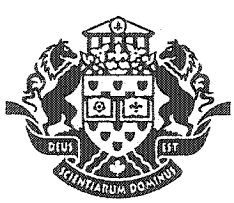

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QUEVILLION, Sophie

AUTEUR DE LA THÈSE - AUTHOR OF THESIS

M.Sc. (Chemistry)

GRADE - DEGREE

Chemistry

FACULTÉ, ÉCOLE, DÉPARTEMENT - FACULTY, SCHOOL, DEPARTMENT

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P. Arya

DIRECTEUR DE LA THÈSE - THESIS SUPERVISOR

EXAMINATEURS DE LA THÈSE - THESIS EXAMINERS

G. Buchanan

T. Durst

J.-M. De Koninck, Ph.D.

LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES

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TOWARD DIVERSITY-ORIENTED SYNTHESIS OF INDOLINE-BASED POLYCYCLIC DERIVATIVES

by

SOPHIE QUEVILLON

B.Sc. (Honours), University of Ottawa, 2001

Thesis Submitted to the
School of Graduate Studies and Research
University of Ottawa

In Partial Fulfillment of the Requirements for the
M.Sc. Degree in the
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Candidate	Supervisor
Sophie Quevillon	Professor Prabhat Arya

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AIBN	2,2'-azobisisobutyronitrile
Bn	benzyl
t-Bu	*tert*-butyl
cat.	catalyst
(cat)	catalytic amount
COSY	^{1}H-^{1}H NMR correlation spectroscopy
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
ddd	doublet doublet of doublets
dddd	doublet doublet doublet of doublets
ddt	doublet doublet of triplets
DIC	*N,N*-diisopropylcarbodiimide
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(*N,N*-dimethylamino)pyridine
DMF	*N,N*-dimethylforamide
eq.	equivalent(s)
g	gram(s)
H	hydrogen
HATU	*O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium hexafluophosphate
HBTU	*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyl-uronium hexafluophosphate
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
Hz	Hertz
IR	infrared
J	coupling constant

LDA	lithium diisopropylamide
m	multiplet
M	molar
N	normal
mg	milligram(s)
mL	milliliter(s)
mp	melting point
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
Ph	phenyl
PHAL	phthalazine
i-Pr	*iso*-propyl
q	quartet
RT	room temperature
s	singlet
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
μL	microlitre(s)

ABSTRACT

There is a growing interest in using diversity-oriented synthesis (DOS) to generate small molecule libraries that are inspired by bioactive natural products. Over the years they have proven to be quite valuable chemical probes for understanding protein functions. Of particular interest is the design of natural product-like chiral scaffolds in which one could explore the three dimensional space around the building block by having several chiral diversity sites.

A novel synthesis to reach an indoline scaffold is described. This template is then utilized to synthesize a seven-membered ring tricyclic derivative through an olefin ring-closing metathesis (RCM) approach. As well, asymmetric diversity-oriented reactions (e.g. asymmetric benzenethiol addition and intramolecular free radical cyclization) were explored with the tricyclic compound with the intention of utilizing these reactions on solid phase for generating a library.

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A mon mari, Christian Banville…

CHAPTER 1: INTRODUCTION

1.1 HUMAN GENOME

The recent completion of the Human-Genome Project[1] has opened the way for further explorations toward providing a better understanding of cellular processes at the molecular level.[2] The assumption is that at least 1000 human genes (there are more than 30,000) are significantly involved in the emergence and course of a disease.[3] As expected, the sequencing of the human genome as well as a large amount of pathogen genomes has resulted in a sudden increase of potential drug targets.[4]

The scientific community is now facing one of the biggest challenges presented to it: the need to determine the functions of these newly discovered genes. To address this challenge, researchers have access to two complementary approaches, these are genetics and chemical genetics.[5]

1.2 GENETIC APPROACH

The genetic approach, also named classical genetics, is the most common, yet indirect, way of determining the cellular functions of a protein. It involves the use of introducing mutations in the genes encoding proteins of interest with the hope that these mutations result in inactivation or activation of a given gene. By inactivating, one can think of deleting, 'knocking-out', or even impairing protein functions at the genetic level, whereas activating is related to gene expression, often oncogenic.[6] In other words, biological systems are explored using genetic methods in which mutations in genes are introduced and the resulting biological effects are examined.[7]

These genetic methods are traditionally performed by two different manners: reverse genetics and forward genetics.[8] Reverse genetics is extensively used in creating models of human disease in other organisms (for example in mice). It requires specific points such as the selection of a gene and the creation of either an organism or a cell with a mutated version of the gene.

Also, a broad search for phenotypic differences between the wild-type and the mutant is essential to identify a biological function for a gene of interest.

In the case of forward genetics, random mutagenesis is performed followed by screening for a desired phenotype. Finally, mapping of the selected mutations provides the identification of the gene. Together, reverse and forward genetics can be considered as a powerful set of tools for dissecting and understanding biological systems. Unfortunately, these methods present some limitations. It can be very difficult and time consuming, for example, to perform forward genetic analyses on mammalian systems due to their large size of genomes. As well, genetic mutations are constitutive, meaning that they cannot easily be turned on and off.

This is where the chemical genetic approach, complementary to the genetic approach, comes into play (*Figure 1*).[9] In this method, small molecules are used to activate or inactivate proteins by direct interactions. By combining chemistry and genetics, several researchers have managed to create specific and reversible 'switches' to investigate the role of genes that have defied functional analysis until today.[10]

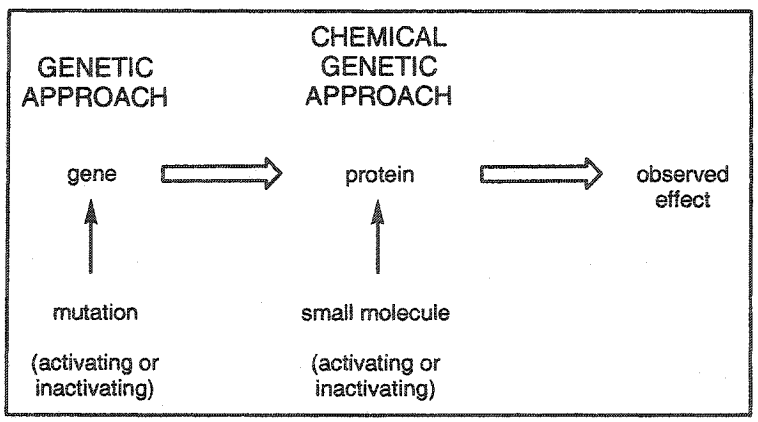


Figure 1. Relationship between genetic and chemical genetic approaches.

1.3 Chemical Genetic Approach

It needs to be appreciated that chemistry has an increasing number of valuable contributions to make in other fields, particularly in the elucidation of biological mechanisms and in target validation.[11] Actually, in recent years, a new field that joins cell biology and synthetic organic chemistry has come forward.[5] This emergence promises to stimulate the discovery of small organic compounds as tools to investigate biochemical pathways.

There is a real potential for using chemical genetics in the study of protein functions now that the entire human genome has been sequenced. The idea of using small molecules to dissect biochemical pathways is not new. Historically, natural compounds were used to activate or inactivate gene functions by direct interaction with the genetic product. In the past decade, the synthesis of numerous natural products and their analogues was performed to explore the functions of cellular proteins.[5] For example, FK506 (**1**), cyclosporin (**2**), and rapamycin (**3**) were used to study signal transduction [*Figure 2(a)*]. Trapoxin (**4**), trichostatin (**5**), and depudecin (**6**) were synthesized to study gene regulation [*Figure 2(b)*]. Finally, discodermolide (**7**) and lactacystin (**8**) were used to learn about cell cycle and cell-cycle checkpoints [*Figure 2(c)*].

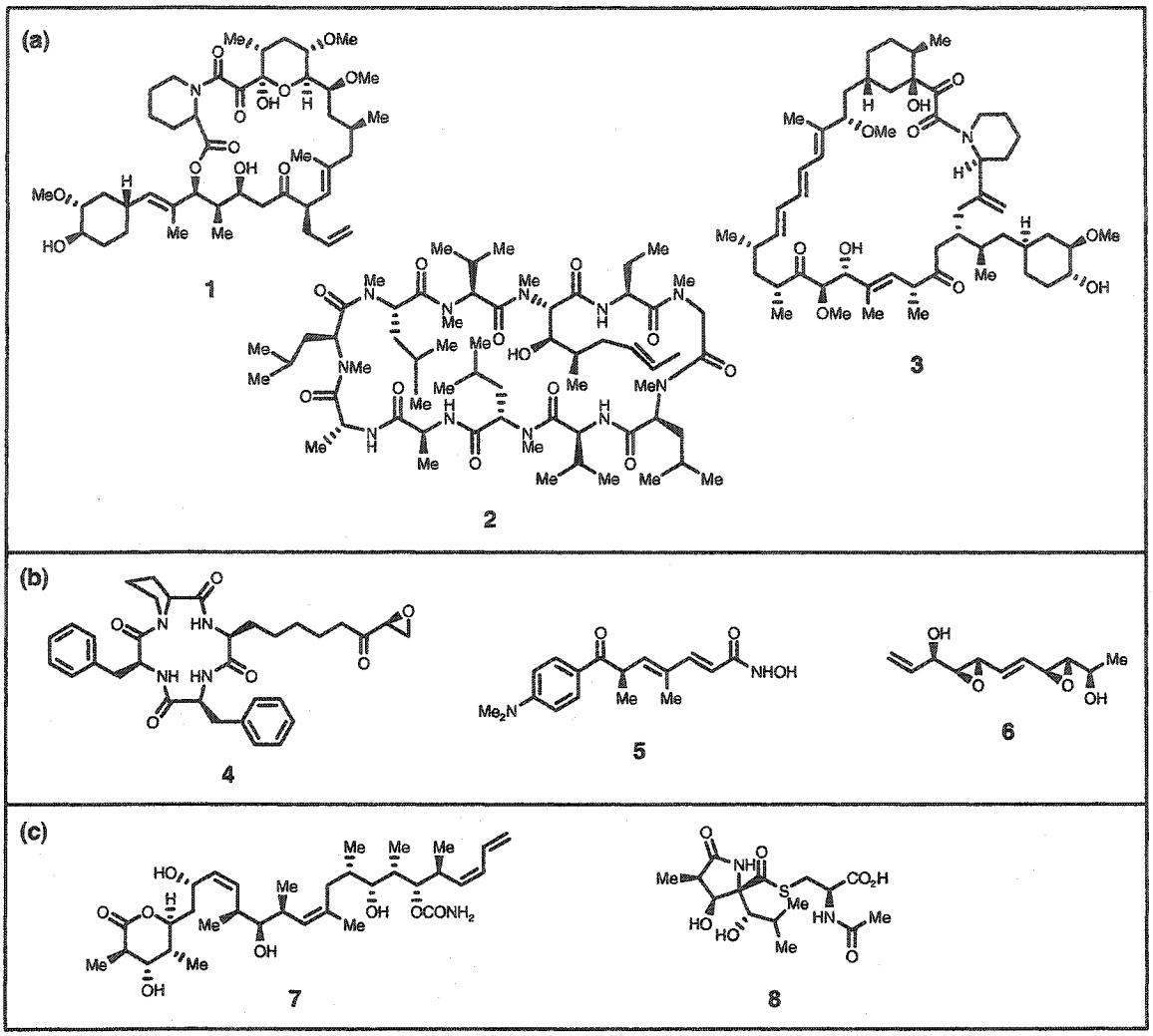


Figure 2. Chemical structures of natural products that have been used to gain new insights in **(a)** signal transduction, **(b)** gene regulation and **(c)** cell cycle and cell-cycle checkpoints.

Synthetic organic chemistry can now be considered as a very powerful genetics-like tool. However, the development of biologically active small molecules as molecular probes needs to be controlled, as compounds with high affinity and specificity are needed. The molecules that have been synthesized for chemical genetics are structural motifs (also named scaffolds) capable of binding to a variety of protein targets with high affinity. These rigid structures, often polycyclic and heteroatomic systems, are capable of orienting substituents in three-dimensional space. Moreover, these compounds need to be cell-

permeable so they can be used as molecular probes to perturb intracellular processes with exquisite precision.[12]

The chemical genetic approach, which uses small molecules to directly alter the functions of proteins to which they bind, has the potential to overcome the limitations of classic genetic analyses in mammalian systems. Two types of chemical genetic approaches are used by scientists for discovery: reverse chemical genetics and forward chemical genetics (*Figure 3*).[6,7,9b]

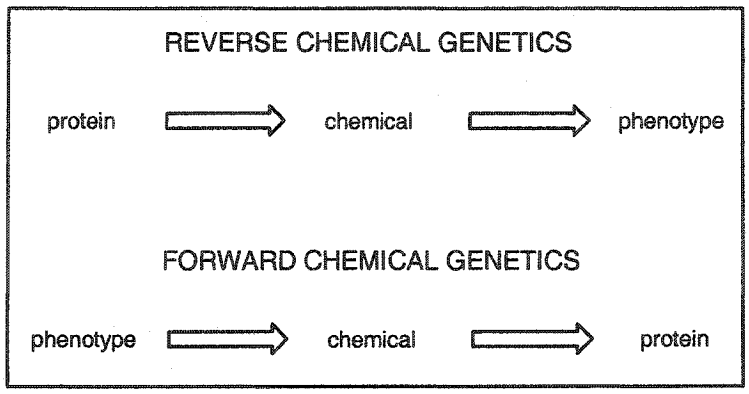


Figure 3. Two major chemical genetic approaches.

Both of these methods have very precise goals. For the reverse genetic approach, the goal is to determine the biological function of a protein by using a small molecule to inhibit its activity *in vivo*. Usually, the small molecule is known to have specific interaction with the protein target. Reverse chemical genetic assays are then mainly designed to explore protein functions. This can be achieved in three steps: first, a protein target is chosen, second, a chemical library is screened for potent and selective inhibitors, and third, these inhibitors are used to elicit a phenotype.

Forward chemical genetic assays are designed to explore biological pathways or processes. The goal is to find proteins that are sensitive to small molecule inhibition. This is accomplished by screening diverse libraries of molecules, usually beginning with a large random collection, then identifying those that show an interesting phenotypic response, and finally identifying the protein target. In the process of forward chemical genetics, three major

components are required. A source or a library of compounds is first needed, which can be natural products (discussed earlier), diversity-oriented synthesis (which will be described later), or commercial collections. Second, a biological assay with a phenotypic screening needs to be created. Finally, the establishment of a strategy for identifying the target(s) of active compounds is essential. The source of these collections of molecules mainly comes from two types of syntheses, target-oriented synthesis and diversity-oriented synthesis. The origins of these two types of syntheses, however, can be traced back to the birth of organic synthesis.

1.4 Total Syntheses

Total organic synthesis was born in the nineteenth century.[13] It was Wöhler that 'gave birth' to the first total synthesis of a natural product in 1828 with his synthesis of urea (see **9** in *Figure 4*). Kolbe accomplished the second major achievement in the history of total synthesis in 1845 by synthesizing acetic acid (see **10** in *Figure 4*). For the first time in the history of organic chemistry, the word 'synthesis' was used by Kolbe to describe the process of assembling a chemical compound from other substances.

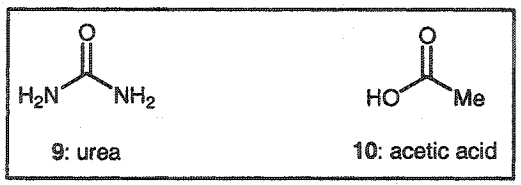


Figure 4. Selected nineteenth century total syntheses of natural products.

As expected, the syntheses that marked the nineteenth century (even if only two were mentioned here) were relatively simple, involving mostly benzenoid compounds. In the twentieth century, total synthesis could be divided into four distinct eras. The first one was named the Pre-World War II Era. This era began with impressive strides and with increasing molecular complexity as well as sophistication in strategy design. A remarkable amount of outstanding examples of total synthesis of this era can be pointed out. Two chemists that

won a Nobel Prize for Chemistry in that period of time, Robinson's one-step synthesis of tropinone (**11**) in 1917 and H. Fischer's synthesis of haemin (**12**) in 1929 (*Figure 5*), are among the remarkable examples.

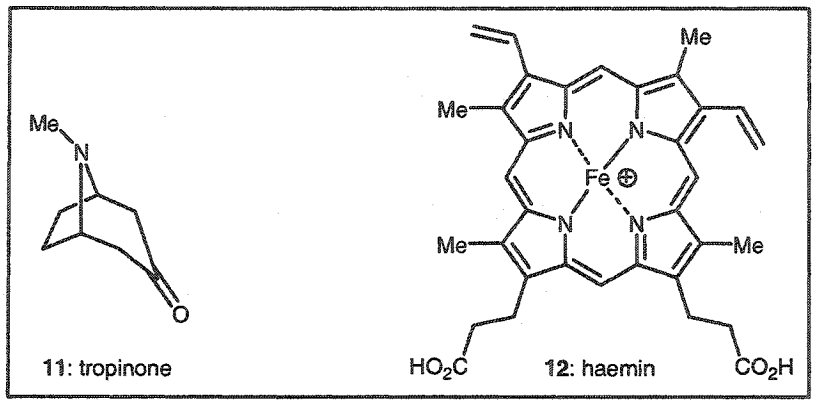
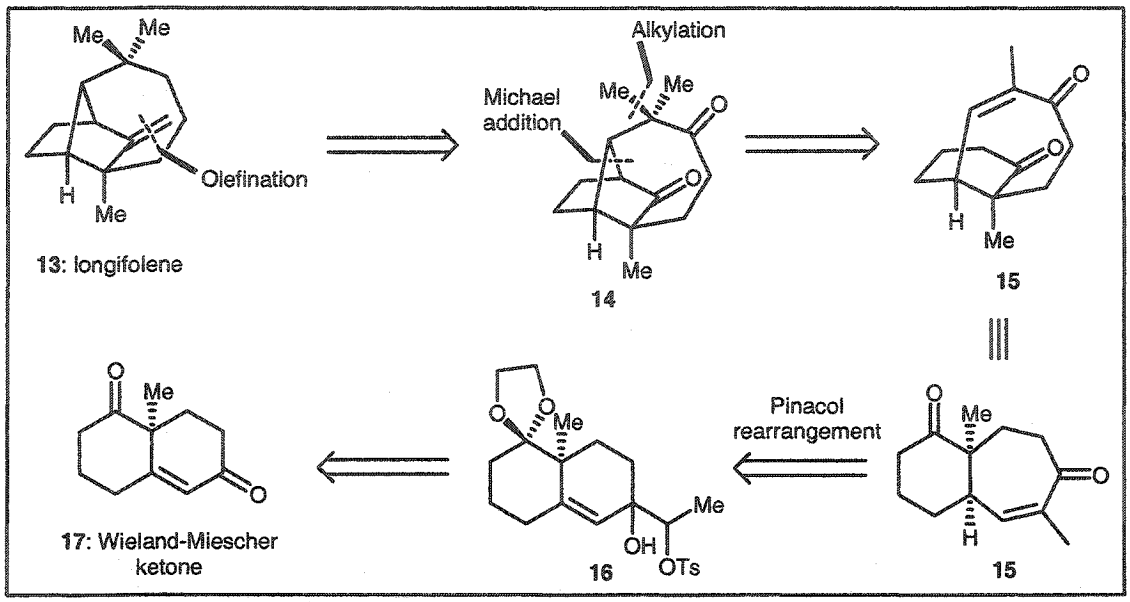


Figure 5. Selected total syntheses of natural products from 1901-1939.

The second era was named the Woodward Era for the well renowned and respected chemist. He actually elevated total synthesis and organic chemistry to a powerful science and a fine art. Woodward and his group were responsible for spectacular synthetic achievements between 1944 and 1981. He also brought mechanistic rational and stereochemical control to the field of organic chemistry.

The Woodward Era was followed by the Corey Era, another outstanding chemist. Two distinctive elements, retrosynthetic analysis and the development of new synthetic methods, marked this period. In fact, it is his synthesis of longifolene[14] (**13**) in 1961 that marked the official introduction of the principles of retrosynthetic analysis (*Scheme 1*). Prior to the Corey Era, most syntheses planning involved the selection of starting materials with structural resemblance to the target molecule.[15] Chemists then had to search for suitable reactions that could convert starting material into the desired target structure.



Scheme 1. Retrosynthetic analysis and strategic bond disconnections of longifolene.

The last period to complete the twentieth century and extend into the twenty-first century is the 1990's Era. Total synthesis has now assumed a more serious role in biology and medicine. Indeed, a new philosophy for total synthesis is present, as it has become an important component of chemical biology. Chemical biology can be defined as the creation of biological response profiles through small molecules selected on the basis of the knowledge of the structure and functions of biological targets.[3] Synthetic chemists are actually moving deeper into biology using powerful tools to probe biological phenomena and making contributions to chemical and functional genomics as mentioned earlier.

Now, bringing back the concept of target-oriented synthesis versus diversity-oriented synthesis, it is obvious that total synthesis is in fact a straightforward example of target-oriented synthesis.

1.5 Target-Oriented Synthesis (TOS)

Target-oriented synthesis, also known as TOS,[16] is generally used in drug discovery efforts involving preselected protein targets. It benefits from a powerful planning algorithm called retrosynthetic analysis. In retrosynthetic planning, key structural elements are recognized in a complex target structure. It is then broken down into simpler molecules by formally performing chemical reactions in the reverse direction.

In a classical manner, lead compounds are derived from the extraction of natural products from plants, animals, insects, or microorganisms. These molecules are made by Nature through many cycles of diversity generation and natural selection. Targets for TOS are usually natural products, but they can also be analogues of natural products and non-natural product derived compounds as potential lead candidates for developing drugs. The only requirement is the preselection of the protein target(s) which are then utilized for developing small molecules as selective binding agents.

Target-oriented synthesis starts with a structurally complex target and the discovery of a simple compound that can be used to start the synthesis (*Figure 6*). TOS is considered as a convergent synthesis as denoted in *Figure 7*. It gathers together complexity-generating reactions and fragment coupling reactions (reactions that join simultaneously two different building blocks). Total synthesis is a time consuming process that leads to the slow identification of drug-like candidates. This is where solid-phase synthesis, combinatorial synthesis, automation for high-throughput synthesis, and diversity-oriented synthesis come into play as emerging tools that address the time factor.[17,18]

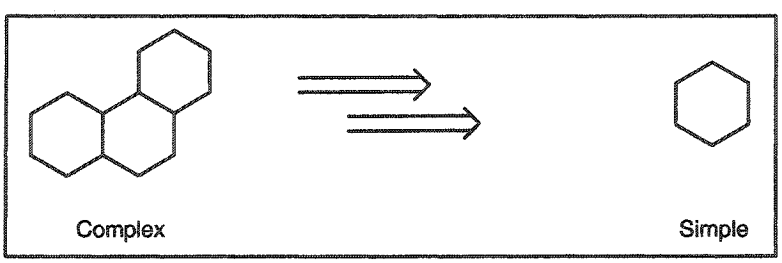


Figure 6. In planning target-oriented synthesis, the goal is to synthesize a particular target.

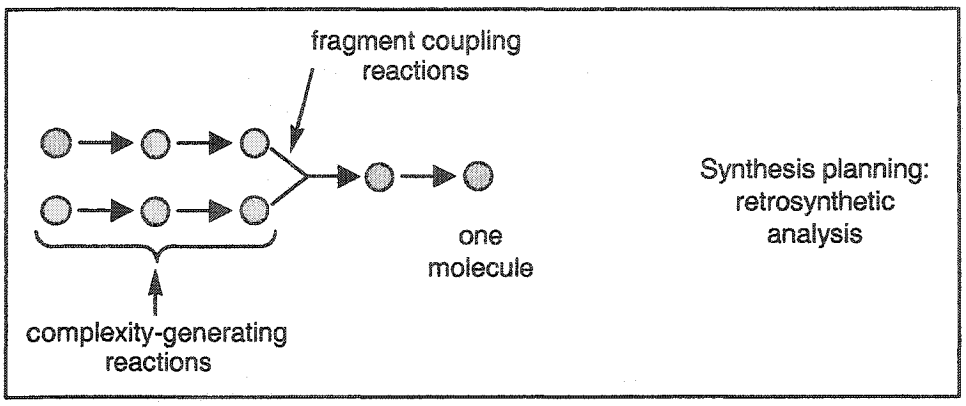


Figure 7. Target-oriented synthesis, a convergent approach.

1.6 Diversity-Oriented Synthesis (DOS)

The key bottleneck is the chemists' inability to efficiently synthesize large collections of molecules with high levels of complexity and diversity. The goal of diversity-oriented synthesis, also known as DOS, is to meet this formidable challenge.[19] In contrast to TOS, DOS is not focused toward a given target. The term 'diversity-oriented synthesis' is actually replacing the explicit practice of generating libraries of 'natural product-like' compounds. The planning of retrosynthetic analysis is therefore ineffective and cannot be applied directly. Instead, diversity-oriented syntheses are analyzed in the direction of the chemical reactions (from reactants to products). This direction of analysis is analogous to TOS before the Corey Era, during which retrosynthetic analysis was developed.

Designing DOS targets also requires synthetic planning but this time in a forward direction. Stuart L. Schreiber has proposed and begun to develop a forward synthetic analysis which maximizes complexity, diversity, and efficiency (*Figure 8*). In the algorithm of forward synthetic analysis, complexity is engendered via tandem complexity-generating reactions and conformational analysis. In turn, diversity is divided into three key elements: building blocks, stereochemistry, and molecular skeleton.

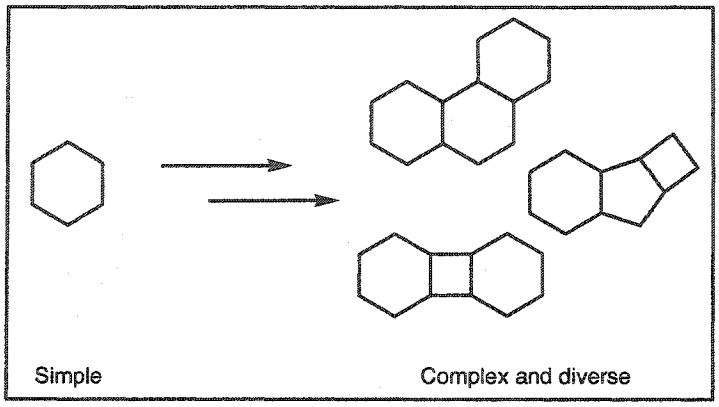


Figure 8. In planning diversity-oriented synthesis, the goal is to synthesize efficiently libraries of pure compounds with maximal structural complexity and diversity.

DOS is considered as a divergent synthesis (*Figure 9*). As just mentioned, it gathers complexity-generating reactions but also multicomponent coupling and diversity-generating reactions. Coming back to chemical genetics, it is now appreciated that complex and diverse collection of small molecules can be used for exploration of cellular and organismal pathways and that DOS is an effective method for synthesizing such compounds efficiently.

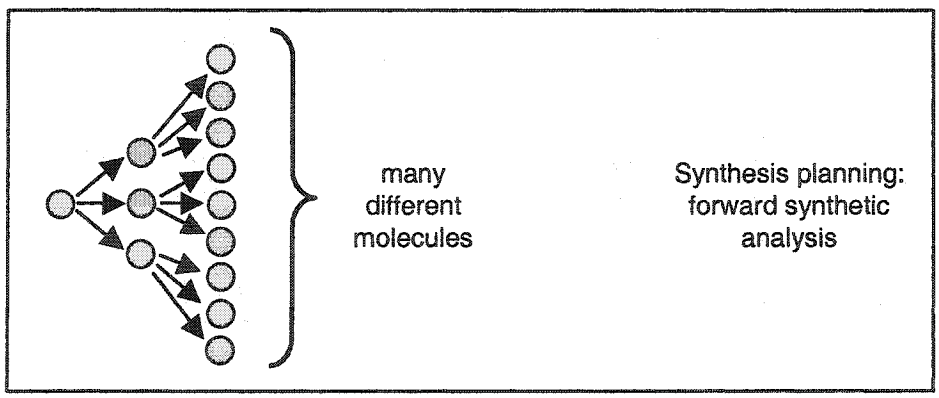


Figure 9. Diversity-oriented synthesis, a divergent approach.

Many examples of diversity-oriented syntheses are reported in the literature. Only three from different authors will be mentioned here. The first one is the preparation of an indolactam library **19** (*Figure 10*) on polymeric supports from Herbert Waldmann and his group.[20] Indolactam was used as a template because the natural product (–)-indolactam V (**18**) is known to be an activator of

protein kinase C which plays many key roles in signal transduction pathways. The central enantiomerically pure building block **21**, the formation of the 9-membered ring and the introduction of residue R_1 (**22**) were synthesized in solution phase [*Scheme 2(a)*]. Residues R_2 and R_3 were introduced while the template **23** was anchored onto the solid support [*Scheme 2(b)*].

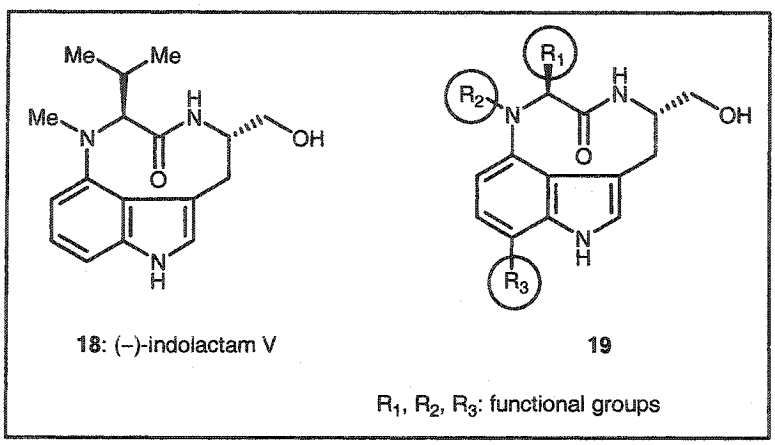
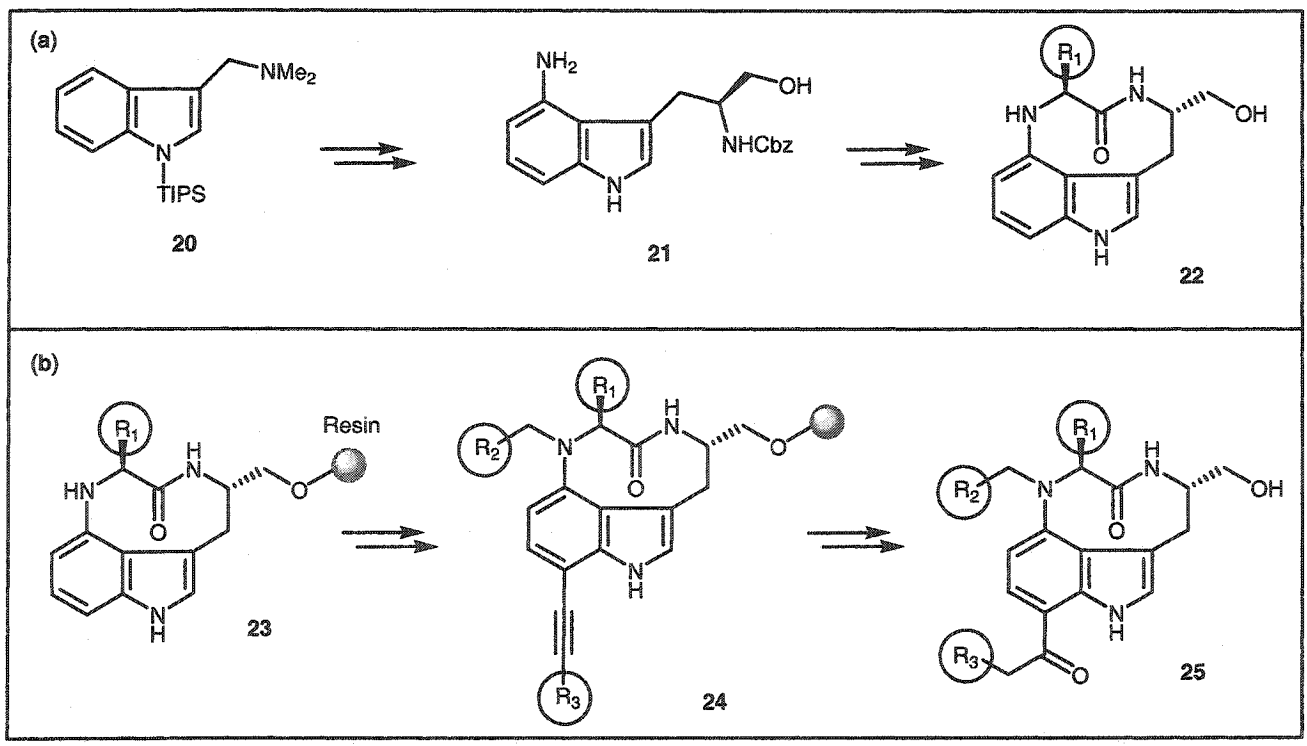
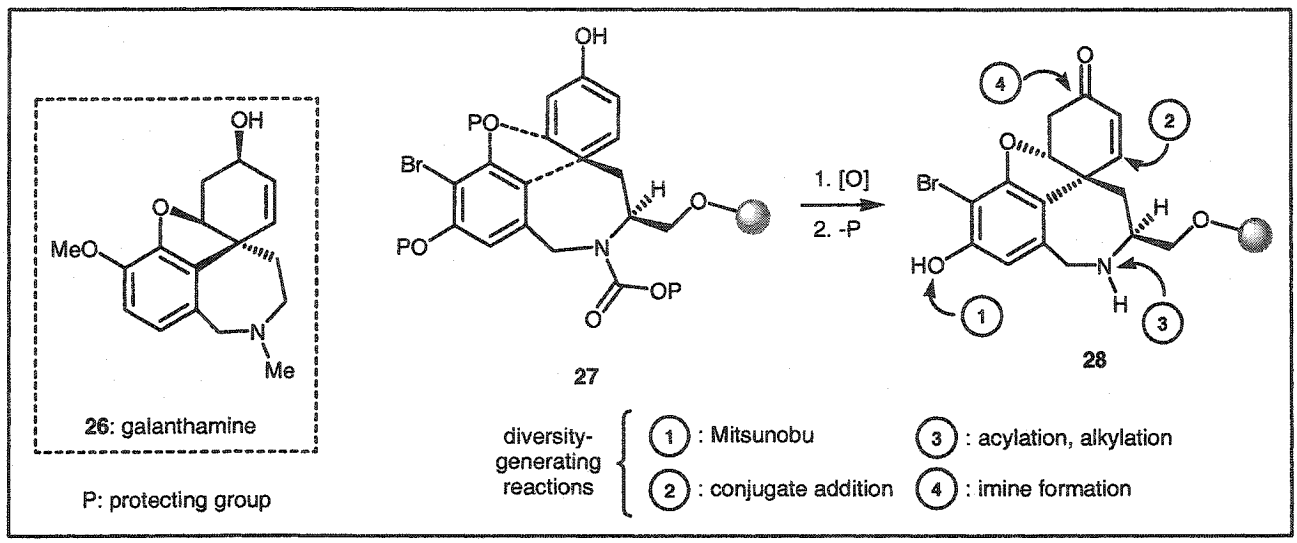


Figure 10. Structures of (–)-indolactam V and analogues for library synthesis.



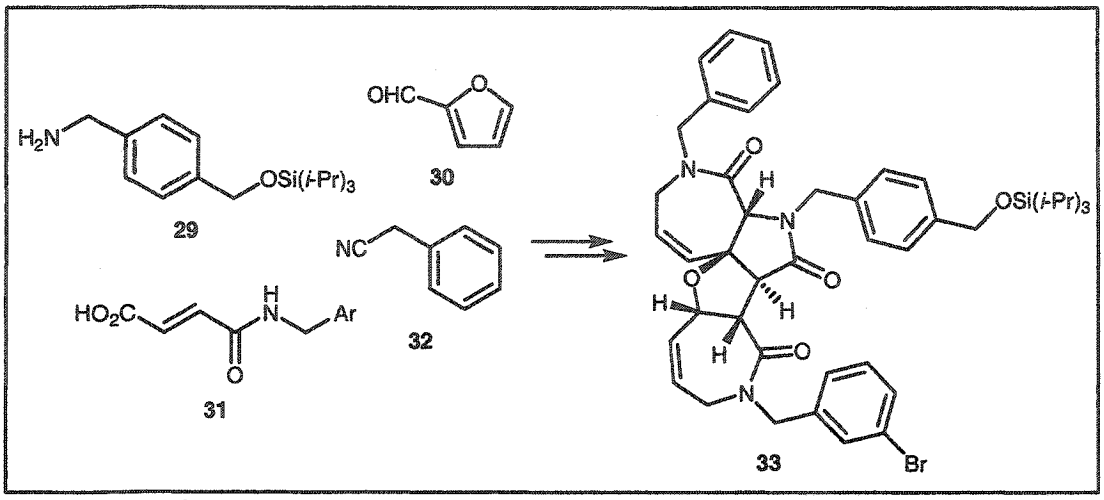
Scheme 2. Indolactam library synthesis. **(a)** Solution phase synthesis of indolactam building block. **(b)** Combinatorial introduction of functional groups R_2 and R_3 on solid phase.

The second example is one from Matthew D. Shair and his group. They use a biomimetic diversity-oriented synthesis to generate galanthamine-like molecules **28**.[21] In this case, galanthamine (**26**), which presents a rigid polycyclic core, was selected not only because of its potent acetylcholinesterase inhibition, but also because it offered a wide range of functionality for diversity-generating reactions (*Scheme 3*). Fortunately, this particular DOS combined with phenotypic screening was successful in identifying an active compound, secramine, that perturbs protein trafficking.



Scheme 3. Biomimetic diversity-oriented synthesis of galanthamine-like molecules.

Finally, the third example is one from Stuart L. Schreiber and his group.[22] The focus of this work was on a planning technique aimed at generating structural complexity in synthetic products in a minimal number of steps. Pairs of complexity-generating reactions were selected in which the product of the first reaction was a substrate for the second reaction. This can be related to tandem reactions in target-oriented synthesis. In this article, four substrates (benzylamine **29**, aldehyde **30**, acid **31** and cyanide **32**) were used to generate the polycyclic derivative **33** in four steps (*Scheme 4*). The complexity-generating reactions involved in this synthesis (in solution phase as well as in solid phase) were the Ugi-4 component coupling, an intramolecular Diels-Alder, and a ring-opening-closing olefin metathesis.



Scheme 4. Example of complexity-generating reactions in DOS.

1.7 Arya's Group Approach to Diversity-Oriented Synthesis

In Arya's group, the approach to DOS is mainly concentrated on three major scaffolds: indoline **34**, benzofuran **35** and tetrahydroquinoline **36** derivatives (*Figure 11*). The project covered in this thesis falls into the first

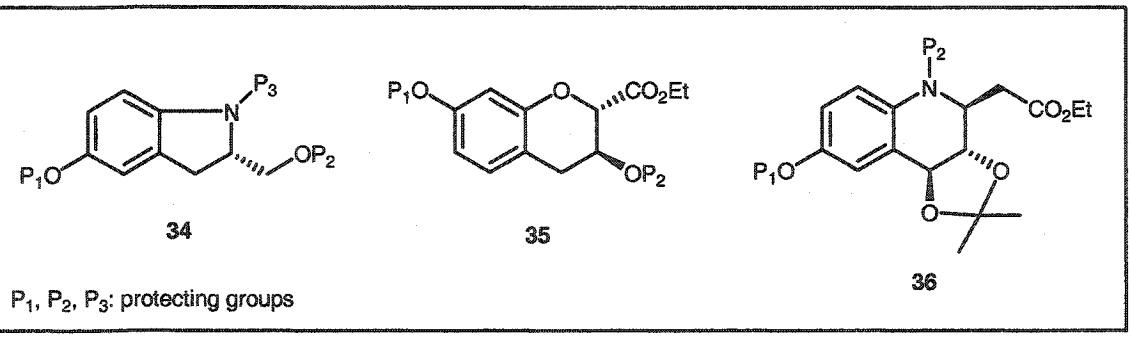


Figure 11. Three major building blocks used in Arya's group to perform DOS.

family. Indoline derivatives are quite abundant in the Nature and are considered important building blocks in medicinal chemistry. In literature, there are some examples of natural products having indole and indoline moieties that exhibit a wide range of biological activities.[23] Several of these examples and related compounds are mentioned in *Figure 12*. Benzastatins E (**37**), F (**38**), and G (**39**) isolated from *Streptomyces nitrosporeus* exhibit some neuronal cell protecting activity.[24] Camptothecin (**40**) extracted from *Camptotheca acuminata* shows

broad-spectrum anticancer activity. Ajmalicine (**41**) coming from *Catharanthus roseus* and *Rauwolfia serpentina* is employed as an antihypertensive. Reserpine (**42**) and deserpidine (**43**) extracted from *Rauwolfia canescens* and *Rauwolfia vomitoria* are used as antihypertensives and tranquillizers.

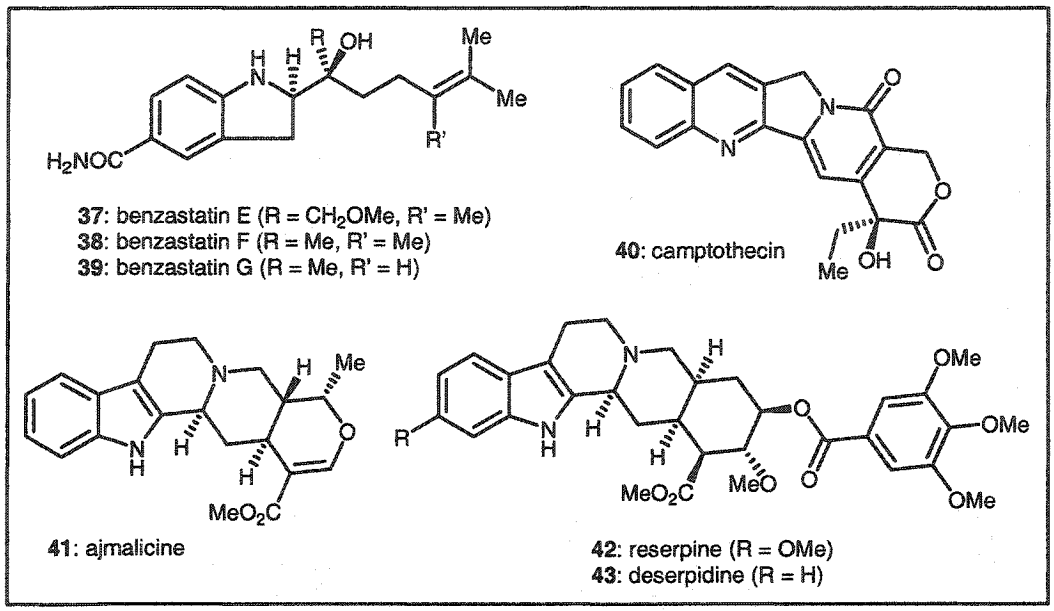
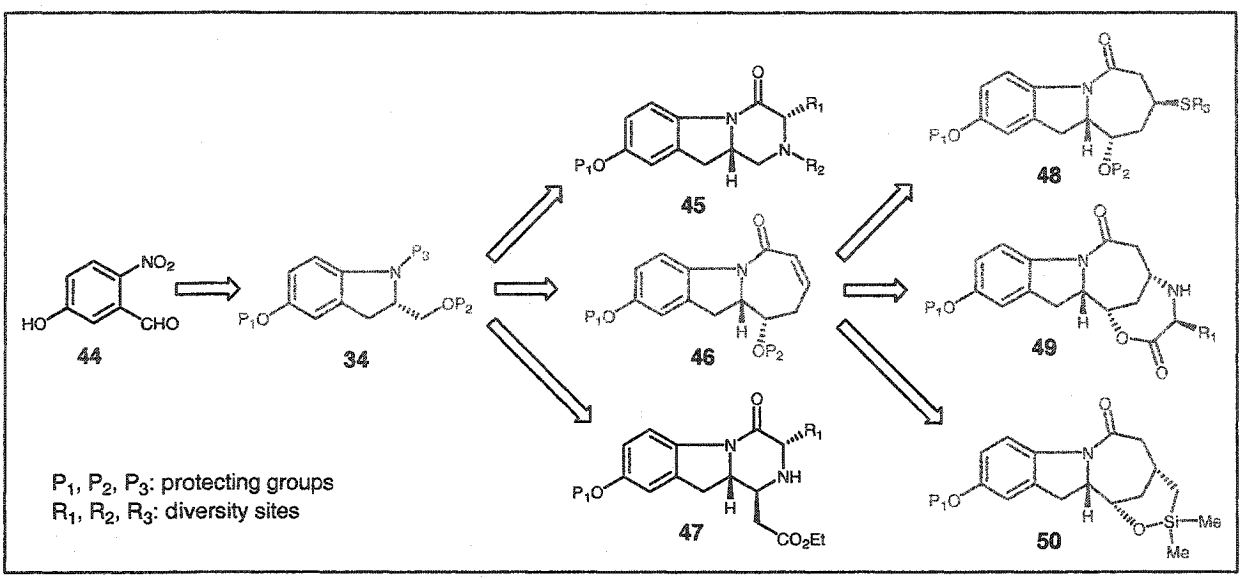


Figure 12. Biologically active indole alkaloid-based natural products.

The approach was to develop the solution phase synthesis of a functionalized indoline template, which would then be utilized in creating complex architectures by employing diversity-oriented synthesis. In comparison to *Figure 9*, in which DOS is presented as a divergent synthesis, the indoline-based amino alcohol scaffold can be exposed to DOS (*Scheme 5*).

The first milestone in this strategy was to successfully develop a total synthesis of the indoline-based amino alcohol derivative **34** in solution starting from the commercially available 5-hydroxy-2-nitrobenzaldehyde (**44**). Then, using divergent syntheses, three new compounds (**45**, **46**, **47**) emerged from the template. These tricyclic derivatives became scaffolds for further DOS.



Scheme 5. DOS approach using indoline as a building block.

Compound **45** was synthesized by using a Mitsunobu strategy. The indoline-based tricyclic derivative **46** was the ultimate target of this project obtained through an olefin ring-closing metathesis reaction. Compound **47**, which is a new member of a family of β-amino esters, synthesized by using an intramolecular asymmetric hetero-Michael addition, opened the door for exploring several diversity sites in library generation.

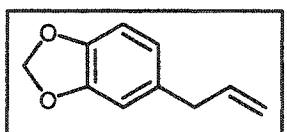
The seven-membered ring template **46** has a few interesting features. It can be anchored onto a solid support due to the presence of a hydroxyl group on the benzene ring, permitting its synthesis on solid phase. The incorporation of a conjugated system, the enamide functionality, opens the door for exploring different complexity- and diversity-generating reactions. Also the secondary hydroxyl group on the ring can be used as a tether to explore intramolecular reactions. As depicted in *Scheme 5* (compounds **48**, **49** and **50**), several reactions were attempted on the tricyclic template **46** in order to explore its ability to control the intramolecular or intermolecular attack of the reagents used.

CHAPTER 2: MODEL STUDY

2.1 INTRODUCTION

The first goal of the project was to demonstrate that the syntheses of the indoline moiety as well as the seven-membered ring template were feasible. Before performing the synthesis with the real system, that is one to which a solid support can be attached, tests needed to be done with a model system.

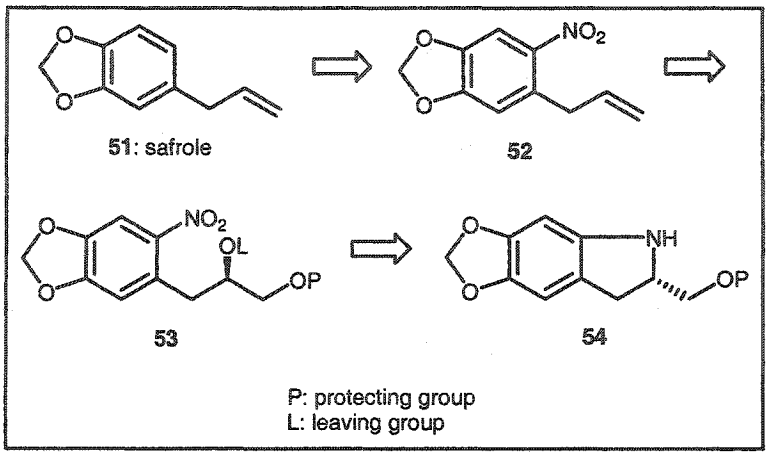
To carry out the model study, a molecule had to be chosen. By searching for available compounds, safrole **51** was found to be a good starting material for preliminary studies. This compound presented the advantage of requiring a minimum number of steps to reach to the indoline scaffold.



