The Development of Stereocontrolled Methods to Obtain a Diverse Set of Tetrahydroquinoline-Based, Natural Product–Inspired Compounds
THE DEVELOPMENT OF STEREOCONTROLLED METHODS TO OBTAIN A DIVERSE SET OF TETRAHYDROQUINOLINE-BASED, NATURAL PRODUCT-INSPIRED COMPOUNDS

by

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# TABLE OF CONTENTS

Table of Contents .............................................................................................................. ii  
List of Figures ..................................................................................................................... vi  
List of Tables ....................................................................................................................... ix  
Abbreviations and Acronyms ............................................................................................... x  
Abstract ................................................................................................................................. xiv  
Acknowledgments ................................................................................................................ xvi

1: Introduction......................................................................................................................... 1  
1.1 Small Molecules or Smart Molecules?!. ........................................................................ 1  
   1.1.1 Drug Discovery Stages ......................................................................................... 1  
   1.1.2 Natural Products vs. Synthetic Drugs ................................................................. 3  
   1.1.3 Small Molecules as Chemical Probes- Modulators of Protein-Protein Interactions ................................................................. 4  
1.2 Combinatorial Chemistry- Some Aspects .................................................................... 5  
   1.2.1 Solution Phase vs. Solid Phase Combinatorial Synthesis .................................. 6  
   1.2.2 Parallel vs. Split-Pool Library Synthesis ............................................................. 7  
   1.2.3 Natural Products as "Role Models" for Combinatorial Chemistry ...................... 8  
1.3 Diversity Oriented Synthesis ......................................................................................... 10  
   1.3.1 Diversity Oriented Synthesis vs. Target Oriented Synthesis .............................. 10  
   1.3.2 Applications of DOS ........................................................................................ 12  
1.4 Protein-Protein Interactions- Closer Look ................................................................ 22  
   1.4.1 Small Molecule Inhibitors of Bcl-2 Family Proteins .......................................... 24  
   1.4.2 Finding Hits Using Validation Tools ................................................................. 27  
1.5 Thesis Objectives .......................................................................................................... 29

2: Synthesis of Tetrahydroquinoline Scaffold .................................................................... 31  
2.1 Design of Scaffold ......................................................................................................... 31  
2.2 Tetrahydroquinoline Core and Related Structures in Nature .................................... 32  
2.3 Tetrahydroquinolines as Pharmaceutical Products ..................................................... 33
2.4 Synthetic Strategies in Literature .................................................. 34
  2.4.1 Reduction of Unsaturated Heterocyclic Ring ................................. 35
  2.4.2 Closure of One Bond ................................................................... 39
  2.4.3 Condensation of Anilines with Aldehydes ...................................... 52
  2.4.4 Reaction of N-Aryl Methyleneiminiums with Alkenes ..................... 54
  2.4.5 From Aldimines (Aniline Imines) .................................................. 59
  2.4.6 By Insertion of C2-C3 Fragment .................................................... 64
  2.4.7 Ring Contraction and Ring Expansion .......................................... 65
2.5 Our Synthesis Approach ................................................................. 67
  2.5.1 Model Study ............................................................................... 67
    2.5.1.1 Synthesis of Aldehyde Precursor .......................................... 60
    2.5.1.2 Chain Extension and Asymmetric Dihydroxylation ................. 69
    2.5.1.3 Regioselective Tosylation and Cyclization .............................. 71
  2.5.2 Scaffold Required for Solid-Phase Synthesis ................................. 73
    2.5.2.1 Homologation and Chain Extension .................................... 74
    2.5.2.2 Protection of Ar-OH and Asymmetric Dihydroxylation .......... 75
    2.5.2.3 Regioselective Tosylation and Cyclization .............................. 76

3: Solution and Solid Phase Synthesis of Tetrahydroquinoline
   Polycyclics. Part A: 10-membered Ring Unsaturated Lactam .................. 78
3.1 Design Strategy ............................................................................... 78
3.2 Ten-membered Rings Having Nitrogen (Lactam) as Natural
   and Pharmaceutical Products ............................................................. 79
3.3 Synthesis of Ten-membered Rings Having Nitrogen (Lactam)
   in Literature .................................................................................. 81
    3.3.1 Ring Closure and Ring Contraction ........................................... 81
    3.3.2 Ring Expansion and Fragmentation .......................................... 86
3.4 Our Synthesis Approach .................................................................. 92
  3.4.1 Model Study ............................................................................... 93
    3.4.1.1 Synthesis of Precursor for RCM Reaction ............................. 93
    3.4.1.2 RCM Reaction to 10-membered Ring Lactam ....................... 96
3.4.1.3 Hetero Michael Reaction on Lactam ............................................. 101
3.4.2 Solid Phase Synthesis ........................................................................... 103
  3.4.2.1 Synthesis of Precursor Having Anchoring Site ............................ 104
  3.4.2.2 Loading and Solid Phase Synthesis of 10-membered Ring Lactam .... 106
  3.4.2.3 Cleavage ...................................................................................... 109

4: Solution and Solid Phase Synthesis of Tetrahydroquinoline Polycyclics. Part B: \(\alpha,\beta\)-Unsaturated \(\gamma\)-Lactam and \(\delta\)-Lactone ........................................ 113

4.1 Design Strategy ......................................................................................... 113
4.2 Pyrrolo[1,2-a]quinolines as Natural and Pharmaceutical Products .......... 114
4.3 Synthesis of Pyrrolo[1,2-a]quinolines and Pyrano[3,2-b]quinolines
  in Literature ................................................................................................. 115
4.4 Our Synthesis Approach .......................................................................... 124
  4.4.1 Solution Phase Synthesis of Tetrahydroquinoline Tricyclic
    Having \(\alpha,\beta\)-Unsaturated \(\gamma\)-Lactam ................................................... 124
  4.4.2 Solution Phase Synthesis of Tetrahydroquinoline Tricyclic
    Having \(\alpha,\beta\)-Unsaturated \(\delta\)-Lactone .................................................. 129
  4.4.3 Solid Phase Synthesis of Tetrahydroquinoline Tricyclic
    Having \(\alpha,\beta\)-Unsaturated \(\gamma\)-Lactam .................................................. 131

5: One-Pot Synthesis of Tetrahydroquinoline-Derived Polycyclic Compounds and Further Exploration ........................................ 135

5.1 Design Strategy ......................................................................................... 135
5.2 Isoindolo[2,1-a]quinolines as Biologically Active Targets ...................... 136
5.3 Synthesis of Isoindolo[2,1-a]quinoline System in Literature ................. 137
5.4 Our Synthesis Approach .......................................................................... 146
  5.4.1 Povarov Reaction: An Extension ....................................................... 147
    5.4.1.1 Mechanism ................................................................................ 149
    5.4.1.2 Synthesis of Tetrahydroquinoline Tricycles ............................... 150
    5.4.1.3 Closer Look at the Mechanism: .................................................. 151
More Evidence for Step-Wise Route ............................................. 155

5.4.2 Synthesis of Tetrahydroquinoline-Derived
Penta- and Hexacycles .................................................................. 158

5.4.2.1 One-Pot Synthesis of Isoindolo[2,1-a]quinoline System ........ 158
5.4.2.2 Mechanistic View ................................................................. 164
5.4.2.3 Further Exploration: Stereoselective Reactions .................... 165

5.5 Future Work ............................................................................. 174

6: Natural Product-inspired, Small Molecule Modulators of
Protein-Protein Interactions Involved in Cell Death Pathways ...... 175

6.1 From ‘Small Molecules' to ‘Cancer Drugs' ................................. 175
6.2 Binding Bcl-2 Proteins to Membranes as the Key Process .......... 177
6.3 Quest for Small Molecules as Modulators of Protein-Protein
Interactions- Past and Current Approaches ................................. 178
6.4 Role of Bcl-2 Family Proteins in the ‘Membrane Permeabilization'... 179
6.5 Biological Evaluation of Tetrahydroquinoline-based
Compounds (In Progress) ............................................................... 182
6.6 Closing Remarks ...................................................................... 184

7: Experimental ............................................................................ 186
7.1 General Methods ....................................................................... 186
7.2 X-ray Crystallography ................................................................. 186
7.3 Procedures ................................................................................. 187

8: Claims to Original Research ...................................................... 225
8.1 Publications .............................................................................. 225
8.2 Presentations ............................................................................. 226

9: References .................................................................................. 228

10: Appendix .................................................................................. 245
List of Figures

Figure 1.1 Stages in the Drug Discovery Process
Figure 1.2 All small molecule new chemical entities-drugs [right, (1981-2006)]
and all available anticancer drugs [left, (1940s-2006)]
Figure 1.3 Parallel Library Synthesis (left) and Split-Pool Synthesis (right)
Figure 1.4 A few examples of alkaloids and Oxygen-enriched natural products
Figure 1.5 'DOS/TOS/Traditional Combinatorial Chemistry' Comparisons
Figure 1.6 Molecular Diversity Spectrum
Figure 1.7 Representative Bioactive Molecules Synthesized using DOS
Figure 1.8 DOS Programs in Arya's Group
Figure 1.9 Structures of small-molecule inhibitors of protein–protein interactions
Figure 1.10 Apoptotic Pathways
Figure 1.11 Therapeutics that target apoptosis, autophagy, and necrosis
Figure 1.12 Validation Tools for DOS
Figure 1.13 Schematic Project Goals
Figure 1.14 Target Molecules as Thesis Objectives
Figure 2.1 Natural Products with Tetrahydroquinoline Core
Figure 2.2 Tetrahydroquinoline Derivatives as Medicines
Figure 3.1 Natural Products Having a 10-membered Ring Nitrogen/Lactam
Figure 3.2 Structure of LE-300
Figure 3.3 COSY of Compound 295 Showing H Correlations
Figure 3.4 Proton Assignments for Compound 295 Using COSY
Figure 3.5 Chemical Shifts for Compound 295
Figure 3.6 $^1$H and $^{13}$C Chemical Shifts Using HSQC
Figure 3.7 Final Assignment of Chemical Shifts Using all Experiments
Figure 3.8 X-ray Structure of Compound 295
Figure 3.9 $^1$H-NMR Spectrum for Thio Compound 296
Figure 3.10 NOESY Spectrum for Thio Compound 296
Figure 3.11 Proton Assignment for Compound 310 Using 2D NMR
Figure 3.12 Revealing $^1$H/$^1$H Coupling by COSY
Figure 3.13 Pattern Likeness at Compound Made in Solution Phase
Figure 3.14 Side-by-Side Comparison of COSY Spectra
Figure 3.15 Superimposed Comparison of COSY Spectra
Figure 4.1 Tricyclic Systems Presenting in This Chapter
Figure 4.2 Interesting Compounds Having Pyrrolo-, Isoindoloquinoline Systems
Figure 4.3 Spatially Close Hydrogens in Compound 54 Revealed by NOESY
Figure 4.4 X-ray Structure of Compound 54
Figure 4.5 Comparison of COSY Spectra between Compounds 54 and 366
Figure 5.1 Isoindoloquinoline and Isoindoloquinolone
Figure 5.2 Synthetic Trends in Our Research
Figure 5.3 Bioactive Isoindoloquinolines
Figure 5.4 Bioactive Compounds Synthesized by Povarov Reaction
Figure 5.5 Protons in Cyclopenta[c]pyridine Fragment
Figure 5.6 Regioselective Formation of 430
Figure 5.7 Proton Correlations and COSY Spectrum for Compound 429
Figure 5.8 X-ray Structures for Tetrahydroquinolines Tricycles 428-430
Figure 5.9 One-pot Synthesis of Cyclopenta[c]isoindolo[2,1-a]quinoline System
Figure 5.10 X-ray Structure of Compound 443
Figure 5.11 Proton Assignment/Correlations and Using COSY/\(^1\)H-NMR Spectra for Compound 444
Figure 5.12 X-ray Structure of Compound 444
Figure 5.13 Compound 443; a Valuable Scaffold in DOS
Figure 5.14 Concave and Convex faces in 443
Figure 5.15 Aliphatic Protons’ Assignment for 446 Using \(^1\)H-NMR and COSY
Figure 5.16 X-ray Structure of Compound 446
Figure 5.17 Protons Assignment and \(^1\)H-NMR Spectrum for Compound 447
Figure 6.1 Disordered Cell Death Causes Abnormality
Figure 6.2 Interactions of Bcl-2 Proteins with Membranes
Figure 6.3 Regulation of Membrane Permeabilization by Bcl-2 Family Proteins
Figure 6.4 Identification of a small molecule inhibitor of membrane permeabilization
Figure 6.5 ANTS release assay for pore formation by Bax
Figure 6.6 Small Molecules Tested for Finding Modulators of Protein-Protein Interaction
Figure 6.7 Tetrahydroquinoline-based Compounds as Bax Inhibitors
List of Tables

Table 3.1 Crystal Data for Compound 295
Table 4.1 Crystal Data for Compound 54
Table 5.1 \(^1\text{H-}
\text{NMR Data (In Part) for Tetrahydroquinolines Tricycles 428-430}
Table 5.2 Crystal Data for Tetrahydroquinoline Tricycles 428-430
Table 5.3 Crystal Data for Compound 443
Table 5.4 Crystal Data for Compound 444
Table 5.5 Crystal Data for Compound 446
### Abbreviations and Acronyms

1D  
1-dimensional

2D  
2-dimensional

Å  
angstrom(s)

Ac  
acetyl

AD mix α  
(DHQ)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$OsO$_4$$\cdot$2H$_2$O

AD mix β  
(DHQD)$_2$PHAL, K$_3$Fe(CN)$_6$, K$_2$OsO$_4$$\cdot$2H$_2$O

Alloc  
allyloxy carbonyl

aq  
aqueous

Ar  
aryl

atm  
 atmosphere(s)

av  
average

9-BBN  
9-borabicyclo[3.3.1]nonyl

Bn, Bzl  
benzyl

BOC, Boc  
tert-butoxycarbonyl

Br  
bromine

br  
broad (spectral)

bs  
broad singlet

Bu, n-Bu  
normal (primary) butyl

t-Bu  
tert-butyl

Bz  
benzoyl

C  
carbon

°C  
degrees Celsius

calcd  
calculated

CAN  
ceric ammonium nitrate

cat  
catalytic

CBZ, Cbz  
benzyloxycarbonyl

CD  
circular dichroism

c-Hex  
c-C$_9$H$_{11}$, cyclohexyl

Cl  
chemical ionization; configuration interaction

Cl  
chlorine

cm$^{-1}$  
wavenumber(s)

cod  
1,5-cyclooctadiene

compd  
compound

concd  
concentrated

concn  
concentration

COSY  
correlation spectroscopy

Cp  
cyclopentadienyl

m-CPBA  
meta-chloroperoxybenzoic acid

δ  
chemical shift in parts per million downfield from tetramethylsilane

d  
day(s); doublet (spectral); deci

DCC  
$N$,$N'$-dicyclohexylcarbodiimide

DCM  
dichloromethane (methylene chloride)
dd Doublet of doublets
dddd Doublet doublet of doublets
ddt Doublet doublet of triplets
dt Doublet of triplets
DEAD diethyl azodicarboxylate
DEPT distortionless enhancement by polarization transfer
DIBALH diisobutylaluminum hydride
DMAP 4-(N,N-dimethylamino)pyridine
DMF dimethylformamide
DMSO dimethyl sulfoxide
DNA deoxyribonucleic acid
DOS Diversity Oriented Synthesis
ED50 dose that is effective in 50% of test subjects
eee Enantiomeric excess
eq equation
equiv equivalent
ES+ Positive electrospray
ESI electrospray ionization
Et ethyl
EtOAc ethyl acetate
F fluoride
FT Fourier transform
g gram(s)
GC gas chromatography
H hydrogen, proton
h hour(s)
HMBC heteronuclear multiple bond correlation
HMQC heteronuclear multiple quantum correlation
HPLC high-performance liquid chromatography
HRMS high-resolution mass spectrometry
HSQC heteronuclear single quantum correlation
Hz hertz
IR infrared
J coupling constant (in NMR spectrometry)
LAH lithium aluminum hydride
LD50 dose that is lethal in 50% of test subjects
LDA lithium diisopropylamide
LHMDS lithium hexamethyldisilazane, lithium bis(trimethylsilyl) amide
m multiplet (spectral); milli
M molar (moles per liter); mega
M+ parent molecular ion
max maximum
MCR multicomponent reaction
Me methyl
MEM (2-methoxyethoxy)methyl
min  minute(s); minimum
mM  millimolar (millimoles per liter)
mol  mole(s); molecular (as in mol wt)
mp  melting point
mRNA  messenger ribonucleic acid
Ms  methylsulfonyl (mesyl)
MS  mass spectrometry
MW  mol wt molecular weight
m/z  mass-to-charge ratio
N  normal (equivalents per liter); nitrogen
NBS  N-bromosuccinimide
NMO  N-methylmorpholine-N-oxide
NMR  nuclear magnetic resonance
NOE  nuclear Overhauser effect
NOESY  nuclear Overhauser effect spectroscopy
Nu  nucleophile
O  oxygen
obsd  observed
PCC  pyridinium chlorochromate
PDC  pyridinium dichromate
Ph  phenyl
PHAL  phthalazine
piv  pivaloyl
ppm  part(s) per million
PPTS  pyridinium para-toluenesulfonate
Pr  propyl
i-Pr  isopropyl
py  pyridine
q  quartet (spectral)
QSAR  Quantitative structure-activity relationship
RCM  ring-closure metathesis
rel  relative
Rr  retention factor
rRNA  ribosomal ribonucleic acid
rt  room temperature
S  sulfurs
s  singlet (spectral)
SN1  unimolecular nucleophilic substitution
SN2  bimolecular nucleophilic substitution
t  triplet (spectral)
TBAF  tetrabutylammonium Fluoride
TBS  tert-butyldimethylsilyl
TBSOTf  tert-butyldimethylsilyl trifluoromethanesulfonate
Teoc  Trimethylsilylthoxycarbonyl
temp  temperature
Tf  trifluoromethanesulfonyl (triflyl)
TFA  trifluoroacetic acid
THF  tetrahydrofuran
THP  tetrahydropyran-2-yl
TLC  thin-layer chromatography
TMS  trimethylsilyl; tetramethylsilane
tRNA transfer ribonucleic acid
Ts  para-toluenesulfonyl (tosyl)
TS  transition state
UV  ultraviolet
vis  visible
vol  volume
wt  weight
w/w  weight per unit weight (weight-to-weight ratio)
Abstract

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

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

After the successful development of the methods in solution, some of the intramolecular and intermolecular stereoselective-based reactions had been tried on solid phase. Developing stereoselective reactions-based methods on solid phase is crucial for the rapid synthesis of analogs. Besides NMR, the
conformation of the bridged 10 and 5-membered ring derivatives were assigned by X-ray studies (Chapter 3 and 4).

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

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

1.1 Small Molecules or Smart Molecules?!

1.1.1 Drug Discovery Stages

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

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

Depending on the satisfactory progress of these trials, which will contain several phases, healthy human volunteers may be recruited in order to evaluate tolerance to the drug (phase I). This will be followed by a trial on patients, in order to evaluate the drug’s efficacy and dosage (phase II) and a complete database of drug safety and efficacy may be obtained through widespread trials on thousands of patients (phase III). Manufacturers will then submit all
documentation to the relevant authority in order for them to make a thorough assessment of the drug's safety, efficacy, and quality. Only a very few drug candidates survive this series of trials. On obtaining official approval, the supplier can then offer the new drug to doctors for treating the disease. These stages are illustrated in Figure 1.1.

Figure 1.1 Stages in the Drug Discovery Process

Dominant role in drug discovery is played by natural products and their derivatives/mimics\textsuperscript{2,3}. Figure 1.2 shows the percentage of drug sources, which discovered for all diseases (left) and cancer (right). 58\% of all drugs and 54\% of cancer drugs are natural product related compounds [Natural (N), biologics (B), vaccines (V), synthetic (S), natural product-like or mimic (NM), natural product-derived (ND), made by total synthesis, but the pharmacophore is from a natural product (S*)].
There are several distinctions between synthetic drugs and natural products. Natural products normally have more chiral centres, thus they are more architecturally complex, however, some natural products, acting as protein receptors, have more simple structures. In addition, natural products often contain more carbon, oxygen, and hydrogen atoms and fewer other elements, including nitrogen, than do synthetic drugs. Many natural products have greater water solubility/polarity and possess molecular masses of over 500 daltons. Therefore, natural products violate Lipinski's 'rule of five' where, according to research, 90% of orally absorbed drugs have fewer than 5 hydrogen-bond donors, fewer than 10 hydrogen-bond acceptors, molecular masses of below 500 daltons, and lipophilicity (measured by log P value-calculated octanol/water partition coefficient) of less than 5.

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

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

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

In the past few years, an interest in this area has sparked because of the growing desire to modulate (and dissect through perturbation) intracellular signaling pathways. The era of post-genomic chemical biology (also known as "Chemical Genomic Age") is challenging the chemistry and biology community to develop programs in which small molecules could be extensively used to enhance our current understanding of intracellular signaling pathways. These pathways are fundamental to cellular functions, in both normal as well as deregulated cellular processes. Usually, these pathways involve multiple, highly complex, and dynamic protein-protein interactions, that are challenging to understand due to limited technology and tools available for studying signaling pathways. A lack of a thorough understanding about their participation in various normal and deregulated processes combined with the formidable challenge to modulate protein-protein interactions in a controlled and in a...
reversible manner, severely limits our ability to develop therapeutic approaches that exploit these pathways for beneficial outcomes. It is anticipated that the successful development of small molecule modulators of protein-protein interactions will create excellent opportunities for biomedical researchers to develop novel therapeutic strategies that would no longer be constrained by the limited set of proteins with enzymatic activity that are encoded in the genome.

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

1.2 Combinatorial Chemistry- Some Aspects

To meet the growing challenges in search of functional small molecules, for more than two decades, the area of combinatorial chemistry is now much engaged in the drug discovery arena. While taking an advantage of high-throughput access to DNAs/RNAs, peptides, and solid phase synthesis tools, the next challenge was to bring this and other related technologies to the small molecule arena. During this time, several outstanding reviews, book chapters and even books have been written on this topic. In general, as a community, we have
been very successful in embracing this area of high-throughput organic synthesis in producing rather simple compounds that are particularly rich in aromaticity and high $sp^2$ content; however, these compounds often lack the features that are frequently found in bioactive natural products.

1.2.1 Solution Phase vs. Solid Phase Combinatorial Synthesis

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

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

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

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

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

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

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

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

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

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

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

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

1.2.2 Parallel vs. Split-Pool Library Synthesis

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

![Figure 1.3 Parallel Library Synthesis (left) and Split-Pool Synthesis (right)](image-url)
1.2.3 Natural Products as "Role Models" for Combinatorial Chemistry

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

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

Members of natural products including alkaloids\textsuperscript{44-47}, flavonoids\textsuperscript{48} and several of their derivatives are known to possess a diverse range of biological properties. Most alkaloids and flavonoids are rich in nitrogen and oxygenated functional groups, and contain "sub-structures" which are ideal for protein binding. Several
alkaloid and flavonoid natural products are known to interfere with protein surfaces and display a wide array of biological activities. Some of the bioactive alkaloids, oxygen-riched natural products and flavonoids are shown in Figure 1.4.

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

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

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

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

1.3 Diversity Oriented Synthesis

1.3.1 Diversity Oriented Synthesis vs. Target Oriented Synthesis

Diversity oriented synthesis aims to prepare natural product-like and/or drug-like compounds with collections of natural product/drug-like small molecules with
diverse structural features. In Target-oriented synthesis (TOS), one particular compound is synthesized using a series of reaction steps. These steps have already been designed by adjusting parameters including stereo/regio chemistry and yield. TOS is normally equivalent to 'Total Synthesis'. A comparison between DOS, TOS and also traditional combinatorial chemistry is illustrated in Figure 1.4.

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

**Figure 1.5 'DOS/TOS/Traditional Combinatorial Chemistry' Comparisons**

As shown in Figure 1.6, TOS locates in one extreme and synthesis of all compounds in the other. This "molecular diversity spectrum" also illustrates DOS, which theoretically should aim to synthesize molecules as close to the right as possible. The combinatorial chemistry program in DOS utilizes stereo- and enantio-selective organic synthesis reactions and is designed to provide small molecules that are rich in (1) stereochemically-defined polyfunctional groups, and (2) conformationally diverse, natural product–like skeletons. On the contrary, with few exceptions, traditional combinatorial chemistry efforts have led to simple compounds. These simple compounds may not be able to populate the chemical space that is occupied by bioactive natural products, and may be less likely to be
useful as modulators of protein-protein interactions and as chemical probes for dissecting dynamic signaling pathways. With DOS, a synthetic platform is already established, re-synthesis at any stage is achievable, and second-generation compounds can be easily obtained.

![Image](image.png)

**Figure 1.6 Molecular Diversity Spectrum**

### 1.3.2 Applications of DOS

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

Some representative compounds synthesized using DOS are presented in Figure 1.7. Secramine 7 (one member of 2,527 compounds) is found to be a specific modulator of protein trafficking out of the Golgi apparatus; haptamide 4 (one member of 4,320 compounds) is an inhibitor of Hap3p-mediated transcription; tetracycle 5 (one member of 2,500 compounds); tubacin 6 (one member of 7,200 compounds) is a tubulin deacetylase inhibitor; macrolide 8 (one member of 36 compounds); macrocyclic biaryl 9 (one member of 1,412 compounds) affects the cardiovascular system during zebrafish development (its enantiomer has no activity).
One of the objectives of high-throughput organic synthesis is to obtain small molecules, which are inspired by natural products but have biological properties beyond those found in naturally occurring molecules. Working with this goal, galanthamine 10, a benzofuran based natural product, decorated with multiple functional groups in a rigid framework was chosen by Shair and co-workers in example of biomimetic synthetic strategy applied for library generation on solid support (Scheme 1.1)\textsuperscript{63,64}. The Galanthamine framework 12 was obtained from the advanced solid supported intermediate 11 in the crucial hypervalent iodine mediated intramolecular oxidative coupling followed by Pd-catalyzed allyl deprotection and spontaneous facially selective cyclization. Four diversity points in 12 were then exploited to build a library of 2527 unique galanthamine-like
small molecules using split-pool technique. The phenolic hydroxy in 12 was treated with several alcohols under Mitsunobu conditions to obtain phenolic ethers, 13 as the first diversity, which was followed by diastereoselective 1,4 addition of thiols to give the adducts 14 with two diversities. The third and fourth diversities were introduced by manipulation of the ring nitrogen in 14 by acylation, followed by imine formation on the carbonyl group to obtain the resin-bound final derivatives 15. The collection of 2527 molecules was cleaved from the silicon-based macrobeads by HF-py. treatment and subjected to phenotypic screening to identify a useful small molecule probe for understanding the mechanism of protein trafficking in secretory pathways (i.e. Secramine 7, Figure 1.7).

