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**STEREOCONTROLLED DIVERSITY ORIENTED SYNTHESIS OF
2H-BENZOPYRAN-BASED NATURAL PRODUCT-LIKE
POLYCYCLICS**

by

P. Kamani Cumaranatunga-Ilangasinghe
M. Sc., Dalhousie University, Halifax, Nova Scotia, 1998

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TO MY MOTHER AND FATHER

SAMAN

AND

BABY DILANKA RUVANGIE

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ABSTRACT

Over the years, it has been shown that natural products that act as highly specific modulators of protein function are complex in nature, highly functionalised and contain few stereogenic centers. There are several examples in literature, where benzopyran-based natural products have been utilized as small molecule chemical probes in understanding protein function. Inspired by the “privileged benzopyrans”, the studies reported in this thesis are centred on the development of a novel method leading to the synthesis of functionalized benzopyran-derived scaffolds. Further, several attempts have been made to obtain natural product-like polycyclic compounds as derivatives of these scaffolds. Our approach has been to develop the synthetic methods initially by solution synthesis. In one case, a partial solid phase synthesis has been achieved that could further be extended to library generation.

The synthetic efforts to obtain several benzopyran-based analogs are reported. These include the development of a novel, stereoselective synthetic route to obtain functionalized benzopyran templates (**71a,b**) and further extensions leading to diverse tricyclic derivatives having medium sized rings with few asymmetric diversity sites. An intramolecular Mitsunobu-based approach was explored to obtain benzopyran-derived tricyclic derivatives having a *cis*- and *trans*-fused lactone moiety (**72**, **73**). Although we were successful in making the amino acid conjugates (**387**, **392**, **395**), we were not successful in making their tricyclic derivatives. Several ring closing metathesis (RCM)-based approaches were also developed to obtain benzopyran-based tricyclic derivatives having functionalized 6- and 8-membered rings, and were successful in making the polyethers (**74**, **75**). Also reported in this chapter is the preliminary work on solid phase synthesis in which benzopyran-based tricyclic compounds with 6- and 8-membered rings were obtained by a RCM approach (**541a,b**).

ABBREVIATIONS AND SYMBOLS

AD mix α	(DHQ) ₂ PHAL, K ₃ Fe(CN) ₆ , K ₂ OsO ₄ •2H ₂ O
AD mix β	(DHQD) ₂ PHAL, K ₃ Fe(CN) ₆ , K ₂ OsO ₄ •2H ₂ O
Bn	benzyl
<i>t</i> -Bu	<i>tert</i> -butyl
°C	degrees Celsius
cat.	catalyst
COSY	¹ H- ¹ H NMR correlation spectroscopy
Cy	cyclohexyl
d	doublet
dd	doublet of doublets
ddt	doublet of doublet of triplets
DIC	<i>N,N</i> -diisopropylcarbodiimide
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
eq.	equivalent(s)
g	gram(s)
H	hydrogen
HATU	O-(7-azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyl-uronium hexafluorophosphate
HBTU	O-benzotriazol-1-yl- <i>N,N,N',N'</i> -tetramethyl-uronium hexafluorophosphate
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet
M	molar
MEM	methoxyethoxymethyl
Ms	methane sulfonyl (mesityl)
MS	mass spectrometry
N	normal
mg	milligram(s)
mL	milliliter(s)
mp	melting point
NOESY	nuclear Overhauser effect spectroscopy
NMR	nuclear magnetic resonance
OTf	trifluoromethanesulfonate
Ph	phenyl
<i>i</i> -Pr	<i>iso</i> -propyl
q	quartet

RT	room temperature
s	singlet
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
Ts	<i>p</i> -toluene sulfonyl chloride (tosyl chloride)
μL	microlitre(s)

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1. INTRODUCTION

Synthetic organic chemistry is a powerful discipline that plays a pivotal role in biomedical research. It provides access to new chemical entities such as natural product analogs, natural product-like scaffolds, and unnatural structures that can be used as small-molecule chemical probes for understanding biological events. The synthetic community has long been engaged in developing efficient methods to generate these architecturally complex natural products and their more simple analogs. In the past few decades, this has driven the need for developing efficient stereo- and enantioselective synthetic methods to keep up with the growing demand for having 3-dimensional, architecturally complex molecules readily available.

In general the pharmaceutical industry has used two types of approaches to have access to potential drug target(s): by organic synthesis and by genetic approaches.^{1,2,3,4,5}

1.1 Organic Synthesis^{6,7,8,9}

Organic synthesis is the preparation of substances by chemical methods. Nature, the master of synthesis, has an amazing ability to build an apparently limitless amount of complicated substances, with various biological activities. Hence, the modern synthetic chemist is continuously challenged by new natural products with an unlimited availability of molecular architectures. One could say that total synthesis is in a constant evolution and flux and not a one time discovery or invention. The synthesis of a complicated molecule is considered to be a very difficult task, where every group and atom must be placed in its proper position. Therefore, synthesis demands virtues of ingenuity, artistic taste, experiment skills, persistence and character.

The original goal of total synthesis was to confirm a structure of a natural product, which was then placed by exploration and discovery of new chemical

reactions to synthesize a particular target, giving rise to Target Oriented Synthesis (TOS, discussed in Section 1.1.1). In the post-genomics chemical biology age, organic synthesis is likely to play an important role, because it allows an access to new chemical entities to be utilized as chemical probes in understanding protein functions. A new area of chemistry called Diversity Oriented Synthesis (DOS, discussed in Section 1.1.3), with the aid of solid phase chemistry and combinatorial synthesis, (discussed in Section 1.1.2) has taken birth to meet with the growing demands of having small molecule chemical probes in biology.

1.1.1 Total Synthesis or Target Oriented Synthesis (TOS)

The history of total synthesis can be divided into 3 stages as synthesis in the (1) 19th century (2) 20th century: pre-World War II and post-World War II and the (3) late 20th century: 1990s.

1.1.1.1 Synthesis in the 19th Century

The synthesis of urea (1, Figure 1.1), from inorganic salt ammonium cyanate, by F. Wohler in 1828, marked the origin of organic synthesis. Other significant synthesis includes the synthesis of indigo by Baeyer (which brought about the German dye industry) and (+)-glucose (2, Figure 1.1) by E. Fischer. The synthesis of glucose initiated the concept of stereochemical control in synthesis, and earned E. Fischer the Nobel Prize for chemistry in 1902.



Figure 1.1 Synthetic milestones of the 19th century.

1.1.1.2 Synthesis in the 20th Century

The 20th century has been considered as the era of enormous scientific advancement and technological progress and can be broadly divided into pre- and post-World War II.

1.1.1.2.1 Pre-World War II

The era began with the strategies to synthesize complex and sophisticated target molecules. Some notable examples include the synthesis of α -terpineol (**3**) by W. H. Perkin in 1904, tropinone (**4**) by R. Robinson in 1917, and haemin (**5**) by H. Fischer in 1929 (Figure 1.2). H. Fischer and R. Robinson both won the Nobel Prize for chemistry in 1929 and 1947 respectively for their synthesis of natural products.

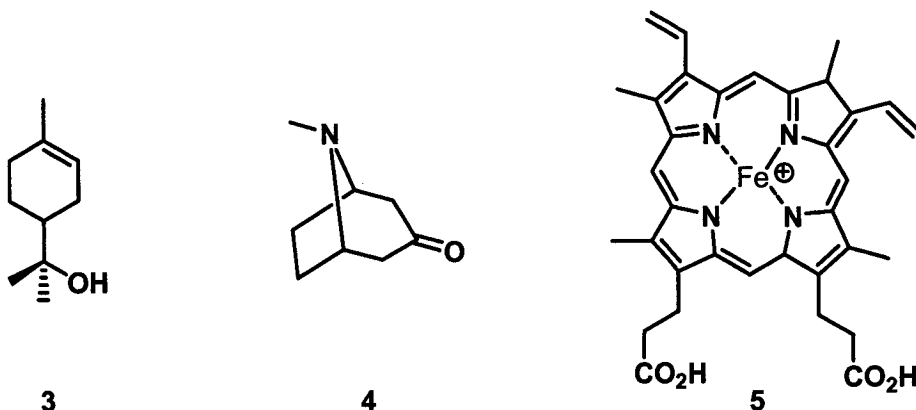


Figure 1.2 Synthetic milestones of the 20th century: pre-World War II era.

1.1.1.2.2 Post-World War II

The post-World War II era has encompassed remarkable achievements in chemical synthesis. For the first time, several molecules were synthesized using multi-step synthesis, which could not have been anticipated in the earlier part of the century. Some examples of molecules synthesized include vitamin A (**6**) by O. Isler in 1949, cortisone (**7**) by R. B. Woodward and R. Robinson in 1951, morphine (**8**) by M. Gates in 1956, penicillin V (**9**) by J. C. Sheehan in 1957 and chlorophyll (**10**) by R. B. Woodward in 1960 (Figure 1.3). The most significant chemist of this era was R. B. Woodward and hence the Post World War II era is

referred to as the 'Woodward era'. He brought about mechanistic rationale and stereochemical control to the field of organic synthesis, and was successful in resolving many daunting problems during the 1940's to the 1960's. His outstanding contributions to synthesis earned him the Nobel Prize in chemistry in 1965. "The synthesis of a complicated molecule is a difficult task, and Nature is the uncontested Master, and Prof. R. B. Woodward is a good second", were some of the words used by Prof. A. Fredga to introduce Prof. R. B. Woodward at the Nobel awards ceremony, paying tribute to a great chemist of the era.

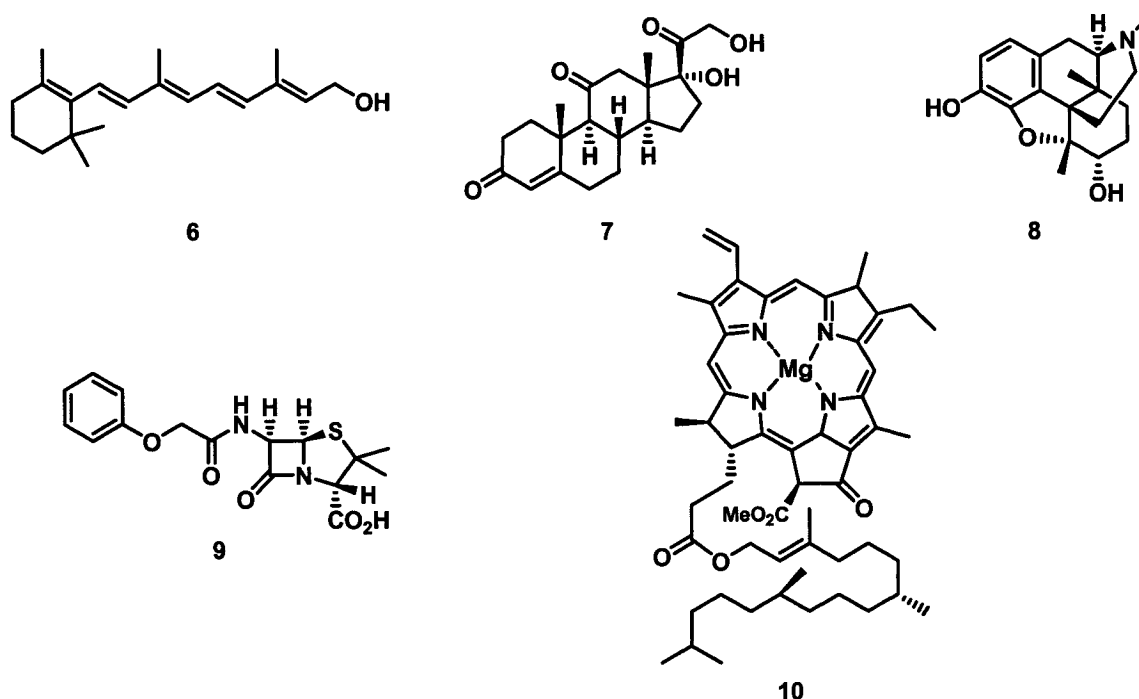


Figure 1.3 Synthetic milestones of the 20th century: post-World War II era

The other prominent scientist of this era was E. J. Corey, who was literally passed on the total synthesis baton from R. B. Woodward at Harvard University, Massachusetts, USA. According to Prof. A. C. Cope, Prof. E. J. Corey's teacher of Synthetic Organic Chemistry, only five important reactions were discovered in the first 50 years of the 20th century. Prof. E. J. Corey's objective was therefore, to develop more general and powerful ways of thinking about synthetic problems, to invent new general reactions and reagents for synthesis, and to design and

execute efficient multi-step syntheses of complex molecules at the limits of modern synthesis. His pursuit brought about an organized approach to synthesis over the existing trial and error approach by the introduction of the theory of 'retrosynthetic analysis'. In 1961, Corey and co-workers synthesized longifolene, (**11**, Figure 1.4)⁹ using principles of retrosynthetic analysis. Prof. E. J. Corey's pioneering contributions to organic synthesis earned him the Nobel Prize for Chemistry in 1990.

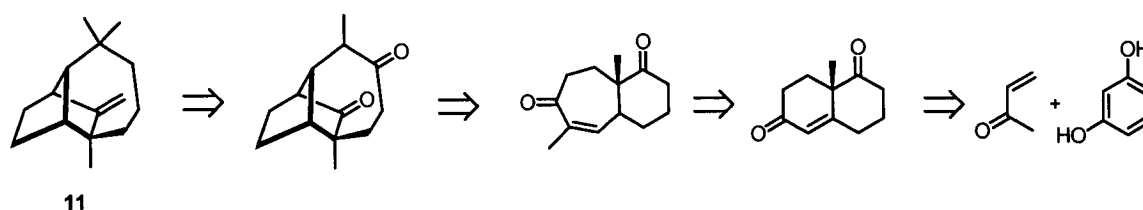


Figure 1.4 Longifolene **11**, and retrosynthetic analysis.

Apart from Woodward and Corey, significant contributions were also made by a number of other chemists. For instance G. Stork is known for the synthesis of steroids, prostaglandins and tetracyclines, as well as development of methodologies such as enamine chemistry, anionic ring closures, and radical chemistry. A. Eschenmoser is famous for his synthesis of colchicines, corrins and vitamin B₁₂. Sir D. H. R. Barton developed methodologies of conformational analysis and free radical chemistry. G. Wittig and H. C. Brown are renowned for the Wittig synthesis and hydroboration of olefins. G. Wittig and H. C. Brown were also awarded the Nobel Prize in chemistry in 1979 for their contributions.

1.1.1.2.3. The Late 20th Century: 1990s

The advances made in the previous era seemed, for a moment to have conquered the major hurdles in chemical synthesis. However, more complex biology driven structures seemed to attract the curiosity of the synthetic chemist, giving rise to the field of Chemical Biology, (discussed in Section 1.4). A few examples include immunosuppressants: FK506 (**62**), cyclosporin (**63**), rapamycin

(64, Figure 1.13), neurotoxins: brevetoxins A and B (12, 13) respectively, and tubulin binding agents: taxol (14) and epothilones (15, Figure 1.5).

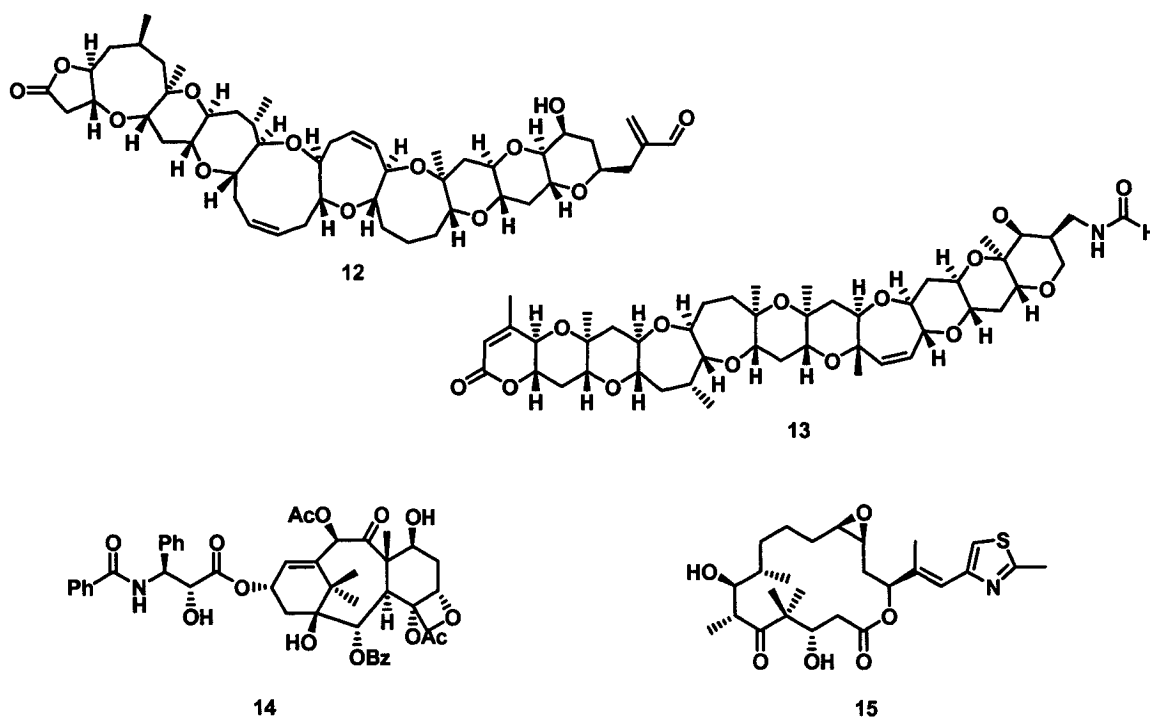


Figure 1.5 Synthetic milestones of the 20th century: 1990s.

Many theories and guidelines were established during the 20th century giving organic synthesis a more organized framework. Electronic theories were also established to understand the mechanistic insights of chemical bonding and conformational analysis. Theories in pericyclic reactions such as the Woodward and Hoffmann rules, to explain Diels – Alder reaction and various 1,3-dipolar cycloaddition reactions. Development of synthetic reactions with hetero-atoms such as nitrogen, phosphorous, boron, sulfur and silicon. Use of organometallic reagents and catalysts such as palladium, ruthenium, and molybdenum, and enzymes in synthesis. Development of stereocontrolled strategies for synthesis in cyclic and acyclic systems to deliver single enantiomers in high enantiomeric excess, such as the Noyori asymmetric catalytic hydrogenation of alkenes and ketones, Katsuki-Sharpless asymmetric catalytic epoxidation of allylic alcohols,

Sharpless asymmetric dihydroxylation of alkenes; cascade reactions – domino reactions, and tandem reactions.

The growing need for understanding gene and protein function in post-genomics age by small molecule chemical probes, has made synthesis assume a new more serious role in biology and medicine. The need to have access to stereo- and enantioselective diverse sets of small molecules in a fast manner has become the driving force leading up to the 21st century. This poses future limitations in target oriented synthesis, Section 1.4.5.1. The use of parallel synthesis and combinatorial synthesis, Section 1.1.2 is believed to meet the demands of productivity, and Diversity Oriented Synthesis, Section 1.1.3 to meet the formidable task of generating highly functionalized, stereospecific, chiral, polycyclic derivatives for high-throughput biological screening.

1.1.2 Combinatorial Synthesis^{3a,4,10,11,12}

Combinatorial chemistry has been around for more than 10 years. It covers a broad range of technologies, and is considered to be the art and science of synthesizing and testing compounds for bioactivity 'en mass' instead of one by one. The aim is to discover lead compounds for developing new drugs and materials more quickly and inexpensively in a way that was formerly impossible.¹³ Combinatorial chemistry is a field that has evolved from solid phase peptide synthesis, pioneered by R. B. Merrifield in the early 1960s. In the early days, combinatorial chemistry was used for the synthesis of peptides and oligonucleotides, and today it has emerged as a tool to construct small organic molecules in large numbers, for drug discovery and catalyst development. Combinatorial chemistry has therefore, encouraged the modern chemist to think more about diversity. This has broadened the horizon from the synthesis of individual compounds to substance libraries and populating structural space.

The principle of combinatorial chemistry has sometimes superseded the traditional trial-and-error selection principle to the trial-and-selection principle. By

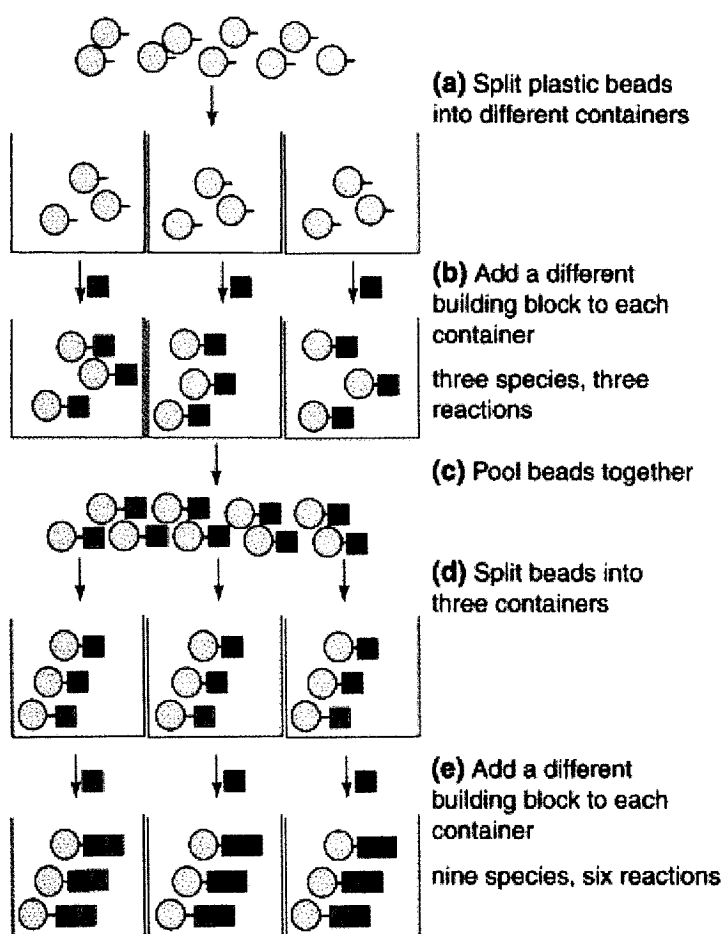
combination and permutation of the individual components, scaffolds and building blocks, all possible molecules or chemotypes in the substance family are synthesized in a simultaneous or parallel manner using parallel or split-pool synthesis, (Section 1.1.2.1). Natural product libraries initially synthesized in this manner had concentrated on chemical diversity without accounting for their biological activity. Some of these natural product libraries have however, been successful uncovering a wealth of information to biology, (Section 1.1.2.2).

1.1.2.1 Automated Parallel Synthesis and Split-Pool Synthesis^{3(a)}

Automated parallel synthesis involves traditional chemical synthesis performed in many small wells in parallel. In the split-pool synthesis, each compound is synthesized on small polystyrene or other types of beads (80-100 μm). It is sometimes referred to as 'one bead-one compound' approach and is analogous to genetic recombination. Separating and recombining the beads during the synthesis, generates a large number of compounds using a small number of synthetic reactions. A synthesis with N number of steps, using M number of containers will yield M^N compounds using $M \times N$ synthetic steps. For example, to make a tetrapeptide library with 20 amino acids using parallel synthesis requires $20 \times 20 \times 20 \times 20$ synthetic reactions, thereby generating 320,000 compounds. On the otherhand to generate the same tetrapeptide library using the split-pool method requires only 80 synthetic reactions ($20 + 20 + 20 + 20$), Figure 1.6. Methods have been developed to identify the reaction sequence of each compound. Hence the compounds are encoded analogues to the genetic code.

1.1.2.2 Natural Product Libraries

Natural product libraries can be broadly classified into (1) pre-fractionated natural product libraries, (2) pure natural product libraries, (3) synthetic and semi-synthetic natural product libraries, (4) focused libraries, (5) generic libraries, and (6) diversity-modified natural scaffold libraries.¹¹ Out of these libraries the major focus is on the last three options.



trends in Biotechnology

Figure 1.6 Schematic representation of a split-pool synthetic sequence.^{3(a)}

The 'focused library' approach uses a biologically active natural product target, which is derivatised to synthesize a small library to explore neighbouring diversity space, Figure 1.7. A few examples of this type of library are the carpanone based library by Shair et al.,¹⁴ the indolactam V based library by Waldmann et al.,¹⁵ the epothilone A and vancomycin based libraries by Nicolaou et al., together with Ellman et al., and the prostaglandins based libraries jointly by Ellman et al., and Janda et al. Some of these examples are discussed in Sections 1.1.3.1 and 1.1.3.2.

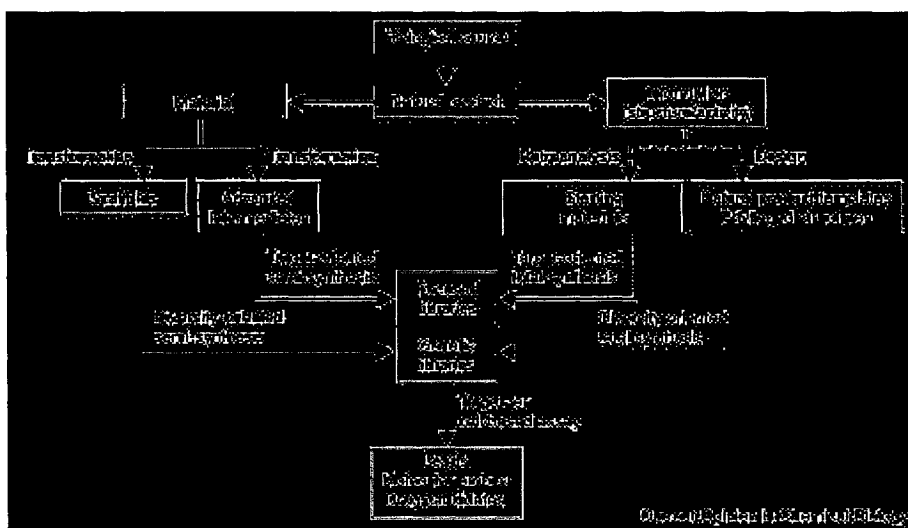


Figure 1.7 Flow diagram of approaches to natural product libraries.¹¹

In contrast to 'focused libraries', 'generic libraries' consist of highly diverse compounds covering large areas in diversity space. It uses highly functionalised, rigid polycyclic natural products as scaffolds, decorated by combinatorial permutations of substituents by chemoselective reactions or protecting group strategies. Generic libraries are a major focus in Prof. S. L. Schreiber's group, Section 1.1.3.4. Nicolaou and coworkers^{16,17} generated a 'generic library' based on a benzopyran core structure, Section 1.1.3.3.

The basis of 'diversity modified natural scaffold libraries' are the use of natural product like scaffolds selected from commercial and in-house databases by their likeness to natural products, molecular weight, number of rings, rotatable bonds, functional groups and biological activity. The scaffolds are either orthogonally protected or have the capability to undergo chemoselective reactions. The diverse substituents bearing pharmacological interests are introduced in a combinatorial way in the final step. This approach has been introduced by Hansske et al.,¹¹ at BioLeads GmbH, in Germany.

1.1.3 Diversity Oriented Synthesis (DOS)

In contrast to TOS, DOS syntheses are not aimed at one particular target, but a collection of compounds having structural complexity and diversity. Therefore, the term 'diversity oriented synthesis' is generally used for the generation of libraries of 'natural product-like' compounds for input into phenotypic assays. In order to obtain a 'positive lead' or a biological response in a phenotypic assay, the compounds generated by DOS have to in most instances bind to protein binding sites or act as inhibitors or promoters of protein-protein interactions. It has been shown that complex natural products have the capacity for such binding (Section 1.4), and therefore, complexity is of primary importance in natural product-like libraries. Diversity too, is equally important as the probability of getting a positive result increases with the diversity of the compound collection. Therefore, one could say that the goal of DOS is to efficiently synthesize a collection of small molecules to perturb disease-related biological pathways, which can be eventually used as new lead compound for developing drugs. Thus to meet the objectives of DOS one needs all the knowledge acquired from TOS, (Section 1.1.1) and solid phase synthesis adapted from the original solid phase peptide synthesis – combinatorial chemistry (Section 1.1.2).

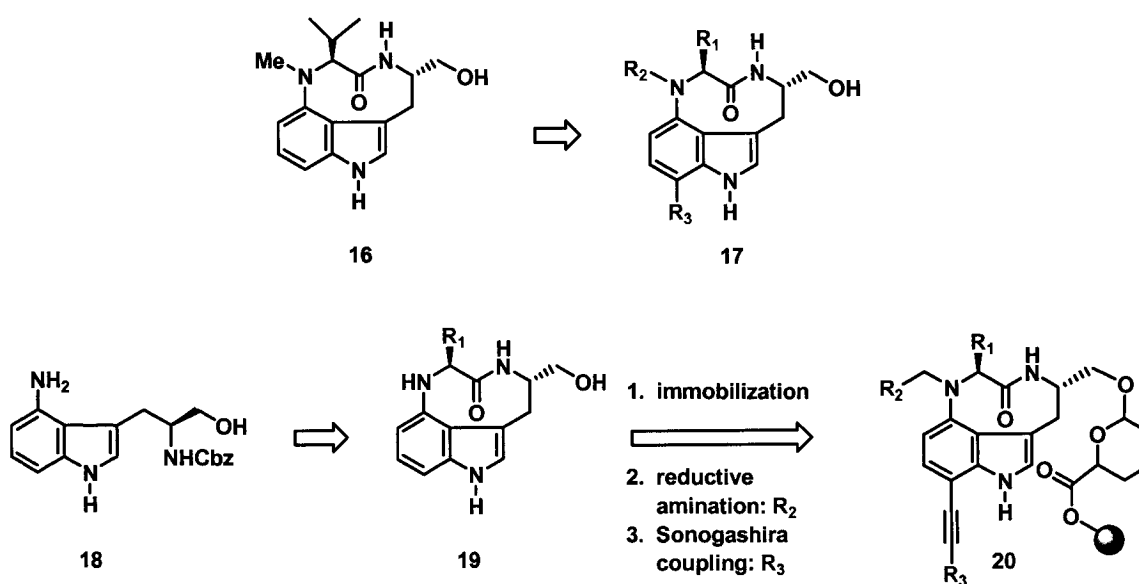
DOS can be broadly classified into four approaches as follows: (1) a focused natural product guided approach, (2) a biomimetic approach, (3) a privileged scaffold based approach and (4) a complex scaffold based approach. Although classified as such these approaches often overlap with one another.^{18,19,20,21}

1.1.3.1 Focused Natural Product Guided Approach

The key feature in this approach is to use a structural framework that has proven to be biologically active to obtain analogs by a focussed library of compounds. The crucial tasks in this approach are to identify such compound classes, and to develop general synthetic approaches to obtain a suitable subset of compounds for biological testing.²² Waldmann and co-workers²³ have used this approach extensively to demonstrate its validity. An example is the synthesis of a 31

compound library based on indolactam V (**16**, Scheme 1.1), a protein kinase C activator. Scheme 1.1 outlines the key reactions. The first diversity point: R_1 , was introduced via an amino acid moiety before the immobilization on to solid support **19**. This was followed by the loading on to the solid support, and further derivatization through a reductive amination to add R_2 . A final Sonogashira coupling added R_3 , to give the template for the library **20**. Biological testing for PKC modulators revealed that a few indolactam V analogs were identified as potent PKC activators.

Scheme 1.1

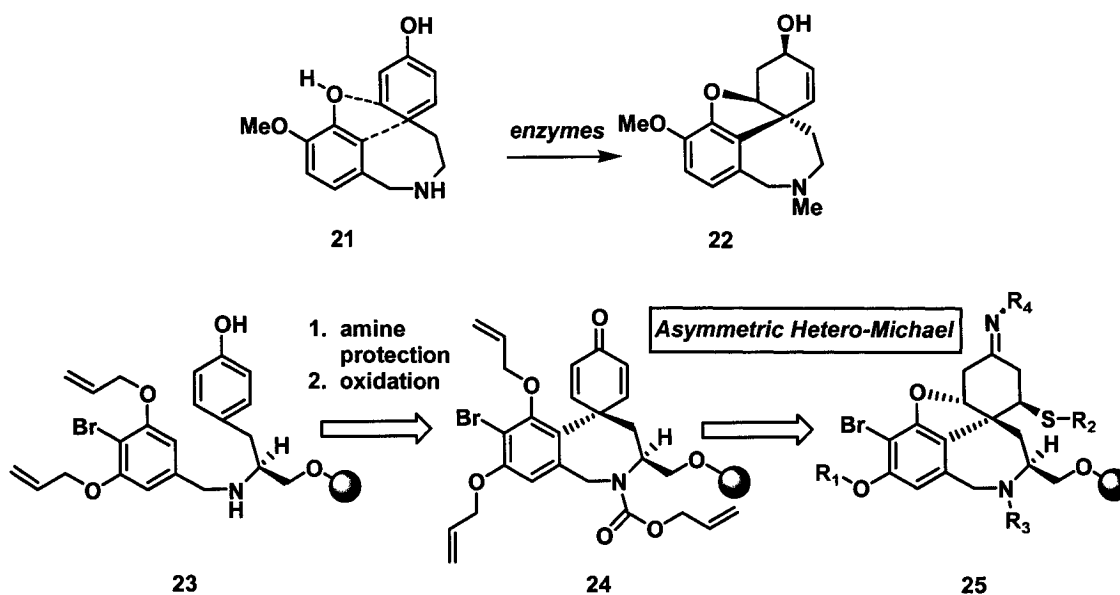


1.1.3.2 Biomimetic Approach

The biomimetic approach uses a natural product template where chemical reactions are made to parallel their biological reactions. The goal is to generate compounds that are more potent than the parent compound. An interesting example is taken from Prof. M. D. Shairs' group²⁴ where they mimicked the enzymatic process of converting norbelladine (**21**) to galanthamine (**22**) by an asymmetric hetero-Michael reaction (Scheme 1.2). Galanthamine, an acetylcholinesterase inhibitor, fulfils the requirements for a small molecule template of having a rigid polycyclic core that lowers the entropy of binding, and having a range of functionalities that can act as diversification sites. This

example however overlaps with the 'privileged structure based approach,' Section 1.1.3.3. The key reactions for the preparation of the template are outlined in Scheme 1.2. Diversities were generated at R₁, by a Mitsunobu reaction; R₂, by an asymmetric hetero-Michael type conjugate addition reaction; R₃, acylation or alkylation reaction, and R₄, by imine formation giving rise to a library of 2527 compounds.

Scheme 1.2



Upon screening the compounds for protein trafficking, it was confirmed that one of these compounds was capable of blocking the secretory pathway, and was named secramine. The parent compound galanthamine however, does not show any effect on the secretory pathway. This study was therefore, successful in achieving the goals of diversity oriented synthesis by exhibiting biological responses beyond the scope of the parent compound.

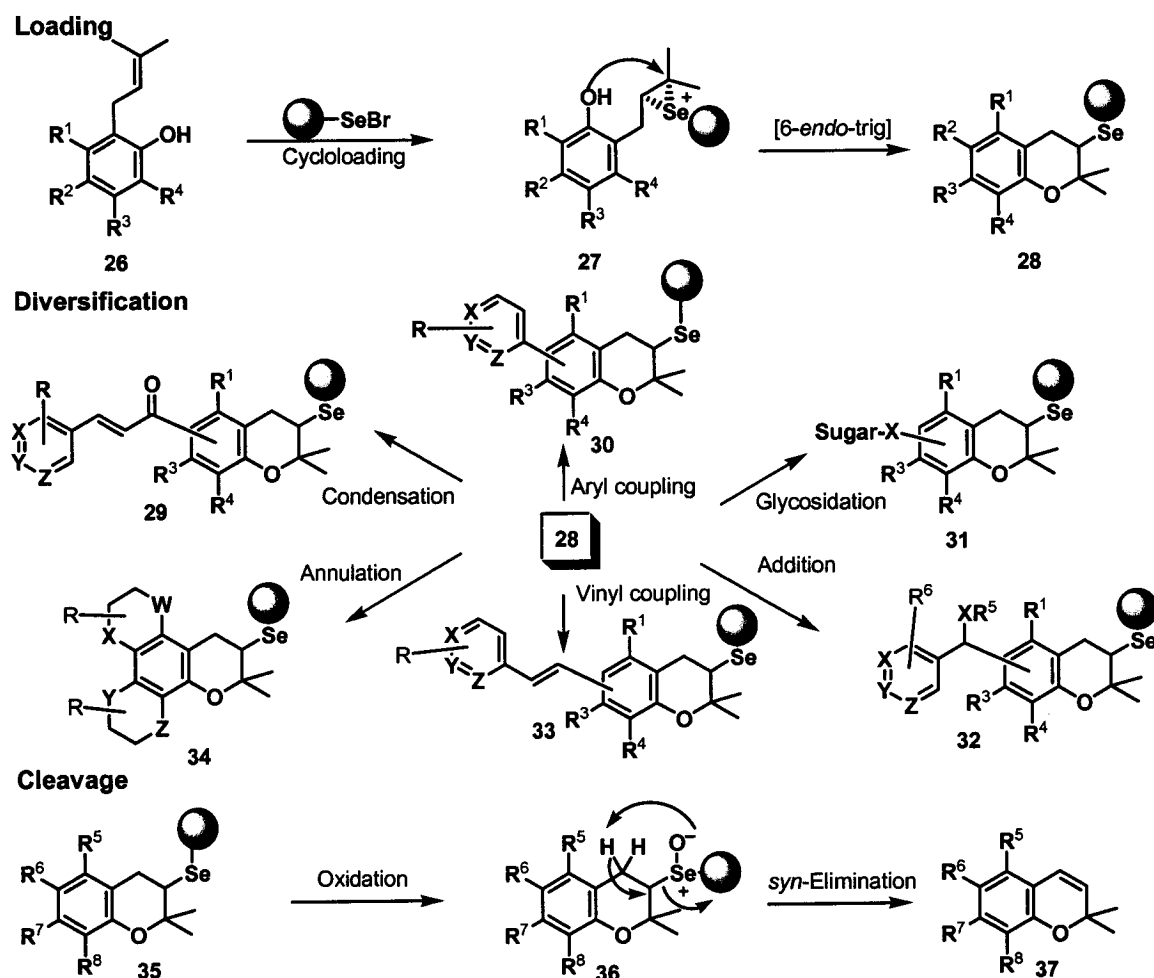
1.1.3.3 Privileged Structure Based Approach

The privileged structure based approach uses scaffolds that are rigid, polycyclic, and contain heteroatoms capable of orienting varied substituent patterns in a well-defined three-dimensional space. The term, coined by B. E. Evans in

1988,²⁵ was to initially describe selected structural types such as benzodiazepines and benzazepines and has now been extended to scaffolds such as indoles and piperidines and many other structural types.

This approach can be demonstrated by an example from Prof. K. C. Nicolaou's group.¹⁶ In their study, the researchers had taken a 2,2-dimethyl benzopyran template **28**, Scheme 1.3. The choice of template was made after evaluating the following criteria: its occurrence in nature, to contain one or more rigid ring systems to facilitate protein binding, be sufficiently lipophilic for cell membrane penetration, molecular weight <500 g mol⁻¹, (see Section 1.4.5.2), and to have a site to immobilize onto solid support.

Scheme 1.3



After preparation of the bicyclic scaffold on solid support (**28**), it was diversified to various structural types such as chalcones (**29**), pyranocoumarins (**34**), chromene glycosides (**31**), stilbenoids, polycyclic steroid biosynthesis inhibitors (**32**), N-heterocycles and pyranoflavones (**30**), giving rise to a 10,000-membered natural product-like library (Scheme 1.3). The library was synthesized using IRORI Nanokan technology with optical encoding to tag the compounds during spilt-pool synthesis, reporting one of the first applications of this technology in high-throughput synthesis

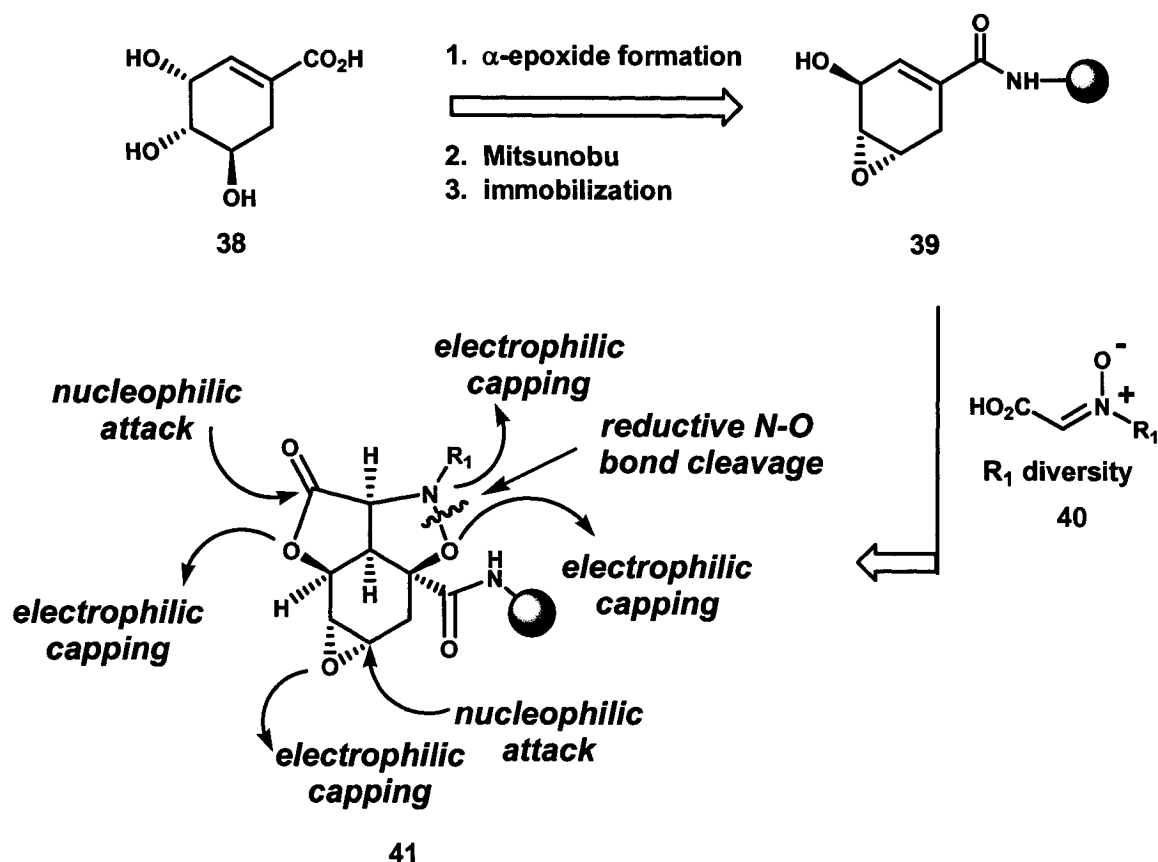
1.1.3.4 An Approach to Synthesis of Complex Natural Product-like Scaffolds

This approach is a relatively new concept pioneered by Prof. S. L. Schreiber and is aimed at generating libraries of compounds with 3-dimensional structural complexity, functionality and diversity. Unlike the natural product guided approaches, the scaffold based approach is aimed at developing novel natural product-like scaffolds efficiently that could further be utilized in exploring the diversity oriented reactions

In one study, Schreiber and co-workers²⁶ used shikimic acid (**38**), a chiral starting material to synthesize a tetracyclic scaffold **41**, and upon diversification to generate a 2,000,000-member library. The key steps in their approach are outlined in Scheme 1.4. Compound **39** was synthesized after epoxidation, Mitsunobu inversion and anchoring onto solid support, which then undergoes a series of asymmetric 1,3-dipolar cycloaddition reactions to generate highly regio- and stereoselective tetracyclic scaffolds **41**. Three new stereogenic centers were created in the process, directed by the orientation of the hydroxyl function of **39**. Further diversification did not require the cumbersome process of protecting group manipulations, and was achieved by the use of organic and organometallic reagents to create a highly functionalized bi- and tri-cyclic compound library.

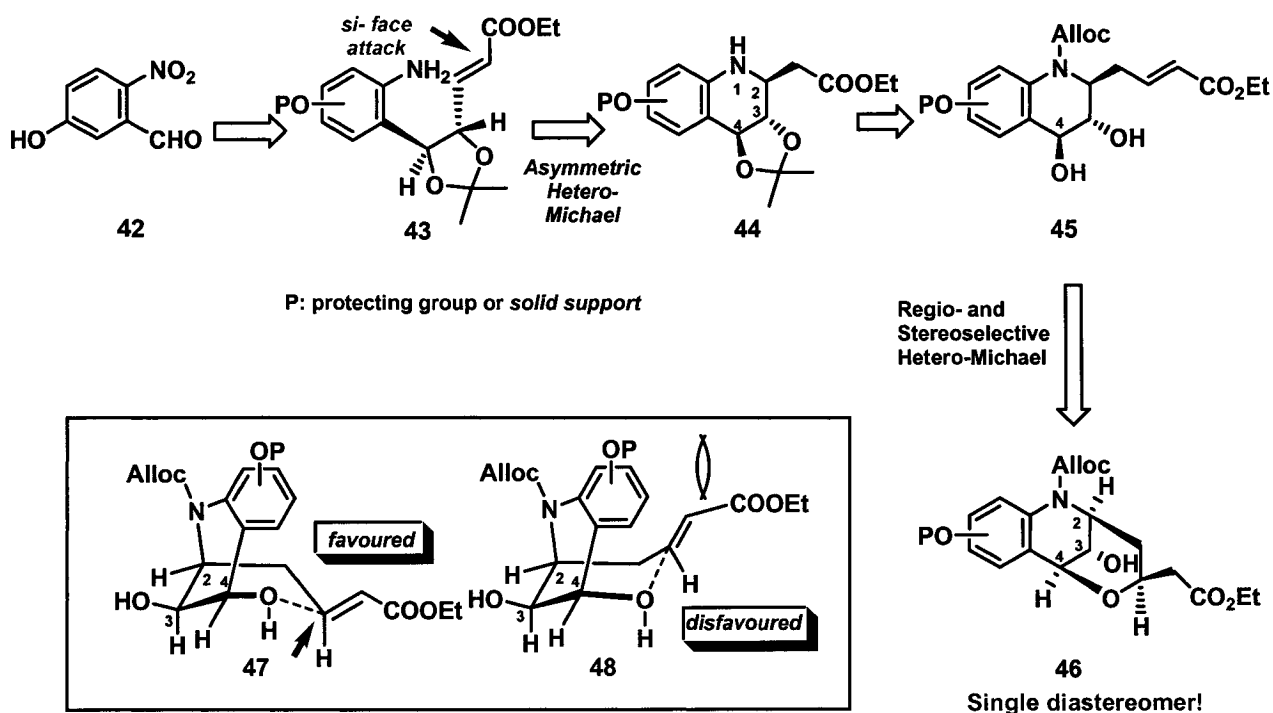
Another example of this approach is the work done in Arya's group,²⁷ where a tricyclic scaffold **46** was generated using an inexpensive achiral starting material.

Scheme 1.4



42, (Scheme 1.5). An enantiopure tetrahydroquinoline-based β -amino acid **44**, was first obtained as a single diastereomer using an asymmetric hetero-Michael reaction. The bicyclic scaffold **44** was then extended to the tricyclic system **46**. This was achieved via a chain extension reaction to **45**, followed by a regio- and stereocontrolled hetero-Michael reaction to give **46**. Compound **46** was confirmed by extensive NMR analysis. A boat-like transition state **47**, over a generally more stable chair-like transition state **48**, was proposed to explain the stereochemical outcome of this reaction. The synthesis has been extended to solid phase, with several diversification sites for library synthesis

Scheme 1.5



Apart from its significant contribution to biological research, DOS has contributed to other areas of chemical research. To highlight some significant milestones in this type of research: it has been instrumental in giving insight to a complex process like asymmetric catalysis, where the design criteria for a suitable catalyst was not well understood. For instance, discoveries made by Copeland and Miller,²⁸ a new acylation catalyst for kinetic resolution, and by Jacobsen and co-workers,²⁹ a catalyst of enantioselective Strecker reaction are examples of how DOS is a powerful tool. The latter has been successfully applied to the enantioselective synthesis of α -amino acids³⁰ and quaternary amino acids.³¹

Although there are many revolutionary discoveries of DOS in the literature, limitations exist.¹ For instance every reaction condition has to be optimized for solid phase, and chemistries performed at each step must be compatible with other functional groups present in the library. Therefore, library optimization can be time consuming. Unanticipated side reactions resulting from functional group

interactions, is another problem. Due to the large number of compounds created within one scaffold an efficient encoding system is required to keep a track of the synthetic history.

Some of these drawbacks of tracking the compounds have been overcome by radio frequency tagging (IRORI technology). On the other hand, the use of 'macrobeads' (approximately 500µm in diameter) obtained with encoding methods have allowed development of split and mix-based approaches to obtain the libraries.¹

Despite the many successes in DOS, prominent scientist Prof. S. Danishefsky³² is rather cautious of the predictions towards the future of DOS. He is not a firm believer that synthesizing compounds with the aid of combinatorial chemistry would reduce the costs of drug discovery nor would pharmacological pipelines be filled with new drugs. He thinks that a small collection of 'smart' compounds may be more valuable than mindless assembly of a large collection of compounds. The ideal solution would be therefore, an interdisciplinary field between TOS and DOS where "DOS benefits from the 'wisdom' of natural products!"

1.2 Synthetic Developments in the Pharmaceutical Industry³³

The first drugs or therapeutics used in medicine were natural products isolated from plants and microorganisms.^{34,35} The greatest impacts on drug discovery are the advances made in organic synthesis (Section 1.1). The evolution of the pharmaceutical industry closely parallels total synthesis, and the two disciplines must be considered in unison. To highlight, until recently the synthetic drugs were used as racemates. Now however, enantiomerically pure drugs have a commanding presence in the global pharmaceutical market. For example Lipitor (atorvastatin, **49**, Figure 1.8), a cholesterol-lowering drug, is a synthetic statin with a polyketide structure. Lipitor disrupts the biosynthesis of cholesterol by competitive reversible inhibition of the rate-limiting enzyme HMG-CoA reductase at the HMG-CoA binding site.^{36,37} Zocor (simvastatin, **50**, Figure 1.8),³⁸ is

another cholesterol lowering drug, synthesized as a single-enantiomer, and together with Lipitor have recorded the highest sales for 2002.³³

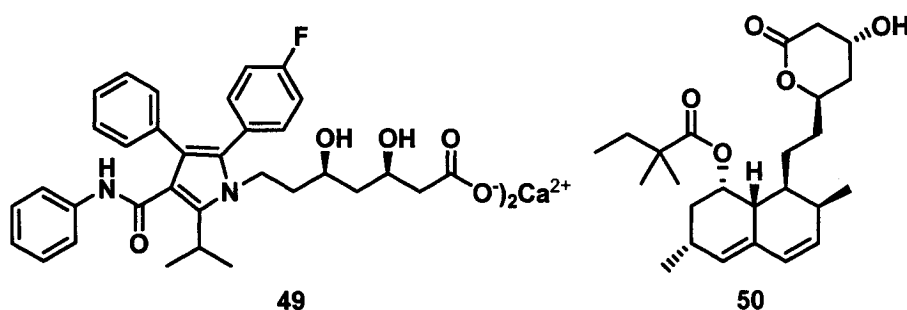


Figure 1.8 Enantiomerically pure synthetic drugs

Synthesis of enantiomerically pure small molecules can be broadly classified into four groups:³³ (1) chiral pool technology, (2) diastereomeric resolution methods, (3) biological asymmetric synthesis methods and (4) chemical asymmetric synthesis methods. The last two methods are discussed at length.

'Biocatalysis' is an emerging trend for resolution. It involves a one-step catalytic transformation in a reactor mediated by an isolated enzyme. Some believe that 'biocatalysis' may be able to solve problems in certain stereoselective C-C bond formation reactions in organic synthesis. For instance, to obtain an enantiopure product from the aldol reaction requires careful handling of conditions to avoid cross- vs self- condensation reactions, and to control stereo- and enantioselectivity. Complex reagents, auxiliaries and catalysts have been used to optimize conditions. Protecting group manipulations, a key strategy in synthesis, which extends the number of steps in a synthetic sequence, is also required. Therefore, selective C-C bond formation is a major challenge in organic synthesis. Using 'biocatalysis' gives rise to highly stereoselective products in one-step and could therefore play an important role in organic synthesis.

The first reported examples of using 'biocatalysis' include the use of acylases, hydantoinases and aminopeptidases in the synthesis of enantiomerically pure amino acids. For example the use of nitrile hydratase in enzymatic bulk production of acrylamide **51** (Figure 1.9) from acrylonitrile.⁴¹

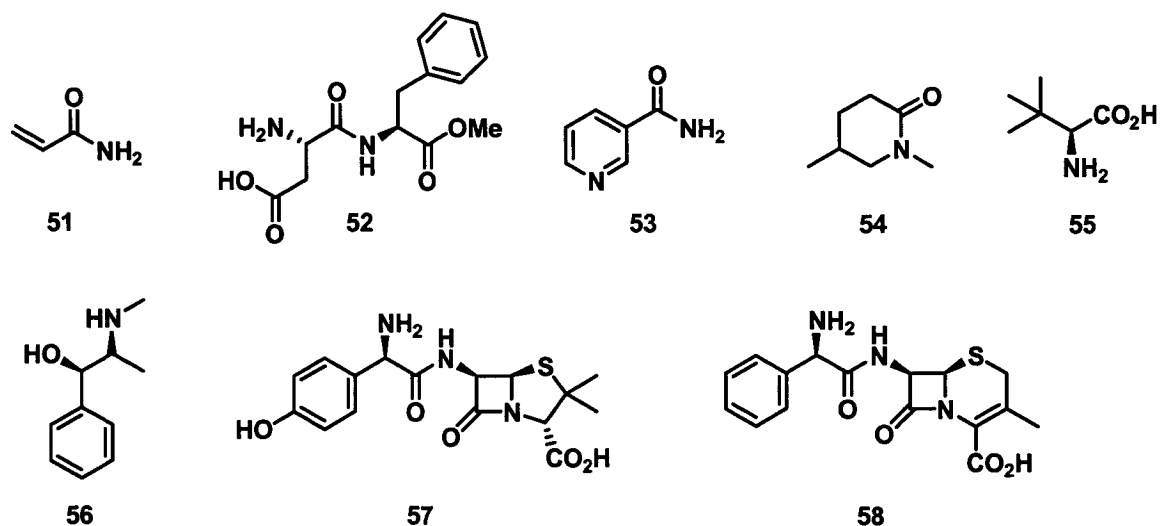


Figure 1.9 Molecules synthesized by the use of enzyme-based approaches

A recent industrial application of using 'biocatalysis' is in the synthesis of enantiomerically pure cyanohydrins, important intermediates in the pharmaceutical and agrochemical industries. The enzyme oxynitrilase is used for this purpose.³⁹ For a specific example is the use of recombinant (S)-hydroxynitrile lyase (HNL) from the rubber tree, for the enantiopure synthesis of (S)-*meta*-phenoxy benzaldehyde cyanohydrin. (S)-*meta*-Phenoxy benzaldehyde cyanohydrin, a pyrethroid derivative, is used in insecticides.

'Biocatalysis' has also been used in the synthesis of the low-calorie sweetener, aspartame (**52**, Figure 1.9) and semi-synthetic β -lactam antibiotics.⁴⁰ A few more examples include nicotinamide (**53**), 1,5-dimethyl-2-piperidone (**54**), (S)-*tert*-leucine (**55**), ephedrine (**56**), amoxicillin (**57**) and cephalexin (**58**, Figure 1.9).⁴¹

Despite the predictions of extensive use of 'biocatalysis' in the future, limitations such as availability, scope of the substrate, and stability of operation exist.⁴¹ For instance most industrial syntheses involve organic molecules which are insoluble in water, whereas enzymatic reactions occur most readily in water. Therefore, the enzyme should be capable of operating in non-aqueous media. Some of these limitations have been overcome by the advances made in genomics⁴² and in high-throughput-screening.⁴³

'Chemocatalytic' asymmetric synthesis method is considered to be the most popular tool in contemporary chiral synthesis. It is believed that any synthesis of a single enantiomer will be far superior to one that requires resolution. Most of the small scale reactions developed are relatively easy to scale up. For example, catalytic asymmetric hydrogenation, a key step in the synthesis of (+)-biotin has been carried out in a multi-ton scale. Another example is the Sharpless dihydroxylation reaction, which has been optimized to be used in a large scale industrial application. One predicts, therefore, that the best industrial synthesis for the future to be the combination of bio- and chemocatalysis, as they are unable to function as independent disciplines.

1.3 Chemical Genetics or Chemical Biology¹⁻⁵

The chemical genetic approach is a complementary approach to the genetic approach and has been given a number of names including the 'pharmacological approach.' Prof. Stuart L. Schreiber, the pioneer or the 'guru' of this approach, defines it as the chemical genetic approach, because of its specificity, generality and similarity to the principles of the genetic approach.⁴⁴ Some of the key researchers of this field, are Craig Crews, Thomas Kodadek, Thomas Mayer, Timothy Mitchison, K. C. Nicolaou, Peter Schultz, Mathew D. Shair, Kevan Shokat and Brent Stockwell.⁴⁵

In the pre-genomics era, chemists were primarily concerned with the structure and synthesis of organic molecules, while the biologists were primarily interested

in their functions. Chemistry and biology as independent disciplines have not been very successful in meeting the demands of the post-genomics era. Therefore, forming an interdisciplinary relationship between the chemists and the biologists in 'chemical biology' is expected to meet the challenges of drug research in the 21st century.^{3a,44}

In the chemical genetics approach, cell permeable small molecules are screened as small molecule probes to perturb intracellular processes. Similar to the genetic approach, these small molecules can act by inhibiting or activating a particular protein or a set of proteins, and tracing the inhibitor or activator back to its target protein provides the link between the target and the phenotype. A few examples of small molecules that can modify the target proteins include, fumagillin that mimic null mutations, and phorbol esters that activate mutations.² In contrast to the genetic approach however, the chemical genetic approach allows small molecules to be added or removed at will and the molecular targets are often unknown, and therefore, aims to yield new information about cellular process. One example where traditional genetics could not identify a good model system was for the genetic analysis of tumour-induced neovascularization.² Fumagillin (**59**, Figure 1.10), an anti-angiogenic natural product, was reported to show new insights to the mechanism – thanks to the chemical genetic approach. Other examples include leptomycin B, (**60**, Figure 1.10, nuclear transport), and capsaicin, (**61**, Figure 1.10, nociceptive signal transduction).

The chemical genetic approach can be subdivided into 'forward' chemical genetic, and 'reverse' chemical genetic approach.

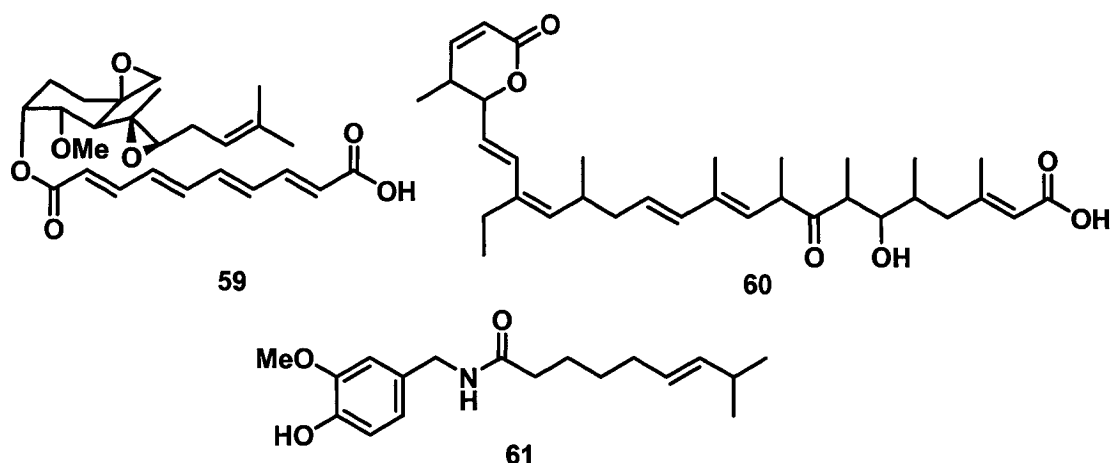


Figure 1.10 Small molecules used as chemical probes in chemical genetics.²

1.3.1 Forward Chemical Genetics^{1,4}

The forward chemical genetic approach is considered as a new method to systematize the discovery and use of small molecules as tools for biological research and drug discovery. It consists of three major components: (1) a collection or 'library' of compounds, which is the source of small molecules, (2) a biological assay with a quantifiable phenotypic output for phenotype-based screening, and (3) a strategy to identify the target(s) of active compounds (Figure 1.11).

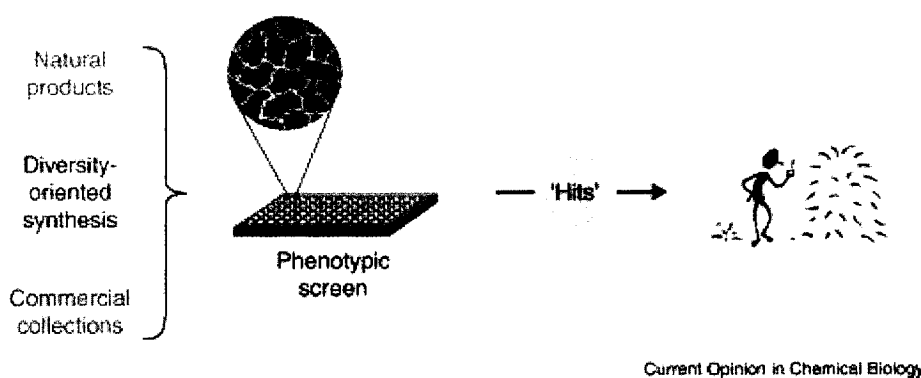


Figure 1.11 Schematic representation of 'forward' chemical genetic approach.¹

1.3.2 Reverse Chemical Genetics

In contrast to the forward genetic approach, the reverse genetic approach uses a small molecule that has a known and specific protein target to alter the function of its target. Similar to the forward genetic approach, the pathways of the altering process are determined and the function on its target is inferred.

1.3.3 Methods of Obtaining Small Molecules

Generally, three methods have been used to obtain small molecules: (1) a general collection of samples from synthetic labs (2) natural products isolated from plant and marine sources, also called the bio-assay guided purification of active compounds from natural products, and (3) by combinatorial / high-throughput synthesis.^{1,3(a)}

The bio-assay guided method or isolation from natural products is a classical method where samples are extracted by solvents. The crude extracts are then assayed for biological activity. The cycle of purification and screening is repeated until a pure compound is isolated. Limitations of this process include difficulty of screening crude mixtures. For instance only the more potent compounds will be screened over the moderately active ones. Apart from this, the time and effort that is needed to purify and identify the active species in extracts limits their usefulness in chemical genetic analysis.

An alternative to the natural product screening is the synthesis of large numbers of natural product-like small molecules using combinatorial approaches such as automated parallel synthesis or split-spool synthesis. This leads to diversity oriented synthesis (DOS), discussed in Section 1.1.3. The compounds generated by DOS are then analysed by phenotype-based screening processes.

Generally, phenotype-based screens are performed on living cells or complex cellular extracts, Figure 1.12.¹ For example by using the ELISA method called 'cytoblot'.⁴⁶ Another more recent method is screening by imaging.⁴⁹ The later

method involves an automated microscope that can image cells grown in multi-well plates for effects such as protein trafficking and mitotic spindle disruption. The discovery of the small molecular peptide calcineurin as a target for FK506 in 1987 marks the first successful application of these types of screening processes.^{1, 3,4,46}

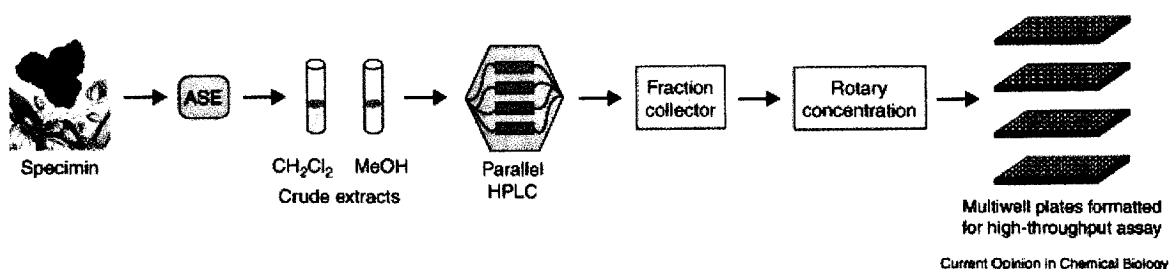


Figure 1.12 A high-throughput approach to the use of natural products in phenotypic assays.

1.3.4 Target Identification^{1,3}

The process of target identification is considered to be somewhat non-systematic. It uses classical methods such as purification of the target from cellular extracts by using an immobilized or a radio-labelled compound, affinity chromatography and biochemical fractionation. More modern biochemical techniques such as expression cloning⁴⁷ and display cloning⁴⁸ methods have also been used. Apart from these, other common methods include transcriptional profiles in yeast and guessing candidate methods. To cite an example of an early success of the last method, Mayer et al.,⁴⁹ used 139 compounds out of a 16,329 small-molecular library to screen for activity in mitosis or cell division. One compound, later named monastrol, arrested cell division in mammalian cells. Monastrol did not target tubulin, whereas, all previously identified small molecular probes had interfered with tubulin. Therefore, monastrol would be a useful tool for studying the mechanism of mitosis without interfering in other cellular processes.

1.3.5 Probes for Chemical Genetics

The probes that are commonly used in chemical genetics can be classified into natural products or natural product-like compounds. They are either isolated from Nature or synthesized in a laboratory.

1.3.5.1 Natural Products as Probes

Historically, natural products like colchicine, a tropolone derivative, found in meadow saffron has been used to treat gout since the 18th century. The identification of the target of colchicine as tubulin by Taylor and co-workers^{50,53} in the late 1960s is a remarkable example of using a small molecule as a probe to discover biological functions. The mechanism of action is by the arrest of the normal cell division cycle, i.e. in mitosis. A few more examples of active compounds isolated from nature include morphine, from the medicinal plant opium by Serturmer and colleagues in 1985,^{3(b),51} and brefeldin A from toxic fungi.⁵²

Since the 1980s many other natural products and their variants have been extensively used in genetic and chemical genetic approaches as probes to monitor cellular functions. A few natural products used in Prof. S. L. Schreiber's group are FK506 (**62**), cyclosporin (**63**) and rapamycin (**64**), to monitor signal transduction; trapoxin (**65**), trichostatin (**66**) and depudecin (**67**), to monitor gene regulation by HDAC (histone deacetylase)-mediated chromatin remodelling; discodermolide (**68**) and lactacystin (**69**), to monitor cell cycle and cell-cycle check points (Figure 1.13).⁴⁴

Although Nature has offered these types of important bio-active natural products, the inherent difficulties in developing practical synthetic methods and obtaining their analogs makes them rather less attractive starting points for drug development. Therefore, the tall order for the modern day chemist is to synthesize natural product-like small molecules that are attractive from the medicinal chemistry stand-point and would have the same potency and

selectivity observed in natural products. There is a belief that the use of small molecules as probes would be successful in the chemical genetic approach when applied to study the cell cycle because of their swift action, i.e. cytoskeletal rearrangements generally occur in a time scale of seconds, which is inaccessible to the traditional genetic approach, but accessible to the chemical genetic approach by the rapid diffusion of small molecules.^{4,44,45,53}

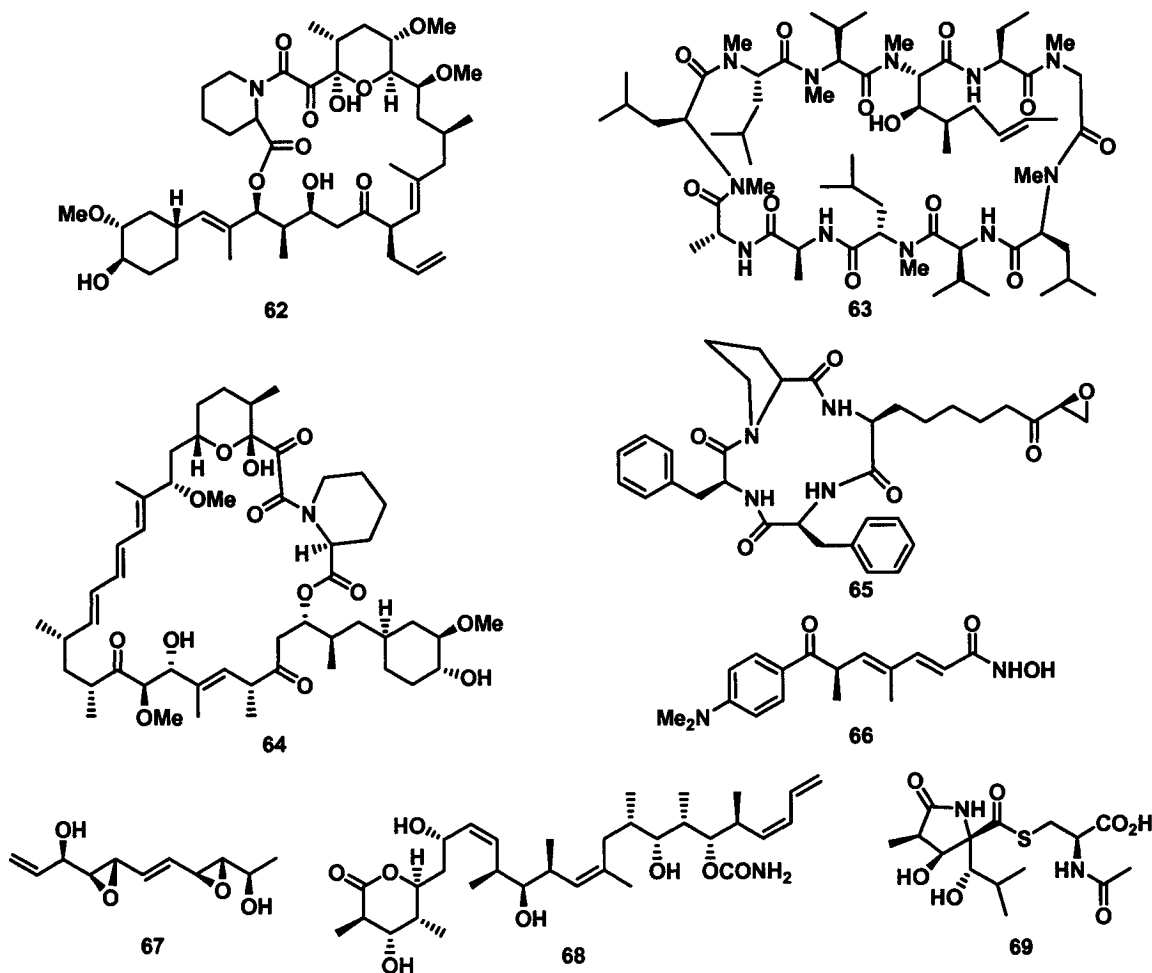


Figure 1.13 Natural products and their variants used as small-molecule probes
In chemical genetics.

1.3.5.2. Definition of Small Molecule Probes^{3,54}

Designing a probe that can be used as a starting lead compound for developing a new drug requires the careful consideration of many factors. One is its ability to permeate the cell membrane so that it could modulate functions at the intracellular interface. The molecular weight of a compound is inversely related to the cell membrane permeability. Low molecular weight organic molecules with molecular weight $<1,500 \text{ g mol}^{-1}$ are generally preferred, and can be further subdivided into simple molecules: molecular weight $<500 \text{ g mol}^{-1}$ with no stereogenic centers and, complex molecules: molecular weight $>500 \text{ g mol}^{-1}$ with at least one stereogenic center.

Although simple molecules have exhibited biological activity, their ability to discriminate between related protein species is limited, due to their small size,. To explain further, a simple molecule with a small surface area generally lacks the chemical functionalities required to exhibit specific binding properties. Whereas complex natural products that are richer in several chiral functional groups are capable of overcoming some of the limitations.^{3(a)}

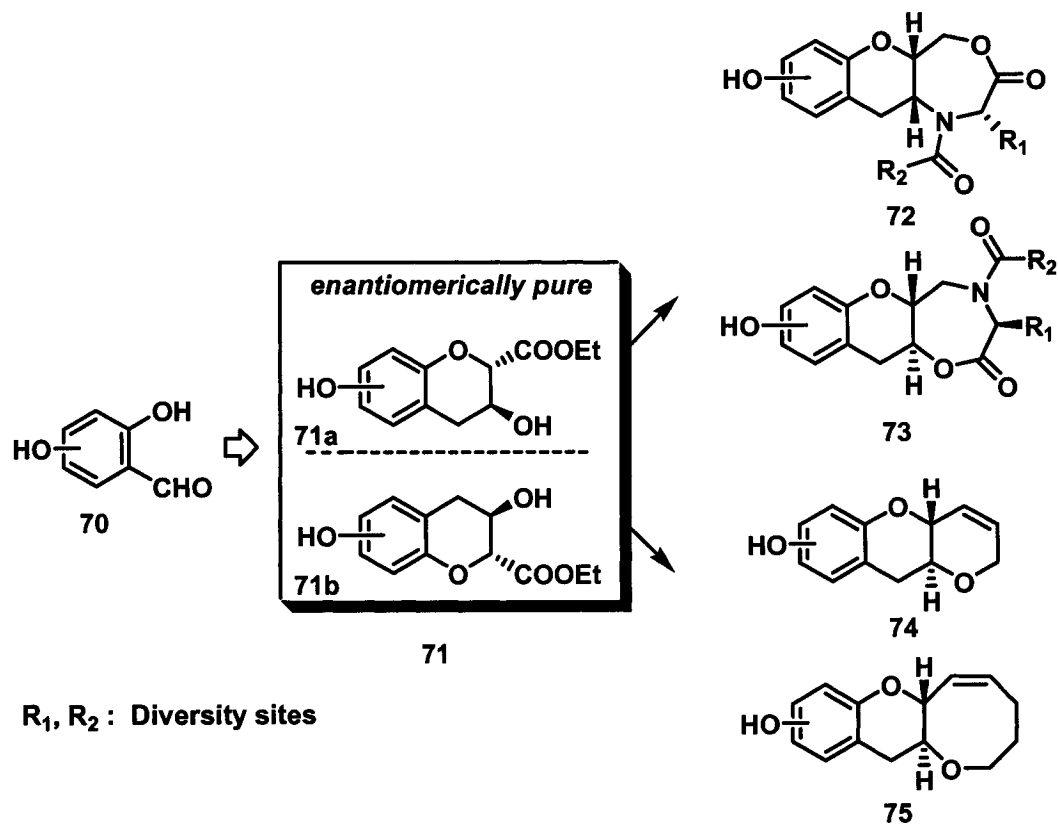
1.4 Thesis Objectives

Diversity oriented synthesis has become an invaluable asset to discover potential drug-like candidates in the pharmaceutical industry. The privileged scaffold approach has the potential for future discoveries of unknown biological targets over the focused natural product guided approach.

In the present investigation, a 2H-benzopyran scaffold (**71**, Scheme 1.6) is considered for the synthesis of a diverse set of compounds: amino acid derived polyphenols (**72**, **73**) and tricyclic polyphenoles (**74**, **75**) with potential diversification sites for library synthesis is considered. The solution phase stereoselective synthesis of the benzopyran scaffold (**71**), and extensions to the amino acid based lactones (**72**, **73**) and to the ring closing metathesis based

polyphenols (**74**, **75**), with some preliminary investigations to solid phase synthesis are discussed.

Scheme 1.6



2. Synthesis of Benzopyran Scaffold

2.1 Design of Scaffold (71)

In this project a benzopyran core structure was the scaffold. Benzopyran was chosen because, benzopyran and related structures occur frequently in Nature (Section 2.2). This abundance has resulted in the evolutionary development of diverse structures. Such compounds were reported to have the capability to show biological activity in a library of related compounds.¹⁶ The approach discussed in this thesis thus follows along the 'privileged' structure based approach discussed in Section 1.1.3.3.

After the identification of the core structure, the strategy was to develop the methodology necessary to functionalize the scaffold to extend it to a collection of compounds. Diversity was to be obtained by building block diversity and stereochemical diversity. This would lead to the solid phase library synthesis of various natural product-like analogs containing the benzopyran core structure. Therefore, the scaffold was designed with the intension of having a few diversity generating sites (eg. two or three). A free phenolic hydroxyl group on the 2H-pyran system would act as a site for immobilization onto solid support, a requirement for solid phase studies and library generation.

The advantage of our approach is that it leads to libraries of compounds focused around several benzopyran-based natural products of biological interest. An amino acid based library Chapter 3, and a polyether/polyphenol based tricyclic library Chapter 4, for instance could be synthesized. This would generate a collection of unique compounds, which demonstrates the powerfulness of creating such diverse polycyclic derivatives. In accordance however, it requires the solution phase and solid phase testing and optimization of a wide variety of reactions, efficient loading and cleavage processes.

The synthesis of the benzopyran scaffold **71** was started with a model study synthesis (Section 2.5.1), prior to the solution phase synthesis (Sections 2.5.2 to 2.5.3). The final route to the scaffold was developed later on in the project, taking advantage of optimized conditions from a similar on-going project from the group. Presently however, the last method is extensively used in all projects related to the benzopyran core structure.

2.2 Abundance of Benzopyran Core and Related Structures in Nature

Benzopyrans belong to the 'polyphenolic' class of natural products. Most polyphenols are of plant origin, and are a characteristic feature of all plant tissue. They are mostly aromatic compounds with hydroxyl substituents, for example flavonoids such as quercetin (**76**), coumarins such as aesculetin (**77**), lignans such as podophyllotoxin (**78**), anthraquinones such as emodin (**79**, Figure 2.1).⁵⁵ Examples of some biologically active plant polyphenols include: multiflorisin (**80**, immunosuppressant activity),⁵⁶ quercetin (**81**) and rubrocrisin (**82**, inhibition of con A and LPS mediated T cell proliferation),⁵⁷ doxorubicin (**83**),⁵⁸ dactinomycin (**84**),⁵⁸ rotenone (**85**)⁵⁹ and deguelin (**86**, anti-cancer activity),⁵⁹ and calanolide A (**87**)⁶⁰ and suksdorfins (**88**, anti-HIV activity, Figure 2.2).⁶¹ Synthetic and semisynthetic bioactive polyphenols such as etoposide (**89**),⁶³ teniposide (**90**),⁶³ etoposide NK-611 (**91**)⁵⁸ and flavopiridol (**92**)⁶² have also exhibited anti-tumour activity, (Figure 2.3).