51: safrole

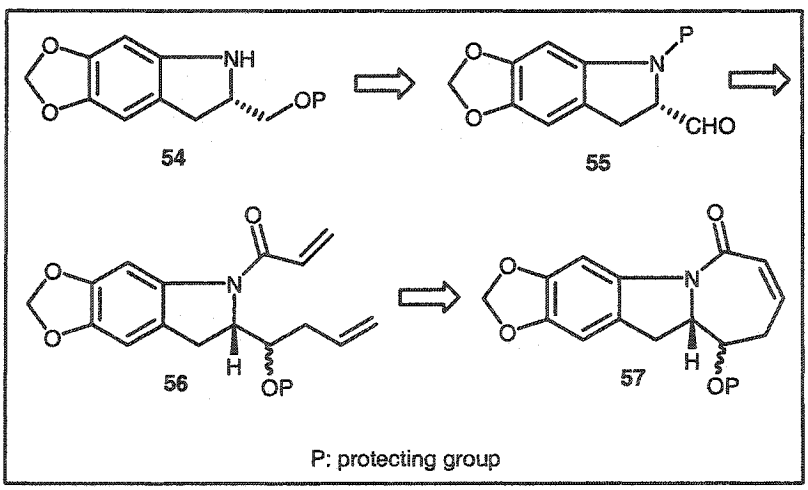
2.2 FORWARD SYNTHETIC ANALYSIS

The forward synthetic analysis of the first milestone of the project began with the introduction of the nitro group on the aromatic ring (**52**) (*Scheme 6*). Then, an asymmetric dihydroxylation reaction was envisaged to introduce functionality in the molecule. Furthermore, these two hydroxyl groups were essential to cyclize and form the β-amino protected alcohol **54**. The formation of the five-membered ring could be induced by converting the secondary alcohol into a leaving group (**53**) followed by reduction of the nitro functionality. With the indoline moiety **54** in hand, the second part of the model study could be put forward.



Scheme 6. Forward synthetic analysis of the indoline moiety.

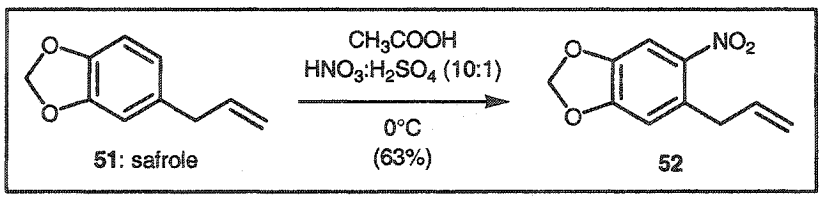
The newly formed amino group would required protection before oxidizing the primary alcohol to generate the aldehyde **55** (*Scheme 7*). The seven-membered ring **57** was planned to be obtained through an olefin ring-closing metathesis strategy. Therefore, compound **56** could be obtained by an allylation reaction followed by an acrylation.



Scheme 7. Forward synthetic analysis of the seven-membered ring template.

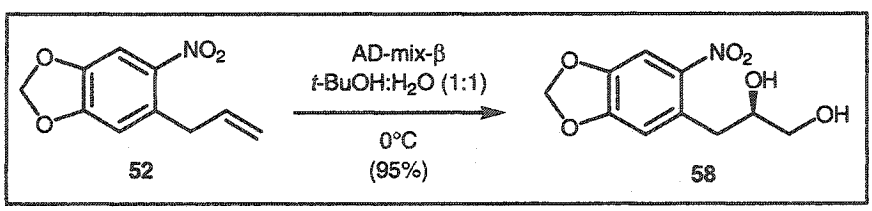
2.3 Synthesis of the Indoline Moiety

The synthesis began by making the nitro derivative **52** of safrole (*Scheme 8*). This was achieved by treating the starting material with a solution of glacial acetic acid and nitric acid.[25] The reaction was not clean, making many undesirable compounds. Fortunately, the desired product was the least polar and could easily be isolated in a 53% yield. The yield was improved by using a mixture of nitric acid and sulfuric acid in a 10 to 1 ratio with glacial acetic acid (63% yield).



Scheme 8. Nitration of safrole.

The next step consisted of introducing a diol in the molecule by executing an asymmetric dihydroxylation (AD) reaction.[26] This was achieved by treating compound **52** with AD-mix-β (*Scheme 9*) in a mixture of *tert*-butanol and water (1:1 ratio). The diol **58** was obtained in a 95% yield and was confirmed by the disappearance of the three alkene hydrogens [δ 5.97 ppm (ddt, J = 13.5, 6.5, 6.4 Hz, 1H), 5.14 ppm (dd, J = 6.5, 1.4 Hz, 1H) and 5.10 ppm (dd, J = 13.5, 1.4 Hz, 1H)] in the ^{1}H NMR spectrum.



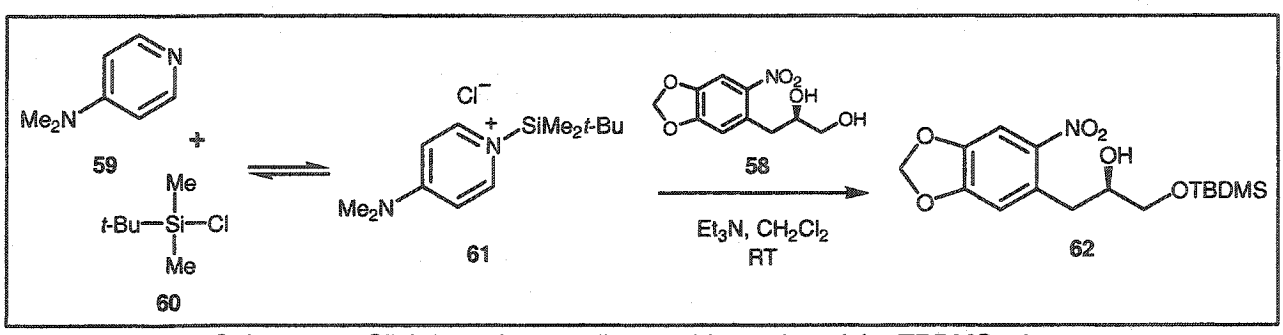
Scheme 9. Asymmetric dihydroxylation reaction.

Before introducing the leaving group on the secondary alcohol to generate the five-membered ring through a displacement reaction, protection of the primary hydroxyl group was required. The first investigation was carried out by

using *tert*-butyldimethylsilyl chloride (TBDMSCl) as a protecting reagent. This group was preferred mainly because it is easy to transform alcohols to their corresponding TBDMS ethers. Also, the TBDMS functional group can be selectively removed under mild acidic or neutral conditions and TBDMS ethers are very stable to a wide range of reaction conditions. More important, the bulkiness of this group would avoid substitution on both alcohols.

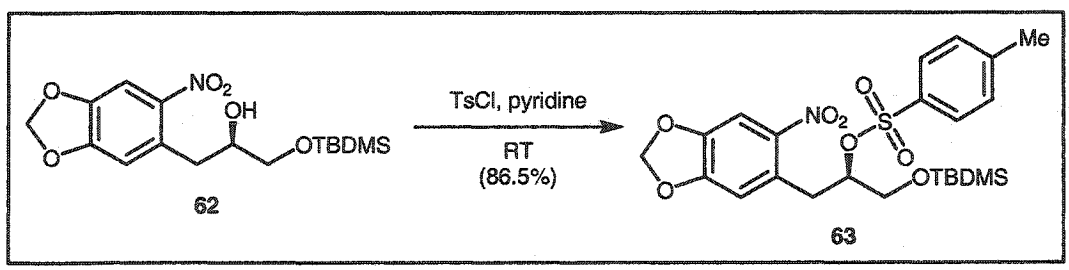
Usually, the method employed to generate TBDMS ethers utilizes an excess of TBDMSCl reagent in DMF containing imidazole, which acts both as an acid acceptor and as an intermediate silyl donor, the *N*-TBDMS-substituted imidazole.[27] In the case of diol **58**, when subjected to TBDMSCl and imidazole in dichloromethane (this solvent presented no dilution problems), only 50% of the desired silyl ether was isolated. By searching the literature for a different procedure, an example with 1,2-diols was identified. The reaction proceeded with predominant formation of the primary monosilyl ether when the diol was subjected to TBDMSCl, triethylamine and DMAP in catalytic amount (0.04 equivalent) in dichloromethane.[28]

With this procedure in hand, the diol **58** was subjected to the same reaction conditions reported in the article (*Scheme 10*). In this case, like it was observed with imidazole, an intermediate silyl donor exists as the *N*-TBDMS-substituted DMAP **61**. Under these conditions, the silyl ether **62** could be obtained in quantitative yields. ^{1}H NMR confirmed the formation of the product. A singlet at 0.94 ppm integrating for 9 protons as well as another singlet at 0.11 ppm integrating for 6 protons supported the presence of the TBDMS group.



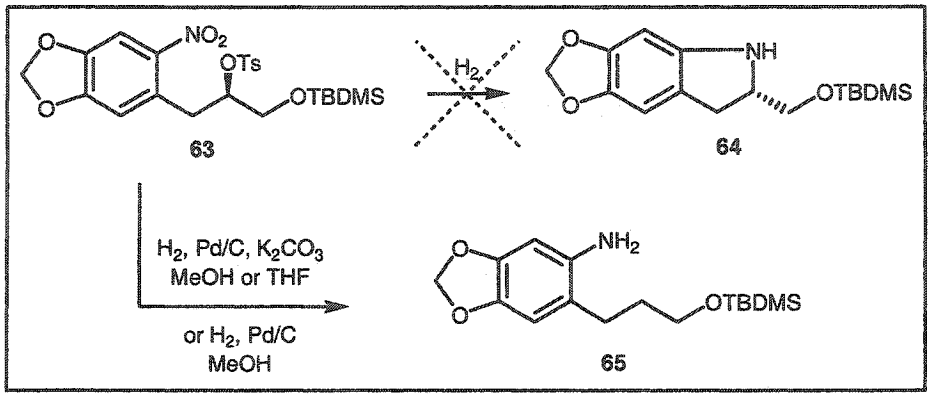
Scheme 10. Silyl donor intermediate and formation of the TBDMS ether.

The next step involved the incorporation of the leaving group on the secondary hydroxyl. *p*-Toluenesulfonyl chloride (TsCl) was the reagent of choice to introduce a leaving group in the molecule. Compound **62** was treated with TsCl in the presence of triethylamine in dichloromethane.[29] Unfortunately, the tosyl derivative was not observed even when DMAP was added to help the reaction to proceed. TBDMS, as mentioned earlier, is a bulky group, as is the Ts group. It is possible to imagine that the base was unable to deprotonate the alcohol resulting in recovering only the starting material. Pyridine was then chosen to perform the reaction and after three days, compound **63** was isolated in 86.5% (*Scheme 11*). The formation of the product was confirmed by ^{1}H NMR. The signals for the aromatic protons of the benzene ring appeared as two sets of doublets: 7.53 ppm (J = 8.2 Hz) and 7.15 ppm (J = 8.2 Hz) integrating for two protons each while the signal for the methyl protons was a singlet at 2.42 ppm.



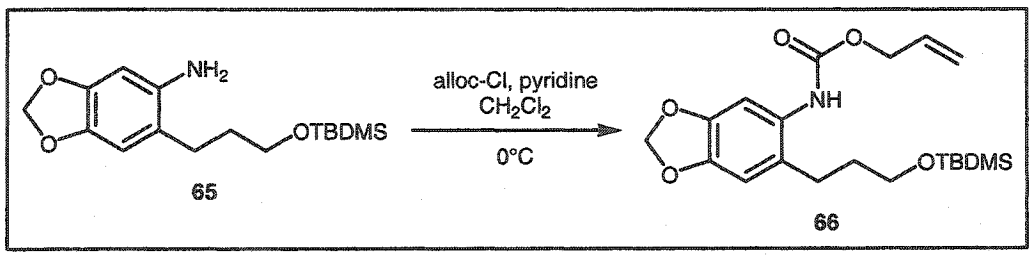
Scheme 11. Tosylation reaction.

Compound **63** was ready to be cyclized. Upon hydrogenation to convert the nitro group into an amino functionality, it was expected that it would form the five-membered ring **64** (*Scheme 12*). Instead, when the nitro derivative **63** was subjected to a hydrogen atmosphere in presence of 10 wt. % palladium on carbon and potassium carbonate in methanol or in THF, only **65** was isolated as a major product. The mass spectrometry of this new compound was 310.2 (M+1), whereas a value of 308 (M+1) was expected if the indoline moiety (**64**) was obtained. This suggested that the leaving group was falling off the molecule before it could cyclize, generating **65**.



Scheme 12. Formation of derivative **65** upon hydrogenation.

By inspecting the ^{1}H NMR spectrum of **65**, the disappearance of the methyl protons at 2.42 ppm and the disappearance of the aromatic protons of the tosyl benzene ring at 7.53 ppm and 7.15 ppm could be seen, indicating the lost of the *O*-tosyl group. Derivative **66** was synthesized by treating **65** with allyl chloroformate (alloc-Cl) in the presence of pyridine in dichloromethane at 0°C (*Scheme 13*) and was confirmed by mass spectrometry as well as ^{1}H NMR.



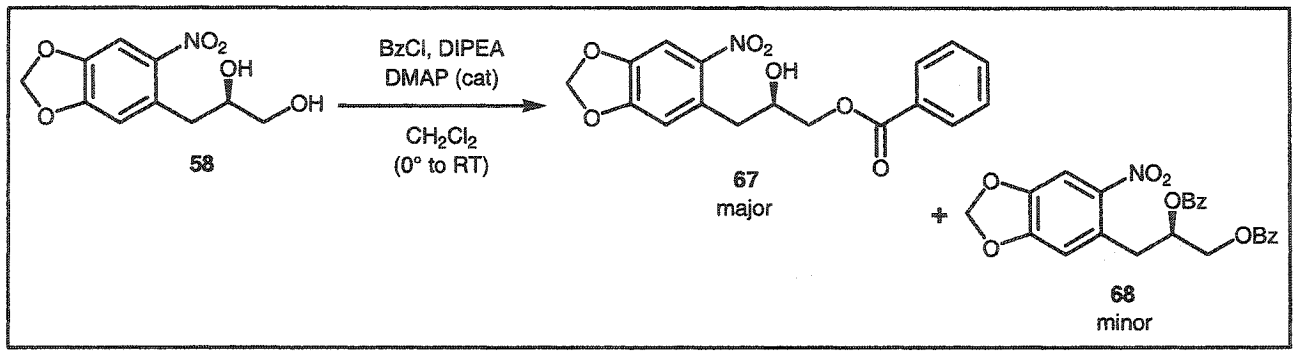
Scheme 13. Introduction of allyloxycarbonyl protecting group.

In light of these results, it was obvious to change the leaving group. Therefore, the tosyl derivative was exchanged for a mesyl group by treating the alcohol **62** with methanesulfonyl chloride (MsCl). Unfortunately, when the mesyl derivative was subjected to the hydrogenation conditions, compound **65** was obtained as the only product.

The strategy to make the indoline moiety had to be changed with the observation of these results. A different protecting group needed to be utilized

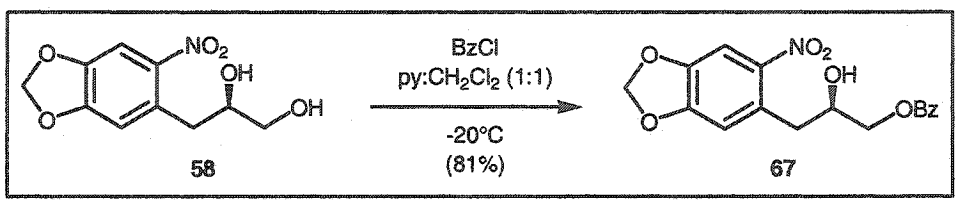
on the primary alcohol in order to achieve the goal. Benzoyl chloride (BzCl) was then used to introduce protection on the primary OH group.

The diol **58** was treated with benzoyl chloride, DIPEA and catalytic amount of DMAP in dichloromethane from 0°C to room temperature, however only 58% of the desired benzoyl derivative **67** could be isolated (*Scheme 14*). Moreover, depending on the reaction time (between 22 and 48 hours), the dibenzoyl derivative **68** was obtained in 10 to 17% yields. Each time the reaction could not be completed, resulting in recovering some starting material.



Scheme 14. Protection of the primary alcohol with benzoyl group.

The reaction conditions had to be changed in order to increase the yield of formation of the benzoyl derivative. Even though pyridine is not a very safe solvent to use, it was chosen as a co-solvent with dichloromethane to perform the benzoylation reaction.[30] Compound **67** was obtained in a 81% yield when the diol was subjected to benzoyl chloride in a mixture of pyridine and dichloromethane (1:1 ratio) at low temperature (*Scheme 15*).



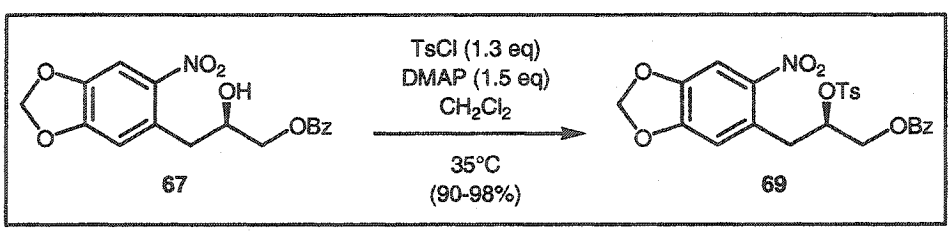
Scheme 15. Benzoylation in pyridine and dichloromethane as co-solvents.

The product was identified by ^{1}H NMR. The aromatic signals of the benzoyl group appeared as a doublet at 8.05 ppm (J = 7.8 Hz) integrating for two hydrogens, as a triplet at 7.58 ppm (J = 7.6 Hz) integrating for one hydrogen and

as a doublet of doublets at 7.45 ppm (J = 7.8, 7.6 Hz) integrating for two hydrogens. Only trace amount of the dibenzoyl compound was observed on TLC when using these reaction conditions. Even after 65 hours of reaction the starting material was still not completely converted into the desired product. Nevertheless, it was satisfactory enough to continue the synthesis.

As with the TBDMS ether **62** (see *Scheme 11*), the secondary hydroxyl still needed to be transformed into a leaving group in order to obtain the five-membered ring compound. The same strategy was kept here, using tosylate as the leaving group. Compound **67** was treated with TsCl in the presence of triethylamine in dichloromethane for 48 hours. It was hoped that better results would be obtained with the benzoyl derivative compared to what was observed with the TBDMS ether. Contrary to the reaction of compound **62** using the same reaction conditions, in this case the tosyl compound was obtained but in a low yield (34%).

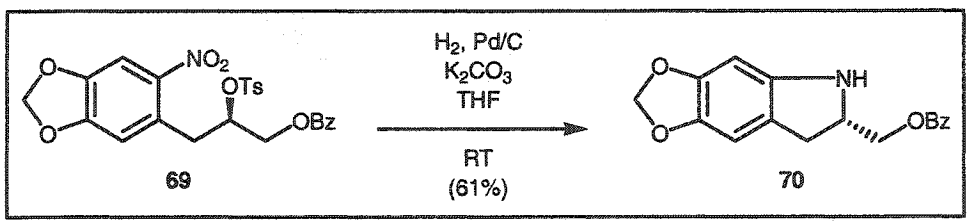
The next alternative was to try the reaction with TsCl and pyridine. This time, the reaction was not complete even after four days and only 45% of the desired compound was isolated. Also, the reaction was not very clean, the starting material was recovered in only 31% yield losing close to 25% of the material. An article was found in the literature that reported using DMAP in dichloromethane with TsCl.[31] The authors used 4.5 equivalents of DMAP and 3 equivalents of TsCl. The idea of using several equivalents of DMAP instead of a catalytic amount was interesting, but 4.5 seemed slightly excessive. Therefore, only 1.5 equivalents of DMAP and 1.3 equivalents of TsCl were used to successfully generate compound **69** (*Scheme 16*).



Scheme 16. The use of DMAP for the tosylation reaction.

Better results, yielding between 90 and 98%, were obtained when the reaction mixture was heated to 35°C and when the solution was more concentrated. The formation of the product was confirmed by the disappearance of the hydroxyl signal at 2.83 ppm in the ^{1}H NMR spectrum. It was also confirmed by the appearance of signals in the aromatic region. The new benzene protons appeared as two sets of doublets at 7.58 ppm (J = 8.2 Hz) and 7.14 ppm (J = 8.2 Hz) integrating for two protons each while the signal for the methyl protons was a singlet at 2.38 ppm.

Hydrogenation was the best choice to convert the nitro group into an amino functionality. It was expected that cyclization would take place almost immediately by a displacement reaction. However, when tosyl derivative **69** was subjected to 10 wt. % palladium on carbon in methanol under a hydrogen atmosphere, nothing happened, only starting material was recovered. It was possible to isolate the cyclic compound **70** in a 61% yield after three days when performing the hydrogenation in THF with potassium carbonate (*Scheme 17*).



Scheme 17. Indoline moiety formation.

^{1}H NMR as well as 2D NMR experiments (COSY, HMQC and HMBC) confirmed the formation of the indoline moiety. The signals of the aromatic protons as well as the methyl hydrogens of the tosyl group disappeared from the ^{1}H NMR spectrum. The proton in the *ortho* position to the nitro functionality shifted upfield, now being next to the NH group.

Hydrogenation in THF with the base present (K_2CO_3) seemed to be the best conditions to reduce the nitro group. The reaction was not clean when performed without potassium carbonate, as decomposition of the product was observed. The base used in this solvent seemed to act as a buffer. These reaction conditions were acceptable to generate the amino group from the nitro

functionality, but the cyclization was much more difficult and requiring long reaction time.

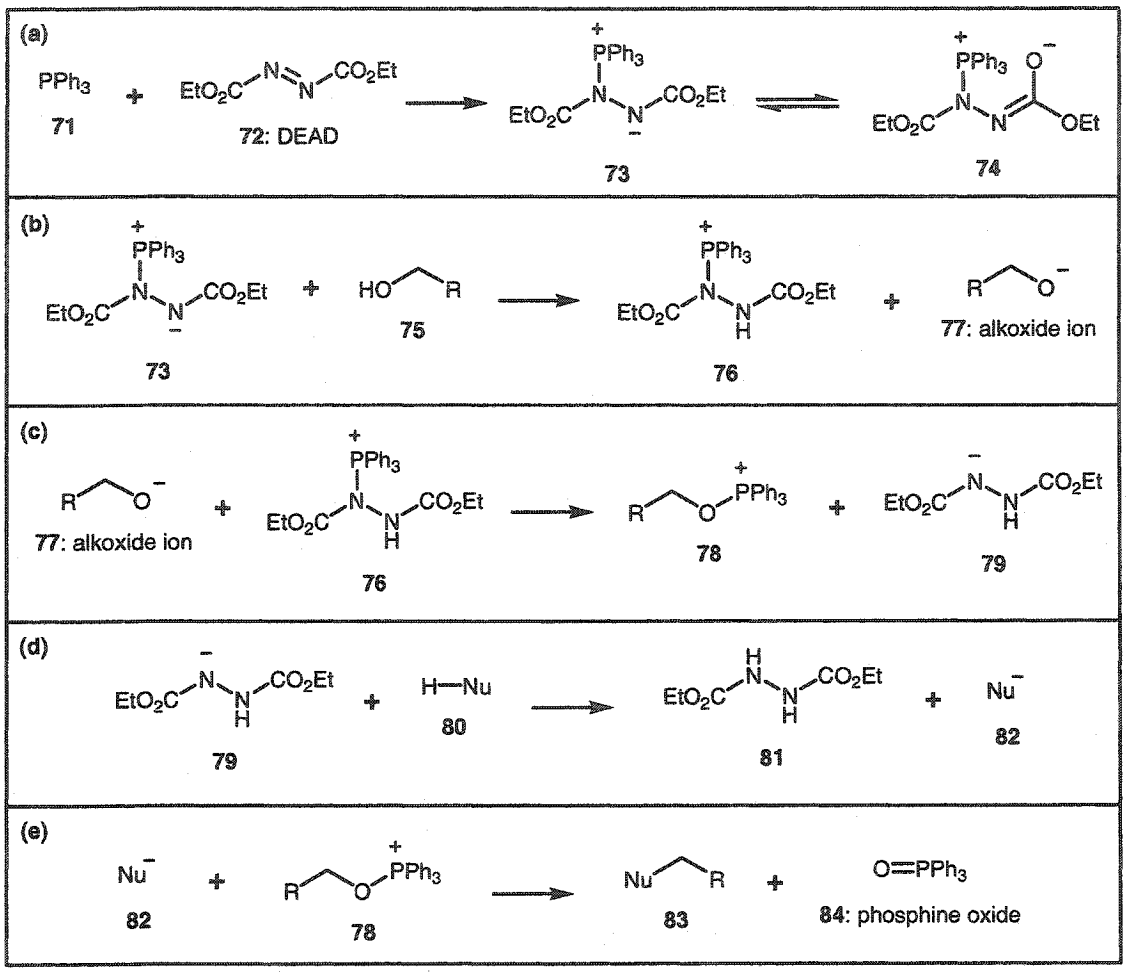
Different conditions were tried to improve cyclization. More equivalents of potassium carbonate were used and the solution was heated, but without improvement. The solvent was changed to acetonitrile, but nothing happened, even upon heating. The solvent and the base were then changed to dichloromethane and DMAP, but again without any success. The best results were finally obtained when the cyclization was induced with potassium carbonate in DMF and heating the reaction mixture to 40°C. The conversion from the amino derivative to the five-membered ring compound was fast but not always complete and the recovering starting material could be resubjected to the cyclization conditions.

2.3.1 Mitsunobu Conditions to Generate the Indoline Building Block

It was worthwhile at this point in the project to think of an alternative strategy to generate the indoline building block. The Mitsunobu reaction, a S_N2 type reaction using phosphorus chemistry, was envisaged. In this case, the OH group is not required to be converted into a better leaving group to perform the displacement reaction. This recent invention from Oyo Mitsunobu generates the S_N2 product in one operation by activating the alcohol *in situ*.[32]

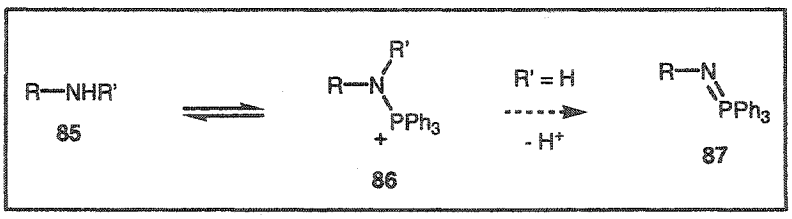
Four reagents are involved in this reaction: the alcohol (which becomes the electrophile), a nucleophile, triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD). The first step of the reaction involves the addition of phosphine **71** to the weak N=N π bond of the azo compound **72** [*Scheme 18(a)*]. The basicity of the anion (**73**) produced in this step is strong enough to remove the proton from the alcohol **75** [*Scheme 18(b)*]. Then, an S_N2 reaction at phosphorus takes place. The new alkoxide ion (**77**) immediately attacks the positively charged phosphorus atom (**76**) displacing a second nitrogen anion and forming the key intermediate in a Mitsunobu-type reaction, the oxyphosphonium ion **78** [*Scheme 18(c)*]. The second basic nitrogen anion (**79**) removes a proton from the nucleophile **80** [*Scheme 18(d)*]. Finally, a S_N2 reaction at carbon is

induced. The anionic nucleophile **82** attacks the phosphorus derivative of the alcohol (**78**) to produce compound **83** with the phosphine oxide **84** as the side product [*Scheme 18(e)*].



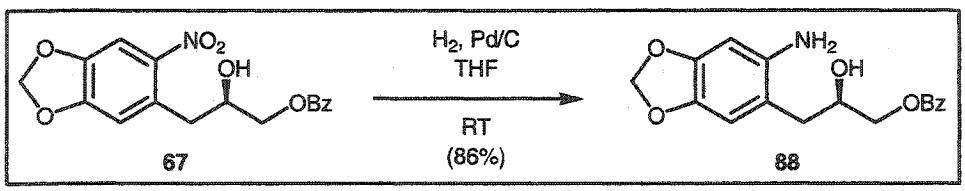
Scheme 18. Synthetic steps of the Mitsunobu reaction.

In Mitsunobu reactions, primary amines are not usually useful for the formation of nitrogen heterocycles due to the iminophosphorane (**87**) formation (*Scheme 19*). But in 1996, the use of a primary aromatic amine in a Mitsunobu cyclization reaction was reported for the first time.[33] The key step actually involved an excess of zinc chloride.



Scheme 19. Iminophosphorane formation from primary amines.

In this project, these special conditions for the Mitsunobu reaction were tried with the amino alcohol derivative. By using this strategy, the route to obtain the indoline scaffold would become shorter. The synthesis started with the nitro derivative without the tosyl group on the secondary alcohol. Compound **67** was subjected to 10 wt. % palladium on carbon in THF under an atmosphere of hydrogen to reduce the nitro functionality. The amino alcohol **88** was isolated in a 86% yield after four hours of hydrogenation (*Scheme 20*).



Scheme 20. Hydrogenation to generate the amino alcohol **88**.

^{1}H NMR confirmed the formation of the product. The signals, appearing as singlets, for the aromatic protons shifted upfield from 7.49 ppm (H_A) and 6.85 ppm (H_B) in the starting material to respectively 6.36 ppm (H_C) and 6.60 ppm (H_D) in the final product (*Figure 13*). The large shift of 1.13 ppm for the hydrogen in the *ortho* position to the nitro functionality was clearly understandable; changing from an electron-withdrawing group (NO_2) to an electron-donating group (NH_2) moves the proton upfield in a shielded region.

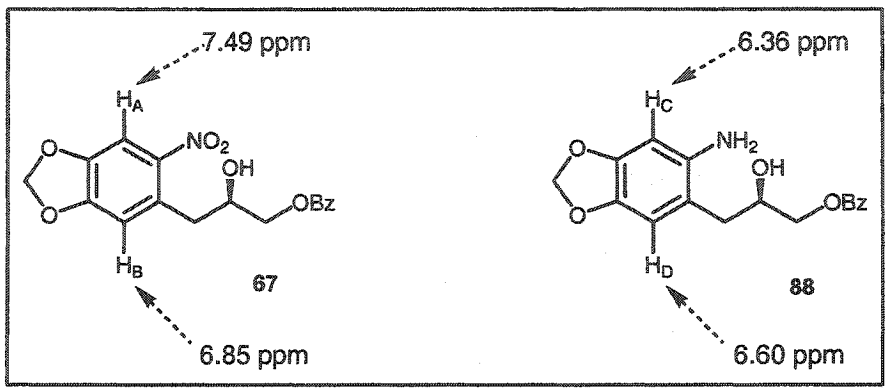
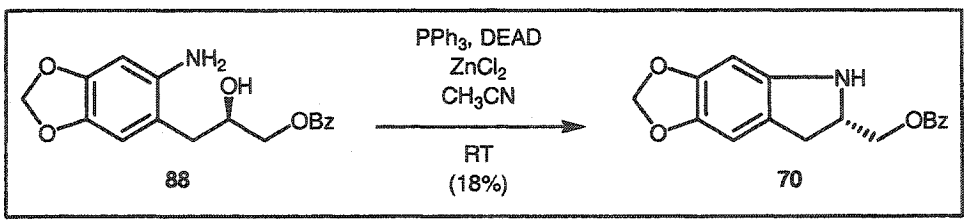


Figure 13. ^{1}H NMR chemical shifts of the aromatic protons of nitro and amino compounds.

Finally, compound **88** was ready to be subjected to the Mitsunobu reaction (*Scheme 21*). Unfortunately, compound **70** was isolated in a very low yield (18%) using this method. Consequently, the leaving group strategy using the tosyl group was kept to synthesize the indoline moiety in the model study.



Scheme 21. Mitsunobu strategy to generate the indoline moiety.

2.4 Synthesis of the Seven-Membered Ring

The next plan was to construct a seven-membered ring to obtain the tricyclic template. Examples of diversity-oriented synthesis of polycyclic derivatives having medium sized rings are not commonly found in the literature.[34] Medium sized rings are the most difficult rings to synthesize. This is mainly because of enthalpic (increased strain in the transition state) and entropic influences (probability of the chain ends meeting).

In this project, it was envisaged to obtain the tricyclic derivative by an olefin ring-closing metathesis (RCM).[35] In solution, RCM has been extensively used to generate enone and enamide[36] moieties. As mentioned in the

introduction, the presence of the enamide functionality was designed into the template.

In the ring-closing metathesis reaction, dienes are converted to cyclic alkene structures in the presence of a metal carbene complex. Different catalysts can be used. Because of their versatility and high reactivity, Schrock's molybdenum catalyst **89** and Grubbs' ruthenium complexes **90** and **91** (*Figure 14*) are mainly used to perform this type of reaction. Grubbs' catalysts **90** and **91** are usually preferred due to their stability to air, moisture and other reaction impurities.[37] Schrock's complex **89** has the major disadvantage of being particularly air- and moisture-sensitive.

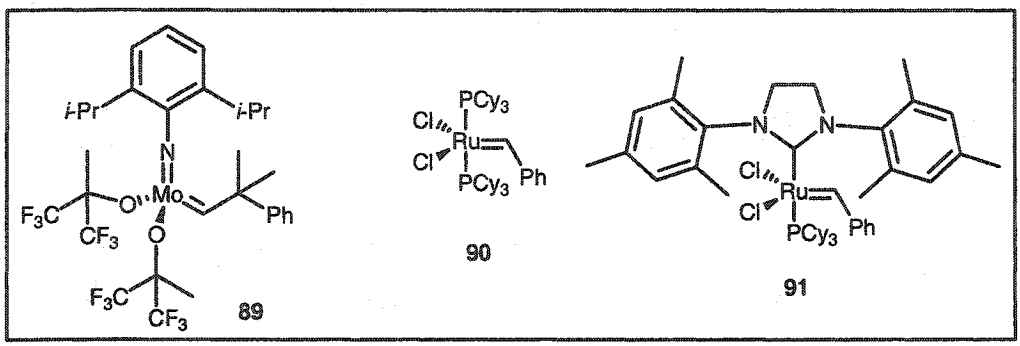
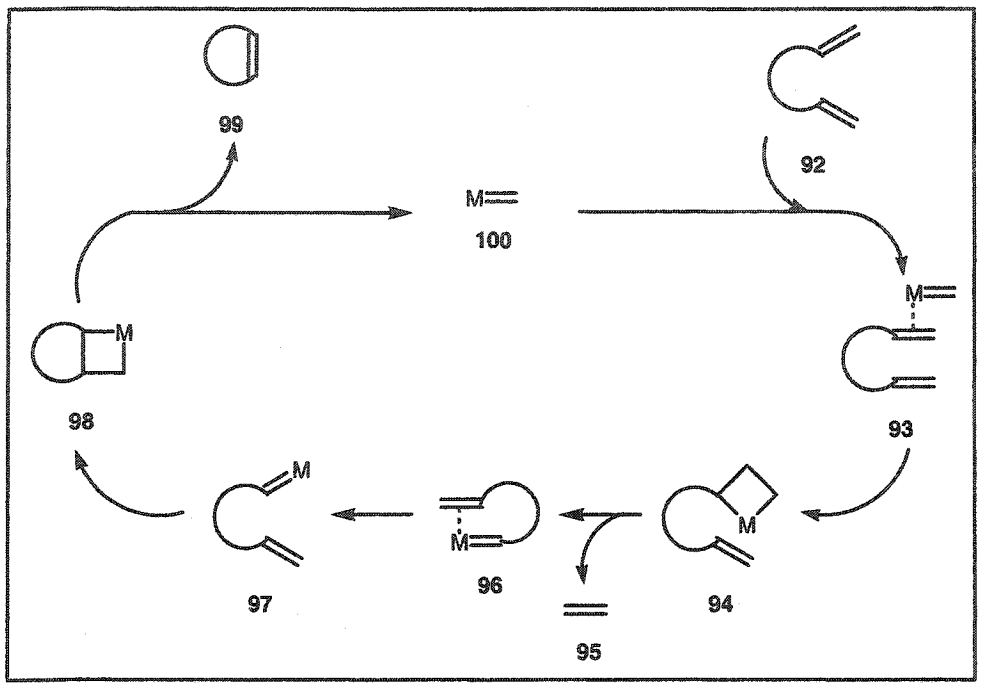


Figure 14. Catalysts used for olefin ring-closing metathesis.

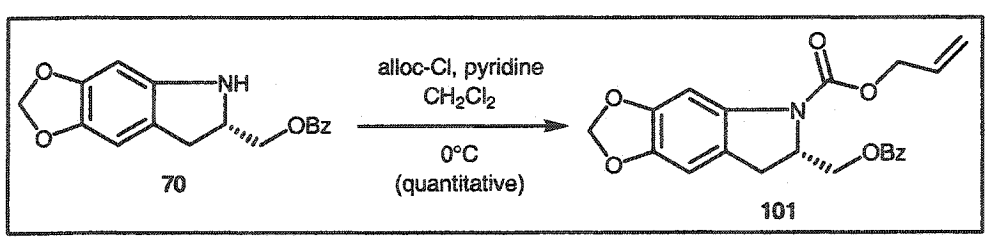
Scheme 22 shows a simplified description of the ring-closing metathesis mechanism.[38] The first step involves the formation of the metallacyclobutane **94** via the π-complex (**93**) formed by a double bond of starting diene **92** and the catalyst **100** which is believed to be the catalytically active complex.[39] Then, [2+2] cycloreversion of **94** leads to carbene complex **97** and the expulsion of volatile ethylene **95** which is the driving force in this retro [2+2] cyclization. First postulated as an intermediate by Grubbs, formation of the π-complex **96** was finally confirmed by X-ray structural analysis.[40] Intramolecular [2+2] cycloaddition of **97** leads to the intermediate **98**. The catalytic cycle is closed upon the release of the product **99**.



Scheme 22. Mechanism of olefin ring-closing metathesis.

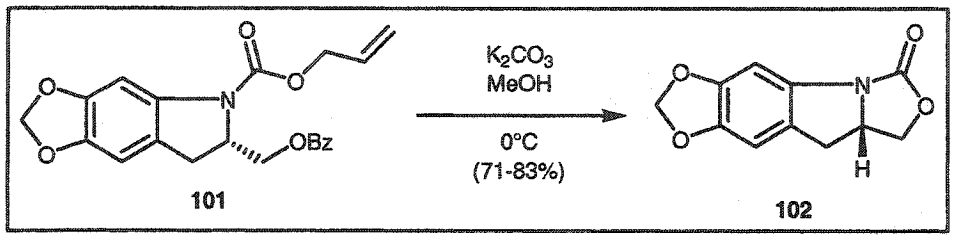
In this cyclization, for entropic reasons, the equilibrium of the reaction is shifted towards the products and the removal of the volatile ethylene drives the equilibrium further in the same direction.

The precursor **109** (see *Scheme 30*) needed to be synthesized in order to perform the RCM reaction with the indoline building block. Coming back to compound **70**, the secondary amino group was protected with allyl chloroformate. The reaction, carried out in dichloromethane with pyridine at 0°C, was very fast (completed within 10 minutes) and led to compound **101** in quantitative yields (*Scheme 23*). The formation of the product was confirmed by the appearance of the three alkene hydrogens [δ 5.98 ppm (broad s, 1H), 5.36 ppm (d, J = 16.9 Hz, 1H) and 5.26 ppm (d, J = 10.1 Hz, 1H)] in the ^{1}H NMR spectrum.



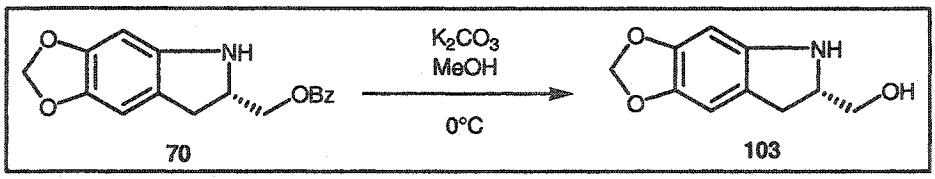
Scheme 23. Protection of the amino group with allyl chloroformate.

The next step involved the removal of the benzoyl protecting group to release the primary alcohol. The hydrolysis took place in methanol with potassium carbonate and the only product isolated was the unexpected cyclic derivative **102** (*Scheme 24*). ^{1}H NMR as well as 2D NMR experiments confirmed the formation of this tetracyclic compound.



Scheme 24. Formation of compound **102** upon hydrolysis.

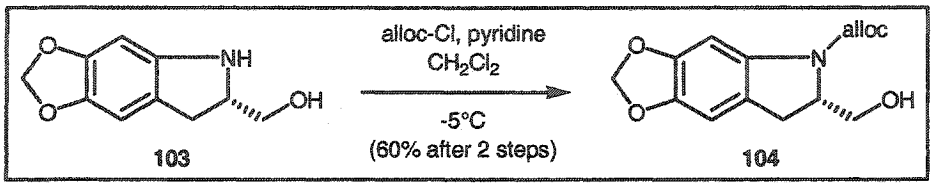
The strategy had to be changed once again. This time, hydrolysis had to be performed before protecting the amino group. Compound **70** was subjected to the same hydrolysis conditions and afforded the cyclic amino alcohol **103** (*Scheme 25*). This compound was not purified because of its polarity and was used as a crude product to continue the synthesis.



Scheme 25. Formation of the cyclic amino alcohol.

The crude mixture **103** was treated with allyl chloroformate and pyridine in dichloromethane at –5°C for 30 minutes (*Scheme 26*). Compound **104** was isolated in a 60% yield (in two steps from **70**). Some diprotected product was seen by TLC and mass spectrometry (M+1: 362.1), but only in small amount. The formation of compound **104** was confirmed by ^{1}H NMR. The presence of the protecting group was characterized by the appearance of four signals in the ^{1}H NMR spectrum [δ 6.03 ppm (m, 1H), 5.41 ppm (d, J = 17.1 Hz, 1H), 5.31 ppm (d, J = 10.4 Hz, 1H) and 4.77 ppm (broad s, 2H)]. At this point, enough material was

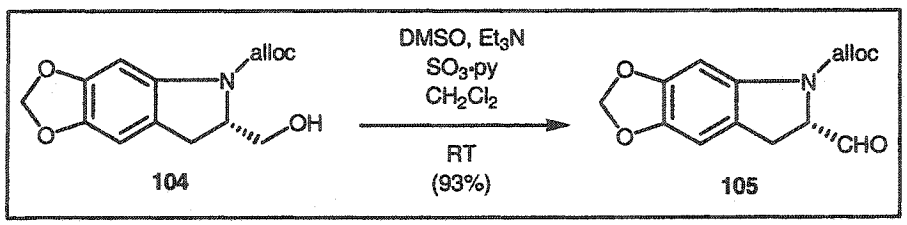
available to carry on the synthesis. Some improvements could have been tried, for example, lowering the temperature and/or changing the base, but they were not necessary at this point.



Scheme 26. Generation of the alloc-protected indoline moiety.

Several oxidation conditions could have been used to generate the aldehyde.[41] In this project, the use of an activated dimethyl sulfoxide reagent with the sulfur trioxide/pyridine complex was utilized.[42] The combination of these reagents in the presence of triethylamine generates a complex that rapidly oxidizes primary and secondary alcohols to respectively aldehydes and ketones in good yields at room temperature.

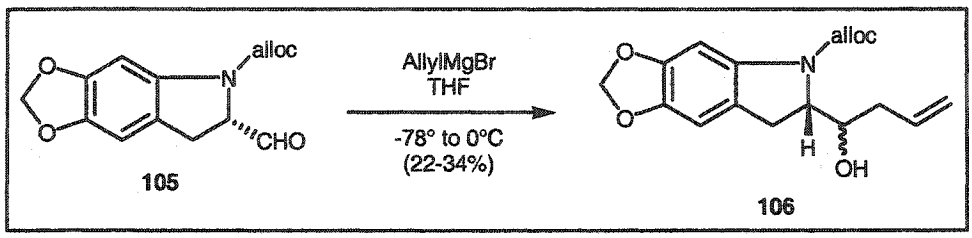
The experimental conditions for oxidation found in the total synthesis of bafilomycin A_1 by Hanessian *et al.* were used to generate aldehyde **105** from alcohol **104** (*Scheme 27*).[43] The reaction was complete after two hours at room temperature generating the aldehyde **105** in a 93% yield. The oxidation product seemed to be relatively stable. The formation of the aldehyde functionality was confirmed by the appearance of a singlet at 9.67 ppm integrating for one proton in the ^{1}H NMR spectrum.



Scheme 27. Oxidation with dimethyl sulfoxide and sulfur trioxide/pyridine complex.

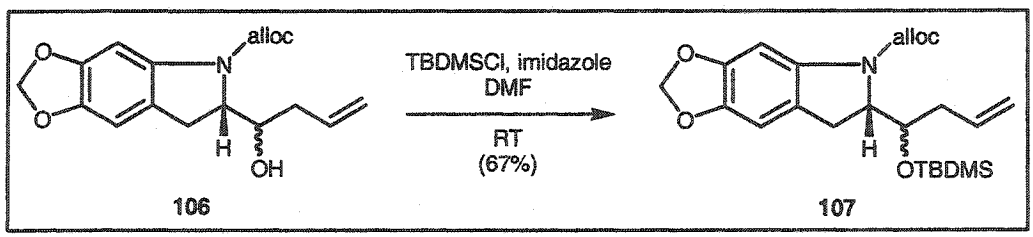
The allylation reaction was the next step. Unfortunately, it turned out that the reaction was low yielding. Allylmagnesium bromide was used in THF at low temperature to generate compound **106** from the aldehyde (*Scheme 28*). Recovering the starting material was not easy, as sometimes the aldehyde would

decompose on the column if the purification took too long. Anywhere from 28 to 59% of starting material could be isolated from the crude mixture. The yield of the allylation reaction could range between 22 and 34%. At that point, it was not possible to say if this step was stereoselective. However, only one new rounded spot was noticed on TLC, so one could speculate that only one product was generated. Of course, it is possible that the Rf values of both isomers are the same. ^{1}H NMR confirmed the formation of the allylic alcohol. The alkene protons appeared as two new doublets of doublets at 5.15 ppm (J = 3.0, 1.1 Hz) and 5.12 ppm (J = 10.7, 1.1 Hz) and as a broad singlet at 5.84 ppm integrating for one proton each.



Scheme 28. Allylation reaction using a Grignard reagent.

The new OH group was protected as a TBDMS ether (*Scheme 29*). The reaction could not be driven to completion but it was possible to recover the starting material. The presence of the protecting group on the hydroxyl was confirmed by the appearance of three singlets at 0.92 ppm (9H), 0.10 ppm (3H) and 0.07 ppm (3H) in the ^{1}H NMR spectrum.

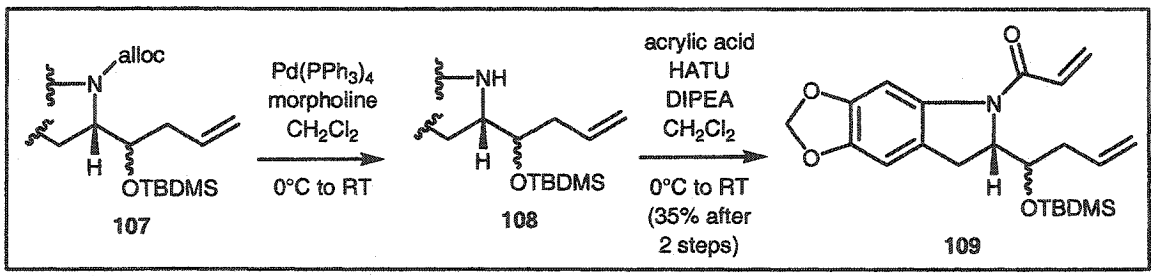


Scheme 29. TBDMS ether formation.

The remaining steps to reach the seven-membered ring were performed only once. The amount of available material was now very small and the stability of these new compounds was unknown, therefore no chances were taken to lose

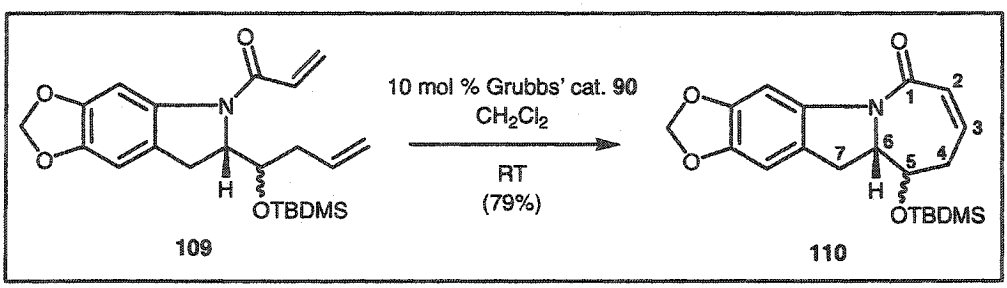
material. No NMR analyses were performed on the intermediates but the formation of the products was followed by mass spectrometry.