Scheme 1.1

Inspired by indole alkaloids, synthesis of a 50-compound library of HR22C16 analogs was achieved by Kapoor et al. HR22C16 is a cell-division inhibitor discovered from a forward-chemical-genetic screen. The resin-bound amino acid 17 (Scheme 1.2), which was obtained from the coupling of Nb-Boc-Nb-allyl-
L-tryptophan 16 with hydroxy-TentaGel resin, was subjected to Pictet–Spengler cyclization using various aldehydes. Following this, the protected cyclic amine 18 was deprotected, derivatized on reaction with different isocyanates and then subjected to hydantoin-forming cleavage from the resin giving 19 as analogous to HR22C16. The overall yield of HR22C16 analogs was 46%, and the products were obtained in >90% purity as determined by HPLC analysis. These compounds were tested using in vitro assays with recombinant Eg5 and identified a lead compound [R1 = m-phenol and R2 = (CH2)3NH2] with an IC50 value of 90±40 nM, thus making it the most potent inhibitor currently available for this key cell-division protein.

Scheme 1.2

Schreiber and co-workers67 explored the use of a triene in cycloaddition reactions for the generation of structurally diverse complex, natural product-like small molecules (Scheme 1.3). Synthesis of the triene was carried out by a method, previously reported by Fallis et al.68 in which indium-mediated alkylation was the key step. The substituted hydroxyl group could undergo elimination, leading to the desired triene. As exemplified with 4-hydroxy-3-methoxybenzaldehyde 21, different aldehydes were immobilized on alkylsilyl macrobeads 20 and subsequently subjected to indium-mediated alkylation followed by hydroxyl elimination, giving the triene 22. This triene was then subjected to two different cycloaddition conditions. In one case, it was treated with different tri/tetra-
substituted dienophiles that led to a single stereoselective Diels-Alder reaction affording only the bicyclic product 23 (explained with trisubstituted dienophile A). However, when 23 was subjected to another round of cycloaddition with different dienophiles, it afforded the tetracyclic product 24 in step-wise manner. In the second case, an interesting observation was made; the reaction of the triene 22 with a disubstituted dienophile (i.e. B) underwent two consecutive cycloaddition reactions resulting in the formation of bis-cycloadduct 25 with complete stereocontrol. This method is highly practical, and by using the split-and-mix synthesis protocol, an encoded library of 29,400 compounds was obtained from 40 different aldehydes and a series of di-, tri- and tetra-substituted dienophiles.

Scheme 1.3

Using natural product-inspired DOS and using modern organic chemistry, our group mainly synthesizes complex polycyclic natural product–like compounds having 3-dimensional skeletal and stereochemical architectures. Our three interested scaffolds are tetrahydroquinoline (26-29), indoline (30-31), and
benzofuran (32). As shown in Figure 1.8, several bicyclic compounds having the above-mentioned scaffolds were investigated. In each series, after completion of synthesis in the solution phase, a manual solid phase strategy is designed which allows us to develop library generation in a high-throughput manner. This trend can be performed for creating a tricyclic system as well.

**Figure 1.8 DOS Programs in Arya’s Group**

Arya and co-workers developed a highly practical, enantioselective synthesis of several tetrahydroquinoline scaffolds 26, 27, and 29 with an increase of complexity and the enantioselective synthesis of hydroquinoline-2-one scaffold 28 (Figure 1.8). Several features of the most complex 29 scaffold make it versatile and amenable to the production of a wide variety of very different polycyclic architectures. The key features include the presence of: (i) the β-amino acid moiety, (ii) the δ-amino acid moiety, (iii) the γ-hydroxy carboxyl ester...
functionality, and (iv) the phenolic hydroxyl group that could be used as an anchoring site during solid-phase synthesis. For obtaining the enantioenriched, tetrahydroquinoline scaffold 29, Arya and co-workers\textsuperscript{70} used commercial available compound 33 as starting material (Scheme 1.4). As an extension to our early finding related to an aza Michael approach\textsuperscript{71}, this was the key reaction to obtain compound 37 from 36 in a stereocontrolled manner. Compound 36 was synthesized from 33 in several steps including (i) phenolic-hydroxy protection using methoxyethoxymethyl chloride (ii) carbon extension by Horner-Wittig-Emmons reaction (giving E-olefin), (iii) Sharpless enantioselective aminohydroxylation (>92% ee)\textsuperscript{72} to give 34, (iv) acetonide protection, (v) reduction of carboxylic ester to afford 35, (vi) oxidation of alcohol 35 to generate aldehyde, and (vii) two carbon extension via a Wittig reaction forming 36. After reducing of nitro group to amino, as observed in a former study from our group, the aza Michael reaction was clean and produced the cyclic \(\beta\)- and \(\delta\)-amino acid derivative 37 in high diastereomeric purity.

**Scheme 1.4**

![Scheme 1.4](image-url)
Arya and co-workers generated a library using \( \text{37} \) as the starting point with the goal of finding small molecule modulators of protein–protein interactions\(^{73} \). Nine created library members from compound \( \text{39} \) (Scheme 1.5) as well as other related intermediates were tested for their ability to bind to Bcl-X\(_L\) and Mcl-1 proteins by \textit{in silico} and \( ^{15}\text{N}-\text{NMR} \) studies. This led to the discovery of a novel, small molecule [MIPRALDEN (named after two lead scientists; Drs. Michael Prakesch and Alexy Denisov), \( \text{40} \)] as a binder to both Mcl-1 and Bcl-X\(_L\).

Compound \( \text{39} \) was prepared from scaffold \( \text{37} \) by (i) \( N\)-Teoc protection, (ii) removing both acetonide and Cbz group using Paladium/carbon catalyzed hydrogenation to form \( \text{38} \), (iii) Alloc protection of the primary amine group, and (iv) hydrolysis of carboxylic ester by Lithium hydroxide to afford acid \( \text{39} \). Solution phase library generation on \( \text{39} \) afforded bis-(4-biphenyl) derivative \( \text{40} \) and 8 other compounds. Since there are currently not many small molecules capable to bind to Mcl-1, this finding is noteworthy.

\begin{center}
\textbf{Scheme 1.5}
\end{center}
Arya and co-workers reported a different synthesis approach that led to skeletally diverse indoline alkaloid-inspired compounds. As shown in Scheme 1.6, same starting material 33 was used. Similar transformations to tetrahydroquinoline system were performed but asymmetric Sharpless dihydroxylation instead of aminohydroxylation was used. Fully protected nitro compound 41 under hydrogenation followed by basic media/heating resulted in indoline-derivative 42 in 80% yield.

**Scheme 1.6**

Several indoline-based bicyclic and tricyclic compounds were synthesized using scaffold 42. Compounds obtained were next subjected to a series of *in vitro* and cellular assays to study their properties as modulators of focal adhesion kinase (FAK) activity. This analysis resulted in the identification of a lead inhibitor of FAK (44, Scheme 1.7), which was also active in a wound healing assay. In addition, this indoline-based compound was able to demonstrate its inhibitory activity in a cell invasion assay (Boyden chamber) which showed its ability to inhibit cell movement on a 3D scale and/or by reducing the cells' ability to form extracellular matrix degrading enzymes (such as matrix metalloproteinases). Compound 44 was synthesized in two steps from 43 by a Grignard reaction followed by acetylation of the generated secondary alcohol.
Enantioselective synthesis of benzofuran-derived, cyclic trans-β-amino acid scaffold 46 (Scheme 1.8) was reported by Arya and co-workers\(^7^5\). Similar steps as the formation of the above-mentioned scaffolds were taken to create enantioriched benzofuran scaffold 46. Many benzofuran-based bicyclic and tricyclic compounds were synthesized from 46. To explore the biological applications, these compounds were subjected to cell-based assays, using NIH3T3 mouse cells to evaluate their potency as cell motility modulators. Compound 47 identified as a potent cell motility inhibitor (IC\(_{50} \approx 40 \, \mu M\) in chamber cell migration assay).

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

1.4 Protein-Protein Interactions- Closer Look

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

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

1) protein ligands do not provide direct links in designing small molecules, and the key interacting residues are generally not completely known, 2) large interfacial areas involved in forming protein–protein interfaces generates difficulty
for small molecules to be competitive, 3) small synthetic peptides cannot mimic the binding region of protein complex because those binding regions are non-adjacent, 4) since many protein-protein interfaces do not exhibit clear pattern, selectivity in targeting a specific protein is difficult, 5) library screening for finding effective modulators of protein-protein interactions identified only few "drug-like" small molecules, and 6) more challenging techniques are needed for detecting direct binding because in many cases biological assays cannot follow enzyme activity.

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

Figure 1.9 Structures of small-molecule inhibitors of protein-protein interactions
As mentioned earlier, due to often unforeseen interactions between small molecules and their target proteins, the challenges in the high-throughput organic synthesis programs are to obtain natural product-inspired molecules with maximum skeletal, stereochemical, conformational and functional group diversities in order to maximize the possibility of finding a 'hit', that can modulate the biological activity of a distinct protein or a network of proteins involved in physiological processes. For more in-dept discussion about this exciting subject, we selected one family of proteins (i.e. Bcl-2) which has extensively studied in the field of 'cancer therapy'.

1.4.1 Small Molecule Inhibitors of Bcl-2 Family Proteins

Programmed cell death or 'Apoptosis' is a fundamental process in the development of organs. It is identified by several morphological and biological changes. There are diseases with inadequate apoptosis such as autoimmune diseases and cancer or excessive apoptosis such as Parkinson's diseases and Alzheimer's. Apoptosis advances via one of the two major pathways; extrinsic and intrinsic. The extrinsic pathway is initiated by ligation of cell-surface death receptors which, carry on the formation of a death-initiating signaling complex (DISC). The intrinsic pathway is activated via a substantial number of stimuli, and needs activation of the multi-domain pro-apoptotic Bcl-2 (B-cell lymphocyte/leukemia-2) family proteins (Bax or Bak) by BH-3 family members (a subgroup of Bcl-2). This activation results in releasing of apoptogenic molecules (cytochrome c, Smac/DIABLO) from mitochondria (Figure 1.10). The released cytochrome c protein binds to and activates a complex called the apoptosome. Both the assembled DISC and the apoptosome lead to the oligomerizing and activating a family of cysteine proteases known as pro-caspases. Caspase activation occurs via a cascade including initiator (DISC-activated caspase-8 and apoptosome-activated caspase-9) and effector (caspase-3) proteases that cause the cellular changes of apoptosis. An inhibitor of apoptosis proteins (IAPs), whose activity is stopped by Smac, can prevent activating caspases.
Several anticancer drugs can also promote apoptosis via upregulation of components of the FAS death-receptor pathway. Some drug-candidates which target apoptosis, autophagy (process involving the degradation of a cell's own components through the lysosomal machinery), and necrosis (unnatural death of cells and living tissues) are introduced in Figure 1.11. Most of these compounds are currently (2007) at clinical trial stages.

Figure 1.10 Apoptotic Pathways

Several anticancer drugs can also promote apoptosis via upregulation of components of the FAS death-receptor pathway. Some drug-candidates which target apoptosis, autophagy (process involving the degradation of a cell's own components through the lysosomal machinery), and necrosis (unnatural death of cells and living tissues) are introduced in Figure 1.11. Most of these compounds are currently (2007) at clinical trial stages.
<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Current status of drug development</th>
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</thead>
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<td></td>
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<td>BH3 BAD mimetic</td>
<td>ABT 737</td>
<td>Phase I</td>
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<tr>
<td>Pan-BCL2 family inhibitor</td>
<td>GX15-070</td>
<td>Phase I</td>
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<td>Caspase inhibitor</td>
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<td>Phase I, Phase II, Preclinical</td>
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<tr>
<td>Death receptor ligand</td>
<td>Mapatumumab</td>
<td>Phase II</td>
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</table>

**Figure 1.11 Therapeutics that target apoptosis, autophagy, and necrosis**

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

As indicated above, anti-and pro-apoptotic Bcl-2 family members meet at the surface of mitochondria and compete to control the releasing of cytochrome c. It is believed that the relative balance of opposing Bcl-2 family members and their
mutual interactions controls the mitochondrial cell death pathway. Although not entirely clear, few theories exist for the mechanism by which the Bcl-2 family members control releasing of cytochrome c:

i) form hetero-dimerization between pro- and anti-apoptotic family members,
ii) regulate caspases,
iii) interaction with other mitochondrial proteins, or
iv) form an ion channel by oligomerization.

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

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

1.4.2 Finding Hits Using Validation Tools

In an ‘Apoptosis’ project in our group, the generated libraries and collected intermediate compounds are screened by i) protein NMR (which can characterize the interactions between proteins and ligands/small molecules); ii) in silico
studies (using computer programs or computational chemistry to predict protein/small molecule interactions); iii) cell viability assays (instead of damaged or death cells, they are based on counting living active cells and normally can detect the process of programmed cell death and be used to distinguish between the mechanisms of cell-death apoptosis, necrosis or cell proliferation\textsuperscript{87}); and iv) small molecules microarrays (molecules immobilized by chemical bonding on the solid surface with diverse linking techniques used for searching for proteins that bind with a specific small molecule)\textsuperscript{88}.

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

**Figure 1.12 Validation Tools for DOS**
1.5 Thesis Objectives

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

Figure 1.13 Schematic Project Goals

A clearer picture is presented in Figure 1.14 in which actual skeletons of tricyclic compounds, such as 53-55, are shown. For compatibility reasons, diversity sites in the tetrahydroquinoline system should be orthogonally protected (compound 52). Preparation of all bicyclic and tricyclic compounds was initially performed in the solution phase. For extending this set of reactions in solid phase, we needed an anchoring site to enable immobilization of our bicyclic system onto a solid support (resin). This task was performed using protected phenolic oxygen that had already been installed on 52 (i.e., OP4). Once P4 was removed, the resulting free phenolic hydroxyl group could be directly attached to the selected resin.
Solid-phase syntheses of tricyclic compounds were then performed using step-wise deprotection of the required arms (e.g., OP₂ and OP₃ to make 55). The last step for tricyclic compound synthesis, in both solution and solid phases, was the 'Ring-Closing Metathesis (RCM)' reaction⁹⁰,⁹¹.

**Figure 1.14** Target Molecules as Thesis Objectives

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

2.1 Design of Scaffold (51)

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

Scheme 2.1

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

2.2 Tetrahydroquinoline Core and Related Structures in Nature

The greatest interest in tetrahydroquinoline is due to its biological activities. Many of these compounds are found in nature. Few examples are provided in Figure 2.1. Galipinine and four tetrahydroquinoline alkaloids from Galipea officinalis trunk bark showed antimalarial activity. Virantmycin an unusual chlorinated tetrahydroquinoline that was originally isolated from a strain of Streptomyces nitrosporeus possesses both strong inhibitory activity against RNA and DNA viruses, and antifungal activity. Dynemicin A produced by cultured soil bacteria is an ene-diyne anticancer antibiotic. An alkaloid called Isoschizogamine,
isolated from *Schizozygia caffaeoides*, shows antifungal property\textsuperscript{95}. Martinelline is an isolate of *Martinella iquitosensis*, which exhibits activity as a bradykinin antagonist and with α-adrenergic, histaminergic, and muscarinic receptors\textsuperscript{96}. Helquinoline isolated from the northern sea bacterium *Janibacter limosus* showed antimicrobial property\textsuperscript{97}. Discorhabdin C (not shown), tetrahydroquinoline-based compound, is a highly cytotoxic pigment from a marine sponge of the genus *Latrunculia*\textsuperscript{98}. Poisoning effect of *Calycanthus floridus* is due to its toxic tetrahydroquinoline-based alkaloid constituent, Calycanthine\textsuperscript{99} (not shown).

---

**Figure 2.1** Natural Products with Tetrahydroquinoline Core

### 2.3 Tetrahydroquinolines as Pharmaceutical Products

Many synthetic tetrahydroquinolines are already used or have been tested as potential drugs. L-689, 560 (Figure 2.2) is a well-known NMDA antagonist\textsuperscript{100}. 

33
IRA-378 showed antirheumatic activity\textsuperscript{101}. Oxamnique possesses the schistosomicide effect\textsuperscript{102} and Nicainoprol has shown antiarrhythmics property\textsuperscript{103}. Hundreds of tetrahydroquinoline derivatives have interesting bio-chemical activity and some are considered as potential pharmaceutical agents from analgesic to antidepressant\textsuperscript{104}.

Figure 2.2 Tetrahydroquinoline Derivatives as Medicines

2.4 Synthetic Strategies in Literature

In this section, the major synthetic methods of tetrahydroquinolines currently in use will be reviewed. Due to the existence of many other related compounds with one or more \( sp^2 \) carbon, such as 2-oxo, 2,4-dioxo, etc., this review only restricts to 1,2,3,4-tetrahydroquinolines in which the C2, C3, and C4 are all \( sp^3 \) hybridized. In addition, in most examples, transformations between tetrahydroquinoline derivatives and other stages of the synthesis will not be covered. Moreover, it is mainly intended to review the literature in the period of 1986-2007. Major
methods have been classified for more clarity (Sections 2.4.1-2.4.7) and a few examples in each section are presented. Despite the effort made to include most methods, this section is therefore not considered comprehensive.

2.4.1 Reduction of Unsaturated Heterocyclic Ring

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

Scheme 2.2

![Scheme 2.2](image)

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

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

Scheme 2.4

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

Scheme 2.5
Quinolines convert to tetrahydroquinolines via 1,2-dihydroquinolines. Dihydroquinoline 64 (Scheme 2.6) is reduced to 2-butyl-tetrahydroquinoline 65 using ethanolic sodium in excellent yield\textsuperscript{111}.

Scheme 2.6

Tetrahydroquinoline 67 (Scheme 2.7) can be readily prepared by hydrogenation of 66 under palladium catalyst\textsuperscript{112}.

Scheme 2.7

As a typical property of an electron rich double bond, wide range of addition reactions can be performed on the C3-C4 of 1,2-dihydroquinolines. Most of these additions are stereospecific. Bromination of 68 (Scheme 2.8) by NBS gives tetrahydroquinoline 69 regioselectively and almost quantitatively\textsuperscript{113}.
Chlorination of dihydroquinoline 70 gives 3,4-dichlorotetrahydroquinoline 71 as shown in Scheme 2.9. Sodium cyanoborohydride in the presence of zinc chloride reduces this intermediate to tetrahydroquinoline 72 illustrating the lability of the substituent at C4114.

Catalytic asymmetric reduction (hydrogenation) has been extensively studied and considered as a versatile method of creating chiral centers. Asymmetric hydrogenation of quinolines using iridium catalyst, iodine, and chiral ligand bisphosphine is an example showing high enantioselectivity (Scheme 2.10). In this reaction optical active tetrahydroquinolines 74 were prepared with high yield115. Several naturally occurring tetrahydroquinolines including angustrureine, galipinine, and cuspareine were prepared by methylation of the generated tetrahydroquinolines 74. Hantzsch esters were used as a source of hydrogen with the same catalyst system116. In some cases, high enantioselectivity up to 88% was observed. The advantage of this method is the mild reaction conditions. Iridium complex-catalyzed asymmetric hydrogenation of same quinolines 73 in a
low molecular weight poly(ethyleneglycol) dimethyl ether/hexane biphasic system was studied\textsuperscript{117}. Several $C_2$-symmetric ligands were used and high yield and enantioselectivity was observed. The advantage of this method is not only the ability for separation of catalysts and products by phase separation, but also retaining reactivity/stereoselectivity of the catalysts for at least three reaction cycles.

**Scheme 2.10**

![Scheme 2.10](image)

**2.4.2 Closure of One Bond**

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

**Scheme 2.11**

![Scheme 2.11](image)
Compound 77 cyclized to 2-oxotetrahydroquinoline 78 by sodium hydroxide in ethanol (Scheme 2.12). Elimination of 2-oxo function occurred by reduction of this intermediate with lithium aluminum hydride affording 3-aminotetrahydroquinoline 79\textsuperscript{119}.

Scheme 2.12

\begin{center}
\begin{align*}
\text{By catalytic reduction on palladium, the nitro group in 80 was converted to an amino group followed by cyclization to afford the intermediate 81 (Scheme 2.13). This intermediate can be isolated from the reaction mixture with 54\% yield. By raising the temperature and pressure of hydrogen, the reaction is proceeded to decarboxylation and reduction of 81 to give tetrahydroquinoline 82\textsuperscript{120}.}
\end{align*}
\end{center}
2-Oxotetrahydroquinoline 84 (Scheme 2.14) was prepared using the reduction of the nitro group in 83 and then removal of the protecting group on the nitrogen. Amino group in 84 was methylated and subsequently reduced to 6,7-dimethoxy-3-(dimethylamino)-1,2,3,4-tetrahydroquinoline 85\textsuperscript{121}. The noted stereochemistry in 85 (at C3), however, inherited from the chiral starting material 83.

**Scheme 2.14**

![Scheme 2.14 Diagram]

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

**Scheme 2.15**

![Scheme 2.15 Diagram]
Sulfuric acid catalyzed cyclization of compound 91 (Scheme 2.16) gives a mixture of cis and trans 4-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline 92\textsuperscript{123}. This is an example for the formation of tetrahydroquinolines via C4-C4a.

Scheme 2.16

![Scheme 2.16](image)

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

Scheme 2.17

![Scheme 2.17](image)

Compound 97 under cyclocondensation and a substitution reaction with the benzene-sulfonate anion (Scheme 2.18) gave tetrahydroquinoline 98 as the major compound\textsuperscript{125}.
Various tetrahydroquinolines were prepared by an intramolecular Diels-Alder reaction of 2-substituted aminofurans\textsuperscript{126}. These 2-aminofurans should contain a substituted alkyne \textsuperscript{99} or a tethered olefin \textsuperscript{101} (Scheme 2.19). It is believed that the initial cycloaddition reaction gives an oxo-bridge cycloadduct, which under nitrogen assisted ring opening followed by proton exchange and dehydration, forms the products (\textsuperscript{100} or \textsuperscript{103}).

Ring closure of compound \textsuperscript{104} (Scheme 2.20) with polyphosphoric acid gave 7-acetyl-amino-1,2,3,4-tetrahydroquinoline-2,4-dione \textsuperscript{105}. After a few steps, the N-alkylated intermediate \textsuperscript{106} under reduction with a BH\textsubscript{3}-THF complex gave the tetrahydroquinoline \textsuperscript{107}\textsuperscript{127}.
Diastereoselective synthesis of 2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters was studied\textsuperscript{128}. This involves the ozonolysis of the double bond in compound 108 (Scheme 2.21) and catalytic hydrogenation. The hydrogenation stage involves a tandem sequence including a) reduction of the nitro group, b) condensation of the resulted amino group with the side chain carbonyl, c) reduction of the resulted nitrogen, and d) reductive amination of the tetrahydroquinoline with formaldehyde (formed at ozonolysis step). Reduction of the final iminium intermediate is diastereoselective; providing products derived from \textit{syn} addition of hydrogen to the molecular face opposite the ester group. Final product is a 2,4-disubstituted tetrahydroquinoline 109 with \textit{cis} relationship between C2 and C4.
Same authors were able to prepare tetrahydroquinoline without alkyl substitution at nitrogen (Scheme 2.22). This was performed by the removal of the formaldehyde produced in ozonolysis step prior to reduction. Catalytic hydrogenation of 110 then afforded the cis-2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylates 111 in excellent yields.

**Scheme 2.22**

![Diagram showing reaction scheme](image)

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

**Scheme 2.23**

![Diagram showing reaction scheme](image)

On the other hand, in the asymmetric epoxidation route, chirality was created using epoxidation and consequent ring opening. Compound 112 (Scheme 2.24), was reduced with iron and hydrochloric acid. Neutralization of the reaction
mixture by the addition of ammonia resulted in forming 3-hydroxy-1,2,3,4-tetrahydroquinoline which was protected as an N-tosylamide 115.

**Scheme 2.24**

![Scheme 2.24](image)

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

**Scheme 2.25**

![Scheme 2.25](image)

In our group, tetrahydroquinoline was prepared through reduction of the nitro group in 119 (Scheme 2.26) and then treatment with LDA (or NaH) to obtain the tetrahydroquinoline derivative 120 as a single enantiomer with 3 stereogenic centres. The crucial ring-closure step includes an asymmetric hetero-Michael
reaction. The stereochemistry of the new stereogenic center was assigned by nOe (observed between H-2 and H-4) and coupling constants (J) for adjacent protons. It appears that acetonide protection of vicinal hydroxyl at C3 and C4 is an influential factor in the observed stereoselectivity. The proposed transition state contains a less-hindered environment and metal coordination in a chair-like fashion. The spatial interaction between the acetonide group and unsaturated ester gives disfavored transition state. Earlier Sharpless dihydroxylation reaction on the alkenes' site formed the enantiopure diol derivative (>90% ee, determined by chiral HPLC) which after a few steps led to compound 119.

Scheme 2.26

Similar approach was performed in compound 121 (Scheme 2.27) to prepare the enantiopure tetrahydroquinoline derivative 122. In this case, Sharpless aminohydroxylation reaction is responsible for the enantioselectivity (>92% ee). This reaction includes the favored chelation/less-hindered transition state accountable for the observed stereochemistry. Tetrahydroquinoline 122 features exceptional properties which allow it to be a base compound in multiple investigations in the group leading to several interesting findings.
Chemistry of carbon-iodine bond was used for the diastereoselective preparation of tetrahydroquinolines. Compound 123 under treatment with IPy$_2$BF$_4$, as the source of iodonium ion, and with a variable amount of HBF$_4$, was cyclized to obtain the tetrahydroquinoline 124 (Scheme 2.28). The intramolecular arylation reaction of heteroatom-linked alkene promoted by iodonium ion in this method has found to be very effective in having high yield and obtaining no evidence for the formation of related heterocyclic structures involving additional rearrangement of the allyl moiety.
Optically pure 2-hydroxymethyl-1,2,3,4-tetrahydroquinoline 128 (Scheme 2.29) was prepared in a few steps\(^{134}\). Compound 125 cyclized to intermediate 126 by intramolecular acylation reaction. Reduction of carbonyl in C4 followed by deprotection led to the final product.

Scheme 2.29

Cyclization of amino aryl chlorides which forms the N-arylated heterocycles can be performed via an intramolecular aryl amination followed by an intermolecular coupling reaction\(^{135}\). For this cycloamination reaction, an in situ formed Pd(0) catalyst associated to \(N,N'\)-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene (SIPr) as a ligand and sodium \(t\)-butoxide as the base for sequential aryl amination were used. \(N\)-arylated-1,2,3,4-tetrahydroquinoline 131 (Scheme 2.30) is prepared in excellent yield using this method.
Palladium-catalyzed intramolecular direct cross-coupling reaction between an aryl iodine and an allyl moiety leads to 2,4-disubstituted 1,2,3,4-tetrahydroquinoline. As shown in Scheme 2.31, trans-2,4-disubstituted-tetrahydroquinolines were successfully synthesized with excellent diastereo-selectivity from allyl acetates. It is believed the amine is responsible for reducing Pd(II) to Pd(0) after each catalytic cycle.

