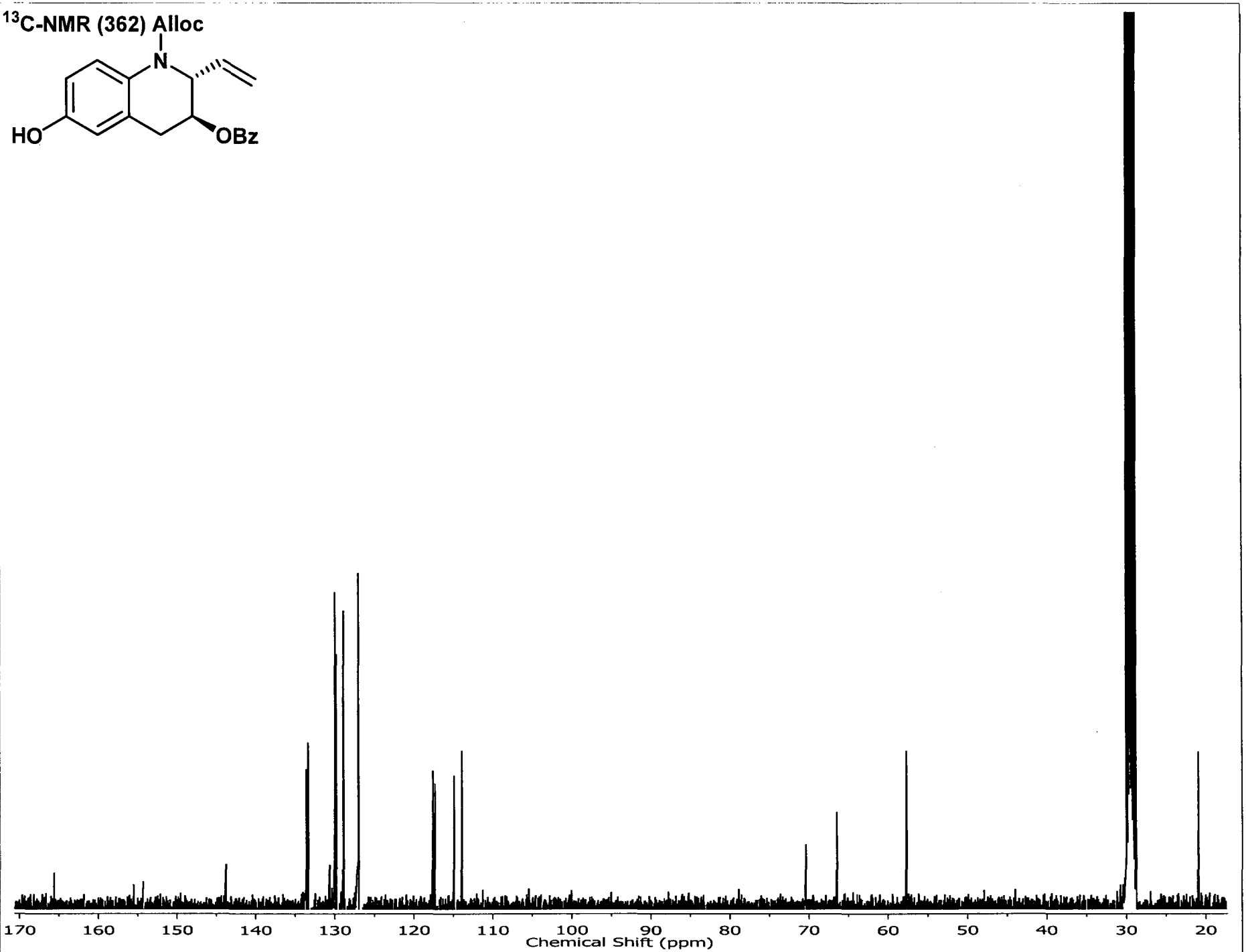
^{13}C-NMR (55)

O
Me
H
N
MEMO
O
H

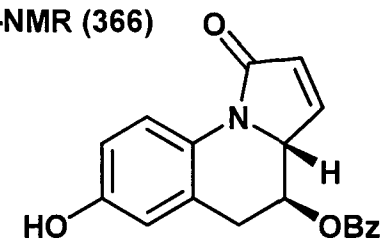

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

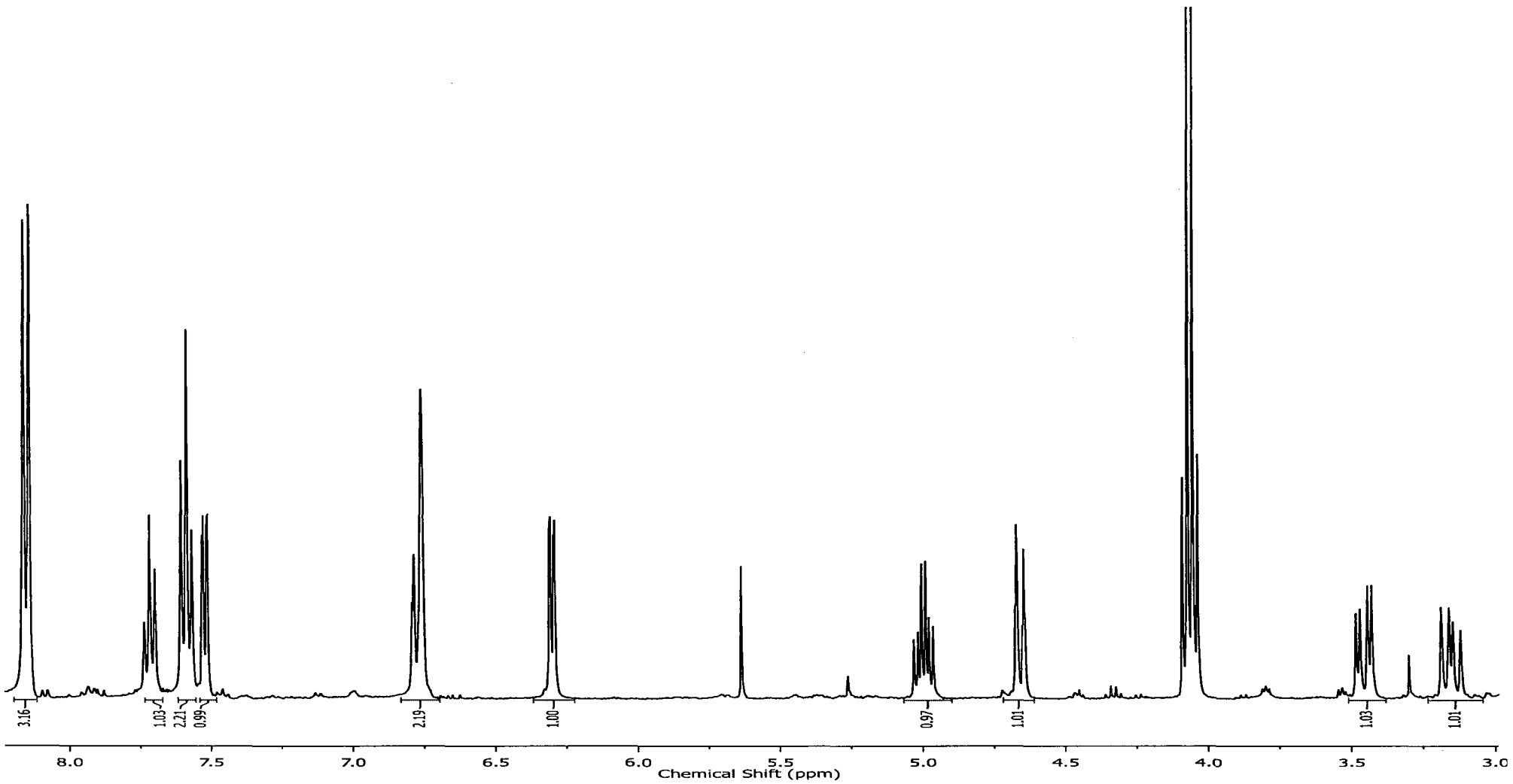

1H-NMR (362)
Alloc
N
HO
OBz
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
Chemical Shift (ppm)

^{13}C-NMR (362) Alloc



^{1}H-NMR (366)