The next step in the strategy involved the removal of the allyloxycarbonyl (alloc) protecting group. To achieve this, palladium (Pd^0) was utilized with morpholine in dichloromethane (*Scheme 30*). The resulting crude mixture was subjected to an acrylation reaction. A coupling reaction was chosen here, reacting the amine with acrylic acid, HATU, and DIPEA in dichloromethane. Compound **109** was obtained in a 35% yield after two steps (see *Scheme 30*). This low yield may be due to the fact that a crude mixture was used to perform the acid coupling or that the coupling reaction was not a good choice. The use of acryloyl chloride, a more reactive coupling reagent, was kept in mind as an alternative method.



Scheme 30. Preparation of the RCM precursor.

The last reaction to be tested with the model system was the olefin ring-closing metathesis. The reaction was tried with the first generation Grubbs' catalyst **90** (see *Figure 14*) in dichloromethane at room temperature (*Scheme 31*). After stirring for only five minutes, the appearance of a strong new spot could be seen on the TLC. Only one spot, which was lower than the starting material, was present on TLC after 40 minutes.



Scheme 31. RCM reaction to generate the seven-membered ring template.

Mass spectrometry revealed that the resulting product had the same mass as the desired cyclic derivative **110**. In the ^{1}H NMR spectrum (*Figure 15*), only two alkene signals could be seen as a multiplet between 6.28-6.22 ppm and as a doublet of doublets at 6.11 ppm (J = 11.6, 2.1 Hz). These two signals corresponded to the protons at C_2 and C_3. The neighbouring hydrogens on C_4 appeared as two signals at 2.62 ppm (ddd, J = 15.8, 6.8, 6.6 Hz) and at 2.36 ppm (dddd, J = 15.8, 6.8, 6.6, 2.1 Hz) integrating for one proton each. The COSY 2D NMR spectrum showed coupling between H_2, H_3 and the two non-equivalent hydrogens of C_4. These in turn showed coupling for the signal at 4.18 ppm (ddd, J = 6.6, 6.6, 2.5 Hz) corresponding to the hydrogen of C_5. The CH_2 at C_7 was seen as two doublets of doublets at 3.30 ppm (J = 15.7, 10.3 Hz) and 3.01 ppm (J = 15.7, 2.9 Hz), both integrating for one hydrogen each. The COSY 2D NMR experiment showed that the CH_2's protons exhibited coupling to themselves as well as to the signal at 4.33 ppm. This was the proton at C_6, which in turn showed coupling to H_5. Now that the compound was confirmed to be cyclic, it was much easier to determine the configuration at the stereogenic centre (C_5) by extensive NMR studies.

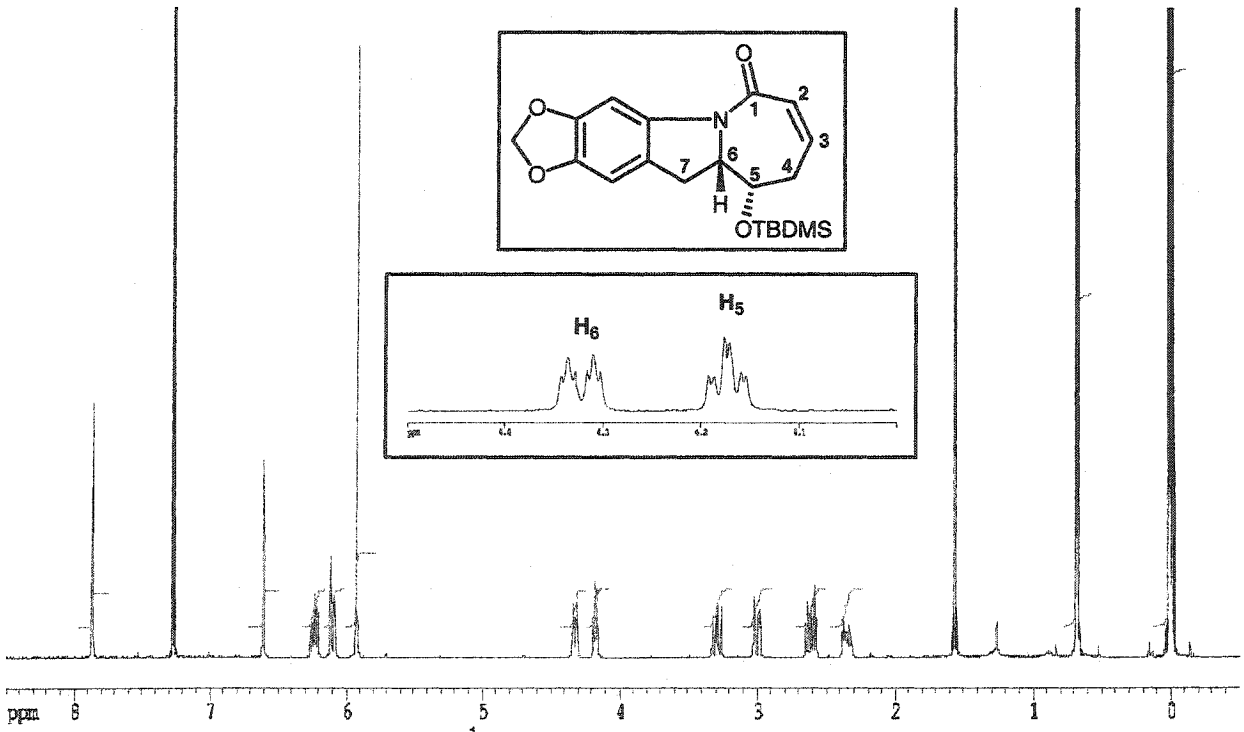


Figure 15. ^{1}H NMR spectrum of compound **110**.

An expansion of the chemical shifts of the hydrogens at C_5 and C_6 is shown in the box of *Figure 15.* The coupling constant between these two protons was found to be approximately 2.5 Hz. This value typically corresponds to a *cis* relationship between H_5 and H_6.[44] If the relationship between H_5 and H_6 was *trans*, a larger coupling constant would have been expected between these two protons (typically 8-13 Hz).

To help confirm the stereochemistry of the compound, a nOe experiment was performed. The nOe difference spectrum is shown in *Figure 16.* After the irradiation of the proton at C_6, a very strong positive nOe was observed for the proton H_5 (4.18 ppm) as well as for one hydrogen of the CH_2 at C_7 (3.30 ppm). A *trans* relationship between H_5 and H_6 would have shown a less intense nOe. This intensity is related to the proximal orientation of the protons involved. In the *cis* product, a distance of 2.39 Å between H_5 and H_6 was obtained by simulated annealing using HyperChem, whereas a value of 3.09 Å was obtained for the *trans* adduct (*Figure 17*). Stronger positive nOe is generally observed when the two protons are in close proximity.

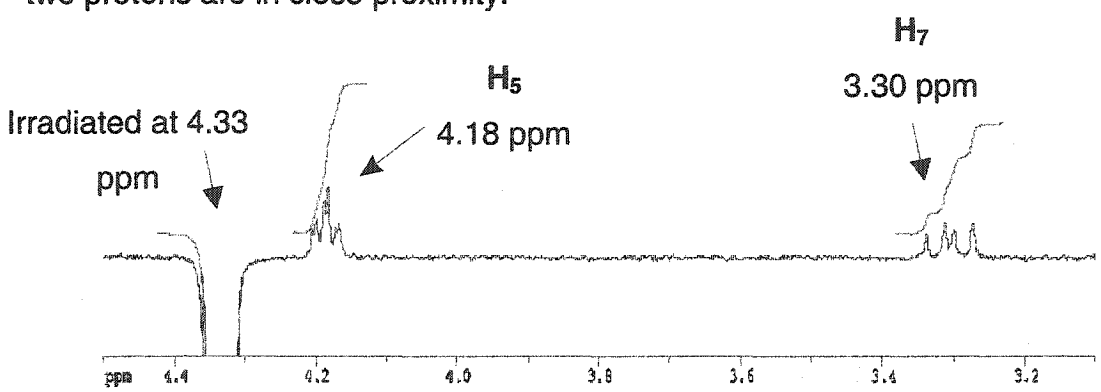


Figure 16. nOe difference spectrum of compound **110**.

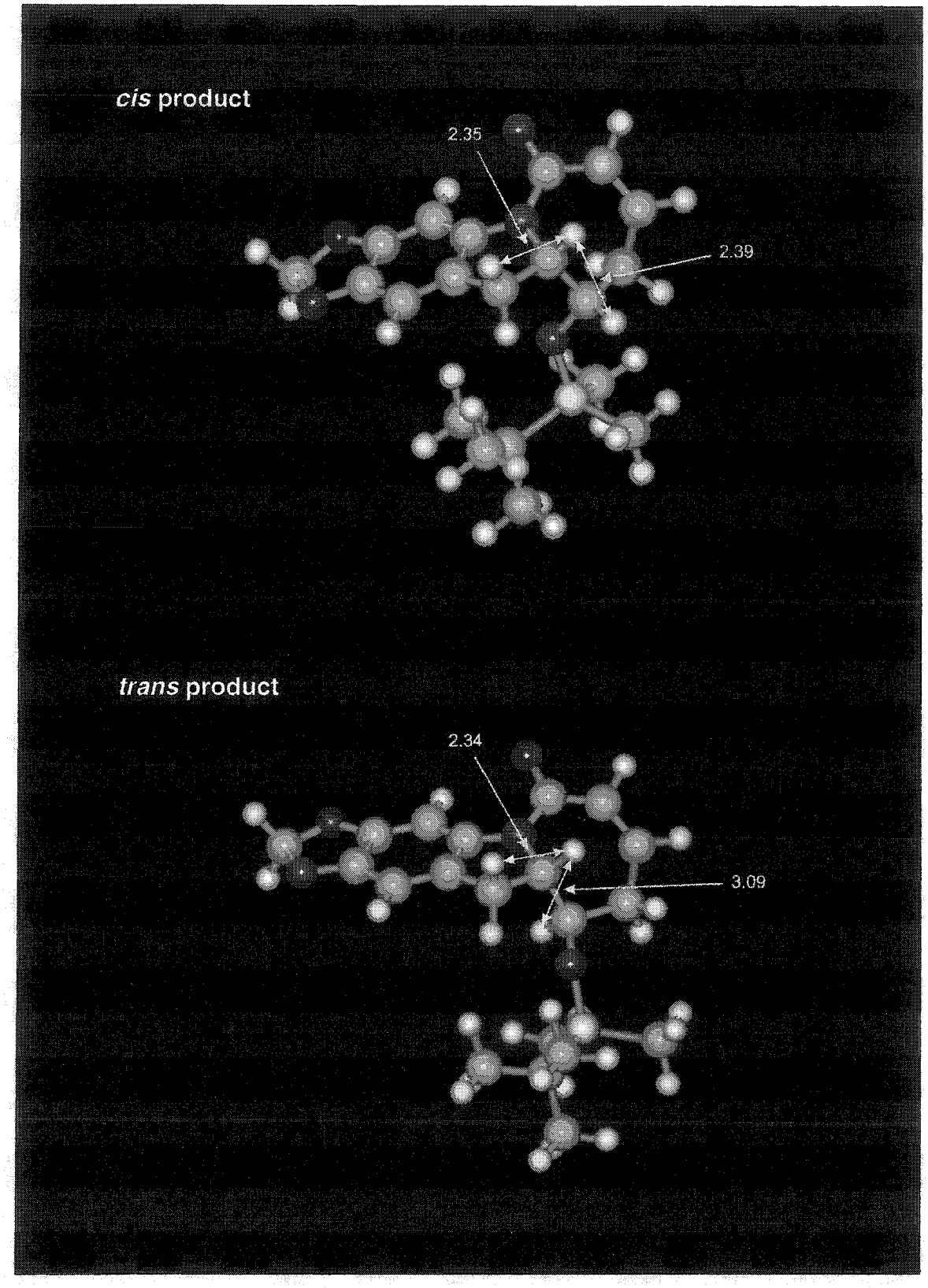


Figure 17. 3D structures of *cis* and *trans* products.

With these results, it was then possible to assign the configuration at the C_5 stereogenic centre. Moreover, with the help of 2D NMR experiments, it was possible to assign each peak of the ^{1}H NMR spectrum to the correct hydrogen in the molecule (*Figure 18*).

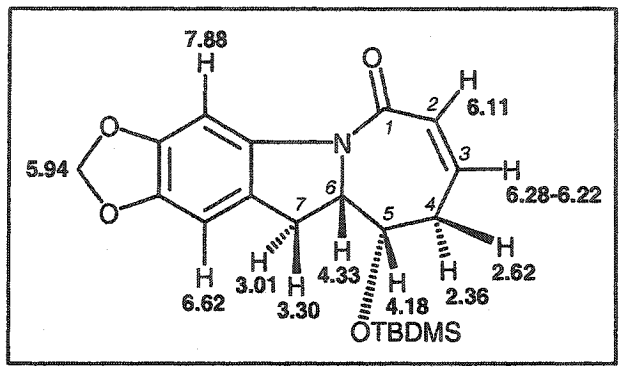


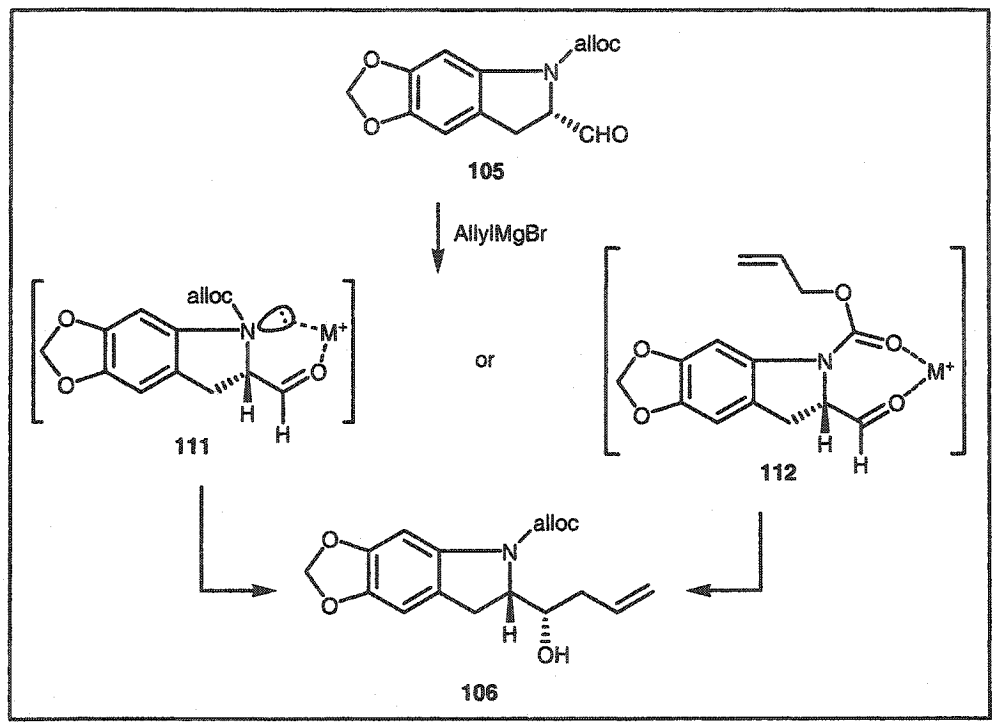
Figure 18. ^{1}H NMR chemical shifts of compound **110**.

2.5 Conclusions

The goals of the model study were successfully achieved. The synthesis of the indoline moiety was possible, but not without some strategic changes. The formation of the seven-membered ring template was also obtained in a good yield using the olefin ring-closing metathesis strategy.

It was now time to try these reactions with a compound possessing a hydroxyl group on the aromatic ring so that it could be anchored onto a solid support. Before undertaking the solid phase chemistry project, the entire sequence needed to be performed in solution. Also, some specific conditions needed to be evaluated. For example, the enantiomeric excess (*ee*) of the dihydroxylation reaction needed to be verified and it was crucial to increase the yield of the allylation reaction. It was highly probable that the allylation reaction was stereoselective since only one cyclic product was formed. With these results, a model could be put forward to explain the outcome of the allylation reaction. A chelation model best explains why this reaction generated the allylic alcohol **106** (*Scheme 32*). Chelation could be possible between the oxygen of the aldehyde and the lone pair of electrons on the nitrogen atom (**111**). It could

also be derived from the chelation between the oxygen of the alloc group and the oxygen of the aldehyde (**112**). In either case, attack of the allyl reagent would come from the less hindered side of the molecule. By looking at the structure, it is easy to imagine that the attack would come from the β-face, on the same side as the hydrogen to generate compound **106**.



Scheme 32. Proposed chelation model for the allylation reaction.

CHAPTER 3: SEVEN-MEMBERED RING SCAFFOLD AND DIVERSITY-ORIENTED SYNTHESES

3.1 INTRODUCTION

Now that the strategy was established with the model system, the next challenge was to reproduce the sequence with a molecule that could be used in solid phase synthesis. A hydroxyl group needed to be present on the benzene ring in order to anchor the scaffold onto a solid support.

One of the main goals of this project involved the generation of the seven-membered ring on solid phase. This would open the door to the generation of combinatorial libraries. The use of solid phase synthesis would facilitate the access to a variety of different compounds, which could then be used as chemical probes in understanding biological processes.

As mentioned earlier, the formation of medium-sized rings is a difficult task. Moreover, the synthesis of these types of rings on solid support is not common.[45] In solution, ring-closing metathesis (RCM) has been extensively used in the formation of enamide moieties, and several examples in the literature validate this approach for exploration on solid phase. Thus, allylation followed by olefin ring-closing metathesis (RCM) could be considered as a versatile approach in the synthesis of the indoline-based tricyclic derivative. Although RCM is acceptable in solution synthesis, there is a lack of good examples that illustrate the utility of this approach in the synthesis of seven-membered ring polycyclic derivatives on solid phase. An attractive feature of this strategy is that the chiral derivative, having an enamide moiety, might further be subjected to asymmetric diversity-based reactions.

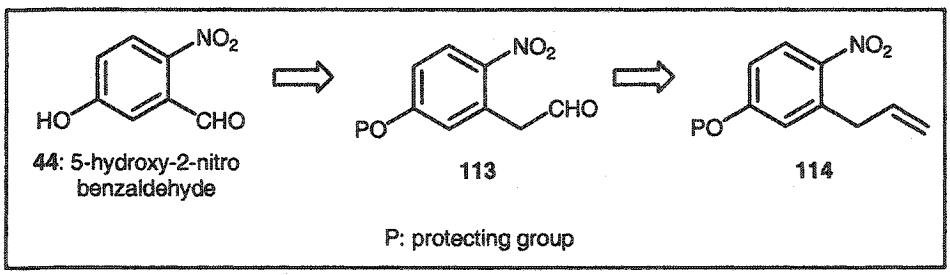
In this project, the synthesis of the entire sequence to reach the seven-membered ring template was achieved. Also, some attempts were made to obtain the tricyclic derivative on solid phase. Finally, several diversity-oriented syntheses of the polycyclic derivative were attempted in solution, including inter-

and intramolecular Michael-type addition reactions and intramolecular free radical chemistry.

3.2 Forward Synthetic Analysis to Obtain the Seven-Membered Ring Scaffold

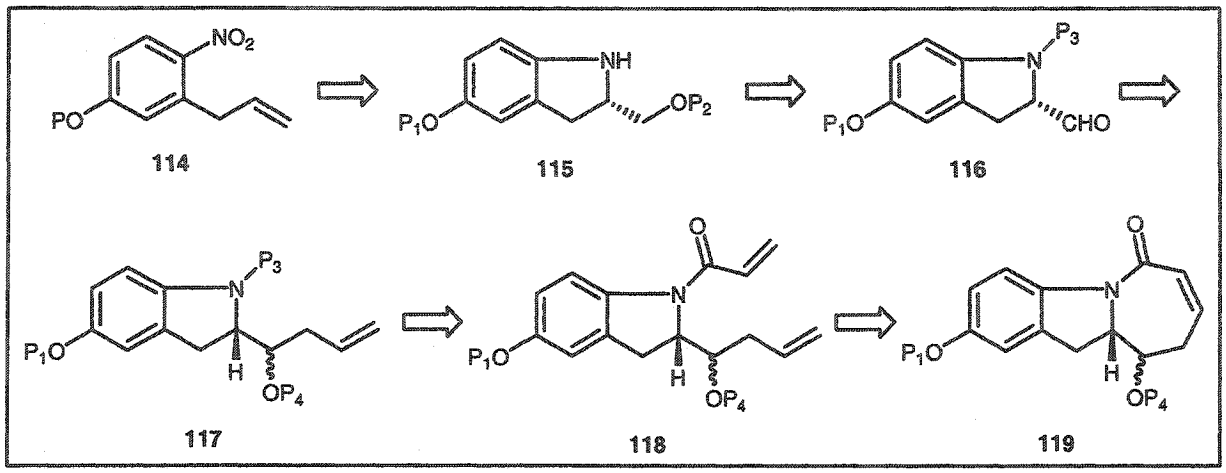
The strategy had to be slightly modified. The starting material was different than safrole, which was used for the model study. 5-Hydroxy-2-nitrobenzaldehyde **44** appeared to be an adequate starting material.

Using the aldehyde functional group of the starting material, it was easy to envisage that a homologation reaction could generate the olefin **114** (*Scheme 33*). Only a few steps would be required to obtain a similar starting material utilized in the model study.



Scheme 33. Forward synthetic analysis to reach **114**.

The rest of the sequence could be identical as the model system. The leaving group strategy could be used to synthesize the five-membered ring **115** (*Scheme 34*). Aldehyde **116** could be utilized to generate the allylic alcohol **117** which would than be transformed into the RCM precursor (**118**). Finally, the seven-membered ring **119** could be generated by using the olefin ring-closing metathesis strategy.



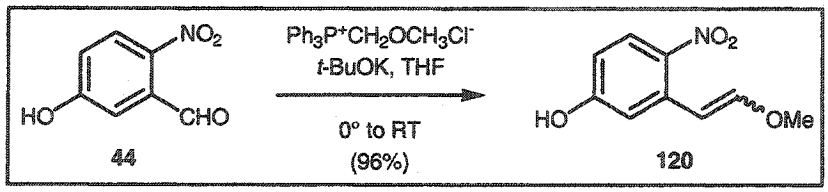
Scheme 34. Forward synthetic analysis to reach the seven-membered ring scaffold.

3.3 Synthesis of the Indoline Template

The first step of this sequence was the protection of the phenolic hydroxyl group of the starting material **44**. The protecting group chosen had to be stable under basic conditions because, if recalling in *Chapter 2*, the benzoyl group was used to protect a primary alcohol and was removed under basic conditions with potassium carbonate in methanol. Also, stability to palladium chemistry was necessary due to its use in the removal of the allyloxycarbonyl group. Moreover, it needed to be stable to hydrogenation conditions because this was used to reduce the nitro to the amino functionality. As a result of these requirements, a benzyl protecting group could not be employed in this synthesis. The best choice was a group that can be removed under acidic conditions. 2-Methoxyethoxymethyl chloride (MEMCl) was chosen as the reagent to protect the phenolic group.

Unfortunately, the presence of the protecting group on the phenolic OH hindered the homologation sequence, as it was impossible to obtain decent yields. It turned out that homologation of compound **44** worked perfectly with the free phenolic hydroxyl group.[46] Consequently, the first step of the synthesis was the formation of the enol ether **120** in a 96% yield (*Scheme 35*). The Wittig reagent was made *in situ* from a chloride salt and potassium *tert*-butoxide. An

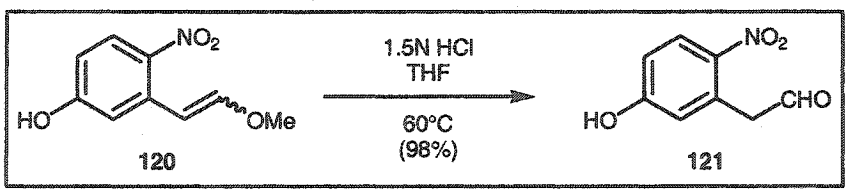
excess amount of base was used to generate the potassium salt of the phenolic OH. A mixture of *cis* and *trans* enol ether was formed. Their separation was difficult, but not required because both compounds could be used for the next reaction. Regardless, enough pure material of each one was isolated for NMR studies.



Scheme 35. Enol ether formation.

^{1}H NMR confirmed the formation of both isomers. The methoxy protons appeared at 3.77 ppm for the *trans* product and at 3.83 ppm for the *cis* adduct. The values of the coupling constant of the alkene protons were used to establish the configuration at the double bond: J = 12.8 Hz for *trans* and J = 7.3 Hz for *cis*.

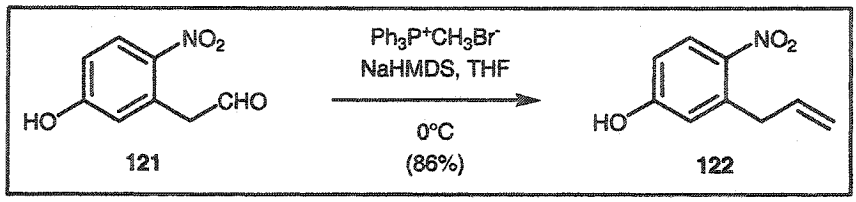
A simple hydrolysis of compound **120** generated the aldehyde **121** in a very high yield (*Scheme 36*). No purification of this product was performed, as the aldehyde decomposed when subjected to silica gel chromatography. ^{1}H NMR spectrum of compound **121** was very clean showing a singlet integrating for one proton at 9.79 ppm (aldehyde) and a multiplet between 4.16-4.13 ppm integrating for two protons (methylene group). In the ^{13}C NMR spectrum, a signal at 198.0 ppm was indicative of the aldehyde functionality. The IR spectrum also showed a C=O absorption signal at 1705 cm^{-1}.



Scheme 36. Hydrolysis of the enol ether.

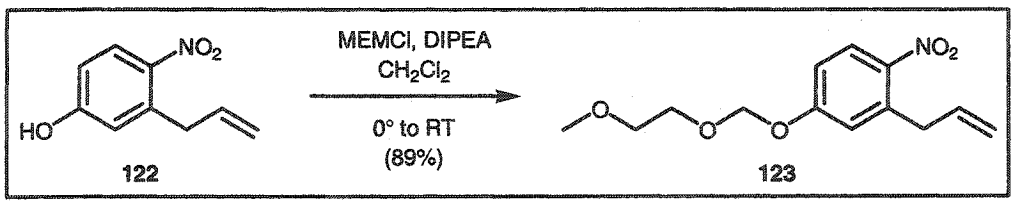
The next step was again a Wittig reaction. Once more, the reagent was generated *in situ* using a bromide salt this time and sodium hexamethyldisylazide as the base. An excess amount of the salt was used to avoid problems with the

aldehyde. An aldol condensation could have been possible between two molecules if some base was present in solution when the aldehyde was added, as the acidity of the benzylic protons favors the formation of an enolate ion.[47] Compound **122** was isolated in a 86% yield and its formation was confirmed by ^{1}H NMR (*Scheme 37*).



Scheme 37. End of the homologation sequence.

At this point, the stable derivative **122** was ready to be protected. The MEMCl reagent, typically used with DIPEA in dichloromethane, was utilized to convert the alcohol into compound **123** (*Scheme 38*). The product was isolated in good yields and four characteristic peaks of the MEM protecting group appeared in the ^{1}H NMR spectrum, which confirmed its formation. These signals corresponded to the methoxy group at 3.39 ppm (3H) and three methylenes integrating for two hydrogens each between 3.85-3.83 ppm, at 3.74 ppm and between 3.58-3.56 ppm.



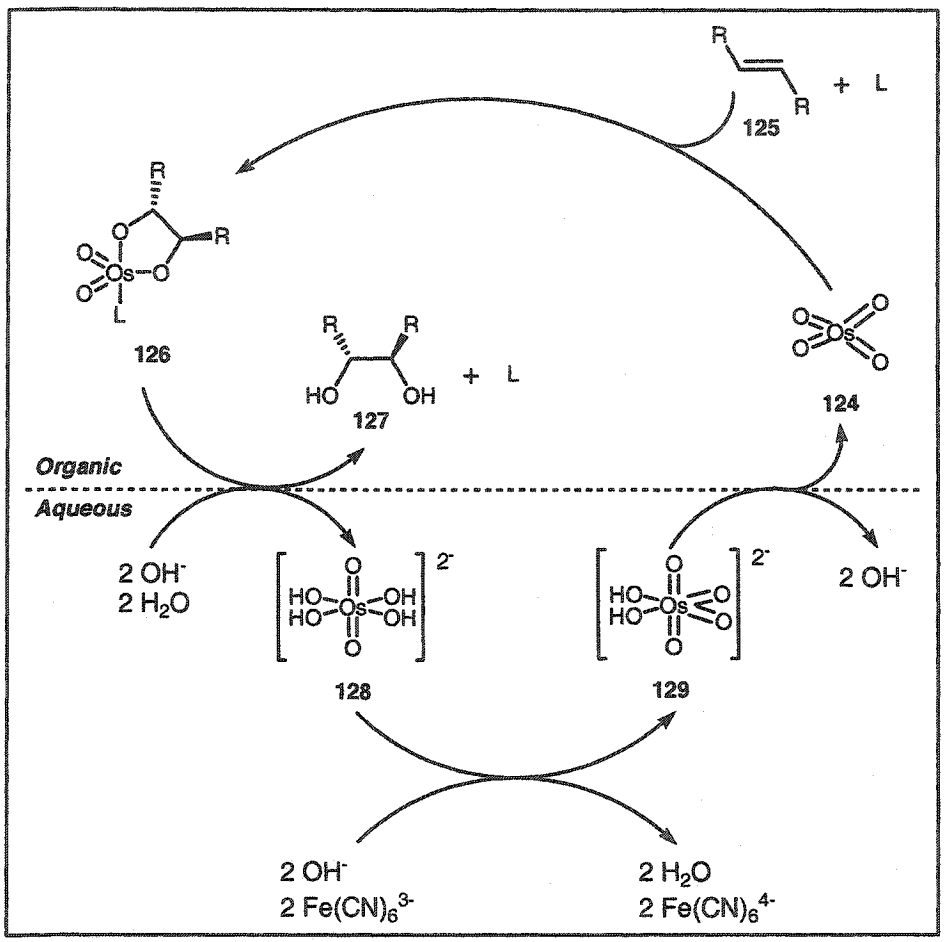
Scheme 38. Protection of the phenolic OH.

3.3.1 Catalytic Asymmetric Dihydroxylation Reaction

The next step in the sequence was the introduction of a diol to further functionalize the molecule. This was achieved by using the catalytic asymmetric dihydroxylation reaction (AD) developed by K. Barry Sharpless.[26]

In this asymmetric osmium mediated dihydroxylation of olefins, modified cinchona alkaloids, dihydroquinidine (DHQD) and dihydroquinine (DHQ), are

used as chiral ligands (L) for osmium. The reaction is performed under two phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant (*Scheme 39*).[48] Under these conditions, only one oxidant is present in the organic layer as OsO_4 (**124**) resulting in high enantioselectivities.



Scheme 39. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant.

Now available to perform the AD reaction is a premix containing all reagents in which $K_2OsO_2(OH)_4$ is used as a source of nonvolatile osmium mixed with an inorganic co-oxidant [$K_3Fe(CN)_6$]. Two types are available, AD-mix-α (**130**) containing $(DHQ)_2PHAL$ ligand and AD-mix-β (**131**) in which $(DHQD)_2PHAL$ ligand is present (*Figure 19*).

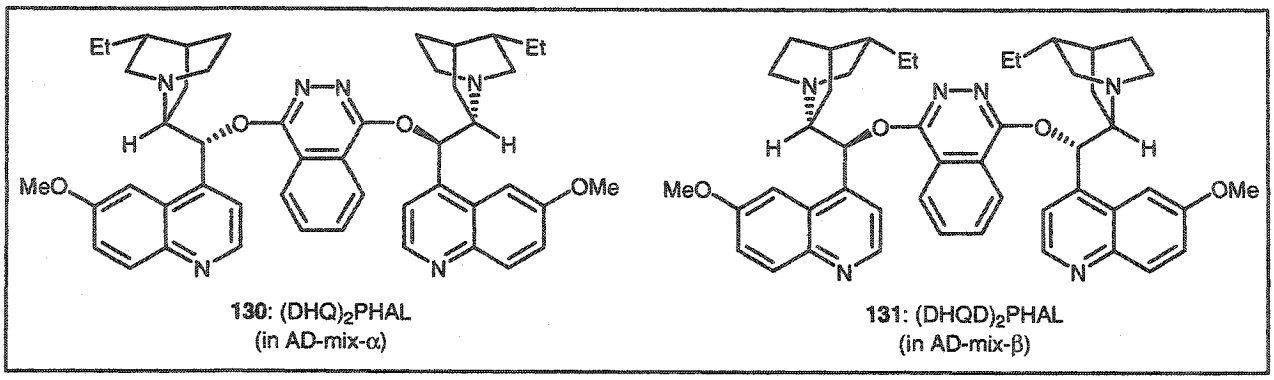
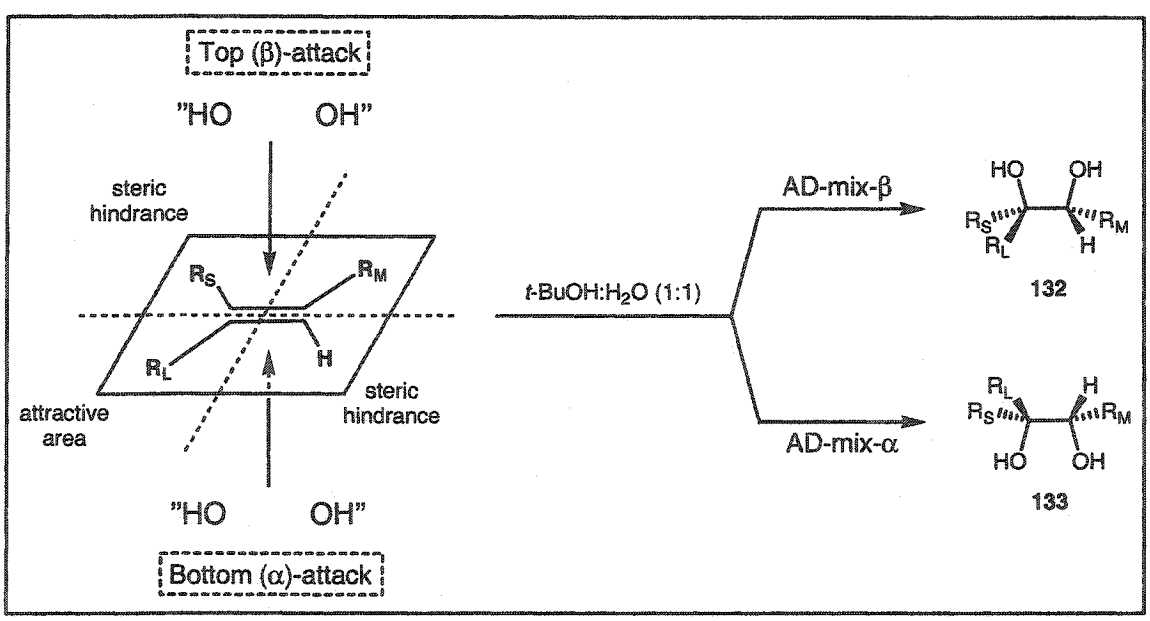


Figure 19. Ligands used in AD-mix-α and AD-mix-β.

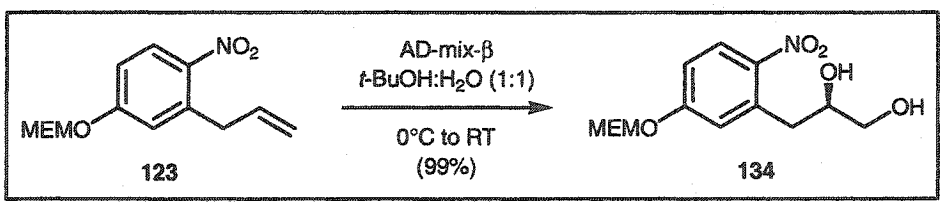
Literature reports that the origin of the enantioselectivity in the AD reaction was discovered by structure-activity studies. These studies pointed out the importance of an enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The geometry of the binding pocket tolerates one large substituents in the *meta* position of the substrate's phenyl ring. However, a second large *meta* substituent seriously interferes with the perpendicular wall of the binding pocket, thereby disrupting it and leading to lower selectivity. These observations led to a diagram for predicting the enantiofacial selectivity in the reaction (*Scheme 40*).



Scheme 40. Diagram allowing the prediction of the face selectivity in the AD of olefins.

In the diagram, the steric barrier spaces can accommodate only the smallest substituents (R_S and H) of the olefin, whereas R_M can be of moderate size. R_L is in an attractive area, well suited to accommodate flat aromatic substituents. An olefin positioned according to these constraints will be attacked either from the top face (β-face) by dihydroquinidine (DHQD) derivatives or from the bottom face (α-face) by dihydroquinine (DHQ) ligands.

In light of this, the Sharpless catalytic asymmetric dihydroxylation was performed with olefin **123** using AD-mix-β (*Scheme 41*). The reaction gave very high yields and spectral data, both NMR and IR, supported the formation of the desired product. In the ^{1}H NMR spectrum, the alkene protons at 5.99 ppm (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.14 ppm (dd, J = 10.2, 1.3 Hz, 1H) and 5.12 ppm (dd, J = 16.8, 1.3 Hz, 1H) disappeared and gave rise to two alcohol signals at 2.69 ppm (d, J = 3.9 Hz, 1H) and 2.29 ppm (broad s, 1H). The diol **134** was also identified by the appearance of a very pronounced O-H stretch at 3418 cm^{-1} in the IR spectrum.



123 **134**

Scheme 41. AD reaction with olefin **123**.

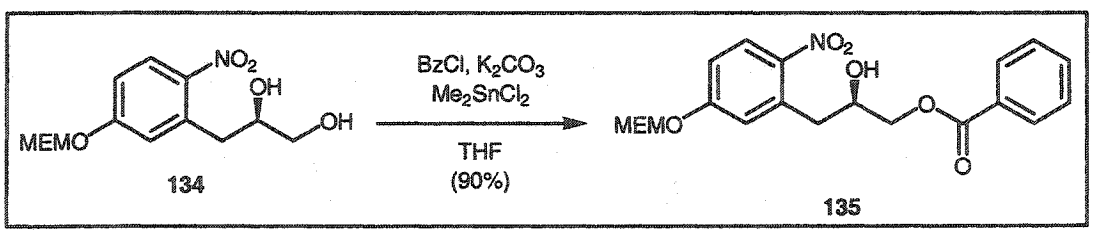
In order to evaluate the enantiomeric excess (*ee*) of the dihydroxylation reaction, the other enantiomer was prepared from the same olefin (**123**) but using AD-mix-α this time. A similar yield was obtained and the ^{1}H NMR spectrum of the diol was compared to compound **134**. Unfortunately but not that surprising, both enantiomers were too polar to be separated by the chiral column used in the high performance liquid chromatography (HPLC). Therefore, the sequence was completed up to the five-membered ring template with both alcohols. At each step, both enantiomers were treated under the same reaction conditions.

3.3.2 Formation of the Five-Membered Ring

The next step involved the protection of the primary alcohol as a benzoyl derivative. The diol **134** was treated with benzoyl chloride (BzCl) and pyridine (1 equivalent) in dichloromethane at low temperature, and afforded **135** in a 89% yield at best. Only up to 8% of the dibenzoyl product was isolated in these conditions. Unfortunately, this procedure was not easily reproducible, as the yield was mainly varying between 50 and 79%. The use of DIPEA instead of pyridine did not help to obtain better yields.

A new method was found in the literature where diols were submitted to BzCl, potassium carbonate and dimethyltin dichloride in THF.[49] Under these conditions, chemo- and stereoselective monobenzoylation of 1,2-diols was possible. The reaction was catalyzed by the organotin compound.

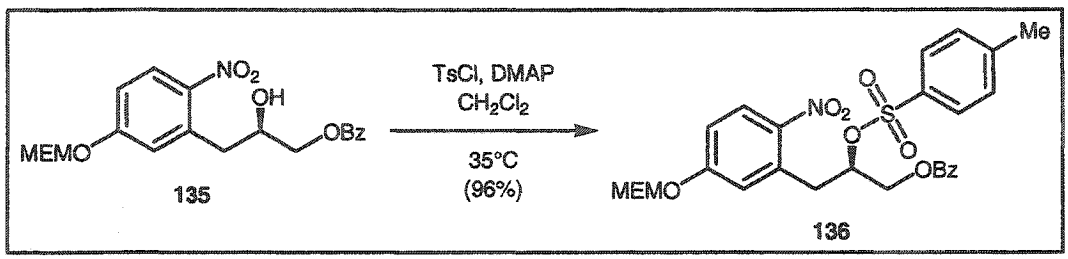
Subsequently, diol **134** was subjected to these benzoylation conditions and afforded the monobenzoyl derivative (**135**) in a 90% yield (*Scheme 42*). This time, the reaction was reproducible on a large scale (8.4 g) without any difficulties. Aromatic signals appeared as a doublet at 8.09 ppm (J = 7.3 Hz, 2H), as a triplet at 7.61 ppm (J = 7.4 Hz, 1H) and as a doublet of doublets at 7.48 ppm (J = 7.4, 7.3 Hz, 2H) in the ^{1}H NMR spectrum confirming the presence of the benzoyl group. As well, the appearance of a signal at 167.1 ppm in the ^{13}C NMR spectrum indicated the presence of a carbonyl ester functional group.



Scheme 42. Monobenzoylation catalyzed by dimethyltin dichloride.

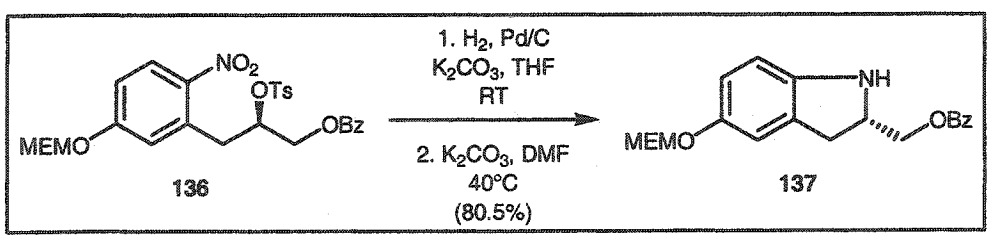
The tosylation reaction was performed under the same conditions as used in the model study. 1.5 equivalents of DMAP were used with TsCl in dichloromethane to generate compound **136** in a 96% yield (*Scheme 43*). The formation of the product was confirmed by the appearance of signals in the

aromatic region of the ^{1}H NMR spectrum and particularly by the appearance of the signal for the methyl protons at 2.35 ppm.



Scheme 43. Tosylation reaction.

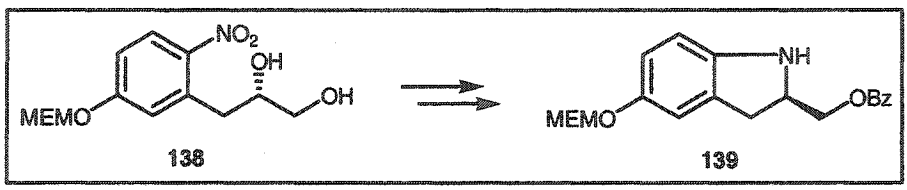
With this *O*-MEM system, the cyclization of the five-membered ring was carried out in two steps. First, compound **136** was subjected to hydrogenation conditions in order to reduce the nitro group into an amine (*Scheme 44*). The amino derivative was not purified and was directly treated with potassium carbonate in DMF to achieve the displacement reaction. The indoline scaffold **137** was isolated in a better yield (80.5%) than with the model system (61%). NMR experiments were performed to confirm its formation. As observed in the model study, the signals of the tosyl group disappeared from the ^{1}H NMR spectrum. The hydrogen in the *ortho* position to the nitro functionality shifted upfield, now sitting next to the secondary amine. The IR spectrum established the presence of the amino group with absorption of the N-H stretching at 3363 cm^{-1}.



Scheme 44. Indoline scaffold synthesis.

3.3.3 Evaluation of the Enantiomeric Excess

As mentioned earlier, the other cyclic enantiomer **139** was genarated from the diol **138** (*Scheme 45*) in a similar manner as for synthesizing **137** from the diol **134**.



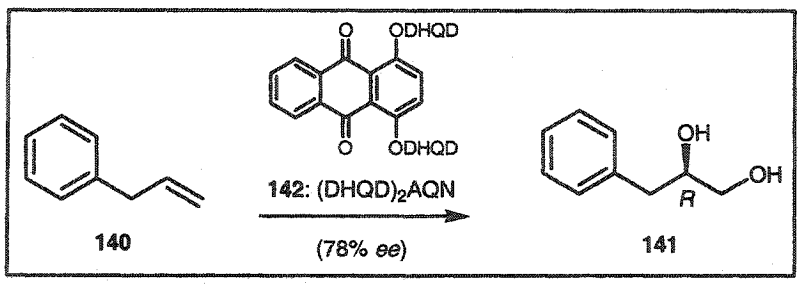
138 **139**

Scheme 45. Synthesis of the cyclic derivative **139**.

High performance liquid chromatography analyses (HPLC equipped with a chiral column) were performed to evaluate the enantiomeric excess (*ee*) of both indoline enantiomers.[50] Both compounds, in a ~1:1 mixture, were injected. A good separation between the two enantiomers was possible when a solution of 10% ethanol in hexane was used. When both compounds were injected separately, either as crude or as pure samples, unsatisfactory results came out. The values of the *ee*'s were calculated to be 17.2% (using the crude mixture) and 16.1% (using pure compound) for indoline **137**, and 9.1% (crude) and 9.6% (pure) for indoline **139**. Such low *ee*'s were very disappointing.

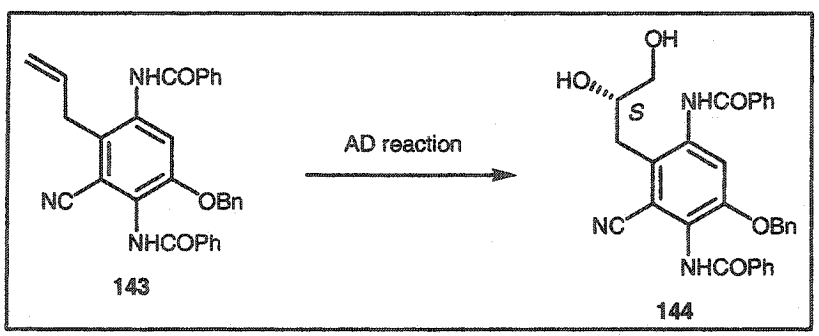
It was already mentioned earlier that because of the geometry of the binding pocket in the AD reaction, one large substituent in the *meta* position of the substrate's phenyl ring can be tolerated. If a second *meta* substituent is present, selectivity of the reaction could be lower. In this project, the long linear *meta* substituent present on the phenyl ring should cause no problem. However, a bulky substrate (NO_2) was occupying the *ortho* position. Was this substituent responsible for the low values of *ee* obtained? Maybe the nitro group seriously interfered with the proposed binding pocket, disrupting it and providing the low results. Also, other factors could be considered here. The olefin used in this synthesis was not a benzylic alkene like most of the examples found in the literature. The methylene group between the phenyl ring and the double bond may have also played a role in the low selectivity of the AD reaction.

An example of asymmetric dihydroxylation reaction with a similar compound (**140**) as in this project was found in the literature.[51] The authors reported a low 44% *ee* for the diol **141** obtained after subjecting the olefin **140** to $(DHQD)_2PHAL$ (see *Figure 19* for the structure of the ligand). The configuration of the alcohol obtained was reported to be *R* as predicted by the model in *Scheme 40*. An improvement in the value of the *ee* was observed when subjecting the alkene **140** to the anthraquinone ligand $(DHQD)_2AQN$ **142** (*Scheme 46*).