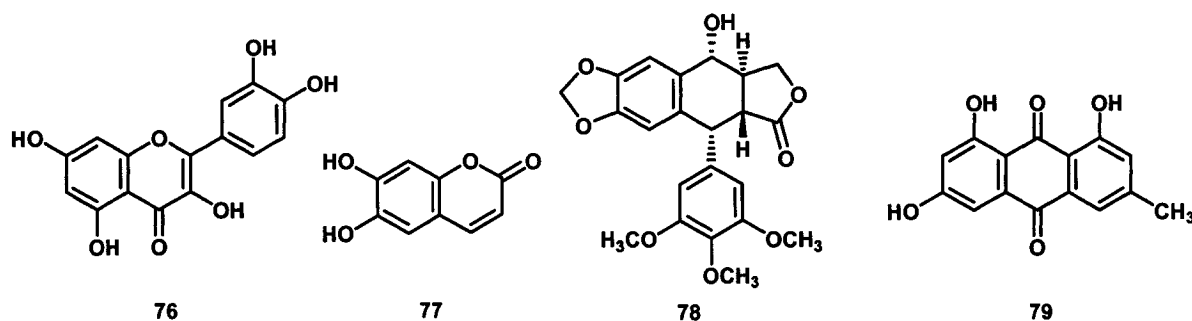


Figure 2.1 Natural products with benzopyran core and relative structures.

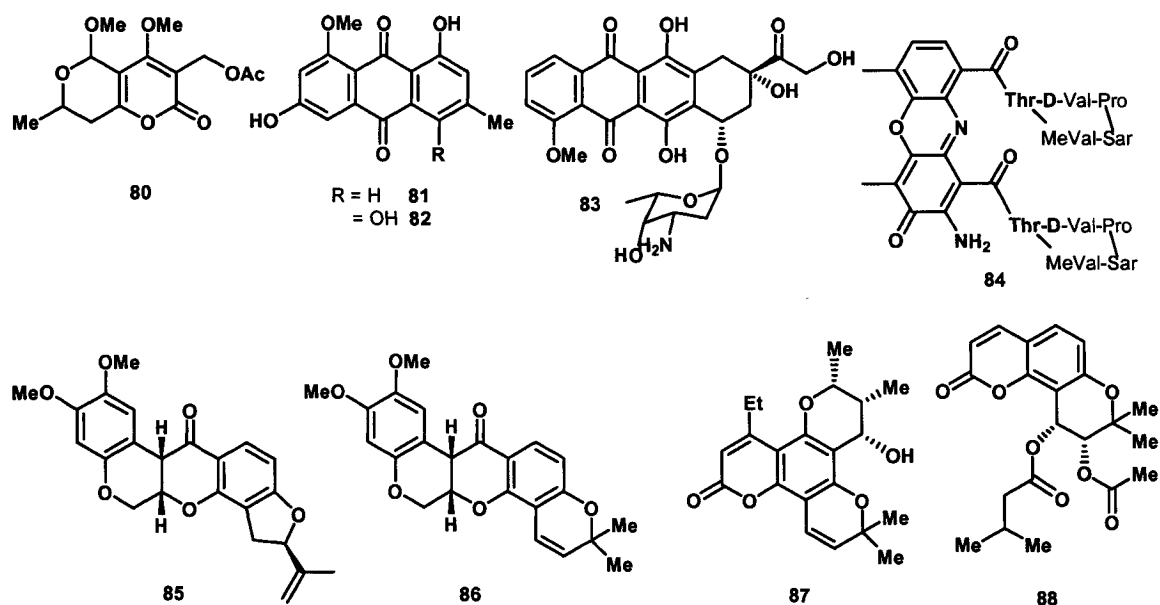


Figure 2.2 Biologically active natural products with benzopyran and related core structures

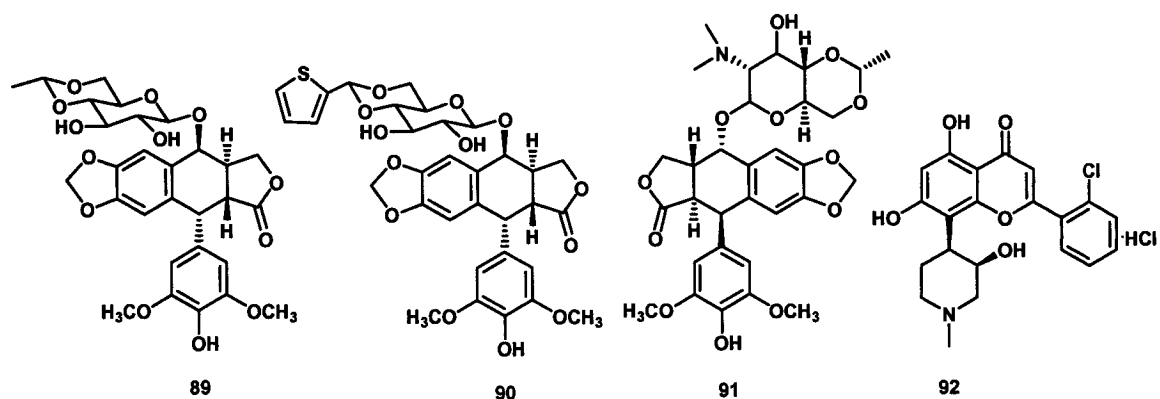


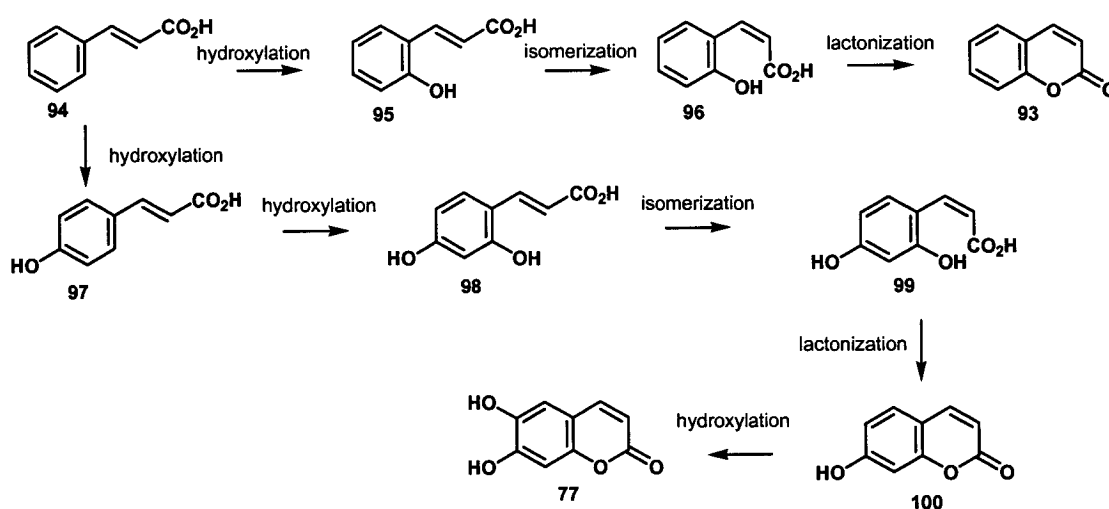
Figure 2.3 Biologically active synthetic and semisynthetic polyphenols with benzopyran and related core structures

2.3 Biosynthesis of Polyphenols^{55,63}

Polyphenolic compounds are formed by the mixed biosynthetic pathways of shikimate and polyketide-derived pathways. This can be illustrated in the biosynthesis of coumarin **93** and its hydroxyl derivative aesculetin (**77**, Scheme 2.1) and the synthesis of flavanoid quercetin (**76**, Scheme 2.2).

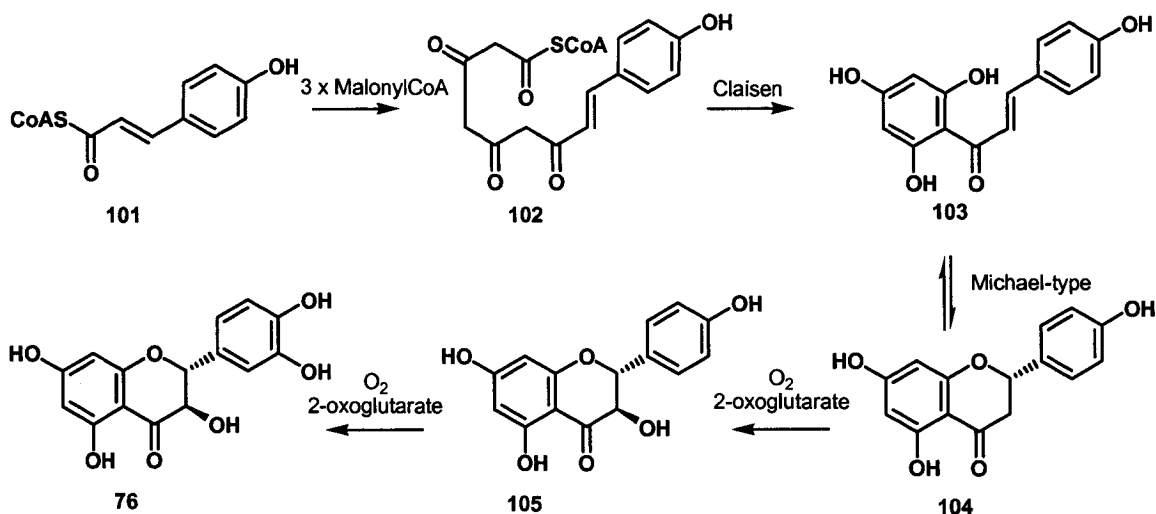
In the synthesis of coumarins (Scheme 2.1), shikimate pathway derived cinnamic acid (**94**) is taken as the starting material. Cinnamic acid (**94**) undergoes hydroxylation at the *ortho*- position **95**, followed by enzymatic trans-cis isomerization **96** and lactonization to give coumarin (**93**). Conversely, hydroxylation on the *para*- position **97**, followed by *ortho*- hydroxylation **98**, isomerization **99**, and lactonization gives umbelliferone (**100**). Umbelliferone (**100**) is then hydroxylated to aesculetin (**77**), rather than going through the general cinnamic acid – coumarin pathway.

Scheme 2.1



Flavanoids (Scheme 2.2), are considered to be synthesized from cinnamoylCoA (**101**) starter unit, to give the chain extended polyketide **102** with three units of malonylCoA. An enzymatic Claisen-like condensation gives the aromatic ring chalcone (**103**), followed by an asymmetric Michael-type reaction generates naringenin (**104**). Modifications to the hydroxylation pattern in the two aromatic rings of naringenin (**104**) gives the quercetin (**76**).

Scheme 2.2



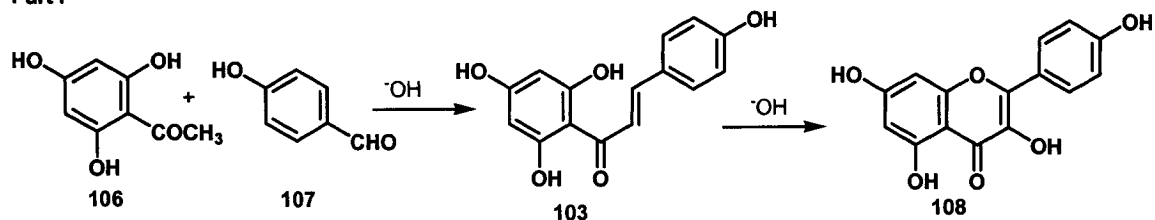
2.4 Synthetic Strategies in the Literature

2.4.1 Classical Approaches

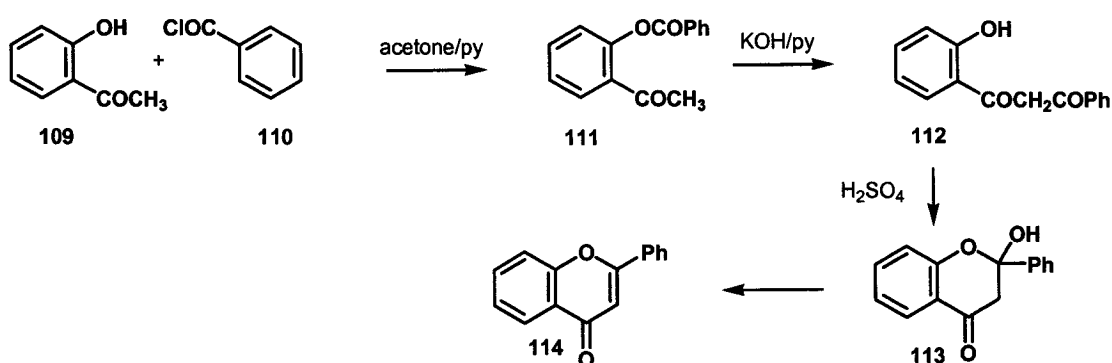
The strategies used for the syntheses of benzopyrans generally follow natural processes and date back to the developments in the classical era by R. Robinson, W. Baker, K. Venkataraman and T. S. Wheeler. To illustrate, the condensation of polyphenol **106** and *p*-hydroxy benzaldehyde (**107**) precursors followed by base induced cyclization gave flavanoid **108** (Scheme 2.3, Part I).⁵⁵ Flavanoids can also be synthesized by the condensation of precursors **109** and **110**, to give the *o*-hydroxy acetophenone (**111**). This is then followed by the base catalyzed (potassium hydroxide in pyridine), Baker – Venkataraman rearrangement of **111** to the *o*-hydroxy dibenzoylmethane (**112**). Acid catalyzed cyclization of **112** to **113**, followed by dehydration gave flavone **114**. Another interesting example is R. Robinson's pioneering synthesis of anthocyanins in the 1930s. An example of his effort together with A. R. Todd is the synthesis of malvin (**117**, Scheme 2.3, Part III). The glycosyl precursors **115** and **116** were condensed in the presence of HCl, to give the flavylum salt and treatment with $Ba(OH)_2$ and mild acid gave the anthocyanin **117**.

Scheme 2.3

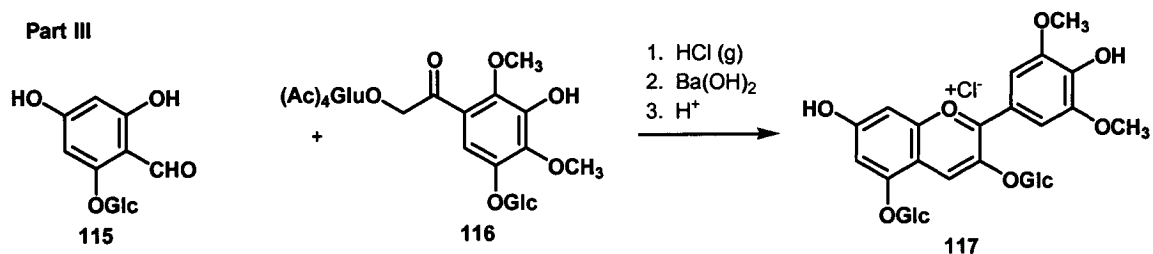
Part I



Part II



Part III

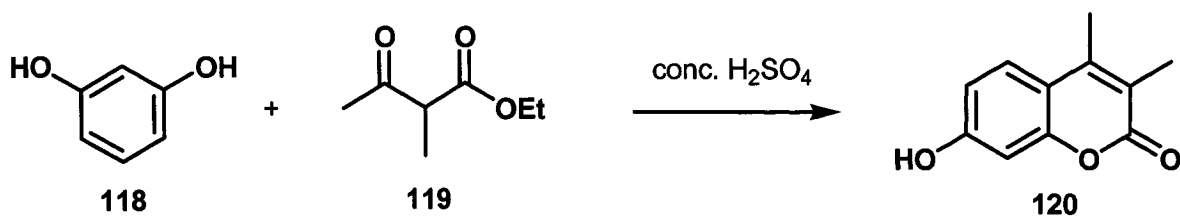


2.4.2 Modern Approaches

A few groups led by Potter et al.,⁶⁴ Lee et al.,⁶⁵ Shiratsuchi et al.,⁶⁶ and Paladini et al.,⁶⁷ have also achieved the synthesis of benzopyrans and its derivatives by condensation methods.

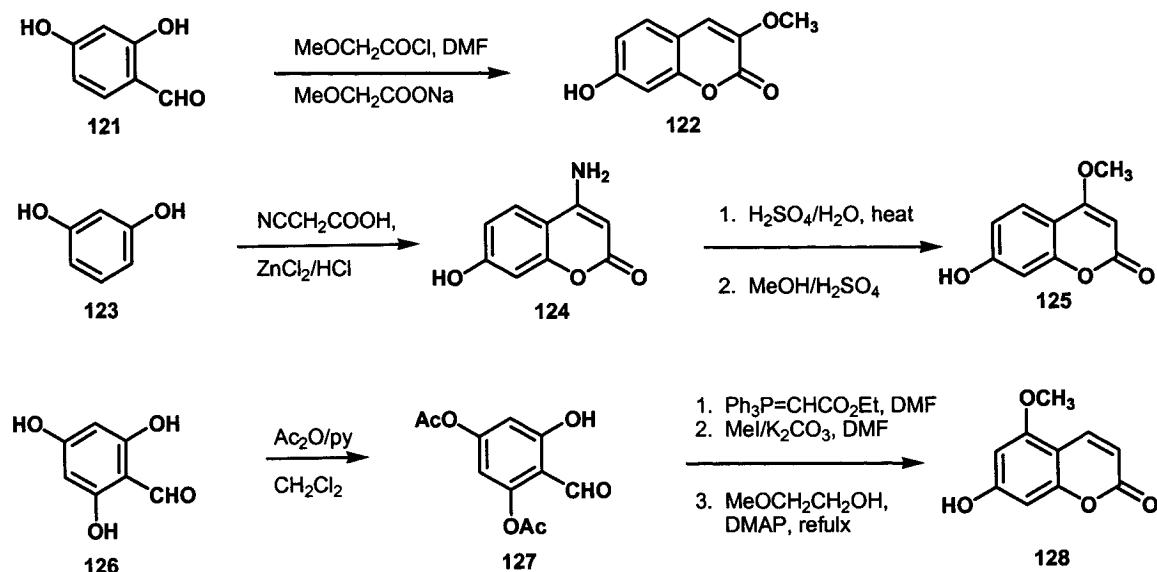
Potter's approach was quite straightforward. Resorcinol (118) was condensed with the keto-ester 119 to give coumarin (120) under acidic conditions (Scheme 2.4).

Scheme 2.4

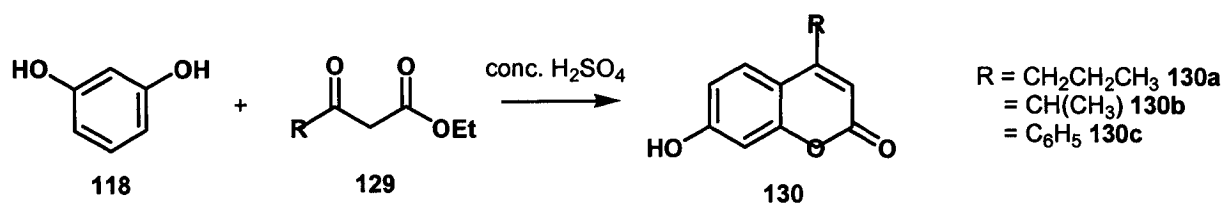


On the other hand, a more extensive study was carried out by Lee et. al.,⁶⁵ to synthesize modified *cis*-khellactones (**141**, Scheme 2.8). Their study was motivated by the early discovery of anti-HIV activity exhibited by Susksdorfin **88** (a *cis*-khellactone).⁶¹ First, they synthesized a series of monomethoxylated 7-hydroxycoumarins **122**, **125**, **128** (Scheme 2.5), methylated 7-hydroxycoumarins **130a,b,c** (Scheme 2.6), and 4-alkyl 7-hydroxycoumarins **131**, **134**, **137** (Scheme 2.7). These were accomplished via condensation of acid chloride or the diesters (**121**→**122**, **123**→**124**, **118**→**129**), and via the Wittig reactions (**127**→**128**, **121**→**131**, **133**→**134**, **136**→**137**).

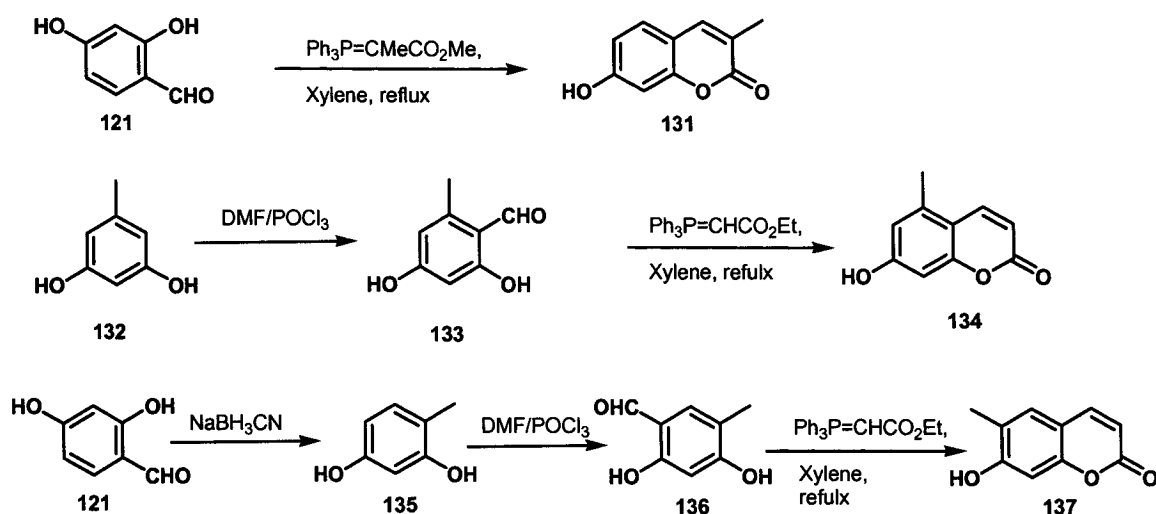
Scheme 2.5



Scheme 2.6



Scheme 2.7

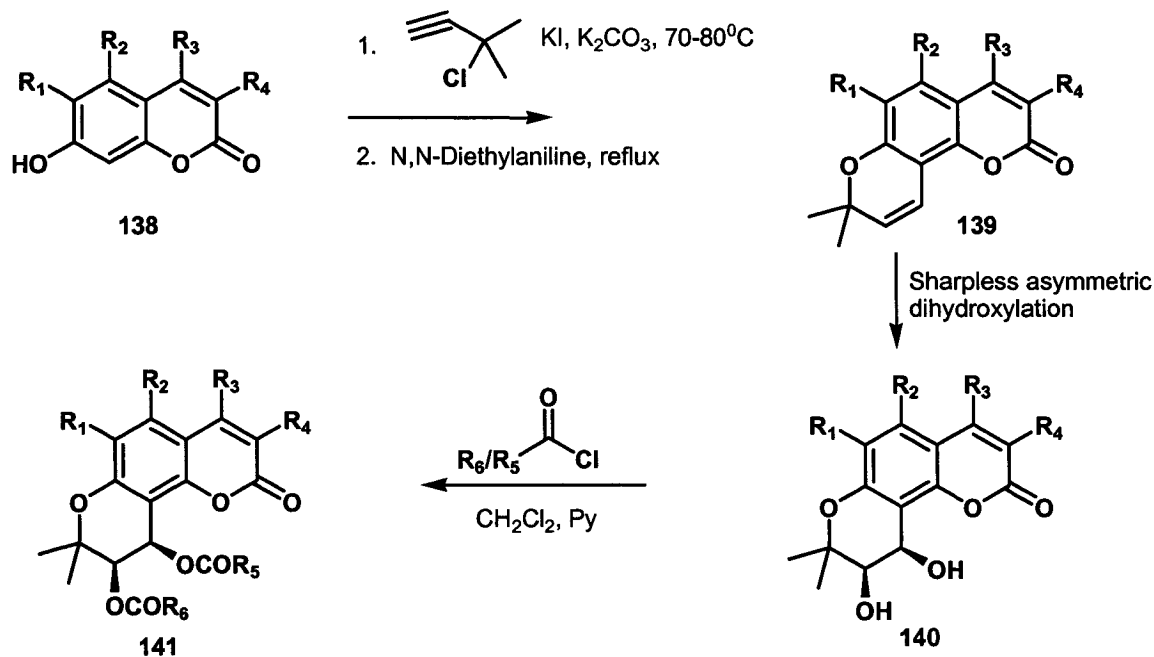


After the initial synthesis of the series, the benzopyrans **138** were further extended to the *cis*-khellactones (**141**, Scheme 2.8). This was a one pot reaction leading to the of forming α,α -dimethylpropargyl ethers, followed by a thermal cyclization. One of the synthetic derivatives had shown extremely potent inhibitory activity against HIV-1 replication in H9 cell line and had a remarkable therapeutic index.⁶¹

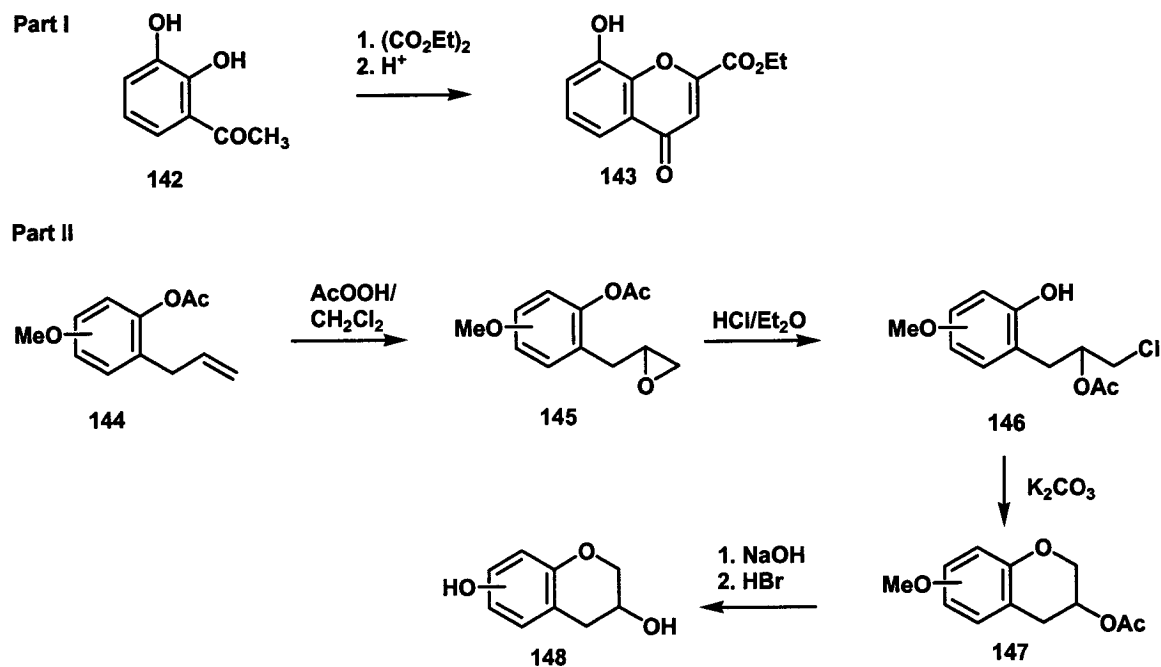
Shiratsuchi and co-workers⁶⁶ used a two-fold strategy in their synthesis. Firstly, the methylketone **142** was reacted with diethyloxalate followed by ring closure under acidic conditions to give chromones **143**, (Scheme 2.9, Part I). Secondly, they reacted suitable methoxy-2-allylphenylacetates **144** to form the epoxides **144**, which upon nucleophilic ring opening forms **146**. This would then proceed

to the ring closure under basic conditions, to give the benzopyrans **147**, (Scheme 2.9, Part II). Compounds **147** were then fully deprotected to the diols **148**.

Scheme 2.8

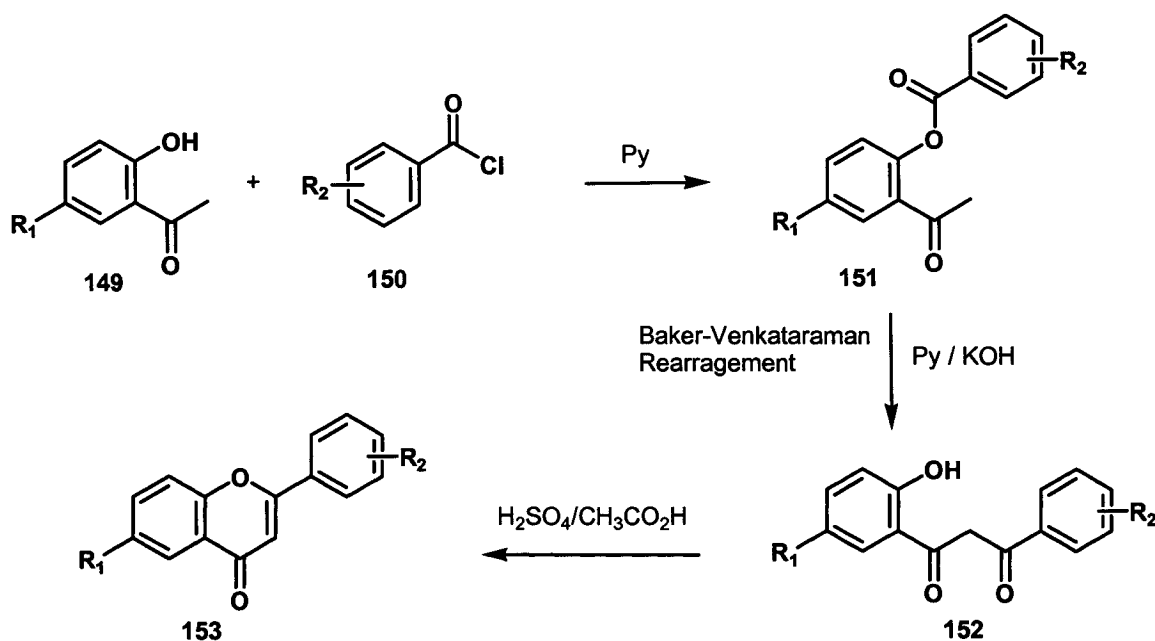


Scheme 2.9



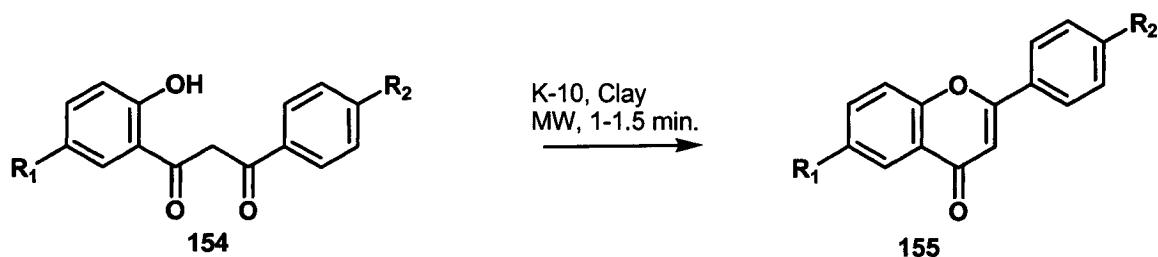
In another solution phase synthetic study, Paladini and co-workers adopted the approach of the condensation of 2-hydroxyacetophenones **149**, with benzoyl chlorides **150** under basic conditions to generate the aromatic esters **151**, (Scheme 2.10). The esters **151** were then subjected to Baker – Venkataraman rearrangement to yield the diketones **152**, which cyclized under acidic conditions to give the benzopyranones **153**.

Scheme 2.10

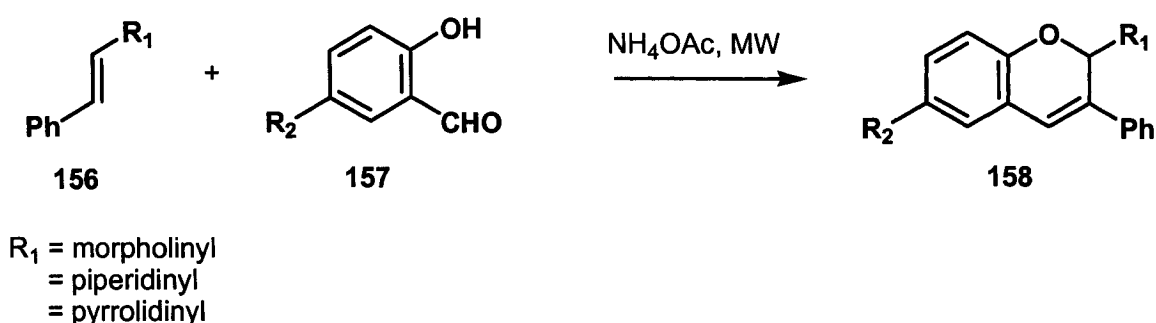


In a different approach, R. S. Varma⁶⁸ used a solvent free, microwave enhanced method to synthesize flavonoids **155** (Scheme 2.11) and benzopyrans **158**, (Scheme 2.12). The flavonoids **155** were synthesized via microwave assisted solid state dehydrative cyclization of o-hydroxydibenzoylmethanes (**154**) in a clay microenvironment (Scheme 2.11). In his synthesis of the benzopyrans (**158**), he used the microwave assisted cyclization after *in situ* generation of enamines **156**, with salicylaldehydes **157** in the presence of catalytic amount of ammonium acetate (Scheme 2.12).

Scheme 2.11



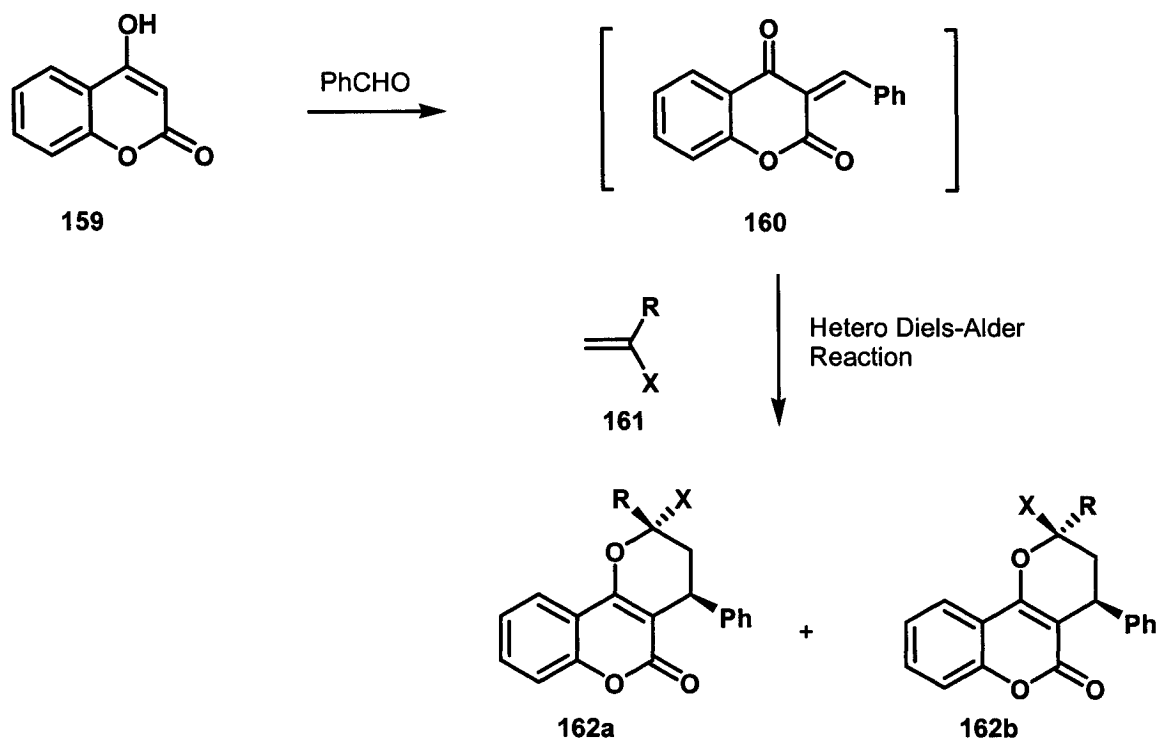
Scheme 2.12



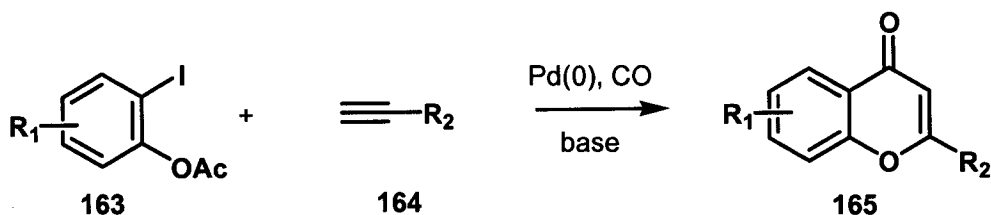
In another study Cravotto et al.,⁶⁹ adopted a pericyclic approach to synthesize a series of pyranocoumarins **162a**, and **162b** using a one-pot three-component Hetero Diels-Alder reaction (HDA, Scheme 2.13). 4-Hydroxycoumarin (**159**) upon treatment with benzaldehyde generated the chromanedione intermediate **160**, which was then reacted with various electron rich alkenes **161** to give the 2,4-disubstituted 3,4-dihydropyranocoumarins **162a** and **162b**. The inverse electron demand created by the diene **160**, and the electron rich dienophiles **161** facilitated the reaction. An analysis of the HOMO-LUMO interactions of the diene and the dienophiles have suggested that vinyl ethers or enamines are the best dienophiles for the reaction.

Yang and co-workers⁷⁰ used the annulation of iodophenol acetates **163** with acetylenes **164** in the presence of a Pd catalyst and carbonylation to construct analogs of flavones **165**, Scheme 2.14. This is a relatively new approach as the use of Pd catalysts for coupling reactions have flourished only during the past

Scheme 2.13



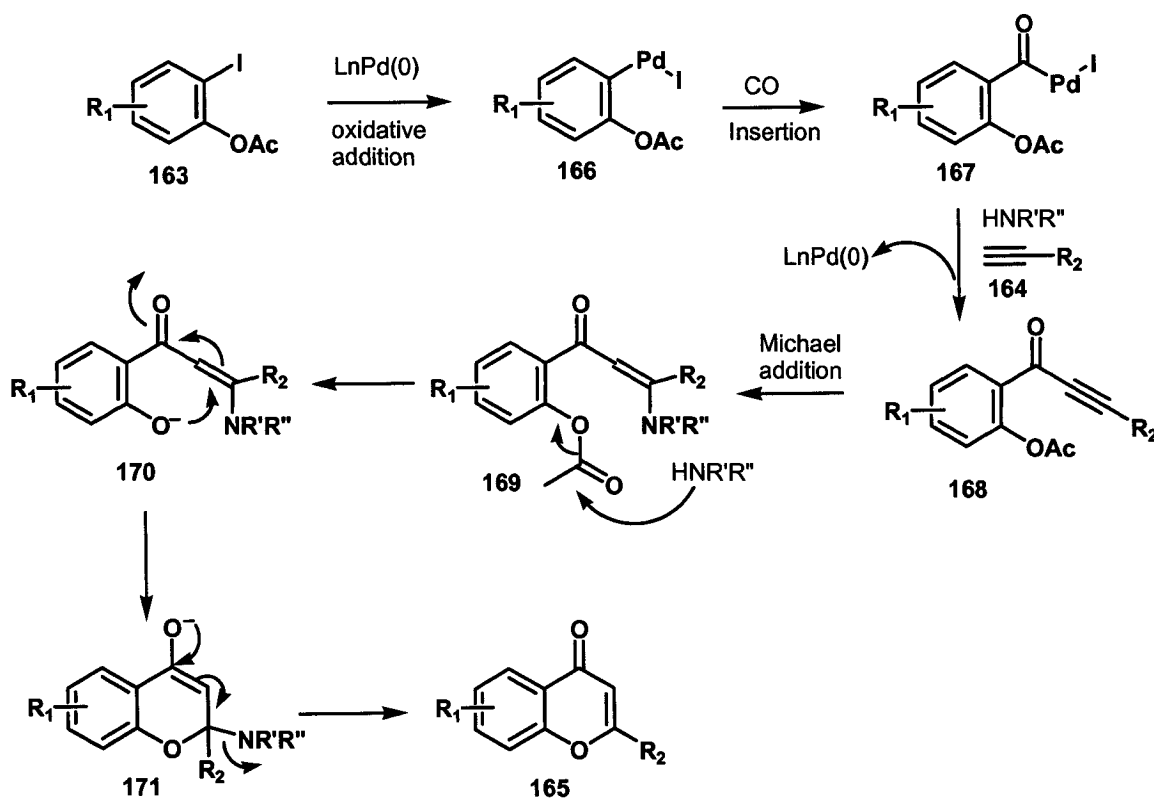
Scheme 2.14



two decades. The reaction proceeded with high regioselectivity. The proposed catalytic cycle is outlined in Scheme 2.15.

Iodophenol acetates **163** underwent six membered ring formation to **171** after Pd (0) coupling **166** and carbonylation to **167**. The precursors **168** were subjected to Michael addition **169**, amine induced hydrolysis to give **170**, and a 6-endo-trig cyclization to obtain **171**. Finally, a keto enol tautomerization generated the flavone **165**. The use of the acetoxy group on **163** rather than a free hydroxyl

Scheme 2.15

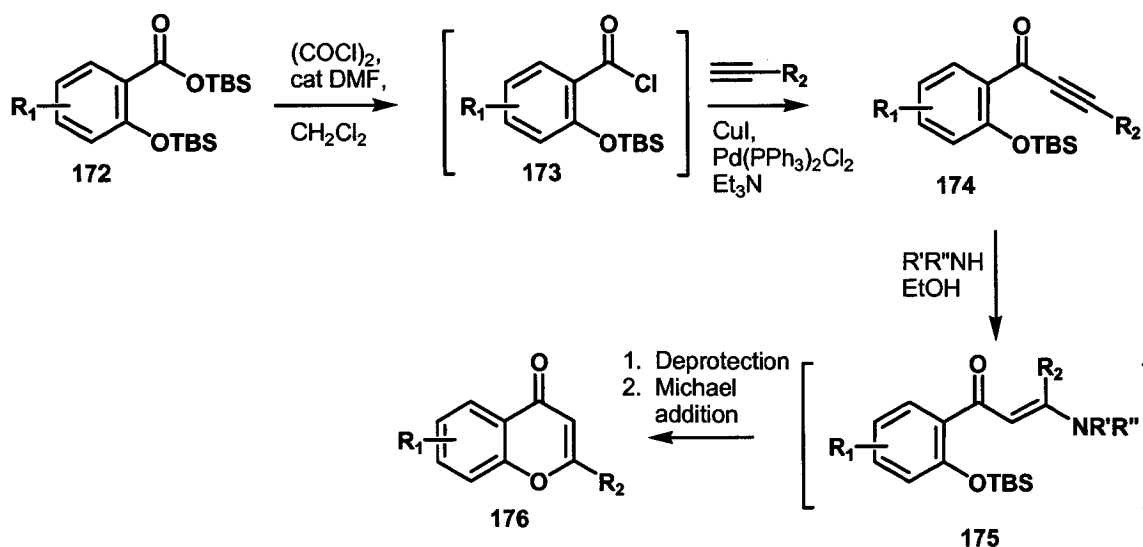


group was very important as it reduces the electron density in the aromatic ring whereby enhancing the formation of the six membered formation over the side reaction of five membered ring formation. The five membered lactonization had been observed when unprotected iodophenols were used for the reaction.⁷⁰

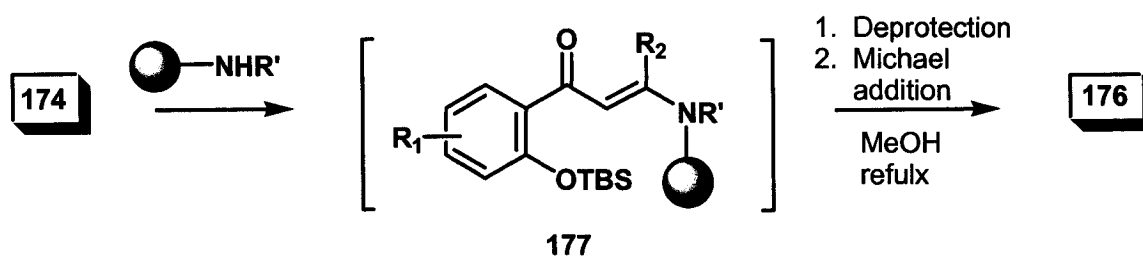
A few groups led by researches R. W. Brueggemeier,^{71a,b} B. T. Watson⁷² and H. D. H. Showalter,⁷³ have used a resin capture strategy to synthesize benzopyran analogs, which have been then extended to combinatorial libraries.

Brueggemeier and co-workers⁷¹ first developed a solution phase synthesis for the benzopyran core structure and then developed a solid phase strategy. In the solution synthesis they chlorinated the *bis*-silylated salicylic acids **172** to the alkynyl ketones **173**, and then performed a series of Sonogoshira coupling reactions with various terminal alkenes to give the alkynones **174** (Scheme 2.16).^{71b} The alkynones **174** were then converted to enaminoketones **175**, prior

Scheme 2.16



Scheme 2.17

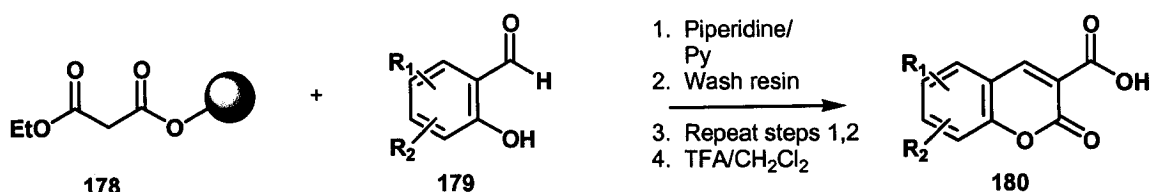


to silyl deprotection of the alcohol thus preventing the unwanted 5-exo-dig cyclized side product formation. The subsequent deprotection of the enaminoketones **175** gave rise to the 6-endo-dig cyclization product **176** via the Michael addition and elimination of the secondary amine. In their solid phase strategy they captured the alkynone intermediates **174** by utilizing resin bound amines to generate the enaminoketones **177**, which were cyclized to the chromones **176** (Scheme 2.17).^{71a} Their strategy therefore, opened the doors to applications in combinatorial chemistry.

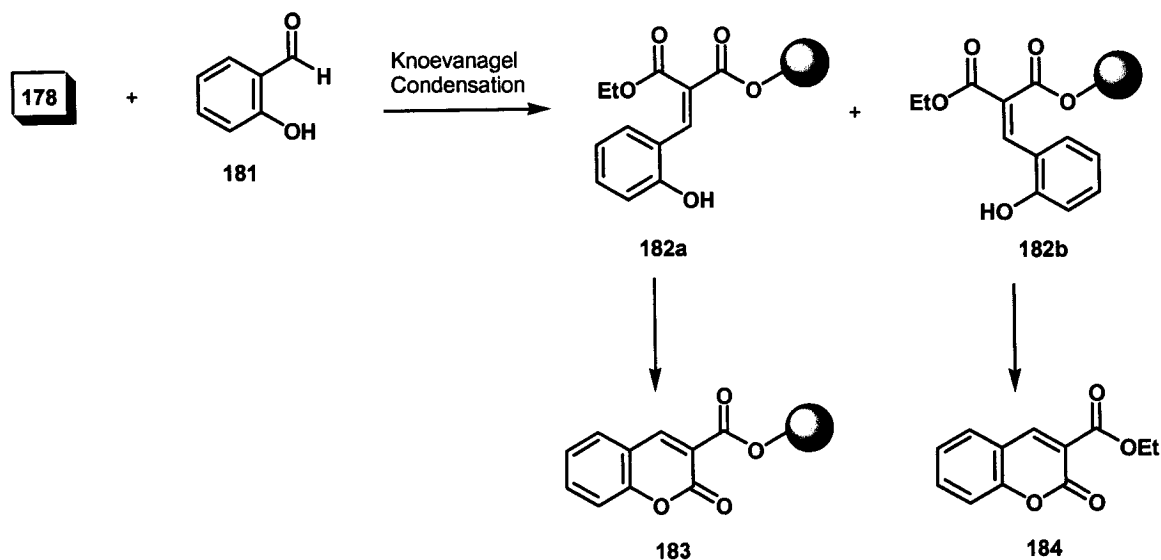
On the other hand Watson et al.,⁷² approach was to use an immobilized diester **178** in a Knoevenagel condensation reaction for the synthesis of coumarins as

shown in Scheme 2.18. The solid support bound ethyl malonate **178** suspended in pyridine was reacted with various substituted *o*-hydroxy arylaldehyds **179** in the presence of a catalytic amount of piperidine which undergoes Knoevenagel condensation to yield the cyclized coumarins. Products were however, isolated only after cleavage from the resin with trifluoroacetic acid/dichloromethane, **180**. The coumarin derivatives **180** were obtained in 16-40% yield. The low yields were explained by the investigation of the mechanism of the reaction with *o*-hydroxybenzaldehyde (**181**, Scheme 2.19). *o*-Hydroxy benzaldehyde (**181**) under Knoevenagel condensation conditions gave a mixture of the E and Z isomers **182a**, **182b** in a 1:1 ratio which in turn produces the resin bound coumarin **183** and coumarin ester **184**, thus reducing the overall yield. This discovery, although resulting in lower yields, generated satisfactory results.

Scheme 2.18

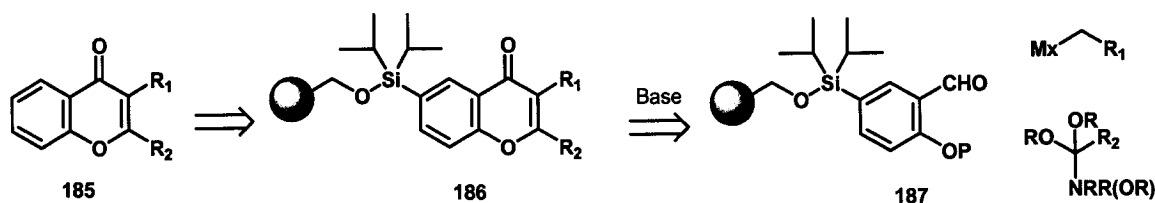


Scheme 2.19

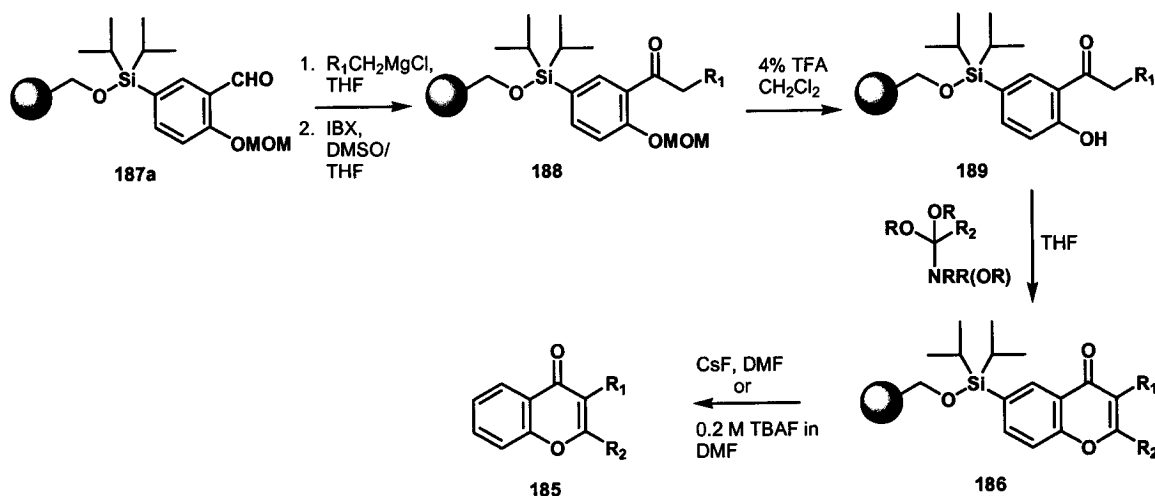


In a different approach, a diisopropylsilyloxy linker bound resin was used in the studies done by Showalter and co-workers⁷³ to synthesize benzopyrans. The diisopropylsilyloxy linker bound resin was developed in their group, and is sensitive to harsh acidic and basic conditions. Their retrosynthetic planning is outlined in Scheme 2.20. After an initial solution phase optimization they proceeded onto solid phase (Scheme 2.21). The chain extension to the resin bound aldehyde **187a** was achieved by a one-pot Grignard reaction with various commercial or synthetically prepared magnesium chlorides to the hydroxyl derivatives and the oxidation of alcohols with IBX to the ketones **188**. The MOM group was then selective deprotected in the presence of the silyl linker by 4% TFA to yield phenols **189** which were then cyclized to the resin bound benzopyranones **186**, by the reacting with various commercially available or synthetic amide acetals. The resin bound compounds were finally cleaved with CsF or 0.2M TBAF/DMF to yield the benzopyranones **185**.

Scheme 2.20



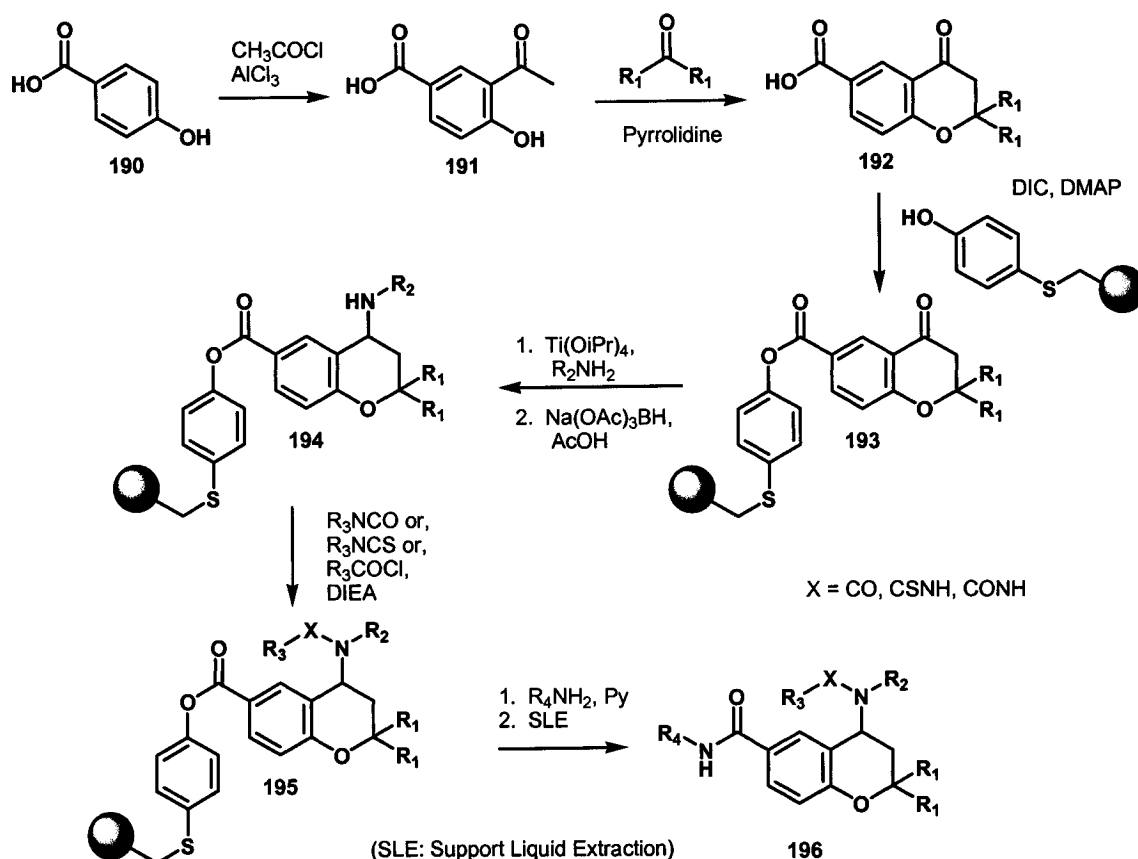
Scheme 2.21



Some groups have synthesized large, thousand membered combinatorial libraries based on the benzopyran scaffold. The work carried-out in three groups headed by J. G. Breitenbucher,⁷⁴ J. J. Baldwin⁷⁵ and K. C. Nicolaou¹⁶ will be presented.

Breitenbucher and co-workers⁷⁴ approach was to first construct the benzopyrans in solution phase and then immobilize them onto the resin via a hydroxythiophenol linker (Scheme 2.22). The linker, being susceptible to nucleophilic attack, was a major draw back in their approach. However, they were successful in synthesizing an 8,488 membered library using optimised reductive amination conditions.

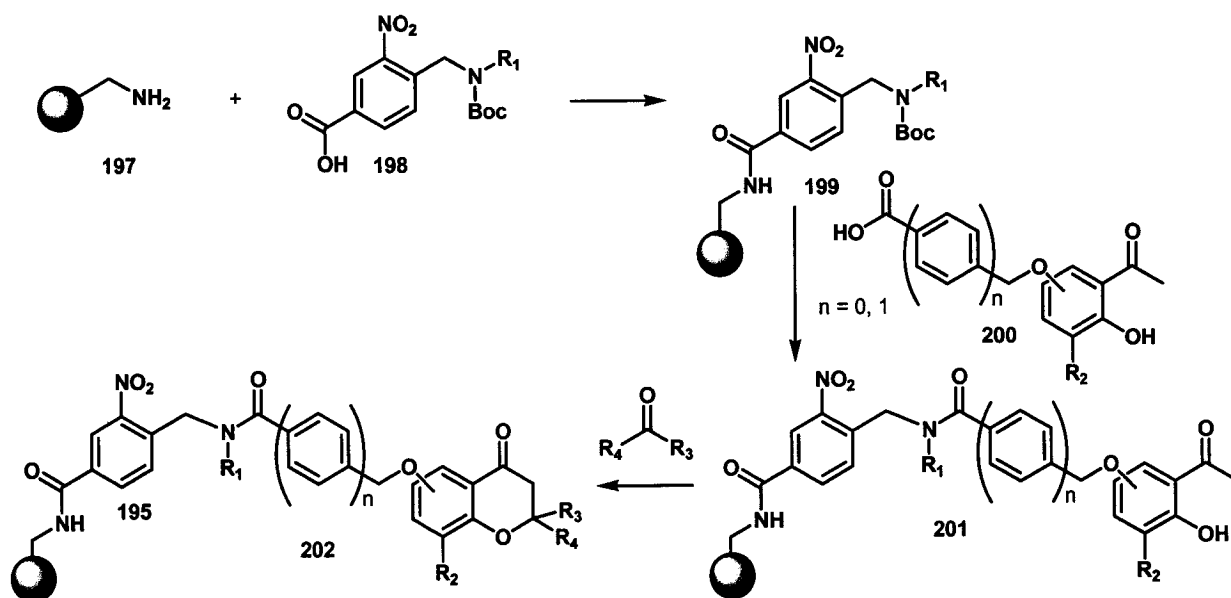
Scheme 2.22



The benzopyrans **192** were synthesized by acylating the *p*-hydroxybenzoic acid (**190**) to yield the ketone **191**, which was then reacted with various symmetrical ketones. The benzopyrans were loaded onto the resin by DIC mediated coupling of the Merrifield/hydroxythiophenol resin to give **193**, and derivatized by $\text{Ti}(\text{O}i\text{Pr})_4/\text{Na}(\text{OAc})_3\text{BH}$ mediated reductive amination of various amines to secondary amines **194**. The amines were further diversified by acylation with isocyanates or acid chlorides **195**, and cleaved by base to give **196**. The excess amine used for cleavage was extracted by 'Support Liquid Extraction (SLE)' procedure.⁷⁶

Unlike Breitenbucher et al., the strategy employed by Baldwin et al.,⁷⁵ was to synthesize the benzopyrans on the solid support. He used a photolabile linker on TentaGel resin to construct a 1263 member dihydrobenzopyranone library. L-Lysine modified Tenta Gel resin (**197**) was coupled to various carboxylic acids **198** which were pre-attached to the photolabile linker *o*-nitro- α -bromo-*p*-toluic acid (Scheme 2.23).

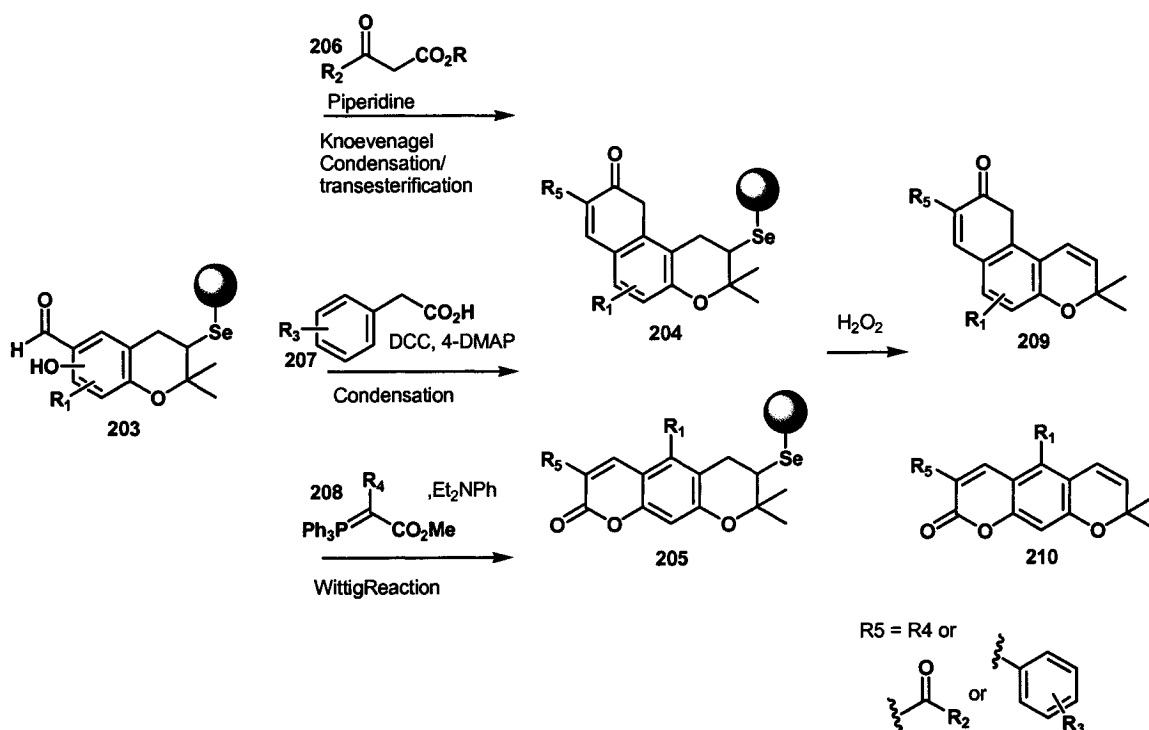
Scheme 2.23



After Boc deprotection to obtain the free amine, the amines were acylated with various acids **200** to give amides **201** which were then reacted with various ketones to yield the benzopyranones **202**. The benzopyranones thus created were subjected to further diversification under many different reaction conditions to generate a library of over 85,000 compounds.

The review of benzopyrans is concluded with K. C. Nicolaou's approach for the synthesis of pyranocoumarins (Scheme 2.24). The benzopyrans **203** were synthesized according to Section 1.1.3.3, which would lead to either angular pyranocoumarins **204** or linear pyranocoumarins **205** depending on the hydroxyl substitution pattern with respect to the aldehyde moiety on **203**. Functionalization of the aldehyde with Knoevenagel condensation/transesterification with esters **206** or a condensation with various acids **207** or by Wittig reaction **208** extended the side chain, which was then followed by lactonization to **204** or **205**. Resin beads were cleaved under oxidative conditions to yield the free pyranocoumarins **209**, **210**.

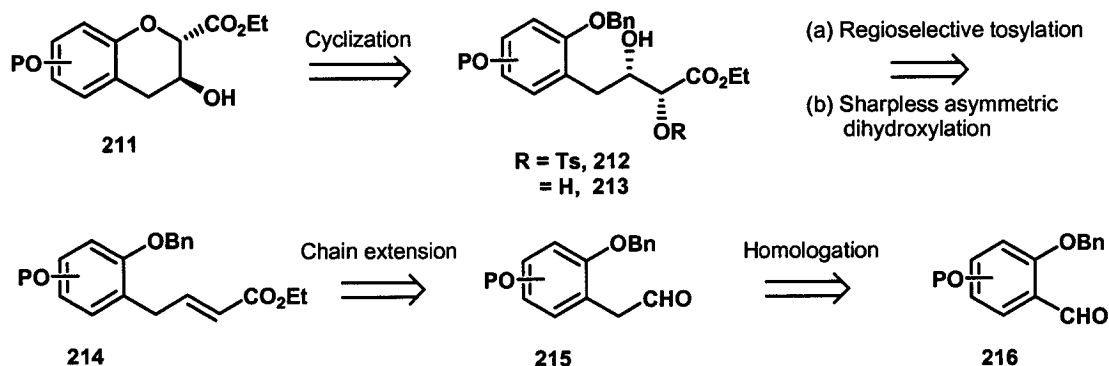
Scheme 2.24



2.5 Our Synthetic Approach

Our approach to the stereoselective synthesis of the benzopyran core structure was centered around three key reactions: (1) homologation of the protected aldehyde **215** from **216**, (2) Sharpless asymmetric dihydroxylation to obtain **213**, and (3) cyclization of **212** by a leaving group strategy via the regioselective tosylation of compound **213**. The retrosynthetic analysis of our approach is outlined in Scheme 2.25. The precedence for the leaving group approach was a procedure established in the group for the synthesis of a benzofuran core structure.⁷⁷

Scheme 2.25



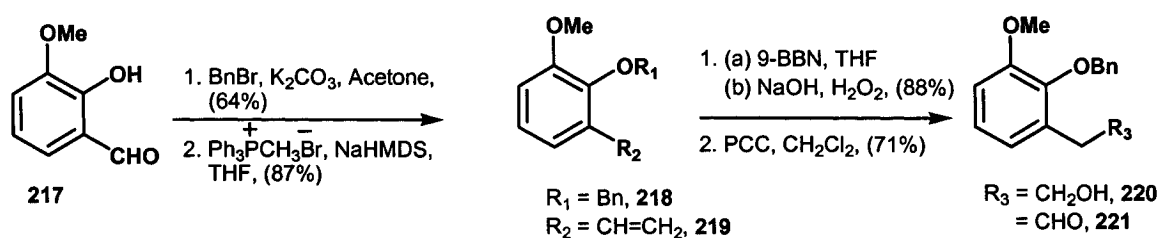
2.5.1 Model Study

2.5.1.1 Homologation

The first key step to be explored was the homologation of the starting aldehyde (Scheme 2.26). The commercially available *o*-vanillin (**217**), a relatively inexpensive compound, was taken as the starting material for the synthesis. After benzyl protection of the hydroxyl group with benzyl bromide (**218**), a one carbon Wittig reaction was performed with triphenyl phosphonium bromide and sodium hexamethyldisilazide (NaHMDS) as the base to obtain the alkene product **219**. The alkene **219** was isolated in an excellent yield of 87%. Benzylation product **218**, was confirmed by MS ($M+1$) 243.0, and by ^1H NMR by the

appearance of a singlet integrating to two protons at 5.20 ppm for the CH₂ group of the benzyl and an extra set of peaks in the aromatic region corresponding to the phenyl group. The alkene **219** was confirmed by MS (M+1), 241.0 and by ¹H NMR which showed signals in the olefin region at 5.38 ppm (dd, J = 11.0, 1.2 Hz, 1H) and 5.88 ppm (dd, J = 17.8, 1.3 Hz, 1H), corresponding to the terminal CH₂, and at 6.95 ppm (d, J = 8.0 Hz, 1H), for the benzylic CH, of the CH=CH₂ group.

Scheme 2.26

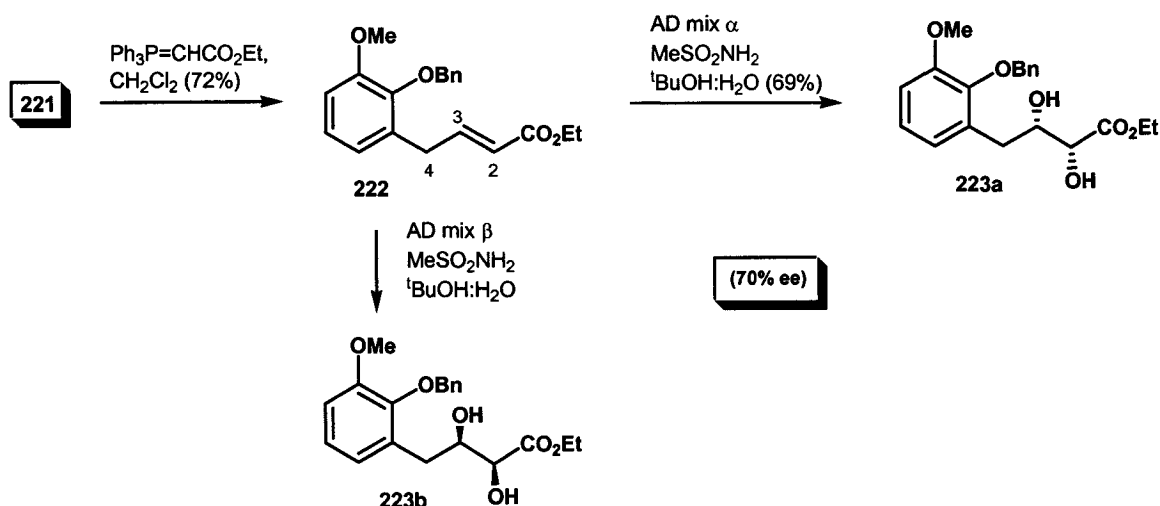


The alkene **219**, was then regioselectively hydroxylated using the bulky boron reagent 9-BBN and oxidatively cleaved to the primary alcohol **220**. Hydroboration of alkenes occur according to the anti-Markovnikov rule, and the selectivity increases with respect to the bulkiness of the boron reagent.⁷⁸ The product was confirmed as the primary alcohol **220** by ¹H NMR, which showed the disappearance of the olefin signals and the appearance of two sets of signals up field at 2.88 ppm and at 3.79 ppm corresponding to two CH₂ groups. The primary alcohol **220** was oxidized with pyridine chlorochromate (PCC) to yield the homologous aldehyde **221**. The aldehyde proved to be rather unstable, and was confirmed by MS and ¹H NMR. The ¹H NMR showed a triplet peak at 9.60 ppm, corresponding to the aldehyde proton. Such chemical shifts are characteristic of the formation of the aldehyde. A weak coupling was sometimes observed for the aldehyde due to the coupling with the benzylic protons.

2.5.1.2 Chain Extension and Enantioselective Dihydroxylation

The synthesis proceeded to extending the chain length with a 2-carbon Wittig reaction. (Carbethoxymethylene) triphenyl phosphorane reagent was used to obtain the extended alkene **222** (Scheme 2.27). Olefin signal for C-2 proton was observed by ^1H NMR at 5.76 ppm as a doublet with a large coupling constant of $J = 15.6$ Hz. This signified the *trans* alkene formation. The other olefin proton closer to the benzylic position, at C-3 was observed further downfield between 7.04-7.07 ppm and was masked with the aromatic hydrogens. The coupling constants for this olefinic proton could not be determined.

Scheme 2.27



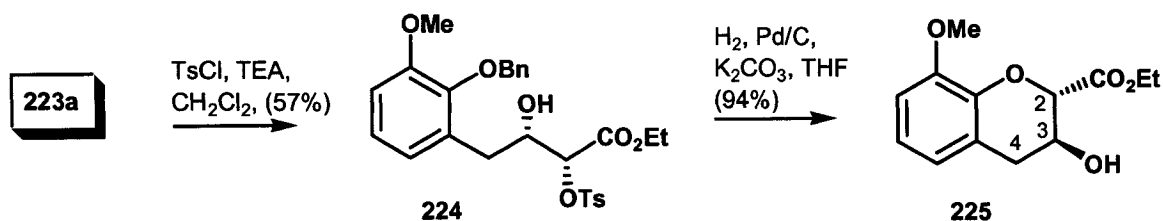
The chain extension was then followed by the Sharpless asymmetric dihydroxylation to produce the diol **223**.⁷⁹ Both diols **223a**, and **223b** were synthesized with AD Mix α and β respectively, and were confirmed by ^1H NMR by the complete disappearance of the olefin signals. Apart from this observation, the benzylic protons at C-4, became diastereotopic at 2.84 ppm (dd, $J = 13.4, 6.1$ Hz, 1H), and at 3.01 ppm (dd, $J = 13.4, 8.2$ Hz, 1H), indicating an asymmetric environment next to it. An up field shift was also observed for the C-2 proton at 4.03 ppm and for the C-3 proton between 4.17-4.25 ppm. The proton at C-3 was

however, masked with the ester CH₂ protons. Peaks were assigned by the analysis of COSY and HSQC NMR spectra. The C-2 hydroxyl proton appeared at 3.16 ppm and that of C-3 at 2.52 ppm. The hydroxyl protons were assigned using COSY, HSQC and HMBC NMR experiments. The yields of this reaction varied with regard to extraction of the polar diols in the presence of many other by products of the reaction, and only a maximum yield of ~ 70% was observed. Both diols were prepared for the purpose of finding out the relative enantiomeric excess (ee) by chiral HPLC. A 70% ee was observed. The low ee of the products from the Sharpless dihydroxylation reaction could be attributed to the fact that the structural differences between groups on the alkene were relatively small. Higher ee's have been observed in the group for Sharpless dihydroxylation when the chain length was one carbon closer to the aromatic ring.⁸⁰

2.5.1.3 Cyclization to the Benzopyran Core

The cyclization to the 2H-benzopyran core was achieved by a leaving group strategy (Scheme 2.28). First, the diol was regioselectively tosylated with tosylchloride (TsCl) to obtain **224** in relatively modest yield of 57% (based on a 72% recovery of starting material). Attempts to optimize this reaction are presented in Table 2.1. The best results were observed when the reaction proceeded from 0°C to RT for ~ 24h. Regioselective tosylation was confirmed by ¹H NMR, by the shift of the proton at C-2 downfield to 4.87 ppm while the proton at C-3 remained as a broad multiplet between 4.08-4.15 ppm, indicative of an electron withdrawing group being in the vicinity of the C-2 proton and not at the C-3 proton, Appendix - Spectrum 1. It was further confirmed by COSY, HSQC and HMBC NMR analysis of the hydroxyl protons (Appendix 1 – Spectra 2, 3, 4 respectively), where the hydroxyl at C-3 remained unshifted at ~ 2.60 ppm and the hydroxyl at C-2 completely disappeared.

Scheme 2.28

Table 2.1 Regioselective tosylation of diol **223a**

Temperature °C	Time h	% Yield
- 10	4	0 (SM)
- 1	16	~ 10
5	24	~ 40
0 to RT	24	57

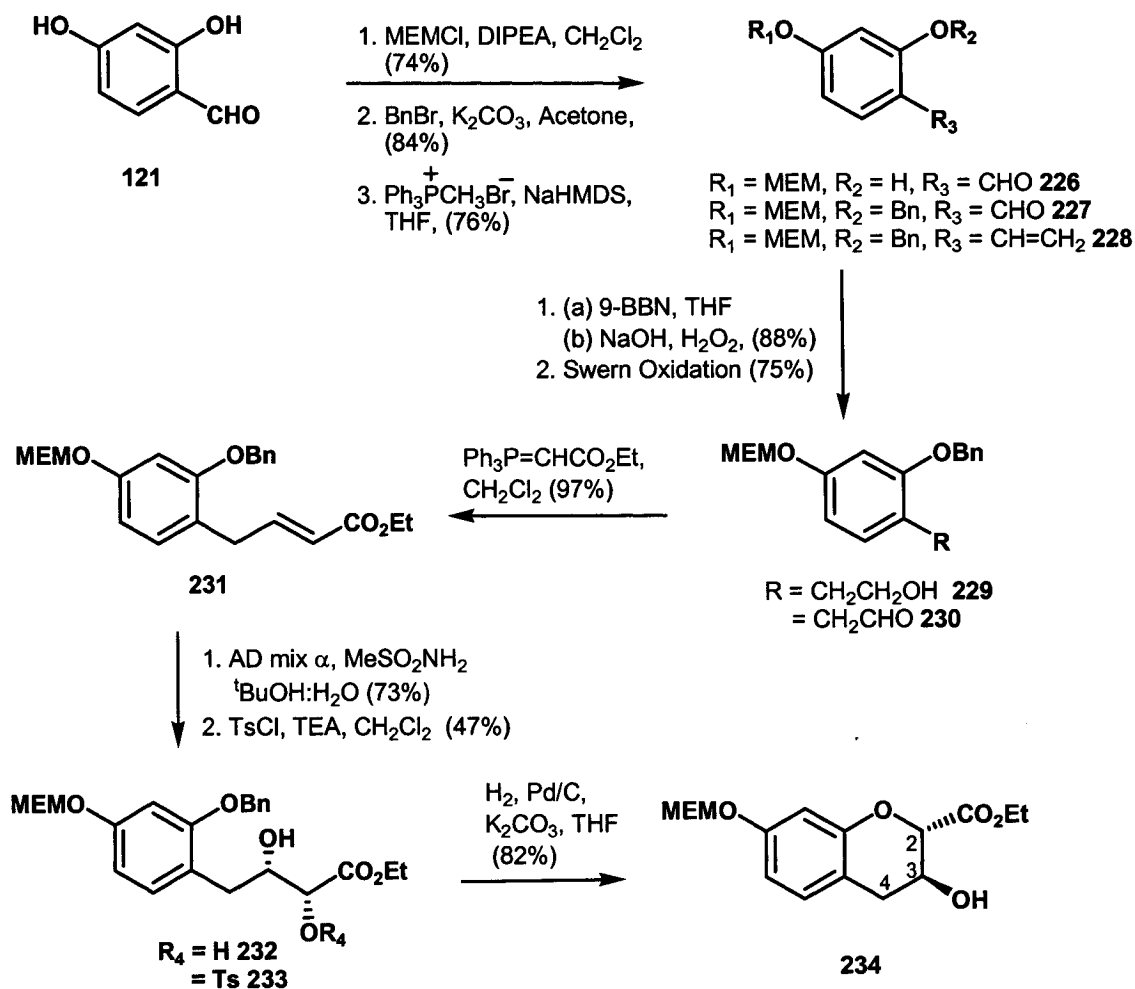
The α -O-tosyl hydroxyl derivative **224** was then subjected to a one-pot debenzylation/cyclization reaction. Debenzylation was performed under reductive conditions with H_2 and Pd/C, and was followed by base induced cyclization to obtain the bicyclic product **225** in 94% yield. Depending on the reaction time and the hydrogen pressure, intermediate products were seen on TLC and by MS. The reaction was sometimes repeated with the addition of fresh reagents, until completion of the reaction. This reaction was monitored by TLC and MS ($M + 1$), 253.2. Cyclization to the newly formed 2H-benzopyran ring system was confirmed by 1H NMR. The diastereotopic protons for the benzylic methylene protons at C-4 were observed at 2.81 ppm (dd, $J = 20.9, 5.5$ Hz) for one proton and at 2.97 ppm (dd, $J = 16.8, 4.6$ Hz) for the other proton. A broad singlet for the proton next to the hydroxyl group at C-3 was observed at 4.41-4.44

ppm (characteristic for exchangeable protons), and the proton next to the ester function at C-2 was seen at 4.74 ppm, Appendix - Spectrum 5. As before the proton assignments were confirmed by COSY and HSQC NMR analysis.

