Progress Towards the Stereoselective Synthesis of Cycleanine

by

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Declaration

I hereby certify that this research is a result of my own investigation and has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree

Signed……
Madira Litedu

I, the undersigned, hereby certify that the above statement is true and correct

Signed……
Professor F. R. van Heerden

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Abstract

The emergence of multi-drug resistance (MDR) to antimalarial and anticancer drugs has stimulated a search for novel MDR inhibitors/reversers. Bisbenzylisoquinoline alkaloids (BBIQ) are potential agents for reversing MDR, especially when used as synergistic enhancers of anticancer and antimalarial drugs with improved therapeutic efficacy. Despite numerous useful biological activities reported for BBIQ's, the various syntheses of individual members remained cumbersome and the overall yields are low. In addition, published methods are non-stereospecific and produced racemates.

The aim of this project was to develop a synthetic pathway for the preparation of cycleanine, a natural BBIQ with a symmetrical structure. The protocols developed for the synthesis of cycleanine will serve as a template for the synthesis of other BBIQ's with more complex structures. The only published total synthesis of cycleanine did not address regioselectivity and stereoselectivity, furthermore, key steps suffered from extremely low yields of the products. Our synthetic pathway is a chiral auxiliary-based asymmetric synthesis that generates enantioselectively a 1,2,3,4-tetrahydroisoquinolines (THIQ) monomers. Cheap, commercially-available starting materials were used to prepare monomers in a regioselective as well as stereoselective manner in good yields. The key feature of this method entails coupling of a chiral β-phenethylamine and halophenylacetaldehyde using the Pictet-Spengler reaction. Due to the difficulties encountered during the course of the preparation of monomers, different methods were tried and formation of unanticipated products rationalised. Dimeric BBIQ's are constituted of monomeric THIQ's which are reported to have array of biological properties including MDR reversing activities, therefore, the total synthesis of cycleanine will serve two purposes.

In this investigation, the THIQ monomers were synthesised by a pathway that avoid harsh reaction conditions. Major reactions employed include nucleophilic aromatic substitutiton, Wittig reaction, hydroboration and IBX oxidation. Some of the steps were attempted on model compounds to optimise the conditions prior to attempting the reaction on cycleanine

precursors. Two major contributions toward the synthesis of BBIQ's were made in this study. The reaction conditions to control the regioselectivity and enantioselectivity of the Pictet-Spengler reaction for the preparation of THIQ moiety were developed. A major drawback of the published syntheses of BBIQ's is the harsh conditions and low yields associated with the Ullmann reaction, which is used in the formation of the diaryl ether bonds. We have shown that the microwave-assisted nucleophilic aromatic substitution of aryl fluorides provide a much superior method for the formation of the key diaryl ether bond.

Although we failed to form the final diaryl ether bond, the pitfalls encountered in the synthetic pathway are discussed and potential solutions are presented. The developed synthetic pathways are of general applicability and therefore can also be employed in the synthesis of other macrocyclic natural products containing diaryl ethers.

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Chapter 2: Fundamental aspects of bisbenzylisoquinolines

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List of abbreviations

ABC	ATP-binding cassette
abs	absolute
Ac	acetyl
AcOH	acetic acid
Ac_2O	acetic anhydride
ACT	artemisin-combination therapy
AIDS	acquired immunodeficiency syndrome
aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
AZT	zidovudine
BBIQ	bisbenzyltetrahydroisoquinolines
BOBCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophophate
^{t}Bu	*tert*-butyl
BuLi	Butyllithium
CBZo	benzyloxycarbonyl
CM	cross-metathesis
conc	concentrated
CDMT	2-chloro-4,6-dimethoxy-1,3,5-triazine
de	diastereomeric excess
DCCD	1,3-dicyclohexylcarbodiimide
DMAC	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfate
DMSO	dimethyl sulfoxide
DMTMM	4-(4,6-dimethoxy-1,3,5-triazen-2-yl)-4-methylmorpholinium chloride

dr	diastereomeric ratio
EDCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
eq	equivalent
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
HAART	highly active antiretroviral
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOAc	acetic acid
HOBt	1-hydroxybenzotriazol
h	hour
Hz	Hertz
IR	infrared spectroscopy
IBX	*o*-iodoxybenzoic acid
LHE	lithium-halogen exchange
lit.	literature
m.p.	melting point
MS	mass spectrometry
ms	molecular sieves
MW	microwave
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NMP	*N*-methylpyrrolidine
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
P-gp	P-glycoprotein
Ph	phenyl

PIs	protease inhibitors
PPA	Polyphoshoric acid
*i*Pr	isopropyl
py	pyridine
RCM	ring closing metathesis
R_f	Retention factor
SARS	severe acute respiratory syndrome
TB	tuberculosis
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TFSA	trifluoromethanesulfonic acid
rt	room temperature
THF	tetrahydrofuran
THIQ	1,2,3,4-tetrahydroisoquinoline
TLC	thin-layer chromatography
TMHD	2,2,6,6-tetramethylheptane-3,5-dione
p-TsOH	*para*-toluenesulfonic acid

CHAPTER 1

Introduction

1.1 Introduction

For thousands of years, infectious diseases have been a major cause of suffering. Despite important advances in the combating of these diseases, they continue to be a cause of serious illness and death in the world. A number of drugs are used against infectious diseases such as TB, HIV/AIDS, malaria and cancer. However, their use is limited by high cost, toxicity and development of microorganisms' resistance. Drugs are the mainstay of the management and prevention of infectious diseases and this is unlikely to change in the near future.

This chapter reviews the dangers of infectious diseases with a focus on malaria, TB, hepatitis C virus (HCV) and HIV/AIDS worldwide. Epidemiology, co-infection within these diseases as well as the current treatments are also outlined. The impact of resistance on the current treatments brings us to the aim of the project, that is, the synthesis of potential multidrug resistance reversers.

1.2 Infectious diseases

The discovery of antibiotics has transformed humanity's approach to infectious diseases and that led to optimism that infectious diseases could be controlled. The existence of safe and effective interventions, such as the development of antibiotics and vaccines, along with improvements in material standards in terms of housing, nutrition, hygiene, sanitation and vector control epidemics led many to predict the end of infectious diseases.[1] However, today we know that this optimism was premature since humanity is faced with another crisis, that is, the ability of microbes to change and adapt.

During the past thirty years, newly discovered infectious diseases such as H1N1 flu (swine flu), H5N1 flu (bird flu), severe acute respiratory syndrome (SARS), ebola and human immunodeficiency virus (HIV) have brought unexpected challenges to mankind.[2] The

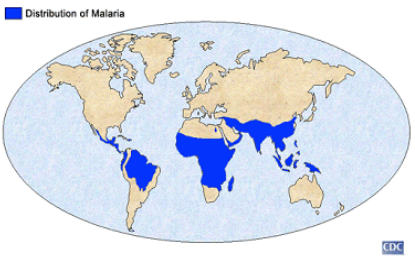
resurgence and emergence of old diseases such as cholera, malaria and TB (tuberculosis), which seem to be under control in developed countries, have become a public health problem in developing countries and are rapidly becoming difficult to treat. A serious problem worldwide associated with the resurgence of old diseases is drug resistance. Furthermore, chronic diseases once thought to be unrelated to infectious diseases are now linked to bacterial, viral or parasitic agents. Research indicates that viruses are involved in 15-20% of all human cancers, for example, cervical cancer, a major killer of women worldwide,[3] is caused by the human papilloma virus.

The following paragraphs will concentrate on HIV/AIDS, malaria, TB and HCV, since these four possesses similarities outlined below. The global epidemiology of HIV/AIDS, malaria, TB and cancer overlap because a significant number of HIV-infected individuals die from TB and they also live in regions where malaria is a problem. In addition, the course of both HIV and cancer is much more rapid and deadly in persons with both diseases.

1.3 Epidemiology

1.3.1 Malaria

Globally 500 million people are infected by malaria and at least 1 million die each year.[4] Although malaria occurs in tropical and subtropical developing countries on all continents, and today 90% of malaria cases and deaths are recorded in sub-Saharan Africa. The individuals most at risk are children under the age of five and pregnant women.[5] The chemotherapy and prophylaxis of malaria have been undermined by the development of worldwide resistance against drugs of *Plasmodium falciparum*, a causative agent of human malaria (Fig. 1.1).



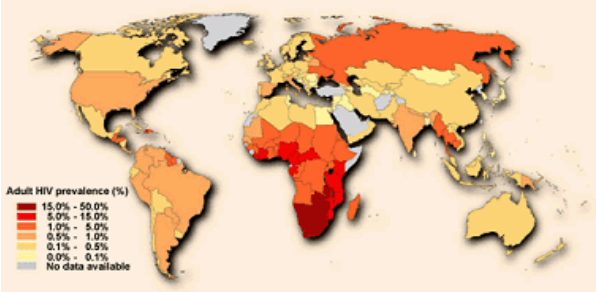
www.malaria.com/info/malaria-countries-map.php

Figure 1.1: Distribution of malaria.*

* Reproduced with permission from WHO

1.3.2 HIV/AIDS

HIV is a retrovirus acquired through sexual contact, from mother to child (during pregnancy, labour or through breast milk), or by contaminated blood, that attacks and gradually depletes an individual's immune capacity to fight off deadly infections, leading to acquired immunodeficiency syndrome (AIDS). It has been estimated that in 2009, 33.3 million people were infected with HIV/AIDS worldwide, with approximately 22.5 million living in sub-Saharan Africa. Around 1.3 million people died from HIV/AIDS in 2009 in this region (Fig. 1.2).[6] Even though treatment is available, a growing number of individuals with HIV develop AIDS because of both drug resistance and toxic side effects of primary drugs. Furthermore, there is evidence that indicates that the development of resistance to one inhibitor quickly leads to insensitivity to the entire family of drugs.[7]

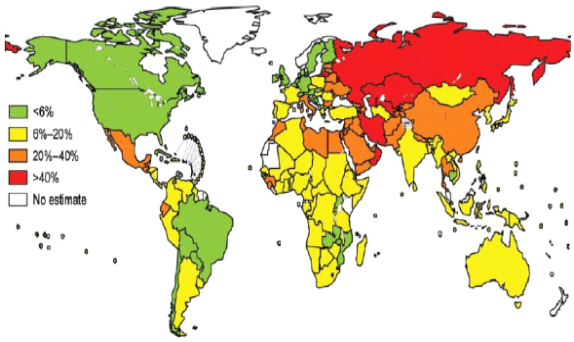


www.who.int/.../en/index3.html

Figure 1.2: HIV prevalence.*

1.3.3 Tuberculosis (TB)

TB, a highly contagious pulmonary infection caused by *Mycobacterium tuberculosis*, continuously exists as a leading infectious disease agent that follows poverty and urban crowding, causing millions of deaths each year. Worldwide, TB remains the world's number one bacterial killer, and current trends suggest that TB will still be among the ten leading deadly diseases in the year 2020.[8] The emergence of extremely drug-resistant TB strains (XDR TB) indicates the survival strategies adopted by the organism to continue mutating the drug targets. Low income and emerging economic groups are more likely to be affected. Africa, more specifically sub-Saharan Africa, has the highest incidence of TB, with approximately 290/100 000 per year (Fig. 1.3).[8] TB cases occur predominantly in the economically most productive age group.



www.worldalmanac.com/blog/2007/12/december

Figure 1.3: Estimated HIV prevalence in TB cases.*

1.3.4 Hepatitis C virus (HCV)

Worldwide about 170 million people are infected with HCV with 2-3% chronically infected[9] accounting for 250 000 deaths annually.[10] Approximately 20% of the infected people may develop cirrhosis over a 20 to 50 year period. These statistics indicate the need for effective, non-toxic, and affordable treatments for HCV.

1.4 Co-infection of malaria, HCV, TB and HIV/AIDS

HIV and malaria overlap in many countries, particularly in sub-Saharan Africa, Asia, Latin America and the Caribbean.[11] HIV infection can increase the risk and severity of malaria infection. Also, individuals in malaria-endemic areas who are considered semi-immune to malaria can develop clinical malaria if infected with HIV. Likewise, when infected with malaria, a person's HIV viral load rises.[12]

TB is the most common opportunistic infection in people living with HIV worldwide. Despite being preventable and treatable, TB is the leading killer in HIV-positive individuals. People with *M. tuberculosis* infection who are HIV-positive, are at risk of developing active TB at a rate of 7 to 10% per year, compared to approximately 8% per lifetime for HIV-negative individuals.[8] Thus, HIV infection tends to increase the severity of TB, while in turn, the host immune response to *M. tuberculosis* can enhance HIV replication and may accelerate the natural course of HIV/AIDS.

* Reproduced with permission from WHO.

HCV is associated with HIV, with an estimated 4 to 5 million people co-infected with HIV/HCV.[13] Due to overlapping transmission routes (transmitted *via* shared needles and other injection equipment), HIV accelerates HCV progression. HIV co-infection significantly increases the risk of developing serious liver diseases.

1.5 Current treatment recommendations

Chemotherapy is the most important treatment of malaria. Chloroquine (**1.1**) resistance in the most pathogenic malaria species, *Plasmodium falciparum*, is widespread. To limit the development of drug resistance, the World Health Organisation (WHO) currently recommends that treatment consists of a combination of drugs that act on different parasite targets and have favourable pharmacokinetic profiles. Among the recommended drugs, the use of an artemisin-combination therapy (ACT) containing artemether (**1.2**) with lumefantrine or artesunate (**1.3**) with either mefloquine (**1.4**) or a combination of sulfadoxine (**1.5**) and pyrimethamine (**1.6**), is regarded as a first line of treatment (Fig. 1.4).[14]

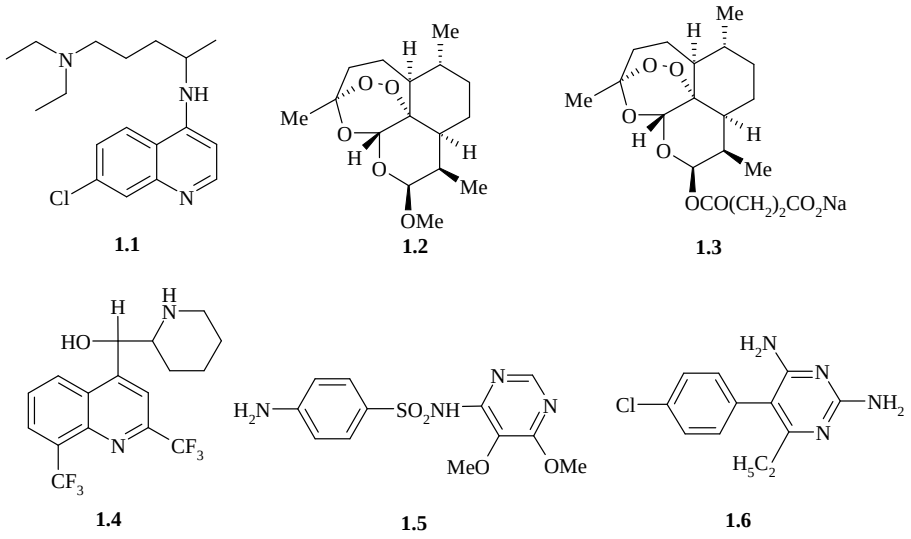


Figure 1.4: The chemical structures of drugs used for malaria.

The most widely used anti-HIV drugs are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The NRTIs include zidovudine (AZT) (**1.7**), stavudine (**1.8**), lamivudine (**1.9**), abacavir, emitricitabine, didanosine and tenofovir, the NNRTIs include nevirapine (**1.10**) and efavirenz (**1.11**) and PIs include saquinavir (**1.12**), ritonavir, tipranavir, among others (Fig. 1.5). Antiretroviral treatment is not curative and drug resistance has been reported.

The current HIV/AIDS treatment known as highly-active antiretroviral treatment (HAART) has proven to be highly effective and particularly in the prevention of drug resistance.[15] It consists of three agents, normally two NRTIs and either an NNRTI or PI. However, HAART treatment is limited by several factors such as costs, shelf life, pill burden, the need for strict adherence to treatment and toxicity.

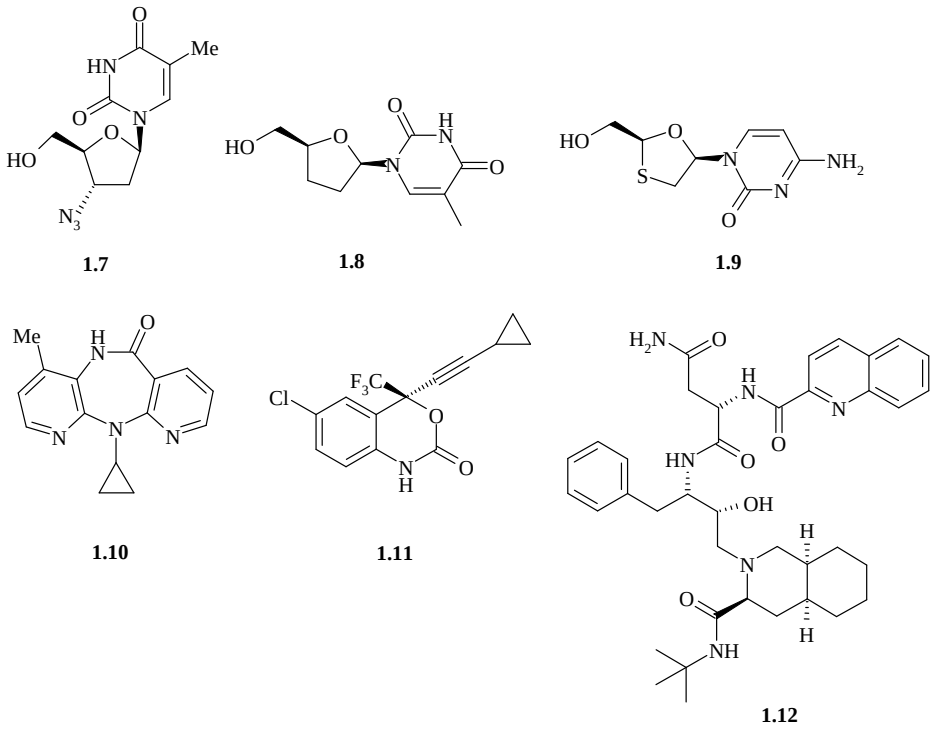


Figure 1.5: The chemical structures of some drugs that are currently used for HIV/AIDS treatment.

The initial treatment of TB takes 6 to 8 months. This treatment consists of four medications taken at least three times a week for two months, followed by 4 to 6 months of two medications daily. The drugs used are rifampin (R) (**1.13**), isoniazid (H) (**1.14**), ethambutol (E) (**1.15**) and pyrazinamide (Z) (**1.16**) which are taken for two months daily or thrice weekly, followed by four months of HR or six months of HE (Fig. 1.6).[16] Treatment of TB in the presence of HIV is complicated by drug-drug interactions. Maximal drug levels or total drug exposure over time of antiretroviral agents may be reduced when these drugs are co-administered with rifamycins, reducing the efficacy of HAART regimens. This limits the treatment of people co-infected who need therapy for both conditions.

With HCV, the aim of therapy is to achieve an undetectable HCV 6 months following therapy and ultimately to reduce hepatic inflammation. The standard therapy is the

injection of pegylated interferon with daily ribavirin capsules, with doses administered according to body weight.[17] Although pegylated interferon is considered to be effective than its predecessor standard interferon, it has limitations to efficacy, tolerability and the problem of drug resistance remains.

It is unfortunate that many of the new drugs are not only expensive, but have serious side effects and most will eventually become ineffective due to the rapid mutation of microorganism. For better control of diseases, already existing cheap drugs must be used more effectively.

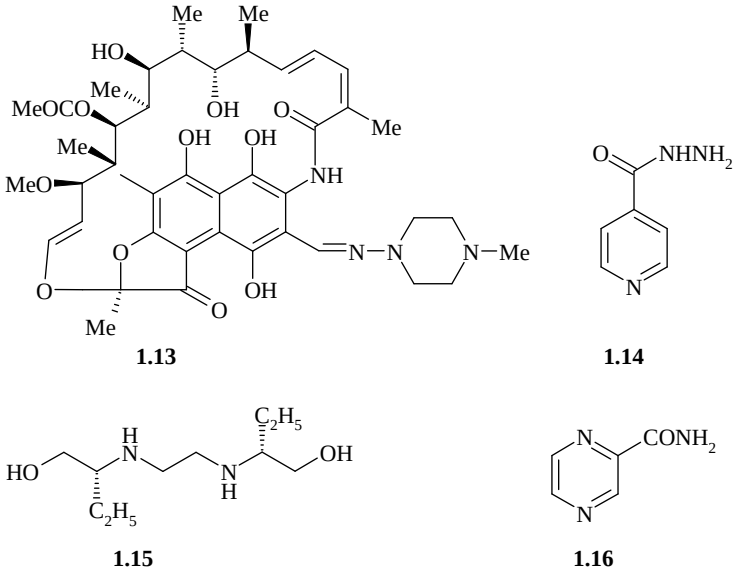


Figure 1.6: The chemical structures of drugs used in TB treatment.

The geographical overlap of malaria, HCV, TB and HIV prevalence increase the likelihood that these diseases co-exist in a large number of individuals. These people will have to use antimalarial, antitubercular, antiretroviral and antihepatitis C drugs at the same time and drug-drug interactions may result from concurrent administration of drugs leading to diminished therapeutic efficacy or increased toxicity. Many antiretroviral agents and antimalarial agents commonly used are metabolised by the same cytochrome P450 enzymes, and antituberculars (rafimycins) are known to be cytochrome P450 enzyme inducers and consequently depending on the drug combinations, the total drug exposure over time will be altered.

1.6 Drug resistance and P-glycoprotein homologues

It came as an unpleasant surprise that shortly after the introduction of various classes of drugs, new pathogenic strains emerged that were no longer susceptible to these drugs. The emergence of resistant microorganisms is known to be a consequence of widespread drugs usage, changes in human ecology, changes in personal behaviour, and human-induced global changes, which result in the survival of genetically modified organisms that can reproduce in the presence of a particular drug.[18] Modifications can come from spontaneous mutations, overexpression of certain genes and overproduction of their gene products or acquisition of genetic material from other microorganisms. These changes can confer resistance in several ways, including an enzyme-catalysed reaction that renders the drug inactive, mutations in the organisms that can result in changes in the biological target, decreased cell-wall permeability by mutation-induced genetic changes. Membrane associated P-glycoproteins (P-gp's) have been found to be overexpressed in multidrug resistance (MDR) cancer cells and they are the most common cause of upregulation of drug efflux.[19]

P-gp's are a member of the ATP-binding cassette (ABC) family and plays a role in drug resistance. P-gp's homologues are found in important epithelial barriers, such as the intestinal epithelium, the blood-brain and blood-nerve barrier, the blood-testis barrier and the materno-fetal barrier, where it prevents drugs in the bloodstreams to cross these epithelial barriers, thereby contributing to low bioavailability of drugs.[21] P-gp's use two ATP molecules to extrude one molecule of drug. Initially the drug and ATP binds to the protein and one ATP is hydrolysed to ADP to efflux the drug. Another ATP is used to reorient the protein to its original conformation, with the release of ADP to complete a catalytic cycle (Fig. 1.7).[22] In cancer chemotherapy P-gp's have been found in untreated malignancies, including neuroblastoma[22] and acute myeloid leukemia.[23]

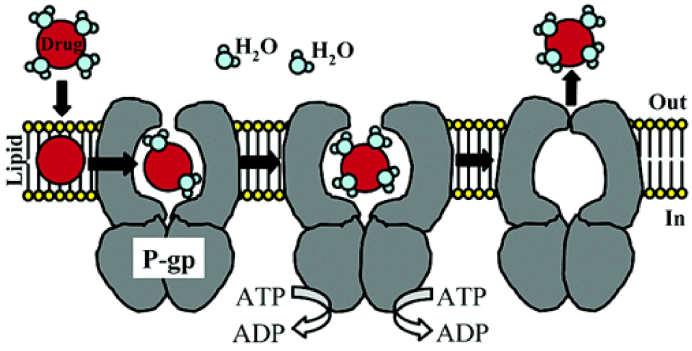


Figure 1.7: P-gp-mediated drug transport.[21]

In drug-resistant malaria the presence of a similar glycoprotein pump has also been observed.[24] It has also been demonstrated that most of the MDR reversing agents inhibit the binding of drugs to P-gp, resulting in a lowered efflux and accumulation of drugs in MDR cells.[25] Furthermore, there is evidence that both mefloquine[26] and PIs[27] can inhibit drug partitioning by inhibiting P-glycoprotein (P-gp) homologues. Therefore, P-gp is a promising target for HIV, TB, HCV and malaria therapies.[15]

Viruses replicate within cells, therefore, drugs that target replication must penetrate into infected cells in sufficiently high concentrations to exert their effect. P-gp's play a role in the low intracellular concentration of drugs and P-gp inhibitors, which can be taken simultaneously with the current drugs, could hopefully increase efficacy as well as shortening the duration of therapy.

