CYCLOPHANES, TRANSANNULAR INVERSE ELECTRON DEMAND DIELS-ALDER REACTIONS AND A FORMAL TOTAL SYNTHESIS OF (±)-STRYCHNINE

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by

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ABSTRACT

Chapter 1 overviews the relationship between cyclophanes and natural product synthesis. The ultimate objective of the present study is to seek a potential employment of cyclophane intermediates *en route* to complex natural product skeleta.

Chapter 2 describes the synthesis of 2,11-dithia[3.3]metacyclophanes bearing sulfur-containing groups at the 6 and 15 positions.

Chapter 3 details the synthesis of some (1,3)indolophanes and the analysis of their conformational behavior. Further study of the hydroboration/Suzuki-Miyaura strategy, as an expedient entry into [3.3]cyclophanes, is also reported.

Chapter 4 presents a synthesis of an indolopyridazinophane, relying on the hydroboration/Suzuki-Miayura strategy. The subsequent transannular inverse electron demand Diels-Alder (IEDDA) reaction of the resulting cyclophane has established efficient access to a highly compact pentacyclic indoloid skeleton.

Chapter 5 demonstrates a formal total synthesis of (±)-strychnine, one of the most complex natural products for its size, by preparing Rawal's key pentacyclic intermediate *via* the cyclophane approach.

ACKNOWLEDGEMENTS

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LIST OF SYMBOLS AND ABBREVIATIONS

Δ	heat
9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
Bn	benzyl
Boc	*t*-butoxycarbonyl
BOP	benzotriazolyl *N*-oxytrisdimethylaminophosphonium hexafluorophosphate
BOP-Cl	*N,N*-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride
bp	boiling point
BTAP	benzyltriethylammonium permanganate
Cbz	benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DIEA	diisopropylethylamine
DMDHPs	10b,10c-dimethyl-10b,10c-dihydropyrenes
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

DNMR	dynamic nuclear magnetic resonance
DPPA	diphenylphosphoryl azide
dppf	bis(diphenylphosphino)ferrocene
EA	electron affinity
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
EDG	electron donating group
ee	enantiomeric excess
ENDOR	electron nuclear double resonance
ESR	electron spin resonance
Et	ethyl
Et_3N	triethyl amine
EtOAc	ethyl acetate
eV	electron volt
EWG	electron withdrawing group
FDA	Food and Drug Administration
FMO	frontier molecular orbital
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple-quantum coherence
HOMO	highest occupied molecular orbital
HREIMS	high resolution electron impact mass spectroscopy
HRMS	high resolution mass spectroscopy
HSAB	hard and soft acids and bases

hv	light
IBX	2-iodoxybenzoic acid
IEDDA	inverse electron demand Diels-Alder
IP	ionization potential
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
LUMO	lowest unoccupied molecular orbital
m-CPBA	*meta*-chloroperoxybenzoic acid
M.p.	melting point
Me	methyl
MPLC	medium pressure liquid chromatography
MS	mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement
PAHs	polycyclic aromatic hydrocarbons
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PE	photoelectron
Piv	pivaloyl
PNA	peptide nucleic acid
RCM	ring closing metathesis

rt	room temperature
TADA	transannular Diels-Alder
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
T_c	coalescence temperature
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPB	1,3,5-triisopropylbenzene
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSE	trimethylsilylethyl
TNF α	tumor necrosis factor α
TosMIC	(*p*-tolylsulfonyl)methyl isocyanide
UV	ultraviolet
VID	valence isomerization-dehydrogenation
VTNMR	variable temperature nuclear magnetic resonance

To my parents, my wife Bilan and my daughter Felicia

CHAPTER 1 Introduction

1.1 Total Synthesis

1.1.1 Organic Synthesis

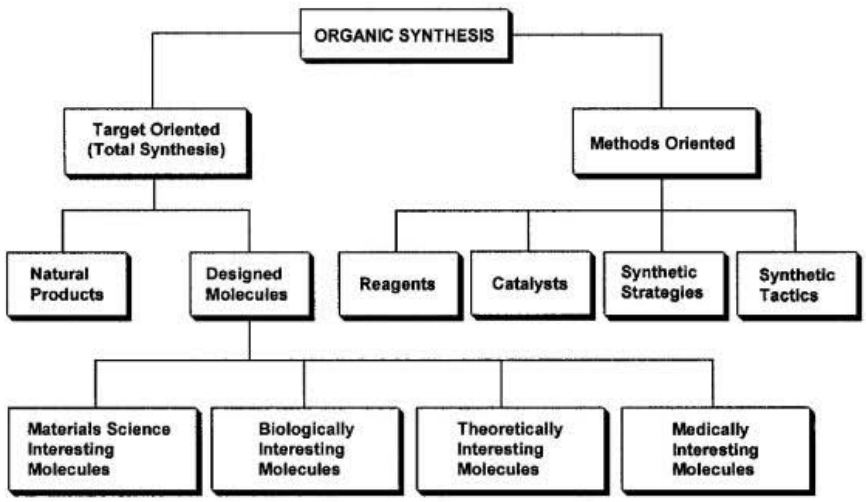

Figure 1.1 Organic synthesis in perspective (Adapted from ref. 1).

"Synthesis" (from the Greek word *synthesis* "to put together") is the process of combining different ideas, influences, or objects into a new whole. As a scientific discipline, synthetic chemistry is the science of assembling more complex molecules through a series of one or more chemical reactions starting from simpler molecules. This discipline can be classified, according to the molecules involved, into synthetic organic chemistry (often used as organic synthesis) and synthetic inorganic chemistry. As suggested by Nicolaou, organic

synthesis can be further divided into two major areas (Figure 1.1), namely target-oriented synthesis (or most commonly termed total synthesis) and methods-oriented synthesis, with some subdivisions.[1] To Woodward,[2] organic synthesis is a great art filled with excitement, adventure and challenge. To Corey,[3] organic synthesis is not only logic and strategy, but also a journey full of speculation, imagination and creation. It is their theories and practices, along with many others' brilliant contributions, that drive organic synthesis as healthily and vigorously as ever and continue to impose beneficial impact on other disciplines, including biology, physics, materials science and medicine.[4]

1.1.2 Total Synthesis

As the flagship of organic synthesis, total synthesis commences with the selection of a target molecule. Depending on the needs and interests of the synthetic chemist, different criteria such as structural verification, biological activity, analog studies, topological studies and the development of new reactions or reagents, are used for selecting target molecules.[5] According to the target molecules pursued, synthetic chemists fall into two groups: those who synthesize old,* naturally occurring compounds and those who prepare new, designed molecules.

Natural products have been continuously fascinating synthetic organic chemists since the birth of total synthesis, marked by Wöhler's rational synthesis

of urea in 1828.[6] The emergence and improvement of powerful purification and analytical techniques, especially column chromatography and nuclear magnetic resonance (NMR) spectroscopy, lead to the discovery of more natural products with ever lower natural abundance and increasing molecular complexity. This, in turn, triggers the desire of synthetic organic chemists to "conquer" them by chemical methods. Work towards the synthesis of natural products provides excellent opportunities for the development of new synthetic strategies.

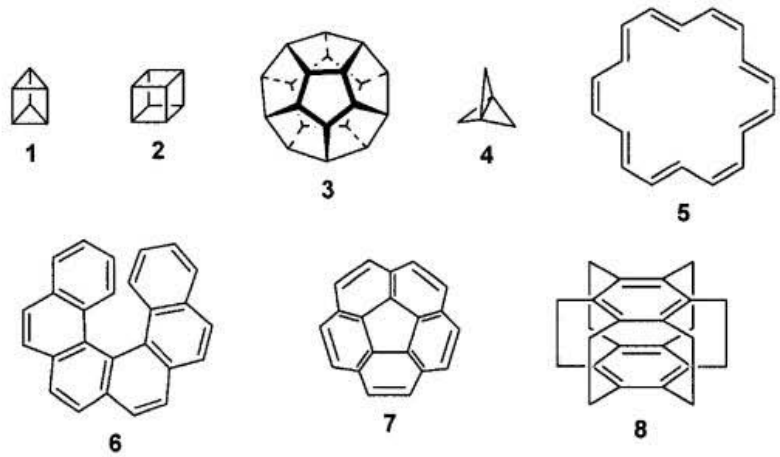

Figure 1.2 Selected designed molecules of theoretical interest.

Creativity is an essential quality for those who aspire to practice total synthesis. On the basis of bonding theories and other structural principles, an organic chemist is free to imagine and design unlimited numbers of new molecules. These designed molecules become potential targets for the second group of synthetic organic chemists. Famous examples of designed molecules of

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* Term "old" indicates their everlasting existence regardless of when they were found.

theoretical interest that have been successfully synthesized are: [3]prismane **1**,[7] cubane **2**,[8,9] dodecahedrane **3**,[10] [1.1.1]propellane **4**,[11] [18]annulene **5**,[12] [6]helicene **6**,[13] corannulene **7**,[14-16] superphane **8**[17] (Figure 1.2) and many other aesthetically pleasing molecular constructs.[18] A theoretically interesting molecule often presents formidable synthetic challenges, which demand a novel synthetic strategy to accomplish its synthesis. Consequently, such a synthesis often pushes back the limits of known chemistry for making carbon-carbon bonds and provides insight into structure, bonding, or fundamental chemical properties of organic compounds.

1.1.3 Relationship between Natural Products and Designed Molecules

As shown in Figure 1.1, target-oriented synthesis can be divided into natural product synthesis and designed molecule synthesis. They seem to be two independent subdisciplines in the field of total synthesis, and some people believe that they have nothing to do with each other. Apparently, this is a misconception, and the truth is that there is an inherent connection between these two areas. From a philosophical point of view, existence determines consciousness whereas consciousness affects existence. Similarly, natural product synthesis is closely related to designed molecule synthesis simply because of the fact that natural products are existing substances and designed molecules are targets created by imagination.

The most fertile area of molecular design is that of biologically interesting molecules. The efficiency of biological systems and the potential for medicinal breakthroughs has prompted a brand new research area in academia and in the pharmaceutical industry, which is continuously fueled by the isolation and structural elucidation of novel biologically active natural products.[19] Frequently, new molecules are designed on the basis of either the structures of biologically active natural products or the mechanisms of ligand-receptor binding in living systems.[20,21] The interplay of molecular design, chemical synthesis and biological evaluation is a powerful multidisciplinary approach to research at the chemistry-biology interface and to drug discovery and development. A beautiful example is the invention of a deoxyribonucleic acid (DNA) mimic, peptide nucleic acid (PNA) (Figure 1.3). Since the elucidation of the double helical structure of DNA, the genetic material, the properties of this remarkable molecule have fascinated chemists, and tremendous efforts have been devoted to understanding its structure and function in the body. Part of the life secret is nucleobase molecular complementarity, which guarantees the storage, transfer and expression of genetic information in living systems. The highly specific recognition through the natural pairing of the nucleobases has become increasingly important in genetic diagnostics and gene therapeutic medicine. Attempts to optimize the properties of DNA have resulted in the synthesis and analysis a huge variety of new DNA derivatives with modifications to the phosphate group, the ribose, or the nucleobases.[22] The most successful change to

the natural structure, however, was made by Nielsen, Egholm, Berg and Buchardt in 1991.[23] PNA was originally designed as a DNA mimic by computer-aided molecular modeling based on the structures of DNA and protein. However, the *N*-(2-aminoethyl)glycine-based pseudopeptide backbone of PNA (Figure 1.3) has proven to be a surprisingly good structural mimic of DNA backbone. Extraordinarily, PNAs bind with higher affinity to complementary DNA than their natural counterparts.[24] Since its discovery, PNA has attracted widespread attention in genetic diagnostics, the development of gene therapeutic drugs, molecular recognition studies and even hypotheses regarding the origin of life.[25-27]

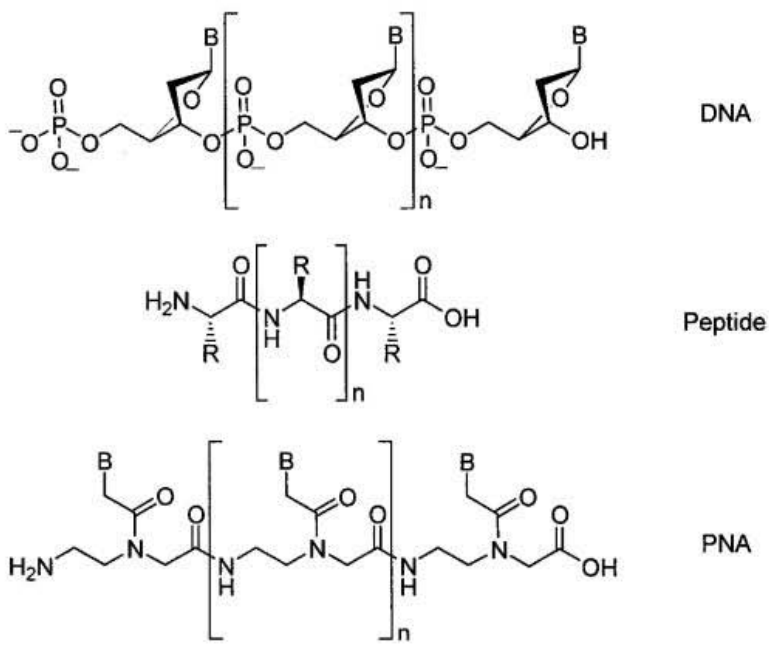


Figure 1.3 Structural comparison of DNA, peptide and PNA.

On the other hand, natural products are also involved in the synthesis of designed molecules as starting materials in cases when they are considered as excellent skeletal sources for the targets. Naturally occurring amino acids are used as major building blocks in the synthesis of designed peptides.[28] Natural products also play a crucial role in the synthesis of theoretically interesting molecules (Figure 1.4). Indene was used as the starting material in the synthesis of isonaphthalene **9**.[29] Dewar benzene **10** was first prepared from phthalic acid.[30] The first synthesis of corannulene **7** (Figure 1.2) began with the natural product acenaphthene.[14] *m*-Xylene found itself many times as starting material in designed molecule synthesis, including [8]metacyclophane **11**,[31] coronene **12**[32] and kekulene **13**.[33] In two of the syntheses of triptycene **14**, anthracene, a natural product, provide the major skeleton.[34,35] Ample natural sources of the above-mentioned starting materials, to a great extent, shortened and ensured the successful synthesis of designed targets.

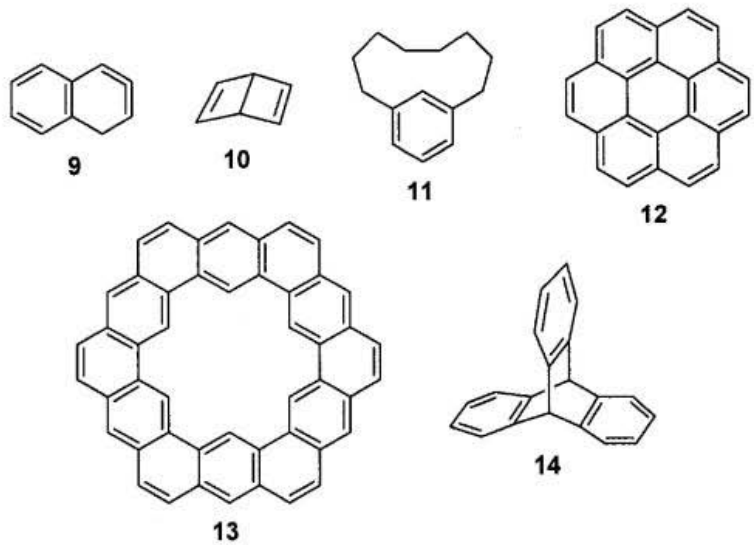


Figure 1.4 Selected designed molecules with natural products as starting materials.

In very few occasions, human beings' imagination is beyond the scope of natural products. The most astonishing example is the prediction of C_{60} **15**, the first fullerene[36-42] (Figure 1.5). Historically, mankind has long had a spiritual affinity with abstract symmetry and an aesthetic fascination for symmetric objects, as evidenced by the stone artifacts with the form of the platonic solids found in Scotland.[43] The first striking property of the C_{60} molecule is its high symmetry. There are 120 symmetry operations, which makes C_{60} one of the most symmetric molecules known. C_{60} was first suggested in 1966 by Jones as a large hollow carbon cage.[37] Soon after that, C_{60} was predicted again by Osawa in 1970[38] and 1971,[39] respectively. Later papers reported Hückel calculation on C_{60} in 1973[40] and 1981.[41] Haymet's study[42] on this molecule coincided very closely with its discovery in 1985 by Kroto, Heath, O'Brien, Curl and Smalley.[44] The

group was actually trying to understand the absorption spectra of interstellar dust which they suspected to be related to some kind of long-chained carbon molecule. Even though that problem was not solved, they accidentally discovered the buckyball C_{60}, which won Curl, Kroto and Smalley the 1996 Nobel prize in chemistry. The C_{60} molecule was named "buckminsterfullerene" after the American architect Richard Buckminster Fuller, who was renowned for his geodesic domes,[45] since the shape of the molecule, a truncated icosahedron, resembles such domes.[44] Not too long ago, graphite and diamond were the only two known modifications (allotropes) of carbon, and their technological importance is enormous.[46] That changed dramatically with the discovery of C_{60}, the third carbon allotrope, and the higher fullerenes soon thereafter.[47] It took ten years before the imaginative theoretical conjectures of Osawa and Yoshida,[38,39,39] and Bochvar and Gal'pern[40] were realized in the discovery of C_{60} in 1985.[44] It took even longer for people to believe that C_{60} is present on earth[48] and might likely exist astrophysically as well.[36] The fact that C_{60} was a designed molecule until it was found occurring naturally indicates that it is not impossible to imagine an existing object before its discovery, even though imagination is normally based on reality.

15

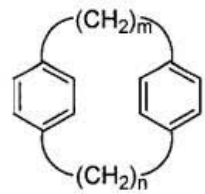
Figure 1.5 Structure of buckminsterfullerene C_{60}.

1.2 Cyclophanes

1.2.1 Origin of Cyclophane Concept

Amongst various designed synthetic targets, cyclophanes have been one of the most influential classes of compounds for several decades in terms of theoretical aspects, synthetic challenges and practical applications.[18,49-52] Interest in cyclophanes originated in 1945[53] and 1946[54] with Dewar's ideas about the possible existence of π complexes as intermediate species in reactions such as the benzidine rearrangement. The rearrangement was thought to involve monoprotonated benzidine as the starting state. The resulting π complexes were presumed to be a molecular sandwich held together by attraction between face-to-face, partially anionic, partially cationic π systems whose rotations and decompositions to the covalent states explained the semidine and benzidine products.[53,54] To seek possible experimental evidence for the hypothesis, Cram assumed that compounds in which two benzene rings are held face-to-face by methylene bridges substituted in their *para* positions would provide mechanistic insight, which prompted them to synthesize a series of [*m.n*]paracyclphanes **16a-c** (Figure 1.6) in 1951.[55] Actually, [2.2]paracyclophane **16a** had been obtained

and partially characterized as trace amounts of by-product in an attempted polymerization of *p*-xylylene by a polymer research group[56] before Cram's rational synthesis. Since then, cyclophane chemistry has become a fast growing research field, and a vast amount of knowledge about their physical, chemical and other properties has been obtained. [18,49-52]



16a (m=2, n=2)
16b (m=2, n=3)
16c (m=2, n=4)

Figure 1.6 Structures of [*m,n*]paracyclophanes **16a-c**.

1.2.2 Definitions and Nomenclatures

The term "cyclophane", coined by Cram in 1951[55] when he published the synthesis of several [*m.n*]paracyclophanes **16a-c** (Figure 1.6) as a trivial class name for such a new type of compounds, can be broken into three parts: *cycl*ic, *ph*enyl and alk*ane*, to express their most characteristic features. Smith defined "cyclophane" as bridged aromatic compounds in the first monograph[57] in this area, which meant bridged arenes in general, while Vögtle and Neumann later suggested reserving this term specifically for bridged benzenes.[58] They introduced the general term "phanes" for what were used to be called cyclophanes. More recently, the International Union of Pure and Applied Chemistry (IUPAC) nomenclature of organic compounds[59] extended the

definition of "cyclophanes" to cyclic systems consisting of mancude*-ring(s), which designates ring(s) formally having the maximum number of noncumulative double bonds, or assemblies of mancude-ring system(s) connected by saturated and/or unsaturated chains.[59] In this thesis, the more accepted term "cyclophanes" is taken to describe those compounds that fall under Smith's definition.[57]

After Cram introduced the term "cyclophane" as a class name in 1951,[55] Schubert suggested a specific nomenclature in 1954,[60] and Cram adopted it thereafter.[61] In 1970, Vögtle developed a more systematic nomenclature,[62] which is now generally accepted. Associated with its definition, IUPAC Recommendations 1998 suggested a totally distinct method, namely "phane nomenclature", to describe "cyclophanes".[63] It is based on the idea that a relatively simple skeleton for a parent hydride can be modified by an operation called "amplification", a process that replaces one or more superatoms of a simplified skeleton by multiatomic structures. In this thesis, all the cyclophane names are derived from Vögtle rules.[62] For a detailed interpretation in English from Vögtle's original version in German, the Ph.D. dissertation by Dr. Vermeij, a previous Bodwell group member, should be consulted.[64]

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* Rings having the maximum number of noncumulative double bonds are termed mancude.

1.2.3 Major Interests

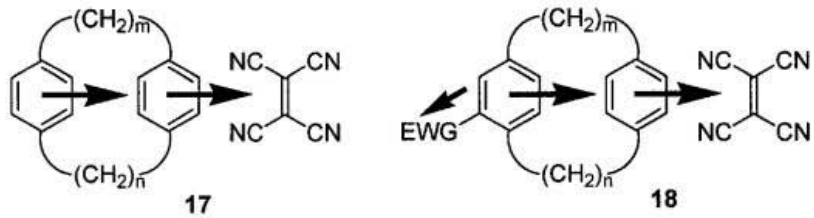
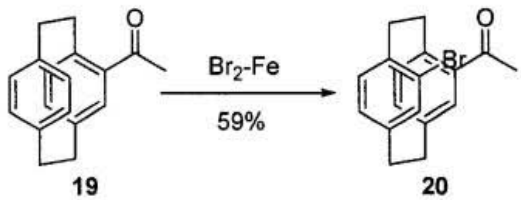


Figure 1.7 Transannular electron effects in π-π complexes.

Cyclophanes, especially small cyclophanes, have been the subjects of broad interest for several decades, largely because of their unusual properties.[18,49-52] One of the earliest studied features was transannular electronic interaction's between parallel benzene nuclei in cyclophanes containing two or more benzene rings.[65] These transannular electronic effects are apparent in the π-π complexes between the homologous π-base [*m.n*]paracyclophanes and the π-acid tetracyanoethylene (Figure 1.7).[66] Except for the position of [2.2]paracyclophane, in this series, the order of π-base strengths correlates with the distance between the two benzene rings. The closer the two rings, the greater the π-base strength becomes, as in **17**. As expected, electron-withdrawing groups in the noncomplexed ring decreased the π basicity of the complexed ring as in **18**. The homologous series of π complexes provided a rainbow-like series of colors, ranging from yellow to deep purple, which supplied a visible example of transannular electronic effects. With the facilitation of more advanced analytical techniques, including photoelectron (PE) spectroscopy,[67] electron spin resonance (ESR) spectroscopy,[68] electron nuclear double resonance (ENDOR)

spectroscopy,[68] and absorption spectroscopy,[69] the studies of transannular electronic effects have been applied to more complex cyclophane systems.



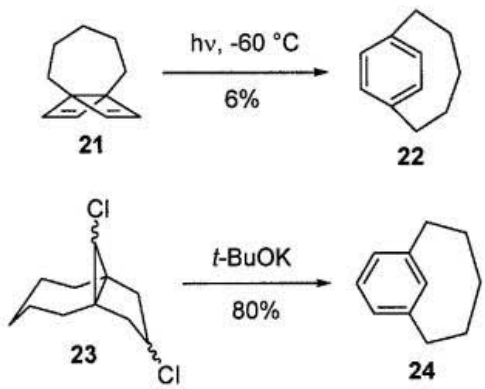
19 20

Scheme 1.1 Transannular directive effects in bromination of **19**.

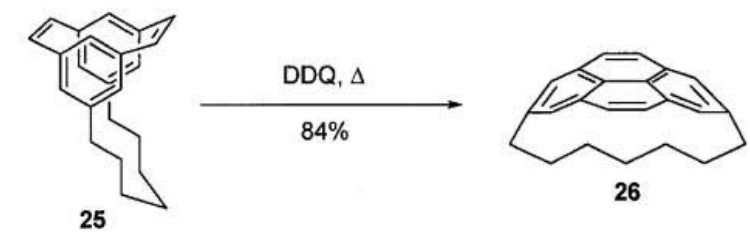
Transannular electronic effects are also demonstrated as directive influences in electrophilic substitution reactions of [2.2]paracyclophanes.[70] Extensive studies have demonstrated that typical electrophilic substitution reactions such as bromination, nitration and Friedel-Crafts acylation readily occur. However, in contrast to the usual electrophilic substitution of arenes, where formation of the σ-intermediate is the slow step, loss of a proton from the σ-intermediate is generally the slow step in electronic substitution of [2.2]paracyclophanes.[71] As evidenced by isotope labeling experiments, the aromatic π-electron cloud of the opposite deck can serve as an internal base. In monosubstituted [2.2]paracyclophanes, a generalization emerged that predominant substitution occurred *pseudo-gem* to the most basic positions or substituents in the already substituted ring, whereas in the absence of such a basic substituent, the orientation of the incoming electrophile is largely random. A typical example is shown in Scheme 1.1. *Pseudo-gem* product **20** was the sole product in bromination of **19**.

As the structural theory of organic chemistry has matured, more investigations have been directed toward defining its boundaries. Organic chemists are excited about predicting and synthesizing internally tortured molecules with "suicidal tendencies" that skirt a line between isolability and self-destruction. Small cyclophanes provide a fine vehicle for study because both aromaticity, which generally implies greater stability,[72] and strain, which normally implies lower stability,[73] are incorporated into them as distinct, but competing, characteristics. Therefore, the question, "how bent can an aromatic ring be?", represents a challenge in molecular design and synthesis. Both [*n*]paracyclophanes and [*n*]metacyclophanes are very well suited for study of the consequence of benzene ring deformation. Obviously, the amount of ring bending will depend on the length of the polymethylene bridge. Intramolecular ring closure methods, such as acyloin cyclization,[74] Friedel-Crafts acylation[75] and Eglinton oxidative coupling[76] for synthesis of [*n*]paracyclophanes, and intermolecular coupling methods, such as Ni-catalyzed cross-coupling of Grignard reagents with aryl dihalides,[77] for synthesis of [*n*]metacyclophanes, have been quite successful. However, new approaches had to be developed to synthesize the lower homologs ($n \leq 8$) because for these strained systems oligomerization predominates over the desired cyclophane (monomer) formation.[78] In principle the increasing strain can be overcome either by the generation of high-energy intermediates (carbenes, radicals) or by the preparation of energy-rich starting materials. According to the latter strategy,

the release of aromatic stabilization energy as a driving force has been particularly valuable. Typical examples are shown in Scheme 1.2.[79,80] In both cases, the energetic advantage of aromatization outweighs, or at least offsets, the elevated strain energy introduced into the small cyclophanes. A recent application of this strategy can be found in the synthesis of strained pyrenophane **26** (Scheme 1.3).[81]



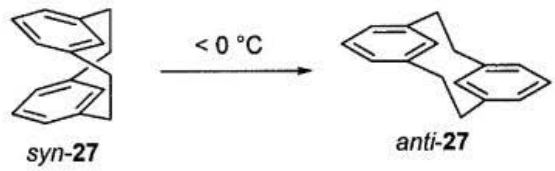
Scheme 1.2 Synthesis of small cyclophanes **22** and **24**.



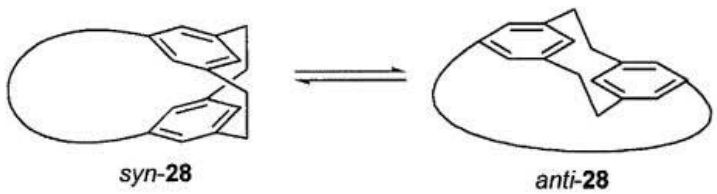
Scheme 1.3 Synthesis of pyrenophane **26**.

Once the synthetic problems are solved, the next stimulus for chemists is to evaluate how unusual the cyclophanes are in terms of structure, physical and chemical properties. Numerous analytical methods have been used to probe a

variety of physical properties of cyclophanes. X-ray crystallographic analysis has afforded the most direct description of the solid-state structural features, such as bond lengths, bond angles, nonplanarity of aromatic rings and proximity of nonbonded atoms, which are responsible for the unique phenomena associated with these compounds.[49] As an orthogonal approach, NMR has been invaluable in providing information regarding the structure and geometry of cyclophanes in solution,[82] which makes studies of conformational behavior possible and fruitful. One of the more thoroughly investigated systems is the [2.2]metacyclophanes.[83] The energy barrier to conformational flipping of the [2.2]metacyclophanes is sufficiently high so that the molecules are commonly regarded as being rigid and existing only as the *anti* conformer at room temperature (Scheme 1.4), as evidenced by the substantial shielding effect of internal protons from the opposite benzene ring.[84] However, in the presence of a third bridge, the conformational behavior of the resulting cyclophanes, termed "tethered [2.2]metacyclophanes", is determined by the length of the tether (Scheme 1.5).[85] In the case of a 13-atom tether, the cyclophane exists as a mixture of *syn* and *anti* conformers that can be separated by column chromatography. By decreasing or increasing the length of the tether, only the *syn* conformer or *anti* conformer result.



Scheme 1.4 Conformational behavior of [2.2]metacyclophanes **27**.

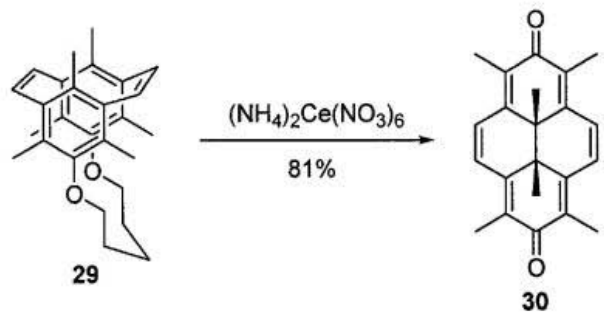


Scheme 1.5 Conformational behavior of tethered [2.2]metacyclophanes **28**.

The strain in the small cyclophanes can be also reflected by their unusual reactivities. Relief of strain in [2.2]paracyclophane can be realized when ring cleavage occurred reversibly at 200 °C to form benzyl-benzyl diradicals.[86] Other examples in this category include Diels-Alder reactions of the benzene ring as a diene and a series of electron-deficient dienophiles, and carbene additions on the benzene ring in [2.2]paracyclophanes.[83]

In addition to fundamental research, cyclophanes have also proved themselves to be valuable in other fields of synthetic chemistry with practical applications. For example, the rigidity of small cyclophanes can serve as a platform to direct stereochemistry. As mentioned above, the presence of a third bridge was used to balance the energies of the *syn* and *anti* conformations in **28** (Scheme 1.5).[85] Another example of use of a tether for stereocontrol can be found in a recently published strategy to synthesize *cis*-10b,10c-dimethyl-

10b,10c-dihydropyrenes (DMDHPs).[87] The majority of known DMDHPs are *trans* isomers because of the general preference for the *anti* conformation of their progenitors, [2.2]metacyclophane-1,9-dienes. Since the tether in **29** locks the *cis* conformation, valence isomerization leads to formation of the *cis*-DMDHP **30** upon the cleavage of the tether (Scheme 1.6).[88]



Scheme 1.6 The use of tether to control the stereochemistry.

A modern concept in cyclophane chemistry involves the use of small cyclophanes as substrates for the preparation of novel polycyclic aromatic hydrocarbons (PAHs) as well as other hydrocarbons.[89,90] Recent examples are shown in a barrelene synthesis[91] and a synthesis of a potential strategic intermediate **31** *en route* to aromatic belts such as **32** (Figure 1.8).[92,93]

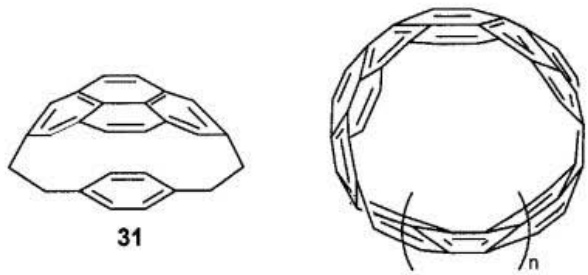


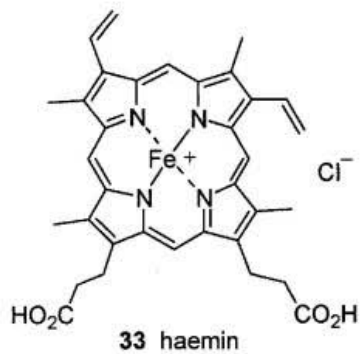
Figure 1.8 Structures of pyrenophane **31** and V gtle belts **32**.

Again, because of strain, ring rotation in small cyclophanes is usually inhibited by their nonbonding steric interactions. As a result, most small cyclophanes possess a plane of chirality.[94] Initiated by Cram's work,[95] cyclophanes have been well studied in coordination chemistry with transition-metals,[96] which make them perfect candidates as chiral ligands in transition-metal catalyzed reactions. Indeed, the use of chiral cyclophanes, in particular [2.2]paracyclophanes, as ligands in stereoselective synthesis, has emerged as an intriguing line of research in cyclophane chemistry. Recently examples have been demonstrated in asymmetric synthesis of amino acids,[97] enantioselective hydrogenation,[98] Pd-catalyzed allylic alkylation,[99] asymmetric epoxidation of allylic alcohols,[100] and enantioselective diethylzinc addition to aldehydes.[101] Furthermore, relatively large cyclophanes, such as calixarenes,[102] tetraphenylenes,[103] and cryptophanes,[104] have been extensively applied in supramolecular chemistry.[105]

1.2.4 Relationship between Cyclophanes and Natural Products

Cyclophanes have been commonly considered as designed molecules. In the field of cyclophane chemistry, a viewpoint people rarely survey or frequently misconceive, similar to the contents described in Section 1.1.3, is the relationship between cyclophanes and natural products. Just as with other designed molecules, cyclophanes are closely related to natural products from the following perspectives.

1.2.4.1 Cyclophane Architectures in Natural Products

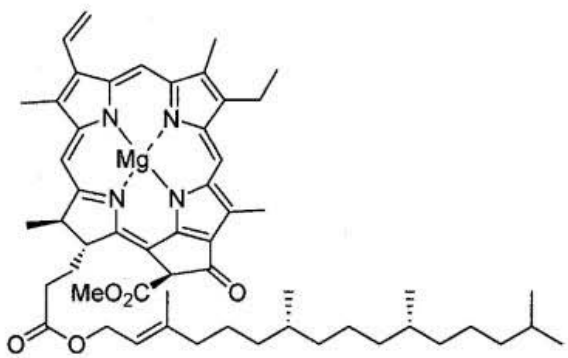


33 haemin

Figure 1.9 Structure of haemin **33**.

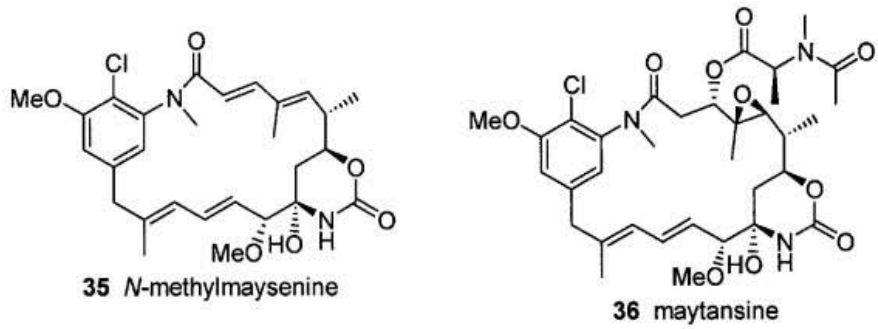
The birth of total synthesis dated back in the nineteenth century with Wöhler's synthesis of urea.[6] The syntheses of the nineteenth century were relatively simple due to the lack of available analytical techniques, well-developed reaction types and known natural products, and the twentieth century began featuring syntheses with increasing molecular complexity and sophisticated strategy design. One of the most notable examples is the total

synthesis of haemin **33** (Figure 1.9) in 1929,[106] which won Fischer the 1930 Nobel prize in chemistry.[4] Haemin, the red pigment of blood and the carrier of oxygen within the human body, belongs to the porphyrin class of compounds and can also be described as a natural [1.1.1.1](2,5)pyrrolophane. Both its structure elucidation and total synthesis were achieved by Fischer.[106,107] The most remarkable feature of Fischer's total synthesis of haemin is the fusion of the two dipyrrole components in succinic acid at 180-190 °C to form the "cyclophane" skeleton in a single step by two C-C bond forming reactions. The intelligent selection of building blocks not only avoided isomer formation, but also addressed the cyclization problem, which is usually the biggest issue in cyclophane synthesis.



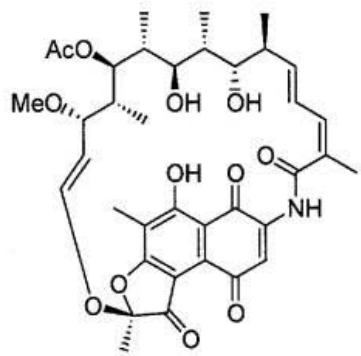
34 chlorophyll a

Figure 1.10 Structure of chlorophyll a **34**.



35 *N*-methylmaysenine **36** maytansine

Figure 1.11 Structures of *N*-methylmaysenine **35** and maytansine **36**.

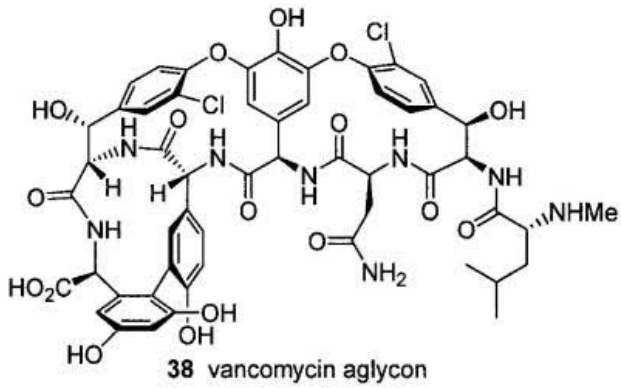


37 rifamycin S

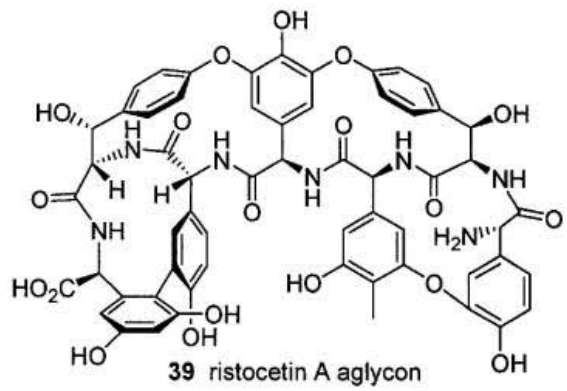
Figure 1.12 Structure of rifamycin S **37**.

Besides natural porphyrins, other types of naturally occurring cyclophanes, including ansamycins (*ansa* from Latin, meaning "handle"),[108] have been reviewed by Vögtle.[50] Being an artist in total synthesis, Woodward won the 1965 Nobel prize in chemistry because of his spectacular synthetic achievements. One of the most striking examples is his total synthesis of chlorophyll a **34**, another natural pyrrolophane (Figure 1.10), in 1960.[109] In 1990, Corey was awarded the Nobel prize in chemistry for his brilliant contribution to development of the theory and methodology of organic synthesis. Amongst

hundreds of natural products synthesized by Corey, *N*-methylmaysenine **35**[110] and maytansine **36**[111] belong to natural [*n*]metacyclophanes (Figure 1.11). Other impressive total syntheses of natural cyclophanes accomplished in the Corey era include those of rifamycin S **37** (Figure 1.12) by Kishi[112,113] and Hanessian.[114]



38 vancomycin aglycon



39 ristocetin A aglycon

Figure 1.13 Structures of vancomycin aglycon **38** and ristocetin aglycon **39**.

The latest era in total synthesis, the 1990s era, is inspired and challenged by entirely new types of structures presented by nature, many of which contain cyclophane architecture. Among those, the vancomycin group (Figure 1.13) has attracted the most synthetic endeavor. Vancomycin, a glycopeptide antibiotic,

was isolated in 1956, from the actinomycete *Amycolatopsis orientalis*,[115] and used for over four decades as a weapon of last resort to combat bacterial disease. With its novel molecular architecture, vancomycin offered a unique opportunity to synthetic chemists to develop new synthetic technologies and strategies. Among the most challenging structural features were its two 16-membered biaryl ether macrocycles and 12-membered biaryl cyclophane system, each of which is associated with an atropisomerism problem.

Total syntheses of vancomycin aglycon have been independently reported by Evans[116,117] and Nicolaou[118-120] in 1998, and later by Boger[121,122] in 1999. A total synthesis of vancomycin itself has been achieved by Nicolaou[123-127] in 1999. Other synthetic studies were reported by Zhu,[128,129] Rao,[130] Sih[131] and Uemura.[132] During the vancomycin campaign, major synthetic efforts have been directed toward designing and developing new methods and strategies to generate the cyclophane moieties. These include S_NAr-based cyclization,[116,117,121,122] triazene-driven ring closure,[118-120,123-127] chloro-deamination[128] and enzymatic oxidative phenolic coupling[131] for biaryl ether formation, and oxidative biaryl coupling[116,117] and Suzuki-Miyaura coupling[132] for biaryl formation. Ristocetin A (Figure 1.13), another vancomycin group member, is an antibiotic produced by the microorganism *Nocardia lurida*.[133] Structurally different from vancomycin, ristocetin A incorporates an additional 14-membered ring with a biaryl ether connection. To date, the total synthesis of ristocetin A has not yet been accomplished. Again, synthetic efforts toward this

target have been mainly focused on construction of the cyclophane moieties, especially the use of biaryl ether formation as the cyclization step. In particular, highly selective and efficient S_NAr reactions, promoted by either manganese[134] or ruthenium,[135-139] were developed by Pearson.

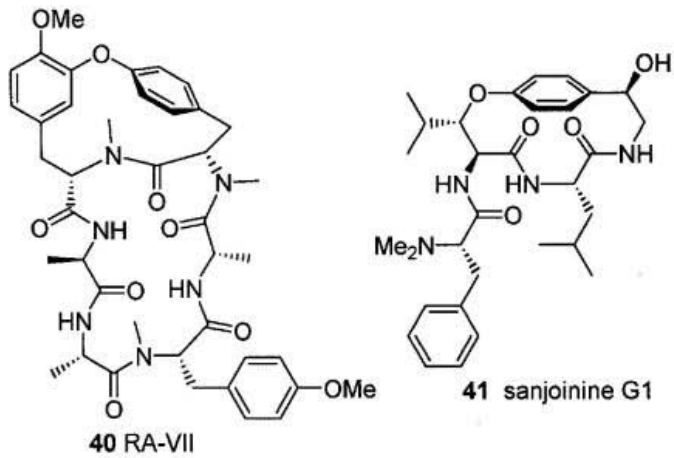
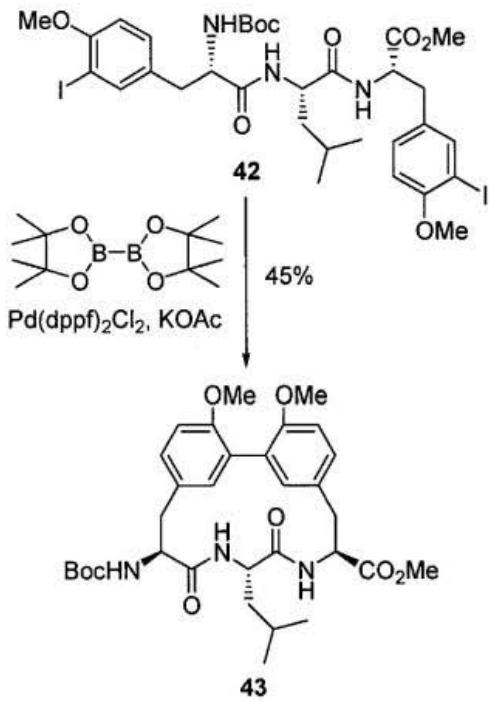


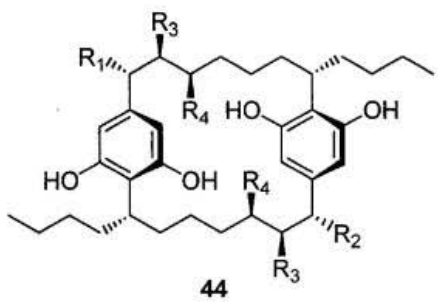
Figure 1.14 Structures of RA-VII **40** and sanjoinine G1 **41**.

Related to the synthetic work on vancomycin group antibiotics, total syntheses of two cyclopeptide alkaloids (Figure 1.14), RA-VII **40**[140] and sanjoinine G1 **41**,[141] have been successfully completed by the Zhu group, who relied heavily on intramolecular S_NAr-based cycloetherification.[142-144]

Among methodological studies regarding biaryl formation to construct cyclophane structures in cyclopeptide alkaloids, a unique domino procedure has been developed in efforts toward the total synthesis of biphenomycins (Scheme 1.7).[145] It involves a sequence of a Miyaura's arylboronic ester synthesis and an intramolecular Suzuki coupling occurring in an ordered fashion.



Scheme 1.7 Cyclophane formation by a domino procedure.

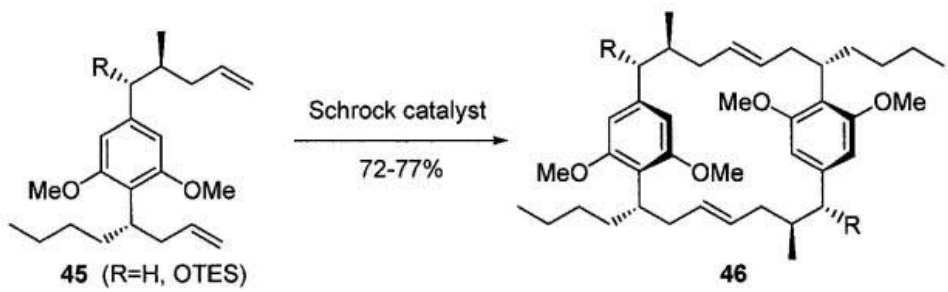


cylindrocyclophanes
A: R_1=OH, R_2=OH, R_3=Me, R_4=H
B: R_1=OH, R_2=OAc, R_3=Me, R_4=H
C: R_1=OH, R_2=H, R_3=Me, R_4=H
D: R_1=OAc, R_2=OAc, R_3=Me, R_4=H
E: R_1=OAc, R_2=H, R_3=Me, R_4=H
F: R_1=H, R_2=H, R_3=Me, R_4=H
nostocyclophane
D: R_1=Me, R_2=Me, R_3=H, R_4=Cl

Figure 1.15 Structures of cylindrocyclophanes A-F and nostocyclophane D.

Despite the structural diversity of designed cyclophanes, naturally occurring paracyclophanes with all-carbon tethers were not reported until 1990, when Moore and co-workers disclosed the isolation of cylindrocyclophane A and nostocyclophane D (Figure 1.15).[146] Five additional members of

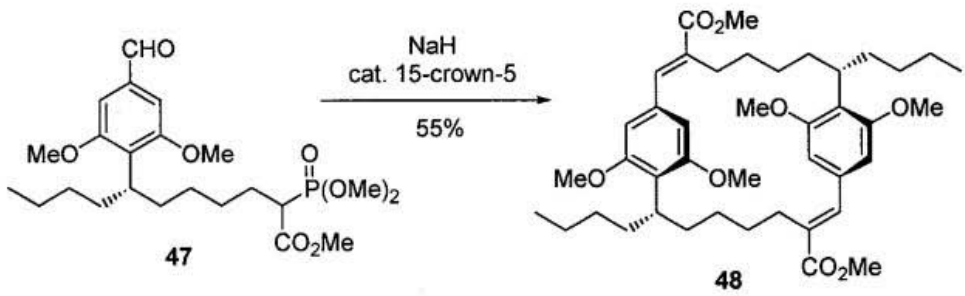
cylindrocyclophane group were then reported in 1992.[147] Interestingly, cylindrocyclophanes A, D and F (Figure 1.15) possess a fascinating C_2-symmetric chiral skeleton. All of the these [7.7]paracyclophanes, which have the appearance of designed molecules but are actually natural products, were found to be the major cytotoxic components in three different strains of the terrestrial blue-green algae *Cylindrospermum lichenforme*, displaying *in vitro* cytotoxicity against certain tumor cell lines.[147]



45 (R=H, OTES) **46**

Scheme 1.8 Ring closing metathesis approach in Smith's synthesis of cylindrocyclophanes A and F.

Total syntheses of some cylindrocyclophanes have been recently completed by utilizing double ring closing metathesis (RCM) reactions (Scheme 1.8)[148-151] and double Horner-Wadsworth-Emmons olefinations (Scheme 1.9)[152] as key steps by Smith and Hoye, respectively. Not surprisingly, the dimerization strategy, which is a dominant one in cyclophane synthesis,[18,49-51] provided a remarkably efficient tactic for assembly of the cylindrocyclophane [7.7]paracyclophane skeleton in both cases.



Scheme 1.9 Horner-Wadsworth-Emmons approach in Hoye's synthesis of cylindrocyclophane A.

Recently, nostocyclyne A **49** (Figure 1.16), a novel polyketide metabolite with an acetylene-containing [14]paracyclophane skeleton, was isolated from a terrestrial *Nostocspermum* that possesses moderate antibacterial activity.[153] Homonuclear and heteronuclear 2D NMR techniques as well as high resolution electron impact mass spectroscopy (HREIMS) determined the gross structure (Figure 1.16) without assigning the absolute stereochemistry. Synthetic work related to it has not been reported.

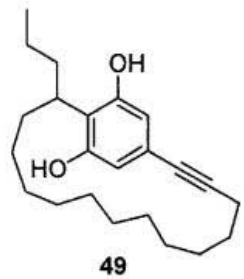
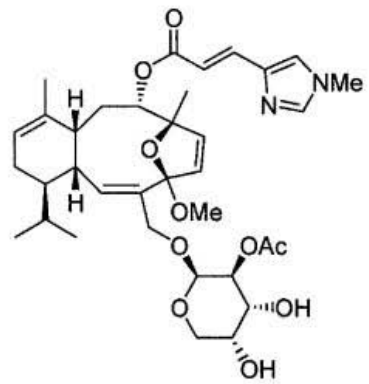


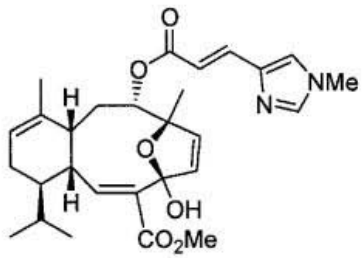
Figure 1.16 Structure of nostocyclyne A **49**.

1.2.4.2 Cyclophane Intermediates in Natural Product Synthesis

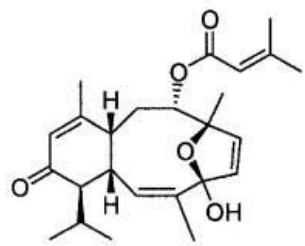
Not only do cyclophanes find themselves incorporated in various natural product skeleta, they also manifest themselves extremely useful as advanced intermediates in natural product synthesis even though the targets themselves may not be naturally occurring cyclophanes. Some prominent examples have been reported lately.



50 eleutherobin



51 sarcodictyin

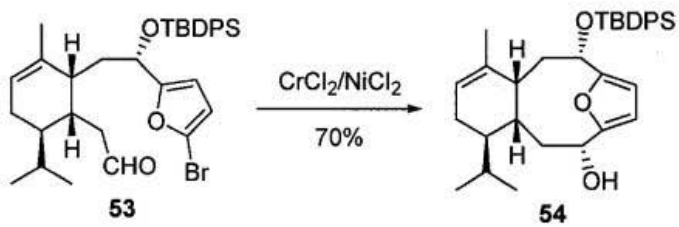


52 valdivone A

Figure 1.17 Structures of eleuthesides **50-52**.

After taxol, one of the most celebrated natural products, was approved by the Food and Drug Administration (FDA) in 1992 for the treatment of ovarian cancer,[154] searches were inspired for other drugs which might operate through

taxol-related modalities of action. Thus, several structurally related marine natural products, loosely classified as eleuthesides, which share the taxol mode of action, were identified. These compounds, including eleutherobin,[155] sarcodictyin,[156] and valdivone A[157] (Figure 1.17), were isolated from different marine sources and were shown to exhibit potent antitumor properties.

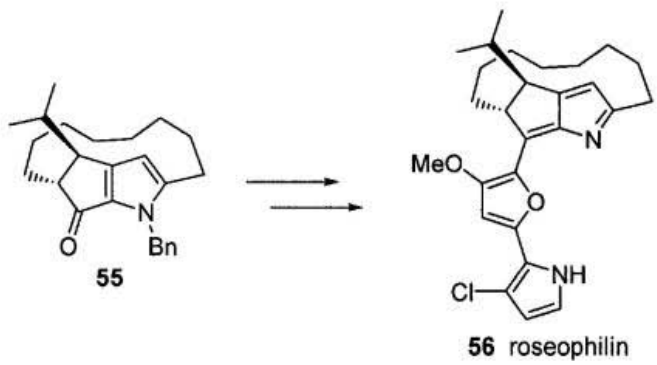


Scheme 1.10 Furanophane intermediate 54 in Danishefsky's approach to eleuthesides.

Along with their interesting structures and scant availability, immediate attention was elicited from the synthetic community, which led to the first total synthesis of eleutherobin in 1997 by Nicolaou.[158] Shortly thereafter, Danishefsky independently disclosed a general route for the total synthesis of all three eleuthesides,[159] where a critical step was the generation of a [6](2.5)-furanophane intermediate **54** by a remarkable and stereoselective Nozaki-Kishi reaction (Scheme 1.10). Relying on this methodology, eleutherobin **50** was synthesized convergently,[160,161] which exemplified the power of total synthesis in delivering scarce natural products for biological investigations.

In 1992, the structure of roseophilin **56** (Scheme 1.11), a novel antibiotic isolated from *Streptomyces griseoviridis*, was elucidated by Seto.[162] This

alkaloid possesses a topologically unique skeleton combining a rather strained macrocyclic entity with an extended heterocyclic chromophore and exhibits cytotoxicity *in vitro* against some tumor cell lines. These properties render roseophilin a lead structure in the search for anticancer agents and a rewarding target for total synthesis. Since it incorporates an azafulvene-type chromophore, a pyrrolophane intermediate **55** (Scheme 1.11) was envisioned as a promising precursor, which indeed served as the key intermediate in Fürstner's elegant synthesis of roseophilin **56** in 1998.[163] The use of pyrrolophane intermediates was also demonstrated feasible in syntheses by Boger[164] and Tius[165,166].

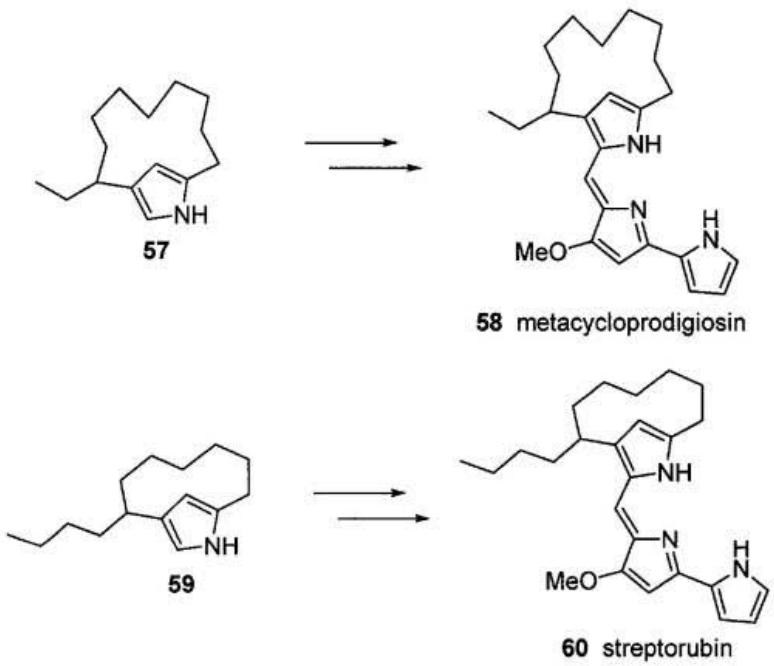


55 **56** roseophilin

Scheme 1.11 Pyrrolophane intermediates **55** in Fηrstner's synthesis of roseophilin **56**.

Because of the similarities in the chromophore and the meta-bridged heterocyclic entities, metacycloprodigiosin **58** and streptorubin B **60** (Scheme 1.12), both potent immunomodulators, were considered as close structural relatives to roseophilin. Taking advantage of the synthetic strategy developed in roseophilin synthesis, Fürstner achieved formal total syntheses of

metacycloprodigiosin **58** and streptorubin B **60** with the assistance of two other pyrrolophanes **57** and **59** (Scheme 1.12).[167] Once again, another two cyclophane intermediates furnished ready access to functional derivatives of metacycloprodigiosin when the same methodology was expanded by the same group (Figure 1.18).[168]



Scheme 1.12 Pyrrolophane intermediates **57** and **59** in Fηrstner's formal syntheses of metacycloprodigiosin **58** and stretorubin B **60**.

Over the past decade there has been a surge in the discovery of biologically active natural products from marine sponges.[169] One class of cytotoxic sponge metabolites that has recently fascinated organic chemists is the manzamine alkaloids. In comparison to terrestrial plant and microbial systems, little was known about their biosynthesis until Baldwin put forward an intriguing

hypothesis in 1992,[170] which involved a transannular Diels-Alder reaction of a bis-(dihydropyridine) species **63** as the key process to assemble the polycyclic framework (Scheme 1.13).

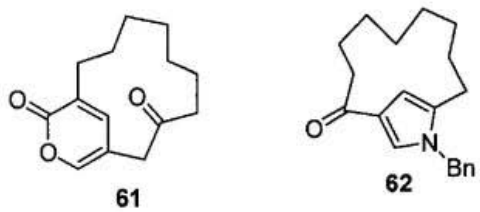
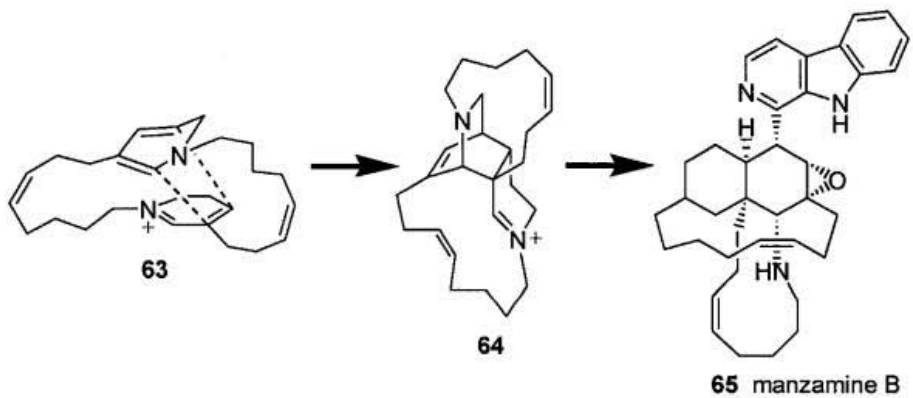


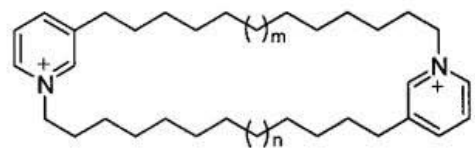
Figure 1.18 Structures of α-pyronophane **61** and pyrrolophane **62** intermediates in synthesis of metacycloprodigiosin derivatives.



Scheme 1.13 Proposed biosynthesis of manzamine B **65**.

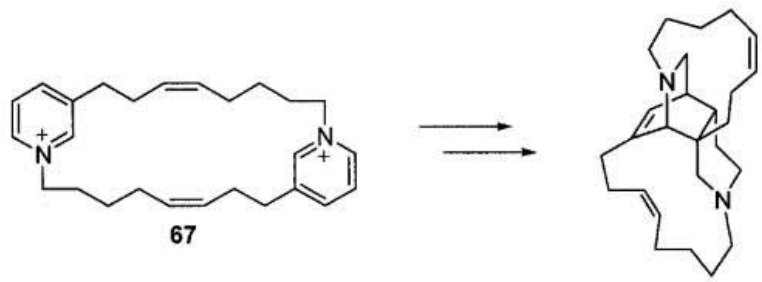
The isolation of the natural cyclophanes **66** (Figure 1.19), analogues of which may be envisaged as ready precursors to **63**, and their biogenetic studies supported Baldwin's hypothesis.[171] More convincing evidence was established after Baldwin accomplished a biomimetic synthesis of keramaphidin B **68** (Scheme 1.14),[172,173] where a pyridinophanium tosylate **67** was involved, by employing his own biosynthetic strategy as illustrated in Scheme 1.13.

Likewise, an analogous cyclophane intermediate **69** served as the key intermediate in a biomimetic synthesis of a series of bis-(oxaquinolizidine) alkaloids (Scheme 1.15).[174]



66 cyclostellettamines A-F (m=1-3, n=1-3)

Figure 1.19 Structures of cyclostellettamines A-F **66**.

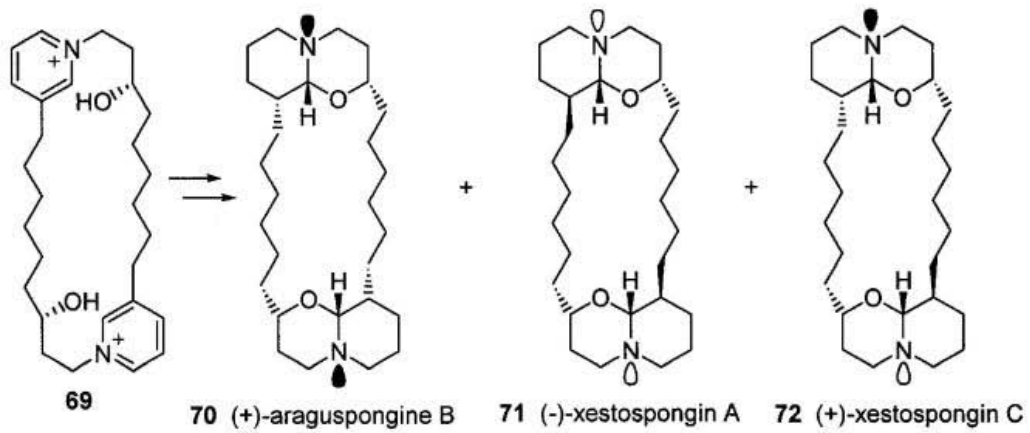


67 **68** keramaphidin B

Scheme 1.14 Pyridinophanium intermediate **67** in Baldwin's biomimetic synthesis of keramaphidin B **68**.

Platelet activation factor antagonist chatancin **73**[175] and sarcophytin **74**[176] were isolated from two different soft coral species of the *Sarcophyton* genus growing thousands of miles apart (Figure 1.20). Both diterpenes have seven stereogenic centers on a *cis-anti-cis* dodecahydrophenanthrene skeleton possessing an almost identical pattern of functionality. Structural and functional similarities hint that both of them belong to a novel tetracyclic diterpene family,

which induced Deslongchamps's postulation that their biosynthesis may involve a transannular Diels-Alder (TADA) reaction.[177]



Scheme 1.15 Pyridinophanium intermediate **69** in Baldwin's biomimetic synthesis of several bis-(oxaquinolizidin) alkaloids **70-72**.

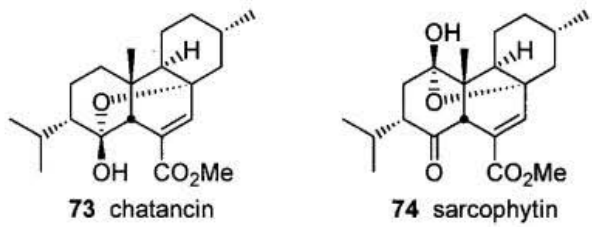


Figure 1.20 Structures of chatancin **73** and sarcophytin **74**.

The hypothesis, with respect to the chatancin biosynthesis, suggested two potentially biomimetic approaches, where two cyclophane intermediates were involved (Figure 1.21), *via* the TADA strategy.[178] In the initial model studies of furanophane approach,[179,180] the key reaction, a TADA reaction, turned out to be strongly solvent-dependent. Under more favorable conditions, tetracycles **78**

(72%) and **79** (8%) were produced, favoring **78** which possesses the chatancin stereochemistry (Scheme 1.16).

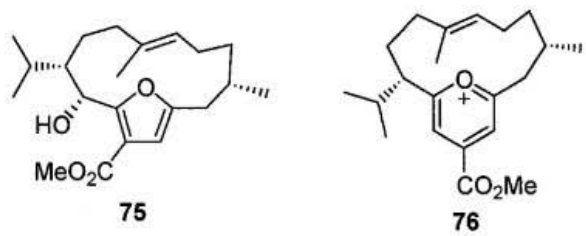
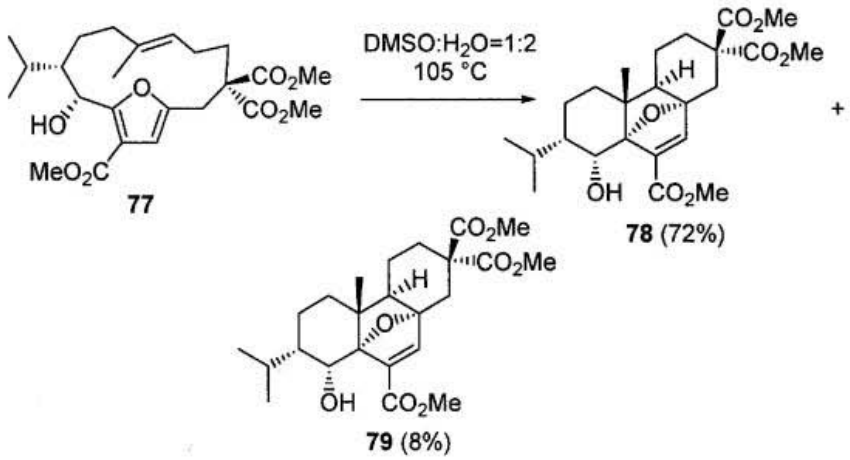
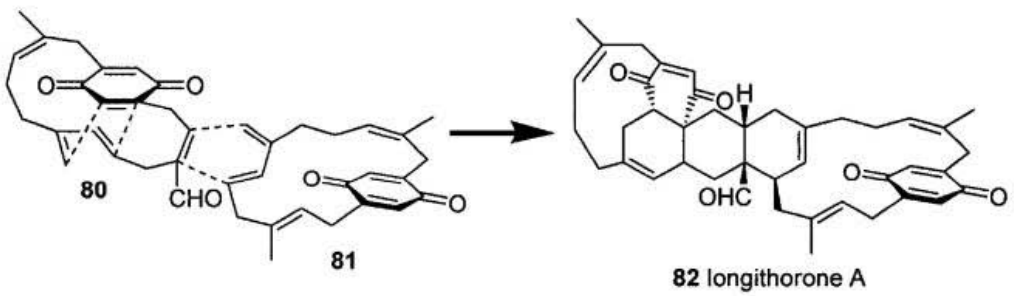


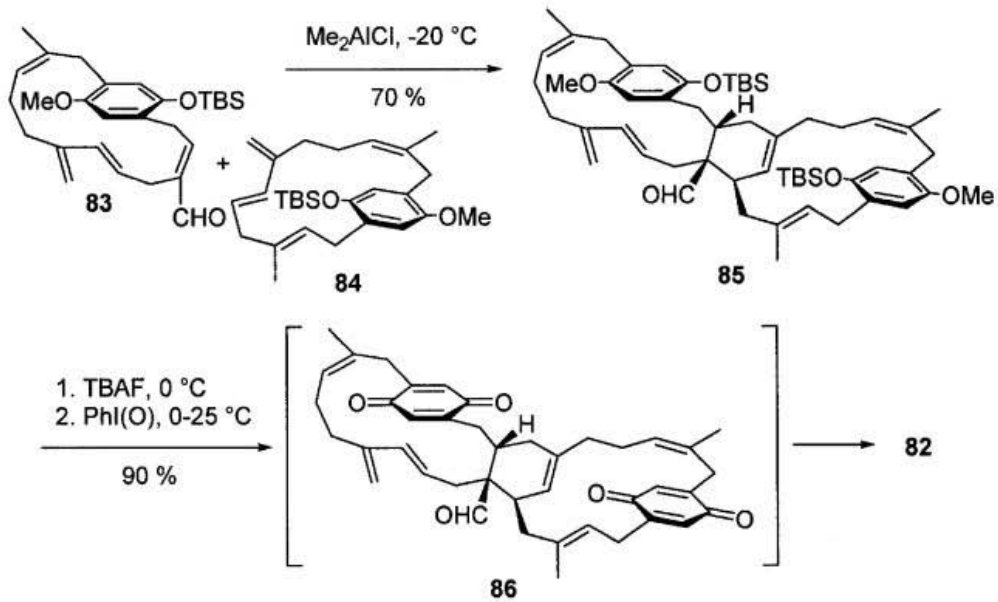
Figure 1.21 Structures of furanophane **75** and pyrylophanium **76**, intermediates in the chatancin biosynthesis.



Scheme 1.16 Model study of Deslongchamps' furanophane approach to chatancin.



Scheme 1.17 Proposed biosynthesis of longithorone A **82**.



Scheme 1.18 Paracyclophane intermediates **83** and **84** in Shair's biomimetic synthesis of longithorone A **82**.

Tunicates have attracted considerable attention as potential sources of lead compounds for anticancer drug due to the variety of novel and cytotoxic compounds they have yielded.[181] In the course of the continuing search for antitumor agents from marine sources, an unprecedented dimeric prenylated quinone, designated longithorone A, was isolated in 1994.[182] The challenge of a synthesis of longithorone A is heightened by the presence of two forms of chirality: stereogenic centers and atropisomerism arising from hindered rotation of the quinone moiety. Along with its isolation, a provocative hypothesis has been presented to explain the biosynthesis of longithorone A **82**, involving an intermolecular Diels-Alder reaction between **80** and **81** and a TADA reaction

across **80** to simultaneously assemble the polycyclic skeleton (Scheme 1.17).[182] Stimulated by this proposal, a biomimetic synthesis of longithorone A has been achieved by Shair in 2002,[183] with two structurally similar [12]paracyclophanes as the key intermediates (Scheme 1.18). Furthermore, the recent isolation of longithorone A relatives, longithorols A **87** and B **88** (Figure 1.22),[184] provides another obvious opportunity for the application of Shair's dimerization strategy without a TADA step.

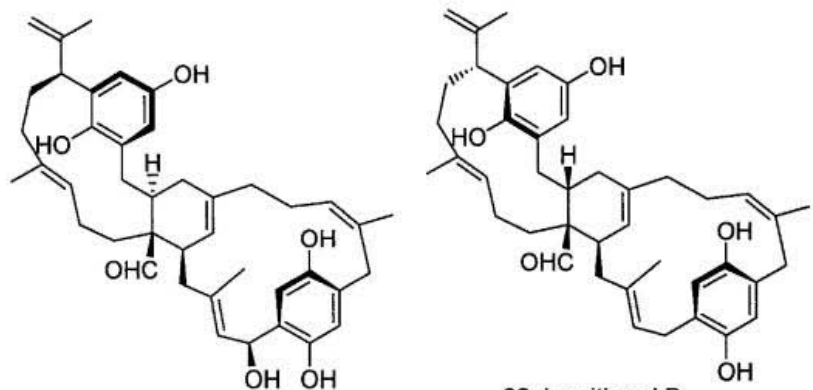


Figure 1.22 Structures of longithorols A **87** and B **88**.

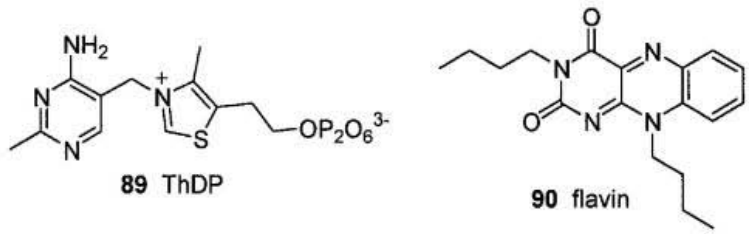
1.2.4.3 Cyclophane Derivatives as Natural Product Functional Mimics

Molecular recognition between molecules is one of the most fundamental processes in biochemical systems. The study of synthetic model systems could contribute to the understanding of these processes and offer new perspectives for the development of pharmaceuticals, enantiomer-selective sensors, catalysts and molecular devices.[105] The synthesis and study of highly structured organic molecular complexes, as an emerging discipline, is called host-guest

chemistry.[105,185] A molecular complex is composed of at least one host and one guest component; they are held together in unique structural relationships by forces other than covalent bonds. The host is an organic molecule or ion whose binding sites converge. The guest is an organic molecule or ion, or a metal ion, whose binding sites diverge. Consequently, hosts tend to be larger and more complicated than guests. In general, guests are abundant, whereas hosts must be designed and synthesized. Among varieties of possible molecular architectures as hosts, cyclophanes have proved to be excellent candidates because of their relatively rigid skeleton and flexible internal cavity.

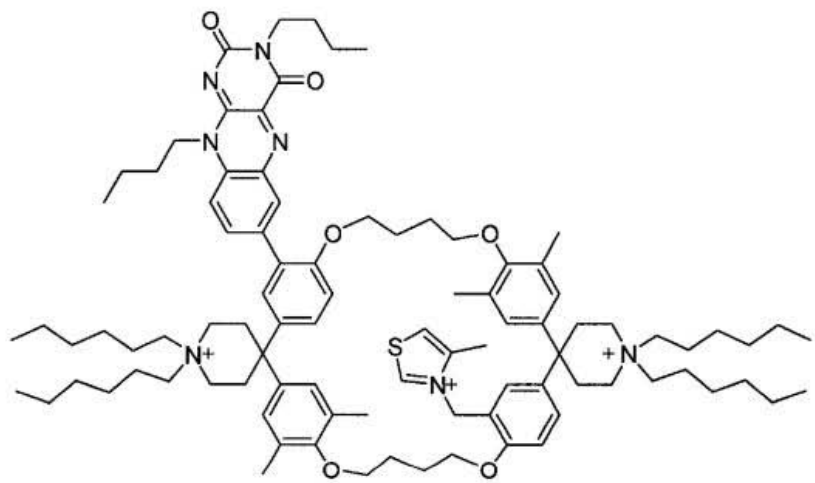
Enzymes are sophisticated proteins having groups that behave catalytically and often require specific cofactors or coenzymes for catalytic performance. One of the most popular branches in host-guest chemistry is the design and synthesis of artificial enzymes, the aim of which is to functionally mimic naturally occurring enzymes by ways of organic synthesis.[186,187] One of the impressive applications of cyclophanes as enzyme mimics is Diederich's pyruvate oxidase mimic.[188,189] Pyruvate oxidase employs two cofactors, ThDP **89** and flavin **90** (Figure 1.23), to catalyze the transformation of pyruvate to acetyl phosphate. Diederich's pyruvate oxidase mimic **91** (Figure 1.24), a cyclophane, combines a well defined binding site with both the ThDP functional core, a thiazolium group, and the flavin attached in covalent fashion. The proximity of the groups to the binding site and the intramolecularity of the oxidation step was therefore expected to improve catalysis relative to previous

two component systems.[190] It should also mimic the situation in the enzyme where the cofactors are bound in the enzyme active site thus increasing the effective concentration of the reagents. Remarkably, the enzyme mimic **91** did act as the expected catalyst on a truly preparative scale with a catalytic turnover of up to 100 cycles. Many other amazing cyclophane systems can be found in the long journey of pursuing synthetic analogues of cytochrome p450, one of nature's oxidative workhorses.[191]



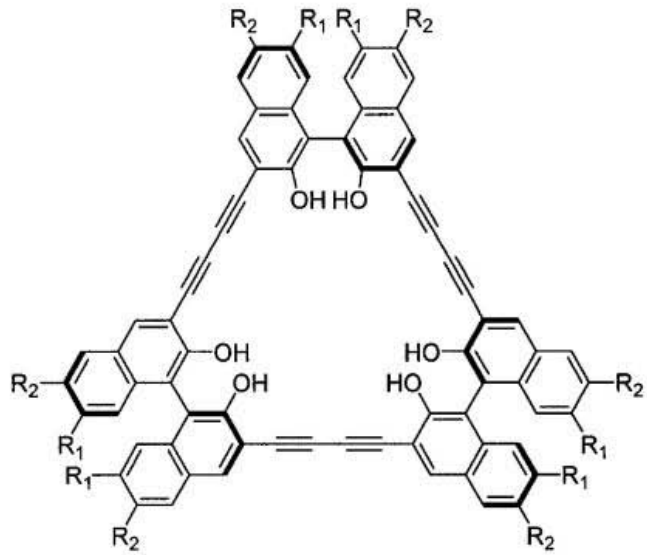
89 ThDP **90** flavin

Figure 1.23 Structures of ThDP **89** and flavin **90**.



91

Figure 1.24 Structure of Diederich's cyclophane mimic **91** for pyruvate oxidase.



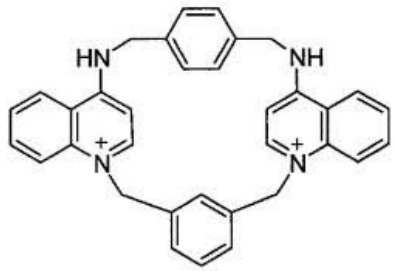
92 (R_1=H, OBn; R_2=H, CH_2CH_2Ph)

Figure 1.25 Structures of cyclophane receptors **92** for carbohydrates.

As one of the most widely distributed types of natural host, proteins are ubiquitously involved as receptors in recognition processes and in enzyme-substrate events with small molecules. There is increasing consensus that investigations with well-defined synthetic receptors, whose binding properties can be systematically varied and analyzed, could make important contributions to the understanding of recognition processes in biology for various types of small molecules, including steroids[192-194] and carbohydrates.[195-197] Based on the knowledge that the complexation of carbohydrates by proteins relies on a subtle balance between hydrophobic and hydrophilic interactions, a series of optically active cyclophane receptors **92** (Figure 1.25) have been synthesized in which three 1,1'-binaphthalene-2,2'-diol spacers are interconnected by buta-1,3-

diynediyl linkers to form highly preorganized cavities lined with six convergent OH groups. These cavities mimic the natural protein recognition sites for carbohydrates by providing a circular array of H-bonding groups for interactions with the substrate.[195] With remarkably enhanced diastereoselectivity and enantioselectivity, one of cyclophane receptors **92** is among the most selective artificial carbohydrate receptors known.

By controlling the movement of K^+ ions through the cell membrane, ion channels selective for K^+ participate in a variety of physiological and pathophysiological processes, thus being, in many cases, suitable targets for therapeutic intervention.[198] The small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channel is found in many cell types, and it has been suggested that there may exist endogeneous modulators of SK_{Ca} channels. The currently available blockers include natural peptidic toxins such as apamin.[199] To circumvent the pharmacokinetic drawbacks of use of peptides as therapeutic agents, efforts have been made to discover potent, non-peptidic SK_{Ca} channel blockers.[200] A small cyclophane **93** (Figure 1.26) has been reported to be the most potent artificial SK_{Ca} channel blocker described to date.[201] Its activity is ascribed to its restricted conformational behavior.



93

Figure 1.26 Structure of cyclophane blocker **93** for SK_{Ca} channels.

1.3 Conclusion

Natural product synthesis and designed molecule synthesis are two subdivisions of the field of total synthesis. The two corresponding groups of synthetic chemists have been, for the most part, working separately for many years. Not until recently, was it realized that the merging of these two areas, e.g. drug discovery, provides unprecedented opportunities to develop new theories, synthetic strategies and technologies, which benefit the field of total synthesis as a whole.

Being one of many types of designed molecules, cyclophanes have been the subject of broad interest for several decades and a wealth of knowledge has been accumulated. The overwhelming majority of work in this area has been fundamental research, but some practical applications have also been demonstrated. In contrast, the relevance of cyclophanes to natural products has not yet obtained widespread attention. To synthesize natural products with cyclophane skeleta, new methodologies developed *en route* to the targets have

enriched cyclophane chemistry. When cyclophanes are used as key intermediates in a natural product synthesis, especially biomimetic ones, cyclophane chemistry furnishes wholly new ideas in terms of both synthetic chemistry and biogenetic studies. As functional mimics of natural products, cyclophanes are invaluable in the course of revealing mechanisms involved in life systems. In all cases, synergistic effects have been observed, and they contribute back to both areas to drive them forward faster than ever.

1.4 Aims of the Present Study

At the outset of this project, there were two separate major areas of interest under active investigation in the Bodwell group, namely cyclophane chemistry[52,81,85,87,88,93,202-209] and methodological studies of inverse electron demand Diels-Alder (IEDDA) chemistry.[210-211] Given the attractive opportunities and challenges provided by the connection of the two subdivisions of total synthesis, the present study is aimed at seeking potential applications for the synthesis of natural products by marrying cyclophane chemistry to IEDDA chemistry. Consequently, synthetic work described in this dissertation falls under both themes.

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CHAPTER 2 Synthesis of *syn*-2,11-Dithia[3.3]metacyclophanes with Sulfur-containing Substituents at the 6 and 15 Positions

2.1 Introduction

2.1.1 Retrosynthetic Analysis of [*n*](2,7)Pyrenophanes

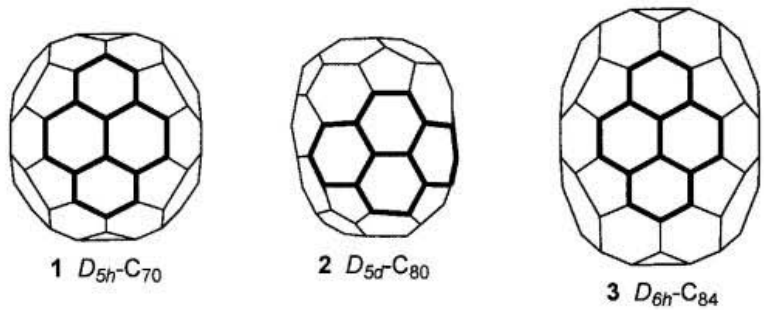
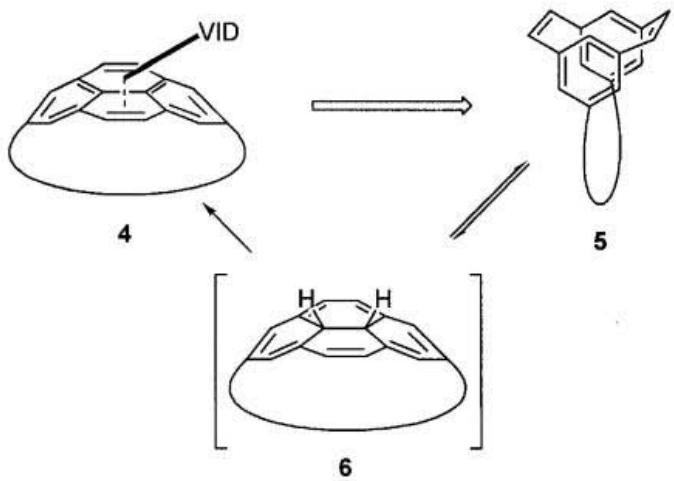


Figure 2.1 Structures of fullerenes, D_{5h}-C_{70}, D_{5d}-C_{80} and D_{6h}-C_{84}. (Double bonds have been removed for clarity)

Polycyclic aromatic hydrocarbons (PAHs) have been of academic interest ever since organic chemistry became a full-fledged scientific discipline in the first half of the nineteenth century.[1] The chemistry of polycyclic aromatic all-carbon compounds has attracted increased attention since the discovery of fullerene C_{60} in 1985.[2] With the ultimate goal of rationally synthesizing C_{60} and other higher fullerenes, a series of most formidable synthetic targets, several approaches have been initiated, one of which involves the synthesis and elaboration of fullerene fragments (buckybowls).[3,4] Since fullerene fragments themselves are highly curved PAHs, traditional cyclophane methodology, which

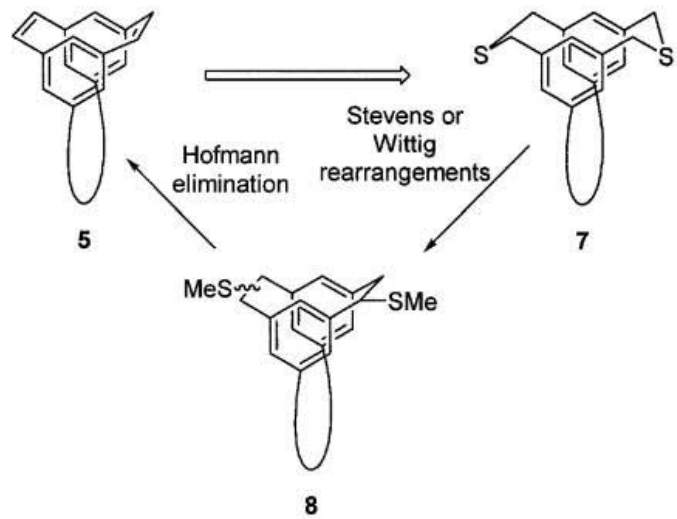
has often been used to generate nonplanar aromatic nuclei in many small cyclophanes, may serve as a potentially efficient entry into fullerene fragment synthesis. The pyrene unit is an attractive target for such studies as it maps onto the surface of some of the higher fullerenes, e.g. D_{5h}-C_{70} **1**,[5] D_{5d}-C_{80} **2**[6] and D_{6h}-C_{84} **3**[7] (Figure 2.1).



Scheme 2.1 Retrosynthetic analysis of (2,7)pyrenophane. (Part I)

As described in Chapter 1, two general synthetic strategies have been employed extensively to combat strain in small cyclophanes. The first strategy uses high-energy intermediates, such as carbenes and radicals, and the second strategy exploits the release of aromatic stabilization energy as the driving force. At the outset of work in the Bodwell group aimed at the synthesis of [*n*]pyrenophanes, the second strategy was chosen because its general potential has been demonstrated several times in the synthesis of some of the smallest and most strained cyclophanes, including [5]metacyclophanes[8] and

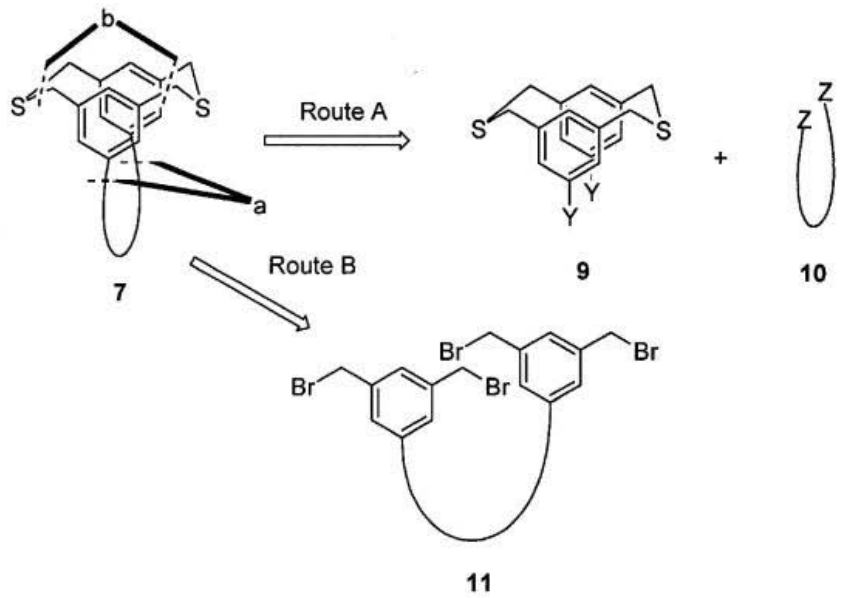
[4]paracyclophanes.[9] In a retrosynthetic analysis, it was anticipated that the curved pyrene unit in (2,7)pyrenophane **4** could be formed by applying the valence isomerization-dehydrogenation (VID) protocol to a cyclophanediene precursor **5** (Scheme 2.1).



Scheme 2.2 Retrosynthetic analysis of (2,7)pyrenophane. (Part II)

The next step in the retrosynthesis is to identify a feasible method to prepare cyclophanediene **5**. Based on well established ring contraction methodology, the dithiacyclophane approach has been the most common way to synthesize cyclophanedienes.[10,11] Consequently, this strategy retrosynthetically leads to a tethered dithiacyclophane **7** by replacing the two double bonds in cyclophanediene **5** with thioether linkages (Scheme 2.2). In the synthetic direction, the first step of the ring contraction process could be established by a Stevens rearrangement[12] or a Wittig rearrangement.[13] to afford the substituted

[2.2]metacyclophane **8**. The conversion of **8** to the desired cyclophanediene **5** should proceed well *via* a Hofmann elimination.[14]



Scheme 2.3 Retrosynthetic analysis of (2,7)pyrenophane. (Part III)

The key functions of the tether in the system under consideration were the introduction of curvature to the pyrene nucleus in **4** and the assurance of a *syn*-geometry in **5** to facilitate the dehydrogenation. The *syn* conformational preference of the tethered dithiacyclophane **7**, which is the preferred conformation of many untethered dithiacyclophanes without internal substituents,[15] formed the basis of Route A in the final stage of the retrosynthesis (Scheme 2.3). In Route A, the tether in **7** was cleaved to give a difunctionalized dithiacyclophane **9** and an acyclic difunctionalized building block **10**. Alternatively, a complementary retrosynthetic cut, Route B, was also identified,

in which the tethered tetrabromide **11** was the disconnection product. Initial synthetic investigations of the first approach indicated that synthesis of certain suitably difunctionalized dithiacyclophanes **9** was difficult; thus the route was eventually abandoned. On the other hand, the second approach has proved to be quite effective, and has resulted in the synthesis of a wide variety of (2,7)pyrenophanes **4**.[16-20]

2.1.2 Unusual X-Ray Crystal Structure of *syn*-6,15-Dicyano-2,11-dithia[3.3]metacyclophane 9a

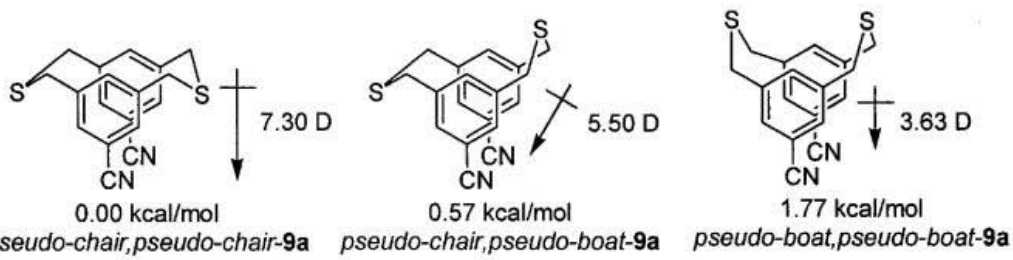
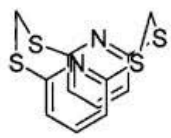


Figure 2.2 AM1 calculated relative heats of formation energies and dipole moments of the bridge conformers of **9a**.

Although Route A in Scheme 2.3 was abandoned for the synthesis of the bent (2,7)pyrenophanes **4**, it triggered interest within the Bodwell group regarding the conformational behavior of the 2,11-dithia[3.3]metacyclophane system. Initial work in this area led to the synthesis of *syn*-6,15-dicyano-2,11-dithia[3.3]metacyclophane **9a** (Figure 2.2).[21] This particular cyclophane shows some very unusual features in its X-ray crystal structure. The most surprising feature is that both bridges adopt the *pseudo-boat* conformation (*pseudo-*

boat,pseudo-boat-**9a**, Figure 2.2), rendering it the first example of a *syn*-2,11-dithia[3.3]metacyclophane to exist in this conformation in the solid state. Neither semiempirical calculations at the AM1 level nor *ab initio* calculations at the 3-21G(*) level of theory predict this to be the most stable conformation for **9a** in the gas phase. AM1 calculations showed the heat of formation of the *pseudo-chair,pseudo-boat* and *pseudo-boat,pseudo-boat* conformers to be 0.57 kcal/mol and 1.77 kcal/mol higher than that of the *pseudo-chair,pseudo-chair* conformer, respectively.



12

13

Figure 2.3 *Pseudo-boat,pseudo-boat* conformations of *syn*-[3.3]pyridinophanes **12** and **13**.

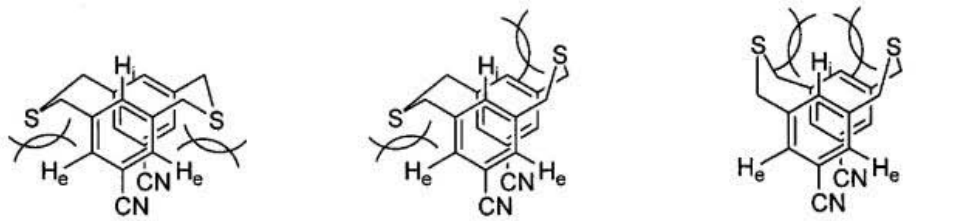
When published X-ray crystal structures of other *syn*-[3.3]metacyclophanes were examined, the majority of structures were found to be of all-carbon-bridged *syn*-[3.3]metacyclophanes[22,23] and *syn*-2,11-dithia[3.3]metacyclophanes.[15] Most of those structures had the bridges in the *pseudo-chair,pseudo-chair* conformation, which is in agreement with the calculations for the gas phase, indicating this conformation to be the one with the lowest energy. Discrepancies between calculations and observations were only encountered in the cases of *syn*-1,3,10,12-tetrathia[3.3](2,6)pyridinophane **12**[24] and *syn*-[3.3](2,6)pyridinophane **13**[23] (Figure 2.3).

In the case of **12**, N-S repulsions (presumably unfavorable alignments of nitrogen and sulfur lone pairs in the *pseudo-chair,pseudo-chair* conformation) were invoked as the probable cause of the unusual bridge conformations. For compound **13**, weak hydrogen bonding between the internal nitrogens and the inner hydrogens of the central methylene groups in the bridges was deemed to be the primary cause for the unusual bridge conformations. The hydrogen bonding argument does not appear to be applicable to *syn*-6,15-dicyano-2,11-dithia[3.3]metacyclophane **9a**, since the heteroatom in this case is a considerably weaker donor (S *vs.* N). Furthermore, this weak hydrogen bonding could presumably occur in a *pseudo-chair* bridge as well as in a *pseudo-boat* bridge.

2.1.3 Hypothesis

The origin of the unusual bridge conformations of **9a** in the solid state was ascribed to dipolar effects,[21] i.e., the molecule adopts the conformation with the smallest dipole moment. As illustrated in Figure 2.2, the dipole moments of the *pseudo-chair,pseudo-chair*, *pseudo-chair,pseudo-boat* and *pseudo-boat,pseudo-boat*-**9a** conformers are calculated to be 7.30, 5.50 and 3.63 D, respectively. In the *pseudo-boat,pseudo-boat* conformer, the vector sum of the dipole moment caused by the two cyano groups aligns directly against that caused by the four C-S bonds in the bridges, which renders the *pseudo-boat,pseudo-boat*-**9a** the one with the smallest dipole moment among the three conformers. If such dipolar effects are indeed responsible for the bridge conformational behavior of **9a** in the

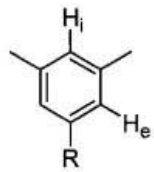
solid state, it was reasoned that 6,15-disubstituted *syn*-2,11-dithia[3.3]metacyclophanes would show a general dependence of the bridge conformations on the electronic properties of the substituents at the 6 and 15 positions. NMR techniques, rather than X-ray single crystal analysis, were chosen to study the conformational effects in such a system because NMR offers easy access to a state where the bridges are free to undergo conformational processes, whereas X-ray methods only reveal single point conformations and crystal packing forces may outweigh subtle energy differences with a particular system.



pseudo-chair,pseudo-chair-**9** *pseudo-chair,pseudo-boat*-**9** *pseudo-boat,pseudo-boat*-**9**

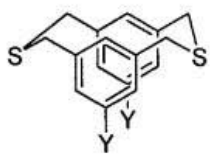
Figure 2.4 Steric deshielding effects of sulfur atoms in different bridge conformers of *syn*-2,11-dithia[3.3]metacyclophanes **9**.

As described in the Ph.D. dissertation of Dr. Vermeij,[3] the approach is predicated on the assumption that the sulfur atom of the *chair* conformation will deshield the proximate aryl hydrogen H_e and the sulfur atom of the *boat* conformation will deshield the proximate aryl hydrogen H_i by the same amount (Figure 2.4).

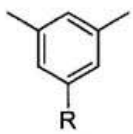


14

Figure 2.5 Structure of *m*-xylenes **14**.



9



14

Cyclophanes	*m*-Xylenes	R
9a	**14a**	CN
9b	**14b**	H
9c	**14c**	Br
9d	**14d**	CO_2Et
9e	**14e**	CO_2H
9f	**14f**	Me
9g	**14g**	NH_2
9h	**14h**	NHAc
9i	**14i**	NO_2
9j	**14j**	OAc
9k	**14k**	OH
9l	**14l**	OMe
9m	**14m**	SH
9n	**14n**	SMe
9o	**14o**	SOMe
9p	**14p**	SO_2Me
9q	**14q**	SC(O)*t*-Bu

Figure 2.6 Structures of *syn*-2,11-dithia[3.3]metacyclophanes **9** and *m*-xylenes **14**.

By comparing the chemical shifts of the aryl protons of cyclophanes **9a-q** to the corresponding 5-substituted *m*-xylenes ("half cyclophanes") **14a-q** (Figure 2.5 and 2.6), in which the differential steric deshielding effect of the sulfur atoms on the internal and the external protons is absent, information regarding

the conformational preferences of the cyclophanes could be obtained. According to Bodwell and Vermeij's hypothesis, a *syn*-2,11-dithia[3.3]metacyclophane that has a preference for the *pseudo-boat,pseudo-boat* conformation in solution is expected to have a large $\Delta\delta H_i$* value and a small $\Delta\delta H_e$ value compared to a cyclophane analogue that mainly adopts the *pseudo-chair,pseudo-chair* conformation. If the preference for one conformer over the other is purely governed by the electronic nature of the substituents of the $\Delta\delta$ values correlates to the distribution of different conformers, it might be possible to correlate the $\Delta\delta$ values to some physical organic parameter that describes the electronic effects of substituents on conformational processes.

The NMR experiments and the correlation studies were performed by Vermeij; therefore, the reader is referred to his Ph.D. dissertation[3] for details. In order to conduct these studies, a range of *syn*-2,11-dithia[3.3]metacyclophanes **9a-q** and their reference compounds, *m*-xylenes **14a-q**, were required (Figure 2.6). This chapter will describe the synthesis of cyclophanes **9m-q** and *m*-xylenes **14m-q**, which were the contributions to this project performed by the author of this thesis.

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* δH is defined as the chemical shift change of the corresponding proton between the reference compound and the cyclophane molecule.

2.2 Results and Discussion

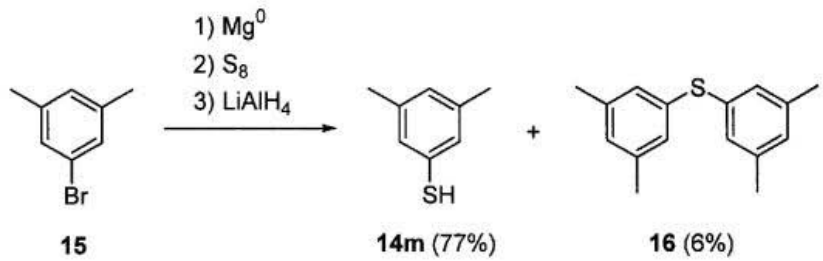
Since most of the reference compounds, *m*-xylenes **14m-q**, were not commercially available and some of them are expected to serve as starting materials in the synthesis of corresponding *syn*-2,11-dithia[3.3]metacyclophanes, the following section contains details of their synthesis.

2.2.1 Synthesis of 5-Substituted *m*-Xylenes 14m-q

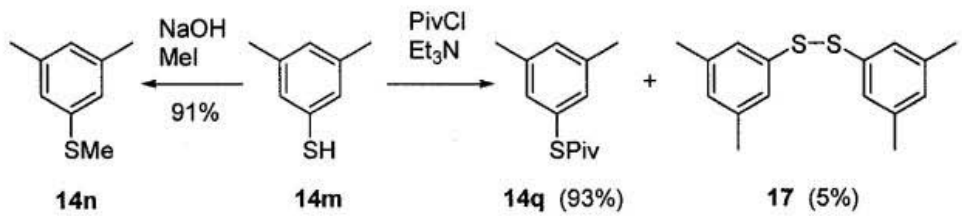
As compounds **14n-q** can be obtained either directly or indirectly, from compound **14m**, the syntheses described below commenced with its synthesis, even though it is commercially available (5 g/$ 98.80 according to the 2000-2001 Aldrich Catalog). Considering the relative experimental ease and general efficiency, an approach involving a sulfur insertion reaction of Grignard reagents[25] was chosen to prepare compound **14m**. Other conventional ways of preparing aryl thiols,[26] such as nucleophilic replacements of aryl halides by metal sulfides, reactions of diazonium salts with sulfur nucleophiles (WARNING!)*, thermal rearrangements of thiocarbonates and thiocarbamates, and aromatic electrophilic substitutions by sulfur electrophiles, and more recent-developed methods, such as aromatic thiocyanation[27] and palladium-catalyzed coupling of aryl triflates with sulfur nucleophiles,[28] were also considered, but the Grignard route eventually proved to be successful. The whole sequence included the initial preparation of a Grignard reagent from bromide **15**, subsequent

* Preliminary work[49] resulted in an explosive decomposition of a diazonium salt.

reaction with elemental sulfur and a final reduction with $LiAlH_4$, which was meant to convert any of the corresponding disulfide to the thiol (Scheme 2.4). Compound **14m** was isolated in 77% yield along with sulfide **16** in 6% yield as the only isolated by-product. This was presumably formed by the nucleophilic attack of the Grignard reagent at a disulfide intermediate.



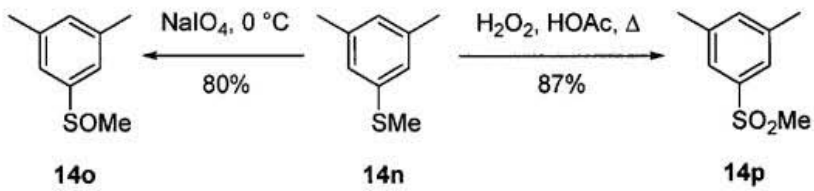
Scheme 2.4 Synthesis of **14m**.



Scheme 2.5 Synthesis of **14n** and **14q** from **14m**.

The preparation of **14n** and **14q** took advantage of the high nucleophilicity of thiolates[29] (Scheme 2.5). Reaction of **14m** with MeI in the presence of NaOH produced **14n** in a yield of 91%. On the other hand, the acylation of **14m** with pivaloyl chloride was promoted by Et_3N to give **14q** in 93% yield. The isolation of disulfide **17** (5%) as the by-product was not overly surprising because thiols

can be readily oxidized by a variety of reagents, including air, to generate disulfides.[30]



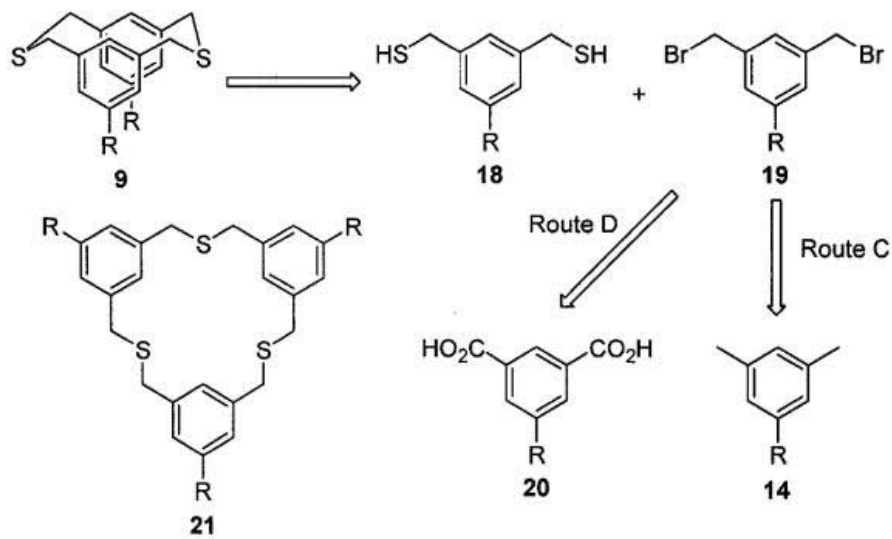
Scheme 2.6 Synthesis of **14o** and **14p** from **14n**.

The synthesis of the other two reference compounds, **14o** and **14p**, appeared straightforward starting from thioether **14n** by oxidation under different conditions (Scheme 2.6). For compound **14o**, $NaIO_4$ was selected as the oxidant because it does not normally oxidize sulfides to sulfones.[31] As expected, **14o** (80%) was generated free from contamination of any sulfone **14p**. When compound **14p** was desired, the oxidation with H_2O_2 in acidic conditions[32] proceeded smoothly with a yield of 87%.

2.2.2 Synthesis of *syn*-2,11-Dithia[3.3]metacyclophanes 9m-q

The traditional synthesis of *syn*-2,11-dithia[3.3]metacyclophanes **9** involves high dilution coupling of two building blocks: a dithiol **18** and a dibromide **19**, often from a common precursor.[11,33] Dithiols **18** can usually be synthesized from dibromides **19**, which can be formed from *m*-xylenes **14** (Route C) via a two-fold free radical benzylic bromination or from isophthalate derivatives **20** (Route D) via a reduction-bromination sequence (Scheme 2.7).

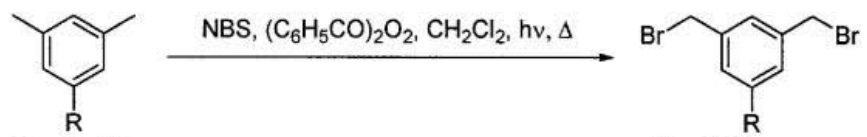
Alternatively, cyclophanes **9** can be synthesized by reacting two equivalents of dibromides **19** with one equivalent of Na_2S/Al_2O_3.[34] The latter approach was preferred in this study because it reduces the number of steps in the synthesis and is compatible with base-sensitive groups, which would require protection if the former approach was taken. The latter approach was known to suffer from the production of a mixture of the desired dimeric cyclophanes **9** and unwanted trimeric cyclophanes **21**, but it was anticipated that these products would be separable.



Scheme 2.7 Retrosynthetic analysis of *syn*-2,11-dithia[3.3]metacyclophanes **9**.

For cyclophane **9m**, the strategy designed by Route C is inappropriate due to the susceptibility of the starting material, thiol **14m**, to oxidation by NBS[26] and the incompatibility of the mercapto group with the benzylic bromide functionality in the proposed cyclization precursor **19m**. The best way to solve

this problem is to protect the mercapto group in **14m** and deprotect it once the cyclophane has been prepared. Since the protected form of cyclophane **9m** itself is a cyclophane, the precursor could be chosen from the other targets *syn*-2,11-dithia[3.3]metacyclophanes **9n-9q**. The immediately obvious candidates were compounds **9n** and **9q**. Cyclophane **9q** was deemed to be the better choice because the pivaloyl group can be deprotected easily by basic hydrolysis,[35] whereas the most commonly used deprotection conditions for methyl thioethers involves either oxidative conditions[36] or strong nucleophiles,[37] which would presumably interfere with the sulfide units in the bridges. The synthesis of cyclophane **9m**, therefore, will be described after the synthesis of cyclophane **9q**.



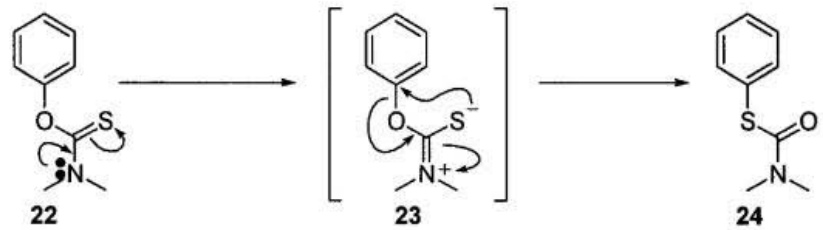
14n R=SMe
14o R=SOMe
14p R=SO_2Me
14q R=SPiv

19n (0%)
19o (undetermined)
19p (48%)
19q (66%)

Scheme 2.8 Synthesis of dibromides **19p** and **19q**.

Since it is shorter, Route C (Scheme 2.7) was followed initially for the synthesis of each of the cyclophanes **9n-q**. Benzylic bromination[38] of **14p** and **14q** yielded the corresponding dibromides **19p** and **19q** in yields of 48% and 66%, respectively (Scheme 2.8). However, the bromination of **14n** failed. In case of **14o**, an ^{1}H NMR spectrum of the crude bromination product showed the presence of the desired dibromide **19o** as well as other less- and over-brominated

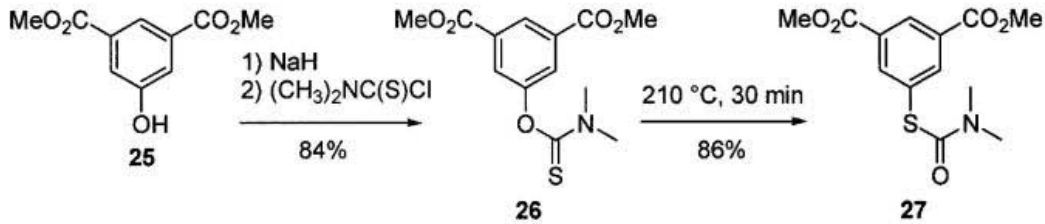
products. The similarity in the polarities of the products prevented the isolation of **19o** in a pure form.



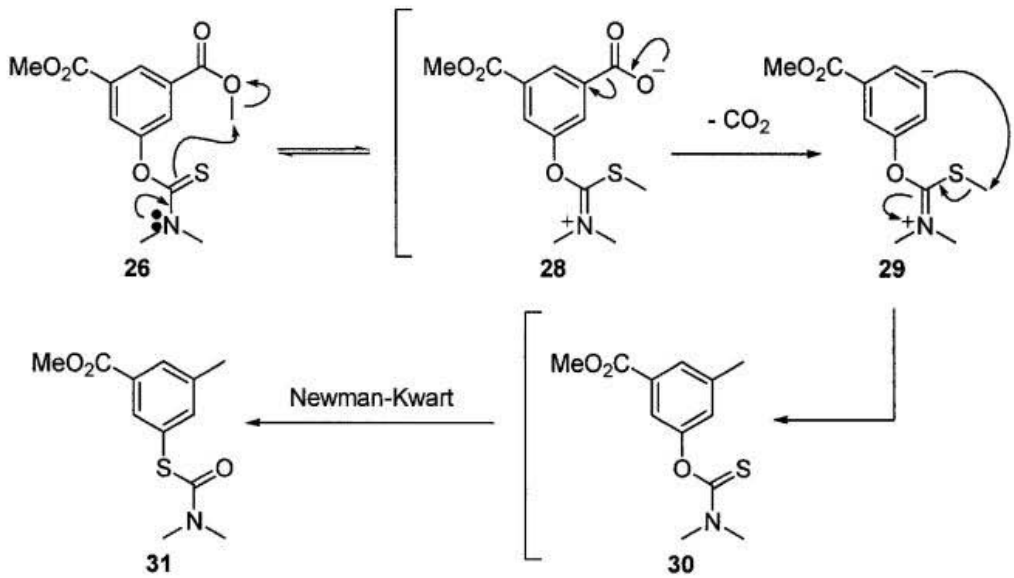
Scheme 2.9 Mechanism for the Newman-Kwart rearrangement of **22**.

Attention was then turned to Route D (Scheme 2.7) to prepare dibromides **19n** and **19o**. Since the corresponding isophthalic acid derivatives **20n** and **20o** are not commercially available, the Newman-Kwart rearrangement,[39,40] one of the most efficient methods to convert phenols to thiophenols, was employed to introduce the required thiol group in a masked form. The Newman-Kwart rearrangement involves a nucleophilic *ipso* attack of the sulfur atom at the aryl carbon holding the oxygen with the assistance of the dimethylamino group in the thiocarbamate derivatives of phenols (Scheme 2.9). Subsequent alkaline hydrolysis usually affords the corresponding aryl thiols in high yield.[39,40]

Starting from the readily available isophthalic acid derivative **25**,[17] treatment with dimethylthiocarbamoyl chloride under basic conditions led to the formation of thiocarbamate **26** in 84% yield (Scheme 2.10). Newman-Kwart rearrangement was then effected by heating compound **26** neat at 210 °C for 30 min to give the expected product **27** in 86% yield.



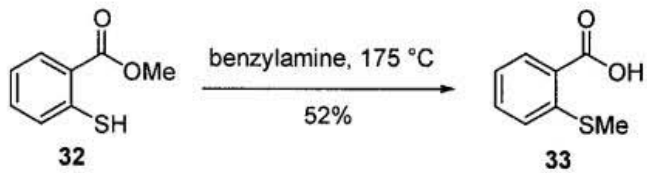
Scheme 2.10 Introduction of a masked thiol group in **27** by a Newman-Kwart rearrangement.



Scheme 2.11 Postulated mechanism for the formation of **31**. For simplicity, the processes are shown occurring intramolecularly rather than (much more likely) intermolecularly.

Unexpectedly, an earlier attempt that involved heating **26** at higher temperature (230 °C) for a longer period of time (1 h) produced compound **31** (29%) as the only isolable product. A proposed mechanism, which involves a sulfur-promoted dealkylation of an ester group, aromatic decarboxylation and a subsequent methylation is shown in Scheme 2.11. To find evidence to support

this proposed mechanism, the literature was surveyed. In 1964,[41] a facile alkyl-oxygen cleavage of esters was reported using PhSNa in DMF at or below room temperature. A related rearrangement was found in an oxygen-sulfur migration of the methyl group from methyl 2-mercaptobenzoate **32** (Scheme 2.12).[42] Later studies by Fujita led to the development of a general procedure for the dealkylation of methyl esters and ring-opening of lactones by using thiols or dialkyl sulfides in the presence of Lewis acids.[43,44] The explanation of the site preference for the nucleophilic attack was based on the principles of Hard and Soft Acids and Bases (HSAB).[45]

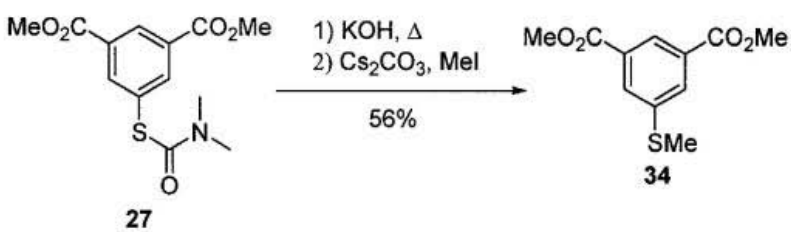


32 **33**

Scheme 2.12 Oxygen-sulfur migration of the methyl group in **32**.

Based on this, a demethylation of **26** (Scheme 2.11) was proposed, which relied on the nucleophilicity of the sulfur atoms of thiocarbamates as in the Newman-Kwart rearrangement. Similar to the case illustrated in Scheme 2.12, the demethylation might be very demanding energetically without the facilitation of either bases or acids. The resulting compound **28** can then undergo an irreversible decarboxylation to furnish aryl anion **29** (Scheme 2.11). The decarboxylation of aromatic carboxylic acids, through an S_E1 mechanism, has been demonstrated to be greatly accelerated by the presence of electron withdrawing groups on the aromatic ring and elevated temperature.[46] The

resulting aryl anion **29** can self-methylate to give **30**. This does not undergo further reaction by an analogous process, presumably due to the lack of an electron withdrawing group present in the decarboxylated analog of **29**. A Newman-Kwart rearrangement of **30** would then provide the observed compound **31** (Scheme 2.11). The preference of the competition between the decarboxylation of **28** and the desired Newman-Kwart rearrangement of **26** seem to depend heavily on the energy input as well as the kinetic profiles of these two processes.

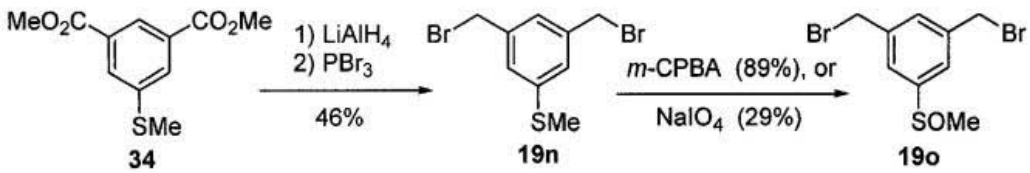


Scheme 2.13 Synthesis of isophthalate **34**.