2.5.2 Benzopyran Scaffold Required for Solid Phase Synthesis

The solution phase organic synthesis proceeded in a similar manner. The starting material was chosen keeping in mind the possibility of solid phase synthesis. Hence, 2,4-dihydroxybenzaldehyde **121** was taken as the starting material (Scheme 2.29). The task at hand was then to independently protect the two hydroxyl groups, as well as finding a suitable protecting group, which was compatible with the rest of the sequence.

Scheme 2.29



MEM hydroxyl protection was considered, as it is a versatile protecting group stable to both basic and neutral hydrogenation conditions. In the first step, the *para*- hydroxyl group was selectively protected with MEMCl to give the OMEM derivative **226**. Mass spectrometric analysis showed a single hydroxyl protection ($M + 1$) 227.2, and ^1H NMR showed proton signals at 3.33 ppm (s, 3H), 3.52 ppm (t, $J = 4.6$ Hz, 2H), 3.78 ppm (t, $J = 4.7$ Hz, 2H) and 5.28 ppm (s, 2H) for the OCH_3 , the two OCH_2 and the OCH_2O groups respectively. The selectivity towards the *para*- position can be explained as the *ortho*- hydroxyl group is hydrogen bonded with the aldehyde, leaving the *para*- hydroxyl group free for reaction, Figure 2.4.

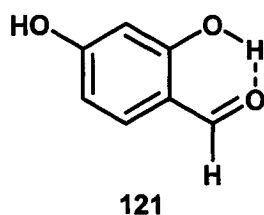


Figure 2.4 Hydrogen bonding of 2,4-dihydroxybenzaldehyde

As with the model study (Section 2.5.1), the *ortho*- hydroxyl group was protected with benzylbromide **227**, followed by chain extension with Wittig reagent **228**, and the alkene **118** was converted to the primary alcohol by oxidative hydroboration to give **229**. As before, benzylation was confirmed by the appearance of extra peaks in the aromatic region as well as an extra singlet for the two benzylic protons at 5.11 ppm for **227**. The olefination product **228** was confirmed by the characteristic coupling constants and olefin signals present in the ^1H NMR, at 5.24 ppm (d, $J = 11.2$ Hz) for the *cis*-terminal proton coupling with the benzylic proton, at 5.75 ppm (d, $J = 17.7$ Hz, 1H) for the *trans*-terminal proton coupling with the benzylic proton, and the benzylic proton at 7.15 ppm (dd, $J = 17.7, 11.1$ Hz, 1H). The olefin signals therefore, could be fully resolved confirming the structure by NMR spectroscopy. Hydroboration and oxidative cleavage to the alcohol was confirmed MS ($M + 1$) 333.3, and the disappearance of the olefin signals in the ^1H NMR spectrum.

Following the model study, the attempt to synthesize the homologous aldehyde **230** by PCC oxidation gave a very poor yield of 46%. A better yield of 75% was obtained with Swern oxidation conditions, (Table 2.2).⁸¹ The generation of the aldehyde was confirmed by MS (M+1) 331.2, and by the characteristic NMR signals as follows: a peak in the ¹H NMR spectrum appearing downfield at 9.71 ppm, in the ¹³C NMR spectrum at 200.7 ppm and a positive peak on the proton decoupled spectrum at 200.7 ppm in the ¹³C (dept 135) NMR.

Table 2.2 Oxidation of alcohol **229** to aldehyde **230**

Reaction	Reagents	Temperature °C	Time h	% Yield
PCC Oxidation	2 eq. PCC, CH ₂ Cl ₂	RT	2	46
SO ₃ •Py Oxidation	excess DMSO, 5 eq. TEA, 4 eq. SO ₃ •py complex, CH ₂ Cl ₂	RT	3-4	cleaved product 226
Swern Oxidation	Step 1: 3 eq. DMSO, 1.2 eq. oxalyl chloride, CH ₂ Cl ₂	- 78 ⁰ C to RT	1	75
	Step 2: 6 eq. TEA	- 78 ⁰ C to RT	1.5	

The homologous aldehyde **230** was then subjected to a second Wittig reaction to yield **231**, followed by a Sharpless dihydroxylation reacting with AD Mix α to generate the diol **232**. The alkene ester formation in **231** was confirmed by the appearance of alkene signals at 5.79 ppm and 7.12-7.16 ppm in the ¹H NMR. Further, the alkene proton at 5.79 ppm showed a characteristic trans coupling

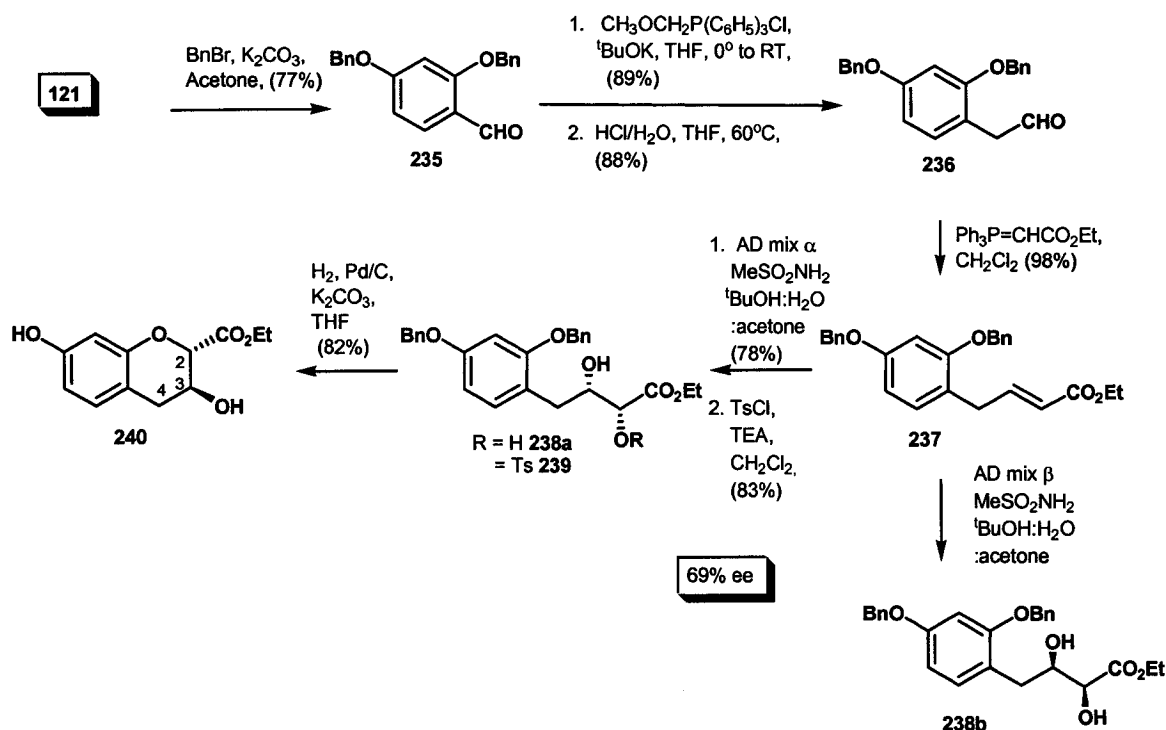
constant of 15.5 Hz. The other proton of the alkene showed a multiplet. The ester protons were observed at 1.29 ppm ($J = 7.1$ Hz, 3H) for the CH_3 group and for the CH_2 group at 4.19 ppm ($J = 7.1$ Hz, 2H), with the characteristic splitting patterns of triplet and quartet respectively. Formation of the diol **232** was confirmed by the disappearance of the alkene signals, and the appearance of hydroxyl protons at 2.31 ppm and 3.12 ppm.

The diol **232** was selectively protected with a tosyl group, once again however, with a poor yield of 47% of **233**. This reaction was not clean, and was revealed by the appearance of many spots on the TLC. As before, the benzylic protons appeared diastereotopic at 2.94 ppm (dd, $J = 13.2, 6.3$ Hz, 1H), and at 3.00 ppm (dd, $J = 13.5, 7.9$ Hz, 1H) in the ^1H NMR indicating the adjacent asymmetric environment. Regioselective tosylation was confirmed using ^1H , COSY, HSQC and HMQC NMR analysis which showed the disappearance of one hydroxyl proton at 3.12 ppm. The other hydroxyl proton remained at 2.31 ppm as before. The α -O-tosyl hydroxy derivative **233** was subjected to debenzylation/cyclization conditions of H_2 , Pd/C and K_2CO_3 to obtain the bicyclic 2H-benzopyran, **234**. The structure was confirmed by MS ($M + 1$) 327.2, and by ^1H NMR - Spectrum 2, Appendix.

2.5.3 Solution Phase Optimization of the Synthesis of Benzopyran Scaffold

In a final attempt to optimize the synthesis, it was felt that the synthesis could be significantly shortened by performing the Wittig reaction with methoxymethyl)triphenyl phosphonium chloride for the homologation. Previous attempts to use similar conditions of generating the Wittig reagent with PPh_3 , $\text{ClCH}_2\text{OCH}_3$, NaHMDS followed by acid hydrolysis had failed both with the model study (Section 2.5.1) and with the MEM system (Section 2.5.2). In the meantime, optimization of the homologation was achieved by another member of the group for a different template, with a completely deprotected alcohol system.⁸² A similar strategy was applied to this system and is outlined in Scheme 2.30.

Scheme 2.30



Since the MEM group was susceptible to acidic conditions, the choice was to protect the hydroxyl groups of the starting 2,4-dihydroxyaldehyde by benzylation, to obtain the dibenzyl aldehyde **235**. Dibenylation was confirmed by the appearance of benzylic protons as 2H, singlets at 5.13 and 5.16 ppm and aromatic signals integrating to 10 protons as a multiplet. The downfield signal at 10.42 ppm in the 1H NMR characteristic of aldehyde protons was observed which gave the corresponding ^{13}C NMR peak at 188.7 ppm.

This was followed by the Wittig reaction and acid catalyzed hydrolysis to the homologous aldehyde **236**. The Wittig product was isolated once as the *cis/trans* mixture. The complete analysis of the products however, was carried-out after the acid hydrolysis - at the aldehyde stage. The homologous aldehyde was confirmed by 1H NMR, which showed an extra peak for the benzylic CH_2 group at 3.65 ppm.

The aldehyde **236**, upon chain extension to the alkene **237**, and dihydroxylation with AD Mix α and β revealed the diols **238a** and **238b**. Chain extension was confirmed as the formation of the trans alkene ester by ^1H NMR as follows: a doublet at 5.82 ppm ($J = 15.6$ Hz, 1H) which indicated trans coupling of one proton, and the other proton as a fully resolved doublet of triplets between 7.12-7.19 ppm ($J = 15.6, 6.7$ Hz, 1H). This was the first instance that it was possible to observe individual coupling of the C-3 proton with the C-2 proton and the benzylic protons at C-4 on either side.

The diol **238a** was confirmed by the disappearance of the alkene signals, and the appearance of the diastereotopic split of the benzylic protons at 2.94 ppm (dd, $J = 13.2, 5.5$ Hz, 1H), and at 3.06 ppm (dd, $J = 13.5, 8.0$ Hz, 1H), and the hydroxyl protons at 2.44 ppm and 3.23 ppm in the ^1H NMR. As in the case of the model study, the relative enantiomeric excess of 69% ee was established for the two diols **238a** and **238b** using chiral HPLC. Once again, the ee was relatively low. Work proceeded on as before with the regioselective tosylation of the diol **238a** to obtain **239** in an excellent yield of 83%. The result was a very welcomed surprise. The product was confirmed by ^1H NMR analysis. As before, the complete disappearance of the hydroxyl proton at 3.23 ppm was observed.

The synthesis was then continued on to the cyclization step, which gave the debenzylated bicyclic diol **240** in 82% yield under reductive conditions, Appendix - Spectrum 7. The ^1H NMR showed two significant peaks at 2.63 ppm and 5.15 ppm, which was not observed in the HSQC spectrum. This indicated that they were two hydroxyl signals. The COSY spectrum showed coupling between proton at 4.42 ppm and hydroxyl proton at 2.63 ppm. This proton and the hydroxyl group are therefore, at the C-3 position, and the hydroxyl group would be the secondary alcohol. The peak at 5.15 ppm would be the phenolic hydroxyl group.

The bicyclic diol **240** can be selectively protected in further solution phase synthesis as one hydroxyl group is aromatic whereas the other is a secondary hydroxyl group having different pK_a values and hence differing reactivities. We were extremely delighted with the final result enabling us to prepare the bicyclic scaffold in relatively good yields in a shorter reaction sequence than what was described in Sections 2.5.1 and 2.5.2. Thus the bicyclic 2H-benzopyran scaffold was finally in place to develop diverse sets of natural product-like compounds.

3. SYNTHESIS OF BENZOPYRAN-BASED POLYCYCLIC DERIVATIVES FROM AMINO ACID CONJUGATES

3.1 Design Strategy

The first objective of the project was to synthesize a diverse collection of compounds based on amino acid conjugates, (**72**, **73**, Scheme 1.6). Amino acids were chosen because of their biological relevance and the ability of having two diversity sites: built in chiral site R and a potential derivatization site -NH_2 (Figure 3.1, **241**, Section 3.2). It was also thought of creating *cis*- and *trans*-fused lactone rings, hence creating a tricyclic system. This system then would satisfy the criteria of small molecular probes with rigid polycyclic cores capable of lowering the entropy factor of protein binding (Section 1.3.5.2). Amino acid conjugates have been used by various researchers to synthesize polycyclic ring systems. For instance, 7-membered ring extensions on scaffolds such as benzodiazepines. Benzodiazepines have shown a range of biological activities (Section 3.3.1). Therefore, the expectation of extensions on a benzopyran scaffold, based on the need to have a rapid access to various analogs by a library synthesis seemed relevant. Three strategies were considered for the extension of the 2H-benzopyran derivative by lactonization: (1) Mitsunobu (Section 3.6.1), (2) leaving group (Section 3.6.2) and (3) reductive amination (Section 3.6.3). It was also thought to create a bicyclic library on the 2H-benzopyran scaffold, with amino acid conjugates as diversity elements, via amino acid coupling or by a reductive amination reaction.

3.2 Amino Acids and Proteins⁸³

Amino acids are the basic components or building blocks of proteins. Proteins are believed to be indispensable agents in biological functions. The analysis of their nature, function, the amount of proteins that are expressed in cells, their interactions with supramolecular structures such as membranes and cytoskeleton, is generally called proteomics.

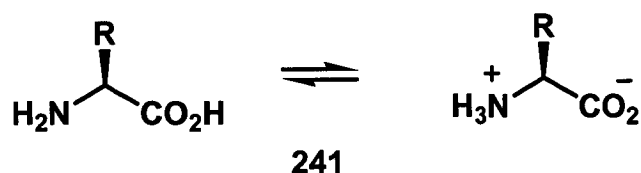


Figure 3.1 Basic structure of amino acids.

The diversity of most proteins in Nature arises from 20 amino acids. This comes about mainly due to reasons such as: (1) their capacity to polymerize, (2) acid – base properties, (3) structure and reactivity of the side chain and (4) chirality.

Amino acids in Nature have a L-configuration and their reactivity is based on their side chain, (R group **241**, Figure 3.1). Reactions of the side chains in turn, can be used to identify functional amino acids at the active sites of enzymes or to label proteins with reagents for further study. Amino acids are also neutral molecules generally having a positive and a negative charge, i.e. zwitterionic. The head-to-tail union of the reactive $-\text{NH}_3^+$ and $-\text{CO}_2^-$ moieties of the 20 common amino acids gives rise to covalently linked peptide bonds, which in turn form proteins - unbranched polymers with $-\text{N}-\text{C}_\alpha-\text{C}-$ peptide backbone. Apart from the 20 amino acids, there are some amino acids such as hydroxylysine and N-methylarginine that occur in proteins. They are called uncommon amino acids. There is yet another class of amino acids although not found in proteins, but biochemically important. Examples include γ -aminobutyric acid (GABA), histamine and adrenaline.

3.3 Literature Approaches to Natural Product-like Scaffolds Derived from Amino Acid Conjugates

3.3.1 Benzodiazepine Derivatives

Benzodiazepine and its derivatives have been reported to show a wide range of biological activities^{84,85} such as anxiolytics, antiarrhythmics, vasopressin antagonists, HIV reverse transcriptase inhibitors, cholecystokinin antagonists, angiotensin converting enzyme inhibitors, endogeneous natriuretic factors and

calcium channel blockers. For instance, benzodiazepine **242** is a cholecystokinin-A (CCK-A) receptor and benzazepine **243** is a peptide angiotensin I.²⁵ Benzodiazepine **244** is an antagonist of oxytocin (OT) (Figure 3.2). Because of their biological significance and their potential, it is believed that benzodiazepines have the ability to influence pharmaceutical research. Benzodiazepines have been reported to be the first family of small molecules to be synthesized on solid support.

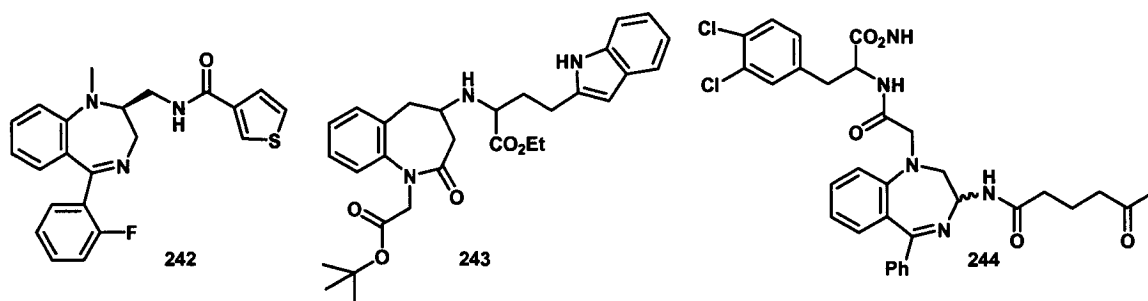
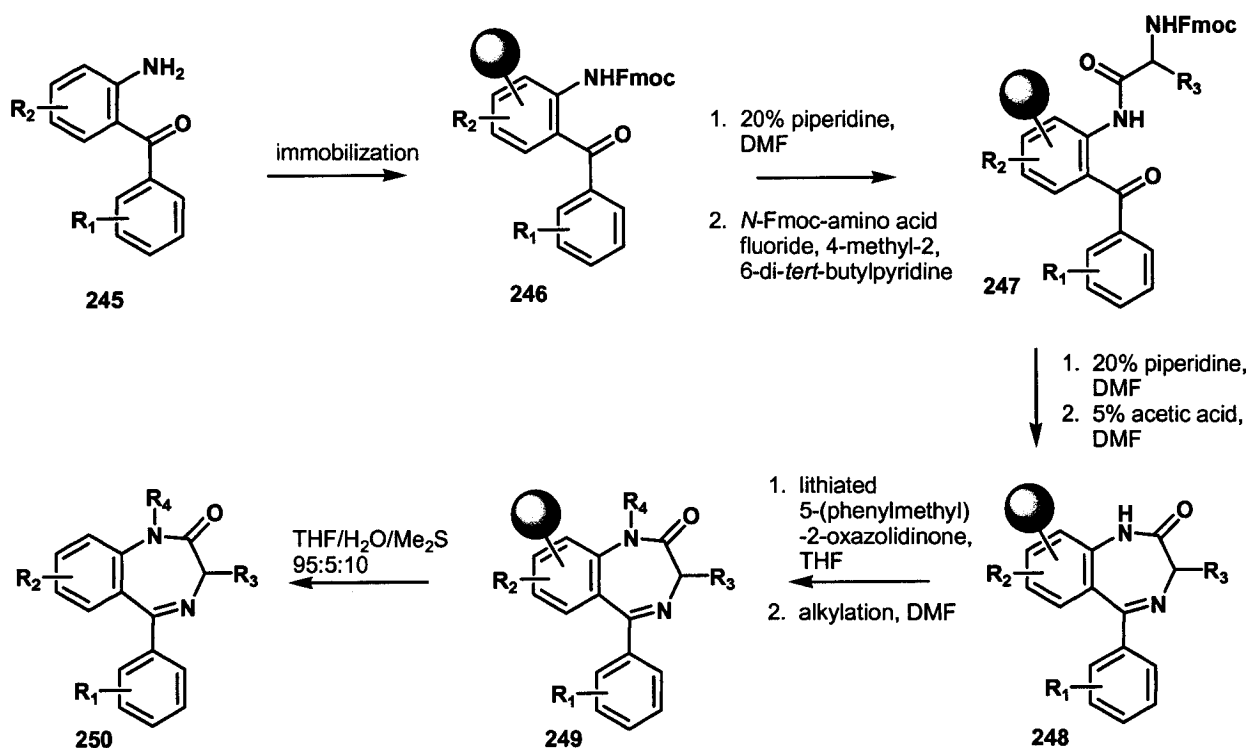


Figure 3.2 Biologically active benzodiazepines and its' derivatives

C. C. Leznoff⁸⁶ first reported the technique of using insoluble polymer supports in organic synthesis, and the first heterocyclic scaffolds prepared on solid support were 1,4-benzodiazepines by Ellman and co-workers⁸⁷ in 1992 (Scheme 3.1). They first immobilized 2-aminobenzophenones (**245**) via either a hydroxy or carboxylic acid functionality, which was followed by Fmoc deprotection and amino acid coupling to **247**. The amine deprotection and acid catalyzed cyclization of **247** then led to the benzodiazepines **248**. The secondary amine **248** was then alkylated to **249** after base mediated deprotonation with lithiated 4-benzyl-2-oxozolidinone, which was finally cleaved to 1,4-benzodiazepine derivatives **250**.

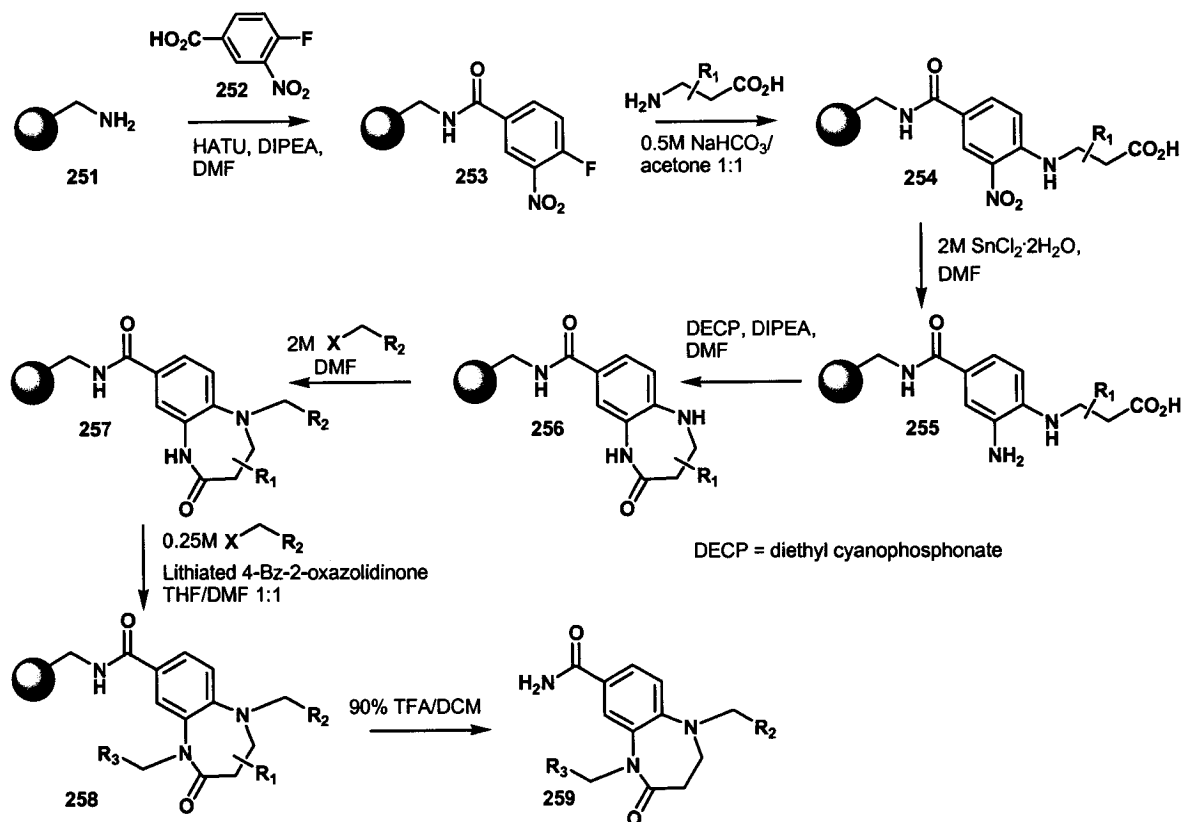
Scheme 3.1



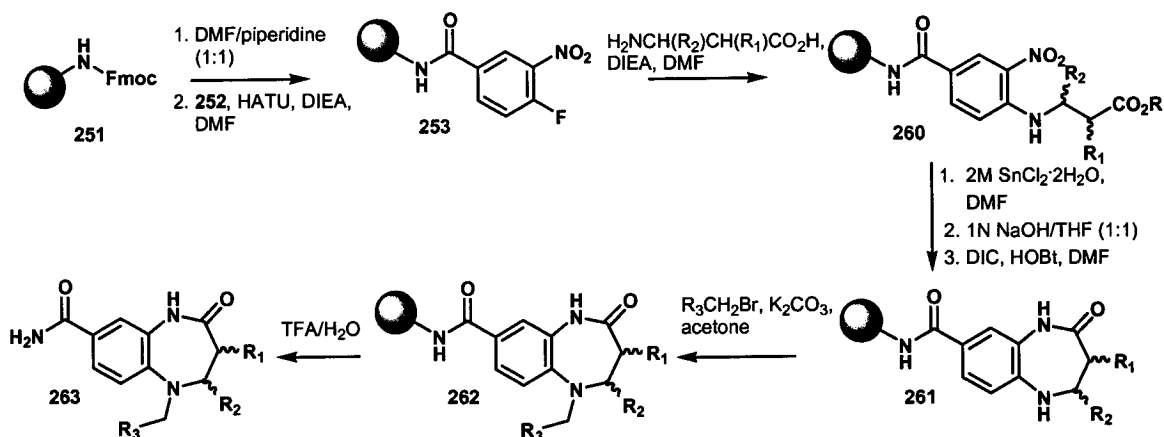
Following the synthesis reported by Ellman et al., Schwarz et al.,⁸⁸ and Lee et al.,⁸⁴ had similar approaches for the solid phase synthesis of 1,5-benzodiazepin-2-ones (Schemes 3.2 and 3.3 respectively). Both groups used the common starting material 4-fluoro-3-nitrobenzoic acid (**252**). This was then linked to a AgroGel-Rink-resin by amino acid coupling with HATU, and DIPEA to obtain the immobilized amide **253**. The amide **253** was then derivatized by an S_NAr-type reaction: nucleophilic substitution by nitrogen at the aromatic fluorine moiety to give **254**, and **260** respectively. This was followed by SnCl₂•H₂O reduction of the nitro to the amine, **255**, cyclization to **256**, and **261**, Schemes 3.2 and 3.3 respectively. Cyclized templates were then derivatized at the nitrogen moieties N(1) and N(5). Schwarz and co-workers used the approach of derivatizing N(5) by acylation with acid chlorides and alkylation with alkyl halides to **257**, followed by N(1) alkylation with alkyl halides in lithiated 4-benzyl-2-oxazolidinone, **258**, Scheme 3.2. Only the alkylation is shown in Scheme 3.2. Under these conditions they had not observed any C- and O-alkylation products. The resin

was finally cleaved with 90% TFA/DCM to yield a collection of compounds (**259**). Whereas Lee et al., derivatized only at the N(5) position with alkyl halides to **262**, followed by TFA/H₂O cleavage to **263**, Scheme 3.3.

Scheme 3.2



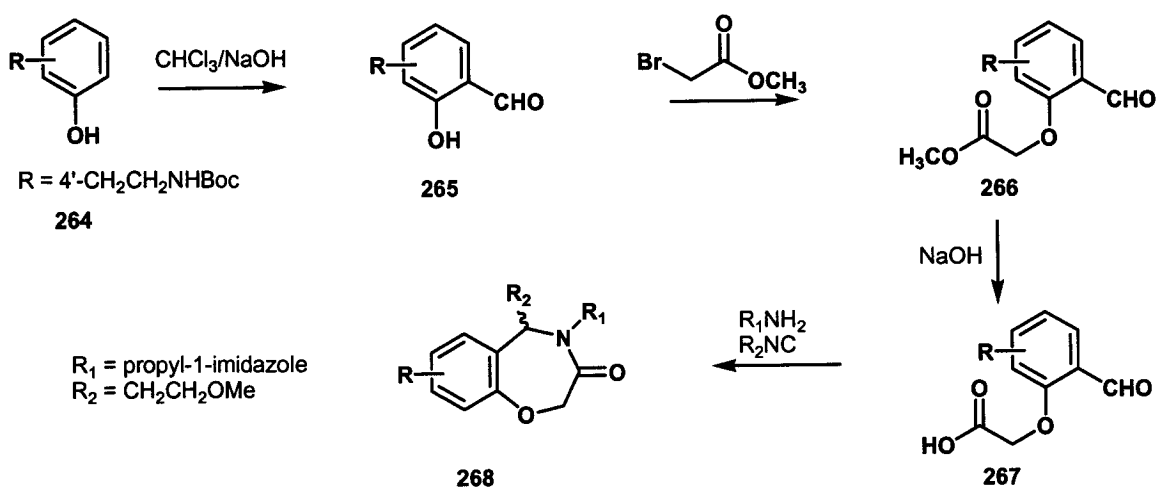
Scheme 3.3



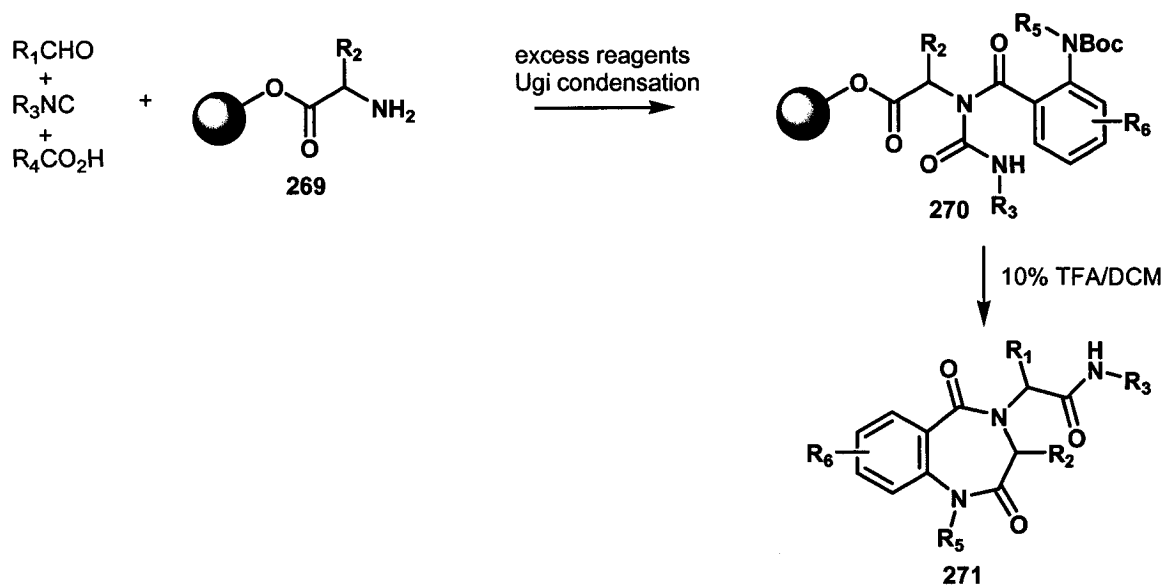
In a completely different approach Zhang and co-workers⁸⁹ used a Ugi three-component condensation (3CC) reaction on a bifunctional template **267** (Scheme 3.4). The synthesis of the Ugi 3CC precursor **267** was achieved by converting the phenols **264** to the aldehydes **265**, under Reimer-Tiemann conditions. This was then followed by alkylation to **266** and saponification to **267**. The precursor **267** was then subjected to Ugi 3CC reaction with primary amines and isocyanides to form the 1,4-benzoxazepin-3-one-5-carboxiamides **268**.

Similar to the approach of Zhang et al., Hulme and co-workers used a Ugi/DeBoc/Cyclization (UDC) strategy for the solid phase synthesis of benzodiazepines, Scheme 3.5.⁹⁰ They coupled the resin bound amino acids with aldehydes, isocyanides and N-Boc anthranilic acid (R_4CO_2H) such that it undergoes a Ugi 4CC to yield **270**. Treatment of **270** with TFA was successful in Boc-deprotection of the secondary amine, cleavage of the resin, and lactonization to the benzodiazepines **271** as a one-pot reaction.

Scheme 3.4



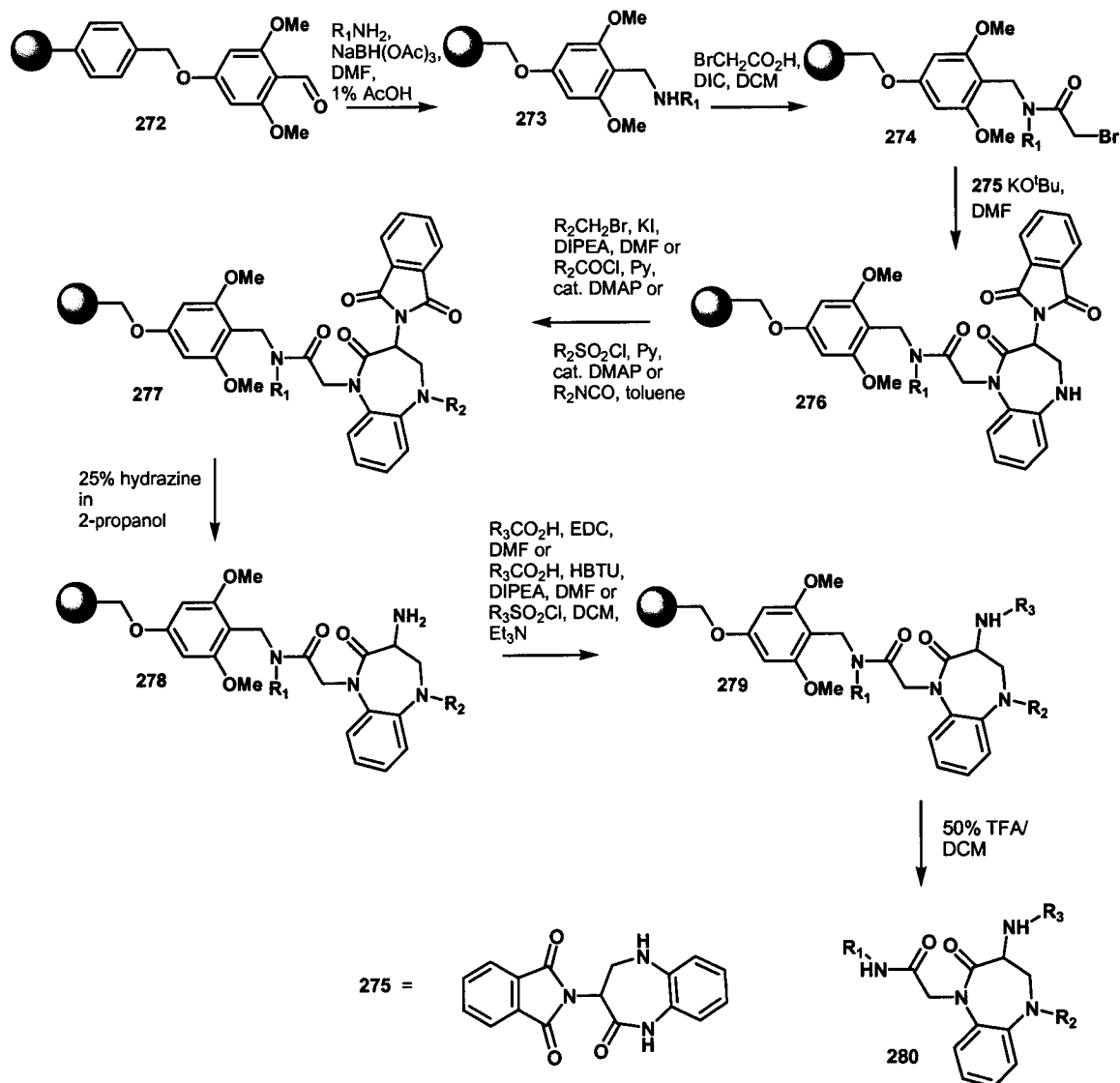
Scheme 3.5



In another investigation, Herpin et al.,⁹¹ was capable of synthesizing a 10,000 membered 1,5-benzodiazepine-2-one library by a direct sorting method. Their solid phase approach is outlined in Scheme 3.6. In the first step they had adopted a reductive amination reaction to immobilize the primary amine to obtain compound **273**, followed by a derivatization with bromoacetic acid to **274**. This was then coupled with benzodiazepine scaffold **275** (previously synthesized) to yield **276**. Functionalization of the N(5) ring nitrogen of the primary amine **276** had been achieved under strong conditions with either alkyl halides, acylchlorides, thionylchlorides, or isocyanates to **277**. Subsequently, the phthalimide protecting group was deprotected to the primary amine **278**, which was further functionalized to **279**, and cleaved to generate a collection of 1,5-benzodiazepine-2-ones **280**.

Apart from the above mentioned benzodiazepines other types of derivatives have also been synthesized. For example substituted octahydrobenzazepinones **285** by Blechert et al.,⁹² (Scheme 3.7) and benzothiazepinones **291** by Houghten et al.,⁸⁵ (Scheme 3.8).

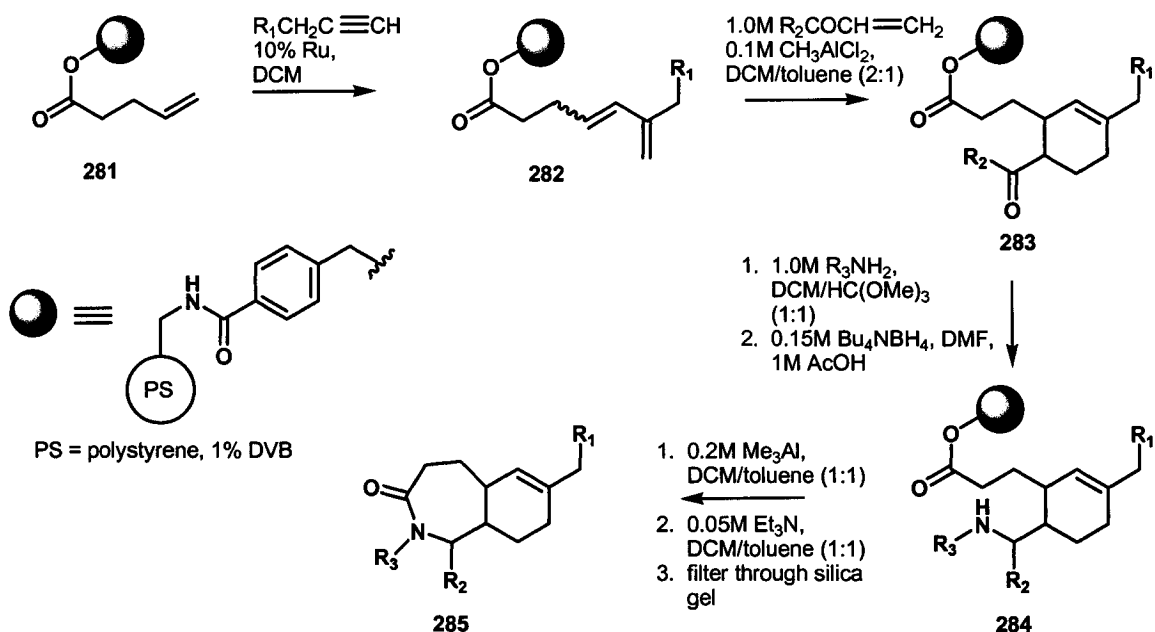
Scheme 3.6



In the synthesis of octahydrobenzazepinones **285** Blechert and co-workers⁹² used yne-ene cross metathesis reaction (CMR), followed by a Diels-Alder cycloaddition reaction, Scheme 3.7. The immobilized alkenoic acid ester **281** was subjected to Ru catalyzed yne-ene CMR which yielded diastereomeric E/Z mixtures of the alkenes **282**. The alkenes **282** were then reacted with dienophiles such as α,β -unsaturated ketones or aldehydes in the presence of a Lewis acid to form the Diels-Alder products **283**. The ketones or aldehydes **283**, were then reductively aminated with primary amines to **284**, which were cyclized

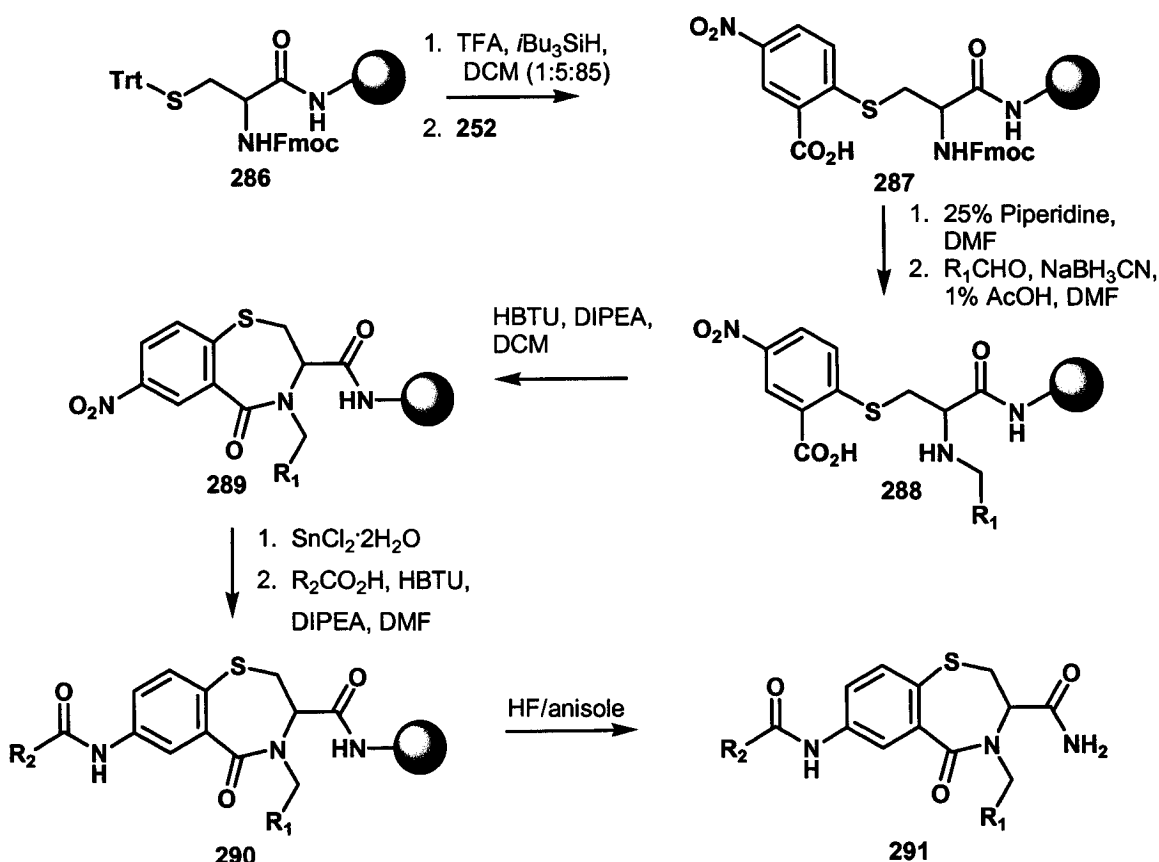
and cleaved to the lactones **285** with Me_3Al and TEA. They were successful in obtaining the 1,2,7-trisubstituted octahydrobenzo[*c*]azepin-3-ones **285** in high purity but as diastereomeric mixtures.

Scheme 3.7



On the other hand Houghten's⁸⁵ approach for the synthesis of benzothiazepinones (**291**, Scheme 3.8), was somewhat similar to the approaches by Ellman et al., Schwarz et al., and Lee et al., discussed earlier. In the synthesis by Houghten and co-workers, the S-moiety of the S-trityl and N-Fmoc protected L-cysteine **286**, was deprotected and coupled with 4-fluoro-3-nitrobenzoic acid **252**, to yield **287**, followed by deprotection of the amine and derivatization to **288** with aldehydes under reductive amination conditions. The acids **288**, were then cyclized to the nitro-benzothiazepines **289**. The nitro group of **289** was subsequently reduced to the amine and further derivatized with carboxylic acids to yield **290**. The resin was finally cleaved to yield a series of benzothiazepinones **291**.

Scheme 3.8



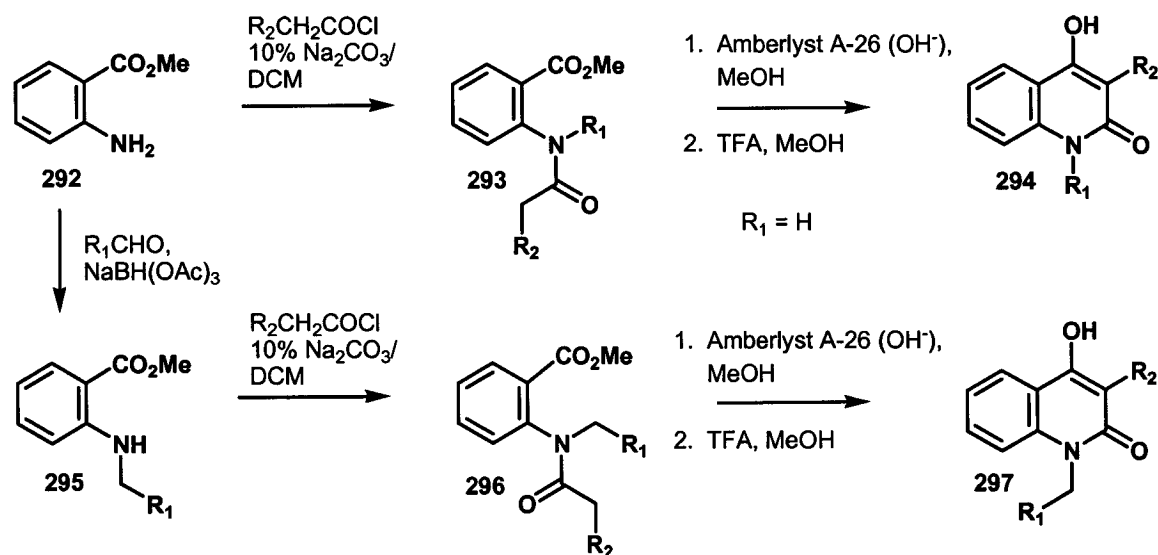
3.3.2 Other Derivatives

For formation of six membered lactam rings such as 4-hydroxyquinolin-2(1*H*)-ones (**294** and **297**, Scheme 3.9), quinolin-2(1*H*)-one-carboxylic acids (**300**, Scheme 3.10) and 3,1-benzoxazine-4-ones (**314**, Scheme 3.13) would be considered in this section. These types of derivatives too, have shown various therapeutic properties and are therefore very much in demand.

Examples from Ganesan et al.,⁹³ were taken for the synthesis of 4-hydroxyquinolin-2(1*H*)-ones (**294** and **297**, Scheme 3.9). In their synthesis, they derivatized methyl anthranilate (**292**) to the acylated secondary amine **293** by a Schotten-Baumann two phase acylation reaction. The amides **293** served as a precursor for the Claisen-type condensation to yield the cyclized quinolinones

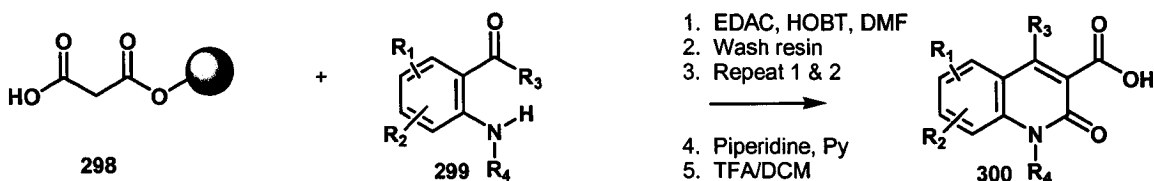
294. An ion-exchange resin catalyzed the reaction as well as helped with the purification process by filtration. TFA was required to cleave the compounds from the resin. In a separate sequence they also derivatized methyl anthranilate **292** under reductive amination conditions to **295**, followed by an acylation to the tertiary amine **296**, which was cyclized as before to 4-hydroxyquinolin-2(1*H*)-ones **297**.

Scheme 3.9



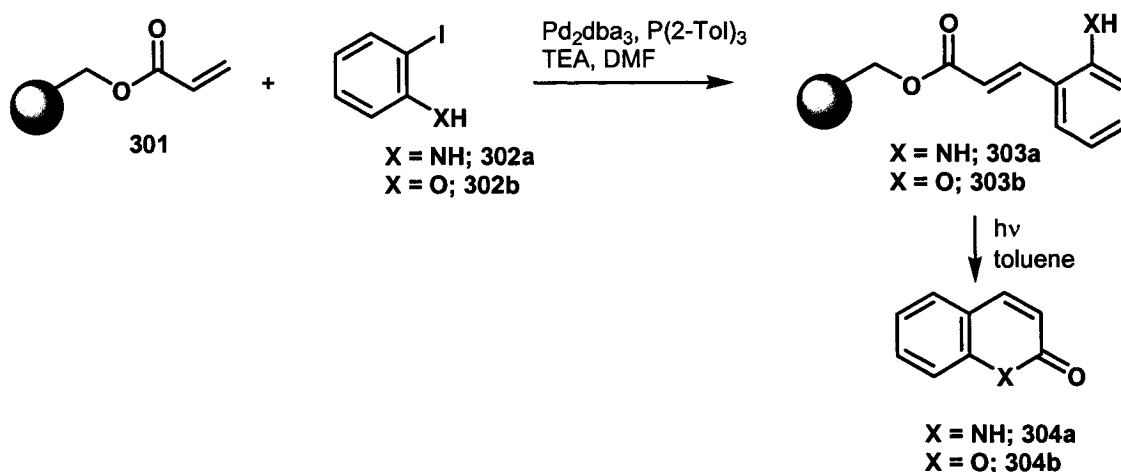
Watson et al,⁹⁴ utilized the Knoevenagel condensation reaction to synthesize quinolin-2(H)-one-3-carboxylic acids (**300**, Scheme 3.10). This approach was similar to their synthesis of coumarins (**184** and **185** Scheme 2.19) previously discussed in Section 2.4.2. Unlike Ganesan's approach of using an ion-exchange resin to temporarily bind the final product, Watson used immobilized malonic acid on Wang resin **298** as the starting point. The first step in their synthesis was to form the amide derivatives by coupling **298** with *o*-aminophenones **299** which was then subjected to Knoevenagel cyclization. The TFA assisted cleavage yielded the quinolin-2(H)-one-3-carboxylic acids **300**. This facile and selective two step synthetic processes developed by Watson and co-workers has the potential of being automated for multi-step solid phase synthesis.

Scheme 3.10

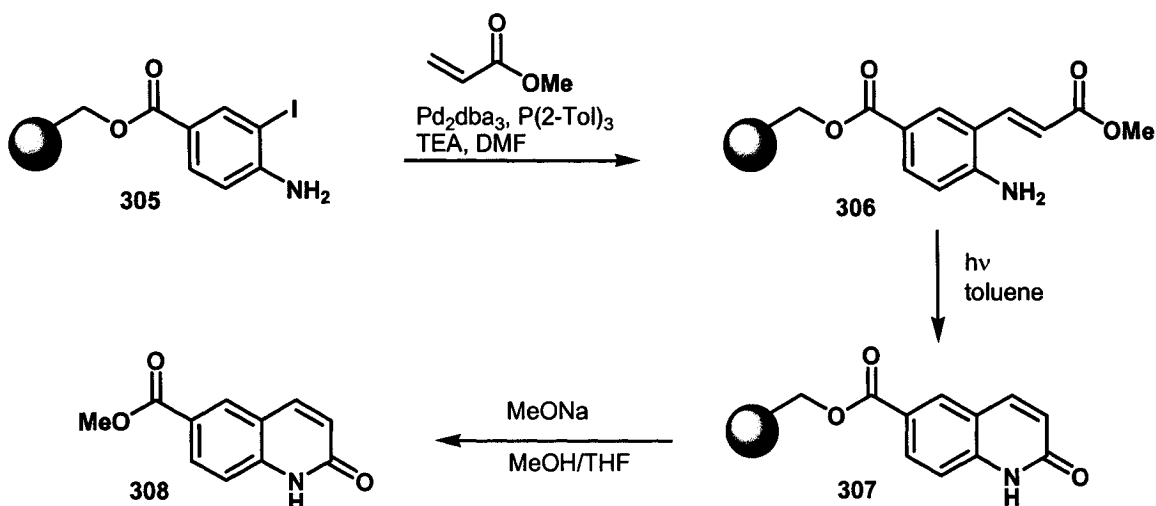


In a different study Kondo et al.,⁹⁵ used the Heck reaction and a photoinduced cyclorelease reaction for the synthesis of 2-quinolone and coumarin (Scheme 3.11). In their investigation of the Heck reaction, they used a REM resin **301** with 2-iodoaniline **302a** and 2-iodophenol **302b** to form the immobilized *o*-substituted cinnamates **303a**, and **303b** respectively. The Heck alkene products thus formed were cyclized and cleaved in a one-pot reaction under irradiation with a 400 W high pressure mercury lamp in toluene to yield cyclized 2-quinolone (**304a**) and coumarin (**304b**). Kondo and co-workers were also successful in achieving a non-cyclorelease type photocyclization (Scheme 3.12). In this approach the immobilized 4-amino-3-iodobenzoate **305** was reacted with methyl acrylate under Heck reaction conditions as reported earlier, to yield the immobilized cinnamate **306**. The photoinduced cyclization of **306**, gave the immobilized quinolone **307**, which was then cleaved with sodium methoxide to methyl-2-quinolone-6-carboxylate **308**.

Scheme 3.11

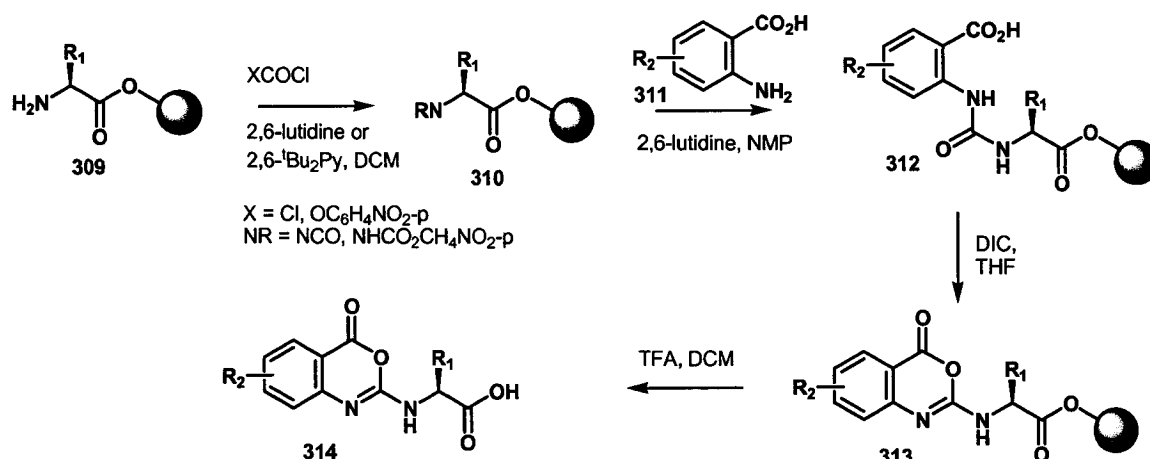


Scheme 3.12



In yet another study, M. F. Gordeev⁹⁶ was successful in synthesizing 3,1-benzoxazine-4-ones (BOX) on solid support **313**, Scheme 3.13. The resin bound amino acids **309** were first converted to isocyanates or carbamates **310** with phosgene or *p*-nitrophenyl chloroformate under basic conditions. Compounds **310** thus prepared were then reacted with anthranilic acids **311** to form the *o*-carboxyphenylurea derivatives **312**, which underwent facile cyclization to the BOX derivatives **313** with DIC or acetic anhydride in THF, or tosyl chloride in pyridine. The cyclization was observed to be completely regioselective, occurring only from the urea oxygen to form the 6-membered ring lactones **313**, without the formation of any isomeric quinaoline-2,4-diones. The resin was finally cleaved by treatment with TFA to yield **314**.

Scheme 3.13



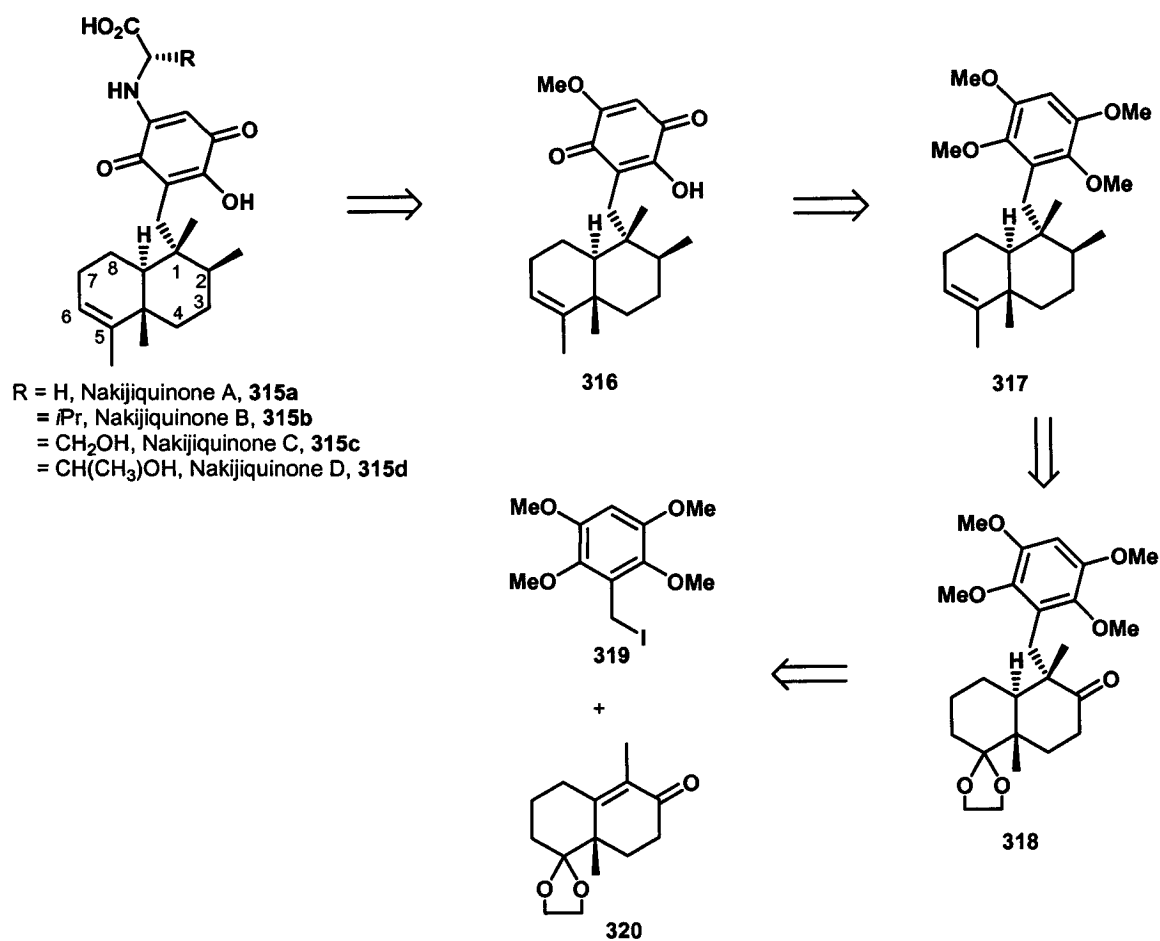
3.4 Literature Approaches to some Interesting Polycyclic Natural Product-like Scaffolds and Library Synthesis

The isolation of natural products with polycyclic structures from organisms has contributed towards large diverse compound libraries covering huge areas in diversity space. In some cases, structurally related sets of natural products have been useful to study the structure-activity relationships. If ligand types or frameworks of certain domain families are already known to exhibit biological activity, they may also be employed as the guiding principle for library development. Examples of this nature have already been discussed in Chapter 2, but for completeness a few more will be considered in this section.

3.4.1 Synthesis of Nakijiquinone Analogues^{97a,b}

Marine sesquiterpene quinones, nakijiquinones (**315a-d**, Scheme 3.14), have exhibited cytotoxic activity against L 1210 murine leukaemia cells, KB human epidermoid carcinoma cells, and Her-2/Neu receptor tyrosine kinase (RTK). More specifically, the Her-2/Neu RTK is reported to be over-expressed in about 30% of primary breast, ovary and gastric carcinomas, and nakijiquinones are the only naturally occurring inhibitors of this oncogene.

Scheme 3.14



Nakijiquinones **315a-d**, consists of three structural elements: amino acid, a *p*-quinoid unit, and a diterpenoid system. Waldmann and co-workers retrosynthetic approach towards the synthesis of nakijiquinones is outlined in Scheme 3.14. Their strategy involved the following key reactions: (1) reductive alkylation of a Wieland-Miescher-type enone **320** with tetramethoxyaryl halide **319**, to yield **318**, (2) oxidative conversion of the aryl ring to a *p*-quinoid system, followed by (3) regioselective saponification of a vinylogous ester to **316**, and finally (4) selective introduction of different amino acids to the remaining vinylogous ester via nucleophilic substitution, giving **315**. They subsequently synthesized a series of nakijiquinones using the forward synthesis of this strategy.^{97a} Their biological studies had an interesting outcome: although the natural nakijiquinones **315a-d**

did not exhibit significant inhibitory activity against the kinase receptor, six members of the library had been identified as kinase inhibitors in the low micromolar range, Figure 3.3. More specifically the C-2 epimer of nakijiquinone C, **321**, was observed to be a potent and selective inhibitor of RTK involved in tumour angiogenesis.

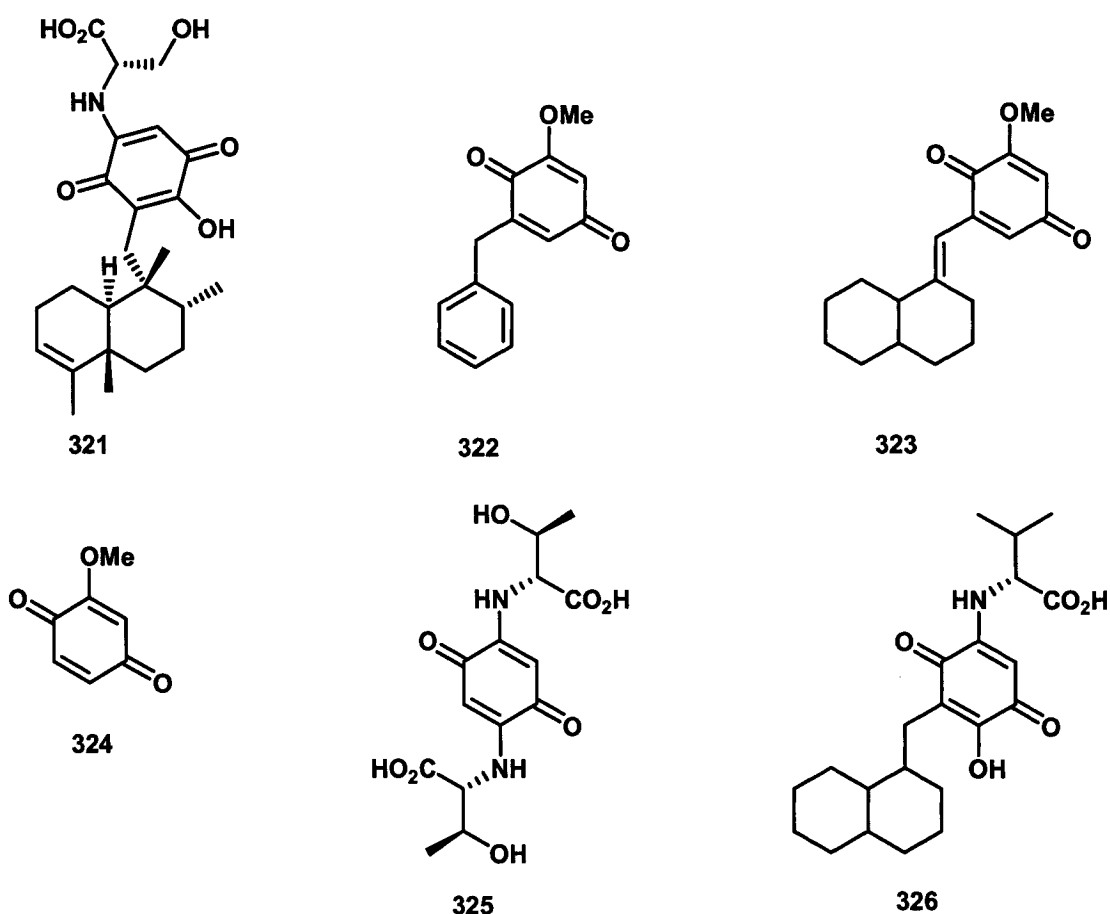


Figure 3.3 Nakijiquinone analogues identified as kinase inhibitors.

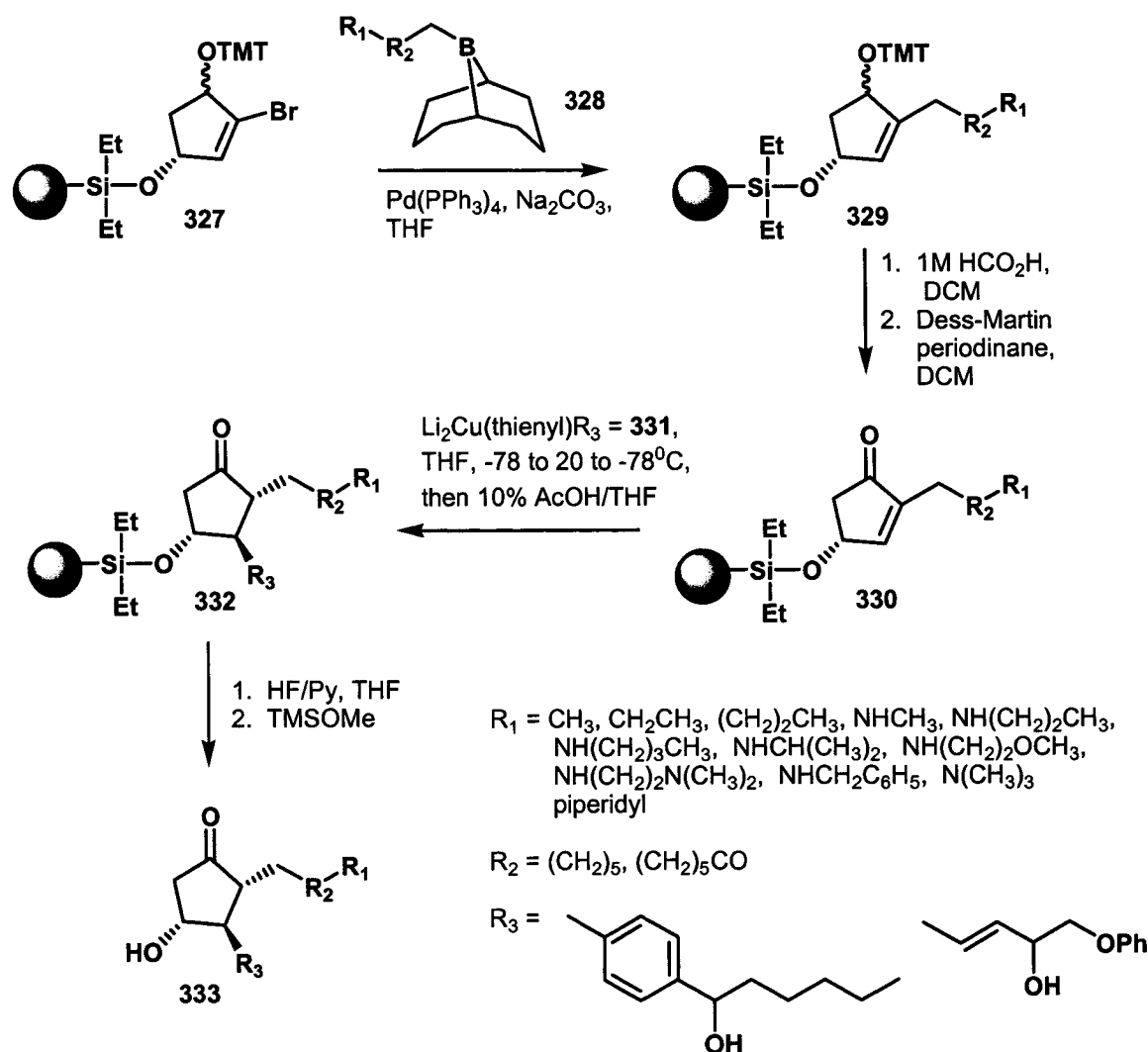
3.4.2 Synthesis of Prostaglandin E₁ Analogues⁹⁸

Prostaglandins play an important role in many physiological processes and have found active in a variety of clinical application such as relief of intraocular pressure caused by glaucoma and as an abortifacient. Despite the early synthetic strategies of E. J. Corey, the synthesis of prostaglandins has continued to be a challenge as they are sensitive to both acidic and basic conditions. A

number of elements of the structure and stereochemistry of the cyclopentane core impact the receptor binding in prostaglandins.

Ellman and co-workers⁹⁸ were successful in synthesizing a library of 26 compounds of the prostaglandin E₁ analogues via parallel Suzuki coupling reactions (Scheme 3.15). In their study, the diversity of the α -chain of the prostaglandins **329** are introduced to the core structure **327** through a Suzuki coupling reaction of alkenes, which were then subjected to in situ hydroboration reaction.

Scheme 3.15

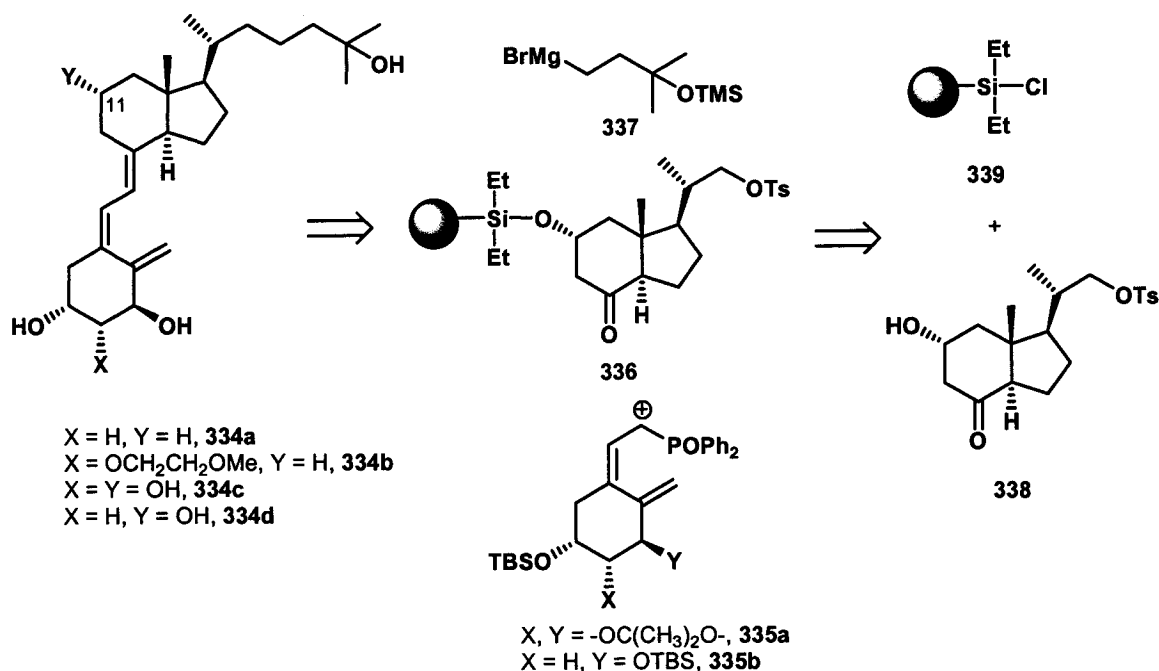


Subsequent removal of the hydroxyl protecting group and mild oxidation under Dess-Martin conditions gave the ketones **330**, which were then subjected to a Michael addition reaction with higher-order cuprates **331** to install the ω -side chain **332**. This process also fixed the relative stereochemistry of the prostaglandins. The resin was then cleaved with dilute HF/pyridine and methoxytrimethylsilane, which removed even the traces of fluoride anions. Hence Ellman and others were successful in synthesizing a collection of prostaglandins for biological testing.

3.4.3 Synthesis of Vitamin D₃ Analogues⁹⁹

Vitamin D₃, in its hormonally active form calcitriol (1 α ,25-Dihydroxyvitamin D₃, **334a**, Scheme 3.16), exhibits many physiological activities such as regulation of cell differentiation and proliferation, intestinal calcium absorption, bone mobilization and bone formation. The vitamin D₃ analogue ED-71 (**344b**), a regulator of calcium metabolism, is supposed to be a promising candidate for the treatment of osteoporosis.

Scheme 3.16



Takahashi et al.,⁹⁹ in his approach to synthesize Vitamin D₃ analogues treated the A ring moieties, CD rings and the side chains as independent units. In their retrosynthetic strategy, Scheme 3.16, the 11-hydroxy CD ring **338** was considered to be the key intermediate. The 11-hydroxy group was used as the site to anchor the resin via the trialkylsilane linker **339**. The silyl linker had been chosen because of its previous historical efficiency and its capability to cleave even in the presence of the unstable triene moiety. The key reactions involved (1) a Horner-Wittig reaction between the A ring moieties **335a,b** and the CD ring **336**, followed by the (2) alkylation with the Grignard reagent **337** to yield the vitamin D₃ analogues **344a-d**. The order of reaction was important to avoid unnecessary side reactions. The Horner-Wittig reaction was performed before the alkylation to avoid C-14 epimerization adjacent to the carbonyl group. Alkylation too, was performed at low temperature to avoid isomerization of the triene. This synthetic protocol can therefore be used to synthesize vitamin D₃ analogues, which can be eventually biologically validated.

3.4.4 Synthesis of Fumitremorgin-type Indolyl Diketopiperazine Analogues^{100a,b}
 Fumitremorgin C (FTC, **340**), a natural product isolated from fungi has been identified as a reversal agent for breast cancer resistant protein. However, FTC induces tremor-activity and other toxic side effects. Since the clinical resistance of cells to chemotherapy is always a major problem in cancer treatment, the identification of a less toxic FTC analogue would be of great interest. With this goal in mind Koomen et al., synthesized a 42 compound library of fumitremorgin-type indolyl diketopiperazines **342**, Figure 3.4. As an extension they also synthesized demethoxy-fumitremorgin C, an analogue of FTC, with a double bond at the C-3 position of the FTC-skeleton, Scheme 3.17, **341a**, **341b**. The compounds thus prepared were screened for breast cancer resistant protein inhibitory activity.

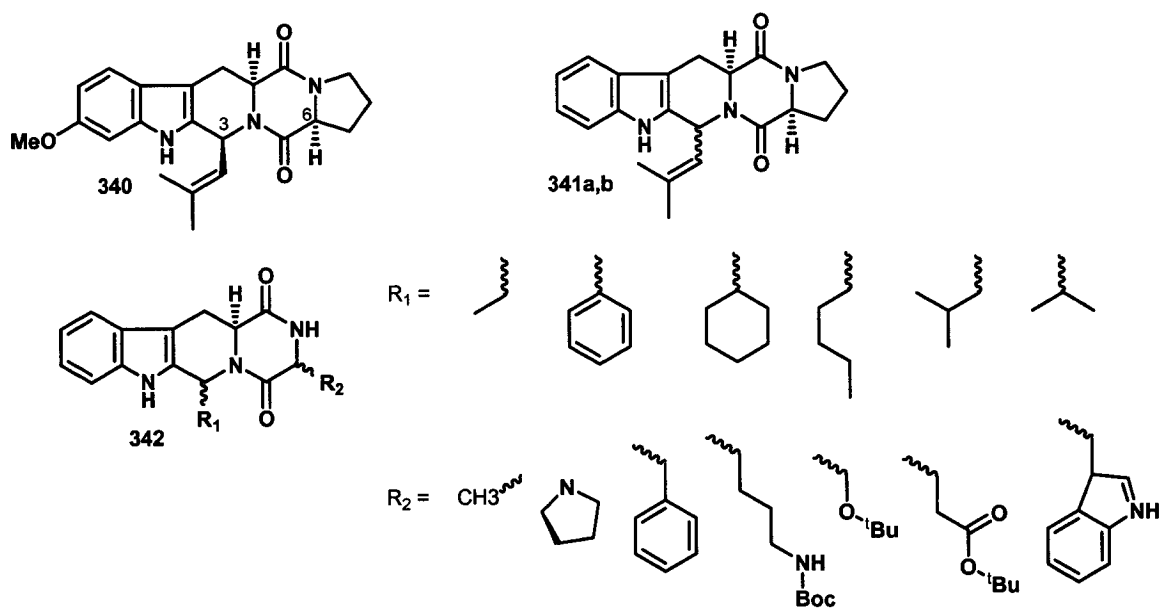
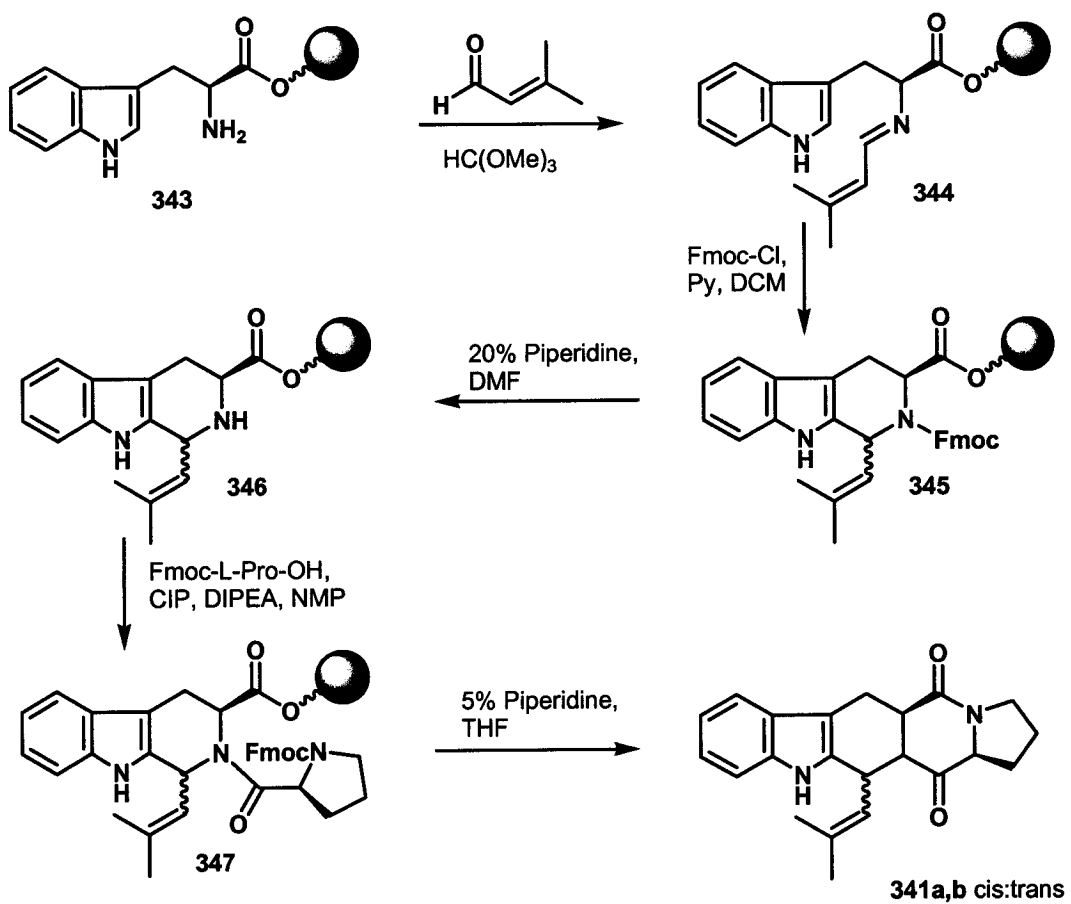


Figure 3.4 Fumitremorgin-type indolyl diketopiperazines.