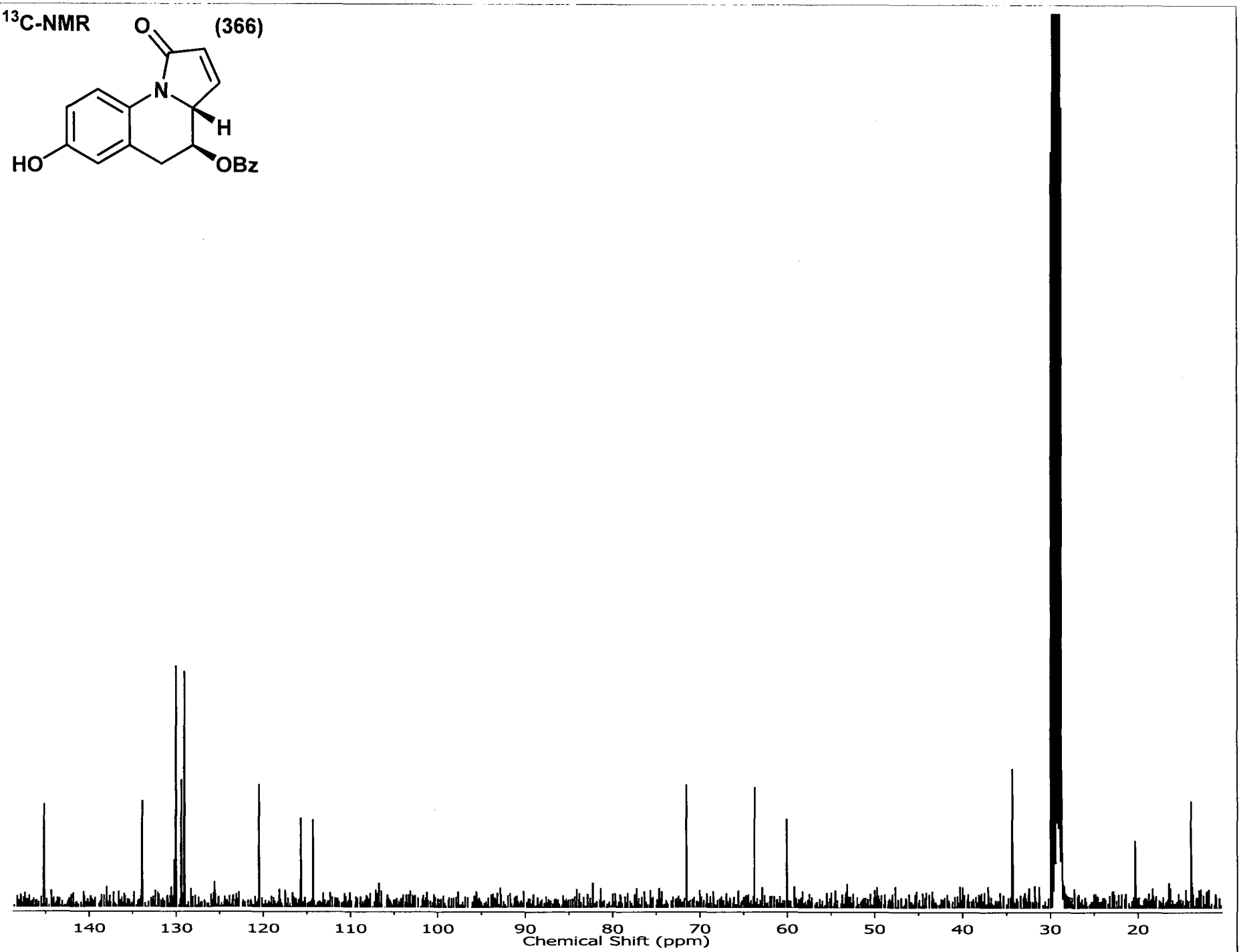

O
N
H
HO
OBz

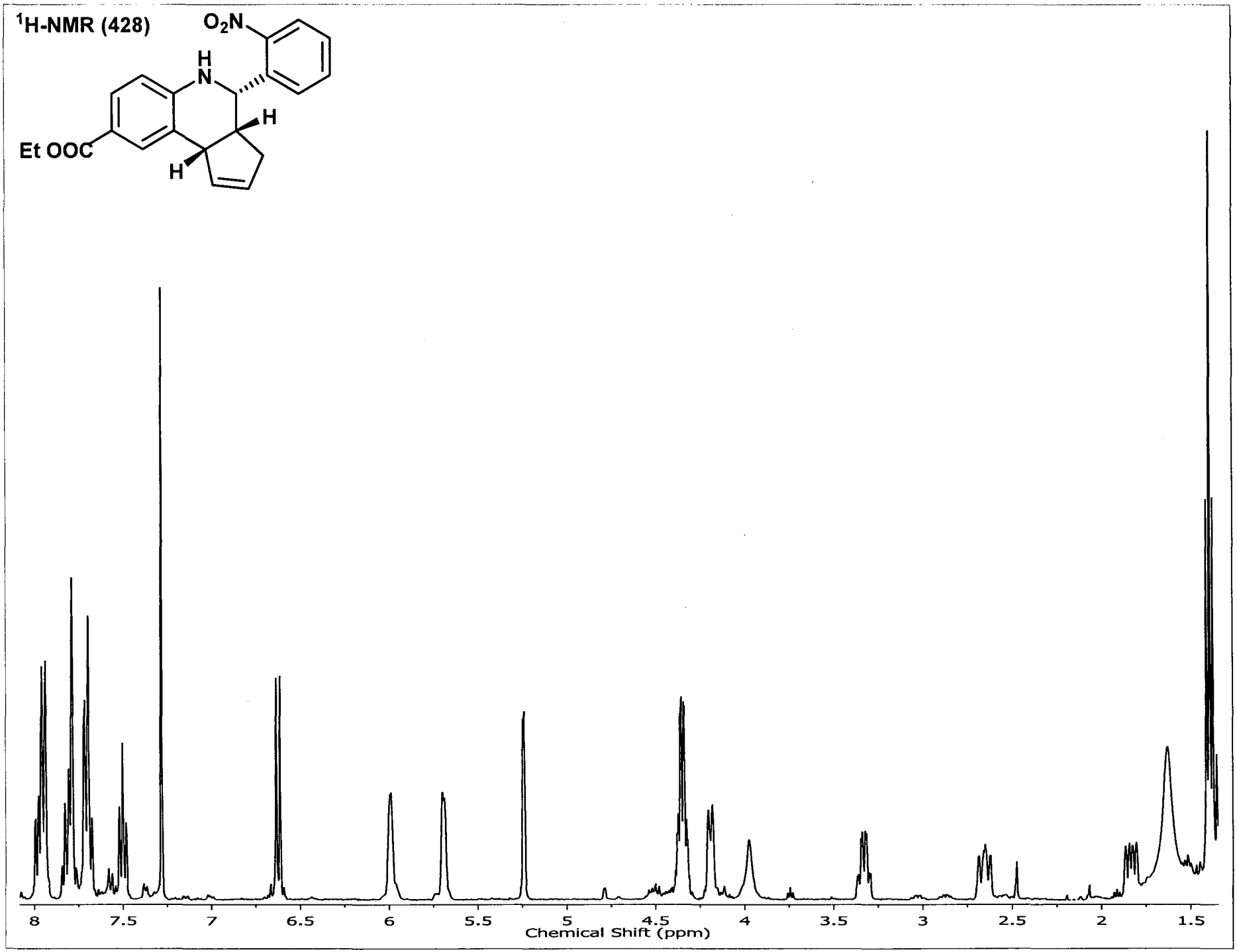

3.16
1.03
2.21
0.99
2.19
1.00
0.97
1.01
1.03
1.01
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Chemical Shift (ppm)