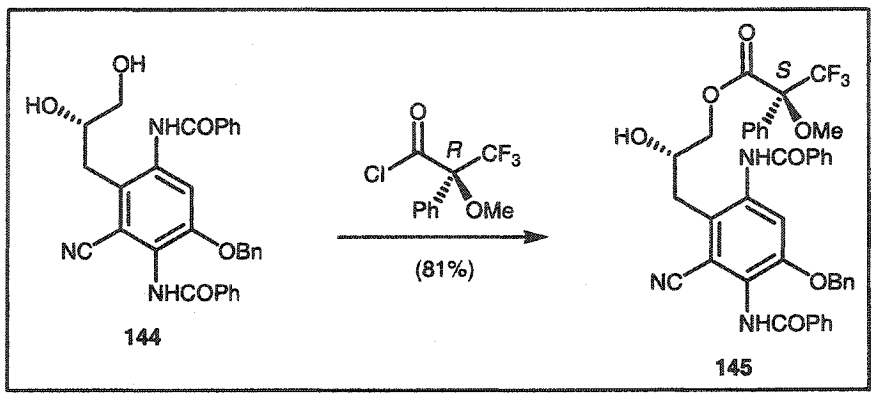
Scheme 46. AD reaction with $(DHQD)_2AQN$ ligand.

It could have been possible to try the AD reaction with this anthraquinone ligand. Another paper, however, was found in which the authors reported surprising conflicting results.[52] When they performed the AD reaction on compound **143** in their synthesis of (+)-duocarmycin A, the absolute configuration obtained was opposite to that predicted from established models (*Scheme 47*).



Scheme 47. AD reaction in the synthesis of (+)-duocarmycin A.

They tried a selection of ligands in different solvents, varying the equivalents of reagents used in the reaction, each time obtaining the opposite absolute configuration. A study of the solvent effect on the asymmetric dihydroxylation of **143** was performed and showed an important variation in both the yield and the value of the *ee*. The authors subjected the (*S*)-Mosher ester of the primary alcohol (**145**) of the major enantiomer, derived from the $(DHQD)_2PHAL$ catalyzed reaction, to X-ray structure analysis in order to confirm their results (*Scheme 48*).



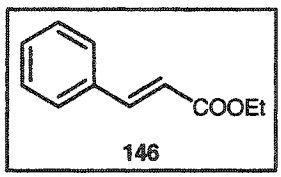
Scheme 48. Formation of the (*S*)-Mosher ester.

Similar observations were made by the authors with the *N-tert*-butyloxycarbonyl (*N*-Boc) derivative of compound **144**, indicating that the degree and sense of asymmetric induction in the AD reaction were not unique to the substrate bearing the *N*-benzoyl protecting group. Moreover, the same observations were made with a substrate containing a tertiary *N*-methylamide in place of the secondary amide of **144**. These results indicated that the potential hydrogen bonding capabilities of the secondary amide or carbamate were not responsible for the reversal in the enantioselectivity. They arrived at a very important conclusion. Such substrates may represent a more general class of olefins for which the AD enantioselectivity is reversed or more difficult to predict.

A similar conclusion could be reached based on the results of the AD attempts on **123** (see *Scheme 41*). Maybe this olefin represents another class of alkenes for which the prediction of the enantiofacial selectivity of the AD reaction

is difficult. To remedy to the low *ee* obtained in this project, a study similar to the one conducted in the article could have been done. This would involve evaluating the use of different ligands in different solvents, the synthesis of Mosher ester derivatives, as well as growing crystals to assign the absolute configuration by X-ray analysis. This investigation would be a project in itself. However, the importance of improving the *ee* warranted some efforts in finding a different strategy to reach the five-membered ring compound.

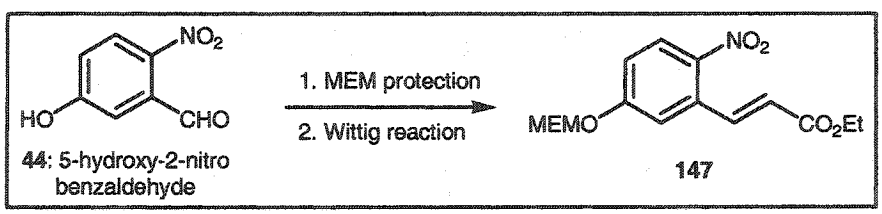
It is known that the asymmetric dihydroxylation with both AD-mix-α [$(DHQ)_2PHAL$] and AD-mix-β [$(DHQD)_2PHAL$] gives good enantiomeric excesses with compound **146**.[26a] Without any substituents on the phenyl ring, it is reasonable to see that there should be no problems in the enantioselectivity of the AD reaction.



146

It was shown that good *ee* (>90%) can be obtained when compound **147** is subjected to $(DHQ)_2PHAL$, even if the phenyl ring is highly substituted. Therefore, the plan was to synthesize the diol from 5-hydroxy-2-nitrobenzaldehyde (**44**) and use Raney® Ni chemistry to remove the benzylic OH group.

The first two steps of the sequence involved the protection of the hydroxyl group with MEMCl followed by a Wittig reaction to obtain the olefin **147** (*Scheme 49*).[53]

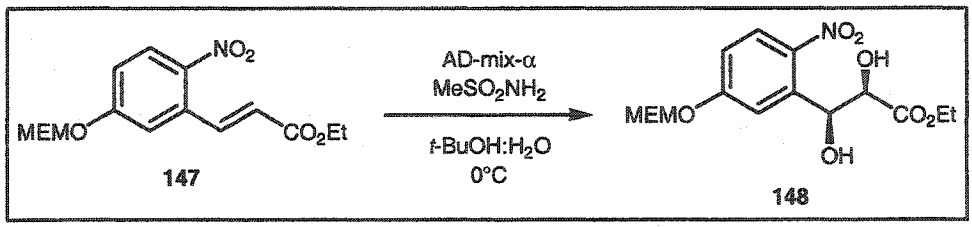


44: 5-hydroxy-2-nitro benzaldehyde

147

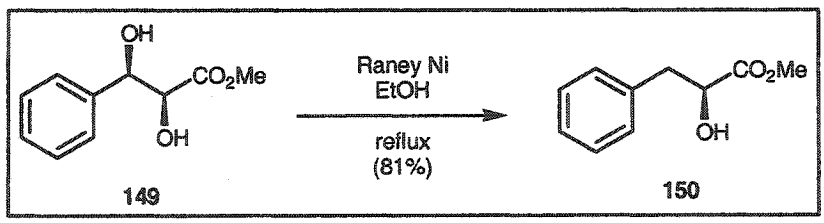
Scheme 49. New strategy to synthesize the indoline moiety.

Derivative **147** was then subjected to an AD reaction using AD-mix-α (*Scheme 50*). This time because the reaction did not involve a terminal olefin, methanesulfonamide was used to accelerate the reaction. The diol **148** was isolated in a good yield and ^{1}H NMR spectrum confirmed its formation.



Scheme 50. AD reaction with derivative **147**.

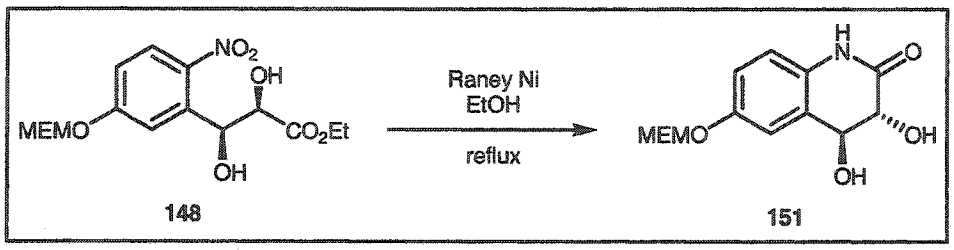
The next step was inspired by a paper that reported subjecting compound **149** to Raney® Ni in the sequence towards the synthesis of the piperazinone rings of pseudotheonamides A_1 and A_2.[54] The reduction of the benzylic hydroxyl group was accomplished and led to the (2*S*)-hydroxy derivative **150** as the exclusive product (*Scheme 51*).



Scheme 51. Reduction of the benzylic hydroxyl group towards the synthesis of pseudotheonamides A_1 and A_2.

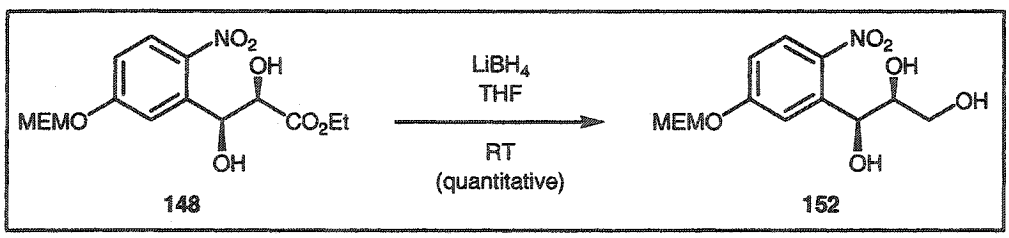
When this procedure was tried with the diol derivative **148**, the reduction of the nitro group was observed as expected, but a cyclization occurred at the same time (*Scheme 52*). The six-membered ring **151** was the only compound isolated from this reaction. ^{1}H NMR confirmed the formation of the product. First, the spectrum showed the disappearance of the ethyl group, CH_2 at 4.32 ppm (q, J = 7.0 Hz) and CH_3 at 1.33 ppm (t, J = 7.1 Hz). Then, the hydrogen in

the *ortho* position to the nitro group shifted from 8.09 ppm (d, J = 9.1 Hz) to 6.82 ppm (d, J = 8.6 Hz) indicating the reduction of NO_2. Finally, the benzylic OH was still present on the molecule due to the presence of only one benzylic hydrogen at 4.68 ppm (d, J = 10.8 Hz).



Scheme 52. Cyclization upon Raney® Ni treatment.

Considering these results, a reduction of the ester was envisaged before submitting the compound to Raney® Ni. Therefore, the diol **148** was subjected to lithium borohydride. The reaction was complete in four hours and afforded the triol **152** quantitatively (*Scheme 53*). The resulting compound was very polar, so no column purification was performed, but the formation of the compound was confirmed by mass spectrometry (M+1: 318.1).

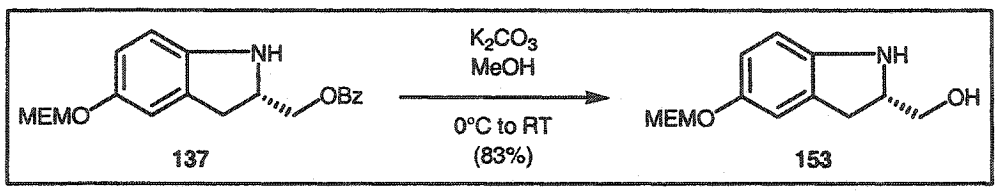


Scheme 53. $LiBH_4$ reduction of the ester.

Unfortunately, the reduction of the benzylic hydroxyl group with Raney® Ni did not work. The only thing that happened was the conversion of the nitro group into an amino functionality. More work was obviously needed to investigate this avenue to the five-membered ring, however this route was abandoned due to time constraints. Moreover, enough bicyclic material was available to finish the sequence up to the seven-membered ring template.

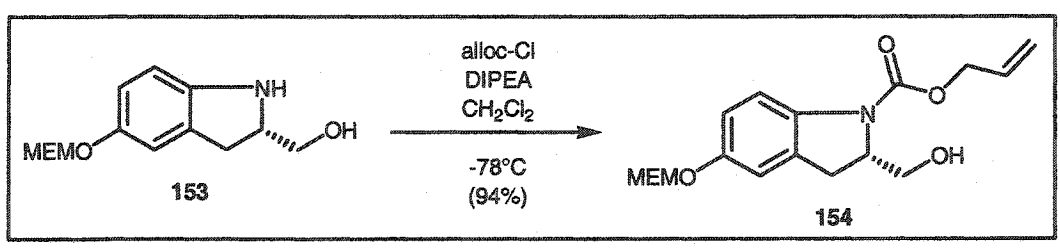
3.4 Synthesis of the Seven-Membered Ring Scaffold

Returning to the indoline scaffold **137**, the next step involved the removal of the benzoyl protecting group as studied with the model system. The hydrolysis was performed in methanol with potassium carbonate and generated the amino alcohol **153** in a 83% yield (*Scheme 54*). The removal of the benzoyl group was characterized by the disappearance of the aromatic proton signals at 8.03 ppm (d, J = 7.3 Hz, 2H), 7.59 ppm (t, J = 7.5 Hz, 1H), and 7.46 ppm (dd, J = 7.5, 7.3 Hz, 2H) in the ^{1}H NMR spectrum. The IR spectrum showed an O-H stretch at 3430 cm^{-1}.



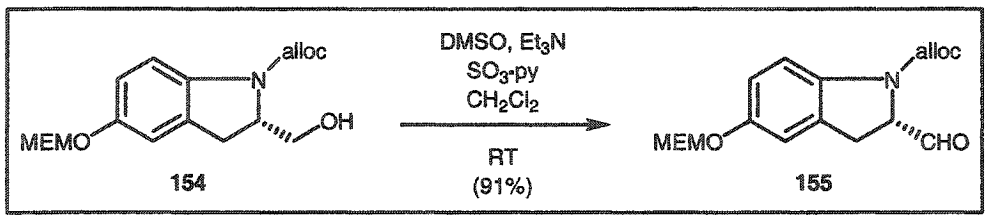
Scheme 54. Hydrolysis of the benzoyl derivative.

The procedure for the protection of the secondary amine with allyl chloroformate was slightly changed because some problems were seen during the model study. As proposed, the base was changed to DIPEA and the temperature was lowered to –78°C (*Scheme 55*). In these conditions, the allyloxycarbonyl (alloc) derivative **154** was produced very quickly (within 30 minutes) in a very high yield. The reaction was clean, always generating only the monosubstituted compound. Spectral data supported the presence of the protecting group. In the ^{1}H NMR spectrum, three alkene protons appeared. As well, the IR spectrum showed a C=O absorption signal at 1682 cm^{-1}.



Scheme 55. Formation of the allyloxycarbonyl derivative **154**.

The sulfur trioxide/pyridine complex was again used to generate the aldehyde. This time, the reaction was complete in three to four hours compared to two hours with the model system. The aldehyde **155** was isolated in a 91% yield (*Scheme 56*) and was confirmed by the appearance of a signal at 9.68 ppm in the ^{1}H NMR spectrum and 199.3 ppm in the ^{13}C NMR spectrum.



Scheme 56. Oxidation of the primary alcohol.

3.4.1 Allylation Reaction

As mentioned in *Chapter 2*, the allylation reaction using allylmagnesium bromide in THF performed on the compound used in the model study gave poor results. It was hoped that these conditions would give better results with the MEM derivative **155**. Unfortunately, once again the yield was very low and recovering the starting material was difficult.

A different allylation condition was found using allylsilane and titanium tetrachloride. In the paper, α-amino aldehydes were subjected to $TiCl_4$ in dichloromethane with allylsilane and excellent results were obtained.[55] Highly stereoselective products were observed due to the coordinative interactions between the aldehyde and $TiCl_4$.

These allylation conditions seemed very promising due to the similarity between aldehydes **155** and **156** (*Figure 20*). Therefore, aldehyde **155** was subjected to allylsilane and titanium tetrachloride in dichloromethane. The course of the reaction was followed by TLC as well as by mass spectrometry. Unfortunately, the allyl derivative could not be isolated.

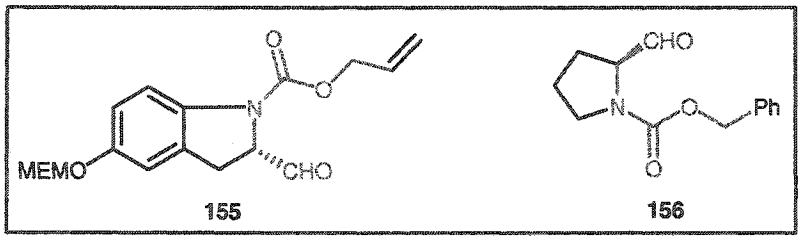
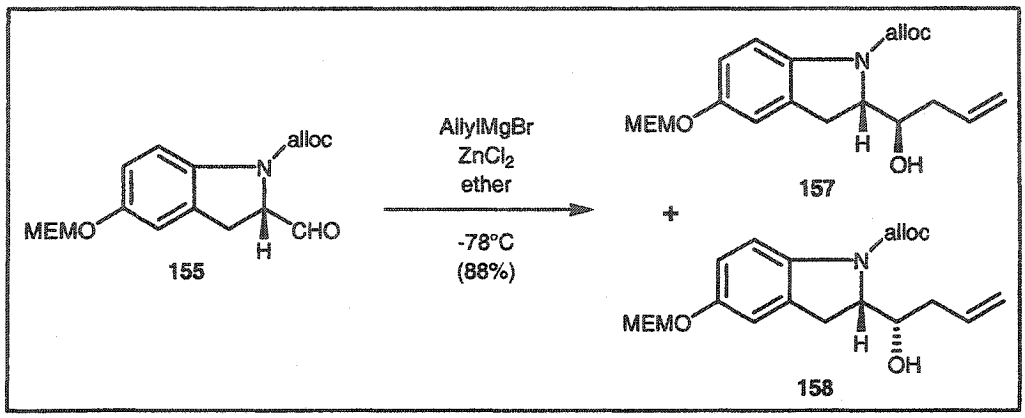


Figure 20. Similar α-amino aldehydes.

Another procedure was found in the literature in which the authors performed the allylation reaction in the presence of allylmagnesium bromide and a Lewis acid ($ZnBr_2$).[56] Compound **155** was then treated with allylmagnesium bromide and $ZnBr_2$ in diethyl ether (ether). After three hours at low temperature, the major product formed was indeed the allylic derivative but missing the allyloxycarbonyl protecting group on the secondary amine. It is known that allyl carbamates can be unstable to Grignard reagents.[57] Since compound **155** had already been subjected to allylmagnesium bromide without any observed loss of the alloc group, the Lewis acid used ($ZnBr_2$) was then suspected to be the cause.

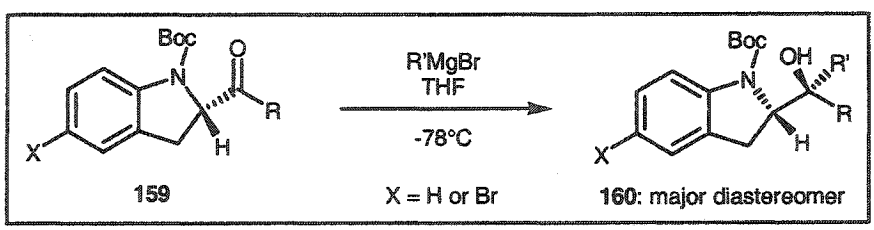
The allylation of aldehyde **155** was then attempted with allylmagnesium bromide and $ZnCl_2$ in ether. This time, two products could be isolated corresponding to the allylic alcohols **157** and **158** (*Scheme 57*). The allyloxycarbonyl group appeared to be stable under these conditions. Increasing the concentration of the reaction mixture from 0.02 to 0.037 M resulted in increasing the yield to up to 88%. The ratio of both compounds did not change much when the concentration was increased (between 1.15:1 and 1.6:1 for **158**:**157**). These results suggested that the allylation reaction was not as stereoselective as observed in the literature.[56]



Scheme 57. Allylation reaction with $ZnCl_2$.

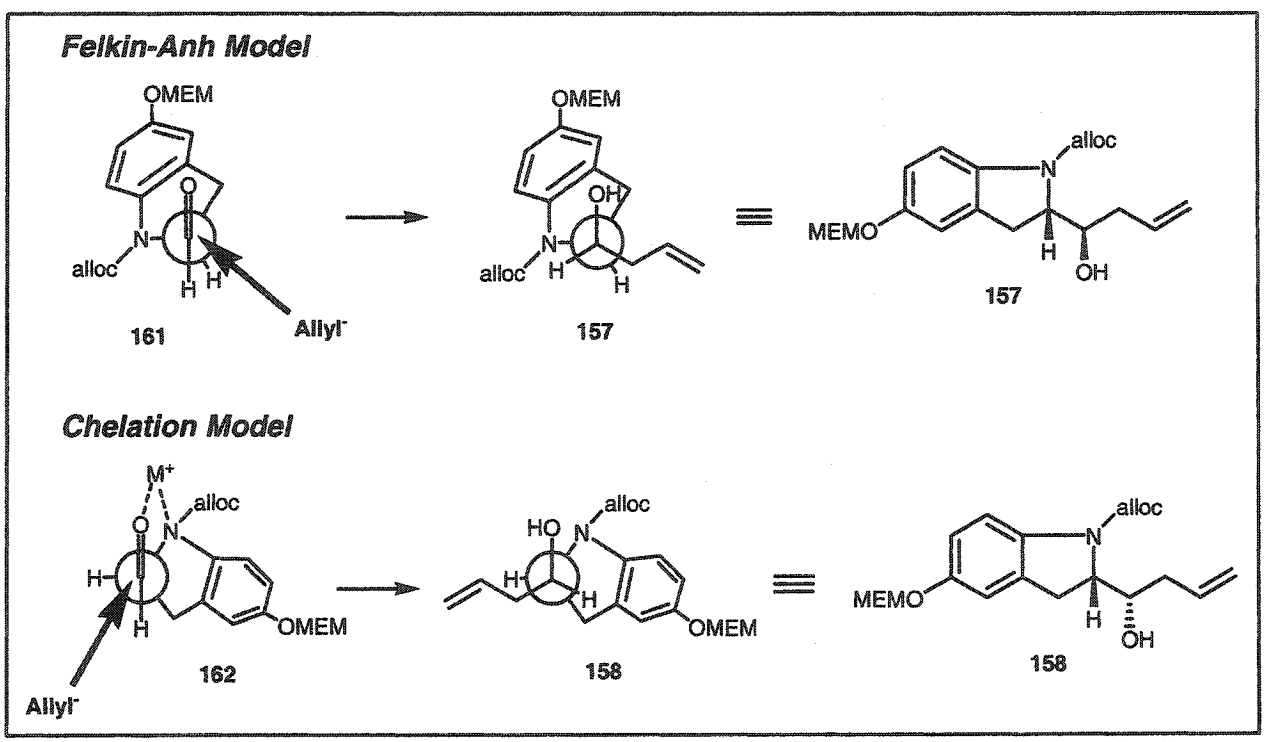
The formation of both alcohols was confirmed by ^1H NMR (the configuration at the stereogenic center of each molecule was determined after the cyclization of both seven-membered rings). The aldehyde signal at 9.68 ppm disappeared from both spectra. Both alcohols were identified by the appearance of a strong O-H stretch in IR spectra. In the ^1H NMR spectrum, the alkene protons of the allylic alcohol **157** appeared as multiplets between 5.90-5.81 ppm (1H) and between 5.16-5.11 ppm (2H). The alkene protons of the allylic alcohol **158** appeared as a broad singlet at 5.83 ppm integrating for one hydrogen and as a multiplet between 5.14-5.09 ppm (2H).

Kogen's group reported a diastereoselective Grignard addition on a carbonyl functionality in their synthesis of (+)-benzastatin E (*Scheme 58*).[58] The conditions used were very similar to what was first tried in this project, that is the Grignard reagent in THF. The authors explained the stereochemical outcome of the facially selective additions in terms of a Felkin-Anh model.



Scheme 58. Diastereoselective Grignard addition to 2-acylindolines.

It was then decided to study the allylation reaction with aldehyde **155** in two solvents and with or without the presence of the Lewis acid. According to their results, treating compound **155** with allylmagnesium bromide without a Lewis acid should generate the allylic alcohol **157** as the major isomer (Felkin-Anh model). On the other hand, compound **158** would be formed as a major diastereomer after subjecting the aldehyde **155** to the same Grignard reagent with $ZnCl_2$ (chelation model). Both models are presented in *Scheme 59.*



Scheme 59. Felkin-Anh and chelation models to explain the formation of allylic alcohols.

The results obtained from this study are presented in *Table 1.* Four parameters were kept constant during each reaction. 3.0 equivalents of the allylmagnesium bromide reagent were used, the temperature was maintained at –78°C, the reaction time was two hours in each case, and the concentration of the solution was between 0.037 and 0.038 M.

Entry	Solvent (type)	$ZnCl_2$ (eq)	allylic alcohol **157** (%)	allylic alcohol **158** (%)	Aldehyde recovered (%)
1	THF	-	19	22	-
2	THF	-	20	-	28
3	ether	-	17	-	35
4	ether	-	32	-	-
5	THF	2.0	38	46.5	-
6	ether	2.0	52	34	-
7	ether	6.0	38.4	35.5	-
8	ether	10.0	30	30	-

Table 1. Study of the allylation reaction on aldehyde **155**.

Low yields were obtained when no Lewis acid was used in either THF or ether. Moreover, these yields were not easily reproducible (entry 1 compared to entry 2, and 3 compared to 4). The results obtained in ether (entries 3 and 4) could be explained by the Felkin-Anh model discussed earlier (see *Scheme 59*). Unfortunately, nothing could be concluded from the results obtained in THF (entries 1 and 2), as in one case both alcohols were isolated.

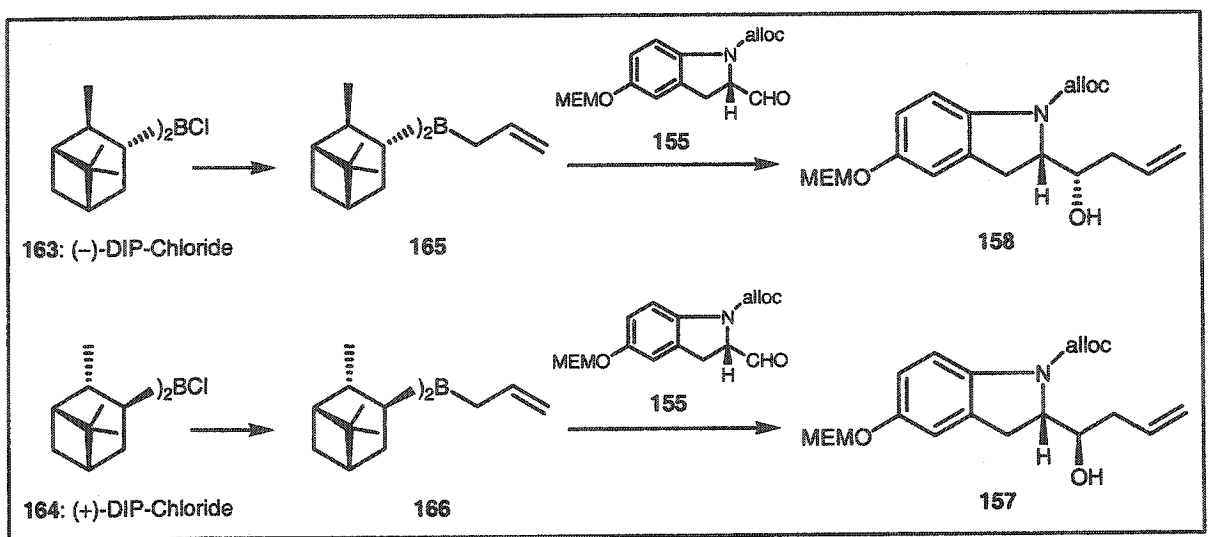
Higher yields were obtained when $ZnCl_2$ was used to perform the reaction in both solvents (entries 5-8). In THF, **158** was the major product formed, probably explained by the chelation model. Unfortunately, results obtained using ether could not be derived from a chelation model even when additional equivalents of the Lewis acid were used to favor that model (entries 7 and 8).

All these results were quite disappointing and were very different than what was observed with the model system (*Chapter 2*). Why was it not possible to obtain similar results then those found in Kogen's article? Was this due to the presence of the *O*-MEM group on the benzene ring? Or was the alloc protecting group behaving differently than the Boc group used in their experiments?

If time was not a constraint, different investigations could have been pursued. The first thing could have been to repeat the reactions found in the article with the same system. Then, the reaction conditions could have been tried on a molecule bearing an alloc group on the amine instead of a Boc protecting group. Finally, the allylation reaction could have been attempted on various derivatives having substituents in different positions on the aromatic ring. This would give a complete study of the effect of substitution on the reaction.

Since it was preferred to obtain only one diastereomer from the allylation reaction, allylation with Brown's reagent ($Ipc_2Ballyl$) was considered. Several examples are found in the literature in which this type of reagent is used to install allylic alcohols with the desired stereochemistry.[59]

The plan was to synthesize both *B*-allyldiisopinocamphenylborane reagents from (–)-DIP-chloride (**163**) and (+)-DIP-chloride (**164**) and use them to generate respectively the allylic alcohol **158** and the allyl derivative **157** from aldehyde **155** (*Scheme 60*). The synthesis of **165** was successful,[60] unfortunately when the aldehyde was subjected to the reagent, compound **158** was only isolated in a very low yield. In future work for this project, a stereoselective allylation reaction is planned to be established, either by repeating the reaction with Brown's reagent or by using the diamine-derived silacycle auxiliary developed by Leighton.[61]

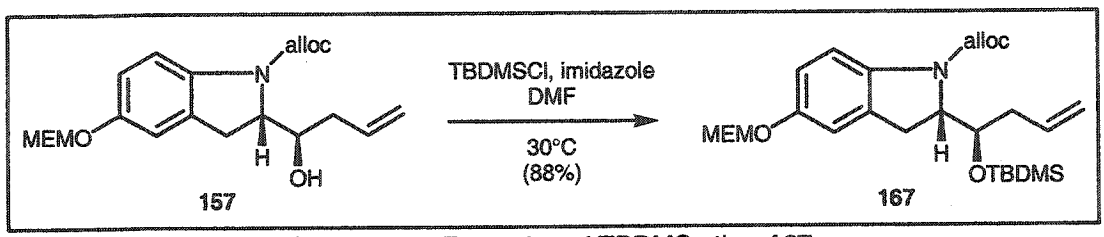


Scheme 60. Use of ($Ipc_2Ballyl$) reagents to generate alcohols **157** and **158**.

3.4.2 Steps Toward Ring-Closing Metathesis

At this point, only four steps were required to obtain the desired seven-membered ring template. It was decided to submit both allylic alcohols to each reaction condition independently in order to compare their reactivity.

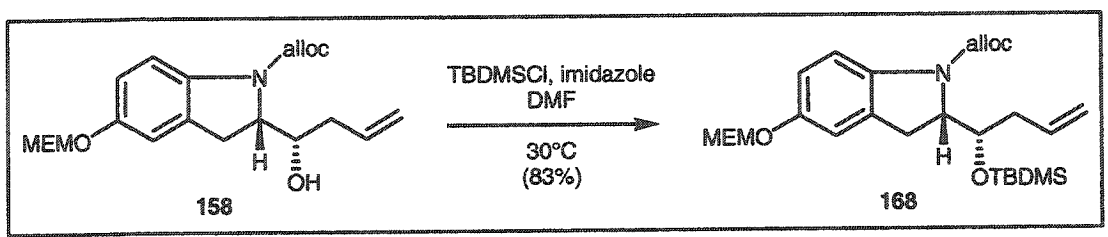
The first reaction of the remaining sequence involved the protection of the secondary alcohol generated from the allylation reaction. TBDMSCl was the reagent used in the presence of imidazole in DMF to transform the OH group of **157** into the TBDMS ether **167** (*Scheme 61*). The reaction mixture was heated to 30°C and afforded compound **167** in a 88% yield (10% of the starting material could also be recovered).



Scheme 61. Formation of TBDMS ether **167**.

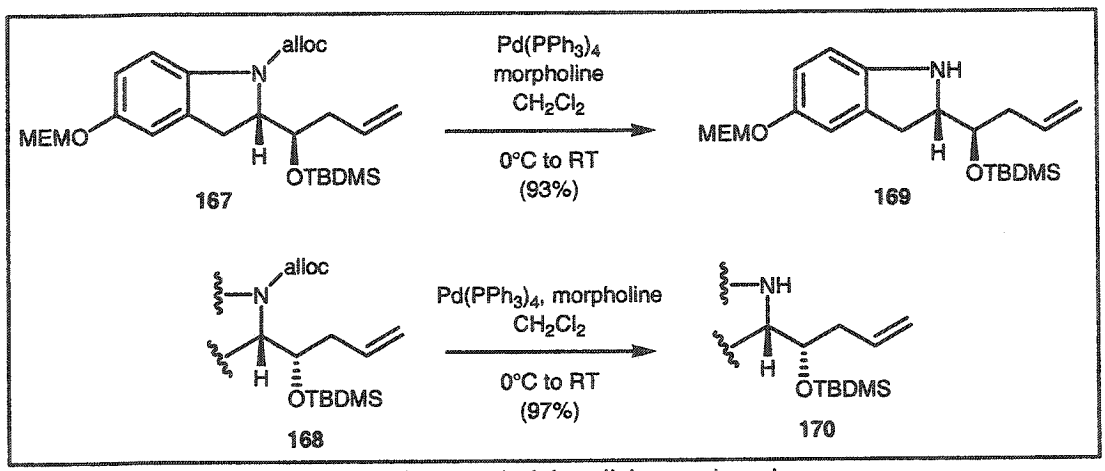
The presence of the protecting group on the alcohol was confirmed by the appearance of three singlets in the ^{1}H NMR spectrum. The TBDMS signals appeared at 0.59 ppm, –0.04 ppm and –0.28 ppm, integrating respectively for 9, 3 and 3 protons.

The other diastereomer **158** was subjected to the same reaction conditions and the TBDMS ether **168** was isolated in a 83% yield (*Scheme 62*). Similarly, signals appearing at 0.92 ppm (s, 9H) and between 0.12-0.08 ppm (m, 6H) in the ^{1}H NMR spectrum confirmed the presence of the TBDMS group. The IR spectrum of both compounds (**167** and **168**) did not show an O-H stretch.



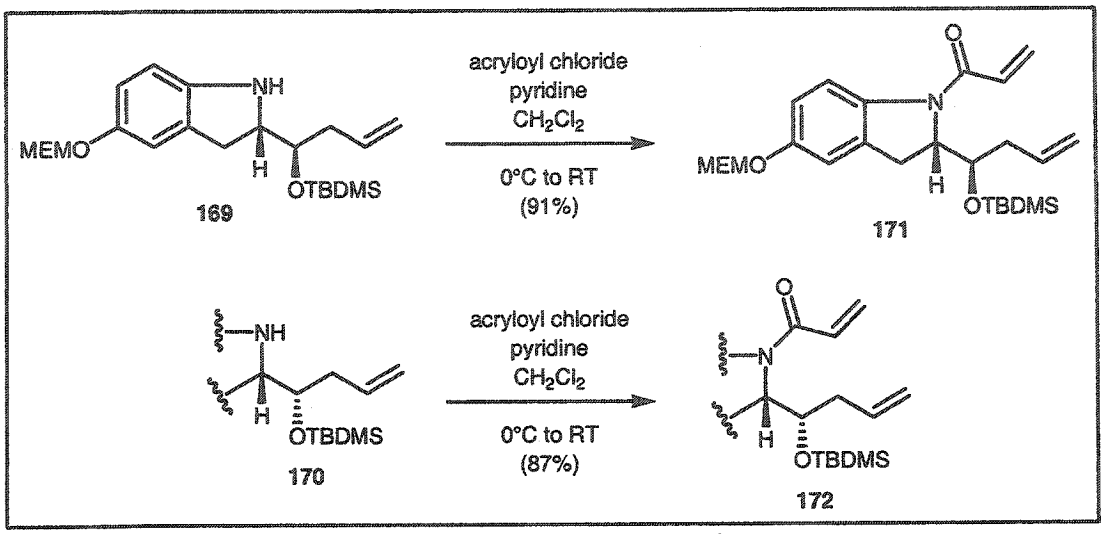
Scheme 62. TBDMS ether derivative **168**.

The next step in the strategy was the removal of the allyloxycarbonyl group protecting the secondary amine. The conditions used with the model system were also used here with both TBDMS ethers. Each compound (**167** and **168**) was treated with tetrakis(triphenylphosphine)-palladium(0) and afforded respectively compounds **169** and **170** (*Scheme 63*). The product **169** was obtained in a 93% yield and was confirmed by the disappearance of the alkene protons of the alloc group at 6.02 ppm (broad s), 5.40 ppm (d, J = 17.1 Hz) and 5.29 ppm (d, J = 10.4 Hz) integrating for one proton each in the ^{1}H NMR spectrum. The adduct **170** was isolated in a 97% yield and its formation was confirmed by the similar alkene hydrogen disappearance in its ^{1}H NMR spectrum.



Scheme 63. Removal of the allyloxycarbonyl group.

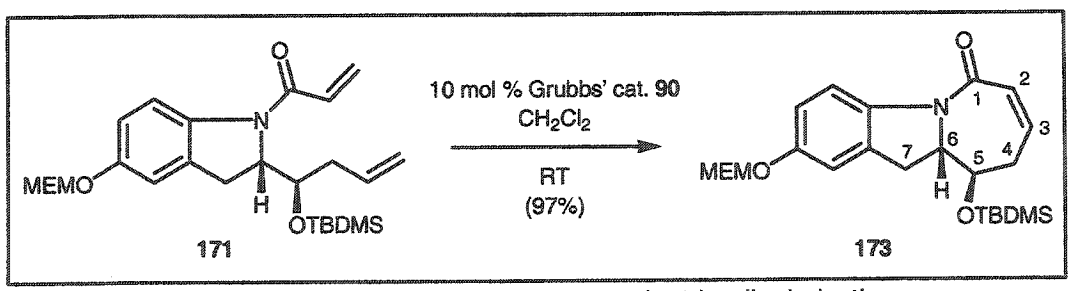
As mentioned in *Chapter 2*, the coupling of the secondary amine with the acrylic acid gave poor results and an alternative method was suggested. Therefore, compounds **169** and **170** were submitted to an acryloylation reaction (*Scheme 64*). The amino derivative **169** was treated with acryloyl chloride and pyridine in dichloromethane for two hours. Compound **171** was isolated in a 91% yield. Three new alkene protons appeared in the ^{1}H NMR spectrum, between 6.58-6.38 ppm integrating for two protons and at 5.79 ppm (d, J = 10.4 Hz) integrating for one proton. In the ^{13}C NMR spectrum, a signal at 163.3 ppm was indicative of the ketone carbon. The IR spectrum also showed a new C=O absorption signal at 1653 cm^{-1}. Similarly, product **172** was obtained from derivative **170** and confirmed by spectral data.



Scheme 64. Acryloylation reaction.

Finally, the last step in the strategy to reach the seven-membered ring compound was the olefin ring-closing metathesis. Both acryloyl derivatives successfully reacted using the first generation Grubbs' catalyst **90** (see *Figure 14*).

The seven-membered ring derivative **173** was obtained in a 97% yield after treating the RCM precursor **171** with 10 mol % catalyst in dichloromethane (*Scheme 65*). The reaction was very fast, completed within 30 minutes.



Scheme 65. RCM reaction to generate the tricyclic derivative.

Only two alkene protons could be seen in the ^1H NMR spectrum of compound **173** (*Figure 21*). These two signals between 6.39-6.33 ppm (m, 1H) and at 6.18 ppm (dd, J = 11.4, 2.1 Hz, 1H) corresponded to the protons at C_2 and C_3. The COSY 2D NMR spectrum showed coupling between these two

hydrogens. The neighbouring hydrogens on C_4, appearing at 2.62 ppm (dddd, J = 16.1, 5.3, 5.2, 2.1 Hz, 1H) and 2.37 ppm (ddd, J = 16.1, 7.4, 3.4 Hz, 1H), also showed coupling to H_2 and H_3 as well as coupling to a signal at 4.07 ppm (ddd, J = 9.1, 5.4, 3.4 Hz, 1H). This was the proton at C_5. In turn, that hydrogen showed coupling for the signal at 4.18 ppm (ddd, J = 9.4, 9.1, 2.7 Hz) corresponding to the hydrogen at C_6. Finally, the CH_2 at C_7 was seen as a multiplet between 3.44-3.37 ppm and as a doublet of doublets at 3.10 ppm (J = 17.0, 2.7 Hz), integrating for one proton each. The COSY 2D NMR experiment showed that the CH_2's protons exhibited coupling to themselves and to H_6.

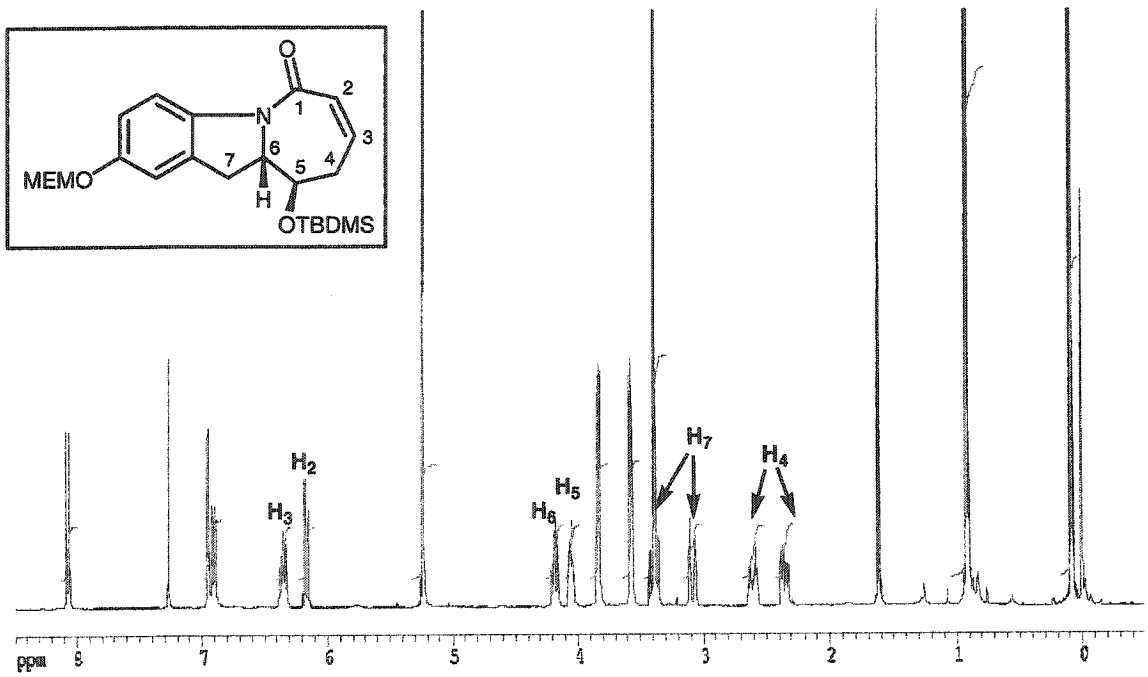


Figure 21. ^{1}H NMR spectrum of the seven-membered ring template **173**.

Once again, as with the model system, the coupling constant between H_5 and H_6 was used to determine the relative configuration at the C_5 stereogenic centre. A value of approximately 9.1 Hz was found, typically corresponding to a *trans* relationship between both protons. Moreover, the nOe difference experiment showed no nOe for the proton H_5 after irradiation of the proton at C_6. Same results were obtained when the proton at C_5 was irradiated. Since the

nOe experiment is used to establish spatial proximity between protons, these observations suggested that both protons were too far from each other to exhibit correlations through space. Therefore, the 3D structure of the tricyclic compound should show a *trans* relationship between H_5 and H_6 (*Figure 22*). *Figure 22* presents also the assignment of each peak of the ^1H NMR to the correct hydrogen in the molecule **173**.

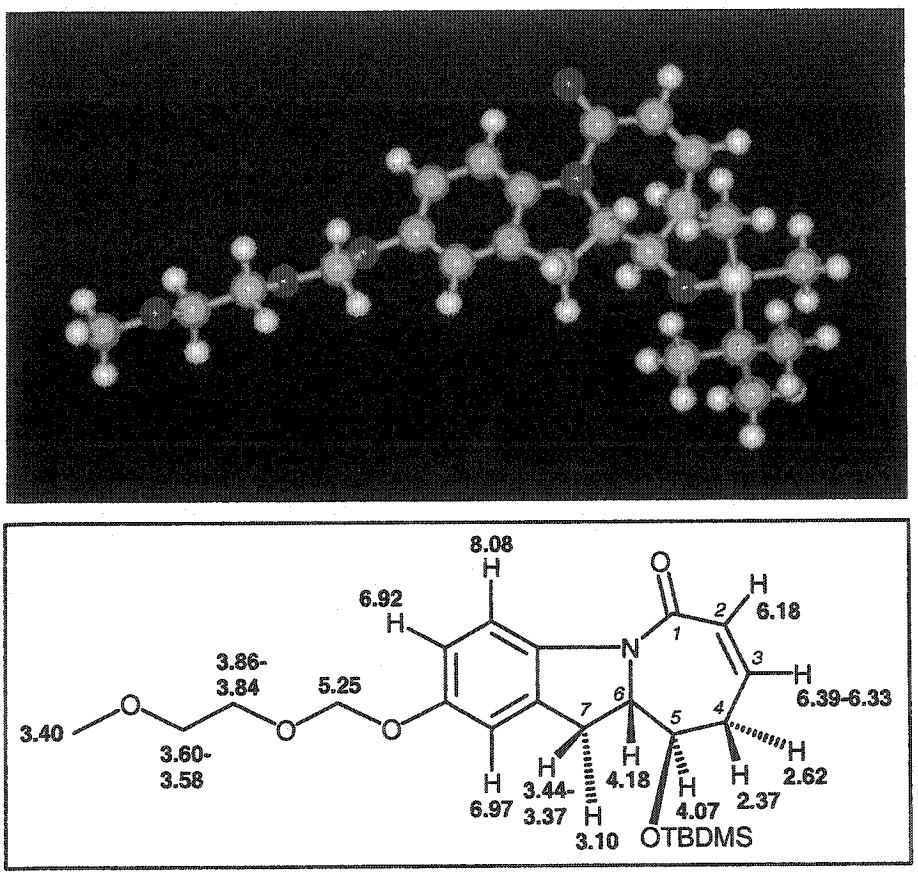
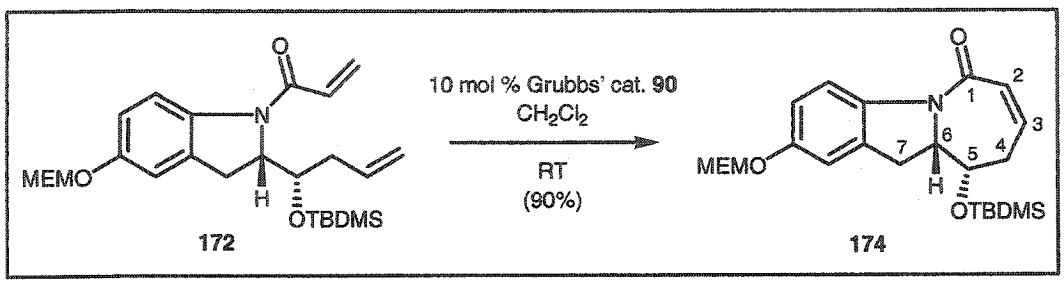


Figure 22. 3D structure and ^1H NMR chemical shifts of compound **173**.

When compound **172** was subjected to the RCM reaction conditions, the seven-membered ring scaffold **174** was isolated in a 90% yield (*Scheme 66*). The reaction was slightly longer than the time needed to generate the ring from the other isomer (1.5 hours compared to 30 minutes). This may be explained by the proximity effect of the ends of the two chains. In compound **172**, the *O*-TBDMS group is pointing towards the area in which the catalyst for the RCM

reaction needs to react with both olefins. Due to this hindrance, the reaction might be slower. This was not the case when derivative **173** was formed from the RCM reaction.



172 174

Scheme 66. RCM reaction to generate derivative **174**.

A similar analogy was carried out for compound **174**. Each peak in the ^1H NMR spectrum (*Figure 23*) was assigned to a proton in the molecule. The COSY 2D NMR spectrum was used to establish the coupling between hydrogens in the seven-membered ring.