Scheme 3.17



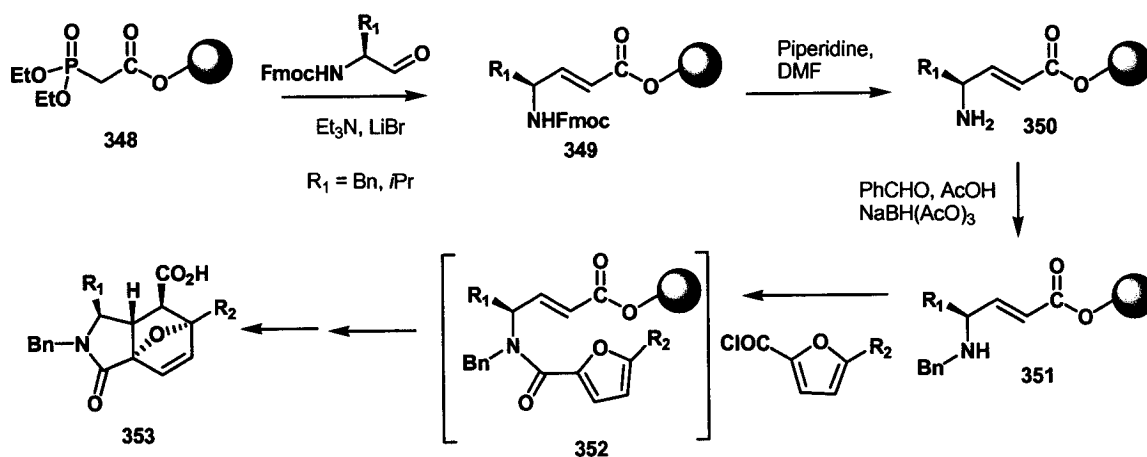
They started the synthesis of demethoxy-fumitremorgin C **341a,b** by reacting the immobilized L-tryptophan indole core **343** with 3-methylcrotonaldehyde to yield the imine **344**, followed by Fmoc protection of the N-moiety and Pictet-Spengler type cyclization to **345**. The N-moiety of the tricyclic compound **345** was deprotected to **346**, and derivatized to the demethoxy-FTC precursor **347**. The final cleavage of the resin and Fmoc deprotection of the N-moiety gave the demethoxy-FTC **341a,b** as a diastereomeric cis/trans mixture of 1:3 ratio. The structure-activity studies performed on the synthetic fumitremorgin-type indolyl diketopiperazine derivatives identified several potent analogues that can be used as leads for breast cancer resistant protein inhibition.

3.5 Literature Approaches to the Synthesis of Oxygen-Heterocyclic Ring-fused Scaffolds

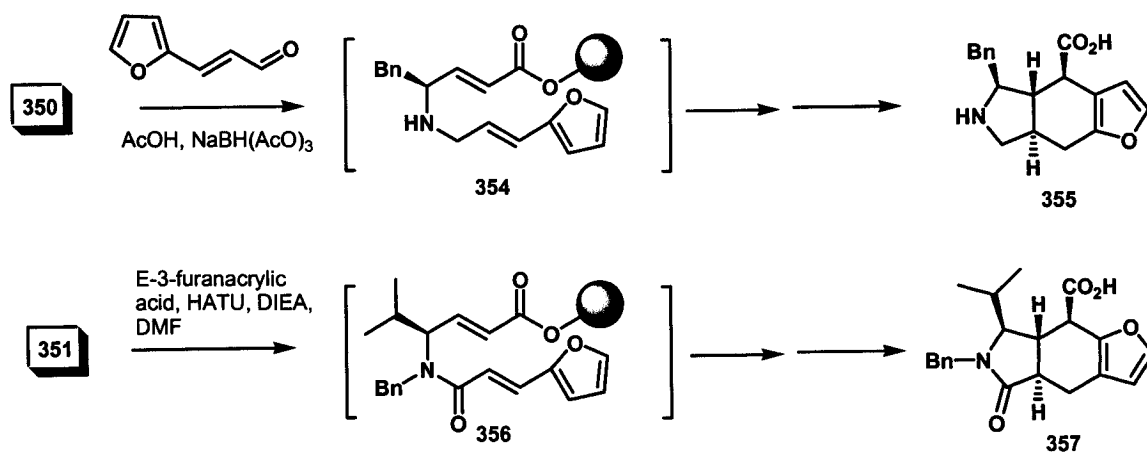
Finally it was thought that the consideration of literature examples where, fused polycyclic ring systems containing oxygen as a hetero-atom was appropriate. Work done by a few authors would be therefore highlighted.

In the study reported by Murray and co-workers,¹⁰¹ they utilized a Diels-Alder strategy to synthesize fused tricyclic ring systems (Scheme 3.18). The immobilized Wittig precursor **348** was reacted with the Fmoc-protected amino aldehydes to yield alkenes, **349**. This was followed by deprotection of the amines **350** and N-benylation to **351**. The secondary amines **351** were then reacted with commercially available substituted furoyl chlorides to generate the Diels-Alder precursors **352**, which underwent cyclization with endo selectivity to obtain epoxyisohydroindolines **353**. They also extended the synthesis to use vinylfuran derivatives to synthesize tricyclic derivatives **355** and **357** (Scheme 3.19).

Scheme 3.18

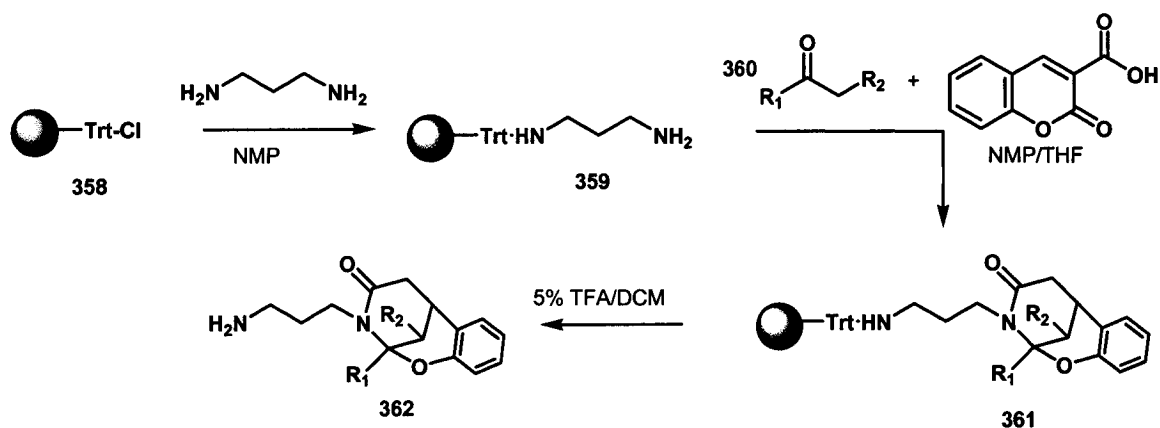


Scheme 3.19



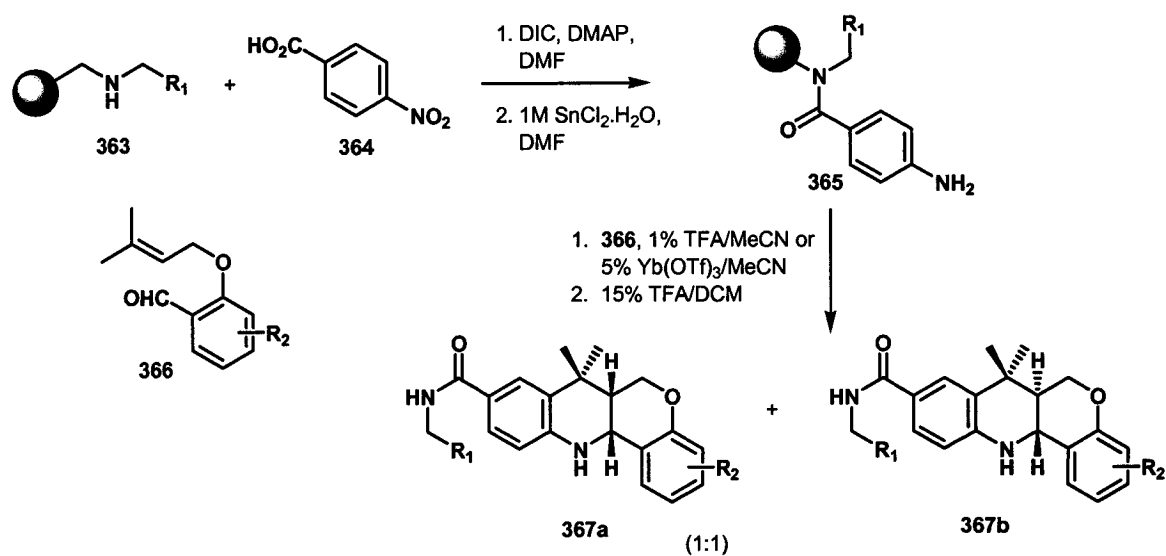
In another study Jonsson et al.,¹⁰² reported the synthesis of oxygen-bridged tetrahydropyridones (**362**, Scheme 3.20). 1,3-Propylene diamine was coupled to the immobilized tritylchloride **358**, to yield the resin bound primary amine **359**, which was reacted with various ketones **360** and coumarin-3-carboxylic acid to yield the tri- and tetracyclic derivatives **361**, depending on the R_1 substituent. The products were cleaved from the resin with TFA, to **362**. Thus they were capable of synthesizing polycyclic oxygen-bridged tetrahydropyridones in a one-pot condensation reaction.

Scheme 3.20



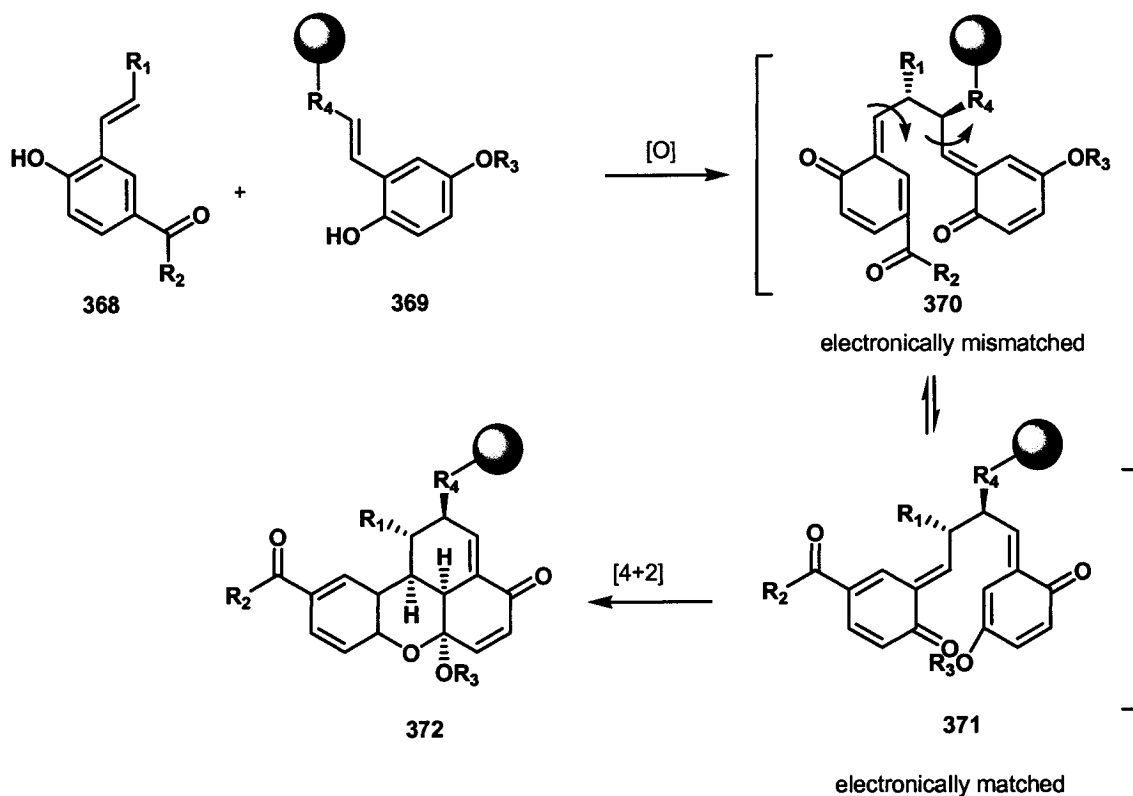
On the other hand Kiselyov and co-workers¹⁰³ used electron-rich olefin substituents in a [4+2] cycloaddition reaction in the presence of a Ytterbium (Yb) catalyst to synthesize tetrahydrochromano[4,3-*b*]quinolines, Scheme 3.21. The resin bound secondary amines **363** were coupled with *p*-nitrobenzoic acid **364**, which was followed by reduction of the nitro- group to yield the anilines **365**. The immobilized anilines **365** were then coupled with electron rich derivatives of salicylic aldehyde **366** in the presence of Yb(OTf)₃ to undergo [4+2] cycloaddition and TFA cleavage to obtain the 1:1 diastereomeric mixtures of the tetrahydrochromanoquinolines **367a** and **367b**.

Scheme 3.21



A solid phase synthesis of Carpanone-like molecules (Scheme 3.22) was achieved by Shair et al.¹⁴ In their synthesis, they used electronically differentiated *o*-hydroxy styrenes in a one-step reaction sequence to construct the carpanone scaffolds. The less reactive, electron deficient phenols **368** were made to react with more reactive, electron rich phenols which were immobilized on solid support **369** under oxidative conditions of $\text{PhI}(\text{OAc})_2$. The heterocoupling of the phenols were observed over homocoupling, giving rise to two possible transition states **370** and **371**. The reaction appeared to proceed via the stable Diels-Alder transition state **371**, leading to the generation of the tetracyclic scaffolds **372**. Removal of the resin and analysis of the structure proved that the scaffold had been synthesized as a single isomer, indicating complete control of the inverse electron demand [4+2] cycloaddition reaction.

Scheme 3.22



3.6 Our Approach to Amino Acid Based Lactones

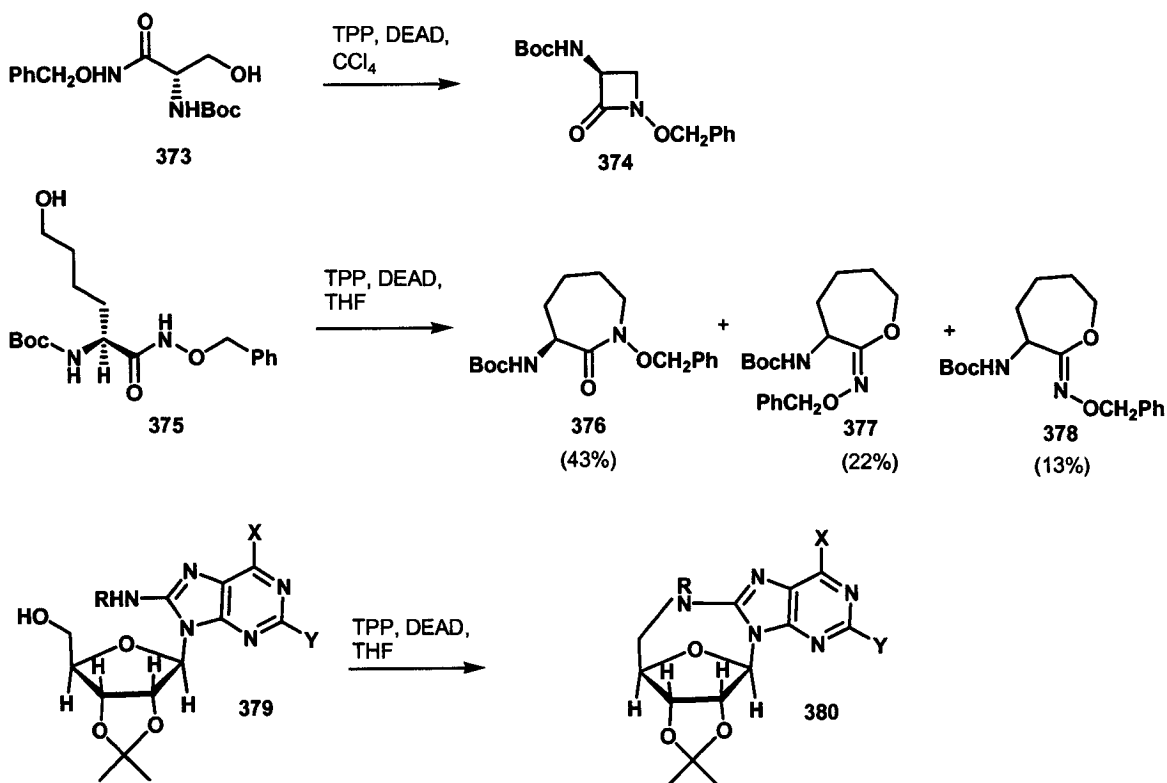
The synthetic strategies considered were in three folds: use of (1) Mitsunobu chemistry to synthesize *cis*- **72** and *trans*-fused lactones **73**, (2) -OMs, mesylate based leaving group chemistry to synthesize *cis*-fused lactones **72**, and (3) a reductive amination based strategy to synthesize *trans*-fused lactones **73**.

3.6.1 Intramolecular Mitsunobu Approach^{104,105}

The reactive moieties of the Mitsunobu reaction are the alcohol and the nucleophile. The nucleophile was an amine functionality in this case. Apart from this a few generalities exists. For most of the Mitsunobu reactions, the solvent of choice has been THF, although other solvents such as dioxane, dichloromethane, benzene etc., have been used. In most cases triphenylphosphine (TPP) has been used to activate the hydroxyl group, together with diethyl or diisopropyl azodicarboxylates (DEAD and DIAD respectively). The temperature is generally maintained around 0 °C to room temperature. The order of adding the reagents are of importance as DEAD is a strong oxidant, Michael acceptor and dienophile and therefore no excess of DEAD should be present in the reaction. Hence, TPP, alcohol and the nucleophile are first dissolved in the solvent and the DEAD added in a dropwise manner at the end.

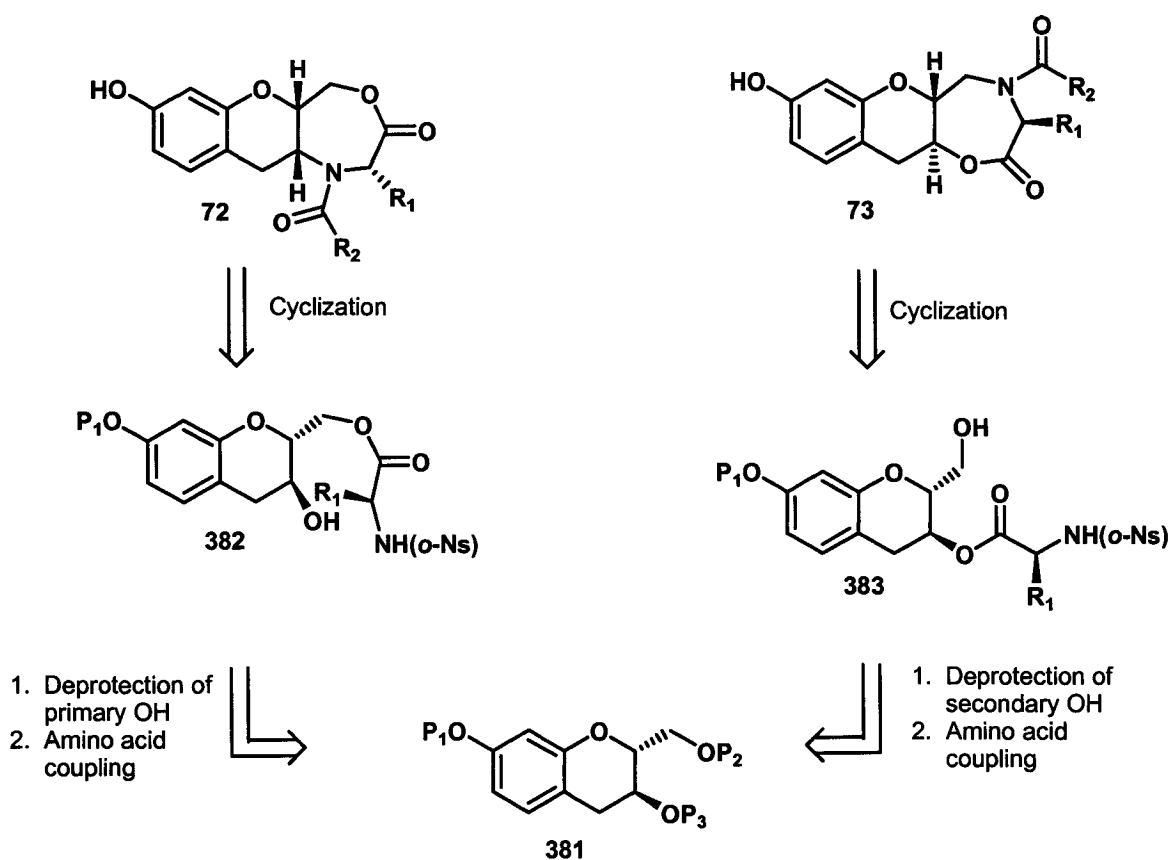
There are many literature examples of using the Mitsunobu approach for the synthesis of small and medium sized lactone rings. Mitsunobu reaction used in D. F. Floyds' synthesis of monobactams **374**,¹⁰⁶ M. J. Millers' synthesis of mycobatins: S2 and cobactin¹⁰⁷ **376** and T. K. Minamotos' synthesis of purine 8,5'-imino and substituted cyclonucleosides¹⁰⁸ **380** are taken as examples, Scheme 3.23.

Scheme 3.23



With such literature precedence, the retrosynthetic planning for the synthesis of *cis*- and *trans*-fused lactones are shown in Scheme 3.24. The key intermediate is the orthogonally protected 2H-benzopyran-triol derivative **381**. The selective deprotection of the primary hydroxyl group followed by amino acid coupling would give **382**. The secondary alcohol **382**, upon Mitsunobu cyclization leads to the *cis*-fused tricyclic lactones **72**. Whereas, the selective deprotection of the secondary alcohol, followed by its amino acid coupling yields **383**, and Mitsunobu cyclization would give the *trans*-fused lactones **73**.

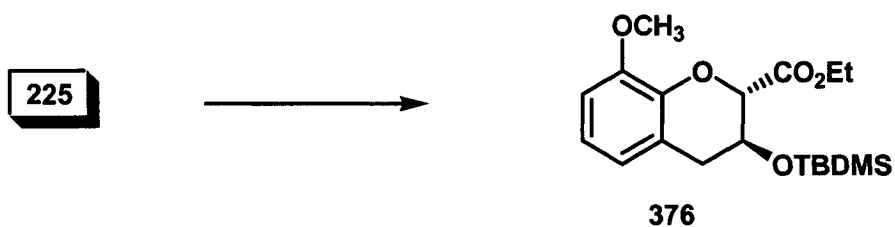
Scheme 3.24



3.6.1.1 Synthesis of *Cis*-fused Amino Acid Lactones (**72**)

The first step was to identify a suitable protecting group for the secondary alcohol. The ideal protecting group was thought to be TBDMS as it is stable under many conditions of acidic, basic, and reduction. At first the TBDMS protection on the model compound **225** was considered, Scheme 3.25, Table 3.1. Attempts to drive the reaction to completion by changing the conditions such as reagent: from less reactive TBDMSCl to more reactive TBDMS(OTf), solvent: less polar CH_2Cl_2 to more polar DMF, or variations in temperature were not very successful. After monitoring the reactions up to an average of 20h for each case only a maximum yield of ~ 50% was observed. Hence it was decided to use the smaller although not as versatile TESCl, with imidazole which gave an excellent yield of 98% (Scheme 3.26).

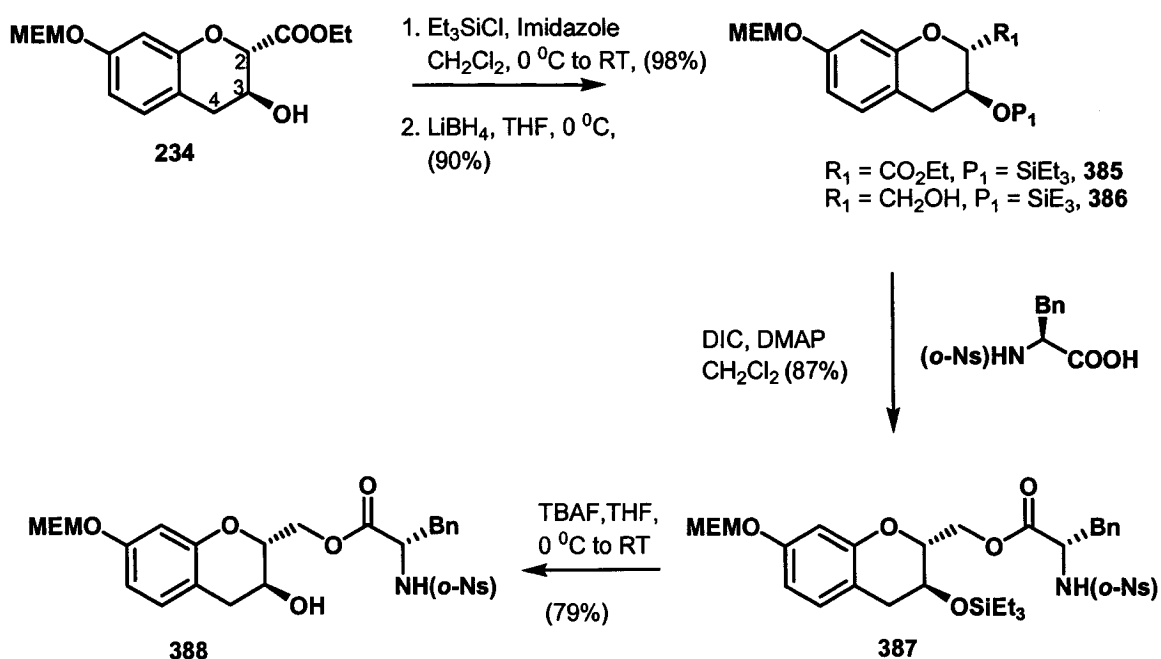
Scheme 3.25

Table 3.1 Silyl protection of secondary hydroxyl from **225** to **376**.

Reagents	Solvent	Temperature °C	Time h	% Yield
1.2 eq. TBDMSCl, 1.5 eq. imidazole	CH ₂ Cl ₂	RT	4h 19.5 h	0
1.2 eq. TBDMSCl, 2 eq. Imidazole, cat. DMP	CH ₂ Cl ₂	RT	20	~10
1 eq. TBDMS(OTf) 2 eq. 2,6-lutidine	CH ₂ Cl ₂	0 to RT	20	~20
1.2 eq. TBDMSCl 1.5 eq. imidazole	DMF	RT	24	~20
2 eq. TBDMS(OTf) 5 eq. 2,6-lutidine	DMF	0 to RT	1 2 20	~30 ~50 ~50
2.4 eq. TBDMSCl 3 eq. Imidazole	DMF	50	2	~30

2 eq. TBDMSCl	DMF	60 to 70	18	~50
2 eq. imidazole				
excess TBDMSCl	DMF	110	18	~50
excess imidazole				

Scheme 3.26



Therefore, the sequence for solution phase organic synthesis was carried out with the MEM phenolic hydroxyl protected bicyclic benzopyran **234**, with TES protection of the secondary hydroxyl group **385**, followed by the reduction of the ester to the primary alcohol **386**, Scheme 3.26. TES protection of the secondary alcohol **385** was confirmed by ^1H NMR, which showed two extra sets of peaks corresponding to the three CH_3 groups at 0.96 ppm (t, $J = 7.9$ Hz, 9H) and the three CH_2 groups at 0.64 ppm (q, $J = 7.9$ Hz, 6H). The formation of the primary alcohol **386** was confirmed by the disappearance of the ester functional group at 1.32 (t, $J = 7.1$ Hz, 3H), and 4.26 ppm (q, $J = 7.1$ Hz, 2H). The appearance of

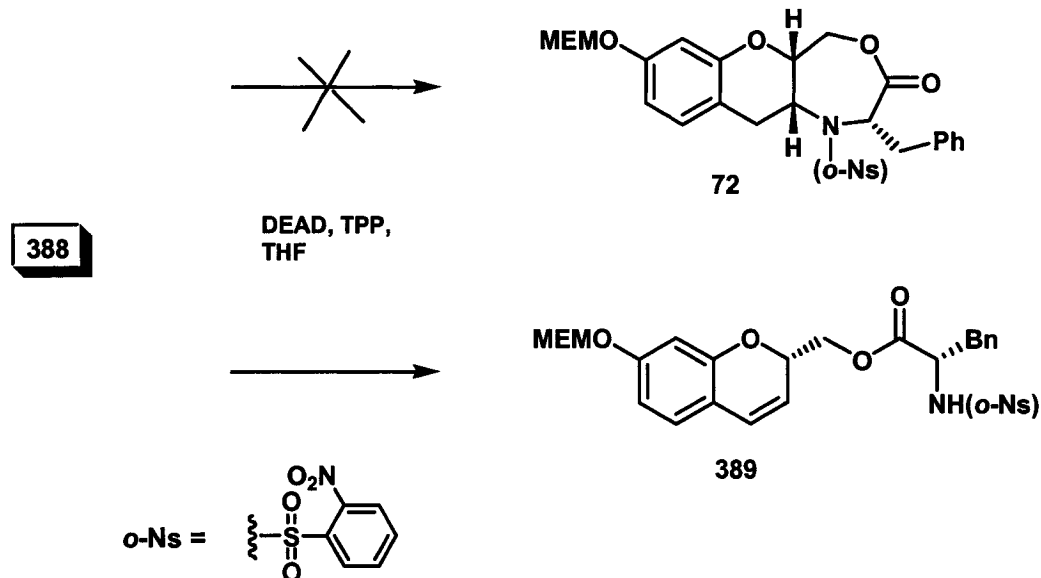
signals corresponding to the hydroxyl group at 2.13 ppm (bs, 1H), and an extra CH₂ group which was diastereotopic between 3.88-3.99 ppm (bm, 1H), and between 4.03-4.09 ppm (m, 2H) further confirmed the synthesis. The latter proton was also confirmed by COSY NMR, which coincided with the ring proton at C-3.

The alcohol **386** was then subjected to amino acid coupling with the more reactive sulfonamide phenylalanine,¹⁰⁹ which was synthesized in our group to yield **387**. The product was confirmed by the disappearance of the alcohol peak at 2.13 ppm and appearance of extra peaks corresponding to the sulfonamide amino acid by ¹H NMR. The sulfonamide amino acid peaks were assigned together with COSY, HSQC and HMBC NMR as follows: CH₂ group between 3.12-3.37 ppm (m, 2H), CH group which is together with the ring C-3 proton between 4.48-4.55 ppm (m, 2H), NH proton at 6.08 ppm (d, J = 8.8, Hz, 1H), and aromatic protons between 7.19-7.23 ppm (m, 5H), 7.60-7.63 ppm (m, 2H), 7.83-7.86 (m, 1H), and 7.97-7.99 ppm (m, 1H). Facile silyl deprotection gave the secondary alcohol **388**. The disappearance of the up field signals corresponding to the TES group confirmed the product formation.

The conditions were now set for the final step of cyclization under Mitsunobu conditions, with DEAD, TPP and THF, Scheme 3.27. The reaction was started at low temperature of 0 °C, and within 0.5 h of reaction time a new spot very high on the TLC plate was detected. Hence reaction was quenched and the products were isolated. Analysis of products by mass spectrometry and ¹H NMR analysis Appendix – Spectrum 8, showed the alkene product **389**, over the cyclized tricyclic lactone **72**. Repeated attempts consistently gave the same products. The eliminated product **389**, was identified by disappearance of the characteristic diastereotopic benzylic CH₂ proton signals at 2.88 ppm (dd, J = 15.8, 5.7 Hz, 1H), and 3.18 ppm (d, J = 6.5 Hz, 2H). The appearance of olefin signals for the C-3 proton at 5.33-5.38 ppm (m, 1H), for the C-4 proton at 6.47 ppm (d, J = 24.5 Hz, 1H) in the ¹H NMR spectrum further confirmed the compound as the alkene

389. At this point however, it was decided to proceed on to the synthesis of the *trans*-fused ring **73**.

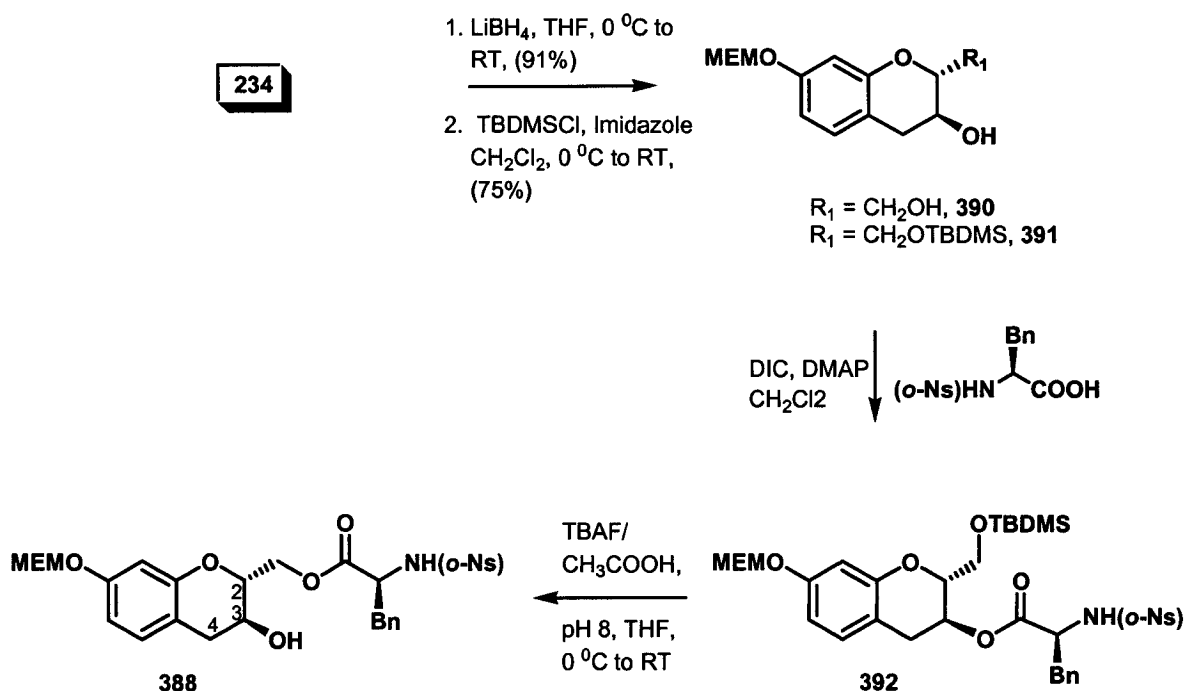
Scheme 3.27



3.6.1.2 Synthesis of *Trans*-fused Amino Acid Lactones (**73**)

For the synthesis of *trans*-fused ring lactones, the ester **234** was first reduced to diol **390**, followed by the selective primary hydroxyl protection with TBDMSCl to **391** Scheme 3.28. Synthesis of the diol was confirmed by ^1H NMR by the disappearance of ester signals at 1.31 ppm (t, $J = 7.1$ Hz, 3H) and at 4.28 ppm (q, $J = 7.1$ Hz, 2H). Extra sets of peaks were observed for the CH_2 protons at C-1 at 4.01 ppm (bs, 2H), and for hydroxyl protons at 2.26 ppm (bs, 1H), and 2.53 ppm (bs, 1H). Hydroxyl protection with TBDMS to yield the secondary alcohol **391** was observed by the two singlet peaks observed at 0.14 ppm for 6H, and 0.94 ppm for 9H, which indicated the presence of two equivalent CH_3 groups and three equivalent CH_3 groups respectively. Although regioselective protection could not be confirmed at this point, it was assumed that the primary hydroxyl group was selective protected as it is more reactive than the more hindered secondary hydroxyl group.

Scheme 3.28



The secondary hydroxyl group was then coupled with the sulfonamide amino acid, phenylalanine, to obtain the amino acid conjugate **392**. The ^1H NMR spectrum of **392** showed characteristic peaks of the amino acid corresponding to ester formation as follows: the diastereotopic C-4 CH_2 group at 3.07 ppm (dd, $J = 13.7, 6.7\text{ Hz}$, 1H) and 3.15 ppm (dd, $J = 13.9, 5.8\text{ Hz}$, 1H), CH proton at 4.45 ppm (q, $J = 7.1\text{ Hz}$, 1H), NH proton at 5.98 ppm (d, $J = 8.7\text{ Hz}$, 1H) and the aromatic signals between 7.10-7.24 ppm (m, 5H), 7.61-7.73 ppm (m, 2H), 7.78 ppm (d, $J = 6.8\text{ Hz}$, 1H) and 7.94 ppm (d, $J = 6.3\text{ Hz}$, 1H). Coupling from the secondary hydroxyl group was confirmed at this point by a HMBC experiment which showed long range coupling between the proton at C-3 that appears at 5.15 ppm (q, $J = 4.9\text{ Hz}$, 1H), with the ester carbonyl carbon at 170.1 ppm in the ^{13}C NMR spectrum. Hence the previous assumption of selective TBDMS protection of the primary hydroxyl group was proven correct.

The amino acid conjugate derivative **392** was then subjected to silyl deprotection at $0\text{ }^\circ\text{C}$, at pH = 8. Unfortunately, however, the observed product was the *trans*-esterified alcohol **388**. The secondary hydroxyl group was confirmed by the

disappearance of the characteristic peaks corresponding to the TBDMS group, which appeared at 0.02 ppm (s, 6H), and at 0.86 ppm (s, 9H) in **392**. The *trans*-esterification was confirmed by a HMBC NMR experiment that showed long range coupling between the diastereotopic CH₂ protons at C-1, which appeared at 4.24 ppm (dd, J = 12.2, 1.8 Hz, 1H), and 4.36 ppm (dd, J = 15.8, 7.4 Hz, 1H), with the ester carbonyl proton at 170.4 ppm in the ¹³C NMR spectrum. Lowering the temperature further resulted in longer reaction time with the same end result. Hence, this approach to synthesize the *trans*-fused tricyclic lactone rings using a Mitsunobu cyclization strategy had to be abandoned.

3.6.2 Leaving Group Approach to Synthesize *Cis*-fused Amino Acid Lactones (**72**)

After having unsuccessful attempts for the formation of the tricyclic derivative by a Mitsunobu cyclization approach, an alternative strategy (i.e. cyclization via a leaving group)¹⁰⁵ was considered. Thus the secondary hydroxyl group in compound **388** was subject to mesylation giving the O-mesyl derivative **393** (Scheme 3.29). Mesylation was confirmed by the multiplet observed for the CH₃ protons of the mesityl group in the ¹H NMR between 3.06-3.16 ppm, which however integrated for 7-protons. A COSY and a HMQC NMR experiment confirmed that 4-protons of this peak corresponded to two CH₂ groups: one CH₂ group at C-4, and of the amino acid side chain. Attempts to cyclize **393** under various conditions Table 3.2, once again proved unsuccessful resulting in either recovered starting material, or elimination and other degraded products.

Scheme 3.29

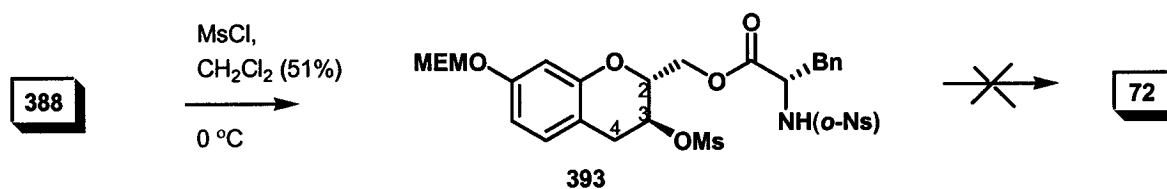


Table 3.2 Cyclization of mesylated secondary alcohol **393** to **72**.

Base	Solvent	Temperature 0°C	Time h	% Yield
TEA	CH ₂ Cl ₂	RT	24	0
DBU	CH ₂ Cl ₂	RT	~50	0
DBU	THF	RT	~24	0
DBU	DMF	RT	2	0
		40	2	0
		60	2 to 4	0
			~16	Decomposed

3.6.3 Reductive Amination Approach to Synthesize *Trans*-fused Amino Acid Lactones (**73**)

As a final attempt it was decided to use a more traditional approach to synthesize amino acid lactones by reductive amination. The first challenge of the approach was to synthesize the aldehyde derivative of the 2H-benzopyran **394**, (Scheme 3.30), without epimerization. Oxidation was carried out in neutral, acidic and basic conditions, Table 3.3, and the basic conditions of SO₃•Py oxidation gave the most successful result. The formation of the aldehyde was confirmed by ¹H NMR, by the disappearance of the signal corresponding to the hydroxyl proton of the alcohol at 2.13 ppm (bs, 1H), and the appearance of a peak downfield at 9.81 ppm (s, 1H). The latter is a typical proton chemical shift observed for aldehyde protons. The oxidation to the aldehyde **394** was further confirmed by HMQC and ¹³C NMR which gave the corresponding carbon signal at 199.8 ppm, typical for

Scheme 3.30

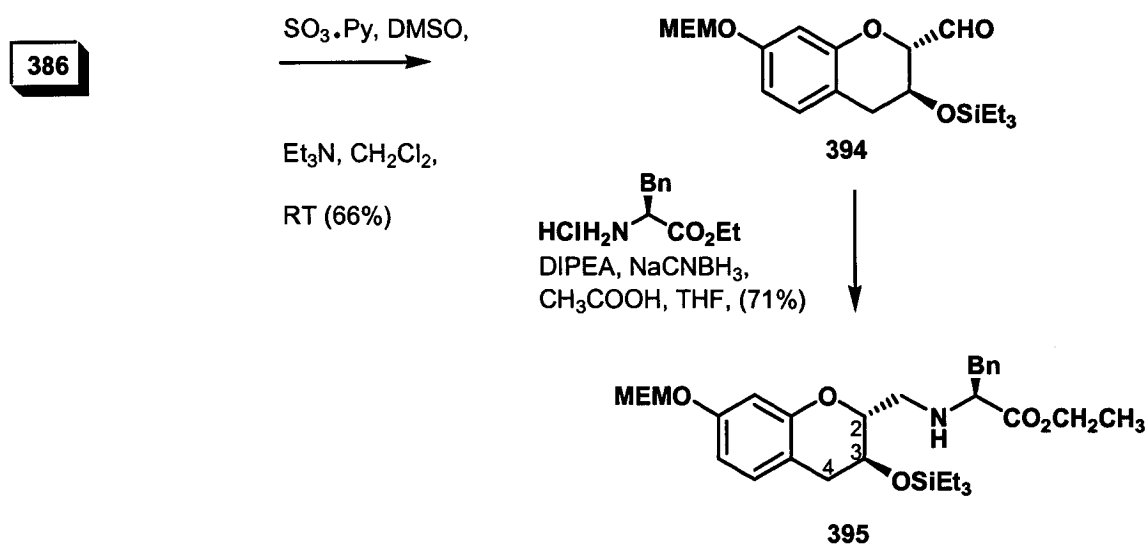


Table 3.3 Oxidation of primary alcohol **386** to aldehyde **394**.

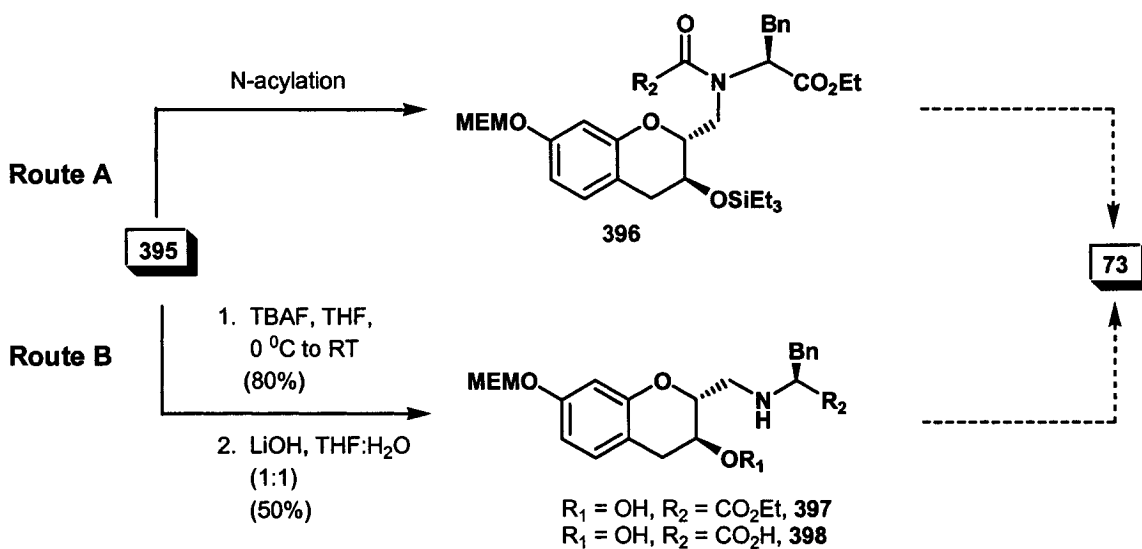
Reaction	Reagents	Temperature °C	Time h	% Yield
Swern Oxidation	Step 1: 3 eq. DMSO,	- 78 to RT	1	0
	1.2 eq. oxalyl chloride, CH_2Cl_2			
	Step 2: 6.2 eq. TEA	- 78 to RT	1	
PDC Oxidation	2 eq. PDC, CH_2Cl_2	RT	2	0
$\text{SO}_3 \cdot \text{Py}$ Oxidation	excess DMSO, 5 eq. TEA, 4 eq. $\text{SO}_3 \cdot \text{Py}$ complex, CH_2Cl_2	RT	2.5	66

carbonyl carbons. It was also noted that depending on the variation in the reaction time by 0.5h could lead to the epimerization of the aldehyde in a 3:1 ratio, based on ^1H NMR analysis.

The aldehyde **394** was then reductively alkylated to the amino acid ester **395**. Alkylation was confirmed by the disappearance of the aldehyde proton signal at 9.81 ppm of the ^1H NMR spectrum as well as the appearance of the signals corresponding to the amino acid. For instance peaks were observed for the reduced carbonyl functionality as diastereotopic CH_2 protons, as two sets of doublet of doublets at 2.80 ppm ($J = 12.1, 5.9$ Hz, 1H) and at 3.11 ppm ($J = 12.1, 3.0$ Hz, 1H). The signals corresponding to the amino acid were observed as, CH proton as a multiplet between 3.54-3.60 ppm (3H) which appears together with the MEM CH_2 protons, CH_2 protons of the benzyl group as a doublet at 2.99 ppm ($J = 7.1$ Hz, 2H), the CH_2 protons of the ester as a triplet at 1.18 ppm ($J = 7.1$ Hz, 3H) and the CH_3 protons of the ester as a quartet at 4.13 ppm ($J = 7.1$ Hz, 2H).

At this point it was thought to investigate two options: Route A – derivatization of amine, followed by cyclization or, Route B: direct cyclization to the lactone followed by derivatization of the amine **73**, Scheme 3.31. We proceeded first on Route A, to acylate the secondary amine **395** to **396** according to Table 3.4. Preliminary NMR analysis of ^1H , COSY and HSQC indicated that acetylation was possible, with $\text{R}_1 = \text{CH}_3$ in **396**. The HMBC experiment showed long-range coupling of the CH_2 group with carbonyl of the CH_3CO group. The yield of route A was poor and therefore, proceeded on to Route B. The first step in this route was the silyl deprotection to alcohol. Although deprotection was achieved with success to give **397**, the ^1H NMR showed two sets of peaks. The result indicated epimerization of proton flanked by the -NH, -Bn and the $-\text{CO}_2\text{Et}$ groups of the alcohol **397**. The product was, however, identified by the disappearance of the peaks corresponding to the TES group at 0.56 ppm (q, $J = 7.7$ Hz, 6H), and at 0.93 ppm (t, $J = 7.9$ Hz, 9H).

Scheme 3.31

Table 3.4 Acylation of secondary amine **395** to **396**

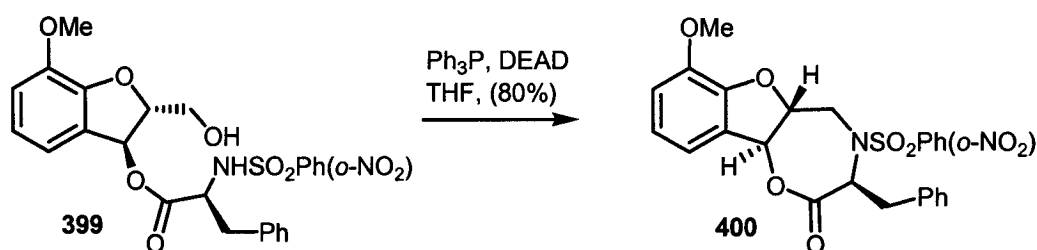
Reagents	Temperature °C	Time h	% Yield
1.2 eq. acetic anhydride, 1.5 eq. TEA, cat. DMAP	0 to RT	3 24	~10
2.5 eq. acetic anhydride, 4.2 eq. TEA, cat. DMAP	0 to RT	17	~25
2.4 eq. benzoic acid, 3 eq. HATU, 6 eq. DIPEA	0 to RT	2.5 24	0
1.5 eq. p-toluic acid, 1.5 eq. HOBt, 1.5 eq. DIC, 3 eq. DIPEA	RT	6.5 24	0
1.2 eq. acetyl chloride, 1.2 eq. TEA, cat. DMAP	0 to RT	2.5 24	Decomposed

Further, the base hydrolysis with LiOH was also attempted but proved to be low yielding. The ^1H NMR of the crude product did not show the peaks corresponding to ethyl ester functional groups CH_3 and CH_2 between 1.16-1.35 ppm and 4.04-4.11 ppm respectively. All other peaks remained as per compound **397**. The result thus indicate the possibility of formation of the acid **398**, however, further studies are required to confirm the product.

3.7 Concluding Remarks

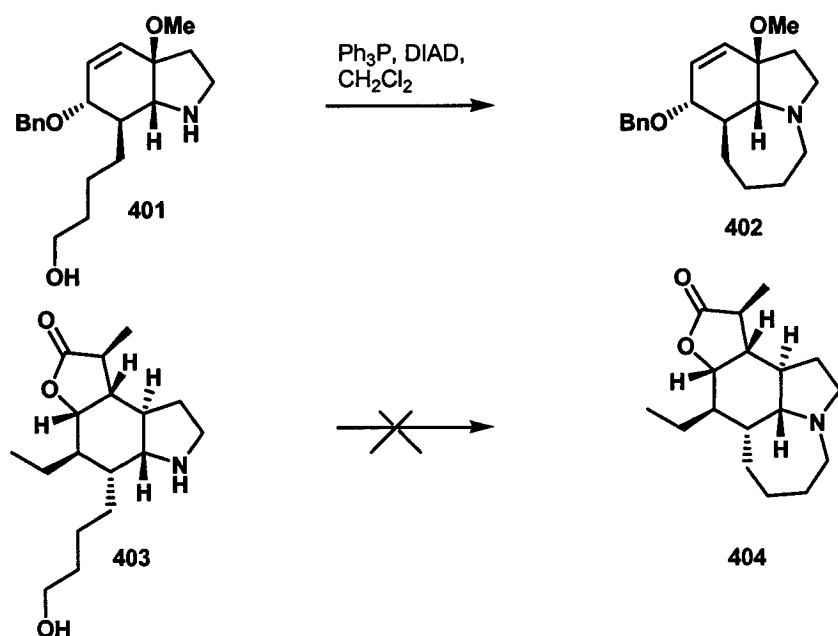
The Mitsunobu strategy has been successfully used in our group to synthesize both *cis*- and *trans*-fused rings **400** on benzofuran based amino acid lactones.⁷⁷ Scheme 3.32 illustrates the *trans*-fused ring formation. Therefore, we were quite optimistic in the initial strategy of using Mitsunobu chemistry to obtain the tricyclic derivative. However, the outcome of this reaction with the benzopyran scaffold was not successful and led to eliminated products over the cyclized products. There is however, literature precedence of such behaviour with regard to Mitsunobu chemistry. One such example was reported by Wipf et al.,¹¹⁰ in their synthesis of (-)-stenine, where cyclization worked for the model **401** to **402**, but not for (-)-stenine itself **404** (Scheme 3.33). Formation of medium size ring by Mitsunobu reaction depends on the rate of cyclization versus side reactions of the activated alcohol. Hence the authors believed that compound **401** was more pre-organized towards the formation of the 7-membered ring than **403**.

Scheme 3.32



A similar argument can be said about the results observed in this study, where the benzofuran based scaffold **399** undergoes cyclization to **400**, but not the benzopyran based scaffold **388** to **72** (Scheme 3.27). The outcome of our study suggests that the presence of the benzylic protons (i.e. prone to elimination) may be playing a pivotal role in the third ring lactone cyclization. The leaving group strategy which is similar to the Mitsunobu approach, also proved unsuccessful. These strategies however, provided a wealth of information, which could be used to smoothen out the path for the future.

Scheme 3.33



The potential, however exists to make the third ring by the reductive amination/lactonization. The reaction sequence is rather long. On the other hand, one could also construct a bicyclic library of compounds based on the benzopyran core with numerous natural and synthetic amino acids for biological testing.

4. SYNTHESIS OF TRICYCLIC POLYETHERS/POLYPHENOLS

4.1 Diversity by Polyethers/Polyphenols

The next objective of the project was to synthesize polyethers **541** (Scheme 4.15) and polyphenols **542** (Scheme 4.15) as extensions to the 2H-benzopyran scaffolds **71**, Scheme 1.6. Polyethers such as brevetoxins (Section 4.2.1), ciguatoxins (Section 4.2.2), and laurencin (Section 4.2.3) have been shown to have extensive biological activities. They have highly complex structures, making it quite a challenge to synthesize. Hence it was thought that extensions to the privileged structure based 2H-benzopyran scaffold via ether and lactone linkages to give rise to six-six, six-seven and six-eight polycyclic ring systems (Section 4.4) would be interesting to explore their biological responses. Such fused ring systems could therefore be used to perform diversity oriented synthesis (DOS), and biological testing.

Medium sized rings of this nature are considered to be rather unstable making them quite a challenge to synthesize, as discussed in Section 4.3.2. There are many strategies in the literature for the synthesis of such ring systems (Section 4.2). The approach taken in this study was the ring closing metathesis (RCM) reaction (Sections 4.3 and 4.4). The catalysts considered were the Grubbs' first and second generation catalysts **468a** (Section 4.3.1) and **470** (Section 4.3.1) respectively. Although RCM has been utilized in the synthesis of medium sized polyphenolic ring derivatives (Section 4.3.3), there are not many examples known in the literature where RCM has been a useful approach to obtain polyphenolic-based polycyclics. Some requirements and challenges of RCM reaction are therefore discussed in Section 4.3.4.

Synthesis of ether and lactone based polyphenolics around the privileged scaffold 2H-benzopyran via the RCM reaction gives rise to potential sites for exploring diversity oriented reactions (Section 4.5). The alkene moiety is one site that one could perform stereoselective reactions, such as epoxidation reaction.

The facial selectivity could be achieved by the ring conformer (Scheme 4.22). A regioselective ring opening of the epoxide by a nucleophile such as an azide, and its derivatization would thus provide an amine functionality. The hydroxyl and amine moieties can be then used as potential diversification sites in **561** (Scheme 4.22).

In order to generate three-dimensional diversity and a library synthesis around the 2H-benzopyran scaffold one needs to perform the solution phase chemistry prior to undertaking a solid phase project. Preliminary investigations on solid support is discussed in Section 4.6. Two types of resins were used during the study. They were the bromo-Wang resin, **566** and silyl linker resin, **573**.

4.2 Literature Approaches to Polyethers

Many studies have been reported for the synthesis of complex polyethers using various approaches. A few such as K. C. Nicolaou et al., synthesis of brevetoxin B (**13** Schemes 4.1, 4.2 and 4.3),¹¹¹ M. Sasaki et al., partial synthesis of ciguatoxin 1B (**424** Scheme 4.4),¹¹² J. S. Clark et al., partial synthesis of ciguatoxin 3C (**445** Scheme 4.5),¹¹³ and A. B. Holmes et al., synthesis of (+)-laurencin (**453** Scheme 4.6)¹¹⁴ will be highlighted.

4.2.1 Synthesis of Brevetoxin B (**13**)

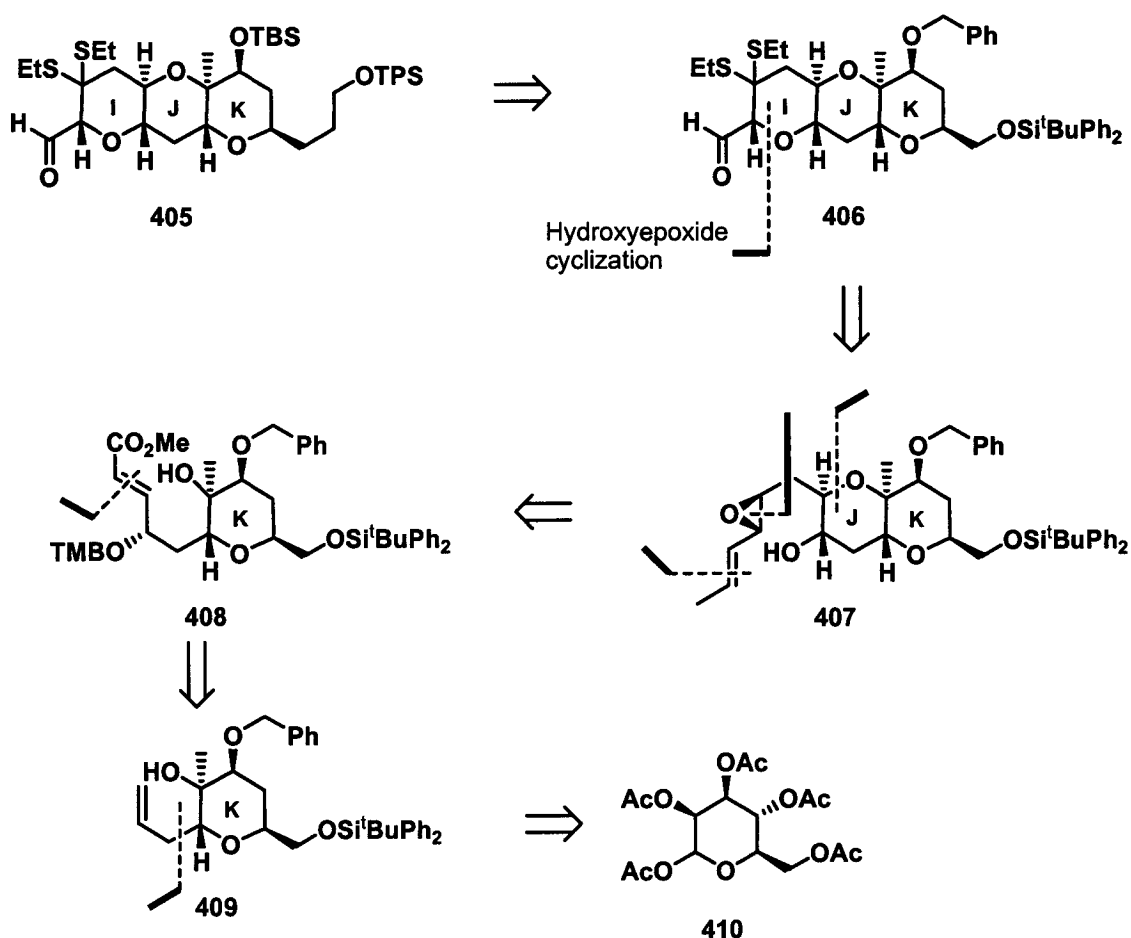
Brevetoxin B, the most prominent member of the brevetoxin family, is a marine natural product, produced by marine alge dinoflagellate *Ptychodiscus brevis* Davis. It has exhibited potent neurotoxic activity by binding to sodium channels. Because of its activity as a biotoxin, brevetoxin B has become the focus of investigation in both chemistry and biology.

The structure of brevetoxin B is highly complex, consisting of ether oxygen atoms, regularly placed on a single carbon chain, giving rise to 11 trans-fused rings, 23 stereogenic centers, and 3 C-C double bonds. The synthetic strategy adopted by Nicolaou and co-workers¹¹⁵ to construct brevetoxin B (**13**) will be

considered. They synthesized brevetoxin in several stages: first the IJK system (Scheme 4.1), followed by DEFG system (Scheme 4.2), extended it to ABCDEFG and the final modifications gave brevetoxin B (Scheme 4.3).

The retrosynthetic analysis for the synthesis of the IJK ring system is outlined in Scheme 4.1. The starting material for the synthesis of the IJK ring system was the chiral starting material D-mannose pentaacetate **410**. This was extended to **409** after derivatization with allyltrimethylsilane and protecting group manipulations. Alkene **409** was then extended further to the Michael precursor

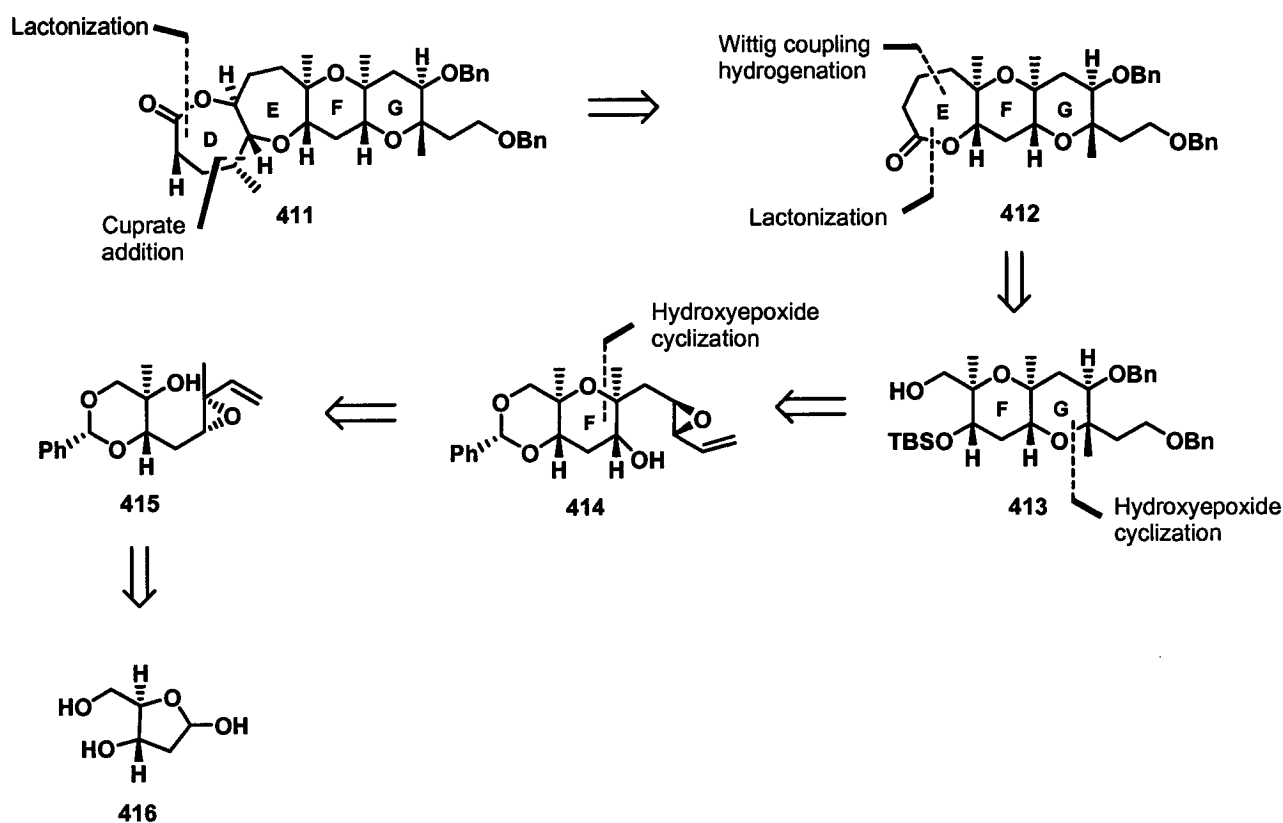
Scheme 4.1¹¹⁶



408 which could subsequently lead to the J ring of **407** on cyclization. The I ring of **406** was constructed via a hydroxyepoxide cyclization which upon protecting group manipulations yielded the IJK ring system **405** of brevetoxin B (**13**).

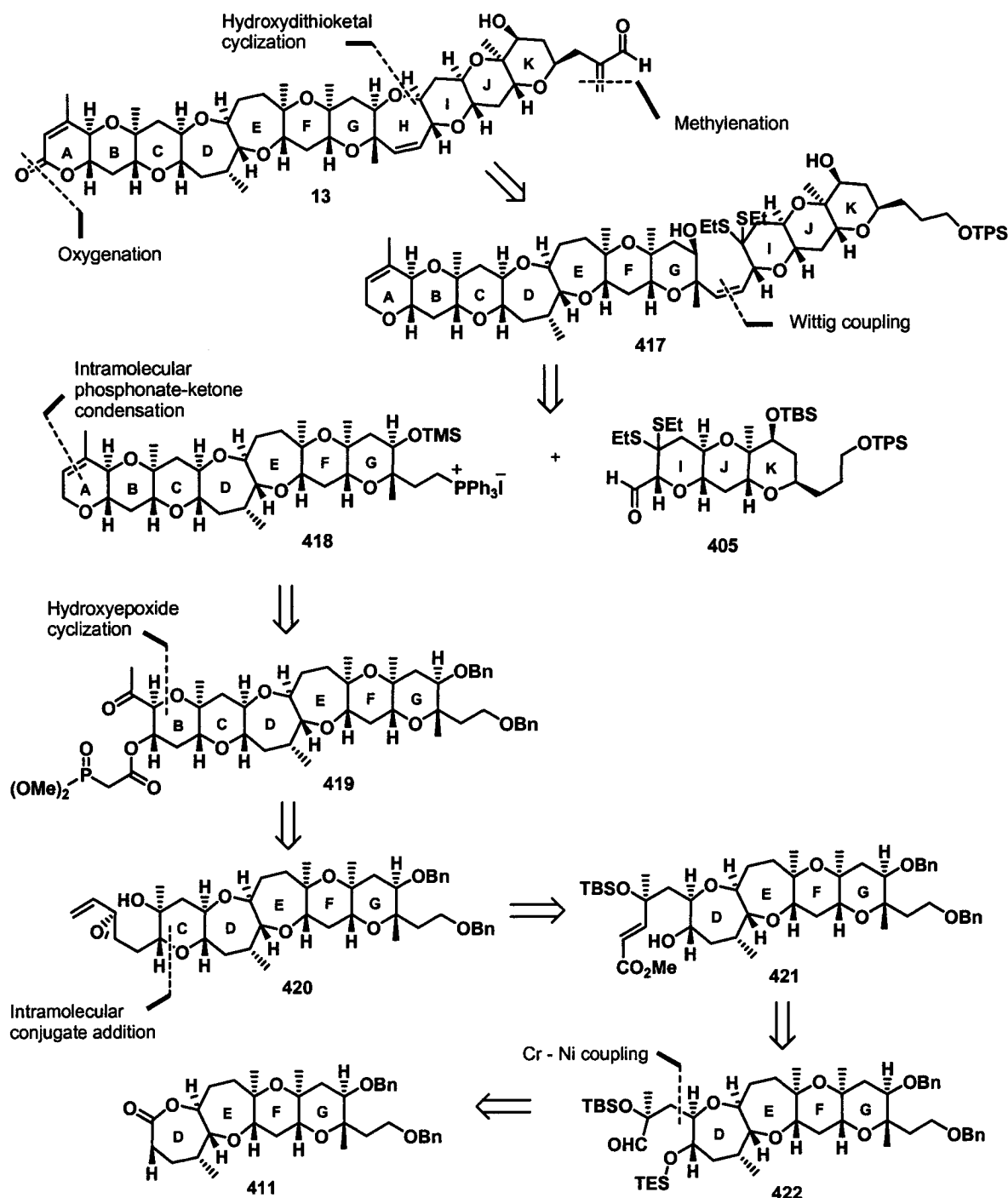
For the synthesis of the DEFG **411** the strategy outlined in Scheme 4.2 was adopted. The synthesis was started with (1) 2-deoxy-D-ribose **416** which was converted to **415** in a number of steps¹¹⁷ (2) hydroxyepoxide cyclization to **414** (3) another hydroxyepoxide cyclization and protecting group manipulations to **413** (4) Swern oxidation, olefination, hydrogenation, desilylation, further oxidation and desilylation followed by lactonization under Yamaguchi protocol resulted in the E ring, **412** (5) derivatization, attachment of a suitable append and another lactonization under Yamaguchi conditions yielded the DEFG system **411**.

Scheme 4.2^{115b}



The synthesis of the ABCDEFG advanced intermediate **418** was derived from DEFG **411** with stepwise extension of the C, B, A rings in that order, Scheme 4.3. The synthesis was carried out as follows: (1) Cr / Ni – based coupling reaction on the D ring to extend the DEFG system **411** to **422** (2) chain extension under

Scheme 4.3^{115c}



Wittig conditions **421**, and an intramolecular conjugate addition to construct the C ring, **420** (3) intramolecular hydroxy epoxide cyclization to construct the B ring **420**, (4) an oxidation, derivatization and Wittig extensions, **419** (5) intramolecular phosphonate-ketone condensation to construct A ring **418**, and the coupling with **405** to give Z-olefin **417** via a Wittig reaction. The final stage involved the (1) deprotection to the hydroxy dithioketal, (2) cyclization of the oxocene H ring, (3) desulfurization and (4) functional group manipulations to yield **13**.

4.2.2 Ciguatoxins

Ciguatoxins (CTX) originates from marine unicellular algae and are principal toxins associated with ciguatera fish poisoning. Similar to the brevetoxins, they too are potent neurotoxins and bind to sodium channels. Their bioactivity and limited availability from natural sources have made ciguatoxins an attractive target for the synthetic chemist. Two synthetic strategies for the partial synthesis of CTX-1B **424** by M. Sasaki et al., (Scheme 4.4)¹¹⁸ and CTX-3C by J. S. Clark et al., (Scheme 4.5)¹¹⁹ have been reported and they will be discussed in this section.

4.2.2.1 Ciguatoxin 1B

In the synthesis of the GHIJKLM ring system **424** of Ciguatoxin CTX-1B (**423**) Sasaki and co-workers used a B-alkyl Suzuki coupling reaction to synthesize the polyether system, Figure 4.1. The key cyclization strategies will be considered in Scheme 4.4. For the synthesis of the G ring they started their synthesis with the methyl α -D-mannopyranoside **425**, which was first converted to the cyclization precursor **426**. This then underwent SmI_2 mediated stereoselective cyclization¹²⁰ to **427**. Compound **427** was further derivatized to **428** to facilitate further coupling reactions at a later stage.

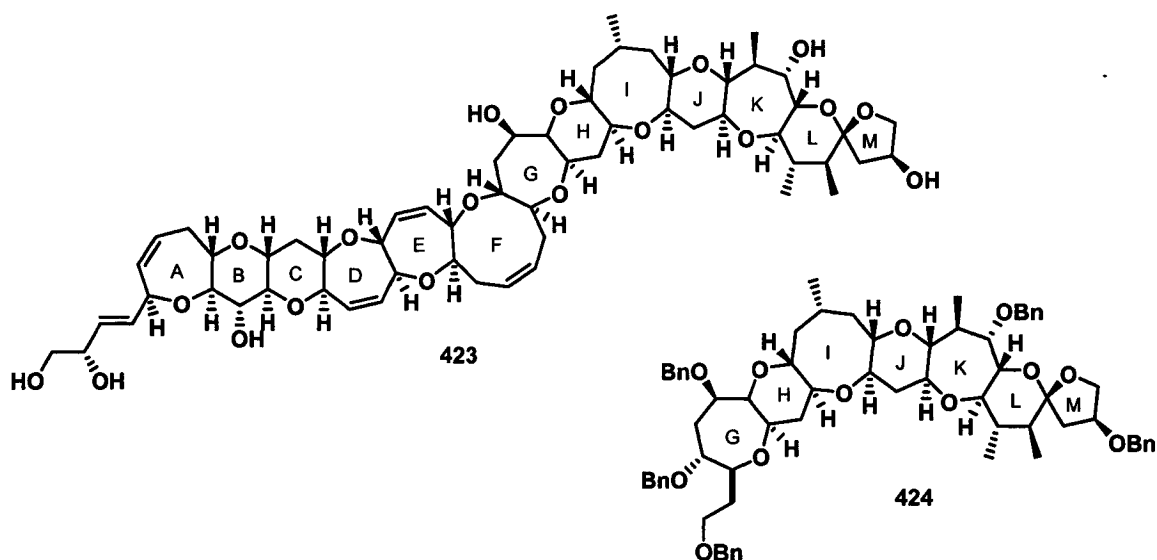
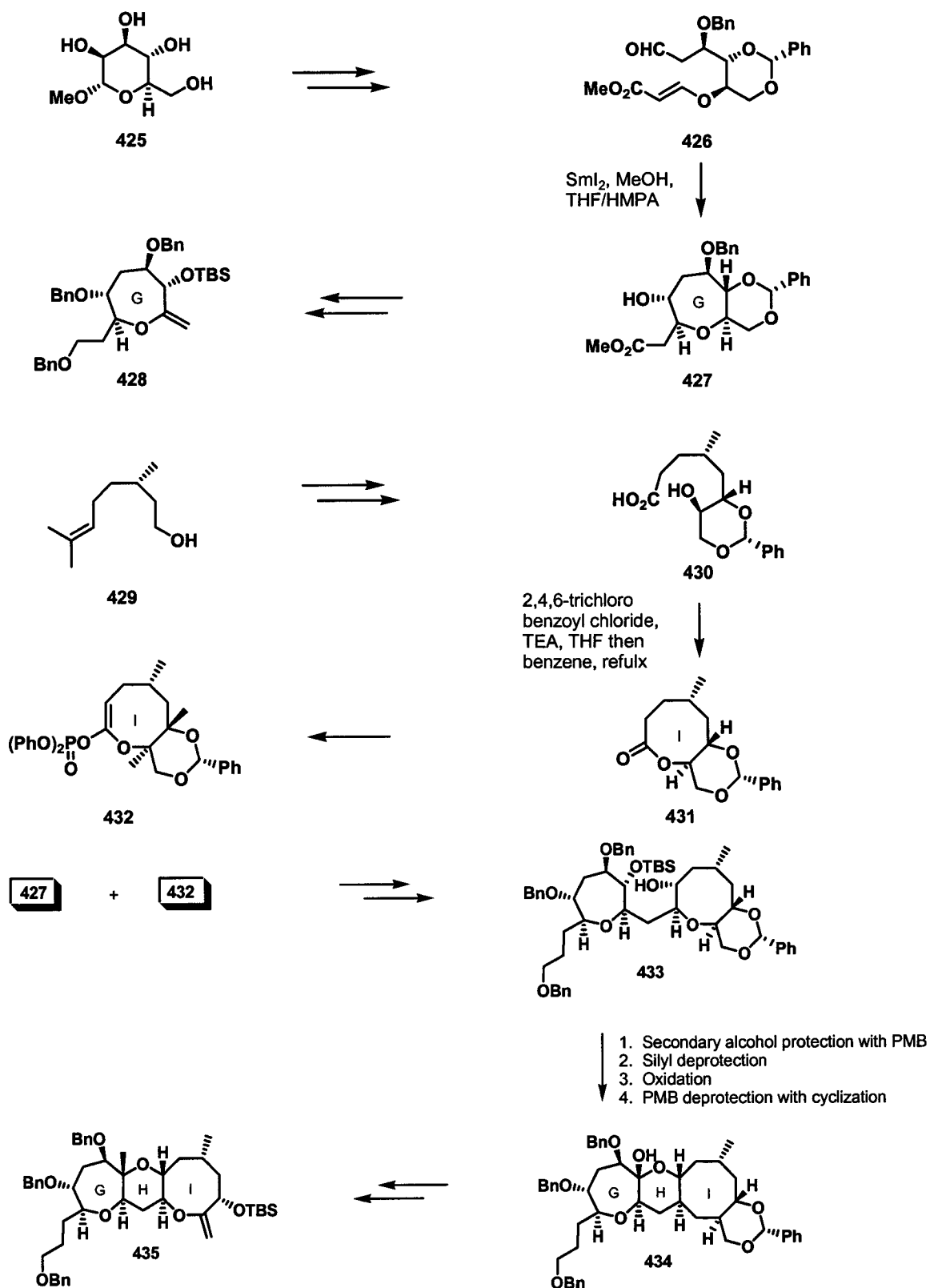


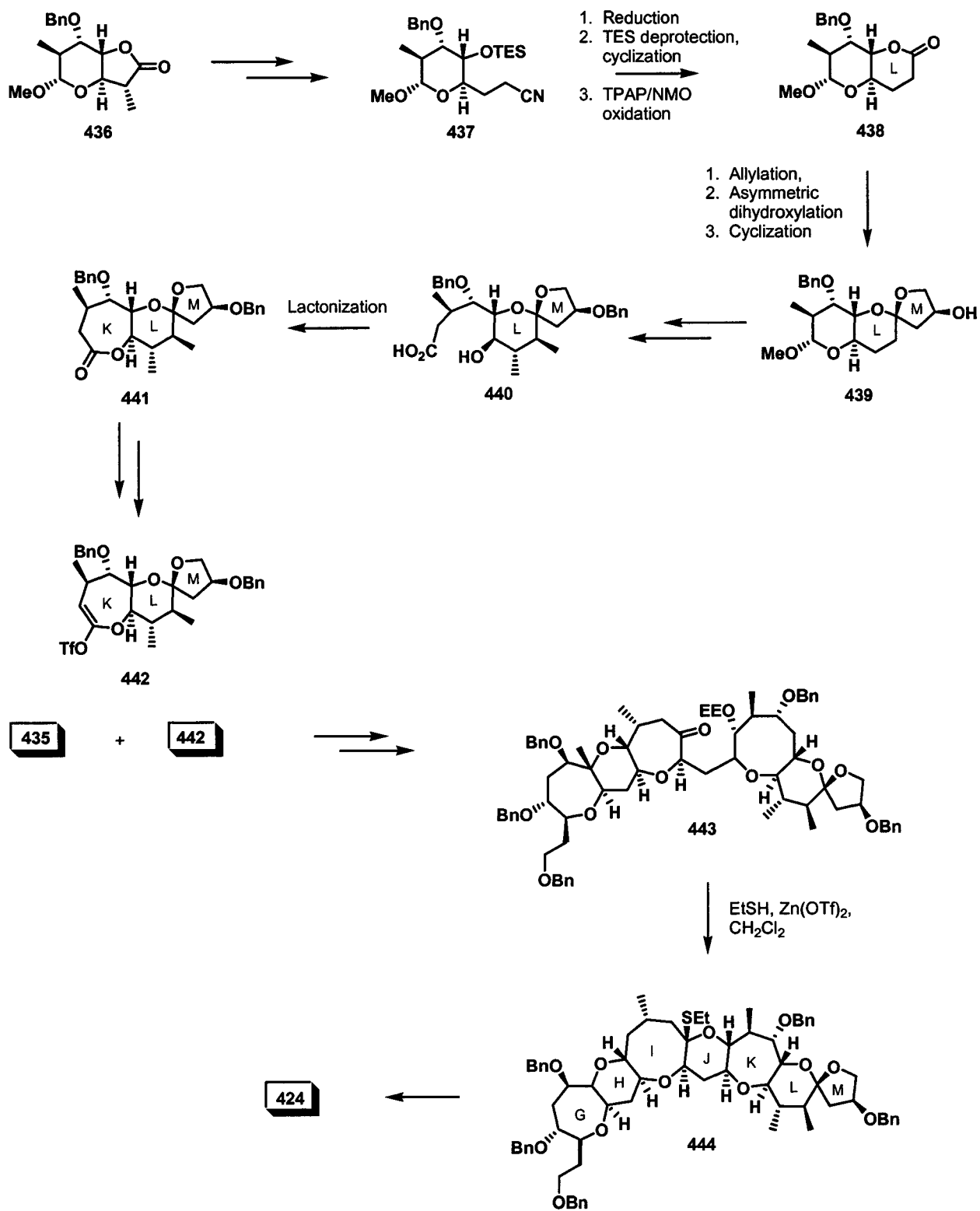
Figure 4.1. Structure of Ciguatoxin CTX-1B (**423**) and the GHIJKLM ring system **424**.