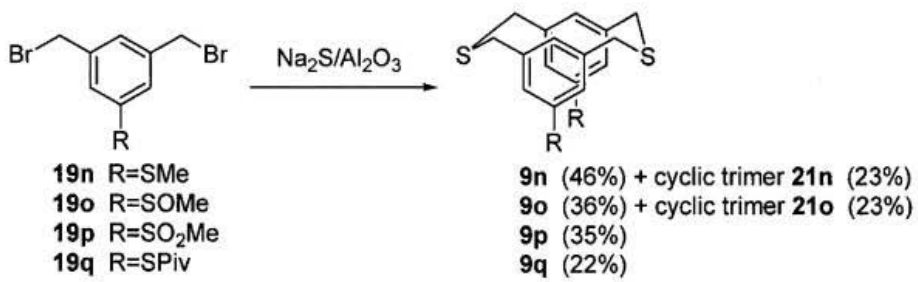
From the Newman-Kwart rearrangement product **27**, a two step sequence composed of basic hydrolysis and alkylation with MeI generated the desired precursor to **9n**, compound **34**, in 56% overall yield (Scheme 2.13).

Convesion of isophthalate **34** to cyclization precursor, dibromide **19n**, was effected by using a $LiAlH_4$ reduction-PBr_3 bromination[47] sequence, which proceeded in 46% yield over two steps (Scheme 2.14). Oxidation of **19n** with $NaIO_4$, as was used in the preparation of **14o**, gave the expected dibromide **19o** in a disappointing yield of 29%, perhaps due to the extremely low solubility of **19n** in H_2O, the preferred medium for $NaIO_4$ oxidation.[31] Alternative mild

conditions using *m*-CPBA[48] furnished the same compound **19o** in a much more satisfactory yield of 89% (Scheme 2.14).

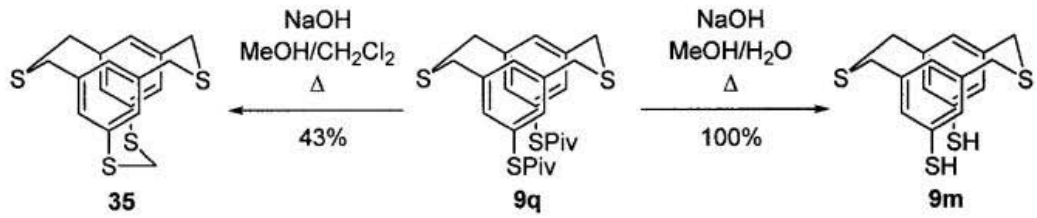


Scheme 2.14 Synthesis of dibromides **19n** and **19o**.



Scheme 2.15 Synthesis of dithiacyclophanes **9n-q**.

The final cyclizations of dibromides **19n-q** were realized by utilizing the Na_2S/Al_2O_3 coupling[34] developed by our group. Under these conditions, dithiacyclophanes **9n** (46%), **9o** (a diastereomeric mixture with a ratio of 1/0.85, 36%), **9p** (35%) and **9q** (22%), were obtained in varied yields, and, in the case of cyclization of **19n** and **19o**, trimeric cyclophanes **21n** and **21o** (a diastereomeric mixture with a ratio of 1/1) were also isolated, both in 23% yields (Scheme 2.15). Significant fractions of cyclic trimers from **19p** and **19q** were also observed, but the isolation from their dimeric cyclophanes was not easy. Therefore, the yields for **9p** and **9q** are actually higher than those listed.



Scheme 2.16 Synthesis of cyclophanes **9m** and **35**.

As proposed, the synthesis of cyclophane **9m** was accomplished by deprotecting the pivaloyl groups in **9q** via basic hydrolysis (Scheme 2.16). Interestingly, the initial trial in the presence of CH_2Cl_2 as a co-solvent afforded only a multibridged cyclophane **35** (43%). This probably originated from the nucleophilic attack of *in situ* generated thiolate ion on CH_2Cl_2 followed by cyclization. To avoid this problem, the reaction conditions were modified to exclude CH_2Cl_2 and **9m** was obtained quantitatively.

2.2.3 NMR Investigations

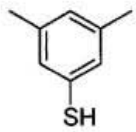
For results of the NMR studies of the bridge conformational behavior of the dithiacyclophanes **9a-q** (Figure 2.6), correlations with physical organic chemistry parameters and some dynamic NMR (DNMR) studies, the thesis of Dr. Vermeij[3] should be consulted.

2.3 Experimental

General Experimental for Chapter 2. Reactions were performed under air unless otherwise indicated. Those experiments with moisture or air sensitive

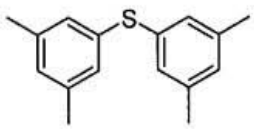
compounds were performed in anhydrous solvents under nitrogen in flame-dried glassware. Solvents for reactions were dried and distilled according to standard procedures. All other solvents were used as received. Chromatographic purifications were accomplished using 230-400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp in most cases and sometimes were also developed in PMA and vanillin dips. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on neat samples or nujol suspensions in KBr discs using a Mattson Polaris FT instrument. ^{1}H NMR spectra were obtained from $CDCl_3$ solutions using a General Electric GE-300 NB instrument operating at 300.1 MHz. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 MHz. Chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$). Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. High resolution mass spectroscopic data were performed by the Mass Spectrometry Centre, Chemistry Department, University of Ottawa, Ottawa, Ontario.

3,5-Dimethylbenzenethiol (14m)



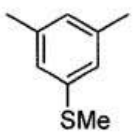
To I_2-activated Mg shavings (3.21 g, 132 mmol) at 0 °C was added a solution of 5-bromo-*m*-xylene (22.2 g, 120 mmol) in dry THF (200 mL) dropwise to afford a grey-brownish suspension. The suspension was heated at reflux for 1 h, cooled to 0 °C on an ice bath, and then sulfur powder (3.85 g, 120 mmol) was added portionwise. The resulting mixture was heated at reflux for 1 h. The mixture was cooled on an ice bath, $LiAlH_4$ (1.37 g, 36.0 mmol) was added portionwise, and the mixture was again brought to reflux for 1 h. The reaction mixture was then cooled again on an ice bath and quenched with EtOAc (15 mL), H_2O (10 mL) and HCl (1.2 N, 100 mL). The resulting mixture was extracted with Et_2O (150 mL×2), and the combined organic layers were extracted with NaOH aqueous solution (1 N, 400 mL). The aqueous layer was acidified with HCl solution (12 N, 40 mL) and extracted with Et_2O (100 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Vacuum distillation at 95-97 °C/8 mm Hg (Aldrich 2000-2001 catalog reported: bp=127.5 °C/50 mm Hg) gave **14m** (12.8 g, 77%) as a clear, colorless oil. IR (nujol) ν=2564 (w), 1601 (m) cm^{-1}. MS *m/z* (%)=139 (11), 138 (100, M^+), 105 (97). ^1H NMR ($CDCl_3$): δ=2.24-2.25 (m, 6H), 3.35 (s, 1H), 6.77-6.78 (m, 1H), 6.89-6.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=21.1, 127.0, 127.4, 130.1, 138.7. Anal. Calcd. for $C_8H_{10}S$: C, 69.51; H, 7.29. Found: C, 69.62; H, 7.29.

3,5-Dimethylphenyl sulfide (16)



Column chromatography (3% CH_2Cl_2/petroleum ether) of the contents of the organic layers after NaOH extraction, from above, gave **16** (943 mg, 6%) as a white solid. M.p.=47-49 °C. IR (nujol) ν=1599 (m), 1583 (m), 867 (m), 836 (m) cm^{-1}. MS *m/z* (%)=243 (22), 242 (100, M^+), 227 (13), 212 (22), 77 (11). ^1H NMR ($CDCl_3$): δ=2.26-2.27 (m, 12H), 6.86-6.87 (m, 2H), 6.96-6.97 (m, 4H). ^{13}C NMR ($CDCl_3$): δ=21.2, 128.6, 128.8, 135.3, 138.7. Anal. Calcd. for $C_{16}H_{18}S$: C, 79.29; H, 7.49. Found: C, 79.03; H, 7.37.

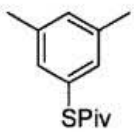
5-(Methylsulfanyl)-*m*-xylene (14n)



To a solution of **14m** (6.91 g, 50.0 mmol) in dry THF (40 mL) was added freshly ground NaOH (6.00 g, 150 mmol) to afford a light yellow slurry. After stirring at room temperature for 1 h, the slurry was treated with MeI (28.4 g, 200 mmol). The reaction mixture was stirred for 12 h, diluted with H_2O (50 mL), and extracted with Et_2O (50 mL×2). The combined organic layers were washed with NaOH aqueous solution (1 M, 60 mL×3) and brine (100 mL), dried over $MgSO_4$,

filtered and concentrated. Vacuum distillation at 67-69 °C/2 mm Hg gave **14n** (6.94 g, 91%) as a clear, colorless oil. IR (KBr) ν=1599 (m), 1583 (m), 867 (m), 836 (m) cm^{-1}. MS *m/z* (%)=153 (11), 152 (100, M^+), 137 (20), 119 (74), 91 (64), 77 (37). ^1H NMR ($CDCl_3$): δ=2.28-2.29 (m, 6H), 2.46 (s, 3H), 6.76-6.77 (m, 1H), 6.88-6.89 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=15.8, 21.3, 124.3, 127.0, 137.9, 138.4. Anal. Calcd. for $C_9H_{12}S$: C, 71.00; H, 7.94. Found: C, 71.50; H, 8.18.

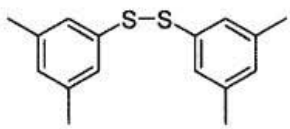
5-(Pivaloylsulfanyl)-*m*-xylene (14q)



To a solution of **14m** (2.76 g, 20.0 mmol) in CH_2Cl_2 (10 mL) and Et_3N (20 mL) at 0 °C was added a solution of pivaloyl chloride (2.89 g, 24.0 mmol) in CH_2Cl_2 (10 mL) slowly. After stirring at room temperature for 12 h, the reaction mixture was treated with HCl (1.2 M, 20 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with HCl (1.2 M, 80 mL×2) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% CH_2Cl_2/petroleum ether) gave **14q** (R_f 0.35, 4.14 g, 93%) as a clear, colorless oil. IR (KBr) ν=1697 (s), 1603 (m), 1583 (m) cm^{-1}. MS *m/z* (%)=223 (1), 222 (6, M^+), 138 (38), 85 (27), 57 (100). ^1H NMR ($CDCl_3$): δ=1.31 (s, 9H), 2.31-2.32 (m, 6H), 7.01-7.02 (m, 3H). ^{13}C NMR ($CDCl_3$): δ=21.1, 27.4, 46.9,

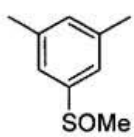
127.3, 131.0, 132.5, 138.7, 205.1. Anal. Calcd. for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.70; H, 8.51.

3,5-Dimethylphenyl disulfide (17)



A by-product, **17** (R_f 0.65, 124 mg, 5%), was also obtained from the above procedure as a clear, colorless oil. IR (KBr) ν=1601 (m), 1578 (m), 838 (m), 662 (m) cm^{-1}. MS *m/z* (%)=275 (19), 274 (100, M^+), 226 (15), 137 (72), 77 (28). ^1H NMR ($CDCl_3$): δ=2.27-2.28 (m, 12H), 6.84-6.85 (m, 2H), 7.11-7.12 (m, 4H). ^{13}C NMR ($CDCl_3$): δ=21.2, 125.0, 129.0, 136.8, 138.7. Anal. Calcd. for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61. Found: C, 70.51; H, 6.91.

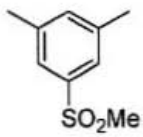
(±)-5-(Methylsulfinyl)-*m*-xylene (14o)



To a solution of $NaIO_4$ (590 mg, 2.76 mmol) in H_2O (5 mL) at 0 °C was added a solution of **14n** (400 mg, 2.63 mmol) dropwise. After the reaction mixture was stirred for 12 h at 0 °C, the white $NaIO_3$ precipitate was removed by gravity filtration and rinsed with CH_2Cl_2 (10 mL). The filtrate was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layers were dried over $MgSO_4$,

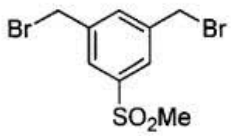
filtered and concentrated. Column chromatography (3% MeOH/CH_2Cl_2) gave **14o** (355 mg, 80%) as a clear, colorless oil. IR (KBr) ν=1606 (w), 1059 (s) cm^{-1}. MS *m/z* (%)=169 (8), 168 (72, M^+), 153 (100), 105 (25), 91 (36), 77 (43). ^1H NMR ($CDCl_3$): δ=2.38-2.39 (m, 6H), 2.71 (s, 3H), 7.11-7.12 (m, 1H), 7.24-7.25 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=21.2, 43.9, 120.8, 132.7, 139.3, 145.4. Anal. Calcd. for $C_9H_{12}OS$: C, 64.25; H, 7.19. Found: C, 64.11; H, 7.00.

5-(Methylsulfonyl)-*m*-xylene (14p)



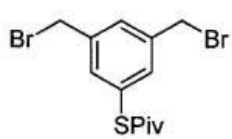
To a solution of **14n** (540 mg, 3.55 mmol) in HOAc (3 mL) at room temperature was injected H_2O_2 (30%, 1.83 mL, 17.8 mmol). After refluxing for 3 h, the reaction mixture was quenched with H_2O (20 mL) at 0 °C, and extracted with Et_2O (25 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (25% EtOAc/petroleum ether) **14p** (570 mg, 87%) as a white solid. M.p.=83-84 °C. IR (nujol) ν=1609 (w), 1315 (s), 1302 (s), 1146 (s) cm^{-1}. MS *m/z* (%)=185 (4), 184 (36, M^+), 169 (18), 121 (20), 105 (100), 77 (33). ^1H NMR ($CDCl_3$): δ=2.40-2.41 (m, 6H), 3.04 (s, 3H), 7.26-7.27 (m, 1H), 7.55-7.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=21.2, 44.5, 124.8, 135.3, 139.4, 140.3. Anal. Calcd. for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.46; H, 6.55.

1,3-Bis(bromomethyl)-5-(methylsulfonyl)benzene (19p)



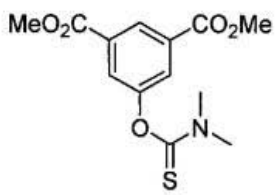
N-Bromosuccinimide (4.91 g, 27.6 mmol) and benzoyl peroxide (291 mg, 1.20 mmol) were added in two equal portions over 2 h to a boiling solution of **14p** (2.20 g, 11.9 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at reflux while being irradiated with a 100 W lamp for 6 h, and then it was cooled to room temperature, washed with H_2O (100 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (30% EtOAc/petroleum ether) gave **19p** (1.98 g, 48%) as a white solid. M.p.=131-133 °C. IR (nujol) ν=1606 (w), 1320 (m), 1296 (s), 1145 (s), 1132 (m) cm^{-1}. MS *m/z* (%)=344 (1, M^+ $^{81}Br_2$), 342 (2, M^+ $^{81}Br^{79}Br$), 340 (1, M^+ $^{79}Br_2$), 263 (100), 261 (98), 182 (46), 103 (28), 77 (43). ^1H NMR ($CDCl_3$): δ=3.10 (s, 3H), 4.52 (s, 4H), 7.71-7.72 (m, 1H), 7.89-7.90 (m, 2H). ^{13}C NMR ($CDCl_3$): δ=30.9, 44.4, 127.5, 134.6, 140.2, 141.7. Anal. Calcd. for $C_9H_{10}Br_2O_2S$: C, 31.60; H, 2.95. Found: C, 31.76; H, 2.84.

1,3 Bis(bromomethyl)-5-(pivaloylsulfanyl)benzene (19q)



N-Bromosuccinimide (3.13 g, 17.6 mmol) and benzoyl peroxide (185 mg, 0.760 mmol) were added in two equal portions over 2 h to a boiling solution of **14q** (1.70 g, 7.60 mmol) in CCl_4 (50 mL). The mixture was stirred at reflux for 5 h, cooled to room temperature, washed with H_2O (100 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (3% EtOAc/petroleum ether) gave **19q** (1.92 g, 66%) as a white solid. M.p.=45-46 °C. IR (nujol) ν=1702 (s), 1600 (w), 1581 (w) cm^{-1}. MS *m/z* (%)=382 (not observed, M^+ $^{81}Br_2$), 380 (0.3, M^+ $^{81}Br^{79}Br$), 378 (not observed, M^+ $^{79}Br_2$), 217 (4), 215 (4), 85 (31), 57 (100). ^1H NMR ($CDCl_3$): δ=1.32 (s, 9H), 4.46 (s, 4H), 7.35-7.36 (m, 2H), 7.43-7.44 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=27.4, 32.0, 47.1, 129.4, 130.3, 135.1, 139.2, 203.8. Anal. Calcd. for $C_{13}H_{16}Br_2OS$: C, 41.07; H, 4.24. Found: C, 41.02; H, 4.20.

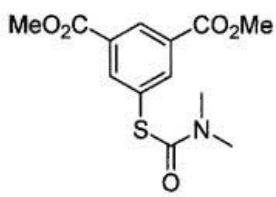
Dimethyl 5-(*N,N*-dimethylthiocarbamoyloxy)isophthalate (26)



To a solution of **25** (8.41 g, 40.0 mmol) in DMF (30 mL) at room temperature was added NaH (60% dispersion in mineral oil, 1.76 g, 44.0 mmol) in small portions over 30 min. After H_2 evolution ceased, *N,N*-dimethylthiocarbamoyl chloride (7.42 g, 60.0 mmol) was added into the mixture at 0 °C in one portion. The reaction mixture was heated at 50 °C for 2 h, diluted with EtOAc (50 mL),

quenched with H_2O (50 mL), and extracted with EtOAc (100 mL×3). The combined organic layers were washed with H_2O (100 mL×4) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (CH_2Cl_2/petroleum ether/EtOAc, 50/45/5) gave **26** (9.95 g, 84%) as a slightly yellow solid. Crystallization from MeOH afforded white, fine needles. M.p.=105-106 °C. IR (nujol) ν=1720 (s), 1536 (s), 1245 (s) cm^{-1}. MS *m/z* (%)=297 (1, M^+), 266 (5), 88 (79), 72 (100). ^1H NMR ($CDCl_3$): δ=3.38 (s, 3H), 3.47 (s, 3H), 3.94 (s, 6H), 7.93 (d, *J*=1.6 Hz, 2H), 8.59 (t, *J*=1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=38.8, 43.4, 52.5, 128.1 (br), 128.4 (br), 131.6, 153.9, 165.4, 187.0. Anal. Calcd. for $C_{13}H_{15}NO_5S$: C, 52.51; H, 5.08; N, 4.71. Found: C, 52.56; H, 5.00; N, 4.66.

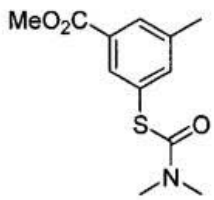
Dimethyl 5-(*N,N*-dimethylcarbamoylsulfanyl)isophthalate (27)



Neat **26** (2.00 g, 6.70 mmol) was heated to 210 °C for 30 min. The resulting mixture was cooled to room temperature and column chromatography (7.5% EtOAc/CH_2Cl_2) gave **27** (1.72 g, 86%) as a white solid. M.p.=106-108 °C. IR (nujol) ν=1733 (s), 1678 (s) cm^{-1}. MS *m/z* (%)=297 (1, M^+), 266 (7), 195 (3), 72 (100). ^1H NMR ($CDCl_3$): δ=3.05 (bs, 3H), 3.11 (bs, 3H), 3.94 (s, 6H), 8.34 (d,

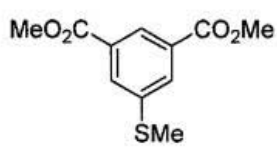
J=1.6 Hz, 2H), 8.70 (t, J=1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=37.0 (br), 52.5, 130.4, 131.2, 131.3, 140.6, 140.7, 165.5. Anal. Calcd. for $C_{13}H_{15}NO_5S$: C, 52.51; H, 5.08; N, 4.71. Found: C, 52.68; H, 5.02; N, 4.62.

Methyl 3-(*N,N*-dimethylcarbamoylsulfanyl)-5-methylbenzoate (31)



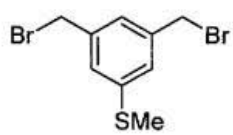
Neat **26** (2.00 g, 6.70 mmol) was heated to 230 °C for 1 h. The resulting mixture was cooled to room temperature and column chromatography (20% EtOAc/CH_2Cl_2) afforded **31** (492 mg, 29%) as a yellow oil. IR (KBr) ν=1721 (s), 1637 (s) cm^{-1}. MS *m/z* (%)=254 (12), 253 (66, M^+), 252 (43), 209 (100), 181 (41), 166 (27). ^{1}H NMR ($CDCl_3$): δ=2.53 (s, 3H), 2.99 (bs, 3H), 3.12 (bs, 3H), 3.93 (s, 3H), 7.46-7.47 (m, 1H), 7.80-7.81 (m, 1H), 7.92-7.93 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=15.3, 35.3, 39.4, 52.3, 124.2 (br), 127.7 (br), 128.6, 130.6, 137.0, 140.3, 165.9, 169.9. Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.77; H, 6.00; N, 5.44.

Dimethyl 5-(methylsulfanyl)isophthalate (34)



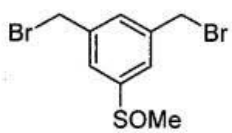
A mixture of **27** (230 mg, 0.770 mmol), and freshly ground KOH (173 mg, 3.08 mmol) in MeOH (15 mL) and H_2O (5 mL) was heated at reflux for 6 h. The reaction mixture was diluted with H_2O (50 mL), washed with CH_2Cl_2 (50 mL×2), acidified with HCl (12 N, 2 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a white solid. The dried solid was then mixed in DMF (10 mL) along with Cs_2CO_3 (1.00 g, 3.08 mmol) to afford a yellow slurry. The slurry was stirred at room temperature for 1 h and treated with a solution of MeI (656 mg, 4.62 mmol) in DMF (5 mL). The resulting mixture was stirred for 12 h, diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with H_2O (100 mL×3) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (CH_2Cl_2) gave **34** (104 mg, 56%) as a white solid. M.p.=103-104 °C. IR (nujol) ν=1723 (s), 1597 (w), 1575 (m) cm^{-1}. MS *m/z* (%)=241 (13), 240 (100, M^+), 209 (86), 181 (29), 166 (20). ^1H NMR ($CDCl_3$): δ=2.56 (s, 3H), 3.95 (s, 6H), 8.06 (d, *J*=1.5 Hz, 2H), 8.41 (t, *J*=1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=15.5, 52.5, 126.9 (br), 130.9 (br), 131.0, 140.4, 165.9. Anal. Calcd. for $C_{11}H_{12}O_4S$: C, 54.99; H, 5.03. Found: C, 54.78; H, 4.86.

1,3-Bis(bromomethyl)-5-(methylsulfanyl)benzene (19n)



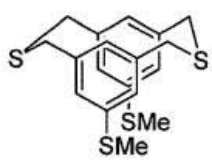
To a slurry of $LiAlH_4$ (370 mg, 9.72 mmol) in dry ether (20 mL) at room temperature was added **34** (390 mg, 1.62 mmol) in dry ether (10 mL) dropwise over 10 min. After stirring for 12 h, the reaction mixture was treated with H_2O (5 mL) and HCl (1.2 N, 50 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated to give a tan solid. To a solution of the dried solid in CH_2Cl_2 (40 mL) at 0 °C was injected PBr_3 (879 mg, 3.24 mmol) dropwise. The reaction mixture was allowed to warm to room temperature upon addition of PBr_3. The resulting mixture was stirred for 3 h, treated with H_2O (30 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (25% CH_2Cl_2/petroleum ether) gave **19n** (233 mg, 46%) as white, fine needles. M.p.=86-88 °C. IR (nujol) ν=1583 (w) cm^{-1}. MS *m/z* (%)=312 (16, , M^+ $^{81}Br_2$), 310 (30, M^+ $^{81}Br^{79}Br$), 308 (15, , M^+ $^{79}Br_2$), 231 (100), 229 (97), 150 (72). ^1H NMR ($CDCl_3$): δ=2.50 (s, 3H), 4.43 (s, 4H), 7.17-7.18 (m, 3H). ^{13}C NMR ($CDCl_3$): δ=15.5, 32.5, 126.1, 126.6, 138.9, 140.2. Anal. Calcd. for $C_9H_{10}Br_2S$: C, 34.86; H, 3.25. Found: C, 34.73; H, 3.12.

(±)-1,3-Bis(bromomethyl)-5-(methylsulfinyl)benzene (19o)



To a solution of **19n** (50 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of *m*-CPBA (assuming 70% purity, 40 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) slowly. After stirring for 1 h, the reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (EtOAc) gave **19o** (47 mg, 89%) as a white solid. M.p.=115-117 °C. IR (nujol) v=1602 (w), 1053 (s) cm^{-1}. MS *m/z* (%)=328 (26, M^+ $^{81}Br_2$), 326 (47, M^+ $^{81}Br^{79}Br$), 324 (24, M^+ $^{79}Br_2$), 313 (35), 311 (68), 309 (34), 247 (100), 245 (98), 232 (97), 230 (95), 151 (26), 77 (62). ^1H NMR ($CDCl_3$): δ=2.77 (s, 3H), 4.51 (s, 4H), 7.55 (t, *J*=1.6 Hz, 1H), 7.60 (d, *J*=1.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=31.5, 43.9, 123.7, 132.1, 140.0, 147.4. Anal. Calcd. for $C_9H_{10}Br_2OS$: C, 33.15; H, 3.09. Found: C, 33.10; H, 2.99.

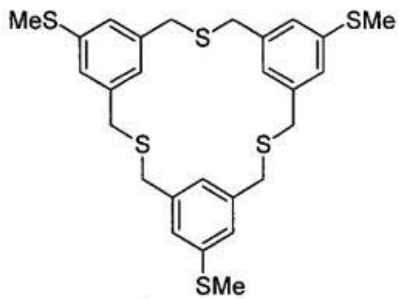
syn-6,15-Bis(methylsulfanyl)-2,11-dithia[3.3]metacyclophane (9n)



To a vigorously stirred solution of **19n** (230 mg, 0.742 mmol) in 10% EtOH/CH_2Cl_2 (55 mL) was added Na_2S/Al_2O_3 (547 mg, 1.48 mmol) in four equal portions over 1 h. After the mixture was stirred at room temperature for an additional 2 h, it was suction filtered through a plug of Celite and concentrated. Immediate column chromatography (50% CH_2Cl_2/petroleum ether) of the residue

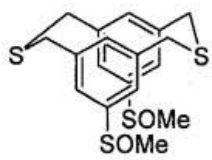
gave **9n** (R_f 0.40, 63 mg, 46%) as a white solid. M.p.=127-128 °C. IR (nujol) ν=1578 (m) cm^{-1}. MS *m/z* (%)=365 (18), 364 (84, M^+), 182 (46), 152 (100), 105 (28). ^1H NMR ($CDCl_3$): δ=2.42 (s, 6H), 3.73 (s, 8H), 6.77 (bs, 4H), 6.78 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ=16.1, 37.9, 125.5, 128.6, 137.6, 138.3. Anal. Calcd. for $C_{18}H_{20}S_4$: C, 59.29; H, 5.53. Found: C, 59.15; H, 5.36.

6,15,24-Tris(methylsulfanyl)-2,11,20-trithia[3.3]metacyclophane (21n)



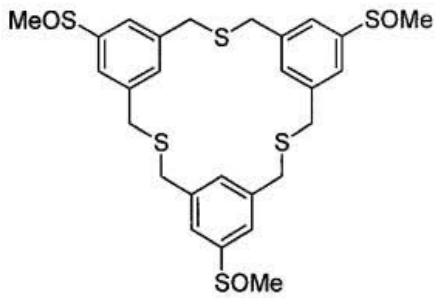
Trimeric isomer, **21n** (R_f 0.32, 32 mg, 23%), was also obtained from the above procedure as a white solid. M.p.=154-155 °C. IR (nujol) ν=1578 (m) cm^{-1}. MS *m/z* (%)=547 (17), 546 (51, M^+), 363 (24), 151 (100). ^1H NMR ($CDCl_3$): δ=2.51 (s, 9H), 3.51 (s, 12H), 6.85 (bs, 3H), 7.18-7.19 (m, 6H). ^{13}C NMR ($CDCl_3$): δ=15.5, 34.7, 125.4, 126.7, 138.7, 139.8. Anal. Calcd. for $C_{27}H_{30}S_6$: C, 59.29; H, 5.53. Found: C, 58.47; H, 5.43. HRMS Calcd. for $C_{27}H_{30}S_6$: 546.0670. Found: 546.0700.

(±)-(*R,*R**/*R**,*S**)-*syn*-6,15-Bis(methylsufinyl)-2,11-dithia[3.3]metacyclophane (9o)**



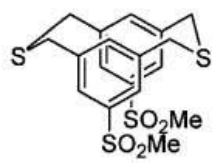
To a vigorously stirred solution of **19o** (260 mg, 0.797 mmol) in 10% $EtOH/CH_2Cl_2$ (55 mL) was added Na_2S/Al_2O_3 (589 mg, 1.59 mmol) in four equal portions over 1 h. After the mixture was stirred at room temperature for additional 5 h, it was suction filtered through a plug of Celite and concentrated. Immediate column chromatography (5% $MeOH/CH_2Cl_2$) of the residue gave isomeric mixture **9o** (diastereomeric ratio 1/0.85, R_f 0.27, 57 mg, 36%) as a white solid. M.p.=207-210 °C. IR (nujol) ν=1598 (w), 1047 (s) cm^{-1}. MS *m/z* (%)=397 (18), 396 (66, M^+), 329 (50), 152 (100), 105 (61). ^1H NMR ($CDCl_3$): δ=2.58/2.59 (ratio 1/0.85, s, 6H), 3.85/3.86 (ratio 1/0.85, s, 8H), 7.10/7.11 (ratio 1/0.85, sb, 4H), 7.30/7.33 (ratio 1/0.85, bs, 2H). ^{13}C NMR ($CDCl_3$): δ=37.9, 38.1, 43.6, 43.9, 121.7, 121.9, 133.6, 133.7, 138.8, 138.9, 145.9, 146.0. Anal. Calcd. for $C_{18}H_{20}O_2S_4$: C, 54.51; H, 5.08. Found: C, 54.13; H, 4.97.

(±)-(*R*,R*,R*/R*,R*,S)-6,15,24-Tris(methylsulfinyl)-2,11,20-trithia[3.3.3]metacyclophane (21o)**



Trimeric isomer, **21o** (diastereomeric ratio 1/1, R_f 0.17, 36 mg, 23%), was also obtained from the above procedure as a white solid. M.p.=212-213 °C. IR (nujol) ν=1599 (w), 1034 (s) cm^{-1}. MS *m/z* (%)=594 (7, M^+), 578 (7), 397 (23), 151 (30), 128 (100). ^1H NMR ($CDCl_3$): δ=2.77 (s, 9H), 3.63 (s, 12H), 7.23/7.25 (ratio 1/1, bs, 3H), 7.59 (bs, 6H). ^{13}C NMR ($CDCl_3$): δ=35.0, 43.8, 122.9, 132.0, 139.7, 147.3. Anal. Calcd. for $C_{27}H_{30}O_3S_6$: C, 54.51; H, 5.08. Found: C, 53.94; H, 5.00.

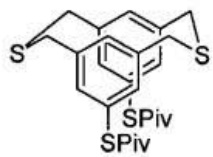
syn-6,15-Bis(methylsulfonyl)-2,11-dithia[3.3]metacyclophane (9p)



To a vigorously stirred solution of **19p** (1.80 g, 5.26 mmol) in 10% EtOH/CH_2Cl_2 (370 mL) was added Na_2S/Al_2O_3 (3.88 g, 10.5 mmol) in four equal portions over 1 h. After the mixture was stirred at room temperature for additional 3 h, it was suction filtered through a plug of Celite and concentrated. Immediate column chromatography (10% EtOAc/CH_2Cl_2) of the residue gave **9p** (393 mg, 35%) as a

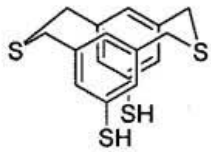
white solid. M.p.=252-254 °C. IR (nujol) ν=1604 (w), 1302 (s), 1137 (s) cm^{-1}. MS *m/z* (%)=429 (2), 428 (15, M^+), 215 (18), 183 (29), 149 (47), 57 (100). ^1H NMR ($CDCl_3$): δ=2.93 (s, 6H), 3.90 (s, 8H), 7.38-7.39 (m, 4H), 7.56 (bs, 2H). ^{13}C NMR ($CDCl_3$): δ=38.0, 44.6, 125.8, 135.7, 139.1, 141.1. Anal. Calcd. for $C_{18}H_{20}O_4S_4$: C, 50.44; H, 4.70. Found: C, 49.92; H, 4.57.

syn-6,15-Bis(pivaloylsulfanyl)-2,11-dithia[3.3]metacyclophane (9q)



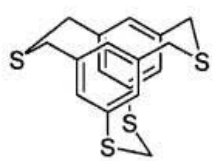
To a vigorously stirred solution of **19q** (2.23 g, 5.87 mmol) in 10% EtOH/CH_2Cl_2 (440 mL) was added Na_2S/Al_2O_3 (4.33 g, 11.7 mmol) in four equal portions over 1 h. After the mixture was stirred at room temperature for additional 3 h, it was suction filtered through a plug of Celite and concentrated. Immediate column chromatography (70% CH_2Cl_2/petroleum ether) of the residue gave **9q** (322 mg, 22%) as a white solid. M.p.=56-58 °C. IR (nujol) ν=1697 (s), 1596 (w), 1580 (w) cm^{-1}. MS *m/z* (%)=505 (2), 504 (7, M^+), 420 (2), 336 (2), 85 (23), 57 (100). ^1H NMR ($CDCl_3$): δ=1.30 (s, 18H), 3.75 (s, 8H), 6.90 (bs, 2H), 6.95-6.96 (m, 4H). ^{13}C NMR ($CDCl_3$): δ=27.4, 37.2, 46.8, 128.1, 132.4, 133.5, 137.8, 204.5. Anal. Calcd. for $C_{26}H_{32}O_2S_4$: C, 61.86; H, 6.39. Found: C, 61.04; H, 6.43. HRMS Calcd. for $C_{26}H_{32}O_2S_4$: 504.1283. Found: 504.1282.

syn-6,15-Bis(hydrosulfanyl)-2,11-dithia[3.3]metacyclophane (9m)



A mixture of **9q** (50 mg, 0.10 mmol) and NaOH (200 mg, 5.00 mmol) in MeOH (8 mL), H_2O (3 mL) and THF (2 mL) was heated at reflux for 12 h. The reaction mixture was acidified with HCl (12 N, 3 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **9m** (33 mg, 100%) as a white solid. M.p.=134-136 °C. IR (nujol) ν=1581 (m) cm^{-1}. MS *m/z* (%)=337 (17), 336 (83, M^+), 199 (11), 168 (44), 138 (100). ^1H NMR ($CDCl_3$): δ=3.42 (s, 2H), 3.70 (s, 8H), 6.78 (bs, 2H), 6.84-6.85 (m, 4H). ^{13}C NMR ($CDCl_3$): δ=37.7, 128.5, 129.3, 130.6, 137.9. Anal. Calcd. for $C_{16}H_{16}S_4$: C, 57.10; H, 4.79. Found: C, 57.12; H, 4.72.

1,3,11,20-Tetrathia[3.3.3](1,3,5)cyclophane (35)



A mixture of **9q** (50 mg, 0.10 mmol) and NaOH (200 mg, 5.00 mmol) in MeOH (5 mL) and CH_2Cl_2 (1 mL) was heated at reflux for 12 h. The reaction mixture was acidified with HCl (12 N, 3 mL) and extracted with CH_2Cl_2 (25 mL×2). The

combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (50% CH_2Cl_2/petroleum ether) gave **35** (15 mg, 43%) as a white solid. M.p. > 250 °C. MS *m/z* (%)=349 (22), 348 (100, M^+), 149 (15), 91 (12). ^1H NMR ($CDCl_3$): δ=3.81-3.93 (m, 8H), 4.92 (bs, 2H), 6.90 (bs, 2H), 7.31 (bs, 4H). ^{13}C NMR ($CDCl_3$): δ=38.2, 42.9, 132.2, 132.5, 134.7 (br), 138.3. HRMS Calcd. for $C_{17}H_{16}S_4$: 348.0134. Found: 348.0145.

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CHAPTER 3 Synthesis and Conformational Behavior of Some (1,3)Indolophanes

3.1 Introduction

3.1.1 Heterophanes

According to Vögtle's classification,[1,2] the cyclophane class of compounds is first divided into two groups: the "carbophanes" and "heterophanes", depending on the structural features of the aromatic nuclei present in the molecule. Carbophanes are cyclophanes in which all the aromatic nuclei are *all*-carbon aromatic rings and the term "heterophanes" is used to designate compounds with at least one heteroaomatic core unit as part of the cyclophane structure. Under the latter category, many different types of heteroaromatic moieties, including π-excessive systems such as furan, pyrrole and thiophene, and π-deficient systems such as pyridine, pyridazine and triazines, have been embodied in cyclophanes in a variety of ways.[3]

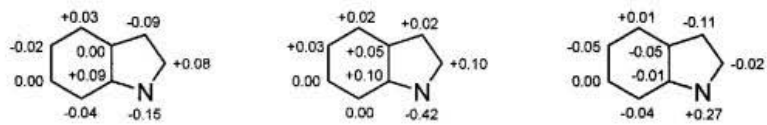
The conformational properties of heterophanes are one of the most widely studied aspects of this class of compounds. This has been accomplished primarily by NMR spectroscopy, X-ray crystallography and ultraviolet (UV) spectroscopy. The principal compounds of interest are small heterophanes, especially [2.2]phanes,[4-6] [3.3]phanes,[4-8] [*n*]phanes[9] (n=6-10) and multibridged phanes.[10] Other fundamental research has been mainly focused on complexation studies with transition metals.[7,11,12]

In terms of synthetic interest, attention has been directed toward searching for new types of heterophanes, pursuing challenging targets, methodological studies and reactivity investigations. The majority of heterophanes belong to one of the following categories: mononuclear π-excessive, multinuclear π-excessive, mononuclear π-deficient or multinuclear π-deficient systems.[3] The relative rarity of systems that are directly related to donor-acceptor type carbophanes,[13] multinuclear π-excessive/π-deficient heterophanes, provided the impetus to the recent synthesis of a series of heterophanes with betaines[14-16] after the first reported examples of such a system.[17,18] Other new types of heterophanes appeared as cyclophanes with some uncommon heteroaromatic moieties, including benzothiazole,[19,20] indolizine,[21] and 1,5,2,4,6,8-dithiatetrazocine,[22] incorporated into the system. As a rich extension of Boekelheide's ground-breaking work on superphane,[23-25] several impressive hetero "superphanes"[26-31] have been accomplished. General synthetic methodologies for the synthesis of small heterophanes have been reported on a few occasions,[32,33] and more extensively for the synthesis of larger heterophanes.[34] Finally, various investigations of the reactivity of heterophanes, such as in cycloadditions,[35,36] have also been conducted.

3.1.2 Indole

Indole is a planar heteroaromatic molecule.[37-39] It belongs to the group of heterocycles designated "π-excessive heteroaromatics", which means that the π-

electron densities on their carbon atoms is greater than that on the carbon atoms of benzene.[40] Being isoelectronic with naphthalene, indole has ten π-electrons, with the heterocyclic nitrogen atom donating two of them, free to circulate throughout the molecule.[37] Its total net atomic electron densities, as the sum of the net sigma atomic electron densities and the net π electron densities, have been obtained from self-consistent field molecular orbital calculations, which gave dipole moments in excellent agreement with experimental values (Figure 3.1).[41] The aromaticity of indole is indicated by the effect of its ring currents in NMR spectra,[37] appreciable resonance energy of 47 kcal/mol,[38,39,42] and its behavior in various chemical reactions.



total net atomic electron densities | net σ atomic electron densities | net π atomic electron densities

Figure 3.1 Total net atomic electron densities, net σ atomic electron densities and net π atomic electron densities of indole (Hydrogen atoms and double bonds have been ommited for clarity).

Resonance theory has been valuable in explaining certain properties and the reactivity of indole qualitatively. In this theory, the mathematical function that represents the properties of the π-electrons of an aromatic system is approximated as a linear combination of the functions of suitable contributing structures. For indole many contributing structures are possible.[37] The most fundamental chemical properties of the indole ring, originating from its

aromaticity, can be predicted by three of the most important of its many resonance structures (Figure 3.2).[39] The development of indole chemistry, initiated by intensive research on the dye indigo, began in the mid-nineteenth century with meaningful investigations regarding its oxidation, reduction and synthesis.[43] As anticipated for a π-excessive heteroromatic compound, indole is highly reactive toward electrophilic reagents, including acids, certain oxidants and many other electrophiles. A variety of theoretical reactivity indices, including the above-described net π atomic electron densities and major resonance structures, predict C3 to be the preferred site of electrophilic substitutions. These theoretical treatments are fully consistent with indole's most fundamental chemical behavior, which has been a subject of study for well over a century.[37-39,44,45] Fruitful work in this area continues to be conducted today.[46]

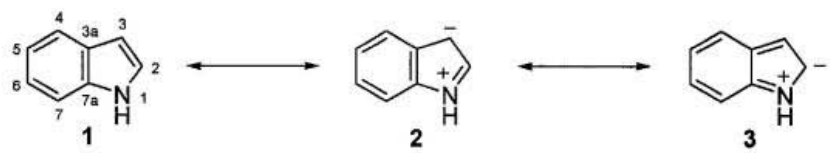
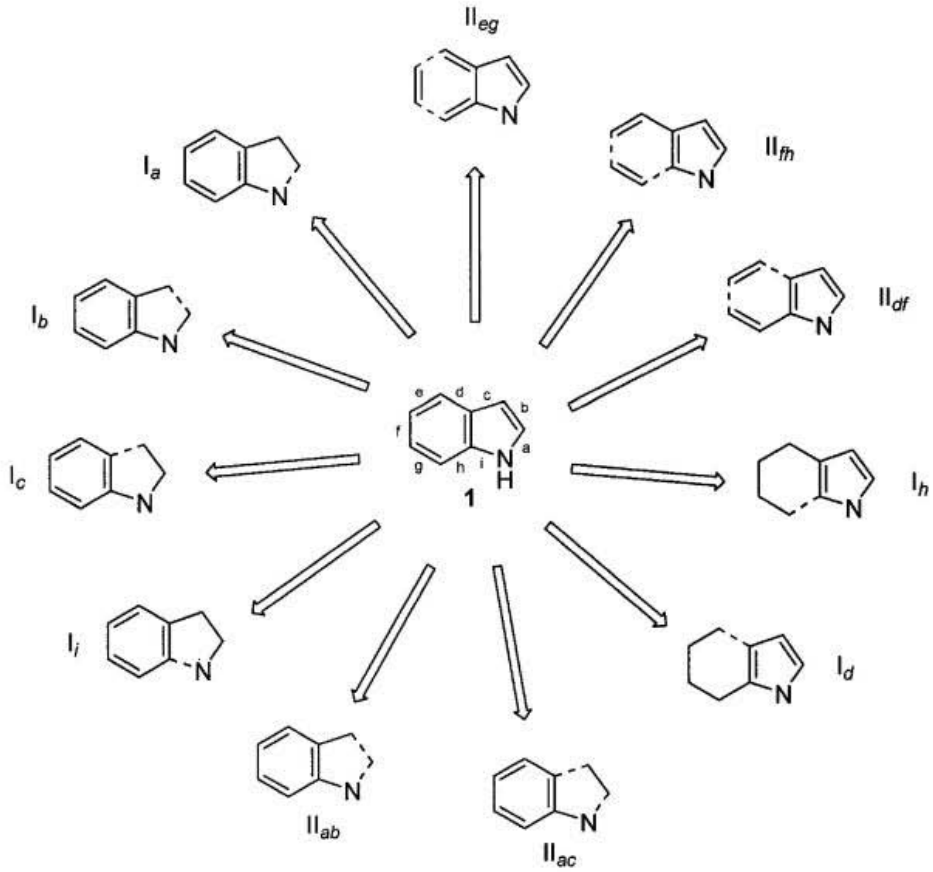


Figure 3.2 Simplified resonance description of indole.

The first preparation of indole dates from 1866 by Baeyer,[47] and the Fischer indole synthesis, which remains the most versatile route for preparing indoles, was first reported in 1883.[48-51] The currently available strategies for the synthesis of the indole nucleus can be classified into eleven categories, according to retrosynthetic bond disconnections (Scheme 3.1).[39]



Scheme 3.1 Retrosynthetic analysis of the indole system.

These strategies can be also viewed as two groups depending on the structures of starting materials involved. The first group(I_a, I_b, I_c, I_i, II_{ab}, and II_{ac}), which represents most indole-forming reactions, begins with benzenoid precursors, and the additional stabilization resulting from the formation of the fused pyrrole ring provides a driving force for indole ring formation. The second group, I_d, I_h, II_{df}, II_{fh}, and II_{eg}, can be described as pyrrole annulation reactions. In terms of reaction types, the indole ring synthesis can be alternatively

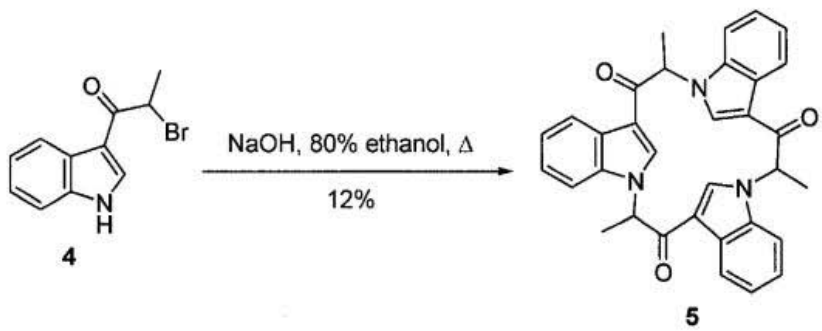
categorized as sigmatropic rearrangements, nucleophilic cyclization, electrophilic cyclization, reductive cyclization, oxidative cyclization, radical cyclization, metal-catalyzed synthesis and cycloadditions.[52]

The principal commercial source of indole is extraction from coal tar.[53] Despite its notorious stench, indole has been used in perfumery because of its pleasant odor in highly diluted solution.[53] The indole ring also appears in many natural products such as indole alkaloids, fungal metabolites, and marine natural products.[39] The biosynthesis of indole alkaloids has been extensively investigated.[54-58] The well-established indole chemistry accumulated from indole chemical reactions and indole ring synthesis, together with the wealth of knowledge about the biosynthesis of indole alkaloids, has resulted in significant developments of synthetic strategies and methodology in indole alkaloid synthesis.[59-62]

3.1.3 Indolophanes

Reports of several thousand individual indole derivatives appear annually in the chemical literature.[39] The primary reason for this sustained interest is the wide range of biological activity found among indoles and the clinical importance of indole alkaloids.[39] With this in mind, it is, however, perhaps surprising that indole, one of the most widely distributed heteroaromatic entities in nature, has been reported to form part of a heterophane only nine times when bridged at the 1 and 3 positions[63-70] and four times when bridged at the 4 and 7

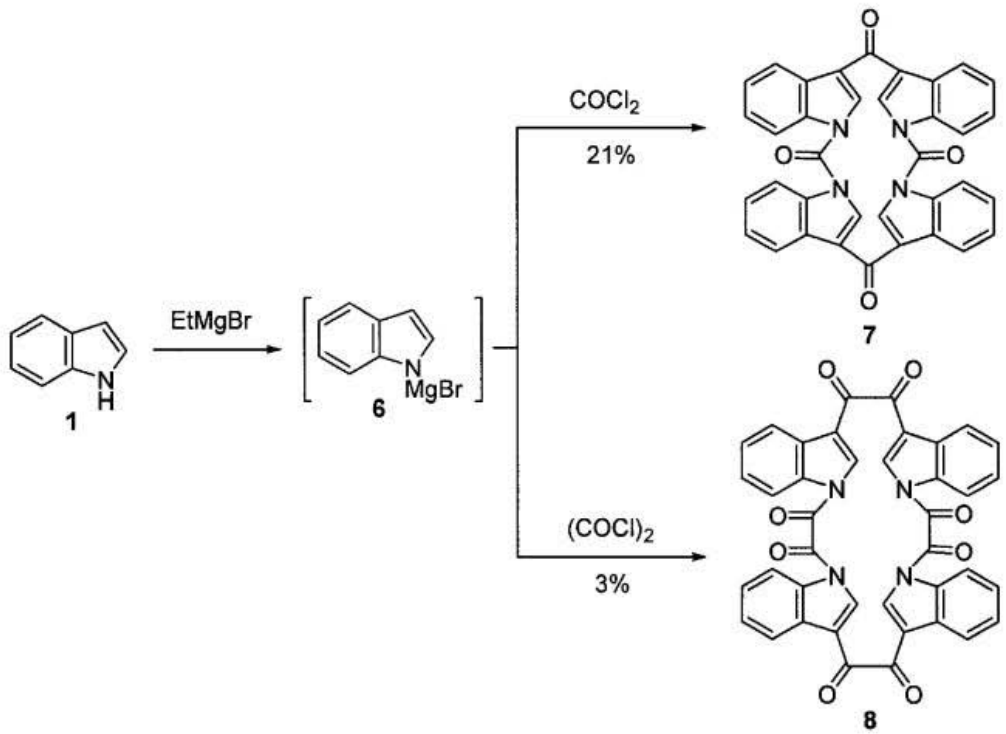
positions.[71,72] There are many naturally occurring indole alkaloids as well as non-natural indole derivatives that feature aliphatic rings fused to the indole nucleus. Although such compounds technically fit the definition of a cyclophane, they are considered to be outside the scope of the current investigation. This blanket omission is directly analogous to that of many orthocyclophanes from the benzenoid family. For example [2]-, [3]-, [4]- and [5]orthocyclophanes are not normally viewed as cyclophanes, but rather as benzocyclobutene, indan, 1,2,3,4-tetrahydronaphthalene and benzocycloheptene, respectively. This is not to say, however, that the *ortho* mode of bridge attachment necessarily disqualifies a compound from being a cyclophane.[73-78]



4 5

Scheme 3.2 Synthesis of the first indolophane **5**.

The first indolophane, trimeric compound **5**, was claimed as an unexpected product by Bergman in 1973 (Scheme 3.2)[63] from their attempted Favorskii rearrangement of 3-(2-bromopropionyl)indole **4**. However, only mass spectroscopic (MS) data and infrared (IR) data were provided to support the structure **5**.

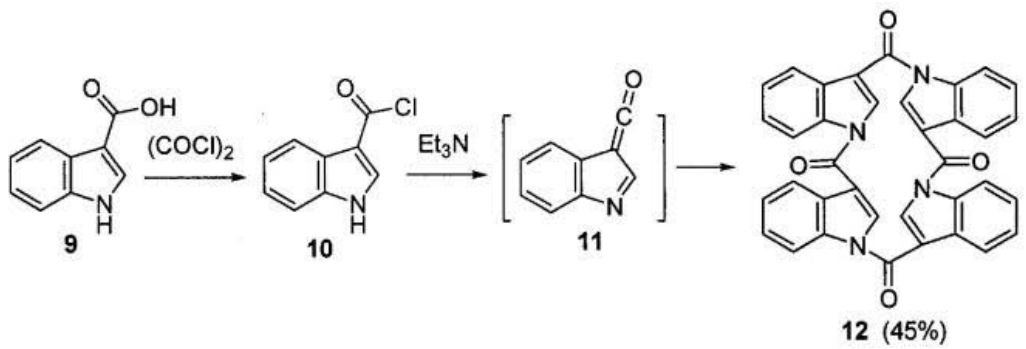


Scheme 3.3 Synthesis of indolophanes 7 and **8**.

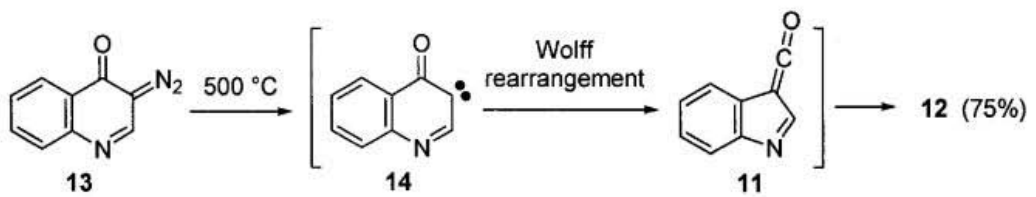
In 1977, Bergman[64] once again published an isolation of two indolophane tetramers, **7** (21%) and **8** (3%), from studies on reactions of the indole magnesium salt **6** with phosgene and oxalyl chloride, respectively (Scheme 3.3). Since the synthesis of indolophanes was not the original intention, the reactions were conducted under non-high-dilution conditions, and thus compounds **7** and **8** were obtained as tetramers, rather than smaller cyclic oligomers, which are normally targeted by cyclophane chemists, in low yields.

In 1991, a head-to-tail isomer of **7**, indolophane tetramer **12**, was reported to be generated in 45% yield from indole-3-carboxylic acid **9** (Scheme 3.4).[65]

Compound **12** was characterized by MS, IR, ^{1}H and ^{13}C NMR and X-ray crystallography. An indolidene ketene **11** was suggested to be the likely precursor of **12**. This was confirmed by another independent synthesis of indolophane **12** (75%) in a recent study of the same ketene species **11** generated by a Wolff rearrangement (Scheme 3.5).[66]



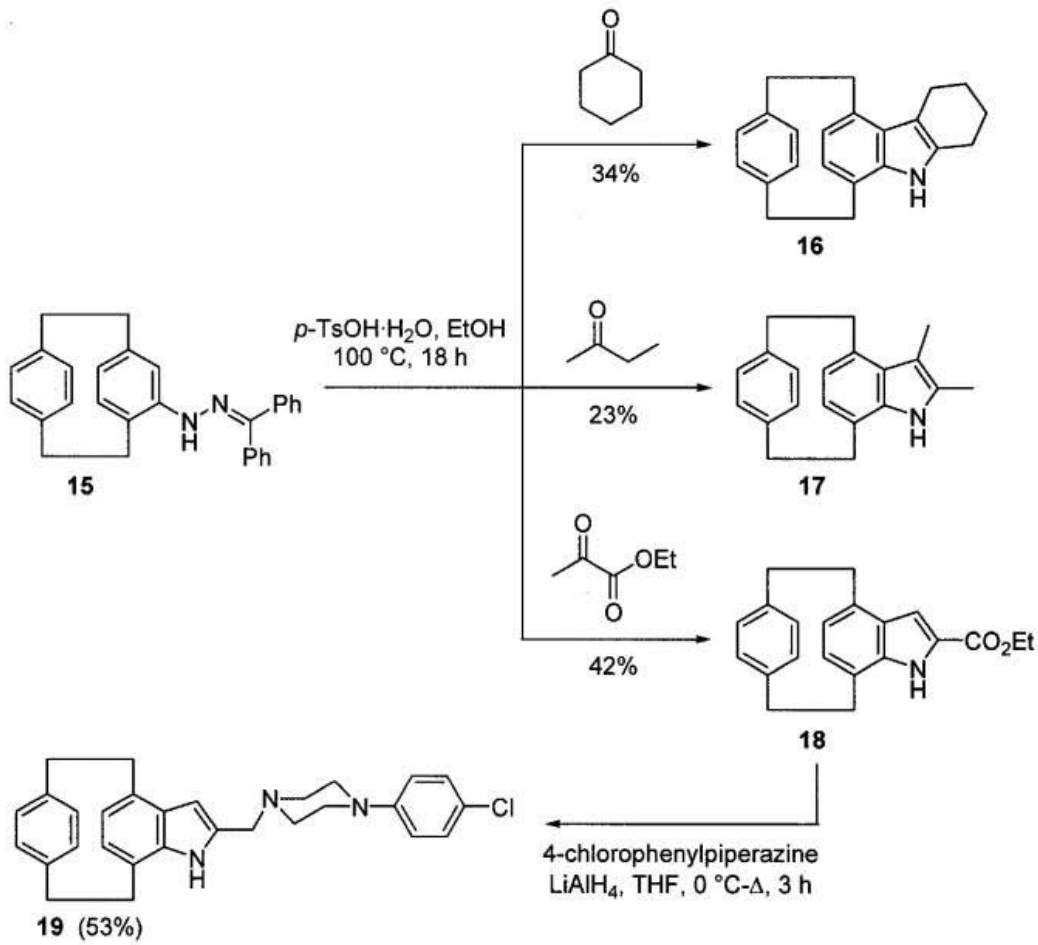
Scheme 3.4 Synthesis of indolophane **12**.



Scheme 3.5 Alternative synthesis of indolophane **12**.

A recent rational synthesis of indolophanes **16-18** was disclosed by Gmeiner[71] *via* the Fischer indole synthesis of a hydrazone-containing [2.2]paracyclophane **15** in low to moderate (23-42%) yields (Scheme 3.6). In order to investigate whether the double-layered [2.2](4,7)indoloparacyclophane moiety can serve as an indole bioisostere, another indolophane **19**, which is

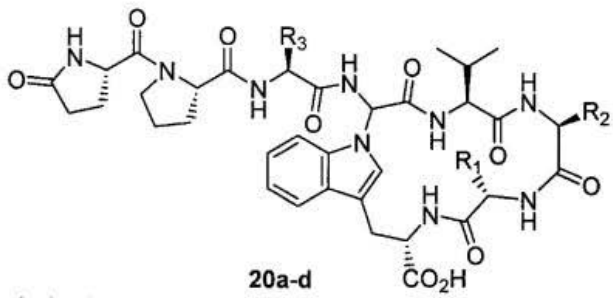
structurally related to piperazinylmethylindoles that were described as strong and selective dopamine D4 receptor ligands, was synthesized in 53% yield by a reductive amination (Scheme 3.6).



Scheme 3.6 Synthesis of indolophanes **16-19**.

As hoped for, indolophane **19** displayed strong and selective affinity for the dopamine D4 receptor subtype, which is of special interest for the treatment of neuropsychiatric disorders.[71] To further address the structure-activity

relationship involving chiral drug candidates, chiral indolophanes, (*R*)-**19** and (*S*)-**19**, were prepared in enantiomerically pure form, starting from corresponding chiral indolophanes, (*R*)-**18** and (*S*)-**18**, respectively.[72] *In vitro* ligand-binding experiments revealed a stereodifferentiation when (*R*)-**19** showed significantly higher affinity for all the dopamine D4 receptor subtypes investigated, which demonstrated the first example of the ability of neuroreceptors to differentiate between planar chiral enantiomers.[72]

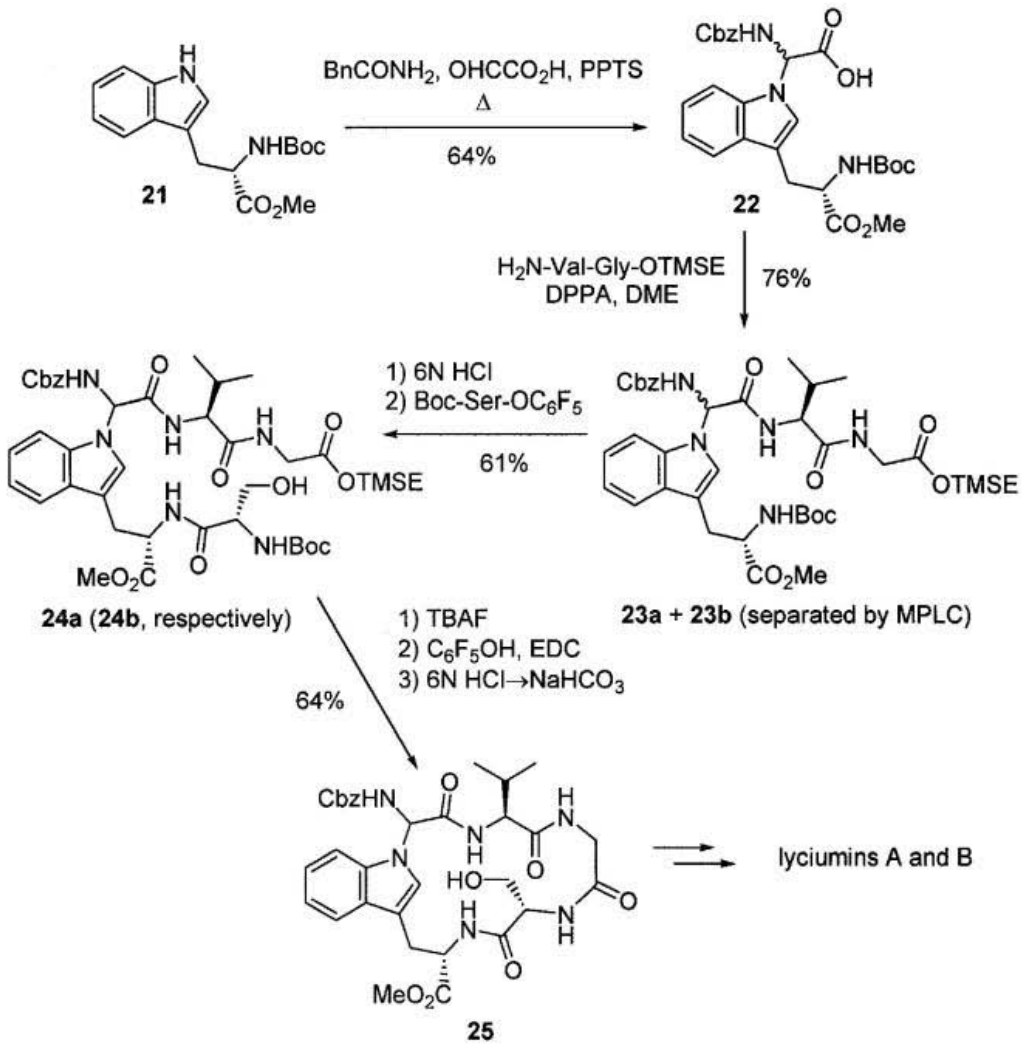


20a-d

lyciumins
A: R_1=hydroxymethyl, R_2=H, R_3=4-hydroxyphenyl
B: R_1=hydroxymethyl, R_2=H, R_3=(3-indolyl)methyl
C: R_1=hydroxymethyl, R_2=benzyl, R_3=4-hydroxyphenyl
D: R_1=*s*-butyl, R_2=H, R_3=4-hydroxyphenyl

Figure 3.3 Structures of lyciumins A-D **20a-d**.

Indolophane structures have also been identified as being present in naturally occurring cyclic peptides, first in lyciumin A and B,[67] and later in lyciumin C and D[68] (Figure 3.3). These four cyclic octapeptides, featuring a macrocyclic (1,3)[14]indolophane skeleton, were isolated from *Lycii Radicis Cortex*, an oriental crude drug used as an antifebrile, a tonic and an antihypertensive agent.

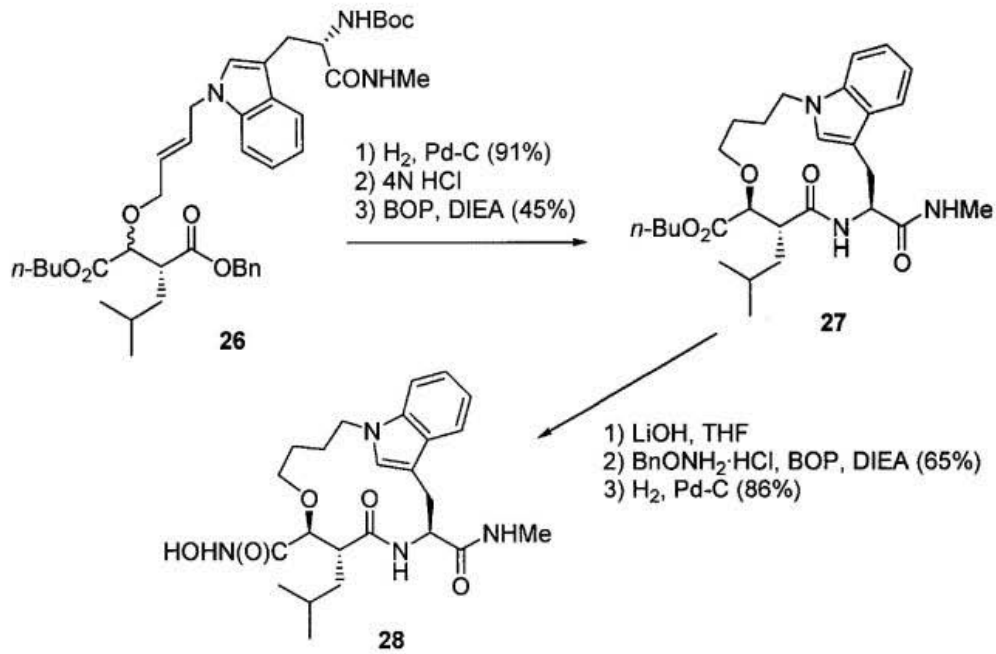


Scheme 3.7 Synthesis of lyciumins A and B.

The total synthesis of lyciumins A and B was first achieved by Schmidt three years after their isolation (Scheme 3.7).[69] Epimeric aminals **22** (64%) were formed in a 1:1 ratio upon treatment of tryptophan **21** with benzyl carbamate and glyoxylic acid hydrate. After coupling with valylglycine ester, the epimers **23a** and **23b** were easily separated by medium pressure liquid chromatography

(MPLC). They were then subjected separately to the further reactions. A deprotection-coupling sequence furnished pentafluorophenyl esters of **24a** and **24b**, respectively. Only one epimer of **24** was able to undergo the final ring closure of the following three-step sequence. Interestingly, the key intermediate obtained, epimerically pure indolophane **25**, was transformed into two synthetic cyclic peptides after another three-step sequence from corresponding side chain peptidyl building blocks. They were shown to be identical to isolated lyciumins A and B in respects of both NMR and optical rotation.[69] However, the authors could not clarify the configuration at the aminal carbon atom of **25**.

A very recent report of an indolophane came from a medicinal chemistry team at DuPont Pharmaceuticals Company. The goal of this work was the discovery of tumor necrosis factor α (TNF- α) converting enzyme inhibitors.[70] A new class of macrocyclic hydroxamic acids was designed, one of which was an indolophane **28** (Scheme 3.8). This involved linking the two termini of acyclic *anti*-succinate-based hydroxamic acids. The key step to form the macrocyclic skeleton was a BOP-promoted amide formation. Only the desired *anti*-diastereomer **27** was produced. The subsequent conversion of ester **27** to indolophane hydroxamic acid **28** was accomplished by a three-step sequence composed of a basic hydrolysis, a hydroxamate formation and a hydrogenolysis. It was shown that indolophane **28** exhibited some inhibition against MMP-1, MMP-3 and TNF- α release.[70]

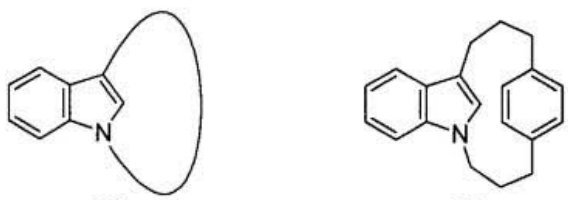


Scheme 3.8 Synthesis of indolophane **28**.

3.1.4 Our Interests

Compared to the numerous studies on the synthesis and reactivity of indoles and indole alkaloids, indolophanes, members of the heterophane family, form a rarely explored field that is in need of more investigation. For indolophanes **5**, **7**, **8** and **12**, information that would be of particular interest to cyclophane chemists, such as structure and conformational behavior, was not given. This is not surprising since the syntheses were not deliberate. Compounds **20a-d**, **25** and **28** clearly fit the cyclophane definition, but fall under the sub-heading of macrocyclic cyclophanes, a class of compounds that are more popular in medicinal and supramolecular chemistry.[79] General interest in the

Bodwell group in the synthesis, structure and conformational behavior of small cyclophanes,[80-86] coupled with the dearth of examples of small indolophanes, spawned a project aimed at the syntheses of some (1,3)indolophanes **29** (Figure 3.4). This system differs from that of compounds **16-19** (Scheme 3.6) by virtue of the attachment points of the bridges, which serve to incorporate the heterocyclic pyrrole unit of the indole nucleus into the cyclophane environment. [3]Paracyclo[3](1,3)indolophane **30** (Figure 3.4) was identified as the first target in this area.



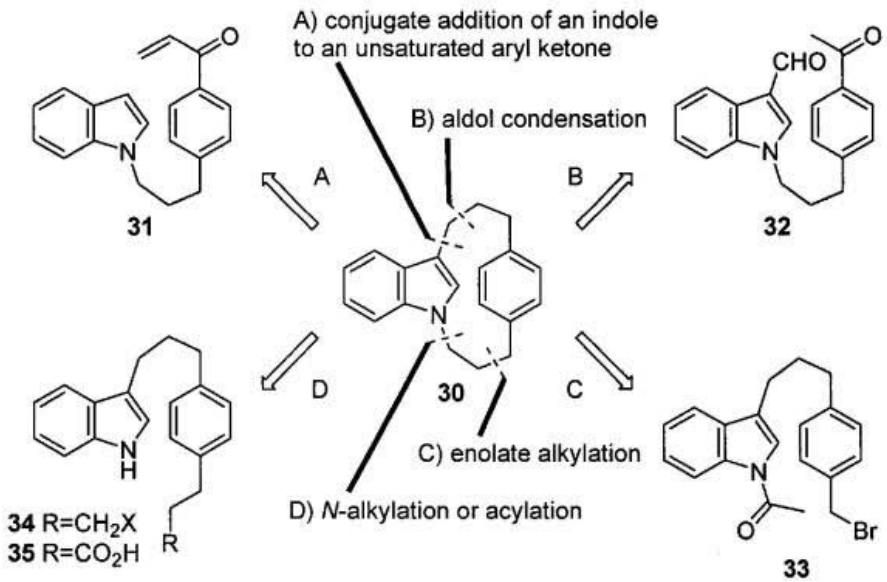
29 **30**

Figure 3.4 Structures of (1,3)indolophanes **29** and **30**.

3.2 Results and Discussion

3.2.1 Synthesis of indolophane 30

3.2.1.1 Retrosynthetic Analysis of Indolophane 30



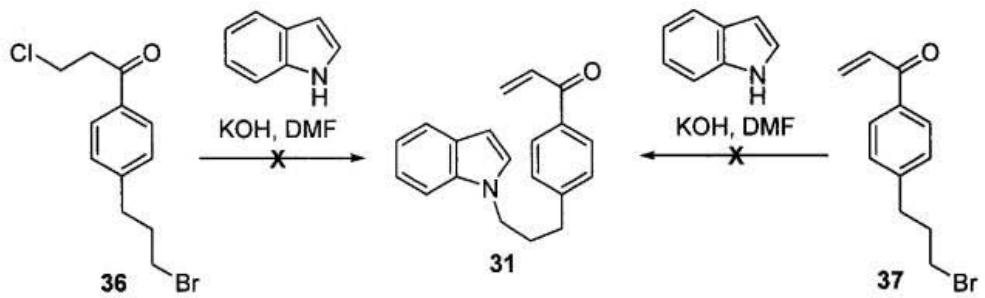
Scheme 3.9 Retrosynthetic analysis of indolophane **30**.

Based on established indole chemistry,[37-39] a retrosynthetic analysis of indolophane **30** led to the identification of four types of bridge-forming/ring-closing strategies (Scheme 3.9). Only strategies for final ring closures are shown. With the bottom bridge* installed first, the final ring closure could be effected by either Strategy A, conjugate addition of an indole to an α,β-unsaturated aryl ketone, or Strategy B, aldol condensation. With the top bridge constructed first, Strategy C, enolate alkylation, or Strategy D, *N*-alkylation or

* The bottom bridge is assigned as the one attached to the indole nitrogen atom.

acylation, were deemed to be reasonable candidates for the final cyclization (Scheme 3.9). In terms of formation of the other bridge, which is not shown in Scheme 3.9, before the final ring closure, compounds **31** and **32** can be taken back further according to either of cuts C and D, and compounds **33-35** can be taken back further according to either of cuts A and B.

3.2.1.2 Strategy A

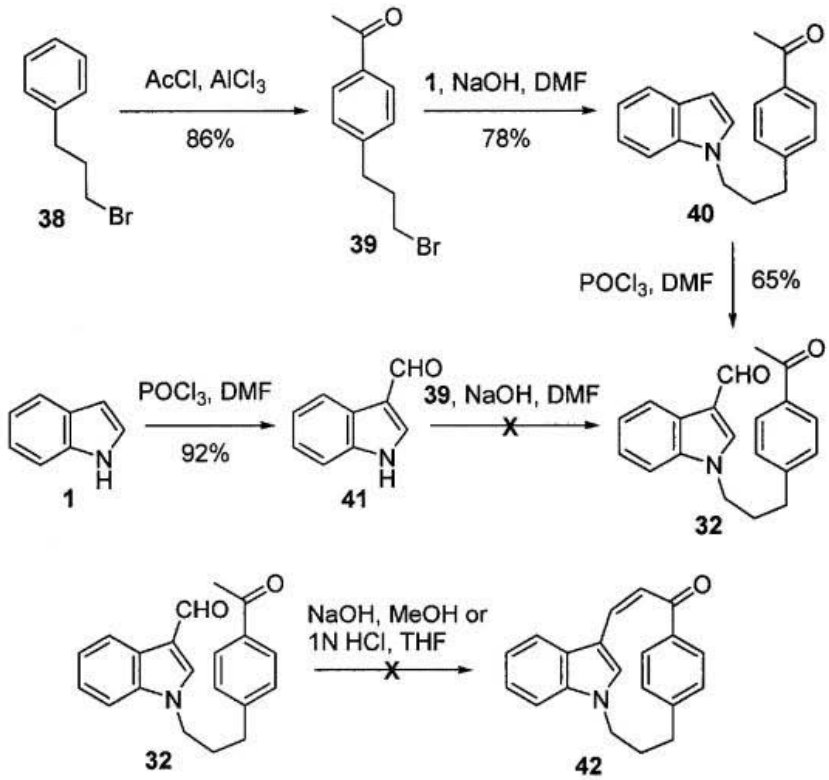


Scheme 3.10 Attempted preparation of **31**.

In order to excecute Strategy A (Scheme 3.9), compound **31** had to be prepared as the precusor for the cyclization. Using a general procedure for the synthesis of *N*-alkylindoles,[87] sequential *N*-alkylation and base-promoted elimination were expected for **36** in one case, and *N*-alkylation was expected for **37** in another case (Scheme 3.10). As will be described later in this chapter, compound **36** was prepared by a Friedel-Crafts acylation of 1-bromo-3-phenylpropane using 3-chloropropionyl chloride, and subsequent DBU-promoted elimination of **36** yielded **37**. However, intractable mixtures were formed in both cases upon reaction with indole, probably due to interference from reactions

occurring at C3 of indole **1**, the multi-electrophilic sites in **36** and competitive conjugate addition to the α,β-unsaturated aryl ketone **37**.

3.2.1.3 Strategy B

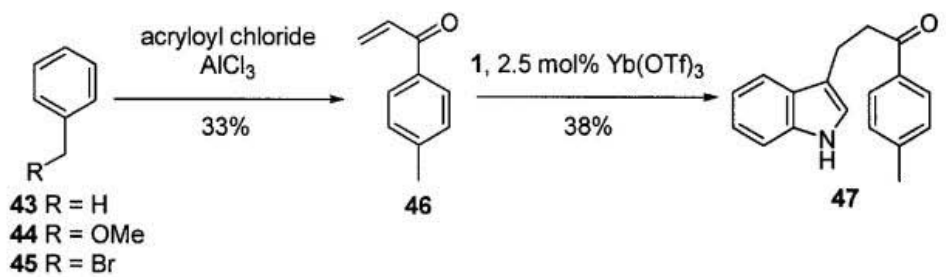


Scheme 3.11 Attempted Strategy B.

The preparation and intramolecular aldol condensation of **32**, according to Strategy B (Scheme 3.9), was the second approach to receive attention (Scheme 3.11). 1-Bromo-3-phenylpropane **38** was acylated to give bromoketone **39** in 86% yield. The bottom bridge was then installed by the *N*-alkylation of indole[87] **1** with **39** in 78% yield. Vilsmeier-Haack formylation[88] of the resulting

compound **40** with $POCl_3$/DMF then afforded ketoaldehyde **32** (65%). An earlier attempt to prepare **32** by the *N*-alkylation of 3-formylindole **41**,[89] which was prepared in 92% yield from indole **1**, yielded none of the desired product. The same was true for attempts to perform the intramolecular aldol reaction of **32** under high dilution and either basic or acidic conditions. Monitoring the reaction by TLC indicated that the starting material was slowly converted into baseline material, which suggests that intermolecular oligomerization was favored under the conditions employed.

3.2.1.4 Strategy C



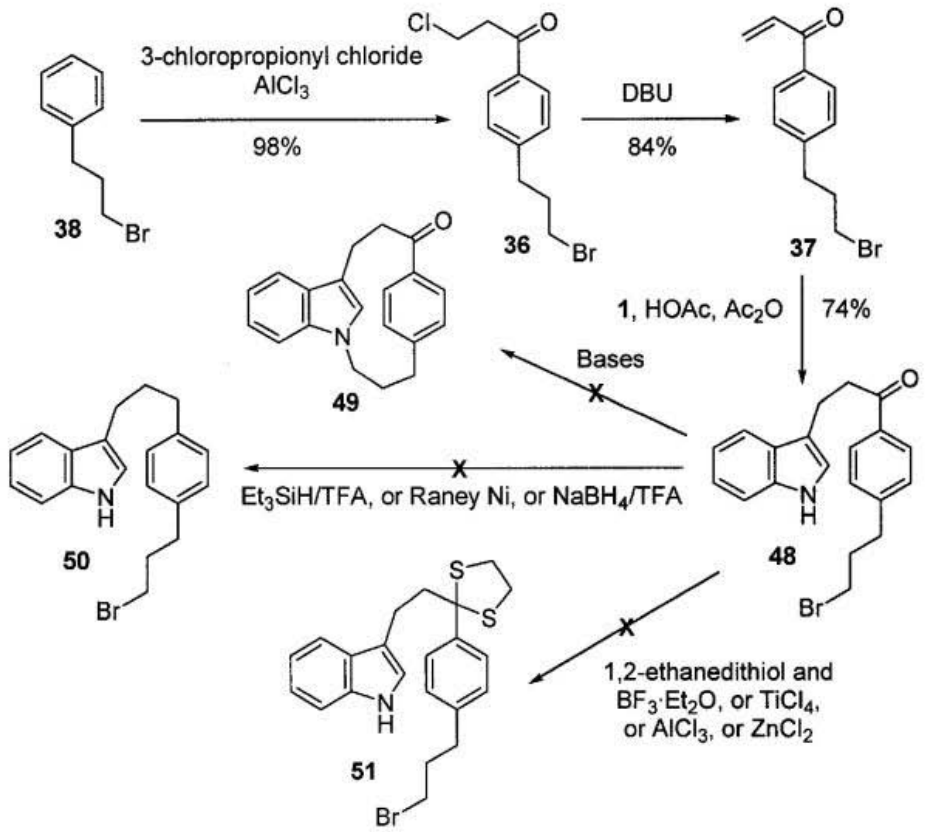
Scheme 3.12 A model study of conjugate addition of indole **1**.

Attention was then turned to Strategy C (Scheme 3.9), which involves the use of a conjugate addition to form the top bridge and an enolate alkylation to form the bottom bridge. The conjugate addition of indole to α,β-unsaturated ketones is well known[90-93] and it has recently been shown by Kerr[94] that this transformation can be achieved under catalysis by $Yb(OTf)_3$ at both ambient and high pressure. A brief model study was undertaken to ascertain whether this

method would be applicable to our studies (Scheme 3.12). Friedel-Crafts acylation of toluene **43** with acryloyl chloride afforded ketone **46** in 33% yield and ambient pressure reaction of this compound with indole in the presence of 2.5 mol% $Yb(OTf)_3$ provided adduct **47** in an equally disappointing yield of 38%. The use of high pressure was not investigated, but has not been ruled out for future studies. It was also found that attempted acylations of methoxymethylbenzene **44** and benzyl bromide **45** failed completely under the conditions used for the preparation of **46**. The incompatibility of substrates with a benzylic substituent in the acylation reaction led to the abandonment of Strategy C (Scheme 3.9).

3.2.1.5 Strategy D

Under Strategy D (Scheme 3.9), the use of a conjugate addition for the formation of the top bridge and *N*-alkylation or acylation for the final ring closure was envisioned. Considering the poor efficiency of the prior Friedel-Crafts acylation with acryloyl chloride (Scheme 3.12), a two-step procedure was designed to generate the required Michael acceptor. This sequence proved to be more successful, as did the use of conventional conditions,[90] rather than the catalysis by $Yb(OTf)_3$, for the conjugate addition (Scheme 3.13).



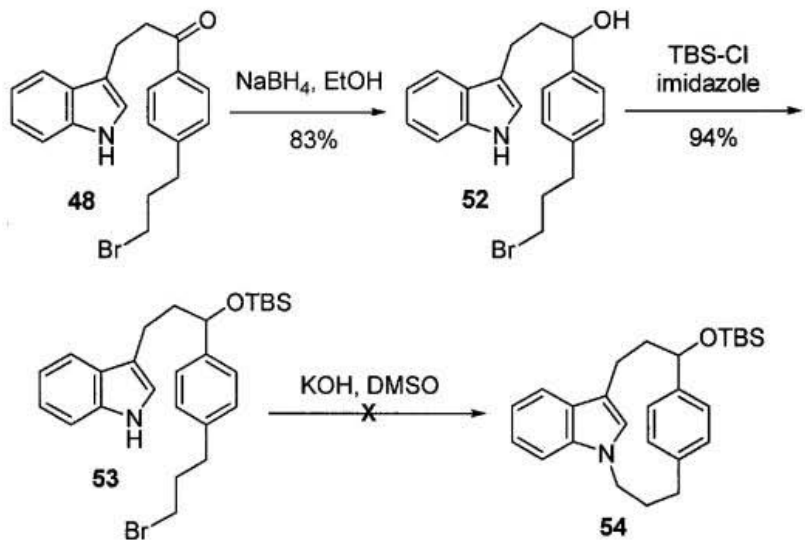
Scheme 3.13 The first attempts under Strategy D.

Friedel-Crafts acylation of bromide **38** with 3-chloropropionyl chloride gave **36** (98%) and subsequent DBU-induced elimination afforded **37** in 84% yield. Treatment of Michael acceptor **37** with indole **1** in the presence of $HOAc/Ac_2O$[90] led to the formation of adduct **48** in 74% yield. The earlier conversion of **39** to **40** (Scheme 3.11) in good yield had demonstrated that a free ketone could indeed be present during the *N*-alkylation of indole, so direct cyclization of **48** was attempted. However, none of the desired product **49** was obtained using a variety of bases, such as K_2CO_3, NaH, NaOH and KOH, in DMF

and/or DMSO. Traces of what appeared (by ^{1}H NMR) to be an arylcyclopropane were isolated, but not in a sufficiently pure form or large enough amount to be confidently identified. The ketone functionality of **48** was likely the problem, not only due to its acidic α hydrogens, but also possibly due to the sp^2 hybridization of the carbon atom. From an examination of molecular models, it appeared as though the presence of the carbonyl group makes it slightly more difficult for the molecule to adopt a geometry in which intramolecular *N*-alkylation can occur than in a system with an sp^3 hybridized carbon atom in the place of the carbonyl group. The direct reduction of the carbonyl group of **48** to give bromide **50** was investigated first. The presence of the primary alkyl bromide augured poorly for Wolff-Kishner and Clemmensen reductions, so alternative methods were investigated. However, the attempted reductions of **48** under conditions, such as Et_3SiH/TFA,[95] Raney Ni[96] and $NaBH_4$/TFA,[97] all failed. A Mozingo reaction was then considered, but the reaction of 1,2-ethanedithiol with **48** in the presence of each of $BF_3{\cdot}Et_2O$,[98,99] $TiCl_4$,[100] $AlCl_3$[101] and $ZnCl_2$[102] failed to give any of desired dithiolane **51**.

Stepwise reduction was then looked at (Scheme 3.14). Treatment of **48** with $NaBH_4$ afforded alcohol **52** in 83% yield and this was protected as its TBS ether **53** (94%). However, reaction of **53** with KOH/DMSO[89] did not produce any of the cyclophane **54**. This might be due to the migration of the TBS group[103] to the more nucleophilic nitrogen anion generated by the deprotonation.

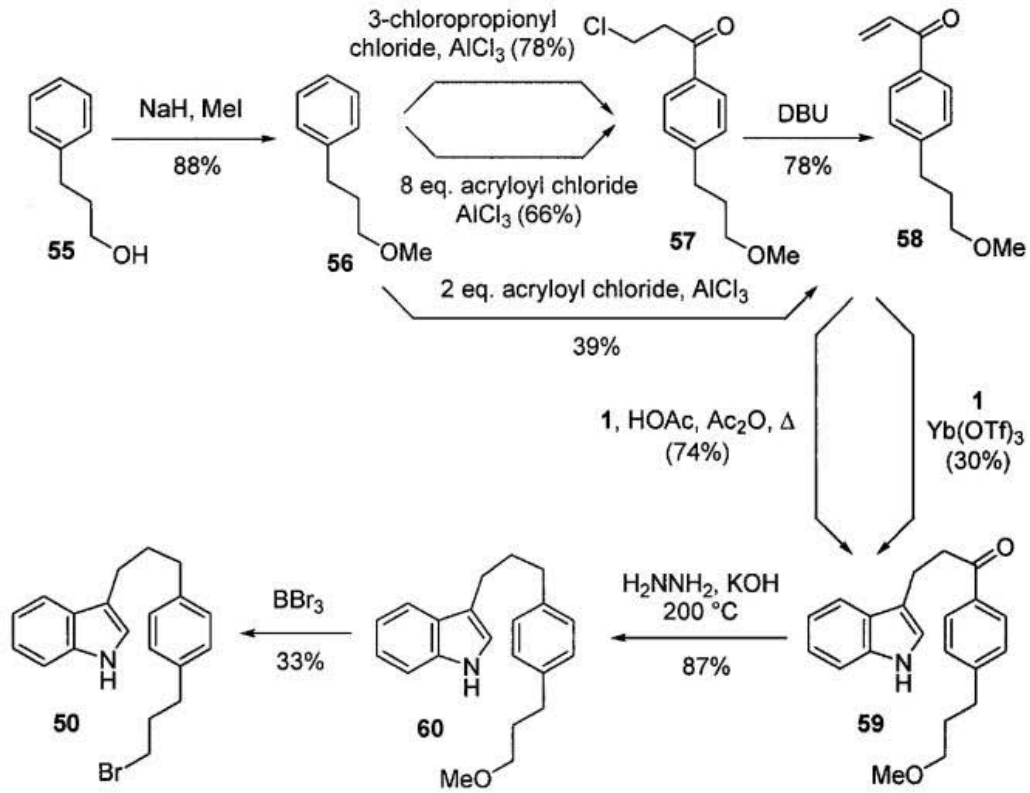
The hybridization of the oxygen-bearing carbon atom alone does not seem to be a deciding factor in the progress of the cyclization.



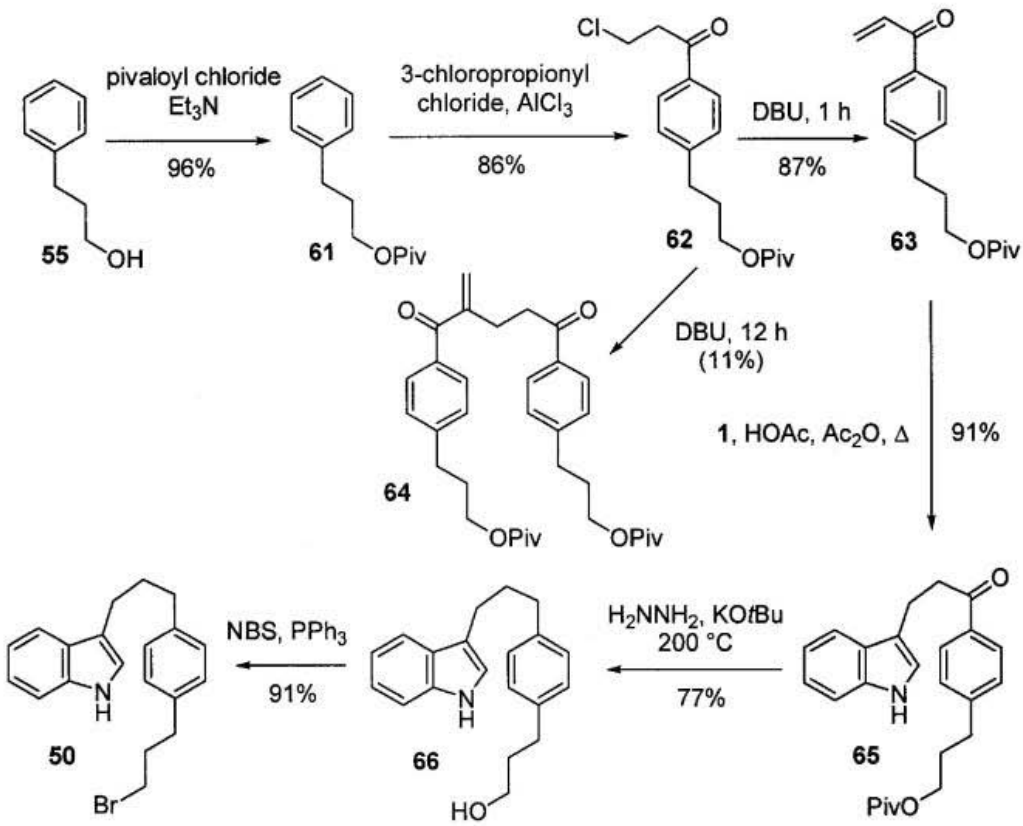
Scheme 3.14 The second attempts under Strategy D.

The strategy was then modified to allow for more forcing Wolff-Kishner reduction of the ketone before introduction of the leaving group necessary for cyclization (Scheme 3.15). 3-Phenyl-1-propanol **55** was protected as its methyl ether **56** (88%) and this compound was acylated as before to give chloroketone **57** (78%). Interestingly, the same product was obtained in 66% yield when **56** was acylated with eight equivalents of acryloyl chloride and ten equivalents of $AlCl_3$, which obviously provided the chloride source for the conjugate addition to the initially formed α,β-unsaturated ketone **58**. Treatment of **57** with DBU afforded the Michael acceptor **58** in 78% yield and the addition of indole **1** in refluxing $HOAc/Ac_2O$ led to the formation of **59** in 74% yield. In line with the

model study, the direct conversion of **56** into **58** (two equivalents of acryloyl chloride and four equivalents of $AlCl_3$, 39%) and the $Yb(OTf)_3$ catalyzed conjugate addition of indole **1** (30%) were found to be lower yielding options. Wolff-Kishner reduction[104] of **59** proceeded in 87% yield and the resulting methyl ether **60** was then cleaved with BBr_3 to afford bromide **50**. However, the yield was only 33%, possibly due to the sensitivity of the indole nucleus to the strong Lewis acid BBr_3.[37,38]



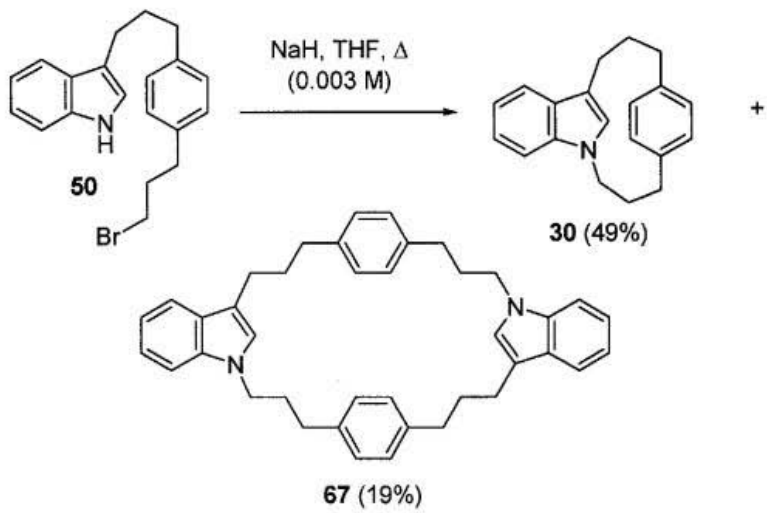
Scheme 3.15 The third attempts under Strategy D.



Scheme 3.16 The fourth attempts under Strategy D.

Although the desired bromide **50** had been successfully prepared, the poor yield of the deprotection step was unsatisfactory. A more successful route involved the use of a less robust protecting group, namely the pivaloyl group (Scheme 3.16). The pivaloyl ester was chosen because it could conceivably be removed during the Wolff-Kishner reduction, thereby saving one step. Accordingly, **55** was esterified with pivaloyl chloride in the presence of Et_3N (96%) and the resulting ester **61** was subjected to the sequence of acylation (**62**, 86%), elimination (**63**, 87%) and conjugate addition of indole **1** (**65**, 91%). The

elimination reaction to give **63** proceeded in excellent yield when allowed to react for one hour, but when the reaction time was increased to 12 h, the only product isolated was **64** (11%), which appeared to be the result of a DBU-promoted[105] self-Baylis-Hillman reaction. Wolff-Kishner reduction of **65** under modified conditions[106] cleanly reduced the ketone and removed the protecting group to afford alcohol **66** in 77% yield. Bromination of **66** using PBr_3[107] gave none of the desired bromide **50**. As with the conversion of **60** to **50** (Scheme 3.15), the acidic conditions may have been incompatible with the indole moiety. An alternative method, which employs NBS/PPh_3,[108] provided the cyclization precursor **50** in 91% yield.



Scheme 3.17 Final ring closure of bromide **50**.

The final ring closure, an intramolecular *N*-alkylation (Scheme 3.17), could be effected upon slow addition of a THF solution of **50** to a refluxing slurry of NaH (ten equivalents) in THF under moderately high dilution.[109] Under

these conditions, 49% of the targeted indolophane **30** was obtained, along with 19% of the cyclic dimer **67**. The overall yield of **30** was 22% over seven steps starting from 3-phenyl-1-propanol **55**.

3.2.2 Conformational Behavior of 30

3.2.2.1 Computational Conformer Search of 30

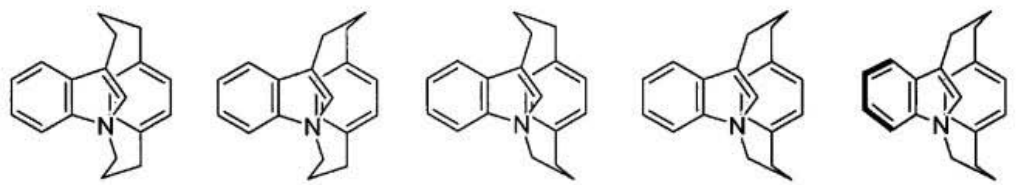


Figure 3.5 AM1-calculated low energy conformers of **30** and their relative energies.

A conformer search of indolophane **30** was carried out at the AM1 level of theory using the Spartan software package (Version 4.0) and Chem3D(Ultra 5.0) MOPAC, and they gave almost identical results. Five conformers, from Spartan calculations, were identified within 5 kcal/mol of the global minimum (Figure 3.5). The lowest energy conformer (C_{chair},N_{chair}) has both bridges in the *pseudo-chair* conformation.[110-113] Flipping the bridge attached to the C-terminus of the indole unit affords a conformer (C_{boat},N_{chair}) that is 0.92 kcal/mol higher in energy, whereas flipping the bridge attached to the N-terminus of the indole moiety to give the C_{chair},N_{boat} conformer is almost twice as costly in energy (1.68 kcal/mol). Although the energy differences in these processes are rather small,

the significant difference in energy between the two bridge flips is somewhat surprising. The origin of this difference is not immediately obvious. The C_{boat},N_{boat} conformer is calculated to lie 3.65 kcal/mol above the global minimum. The fifth conformer (*tilt*-C_{boat},N_{boat} - 4.40 kcal/mol) was unexpected. It resembles the C_{boat},N_{boat} conformer, but the angle between the indole nucleus and the benzene ring is considerably greater.

3.2.2.2 NMR Studies of 30

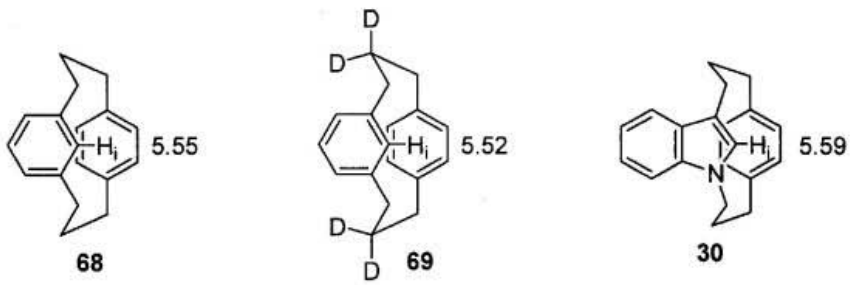


Figure 3.6 Chemical shifts of internal protons of some structurally similar [3.3]cyclophanes **68**, **69** and **30**.

The ^{1}H NMR spectrum of indolophane **30** (Figure 3.6) exhibits a sharp singlet at δ 5.59, which was assigned to the internal proton of the indole deck. By comparison, the internal protons of [3.3]metaparacyclophanes **68** and **69** (Figure 3.6) are observed at δ 5.55[111,112] and δ 5.52,[113] respectively. The significant high field shift of this proton indicates that, as expected, it occupies an average position well inside the shielding cone of the benzenoid ring in solution. The analogous proton of **50**, the direct precursor of **30**, is observed at δ 6.95. The protons of the benzenoid deck are observed as a slightly broadened

AB system at δ 6.65 and 6.57. That only one AB system is observed suggests that a degenerate ring flipping process (Figure 3.7) analogous to that described for [2.2]metaparacyclophanes[114-116] (No such conformational studies have been reported on [3.3]metaparacyclophanes **68** and **69**) occurs rapidly on the NMR time scale at room temperature.

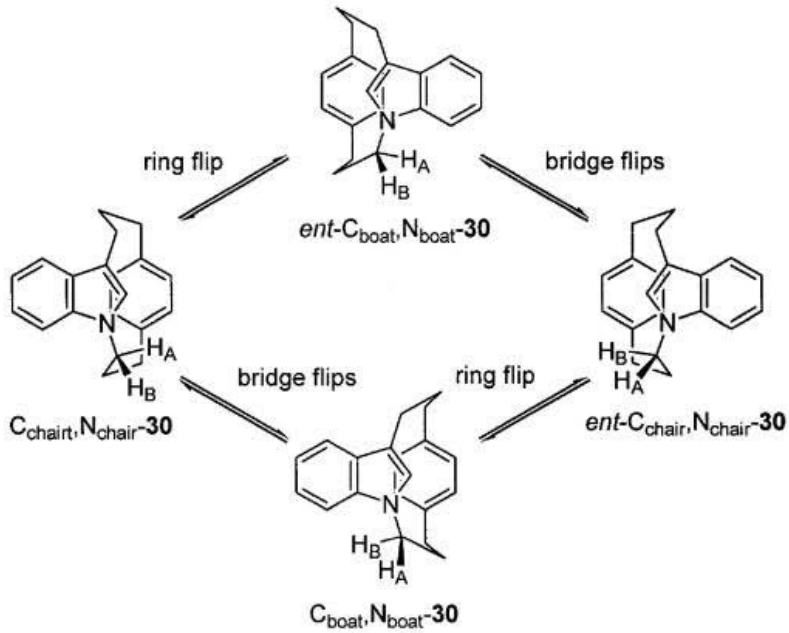


Figure 3.7 Selected conformational processes in **30**.

Although either one of two conformational processes, ring flipping of the indole deck and ring rotation of the benzenoid deck that have been similarly described in other [3.3]metaparacyclophanes systems by Shinmyozu,[117] could be responsible for this degeneration, an examination of molecular models indicated that the former process is considerably easier than the latter. Therefore, ring flipping of the indole deck is ascribed for the degenerate signal of the *p*-

phenylene protons in **30**. The slight broadening observed in the AB spectrum suggests that room temperature is not too distant from the coalescence temperature for the conformational process. The signals of the diastereotopic NCH_2 group are observed as a narrow multiplet centered at δ 4.00 and the remaining bridge protons are observed as five groups of multiplets in the range of δ 2.05-2.85, implying that the wobble of both bridges (Figure 3.7) is also fast on the NMR time scale at room temperature.

By comparison, cyclic dimer **67** exhibits a much simpler ^1H NMR spectrum than **30**. The internal protons of the indole units appear as a singlet at δ 6.70, which is in the normal range as compared to the analogous proton of the cyclization precursor **50** (δ 6.95), and the bridge protons all give clean triplets or quintets. For example, the NCH_2 signals are observed as a well resolved triplet (J=6.6 Hz) at δ 4.03.

A dynamic NMR (DNMR) study of **30** was undertaken to determine the energy barrier of the ring flip (Figure 3.8). Upon cooling, the AB spectrum for the benzenoid deck and the signals for the bridge protons all broaden further. At –90 °C, the protons of the benzenoid deck are resolved into an ABXY system. The higher field part is observed at δ 6.21 and 6.00, whereas the lower field part can be seen at δ 7.04 and 6.94, overlapped somewhat with two of the external aromatic signals of the indole moiety. Since the NCH_2 signals were well separated from other resonances, they were used for the determination of the energy barrier. The low temperature spectrum consists of two doublets of

doublets centered at δ 4.25 and 3.63. The coalescence temperature (T_c) of these signals is 236±3 K and $\Delta\nu$=185.5 Hz, giving k_c=412.2 and $\Delta G^{\ddagger}$=10.9±0.2 kcal/mol, according to the Gutowsky-Holm equation:[118] $\Delta G^{\ddagger}$ (kcal/mol)=$2.303\times1.9872\times T_c\times(10.319-\log k_c+\log T_c)$, where $k_c=\Delta\nu\times\pi/2^{1/2}$. There does not appear to be any prior determination of the energy barrier for the ring flip in any [3.3]metaparacyclophane with no internal substituent, although the reported ^{1}H NMR spectra indicate rapid interconversion at room temperature.[111-113,119]

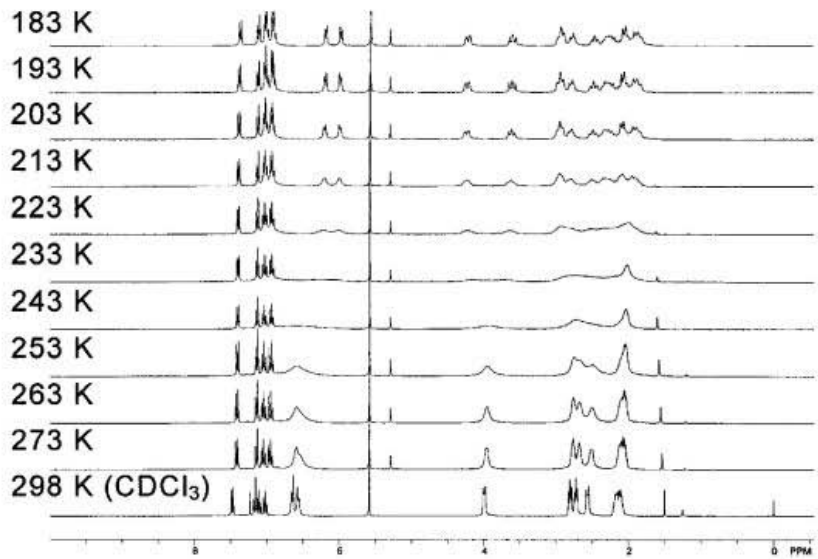
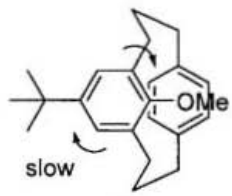


Figure 3.8 DNMR spectra of **30**.

Since none of the bridge flips that interconvert the various bridge conformers shown in Figure 3.5 result in an exchange in the environments of the diastereotopic NCH_2 protons (or any of the other diastereotopic CH_2 groups in the bridges), it must be a ring flip that was observed in the DNMR study. A ring

flip of the C_{chair},N_{chair} conformation gives rise to a C_{boat},N_{boat} conformer, which can then undergo two bridge flips to arrive at another C_{chair},N_{chair} conformation (Figure 3.7). The new C_{chair},N_{chair} conformer is the enantiomer of the starting conformer and the ring flip is thus a mechanism for racemization of the chiral indolophane **30**.



70

Figure 3.9 The internal methoxy group retards the ring flip in **70**.

In fact, the full set of conformational processes is more complicated than that depicted in Figure 3.7. Each of the bridge conformers shown in Figure 3.5 (and others that lie higher in energy than 5 kcal/mol above the calculated minimum) can undergo a ring flip that is necessarily accompanied by a flip of both bridge conformations and inverts the enantiomeric sense of the molecular skeleton. With an energy barrier between these two enantiomeric sets of bridge conformers of 10.9±0.2 kcal/mol, the prospects of resolving them, even at low temperature, are bleak. Intuitively, one would conclude that the introduction of a bulky substituent at the internal position of the indole nucleus and/or the shortening of the bridges should significantly enhance the chances of doing so. In consulting the literature, the energy barrier to ring inversion of [2.2]metaparacyclophane has been observed to be 20.6 kcal/mol.[114-116] The

internal methoxy group in [3.3]metaparacyclophane **70** (Figure 3.9) has been introduced to slow the rate of ring flipping in **70** at room temperature.[117] It would therefore seem that both a shortening of the bridges and the presence of an internal substituent will be required for resolution to be a viable option.

3.2.2.3 X-ray Crystal Structures of 30 and 67

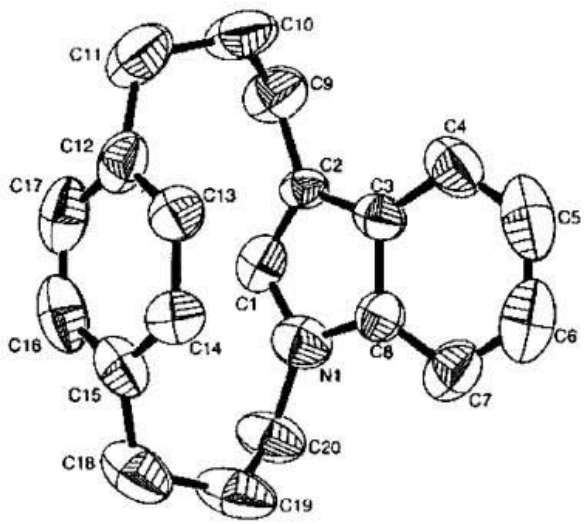


Figure 3.10 ORTEP representation of **30** in the crystal. The crystallographic numbering differs from systematic. Selected bond angles (°): C(2)-C(9)-C(10) 115.7(3), C(9)-C(10)-C(11) 116.9(3), C(10)-C(11)-C(12) 113.1(3), C(15)-C(18)-C(19) 113.2(3), C(18)-C(19)-C(20) 118.1(3), C(19)-C(20)-N(1) 115.9(2).

An X-ray crystal structure determination of **30** (Figure 3.10) revealed that the two aromatic core units are very close to being aligned along the same pseudo mirror plane. The indole moiety is virtually planar, while the benzene ring is slightly boat shaped, with α^3=6.0 ° at the end where the bridge leads to

the to N terminus of the indole unit and 5.6 ° at the end where the bridge leads to the to C terminus of the indole unit. The angle formed by the best planes of the indole ring system and benzene ring is 9.0 °. The calculated position of the internal hydrogen atom of the indole unit is, as expected, directly over the benzene ring. The bond lengths and angles of **30** are within normal ranges, except for the C-C-C and C-C-N bond angles of the bridges, which are somewhat greater than normal, ranging from 113.1 ° at C11 to 118.1 ° at C19.

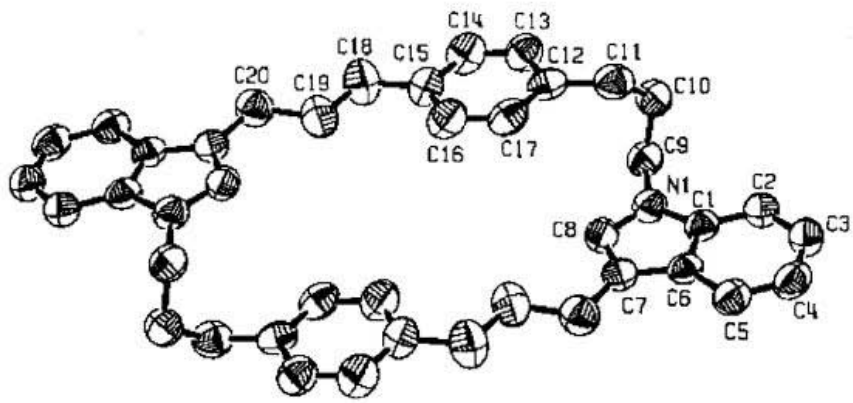
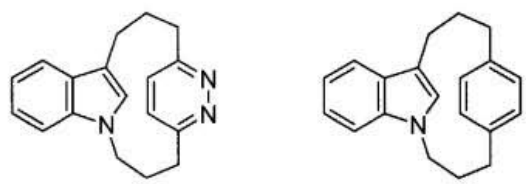


Figure 3.11 ORTEP representation of **67** in the crystal. The crystallographic numbering differs from systematic. Selected bond angles (°): N(1)-C(9)-C(10) 113.0(3), C(9)-C(10)-C(11) 114.8(4), C(10)-C(11)-C(12) 114.8(4), C(15)-C(18)-C(19) 114.9(4), C(18)-C(19)-C(20) 113.6(4), C(7)-C(20)-C(19) 113.2(4).

The crystal structure of the macrocyclic dimer **67** was also determined by X-ray methods (Figure 3.11). The two monomeric units of **67** are related by crystallographic symmetry. The molecule has adopted a two tiered structure with each tier containing an indole ring, a benzene ring and five of the six bridge carbons. The distance across the central cavity, as measured by the distance

between hydrogen atoms attached to the two crystallographically equivalent C8 atoms, is 6.91 Å. The aromatic nuclei do not deviate significantly from planarity. As in the case of **30**, the bond lengths and angles are within normal ranges, except for the C-C-C and C-C-N bond angles of the bridge atoms. These range from 113.2 ° at C20 to 114.9 ° at C18. Whereas the unexpectedly high values might be explained by a small amount of molecular strain in **30**, the same argument cannot be made for **67**. Crystal packing forces may well be responsible for this phenomenon.

3.2.3 Hydroboration/Suzuki-Miyaura Strategy



71 **30**

Figure 3.12 Structures of two structurally related indolophanes **71** and **30**.

For studies of transannular inverse electron demand Diels-Alder (IEDDA) reactions in cyclophane systems (see Chapter 4), an indolopyridazinophane **71** (Figure 3.12), which is structurally related to indolophane **30**, was identified as an appropriate parent system. Given the structural similarity between compound **71** and **30**, it was anticipated that a synthetic approach analogous to Strategy D (Section 3.2.1), would lead to cyclophane **71**. However, this approach proved to be unsuitable. Several other synthetic plans also failed, but a

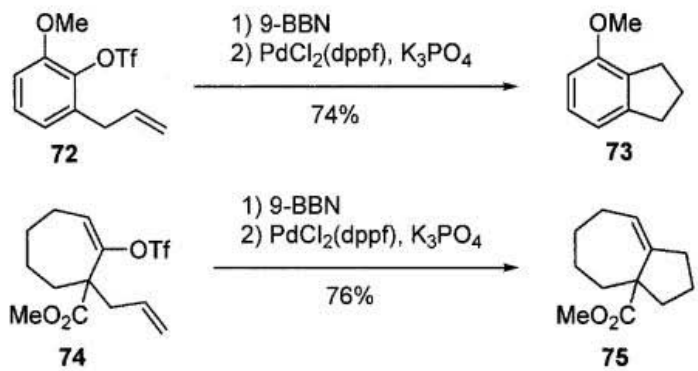
hydroboration/Suzuki-Miyaura strategy ultimately proved to be successful.[119] For a detailed description of the chronological development of this strategy and the synthesis of indolopyridazinophane **71** by using hydroboration/Suzuki-Miyaura sequence, the reader is referred to Chapter 4 in this dissertation.

3.2.3.1 Literature Review of the Hydroboration/Suzuki-Miyaura Sequence in Ring Closure Reactions

Transition metal catalyzed cross-coupling reactions have revolutionized modern organic chemistry. Many highly efficient and mild protocols have emerged from the mastery of such reactions, particularly in multifunctional settings.[120-123] Being one of the most utilized cross-coupling reactions, the Suzuki-Miyaura reaction is extremely useful in C-C bond-forming processes, especially between two sp^2 carbon atoms.[124,125] Recent studies on this reaction have mainly focused on mechanistic aspects,[126] synthetic usage[127] and catalyst modifications.[128-130]

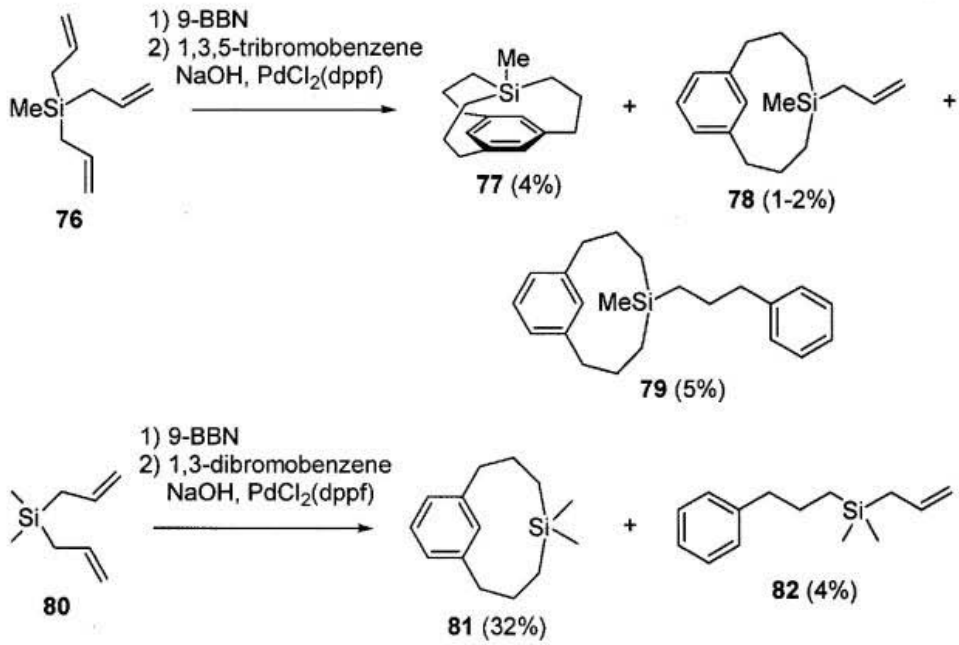
When combined with another highly efficient organometallic process, i.e. hydroboration,[131,132] the resulting hydroboration/Suzuki-Miyaura sequence is distinguished from traditional Suzuki-Miyaura cross-coupling reactions in that reaction occurs between an alkyl borane (as opposed vinyl or aryl borane) and an aryl or vinyl halide, triflate or enol phosphate.[133] The intramolecular version of this sequence supplies a feasible entry to various-sized ring systems. The first examples of such applications were demonstrated by Miyaura and co-workers,

who synthesized five- and six-membered rings using aryl or vinyl halides that were functionalized with terminal olefins.[134] However, attempts to gain access to smaller or larger rings by using this cyclization protocol were unsuccessful. Clearly, competing oligomerization processes constitute risk factors that darken the prospects for cyclization. A later study found that both aryl and vinyl triflates were also good substrates for the intramolecular reaction (Scheme 3.18).[135]



Scheme 3.18 Synthesis of five-membered rings using the hydroboration/Suzuki-Miyaura sequence.

When high dilution was used, moderate success was achieved in the syntheses of several small cyclophanes (Scheme 3.19).[136,137] Cyclophanes **77** and **81** were obtained in yields of 4% and 32%, respectively, along with other undesired side products.

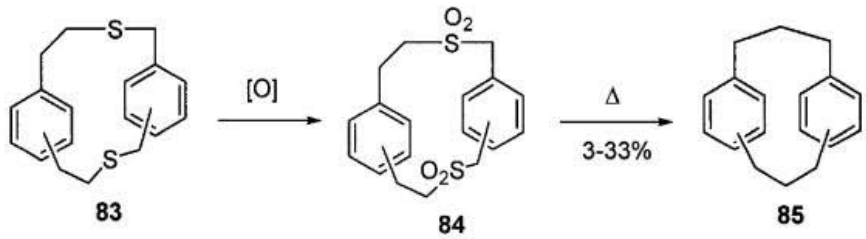


Scheme 3.19 Macrocyclization using the hydroboration/Suzuki-Miyaura sequence.

3.2.3.2 Synthetic Approaches to [3.3]Cyclophanes

[3.3]Cyclophanes are pivotal structures among [*m.n*]cyclophanes because they are intermediate in ring size between [2.2]cyclophanes, where ring strain and transannular effects are pronounced, and [4.4]cyclophanes, where these effects are absent.[138] Until about three decades ago, the alkylation of malonic esters was one of the most important methods for the synthesis of [3.3]cyclophanes.[139] However, the low yield in the key cyclization step and tedious route prevent its further application in synthesis of [3.3]cyclophanes.