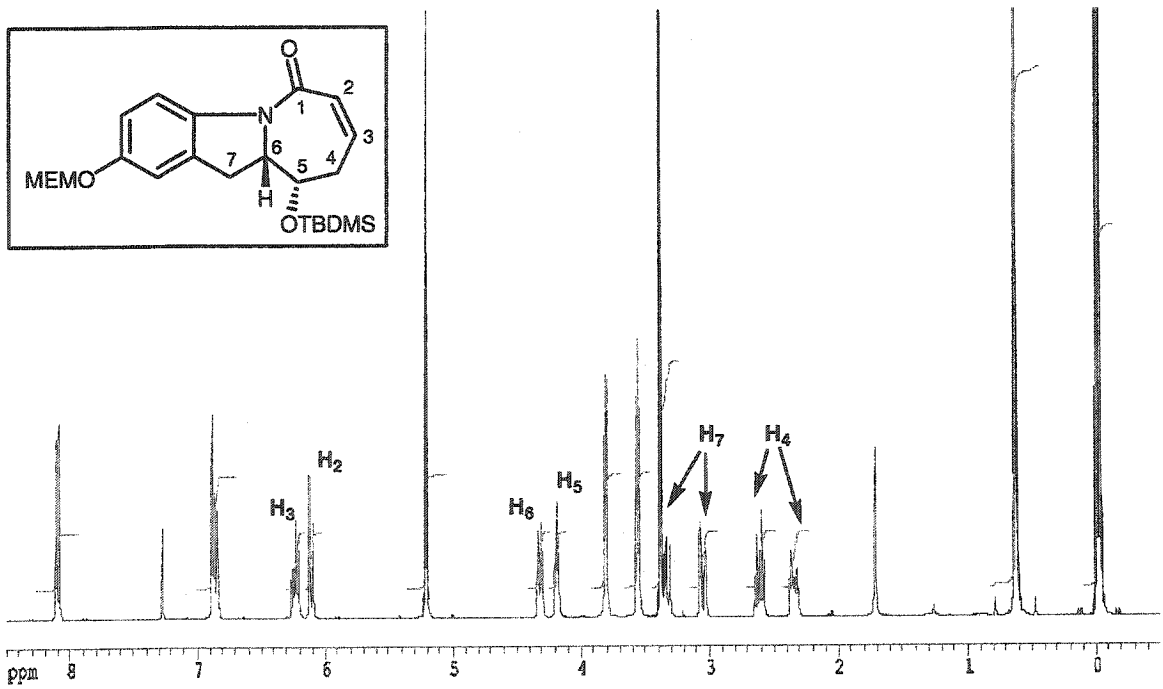


Figure 23. ^1H NMR spectrum of the seven-membered ring template **174**.

The coupling constant between the protons at C_5 and C_6 was found to be approximately 2.4 Hz. This value typically corresponds to a *cis* relationship between H_5 and H_6 as observed for the model system in *Chapter 2*. To help confirm the stereochemistry of the compound, a nOe experiment was performed. After the irradiation of the proton at C_6 (4.31 ppm), a very strong positive nOe was observed for the proton H_5 (4.18 ppm) and for the proton at 3.34 ppm. With these results supporting the *cis* relationship between H_5 and H_6, a 3D model of the seven-membered ring **174** was simulated (*Figure 24*).

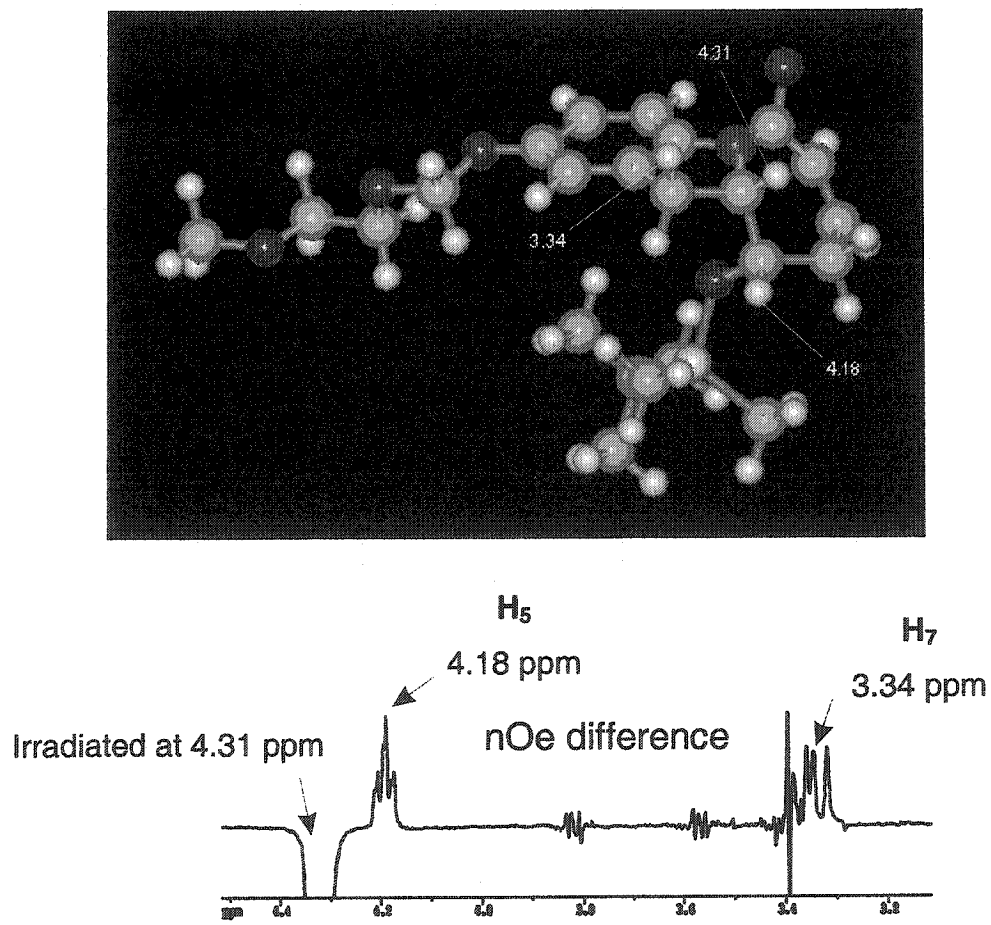


Figure 24. 3D structure and nOe difference spectrum of compound **174**.

Finally, it was possible to assign each peak of the ^{1}H NMR spectrum to the correct hydrogen with the help of 2D NMR experiments (*Figure 25*).

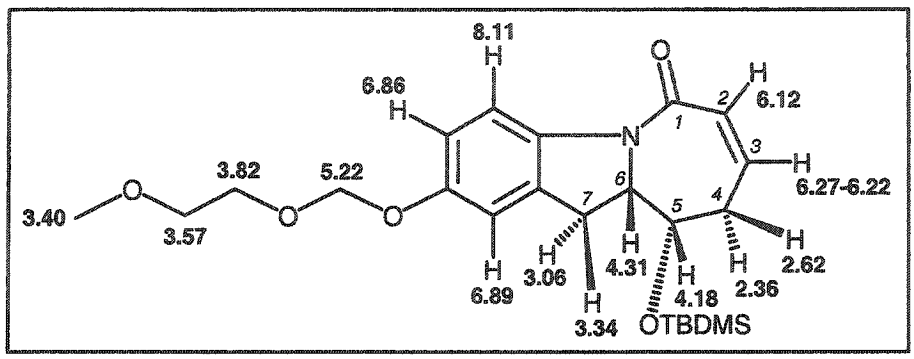


Figure 25. ^{1}H NMR chemical shifts of compound **174**.

3.5 Solid Phase Synthesis

The next challenge of the project was to transfer the chemistry developed in solution onto solid phase.[62] Solid phase organic synthesis is very attractive from different perspectives. It allows simple separation of intermediates from soluble components of a reaction mixture by filtration. Also, the reactions can be driven to completion by using a high concentration of reactants (in excess) in solution. The repetitive process (adding reagents, mixing, washing) allows for automation of solid phase synthesis.

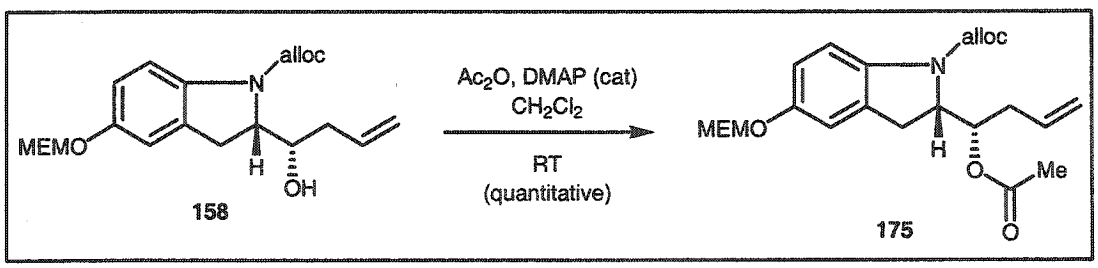
Solid phase organic synthesis has become a powerful tool for production of combinatorial libraries. With the emergence of high-throughput screening for biological evaluation for hits and leads, combinatorial libraries have become very important for pharmaceutical and agricultural chemistry.

As already mentioned, one important goal of the project was to build the seven-membered ring scaffold on solid support, thereby opening the door to explore asymmetric diversity-oriented reactions. The solid phase organic synthesis of small molecules depends greatly on the adaptation of solution reactions to solid phase. The plan was to immobilize the compound arising from the allylation reaction (of course, after protecting the secondary alcohol) onto a solid support. This would allow the synthesis of the tricyclic derivative from the

bicyclic scaffold on solid phase. The key step would be the RCM reaction, which is known to work well on solid support.[62b] Another important step of the synthesis would be the removal of the allyloxycarbonyl protecting group. This is also known to work, as different conditions can be found in the literature for the alloc group removal in solid phase synthesis.[63]

The first step towards the solid phase synthesis involved the removal of the protecting group on the phenolic OH. Therefore, the TBDMS ether **167** (see *Scheme 63*) was treated with *p*-toluenesulfonic acid (*p*-TSA) in ethanol. The MEM group was removed as desired, but the loss of the TBDMS group protecting the secondary hydroxyl was also observed.

A new group, stable to acidic conditions, had to be chosen to protect the secondary alcohol. An acetate was tried and compound **175** was obtained in a quantitative yield from the allylic alcohol **158** (*Scheme 67*). The appearance of a signal at 1.96 ppm integrating for three protons in the ^{1}H NMR spectrum confirmed the presence of the acetate group. As well, a signal at 170.6 ppm appeared in the ^{13}C NMR spectrum.

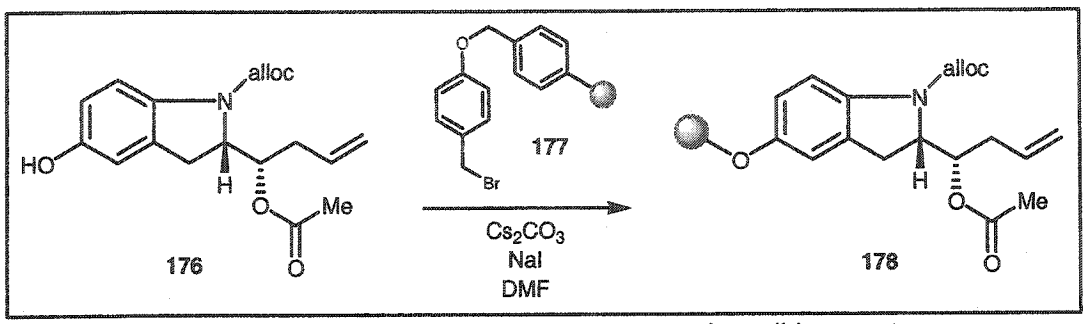


Scheme 67. Acetate derivative formation.

The acetate derivative **175** was then submitted to the same reaction conditions (*p*-TSA, ethanol) to remove the MEM group. The desired free phenolic compound (**176**) was isolated in a low 32% yield. The other compound obtained was unfortunately the derivative that had lost the acetate group from the secondary hydroxyl (46% yield).

At that point, enough material was isolated to try a first attempt on solid support. The resin used was a brominated Wang resin **177** [4-(bromomethyl)

phenoxymethyl polystyrene]. The compound **176** was anchored onto the resin with cesium carbonate and sodium iodide in DMF (*Scheme 68*).



Scheme 68. Loading of derivative **176** onto the solid support.

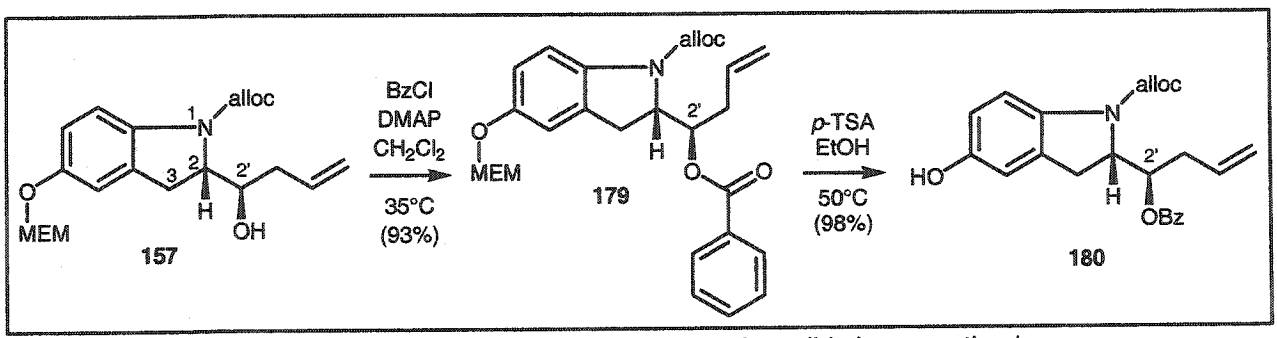
In order to evaluate the loading of the compound, a small amount of the resin was treated with 10% TFA in dichloromethane at room temperature. The starting material recovered was stable to the cleavage conditions according to the TLC and to mass spectrometry. Unfortunately, the loading was found to be only 50%. The sequence was continued further with the intention of obtaining the seven-membered ring derivative on solid phase. At each step, a small quantity of the compound was cleaved (using 10% TFA in dichloromethane) from the resin in order to obtain the mass spectrum and check the purity by TLC.

The conditions to remove the allyloxycarbonyl group in solid phase chemistry are slightly different than those used in solution synthesis.[61a] The resin was submitted to acetic acid, 4-methylmorpholine and $Pd(PPh_3)_4$ in dichloromethane. The acryloylation reaction was performed by treating the resin with acryloyl chloride and pyridine in dichloromethane. Finally, the RCM reaction was tried using 15 mol % Grubbs' catalyst (see **90** in *Figure 14*) in dichloromethane. Unfortunately, the products cleaved from the support did not show the expected signals for M+1 ion as observed in solution synthesis.

The reasons for the failures of this first attempt are not clear at this stage. Was the acetate protecting group stable enough? Were the conditions used for the acryloylation appropriate? Was 15 mol % Grubbs' catalyst sufficient for the reaction to proceed? Was the proper resin used for the solid phase synthesis?

Subsequently, it was decided to bring a few modifications to the solid phase protocol. First, the acetate group protecting the secondary alcohol was substituted for the more stable benzoyl derivative. As well, an acrylic acid coupling (with DIPEA and HBTU in dichloromethane) was chosen instead of using the acryloyl chloride to generate the RCM precursor. This was probably a safer condition since acid couplings are known to work well on solid support.

Compound **179** was generated in a 93% yield from the allylic alcohol derivative **157** (*Scheme 69*). Five new signals in the aromatic region appeared in the ^{1}H NMR spectrum, indicating the presence of the benzoyl moiety. A huge shift towards the deshielded region (4.08 to 5.61 ppm) could be observed for the proton at $C_{2'}$, confirming the protection of the hydroxyl by the benzoyl group. The derivative **179** was then treated with *p*-TSA in ethanol and afforded compound **180** in a 98% yield (see *Scheme 69*). The removal of the MEM group was confirmed by the disappearance of the methylene (5.21, 3.85, 3.59 ppm) and the methoxy (3.40 ppm) signals characteristic of that group in the ^{1}H NMR spectrum.



Scheme 69. Preparation of derivative **180** for solid phase synthesis.

Using the same conditions as with the acetate derivative, the loading of compound **180** onto the resin was very low (33%). Regardless, the solid phase steps were completed, but no promising results were obtained. After cleaving the final product from the resin, the parent molecular ion peak for the expected cyclic product in mass spectrometry could not be observed.

The loading was barely adequate with the compound having an acetate group. It turned out to be poor with the bulkier benzoyl protecting group. Maybe the low yields in loading were due to the bulkiness of the molecule causing

hindrance with the polymer. Therefore, a spacer may be needed between the polymer and the compound in order to reduce this hindrance.

Developed in 2001,[64] a new alkyl tethered diisopropylarylsilane linker on polystyrene beads (**181**) is now available from Sigma-Aldrich (*Figure 26*). In future work, this new silicon linker, suitable for diversity-oriented synthesis of phenolic systems,[65] could be used to obtain the tricyclic derivative having a seven-membered ring moiety.

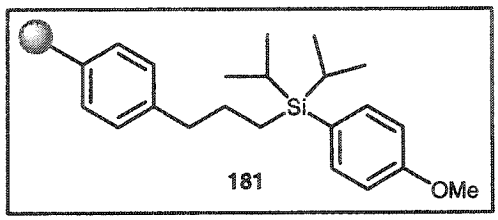


Figure 26. The alkylsilyl-tethered solid support.

3.6 Diversity-Oriented Syntheses

The final goal of the project was to explore the potential of the seven-membered ring derivative in asymmetric diversity-oriented reactions required in a library generation. Three types of reactions were selected: intermolecular and intramolecular Michael-type additions, as well as free radical chemistry using silicon-tethered reactions. The Michael-type conjugate additions to α,β-unsaturated carbonyl systems have been recognized as one of versatile functionalization methods in organic synthesis.

3.6.1 Intermolecular Michael-type Additions

The first attempt was to try to generate an epoxide from the double bond of the enamide moiety using hydrogen peroxide and sodium hydroxide in methanol.[66] Unfortunately, only starting material was recovered from the reaction. This was tried only once, further work is warranted to explore the epoxidation with other oxidizing agents.

The addition of a Grignard reagent (vinylmagnesium bromide) on the template was then tried with cupper iodide and a Lewis acid ($BF_3 \cdot Et_2O$).[67] Once

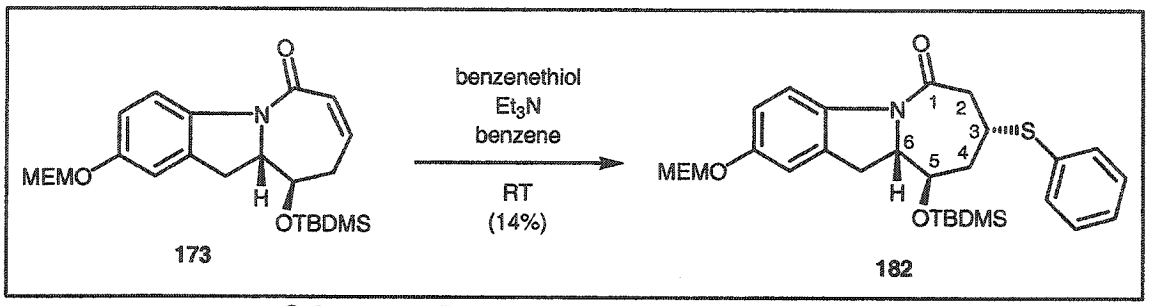
again the reaction did not proceed as expected. Instead, these conditions only removed the MEM protecting group from the phenolic OH.

At this point, the reactivity of the conjugated system was suspected. Maybe the reactivity was much lower than hoped because of the enamide functionality. As a last attempt, it was decided to perform the conjugate addition using thiol as the nucleophile. This could be a useful asymmetric diversity-oriented reaction because several thiols are commercially available. It has been shown in the literature that this reaction could also be performed on solid phase.[21]

Many examples of asymmetric Michael additions of thiols are reported in the literature. In most cases, a chiral auxiliary is utilized for the facial selective attack of the nucleophile.[68]

The plan was to demonstrate that the addition of a thiol nucleophile on the seven-membered ring template was feasible. Moreover, an important aspect of this plan was to explore the facial selective attack, in which the nucleophile would approach from the side opposite to the bulky *O*-TBDMS group. For the test study, benzenethiol was chosen as the nucleophile. The reaction was first attempted with compound **173** in THF with DIPEA. No new product was formed after several days. The solution was concentrated and kept in the freezer. A TLC of the mixture was then made before purification in order to recover the starting material. Surprisingly, a new spot appeared on TLC. The compound obtained, after column chromatography, was the thiol derivative.

The base chosen, DIPEA, was maybe not good enough for this reaction. Triethylamine is better known to catalyze the addition of thiols.[69] Therefore, the reaction was repeated with triethylamine in THF. The thiol derivative could not be isolated, even when trying the reaction in dichloromethane. The best results were obtained in benzene with triethylamine at room temperature (*Scheme 70*). After 40 hours of reaction, compound **182** could be isolated in only 14% yield.



Scheme 70. Formation of the thiol derivative **182.**

The formation of the product was confirmed by the disappearance of the alkene protons between 6.39-6.33 ppm (m, 1H) and at 6.18 ppm (dd, J = 11.4, 2.1 Hz, 1H) in the ^{1}H NMR spectrum. To evaluate if the attack of the thiol was facial selective, the relationship between the protons at C_3 and C_5 needed to be studied by a NOESY 2D NMR experiment. However, these two hydrogens had the same chemical shift in deuterated chloroform ($CDCl_3$), preventing the use of this experiment. A spectrum of the product was taken in deuterated benzene (C_6D_6). In this solvent, both protons had different chemical shifts and the NOESY 2D NMR spectrum did not show any correlation through space for the protons at C_3 and C_5. With these results, it was possible to postulate that the reaction was indeed a stereoselective Michael-type addition of benzenethiol. The 3D structure of compound **182** is presented in *Figure 27.*

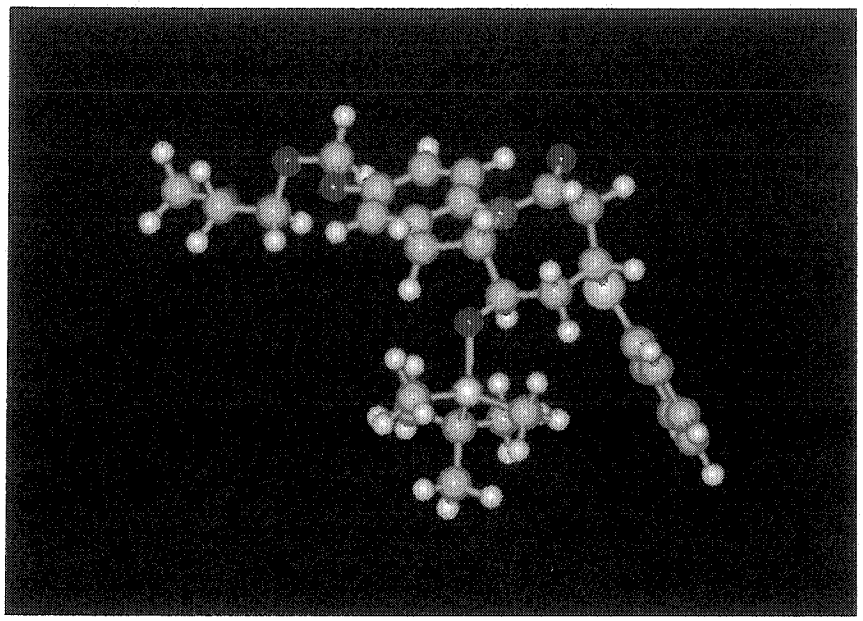
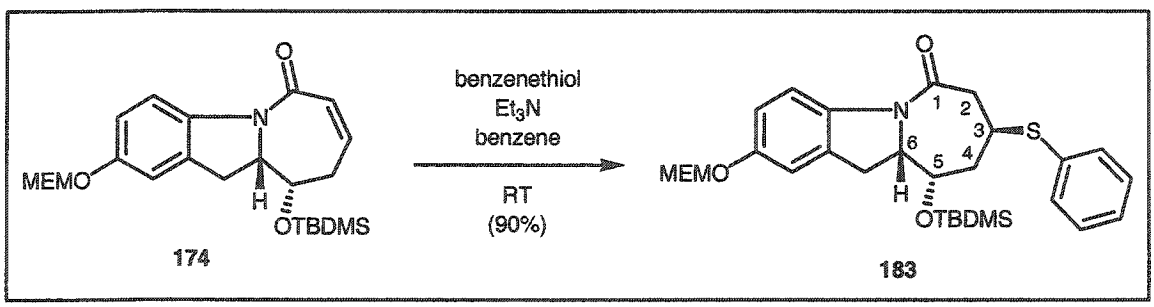


Figure 27. 3D structure of **182.**

Interestingly, when the reaction was tried with compound **174** in benzene with triethylamine for 40 hours, derivative **183** was obtained in a 90% yield (*Scheme 71*). Once again, the formation of this product was confirmed by the disappearance of the alkene protons in the ^{1}H NMR spectrum [δ 6.27-6.22 ppm (m, 1H) and 6.12 ppm (dd, J = 11.6, 2.1 Hz, 1H)].



Scheme 71. Asymmetric Michael-type addition of benzenethiol.

The facial selective attack of benzenethiol was proven by the NOESY 2D NMR experiment in which no correlation through space was observed between protons at C_3 and C_5 (*Figure 28*). A 3D structure of the thiol derivative **183** was then obtained by simulated annealing using HyperChem (*Figure 29*).

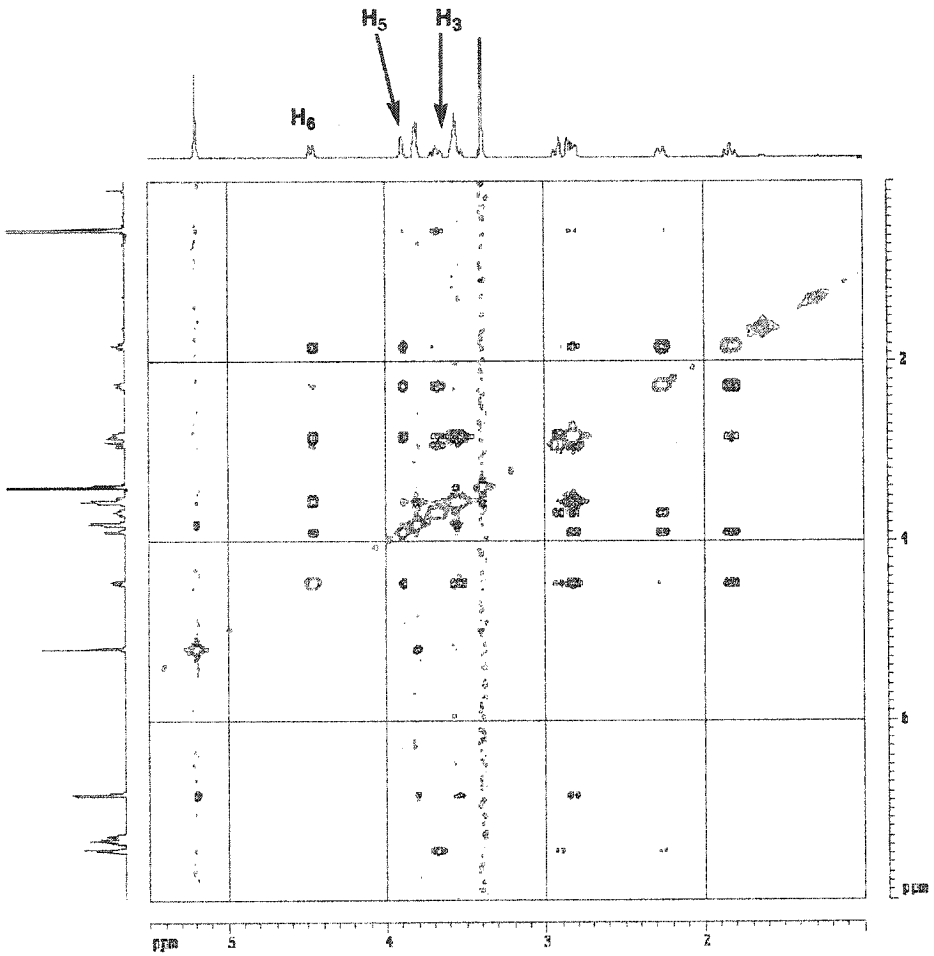


Figure 28. NOESY 2D NMR spectrum of compound **183** in $CDCl_3$.

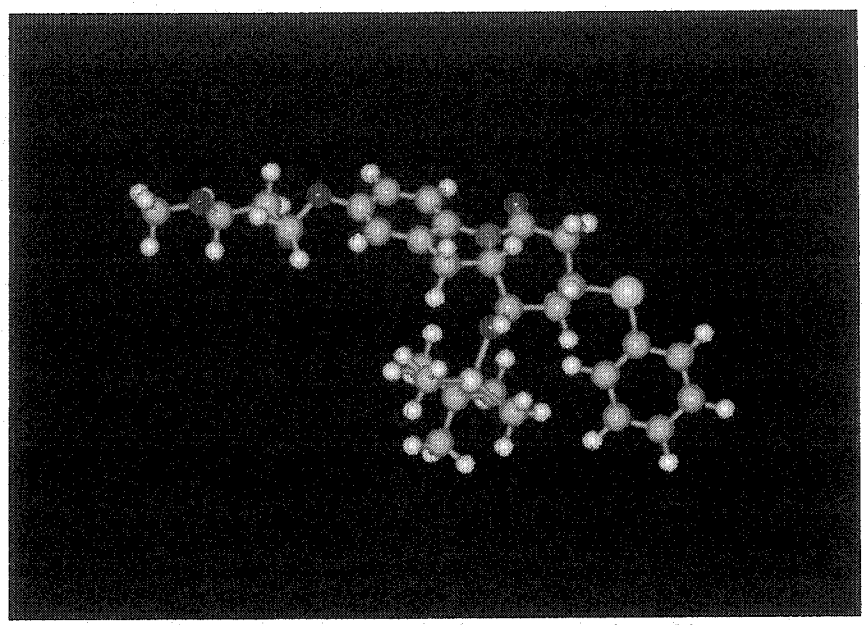


Figure 29. 3D structure of thiol derivative **183**.

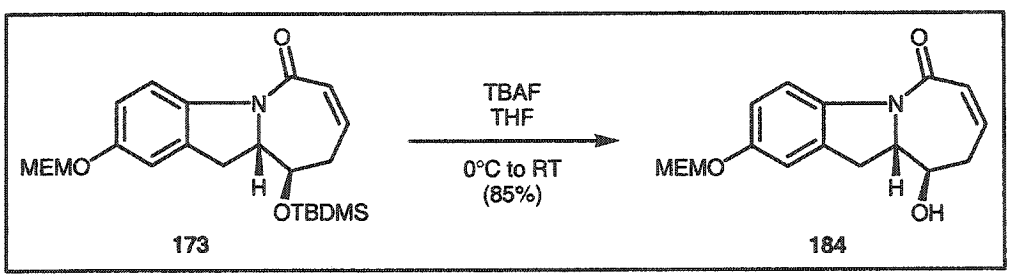
In order to evaluate the reactivity of the benzenethiol addition in different solvents, the reaction was repeated with derivative **174** using the same conditions (concentration, reaction time, temperature) in dichloromethane and in THF. The product obtained was the same as in benzene solvent, except that the yields were very different. In dichloromethane, the product was isolated in a 10% yield with 81% of recovered starting material. The yield of the reaction in THF was 78% with the recovery of the starting material (17% yield).

In conclusion, benzene seemed the best solvent to be used to perform the benzenethiol addition on the seven-membered ring scaffold. Surprisingly, the reaction of benzenethiol with **174** was better and faster than with **173**. By looking at the 3D structure of **173** (see *Figure 22*), the proton at C_5, pointing towards the centre of the ring, is partially hindering the attack of the thiol from the bottom face. This may result in a slow and low yielding reaction. The TBDMS group of **174** is clearly blocking the bottom face (α-face) thus favouring the attack of the thiol from the top face (β-face) (see *Figure 24*). Electronic factors may also be playing a role with steric hindrance, so at this moment, it is not completely clear why such results were obtained.

3.6.2 Intramolecular Michael-type Additions

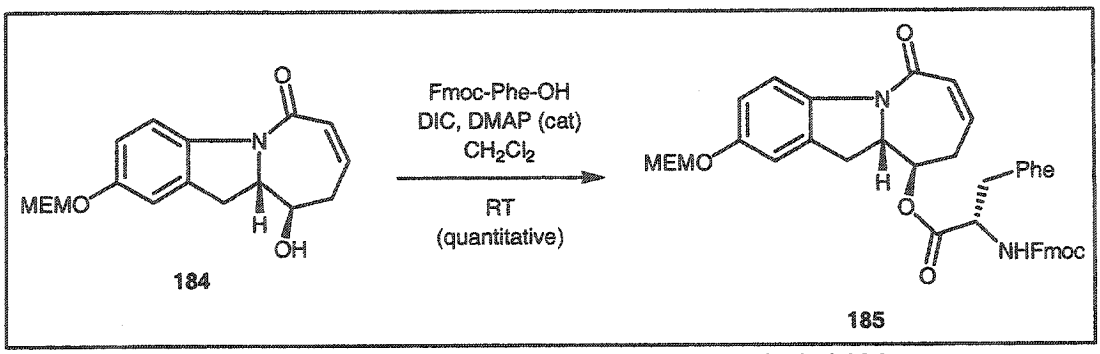
In this section, the strategy envisaged was to couple an amino acid (AA) to the secondary alcohol in the seven-membered ring. The stereochemistry at that centre would direct the facial attack of the NH_2 end group of the amino acid onto the double bond. The AA would bring the diversity in a future library generation. Also, further diversification could be possible by cleaving the ester bond of the amino acid conjugate.

This intramolecular Michael-type addition was first tried with compound **173**. The TBDMS group was removed with TBAF in THF in a 85% yield (*Scheme 72*). The formation of the product **184** was confirmed by the disappearance of the singlets of the TBDMS group in the ^1H NMR spectrum and the appearance of a broad singlet at 2.19 ppm (OH). The IR spectrum revealed that the alcohol had been deprotected by the presence of an O-H stretching signal at 3369 cm^{-1}.



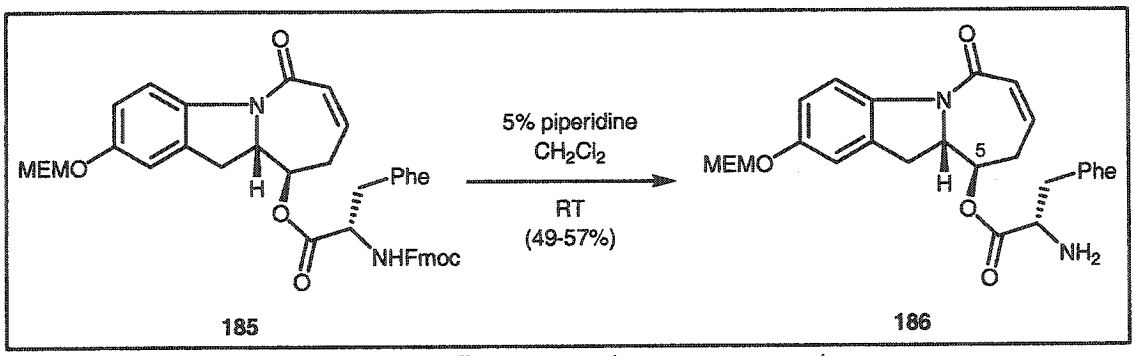
Scheme 72. TBDMS removal.

The amino acid chosen was the phenylalanine (Phe) with the fluorenylmethyloxycarbonyl (Fmoc) group protecting the amine. The coupling was first attempted with 1.25 equivalents of DIC and 1.0 equivalent of amino acid in dichloromethane but afforded the expected compound in a low 56% yield. The coupling was then repeated with double amounts of reagents (2.5 eq. of DIC and 2.0 eq. of AA) in the same solvent. The reaction gave the amino acid derivative **185** in a quantitative yield (*Scheme 73*).



Scheme 73. Coupling of phenylalanine to the alcohol **184**.

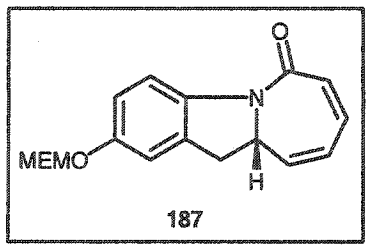
The compound **185** was then subjected to a solution of 5% piperidine in dichloromethane in order to remove the Fmoc group (*Scheme 74*). This reaction did not give the free NH_2 derivative **186** in good yields (49 to 57%), but the formation of the compound was confirmed by ^1H NMR analysis.



Scheme 74. Fmoc protecting group removal.

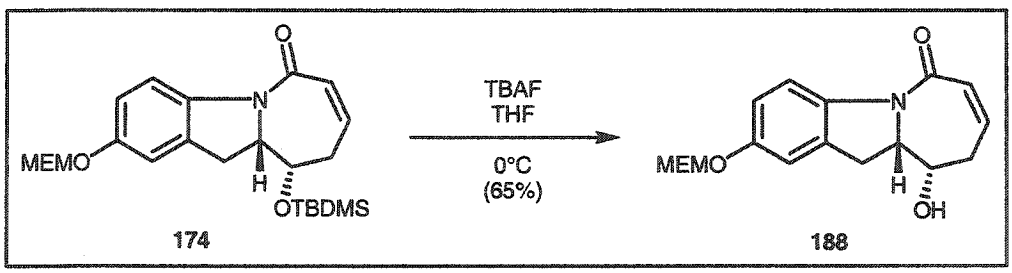
The last step of this sequence involved the cyclization of a new ring, generated from the attack of the NH_2 on the conjugated system. Three different conditions were tried. LDA was used in THF at –78°C but no reaction occurred. The temperature of the mixture was then raised to room temperature but only the hydrolysis of the ester bond of the amino acid side chain was observed. Sodium hydride was then tried in THF at 0°C. Once again the reaction mixture was brought to room temperature. This time a new spot appeared on TLC. The reaction was complete within four hours and generated the eliminated compound **187**, as confirmed by NMR experiments. One last attempt was tried with potassium carbonate in DMF. At room temperature, no product was formed and

the starting material was recovered. When the mixture was heated, the formation of the eliminated product (**187**) could be observed.



187

To explore the scope of this reaction with the diastereomeric hydroxyl derivative, the sequence was repeated with compound **188**. Surprisingly, the TBDMS removal was more difficult with compound **174**. The reaction mixture needed to be kept at 0°C, otherwise the formation of the eliminated compound **187** was observed. For some reasons, the seven-membered ring compound **188** seemed more prone to generate the eliminated product than the other diastereomer. The alcohol **188** was obtained in a 65% yield (*Scheme 75*). The disappearance of the signals of the TBDMS group and the appearance of the OH signal at 1.89 ppm in the ^{1}H NMR spectrum, as well as a pronounced O-H stretch at 3349 cm^{-1} in the IR spectrum confirmed the formation of the compound.

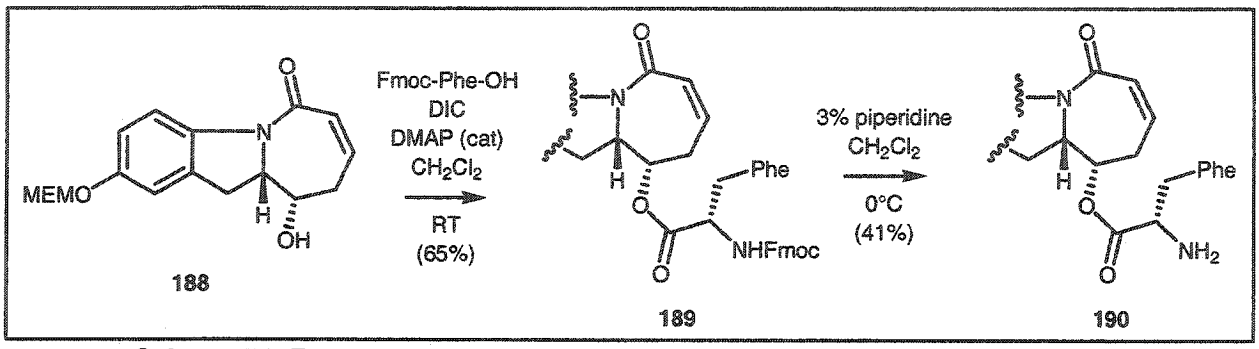


174 **188**

Scheme 75. Formation of the alcohol **188**.

The amino acid coupling was tried once and the conjugated product **189** was obtained in a 65% yield (*Scheme 76*). The removal of the Fmoc protecting group was first tested on a small scale. The expected compound was formed but the major product isolated was the eliminated derivative **187**. The reaction was repeated with 3% piperidine in dichloromethane instead of using a solution of 5%, and the amine derivative **190** was generated in a low 41% yield (see

Scheme 76). The formation of both compounds **189** and **190** was confirmed by NMR analyses.



Scheme 76. Formation of the precursor for the intramolecular Michael-type addition.

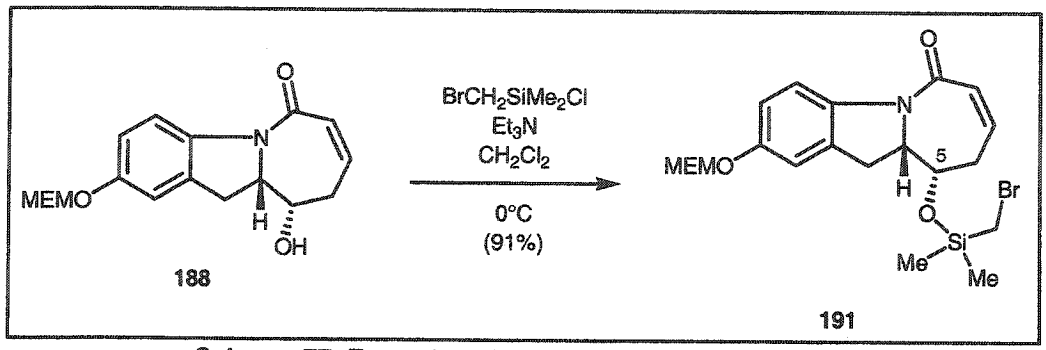
Extra precautions had to be taken in choosing the conditions to cyclize the compound due to its ease at generating the eliminated product. It was decided to try the reaction in DMF without any base present. After heating the reaction mixture to approximately 45°C for 24 hours, the solution was concentrated and the compound dried. A ^{1}H NMR of the product obtained from this reaction was performed, hoping to see the disappearance of the olefinic hydrogens from the spectrum. Unfortunately, signals from 6.29 to 6.16 ppm were still present suggesting that the double bond remained untouched by the NH_2 group. The use of the amino acid strategy did not succeed in generating a diversity-oriented reaction.

3.6.3 Silicon-Tethered Strategy

Intramolecular reactions tend to display a high degree of stereoselectivity. One kind of this type of reaction would be the silicon-tethered reactions.[70] A well studied silicon-based tethered reaction is the intramolecular free radical cyclization employing the temporary silicon connection approach. Indeed, a silicon tether allows the generation of a radical centre on one end that reacts with a proximal radical acceptor with regio- and stereocontrol at the reacting centres.

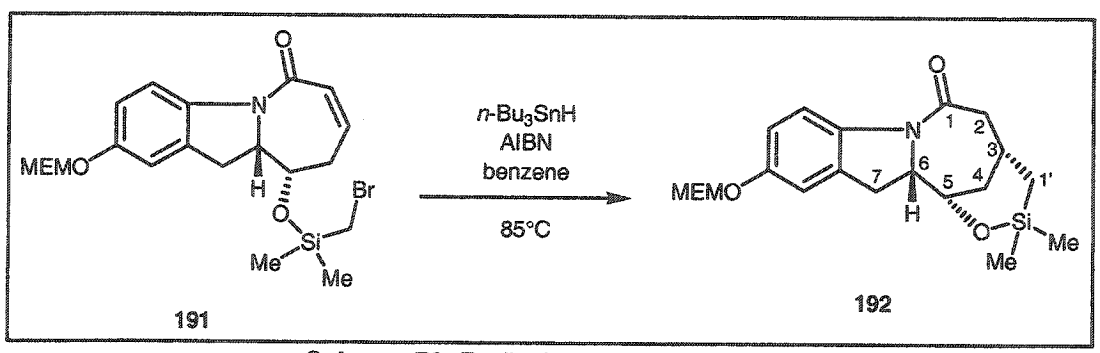
A French group reported the application of the Stork silyl methyl radical cyclization reaction[71] using allylic alcohols.[72] This approach seemed very interesting. It was then decided to try this type of intramolecular reaction with

both seven-membered ring scaffolds. Using the conditions to generate the silicon-tethered compound, the alcohol **188** was treated with (bromomethyl)-chlorodimethylsilane and triethylamine in dichloromethane (*Scheme 77*). The precursor **191** of the free radical reaction was obtained in a 91% yield. A methylene signal appeared as a singlet at 2.32 ppm in the ^{1}H NMR spectrum, indicating the presence of the tether. The methyl groups on the silicon atom appeared as two singlets at 0.17 and 0.14 ppm.



Scheme 77. Formation of the silicon-tethered compound.

Since the C_5 stereogenic centre had the configuration shown in **191**, the tether was located right under the double bond. The chances that the next reaction worked were very good. A solution of compound **191** in benzene was heated to reflux, and a benzene solution of tri-*n*-butyltin hydride and AIBN, used as a radical initiator, was slowly added (*Scheme 78*).[73]



Scheme 78. Radical cyclization reaction.

The reaction could not be followed by TLC, due to the same Rf values of both starting material and product. The reaction was stopped after four hours and a column chromatography was performed to purify the compound. The ^{1}H NMR spectrum showed a mixture of two compounds: the starting material and a new product. In order to identify the new compound formed, a high performance liquid chromatography (HPLC) had to be done.[74] Unfortunately, the mass spectra of the compounds separated by HPLC was not referring to the desired cyclic product. TFA used as a counter ion in the separation was then suspected to decompose the molecules. The separation was tried once again without TFA and this time gave three products. The alcohol **188** (see *Scheme 77*) with M+1: 320.2, the starting material **191** (M+1: 470.2) and a compound with M+1: 392.2. This new product could have had two structures: the desired cyclic derivative **192** or the trimethylsilyl (TMS) derivative generated from the trapping of the CH_2 radical by a hydride.

Happily, the compound formed from the free radical reaction was the cyclized product **192**. The ^{1}H NMR spectrum (*Figure 30*) showed the disappearance of the olefinic signals between 6.29-6.23 ppm (m, 1H) and at 6.13 ppm (dd, J = 11.6, 1.9 Hz, 1H). It also showed a shift of the protons at $C_{1'}$ to 1.16-1.02 ppm. With the help of a NOESY 2D NMR experiment, it was possible to establish that the compound was adopting the configuration shown in *Figure 30*.