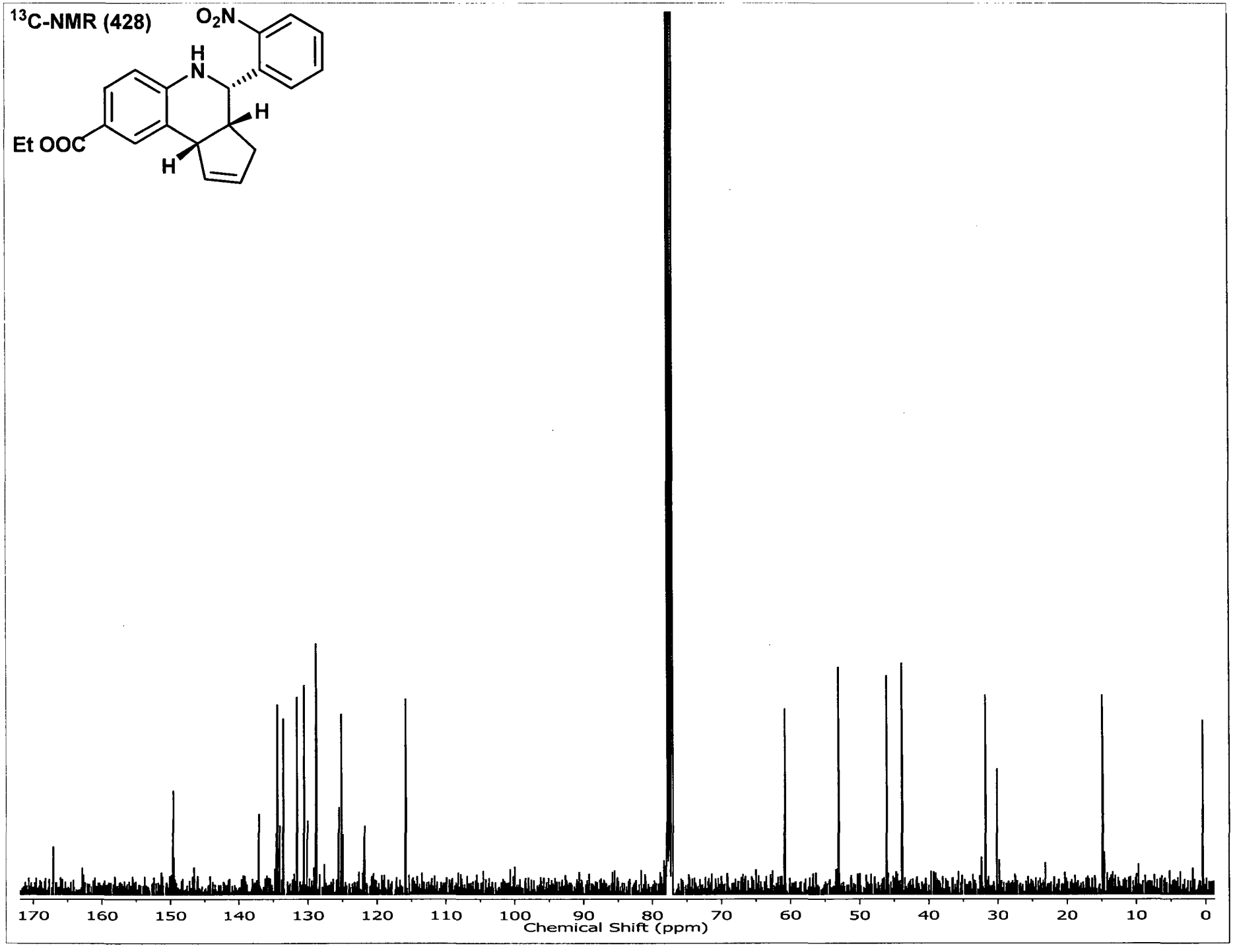
^{13}C-NMR

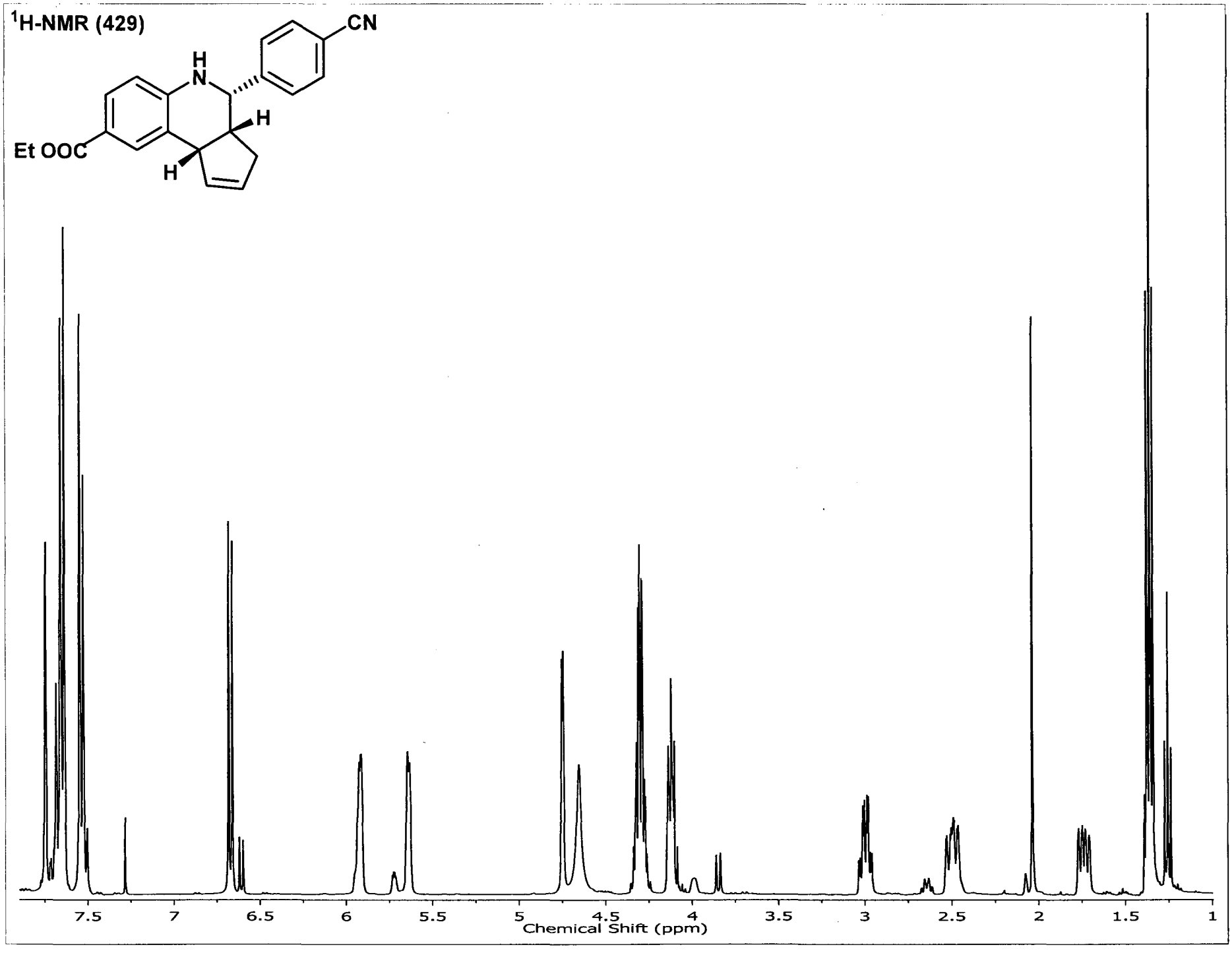
O
N
H
HO
OBz

(366)

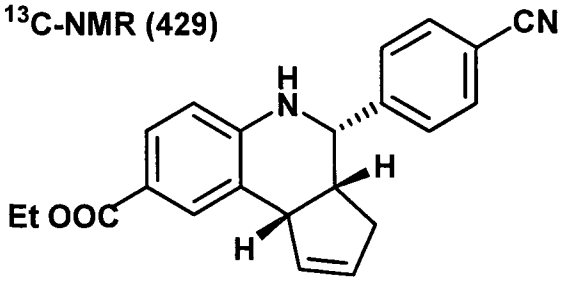

140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)