1.7 Bisbenzyltetrahydroisoquinolines as potential MDR reversers

Plants have been used as medicines for millennia and they have been the main medicinal agents available to humans. Today most of the people in developing countries still consult traditional medicine practitioners and use local medicinal plants for primary health care. The abundant biosynthetic pathways in plants have provided a number of lead structures that have been used in drug development.

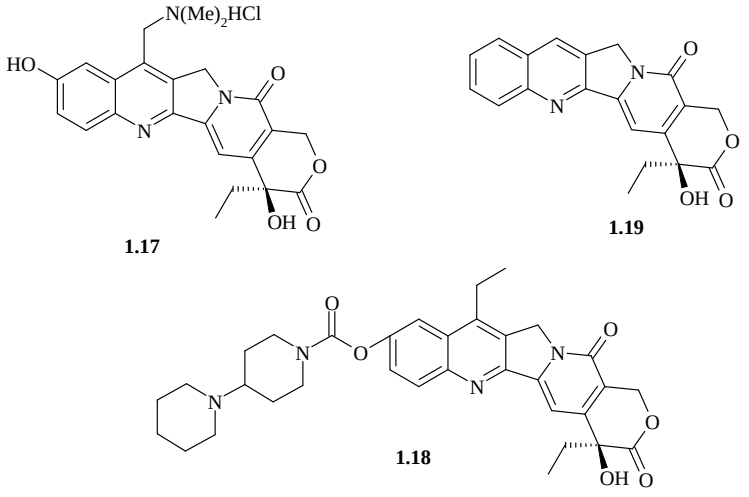


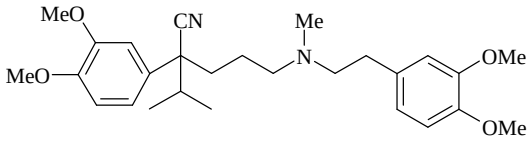
Figure 1.8: Plant-derived products used in the discovery of drugs.

A typical example is , camptothecin (**1.17**), a monoterpenoid alkaloid isolated from the Chinese ornamental tree *Camptotheca acuminate*,[28] from which two derivatives, topotecan

(**1.18**) and irinotecan (**1.19**) (a pro-drug), less toxic and more stable than camptothecin (**1.17**) (Fig. 1.8), were developed and are currently used for the treatment of colorectal and ovarian cancers.[29] Alkaloids (generally defined as nitrogen-containing natural molecules, independently of the basic character of the nitrogen) are abundant secondary metabolites in plants with well-known toxic, hallucinogenic and euphoric properties. In a review by Teodori *et al.*,[30] several natural compounds with MDR-inhibiting properties, amongst them alkaloids, were listed. The general features that were reported important for MDR antagonism, are high lipophilicity, presence of a protonable nitrogen atom and one or more aromatic rings.[30]

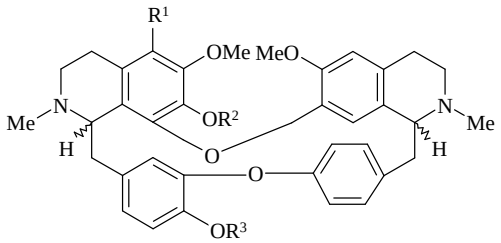
Among the alkaloids, bisbenzyltetrahydroisoquinolines (BBIQ's) constitute a broad group of homodimeric benzylisoquinolines, with more than 400 examples known.[31] BBIQ's represent 40% of the total number of alkaloids isolated from plants of the Menispermaceae, hence, they are considered good chemical markers for this family.

As mentioned, it has been suggested that MDR can be reversed by hydrophobic molecules with two planar aromatic rings and a tertiary basic nitrogen that can be protonated at physiologic pH.[32] A calcium blocker verapamil (**1.20**), a representative of this class, is effective against malaria. However, it is toxic at levels high enough to affect MDR reversal.[33] With the known structural requirement for MDR reversers, BBIQ's are potential drug targets.



1.20

BBIQ's have attracted the attention of synthetic organic chemists and pharmacologists due to their complex structures and wide range of biological activities, namely, antibacterial and antifugal,[34] cytotoxic,[35] antimalarial,[36] anticancer,[37] hypotensive[38]and antiplasmodial[39] activities. BBIQ's as MDR reversers have been documented.[40,41,42,43,44,45] Van Dyke[46] tested the tetrandrine family of compounds as well as non-tetrandrine compounds to determine the efficiency of BBIQ's as MDR reversers against drug resistant strain of *P. falciparum* and with cancer cells with MDR in conjugation with primary drugs known to be effective against malaria and particular cancers *in vivo* (Figs 1.9 and 1.10).



	Configuration	R^1	R^2	R^3
Tetrandrine	*S, S*	H	Me	Me
Isotetrandrine	*R, S*	H	Me	Me
Phaeanthine	*R, R*	H	Me	Me
Hernandezine	*S, S*	OMe	Me	Me
Pycnamine	*R, R*	H	Me	H
Berbamine	*R, S*	H	Me	H
Fangchinoline	*S, S*	H	H	Me
Obamegine	*R, S*	H	H	H

Figure 1.9: Representatives of the tetrandrine family tested for MDR inhibition.

Of the nine tetrandrine-like compounds, only tetrandrine, isotetrandrine, berbamine and hernandezine potentiate the primary drugs against MDR cells. The non-tetrandrine compounds tested include cycleanine (**1.21**), cepharanthine (**1.22**) and thalicarpine (**1.23**). Even though cycleanine (**1.21**) showed a relative low activity in potentiation of primary drugs against MDR cells, the lack of cytotoxicity observed with cycleanine is remarkable among the BBIQ's tested to date. Moreover, cycleanine have showed activity against HIV-1 and HIV-2 with high activity against HIV-2 with IC_{50} of 1.83 µg/ml.[47]

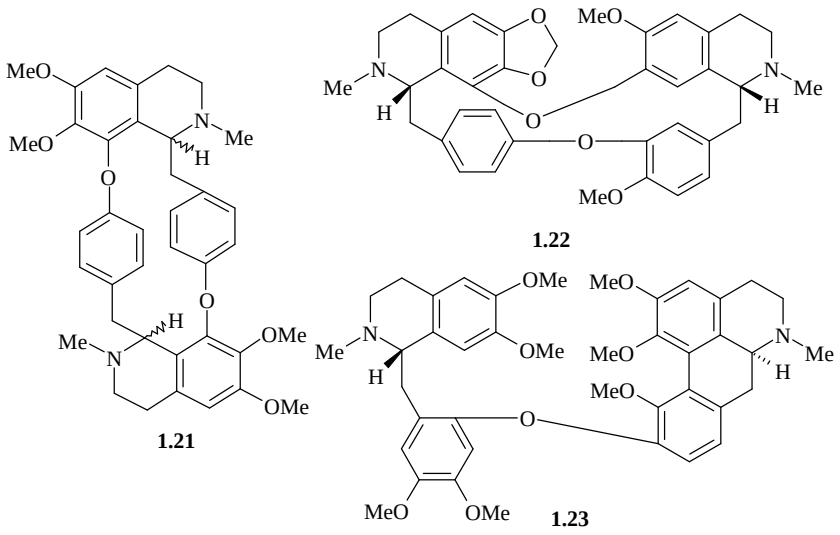


Figure 1.10: Non-tetrandrine compounds tested for MDR inhibition.

The inherent antimalarial and/or anticancer activities of BBIQ's combined with their ability to reverse MDR, make these compounds interesting candidates for drug discovery.

1.8 Hypothesis and objectives

Despite numerous useful biological activities reported for BBIQ's, the various syntheses of individual members remained cumbersome and the overall yields are low. The published methods are non-stereospecific and produce racemates. The aim of this project was to develop a synthetic pathway for the preparation of cycleanine (**1.21**). Cycleanine (**1.21**) is considered to be the least complex member of the BBIQ's due to its symmetrical nature and its synthesis is expected to be simple, however, several attempts have met with failure. The total synthesis of cycleanine (**1.21**) will serve as a template for the preparation of more complex BBIQ's. Furthermore, it will be possible to modify the structure and to find more effective MDR inhibitors or reversers with low toxicity.

The overall objective of this study relates to the development of synthetic routes for cycleanine (**1.21**). The main aims were:

- Planning of efficient methodologies related to cost and time towards total synthesis of cycleanine (**1.21**)
- Flexible and versatile strategies which allow synthesis of intermediates

- Synthesis of the monomeric tetrahydroisoquinoline moiety in stereoselective and regioselective manner
- Synthesis of highly enantiomerically-pure intermediates
- Regioselective formation of the ether linkage through phenol coupling
- Optimisation of the yields throughout the multistep synthesis
- Employment of simple experimental protocols with mild reaction conditions
- Ring closure of the intermediate to form a macrocyclic cycleanine (**1.21**).

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CHAPTER 2

Fundamental Aspects of Bisbenzyltetrahydroisoquinolines: Literature Review

2.1 Introduction

This chapter details the classification of bisbenzyltetrahydroisoquinoline (BBIQ) alkaloids according to the number of bonds joining the two monomers, with examples focussed mostly on compounds with diphenyl ether linkages. Selected previous total syntheses of BBIQ's are also outlined. Different synthetic methods for the preparation of the monomers followed by the protocols to the key diaryl ether linkages are described.

2.2 Classification of bisbenzyltetrahydroisoquinoline alkaloids

Bisbenzyltetrahydroisoquinoline (BBIQ) alkaloids are dimeric compounds assembled from two benzylisoquinoline or in most cases benzyltetrahydroisoquinoline monomers. The two moieties are normally connected by one or more diaryl ether bridges, but in some cases carbon-carbon bonds or a methylenoxy bridge may also be present. The BBIQ alkaloids are classified according to the nature, the number, and the attachment points of the bridges. In each subgroup, the alkaloids differ by the nature of their oxygenated substituents, the degree of unsaturation of the heterocyclic rings and the stereochemistry of the two chiral centres, C-1 and C-1'. The numbering of the skeleton and the systematic classification describing the oxygenation and dimerisation patterns of BBIQ's follow the convention established by Shamma and Moniot[1] (Figure 2.1). The more highly oxygenated half constitutes the left hand side of the dimer.

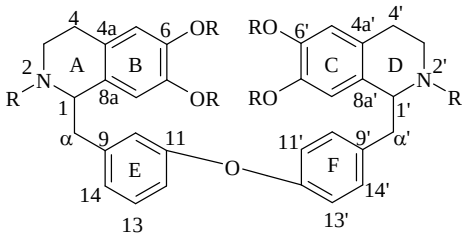
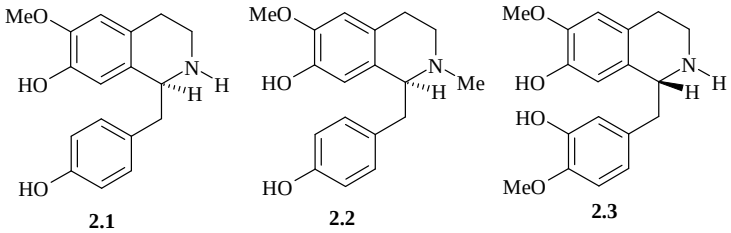


Figure 2.1: Numbering of BBIQ's.

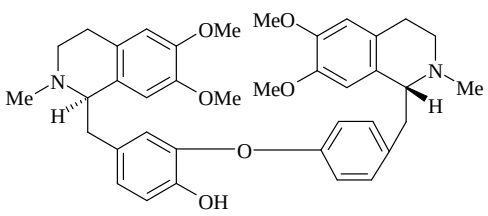
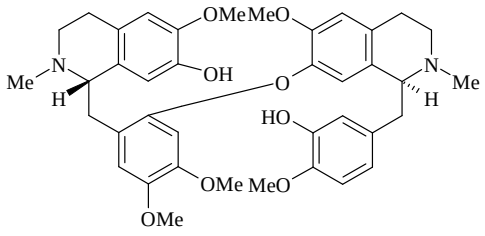
Most BBIQ's are formed by the condensation of coclaurine (**2.1**) or *N*-methylcoclaurine (**2.2**)**,** with a minority originating from *N*-methylcoclaurine (**2.2**) and reticuline (**2.3**) and exceptions resulting from the condensation of two reticuline molecules, hence, they can be divided into three categories, namely biscoclaurines, coclaurine-reticulines and bisreticulines.



Fundamental types of BBIQ's can be distinguished according to the number of bonds binding the two halves and can be further subcategorised according to the position of the bonds (head or tail). Presented below are examples of BBIQ's highlighting the structural variations that exist within this class of alkaloids and special attention has been given to those possessing the diphenyl ether moiety.

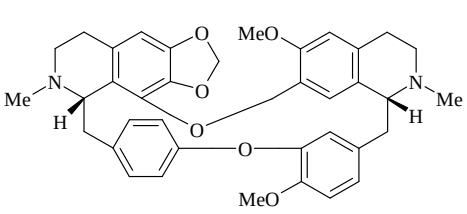
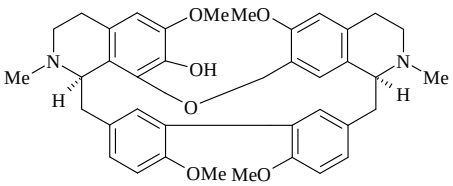
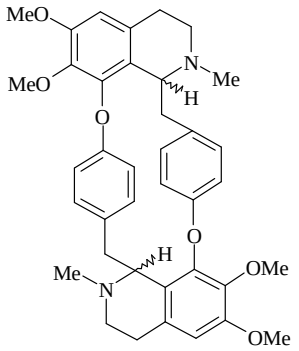
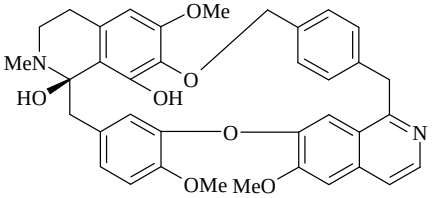
The simplest members are those in which the two halves are joined together by a tail-to-tail linkage (the isoquinoline portion is referred as the head and the benzyl portion as the tail) (Table 2.1). Most of the BBIQ's linked tail-to-tail possess the *R,R*-configuration at C-1 and C-1' and they are linked by the diphenyl ether linkage, the vasodilator dauricine (**2.4**) provides an example of this type. Malekulatine (**2.5**), isolated from *Hernandia sonora,*[2] represents a subgroup of alkaloids with a head-to-tail diphenyl ether linkage. No head-to-head single-bonded BBIQ have been reported to date.

Table 2.1: BBIQ's connected by one bond.

Diphenyl ether tail-to-tail	Diphenyl ether head-to-tail
	
Dauricine (**2.4**)	Malekulatine (**2.5**)

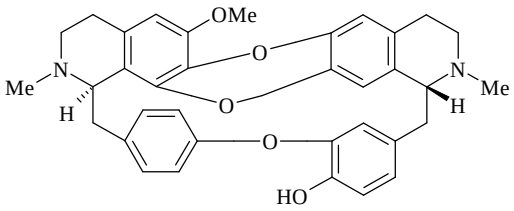
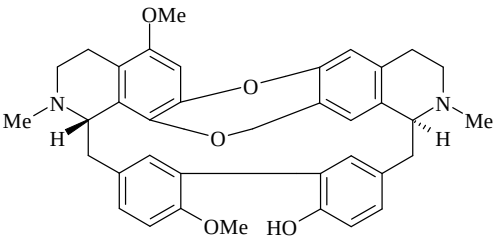
The biscoclaurine alkaloid, cepharanthine (**1.22**), is a potent agent against the multidrug-resistant cancer cells that overexpress P-gp.[3] It is a member of the alkaloids with head-to-head and tail-to-tail diphenyl ethers, featuring a unique methylenedioxy group on its benzylisoquinoline moiety (Table 2.2). A potent antimalarial agent monterine (**2.6**) belongs to a subgroup of alkaloids with diphenyl ether as well as diaryl bonds. Cycleanine (**1.21**), a symmetrical isochondoderine BBIQ containing eight electron-donating sites, is considered as a true dimer consisting of the same two benzylisoquinoline moieties. Cycleatjehenine (**2.7**) belongs to a subgroup of BBIQ's with the two benzylisoquinoline moieties linked by diphenoxy head-to-tail and methylenoxy head-to-tail bridges. This subgroup possesses a fully unsaturated isoquinoline ring and has been isolated so far only from C*yclea atjehenisis*.[4]

Table 2.2: BBIQ's connected by two bonds.

Diphenyl ether head-to-head Diphenyl ether tail-to-tail 	Diphenyl ether head-to-head Phenyl-phenyl tail-to-tail 
Cepharanthine (**1.22**)	Monterine (**2.6**)
Diphenyl ether head-to-tail Diphenyl ether tail-to-head 	Phenyl-benzyl ether head-to-tail Diphenyl ether tail-to-head 
Cycleanine (**1.21**)	Cycleatjehenine (**2.7**)

Only a minority of compounds falls within the category where the two monomers are connected by three bonds (Table 2.3). Cocsoline (**2.8**), with a dibenzo-*p*-dioxin system, is a representative of this subgroup. Tiliaresine (**2.9**) belongs to a subgroup of BBIQ's in which the tails are coupled through a direct carbon-carbon bond, rather than through the more common diaryl ether bridge. Variants of the compounds displayed in Table 2.3 are known primarily as arising from the isomerisation at C-1 of the isoquinoline rings, as well as the degree of *O*-methylation.

Table 2.3: BBIQ's connected by three bonds.

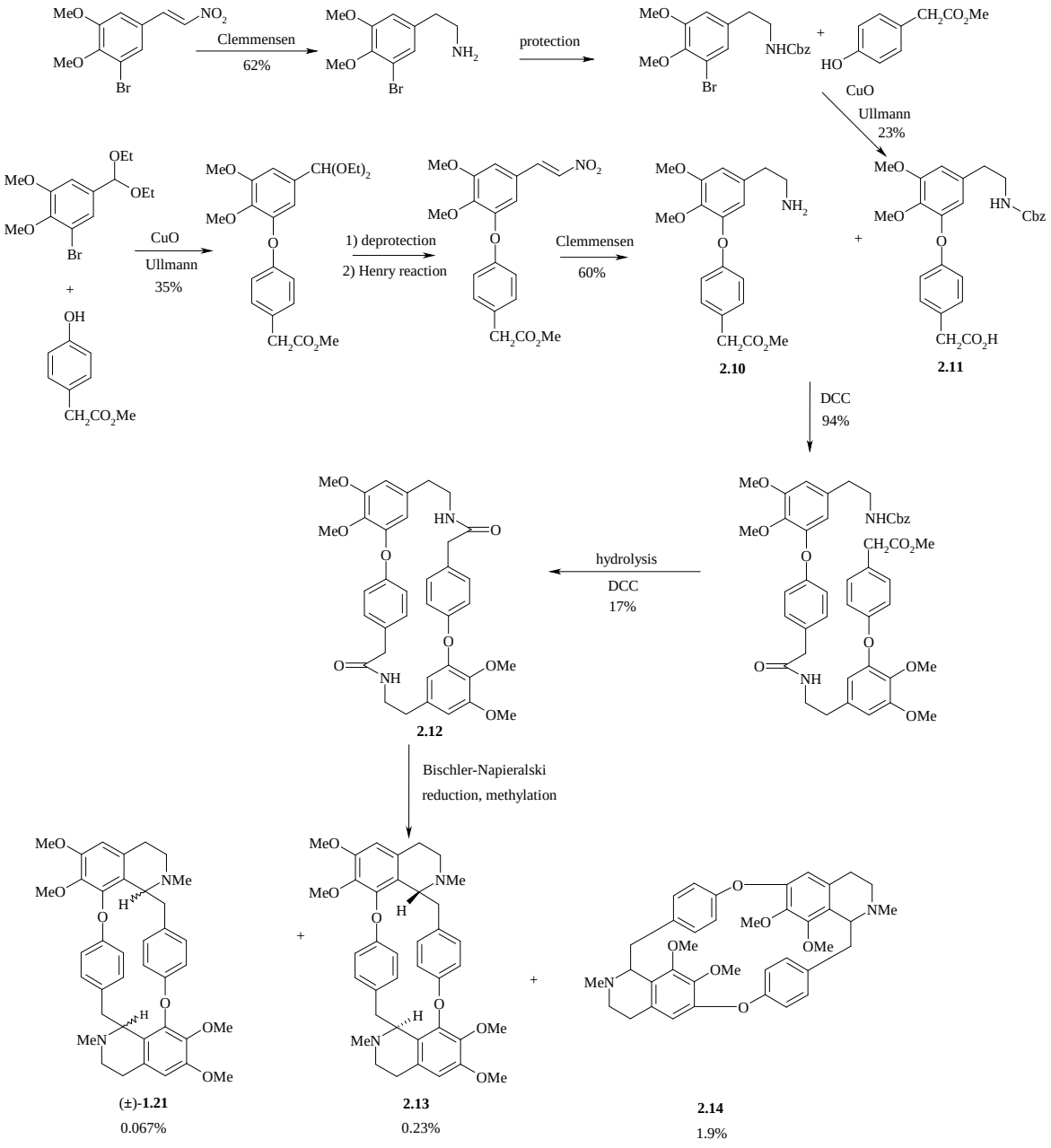
Diphenyl ether head-to-head Phenyl ether tail-to-tail	Diphenyl ether head-to-head Phenyl-phenyl tail-to-tail
	
Cocsoline (**2.8**)	Tiliaresine (**2.9**)

2.3 Previous synthetic studies of bisbenzyltetrahydroisoquinolines

In general, the original goal of total synthesis to confirm the structure of natural products has been slowly replaced by the biological importance of the compounds and/or the discovery of new chemistry along the pathway to the target molecule. Although various efforts in a number of laboratories have generated several approaches over the last five decades, there are only a few successful total syntheses of BBIQ's. This suggests that BBIQ's are very challenging molecules in terms of synthetic targets and it is evident that a lot of work still needs to be done in this arena. The following paragraphs review synthetic approaches to selected BBIQ's.

2.3.1 Synthesis of cycleanine (1.21)

Discovered by Kondo *et al.*[5] from *Cyclea insularis* (Makino) Diels in 1937, cycleanine (**1.21**) proved to be a true dimer with a symmetrical structure involving two diphenyl ether linkages. Almost thirty years after its isolation, Tomita *et al.*[6] reported the only published total synthesis of cycleanine (**1.21**) (Scheme 2.1). Ullmann reactions were used in the assembly of the crucial intermediates **2.10** and **2.11**.



Scheme 2.1: Synthesis of cycleanine (**1.21**).

Condensation of **2.10** and **2.11** utilising *N*,*N*'-dicyclohexylcarbodiimide (DCCD) gave a viscous oily amide, which was further converted to cyclobisamide **2.12** in 17% yield, thereby setting the stage for the key Bischler-Napieralski cyclisation. This Bischler-Napieralski reaction proved to be particularly efficient and well suited to afford a macrocyclic system with concomitant formation of the two stereogenic centres. However, cyclisation of cyclobisamide **2.12** gave cycleanine (**1.21**) in a low yield (0.067%), together with two isomers **2.13** (0.23%) and **2.14** (1.9%), showing the lack of regioselectivity as well as stereoselectivity of this route. This route was also not enantioselective.