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

**Scheme 2.32**

\[
\begin{align*}
\text{R}_1, \text{R}_2, \text{R}_3 = \text{H, Cl, Me} \\
\text{R}_4 = \text{H, Cl, F, Me}
\end{align*}
\]

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

**Scheme 2.33**

Tetrahydroquinolines 142 (Scheme 2.34) were prepared under the Heck-type cyclization reaction on \( \alpha, \beta \)-unsaturated carbonyls 141 with complete control of the stereochemistry of the double bond.
Enantiomerically enriched 2-substituted tetrahydroquinolines 144 shown on Scheme 2.35 were synthesized via the Pd(0)-catalyzed intramolecular hydroamination of aniline-alkynes 143\(^{140}\).

2.4.3 Condensation of Anilines with Aldehyde

\(p\)-Toluidine 145 reacted with two molecules of acetaldehyde (Scheme 2.36). A mixture of \emph{cis} 146 and \emph{trans} 147 isomer of 2,6-dimethyl-4-hydroxy-1,2,3,4-tetrahydroquinoline (1:2 ratio) were observed\(^{141}\).
Condensation of aniline with acetaldehyde gives imine 149 (Scheme 2.37). A cycloaddition reaction between this imine and its enamine tautomer produces compound 150 with unknown stereochemistry\textsuperscript{142}.

3-Methyl-nitrobenzene 151 in ethanol and in the presence of titanium dioxide and under irradiation gives 4-ethoxy-2-methyl-1,2,3,4-tetrahydroquinoline (152, Scheme 2.38)\textsuperscript{143}. This can be explained by reduction of the nitro group followed by oxidation of ethanol to acetaldehyde and finally condensation of these compounds.
2.4.4 Reaction of N-Aryl Methyleneiminiums with Alkenes

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

Scheme 2.39

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

Scheme 2.40

Similar substrate 160 reacts with the ethyl vinyl ether (Scheme 2.41). The intermediate stabilized by the ethoxyl group (not shown), cyclized to 4-ethoxy-
tetrahydroquinoline 161. Other 4-substituted tetrahydroquinolines 162 are also prepared with this compound with average to good yield\textsuperscript{145}.

**Scheme 2.41**

![Scheme 2.41](image)

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

**Scheme 2.42**

![Scheme 2.42](image)

In another example of benzotriazole methodology, N-[(benzotriazol-1-yl)alkyl]-anilines 160 (Scheme 2.43) with 1-vinyl-2-pyrrolidinone afforded 4-(pyrrolidinon-1-yl)tetrahydroquinolines 166 in high yields\textsuperscript{146}.
Nitrotoluidine 167 upon treatment with formaldehyde and styrene or its methyl derivative in the presence of trifluoroacetic acid converted to tetrahydroquinolines 168 (Scheme 2.44). In this case, the generated \(N\)-arylmethyleneiminium cation was trapped by the alkene\(^{147}\).

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

![Scheme 2.45](image)

*N-Methyl-N-(phenylthiomethyl)aniline 172 also showed very good results (Scheme 2.46). A series of tetrahydroquinoline (173-176) prepared using the reaction of compound 172 with styrene, cyclopentane, *cis*- and *trans*-1-phenylpropane catalyzed by titanium chloride-triphenylphosphine\(^{149}\).*

Scheme 2.46

![Scheme 2.46](image)

Condensation of *N*-methylaniline 177 with formaldehyde and arylsulfinic acid produced the \(\alpha\)-arylaminomethyl sulfone 178 (Scheme 2.47) which upon treatment with styrene gave tetrahydroquinoline 179\(^{150}\).
Scheme 2.47

\[ \text{Me} \]
\[ \text{NH} \]
\[ \text{Me} \]
\[ \text{4-MeC}_6\text{H}_4\text{SO}_2\text{H} \]
\[ \text{HCHO 92\%} \]
\[ \text{PhCH=CH}_2 \]
\[ \text{SnCl}_4 72\% \]

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

Scheme 2.48

\[ \text{Me} \]
\[ \text{N} \]
\[ \text{Me} \]
\[ \text{RuCl}_2(\text{PPh}_3)_3 \]
\[ \text{t-BuOOH 93\%} \]
\[ \text{CH}_2=\text{CHCH}_2\text{Me} \]
\[ \text{TiCl}_4 41\% \]

Oxidation of 4-methyl-*N*,*N*-dimethyl aniline 183 (Scheme 2.49) with nitric oxide in the presence of boron trifluoride as lewis acid leads to the formation of *N*-(*arylamino*)-*N*-methyleneiminium cation 184. This cation trapped with tetramethylethylene to give tetrahydroquinoline 185\(^{152}\).
N,N-Dimethyl aniline 180 (Scheme 2.50) similarly oxidized with oxygen/iron salt and trapped with vinyl n-butyl ether to afford 4-n-butoxytetrahydroquinoline 186\textsuperscript{153}.

### 2.4.5 From Aldimines (Aniline Imines)

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

---

**Scheme 2.49**

\[ \text{Scheme 2.49} \]

**Scheme 2.50**

\[ \text{Scheme 2.50} \]

---

59
Scheme 2.51

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

Scheme 2.52

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

Scheme 2.53
Alternatively, alkoxycarbonyl groups can be used in the synthesis of aniline alkylimines. In a structure-activity relationship for finding antagonists at the glycine site of the NMDA receptors, iminocaboxylic ester 194 (Scheme 2.54) was used to prepare tetrahydroquinoline 195\textsuperscript{157}.

**Scheme 2.54**

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

**Scheme 2.55**
Spiro-tetrahydroquinolines 200 (Scheme 2.56) were stereoselectively prepared by using chiral keto-sugar 199 derived from sucrose\textsuperscript{159}. It is believed that the reaction occurs via the inverse electron demand aza Diels-Alder reaction of the imine intermediate resulted from condensation of keto-sugar/aniline and its tautomer (self-cycloaddition).

**Scheme 2.56**

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

**Scheme 2.56**
A recent interesting research reported the preparation of tetrahydroquinolines by the reaction of arylvinylidene cyclopropanes 204 (Scheme 2.57) with ethyl-(arylimino)acetates 205 in the presence of Lewis acid\(^1\). Depending on the electronic nature of 205 and Ar or Ar' groups of 204, the final product would differ; for the synthesis of tetrahydroquinoline derivatives, electron-donating groups should be used. The reaction is believed to proceed via an intramolecular Friedel-Crafts pathway. In the case of using electron-poor aromatic groups, the mixture of tetrahydroquinoline and pyrrolidine (probably via [3+2] cycloaddition reaction pathway) was observed.

**Scheme 2.57**

![Scheme 2.57](image)

An Intramolecular cycloaddition of chiral nitrone have shown to be useful in the synthesis of 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines\(^2\). As shown in Scheme 2.58, cycloaddition reaction on nitrone intermediates 208 prepared from aromatic aldehydes 207 and (R)-\(\alpha\)-(hydroxymethyl)benzylhydroxylamine led to the separable diastereomic mixture of tricyclics 209 (major) and 211 (minor). These compounds were subjected to hydrogenation in methanol in the presence of Pd(OH)\(_2\) affording corresponding 4-amino-3-hydroxymethyl-1,2,3,4-tetrahydroquinolines 210 and 212, respectively.
2.4.6 By Insertion of C2-C3 Fragment

Cycloaddition reactions on ortho-methyleneiminoquinones produce C2 and C3 substituted 1,2,3,4-tetrahydroquinolines. As shown in Scheme 2.59, 2-azido-1-methylindole 213 under thermal cleavage gave 214 which trapped by dimethyl fumarate to afford tetrahydroquinoline 215\textsuperscript{163}.
In another study\(^{164}\), silylated ammonium salt 216 (Scheme 2.60), under elimination catalyzed by fluoride, gives ortho-methyleneiminoquinone 217 which is trapped by diethyl fumarate to afford tetrahydroquinoline 218 in 85% yield.

### 2.4.7 Ring Contraction and Ring Expansion

3-chloro-2,3,4,5-tetrahydro-1H-benzazepin-2-ones react with amines leading to ring contraction and give 2-amino-1,2,3,4-tetrahydroquinolines\(^{165}\). For example, 3-chloro-3-phenyl-2,3,4,5-tetrahydro-1H-benzazepin-2-one 219 (Scheme 2.61) upon reflux condition with piperidine converted to 2,2-disubstituted tetrahydroquinoline 220 in excellent yield.
Reduction by lithium aluminum hydride on 1-(methoxyamino)-1-methylindane 221 (Scheme 2.62) leads to ring expansion and gives 2-methyl-1,2,3,4-tetrahydroquinoline 222\(^{166}\).

In the final stage of (R)-(+)\(^{\text{\textregistered}}\)-4-ethyl-1,2,3,4-tetrahydroquinoline 224 (Scheme 2.63) synthesis, the unstable mesylate compound 223 treated with excess DIBAL to provide the chiral tetrahydroquinoline 224 by ring expansion\(^{157}\). It is believed the reaction proceeds through the organoaluminum promoted Beckmann rearrangement of the oxime sulfonate; a method developed by Yamamoto\(^{168}\). This reaction will be revisited in Chapter 3.
2.5 Our Synthesis Approach

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

Scheme 2.64

2.5.1 Model Study

It was decided that preliminary synthesis steps were performed on the model system. This could offer the ability to explore various reactions and synthesis of
complex cyclic compounds and monitoring the feasibility for the expansion to solid-phase synthesis. For this aim, we were looking for the closest and preferably inexpensive starting material. Luckily, we found a suitable candidate for this important task. An inexpensive natural product named 'Safrole' was chosen. Safrole (225, Scheme 2.65) is a colorless oil extracted from sassafras or camphor oil and found naturally in several other plants such as basil, cinnamon, nutmeg, and pepper.\textsuperscript{169}

2.5.1.1 Synthesis of Aldehyde Precursor

For the synthesis of the aldehyde precursor 227, the first performed reaction was the nitration of safrole (Scheme 2.65). Nitration achieved using a mixture of nitric and sulfuric acid in glacial acetic acid as solvent. This reaction performed at 0°C for 2 hours and monitored by TLC. Although many side products, mainly dark oils, were also produced, the desired 6-nitrosafrole 226 was afforded in 70% yield after column chromatography. $^1$H-NMR showed two singlet peaks of aromatic ring, i.e., at 7.51 and 6.78 ppm, expected for 6-nitrosafrole. Other possibilities namely nitration at C4 position which would show two doublets and nitration at C7 which would show two downfield peaks were most likely not the case. Moreover, due to electron-donating nature of oxygens in dioxolane ring and in allyl group (ortho and para directors), it is expected that nitration (electrophilic aromatic substitution) occurs in C7, C4 & C6, and C4 & C6 (for O$_1$, O$_3$ and allyl, respectively). Less steric hindrance at C6 (compared with C4) and more importantly, $p$-position (to O$_3$) likely resulted in the observed nitration. More accurately, this can be explained by induction (alkoxy more than allyl) and more importantly by resonance (oxygens' lone pair participation) effects.
The desired aldehyde 227 prepared by ozonolysis of nitrosafrole 226 (Scheme 2.66). This reaction smoothly and effectively afforded the aldehyde needed for the next step in 95% yield. Peaks observed at 9.83 ppm and 197.3 ppm in $^1$H-NMR and $^{13}$C-NMR (respectively) are indicators for the existence of the aldehyde functionality.

2.5.1.2 Chain Extension and Asymmetric Dihydroxylation

With aldehyde in hand, we performed the chain extension using Wittig reaction (Scheme 2.67). Aldehyde 227 was reacted with (carboxymethylene)-triphenylphosphorane in dichlormethane at room temperature. Reaction was monitored by TLC and finished in 4 hours. After purification by column chromatography, the desired (E) $\alpha,\beta$-unsaturated ethylester 228 afforded in 82%. During the reaction, a second spot, with much lower concentration, noted in TLC plates. After separation, this portion was tested by mass spectroscopy; same peak (M+1) of 279.1 was found suggesting the minor amount of Z isomer was also produced. However, we expected to observe the E isomer as a major compound due to the use of the stabilized Wittig reagent. $^1$H-NMR revealed the peaks for ethyl ester...
group and *trans* hydrogens by their coupling constant (*J* = 15.6 Hz). Moreover, existence of \(^{13}\)C-NMR peaks for carbonyl group (in ethyl ester) and olefinic carbons proved the synthesis of the desired compound 228.

**Scheme 2.67**

![Diagram](image)

Enantioriched diol 229 (Scheme 2.68) was prepared by Sharpless asymmetric dihydroxylation of olefin 228\(^{170a}\) using commercially available 'AD-mix α' containing Potassium osmate \(K_2\text{OsO}_2(\text{OH})_4\) as the source of Osmium tetroxide, Potassium ferricyanide \(K_3\text{Fe(CN)}_6\), which is the re-oxidant in the catalytic cycle, Potassium carbonate, and chiral ligand \((\text{DHQ})_2\text{PHAL}\) (a phthalazine adduct with dihydroquinine) in \(t\)-Butanol/water mixture as the solvent and finally methane-sulfonamide (using as a reagent for better yield) at 0°C. Checking by TLC revealed the end of the reaction in 40 hours. Purification by column chromatography provided diol 229 in 68% yield. The complete structure elucidation was performed using 1D and 2D NMR. The enantiomeric excess of the product was 90% as determined by chiral HPLC. Therefore, this key reaction generates two chiral centres enantioselectively that remain in all subsequence products prepared in the synthesis of tetrahydroquinoline scaffold, its derivatives and cyclic complex compounds.

**Scheme 2.68**

![Diagram](image)
2.5.1.3 Regioselective Tosylation and Cyclization

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

**Scheme 2.69**

In addition, we should not ignore the possibility of intramolecular hydrogen bonding between hydrogen at β-hydroxy group and carbonyl of ester functionality, which prevents the easy tosylation of β-hydroxyl group (229a in Scheme 2.70)\(^{170d}\). Although one can argue the possibility of an intramolecular hydrogen bonding between hydrogen at an α-hydroxy group and the carbonyl of ester (229b). Again, it seems the steric effect plays an important role in the observed regioselectivity, since the hydroxy group in 229a is more accessible.
than the one on 229b. For better regioselectivity, this reaction performed at 0°C and took 90 hours to complete. Although in higher temperature, starting material disappeared in a shorter time, a mixture of desired and undesired compounds, namely bis-tosyl and β-position tosyl (with different Rf value than α-isomer) were observed. Separation and characterization of these unwanted compounds were difficult despite observing their related mass peaks. ¹H-NMR revealed the existence of aromatic methyl (singlet at 2.46 ppm, 3H) and hydrogens (7.88 ppm, 2H and 7.37 ppm, 2H) within tosyl group.

Scheme 2.70

O-Tosyl compound 230 upon reduction conditions with hydrogen and palladium-carbon catalyst in the presence of a mild base, i.e., Potassium carbonate cyclized to give our tetrahydroquinoline scaffold 231 in 82% yield (Scheme 2.71). The acyclic amine intermediate was not isolated and the next step, i.e., cyclization, proceeded in the same pot. Structure elucidation performed using 1D and 2D NMR. As expected, aromatic hydrogens, which are now adjacent to a 6-membered ring, are more shielded resulting in an upfield shift (6.49 and 6.24 ppm compared to 7.51 and 6.82 ppm, respectively, in former acyclic tosylated compound 230). The aromatic hydrogen adjacent to nitrogen was more affected (more than 1 ppm) due to reducing of nitro to the amine group.
The overall yield for the synthesis of tetrahydroquinoline 231 from safrole was 27% (6 steps). For further projects in the model study, more than 4 grams of this compound was efficiently prepared and subjected to the next synthesis steps (Chapter 3).

2.5.2 Scaffold Required for Solid-Phase Synthesis

For developing a solid-phase synthesis project, we needed compound 232 (Scheme 2.72), in which the phenolic hydroxyl moiety easily could be obtained (compound 233) and utilized as an anchoring site for the solid phase (solid supported compound 234). Since all the three arms in tetrahydroquinoline 51 will be used in solid phase synthesis, there is a need for orthogonal protection of free amine, free hydroxyl, and also ester (reduced to alcohol) moiety. Therefore, fully protected tetrahydroquinoline 232 was prepared (Chapter 3 and Chapter 4).
An enantioselective synthesis of compound 51 was developed with an approach similar to that discussed earlier in the model study (Section 2.5.1). The synthesis of 51 was achieved in a few steps from 5-hydroxy-2 nitrobenzaldehyde 235 (Scheme 2.73) in three major stages: (1) homologation and chain extension, (2) protection of phenolic hydroxyl group and Sharpless asymmetric dihydroxylation, and (3) regioselective tosylation and cyclization. This synthesis differs from model study in almost halfway through it.

### 2.5.2.1 Homologation and Chain Extension

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

Scheme 2.73

$\text{Ph}_3\text{PCH}_2\text{OMeCl}$
$\text{KOf-Bu, THF}$
$0^\circ\text{C to r.t., 16 h}$
$\text{95\%}$

Enol-ether 236 was hydrolyzed by hydrochloric acid in THF/water at 60°C during 16 hours to generate aldehyde 237 in 98% yield (Scheme 2.74). Replacement of hydrogens in enol-ether with aldehyde hydrogen (9.79 ppm) and benzylic
methylene (4.13-4.16 ppm, 2H) confirmed by $^1$H-NMR. Moreover, $^{13}$C-NMR showed the carbonyl peak (aldehyde) at 198.0 ppm.

**Scheme 2.74**

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

**Scheme 2.75**

2.5.2.2 Protection of Phenolic Hydroxy and Asymmetric Dihydroxylation

Phenolic hydroxyl group in 238 was protected as MEM (methoxyethoxymethyl)-ether using MEMCl and $N,N$-diisopropylethylamine (DIPEA) as the base in dichloromethane in 90% yield (Scheme 2.76). Appearance of MEM hydrogen peaks in $^1$H-NMR of the product 239 [i.e. 2 singlets at 5.36 ppm (2H, -OCH$_2$O-) and 3.39 ppm (3H, -OMe) and 2 multiplets at 3.57 and 3.84 ppm (-OCH$_2$CH$_2$O-)]
confirmed the synthesis. $^{13}$C-NMR also revealed four additional peaks related to MEM group at 93.7, 71.8, 68.6, and 59.5 ppm.

Scheme 2.76

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

Scheme 2.77

2.5.2.3 Regioselective Tosylation and Cyclization

Regioselective tosylation of diol 240 performed with the similar conditions as the model study to afford $\alpha$-O-tosyl compound 241 in 88% yield (Scheme 2.78). $^1$H-NMR revealed the existence of aromatic methyl (singlet at 2.46 ppm, 3H) and hydrogens (two doublets at 7.89 ppm, 2H and 7.37 ppm, 2H) in tosyl group. $^{13}$C-NMR showed carbonyl (ester) peak and 12 aromatic carbons.
Finally, O-tosyl compound 241 under reduction conditions, i.e., hydrogen and palladium/carbon catalyst, gave the amine intermediate (not shown) and in the presence of potassium carbonate (as base) cyclized to tetrahydroquinoline derivative 51 in good yield (82%).

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

Part A: 10-membered Ring Unsaturated Lactam

3.1 Design Strategy

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

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

Scheme 3.1

![Scheme 3.1](image_url)
Successful results in this model study would encourage us to extend our synthesis to the solid phase (Section 3.4.2).

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

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

![Figure 3.1 Natural Products Having a 10-membered Ring Nitrogen/Lactam](image)
Cripowellin A and B, two amaryllidaceae alkaloids isolated from bulbs of *crinum powelli*\(^{172}\) have shown strong insecticidal properties. A small group of halogenated indole-imidazole alkaloids, namely chartelline A, B, and C, were isolated from marine bryozoan *Chartella papyracea*\(^{173}\). Despite the lack of biological activity to date, their unique structural complexity make chartellines as valuable targets in total synthesis projects.

Dysazecine is the first alkaloid having a dibenz[\(d,f\)]azecine skeleton, which is found in leaves of *dysoxylum lenticellare*\(^{174}\). Although an extract of this plant including dysazecine showed strong cardioactivity, the responsible compound or compounds for the reactivity have not yet been identified\(^{175}\). LE-300 (Figure 3.2) is found to be one of the most potent D\(_5\)-selective dopamine-receptor antagonists known so far\(^{176}\). LE-300 is not a naturally occurring compound, but has the dibenz-azecine skeleton, similar to dysazecine, in its structure.

![Figure 3.2 Structure of LE-300](image)

**Figure 3.2** Structure of LE-300

Synthetic efforts for constructing these compounds will be discussed in Section 3.3.
3.3 Synthesis of Ten-membered Rings Having Nitrogen (Lactam) in Literature

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

3.3.1 Ring Closure and Ring Contraction

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

Scheme 3.2
A similar approach was performed by Vilarrasa and co-workers using activated anhydride\textsuperscript{178}. In Scheme 3.3, secondary azido compound 247, under treatment with excess tributylphosphine and DMAP, (high-dilution) resulted in 10-membered ring lactam 245, again with 25\% undesired product. On the other hand, this method was found particularly effective in preparing amides and peptides. It was believed the reaction involves a direct aza-Wittig-like reaction.

Scheme 3.3

\[
\begin{align*}
\text{N}_3 & \quad \text{Me} \\
\text{O} & \quad \text{Bu}_3\text{P}, \text{DMAP} \\
\text{COAr} & \quad 80 \degree \text{C}, \text{benzene} \\
\rightarrow & \quad 38\% \text{ (monomer)} \\
& \quad 25\% \text{ (dimer)} \\
\end{align*}
\]

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

Scheme 3.4

\[
\begin{align*}
\text{Br} & \quad \text{R} \\
\text{N} & \quad \text{Bu}_3\text{SnH}, \text{AIBN} \\
\text{O} & \quad \text{benzene, } 80\degree \text{C} \\
\rightarrow & \quad 60\% \text{ and } 45\% \\
\text{R}= \text{C} & \quad \text{R}’= \text{SiMe}_3, \text{H} \\
\text{=CSiMe}_3, \text{C} & \quad \text{C} \equiv \text{CH} \\
\end{align*}
\]

This reaction was repeated in a di-methoxy derivative of bromoacetylene 250 by Saa and co-workers\textsuperscript{180}. Yield of 251 in this case improved to 71\%, shown in Scheme 3.5.
Shea and Lease observed an unprecedented reaction that resulted in the formation of a 10-membered-ring lactam\(^{181}\). Scheme 3.6 shows that thermolysis of acetate 252 gave 10-membered-ring lactam 254. \(N\)-acyl imine 253 undergoes an intramolecular ene reaction. This is the first example of a type 3 intramolecular imino-ene rearrangement, which indicates the enophile is tethered to the 3-position of the ene.

Macrolactamization via palladium \(\pi\)-allyl alkylation was studied by Johnson and co-workers\(^{182a}\). Benzyltrimethylammonium methyl carbonate is the source of slowly formed methoxide. Scheme 3.7 shows an example of this method giving 10-membered-ring lactam 256 from 255. Synthesis of CGS25155, an inhibitor of neutral endopeptidase (NEP) 24.11, was performed using this method.
A novel cycloisomerization is used for the synthesis of medium and large rings via allenes by Trost and co-workers\textsuperscript{182b}. 10-membered-ring lactam 258 in Scheme 3.8 was prepared using Pd(0)-catalyzed cyclization of allene 257. Allen served as the precursor to the allyl ester.

Katzenellenbogen and co-workers prepared ten-membered-ring lactam stereoselectively with two methods\textsuperscript{183}. In their macrolactamization route, cyclization of amino ester 259 (Scheme 3.9) in the presence of a base resulted in lactam 260 with 87\% ee. However, the yield was poor.
As shown in Scheme 3.10, the more efficient route used a ring-closing metathesis reaction with Grubbs' catalyst. This is the first example of cyclization using an RCM reaction to create a 10-membered-ring lactam. The reaction on 261 gave only one diastereomer (262) in 65% yield with a double bond in E form.

Scheme 3.10

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

Scheme 3.11

In the elegant synthesis of (±)-chatelline C by Baran and Shenvi, an inspired biosynthetic route was introduced for constructing the 10-membered-ring in the
chatelline molecule. As shown in Scheme 3.12, compound 265 in one pot gave the necessary compound 266 containing a core of chatelline, a 10-membered nitrogen ring. It was believed the reaction involves:

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

Scheme 3.12

3.3.2 Ring Expansion and Fragmentation

A notable reaction reported by Edstrom involved the reaction of 2-vinyl-azacycles, such as 267 (Scheme 3.13), with the appropriate ketene creating zwitterionic intermediate 268, which underwent [3,3] ring expansion to give lactam 269 in excellent yield.
A photochemical variant of the reaction presented above was investigated by Hegedus and co-workers\textsuperscript{187}. Chromium carbene complex 270 (Scheme 3.14) in the presence of tertiary allylic amine 267 under photolysis, generates a zwitterionic intermediate which by [3,3] sigmatropic rearrangement gave 10-membered-ring unsaturated lactam 269. However, the yield was poor.

\begin{equation}
\begin{align*}
\text{Ph} & & \text{CO} \rightarrow \text{Me} \\
\text{Ph} & & \text{OMe} \\
\text{Me} & & \text{Ph} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{Ph} & & \text{OMe} \\
\text{Me} & & \text{Ph} \\
\end{align*}
\end{equation}

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

\begin{equation}
\begin{align*}
\text{Ph} & & \text{OMe} \\
\text{Me} & & \text{Ph} \\
\end{align*}
\end{equation}

\begin{equation}
\begin{align*}
\text{Ph} & & \text{OMe} \\
\text{Me} & & \text{Ph} \\
\end{align*}
\end{equation}
For construction of small to medium sized ring lactams, Kim et al. used an intramolecular addition of aminyl radicals to carbonyl groups. Azido groups were used as precursors for aminal radicals, as shown in Scheme 3.16. Interamolecular addition of aminal radicals to a more reactive carbonyl group, and following ring expansion, resulted in 10-membered-ring lactam 274 in excellent yield.
During the design and synthesis of active macrocyclic neutral endopeptidase (NEP) 24.11 inhibitors, MacPherson et al. used a simple ring expansion method for the synthesis of 10-membered ring lactams. Treatment of 9-membered ring carbocycle 275 (Scheme 3.17) with sodium azide and methanesulfonic acid gave lactam 276. This research led to several promising results including Johnson's work (explained in Section 3.3.1 above).

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

Suh et al. in the synthesis of lactams with substitution at the α-position of the carbonyl used an Aza-Claisen rearrangement of amide enolate. As explained in Scheme 3.19, a ring expansion reaction of 1-acyl-2-vinylpiperidines or 1-acyl-
2-vinylpiperazines (279) occurred under heating with a strong base through aza-Claisen rearrangement of amide enolates 280. The provided lactams 281 in moderate to excellent yield can introduce various substitutions at the \( \alpha \)-position of the carbonyl moiety.