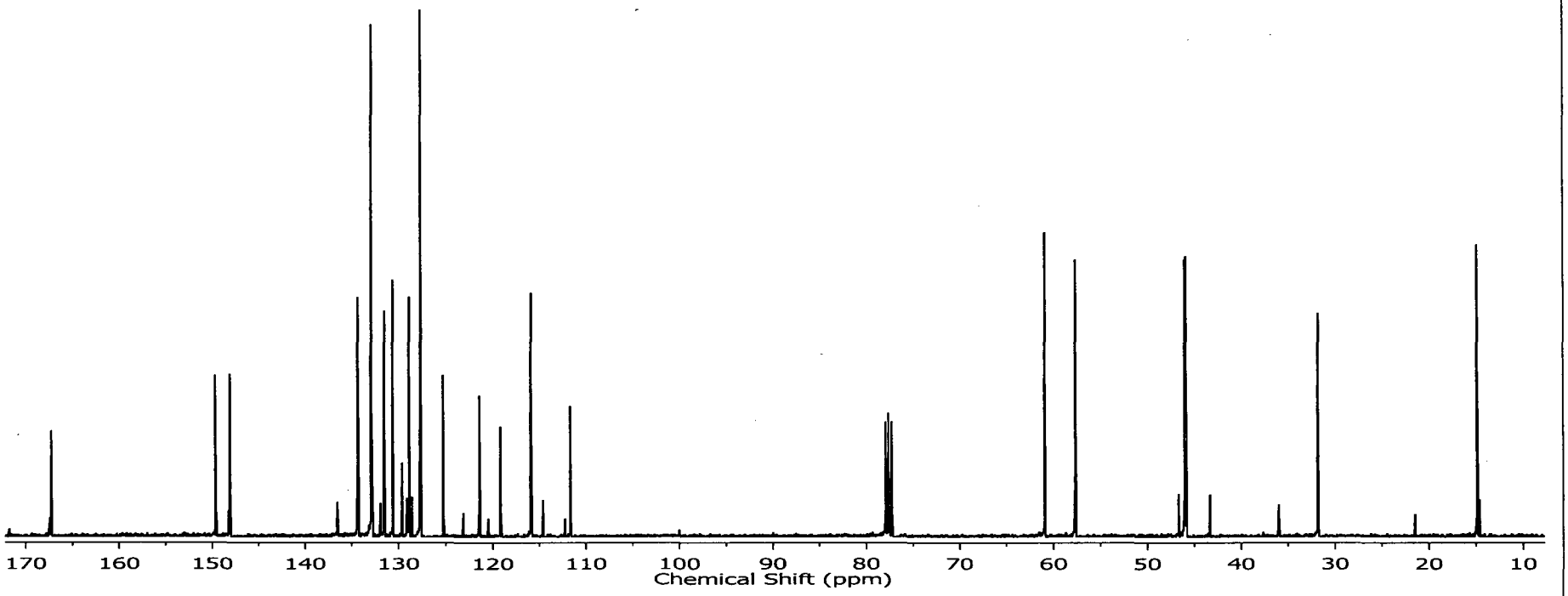

1H-NMR (428)
O2N
H
N
H
Et OOC
H
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
Chemical Shift (ppm)


13C-NMR (428)
O2N
H
N
H
H
Et OOC
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)


1H-NMR (429)
CN
H
N
H
Et OOC
H
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
Chemical Shift (ppm)

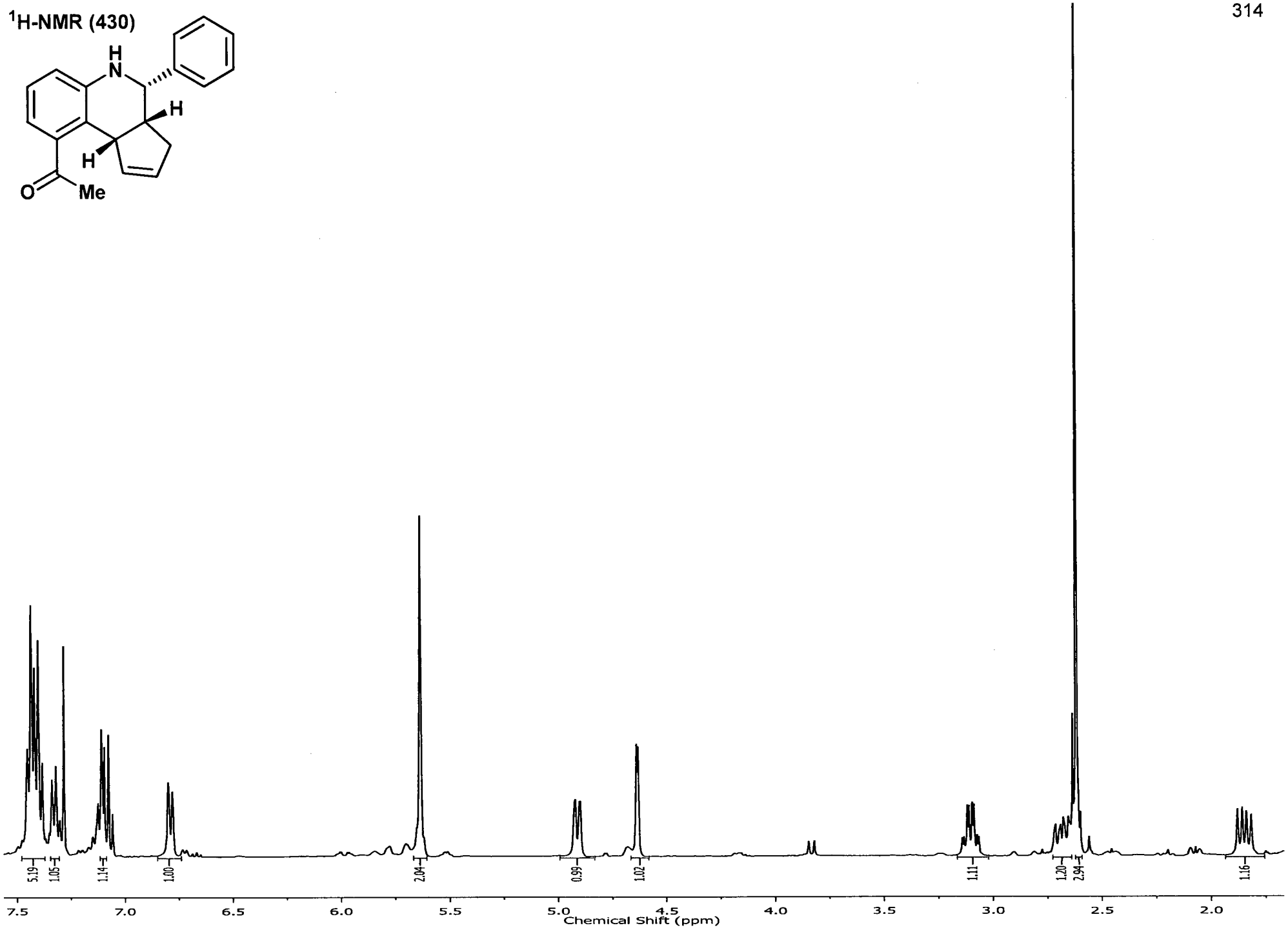
^{13}C-NMR (429)