One of the more popular methods is desulfurization of dithia[4.4]cyclophanes by either pyrolysis or photolysis (Scheme 3.20).[111,112,140] Pyrolytic desulfurization often offers better options and some other multibridged and multilayered [3.3]cyclophanes have been also prepared by this approach.



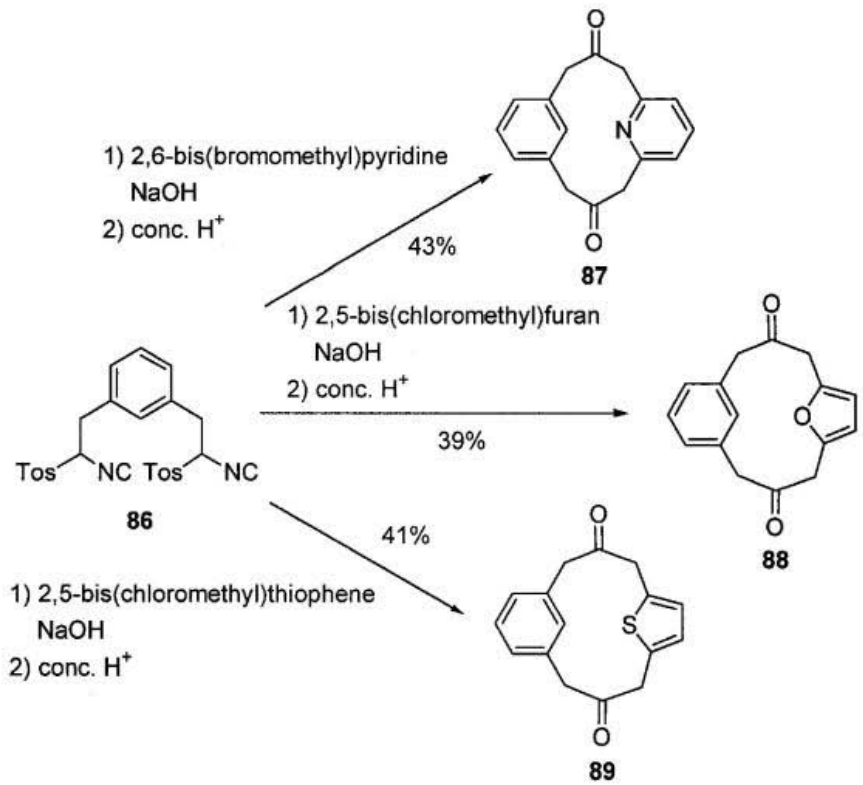
Scheme 3.20 Syntheses of [3.3]cyclophanes **85** *via* dithia[4.4]cyclophane approach.

Another general strategy, the (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) method, has been developed by Inazu[141] and Sasaki.[142] The application of this methodology has resulted in the successful syntheses of several [3.3]heterophanes, e.g. **87**-**89** (Scheme 3.21).[33]

3.2.3.3 Synthesis of [3.3]Indolophanes

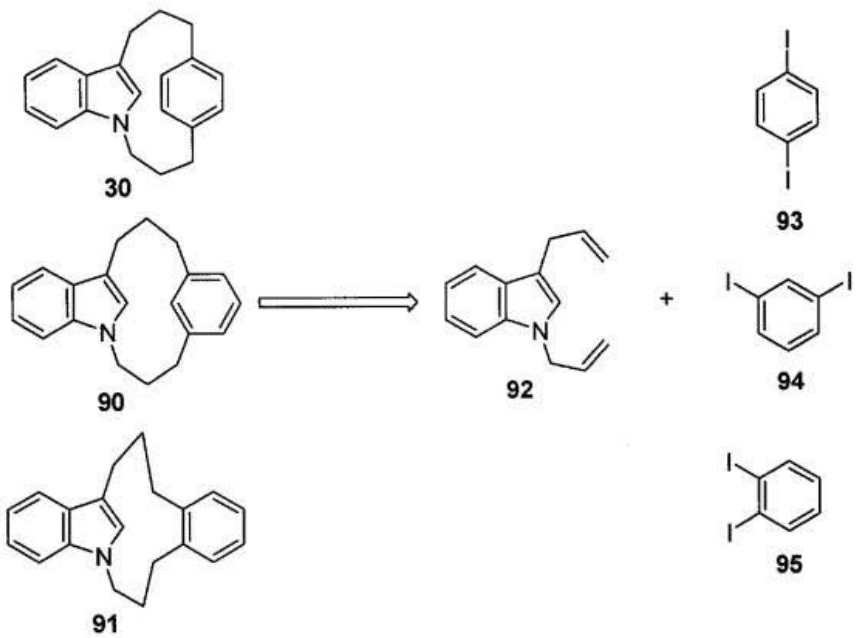
The synthesis of indolopyridazinophane **71**[119] was the first example of the use of hydroboration/Suzuki-Miyaura sequence for the preparation of a [3.3]cyclophane. With the advantages of brevity, mild conditions and wide-ranging functionality tolerance,[133] the generality of the approach for the synthesis of [3.3]cyclophanes was then investigated. The isomeric

[3.3](1,3)indolophanes **30**, **90** and **91** were identified as a logical series of targets (Scheme 3.22).

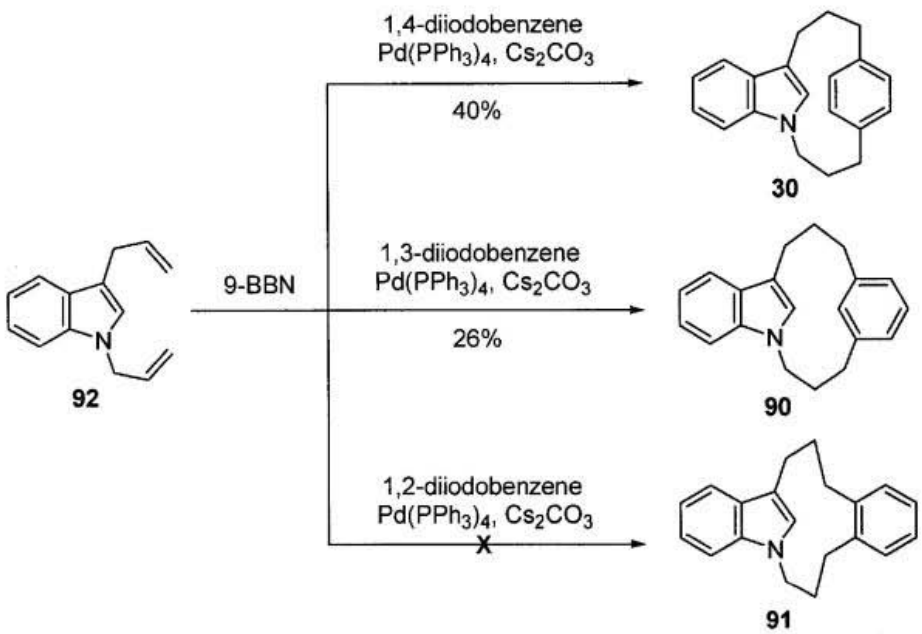


Scheme 3.21 Syntheses of [3.3]cyclophanes **87-89** by TosMIC method.

Based on the hydroboration/Suzuki-Miyaura strategy, retrosynthetic analysis of **30**, **90** and **91** simply gives 1,3-diallylindole **92** and the commercially available diiodobenzenes **93-95** (Scheme 3.22).



Scheme 3.22 Retrosynthetic analysis of [3.3](1,3)indolophanes **30**, **90** and **91**.



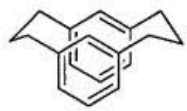
Scheme 3.23 Syntheses of [3.3](1,3)indolophanes **30** and **90** using the hydroboration/Suzuki-Miyaura sequence.

1,3-Diallylindole **92**, the same key intermediate also used in the synthesis of **71**, was synthesized by a two-step and alternative three-step sequences with overall yields of 46% and 75%, respectively (see Chapter 4 for detailed synthetic description). With compound **92** in hand, the synthesis of **30** (Scheme 3.23) was tried first to see how the hydroboration/Suzuki-Miyaura sequence would compare to the synthetic approach presented in Section 3.2.1. The cyclization proceeded smoothly to afford **30** in 40% yield free from the contamination of cyclic dimer **67**. Therefore, despite the modest yield of the key hydroboration/Suzuki-Miyaura reaction, the synthesis of indolophane **30** was greatly improved from a seven-step sequence with an overall yield of 22% to a four-step sequence with an overall yield of 30% by using this approach. Syntheses of the other two cyclophane isomers **90** and **91** were then attempted. [3]Metacyclo[3](1,3)indolophane **90** was obtained in 26% yield starting from **92** and 1,3-diiodobenzene. Disappointingly, the attempted synthesis of the last cyclophane in this series, **91**, met with complete failure. This may be a consequence of significantly higher steric energy in **91** (24.0 kcal/mol) compared to that in **30** (15.0 kcal/mol) and **90** (12.6 kcal/mol), which was revealed by MM2 calculations of their global minima, N_{chair},C_{chair} conformers, using Chem3D Ultra 5.0 software package.

3.2.4 Conformational Behavior of 90

For general interest, the conformational behavior of **90** was investigated following its synthesis. To put this in perspective, a description of previous conformational studies of structurally related [3.3]metacyclophanes is presented below.

3.2.4.1 Conformational Behavior of [3.3]Metacyclophanes



96

Figure 3.13 Lowest energy conformation of *syn*-[3.3]metacyclophane **96**.

The parent [3.3]metacyclophane **96** (Figure 3.13) was first synthesized in 1976.[139] After several reports of other syntheses,[111,112,143] Semmelhack published a leading paper on the conformational behavior of this compound in 1985.[144] According to molecular mechanics calculations, the conformational energy global minimum of **96** corresponds to the *syn* form with both bridges in the *pseudo-chair* conformation (Figure 3.13), which was also found in the solid state by single crystal X-ray analysis. In solution, two conformers could be observed by ^{1}H NMR (270 MHz) below 223 K, both of which were assigned the *syn* conformation by the chemical shift of the internal protons. The major conformer was assigned the *pseudo-chair,pseudo-chair* conformation and the minor isomer was assigned the *pseudo-chair,pseudo-boat* conformation based on

the computational results. However, this study implied that the only important dynamic process in **96** was bridge wobbling (chair-to-boat interconversion).

In contrast, Shinmyozu demonstrated that benzene ring inversion was present as well as bridge wobble based on their studies on deuterated [3.3]metacyclophanes **97** and **98** (Figure 3.14).[113,145] In both cases, *syn* conformers were shown present as the sole conformation both in the crystal and in solution according to X-ray and ^{1}H NMR studies. The benzylic protons of deuterated cyclophane **97** appeared as a singlet at 283 K.[113] When an ethylenedioxy tether was installed to eliminate the possibility of benzene ring inversion, the benzylic protons of **98** were observed as an AB system.[145] Based on the different ^{1}H NMR patterns of benzylic protons in **97** and **98**, they concluded that benzene ring inversion must occur in addition to bridge wobble. Meanwhile, they also found that the energy barrier for benzene ring inversion was much lower than that of bridge wobble because the former process could not be detected by VTNMR even below 183 K.[113]

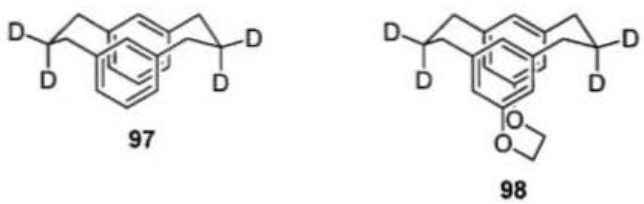
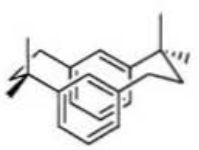


Figure 3.14 Structures of deuterated [3.3]metacyclophanes **97** and **98**.

A further study of a [3.3]metacyclophane **99** (Figure 3.15) was undertaken by Fukazawa.[146] The ^{1}H NMR spectrum of **99** at 177 K indicated the presence of

the three possible bridge conformers (*chair,chair*, *chair,boat* and *boat,boat*) with a *syn* arrangement of the benzene rings. These conformers interconvert by wobble motions of the bridges and aromatic ring flips to give their respective mirror images. The barrier for the benzene ring flipping process was found to be smaller (9.3 kcal/mol at 190 K) than the barriers of the wobble motions of the bridges (13.4 kcal/mol at 270 K). It also suggested that benzene ring flipping gave rise to *syn-syn'* interconversion *via* undetectable *anti* isomers. Recent computational and VTNMR work by Mitchell[147] supports the notion that *anti* conformers, although not observable by NMR, are important in the interconversions of *syn* and *syn'* conformers.



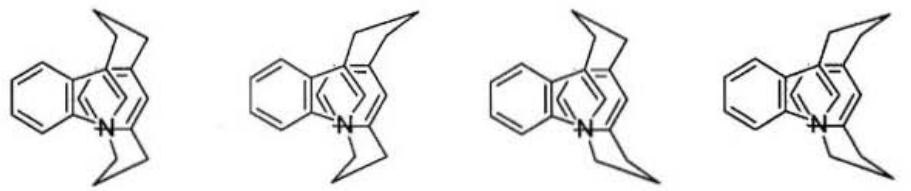
99

Figure 3.15 Structure of 1,1,10,10-tetramethyl[3.3]metacyclophane **99**.

Based on the previous investigations on [3.3]metacyclophanes with all-carbon bridges, certain assumptions were made prior to the study of the conformational behavior of indolophane **90**: (a) aromatic ring inversions are present as well as bridge wobbles; (b) aromatic ring inversions have smaller energy barriers than bridge wobbles.

3.2.4.2 Computational Studies of 90

Calculations using Chem3D (Ultra 5.0) MOPAC at the AM1 and MM2 levels of theory were preformed to determine the energy differences between the four most likely *syn* conformers. They were calculated to lie within 3 kcal/mol of the global minimum (Figure 3.16). Similar to the results for **30** (Figure 3.5), the lowest energy conformer (*syn*-C_{chair},N_{chair}) has both bridges in the *pseudo-chair* conformation.



	syn-C_{chair},N_{chair}-**90**	*syn*-C_{boat},N_{chair}-**90**	*syn*-C_{chair},N_{boat}-**90**	*syn*-C_{boat},N_{boat}-**90**
(AM1):	0.00 kcal/mol	0.82 kcal/mol	1.55 kcal/mol	2.46 kcal/mol
(MM2):	0.00 kcal/mol	0.36 kcal/mol	0.54 kcal/mol	1.02 kcal/mol

Figure 3.16 AM1- and MM2-calculated low energy conformers of **90** and their relative energies.

Flipping the bridge attached to the C-terminus of the indole unit affords a conformer (*syn*-C_{boat},N_{chair}) that is 0.82 kcal/mol by AM1 or 0.36 kcal/mol by MM2 higher in energy, whereas flipping the bridge attached to the N-terminus of the indole moiety to give the *syn*-C_{chair},N_{boat} conformer is almost twice as costly in energy (1.55 kcal/mol by AM1 and 0.54 kcal/mol by MM2). This surprisingly significant difference in energy between the two bridge flips was also found in the case of **30** (Figure 3.5). Originally, all the relative *anti* conformers were also calculated. Although the most stable *anti* conformer (*anti*-C_{boat},N_{chair}-**90**) has a

similar AM1-calculated energy to *syn*-C_{boat},N_{chair} (0.74 kcal/mol higher in energy than the global minimum), the parallel MM2 calculations revealed a steric energy difference of 6.99 kcal/mol compared to *syn*-C_{chair},N_{chair} conformer. However, the origin of this observed discrepancy between AM1 and MM2 calculations on this system is not clear. In consulting the literature, very close values were analogously reported in molecular mechanics analyses of [3.3]metacyclophanes **96**[144] and **99**[146] (6.57 kcal/mol in case of **96** and 6.69 kcal/mol in case of **99**). A detailed analysis of the steric energies suggested that more than half of the extra energy of the *anti* conformation came from torsional strain within the bridging chains, which served as a rationale for the predominance of the *syn* structure.[146]

3.2.4.3 ^{1}H NMR ($CDCl_3$) Spectrum of 90

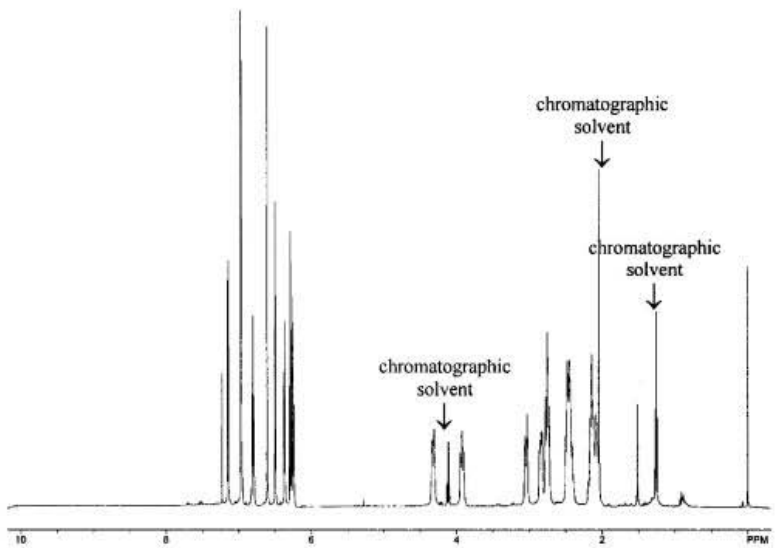


Figure 3.17 ^{1}H NMR ($CDCl_3$) spectrum of **90** at room temperature.

The ^{1}H NMR spectrum of indolophane **90** in $CDCl_3$ at room temperature (Figure 3.17) exhibits a sharp singlet at δ 6.61, which was assigned to the internal proton of the benzenoid deck based on by COSY data (cross peaks to the *meta* protons). By comparison, the analogous protons of **96**[144], **97**[113] and **99**[146] are observed at δ 6.88, 6.90 and 7.00, respectively. In accord with the computational results, the predominance of the *syn* conformer is suggested by this relatively small upfield shift (0.35 ppm) by comparison with chemical shift of the internal proton from a reference compound (*m*-xylene) at room temperature. The internal proton of the indole deck is observed at δ 6.50, which is consistent with the *syn* conformation of **90** in solution. This compares to the analogous proton of **30** (δ 5.59), which is deeper in the shielding cone of the opposing benzenoid deck.[148] On the other hand, the signals of the diastereotopic NCH_2 group are observed as a part of an ABXY system centered at δ 4.33 and 3.93, and the remaining bridge protons are observed as a series of multiplets in the range of δ 2.08-3.06. This observed ^{1}H NMR pattern of bridge protons corresponds surprisingly well with that of bridge protons of **30** at low temperatures (203, 193 and 183 K) (Figure 3.8). At those temperatures, the indole ring flipping of **30** is retarded. Analogously, conclusions could be drawn that either one of the bridge wobbles in **90** freezes out at room temperature as bridge wobbles are assumed to have higher energy barrier than aromatic ring inversions. To obtain more insight into the conformational processes, DNMR spectra were examined at 500 MHz over the temperature range of 183-373 K.

Toluene-d_8 was chosen as the solvent because of its higher range of accessible temperatures than $CDCl_3$.

3.2.4.4 ^{1}H DNMR (Tol-d_8) Studies of 90

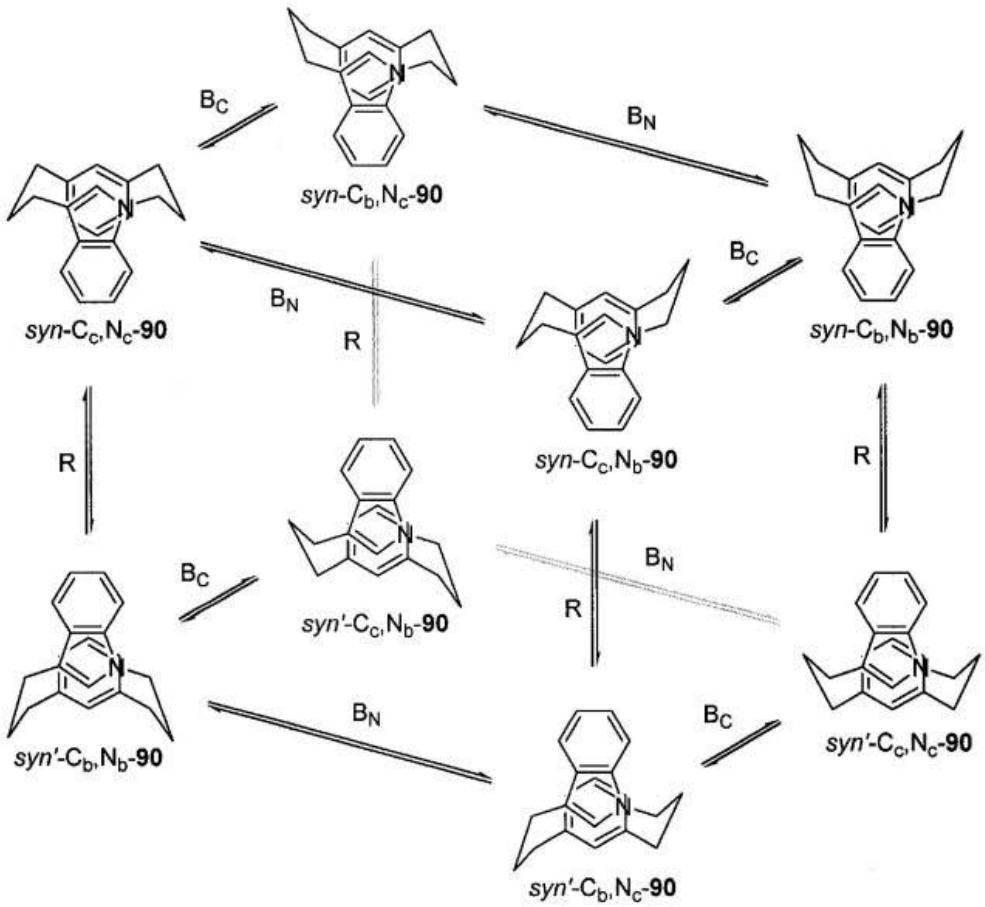


Figure 3.18 Selected conformational processes in **90**. B_C=C-bridge wobble; B_N=N-bridge wobble; R=ring inversions.

Selected conformational processes of **90** are depicted in Figure 3.18. Applying Mitchell's results,[147] ring inversions (R) of the indole deck and the

benzenoid deck were considered to be occurring rapidly through a very short-lived *anti* conformation (or with a very low concentration of the *anti* conformer) to achieve a *syn-syn'* interconversion, which was also confirmed by the fact that neither ^{1}H NMR ($CDCl_3$) nor ^{1}H DNMR (Tol-d_8) spectra of **90** detected any traces amount of *anti* conformers.[113]

As shown in Figure 3.18, none of the illustrated interconversions alone involves an exchange in the environments of the diastereotopic NCH_2 protons (or any of the other diastereotopic CH_2 groups in the bridges). This can be accomplished by a full set of different types of interconversions because the exchange within any group of diastereotopic protons can be effected only when the racemization of a given conformer is realized. This is to say that the chemical shift degeneracy of any pair of geminal protons in the bridges must originate from all three conformational processes, including C-bridge wobble (B_C), N-bridge wobble (B_N) and ring inversions (R). For example, racemization of *syn*-C_c,N_c-**90** could begin from any of the total three directions, but any chosen route that leads to *syn'*-C_c,N_c-**90** is composed of at least one B_C, one B_N and one R, irrespective of the path taken or the number of steps. Consequently, the cessation of any one type of conformational process should stop the exchange of all the pairs of diastereotopic protons in the bridges and thus lead to the observation of two distinct signals for each pair of them, barring a chemical shift degeneracy. Based on this, the observation of two distinct multiplets for the NCH_2 group in ^{1}H NMR spectrum of **90** in $CDCl_3$ at room temperature suggests

that at least one type of conformational processes is either slow or fully stopped. If only one conformational process is slow, according to the previously described assumption that bridge wobbles have higher activation energies than ring inversions, the restricted process should be one of the bridge wobbles. Arbitrarily, restricted N-bridge wobble is ascribed for the observed ^{1}H NMR spectrum of **90** at room temperature. However, this is to be confirmed by computational calculations for corresponding transition states, which forms part of the future work.

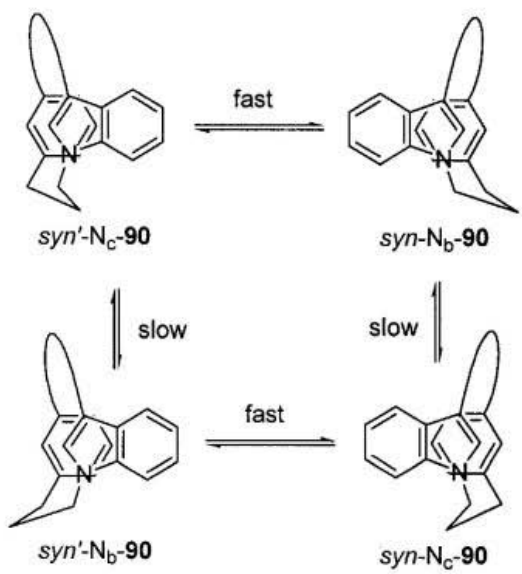


Figure 3.19 Restriction of N-bridge wobble in **90**.

Since ring inversions are presumably still occurring rapidly, *syn'*-N_b-**90**, which is magnetically equivalent to *syn*-N_b-**90**, is in a fast equilibrium with *syn*-N_c-**90**, which is magnetically equivalent to *syn'*-N_c-**90** (Figure 3.19). Therefore,

the observed NCH_2 proton signals are the result of an average between N_b-**90** and N_c-**90** conformers. This is consistent with the observed ^1H NMR spectrum of **90**.

If two conformational processes, namely N-bridge and C-bridge wobbles, are considered slow at ambient temperature, at least two isomers, with relationship between two bridges of *pseudo-cis* or *pseudo-trans*, should have appeared in the ^1H NMR spectrum. If all of the conformational processes are retarded, the ^1H NMR spectrum would have been a combination of signals from all four lower energy conformers.

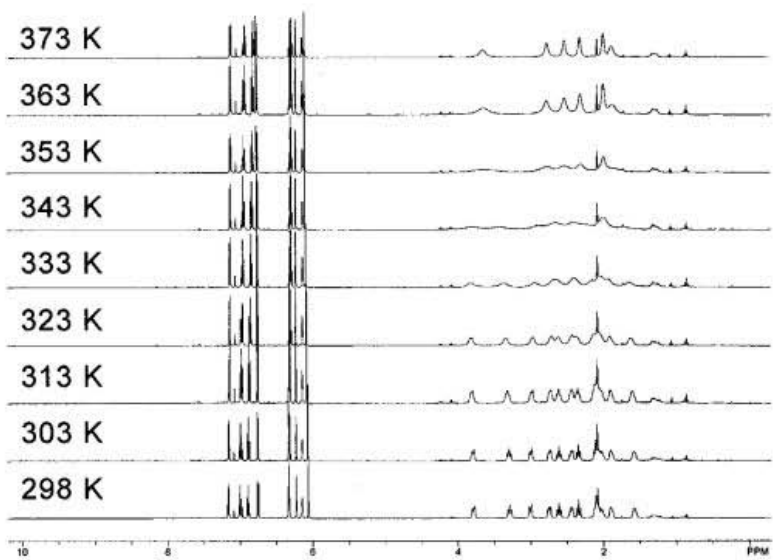


Figure 3.20 ^1H DNMR (Tol-d_8) spectra of **90** at 298-373 K.

As the temperature is raised, the multiplets of bridge protons begin to collapse and give rise to six broad signals at 373 K (Figure 3.20). One could imagine that a ^1H NMR spectrum with a similar bridge signal pattern to that of **30** at room temperature would be obtained at a higher temperature. During the

above heating process, no appreciable changes, as expected, were noticed in the chemical shifts of the aromatic protons of **90**. Since the NCH_2 signals were well separated from other resonances, they were used for the determination of the energy barrier for what is presumed to be N-bridge wobble. The ambient temperature spectrum consists of two narrow multiplets centered at δ 3.79 and 3.29. The coalescence temperature (T_c) of these signals is 351±5 K and $\Delta\nu$=247.6 Hz, giving k_c=550.0 and $\Delta G^{\ddagger}$=16.3±0.2 kcal/mol, according to the Gutowsky-Holm equation[118] described in Section 3.2.2.2.

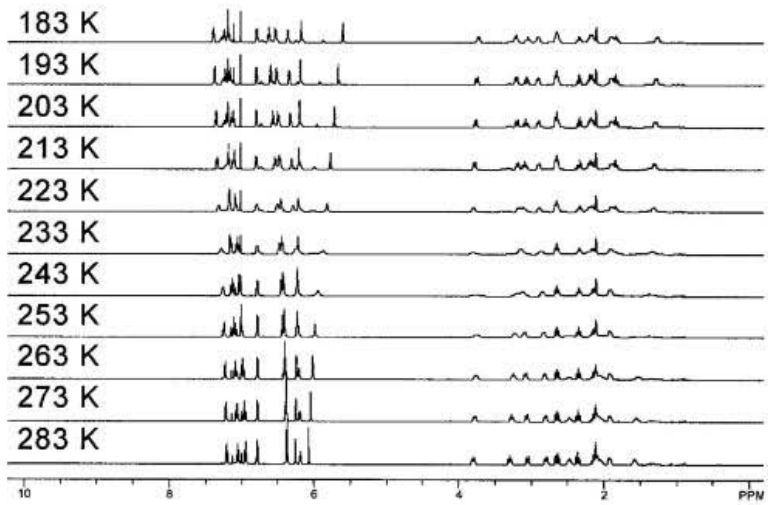


Figure 3.21 ^{1}H DNMR (Tol-d_8) spectra of **90** at 283-183 K.

Upon lowering the temperature, changes appear in both bridge and aromatic proton regions (Figure 3.21). The change of the signal due to the internal aryl protons is especially characteristic. They are observed at δ 6.23 for the benzenoid deck and δ 6.06 for the indole deck at ambient temperature. As

the sample is cooled, they broaden, and the internal proton of the indole deck splits into two peaks with unequal intensities (ratio 10:3), which correspond to two isomers, below 203 K. At 183 K, the internal proton of the indole deck can be unambiguously determined to resolve into two signals at δ 5.86 (minor) and 5.58 (major). The other aromatic protons behave quite similarly, but due to the extensive overlapping of the signals at 183 K, it is difficult to analyze the detailed mode of signal separation. The aliphatic protons broaden first as the temperature is decreased to about 243 K, and then sharpen back as the temperature is further lowered. Again, the extensive overlapping of signals prevented the analysis of the dynamic processes of bridge protons even though significant changes seem to occur by comparison of the spectra from the cooling process. The only distinguishable change at 183 K is the observation of two minor multiplets centered at δ 3.29 and 2.72, which correspond to the minor isomer based on the aromatic proton signals. Since it was reported that both the coalescence temperature method and the more accurate line-shape analysis method had been applied for two peaks of different intensities with very close results,[146] the Gutowsky-Holm equation[118] was employed again to determine the energy barrier for this conformational process observed upon cooling. This dynamic process was assigned C-bridge wobble (*vide infra)*, and its activation energy, using internal proton signals of the indole ring at 183 K, was calculated to be 10.9±0.2 kcal/mol based on T_c=233±5 K, Δν=138.0 Hz and k_c=306.6.

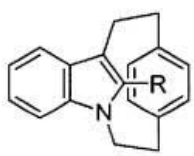
From the behavior of the temperature-dependent signal change of both aromatic and aliphatic protons, the detailed process of conformational interconversions can be clarified. As described previously, the complex signal pattern of diastereotopic protons in the bridges, including the NCH_2 group, suggest that N-bridge wobble is slow or fully stopped at ambient temperature. Upon heating, the mobility of the N-bridge is increased as evidenced by gradual degeneration of those diastereotopic bridge protons. Since the aliphatic protons also broaden first as the temperature is lowered, a conclusion can be drawn that N-bridge wobble is fully stopped rather than slowed down at room temperature. The second conformational process observed is assigned as C-bridge wobble again based on the assumption that bridge wobbles have higher activation energy than ring inversions, which was also the basis for conformational determination in other [3.3]metacyclophanes without hetero atoms[113,146] or with hetero atoms in the bridges.[7] The reason that only two isomers are observed can be understood by examining Figure 3.18. At temperatures below 223 K (Figure 3.21), both the N-bridge and C-bridge wobbles are slow, which can be reflected in Figure 3.18 as the inoperation of all the B_N and B_C processes. As a result, only four interconversions are taking place, exclusively by ring inversion. This involves four pairs of structures: *syn*-C_c,N_c/*syn'*-C_b,N_b, *syn*-C_b,N_c/*syn'*-C_c,N_b, *syn*-C_c,N_b/*syn'*-C_b,N_c and *syn*-C_b,N_b/*syn'*-C_c,N_c. Since the first and last pairs form an enantiomeric set and the second and third pairs form another, only two isomers are observed by ^1H NMR. On the basis of calculated energies (Figure 3.16), the

major diastereomer is assigned to the conformers with *cis* bridges (*syn*-C_c,N_c, *syn*-C_b,N_b and their enantiomers, presumably weighted in favor of *syn*-C_c,N_c), and the minor diastereomer is assigned to the conformers with *trans* bridges (*syn*-C_c,N_b, *syn*-C_b,N_c and their enantiomers). The ratio of 10:3, which corresponds to a ΔG of 0.73 kcal/mol, is based on the integrals of analogous internal protons of the indole deck. The possibility that both C-bridge wobble and ring inversion cease below 223 K is ruled out by the expectation of the observation of four pairs of diastereomers in this instance. Apparently, the activation energy for aromatic ring inversion is, however, beyond the detection limit of the described method.

The conformational behavior of [3.3]metacyclophanes has been extensively investigated for about twenty years and a wealth of information has been collected,[149] which makes it possible to examine more complex system such as **90** without the need to re-establish certain aspects of the conformational behavior. The complexity of conformational behavior of **90** originates from an element of asymmetry in the molecule arising from the presence of the heteroaromatic indole ring. On the other hand, this system is unique in that it is the first example where energy barriers of two different bridge wobbles have been determined in the [*m.n*]cyclophane family. Unfortunately, attempts to obtain a suitable crystal of **90** for X-ray analysis from a variety of solvents were fruitless.

3.3 Conclusions and Future Directions

As described in Section 3.2.1, the first targeted synthesis of (1,3)indolophane **30** was achieved by a relatively short (seven steps) synthetic pathway in a respectable (22%) overall yield. The solid state structure of **30** and its cyclic dimer **67** were determined by single crystal X-ray analysis. A ring flip that interconverts two enantiomeric sets of equilibrating bridge conformers of **30** with an energy barrier of 10.9±0.2 kcal/mol was observed by DNMR. This is the first example of the determination of the energy barrier for the ring flip in [3.3]metaparacyclophanes and their structurally related analogues with no internal substituent. With an energy barrier of 10.9±0.2 kcal/mol, the probability of resolving chiral cyclophane **30** is very low. The introduction of a bulky substituent at the internal position of the indole nucleus and/or the shortening of the bridges should significantly enhance the chances of doing so. Therefore, synthesis of a series of [2]paracyclo[2](1,3)indolophanes **100** (Figure 3.22) with internal substituents of different sizes could provide a means of fine tuning the conformational behavior of (1,3)indolophanes and ultimately achieve the pratical resolution of such chiral systems.



100

Figure 3.22 Structure of [2]paracyclo[2](1,3)indolophanes **100**.

A second synthesis (Section 3.2.3) of indolophane **30** was then accomplished using the hydroboration/Suzuki-Miyaura strategy, which was developed in a transannular IEDDA study of an indolopyridazinophane system (Chapter 4). This synthesis was substantially shorter (four steps) and higher yielding (30%) compared to the first synthesis. To expand the scope of this strategy in synthesizing [3.3]cyclophanes, further study was required, which led to a synthesis of another novel (1,3)indolophane **90**. The asymmetry in this [3.3]metacyclophane caused by the presence of the indole nucleus provided an opportunity to differentially determine energy barriers for individual bridge wobbles, which rendered it the first example of this kind in the whole [*m.n*]cyclophane family. However, the extensive overlapping of signals and complicated spectral changes prevented the analysis of the dynamic processes of both bridges.[113] Deuterated indolophane **101** (Figure 3.23) would be expected to exhibit much simpler spectra and thus supply a vehicle for more detailed study into this point.

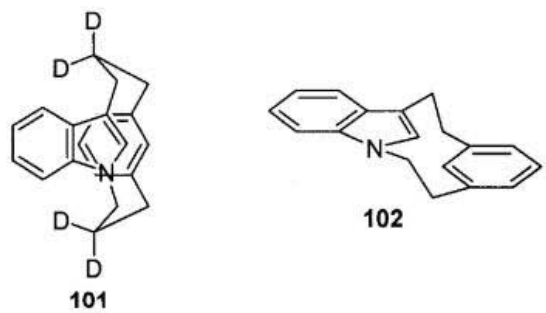


Figure 3.23 Structures of indolophanes **101** and **102**.

A structurally related and more ambitious target, indolophane **102** (Figure 3.23), is also of special interest in that its conformational behavior could be compared to that of the [2.2]metacyclophanes.

The synthesis of compound **91**, a regioisomer of **30** and **90**, by the hydroboration/Suzuki-Miyaura protocol failed, presumably due to an increased steric energy. If this is indeed the case, the use of more powerful Buchwald's ligands[150,151] or solvents with higher boiling point at elevated temperature[134,152] could solve the synthetic problem.

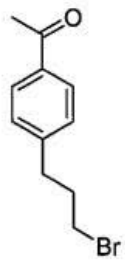
Additionally, a more thorough study is needed to realize the full potential of the hydroboration/Suzuki-Miyaura strategy in the synthesis of other cyclophane systems. A broad range of cyclophanes, including [2.2]cyclophanes with varying aromatic core units bridged at different positions, their related [3.3]cyclophanes and higher homologues, will provide logical targets. This work may furnish an expedient route to indolophanes **100** (Figure 3.22) and **102** (Figure 3.23), which can be visualized as coming from 1,3-divinylindole derivatives and 1,4-diiodobenzene or 1,3-diiodobenzene.

3.4 Experimental

General Experimental for Chapter 3. Reactions were performed under air unless otherwise indicated. Those experiments with moisture or air sensitive compounds were performed in anhydrous solvents under nitrogen in flame-dried glassware. Solvents for reactions were dried and distilled according to standard

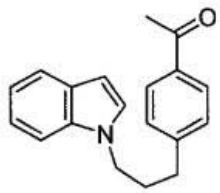
procedures. All other solvents were used as received. Chromatographic purification was accomplished with 230-400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on neat samples or nujol suspensions on KBr discs using a Mattson Polaris FT instrument. ^{1}H NMR spectra were obtained from $CDCl_3$ solutions using a General Electric GE-300 NB instrument or a Bruker Avance 500 instrument operating at 300.1 and 500.1 MHz, respectively. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 and 125.77 MHz. Chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$). Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. High resolution mass spectroscopic data were performed by the Mass Spectrometry Centre, Chemistry Department, University of Ottawa, Ottawa, Ontario.

1-Bromo-3-(4-acetylphenyl)propane (39)



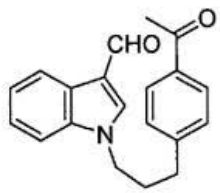
To a suspension of $AlCl_3$ (5.87 g, 44.0 mmol) in CH_2Cl_2 (60 mL) at 0 °C was injected acetyl chloride (3.14 g, 40.0 mmol). A solution of 1-bromo-3-phenylpropane **38** (3.98 g, 20.0 mmol) in CH_2Cl_2 (20 mL) was then added dropwise with stirring to the resulting mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (100 mL) and aqueous HCl solution (12 N, 10 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with brine (100 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) afforded **39** (4.15 g, 86%) as a clear, colorless liquid. IR (KBr) ν=1682 (s), 1607 (m) cm^{-1}. MS *m/z* (%)=242 (11, M^+ ^{81}Br), 240 (11, M^+ ^{79}Br), 227 (99), 225 (100), 183 (11), 181 (34), 133 (13), 118 (20). ^1H NMR ($CDCl_3$, 300 MHz) δ=2.14-2.24 (m, 2H), 2.59 (s, 3H), 2.83-2.87 (m, 2H), 3.39 (t, *J*=6.7 Hz, 2H), 7.30 (d, *J*=8.6 Hz, 2H), 7.90 (d, *J*=8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=26.6, 32.7, 33.6, 33.9, 128.6, 128.8, 135.4, 146.3, 197.7. Anal. Calcd. for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 55.09; H, 5.67.

1-(3-(4-Acetylphenyl)propyl)indole (40)



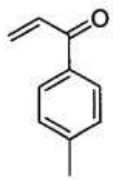
To a suspension of freshly ground NaOH (664 mg, 16.6 mmol) in DMF (20 mL) at room temperature was added a solution of indole **1** (970 mg, 8.28 mmol) in DMF (5 mL). After the mixture was further stirred for 1 h, a solution of **39** (1.00 g, 4.15 mmol) in DMF (10 mL) was added. After stirring for 12 h, the reaction mixture was diluted with a mixture of H_2O (50 mL) and aqueous HCl solution (12 N, 1.5 mL), and extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (18% EtOAc/hexane) gave **40** (896 mg, 78%) as a clear, colorless oil. IR (KBr) ν=1735 (m), 1680 (s), 1607 (m) cm^{-1}. MS *m/z* (%)=278 (7), 277 (34, M^+), 131 (77), 130 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.14-2.23 (m, 2H), 2.57 (s, 3H), 2.63-2.68 (m, 2H), 4.12 (t, *J*=7.0 Hz, 2H), 6.50 (d, *J*=2.9 Hz, 1H), 7.06-7.29 (m, 6H), 7.64 (d, *J*=7.6 Hz, 1H), 7.87 (d, *J*=8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=26.5, 31.1, 32.9, 45.5, 101.2, 109.2, 119.3, 121.0, 121.4, 127.6, 128.4, 128.5, 128.6, 135.3, 135.9, 146.7, 197.7. Anal. Calcd. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05. Found: C, 81.85; H, 6.67; N, 5.03.

3-Formyl-1-(3-(4-acetylphenyl)propyl)indole (32)



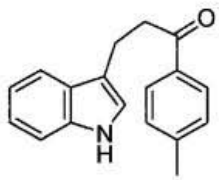
$POCl_3$ (153 mg, 1.00 mmol) was mixed with DMF (3 mL) at room temperature. A solution of **40** (116 mg, 0.418 mmol) in DMF (3 mL) was added dropwise to the resulting solution. After stirring at room temperature for 2 h, the reaction mixture was poured into ice (10 mL), treated with aqueous NaOH solution (0.5 N, 10 mL), boiled for 3 min, and extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine (50 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (60% EtOAc/hexane) gave **32** (83 mg, 65%) as a light yellow powder. M.p.=74-76 °C. IR (nujol) ν=1680 (m), 1657 (s), 1606 (m) cm^{-1}. MS *m/z* (%)=306 (20), 305 (83, M^+), 159 (73), 158 (66), 130 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.23-2.33 (m, 2H), 2.59 (s, 3H), 2.71-2.76 (m, 2H), 4.21 (t, *J*=7.1 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 2H), 7.30-7.36 (m, 3H), 7.69 (s, 1H), 7.90 (d, *J*=8.3 Hz, 2H), 8.30-8.33 (m, 1H), 10.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=26.6, 30.6, 32.8, 46.4, 109.9, 118.3, 122.2, 123.0, 124.3, 125.5, 128.5, 128.8, 135.6, 137.0, 137.9, 145.7, 184.4, 197.6. Anal. Calcd. for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.35; H, 6.35; N, 4.48.

4-Methyl-1-(1-oxo-2-propenyl)benzene (46)



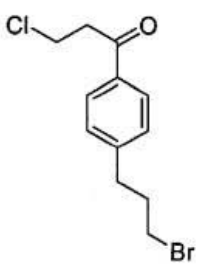
To a suspension of $AlCl_3$ (1.33 g, 10.0 mmol) in CH_2Cl_2 (8 mL) at 0 °C was injected acryloyl chloride (540 mg, 5.97 mmol). A solution of toluene **43** (460 mg, 4.99 mmol) in CH_2Cl_2 (2 mL) was added dropwise to the resulting stirred mixture. After stirring in the dark at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and HCl solution (12 N, 20 mL), and extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL×3) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (67% CH_2Cl_2/hexane) gave **46** (242 mg, 33%) as a slightly yellow liquid. IR (KBr) ν=1668 (s), 1605 (m) cm^{-1}. MS *m/z* (%)=147 (3), 146 (27, M^+), 119 (100), 91 (58). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.42 (s, 3H), 5.90 (dd, *J*=10.4, 1.6 Hz, 1H), 6.43 (dd, *J*=16.8, 1.5 Hz, 1H), 7.16 (dd, *J*=17.1, 10.5 Hz, 1H), 7.28 (d, *J*=8.2 Hz, 2H), 7.86 (d, *J*=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=21.6, 128.8, 129.3, 129.7, 132.3, 134.7, 143.9, 190.5. Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.91; H, 6.84.

3-(3-(4-Methylphenyl)-3-oxopropyl)indole (47)



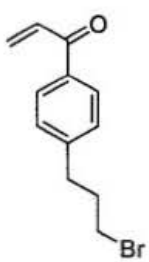
To a solution of **46** (146 mg, 1.00 mmol) in CH_3CN (3 mL) at room temperature was added indole **1** (234 mg, 2.00 mmol). $Yb(OTf)_3$ (16 mg, 0.026 mmol) was added to the resulting solution. After stirring for 24 h, the reaction mixture was columned directly (15% EtOAc/hexane) to afford **47** (100 mg, 38%) as a white solid. M.p.=134-136 °C. IR (nujol) ν=1668 (s), 1608 (m) cm^{-1}. MS *m/z* (%)=264 (6), 263 (33, M^+), 144 (65), 130 (100), 119 (21). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.39 (s, 3H), 3.18-3.23 (m, 2H), 3.33-3.38 (m, 2H), 7.02 (d, *J*=2.6 Hz, 1H), 7.10-7.20 (m, 2H), 7.23 (d, *J*=7.9 Hz, 2H), 7.34 (d, *J*=7.7 Hz, 1H), 7.63 (d, *J*=7.8 Hz, 1H), 7.86 (d, *J*=8.3 Hz, 2H), 7.98 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=19.8, 21.6, 39.2, 111.2, 115.5, 118.7, 119.3, 121.6, 122.0, 127.2, 128.1, 129.2, 134.45, 136.3, 143.7, 199.6. Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.95; H, 6.69; N, 5.35.

1-(3-Chloro-1-oxopropyl)-4-(3-bromopropyl)benzene (36)



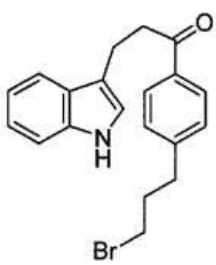
To a suspension of $AlCl_3$ (1.60 g, 12.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C was injected 3-chloropropionyl chloride (1.27 g, 10.0 mmol). A solution of 1-bromo-3-phenylpropane **38** (1.00 g, 5.02 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and aqueous HCl solution (12 N, 10 mL), and extracted with CH_2Cl_2 (40 mL×3). The combined organic layers were washed with H_2O (50 mL×3) and brine (50 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **36** (1.42 g, 98%) as a white powder. M.p.=75-77 °C. IR (nujol) ν=1677 (s), 1606 (m) cm^{-1}. MS *m/z* (%)=292 (not observed, M^+ $^{81}Br^{37}Cl$), 290 (0.9, M^+ $^{81}Br^{35}Cl$ and $^{79}Br^{37}Cl$), 288 (0.8, M^+ $^{79}Br^{35}Cl$), 227 (99), 225 (100), 181 (22), 118 (16). ^1H NMR ($CDCl_3$): δ=2.14-2.24 (m, 2H), 2.83-2.88 (m, 2H), 3.39 (t, *J*=6.4 Hz, 2H), 3.44 (t, *J*=7.1 Hz, 2H), 3.93 (t, *J*=7.1 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H), 7.90 (d, *J*=8.3 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=32.7, 33.6, 34.0, 38.7, 41.2, 128.4, 128.9, 134.6, 146.9, 196.3. Anal. Calcd. for $C_{12}H_{14}BrClO$: C, 49.77; H, 4.87. Found: C, 49.79; H, 4.78.

1-(1-Oxo-2-propenyl)-4-(3-bromopropyl)benzene (37)



To a solution of **36** (290 mg, 1.00 mmol) in CH_2Cl_2 (15 mL) was added DBU (152 mg, 1.00 mmol), and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with aqueous HCl solution (0.12 N, 30 mL) and extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with brine (50 mL×4), dried over $MgSO_4$, filtered and concentrated. Column chromatography (CH_2Cl_2) gave **37** (213 mg, 84%) as a slightly yellow liquid. IR (KBr) ν=1668 (s), 1605 (s) cm^{-1}. MS *m/z* (%)=254 (23, M^+ ^{81}Br), 252 (25, M^+ ^{79}Br), 227 (99), 225 (100), 145 (29), 117 (43). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.15-2.24 (m, 2H), 2.83-2.88 (m, 2H), 3.40 (t, *J*=6.3 Hz, 2H), 5.92 (dd, *J*=10.7, 1.9 Hz, 1H), 6.44 (dd, *J*=16.9, 1.4 Hz, 1H), 7.16 (dd, *J*=16.9, 10.3 Hz, 1H), 7.32 (d, *J*=8.1 Hz, 2H), 7.90 (d, *J*=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=32.7, 33.6, 34.0, 128.8, 129.1, 129.9, 132.3, 135.4, 146.2, 190.5. Anal. Calcd. for $C_{12}H_{13}BrO$: C, 56.94; H, 5.18. Found: C, 57.08; H, 5.20.

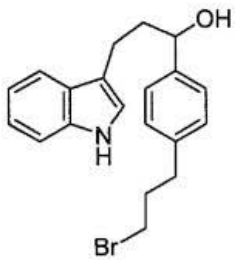
3-(3-(4-(3-Bromopropyl)phenyl)-3-oxopropyl)indole (48)



A solution of **37** (3.80 g, 15.0 mmol) and indole **1** (6.79 g, 58.0 mmol) in CH_2Cl_2 (40 mL), HOAc (30 mL), and Ac_2O (10 mL) was heated at reflux for 6 h. The reaction mixture was concentrated, diluted with saturated aqueous $NaHCO_3$

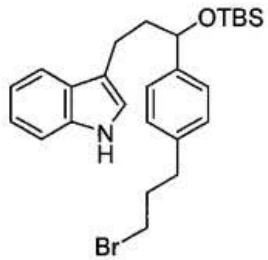
solution (100 mL), and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (25% EtOAc/hexane) gave **48** (4.11 g, 74%) as a yellow solid. M.p.=98-100 °C. IR (nujol) ν=3401 (s), 1675 (s), 1603 (m) cm^{-1}. MS *m/z* (%)=371 (8, M^+ ^{81}Br), 369 (8, M^+ ^{79}Br), 227 (12), 225 (12), 144 (72), 130 (100), 117 (16). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.12-2.22 (m, 2H), 2.81-2.85 (m, 2H), 3.19-3.24 (m, 2H), 3.34-3.40 (m, 4H), 7.05 (d, *J*=2.0 Hz, 1H), 7.10-7.23 (m, 2H), 7.27 (d, *J*=8.6 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 1H), 7.64 (d, *J*=7.7 Hz, 1H), 7.90 (d, *J*=8.0 Hz, 2H), 7.97 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=19.7, 32.7, 33.6, 33.9, 39.2, 111.1, 115.5, 118.7, 119.3, 121.5, 122.0, 127.2, 128.4, 128.8, 135.2, 136.3, 146.1, 199.5. Anal. Calcd. for $C_{20}H_{20}BrNO$: C, 64.87; H, 5.44; N, 3.78. Found: C, 65.56; H, 5.55; N, 3.74. A triplet at δ=3.51 and a multiplet at δ=2.06-2.10 due to a minor unidentified impurity were observed in the ^1H NMR spectrum. Neither crystallization, chromatography, nor sublimation succeeded in removing this impurity. Acceptable analytical data were not obtained for this compound.

(±)-3-(3-(4-(3-Bromopropyl)phenyl)-3-hydroxypropyl)indole (52)



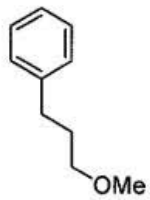
To a suspension of **48** (100 mg, 0.270 mmol) in EtOH (15 mL) at 0 °C was added $NaBH_4$ (102 mg, 2.70 mmol) portionwise. After stirring at room temperature for 5 h, the reaction mixture was concentrated, treated with HCl solution (1.2 N, 20 mL), and extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with brine (50 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (40% EtOAc/hexane) gave **52** (83 mg, 83%) as a sticky, yellow liquid. IR (KBr) ν=3545 (w), 3418 (s), 1618 (w) cm^{-1}. MS *m/z* (%)=373 (3, $M^{+\,81}Br$), 371 (3, $M^{+\,79}Br$), 144 (12), 131 (100), 130 (73), 118 (12), 117 (13). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.01-2.18 (m, 4H), 2.41 (bs, 1H), 2.65-2.84 (m, 4H), 3.43 (t, *J*=6.6 Hz, 2H), 4.58-4.62 (m, 1H), 6.76 (d, *J*=2.1 Hz, 1H), 7.03-7.21 (m, 7H), 7.51 (d, *J*=7.7 Hz, 1H), 7.92 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=21.4, 33.1, 33.5, 34.0, 39.0, 73.8, 111.1, 115.6, 118.8, 119.0, 121.2, 121.7, 126.1, 127.3, 128.5, 136.2, 139.7, 142.4. Anal. Calcd. for $C_{20}H_{22}BrNO$: C, 64.52; H, 5.96; N, 3.76. Found: C, 64.88; H, 5.98; N, 3.52.

(±)-3-(3-(4-(3-Bromopropyl)phenyl)-3-*tert*-butyldimethylsilyloxypropyl)indole (53)



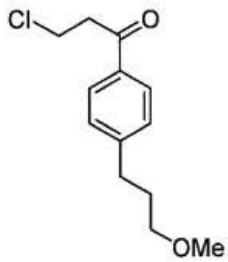
To a solution of **52** (400 mg, 1.07 mmol) and imidazole (374 mg, 5.49 mmol) in DMF (25 mL) at room temperature was added TBS-Cl (829 mg, 5.50 mmol). After stirring for 12 h, the reaction mixture was quenched with H_2O (50 mL), and extracted with diethyl ether (50 mL×3). The combined organic layers were washed with H_2O (50 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (15% EtOAc/hexane) gave **53** (497 mg, 94%) as a clear, colorless oil. IR (KBr) ν=3423 (s), 1619 (w) cm^{-1}. MS *m/z* (%)=487 (0.2, M^+ ^{81}Br), 485 (0.2, M^+ ^{79}Br), 355 (3), 353 (3), 309 (20), 204 (13), 131 (45), 130 (100), 117 (17). ^1H NMR ($CDCl_3$, 300 MHz): δ=–0.14 (s, 3H), 0.05 (s, 3H), 0.92 (s, 9H), 2.02-2.14 (m, 4H), 2.73-2.83 (m, 4H), 3.51 (t, *J*=6.7 Hz, 2H), 4.73-4.77 (m, 1H), 6.92 (d, *J*=2.1 Hz, 1H), 7.06-7.36 (m, 7H), 7.54 (d, *J*=7.8 Hz, 1H), 7.84 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=–4.9, –4.6, 18.3, 21.2, 25.9, 32.4, 34.0, 41.0, 44.3, 74.6, 111.0, 116.6, 118.9, 119.0, 120.8, 121.9, 126.1, 127.5, 128.1, 136.3, 139.1, 143.5. Anal. Calcd. for $C_{26}H_{36}BrNOSi$: C, 64.18; H, 7.46; N, 2.88. Found: C, 69.01; H, 7.98; N, 2.96. No trace of the impurity observed in the NMR spectra of **48** was observed here. Nevertheless the results of combustion analysis were repeatedly ≥5% too high for C.

1-Methoxy-3-phenylpropane (56)



To a suspension of NaH (8.00 g, 200 mmol) in anhydrous THF (40 mL) at room temperature was added dropwise a solution of 3-phenyl-1-propanol **55** (13.6 g, 100 mmol) in THF (50 mL). The mixture was stirred for 0.5 h, and MeI (56.8 g, 400 mmol) was injected slowly. After stirring for 10 h, the reaction mixture was quenched with H_2O (50 mL), and extracted with diethyl ether (100 mL×4). The combined organic layers were washed with H_2O (100 mL×4) and brine (150 mL), dried over $MgSO_4$, filtered and concentrated carefully. Vacuum distillation (79-80 °C, 3 mm Hg) gave **56** (13.2 g, 88%) as a clear, colorless liquid. IR (KBr) ν=1603 (w) cm^{-1}. MS *m/z* (%)=150 (1, M^+), 118 (100), 117 (68), 91 (60). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.84-1.94 (m, 2H), 2.66-2.71 (m, 2H), 3.34 (s, 3H), 3.38 (t, *J*=6.5 Hz, 2H), 7.18-7.31 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=31.3, 32.3, 58.5, 71.9, 125.8, 128.3, 128.4, 142.0. Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.89; H, 9.50.

1-(3-Chloro-1-oxopropyl)-4-(3-methoxypropyl)benzene (57)

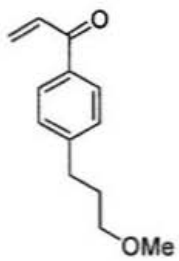


Method A. To a suspension of $AlCl_3$ (1.60 g, 12.0 mmol) in CH_2Cl_2 (18 mL) at 0 °C was injected 3-chloropropionyl chloride (1.27 g, 10.0 mmol). A solution of **56** (751 mg, 5.00 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h, the reaction mixture was poured into a mixture of ice water (50 mL) and aqueous HCl solution (12 N, 10 mL) and extracted with CH_2Cl_2 (40 mL×3). The combined organic layers were washed with H_2O (50 mL×3) and brine (50 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **57** (939 mg, 78%) as white crystals. M.p.= 47-49 °C. IR (nujol) ν=1675 (s), 1607 (m) cm^{-1}. MS *m/z* (%)=242 (not observed, $M^{+\,37}Cl$), 240 (0.5, $M^{+\,35}Cl$), 208 (19), 177 (54), 145 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.86-1.95 (m, 2H), 2.74-2.79 (m, 2H), 3.35 (s, 3H), 3.38 (t, *J*=6.4 Hz, 2H), 3.44 (t, *J*=6.9 Hz, 2H), 3.93 (t, *J*=7.1 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 7.89 (d, *J*=7.9 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=30.8, 32.4, 38.8, 41.1, 58.6, 71.5, 128.2, 128.8, 134.2, 148.4, 196.3. Anal. Calcd. for $C_{13}H_{17}ClO_2$: C, 64.86; H, 7.12. Found: C, 64.89; H, 7.17.

Method B. To a suspension of $AlCl_3$ (66.7 g, 500 mmol) in CH_2Cl_2 (100 mL) at 0 °C was injected acryloyl chloride (36.2 g, 400 mmol). A solution of **56** (7.51

g, 50.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 6 h with protection of aluminum foil from light, the reaction mixture was poured into ice water (500 mL) containing aqueous HCl solution (12 N, 50 mL), and extracted with CH_2Cl_2 (200 mL×3). The combined organic layers were washed with H_2O (200 mL×3) and brine (200 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **57** (7.94 g, 66%) as white crystals.

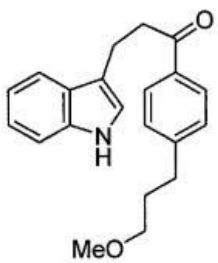
4-(3-Methoxypropyl)-1-(1-oxo-2-propenyl)benzene (58)



A solution of **57** (6.02 g, 25.0 mmol) in CH_2Cl_2 (150 mL) was treated with DBU (4.57 g, 30.0 mmol) at room temperature for 1 h. The reaction was quenched with HCl solution (0.12 N, 200 mL) and extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were washed with brine (200 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **58** (3.98 g, 78%) as a clear, colorless oil. IR (KBr) ν=1659 (s), 1605 (s) cm^{-1}. MS *m/z* (%)=204 (1, M^+), 172 (62), 145 (100), 117 (24). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.86-1.95 (m, 2H), 2.74-2.79 (m, 2H), 3.34 (s, 3H), 3.38 (t, *J*=6.2 Hz,

2H), 5.90 (dd, J=10.6, 1.9 Hz, 1H), 6.43 (dd, J=17.2, 1.6 Hz, 1H), 7.17 (dd, J=16.9, 10.4 Hz, 1H), 7.30 (d, J=8.3 Hz, 2H), 7.89 (d, J=8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=30.8, 32.3, 58.5, 71.5, 128.7, 128.9, 129.7, 132.2, 135.0, 147.8, 190.4. Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.08; H, 8.01.

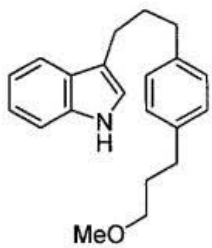
3-(3-(4-(3-Methoxypropyl)phenyl)-3-oxopropyl)indole (59)



A solution of **58** (3.06 g, 15.0 mmol) and indole **1** (7.03 g, 60.0 mmol) in CH_2Cl_2 (40 mL), HOAc (30 mL), and Ac_2O (10 mL) was heated at reflux for 6 h. The reaction mixture was concentrated, diluted with saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (30% EtOAc/hexane) gave **59** (3.48 g, 74%) as a white powder. M.p.=82-84 °C. IR (nujol) ν=3262 (s), 1673 (s), 1607 (w) cm^{-1}. MS *m/z* (%)=322 (7), 321 (30, M^+), 144 (79), 130 (100), 117 (18). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.84-1.94 (m, 2H), 2.71-2.76 (m, 2H), 3.19-3.24 (m, 2H), 3.34 (s, 3H), 3.35-3.39 (m, 4H), 7.04 (d, J=2.0 Hz, 1H), 7.10-7.27 (m, 4H), 7.35 (d, J=8.4 Hz, 1H), 7.64 (d, J=7.7 Hz, 1H), 7.89 (d, J=8.7 Hz,

2H), 8.00 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=19.7, 30.9, 32.3, 39.2, 58.6, 72.6, 111.1, 115.5, 118.7, 119.3, 121.6, 122.0, 127.2, 128.2, 128.7, 134.9, 136.3, 147.7, 199.6. Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.43; H, 7.13; N, 4.24.

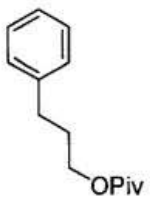
3-(3-(4-(3-Methoxypropyl)phenyl)propyl)indole (60)



To a suspension of **59** (1.00 g, 3.11 mmol) in diethylene glycol (30 mL) were added freshly ground KOH (505 mg, 9.00 mmol) and hydrazine hydrate (85%, 1.5 mL). The reaction mixture was heated at 200 °C in a silicone oil bath for 6 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (50 mL×3), dried with $MgSO_4$, filtered and concentrated. Column chromatography (25% EtOAc/hexane) gave **60** (831 mg, 87%) as a light yellow oil. IR (KBr) ν=3420 (s), 3314 (m), 1619 (w) cm^{-1}. MS *m/z* (%)=308 (5), 307 (19, M^+), 131 (74), 130 (100), 117 (11). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.83-1.92 (m, 2H), 1.97-2.08 (m, 2H), 2.62-2.70 (m, 4H), 2.76-2.81 (m, 2H), 3.33 (s, 3H), 3.38 (t, *J*=6.4 Hz, 2H), 6.91 (d, *J*=1.7 Hz, 1H), 7.06-7.19 (m, 6H), 7.30 (d, *J*=8.3 Hz, 1H), 7.57 (d, *J*=7.2 Hz, 1H), 7.90 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=24.7, 31.3, 31.7,

31.9, 35.3, 58.5, 72.0, 111.0, 116.5, 118.9, 119.0, 121.1, 121.8, 127.5, 128.3, 128.4, 136.3, 139.1, 139.9. Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.77; H, 8.23; N, 4.50.

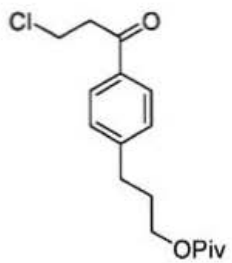
3-Phenylpropyl-2,2-dimethylpropanoate (61)



To a solution of 3-phenyl-1-propanol **55** (13.6 g, 100 mmol) in CH_2Cl_2 (50 mL) and triethylamine (100 mL) at 0 °C was added dropwise a solution of pivaloyl chloride (13.3 g, 110 mmol) in CH_2Cl_2 (50 mL) over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was quenched with H_2O (40 mL) and extracted with EtOAc (100 mL×3) The combined organic layers were washed with aqueous HCl solution (1.2 N, 100 mL×2) and brine (100 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% EtOAc/petroleum ether) afforded **61** (21.2 g, 96%) as a clear, colorless liquid. IR (KBr) ν=1729 (s), 1604 (w) cm^{-1}. MS *m/z* (%)=220 (1, M^+), 118 (100), 117 (42). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.21 (s, 9H), 1.91-2.01 (m, 2H), 2.67-2.72 (m, 2H), 4.08 (t, *J*=6.5 Hz, 2H), 7.17-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=27.2, 30.3, 32.1, 38.7, 63.5, 126.0, 128.4,

141.2, 178.5. Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.40; H, 9.40.

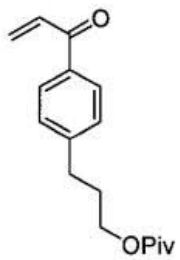
3-(4-(3-Chloro-1-oxopropyl)phenyl)propyl-2,2-dimethylpropanoate (62)



To a suspension of $AlCl_3$ (20.5 g,154 mmol) in CH_2Cl_2 (250 mL) at 0 °C was injected 3-chloropropionyl chloride (16.3 g, 128 mmol). A solution of **61** (18.8 g, 85.3 mmol) in CH_2Cl_2 (100 mL) was added dropwise to the resulting stirred mixture. After stirring at room temperature for 7 h, the reaction mixture was poured into ice water (400 mL) containing aqueous HCl solution (12 N, 30 mL) and extracted with CH_2Cl_2 (100 mL×2). The combined organic layers were washed with brine (300 mL×4), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **62** (22.8 g, 86%) as a clear, colorless oil. IR (KBr) ν=1725 (s), 1685 (s), 1604 (m) cm^{-1}. MS *m/z* (%)=312 (1, M^+ ^{37}Cl), 310 (3, M^+ ^{35}Cl), 208 (15), 145 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.22 (s, 9H), 1.94-2.03 (m, 2H), 2.74-2.79 (m, 2H), 3.44 (t, *J*=6.7 Hz, 2H), 3.92 (t, *J*=6.8 Hz, 2H), 4.08 (t, *J*=6.3 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 7.90 (d, *J*=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=27.2, 29.9, 32.2, 38.7,

41.2, 63.2, 128.3, 128.8, 134.5, 147.6, 178.5, 196.3. Anal. Calcd. for $C_{17}H_{23}ClO_3$: C, 65.69; H, 7.46. Found: C, 65.44; H, 7.59.

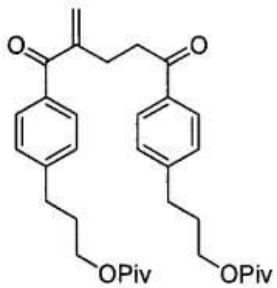
3-(4-(1-Oxo-2-propenyl)phenyl)propyl-2,2-dimethylpropanoate (63)



A solution of **62** (335 mg, 1.08 mmol) in CH_2Cl_2 (15 mL) was added DBU (182 mg, 1.20 mmol), and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with aqueous HCl solution (0.12 N, 10 mL), diluted with H_2O (20 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with brine (30 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **63** (256 mg, 87%) as a slightly yellow oil. IR (KBr) ν=1727 (s), 1670 (s), 1606 (s) cm^{-1}. MS *m/z* (%)=274 (1, M^+), 172 (72), 145 (100), 117 (23). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.22 (s, 9H), 1.95-2.04 (m, 2H), 2.74-2.79 (m, 2H), 4.09 (t, *J*=6.6 Hz, 2H), 5.92 (dd, *J*=10.2, 1.8 Hz, 1H), 6.44 (dd, *J*=17.2, 1.9 Hz, 1H), 7.17 (dd, *J*=17.3, 10.7 Hz, 1H), 7.30 (d, *J*=8.5 Hz, 2H), 7.90 (8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=27.2, 29.9, 32.2, 38.8, 63.3, 128.7, 129.0, 129.9,

132.3, 135.3, 147.0, 178.5, 190.5. Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.15; H, 8.08.

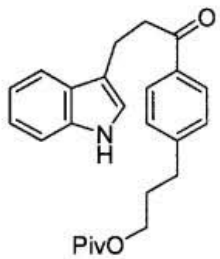
2-Methylene-1,5-bis(4-(3-(2,2-dimethylpropanoxy)propyl)phenyl)-1,5-dioxopentane (64)



A solution of **62** (9.50 g, 30.6 mmol) in CH_2Cl_2 (170 mL) was added DBU (5.63 g, 37.0 mmol), and the resulting mixture was stirred at room temperature for 12 h. The reaction was quenched with a mixture of H_2O (100 mL) and aqueous HCl solution (12 N, 6 mL), and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with brine (100 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/hexane) gave **64** (891 mg, 11%) as a light yellow oil. IR (KBr) ν=1727 (s), 1684 (s), 1654 (s), 1608 (m) cm^{-1}. MS *m/z* (%)=549 (6), 548 (15, M^+), 446 (16), 301 (38), 247 (47), 199 (14), 145 (65). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.21 (s, 18H), 1.95-2.04 (m, 4H), 2.73-2.78 (m, 4H), 2.90 (t, *J*=7.5 Hz, 2H), 3.21 (t, *J*=7.3 Hz, 2H), 4.05-4.11 (m, 4H), 5.65 (s, 1H), 5.93 (s, 1H), 7.24-7.28 (m, 4H), 7.70 (d, *J*=8.2 Hz, 2H), 7.92 (d, *J*=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=27.2, 27.5, 29.8, 29.9, 32.1,

37.1, 38.7, 63.2, 63.3, 126.4, 128.3, 128.3, 128.6, 129.9, 134.8, 135.6, 146.2, 146.8, 146.9, 178.4, 197.7, 198.8 (Four signals are missing, presumably due to overlapping). Anal. Calcd. for $C_{34}H_{44}O_6$: C, 74.42; H, 8.08. Found: C, 74.25; H, 8.36.

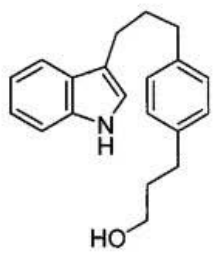
3-(4-(3-(3-Indolyl)-1-oxopropyl)phenyl)propyl-2,2-dimethylpropanoate (65)



A solution of **63** (8.51 g, 31.0 mmol) and indole **1** (4.45 g, 38.0 mmol) in CH_2Cl_2 (100 mL), HOAc (120 mL), and Ac_2O (40 mL) was heated at reflux for 2 d. The reaction mixture was concentrated, diluted with saturated aqueous $NaHCO_3$ solution (200 mL), and extracted with EtOAc (100 mL×3). The combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **65** (11.1 g, 91%) as a light yellow solid. M.p.=53-55 °C. IR (nujol) ν=3436 (s), 1721 (s), 1673 (s), 1602 (m) cm^{-1}. MS *m/z* (%)=392 (7), 391 (27, M^+), 145 (34), 144 (59), 130 (100), 117 (13). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.21 (s, 9H), 1.92-2.03 (m, 2H), 2.71-2.76 (m, 2H), 3.19-3.24 (m, 2H), 3.34-3.39 (m, 2H), 4.06 (t, *J*=6.6 Hz, 2H), 7.03 (d, *J*=1.8 Hz, 1H), 7.10-7.22 (m, 2H), 7.24 (d, *J*=8.2 Hz, 2H), 7.35 (d, *J*=7.7 Hz, 1H), 7.63 (d, *J*=7.8 Hz, 1H), 7.89 (d, *J*=8.6 Hz, 2H),

8.04 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=19.8, 27.2, 29.9, 32.2, 38.8, 39.3, 63.3, 111.2, 115.4, 118.7, 119.3, 121.6, 122.0, 127.2, 128.4, 128.6, 135.1, 136.3, 146.8, 178.6, 199.6. Anal. Calcd. for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47; N, 3.58. Found: C, 76.76; H, 7.67; N, 3.58.

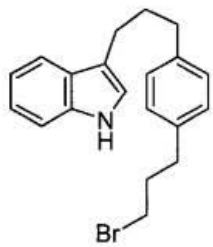
3-(4-(3-(3-Indolyl)-1-oxopropyl)phenyl)propan-1-ol (66)



To a suspension of **65** (10.3 g, 26.3 mmol) in diethylene glycol (200 mL) were added potassium *tert*-butoxide (8.87 g, 79.0 mmol) and hydrazine hydrate (85%, 15 mL). The reaction mixture was heated at 200 °C in a silicone oil bath for 2 d. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL×4). The combined organic layers were washed with brine (100 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (50% EtOAc/petroleum ether) gave **66** (5.94 g, 77%) as a light yellow solid. M.p.=42-44 °C. IR (nujol) ν=3385 (s), 3242 (m), 1616 (w) cm^{-1}. MS *m/z* (%)=294 (3), 293 (12, M^+), 131 (49), 130 (72), 87 (55). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.35 (bs, 1H), 1.82-1.92 (m, 2H), 1.98-2.08 (m, 2H), 2.64-2.70 (m, 4H), 2.76-2.81 (m, 2H), 3.66 (t, *J*=6.6 Hz, 2H), 6.95 (d, *J*=1.9 Hz, 1H), 7.07-7.22 (m, 6H), 7.33 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.91 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5

MHz): δ=24.7, 31.6, 31.7, 34.2, 35.3, 62.3, 111.0, 116.5, 118.9, 119.0, 121.1, 121.8, 127.5, 128.3, 128.5, 136.3, 139.0, 140.0. Anal. Calcd. for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.74; H, 8.15; N, 4.76.

3-(3-(4-(3-Bromopropyl)phenyl)propyl)indole (50)

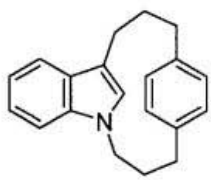


Method A. To a solution of **60** (587 mg, 1.91 mmol) in CH_2Cl_2 (30 mL) at 0 °C was injected dropwise BBr_3 (1.0 M in CH_2Cl_2, 5.7 mL). The reaction mixture was then stirred at room temperature for 4 h. The reaction mixture was quenched with H_2O (5 mL) and extracted with diethyl ether (100 mL×4). The combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (15% EtOAc/petroleum ether) gave **50** (224 mg, 33%) as a white solid. M.p.=44-45 °C. IR (nujol) ν=3421 (s), 1618 (w) cm^{-1}. MS *m/z* (%)=357 (8, M^+ ^{81}Br), 355 (8, M^+ ^{79}Br), 131 (77), 130 (100), 117 (10). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.98-2.18 (m, 4H), 2.65-2.81 (m, 6H), 3.38 (t, *J*=6.7 Hz, 2H), 6.95 (d, *J*=1.9 Hz, 1H), 7.07-7.22 (m, 6H), 7.33 (d, *J*=7.8 Hz, 1H), 7.58 (d, *J*=8.5 Hz, 1H), 7.84 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=24.7, 31.7, 33.3, 33.5, 34.2, 35.3, 111.0, 116.5, 119.0, 119.0, 121.1, 121.8,

127.5, 128.4, 128.5, 136.3, 137.8, 140.3. Anal. Calcd. for $C_{20}H_{22}BrN$: C, 67.42; H, 6.22; N, 3.93. Found: C, 67.65; H, 6.39; N, 3.94.

Method B. To a solution of **66** (1.76 g, 6.00 mmol) and triphenylphosphine (1.89 g, 7.21 mmol) in DMF (60 mL) at 20 °C was added dropwise a solution of *N*-bromosuccinimide (1.28 g, 7.19 mmol) in DMF (30 mL). The resulting solution was warmed to 50 °C for 40 min and then stirred at room temperature for 24 h. The reaction mixture was quenched with methanol (10 mL), diluted with H_2O (100 mL) and extracted with EtOAc (100 mL×3). The combined organic layers were washed with brine (80 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (15% EtOAc/petroleum ether) gave **50** (1.98 g, 91%) as a white solid.

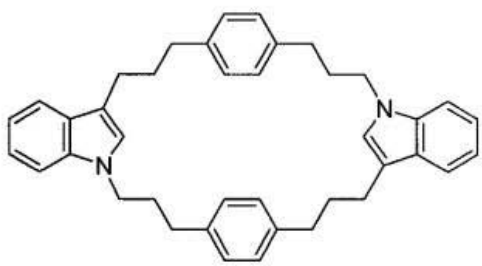
[3]Paracyclo[3](1,3)indolophane (30)



Method A. To a boiling suspension of NaH (60% dispersion in mineral oil, 292 mg, 7.30 mmol) in anhydrous THF (200 mL) was injected by a syringe pump a solution of **50** (260 mg, 0.730 mmol) in THF (50 mL) over 20 h. The resulting mixture was further heated at reflux for 1 h. The reaction mixture was quenched with H_2O (4 mL) and extracted with CH_2Cl_2 (50 mL×3). The combined organic layers were washed with brine (50 mL×2), dried over $MgSO_4$, filtered and

concentrated. Column chromatography (5% EtOAc/petroleum ether) gave **30** (99 mg, 49%) as white crystals. M.p.=64-66 °C. IR (nujol) ν=1612 (w) cm^{-1}. MS *m/z* (%)=276 (23), 275 (100, M^+), 157 (24), 145 (43), 144 (74). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.07-2.21 (m, 4H), 2.55-2.58 (m, 2H), 2.71-2.75 (m, 2H), 2.79-2.83 (m, 2H), 3.98-4.01 (m, 2H), 5.59 (s, 1H), 6.57 (d, *J*=6.8 Hz, 2H), 6.65 (d, *J*=7.4 Hz, 2H), 6.99-7.18 (m, 3H), 7.48 (d, *J*=7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=24.4, 27.5, 28.1, 35.0, 36.1, 46.7, 109.4, 113.4, 117.7, 119.1, 120.1, 126.4, 127.2, 127.6, 128.8, 133.9, 137.5, 139.5. Anal. Calcd. for $C_{20}H_{21}N$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.13; H, 7.83; N, 5.07.

[3]Paracyclo[3](1,3)indolo[3]paracyclo[3](1,3)indolophane (67)



Indolophane dimer **67** (38 mg, 19%) was also afforded from above procedure as white crystals. M.p.=173-175 °C. MS *m/z* (%)=551 (14), 550 (32, M^+), 275 (39), 145 (22), 144 (57). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.01-2.11 (m, 4H), 2.14-2.24 (m, 4H), 2.54 (t, *J*=6.6 Hz, 4H), 2.65-2.70 (m, 4H), 2.77 (t, *J*=7.1 Hz, 4H), 4.03 (t, *J*=6.6 Hz, 4H), 6.70 (s, 2H), 7.07-7.24 (m, 12H), 7.36 (d, *J*=8.2 Hz, 2H), 7.62 (d, *J*=7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=23.8, 29.7, 30.6,

31.5, 34.5, 44.5, 109.4, 114.4, 118.5, 119.1, 121.2, 125.9, 128.3, 128.6, 128.7, 136.3, 137.9, 140.4. Anal. Calcd. for $C_{40}H_{42}N_2$: C, 87.23; H, 7.69; N, 5.09. Found: C, 87.01; H, 7.71; N, 5.02.

Crystal Structure Determination of 30: colorless irregular crystal (0.30×0.25×0.40 mm) from methanol, $C_{20}H_{21}N$, M=275.39, monoclinic, C2/c (#15), Z=8, a=16.729(2), b=10.208(2), c=19.902(2) Å, β=113.601(7), V=3115.3(7) Å^3, D_c=1.174 g cm^{-3}, F(000)=1184, μ (Cu-Kα)=5.10 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer 26 °C with graphite monochromated Cu-Kα radiation (λ=1.54178 Å), ω-2θ scan type with ω scan width=1.42+0.14 tan θ, ω scan speed 8.0° min^{-1} (up to 5 rescans for weak reflections), 2569 reflections measured, 2470 unique (R_{int}=0.013), Lorentz-polarization, empirical absorbtion (max., min. corrections=1.00, 0.95) and secondary extinction (coefficient: 1.46717×10^{-6}) corrections, giving 1877 with I>2σ(I). Solution and refinement by direct methods (SIR92) using the teXsan package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 191 variable parameters led to R=0.058 and R_w=0.059, GOF=3.46.

Crystal Structure Determination of 67: colorless irregular crystal (0.15 x 0.15 x 0.45 mm) from heptane, $C_{40}H_{42}N_2$, M=550.79, monoclinic, $P2_1/c$ (#14), Z=2,

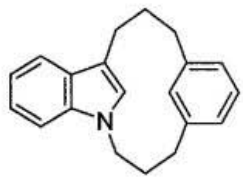
a=15.426(2), b=5.384(2), c=20.049(1) Å, β=111.592(7), V=1548.4(5) $Å^3$, D_c=1.181 g cm^{-3}, F(000)=592, μ (Cu-Kα)=5.13 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer at 26 °C with graphite monochromated Cu-Kα radiation (λ=1.54178 Å), ω-2θ scan type with ω scan width=1.31+0.14 tan θ, ω scan speed 8.0° min^{-1} (up to 10 rescans for weak reflections), 2683 reflections measured, 2579 unique (R_{int}=0.034), Lorentz-polarization and secondary extinction (coefficient: 1.13855×10^{-6}) corrections, giving 1413 with $I>2\sigma(I)$. Solution and refinement by direct methods (SIR92) using the teXsan package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 254 variable parameters led to R=0.053 and R_w=0.052, GOF=2.32.

[3]Paracyclo[3](1,3)indolophane (30)

Method B. Neat 1,3-diallylindole **92** (see Chapter 4 for synthetic details) (197 mg, 1.00 mmol) was treated with 9-BBN (0.5 M in THF, 12 mL, 6.0 mmol) at 0 °C. The mixture was stirred for 12 h, treated with H_2O (180 mg, 10.0 mmol) and added into a solution of 1,4-diiodobenzene **93** (330 mg, 1.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) in THF (150 mL). The mixture was heated to 50 °C and aqueous Cs_2CO_3 solution (2 M, 2 mL) was added. After boiling for 12 h, the brown mixture was concentrated, diluted with H_2O (20 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine (25

mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% EtOAc/petroleum ether) gave **30** (110 mg, 40%) as white crystals.

[3]Metacyclo[3](1,3)indolophane (90)



Neat 1,3-diallylindole **92** (see Chapter 4 for synthetic details) (197 mg, 1.00 mmol) was treated with 9-BBN (0.5 M in THF, 12 mL, 6.0 mmol) at 0 °C. The mixture was stirred for 12 h, treated with H_2O (180 mg, 10.0 mmol) and added into solution of 1,3-diiodobenzene **94** (330 mg, 1.00 mmol), $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) in THF (150 mL). The mixture was heated to 50 °C and aqueous Cs_2CO_3 solution (2 M, 2 mL) was added. After boiling for 12 h, the brown mixture was concentrated, diluted with H_2O (20 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (10% CH_2Cl_2/petroleum ether) gave **90** (72 mg, 26%) as a white solid. M.p.=103-104 °C. IR (nujol) ν=1653 (w) cm^{-1}. MS *m/z* (%)=276 (22), 275 (100, M^+), 145 (42), 144 (71). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.08-2.19 (m, 3H), 2.41-2.50 (m, 3H), 2.73-2.77 (m, 2H), 2.82-2.86 (m, 1H), 3.03-3.06 (m, 1H), 3.90-3.95 (m, 1H), 4.31-4.34 (m, 1H), 6.24-6.30 (m, 2H), 6.36-6.38 (m, 1H), 6.50 (bs, 1H), 6.61 (s, 1H), 6.79-6.82 (m, 1H), 6.95-6.98 (m, 2H), 7.15 (d, *J*=7.8 Hz, 1H). ^{13}C NMR

($CDCl_3$, 125.8 MHz): δ=26.4, 28.8, 29.0, 34.6, 36.8, 47.3, 109.6, 113.8, 117.6, 119.5, 120.3, 123.3, 124.4, 125.4, 127.8, 127.9, 130.8, 136.1, 136.4, 140.0. HRMS Calcd. for $C_{20}H_{21}N$: 275.1673. Found: 275.1680.

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CHAPTER 4 Synthesis, Conformational Behavior and Transannular Inverse Electron Demand Diels-Alder Reaction of [3](1,3)Indolo[3](3,6)pyridazinophane

4.1 Introduction

4.1.1 The Chemical Behavior of Cyclophanes

Cyclophanes have been the subject of broad interest not only because of their unusual structures and interesting conformational properties, but also due to their unique reactivity. Being one of the most important concerns in this field, the chemical reactivity of a variety of cyclophane systems, including [*n*]cyclophanes, heterophanes, condensed benzenoid cyclophanes, nonbenzenoid cyclophanes, multibridged cyclophanes and multilayered cyclophanes, has been comprehensively investigated.[1] Most reactions that have been studied are intermolecular reactions. Small cyclophanes frequently exhibit abnormal chemical properties, which are usually ascribed to transannular electronic effects between two or more arene nuclei, e.g. in electrophilic aromatic substitutions[2] and skeletal rearrangements,[3] or molecular strain, e.g. in Diels-Alder reactions,[4] hydrogenations[5] and carbene additions.[6]

In parallel, transannular* reactions of particular interest are dehydrogenations[7-9] and pericyclic reactions.[10-13] Regardless of the nature of the reaction patterns and reaction types, most studies on small cyclophanes have been fundamental. Only on a few occasions have small cyclophanes found synthetic application.[14-17]

One of the important structural features of many small cyclophanes is that two aromatic systems can be held closely in a specific orientation with respect to one another. This being the case, it may initially appear to be surprising as this feature has not yet been exploited synthetically. However, the virtual mutual exclusivity of cyclophane chemistry and natural product synthesis over the past decades renders this oversight less surprising. Given such a structural relationship, reaction between the two arenes would be expected to occur with complete regiochemical control and with the large entropic advantages of transannular reactions. If resulting products were to bear structural resemblance to important classes of natural products and lend themselves to further elaboration, this "cyclophane route" could conceivably supply not only a facile entry to those groups of natural products, but also establish a link between the two subdivisions of total synthesis (Chapter 1).

The initial challenge in pursuit of this goal is to design and synthesize cyclophanes that are not only capable of transannular reaction between the two

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* The term "transannular" is used here to distinguish from "intramolecular" in normal sense since cyclophane's macrocyclic environment brings participating components to a closer

decks, but also generate natural product-related skeleta. In line with our methodological studies on inverse electron demand Diels-Alder (IEDDA) chemistry,[18-23] it was envisaged that a transannular IEDDA reaction could be realized if a heteroaromatic azine ring were to be incorporated into an indolophane system. This is based on the fact that indoles and azines can respectively serve as dienophiles and dienes in IEDDA reactions.[24-26] The resulting products would possess the skeleton of potential indole alkaloids.

4.1.2 Diels-Alder Reactions

Besides electrophilic, nucleophilic and free radical additions, the addition to a double or triple bond can take place by a cyclic mechanism, where the attack at the two carbon atoms of the double or triple bond is simultaneous. To distinguish from other additions, reactions through the latter type of mechanism are called cycloaddition reactions.[27] The majority of cycloaddition reactions involve either a four-, five- or six-membered transition state. The most important reaction of this type is known as the Diels-Alder reaction.

The Diels-Alder reaction, first described in detail by Diels and Alder in 1928,[28] has undoubtedly become one of the most useful reactions for the formation of six-membered rings in organic synthesis.[29] Corey categorized it as one of the powerful reactions, i.e. those defined as synthetic reactions which reliably increase molecular complexity.[30,31] All available data indicate that the

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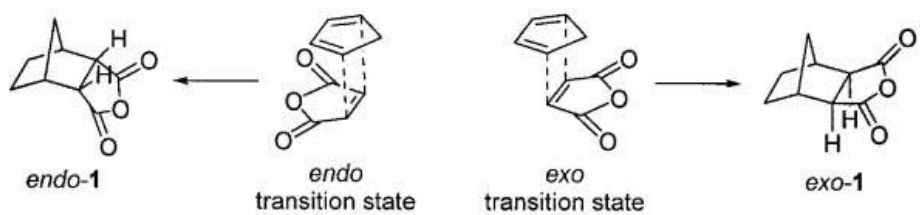
proximity than that by other intramolecular relationships.

reaction proceeds stereospecifically by a suprafacial addition of a conjugated 1,3-diene to the multiple bond of a dienophile. The stereospecificity with respect to both the diene and the dienophile suggests either that the reaction is concerted or that if the process involves two discrete bond-making steps, the second must occur much faster than bond rotation in the intermediate. The most widely held view is that the Diels-Alder reaction is a concerted process, but it is also recognized that there is the possibility that the extent of bond making at the two sites may be different, thus in an asynchronous manner, at the transition state. Another stereochemical feature of the Diels-Alder reaction is addressed by the "Alder rule" or as it is also called, the rule of maximum accumulation of unsaturation.[27] The empirical observation is that if two isomeric adducts are possible, the one that has the conjugated unsaturated units aligned over one another in the transition state leading to it will be the preferred product, as illustrated by the Diels-Alder reaction of maleic anhydride with cyclopentadiene (Scheme 4.1).



Scheme 4.1 Transition states in the Diels-Alder reaction of maleic anhydride with cyclopentadiene.

The addition of dienophiles to dienes is usually stereoselective in favor of the *endo* isomer (e.g., *endo*-**1**), even though it is the more sterically conjested

isomer and is usually thermodynamically less stable than the *exo* isomer (e.g., *exo*-**1**). In an *endo* transition state (Scheme 4.1), the π electrons of the carbonyl groups in the dienophile are aligned to permit interaction with the π system of the diene, which is favored according to the Alder rule.

Frontier Molecular Orbital (FMO) theory has been successfully used to explain and predict the reactivity and selectivity of Diels-Alder reactions between diene-dienophile pairs.[32,33] In FMO theory, the highest energy orbital containing bonding electrons is called the highest occupied molecular orbital (HOMO). Experimentally, the HOMO energy is the negative of the ionization potential (IP) of the molecule. In terms of chemical reactivity, the HOMO is the orbital that donates electrons. The next higher energy orbital does not contain electrons, but is the next available energy level if electrons are accepted. The energetic property that describes the acceptance of electrons is the electron affinity (EA), and the corresponding orbital is called the lowest unoccupied molecular orbital (LUMO). Experimentally, the energy of the LUMO is taken to be the negative of the electron affinity of the molecule. In a two-component reaction model such as the Diels-Alder reaction, the LUMO of one component would be expected to accept electrons from the HOMO of the other component. In the terminology of orbital symmetry classification, the Diels-Alder reaction is a $[4\pi_s+2\pi_s]$ process, signifying cycloaddition of a four-π-electron system and a two-π-electron system, with both sets of orbitals reacting in a suprafacial mode. According to Woodward-Hoffmann rules,[33] the Diels-Alder reaction is a

thermally allowed process because suprafacial interactions of $HOMO_{diene}$-$LUMO_{dienophile}$ or $LUMO_{diene}$-$HOMO_{dienophile}$ can be realized with the conservation of orbital symmetry (Figure 4.1). The energy difference, ΔE, between the most strongly interacting HOMO and LUMO in a diene-dienophile pair is used to predict reactivities.

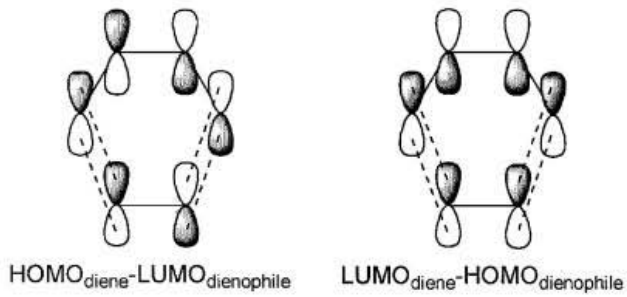


Figure 4.1 Two possible HOMO-LUMO interactions in the Diels-Alder reaction.

With the application of FMO theory, the Diels-Alder reaction has been further classified into three types of cycloaddition reactions: the normal electron demand Diels-Alder reaction, the neutral Diels-Alder reaction and the inverse electron demand Diels-Alder (IEDDA) reaction, based on the electronic nature of the diene and dienophile and the resulting interactions of the molecular orbitals involved (Figure 4.2).[34]

The initial Diels-Alder reaction studied by Diels and Alder[28] is today referred to as the normal Diels-Alder reaction*, the rate of which is accelerated by electron donating groups (EDG) on the diene and electron withdrawing groups

(EWG) on the dienophile. From an FMO point of view, an EDG in the diene increases the $HOMO_{diene}$ energy, whereas an EWG in the dienophile decreases the $LUMO_{dienophile}$ energy. Both effects strengthen the dominant $HOMO_{diene}$-$LUMO_{dienophile}$ interaction in the Diels-Alder reaction, and hence the reaction rate is accelerated by the specific electronic properties of the substituents in the 4π and 2π components. Typically, the normal Diels-Alder reaction has serviced the preparative needs of the organic chemistry community and continues to be the overwhelmingly most popular of the three.

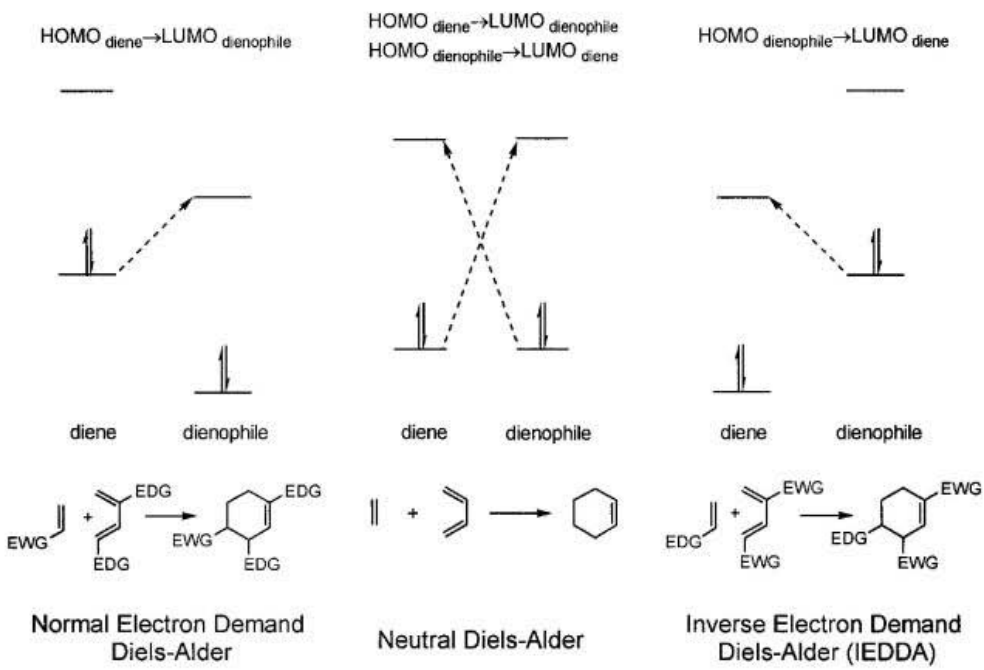


Figure 4.2 Classification of Diels-Alder reactions.

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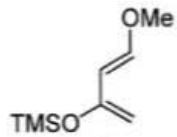
* The normal electron demand Diels-Alder reaction is by far the most common type. In fact, the terms "Diels-Alder reaction" and "normal Diels-Alder reaction" are generally understood to imply normal electron demand.



2

Figure 4.3 Structure of Danishefsky's diene **2**.

The most celebrated electron-rich diene in the normal Diels-Alder reaction is Danishefsky's diene **2** ((*E*)-1-methoxy-3-trimethylsilyloxy-1,3-butadiene) (Figure 4.3), which can be easily prepared (nowadays commercially available) and readily reacts with a wide variety of electron-poor dienophiles.[35] Danishefsky's diene **2**, a diene with two strong EDGs (methoxy and trimethylsilyloxy groups) substituted in a complementary orientation (1,3- *versus* 1,2-, 1,4-, and 2,3-substitution patterns), was first reported in 1974[36] and has found widespread utility in organic synthesis.[37] The regiochemistry of the adducts, also accounted for by the Alder rule,[38] is predictable by using orbital coefficients (Figure 4.4). As a general rule, the $HOMO_{diene}$ has its largest coefficient at C4 when there is an EDG at C1 or C3, and has its largest coefficient at C1 when there is an EDG at C2 or C4. Therefore, substitution of EDGs at both C1 and C3 can take maximum advantage of $HOMO_{diene}$-increasing effects and meanwhile place the largest coefficient at C4. Analogously, for a dienophile bearing a single EWG, the $LUMO_{dienophile}$ with EWG has a larger coefficient at the carbon which is β to the substituent. According to FMO theory, the strongest $HOMO_{diene}$-$LUMO_{dienophile}$ interaction therefore occurs preferentially between C4 of the diene and C2 of the dienophile (A in Figure

4.4). The degree of regiochemical control is dependent on the energetic difference between A and B interactions.

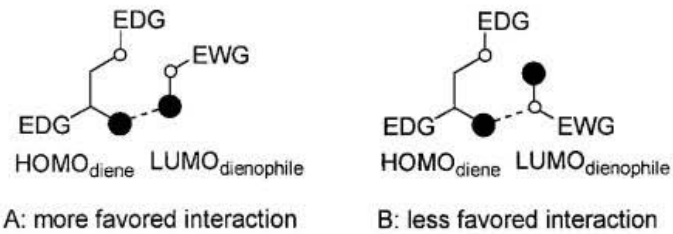
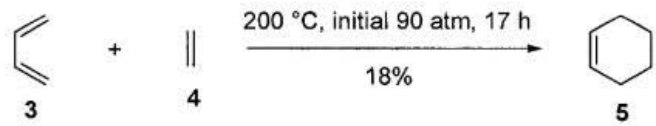


Figure 4.4 Regiochemical interpretation of the normal Diels-Alder reaction involving an electron-rich diene and a mono-substituted electron-poor dienoplile.

The second type, the neutral Diels-Alder reaction (Figure 4.2), has only rarely been observed.[34] As far as its electronic demand is concerned, this is believed to be a hybrid between the normal and the IEDDA type. Due to its notoriously vigorous conditions and low yields (as exemplified in Scheme 4.2),[39] the neutral Diels-Alder reaction is of very little use in organic synthesis.

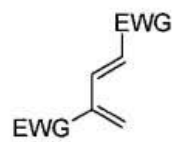


Scheme 4.2 A neutral Diels-Alder reaction between 1,3-butadiene **3** and ethylene **4**.

4.1.3 IEDDA Reactions

The last type of the Diels-Alder reaction, the IEDDA reaction (Figure 4.2), applies the complementary set of substituent effects to those in the normal Diels-Alder reaction, i.e. EWGs on the diene and EDGs on the dienophile. This

leads to a contraction of the $LUMO_{diene}$-$HOMO_{dienophile}$ energy separation, which renders this the more relevant interaction. The regiochemical control can be interpreted in terms of orbital coefficients in an analogous fashion to the normal Diels-Alder reaction (*vide supra*). The reversal of the "normal" electronic properties in the 4π and 2π components was initially proposed by Bachmann and Deno in 1949,[40] and soon after that the IEDDA reaction was applied in synthesis[41] and verified by kinetic data.[42] In contrast to the thoroughly studied and maturely developed normal Diels-Alder reaction, the IEDDA reaction is less common by far in terms of synthetic application and appearance in the literature, despite the comparable fundamental rate acceleration, regiocontrol and stereocontrol available through its use. Nevertheless, the IEDDA reaction has received and continues to receive considerable attention from both a methodological[24,25,43-49] and a synthetic perspective.[50-58]



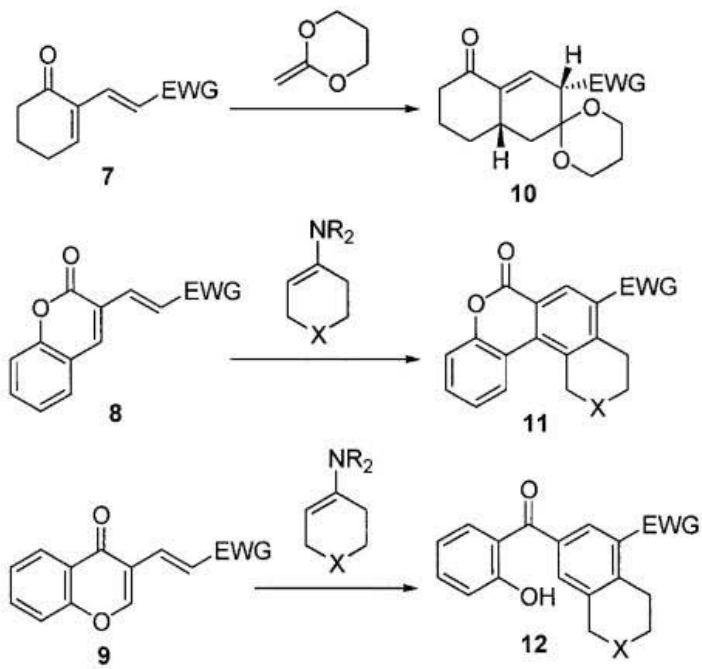
6

Figure 4.5 Structure of a potential electron-poor diene **6**.

Particularly high reactivity would be expected from electron-poor dienes **6** (Figure 4.5), which bear EWGs at C1 and C3 of the diene unit. This substitution pattern renders them an electronic complement to Danishefsky's diene **2** (Figure 4.3). The expectation of high reactivity was borne out somewhat by the observation that a series of dienes **6** (EWGs being all possible combinations of

CO_2Me and CN) polymerized readily.[59] No IEDDA chemistry of dienes **6** has been reported.

Bodwell and coworkers have investigated the synthesis and IEDDA applications of all-carbon electron-poor dienes.[18,23,60] It was found that the annulated versions of **6**, i.e. **7-9**, provided a balance between reactivity and stability (Scheme 4.3). In the cases of **8** and **9**, domino processes were observed.



EWG=CO_2R, CN, C(O)R, SO_2R X=$(CH_2)_n$, O, S, NR

Scheme 4.3 IEDDA reactions of electron-poor dienes **7-9**.

In addition to the judicious use of substituents on the diene and dienophile, rate enhancement in the Diels-Alder reaction has also been achieved by other means, including catalysis by Lewis acids,[61,62] reaction in aqueous media[62] and reaction under high pressure.[63] Another straightforward and

effective method is the incorporation of one or more heteroatoms into either the diene,[24,25] the dienophile[64] or both.[50] This approach is directly related to the use of complementarily substituted diene-dienophile partners, since it can also result in the lowering of the relevant HOMO-LUMO gap in any given type of Diels-Alder reactions. The resulting reaction type, also known as the hetero Diels-Alder reaction, expands the scope of the Diels-Alder reaction to include the formation of heterocyclic six-membered ring systems. The elegance of this methodology, especially in the IEDDA reaction, has been demonstrated in an excellent monograph by Boger and Weinreb.[50] In fact, nitrogen-containing benzenoid aromatics (azines), including pyridines, diazines, triazines and tetrazines, have been widely utilized as aromatic dienes in IEDDA reactions,[24,25,54-58] and the utility of these reactions has been firmly established in recent applications in natural product synthesis.[65-73]

As alluded to above, another intriguing feature of IEDDA reactions is that aromatic dienophiles can be engaged. Electron-excessive heteroaromatic molecules, such as furan, pyrrole, thiophene and oxazole derivatives, have been widely used as dienes in the normal Diels-Alder reaction despite the fact that harsh conditions or catalysts are often required.[74] In contrast, a number of IEDDA reactions involving these compounds as dienophiles have been reported.[75-82] That these dienophiles will react with active dienes, such as heteroaromatic azadienes, means that both the diene and dienophile can be aromatic species. Being unheard of in the normal Diels-Alder reaction, this

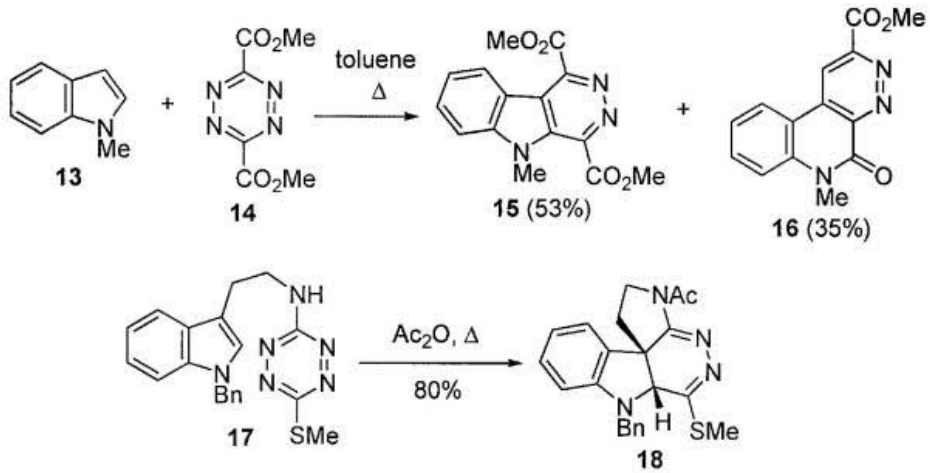
represents one example of a clear advantage of the IEDDA reaction over the normal Diels-Alder reaction. This also forms the basis of this study on transannular IEDDA reactions within cyclophanes, where the reaction is expected to occur between an indole moiety and a heteroaromatic azine ring.

4.1.4 Indole in the IEDDA Reaction

Enamines are known to be dienophilic in IEDDA reactions.[24,25,50] It is therefore not surprising that indole, a natural enamine,[83] can serve as a dienophile in the IEDDA reaction. Of the numerous examples of indole-involved IEDDA reactions, the contributions from the Snyder group are especially noteworthy.[26] Since the aromaticity of the 10π electron system reduces the reactivity, indoles are not very reactive dienophiles in IEDDA reactions and, consequently, highly electron-poor azadienes have to be employed, even in intramolecular processes. Subsequent loss of the nitrogen gas by a retro hetero Diels-Alder reaction and aromatization by dehydrogenation if applicable, normally provide the driving force.

1,2,4,5-Tetrazines have long been known to act as excellent electron-poor dienes in IEDDA reactions with electron-rich dienophiles.[24,25,50] Many examples have been published on IEDDA reactions between indoles and 1,2,4,5-tetrazines,[26] with typical examples shown in Scheme 4.4.[84] In the case of the intermolecular reaction between **13** and **14**, an IEDDA reaction followed by extrusion of nitrogen gas from the initial adduct and dehydrogenation yielded

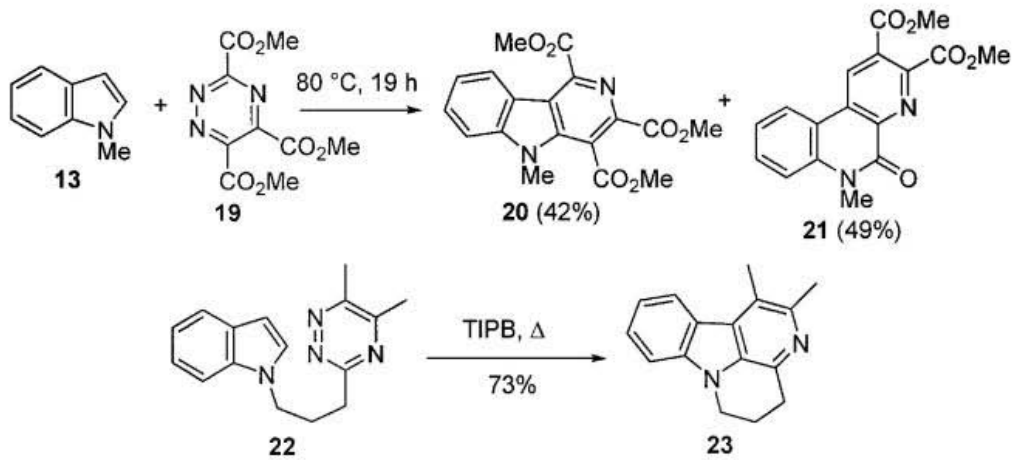
compound **15** (53%). A rearranged product, **16** (35%), was also observed. In the case of the intramolecular reaction of **17**, the expected entropic advantage[85,86] effectively promoted the process between the indole moiety of **17** and the less electron-poor 1,2,4,5-tetrazine moiety.



Scheme 4.4 The IEDDA reaction of indoles with 1,2,4,5-tetrazines.

1,2,4-Triazines, though less reactive than 1,2,4,5-tetrazines, are also well established as good heteroaromatic azadienes for the IEDDA reaction.[24,25,50] Reaction with indoles in an analogous fashion to those with 1,2,4,5-tetrazines has the potential to generate carbolines.[26] As exemplified in Scheme 4.5,[87] IEDDA reaction of **13** with **19** gave similar products, **20** (42%) and **21** (49%) with comparable yields to the corresponding reaction with 1,2,4,5-tetrazine **14** (Scheme 4.4). Again, entropic effects in **22** led to a smooth formation of **23** (73%) without the need for activating the 1,2,4-triazine moiety by the attachment

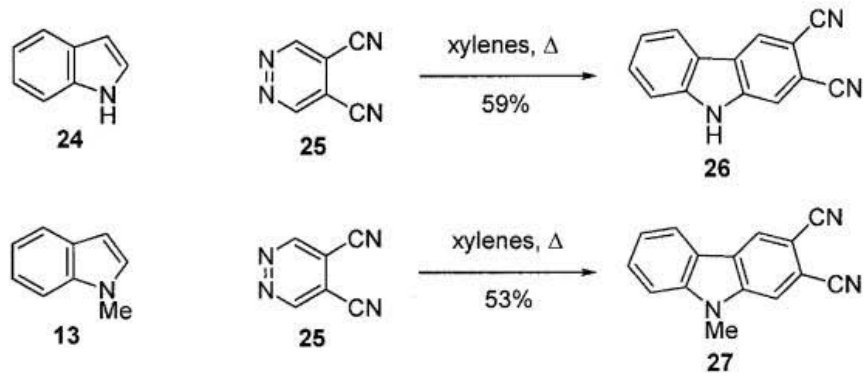
of EWGs. Not surprisingly, the corresponding intermolecular reaction was claimed to be unsuccessful.



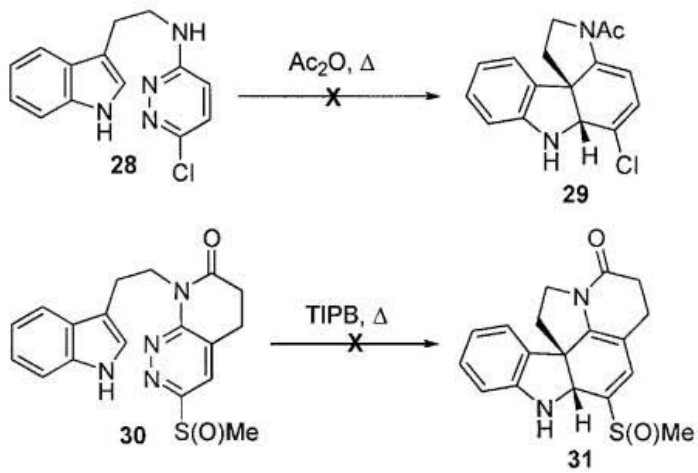
Scheme 4.5 The IEDDA reaction of indoles with 1,2,4-triazines.

Pyridazines (1,2-diazines) are notoriously unreactive dienes in the IEDDA reaction due to their higher LUMO levels, yet several examples of their participation in such reactions with the facilitation of strong EWGs have nevertheless been documented.[24,25,50] By comparison with 1,2,4,5-tetrazines (Scheme 4.4) and 1,2,4-triazines (Scheme 4.5), the intermolecular IEDDA reactions between indoles and pyridazines required stronger EWGs (CN versus CO_2Me) and harsher conditions (150 °C versus 110 °C and 80 °C). The yields (**26**, 59%, **27**, 53%) were also lower (Scheme 4.6).[88] The analogous intramolecular process between an indole nucleus and a non-activated (**28**) or a less-activated (**30**) pyridazine moiety resulted in failure even under forcing conditions (Scheme 4.7).[84] Nevertheless, the indole-pyridazine pairing is

particularly attractive because successful IEDDA reaction between them would provide direct access to the reduced carbazole construct (as in **29** and **31**),[26] which is present in a wide array of indole alkaloids.[89,90]



Scheme 4.6 The IEDDA reaction of indoles with pyridazines.



Scheme 4.7 Unsuccessful intramolecular IEDDA reactions between the indole nucleus and the pyridazine moiety.

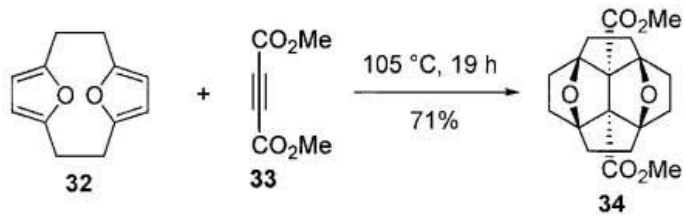
4.1.5 Transannular Diels-Alder Reactions

Being one of the most impressive processes in organic synthesis, transannular reactions achieve a substantial increase in molecular complexity, usually with high efficiency and impressive chemo-, regio- and stereoselectivities. These benefits can be traced back to entropic advantages and conformational restrictions within the macrocyclic environment. The Diels-Alder reaction provides an excellent reaction system for studies on transannular processes since it is a thermally allowed reaction that only requires heat for activation.[91] A spectacular outcome characterizes the transannular Diels-Alder (TADA) reaction. A tricyclic ring system and up to four new stereogenic centers are generated simultaneously. It is especially attractive when the participating components are innately sluggish Diels-Alder reactants, such as non-activated or poly-substituted dienes and/or dienophiles. Such systems are often not well suited for reaction in intermolecular or even intramolecular settings. Furthermore, the special nature of a transannular process renders it useful as a mechanistic probe for the Diels-Alder reaction itself.[92] Together with detailed investigations of theoretical aspects,[93,94] the TADA reaction has the potential to be one of the most powerful and important synthetic tools in modern organic synthesis for the construction of polycyclic frameworks.[91]

Since the main structural feature that accounts for the regio- and stereocontrol in TADA reactions is the restricted conformational behavior, small cyclophanes, for which conformational behavior is one of the prime sources of

interest, would appear to be a logical choice for the study of transannular IEDDA reactions. Moreover, small cyclophane systems might be expected to participate in the TADA reaction with excellent stereoselectivity, owing to the rigidity of the aromatic nuclei and the consequent restriction in the conformational behavior of the macrocycle.

As detailed in Chapter 1, cyclophane intermediates have been several times employed for TADA reactions in natural product synthesis. In efforts toward a total synthesis of chatancin, a platelet activation factor antagonist, TADA reactions have been executed in a furanophane structure.[95-97] In another report, a TADA reaction of a cyclophane-derived intermediate has been applied to a remarkable synthesis of longithorone A[98] based on a proposed biosynthesis.[99] TADA reactions were also observed for several small cyclophanes during investigations of their chemical properties.[10-12,100-103]

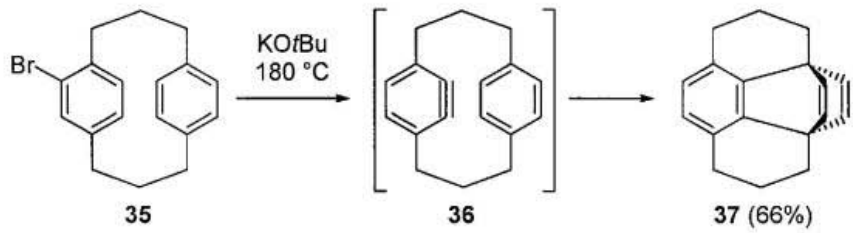


32 33 34

Scheme 4.8 A transannular Diels-Alder reaction involving furanophane **32**.

[2.2](2,5)Furanophane **32** underwent a facile addition with dimethyl acetylenedicarboxylate **33** to produce highly condensed polycyclic compound **34** in 71% yield. This product presumably arises through two consecutive Diels-

Alder reactions, the second one being a transannular process (Scheme 4.8).[10] Similar reactions have also been observed in other furanophane systems.[11]

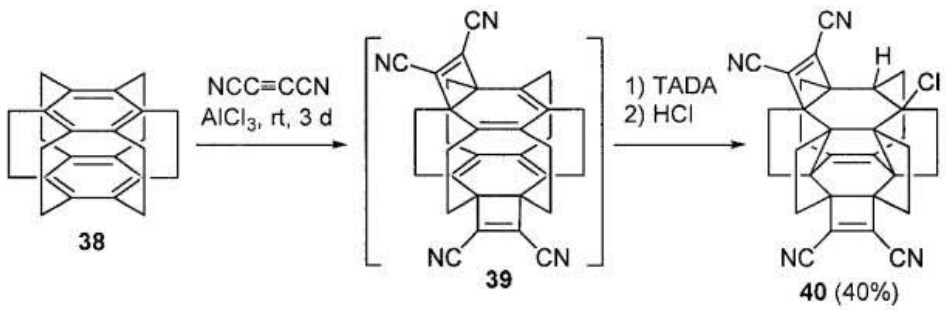


Scheme 4.9 Transannular Diels-Alder reaction in cyclophane **36**.