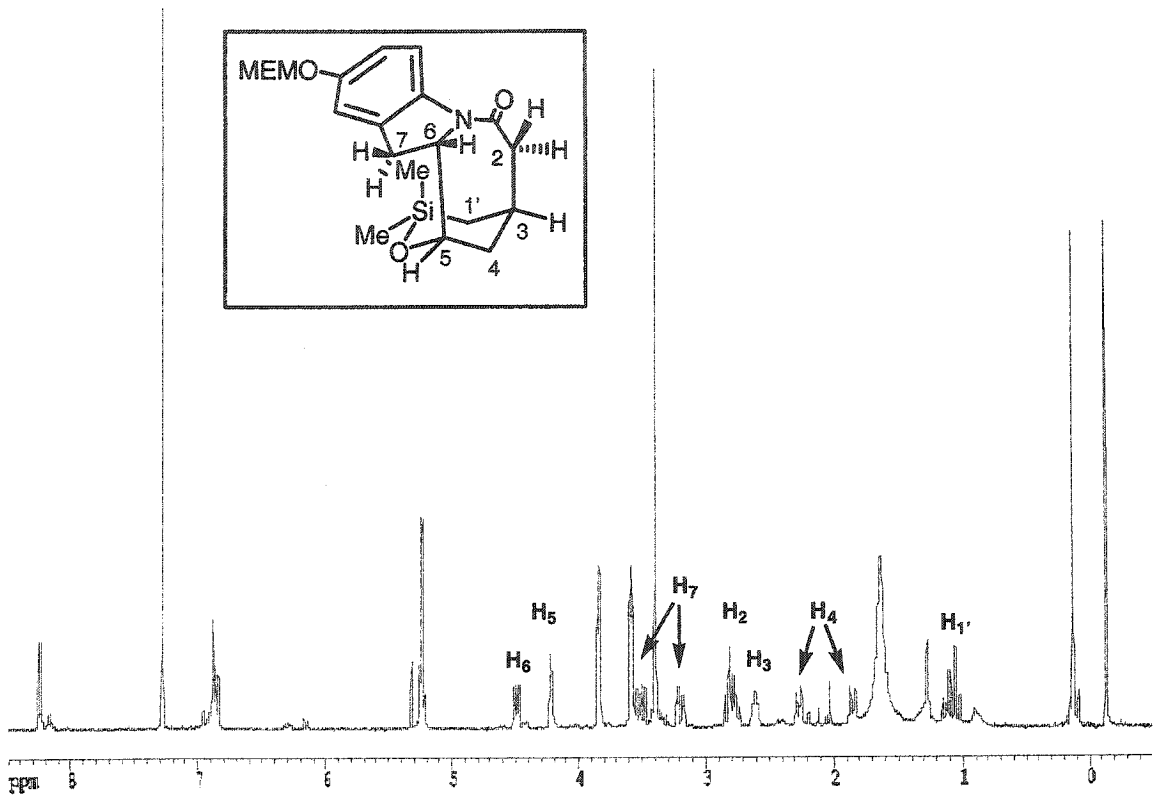
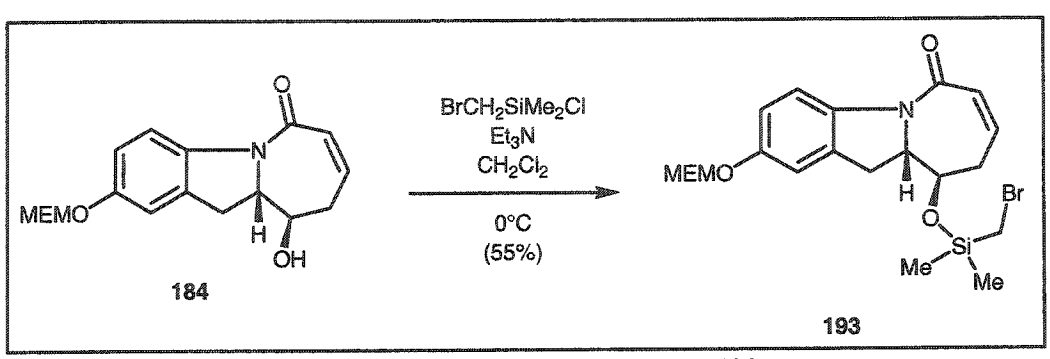


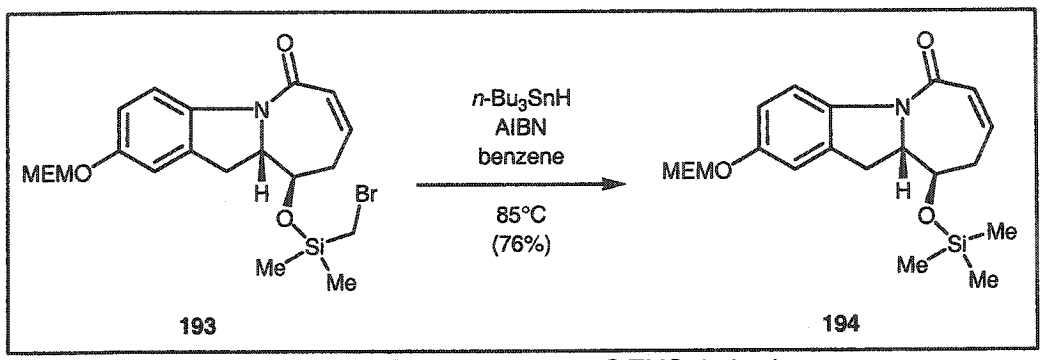
Figure 30. ^{1}H NMR spectrum of the cyclic derivative **192**.

Even if the chances were very low to obtain the cyclic compound from the other isomer, the sequence was tried with the alcohol derivative **184**. Compound **193** was obtained in a 55% yield (*Scheme 79*). The presence of the silicon tether could be confirmed by the appearance of signals at 2.50 ppm (2H) and 0.33 ppm (6H) in the ^{1}H NMR spectrum.



Scheme 79. Formation of derivative **193**.

As expected, when compound **193** was submitted to the free radical reaction conditions, no cyclic derivative was obtained. The only product isolated (76% yield) from the silicon-tethered reaction was the *O*-TMS derivative **194** (*Scheme 80*). The CH_2 radical group was not able to reach the double bond of the seven-membered ring, instead it was reduced. The compound obtained was analyzed by ^1H NMR in which, the olefinic protons were still there, the methylene signal at 2.50 ppm disappeared and a new methyl group appeared close to 0 ppm (Si-CH_3 region).



Scheme 80. Generation of the *O*-TMS derivative.

3.7 Conclusions and Future Work

To conclude, many goals were achieved in this project. To start, a novel method to obtain indoline scaffold has been established. The enantioselective dihydroxylation reaction was not absolutely necessary to study the outcome of the following reactions in the sequence. The racemic mixture was used as such, and can also be tested for biological activity. If compounds turned out to be active, some alternative strategies were suggested in order to obtain enantiopure products.

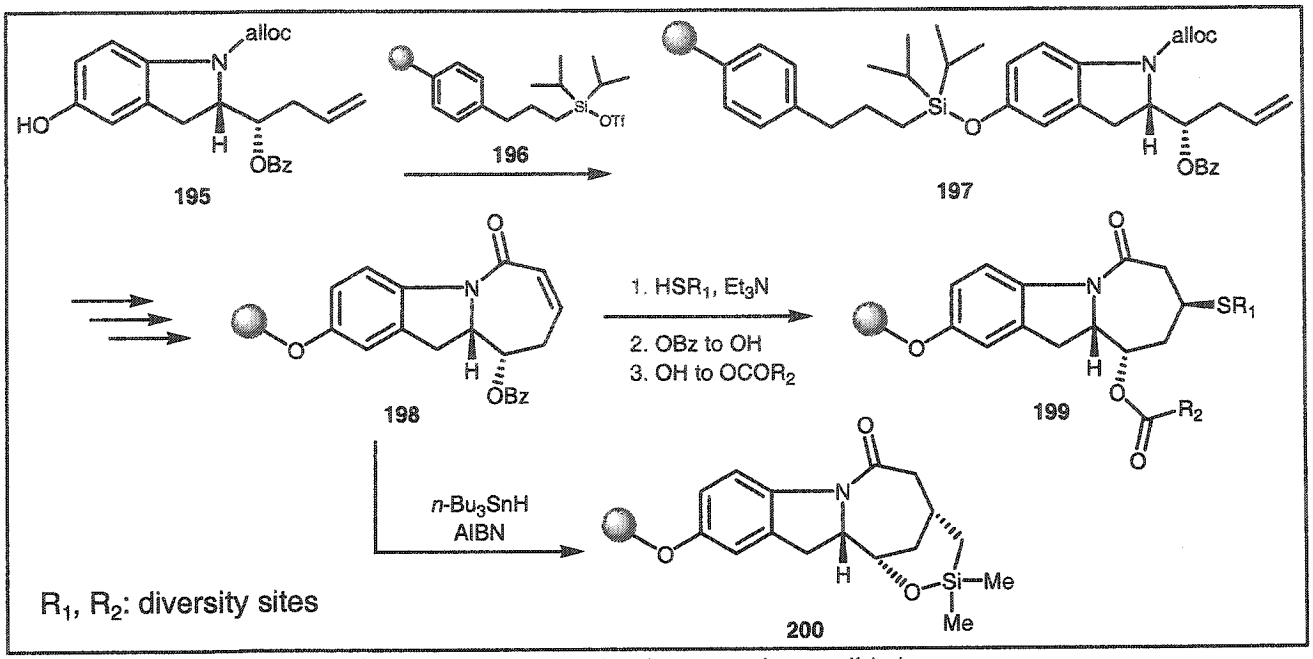
The sequence used to generate the seven-membered ring template was successful. Unfortunately, the allylation reaction was not stereoselective but some solutions were presented to correct the situation. Consequently, it was demonstrated that both allylic alcohol derivatives could be cyclized under the

olefin ring-closing metathesis conditions. Moreover, the seven-membered ring compound having a *cis* relationship between protons at C_5 and C_6 was found to be more reactive than the other diastereomer.

One of the main goals of this project was to synthesize the seven-membered ring template onto a solid support. Unfortunately, the use of a brominated Wang resin to immobilize the indoline scaffold did not give satisfactory results, but with the new solid support available, there are very good chances to achieve this goal. Due to the time limitations, other loading options could not be tried and will be investigated in future.

It was discovered that the seven-membered ring compound **173** was not suitable in performing diversification reactions. In turn, it was demonstrated that the other diastereomer (**174**) could be diversified using DOS. Since the addition of the benzenethiol was facial selective, a library of thiol derivatives could be generated using this strategy. Also, it was demonstrated that the free radical cyclization using the silicon-tethered reaction was possible with derivative **191**. An oxidative cleavage of the tether is possible, generating a diol ready for further diversity.

Finally, future work would be to generate the seven-membered ring template **198** on solid phase (*Scheme 81*). Then, the stereofacial selectivity of the thiol addition on the conjugated system could be studied on solid support (**199**). It would also be interesting to apply the asymmetric free radical cyclization reaction onto solid phase (**200**).



Scheme 81. In planning future work on solid phase.

The compounds synthesized during this project are in themselves a small library and will be utilized for biological testing.

CHAPTER 4: EXPERIMENTAL PROCEDURES

4.1 GENERAL

The infrared (IR) spectra of various compounds were obtained either as neat films, or as a Nujol mull on sodium chloride plates. All IR spectra were recorded on an Excalibur Series Digilab FTS 3000 MX Fourier transform infrared spectrometer (FTIR) and the data were recorded in reciprocal centimeters (cm^{-1}). The reference used was the atmospheric infrared spectrum and this was subtracted from all % transmittance spectra.

The nuclear magnetic resonance spectra (NMR) of all compounds were either measured in a solution of deuterated chloroform ($CDCl_3$), deuterated benzene (C_6D_6), or deuterated acetone [$(CD_3)_2CO$]. The proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 400 MHz on a Bruker DRX-400 spectrometer. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (δ scale). The multiplicity, coupling constants (J in Hz), and number of protons were indicated in parentheses after each chemical shift. The carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz on a Bruker DRX-400 spectrometer. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane (δ scale).

Low resolution mass spectra (MS) were determined on a VG Quattro I (Micromass) mass spectrometer equipped with a pneumatically-assisted electrospray ionization (ES) source, operating in positive mode. High resolution mass spectrometry (HRMS) was performed on a Joel JMS-AX505H mass spectrometer and the molecular weight of all compounds were examined by FAB (Fast Atom Bombardment) accurate mass experiments.

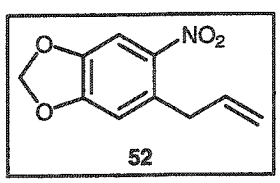
The melting points of crystalline products were measured on a Fisher-Johns Melting Point Apparatus by placing the compound between two small oval sheets of glass and are uncorrected.

Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents and products. Reactions were monitored by thin layer chromatography (TLC) using commercial glass plates pre-coated (250 μm layer thickness) with silica gel 60 F_{254} (E. Merck). The TLC spots were viewed under ultraviolet light and by heating the TLC plate after treatment with a solution of ammonium molybdate in 10% aqueous H_2SO_4. Conventional flash column chromatography, using Silicycle Ultra Pure Silica Gel (230-400 mesh), was performed to purify all compounds. Removal of organic solvents was performed by roto-evaporation on a Büchi R-114 Rotovapor using a Buchi B-178 vacuum system. Trace solvents were removed on a high vacuum pump.

All moisture sensitive reactions were carried out using dry, distilled solvents. Some solvents were kept in constantly maintained stills and freshly distilled prior to use. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled over a mixture of sodium and benzophenone. Dichloromethane (CH_2Cl_2) and benzene were distilled over calcium hydride. All commercial starting materials were purchased from Sigma-Aldrich Chemical Company, Nova Biochem or Strem.

4.2 Syntheses for Model Study System

Nitro derivative **52**

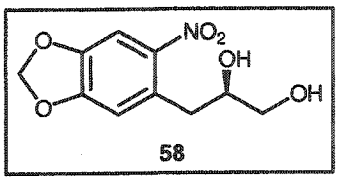


52

To a solution of safrole **44** (5.0 mL, 33.757 mmol) in glacial acetic acid (22.0 mL) at 0°C, a solution (10:1 ratio) of nitric acid and sulfuric acid (4.81 mL) was added drop wise. After 2 hours at 0°C, ethyl acetate (182 mL) was added and the layers were separated. The combined organic layer was washed with water (4 x 110 mL) and with saturated sodium bicarbonate solution (2 x 110 mL), dried over sodium sulfate, filtered and concentrated. Purification by column

chromatography (15% ethyl acetate in hexanes) afforded 4.4043 g (63%) of **52** as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.78 (s, 1H), 6.11 (s, 2H), 5.97 (ddt, *J* = 13.5, 6.5, 6.4 Hz, 1H), 5.14 (dd, *J* = 6.5, 1.4 Hz, 1H), 5.10 (dd, *J* = 13.5, 1.4 Hz, 1H), 3.67 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 146.0, 144.0, 132.0, 117.5, 111.0, 106.0, 103.0, 70.0, 38.0; MS (ES+) *m/z* (M+1) 208.1.

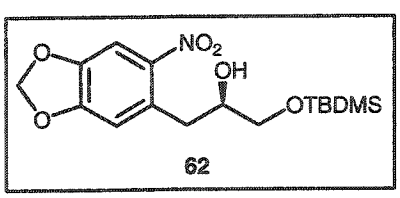
Diol **58**



58

To a solution of *tert*-butanol (15.15 mL) and water (15.15 mL), AD-mix-β (4.244 g) was added. The mixture was stirred at room temperature until both phases were clear and then cooled to 0°C before the olefin **52** (0.628 g, 3.03 mmol) was added. The heterogeneous slurry was stirred vigorously at 0°C for 3 hours. The reaction was quenched with sodium sulfite (4.545 g) at 0°C and stirred to warm up to room temperature over a period of 30 minutes. Ethyl acetate (30 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (15% ethyl acetate in hexanes) afforded 0.6972 g (95%) of **58** as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.86 (s, 1H), 6.12 (s, 2H), 4.07-4.01 (m, 1H), 3.79 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.58 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.16 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.94 (dd, *J* = 13.6, 8.4 Hz, 1H), 2.42 (broad s, 1H, OH), 2.01 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 147.5, 144.0, 131.0, 112.5, 106.5, 104.5, 72.5, 66.5, 37.5; MS (ES+) *m/z* (M+1) 242.1.

Silyl ether **62**

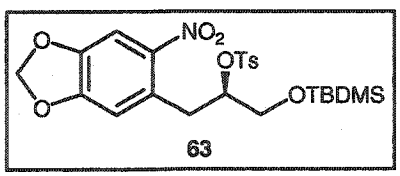


62

To a solution of diol **58** (23.8 mg, 0.099 mmol) in dichloromethane (3 mL) at room temperature, were added triethylamine (33μL, 0.237 mmol), DMAP

(10.0 mg, 0.009 mmol) and *tert*-butyldimethylsilyl chloride (35.7 mg, 0.237 mmol). The reaction mixture was stirred at room temperature for 24 hours. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (10% ethyl acetate in hexanes) afforded 35.1 mg (100%) of **62** as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 6.88 (s, 1H), 6.10 (dd, *J* = 4.9, 1.1 Hz, 2H), 3.97-3.94 (m, 1H), 3.76 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.55 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.15 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.88 (dd, *J* = 13.7, 8.8 Hz, 1H), 2.56 (d, *J* = 4.8 Hz, 1H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.0, 144.0, 131.0, 112.5, 106.0, 104.0, 73.0, 67.5, 37.5, 26.0, -5.0; MS (ES+) *m/z* (M+1) 356.2.

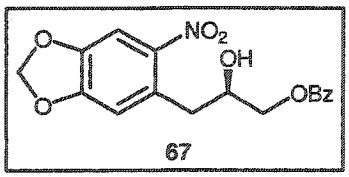
Derivative **63**



63

To a solution of the silyl ether **62** (65.0 mg, 0.184 mmol) in pyridine (3.5 mL) was added *p*-toluenesulfonyl chloride (38.0 mg, 0.202 mmol). The reaction mixture was stirred at room temperature for 3 days. The solvent was evaporated and the resulting mixture was diluted with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (10% ethyl acetate in hexanes) afforded 81.0 mg (86.5%) of **63** as a yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.32 (s, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.64 (s, 1H), 6.10 (dd, *J* = 25.9, 1.1 Hz, 2H), 4.82-4.78 (m, 1H), 3.90-3.89 (m, 2H), 3.44 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.92 (dd, *J* = 14.1, 9.7 Hz, 1H), 2.42 (s, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.5, 145.0, 142.5, 134.0, 130.5, 129.0, 104.0, 83.0, 65.0, 36.0, 26.0, 22.0, -5.0; MS (ES+) *m/z* (M+1) 510.2.

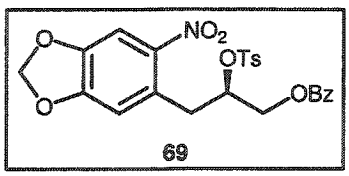
Benzoyl derivative **67**



67

To a solution of diol **58** (1.5082 g, 6.253 mmol) in a mixture of pyridine (50 mL) and dichloromethane (50 mL) was added benzoyl chloride (726 μL, 6.253 mmol) at –20°C. The reaction mixture was stirred for 67 hours. The solvents were evaporated and the resulting mixture was diluted with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (15% ethyl acetate in hexanes) afforded 1.7584 g (81%) of **67** as a yellow oil and 0.1975 g (13%) of starting material; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.49 (s, 1H), 7.45 (dd, *J* = 7.8, 7.6 Hz, 2H), 6.85 (s, 1H), 6.08 (s, 2H), 4.45 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.37 (dd, *J* = 11.3, 5.9 Hz, 1H), 4.30 (broad s, 1H), 3.28 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.03 (dd, *J* = 13.6, 8.6 Hz, 1H), 2.83 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 152.5, 147.5, 144.0, 135.0, 130.5, 129.5, 112.5, 106.0, 104.0, 71.0, 69.0, 39.0; MS (ES+) *m/z* (M+1) 346.1.

Compound **69**

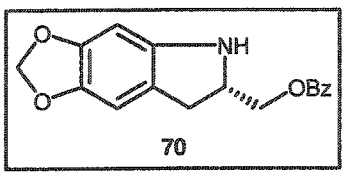


69

To a solution of the benzoyl derivative **67** (1.0944 g, 3.169 mmol) in dichloromethane (38 mL), DMAP (0.5808 g, 4.754 mmol) was added followed by *p*-toluenesulfonyl chloride (0.7855 g, 4.12 mmol). The reaction mixture was stirred at 35°C for 24 hours. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (15% to 50% ethyl acetate in hexanes) afforded 1.5541 g (98%) of **69** as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 0.9 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 7.9, 7.6 Hz, 2H), 7.42 (s, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 6.12 (dd, *J* = 24.8, 1.0 Hz, 2H), 5.21-5.17 (m, 1H), 4.56 (d, *J* = 4.7 Hz, 2H), 3.53 (dd, *J* = 14.0, 3.4 Hz, 1H), 3.04 (dd, *J* = 14.0, 9.4

Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 153.0, 148.0, 145.5, 142.5, 134.5, 131.0, 130.5, 128.0, 127.5, 113.0, 106.0, 104.0, 80.0, 66.0, 37.0, 22.0; MS (ES+) *m/z* (M+1) 500.1.

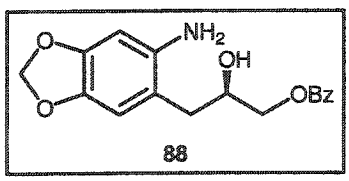
Indoline moiety **70**



70

To a solution of **69** (17.2 mg, 0.034 mmol) in THF (2.5 mL), nitrogen was bubbled before palladium 10 wt. % on activated carbon (0.003 g) and potassium carbonate (7.2 mg, 0.052 mmol) were added. The reaction mixture was stirred under a hydrogen atmosphere for 3 days. The reaction was filtered through celite using ethyl acetate and concentrated. Purification by column chromatography (10% ethyl acetate in hexanes) afforded 6.2 mg (61%) of **70** as a pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.47 (dd, J = 7.9, 7.5 Hz, 2H), 6.65 (s, 1H), 6.29 (s, 1H), 5.86 (d, J = 3.6 Hz, 2H), 4.45 (dd, J = 10.4, 4.1 Hz, 1H), 4.32 (dd, J = 10.4, 7.7 Hz, 1H), 4.29-4.26 (m, 1H), 3.84 (broad s, 1H, NH), 3.18 (dd, J = 15.4, 8.6 Hz, 1H), 2.80 (dd, J = 15.4, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 147.5, 145.0, 140.5, 134.5, 131.0, 129.0, 119.5, 106.0, 101.0, 94.0, 69.0, 59.5, 34.0; MS (ES+) *m/z* (M+1) 298.1.

Amino alcohol **88**

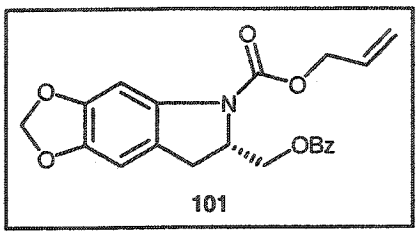


88

To a solution of **67** (0.1043 g, 0.302 mmol) in THF (15 mL), nitrogen was bubbled before palladium 10 wt. % on activated carbon (31.3 mg) was added. The reaction mixture was stirred under a hydrogen atmosphere for 4 hours. The reaction was filtered through celite using ethyl acetate. The resulting solution was concentrated, dried and afforded 81.6 mg (86%) of **88** as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.48 (dd, J = 7.8, 7.6 Hz, 2H), 6.60 (s, 1H), 6.36 (s, 1H), 5.88 (s, 2H), 4.44 (dd, J = 11.1, 3.7 Hz, 1H), 4.35-4.26 (m, 2H), 2.81 (d, J = 5.8

Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 148.0, 142.0, 140.0, 134.5, 130.0, 129.0, 115.0, 110.0, 101.5, 99.5, 72.0, 69.0, 35.5; MS (ES+) *m/z* (M+1) 316.1.

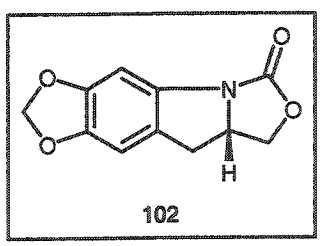
Allyloxycarbonyl derivative **101**



101

To a solution of **70** (62.7 mg, 0.211 mmol) in dichloromethane (6 mL) at 0°C, were added pyridine (34 μL, 0.422 mmol) and allyl chloroformate (34 μL, 0.316 mmol). The reaction mixture was stirred at 0°C for 30 minutes. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (15% ethyl acetate in hexanes) afforded 80.4 mg (100%) of **101** as a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.5 Hz, 2H), 7.56-7.53 (m, 2H), 7.39 (dd, *J* = 7.8, 7.6 Hz, 2H), 6.67 (s, 1H), 5.98 (broad s, 1H), 5.94 (dd, *J* = 5.9, 1.3 Hz, 2H), 5.36 (d, *J* = 16.9 Hz, 1H), 5.26 (d, *J* = 10.1 Hz, 1H), 4.90 (broad s, 1H), 4.74 (broad s, 1H), 4.64 (broad s, 1H), 4.49 (broad s, 1H), 4.42 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.37 (dd, *J* = 15.9, 9.8 Hz, 1H), 2.90 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 147.0, 144.5, 137.0, 130.5, 129.5, 126.0, 124.8, 119.8, 105.5, 102.0, 98.5, 66.5, 66.0, 59.0, 32.0; MS (ES+) *m/z* (M+1) 382.1.

Tetracyclic compound **102**

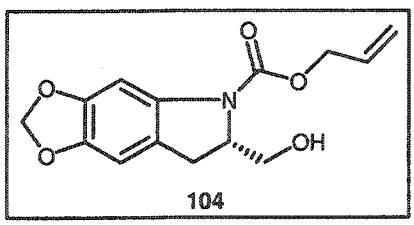


102

To a solution of the allyloxycarbonyl derivative **101** (15.3 mg, 0.040 mmol) in methanol (2 mL) at 0°C, potassium carbonate (6.7 mg, 0.048 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred for 20 hours. Methanol was removed and the mixture was diluted with dichloromethane. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% ethyl

acetate in hexanes) afforded 9.2 mg (83%) of **102** as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 1H), 6.68 (s, 1H), 5.97 (dd, *J* = 9.9, 1.3 Hz, 2H), 4.90 (dddd, *J* = 9.3, 8.7, 8.6, 7.9 Hz, 1H), 4.77 (dd, *J* = 8.6, 8.5 Hz, 1H), 4.28 (dd, *J* = 8.6, 7.8 Hz, 1H), 3.17 (dd, *J* = 15.4, 8.8 Hz, 1H), 3.02 (dd, *J* = 15.4, 9.3 HZ, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 147.5, 146.0, 135.5, 125.0, 106.0, 102.5, 99.0, 72.0, 60.5, 36.0; MS (ES+) *m/z* (M+1) 220.1.

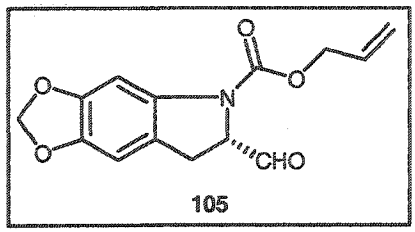
Alcohol **104**



104

To a solution of **70** (0.1422 g, 0.478 mmol) in methanol (24 mL) at 0°C, potassium carbonate (73.6 mg, 0.526 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. Methanol was removed and the mixture was diluted with dichloromethane. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, concentrated and dried to afford the crude **103**. To a solution of the crude **103** in dichloromethane (20 mL) at –5°C, were added pyridine (46 μL, 0.574 mmol) and allyl chloroformate (55 μL, 0.522 mmol). The reaction mixture was stirred at –5°C for 30 minutes. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% to 30% ethyl acetate in hexanes) afforded 79.9 mg (60% after two steps) of **104** as a pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.65 (s, 1H), 6.03 (m, 1H), 5.94 (s, 2H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.31 (d, *J* = 10.4 Hz, 1H), 4.77 (broad s, 2H), 4.67 (broad s, 1H), 3.77-3.73 (m, 2H), 3.29 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.78 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 146.0, 143.0, 119.0, 105.5, 102.0, 67.0, 65.5, 62.5, 31.0; MS (ES+) *m/z* (M+1) 278.1.

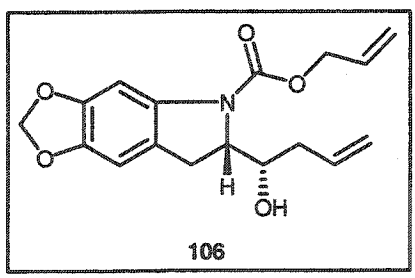
Aldehyde **105**



105

To a solution of **104** (69.5 mg, 0.251 mmol) in dichloromethane (2.7 mL) at room temperature were added dimethyl sulfoxide (0.70 mL), triethylamine (175 µL, 1.253 mmol) and sulfur trioxide/pyridine complex (0.1595 g, 1.002 mmol). The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched by adding a saturated ammonium chloride solution (2 mL) and extracted with ethyl acetate. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (5% to 50% ethyl acetate in hexanes) afforded 63.9 mg (93%) of **105** as an oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.57 (s, 1H), 6.64 (s, 1H), 6.04 (broad s, 1H), 5.95 (d, *J* = 2.6 Hz, 2H), 5.42-5.26 (m, 2H), 4.88-4.85 (m, 1H), 4.72 (s, 2H), 3.41-3.34 (m, 1H), 3.11 (dd, *J* = 16.3, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5, 183.5, 147.5, 145.0, 136.0, 120.0, 105.5, 102.5, 99.0, 75.0, 67.5, 30.0; MS (ES+) *m/z* (M+1) 276.1.

Allylic alcohol **106**

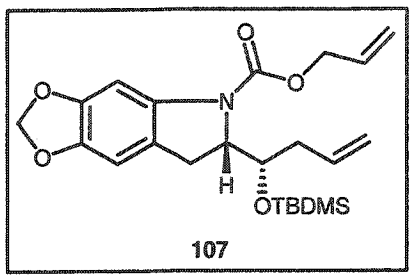


106

To a solution of **105** (10.0 mg, 0.037 mmol) in THF (1 mL) at –78°C was added allylmagnesium bromide (1.0 M in ether, 41 µL, 0.041 mmol). The reaction mixture was stirred at 0°C for 2 hours. The reaction was quenched by adding a saturated ammonium chloride solution (0.5 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (5% ethyl acetate in hexanes) afforded 4.0 mg (34%) of **106** as a colourless oil and 2.9 mg (28%) of starting material; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (broad s, 1H), 6.64 (s, 1H), 6.07-5.97 (m, 1H), 5.94 (s, 2H), 5.84 (broad s, 1H), 5.39 (dd, *J* = 17.2, 1.3 Hz,

1H), 5.30 (dd, J = 10.4, 1.2 Hz, 1H), 5.15 (dd, J = 3.0, 1.1 Hz, 1H), 5.12 (dd, J = 10.7, 1.1 Hz, 1H), 4.75 (d, J = 5.6 Hz, 2H), 4.68 (ddd, J = 9.9, 6.2, 2.3 Hz, 1H), 3.93 (broad s, 1H), 3.22 (dd, J = 16.2, 10.0 Hz, 1H), 2.88 (d, J = 16.1 Hz, 1H), 2.25 (broad s, 1H), 2.06 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 147.0, 144.0, 140.0, 136.0, 135.0, 132.5, 119.5, 119.0, 105.5, 101.0, 99.5, 73.0, 67.0, 65.0, 37.5, 29.5; MS (ES+) *m/z* (M+1) 318.1.

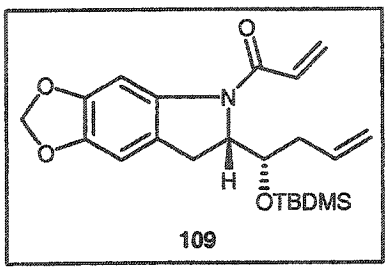
TBDMS ether **107**



107

To a solution of **106** (16.5 mg, 0.052 mmol) in DMF (0.3 mL) at room temperature, were added imidazole (6.7 mg, 0.099 mmol) and *tert*-butyldimethylsilyl chloride (14.1 mg, 0.094 mmol). The reaction mixture was stirred at room temperature for 24 hours. The solvent was evaporated and the resulting mixture was diluted with dichloromethane. The solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (5% ethyl acetate in hexanes) afforded 15.1 mg (67%) of **107** as a yellowish oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (broad s, 1H), 6.63 (s, 1H), 6.01 (broad s, 1H), 5.93 (d, J = 1.1 Hz, 2H), 5.72-5.70 (m, 1H), 5.39 (dd, J = 17.2, 1.0 Hz, 1H), 5.30 (dd, J = 10.5, 0.9 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 4.91 (dd, J = 17.1, 1.4 Hz, 1H), 4.72 (broad s, 2H), 4.56 (broad s, 1H), 4.12 (broad s, 1H), 3.10 (d, J = 6.6 HZ, 2H), 2.01-1.90 (m, 2H), 0.92 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 144.0, 138.0, 136.0, 133.0, 124.0, 120.0, 117.5, 105.5, 102.0, 99.0, 72.0, 66.0, 64.0, 35.5, 29.0, 26.0, -4.5; MS (ES+) *m/z* (M+1) 432.3.

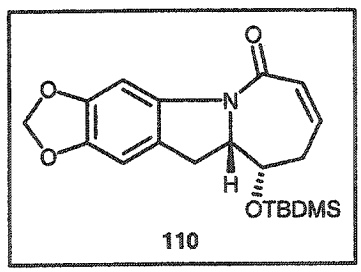
RCM precursor **109**



109

To a solution of **107** (15.0 mg, 0.035 mmol) in dichloromethane (2 mL) at 0°C, were added $Pd(PPh_3)_4$ (2.0 mg, 0.002 mmol) and morpholine (6.4 μL, 0.073 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 hours. The solvent was evaporated and afforded crude **108**; MS (ES+) *m/z* (M+1) 348.2. To a solution of the crude **108** in dichloromethane (2 mL) at 0°C, were added DIPEA (12.1 μL, 0.070 mmol), HATU (14.5 mg, 0.0382 mmol) and acrylic acid (2.6 μL, 0.038 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (5% ethyl acetate in hexanes) afforded 4.9 mg (35% after two steps) of **109** as a pale yellow oil; MS (ES+) *m/z* (M+1) 402.2.

Seven-membered ring template **110**



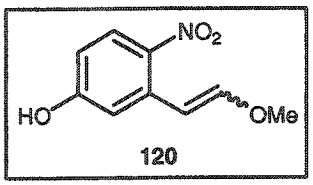
110

To a solution of **109** (4.9 mg, 0.012 mmol) in dichloromethane (1 mL) at room temperature was added a solution of Grubbs' catalyst **90** (10 mol %, 1.0 mg, 0.001 mmol) in dichloromethane (1 mL). The reaction mixture was allowed to stir at that temperature for 40 minutes. The solvent was evaporated. Purification by column chromatography (25% ethyl acetate in hexanes) afforded 3.6 mg (79%) of product as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 6.62 (s, 1H), 6.28-6.22 (m, 1H), 6.11 (dd, *J* = 11.6, 2.1 Hz, 1H), 5.94 (s, 2H), 4.33 (ddd, *J* = 10.3, 2.9, 2.5 Hz, 1H), 4.18 (ddd, *J* = 6.6, 6.6, 2.5 Hz, 1H), 3.30 (dd, *J* = 15.7, 10.2 HZ, 1H), 3.01 (dd, *J* = 15.7, 2.9 Hz, 1H), 2.62 (ddd, *J* = 15.8, 6.8, 6.6 Hz, 1H), 2.36 (dddd, *J* = 15.8, 6.8, 6.6, 2.1 Hz, 1H), 0.69 (s, 9H), 0.02 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.5, 144.0, 138.0, 135.5, 130.0, 124.8, 105.2, 101.0, 100.2, 76.5, 64.5, 37.5, 32.5, 25.5, 18.0, -4.5; MS (ES+) *m/z* (M+1) 374.2.

4.3 Syntheses for MEM Derivatives

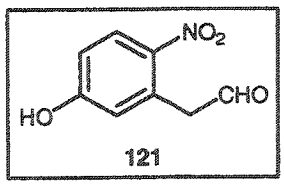
Enol ether **120**



120

To a suspension of (methoxymethyl)-triphenylphosphonium chloride (19.74 g, 57.59 mmol) in THF (162 mL) at 0°C was added drop wise potassium *tert*-butoxide (1.0M in THF, 120 mL, 119.99 mmol). The resulting mixture was stirred at 0°C for 1 hour. A solution of 5-hydroxy-2-nitrobenzaldehyde (8.02 g, 47.996 mmol) in THF (71 mL) was then added drop wise at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding water (178 mL) at 0°C. After removal of THF, the aqueous layer was acidified to pH 6 by adding a 2N HCl solution at 0°C and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (10% to 30% ethyl acetate in hexanes) afforded 9.02 g (96%) of **120** as a yellow oil; IR (Nujol) 3289, 1634, 1614, 1568, 1502, 1461, 1212, 814 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) of *trans* δ 8.02 (d, *J* = 9.0 Hz, 1H), 7.05 (d, *J* = 12.8 Hz, 1H), 6.86 (s, 1H), 6.72 (d, *J* = 9.0 Hz, 1H), 6.56 (d, *J* = 12.8 Hz, 1H), 5.47 (broad s, 1H, OH), 3.77 (s, 3H); ^1H NMR (400 MHz, $CDCl_3$) of *cis* δ 7.94 (d, *J* = 9.0 Hz, 1H), 7.56 (d, *J* = 2.8 Hz, 1H), 6.71 (dd, *J* = 9.0, 2.8 Hz, 1H), 6.34 (d, *J* = 7.3 Hz, 1H), 5.91 (d, *J* = 7.3 Hz, 1H), 5.51 (broad s, 1H, OH), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) of *trans* δ 159.9, 152.9, 141.2, 135.9, 128.6, 113.8, 113.4, 101.7, 57.1; ^{13}C NMR (100 MHz, $CDCl_3$) of *cis* δ 159.3, 151.6, 141.2, 133.4, 127.9, 117.4, 113.6, 99.9, 61.5; HRMS (FAB) *m/z* (MH^+) calcd 196.0610 for $C_9H_{10}NO_4$, obsd 196.0603.

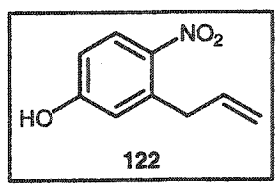
Aldehyde **121**



121

To a solution of **120** (9.02 g, 46.216 mmol) in THF (122 mL) was added a 1.5N HCl solution (243 mL). The mixture was then heated to 60°C and stirred overnight. After removal of THF, the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine solution several times until neutral. The organic layer was dried over sodium sulfate, filtered and concentrated to afford 8.18 g (98%) of crude aldehyde **121** as a solid; mp 101.8-103.0°C; IR (Nujol) 3243, 1705, 1593, 1527, 1457, 843 cm^{-1}; ^1H NMR [400 MHz, $(CD_3)_2CO$] δ 9.79 (s, 1H), 8.13 (d, *J* = 9.0 Hz, 1H), 6.98 (dd, *J* = 9.0, 2.7 Hz, 1H), 6.91 (d, *J* = 2.6 Hz, 1H), 4.16-4.13 (m, 2H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 198.0, 163.5, 142.1, 128.9, 120.9, 115.8, 49.5; HRMS (FAB) *m/z* (MH^+) calcd 182.0453 for $C_8H_8NO_4$, obsd 182.0490.

Olefin **122**

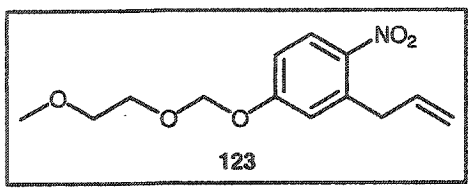


122

To a suspension of methyltriphenylphosphonium bromide (40.32 g, 112.87 mmol) in THF (440 mL) at 0°C was added drop wise sodium hexamethyldisylazide (1.0M in THF, 104 mL, 103.84 mmol). The resulting mixture was stirred at 0°C for 1 hour. A solution of **121** (8.18 g, 45.15 mmol) in THF (40 mL) was then added drop wise at 0°C. The reaction mixture was stirred at 0°C for 2 hours. The reaction was quenched by adding water (~290 mL) at 0°C. After removal of THF, the aqueous layer was acidified to pH 6 by adding a 2N HCl solution at 0°C and extracted with ethyl acetate. The organic layers were dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (15% ethyl acetate in hexanes) afforded 6.97 g (86%) of **122** as a yellow oil; IR (Nujol) 3321, 1618, 1574, 1516, 1462, 1068, 1038, 914, 831 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.4, 2.3 Hz, 1H), 6.84-6.82 (m, 2H), 6.47 (broad s, 1H, OH), 5.98 (ddt, *J* = 16.9, 10.0, 6.5 Hz, 1H), 5.14 (dd, *J* = 10.0, 1.3 Hz, 1H), 5.10 (dd, *J* = 17.0, 1.3 Hz, 1H), 3.73 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

160.6, 142.3, 139.4, 135.3, 128.5, 118.5, 117.7, 114.4, 38.1; HRMS (FAB) *m/z* (MH^+) calcd 180.0661 for $C_9H_{10}NO_3$, obsd 180.0611.

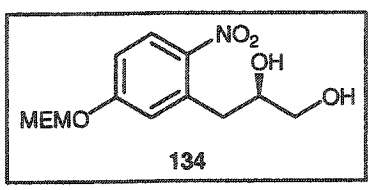
MEM derivative **123**



123

To a solution of **122** (3.76 g, 20.97 mmol) in dichloromethane (110 mL) were added DIPEA (7.31 mL, 41.95 mmol) and MEMCl (3.59 mL, 31.46 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and was overnight. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 5.01 g (89%) of **123** as a pale yellowish oil; IR (neat) 2925, 1607, 1580, 1519, 1160, 1108, 1069, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.9 Hz, 1H), 7.03-6.99 (m, 2H), 5.99 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.35 (s, 2H), 5.14 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.12 (dd, *J* = 16.8, 1.3 Hz, 1H), 3.85-3.83 (m, 2H), 3.74 (d, *J* = 6.4 Hz, 2H), 3.58-3.56 (m, 2H), 3.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 143.3, 138.6, 135.4, 127.8, 119.2, 117.5, 114.5, 93.6, 71.9, 68.5, 59.4, 38.1; HRMS (FAB) *m/z* (MH^+) calcd 268.1185 for $C_{13}H_{18}NO_5$, obsd 268.1364.

Diol **134**

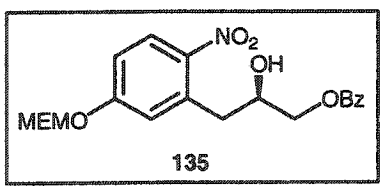


134

To a solution of *tert*-butanol (94 mL) and water (94 mL), AD-mix-β (26.22 g) was added. The mixture was stirred at room temperature until both phases were clear and then cooled at 0°C before the olefin **123** (5.01 g, 18.73 mmol) was added. The heterogeneous slurry was stirred vigorously from 0°C to room temperature during 24 hours. The reaction was quenched with sodium sulfite (28.09 g) at 0°C and stirred to warm up to room temperature over a period of 30 minutes. Ethyl acetate (187 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 94 mL). The combined

organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (50% to 75% ethyl acetate in hexanes, followed by 5% methanol in dichloromethane) afforded 5.60 g (99%) of **134** as a pale yellow oil; IR (neat) 3418, 2931, 2884, 1611, 1579, 1518, 1161, 1105, 1072, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.1 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 7.03 (dd, *J* = 9.1, 2.7 Hz, 1H), 5.35 (s, 2H), 4.04 (broad s, 1H), 3.84 (t, *J* = 4.5 Hz, 2H), 3.77 (d, *J* = 11.0 Hz, 1H), 3.61-3.58 (m, 1H), 3.58-3.56 (m, 2H), 3.36 (s, 3H), 3.22 (dd, *J* = 13.4, 4.3 Hz, 1H), 3.02 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.69 (d, *J* = 3.9 Hz, 1H, OH), 2.29 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 143.6, 137.1, 127.9, 120.4, 115.1, 93.6, 72.5, 71.8, 68.4, 66.5, 59.3, 37.7; HRMS (FAB) *m/z* (MH^+) calcd 302.1240 for $C_{13}H_{20}NO_7$, obsd 302.1170.

Benzoyl derivative **135**

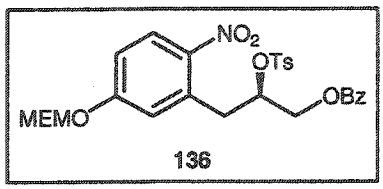


135

To a solution of diol **134** (5.60 g, 18.59 mmol) in dichloromethane (115 mL) at –5°C, pyridine (1.5 mL, 18.59 mmol) was added followed by benzoyl chloride (2.16 mL, 18.59 mmol). The reaction mixture was stirred at –5°C for 24 hours. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (25% to 50% ethyl acetate in hexanes) afforded 6.72 g (89%) of **135** as a yellow oil; IR (neat) 3464, 2933, 2892, 1717, 1608, 1581, 1518, 1123, 1071, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.3 Hz, 2H), 8.07 (d, *J* = 9.3 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (dd, *J* = 7.4, 7.3 Hz, 2H), 7.10 (d, *J* = 2.6 Hz, 1H), 7.05 (dd, *J* = 9.2, 2.6 Hz, 1H), 5.35 (s, 2H), 4.49 (dd, *J* = 11.3, 3.9 Hz, 1H), 4.43 (dd, *J* = 11.4, 5.8 Hz, 1H), 4.38-4.32 (m, 1H), 3.83 (t, *J* = 4.5 Hz, 2H), 3.57-3.55 (m, 2H), 3.37 (s, 3H), 3.37 (dd, *J* = 13.3, 4.1 Hz, 1H), 3.16 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.59 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 161.0, 143.7, 136.5, 133.9, 133.6, 130.5, 130.1, 128.9, 128.1, 120.5, 115.2, 93.6, 71.8, 70.6, 68.8, 68.5,

59.4, 38.2; HRMS (FAB) *m/z* (MH^+) calcd 406.1502 for $C_{20}H_{24}NO_8$, obsd 406.1577.

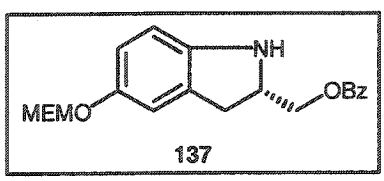
Compound **136**



136

To a solution of **135** (6.72 g, 16.57 mmol) in dichloromethane (75 mL), DMAP (3.04 g, 24.85 mmol) was added followed by *p*-toluenesulfonyl chloride (4.11 g, 21.54 mmol). The reaction mixture was stirred at 35°C overnight. The reaction was quenched by adding water and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (50% ethyl acetate in hexanes) afforded 8.92 g (96%) of **136** as a pale yellow oil; IR (Nujol) 1718, 1581, 1515, 1176, 1098, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.3, 1.2 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.47 (dd, *J* = 7.5, 7.4 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.00 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.97 (d, *J* = 2.6 Hz, 1H), 5.33 (dd, *J* = 17.6, 7.2 Hz, 2H), 5.22-5.19 (m, 1H), 4.56-4.54 (m, 2H), 3.87-3.84 (m, 2H), 3.62-3.58 (m, 3H), 3.40 (s, 3H), 3.12 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 161.2, 144.9, 142.7, 134.5, 133.7, 133.5, 130.2, 130.1, 129.8, 128.8, 128.3, 127.9, 121.3, 115.7, 93.7, 79.4, 71.8, 68.7, 65.7, 59.4, 37.3, 22.0; HRMS (FAB) *m/z* (MH^+) calcd 560.1590 for $C_{27}H_{30}NO_{10}S$, obsd 560.1335.

Indoline template **137**

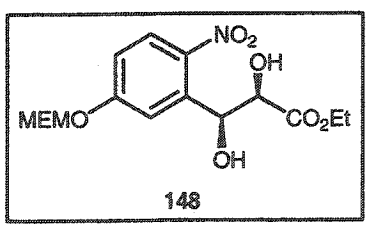


137

To a solution of **136** (8.92 g, 15.94 mmol) in THF (80 mL), nitrogen was bubbled before palladium 10 wt. % on activated carbon (2.68 g) and potassium carbonate (6.69 g, 47.82 mmol) were added. The reaction mixture was stirred under a hydrogen atmosphere for 48 hours. The reaction was filtered through celite using ethyl acetate, concentrated and then dried. No purification was performed at this stage. The crude material was

diluted in DMF (48 mL). Potassium carbonate (6.69 g, 47.82 mmol) was added and the reaction mixture was stirred and heated at 40°C for 26 hours. The reaction mixture was diluted with dichloromethane (48 mL) and then filtered through celite and rinsed with the same solvent to remove most of the potassium carbonate (solid). The solvents were removed and the residue was further diluted with dichloromethane. The organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% to 30% ethyl acetate in hexanes) afforded 4.55 g (80% after 2 steps) of **137** as a pale yellow oil; IR (neat) 3363, 2933, 2887, 1719, 1602, 1491, 1275, 1112, 1072, 1014, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 7.5, 7.3 Hz, 2H), 6.91 (s, 1H), 6.77 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.19 (s, 2H), 4.45 (dd, *J* = 10.4, 4.0 Hz, 1H), 4.34-4.26 (m, 2H), 4.00 (broad s, 1H, NH), 3.85 (t, *J* = 4.7 Hz, 2H), 3.61-3.58 (m, 2H), 3.41 (s, 3H), 3.25 (dd, *J* = 15.8, 8.6 Hz, 1H), 2.87 (dd, *J* = 15.8, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 151.5, 145.6, 133.5, 130.3, 130.0, 129.5, 128.8, 116.3, 114.8, 110.4, 95.2, 72.1, 68.5, 67.8, 59.4, 58.5, 33.6; HRMS (FAB) *m/z* (M^+) calcd 357.1576 for $C_{20}H_{23}NO_5$, obsd 357.2052.

Diol **148**

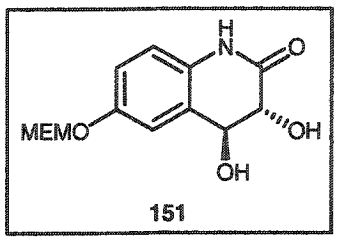


148

To a solution of *tert*-butanol (3.8 mL) and water (3.8 mL), AD-mix-α (1.0759 g) and methanesulfonamide (73.1 mg, 0.768 mmol) were added. The mixture was stirred at 0°C for 15 minutes before the olefin **147** (0.250 g, 0.768 mmol) was added. The heterogeneous slurry was stirred vigorously from 0°C to room temperature during 24 hours. The reaction was quenched with sodium sulfite (1.153 g) at 0°C and stirred to warm up to room temperature over a period of 1 hour. Ethyl acetate was added and the aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with a 2N KOH solution and was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (50% ethyl acetate in

hexanes) afforded 0.1485 g (54%) of **148** as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 9.1 Hz, 1H), 7.46 (d, *J* = 2.6 Hz, 1H), 7.08 (dd, *J* = 9.1, 2.6 Hz, 1H), 5.82 (d, *J* = 4.4 Hz, 1H), 5.35 (s, 2H), 4.51 (d, *J* = 4.4 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.83-3.80 (m, 2H), 3.55-3.48 (m, 4H), 3.33 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 161.7, 141.4, 140.0, 127.8, 117.0, 115.7, 93.7, 73.5, 71.8, 70.4, 68.4, 62.8, 59.3, 14.5; MS (ES+) *m/z* (M+1) 360.2.