**Scheme 3.19**

![Scheme 3.19 Diagram](image)

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

**Scheme 3.20**

![Scheme 3.20 Diagram](image)

Evans and co-workers prepared an unsaturated 10-membered ring lactam by the Claisen rearrangement of the vinyl-substituted compounds and using 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU)\textsuperscript{195}. Oxidation of selenide 284 (Scheme 3.21) with sodium periodate, followed by heating in the presence of DBU gave lactam 286 via a Claisen rearrangement of vinyl ketene aminal 285.
As pointed out in Section 3.2, LE-300 is found to be a dopamine antagonist. The strategy to synthesize this compound involves a ring expansion reaction. N-methylation of pentacyclic 287 (Scheme 3.22) resulted in quaternary quinolizinium salt 288 with very good yield. Treatment of this intermediate with sodium in liquid ammonia induced ring expansion and afforded LE-300.

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

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

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

### Scheme 3.24

![Scheme 3.24 Diagram]

#### 3.4.1.1 Synthesis of Precursor for RCM Reaction

For preparing the precursor needed for RCM reaction, secondary amine and alcohol in our tetrahydroquinoline scaffold should be modified considering the orthogonal nature of the protecting groups. On the other hand, if ethyl ester group reduces to primary alcohol, it will provide another active diversity site for further synthetic exploration. Therefore, this section contains the synthesis of the
RCM precursor through manipulation of active sites. First, ethyl ester group in our scaffold 231 (Scheme 3.25) was reduced to primary alcohol (not shown) using lithium borohydride in THF. It was found that the provided amino diol was difficult for purification by column chromatography (very polar) and quite unstable. Therefore, it was decided that the next step would continue without complete purification of amino diol. Selective protection of the amino alcohol was performed using allylchloroformate in the presence of pyridine at 0°C to afford alloc-N-protected diol 291. Purification by column chromatography was feasible then. Mass spectrum showed the peak 307.1 (M+1). The indicative peaks in \( ^1\text{H} \) and \( ^{13}\text{C} \)-NMR, such as olefinic protons [(5.95 ppm, m, 1H), (5.39 ppm, d, 1H), and (5.31 ppm, d, 1H)] and carbon in carbonyl position (155.5 ppm), also proved the correct synthesis.

**Scheme 3.25**

![Scheme 3.25](image)

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

**Scheme 3.26**

![Scheme 3.26](image)
As the two terminal olefins (i.e. at position-1 and 3 of the tetrahydroquinoline) are needed for constructing the RCM precursor, secondary hydroxide at 3-position was first equipped with the required terminal olefin. This was performed by the coupling reaction between alcohol 292 (Scheme 3.27) and 4-pentenoic acid in the presence of DMAP and also N,N'-Diisopropylcarbodiimide (DIC) as carboxylic acid activator. High yield for 293 (81%) was observed in this reaction as well. Extra peaks for pentenoyl ester group in $^1$H and $^{13}$C-NMR (such as 172.6 ppm for carbonyl ester) showed the successful esterification.

Scheme 3.27

To install the second terminal olefin in nitrogen arm and synthesis of the desired precursor for RCM reaction, we had to replace N-alloc group with an acryl group. For this aim, first the alloc group was removed by the treatment of compound 293 with Pd(0) catalyst in the presence of morpholine (Scheme 3.28). It was decided the next reaction would be performed without purification of the free amine. Therefore, the resulted free amine was subjected to acrylation with acryloyl chloride/py system in DCM to provide our required product 294 for the next step. Peak 474.2 (M+1) appeared in mass spectra and $^1$H-NMR showed disappearance of methylene hydrogens in O-CH$_2$-vinyl (of alloc group) around 4.8 ppm
3.4.1.2 RCM Reaction to 10-membered Ring Lactam

With RCM precursor 294 in hand, the first attempt was performed using Grubbs' 1st generation catalyst in DCM and reflux. No apparent progress in the reaction was noted after 1 hour and starting material stayed intact. However, with the same conditions and when Grubbs' 2nd generation catalyst was used instead, a considerable improvement including the appearance of a new spot in TLC was seen after one hour (Scheme 3.29). Work up and subsequent purification, resulted in the formation of a light green solid (295) and a small amount of recovered starting material. First sign of the successful reaction was proved by mass peak of 446.4 (M+1) which also showed M-28 from RCM precursor, meaning an ethylene molecule (a reliable indication in a successful RCM reaction) left the molecule.
This product, found as our tetrahydroquinoline having 10-membered ring lactam, was extensively examined by 1D [$^1$H-NMR, $^{13}$C-NMR (DEPT)], 2D NMR (COSY, HSQC) and X-ray crystallography. Figure 3.3 shows COSY and $^1$H/$^1$H coupling. Hydrogen correlations in the right hemisphere of the molecule showed in RED and BLUE. Based on these correlations, possible location of each proton was identified (in numbers).

![Figure 3.3 COSY of Compound 295 Showing H Correlations](image)

With this information in hand, we were able to make initial assignment for proton signals (please see Figure 3.4).
The $^1$H/$^1$H coupling information in the COSY spectrum allows us to make initial assignments of many of the $^1$H signals. Note: $J_{se} = 11$ Hz which is consistent with a cis double bond.

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

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

**Figure 3.5** Chemical Shifts for Compound 295
Another 2D experiment, i.e., HSQC provides $^1$H/$^{13}$C correlations. It guides us to assign $^{13}$C signals for all carbons, which have attached protons. Figure 3.6 shows $^1$H chemical shifts in RED and $^{13}$C chemical shifts in BLUE.

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

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

**Figure 3.7 Final Assignment of Chemical Shifts Using all Experiments**
Bright crystalline solid encouraged us to try recrystallization and a possible X-ray crystallography. After several attempts, and luckily enough, we were able to recover a crystal ideal for X-ray crystallography. X-ray structure of compound 295 is shown in Figure 3.8. From the X-ray structure, it appears the 10-membered ring is projected out of the tetrahydroquinoline plane and the double bond is not aligned with the amide functional group.

![Figure 3.8 X-ray Structure of Compound 295](image)

Crystal data of compound 295 is presented in Table 3.1.

**Table 3.1 Crystal Data for Compound 295**

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</tr>
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</tr>
<tr>
<td>Temperature</td>
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<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)</td>
</tr>
</tbody>
</table>
3.4.1.3 Hetero Michael Reaction on Lactam

One of the reactions we tried on our polycyclic compound was Michael addition. In spite of milder activity of lactam (amide) functionality in Michael addition compared with other carbonyl compounds, this α,β-unsaturated lactam still should be active as Michael acceptor. Treatment of our lactam with benzenethiol, benzyllthiol, and phenylethanethiol in the presence of triethylamine showed no progress as hetero(thio) Michael reaction. We believed if thiol was first deprotonated and then added to our lactam, the reaction may proceed better. Therefore, we treated phenylethanethiol with n-butyl lithium at -78°C in THF and then, while stirring, let it to get warm to room temperature during 16 hours. This
mixture containing lithium phenylethanolthiolate (salt) then added to our lactam 295 (Scheme 3.30). After 2 hours, starting material disappeared and new spot completed (checking by TLC). Mass spectrum, as the primary sign of the successful reaction, showed us the peak of 584.2 (M+1 for 296). It should be noted the same procedure with benzenethiol and benzylthiol had no reaction likely because of steric hindrance accompanying them.

**Scheme 3.30**

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

![Figure 3.9 $^1$H-NMR Spectrum for Thio Compound 296](image-url)

The mass spectrum indicated that the thiol addition reaction had worked as expected, but the $^1$H NMR gave broad lines and more signals than there should have been.
We also performed NOESY experiment. As shown in Figure 3.10, we highlighted some of the cross-peaks arise from chemical exchange as opposed to proximity through space (marked in RED).

![NOESY Spectrum for Thio Compound 296](image)

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

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

### 3.4.2 Solid Phase Synthesis

To the best of our knowledge, the solid phase synthesis of a polycyclic compound containing a 10-membered ring unsaturated lactam has never been reported. However, later, several other researchers in our group prepared
compounds with a variety of ring size (including 10-membered ring). For developing a solid-phase synthesis project, we needed compound 297 (Scheme 3.31), in which the phenolic hydroxyl moiety utilized as an anchoring site for the solid phase. Since all three arms in tetrahydroquinoline 51 will be used in solid phase stages, there is a need for orthogonal protection of free amine, free hydroxyl, and also ester (reduced to alcohol) moiety. Therefore, fully protected tetrahydroquinoline was prepared. An enantioselective solid phase synthesis of compound 299 was developed with an approach similar to that discussed earlier in the model study (section 3.4.1). The solid phase synthesis of compound 299 was achieved in a few steps from 51 in three main stages: (1) synthesis of the precursor 297 (2) loading and solid phase synthesis of compound 299, and (3) cleavage from the solid support.

Scheme 3.31

3.4.2.1 Synthesis of Precursor Having Anchoring Site

This series of reactions are similar to the previous ones in solution phase. Ethyl ester group in tetrahydroquinoline 51 (Scheme 3.32) reduced to primary alcohol using lithium borohydride in THF. Next step proceeded without complete
purification of amino diol. Selective protection of the amino alcohol performed using allylchloroformate in the presence of pyridine at 0°C to afford alloc-N-protected diol 300. The indicative peaks in $^1$H-NMR, such as olefinic protons [(5.91 ppm, m, 1H), (5.33 ppm, d, 1H), and (5.27 ppm, d, 1H)] proved the right reaction. Compared with the model study, yield was good (78%).

**Scheme 3.32**

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

**Scheme 3.33**

Since the precursor for solid phase synthesis was better to have one free hydroxyl group for high yield loading, it was decided that the remaining secondary hydroxyl group in 301 would be also protected. Therefore, the remaining hydroxyl group was protected as alloc (Scheme 3.34). The reaction proceeded smoothly and gave the fully protected tetrahydroquinoline 302 in 85%
yield. It was quite straightforward to make sure we reached to the right compound by looking at $^{13}$C-NMR spectrum. The noted peaks at 155.1 and 154.5 ppm suggested that two carbonyls (in alloc groups) existed.

**Scheme 3.34**

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

**Scheme 3.35**

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

With the precursor in hand, we were able to perform the loading. For loading, we used bromo Wang resin 303 (Scheme 3.36), in the solid phase synthesis$^{199a}$. It is one of the commonly utilized solid supports for carboxylic acids and for alcohols (phenols). The linker is attached to the resin through a phenyl ether bond and the
phenolic substrate is bound to the linker by an ether bond. Loading can be achieved by treatment of the resin with phenolic compound 304 (or alcohol) in the presence of sodium iodide and cesium carbonate. The linkage is quite stable in a variety of reaction conditions but cleaves by the short treatment with an acid, normally TFA. Therefore, after solid phase reaction steps (305 to 306), the desired compound 307 will be formed by cleavage using TFA. It should be noted that between each step in solid phase reactions, several washing with different kind of solvents must be performed. Obviously, it removes all unused reagents and prepares the resin for the next reaction.

Scheme 3.36

Compound 303 (Scheme 3.37) was immobilized onto the solid support using the conditions mentioned above. For better loading, one equivalent of resin with two equivalents of the substrate was stirred for 48 hours. Remaining starting material (purified by column chromatography) pointed out the loading succeeded with 85% yield. The resin 308 was used as the starting material in our solid phase synthesis. It should be mentioned that products in each step were confirmed by
mass spectrum. This can be easily performed by quick cleavage of a small portion of the resin (around 1 mg).

Scheme 3.37

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

Scheme 3.38

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

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

Scheme 3.40

3.4.2.3 Cleavage

Treatment of the resin 299 (Scheme 3.41) with 5% TFA for 1 hour was enough for cleavage. Purification of tricyclic 310 by flash column chromatography, although showed a blurred spot in TLC, provided the overall yield of 40% (5 steps). This meant average 83% for each step. For proper characterization, compound 310 was extensively studied by 1D and 2D NMR as follows.
Using 2D NMR, i.e., COSY and HSQC, we were able to verify the presence of compound 310. As shown in Figure 3.11, we assigned all the protons in the molecule (in RED). The cis relationship around the double bond confirmed by the coupling constant of $J = 11.6 \text{ Hz}$. 

Figure 3.11 Proton Assignment for Compound 310 Using 2D NMR

Similar to model study, COSY enabled us to find the relationship between protons in RED and BLUE as shown in Figure 3.12.
The COSY experiment detects $^1H/^1H$ coupling.

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

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

This is the COSY for Compound 14 which was a model compound (i.e., synthesized in solution). Note that this spectrum is similar to that for Compound 22, thus confirming that the solid-phase synthesis worked as expected.

**Figure 3.13 Pattern Likeness at Compound Made in Solution Phase**
Finally, for better comparison between two COSY spectra, it is useful to show those results side-by-side (Figure 3.14) followed by their superimposed version (Figure 3.15).

**Figure 3.14** Side-by-Side Comparison of COSY Spectra

**Figure 3.15** Superimposed Comparison of COSY Spectra
4: Solution and Solid Phase Synthesis of Tetrahydroquinoline Polycyclics.

Part B: α,β-Unsaturated γ-Lactam and δ-Lactone

4.1 Design Strategy

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

![Figure 4.1 Tricyclic Systems Presenting in This Chapter](image)

This chapter will discuss solution and solid phase synthesis of our pyrroloquinoline, and solution phase synthesis of pyranoquinoline. As illustrated in Scheme 4.1, tetrahydroquinoline-based tricyclic containing α,β-unsaturated γ-lactam (54) and δ-lactone (55) were prepared from our tetrahydroquinoline scaffold (301), the synthesis of which was explained in Section 3.4.2.1.
4.2 Pyrrolo[1,2-a]quinolines as Natural and Pharmaceutical Products

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

Interestingly, synthetic compounds known as 5, 11-dioxosubstituted isoindolo-[2,1-a]quinolines 313 have protective effects against N\(_2\)-induced hypoxia\(^{201}\). We
will re-examine the isoindolo[2,1-a]quinoline system in Chapter 5, and explore its chemistry more comprehensively.

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

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

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

![Scheme 4.2](image)

Twenty years later and in a novel approach, Saegusa and co-workers synthesized pyrroloquinoline 311 (Scheme 4.3) by the fluoride anion induced intramolecular aza Diels-Alder reaction\textsuperscript{203}. Ortho-quinone methide N-alkenylimine
intermediate 317, from fluoride induced 1,4-elimination of 316, underwent the key Diels-Alder reaction to afford 311 in 59% yield. Later, Storr et al. performed this method by using ‘flash vacuum pyrolysis’ affording several other systems in moderate yields\textsuperscript{204,205}.

**Scheme 4.3**

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

**Scheme 4.4**

Reinhoudt et al. performed an interesting structural investigation in pyrrolo[1,2-a]quinolines\textsuperscript{207-208}. They proved the long π-system (donor-π-acceptor) is inherently chiral and pyrrolidine ring is forced slightly (around 10°) out of plane. In cyclization reaction shown in Scheme 4.5, only one of the enantiomeric donor-π-acceptor systems of compound 322 was formed. This is due to asymmetric induction of the chiral atom in the pyrrolidine ring of 321.
Meyers and Milot prepared scaffold 311 (Scheme 4.6) by hydrazinolysis of tetrahydroquinoline 323. Generated free amine intermediate is responsible for the observed cyclization.

Compound 324 (Scheme 4.7) underwent intramolecular cyclodehydration via alkoxyphosphonium salt 325 to create compound 311. The observed yield (55%) was moderate compared to indole system (87%).
Cha et al. prepared 311 (Scheme 4.8) from titanium-mediated coupling of ω-vinyl lactam 326\textsuperscript{211}. Compound 326 upon reaction with cyclopentylmagnesium chloride in the presence of triisopropyltitanium (VI) chloride produced di-i-propoxytitana-cyclopentane intermediate which upon ring opening converted to 327 (43%) and 311 (27%). It was believed that the methyl group in 327 derived from reductive elimination of the hydridotitanate intermediate and not from hydrolysis of Ti-C bond.

Scheme 4.8

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

Scheme 4.9

Pearson and Fang reported the synthesis of pyrroloquinoline 311 along with pyrroloisoquinoline 335 with the method explained in Scheme 4.10\textsuperscript{213}. Iminium ions 333 and 334, prepared from treatment of azido compound 331 with trifluoromethanesulfonic acid, under \textit{in situ} reduction with sodium borohydride
gave a mixture of 311 and 335. Aryl migration occurred in the rearrangement of aminodiazonium 332 in an intramolecular Schmidt reaction\textsuperscript{214}.

**Scheme 4.10**

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

**Scheme 4.11**
Payne et al. synthesized pyrroloquinoline-3-one from aryl epoxyazides\textsuperscript{216}. As shown in Scheme 4.12, this occurred from cascades of electron-deficient reactions a) epoxide opening in 340, b) electrophilic amination of the arene to give 343, c) alkyl shift (cleavage of aziridine) to bridged compound 344, and d) regiospecific ring-contraction (by assistance from oxygen) to pyrroloquinoline-3-one 341.

Scheme 4.12

![Scheme 4.12 Diagram](image)

Alcaide and co-workers made pyrroloquinoline-2-one from \(\beta\)-lactams\textsuperscript{217}. For example \(\beta\)-lactam 345 (Scheme 4.13) under treatment with sodium methoxide and amide bond cleavage (rearrangement) afforded tricyclic 346 quantitatively. Chirality transfer occurred when an enantiomerically pure substrate was used.

Scheme 4.13

![Scheme 4.13 Diagram](image)
Intramolecular rhodium (II) catalyzed carbenoid insertion reaction into aromatic C-H bond was used by Ray et al. for preparing pyrroloquinoline-1,4-diones. As shown in Scheme 4.14, diazoketones in the presence of rhodium(II) acetate regioselectively converted to the substituted 3,3a-dihydro-2H,5H-pyrrolo[1,2-a]quinoline-1,4-diones in good yields.

Scheme 4.14

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

Scheme 4.15

Che and Liu recently displayed the synthesis of substituted pyrrolo[1,2-a]-quinolines using a gold-catalyzed tandem reaction in aqueous media. 1,4-
aminoalkynes 350 (Scheme 4.16) with alkynes and an Au(I) catalyst in water underwent tandem cyclization to produce diversity substituted pyrroloquinolines 351 in good-to-excellent yields. Two new C-C bonds and one new N-C bond were formed in one pot. The proposed mechanism involves the generation of an enamine and the cyclization of the propargylamine, resulting from the attack of alkyne on the enamine.

### Scheme 4.16

![Scheme 4.16](image)

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

Perumal and co-workers claimed a synthetic method for pyrano[3,2-b]quinoline\(^{221a}\). Treatment of aniline or \(p\)-methoxyaniline and O-prenylsalicylic aldehyde 352 (Scheme 4.17a) in the presence of sulfamic acid and in mild-reaction conditions yielded the 1:1 diastereoisomeric mixture of benzopyrano[3,2-b]quinolines 353. Chapter 5 further discusses this type of intramolecular imino Diels-Alder reaction.
Interestingly, after a closer look at the above reaction, it appears that the product was not correctly identified. As shown in Scheme 4.17b, Schiff base 354 resulted from the reaction of anilines, and O-prenylsalicylic aldehyde (352) is expected to participate in a cycloaddition (imino Diels-Alder) reaction and form the chromeno[4,3-b]quinoline derivative 355— not benzopyrano[3,2-b]quinolines 353.

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

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

**Scheme 4.18**

![Scheme 4.18](image)

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

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

For the synthesis of the RCM precursor (356), we started from 301 (Scheme 4.19). Positions 1 and 2 in tetrahydroquinoline had to be modified to accommodate two terminal olefins. Before this task, the secondary hydroxyl group in 301 should be first blocked to minimize the formation of undesired side products. Benzoyl protection on 301 using coupling conditions resulted in fully protected tetrahydroquinoline 357 in an excellent yield. \(^1\)H-NMR showed a doublet at 7.94 ppm (\(J = 7.3, 2\)H) suggesting two new aromatic protons close to carbonyl. This carbonyl in benzoyl group also showed a peak at 166.1 ppm in \(^{13}\)C-NMR.
The next step was to prepare one terminal olefin at position 2 of our tetrahydroquinoline. In order to do so, the TBS group was first removed, at which point a fully protected compound 357 (Scheme 4.20) was treated with tetra-n-butylammonium fluoride (TBAF) in acetic acid, and cleanly gave compound 358 with a free, secondary alcohol moiety. Disappearance of TBS peaks in both $^1$H-NMR [0.82 (9H) and -0.01 (6H) ppm], and $^{13}$C-NMR [18.4 and -5.2 ppm] suggested that a successful deprotection reaction took place.

Oxidation of this alcohol (358), with a SO$_3$-pyridine system and a subsequent Wittig reaction, afforded compound 359 with the desired terminal olefin (Scheme 4.21). Due to the instability of the aldehyde, isolation at the oxidation stage was not efficient. Therefore, the next step was conducted (i.e. a Wittig reaction) without purification of the aldehyde intermediate. Although successful, the yield was slightly lower than expected (55% for two steps); mass spectrum showed peak 468.4 (M+1) and olefinic hydrogens and carbons appeared on $^1$H-NMR and $^{13}$C-NMR, respectively.
Formation of the RCM precursor was achieved using the installation of the second terminal olefin. Similar to the procedure explained in chapter 3 (Section 3.4.1.1), alloc was replaced with an acryl group using a 2 step-reaction of N-deprotection, with Pd(0) in compound 359 proceeded by the installment of acryl in the nitrogen atom (Scheme 4.22), all without purifying the amine intermediate. This resulted in the formation of our desired compound 360, with an average yield of 83% in each step. Although proven with all other methods (mass, $^{13}$C-NMR, and 2D NMR), the disappearance of methylene hydrogens in "O-CH$_2$-olefin" of alloc group, in 4.50-4.60 ppm, was the easiest way verify the successful reaction. In addition, the presence of a carbonyl peak in $^{13}$C-NMR for the acryl group (which appeared at 155.7 ppm) further validated the reaction.

Scheme 4.22

In the final stage of our synthesis, RCM reaction using first generation Grubbs' catalyst on 360 (Scheme 4.23) cleanly afforded pyrrolo[1,2-a]quinoline 54 in 80% yield. Structure of this tricyclic compound containing $\alpha,\beta$-unsaturated $\gamma$-lactam (5-membered ring lactam) was comprehensively studied by mass, 1D NMR, 2D NMR, and finally with X-ray crystallography. $^1$H-NMR showed olefinic ($\alpha,\beta$-
unsaturated) hydrogens at 6.38 and 7.28 ppm. However, best indication for RCM reaction is the expulsion of the ethylene molecule, which resulted in reducing the number of hydrogens and carbons by six and two, respectively. Counting H and C atoms in 1D-NMR spectra revealed this ethylene expulsion.

Scheme 4.23

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

Figure 4.3 Spatially Close Hydrogens in Compound 54 Revealed by NOESY

Compound 54 under recrystallization using Ethyl acetate/DCM/Hexanes system gave a dark yellow crystal. X-ray crystallography enabled us for the ultimate
assignment (Figure 4.4). Crystal data for this compound is presented in Table 4.1.

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

**Table 4.1 Crystal Data for Compound 54**

<table>
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<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td>409.42</td>
</tr>
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4.4.2 Solution Phase Synthesis of Tetrahydroquinoline Tricyclic Having \(\alpha,\beta\)-Unsaturated \(\delta\)-Lactone

In section 4.1 (Scheme 4.1), the starting material 301 for both syntheses of tricyclics 54 and 55 is shown. However, for the synthesis of pyranoquinoline 55, we are pleased that we were actually able to prepare our target using compound 359 (the synthesis is explained in Section 4.4.1) and save 4 steps. In this section, the stages required for the synthesis of our pyrano[3,2-b]quinolin-2-one 55 will be discussed. Our approach to the synthesis of this system again was RCM reaction although no other method was found. Since terminal olefin has already been installed in C-2 position of our tetrahydroquinoline compound 359 (Scheme 4.24), we needed to place an acryl group for proceeding by RCM reaction. Scheme 4.24 shows the first two steps for this synthesis. Reduction by lithium aluminum hydride on 359 successfully removed both alloc (amide) and benzoyl (ester) groups. The provided amino alcohol (not shown) isolated and fully characterized. Disappearance of two carbonyl peaks in \(^{13}\)C-NMR indicated that -Nalloc and benzoyl group had been removed. 1D DEPT-135 NMR also depicted -CH- (\(-\text{CH}_3\)-) and -\(\text{CH}_2\)- in the compound. The secondary amine in this amino alcohol was selectively acyl protected by acetic anhydride and 4-dimethylaminopyridine (DMAP) as the base to afford 361. Temperature for this reaction was kept at -129.
10°C for better selectivity. Peaks for acetyl group appeared in 1D NMR, i.e., 2.07 ppm (s, 3H) in 1H-NMR for OC-CH$_3$ and 170.9 ppm in 13C-NMR for carbonyl group. Moreover, DEPT-135 again showed all CH$_{1,2,3}$.

Scheme 4.24

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

Scheme 4.25
4.4.3 Solid Phase Synthesis of Tetrahydroquinoline Tricyclic Having \( \alpha,\beta \)-Unsaturated \( \gamma \)-Lactam

Ring-closing metathesis reaction was also the preferred method for our solid phase synthesis. In the previous section, we pointed out that for preparing our second tricyclic system, one of our intermediates from first synthesis was used (i.e. compound 359). For the solid phase synthesis of pyrrolo[1,2-\( \alpha \)]quinoline system we again started with the same intermediate 359 simply because it owned the all features we needed for a successful solid phase synthesis including orthogonally protecting groups and the potential anchoring site. Furthermore, it had one arm already equipped with olefin moiety suitable for the RCM reaction. Unlike the hardship we experienced for removal of MEM group in Section 3.4.2.1, treatment of tetrahydroquinoline 359 (Scheme 4.26) with \( p \)-TSA in methanol generated phenolic compound 362 in excellent yield. Comparison of \( ^1 \)H-NMR spectra of 359 and 362 signalled the complete removal of MEM group (from \( \text{CH}_3-O-\text{CH}_2-\text{CH}_2-O-\text{CH}_2-O\text{Ar} \)) which its protons used to be appeared around 3.4, 3.6, 3.8, and 5.2 ppm. However, other 1D and 2D NMR experiments were also performed.

Scheme 4.26

![Scheme 4.26](image)

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

131
Alloc group removed using typical palladium(0)/methylmorpholine system and replaced by acryl using acroyl chloride/pyridine (Scheme 4.28). It should be reminded that each step was checked using mass spectroscopy. Resin 364 then was equipped with two arms needed for a metathesis reaction.

RCM reaction performed on 364 using second-generation Grubbs' catalyst in refluxed DCM for 6 hours (Scheme 4.29). Small amount of resin 365 was cleaved and submitted for mass analysis. M+1 peak (322.2) convinced us about our successful reaction.
The remaining resin 365 under treatment with TFA was cleaved (Scheme 4.30) and purified by column chromatography. The overall yield was found to be 42% (four steps).