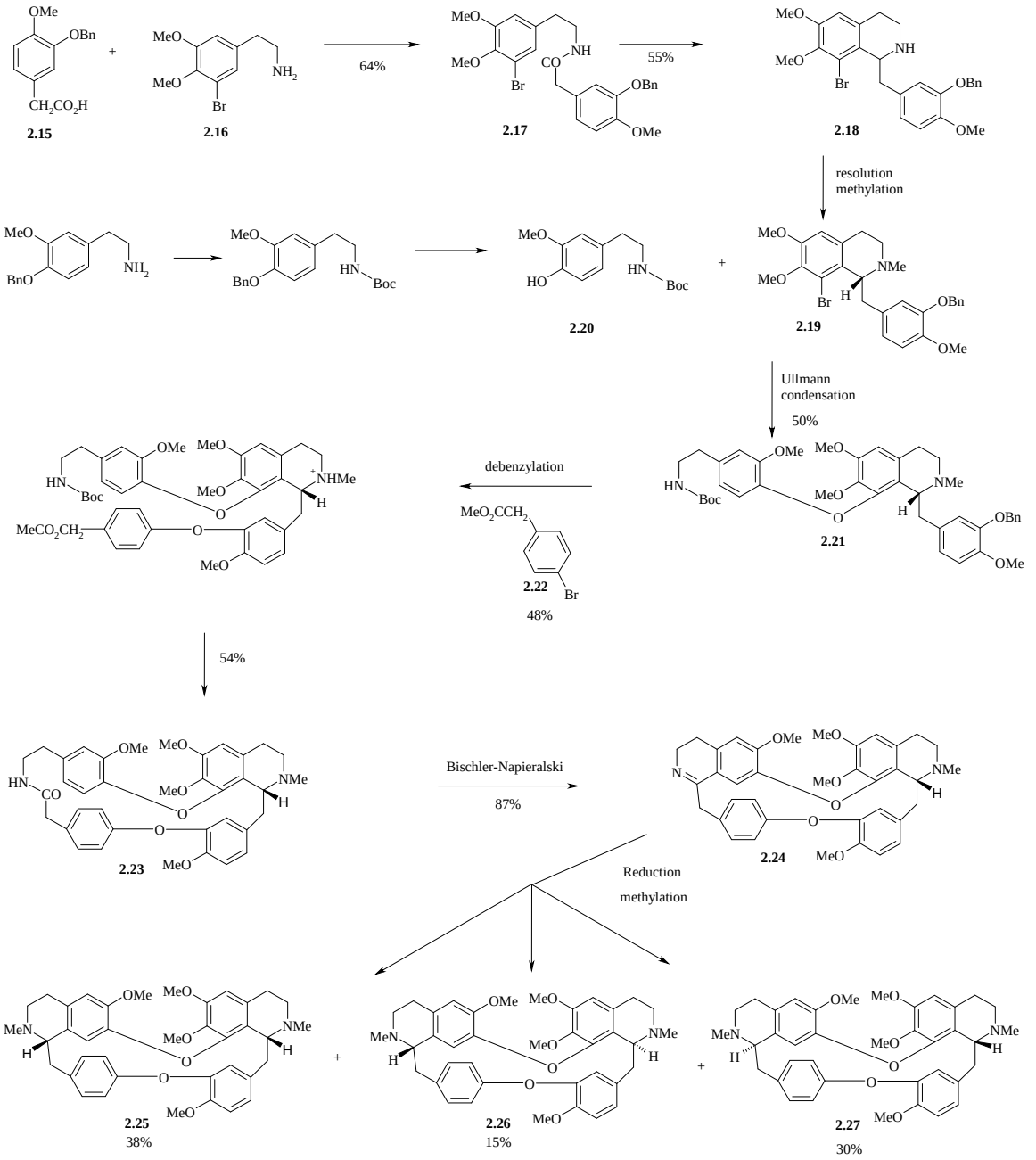
2.3.2 Synthesis of isotetrandrine (2.25), tetrandrine (2.26) and phaeanthine (2.27)

The arrival of tetrandrine (first isolation in 1935)[7] and its relatives, collectively known as the tetrandrine family, on the scene in the 1930's presented a new synthetic challenge. In addition to constructing the macrocyclic framework, one must also address the challenge of obtaining the correct stereoisomers. Inubushi and co-workers[8] were the first to complete the total synthesis of isotetrandrine (**2.25**), tetrandrine (**2.26**) and phaeanthine (**2.27**) by a common pathway (Scheme 2.2).

They adopted the strategy of first synthesising the tetrahydroisoquinoline *via* the Bischler-Napieralski reaction followed by formation of the diphenyl ether under Ullmann conditions. The intermediate **2.17** was prepared from the acid **2.15** and amine **2.16** and the reduced Bischler-Napieralski product **2.18** was resolved by using tartaric acid. Compound **2.17** has two sites available for cyclisation, but the original publication did not comment on the regioselectivity of the ring closure. Ullmann reaction between **2.19** and **2.20** gave **2.21** in 50% yield and the second Ullmann reaction between **2.21** and methyl *p*-bromophenylacetate afforded compound **2.22** in 48%. Cyclisation of **2.23** under Bischler-Napieralski reaction furnished **2.24** in 87%.

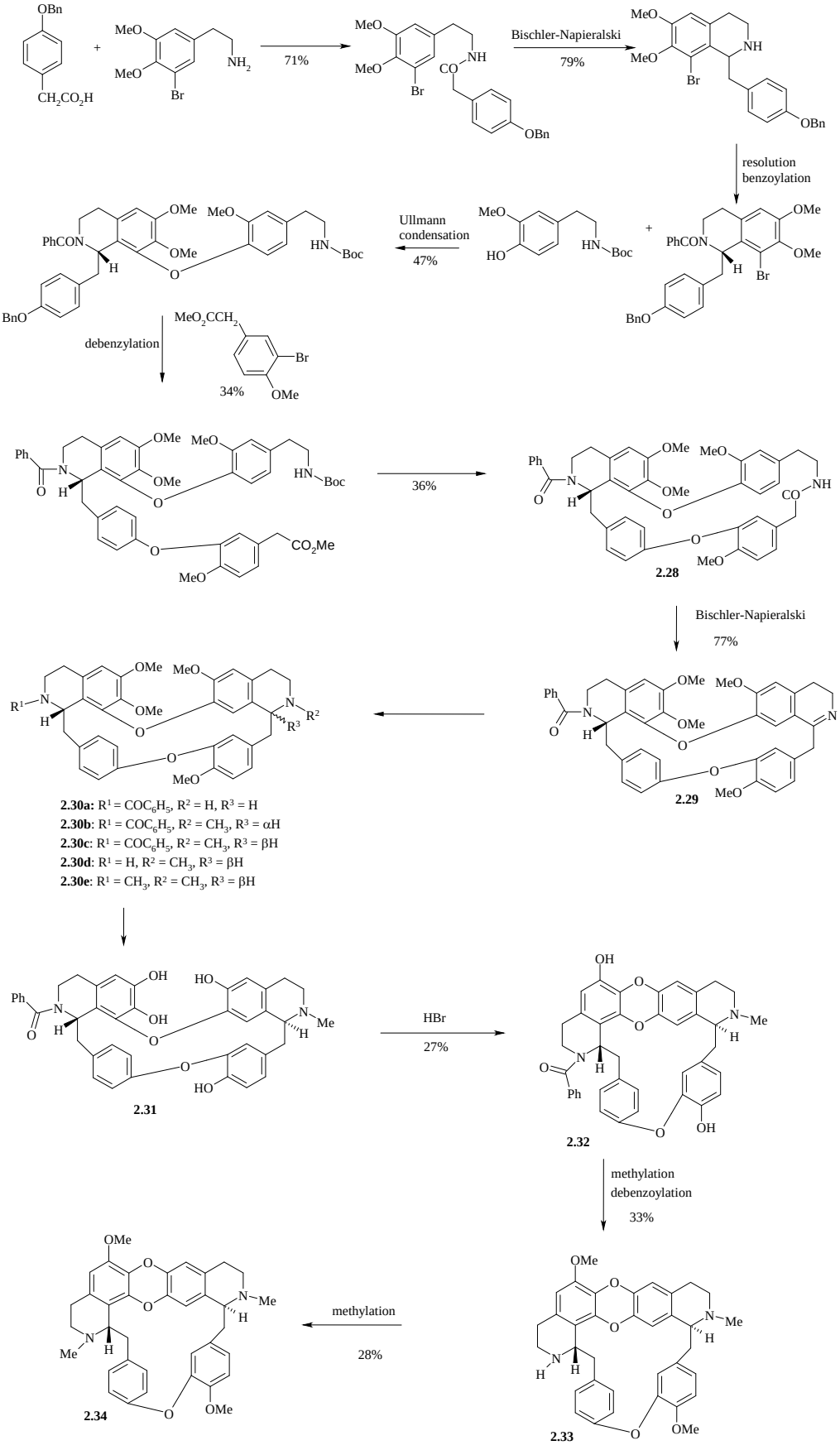
Reduction of 3,4-dihydroisoquinoline **2.24** under different sets of conditions gave different products. Reduction using zinc in ethanol-20% aqueous sulfuric acid followed by methylation afforded tetrandrine (**2.26**). Separation of diastereomers obtained by reduction using sodium borohydride in methanol at room temperature gave a mixture of isotetrandrine (**2.25**) and phaeanthine (**2.27**). Repetition of reactions in this scheme makes the route viable, for example, two sequential Ullmann reactions between **2.19** and **2.20** and

a second one between **2.21** and **2.22**, and two Bischler-Napieralski reactions of **2.17** to **2.18** and **2.23** to **2.24**. However, in this route the final stage is equivocal, because the direction of the Bischler-Napieralski reaction and stereoselectivity is not controlled.



Scheme 2.2: Synthesis of isotetrandrine (**2.25**), tetrandrine (**2.26**) and phaeanthine (**2.27**).

2.3.3 Synthesis of obaberine (2.30e), trilobine (2.33) and isotrilobine (2.34)



Scheme 2.3: Synthesis of obaberine (**2.30e**), trilobine (**2.33**) and isotrilobine (**2.34**).

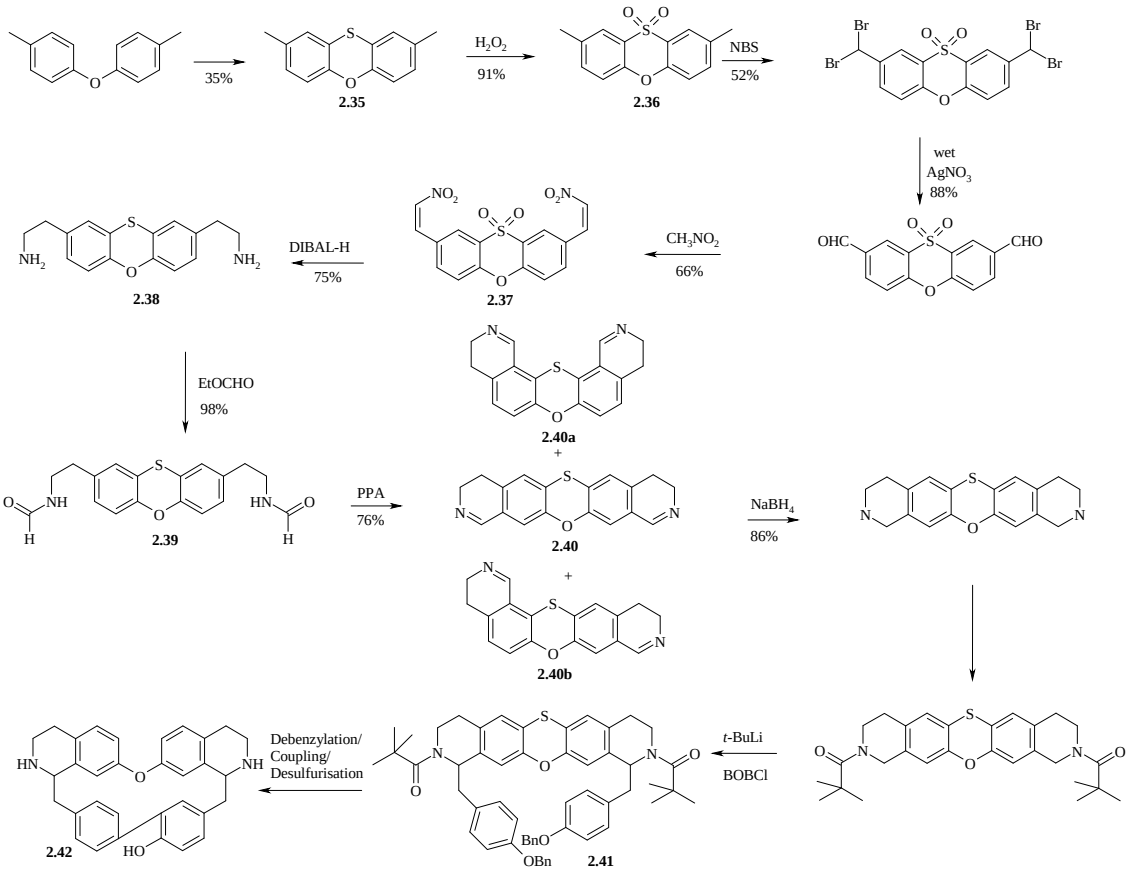
Following their success with the synthesis of isotetrandrine (**2.25**), tetrandrine (**2.26**) and phaeanthine (**2.27**), Inubushi *et al.*[9] reported the total synthesis of obaberine (**2.32**), trilobine (**2.33**) and isotrilobine (**2.34**) (Scheme 2.3). Stimulated by the antitumor effect of isotrilobine (**2.34**) against HeLa and HeLa-S_3 cells, Ehrlich ascites carcinoma (ascites tumor) and Sarcoma-180 (solid tumor),[10] the group embarked on the total synthesis of obaberine (**2.30e**) trilobine (**2.33**) and isotrilobine (**2.34**). The same strategy employed for the synthesis of the tetrandrine family was used.

The major highlight of this method was the highly regioselective Bischler-Napieralski cyclisation of the amide **2.28** to give regioisomer **2.29** as the sole product in a yield of 77%. Sodium borohydride reduction of compound **2.29** gave a diastereoisomeric mixture of **2.30a** in 90% yield and a subsequent *N*-methylation resulted in mixture of compounds **2.30b** and **2.30c**. Hydrogenation of **2.30c** afforded **2.30d** and *N*-methylation with formalin-$NaBH_4$ furnished obaberine (**2.30e**) in 30% yield from **2.30d**. Reduction of **2.30b** followed by demethylation gave the per-*O*-demethylated product **2.31**, which set the stage for the preparation of the dibenzo-*p*-dioxin nucleus which was formed by the treatment of **2.31** with HBr. Methylation and a subsequent hydrogenolysis of **2.32** afforded trilobine (**2.33**). Trilobine (**2.33**) was transformed into isotrilobine (**2.34**) by *N*-methylation. This is the only report to date presenting the total synthesis of a BBIQ containing three diphenyl ether linkages. Furthermore, this total synthesis demonstrates the power of synthesis to deliver large numbers of complex structures for biological investigations.

2.3.4 Approach towards macrocyclic BBIQ analogues by Al-Hiari and co-workers

The challenging molecular architecture, coupled with the biological actions of BBIQ's prompted Al-Hiari *et al.*[11] to undertake studies toward the total synthesis of a BBIQ (Scheme 2.4). Their attempt was based on the incorporation of a sulfur 'stitch', which would hold the BBIQ in an appropriate conformation for cyclisation. The key intermediate **2.37** was synthesised *via* bromination of phenoxathiin dioxide **2.36**, formed from oxidation of phenoxathiin **2.35**. Regeneration of the sulfone linkage by DIBAL from the dinitro derivative **2.37** was necessary for ring closure after formylation. Cyclisation of the diformyl derivative **2.39** to pentacyclic imine **2.40** yielded two more undesired products (**2.40a** and **2.40b**) where cyclisation occurred in inappropriate positions of **2.39**. Since the products decompose in solution, they were not separated, hence, after the poor prospects of

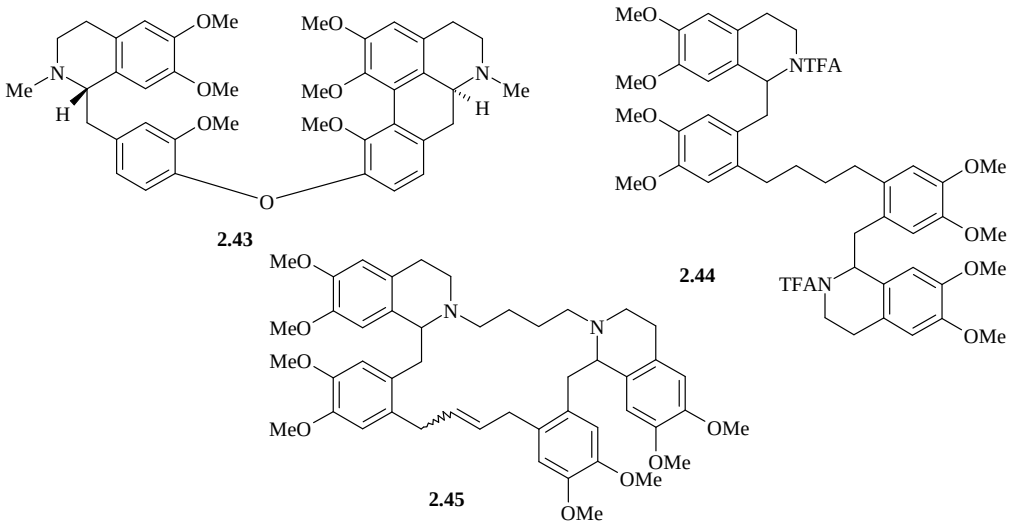
the envisaged Grignard reaction, the mixture was *N*-derivatised, lithiated and alkylated to compound **2.41**. Even though this group did not manage to do debenzylation, coupling and desulfuration that was required to give **2.42**, their synthesis deserves special mention.



Scheme 2.4: Approach to the total synthesis of BBIQ by Al-Hiari and co-workers.

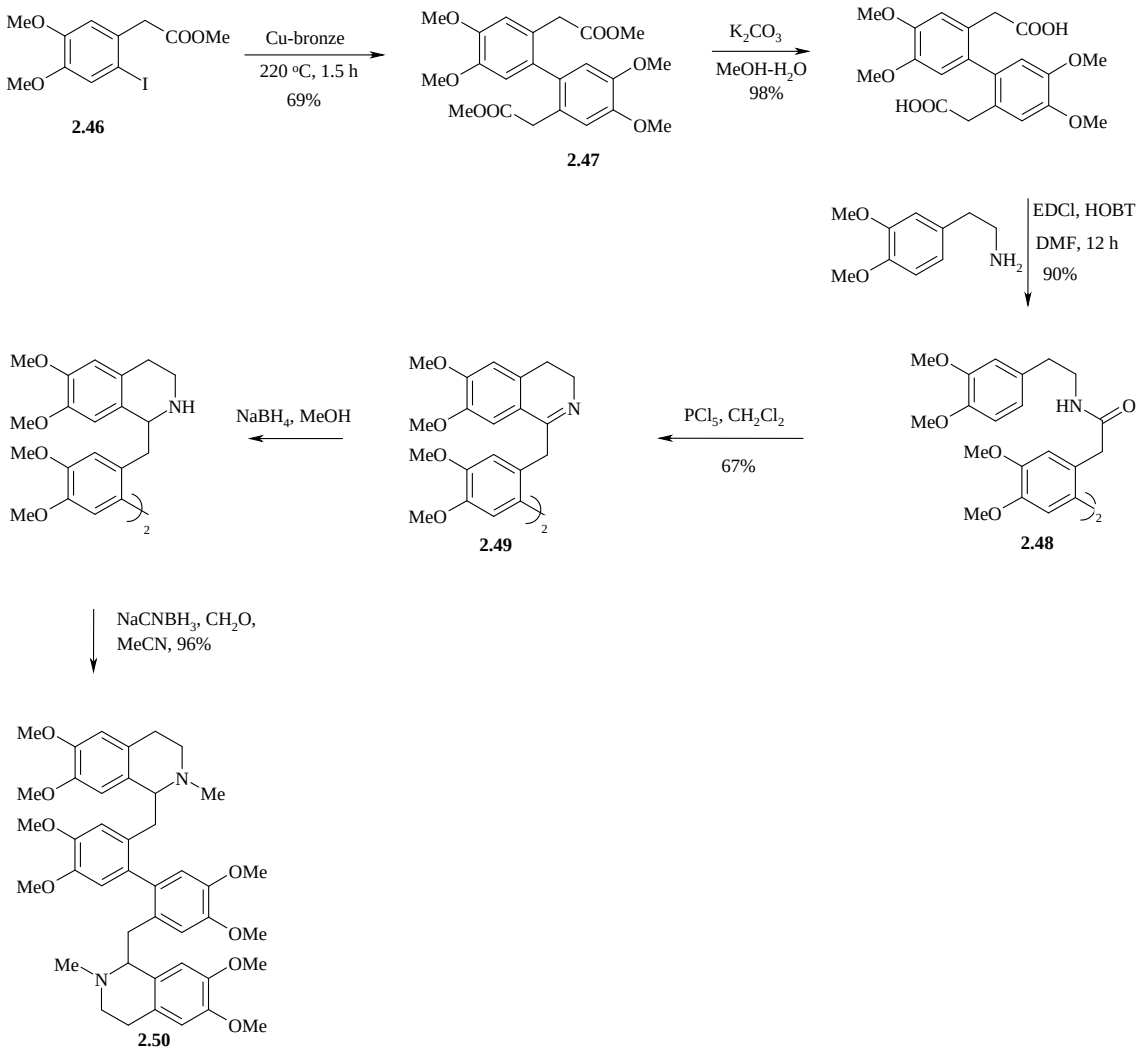
2.3.5 Synthesis of the laudanosine analogues

Thalicarpine (**2.43**), a BBIQ comprised of the benzylisoquinoline *S*-laudanosine connected with an ether linkage to an aporphine moiety, is active against Walker 256 carcinoma cells and Lewis lung tumor system.[12,13]



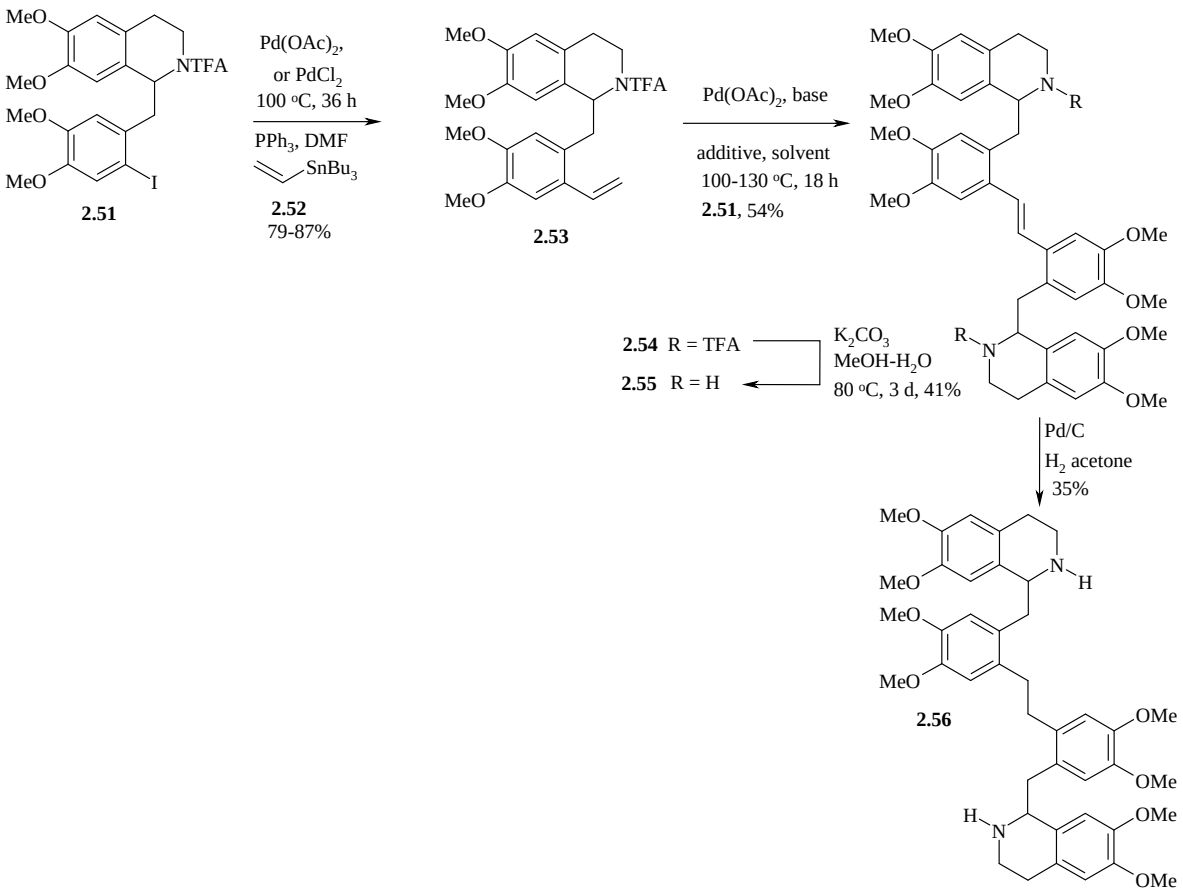
2.43 **2.44** **2.45**

Inspired by the complex structure and biological activity of thalicarpine (**2.43**), the Pyne[14] group at Wollongong University investigated the total synthesis of unnatural laudanosine analogues such as **2.44**, **2.45** and **2.50**. The preparation of **2.50** involved the Ullmann condensation of **2.46** to the key biaryl bond in **2.47** early in the synthesis followed by the construction of the BBIQ. The biphenyl **2.48** was converted to **2.49** using a standard Bischler-Napieralski cyclisation with a subsequent reduction-methylation to yield **2.50** (Scheme 2.5).