The synthesis of the enol phosphate **432** representing the I ring, was initiated with (S)-(-)-citronellol (**429**). The cyclization of **429** to the I ring **430**, was achieved under Yamaguchi conditions. Derivatization and coupling of precursors **428** and **432** to yield **433** paved the way to the synthesis of the GHI ring system **435** under standard conditions. The KLM ring system **442** was synthesized independently starting with the bicyclic lactone **436**. Formation of the L ring **438** was achieved via the hemiacetal to lactone cyclization under oxidation conditions of TPAP/NMO. The formation of the spiroketal M ring **439** was accomplished by an asymmetric dihydroxylation with Corey's ligand. The crucial step of the synthesis was the B-alkyl Suzuki coupling between the precursors hydroxylated **435** and **442** to eventually yield the GHIJKLM ring system **424**. The J ring was formed by the reaction of **443** with EtSH and $\text{Zn}(\text{OTf})_2$.

Scheme 4.4



Scheme 4.4, cont....



4.2.2.2 Ciguatoxin 3C¹¹⁹

Ciguatoxin CTX-3C (**445**), consists of 13 rings with saturated and unsaturated medium-sized rings. Clark and co-workers adopted the approach of constructing the ABC ring system of CTX-3C (**446**, Figure 4.2), in a two-directional manner. They performed double RCM reactions on allylic ethers, enol ether or alkynyl ether or any other such combinations to construct **446** (Scheme 4.5). They started their synthesis with commercially available tri-*o*-acetyl-D-glucal **447**, which was transformed to the alkene **448**. This was followed by epoxidation, and diastereoselective ring opening with allylmagnesium bromide/ZnCl₂, to yield the alcohol **449**. Further allylation and protecting group manipulations gave the primary triflate **450**. Compound **450** then underwent chain extension upon treatment with trimethylsilylacetylide, TES deprotection and reduction with Lindlar catalyst to yield the alcohol **451**. The alcohol **451** was then converted to the alkynyl ether **452**, which was the precursor for the crucial RCM reaction. A two directional RCM reaction in the presence of Grubbs' catalyst yielded the ABC ring system of CTX-3C, **446**.

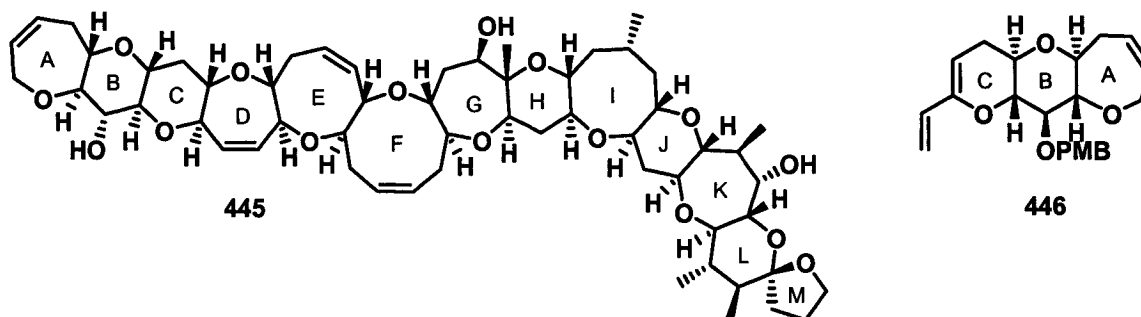
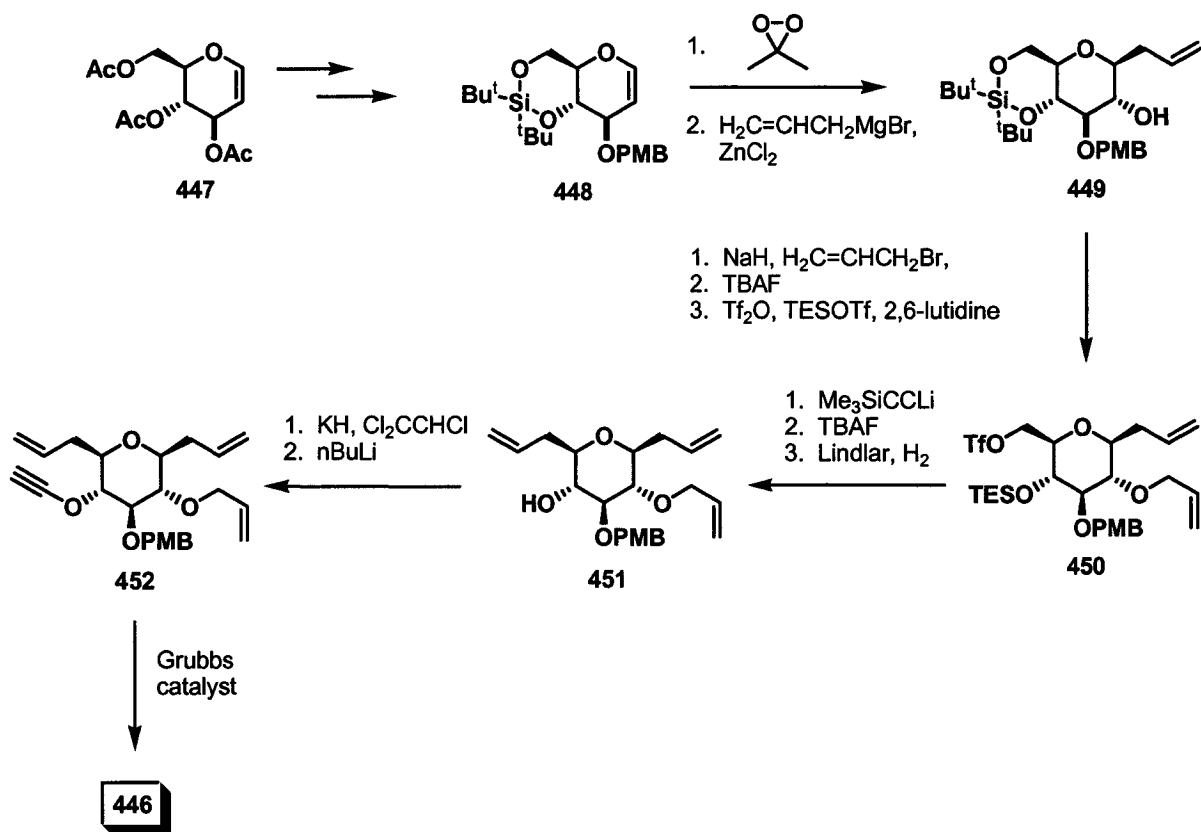


Figure 4.2 Structure of Ciguatoxin CTX-3C **445** and the ABC ring system **446**.

4.2.3 Laurencin

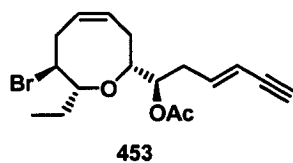
(+)-Laurencin (**453**), an eight membered ring ether, is the prototypical member of marine natural product cyclic ethers isolated from red algae and marine organisms that feed on *Laurencia* species. Many approaches to the synthesis of these types of natural products are reported, the approach taken by

Scheme 4.5

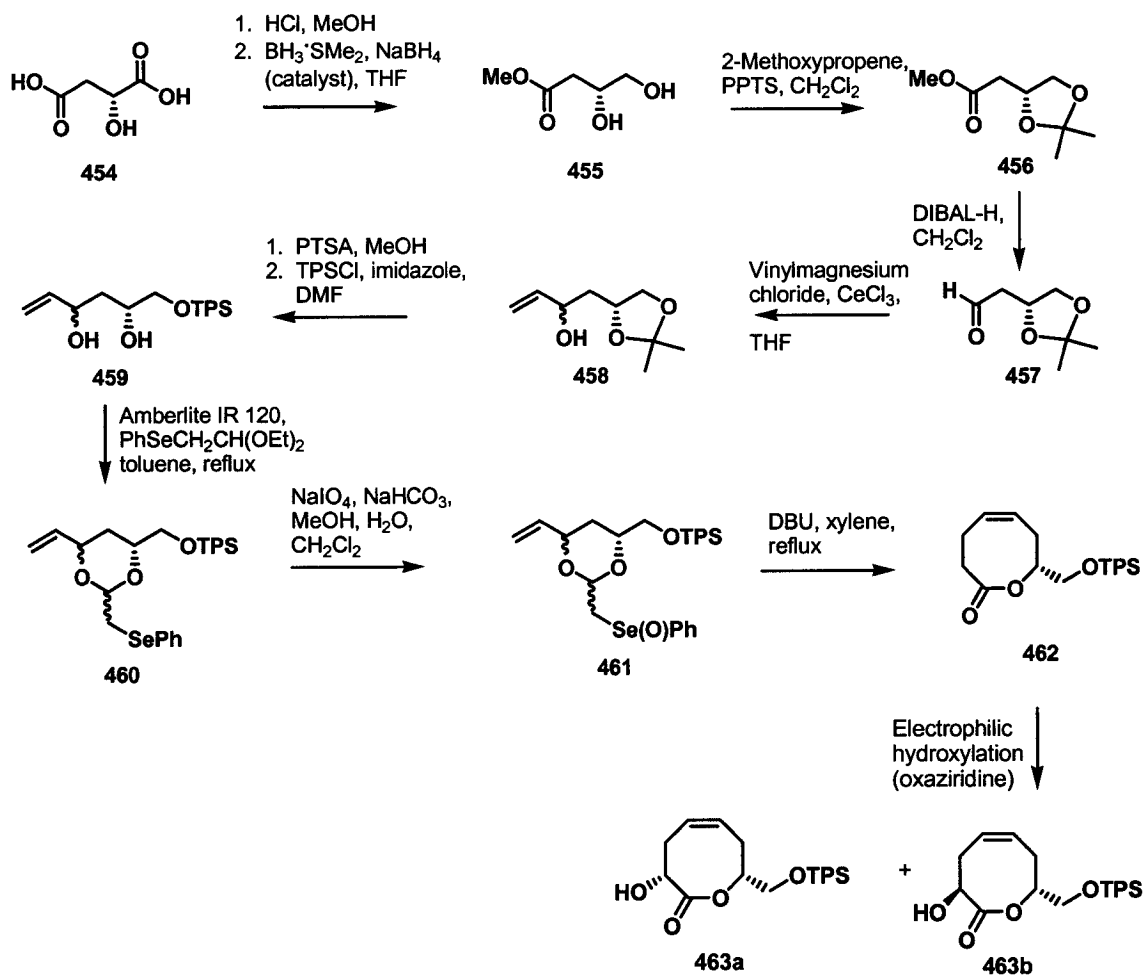


Holmes and co-workers¹¹⁴ will be considered. Their strategy in general was to use ring expansion reactions of cyclic ketones and vinyl substituted ketene acetals to produce saturated and unsaturated medium ring lactones respectively. Lactones thus produced have been extended to 2,*n*-disubstituted cyclic ethers by Tebbe methylenation and subsequent functionalization of the enol ether double bond. The total synthesis of (+)-laurencin (**453**) consisted of 27 steps. The key steps of their synthesis were: (1) methylenation of lactone followed by, (2) intramolecular hydrosilation of enol ether, and (3) one carbon homologation of diol to give the cyclic ether. The lactone **463a** was synthesized by two routes: Route A - a Claisen ring expansion followed by α -hydroxylation, and Route B - by Yamaguchi lactonization, Scheme 4.6. Further elaboration of the (*E*)-pentenyl side chain and introduction of bromine had completed the synthesis of (+)-laurencin (**453**).

Scheme 4.6

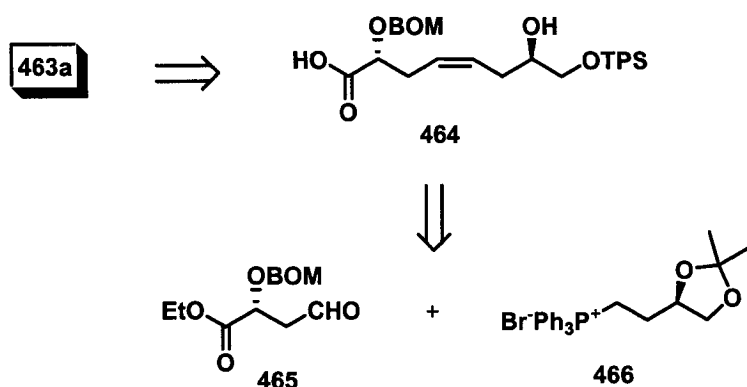


Route A



Scheme 4.6 cont..

Route B



The starting material in route A was the (R)-malic acid **454**, Scheme 4.6. This was esterified and selectively reduced to the diol **455**. It was then protected as the acetonide **456**. This was followed by the reduction of the ester function in **456** to the aldehyde **457** and condensation with vinylmagnesium chloride to yield allylic alcohol **458** as a (1:1) diastereomeric mixture. The isomeric mixture was then subjected to acetonide deprotection, followed by selective protection of the primary alcohols to yield **459**. The alcohols **459** were then converted to the acetals **460**, oxidized to **461**, which then underwent [3,3]-sigmatropic rearrangement to the lactones **462**. The lactones were converted to the alcohols **463a** and **463b** via an enolate hydroxylation reaction with oxaziridine derivative to set up the precursors for the total synthesis of (+)-laurencin (**453**).

The retrosynthetic analysis of the alternate route for the synthesis of the lactone **463a** - route B is outlined in Scheme 4.6. The hydroxy acid **464** was considered as the precursor for the lactonization under Yamaguchi protocol to yield the α -hydroxy lactone **463a**. The cis-alkene **464** was synthesized by Wittig reaction. The corresponding Wittig precursors **465** and **466** were obtained by (R)-malic acid (**454**).

4.3 Ring Closing Metathesis Approach to Polyphenols

4.3.1 Catalyst

The first generation of metathesis catalysts were the “Ziegler-type” catalysts that were used in olefin polymerization reactions. These catalysts however, exhibit high reactivity at the expense of poor compatibility with polar functional groups, due to a strongly Lewis-acidic and alkylating character. Research in organometallic chemistry have led to the discovery of versatile transition metal catalysts. For instance metal alkylidene complexes such as molybdenum alkylidene complexes **467a** and **467b** developed by R. R. Schrock and co-workers,¹²¹ ruthenium carbene complexes **468a** and **468b** developed by R. H. Grubbs and co-workers¹²² and the Tebbe reagent **469** developed by F. N. Tebbe and co-workers,¹²³ Figure 4.3.

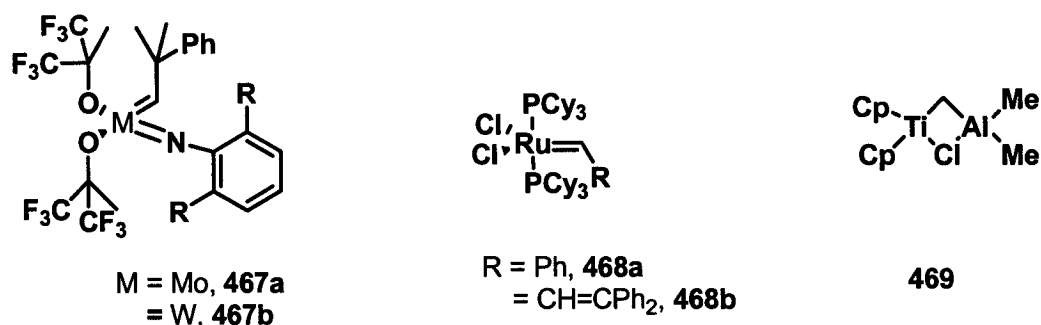


Figure 4.3 Some metathesis catalysts.

4.3.1.1 Schrock's Catalysts^{121,124}

Schrock's tetracoordinate alkylidene complexes **467a** and **467b**, were one of the first developed versatile catalysts used in metathesis reactions. For a long time they were the only metathesis catalyst capable of performing the RCM reaction. Although they are commercially available, they are quite sensitive toward oxygen and moisture and must be handled in rigorously dried solvents using Schlenck techniques. Despite its sensitivity **467a** has been successfully used for the synthesis of strained medium-sized rings, and has shown tolerance towards

generation catalysts, (**470**, **471**, **472**, **473**, Figure 4.4). They exhibit significantly higher activity than the parent carbene catalyst¹²⁶ **468a**, and come close to or even surpass the Schrock's molybdenum catalyst **467a**. They too, are stable to heat, oxygen and moisture, and tolerates a variety of functional groups, making them an extremely versatile tool in metathesis reactions.

The general types of metathesis reactions catalyzed by these types of catalysts include, (1) ring closing metathesis (RCM), **474** $\rightarrow$ **475** (2) ring opening metathesis (ROM), **475** $\rightarrow$ **474** (3) ring opening metathesis polymerization (ROMP), **475** $\rightarrow$ **476** (4) acyclic diene metathesis polymerization (ADMET), **474** $\rightarrow$ **476** and (5) cross metathesis reactions (CM), **477** + **478** $\rightarrow$ **479**, **480**, **481** Figure 4.5. The proposed catalytic cycle for the catalyst during RCM **474** $\rightarrow$ **475** reactions is shown in Figure 4.6. The forward process is entropically favoured as it cuts one substrate molecule into two products. One being a stable volatile substance such as ethylene.

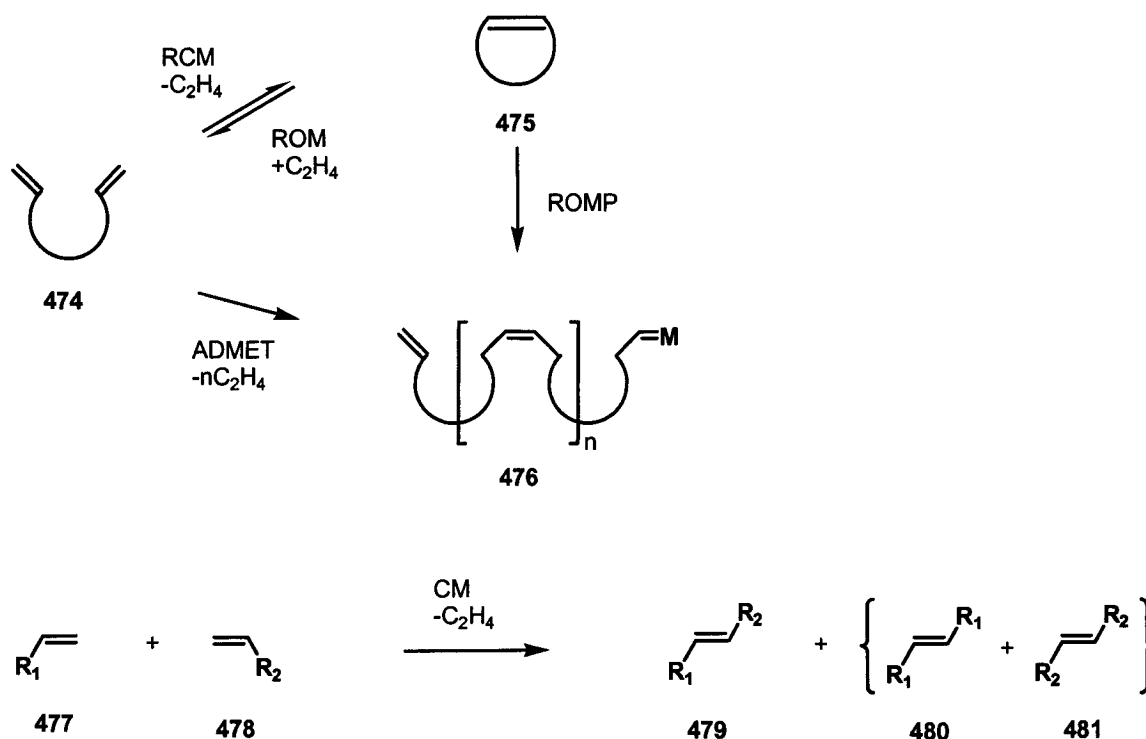


Figure 4.5 General types of metathesis reactions.

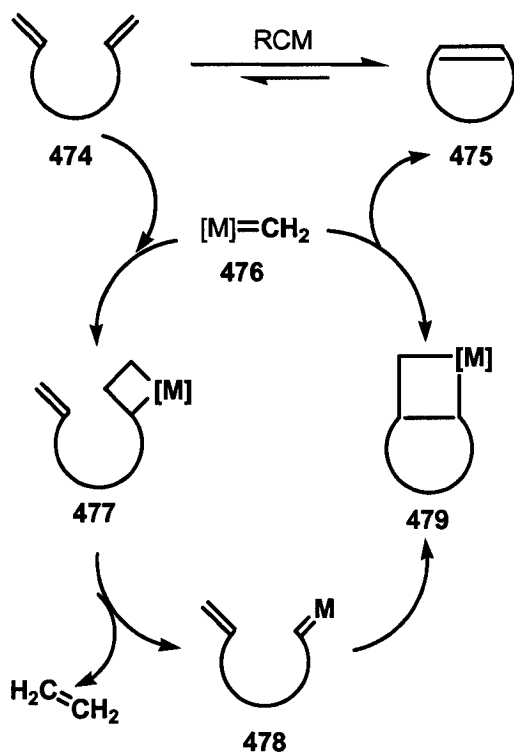


Figure 4.6 Catalytic cycle of RCM reaction

4.3.2 Medium Size Rings¹²⁷

Compounds having a ring size in the range of 8 to 11 atoms are generally defined as medium ring compounds. These types of compounds are reported to be more difficult to synthesize by cyclization methods than macrocyclic compounds (ring size ≥ 12 atoms), due to unfavourable entropy and enthalpy effects. As the carbon chain becomes too long, the probability of the two chain termini to react decreases. This gives rise to an unfavourable entropic effect. The unfavourable enthalpic effects are caused by steric interactions such as, the torsional strain in single bonds, deviation from the ideal bond angles, and transannular strain. The strain of forming medium ring compounds can be related to their heat of formation and their relative strain energy with respect to cyclohexane. For instance the heat of formation of a 6 membered ring is -29.5 kcal/mol, whereas for an 8 membered ring is -29.7 kcal/mol and therefore, not too different. However the strain energy for the 6 membered ring is 0 kcal/mol

and 8 membered ring is 9.6 kcal/mol respectively. The latter constitutes for the difficulty in cyclization of the 8-membered ring.

4.3.3 Literature Approaches to Medium Size Rings via RCM

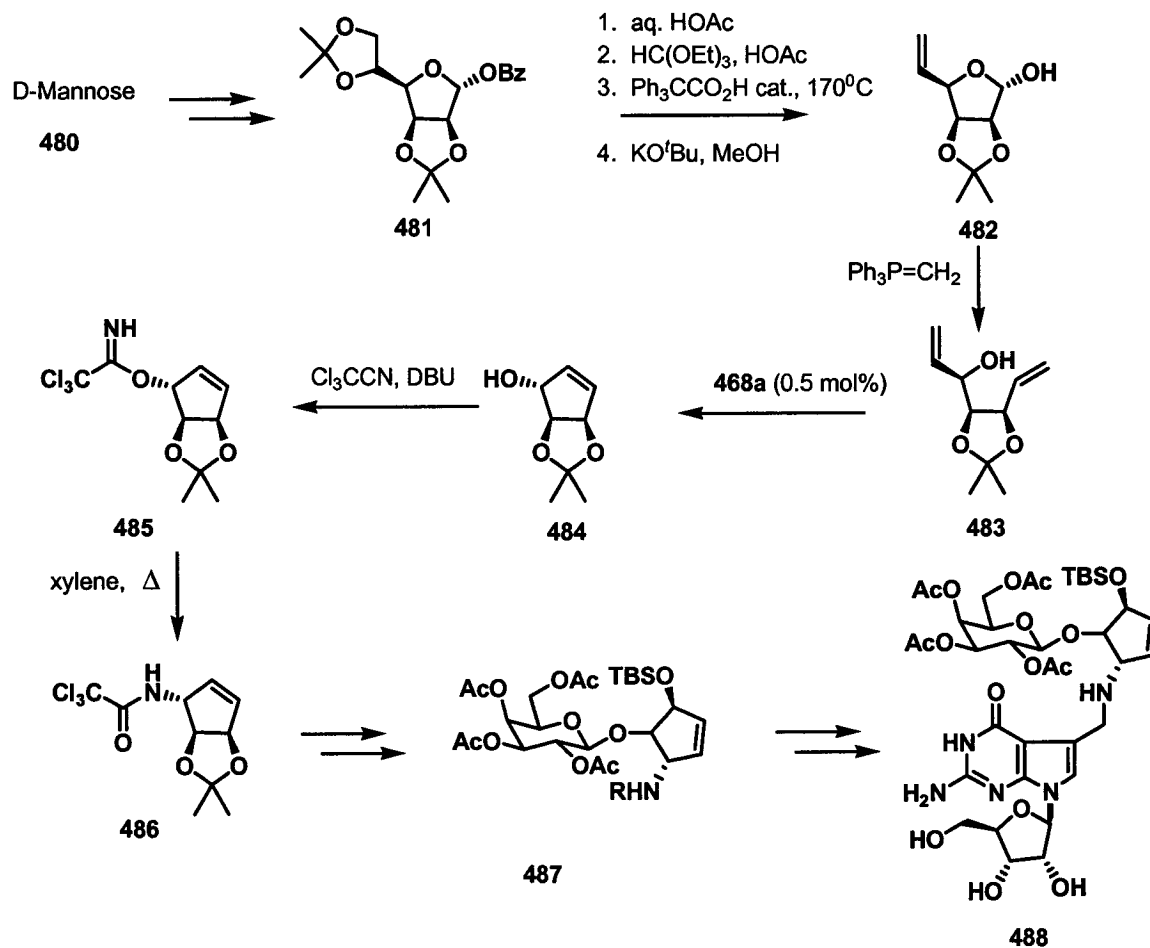
RCM reactions have been extensively used for the synthesis of small, medium and macrocyclic rings, having various types of peripheral functional groups. A few selected applications will be considered in this section.

Polyoxygenated carbocycles derived from carbohydrates have become important because of their biological significance. Therefore, many applications have been reported where sugar-derived dienes were transformed into enantiomerically pure carbocycle derivatives by RCM. For instance the synthesis of unusual cyclopentene moiety of nucleoside Q (**488**, Scheme 4.7), by van Boom and co-workers¹²⁸ is one such example. The mannofuranose derivative **481** had been derived from its parent sugar mannose **480**. An acetal moiety of compound **481** was regioselectively cleaved, which underwent acid catalyzed thermal rearrangement to alkene **482**. The alkene **482** was converted to the dialkene **483** via protecting group manipulations and Wittig reaction. The RCM precursor **483** was converted to the cyclopentene **484** with Grubbs first generation catalyst **468a**. Further derivatizations and protecting group manipulations resulted in the synthesis of nucleoside Q, **488**.

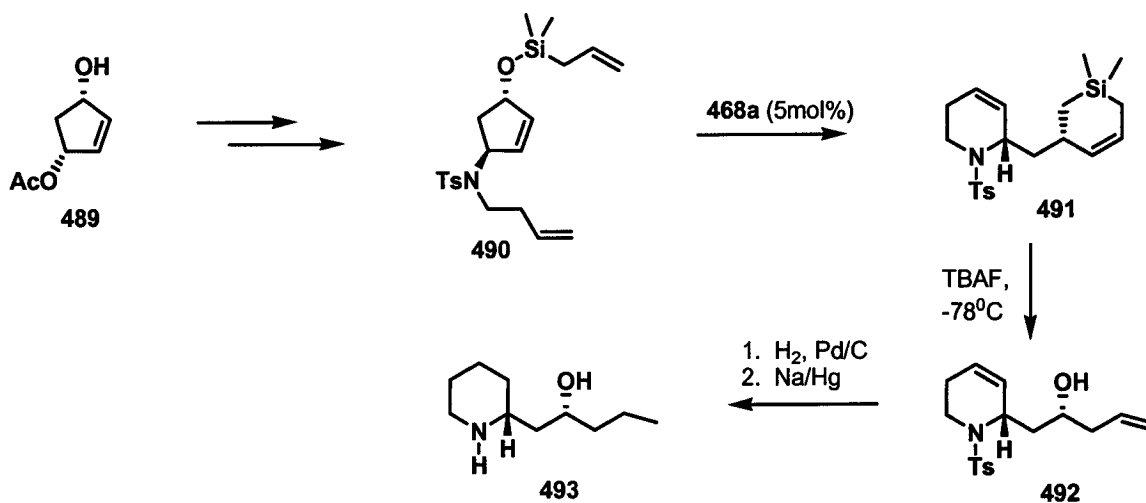
Another interesting study was done by Blechert and co-workers¹²⁹ where the metathesis reaction was applied as a cascade ring shuffling reaction in the synthesis of six membered rings in the total synthesis (-)-halosaline (**493**, Scheme 4.8). The mono-acetate protected alcohol **489** had been obtained by an enzymatic deprotection of the diacetate precursor. The RCM precursor **490** was synthesized by first derivatization of the deprotected hydroxyl with allyldimethylchlorosilane followed by the cleavage of the acetate group and further derivatization of this hydroxyl group under Mitsunobu conditions. Cyclization was achieved via a ring shuffling metathesis reaction with Grubbs

catalyst **468a**, which yielded bicyclic product **491**. (-)-Halosaline **493** was eventually synthesized under the specified conditions.

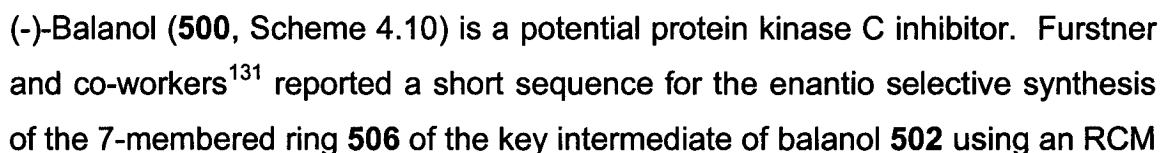
Scheme 4.7



Scheme 4.8

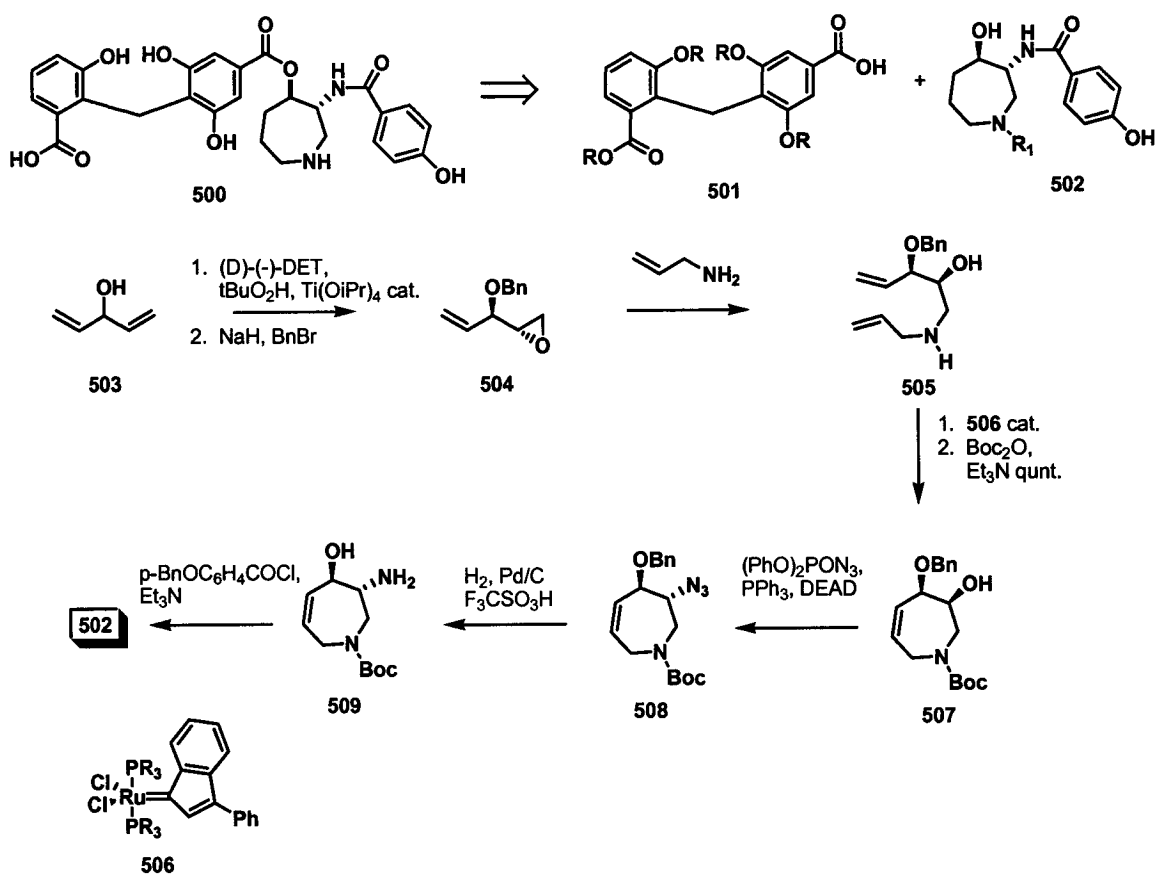


Scheme 4.9



strategy. The divinylcarbinol **503** was converted to the epoxide under Sharpless epoxidation conditions and the hydroxyl protection gave **504**. Regioselective opening of the oxirane ring with allylamine yielded the RCM precursor **505**. The diene **505** underwent a facile ring closing metathesis reaction with a Grubbs first generation catalyst **506**, which was followed by a secondary amine protection to yield **507**. The free hydroxyl group was converted to the azide under Mitsunobu conditions to give **507**, the azide reduced to primary amine **508** and condensed with the suitable acid chloride to yield the key intermediate **502**.

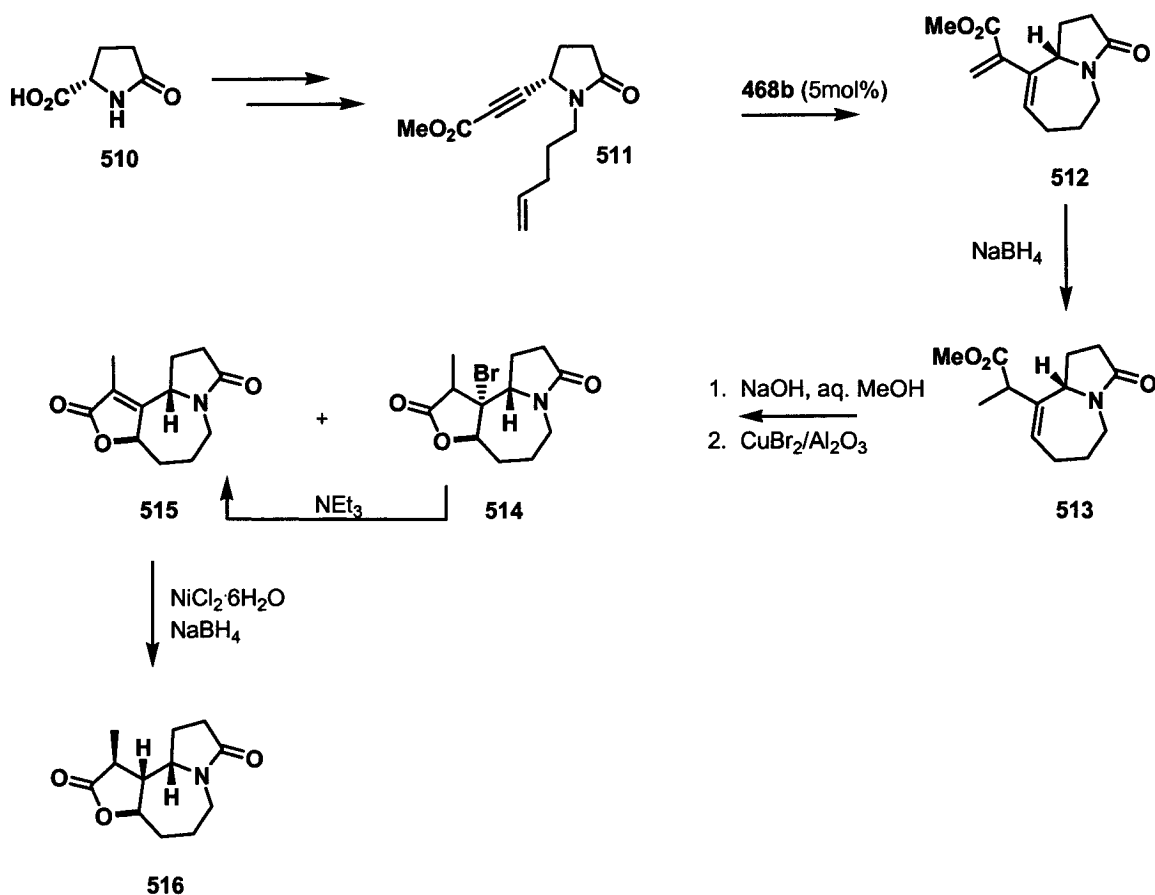
Scheme 4.10



Mori and co-workers¹³² were successful in using the 'enyne metathesis' reaction for the synthesis of (-)-stemoamide (**516**, Scheme 4.11). The enyne RCM precursor **511** was synthesized using pyroglutamic acid **510** as the starting

material, which underwent enyne metathesis with Grubbs first generation catalyst **468b** to yield the 7-membered cyclic diene **512**. The regioselective reduction of the external double bond to **513**, followed by bromolactonization gave a mixture of **514** and **515**. Brominated product was recycled to the eliminated product **515**, which was finally reduced to yield (-)-stemoamide (**516**).

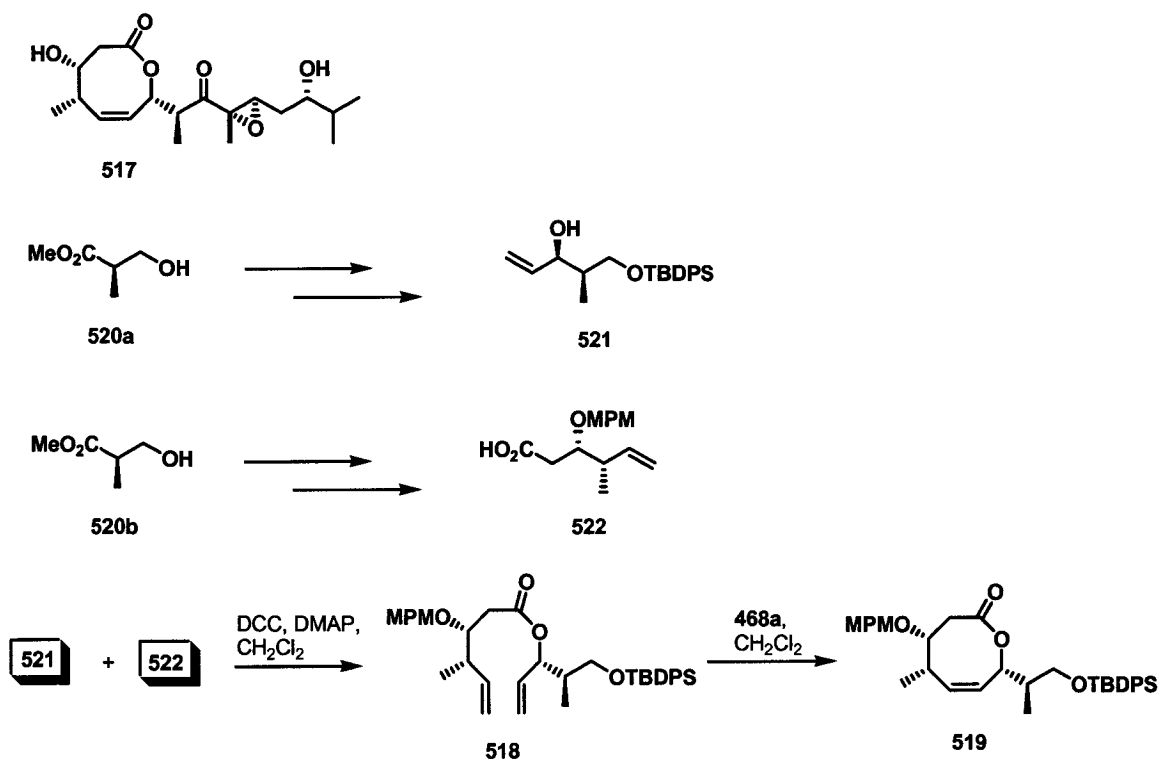
Scheme 4.11



There are many examples of the synthesis of 8-membered lactones via RCM reaction. One such recent example is the total synthesis of octalactin A (**517**, Scheme 4.12), by Buszek and co-workers.¹³³ Octalactin A, exhibits potent toxicity against certain human colon cancer cell lines, and has become a promising new anticancer agent. The important milestone in their synthesis was to synthesize the key oxocene **519**. The starting material for the synthesis the

precursors **521** and **522** were, (R)- and (S)-3-hydroxy-2-methylpropionates **520a** and **520b**. These precursors were synthesized under standard conditions.

Scheme 4.12



4.3.4 Criteria for Medium Sized Ring Formation by RCM Reactions¹³⁴

The use of RCM reactions for the synthesis of medium sized rings is a relatively new area of its application. In order to facilitate facile cyclization, several features are installed in the substrate. For instance, having pre-existing rings or the attachment of olefinic side chains to lactams have facilitated cyclization. An example of the latter is the synthesis of lactams **523** to **525** (Figure 4.7).¹³⁵ Macrocyclic rings can be annulated onto β -lactams as in the case of the synthesis of **526** and **527**,¹³⁶ or to pyrrolidine rings as in the case of compounds **528** and **529**,¹³⁷ (Figure 4.7). Bridging medium sized rings have been constructed via an 'inside-outside' mechanism by M. E. Krafft et al.,¹³⁸ as shown in Scheme 4.13.

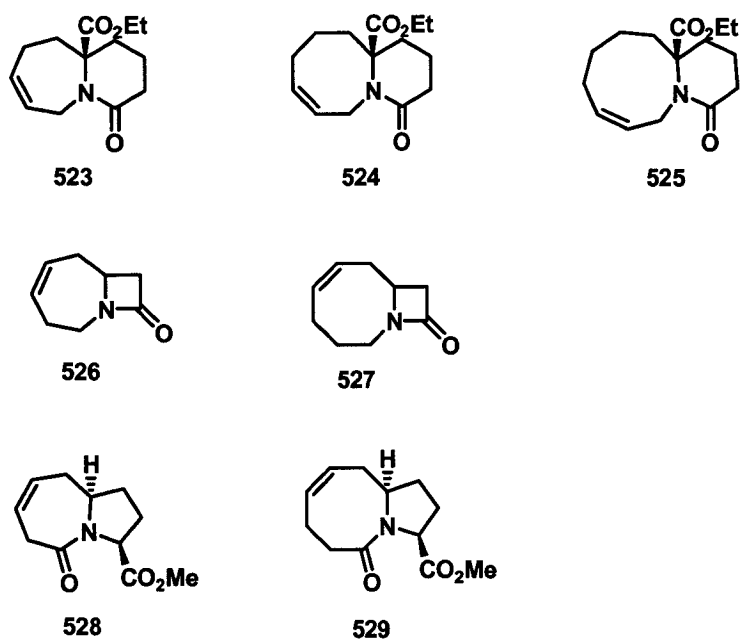
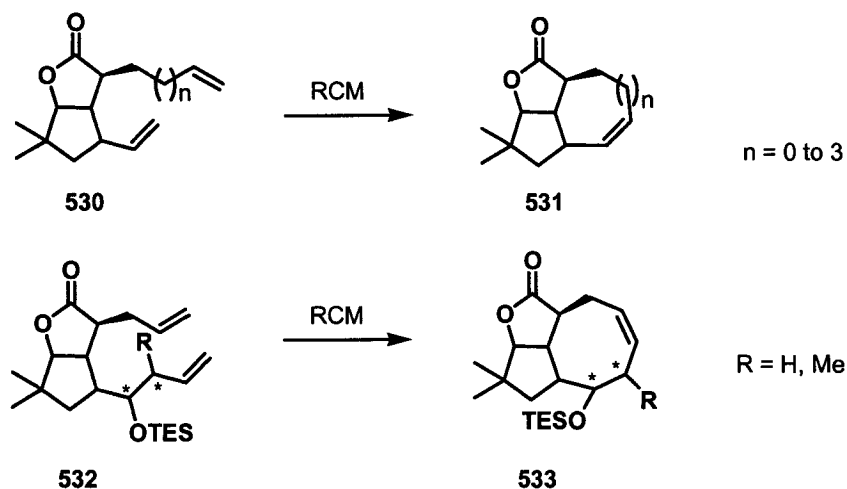


Figure 4.7 Some medium ring templates synthesized by RCM reactions.

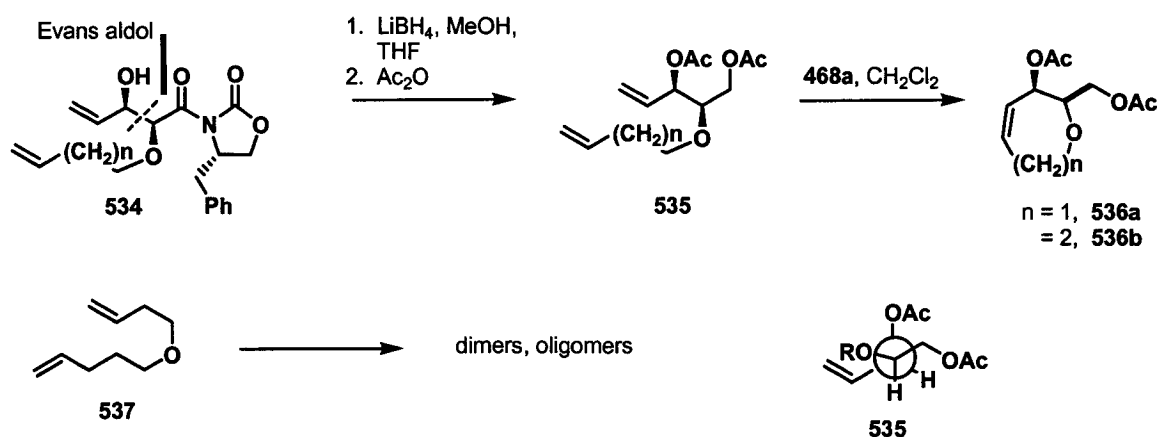
Scheme 4.13



Apart from having rings to control RCM ring cyclization, Crimmins and co-workers¹³⁹ have demonstrated that the substituents on the alkyl chain of the ether alkenes can support cyclization. For example, in one of their studies, an Evans aldol reaction between the glycolate imides with acrolein formed the α,β -

dihydroxy acid derivative **534**, (Scheme 4.14). Reduction and acetylation of **534** gave rise to the RCM precursor **535**, which was then cyclized with Grubbs catalyst **468a** to **536a** and **536b**. The corresponding simple ether **537** however, did not cyclize, and resulted in yielding dimers and oligomers. These results were explained in terms of the 'gauche effect' of the 1,2-dioxygen substituents on **535**, which promotes cyclization. Crimmins et. al., successfully applied this concept in their synthesis of (+)-laurencin.¹⁴⁰

Scheme 4.14



It has been reported that five to six and twelve to eighteen membered ring lactones can be generally synthesized in good yield. The formation of eight membered ring lactones had been 10⁶ times less rapid than the five membered ring lactones. This observation has been explained via the conformers of the lactones. Lactones can exist in two conformers such as Z (syn) **538** and E (anti) **539**, Figure 4.8.¹²⁷ The syn form is believed to be more stable than the anti form by 2-8 kcal/mol. The seven membered rings are generally formed after being forced into the disfavoured anti conformer. Eight and nine membered ring lactones can exist in an equilibrium between syn and anti conformations, while for larger systems of ten and eleven membered ring lactones the syn form is the major conformer.

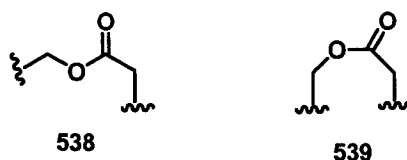


Figure 4.8 Conformations of lactone function.

Studies done by A. Furstner et al.,¹⁴¹ have revealed that the formation of cyclic systems by RCM requires the assistance of a properly positioned functionalities on the diene substrate. The functionalities include esters, amides, ketones and ethers. The polar functionalities co-ordinate on to the emerging carbene unit whereby assists the assembly of the reacting sites within the co-ordination sphere of the metal, and favours cyclization over competing oligomerization (**540**, Figure 4.9). If however, the chelate becomes very stable the RCM reaction would not take place. Thus the distance between the alkene units and polar groups, and the relative orientation and affinity play a critical role in RCM reactions.

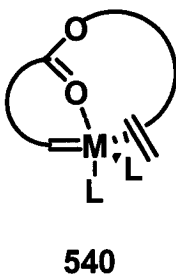


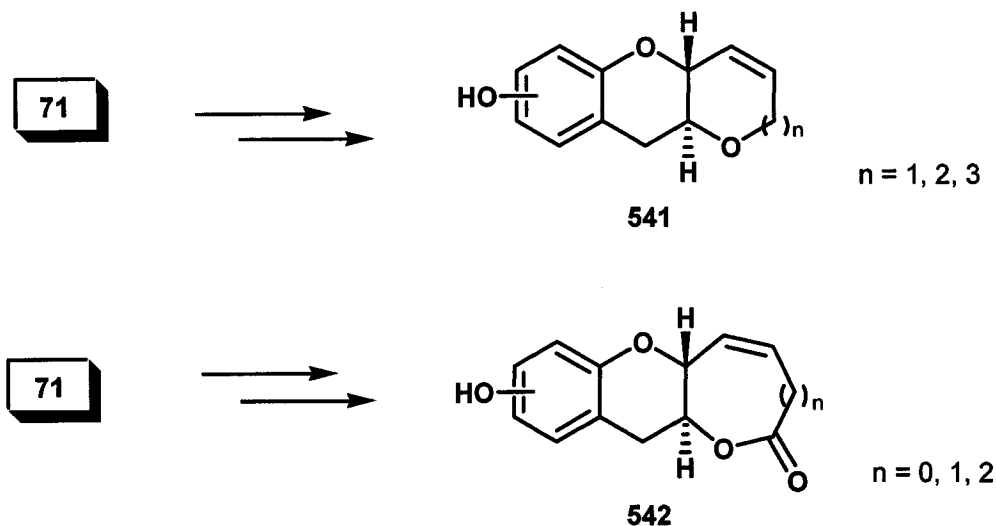
Figure 4.9 Proposed co-ordination structure for RCM.

4.4 Our Approach to Solution Phase Organic Synthesis

Due to their biological relevance, medium size rings of ether and lactone origin have become interesting targets in organic synthesis. As these types of rings are relatively unstable compared to smaller and larger macrocyclic rings, their synthesis is always a challenge. Hence the interest was to synthesize a series of medium sized rings with ether and lactone functionalities, Scheme 4.15. The strategy was to use RCM reactions for the construction of the rings. Subsequent

to the synthesis of medium sized rings the interest was in performing asymmetric reactions on the newly formed double bonds, which were hypothesized to be directed by the ring conformation of the 2H-pyran system.

Scheme 4.15

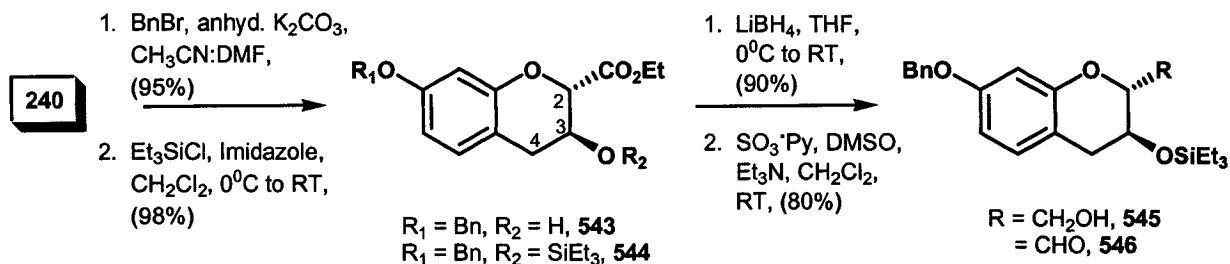


4.4.1 Benzopyran-based Polycyclics with additional Six Membered Rings

4.4.1.1 Six Membered Ether Rings

The strategy for the synthesis of the RCM precursor dienes was to have extensions from the aldehyde and the alcohol moieties of the 2H-pyran system. Since relatively poor yields of 66% were observed for the aldehyde formation with the MEM-phenol protected system (**394**, Scheme 3.30), it was thought of attempting to form the aldehyde with benzyl-phenol protected system (**546**, Scheme 4.16).

Scheme 4.16



The bicyclic phenol **240** was reacted with benzylbromide in acetonitrile and DMF to facilitate regioselective hydroxyl protection giving **543** (Scheme 4.16). The phenolic hydroxyl groups are more polar than a secondary hydroxyl group. Therefore, a polar solvent like DMF would solvate the negative charge of the phenolic hydroxyl group making it more reactive towards its protection. The benzylation was confirmed by ¹H NMR, by the appearance of an extra set of peaks, as a multiplet in the aromatic region between 7.34-7.45 ppm for 5H and singlet at 5.05 ppm for 2H corresponding to the benzylic protons. The hydroxyl proton at 2.59 ppm was confirmed as the secondary hydroxyl, as it appears up field and remains almost unshifted at 2.63 ppm from going from fully deprotected phenol **240**. Further evidence was the complete disappearance of the singlet at 5.15 ppm corresponding to the phenolic hydroxyl of **240**. This peak did not appear in **543**.

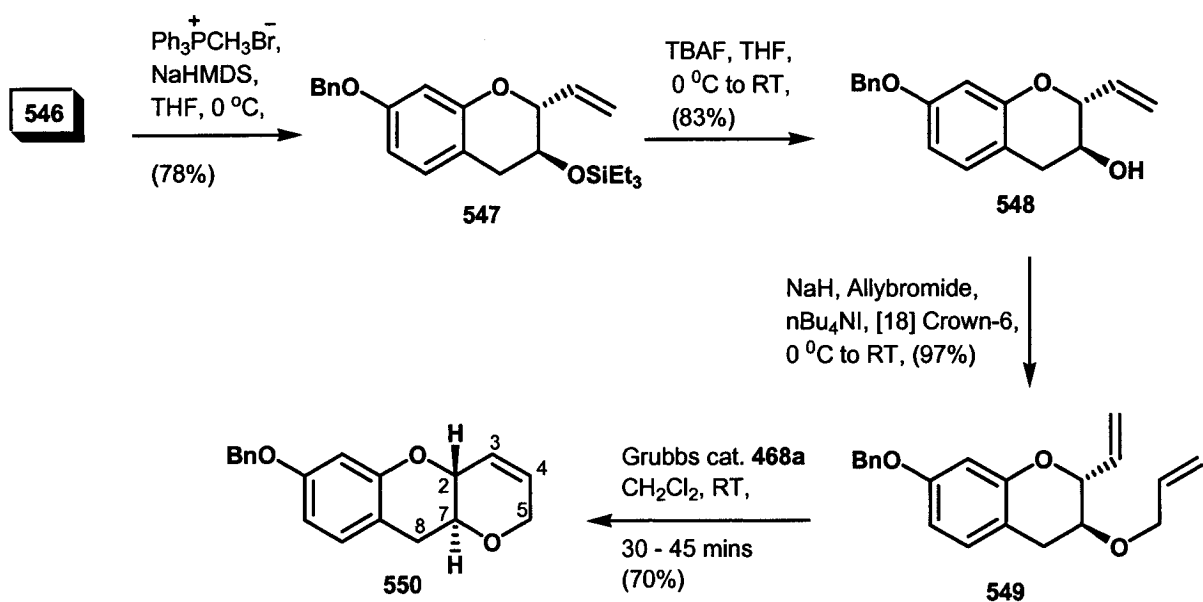
As for the MEM-system the alcohol **543** was then silylated with TESCl to yield **544**. The product was confirmed by the disappearance of the hydroxyl signal at 2.59 ppm and the appearance of signals corresponding to the TES group in the ¹H NMR. For instance a quartet at 0.64 ppm (J = 7.9 Hz) integrating to 6-protons and a triplet at 0.97 ppm (J = 7.9 Hz) integrating to 9-protons indicating TES protection of the secondary hydroxyl group and compound **544**.

The ester **544**, was subjected to reduction to the primary hydroxyl under standard conditions of LiBH₄ yielding **545**, and then oxidized to **546** by SO₃•py. Reduction was confirmed by the extra set of peaks at 2.07 ppm corresponding to the

primary alcohol and for the CH₂ group, as two diastereotopic protons between 3.91-3.99 ppm and 4.01-4.10 ppm in the ¹H NMR. The peaks were confirmed using COSY, and HSQC NMR data. Similarly the oxidation was confirmed by ¹H NMR: where a peak was observed downfield at 9.85 ppm for a single proton, which is typical for aldehyde protons. The corresponding HSQC and ¹³C NMR further confirmed the result as the carbon shift attached to this proton appeared at 199.8 ppm, which signified carbonyl carbon.

The aldehyde was then extended to the alkene by a Wittig reaction, providing **547**, (Scheme 4.17). The olefin signals observed at 5.36 ppm (d, J = 10.8 Hz, 1H) indicate cis coupling with the C-2 proton, and at 5.52 ppm (d, J = 17.3 Hz, 1H) its trans coupling in the ¹H NMR. The C-2 proton also appeared as a single proton multiplet between 6.00-6.09 ppm.

Scheme 4.17



The alcohol was deprotected with TBAF to give **548**, and alkylated with allylbromide in the presence of nBu₄NI and [18]-crown-6 to yield the RCM precursor **549**. Formation of the alcohol **548** was observed by the disappearance

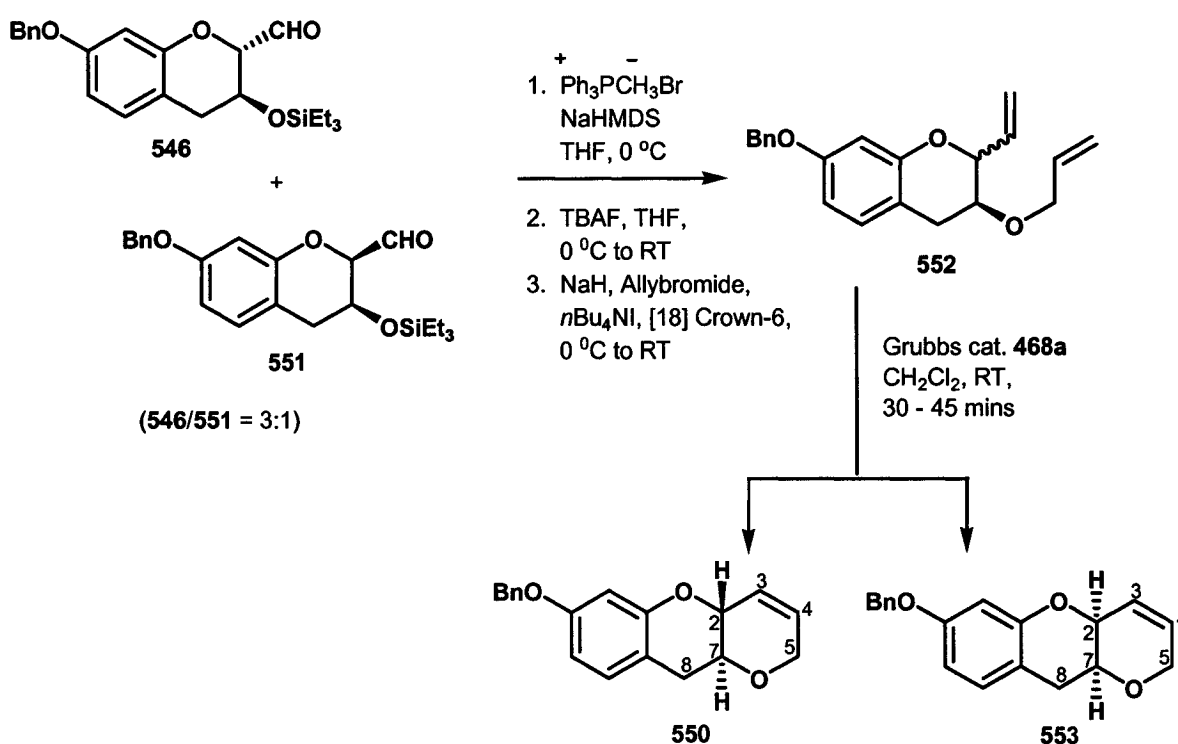
of the proton signals corresponding to the TES group in the ^1H NMR spectrum. Alkylation was confirmed by ^1H and COSY NMR as follows: the C-5, CH_2 group between 4.12-4.20 ppm as 2H multiplet, the olefin signals between 5.91-6.02 ppm as a 2H multiplet (overlaps with the other olefin signal) and the terminal protons at 5.22 ppm (d, $J = 10.3$ Hz, 1H) for trans coupling with the proton between 5.91-6.02 ppm, and at 5.30 ppm (d, $J = 9.0$ Hz, 1H) for its cis coupling.

The dialkene **549** was then subjected to the RCM reaction with Grubbs first generation catalyst **468a**, which resulted in the successful formation of the tricyclic polyether **550**. Extensive NMR analysis was performed to completely characterize the structure, Appendix - ^1H , COSY and HMQS NMR slicings Spectra 9, 10, 11 respectively. The ring protons were assigned using ^1H and COSY NMR. The CH_2 protons at C-5 appear between 4.28-4.39 ppm as a 3H multiplet. The extra proton was identified by COSY as the proton at the ring fused site of C-2. The olefin signals at C-4 and C-3 appear at 5.94 ppm (d, $J = 10.1$ Hz, 1H) and at 6.04 ppm (d, $J = 10.0$ Hz, 1H) and could not be resolved, as the coupling with the adjoining protons at C-5 for C-4 and C-2 for C-3 also appear together in the spectrum. The trans coupling between C-2 and C-7 protons were confirmed by HMQC NMR experiments for the C-2 proton that shows a coupling of $J = 8-9$ Hz, typical for these types of systems.¹⁴²

The cis-fused ring system was also synthesized starting from the aldehyde **551** (3:1 ratio of epimers according to ^1H NMR, Scheme 4.18). Wittig reaction, deprotection of alcohol and allylation to yield **552** was carried out for the mixture, and was only resolved after cyclization with Grubbs catalyst **548a** to yield the cis-fused tricyclic polyether **553**. The structure was confirmed by extensive NMR experiments Appendix - Spectrums 12, 13 and 14 respectively for ^1H , COSY and GOESY NMR spectra. The ^1H and COSY NMR revealed that the C-5 CH_2 protons and C-2 proton appeared as a 3H multiplet between 3.89-3.40 ppm, which was similar to that observed for the trans-fused tricyclic ether **550**. The olefin proton signals at C-4 and C-3 were shown as a 2H multiplet between 6.92-

6.10 ppm. The C-7 proton appeared at 3.97 ppm. In order to confirm the cis-fused ring system, a NOSEY NMR experiment was carried out by irradiating the C-7 proton. However, a reasonable conclusion could not be arrived at by this experiment as the signal corresponding to the C-2 proton occurs together with the C-5 protons. Hence a GOESY NMR experiment¹⁴³ was carried out, where the C-7 proton was irradiated. The experiment showed an enhancement of C-2 protons at 4.30 ppm relative to the C-5 protons at 3.50 ppm. This result indicates that the two protons at C-2 and C-7 are closer in space confirming a cis-fused ring system over a trans-fused ring system.

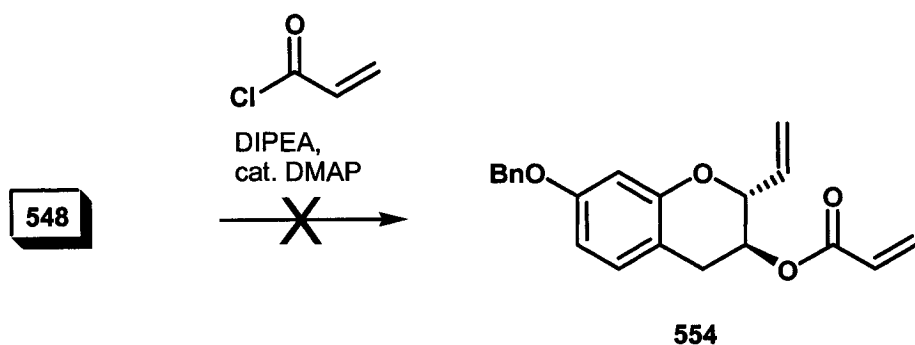
Scheme 4.18



4.4.1.2 Six Membered Lactone Ring

In order to synthesize the six membered lactone, first it was necessary to synthesize the RCM precursor **554**, Scheme 4.19. Therefore, it was decided to react the alcohol **548** with acryloyl chloride under various conditions, Table 4.1.

Scheme 4.19

Table 4.1 Synthesis of acrylic ester **554**.

Solvent	Temperature °C	Reaction Time h	Observations
CH ₂ Cl ₂	0 to RT	2	SM
	30	0.5	SM disappeared but no product formation.
CH ₂ Cl ₂	reflux at 30	0.5	No product formation.
CH ₂ Cl ₂	-78 to RT to 40	1	SM disappeared, decomposed products
DMF	-78 to RT	1	SM

The reaction was monitored by TLC and MS. The TLC sometimes showed a spot a little less polar appearing just above the starting alcohol **548**. Upon MS analysis, revealed that it was not the product. Therefore, we were not successful in synthesizing the dialkene **554** with acryloyl chloride. A similar observation was

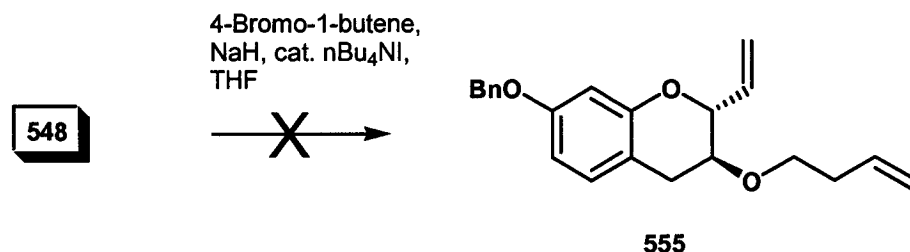
made by another member of the group when trying to synthesize the acrylic ester with acryloyl chloride. Hence it was decided to move on, due to time constraints. However, a suitable alternative would have been to couple with the corresponding acrylic acid. This was attempted only once with DCC, DMAP in DCM and the reaction was monitored for almost 40 h. A significant spot on TLC corresponding to a non-polar compound moving almost with the solvent front, in 35% EtOAc:Hexanes solvent system, was observed. More analytical work is needed to confirm the synthesis, and to synthesize in large scale.

4.4.2 Benzopyran-based Polycyclics with additional Seven Membered Rings

4.4.2.1 Seven Membered Ether Ring

The synthesis of the dialkene precursor **555**, Scheme 4.19 for the formation of the seven-membered ring ether was anticipated to be synthesized as considered before, for the six-membered ring ether **549**, Scheme 4.17. Although the conditions in Table 4.2 were considered, the reaction was not successful.

Scheme 4.19



4.4.2.2 Seven Membered Lactone Ring

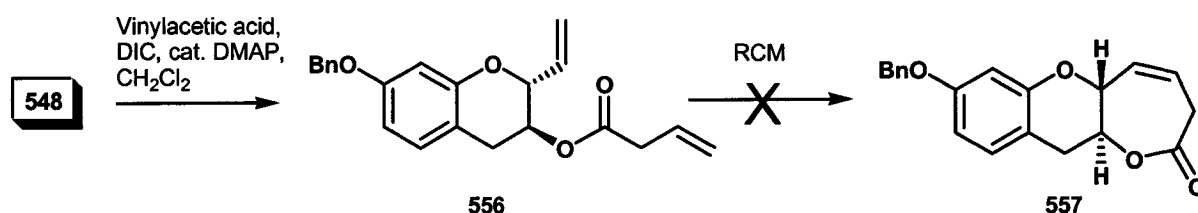
The synthesis of the seven membered ring was attempted via the acid coupling to the alcohol **548**, Scheme 4.20. The RCM precursor **556** was synthesized in 81% yield by the coupling of alcohol **548** with vinylacetic acid in the presence of DIC and cat. DMAP. The product was confirmed by ^1H NMR as follows: one set of CH_2 protons appeared as doublet at 3.12 ppm ($J = 6.9$ ppm), and the second set of olefin protons as a 3H multiplet between 5.16-5.20 ppm. These protons overlap with the C-3 proton. The ^{13}C NMR showed a significant peak downfield

at 171.4 ppm that is typical for a ester carbonyl carbon. The CH₂ protons were further confirmed by an HMBC NMR experiment that showed long range coupling between these protons and the carbonyl carbon.

Table 4.2 Synthesis of dialkene **555**.

Solvent	Temperature °C	Reaction Time h	Observations
THF	0 to RT	2	SM
	35	3	SM
	35	~24	SM
	45	~24	SM
DMF	40	1 to ~ 48	SM

Scheme 4.20



The dialkene **556** was then subjected to cyclization under RCM conditions with Grubbs first generation and second generation catalyst **468a** and **470** respectively, Table 4.3. The major spots of the last entry of table 4.3 were isolated and analyzed by NMR and MS. Their spectroscopic properties were not consistent with the anticipated structure **557**.

Table 4.3 Attempted cyclization of dialkene **556** to **557** via RCM reaction.

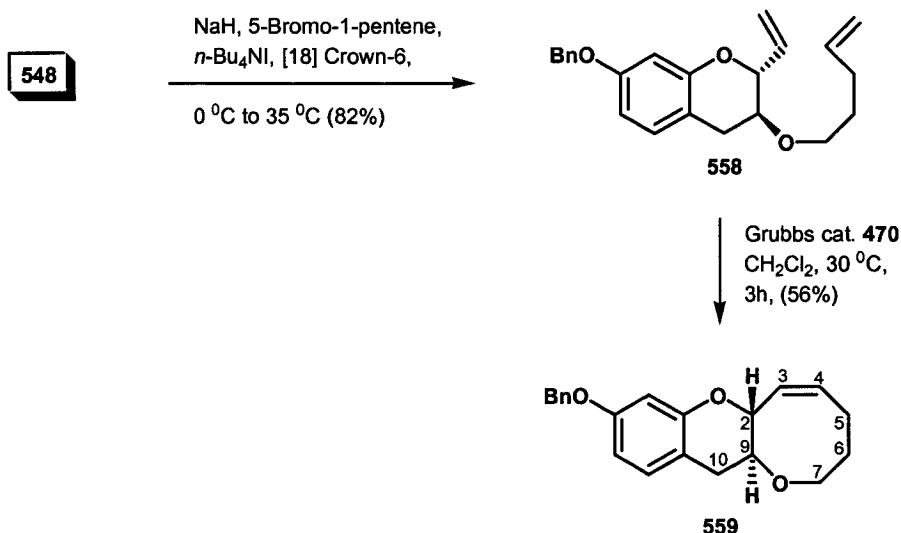
Catalyst	Temperature 0°C	Time h	Observations
468a	0 to RT	2	~90% SM
	30	2	~90% SM
	30	24	~90% SM
468a	40	2.5	SM
cat.	RT	~ 18	SM
Ti(O<i>i</i>Pr)₄¹⁴⁴	RT	~ 48	SM
470	RT	2	~70% SM and decomposition
	37	4	~70% SM and decomposition
	37	24	~10% SM and decomposition

4.4.3 Benzopyran-based Polycyclics with Additional Eight Membered Ring Ether

As for the previous ether systems, the RCM precursor **558** was synthesized by an alkylation reaction with 5-bromo-1-pentene in the presence of a catalytic amount of $n\text{Bu}_4\text{NI}$ (Scheme 4.21). The alkylation was confirmed by ^1H and COSY NMR analysis, which showed three new sets of peaks corresponding to three sets of CH_2 groups in the new side chain at 1.70 ppm, 2.14 ppm and between 3.52-3.66 ppm corresponding to the CH_2 group in the center, adjacent to the olefin and adjacent to the oxygen heteroatom respectively. The extra set of peaks corresponding to the second olefin was also observed. The terminal olefinic protons were observed as a 4H multiplet between 4.98-5.06 ppm, and

appeared together with the benzyl CH₂ protons of the benzyl-OH protecting group. The signal for the other olefin proton of the pentene chain was a multiplet between 5.78-5.86 ppm.

Scheme 4.21



The RCM precursor **558** thus formed was then subjected to the RCM reaction with the Grubbs first generation catalyst **486a**. In this case, although product formation was observed by TLC, the reaction did not proceed to completion even after 48h. Therefore decided to repeat the reaction with Grubbs second generation catalyst **470**. Successful cyclization was observed within 3h, which resulted in the formation of the 8-membered cyclic ether **559** with a yield of 56%. Cyclization and ring conformation was determined by extensive NMR experiments Appendix – Spectrums 15, 16, 17 for ¹H, COSY and NOESY spectra respectively, and modelling studies - Appendix. The ring CH₂ protons at C-7, C-6, C-5 and at C-10 were all diastereotopic, and generally appeared as multiplets or as doublet of doublets of 1H chemical shifts each. Hence, C-7 protons between 3.64-3.71 ppm (1H, m) and at 4.04 ppm (1H, dd, J = 11.6, 5.3 Hz); C-6 protons at 1.41 ppm (1H, t, J = 8.8 Hz) and between 1.99-2.05 ppm (1H, m); C-5 protons between 2.13-2.16 ppm (1H, m) and 2.45-2.49 ppm (1H, m); and the C-10 protons at 2.80 ppm (1H, dd, J = 15.7, 10.4 Hz) and at 3.04 ppm (1H, dd, J =

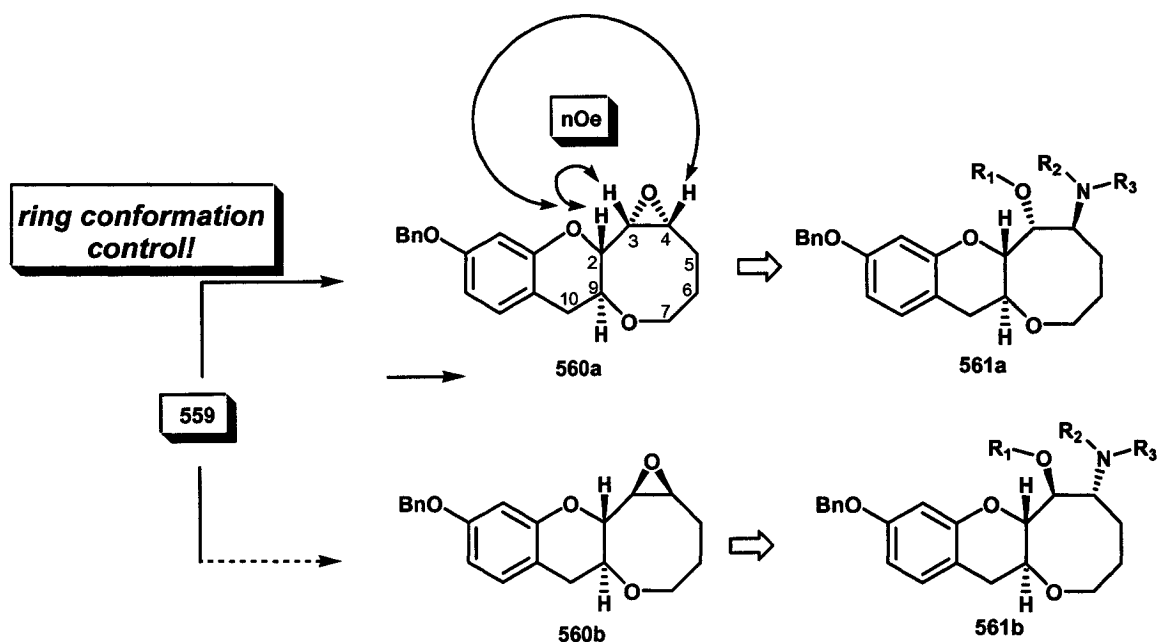
15.8, 6.0 Hz). The olefin protons at C-4 and C-3 appeared at 5.75 ppm (q, $J = 8.8$ Hz) and at 5.85 ppm (dd, $J = 11.1, 5.0$ Hz) respectively, in the ^1H NMR. The protons at the trans-fused ring junction, appeared as multiplets between 3.55-3.61 ppm, and between 4.51-4.54 ppm, for the C-9 and C-2 protons respectively.