Scheme 4.30

In spite of the limited amount of pyrroloquinoline 365 formed, we were able to characterize it completely. Comparing with tricyclic compound 54, complete sets of protons in NMR for 366 was observed. As expected, the difference was the disappearance of MEM protons and carbons in NMR spectra. 2D NMR spectra were also used for the final assignment. For instance, COSY spectrum showed the similar pattern as 54. Comparison of the two COSY spectra presented in Figure 4.5.
In this chapter, we explained the solution and solid phase synthesis of tetrahydroquinoline system pyrrolo[1,2-a]quinoline and also solution phase synthesis of pyrano[3,2-b]quinoline. Unfortunately, any attempts for the solid phase synthesis of the latter were not successful.
5: One-Pot Synthesis of Tetrahydroquinoline-Derived Polycyclics and Further Exploration

5.1 Design Strategy

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

Figure 5.1 Isoindoloquinoline and Isoindoloquinolone

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

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

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

Figure 5.3 Bioactive Isoindoloquinolines
5.3 Synthesis of Isoindolo[2,1-a]quinoline System in Literature

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

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

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

Ten years later Igeta and co-workers reported the synthesis of 5H-isindolo[2,1-a]quinolin-11-one (Scheme 5.2) by treatment of o-(α-quinolyl)benzylidene diacetae with diluted hydrochloric acid followed by neutralization. Aldehyde formed by the acidic hydrolysis of, cyclizes (nucleophilic attack of nitrogen to carbonyl) to give. Neutralization by sodium bicarbonate leads to the formation of enol which ketonized to afford the more stable isindoloquinoline compound. These two indicated syntheses which used isindole attachment to quinolines, suffered from low yields.
Reinhoudt et al. used dinitrile compound 380 (Scheme 5.3) in their synthesis of isoindoloquinoline 382\textsuperscript{226}. The reaction may proceed through a [1,5] hydrogen shift in 380 resulted in the formation of dipolar intermediate 381 which undergoes an intramolecular nucleophilic addition of carbanion to iminium forming 382.

Scheme 5.3

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

Scheme 5.4
In Kumar et al. methodology, \(N\)-phenyl-(triphenylphosphoranylidene)ethenimine was used\(^{228}\). \(N\)-phthaloylanthranilic acid \(386\) was treated in the conditions shown in Scheme 5.5 and converted to isoindolo[2,1-\(a\)]quinoline-5,11-dione \(387\) in 70% yield. The proposed mechanism involves a carboxyl group addition of \(386\) to the \(\text{C} = \text{C}\) bond of the ylide resulted in the formation of \(O\)-acylimidate \(388\). Phenyl isocyanate elimination from \(389\) leads to acylphosphorane \(390\), which undergoes an intramolecular Wittig reaction to afford \(387\). Formation of \(389\) from ester carbonyl migration in \(388\) was proven by isolation and characterization of \(389\) at milder conditions. Vorbruggen and co-workers earlier reported cyclization of \(386\) by triphenylphosphine/CCl\(_4\) in dichloromethane\(^{229}\). However, the product was found to be 6-chloroisooindolo[2,1-\(a\)]quinoline-5,11-dione.

**Scheme 5.5**

Kim and Keum reported the synthesis of \(387\) using quinolonecarboxylic acids\(^{230}\). \(\alpha\)-Amidoacetophenone \(392\) (Scheme 5.6) which can be prepared from phthalimide and \(\alpha\)-bromoacetophenone \(391\) using Copper(I)oxide, cyclized to quinolonecarboxylic acid \(393\) in alkaline medium. Orthoester and a catalytic amount of sulfuric acid then afforded isoindolo[2,1-\(a\)]quinoline-5,11-dione \(387\).
Sui et al. who successfully prepared bioactive isoindoloquinolines 369 (Figure 5.3), synthesized isoindoloquinoline-diones 395 by treatment of 2-aminoacetophenones 394 (Scheme 5.7) with phthalic anhydrides in basic medium\textsuperscript{222}. Intermediate 394 was prepared from acylation of anilines with methoxyacetonitrile in the presence of trichloroborane. However, yields in both reactions vary from low to moderate. Mechanism contains an initial formation of amide by nucleophilic attack of nitrogen to phthalic anhydride followed by cyclization of the resulted amide. The reaction proceeded in basic/heat condition to form compound 395.
Scheme 5.7

\[
\text{NH}_2 \xrightarrow{\text{MeOCH}_2\text{CN}} \text{NH}_2 \text{O} \xrightarrow{\text{BCl}_3, 7-68\%} \text{NH}_2 \text{O} \xrightarrow{\text{Et}_3\text{N/} \text{Xylene}} \text{OMe} \xrightarrow{\text{reflux, 35-74\%}} \text{OMe}^2
\]

\[R_1 = 2,4-\text{F}_2 \text{ or (OMe)}_2 \quad R_2 = \text{H, 8,9-Cl}_2, \text{Me}_2, (\text{OMe})_2\]

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

Scheme 5.8

\[
\text{NaN}_3, \text{acetone} \xrightarrow{\text{H}_2\text{O, heat, 6h}} 76\% \quad \text{BuLi}, 80^\circ\text{C, 3h then} 125^\circ\text{C, 3h} \xrightarrow{72\%} \text{BuLi}, 80^\circ\text{C, 3h then} 125^\circ\text{C, 3h}
\]

\[\text{Vorbruggen et al. reported cyclization of 386 (Scheme 5.9) by triphenylphosphine/CCl}_4 \text{ in dichloromethane}^{229}. \text{However, product was found to be 6-chloroisoi} \text{ndolo[2,1-a]quinoline-5,11-dione 399. Proposed mechanism involves the initial formation of intermediate 2-[(1-(dichloromethylene))-3-}\]

142
oxoisindolin-2-yl]benzoyl chloride 400 which under Wittig-type reaction converts to 399.

Scheme 5.9

![Scheme 5.9 Diagram]

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

Scheme 5.10

![Scheme 5.10 Diagram]

Epsztajn et al. prepared isoindoloquinolones from hydroxyisoindolinones. 2-aryl-3-hydroxyisoindol-1-one 404 (Scheme 5.11) treated with diethyl malonate in
acetic anhydride in the presence of methanesulfonic acid to form isoindolo[2,1-a]quinoline-5,11-dione 405. Yields were poor despite the acceptable generality.

Scheme 5.11

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

Scheme 5.12

Russian chemists in recent years seriously worked on the synthetic methods of isoindoloquinoline system. Zubkov and his colleagues used 3-aryl-2-methallyl-3-aza-10-oxatricyclo[5.2.1.01,5]dec-8-ene-6-carboxylic acids 409 (Scheme 5.13) as precursor for the synthesis of isoindoloquinolines 410. 4-α-Furyl-4-N-
arylaminobut-1-enes 408 and maleic anhydride underwent the N-acylation/intramolecular [4+2] cycloaddition reaction to form 409. Dehydration/aromatization of the oxabicyclic fragment of 409 using phosphoric acid followed by an intramolecular cyclization of the methallyl [-CH₂CH(Me)=CH₂] group resulted in 410.

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

As mentioned in section 5.1, the main purpose of this work is the preparation of isoindolo[2,1-a]quinoline system directly from N-aryl compounds. This interest fortunately led us to the novel synthesis of cyclopenta[c]-isoindolo[2,1-a]-quinoline-11-one derivatives 416 (Scheme 5.15) using simple and commercially available starting materials\textsuperscript{221b}. We are also pleased that the presenting reaction was performed in one-pot (tandem type). Consequently, it is considered a multicomponent reaction.
This complex pentacyclic system (hexacyclic system when aminonaphthalene used) contains three stereogenic centres and a few sites for further exploration. In the remaining section of this chapter, we will discuss many aspects of the mechanism, characterization of polycyclics, further reactions in the system, etc. Since the key step for the above transformation is multicomponent 'Povarov' reaction, we will begin with this subject.

5.4.1 Povarov Reaction: An Extension

Utilizing multi-component reactions (MCR) is a well-recognized approach to obtain heterocyclic compounds\textsuperscript{238,240}. Povarov reported an interesting multi-component reaction using amines, aldehydes, electron-rich olefins and an acid (or Lewis acid) as the catalyst to prepare substituted tetrahydroquinolines\textsuperscript{241}. During past 40 years, many scientists continue to explore this reaction\textsuperscript{242}. The great interest in making tetrahydroquinoline scaffold using this method and the promising biological activities associated with this scaffold were also acknowledged in many patents. Compounds presented in Figure 5.4 are only two examples of bioactive molecules, which were prepared using Povarov reaction. G-protein-coupled receptor (GPR-30) is a cell surface receptor, which with high affinity binds estrogen. The first GPR-30 specific agonist \textit{417} which is capable of activating GPR-30 in complex environments was identified by the teams of Oprea and Prossnitz\textsuperscript{243}. Methicillin-resistant \textit{Staphylococcus aureus} (MRSA) is a
bacterium responsible for infections difficult to treat. Antibacterial agents with potent \textit{in vitro} activity versus MSRA discovered by Hoemann and his team.

![Figure 5.4 Bioactive Compounds Synthesized by Povarov Reaction](image)

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

Aza Diels-Alder reaction between electron-deficient Schiff base and electron-rich alkene is one of the most convenient routes to the synthesis of N-heterocycles. The tetrahydroquinoline obtained through Povarov type reaction can be viewed as being formed through either a concerted inverse electron demand hetero Diels-Alder reaction with intermediacy of 423 (Scheme 5.17-simplified) or via a step-wise process beginning from the addition of an olefin to an iminium ion forming carbocation 424 as an intermediate followed by an intramolecular electrophilic aromatic substitution (Friedel-Crafts) reaction to create tetrahydroquinoline 425. Despite initial proposed mechanism by Povarov and a few groups in favor of the cycloaddition route, many other chemists found the step-wise route more complying with their observed results. Both mechanisms, however, can appropriately explain the regio- and stereo-selective nature of the reaction. Almost all the reported works on the mechanism of this reaction have stressed their approach on the olefin and/or the azabutadiene fragment but rarely on the aromatic ring. Our approach to the mechanism of Povarov reaction and to
further synthesis of complex polycyclics has also considered the role of the aromatic substitutions (Sections 5.4.1.3 and 5.4.2.2 below).

Scheme 5.17

5.4.1.2 Synthesis of Tetrahydroquinoline Tricycles

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

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

Figure 5.5 Protons in Cyclopenta[c]pyridine Fragment

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

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<th>H$_3$</th>
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Tetrahydroquinoline 430 was afforded not only stereoselectively but also regioselectively. 1D and 2D NMR confirmed the synthesized product is in fact 430 and not 431 (Figure 5.6). The explanation for this noted regio-selectivity will be discussed in the next section (Section 5.4.1.3).

![Figure 5.6 Regioselective Formation of 430](image)

As sample, COSY spectrum of tetrahydroquinoline tricyclic compound 429 is shown in Figure 5.7. Each color represents the correlation between marked couple protons. H$_{4a}$ and H$_{4b}$ are diastereomeric protons, therefore; we expected to see not only two different chemical shifts but also two different correlation patterns. Interestingly, each olefinic proton, i.e., H$_5$ and H$_6$, also showed a relationship with either H$_{4a}$ or H$_{4b}$.
Finally, by recrystallization of all three prepared tetrahydroquinoline tricycles and taking X-ray, the entire characterization package completed. In Figure 5.8, the X-ray structure for each compound (428 to 430) was presented. Note the stereoselectivity for all compounds (only one diastereomer) and regioselectivity (for 430).
Figure 5.8 X-ray Structures for Tetrahydroquinolines Tricycles 428-430

Crystal data for these compounds are presented in Table 5.2.

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<td>616</td>
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<td>0.35 x 0.20 x 0.08 mm³</td>
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<td>-21 ≤ h ≤ 21</td>
</tr>
<tr>
<td></td>
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<td>-12 ≤ k ≤ 12</td>
<td>-10 ≤ k ≤ 10</td>
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<tr>
<td></td>
<td>-20 ≤ l ≤ 20</td>
<td>-17 ≤ l ≤ 16</td>
<td>-21 ≤ k ≤ 21</td>
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<tr>
<td>Reflections collected</td>
<td>20761</td>
<td>10945</td>
<td>18429</td>
</tr>
</tbody>
</table>

154
5.4.1.3 Closer Look at the Mechanism: More Evidence for Step-Wise Route

In Section 5.3 (Scheme 5.14) based on the work by Zubkov and co-workers, the chloro compound 413 was the major product. We suggested this result might be due to more stability of the carbocation intermediate 415 (compared to 414). If a [4+2] cycloaddition mechanism predominantly occurs, compound 412 will be expected to be the major product because of its less steric hindrance. However, this example cannot resolve all the issues about the mechanism simply because both products were observed. As seen above, although compounds 428 and 429 were formed with complete diastereoselection, compound 430 was afforded with complete regio- and diastereoselectivity. This regioselectivity cannot be explained by the concerted hetero Diels-Alder reaction as both 430 and 431 expected to be observed. As a matter of fact, due to steric hindrance, compound 431 is expected to be the major product. For a better explanation for this observation, a more detailed step-wise mechanism is presented in Scheme 5.19. Intermediate 433 was initially formed from Schiff base 432 and cyclopentadiene. The electron demanding allylic carbocation 433 is stabilized by neighboring group R2 on the aromatic ring affording 434. Re-aromatization on 434 gives the product 435. Carbication 433 should not be predominate intermediate unless by assistance from R2.
On the other hand, less crowded allylic carbocation 436 (Scheme 5.20) would generate tetrahydroquinoline 437 exclusively. Concerted [4+2] cycloaddition route would afford a mixture of regioisomeric products due to free N-Ar bond rotation prior to addition. Observation by other chemists such as Zubkov, showed mixtures of products were formed which overweighs neither of the explained mechanisms.

The only remaining possibility for the unique formation of 430 is the step-wise route through carbocation 438 illustrated in Scheme 5.21. Non-bonding pairs of
electrons in Oxygen in keto group theoretically can stabilize 438 and make it the predominant carbocation intermediate. In our performed reaction, in fact, 438 must be the only generated carbocation. Electron rich neighboring groups orient in close proximity with allylic carbocation. Another evidence for this conclusion will be presented in Section 5.4.2.2.

**Scheme 5.21**

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

**Scheme 5.22**
5.4.2 Synthesis of Tetrahydroquinoline-Derived Penta- and Hexacycles

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

![Figure 5.9 One-pot Synthesis of Cyclopenta[c]isoindolo[2,1-a]quinoline System](image)

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

3-Ethyl-11-oxo-cyclopenta[c]isoindolo[2,1-a]quinoline-carboxylate 443 (Scheme 5.23) was synthesized by a multicomponent reaction using ethyl-4-aminobenzoate, 2-carboxybenzaldehyde, and cyclopentadiene in the presence of trifluoroacetic acid. Acetonitrile as the solvent and other conditions are similar for preparing tricyclic compounds in Section 5.4.1.2. Although the reaction took 40 hours to complete, only one product was observed by TLC.
Crude mass spectrum showed a distinct peak at 346.3 corresponding to M+1. After purification, structural elucidation of this compound was performed using 1D NMR (\(^1H\) and \(^{13}C\)), 2D NMR (COSY, HSQC), and finally by X-ray crystallography. The pattern observed in 1D and 2D spectra were similar to those for compound 428-430 (Figure 5.5 and 5.7). However, the difference appeared in \(^{13}C\)-NMR by finding an extra peak for carbonyl group (in \(\gamma\)-lactam) around 166.8 ppm. Product itself was in a form of crystalline solid (white in color). We recrystallized compound 443 and took its X-ray diffraction. X-ray structure of our pentacyclic compound presents in Figure 5.10.

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

Crystal data for this compound is provided in Table 5.3.
Exploring the regioselectivity of this reaction and comparing the outcome with the previous Pavarov reaction in the synthesis of compound 430 was our next stage. As shown in Figure 5.6, complete regioselectivity on the aromatic ring of 430 was observed. This time we used 2-aminonaphthalene instead as our amine but the

<table>
<thead>
<tr>
<th>Table 5.3 Crystal Data for Compound 443</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identification code</strong></td>
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<tr>
<td><strong>Empirical formula</strong></td>
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<tr>
<td><strong>Formula weight</strong></td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
</tr>
<tr>
<td><strong>Space group</strong></td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
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<tr>
<td>a = 13.299(5) Å</td>
</tr>
<tr>
<td>b = 8.521(3) Å</td>
</tr>
<tr>
<td>c = 14.969(5) Å</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td><strong>Z</strong></td>
</tr>
<tr>
<td><strong>Density (calculated)</strong></td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
</tr>
<tr>
<td><strong>θ range for data collection</strong></td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
</tr>
<tr>
<td><strong>Independent reflections</strong></td>
</tr>
<tr>
<td><strong>Completeness to theta = 29.05°</strong></td>
</tr>
<tr>
<td><strong>Absorption correction</strong></td>
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<td><strong>Refinement method</strong></td>
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<td><strong>Data / restraints / parameters</strong></td>
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<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
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<td><strong>Final R indices [l&gt;2sigma(l)]</strong></td>
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<td><strong>R indices (all data)</strong></td>
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<tr>
<td><strong>Largest diff. peak and hole</strong></td>
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</table>
same reagents and conditions (Scheme 5.24). TLC showed an appearance of just one product. After purification, complete data analysis was performed using mass spectra, 1D NMR (¹H, ¹³C, DEPT), 2D NMR (COSY, HSQC, HMBC), and finally by X-ray crystallography which confirmed our synthesis (444). The full name of this hexacyclic compound which its commercial form has no defined stereochemistry, found to be '4c,7,7a,7b-tetrahydro-12H-benzo[f]cyclopenta[c]-isoindolo[2,1-a]quinoline-12-one'. No reported synthesis of this commercial compound was found.

Scheme 5.24

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

This compound was re-crystallized for the purpose of providing suitable crystal form for the X-ray diffraction. X-ray structure and crystal data of this hexacyclic compound presents in Figure 5.12 and Table 5.4, respectively.
Figure 5.12 X-ray Structure of Compound 444

Table 5.4 Crystal Data for Compound 444

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<td>Temperature</td>
<td>125(2) K</td>
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<td>Wavelength</td>
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<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
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<td>Space group</td>
<td>P2(1)2(1)2(1)</td>
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<tr>
<td></td>
<td>c = 14.410(18) Å, γ = 90°</td>
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<td>0.277 and -0.263 eÅ$^{-3}$</td>
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### 5.4.2.2 Mechanistic View

It seems reasonable if we assume this tandem reaction contains; a) Schiff base preparation from nucleophilic attack of amine to more reactive carbonyl function of 2-carboxybenzaldehyde, i.e., aldehyde, b) reaction of Schiff base with cyclopentadiene, and c) intramolecular condensation (dehydration) of the formed secondary amine (located at tetrahydroquinoline core) to o-carboxylic acid function resulted in the formation of a γ-lactam ring meaning the construction of whole polycyclic system. This mechanism, however, may simply be explained by a Povarov/cyclocondensation tandem reaction. In Section 5.4.1.3, we provided an evidence for a step-wise route through a stabilized carbocation 433. If R$_2$ could stabilize 433 by keeping allylic carbocation in close proximity to itself, we would expect to observe 435 exclusively.

**Scheme 5.25**

![Scheme 5.25](image)

As we explained before, carbocation 438 will afford 430 (only) by its ability to self-stabilizing (Scheme 5.26). The similar approach may apply for product 444.
by forming self-stabilized carbocation 446. However, in this case there is no non-bonding pair(s) of the electron but only the electron-rich environment within naphthalene's second ring. This complete regioselectivity cannot be rationalized by a concerted cycloaddition mechanism.

Scheme 5.26

5.4.2.3 Further Exploration: Stereoselective Reactions

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

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

Figure 5.14 Concave and Convex faces in 443

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

Scheme 5.27

NMR data analysis and X-ray crystallography confirmed our proposed structure. Since the proton pattern in 446 is quite different from previous compounds, especially on cyclopenta[c] ring, we look at the aliphatic protons of the molecule more closely. As shown in Figure 5.15, aliphatic protons are numbered and COSY spectrum showing the hydrogen's relationships (in different colors), is provided. Finally, the assignment for the aliphatic protons is presented in $^1$H-NMR. Correlations between H$_6$-H$_5$ and also H$_6$-H$_{3a}$ appeared weakly (showed in dotted lines).

This reaction was highly facial selective since only β-epoxide was observed. The epoxide ring added two more stereogenic centres to 443, so this number for hexacyclic 446 has now reached to five.
Figure 5.15 Aliphatic Protons Assignment for 446 Using $^1$H-NMR and COSY
As the most reliable and precise structure determination, X-ray crystallography was performed on this compound. X-ray structure of polycyclic 446 as well as X-ray data have provided in Figure 5.15 and Table 5.5, respectively.

![Figure 5.15 X-ray Structure of Compound 446](image)

Table 5.5 X-ray Data for Compound 446

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<tr>
<td>Wavelength</td>
<td>0.71070 Å</td>
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<td>Crystal system</td>
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<td>Space group</td>
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</tr>
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<td>a</td>
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<tr>
<td>b</td>
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<tr>
<td>c</td>
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<td>Volume</td>
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<tr>
<td>Z</td>
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<tr>
<td>Density (calculated)</td>
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</tr>
<tr>
<td>Crystal size</td>
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</tbody>
</table>
Since epoxide-opening reaction provides, at least two diversity sites, any nucleophile capable of the reaction can be considered. For ring opening, we decided to use p-bromoaniline; it is a good nucleophile having a symmetrical structure (easier for NMR assignment) which provides an additional secondary amine for diversification purpose. However, we did not know about the regioselective nature of this reaction. By looking at the structure of epoxide 446, especially its X-ray (Figure 5.15), it seems there is a difference for α-nucleophilic attack between two side of the epoxide ring. However, the size of the nucleophile also plays an influential role in the regioselectivity. As showed in Scheme 5.28, nucleophilic attack from the right side of the epoxide (green arrow) would give 447 and from the left (red arrow) would afford its regioisomer (448). Without any further guess, we performed the reaction using p-bromoaniline in the presence of the Lewis acid (boron trifluoride). One single compound appeared as the product meaning the complete regioselectivity was achieved.
Compound 447, the most complex cyclic compound in our research, has some interesting features:

a) it has 5 stereogenic centres,

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

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

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

e) reaction performed in only 3 stages, and finally

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

Scheme 5.28
Since in this case we were not able to get the X-ray structure, we should assign the molecule using NMR. For this task, we used $^1$H-NMR, $^{13}$C-NMR, COSY, and HSQC. For the complete structure determination, we worked on aromatic and aliphatic protons separately similar to the previous compounds. Then, combination of those provided us the complete assignment. Interesting 'problem solving' was performed but this stage will not be fully explained with details because of prevention from repeating. Final $^1$H-NMR with integration is presented in Figure 5.16 (NMR spectrum has moved up slightly for more clarity). All hydrogens were numbered except OH and NH, which could not accurately find. On the other hand, peaks corresponded to solvents (chloroform, ethyl acetate, and hexane) did not integrate. Based on full information we gathered, we can now claim the epoxide ring opening reaction on 446 proceeded regioselectively (and stereospecific) since pure product contains only 447.
Figure 5.16 Protons Assignment and $^1$H-NMR Spectrum for Compound 447
5.5 Future Work

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

Scheme 5.29

[Diagram showing the synthesis process]

Library designation has already been performed. The above solid phase synthesis and any successful results on library generation are expected to communicate as soon as they are available.
6: Natural Product-inspired, Small Molecule Modulators of Protein-Protein Interactions Involved in Cell Death Pathways

6.1 From ‘Small Molecules’ to ‘Cancer Drugs’

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

Figure 6.1 Disordered Cell Death Causes Abnormality\textsuperscript{251}
Due to the importance of protein-protein interactions, the ability to interfere with these processes is means for therapeutic intervention because then it becomes possible to modify protein functioning within the cell. To affect the function of selected proteins, small organic modulators of protein-protein interactions can be utilized. In addition to drug development and validation, these cell permeable molecules will allow further research into the physiological cellular processes (such as abnormal signal transduction). Numerous successes have come from the discovery of these protein-protein interaction modulators, most importantly in the field of cancer. As indicated in Chapter 1, several protein-protein interactions involved with apoptosis are subjected to inhibition by small organic molecules and have helped define proteins such as the Bcl-2 family as possible drug targets. More specifically, the mitochondria appear to be a great target for small compounds that interfere with apoptosis.

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

In apoptosis, the design of small organic compounds that interfere with the interactions between the Bcl-2 family proteins will guide on the ways in which cells function and may actually lead to new successful drug therapies. Chemists
have developed several novel techniques to identify such modulators: high throughput techniques to obtain bioactive natural product-inspired small molecules (or diversity-oriented synthesis- see Chapter 1) and high throughput screening (HTS). In general, HTS uses automation and allows researchers to screen for biological responses in a high-throughput manner for specific activity, against libraries of molecules in a timely fashion. In other words, HTS is valuable to identify rapidly any active compounds, "hits", which modulate a specific cellular process in which case can be used as a starting point to understand protein-protein interactions. Both these tools as well as a combination of rational design have used to create modulators of protein-protein interaction. It is worth noting, however, that even though HTS has been very beneficial for such screenings, the fact still remains that this approach is distinct from the activity in a living organism, and conclusions about the reactivity of a specific small molecule may be incomplete. In addition, as discussed above, many challenges still remain for researchers to get a better picture of the whole process.

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

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

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

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

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

Having some structural information available for soluble Bcl-2, Bcl-XL, Mcl-1 by NMR and X-ray and knowing the protein-protein interactions with pro-apoptotic proteins (e.g. Bak, Bax and Bad) has provided a starting point in developing approaches to obtain small molecules. Using structural information for Bcl-2 and Bcl-XL, Fesik’s team at Abbott has been working for several years in developing
small molecules using the NMR fragment-based\textsuperscript{25}. Different binding domains of a protein target are individually screened by NMR to identify weak binders, called "active fragments". Using these fragments, various stitching approaches link them to get more potent lead compounds. Fesik's team successfully developed the synthesis of a lead compound, ABT 737 by first identifying two active fragments.

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

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

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

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

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

During the initial evaluation stage of this assay, a tetrahydroquinoline-based compound (in our lab), B2P199F1, was found to be an inhibitor of membrane permeabilization. Its activity was quite significant compared to compound NJ-307.
(also from our lab), which displayed no considerable modulator activity (Figure 6.4). This natural product-inspired compound B2P199F1, inhibits tBid-Bax which mediates pore formation. Although this is the opposite effect of what we actually would like to induce cell death in cancer cells, it is quite an interesting molecule for other fields such as neural degeneration.

![Figure 6.4 Identification of a small molecule inhibitor of membrane permeabilization](image)

In collaboration with McMaster University, all compounds will be screened using the HTS tools available at the McMaster Bio-photonics Facility. All compounds will also be screened using a liposome based dye release assay (Figure 6.5) to see whether they modulate the function of tBid or Bax. This dye release assay will determine if these small organic modulators will inhibit or activate these Bcl-2 families of proteins. In this assay, a fluorophore, ANTS (8-aminonaphthalene-1,3,6-trisulfonic acid) and a quencher, DPX (p-xylene-bis-pyridinium bromide) are submitted within a liposome. DPX acts to quench the fluorescence of ANTS but because of permeabilization of the mitochondrial membrane, these molecules are subsequently released and separated to allow dye fluorescence. This assay will permit measuring interactions between proteins within the membrane.
ANTS ~ 8-aminonaphthalene-1,3,6-trisulfonic acid
Highly fluorescent water soluble
(excitation 390 nm, emission 530 nm).