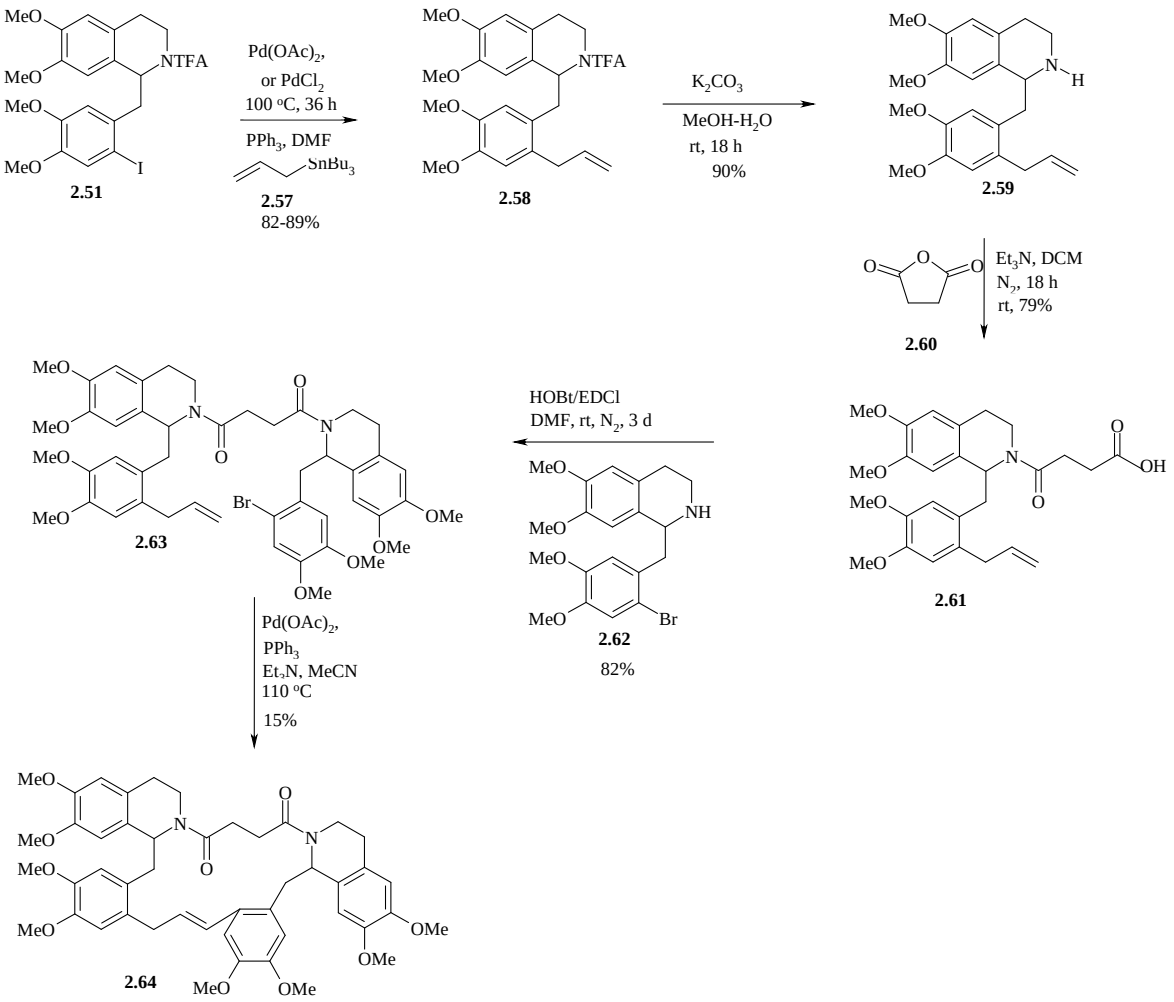
Scheme 2.5: Pyne and co-workers synthesis of thalicarpine analogue.

Following this success, the same group presented the synthesis of similar compounds using the Mizoroki-Heck and Sonogashira coupling reactions.[15] Their approach to the target compounds with an alkene linker used racemic *N*-trifluoroacetyl-2'-iodonorlaudanosine (**2.51**) as starting material (Scheme 2.6). A palladium-catalysed reaction using Stille's conditions between **2.51** and **2.52** gave **2.53** in 79% yield when palladium chloride was used with palladium acetate providing better yields of 87%. The Mizoroki-Heck reaction between **2.51** and **2.53** resulted in two geometric isomers which were inseparable by column chromatography, but the major isomer **2.54** precipitated from MeOH. Base-catalysed hydrolysis of **2.54** afforded a dimer with an alkene linker **2.55** which after hydrogenation furnished the target compound **2.56**. This method is short and straightforward, however, regioselectivity and stereoselectivity problems are not dealt with.



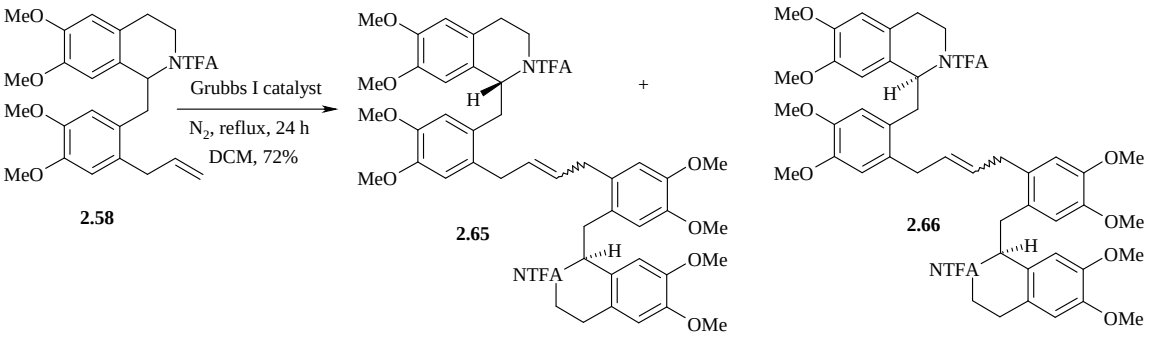
Scheme 2.6: Palladium-catalysed synthesis of the novel laudanosine dimer.

Similarly the macrocycle **2.64** was prepared by palladium-catalysed reaction using Stille's conditions. Thus, *N*-trifluoroacetyl-2'-iodonorlaudanosine (**2.51**) was condensed with an alkene **2.52** to furnish **2.58**, which was hydrolysed to **2.59**. Acylation of secondary racemic amine **2.59** with succinic anhydride (**2.60**) gave the amide **2.61**. Coupling between the amide **2.61** and 2'-bromobenzylisoquinoline derivative gave **2.63** in 82% yield. The desired macrocycle **2.64** was formed in 15% yield under traditional Heck reaction conditions [$Pd(OAc)_2$, PPh_3 and Et_3N] (Scheme 2.7).



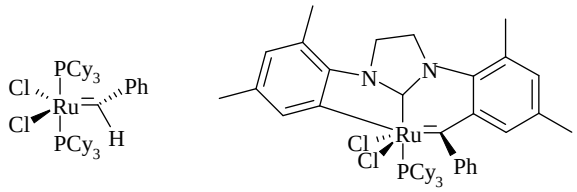
Scheme 2.7: Palladium-catalysed synthesis of the macrocyclic laudanosine.

Prompted by the potential anticancer activity of BBIQ's, Batenburg-Nguyen *et al.*[16] have reported the synthesis of laudanosine dimers based on ruthenium-mediated cross-metathesis (CM) reactions as well ruthenium-catalysed ring closing metathesis (RCM) for the synthesis of conformationally restricted macrocyclic BBIQ derivatives. This method used the same starting compound **2.58**, but coupling and ring closing was achieved by metathesis reactions. The derivative **2.58** was treated with Grubbs I (**2.67**) catalyst to afford the homocoupled isomers **2.65** and **2.66** in 72% yield (Scheme 2.8). Yet, when 2'-vinyllaudanosine was subjected under the same CM conditions, no homocoupled products could be obtained. However, changing from Grubbs I (**2.67**) to Grubbs II (**2.68)** catalysts (Fig 2.3) resulted in increased reactivity of the alkene and more product was obtained.



Scheme 2.8: Ruthenium-mediated cross-metathesis (CM) synthesis of the novel laudanosine dimers.

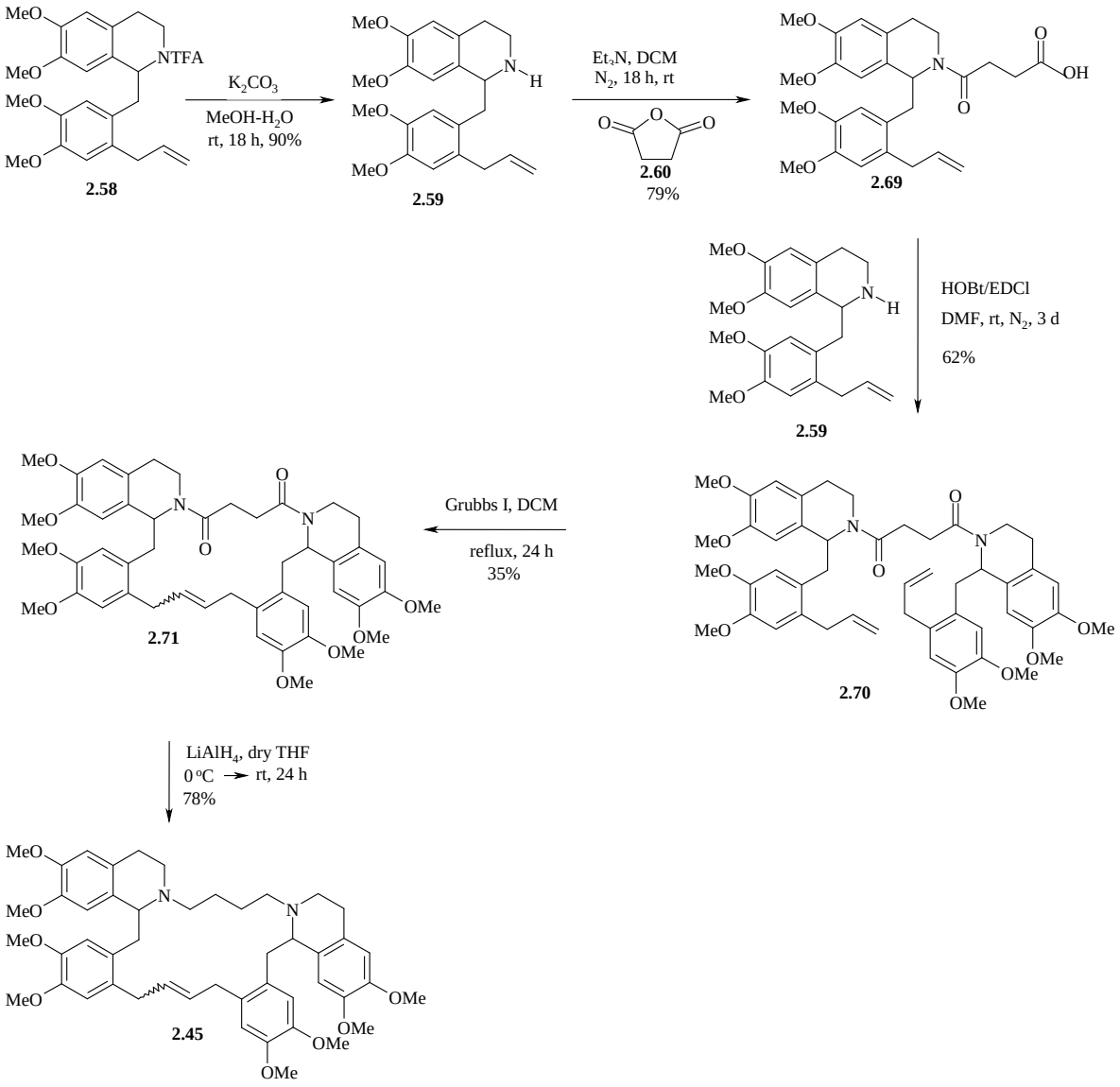
RCM was used to construct the target compound **2.45** (Scheme 2.9). Base-catalysed deprotection of **2.58** and a subsequent acylation of amine **2.59** with succinic acid (**2.60**) afforded the carboxylic acid **2.69**. The slow amide coupling reaction (over 3 days) between **2.59** and **2.69** afforded **2.71** in 62% yield. Intramolecular RCM of **2.70** using Grubbs I (**2.67**) catalyst in DCM afforded **2.71** in 35% yield, and reduction of the carbonyl groups afforded the target compound **2.45**.



Grubbs' catalyst I — **2.67**

Grubbs' s catalyst II — **2.68**

Figure 2.2: Grubbs'catalysts **2.67** and **2.68**.



Scheme 2.9: Ruthenium-mediated cross-metathesis (CM) synthesis of the macrocyclic laudanosine.

Within our group, the isolation of small amounts of BBIQ's from plant materials by Helene de Wet[17] emphasised the importance to embark on the total synthesis of BBIQ's to produce more material needed for biological testing. In the field of total synthesis of BBIQ's Maumela[18] (from our group) has made a valuable contribution. Most importantly, his endeavour led to the development of useful synthetic reactions. Amongst them are the improvement of the Ullmann coupling between electron-rich aryl halides and electron-poor phenols.

Most BBIQ's have been prepared by the condensation of two appropriate benzyltetrahydroisoquinoline monomers to form the biaryl ether. The following paragraphs discuss different synthetic methods for the preparation of bisbenzylisoquinoline monomers, *i.e.* the Bischler-Napieralski, Pomeranz-Fritsch and Pictet-Spengler reactions. The method that we used, the Pictet-Spengler reaction, is discussed in greater detail with special emphasis on reaction mechanism, regioselectivity as well substrates dependence. Detailed protocols for the preparation of the key diaryl ether linkages are also described.

2.4 Methods for the synthesis of tetrahydroisoquinolines

The 1,2,3,4-tetrahydroisoquinoline (THIQ) scaffold is present in both natural and synthetic organic compounds with a variety of important biological activities such as antitumour,[19,20] antithrombotic,[21] antimicrobial,[22] P-gp modulators,[23] antimalarial,[24] hypothermic,[25] increased estrogen receptor modulation,[26] bradycardic,[27] neuroprotective or neurotoxic[28] and antiplatelet aggregation.[29,30] A number of elegant enantioselective methods, including the metal-catalysed cyclisation reactions,[31] the Pomeranz-Fritsch reaction,[32] Bischler-Napieralski,[33] Pictet-Spengler cyclisation[34] have been developed to synthesise theses compounds. The largest part of the enantioselective approaches is based on asymmetric hydrogenation of cyclic imines accessed by the Bischler-Napieralski reaction.[35]

Approaches towards the synthesis of the isoquinoline framework can be categorised into 15 different methods.[36,37] The commonly used types in the literature includes strategies consisting of elaboration of the heterocyclic ring through the formation of one C-C or C-N bond (Fig. 2.3). However, synthetic protocols of Types 1 (Bischler-Napieralski and Pictet-Spengler), 2 and 5 (Pomeranz-Fritsch and its modifications) are the most widely used for the construction of tetrahydroisoquinolines. These methods allow the synthesis of an enantiopure 1-substituted-tetrahydroisoquinoline in two steps: cyclisation and creation of the stereocentre, although only the Pictet-Spengler reaction creates the stereogenic carbon at C-1 simultaneous with the ring closure.

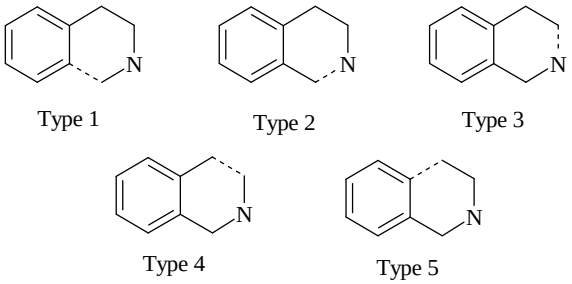
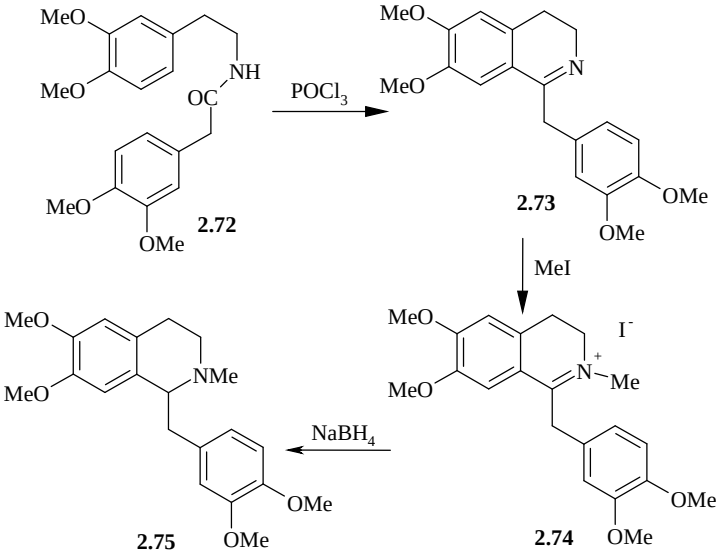


Figure 2.3: Heterocyclic ring formation of isoquinolines.

2.4.1 Bischler-Napieralski reaction

The Bischler-Napieralski reaction involves the conversion of a *N*-acyl-β-phenethylamide (**2.72**) into its 3,4-dihydroisoquinoline **2.73** in the presence of a Lewis acid, followed by reduction of **2.74** to THIQ **2.75** since most of the isoquinolines exist as tetrahydro derivatives (Scheme 2.10).

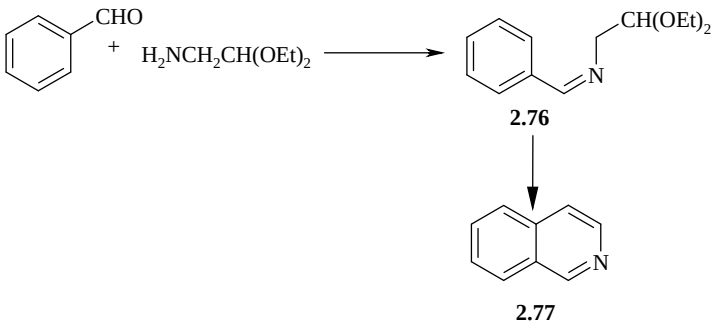


Scheme 2.10: Formation of laudanosine *via* the Bischler-Napieralski reaction.[38]

2.4.2 Pomeranz-Fritsch reaction

The Pomeranz-Fritsch reaction represents a synthetic method for Type 5 synthesis entailing cyclisation of benzalaminoacetal under acid-catalysed conditions. The benzalaminoacetal **2.76** is prepared by condensation of aldehyde and aminoacetal and the successive cyclisation leads to the isoquinoline **2.77** (Scheme 2.11). The yields of isoquinolines vary from zero to more than 80%, with 3-hydroxy and 3-alkoxy bezaldehyde

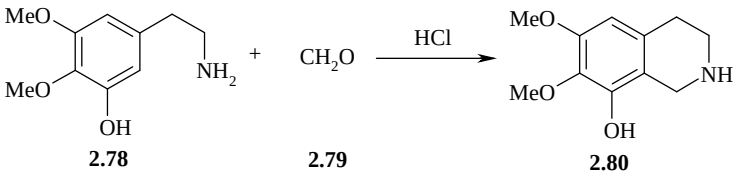
giving satisfactory results, whereas, 2- or 4-alkoxy derivatives afford the isoquinolines in low yields or no products,[39,40] and this renders the Pictet-Spengler reaction a method of choice.



Scheme 2.11: The Pomeranz-Fritsch reaction for the formation of isoquinoline **2.77**.

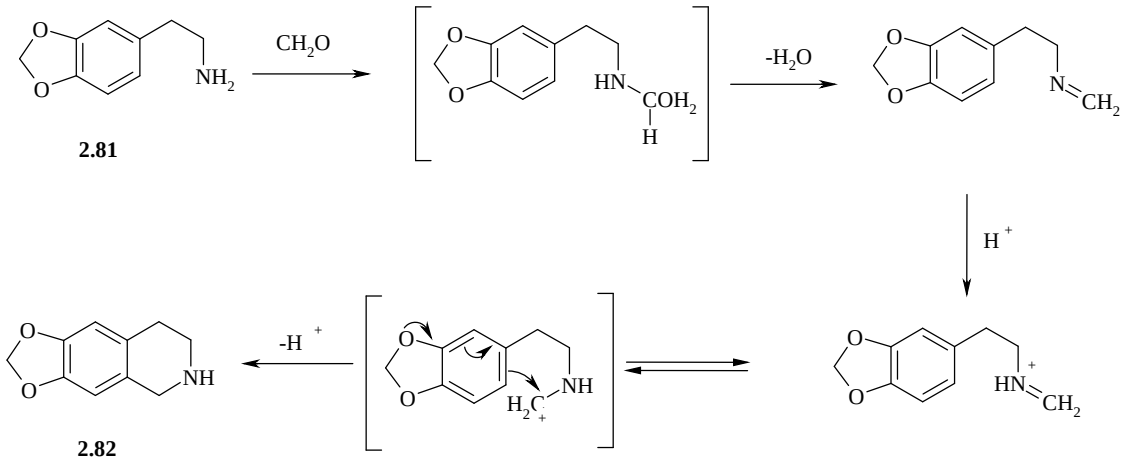
2.4.3 Pictet-Spengler reaction

The Pictet-Spengler reaction involves a Mannich-type reaction, wherein β-phenethylamine **2.78** condenses with formaldehyde (**2.79**) in the presence of acid to yield a THIQ **2.80** (Scheme 2.12).



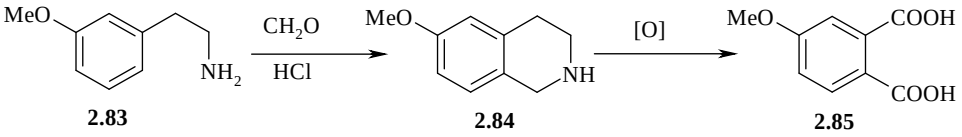
Scheme 2.12: The Pictet-Spengler condensation to the 1,2,3,4-tetrahydroisoquinoline **2.80**.

The reaction mechanism of the Pictet-Spengler reaction consists of the formation of a Schiff base as an intermediate which can be cyclised in the presence of the acid. The mechanism of the formation of norhydrohydrastinine (**2.82**) from homopiperonylamine (**2.81**) is illustrated in Scheme 2.13.