To provide evidence for the intermediacy of a perpendicular arrangement of the benzene rings during the conformational processes of [3.3]cyclophanes, a dehydrobenzene derivative **36** was generated by treatment of KO*t*-Bu on 5-bromo[3.3]paracyclophane **35**. The resulting aryne **36** reacted with the opposing benzene ring in a transannular fashion, presumably through the desired "perpendicular" transition state, to yield benzobarrelene **37** (66%) (Scheme 4.9).[12]

An interesting cascade of addition reactions was observed for superphane **38** when attempts were made to overcome its inertness in Diels-Alder reactions with Lewis acid catalysis (Scheme 4.10).[100] When **38** and dicyanoacetylene **39** were mixed in the presence of $AlCl_3$ at room temperature for three days, polycycle **40**, the structure of which was determined by X-ray analysis, was produced. The yield of 40% is impressive, considering the number of reactions involved. A reasonable mechanism was proposed, involving initial two successive [2+2]cycloadditions of dicyanoacetylene to afford intermediate **39**, a

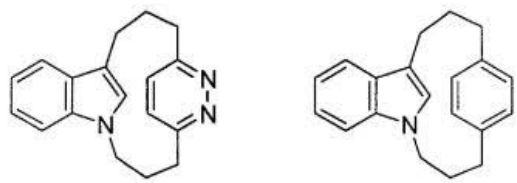
subsequent TADA reaction and a final addition of HCl to yield the isolated polycycle **40**.



Scheme 4.10 Transannular Diels-Alder reaction in **39**.

It is clear that the success of the above-mentioned reactions can be at least partially ascribed to the great entropic advantage arising from cyclophane environments because one of the least reactive dienes known, benzene, could even be engaged. However, all of the successful examples listed above employed an activation process, such as the generation of benzyne, to make one or both of the π components more reactive. Although both aromatic decks were involved in each case, TADA reactions between two unmodified and unactivated aryl rings are still unknown. As described previously, IEDDA reactions between an indole ring and a pyridazine moiety, featuring a promising potential in indoloid synthesis,[26] failed to proceed intramolecularly.[84] Given the much more pronounced entropic effects of transannular reactions compared to those of intermolecular and intramolecular processes, the corresponding reaction was envisioned to be more likely to take place in a transannular manner. Therefore, the initial tasks for this project included the design and synthesis of such an

indolopyridazinophane. Since it was shown that three-atom bridges exhibited higher efficiency in intramolecular IEDDA reactions of indole nuclei than shorter and longer tethers,[26] [3](1,3)indolo[3](3,6)pyridazinophane **41** (Figure 4.6) was identified as the first target. Furthermore, it was anticipated that a synthetic approach similar to the one employed for the prior synthesis of a structurally related cyclophane **42**[104] (see Chapter 3) could be applied (Figure 4.6).



41 **42**

Figure 4.6 Structures of cyclophanes **41** and **42**.

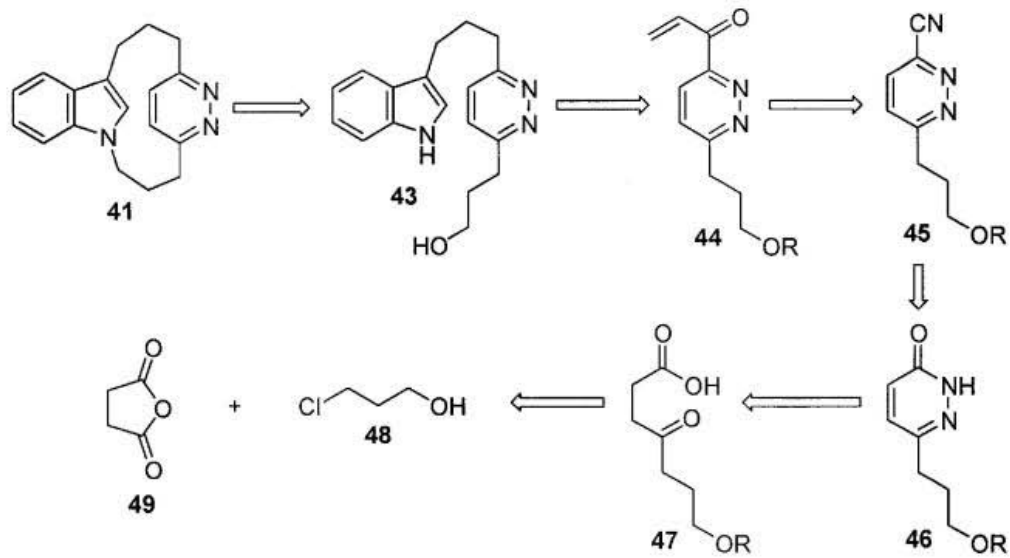
4.2 Results and Discussion

4.2.1 Synthesis of Indolopyridazinophane 41

4.2.1.1 Conjugate Addition Pathway

As described in Chapter 3, reports of the synthesis and study of indolophanes are rare. Having successfully prepared indolophane **42** by a seven-step sequence[104] (see Chapter 3), it was hoped that a similar synthetic approach would lead to indolopyridazinophane **41**. Accordingly, the first retrosynthetic analysis of **41** was based on the strategy used for the synthesis of **42**, i.e. with *N*-alkylation as the method for the final ring closure (Scheme 4.11). Thus the first

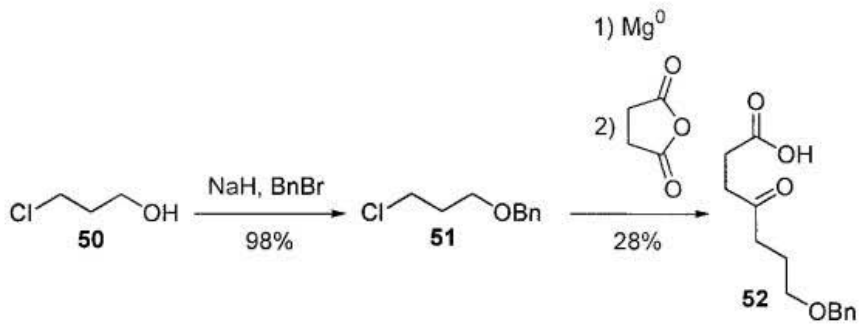
retrosynthetic cut of **41** gave acyclic alcohol **43**, which could lead to the direct cyclization precursor, a bromide, by mild bromination. Also taken from the synthesis of **42**, conjugate addition of indole was chosen to build the top bridge. This gave a Michael acceptor **44**, which contains all of the necessary six carbon atoms in the future bridges of **41**.



Scheme 4.11 The first retrosynthetic analysis of **41**.

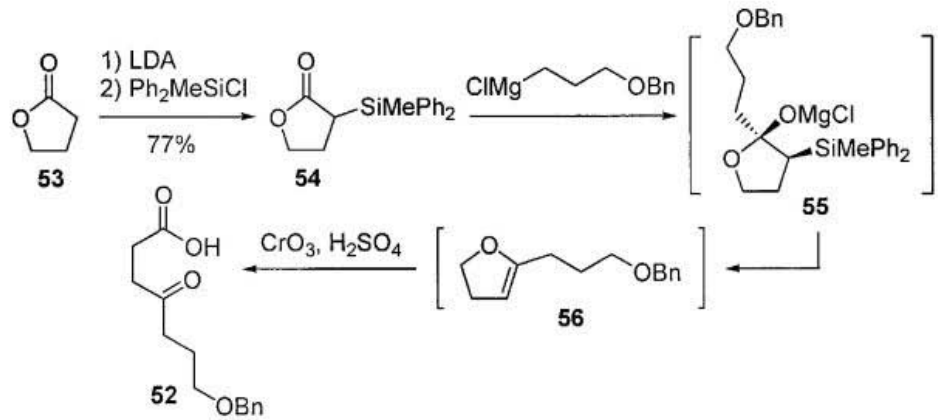
Because of the relative inertness of the pyridazine ring (a π-deficient heteroaromatic)[105] toward electrophilic aromatic substitution, the Friedel-Crafts acylation-DBU elimination sequence was considered inappropriate for the preparation of **44**. Reaction of nitrile **45** with a vinyl Grignard reagent[106] was selected instead. Nitrile **45** was then taken back further to pyridazinone **46** by cyanation of aromatic halides[107] and halogenation of pyridazinones.[108,109] In a survey of the chemical literature, it was found that cyclophanes containing a

pyridazine unit, i.e. pyridazinophanes, are even rarer than the already uncommon indolophanes. The well-established condensation of acyclic compounds, with the proper functionality on C1 and C4, and hydrazines offered what appeared to be a reasonable approach to the pyridazine nucleus.[110,111] This approach also formed the basis of the retrosynthetic transform of **46** to 1,4-ketoacid **47**, which could be produced by reaction of a Grignard reagent derived from **48** with succinic anhydride **49**.[112]



Scheme 4.12 Synthesis of 1,4-ketoacid **52**.

The robust, yet easily removable, benzyl group[113] was chosen as a protecting group for the hydroxy group in **43** and its progenitors (Scheme 4.12). Reaction of 3-chloro-1-propanol **50** with benzyl bromide in the presence of NaH yielded benzyl ether **51** in 98% yield. After the formation of the Grignard reagent from **51** by the action of activated magnesium,[114] treatment with succinic anhydride **49** afforded 1,4-ketoacid **52** (28%).

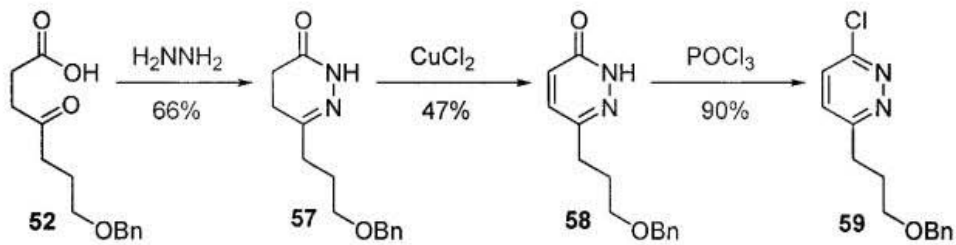


Scheme 4.13 Alternative synthesis of **52**.

The low yield in the formation of **52** prompted a search for alternative preparations (Scheme 4.13). Attention was then turned to a general route to 1,4-ketoacids reported by Larson.[115] The sequence involves an initial nucleophilic attack of a Grignard reagent to the lactone functionality in **54** from the face opposite to the bulky diphenylmethylsilyl group, followed by a Peterson-olefination-like reaction to give dihydrofuran derivative **56** and a final Jones oxidation to produce the desired 1,4-ketoacid **52**. However, the oxidation generated an intractable mixture, possibly due to the instability of the benzyl ether under strongly oxidizing conditions.[116]

In spite of the unsatisfactory preparation of **52**, the synthesis was carried on (Scheme 4.14). The condensation of **52** with hydrazine[117] yielded dihydropyridazinone **57** (66%), which was oxidized using $CuCl_2$[118,119] to furnish pyridazinone **58** (47%). The subsequent reaction with $POCl_3$[120] supplied chloropyridazine **59** in 90% yield. The limited amount (97 mg) of compound **59**

prompted a re-examination of the feasibility of the retrosynthetic analysis shown in Scheme 4.11. The cyanation of dichloropyridazine by using KCN or CuCN in the presence or absence of $Pd(PPh_3)_4$ was attempted, but met with failure. It was also found that methods for the cyanation of pyridazine halides were much less common and also less efficient[121] than those of other aromatic halides.[107] Together with the potentially low yield in the Grignard addition to pyridazine nitriles as shown by Nakagome and Castle,[122] it was deemed impractical to further elaborate on **59** according to the first retrosynthetic analysis (Scheme 4.11).

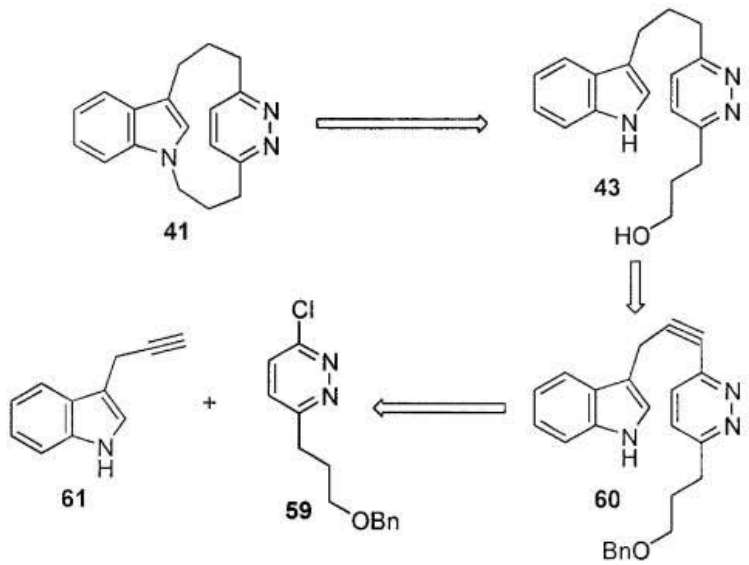


Scheme 4.14 Synthesis of chloropyridazine **59**.

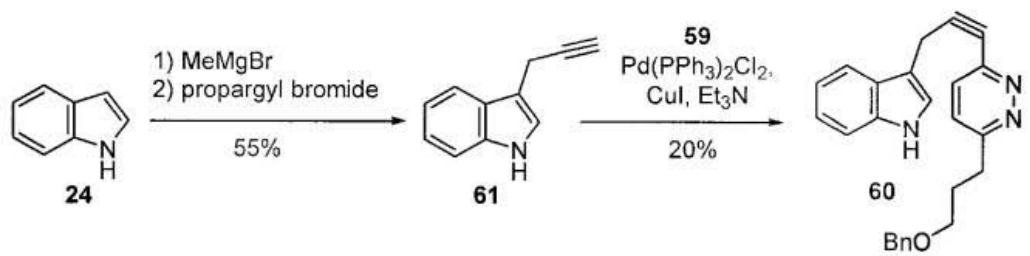
4.2.1.2 1st Sonogashira Coupling Pathway

Compound **59** found its position in the second retrosynthetic analysis of **41** (Scheme 4.15). Keeping most aspects similar to the analysis illustrated in Scheme 4.11, a sequence was proposed with a Sonogashira coupling[123] instead of the indole conjugate addition to construct the top bridge. Alcohol **43** could be formed by a spontaneous hydrogenation of the triple bond and deprotection of

the benzyl group in **60** under the same conditions. The Sonogashira coupling transform led to **59** and 3-propargylindole **61**.



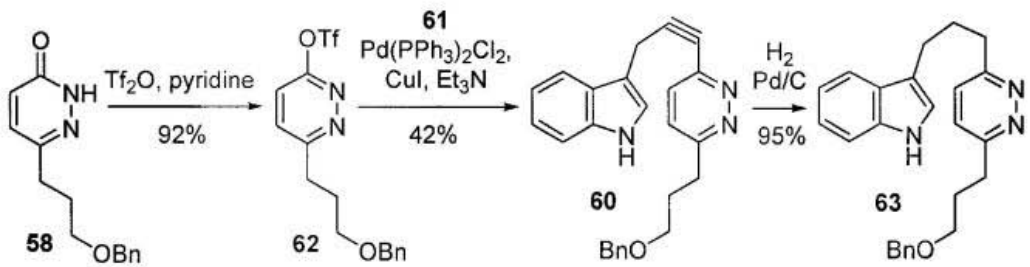
Scheme 4.15 The second retrosynthetic analysis of **41**. Erroneous bond angles on both sides of some triple bonds in the present and following schemes have been arranged as such to conserve space.



Scheme 4.16 Synthesis of **60**.

Initially, 3-propargylindole **61**[124] was prepared by a selective C3-substitution of the magnesium salt of indole with propargyl bromide in 55% yield (Scheme 4.16). The subsequent Sonogashira coupling of **61** and **59** in the

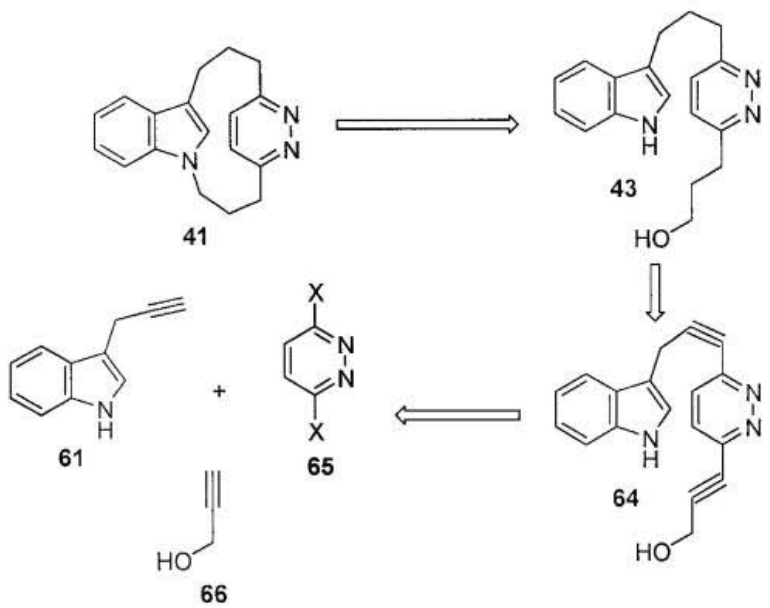
presence of $Pd(PPh_3)_2Cl_2$, CuI and Et_3N afforded desired alkyne **60** (20%), the low yield of which can be explained by the relatively low reactivity of chlorides compared to bromides, iodides and triflates in Pd-catalyzed reactions.[125] An alternative synthesis of **60** was achieved based on the observation that pyridazine triflates[126] are excellent substrates in Sonogashira couplings (Scheme 4.17).



Scheme 4.17 Synthesis of **63**.

The corresponding pyridazine triflate **62** (92%) was prepared by reacting **58** with triflic anhydride in the presence of pyridine. Subjection of **62** to a Sonogashira reaction with **61** then led to the formation of **60** in 42% yield. Unexpectedly, the following catalytic hydrogenation of **60** reduced the triple bond smoothly, but left the benzyl group intact to yield **63** (95%). Since other deprotection methods of benzyl ethers involve strongly reductive, oxidative, basic or acidic conditions,[113] the likely incompatibility of these conditions with either the indole or the pyridazine nucleus in **63** led to the decision to abandon this rather tedious route.

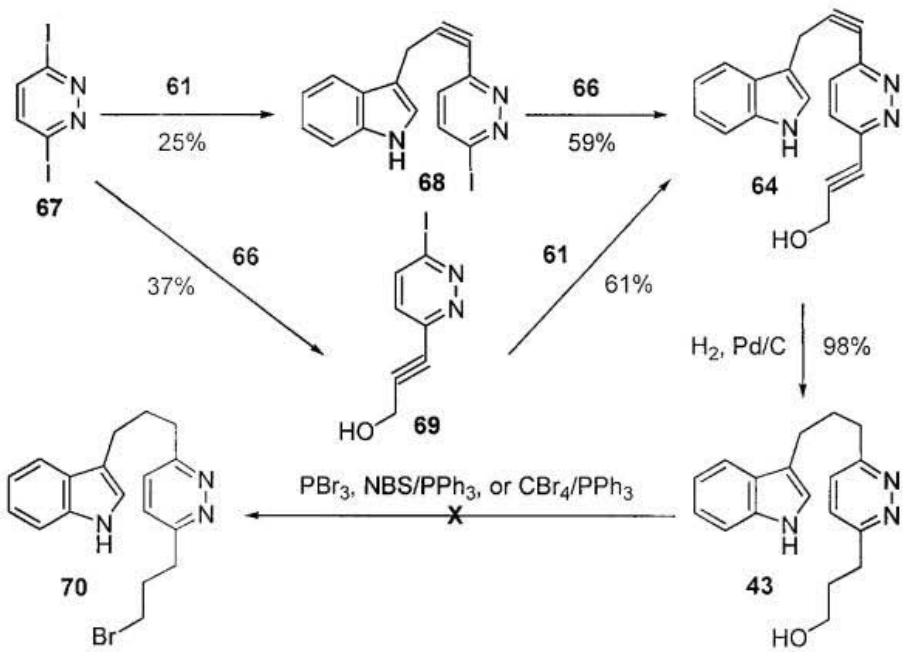
4.2.1.3 2nd Sonogashira Coupling Pathway



Scheme 4.18 The third retrosynthetic analysis of **41**.

It was clearly demonstrated that Sonogashira coupling was effective on shortening the synthetic sequence by comparing the routes described above. Another retrosynthetic analysis of **41** (Scheme 4.18), relying more heavily on this powerful chemistry, was performed. Two successive Sonogashira coupling reactions were proposed to install both bridges in **64**. Three key features of this work are worth mentioning: (1) both alkynyl functionalities in **64** could be hydrogenated at the same time, thus shortening the sequence; (2) in the majority of Pd-catalyzed reactions,[125] there is no need to protect hydroxy groups, which obviates the need for a protection/deprotection procedure, but also saves experimental work by requiring commercially available propargyl alcohol **66** as

one of the starting materials; (3) readily available, symmetric 3,6-dihalopyridazines **65** are used instead of having to construct the pyridazine nucleus as in last two approaches.

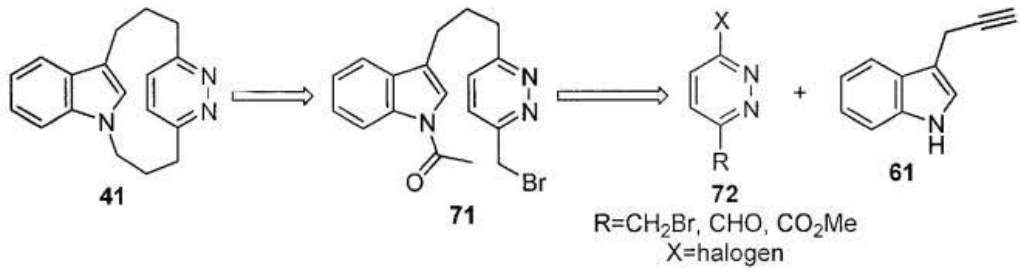


Scheme 4.19 Attempted synthesis of cyclization precursor **70**.

Based on the experience in the 1st Sonogashira coupling pathway, 3,6-diiodopyridazine **67**, which is easily accessible from commercial 3,6-dichloropyridazine[127] and is very reactive in Sonogashira couplings,[128] was employed as the starting material (Scheme 4.19). Beginning with **67**, two complementary Sonogashira sequences were effected to prepare diyne **64**. The first sequence was composed of two Sonogashira couplings (**67→68**, 25%, **68→64**, 59%), with the carbon atoms of what was slated to become the top bridge being installed first. This furnished **64** in an overall yield of 15%.

Performing the two Sonogashira couplings in a more convergent order constituted the second route (**67**→**69**, 37%, **69**→**64**, 61%), which yielded **64** in 23% yield over two steps. The subsequent catalytic hydrogenation led to formation of the desired alcohol **43** (98%) in an excellent yield. However, the seemingly trivial conversion of **43** into the direct cyclization precursor **70**, the analogue of which was successfully exploited in the synthesis of **42** (Chapter 3), could not be achieved. Brominations under mild conditions, including PBr_3,[129] NBS/PPh_3[130] and CBr_4/PPh_3,[131] yielded none of the bromide **70**. The same was true for an attempt to convert **70** into its mesylate using MsCl/Et_3N.[132] The observation of triphenylphosphine oxide and UV-active baseline materials in trials with NBS/PPh_3 and CBr_4/PPh_3 suggested that bromide **70** was possibly formed as an intermediate, which immediately underwent a 5-exo-tet cyclization, the nucleophile being the proximate nitrogen atom of the pyridazine ring. This could produce a pyridazinium salt that would not be expected to be chromatographically mobile. Whatever the cause for the failure to convert the hydroxy group in **43** into a leaving group, this was clearly a dead end and the *N*-alkylation strategy was abandoned. Alternative ideas had to be considered.

4.2.1.4 Enolate Alkylation Strategy

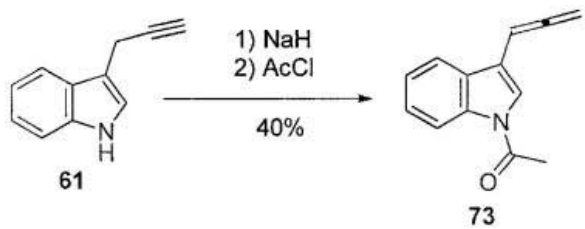


Scheme 4.20 The fourth retrosynthetic analysis of **41**.

Upon reviewing the course of the synthetic work toward **42** described in Chapter 3, it was noticed that the enolate alkylation strategy was discarded only because the requisite Michael acceptor with a benzylic substituent, necessary to build the top bridge, was not easy to prepare. The use of the Sonogashira coupling, instead of the originally proposed indole conjugate addition, to construct the top tether sparked the reconsideration of this strategy. Of particular significance was the known compatibility of benzylic substituents with Sonogashira chemistry[125] (Scheme 4.20). Similar to the retrosynthetic analysis of **42** (Chapter 3), bromide **71** was envisaged as the cyclization precursor for **41**. A further cut led to two building blocks: 3-propargylindole **61** and pyridazine halides **72**.

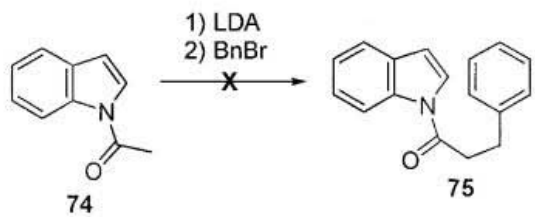
The installation of the amide functionality necessary for indole enolate formation was attempted first (Scheme 4.21). The commonly used *N*-acylation procedure under strongly basic conditions, however, afforded compound **73**

(40%), which originated from a rearrangement of the alkynyl group in **61** to an allene functionality.

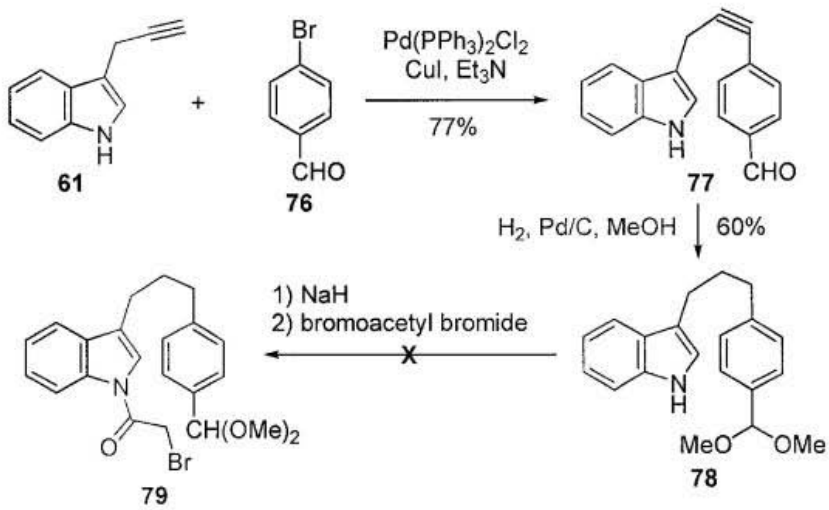


Scheme 4.21 *N*-Acylation of **61**.

A parallel attempt to generate and alkylate the enolate of *N*-acetylindole **74**[133] failed to give desired product **75** (Scheme 4.22). The major product was indole itself, and the minor products, according to an analysis of the ^{1}H NMR spectrum of the crude mixture, were 3-benzylindole and 2-benzylindole. Since attempted chromatographic separation of the product mixture failed, the structural assignments of the minor products had to remain tentative. This was presumably due to the consequence of formation of a ketene species and an indole lithium salt instead of that of the desired enolate.



Scheme 4.22 A model study of generating an indole enolate from **74**.



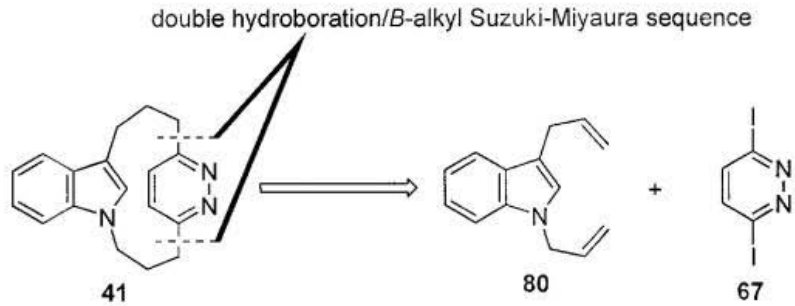
Scheme 4.23 Another attempt of enolate alkylation approach.

Attention was then turned to the use of a modified Reformatsky reaction mediated by SmI_2,[134] as the cyclization approach (Scheme 4.23). Since the proposed starting material **72** (Scheme 4.20) needed to be synthesized, a model study using commercially available benzenoid analogue **76** was conducted. A Sonogashira coupling with **61** furnished alkynyl aldehyde **77** in 77% yield. In the following reaction under catalytic hydrogenation conditions, Pd-C acted as both a hydrogenation catalyst and a Lewis acid to promote the formation of the acetal moiety in **78** (60%). Unfortunately, the treatment of the anion derived from **78** with bromoacetyl bromide failed to supply compound **79**, possibly due to the multiple reactivity of bromoacetyl bromide.[135]

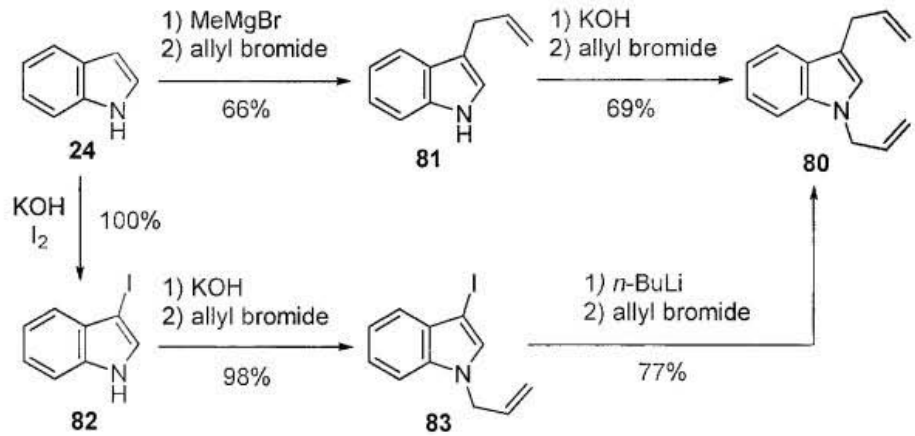
4.2.1.5 The Hydroboration/*B*-alkyl Suzuki-Miyaura Strategy

Although all the plans (*vide supra*) failed in the middle or right at the end of the attempted routes to **41**, the prominent position of the Sonogashira reaction was firmly established as a C-C bond forming tool in terms of efficiency, simplicity and functional group tolerance. This underscores a characteristic feature of contemporary organic chemistry, namely that transition metal catalyzed cross-coupling reactions play an increasingly pivotal role.[125,136,137] To further take advantage of these powerful transformations, it was visualized that other such reactions could serve as key steps in more concise and atom economical approaches, especially if they were to be used in a manner that exploits symmetry.

Being one of the most utilized cross-coupling reactions, the Suzuki-Miyaura reaction is extremely useful in organic synthesis.[138,139] When combined with another highly efficient organometallic process, hydroboration,[140] the resulting *B*-alkyl Suzuki-Miyaura reaction is distinguished from conventional Suzuki-Miyaura reactions in that a reaction occurs between an alkyl borane and an aryl or vinyl halide or pseudo halide.[141] This has been shown to be an effective method for the formation of medium- to large-sized rings.[142-144] On the basis of this chemistry, a retrosynthetic analysis of **41** was performed, which involved a more symmetrical application of this methodology: a two-fold sequential hydroboration/*B*-alkyl Suzuki-Miyaura cross-coupling (Scheme 4.24).



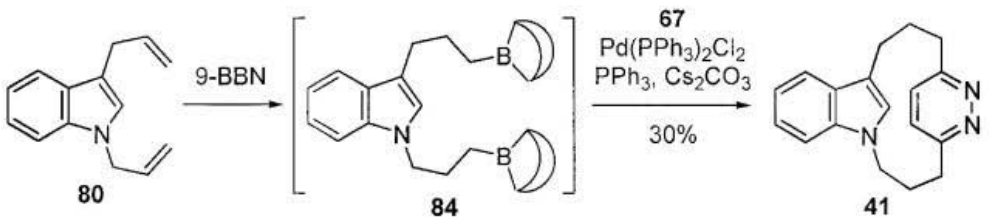
Scheme 4.24 The fifth retrosynthetic analysis of **41**.



Scheme 4.25 Synthesis of 1,3-diallylindole **80**.

To execute the proposed synthetic route to **41**, 1,3-diallylindole **80** was required as the key intermediate (Scheme 4.25). It was first synthesized using successive allylations at the 3- and 1-positions by manipulating the counterions in the generated indole salts.[145] The use of magnesium, which can tightly coordinate with the indole nitrogen atom and thus reduce its nucleophilicity, as the counterion led to the selective allylation of indole **24** at C3[146-148] to give **81**[149] in 66% yield. The employment of the more loosely complexed potassium

cation favored an *N*-allylation[150,151] to afford **80** (69%). A three-step sequence was subsequently found to be higher yielding. Iodination of indole in the presence of KOH gave 3-iodoindole **82**[152] quantitatively, and this was *N*-allylated to produce **83** in 98% yield. Treatment of this compound with *n*-BuLi followed by allyl bromide then furnished **80** in a yield of 77%. The overall yield of **80** by this sequence was 75%, as compared to 46% for the two-step protocol.



Scheme 4.26 Synthesis of **41**.

With ready access to **80**, the synthesis of **41** was then attempted (Scheme 4.26). Treatment of **80** with 9-BBN presumably gave the doubly hydroborated species **84**, which was not isolated, but rather reacted immediately with 3,6-diiodopyridazine **67** under Suzuki-Miyaura conditions.[138,141] Gratifingly, the desired [3](1,3)indolo[3](3,6)pyridazinophane **41** was obtained in 30% yield. No other cyclic oligomers were isolated. In summary, **41** was synthesized in three and four steps with overall yields of 14% and 23%, respectively. For a cursory study of the generality of this strategy in the synthesis of [3.3]cyclophanes, the reader is referred to Chapter 3.

4.2.2 Conformational Behavior of 41

4.2.2.1 Computational Studies of 41

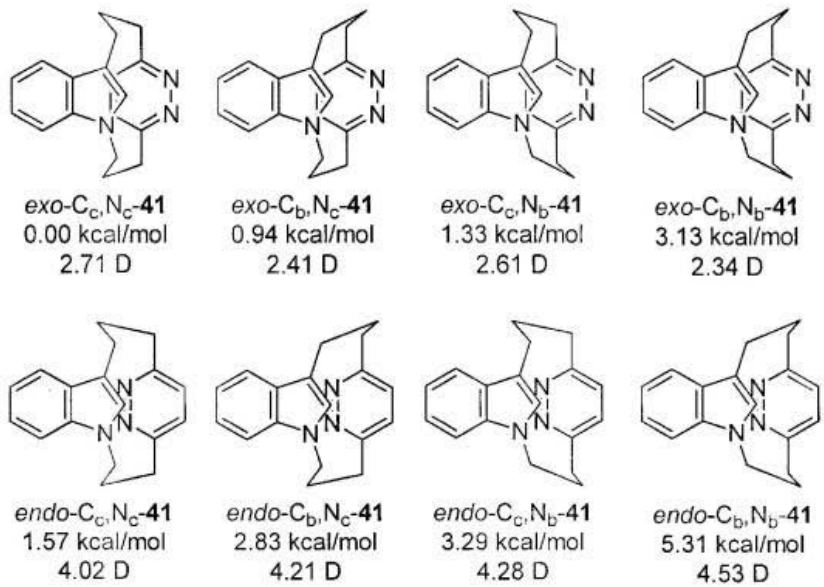


Figure 4.7 AM1 calculated relative energies and dipole moments of low energy conformers of **41**.

Calculations using Chem3D (Ultra 5.0) MOPAC at the AM1 level of theory were performed to determine the relative energies and the dipole moments of the eight most likely low energy conformers of **41** (Figure 4.7). They were calculated to be within 6 kcal/mol of the global minimum. In contrast to indolophane **42**, an extra element of dissymmetry, in addition to the one brought by the indole ring, was introduced by the pyridazine moiety in **41**, which accounts for the larger number of conformers that were considered for **41** as compared to **42** (Chapter 3). Consequently, the additional terms *endo* and *exo* were applied to assign the relative orientation of the two arenes in **41**. The term

endo is used to describe conformers in which the nitrogen atoms of the pyridazine ring are situated underneath the indole system. The term *exo* is used to describe conformers in which the nitrogen atoms of the pyridazine ring are situated away from the indole system. Similar to the results from a conformer search of **42** (Chapter 3), the lowest energy conformer (*exo*-C_c,N_c) has both bridges in the *pseudo-chair* conformation. Flipping the bridge attached to the C-terminus of the indole unit affords a conformer (*exo*-C_b,N_c) that is 0.94 kcal/mol higher in energy, whereas flipping the bridge attached to the N-terminus of the indole moiety to give the *exo*-C_c,N_b conformer is much more costly in energy (1.33 kcal/mol). Analogous energy differences were observed in the case of **42** (Chapter 3). The *exo*-C_b,N_b conformer is calculated to lie 3.13 kcal/mol above the global minimum. The *endo* conformers were also computationally analyzed. Each *endo* conformer was found to be in the range of 1.57-2.18 kcal/mol higher in energy, and in the range of 1.31-2.19 D higher in dipole moment than its corresponding *exo* isomer. The implications of these results will be discussed in the following sections.

4.2.2.2 NMR studies of 41

The 500 MHz ^{1}H NMR spectrum of **41** at room temperature (Figure 4.8) exhibits a singlet at δ 5.78, which is assigned to the internal proton of the indole deck. This is slightly less shielded than the analogous proton of **42** (δ 5.59),[153] but still much more strongly shielded than the corresponding proton of the direct

cyclophane precursor **80** (δ 6.87). The protons on the pyridazine ring appear as an AX system at δ 6.13 and 6.33. These chemical shifts are 1.07 and 0.87 ppm, respectively, upfield from the aromatic proton of the reference compound 3,6-dimethylpyridazine **85** (δ 7.20).[154] However, they cannot easily be differentiated.

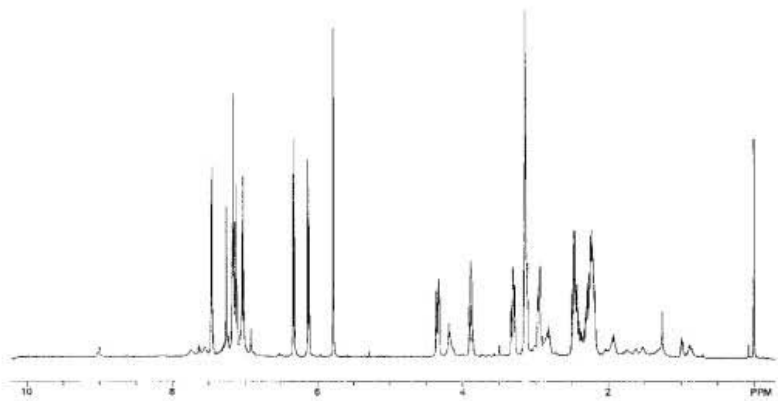


Figure 4.8 ^{1}H NMR ($CDCl_3$) spectrum of **41** at room temperature.

By comparison, in the ^{1}H NMR spectrum of **42** at 183 K, the *endo* protons of the benzene deck (the protons situated underneath the indole deck) were observed at δ 6.00 and 6.21,[153] high-field shifted by 1.06 and 0.85 ppm, respectively, from the aromatic signal for the reference compound *p*-xylene **86** (δ 7.06). The *exo* protons of the benzene deck (δ 6.94 and 7.04) in **42**, however, have chemical shifts very similar to those of **86**. These almost identical

shielding effects strongly suggest that the ring conformation of **41** is predominantly, if not exclusively, *exo* in solution as shown in Figure 4.9.

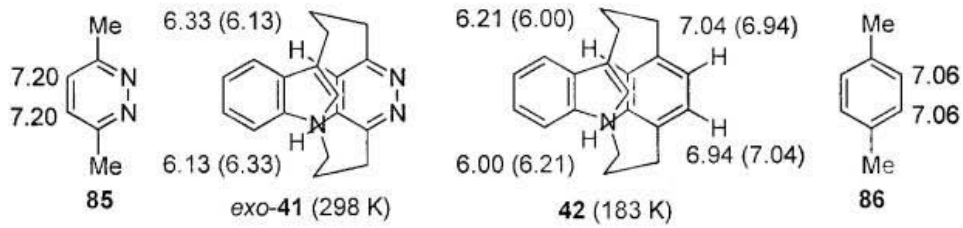
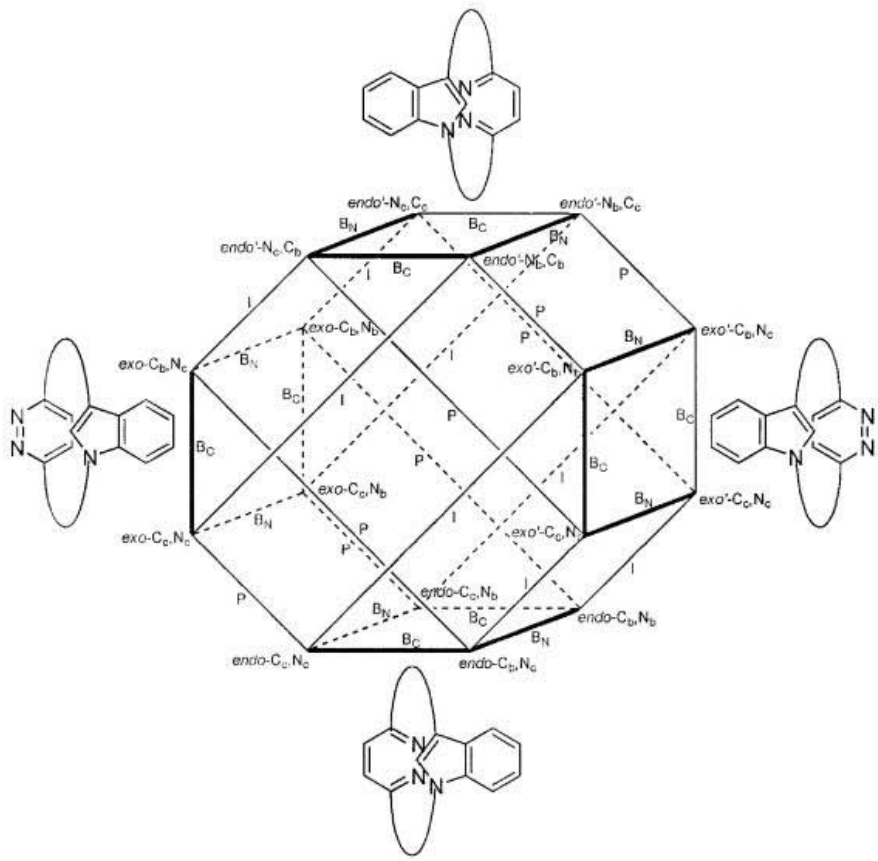


Figure 4.9 Chemical shift comparison of aromatic protons between cyclophanes and their reference compounds.

This unusual conformational rigidity can only be caused by both the indole ring flip and the pyridazine ring flip being slow. If this is the case, then the exchange of environment of each pair of diastereotopic CH_2 protons in the bridges, including NCH_2 protons, should also be slow on the NMR time scale. Two separate resonances would then be expected for each CH_2 group and this is indeed the case. For example, the NCH_2 group appears as two multiplets centered at δ 3.89 and 4.35. The remaining bridge protons are observed as a series of multiplets in the range of δ 2.18-3.34. As anticipated, this observed pattern of the bridge protons corresponds well with that of the bridge protons in **42** at low temperatures (203, 193 and 183 K) (Chapter 3), when the indole ring flip was slow. To see whether these ring flips would occur more quickly at higher temperatures, a sample of **41** in toluene-d_8 was gradually heated in the spectrometer. However, the molecule appears to be rather rigid as its ^{1}H NMR spectrum does not change up to a temperature of 373 K. Since spectroscopic

change attributable to the conformational processes of the bridge wobbles in **42** (Chapter 3) was not observed upon cooling, analogous experiments were not performed on compound **41**.

4.2.2.3 Conformational Processes in 41



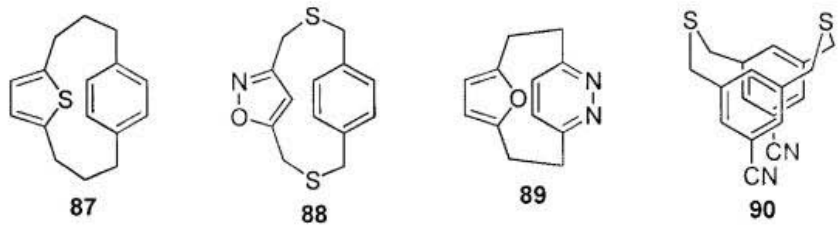
B$_C$=C-bridge wobble, B$_N$=N-bridge wobble, I=indole ring flip, P=pyridazine ring flip

Figure 4.10 Selected conformational processes in **41**.

Analysis of a molecular model of **41** revealed that this cyclophane has a considerably more complicated set of conformational processes available to it

than does indolophane **42**.[153] Selected conformational processes of **41**, involving eight conformers arising from all permutations of *endo-exo* orientations of the two arenes and *chair/boat* conformations of the two unique bridges, are depicted in Figure 4.10. In addition to the elements of dissymmetry introduced by the indole and pyridazine rings, the conformational processes are also complicated by racemizations (**41** is a chiral cyclophane). Therefore, a total of sixteen structures, including four *endo* conformers, their mirror images (*endo'* conformers), four *exo* conformers and their mirror images (*exo'* conformers), have been considered. Either one of the bridge wobbles (B_C or B_N) of any conformers gives rise to its next bridge conformer within the given set of *endo*, *endo'*, *exo* or *exo'* conformers. Indole ring flip (I) of a conformer reaches its *endo/exo* isomer in the neighboring set of conformers, with concomitant change of both bridge conformations, e.g. *exo*-C_c,N_c→ *endo'*-C_b,N_b, whereas pyridazine ring flip (P) causes a conformer to arrive at its *endo/exo* isomer without bridge conformational changes, e.g. *exo*-C_c,N_c→ *endo'*-C_c,N_c. None of the illustrated interconversions alone involves an exchange in the environments of the diastereotopic NCH_2 protons (or any of the other diastereotopic CH_2 groups in the bridges). Any given racemization shown in Figure 4.10 can be fastest reached by four steps, comprising a full set of the different types of processes (B_C, B_N, I and P). If this occurs rapidly on the NMR time scale, a degenerate signal for each set of diastereotopic protons in the bridges is expected. A

restriction of any of the conformational processes would result in the observed inequivalencies for the bridge protons in **41** (Figure 4.8).



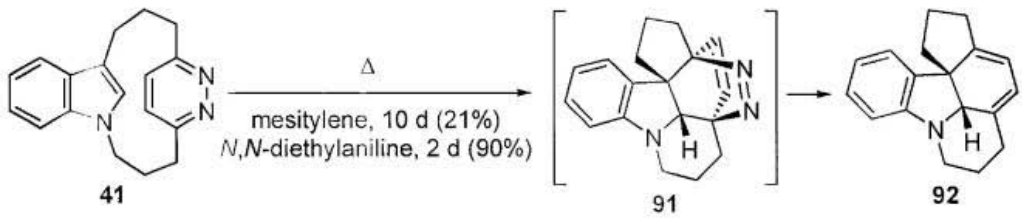
87 **88** **89** **90**

Figure 4.11 Structures of cyclophanes with unusual conformational behavior.

If the most energetically demanding process were any of the bridge flips, then the I and P processes would occur quickly. Since either one of these realizes an exchange of the pyridazine protons between *endo* and *exo* orientations, one would not expect to see such a high field shift of the pyridazine protons. The slow processes are therefore ascribed to restrictions of both I and P. Ring conformational rigidity at room temperature is common in [2.2]metaparacyclophane systems, but unknown for their [3.3] homologs[155] without internal substituents. The increased energy barriers for aromatic ring flips were also reported for cyclophanes **87**[156] and **88**[157] as compared to their benzenoid analogs (Figure 4.11). It was postulated that this was due to the smaller size of meta-bridged heteroaromatic rings compared to a meta-substituted benzene ring.[157] In studies on the conformational behavior of furanopyridazinophane **89**,[110] it was found to be locked in the *syn* conformation with the furan oxygen atom and pyridazine nitrogen atoms on the same side, which presented an arene orientation similar to **41**. The authors concluded that it

originated from the greater steric demand of a nitrogen atom with its lone pair electrons than that of an aromatic CH group. As described in Chapter 2, an X-ray analysis of cyclophane **90** revealed the unusual structural feature of both bridges having adopted the *pseudo-boat* conformation, a conformer calculated to be higher in energy than its isomer with two *pseudo-chair* bridge conformations.[158] A dipolar effect was postulated to be the origin of the surprising behavior. The conformational rigidity of **41** is significantly higher than that exhibited by **87** and **88** since the ^{1}H NMR spectrum of **41** remains unchanged upon heating to 373 K, and the well resolved signals, even at 373 K, indicate that both of I and P are still very slow. As described before, the computational results revealed that *endo* conformers are higher both in energy and dipole moment than their corresponding *exo* conformers. Coupled with an examination of the molecular model, it is likely that the surprisingly high conformational rigidity of **41** comes from the combined effects of the smaller meta-bridged indole ring, more sterically demanding nitrogen atoms of the pyridazine ring, and energy and dipole moment differences between the *endo/exo* conformers in the molecular structure. Intuitively, resolving the two enantiomeric *exo* isomers of **41** should be practical given its highly rigid conformation in solution.

4.2.3 Transannular IEDDA Reaction of 41



Scheme 4.27 Transannular IEDDA reaction of **41**.

Transannular IEDDA reaction of **41** was attempted under thermal conditions (Scheme 4.27). Heating **41** in mesitylene (bp= 162-164 °C) led to the formation of pentacyclic product **92** (21%), presumably via a transannular IEDDA reaction followed by expulsion of nitrogen gas in a retro Diels-Alder fashion. Adduct **91** is the result of a transannular IEDDA reaction of **41** from an *exo* conformation. Reaction from the *endo* conformation would afford a different diastereoisomer, but it would also produce (±)-**92** upon release of nitrogen. The sluggishness of this reaction and the apparently low solubility of **41** in mesitylene, even at reflux, prompted the use of *N,N*-diethylaniline[68] (bp=217 °C), in which **41** dissolved readily. This modification increased the yield dramatically to 90% and shortened the reaction time to 2 d. The overall yield of **92** from indole was 12% by the four-step route and 20% by the five-step sequence.

With regard to the relative stereochemistry in **92**, AM1 calculation using Chem 3D Ultra 5.0 (MOPAC) predicts that the expected *cis* isomer **92** is approximately 35 kcal/mol lower in energy than the corresponding *trans* isomer.

Nevertheless, a NOE experiment was performed to support the stereochemical assignment (Figure 4.12). Irradiation of the proton at δ 4.16, which is assigned to the methine proton next to the nitrogen atom, resulted in a 0.9% enhancement of the multiplet centered at δ 1.93 and a 1.9% enhancement of the multiplet centered at δ 1.81. Each of these two proton multiplets was shown using ^{1}H-^{1}H COSY, HMQC and HMBC experiments to be due to overlapping signals of one homoallylic and one bishomoallylic proton of the five-membered ring. Although the specific interactions could not be identified unambiguously, the enhancements of signals in the five-membered ring would not be expected for the *trans* isomer. Expected enhancements (1,3-diaxial relationships to the irradiated methine proton) of one of NCH_2 protons (δ 3.22, 1.2%) and one of the allylic CH_2 protons (δ 2.19, 1.2%) in the piperidine ring were also observed.

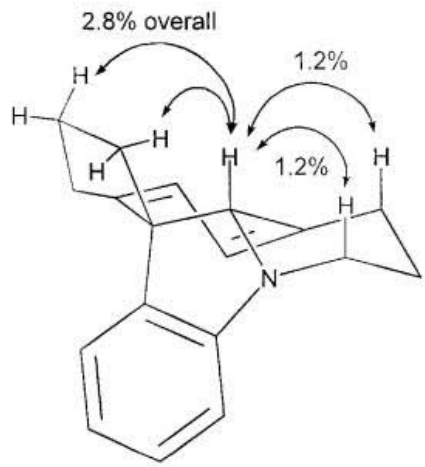


Figure 4.12 NOE enhancements observed in **92**.

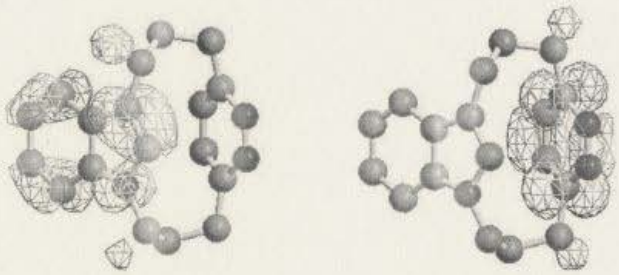


Figure 4.13 Calculated HOMO and LUMO surfaces of **41** and their energies.

To assign the nature of the electronic demand of the reaction, the HOMO-LUMO interaction in **41** was revealed by Chem3D MOPAC calculations at the PM1 levels of the theory (Figure 4.13). The HOMO energy was calculated to be –8.35 eV, and its corresponding surface was found lying on the indole nucleus with the highest concentration at indole's C3. The LUMO energy was calculated to be –0.43 eV, and its surface was shown on the pyridazine moiety. The calculated $HOMO_{dienophile}$-$LUMO_{diene}$ with an energy gap of 7.92 eV determined the inverse electron demand nature of the TADA reaction of **41**.

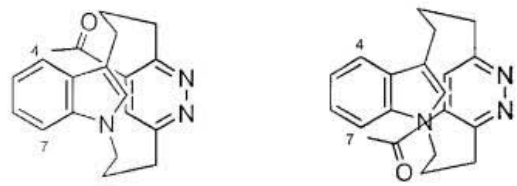
4.3 Conclusions and Future Directions

The synthesis of [3](1,3)indolo[3](3,6)pyridazinophane **41** was accomplished by three-step and four-step sequences in overall yields of 14% and 23%, respectively, by using a hydroboration/*B*-alkyl Suzuki-Miyaura cross-coupling reaction as the ring closure approach.

NMR studies of **41** revealed its surprisingly rigid *exo* conformation in solution even at the temperature of 373 K. With assistance of computational studies on **41** and previous results for some [3.3]metaparacyclophanes, this unusual structural feature was ascribed to the combined effects of the smaller meta-bridged indole ring as compared with benzene ring, the more sterically demanding nitrogen atoms of the pyridazine moiety than aromatic CH groups, and the energy and dipole moment differences between the *endo/exo* isomers of **41**. Unfortunately, **41** was isolated as an oil, which ruled out an X-ray crystallographic determination of its solid-state structure. Given its highly rigid conformation with the preference of *exo* form, resolving the corresponding enantiomers should be feasible since both indole and pyridazine ring flips, necessary for an *exo/endo* switch as well as an *exo/exo'* racemization, are restricted even at elevated temperatures.

On the other hand, cyclophane **41**, a donor-acceptor system, also gives an opportunity to study transannular electronic effects that were observed by UV spectroscopy in a similar cyclophane **89**[110] (Figure 4.11). As described in Chapter 1, transannular electronic effects in cyclophanes also appeared as directive influences in electrophilic aromatic substitutions, where the electrophilic attack predominantly occurred at the aromatic carbon atom that is *pseudo-gem* to the carbon from an opposing arene deck bearing more basic substituent such as a carbonyl group.[1] With this in mind, the introduction of a carbonyl group on the pyridazine moiety would strengthen the transannular

electronic effects by further lowering the π electron density of the acceptor. Furthermore, this would also facilitate the electrophilic substitutions of the benzenoid ring on the indole moiety, which are well known for their poor regiocontrol,[145] in the resulting cyclophanes **93** and **94** (Figure 4.14) to preferentially take place at C4 and C7 positions, respectively.

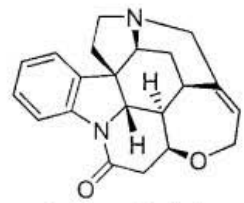


93 **94**

Figure 4.14 Structures of carbonylated indolopyridazinophanes **93** and **94**.

Due to a much more pronounced entropic advantage, dienes and dienophiles that do not normally react in intermolecular nor intramolecular fashion often yield cycloadducts via TADA reactions.[91] This spectacular feature, along with high degrees of chemo- and stereoselectivities, was exemplified again in molecule **41**. The transannular IEDDA reaction of **41**, analogs of which failed to undergo intramolecular reaction,[84] proceeded in a superb yield and represents the first example of a TADA reaction between two unmodified and unactivated arene decks within a cyclophane molecule. More importantly, the main objective of using a transannular reaction of a cyclophane to rapidly construct a polycyclic system that is structurally related to an important class of natural products has been achieved. This established facile access to a pentacyclic indoloid system **92** by the extrusion of nitrogen in a retro Diels-Alder fashion following the initial

transannular IEDDA reaction. Not only does **92** contain a reduced carbazole moiety, but the former bridges of the cyclophane progenitor also manifest themselves as fused five- and six-membered rings that render the skeleton of **92** structurally very similar to five of the seven rings of strychnine **95** (Figure 4.15). The obvious next task, an application of the "cyclophane approach" to a synthesis of **95**, will be described in Chapter 5.



95 (strychnine)

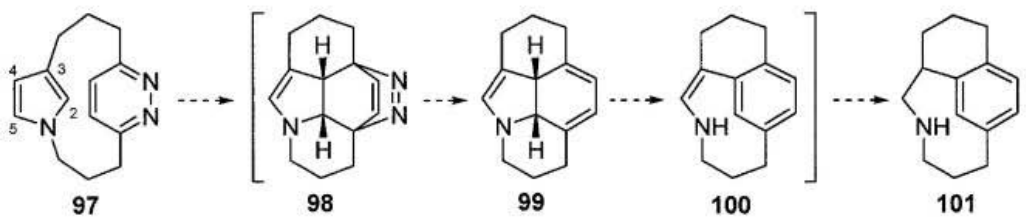
Figure 4.15 Structure of strychnine **95**.

96

Figure 4.16 Structure of modified indolopyridazinophane **96**.

Once the resolution of the two *exo* enantiomers of **41** is accomplished taking advantage of its conformational rigidity, an asymmetric transannular IEDDA reactions of (+)-**41** or (−)-**41** would be promising if the reaction outpaces the racemization. Even if it is not the case at the high temperature (217 °C) necessary for the desired reaction, introduction of internal substituents with appropriate electronic properties to the cyclophane such as **96** (Figure 4.16)

would certainly enhance the chances for an asymmetric reaction by increasing the energy barrier for ring flips and decreasing the energy requirement for the IEDDA reaction through complementarily lowering the $HOMO_{dienophile}$-$LUMO_{diene}$ gap. Furthermore, the SMe group should be readily removed by using Raney Ni upon IEDDA reaction and the carbonyl group could be used as a handle for further synthetic elaborations.



Scheme 4.28 Postulated TADA reaction of cyclophane **97**.

The transannular IEDDA reaction should not be limited only to the indolopyridazinophane system. Cyclophane **41** has only one possible dienophilic entity. If there are two dienophilic double bonds present in one aromatic ring, which in the case of the pyrrole ring has been used as the dienophile in IEDDA reactions,[76,80] some reasonable expectations can be made on the resulting pyridazinopyrrolophane **97** (Scheme 4.28). Examination of the molecular model of **97** revealed that pyridazine/pyrrole 4,5-double bond interaction offers an approximately parallel alignment, which is favored in a Diels-Alder transition state, whereas pyridazine/pyrrole 2,3-double bond interaction exihibits a slightly twisted alignment, which is probably less favored when approaching the transition state of a Diels-Alder reaction.

Another argument comes from the steric sensitivity of the Diels-Alder reaction[159,160] with regard to both diene and dienophile; therefore, the competition should favor the less-substituted 4,5-double bond over the more-substituted 2,3-double bond from the pyrrole nucleus as the potential dienophile. Tetracycle **99** should be generated by the transannular IEDDA/retro Diels-Alder sequence, and the absence of the tether at the original C4 of the pyrrole ring leaves an opportunity for the six-membered ring bearing two double bonds in **99** to be aromatized by eliminating the enamine moiety of **100**. Further elaborations on **100** could furnish a [6]metacyclophane **101**, a cyclophane that would possess a nonplanar benzene ring, if subjected to reducing conditions. From a synthetic point of view, 3-iodopyrrole, which could be used as the intermediate to prepare 1,3-diallylpyrrole (Scheme 4.25) that should in turn serve as the precursor to **97** by the hydroboration/*B*-alkyl Suzuki-Miyaura Strategy, is readily accessible.[161,162]

4.4 Experimental

General Experimental for Chapter 4. Reactions were performed under air unless otherwise indicated. Those experiments with moisture or air sensitive compounds were performed in anhydrous solvents under nitrogen in flame-dried glassware. Solvents for reactions were dried and distilled according to standard procedures. All other solvents were used as received. Chromatographic purifications were accomplished with 230-400 mesh silica gel. TLC plates were

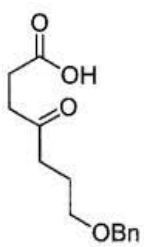
visualized using a short wave (254 nm) UV lamp in most cases and sometimes were also developed in PMA or vanillin dips. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on neat samples or nujol suspensions in KBr discs using a Mattson Polaris FT instrument. ^{1}H NMR spectra were obtained from $CDCl_3$ or DMSO-d_6 solutions using a General Electric GE-300 NB instrument or a Bruker Avance 500 instrument operating at 300.1 and 500.1 MHz, repectviely. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 or 125.77 MHz. Chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$ and δ 39.5 for DMSO-d_6). Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. High resolution mass spectroscopic data were obtained by the Mass Spectrometry Center, Chemistry Department, University of Ottawa, Ottawa, Ontario.

(3-Chloropropoxymethyl)benzene (51)

To a solution of **50** (9.45 g, 100 mmol) and benzyl bromide (25.7 g, 150 mmol) in anhydrous THF (200 mL) at −78 °C was added NaH (6.00 g, 150 mmol) in one portion. The resulting suspension was allowed to warm up slowly to room

temperature and then stirred for 12 h. The reaction mixture was treated with H_2O (10 mL), concentrated and extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (40% CH_2Cl_2/petroleum ether) gave **51** (18.1 g, 98%) as a colorless oil. IR (KBr) ν=1604 (w) cm^{-1}. MS *m/z* (%)=186 (0.7, $M^{+\,37}Cl$), 184 (2, $M^{+\,35}Cl$), 91 (100), 79 (16), 65 (12). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.02-2.10 (m, 2H), 3.62 (t, *J*=5.9 Hz, 2H), 3.67 (t, *J*=6.5 Hz, 2H), 4.52 (s, 2H), 7.26-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=32.8, 42.0, 66.7, 73.1, 127.6, 128.4, 138.2 (One fewer aromatic signal was observed, presumably due to overlaps). Anal. Calcd. for $C_{10}H_{13}ClO$: C, 65.04; H, 7.10. Found: C, 65.44; H, 7.26.

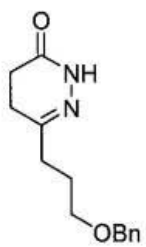
7-Benzyloxy-4-oxoheptanoic acid (52)



To a slurry of I_2-activated magnesium (267 mg, 11.0 mmol) in anhydrous THF (3 mL) at room temperature was added a solution of **51** (1.85 g, 10.0 mmol) in anhydrous THF (15 mL). The resulting suspension was heated at reflux for 3 h, cooled to 0 °C and then transferred by cannula to a suspension of **49** (1.50 g, 15.0 mmmol) in anhydrous THF (20 mL) at –78 °C. The slurry was stirred for 2

h, treated with HCl (10%, 20 mL), concentrated and basified with NaOH (4 M, 25 mL). The resulting mixture was washed with CH_2Cl_2 (30 mL), acidified with concentrated aqueous HCl solution (15 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford **52** (711 mg, 28%) as a yellow oil, which was used in the next step without further purification. IR (KBr) ν=3207 (s, br), 2957 (s), 1738 (s), 1715 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ=1.86-1.95 (m, 2H), 2.54-2.73 (m, 6H), 3.48 (t, *J*=6.0 Hz, 2H), 4.47 (s, 2H), 7.28-7.37 (m, 5H).

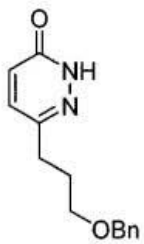
6-(3-Benzyloxypropyl)-4,5-dihydro-2*H*-pyridazin-3-one (57)



To a dispersion of **52** (660 mg, 2.64 mmol) in $NH_2NH_2 \cdot xH_2O$ (85%, 20 mL) was added ethanol (10 mL). The resulting homogeneous solution was heated at reflux for 3 h and then stirred at room temperature for additional 12 h. The reaction mixture was concentrated *in vacuo* and subjected directly to column chromatography (4% MeOH/CH_2Cl_2) to give **57** (430 mg, 66%) as a light brown solid. M.p.=83-84 °C. IR (nujol) ν=3221 (s), 1666 (s), 1648 (s) cm^{-1}. MS *m/z* (%)=247 (0.3), 246 (3, M^+), 155 (20), 112 (59), 91 (100). ^1H NMR ($CDCl_3$, 300 MHz): δ=1.84-1.93 (m, 2H), 2.36-2.51 (m, 6H), 3.52 (t, *J*=6.0 Hz, 2H), 4.50 (s,

2H), 7.28-7.38 (m, 5H), 8.32 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=24.8, 26.0, 26.1, 33.4, 69.3, 73.0, 127.7, 128.4, 138.2, 155.6, 167.4 (One fewer aromatic signal was observed, presumably due to overlaps). Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.29; H, 7.47; N, 11.27.

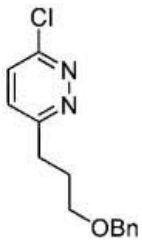
6-(3-Benzyloxypropyl)-2*H*-pyridazin-3-one (58)



To a solution of **57** (380 mg, 1.54 mmol) in MeCN (15 mL) at room temperature was added $CuCl_2$ (456 mg, 3.39 mmol). The resulting dark green solution was heated at reflux for 2 h and then cooled to room temperature. The reaction mixture was diluted with EtOAc (50 mL), washed with HCl (10%, 25 mL×3), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/ CH_2Cl_2) gave **58** (179 mg, 47%) as a white solid. M.p.=95-97 °C. IR (nujol) ν=3131 (m), 1672 (s), 1654 (s), 1602 (s) cm^{-1}. MS *m/z* (%)=245 (0.3), 244 (0.9, M^+), 153 (34), 138 (30), 110 (79), 91 (100). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.92-2.01 (m, 2H), 2.72 (t, *J*=7.6 Hz, 2H), 3.52 (t, *J*=6.1 Hz, 2H), 4.50 (s, 2H), 6.88 (d, *J*=9.7 Hz, 1H), 7.14 (d, *J*=9.7 Hz, 1H), 7.28-7.38 (m, 5H), 11.8 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=28.1, 31.1, 68.9, 73.0, 127.7, 128.4, 130.0, 134.2, 138.2, 148.5, 161.5 (One fewer aromatic signal was observed,

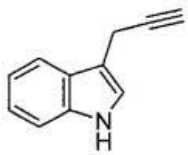
presumably due to overlaps). Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.86; H, 6.59; N, 11.39.

3-(3-Benzyloxypropyl)-6-chloropyridazine (59)



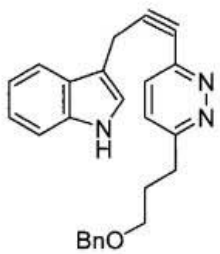
A solution of **58** (100 mg, 0.41 mmol) in $POCl_3$ (5 mL) was heated at reflux for 1 h. The mixture was cooled and then carefully treated with ice water (5 mL), neutralized with NaOH (5 M, 10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (2% MeOH/ CH_2Cl_2) gave **59** (97 mg, 90%) as a light brown oil. IR (KBr) ν=1665 (s), 1595 (s) cm^{-1}. MS *m/z* (%)=263 (0.5, M^+), 171 (31), 128 (100), 91 (61). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.05-2.15 (m, 2H), 3.08 (t, *J*=7.6 Hz, 2H), 3.54 (t, *J*=6.1 Hz, 2H), 4.49 (s, 2H), 7.25-7.38 (m, 7H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=29.2, 32.3, 68.9, 72.9, 127.6, 127.7, 128.0, 128.3, 128.9, 138.2, 155.0, 162.6. Anal. Calcd. for $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.22; H, 5.70; N, 10.50.

3-Prop-2-ynyl-1*H*-indole (61)



To a solution of **24** (14.1 g, 120 mmol) in anhydrous THF (100 mL) at 0 °C was added MeMgBr (3.0 M, 40 mL). The resulting brown solution was stirred at room temperature for 2 h and then cooled to 0 °C. To this was added propargyl bromide (80%, 22.3 g, 150 mmol). The reaction mixture was stirred for 12 h, treated with first H_2O (20 mL), then HOAc (12 mL), concentrated and extracted with EtOAc (100 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL×2) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Vacuum distillation at 106-108 °C/0.5 mm Hg (lit.:[124] 143-145 °C/2 mm Hg) gave **61** (10.3 g, 55%) as a white wax. M.p.=44-45 °C. IR (nujol) ν=3418 (s, br), 3283 (s), 2110 (m), 1639 (s), 1616 (m) cm^{-1}. MS *m/z* (%)=156 (10), 155 (84, M^+), 154 (100), 127 (30), 77 (39). ^1H NMR ($CDCl_3$, 300 MHz): δ=2.14 (t, *J*=1.6 Hz, 1H), 3.69 (dd, *J*=2.7, 1.1 Hz, 2H), 7.11-7.24 (m, 3H), 7.33-7.36 (m, 1H), 7.64 (d, *J*=8.1 Hz, 1H), 7.93 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ=15.2, 69.1, 82.3, 111.0, 111.2, 118.6, 119.5, 122.0, 122.3, 126.5, 136.4. Anal. Calcd. for $C_{11}H_9N$: C, 85.13; H, 5.85; N, 9.02. Found: C, 85.09; H, 5.66; N, 8.91.

3-{3-[6-(3-Benzyloxypropyl)pyridazin-3-yl]prop-2-ynyl}-1*H*-indole (60)

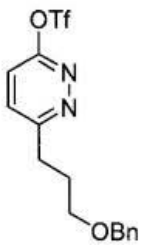


Method A. To a solution of **61** (88 mg, 0.57 mmol) and **59** (50 mg, 0.19 mmol) in anhydrous THF (4 mL) was added Et_3N (2 mL), $Pd(PPh_3)_2Cl_2$ (7 mg, 0.01 mmol) and CuI (2 mg, 0.01 mmol). The resulting mixture was heated to 50 °C for 12 h and extracted with CH_2Cl_2 (20 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (40% EtOAc/ CH_2Cl_2) gave **60** (15 mg, 20%) as a yellow oil. IR (KBr) ν=2115 (m), 1645 (s) cm^{-1}. MS *m/z* (%)=382 (4), 381 (16, M^+), 277 (100), 262 (81), 183 (54), 91 (55). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.07-2.13 (m, 2H), 3.08 (t, *J*=7.6 Hz, 2H), 3.54 (t, *J*=6.1 Hz, 2H), 3.98 (s, 2H), 4.49 (s, 2H), 7.13-7.39 (m, 11H), 7.69 (d, *J*=7.9 Hz, 1H), 8.28 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=16.3, 29.3, 32.9, 69.1, 73.0, 78.2, 93.0, 110.2, 111.3, 118.6, 119.6, 122.3, 125.8, 126.7, 127.6, 127.7, 128.4, 129.5, 136.4, 138.3, 146.4, 161.4 (One fewer aromatic signal was observed, presumably due to overlaps). HRMS Calcd. for $C_{25}H_{23}N_3O$: 381.1840. Found: 381.1825.

Method B. To a solution of **61** (40 mg, 0.26 mmol) and **62** (32 mg, 0.085 mmol) in anhydrous THF (2 mL) was added Et_3N (1 mL), $Pd(PPh_3)_2Cl_2$ (3 mg, 0.004 mmol) and CuI (1 mg, 0.005 mmol). The resulting mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred for additional 5 h, treated with

H_2O (15 mL) and then extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered and concentrated. Preparative thin layer chromatography (2.5% MeOH/ CH_2Cl_2) gave **60** (14 mg, 42%) as a yellow oil.

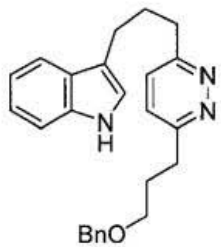
Trifluoromethanesulfonic acid 6-(3-benzyloxy-propyl)pyridazin-3-yl ester (62)



To a solution of **58** (24 mg, 0.098 mmol) in pyridine (2 mL) at 0 °C was added triflic anhydride (56 mg, 0.20 mmol). The resulting orange solution was stirred for 6 h, treated with H_2O (10 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Preparative thin layer chromatography (2% MeOH/CH_2Cl_2) gave **62** (34 mg, 92%) as a colorless oil. IR (KBr) ν=1644 (m) cm^{-1}. MS *m/z* (%)=376 (not observed, M^+), 285 (19), 242 (49), 109 (50), 91 (100). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.11-2.17 (m, 2H), 3.16 (t, *J*=6.3 Hz, 2H), 3.56 (t, *J*=5.9 Hz, 2H), 4.49 (s, 2H), 7.26-7.36 (m, 6H), 7.49 (d, *J*=8.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=29.1, 32.4, 68.8, 73.0, 120.2, 127.6,

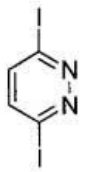
127.7, 128.4, 131.3, 138.2, 159.0, 165.2. Acceptable analytical data were not obtained for this compound.

3-{3-[6-(3-Benzyloxypropyl)pyridazin-3-yl]propyl}-1*H*-indole (63)



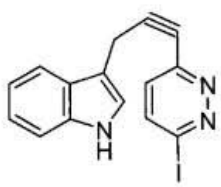
To a solution of **60** (9.0 mg, 0.024 mmol) in MeOH (4 mL) was added Pd/C (10%, 4.0 mg). The resulting black slurry was stirred under a H_2 atmosphere at room temperature for 4 h, suction filtered and concentrated. Preparative thin layer chromatography (40% EtOAc/CH_2Cl_2) gave **63** (8.6 mg, 95%) as a light yellow oil. IR (KBr) ν=1620 (m) cm^{-1}. MS *m/z* (%)=385 (not observed, M^+), 277 (7), 159 (54), 97 (35), 69 (100). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.08-2.14 (m, 2H), 2.17-2.23 (m, 2H), 2.86 (t, *J*=7.3 Hz, 2H), 3.01-3.06 (m, 4H), 3.55 (t, *J*=6.1 Hz, 2H), 4.50 (s, 2H), 7.01 (s, 1H), 7.08-7.36 (m, 10H), 7.59 (d, *J*=7.8 Hz, 1H), 8.04 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=24.7, 29.3, 29.8, 32.6, 35.6, 69.3, 72.9, 111.1, 115.9, 118.9, 119.1, 121.5, 121.9, 126.3, 126.4, 127.4, 127.5, 127.7, 128.4, 136.4, 138.4, 161.0, 161.5. Acceptable analytical data were not obtained for this compound.

3,6-Diiodopyridazine (67)[127]



A slurry of 3,6-dichloropyridazine (10.0 g, 67.1 mmol) and iodine monochloride (5.50 g, 33.9 mmol) in aqueous HI solution (50%, 50 mL) was heated at 80 °C for 24 h. The reaction mixture was poured into ice water (300 mL), neutralized with KOH (20%, 120 mL), and suction filtered. The precipitate was washed with H_2O (3 L), aqueous $Na_2S_2O_3$ solution (10%, 50 mL) and hexane (10 mL). The residue was recrystallized from EtOAc to afford **67** (17.0 g, 76%) as a light brown solid. M.p.=155-156 °C (lit.:[127] 157-158 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ=7.87 (s, 2H). ^{13}C NMR (DMSO-d_6, 75.5 MHz): δ=126.9, 138.3.

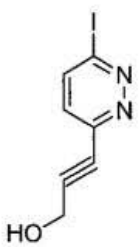
3-[3-(6-Iodopyridazin-3-yl)prop-2-ynyl]-1*H*-indole (68)



To a solution of **67** (332 mg, 1.00 mmol) in DMF (6 mL) was added Et_3N (3 mL), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.050 mmol) and CuI (10 mg, 0.053 mmol). The resulting mixture was stirred at room temperature for 20 min before a solution of **61** (155 mg, 1.00 mmol) in DMF (2 mL) was added to it. The reaction mixture was stirred for 4 h, treated with H_2O (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with H_2O (25 mL×2) and brine (25

mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (8% EtOAc/CH_2Cl_2) gave **68** (90 mg, 25%) as a white solid. M.p.=169-171 °C. IR (nujol) ν=3303 (s), 2242 (m), 1632 (w) cm^{-1}. MS *m/z* (%)=360 (18), 359 (100, M^+), 232 (34), 179 (30), 154 (17). ^1H NMR (DMSO-d_6, 500 MHz): δ=4.03 (s, 2H), 7.01-7.04 (m, 1H), 7.10-7.13 (m, 1H), 7.34-7.35 (m, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=8.7 Hz, 1H), 7.63 (d, *J*=7.9 Hz, 1H), 8.13 (d, *J*=8.7 Hz, 1H), 11.0 (bs, 1H). ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ=15.5, 77.1, 95.6, 108.0, 111.5, 118.3, 118.6, 121.3, 123.2, 125.0, 126.4, 130.7, 136.3, 136.7, 146.8. Anal. Calcd. for $C_{15}H_{10}IN_3$: C, 50.16; H, 2.81; N, 11.70. Found: C, 50.12; H, 2.71; N, 11.66.

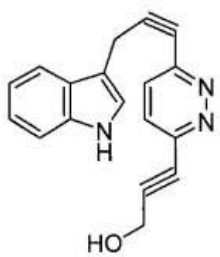
3-(6-Iodopyridazin-3-yl)prop-2-ynyl-1-ol (69)



To a solution of **67** (3.98 g, 12.0 mmol) and **66** (561 mg, 10.0 mmol) in DMSO (20 mL) was added diisopropylamine (10 mL), $Pd(PPh_3)_2Cl_2$ (211 mg, 0.301 mmol) and CuI (57 mg, 0.30 mmol). The resulting mixture was stirred at room temperature for 12 h, treated with H_2O (50 mL) and extracted with EtOAc (100 mL×3). The combined organic layers were washed with H_2O (200 mL×3) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Column

chromatography (5% MeOH/CH_2Cl_2) gave **69** (967 mg, 37%) as a light yellow solid. M.p.=120-122 °C. IR (nujol) ν=3258 (s), 2232 (m) cm^{-1}. MS *m/z* (%)=261 (8), 260 (90, M^+), 127 (23), 77 (72). ^1H NMR (DMSO-d_6, 500 MHz): δ=4.38-4.39 (m, 2H), 5.54-5.56 (m, 1H), 7.52 (d, *J*=8.6 Hz, 1H), 8.17 (d, *J*=8.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ=49.4, 80.0, 95.5, 125.5, 130.6, 136.9, 146.3. Anal. Calcd. for $C_7H_5IN_2O$: C, 32.33; H, 1.94; N, 10.77. Found: C, 32.22; H, 1.84; N, 10.31.

3-{6-[3-(1*H*-Indol-3-yl)prop-1-ynyl]pyridazin-3-yl}prop-2-yn-1-ol (64)

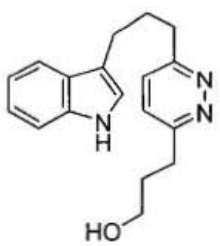


Method A. To a solution of **68** (40 mg, 0.11 mmol) in DMF (2 mL) was added Et_3N (1 mL), $Pd(PPh_3)_2Cl_2$ (4 mg, 0.006 mmol) and CuI (1 mg, 0.005 mmol). The resulting mixture was stirred at room temperature for 15 min before a solution of **66** (9.0 mg, 0.16 mmol) in DMF (0.5 mL) was added into it. The reaction mixture was stirred for 4 h, treated with H_2O (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with H_2O (25 mL×2) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (7% MeOH/CH_2Cl_2) gave **64** (19 mg, 59%) as a light brown solid. M.p. > 250 °C. IR (nujol) ν=3244 (s), 2242 (m), 2226 (m), 1660 (m)

cm^{-1}. MS *m/z* (%)=288 (21), 287 (100, M^+), 205 (10), 115 (8). ^1H NMR (DMSO-d_6, 500 MHz): δ=4.06 (s, 2H), 4.40 (d, *J*=5.6 Hz, 2H), 5.54 (t, *J*=5.7 Hz, 1H), 7.01-7.04 (m, 1H), 7.10-7.13 (m, 1H), 7.34-7.35 (m, 1H), 7.39 (d, *J*=8.1 Hz, 1H), 7.64 (d, *J*=7.7 Hz, 1H), 7.75-7.80 (m, 2H), 10.98 (bs, 1H). ^{13}C NMR (DMSO-d_6, 125.8 MHz): δ=15.5, 49.4, 77.7, 80.6, 95.4, 95.7, 108.1, 111.5, 118.3, 118.6, 121.3, 123.2, 126.4, 129.3, 129.4, 136.3, 144.9, 145.7. HRMS Calcd. for $C_{18}H_{13}N_3O$: 287.1058. Found: 287.1042.

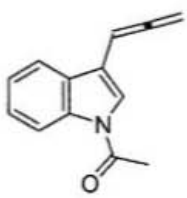
Method B. To a solution of **69** (260 mg, 1.00 mmol) in DMF (4 mL) was added Et_3N (2 mL), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.050 mmol) and CuI (10 mg, 0.053 mmol). The resulting mixture was stirred at room temperature for 15 min before a solution of **61** (171 mg, 1.10 mmol) in DMF (2 mL) was added into it. The reaction mixture was stirred for 4 h, treated with H_2O (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with H_2O (20 mL×2) and brine (20 mL×2), dried over $MgSO_4$, filtered and concentrated. Column chromatography (7% MeOH/CH_2Cl_2) gave **64** (174 mg, 61%) as a light brown solid.

3-{6-[3-(1*H*-Indol-3-yl)propyl]pyridazin-3-yl}propan-1-ol (43)



To a solution of **64** (120 mg, 0.418 mmol) in MeOH (50 mL) was added Pd/C (10%, 30 mg). The resulting black slurry was stirred under a H_2 atmosphere at room temperature for 4 h, suction filtered and concentrated. Column chromatography (10% MeOH/CH_2Cl_2) gave **43** (121 mg, 98%) as a light yellow oil. IR (KBr) v=3271 (s), 1620 (w), 1592 (w) cm^{-1}. MS *m/z* (%)=296 (2), 295 (5, M^+), 152 (100), 108 (27). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.01-2.06 (m, 2H), 2.16-2.22 (m, 2H), 2.85 (t, *J*=7.4 Hz, 2H), 3.00-3.06 (m, 4H), 3.17 (bs, 1H), 3.72 (t, *J*=6.1 Hz, 2H), 6.98-6.99 (m, 1H), 7.07-7.10 (m, 1H), 7.14-7.21 (m, 3H), 7.34 (d, *J*=8.2 Hz, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 8.33 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=24.6, 29.7, 31.6, 32.5, 35.5, 61.7, 111.1, 115.6, 118.7, 119.0, 121.6, 121.7, 126.7, 126.8, 127.4, 136.4, 161.0, 161.6. HRMS Calcd. for $C_{18}H_{21}N_3O$: 295.1683. Found: 295.1682.

1-Acetyl-3-allenyl-1*H*-indole (73)



To a slurry of NaH (480 mg, 12.0 mmol) in DMF (15 mL) was added dropwise a solution of **61** (1.55 g, 10.0 mmol). The resulting brown mixture was stirred at room temperature for additional 1 h, cooled to 0 °C, and acetyl chloride (2.36 g, 30.1 mmol) was injected into it. The reaction mixture was stirred for 12 h, treated with H_2O (5 mL) and extracted with EtOAc (50 mL×3). The combined

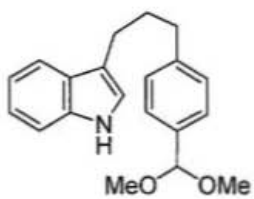
organic layers were washed with H_2O (50 mL×2), dried over Na_2SO_4, filtered and concentrated. Column chromatography (65% CH_2Cl_2/petroleum ether) gave **73** (789 mg, 40%) as a white wax. M.p.=67-69 °C. IR (nujol) ν=1935 (w), 1702 (s), 1660 (m), 1599 (w) cm^{-1}. MS *m/z* (%)=198 (7), 197 (44, M^+), 154 (100), 127 (30). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.61 (s, 3H), 5.24 (dd, *J*=6.8, 1.1 Hz, 2H), 6.32-6.35 (m, 1H), 7.25-7.39 (m, 3H), 7.95 (d, *J*=7.5 Hz, 1H), 8.42-8.44 (m, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=24.0, 78.6, 85.0, 115.3, 116.6, 120.0, 122.3, 123.7, 125.6, 128.9, 136.4, 168.2, 211.3. HRMS Calcd. for $C_{13}H_{11}NO$: 197.0840. Found: 197.0831.

4-[3-(1*H*-Indol-3-yl)prop-1-ynyl]benzaldehyde (77)

To a solution of **76** (740 mg, 4.00 mmol) in anhydrous THF (12 mL) was added Et_3N (6 mL), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.199 mmol) and CuI (38 mg, 0.20 mmol). The resulting orange slurry was stirred at room temperature for 15 min before a solution of **61** (745 mg, 4.80 mmol) in anhydrous THF (6 mL) was added to it. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, treated with H_2O (10 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Column chromatography (30%

EtOAc/petroleum ether) gave **77** (800 mg, 77%) as a light yellow solid. M.p.=124-125 °C. IR (nujol) ν=3427 (m), 2236 (w), 1692 (s), 1601 (m) cm^{-1}. MS *m/z* (%)=260 (19), 259 (100, M^+), 230 (31), 202 (16), 154 (17). ^1H NMR ($CDCl_3$, 500 MHz): δ=3.95 (s, 2H), 7.15-7.24 (m, 3H), 7.38 (d, *J*=8.0 Hz, 1H), 7.56 (d, *J*=7.8 Hz, 2H), 7.70 (d, *J*=7.7 Hz, 1H), 7.79 (d, *J*=7.8 Hz, 2H), 8.06 (bs, 1H), 9.97 (s, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=16.4, 80.6, 92.8, 110.9, 111.3, 118.7, 119.6, 122.0, 122.3, 126.7, 129.5, 130.3, 132.1, 135.1, 136.4, 191.5. HRMS Calcd. for $C_{18}H_{13}NO$: 259.0996. Found: 259.1017.

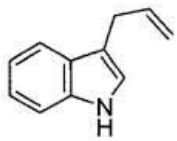
3-[3-(4-Dimethoxymethylphenyl)propyl]-1*H*-indole (78)



To a solution of **77** (50 mg, 0.19 mmol) in MeOH (10 mL) was added Pd/C (10%, 12 mg). The resulting black slurry was stirred under H_2 atmosphere at room temperature for 4 h, suction filtered and concentrated. Column chromatography (25% EtOAc/petroleum ether) gave **78** (35 mg, 60%) as a colorless oil. IR (KBr) ν=3424 (s), 1615 (m), 1582 (w) cm^{-1}. MS *m/z* (%)=310 (0.5), 309 (2, M^+), 277 (63), 262 (10), 130 (100). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.01-2.07 (m, 2H), 2.71 (t, *J*=7.6 Hz, 2H), 2.78 (t, *J*=7.6 Hz, 2H), 3.33 (s, 6H), 5.37 (s, 1H), 6.94 (s, 1H), 7.08-7.11 (m, 1H), 7.16-7.23 (m, 3H), 7.32-7.36 (m, 3H), 7.57 (d, *J*=7.8 Hz,

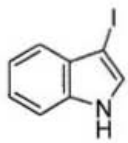
1H), 7.91 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=24.7, 31.6, 35.4, 52.7, 103.4, 111.0, 116.4, 118.9, 119.1, 121.1, 121.8, 126.6, 127.5, 128.3, 135.4, 136.3, 142.8. HRMS Calcd. for $C_{20}H_{23}NO_2$: 309.1728. Found: 309.1744.

3-Allyl-1*H*-indole (81)[149]



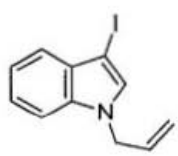
To a solution of **24** (14.1 g, 120 mmol) in anhydrous THF (100 mL) at 0 °C was added MeMgBr (3.0 M, 44 mL). The resulting brown solution was stirred at room temperature for 1 h and allyl bromide (17.4 g, 144 mmol) was injected into it neat at room temperature. The reaction mixture was stirred for 12 h, treated with first H_2O (20 mL) then HOAc (12 mL), concentrated and extracted with EtOAc (50 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL×3) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Vacuum distillation at 92-95 °C/0.5 mm Hg (lit.:[149] 94-98 °C/0.3 mm Hg) gave **81** (12.5 g, 66%) as a colorless oil. MS *m/z* (%)=158 (12), 157 (100, M^+), 130 (96), 103 (9). ^{1}H NMR ($CDCl_3$, 500 MHz): δ=3.51-3.53 (m, 2H), 5.05-5.08 (m, 1H), 5.14-5.18 (m, 1H), 6.03-6.11 (m, 1H), 6.96-6.97 (m, 1H), 7.09-7.12 (m, 1H), 7.17-7.20 (m, 1H), 7.33 (d, *J*=8.3 Hz, 1H), 7.60 (d, *J*=8.0 Hz, 1H), 7.89 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=29.8, 111.0, 114.5, 115.2, 119.1, 119.2, 121.6, 122.0, 127.4, 136.4, 137.3.

3-Iodo-1*H*-indole (82)[152]



To a slurry of **24** (11.7 g, 100 mmol) and freshly ground KOH powder (14.0 g, 250 mmol) in DMF (150 mL) at room temperature was slowly dropped a solution of I_2 (25.7 g, 101 mmol) in DMF (150 mL). The mixture was stirred for 1 h, poured into a cold NH_4OH (0.5%)- and $Na_2S_2O_5$ (0.1%)-containing aqueous solution (2 L) to afford a white precipitate. After the solvents were removed by suction filtration, the residue was washed with cold water (200 mL×3) and dried under vacuum until a constant weight was reached. The resulting **82**[152] (24.4 g, 100%) was obtained as a white solid, and was used for the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.19-7.27 (m, 3H), 7.35 (d, *J*=7.8 Hz, 1H), 7.46 (d, *J*=7.8 Hz, 1H), 8.30 (bs, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=57.6, 111.2, 120.8, 121.0, 123.2, 128.4, 129.8, 135.6.

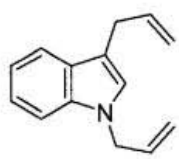
1-Allyl-3-iodo-1*H*-indole (83)



To a solution of **82** (2.43 g, 10.0 mmol) in CH_2Cl_2 (50 mL) was added freshly ground KOH powder (85%, 2.64 g, 40.0 mmol) to afford a brown slurry. The

slurry was stirred for 1 h at room temperature and treated with allyl bromide (1.50 g, 12.0 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (100% CH_2Cl_2) gave **83** (2.78 g, 98%) as a light yellow oil. IR (KBr) ν=1643 (m), 1610 (m) cm^{-1}. MS *m/z* (%)=284 (16), 283 (100, M^+), 242 (42), 156 (30), 115 (32). ^1H NMR ($CDCl_3$, 500 MHz): δ=4.70-4.72 (m, 2H), 5.09-5.14 (m, 1H), 5.21-5.23 (m, 1H), 5.92-6.00 (m, 1H), 7.17-7.21 (m, 2H), 7.22-7.28 (m, 2H), 7.42-7.46 (m, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=49.1, 55.6, 109.7, 117.9, 120.4, 121.2, 122.7, 130.5, 131.7, 132.9, 136.1. HRMS Calcd. for $C_{11}H_{10}IN$: 282.9860. Found: 282.9862.

1,3-Diallyl-1*H*-indole (80)

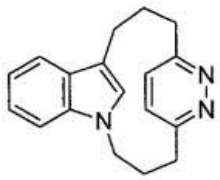


Method A. To a solution of **81** (9.43 g, 60.0 mmol) in THF (100 mL) was added freshly ground KOH powder (85%, 15.84 g, 240 mmol) to afford a brown slurry. The slurry was stirred for 1 h at room temperature and then treated with allyl bromide (11.22 g, 90.0 mmol). The resulting mixture was stirred at room temperature for 2 h, diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (50

mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (10% CH_2Cl_2/petroleum ether) gave **80** (8.22 g, 69%) as a clear, colorless oil. IR (KBr) ν=1639 (m), 1614 (m) cm^{-1}. MS *m/z* (%)=198 (16), 197 (100, M^+), 170 (59), 156 (41), 128 (26), 77 (14). ^1H NMR ($CDCl_3$, 500 MHz): δ=3.50-3.52 (m, 2H), 4.65-4.67 (m, 2H), 5.04-5.18 (m, 4H), 5.93-6.01 (m, 1H), 6.02-6.10 (m, 1H), 6.87 (s, 1H), 7.07-7.10 (m, 1H), 7.17-7.20 (m, 1H), 7.27-7.28 (m, 1H), 7.57-7.59 (m, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=29.8, 48.6, 109.5, 113.3, 115.0, 117.1, 118.8, 119.2, 121.5, 125.4, 128.0, 133.6, 136.6, 137.4. HRMS Calcd. for $C_{14}H_{15}N$: 197.1204. Found: 197.1215.

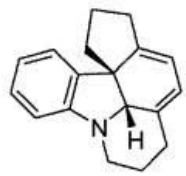
Method B. To a solution of *n*-BuLi (1.6 M in hexanes, 11 mL, 18 mmol) in anhydrous THF (30 mL) at –78 °C was injected **83** (2.26 g, 7.98 mmol) to afford a light yellow slurry. The slurry was stirred at –78 °C for 30 min and then treated with allyl bromide (5.99 g, 48.0 mmol). The mixture was slowly brought up to room temperature, and left for 1 h. The mixture was then treated with H_2O (20 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (10% CH_2Cl_2/petroleum ether) gave **80** (1.22 g, 77%) as a clear, colorless oil.

[3](1,3)Indolo[3](3,6)pyridazinophane (41)



Neat **80** (197 mg, 1.00 mmol) was treated with 9-BBN (0.5 M in THF, 12 mL, 6.0 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, treated with H_2O (180 mg, 10.0 mmol) and added to a solution of **67** (332 mg, 1.00 mmol), $Pd(PPh_3)_2Cl_2$ (140 mg, 0.20 mmol) and PPh_3 (105 mg, 0.40 mmol) in THF (150 mL). The mixture was heated to 50 °C and aqueous Cs_2CO_3 solution (2 M, 2 mL) was added to it. The brown slurry was heated at reflux for 12 h, concentrated, diluted with H_2O (20 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Preparative thin layer chromatography (5% MeOH/CH_2Cl_2) gave **41** (83 mg, 30%) as an orange oil. IR (KBr) ν=2239 (m), 1611 (w), 1592 (w), 1548 (m) cm^{-1}. MS *m/z* (%)=278 (10), 277 (41, M^+), 170 (20), 134 (31), 108 (100). ^1H NMR ($CDCl_3$, 500 MHz): δ=2.18-2.28 (m, 3H), 2.43-2.50 (m, 2H), 2.93-2.97 (m, 1H), 3.12-3.15 (m, 3H), 3.28-3.34 (m, 1H), 3.86-3.91 (m, 1H), 4.32-4.37 (m, 1H), 5.78 (s, 1H), 6.12 (d, *J*=8.5 Hz, 1H), 6.33 (d, *J*=8.6 Hz, 1H), 7.01-7.04 (m, 1H), 7.11-7.18 (m, 2H), 7.46 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=23.9, 26.7, 27.8, 35.1, 36.3, 46.2, 109.4, 114.1, 118.3, 119.2, 120.9, 123.9, 125.7, 126.5, 127.0, 134.0, 160.3, 161.9. HRMS Calcd. for $C_{18}H_{19}N_3$: 277.1578. Found: 277.1562.

(±)-(3a*S,10b*R**)-1,2,3,9,10,10b-Hexahydro-8*H*-cyclopenta[*d*]pyrido[1,2,3-*lm*]carbazole (92)**



Method A. A slurry of **41** (70 mg, 0.25 mmol) in mesitylene (2 mL) was heated at reflux for 10 d. Column chromatography (CH_2Cl_2) gave **92** (13 mg, 21%) as a brown oil. IR (KBr) ν=1705 (m), 1598 (m) cm^{-1}. MS *m/z* (%)=250 (9), 249 (48, M^+), 220 (100), 204 (14). ^1H NMR ($CDCl_3$, 500 MHz): δ=1.49-1.61 (m, 2H), 1.80-1.87 (m, 2H), 1.89-1.96 (m, 2H), 2.16-2.21 (m, 1H), 2.33-2.37 (m, 1H), 2.55-2.62 (m, 1H), 2.75-2.80 (m, 1H), 3.19-3.25 (m, 1H), 3.81-3.86 (m, 1H), 4.16 (s, 1H), 5.55-5.56 (m, 1H), 5.66-5.67 (m, 1H), 6.49 (d, *J*=7.8 Hz, 1H), 6.62-6.65 (m, 1H), 6.89-6.91 (m, 1H), 7.06-7.09 (m, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ=21.2, 22.2, 30.1, 32.2, 40.7, 44.9, 54.2, 72.1, 107.1, 115.1, 117.8, 119.6, 122.6, 127.7, 131.2, 137.9, 143.9, 149.1. HRMS Calcd. for $C_{18}H_{19}N$: 249.1517. Found: 249.1513.

Method B. A solution of **41** (15 mg, 0.054 mmol) in *N,N*-diethylaniline (0.5 mL) was heated at reflux for 2 d. Preparative thin layer chromatography (2.5% EtOAc/petroleum ether) gave **92** (12 mg, 90%) as a brown oil.

4.5 References

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CHAPTER 5 A Formal Total Synthesis of (±)-Strychnine by the Cyclophane Approach

5.1 Introduction

Prior to the discussion of a practical application of the cyclophane approach to a formal total synthesis of strychnine is detailed, the background regarding this complex heptacyclic indole alkaloid will be reviewed.

5.1.1 History of Strychnine

The indole alkaloids are defined as the natural products containing either the indole nucleus, or an oxidized, reduced or substituted equivalent of it.[1] With respect to their structural features, the indole alkaloids can be further divided into two major classes. The first class is that of the simple indole alkaloids without a structural uniformity, having only the indole nucleus or a direct derivative as a common feature. The second class, more complex indole alkaloids, have been additionally classified into several types according to their characteristic skeleta,[1] two of which, strychnan and aspidospermatan types, are refered to as *Strychnos* alkaloids on the basis of their biogenesis.[2,3] *Strychnos* alkaloids, structurally characterized by the presence of an unrearranged monoterpene unit, are one of the most populous classes of indole alkaloids.[4]

Different *Strychnos* species, a genus of South American plants, members of the family of *Loganiaceae*, are the source of curare, the notorious arrow and

dart poison of the South American Indians. The African and Asian plants serve as bases for the manufacture of the infamous poison strychnine **1** (Figure 5.1), the most celebrated *Strychnos* alkaloid, which has a long and mysterious history. First isolated in 1818 by Pelletier and Caventou[5] from the beans of *Strychnos ignatii*, strychnine was one of the first alkaloids obtained in pure form. It was shown to be a poison at the time of its isolation, and a dose of 50-100 mg is lethal for an adult human by a gradual conversion of respiratory system paralysis to asphyxiation.[6] Its renowned toxicity arises from the blocking of postsynaptic inhibition in the spinal cord and lower brain system where it antagonizes the neuronal receptor for glycine,[7] and this property has made strychnine an extremely useful pharmacological tool, as documented in many medicinal publications.

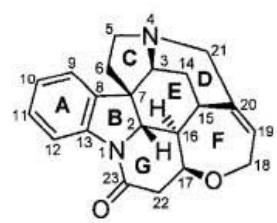


Figure 5.1 Structure of strychnine **1** with its biogenetic numbering and ring labeling.

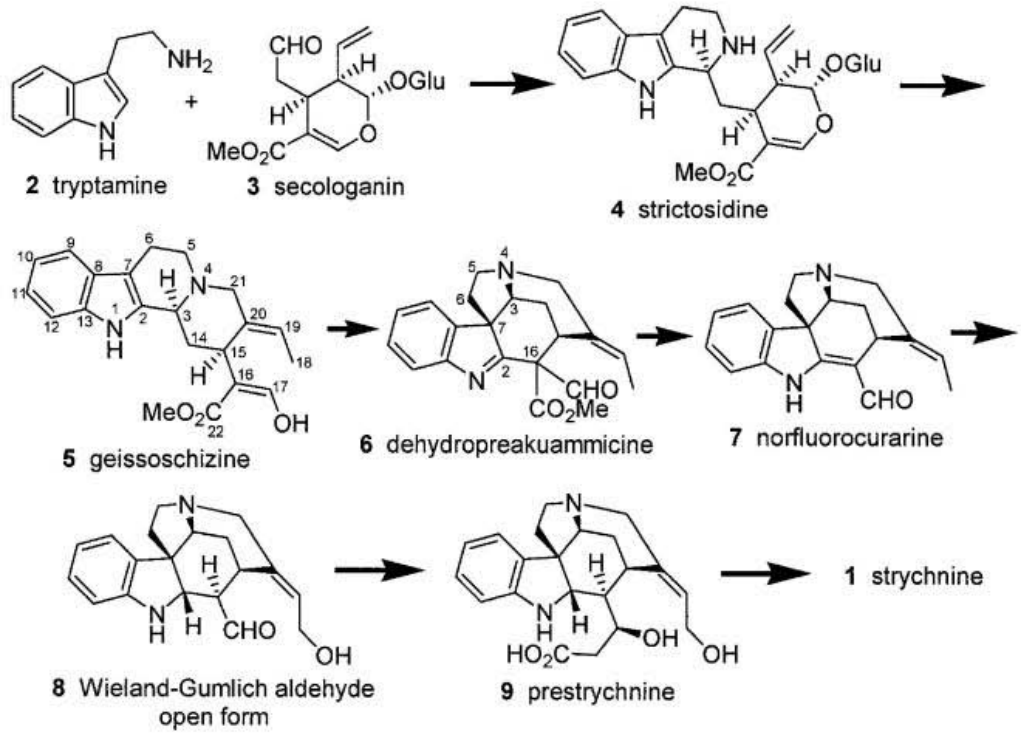
With its highly compact heptacyclic architecture assembled from only twenty-four skeletal atoms, strychnine earned the description by Robinson as the most complex substance known for its molecular size.[8] Its intricate structural complexity is also due to the presence of six contiguous asymmetric carbon

atoms, five of which are within one saturated six-membered ring (E ring). Given its exceedingly complex structure, it is not surprising that, since its isolation, over a century passed before strychnine's structure was finally determined by Woodward and Brehm in 1948.[9] The structure elucidation of strychnine depended heavily on the initial elemental analysis in 1838[10] and the following large number of degradative studies, before the advent of modern spectroscopic techniques, with major contributions from Leuchs and Robinson.[11,12] Two independent X-ray crystallographic investigations[13,14] provided its relative stereochemistry, and the absolute stereochemistry of strychnine, as shown in Figure 5.1, was established by a later X-ray crystal structure analysis in 1956.[15]

5.1.2 Biosynthesis of Strychnine

Based on extensive biogenetic studies on monoterpenoid indole alkaloids, the biosynthesis of strychnine is quite well understood (Scheme 5.1).[1,16] Monoterpenoid indole alkaloids contain two structural elements: tryptamine **2**, containing the indole nucleus, and a C_9 or C_{10}-monoterpene moiety from secologanin **3**. The enzymatically catalyzed Pictet-Spengler condensation of **2** and **3** initiates strychnine's biosynthesis to provide strictosidine **4**, a possible universal key intermediate in indole alkaloid biosynthesis. After a hydrolysis catalyzed by β-glucosidase, the aglycone of **4** undergoes a ring opening at the hemiacetal carbon to generate a very reactive dialdehyde, one component of which condenses with the free secondary amine to produce an iminium species,

dehydrogeissoschizine (structure not shown). Geissoschizine **5**, another widely recognized intermediate in indole alkaloid biosynthesis, is the result of a reduction of dehydrogeissoschizine in the presence of NADPH-containing enzymes.



Scheme 5.1 Biosynthesis of strychnine **1**.

The subsequent oxidative cyclization of **5**, followed by a skeletal rearrangement, establishes the characteristic framework of the *Strychnos* alkaloids in the resulting dehydropreakuammicine **6**, but the details of the processes remain unclear. After a decarboxylation to lose C22, the C_{10}-monoterpene unit in **6** leads to a C_9-monoterpene unit in norfluorocurarine **7**,

which, upon an unknown ordered sequence of hydroxylation at C18 and reduction of the enamine double bond, arrives at the open form of the Wieland-Gumlich aldehyde **8**, a common precursor to many *Strychnos* alkaloids. The unique part of strychnine's biosynthesis is the involvement of prestrychnine **9**, a compound with two extra carbon atoms compared to **8**. These carbon atoms, C22 and C23 of strychnine (Figure 5.1), originate from acetic acid, as first suggested by Robinson. The validity of the hypothesis was implied by his attempts to degrade strychnine to **8** and then re-synthesize strychnine by condensation with acetic acid because "that is the way the plant does it, and that is the way I want to do it".[17] The process, proven by Schlatter in 1969,[18] occurs by an aldol condensation involving acetyl-CoA to afford **9**, which undergoes two successive ring closures to furnish strychnine. Considering the significant influence of strychnine's biosynthesis on its chemical synthesis (*vide infra*), the biogenetic numbering and ring labeling (Figure 5.1) is used throughout this chapter.

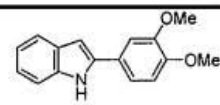
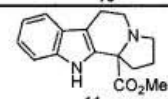
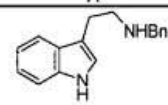
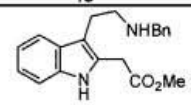
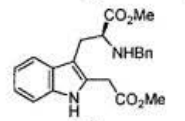
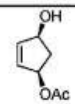
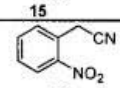
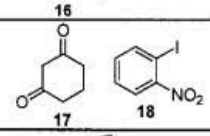
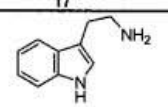
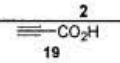
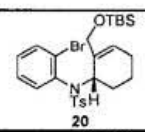
5.1.3 Chemical Synthesis of Strychnine

5.1.3.1 Overview

The ingenuity of organic chemists has been stretched not only during the unraveling of the details of indole alkaloid structures, but also especially in the pursuit of the synthesis of these complex, naturally occurring compounds. Strychnine, one of the most complex natural products of its molecular size, has fascinated organic chemists for almost two centuries since its isolation in 1818.[5]

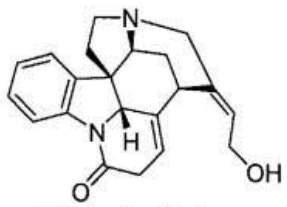
The classical total synthesis of strychnine by Woodward[19,20] in 1954 represents a landmark in the field of total synthesis and remained the sole successful approach to this complex heptacyclic compound for about four decades until this spectacular feat was achieved again by Magnus in 1992.[21,22] Almost simutaneously, Stork[23] disclosed another synthesis at the Ischia Advanced School of Organic chemistry in Italy. However, this work has not been published in a peer-reviewed journal. Kuehne subsequently accomplished the synthesis of strychnine twice once in 1993[24] and once 1998,[25] using the same fundamental approach, but different precursors. The first asymmetric synthesis of strychnine was reported by Overman[26,27] in 1993, which afforded both the natural enantiomer, (−)-strychnine and the dextro isomer, (+)-strychnine. Shortly afterwards, Rawal[28] communicated a very concise synthesis of strychnine, which still remains the one with the highest overall yield reported to date. More recently, Bonjoch/Bosch[29,30] and Martin[31] have independently completed two formal syntheses of strychnine based on Overman's intermediates.

Table 5.1 General features of strychnine syntheses

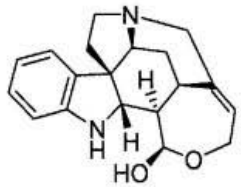
Main Author	Year [a]	Overall Yield [b]	Length (steps) [c]	Starting Material(s)	Direct Precursor
Woodward	1954	0.00006%	28	 10	isostrychnine
Magnus	1992	0.034%	27	 11	Wieland-Gumlich aldehyde
Stork	1992	—	15	 12	Wieland-Gumlich aldehyde
Kuehne	1993 1998*	1.4% (1993) 5.3% (1998)	17 (1993) 14 (1998)	 13 (1993)  14 (1998)	isostrychnine (1993) Wieland-Gumlich aldehyde (1998)
Overman	1993*	3.2%	24	 15	Wieland-Gumlich aldehyde
Rawal	1994	10%	15	 16	isostrychnine
Bonjoch/ Bosch	1999*	0.15%	15	 17 18	Wieland-Gumlich aldehyde
Martin	2001	1.0%	16	 2	Wieland-Gumlich aldehyde
Vollhardt	2000	0.56%	14	 19	isostrychnine
Mori	2002	0.17%	21	 20	isostrychnine

[a] The syntheses marked with a "*" are asymmetric ones. [b] The overall yield is calculated based on the starting material(s) claimed by the authors and the highest yield is listed if multiple routes are available. [c] The total steps are counted according to the longest linear sequence.

Parallel to the synthetic efforts toward strychnine, two excellent reviews, first in 1994[32] and then in 2000,[33] covered the most fruitful achievements including Woodward's pioneering work.[19,20] However, the sustained interest and endeavour in pursuit of this attractive synthetic target revealed two more recent formal total syntheses, one by Vollhardt[34,35] and another by Mori,[36] published at the beginning of the twenty first century.



21 isostrychnine



22 Wieland-Gumlich aldehyde

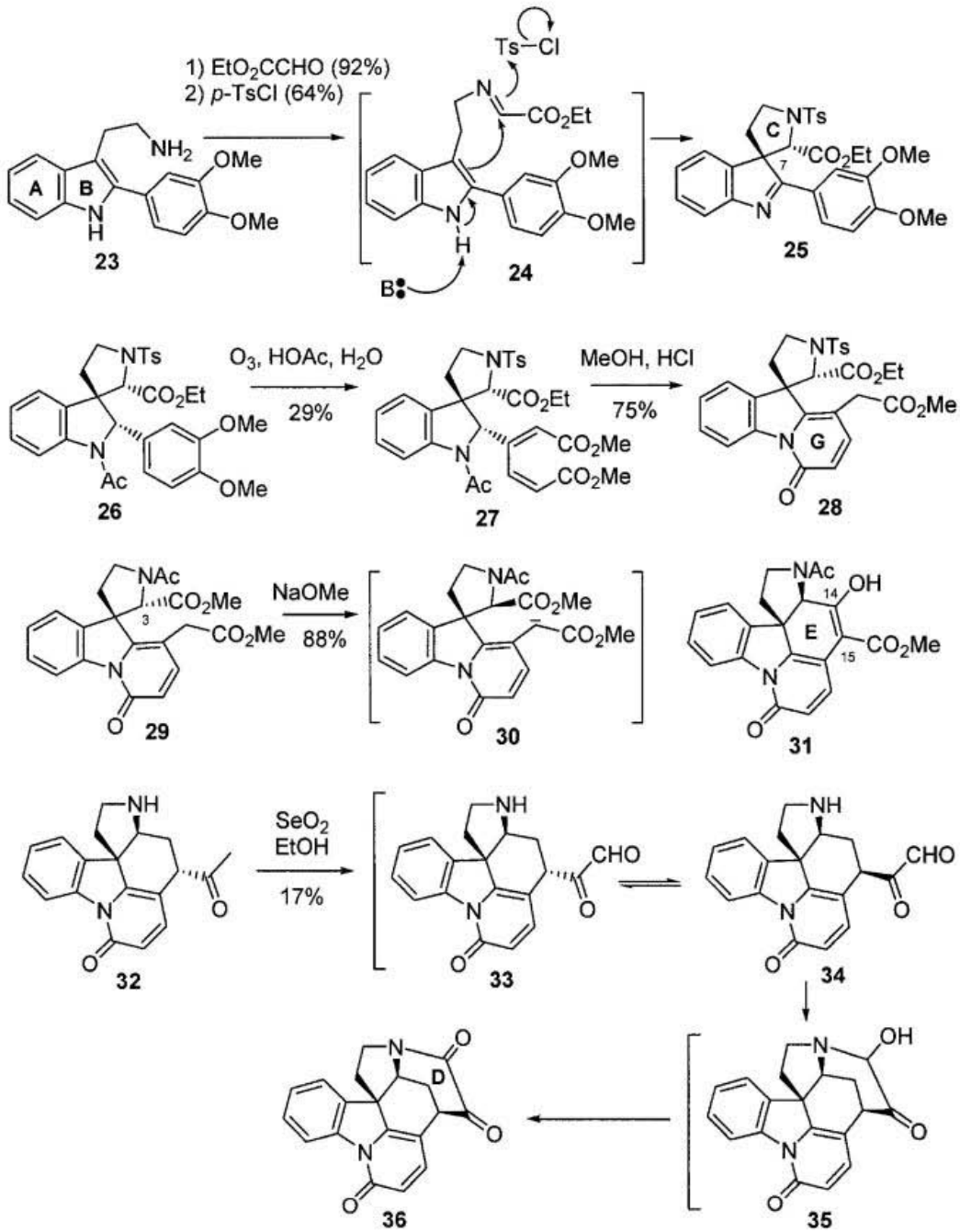
Figure 5.2 Structures of isostrychnine **21** and Wieland-Gumlich aldehyde **22**.

The general features of previously reported syntheses of strychnine, including the year that they were reported, the starting material(s) employed, the direct precursors to strychnine, the length of the synthetic sequence and the overall yields, are summarized in Table 5.1. Interestingly, all of the syntheses reported so far have used either isostrychnine **21** or the Wieland-Gumlich aldehyde **22** (Figure 5.2) as the direct precursor for the final product. Both of these compounds were directly correlated with strychnine by degradative investigations. Isostrychnine **21** was obtained as the major product from a base- or acid-treatment of strychnine. Its formation involves a retro Michael addition and a double bond migration.[37,38] It was converted back to strychnine by Prelog in 1948,[39] with a yield of 20% when subjected to hot, alcoholic potassium

hydroxide. The Wieland-Gumlich aldehyde **22**, another degradation product of strychnine, was isolated before isostrychnine **21**.[40,41] However, its conversion into strychnine, albeit in a higher yield of 68%, was first reported in 1953,[42] which was later than that of isostrychnine **21** and around the same time when strychnine was first chemically synthesized. The key features of the individual synthesis will be highlighted in the following sections.

5.1.3.2 Woodward's Synthesis

Woodward's precise foresights, adventurous manipulations and artistic strategies are incisively and vividly exhibited in his historic synthesis of strychnine,[19,20] which was accomplished at a time when organic synthesis was far less mature than it is today. Even to such an undebated master of organic chemistry, this achievement clearly filled Woodward with incredible excitement, who wrote "Strychnine!" as the first sentence of the full paper, which was published in 1963.[20] In terms of ring assembly, Woodward's strategy is rather straightforward with a single ring constructed at each key stage. This can be described as an A→AB→ABC→ABCG→ABCEG→ABCDEG→ABCDEFG sequence (Scheme 5.2).



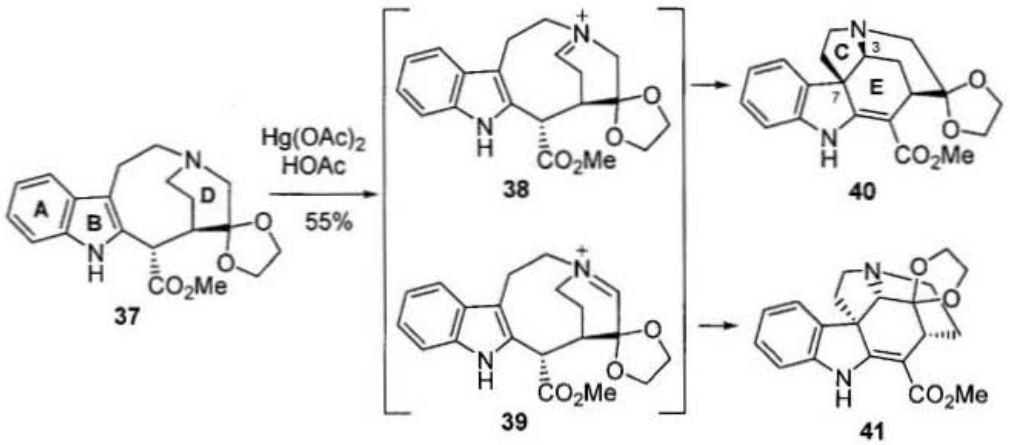
Scheme 5.2 Highlights of Woodward's synthesis.