There was also an interest to determine the conformation of the newly formed 8-membered ether ring. Hence two types of experiments were carried out independent of each other. They were a NOESY NMR experiment and a mathematical modelling experiment using Hyperchem 5.1. It was interesting to note that both experiments gave the same result, and that the 8-membered cyclic ether exists in a boat conformation. The NOESY NMR experiment showed significant coupling between the proton at C-2 with one proton each at C-5 and C-10. The result indicated that these protons were close in space. In order to explain this result the 8-membered ring, thus needs to be in a boat-like conformation, Appendix - Spectrum 17. Simultaneously, the mathematical modelling experiment revealed the lowest energy conformer for the 8-membered ether ring was the boat-like conformer, Appendix - 18.

4.5 Stereoselective Epoxidation on Eight Membered Ring Polyether System

As the eight membered ring gave an interesting result, the interest was to extend the synthetic strategy to investigate a ring conformation controlled asymmetric induction on the double bond (Scheme 4.22). A stereoselective epoxidation **560** followed by a regioselective ring opening **561** was hypothesized. To verify it was thought first to synthesize the epoxide **560**.

Scheme 4.22



Initial attempts to synthesize the epoxide by reacting with mCPBA, and oxone/ NaHCO_3 ¹⁴⁵ were not successful and resulted in decomposition of the starting material. However, the epoxidation reaction under neutral conditions of dioxirane¹⁴⁶ showed signs of epoxide formation in 90% yield. Preliminary ^1H NMR experiments showed the disappearance of the signals corresponding to the olefin protons at C-4, 5.75 ppm and C-3, at 5.85 ppm indicating a fully saturated compound. Further ^1H , COSY, HSQC, NOESY NMR studies were done¹⁴⁷ to assign the stereochemistry of the epoxide, Appendix - Spectrums 19, 20, 21, 22 respectively. A single set of peaks were observed in the ^1H NMR which confirmed the formation of a single diastereomer. The C-3 and C-4 protons were observed at 3.17 ppm and 3.12 ppm respectively in the ^1H NMR. An up field shift of these protons with respect to the olefin signals observed earlier also indicated an adjacent electronegative atom in the system. The bridge protons at C-2 and C-9 overlapped with one another and appeared between 3.74 - 3.77 ppm. However these protons showed coupling with the protons at C-3 and C-4 in the NOESY NMR spectrum. The proton at C-9 would be somewhat far way to show significant NOESY NMR coupling with the C-3 and C-4 protons and therefore,

the NOESY NMR coupling observed would be with the C-2 protons. Hence the protons at C-2, C-3 and C-4 would all be on the same face. Thus one could conclude that the α -epoxide was formed as a single diastereomer **560a**. The result also confirms ring controlled formation of the epoxide as predicted by the modelling studies. In other words, the boat-like structure of the **559** and the *trans*-fused ring junction controls the formation of the single epoxide on the same side of the proton at C-9.

4.6 Solid Phase Organic Synthesis

As considered before in Section 1.1.2 of Chapter 1, the synthesis of many analogues that can be used as lead compounds in the drug industry has been a pressing requirement in the modern era. To address this demand, powerful chemical and biological methods have been developed for the generation of large combinatorial libraries that can be screened for a potential drug. Dolle and co-workers¹⁴⁸ have published five extensive reviews titled "Comprehensive Survey of Combinatorial Library Synthesis: 1998, 1999, 2000, 2001 and 2002", which gives a flavour and potential of solid phase synthesis. Of the compounds considered, small organic molecules of molecular weight <600-700 have reported favourable pharmacokinetics, making them the major focus of library synthesis (Section 1.3.5). Arya et al., in their review cover several aspects of 'high-throughput synthesis of natural product-like complex polycyclics'.²¹ The advantage of the solid phase approach over traditional organic synthesis include, (1) excess reagents can be used to drive the reaction to completion, (2) fast purification by washing away excess reagents, (3) products can be isolated by cleaving from the support and filtration, (4) can be automated, and (5) split-mix approach gives access to a large number of compounds. This section covers a few general aspects towards solid phase synthesis.

4.6.1 Strategies towards Library Synthesis

A number of general strategies have been developed for the synthesis of compound libraries on solid support. Most of these strategies were initially

demonstrated with peptide libraries, and are now however, applied to other classes of compounds. They include (1) synthesis of compounds in a discrete manner or parallel synthesis, (2) split and pool synthesis and (3) by a deconvolution strategy of soluble libraries.

The solid phase parallel synthesis of compounds requires the use of parallel reaction vessels. This approach is relatively simple for obtaining a number of compounds simultaneously.

Unlike the method of parallel synthesis, the split and pool method accommodates a large number of compounds. Details of this method has already been considered in Section 1.1.2.1. Ideally, equimolar mixtures of reactants are sufficient in each synthetic step. It has however, been observed that reactants in a mixture do not have the same reactivity, and in most cases highly dependent upon its structure. Therefore, an excess of reagents are used at each step. The complication in this method is that a suitable "tracking" method (Section 4.6.3) is required to identify the compounds at each step.

In the deconvolution method pools of compounds are prepared such that each separate pool has defined building blocks at either one or two positions, and at the remaining positions all combinations of building blocks are incorporated. The optimal building block(s) is selected by determining the biological activity of each pool(s). A second round of synthesis is performed in a similar manner, and the process is continued until all positions are defined.¹⁴⁹

4.6.2 Analysis of Compounds

Two types of analytical methods are widely used in library synthesis. They are the (1) 'on bead' analysis and the (2) 'off bead' analysis. In the on-bead method, compounds synthesized are assayed while still being attached to the resin beads. This approach is possible in the 'split and mix' method because each compound is prepared on a single bead. On the other hand, in the off-bead

method, a representative sample is cleaved from the large pool of compounds and analyzed.

The 'on bead' compounds are treated with fluorescent label and analyzed by the use of a fluorescence activated cell sorting (FACS) instrument. Other analytical methods such as NMR and IR have also been used. Whereas in the off-bead method, mass spectrometric methods such as electron impact and electrospray techniques have been widely used to analyse compounds.

4.6.3 Encoding Techniques

When large collections of compounds are synthesized specially in the case of 'split and mix' synthesis, an efficient encoding system is required to track the compounds. Generally used techniques include chemical encoding and nonchemical encoding methods. The latter technique has become popular with the use of a radio frequency and optical encoding systems coupled with microreactor technology developed at IRORI, Figures 4.10.^{16(b)}

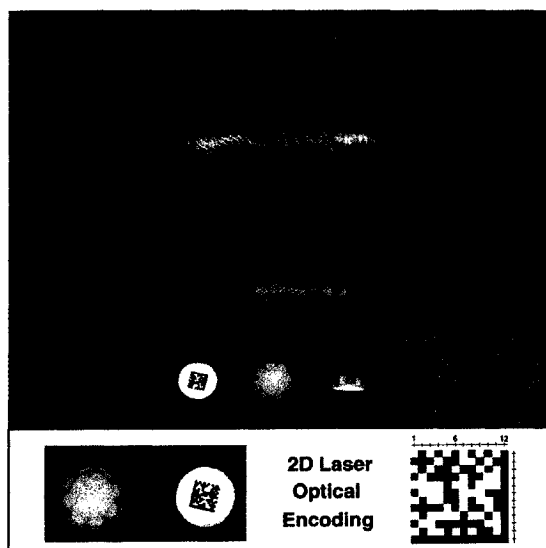


Figure 4.10 IRORI radio frequency and optical encoded macrokans and nanokans.

Although IRORI technologies have their own share of disadvantages, the major advantages are, that the encoding does not require chemical manipulations, nor does it limit the types of chemistries that can be performed in the library. Apart from this, each compound can be easily tracked and identified at every stage. The cleavage of individual kans gives a sufficient quantity of the compounds that can be characterized by standard analytical techniques.

4.6.4 Solid Supports^{149,150}

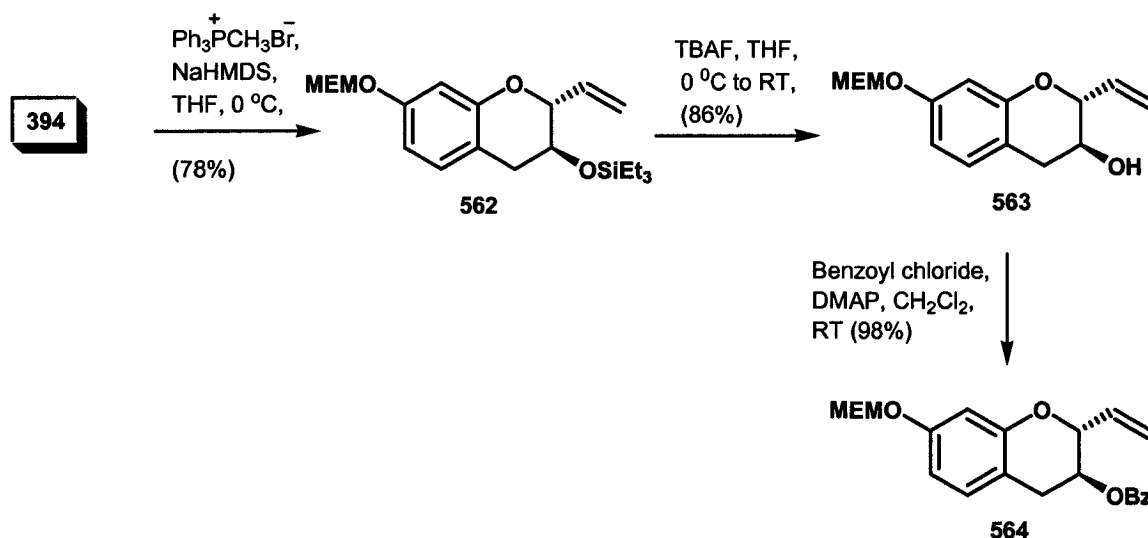
The solid support is an insoluble material to which a compound is covalently attached during a synthetic sequence. A large majority of library studies use two types of solid supports: (1) polystyrene cross-linked resins with 1-2% divinylbenzene (PS/DVB), and (2) polystyrene-polyethylene glycol copolymer (PS/ PEG) resins. The PS/DVB or the Merrifield resins are mechanically stable, economical and provide a high level of concentration of the functional group required to immobilize the organic compound onto solid support. The disadvantage of this type of resins is that they do not solvate well in protic solvents, making them less accessible to reaction sites. This in turn results in slow rates of reaction. On the other hand the PS/PEG resins are well solvated in protic solvents, making the reaction sites more accessible, which give greater rates of reaction. Limitations include, high dollar cost, reduced loading levels and mechanical instability.

4.7 Our Approach to Solid Phase Organic Synthesis

With the long term plan of a library synthesis and to investigate asymmetric synthetic-based reactions on six- and eight-membered polyethers, optimisations towards solid phase synthesis of these scaffolds were undertaken. The first considerations were to come-up with a suitable template to be immobilized onto solid support and to choose a suitable solid support capable of withstanding the reaction conditions required in the synthesis sequence. A secondary hydroxyl protected bicyclic 2H-pyran **564** (Scheme 4.23) was considered to be ideal for solid phase immobilization to **567** (Scheme 4.24). The protecting group that was

used for the synthesis was benzoyl, P = Bz so that the template had orthogonal protection and each reaction moiety could be considered independent of each other (see compound **564**). The choice of the resin was to use the bromo-Wang resin based on literature evidence¹⁵¹ and the success of its use in the group for a similar template.¹⁵²

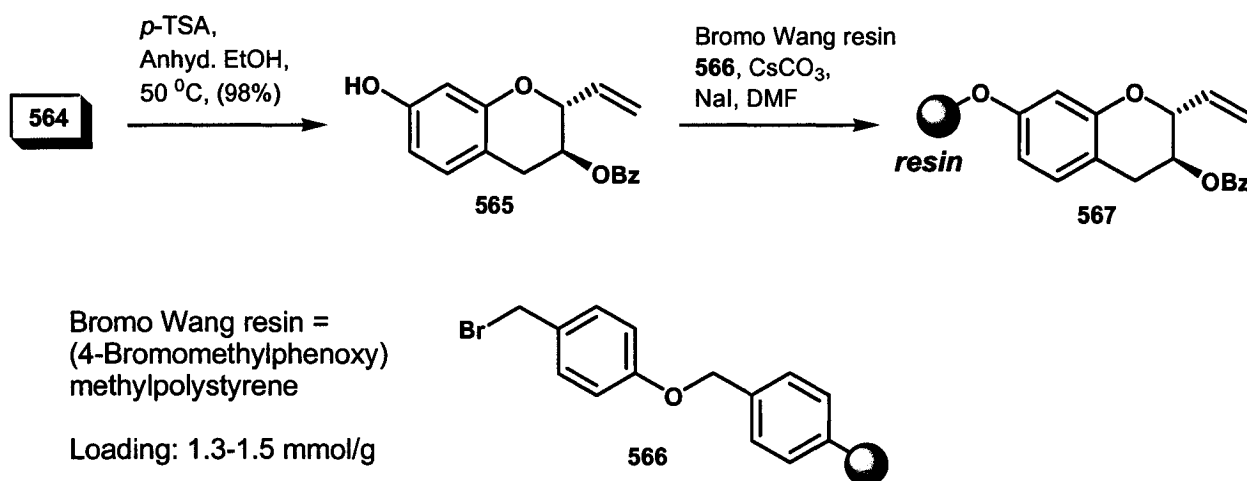
Scheme 4.23



The alkene alcohol **563**, (Scheme 4.23) was synthesized in similar fashion to its benzyl protected counter part **548** (Scheme 4.17). The olefin **562** was synthesized according to Wittig protocol. Product formation was confirmed by the appearance of olefinic signals at 5.23 ppm (dd, $J = 10.6, 1.4$ Hz, 1H) and 5.49 ppm (d, $J = 17.3, 1.5$ Hz, 1H) for the terminal CH_2 group and at 5.98-6.06 ppm (m, 1H) for the penultimate CH proton, in the ^1H NMR. The olefination was followed by silyl deprotection to alcohol **563** and reprotection of alcohol to **564**. The secondary alcohol **563** was identified by the disappearance of the signal corresponding to the TES group: for the CH_2 protons at 0.64 ppm (q, $J = 8.0$ Hz, 6H), and for the CH_3 protons at 0.98 ppm (t, $J = 7.9$ Hz, 9H) in the ^1H NMR. Benzoylation to **564** was observed by the extra five proton signals in the aromatic region at 7.40-7.45 ppm (m, 2H), 7.54-7.59 ppm (m, 1H), and 8.19 ppm (d, $J = 8.2$ Hz, 2H) of the ^1H NMR spectrum, and significant carbonyl signal at 165.8

ppm in the ^{13}C NMR. Benzoylation at the secondary hydroxyl position was further confirmed by an HMBC NMR experiment, which showed a long-range coupling between the proton at C-3, which appears together with a terminal olefin proton at 5.31-5.40 (m, 2H), with the carbonyl carbon of the benzoyl group. The position of the C-3 proton was confirmed by a COSY experiment.

Scheme 4.24

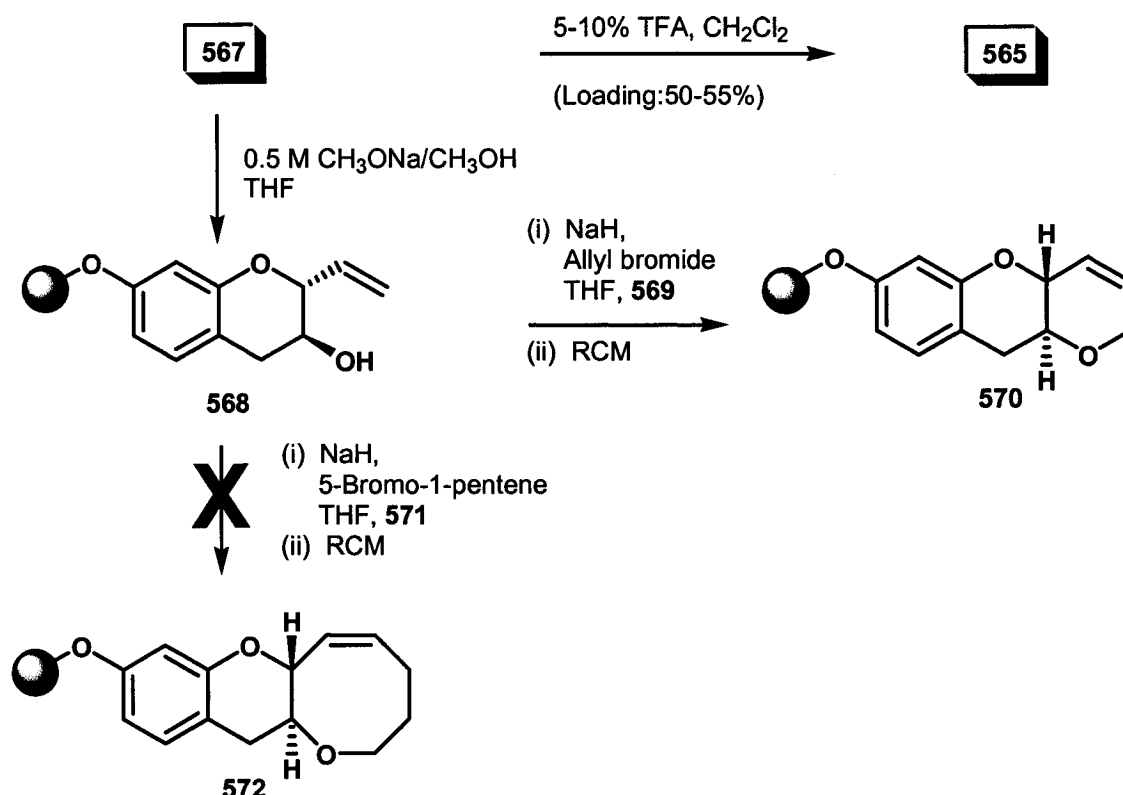


The next step was to selectively deprotect MEM group of **564**. Initial attempt to deprotect the MEM group under standard conditions of ZnBr_2 in dichloromethane¹⁵³ according to MS, resulted in the decomposition of the starting material. Hence this method was unsuccessful. Conditions were then optimized with *p*-toluene sulfonic acid in anhydrous ethanol to yield the MEM deprotected phenol **565** in quantitative yield of 98%. This was confirmed by ^1H NMR, which showed no signals corresponding to the MEM group which generally appeared at 3.40 ppm (s, 3H) for the OCH_3 protons, at 3.59 ppm (t, $J = 4.7$ Hz, 2H), and between 3.84-3.86 (m, 2H) for the $-\text{OCH}_2\text{CH}_2\text{O}-$ protons, and at 5.23 ppm (s, 2H) for the $-\text{OCH}_2$ protons.

At this point, the scaffold was ready for loading onto the solid support. Several attempts to load the compound onto the bromo-Wang resin **566** gave variable extents of loaded **567**, (Scheme 4.24).¹⁵³ The maximum loading observed was

50-55% on the basis of the recovered starting material upon cleavage with 5% TFA **565** (Scheme 4.25). This was then followed by deprotection of the benzoyl group to give **568**. At this point, the resin bound secondary alcohol was partitioned into two reactors, and was treated separately with allylbromide and 5-bromo-1-pentene to yield the RCM precursors **569** and **571** respectively. These immobilized precursors were then subjected to the RCM reaction.

Scheme 4.25

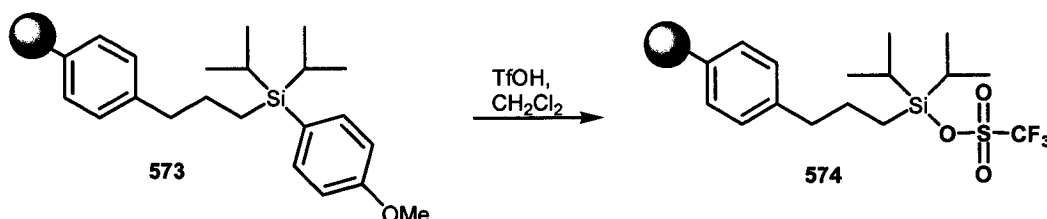


Although formation of the six-membered ether **570** was observed, the corresponding eight-membered ring ether **572** was not observed. Product formation at each step was confirmed by cleaving a small sample of the resin bound template and MS analysis. Several attempts were made to optimize conditions with the bromo-Wang resin, but without much success. After further investigation of the reaction sequence, the poor yielding step was identified as being the alkylation step. Hence it was decided to explore the use of alkylsilyl-tethered resin **573**, (Scheme 4.26) in order to optimize this step. The alkylsilyl-

thered resin is reported to have the capacity to immobilize sterically crowded secondary alcohols and phenols.¹⁵⁴ Hence it was considered to be a good alternative.

Scheme 4.26

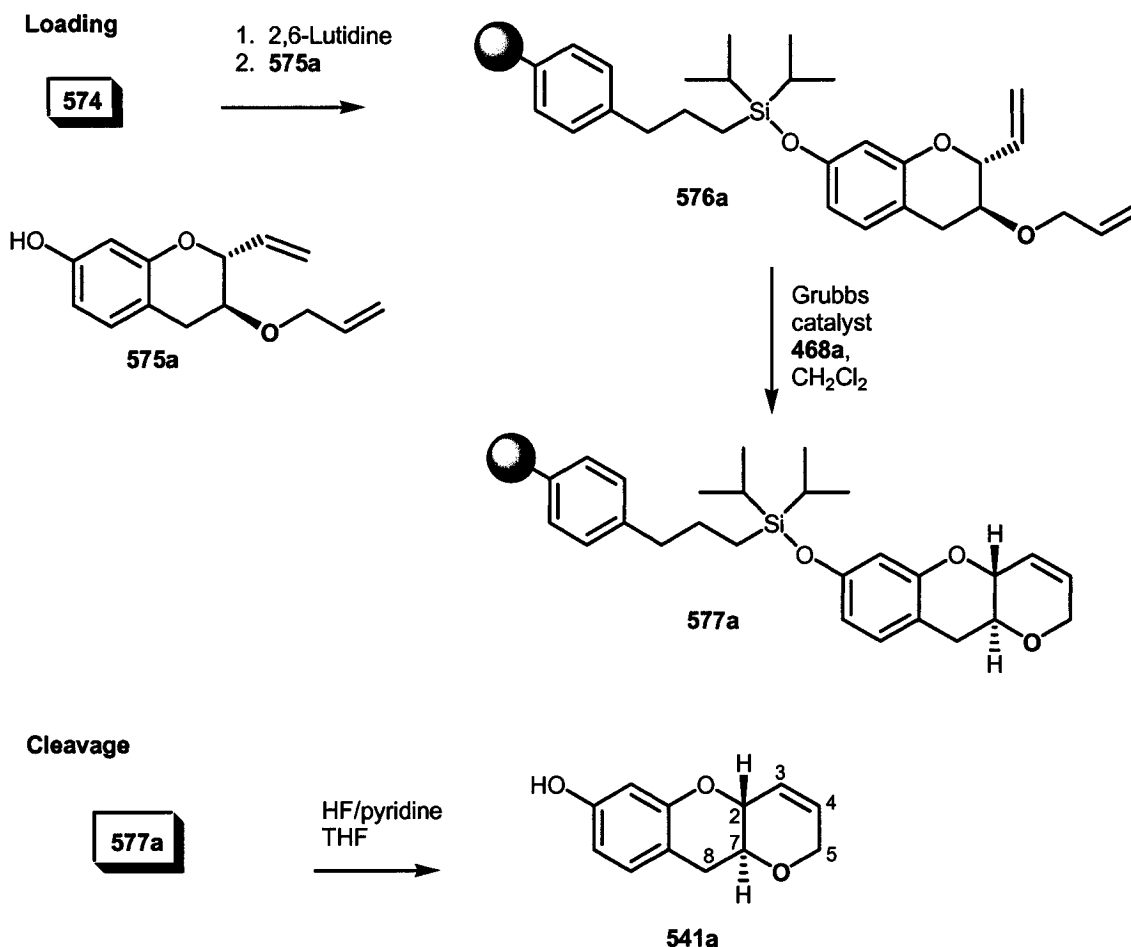
Activation



The first task was to synthesize the active form of the commercially available resin **573** (Scheme 4.26). The (4-methoxyphenyl)diisopropylsilylpropyl polystyrene **573** was first dried in a lyophilizer *in vacuo* for 24h. To the resin **573** was then added the trifluoromethanesulfonic acid to convert it to its active form **574**. The colourless resin changed to a bright orange/red colour upon activation as indicated by Schreiber et al.¹⁵⁴

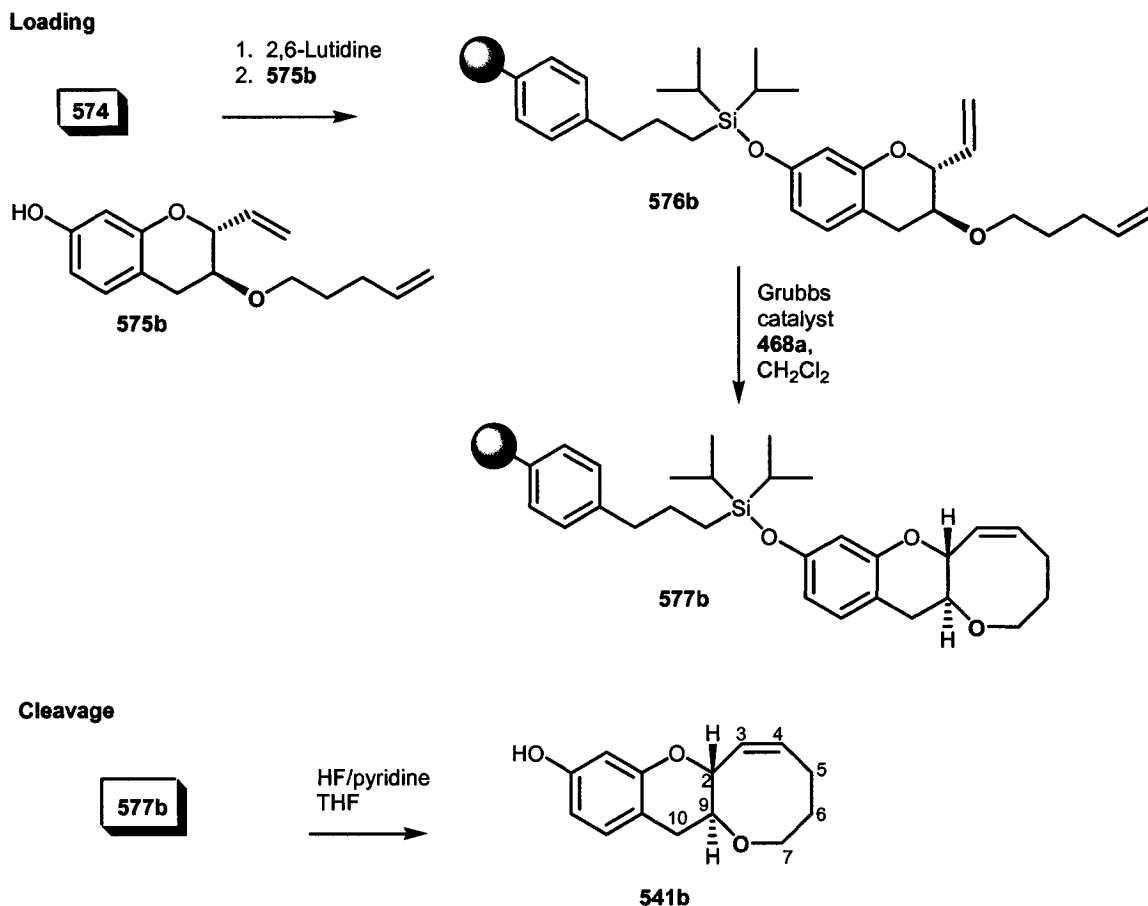
The activated resin **574** was partitioned into two 50 mg batches and then treated with 2,6-lutidine as preparation for the loading of the RCM precursors **575a** and **575b** (Schemes 4.27 and 4.28 respectively).¹⁴⁷ The loading calculated upon mass balance which gave 92% loading for precursor **575a** and 88% loading in the case of precursor **575b**. Upon excellent loadings of the precursors, the reaction was carried onto the next stage, which was the RCM reaction. The immobilized RCM precursors **576a** and **576b** both cases were treated with first generation Grubbs' catalyst **468a** at 40 °C in an Ar-atmosphere for 24h to yield **577a** and **577b** respectively. The resins were independently cleaved with HF/pyridine to yield tricyclic phenols **541a** and **541b** in 75% and 61% yields respectively.

Scheme 4.27



The tricyclic phenol product **541a** was confirmed by MS (205.3, M + 1 peak) which was further analyzed by ¹H NMR spectroscopy. The benzylic C-8 protons were observed as doublet of doublets at 2.84 ppm (J = 14.7, 11.0 Hz, 1H) and at 3.03 ppm (J = 14.8, 5.8 Hz, 1H). The olefinic protons at C-3 and C-4 were observed as doublets in the characteristic region at 5.91 ppm (J = 10.2 Hz, 1H), and at 6.02 ppm (J = 10.1 Hz, 1H). The three aromatic protons were observed at 6.55 ppm, 6.66 ppm and 7.00 ppm respectively. The remaining bridge protons at C-7, C-2 and C-5 protons were observed at 3.66-3.74 (m, 1H), 4.28-4.38 (m, 3H) respectively.

Scheme 4.28



For the tricyclic derivatives **541a**, the cleaved product **541b** was characterized by both MS and ¹H NMR spectroscopy. The MS analysis gave a (M+1) ion peak at 233.3. The ¹H NMR spectroscopic analysis showed the clearly defined diastereotopic CH₂ protons at C-10 as doublet of doublets at 2.78 ppm (J = 15.7, 10.4 Hz, 1H) and at 3.02 ppm (J = 15.8, 6.0 Hz, 1H), and the characteristic olefinic protons at C-3 at 5.86 ppm (dd, J = 11.1, 4.9 Hz, 1H) and C-4 protons at 5.77 ppm (q, J = 8.8 Hz, 1H). The three aromatic protons were observed at 6.53 ppm, 6.56 ppm and 6.69 ppm. The protons at C-2 and C-9 were observed between 4.52–4.54 ppm and 3.57–3.61 ppm respectively. Finally the remaining CH₂ protons around the 8-membered ring appeared as single proton multiplets follows: 1.39 ppm, 1.95–2.05 ppm, 2.10–2.16 ppm, 2.45–2.51 ppm, 2.78 ppm, 3.02 ppm, 3.63–3.69 ppm, 4.05 ppm.

4.8 Concluding Remarks

The synthesis of benzopyran-derived tricyclic polyethers using the RCM reaction was completed with success. The initial success with the solid phase synthesis is encouraging for further developing a combinatorial chemistry program on this scaffold. Hence, it looks promising towards synthesizing a reasonably sized library for biological testing.

The synthesis of benzopyran-derived tricyclic lactones, however, was not a success story. Although there are examples in the literature for the synthesis of six-membered and macrocyclic lactones,^{124,130,133,141,144,155,156,157} the attempts to synthesize the seven-membered lactone using the RCM strategy, was not successful. The main difference observed in the literature examples and this study is that there is more flexibility involved with the RCM precursors of the literature examples. Whereas there is restricted flexibility imposed by the 2H-benzopyran scaffold in this study. This could play a role for the unsuccessful outcome. Apart from this, it is believed that the cyclization was not successful because the ester needs to be forced into the less favourable anti-configuration **539**, (Figure 4.8). Another added disadvantage could be that it may not have the correct orientation of the polar ester functionality discussed in Section 4.3.4, **540** Figure 4.9.

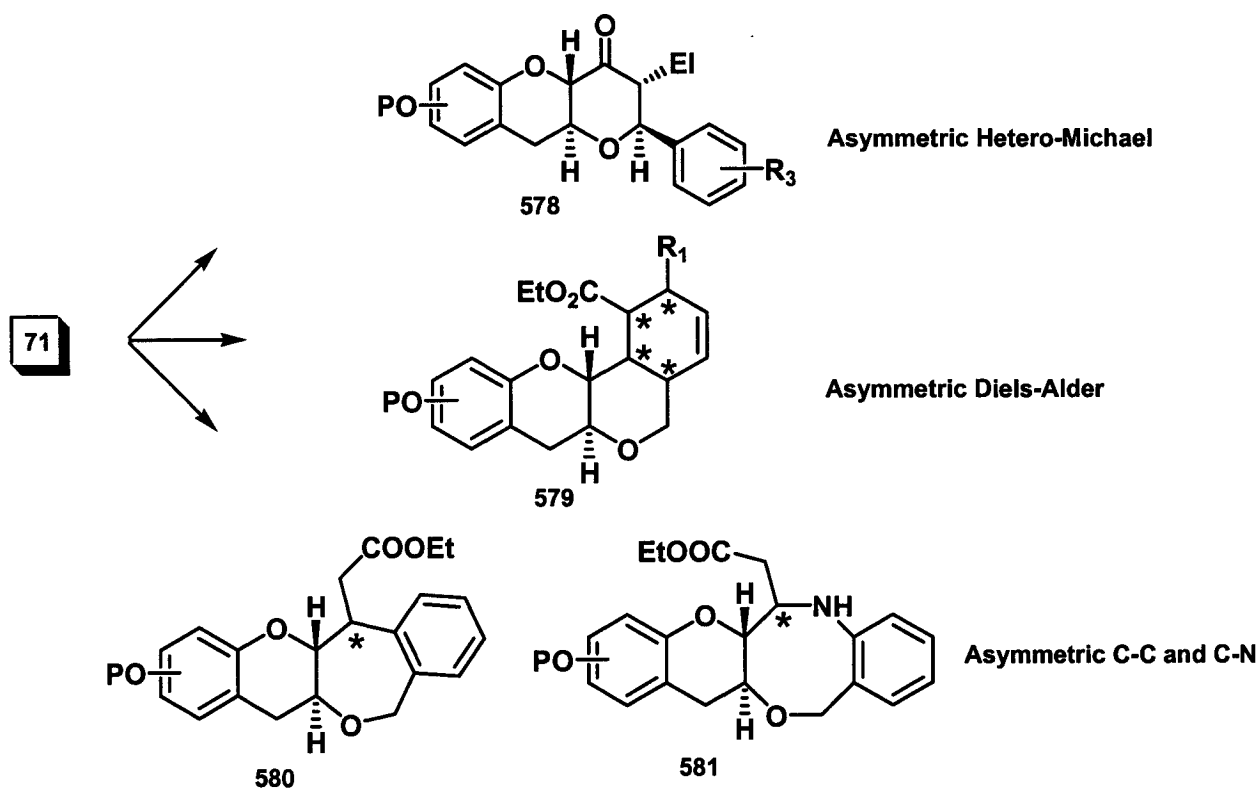
5. FUTURE DIRECTIONS

The future of the 2H-benzopyran project can be considered in two folds: (1) chemically – by the different types of scaffold development via asymmetric cascade reactions, Section 5.1 and (2) the biological testing of a library synthesized by IRORI technology, Section 5.2.

5.1 Future in Chemical Synthesis

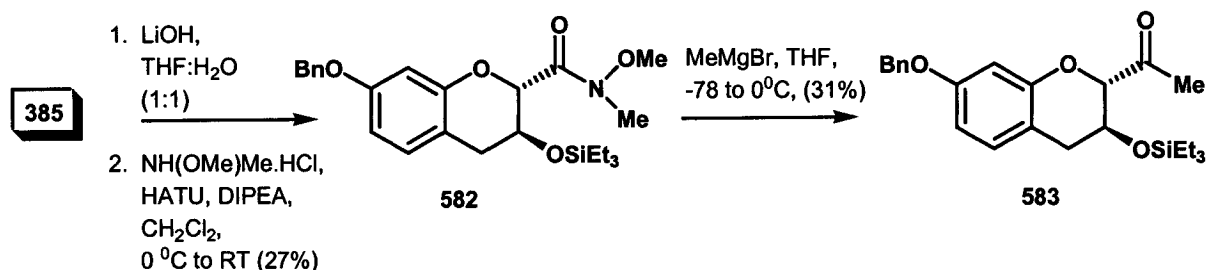
The ongoing projects on the benzopyran template are to synthesize tetracyclic scaffolds via (1) an asymmetric Hetero-Michael reaction to yield **578** (2) an asymmetric Diels-Alder reaction to yield **579** and (3) a transition metal catalyzed asymmetric C-C and C-N bond forming reaction to yield **580** and **581**, respectively (Scheme 5.1).

Scheme 5.1

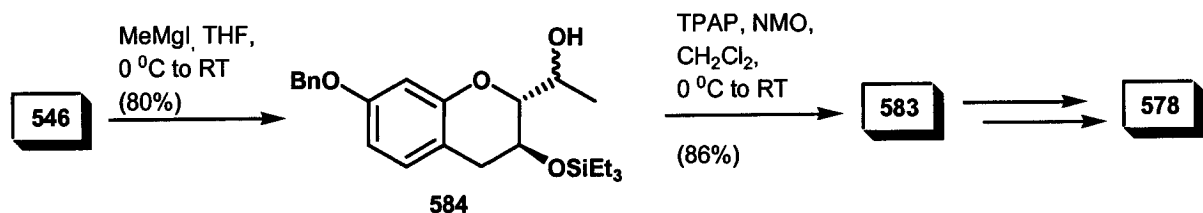


The asymmetric Hetero-Michael project was initiated with the hope of using Weinreb reaction to obtain compound **583** via **582** (Scheme 5.2). Although shorter routes were available for the synthesis of the methylketone, the primary concern was to prevent epimerisation of the α -substituted carboxyl ester derivatives. Therefore, mild conditions such as the preparation of the Weinreb amide **582** was considered. The results however, indicated poor yields for both the amide formation **582** (27% for the two steps) and ketone formation **583** via Grignard reaction (31%). Hence an alternate route was attempted, Scheme 5.3. In this route the aldehyde **546** was converted to the secondary alcohol **584** via Grignard reaction. A quantitatively good yield of 80% was observed for this reaction. The alcohol was then oxidized to the ketone **583** with TPAP, NMO.¹⁵⁸ Products were confirmed by MS and ¹H NMR analysis. The methylketone can then be extended to scaffolds such as **578**, using an asymmetric Hetero-Michael type reaction.¹⁵⁹

Scheme 5.2



Scheme 5.3



The key intermediates for the Diels-Alder cycloaddition reaction, and transition metal catalyzed asymmetric cascade reactions can be considered as **585**, **586**

and **587**, Figure 5.1. Preliminary results from the group¹⁶⁰ have indicated that the metal catalyzed asymmetric C-C bond formation reaction is feasible using $\text{Ni}(\text{cod})_2$ as a catalyst,^{161,162} **590**, (Scheme 5.4). The Diels-Alder project too, has been initiated by the use of sorbol bromide¹⁶³ to synthesize the key precursor **585**, Figure 5.1

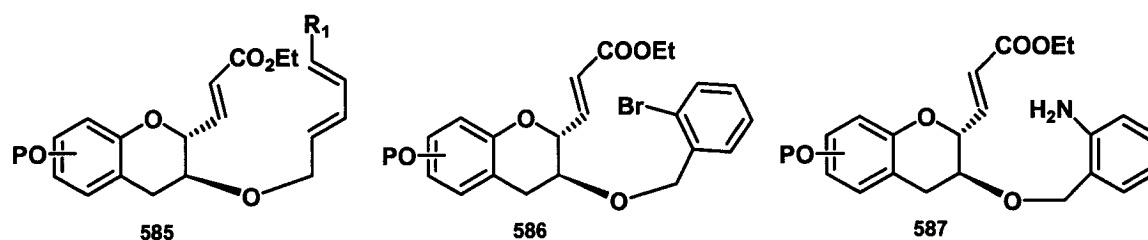
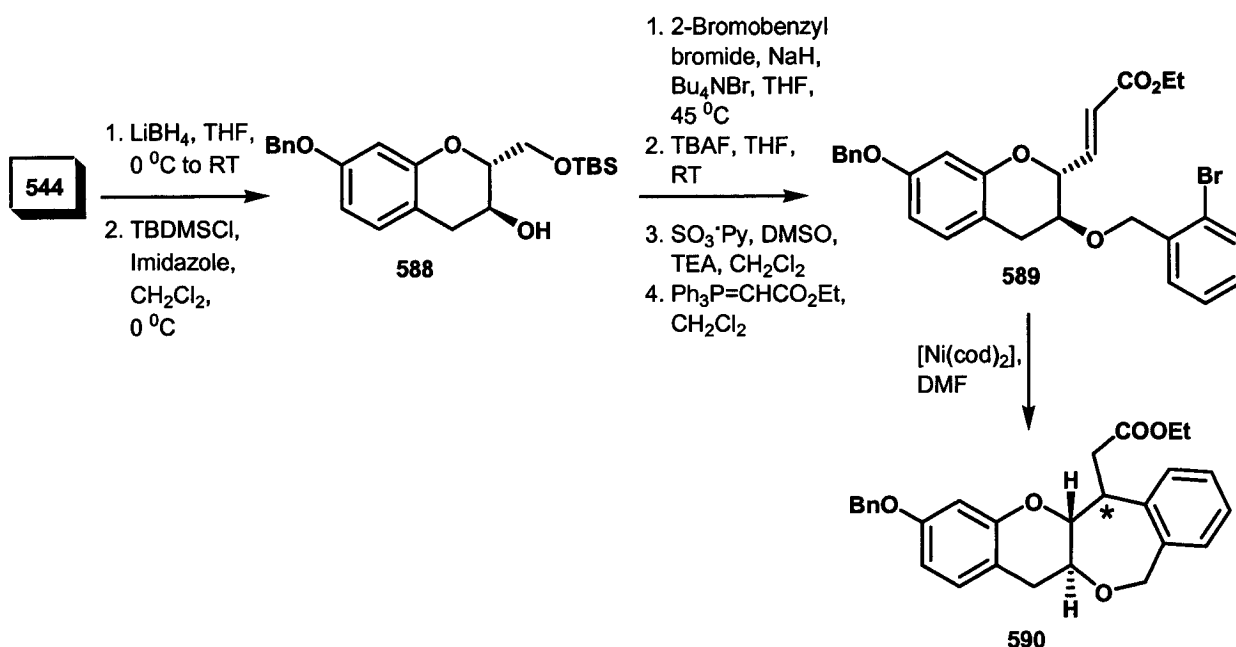


Figure 5.1 Key intermediates of asymmetric cascade reactions.

Scheme 5.4



5.2 Future in Biological Testing¹⁶⁴

The long-term goal of the group is to understand the eukaryotic protein synthesis by use of small-molecules. The strategy is to explore the ability of small molecules to affect the functions of mRNA's, Figure 5.2. For instance for the

small molecules, (1) to inhibit translation process in the cell by binding to mRNA, (2) to engage in protein/RNA complexes, and to (3) behave as RNase mimics. The interest also exists to identify novel inhibitors of eukaryotic protein synthesis by high-throughput chemical screening and bioinformatics.

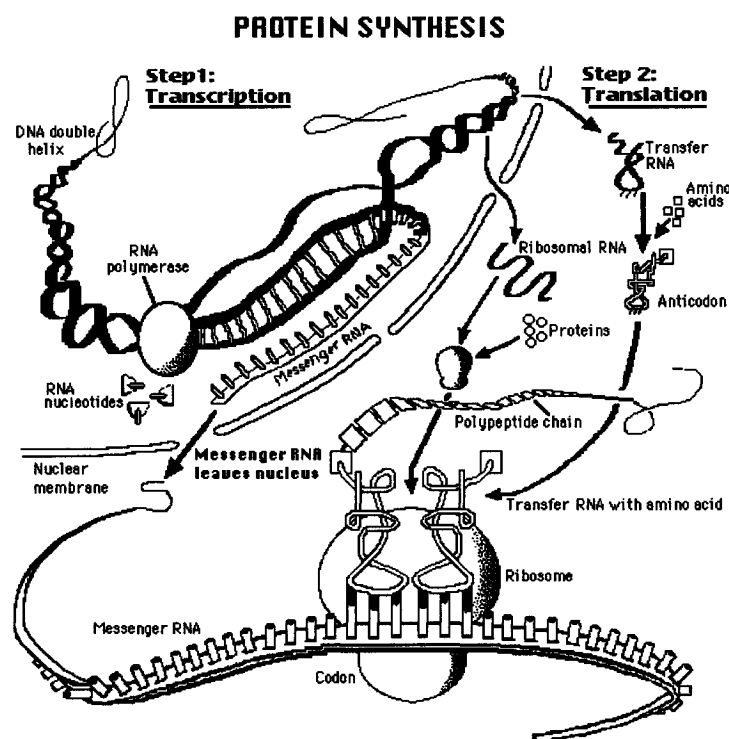


Figure 5.2 Two main information pathways in the cell: transcription and translation.

6. EXPERIMENTAL

6.1 General Methods of Analysis

Proton Nuclear Magnetic Resonance (NMR) spectra were recorded in CDCl_3 on a Bruker DRX 400 NMR Spectrometer, operating at 400.13 MHz for proton and 100.61 MHz for carbon. Chemical shifts were referenced to CDCl_3 at 7.27 ppm for ^1H spectra and at 77.23 ppm for ^{13}C spectra.

Low Resolution Mass Spectra (LRMS) using Electrospray (ES) were recorded on a VG Quattro I (Micromass) mass spectrometer. High Resolution Mass Spectra (HRMS) using Fast Atomic Bombardment (FAB) were recorded on JEOL AX 505 H spectrometer.

High Performance Liquid Chromatography (HPLC) using a Chiralcel OD" 250mm x 4.6mm chiral column, were recorded using Agilent 1090 liquid chromatograph equipped with diode array detector. The mobile phase compositions are stated for each case.

Melting points were determined on Fisher-Johns melting point apparatus and are uncorrected. Infrared (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. Samples were prepared as neat thin films or as thin films of carbon tetrachloride solution of the compounds or as sodium chloride discs.

Thin Layer Chromatography (TLC) was performed on silica gel 60 F₂₅₄ 250 μm coated on glass analytical TLC plates purchased from Merck KGaA, Germany. TLC spots were visualized under UV light of wavelength 254 nm, and heating the plate after treatment with visualizing agent. The visualizing agent was a solution

of 2% cerium sulfate, 5% ammonium molybdate and 18% concentrated sulfuric acid (w/v).

Product purifications were carried-out by conventional flash chromatography under nitrogen pressure with silica gel 230-400 mesh purchased from Silicycle, Canada. Solvents were evaporated *in vacuo* using a BUCHI Vacuum System B-178 rotary evaporator. Trace solvents were removed on a high vacuum pump.

All non aqueous reactions were performed under a nitrogen atmosphere using oven dried glassware, and dry solvents. Reactions performed at room temperature refer to a temperature of 21 – 23⁰C.

6.2 Solvents and Reagents

Chromatographic columns were eluted with ethyl acetate and hexanes. Hexanes refer to a mixture of 5 isomers of hexane and methylcyclopentane. Dichloromethane, acetonitrile and tetrahydrofuran (THF) were freshly distilled over calcium hydride, sodium hydride, and sodium and benzophenone respectively. Solvents were purchased from Merck KGaA, Germany. Grubbs catalysts were purchased from Strem Chemical Inc., USA, amino acids and resins from Novabiochem Corp., USA and all other chemicals and anhydrous solvents from Aldrich Chemical Company, and were used without prior purification.

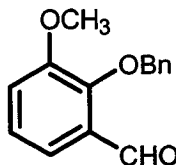
6.3 Computer Modelling Studies

Computer generated modelling studies were done using Hyperchem 5.1 for the computation of the lowest energy conformers.

6.4 Synthesis of Benzopyran Scaffold

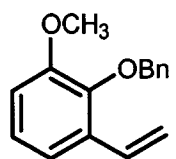
6.4.1 Model Studies

2-Benzyloxy-3-methoxy-benzaldehyde (**218**)



The procedure was adapted from Green's Protective groups in Organic Synthesis.¹⁶⁵ To a solution of o-vanillin **217** (20.0 g, 130 mmol) in acetone, was added anhydrous potassium carbonate (27.6 g, 200 mmol), and benzylbromide (17.1 mL, 143 mmol). The reaction mixture was stirred overnight at room temperature. The resulting product was filtered through celite, washed with acetone and ethylacetate. Solvents were evaporated on a rotor-evaporator. The crude product was dissolved in dichloromethane and washed with brine. The aqueous layer was further extracted with dichloromethane. The organic layers were combined, dried with anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 10%, 15% to 25% ethylacetate:hexanes to yield 26.28 g (84%) of the benzylated product **218** as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = ppm 3.91 (s, 3H), 5.20 (s, 2H), 7.13-7.18 (m, 2H), 7.35-7.42 (m, 6H), 10.29 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) ppm 56.5, 76.7, 118.4, 119.5, 124.7, 128.9, 129.0, 129.1, 130.8, 136.8, 151.5, 153.5, 190.7; LRMS: MS (ES+) m/z = 243.0 (M+1); HRMS (FAB): calcd for C₁₅H₁₄O₃ (M+) 242.1072, found 242.0943.

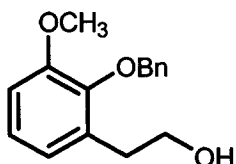
2-Benzyloxy-1-methoxy-3-vinyl-benzene (**219**)



The procedure was adapted from Overman et al.,¹⁶⁶ and Sondheimer et al.¹⁶⁷ To a suspension of triphenyl phosphoniumbromide (14.3 g, 40 mmol) in THF at 0 °C was added 1.0 M sodium hexamethyldisilazide in THF (170 mL, 40 mmol) and stirred at room temperature for 1h, to generate the Wittig product. The benzylated o-vanillin **218** (5 g, 20 mmol) was dissolved in THF and to it was added at 0 °C the above Wittig reagent under an inert atmosphere and nitrogen pressure. The resulting reaction mixture was stirred and warmed from 0 °C to room temperature overnight. The reaction was quenched at 0 °C by adding pieces of ice and THF

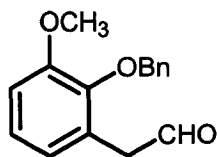
was rotor-evaporated. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and column purified with 10% ethylacetate:hexanes to yield a 4.17 g (87%) of the alkene product. Yellow liquid. ^1H NMR (400 MHz, CDCl_3) δ = (ppm) 3.95 (s, 3H), 5.11 (s, 2H), 5.38 (dd, J = 11.0, 1.2 Hz, 1H), 5.88 (dd, J = 17.8, 1.3 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.14-7.28 (m, 3H), 7.44-7.50 (m, 3H), 7.61 (s, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 56.3, 75.6, 112.2, 115.6, 118.3, 124.6, 128.4, 128.7, 128.9, 131.9, 132.6, 138.2, 146.1, 153.6; LRMS: MS (ES+) m/z = 241.0 (M+1); HRMS (FAB): calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$ (M+) 240.1208, found 240.1150.

2-(2-Benzyloxy-3-methoxy-phenyl)-ethanol (220)



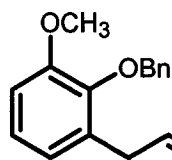
Hydroboration reaction was optimized in the group as per conditions given by Borger et al.,¹⁶⁸ and Nicolaou et al.¹¹⁵ To a solution of the alkene **219** (4.0 g, 15.5 mmol) in THF at 0 $^{\circ}\text{C}$ was added 0.5M 9-BBN in THF (70 mL, 34 mmol) and refluxed overnight. The reaction was quenched by adding 3N NaOH (60 mL, 170 mmol) and 30% H_2O_2 (40 mL, 340 mmol) at 0 $^{\circ}\text{C}$, and stirring at room temperature for 1h. The solvent was rotor-evaporated and the aqueous layer was extracted with ethylacetate. The organic layers were washed with brine, dried with anhydrous magnesium sulfate, concentrated column purified with 25% ethyl acetate:hexanes to yield a 3.85 g (88%) of the hydroxyl product. Yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = (ppm) 2.09-2.12 (bs, 1H), 2.88 (s, 2H), 3.79 (t, J = 6.6 Hz, 2H), 3.92 (s, 3H), 5.08 (s, 2H), 6.85 (dd, J = 7.6, 1.3 Hz, 1H), 6.89 (dd, J = 8.2, 1.4 Hz, 1H), 7.07 (t, J = 7.9 Hz, 1H), 7.37-7.44 (m, 3H), 7.52 (d, J = 7.0 Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 34.3, 56.2, 63.6, 75.2, 111.4, 123.0, 128.4, 128.6, 128.7, 128.8, 128.9, 138.2, 146.6, 153.3; LRMS: MS (ES+) m/z = 259.2 (M+1); HRMS (FAB): calcd for $\text{C}_{16}\text{H}_{18}\text{O}_3$ (M+) 258.1275, found 258.1256.

(2-Benzyloxy-3-methoxy-phenyl)-acetaldehyde (221)



The procedure for oxidation with pyridinium chlorochromate (PCC) was adapted from E. J. Corey and J. W. Suugs.¹⁶⁹ To a solution of the hydroxyl product **220** (3.85 g, 15 mmol) in dichloromethane was added pyridinium chlorochromate (4.96 g, 1.5) and stirred at room temperature for 2h. The reaction was quenched by addition of ether, and the solid precipitate was washed with ether and ethylacetate. The resulting suspension was filtered through celite, solvents rotor-evaporated, and column purified with gradient elution of 5%, 15%, 35%, 50% to 70% ethyl acetate:hexanes to yield 2.73 g (71%) of the homologous aldehyde product. Yellow oil. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 3.61 (d, J = 2.1 Hz, 2H), 3.94 (s, 3H), 5.08 (s, 2H), 6.78 (dd, J = 7.6, 1.3 Hz, 1H), 6.96 (dd, J = 8.3, 1.4 Hz, 1H), 7.10 (t, J = 7.9, 1H), 7.36-7.47 (m, 5H), 9.60 (t, J = 2.1 Hz, 1H); LRMS: MS (ES+) m/z = 257.2 (M+1); HRMS (FAB): calcd for C₁₆H₁₆O₃ (M+) 256.1095, found 256.1099.

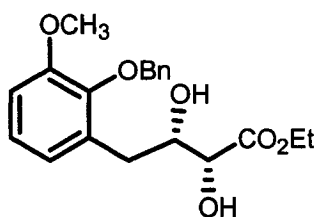
4-(2-Benzyloxy-3-methoxy-phenyl)-but-2-enoic acid ethyl ester (222)



The ester was synthesized under standard conditions. To a solution of the homo-aldehyde **221** (3.37 g, 13.16 mmol) in dichloromethane was added (carbethoxymethylene) triphenyl phosphorane (10.07 g, 28.9 mmol) and stirred overnight at room temperature. The solvent was rotor-evaporated and column purified with 10% ethyl acetate:hexanes to yield 3.1 g (72%) of the *trans*-alkene product. Pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = (ppm) 1.30 (t, J = 7.1, 3H), 3.49 (dd, J = 6.6, 1.1 Hz, 2H), 3.92 (s, 3H), 4.19 (q, J = 7.1 Hz, 2H), 5.05 (s, 2H), 5.76 (d, J = 15.6 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 7.2 Hz, 1H), 7.04-7.07 (m, 2H), 7.37-7.43 (m, 3H), 7.47 (d, J = 7.1 Hz, 2H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 14.7, 33.1, 56.2, 60.6, 75.2, 111.6, 122.6, 124.6, 124.7, 128.4, 128.6, 128.8, 132.4, 138.2, 146.3, 147.8, 153.4, 166.9; LRMS: MS (ES+)

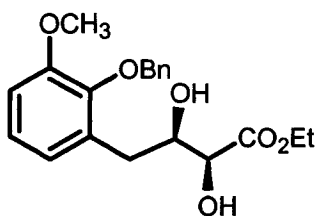
$m/z = 327.4$ ($M+1$); HRMS (FAB): calcd for $C_{20}H_{22}O_4$ ($M+$) 326.1519, found 326.1518.

4-(2-Benzyloxy-3-methoxy-phenyl)-2,3-dihydroxy-butyrlic acid ethyl ester (223a)



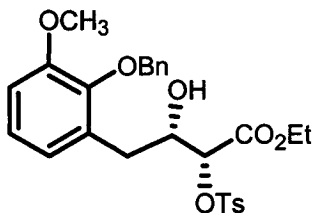
The diol was prepared according to the Sharpless catalytic asymmetric dihydroxylation conditions.⁷⁹ To a solution of *t*-butanol:water (1:1, 10 mL) was added *trans*-alkene product **222** (0.5 g, 1.53 mmol) and stirred until it was completely dissolved. AD-mix- α (2.14 g) was added at 0 °C and stirred for 15 min. To this reaction mixture methanesulfonamide (0.15 g) was added at 0 °C and stirred for 24h at room temperature. The reaction mixture was quenched by adding sodium thiosulfate (2.14 g) at 0 °C, and being stirred for 1h at room temperature. The organic layer was separated and the aqueous layer extracted with ethylacetate. The organic layers were combined and washed with 2N KOH, dried with anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 20%, 50% to 67% ethyl acetate:hexanes to yield 0.37 g (69%) of the diol product. White solid. 1H NMR: (400 MHz, $CDCl_3$) δ = (ppm) 1.27, (t, $J = 7.1$ Hz, 3H), 2.52 (d, $J = 7.8$ Hz, 1H), 2.84, (dd, $J = 13.4, 6.1$ Hz, 1H), 3.01, (dd, $J = 13.4, 8.2$ Hz, 1H), 3.16 (d, $J = 6.2$ Hz, 1H), 3.91 (s, 3H), 4.03 (dd, $J = 6.1, 1.6$ Hz, 1H), 4.17-4.24 (m, 3H), 5.07 (s, 2H), 6.88 (t, $J = 8.8$ Hz, 2H), 7.07 (t, $J = 7.9$ Hz, 1H), 7.36-7.42 (m, 3H), 7.50 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) = (ppm) 14.5, 35.5, 56.2, 62.2, 72.9, 73.5, 75.3, 111.7, 123.4, 124.8, 128.5, 128.7, 128.9, 132.2, 137.9, 146.6, 153.2, 173.7; R_f : Chiral HPLC R_t = 28.02 (min) EtOH/Hex = 3:97, ee = 70%; LRMS: MS (ES+) $m/z = 361.3$ ($M+1$); HRMS (FAB): calcd for $C_{20}H_{24}O_6$ ($M+$) 360.1633, found 360.1573.

4-(2-Benzyloxy-3-methoxy-phenyl)-2,3-dihydroxy-butyric acid ethyl ester (223b)



To a solution of *t*-butanol:water (1:1, 5 mL) was added *trans*-alkene product **222** (0.25 g, 0.78 mmol) and stirred until it was completely dissolved. AD-mix- α (1.09 g) was added at 0 °C and stirred for 15 min. To this reaction mixture methanesulfonamide (0.074 g) was added at 0 °C and stirred for 24h at room temperature. The reaction mixture was quenched by adding sodium thiosulfate (1.09 g) at 0 °C, and being stirred for 1h at room temperature. The organic layer was separated and the aqueous layer extracted with ethylacetate. The organic layers were combined and washed with 2N KOH, dried with anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 20%, 50% to 67% ethyl acetate:hexanes to yield the diol product (yield was not optimized).

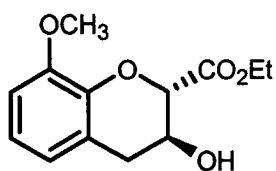
4-(2-Benzyloxy-3-methoxy-phenyl)-3-hydroxy-2-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (224)



The procedure for the regioselective tosylation was adapted from P. Arya and B. V. N. B. S. Sarma.⁷⁷ To a solution of the diol **223a** (0.1 g, 0.28 mmol) in dichloromethane was added at 0 °C excess triethylamine (400 μ L, 3 mmol), and *p*-toluene sulfurnoyl chloride (0.053 g, 0.28 mmol). The reaction mixture was stirred from 0 °C to room temperature, overnight. The reaction was quenched by addition of water, and the organic layer was separated. The aqueous layer was further extracted with dichloromethane. The organic layers were combined, dried with anhydrous magnesium sulfate, concentrated and column purified with 35% ethyl acetate:hexanes to yield the tosylated alcohol 0.82 g (57%). Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 1.17 (t, *J* = 7.1 Hz, 3H), 2.46 (s, 3H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.69 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.91 ((dd, *J* = 13.9, 9.6 Hz, 1H), 3.91 (s, 3H), 4.08-4.15 (m, 2H), 4.21-4.30 (m, 1H), 4.87 (d, *J* = 2.7 Hz, 1H), 5.04 ((q, *J* = 11.8 Hz, 2H), 6.78

(d, $J = 6.7$ Hz, 1H), 6.89 (d, $J = 7.1$ Hz, 1H), 7.06 (t, $J = 7.9$ Hz, 1H), 7.32-7.41 (m, 5H), 7.46 (d, $J = 6.7$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.6, 22.1, 35.0, 56.2, 62.3, 72.7, 75.2, 79.9, 112.0, 123.3, 124.8, 128.3, 128.6, 128.8, 128.9, 130.1, 131.6, 133.7, 137.8, 145.5, 146.4, 153.1, 167.5; LRMS: MS (ES+) $m/z = 515.4$ (M+1); HRMS (FAB): calcd for $\text{C}_{27}\text{H}_{30}\text{O}_8\text{S}$ (M+) 514.1703, found 514.1661.

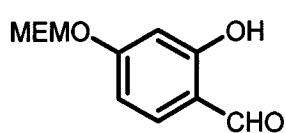
3-Hydroxy-8-methoxy-chroman-2-carboxylic acid ethyl ester (225)



Cyclization was achieved under conditions used by P. Arya and B. V. N. B. S. Sarma.⁷⁷ To a solution of the tosylated alcohol **224** (0.82 g, 0.16 mmol) in THF, under a vigorous bubbling of nitrogen, was added anhydrous potassium carbonate (0.4 g, 0.32 mmol) and Pd/C (0.28, 33%). The reaction mixture was stirred at room temperature under pressurized hydrogen for 48h. The reaction mixture was filtered through celite, the solvent was rotor-evaporated and column purified with gradient elution of 40% to 50% ethyl acetate:hexanes to yield the bicyclic benzopyran product 0.04 g (94%). White solid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.26 (t, $J = 7.1$ Hz, 3H), 2.81 (dd, $J = 16.8, 5.5$ Hz, 1H), 2.97 (dd, $J = 16.8, 4.6$ Hz, 1H), 3.87 (s, 3H), 4.21-4.27 (m, 2H), 4.41-4.44 (bs, 1H), 4.74 (d, $J = 4.6$ Hz, 1H), 6.65 (d, $J = 7.6$ Hz, 1H), 6.76 (d, $J = 7.6$ Hz, 1H), 6.86 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.5, 31.5, 56.4, 62.2, 64.4, 110.2, 119.6, 121.6, 121.7, 122.4, 142.2, 148.5, 169.9; LRMS: MS (ES+) $m/z = 253.2$ (M+1); HRMS (FAB): calcd for $\text{C}_{13}\text{H}_{16}\text{O}_5$ (M+) 252.1005, found 252.0998.

6.4.2 Solution Phase Studies for Solid Phase Synthesis

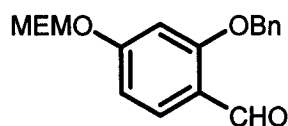
2-Hydroxy-4-(2-methoxy-ethoxymethoxy)-benzaldehyde (226)



MEM-protection of the 2,4-dihydroxybenzaldehyde **121** was adapted from Greens' book of 'Protective groups in Organic Synthesis'.¹⁶⁵ To a suspension of the 2,4-

dihydroxybenzaldehyde **121** (10.0 g, 72.4 mmol) in dichloromethane, was added at 0 °C, DIPEA (15.2 mL, 86.88 mmol) and MEM-chloride (8.3 mL, 72.4 mmol). The reaction mixture was stirred from 0 °C to room temperature overnight. The resulting reaction mixture was quenched, by adding water. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried with anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 20% to 30% ethyl acetate:hexanes to yield 12.09 g (74%) of the mono-MEM protected product. Colourless liquid. ¹H NMR (400 MHz, CDCl₃) δ = ppm 3.33 (s, 3H), 3.52 (t, J = 4.6 Hz, 2H), 3.78 (t, J = 4.7 Hz, 2H), 5.28 (s, 2H), 6.56 (d, J = 2.2, 1H), 6.62 (dd, J = 8.6, 2.2 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 9.68 (s, 1H), 11.32 (s, 1H); ¹³C NMR: (100 MHz, CDCl₃) ppm 59.9, 67.5, 71.9, 93.0, 103.9, 110.1, 130.1, 135.1, 153.2, 195.1; LRMS: MS (ES+) m/z = 227.2 (M+1); HRMS: (FAB): calcd for C₁₁H₁₅O₅ (M+1) 227.0931, anal. calcd for C₁₁H₁₄O₅ C, 58.40; H, 6.24; O, 35.36 found 226.0841.

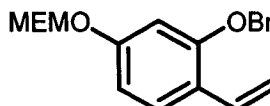
2-Benzoyloxy-4-(2-methoxy-ethoxymethoxy)-benzaldehyde (**227**)



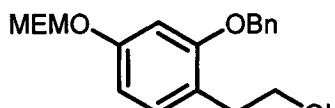
To a solution of MEM-protected hydroxyaldehyde **226** (12.07 g, 53.35 mmol) in acetone, was added anhydrous potassium carbonate (18.43 g, 133.4 mmol), and benzylbromide (7.62 mL, 64.02 mmol). The reaction mixture was stirred overnight at room temperature. The resulting product was filtered through celite, washed with acetone and ethylacetate, solvents were evaporated on a rotor-evaporator and column purified with gradient elution of 30% to 40% ethyl acetate:hexanes to yield 14.21 g (84%) of the benzyl-protected product. Yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ = ppm 3.33 (s, 3H), 3.50-3.52 (m, 2H), 3.77-3.79 (m, 2H), 5.11 (s, 2H), 5.27 (s, 2H), 6.69-6.71 (m, 2H), 7.35-7.42 (m, 5H), 7.78 (d, J = 8.6 Hz, 1H), 10.38 (s, 1H); ¹³C NMR: (100 MHz, CDCl₃) ppm 58.1, 67.5, 70.8, 71.1, 88.1, 100.1, 109.2, 125.0, 125.2, 125.5, 129.2, 130.0, 137.2, 157.2, 189.8; LRMS: MS (ES+) m/z = 317.3 (M+1); HRMS: (FAB): calcd for

C₁₈H₂₁O₅ (M+1) 317.1422, anal. calcd for C₁₈H₂₀O₅ C, 68.34; H, 6.37; O, 25.29 found 316.1311

2-Benzyloxy-4-(2-methoxy-ethoxymethoxy)-1-vinyl-benzene (228)

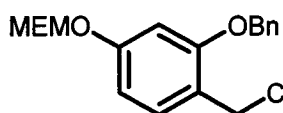
 To a suspension of triphenyl phosphoniumbromide (32.09 g, 89.84 mmol) in THF at 0 °C was added 1.0 M sodium hexamethyldisilazide in THF (89.8 mL, 89.84 mmol) and stirred at room temperature for 1h, to generate the Wittig reagent. The dihydroxy-protected benzaldehyde **227** (14.21 g, 44.92 mmol) was dissolved in THF and at 0 °C the above Wittig reagent was added to it, under an inert atmosphere and pressure. The resulting reaction mixture was stirred and warmed from 0 °C to room temperature overnight. The reaction was quenched at 0 °C by adding pieces of ice, filtered through celite and THF was rotor-evaporated. The aqueous solution was extracted with ethylacetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and column purified with gradient elution of 20% to 30% ethylacetate:hexanes to yield a 10.78 g (76%) of the alkene product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 3.43 (s, 3H), 3.58-3.60 (m, 2H), 3.85-3.88 (m, 2H), 5.12 (s, 2H), 5.24 (d, J = 11.2 Hz, 1H), 5.31 (s, 2H), 5.75 (d, J = 17.7 Hz, 1H), 6.77 (s, 2H), 7.15 (dd, J = 17.7, 11.1 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 7.43-7.52 (m, 5H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 57.5, 67.1, 70.0, 71.2, 93.5, 101.1, 109.5, 113.2, 113.3, 127.1, 128.1, 128.5, 129.2, 130.1, 137.2, 157.5; LRMS: MS (ES+) m/z = 315.3 (M+1); HRMS: (FAB): calcd for C₁₉H₂₂O₄ (M+) 314.1812, found 314.1518.

2-Benzyloxy-4-(2-methoxy-ethoxymethoxy)-1-vinyl-benzene (229)

 To a solution of the alkene **228** (10.41 g, 33.17 mmol) in THF at 0 °C was added 0.5M 9-BBN in THF (166 mL, 83 mmol) and refluxed overnight. The reaction was quenched by adding 3N NaOH (110 mL, 330 mmol) and 30% H₂O₂ (75 mL, 660 mmol) at 0 °C, and stirring at room temperature for 1h. The solvent was rotor-

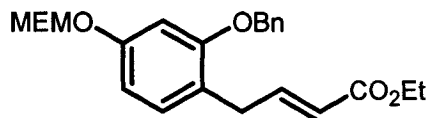
evaporated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with brine, dried with anhydrous magnesium sulfate, concentrated column purified with gradient elution of 50% to 65% ethyl acetate:hexanes to yield 9.71 g (88%) of the hydroxyl product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.90 (t, J = 6.6 Hz, 2H), 3.40 (s, 3H), 3.56-3.58 (m, 2H), 3.80-3.84 (m, 4H), 5.07 (s, 2H), 5.25 (s, 2H), 6.67 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 7.39-7.45 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 34.0, 59.4, 63.2, 68.0, 70.4, 72.0, 94.1, 101.9, 108.3, 121.2, 127.9, 128.5, 129.0, 131.7, 137.3, 157.9; LRMS: MS (ES+) m/z = 333.3 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{19}\text{H}_{24}\text{O}_5$ ($M+$) 332.1648, found 332.1624.

[2-Benzoyloxy-4-(2-methoxy-ethoxymethoxy)-phenyl]-acetaldehyde (230)



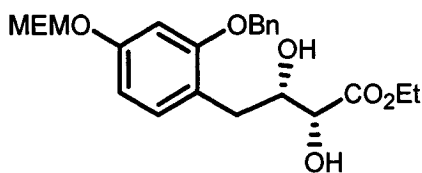
The procedure for Swern oxidation was adapted from S. M. Parra.⁸¹ To a solution DMSO (5.13 mL, 72.3 mmol) in dichloromethane was added at -78°C , oxalyl chloride (2.57 mL, 28.9 mmol) and stirred for 5 –10 min. To this reaction mixture, was added under pressure and an inert atmosphere, a solution of the hydroxyl product **229** (8.01 g, 21.07 mmol) in dichloromethane and stirred at -78°C for 1h. The reaction was quenched by addition of excess of triethylamine (20.8 mL, 149.42 mmol) at -78°C . The solvents were rotor-evaporated, and column purified with gradient elution of 40% to 50% ethylacetate:hexanes to yield 5.23 g (75%) of the homologous aldehyde product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 3.40 (s, 3H), 3.56-3.59 (m, 2H), 3.65 (d, J = 1.8Hz, 2H), 3.83-3.85 (m, 2H), 5.07 (s, 2H), 5.27 (s, 2H), 6.71-6.76 (m, 2H), 7.08 (d, J = 8.3 Hz, 1H), 7.40-7.43 (m, 5H), 9.71 (d, J = 1.9 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm); 45.3, 59.4, 68.1, 70.9, 71.9, 72.0, 94.0, 101.9, 108.5, 115.3, 127.6, 128.4, 129.0, 132.1, 137.0, 157.9, 200.7; LRMS: MS (ES+) m/z = 331.2 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{19}\text{H}_{22}\text{O}_5$ ($M+$) 330.1467, found 330.1467.

4-[2-Benzyloxy-4-(2-methoxy-ethoxymethoxy)-phenyl]-but-2-enoic acid ethyl ester (231)



A solution of the homo-aldehyde **230** (4.4 g, 13.32 mmol) in dichloromethane and (carbethoxymethylene) triphenyl phosphorane (10.21 g, 29.3 mmol) was stirred overnight at room temperature. The solvent was rotor-evaporated and column purified with 40% ethyl acetate:hexanes to yield 5.25 g (97%) of the *trans*-alkene product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.29 (t, J = 7.1 Hz, 3H), 3.40 (s, 3H), 3.51 (d, J = 6.6 Hz, 2H), 3.56-3.58 (m, 2H), 3.82-3.85 (m, 2H), 4.19 (q, J = 7.1 Hz, 2H), 5.06 (s, 2H), 5.26 (s, 2H), 5.79 (d, J = 15.5 Hz, 1H), 6.66 (dd, J = 8.3, 2.12 Hz, 1H), 6.72 (d, J = 2.1 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 7.12-7.16 (m, 1H), 7.33-7.44 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.8, 32.9, 59.4, 68.0, 70.3, 70.4, 72.0, 94.1, 101.9, 108.3, 120.4, 122.1, 127.6, 127.7, 128.3, 130.0, 137.3, 148.0, 157.6, 166.7; LRMS: MS (ES+) m/z = 401.3 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{23}\text{H}_{28}\text{O}_6$ ($M+$) 400.1896, found 400.1886.

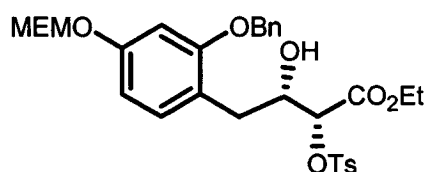
4-[2-Benzyloxy-4-(2-methoxy-ethoxymethoxy)-phenyl]-2,3-dihydroxy-butyric acid ethyl ester (232)



To a solution of *t*-butanol:water (1:1, 60 mL) was added *trans*-alkene product **231** (4.8 g, 11.99 mmol) and stirred until it was completely dissolved. AD-mix- α (16.8 g) was added at 0 $^{\circ}\text{C}$ and stirred for 15 min. Methanesulfonamide (1.14 g) was added at 0 $^{\circ}\text{C}$ and the mixture was stirred for 24h at room temperature. The reaction mixture was quenched by adding sodium thiosulfate (16.8 g) at 0 $^{\circ}\text{C}$, and being stirred for 1h at room temperature. The organic layer was separated and the aqueous layer extracted with ethyl acetate. The organic layers were combined and washed with 2N KOH, dried with anhydrous magnesium sulfate, concentrated and column purified with 50% ethylacetate:hexanes to yield 3.78 g (73%) of the diol product.

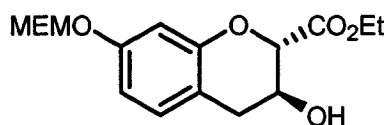
Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.25, (t, J = 7.1 Hz, 3H), 2.31 (bs, 1H), 2.94 (dd, J = 13.2, 6.3 Hz, 1H), 3.00, (dd, J = 13.5, 7.9 Hz, 1H), 3.12 (bs, 1H), 3.39 (s, 3H), 3.55-3.57 (m, 2H), 3.81-3.83 (m, 2H), 4.07 (d, J = 4.1 Hz, 1H), 4.20-4.27 (m, 3H), 5.08 (s, 2H), 5.24 (s, 2H), 6.66 (dd, J = 8.6, 2.6 Hz, 1H), 6.72 (d, J = 2.2 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.33-7.46 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 15.2, 34.8, 59.7, 61.1, 67.2, 70.1, 70.2, 73.1, 73.5, 73.8, 74.1, 95.1, 101.2, 109.5, 125.1, 125.7, 130.1, 137.4, 157.2, 166.3; R_f : Chiral HPLC R_t = 15.62 (min) EtOH/ ee = 70%; LRMS: MS (ES+) m/z = 435.3 (M+1); HRMS: (FAB): calcd for $\text{C}_{23}\text{H}_{30}\text{O}_8(\text{M}^+)$ 434.1932, found 434.1941.

4-[2-Benzyloxy-4-(2-methoxy-ethoxymethoxy)-phenyl]-3-hydroxy-2-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (233)



To a solution of the diol **232** (1.0 g, 2.3 mmol) in acetonitrile was added at 0 $^{\circ}\text{C}$ DIPEA (1 mL, 5.75 mmol), catalytic amount of DMAP and *p*-toluene sulfurnoyl chloride (0.48 g, 2.53 mmol). The reaction mixture was stirred overnight from 0 $^{\circ}\text{C}$ to room temperature. The reaction was quenched by addition of water, and the organic layer was separated. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried with anhydrous magnesium sulfate, concentrated and column purified with 35% ethyl acetate:hexanes to yield the tosylated alcohol 0.42 g (47%). Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.17 (t, J = 7.1 Hz, 3H), 2.31 (bs, 1H), 2.46 (s, 3H), 2.81 (dd, J = 13.9, 4.6 Hz, 1H), 2.88 (d, J = 8.9 Hz, 1H), 3.40 (s, 3H), 3.56-3.58 (m, 2H), 3.81-3.83 (m, 2H), 4.11 (q, J = 4.1 Hz, 2H), 4.33-4.37 (bm, 1H), 4.91 (d, J = 2.8 Hz, 1H), 5.07 (s, 2H), 5.25 (s, 2H), 6.63 (dd, J = 8.2, 2.2 Hz, 1H), 6.69 (d, J = 2.1 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.33-7.42 (m, 7H), 7.86 (d, J = 8.2 Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.3, 22.1, 34.6, 59.4, 62.3, 68.0, 70.5, 72.0, 72.1, 79.9, 94.0, 101.9, 108.5, 119.3, 127.6, 128.4, 129.1, 130.1, 132.2, 133.7, 137.0, 145.5, 157.8, 158.0, 167.7; LRMS: MS (ES+) m/z = 589.2 (M+1); HRMS: (FAB): calcd for $\text{C}_{30}\text{H}_{36}\text{O}_{10}\text{S}(\text{M}^+)$ 588.2070, found 588.2029.

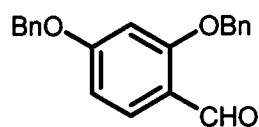
3-Hydroxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-carboxylic acid ethyl ester (234)



To a solution of tosylated alcohol **233** (1.4 g, 2.37 mmol) in THF, under a vigorous bubbling of nitrogen, was added anhydrous potassium carbonate (0.82 g, 5.93 mmol) and Pd/C (0.42, 30%). The reaction mixture was stirred at room temperature under pressurized hydrogen for 24h. The reaction mixture was filtered through celite, the solvent was then rotor-evaporated and column purified with 40% ethyl acetate:hexanes to yield the bicyclic benzopyran product 0.63 g (82%). Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.31 (t, J = 7.1 Hz, 3H), 2.77 (dd, J = 16.4, 5.8 Hz, 1H), 2.96 (dd, J = 16.3, 4.8 Hz, 1H), 3.39 (s, 3H), 3.56-3.58 (m, 2H), 3.81-3.83 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.38-4.41 (m, 1H), 4.58 (d, J = 5.7 Hz, 1H), 5.24 (s, 2H), 6.65 (dd, J = 8.3, 2.4 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.5, 31.3, 59.4, 62.3, 64.7, 68.1, 72.0, 93.3, 104.8, 110.7, 112.2, 131.0, 153.4, 157.5, 170.1; LRMS: MS (ES+) m/z = 327.2 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{16}\text{H}_{22}\text{O}_7$ ($M+$) 326.1387, found 326.1366.