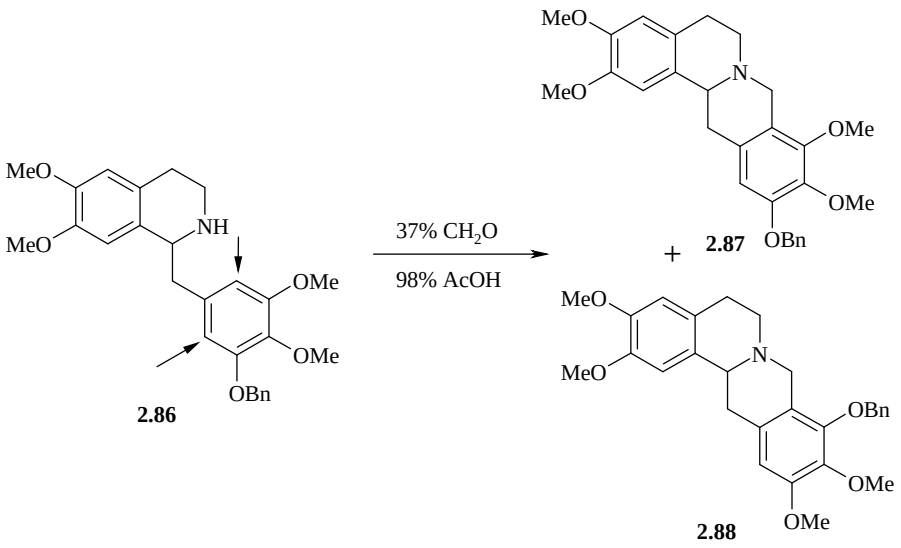
Scheme 2.13: Reaction mechanism of the Pictet-Spengler reaction.

Ring closure depends on the nature and position of the aromatic substituents of the β-phenethylamine moiety of the imine, with the presence of the electron-donating hydroxy or alkoxy group at the *para* position of cyclisation essential. Thus, the reaction of phenethylamine **2.83** with formaldehyde yields only 1,2,3,4-tetrahydro-6-methoxyisoquinoline (**2.84)** and no 8-methoxy product was isolated. Oxidation of **2.84** proved the structure to be 4-methoxyphthalic acid[41] (**2.85**) (Scheme 2.14).



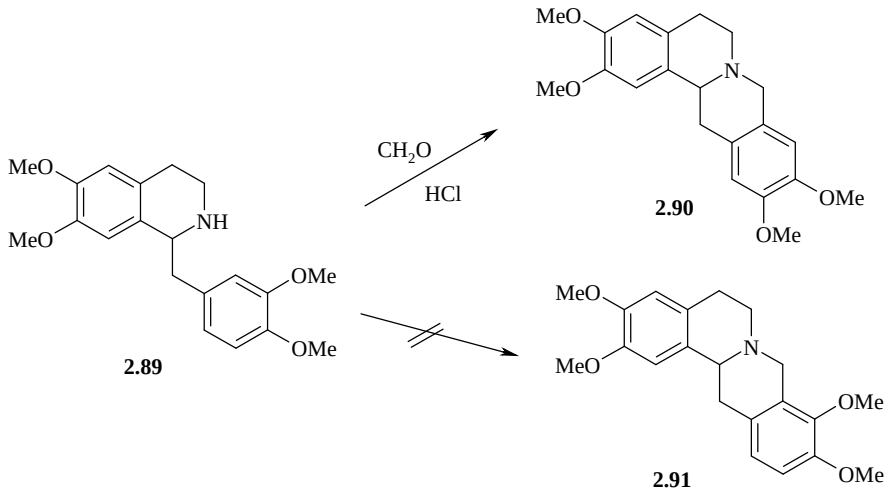
Scheme 2.14: Formation of 4-methoxyphthalic acid.

The product obtained by cyclisation of a 3,4-dialkoxy-β-phenethylamine is always the 6,7-dialkoxy derivatives and 7,8-dialkoxy derivatives are not formed. A mixture of the two tetrahydroisoquinoline derivatives is isolated when both *ortho* positions are activated. This reaction is illustrated by the condensation of 1-(3-benzyloxy-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2.86**) with formaldehyde to give two products **2.87** and **2.88** with **2.88** being the minor isomer due to steric reasons (Scheme 2.15).[42]



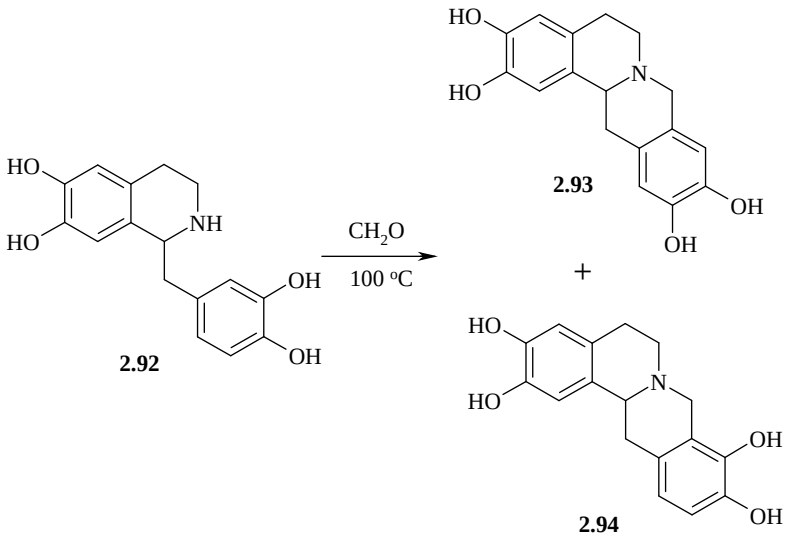
Scheme 2.15: Regioselectivity in the Pictet-Spengler reaction.

Generally, cyclisation has a tendency to occur at the *para* position to an alkoxy group, for example, during synthesis of tetrahydro-*ψ*-berberine (**2.90**) from 1-veratrylnorhydrohrastinine (**2.89**) product **2.91** was not isolated (Scheme 2.16).[43]



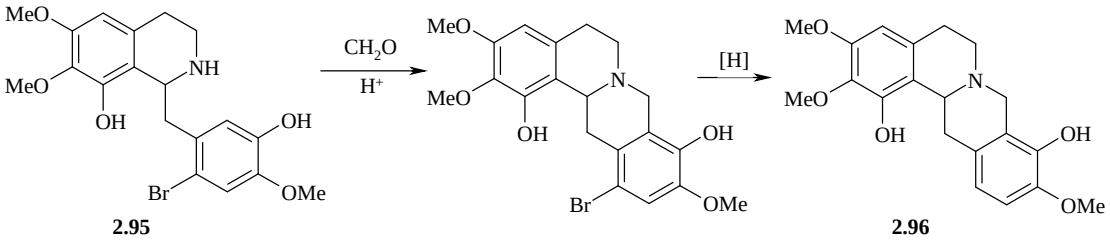
Scheme 2.16: Synthesis of tetrahydro-*ψ*-berberine

On the other hand, if the alkoxy groups are replaced by hydroxy groups as in compound **2.92**, then the ring closure proceeds to both *ortho* and *para* positions. Thus, treatment of tetrahydropapaveroline (**2.92**) with formaldehyde afforded a mixture of **2.93** and **2.94** in equal amounts (Scheme 2.17).



Scheme 2.17: Regioselectivity in the presence of free hydroxy groups

The presence of the free hydroxy groups in the benzyl residue activates the *ortho* position. In the case where both *para* and *ortho* positions are available for cyclisation, Kametani decided to use bromine as a blocking group to direct cyclisation to *ortho* position. Thus, capaurine (**2.96**) was synthesised by the Pictet-Spengler reaction of the 1-(2-bromo-4-methoxy-5-hydroxybenzyl)isoquinoline (**2.95**), followed by a reductive cleavage of the aryl bromide[44] (Scheme 2.18).



Scheme 2.18: Synthesis of capaurine (**2.96**).

2.4.4 Asymmetric synthesis of tetrahydroisoquinolines

Most of the 1-substituted THIQ alkaloids in nature possess the 1*S* absolute configuration, but there are few with 1*R*-configuration and the two enantiomers exhibit different biological activities. However, the methods described above did not address the absolute configuration associated with THIQ's. Enantioselective syntheses of THIQ's in the

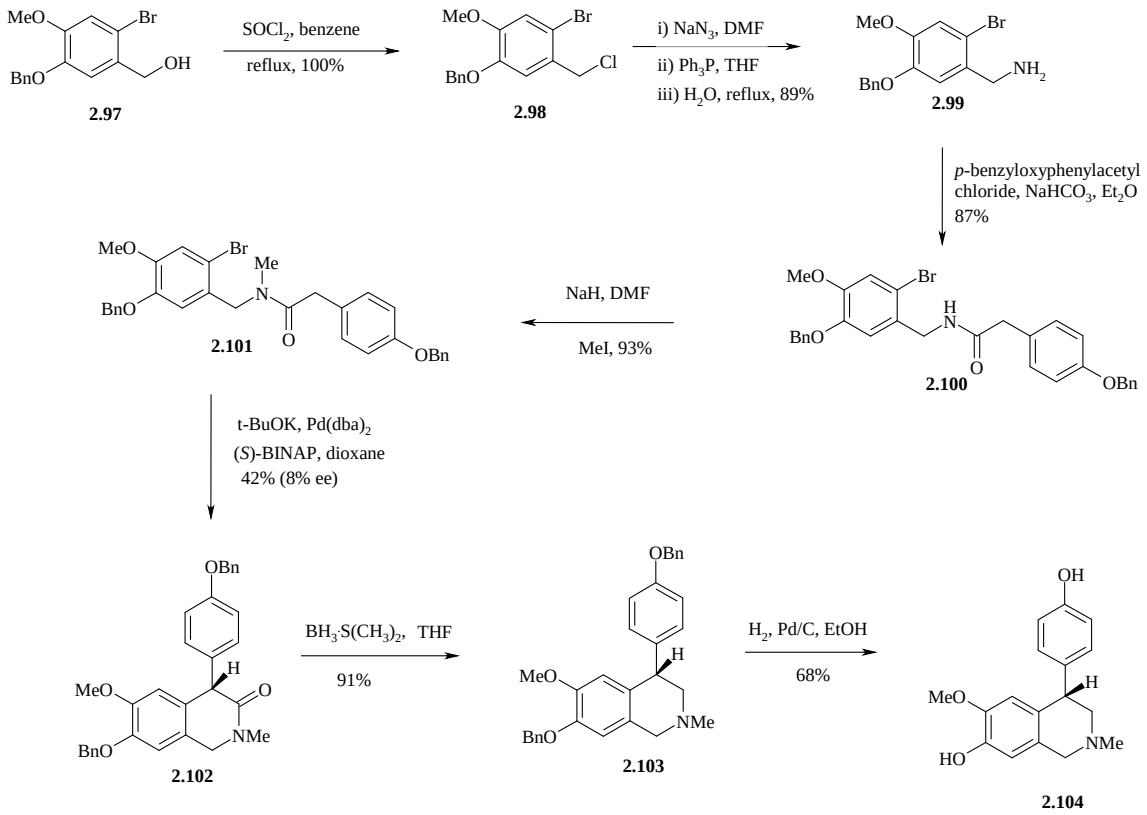
literature involve mostly the use of chiral auxiliaries. Asymmetric syntheses of THIQ's are based generally on the stereochemical modification of the traditional methods, which are:

1) Metal-catalysed cyclisation reactions
2) Pomeranz-Fritsch reaction
3) Bischler-Napieralski reaction (most enantioselective syntheses involve reduction of the resulting imine with a chiral hydride reducing agent or asymmetric catalytic hydrogenation)
4) Pictet-Spengler cyclisation

The following paragraphs intend to discuss these methods briefly.

2.4.4.1 Metal-catalysed cyclisation reactions

The palladium-catalysed coupling reaction of an aryl halide or vinyl halide with an enolate is a promising procedure to construct the carbon framework of heterocyclic THIQ's. Honda *et al.*[45] employed this type of coupling reaction for the synthesis of the basic skeleton of the tetrahydroisoquinoline in the synthesis of cherylline (**2.104**) (Scheme 2.19). The amide **2.100** was prepared in six steps from the alcohol **2.97** *via* chloride **2.98**. The Schotten-Baumann reaction of amine **2.99** with *p*-benzyloxyphenylacetyl chloride gave amide **2.100**. The Pd-catalysed intramolecular coupling reaction of **2.101** in the presence of 0.1 eq. $Pd(dba)_2$, 1.5 eq. *t*-BuOK and chiral ligand *S*-BINAP in refluxing dioxane, gave **2.102** in 42% yield with only 8% *ee* (based on HPLC).

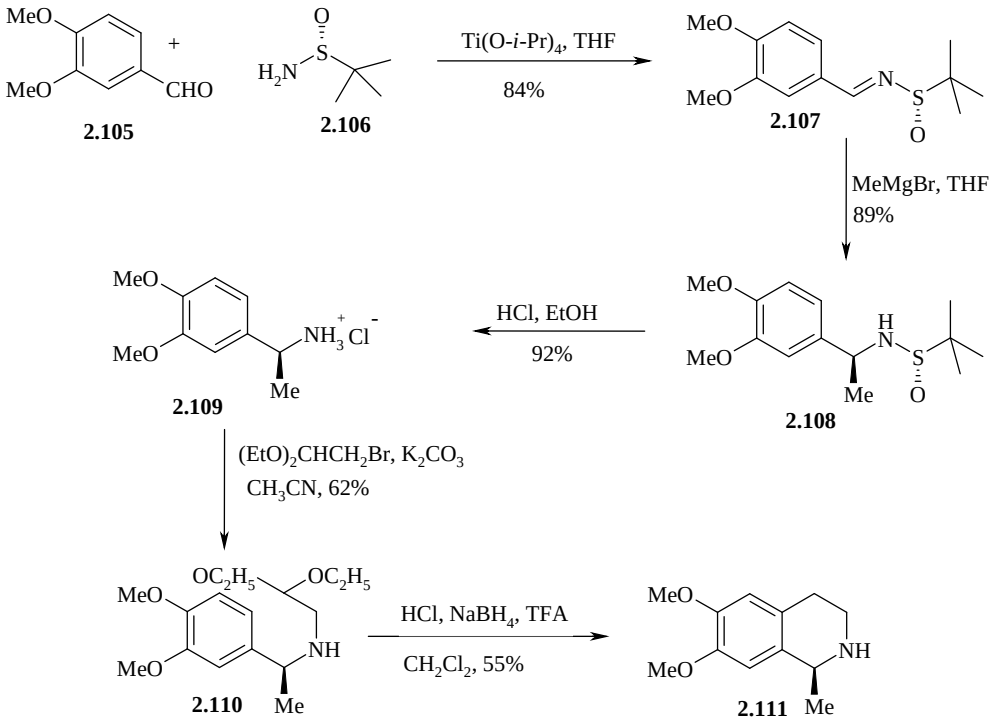


Scheme 2.19: Synthesis of cherylline (**2.104**).

2.4.4.2 The Pomeranz-Fritsch reaction

The original Pomeranz-Fritsch method has been improved and modified in many ways. A useful modification was developed by Bobbit[46] as a two-step procedure in which the Pomeranz-Fritsch imine was hydrogenated in situ to the aminoacetal. Enantiopure *N*-sulfinimines have played a role in the asymmetric synthesis of amines, providing access to synthesis of natural products such as THIQ's. Grajewska and Rozwadowska[47] reported the synthesis of *S*-salsolidine (**2.111**) based on diastereoselective modification of Pomeranz-Fritsch methodology (Scheme 2.20). *S*-salsolidine (**2.111**) was prepared in a five-step reaction sequence from condensation of 3,4-dimethoxybenzaldehyde (**2.105**) with *R*-*N*-*tert*-butanesulfinylamide (**2.106**) in the presence of Ti(O-*i*-Pr)$_4$ to give sulfinimine **2.107** in 84% yield. Condensation of **2.107** with a Grignard reagent under optimised conditions afforded sulfinamide **2.108** with 98:2 *dr* with the absolute configuration being *S*, recrystallisation lead to improvement of the *de* to 99%. Removal of the *N*-sulfinyl auxiliary afforded **2.109**, which was alkylated to give the Pomeranz-Fritsch amine **2.110**.

A one-pot hydrolysis and reduction of **2.110** furnished **2.111** in 55% yield. This method gave (*S*)-salsolidine (**2.111**) in 24% overall yield with 98% *ee*.



Scheme 2.20: Synthesis of *S*-salsolidine (**2.111**).

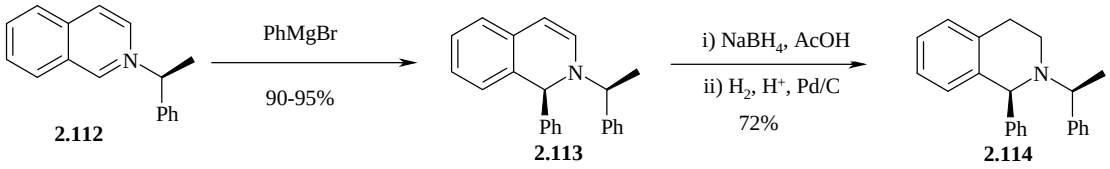
2.4.4.3 The Bischler-Napieralski reaction

The Bischler-Napieralski reaction has been the most frequently explored approach to the asymmetric synthesis of THIQ's. Reduction of the 3,4-dihydroisoquinoline is crucial for the stereochemical outcome and this step can be achieved by either diastereoselective or enantioselective synthesis.

2.4.4.3.1 Diastereoselective synthesis

Hydride reduction or catalytic hydrogenation of chiral 1-substituted 3,4-dihydroisoquinolines or the corresponding 3,4-dihydroisoquinolinium salts have been found to give excellent results. In most cases, a chiral auxiliary was appended to the imine nitrogen. Barbier *et al.*,[48] in their synthesis of 1-alkyl, 3-alkyl and 1,3-dialkyl-1,2,3,4-tetrahydroisoquinolines, used the chiral isoquinolium salt **2.112** (Scheme 2.21). The

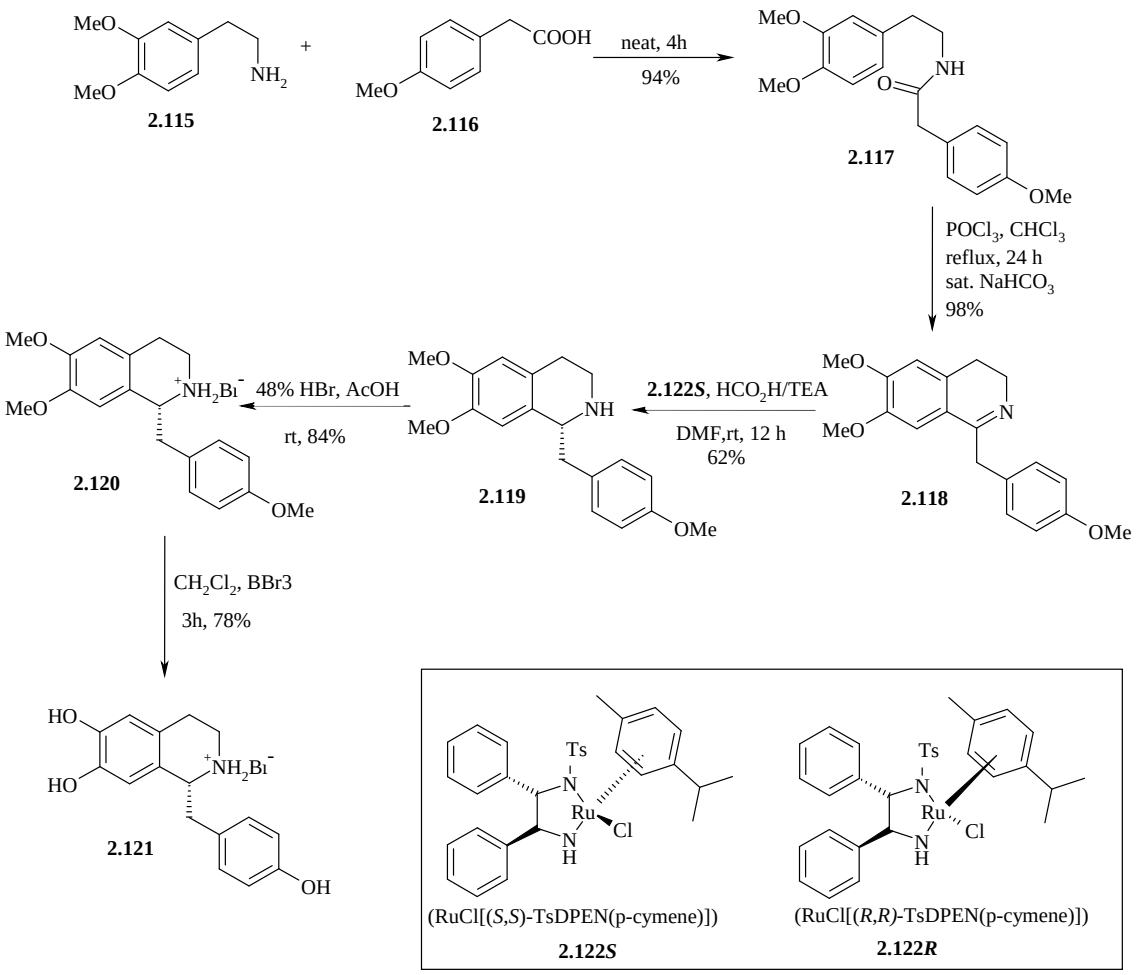
reaction of salt **2.112** with a Grignard reagent gave 1-substituted dihydroisoquinolines in quantitative yields. In the preparation of **2.114**, the intermediate **2.113** was obtained in good *de* (74%) and isolated in 72% yield after recrystallisation. The absolute stereochemistry of C-1 in **2.114** was found to be *S* from the X-ray structure of **2.113**, however, this configuration was reported to be *R* in several papers. [35]



Scheme 2.21: Synthesis of 1-alkyl-1,2,3,4-tetrahydroisoquinoline **2.114**.

2.4.4.3.2 Enantioselective synthesis

Asymmetric synthesis of isoquinoline alkaloids accessed by the Bischler-Napieralski cyclisation is based on the reduction of the resulting prochiral amine with a chiral hydride reducing agents or hydrogenation in the presence of chiral catalysts. Pyo *et al.*[49] used Noyori's catalyst, RuCl[(*S*,*S*)-TsDPEN](p-cymene)] (**2.122***S*) and RuCl[(*R*,*R*)-TsDPEN](p-cymene)] (**2.122***R*), in the synthesis of *S*-higenamine and *R*-higenamine, respectively (Scheme 2.22). Commercially available amine **2.115** and phenylacetic acid **2.116** were heated to provide amide **2.117** (94% yield), which was subjected to Bischler-Napieralski cyclisation to form imine **2.118** in 98% yield. Catalytic asymmetric reduction of **2.118**, gave **2.119** in 62% yield with 99% *ee*. Treatment of **2.119** with HBr-AcOH afforded the salt **2.120** in 84% yield, and subsequent methylation furnished **2.120** in 78% yield in >99% *ee*.