CN
H
N
H
Et OOC
H

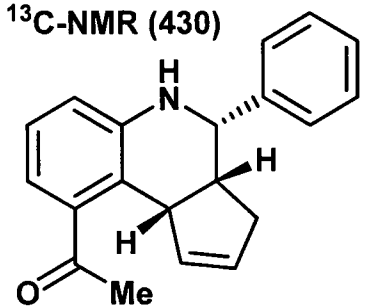

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

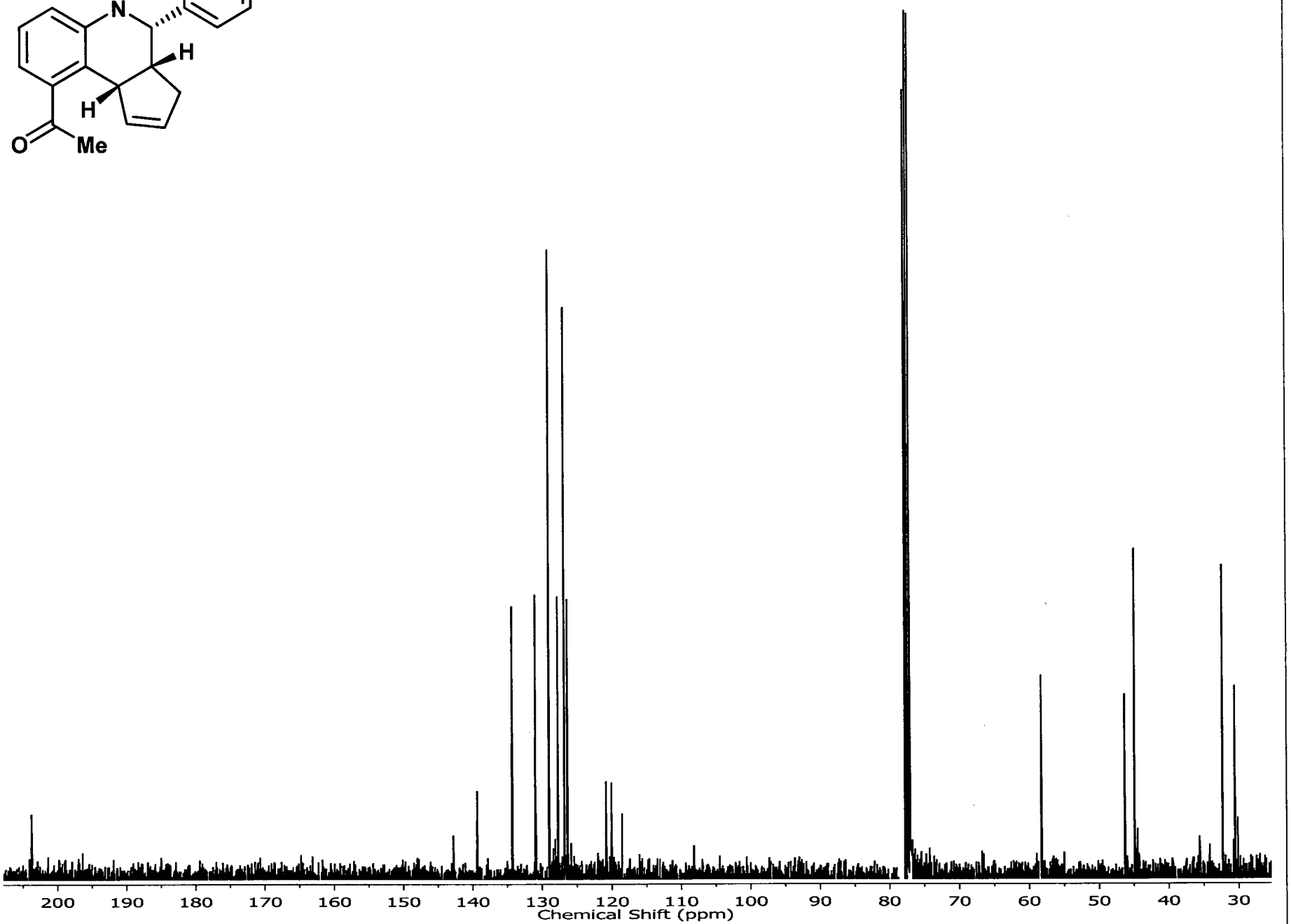
^{1}H-NMR (430)

H
N
H
H
O
Me

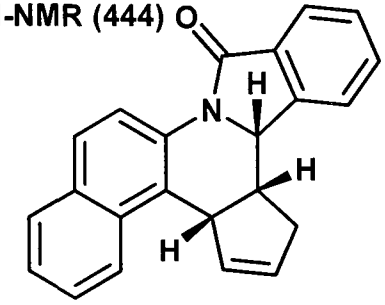

5.19
1.05
1.14
1.00
2.04
0.99
1.02
1.11
1.20
2.94
1.16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
Chemical Shift (ppm)

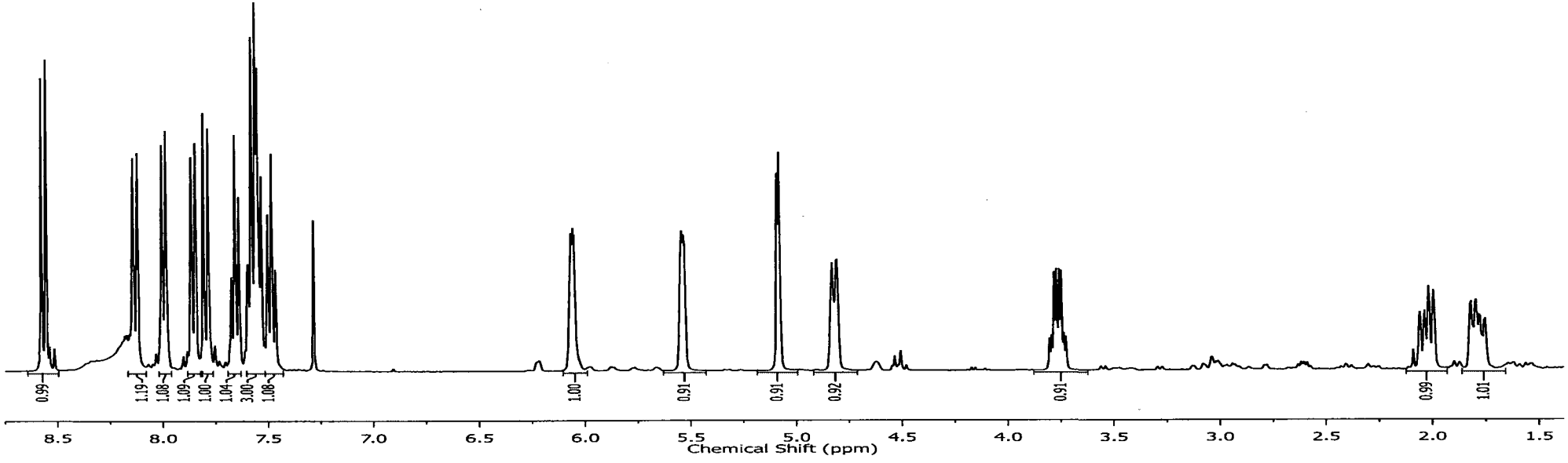
^{13}C-NMR (430)


H
N
H
H
O
Me

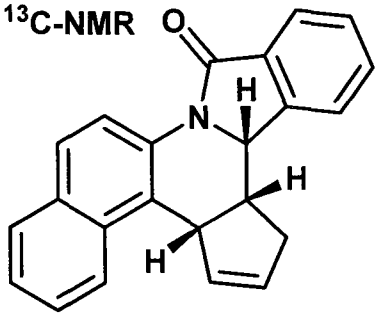

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
Chemical Shift (ppm)

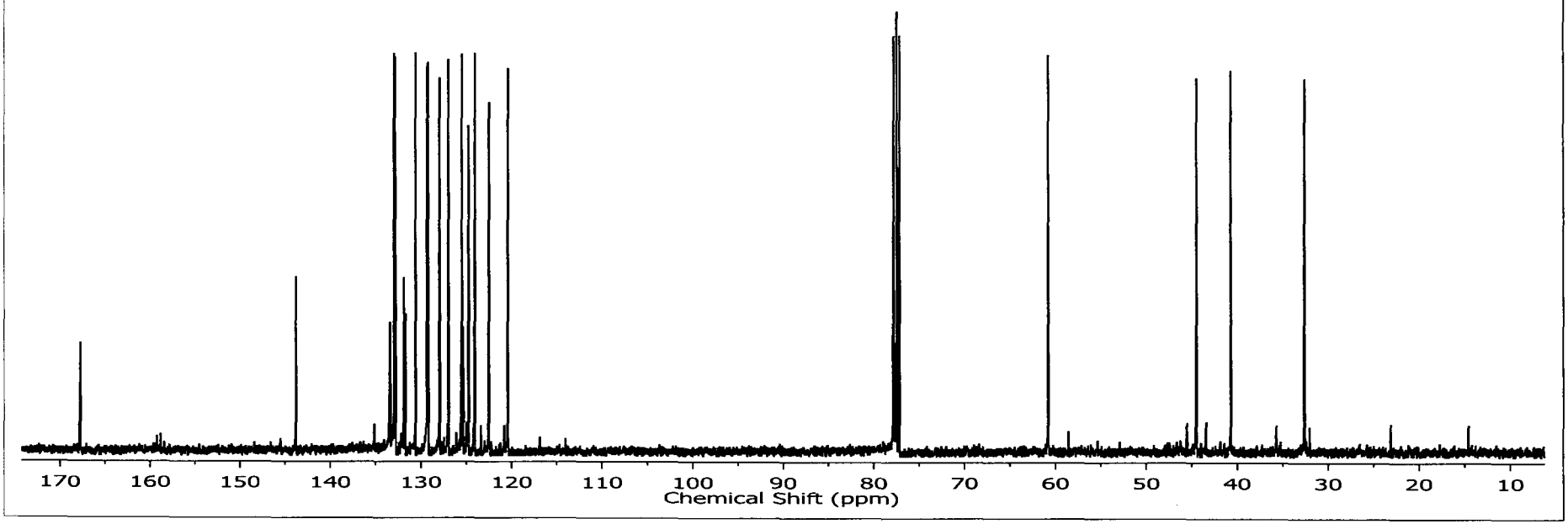
^{1}H-NMR (444)