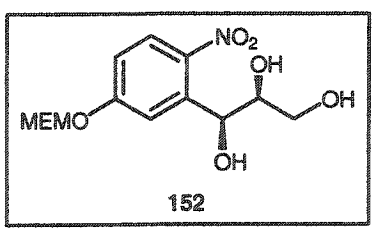
Six-membered ring derivative **151**



151

To a slurry of activated Raney® Ni (40.0 mg) in degassed ethanol anhydrous (2 mL) was added diol **148** (13.8 mg, 0.038 mmol) using ethanol. The reaction mixture was stirred vigorously at reflux for 24 hours. The solution was filtered through celite and rinsed with dichloromethane. The solvent was removed and compound **151** was dried; ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ 7.25 (s, 1H), 6.95 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 5.24 (s, 2H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.10 (d, *J* = 10.8 Hz, 1H), 3.83-3.80 (m, 2H), 3.59-3.56 (m, 2H), 3.35 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ 171.4, 154.1, 129.6, 128.2, 117.0, 116.4, 114.5, 94.0, 72.6, 71.8, 70.8, 67.7, 58.1; MS (ES+) *m/z* (M+1) 284.1.

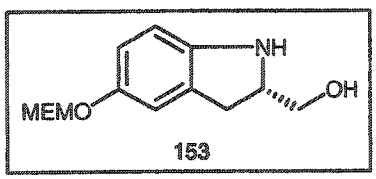
Triol **152**



152

To a solution of **148** (44.8 mg, 0.125 mmol) in THF (2 mL) at 0°C, was added lithium borohydride (2.0 M in ether, 125 µL, 0.249 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was quenched by adding a saturated ammonium chloride solution (1 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated to afford 39.5 mg (100%) of **152** as an oil; MS (ES+) *m/z* (M+1) 318.1.

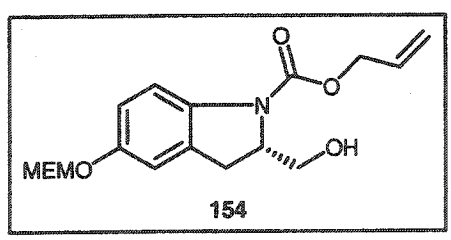
Amino alcohol **153**



153

To a solution of **137** (0.4237 g, 1.18 mmol) in methanol (20 mL) at 0°C, potassium carbonate (0.2489 g, 1.78 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours. Methanol was removed and the mixture was diluted with dichloromethane. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes followed by 4% methanol in dichloromethane) afforded 0.2482 g (83%) of **153** as a yellowish oil; IR (neat) 3430, 3364, 2930, 1722, 1601, 1491, 1280, 1111, 1072, 1013, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.77 (dd, J = 8.4, 2.3 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 5.18 (s, 2H), 4.07-4.04 (m, 1H), 3.86-3.84 (m, 2H), 3.73 (dd, J = 10.8, 3.8 Hz, 1H), 3.60-3.56 (m, 3H), 3.41 (s, 3H), 3.11 (dd, J = 16.0, 9.2 Hz, 1H), 2.84 (dd, J = 16.0, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 145.7, 130.8, 116.2, 114.7, 111.0, 95.1, 72.1, 67.8, 65.5, 61.1, 59.4, 32.8; HRMS (FAB) *m/z* (M^+) calcd 253.1314 for $C_{13}H_{19}NO_4$, obsd 253.1287.

Allyloxycarbonyl **154**

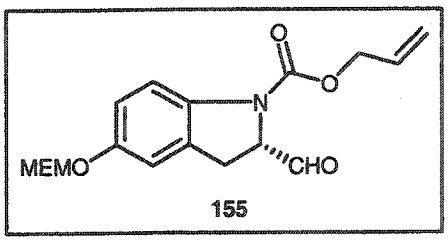


154

To a solution of **153** (0.2482 g, 0.98 mmol) in dichloromethane (20 mL) at –78°C, were added DIPEA (170.7 µL, 0.98 mmol) and allyl chloroformate (104 µL, 0.98 mmol). The reaction mixture was stirred at –78°C for 1.5 hours. The reaction was quenched by adding a saturated ammonium chloride solution (11 mL) at –78°C and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (50% to 75% ethyl acetate in hexanes) afforded 0.3119 g (94%) of **154** as a colourless oil; IR (Nujol) 3464, 1682, 1492, 1458, 1078, 1034, 1000, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (broad s, 1H), 6.92 (s, 1H), 6.89 (d, J = 8.8 Hz,

1H), 6.07-5.99 (m, 1H), 5.41 (d, J = 17.5 Hz, 1H), 5.31 (d, J = 10.4 Hz, 1H), 5.23 (s, 2H), 4.78 (s, 2H), 4.67 (broad s, 1H), 3.85-3.83 (m, 2H), 3.80-3.73 (m, 2H), 3.60-3.57 (m, 2H), 3.40 (s, 3H), 3.36 (dd, J = 16.5, 10.1 Hz, 1H), 2.82 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 132.7, 132.0, 118.9, 116.6, 115.8, 113.8, 94.4, 72.0, 68.0, 67.2, 66.5, 62.0, 59.4, 31.7; HRMS (FAB) *m/z* (M^+) calcd 337.1525 for $C_{17}H_{23}NO_6$, obsd 337.1549.

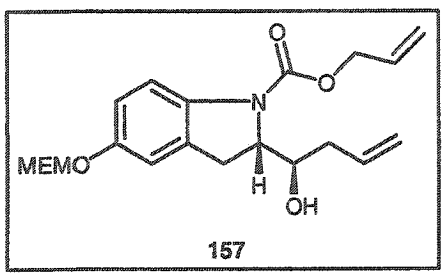
Aldehyde **155**



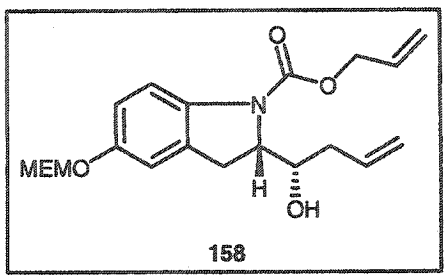
155

To a solution of **154** (98.2 mg, 0.291 mmol) in dichloromethane (3.2 mL) at room temperature were added dimethyl sulfoxide (0.81 mL), triethylamine (203 μL, 1.46 mmol) and sulfur trioxide/pyridine complex (0.1853 g, 1.16 mmol). The reaction mixture was stirred at room temperature for 3 hours. The reaction was quenched by adding a saturated ammonium chloride solution (3 mL) and extracted with ethyl acetate. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (25% ethyl acetate in hexanes) afforded 89.0 mg (91%) of **155** as a yellow oil; IR (Nujol) 1725, 1493, 1458, 1149, 1003, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.83 (d, J = 8.5 Hz, 1H), 6.95-6.93 (m, 2H), 5.96-5.95 (m, 1H), 5.46-5.25 (m, 2H), 5.23 (s, 2H), 4.96-4.73 (m, 3H), 3.85-3.82 (m, 2H), 3.59-3.57 (m, 2H), 3.48-3.44 (m, 1H), 3.40 (s, 3H), 3.19 (dd, J = 16.8, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 154.2, 132.4, 118.9, 116.5, 116.1, 113.7, 94.4, 72.0, 68.0, 67.6, 66.8, 66.4, 59.4, 30.4, 29.4; HRMS (FAB) *m/z* (M^+) calcd 335.1369 for $C_{17}H_{21}NO_6$, obsd 335.1573.

Allylic alcohols **157** and **158**



157

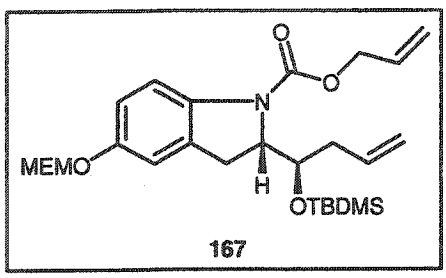


158

To a stirred solution of zinc chloride (1.0 M in ether, 5.41 mL, 5.41 mmol) in ether (30 mL) at –78°C was added a solution of **155** (0.4534 g, 1.35 mmol) in ether (6 mL). The mixture was stirred for 30 minutes at –78°C before the addition of allylmagnesium bromide (1.0 M in ether, 8.11 mL, 8.11 mmol). The reaction mixture was stirred at –78°C for 2 hours. The reaction was quenched by adding a saturated ammonium chloride solution (10 mL) at –78°C. The ethereal layer was washed with saturated sodium chloride solution. The aqueous layers were extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (30% ethyl acetate in hexanes) afforded 0.2095 g (41%) of **157** as an off-white solid (mp 55.0-57.0°C) and 0.2402 g of **158** as a pale yellow oil; alcohol **157** IR (neat) 3443, 2926, 1696, 1602, 1491, 1129, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (broad s, 1H), 6.91 (s, 1H), 6.87 (dd, J = 8.8, 2.2 Hz, 1H), 6.06-5.97 (m, 1H), 5.90-5.81 (m, 1H), 5.39 (d, J = 17.1 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.22 (s, 2H), 5.16-5.11 (m, 2H), 4.75 (d, J = 4.2 Hz, 2H), 4.58 (broad s, 1H), 4.08 (broad s, 1H), 3.84-3.82 (m, 2H), 3.58 (t, J = 4.6 Hz, 2H), 3.39 (s, 3H), 3.28-3.21 (m, 1H), 3.08 (broad s, 1H), 2.24 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 134.8, 132.7, 132.6, 118.8, 118.3, 116.4, 115.5, 113.5, 94.4, 72.8, 72.0, 67.9, 67.0, 64.2, 59.4, 37.6, 29.7; HRMS (FAB) *m/z* (M^+) calcd 377.1838 for $C_{20}H_{27}NO_6$, obsd 377.1767; alcohol **158** IR (neat) 3430, 2925, 1700, 1601, 1491, 1126, 1007, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (broad s, 1H), 6.91-6.87 (m, 2H), 6.06-5.97 (m, 1H), 5.83 (broad s, 1H), 5.39 (dd, J = 17.2, 1.3 Hz, 1H), 5.29 (dd, J = 10.4, 1.3 Hz, 1H), 5.22 (s, 2H), 5.14-5.09 (m, 2H), 4.75 (d, J = 5.5 Hz, 2H), 4.68-4.66 (m, 1H), 3.94 (broad s, 1H), 3.85-3.81 (m, 2H), 3.59-3.56 (m, 2H), 3.39

(s, 3H), 3.27-3.17 (m, 1H), 3.01-2.93 (m, 1H), 2.24 (broad s, 1H), 2.06 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 134.7, 132.8, 132.6, 118.8, 116.9, 115.7, 113.5, 94.5, 72.0, 68.0, 66.9, 59.4, 30.5; HRMS (FAB) *m/z* (M^+) calcd 377.1838 for $C_{20}H_{27}NO_6$, obsd 377.1840.

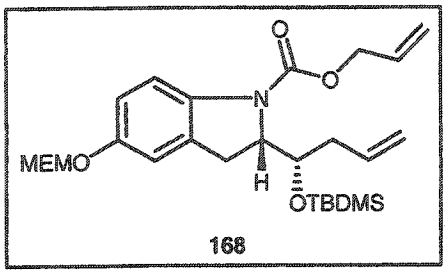
TBDMS ether **167**



167

To a solution of **157** (0.2095 g, 0.555 mmol) in DMF (5 mL) at room temperature, were added imidazole (0.0945 g, 1.39 mmol) and *tert*-butyldimethylsilyl chloride (0.1924 g, 1.28 mmol). The reaction mixture was stirred at 30°C for 24 hours. The solvent was evaporated and the resulting mixture was diluted with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 0.2414 g (88%) of **167** as a colourless oil and 20.6 mg (10%) of starting material; IR (neat) 2929, 2856, 1700, 1651, 1493, 1251, 1129, 992, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (broad s, 1H), 6.88 (s, 1H), 6.80 (broad s, 1H), 6.02 (broad s, 1H), 5.83 (broad s, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.29 (d, J = 10.4 Hz, 1H), 5.20 (s, 2H), 5.17-5.09 (m, 2H), 4.78-4.74 (m, 2H), 4.49 (broad s, 1H), 4.38-4.25 (m, 1H), 3.83-3.80 (m, 2H), 3.57 (t, J = 4.7 Hz, 2H), 3.40 (s, 3H), 3.20 (d, J = 15.6 Hz, 1H), 3.08 (dd, J = 15.7, 10.4 Hz, 1H), 2.29-2.27 (m, 2H), 0.59 (s, 9H), -0.04 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 134.7, 133.1, 118.6, 117.8, 115.9, 115.0, 113.2, 94.5, 72.7, 72.0, 67.8, 66.7, 63.6, 59.4, 39.9, 28.0, 25.8, 18.0, -4.2, -5.1; HRMS (FAB) *m/z* (MH^+) calcd 492.2781 for $C_{26}H_{42}NO_6Si$, obsd 492.2822.

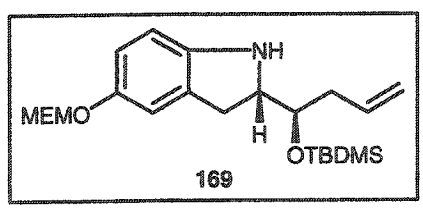
TBDMS ether **168**



168

To a solution of **158** (0.3183 g, 0.843 mmol) in DMF (8 mL) at room temperature, were added imidazole (0.1435 g, 2.11 mmol) and *tert*-butyldimethylsilyl chloride (0.2924 g, 1.94 mmol). The reaction mixture was stirred at 30°C for 24 hours. The solvent was evaporated and the resulting mixture was diluted with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 0.3450 g (83%) of **168** as a colourless oil; IR (neat) 2929, 2888, 2857, 1712, 1646, 1491, 1261, 1131, 1079, 1008, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.0 Hz, 1H), 6.89 (s, 1H), 6.87 (broad s, 1H), 6.02 (broad s, 1H), 5.70 (broad s, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.29 (dd, *J* = 10.5, 0.8 Hz, 1H), 5.23 (s, 2H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.88 (d, *J* = 18.2 Hz, 1H), 4.75 (broad s, 2H), 4.56 (broad s, 1H), 4.14 (broad s, 1H), 3.84 (t, *J* = 4.6 Hz, 2H), 3.59 (t, *J* = 4.6 Hz, 2H), 3.40 (s, 3H), 3.17-3.15 (m, 2H), 1.95-1.88 (m, 2H), 0.92 (s, 9H), 0.12-0.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 135.8, 133.0, 119.1, 117.2, 116.2, 115.4, 113.4, 94.5, 72.0, 68.0, 66.5, 62.9, 59.4, 35.4, 29.0, 26.2, 18.4, -4.2; HRMS (FAB) *m/z* (M^+) calcd 491.2703 for $C_{26}H_{41}NO_6Si$, obsd 491.2758.

Compound **169**

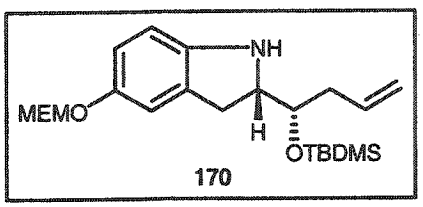


169

To a solution of **167** (0.3978 g, 0.809 mmol) in dichloromethane (16 mL) at 0°C, were added $Pd(PPh_3)_4$ (93.5 mg, 0.081 mmol) and morpholine (148 μL, 1.70 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4.5 hours. The solvent was evaporated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 0.3072 g (93%) of **169** as a yellow oil; IR (neat) 3358, 2929, 2857, 1492, 1252, 1076, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 2.4

Hz, 1H), 6.73 (dd, J = 8.4, 2.4 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 5.91 (dddd, J = 17.2, 10.1, 7.1, 7.1 Hz, 1H), 5.17 (s, 2H), 5.12-5.07 (m, 2H), 3.92-3.87 (m, 1H), 3.86-3.83 (m, 2H), 3.77-3.76 (m, 1H), 3.60-3.58 (m, 2H), 3.40 (s, 3H), 3.08 (dd, J = 16.0, 9.2 Hz, 1H), 2.86 (dd, J = 16.0, 8.2 Hz, 1H), 2.33-2.30 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 146.5, 135.5, 130.7, 117.4, 116.0, 114.6, 109.9, 95.2, 75.7, 72.1, 67.8, 64.2, 59.4, 39.0, 33.5, 26.2, 18.5, -3.8, -4.0; HRMS (FAB) m/z (M^+) calcd 407.2492 for $C_{22}H_{37}NO_4Si$, obsd 407.2861.

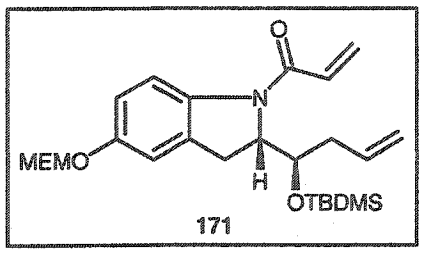
Compound **170**



170

To a solution of **168** (0.2003 g, 0.407 mmol) in dichloromethane (8 mL) at 0°C, were added $Pd(PPh_3)_4$ (47.1 mg, 0.041 mmol) and morpholine (74.6 μL, 0.856 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The solvent was evaporated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 0.1619 g (97%) of **170** as a yellow oil; IR (neat) 3389, 2929, 2857, 1492, 1254, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.74 (dd, J = 8.3, 2.2 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 5.97-5.87 (m, 1H), 5.17 (s, 2H), 5.13-5.08 (m, 2H), 3.86-3.83 (m, 2H), 3.81-3.79 (m, 1H), 3.71-3.69 (m, 1H), 3.60-3.58 (m, 2H), 3.41 (s, 3H), 3.02 (dd, J = 15.8, 8.7 Hz, 1H), 2.69 (dd, J = 15.8, 7.7 Hz, 1H), 2.42-2.36 (m, 1H), 2.27-2.20 (m, 1H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 146.0, 134.6, 130.2, 117.6, 116.1, 114.7, 109.9, 95.2, 75.4, 72.1, 67.8, 64.4, 59.4, 39.2, 33.0, 26.3, 18.5, -3.8, -4.0; HRMS (FAB) m/z (M^+) calcd 407.2492 for $C_{22}H_{37}NO_4Si$, obsd 407.2737.

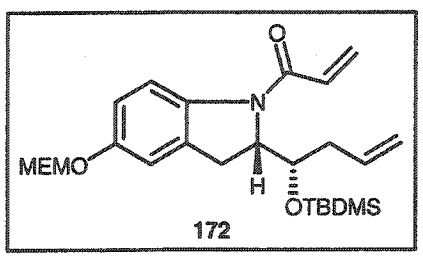
Acryloyl derivative **171**



171

To a solution of **169** (0.3072 g, 0.754 mmol) in dichloromethane (22 mL) at 0°C, were added pyridine (122 μL, 1.507 mmol) and acryloyl chloride (67 μL, 0.829 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was quenched by adding a saturated ammonium chloride solution (2 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (10% ethyl acetate in hexanes) afforded 0.3182 g (91%) of **171** as a yellowish oil; IR (neat) 2929, 2886, 2857, 1653, 1615, 1488, 1254, 1103, 1074, 989, 852 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 6.83 (d, J = 8.3 Hz, 1H), 6.58-6.38 (m, 2H), 5.89-5.83 (m, 1H), 5.79 (d, J = 10.4 Hz, 1H), 5.21 (s, 2H), 5.19 (s, 2H), 4.58 (d, J = 8.8 Hz, 1H), 3.98 (s, 1H), 3.81 (t, J = 4.2 Hz, 2H), 3.57 (t, J = 4.2 Hz, 2H), 3.40 (s, 3H), 3.27-3.12 (m, 2H), 2.31-2.30 (m, 2H), 0.57 (s, 9H), -0.06 (s, 3H), -0.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 154.6, 138.9, 134.7, 133.8, 130.4, 129.1, 119.2, 118.8, 115.0, 112.7, 94.3, 75.2, 72.0, 67.8, 62.2, 59.4, 39.9, 28.7, 25.7, 17.9, -4.4, -5.2; HRMS (FAB) *m/z* (MH^+) calcd 462.2676 for $C_{25}H_{40}NO_5Si$, obsd 462.2879.

Acryloyl derivative **172**

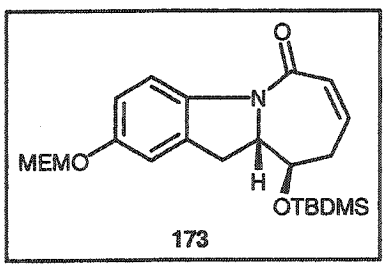


172

To a solution of **170** (0.2622 g, 0.643 mmol) in dichloromethane (19 mL) at 0°C, were added pyridine (104 μL, 1.286 mmol) and acryloyl chloride (57.5 μL, 0.708 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hours. The reaction was quenched by adding a saturated ammonium chloride solution (10 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column

chromatography (20% ethyl acetate in hexanes) afforded 0.2588 g (87%) of **172** as a yellowish oil; IR (neat) 2929, 2886, 2858, 1653, 1615, 1487, 1255, 1097, 1007, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 6.93 (s, 1H), 6.91 (broad s, 1H), 6.71 (dd, *J* = 16.6, 10.3 Hz, 1H), 6.49 (d, *J* = 16.6, 1H), 5.88-5.75 (m, 2H), 5.25 (s, 2H), 5.09 (d, *J* = 9.9 Hz, 1H), 5.02 (d, *J* = 17.3 Hz, 1H), 4.55-4.51 (m, 1H), 3.85 (t, *J* = 4.6 Hz, 2H), 3.75 (broad s, 1H), 3.59 (t, *J* = 4.6 Hz, 2H), 3.40 (s, 3H), 3.25 (dd, *J* = 16.3, 8.8 Hz, 1H), 2.96 (d, *J* = 16.4 Hz, 1H), 2.18 (broad s, 1H), 2.12-2.07 (m, 1H), 0.90 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 154.7, 137.8, 134.3, 133.2, 130.0, 128.5, 119.6, 118.4, 115.6, 113.1, 94.4, 76.7, 72.7, 72.0, 68.0, 62.8, 59.4, 37.1, 31.1, 26.2, 18.4, -4.1, -4.3; HRMS (FAB) *m/z* (MH^+) calcd 462.2676 for $C_{25}H_{40}NO_5Si$, obsd 462.2653.

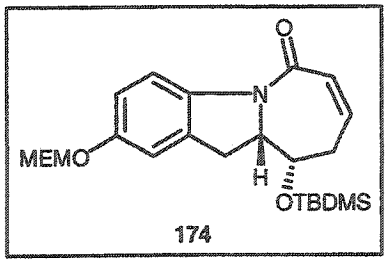
Seven-membered ring scaffold **173**



173

To a solution of **171** (24.8 mg, 0.054 mmol) in dichloromethane (5 mL) at room temperature was added a solution of Grubbs' catalyst **90** (10 mol %, 4.4 mg, 0.005 mmol) in dichloromethane (1 mL). The reaction mixture was allowed to stir at that temperature for 30 minutes. The solvent was evaporated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 22.5 mg (97%) of **173** as an off-white oil; IR (Nujol) 1664, 1594, 1248, 1080, 1000, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.8 Hz, 1H), 6.97 (s, 1H), 6.92 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.39-6.33 (m, 1H), 6.18 (dd, *J* = 11.4, 2.1 Hz, 1H), 5.25 (s, 2H), 4.18 (ddd, *J* = 9.4, 9.1, 2.7 Hz, 1H), 4.07 (ddd, *J* = 9.1, 5.4, 3.4 Hz, 1H), 3.86-3.84 (m, 2H), 3.60-3.58 (m, 2H), 3.40 (s, 3H), 3.44-3.37 (m, 1H), 3.10 (dd, *J* = 17.0, 2.7 Hz, 1H), 2.62 (dddd, *J* = 16.1, 5.3, 5.2, 2.1 Hz, 1H), 2.37 (ddd, *J* = 16.1, 7.4, 3.4 Hz, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.7, 137.3, 136.2, 132.4, 129.1, 118.3, 115.8, 113.5, 94.4, 72.0, 68.0, 64.5, 59.4, 36.5, 33.0, 26.1, 18.3, -3.8, -4.2; HRMS (FAB) *m/z* (MH^+) calcd 434.2363 for $C_{23}H_{36}NO_5Si$, obsd 434.2368.

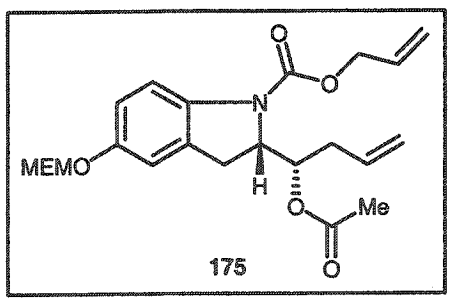
Seven-membered ring scaffold **174**



174

To a solution of **172** (0.1351 g, 0.293 mmol) in dichloromethane (24 mL) at room temperature was added a solution of Grubbs' catalyst **90** (10 mol %, 24.1 mg, 0.029 mmol) in dichloromethane (1 mL). The reaction mixture was allowed to stir at that temperature for 1.5 hours. The solvent was evaporated. Purification by column chromatography (40% ethyl acetate in hexanes) afforded 0.1147 g (90%) of **174** as an off-white solid; mp 98.5-100.0°C; IR (Nujol) 1644, 1594, 1250, 1105, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.7 Hz, 1H), 6.89 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.27-6.22 (m, 1H), 6.12 (dd, J = 11.6, 2.1 Hz, 1H), 5.22 (s, 2H), 4.31 (ddd, J = 10.3, 2.7, 2.5 Hz, 1H), 4.18 (ddd, J = 6.6, 6.4, 2.4 Hz, 1H), 3.82 (t, J = 4.7 Hz, 2H), 3.57 (t, J = 4.6 Hz, 2H), 3.40 (s, 3H), 3.34 (dd, J = 16.1, 10.3 Hz, 1H), 3.06 (dd, J = 16.1, 2.8 Hz, 1H), 2.62 (ddd, J = 15.8, 6.8, 6.6 Hz, 1H), 2.36 (dddd, J = 15.8, 6.7, 6.5, 2.2 Hz, 1H), 0.64 (s, 9H), 0.005 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 154.4, 138.6, 135.7, 133.3, 129.7, 117.9, 115.3, 112.7, 94.4, 76.5, 72.0, 67.8, 63.3, 59.4, 36.9, 32.7, 25.7, 18.0, -3.7, -4.8; HRMS (FAB) *m/z* (MH^+) calcd 434.2363 for $C_{23}H_{36}NO_5Si$, obsd 434.2327.

Acetate derivative **175**

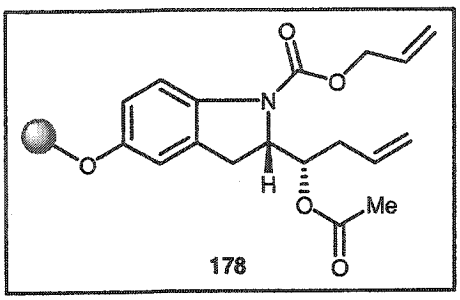


175

To a solution of **158** (0.2402 g, 0.636 mmol) in dichloromethane (7 mL) were added acetic anhydride (180.5 μL, 1.909 mmol) and DMAP (7.8 mg, 0.064 mmol). The resulting mixture was allowed to stir at room temperature for 24 hours. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated to afford 26.6 mg (100%) of **175** as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (broad s, 1H), 6.89-6.87 (m, 2H), 6.08-5.98 (m, 1H), 5.68-5.64 (m, 1H), 5.42 (d, J = 17.2 Hz, 1H), 5.30-5.27 (m, 2H), 5.22 (s, 2H), 5.00-4.95 (m, 2H), 4.80-4.74 (m, 3H), 3.84-3.82 (m, 2H), 3.58-3.56 (m, 2H), 3.39 (s, 3H),

3.27 (dd, J = 16.8, 10.0 Hz, 1H), 2.98 (broad s, 1H), 2.21 (broad s, 2H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 154.1, 133.8, 132.8, 118.6, 118.1, 116.7, 115.7, 113.3, 94.4, 72.1, 72.0, 67.8, 67.7, 66.8, 59.4, 33.4, 30.7, 21.5; MS (ES+) *m/z* (M+1) 420.3.

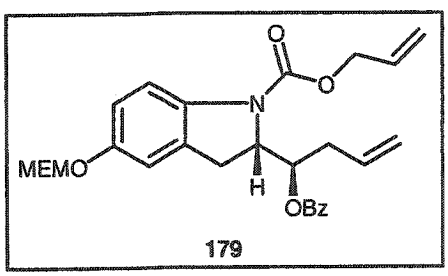
Resin **178**



178

To a suspension of 4-(bromomethyl) phenoxymethyl polystyrene (83.9 mg, 0.1001 mmol) was added **176** (66.7 mg, 0.201 mmol) followed by cesium carbonate (65.6 mg, 0.201 mmol) and sodium iodide (30.2 mg, 0.201 mmol). The resulting mixture was gently stirred for 3 days and then filtered. The resin was washed with methanol (1x), DMF (3x), water (3x), methanol (3x) and dichloromethane (3x) and dried to afford resin **178**.

Benzoyl derivative **179**

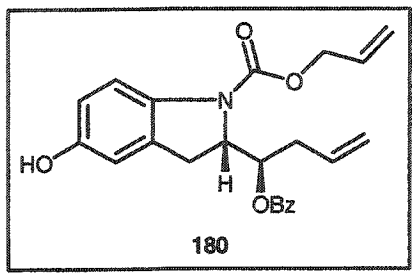


179

To a solution of **157** (0.1875 g, 0.497 mmol) in dichloromethane (6 mL), were added DMAP (0.1214 g, 0.994 mmol) and benzoyl chloride (86.5 µL, 0.745 mmol). The reaction mixture was stirred at 35°C for 1 hour. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (30% ethyl acetate in hexanes) afforded 0.2226 g (93%) of **179** as a colourless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.28-7.24 (m, 3H), 6.98 (s, 1H), 6.76 (d, J = 7.6 Hz, 1H), 6.00-5.98 (m, 1H), 5.87-5.85 (m, 1H), 5.61 (broad s, 1H), 5.36 (dd, J = 17.9, 0.7 Hz, 1H), 5.26 (dd, J = 10.5, 0.6 Hz, 1H), 5.21-5.17 (m, 3H), 5.13 (d, J = 10.2 Hz, 1H), 4.80-4.74 (m, 3H), 3.86-3.84 (m, 2H), 3.60-3.58 (m, 2H), 3.40 (s, 3H), 3.35 (dd, J = 16.2, 10.1 Hz, 1H), 3.23 (dd, J = 16.2, 1.6 Hz, 1H), 2.65-2.58 (m, 1H), 2.44 (broad s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 153.9, 133.2, 133.1, 132.9, 129.8, 128.4, 118.8, 118.5, 116.2, 115.6, 113.4, 94.7, 72.0, 67.9, 66.8, 59.4, 35.5; MS (ES+) *m/z* (M+1) 482.3.

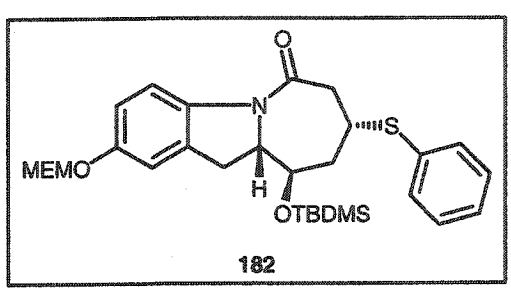
Phenol derivative **180**



180

To a solution of **179** (0.2131 g, 0.442 mmol) in anhydrous ethanol (12 mL), was added *p*-toluenesulfonic acid monohydrate (0.1094 g, 0.575 mmol). The reaction mixture was stirred overnight at 50°C. The solvent was evaporated and the resulting mixture was diluted with dichloromethane and washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (30% ethyl acetate in hexanes) afforded 0.1698 g (98%) of **180** as a yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.30-7.26 (m, 3H), 6.77 (s, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.98 (broad s, 1H), 5.86 (broad s, 1H), 5.61 (broad s, 1H), 5.36 (dd, *J* = 17.2, 0.9 Hz, 1H), 5.26 (dd, *J* = 10.5, 0.9 Hz, 1H), 5.19 (dd, *J* = 17.1, 1.2 Hz, 1H), 5.13 (d, *J* = 10.5 Hz, 1H), 4.78 (s, 2H), 4.79 (broad s, 2H), 3.38-3.31 (m, 1H), 3.21 (d, *J* = 15.3 Hz, 1H), 2.64-2.58 (m, 1H), 2.44 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 152.1, 133.2, 133.1, 132.8, 129.8, 128.5, 118.8, 118.5, 116.4, 113.9, 111.9, 77.1, 66.7, 35.4; MS (ES+) *m/z* (M+1) 394.2.

Thiol derivative **182**

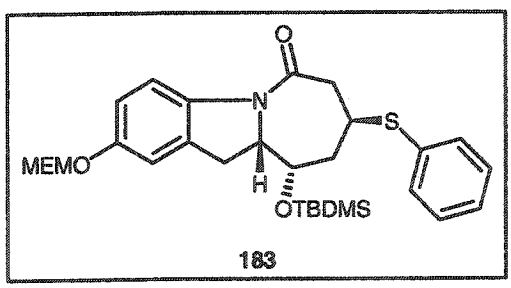


182

To a solution of **173** (15.1 mg, 0.035 mmol) in benzene (560 μL) was added benzenethiol (10.7 μL, 0.104 mmol) and triethylamine (14.6 μL, 0.104 mmol). The reaction mixture was allowed to stir for 40 hours at room temperature. The solvent was evaporated. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 2.7 mg (14%) of **182** as

a colourless oil and 0.128 g (85%) of starting material; IR (Nujol) 1654, 1599, 1086, 1007, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.38-7.28 (m, 3H), 6.91 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 5.24 (s, 2H), 4.33 (ddd, *J* = 9.6, 9.4, 2.9 Hz, 1H), 3.84 (t, *J* = 4.5 Hz, 2H), 3.57 (t, *J* = 4.5 Hz, 2H), 3.47-3.40 (m, 2H), 3.40 (s, 3H), 3.40-3.34 (m, 1H), 3.26 (dd, *J* = 17.3, 9.7 Hz, 1H), 2.88-2.86 (m, 2H), 2.43 (d, *J* = 13.3 Hz, 1H), 1.84-1.75 (m, 1H), 0.90 (s, 9H), -0.002 (s, 3H), -0.03 (s, 3H); ^1H NMR (400 MHz, C_6D_6) δ 8.75 (d, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.03-7.00 (m, 4H), 6.96-6.92 (m, 1H), 4.98 (d, *J* = 4.2 Hz, 2H), 3.64-3.60 (m, 3H), 3.33-3.31 (m, 1H), 3.25 (t, *J* = 4.9 Hz, 2H), 3.22-3.17 (m, 1H), 3.14-3.13 (m, 1H), 3.05 (s, 3H), 3.04-3.00 (m, 1H), 2.83 (dd, *J* = 17.1, 10.1 Hz, 1H), 2.48 (dd, *J* = 12.6, 12.6 Hz, 1H), 2.26 (d, *J* = 13.1 Hz, 1H), 1.63-1.54 (m, 1H), 0.85 (s, 9H), -0.18 (s, 3H), -0.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 154.7, 137.4, 133.6, 133.1, 131.8, 129.6, 128.2, 118.4, 115.6, 113.1, 94.4, 72.0, 71.7, 68.0, 65.8, 59.4, 46.3, 44.9, 40.9, 31.6, 26.1, 18.4, -3.9, -4.5; ^{13}C NMR (100 MHz, C_6D_6) δ 168.7, 155.0, 138.0, 134.5, 132.3, 131.6, 129.4, 128.0, 127.8, 127.5, 118.6, 115.7, 113.1, 94.2, 72.0, 71.6, 68.1, 65.2, 58.6, 46.3, 44.7, 40.2, 31.4, 25.9, 18.1, -4.4, -4.9; HRMS (FAB) *m/z* (M^+) calcd 543.2475 for $C_{29}H_{41}NO_5SSi$, obsd 543.2828.

Thiol derivative **183**



183

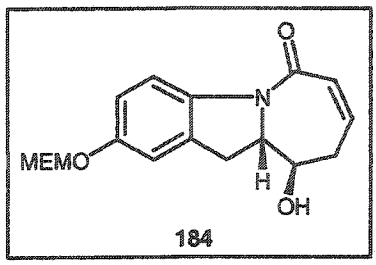
To a solution of **174** (13.5 mg, 0.031 mmol) in benzene (500 μL) was added benzenethiol (10 μL, 0.093 mmol) and triethylamine (13 μL, 0.093 mmol). The reaction mixture was allowed to stir for 41.5 hours at room temperature. The solvent was evaporated. Purification by column chromatography (50% ethyl acetate in hexanes) afforded 15.2 mg (90%) of **183** as a white solid; mp 95.5-97.0°C; IR (neat) 2953, 2929, 2857, 1653, 1599, 1487, 1440, 1254, 1094, 1008, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.37-7.27 (m, 3H), 6.84-6.82 (m, 2H), 5.20 (s, 2H), 4.47 (dd, *J* = 10.7, 3.0 Hz, 1H), 3.89 (s, 1H), 3.82-3.80 (m, 2H), 3.68 (dd, *J* =

12.0, 12.0 Hz, 1H), 3.58-3.52 (m, 3H), 3.39 (s, 3H), 2.92 (d, J = 13.6 Hz, 1H), 2.86-2.80 (m, 2H), 2.26 (d, J = 13.9 Hz, 1H), 1.83 (ddd, J = 14.1, 14.1, 2.0 Hz, 1H), 0.54 (s, 9H), -0.14 (s, 3H), -0.15 (s, 3H); ^{1}H NMR (400 MHz, C_6D_6) δ 8.71 (d, J = 8.7 Hz, 1H), 7.42 (d, J = 7.4 Hz, 2H), 7.01 (dd, J = 7.5, 7.5 Hz, 2H), 6.94-6.91 (m, 3H), 4.99 (s, 2H), 3.86-3.81 (m, 1H), 3.64 (t, J = 5.0 Hz, 2H), 3.49 (dd, J = 10.8, 3.0 Hz, 1H), 3.29 (t, J = 5.0 Hz, 2H), 3.16-3.13 (m, 2H), 3.08 (s, 3H), 2.90 (dd, J = 16.4, 10.8 Hz, 1H), 2.46 (dd, J = 12.6, 12.6 Hz, 1H), 2.30 (dd, J = 16.5, 2.6 Hz, 1H), 2.07 (d, J = 13.9 Hz, 1H), 1.36 (ddd, J = 14.0, 13.9, 1.9 Hz, 1H), 0.59 (s, 9H), -0.26 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 154.1, 139.4, 133.8, 133.1, 131.8, 129.6, 128.1, 117.7, 115.5, 112.4, 94.4, 74.1, 72.0, 67.8, 63.1, 59.4, 45.8, 44.7, 38.8, 36.1, 25.5, 17.9, -4.0, -5.2; ^{13}C NMR (100 MHz, C_6D_6) δ 168.2, 154.4, 140.0, 134.7, 132.2, 131.6, 129.4, 128.0, 127.8, 127.4, 117.8, 115.6, 112.4, 94.4, 74.0, 72.0, 67.9, 62.4, 58.6, 45.9, 44.5, 38.6, 35.8, 25.4, 17.8, -4.4, -5.5; HRMS (FAB) *m/z* (M^+) calcd 543.2475 for $C_{29}H_{41}NO_5SSi$, obsd 543.2523.

To a solution of **174** (11.4 mg, 0.026 mmol) in DCM (422 μL) was added benzenethiol (8 μL, 0.079 mmol) and triethylamine (11 μL, 0.079 mmol). The reaction mixture was allowed to stir for 40 hours at room temperature. The solvent was evaporated. Purification by column chromatography (50% ethyl acetate in hexanes) afforded 1.5 mg (10%) of **183** as a white solid and 9.2 mg (81%) of starting material.

To a solution of **174** (12.1 mg, 0.028 mmol) in THF (448 μL) was added benzenethiol (8.6 μL, 0.084 mmol) and triethylamine (11.7 μL, 0.084 mmol). The reaction mixture was allowed to stir for 40 hours at room temperature. The solvent was evaporated. Purification by column chromatography (50% ethyl acetate in hexanes) afforded 11.9 mg (78%) of **183** as a white solid and 2.1 mg (17%) of starting material.

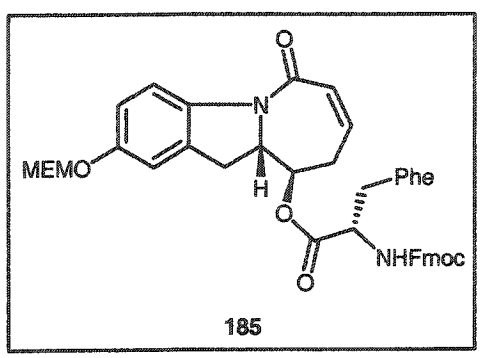
Alcohol **184**



184

To a solution of **173** (8.0 mg, 0.018 mmol) in THF (1 mL) at 0°C was added drop wise TBAF (1.0 M in THF, 18.5 µL, 0.018 mmol). The reaction mixture was allowed to warm to room temperature and stir for 50 minutes. The reaction was quenched by adding a saturated ammonium chloride solution (0.5 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes) afforded 5.0 mg (85%) of **184** as a white solid; mp 95.5-97.0°C; IR (Nujol) 3370, 1636, 1586, 1105, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.8 Hz, 1H), 6.96 (s, 1H), 6.92 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.44-6.38 (m, 1H), 6.20 (dd, *J* = 11.4, 2.2 Hz, 1H), 5.28 (s, 2H), 4.19 (ddd, *J* = 9.4, 9.3, 2.7 Hz, 1H), 4.12 (ddd, *J* = 9.2, 5.7, 2.9 Hz, 1H), 3.86-3.83 (m, 2H), 3.60-3.57 (m, 2H), 3.48 (dd, *J* = 16.9, 9.5 Hz, 1H), 3.40 (s, 3H), 3.21 (dd, *J* = 16.9, 2.6 Hz, 1H), 2.69 (dddd, *J* = 16.1, 5.6, 5.3, 2.2 Hz, 1H), 2.44 (ddd, *J* = 16.2, 7.6, 2.9 Hz, 1H), 2.19 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.8, 137.1, 135.7, 132.3, 129.6, 118.3, 115.9, 113.6, 94.4, 77.1, 72.0, 68.0, 64.0, 59.4, 35.9, 33.2; HRMS (FAB) *m/z* (MH^+) calcd 320.1498 for $C_{17}H_{22}NO_5$, obsd 320.1595.

Compound **185**

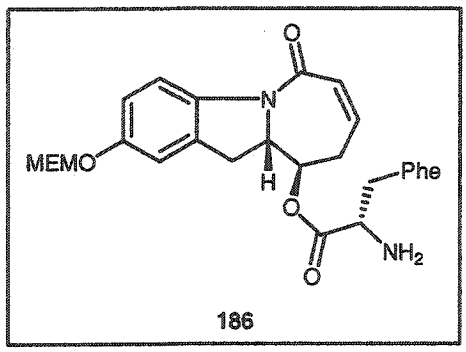


185

To a solution of **184** (18.7 mg, 0.058 mmol) in dichloromethane (2 mL), Fmoc-Phe-OH amino acid (45.4 mg, 0.117 mmol), DIC (23 µL, 0.1464 mmol) and DMAP (0.7 mg, 0.006 mmol) were added. The resulting mixture was stirred at room temperature for 3 hours. The organic solution was washed with

saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated to afford 40.3 mg (100%) of **185** as a colourless oil; MS (ES+) *m/z* (M+1) 689.5.

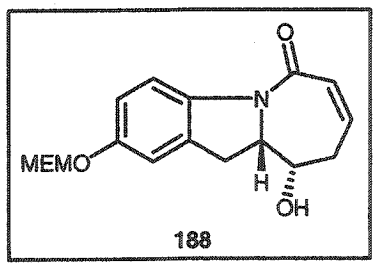
Amino acid conjugate **186**



186

Compound **185** (50.8 mg, 0.074 mmol) was stirred in a mixture of 5% piperidine in dichloromethane (8.5 mL of solution) at room temperature for 3 hours. The organic solution was washed with a 2N HCl solution until pH neutral. The combined organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes) afforded 19.5 mg (57%) of **186** as a colourless oil; MS (ES+) *m/z* (M+1) 467.3.

Alcohol **188**

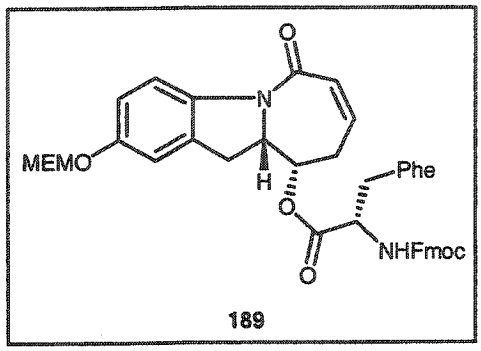


188

To a solution of **174** (43.8 mg, 0.101 mmol) in THF (2.5 mL) at 0°C was added TBAF drop wise (1.0 M in THF, 101 µL, 0.101 mmol). The reaction mixture was stirred at 0°C for 3 hours. The reaction was quenched by adding a saturated ammonium chloride solution (1.5 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes) afforded 21.0 mg (65%) of **188** as a white solid; mp 107.5-108.5°C; IR (Nujol) 3349, 1636, 1577, 1083, 1014, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 1H), 6.94 (s, 1H), 6.90 (dd, *J* = 8.8, 1.7 Hz, 1H), 6.31-6.25 (m, 1H), 6.12 (dd, *J* = 11.8, 1.4 Hz, 1H), 5.24 (d, *J* = 2.0 Hz, 2H), 4.40 (ddd, *J* = 10.3, 3.0, 1.9 Hz, 1H), 4.19 (ddd, *J* = 6.6, 6.4, 1.8 Hz, 1H), 3.83 (t, *J* = 4.6 Hz, 2H), 3.58 (t, *J* = 4.6 Hz, 2H), 3.45-3.39 (m, 1H), 3.39 (s, 3H), 3.31 (dd, *J* = 16.4, 3.0 Hz, 1H), 2.80 (ddd, *J* = 16.4, 6.8, 6.6 Hz, 1H), 2.44-2.39 (m,

1H), 1.89 (broad s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 154.8, 138.2, 136.2, 133.1, 129.3, 118.3, 115.6, 113.0, 94.3, 75.4, 72.0, 68.0, 62.8, 59.4, 36.8, 32.4; HRMS (FAB) *m/z* (MH^+) calcd 320.1498 for $C_{17}H_{22}NO_5$, obsd 320.1487.

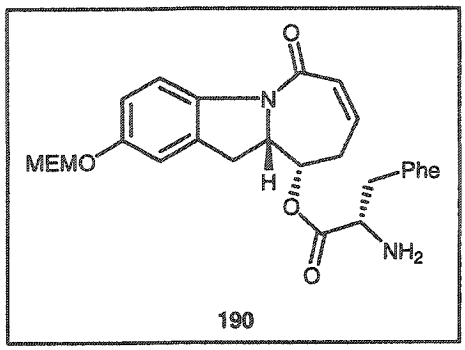
Compound **189**



189

To a solution of **188** (44.6 mg, 0.140 mmol) in dichloromethane (5 mL), Fmoc-Phe-OH amino acid (0.1082 g, 0.279 mmol), DIC (54.6 μL, 0.349 mmol) and DMAP (1.7 mg, 0.014 mmol) were added. The resulting mixture was stirred at room temperature for 3 hours. The organic solution was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated to afford 62.5 mg (65%) of **189** as a colourless oil; IR (neat) 3315, 2928, 2895, 1723, 1654, 1611, 1594, 1537, 1487, 1198, 1080, 1007 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.32-7.25 (m, 5H), 6.97-6.87 (m, 4H), 6.28-6.18 (m, 2H), 5.37 (broad s, 1H), 5.11 (s, 2H), 5.00 (d, *J* = 8.1 Hz, 1H), 4.56 (d, *J* = 10.2 Hz, 1H), 4.42-4.33 (m, 2H), 4.24-4.14 (m, 2H), 3.71-3.68 (m, 2H), 3.46-3.44 (m, 3H), 3.34 (s, 3H), 2.93-2.75 (m, 3H), 2.58 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.42 (d, *J* = 18.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 165.6, 155.9, 154.7, 144.2, 141.7, 137.9, 136.0, 134.9, 132.0, 129.8, 129.7, 129.4, 129.0, 128.1, 127.7, 127.6, 127.4, 125.5, 125.4, 120.4, 118.2, 115.8, 112.9, 94.3, 94.2, 78.3, 72.0, 71.9, 67.9, 67.4, 64.8, 61.0, 59.4, 55.4, 47.4, 38.0, 33.1, 32.7, 31.0, 19.5, 14.1; HRMS (FAB) *m/z* (M^+) calcd 688.2785 for $C_{41}H_{40}N_2O_8$, obsd 688.3200.