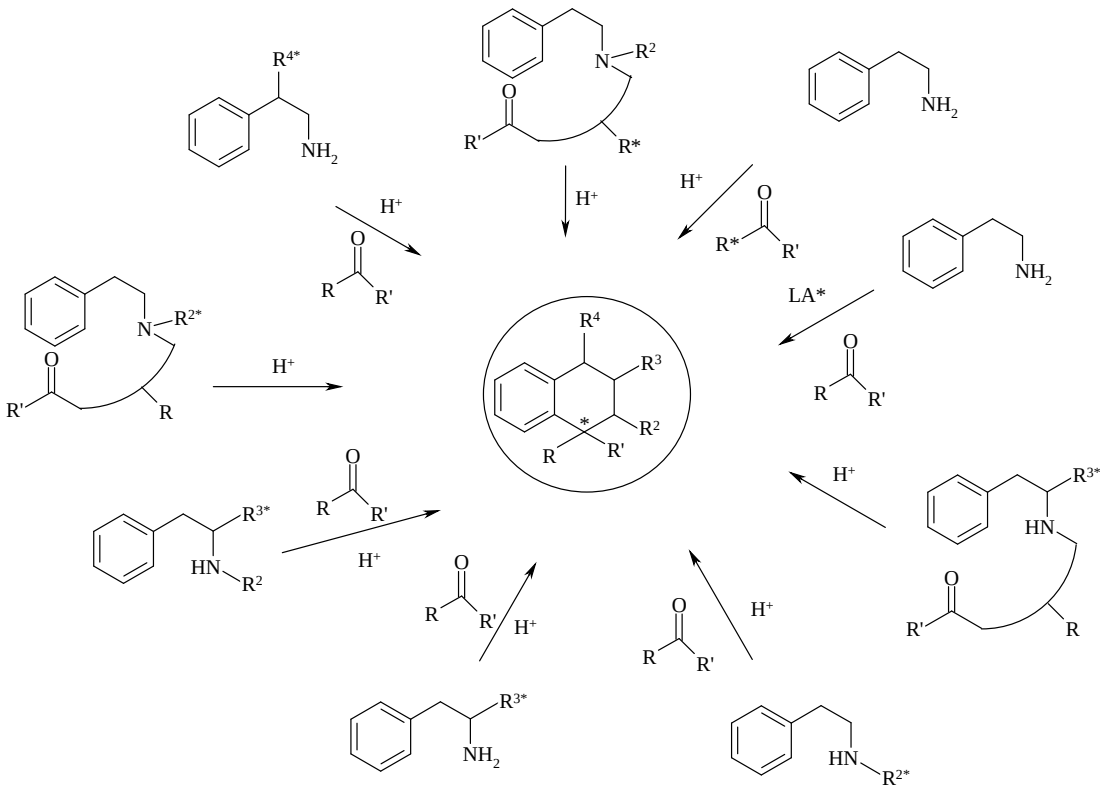


Scheme 2.22: Synthesis of *R*-higenamine (**2.121**).

2.4.4.4 The Pictet-Spengler cyclisation

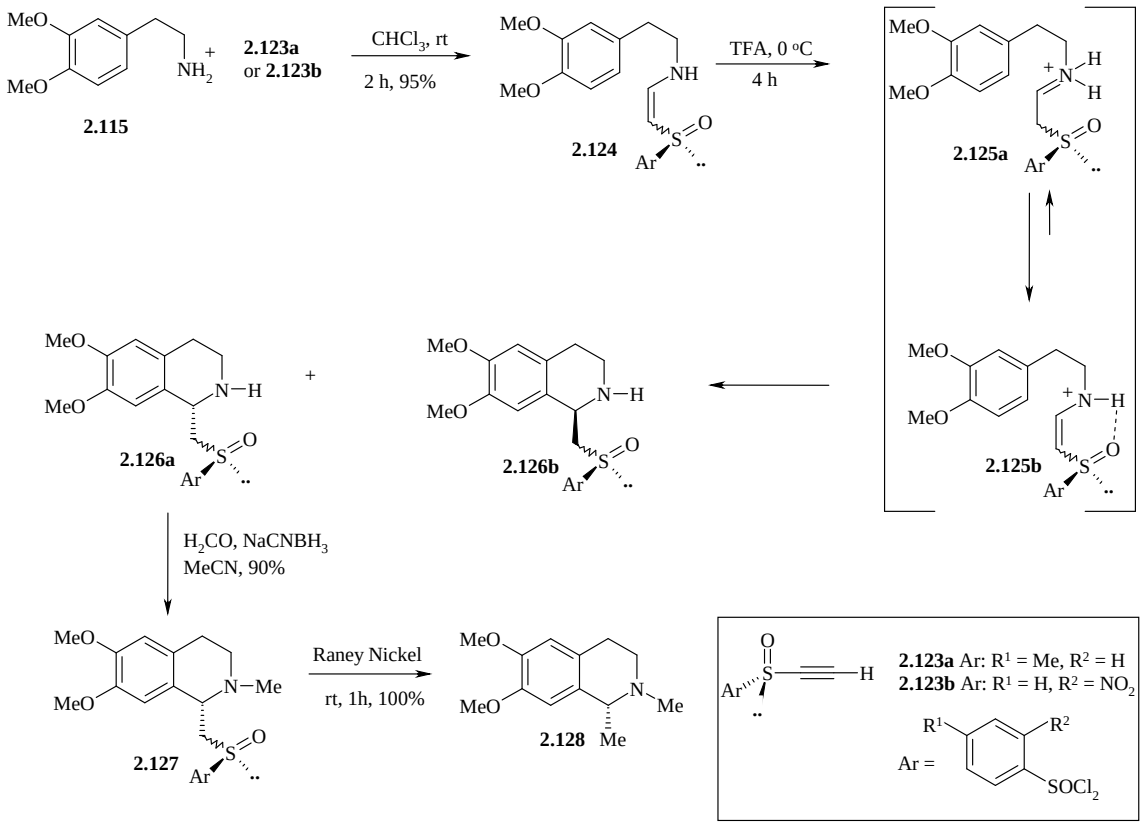
The Pictet-Spengler reaction is a convenient method for the synthesis of THIQ's since the stereogenic centre is generated simultaneously with the ring closure in a one-pot process. In the syntheses that have been carried out in an asymmetric manner, the chirality transfer occurred from the chiral auxiliary introduced to either the β-arylethylamine or the aldehyde component, thus involving a diastereoselective synthesis.

These methods include the use of 1,4-chirality[50] and 1,3-chirality[51] transfers (Scheme 2.19). Optically-active aldehydes and ketones[52] tethered to the amino group of β-phenethylamine[53] have found wide use in the syntheses of THIQ's and other syntheses include combinations of the above strategies.[54]



Scheme 2.23: Approaches to the stereoselective synthesis of 1-substituted THIQ.

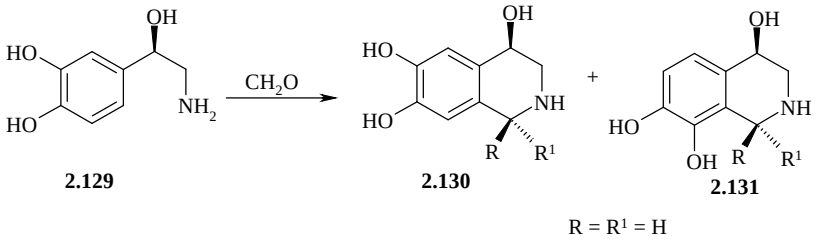
Lee *et al.*[55] subjected the prepared chiral acetylenic sulfoxide **2.123a** or **2.123b** to a conjugate addition with 3,4-dimethoxyphenethylamine (**2.115**) to afford vinyl sulfoxide **2.124**, which was cyclised in chloroform with TFA catalysis to form a mixture of **2.126a** and **2.126b** (Scheme 2.24). Taking the yield and diastereoselectivity into account, the best results were achieved in the presence of TFA at 0 ºC. Sulfoxide **2.126a** was reductively *N*-methylated to **2.127** and then desulfurised with Raney nickel to carnegine [(+)-**2.128**]. The higher diastereoselectivity achieved was rationalised by assuming that the imine **2.125a** and the enamine **2.125b** are in equilibrium, with the enamine being the predominant species.



Scheme 2.24: Synthesis of carnegine (**2.128**)

The same group disclosed an interesting feature when using *N*-methyl-3,4-dimethoxy-β-phenethylamine as a starting amine and a nitro derivative as a chiral sulfoxide. Cyclisation proceeds with reverse diastereoselectivity. Raney nickel desulfurisation of the chiral auxiliary provides *S*-salsolidine and this is a more convergent way of synthesising this natural product.

The regiochemical control was investigated by Bates[56] in reactions between epinephrine **2.129** and excess formaldehyde or acetaldehyde in aqueous solution between pH of 0.7 to 7 (Scheme 2.25). At pH 5, a 88:12 ratio of **2.130** and **2.131** was obtained after 2.5 minutes, however, the product disappeared over the course of several hours due to the presence of excess formaldehyde, which causes formation of a polymeric substance. At low pH, cyclisation occurred almost exclusively *para* to the activating hydroxy group. Under neutral conditions, substantial cyclisation *ortho* to the activating hydroxy group also takes place.



Scheme 2.25: Regioselective synthesis of 1,2,3,4-tetrahydro-4,6,7-isoquinolinetriols **2.130** and **2.131**.

Although the 1-substituted tetrahydroisoquinoline alkaloids are readily synthesised in an asymmetric manner, there is no one general method that would secure preparation of all types of isoquinoline alkaloids with high optical purity employing simple procedures. Usually, the applied methodologies suffer from various limitations such as moderate yields and/or unsatisfactory regio- and stereoselectivity. Therefore, the question of finding more efficient and/or simpler synthetic strategy still remains a critical challenge to organic chemists.

2.5 Construction of diaryl ethers

2.5.1 Introduction

The presence of the diaryl ether subunit in a number of synthetically challenging and medicinally important natural products such as vancomycin[57] (**2.132**, antibiotic), (-)-K-13[58] (**2.133**, angiotensin-converting enzyme inhibitor), bastadin[59] (**2.134**, antitumour agent), the purely synthetic bioactive agents such as LY293111[60] (**2.135**, LTB_4 receptor antagonist) as well as combretastatin D-2[61] (**2.136**, antifungal) (Fig. 2.5), has renewed efforts in developing strategies for its construction.

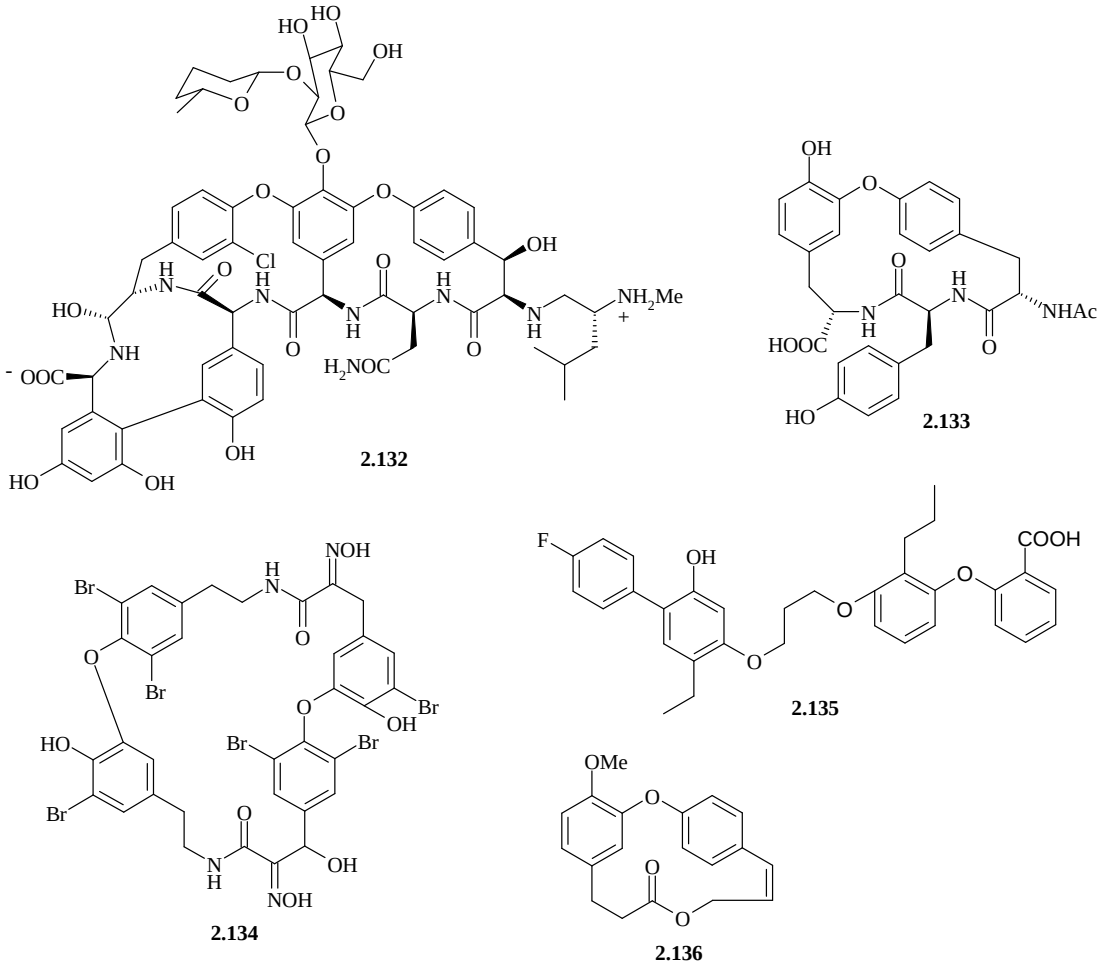
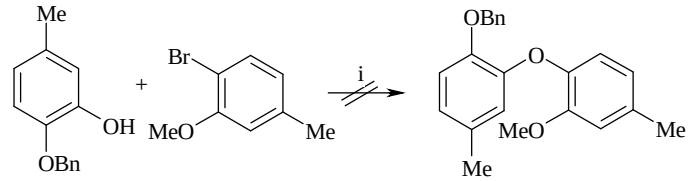


Figure 2.4: Natural products with a diaryl ether subunits.

As mentioned in the beginning of this Chapter (Section 2.2), bisbenzylsoquinoline alkaloids are built up of one more diaryl ether linkages. Various methods for the preparation of diaryl ethers are known. However, methods for the construction of diaryl ethers that are compatible with sensitive functional groups and stereogenic centres in a variety of complex molecules are needed. Generally, diaryl ethers can be synthesised by means of a copper-catalysed Ullmann diaryl ether coupling, palladium-catalysed Buchwald-Hartwig reaction, nucleophilic aromatic substitution, coupling of phenols with arylboronic acids, oxidative coupling and nucleophilic aromatic additions to metal-arene complexes.[62] The following sections will concentrate on various methods for construction of diaryl ethers.

2.5.2 Intermolecular Ullmann Diaryl Ether Coupling

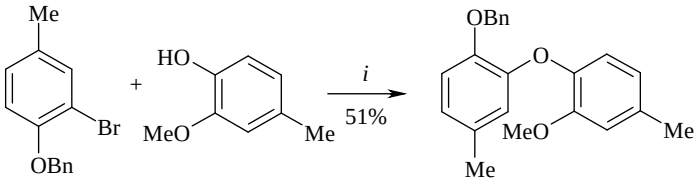
Since Fritz Ullmann[63] and Irma Goldberg[64] started their pioneering work on copper-mediated and catalysed coupling reactions more than a hundred years ago, there has been a widespread interest in developing methods for the synthesis of diaryl ethers using Cu(I) catalyst. Diaryl ether formation under Ullmann conditions in the presence of copper depends strongly on the substitution pattern of both the aryl halide and the phenols. For example, Xing *et al.*[65] described the unsuccessful preparation of diaryl ether **2.139** by coupling 2-benzyloxy-5-methylphenol (**2.137**) with 1-bromo-2-methoxy-4-methylbenzene (**2.138**) in the presence of 5 mol% of $(CuOTf)_2PhMe$ and caesium carbonate in pyridine at 110 ºC (Scheme 2.26).



2.137 **2.138** **2.139**

Scheme 2.26: *Reagents and conditions:* i) $(CuOTf)_2PhMe$, Cs_2CO_3, pyridine, 110 ºC, 24 h.

However, utilising identical reaction conditions, 1-(benzyloxy)-2-bromo-4-methylbenzene (**2.140**) reacted with 2-methoxy-4-methylphenol (**2.141**) to give the diaryl ether **2.139** in 51% yield (Scheme 2.27).

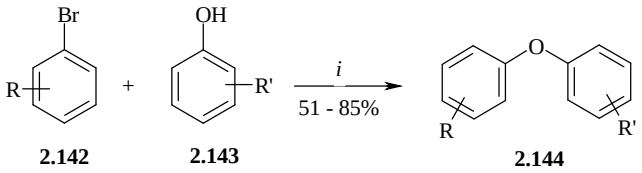


2.140 **2.141** **2.139**

Scheme 2.27: *Reagents and conditions:* i) $(CuOTf)_2PhMe$, Cs_2CO_3, pyridine, 110 ºC, 24 h.

Conventional Ullmann reaction usually requires harsh conditions – at least stoichiometric amounts of copper, large excess of phenols and high temperatures, due to the poor nucleophilicity of the phenoxide and the low reactivity of the aryl halides involved.[66] Addition of a suitable ligand and a base (usually caesium carbonate) enhanced solubility of the copper ions and consequently more efficient catalysis compared to the classical

Ullmann coupling reaction, can be achieved at lower temperatures. Song and co-workers[67] reported the use of 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as a suitable ligand for coupling various aryl bromides and phenols (Scheme 2.28), with aryl halides possessing electron-donating groups affording better yield in this modification than in classical Ullmann procedures. However, electron-poor phenols did not react to give the desired products and phenols with *ortho* methoxy and acetoxy substituents reacted slowly. Another key problem to Ullmann-type reactions is the racemisation of the chiral centres present in a system. Cai *et al.*[68] established a mild and nonracemising conditions for Ullmann-type diaryl ether formation between aryl halides and phenols. For example, coupling of 4-iodophenylacetone and *N*-trityl-L-tyrosine methyl ester catalysed by CuI and *N*,*N*-dimethylglycine gave the desired coupled product in 92% yield without any racemisation.

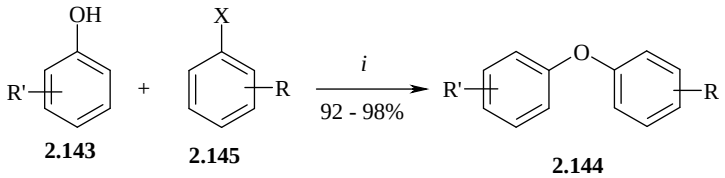


2.142 **2.143** **2.144**

R = Me, Ac, CN, OMe, NMe_2 R’ = Me, CO_2*i*-Pr, F, OMe

Scheme 2.28: *Reagents and conditions:* i) CuCl, THMD, Cs_2CO_3, NMP, 120 ºC, 24 h.

N,*N*-dimethylglycine was reported[69,70] to be a very effective ligand in dioxane at lower temperatures (~ 90 ºC), with both electron-rich and poor halides being suitable substrates. Steric hindrance in reacting substrates disfavoured the reaction and this obstacle was overcome by using higher temperatures and catalyst and, for example, reaction of 2-bromotolouene (**2.142**) and 4-methoxyphenol (**2.143**) gave good yields of **2.144** at 105 º C. Also the use of 1,10-phenanthroline as a ligand and potassium fluoride supported on aluminium oxide as a base was reported[71] to improve the yields of diaryl ethers (Scheme 2.29).

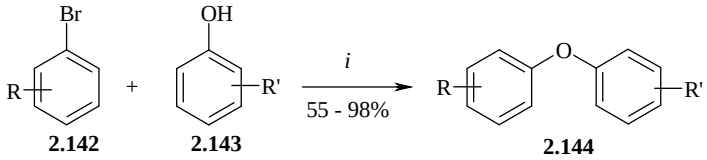


2.143 **2.145** **2.144**

R = H, Me, OMe, CF_3, Br R’ = H, 2-Me, 4-Me

Scheme 2.29: *Reagents and conditions:* i) 1, 10-phenanthroline (20 mol%), CuI (10%), KF/Al_2O_3, toluene or dioxane, 110 ºC, 6-15h.

Gujadhur and Venkataraman[72] reported the use of the $Cu(PPh_3)_3Br$ complex, which is air and moisture stable and soluble in most organic solvents, to couple phenols with electron-deficient aryl bromides such as 4-bromo-1-nitrobenzene and 4-bromobenzonitrile in *N*-methylpyrrolidinone (Scheme 2.30).



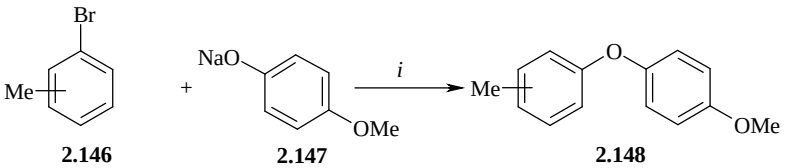
2.142 **2.143** **2.144**

R = NO_2, Me, CN, OMe, NMe_2, CO_2Me R' = Me

Scheme 2.30: *Reagents and conditions:* i) $Cu(PPh_3)_3Br$, Cs_2CO_3 (3 eq.), NMP, 100 ºC, 48h.

2.5.3 Intermolecular Palladium-Catalysed diaryl ether coupling reactions

Formation of diaryl ether using this method utilises ligands in the presence of catalytic amount of palladium ions. The high price of palladium still remains the major drawback for this method. Various ligands have been used to obtain diaryl ethers in satisfactory yields. An example using di-*tert*-butylphosphino-pentaphenylferrocene is outlined in Scheme 2.31. A steric effect was observed in the reaction of an aryl halide with *ortho* substituents, which react faster (already at 80 ºC) than the unhindered aryl halides which required heating to 100 ºC. Contrary to Cu-mediated diaryl ether synthesis, aryl bromides and chlorides react faster than the aryl iodides. It was observed that the coupling reaction utilising 1,1'-bis(di-*tert*-butylphoshino)ferrocene (D'BPF) as a ligand could be performed even at room temperature, this is a significant advantage compared to the latest improvements in Ullmann coupling reactions.



2.146 **2.147** **2.148**

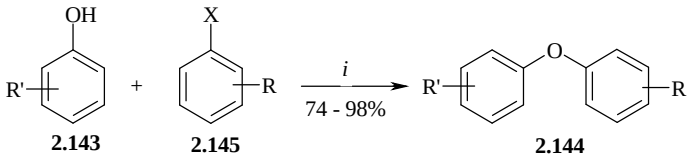
R = H, Ph, C_6H_4-*p*-CF_3, C_6H_4-*p*-OMe

Scheme 2.31: *Reagents and conditions:* i) $Pd(dba)_2$, di-*tert*-butylphosphino-pentaphenylferrocene, toluene, 40 ºC or 80 ºC, 2-24 h.

Buchwald and co-workers[73] reported formation of diaryl ethers from a wide range of aryl halides and phenols in high to excellent yields using electron-rich, sterically bulky ligands. A representative of this method is the chemoselective coupling of 1-bromo-4-chlorobenzene with 2-isopropylphenol to give 4-chlorophenyl-2-isopropyl phenyl ether in 80% yield. Substituted phenols, even those with bulky substituents, are excellent substrates for this reaction. Low yields in the case of aryl halides with electron-withdrawing groups at the *ortho* position make this method unfavourable. Furthermore, many of the ligands developed by Buchwald are either very expensive or not available commercially.

2.5.4 Nucleophilic aromatic substitution

The formation of diaryl ethers by nucleophilic aromatic substitution with activated substrates is considered mild and more environmentally benign. Various electron-withdrawing functional groups (nitro, triazenyl and methylcarbonyl) were used to activate the aromatic skeleton towards nucleophilic substitution with phenols. Wang and co-workers[74,75] developed a microwave-assisted diaryl ether synthesis from electron-deficient phenols and aryl halides with good tolerance of sensitive functional groups and high yields (79-98%) (Scheme 2.32).

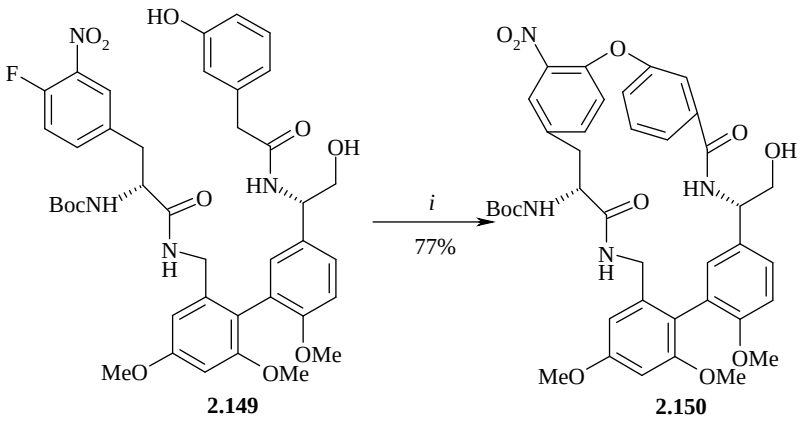


Scheme 2.32: *Reagents and conditions:* i) K_2CO_3, DMSO, MW (300W), 5-10 min.