O
N
H
H
H


0.99
1.19
1.08
1.09
1.00
1.04
3.00
1.08
1.00
0.91
0.91
0.92
0.91
0.99
1.01
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

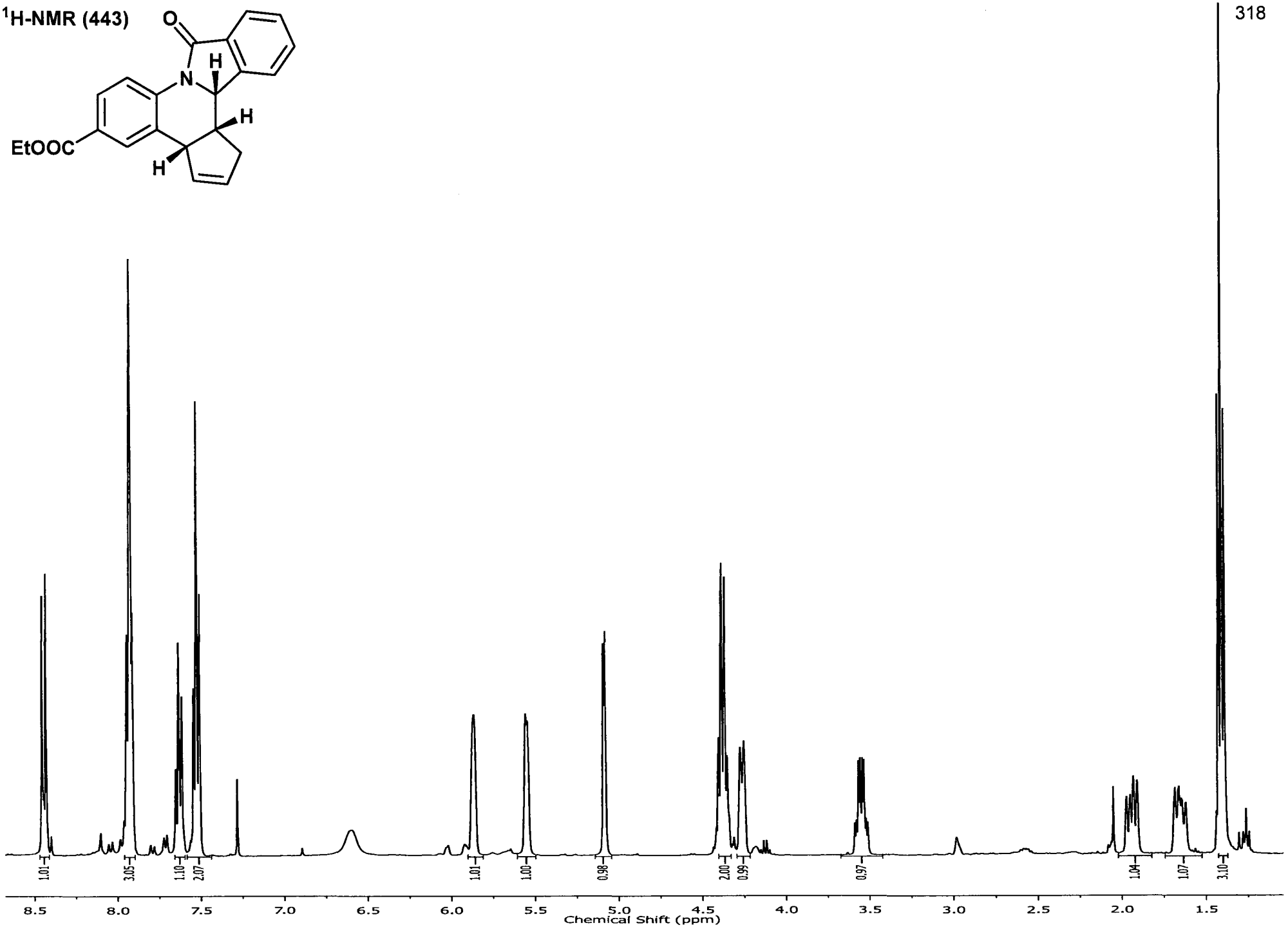
^{13}C-NMR (444)


O
N
H
H
H

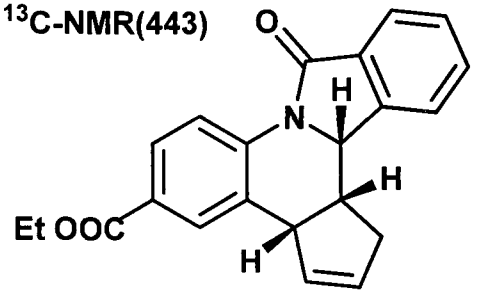

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

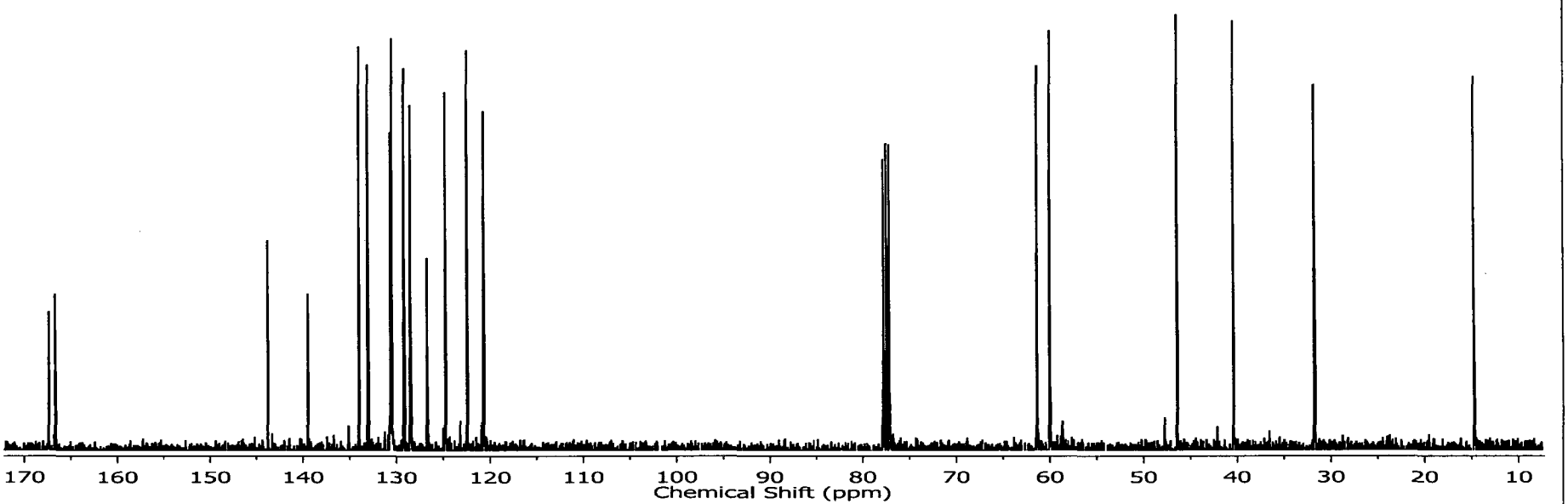
^{1}H-NMR (443)