ANTS quenched by DPX

Figure 6.5 ANTS release assay for pore formation by Bax

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

As indicated above, assessment of membrane destabilizing property by small molecules would achieve by monitoring the release of liposomal inner content and typically, fluorescent dyes such as ANTS/DPX, are used as markers of inner content release. Most tetrahydroquinoline-based compounds prepared in this project and several other structurally similar compounds synthesized in other unfinished/unsuccessful studies were being tested with the methodology explained above to find the promising ‘hits’ as modulators of Bcl-2-membrane interactions. Structures of 52 compounds submitted for this assay have shown in Figure 6.6.
Several tetrahydroquinoline-based small molecules showed inhibitor activity against Bax. Although a number of stages should perform in order to attain a reliable 'hit', these preliminary results have demonstrated the potential capability of this kind of small molecules as modulators of protein-protein interactions. The diagrams illustrated in Figure 6.7 show the initial testing results obtained from four different tetrahydroquinoline-based compounds. The IC\textsubscript{50} [\textit{i.e.,} the half-maximal inhibitory concentration; the concentration of a substance that is required for 50% inhibition of a biological or biochemical function (in this case, 'protein binding') \textit{in vitro}] for compounds B4P050brut and SSB321A (diagram A and C in Figure 6.7, respectively) reported as around 10 \( \mu \text{M} \) and for compound SSB326A (diagram B) in a range of 5-10 \( \mu \text{M} \), whereas for compound B4P017brut (diagram D) was not assessable yet. Large error bars generally indicate solubility problems.
Figure 6.7 Tetrahydroquinoline-based Compounds as Bax Inhibitors

6.6 Closing Remarks

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

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

7.1 General Methods

The materials were obtained from commercial suppliers and used without purification. THF and CH$_2$Cl$_2$ were distilled under N$_2$ over sodium/benzophenone and CaH$_2$ respectively. All NMR experiments were recorded on an AC-BRÜKER instrument (400 MHz). Unless otherwise noted, proton and carbon chemical shifts are reported in ppm using residual CHCl$_3$ as an internal standard at 7.26 and 77.0 ppm respectively. Analysis by mass spectrometry was performed on a VG Quattro I (Micromass) mass spectrometer equipped with pneumatically-assisted electrospray ionization source, operating in positive mode. The enantiomeric excess was determined by chiral HPLC, Hewlett-Packard (Agilent) 1090 LC equipped with Diode Array Detector and CHIRACEL-OD column. The HPLC spectra were recorded on a Gilson Combinatorial Chromatography System with 215 Liquid Handler / Injector and equipped with a Vydac C-18 Monomeric column and a Diode Array Detector.

7.2 X-ray crystallography

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

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

![Structural formula of Compound 226]

To a solution of safrole (10 g, 61.73 mmol) in glacial acetic acid (40 mL) at 0°C, a solution (10:1 ratio) of nitric acid and sulfuric acid (10 mL) was added drop wise. After 2 hours at 0°C, ethyl acetate (350 mL) was added and the layers were separated. The combined organic layer was washed with water (4 x 250 mL) and saturated sodium bicarbonate solution (2 x 250 mL), dried over magnesium sulphate and then concentrated after filtration. Purification by column chromatography (20% ethyl acetate in hexanes) afforded 8.93 g (70%) of nitrosafrole (226) as a yellow solid. Rf: 0.53 (4:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 208.1 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.49 (s, 1H), 6.76 (s, 1H), 6.09 (s, 2H), 5.97 (ddt, $J$ = 13.5, 6.5, 6.4 Hz, 1H), 5.12 (dd, $J$ = 6.5, 1.4 Hz, 1H), 5.08 (dd, $J$ = 13.5, 1.4 Hz, 1H), 3.65 (d, $J$ = 6.4 Hz, 2H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 152.5, 146.0, 144.0, 132.0, 117.5, 111.0, 106.0, 103.0, 70.0, 38.0 ppm

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

![Structural formula of Compound 227]

A solution of 8.93 g (43.14 mmol) of 226 in 100 mL methanol was treated at 0°C with a stream of ozone via a sintered diffuser until the TLC showed disappearance of the starting material (~4 hours). Excess ozone was then removed under a positive flow of nitrogen. This was then followed by the addition of dimethylsulfide (9 mL, 118.0 mmol) and the mixture kept at room
temperature for one hour. After being stored in the freezer for overnight, the pale yellow crystals appeared. The solid was then filtered and washed with cold methanol. Recrystallization from methanol afforded pure product, **227** (8.56 g, 95%). \( R_f: 0.21 \) (4:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 280.1 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \( \delta = 9.83\) (s, 1H), 7.68 (s, 1H), 6.72 (s, 1H), 6.16 (s, 2H) and 4.06 (s, 2H) ppm. \(^{13}\)C-NMR: (100 MHz, CDCl\(_3\)) \( \delta = 197.3, 152.7, 148.1, 143.2, 125.9, 112.3, 106.5, 103.6, 49.2 \) ppm.

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

To a solution of **227** (8.56 g, 40.98 mmol) in dried dichloromethane (100 mL) was added (carboxymethene)triphenylphosphorane (18.56 g, 53.27 mmol) at room temperature. The reaction mixture was stirred until the starting material disappeared (4 h). The reaction was quenched with saturated ammonium chloride solution, washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) giving compound **228** as a yellow solid (82% trans, 16% cis, 9.38 g trans product). \( R_f: 0.81 \) (1:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 279.1 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \( \delta = 7.50\) (s, 1H), 7.04 (d, \( J = 15.6 \) Hz, 1H), 7.01 (s, 1H), 6.21 (dt, \( J = 7, 15.6 \) Hz, 1H), 6.13 (s, 2H), 4.21 (q, \( J = 7 \) Hz, 2H), 3.31 (dd, \( J = 1.5, 7 \) Hz, 2H), 1.31 (t, \( J = 7 \) Hz, 3H) ppm. \(^{13}\)C-NMR: (100 MHz, CDCl\(_3\)) \( \delta = 166.5, 152.3, 145.4, 130.3, 129.5, 123.5, 111.1, 106.3, 105.5, 103.4, 60.8, 36.6 \) and 14.6 ppm.

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

188
To a 1 L round-bottomed flask equipped with a magnetic stirrer, were added t-BuOH (170 mL), water (170 mL) and AD mix-α (47.27 g). To this mixture, methanesulfonamide (3.19 g, 33.62 mmol) was then added. The mixture is stirred at room temperature until both phases are clear and cooled to 0 °C. Compound 228 (9.37 g, 33.62 mmol) was then added to this mixture and further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time: approx. 40h). The reaction was quenched at 0°C by the addition of sodium sulfite (50.0 g), warmed to room temperature and further stirred for 1 hour. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2N KOH, dried over magnesium sulfate and then concentrated. Purification by flash chromatography (silica gel, 50% ethyl acetate in hexanes) gave pure diol 229 as a yellow oil (7.15 g, 68%). Rf: 0.19 (1:1, hexane:ethyl acetate). LRMS: MS (ES+) m/z = 313.1 (M+1). \(^1H\)-NMR: (400 MHz, CDCl₃) δ 7.56 (s, 1H), 6.88 (s, 1H), 6.12 (s, 2H), 4.32 (q, J = 7 Hz, 2H), 4.18 (dd, J = 2.5 Hz, 1H), 3.51 (s, 1H), 3.23 (d, J =1 Hz, 1H), 3.20 (dd, J = 5.5 & 9 Hz, 2H), 2.35 (d, J = 9.1 Hz, 1H) and 1.33 (t, J = 7 Hz, 3H) ppm. \(^13C\)-NMR: (100 MHz, CDCl₃) δ = 173.5, 152.2, 147.4, 143.7, 130.9, 112.2, 106.1, 103.6, 73.2, 73.0, 62.8, 38.4 and 14.6 ppm.

**Compound 230:** (2R,3S) ethyl-3-hydroxy-4-(6-nitrobenzo[d][1,3]dioxol-5-yl)-2-(tosyloxy)butanoate
To a stirred solution of diol 229 (7.15 g, 22.84 mmol) in dichloromethane (200 mL) at 0 °C under nitrogen was added triethylamine (4.17 mL, 29.69 mmol) followed by p-toluenesulfonyl chloride (4.35 g, 22.84 mmol). The solution was then stirred for 90 hours at 0°C, the reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the tosyl derivative 230 (9.38 g, 88 %) as an oil. Rf: 0.67 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 467.1 (M+1). 1H-NMR: (400 MHz, CDCl3) δ = 7.88 (d, J = 8.4 Hz, 2H), 7.51 (s, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 6.11 (d, J = 2.8 Hz, 2H), 4.99 (d, J = 3.3 Hz, 1H), 4.34 (bs, 1H), 4.13 (q, J = 7 Hz, 2H), 3.14 (m, 1H), 2.97 (m, 1H), 2.60 (s, 1H), 2.46 (s, 3H) and 1.21 (t, J = 7 Hz, 3H) ppm. 13C-NMR: (100 MHz, CDCl3) δ = 167.3, 152.3, 147.6, 145.9, 143.5, 133.3, 130.1, 128.7, 128.2, 112.3, 106.3, 103.4, 79.9, 72.3, 62.7, 37.7, 22.1 and 14.4 ppm.

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

![Compound 231](image)

To a solution of 230 (9.38 g, 20.08 mmol) in dry THF (250 mL), added oven dried potassium carbonate (5.54 g, 40.16 mmol) and Pd-C (1.87 g, 20% w/w - added under nitrogen). The mixture was then hydrogenated for 40 h (monitored by TLC). After completion of the reaction, the mixture filtered, washed several times with ethyl acetate and then concentrated. Column chromatography on silica gel (20% to 50% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative 231 as a yellow oil (4.35 g, 82%). Rf: 0.53 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 265.1 (M+1). 1H-NMR: (400 MHz, CDCl3) δ= 6.49 (s,1H), 6.24 (s,1H), 5.85 (s, 2H), 4.35 (q, J = 5.7 Hz, 1H), 4.27 (dq, J = 2.3 & 7 Hz, 2H), 3.89 (d, J = 6 Hz, 1H), 3.51 (s, 1H), 2.83 (dd, J = 4.8 and 15.3 Hz, 2H), 1.21 (t, J = 7 Hz, 3H) ppm.
1.49 (m, 1H) and 1.32 (t, J = 7 Hz, 3H) ppm. $^{13}$C-NMR-DEPT-135: (100 MHz, CDCl$_3$) δ = 109.8, 101.0, 97.1, 65.2, 62.1, 59.8, 33.8, and 14.6 ppm.

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

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

To a stirred solution of the amino alcohol obtained from the above reaction in anhydrous dichloromethane (40 mL) at 0°C, was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34 mL, 3.14 mmol). After stirring for 45 minutes at 0°C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate giving product 291 (630 mg, 54% over two steps) as a yellow oil. $R_f$: 0.09 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 307.1 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) δ = 6.48 (s, 1H), 6.16 (s, 1H), 5.95 (m, 1H), 5.83 (s, 2H), 5.39 (d, J = 17.7 Hz, 1H), 5.31 (d, J = 10.2 Hz, 1H), 4.65 (dt, J = 5.7, 1.3 Hz, 2H), 4.32 (m, 1H), 4.20 (m, 1H), 3.97 (q, J = 6.5 Hz, 1H), 3.46 (s, 1H), 2.89 (m, 1H) and 2.74 (m, 1H) ppm. $^{13}$C-NMR: (100 MHz,
Compound 292: (6R,7S)-allyl 6-((tert-butyldimethylsilyloxy)methyl)-7-hydroxy-7,8-dihydro[1,3]dioxolo[4,5-g]quinoline-5(6H)-carboxylate

To a stirred solution of 291 (630 mg, 2.05 mmol) in dichloromethane (10 mL) at 0°C was added imidazole (280.0 mg, 4.1 mmol) followed by TBDMSCI (370 mg, 2.46 mmol). The mixture was stirred at 0°C for additional 75 minutes. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with 10-20% ethyl acetate in hexanes afforded 700 mg (81%) of 292 as a yellow oil. \( R_f: 0.57 \) (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 421.2 (M+1). \( ^1H\)-NMR: (400 MHz, CDCl\( _3 \)) \( \delta = 6.97 \) (s, 1H), 6.59 (s, 1H), 5.96 (m, 1H), 5.92 (d, \( J = 7.5 \) Hz, 2H), 5.32 (d, \( J = 17 \) Hz, 1H), 5.24 (d, \( J = 10.6 \) Hz, 1H), 4.68 (m, 2H), 4.26 (m, 1H), 3.96 (m, 1H), 3.88 (m, 1H), 3.46 (t, \( J = 9 \) Hz, 1H), 2.82 (d, \( J = 3 \) Hz, 1H), 2.79 (d, \( J = 4.5 \), 14 Hz, 1H), 2.62 (m, 1H), 0.86 (s, 9H), 0.05 (d, \( J = 8.5 \) Hz, 6H) ppm. \( ^{13}C\)-NMR: (100 MHz, CDCl\( _3 \)) DEPT-135: \( \delta = 118.4, 101.5, 67.1, 64.6, 34.9 \) ppm (methylenes) and 155.1, 146.4, 145.1, 132.8, 130.4, 122.8, 107.8, 107.1, 71.9, 62.0, 26.2, 18.5, - 5.2 ppm

Compound 293: (6R,7S)-allyl 6-((tert-butyldimethylsilyloxy)methyl)-7-(pent-4-enoyloxy)-7,8-dihydro-[1,3]dioxolo[4,5-g]quinoline-5(6H)-carboxylate
To a stirred solution of 292 (690 mg, 1.65 mmol) in dichloromethane (50 mL) were added DIC (0.53 mL, 3.32 mmol), DMAP (20 mg, 0.166 mmol) and 4-pentenoic acid (0.26 mL, 2.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24h. After quenching the reaction with saturated ammonium chloride, the aqueous layer was extracted twice with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash chromatography using 10% ethyl acetate in hexanes afforded compound 293 (680 mg, 81%). Rf: 0.76 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 503.2 (M+1). ¹H-NMR: (400 MHz, CDCl₃) δ = 7.06 (s, 1H), 6.57 (s, 1H), 5.98 (m, 1H), 5.93 (d, J = 7 Hz, 2H), 5.81 (m, 1H), 5.34 (d, J = 17 Hz, 1H), 5.25 (d, J = 10.6 Hz, 1H), 5.16 (q, J = 5.5 Hz, 1H), 5.05 (d, J = 17 Hz, 1H), 5.00 (d, J = 10.6 Hz, 1H), 4.64-4.73 (m, 3H), 5.58 (d, J = 6.5 Hz, 2H), 2.96 (dd, J = 5.6, 15.6 Hz, 1H), 2.69 (dd, J = 6 & 16 Hz, 1H), 2.34-2.43 (m, 4H), 0.82 (s, 9H) and 0.01 (d, J = 10.6 Hz, 6H) ppm. ¹³C-NMR: (100 MHz, CDCl₃) δ= 172.6, 155.2, 146.5, 145.1, 136.9, 132.8, 130.7, 118.4, 115.9, 107.9, 106.9, 101.5, 70.0, 67.1, 62.3, 58.6, 34.0, 31.4, 29.2, 26.1, 18.4 and - 5.2 ppm
To a solution of 293 (670 mg, 1.33 mmol) in dichloromethane (25 mL) at 0°C under nitrogen were added tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.08 mmol) and morpholine (0.235 mL, 2.7 mmol). After stirring for 40 minutes at room temperature, dichloromethane was evaporated. The crude residue obtained was utilized in next reaction without purification. To a solution of above amine residue in dry dichloromethane (10 mL) at 0°C under nitrogen were added pyridine (0.22 mL, 2.7 mmol) and acryloyl chloride (0.137 mL, 1.62 mmol). After stirring at room temperature for 70 minutes, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted two times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded 340 mg compound 294 as an oil (53% for two steps). Rf: 0.28 (4:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 474.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 6.67 (s, 1H), 6.53 (m, 2H), 6.47 (s, 1H), 5.99 (s, 1H), 5.94 (s, 1H), 5.82 (m, 1H), 5.71 (d, $J$ = 12.1 Hz, 1H), 5.03-5.12 (m, 3H), 4.80 (s, 1H), 3.67 (d, $J$ = 4Hz, 2H), 2.97 (dd, $J$ = 5.5, 14.1 Hz, 1H), 2.58 (t, $J$ = 11.3 Hz, 1H), 2.36-2.46 (m, 4H), 0.76 (s, 9H) and - 0.03 (d, $J$ = 4.5 Hz, 6H) ppm.

**Compound 295**

To a solution of 294 (340 mg, 0.72 mmol) of in dry dichloromethane (340 mL) at room temperature under nitrogen was added 2nd generation of Grubbs catalyst (122 mg, 0.144 mmole, 0.2 equiv). After refluxing at 45°C for 1 hour under nitrogen, the reaction mixture was cooled to room temperature and the solvent was evaporated in vacuo. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded 320 mg compound 295 as an oil (50% for two steps). Rf: 0.28 (4:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 476.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 6.67 (s, 1H), 6.53 (m, 2H), 6.47 (s, 1H), 5.99 (s, 1H), 5.94 (s, 1H), 5.82 (m, 1H), 5.71 (d, $J$ = 12.1 Hz, 1H), 5.03-5.12 (m, 3H), 4.80 (s, 1H), 3.67 (d, $J$ = 4Hz, 2H), 2.97 (dd, $J$ = 5.5, 14.1 Hz, 1H), 2.58 (t, $J$ = 11.3 Hz, 1H), 2.36-2.46 (m, 4H), 0.76 (s, 9H) and - 0.03 (d, $J$ = 4.5 Hz, 6H) ppm.
evaporated. Purification of the residue by flash chromatography over silica gel using 20% ethyl acetate in hexanes afforded the 10-membered macrocycle derivative 295 (210 mg, 65%) of as a light green crystalline solid. Rf: 0.35 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 446.4 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 7.18\) (s, 1H), 6.57 (s, 1H), 6.28 (d, \(J = 11.5\) Hz, 1H), 5.96 (d, \(J = 11.5\) Hz, 2H), 5.85 (td, \(J = 11.6\) & 4.5 Hz, 1H), 5.41 (m, 1H), 4.38 (td, \(J = 8.2\) & 2.6 Hz, 1H), 3.49-3.55 (m, 2H), 3.00 (m, 1H), 2.82-2.87 (m, 2H), 2.61 (m, 1H), 2.17-2.23 (m, 2H), 0.87 (s, 9H), -0.03 (d, \(J = 4\) Hz, 6H) ppm. \(^13\)C-NMR: (100 MHz, CDCl\(_3\)); DEPT-135: \(\delta = 101.6, 60.6, 33.4, 29.0, 25.9\) ppm (methylene) and 172.4, 169.7, 146.1, 133.6, 128.9, 119.5, 128.6, 60.8, 32.0, 26.2, 26.1, 26.0, 25.7, 18.5, 5.2 ppm.

**Compound 296**

![Chemical Structure](image)

To a solution of benzene ethanethiol (0.336 mL, 2.5 mmol) in freshly distilled THF (9.0 mL) slowly at -78 °C was added \(n\)-butyl lithium (1.0 mL, 2.5 mmol). The mixture was stirred overnight (16 hours) at ambient temperature. To a stirred solution of 295 (20.0 mg, 0.045 mmol) in dry THF (10 mL) at -20 °C under nitrogen was added the lithium salt solution (0.36 mL, 0.09 mmol, 2 equiv) of the freshly prepared solution. After stirring at this temperature for 2 hours, a solution of saturated ammonium chloride was added and the aqueous layer extracted by dichloromethane. The combined organic layer was dried by magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography over silica gel using 10% ethyl acetate in hexanes afforded the hetero Michael product 296 (20 mg, 76 %) as a yellow oil. Rf: 0.60 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 584.2 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 7.29-7.33\) (m, 2H), 7.21-
7.25 (m, 3H), 6.65 (s, 1H), 6.35 (s, 1H), 5.97 (s, 2H), 5.26-5.30 (m, 1H), 3.71 (m, 1H), 3.50-3.55 (m, 2H), 3.39 (m, 1H), 2.99-3.05 (m, 1H), 2.90-2.93 (m, 2H), 2.84-2.86 (m, 1H), 2.80-2.83 (m, 2H), 2.60-2.69 (m, 2H), 2.56 (m, 1H), 2.38-2.43 (m, 1H), 1.85-1.94 (m, 2H), 0.89 (s, 9H), 0.03 (d, J = 11.3 Hz, 6H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) δ = 177.0, 170.6, 146.6, 140.6, 130.7, 128.9, 126.8, 120.1, 109.7, 109.2, 107.6, 107.1, 101.7, 68.0, 61.0, 58.1, 44.3, 42.6, 36.3, 33.5, 32.2, 29.2, 26.1, 18.5, 14.5 and -5.1 ppm.

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

![Structure of Compound 236](image)

To a suspension of (methoxymethyl)-triphenylphosphonium chloride (25.5 g, 72 mmol) in THF (175 mL) at 0°C was added dropwise potassium tert-butoxide (1.0M in THF, 150 mL, 150 mmol). The resulting mixture was stirred at 0 °C for 1 hour. A solution of 5- hydroxy-2-nitrobenzaldehyde (10.0 g, 60 mmol) in THF (100 mL) was added drop wise at 0°C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding water (200 mL) at 0°C. After removal of THF, the aqueous layer was acidified to pH 6 by adding a 2N HCl solution at 0°C and then extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, filtered and concentrated. Purification by column chromatography (25% ethyl acetate in hexanes) afforded 236 (11.2 g, 95%) as a yellow oil. R$_f$: 0.68 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 196.1 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) δ = 8.02 (d, J = 9.0 Hz, 1H), 7.05 (d, J = 12.8 Hz, 1H), 6.86 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.56 (d, J = 12.8 Hz, 1H), 5.47 (bs, 1H), 3.77 (s, 3H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) δ = 159.9, 152.9, 141.2, 135.9, 128.6, 113.8, 113.4, 101.7, 57.1 ppm.

**Compound 237:** 2-(5-hydroxy-2-nitrophenyl)acetaldehyde
To a solution of 236 (11.2 g, 57.5 mmol) in THF (150 mL) was added 1.5N HCl solution (300 mL). The mixture was then heated to 60°C and stirred overnight. The reaction mixture cooled to 0°C and neutralized with saturated sodium carbonate solution. After the THF removal, the aqueous layer was extracted with ethyl acetate (3 x 200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to afford 10.15 g (98%) of the crude aldehyde 237 as a solid (mp 101.8-103.0 °C). Rf: 0.53 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 180.1 (M+1). ¹H-NMR: (400 MHz, CDCl₃) δ = 9.78 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 6.97 (dd, J = 2.4 & 9.0 Hz, 1H), 6.91 (d, J = 2.4 Hz, 1H), 4.15 (s, 2H) ppm. ¹³C-NMR: (100 MHz, CDCl₃) δ= 198.0, 163.5, 142.1, 128.9, 120.9, 115.8, 49.5 ppm.

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

To a solution of 237 (10.15g, 56.0 mmol) in dry dichloromethane (200mL) was added (carboxymethelene)triphenylphosphorane (23.4g, 67.0 mmol) at room temperature. The reaction mixture was refluxed at 45°C until the starting material disappeared (TLC ~1h). The reaction was quenched with saturated ammonium chloride solution at room temperature, washed with water and brine. The organic phase was dried over magnesium sulfate. After solvent evaporation, the crude product was purified by flash column chromatography on silica gel (10-30% ethyl acetate in hexanes). The product 238 was obtained as a yellow solid (80% trans, 10% cis; 11.25 g trans product). Rf: 0.68 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 252.1 (M+1). ¹H-NMR: (400 MHz, CDCl₃) δ= 7.97 (d,
$J = 9 \text{ Hz, 1H}$, $7.12 \text{ (m, 1H)}$, $6.99 \text{ (m, 1H)}$, $6.74 \text{ (d, } J = 2.8 \text{ Hz, 1H)}$, $6.22 \text{ (m, 1H)}$, $5.84 \text{ (d, } J = 15.6 \text{ Hz, 1H)}$, $4.24 \text{ (q, } J = 7 \text{ Hz, 2H)}$, $3.86 \text{ (d, } J = 6.5 \text{ Hz, 1H)}$, $3.37 \text{ (d, } J = 7 \text{ Hz, 1H)}$, $1.33 \text{ (t, } J = 7 \text{ Hz, 3H)}$ ppm. $^{13}$C-NMR: $(100 \text{ MHz, CDCl}_3)$ $\delta = 167.9$, $161.1$, $146.4$, $142.0$, $136.5$, $128.4$, $123.1$, $118.9$, $115.4$, $61.7$, $37.6$, $14.5$ ppm.

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

To a solution of 238 (11.25 g, 44.8 mmol) in dry dichloromethane (150 mL) at $0^\circ \text{C}$ under nitrogen were added DIPEA (11.7 mL, 67 mmol) and MEMCl (10.4 mL, 67 mmol). After stirring for 2 hours at ambient temperature, the reaction mixture was quenched by a solution of saturated ammonium chloride. The aqueous layer extracted by dichloromethane and the combined organic layer dried over magnesium sulfate, filtered and concentrated in vacuo. Flash column chromatography with silica gel using 30% ethyl acetate in hexanes afforded 13.65 g (90%) of 239 as an oil. $R_f$: 0.69 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 340.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta = 8.02 \text{ (d, } J = 9 \text{ Hz, 1H)}$, $7.20 \text{ (m, 1H)}$, $7.06 \text{ (m, 1H)}$, $6.29 \text{ (m, 1H)}$, $5.80 \text{ (d, } J = 16 \text{ Hz, 1H)}$, $5.36 \text{ (m, 2H)}$, $4.20 \text{ (q, } J = 7 \text{ Hz, 2H)}$, $3.88 \text{ (d, } J = 6.5 \text{ Hz, 1H)}$, $3.82-3.86 \text{ (m, 2H)}$, $3.55-3.59 \text{ (m, 2H)}$, $3.39 \text{ (s, 3H)}$, $3.32 \text{ (d, } J = 7 \text{ Hz, 1H)}$ and $1.30 \text{ (t, } J = 7.5 \text{ Hz, 3H)}$ ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta = 171.4$, $161.3$, $145.3$, $136.3$, $127.9$, $123.7$, $119.7$, $116.3$, $115.3$, $93.7$, $71.8$, $68.6$, $61.1$, $59.5$, $37.6$, $14.6$ ppm.