Solvent-free phase-transfer and microwave conditions for the synthesis of diaryl ether were investigated,[76] phase-transfer catalysts investigated includes $Bu_4N^+Br^-$, $MeOct_3N^+Cl^-$ and 18-crown-6. In the presence of the ion pairs microwave influence played a major role in enhancement of the reaction. Microwave also enhances the reaction of non-activated substrates. The microwave-assisted aromatic nucleophilic substitution was preferable to

the classic S_NAr reaction since it minimised the amount of by-products and the use of difficult-to-remove polar solvents.

Nucleophilic aromatic substitution was reported in the synthesis of macrocyclic ring of vancomycin by Zhu and co-workers.[77] The macrocycle **2.150** was synthesised in one step form **2.149** using potassium carbonate and the crown ether 18-C-6 in THF (Scheme 2.33).



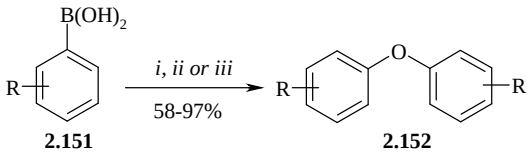
Scheme 2.33: *Reagents and conditions:* i) K_2CO_3, 18-C-6, THF, 50 ºC.

2.5.5 Coupling of phenols with arylboronic acids

Diaryl ethers synthesis by the cross-coupling of phenols and arylboronic acids promoted by copper(II) was reported independently by Chan *et al.*[78] and Evans *et al.*[79] Recent advancement of *O*-arylation with boronic acids gained interests due to the mild reaction conditions (room temperature, weak base, ambient atmosphere) and the toleration of various substrates. Evans and co-workers[79] developed a protocol for phenol arylation with aryl boronic acids with reasonable yields. In addition, electron-rich aryl boronic acids performed better than the unsubstituted parent phenylboronic acid.

It was also observed that phenylboronic acid is readily converted to $(PhBO)_3$, which could be the active species for arylation. Furthermore, it was speculated that the addition of molecular sieves promotes formation of the borixine form which is more efficient than coupling with phenylboronic acid. Petasis and co-workers[80] and Sagar *et al.*[81] reported the conversion arylboronic acid **2.151** into phenols and a subsequent coupling of both species to form symmetrical diaryl ethers **2.152** in a one-pot reaction. Moreover, this method

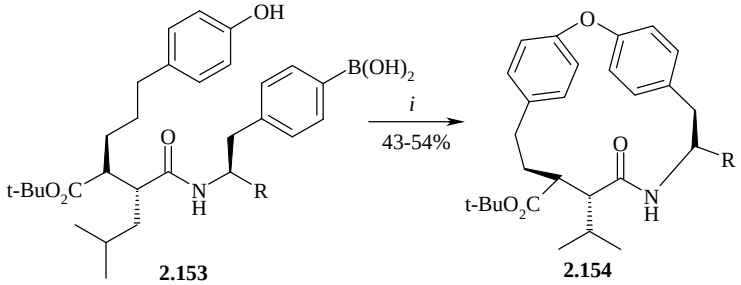
tolerates a great variety of electron-rich and electron-poor substituents and the products are afforded in good to excellent yields (Scheme 2.34).



2.151 **2.152**

Scheme 2.34: *Reagents and conditions:* i) H_2O_2 (30%), CH_2Cl_2; ii) $Cu(OAc)_2$, Et_3N, CH_2Cl_2, ms, 25 ºC; iii) $Cu(OAc)_2$, Et_3N, H_2O, CH_2Cl_2-MeCN, 25 ºC.

Intramolecular coupling of the arylboronic acid **2.153** to yield the macrocyclic diaryl ether **2.154** was reported by Decicco *et al*.[82] in the preparation of macrocyclic metalloproteinase inhibitors (Scheme 2.35).



2.153 **2.154**

Scheme 2.35: *Reagents and conditions:* i) $Cu(OAc)_2$, Et_3N, CH_2Cl_2, ms, 25 ºC.

2.6 Conclusion

Targeting complex structures like BBIQ's demand more effective reactions in terms of accomplishing bond constructions and functional group transformation. A closer look at syntheses of BBIQ's, that is, their total synthesis and synthesis of the monomers, unravels the possible routes and intermediates from which one can choose the most likely route to succeed. Lack of regioselectivity, stereoselectivity and low yields makes the previous synthetic routes described unattractive. Therefore, a process suitable for large scale preparations of BBIQ's based on asymmetric synthesis of tetrahydroisoquinoline monomer, diaryl ether bond incorporated to the pre-existing optical pure tetrahydroisoquinoline and macrocyclisation of the intermediate will be efficient. The rational thinking was to be further advanced so that the stereo- and regiocontrol strategies are to dominate synthetic planning before being completed. A judicious choice of optically

active starting materials as well as high convergent strategy that utilize the same type of reactions will allow a rapid access to the target compound cycleanine (**1.21**). In addition, it was necessary to develop a process that preserved the enantiomeric purity of the readily epimerisable stereogenic centre s in subsequent reactions. Furthermore, convenient purification points had to be established to avoid purification methods that are inconsistent with large-scale synthesis.

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CHAPTER 3

Results and Discussion

3.1 Introduction

This chapter outlines our approach towards the synthesis of cycleanine (**3.1**).[*] In total synthesis, retrosynthetic analysis is a key step in devising possible synthetic strategies for the construction of a target compound. As discussed in Chapters 1 and 2, bisbenzyltetrahydroisoquinolines (BBIQ's) have interesting biological activities, yet a limited number of attempts towards their total syntheses have been published. The aim of this investigation was to develop a strategy towards the total synthesis of the BBIQ cycleanine (**3.1**). Although this BBIQ is only moderately active in a number of assays, it has a low toxicity and has a good selectivity index.[1] More importantly, although the diversity of pharmacological effects observed within the BBIQ alkaloids is a function of the differences in chemical structure, cycleanine (**3.1**) is a good model compound to develop synthetic strategies for head-to-tail BBIQ's due to its symmetrical nature. The only published total synthesis of cycleanine (**3.1**) (Scheme 2.1) did not address the problems of regioselectivity and stereoselectivity. In addition, key steps for this synthesis, such as the Ullmann condensation and the Bischler-Napieralski reaction, gave low yields and the final step gave cycleanine (**3.1**) in an extremely low yield (0.067%).[2]

A literature review of the synthetic methods for BBIQ's (Chapter 2) clearly indicates that the two main challenges in the total synthesis of these compounds are the stereoselective preparation of the tetrahydroisoquinoline moiety and the regioselective diaryl ether formation. In our retrosynthetic analysis of cycleanine (**3.1**), many disconnections were considered to evaluate all the possibilities before one pathway was selected. Cycleanine (**3.1**) contains two stereogenic centres and the initial goal of our synthetic strategy was to install, stereospecifically, the two stereogenic centres in a way that avoids resolution or chiral chromatography.

[*] Cycleanine is numbered cycleanine (**1.21**) for the structures not showing the absolute stereochemistry in Chapters 1 and 2 and **3.1** for the structures indicating the stereochemistry.

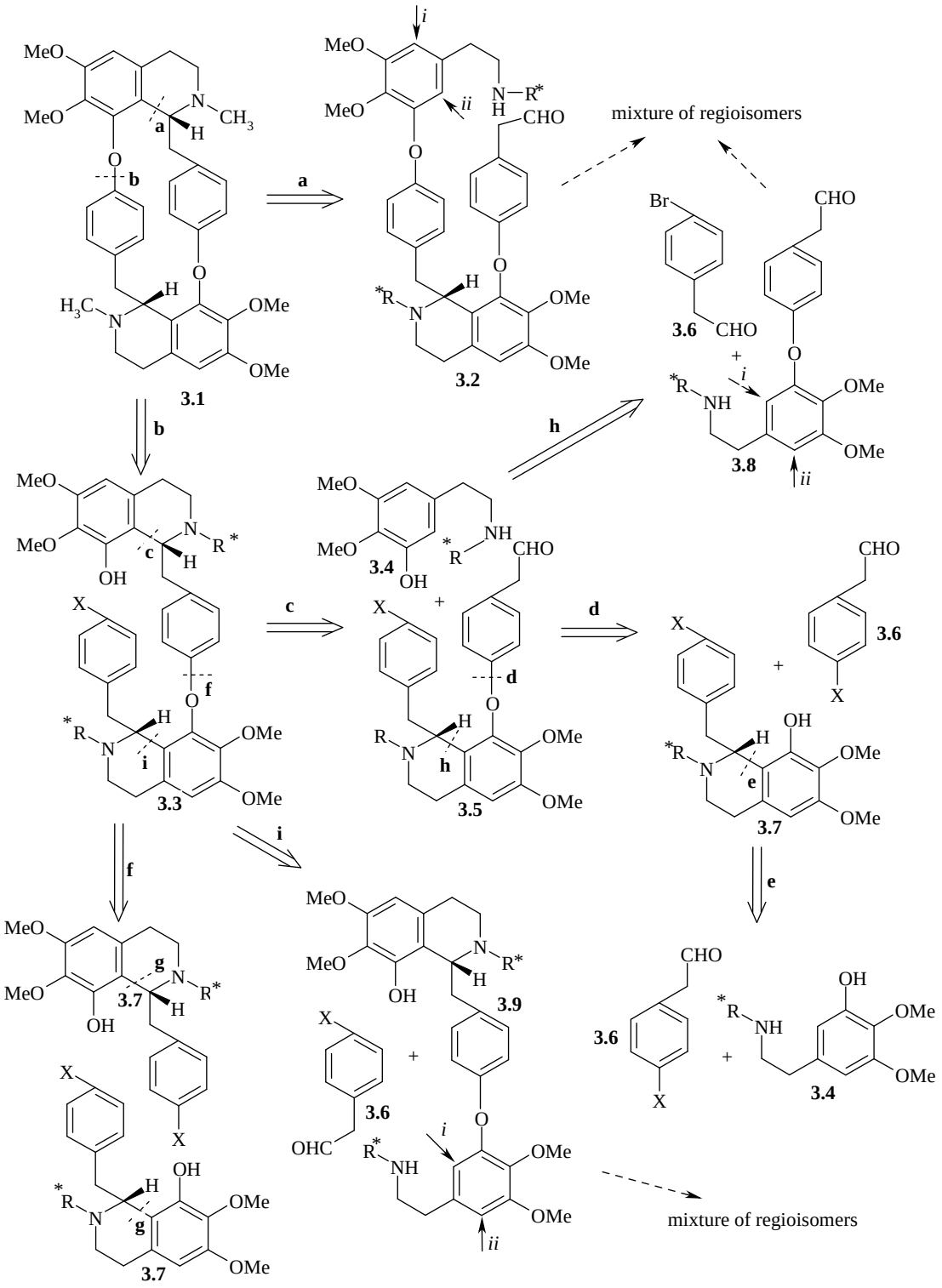
3.2 Retrosynthetic analysis

The formidable architecture of BBIQ's comprises a host of complicated problems that are certain to challenge the ability of any synthetic chemist. Nature's likely synthesis of these natural products suggests several potential avenues to render this target more manageable. In the literature, a number of synthetic methods for the synthesis of 1,2,3,4-tetrahydroisoquinolines (THIQ) are reported (see Section 2.4). In our study the synthetic strategy based on a Pictet-Spengler reaction for the construction of the THIQ monomers was opted for. While many disconnections could be considered for the synthesis of cycleanine (**3.1**), five main strategies were evident from the viewpoint of a rational retrosynthetic analysis, as outlined in Scheme 3.1.

Route **a** could lead to a mixture of two possible isomers since there are two positions (denoted *i* and *ii* in Scheme 3.1) available for cyclisation of **3.2** (see last step in Scheme 2.1). Following route **b**, **3.1** could be obtained from **3.3** by a number of methods to form diaryl ethers. The second diaryl ether functionality could be constructed from two identical monomers **3.7** (route **f**). Though **3.1** can be formed directly from **3.7**, this condensation reaction is prone to polymerisation to form side products. Therefore, following this route, a stepwise coupling of the two THIQ monomers is advisable.

Routes **h** and **i** *via* **b** could also be followed, nevertheless, the problem posed by both these two routes is once again the possible formation of a mixture of regioisomers. For route **h**, condensation of **3.8** and **3.6** could lead to the formation of regioisomers due to the presence of two positions on **3.8** (denoted *i* and *ii*) available for electrophilic aromatic substitution. Following route **i**, the presence of two possible modes of cyclisation also poses problems since **3.9** also contains two possible sites for cyclisation (denoted *i* and *ii* in Scheme 3.1).

Route **e** through **b**, **c** and **d** seemed to be the best option since **3.3** could be formed from **3.5** and **3.4** by a Pictet-Spengler or Bischler-Napieralski reaction and the presence of the free hydroxy on **3.4** was envisaged to control the site of cyclisation in the formation of **3.3**. Similarly, the site of cyclisation will also be controlled by the presence of a free hydroxy in **3.4** in the formation of **3.7**. This approach is preferable for the formation of cycleanine (**3.1**) and the main attribute of this strategy is its convergence because of the utilisation of the same materials (**3.4** and **3.6**) and reactions (Pictet-Spengler and diaryl ether formation).



Scheme 3.1: Retrosynthetic analysis of cycleanine (**3.1**).

Cycleanine (**3.1**) is a chiral compound, with a *R*-configuration at both stereocentres and, therefore, our challenge in this synthesis was to address the stereoselective synthesis of the THIQ monomer. A diverse array of enantioselective methods have been developed to

access homochiral THIQ monomers, mostly involving the use of chiral auxiliaries (see Section 2.4.4). These methods include

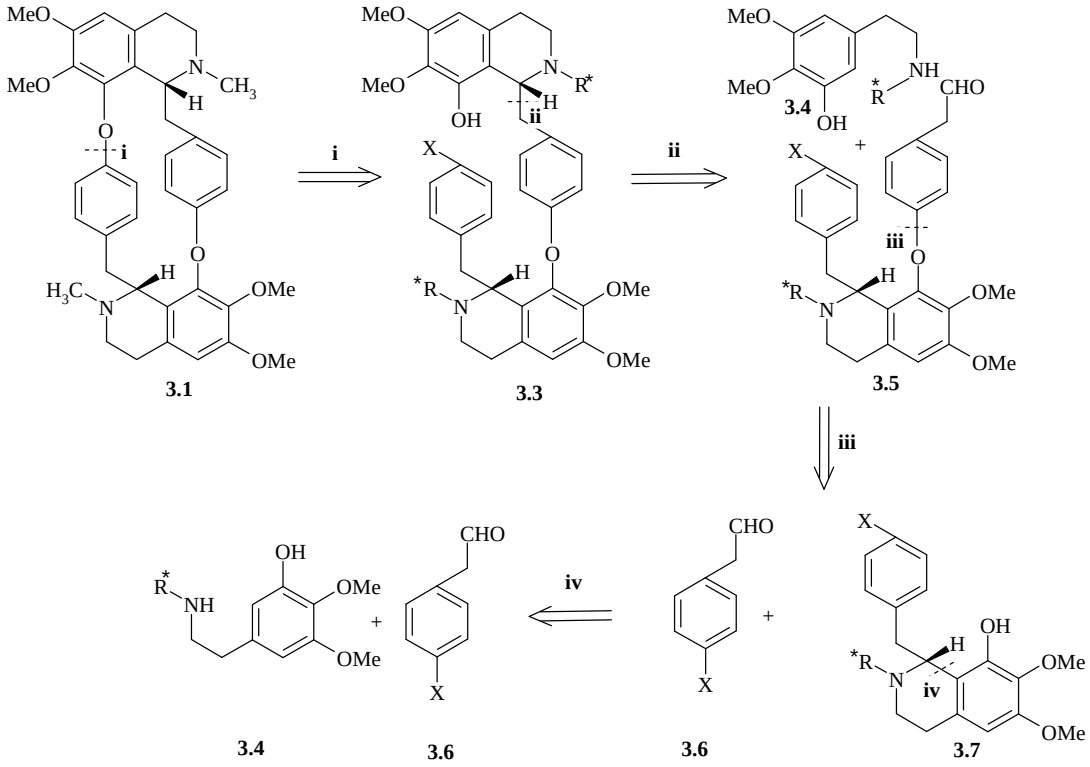
- Metal-catalysed cyclisation reactions[3]
- Pomeranz-Fritsch reaction[4]
- Bischler-Napieralski reaction[5]
- Pictet-Spengler cyclisation[6]
- Asymmetric hydrogenation of cyclic imines accessed by the Bischler-Napieralski reaction (entails the largest part of the enantioselective synthesis of THIQ).[7]

The metal-catalysed formation of cherylline (**2.104**) gave the cyclised product in a low yield (42%) with low enantioselectivity (8%) due to the presence of the easily enolisable benzylic proton in the cyclisation product. Furthermore, palladium is an expensive metal and this makes this method less attractive. Although the Pomeranz-Fritsch reaction was appealing in terms of enantioselectivity during the synthesis of salsolidine (**2.111**), after formation of the chiral sulfinamide **2.108**, there are two more steps before cyclisation to the final product and this contribute to the low overall yield of the target product.

The Bischler-Napieralski reaction seemed interesting, nevertheless, the preparation and isolation of the unstable imine intermediates raised uncertainties. However, the good enantioselectivity and yields obtained by this method must be noted. The methods above allow the synthesis of enantiopure 1-substituted tetrahydroisoquinoline, but only the Pictet-Spengler reaction creates the stereogenic carbon at C-1 simultaneous with the ring closure, whereas in other methods two different steps are required. The good yields, good enantioselectivity and regioselectivity associated with the Pictet-Spengler reaction motivated us to make this the method of choice in this study (see Section 2.4.4).

A closer look at possible routes (Scheme 3.1) resulted in the development of a strategy for the diastereoselective and convergent synthesis of cycleanine (**3.1**) that also controls the stereochemistry of the molecule at both stereogenic carbons 1 and 1'. The retrosynthetic analysis depicted in Scheme 3.2 is based on the following disconnections: the macrocyclic ring **3.1** could be constructed by the intramolecular diaryl ether formation of intermediate **3.3**, derived by the condensation of **3.4** and **3.5** by means of a Pictet-Spengler reaction. Preparation of **3.5** could be achieved by a S_NAr reaction, Ullmann coupling or any other diaryl ether coupling methods of halophenylacetaldehyde **3.6** and THIQ **3.7**. If R in **3.4** is

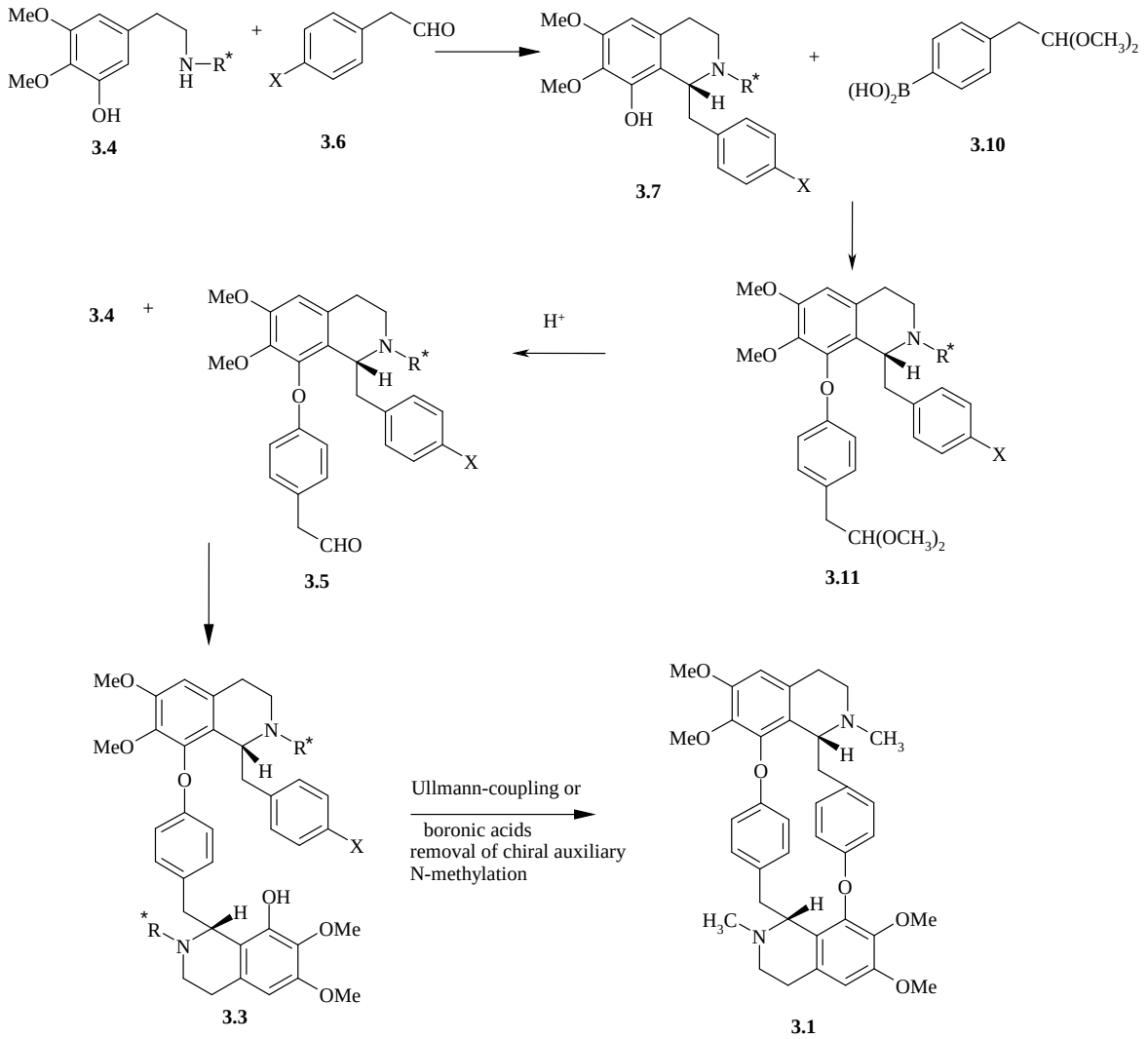
a chiral auxiliary, a Pictet-Spengler reaction between **3.4** and **3.6** could lead to the homochiral THIQ **3.7**. Therefore, the stereoselectivity of the whole route will be governed by this condensation. Furthermore, the Pictet-Spengler reaction would be repeated twice in the route and the same compounds **3.4** and **3.6** would be employed and this will allow a rapid access to the target compound cycleanine (**3.1**) with a small number of compounds to be prepared.



Scheme 3.2: Preferred retrosynthetic analysis of cycleanine (**3.1**).

The synthesis was planned according to Scheme 3.3, starting with the coupling of β-phenethylamine **3.4** and halophenylacetaldehyde **3.6,** using the Pictet-Spengler reaction. In contrast to the previous synthesis of cycleanine (**3.1**),[2] our approach was envisaged to be chiral-auxiliary based, which will give optical-enriched precursors, while Tomita's method was appropriate for racemates. Enantioselectivity was to be controlled by the chiral auxiliary R^* present in the β-phenethylamine **3.4**. The reactivity, regio- and stereoselectivity of the Pictet-Spengler reaction depend greatly on the nature of the starting chiral auxiliary amine, degree of activation of the cyclising benzene ring of the relevant imines, the substituents on the phenylacetaldehyde ring as well as the reaction conditions. In order to assess these factors, different halophenylacetaldehydes **3.6** (X = electron-

withdrawing or electron-donating) will be prepared in this study. Diaryl ether formation was planned by means of the coupling of boronic acid **3.10** with the tetrahydroisoquinoline **3.7**. Hydrolysis of the protected aldehyde **3.11**, followed by another Pictet-Spengler reaction between **3.4** and **3.5**, should form the desired product **3.3**. The final cyclisation to the macrocylic compound **3.1** was hoped to be achieved *via* either an Ullmann or a boronic acid coupling reaction (Scheme 3.3). β-Phenethylamine **3.4** will be utilised for the preparation of both THIQ monomers, therefore, in the following paragraph the synthesis of **3.4** will be discussed. Subsequent sections will describe the synthesis of halophenylacetaldehydes **3.6**.



Scheme 3.3: Envisaged synthesis of cycleanine (**3.1**).