Starting from the AB ring-containing 2-veratrylindole **10** (Table 5.1), which was readily available through a Fischer indole synthesis between phenylhydrazine and acetoveratrone,[43] the crucial spirocenter at C7 along with the C ring were established by a Mannich cyclization of Schiff base **24**. This was the condensation product of tryptamine derivative **23** and ethyl glyoxylate. Compound **25** was obtained as the sole product. Strongly influenced by his own hypothesis about strychnine's biogenesis,[44] Woodward then elaborated on the veratryl moiety in **26** by ozonolysis and a subsequent hydrolysis-lactamization-isomerization sequence to afford **28** with the G ring formed. Ring E was then generated by a sequential epimerization at C3 and Dieckmann condensation of compound **29**, forming the C14-C15 bond in the product **31**. A remarkable cascade oxidation of **32** by using SeO_2 constructed the D ring in structure **36**, which, in turn, led to isostrychnine **21** *via* an allylic isomerization. Finally, the F ring was formed by the known procedure of converting **21** to strychnine.[39]

5.1.3.3 Magnus' Synthesis

Based on the synthetic strategy developed by Harley-Mason,[45,46] Magnus successfully applied a transannular iminium ion cyclization in his synthesis of strychnine in 1992,[21,22] which was the first synthesis *via* the Wieland-Gumlich aldehyde. Magnus' synthesis started with tetracyclic amine **11** (Table 5.1), a compound previously used in a total synthesis of vinblastine,[47] and the rings were assembled by a sequence of AB→ABD→ABCDE→ABCDEF→ABCDEFG,

where the ABD→ABCDE conversion was achieved by a transannular oxidative cyclization (Scheme 5.3).

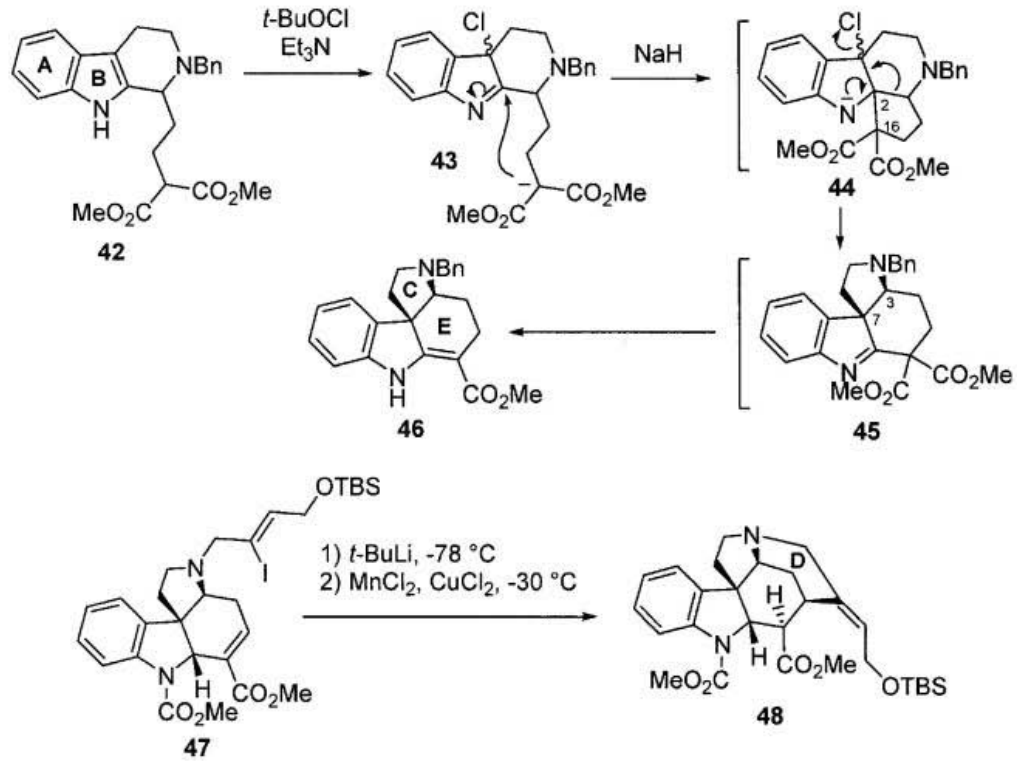


Scheme 5.3 Highlights of Magnus' synthesis.

A chloroformate-induced fragmentation of **11** installed the nine-membered ring system required for the desired transannular process, and the D ring in **37** was accomplished by an efficient intramolecular conjugate addition. The key reaction, transannular cyclization of the *in situ* generated iminium salt **38**, was realized with an excellent regiocontrol of 17:1 in favor of the desired pentacyclic product **40** (55% combined yield with **41**). Two rings, C and E, together with the spirocenter C7, were simultaneously constructed by a C7-C3 bond formation, taking advantage of the nucleophilicity of indole's enamine β-carbon. Subsequent synthetic operations were required to introduce the F ring in Wieland-Gumlich aldehyde **22**, and the final achievement of strychnine followed the reported protocol with malonic acid,[42] thereby establishing the G ring.

Despite the laborious sequence (the 27-step synthesis is negligibly shorter than Woodward's 28-step route completed in 1954), a general synthetic strategy for synthesis of *Strychnos* alkaloids was demonstrated and the overall yield (0.034%) was improved by a factor of 1000 over Woodward's synthesis.

5.1.3.4 Stork's Synthesis



Scheme 5.4 Highlights of Stork's synthesis.

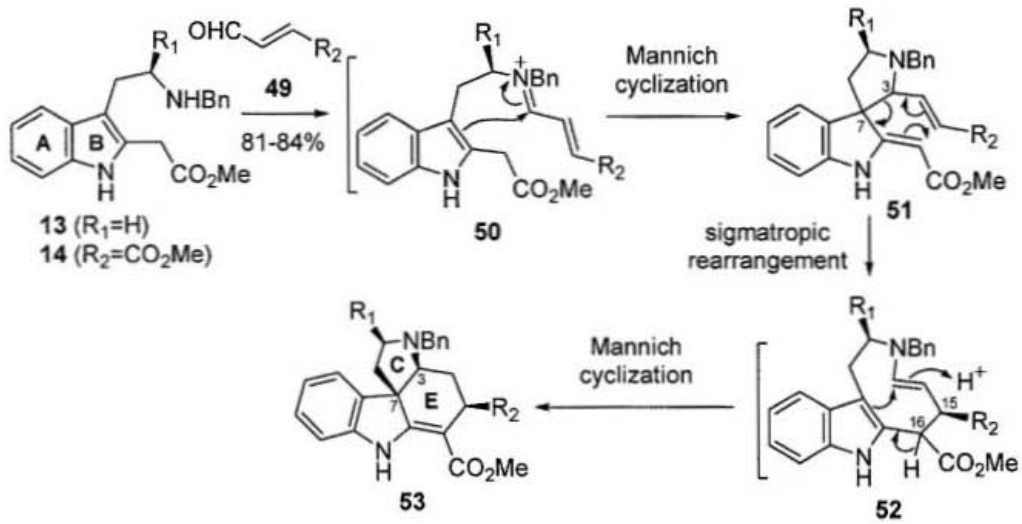
In Stork's synthesis,[23] the rings were created in the order of AB→ABCE→ABCDE→ABCDEF→ABCDEFG. Starting from N_b-benzyltryptamine **12** (Table 5.1), a Pictet-Spengler condensation gave compound

42, which was ready for a sequence of oxidative cyclization and subsequent skeletal rearrangement (Scheme 5.4). Initially, chloroindolenine **43** was formed by the action of *t*-BuOCl on **42**, and this subsequently underwent an intramolecular imine cyclization to form the C2-C16 bond in **44** and a skeletal rearrangement to connect C3 to C7, thus introducing the spirocenter C7 in **45**. Tetracycle **46** was ultimately produced by the simultaneous closure of the C and E rings from such a sequence. Another noteworthy ring assembly was that of the D ring in **48** by an intramolecular conjugate addition of a vinyl organometallic species derived from **47**. The F and G rings in the target were constructed in a similar manner to that of Magnus' synthesis (*vide supra*). Stork's synthesis followed the previously developed methodology of an oxidative cyclization/skeletal rearrangement sequence.[48] Although one of the key steps, intramolecular conjugate addition, suffered from a poor yield (~35%),[33] the sequence was significantly shorter (15 steps) than Woodward's (28 steps) and Magnus' (27 steps) syntheses.

5.1.3.5 Kuehne's Syntheses

As an extension of the general pyrrolocarbazole approach to both strychnan[49-51] and aspidospermatan[52-54] types of *Strychnos* alkaloids, strychnine was twice synthesized by Kuehne, in 1993[24] *via* isostrychnine and in 1998[25] *via* the Wieland-Gumlich aldehyde. Both of these syntheses employed a tandem Mannich-sigmatropic rearrangement-Mannich cyclization process (Scheme 5.5).

The ring systems were sequentially established as AB→ABCE→ABCDE→ABCDEG→ABCDEFG in the 1993 isostrychnine approach and AB→ABCE→ABCDE→ABCDEF→ABCDEFG in the 1998 Wieland-Gumlich aldehyde approach.



Scheme 5.5 Highlights of Kuehne's syntheses.

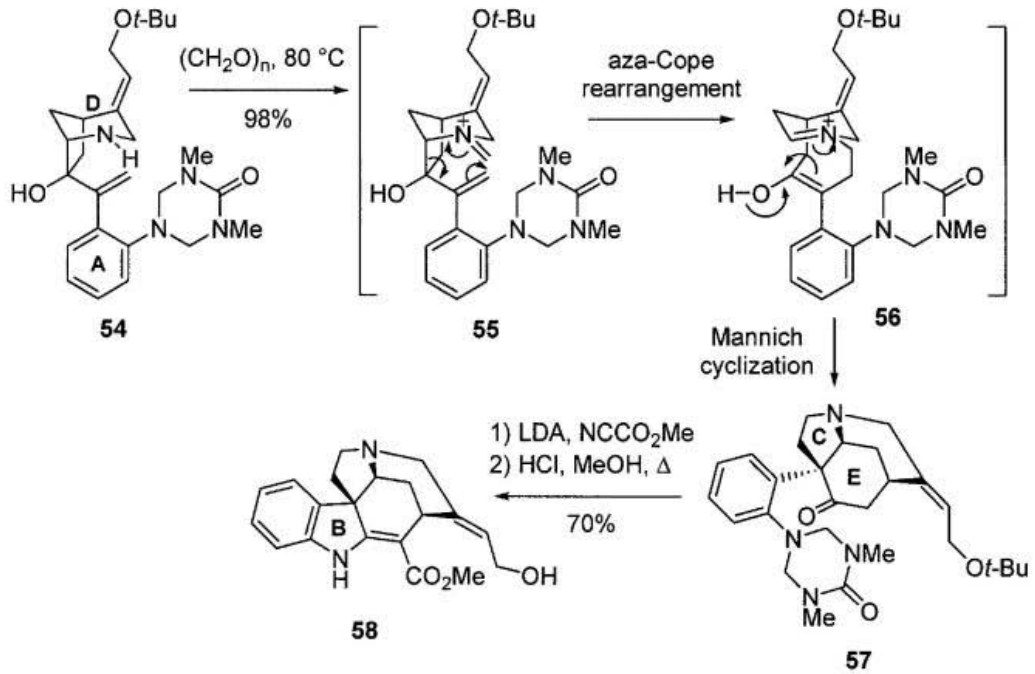
The two syntheses differ by the divergence of the common pyrrolocarbazole intermediate **53** into their respective precursors. In the tandem processes, readily available starting materials **13**[55] and **14**[25] were initially condensed with aldehyde **49** to give iminium species **50**, in which the first Mannich cyclization occurred to form the C7-C3 bond in **51**. The following sigmatropic rearrangement of **51** generated the C15-C16 bond to afford **52**. The final step of the sequence, the second Mannich cyclization, was promoted by acidic conditions to re-form the C7-C3 bond that was broken during the previous

rearrangement. Rings C and E were thereby permanently fixed within the structure of **53**. Compound **13** was used as the starting material in the racemic synthesis of strychnine in 1993.[24] The ester group of **14** derived from tryptophan, which was removed by a three-step sequence right after the desired tandem process, was exploited to introduce the absolute stereochemistry, thus furnishing an enantioselective synthesis in 1998.[25] In both syntheses, ring D was constructed by an intramolecular electrophilic *N*-alkylation, whereas the F and G rings were closed in different orders according to the direct strychnine precursors that were pursued. Kuehne not only synthesized strychnine twice *via* different, albeit related, routes but also improved the overall yield (1.4% in 1993 and 5.3% in 1998) by a factor of 100,000 compared to Woodward's synthesis!

5.1.3.6 Overman's Synthesis

Overman's tandem cationic aza-Cope rearrangement-Mannich cyclization protocol, based on the observation that the presence of a charged atom in a molecule undergoing bond reorganization can substantially reduce the required activation energy, has been extensively employed in the synthesis of complex alkaloids.[56] This strategy also found a beautiful application in an asymmetric synthesis of strychnine,[26,27] which led to both natural (–)-strychnine and unnatural (+)-strychnine. The source of chirality for Overman's synthesis was optically pure compound **15** (Table 5.1), which could be obtained in high enantiomeric purity on a large scale from the enzymatic hydrolysis of *cis*-1,4-

diacetoxycyclopentene with electric eel acetylcholinesterase.[57] The rings were installed by a sequence of A→AD→ACDE→ABCDE→ABCDEF→ABCDEFG, where the key tandem transformation took place in AD→ACDE conversion (Scheme 5.6).

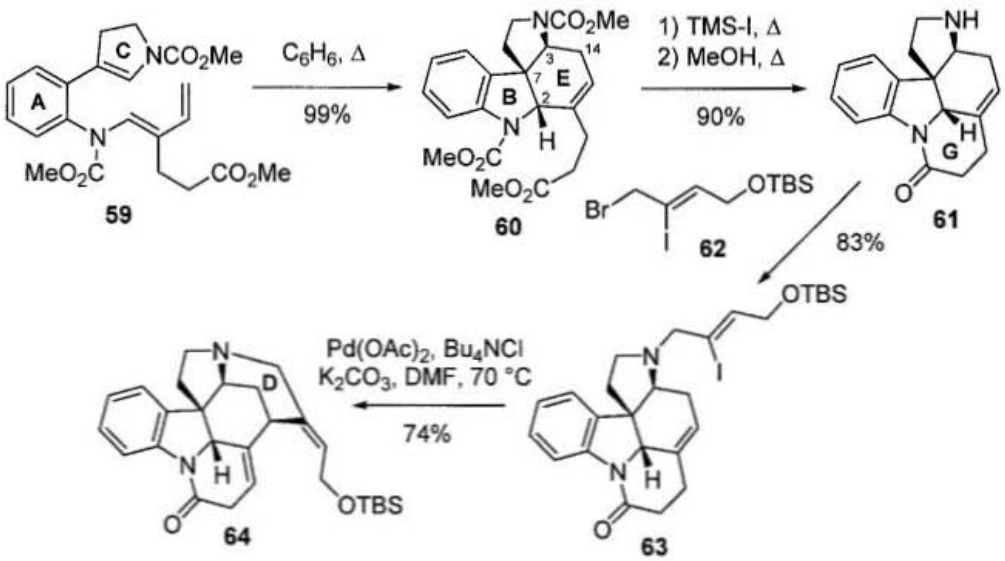


Scheme 5.6 Highlights of Overman's synthesis.

Rings A and D were put into place by two successive Pd-catalyzed coupling reactions. The remarkable tandem aza-Cope rearrangement-Mannich cyclization sequence of **54** proceeded in a desired fashion with extremely high efficiency (98%) to afford pentacyclic diamine **57**, which possessed the C and E ring system in strychnine. The resulting compound **57** was immediately first methoxycarbonylated using Mander's reagent[58] and subsequently treated with

methanolic HCl to hydrolyze both the triazone and *t*-butyl protecting groups with a spontaneous construction of B ring in **58** through enamine formation. Overman's synthesis was the first asymmetric route to strychnine, featuring a powerful tandem transformation and an impressively high overall yield (3.2%) considering the relatively long sequence (24 steps).

5.1.3.7 Rawal's Synthesis



Scheme 5.7 Highlights of Rawal's synthesis.

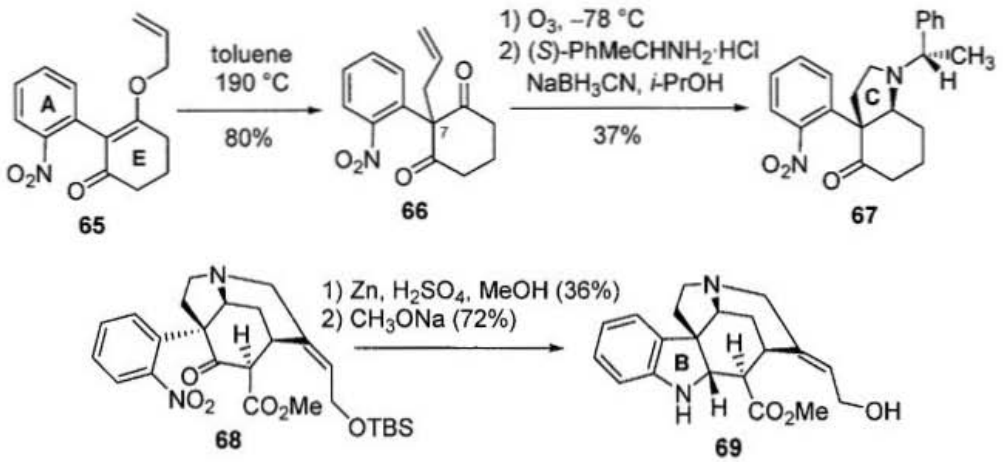
In 1994, Rawal[28] published a short and stereocontrolled synthesis of strychnine *via* isostrychnine, in which the core ring system was assembled by the A→AC→ABCE→ABCEG→ABCDEG→ABCDEFG sequence. The synthesis relied on the general strategy developed in the synthesis of pentacyclic strychnan skeleton.[59-61] Commencing with commercially available 2-

nitrophenylacetonitrile **16** (Table 5.1), a five-step sequence with an overall yield of 79%, which involved a highly efficient ring expansion, was effected to install the C ring in **59** (Scheme 5.7). A thermally-induced intramolecular Diels-Alder reaction of triene **59** proceeded in nearly quantitative yield (99%) to give compound **60**, in which the B and E rings were established upon bond formations between C2-C7 and C3-C14. After the deprotection of the two methoxycarbonyl groups of **60** by treatment with TMS-I, the resulting diamine underwent a lactamization, thus furnishing the G ring (90%). Due to the instability of **61**, it was immediately allylated with allylic bromide **62**. The vinyl iodide moiety of the resulting pentacycle **63** (83%) was then exploited to introduce the D ring in **64** by an intramolecular Heck reaction, which proceeded with complete stereocontrol in 74% yield. In spite of the less efficient isostrychnine→strychnine ending as compared to the Wieland-Gumlich aldehyde route, Rawal achieved a remarkable overall yield of 10%, which is still the highest of all of the syntheses reported to date.

5.1.3.8 Bonjoch/Bosch's Synthesis

As the culmination of studies on *Strychnos* alkaloid synthesis,[62] Bonjoch and Bosch published an enantioselective approach to strychnine.[29,30] Similar to Woodward's synthesis, the construction of the skeleton involved the establishment of just one ring in each key stage (A→AE→ACE→ACDE→ABCDE→ABCDEF→ABCDEFG). The synthesis

used commercially available 1,3-cyclohexanedione **17** and 1-iodo-2-nitrobenzene **18** as the starting materials and featured two reductive aminations as key reactions (Scheme 5.8).

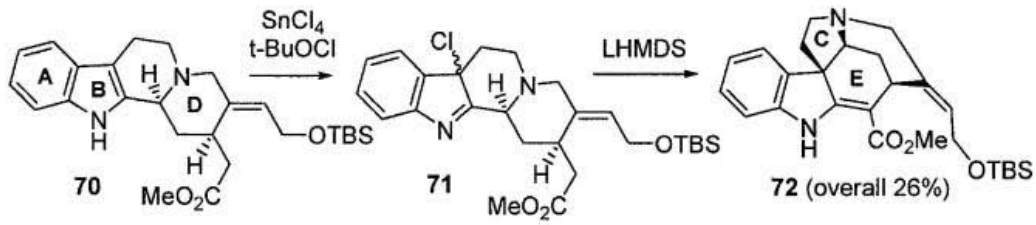


Scheme 5.8 Highlights of Bonjoch/Bosch's synthesis.

Different from all other approaches, the generation of C7 spirocenter in **66** (80%) was not associated with any ring closure. Instead, it was generated by a Claisen rearrangement of compound **65**. After the double bond of **66** was ozonolyzed, an asymmetric double reductive amination using an enantiomerically pure chiral amine created the C ring in compound **67** (37%). Another reductive amination of **68** at a later stage went through Overman's intermediate **58** (Scheme 5.6). The following base-promoted epimerization of the resulting compound furnished **69**, another intermediate that appeared in Overman's synthesis.[26,27] The poor overall yield of 0.15% could be attributed primarily to the low efficiency of the two reductive amination processes (37% and 36% as

shown in Scheme 5.8). Nevertheless, a new general entry to *Strychnos* alkaloids was established.

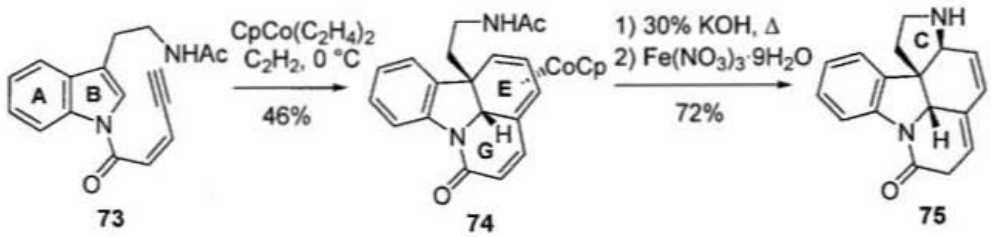
5.1.3.9 Martin's Synthesis



Scheme 5.9 Highlights of Martin's synthesis.

In 1996, Martin developed a new synthetic strategy to the synthesis of *Strychnos* alkaloids,[63] which led to a biomimetic synthesis of strychnine in 2001[31] *via* the Wieland-Gumlich aldehyde. Rings were assembled as AB→ABD→ABCDE→ABCDEF→ABCDEFG, in which the transformation of ABD→ABCDE is shown in Scheme 5.9. The tandem oxidative cyclization/skeletal rearrangement of **70**, involving chloroindolenine species **71**, resembled the key transformation in Stork's synthesis (*vide supra*) and installed the C and E rings at same time. The synthesis was accomplished in a concise manner (16 steps starting from tryptamine) and in respectable overall yield of 1.0%.

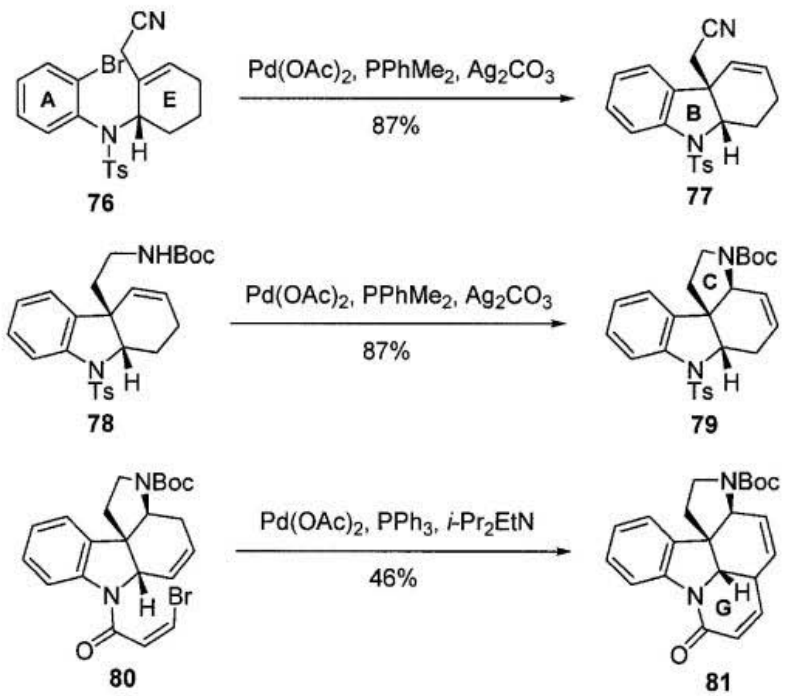
5.1.3.10 Vollhardt's Synthesis



Scheme 5.10 Highlights of Vollhardt's synthesis.

Cobalt-mediated [2+2+2] cycloadditions can proceed effectively when one of the 2π components is the indole enamine double bond.[64-66] Based on this well-developed methodology, Vollhardt finally in 2000[34,35] accomplished a formal total synthesis of strychnine *via* isostrychnine, in which the skeleton was constructed in the AB→ABCE→ABCEG→ABCDEG→ABCDEFG sequence. Starting with propiolic acid **19** (Table 5.1), a five-step sequence provided an acid chloride, which reacted with N^{10}acetyltryptamine to give **73** in 78% yield (Scheme 5.10). This compound then underwent a cobalt-mediated [2+2+2] cycloaddition in 46% yield to afford the organometallic species **74**, assembling the E and G rings simutaneously. Closure of the C ring occurred upon oxidative demetalation of the primary amine derived from **74** to generate pentacycle **75** in a formal [1,8]-conjugate addition. Ring D was constructed by either a radical cyclization to achieve one of Rawal's intermediates, or an intramolecular Heck reaction to give one of Woodward's intermediates. Being just 14 steps from propiolic acid to strychnine, Vollhardt's synthesis constituted the shortest route to strychnine reported to date.

5.1.3.11 Mori's Synthesis



Scheme 5.11 Highlights of Mori's synthesis.

Most recently, Mori published another enantioselective synthesis of strychnine *via* isostrychnine.[36] Relying on methodological studies of Pd-catalyzed asymmetric allylic substitution,[67,68] the initial application of this methodology in the synthesis of *Strychnos* alkaloids led to the enantioselective preparation of dehydrotubifoline and tubifoline.[69] One year later, the same strategy was employed to conquer strychnine, in which the framework was established by addition of one ring at each stage in a sequence of A→AE→ABE→ABCE→ABCEG→ABCDEG→ABCDEFG. The synthesis

commenced with enantiomerically pure compound **20** (Table 5.1), which was prepared by a Pd-catalyzed asymmetric allylic substitution in the presence of a chiral ligand in 80% yield and 84% ee. Compound **20** served as the source of chirality. A few transformations gave nitrile **76**, which in turn underwent an intramolecular Heck reaction to construct the B ring in **77** (87%) (Scheme 5.11). Ring C was created by another Pd-catalyzed coupling reaction of **78** with complete diastereocontrol to afford tetracycle **79** (87%). Ring G in **81** was again installed by an intramolecular Heck reaction of **80** in 46% yield. Assembly of the D ring followed similar lines to Rawal's and Vollhardt's syntheses (*vide supra*). The uniqueness of Mori's synthesis is the extensive use of Pd-catalyzed reactions. Except for the F ring construction in the conversion of isostrychnine to strychnine,[39] each of ABCDEG rings was put into place by a Pd-catalyzed reaction.

5.1.3.12 Summary

The variety of chemistry exhibited in successful[19-31,34-36] as well as attempted[70-75] syntheses of strychnine, is truly remarkable. It is no exaggeration to say that strychnine synthesis is a microcosm of total synthesis, encompassing everything from conventional organic transformations to modern synthetic operations, from single step reactions to tandem multistep processes, from consecutive routes to convergent pathways, from racemic preparations to asymmetric syntheses with chirality derived from either enzymatic

desymmetrization, starting material or catalyst ligand, and also from sequences designed by retrosynthetic analysis to approaches based on biogenetic studies. The complexity of the strychnine framework continues to fascinate organic chemists, who are thrilled to pursue challenging synthetic targets. The remainder of this chapter will describe a further contribution to the strychnine history: a formal total synthesis of (±)-strychnine by the "cyclophane approach".

5.2 Results and Discussion

5.2.1 Retrosynthetic Analysis

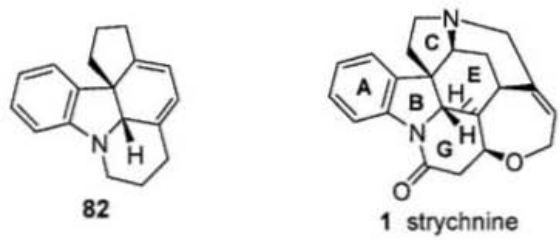
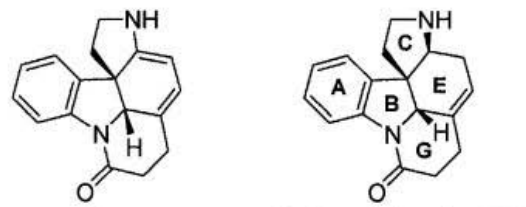


Figure 5.3 Structural similarity between pentacycle **82** and strychnine **1**.

As detailed in Chapter 4, the transannular IEDDA reaction in an indolopyridazinophane system, followed by a retro Diels-Alder reaction to release nitrogen gas, was shown to provide facile access to a compact pentacyclic indoloid skeleton **82** (Figure 5.3). By comparing the structures of pentacycle **82** and strychnine **1**, it is immediately evident that the molecular skeleton of **82** possesses striking similarities to the ABCEG core of the strychnine framework. Moreover, the relative stereochemistry between the two asymmetric centers in **82** corresponds perfectly with that between C2 and the

crucial C7 spirocenter in strychnine **1**. This close structural resemblance, coupled with an interest in the search for applications of cyclophane methodology in natural product synthesis, stimulated work aimed at a total synthesis of strychnine **1** based on the transannular IEDDA strategy in cyclophane systems. By examining the structural difference between **82** and **1**, the nitrogen atom at the 4 position and the lactam oxygen atom bonded to C23 stood out as the key structural elements that needed to be incorporated in a potential strychnine precursor.



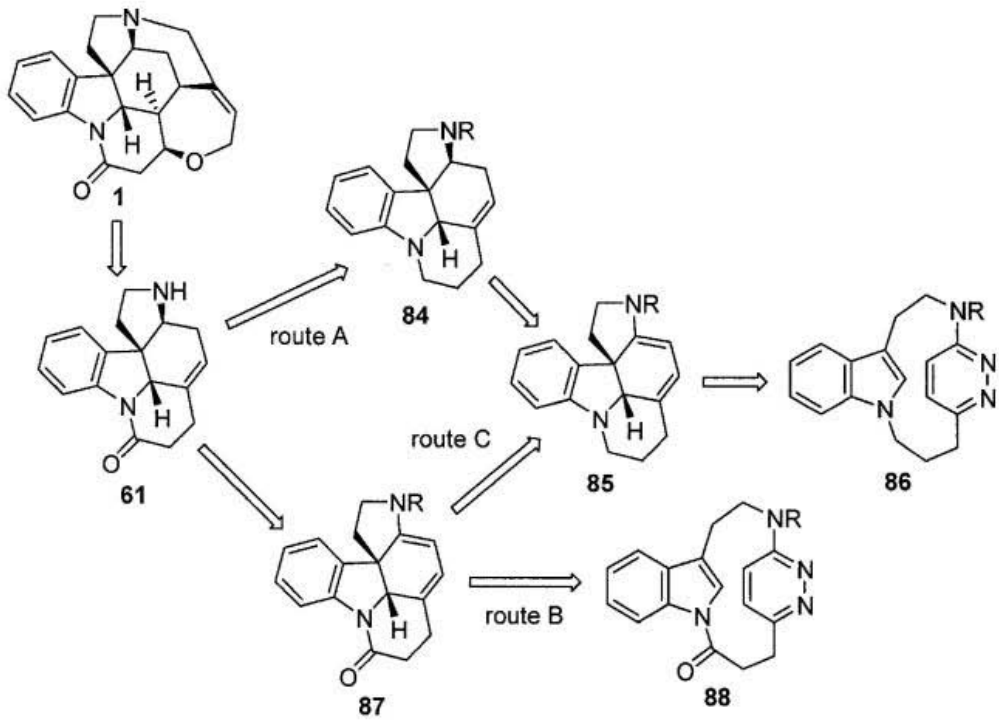
83 **61** Rawal's key ABCEG intermediate

Figure 5.4 Structural similarity between modified pentacycle **83** and Rawal's key ABCEG intermediate **61**.

When these modifications were applied to structure **82**, another pentacyclic compound **83** resulted (Figure 5.4). The presence of a secondary enamine, which is known to be a particularly reactive group,[76-78] immediately caused concern about the stability of this compound. Thus the nitrogen atom in question required protection during the key transannular IEDDA reaction. Since the β-carbon of the enamine function in **83** corresponds to strychnine's C14, an unsubstituted sp^3 center, a chemoselective and stereoselective reduction of the protected enamine double bond was identified as a logical transformation to

directly follow the transannular IEDDA reaction. The achievement of good chemoselectivity was anticipated to be viable because the two conjugated double bonds in **83** are considerably more differentiated than those in **82** due to the presence the nitrogen atom. A stereoselective reduction would afford a *cis* ring junction between the C and E rings in compound **61** (Figure 5.4), which corresponds to the proper stereochemical outcome for the construction of strychnine. Since **61** appeared as a key intermediate in Rawal's synthesis[28] (*vide supra*), the first-generation application of the cyclophane approach to indole alkaloid synthesis was directed toward a formal total synthesis of strychnine.

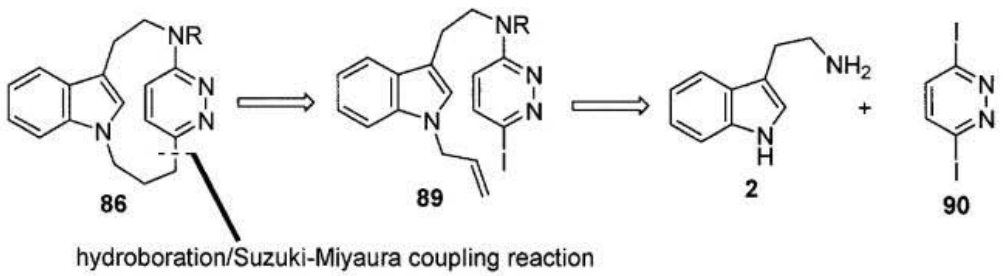
On the basis of these considerations, a retrosynthetic analysis back to the cyclophane stage was devised (Scheme 5.12). The first set of disconnections, as described above, affords Rawal's intermediate **61**. In the synthetic direction, this corresponds to a sequence including an *N*-allylation, an intramolecular Heck reaction, an acid-mediated deprotection and the base-promoted isomerization-intramolecular oxa-Michael addition sequence.[28] Being one of the skeletal atoms of strychnine, N4 was included at the starting cyclophane stage (compounds **86** and **88**).



Scheme 5.12 Retrosynthetic analysis of strychnine based on the cyclophane approach

On the other hand, the lactam oxygen atom attached to C23 was envisioned as being brought into the skeleton of **61** either after (Routes A and C) or before (Route B) the transannular IEDDA step, which led back to cyclophanes **86** and **88**, respectively. In the synthetic direction, Routes A and C diverge at compound **85**, and Routes B and C converge at compound **87**. Further retrosynthetic cuts of cyclophanes **86** and **88** will be described in the following sections.

5.2.2 Route C

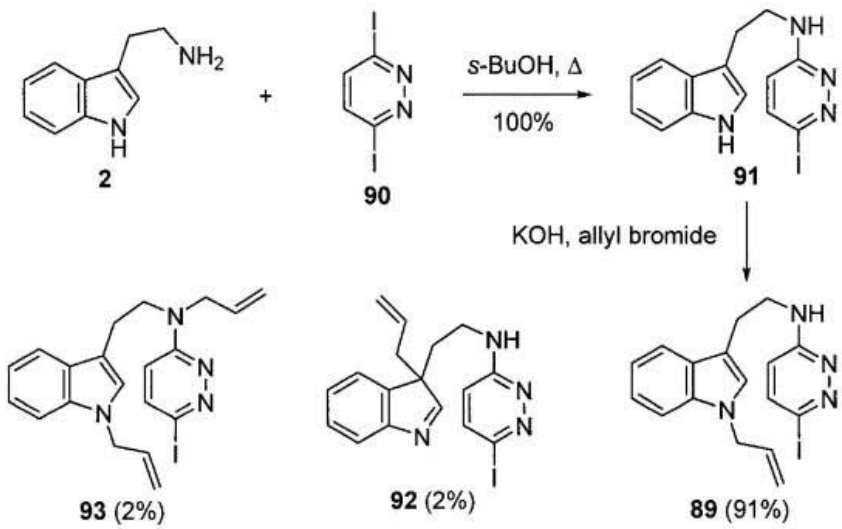


Scheme 5.13 Retrosynthetic analysis of cyclophane **86**.

Taking advantage of the hydroboration/Suzuki-Miyaura strategy described in Chapters 3 and 4, indolopyridazinophane **86** was cut retrosynthetically to give allyl iodide **89**, which was taken back further to tryptamine **2** and 3,6-diiodopyridazine **90** by the sequential transforms of nucleophilic aromatic substitution and *N*-allylation of an indole unit (Scheme 5.13).

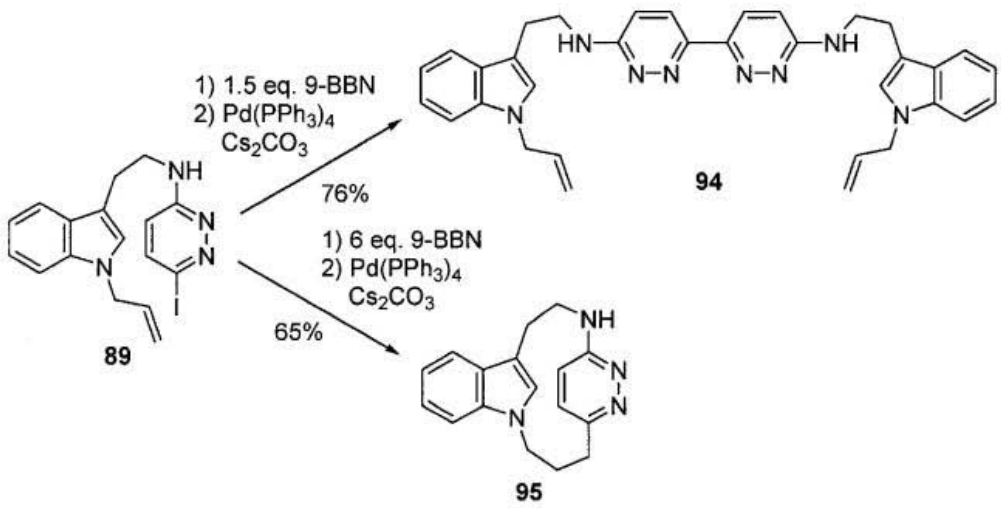
The aminolysis of pyridazine halides is well documented,[79,80] so synthetic work towards strychnine commenced with the reaction between tryptamine **2** and 3,6-diiodopyridazine **90**[81] (Scheme 5.14). This was initially performed in the most commonly used solvent, ethanol (bp=78 °C), with a slight excess of **2** (1.1 equivalents). Under these conditions, the yield of the desired tryptaminopyridazine **91** ranged from 41% and 54%. The use of 4.0 equivalents of **2** increased the yield to 97%. However, the relatively high price of **2** ($ 33.60/10 g according to 2000-2001 Aldrich Catalog) and its troublesome recovery prompted the search for a superior alternative. This was realized through the use of *s*-BuOH (bp=98 °C) as the solvent, which allowed the use of

an almost stoichiometric amount of **2** (1.1 equivalents) to yield **91** quantitatively. The subsequent *N*-allylation of the indole nucleus was performed on **91** using allyl bromide in the presence of KOH. This yielded three products, namely **89** (91%), **92** (2%) and **93** (2%). As expected,[82,83] the use of K^+ as the counterion for the indole salt favored *N*-allylation (**89**, 91%) over the unwanted C3-allylation (**92**, 2%). Another minor product **93** was the result of *N*-allylations of both the indole nitrogen atom and the secondary amine in **91**.



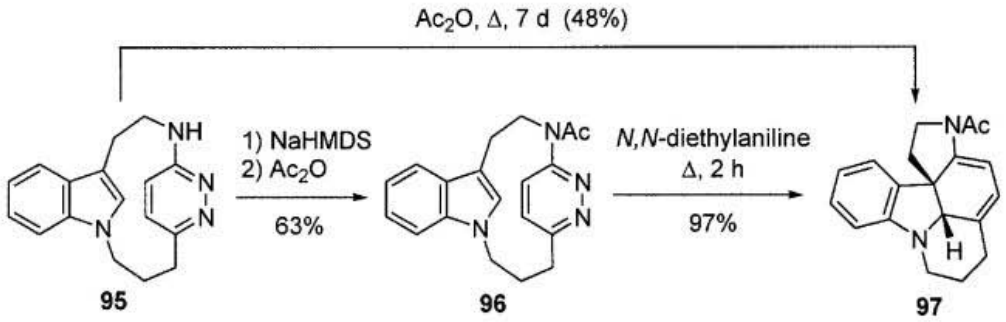
Scheme 5.14 Synthesis of cyclization precursor **89**.

With ready access to compound **89**, the hydroboration/Suzuki-Miyaura sequence was then attempted (Scheme 5.15). The initial attempt employed 1.5 equivalents of the hydroborating reagent (9-BBN) and this led to the formation of compound **94** (76%), the result of the homocoupling of **89**.



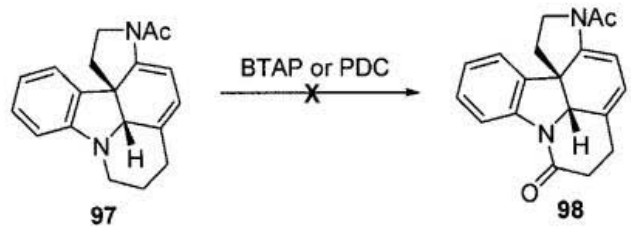
Scheme 5.15 Synthesis of indolopyridazinophane **95**.

This result indicated that the co-ordination of 9-BBN to the secondary amino nitrogen atom and one of basic pyridazine nitrogen atoms occurred considerably faster than the desired hydroboration,[84,85] thus leaving the allyl group in **94** intact. Even though reductive homocouplings of halides have been reported under non-reductive conditions,[86,87] it may well be that the catalyst ligand PPh_3 served as a reducing agent here. The amount of 9-BBN was therefore increased to 6 equivalents in the hopes of circumventing this problem. Gratifyingly, the desired indolopyridazinophane **95** was obtained in 65% yield under these conditions. No other products were isolated.



Scheme 5.16 Transannular IEDDA chemistry of **95**.

The transannular IEDDA reaction of **95** was tried without delay (Scheme 5.16). Since intramolecular IEDDA reactions of tryptamine-tethered azines were known to require acylation of the secondary amine,[88] initial attempts to bring about transannular IEDDA in system **95** were conducted under acylating conditions. The rationale for implementing this maneuver was to dampen the electron donating ability of the nitrogen atom. Compound **95** was subjected to the *in situ* acetylation procedure employed by Boger for inducing intramolecular IEDDA reactions between pyridazines and tethered alkynes.[89] Heating **95** at reflux in acetic anhydride (bp=138-140 °C) for 7 d produced the desired *N*-acetylated pentacycle **97** in 48% yield. An alternative two-step sequence was found to be more favorable in terms of both reaction time and yield. Acetylation of **95** by acetic anhydride in the presence of the strong base NaHMDS gave acetylated cyclophane **96** (63%), which, upon heating in *N,N*-diethylaniline (bp=217 °C) for 2 h, was converted into **97** (97%) in nearly quantitative yield.



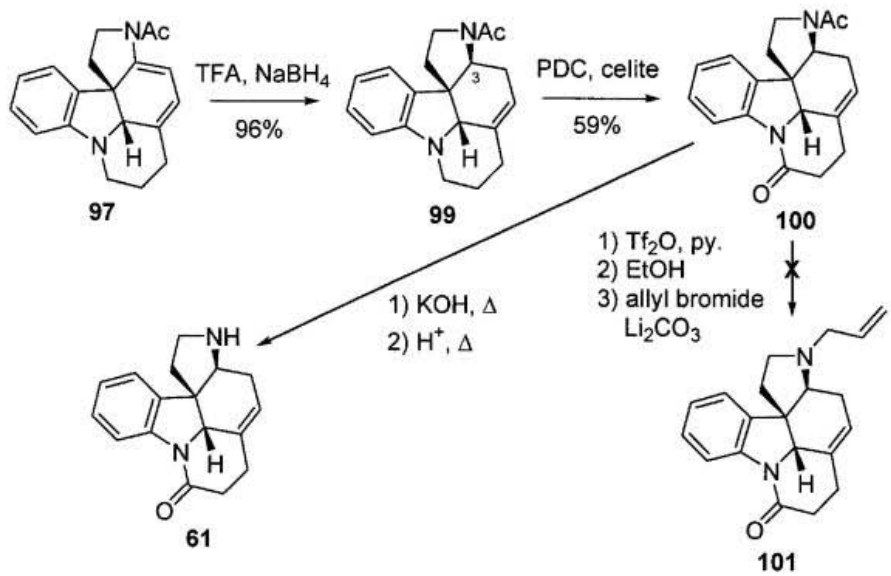
Scheme 5.17 Unsuccessful attempts at processing according to Route C.

With **97** in hand, Route C (Scheme 5.12) was first investigated by attempted oxidation of the piperidine ring in **97** to the lactam functionality in **98** (Scheme 5.17). It was known that such a task had been achieved previously by using benzyltriethylammonium permanganate (BTAP) during Snyder's construction of the canthin-6-one skeleton,[90] so the same conditions were applied to compound **97**. Unfortunately, an intractable mixture was generated. The same was true when pyridinium dichromate (PDC) was employed as the oxidant.[91] Suspecting that the failure of these reactions might be linked to the sensitivity of the enamide unit in **97** toward oxidation, Route C was abandoned.

5.2.3 Route A

Attention was then switched to Route A (Scheme 5.12), in which the order of the oxidation and reduction steps was reversed (Scheme 5.18). The chemical reduction of enamines, which is usually achieved by hydride transfer reagents under acidic conditions,[76] depends on the initial formation of an iminium ion.[92] Sodium borohydride in a carboxylic acid appeared to be the most popular choice.[93,94] As was desirable in the case of **97**, these conditions normally reduce

enamine systems with two conjugated double bonds to give products in favor of the homoallylic amine, which results from 1,2-reduction.[95] However, this selectivity was reported to decrease with increasing acidity of the medium.[96] Therefore, the initial attempt to reduce **97** was made by using $NaBH_4$/HOAc. However, the starting material was recovered (>90%) with none of the desired product being detected. The inertness of **97** to $NaBH_4$/HOAc[93,95] was likely associated with the decreased nucleophilicity of the enamine β-carbon due to the presence of the electron withdrawing acetyl group attached to nitrogen.



Scheme 5.18 The first formal total synthesis of (±)-strychnine by the cyclophane approach.

A stronger acid, TFA, was then employed.[94,97,98] The reaction turned out to be surprisingly effective, giving desired product **99** in 96% yield with complete chemo- and stereoselectivities. Although the absence of NOE effects

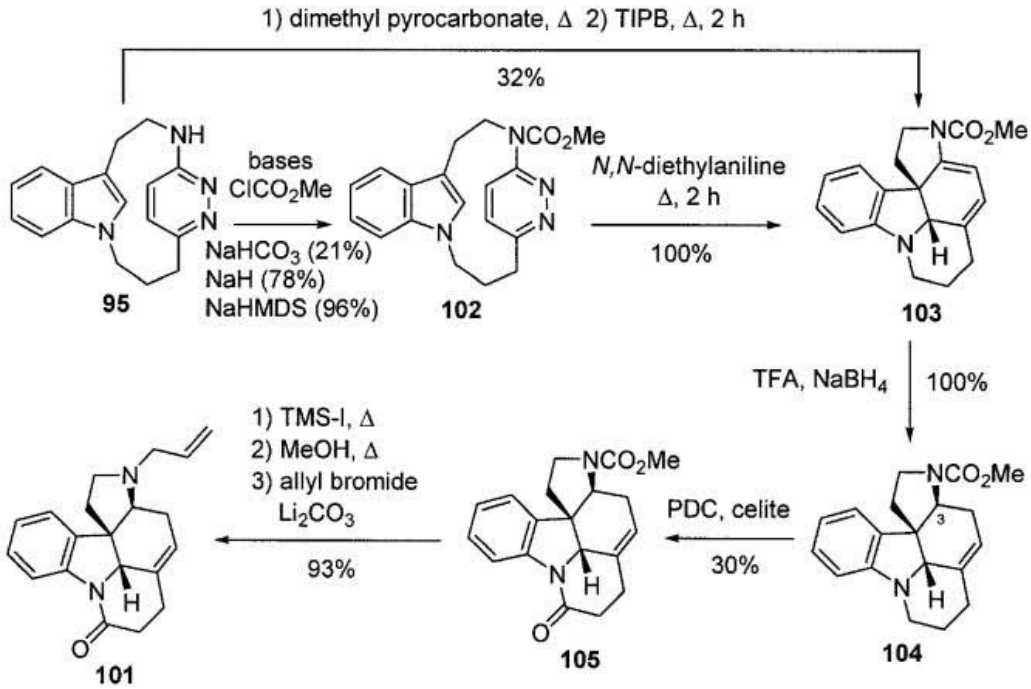
between the two methine protons in **99** cannot be used to unambiguously assign its relative stereochemistry, AM1 calculations (Chem3D Ultra 5.0 MOPAC) predicted that **99** is 9.51 kcal/mol lower in energy than its C3 (strychnine numbering) epimer (*trans* [6,5]ring junction). More conclusive evidence for the stereochemical assignment was obtained later (*vide infra*).

The subsequent oxidation of **99** was expected to be a chemo- and regioselective reaction. The expectation of chemoselectivity (carbons adjacent to the tertiary amino group *versus* those adjacent to the amide function in **99**) came from the documented higher propensity of the more basic tertiary amino group than the less basic amide moiety toward oxidation.[99] The expectation of regioselectivity (NCH_2 carbon *versus* NCH carbon in **99**) was based on others' observations that such oxidations occurred more favorably at the less substituted carbon next to the nitrogen atom,[99] presumably as a result of a kinetically controlled process. Even so, the oxidation of tertiary amines to the corresponding tertiary amides is a nontrivial task. A variety of oxidants, namely CrO_3/pyridine,[100] MnO_2,[101] $KMnO_4$,[102] BTAP,[103] *t*-BuO_2H,[104] Hg(II)-EDTA,[105] I_2,[106] diethyl azodicarboxylate,[107] are known to accomplish this transformation. Considering the compatibility of the oxidants with the double bond in **99**, chromium-based reagents[108] and diethyl azodicarboxylate[107] were selected for a model study on the oxidation of *N,N*-dimethylaniline to *N*-methylformanilide. The latter reagent was immediately found unsuitable since no trace of *N*-methylformanilide was detected under the conditions employed. In the former

group of oxidants, CrO_3/pyridine[100] (also known as Collins' reagent[109]), PCC[110] and PDC were tried. PCC and PDC were selected because of their structural similarity to Collins' reagent, commercial availability and safe handling, even though they have not been reported to be applicable in such an oxidation. Initially, PDC was found to be superior to CrO_3/pyridine, whereas PCC failed completely under analogous conditions. The sluggish filtration associated with PDC and CrO_3/pyridine reagents then prompted us to develop more convenient methods by using solid-supported reagents. Different solid supports, including silica, celite and alumina, were used as additives, and finally PDC/celite showed the highest efficiency by producing *N*-methylformanilide in up to 89% yield. After the model study, the conditions employed for this result were applied to the system of interest, **99**. The desired oxidation product **100** was chemo- and regioselectively produced in 59% yield. Since **100** already possesses the complete molecular skeleton of Rawal's intermediate **61**, it only remained to remove the acetyl protecting group to complete a formal total synthesis of strychnine.

The traditional base-promoted hydrolysis was anticipated to smoothly cleave both amide groups and subsequent treatment with acid was envisaged as a means of re-cyclizing the δ-valerolactam unit from its hydrolyzed open form to reach the final product **61**. However, only trace amount (<1 mg, <10%) of compound **61** was isolated. As in Rawal's synthesis[28], good HRMS data were nevertheless obtained to support the structure of **61**. The poor yield probably

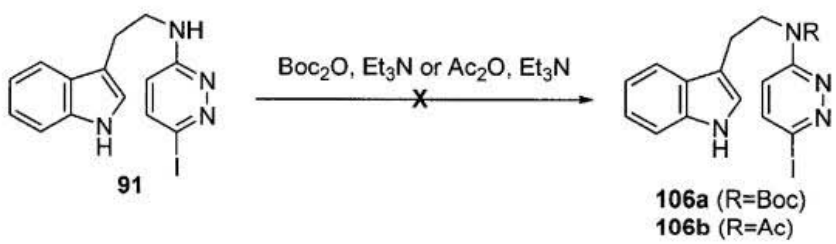
had to do with the combination of the vigorous reaction conditions and the relative instability of **61** described by Rawal.[28] Alternatively, more selective conditions for hydrolyzing the acetamide function were sought. Unfortunately, the use of triflic anhydride and pyridine followed by treatment with ethanol[111,112] and subsequent *N*-allylation[113] did not lead to the formation of the *N*-allylated derivative **101**.



Scheme 5.19 The second formal total synthesis of (±)-strychnine by the cyclophane approach.

A more successful route to **61** involved the use of a different protecting group for the secondary amine (Scheme 5.19). The methyl carbamate was chosen because: (1) as for the acetyl group, its electron withdrawing nature

should still allow the nitrogen atom it is protecting to survive the PDC oxidation (Scheme 5.18); and (2) it could readily be removed by using much milder conditions (TMS-I)[114] than the strongly basic conditions required to deprotect the acetyl group of **100** (Scheme 5.18). The *in situ* acylation procedure was first tried using dimethyl pyrocarbonate as both the reaction medium and the reagent. Heating **95** in dimethyl pyrocarbonate resulted in the formation of an intermediate with similar polarity to the starting material by TLC, which was, without purification, subjected to boiling 1,3,5-triisopropylbenzene (TIPB) (bp=232-236 °C) to give the desired pentacycle **103** in only 32% yield. The intermediate was later thought to be compound **102** judged by the similarity of its polarity to an authetic sample. The fact that the *in situ* acylation procedure stopped at the protection step rather than proceeding through the transannular IEDDA reaction was perhaps related to the propensity of dimethyl pyrocarbonate to decompose under thermal conditions (bubbles were observed while heating). A stepwise sequence led to much more satisfactory results, even though an extra step was required.



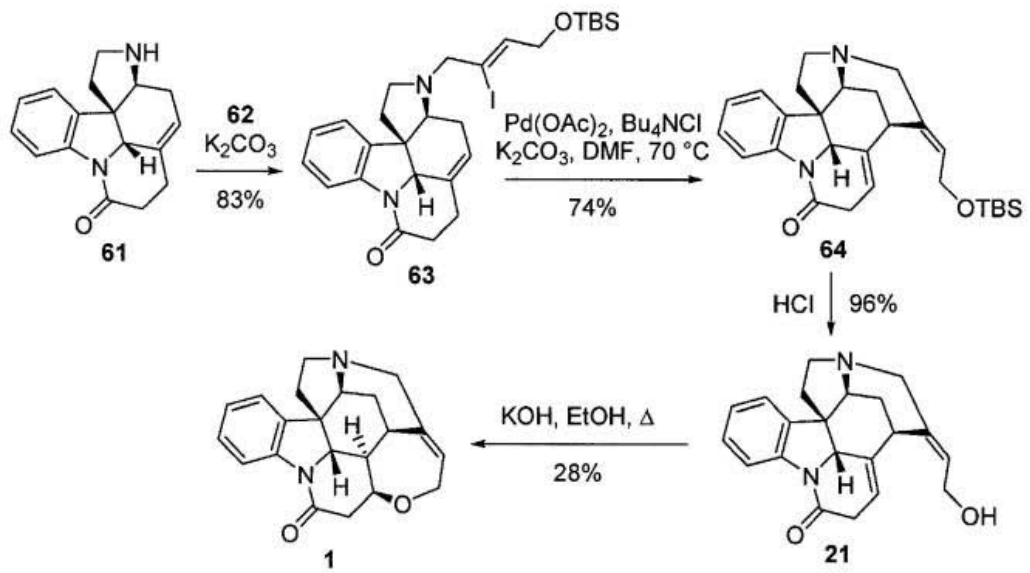
91

106a (R=Boc)
106b (R=Ac)

Scheme 5.20 Unsuccessful attempted protections of **91**.

It had been observed earlier that attempted protections of the secondary amine in **91** with either Boc or an acetyl group under standard conditions only returned the starting material (Scheme 5.20). This indicated that this particular secondary amine was not as nucleophilic as analogous aniline nitrogen atoms due to the electron deficient nature of the heteroaromatic pyridazine moiety. Consequently, it was decided to conduct the protection of the amino group in **95** under much stronger basic conditions. Different bases were tested and NaHMDS gave the best results, affording cyclophane carbamate **102** in 96% yield (Scheme 5.19). The subsequent thermally-induced transannular IEDDA reaction of **102** proceeded smoothly to furnish pentacyclic compound **103** quantitatively. Again, superb results were obtained from the ensuing reduction of the enamide double bond of **103** to generate **104** (100%) with complete chemo- and stereocontrol. Similar to the case of **99** (Scheme 5.18), the absence of NOE effects between methine protons in **104** and the AM1 calculated energy difference (6.26 kcal/mol) between **104** and its C3 epimer (*trans* [6,5]ring junction isomer) were used to assign the relative stereochemistry of **104** as shown in Scheme 5.19. PDC/celite oxidation of **104** produced desired lactam **105**, but only in 30% yield. This low yield might be a consequence of the possibly higher propensity of the carbamate functionality in **104** toward oxidation than the amide group in **99** (Scheme 5.18). Rawal's intermediate **61** was generated upon reaction of **105** with TMS-I,[115] but attempts to purify it by chromatography led to no increase in the quality of the NMR spectra and drastic reductions in the yield. Since the

next step in Rawal's synthesis was an *N*-allylation, the crude product of deprotection was subjected to immediate allylation with allyl bromide. Vollhardt's conditions[35] (Li_2CO_3 in DMF) were employed here because they were reported to provide the best yield in a similar reaction when compared with several other sets of conditions. The *N*-allylated pentacycle **101** was formed in an excellent yield of 93%, suggesting that its progenitor **61** was prepared from **105** with at least the same efficiency (≥93%).

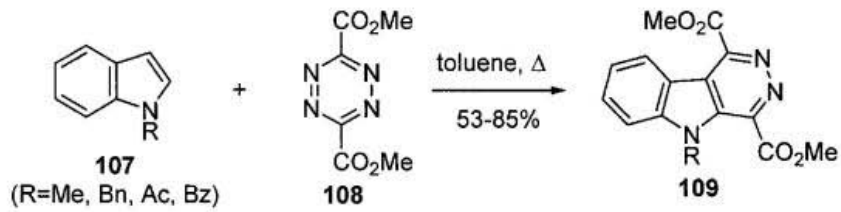


Scheme 5.21 Rawal's total synthesis of strychnine **1** starting from **61**.

Starting from compound **61**, Rawal[28] was able to synthesize strychnine by a four-step sequence in an overall yield of 16.5%, if applying the higher yield (28%) for the isostrychnine→strychnine conversion claimed by Kuehne[24] (Scheme 5.21). In the present study, Rawal's key intermediate **61** was afforded in eight steps with an overall yield of equal to or greater than 15.8% *via* the

cyclophane approach. Incorporating Rawal's and Kuehne's work, the formal total synthesis of (±)-strychnine was therefore successfully accomplished with a synthetic sequence of twelve steps, starting from tryptamine and 3,6-diiodopyridazine, in 2.6% overall yield.

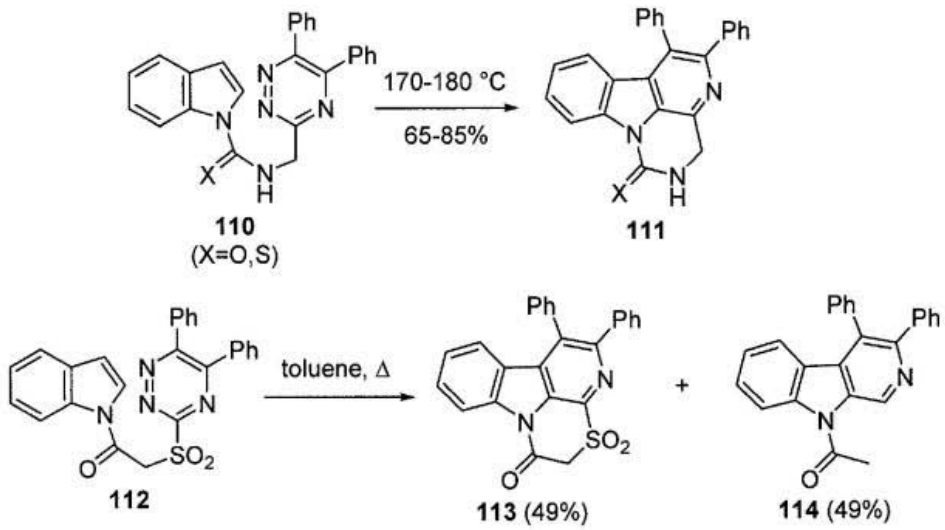
5.2.4 Route B



Scheme 5.22 Intermolecular IEDDA reactions between indoles **107** and 1,2,4,5-tetrazine **108**.

The final route illustrated in Scheme 5.12, Route B, involves the installation of the protected secondary amine and lactam carbonyl group, both of which are absent in **82** (Figure 5.3), prior to the transannular IEDDA reaction. According to Snyder's results,[88,116] acetylation of the indole nitrogen atom of tryptamine units tethered *via* their side-chain nitrogen atoms to 1,2,4,5-tetrazines and 1,2,4-triazines prevented intramolecular IEDDA reactions from proceeding. On the other hand, indoles bearing EWGs on their nitrogen atoms functioned comparably to *N*-alkylated indoles as dienophiles in intermolecular IEDDA reactions with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate **108** to give products **109** after aromatization of the initial adducts (Scheme 5.22).[117,118] Furthermore, intramolecular IEDDA reactions between the *N*-carbonylated indole nucleus and

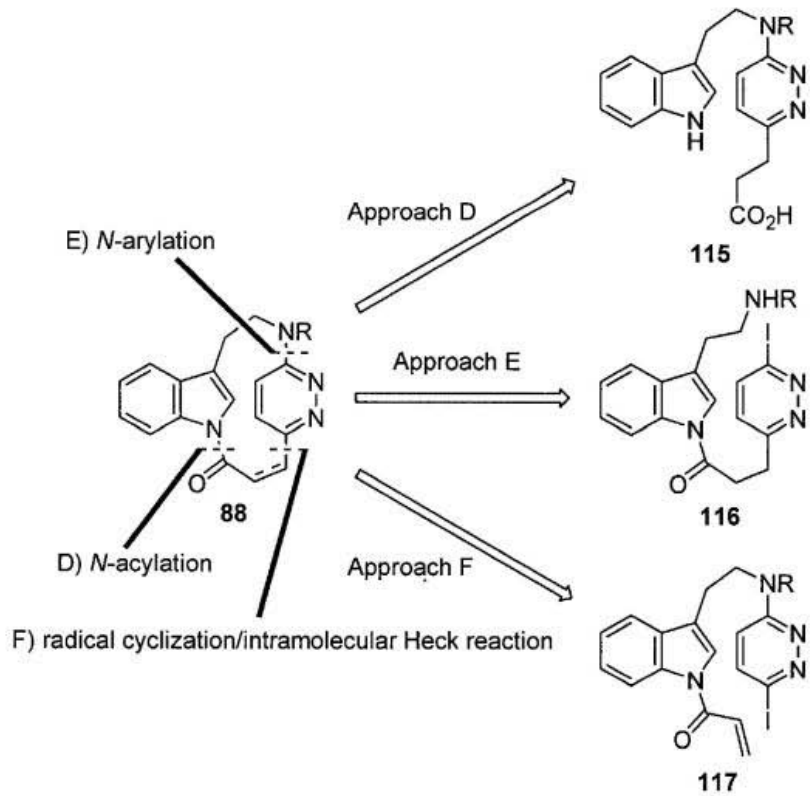
the non-activated 1,2,4-triazine moiety were effectively performed in indole *N*-tethered 1,2,4-triazine systems (Scheme 5.23).[88,119,120]



Scheme 5.23 Intramolecular IEDDA reactions of **110** and **112**.

It is therefore unclear whether the decreased dienophilicity of the indole enamine double bond with an acetyl group on the indole nitrogen atom in tryptamine-tethered systems is due to the lowered HOMO energy of the enamine double bond or the raised stereo interactions in tryptamine-containing systems (mono-substituted indole enamine double bond) compared to those in systems with tether attached to the indole nitrogen atom (unsubstituted indole enamine double bond). Intuitively, an EWG at indole nitrogen atom would be expected to lower the HOMO, thus disfavoring IEDDA reaction. On the other hand, this would serve to decrease the aromaticity of the indole nucleus by partially engaging the lone pair of electrons on the nitrogen atom. The diminishing of a

disincentive to react would be expected to favor IEDDA reaction. That reasonable arguments can be made in opposite directions renders the situation regarding the dienophilicity of the indole enamine double bond nebulous.

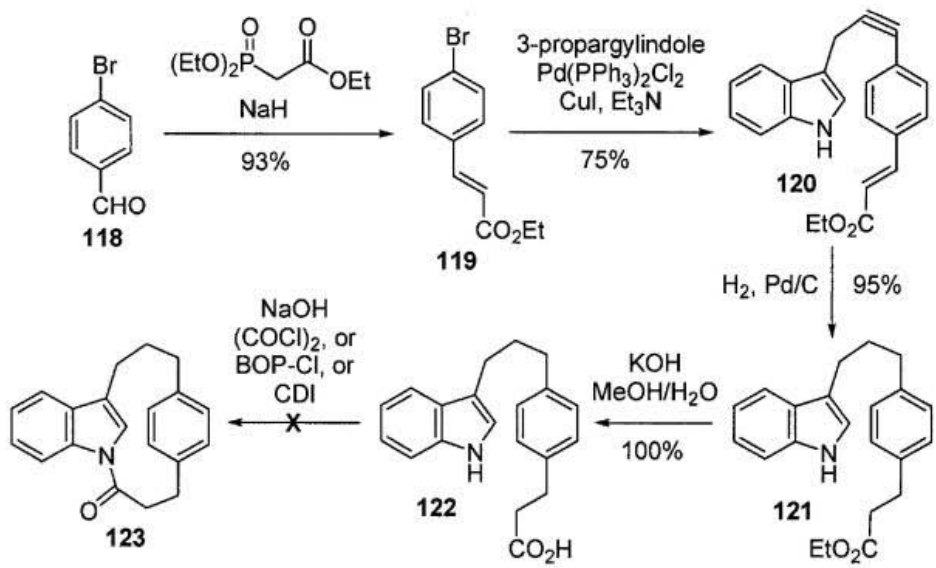


Scheme 5.24 Retrosynthetic analysis of cyclophane **88**.

This inspired an investigation aimed at providing experimental evidence as to which factor dictates the reactivity of indole as an IEDDA dienophile. With the ultimate target being cyclophane **88** (Scheme 5.24), this investigation became one and the same with the pursuit of Route B (Scheme 5.12). Considering that the amine to amide oxidations in Route A were the poorest

yielding steps *en route* to **61**, it was hoped that the introduction of an amide group before the key cyclization would pave the way to the development of a more efficient synthesis.

For the preparation of **88**, three types of bridge-forming/ring-closing reactions were planned based on the experience from the synthesis of other (1,3)indolophanes (Chapters 3 and 4), namely D) *N*-acylation, E) *N*-arylation and F) radical cyclization/intramolecular Heck reaction (Scheme 5.24). Only the final ring closures are shown, but compound **115** can be taken back further according to cuts E and F, **116** according to cuts D and F, and **117** according to cuts D and E.



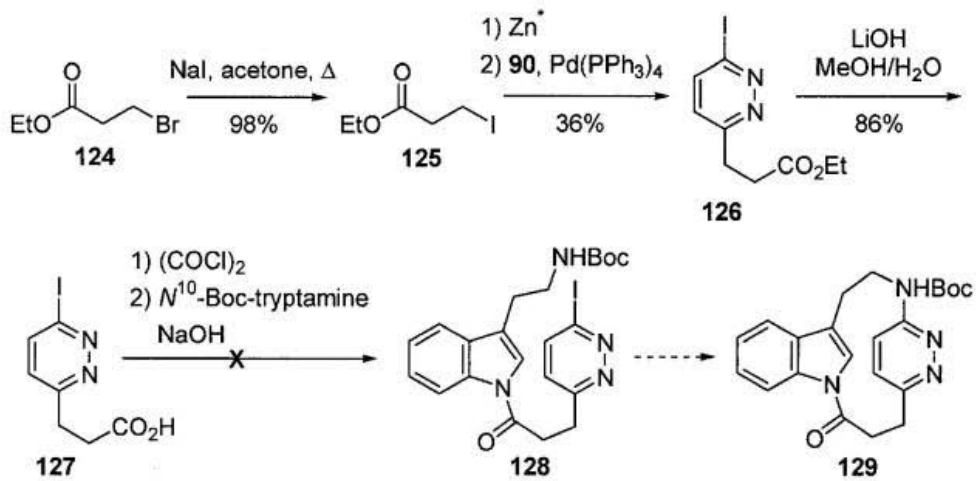
Scheme 5.25 Attempted synthesis of cyclophane **123**.

Being one of the not attampted strategies in the synthesis of [3]paracyclo[3](1,3)indolophane (Chapter 3), Approach D was first investigated

on a model system, in which the tether atoms are all carbons and the pyridazine ring of **115** was replaced by a benzene ring (Scheme 5.25). The rationale for doing so was to probe the applicability of *N*-acylation as the final ring-closing method. Ethyl *trans*-4-bromocinnamate **119**, although commercially available ($ 170.00/25 g according to the 2000-2001 Aldrich Catalog), was conveniently prepared by subjecting 4-bromobenzaldehyde **118** to a Horner-Wadsworth-Emmons reaction.[121] The yield of **119** was 93%. A subsequent Sonogashira coupling[122] with 3-propargylindole provided enyne **120** (75%), which was in turn catalytically hydrogenated to furnish compound **121** in 95% yield. After hydrolysis of the ester group in **121**, acid **122** was generated quantitatively. Unfortunately, attempted lactam formation in the presence of several common reagents used to activate carboxyl groups in ring closures[123] all failed, indicating that *N*-acylation is in fact not suitable for the ring-closing method in the synthesis of *N*-acylindole-containing cyclophanes.

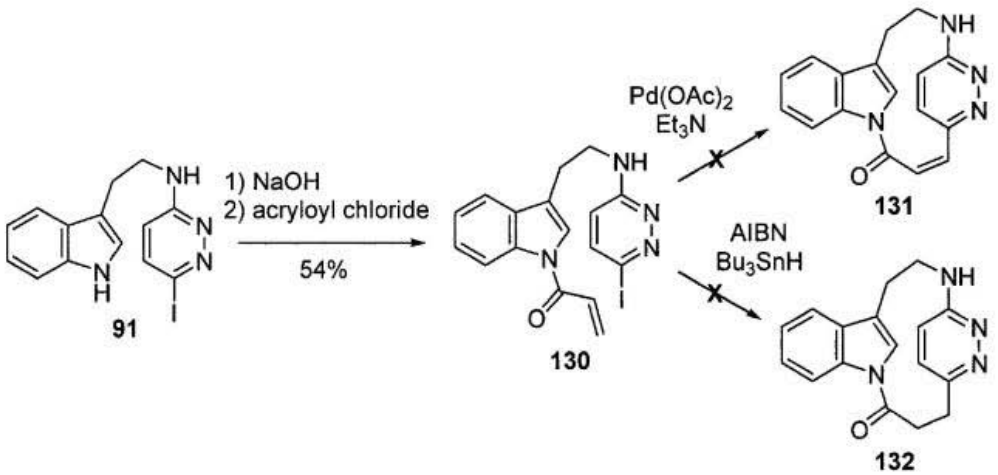
N-Acylation was then tried as the bridge-forming reaction according to Approach E (Scheme 5.26). Negishi reaction[124-126] was chosen as the method for formation of the bottom bridge. A Finkelstein reaction converted bromide **124** to iodide **125**[127] in 98% yield. After treatment of **125** with activated Zn,[127,128] the resulting mono-organozinc reagent reacted with 3,6-diiodopyridazine **90** to afford compound **126** (36%). This was subjected to a base-mediated hydrolysis to produce acid **127** (86%). However, the subsequent acylation of N^{10}-Boc-tryptamine under standard conditions did not yield any of the desired product

128, which was envisaged as the direct precursor to cyclophane **129**. This unsuccessful acylation might be due to a similar reason to that in the case of a failed attempt to prepare the cyclization precursor to [3](1,3)indolo[3](3,6)pyridazinophane (Chapter 4), i.e. formation of a five-membered ring fused to the pyridazine moiety.



Scheme 5.26 Attempted synthesis of cyclophane **129**.

The last approach to receive attention was the preparation and radical cyclization/intramolecular Heck reaction of compound **117** (Scheme 5.27). Under moderately basic conditions, the nitrogen anion of the indole nucleus in **91** underwent acylation upon reaction with acryloyl chloride to afford compound **130** in 54% yield. Unfortunately, subsequent attempts to perform an intramolecular Heck reaction[129-131] or radical cyclization[132-134] produced none of the desired cyclophanes **131-132**.



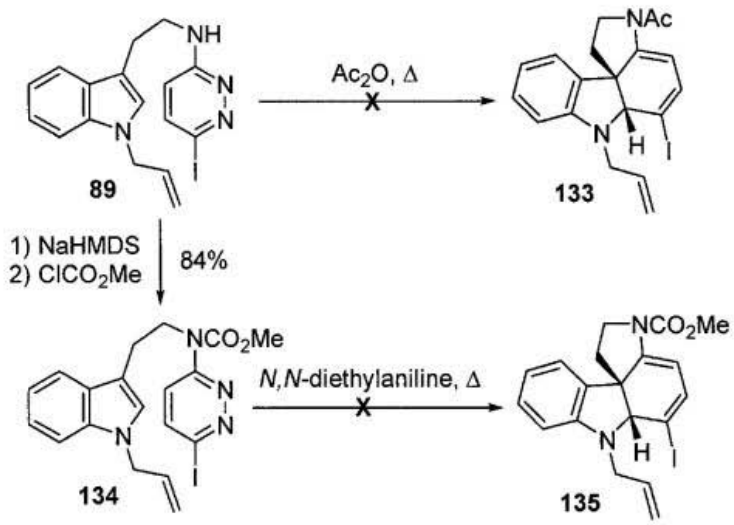
Scheme 5.27 Attempted synthesis of cyclophanes **131** and **132**.

Discouragingly, all attempts to introduce the lactam functionality at the cyclophane stage failed. However, all reasonable possibilities for the synthesis of cyclophane **88** or derivatives have not yet been ruled out and future efforts will be directed toward this unfulfilled task.

5.2.5 Relevant Considerations and Confirmations

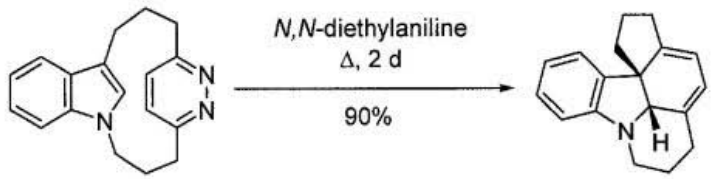
The formal total synthesis of strychnine presented earlier relied on a key transformation: a sequential transannular IEDDA/retro Diels-Alder process. Therefore, the entire work rests upon cyclophane intermediates, which are required to provide a transannular environment for this vital synthetic operation. Snyder has reported[116] that related intramolecular reactions of several tryptamine-tethered pyridazine systems were unsuccessful. It thus seemed reasonable to firmly establish that the transannular environment was in fact

critical in the systems studied here. This was indeed found to be the case (Scheme 5.28).



Scheme 5.28 Unsuccessful attempts of intramolecular IEDDA reactions of compounds **89** and **134**.

Compound **89**, the precursor to cyclophane **95**, was subjected to both *in situ* acylation and successive acylation/intramolecular IEDDA procedures that were described previously in this chapter. It was first heated in acetic anhydride, but none of the desired product **133** was detected, even after two days. In the corresponding stepwise process, **89** was first converted into carbamate **134** in 84% yield. However, heating **134** in *N,N*-diethylaniline at reflux failed to produce compound **135**. In both cases, prolonged heating resulted in only apparent decomposition of the starting materials. The great benefits of the TADA reaction has once again been demonstrated.[135]



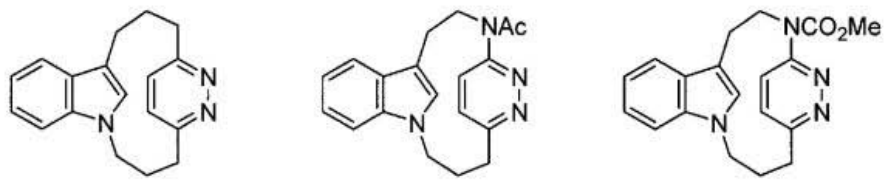
136 82

Scheme 5.29 Transannular IEDDA reaction of cyclophane **136**.

As described in Chapter 4, indolopyridazinophane **136** underwent similar transannular IEDDA reaction to afford pentacycle **82** (Scheme 5.29). The reaction required heating in *N,N*-diethylaniline at reflux for 2 d to achieve a yield of 90%. TLC analysis at a several-hour-interval prior to the due time showed the co-existence of both **136** and **82** with different ratios. In contrast, analogous reactions of indolopyridazinophanes **96** and **102** proceeded much faster (2 h) in slightly higher yields (97-100%). The significant difference in the reaction rate prompted a low level theoretical investigation. PM3 calculations were performed using Chem3D Ultra 5.0 MOPAC to determine the $HOMO_{dienophile}$-$LUMO_{diene}$ energy differences in these three cyclophanes (Figure 5.5, only the C_{chair},N_{chair} conformer, the isomer with the lowest energy by calculation, was examined for each individule cyclophane). The HOMO-LUMO gap in **136** (7.92 eV*) is higher than those in **96** (7.73 eV) and **102** (7.80 eV) by 0.19 eV and 0.12 eV, respectively, which might be responsible for the relatively low reactivity of compound **136**.

* 1 eV=23.06 kcal.

On the other hand, the smaller difference (0.07 eV) in the HOMO-LUMO gaps of **96** and **102** is in accord with their similar reactivities. However, more reliable conclusions can only be made based on systematic kinetic investigations. A similar trend of substituent effects on a diene system was revealed when van der Plas applied intramolecular IEDDA reactions of alkyne-tethered pyrimidines to synthesize tricyclic annelated pyridines.[136]



136
HOMO-LUMO: 7.92 eV

96
HOMO-LUMO: 7.73 eV

102
HOMO-LUMO: 7.80 eV

Figure 5.5 PM3-calculated $HOMO_{dienophile}$-$LUMO_{diene}$ energy differences in indolopyridazinophanes **136**, **96** and **102**.

Snyder has demonstrated that the intramolecular IEDDA reactions of tryptamine-tethered 1,2,4,5-tetrazine and 1,2,4-triazine systems benefit from an *in situ* acylation protocol by *N*-acylation of both the tether and azine ring nitrogen atoms.[116] However, this phenomenon did not manifest itself appreciably when applied to cyclophane **95**. On the contrary, the stepwise sequence worked far more efficiently than the *in situ* acylation process (*vide supra*). Given the difference in boiling points of the solvents (*N,N*-diethylaniline bp=217 °C for the stepwise sequence and acetic anhydride bp=130 °C for the *in situ* acylation process) and the structural characteristics of the resulting products, this observed distinction can be ascribed to the combination of energetic effects and the

product sensitivity. Acetic acid is the by-product generated in the *in situ* acylation process, and desired products **97** and **103** both have an enamide functionality, which is presumably sensitive to acidic conditions. By comparison, Snyder's products[116] from his intramolecular IEDDA reactions have an acid-stable amidine moiety in the analogous position to the enamide groups of **97** and **103**.

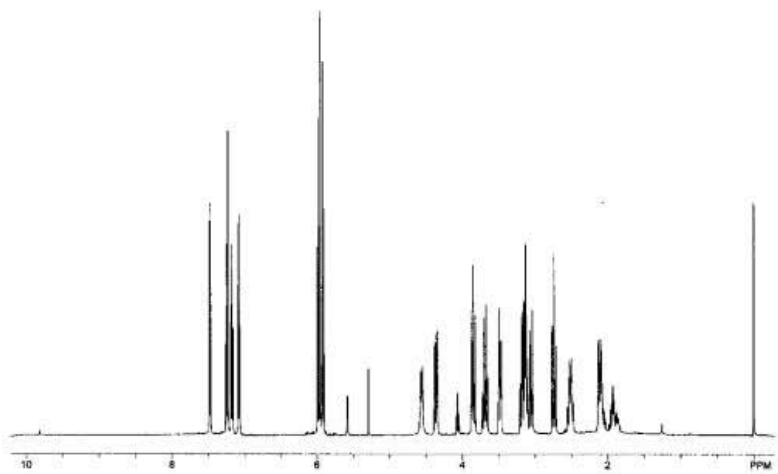
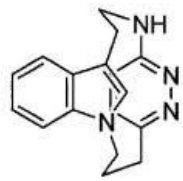


Figure 5.6 ^{1}H NMR ($CDCl_3$) spectrum of **95** at room temperature.

Since the original intention of synthesizing cyclophane **95** (Scheme 5.15) was to achieve the formal total synthesis of strychnine, its conformational behavior was not investigated in detail as part of that study. Nevertheless, a glimpse can be seen by examining the ^{1}H NMR spectrum of **95** at room temperature (Figure 5.6). The 500 MHz ^{1}H NMR spectrum of **95** exhibits a singlet at δ 5.95, which is assigned to the internal proton of the indole deck. The

highfield shift of this proton compared to the corresponding proton of the precursor molecule **89** (δ 7.17) indicates that, as expected, it is located well inside the shielding cone of the pyridazine ring in solution. In considering the pyridazine ring of **95**, the ^{1}H NMR spectrum of the reference compound 3-amino-6-methylpyridazine would be needed. However, a literature search for information regarding that compound[137-139] was fruitless. Therefore, a very unstringent assumption had to be made first. The aromatic protons of *p*-xylene are observed at δ 7.05, and in *p*-toluidine they are observed at δ 6.58 for the position *ortho* to the amino group and at δ 6.95 for the position *meta* to the amino group. Consequently, the amino group introduces shielding effects of 0.47 and 0.10 ppm into its *ortho* and *meta* positions, respectively. Applying the same effects caused by the amino group on 3,6-dimethylpyridazine (δ 7.20),[140] the aromatic signals of 3-amino-6-methylpyridazine are expected to appear at δ 6.73 for the position *ortho* to the amino group and at δ 7.10 for the position *meta* to the amino group. The protons on the pyridazine ring in **95** show up as an AB system at δ 5.92 and 5.99. These chemical shifts are 0.81 and 1.11 ppm, respectively, upfield from the aromatic protons of the reference compound based on the assumed chemical shifts. Very similar values of 0.87/1.07 and 0.85/1.06 were observed for indolopyridazinophane **136** (Chapter 4) and [3]paracyclo[3](1,3)indolophane (Chapter 4), respectively, according to the comparison with their reference compounds. These values have been used as evidence that those corresponding protons are in the *endo* (Chapter 4) position in

terms of orientation between the indole and the other arene ring within the cyclophane molecules. Therefore, compound **95** is postulated to exist in a single *exo* conformation (the pyridazine nitrogens are situated away from the indole ring) in solution at room temperature (Figure 5.7).



exo-**95**

Figure 5.7 *Exo* conformation of **95**.

Analysis of a molecular model of **95** revealed that this cyclophane possesses conformational processes no less complicated than those of **136** (Chapter 4). Since ^{1}H NMR spectra of **95** and **136** display a similar pattern for the bridge protons, the rigid *exo* conformation of **95** is attributed to the restricted flipping of both indole and pyridazine rings on the basis of the comformational determination of **136** (Chapter 4). More thorough studies with the assistance of computational studies, X-ray crystallography and DNMR analysis are required to draw further conclusions.

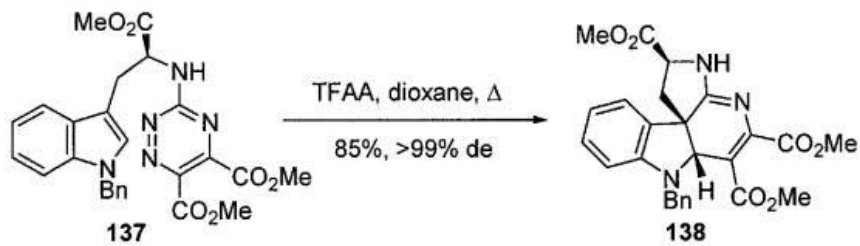
5.3 Conclusions and Future Directions

Owing to the exceptionally complex architecture for the relatively small molecular size, strychnine **1** presents a timeless and a most formidable synthetic challenge. Our preliminary studies on transannular IEDDA reaction of

indolopyridazinophane system (Chapter 4) allowed us to rapidly access a highly compact pentacyclic indoloid framework with excellent efficiency. Inspired by the structural similarity of the pentacyclic system to the ABCEG core unit of strychnine's skeleton, the "cyclophane approach" based on transannular IEDDA chemistry has been applied to a total synthesis of strychnine. Fortunately, this approach has provided an entry into Rawal's key ABCEG intermediate **61**, demonstrating a conceptually novel route to (±)-strychnine. The overall yield of Rawal's intermediate **61** from tryptamine was 15.8% over eight steps and the formal overall yield of strychnine from tryptamine was 2.6% over twelve steps. Thus the synthesis detailed in this chapter constitutes the shortest route to strychnine yet reported. However, the best overall yield still belongs to Rawal.[28] In terms of ring assembles, our synthetic strategy can be described as a sequence of AB→ABCEG→ABCDEG→ABCDEFG, among which the very productive key conversion of AB→ABCEG resulted in the generation of two stereogenic centers (including the crucial C7 spiro carbon) with the correct relative stereochemistry and the simultaneous construction of three rings (C, E and G) in a quantitative yield.

In the overview of strychnine synthesis (Table 5.1), only four asymmetric approaches have been reported.[25-27,29,30,36] Bearing this in mind, the development of an enantioselective method *via* our cyclophane route is the first of interest among several future directions.

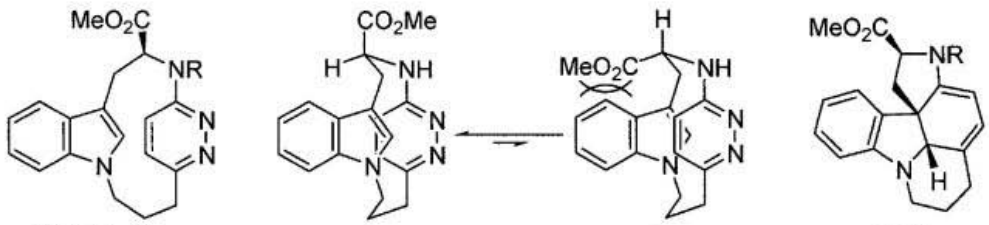
As discussed in Section 5.2.5, cyclophane **95** is believed to be in an *exo* conformation in solution at room temperature. If its acetyl derivative **96** and carbamate derivative **102** have the same conformational preference, resolving these three chiral cyclophanes becomes possible. More excitingly, asymmetric transannular IEDDA reaction can be expected from either enantiomer of **96** or **102** as long as the conformational rigidity remains at high temperature (see Chapter 4 for more detailed discussion), thus establishing an access to both natural (–)-strychnine and unnatural (+)-strychnine depending on the chirality of the cyclophane intermediate involved.



Scheme 5.30 A diastereoselective intramolecular IEDDA reaction.

The amino acid chirality was used by Snyder[116] to control the facial selectivity of an intramolecular IEDDA reaction of a (–)-tryptophan-tethered 1,2,4-triazine **137** (Scheme 5.30). Refluxing **137** with trifluoroacetic anhydride (TFAA) in dioxane produced tetracycle **138** as the sole product (>99% de), the loss of the trifluoroacetate group occurring during purification. The complete diastereo control was ascribed to a preferred conformation, which would result in *si*-face approach of the triazine subunit to the indole ring. The alternative conformation, which would lead to IEDDA reaction across the *re*-face and was

not observed, suffers a *gauche* interaction. Since the conformation of cyclophane **95** is locked at ambient temperature (*vide supra*), its (–)-tryptophan derivatives **139a-c** (Figure 5.8) are therefore anticipated to demonstrate similar behavior.



139a (R=H)
139b (R=Ac)
139c (R=CO_2Me)

A

B

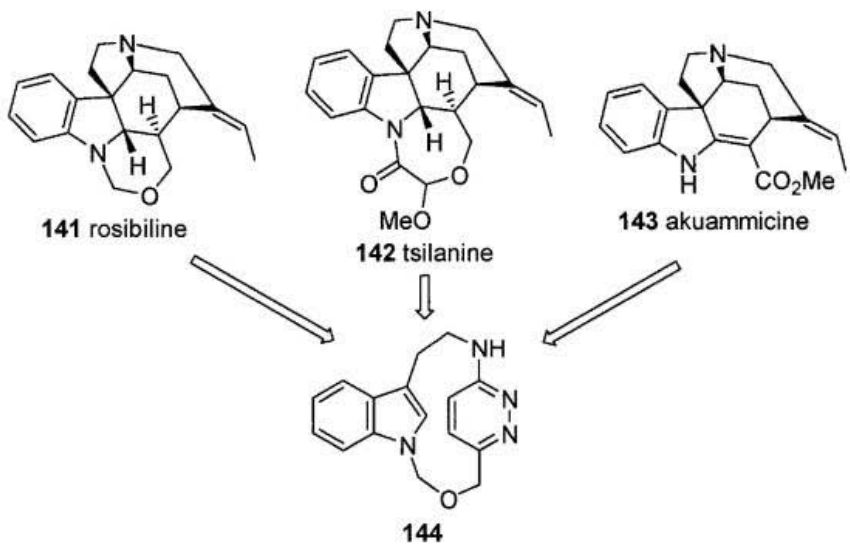
140b
140c

Figure 5.8 Conformational preference of cyclophanes **139a-c** and the structure of products from their transannular IEDDA reactions.

Applying Snyder's hypothesis, the syntheses of **139a-c** themselves by the hydroboration/Suzuki-Miyaura strategy would be expected to be diastereoselective in favor of conformation A to avoid the *gauche* interaction (conformation B) between the arene rings and the ester functionality (Figure 5.8). When it comes to the transannular IEDDA reaction of **139b-c**, this effect should be even more pronounced since their conformations are fixed. The desired products **140b-c**, resulting from conformation A, would therefore possess the correct relative and absolute stereochemistry of (–)-strychnine. As shown by Kuehne,[25] the methyl ester moiety could be readily removed by a three-step sequence in good yield. Moreover, this potential asymmetric approach requires starting materials ($ 22.70 for 10 g of (–)-tryptophan and $ 22.20 for 5 g of (–)-

tryptophan methyl ester hydrochloride) with comparable prices (according to the 2000-2001 Aldrich Catalog) as that ($ 33.60 for 10 g of tryptamine) of the previously discussed resolution approach, but offers much higher optical efficiency.

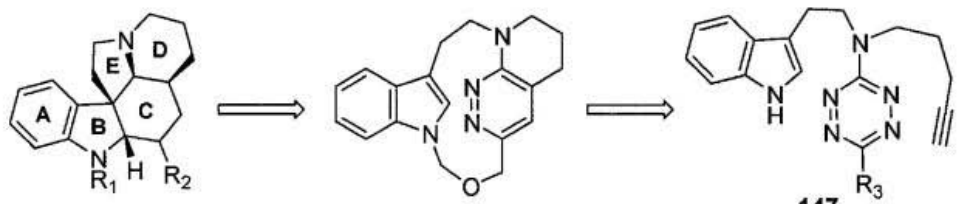
Since *Strychnos* alkaloids all have a characteristic skeleton, which is close to that of strychnine, our cyclophane approach should serve as a general entry into them. Furthermore, a common cyclophane intermediate to several targets is possible (Scheme 5.31).



Scheme 5.31 A possible common cyclophane intermediate **144** to strychnan group members **141**, **142** and **143**.

If the synthetic strategy is modified based on Boger's[141] and Snyder's[116] ideas, aspidosperma alkaloids, another very populous group of indole alkaloids, are accessible (Scheme 5.32). Rings C and E of aspidosperma alkaloid core **145** could be assembled by a transannular IEDDA reaction of cyclophane **146**, which

has a cleavable bottom tether similar to **144**. The pyridazine moiety in **146** should be readily introduced by an intramolecular IEDDA reaction between the alkynyl tether and the tetrazine unit in compound **147**.



145 aspidosperma alkaloid core

146

147

Scheme 5.32 Potential access to aspidosperma alkaloids *via* our cyclophane approach.

5.4 Experimental

General Experimental for Chapter 5. Reactions were performed under air unless otherwise indicated. Those experiments with moisture or air sensitive compounds were performed in anhydrous solvents under nitrogen in flame-dried glassware. Solvents for reactions were dried and distilled according to standard procedures. All other solvents were used as received. Chromatographic purifications were accomplished with 230-400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp in most cases and sometimes were also developed in PMA or vanillin dips. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on neat samples or nujol suspensions in KBr discs using a Mattson Polaris FT

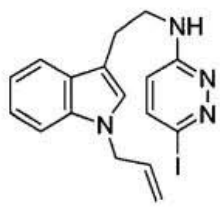
instrument. ^{1}H NMR spectra were obtained from $CDCl_3$ or DMSO-d_6 solutions using a Bruker Avance 500 instrument operating at 500.1 MHz. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 125.77 MHz. Chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$ and δ 39.5 for DMSO-d_6). Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. High resolution mass spectroscopic data were performed by the Mass Spectrometry Center, Chemistry Department, University of Ottawa, Ottawa, Ontario.

[2-(1*H*-Indol-3-yl)ethyl](6-iodo-pyridazin-3-yl)amine (91)

A suspension of tryptamine **2** (8.58 g, 53.6 mmol) and 3,6-diiodopyridazine **90** (16.6 g, 50.0 mmol) in *sec*-butanol (30 mL) was heated at reflux for 4 d. Column chromatography (15% acetone/CH_2Cl_2) gave **91** (18.2 g, 100%) as a yellow solid. M.p.=173-175 °C. IR (nujol) ν=3260 (s), 1595 (s), 1566 (m) cm^{-1}. MS *m/z* (%)=364 (0.2, M^+), 222 (4), 143 (100), 130 (41). ^{1}H NMR (DMSO-d_6): δ=2.97 (t, *J*=7.4 Hz, 2H), 3.56-3.60 (m, 2H), 6.61 (d, *J*=9.3 Hz, 1H), 6.96-6.99 (m, 1H),

7.05-7.08 (m, 1H), 7.12 (t, *J*=11.2 Hz, 1H), 7.16-7.17 (m, 1H), 7.34 (d, *J*=8.7 Hz, 1H), 7.52 (d, *J*=9.2 Hz, 1H), 7.56 (d, *J*=7.9 Hz, 1H), 10.81 (bs, 1H). ^{13}C NMR (DMSO-d_6): δ=24.4, 41.5, 111.3, 111.6, 111.8, 117.1, 118.2, 118.3, 120.9, 122.7, 127.2, 136.2, 136.4, 158.1. Anal. Calcd. for $C_{14}H_{13}IN_4$: C, 46.17; H, 3.60; N, 15.38. Found: C, 46.51; H, 3.53; N, 15.63.

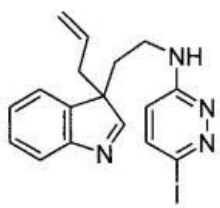
[2-(1-Allyl-1*H*-indol-3-yl)ethyl](6-iodo-pyridazin-3-yl)amine (89)



To a solution of **91** (3.64 g, 10.0 mmol) in DMF (40 mL) at room temperature was added freshly ground KOH powder (2.64 g, 40.0 mmol). After the mixture was stirred for 1 h, allyl bromide (1.25 g, 10.0 mmol) was added into it. The reaction mixture was stirred for an additional 2 h and diluted with H_2O (50 mL) to produce a light yellow precipitate. The mixture was suction filtered, and the filtrate was extracted with EtOAc (50 mL×3). The combined organic layers were washed with H_2O (50 mL×3), dried over $MgSO_4$, filtered, concentrated and combined with the suction filtration residue. Column chromatography (5% EtOAc/CH_2Cl_2) gave **89** (R_f 0.18, 3.66 g, 91%) as a white solid. M.p.=171-172 °C. IR (nujol) ν=3232 (s), 1590 (s), 1556 (m) cm^{-1}. MS *m/z* (%)=404 (0.2, M^+), 183 (100), 170 (38). ^{1}H NMR (DMSO-d_6): δ=2.97 (t, *J*=7.4 Hz, 2H), 3.56-3.60

(m, 2H), 4.76 (d, *J*=5.4 Hz, 2H), 5.03 (dd, *J*=17.2, 1.3 Hz, 1H), 5.13 (dd, *J*=10.1, 1.2 Hz, 1H), 5.93-6.00 (m, 1H), 6.60 (d, *J*=9.4 Hz, 1H), 7.01-7.03 (m, 1H), 7.10-7.13 (m, 2H), 7.17(s, 1H), 7.38 (d, *J*=8.2 Hz, 1H), 7.52 (d, *J*=9.4 Hz, 1H), 7.59 (d, *J*=7.9 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ=24.3, 41.5, 47.9, 109.9, 111.6, 116.6, 117.0, 118.5, 118.7, 121.1, 126.2, 127.7, 128.5, 134.5, 136.0, 136.4, 158.1. Anal. Calcd. for $C_{17}H_{17}IN_4$: C, 50.51; H, 4.24; N, 13.86. Found: C, 50.19; H, 4.18; N, 13.91.

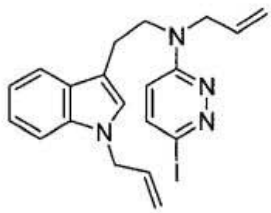
[2-(3-Allyl-3*H*-indol-3-yl)ethyl](6-iodo-pyridazin-3-yl)amine (92)



Compound **92** (R_f 0.36, 96 mg, 2%) was also obtained from above procedure as a white solid. M.p.=194 °C (decomp.). IR (nujol) ν=3400 (m), 1604 (m), 1575 (s) cm^{-1}. MS *m/z* (%)=405 (12), 404 (51, M$^+$), 376 (53), 277 (43), 236 (44), 130 (100). ^{1}H NMR (DMSO-d_6): δ=2.16-2.28 (m, 2H), 2.43-2.54 (m, 2H), 2.97-3.03 (m, 1H), 3.71-3.75 (m, 1H), 5.02-5.09 (m, 2H), 5.42-5.43 (m, 1H), 5.69-5.77 (m, 1H), 6.48 (d, *J*=7.7 Hz, 1H), 6.55 (bs, 1H), 6.61-6.64 (m, 1H), 6.82 (d, *J*=9.4 Hz, 1H), 6.93-6.96 (m, 1H), 7.12 (d, *J*=7.1 Hz, 1H), 7.71 (d, *J*=9.2 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ=35.1, 42.3, 45.5, 56.4, 79.4, 108.7, 112.2, 115.7, 117.5,

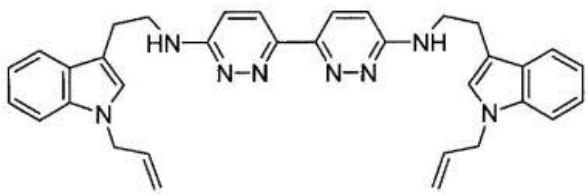
118.1, 123.0, 127.8, 132.0, 134.3, 136.7, 149.8, 156.2. HRMS Calcd. for $C_{17}H_{17}IN_4$: 404.0499. Found: 404.0487.

Allyl[2-(1-allyl-1*H*-indol-3-yl)ethyl](6-iodo-pyridazin-3-yl)amine (93)



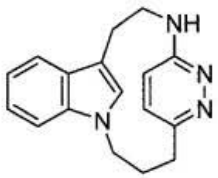
Compound **93** (R_f 0.64, 101 mg, 2%) was also obtained from above procedure as a brown oil. IR (KBr) ν=1643 (w), 1613 (w) cm^{-1}. MS *m/z* (%)=445 (0.1), 444 (1, M^+), 183 (100), 170 (44). ^1H NMR ($CDCl_3$): δ=3.07-3.10 (m, 2H), 3.81-3.84 (m, 2H), 4.03-4.04 (m, 2H), 4.64-4.66 (m, 2H), 5.03-5.19 (m, 4H), 5.75-5.83 (m, 1H), 5.89-5.97 (m, 1H), 6.35 (d, *J*=9.4 Hz, 1H), 6.90 (s, 1H), 7.10-7.13 (m, 1H), 7.18-7.22 (m, 1H), 7.28 (d, *J*=8.3 Hz, 1H), 7.32 (d, *J*=9.5 Hz, 1H), 7.61 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=23.1, 48.6, 49.6, 51.2, 109.6, 110.1, 111.9, 113.5, 116.8, 117.2, 118.8, 119.1, 121.7, 125.9, 127.9, 132.5, 133.4, 136.4, 136.5, 157.8. HRMS Calcd. for $C_{20}H_{21}IN_4$: 444.0812. Found: 444.0814.

N^6,$N^{6'}$-Bis[2-(1-allyl-1*H*-indol-3-yl)ethyl][3,3']bipyridazinyl)-6,6'-diamine (94)



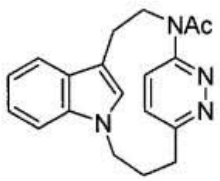
Solid **89** (100 mg, 0.247 mmol) was treated with 9-BBN (0.5 M in THF, 0.75 mL, 0.38 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h, diluted with THF (10 mL), and injected into a refluxing slurry of $Pd(PPh_3)_4$ (58 mg, 0.050 mmol) and Cs_2CO_3 (244 mg, 0.749 mmol) in THF (50 mL) over 2.5 h. The resulting mixture was heated at reflux for an additional 12 h, concentrated, and extracted with EtOAc (25 mL×2). The combined organic layers were washed with H_2O (25 mL×2) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **94** (52 mg, 76%) as a white solid. M.p.=204-206 °C. IR (nujol) ν=1606 (m) cm^{-1}. MS *m/z* (%)=554 (0.4, M^+), 183 (100), 170 (21). ^1H NMR ($CDCl_3$): δ=3.16 (t, *J*=6.5 Hz, 4H), 3.82-3.86 (m, 4H), 4.68-4.69 (m, 4H), 4.85-4.87 (m, 2H), 5.10 (dd, *J*=7.0, 1.3 Hz, 2H), 5.19 (dd, *J*=10.3, 1.3 Hz, 2H), 5.93-6.01 (m, 2H), 6.65 (d, *J*=9.3 Hz, 2H), 6.97 (s, 2H), 7.10-7.13 (m, 2H), 7.20-7.24 (m, 2H), 7.31 (d, *J*=8.3 Hz, 2H), 7.61 (d, *J*=8.0 Hz, 2H), 8.34 (d, *J*=9.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ=25.1, 42.2, 48.7, 109.7, 111.8, 114.2, 117.4, 118.9, 119.1, 121.8, 125.2, 126.0, 128.0, 133.4, 136.6, 149.4, 158.8. HRMS Calcd. for $C_{34}H_{34}N_8$: 554.2904. Found: 554.2924.

13-Aza-[3](1,3)indolo[3](3,6)pyridazinophane (95)



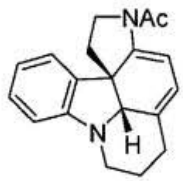
Solid **89** (2.02 g, 5.00 mmol) was treated with 9-BBN (0.5 M in THF, 60 mL, 30 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, treated with H_2O (900 mg, 50.0 mmol) and injected into a refluxing slurry of $Pd(PPh_3)_4$ (1.16 g, 1.00 mmol) and Cs_2CO_3 (6.52 g, 20.0 mmol) in THF (600 mL) over 6 h. The resulting mixture was heated at reflux for an additional 2 d, concentrated, diluted with H_2O (50 mL) and extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **95** (905 mg, 65%) as a light yellow foam. IR (nujol) ν=1598 (s) cm^{-1}. MS *m/z* (%)=279 (9), 278 (45, M^+), 157 (20), 121 (100), 109 (65). ^1H NMR ($CDCl_3$): δ=2.09-2.13 (m, 1H), 2.50-2.53 (m, 1H), 2.71-2.77 (m, 1H), 3.04-3.07 (m, 1H), 3.10-3.20 (m, 2H), 3.46-3.50 (m, 1H), 3.65-3.72 (m, 1H), 3.82-3.88 (m, 1H), 4.34-4.38 (m, 1H), 4.55-4.57 (m, 1H), 5.91-5.93 (m, 1H), 5.95 (s, 1H), 5.98-6.00 (m, 1H), 7.07-7.09 (m, 1H), 7.16-7.19 (m, 1H), 7.23-7.26 (m, 1H), 7.48 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=26.0, 29.5, 34.5, 46.4, 46.9, 109.8, 112.3, 116.1, 118.5, 118.7, 121.3, 124.6, 126.9, 128.4, 133.9, 154.8, 163.5. HRMS Calcd. for $C_{17}H_{18}N_4$: 278.1530. Found: 278.1528.

13-Acetyl-13-aza-[3](1,3)indolo[3](3,6)pyridazinophane (96)



To a solution of NaHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol) in anhydrous THF (5 mL) at –78 °C was added a solution of **95** (139 mg, 0.500 mmol) in anhydrous THF (5 mL). After the resulting solution was stirred at –78 °C for 30 min, Ac_2O (153 mg, 1.50 mmol) was injected into it. The reaction mixture was stirred at room temperature for 3 h, treated with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **96** (101 mg, 63%) as a light brown solid. M.p.=178-181 °C. IR (nujol) v=1733 (m), 1657 (s), 1580 (w) cm^{-1}. MS *m/z* (%)=321 (9), 320 (39, M^+), 277 (9), 151 (100), 121 (54). ^1H NMR ($CDCl_3$): δ=2.22 (s, 3H), 2.25-2.29 (m, 1H), 2.46-2.54 (m, 1H), 2.67-2.72 (m, 1H), 3.06-3.10 (m, 1H), 3.17-3.22 (m, 1H), 3.37-3.43 (m, 1H), 3.70-3.75 (m, 1H), 3.91-3.96 (m, 1H), 4.39-4.43 (m, 1H), 5.01-5.05 (m, 1H), 5.84 (s, 1H), 6.24-6.26 (m, 1H), 6.29-6.31 (m, 1H), 7.06-7.09 (m, 1H), 7.17-7.23 (m, 2H), 7.46 (d, *J*=7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=23.1, 25.6, 26.7, 34.8, 45.5, 46.3, 109.7, 112.3, 118.8, 119.0, 121.5, 123.6, 126.2, 126.7, 126.8, 133.9, 158.1, 160.6, 170.1. HRMS Calcd. for $C_{19}H_{20}N_4O$: 320.1636. Found: 320.1659.

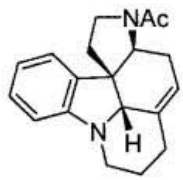
(±)-(3a*S,10b*R**)-1-Acetyl-1,2,3,9,10,10b-hexahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (97)**



Method A. A mixture of **95** (250 mg, 0.898 mmol) in acetic anhydride (2 mL) was heated at reflux for 7 d. The resulting mixture was cooled to room temperature, and column chromatography (2.5% MeOH/CH_2Cl_2) gave **97** (126 mg, 48%) as a brown solid. M.p.=175-177 °C. IR (nujol) ν=1669 (m), 1641 (s), 1598 (w) cm^{-1}. MS *m/z* (%)=293 (23), 292 (100, M^+), 249 (74), 221 (46), 75 (31). ^1H NMR ($CDCl_3$) (This compound appears as a mixture of rotamers with an approximate ratio of 1.0/0.3, and only the signals of the major rotamer are given here.): δ=1.54-1.56 (m, 2H), 2.07-2.11 (m, 1H), 2.15-2.21 (m, 1H), 2.26 (s, 3H), 2.35-2.37 (m, 2H), 3.19-3.25 (m, 1H), 3.80-3.85 (m, 3H), 4.26 (s, 1H), 5.62-5.63 (m, 1H), 6.53-6.56 (m, 2H), 6.65-6.68 (m, 1H), 6.89 (d, *J*=7.0 Hz, 1H), 7.11-7.14 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=22.1, 24.5, 31.7, 36.9, 44.7, 47.3, 52.6, 72.0, 103.6, 107.8, 118.3, 120.2, 122.0, 127.9, 128.6, 134.9, 139.4, 148.9, 169.0. HRMS Calcd. for $C_{19}H_{20}N_2O$: 292.1575. Found: 292.1578.

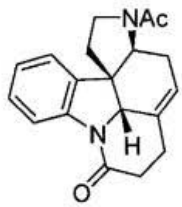
Method B. A solution of **96** (71 mg, 0.22 mmol) in *N*,*N*-diethylaniline (2 mL) was heated at reflux for 2 h. The resulting mixture was cooled to room temperature, and column chromatography (2.5% MeOH/CH_2Cl_2) gave **97** (63 mg, 97%) as a brown solid.

(±)-(3a*S,10b*R**,12a*S**)-1-Acetyl-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (99)**



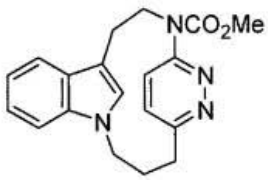
To a solution of **97** (59 mg, 0.17 mmol) in CaH_2-dried benzene (2 mL) at room temperature was added $NaBH_4$ (100 mg, 2.64 mmol) in one portion. The resulting slurry was cooled to 0 °C, and TFA (4 mL) was injected dropwise into it. The slurry was stirred at room temperature for 12 h, concentrated, diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (2.5% MeOH/CH_2Cl_2) gave **99** (49 mg, 96%) as a light yellow solid. M.p.=173-175 °C. IR (nujol) ν=1638 (s), 1595 (w) cm^{-1}. MS *m/z* (%)=295 (23), 294 (100, M^+), 208 (42), 180 (31). ^1H NMR ($CDCl_3$): δ=1.55-1.66 (m, 2H), 1.98-2.01 (m, 2H), 2.14 (s, 3H), 2.18 (bs, 2H), 2.25-2.27 (m, 1H), 3.21-3.30 (m, 2H), 3.59-3.62 (m, 1H), 3.66-3.75 (m, 3H), 3.90 (s, 1H), 5.38-5.39 (m, 1H), 6.55 (d, *J*=7.8 Hz, 1H), 6.64-6.67 (m, 1H), 7.01 (d, *J*=7.3 Hz, 1H), 7.10-7.14 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=23.6, 24.8, 28.9, 33.2, 35.1, 44.5, 47.1, 53.1, 59.0, 70.8, 108.7, 117.5, 122.2, 124.0, 128.2, 132.8, 134.3, 149.8, 171.3. HRMS Calcd. for $C_{19}H_{22}N_2O$: 294.1731. Found: 294.1732.

(±)-(3a*S,10b*R**,12a*S**)-1-Acetyl-8-oxo-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (100)**



To a yellow slurry of PDC (527 mg, 1.40 mmol) and celite (527 mg) in CH_2Cl_2 (8 mL) at room temperature was added a solution of **99** (40 mg, 0.14 mmol) in CH_2Cl_2 (6 mL) to afford a dark brown slurry. The resulting mixture was stirred for 3 d, diluted with CH_2Cl_2 (15 mL) and suction filtered. Column chromatography (2.5% MeOH/CH_2Cl_2) of the concentrated filtrate gave **100** (25 mg, 59%) as a white foam. IR (nujol) ν=1661 (m) cm^{-1}. MS *m/z* (%)=309 (22), 308 (100, M^+), 265 (11), 222 (60). ^1H NMR ($CDCl_3$): δ=2.00-2.14 (m, 3H), 2.17 (s, 3H), 2.42-2.52 (m, 2H), 2.72-2.80 (m, 2H), 3.33-3.37 (m, 1H), 3.66-3.69 (m, 1H), 3.76-3.82 (m, 2H), 4.50 (s, 1H), 5.50-5.51 (m, 1H), 7.03-7.06 (m, 1H), 7.09-7.10 (m, 1H), 7.25-7.28 (m, 1H), 8.07 (d, *J*=7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=23.6, 25.5, 28.1, 32.7, 37.6, 46.8, 52.2, 60.0, 66.4, 116.6, 123.0, 123.7, 123.8, 128.9, 131.5, 131.6, 142.1, 171.7, 173.3. HRMS Calcd. for $C_{19}H_{20}N_2O_2$: 308.1524. Found: 308.1549.

13-Methoxycarbonyl-13-aza-[3](1,3)indolo[3](3,6)pyridazinophane (102)



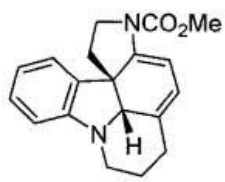
Method A. To a solution of **95** (130 mg, 0.467 mmol) in CH_2Cl_2 (4 mL) was added saturated aqueous $NaHCO_3$ solution (6 mL). To the above mixture at room temperature was injected $ClCO_2Me$ (88 mg, 0.93 mmol) dropwise. The resulting slurry was stirred for 12 h and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **102** (33 mg, 21%) as a light yellow foam. IR (nujol) ν=1716 (s), 1610(m) cm^{-1}. MS *m/z* (%)=337 (6), 336 (27, M^+), 304 (38), 169 (100), 135 (51). ^1H NMR ($CDCl_3$): δ=2.23-2.27 (m, 1H), 2.47-2.55 (m, 1H), 2.76-2.79 (m, 1H), 3.07-3.18 (m, 2H), 3.32-3.38 (m, 1H), 3.79 (bs, 3H), 3.91-3.96 (m, 1H), 4.28-4.39 (m, 2H), 4.59-4.63 (m, 1H), 5.95 (bs, 1H), 6.26-6.30 (m, 2H), 7.04-7.07 (m, 1H), 7.13-7.20 (m, 2H), 7.43 (d, *J*=7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=24.7, 26.8, 34.8, 46.5, 49.0, 53.2, 109.5, 110.5 (b), 118.6, 118.9, 121.3, 124.9, 125.3, 126.9, 128.0 (b), 133.7, 155.0, 158.4 (b), 160.0. HRMS Calcd. for $C_{19}H_{20}N_4O_2$: 336.1585. Found: 336.1559.

Method B. To a solution of **95** (139 mg, 0.500 mmol) in anhydrous THF (10 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 120 mg, 3.00 mmol) in one portion. The resulting slurry was stirred at room temperature for 2 h, cooled again to 0 °C and treated with $ClCO_2Me$ (284 mg, 3.00 mmol). The reaction

mixture was stirred at room temperature for 12 h, treated with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **102** (131 mg, 78%) as a light yellow foam.

Method C. To a solution of NaHMDS (1.0 M in THF, 3.0 mL, 3.0 mL) in anhydrous THF (10 mL) at –78 °C was added a solution of **95** (278 mg, 1.00 mmol) in anhydrous THF (10 mL). After the resulting solution was stirred at –78 °C for 1 h, $ClCO_2Me$ (378 mg, 4.00 mmol) was injected into it. The reaction mixture was stirred at room temperature for 3 h, treated with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (25 mL×3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave **102** (323 mg, 96%) as a light yellow foam.

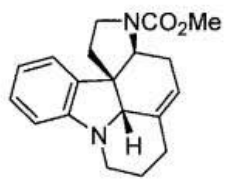
(±)-(3a*S,10b*R**)-1-Methoxycarbonyl-1,2,3,9,10,10b-hexahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (103)**



Method A. A mixture of **95** (50 mg, 0.18 mmol) in dimethyl pyrocarbonate (2 mL) was heated at reflux for 12 h, and diluted with 1,3,5-triisopropylbenzene (2 mL). The resulting mixture was heated again at reflux for 2 h and cooled to room temperature. Column chromatography (5% EtOAc/CH_2Cl_2) gave **103** (18 mg, 32%) as a white solid. M.p.=182-183 °C. IR (nujol) ν=1711 (s), 1657 (m), 1593 (m) cm^{-1}. MS *m/z* (%)=309 (21), 308 (100, M^+), 249 (26), 221 (31). ^1H NMR (DMSO-d_6, 373 K): δ=1.41-1.54 (m, 2H), 1.87-1.90 (m, 1H), 2.10-2.23 (m, 2H), 2.30-2.33 (m, 1H), 3.16-3.22 (m, 1H), 3.64-3.69 (m, 1H), 3.77-3.84 (m, 5H), 4.26 (s, 1H), 5.56-5.57 (m, 1H), 5.88-5.90 (m, 1H), 6.56-6.60 (m, 2H), 6.79 (d, *J*=7.1 Hz, 1H), 7.04-7.07 (m, 1H). ^{13}C NMR (DMSO-d_6, 373 K): δ=21.3, 30.6, 35.6, 43.4, 45.0, 51.8, 52.1, 70.6, 98.8, 106.7, 117.0, 118.3, 121.0, 126.8, 127.6, 134.4, 138.9, 148.5, 152.4. HRMS Calcd. for $C_{19}H_{20}N_2O_2$: 308.1524. Found: 308.1519.