**Compound 240:** (2R,3S)-ethyl 2,3-dihydroxy-4-(5-(((2-methoxyethoxy)methoxy)-2-nitrophenyl)butanoate
To a 1 L round-bottomed flask equipped with a magnetic stirrer, were added t-BuOH (200 mL), water (200 mL) and AD mix-α (56.4 g). To this mixture, methanesulfonamide (3.83 g, 40.27 mmol) was then added. The mixture is stirred at room temperature until both phases are clear and cooled to 0 °C. Compound 239 (13.65 g, 40.27 mmol) was then added to this mixture and further stirred vigorously at room temperature until TLC revealed the absence of the starting olefin (time: approx. 40h). The reaction was quenched at 0 °C by the addition of sodium sulfite (60.0 g), warmed to room temperature and further stirred for 1 hour. The reaction mixture was then extracted several times with ethyl acetate. The combined organic layer was washed with 2N KOH, dried over magnesium sulfate and then concentrated. Purification by flash chromatography (silica gel, 25-8% ethyl acetate in hexanes) gave pure diol as a yellow oil (240, 10.5 g, 70%; 90% ee determined by chiral HPLC OD column). Rf: 0.29 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 374.2 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 8.23 (d, J = 9.1 \text{ Hz}, 1\text{H}), 7.42 (d, J = 2.5 \text{ Hz}, 1\text{H}), 7.20 (dd, J = 2.5 \text{ and } 9.1 \text{ Hz}, 1\text{H}), 6.17 (d, J = 4\text{ Hz}, 1\text{H}), 5.42 (m, 1\text{H}), 5.37 (m, 2\text{H}), 5.15 (s, b, 1\text{H}), 3.86 (m, 1\text{H}), 3.83 (t, J = 4.6\text{Hz}, 2\text{H}), 3.55-3.59 (m, 2\text{H}), 3.36-3.40 (m, 1\text{H}), 3.36 (s, 3\text{H}), 3.03 (dd, J = 6.1 \text{ and } 17.5 \text{ Hz}, 1\text{H}), 2.74 (dd, J = 1.5 \text{ and } 18 \text{ Hz}, 1\text{H}), 1.94 (bs, 1\text{H}) \text{ and } 1.32 (m, 3\text{H}) \text{ ppm.} \(^{13}\)C-NMR: (100 MHz, CDCl\(_3\)) \(\delta = 174.9, 162.1, 133.4, 128.3, 117.5, 116.1, 93.7, 82.6, 71.8, 69.8, 68.6, 59.4, 38.7, 14.5 \text{ ppm.} \)
**Compound 241**: (2R,3S)-ethyl 3-hydroxy-4-(5-((2-methoxyethoxy)methoxy)-2-nitrophenyl)-2-(tosyloxy)butanoate

![Structural formula of Compound 241]

To a stirred solution of diol 240 (10.5 g, 28.15 mmol) in dichloromethane (100 mL) at 0 °C under nitrogen was added triethylamine (5.9 mL, 42.2 mmol) followed by p-toluenesulfonyl chloride (5.37 g, 28.14 mmol). The solution was then stirred for 90 hours at 0°C, the reaction mixture was diluted with dichloromethane and water, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded the tosyl derivative 241 (13.0 g, 88 %) as an oil. Rf: 0.37 (1:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 528.3.1 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) δ = 8.05 (d, J= 9.1 Hz, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.01-7.06 (m, 2H), 5.33 (q, J= 7.1 Hz, 2H), 5.02 (d, J = 3 Hz, 1H), 4.37 (bs, 1H), 4.12-4.18 (m, 2H), 3.81 (t, J = 4.5 Hz, 2H), 3.54 (t, J = 4.5 Hz, 2H), 3.34 (s, 3H), 3.21 (m, 1H), 3.05 (m, 1H), 2.73 (d, J = 8.1 Hz, 1H), 2.46 (s, 3H) and 1.20 (t, J = 7 Hz, 3H) ppm. \(^1^3\)C-NMR: (100 MHz, CDCl\(_3\)) δ = 167.3, 161.1, 145.8, 143.4, 136.0, 133.6, 130.1, 128.5, 128.1, 120.6, 118.4, 116.9, 115.5, 93.6, 80.1, 72.0, 68.6, 62.6, 60.8, 59.4, 38.2, 21.7, 14.3 ppm.

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

![Structural formula of Compound 51]
To a solution of 241 (13.0 g, 24.77 mmol) in dry THF (250 mL), were added oven dried potassium carbonate (6.84 g, 49.5 mmol) and 10% Pd-C (1.87 g, 20% w/w, added under nitrogen). The mixture was then hydrogenated for 30 h (monitored by TLC). After completion of the reaction, the mixture was filtered, washed several times with ethyl acetate and then concentrated. Column chromatography on silica gel (20%-70% ethyl acetate in hexanes) afforded the tetrahydroquinoline derivative 51 as an oil (6.8 g, 84%). Rf: 0.56 (1:3, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 326.3 (M+1). 1H-NMR: (400 MHz, CDCl3) δ = 7.58 (d, J = 8.5 Hz, 1H), 7.00 (dd, J = 2.5, 8.5 Hz, 1H), 6.94 (s, 1H), 5.31 (d, J = 2.5 Hz, 2H), 5.17 (m, 1H), 4.83 (t, J = 6.5 Hz, 1H), 4.47 (dq, J = 1.8, 7.2 Hz, 2H), 3.85 (t, J = 4.8 Hz, 2H), 3.58 (t, J = 4.8 Hz, 2H), 3.40 (s, 3H), 3.05-3.09 (m, 2H), 1.63 (bs, 1H), 1.46 (t, J = 7 Hz, 3H) ppm. 13C-NMR: (100 MHz, CDCl3) δ = 165.8, 158.9, 155.9, 136.9, 131.5, 128.5, 116.5, 115.6, 93.7, 72.0, 68.3, 62.8, 62.2, 59.5, 32.9, 14.7 ppm.

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

To a stirred solution of 51 (1.0 g, 3.08 mmol) of in anhydrous THF (30 mL) at 0°C under nitrogen was added lithium borohydride (2 M in THF, 3.08 mL, 6.16 mmol). After stirring for 1.0 h at room temperature under nitrogen, the reaction was quenched slowly with saturated aqueous ammonium chloride. Following evaporation of THF, the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. After evaporation of the solvent, the residue was used directly for the next step without further purification. To a stirred solution of the amino alcohol
obtained from the above reaction in anhydrous dichloromethane (20 mL) at 0°C, was added pyridine (0.25 mL, 3.14 mmol) and allyl chloroformate (0.34 mL, 3.14 mmol). After stirring for 40 minutes at 0°C, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with hexanes and ethyl acetate giving product 300 (880 mg, 78% over two steps) as a yellow oil. Rf: 0.48 (1:4, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 368.1 (M+1). 1H-NMR: (400 MHz, CDCl3) δ = 7.34-7.50 (m, 1H), 6.90 (d, J = 9.5 Hz, 1H), 6.84 (s, 1H), 5.84-6.01 (m, 1H), 5.33 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 9.6 Hz, 1H), 5.24 (s, 2H), 4.71 (td, J= 5.1 and 13.6 Hz, 1H), 4.62-4.67 (m, 1H), 4.59 (d, J = 5.5 Hz, 1H), 4.24-4.32 (m, 1H), 4.11-4.19 (m, 1H), 3.94-4.02 (m, 1H), 3.83 (t, J = 5.1 Hz, 2H), 3.58 (t, J = 4.3 Hz, 2H), 3.39 (s, 3H), 2.85-2.93 (m, 1H) and 2.72-2.80 (m, 1H) ppm.

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

To a stirred solution of 300 (880.0 mg, 2.4 mmol) in dichloromethane (20 mL) at 0°C was added imidazole (326.0 mg, 4.8 mmol) and TBDMSCI (370 mg, 2.46 mmol). The mixture was stirred at 0°C for additional 25 minutes. The reaction was quenched with saturated ammonium chloride and the aqueous layer was extracted three times with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and then concentrated in vacuo. The residue was purified by column chromatography over silica gel with 20% ethyl acetate in hexanes afforded 960 mg (83%) of 301 as a yellow oil. Rf: 0.84 (1:4,
hexane: ethyl acetate). LRMS: MS (ES+) m/z = 482.3 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.38 (d, $J$ = 8 Hz, 1H), 6.90 (dd, $J$ = 2.8 and 9 Hz, 1H), 6.87 (s, 1H), 5.96 (m, 1H), 5.33 (d, $J$ = 17.5 Hz, 1H), 5.25 (s, 2H), 5.23 (m, 1H), 4.69 (qd, $J$ = 5.5 Hz, 2H), 4.29 (m, 1H), 4.01 (m, 1H), 3.94 (m, 1H), 3.84 (t, $J$ = 4.5 Hz, 2H), 3.58 (t, $J$ = 4.5 Hz, 2H), 3.46 (t, $J$ = 9.3 Hz, 1H), 3.40 (s, 3H), 2.88 (m, 1H), 2.78 (bs, 1H), 2.71 (m, 1H), 0.87 (s, 9H) and 0.06 (d, $J$ = 11.3 Hz, 6H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 155.1, 154.7, 132.8, 131.0, 130.7, 126.4, 118.3, 115.9, 115.1, 94.1, 72.0, 71.7, 68.0, 67.0, 64.8, 61.9, 59.4, 34.9, 26.2, 18.5, -5.1 ppm.

**Compound 302:** (2R,3S)-allyl 3-(allyloxy carbonyloxy)-2-((tert-butyldimethylsilyloxy)-methyl)-6-((2-methoxyethoxy)methoxy)-3,4-dihydroquinoline-1(2H)-carboxylate

![Chemical Structure](image)

To a stirred solution of 301 (960 mg, 2.0 mmol) in anhydrous dichloromethane (30 mL) at room temperature was added pyridine (0.323 mL, 4.0 mmol) and allylchloroformate (0.437 mL, 4.0 mmol). After stirring for 48 hours at room temperature, the reaction was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was dried with anhydrous magnesium sulfate, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel with hexanes and ethyl acetate and afforded 960 mg (85%) of the product 302 as a yellow oil. R$_f$: 0.74 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 566.3 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.47 (s, 1H), 6.91 (dd, $J$ = 2.5, 9 Hz, 1H), 6.84 (d, $J$ = 2.5 Hz, 1H), 5.93-5.98 (m, 2H), 5.35 (m, 1H), 5.30 (m, 1H), 5.24 (s, 2H), 5.20-5.25 (m, 2H), 5.08 (m, 1H), 4.79 (q, $J$ = 5 Hz, 1H), 4.68 (qd, $J$ = 5.5 Hz, 2H), 4.63 (d, $J$ = 5.5 Hz, 2H), 3.83 (t, $J$ = 4.5 Hz, 2H),...
3.65 (m, 1H), 3.60 (m, 1H), 3.58 (t, J= 4.5 Hz, 2H), 3.40 (s, 3H), 3.08 (m, 1H), 2.88 (m, 1H), 0.81 (s, 9H), -0.01 (d, J= 8.5 Hz, 6H) ppm. 13C-NMR: (100 MHz, CDCl3) δ= 155.1, 154.5, 132.9, 131.9, 131.3, 126.4, 119.3, 118.2, 116.0, 115.4, 94.1, 73.7, 72.0, 70.1, 68.9, 68.0, 67.0, 62.4, 59.4, 58.2, 31.4, 26.1, 18.4, 10.6, -5.2 ppm.

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

![Chemical Structure](image)

To a stirred solution of 302 (960 mg, 1.7 mmol) and zinc bromide (1.9 g, 8.5 mmol) in dichloromethane (50 mL) under nitrogen was stirred at room temperature for 24 hours. After filtration and evaporation of the solvent, purification was carried out by column chromatography over silica gel using 20-50% ethyl acetate in hexanes giving the free phenol 303 (480 mg, 60%). Rf: 0.24 (2:1, hexane: ethyl acetate). LRMS: MS (ES+) m/z = 478.4 (M+1). 1H-NMR: (400 MHz, CDCl3) δ = 7.41 (s, 1H), 6.68 (dd, J= 2.8 and 8.8 Hz, 1H), 6.58 (d, J = 2.5 Hz, 1H), 5.91-6.02 (m, 2H), 5.33-5.41 (m, 2H), 5.32 (m, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.24 (d, J = 10.5 Hz, 1H), 5.05 (q, J = 5.5 Hz, 1H), 4.78 (q, J = 4.0 Hz, 1H), 4.69 (qd, J = 5.5, 13.5 Hz, 2H), 4.64 (d, J = 5.5 Hz, 2H), 3.59-3.64 (m, 2H), 3.04 (m, 1H), 2.84 (m, 1H), 0.82 (s, 9H) and -0.01 (d, J= 7 Hz, 6H) ppm. 13C-NMR: (100 MHz, CDCl3) δ= 155.3, 154.7, 153.2, 132.8, 131.8, 129.9, 126.6, 119.4, 118.2, 115.0, 114.4, 73.9, 68.9, 67.1, 62.4, 58.3, 31.3, 26.1, 18.4, -5.2 ppm.
Compound 308

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

Compound 308’

To a suspension of resin 308 (61.0 mg) in methanol (2.5 mL) was added NaOMe (0.4 mL, 0.2 mmol, 0.5 M in methanol) at room temperature. The mixture was stirred gently for 8 hours. Following this, the resin was filtered and then washed
with methanol (x 3), DMF (x 3), water (x 3), methanol (x 3), dichloromethane (x 3) and dried under vacuum.

**Compound 309**

\[
\begin{array}{c}
\text{Alloc} \quad \text{OTBS} \\
\end{array}
\]

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

**Compound 309'**

\[
\begin{array}{c}
\text{H} \quad \text{OTBS} \\
\end{array}
\]

To a suspension of resin 309 obtained from the previous reaction in DCM (3.0 mL) was added tetrakis(triphenylphosphine) palladium(0) (33.0 mg, 0.03 mmol) dissolved in dry dichloromethane (3.0 mL). To this mixture were added a mixture of N-methylmorpholine (0.12 mL) and acetic anhydride (0.12 mL). The reaction mixture was bubbled under nitrogen for 18 hours. The resin was washed consecutively with DMF, water, methanol and dichloromethane (two times each) and then dried on a vacuum pump for overnight.
Compound 298

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

Compound 299

In a RB flask, the above resin 298 was suspended in dichloromethane (5.0 mL) under nitrogen. To this solution, was added a 2nd generation Grubbs catalyst (51 mg, 0.06 mmol) dissolved in dichloromethane (4.0 mL). The reaction mixture was warmed to 40 °C and stirred for 6 hours. The mixture was brought to room temperature and then the resin was washed with dichloromethane, methanol and dichloromethane (3 times each) and finally was dried over high vacuum pump.
The resin 299 was treated with 5% TFA in anhydrous dichloromethane (10 mL) at room temperature for 1 hour. Following this, it was washed twice with dichloromethane, filtered and the solvent evaporated. The residue was then purified by flash column chromatography over silica gel using 10% ethyl acetate and hexanes giving 12.0 mg of the final product 310 in overall 40% for 5 steps. 

\[ R_f: 0.28 \] (2:1, hexane: ethyl acetate). 

\[ ^1H-NMR: \ (400 \text{ MHz}, \text{CDCl}_3) \ \delta = 7.56 \text{ (m, 1H), 6.73 (dd, } J = 2.8 \& 8.8 \text{ Hz, 1H), 6.59 (d, } J = 3 \text{ Hz, 1H), 6.30 (d, } J = 11.6 \text{ Hz, 1H), 5.85 (td, } J = 4 \& 11.8 \text{ Hz, 1H), 5.41 (m, 1H), 4.40 (m, 1H), 3.46-3.56 (m, 2H), 3.04 (m, 1H), 2.92 (m, 1H), 2.84 (m, 1H), 2.61 (m, 1H), 2.32 (m, 1H), 2.29 (m, 1H), 0.87 (s, 9H) and -0.05 (d, } J = 4 \text{ Hz, 6H) ppm.} \]

\[ ^13C-NMR: \ (100 \text{ MHz, CDCl}_3) \ \delta = 172.5, 169.8, 162.8, 153.8, 134.9, 133.7, 130.6, 129.4, 128.9, 127.5, 115.2, 114.3, 66.7, 60.8, 33.4, 28.9, 26.1, 18.5, -5.2 \text{ ppm.} \]

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

To a stirred solution of 301 (1.2 g, 2.5 mmole) in 100mL dried dichloromethane at 0°C were added 0.8 mL (5 mmole) of DIC and 0.3 g (2.5 mmole) of DMAP followed by benzoic acid (0.457 g, 3.75 mmole). After being stirred for 24 hours
at room temperature, the reaction mixture was processed with dichloromethane and ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded 357 as a dark brown solid; 1.38 g (95%). Rf: 0.62 in 35% Ethyl acetate/Hexanes. Molecular Weight and Formula: 585.3, C31H43N08Si. LRMS: MS (ES+) m/z = 586.4 (M+1). \( ^1H\)-NMR: (400 MHz, CDCl\(_3\)) \( \delta = 7.94 \text{(d, } J=7.3 \text{ Hz, } 2H), 7.52 \text{(s, } 1H), 7.51 \text{(m, } 1H), 7.38-7.45 \text{(m, } 2H), 6.93 \text{(dd, } J= 3.0 \text{ & } 9.0 \text{ Hz, } 1H), 6.85 \text{(m, } 1H), 5.80-5.90 \text{(m, } 1H), 5.51 \text{(m, } 1H), 5.24 \text{(m, } 3H), 5.12 \text{(d, } J= 10.3 \text{ Hz, } 1H), 4.92 \text{(m, } 1H), 4.58 \text{(s, } 2H), 3.83 \text{(m, } 2H), 3.60-3.70 \text{(m, } 2H), 3.57 \text{(m, } 2H), 3.39 \text{(s, } 3H), 3.15 \text{(m, } 1H), 2.97 \text{(m, } 1H), 0.82 \text{(s, } 9H), -0.01 \text{(d, } J= 6.0 \text{ Hz, } 6H) \text{ ppm.} \( ^{13}C\)-NMR: (100 MHz, CDCl\(_3\)) \( \delta = 172.7, 166.1, 155.5, 154.5, 137.6, 133.5, 132.7, 131.0, 130.3, 128.9, 126.7, 118.4, 116.1, 115.3, 94.1, 72.0, 68.0, 67.0, 62.2, 59.4, 58.1, 50.6, 43.1, 26.1, 18.4, -5.2 \text{ ppm.}

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

![Chemical Structure](image)

To a solution of compound 357 (1.2 g, 2.5 mmole) in 100mL dried dichloromethane at 0°C while stirring were added 0.8 mL (5 mmole) of DIC and 0.3 g (2.5 mmole) of DMAP followed by benzoic acid (0.457 g, 3.75 mmole). After stirring for 24 hours at room temperature, the reaction mixture was processed with dichloromethane and ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography on silica gel (20% ethyl acetate in hexanes) afforded a dark brown solid; 1.38 g (95%). A solution of TBAF (2.5 mL, 2.5 mmole) and Acetic acid (0.15 mL) in THF was added to the solution of the ester compound (1.3 g, 2.2 mmole) in THF at 0°C. The reaction
mixture was stirred for 5 hours. The reaction was processed with ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated in vacum. Column chromatography on silica gel (50% ethyl acetate in hexanes) afforded compound 358 as a dark yellow oil; 1.02 g (98%). R<sub>f</sub> 0.13 in 35% Ethyl acetate/Hexanes. Molecular Weight and Formula: 471.4, C<sub>25</sub>H<sub>29</sub>NO<sub>8</sub> LRMS: MS (ES+) m/z = 472.4 (M+1) ¹H-NMR: (400 MHz, CDCl<sub>3</sub>) δ= 8.01 (d, J= 7.0 Hz, 2H), 7.58 (t, J= 7.8 Hz, 1H), 7.48 (m, 1H), 7.43 (t, J= 7.8 Hz, 2H), 6.97 (dd, J= 2.8 & 9.0 Hz, 1H), 6.89 (m,1H), 5.81-5.91 (m, 1H), 5.37 (m,1H), 5.27 (s, 2H), 5.23 (m,1H), 5.15 (d, J= 10.3 Hz, 1H), 4.96 (m,1H), 4.60 (d, J= 4.8 Hz, 2H), 3.85 (m, 2H), 3.73 (m, 1H), 3.63 (m, 1H), 3.60 (m, 2H), 3.40 (s, 3H), 3.13 (m,1H), 2.99 (m,1H) ppm. ¹³C-NMR: (100 MHz, CDCl<sub>3</sub>) δ= 166.2, 154.9, 133.7, 132.5, 130.4, 130.2, 130.1, 129.1, 128.8, 127.1, 126.8, 118.7, 116.1, 115.7, 94.1, 72.0, 68.1, 67.3, 62.3, 59.4, 23.9, 22.7, 21.3 ppm.

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

To a solution of the alcohol 358 (1 g, 2.1 mmol) in 100 mL DCM was added triethylamine (0.87 mL, 6.3 mmol) at 0°C. To the above solution, 875 mg SO₃.Py (6.3 mmol) in 6 mL DMSO was added over 10 min. The reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated ammonium chloride solution, extracted with DCM, and dried over anhydrous magnesium sulfate. The organic solvent was concentrated, and the crude aldehyde derivative was then directly subjected to the Wittig reaction. For making the Wittig reagent, to a solution of methyltriphenylphosphonium bromide (2 g, 4.76 mmol) in 20 mL of THF was added NaHMDS (3.5 mL, 3.5 mmol) at -78 °C. The reaction mixture was stirred for 1 h at 0°C and the solution turned to
yellow color. To this solution was added the former crude aldehyde (0.98 g, 2.09 mmol) in THF (50 mL) at -78 °C. The reaction mixture was warmed to 0°C and then stirred at this temperature for 20 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate, dried over magnesium sulfate, and concentrated. The crude residue was purified by column chromatography using 20% EtOAc in hexanes to obtain 540 mg (1.16 mmole) of compound 359 as a brown oil (55% for 2 steps). Rf: 0.69 in 50% Ethyl acetate/Hexanes Molecular Weight and Formula: 467.4, C26H29NO7 LRMS: MS (ES+) m/z = 468.4 (M+1). 

\[
{^1}H-NMR: (400 MHz, CDCl_3) \delta = 7.96 (d, J= 7.1 Hz, 2H), 7.61 (m, 1H), 7.55 (m, 1H), 7.40 (t, J= 7.5 Hz, 1H), 7.40 (t, J= 7.5 Hz, 2H), 6.96 (dd, J= 2.5 & 9.0 Hz, 1H), 6.83 (m, 1H), 5.70-5.81 (m, 2H), 5.45-5.50 (m, 2H), 5.30 (m, 1H), 5.28 (s, 2H), 5.17-5.23 (m, 2H), 5.09 (d, J= 10.0 Hz, 1H), 4.53 (m, 2H), 3.85 (t, J= 4.5 Hz, 2H), 3.59 (t, J= 4.5 Hz, 2H), 3.40 (s, 3H), 3.16 (m, 1H), 3.01 (m, 1H) ppm. \n\]

\[
{^{13}}C-NMR: (100 MHz, CDCl_3) \delta = 166.2, 155.7, 154.3, 133.6, 132.8, 132.6, 130.7, 130.2, 130.1, 128.7, 127.0, 126.8, 118.7, 118.5, 116.1, 115.4, 94.1, 72.0, 7.0.4, 68.0, 67.1, 59.4, 57.9, 30.1 ppm. \n\]

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

To a solution of 530 mg (1.13 mmole) of compound 359 in 25 mL dichloromethane at 0°C under nitrogen were added tetrakis-(triphenylphosphine)palladium(0) (76 mg, 0.07 mmole) and morpholine (0.2 mL, 2.26 mmole). After stirring for 3 hours at room temperature, dichloromethane was evaporated. The crude amine obtained was utilised in next reaction without
purification. To a solution of the provided amine in 10 mL dry dichloromethane at 0°C under nitrogen were added pyridine (0.18 mL, 2.26 mmole) and acryloyl chloride (0.14 mL, 1.69 mmole). After stirring at room temperature for 1 hour, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. Purification by flash chromatography over silica gel with 10% ethyl acetate in hexanes afforded 336 mg (0.77 mmole, 68% over 2 steps) of compound 360 as a dark brown oil. Rf 0.43 in 50% Ethyl acetate/Hexanes.

Molecular Weight and Formula: 437.4, C_{25}H_{27}NO_{6} LRMS: MS (ES+) m/z = 438.4 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\textsubscript{3}) \(^{\delta} = 7.95\) (d, \(J = 7.0\) Hz, 2H), 7.54 (m, 1H), 7.45 (m, 1H), 7.40 (t, \(J = 7.5\) Hz, 2H), 6.95 (dd, \(J = 2.8\) & 8.8 Hz, 1H), 6.91 (m, 1H), 6.55-6.62 (m, 1H), 6.40-6.49 (m, 1H), 5.78 (q, \(J = 5.0\) Hz, 1H), 5.74 (m, 2H), 5.41 (m, 1H), 5.30 (m, 1H), 5.27 (s, 2H), 5.21 (d, \(J = 10.0\) Hz, 1H), 3.85 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H), 3.18 (dd, \(J = 5.0\) & 17.1 Hz, 1H), 3.00 (dd, \(J = 4.3\) & 17.1 Hz, 1H) ppm. \(^{13}\)C-NMR: (100 MHz, CDCl\textsubscript{3}) \(^{\delta} = 166.1, 155.5, 137.6, 133.6, 133.2, 131.0, 130.9, 130.1, 129.7, 129.0, 128.8, 127.1, 126.8, 118.6, 116.8, 115.3, 94.1, 72.0, 68.2, 59.5, 31.2, 22.7, 21.3 ppm.

**Compound 54**

To a solution of 300 mg (0.73 mmole) of compound 308 in 300 mL anhydrous dichloromethane at room temperature under nitrogen was added 120 mg (0.146 mmole, 0.2 eq) of 1\(^{st}\) generation of Grubbs catalyst. After refluxing at 45°C for 2 hours under nitrogen, the solvent evaporated. Purification of the residue by flash chromatography over silica gel using 20% ethyl acetate in hexanes afforded 238
mg (0.58 mmole, 80%) of compound 54 as a brown oil. Rf: 0.58 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 409.4, C_{23}H_{23}NO_6 LRMS: MS (ES+) m/z = 410.4 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 8.28\) (d, \(J = 9.0\) Hz, 1H), 8.12 (d, \(J = 7.3\) Hz, 2H), 7.66 (t, \(J = 7.5\) Hz, 1H), 7.53 (t, \(J = 7.5\) Hz, 2H), 7.28 (m, 1H), 7.03 (dd, \(J = 2.5\) & 9.3 Hz, 1H), 6.93 (d, \(J = 2.5\) Hz, 1H), 6.38 (dd, \(J = 1.8\) & 6.0 Hz, 1H), 5.27 (s, 2H), 5.06 (td, \(J = 5.8\) & 10.5 Hz, 1H), 4.48 (dt, \(J = 1.8\) & 10.5 Hz, 1H), 3.84 (m, 2H), 3.58 (m, 2H), 3.53 (m, 1H), 3.40 (s, 3H), 3.11 (m, 1H) ppm. \(^{13}\)C-NMR: (100 MHz, CDCl\(_3\)) \(\delta = 168.9, 165.8, 154.0, 144.1, 134.1, 130.4, 130.2, 129.8, 129.1, 128.8, 125.1, 120.9, 116.9, 116.2, 94.1, 72.0, 71.3, 68.0, 64.0, 59.5, 34.8\) ppm. X-Ray within supplementary data.