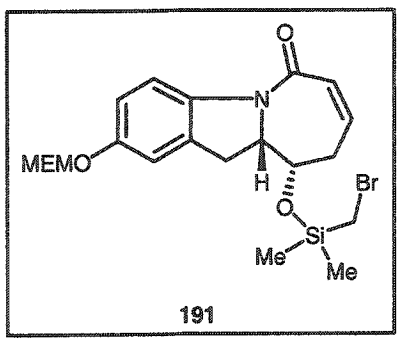
Amino acid conjugate **190**



190

Compound **189** (60.1 mg, 0.087 mmol) was stirred in a mixture of 3% piperidine in dichloromethane (10 mL of solution) at 0°C for 3 hours. The organic solution was washed with a 2N HCl solution until pH neutral. The combined organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes) afforded 16.8 mg (41%) of **190** as a colourless oil; IR (neat) 3378, 2928, 1735, 1654, 1612, 1595, 1487, 1169, 1077, 1005 cm^{-1}; HRMS (FAB) *m/z* (M^+) calcd 467.2182 for $C_{26}H_{31}N_2O_6$, obsd 467.2243.

Free radical precursor **191**

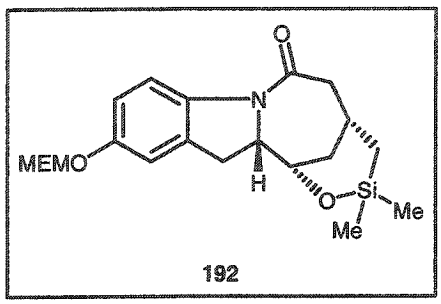


191

To a solution of **188** (29.0 mg, 0.091 mmol) in dichloromethane (2 mL) at 0°C, were added triethylamine (25.3 µL, 0.182 mmol) and (bromomethyl)-chlorodimethylsilane (18.6 µL, 0.136 mmol). The reaction mixture was stirred at 0°C for 4.5 hours. The reaction was quenched by adding a saturated ammonium chloride solution (1 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (75% ethyl acetate in hexanes) afforded 38.8 mg (91%) of **191** as a yellowish oil; IR (neat) 2894, 1653, 1614, 1594, 1487, 1253, 1097, 1005, 842 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6 Hz, 1H), 6.92-6.89 (m, 2H), 6.29-6.23 (m, 1H), 6.13 (dd, *J* = 11.6, 1.9 Hz, 1H), 5.25 (s, 2H), 4.37-4.31 (m, 2H), 3.84 (t, *J* = 4.6 Hz, 2H), 3.58 (t, *J* = 4.6 Hz, 2H), 3.40 (s, 3H), 3.40-3.34 (m, 1H), 3.12 (dd, *J* = 16.2, 2.7 Hz, 1H), 2.70-2.64 (m, 1H), 2.45-2.41 (m, 1H), 2.32 (d, *J* = 3.7 Hz, 2H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.5, 138.5, 135.5, 133.1, 129.8, 118.0, 115.4,

112.7, 94.4, 77.1, 72.0, 67.9, 63.0, 59.4, 36.7, 32.5, 16.3, -2.1; HRMS (FAB) *m/z* (M^+) calcd 469.0920 for $C_{20}H_{28}BrNO_5Si$, obsd 469.096.

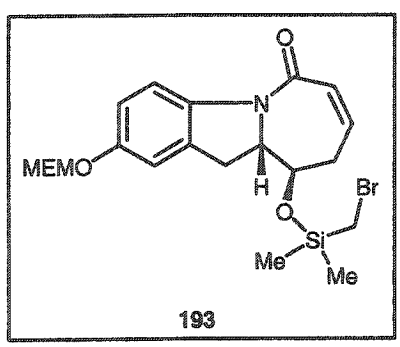
Compound **192**



192

To a refluxing solution of **191** (38.8 mg, 0.083 mmol) in benzene (8 mL) was added a solution of tri-*n*-butyltin hydride (66.7 μL, 0.248 mmol) and AIBN (6.8 mg, 0.041 mmol) in degassed benzene (2.7 mL) over a period of 30 minutes. The resulting mixture was refluxed for 4 hours before the solution was cooled to room temperature. The solvent was evaporated. Purification by HPLC afforded **192** as a yellow oil; IR (neat) 2920, 1647, 1595, 1487, 1251, 1098, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8, 1H), 6.88-6.84 (m, 2H), 5.26-5.22 (m, 2H), 4.52-4.48 (m, 1H), 4.22 (s, 1H), 3.85-3.83 (m, 2H), 3.59-3.57 (m, 2H), 3.51 (dd, *J* = 16.6, 10.8 Hz, 1H), 3.40 (s, 3H), 3.20 (dd, *J* = 16.6, 5.7 Hz, 1H), 2.84-2.74 (m, 2H), 2.61 (s, 1H), 2.27 (d, *J* = 14.8 Hz, 1H), 1.86 (d, *J* = 14.7 Hz, 1H), 1.16-1.02 (m, 2H), 0.13 (s, 3H), -0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.1, 139.3, 132.2, 118.4, 115.3, 112.5, 94.4, 74.7, 72.0, 68.0, 64.2, 59.4, 46.8, 40.4, 36.0, 26.3, 15.0, 4.5, 2.1; HRMS (FAB) *m/z* (MH^+) calcd 392.1893 for $C_{20}H_{30}NO_5Si$, obsd 392.1844.

Silicon-tethered compound **193**

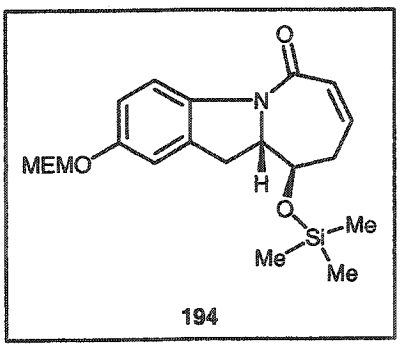


193

To a solution of **184** (29.1 mg, 0.091 mmol) in dichloromethane (2 mL) at 0°C, were added triethylamine (25.4 μL, 0.182 mmol) and (bromomethyl)-chlorodimethylsilane (18.8 mg, 14 μL, 0.100 mmol). The reaction mixture was stirred at 0°C for 6 hours. The reaction was quenched by adding a saturated ammonium chloride solution (1 mL) and extracted with dichloromethane. The combined organic layer was washed with saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated.

Purification by column chromatography (75% ethyl acetate in hexanes) afforded 23.6 mg (55%) of **193** as a yellowish oil and 9.5 mg (33%) of starting material; IR (Nujol) 1653, 1252, 1097, 1001, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.92 (dd, J = 8.8, 2.4 Hz, 1H), 6.41-6.35 (m, 1H), 6.19 (dd, J = 11.4, 2.3 Hz, 1H), 5.25 (s, 2H), 4.25-4.16 (m, 2H), 3.86-3.84 (m, 2H), 3.60-3.57 (m, 2H), 3.46-3.40 (m, 1H), 3.40 (s, 3H), 3.11 (dd, J = 17.0, 2.5 Hz, 1H), 2.66 (dddd, J = 16.1, 5.2, 5.2, 2.3 Hz, 1H), 2.50 (s, 2H), 2.42 (ddd, J = 16.1, 7.5, 3.0 Hz, 1H), 0.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.8, 137.2, 135.8, 132.2, 129.4, 118.3, 115.9, 113.6, 94.4, 78.5, 72.0, 68.0, 64.1, 59.4, 36.2, 33.0, 16.1, -1.8, -1.9; HRMS (FAB) *m/z* (M^+) calcd 469.0920 for $C_{20}H_{28}BrNO_5Si$, obsd 469.078.

TMS derivative **194**



194

To a refluxing solution of **193** (16.5 mg, 0.035 mmol) in benzene (1.5 mL) was added a solution of tri-*n*-butyltin hydride (28.3 μL, 0.105 mmol) and AIBN (2.9 mg, 0.017 mmol) in degassed benzene (500 μL) over a period of 5 minutes. The resulting mixture was refluxed 5 hours before the solution was cooled to room temperature. The solvent was evaporated. Purification by column chromatography (50% ethyl acetate in hexanes) afforded 10.5 mg (76%) of **194** as a yellow oil; IR (neat) 2957, 1654, 1487, 1252, 1084, 1011, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 6.94-6.91 (m, 1H), 6.41-6.35 (m, 1H), 6.18 (dd, J = 11.4, 2.0 Hz, 1H), 5.24 (s, 2H), 4.20 (ddd, J = 9.4, 9.4, 2.6 Hz, 1H), 4.09-4.05 (m, 1H), 3.86-3.84 (m, 2H), 3.60-3.58 (m, 2H), 3.44-3.37 (m, 1H), 3.40 (s, 3H), 3.07 (dd, J = 17.0, 2.5 Hz, 1H), 2.66-2.61 (m, 1H), 2.36 (ddd, J = 16.2, 7.4, 3.3 Hz, 1H), 0.17 (s, 6H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.7, 137.3, 136.2, 132.3, 129.2, 118.3, 115.8, 113.5, 94.4, 77.9, 72.0, 68.0, 64.3, 59.4, 36.4, 32.9, 1.4, 0.7; HRMS (FAB) *m/z* (MH^+) calcd 392.1893 for $C_{20}H_{30}NO_5Si$, obsd 392.2065.

CLAIMS TO ORIGINAL RESEARCH

1. The development of a novel synthetic route to indoline scaffold.

2. The synthesis of the indoline-based tricyclic derivative using the olefin ring-closing metathesis (RCM) approach.

3. The exploration of diversity-oriented synthesis (DOS) with the tricyclic compound, in which asymmetric benzenethiol addition (intermolecular) and asymmetric free radical-based C-C bond formation (intramolecular) were performed.

4. Publication: Arya, P.; Joseph, R.; Quevillon, S.; Wei, C.-Q.; Leek, D. M., submitted 2003.

5. Oral presentation: 'Towards Enantiopure Library Synthesis of Indole Alkaloid-like Polycyclic Derivatives' Quevillon, S.; Arya P.; OCCI Day Conference, May 6th 2002, Carleton University, Ottawa, Ontario, Canada.

6. Poster presentations: (a) 'Enantioselective Approach to Hydroxyindole-derived, Natural Product-like Polycyclic Derivatives for the High-throughput Synthesis Development' Quevillon, S.; Joseph, R.; Czechura, P.; Arya, P.; 12th Québec-Ontario Minisymposium in Synthetic and Bioorganic Chemistry, November 9/11, 2001, Sherbrooke University, Sherbrooke, Québec, Canada. (b) 'Toward Diversity-Oriented Asymmetric Synthesis of Indoline-Based Polycyclic Derivatives with Medium Sized Rings' Quevillon, S.; Joseph, R.; Arya, P.; 13th Québec-Ontario Minisymposium in Synthetic and Bioorganic Chemistry, November 8/10, 2002, Queen's University, Kingston, Ontario, Canada.

7. Conference contributions (invited talks): (a) Frontiers in Chemical and Structural Biology, 2003, McGill University, Montreal, Québec, Canada. (b) CHI Meeting 'Advancing Library Design and Organic Synthesis', 2003, San Diego, USA.

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53. I would sincerely like to thank Dr Samuel Couve-Bonnaire for providing me few hundred milligrams of compound **147**.

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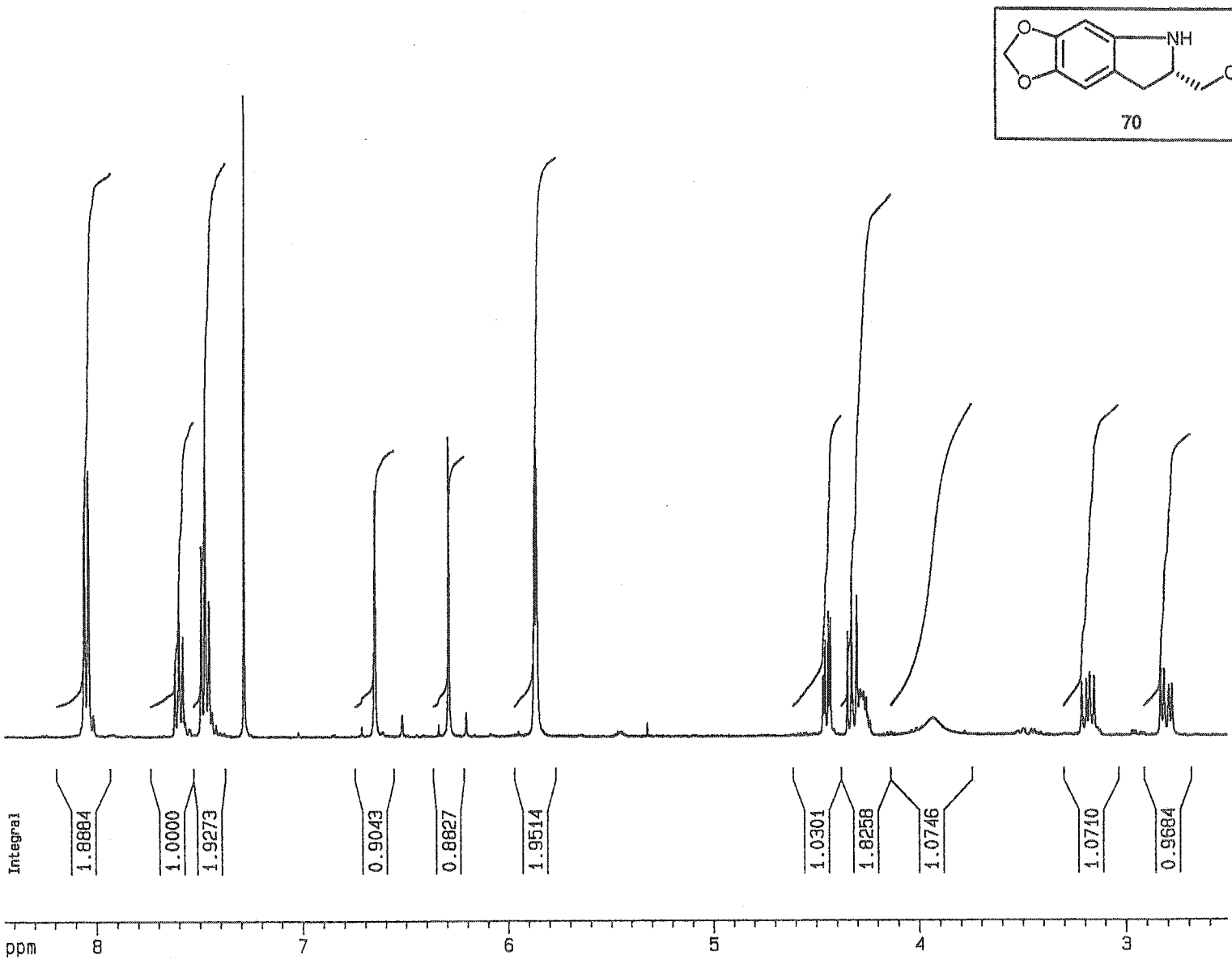
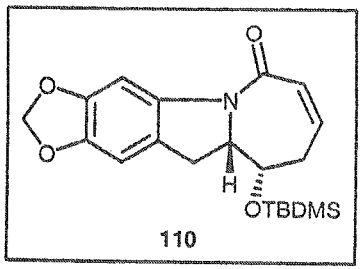
74. Gilson Combinatorial HPLC with a 215 Liquid Handler was used for the purification of compound **192**. The analytical column used was a reverse phase Vydac C-18 Monomeric column (4.0mm x 300mm). The semi-preparative column was also a reverse phase Vydac C-18 Monomeric column (40mm x 300mm).

APPENDIX

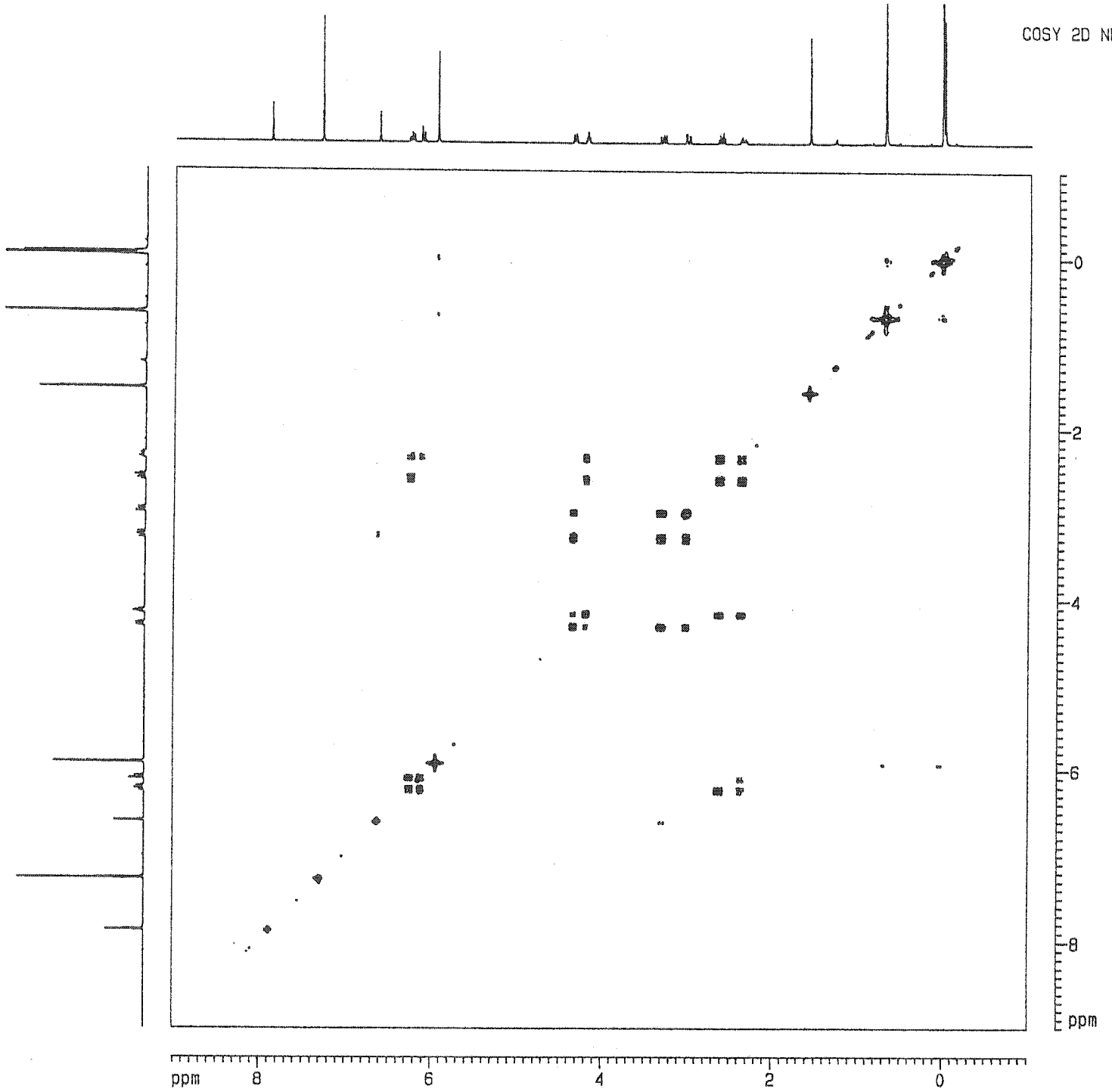
1H NMR Spectrum of the Indoline Moiety 70, CDCl3



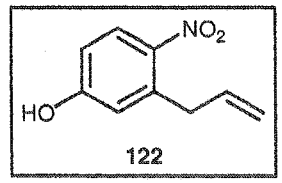
COSY 2D NMR Spectrum of the Seven-Membered Ring Template 110, CDCl3



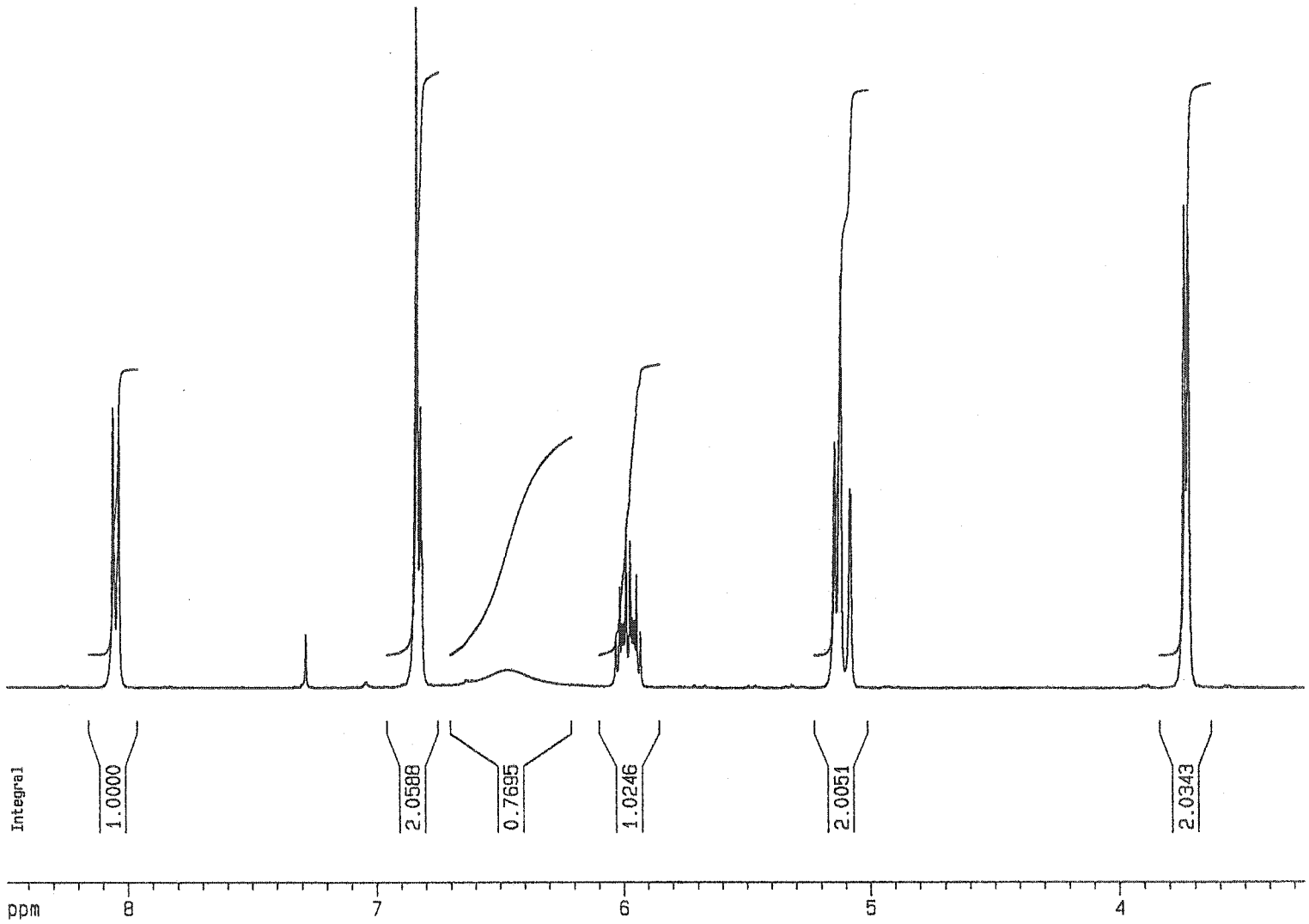
110



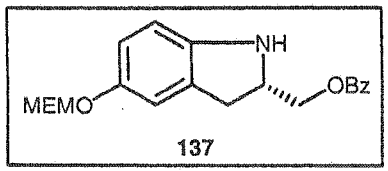
1H NMR Spectrum of the Olefin 122, CDCl3



122

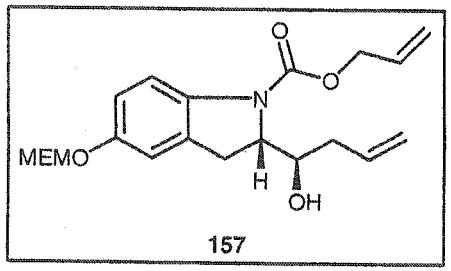


1H NMR Spectrum of the Indoline Template 137, CDCl3



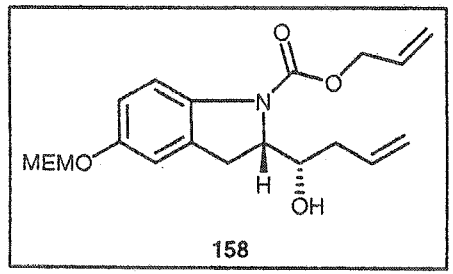
137

1H NMR Spectrum of the Allylic Alcohol 157, CDCl3



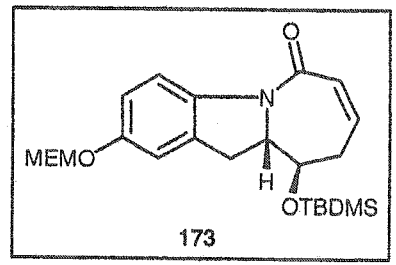
157

1H NMR Spectrum of the Allylic Alcohol 158, CDCl3



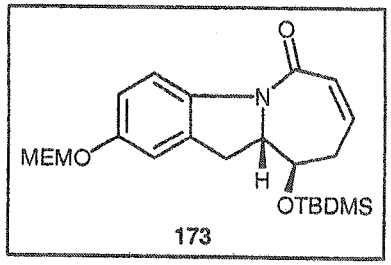
158

13C NMR Spectrum of the Seven-Membered Ring Scaffold 173, CDCl3

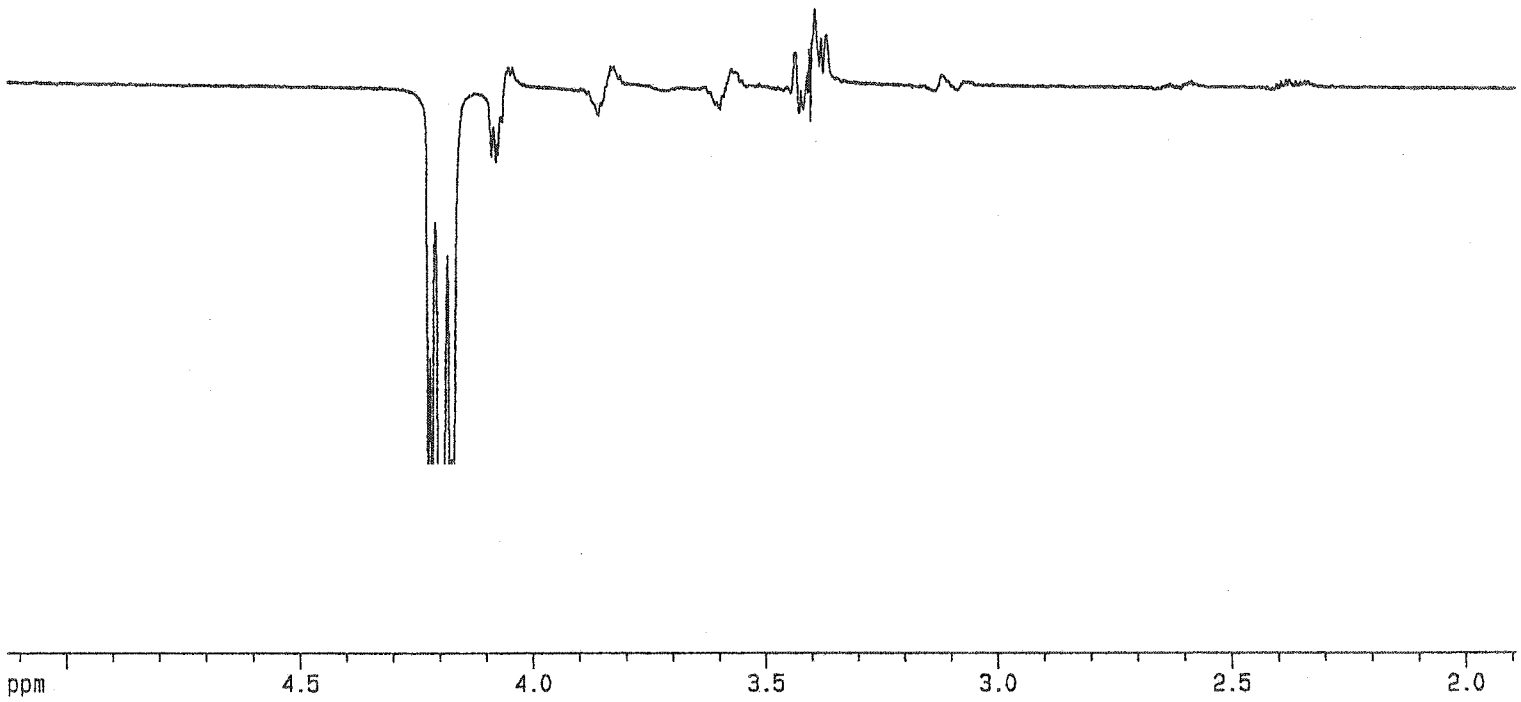


173

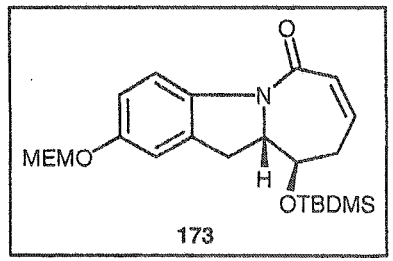
nOe Difference Spectrum of the Seven-Membered Ring Scaffold 173, CDCl3



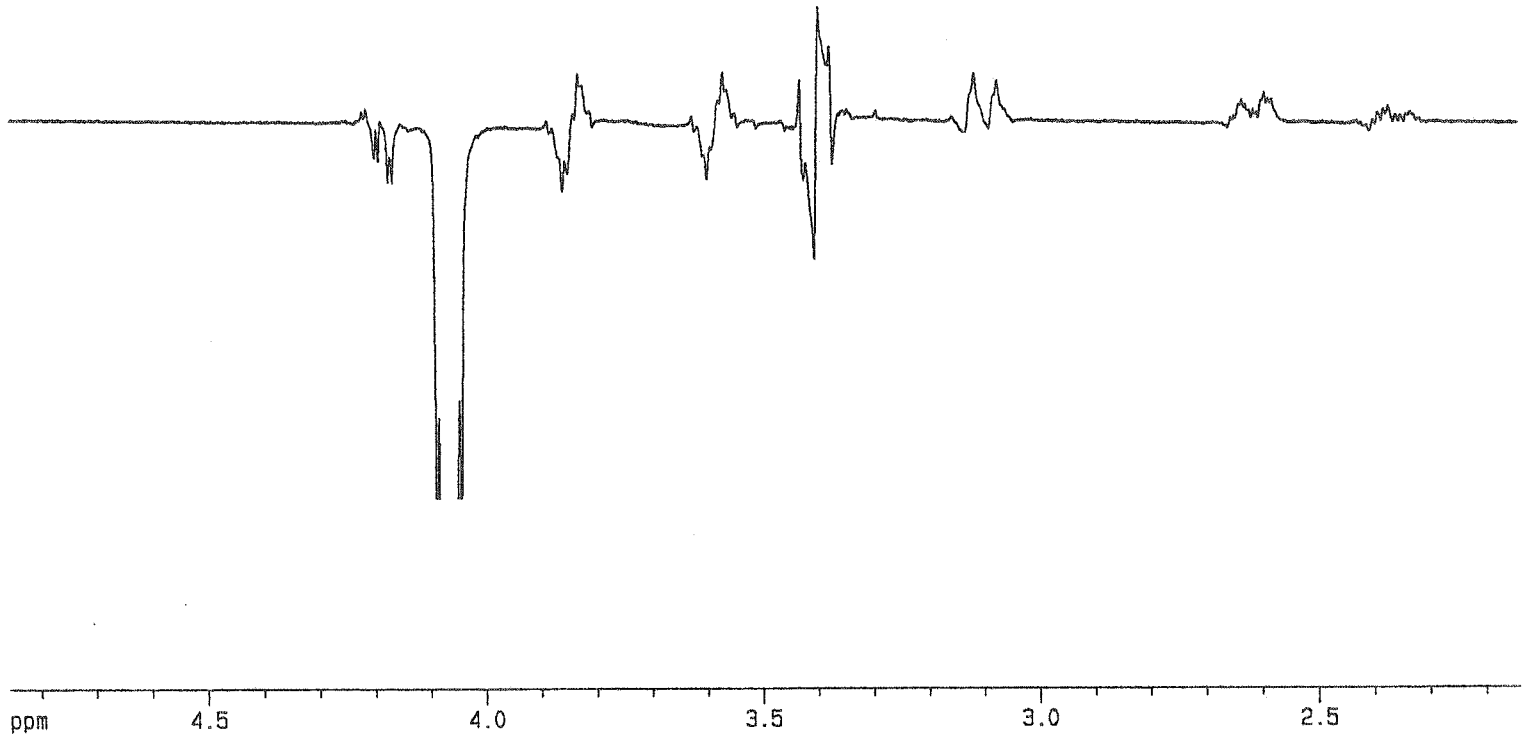
173



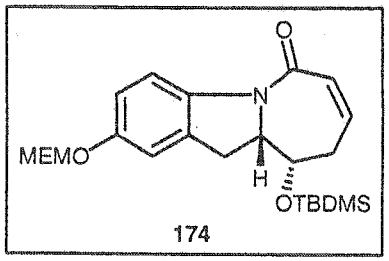
nOe Difference Spectrum of the Seven-Membered Ring Scaffold 173, CDCl3



173

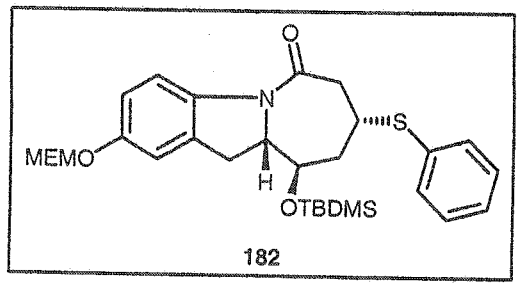


13C NMR Spectrum of the Seven-Membered Ring Scaffold 174, CDCl3



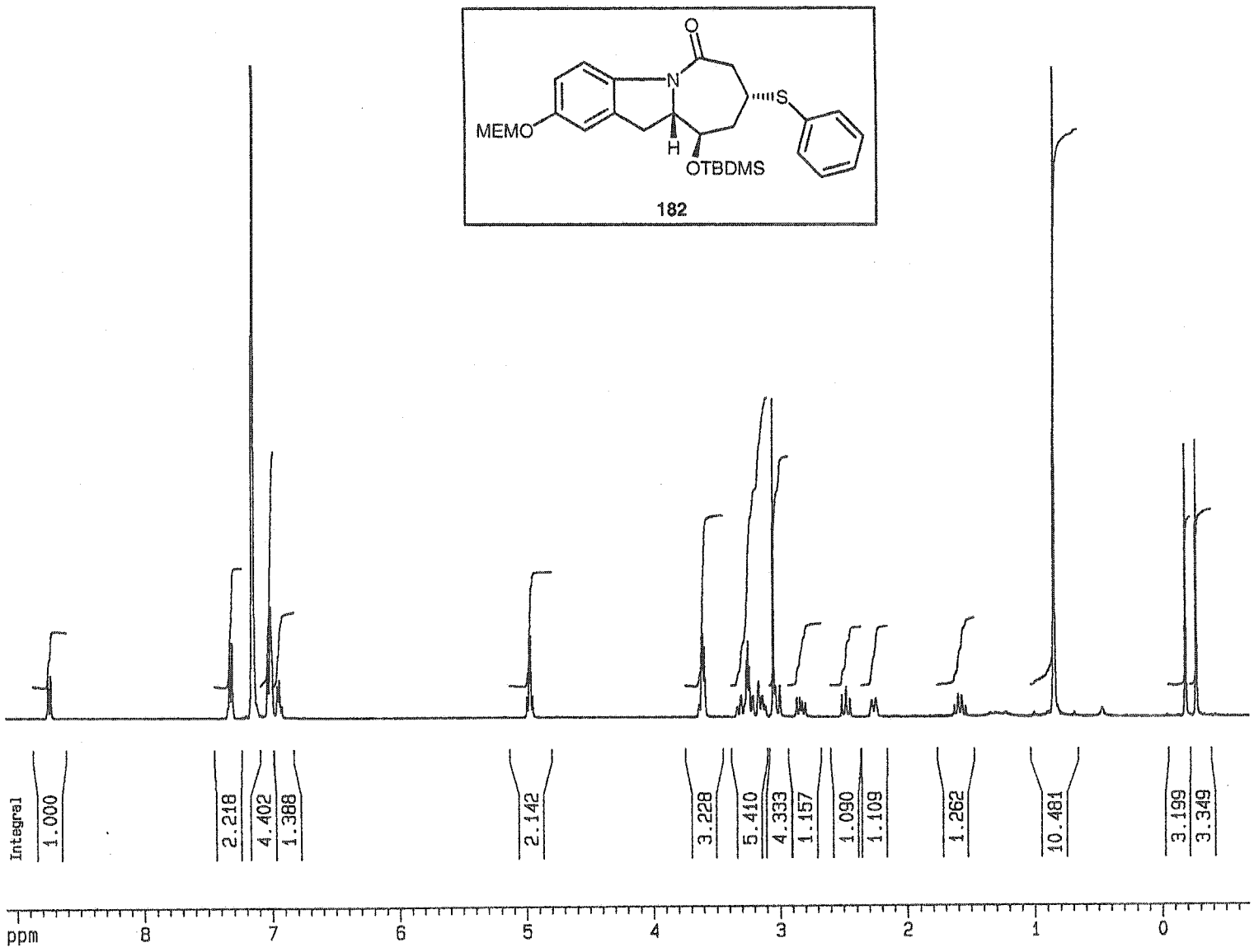
174

1H NMR Spectrum of the Thiol Derivative 182, CDCl3

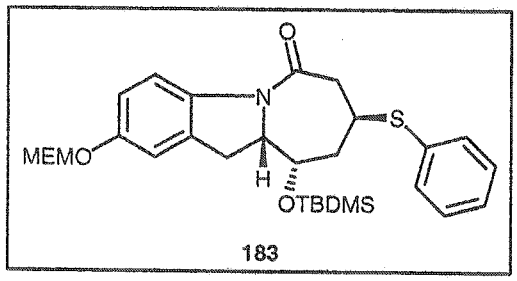


182

1H NMR Spectrum of the Thiol Derivative 182, C6D6

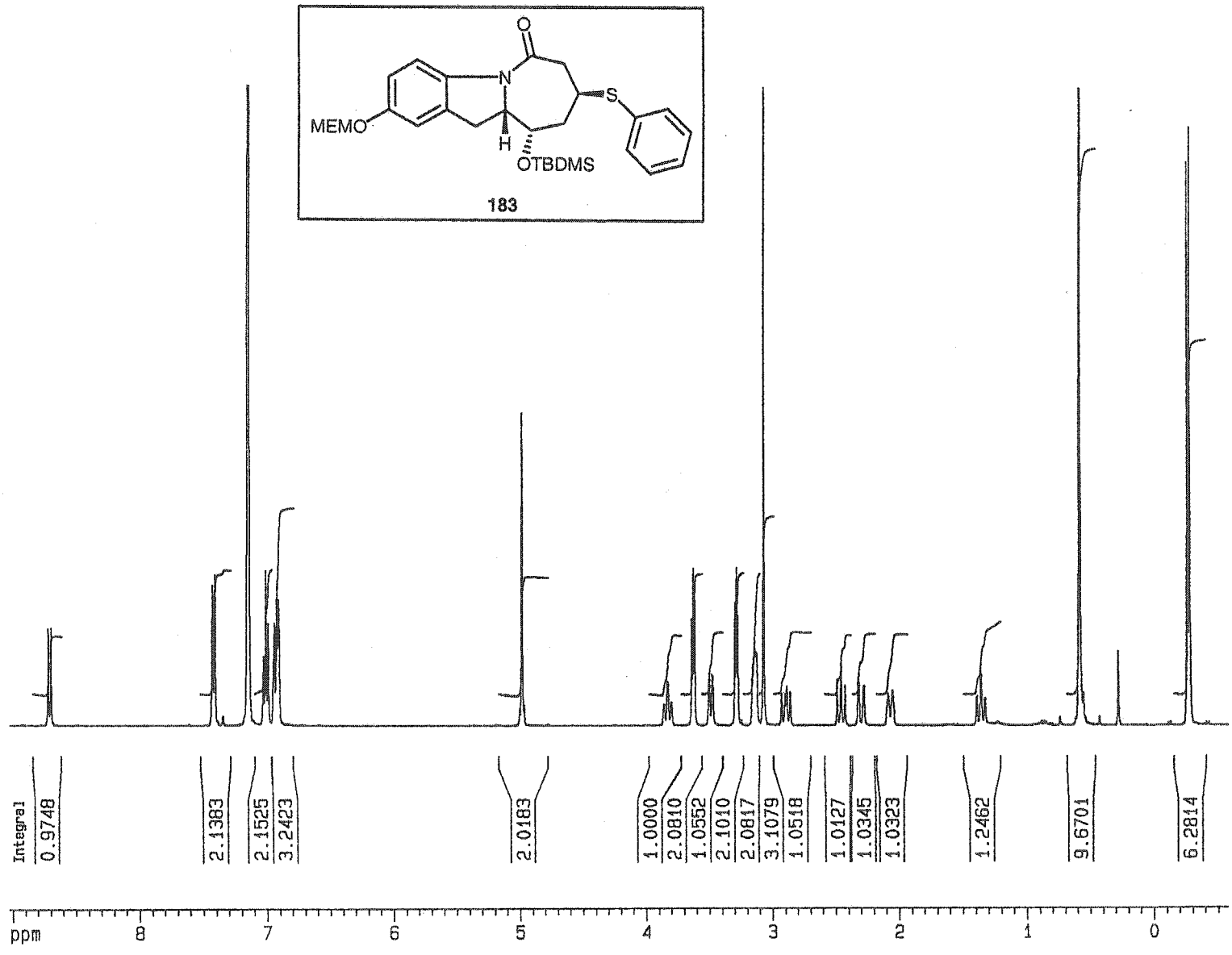


1H NMR Spectrum of the Thiol Derivative 183, CDCl3

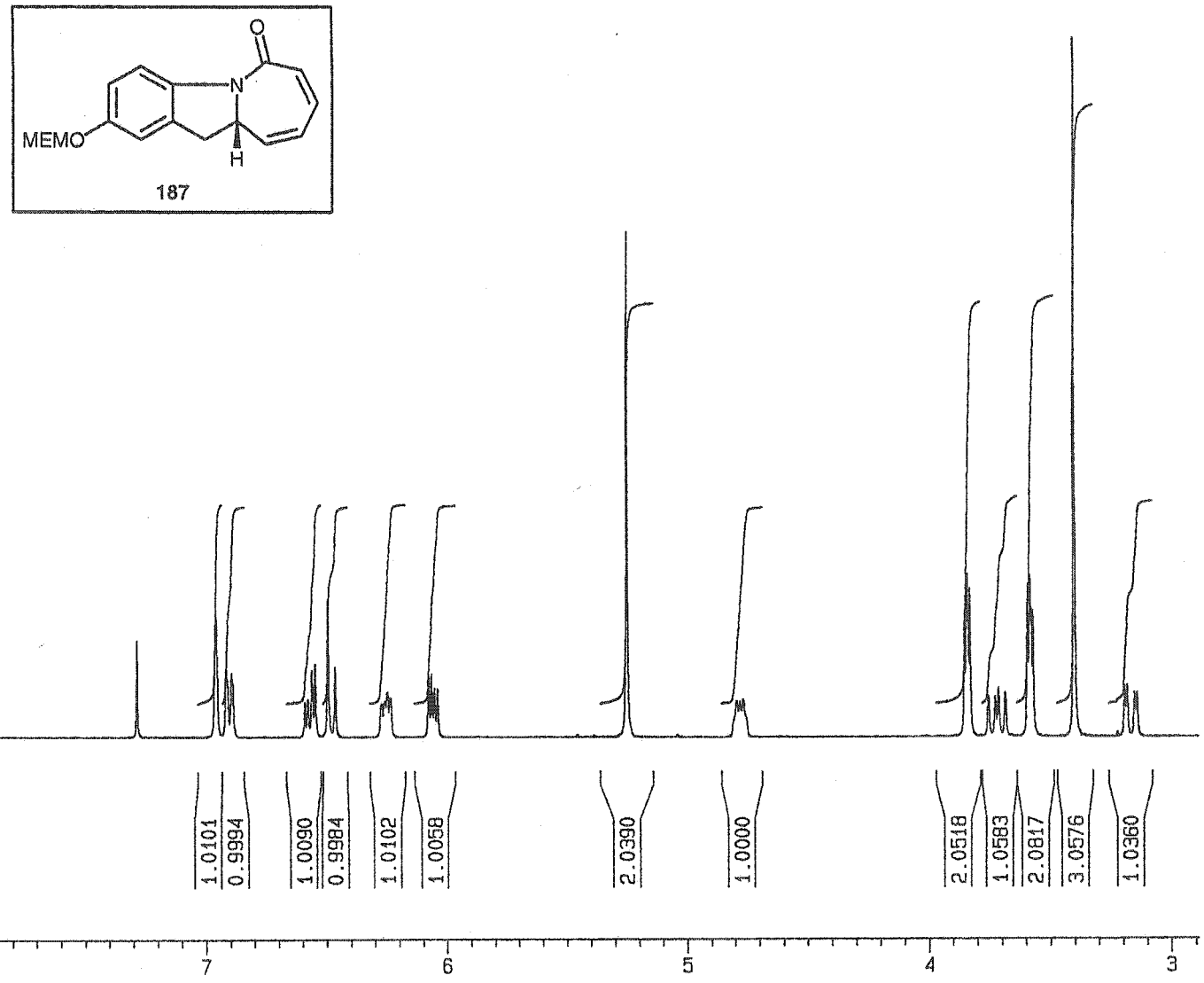


183

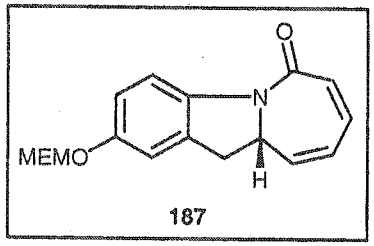
1H NMR Spectrum of the Thiol Derivative 183, C6D6



1H NMR Spectrum of the Eliminated Product 187, CDCl3

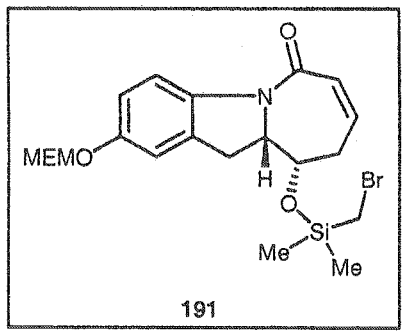


13C NMR Spectrum of the Eliminated Product 187, CDCl3



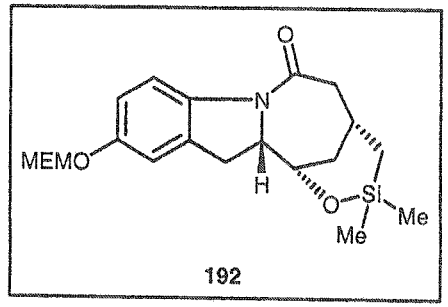
187

1H NMR Spectrum of the Free Radical Precursor 191, CDCl3



191

1H NMR Spectrum of the Compound 192, CDCl3



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