Method B. A solution of **102** (300 mg, 0.892 mmol) in *N*,*N*-diethylaniline (2 mL) was heated at reflux for 2 h. Column chromatography (5% EtOAc/CH_2Cl_2) gave **103** (274 mg, 100%) as a white solid.

(±)-(3a*S,10b*R**,12a*S**)-1-Methoxycarbonyl-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (104)**

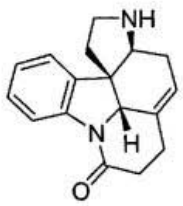


To a solution of **103** (89 mg, 0.29 mmol) in CaH_2-dried benzene (6 mL) at room temperature was added $NaBH_4$ (200 mg, 5.29 mmol) in one portion. The resulting slurry was cooled to 0 °C, and TFA (8 mL) was injected dropwise into it. The slurry was stirred at room temperature for 12 h, concentrated, diluted with saturated aqueous $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (25 mL×3). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$ and filtered. A clean sample of **104** (90 mg, 100%) as a white foam was afforded after concentration of the organic layers under reduced pressure and used in the next step without further purification. IR (nujol) ν=1715 (s), 1598 (m) cm^{-1}. MS *m/z* (%)=311 (22), 310 (100, M^+), 208 (47), 180 (37). ^1H NMR ($CDCl_3$): δ=1.55-1.68 (m, 2H), 1.91-1.95 (m, 2H), 2.09-2.19 (m, 2H), 2.25-2.28 (m, 1H), 2.83-3.04 (m, 1H), 3.24-3.30 (m, 1H), 3.60 (bs, 3H), 3.71-3.72 (m, 1H), 3.75 (s, 3H), 3.88 (s, 1H), 5.38 (bs, 1H), 6.54 (d, *J*=7.8 Hz, 1H), 6.64-6.66 (m, 1H), 7.06 (d, *J*=7.2 Hz, 1H), 7.09-7.12 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=24.9, 28.6 (b), 33.3, 34.7 (b), 44.5, 45.8 (b), 52.2, 53.4, 58.6 (b), 70.7, 108.5, 117.6, 121.6 (b), 124.4, 128.1, 132.8, 134.8 (b), 139.1, 149.7. HRMS Calcd. for $C_{19}H_{22}N_2O_2$: 310.1680. Found: 310.1708.

(±)-(3a*S,10b*R**,12a*S**)-1-Methoxycarbonyl-8-oxo-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (105)**

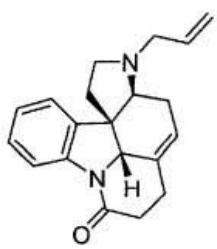
To a yellow slurry of PDC (978 mg, 2.60 mmol) and celite (978 mg) in CH_2Cl_2 (7 mL) at room temperature was added a solution of **104** (80 mg, 0.26 mmol) in CH_2Cl_2 (6 mL) to afford a dark brown slurry. The mixture was stirred for 3 d, diluted with CH_2Cl_2 (20 mL) and suction filtered. Column chromatography (30% EtOAc/CH_2Cl_2) of the concentrated filtrate gave **105** (25 mg, 30%) as a light yellow solid. M.p.=182-184 °C. IR (nujol) ν=1690 (s), 1596 (m) cm^{-1}. MS *m/z* (%)=325 (23), 324 (100, M^+), 222 (62). ^1H NMR ($CDCl_3$): δ=1.95-2.02 (m, 2H), 2.09-2.15 (m, 1H), 2.42-2.52 (m, 2H), 2.70-2.78 (m, 2H), 3.11 (bs, 1H), 3.70-3.75 (m, 3H), 3.77 (s, 3H), 4.48 (s, 1H), 5.50-5.51 (m, 1H), 7.02-7.05 (m, 1H), 7.15 (d, *J*=7.6 Hz, 1H), 7.24-7.27 (m, 1H), 8.06 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=25.6, 28.0 (b), 32.7, 37.2 (b), 45.8 (b), 52.4, 52.7 (b), 59.5 (b), 66.4, 116.5, 122.4, 123.8, 124.2, 128.8, 131.6, 132.1, 142.0, 158.0, 173.2. HRMS Calcd. for $C_{19}H_{20}N_2O_3$: 324.1473. Found: 324.1493.

(±)-(3a*S,10b*R**,12a*S**)-8-Oxo-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (61)**



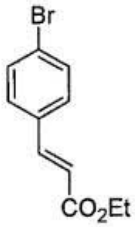
A solution of **105** (6 mg, 0.02 mmol) in chloroform (4 mL) at room temperature was treated with TMS-I (0.5 mL, 3.5 mmol). The mixture was heated at reflux for 6 h, cooled to room temperature, treated with methanol (5 mL) and heated at reflux again for 6 h. The solution was concentrated, diluted with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford crude **61** as a yellow oil. This compound was relatively unstable and attempted purification resulted in significant loss of mass, probably due to decomposition. Therefore, it was immediately subjected to the next step. HRMS Calcd. for $C_{17}H_{18}N_2O$: 266.1418. Found: 266.1430.

(±)-(3a*S,10b*R**,12a*S**)-1-Allyl-8-oxo-1,2,3,9,10,10b,12,12a-octahydro-8*H*-pyrido[1,2,3-*lm*]pyrrolo[2,3-*d*]carbazole (101)**



A solution of the crude product from the above procedure in DMF (4 mL) was treated with Li_2CO_3 (10 mg, 0.14 mmol) and a solution of allyl bromide (7.0 mg, 0.058 mmol) in DMF (1 mL) at room temperature. The reaction mixture was stirred at room temperaturefor 24 h, treated with H_2O (15 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL×2), dried over Na_2SO_4, filtered and concentrated. Preparative thin layer chromatography (5% MeOH/CH_2Cl_2) gave **101** (8.2 mg, 93%) as a tan solid. M.p.=121-123 °C. IR ($CHCl_3$) ν=1671 (s), 1600 (w) cm^{-1}. MS *m/z* (%)=307 (15), 306 (74, M^+), 305 (100), 291 (7), 265 (7), 222 (22), 180 (19), 167 (20). ^1H NMR ($CDCl_3$): δ=1.84-1.91 (m, 2H), 1.95-2.01 (m, 1H), 2.21-2.25 (m, 1H), 2.40-2.51 (m, 3H), 2.67-2.78 (m, 3H), 2.88-2.92 (m, 1H), 3.30-3.35 (m, 1H), 3.54-3.58 (m, 1H), 4.41 (s, 1H), 5.14-5.16 (m, 1H), 5.26-5.29 (m, 1H), 5.49-5.50 (m, 1H), 5.97-6.02 (m, 1H), 7.00-7.04 (m, 1H), 7.18-7.21(m, 1H), 7.71 (d, *J*=7.4 Hz, 1H), 8.02 (d, *J*=7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=25.8, 27.0, 32.7, 38.7, 50.5, 52.4, 56.9, 65.7, 67.3, 116.0, 116.5, 121.9, 123.7, 126.1, 128.0, 133.0, 134.5, 136.1, 141.7, 172.8. HRMS Calcd. for $C_{20}H_{22}N_2O$: 306.1731. Found: 306.1735.

Ethyl 4-bromocinnamate (119)

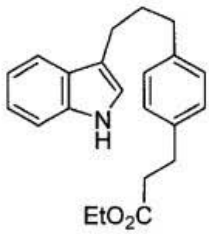


To a slurry of NaH (60% dispersion in mineral oil, 1.2 g, 30 mmol) in anhydrous THF (30 mL) at 0 °C was added triethyl phosphonoacetate (7.17 g, 32.0 mmol) dropwise. The resulting yellow solution was stirred at 0 °C for 45 min, and a solution of **118** (3.70 g, 20.0 mmol) in anhydrous THF (10 mL) was added into it. The reaction mixture was then heated at reflux for 2 h, cooled to room temperature, treated with H_2O (20 mL) and extracted with EtOAc (50 mL×2). The combined organic layers were washed with saturated aqueous $Na_2S_2O_5$ (100 mL×3), dried over Na_2SO_4, filtered and concentrated. Column chromatography (9% EtOAc/petroleum ether) gave **119** (4.72 g, 93%) as a colorless oil. This compound is also commercially available at a rate of $ 170.00/25 g (Aldrich 2000-2001 catalog). ^{1}H NMR ($CDCl_3$): δ=1.33 (t, *J*=7.1 Hz, 3H), 4.26 (q, *J*=7.2 Hz, 2H), 6.42 (d, *J*=16.1 Hz, 1H), 7.38 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 7.61 (d, *J*=16.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=14.3, 60.6, 119.0, 124.4, 129.4, 132.1, 133.4, 143.1, 166.6.

Ethyl 4-[3-(1*H*-indol-3-yl)-prop-1-ynyl]cinnamate (120)

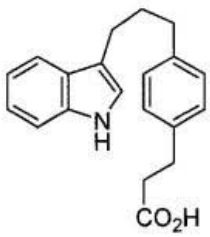
To a solution of **119** (340 mg, 1.33 mmol) in THF (4 mL) was added Et_3N (2 mL), $Pd(PPh_3)_2Cl_2$ (47 mg, 0.067 mmol) and CuI (13 mg, 0.068 mmol). The resulting black slurry was heated at reflux for 6 h, cooled to room temperature and extracted with EtOAc (25 mL×2). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. Column chromatography (25% EtOAc/petroleum ether) gave **120** (329 mg, 75%) as a light yellow solid. M.p.=127-128 °C. IR (nujol) v=3357 (s), 2237 (w), 1697 (s), 1649 (m), 1600 (w) cm^{-1}. MS *m/z* (%)=330 (25), 329 (100, M^+), 300 (33), 254 (18), 128 (33). ^1H NMR ($CDCl_3$): δ=1.33 (t, *J*=7.2 Hz, 3H), 3.93-3.94 (m, 2H), 4.26 (q, *J*=7.2 Hz, 2H), 6.41 (d, *J*=16.0 Hz, 1H), 7.14-7.17 (m, 1H), 7.20-7.25 (m, 2H), 7.37 (d, *J*=7.9 Hz, 1H), 7.43 (s, 4H), 7.64 (d, *J*=16.1 Hz, 1H), 7.70 (d, *J*=8.1 Hz, 1H), 8.04 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ=14.3, 16.4, 60.5, 80.9, 90.4, 111.2, 111.3, 118.6, 118.8, 119.6, 122.0, 122.3, 125.8, 126.7, 127.8, 132.1, 133.7, 136.5, 143.8, 166.9. Anal Calcd. for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.07; H, 5.81; N, 4.22. HRMS Calcd. for $C_{22}H_{19}NO_2$: 329.1415. Found: 329.1433.

Ethyl 3-{4-[3-(1*H*-indol-3-yl)-propyl]phenyl}propionate (121)



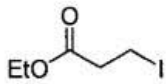
To a solution of **120** (50 mg, 0.15 mmol) in MeOH (10 mL) was added Pd/C (10%, 12 mg). The resulting black slurry was stirred under a H_2 atmosphere at room temperature for 4 h, suction filtered and concentrated. Column chromatography (20% EtOAc/petroleum ether) gave **121** (49 mg, 95%) as a white solid. M.p.=42-43 °C. IR (nujol) ν=3326 (s), 1718 (s), 1620 (w) cm^{-1}. MS *m/z* (%)=336 (4), 335 (17, M^+), 290 (5), 130 (100), 117 (12). ^1H NMR ($CDCl_3$): δ=1.23 (t, *J*=7.1 Hz, 3H), 2.03 (quintet, *J*=7.7 Hz, 2H), 2.60 (t, *J*=7.9 Hz, 2H), 2.68 (t, *J*=7.8 Hz, 2H), 2.79 (t, *J*=7.6 Hz, 2H), 2.92 (t, *J*=7.9 Hz, 2H), 4.12 (q, *J*=7.2 Hz, 2H), 6.95-6.96 (m, 1H), 7.08-7.13 (m, 5H), 7.16-7.19 (m, 1H), 7.34 (d, *J*=8.1 Hz, 1H), 7.58 (d, *J*=7.8 Hz, 1H), 7.91 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ=14.2, 24.7, 30.6, 31.7, 35.3, 36.0, 60.4, 111.0, 116.6, 118.9, 119.1, 121.1, 121.8, 127.6, 128.2, 128.6, 136.3, 137.8, 140.4, 173.0. Anal. Calcd. for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18. Found: C, 78.94; H, 7.60; N, 4.19.

3-{4-[3-(1*H*-Indol-3-yl)-propyl]phenyl}propionic acid (122)



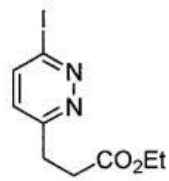
To a solution of **121** (130 mg, 0.388 mmol) in MeOH (6 mL) was added a solution of KOH (109 mg, 1.94 mmol) in H_2O (5 mL). The resulting cloudy mixture was heated at reflux for 4 h and concentrated under reduced pressure. After the residue was dissolved in H_2O (5 mL), the solution was cooled to 0 °C, treated with aqueous HCl solution (1.2 N, 5 mL) to afford a light brown precipitate and extracted with EtOAc (25 mL×2). The combined organic layers were dried over Na_2SO_4 and filtered. Acid **122** (120 mg, 100%) was obtained as a tan solid after concentration of the organic layers under reduced pressure and then used in the next step without further purification. M.p.=146-147 °C. IR (nujol) ν=3407 (s), 1699 (s), 1616 (w) cm^{-1}. MS *m/z* (%)=308 (7), 307 (30, M^+), 130 (100), 117 (16). ^1H NMR ($CDCl_3$): δ=2.01-2.07 (m, 2H), 2.65-2.70 (m, 4H), 2.79 (t, *J*=7.3 Hz, 2H), 2.93 (t, *J*=7.8 Hz, 2H), 6.96-6.97 (m, 1H), 7.08-7.14 (m, 5H), 7.16-7.20 (m, 1H), 7.34 (d, *J*=8.2 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.89 (bs, 1H), 10.85 (bs, 1H). ^{13}C NMR ($CDCl_3$): δ=24.7, 30.2, 31.6, 35.3, 35.5, 111.0, 116.6, 119.0, 119.1, 121.1, 121.9, 127.6, 128.1, 128.6, 136.4, 137.4, 140.6, 178.3. HRMS Calcd. for $C_{20}H_{21}NO_2$: 307.1571. Found: 307.1578.

Ethyl 3-iodopropionate (125)



A mixture of **124** (1.81 g, 10.0 mmol) and NaI (2.25 g, 15.0 mmol) in acetone (20 mL) was heated at reflux for 12 h. The reaction mixture was concentrated under reduced pressure, diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (25 mL×2). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and filtered. Iodide **125**[127] (2.23 g, 98%) was obtained as a light yellow oil after concentration of the organic layers under reduced pressure and then used in the next step without further purification. MS *m/z* (%)=229 (0.7), 228 (10, M^+), 200 (27), 183 (13), 155 (38), 101 (44), 73 (100). ^1H NMR ($CDCl_3$): δ=1.29 (t, *J*=7.2 Hz, 3H), 2.97 (t, *J*=7.2 Hz, 2H), 3.33 (t, *J*=7.1 Hz, 2H), 4.19 (q, *J*=7.2 Hz, 2H).

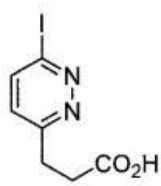
Ethyl 3-(6-iodopyridazin-3-yl)propionate (126)



Granular Zn (568 mg, 8.69 mmol) was treated with a solution of 1,2-dibromoethane (82 mg, 0.44 mmol) in anhydrous THF (1.5 mL). The suspension was brought to reflux and then cooled to room temperature right away. This process was repeated for three times in total before TMS-Cl (38 mg, 0.35 mmol) was injected into the mixture. The resulting slurry was stirred at room

temperature for 30 min, and a solution of **125** (1.80 g, 7.89 mmol) in anhydrous THF (3.5 mL) was added. The mixture was then heated at reflux for 3 h, cooled to room temperature and cannulated to a mixture of **90** (2.62 g, 7.89 mmol) and $Pd(PPh_3)_4$ (456 mg, 0.395 mmol) in DMF (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 12 h, treated with H_2O (10 mL) and extracted with EtOAc (50 mL×2). The combined organic layers were washed with H_2O (50 mL×2) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Column chromatography (20% EtOAc/CH_2Cl_2) gave **126** (869 mg, 36%) as a brown oil. IR (KBr) ν=1736 (s), 1562 (w) cm^{-1}. MS *m/z* (%)=307 (3), 306 (11, M^+), 261 (31), 233 (100), 191 (7), 141 (13). ^1H NMR ($CDCl_3$): δ=1.24 (t, *J*=7.1 Hz, 3H), 2.90 (t, *J*=7.1 Hz, 2H), 3.20 (t, *J*=7.1 Hz, 2H), 4.12 (q, *J*=7.1 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 1H), 7.75 (d, *J*=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=14.1, 30.4, 32.5, 60.7, 123.1, 128.1, 136.9, 161.3, 172.4. HRMS Calcd. for $C_9H_{11}N_2O_2$: 305.9867. Found: 305.9854.

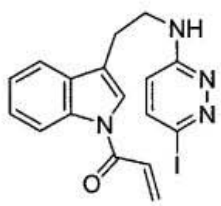
3-(6-Iodopyridazin-3-yl)propionic acid (127)



To a solution of **126** (306 mg, 1.00 mmol) in THF/MeOH/H_2O (3/1/1, 5 mL) at room temperature was added freshly ground $LiOH\theta H_2O$ powder (84 mg, 2.0 mmol). The resulting slurry was stirred at room temperature for 1 h,

concentrated under reduced pressure and diluted with H_2O (5 mL). The aqueous solution was then acidified with HCl aqueous solution (1.2 N, 2 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were dried over $MgSO_4$ and filtered. Acid **127** (239 mg, 86%) was obtained as a white solid after concentration of the organic layers under reduced pressure and then used in the next step without further purification. M.p.=133-135 °C. IR (nujol) ν=1695 (s), 1564 (w) cm^{-1}. MS *m/z* (%)=279 (3), 278 (25, M^+), 233 (100), 191 (11), 141 (23). ^1H NMR ($CDCl_3$): δ=1.63 (bs, 1H), 2.98 (t, *J*=6.9 Hz, 2H), 3.22 (t, *J*=6.9 Hz, 2H), 7.09 (d, *J*=8.6 Hz, 1H), 7.78 (d, *J*=8.7 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ=30.0, 32.0, 124.7, 128.6, 136.9, 161.6, 173.5. HRMS Calcd. for $C_7H_7IN_2O_2$: 277.9554. Found: 277.9538.

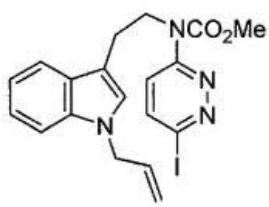
[2-(1-Acryloyl-1*H*-indol-3-yl)ethyl](6-iodo-pyridazin-3-yl)amine (130)



To a solution of **91** (1.00 g, 2.75 mmol) in DMF (4 mL) at room temperature was added freshly ground NaOH powder (440 mg, 11.0 mmol). The resulting slurry was stirred for 1 h, cooled to 0 °C and treated with acryloyl chloride (373 mg, 4.12 mmol). The reaction mixture was stirred for an additional 15 min, treated with H_2O (10 mL) and extracted with CH_2Cl_2 (50 mL×2). The combined organic

layers were washed with H_2O (50 mL×4), dried over $MgSO_4$, filtered and concentrated. Column chromatography (2.5% MeOH/CH_2Cl_2) gave **130** (616 mg, 54%) as a tan solid. M.p.=85-87 °C. IR (nujol) ν=1690 (s), 1645 (m) cm^{-1}. MS *m/z* (%)=419 (1), 418 (2, M^+), 229 (52), 197 (80), 143 (100), 130 (49). ^1H NMR ($CDCl_3$): δ=3.09 (t, *J*=6.7 Hz, 2H), 3.78-3.82 (m, 2H), 4.78 (bs, 1H), 6.03 (dd, *J*=10.3, 1.1 Hz, 1H), 6.32 (d, *J*=9.4 Hz, 1H), 6.65 (dd, *J*=16.7, 1.1 Hz, 1H), 6.92 (dd, *J*=16.6, 10.4 Hz, 1H), 7.30-7.33 (m, 1H), 7.37-7.41 (m, 3H), 7.56 (d, *J*=7.7 Hz, 1H), 8.50 (d, *J*=8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=24.9, 41.2, 111.5, 115.7, 117.1, 118.8, 119.7, 122.2, 123.9, 125.5, 127.9, 130.5, 132.0, 136.2, 137.2, 158.0, 163.6. HRMS Calcd. for $C_{17}H_{15}IN_4O$: 418.0292. Found: 418.0288.

Methyl *N*-[2-(1-allyl-1*H*-indol-3-yl)ethyl]-*N*-(6-iodopyridazin-3-yl)carbamate (134)



To a solution of NaHMDS (1.0 M in THF, 1.5 mL, 1.5 mmol) in anhydrous THF (10 mL) at –78 °C was added a slurry of **89** (404 mg, 1.00 mmol) in anhydrous THF (10 mL). After the resulting solution was stirred at –78 °C for 30 min, $ClCO_2Me$ (378 mg, 4.00 mmol) was injected into it. The reaction mixture was stirred at room temperature for 2 h, treated with saturated aqueous $NaHCO_3$

solution (10 mL) and extracted with EtOAc (25 mL×2). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Column chromatography (5% EtOAc/CH_2Cl_2) gave **134** (388 mg, 84%) as a yellow oil. IR (nujol) ν=1716 (s), 1611 (w) cm^{-1}. MS *m/z* (%)=462 (0.4, M^+), 183 (100), 170 (35). ^1H NMR ($CDCl_3$): δ=3.18-3.21 (m, 2H), 3.77 (s, 3H), 4.39-4.42 (m, 2H), 4.64 (d, *J*=5.4 Hz, 2H), 5.07 (dd, *J*=17.1, 1.2 Hz, 1H), 5.19 (dd, *J*=10.1, 1.1 Hz, 1H), 5.90-5.98 (m, 1H), 6.90 (s, 1H), 7.10-7.13 (m, 1H), 7.17-7.20 (m, 1H), 7.26 (d, *J*=8.0 Hz, 1H), 7.60 (s, 2H), 7.66 (d, *J*=7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ=24.4, 47.9, 48.6, 53.4, 109.5, 111.7, 117.3, 118.9, 119.0, 119.1, 121.6, 123.8, 126.0, 128.2, 133.5, 136.3, 137.0, 155.1, 157.1. HRMS Calcd. for $C_{19}H_{19}IN_4O_2$: 462.0554. Found: 462.0584.

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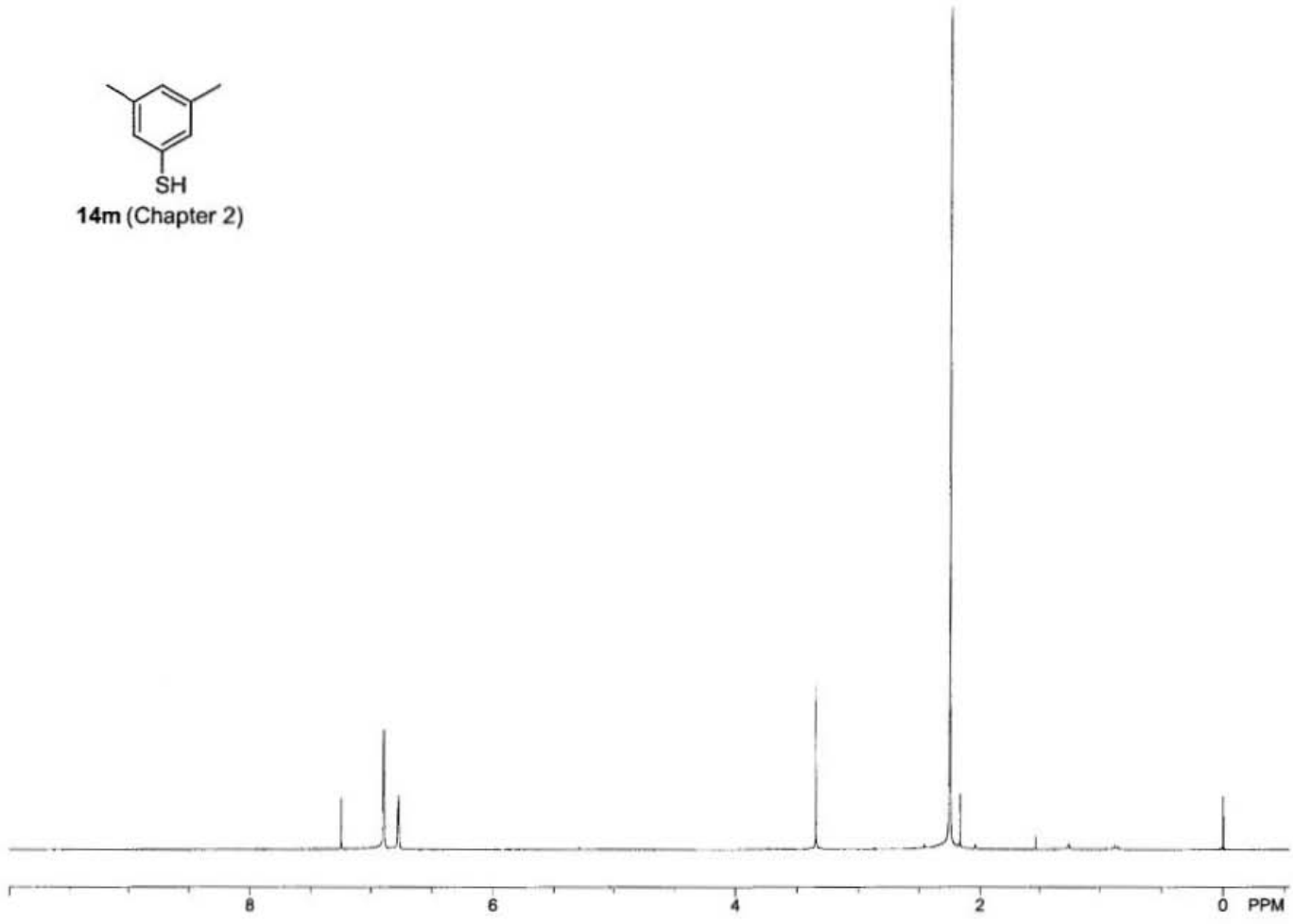
APPENDIX Selected NMR Spectra

Compounds appear in the order in which they are described in the Experimental sections of the corresponding chapters.



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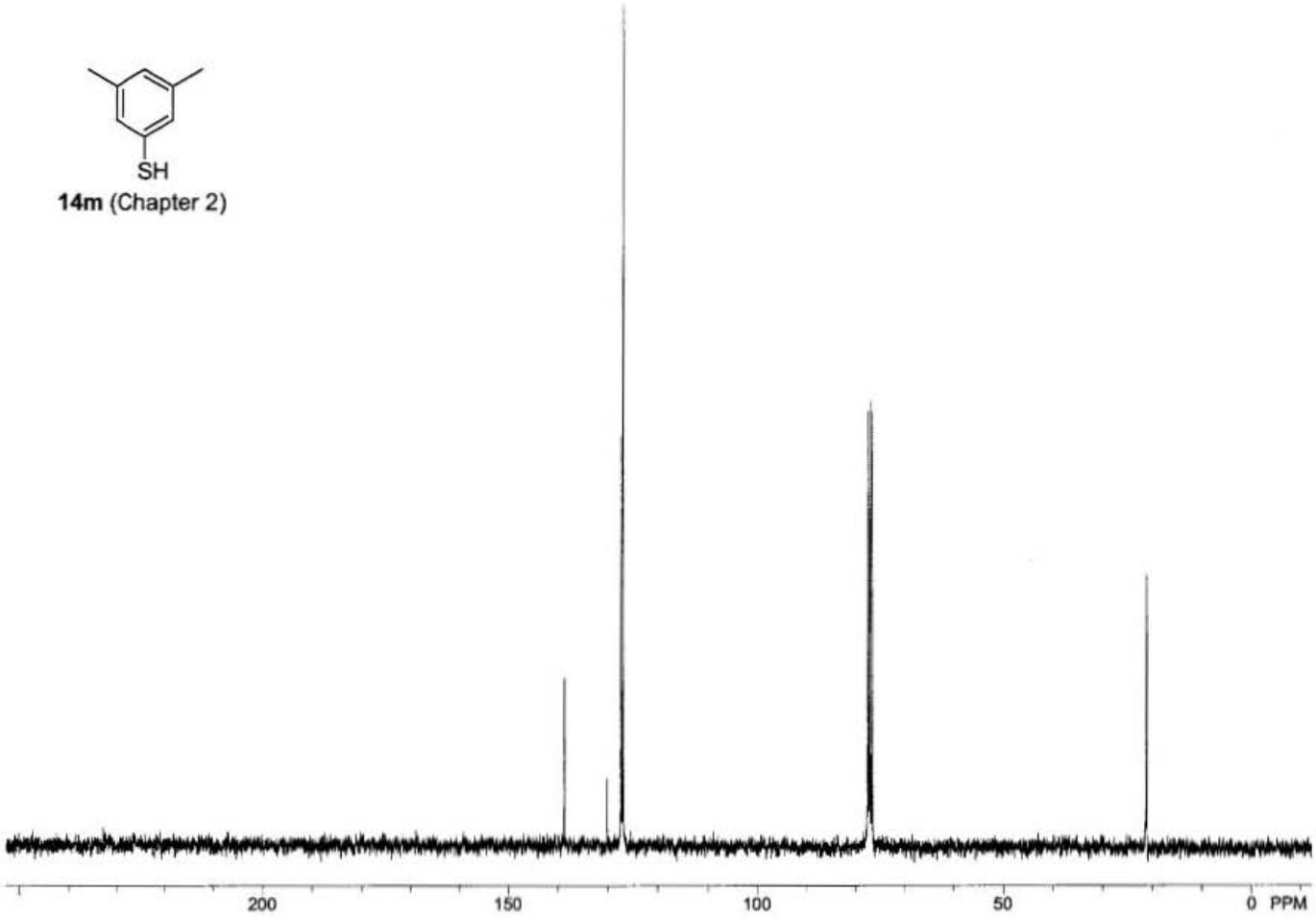

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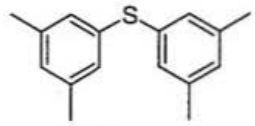

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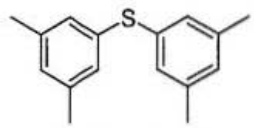

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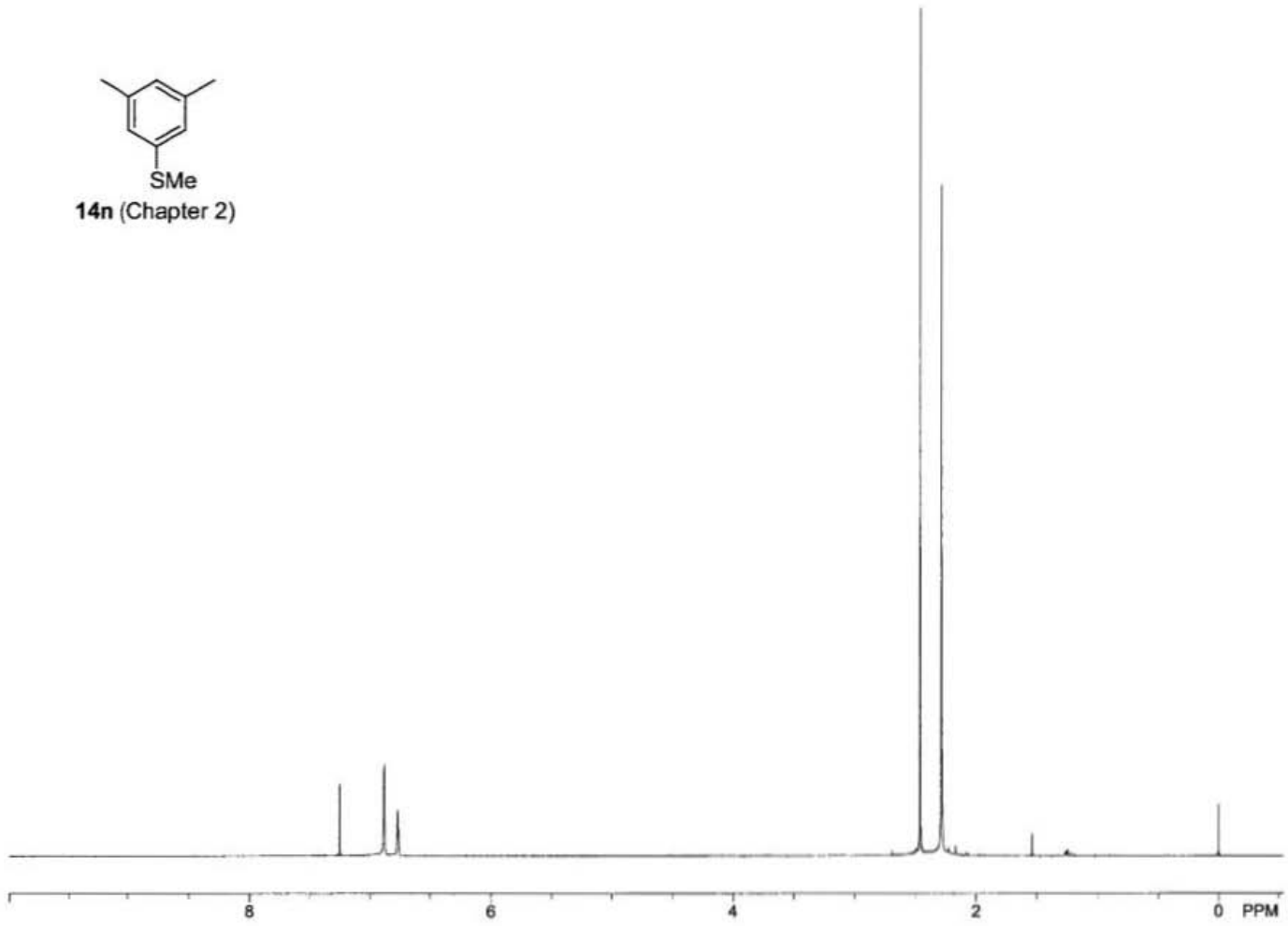

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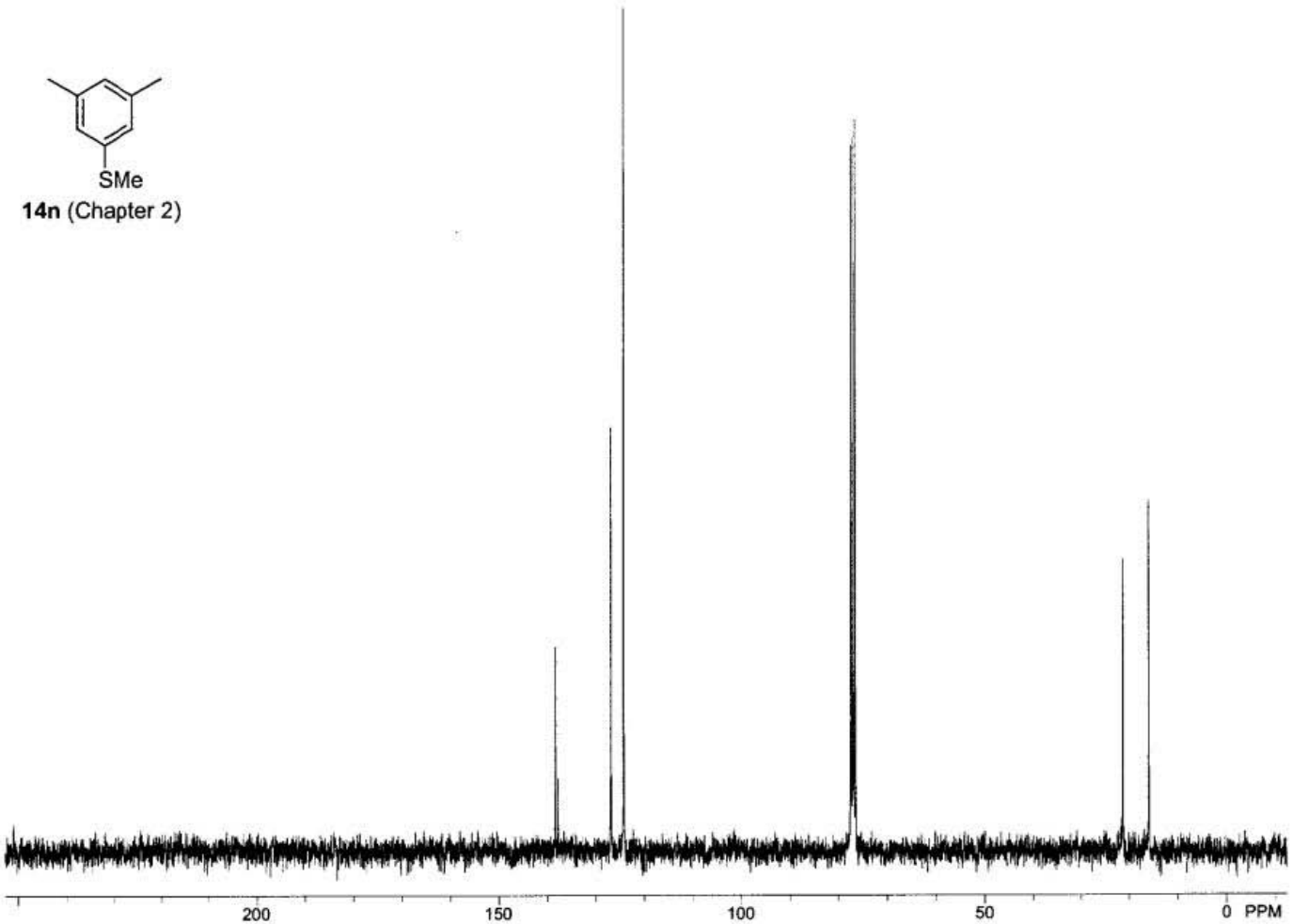

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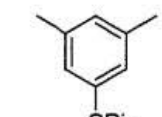

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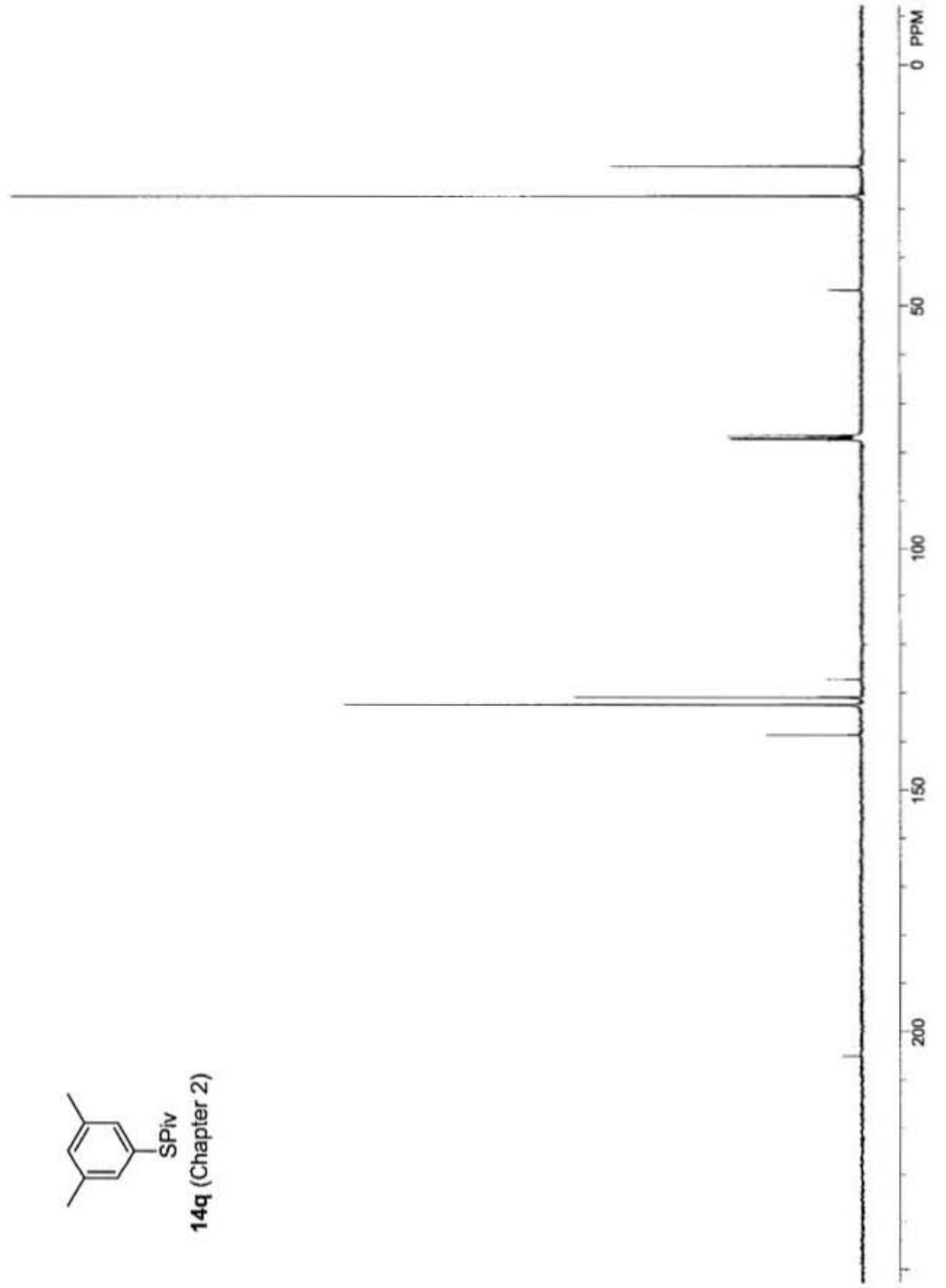
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14q (Chapter 2)
0 PPM
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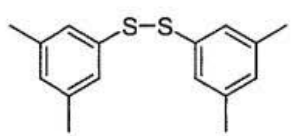
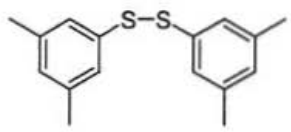
100
150
200



17 (Chapter 2)



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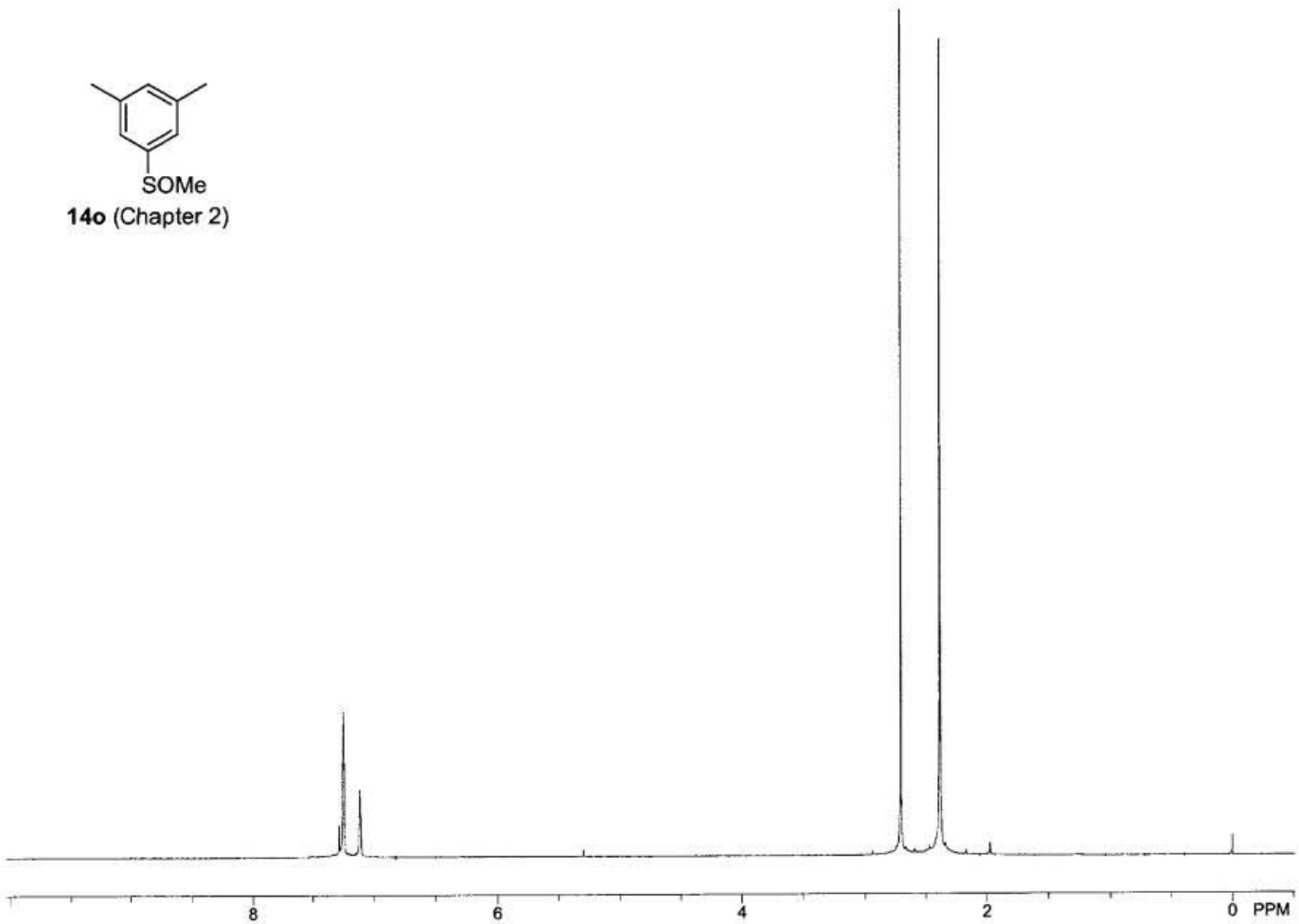

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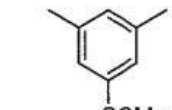

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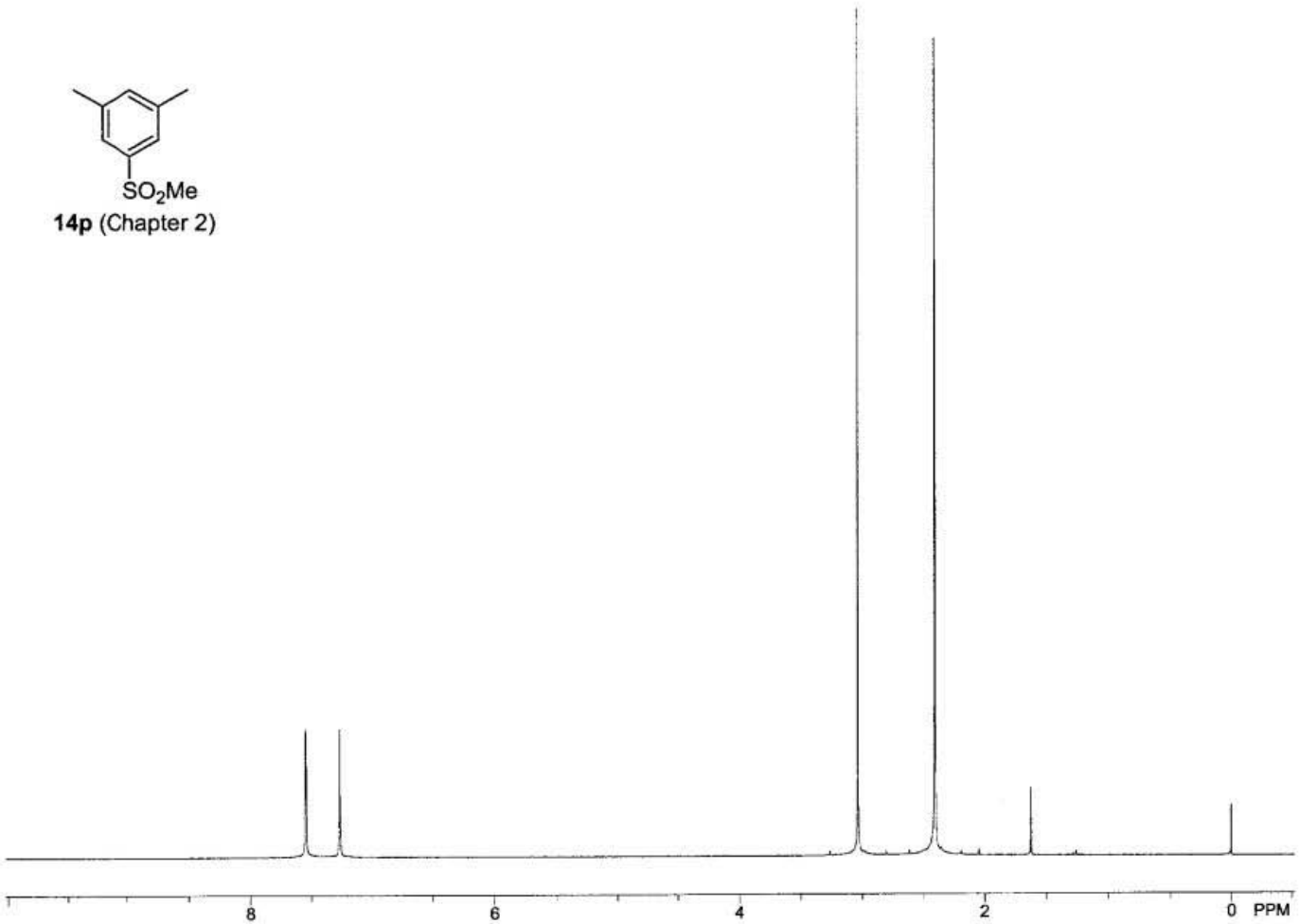
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6
4
2
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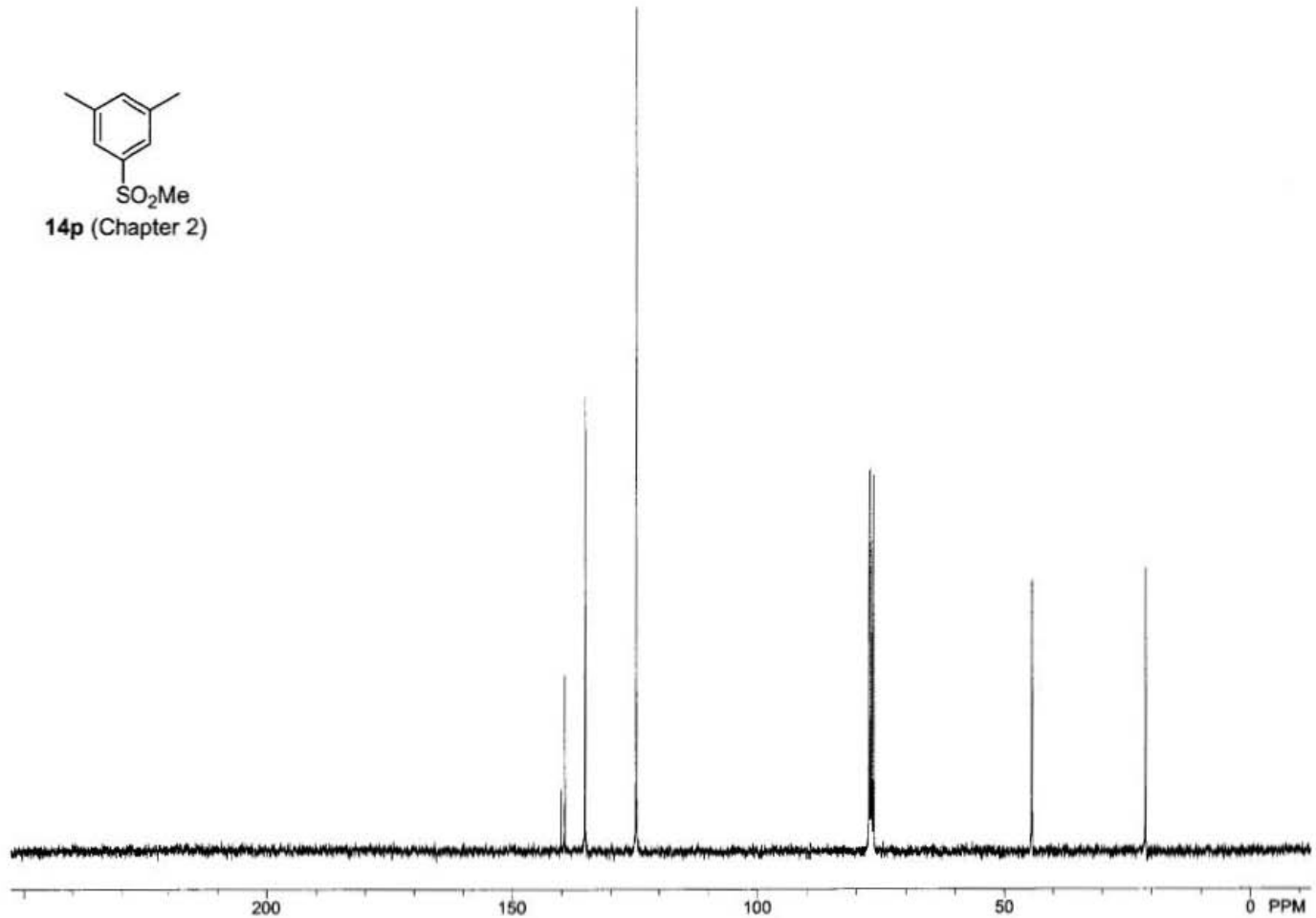

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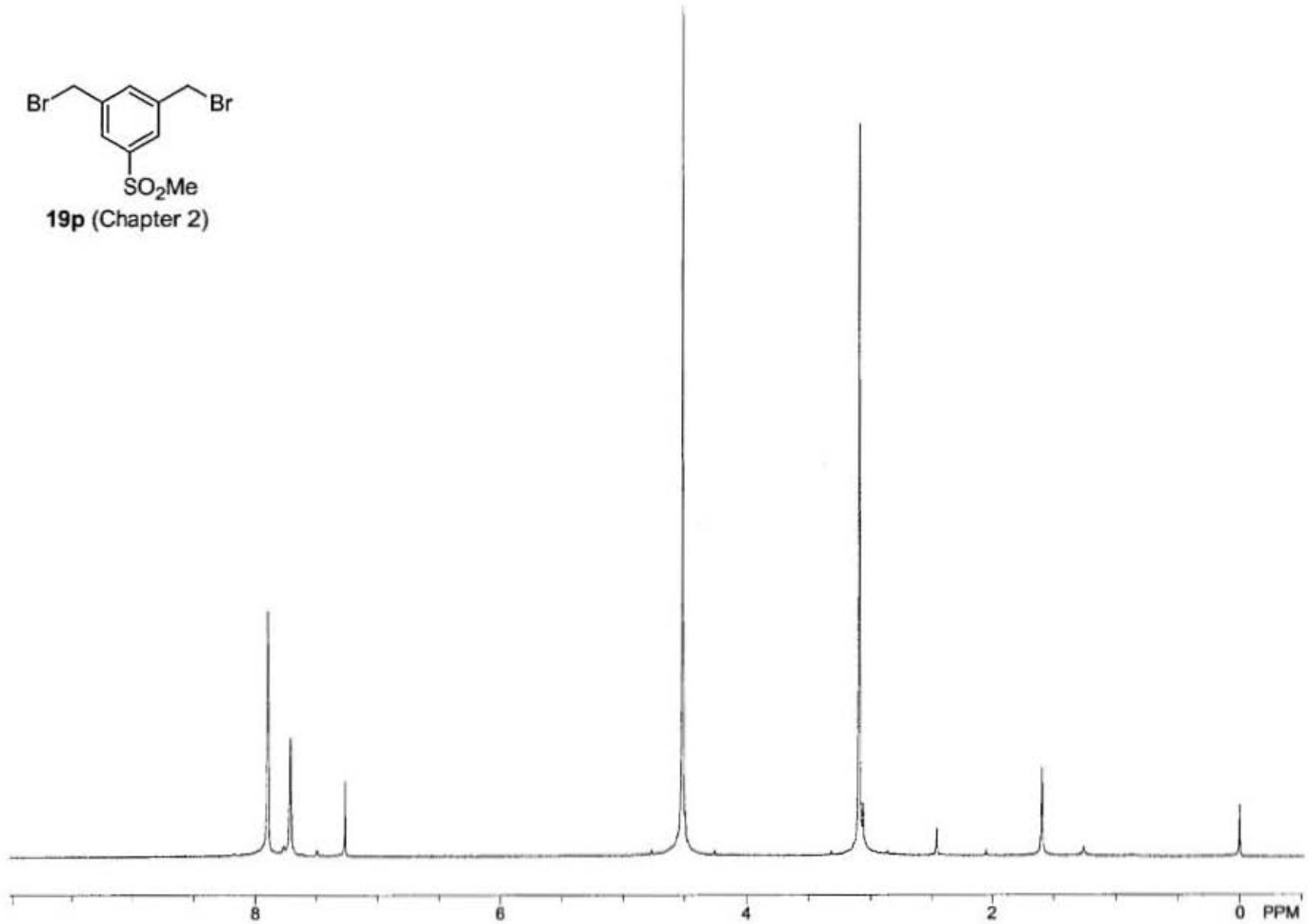

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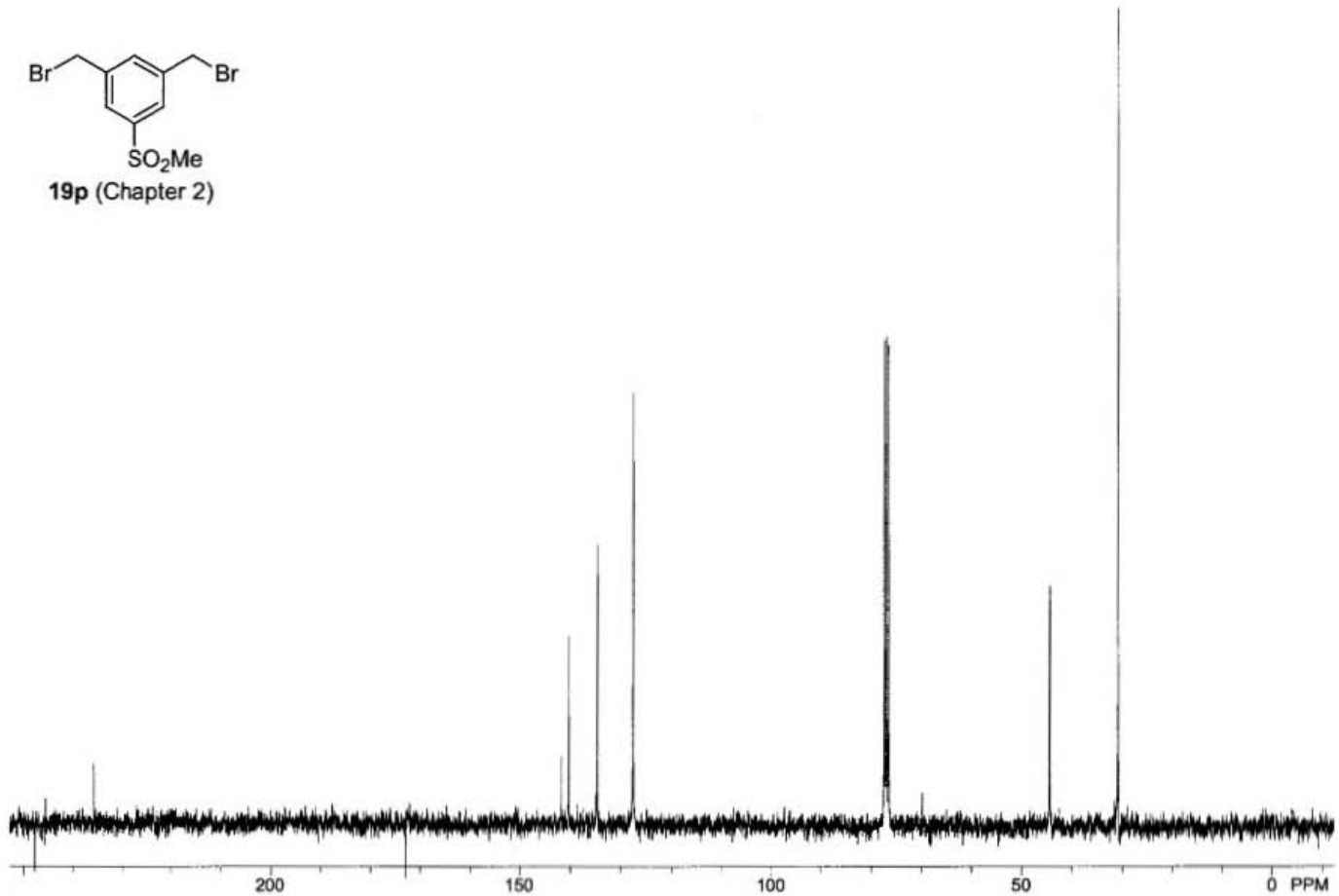

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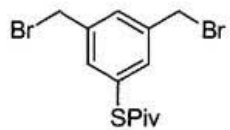

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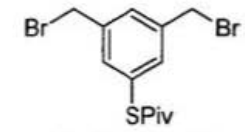

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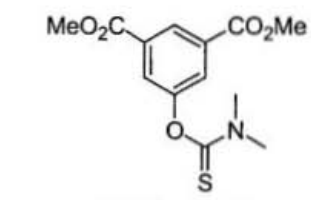

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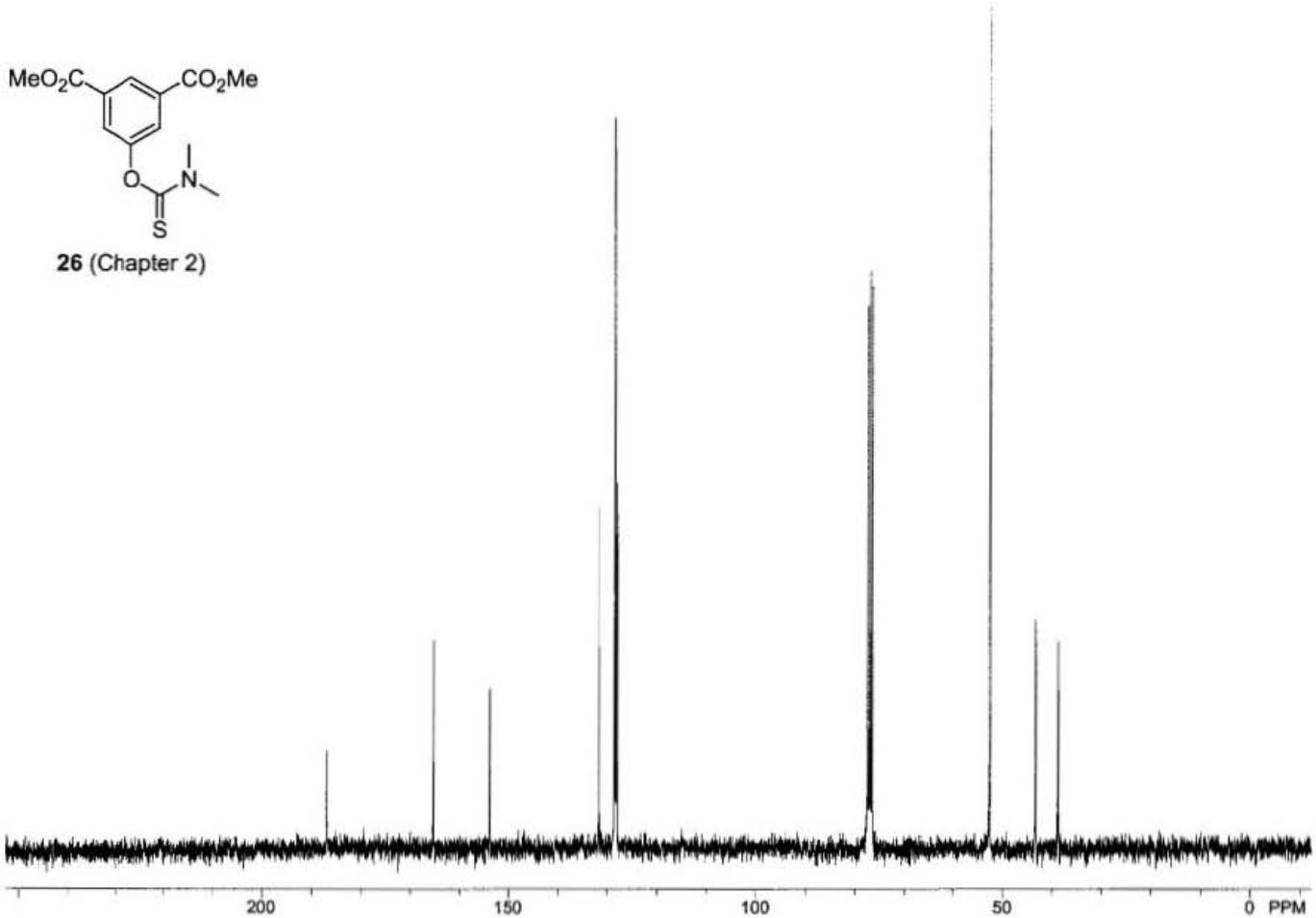

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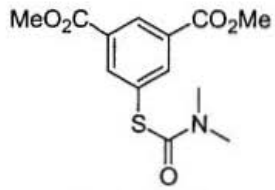

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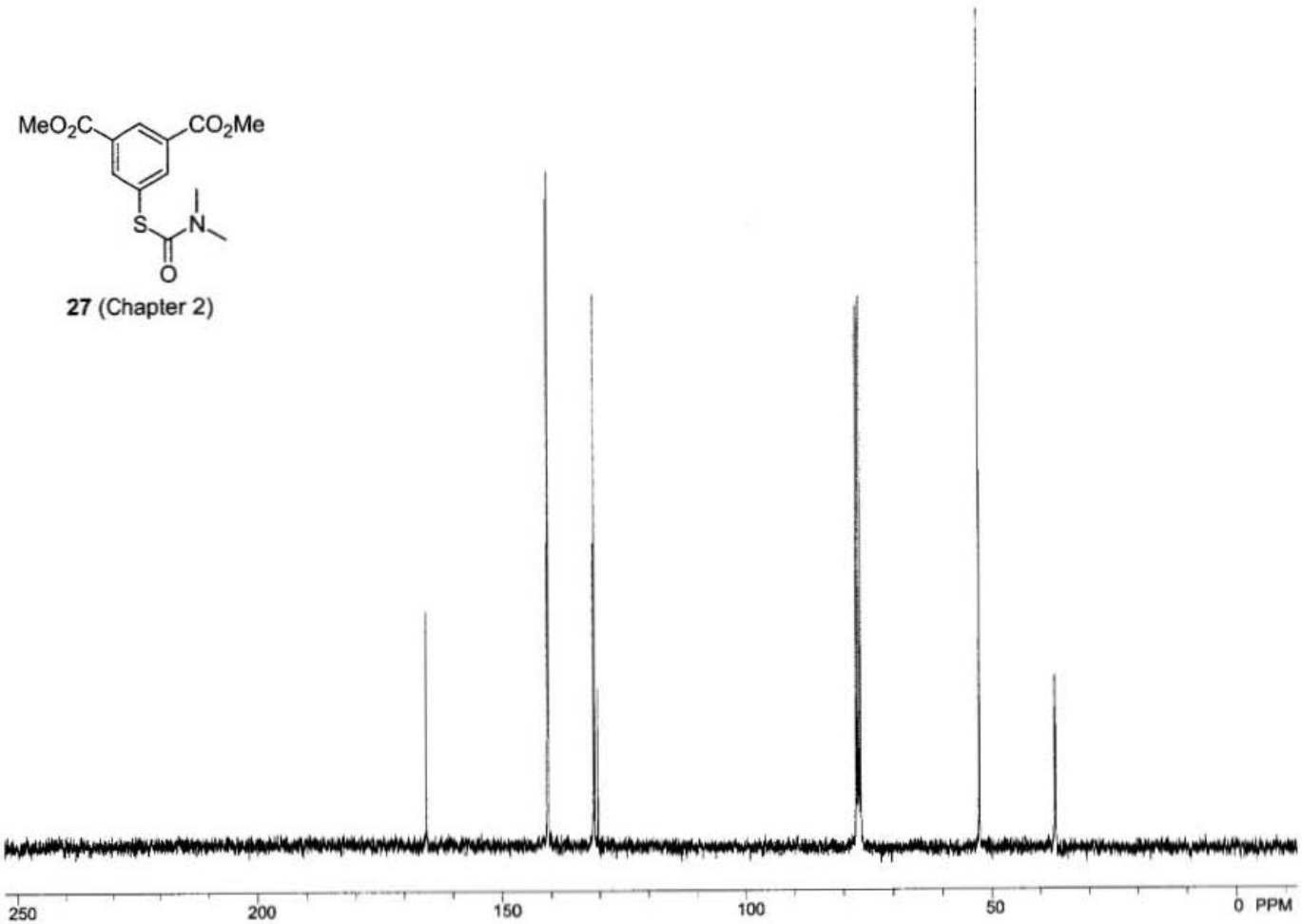

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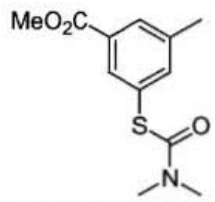

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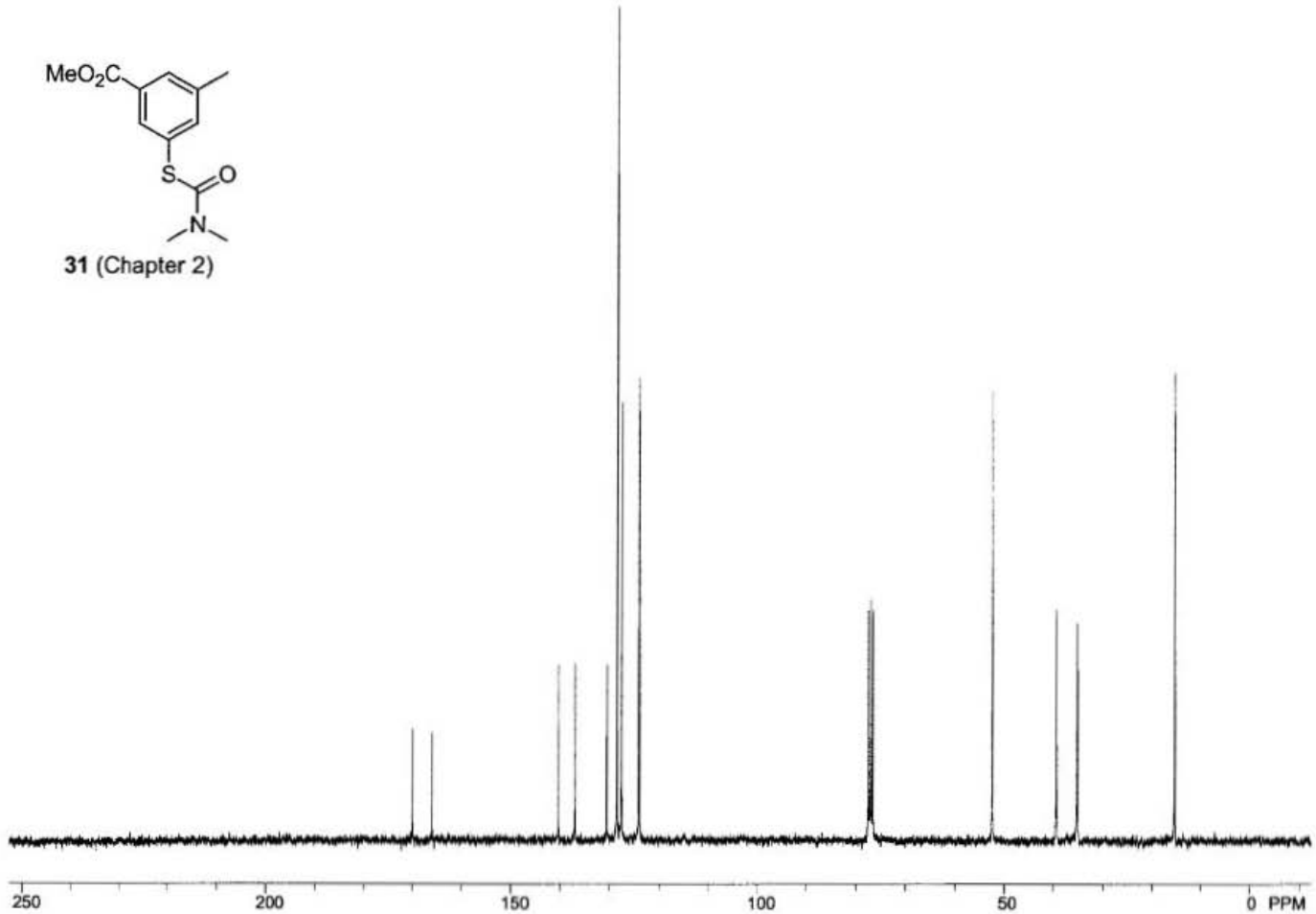

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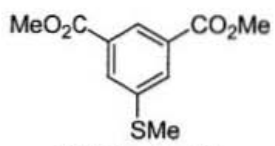

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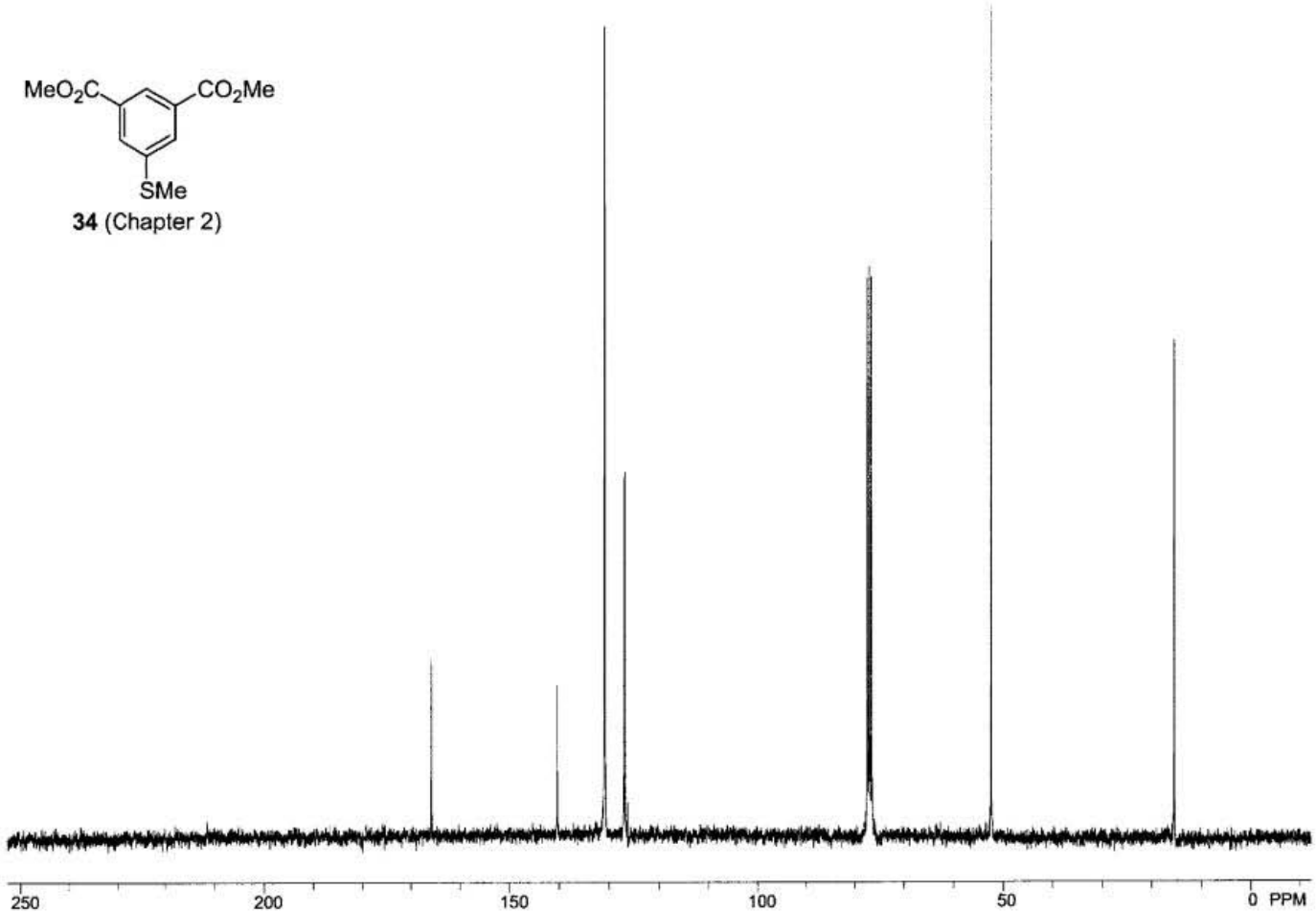
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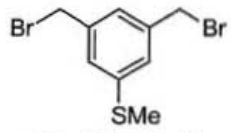

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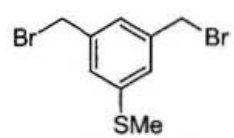

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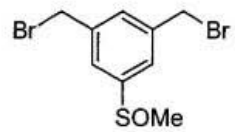

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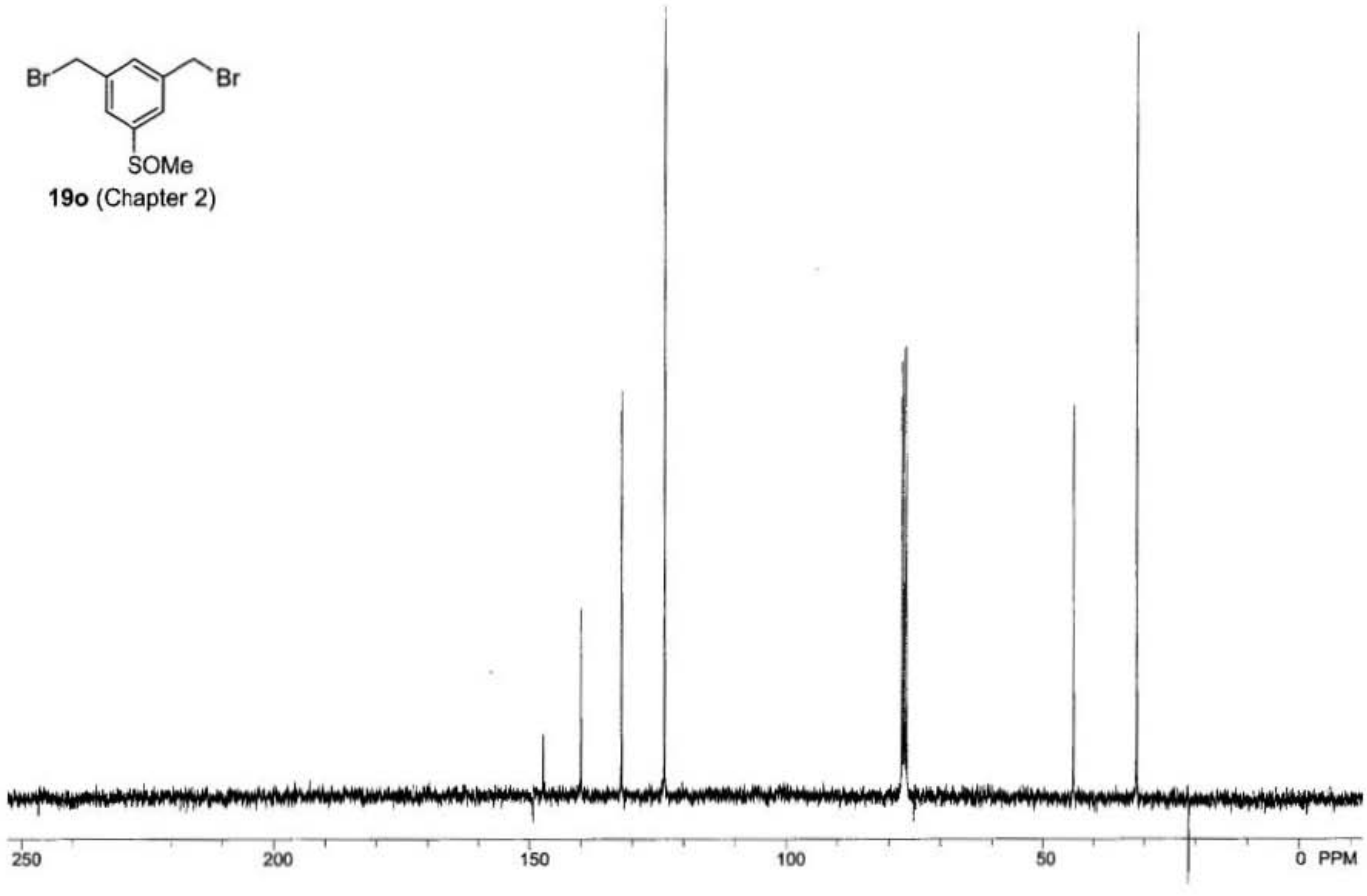

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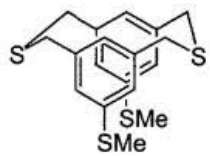

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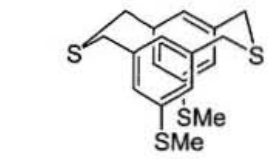

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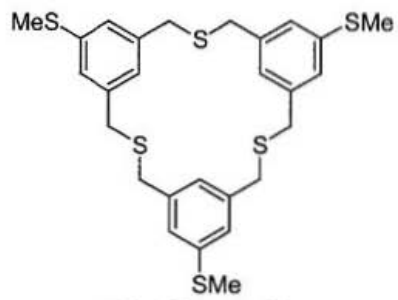

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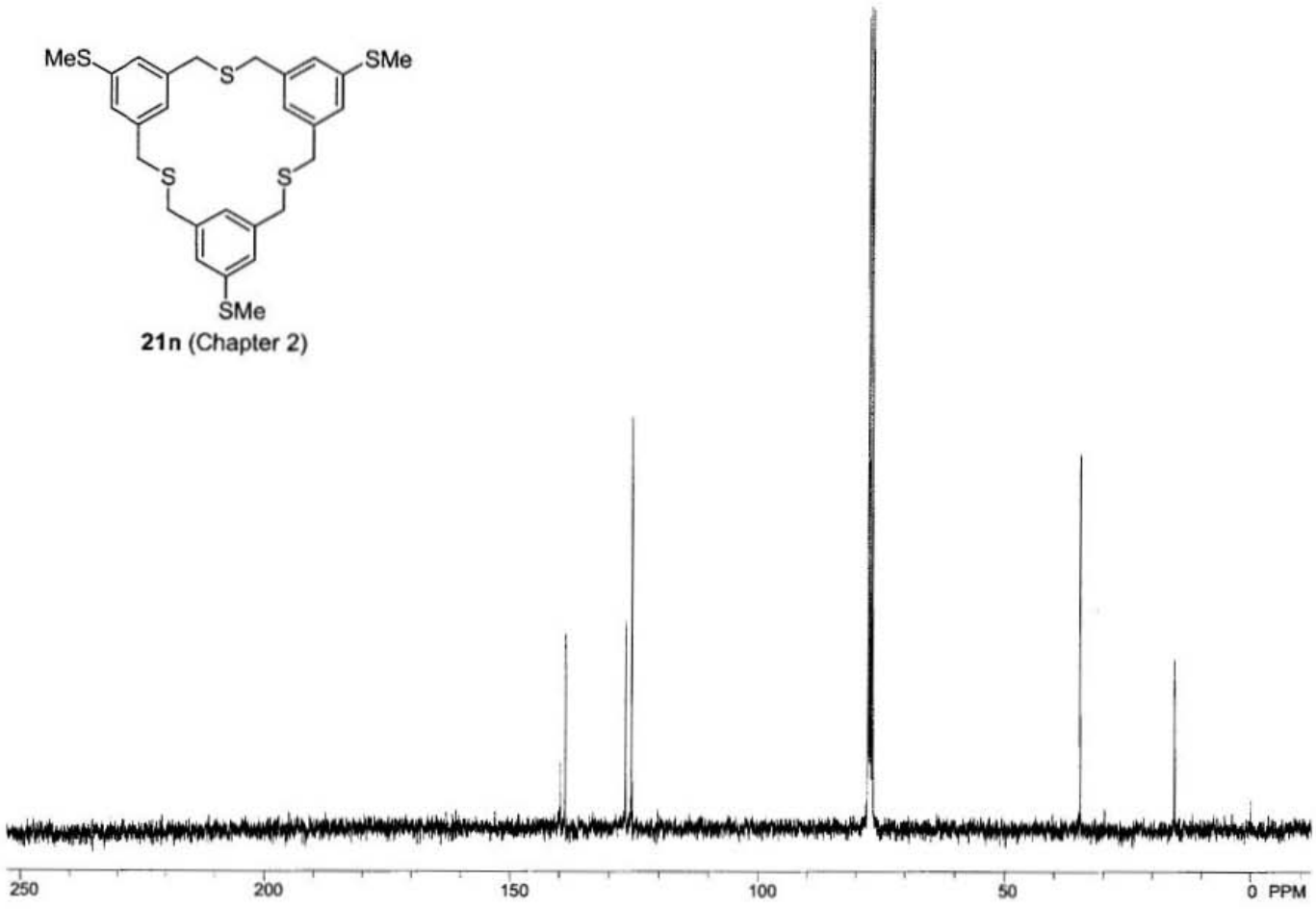

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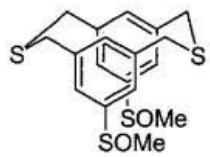

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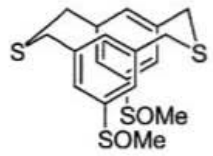

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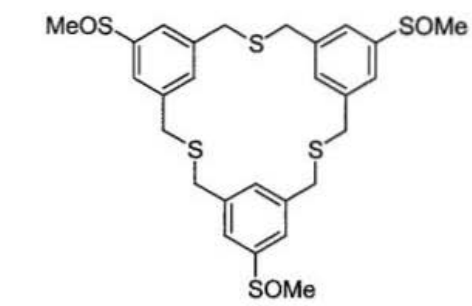

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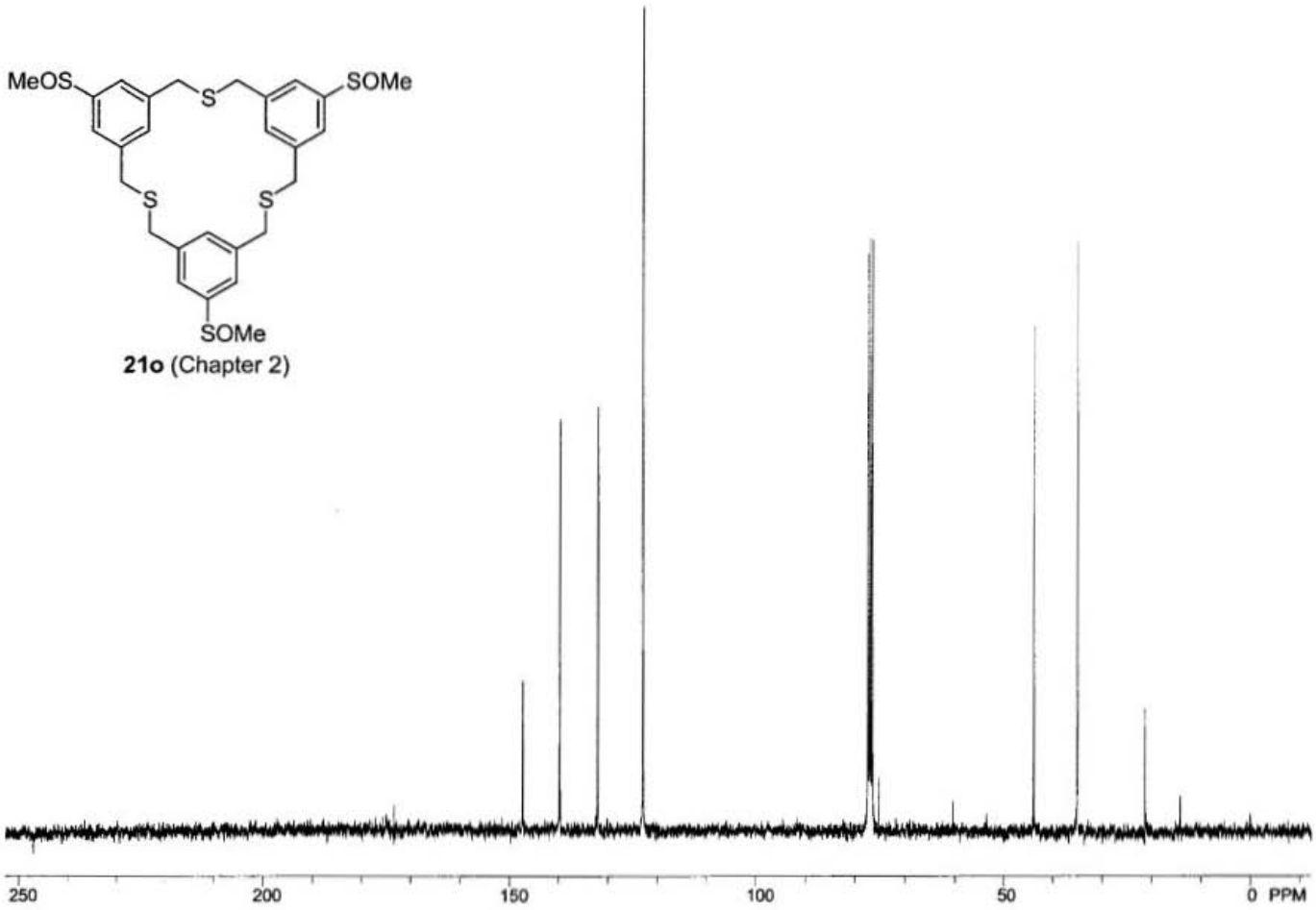

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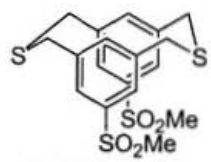

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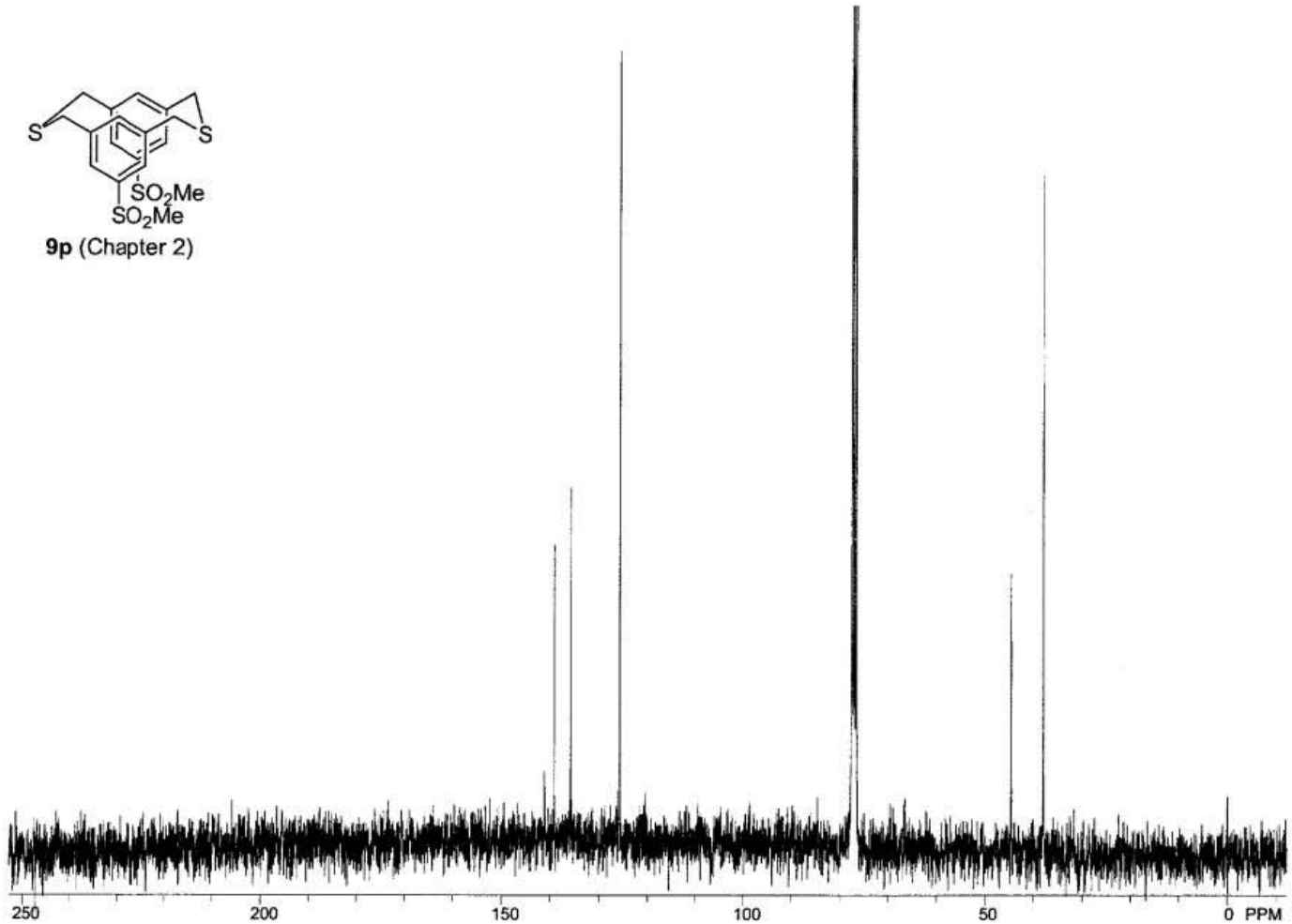
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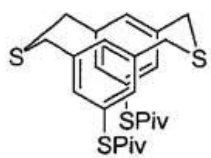

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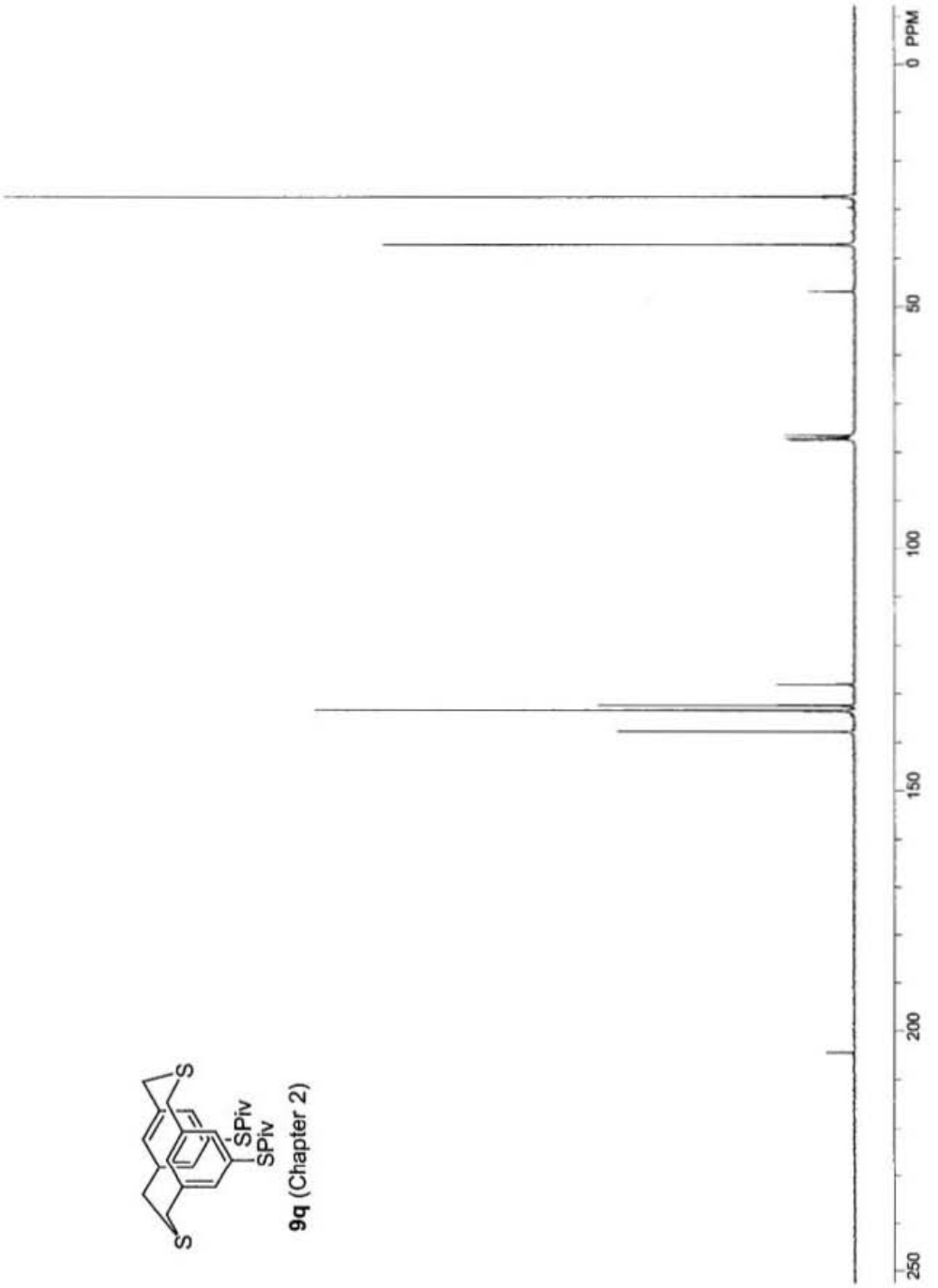

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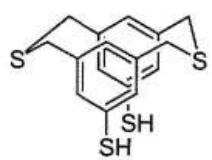

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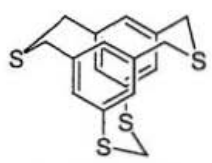

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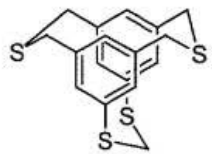

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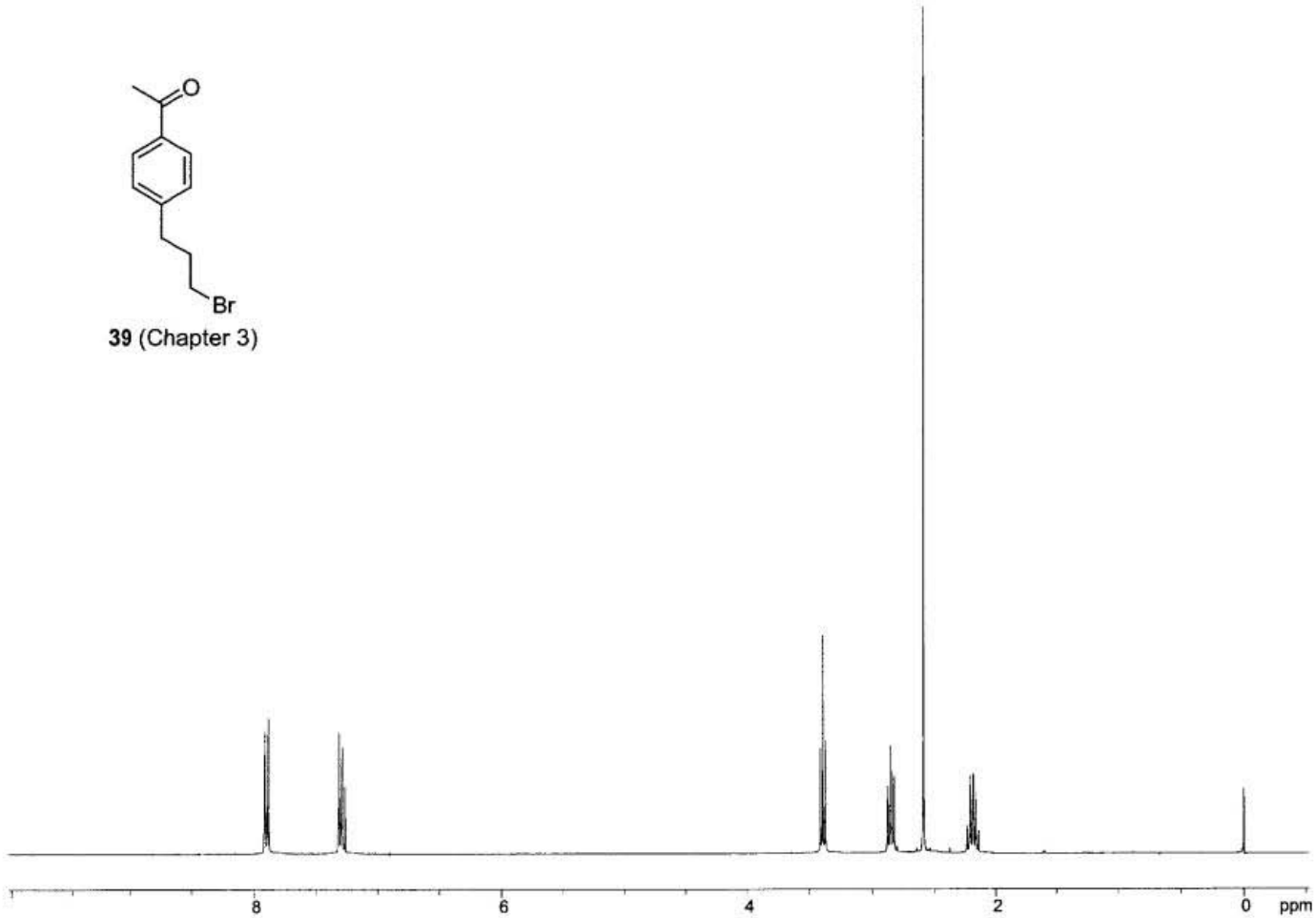

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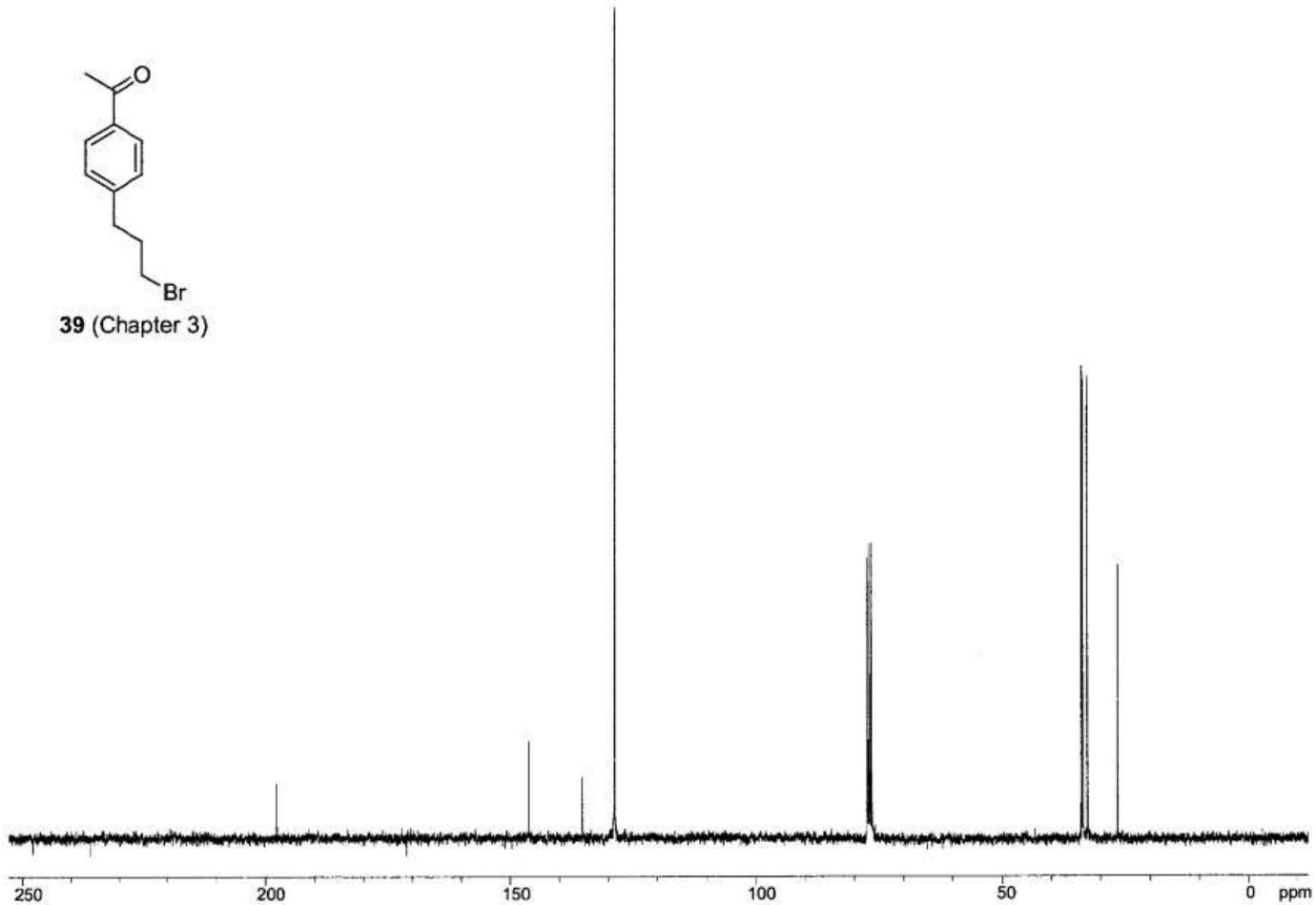

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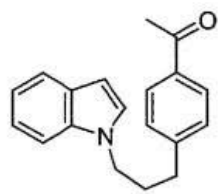

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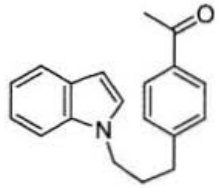

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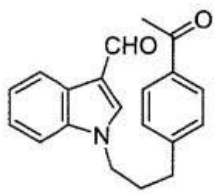

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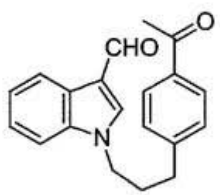

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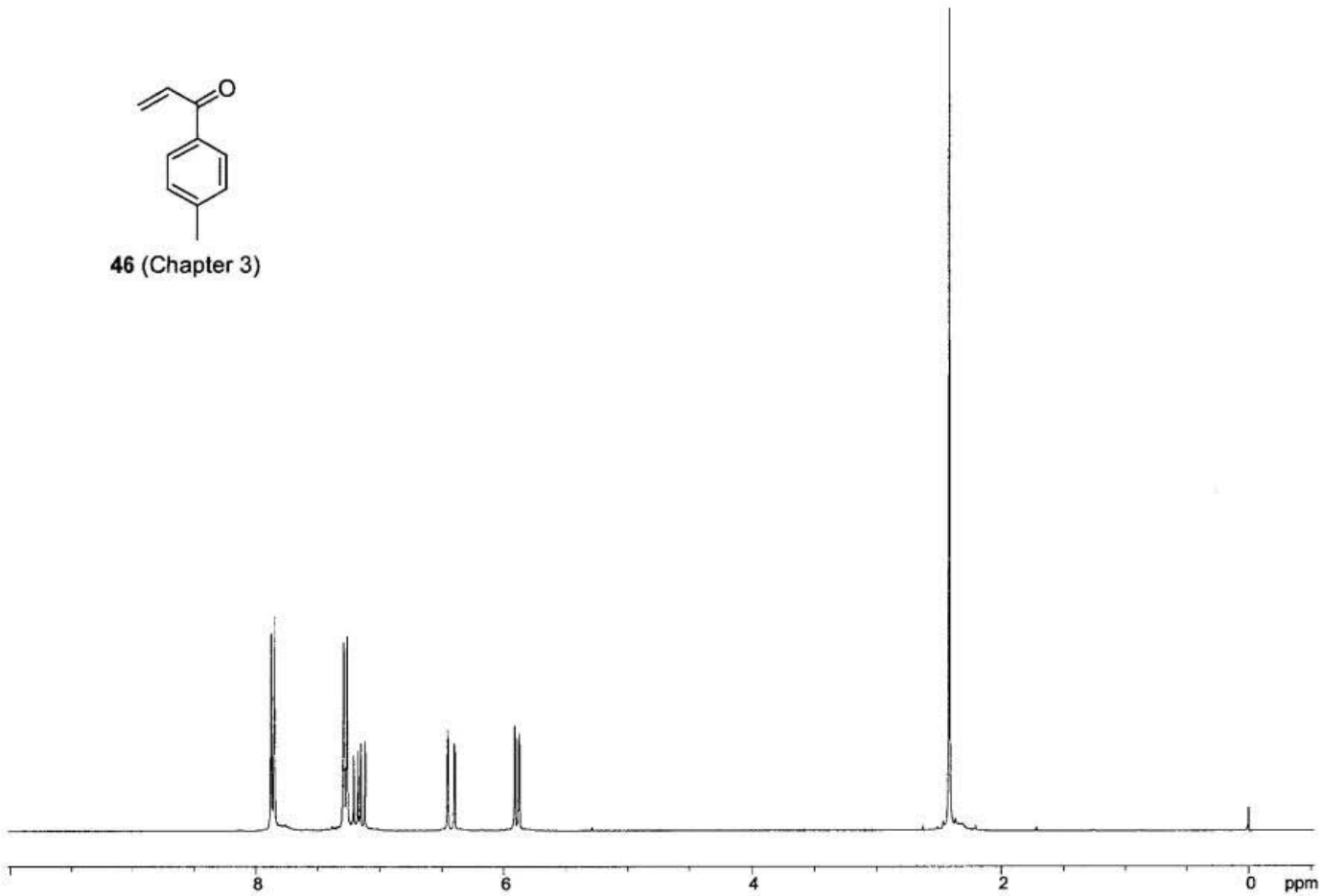

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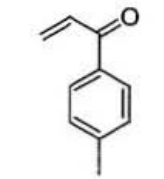

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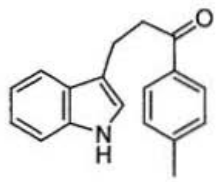

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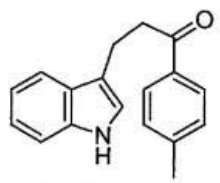

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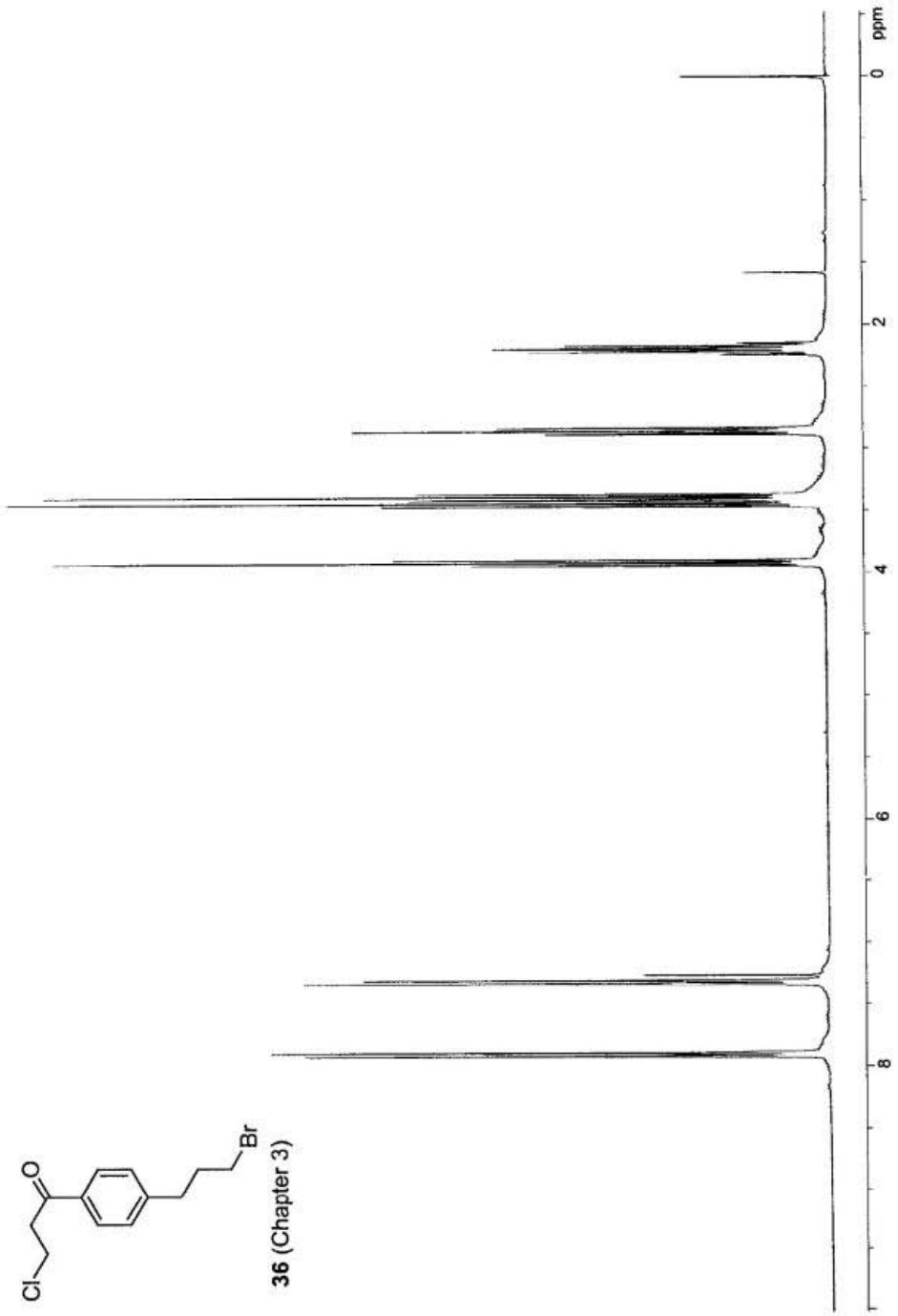
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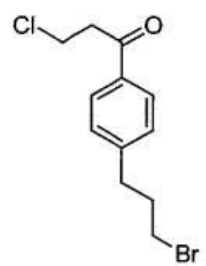

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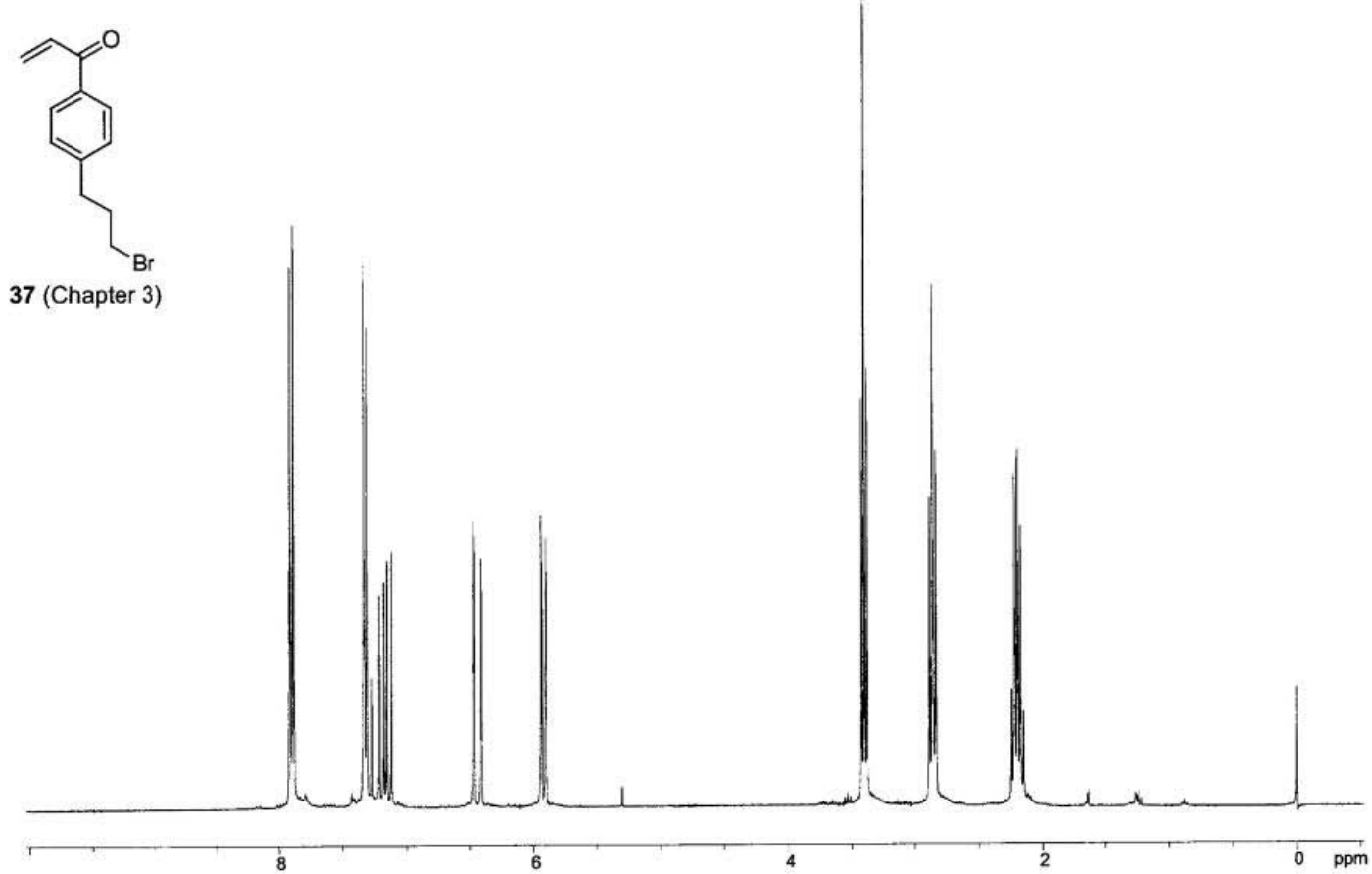