O
N
H
H
H
EtOOC


1.01
3.05
1.10
2.07
1.01
1.00
0.98
2.00
0.99
0.97
1.04
1.07
3.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
Chemical Shift (ppm)

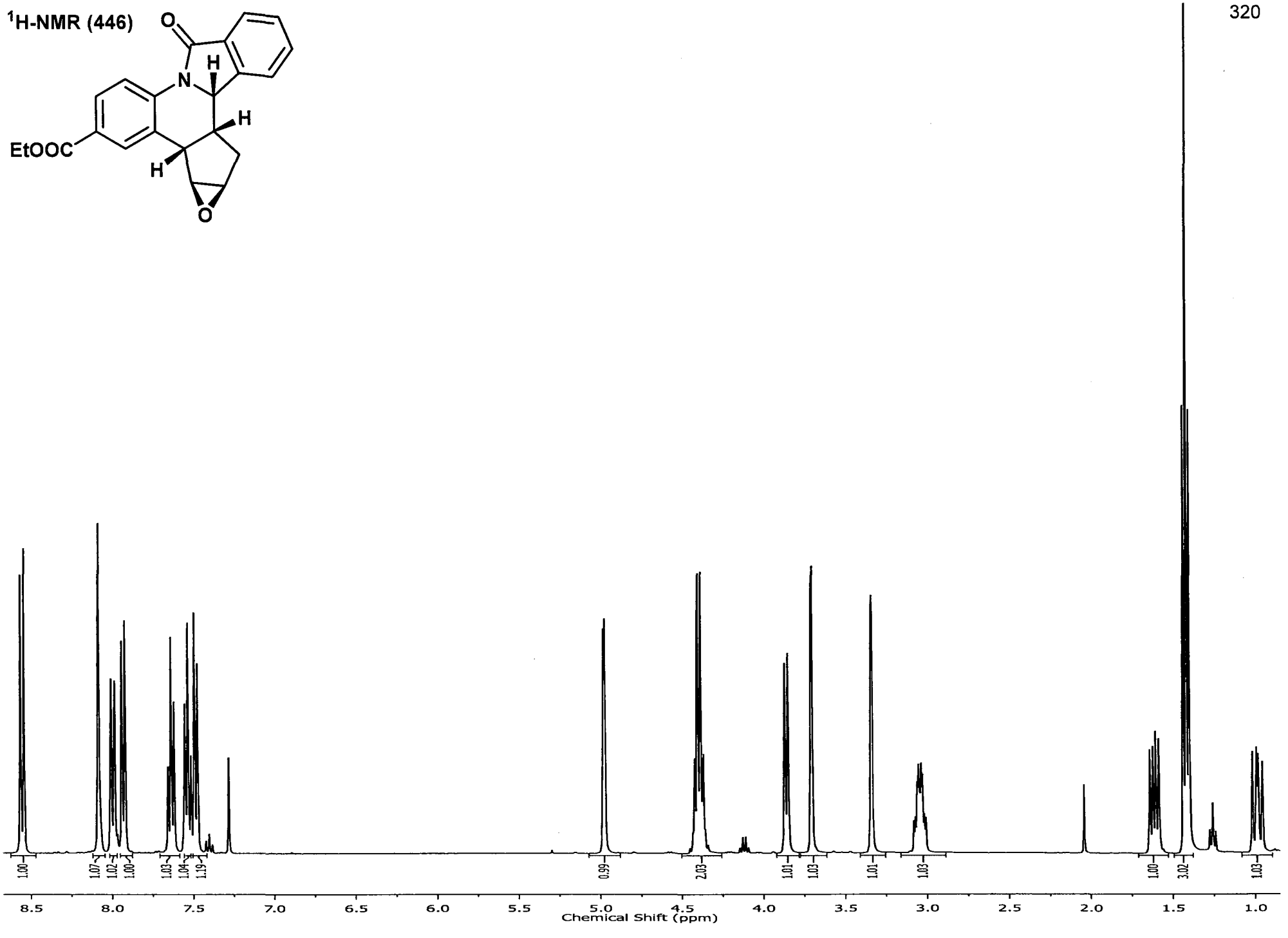
^{13}C-NMR(443)