6.4.3 Optimization of Solution Phase Synthesis

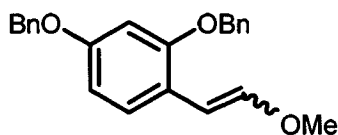
2,4-Bis-benzyloxy-benzaldehyde (235)



To a suspension of the 2,4-dihydroxy benzaldehyde **121** (10.0 g, 72.4 mmol), and anhydrous potassium carbonate (50.03 g, 326 mmol) in acetone, was added benzylbromide (21.5 mL, 181 mmol). The reaction mixture was stirred overnight at room temperature. The resulting product was filtered through celite and washed with acetone and ethylacetate. The solvents were evaporated on a rotor-evaporator and column purified with gradient elution of 20% to 40% ethylacetate:hexanes to yield 18.6 g (80%) of the dibenzylated product. White solid; 53-55 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ = ppm 5.13 (s, 2H), 5.16 (s, 2H), 6.63, (d, J = 1.9 Hz, 1H), 6.67 (d, J = 8.5 Hz, 1H), 7.36-7.47 (m, 10H), 7.87 (d, J = 8.7 Hz, 1H), 10.42 (s, 1H); ^{13}C NMR:

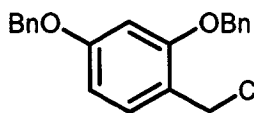
(100 MHz, CDCl₃) ppm 70.8, 100.5, 107.4, 119.9, 127.7, 128.0, 128.7, 128.8, 129.2, 131.0, 135.7, 188.7; LRMS: MS (ES+) *m/z* = 319.1 (M+1); HRMS: (FAB): calcd for C₂₁H₁₈O₃ (M+) 318.1244, found 318.1256.

2,4-Bis-benzyloxy-1-(2-methoxy-vinyl)-benzene



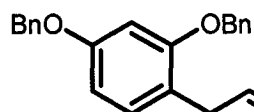
To a suspension of (methoxymethyl)triphenyl phosphonium chloride (12.9 g, 37.7 mmol) in THF at 0 °C was added 1.0 M potassium *t*-butoxide in THF (78.5 mL, 78.5 mmol) and stirred at room temperature for 1h, to generate the Wittig reagent. The 2,4-dibenzyl benzyaldehyde **235** was dissolved in THF and at 0 °C the above Wittig reagent was added to it, under an inert atmosphere and nitrogen pressure. The resulting reaction mixture was stirred and warmed from 0 °C to room temperature overnight. The reaction was quenched at 0 °C by adding water and THF was rotor-evaporated. The aqueous solution was then neutralized until pH 6 by adding 2N HCl, extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was column purified with 20% ethyl acetate:hexanes to yield a 9.73 g (90%) of the methoxy-enol ether product. White solid. ¹H NMR (400 MHz, CDCl₃) δ = (ppm) cis: 3.78 (s, 3H), 5.06-5.10 (m, 8H), 5.70 (d, *J* = 7.1 Hz, 1H), 6.13 (d, *J* = 7.2 Hz, 1 H), 6.56-6.64 (m, 4H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.28-7.48 (m, 20H), 8.01 (d, *J* = 9.2 Hz, 1H), trans: 3.67 (s, 3H), 6.06 (d, *J* = 12.9 Hz, 1H), 7.09 (d, *J* = 12.9 Hz, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 56.9 (t), 60.9 (c), 70.7, 99.1 (c), 100.9 (t), 101.5, 106.3, 106.7, 118.8, 119.2, 127.2, 128.0, 128.4, 128.5, 128.9, 129.1, 130.7, 137.5, 147.0 (c), 148.9 (t); LRMS: MS (ES+) *m/z* = 347.1 (M+1); HRMS: (FAB): calcd for C₂₃H₂₂O₃ (M+) 346.1738, found 346.1569.

(2,4-Bis-benzyloxy-phenyl)-acetaldehyde (236)



Synthesis of the homologous aldehyde was adopted from the conditions optimized by P. Arya and C.-Q. Wei.¹⁷⁰ To a solution of the 2,4-dibenzyl methoxy-enol ether (9.70 g, 28 mmol) in THF was added 2N HCl (115 mL). The mixture was stirred overnight at 60 °C. After removal of THF, the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine until neutral to pH (pH = 7). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to yield 8.21 g (88%) of crude aldehyde. Yellow liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 3.65 (d, J = 1.8 Hz, 2H), 5.65 (s, 4H), 6.65 (dd, J = 8.2, 2.2 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 7.10 (d, J = 8.2, 1H), 7.3-7.4 (m, 10 H), 9.73 (t, J = 1.9 Hz, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 45.3, 70.7, 101.2, 106.3, 114.5, 127.7, 128.4, 128.9, 132.1, 137.2, 160.1, 200.8; LRMS: MS (ES+) m/z = 333..1 (M+1); HRMS: (FAB): calcd for C₂₂H₂₀O₃ (M+) 332.1398, found 332.1412.

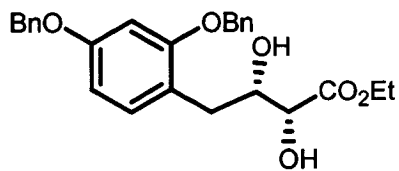
4-(2,4-Bis-benzyloxy-phenyl)-but-2-enoic acid ethyl ester (237)



To a solution of the 2,4-dibenzyl homo-aldehyde **236** (7.48 g, 22.51 mmol) in dichloromethane was added (carbethoxymethylene) triphenyl phosphorane and stirred overnight at room temperature. The solvent was rotor-evaporated and column purified with 10% ethylacetate:hexanes to yield 6.63 g (74%) of the *trans*-alkene product. White solid; M. pt. 46-48 °C; ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 1.32 (t, J = 7.1 Hz, 3H), 3.55 (d, J = 6.6 Hz, 2H), 4.23 (q, J = 14.3, 7.1 Hz, 2H), 5.07 (s, 4H), 5.82 (d, J = 15.6 Hz, 1H), 6.58 (dd, J = 8.3, 1.1 Hz, 1H), 6.66 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.12-7.19 (dt, J = 15.6, 6.7 Hz, 1H), 7.36-7.45 (m, 10H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 15.1, 33.0, 60.5, 70.5, 102.0, 106.5, 123.0, 126.8, 128.5, 129.2, 132.0, 134.5,

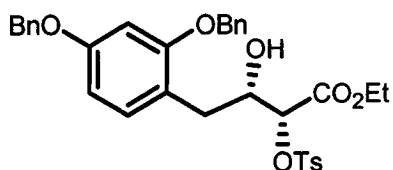
137.0, 151.9, 149.5, 177.0; LRMS: MS (ES+) m/z = 403.3 (M+1); HRMS: (FAB): calcd for $C_{26}H_{26}O_4$ (M+) 402.1815, found 402.1831.

4-(2,4-Bis-benzyloxy-phenyl)-2,3-dihydroxy-butyric acid ethyl ester (238a)



To a solution of *t*-butanol:acetone:water (1:1:1, 82 mL) was added dibenzylated alkene **237** (6.43 g, 15.98 mmol) and the mixture was stirred until it was completely dissolved. AD-mix- α (22.37 g) was added at 0 °C and stirred for 15 min. To this reaction mixture methanesulfonamide was added at 0 °C and stirred for 24h at room temperature. The reaction mixture was quenched by adding sodium thiosulfate (22.4 g) at 0 °C, and stirring for 1h at room temperature. The acetone was then rotor-evaporated and the aqueous layer extracted with ethyl acetate. The organic layers were combined and washed with 2N KOH, dried with anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 10%, 20%, 50% ethyl acetate:hexanes to yield 6.31 g (90%) of the diol product. White solid; M. pt. 87-90 °C; 1H NMR: (400 MHz, $CDCl_3$) δ = (ppm) 1.29, (t, J = 7.1 Hz, 3H), 2.44 (bs, 1H), 2.94, (dd, J = 13.2, 5.5 Hz, 1H), 3.06, (dd, J = 13.5, 8.0 Hz, 1H), 3.23 (bs, 1H), 4.11 (s, 1H), 4.26-4.31 (m, 3H), 5.06 (s, 2H), 5.10 (s, 2H), 6.59 (dd, J = 8.3, 2.2 Hz, 1H), 6.66 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 7.35-7.47 (m, 10H); ^{13}C NMR: (100 MHz, $CDCl_3$) = (ppm) 14.6, 35.1, 62.3, 70.6, 72.9, 73.7, 101.2, 106.2, 127.6, 127.8, 128.4, 128.5, 129.0, 129.4, 132.3, 174.0; Chiral HPLC R_t = 15.62 (min) EtOH/ ee = 70%; LRMS: MS (ES+) m/z = 437.2 (M+1); HRMS: (FAB): calcd for $C_{26}H_{28}O_6$ (M+) 436.1869, found 436.1886.

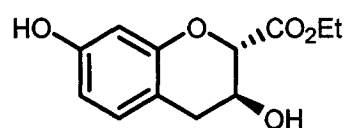
4-(2,4-Bis-benzyloxy-phenyl)-3-hydroxy-2-(toluene-4-sulfonyloxy)-butyric acid ethyl ester (239)



To a solution of the diol **238a** (6.25 g, 14.33 mmol) in dichloromethane was added at -5 °C triethylamine (5 mL, 35.83 mmol), catalytic amount

of DMAP, and *p*-toluene sulfuryl chloride (3.01 g, 15.76 mmol). The reaction mixture was stirred at -5°C overnight. The reaction was quenched by the addition of water. The organic layer was separated. The aqueous layer was further extracted with dichloromethane. The organic layers were combined, dried with anhydrous magnesium sulfate, concentrated and column purified with 40% ethyl acetate:hexanes to yield the tosylated alcohol 6.18 g (73%). White solid; M. pt. $83-88^{\circ}\text{C}$; ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.18, (t, J = 7.1 Hz, 3H), 2.30 (bs, 1H), 2.46 (s, 3H), 2.83 (dd, J = 13.9, 4.7 Hz, 1H), 2.92 (dd, J = 13.9, 8.7, 1H), 4.08-4.16 (m, 2H), 4.38 (bs, 1H), 4.93 (d, J = 2.7 Hz, 1H), 5.04 (s, 2H), 5.07 (s, 2H), 6.54 (dd, J = 8.3, 2.2 Hz, 1H), 6.62 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H), 7.28-7.45 (m, 12H), 7.87 (d, J = 8.23 Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.3, 22.1, 34.6, 62.2, 70.5, 72.1, 79.9, 101.2, 118.4, 127.6, 127.7, 127.9, 128.4, 128.6, 129.1, 130.1, 133.8, 137.1, 145.5, 157.9, 167.7; LRMS: MS (ES+) m/z = 591.3 (M+1); HRMS: (FAB): calcd for $\text{C}_{33}\text{H}_{34}\text{O}_8\text{S}$ (M+) 590.1896, found 590.1974.

3,7-Dihydroxy-chroman-2-carboxylic acid ethyl ester (240)



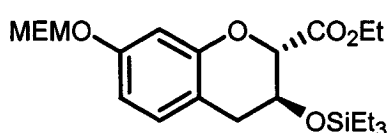
To a solution of tosylated alcohol **239** (5.87 g, 9.94 mmol) in THF, under a vigorous bubbling of nitrogen, was added anhydrous potassium carbonate (6.87 g, 49.68 mmol) and Pd/C (2 g, 33%). The reaction mixture was stirred at room temperature under pressurized hydrogen for 48h. The reaction was quenched by filtration through celite. The solvent was then rotor-evaporated and column purified with 50% ethyl acetate:hexanes to yield the bicyclic diol 2.01 g (85%). White solid; M. pt. $95-98^{\circ}\text{C}$; ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.29 (t, J = 7.1 Hz, 3H), 2.63 (d, J = 6.4 Hz, 1H), 2.77 (dd, J = 16.3, 5.7 Hz, 1H), 2.96 (dd, J = 16.4, 4.7 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 4.42 (t, J = 5.5 Hz, 1H), 4.61 (dd, J = 5.6, 1.0 Hz, 1H), 5.15 (s, 1H), 6.44-6.48 (m, 2H), 6.91 (d, J = 8.12 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 14.5, 31.1, 32.0, 62.4, 64.8, 103.9, 109.9,

110.8, 131.3, 153.4, 155.9, 170.2; LRMS: MS (ES+) m/z = 239.1 (M+1); HRMS: (FAB): calcd for $C_{12}H_{14}O_5$ (M+) 238.0836, found 238.0841.

6.5 Synthesis of Amino Acid Based Lactones

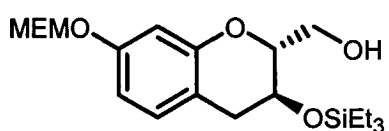
6.5.1 Cis-fused Rings – Mitsunobu Strategy

7-(2-Methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-carboxylic acid ethyl ester (385)



Silyl protection of the secondary alcohol was achieved under standard conditions. To a solution of the benzopyran alcohol **234** (0.52 g, 1.59 mmol) in dichloromethane was added at 0 °C, imidazole (0.27 g, 3.98 mmol) and triethylsilylchloride (455 μ L, 2.71 mmol), and was stirred at 0 °C for 4.5 h. The reaction was quenched by the addition of water. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, concentrated and column purified with 30% ethyl acetate:hexanes to yield 0.69 g (98%) of the silylether- benzopyran product. Colourless liquid. 1H NMR: (400 MHz, $CDCl_3$) δ = (ppm) 0.64 (q, J = 7.9 Hz, 6H), 0.96 (t, J = 7.9 Hz, 9H), 1.32 (t, J = 7.1 Hz, 3H), 2.74 (dd, J = 15.8, 7.1 Hz, 1H), 2.90 (dd, J = 15.8, 4.9 Hz, 1H), 3.38 (s, 3H), 3.55-3.57 (m, 2H), 3.80-3.83 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.36-4.39 (m, 1H), 4.43 (d, J = 6.6 Hz, 1H), 5.23 (s, 2H), 6.63 (dd, J = 10.7, 2.3 Hz, 2H), 6.92 (d, J = 8.0 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) = (ppm) 5.2, 7.1, 14.5, 33.3, 59.4, 61.9, 65.9, 68.0, 72.0, 94.0, 104.7, 110.1, 113.1, 130.5, 153.8, 157.2, 170.1; LRMS: MS (ES+) m/z = 440.2 (M+1); HRMS: (FAB): calcd for $C_{22}H_{36}O_7Si$ (M+) 440.2245, found 440.2230.

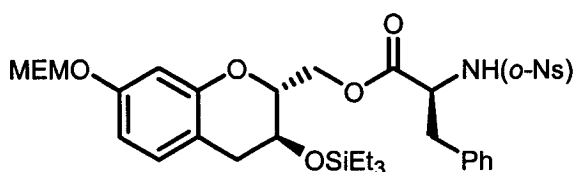
[7-(2-Methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-yl]-methanol (386)



Reduction to the primary alcohol was successful under standard conditions. To a solution of the

benzopyran ester **385** (0.70 g, 1.59 mmol) in THF at 0 °C, was added 2.0 M LiBH₄ in THF (2.40 mL, 4.77 mmol) and stirred from 0 °C to room temperature overnight. The reaction was quenched by addition of pieces of ice and THF was rotor-evaporated. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 30% ethyl acetate:hexanes to yield a 0.57 g (90%) of the benzopyran alcohol product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 0.69 (q, J = 7.9 Hz, 6H), 1.01 (t, J = 7.9 Hz, 9H), 2.13 (bs, 1H), 2.79 (dd, J = 15.2, 10.1 Hz, 1H), 2.95 (dd, J = 15.3, 5.7 Hz, 1H), 3.40 (s, 3H), 3.56-3.59 (m, 2H), 3.81-3.85 (m, 3H), 3.88-4.00 (bm, 1H), 4.02-4.09 (m, 2H), 5.23 (s, 2H), 6.60 (dd, J = 8.6, 2.4 Hz, 2H), 6.95 (d, J = 8.3 Hz, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 5.3, 7.2, 35.4, 59.4, 62.7, 65.3, 68.0, 72.0, 94.0, 104.4, 109.9, 114.3, 130.5, 154.8, 157.2; LRMS: MS (ES+) m/z = 399.2 (M+1).

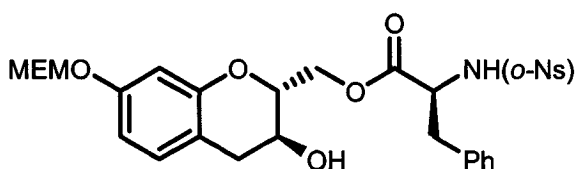
2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 7-(2-methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-ylmethyl ester (387)



Amino acid coupling was optimized under standard conditions. To a solution of the benzopyran alcohol **386** (30 mg, 0.075 mmol) in dichloromethane was added DIC (14 μL, 0.09 mmol), a catalytic amount of DMAP and sulfonamide amino acid (29.1 mg, 0.083 mmol). The mixture was stirred for 1h at room temperature. The reaction was quenched by addition of water and aqueous layer was extracted with dichloromethane. The organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 35% ethyl acetate:hexanes to yield 47.8 mg (87%) of the aminoacid-coupled benzopyran product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 0.64 (q, J = 7.7 Hz, 6H), 0.98 (t, J = 7.9 Hz, 9H), 2.73 (dd, J = 15.3, 9.3 Hz, 1H), 2.93 (dd, J = 15.5, 5.3 Hz, 1H), 3.12-3.37 (m, 2H), 3.37 (s, 3H),

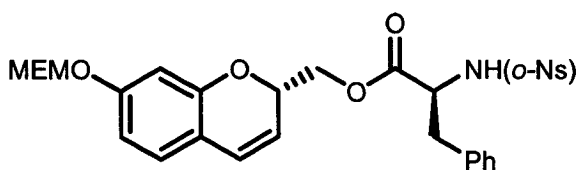
3.55-3.58 (m, 2H), 3.82-3.84 (m, 4H), 4.11-4.16 (m, 1H), 4.48-4.55 (m, 2H), 5.24 (s, 2H), 6.08 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.19-7.23 (m, 5H), 7.60-7.63 (m, 2H), 7.83-7.86 (m, 1H), 7.97-7.99 (m, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.4, 7.2, 14.6, 35.2, 39.8, 58.2, 59.4, 64.7, 65.2, 68.1, 94.8, 104.5, 110.1, 113.7, 125.2, 126.1, 127.8, 128.1, 129.1, 129.8, 130.5, 133.7, 134.6, 135.1, 147.9, 154.3, 157.3, 170.6; LRMS: MS (ES+) m/z = 731.2 (M+1).

2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 3-hydroxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-ylmethyl ester (388)



The procedure for the silyl deprotection was adapted from Green et al.¹⁶⁵ To a solution of the benzopyran-silylether **387** (50.5 mg, 0.069 mmol) in THF was added at 0 °C 1.0 M TBAF (120 μL , 0.12 mmol) in THF, and stirred from 0 °C to room temperature overnight. The reaction was quenched by adding water, solvent was rotor-evaporated, and the aqueous layer was extracted with ethylacetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 50% to 100% ethyl acetate:hexanes to yield 33.6 mg (79%) of the hydroxyl benzopyran product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.68 (dd, J = 15.7, 9.3 Hz, 1H), 2.88 (dd, J = 15.8, 5.7 Hz, 1H), 3.18 (d, J = 6.5 Hz, 2H), 3.38 (s, 3H), 3.48-3.50 (m, 1H), 3.56-3.58 (m, 2H), 3.77-3.81 (m, 3H), 3.82-3.84 (m, 2H), 4.22 (dd, J = 12.1, 2.3 Hz, 1H), 4.38 (dd, J = 12.1, 3.7 Hz, 1H), 4.53 (t, J = 6.6 Hz, 1H), 5.25 (s, 2H), 6.57 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 10.7, 4.8 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.16 (s, 5H), 7.66 (td, J = 5.0, 1.8 Hz, 2H), 7.74 (dd, J = 7.3, 2.0 Hz, 1H), 8.00-8.02 (m, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 33.3, 39.5, 39.6, 58.3, 63.2, 64.7, 68.1, 72.0, 93.9, 104.5, 110.3, 113.7, 126.2, 127.9, 129.1, 129.2, 129.7, 130.6, 130.8, 133.4, 134.2, 135.0, 147.8, 154.3, 157.3, 171.6; LRMS: MS (ES+) m/z = 617.1 (M+1); HRMS:

2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 7-(2-methoxy-ethoxymethoxy)-2H-chromen-2-ylmethyl ester (389)

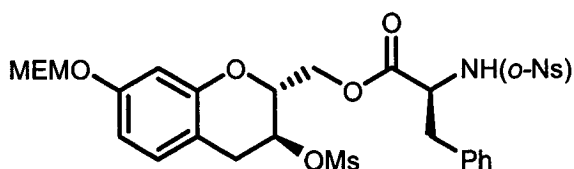


Cyclization was attempted from conditions adapted from Mitsunobu et al.¹⁰⁴ To a solution of the benzopyran alcohol **388** (83.5 mg, 0.14 mmol) in

THF was added at 0 °C, triphenylphosphine (73.4 mg, 0.28 mmol) and DEAD (44 µL, 0.28 mmol) and was stirred at 0 °C for 30 min. The reaction was quenched by rotor-evaporation of the solvent and column purified with gradient elution of 50% to 60% ethyl acetate:hexanes to yield 53.7 mg (64%) of the eliminated product. Yellow liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 3.02 (dd, J = 13.9, 7.1 Hz, 1H), 3.12 (dd, 11.2, 5.7 Hz, 1H), 3.38 (s, 3H), 3.55-3.57 (m, 2H), 3.81-3.83 (m, 2H), 4.02-4.05 (m, 1H), 4.10-4.14 (m, 1H), 4.48 (bs, 1H), 4.88-4.90 (bm, 1H), 5.25 (s, 2H), 5.33-5.38 (m, 1H), 6.02 (bs, 1H), 6.47 (d, J = 24.5 Hz, 1H), 6.51 (s, 1H), 6.61 (dd, J = 8.3, 2.4 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.13-7.28 (m, 5H), 7.66-7.68 (m, 2H), 7.83-7.86 (m, 1H), 7.96-7.99 (m, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 40.0, 58.7, 60.1, 66.1, 67.5, 72.3, 74.5, 94.1, 105.0, 110.1, 118.9, 125.3, 126.0, 126.2, 127.0, 127.2, 128.1, 129.1, 129.3, 129.6, 130.0, 133.9, 134.1, 157.2, 160.3, 170.1; LRMS: MS (ES+) m/z = 599.1 (M+1).

6.5.2 Cis-fused Rings – Leaving Group Strategy

2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 3-methanesulfonyloxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-ylmethyl ester (393)



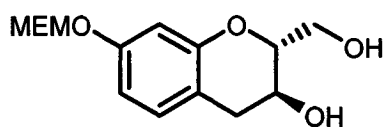
Mesylation of the secondary alcohol was done from conditions adapted from Yamagata and co-workers.¹⁷¹ To a solution of the benzopyran alcohol **388**

(33.9 mg, 0.055 mmol) in dichloromethane was added at 0 °C triethylamine (18 µL, 0.13 mmol), catalytic amount of DMAP and mesityl chloride (6.5 µL, 0.083

mmol). The reaction was stirred from 0 °C to room temperature overnight. The reaction was quenched by adding water, solvent was rotor-evaporated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 50% to 80% ethyl acetate:hexanes to yield 19.5 mg (51%) of the mesylated benzopyran product. Yellow liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 3.06-3.16 (m, 7H), 3.38 (s, 3H), 3.56-3.59 (m, 2H), 3.32-3.85 (m, 2H), 4.13-4.16 (m, 1H), 4.28-4.33 (m, 2H), 4.50-4.56 (m, 1H), 4.75-4.81 (m, 1H), 5.26 (s, 2H), 6.04 (d, J = 8.6 Hz, 1H), 6.59 (d, J = 2.5 Hz, 1H), 6.70 (t, J = 6.6 Hz, 1H), 6.96-6.99 (m, 1H), 7.14-7.21 (m, 5H), 7.42-7.81 (m, 3H), 7.98-8.00 (m, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 31.1, 39.2, 42.5, 58.2, 59.4, 63.5, 68.2, 71.7, 74.4, 93.3, 104.8, 111.0, 113.6, 125.9, 127.7, 127.8, 129.1, 129.8, 130.5, 130.8, 131.0, 133.3, 133.4, 133.8, 153.6, 153.7, 157.7; LRMS: MS (ES+) m/z = 695.0 (M+1).

6.5.3 Trans-fused Rings – Mitsunobu Strategy

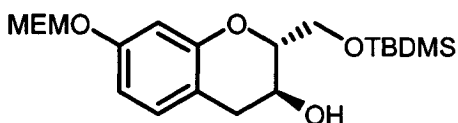
2-Hydroxymethyl-7-(2-methoxy-ethoxymethoxy)-chroman-3-ol (390)



Synthesis of the diol was achieved under standard conditions. To a solution of the benzopyran ester **234** (0.200 g, 0.61 mmol) in THF was added at 0 °C, 2.0M LiBH₄ (763 μL, 1.53 mmol), and was stirred at 0 °C for 2.5h. The reaction was quenched by the addition of pieces of ice, solvent evaporated, the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, concentrated and column purified with gradient elution of 60% to 70% ethyl acetate:hexanes to yield 0.16 g (91%) of the diol-benzopyran product. White solid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 2.26 (bs, 1H), 2.53 (bs, 1H), 2.79 (dd, J = 15.4, 9.6 Hz, 1H), 3.04 (dd, J = 15.5, 5.6 Hz, 1H), 3.40 (s, 3H), 3.57-3.59 (m, 2H), 3.81-3.84 (m, 2H), 3.89 (p, J = 4.2 Hz, 1H), 4.01 (bs, 2H), 4.13-4.16 (bm, 1H), 5.23 (s, 2H), 6.53 (d, J = 2.4 Hz, 1H), 6.64 (dd, J = 8.3, 2.5 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H); ¹³C NMR: (100 MHz,

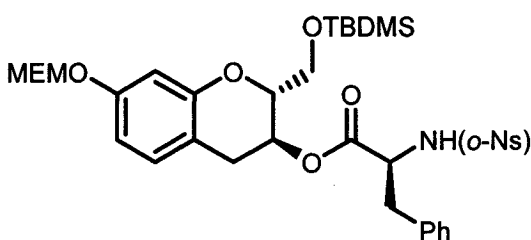
CDCl_3) = (ppm) 33.7, 59.4, 63.0, 64.8, 68.0, 72.0, 94.0, 104.5, 110.2, 113.8, 130.6, 154.5, 157.3; LRMS: MS (ES+) m/z = 285.1 (M+1); HRMS: (FAB): calcd for $\text{C}_{14}\text{H}_{20}\text{O}_6$ (M+) 284.1277, found 284.1260.

2-(tert-Butyl-dimethyl-silanyloxymethyl)-7-(2-methoxy-ethoxymethoxy)-chroman-3-ol (391)



Silyl protection of the primary alcohol was optimized from Green et al.¹⁶⁵ To a solution of the benzopyran diol **390** (0.12 g, 0.44 mmol) in dichloromethane was added at 0 °C, imidazole (45 mg, 0.66 mmol), TBDMSCl (66.3 mg, 0.44 mmol). The reaction was quenched by addition of water. The aqueous solution was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 40%, 50% to 70% ethyl acetate:hexanes to yield a 0.13 g (75%) of the primary-hydroxyl protected benzopyran alcohol product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.14 (s, 6H), 0.94 (s, 9H), 2.76 (dd, J = 15.6, 9.2 Hz, 1H), 3.03 (dd, J = 15.6, 5.5 Hz, 1H), 3.28 (bs, 1H), 3.40 (s, 3H), 3.56-3.58 (m, 2H), 3.78-3.83 (m, 2H), 3.89 (d, J = 5.9 Hz, 2H), 4.08-4.15 (m, 2H), 5.23 (s, 2H), 6.55 (s, 1H), 6.62 (d, J = 8.3 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) , -5.1, 18.6, 26.2, 32.9, 59.4, 65.3, 67.0, 68.0, 94.0, 104.4, 108.8, 109.8, 113.8, 130.7, 154.4, 157.2; LRMS: MS (ES+) m/z = 399.2 (M+1); HRMS: (FAB): calcd for $\text{C}_{20}\text{H}_{34}\text{O}_6\text{Si}$ (M+) 398.2054, found 398.2125.

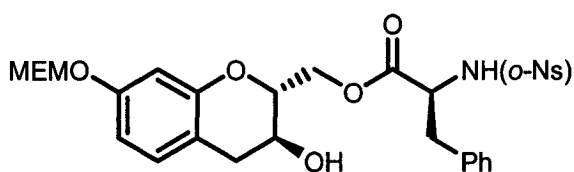
2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 2-(tert-butyl-dimethyl-silanyloxymethyl)-7-(2-methoxy-ethoxymethoxy)-chroman-3-yl ester (392)



To a solution of the benzopyran alcohol **391** (30 mg, 0.075 mmol) in dichloromethane was added DIC (15 μL ,

0.09 mmol), a catalytic amount of DMAP and sulfonamide amino acid (30 mg, 0.083 mmol). The mixture was stirred overnight at room temperature. The reaction was quenched by addition of water and the aqueous layer was extracted with dichloromethane. The organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 30% ethyl acetate:hexanes to yield 40.3 mg (74%) of the aminoacid-coupled benzopyran product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.02 (s, 6H), 0.86 (s, 9H), 2.52 (dd, J = 16.6, 4.6 Hz, 1H), 2.91 (dd, J = 16.9, 4.8 Hz, 1H), 3.07 (dd, J = 13.7, 6.7 Hz, 1H), 3.15 (dd, J = 13.9, 5.8 Hz, 1H), 3.40 (s, 3H), 3.59 (t, J = 4.5, 2H), 3.64 (dd, J = 11.0, 5.5 Hz, 1H), 3.73 (dd, J = 11.1, 4.5 Hz, 1H), 3.84 (t, J = 4.5 Hz, 2H), 3.85 (d, J = 4.9 Hz, 1H), 4.45 (q, J = 7.1 Hz, 1H), 5.15 (q, J = 4.9 Hz, 1H), 5.24 (s, 2H), 5.98 (d, J = 8.7 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.63 (dd, J = 8.3, 2.5 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.10-7.24 (m, 5H), 7.61-7.73 (m, 2H), 7.78 (d, J = 6.8, 1H), 7.94 (d, J = 6.3 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) -4.9, 14.6, 18.6, 21.5, 26.2, 27.8, 39.6, 58.1, 59.4, 60.8, 62.6, 68.1, 72.0, 76.3, 93.9, 104.8, 109.8, 111.9, 126.1, 127.9, 129.8, 130.4, 133.3, 133.8, 135.0, 147.9, 152.9, 157.4, 170.1; LRMS: MS (ES+) m/z = 731.2 (M+1); HRMS: (FAB): calcd for $\text{C}_{35}\text{H}_{46}\text{N}_2\text{O}_{11}\text{SSi}$ (M+) 730.2543, found 730.2592.

2-(2-Nitro-benzenesulfonylamino)-3-phenyl-propionic acid 3-hydroxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-ylmethyl ester (388)

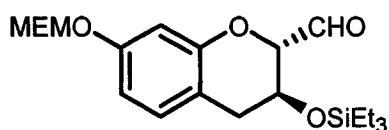


To a solution of the benzopyran-silylether **392** (0.15 g, 0.2 mmol) in THF was added at 0 °C and at pH 8 (with acetic acid) 1.0 M TBAF (240 μL , 0.24 mmol) in THF, and stirred from 0°C to room temperature overnight. The reaction was quenched by adding water, solvent was rotor-evaporated, and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 50% to 100% ethyl acetate:hexanes to yield 83.5 mg (70%) of the trans-esterified hydroxyl benzopyran product. Colourless liquid. ^1H

NMR: (400 MHz, CDCl₃) δ = (ppm) 2.67 (dd, J = 15.7, 9.4 Hz, 1H), 2.88 (dd, J = 15.7, 5.8 Hz, 1H), 3.17 (d, J = 6.4 Hz, 2H), 3.37 (s, 3H), 3.51-3.53 (m, 1H), 3.55-3.57 (m, 2H), 3.77-3.79 (m, 3H), 4.24 (dd, J = 12.2, 1.8 Hz, 1H), 4.36 (dd, J = 15.8, 7.4 Hz, 1H), 4.52 (t, J = 6.6 Hz, 1H), 5.24 (s, 2H), 6.56 (d, J = 2.2 Hz, 1H), 6.65 (dd, J = 8.3, 2.2 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.16 (s, 5H), 7.64-7.67 (m, 3H), 7.72-7.75 (m, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 33.3, 39.4, 39.6, 58.4, 59.4, 63.3, 64.8, 68.1, 72.0, 93.9, 104.5, 110.3, 113.7, 126.1, 127.9, 129.1, 129.7, 129.8, 130.6, 130.8, 133.4, 134.0, 135.1, 154.0, 157.3, 170.4; LRMS: MS (ES+) m/z = 617.1 (M+1).

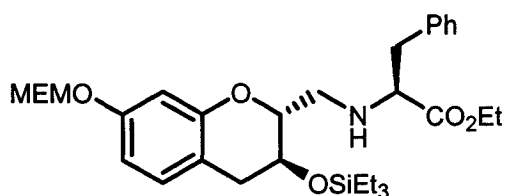
6.5.3 Trans-fused Rings – Reductive Amination Strategy

7-(2-Methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-carbaldehyde (394)



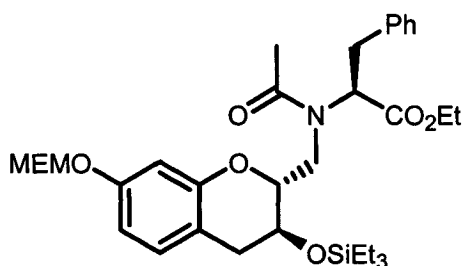
Synthesis of the aldehyde was adapted from Hanessian et al.¹⁷² To a solution of the benzopyran alcohol **386** (91.6 mg, 0.23 mmol) in dichloromethane was added in the order of excess DMSO (650 μ L), triethylamine (160 μ L, 1.15 mmol), sulfurtrioxide pyridine (0.146 g, 0.92 mmol) and stirred for 2h at room temperature. The reaction was quenched by addition of saturated ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 20% to 30% ethyl acetate:hexanes to yield a 72.8 mg (80%) of the benzopyran aldehyde product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 0.65 (q, J = 7.4 Hz, 6H), 0.97 (t, J = 7.9 Hz, 9H), 2.79 (dd, J = 15.8, 6.7 Hz, 1H), 2.91 (dd, J = 15.8, 4.7 Hz, 1H), 3.39 (s, 3H), 3.58 (t, J = 4.5 Hz, 2H), 3.83 (t, J = 4.6 Hz, 2H), 4.12 (q, J = 7.4 Hz, 2H), 5.23 (s, 2H), 6.65 (dd, J = 8.4, 2.3 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 9.81 (s, 1H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 5.2, 7.1, 33.9, 59.4, 65.1, 68.1, 83.3, 94.0, 104.5, 110.5, 113.2, 130.7, 153.5, 157.4, 199.8; LRMS: MS (ES+) m/z = 397.2 (M+1); HRMS: (FAB): calcd for C₂₀H₃₂O₆Si (M+) 396.1971, found 396.1968.

2-([7-(2-Methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-ylmethyl]-amino)-3-phenyl-propionic acid ethyl ester (395)



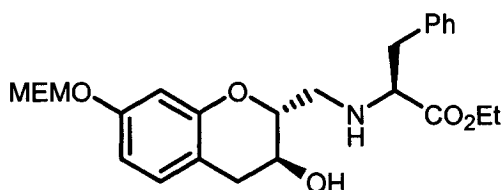
Alkylation under reductive conditions was optimized from a procedure by P. Arya.¹⁷³ To a solution of the phenylalanine hydrochloride salt (32 mg, 0.14 mmol) in THF was added DIPEA (25 μ L, 0.14 mmol) and stirred for 0.5 h to generate the free amine. The benzopyran aldehyde **394** (49 mg, 0.12 mmol) was dissolved in THF and buffered to pH 6, by the addition of acetic acid. To the buffered solution of the aldehyde was added, at 0 $^{\circ}$ C the previously generated free amine, and stirred for 1h. To the reaction mixture was then added sodium cyanoborohydride (9 mg, 0.14 mmol) in acetic acid, and stirred overnight at room temperature. The reaction was neutralized by addition of saturated sodium bicarbonate and the aqueous layer was extracted with ethylacetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 30% ethyl acetate:hexanes to yield 49.4 mg (71%) of the alkylated amine benzopyran product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.63 (q, J = 7.8 Hz, 6H), 0.99 (t, J = 7.9 Hz, 9H), 1.18 (t, J = 7.1 Hz, 3H), 2.73 (dd, J = 15.3, 9.7 Hz, 1H), 2.80 (dd, J = 12.1, 5.9 Hz, 1H), 2.90 (dd, J = 15.4, 5.6 Hz, 1H), 2.99 (d, J = 7.1 Hz, 2H), 3.11 (dd, J = 12.0, 3.0 Hz, 1H), 3.40 (s, 3H), 3.54-3.60 (m, 3H) 3.82-3.85 (m, 3H), 4.01-4.09 (m, 1H), 4.13 (q, J = 7.1, 2H), 5.24 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 6.60 (dd, J = 8.3, 2.3 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 7.21-7.32 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.4, 7.3, 14.6, 35.3, 40.2, 48.6, 59.4, 60.9, 63.7, 66.6, 68.0, 77.6, 80.0, 94.0, 104.5, 109.6, 127.0, 128.7, 129.7, 130.4, 137.9, 154.9, 157.1, 174.8; LRMS: MS (ES $^{+}$) m/z = 574.3 (M+1); HRMS: (FAB): calcd for $\text{C}_{31}\text{H}_{48}\text{NO}_7\text{Si}$ (M+1) 574.3232, anal calcd for $\text{C}_{31}\text{H}_{47}\text{NO}_7\text{Si}$ C, 64.89; H, 8.26; N, 2.44; O, 19.52; Si, 4.89, found 573.3122.

2-{Acetyl-[7-(2-methoxy-ethoxymethoxy)-3-triethylsilanyloxy-chroman-2-ylmethyl]-amino}-3-phenyl-propionic acid ethyl ester (396)



Derivatization to the amide was attempted under standard conditions. To a solution of the benzopyran amine **395** (50 mg, 0.086 mmol) in dichloromethane was added at 0 °C triethylamine (58 μ L, 0.43 mmol), a catalytic amount of DMAP and acetic anhydride (30 μ L, 0.30 mmol), and stirred from 0 °C to room temperature overnight. The reaction was quenched by the addition of saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 25% to 50% ethyl acetate:hexanes to yield 5.4 mg (25%, based on recovery of starting material) of the acylated amine benzopyran product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.56 (q, J = 7.7 Hz, 6H), 0.93 (t, J = 7.9 Hz, 9H), 1.13 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 2.67 (dd, J = 15.2, 9.9 Hz, 1H), 2.90 (dd, J = 15.0, 5.7 Hz, 1H), 3.19 (d, J = 15.6 Hz, 1H), 3.32-3.46 (m, 6H), 3.57-3.58 (m, 2H), 3.68 (q, J = 15.1, 9.1 Hz, 1H), 3.77-3.81 (m, 3H), 4.07-4.10 (m, 1H), 4.14 (q, J = 6.4 Hz, 2H), 5.21 (s, 2H), 6.48 (s, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 7.21-7.28 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.4, 7.2, 14.5, 22.6, 35.5, 52.9, 59.4, 61.5, 63.3, 66.4, 68.1, 72.0, 93.9, 104.5, 110.0, 113.9, 126.7, 128.7, 129.7, 129.8, 130.4, 139.0, 154.4, 157.2, 170.9, 172.0; LRMS: MS (ES+) m/z = 616.5 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{33}\text{H}_{50}\text{O}_8\text{Si}$ ($M+1$) 616.1738, anal calcd for $\text{C}_{33}\text{H}_{49}\text{NO}_8\text{Si}$ C, 64.36; H, 8.02; N, 2.27; O, 20.78; Si, 4.56, found 615.3227.

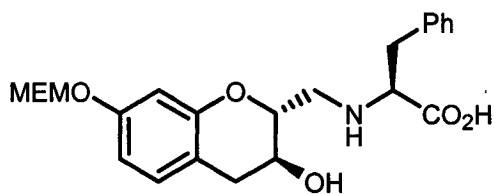
2-[[3-Hydroxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-ylmethyl]-amino]-3-phenyl-propionic acid ethyl ester (397)



To a solution of the benzopyran- silylether **396** (20 mg, 0.035 mmol) in THF was added at 0 °C 1.0 M TBAF (70 µL, 0.07 mmol) in THF, and stirred from 0 °C to room

temperature overnight. The reaction was quenched by adding water, solvent was rotor-evaporated, and the aqueous layer was extracted with ethylacetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 40% to 100% ethyl acetate:hexanes to yield 12.7 mg (80%) of the hydroxyl benzopyran product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 1.15-1.35 (m, 3H), 2.65-3.10 (m, 5H), 3.40 (s, 3H), 3.54-3.60 (m, 2H), 3.61-3.66 (m, 1H), 3.69-3.76 (m, 1H), 3.80-3.85 (m, 2H), 3.86-3.94 (m, 1H), 3.98-4.10 (m, 1H), 4.05-4.14 (m, 2H), 5.24 (s, 2H), 6.52-6.68 (m, 2H), 6.92-7.00 (m, 1H), 7.11-7.32 (m, 5H); LRMS: MS (ES+) m/z = 460.2 (M+1)

2-[[3-Hydroxy-7-(2-methoxy-ethoxymethoxy)-chroman-2-ylmethyl]-amino]-3-phenyl-propionic acid (398)



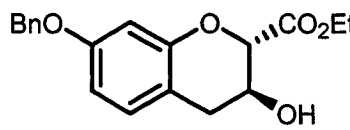
Base hydrolysis was done under standard conditions. To a solution of the benzopyran amine ester **397** (15.2 mg, 0.033 mmol) in THF:H₂O (1:1) was added at 0 °C, hydrated

lithiumhydroxide (7 mg, 0.16 mmol), and stirred from 0 °C to room temperature overnight. The reaction was quenched by the addition of 1N HCl until pH 7. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated to yield 7 mg (50%) of the benzopyran amino acid product.

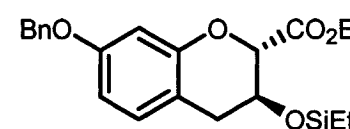
6.6 Synthesis of Tricyclic Polyphenols

6.6.1 General Method

7-Benzyloxy-3-hydroxy-chroman-2-carboxylic acid ethyl ester (543)

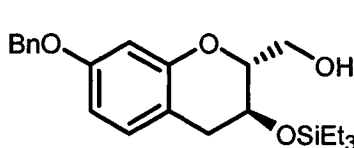
 To a solution of bicyclic diol **240** (2 g, 8.4 mmol) in acetonitrile:DMF (10:1) was added anhydrous potassium carbonate (2.9 g, 21 mmol) and benzylbromide (1.2 mL, 10.1 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by filtering through celite. The solvents were then rotor-evaporated, and column purified with 40% ethyl acetate:hexanes to yield the benzylated alcohol 1.74 g (95%). White solid; M. pt. 69-71 °C; ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 1.32 (t, J = 7.1 Hz, 3H), 2.75 (dd, J = 15.7, 7.1 Hz, 1H), 2.90 (dd, J = 15.8, 4.8 Hz, 1H), 4.23-4.30 (m, 2H), 4.39 (dd, J = 6.8, 5.0 Hz, 1H), 4.44 (d, J = 6.5 Hz, 1H), 5.03 (s, 2H), 6.57 (s, 1H), 6.58 (d, J = 3.9 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 7.33-7.44 (m, 5H); ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 14.5, 31.3, 62.3, 64.8, 70.5, 79.2, 102.8, 110.0, 110.9, 127.9, 128.3, 128.9, 131.1, 137.4, 153.4, 159.1, 170.2; LRMS: MS (ES+) m/z = 443.4 (M+1).

7-Benzyloxy-3-triethylsilyloxy-chroman-2-carboxylic acid ethyl ester (544)

 To a solution of the benzopyran alcohol **543** (0.87 g, 2.66 mmol) in dichloromethane was added at 0 °C, imidazole (0.4 g, 5.85 mmol) and triethylsilylchloride (670 μL, 3.98 mmol), and was stirred at 0 °C for 6h. The reaction was quenched by the addition of water. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, concentrated and column purified with 15% ethyl acetate:hexanes to yield 1.15 g (98%) of the silylether- benzopyran product. Colourless liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 0.64 (q, J = 7.9 Hz, 6H), 0.97 (t, J = 7.9 Hz, 9H), 1.32 (t, J = 7.1 Hz, 3H), 2.75 (dd, J = 15.7, 7.1 Hz, 1H), 2.90 (dd, J = 15.8, 4.8 Hz, 1H),

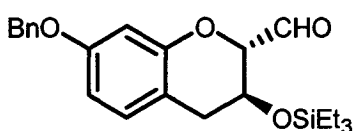
4.23–4.30 (m, 2H), 4.39 (dd, $J = 6.8, 5.0$ Hz, 1H), 4.44 (d, $J = 6.5$ Hz, 1H), 5.03 (s, 2H), 6.57 (s, 1H), 6.58 (d, $J = 3.9$ Hz, 1H), 6.92 (d, $J = 9.1$ Hz, 1H), 7.33–7.44 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.3, 7.1, 14.5, 33.3, 61.9, 67.0, 70.5, 79.2, 102.7, 109.5, 112.0, 127.9, 128.3, 128.9, 130.6, 137.4, 153.9, 158.9, 170.2; LRMS: MS (ES+) $m/z = 443.4$ (M+1); HRMS: (FAB): calcd for $\text{C}_{25}\text{H}_{34}\text{O}_5\text{Si}$ (M+) 442.2478, found 442.2176.

(7-Benzoyloxy-3-triethylsilanyloxy-chroman-2-yl)-methanol (**545**)



To a solution of the benzopyran ester **544** (0.558 g, 1.26 mmol) in THF at 0°C , was added 2.0 M LiBH_4 in THF (2.84 mL, 5.67 mmol) and stirred from 0°C to room temperature overnight. The reaction was quenched by addition of pieces of ice and THF was rotor-evaporated. The aqueous solution was extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 25% ethyl acetate:hexanes to yield a 0.43 g (90%) of the benzopyran alcohol product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.69 (q, $J = 7.9$ Hz, 6H), 1.02 (t, $J = 7.9$ Hz, 9H), 2.07 (t, $J = 6.5$ Hz, 1H), 2.79 (dd, $J = 15.1, 10.1$ Hz, 1H), 2.95 (dd, $J = 15.2, 5.7$ Hz, 1H), 3.82–3.86 (m, 1H), 3.91–4.00 (m, 1H), 4.01–4.10 (m, 2H), 5.04 (s, 2H), 6.50 (s, 1H), 6.58 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.96 (d, $J = 8.4$ Hz, 1H), 7.34–7.45 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.4, 7.2, 35.3, 62.8, 65.5, 70.5, 80.3, 102.6, 109.1, 113.2, 127.8, 128.3, 129.0, 130.5, 137.4, 154.8, 158.9; LRMS: MS (ES+) $m/z = 401.2$ (M+1); HRMS: (FAB): calcd for $\text{C}_{23}\text{H}_{32}\text{O}_4\text{Si}$ (M+) 400.2161, found 400.2070.

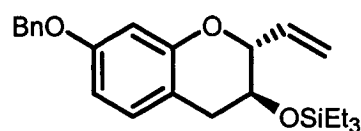
7-Benzoyloxy-3-triethylsilanyloxy-chroman-2-carbaldehyde (**546**)



To a solution of the benzopyran alcohol **545** (0.424 g, 1.06 mmol) in dichloromethane was added in the order of excess DMSO (3 mL), triethylamine (738 μL , 5.29 mmol), sulfurtrioxidepyridine (0.674 g, 4.24 mmol) and stirred for 2h at room

temperature. The reaction was quenched by addition of saturated ammonium chloride. The aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with gradient elution of 10% to 25% ethyl acetate:hexanes to yield a 0.363 g (86%) of the benzopyran aldehyde product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.65 (q, J = 7.8 Hz, 6H), 1.00 (t, J = 7.9 Hz, 9H), 2.81 (dd, J = 6.9, 6.8 Hz, 1H), 2.93 (dd, J = 4.9, 4.7 Hz, 1H), 4.32-4.38 (m, 2H) 5.05 (s, 2H), 6.61-6.64 (m, 2H), 6.94 (t, J = 7.4 Hz, 1H), 7.40-7.46 (m, 5H), 9.85 (d, J = 9.7 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.19, 7.03, 65.25, 65.92, 70.5, 82.0, 83.28, 102.72, 109.81, 112.1, 127.85, 128.4, 128.98, 130.82, 137.3, 153.6, 199.80; LRMS: MS (ES+) m/z = 399.3 (M+1); HRMS (FAB): calcd for $\text{C}_{23}\text{H}_{31}\text{O}_4\text{Si}$ (M+1) 399.2343, anal calcd for $\text{C}_{23}\text{H}_{30}\text{O}_4\text{Si}$ C, 69.31; H, 7.59; O, 16.06; Si, 7.05, found 398.1913.

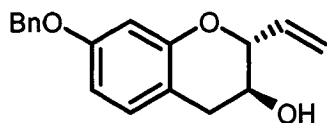
(7-Benzyloxy-2-vinyl-chroman-3-yloxy)-triethyl-silane (547)



Wittig terminal olefination was adopted from Nicolaou et al.^{115c} To a suspension of methyltriphenylphosphonium bromide (0.27 g, 0.75 mmol) in THF at 0 °C was added 1.0 M NaHMDS in THF (625 μL , 0.63 mmol) and stirred at room temperature for 1h to generate the Wittig product. To a separate solution of the aldehyde (0.073 g, 0.18 mmol) in THF at 0 °C was added under an inert atmosphere and pressure the above Wittig product and stirred at 0 °C for 0.5h. The reaction was quenched by adding pieces of ice and filtered through celite. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with 10% ethyl acetate:hexanes to yield 0.088 g (88%) of the bicyclic alkene. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 0.67 (q, J = 7.9 Hz, 6H), 1.01 (t, J = 7.9 Hz, 9H), 2.79 (dd, J = 15.5, 8.7 Hz, 1H), 2.97 (dd, J = 15.5, 5.3 Hz, 1H), 3.92 (q, J = 2.6 Hz, 1H), 4.31 (t, J = 6.8 Hz, 1H), 5.05 (s, 2H), 5.36 (d, J = 10.8 Hz, 1H), 5.52 (d, J = 17.3 Hz, 1H), 6.00-6.09 (m, 1H), 6.57 (bs, 2H), 6.96

(d, $J = 8.1$ Hz, 1H), 7.33-7.47 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 9.5, 10.0, 48.1, 48.2, 70.0, 71.5, 74.0, 81.0, 89.9, 106.1, 113.8, 120.1, 120.2, 130.1, 130.2, 130.5, 134.5, 140.1; LRMS: MS (ES+) $m/z = 397.3$ (M+1); HRMS: (FAB): calcd for $\text{C}_{24}\text{H}_{32}\text{O}_3\text{Si}$ (M+) 396.2139, found 396.2121.

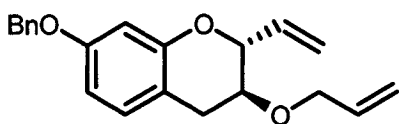
7-Benzoyloxy-2-vinyl-chroman-3-ol (548)



To a solution of the silylated alcohol **547** (0.16 g, 0.41 mmol) in THF at 0°C was added 1.0 M TBAF in THF (823 μL , 0.82 mmol) and stirred at room temperature for 2h. The reaction was quenched by adding water, and the solvent was rotor-evaporated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with 30% ethyl acetate:hexanes to yield 0.102 g (88%) of the bicyclic alcohol product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.99 (bs, 1H), 2.75 (dd, $J = 15.9, 7.0$ Hz, 1H), 3.03 (dd, $J = 15.9, 4.8$ Hz, 1H), 3.95 (q, $J = 5.6$ Hz, 1H), 4.43 (t, $J = 6.2$ Hz, 1H), 5.04 (s, 2H), 5.40 (d, $J = 10.6$, 1H), 5.48 (d, $J = 17.1$ Hz, 1H), 5.89-5.98 (m, 1H), 6.58 (d, $J = 9.1$ Hz, 2H), 6.98 (d, $J = 8.3$ Hz, 1H), 7.33-7.46 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 31.8, 31.9, 66.1, 70.1, 73.5, 81.1, 88.2, 103.5, 111.1, 119.9, 120.0, 129.8, 130.0, 130.2, 134.5, 135.1; LRMS: MS (ES+) $m/z = 283.2$ (M+1).

6.6.2 Six-membered Ring Ether

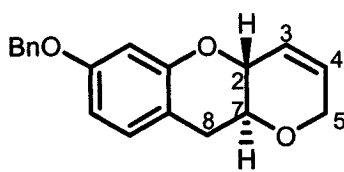
3-Allyloxy-7-benzyloxy-2-vinyl-chroman (549)



Allylation was optimized from Clark et al.¹¹⁹ To a solution of the alcohol **548** (0.025 g, 0.089 mmol) in THF at 0°C was added catalytic amount of $n\text{Bu}_4\text{NI}$, 95% sodium hydride (0.005 g, 0.21 mmol) and stirred for 15 min. To this reaction mixture allylbromide (12 μL , 0.14 mmol) was added at 0°C and stirred, while being warmed from 0°C to room temperature overnight. The reaction was quenched by adding sat. NH_4Cl at 0°C and the solvent was rotor-evaporated.

The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with 10% ethyl acetate:hexanes to yield 0.034 g (97%) of the bicyclic dialkene RCM-precursor. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.79 (dd, J = 15.8, 6.6 Hz, 1H), 3.02 (dd, J = 15.9, 4.7 Hz, 1H), 3.70 (q, J = 5.8 Hz, 1H), 4.12-4.20 (m, 2H), 4.57 (t, J = 5.4 Hz, 1H), 5.04 (s, 2H), 5.22 (d, J = 10.3 Hz, 1H), 5.30 (d, J = 8.9 Hz, 1H), 5.34 (s, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.91-6.02 (m, 2H), 6.56 (s, 2H), 6.96 (d, J = 7.8 Hz, 1H), 7.32-7.46 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 29.4, 70.5, 70.6, 72.6, 73.6, 78.3, 102.8, 108.9, 112.4, 117.7, 118.4, 127.7, 128.9, 130.7, 133.9, 135.2, 142.5, 154.4, 158.9; LRMS: MS (ES+) m/z = 323.2 (M+1); HRMS: (FAB): calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3$ (M+) 322.1676, found 322.1569.

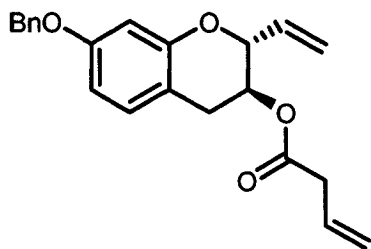
6-Benzyloxy-2,4a,9,9a-tetrahydro-1,10-dioxanthracene (550)



The RCM reaction was optimized under standard conditions. To a solution of the bicyclic dialkene RCM-precursor **549** (0.021 g, 0.065 mmol) in dichloromethane was added 10% mole Grubbs first generation catalyst **468a** (PCy_3) $_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (0.005 g) and stirred for 2.5h. The solvent was rotor-evaporated and column purified with 10% ethyl acetate:hexanes to yield 0.019 g (70%) of the tricyclic product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.84 (dd, J = 14.9, 11.1 Hz, 1H), 3.01 (dd, J = 15.0, 5.8 Hz, 1H), 3.67-3.74 (m, 1H), 4.28-4.39 (m, 3H), 5.04 (s, 2H), 5.94 (d, J = 10.1 Hz, 1H), 6.04 (d, J = 10.0 Hz, 1H), 6.53 (d, J = 2.3 Hz, 1H), 6.64 (dd, J = 8.4, 2.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 7.28-7.45 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 31.9, 70.5, 71.8, 72.9, 103.0, 109.3, 113.5, 125.7, 127.8, 128.3, 128.8, 128.9, 129.1, 131.1, 137.4, 155.6, 158.8; LRMS: MS (ES+) m/z = 294.1 (M+1); HRMS: (FAB): calcd for $\text{C}_{19}\text{H}_{18}\text{O}_3$ (M+) 294.1294, found 294.1256.

6.6.3 Seven-membered Ring Lactone

But-3-enoic acid 7-benzyloxy-2-vinyl-chroman-3-yl ester (556)

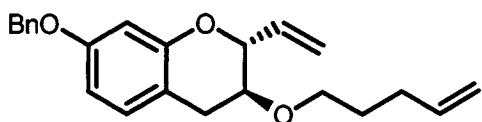


To a solution of the benzopyran alcohol **548** (20 mg, 0.071 mmol) in dichloromethane was added DIC (23 μ L, 0.14 mmol), a catalytic amount of DMAP and vinylacetic acid (9 μ L, 0.11 mmol). The mixture was stirred for 24h at room temperature. The reaction

was quenched by addition of water and aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 20% ethyl acetate:hexanes to yield 20.5 mg (83%) of the aminoacid-coupled benzopyran product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.80 (dd, J = 16.5, 5.3 Hz, 1H), 3.06 (dd, J = 15.6, 4.9 Hz, 1H), 3.12 (d, J = 6.9 Hz, 2H), 4.68 (t, J = 5.2 Hz, 1H), 5.05 (s, 2H), 5.16-5.20 (m, 3H), 5.32 (d, J = 10.7 Hz, 1H), 5.43 (d, J = 17.2 Hz, 1H), 5.84-5.94 (m, 2H), 6.59 (d, J = 7.8 Hz, 2H), 6.93-7.28 (m, 1H), 7.33-7.46 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 28.0, 39.4, 68.1, 70.5, 76.5, 77.8, 102.9, 108.9, 109.1, 111.4, 118.9, 119.2, 127.9, 128.4, 130.6, 134.1, 137.4, 153.9, 159.1, 171.4.

6.6.4 Eight-Membered Ring Ether

7-Benzyloxy-3-pent-4-enyloxy-2-vinyl-chroman (558)

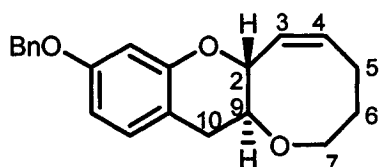


To a solution of the alcohol **548** (0.020 g, 0.071 mmol) in THF at 0 $^{\circ}\text{C}$ was added catalytic amount of $n\text{Bu}_4\text{NI}$, 95% sodium

hydride (0.008 g, 0.33 mmol) and stirred for 15 min. To this reaction mixture 5-bromo-1-pentene (30 μ L, 0.25 mmol) was added at 0 $^{\circ}\text{C}$ and stirred at 35 $^{\circ}\text{C}$. The reaction was quenched by adding a solution of sat. NH_4Cl at 0 $^{\circ}\text{C}$ and the solvent was rotor-evaporated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with 10% ethyl acetate:hexanes to yield 0.020 g (82%) of

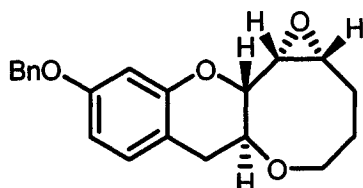
the bicyclic dialkene RCM-precursor. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.70 (p, J = 7.1, 6.8 Hz, 2H), 2.14 (q, J = 7.1 Hz, 2H), 2.77 (dd, J = 15.9, 6.8 Hz, 1H), 2.99 (dd, J = 15.9, 4.8 Hz, 1H), 3.52-3.66 (m, 3H) 4.53 (t, J = 5.8 Hz, 1H), 4.99-5.06 (m, 4H), 5.32 (d, J = 10.6 Hz, 1H), 5.47 (d, J = 17.2 Hz, 1H), 5.78-5.86 (m, 1H), 5.96-6.04 (m, 1H), 6.57 (d, J = 6.7 Hz, 2H), 6.95 (d, J = 8.9 Hz, 1H), 7.32-7.46 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 29.4, 30.6, 69.0, 69.1, 70.4, 73.5, 77.1, 78.3, 102.7, 108.8, 112.5, 115.3, 118.1, 128.3, 130.6, 134.0, 135.4, 137.5, 138.6, 154.4, 158.9; LRMS: MS (ES+) m/z = 351.1 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{23}\text{H}_{26}\text{O}_3$ ($M+$) 350.2157, found 350.1882.

3-Benzyloxy-5a,8,9,10,11a,12-hexahydro-5,11-dioxacycloocta[b]naphthalene (559)



To a solution of the bicyclic dialkene RCM-precursor (0.014 g, 0.041 mmol) in dichloromethane was added 20% mole Grubbs second generation catalyst **470** (0.008 g) and stirred for 2.5h. The solvent was rotor-evaporated and column purified with 10% ethyl acetate:hexanes to yield 0.010 g (57%) of the tricyclic product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.41 (t, J = 8.83 Hz, 1H), 1.99-2.05 (m, 1H), 2.13-2.16 (m, 1H), 2.45-2.49 (m, 1H), 2.80 (dd, J = 15.7, 10.4 Hz, 1H), 3.04 (dd, J = 15.8, 5.9 Hz, 1H), 3.55-3.71 (m, 1H), 3.64-3.70 (m, 1H), 4.04 (dd, J = 11.6, 5.3, 1H), 4.51-4.54 (bm, 1H), 5.03 (s, 2H), 5.75 (q, J = 8.8 Hz, 1H), 5.85 (dd, J = 11.1, 5.0 Hz, 1H), 6.51 (d, J = 2.3 Hz, 1H), 6.56 (dd, J = 8.3, 2.4 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 7.32-7.45 (m, 5H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 24.0, 29.3, 32.8, 68.0, 70.5, 76.5, 102.4, 109.0, 113.6, 127.8, 128.3, 129.0, 129.4, 130.2, 132.7, 137.5, 154.6, 158.7, 158.9; LRMS: MS (ES+) m/z = 323.2 ($M+1$); HRMS: (FAB): calcd for $\text{C}_{21}\text{H}_{22}\text{O}_3$ ($M+$) 322.1724, found 322.1569.

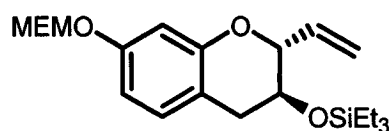
Epoxide (560a)



To a solution of the tricyclic alkene **559** (0.05 g, 0.15 mmol) in dichloromethane was added at 0 °C dioxirane¹⁴⁶ and stirred for 2h. The solvent was rotor-evaporated and column purified with 10% ethyl acetate:hexanes to yield 0.045 g (90%) of the epoxide product. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 1.50-1.52 (m, 1H), 1.64 (bt, J = 4.7 Hz, 1H), 1.96 (bt, J = 5.0 Hz, 1H), 2.25 (dd, J = 10.7, 2.6 Hz, 1H), 2.79 (dd, J = 15.8, 9.4 Hz, 1H), 3.04 (d, J = 9.7 Hz, 1H), 3.09-3.14 (m, 1H), 3.18 (t, J = 5.3 Hz, 1H), 3.66 (td, J = 12.1, 3.3 Hz, 1H), 3.74-3.77 (m, 2H), 4.12-4.16 (m, 1H) 5.04 (s, 2H), 6.56-6.58 (m, 2H), 6.96 (d, J = 8.0 Hz, 1H), 7.28-7.45 (m, 5H), ¹³C NMR: (100 MHz, CDCl₃) = (ppm) 24.6, 25.9, 31.8, 54.5, 57.9, 69.1, 70.5, 73.9, 80.1, 102.5, 109.3, 112.7, 127.8, 128.3, 128.9, 130.2, 137.4, 154.1, 158.9. The stereochemistry was assigned by NOESY NMR experiments.

6.6.2 Solid Phase Organic Synthesis

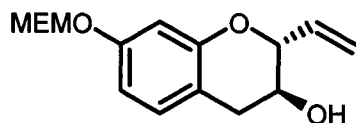
Triethyl-[7-(2-methoxy-ethoxymethoxy)-2-vinyl-chroman-3-yloxy]-silane (**563**)



To a suspension of methyltriphenylphosphonium bromide (0.59 g, 1.64 mmol) in THF at 0 °C was added 1.0 M NaHMDS in THF (1.5 mL, 1.48 mmol) and stirred at room temperature for 1h to generate the Wittig product. To a separate solution of the aldehyde **394** (0.326 g, 0.82 mmol) in THF at 0 °C was added under an inert atmosphere and pressure the above Wittig product and stirred at 0 °C for 0.5h. The reaction was quenched by adding pieces of ice and filtered through celite. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with 25% ethyl acetate:hexanes to yield 0.253 g (78%) of the bicyclic alkene. Pale yellow liquid. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 0.64 (q, J = 7.9 Hz, 6H), 0.98 (t, J = 7.9 Hz, 9H), 2.7 (dd, J = 15.6, 8.8 Hz, 1H), 2.93 (dd, J = 15.6, 5.3 Hz, 1H), 3.40 (s, 3H), 3.57-3.59 (m, 2H), 3.82-3.84 (m, 2H), 3.86-3.91 (m, 1H), 4.26-4.29 (m, 1H), 5.24 (s, 2H), 5.23 (dd, J = 10.6, 1.4 Hz, 1H), 5.49 (dd, J = 17.3, 1.5 Hz, 1H), 5.98-6.06 (m, 1H), 6.62 (s, 2H), 6.94 (d, J = 8.5 Hz, 1H);

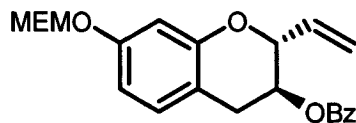
^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 5.1, 7.1, 35.0, 59.8, 67.5, 67.6, 72.1, 80.5, 94.1, 105.0, 110.0, 117.9, 118.1, 140.1, 153.2, 155.8; LRMS: MS (ES+) m/z = 395.3 (M+1).

7-(2-Methoxy-ethoxymethoxy)-2-vinyl-chroman-3-ol (563)



To a solution of the silylated alcohol **562** (0.25 g, 0.64 mmol) in THF at 0 $^{\circ}\text{C}$ was added 1.0 M TBAF in THF (1.28 mL, 1.28 mmol) and stirred at room temperature for 2h. The reaction was quenched by adding water, and the solvent was rotor-evaporated. The aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried with anhydrous magnesium sulfate, column purified with gradient elution of 20% to 70% ethyl acetate:hexanes to yield 0.155 g (86%) of the bicyclic alcohol product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.75 (dd, J = 16.0, 7.1 Hz, 1H), 3.03 (dd, J = 15.9, 4.9 Hz, 1H), 3.40 (s, 3H), 3.58 (t, J = 4.7 Hz, 2H), 3.83 (t, J = 4.6 Hz, 2H), 3.95 (q, J = 6.2 Hz, 1H), 4.42 (t, J = 6.4 Hz, 1H), 5.24 (s, 2H), 5.39 (d, J = 10.6 Hz, 1H), 5.48 (d, J = 17.4 Hz, 1H), 5.87-5.97 (m, 1H), 6.63-6.66 (m, 2H), 6.97 (d, J = 9.0 Hz, 1H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 32.1, 59.5, 67.5, 68.1, 72.5, 81.0, 94.9, 105.0, 110.8, 120.0, 132.5, 135.8, 153.3, 157.2; LRMS: MS (ES+) m/z = 281.2 (M+1).

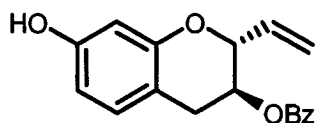
Benzoic acid 7-(2-methoxy-ethoxymethoxy)-2-vinyl-chroman-3-yl ester (564)



To a solution of the benzopyran alcohol **563** (0.15 g, 0.55 mmol) in dichloromethane was added DMAP (0.134g, 1.1 mmol) and benzoyl chloride (96 μL , 0.83 mmol). The mixture was stirred for 2h at room temperature. The reaction was quenched by addition of brine and the aqueous layer was extracted with dichloromethane. The organic layers were dried over anhydrous magnesium sulfate, filtered, concentrated and column purified with 25% ethyl

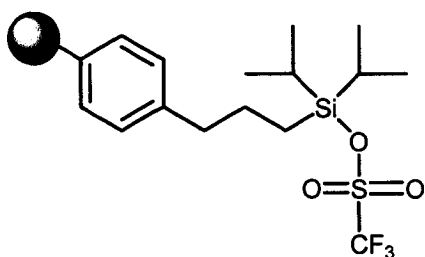
acetate:hexanes to yield 211.2 mg (98%) of the benzoylated benzopyran product. Colourless liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.94 (dd, J = 16.5, 5.5 Hz, 1H), 3.18 (dd, J = 16.2, 4.8 Hz, 1H), 3.40 (s, 3H), 3.59 (t, J = 4.7 Hz, 2H), 3.84-3.86 (m, 2H), 4.81 (t, J = 5.0 Hz, 1H), 5.23 (s, 2H), 5.31-5.40 (m, 2H), 5.48 (d, J = 17.2 Hz, 1H), 5.91-5.95 (m, 1H), 6.66 (dd, J = 10.7, 5.0 Hz, 1H), 6.69 (d, J = 2.3 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 7.40-7.45 (m, 2H), 7.54-7.59 (m, 1H), 8.2 (d, J = 8.19 Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 28.4, 59.5, 68.1, 69.0, 72.0, 76.7, 77.5, 94.0, 104.8, 110.1, 119.0, 128.8, 130.1, 130.6, 133.6, 134.0, 153.4, 156.8, 165.8; LRMS: MS (ES+) m/z = 385.2 ($M+1$); HRMS (FAB): calcd for $\text{C}_{22}\text{H}_{24}\text{O}_6$ ($M+$) 384.1529, found 384.1573.

Benzoic acid 7-hydroxy-2-vinyl-chroman-3-yl ester (565)



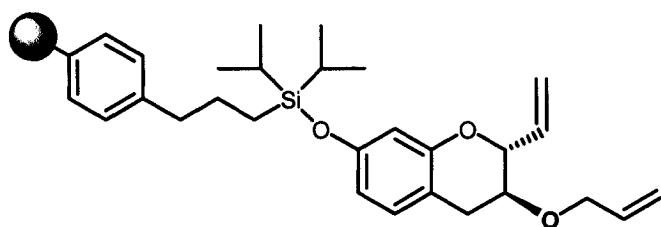
To a solution of the MEM-protected phenol **564** (0.18 g, 0.46 mmol) in anhydrous ethanol was added *p*-toluenesulfonic acid (0.105 g, 0.55 mmol) and refluxed at 50 $^{\circ}\text{C}$ for 24h. The reaction was quenched by the addition of an excess of triethylamine. The solvents were rotor-evaporated, and column purified with 40% ethyl acetate:hexanes to yield 0.13 g (98%) of the bicyclic phenol product. Yellow liquid. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 2.95 (dd, J = 16.5, 5.5 Hz, 1H), 3.18 (dd, J = 16.2, 4.8 Hz, 1H), 4.83 (t, J = 5.0 Hz, 1H), 5.33-5.40 (m, 2H), 5.47 (d, J = 17.2 Hz, 1H), 5.92-5.95 (m, 1H), 6.65-6.67 (m, 2H), 6.69 (d, J = 2.3 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 7.41-7.45 (m, 2H), 7.54-7.59 (m, 1H), 8.22 (d, J = 8.2 Hz, 2H); ^{13}C NMR: (100 MHz, CDCl_3) = (ppm) 28.4, 68.0, 69.1, 76.7, 77.4, 77.8, 104.8, 110.2, 119.0, 128.8, 130.3, 130.6, 133.6, 133.7, 134.1, 153.8, 157.7, 165.9; LRMS: MS (ES+) m/z = 297.1 ($M+1$); HRMS (FAB): calcd for $\text{C}_{18}\text{H}_{16}\text{O}_4$ ($M+$) 296.1085, found 296.1049.

Activation of resin to **574**



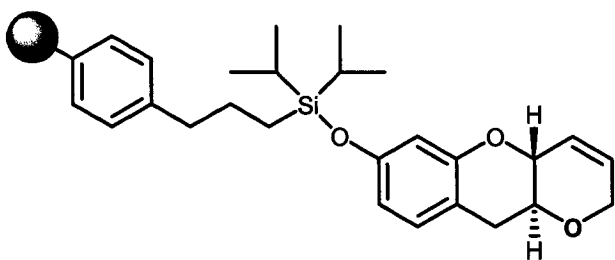
The silicon-functionalized resin **573** (1.4 mmol/g) was dried under high vacuum for 24h. Of the dried resin (50 mg, 0.07 mmol) was transferred into a polypropylene column fitted with a stopcock, and allowed to swell in dichloromethane (0.5 mL) in an inert Ar-atmosphere for 30 min. The excess solvent was subsequently drained-off under a positive Ar-pressure. To the column was then added 5% trifluoromethanesulfonic acid/dichloromethane (850 μ L) and stirred for 30 min. The resin changed colour to a bright red/orange colour upon addition of the acid. After activation was completed, the excess acid was removed, and the resin was washed by two dichloromethane washes.

Immobilized-3-Allyloxy-2-vinyl-chroman-7-ol (**576a**)



To the activated resin **574** was added 2,6-lutidine (65 μ L, 0.56 mmol) and stirred for 15 min. This was followed by the addition of the phenolic-RCM precursor **575a** (33 mg, 0.14 mmol) and being stirred for 12h. The reaction was quenched, by eluting excess reagents and solvent. The resin was subsequently washed in 30 min. intervals as follows: dichloromethane (4mL x 2), THF (4 mL x 2), THF/H₂O (1:1, 4 mL x 2), DMF (4 mL x 2) and finally with THF (4 mL x 2). The resin was then air dried for 1h, and further dried *in vacuo* for 24h. The recovered material from the washings were combined and column purified with 20% ethyl acetate:hexanes to yield 18 mg (8%) of the starting material. Hence the loading efficiency was 92% based on mass balance.

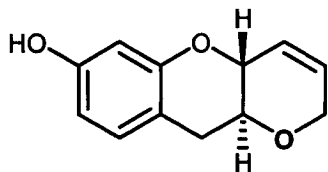
Immobilized-2-(4,4a,6,8a-Tetrahydro-3H-pyrano[3,2-b]pyran-2-ylidene)-ethanol (**577a**)



To the immobilized dialkene **576a** (50 mg, 0.064 mmol) in 10 mL dichloromethane was added Grubbs catalyst **468a** (53 mg, 0.064 mmol) and refluxed at 40 °C for 24 h. The

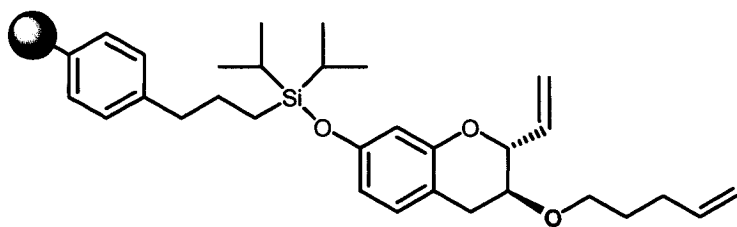
reaction was quenched by filtering-off the excess solvents and reagents from the resin. The resin was then washed in 30 min. intervals as follows: dichloromethane (5 mL x 2), THF (5 mL x 2), THF/H₂O (1:1, 5 mL x 2), DMF (5 mL x 2) and finally with THF (5 mL x 2). The resin was then air dried for 1h, and further dried *in vacuo* for 24h.

2-(4,4a,6,8a-Tetrahydro-3H-pyrano[3,2-b]pyran-2-ylidene)-ethanol (**541a**)



To the immobilized RCM product **576a** (50.0 mg, 0.064) in the polypropylene column, was added THF (5.0 mL) and allowed to swell for 30 min. To it was then added HF/pyridine (1 mL, HF/py 7:3 ratio), and agitated for 2h. The excess HF was quenched by the addition of methoxytrimethylsilane (200 μ L). The beads were further agitated for 30 min. to ensure the completel quenching of HF. The solvents were removed and the resin was washed with THF (5 mL x 2). The THF layers were concentrated to and colum purified with 35% ethylacetate:hexanes to yield 8.9 mg (70%) of the tricyclic phenol. ¹H NMR: (400 MHz, CDCl₃) δ = (ppm) 2.84 (dd, J = 14.7, 11.0 Hz, 1H), 3.03 (dd, J = 14.8, 5.8 Hz, 1H), 3.66-3.74 (m, 1H), 4.28-4.38 (m, 3H), 5.91 (d, J = 10.2 Hz, 1H), 6.02 (d, J = 10.1 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 8.4, 2.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H);LRMS: MS (ES+) m/z = 205.3 (M+1).

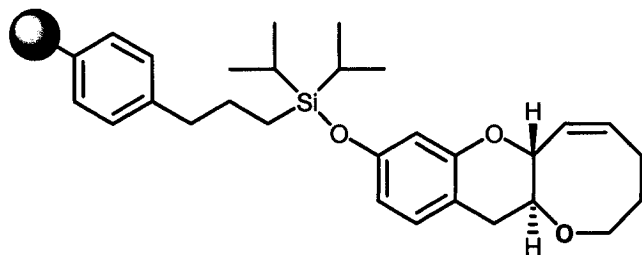
Immobilized-3-Pent-4-enyloxy-2-vinyl-chroman-7-ol (**576b**)



To the activated resin **574** (50 mg, 0.07 mmol) was added 2,6-lutidine (65 μ L, 0.56 mmol) and stirred for

15 min. This was followed by the addition of the phenolic-RCM precursor **575b** (36 mg, 0.14 mmol) and stirred for 12h. The reaction was quenched, by eluting excess reagents and solvent. The resin was subsequently washed in 30 min. intervals as follows: dichloromethane (5 mL x 2), THF (5 mL x 2), THF/H₂O (1:1, 5 mL x 2.), DMF (5 mL x 2) and finally with THF (5 mL x 2). The resin was then air dried for 1h, and further dried *in vacuo* for 24h. The recovered material from the washings were combined, and column purified with 20% ethyl acetate:hexanes to yield 20 mg (12%) of recovered starting material. Hence the loading efficiency was 88% based on mass balance.

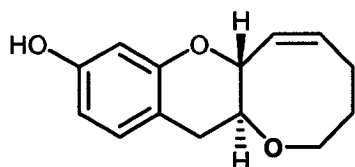
Immobilized-5a,8,9,10,11a,12-Hexahydro-5,11-dioxo-cycloocta[b]naphthalen-3-ol (**577b**)



To the immobilized dialkene **576b** (50 mg, 0.06 mmol) in 10 mL of dichloromethane was added Grubbs catalyst **468a** (50 mg, 0.06 mmol) and refluxed at 40 $^{\circ}$ C

for 24 h. The reaction was quenched by filtering-off the excess solvents and reagents from the resin. The resin was then washed in 30 min. intervals as follows: dichloromethane (5 mL x 2), THF (5 mL x 2), THF/H₂O (1:1, 5 mL x 2), DMF (5 mL x 2) and finally with THF (5 mL x 2). The resin was then air dried for 1h, and further dried *in vacuo* for 24h.