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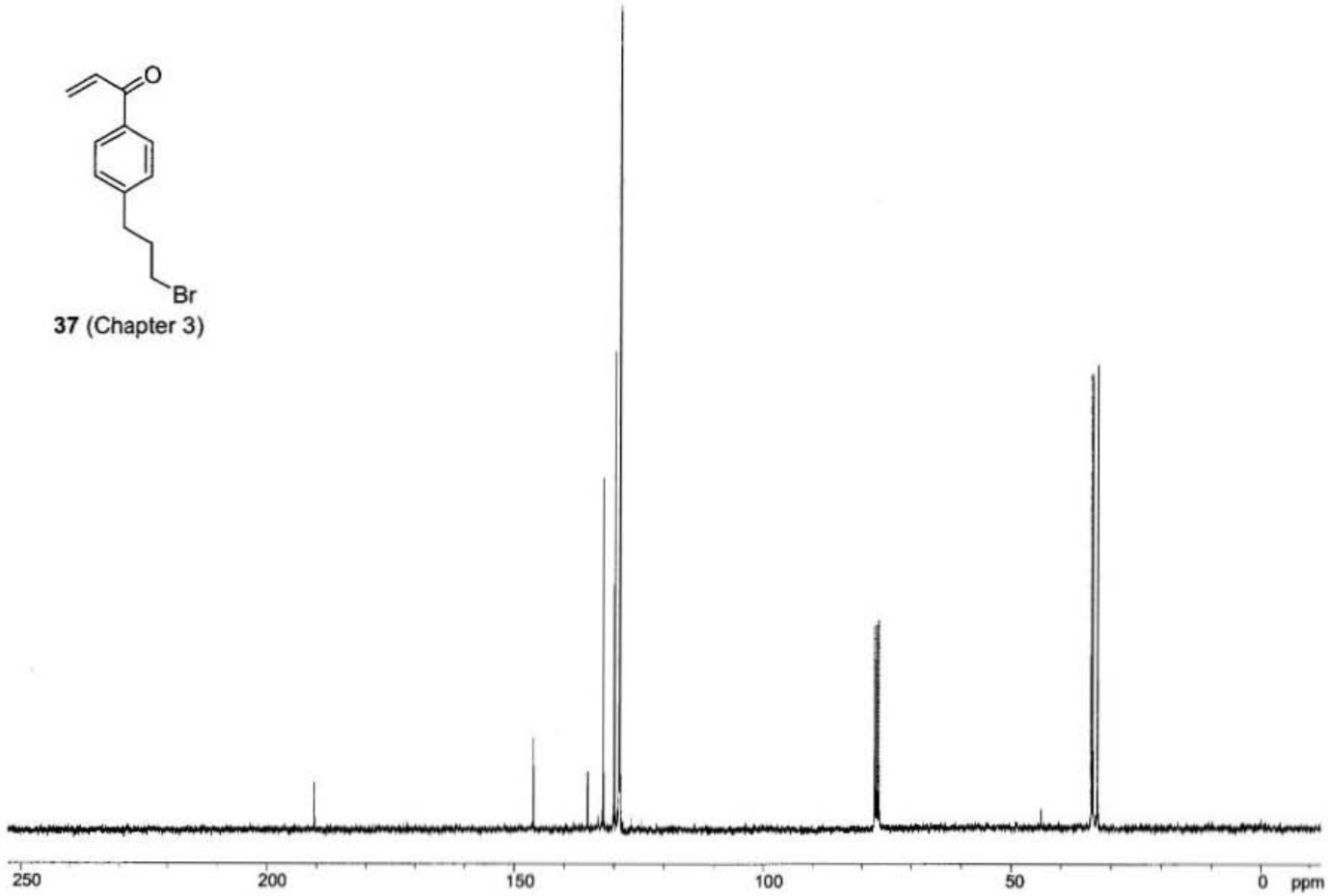

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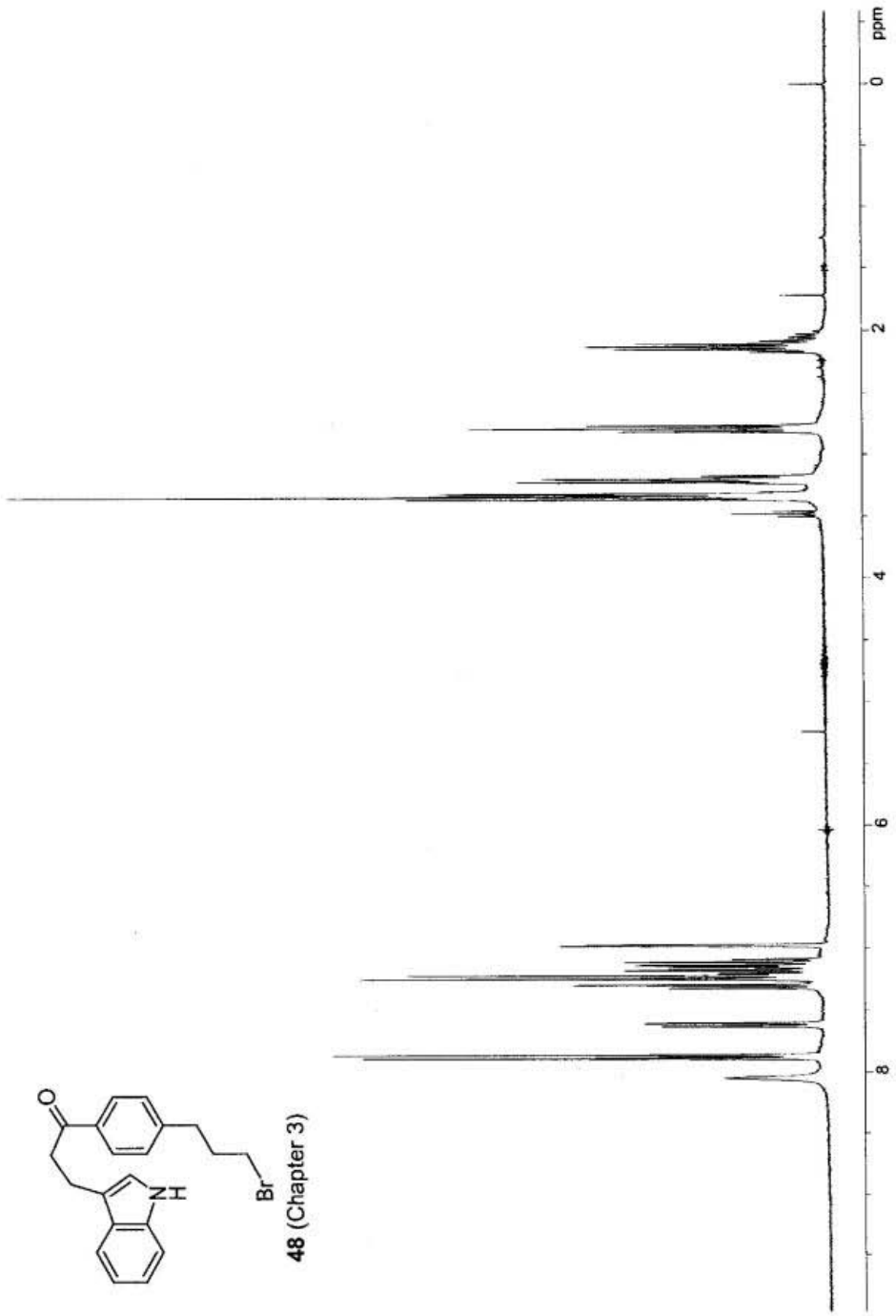

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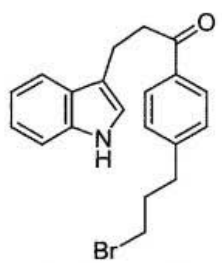

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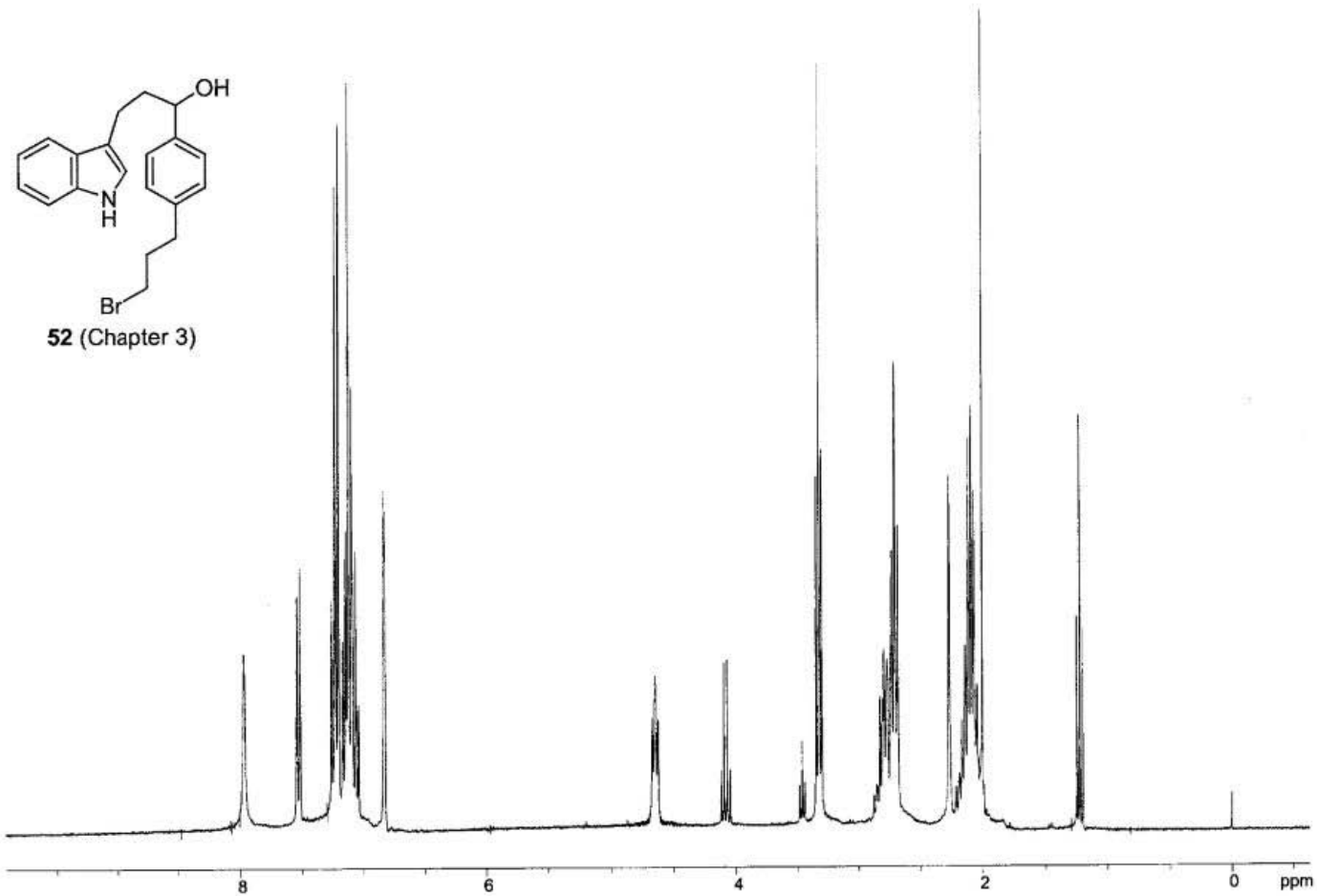

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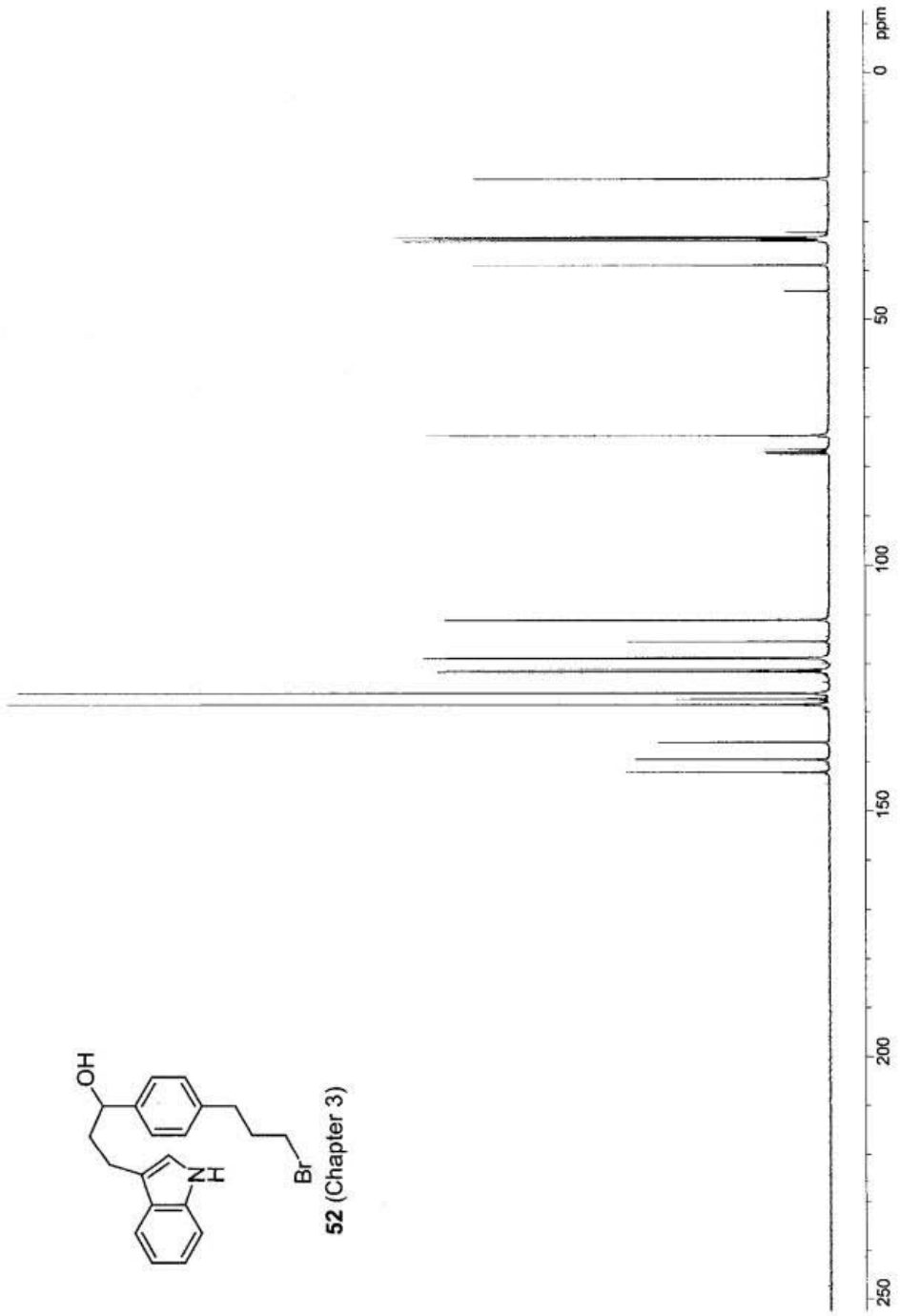

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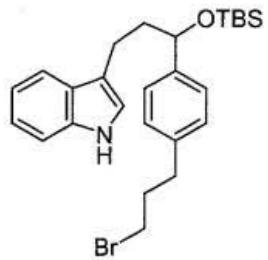

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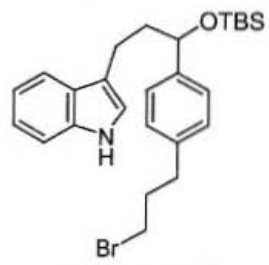

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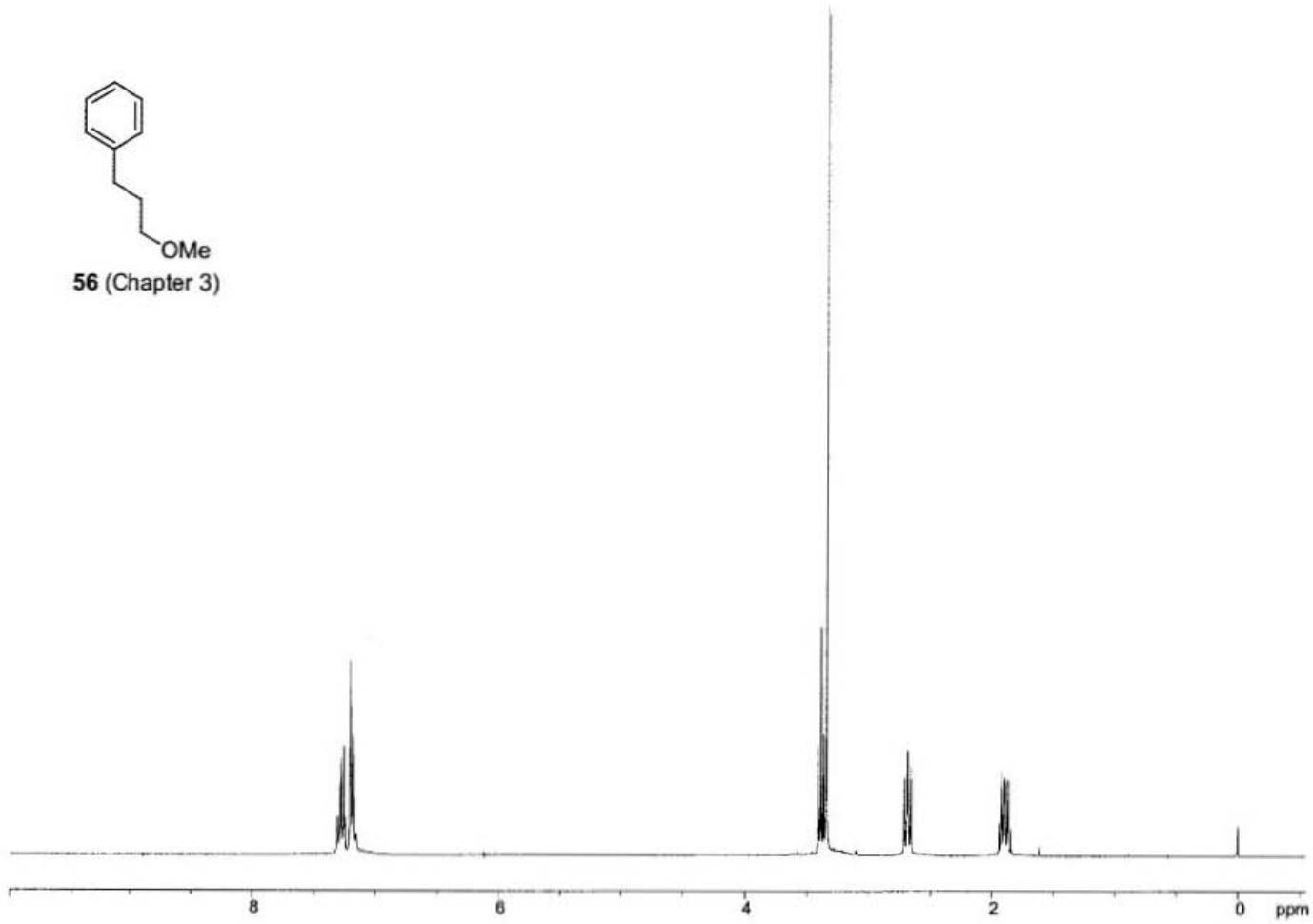

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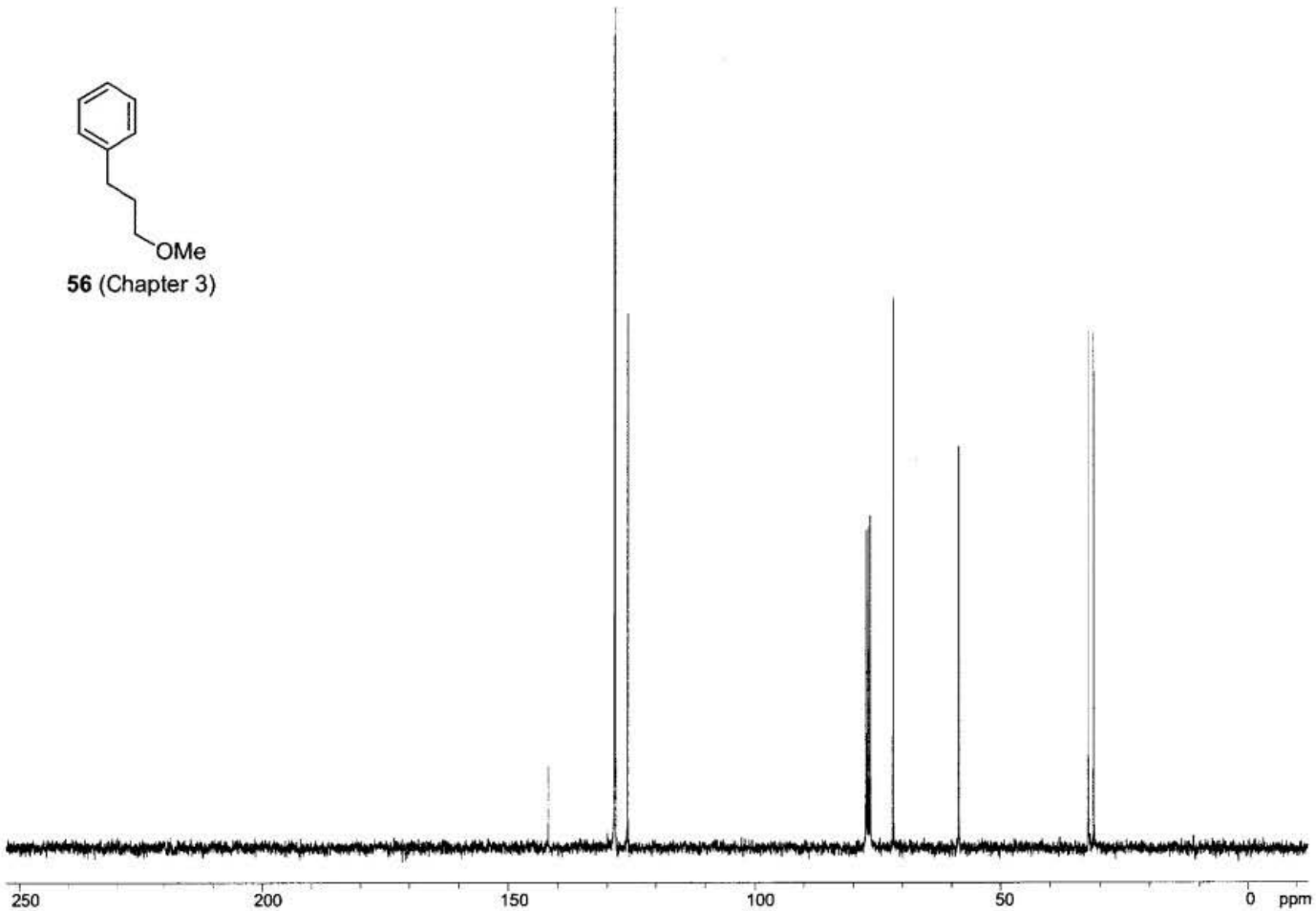

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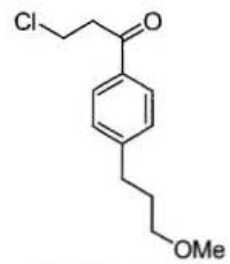

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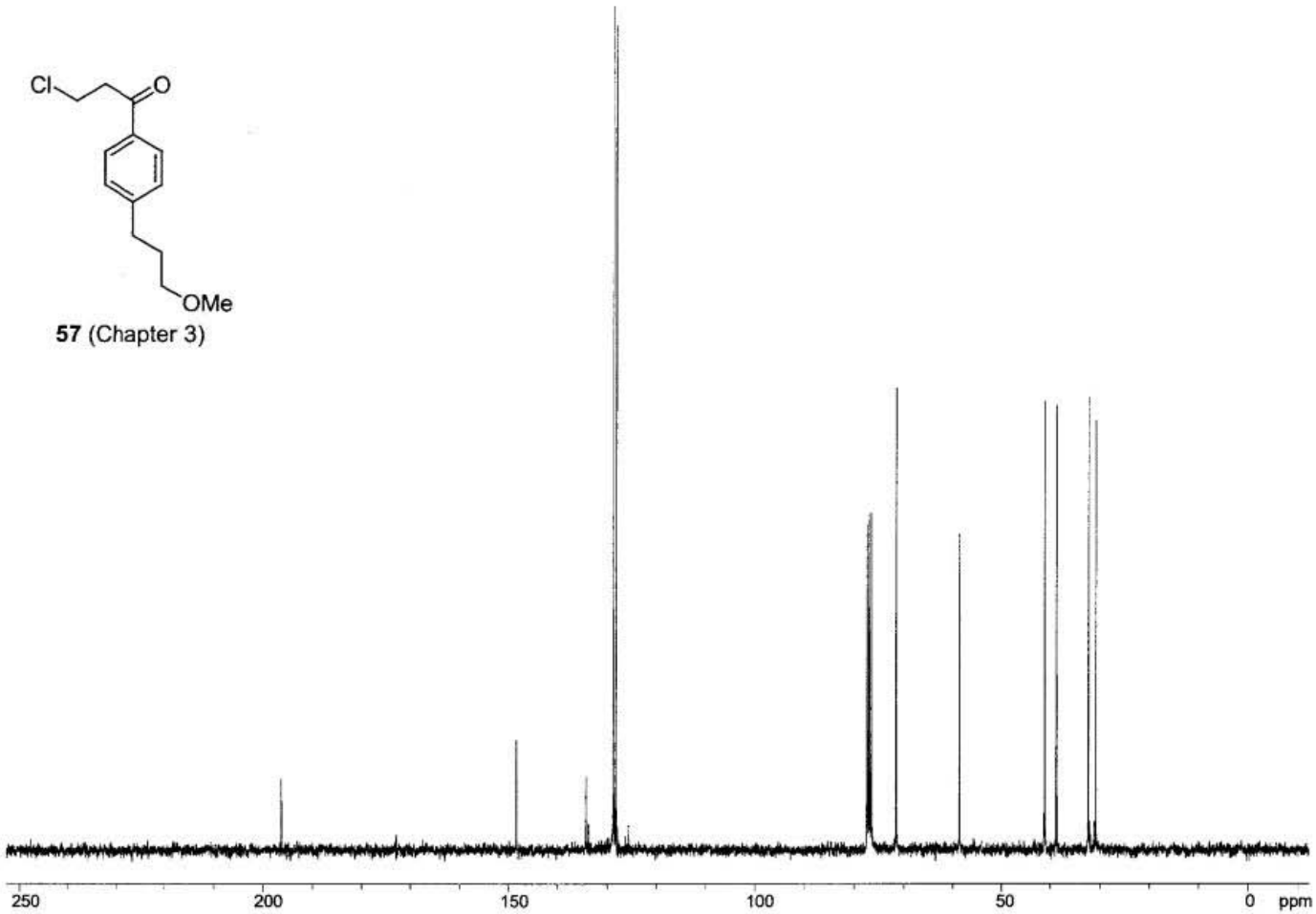

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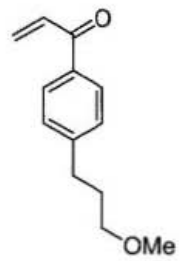

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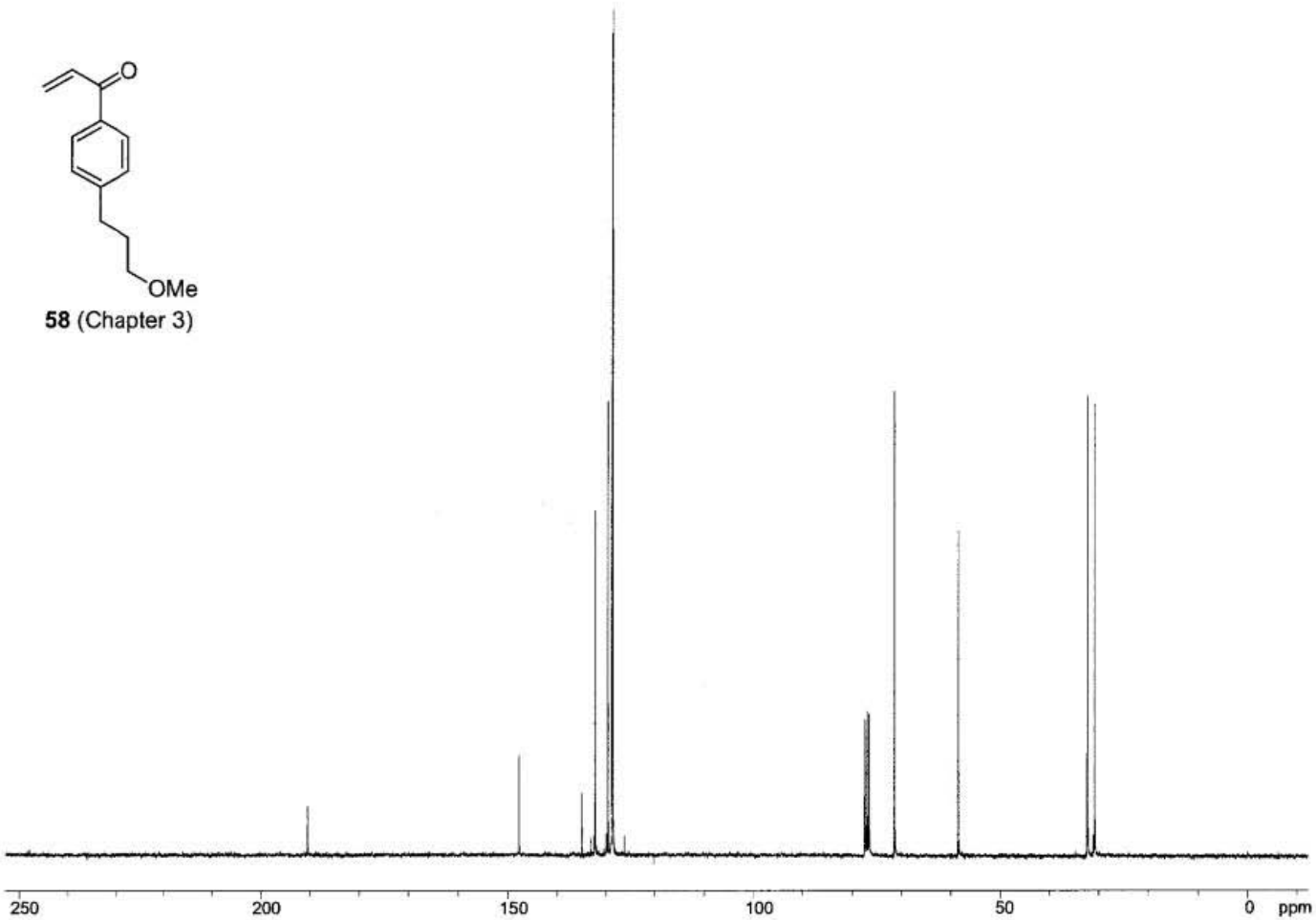

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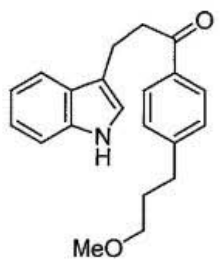

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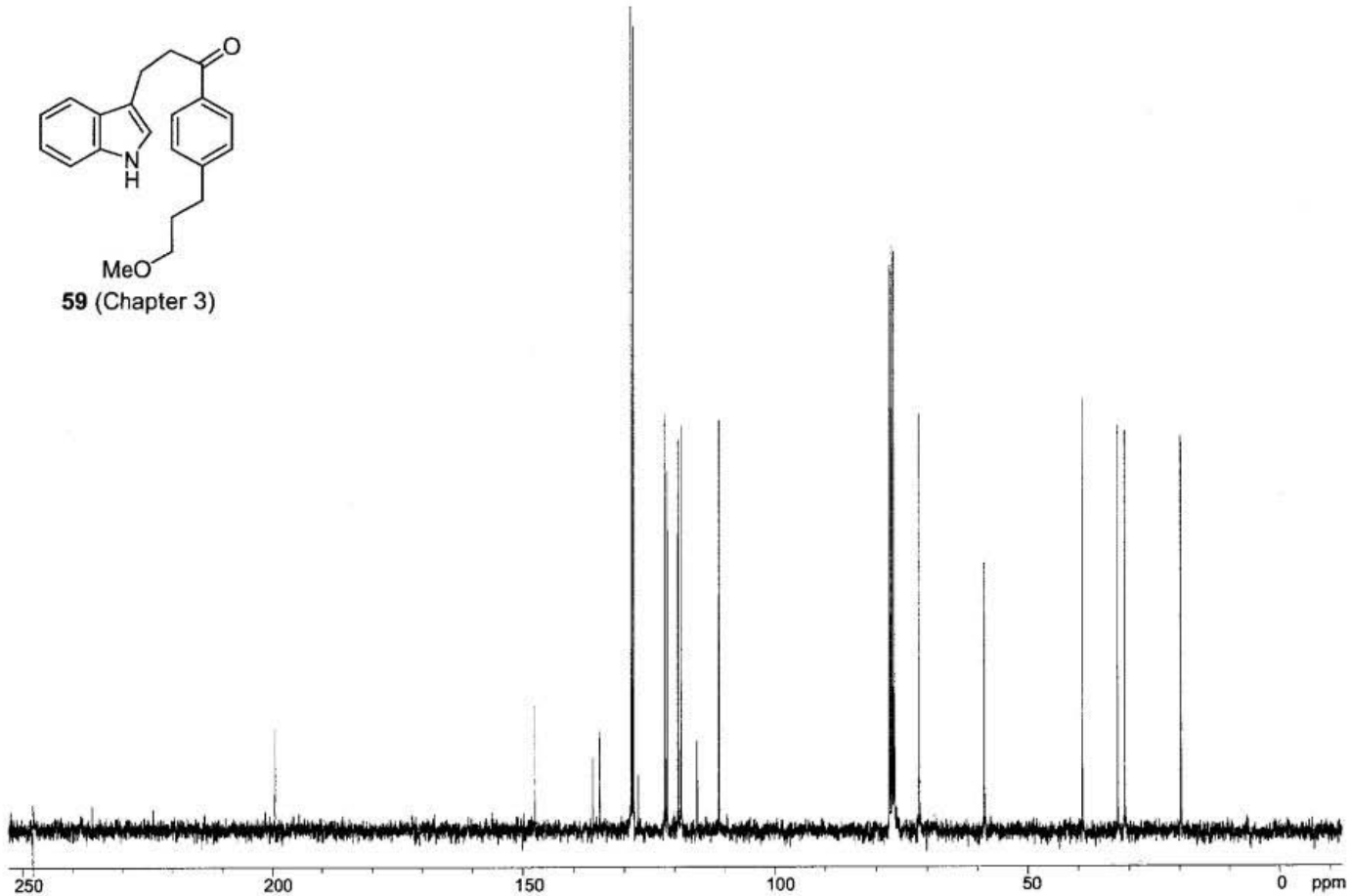

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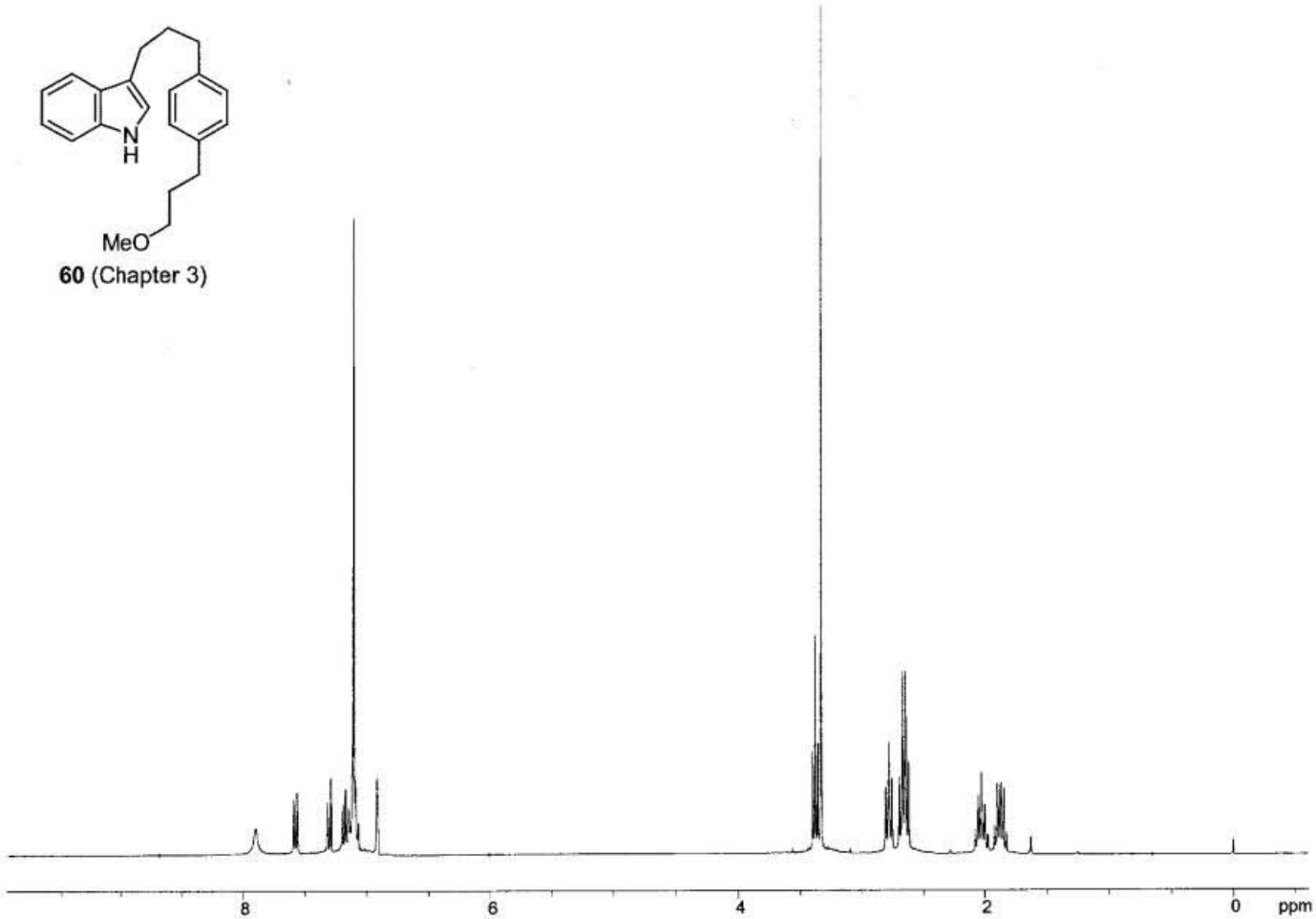

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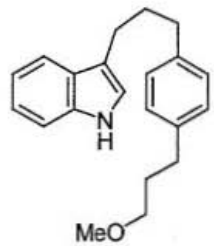

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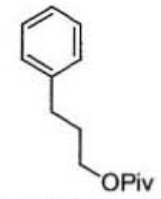

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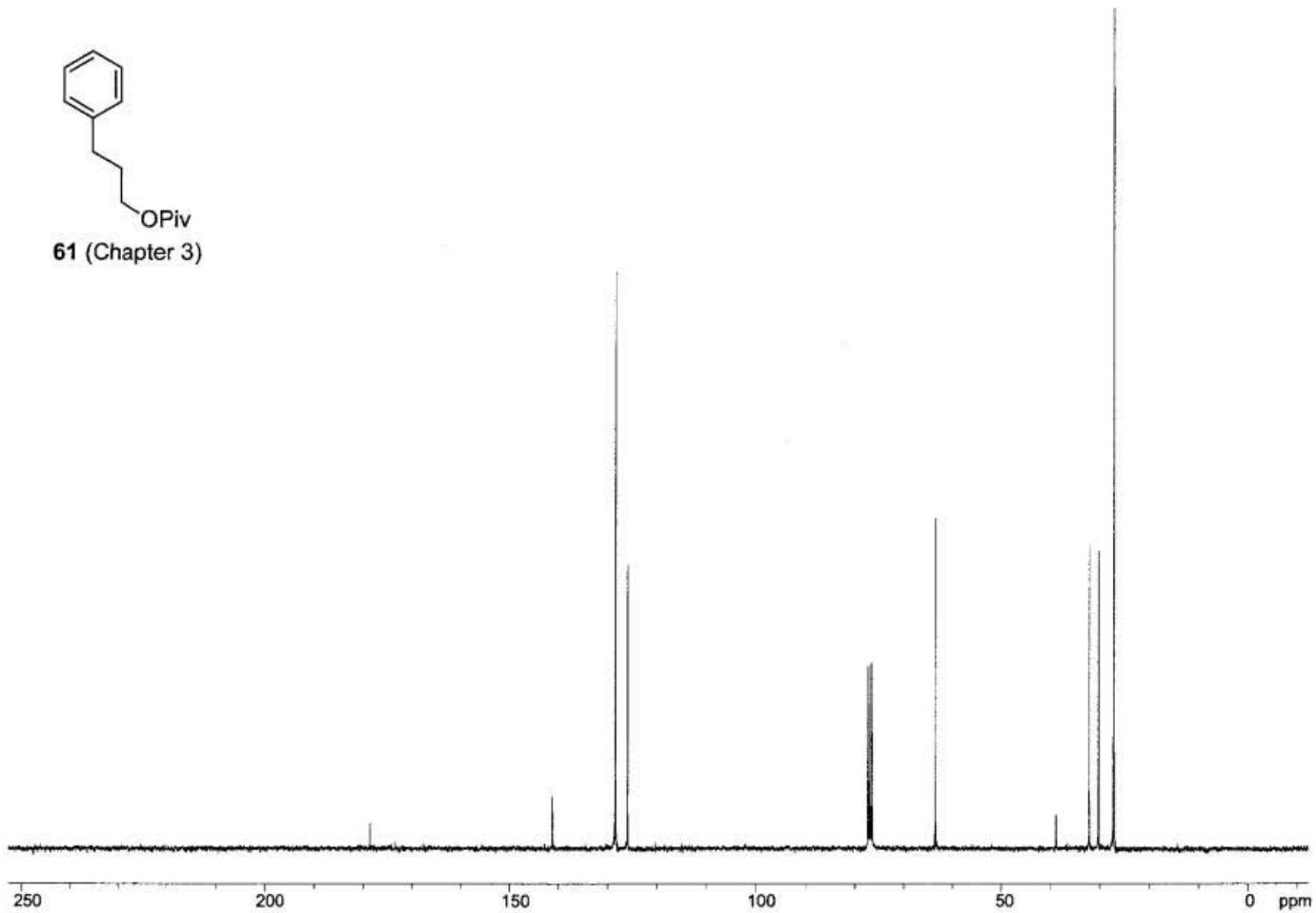

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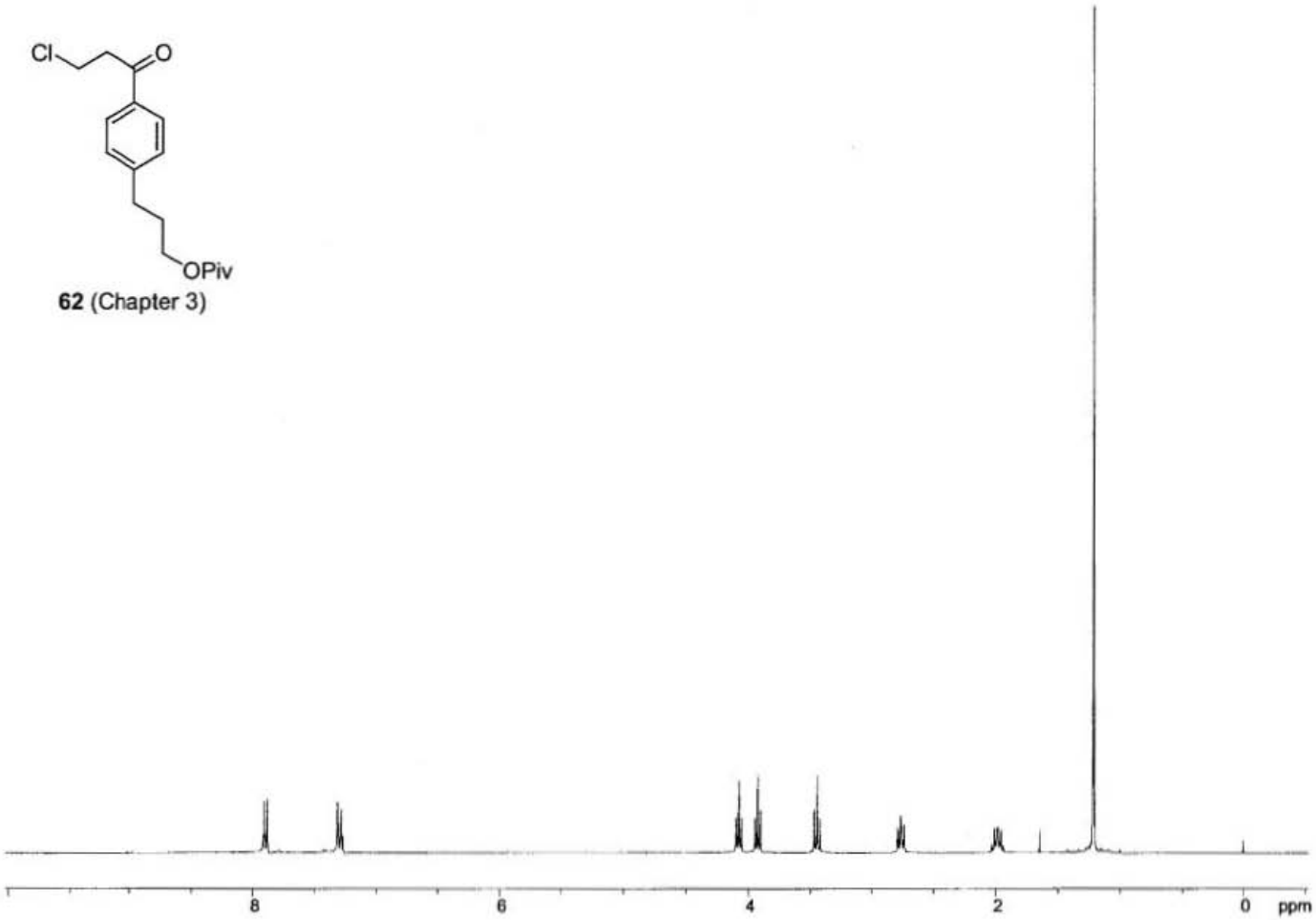

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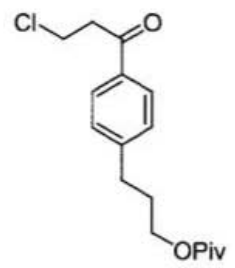

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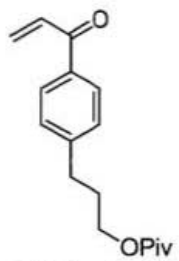

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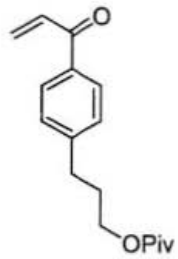

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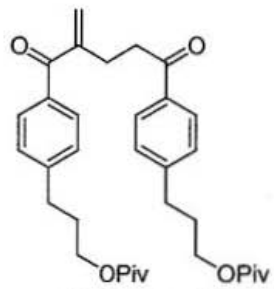

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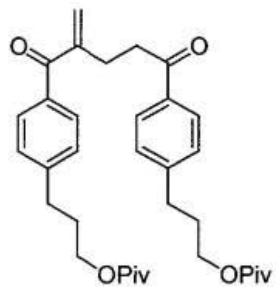

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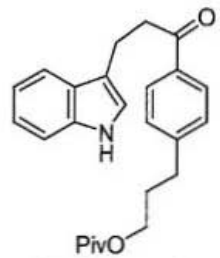

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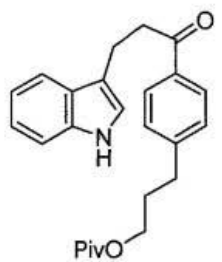

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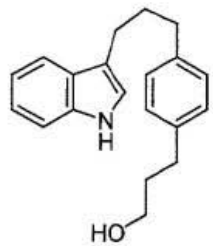

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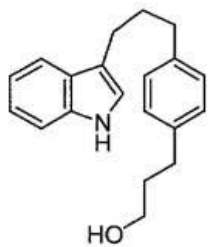

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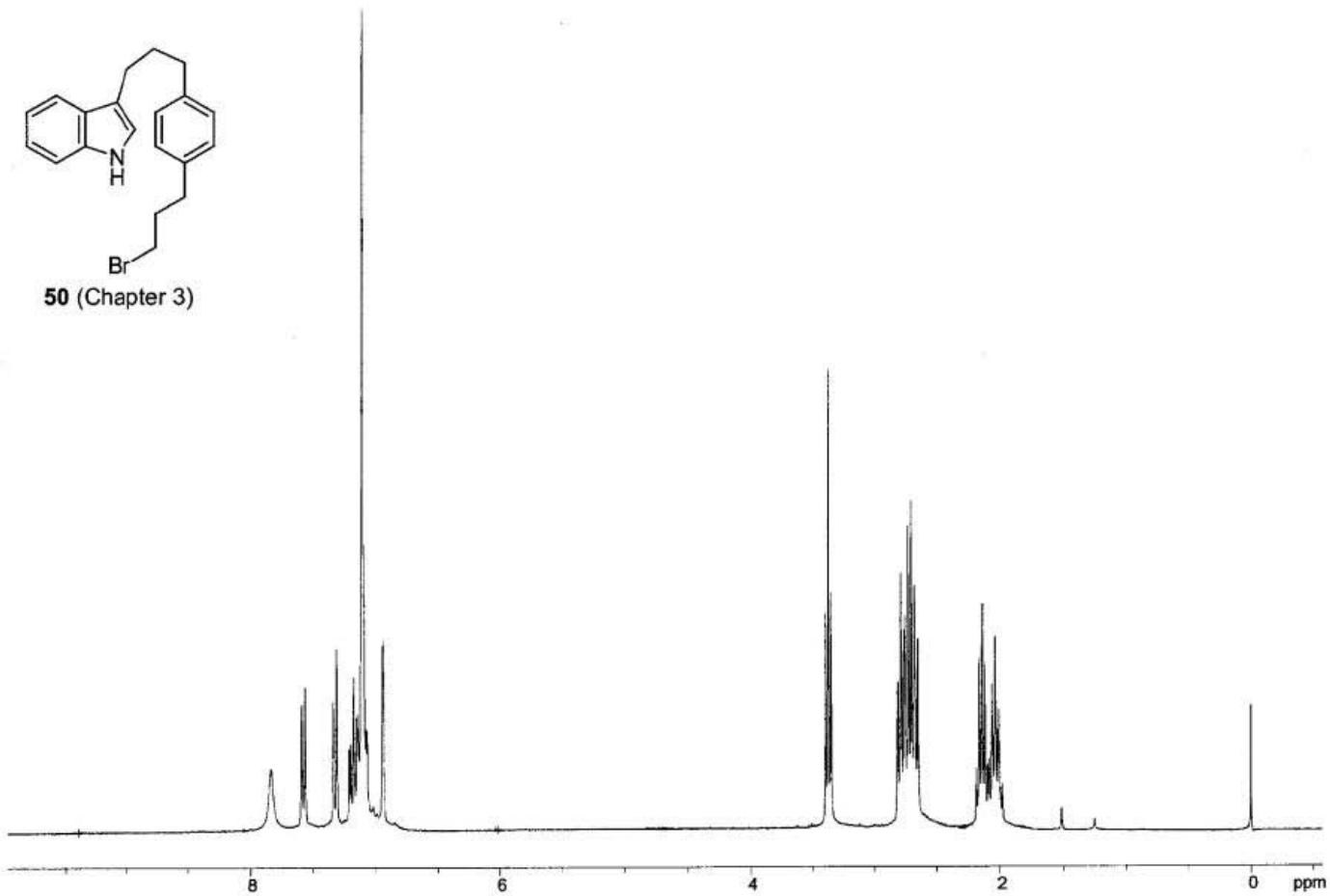

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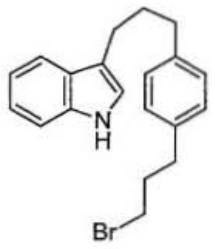

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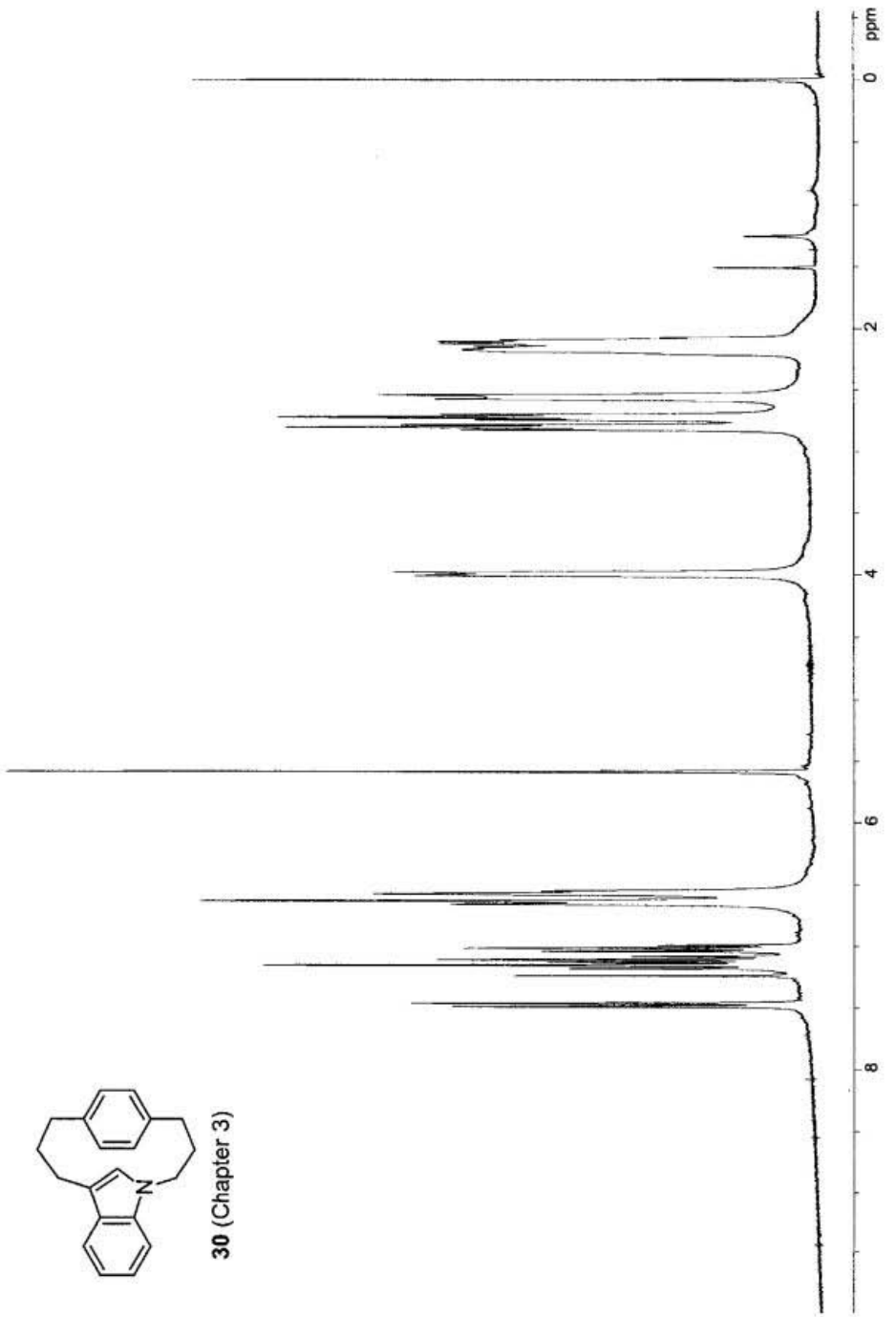

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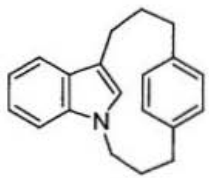

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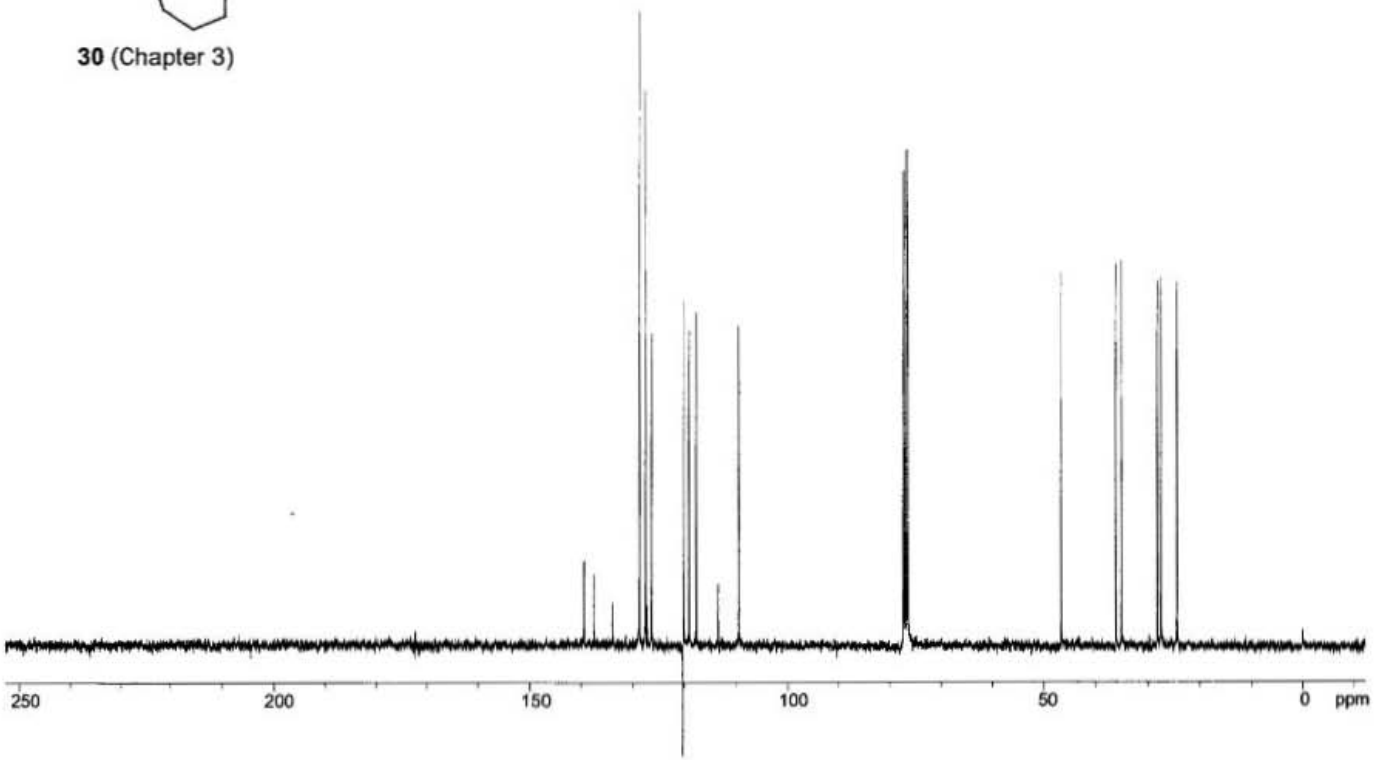

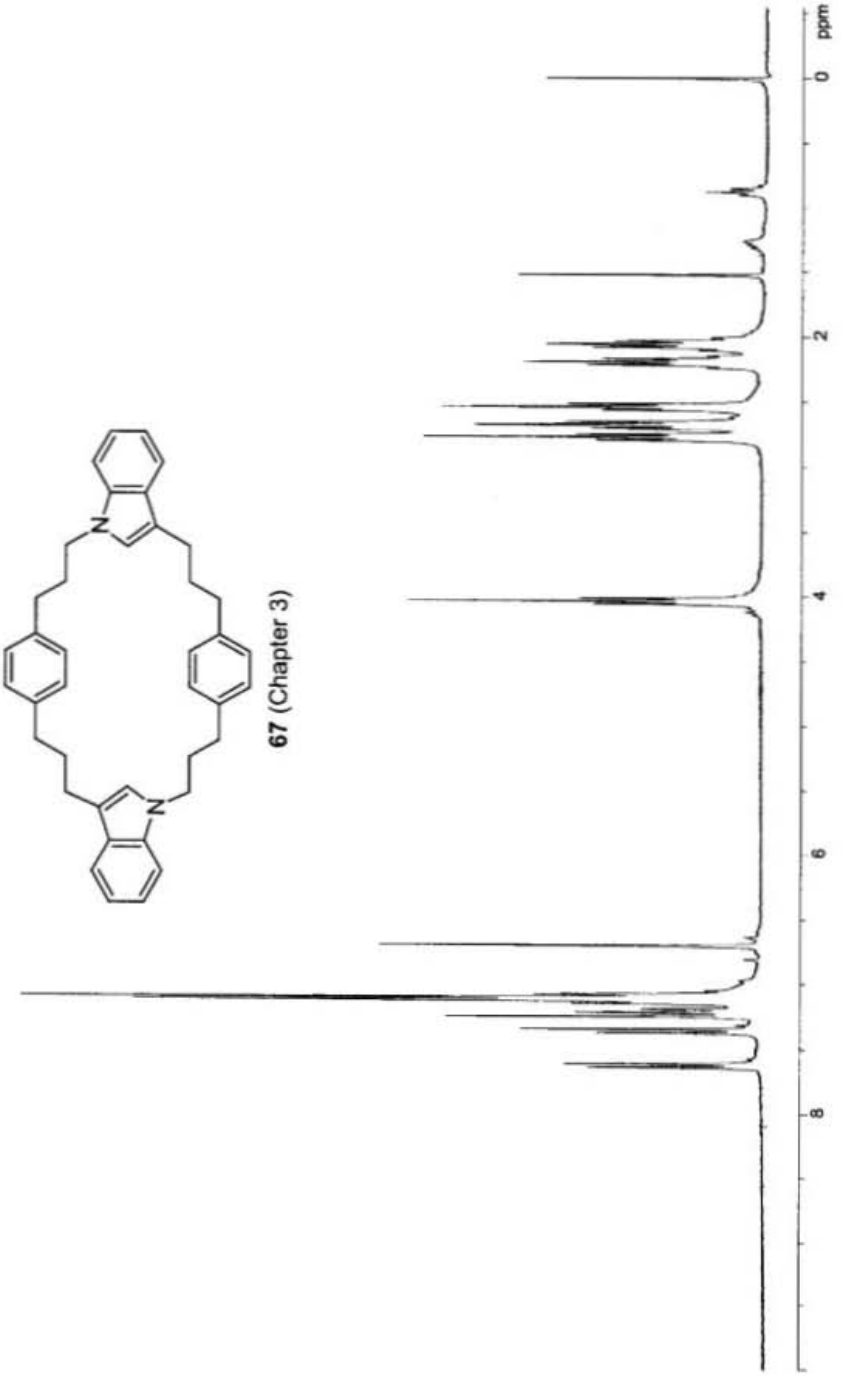
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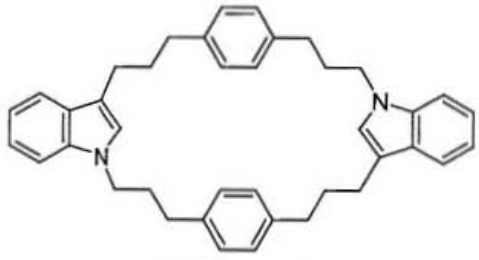

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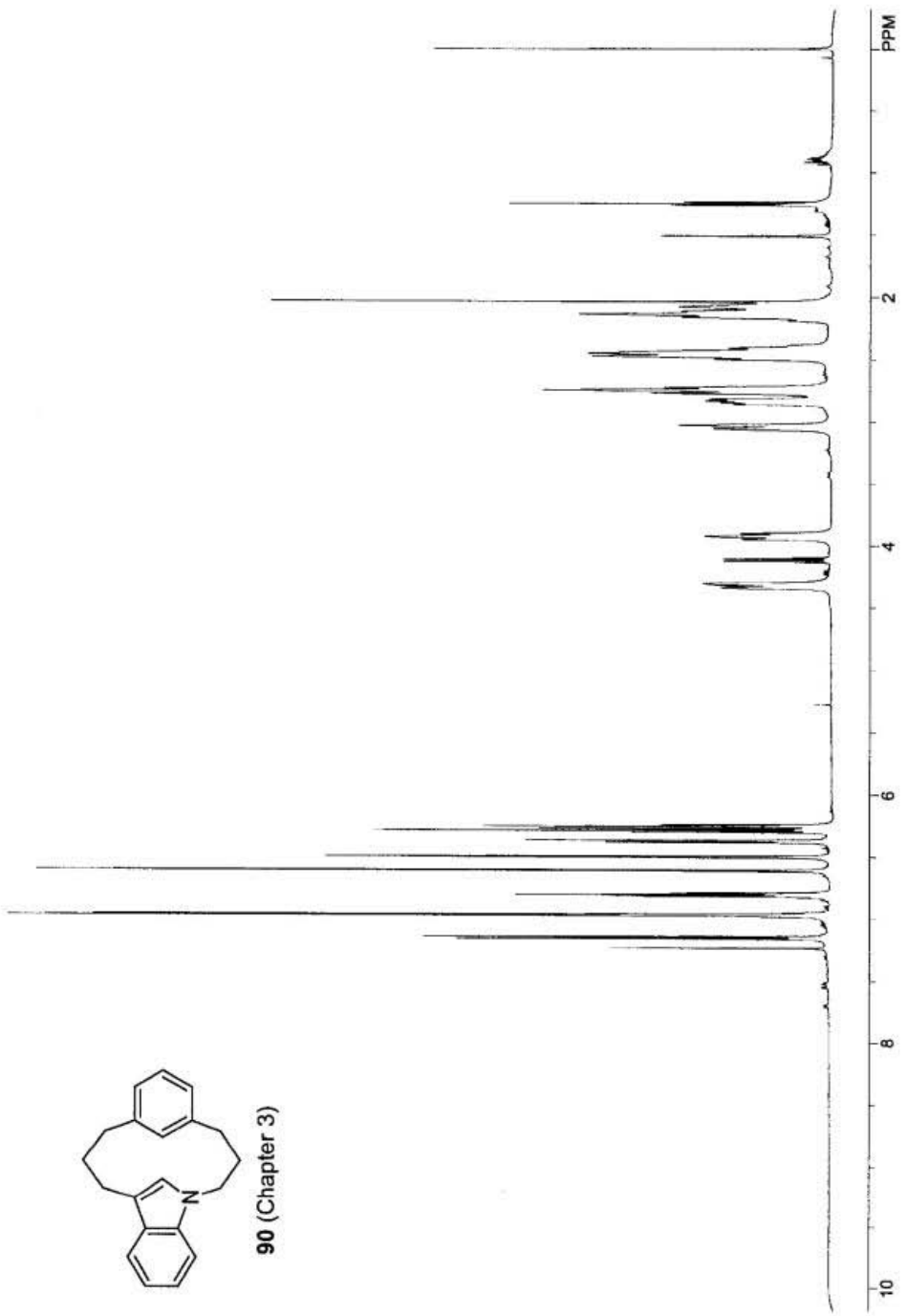

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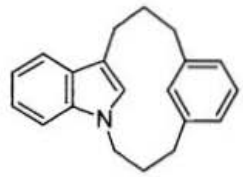

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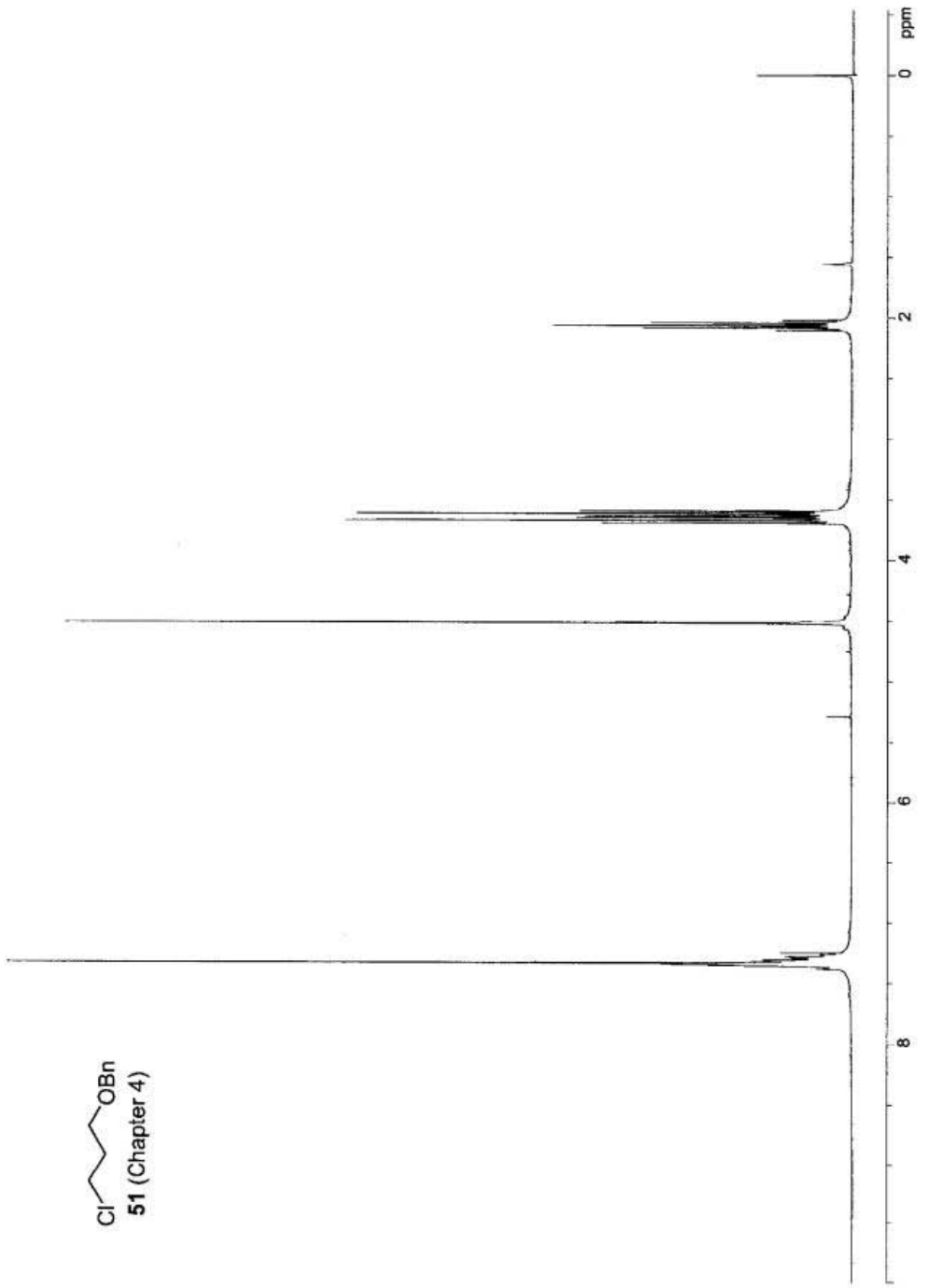
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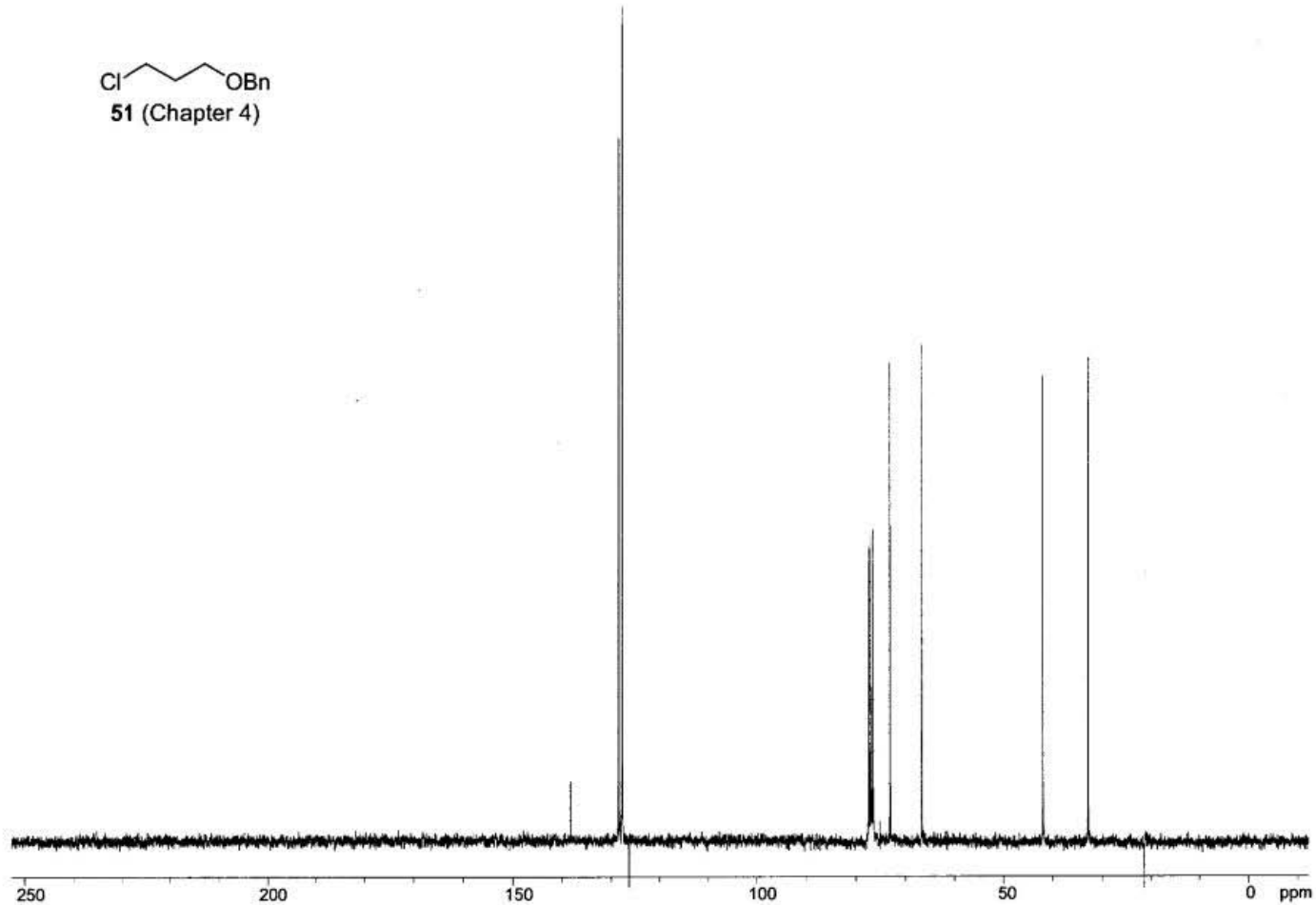
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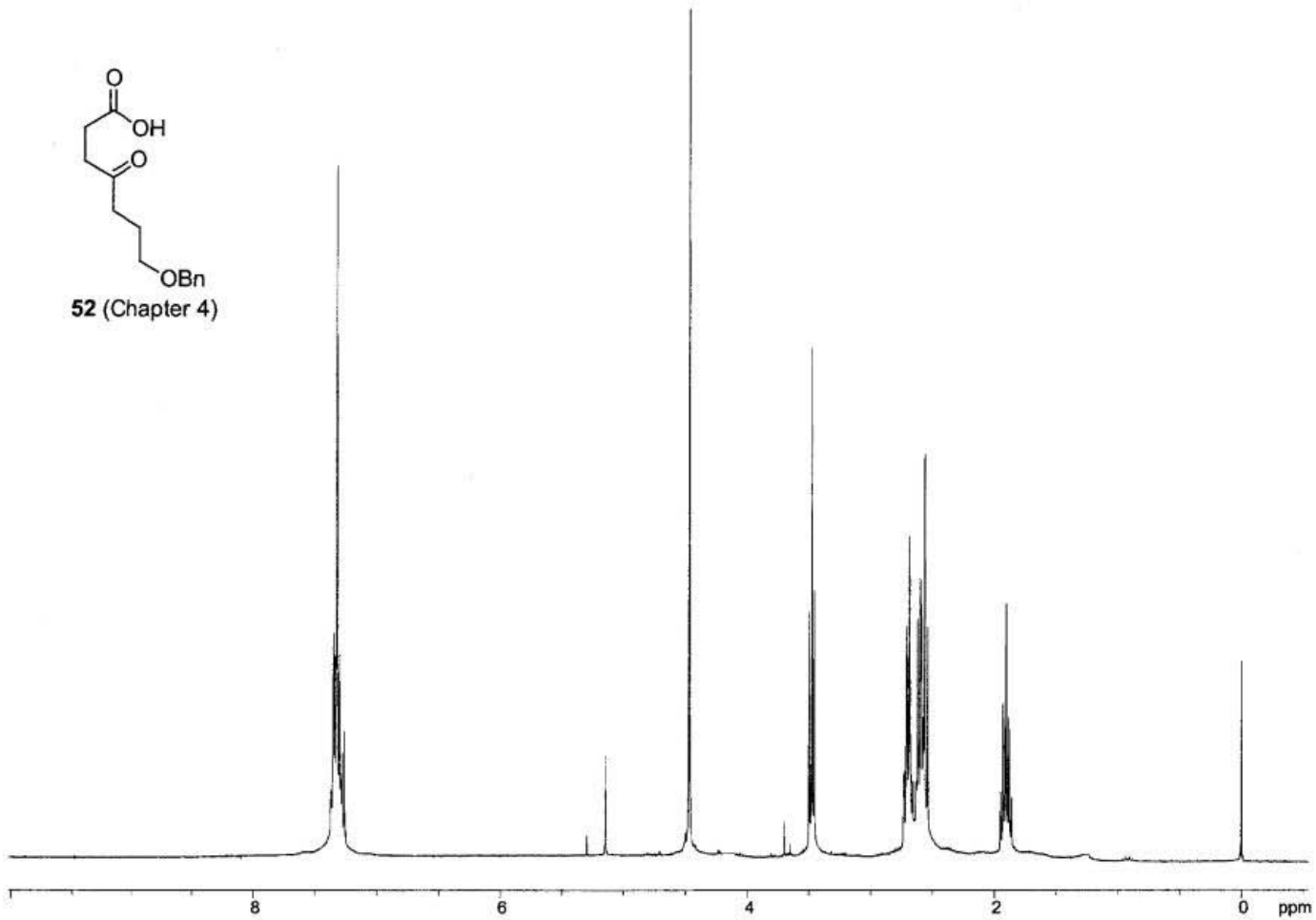

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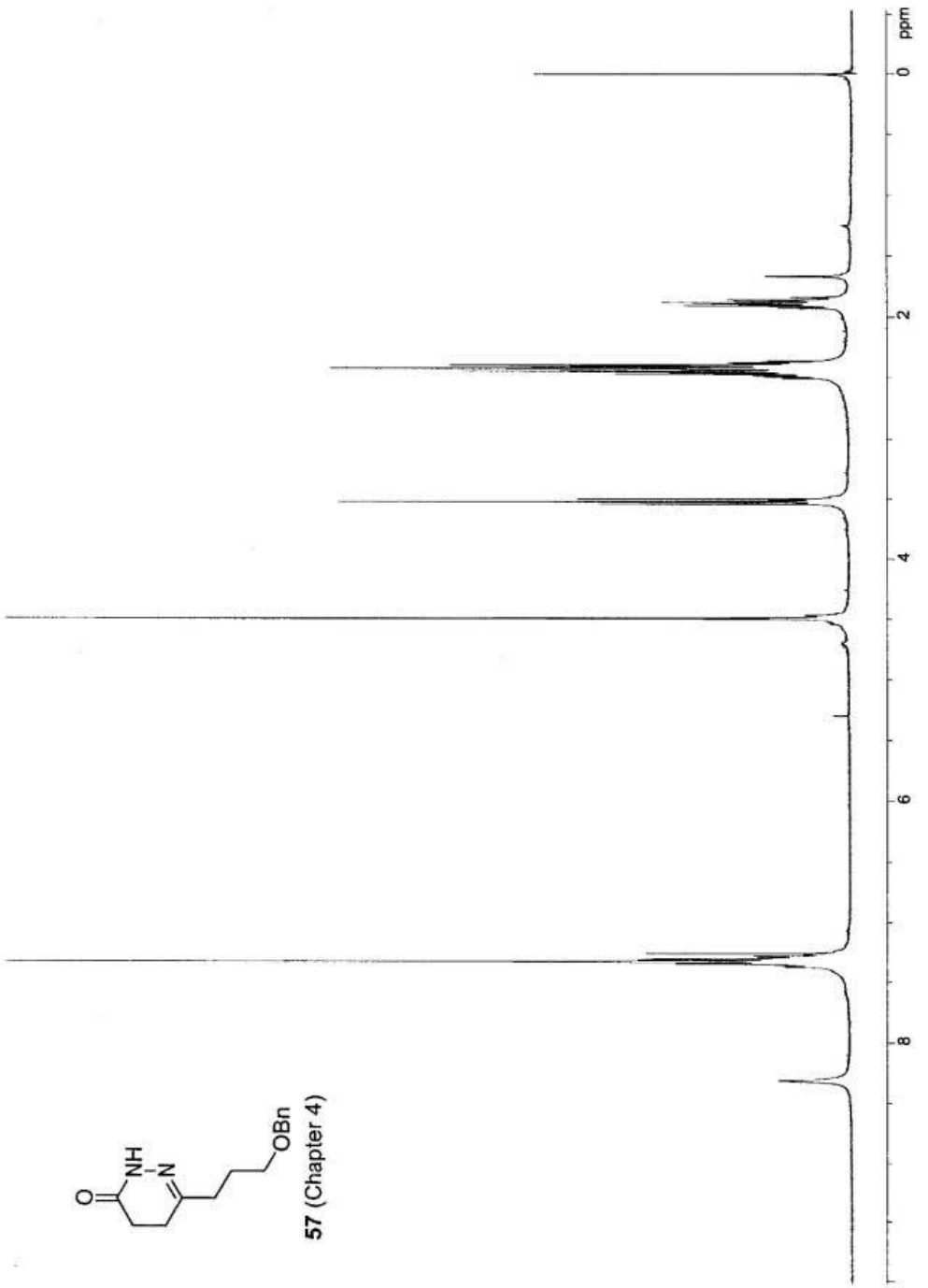

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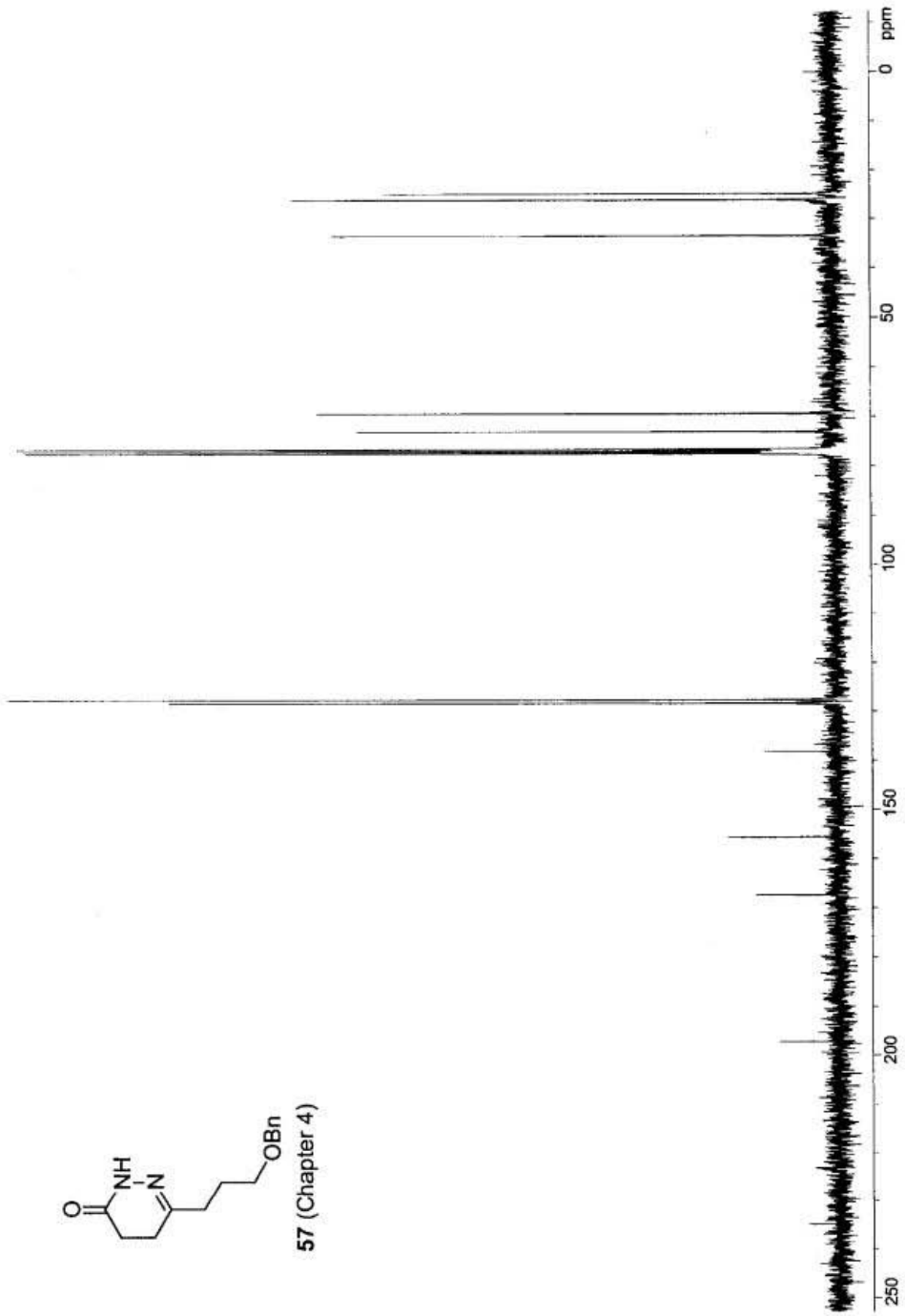

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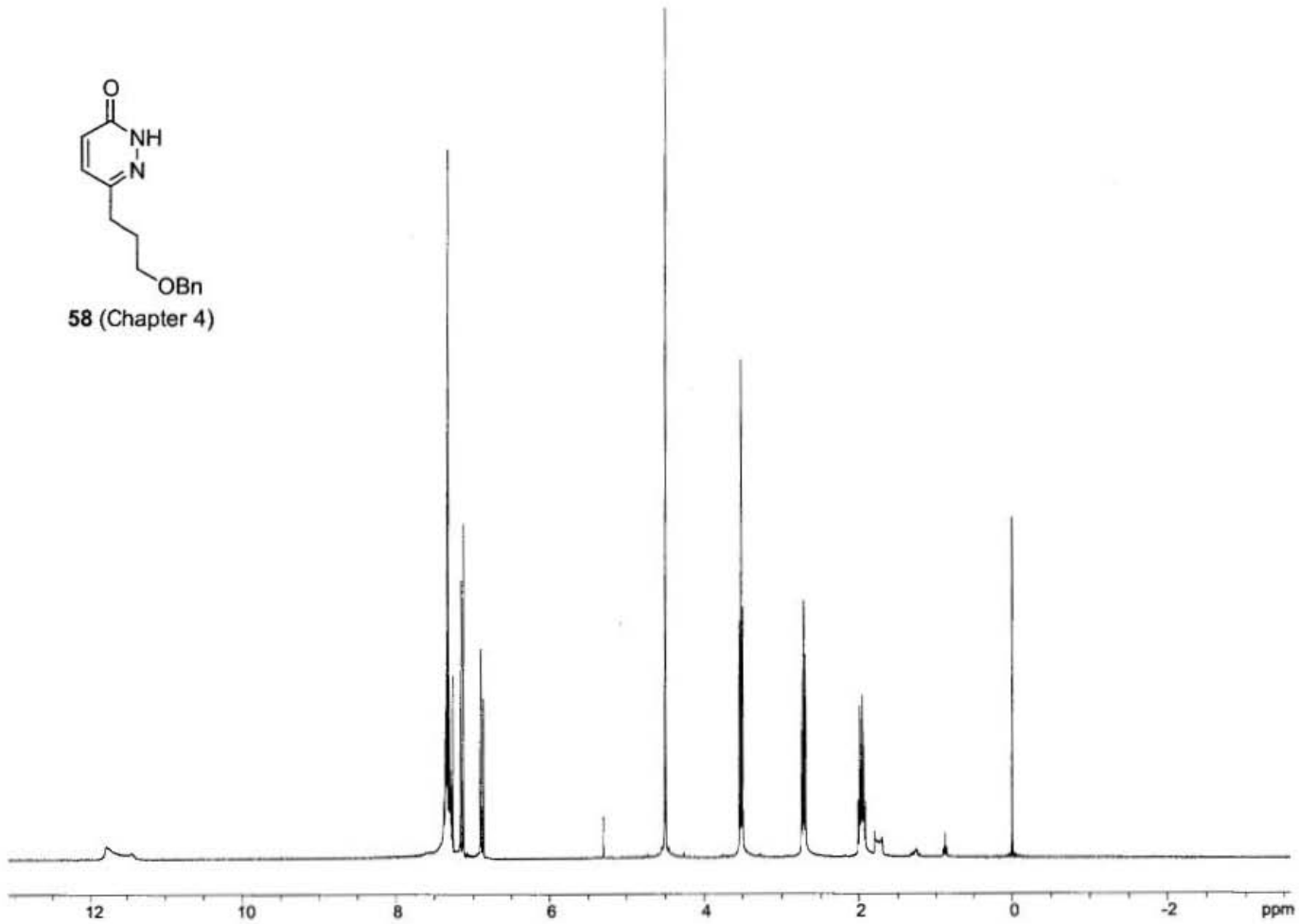

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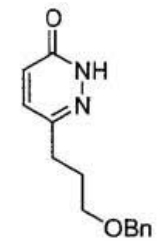

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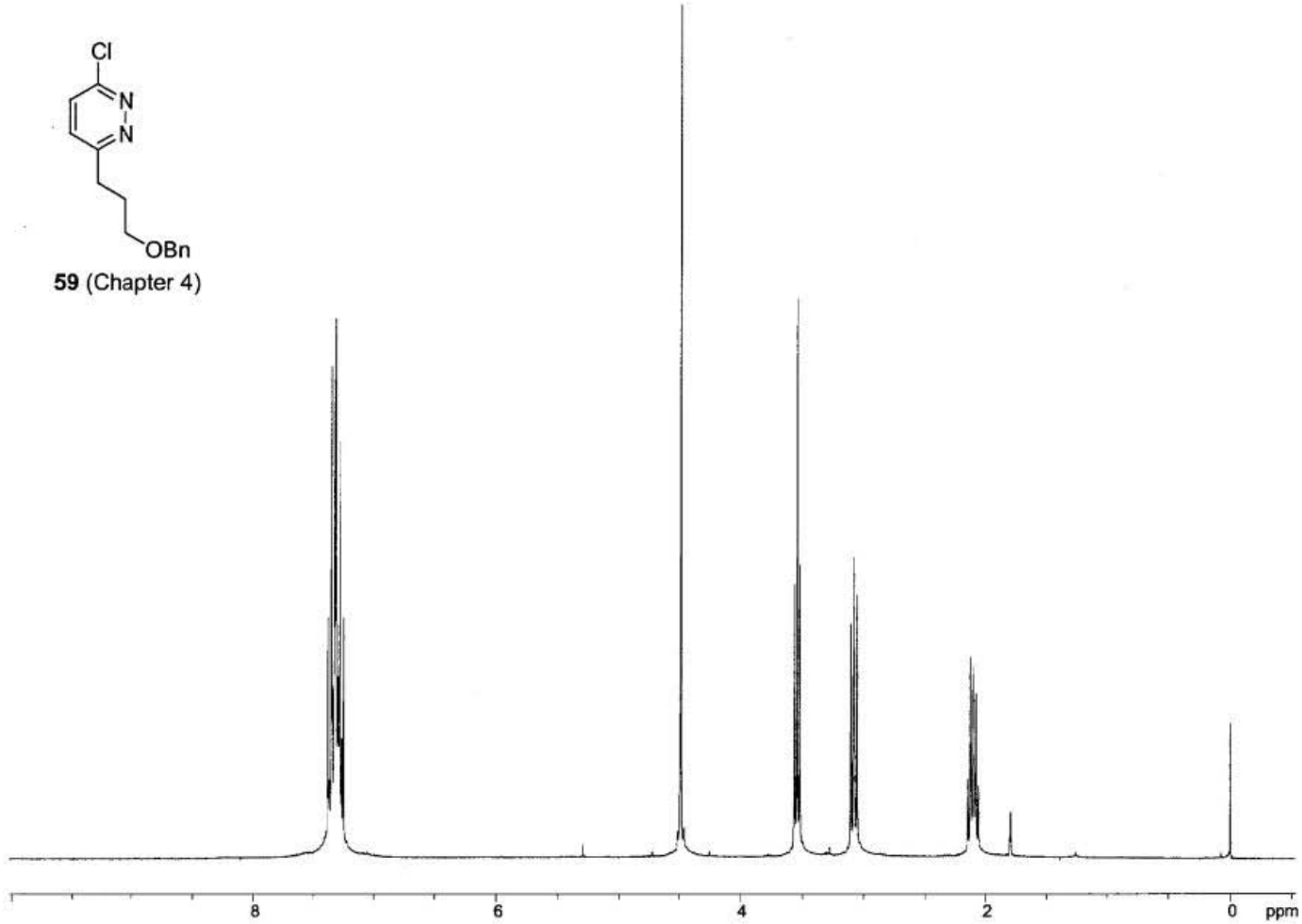

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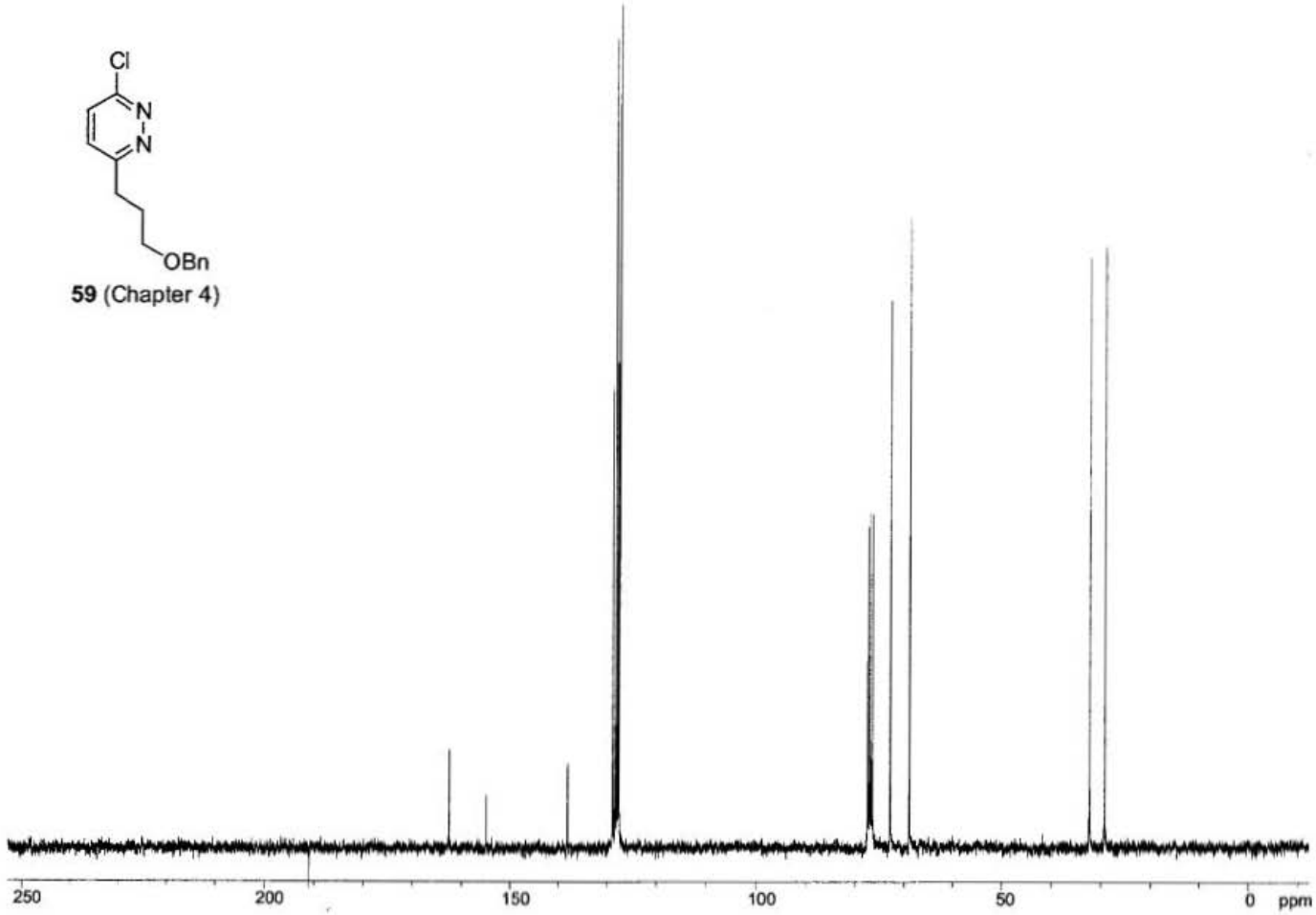

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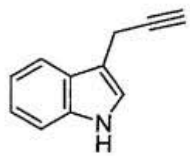

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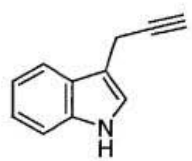

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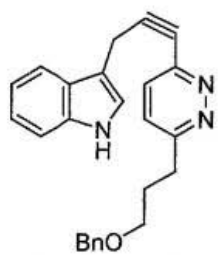

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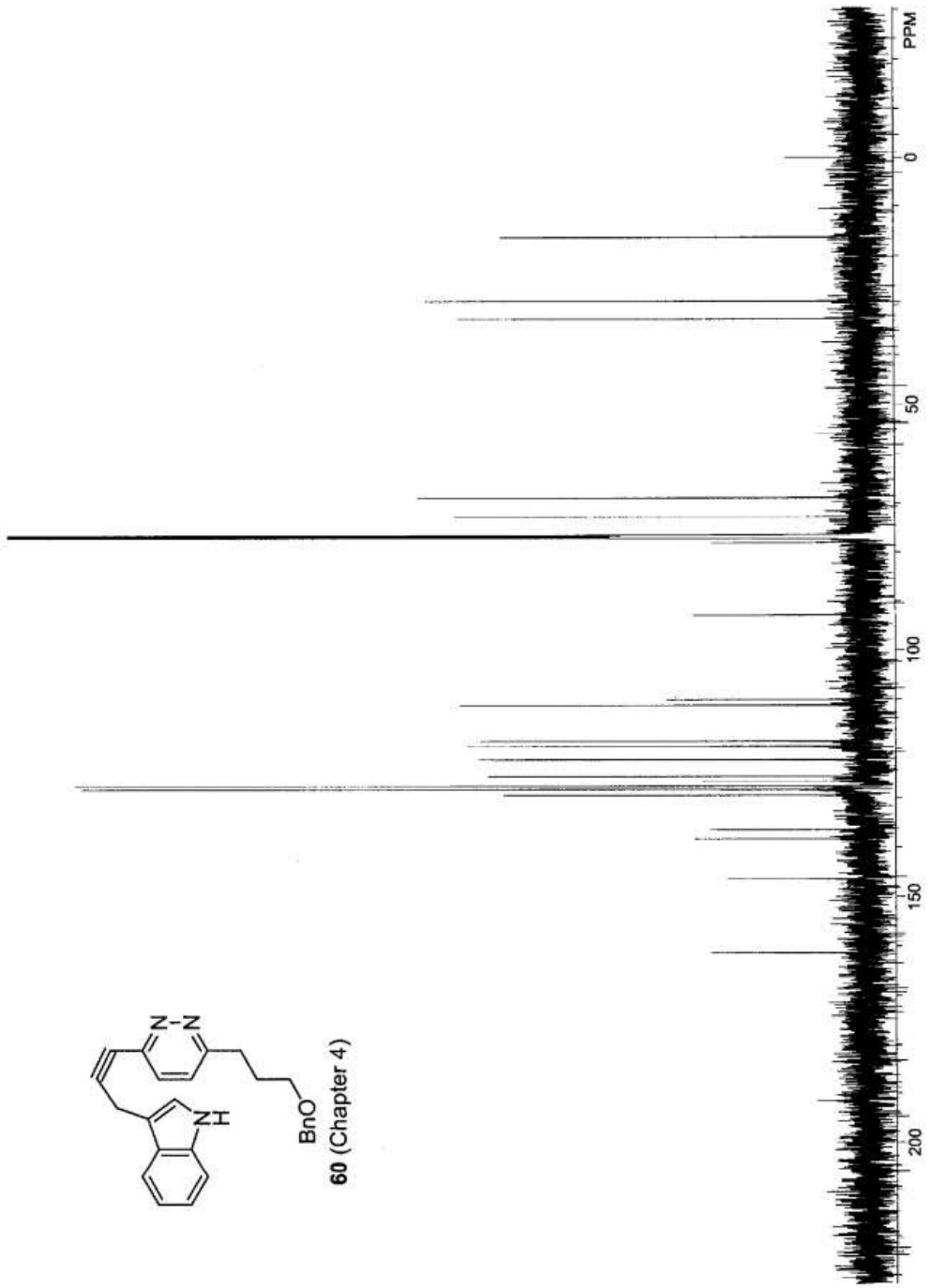

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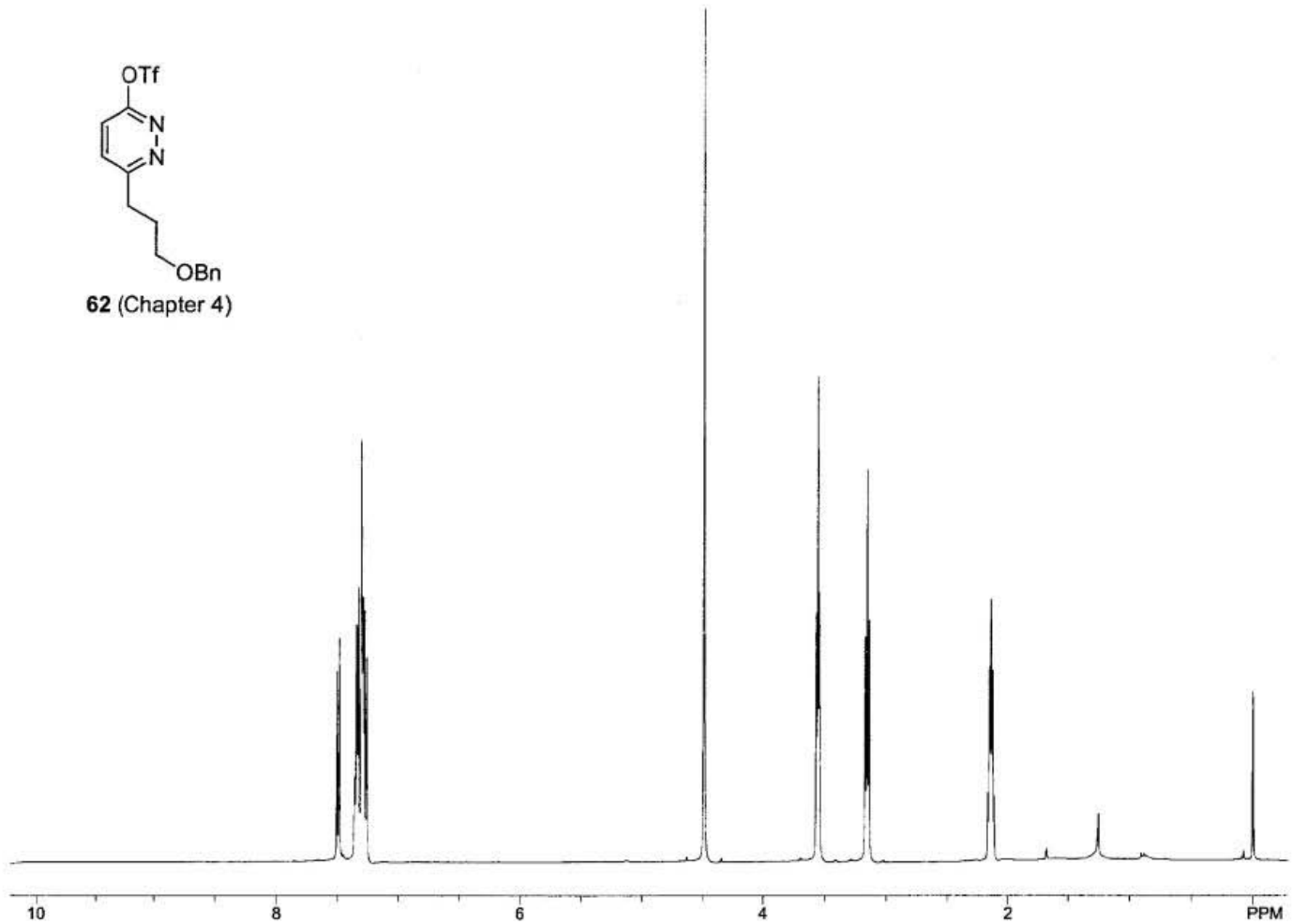

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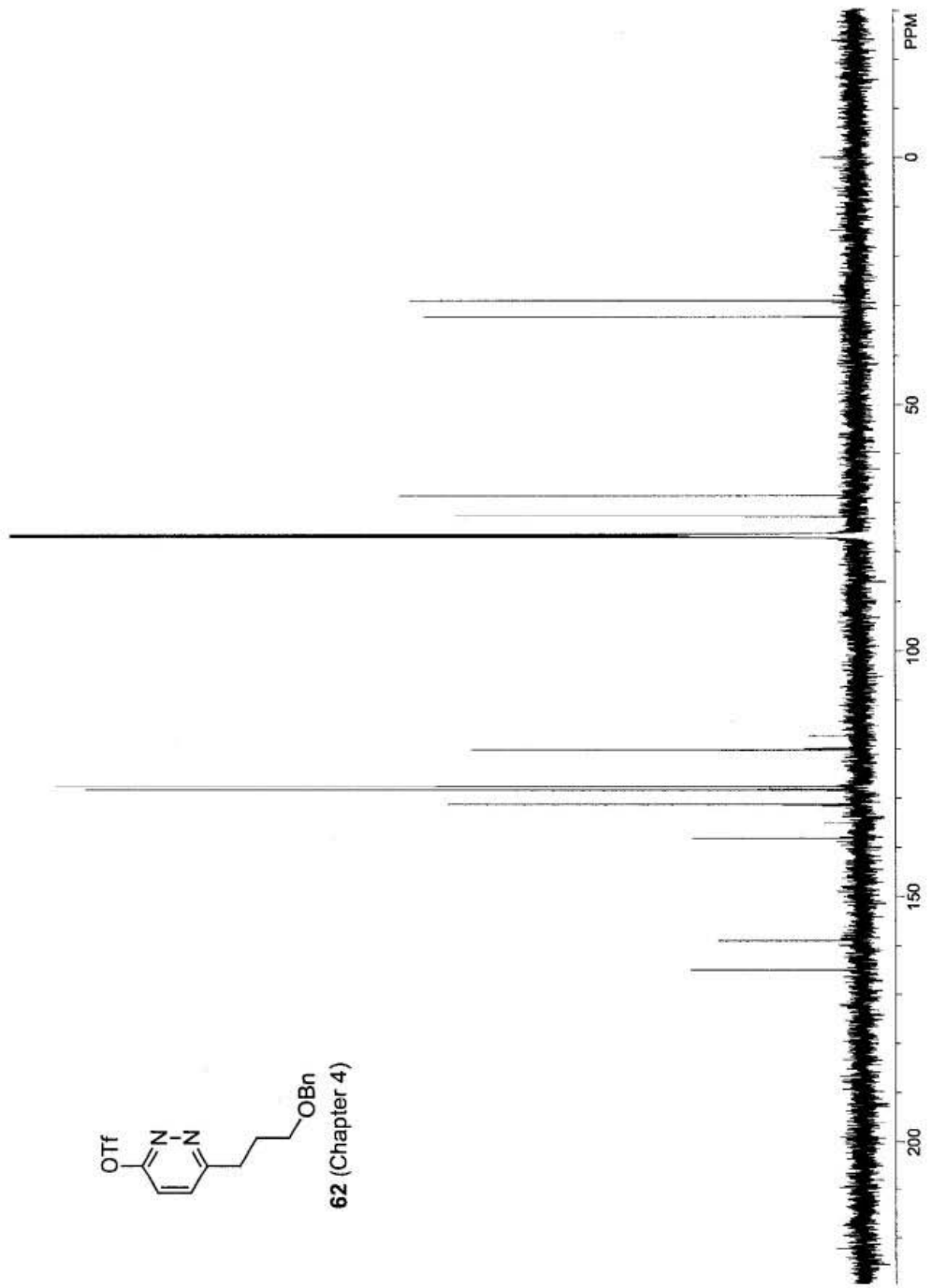
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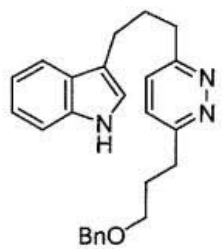

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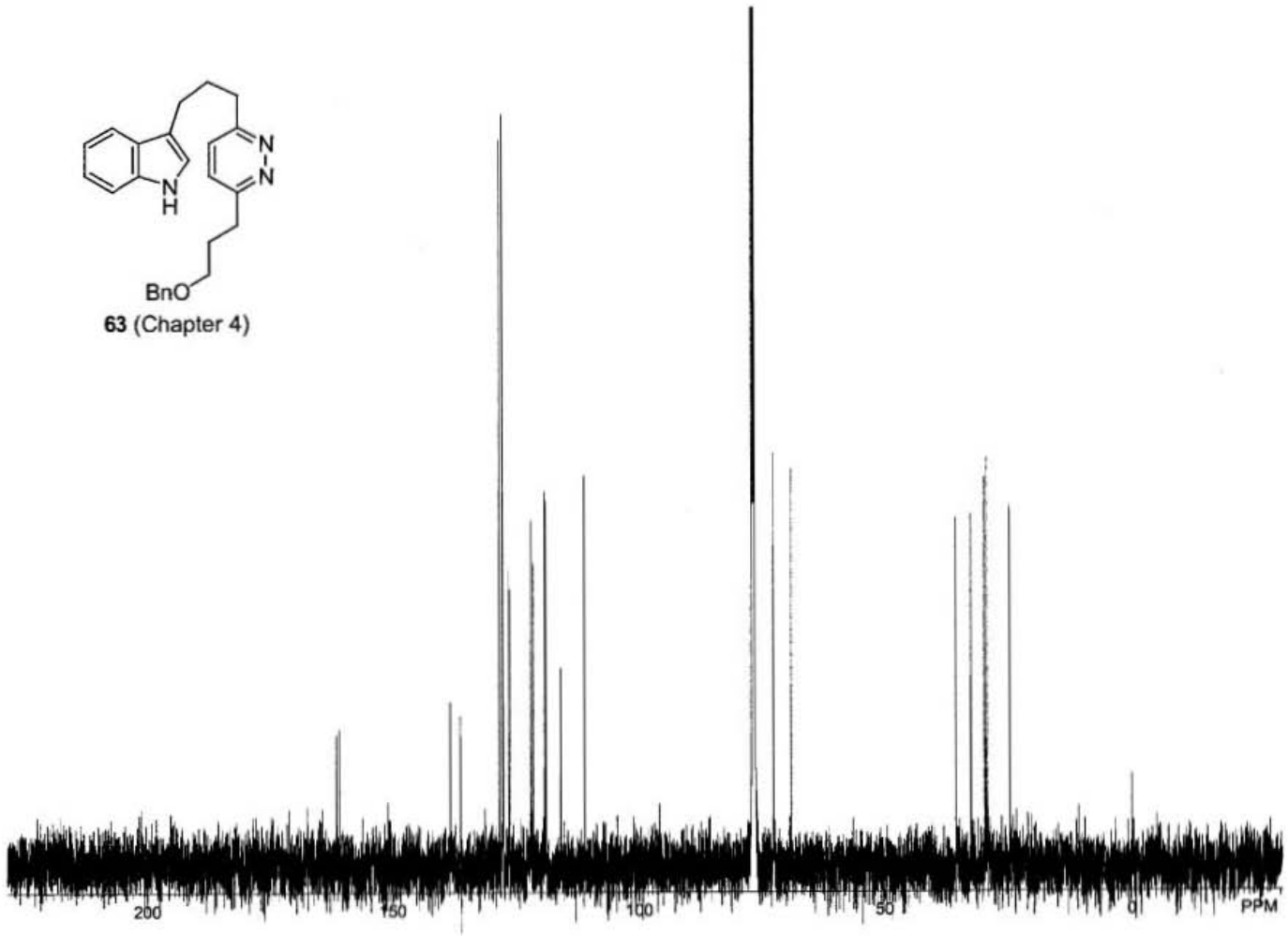

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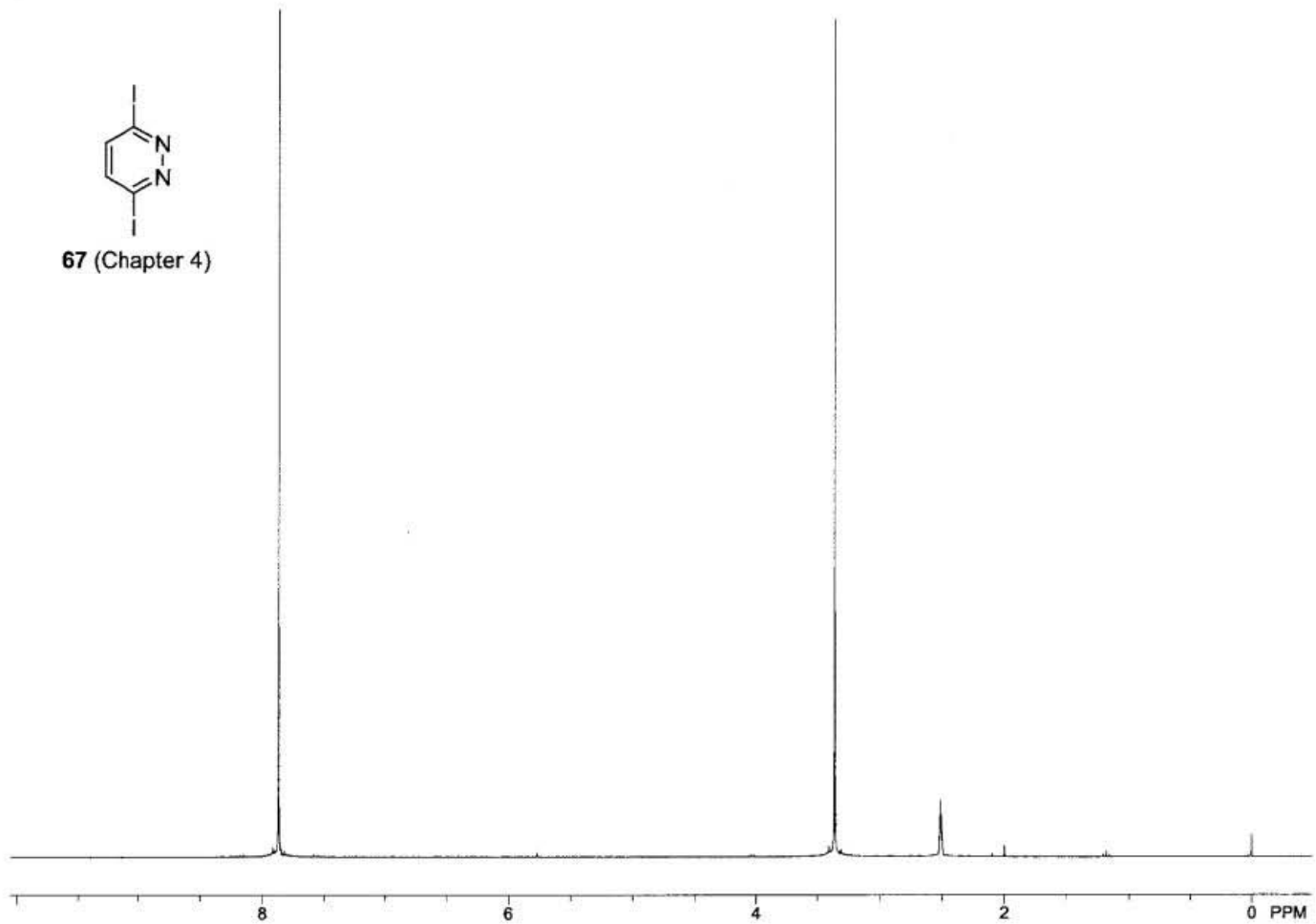

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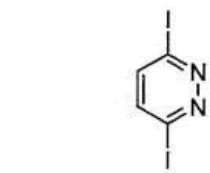

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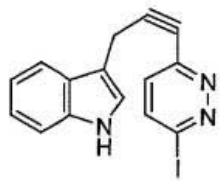