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

To a stirred solution of 100 mg (0.21 mmole) 359 in 10 mL THF was added 0.21 mL (0.21 mmole) of a 1M LiAlH\(_4\) solution at 0°C under nitrogen. After stirring for 5 hours at room temperature, the reaction was quenched with methanol and ammonium chloride solution, extracted with DCM, and dried over anhydrous magnesium sulfate. The organic solvent was concentrated and the residue was purified by column chromatography using 50% ethyl acetate in hexanes to obtain 48 mg (1.16 mmole) of compound 359’ as a dark brown oil (82%). Rf: 0.18 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 279.3, C\(_{15}\)H\(_{21}\)NO\(_4\) LRMS: MS (ES+) m/z = 280.3 (M+1) \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 6.78\) (m, 2H), 6.51 (d, \(J = 8.5\) Hz, 1H), 5.80-5.88 (m, 1H), 5.34 (dt, \(J = 1.3\) & 17.0 Hz, 1H), 5.26 (dt, \(J = 1.3\) & 10.3 Hz, 1H), 5.17 (s, 2H), 3.93 (q, \(J = 6.0\) Hz, 1H), 3.84 (m, 2H), 3.71 (m, 1H), 3.59 (m, 2H), 3.40 (s, 3H), 2.99 (m, 1H), 2.78 (m, 1H) ppm \(^{13}\)C-
NMR: (100 MHz, CDCl$_3$) $\delta$ = 150.2, 138.0, 120.1, 118.7, 118.5, 116.7, 115.6, 115.2, 95.0, 72.1, 67.8, 67.2, 60.9, 59.4, 33.7 ppm.

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

To a stirred solution of 40 mg (0.143 mmole) amino alcohol 359' in 5 mL, 0.15 mL (0.15 mmole) anhydride acetic and 19 mg (0.15 mmole) DMAP were added at -10°C and stirred for 3 hours. The reaction was processed with ammonium chloride solution, dried over magnesium sulfate, filtered and concentrated. Column chromatography over silica gel (10% ethyl acetate in hexanes) afforded compound 361 as a dark oil; 42 mg (92%). $R_f$: 0.52 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 321.2, C$_{17}$H$_{23}$NO$_5$ LRMS: MS (ES+) m/z = 322.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 6.79 (m, 1H), 6.73 (s, 1H), 6.52 (d, $J$= 8.5 Hz, 1H), 5.80-5.89 (m, 1H), 5.32 (dt, $J$= 1.3, 17.0 Hz, 1H), 5.22 (d, $J$= 10.3 Hz, 1H), 5.17 (s, 2H), 5.10 (m, 1H), 3.87 (m, 1H), 3.84 (m, 2H), 3.59 (m, 2H), 3.40 (s, 3H), 3.04 (m, 1H), 2.81 (m, 1H), 2.07 (s, 3H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 170.9, 150.0, 137.5, 119.4, 118.3, 118.1, 116.8, 115.7, 115.2, 95.0, 72.1, 69.4, 67.8, 59.4, 57.9, 30.9, 21.7 ppm.

**Compound 55**
To a stirring solution of compound 361 (30 mg, 0.093 mmole) in 10mL dried dichloromethane at 0°C were added pyridine (0.016 mL, 0.186 mmole) and acryloyl chloride (0.017 mL, 0.186 mmole). After stirring at room temperature for 1 hour, the reaction was quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted with dichloromethane (2 x 2 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude product was utilized in the next reaction without purification. To the above crude compound in 50 mL anhydrous dichloromethane at room temperature under nitrogen was added 16 mg (0.019 mmole, 0.2 eq) of 1st generation of Grubbs catalyst. After refluxing at 45°C for 2 hours under nitrogen, the solvent evaporated. Purification of the residue by flash chromatography over silica gel using 50% ethyl acetate in hexanes afforded 20 mg (62% in 2 steps) of compound 55 as a dark brown oil. Rf: 0.31 (in 50% Ethyl acetate/Hexanes running 2 times). Molecular Weight and Formula: 347.2, C_{18}H_{21}NO_{6} LRMS: MS (ES+) m/z = 348.2 (M+1). \(^1\)H-NMR: (400 MHz, CDCl\(_3\)) \(\delta = 8.24 (d, J = 9.0 Hz, 1H), 7.22 (m, 1H), 7.00 (m, 1H), 6.90 (s, 1H), 6.36 (m, 1H), 5.25 (s, 2H), 4.75-4.82 (m, 1H), 4.31 (m, 1H), 3.83 (m, 2H), 3.58 (m, 2H), 3.48 (m, 1H), 3.40 (s, 3H), 2.94 (m, 1H), 2.19 (s, 3H) ppm. \(^13\)C-NMR: (100 MHz, CDCl\(_3\)) \(\delta = 170.1, 168.8, 154.0, 144.1, 130.4, 128.9, 125.1, 120.9, 116.8, 116.1, 94.0, 72.0, 70.9, 68.0, 63.7, 59.5, 34.7, 21.4 \text{ ppm.}

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

![Chemical Structure](image)

To a solution of compound 359 (25 mg, 0.053 mmol) in 10 mL of anhydrous CH\(_2\)Cl\(_2\)/methanol (9:1) solution was added p-toluenesulfonyl acid monohydrate (10 mg, 0.053 mmol), and the mixture was refluxed for 1.5 h. The reaction
mixture was cooled and concentrated under vacuum. The residue was dissolved in CH$_2$Cl$_2$ and washed with water (2 x 10 mL), and the organic layer was dried over anhydrous magnesium sulfate. Purification of the residue by flash chromatography over silica gel using 50% ethyl acetate in hexanes afforded 19 mg (95%) of compound 362 as a brown oil. R$_f$: 0.7 (in 50% Ethyl acetate/Hexanes). Molecular Weight and Formula: 379.2, C$_{22}$H$_{21}$NO$_5$ LRMS: MS (ES+) m/z = 380.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.92 (m, 2H), 7.80 (m, 2H), 7.63 (t, J= 7.5 Hz, 1H), 7.40-7.50 (m, 2H), 6.74 (dd, J= 3.0 & 8.8 Hz, 1H), 6.64 (m, 1H), 5.81-5.90 (m, 2H), 5.52 (m, 1H), 5.49 (m, 1H), 5.29 (m, 1H), 5.21 (m, 1H), 5.18 (m, 1H), 5.08 (d, J= 10.8 Hz, 1H), 4.51 (m, 2H), 3.16 (m, 1H), 3.00 (m, 1H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 166.6, 165.6, 154.2, 143.8, 133.5, 133.3, 130.6, 129.9 129.8, 128.8, 127.1, 127.0, 117.5, 117.3, 114.9, 113.9, 70.4, 66.5, 57.7, 20.9 ppm.

**Compound 363**

22 mg (0.04 mmole) of bromo wang resin (1.7 mmole/g) was preliminary washed several times with dichloromethane and DMF, then swollen 30 min in DMF. Onto the resin in 1mL of anhydrous DMF, 30 mg (0.08 mmole) of compound 362, predissolved in 1mL of anhydrous DMF was added. 12 mg (0.08 mmole) of sodium iodide and 26 mg (0.08 mmole) of cesium carbonate, both beforehand dried over night in the oven, were added to the solution. The mixture was bubbled vigorously by nitrogen while stirring for 48 hours. The resin was successively washed with Methanol (2 x 2 mL), DMF (2 x 2 mL), water (2 x 2 mL), Methanol (2 x 2 mL) and dichloromethane (3 x 2 mL) and then dried under vacuum for a few hours. The filtrates containing starting material in DMF were evaporated and the residue was dissolved in DCM. The organic phase was washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography on silica gel (25% ethyl acetate in
hexanes). 16 mg (0.044 mmole) of recovered starting material was obtained, giving an indirect yield for the loading step of 90%. The loading was found as 1.53 mmole/g of resin. 1 mg of the resin was subjected to cleavage in 5% TFA in dichloromethane for 1 hour. The resin was then filtered and washed several times with dichloromethane. The solvent was evaporated and dried under vacuum. ESI-MS showed only the expected compound and the TLC showed one major spot. Molecular Weight and Formula: 379.2, C_{22}H_{21}NO_{5} LRMS: MS (ES+) m/z = 380.2 (M+1). To 12 mg (0.032 mmole) of compound-resin, 6 mg (0.006 mmole) of tetrakis-(triphenylphosphine)palladium(0) dissolved in 2 mL of dry dichloromethane was added. To this mixture, 0.02 mL of N-methylmorpholine and 0.02 mL of anhydride acetic were added. The reaction mixture was bubbled under nitrogen for 15 hours and then was washed consecutively with DMF, water, methanol and dichloromethane (two times each with 2 mL). The resin was dried on vacuum pump over night to afford compound 13. No further purification was performed.

**Compound 365**

To a suspension of 8 mg (0.028 mmole) of resin compound 363' in dichloromethane (2 mL) were added 0.08 mL (0.54 mmole) of triethylamine and 0.034 mL (0.4 mmole) of acryloyl chloride. The mixture was bubbled by a flow of nitrogen for 24 hours. The resin was washed with DMF(2 × 2 mL), methanol (2 × 2 mL) and dichloromethane (3 × 2 mL) and then dried over high vacuum pump. Molecular Weight and Formula: 349.4, C_{21}H_{19}NO_{4} LRMS: MS (ES+) m/z = 350.4 (M+1).
To 8 mg (0.022 mmole) of the above resulted diene under nitrogen was added 4 mL of dichloromethane. To this, a solution of 10 mg (0.012 mmole) of 2nd Grubbs catalyst in 2 mL dichloromethane was added. The reaction mixture was warmed to 40°C and stirred for 6 hours. The mixture was cooled to room temperature and the resin was washed with dichloromethane, methanol and dichloromethane (3 times each with 2 mL) and finally was dried over high vacuum pump to afford compound 365. Molecular Weight and Formula: 321.3, C_{19}H_{15}NO_{4}. LRMS: MS (ES+) m/z = 322.3 (M+1)

**Compound 366**

Resin compound 365 was treated with 2 mL solution of 5% TFA in anhydrous dichloromethane at room temperature for 1 hour. Following this, the resin was washed two times with dichloromethane, filtered and the solvent was evaporated. The residue was then purified by flash column chromatography over silica gel using 10% ethyl acetate and hexanes. 4 mg (0.012 mmole, 42% over 3 steps) of compound 366 as a dark brown oil was afforded. Molecular Weight and Formula: 321.3, C_{19}H_{15}NO_{4}. LRMS: MS (ES+) m/z = 322.2 (M+1). \(^1^H\)-NMR: (400 MHz, CDCl\(_3\)) \(\delta\) = 8.34 (s, 1H), 8.15 (m, 3H), 7.72 (t, \(J = 7.5\) Hz, 1H), 7.59 (t, \(J = 7.5\) Hz, 2H), 7.52 (m, 1H), 6.77 (m, 2H), 6.30 (dd, \(J = 1.8\) & 6.0 Hz, 1H), 5.00 (td, \(J = 5.8\) & 10.5 Hz, 1H), 4.66 (dt, \(J = 1.5\) & 10.5 Hz, 1H), 3.46 (m, 1H), 3.16 (m, 1H) ppm. \(^1^C\)-NMR: (100 MHz, CDCl\(_3\)) \(\delta\) = 170.4, 168.4, 154.0, 145.2, 133.9, 130.2, 130.0, 129.4, 129.0, 125.6, 120.5, 115.7, 115.6, 114.3, 71.6, 63.7, 34.3 ppm.

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

218
To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-nitrobenzaldehyde (362 mg, 2.4 mmol) was added. After stirring for 4.5 hours (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.81 g of orange solid was afforded (93%). Rf: 0.56 (65:35, Hex.:ethyl acetate) Molecular Weight and Formula: 364.4, C_{21}H_{20}N_{2}O_{4} LRMS: MS (ES+) m/z = 365.2 (M+1) \^{1}H-NMR: (400 MHz, CDCl_3) \delta = 7.95 (d, J= 8.0 Hz, 2H), 7.79 (s, 1H), 7.66-7.73 (m, 2H), 7.50 (t, J= 8.0 Hz, 1H), 6.62 (d, J= 8.5 Hz, 1H), 5.97- 6.01 (m,1H), 5.67- 5.71 (m, 1H), 5.24 (d, J= 3 Hz, 1H), 4.35 (qd, J= 2.5 & 7.0 Hz, 2H), 4.19 (d, J= 9.0 Hz, 1H), 3.98 (bs, 1H), 3.33 (qd, J= 3.0 & 9.0 Hz, 1H), 2.61- 2.70 (m, 1H), 1.84 (dd, J= 8.5 & 15.5 Hz, 1H), 1.39 (t, J= 7.0 Hz, 3H) ppm \^{13}C-NMR: (100 MHz, CDCl_3) \delta = 167.1, 149.6, 137.1, 134.4, 134.1, 133.5, 131.6, 130.5, 130.1, 128.8, 125.5, 125.1, 124.9, 121.8, 115.8, 60.8, 53.1, 46.1, 43.9, 30.1, 14.7 ppm.

**Compound 429:** (3aR,4S,9bS)-ethyl 4-(4-cyanophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-carboxylate
To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 4-cyanobenzaldehyde (314 mg, 2.4 mmol) was added. After stirring for 2 hours (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.75 g of white solid was afforded (91%). Rf: 0.58 (65:35, Hex.:ethyl acetate) Molecular Weight and Formula:

344.4, C_{22}H_{20}N_{2}O_{2} LRMS: MS (ES+) m/z = 345.3(M+1) \[^{1}\]H-NMR: (400 MHz, CDCl\(_3\)) \(\delta\) = 7.75 (s, 1H), 7.62-7.69 (m, 3H), 7.54 (d, \(J=8.3\) Hz, 2H), 6.67 (d, \(J=8.5\) Hz, 1H), 5.89- 5.95 (m, 1H), 5.62- 5.66 (m, 1H), 4.75 (d, \(J=3.0\) Hz, 1H), 4.66 (bs, 1H), 4.30 (qd, \(J=2.3\) & 7.0 Hz, 2H), 4.10- 4.15 (m, 1H), 3.00 (qd, \(J=3.5\) & 9.0 Hz, 1H), 2.44- 2.54 (m, 1H), 1.74 (dd, \(J=8.5\) & 15.5 Hz, 1H), 1.36 (t, \(J=7.0\) Hz, 3H) ppm. \[^{13}\]C-NMR: (100 MHz, CDCl\(_3\)) \(\delta\) = 167.3, 149.6, 148.1, 136.5, 134.3, 132.8, 131.5, 130.6, 129.3, 128.5, 127.6, 125.2, 121.4, 119.1, 115.8, 111.6, 60.9, 57.7, 45.9, 31.8, 21.5, 14.7 ppm.

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

To a mixture of 3'-aminoacetophenone (324 mg, 2.4 mmol), trifluoroacetic acid (0.18 mL, 2.3 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), benzaldehyde (0.24 mL, 2.4 mmol) was added. After stirring for 1 hour (TLC monitoring), the excess solvent was evaporated and the residue was subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.51 g of bright yellow solid was afforded (79%). Rf: 0.59 (65:35, Hex.:ethyl acetate).
C_{20}H_{19}NO LRMS: MS (ES+) m/z = 290.2 (M+1). $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 7.38-7.46 (m, 5H), 7.30-7.34 (m, 1H), 7.06-7.12 (m, 1H), 6.79 (d, $J$ = 7.0 Hz, 1H), 5.62 - 5.65 (m, 2H), 4.91 (d, $J$ = 9.0 Hz, 1H), 4.64 (d, $J$ = 3.0 Hz, 1H), 3.10 (qd, $J$ = 3.0 & 9.0 Hz, 1H), 2.65 - 2.72 (m, 1H), 2.62 (s, 3H), 1.85 (dd, $J$ = 9.0 & 16.1 Hz, 1H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 203.7, 142.8, 139.3, 134.3, 130.9, 129.0, 128.9, 127.7, 126.8, 126.3, 120.8, 120.0, 118.5, 58.3, 46.3, 44.9, 32.3, 30.5 ppm.

**Compound 444**

![Compound 444](image)

To a mixture of 2-aminonaphthalene (343 mg, 2.4 mmol), trifluoroacetic acid (0.37 mL, 4.8 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-carboxybenzaldehyde (360 mg, 2.4 mmol) was added. After stirring for 40 hours (TLC monitoring), the solvent was evaporated, the crude was dissolved in dichloromethane, washed with dilute sodium bicarbonate solution, dried over magnesium sulfate and subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.60 g of white solid was afforded (78%). R$_f$: 0.53 (65:35, Hex.:ethyl acetate). C$_{23}$H$_{27}$NO LRMS: MS (ES+) m/z = 324.3(M+1) $^1$H-NMR: (400 MHz, CDCl$_3$) $\delta$ = 8.56 (d, $J$ = 9.0 Hz, 1H), 8.13 (d, $J$ = 8.5 Hz, 1H), 7.99 (d, $J$ = 7.5 Hz, 1H), 7.85 (d, $J$ = 8.0 Hz, 1H), 7.79 (d, $J$ = 9.0 Hz, 1H), 7.66 (t, $J$ = 7.0 Hz, 1H), 7.53 - 7.60 (m, 3H), 7.48 (t, $J$ = 7.5, 1H), 6.04 - 6.08 (m, 1H), 5.52 - 5.56 (m, 1H), 5.08 (d, $J$ = 3.5 Hz, 1H), 4.82 (d, $J$ = 9.0 Hz, 1H), 3.76 (qd, $J$ = 4.0 & 9.0 Hz, 1H), 2.03 (dd, $J$ = 9.0 & 16.6 Hz, 1H), 1.75 - 1.83 (m, 1H) ppm. $^{13}$C-NMR: (100 MHz, CDCl$_3$) $\delta$ = 167.7, 143.8, 133.4, 133.3, 133.0, 132.8, 131.9, 131.7, 130.6, 129.4,
129.2, 127.9, 127.0, 125.5, 125.4, 124.7, 124.0, 122.5, 120.4, 60.8, 44.5, 40.7, 32.6 ppm.

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

To a mixture of 4-aminobenzoic acid ethyl ester (396 mg, 2.4 mmol), trifluoroacetic acid (0.37 mL, 4.8 mmol) and cyclopentadiene (0.6 mL, 7.2 mmol) in acetonitrile (10 mL), 2-carboxybenzaldehyde (360 mg, 2.4 mmol) was added. After stirring for 40 hours (TLC monitoring), the solvent was evaporated, the crude was dissolved in dichloromethane, washed with dilute sodium bicarbonate solution, dried over magnesium sulfate, filtered and subjected to column chromatography with ethyl acetate and hexanes as eluent; 0.65 g of white solid was afforded (79%). Rf: 0.55 (65:35, Hex.:ethyl acetate) C_{22}H_{19}NO_{3} LRMS: MS (ES+) m/z = 346.3 (M+1) ¹H-NMR: (400 MHz, CDCl₃) δ = 8.44 (d, J= 9.0 Hz, 1H), 7.90-7.95 (m, 3H), 7.63 (t, J= 8.0 Hz, 1H), 7.53 (t, J= 7.0 Hz, 2H), 5.84-5.89 (m, 1H), 5.53-5.57 (m, 1H), 5.09 (d, J= 4.0 Hz, 1H), 4.38 (qd, J= 1.5 & 7.0 Hz, 2H), 4.26 (d, J= 8.5 Hz, 1H), 3.55 (qd, J= 4.0 & 9.0 Hz, 1H), 1.94 (dd, J= 9.0 & 16.6 Hz, 1H), 1.60-1.70 (m, 1H), 1.41 (t, J= 7.0 Hz, 3H) ppm. ¹³C-NMR: (100 MHz, CDCl₃) δ = 166.8, 166.2, 143.3, 139.0, 133.5, 132.6, 132.5, 130.2, 130.1, 130.0, 128.7, 128.0, 126.2, 124.3, 122.0, 120.1, 60.9, 59.5, 46.0, 39.9, 31.3, 14.3 ppm.
To a solution of 443 (450 mg, 1.3 mmol) in dichloromethane (10 mL) was added 3-chloroperoxybenzoic acid (380 mg, 1.43 mmol). The reaction mixture was stirred for 3 hours (TLC monitoring). After quenching with saturated sodium bicarbonate solution, the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate, filtered and purified by column chromatography (hexanes:ethyl acetate; 5:1). A white solid as major compound 446 was afforded; 300 mg (83%). R\textsubscript{f}: 0.40 (65:35, Hex.:ethyl acetate). 

C\textsubscript{22}H\textsubscript{19}NO\textsubscript{4}: LRMS: MS (ES+) m/z = 362.2 (M+1). \textsuperscript{1}H-NMR: (400 MHz, CDCl\textsubscript{3}) \textsuperscript{δ}= 8.56 (d, J= 9.0 Hz, 1H), 8.08 (s, 1H), 8.00 (dd, J= 1.5 & 15.6 Hz, 1H), 7.93 (d, J= 7.5 Hz, 1H), 7.64 (t, J= 7.5 Hz, 1H), 7.53 (t, J= 7.5 Hz, 1H), 7.48 (d, J= 7.5 Hz, 1H), 4.98 (d, J= 3.5 Hz, 1H), 4.40 (qd, J= 1.5 & 7.5 Hz, 2H), 3.86 (d, J= 7.5 Hz, 1H), 3.71 (d, J= 2.5 Hz, 1H), 3.34 (bs, 1H), 3.04 (qd, J= 3.5, 10 Hz, 1H), 1.61 (dd, J = 7.5, 14.6 Hz, 1H), 1.42 (t, J= 7.5 Hz, 3H), 0.99 (dd, J= 10.0, 14.1 Hz, 1H) ppm. \textsuperscript{13}C-NMR: (100 MHz, CDCl\textsubscript{3}) \textsuperscript{δ}= 166.5, 165.9, 142.6, 139.7, 132.8, 132.4, 130.8, 128.9, 128.8, 126.1, 124.3, 124.2, 121.9, 120.1, 61.5, 61.0, 58.2, 56.6, 40.9, 35.3, 26.0, 14.3 ppm.
To a solution of 446 (155 mg, 0.45 mmol) and boron trifluoride diethyl etherate (0.057 mL, 0.45 mmol) in dichloromethane (10 mL), 4-bromoaniline (160 mg, 0.9 mmol) was added. After completion of the reaction (5 hours, TLC), the reaction was quenched by ammonium chloride solution. The aqueous layer was extracted by dichloromethane. Combined organic layer was dried over magnesium sulfate and filtered. Column chromatography (hexanes:ethyl acetate; 4:1) was afforded a white solid 447; 185mg (77%). Rf 0.37 (65:35, Hex.:ethyl acetate). C_{28}H_{25}BrN_{2}O_{4} LRMS: MS (ES+) m/z = 533.3, 535.3 (M+1). \textsuperscript{1}H-NMR: (400 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} = 8.45 (d, J= 8.5 Hz, 1H), 8.05 (s, 1H), 7.96 (dd, J= 1.8 & 8.5 Hz, 1H), 7.92 (d, J= 7.5 Hz, 1H), 7.64 (td, J= 1.0 & 7.5 Hz, 1H), 7.49-7.55 (m, 2H), 7.11 (d, J= 9.0 Hz, 2H), 6.33 (d, J= 8.8 Hz, 2H), 4.93 (d, J= 4.0 Hz, 1H), 4.34 (qd, J= 1.5, 7.0 Hz, 2H), 3.94 (t, J= 4.5 Hz, 1H), 3.69 (m, 1H), 3.49-3.56 (m, 1H), 3.43-3.49 (m, 1H), 1.81-1.89 (m, 1H), 1.38 (t, J= 7.0 Hz, 3H), 0.79-0.89 (m, 1H) ppm. \textsuperscript{13}C-NMR: (100 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} = 167.3, 166.7, 146.5, 143.1, 139.5, 133.2, 132.8, 132.3, 130.8, 129.4, 129.2, 129.1, 126.8, 124.9, 122.6, 120.5, 115.5, 109.8, 86.2, 61.5, 60.9, 59.7, 47.3, 37.5, 30.3, 14.7 ppm.
8. Claims to Original Research

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

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

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

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

8.1 Publications


8.2 Presentations


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


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


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10: Appendix

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

1. $^1$H-NMR
2. $^{13}$C-NMR
3. Chiral HPLC (if applicable)
$^{13}$C-NMR (227)

![Chemical Shift Spectrum](image)

Chemical Shift (ppm)
$^{1}$H-NMR (228)
For Sample: SH 3.3
Inj. volume: 30.00 ul
Comments: 70/30 hexane/ethanol
Column Name: CHIRALCEL OD
Flow: 1.0 ml/min
Instrument Method: 30A_70C
Date Acquired: 04/16/03 12:57:57 PM

Report Method: NP_1
Vial: 1
Injection: 2
Acq Meth Set: NP_30A_70C
Processing Method: NP_1
Proc Chan: 240nm
Date Processed: 04/16/03 01:24:45 PM

Peak Results

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\[ \text{GOOEt} \]

\[ \text{OH} \]

\[ \text{253} \]
$^{13}$C-NMR (230 MHz)

Chemical Shift (ppm)

- $170$ ppm
- $160$ ppm
- $150$ ppm
- $140$ ppm
- $130$ ppm
- $120$ ppm
- $110$ ppm
- $100$ ppm
- $90$ ppm
- $80$ ppm
- $70$ ppm
- $60$ ppm
- $50$ ppm
- $40$ ppm
- $30$ ppm
- $20$ ppm
- $10$ ppm
- $0$ ppm
$^{13}$C-NMR (238)

![C-NMR spectrum diagram](image-url)
Chemical Shift (ppm)
$^{13}$C-NMR (240)

MEMO

\[ \text{NO}_2 \]

\[ \text{OH} \]

\[ \text{COOEt} \]

\[ \text{OH} \]

Chemical Shift (ppm)

180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
$^{13}$C-NMR (241)

MEMO

Chemical Shift (ppm)
$^1$H-NMR (51)
$^{13}$C-NMR (292) Alloc

![Chemical Shift Graph]

- Chemical Shift (ppm) range: -10 to 160
- Peaks at different ppm values indicate various carbon signals

273
$^1$H-NMR (293) Alloc
$^{13}$C-NMR (293) Alloc

Chemical Shift (ppm)
$^{13}$C-NMR spectrum of S-CH$_2$CH$_2$Ph (296)
$^{1}{H}$-NMR (300 MHz)
$^{13}$C-NMR (301)

Alloc

OTBS

OH

MEMO
$^1$H-NMR (303 MHz)

Chemical Shift (ppm)
$^1$H-NMR (359) Alloc

MEMO

OBz

Chemical Shift (ppm)
$^{13}$C-NMR (359)
$^{1}$H-NMR (359)

MEMO
H-NMR (362) Alloc

Chemical Shift (ppm)
$^{13}$C-NMR (362) Alloc

![Chemical Shift Graph]

Chemical Shift (ppm)

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
$^1$H-NMR (428)
13C-NMR (428)
$^1$H-NMR (429)

Chemical Shift (ppm)
$^1$H-NMR (447)