5a,8,9,10,11a,12-Hexahydro-5,11-dioxo-cycloocta[b]naphthalen-3-ol (**541b**)



To the immobilized RCM product **576b** (40.0 mg, 0.048 mmol) in the polypropylene column was added THF (4.0 mL) and allowed to swell for 30 min. To it was then added HF/pyridine (800 μ L, HF/py 7:3 ratio), sealed and agitated for 2h. The excess HF was quenched by the addition of methoxytrimethylsilane (160 μ L). The beads were further agitated for 30 min. to ensure the complete quenching of HF. The solvents were removed and the resin washed with THF (4 mL x 2). The THF layers were concentrated and column purified with 20% ethylacetate:hexanes to yield 6.8 mg (61%) of the tricyclic phenol. ^1H NMR: (400 MHz, CDCl_3) δ = (ppm) 1.39 (t, J = 7.9 Hz, 1H), 1.95-2.05 (m, 1H), 2.10-2.16 (m, 1H), 2.45-2.51 (m, 1H), 2.78 (dd, J = 15.7, 10.4 Hz, 1H), 3.02 (dd, J = 15.8, 6.0 Hz, 1H), 3.57-3.61 (m, 1H), 3.63-3.69 (m, 1H), 4.05 (dd, J = 11.4, 5.3 Hz, 1H), 4.52-4.54 (bm, 1H), 5.77 (q, J = 8.8 Hz, 1H), 5.86 (dd, J = 11.1, 4.9 Hz, 1H), 6.53 (d, J = 2.2 Hz, 1H), 6.56 (dd, J = 8.3, 2.3 Hz, 1H), 6.69 (d, J = 8.3 Hz, 1H); LRMS: MS (ES+) m/z = 233.3 (M+1).

7. CLAIMS TO ORIGINAL RESEARCH

1. Successfully developed a new stereoselective approach to the synthesis of functionalized benzofuran scaffolds. The key steps in our approach were (i) Sharpless asymmetric dihydroxylation and (ii) regioselective tosylation.
2. Successfully applied the RCM approach to obtain benzopyran-derived tricyclic derivatives having six- and eight-membered rings.
3. Demonstrated the stereoselective epoxide formation directed by the eight membered ring conformation.
4. Demonstrated the possibility of developing a solid phase method to obtain tricyclic derivative by a RCM approach.
5. The work reported in this thesis has been presented at the following conferences:

Kamani Ilangasinghe, Majid Rastegar, Bugga V. N. B. S. Sarma, Prabhat Arya. Diversity Oriented Synthesis of Stereoselective Natural Product-like Derivatives on a Benzopyran-template. *The 39th IUPAC Congress and 86th Conference of the Canadian Society for Chemistry*, Ottawa, ON, Canada, August 10 - 15, 2003.

Kamani Ilangasinghe, Bugga V. N. B. S. Sarma, Prabhat Arya. Toward Benzopyran-derived Natural Product-like Polycyclic Derivatives by Diversity-Oriented Synthesis. *The 13th Quebec - Ontario Minisymposium in Synthetic and Bioorganic Chemistry*, Kingston, ON, Canada, 2002.

Bugga V. N. B. S. Sarma, Doug Chou, Bojana Rakic, **Kamani Ilangasinghe**, Jeff Manzer, Prabhat Arya. Toward the High-throughput Synthesis of Chiral, Enantiomerically Pure, Natural Product-like Compounds. *The 2nd Annual Genomic Meeting – National Research Council of Canada*, Genome Institute

for Biodiagnostics, Winnipeg, Manitoba, Canada, 2001.

Kamani Ilangasinghe, Bugga V. N. B. S. Sarma, Prabhat Arya. Towards the Enantioselective Synthesis of Benzopyran-derived, Natural Product-like Compounds. *The 12th Quebec - Ontario Minisymposium in Synthetic and Bioorganic Chemistry*, Sherbrooke, QC, Canada, 2001.

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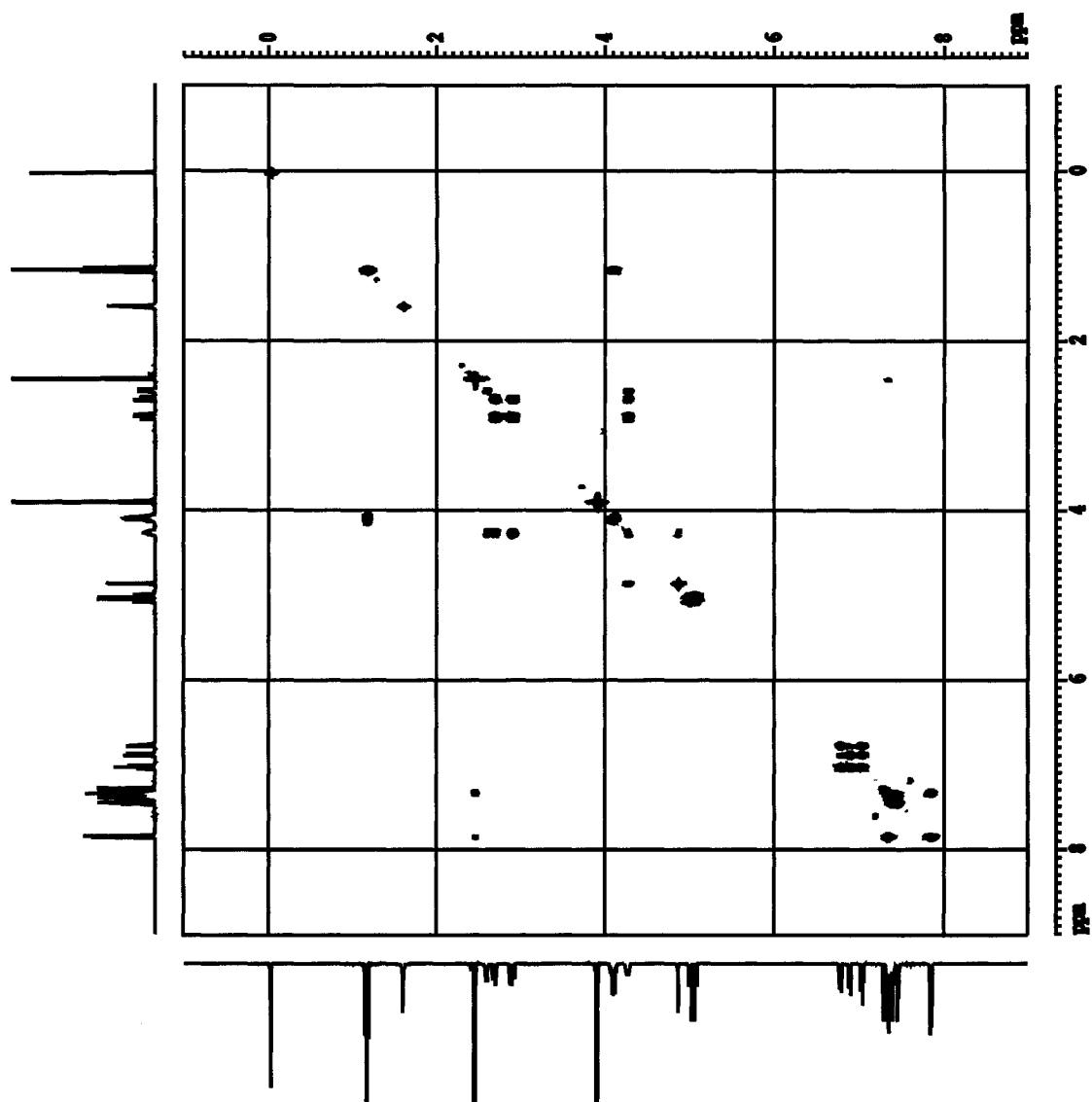
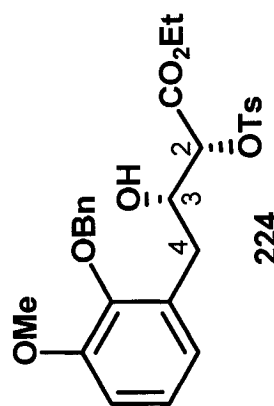
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APPENDIX

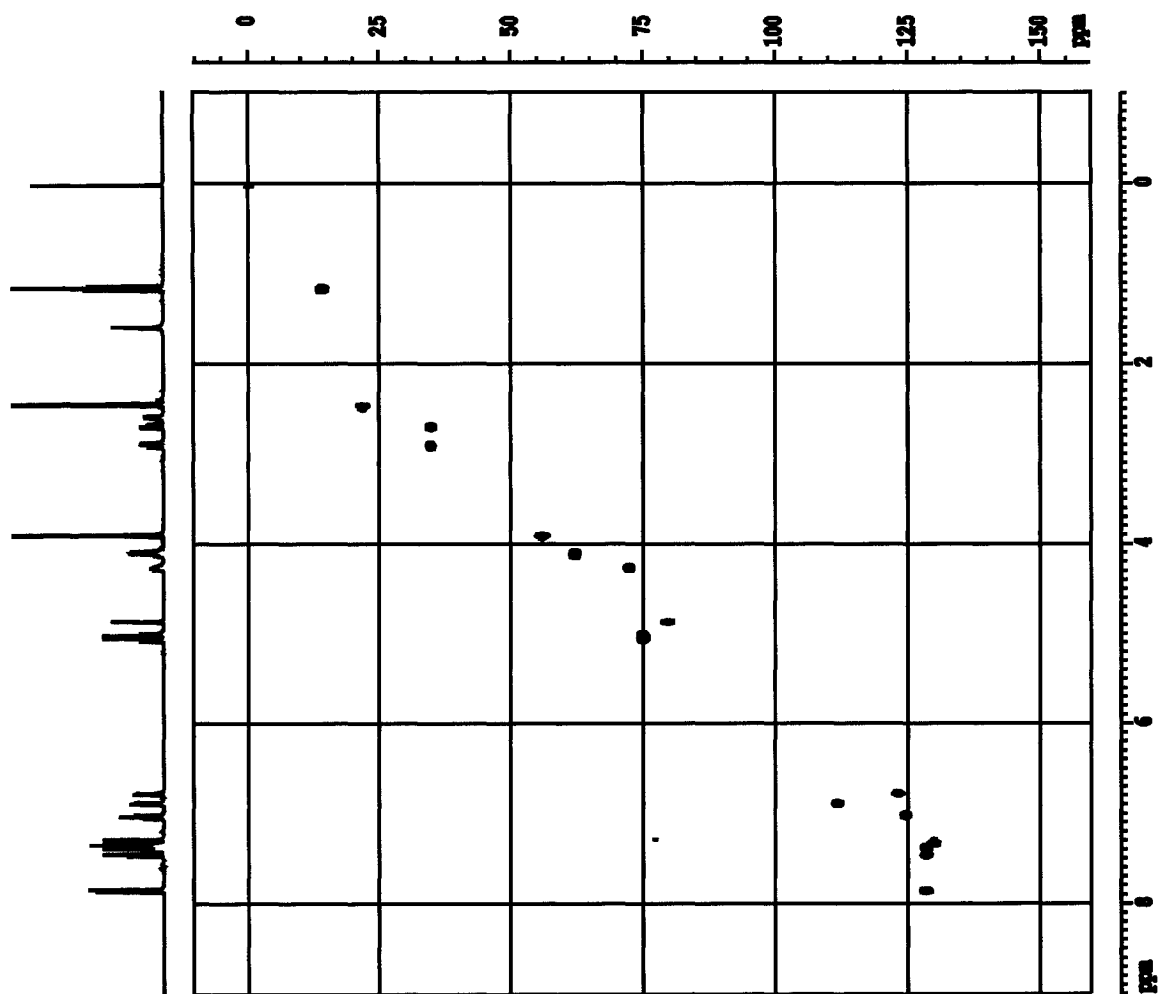
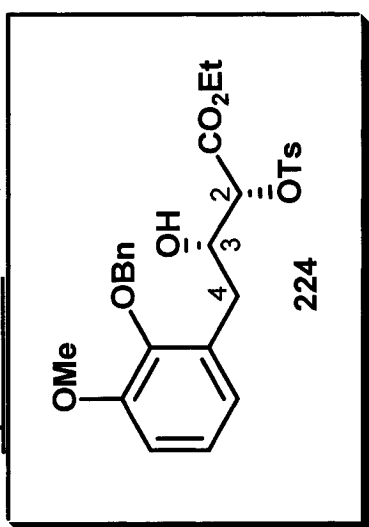
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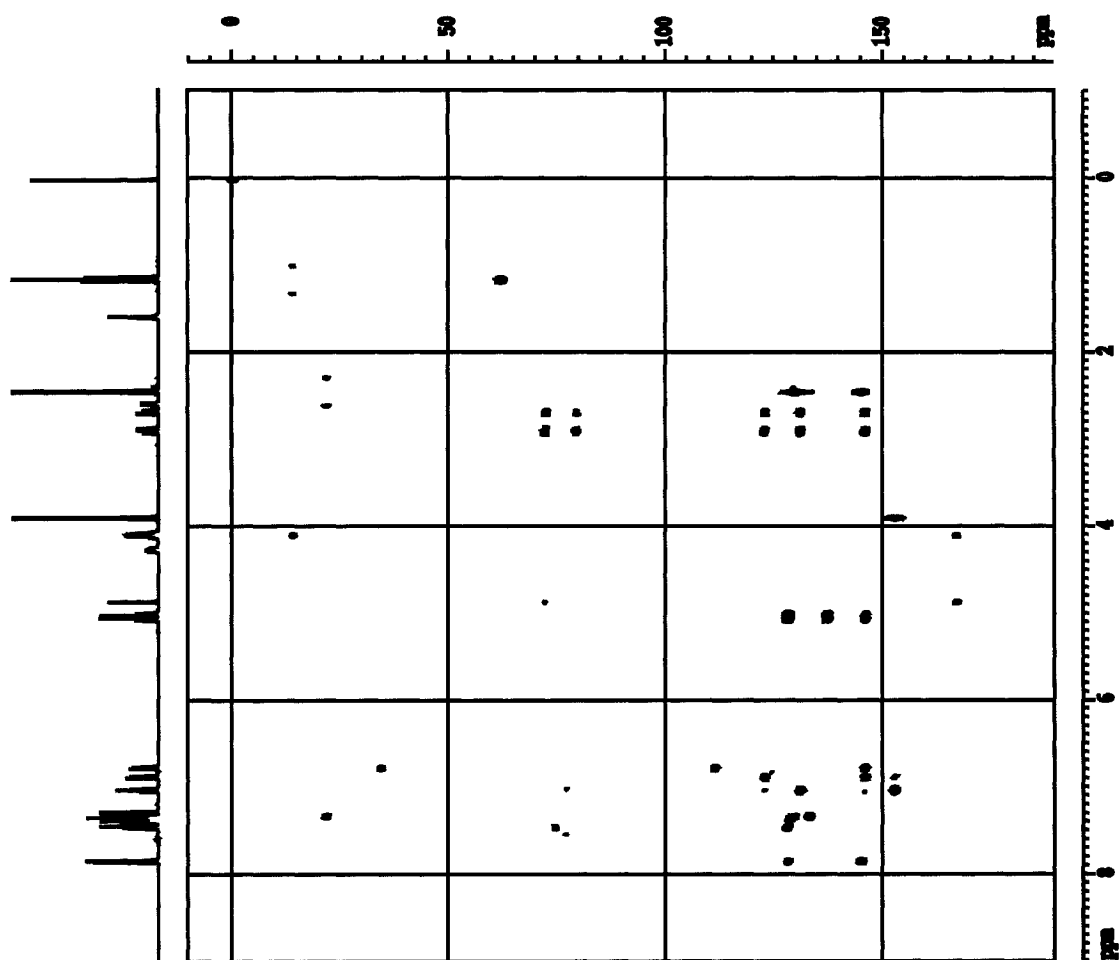
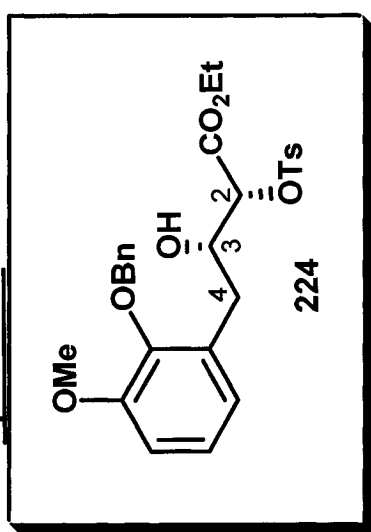
Spectrum 2: COSY NMR



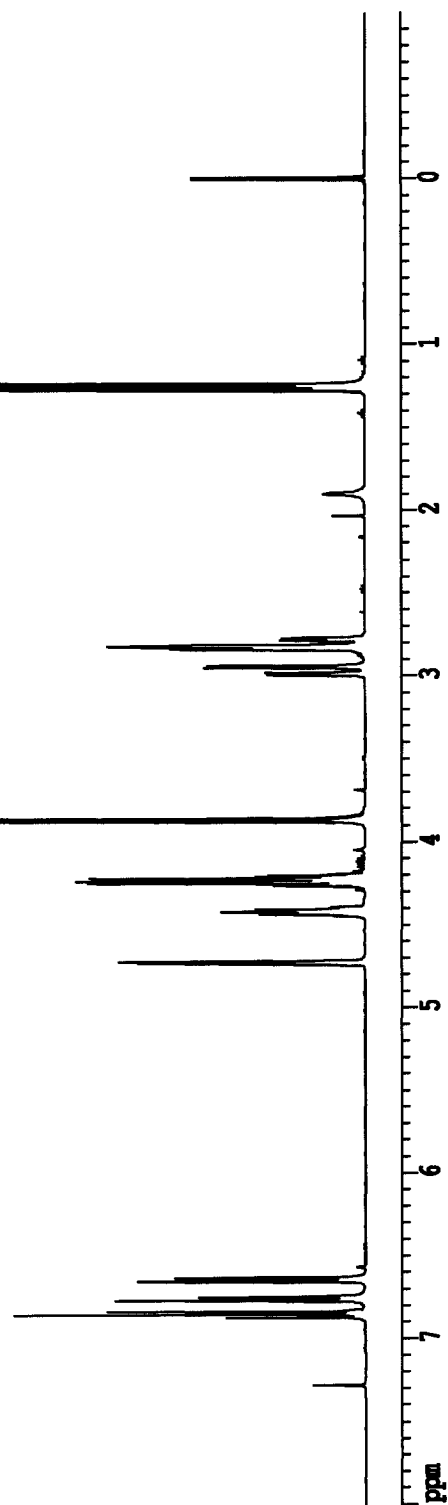
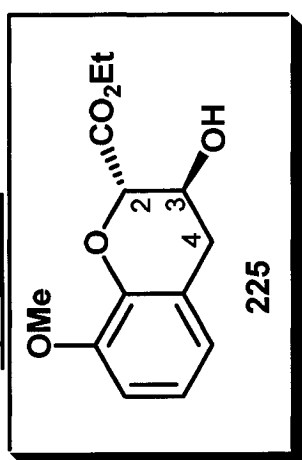
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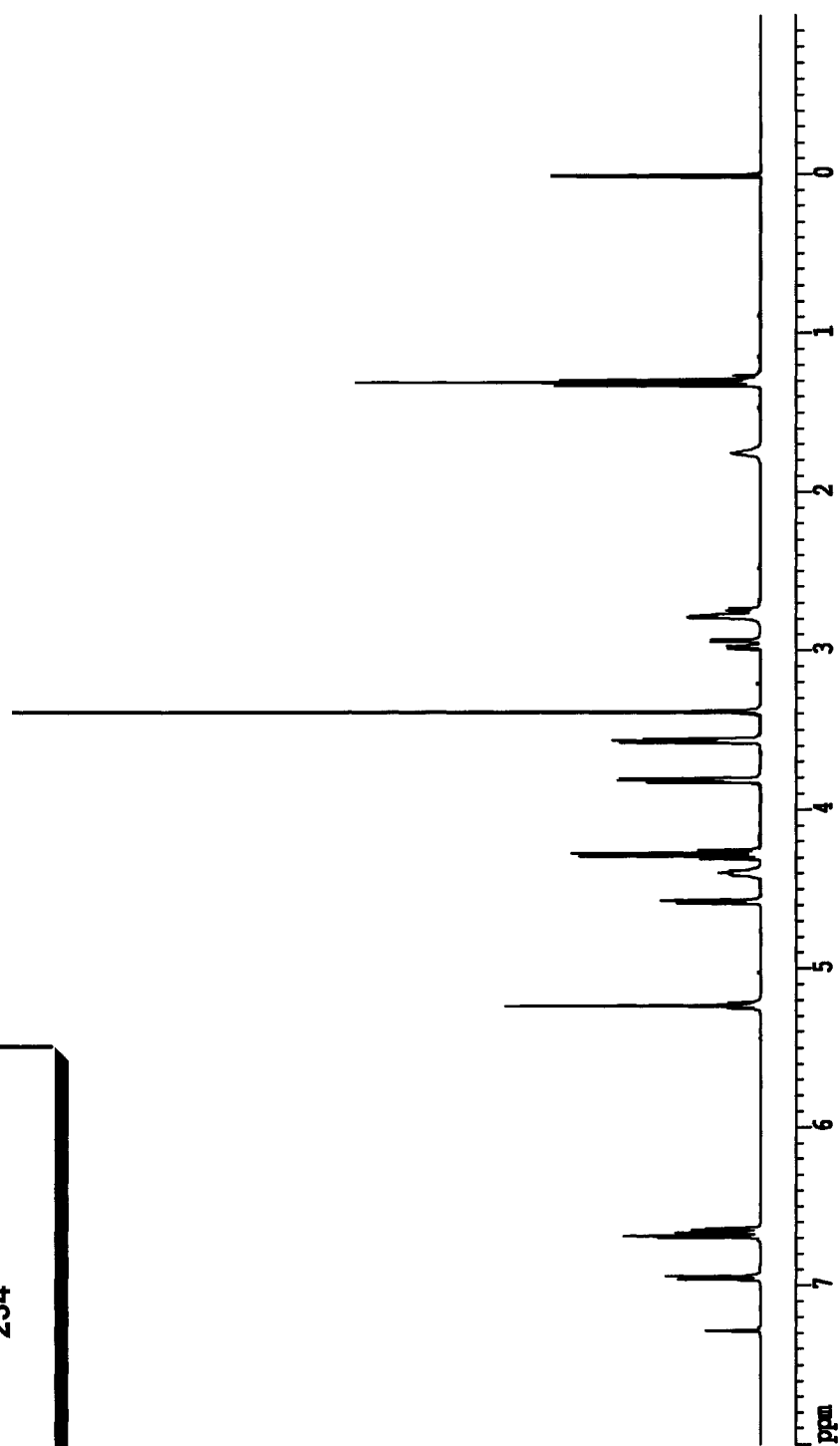
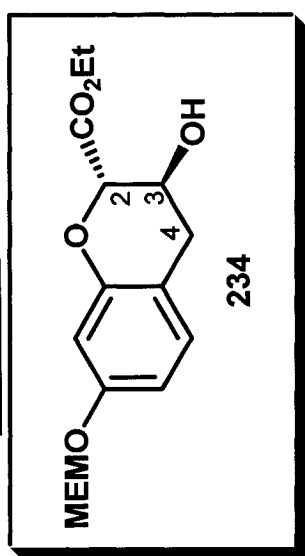
Spectrum 4:HMBC NMR



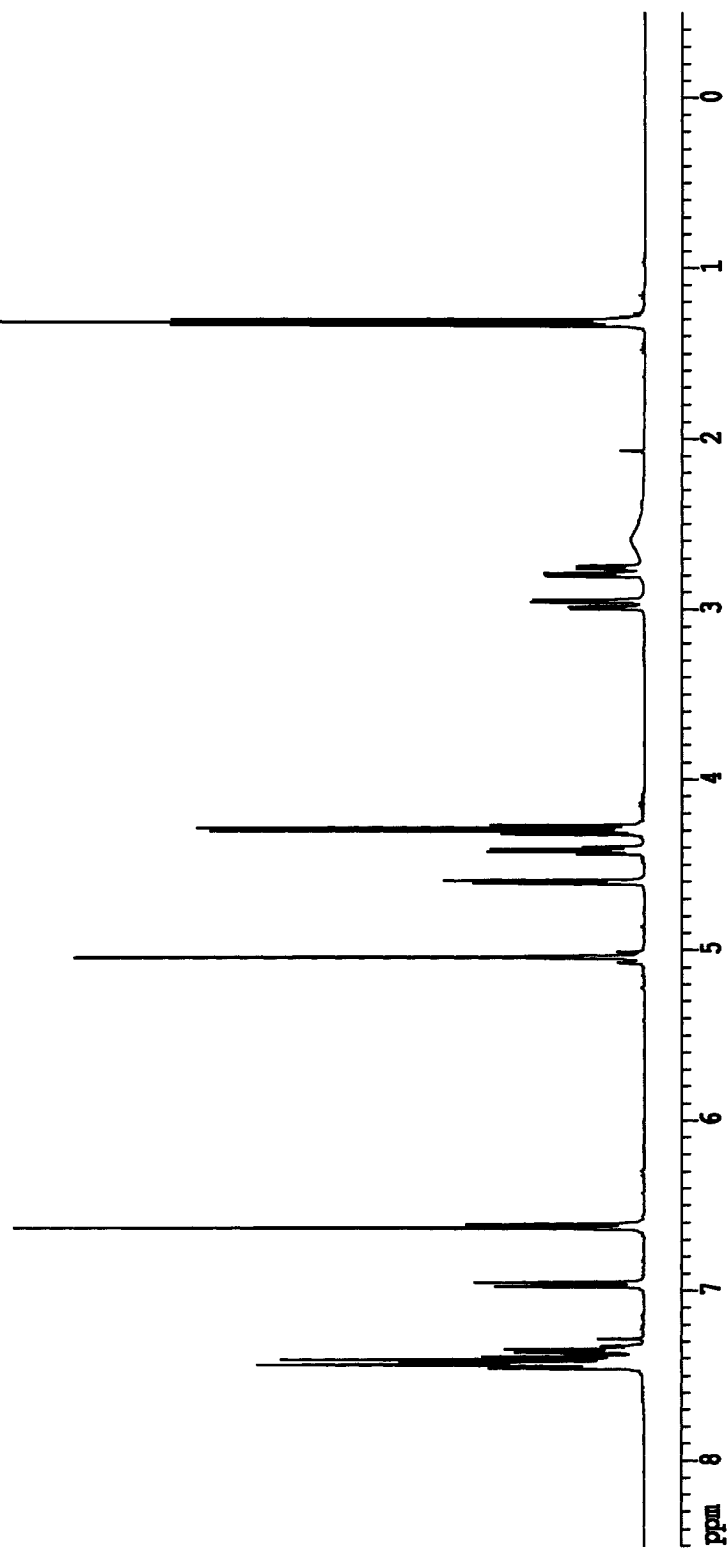
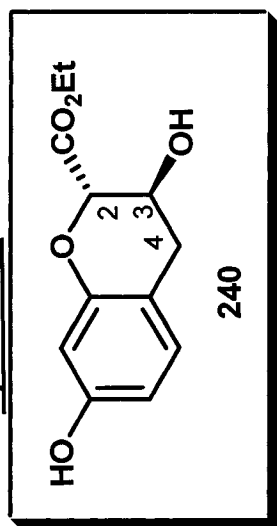
Spectrum 5: ^1H NMR



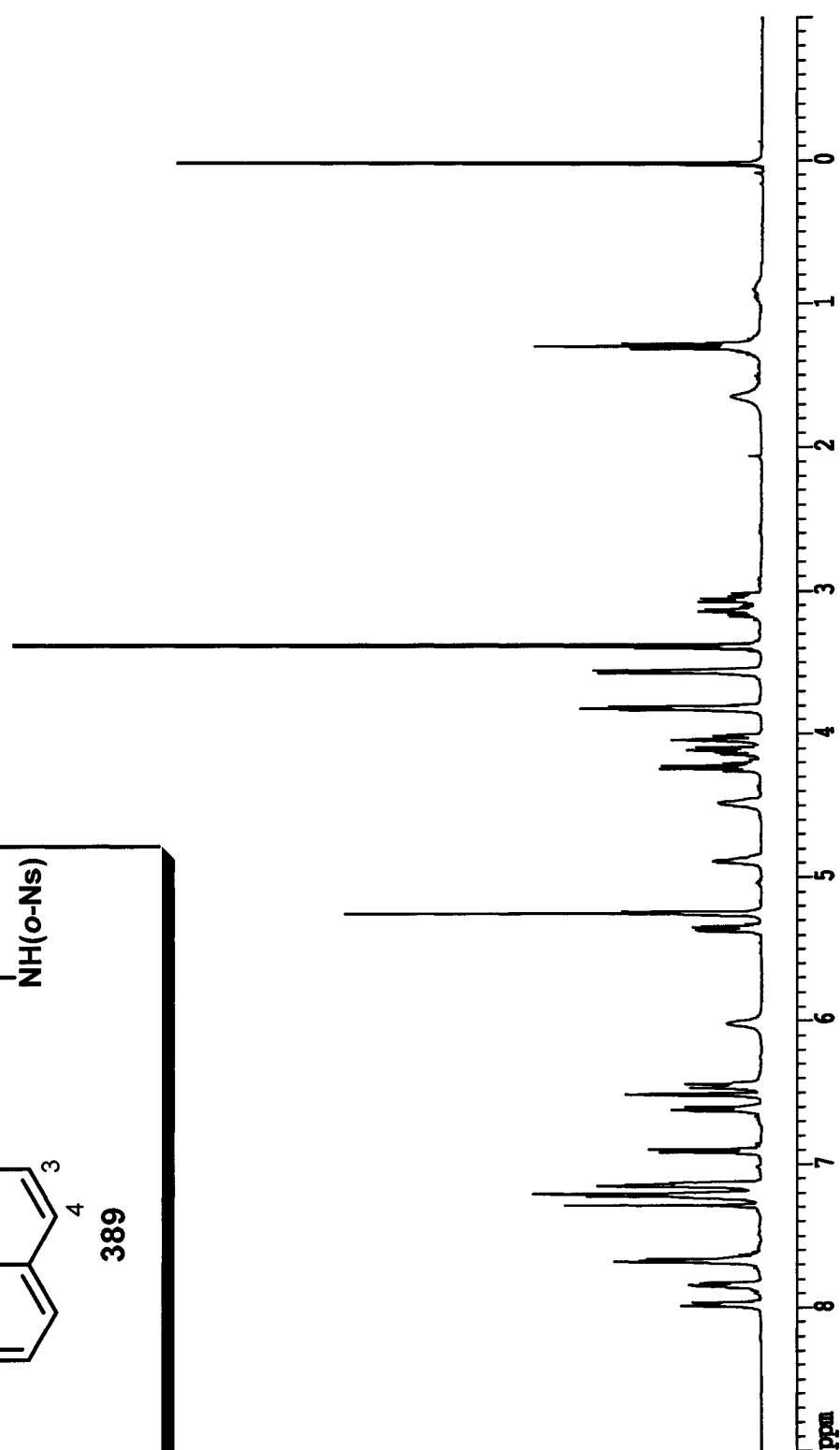
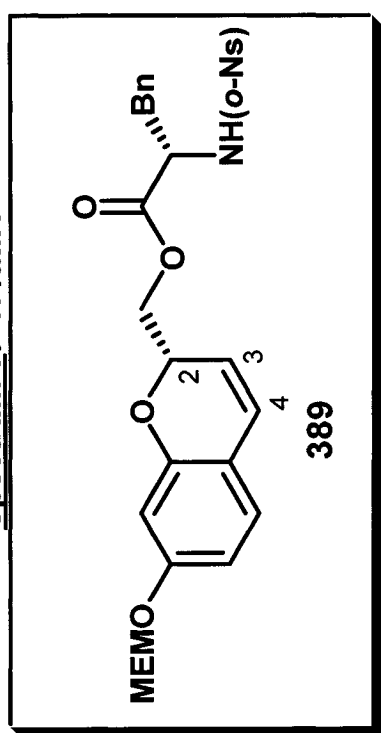
Spectrum 6: ^1H NMR



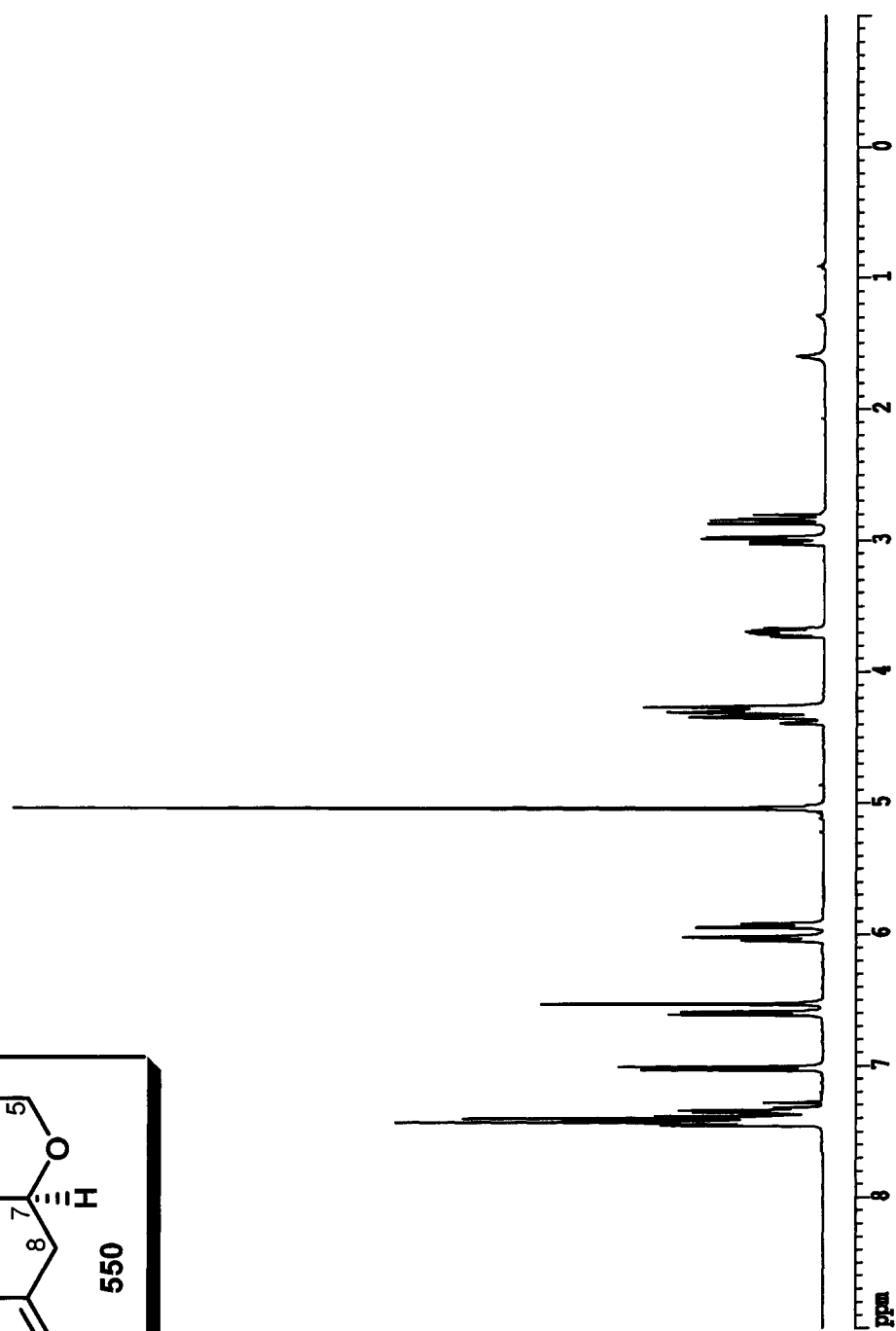
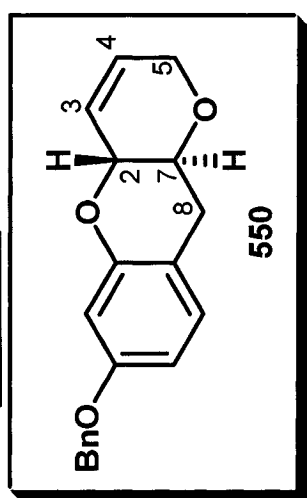
Spectrum 7: ^1H NMR



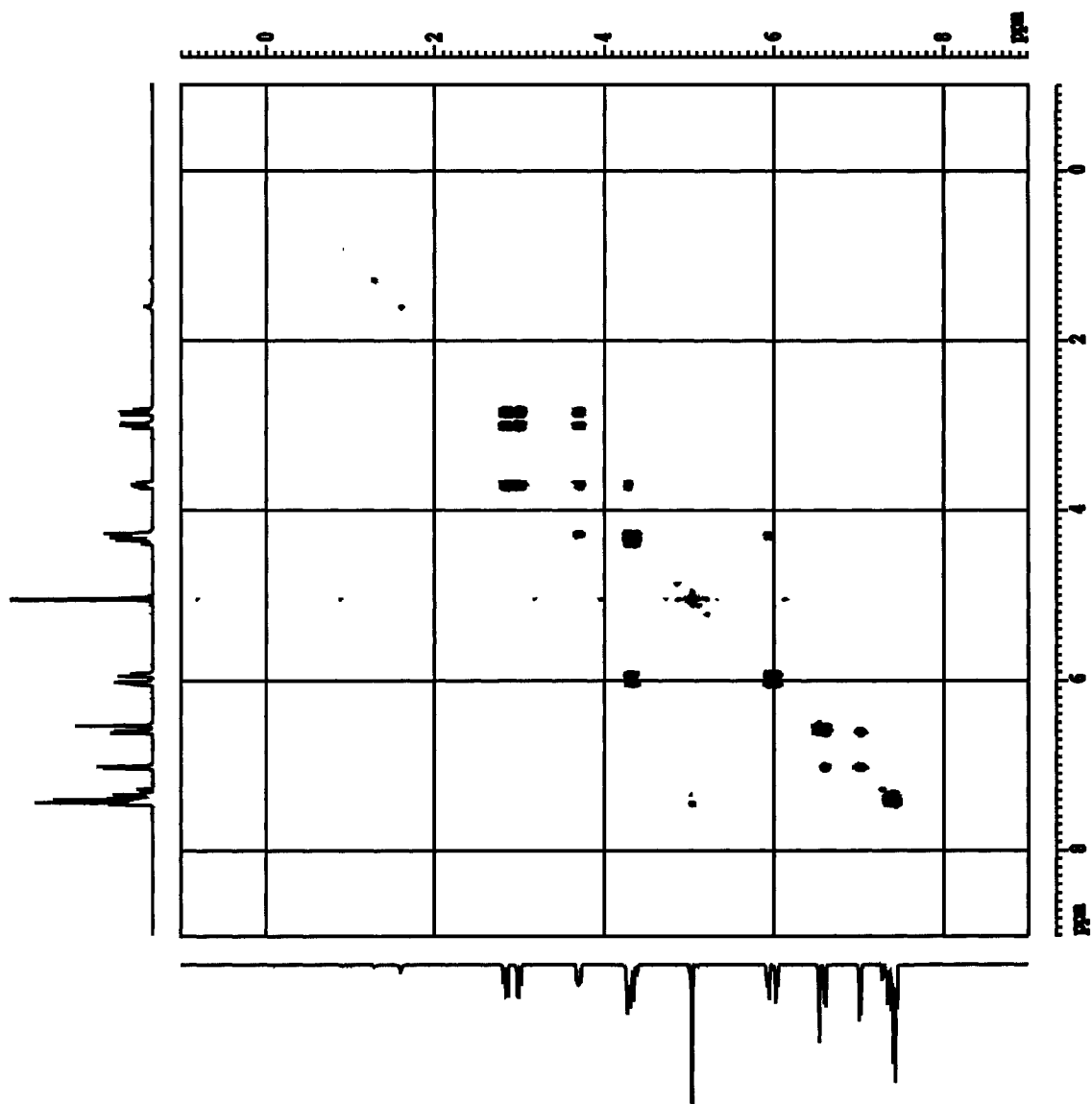
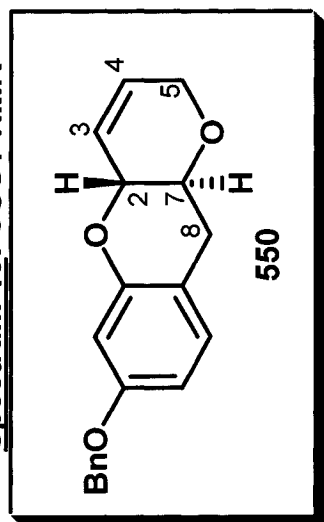
Spectrum 8: ^1H NMR



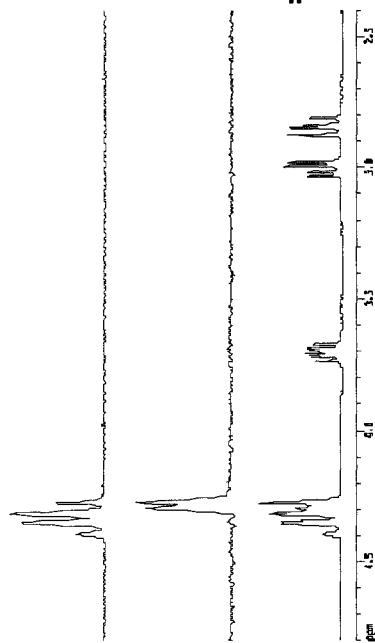
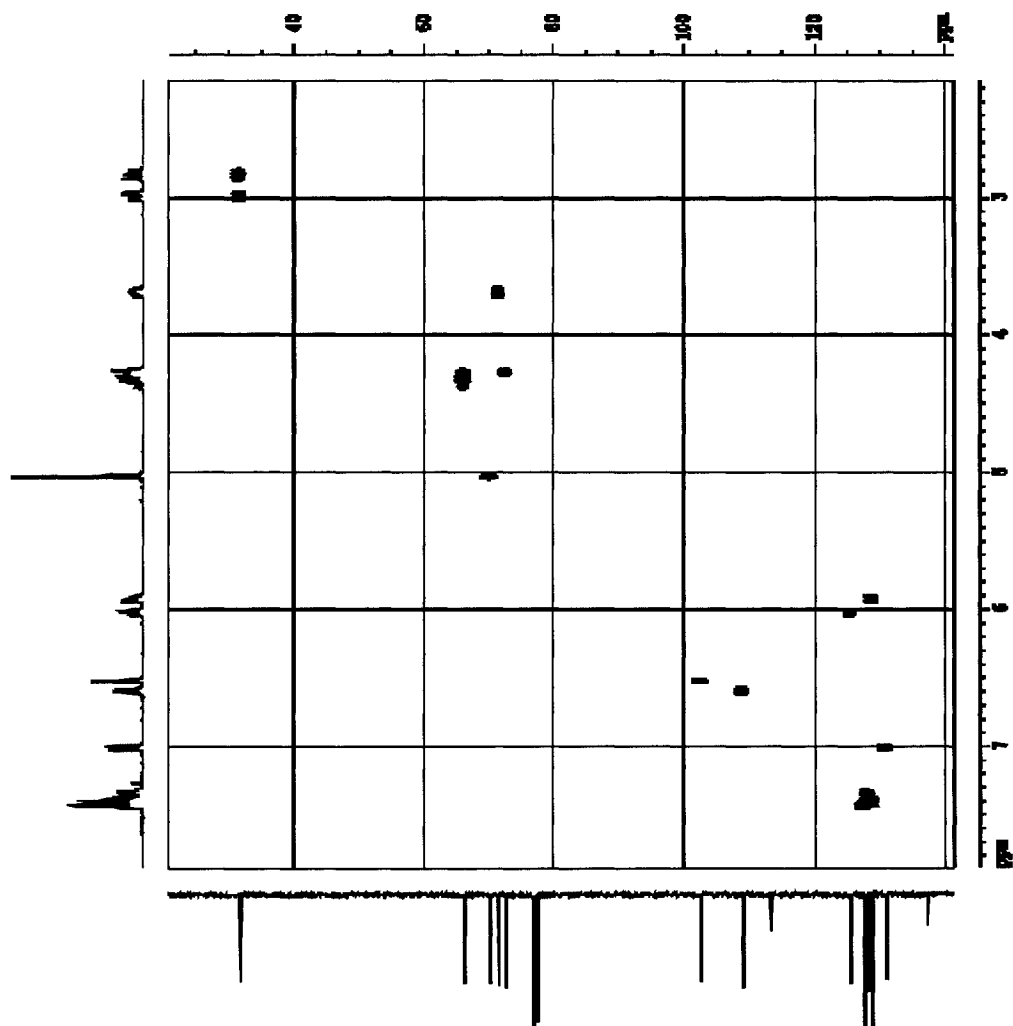
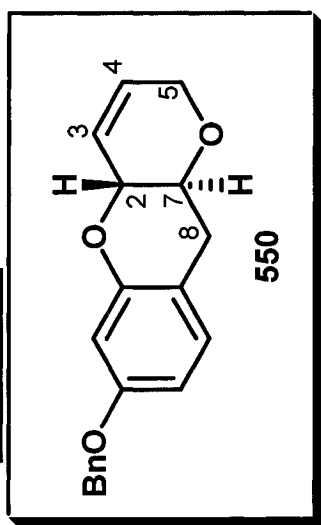
Spectrum 9: ^1H NMR



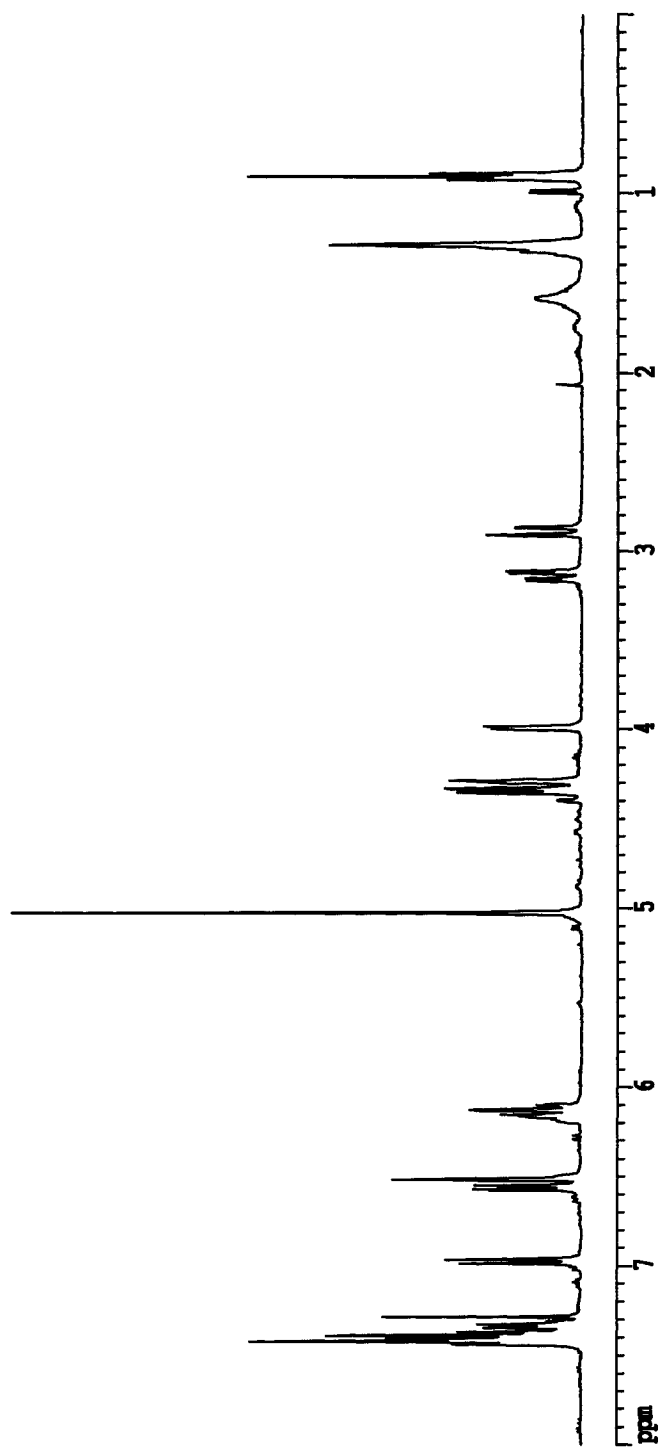
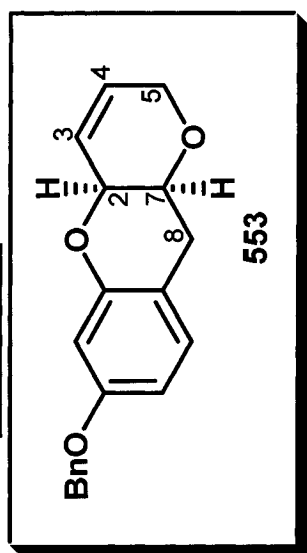
Spectrum 10: COSY NMR



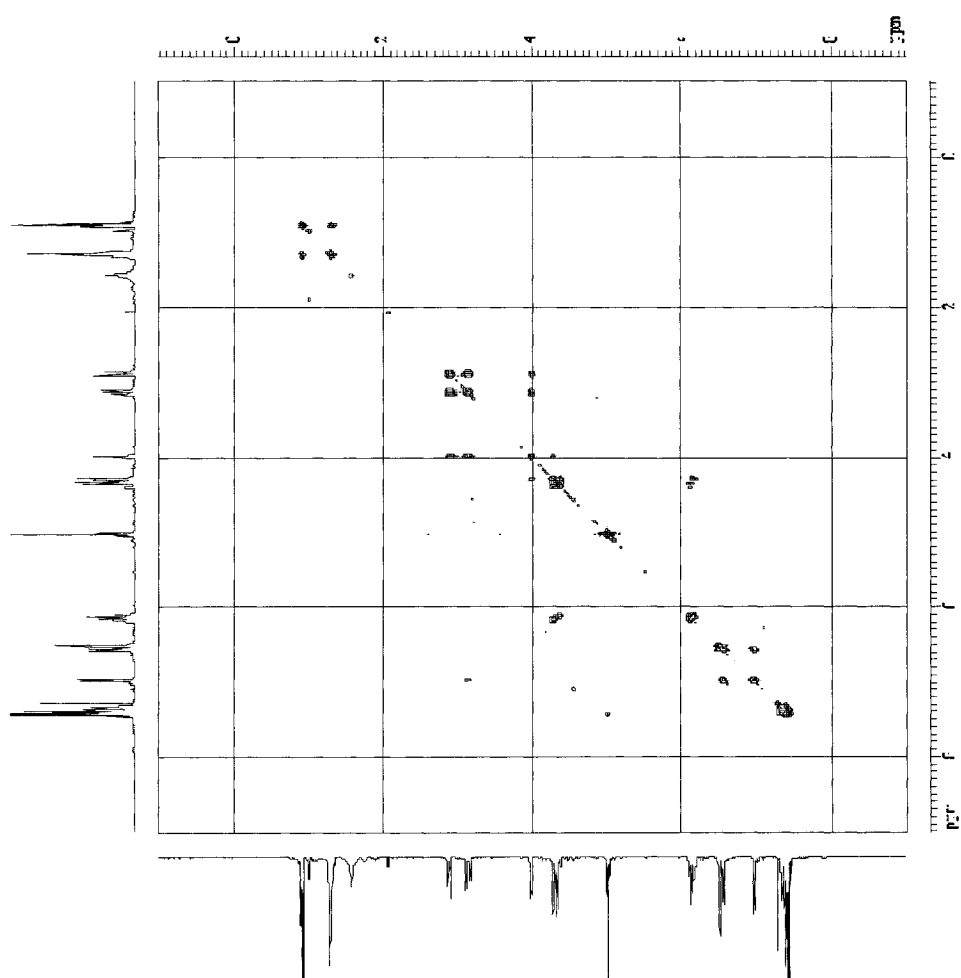
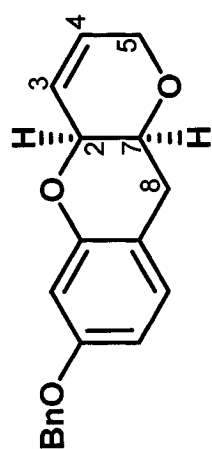
Spectrum 11: HMQS NMR



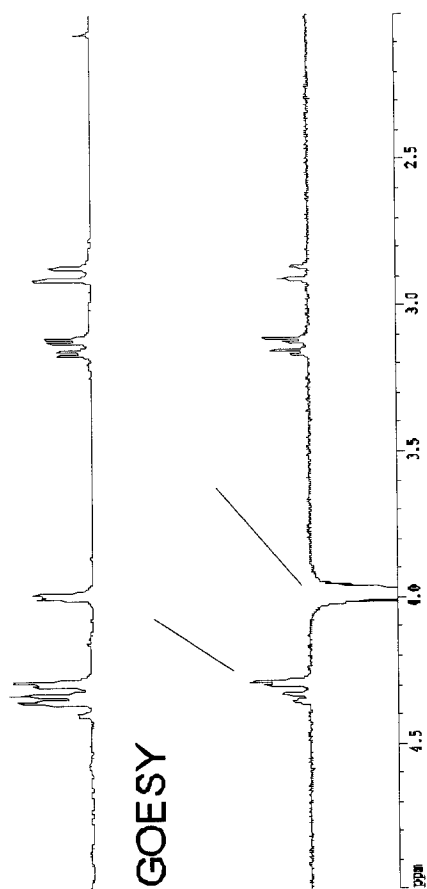
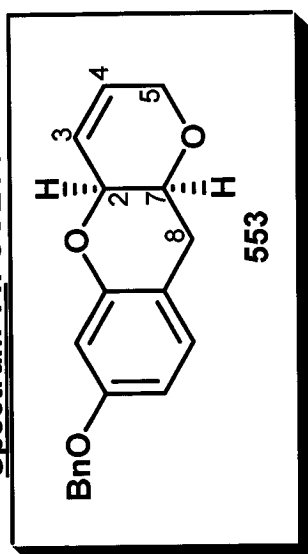
Spectrum 12: ^1H NMR



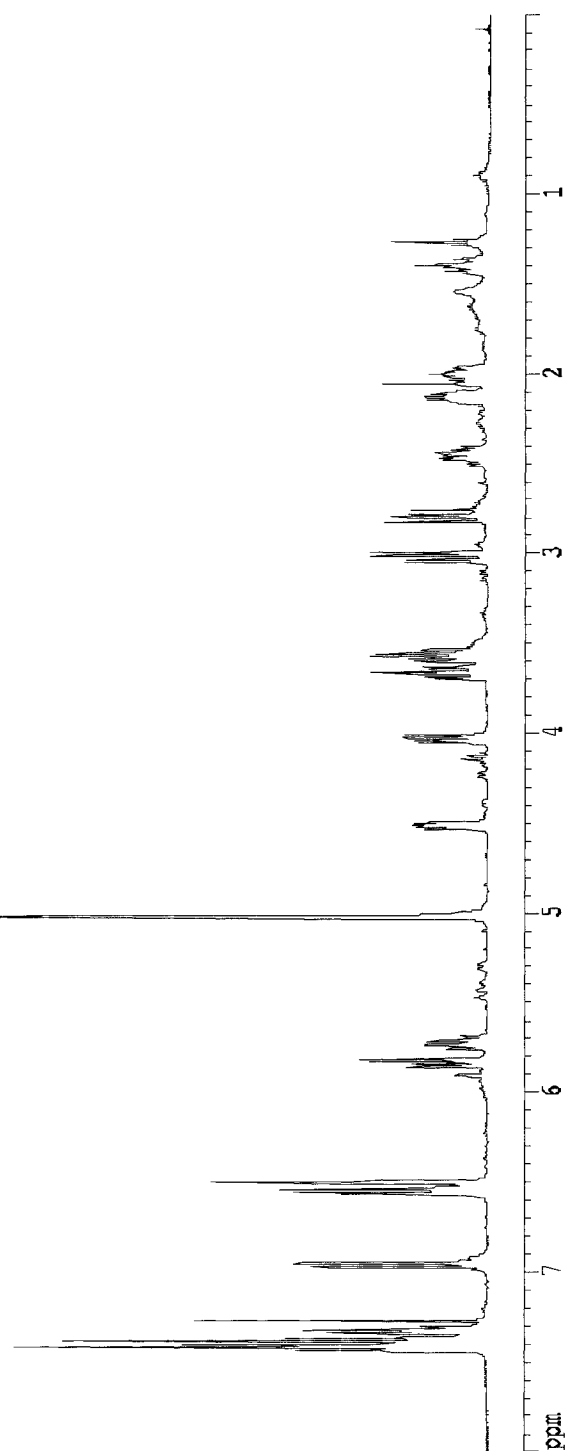
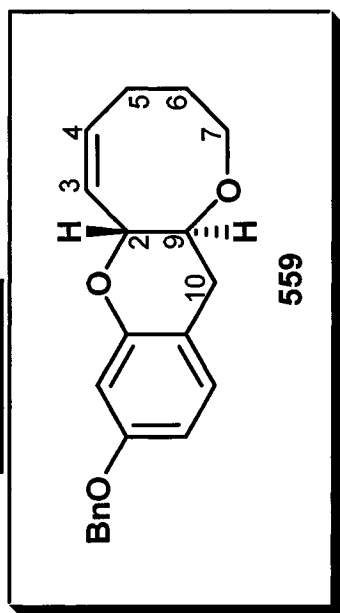
Spectrum 13: COSY NMR



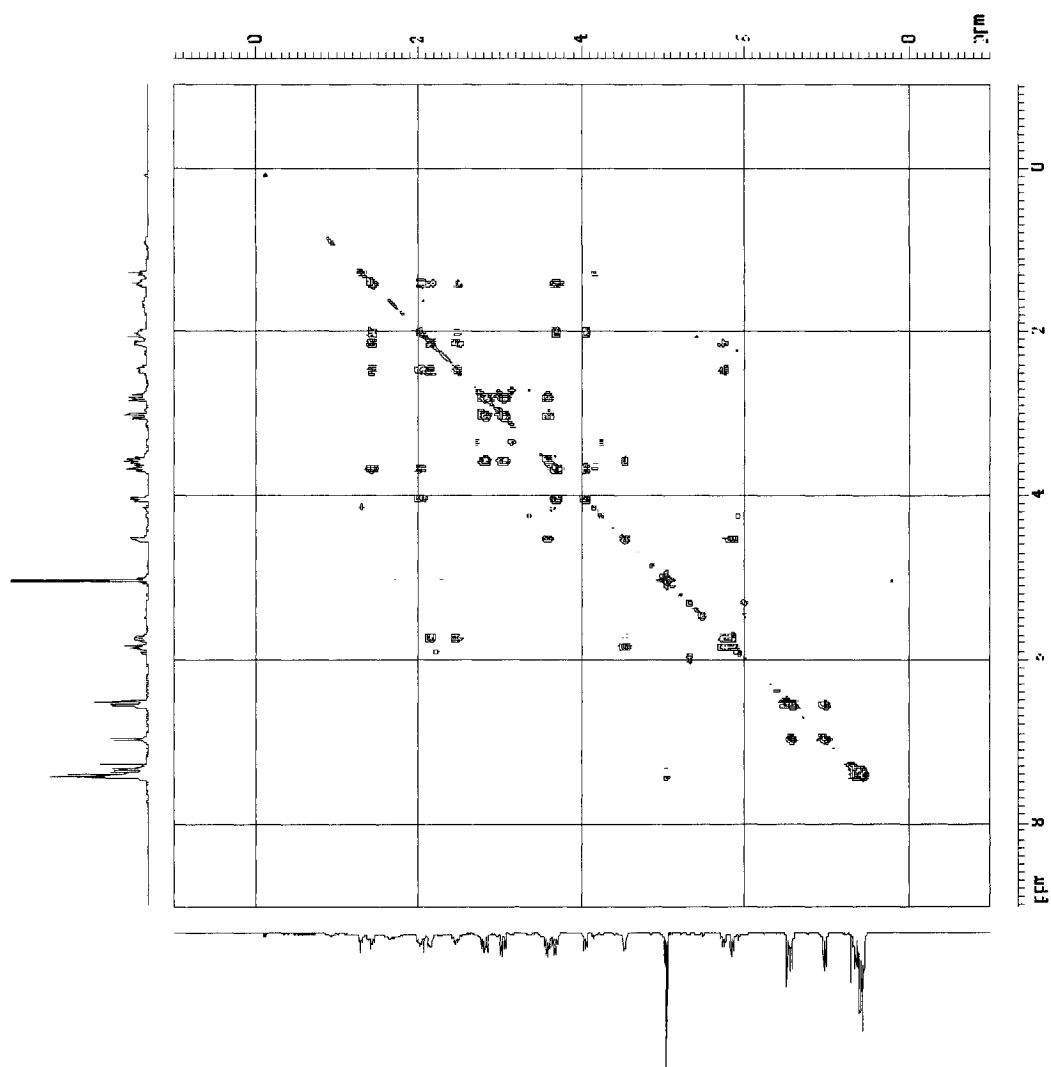
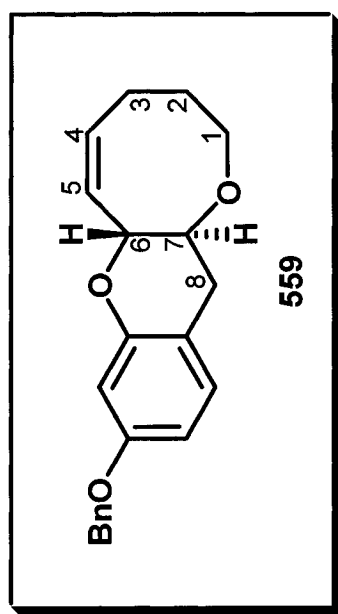
Spectrum 14: GOESY NMR



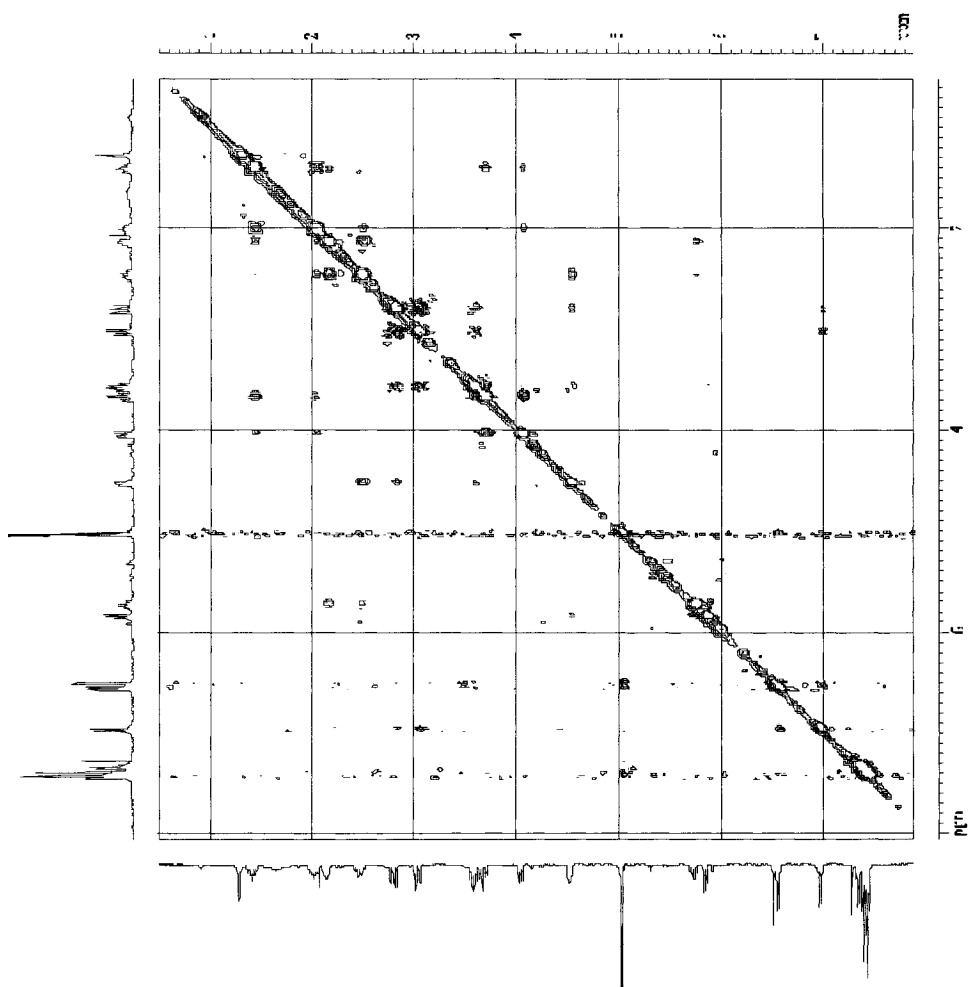
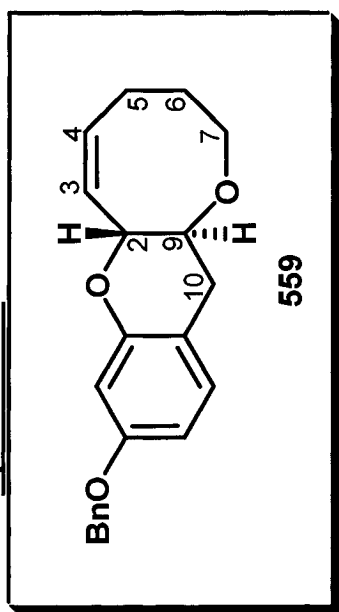
Spectrum 15: ^1H NMR



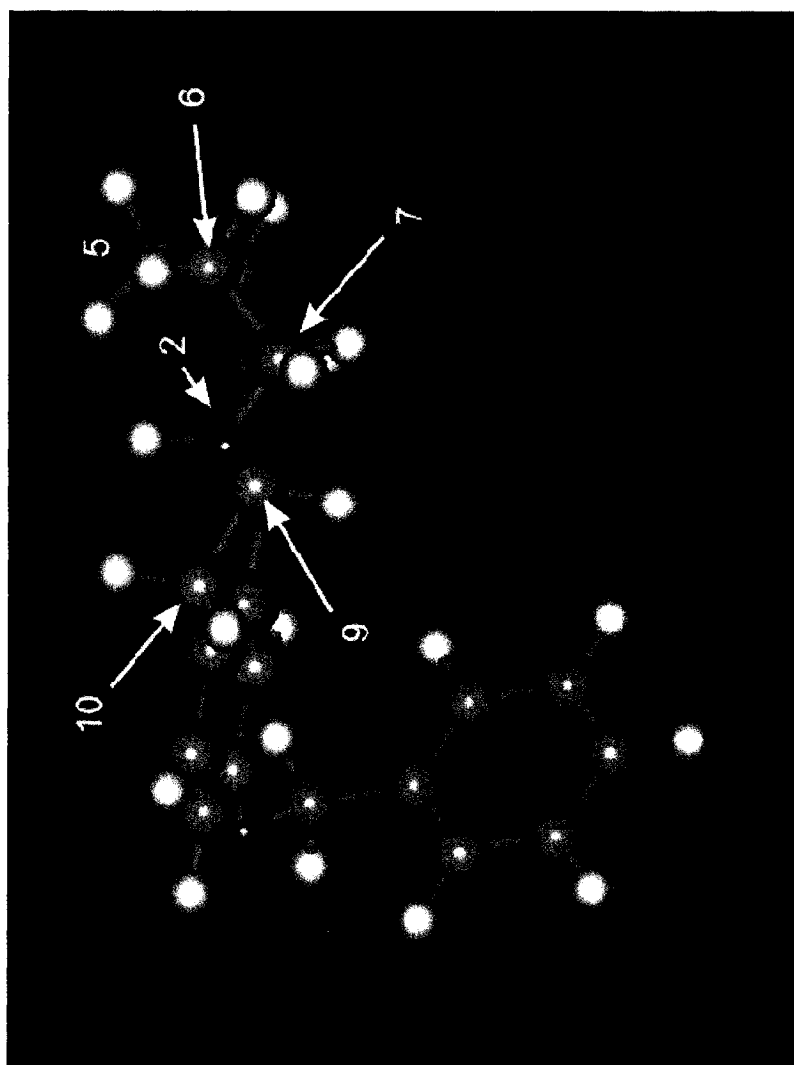
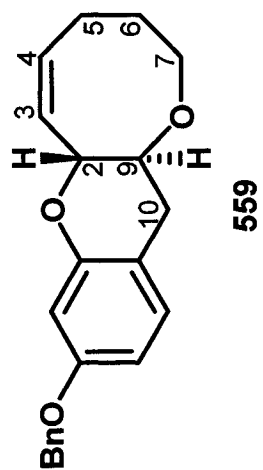
Spectrum 16: COSY NMR



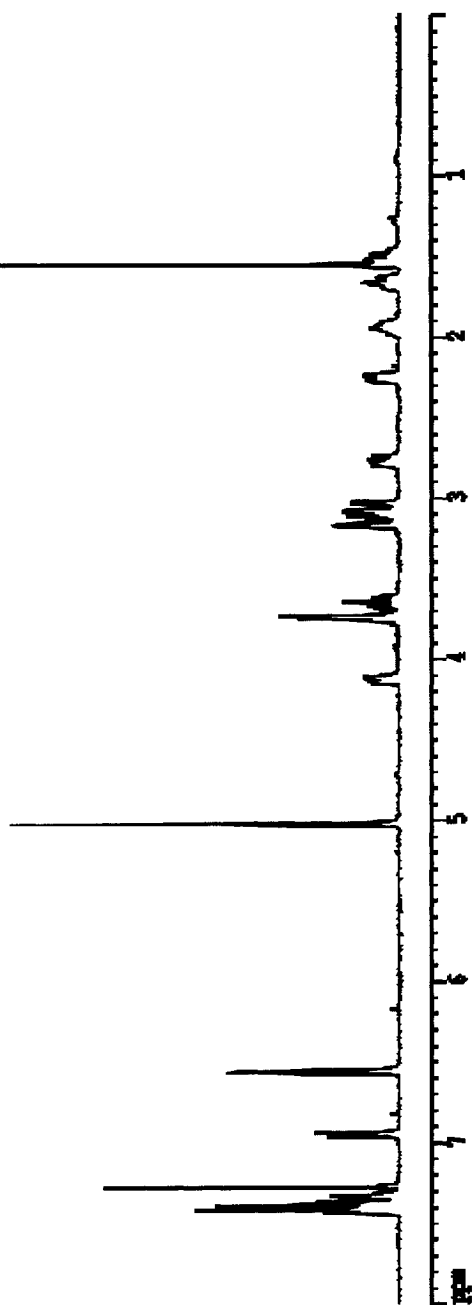
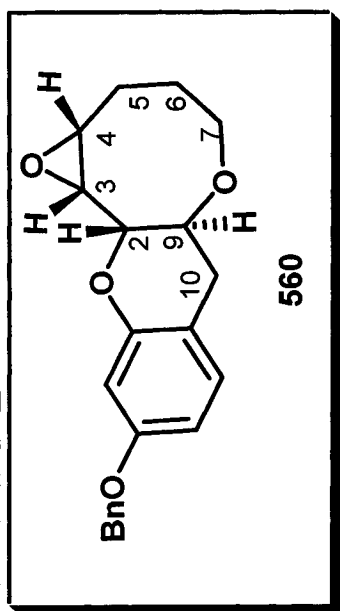
Spectrum 17: NOESY NMR

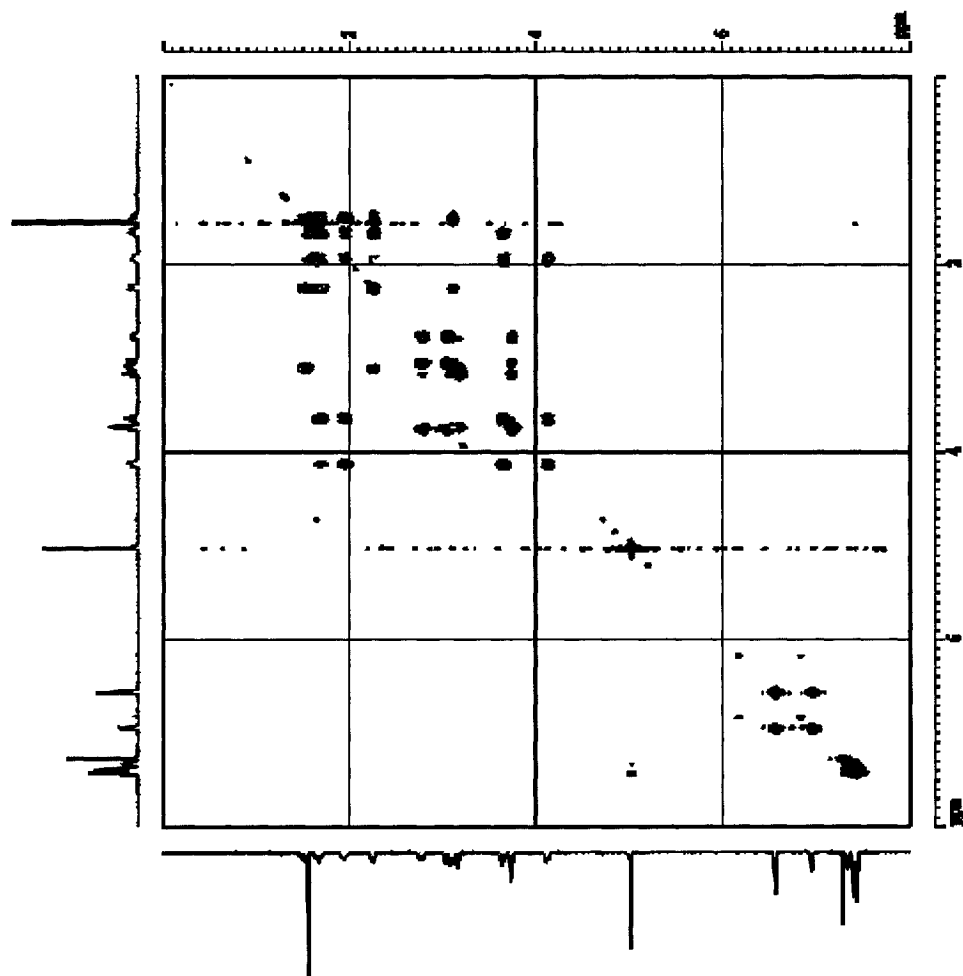


Spectrum 18: Modelling Study

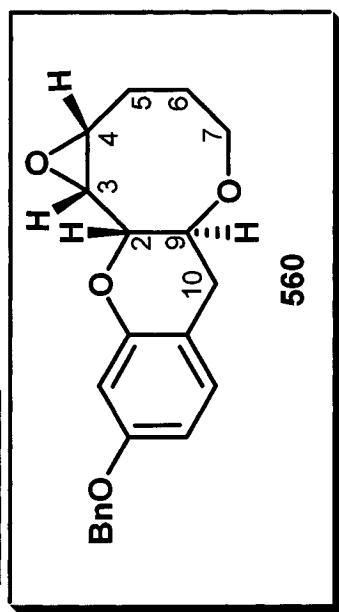


Spectrum 19: ^1H NMR

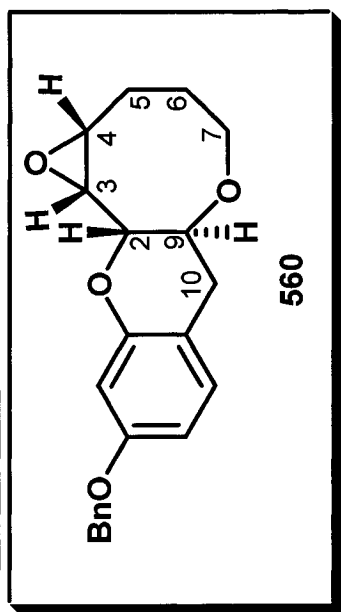




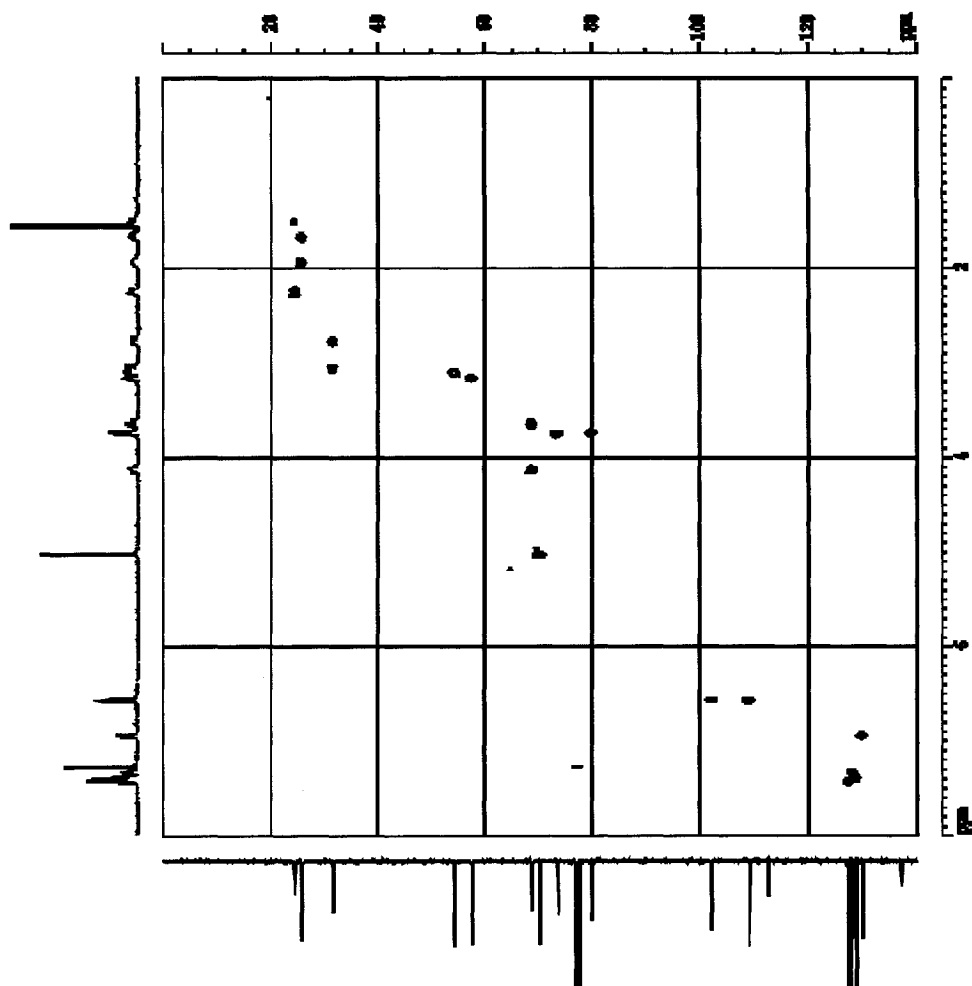
Spectrum 20: COSY NMR



Spectrum 21: HSQC NMR



560



Spectrum 22: NOESY NMR