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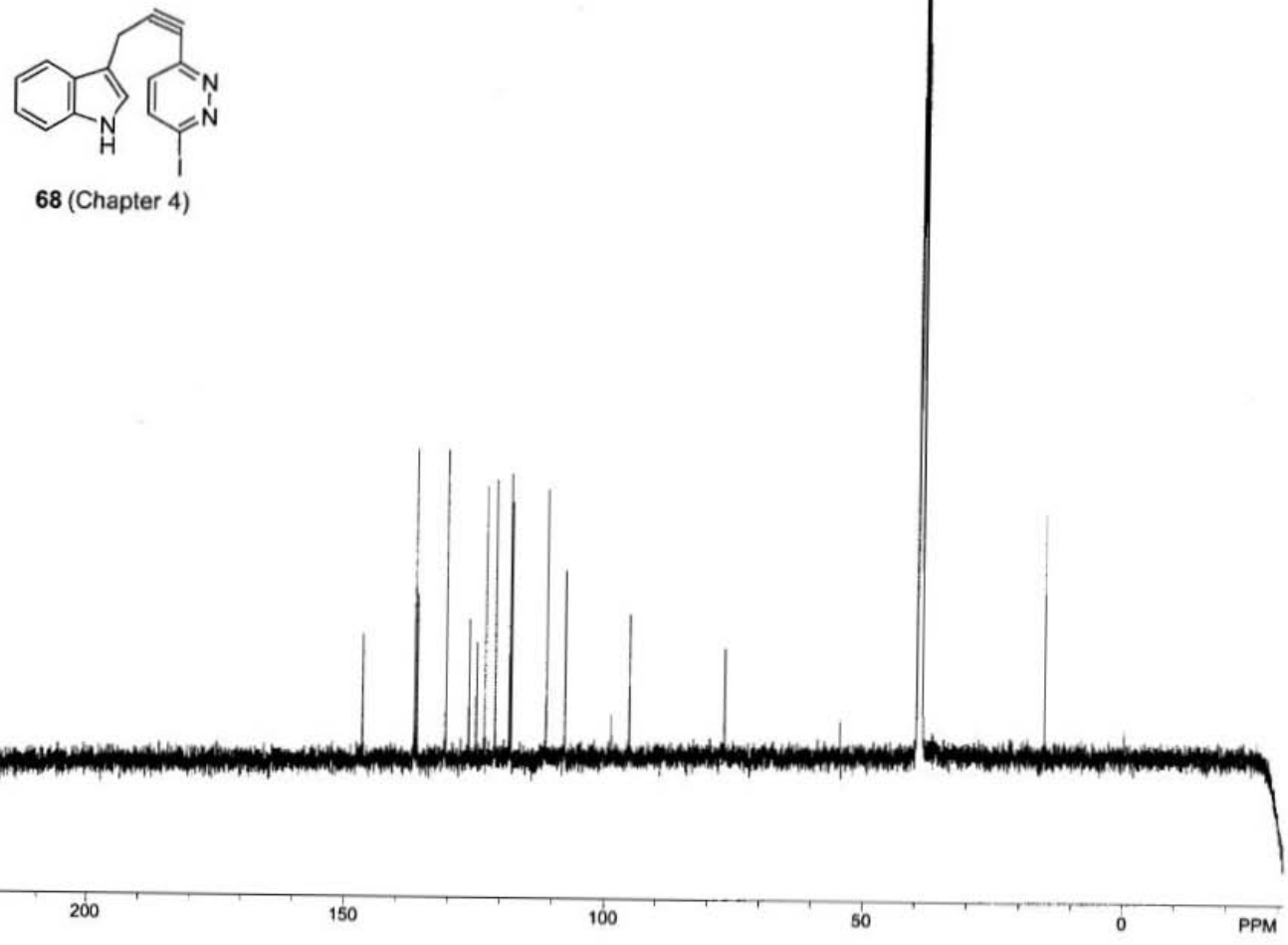

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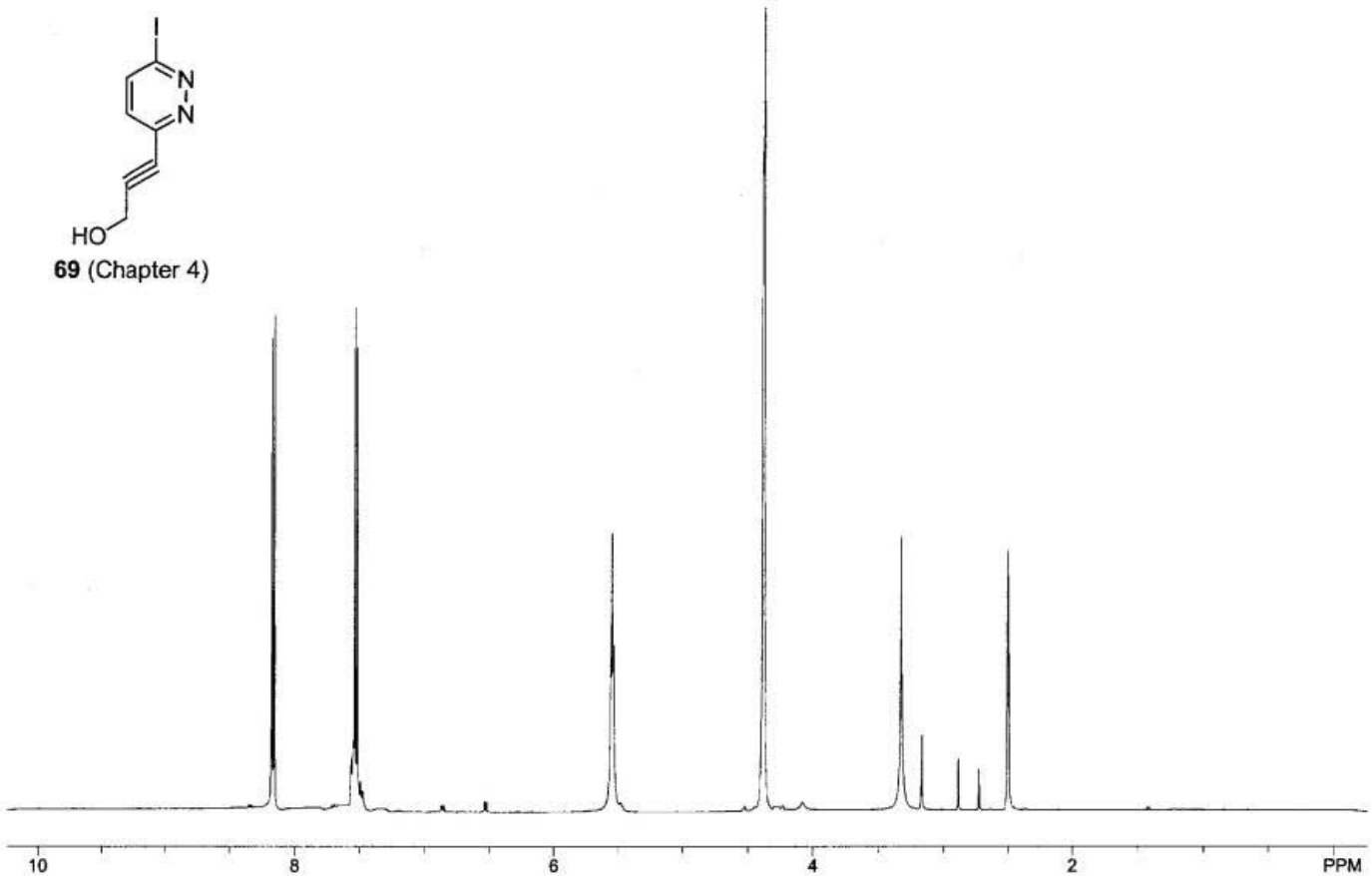

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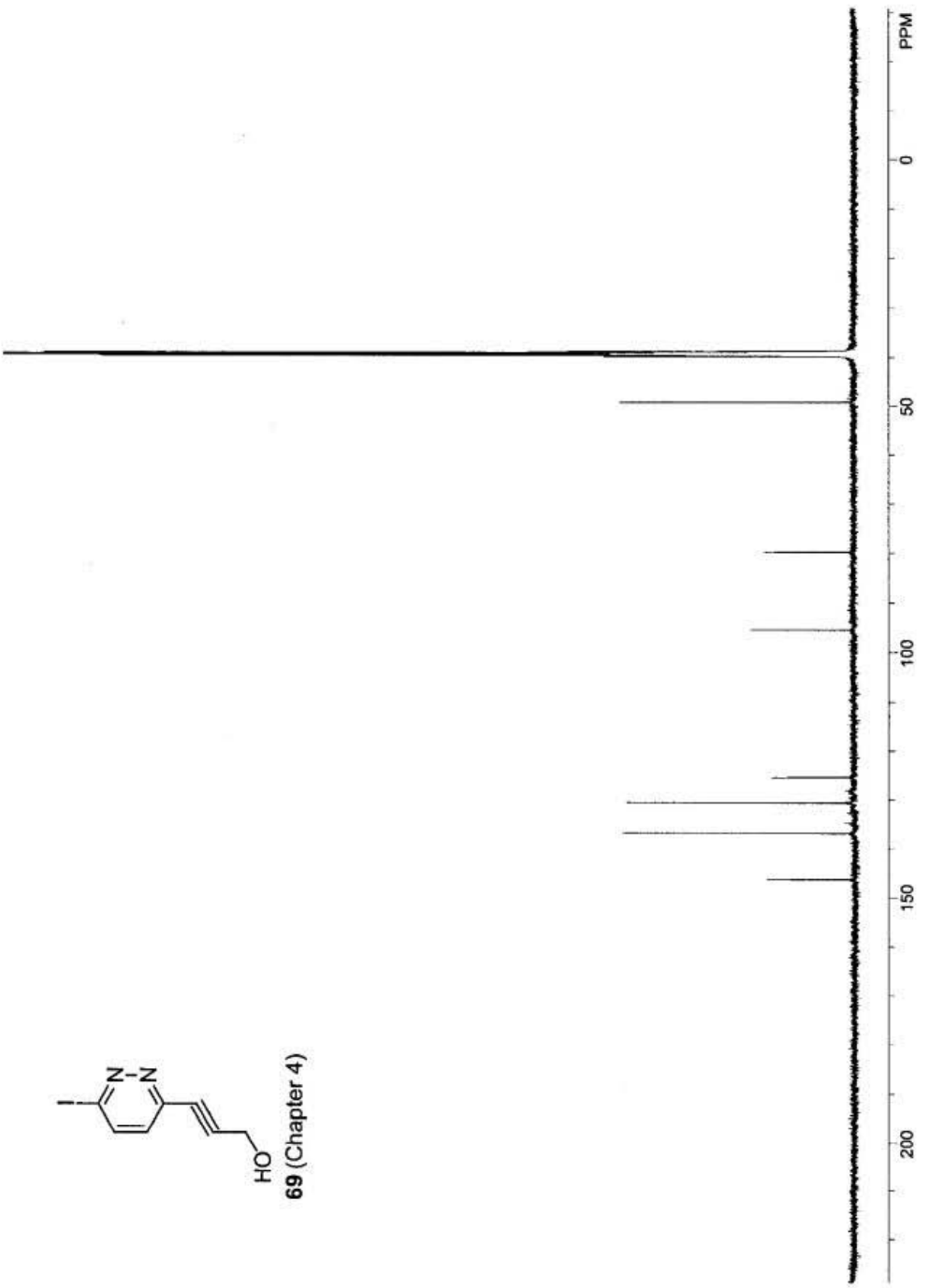

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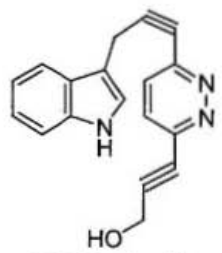

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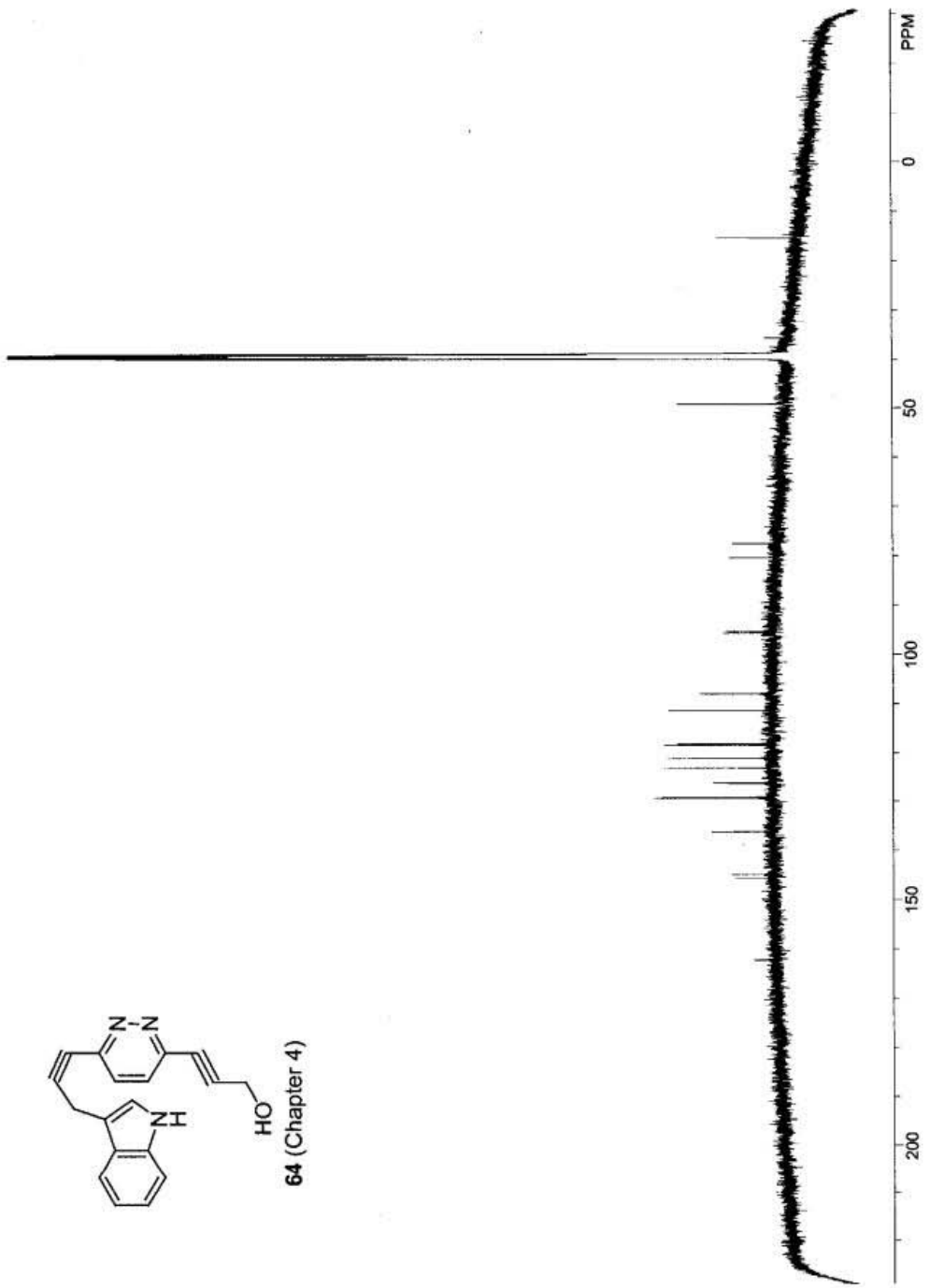

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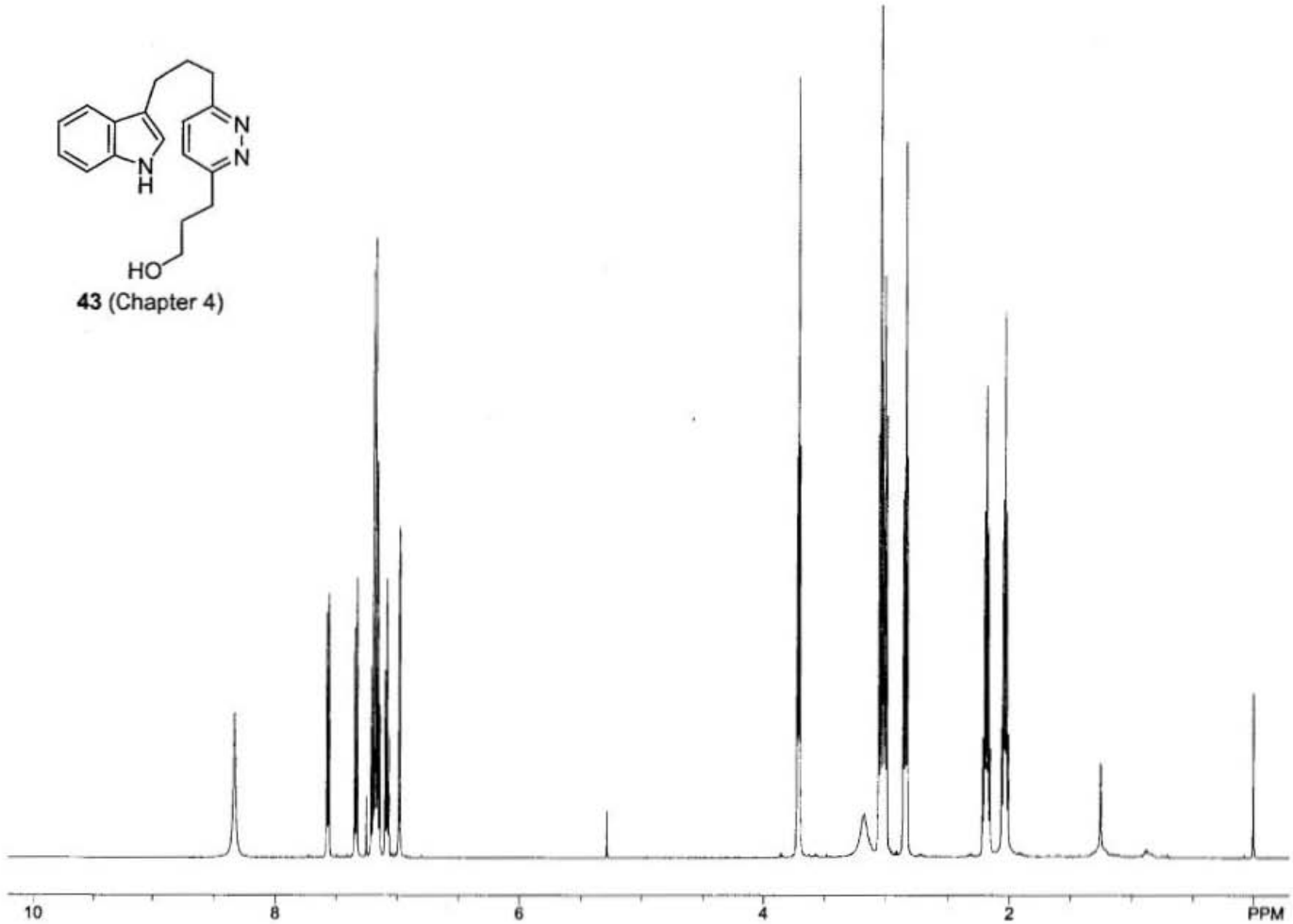

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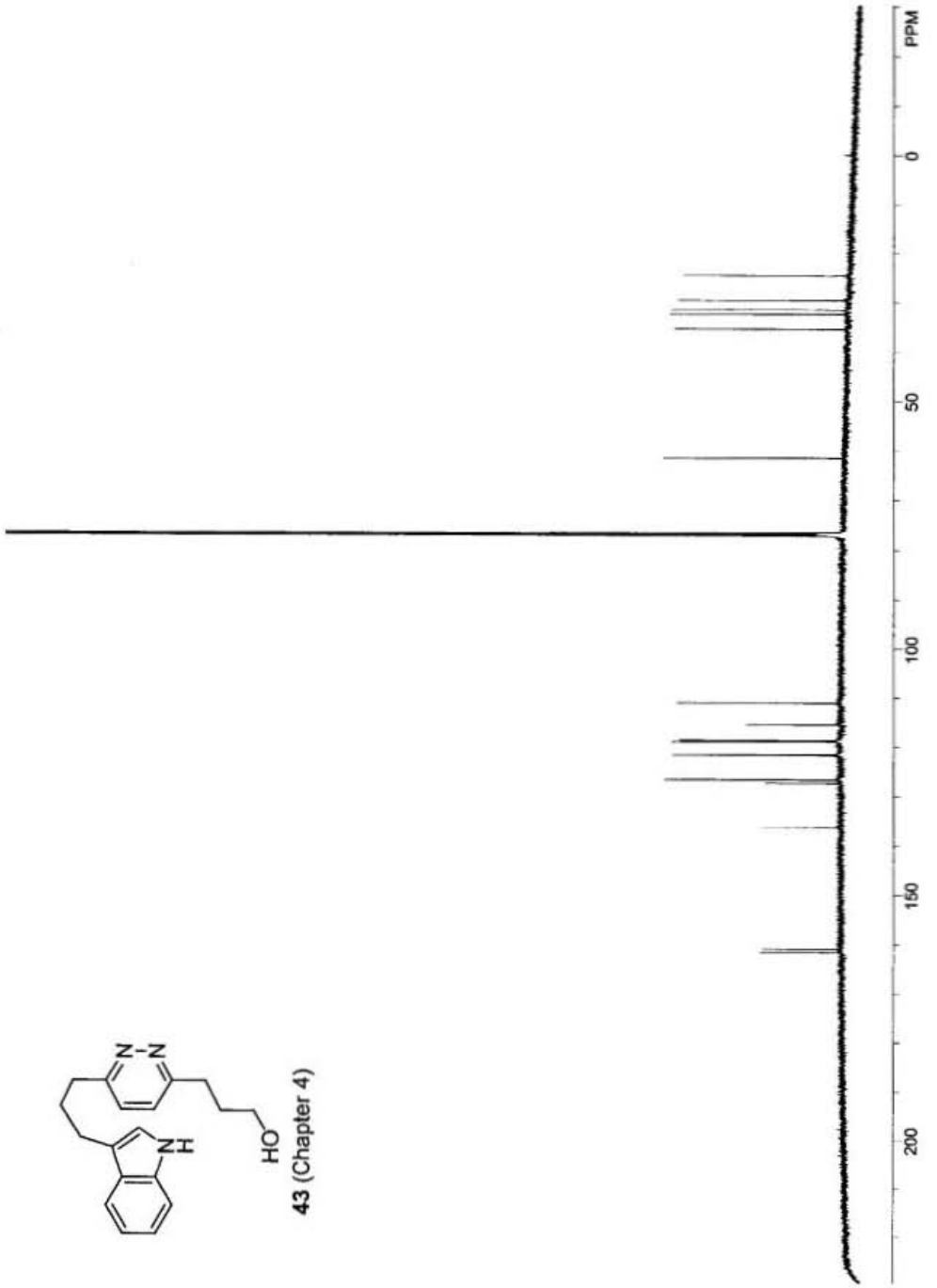

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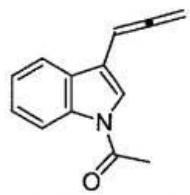

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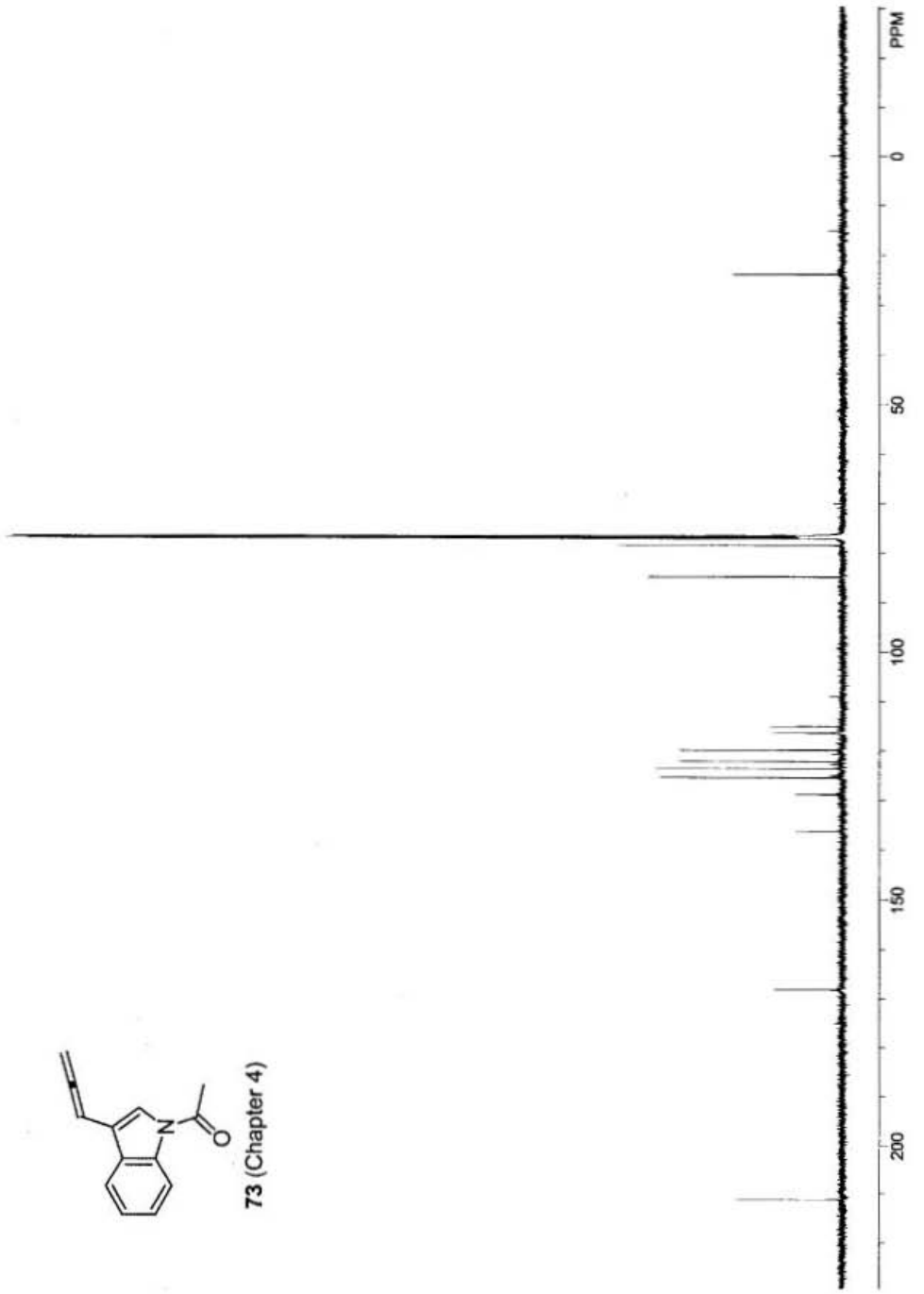

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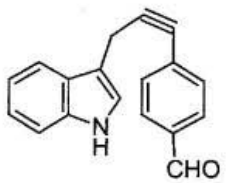

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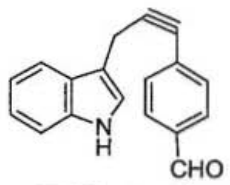

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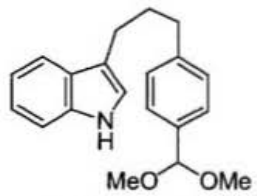

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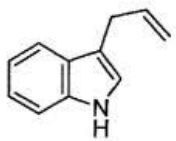

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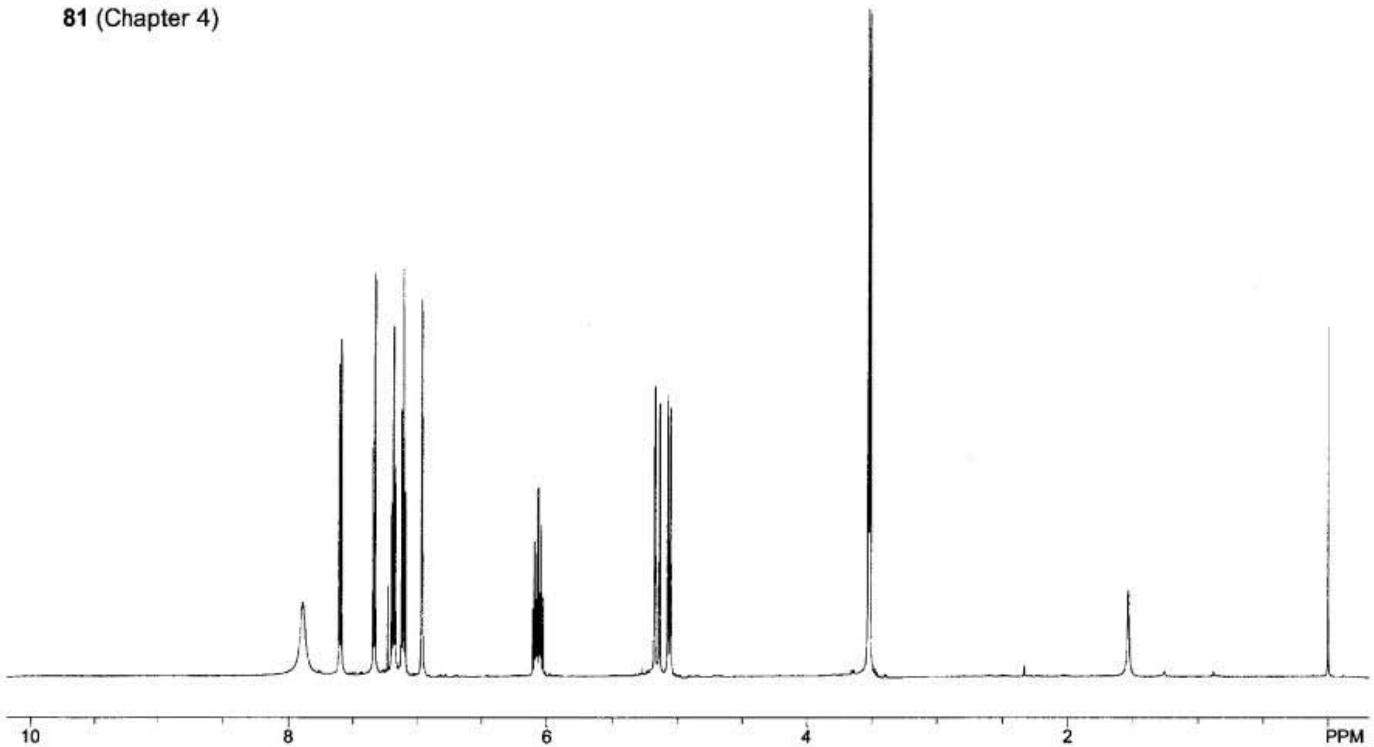

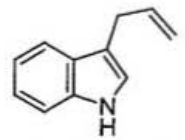

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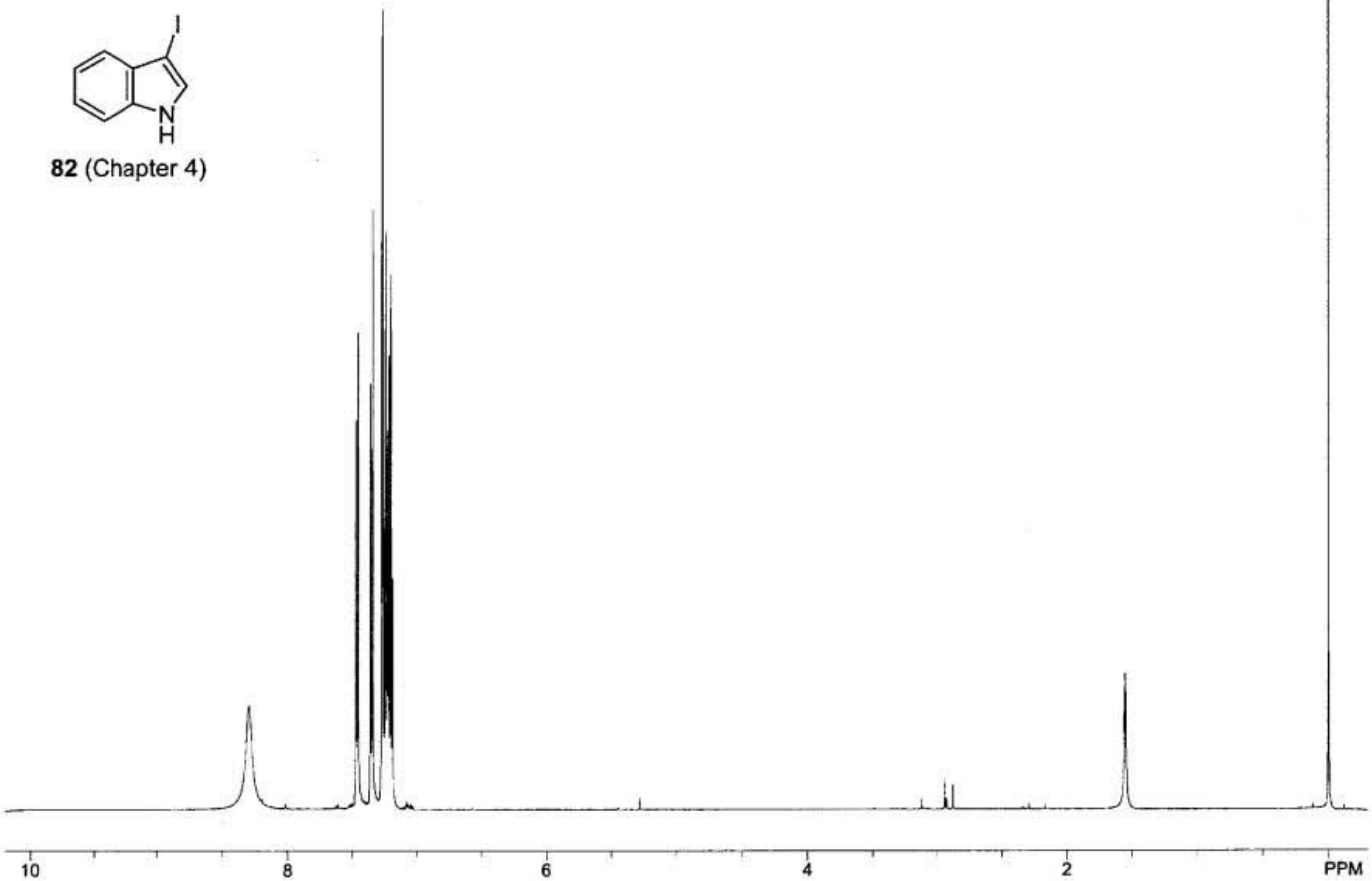

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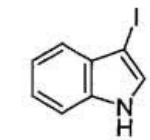

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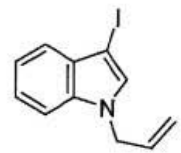

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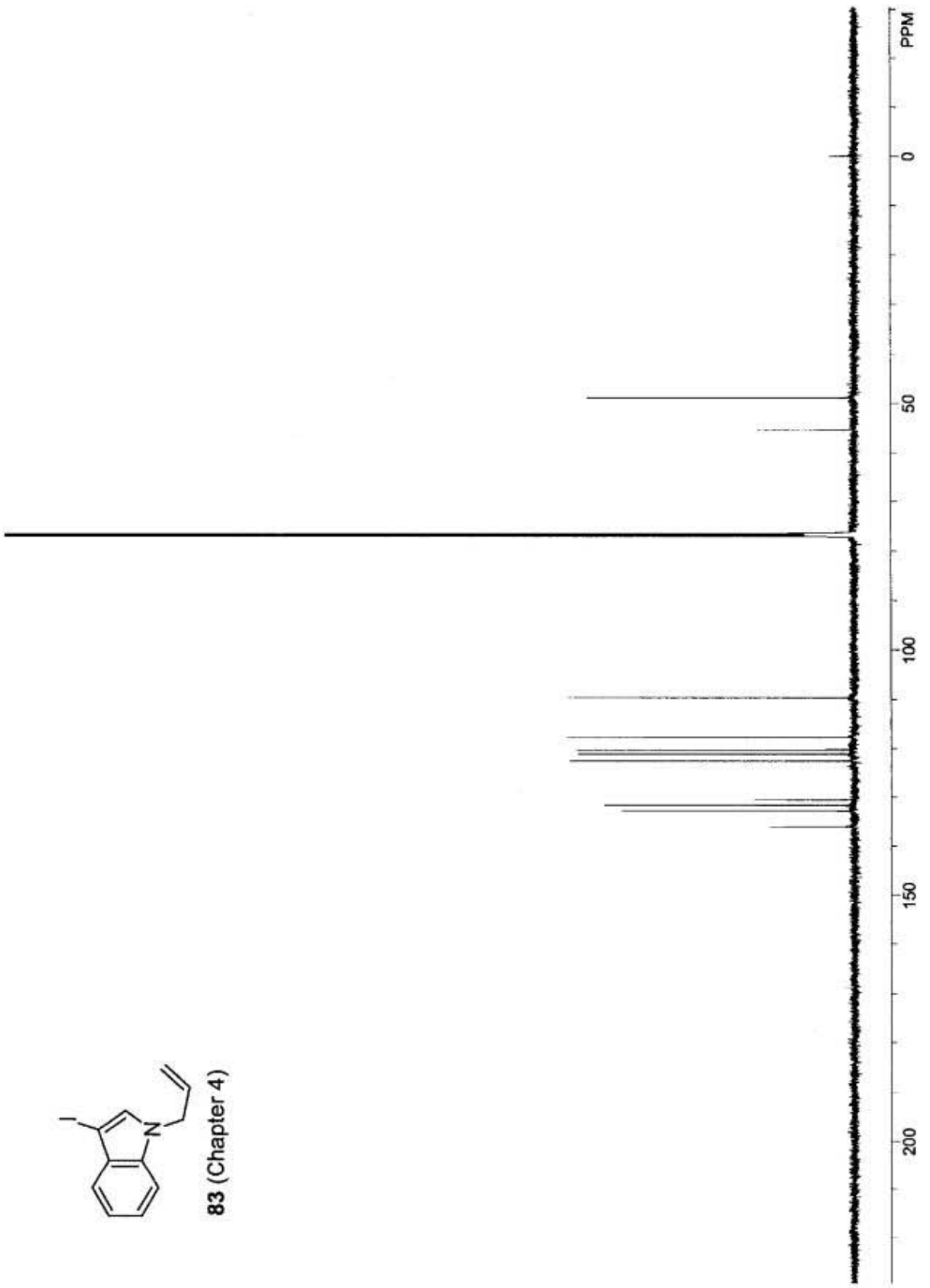

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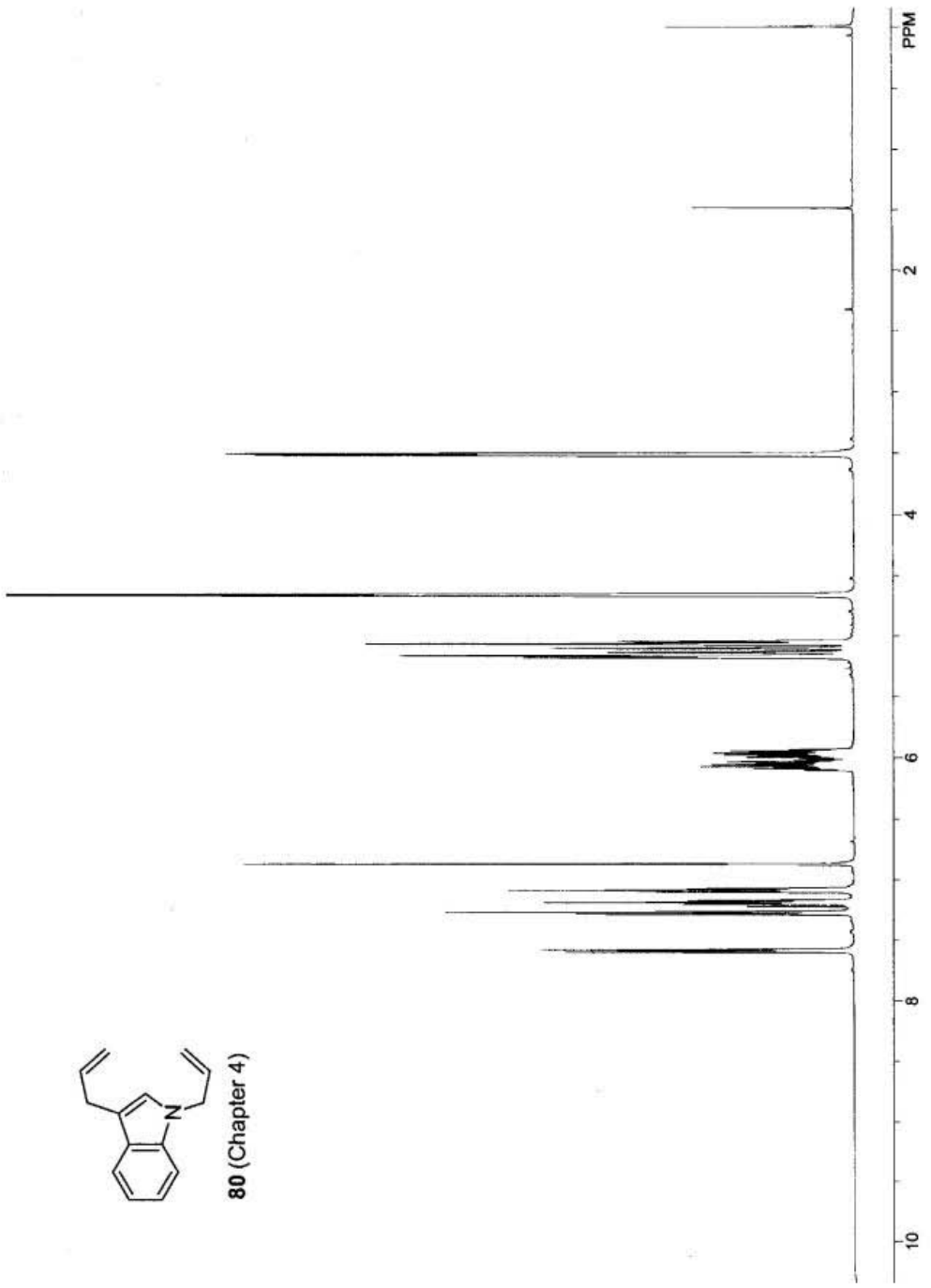

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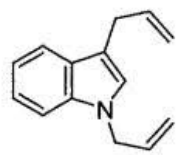

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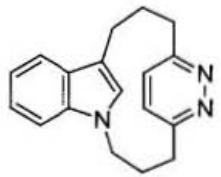

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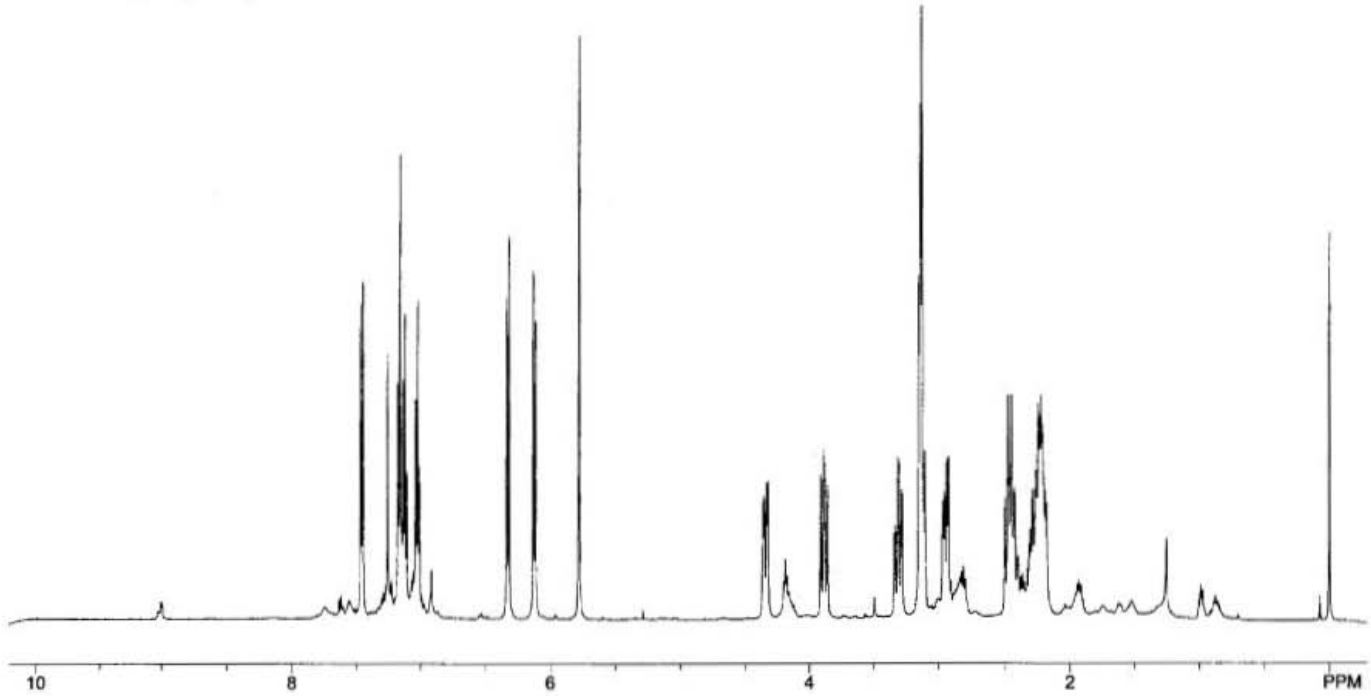

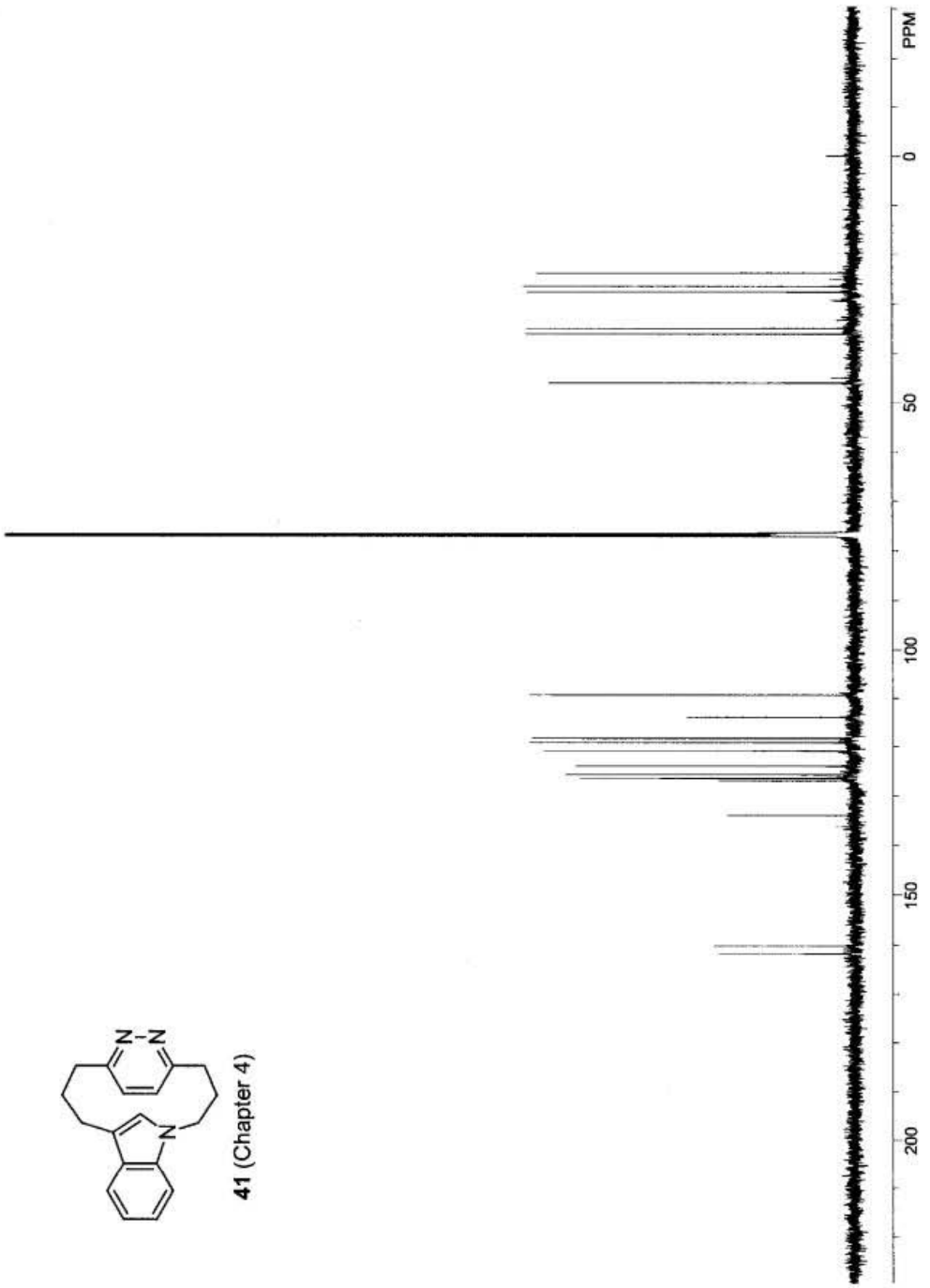

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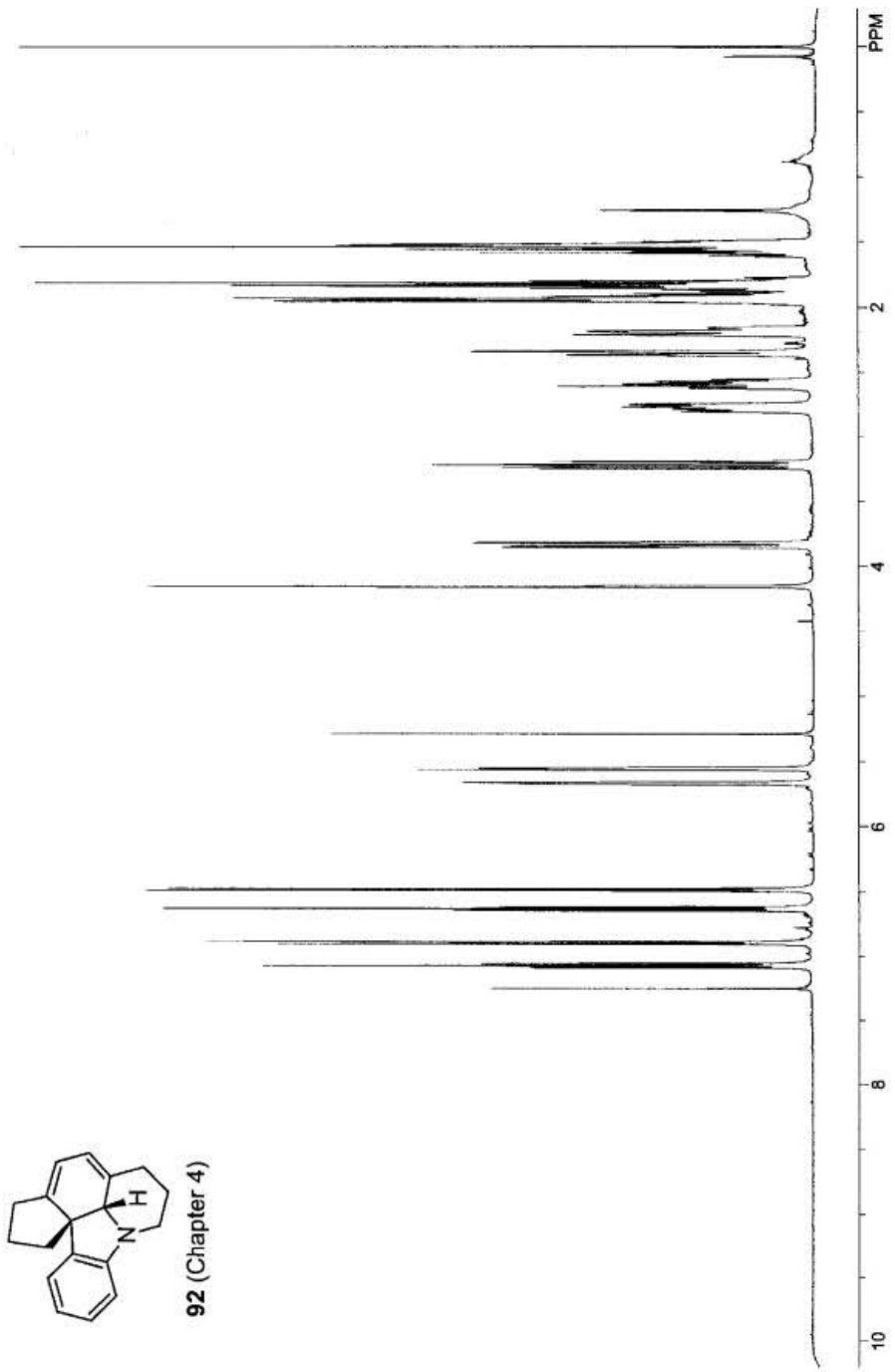

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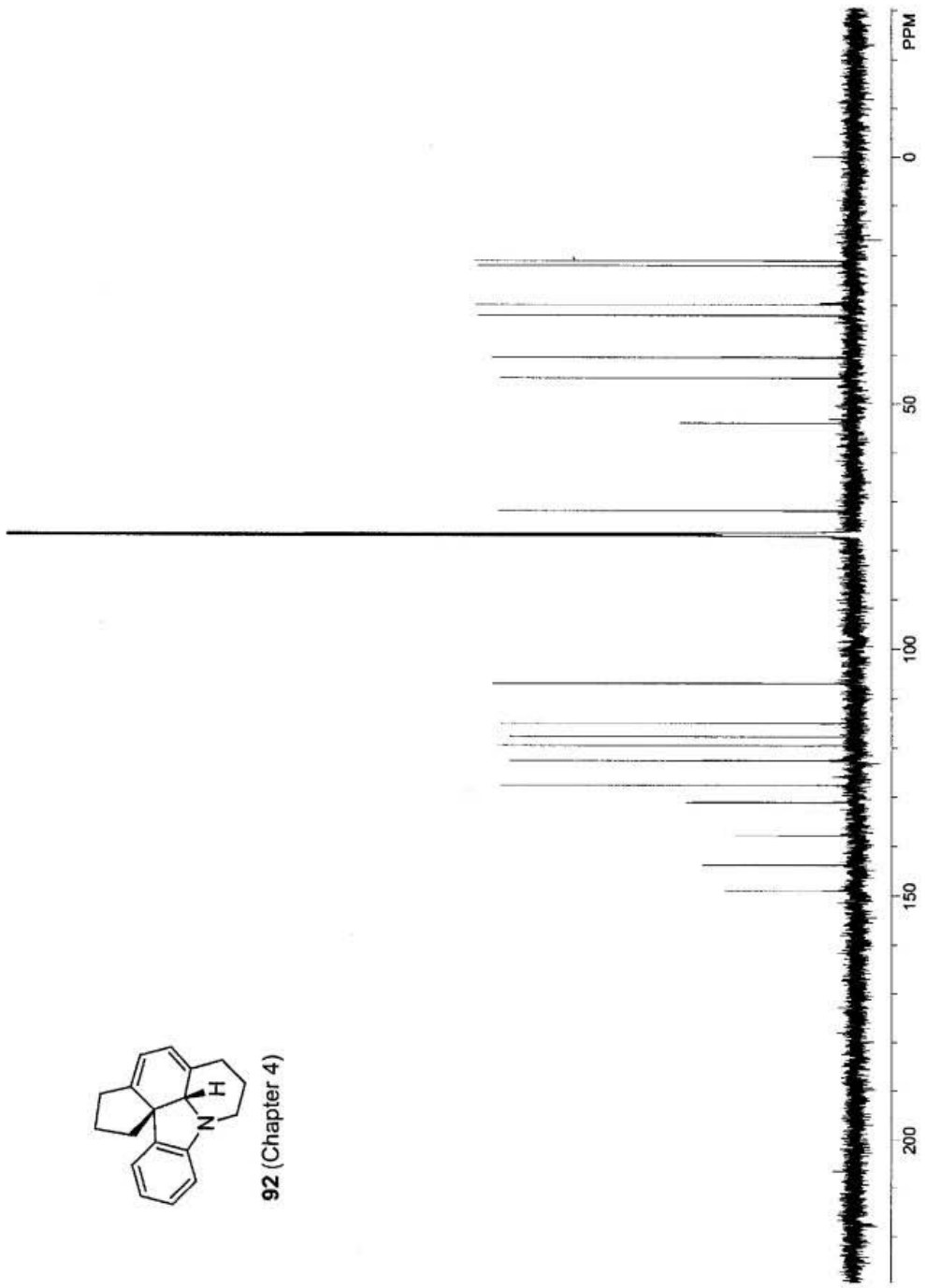

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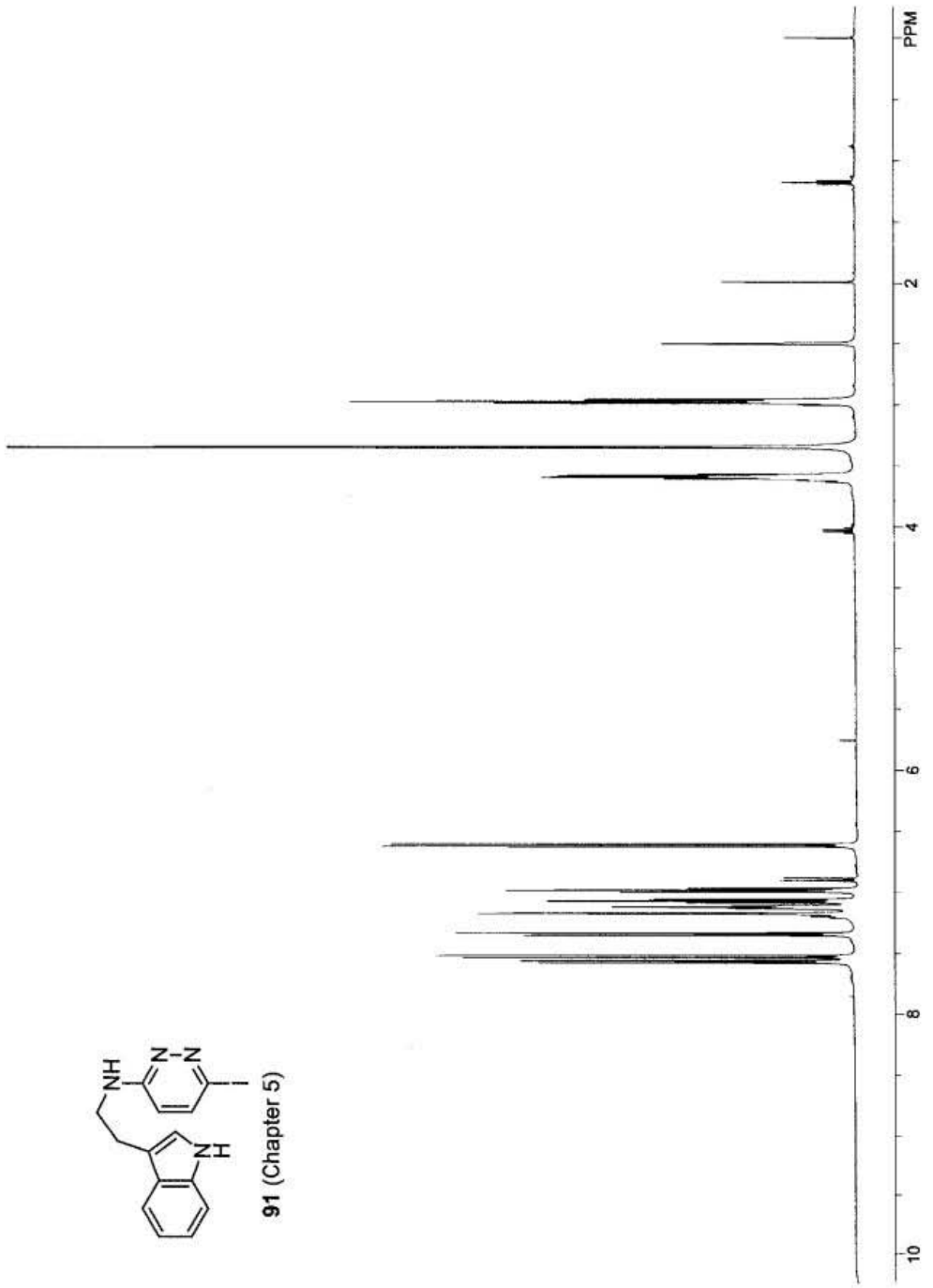

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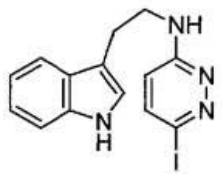

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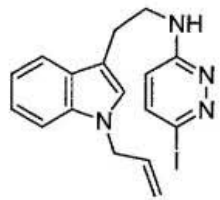

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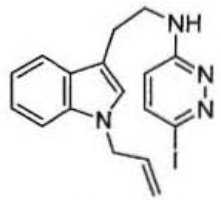

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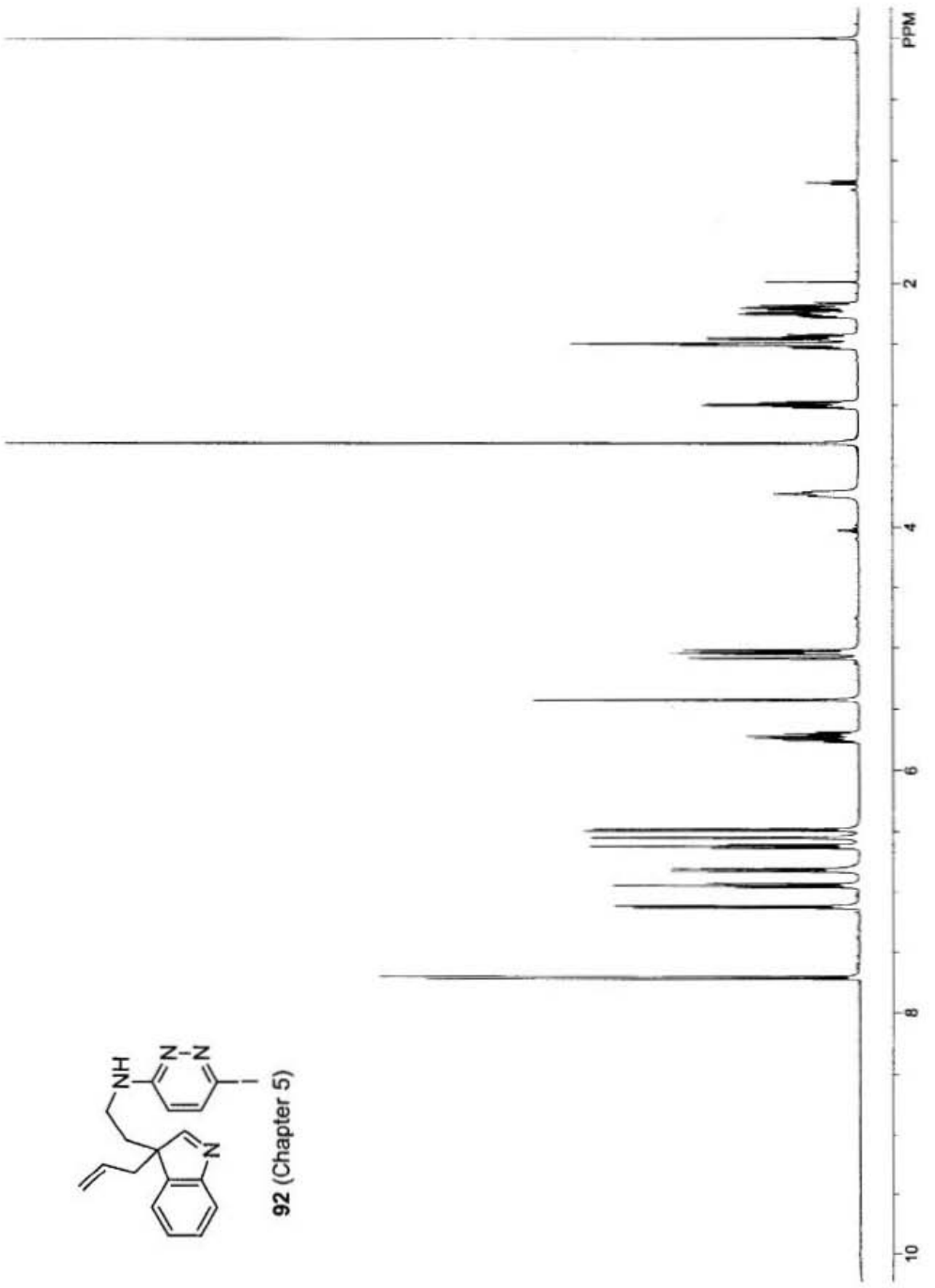

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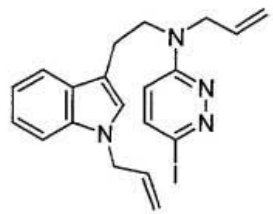

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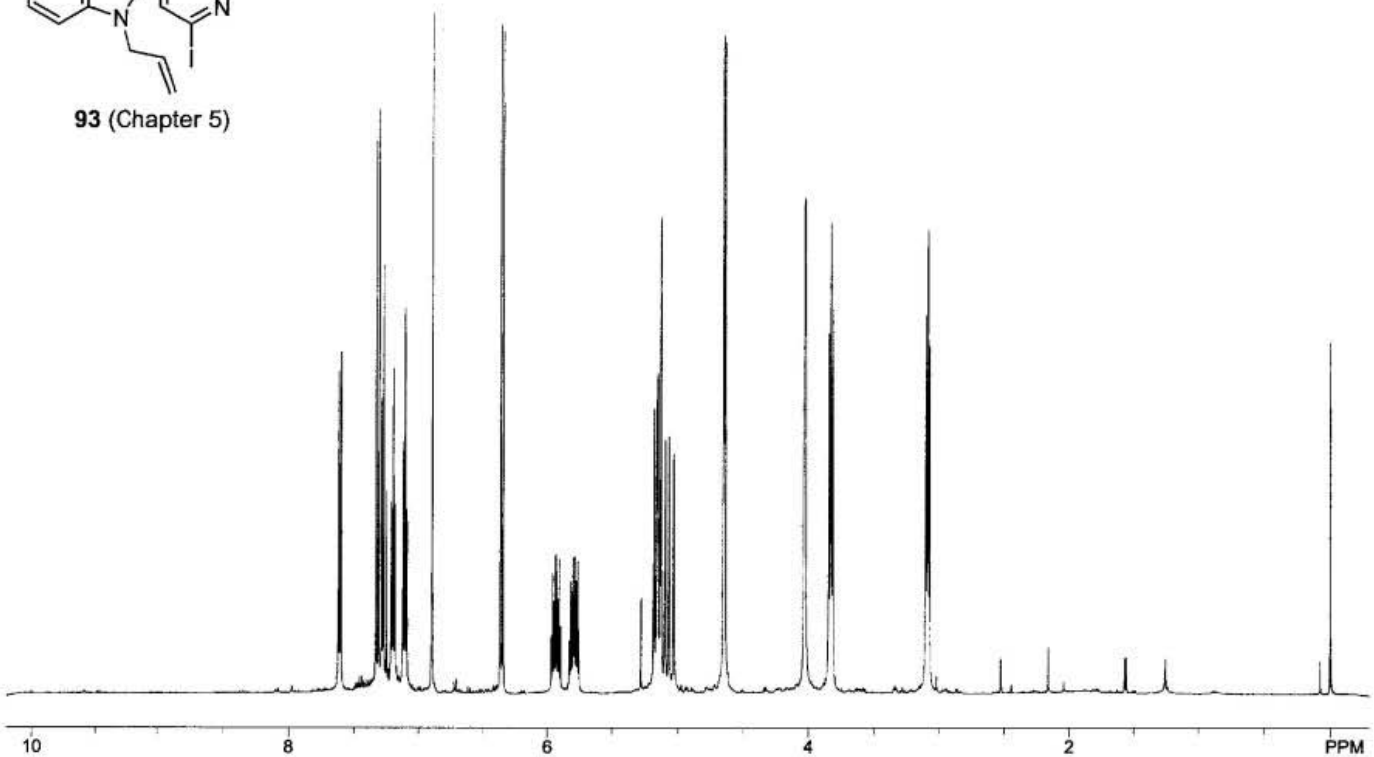

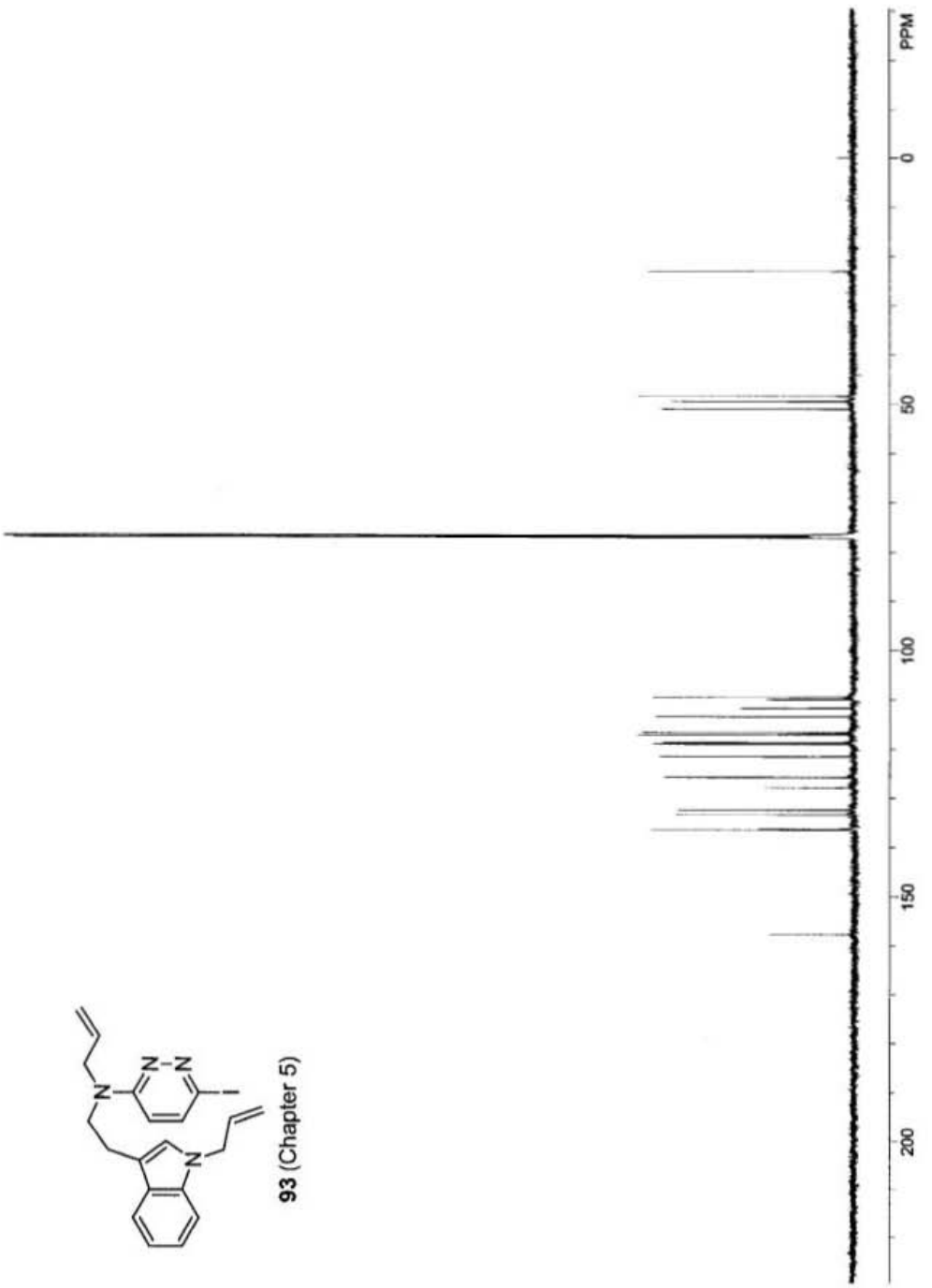

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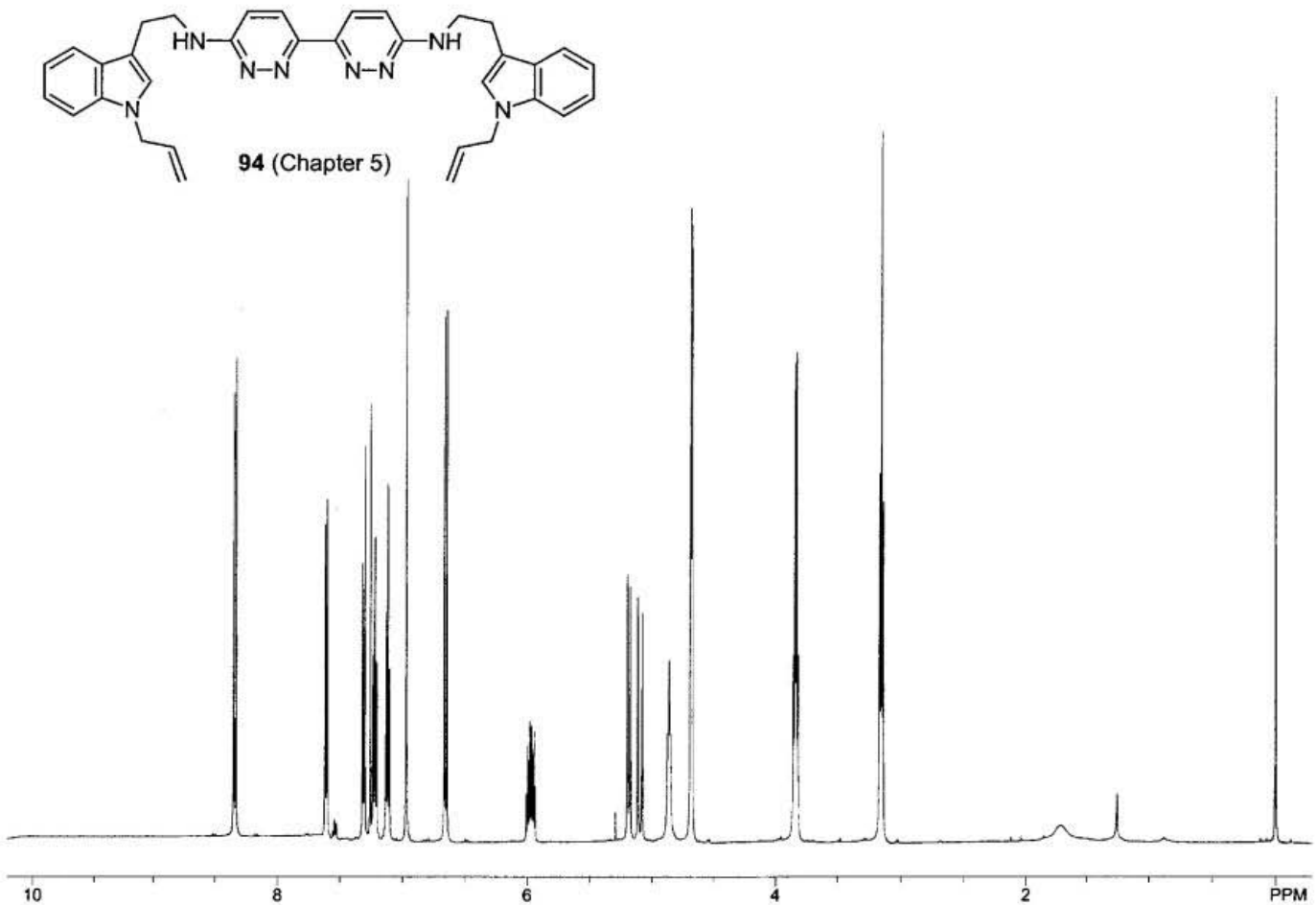

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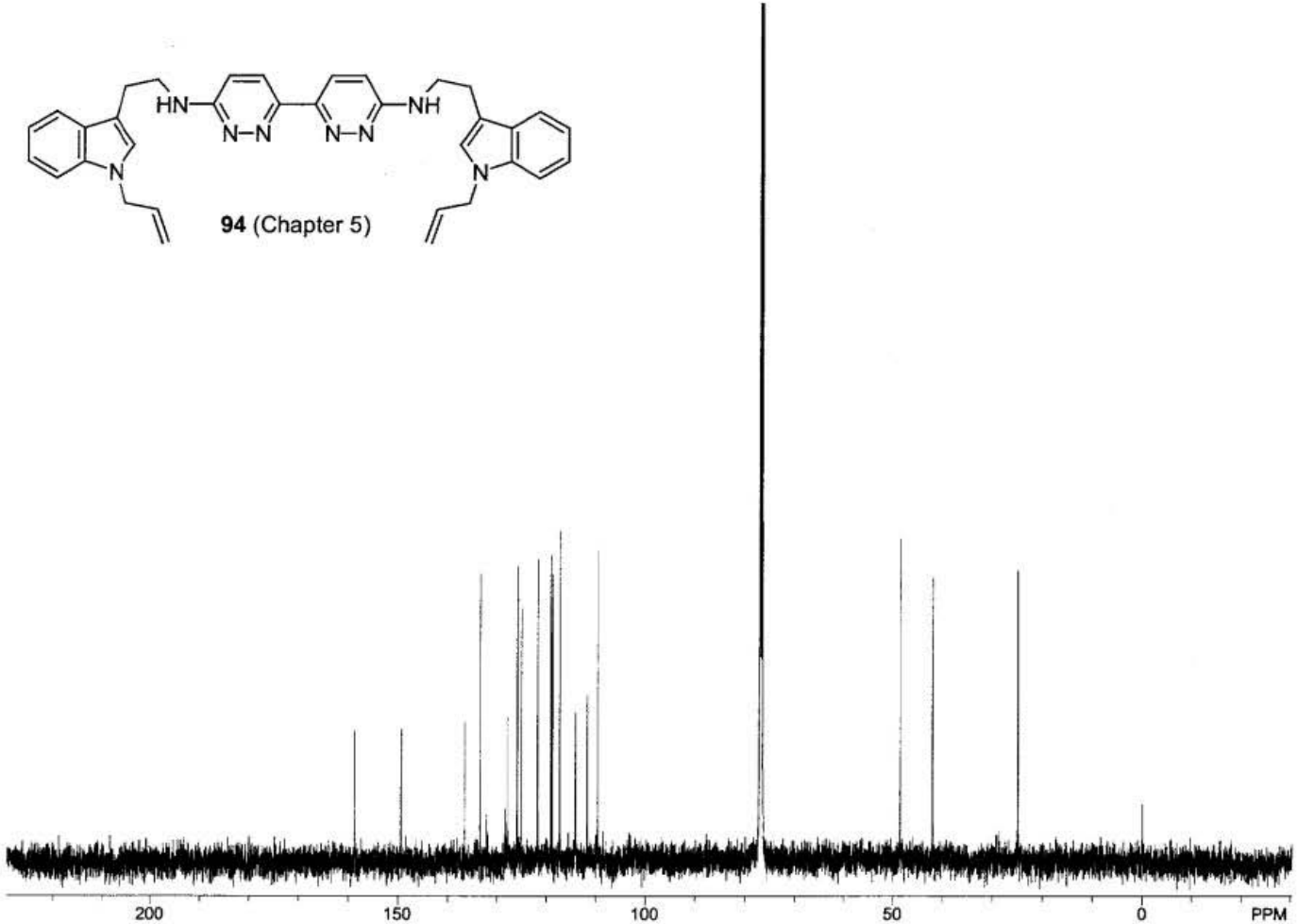

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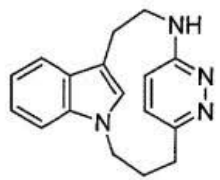

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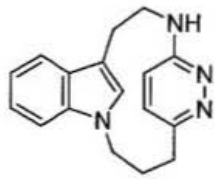

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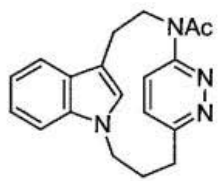

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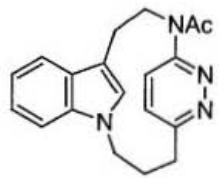

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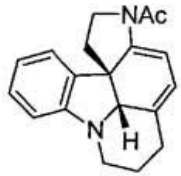

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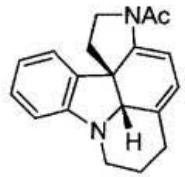

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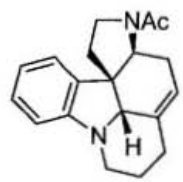

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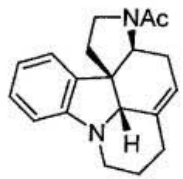

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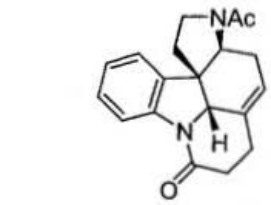

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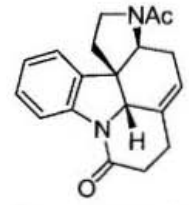

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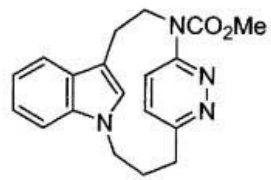
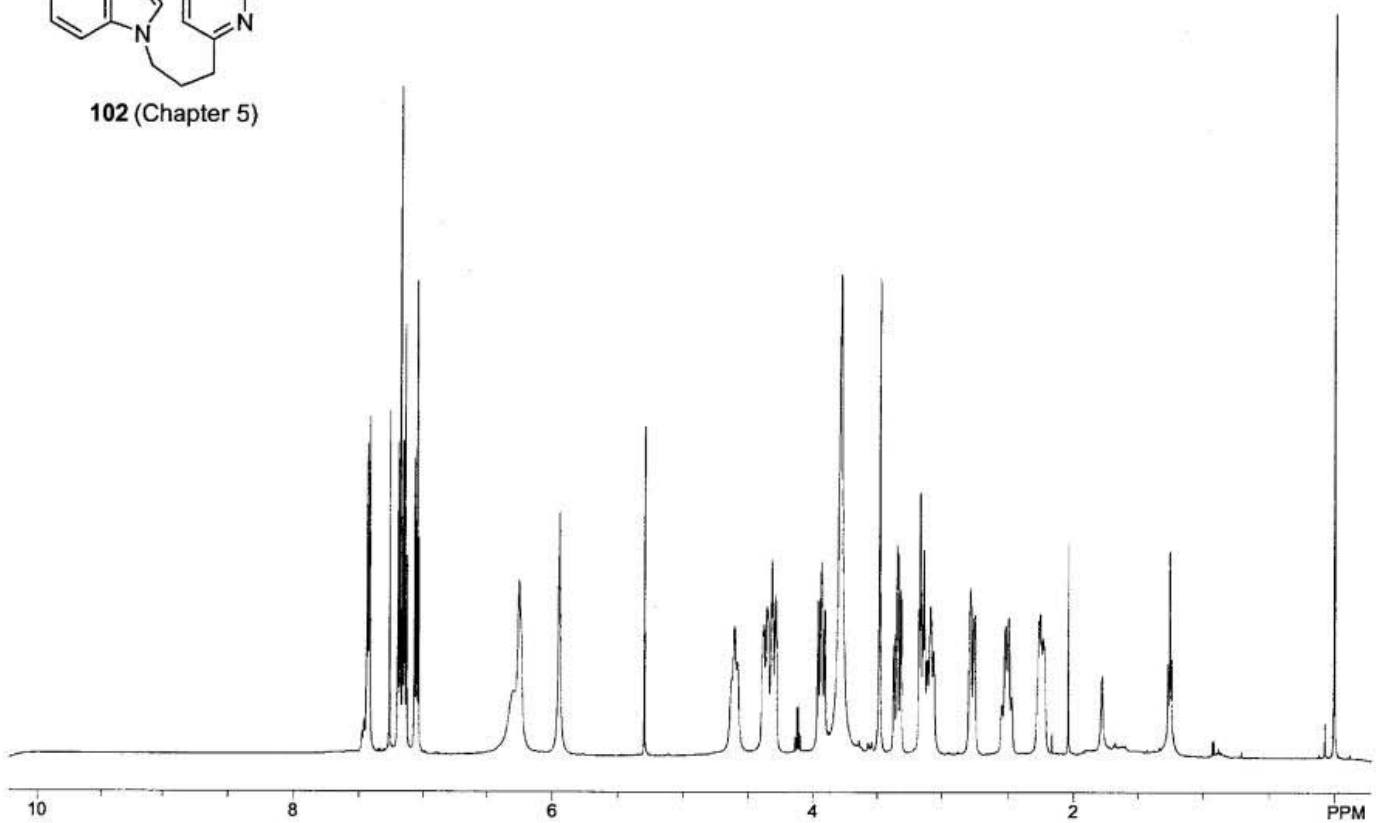
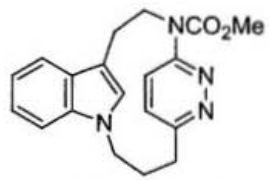


102 (Chapter 5)





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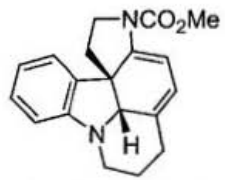

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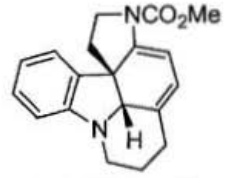

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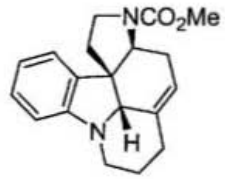

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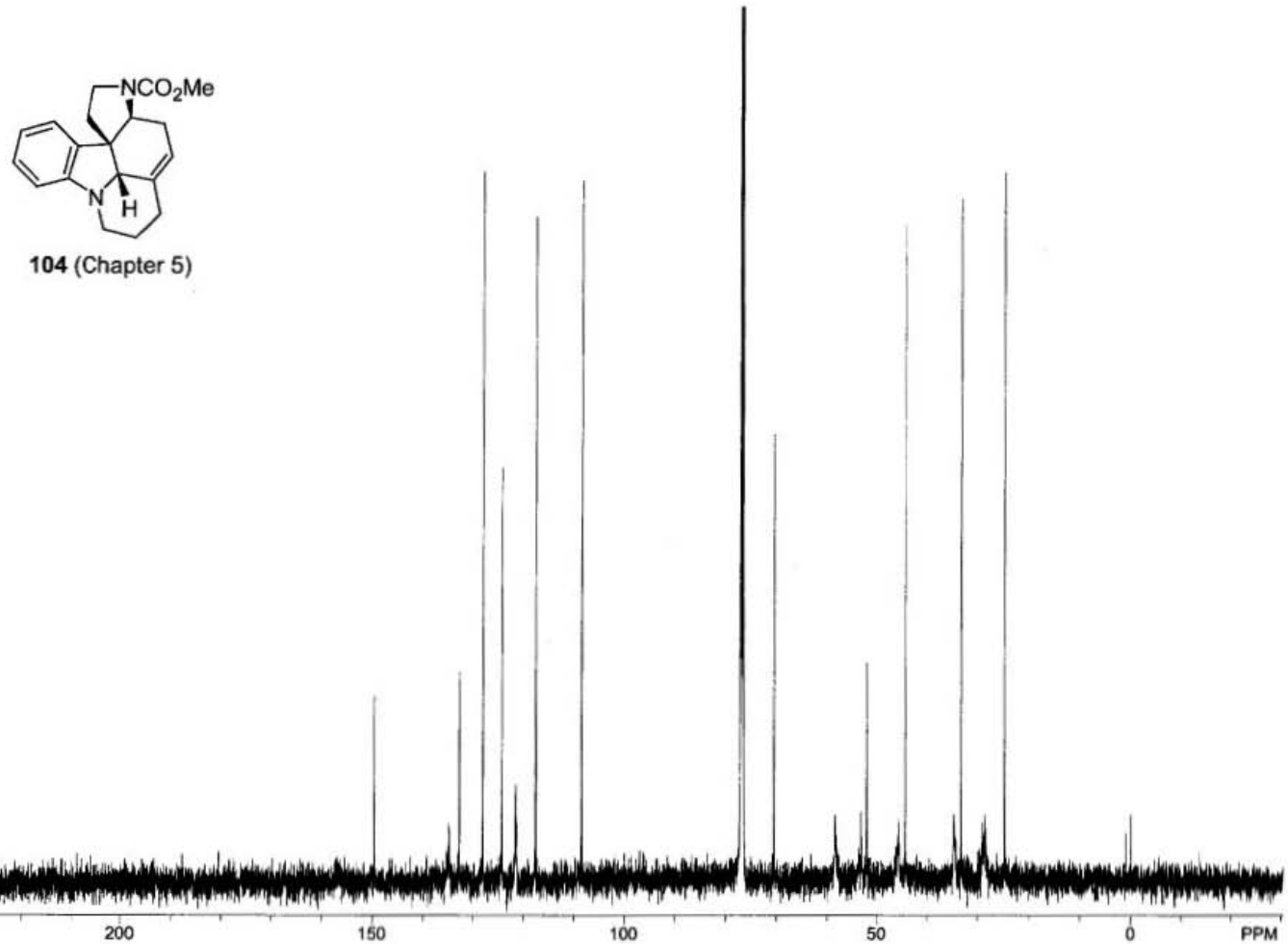

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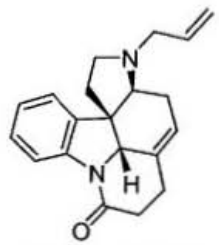

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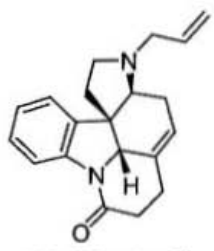

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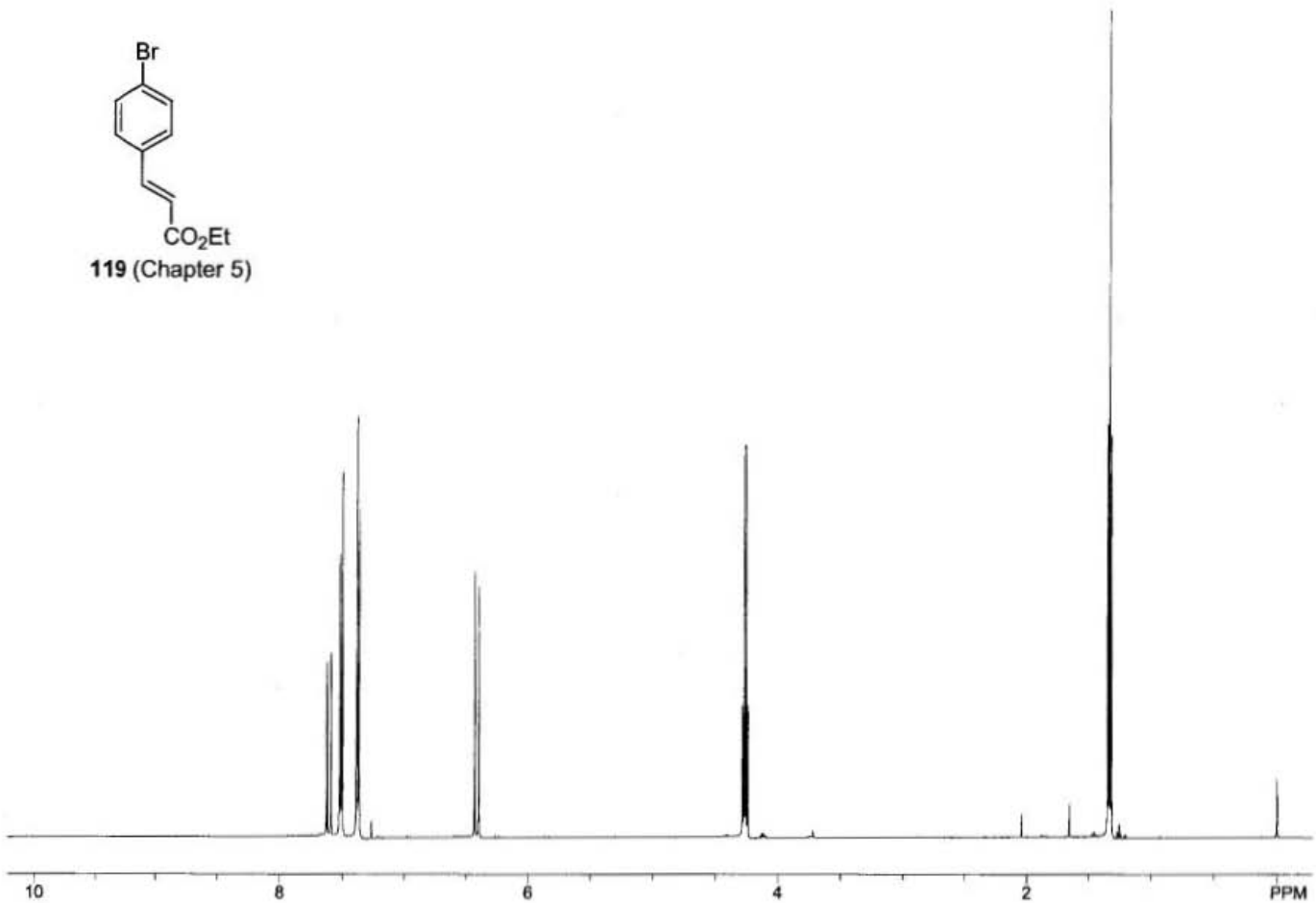

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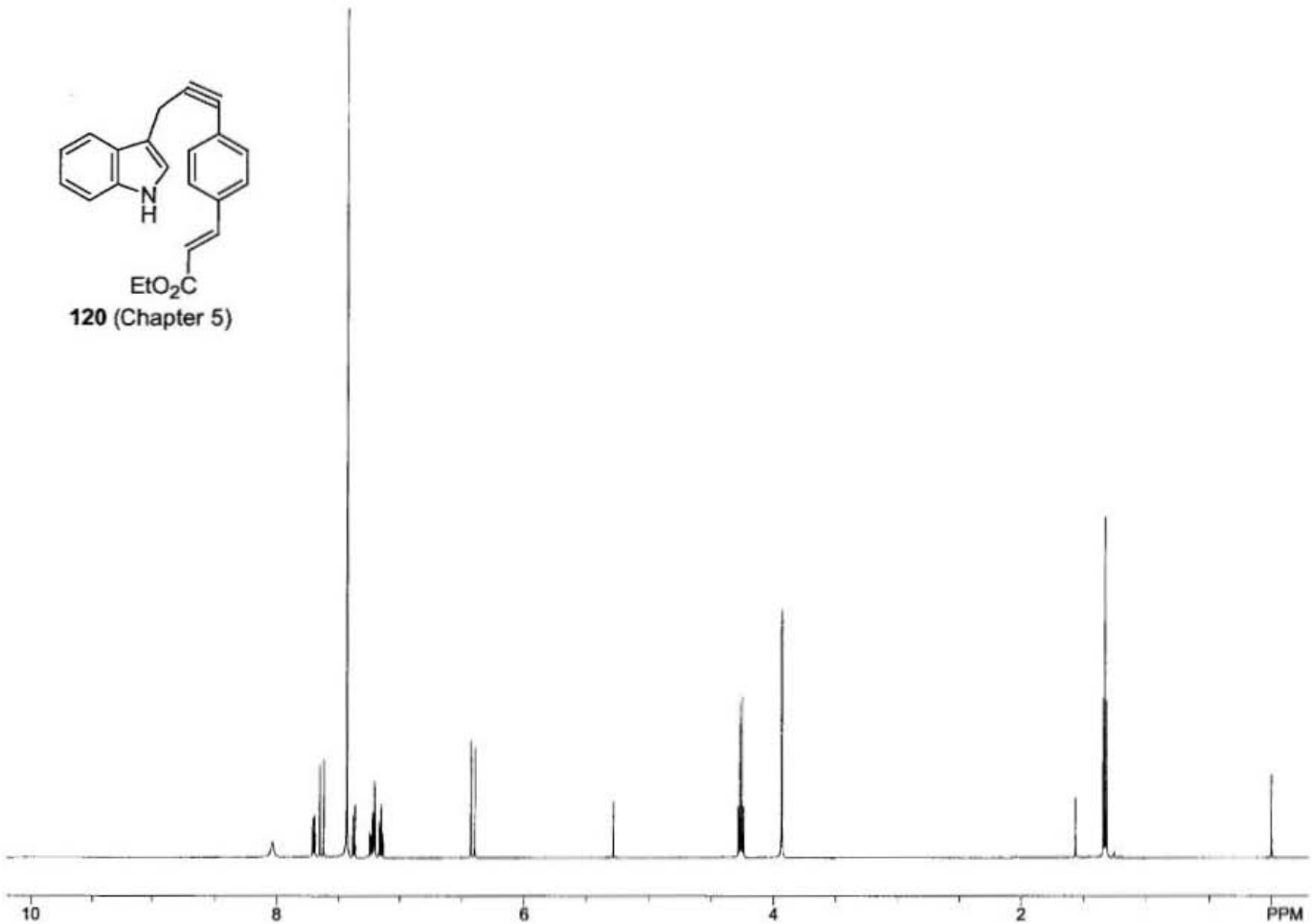

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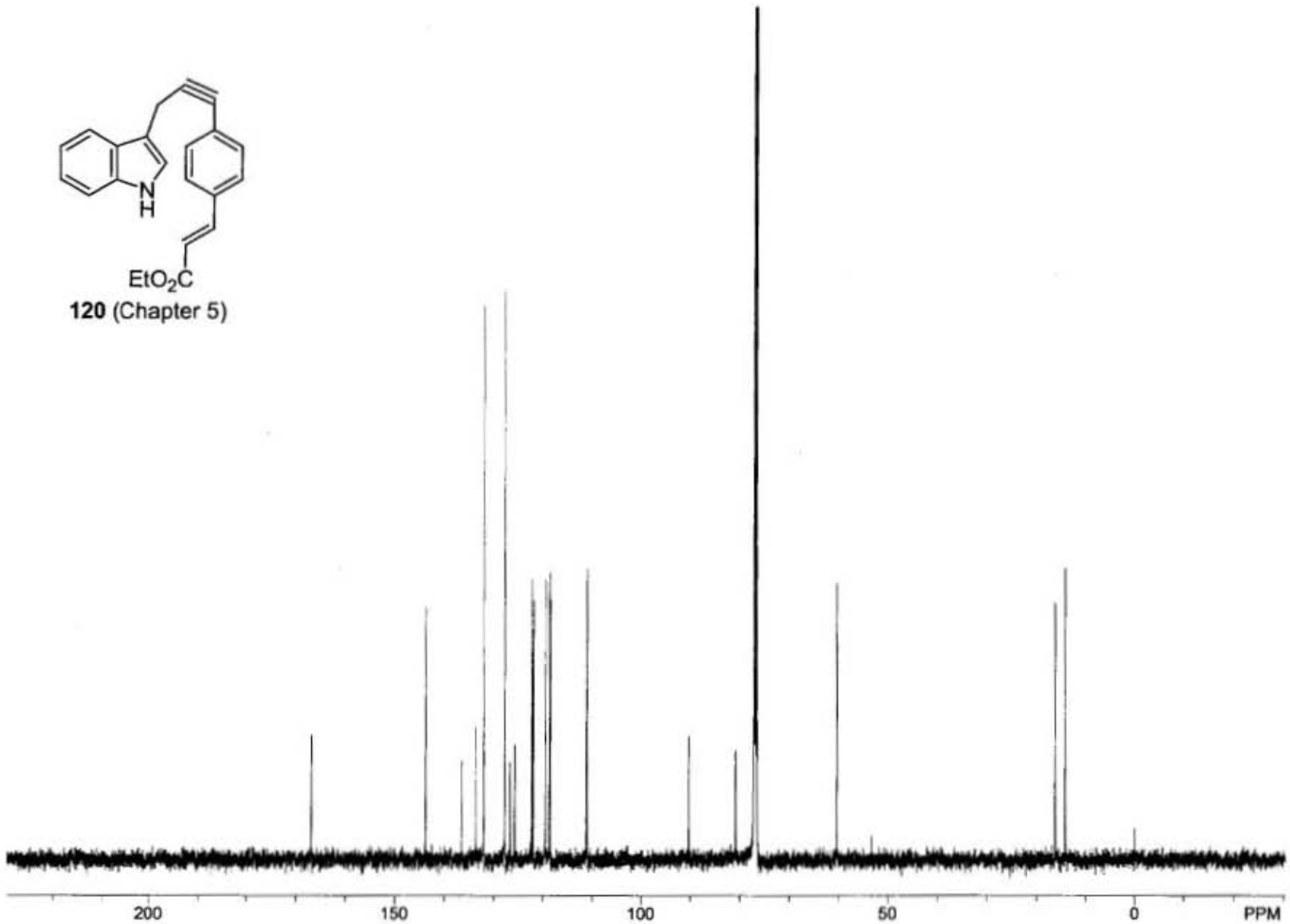

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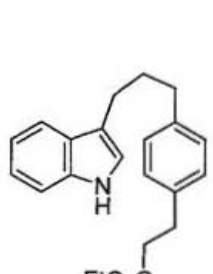

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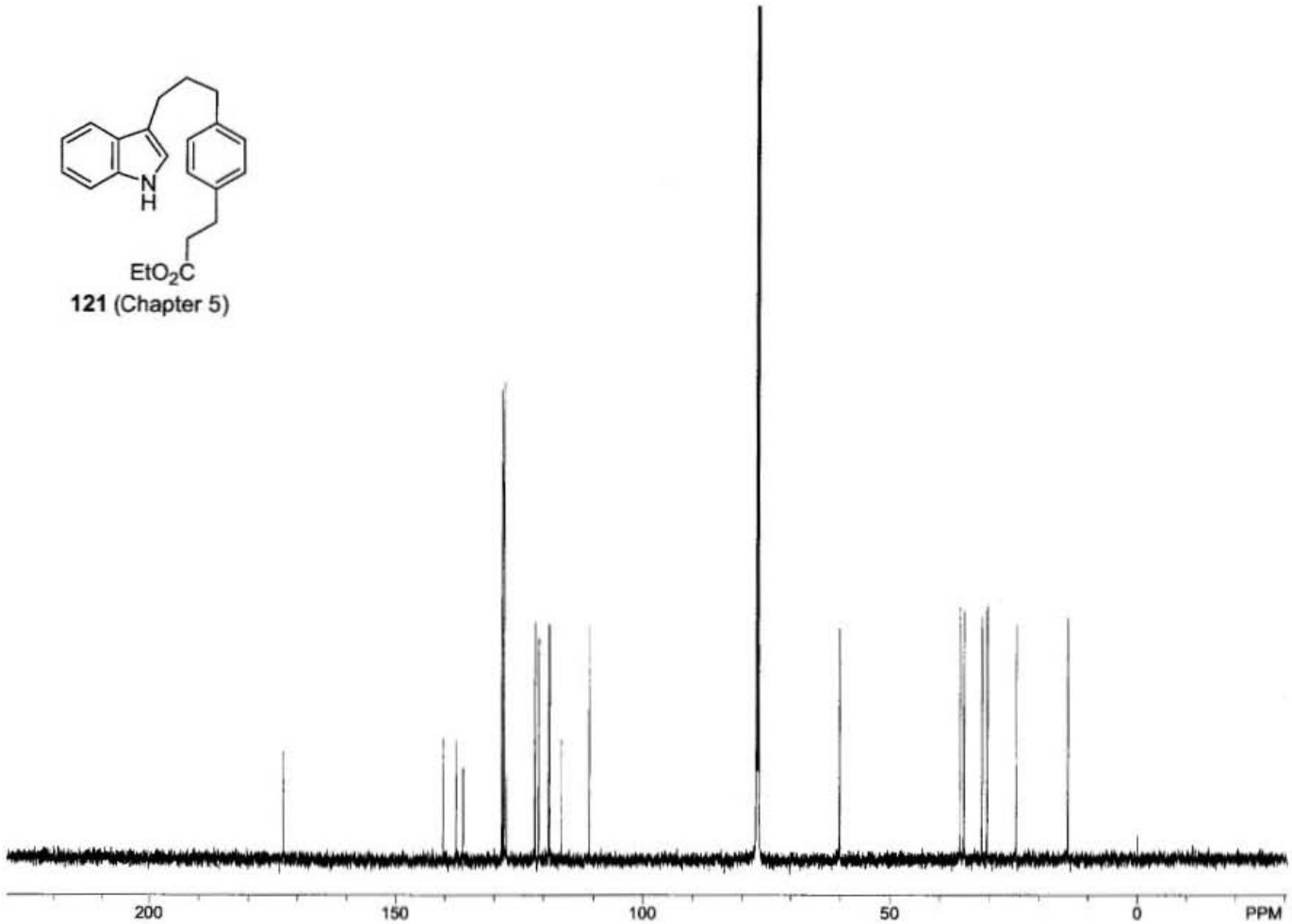

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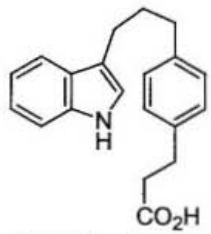

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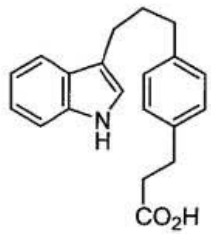

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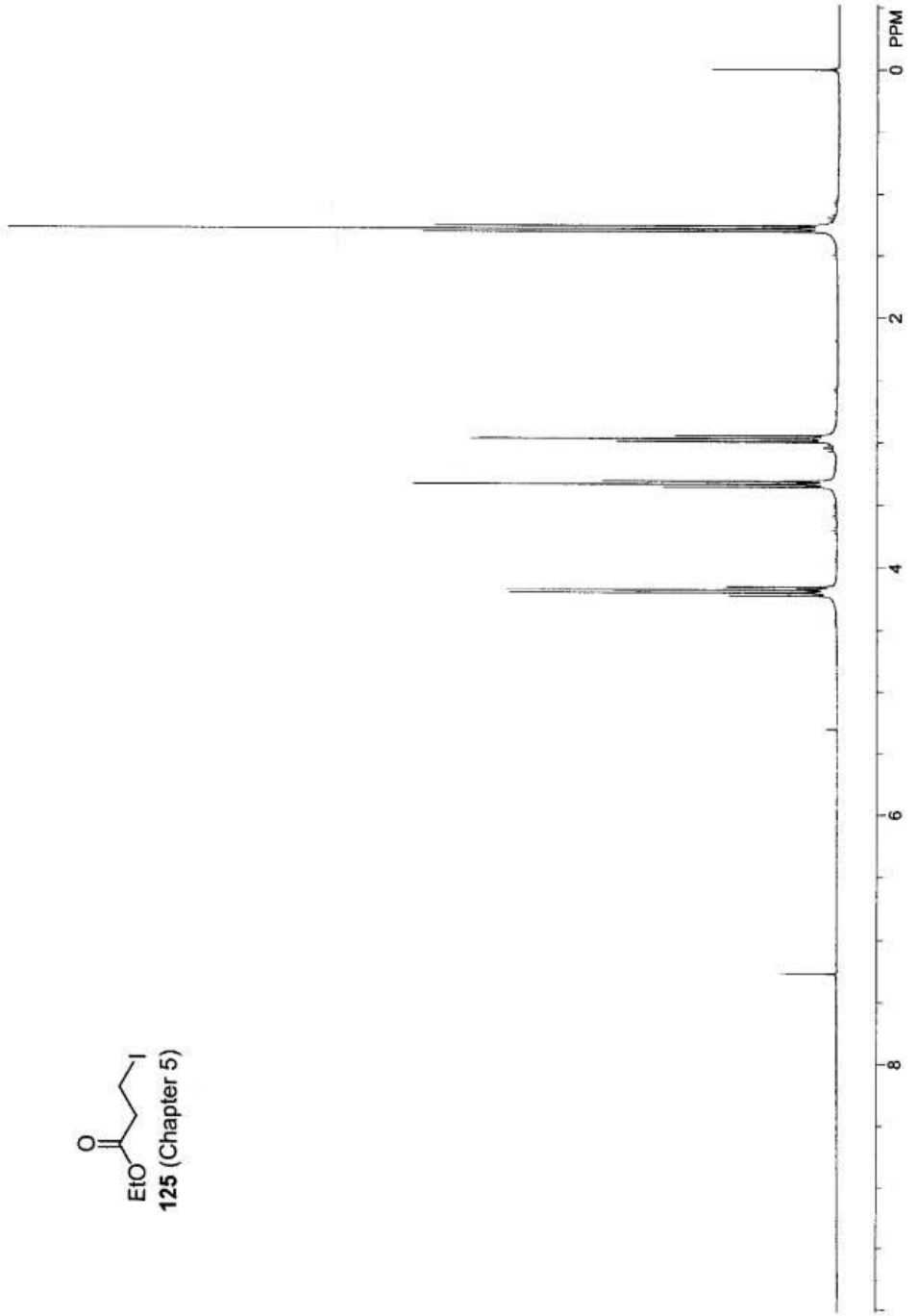
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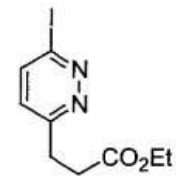

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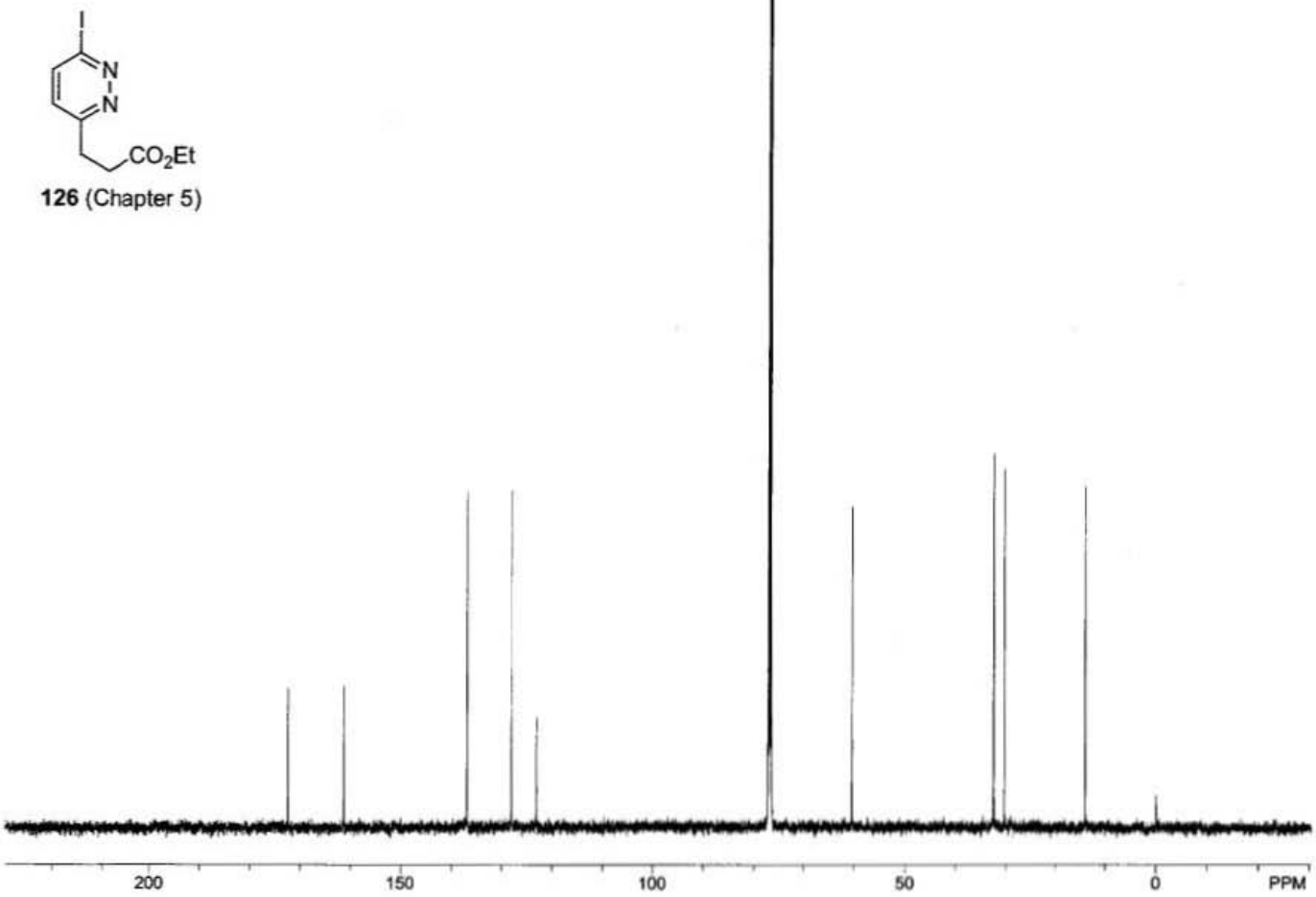

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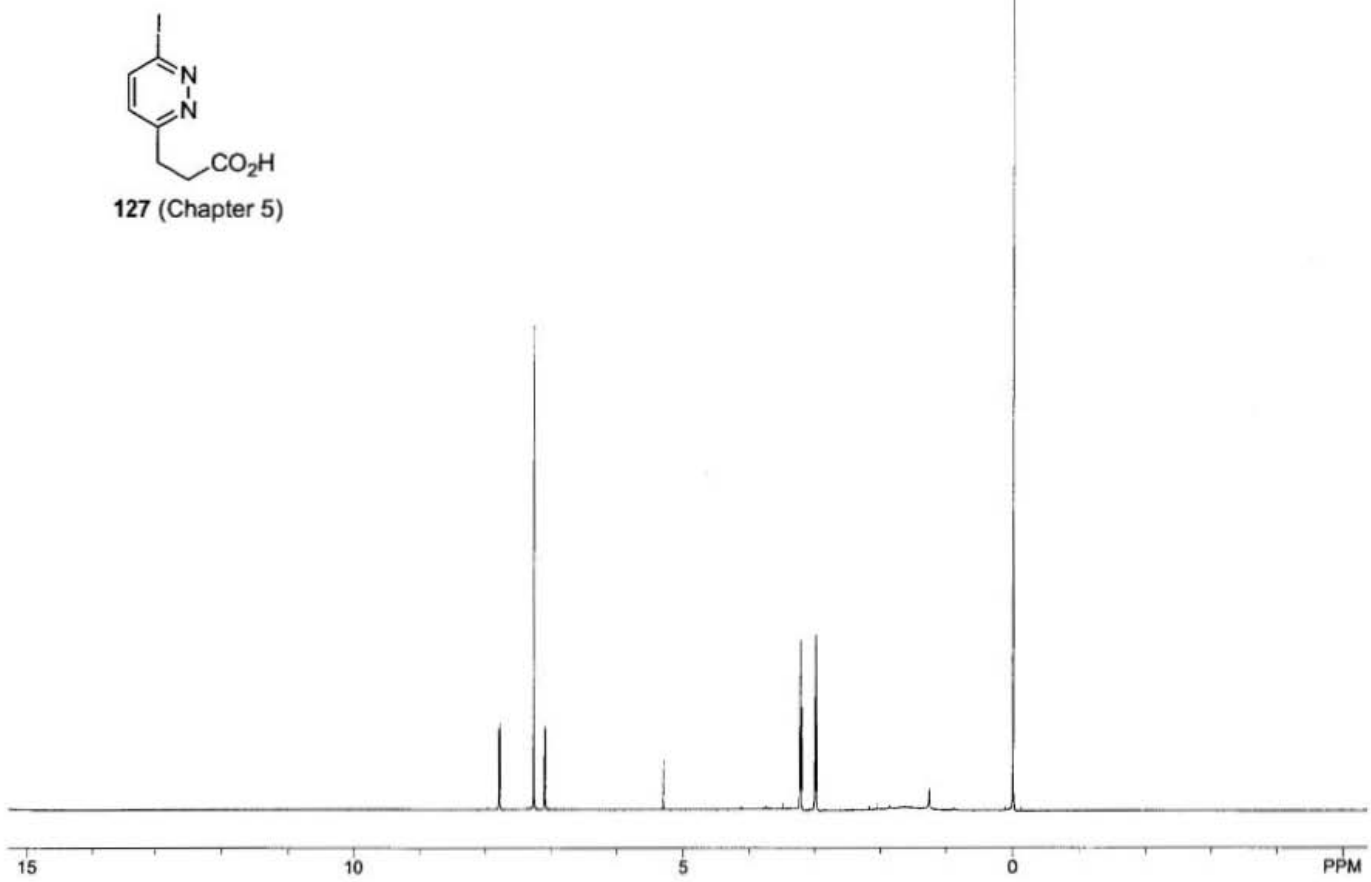

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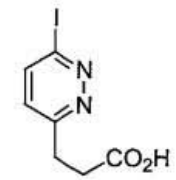

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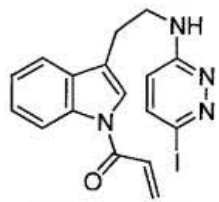

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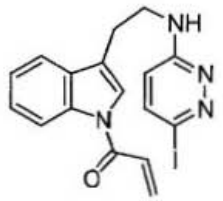

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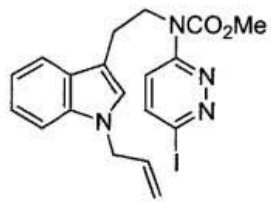

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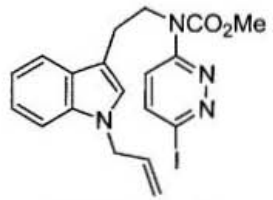

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