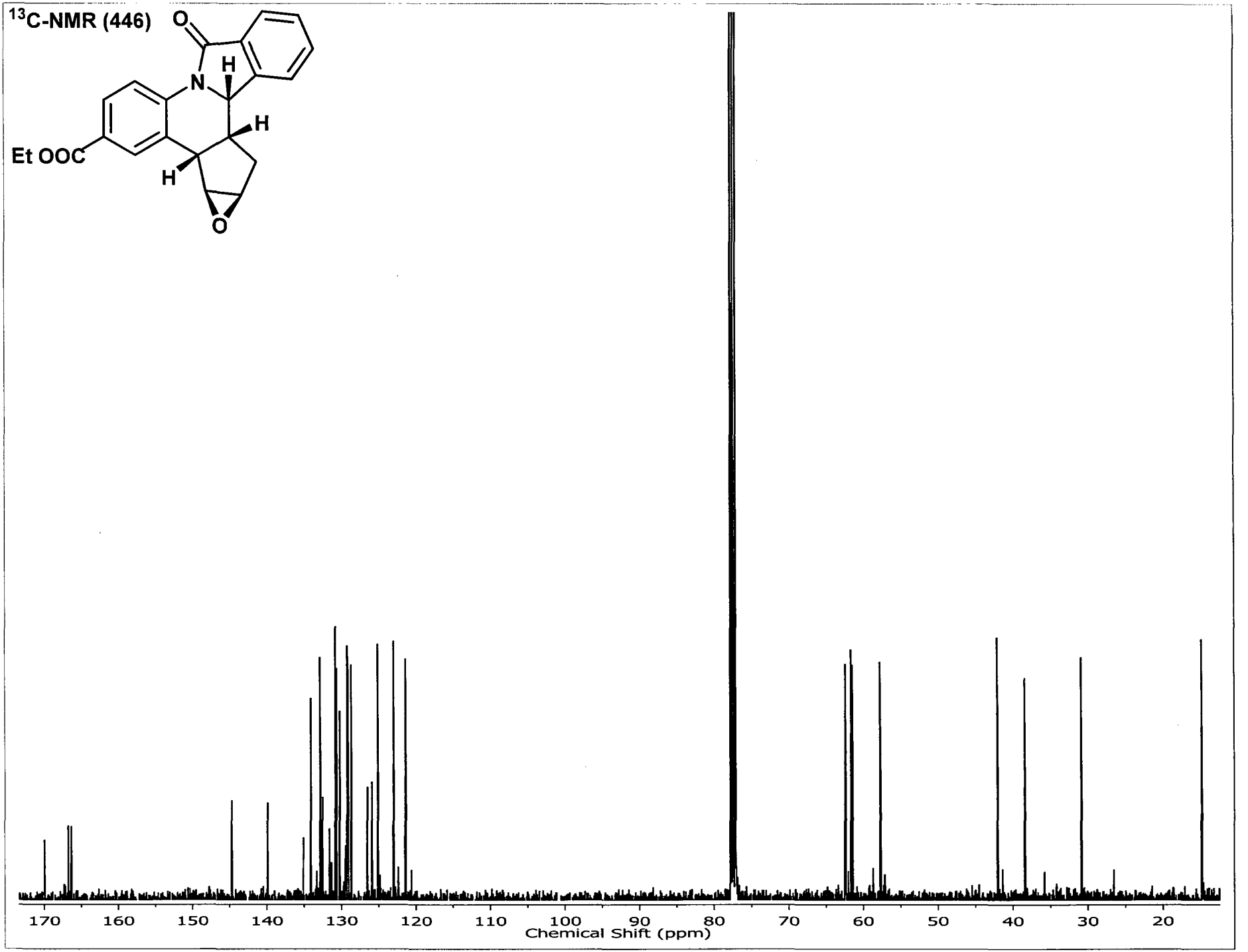

O
N
H
H
H
Et OOC

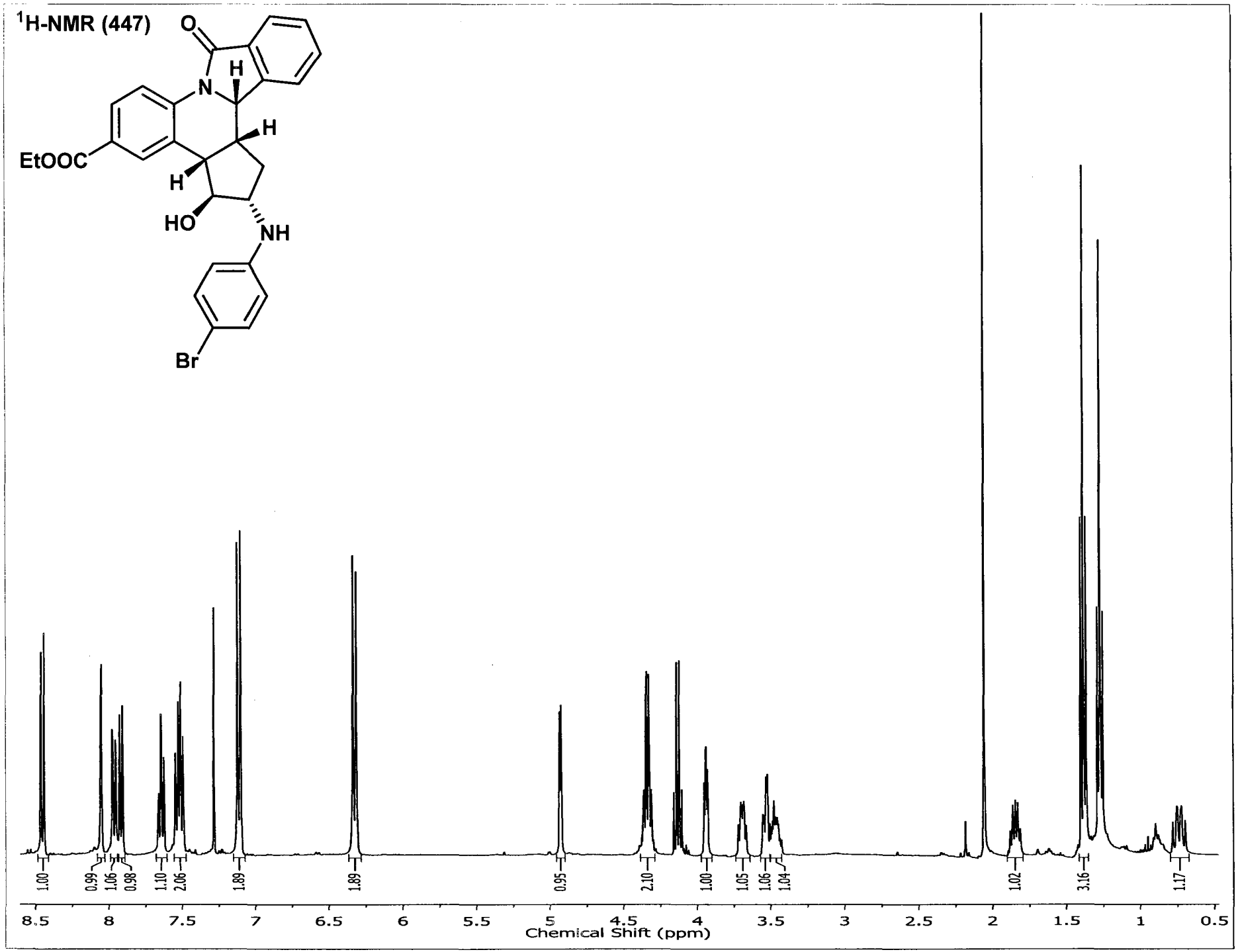

170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)

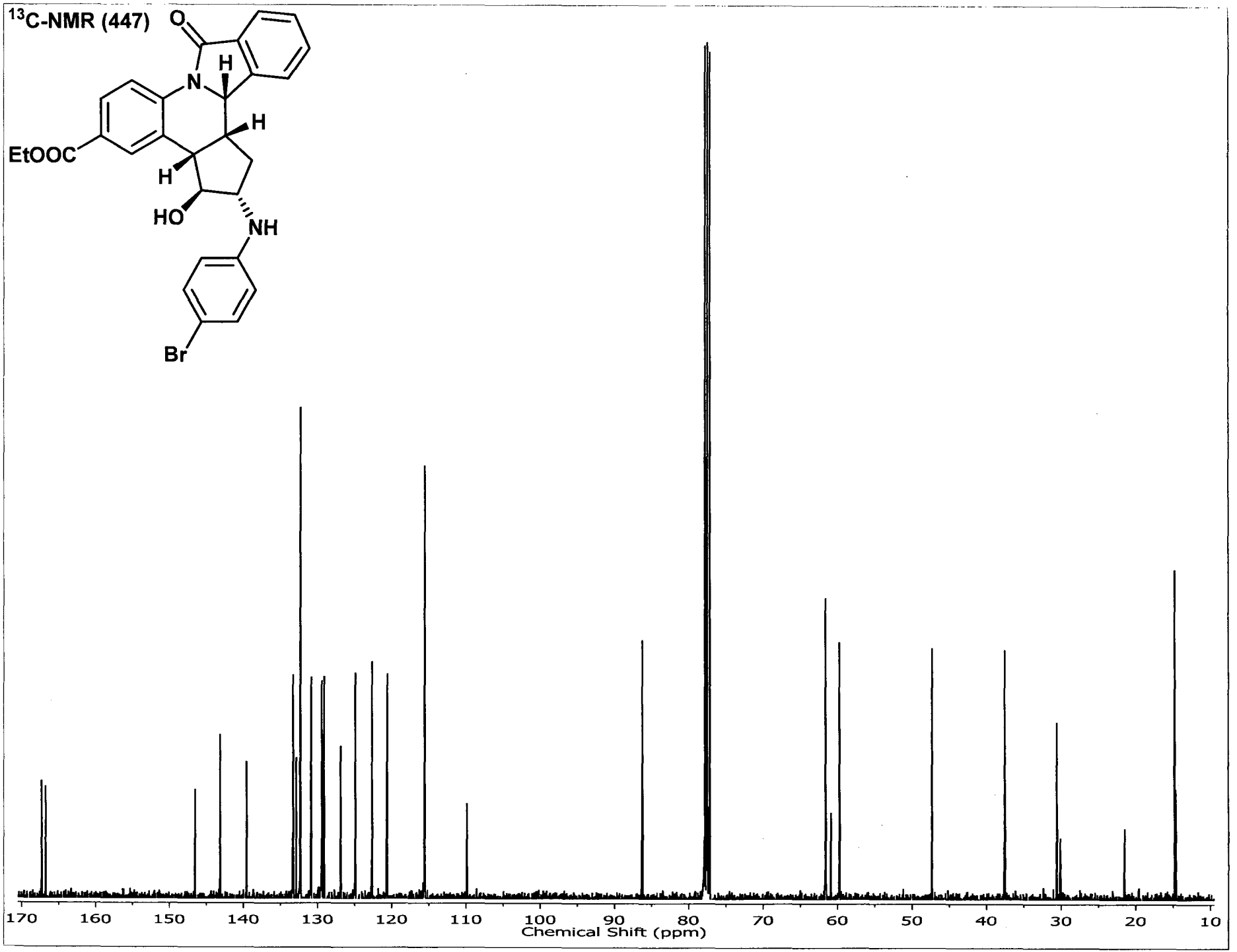
^{1}H-NMR (446)

O
N
H
H
EtOOC
H
O


1.00
1.07
1.02
1.00
1.03
1.04
1.19
0.99
2.03
1.01
1.03
1.01
1.03
1.00
3.02
1.03
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Chemical Shift (ppm)


13C-NMR (446)
O
N
H
H
H
Et OOC
O
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
Chemical Shift (ppm)


1H-NMR (447)
O
H
N
H
EtOOC
H
HO
NH
Br
1.00
0.99
1.06
0.98
1.10
2.06
1.89
1.89
0.95
2.10
1.00
1.05
1.06
1.04
1.02
3.16
1.17
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
Chemical Shift (ppm)


13C-NMR (447)
O
N
H
H
EtOOC
H
HO
NH
Br
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
Chemical Shift (ppm)