3.3 Preparation of hydroxylated β-phenethylamine 3.4

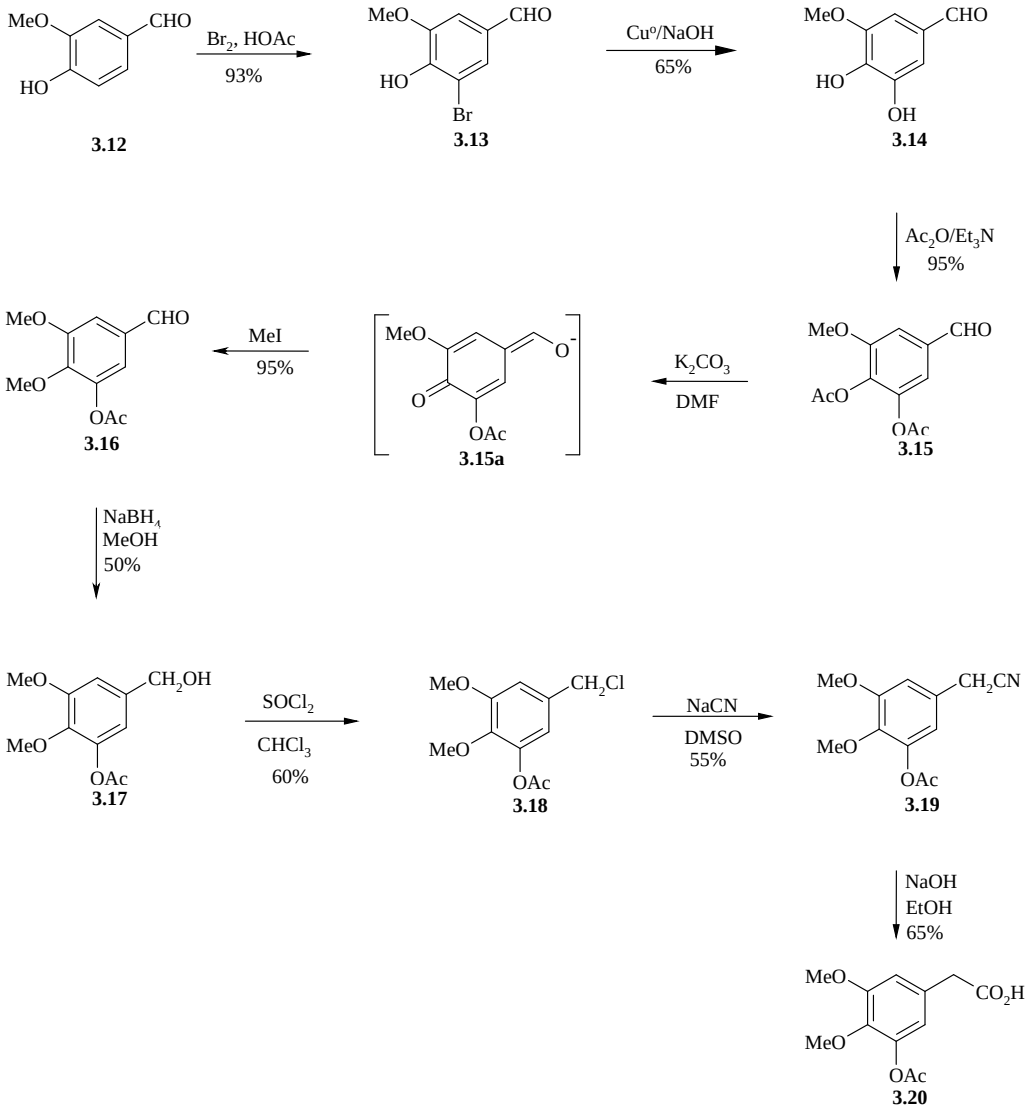
The first challenge we faced in this project was to construct the stereogenic centre in compound **3.7** in an enantioselective manner. For the above-mentioned reasons and from a practical and economical perspective, we reasoned that the Pictet-Spengler reaction would be our first choice for the synthesis of chiral **3.7**. Prior to cyclisation to **3.7**, it was necessary to gain access to the chiral **3.4**. The availability of commercial *R*- and *S*-phenethylamine enantiomers as well as the good diastereoselectivity achieved in the reduction of the Bischler-Napieralski product containing this chiral auxiliary, prompted us to use it as chiral auxiliary tethered to our β-phenethylamine. For example, *S*-α-methylbenzylamine was found to be an efficient chiral auxiliary in the multistep synthesis of (-)-tejedine, a *seco*-bisbenzylisoquinoline alkaloid, where cyclisation and subsequent reduction gave the THIQ moiety in 40% yield and with 99% *de*.[8] The convenient reductive removal of the chiral auxiliary at the end of the transformation justifies the choice of this chiral auxiliary. To control the regioselectivity of the Pictet-Spengler reaction, the presence of the free hydroxy group on the phenyl ring of **3.4** will play an important role (Section 2.4.4.4). Furthermore, it is known that diaryl ether formation between phenols and electron-rich aryl halides is problematic, therefore, a method directed towards the synthesis of electron-rich phenol **3.7** and an electron-poor halide will be employed. Diaryl ether **3.11** was envisaged to be formed from THIQ **3.7** and the boronic acid **3.10**. In the next section, the preparation of phenethylamine **3.4** *via* a phenylacetic acid will be presented.

3.3.1 Synthesis of phenylacetic acid intermediate

Our first target was the preparation of β-phenethylamine **3.4** with R^* = $CH(CH_3)Ph$. Vanillin (**3.12**) proved to be an effective starting material for the preparation of β-phenethylamine **3.4**, since the substituents on the aryl ring of **3.4** are similar to the aryl ring of vanillin (**3.12**). The free hydroxy on position three will be introduced first *via* bromination, followed by methylation of 4-hydroxy and conversion of the aldehyde to a chiral amine in subsequent transformations.

Bromination of vanillin (**3.12**) gave 3-bromovanillin (**3.13**) in a good yield (93%). Bromination occurred preferentially at the *ortho*-position to the free hydroxy group and

this emphasise the importance of the free hydroxy on C-4**.** Subsequent copper(I)-assisted hydrolysis of **3.13** afforded **3.14**. The formation of dihydroxy compound **3.14** was achieved in moderate yield (65%) due to the high solubility of the product in water and as a result, during workup some of the product was lost in the aqueous layer upon extraction with ethyl acetate. Selective methylation of **3.14** with methyl iodide resulted in a mixture of mono- and dimethylated derivatives of **3.14**. Therefore, a method for selective methylation developed by Zhu *et al.*[9] and Pearson *et al.*[10] on selective alkylation of the 4-OH of gallic acid was employed by utilising the diacetate **3.15** in the presence of MeI and K_2CO_3, affording **3.16** (Scheme 3.4).

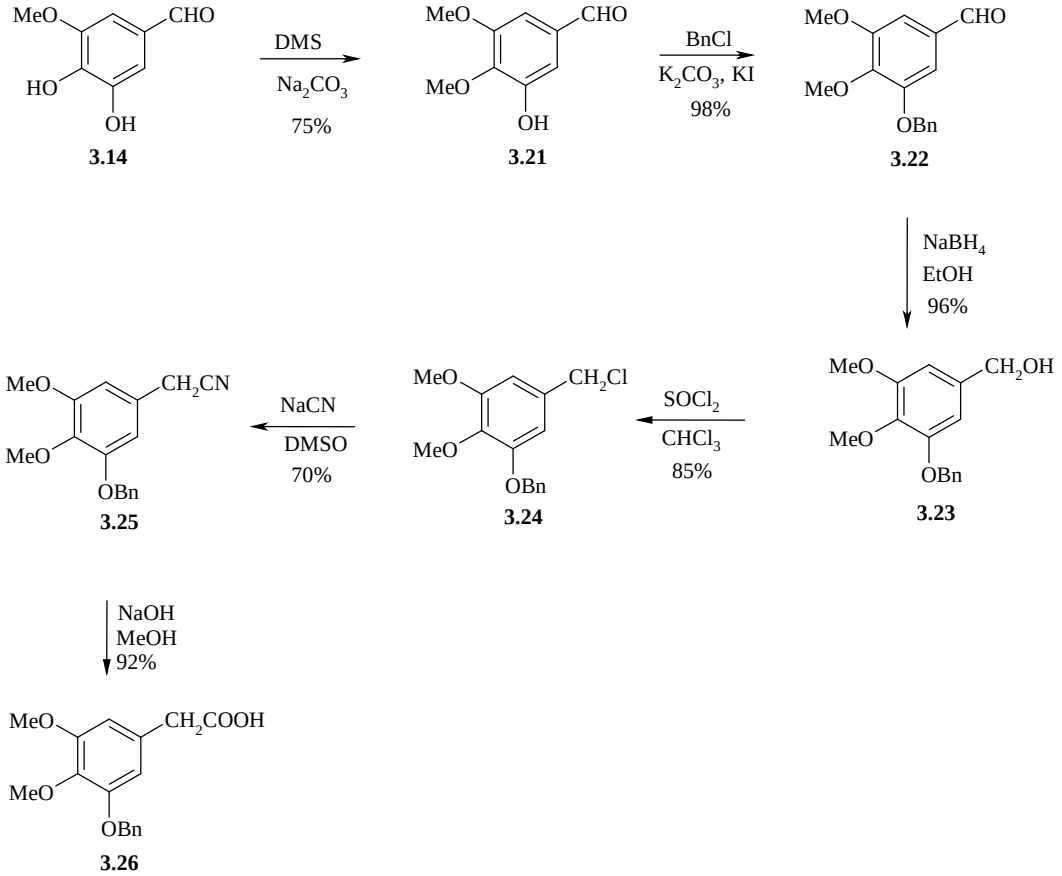


Scheme 3.4: Preparation of acetylated phenylacetic acid.

The increased acidity of the 4-hydroxy group of **3.14** due to the *para* electron-withdrawing substituent, renders it more reactive towards alkylation. The chemoselective methylation

of **3.14** involves heating of the diacetate **3.15** with K_2CO_3 and methyl iodide in DMF. The selectivity of this reaction is attributed to the hydrolysis of the *p*-acetate group in **3.15** to form the intermediate **3.15a**, which is stabilised by conjugation.

A nOe experiment on **3.16** confirmed the position of the acetoxy group. Correlations between the acetoxy protons and one methoxy group and an aromatic proton were observed. Benzaldehyde was homologated to phenylacetic acid by standard methods. Reduction of **3.16** to the benzyl alcohol **3.17** was achieved in moderate yield (50%), chlorination to **3.18** in 60% yield, cyanation was accomplished in 55% yield and the subsequent hydrolysis of **3.19** to **3.20** in 65% yield.



Scheme 3.5: Preparation of benzylated phenylacetic acid.

Protection of the 5-hydroxy as the *O*-acetyl in **3.16** suffered drawbacks due to the lability of the *O*-acetoxy in subsequent reactions, and compounds **3.17** to **3.20** were obtained in low yields. Changing the protecting group to *O*-benzyl resulted in the exclusive formation of the desired intermediates (Scheme 3.5). The methylating reagent was changed to DMS and a good yield (75%) of the selectively methylated product **3.21** was obtained under

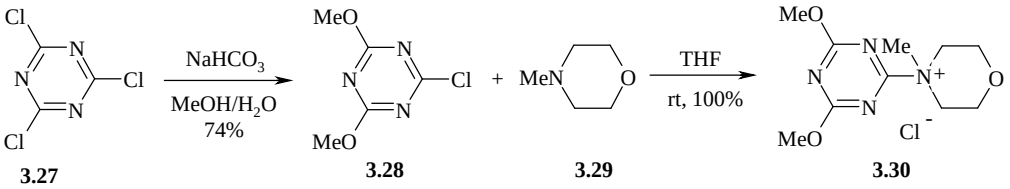
optimised reaction conditions, together with a minor amount of the dimethylated derivative of **3.14**. The ^{1}H NMR spectrum of the product **3.21** showed the presence of two methoxy groups and two *meta*-coupled aromatic protons. A nOe experiment confirmed the positions of the methoxy groups with a strong correlation between only one methoxy group and a *meta*-coupled aromatic proton. The reduction-chlorination-cyanation-hydrolysis sequence gave phenylacetic acid **3.26**, with the structures of all the intermediates confirmed by NMR, m.p. and MS. Protection of the 3-OH with a benzyl group increased the yields of the reactions. An additional five aromatic protons at δ_H 7.33-7.46 in the ^{1}H NMR spectrum of **3.22** and the disappearance of a broad OH signal in the IR spectrum, confirmed the formation of **3.22**. The absence of the aldehyde proton at δ_H 9.64 in the ^{1}H NMR spectrum of **3.23** and the appearance of a broad OH signal in the IR spectrum corroborated the formation of **3.23**. The change in chemical shift of the methylene protons from δ_H 3.64 to 3.54 in the ^{1}H NMR spectrum (Plate 1) as well as the presence of a carbonyl carbon at δ_C 176.8 in the ^{13}C NMR spectrum, m.p. 108-100 ºC and the MS (*m/z* 301.1077 $[M-H]^-$) confirmed the formation of **3.26**. With phenylalcetic acid **3.26** in hand, a good condensation method with the chiral amine needed be employed.

3.3.2 Condensation of the phenylacetic acid and the chiral amine

Given that *S*-α-methylbenzylamine was found to be an efficient chiral auxiliary in the multistep synthesis of (-)-tejedine, where reduction of the intermediate imine gave the *S*-configuration of the newly formed stereogenic centre with 99% *de*,[8] we envisaged that the *R*-α-methylbenzylamine would also give the *R*-isomer of the new stereogenic centre of the THIQ in the Pictet-Spengler reaction. Only one reference where this chiral auxiliary was used to influence the stereochemistry in the formation of a THIQ by the Pictet-Spengler reaction, was found.[11] In the product, the stereochemistry at C-1 was in accordance to the selectivity observed for the Bischler-Napieralski reaction. However, the product in this reaction is 1-phenylsulfone not a 1-benzyltetrahydroisoquinoline. Both the chiral centres of cycleanine (**3.1**) have the *R*-configuration. The formation of the chiral β-phenethylamine will be *via* the amide formation. As a result, many methods for the synthesis of amides by direct combination of carboxylic acids and amines have been investigated. The most common being the conversion of a carboxylic acid moiety to a more reactive functional group, such as an acyl chloride, mixed anhydride, acyl azide, *N*-acylbenzotriazoles, or active esters, or *via* the *in situ* activation of the carboxylic group by

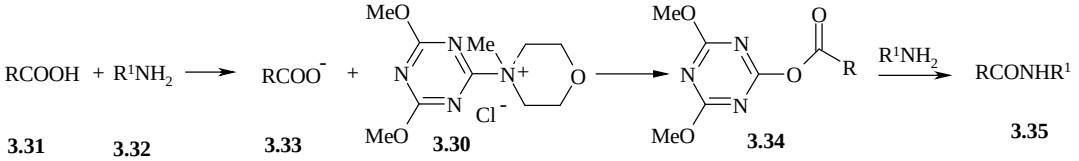
some peptide coupling reagents such as benzotriazol-1-yl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP)[12] and *N*,*N*-dicyclohexylcarbodiimide (DCC).[13] The disadvantages of these methods are the modest yields, expensive coupling reagents and difficulty in removal of the excess reagent and byproducts.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (**3.30**) (DMTMM),[14] formed by the reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) (**3.28**) with *N*-methylmorpholine (NMM) (**3.29**), was reported to be an efficient agent for condensing amines and carboxylic acids (Scheme 3.6).[15] DMTMM can be used to couple various carboxylic acids with either primary or secondary amines to give amides in excellent yields. The versatility, solubility (soluble in MeOH, water and EtOH), as well as the stability of DMTMM (**3.30**) made it the reagent of choice.



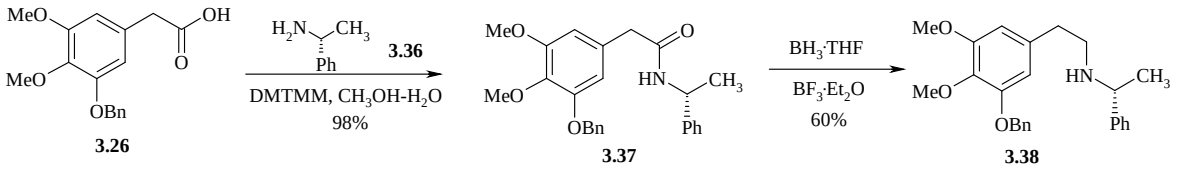
Scheme 3.6: Formation of DMTMM (**3.30**).

The order of addition of the reagents is the key to successful preparation of amides in the presence of DMTMM. Initially carboxylic acid **3.31** must be added together with amine **3.32** to form a carboxylate anion **3.33**, followed by addition of DMTMM (**3.30**) to give an activated ester **3.34**. In the first step, the amine will play the role of a catalyst in the coupling of the acid with DMTMM (**3.30**), leading to the formation of **3.34**. In the second step, the amine reacts as a nucleophile to yield the product **3.35**. As inexpensive cyanuric chloride is used for the large-scale synthesis of CDMT (**3.28**), the reaction is also economically advantageous.



Scheme 3.7: Reaction mechanism for amide formation with DMTMM (**3.30**).

Condensation of the phenylacetic acid **3.26** with *R*-1-phenethylamine (**3.36**) afforded amide **3.37** in 98% yield with $[\alpha]_D^{25}$ = +42.4 (*c* = 1.1 MeOH) (Scheme 3.8). Incorporation of the chiral amine was very important and this will be discussed in more details in the section on the Pictet-Spengler reaction. The expected aromatic protons, that is, a pair of *meta*-coupled doublets (δ_H 6.44 and 6.48) and a multiplet of ten aromatic protons at δ_H 7.19-7.40 (10H, m, ArH) were evident in the ^{1}H NMR spectrum of **3.37**. Furthermore, the ^{1}H NMR spectrum displayed two methoxy singlets, a broad NH singlet as well as a methylene singlet and the methyl doublet. The structure was further corroborated by ^{13}C NMR, MS (*m/z* 428.1838 $[M+Na]^+$) and IR (NH absorption at 3639 cm^{-1}).

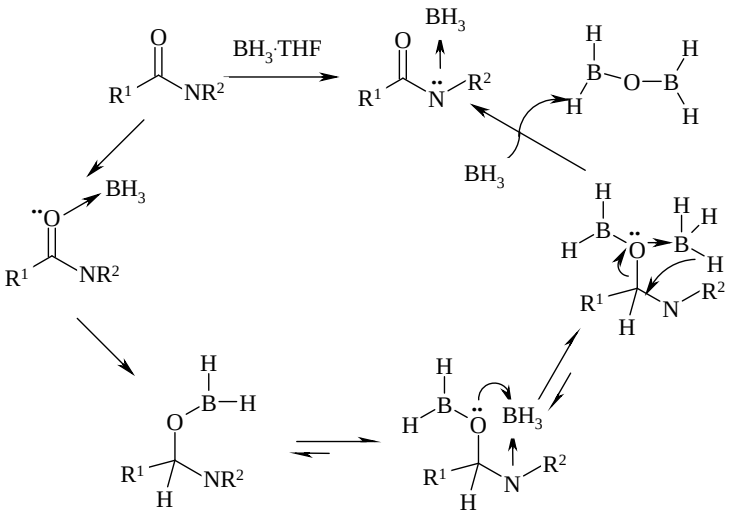


Scheme 3.8: Incorporation of a chiral auxiliary **3.36** to phenylacetic acid **3.26**.

Although lithium aluminium hydride ($LiAlH_4$) is a reagent for the reduction of amides to amines, borane makes a good alternative given that its chemoselectivity is different from that of $LiAlH_4$. It is known that boranes have the ability to reduce amides in the presence of esters and their reactivity is driven by the fact that they can accept an electron pair to their empty *p*-orbital.

The borane-tetrahydrofuran complex (BH_3·THF) is the most reactive of all the borane complexes due to the weak coordination of borane to THF and this was corroborated by the fact that reduction of **3.37** using the borane-methyl sulfide complex gave the desired product **3.38** in a low yield of 10%. This is in accordance with the findings by Grajewska and Rozwadowska[16] in the synthesis of *O*-methylbharatamine. The reaction between the BH_3·THF and the amide produced several intermediates that are ultimately converted to a borane-amine complex (Scheme 3.9).[17] Thus, to reduce the amide to the amine, five hydride equivalents are required. Two of the hydrides are used to reduce the amide to the amine and the other three hydrides are utilised to form the amine-borane complex. The high yield and simple isolation of the reduced product have made the borane complex the reducing agent of choice.

Reduction of the amide **3.37** with the BH_3·THF complex in the presence of BF_3·OEt_2 gave amine **3.38** (Scheme 3.8). The presence of the Lewis acid BF_3·OEt_2 in the reaction accelerates the reaction by coordinating with the carbonyl group of **3.37**, thereby increasing the electrophilic character of the carbon. This lowers the amount of BH_3·THF complex required for the reaction and accelerates the rate of the reaction, hence increasing the yield of the reaction. The change in chemical shift of the doublet from δ_H 1.38 to δ_H 1.34 (methyl group) in the ^{1}H NMR spectrum of **3.38**, and also the appearance of the multiplet of four protons at δ_H 2.70-2.74 indicates the presence of two methylene groups. The absence of the carbonyl signal at δ_C 169.8 in the ^{13}C NMR spectrum of **3.38** as well as MS data (*m/z* 414.2045 $[M+Na]^+$) supported the formation of the amine.



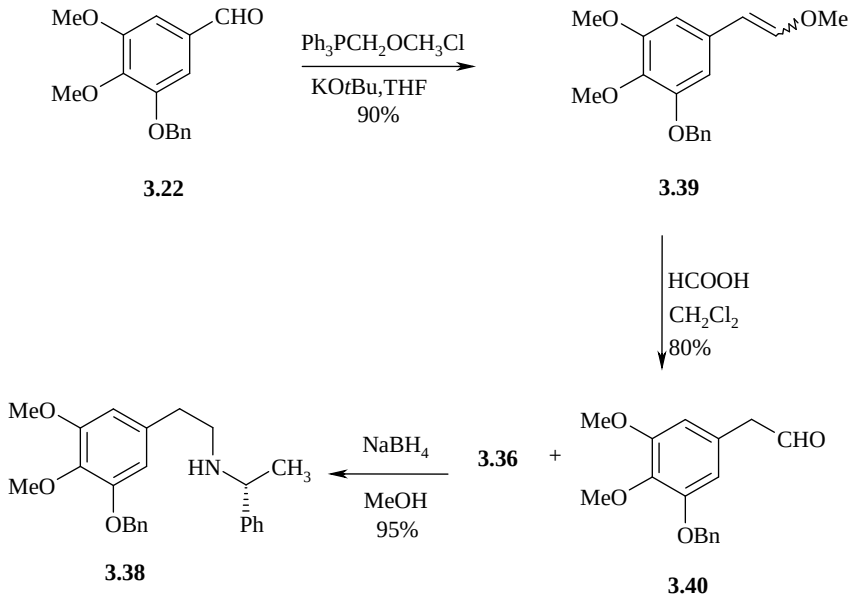
Scheme 3.9: Reaction mechanism for amide reduction.

At a later stage when more starting materials were needed, we looked at a shorter reaction sequence to prepare **3.38**, and it was found that compound **3.38** could also be prepared in three steps from compound **3.22**, where compound **3.22** is homologated *via* enol ether formation of **3.39** followed by hydrolysis to phenylacetaldehyde **3.40**. The main problem in this reaction sequence, was to get optimised experimental conditions for the hydrolysis of the enol ether **3.39**. After much experimentation, it was found that hydrolysis performed in methylene chloride in the presence of formic acid gave the desired product **3.40** in 80% yield. In a subsequent one pot reaction, **3.40** was condensed of with the chiral amine **3.36** to form the imine and *in situ* $NaBH_4$ reduction afforded **3.38** in 95% yield. Direct reductive amination of aldehydes normally uses additives such as catalysts (to

facilitate formation of imines and to activate C=N for preferential reduction) and dehydrating agents.[18] In our case, since sodium borohydride reduces the imine readily and the presence of the catalyst was not necessary, it was important to ensure that all the starting material was consumed prior to addition of $NaBH_4$ to prevent competing reactions. No dehydrating agent was used in this novel reductive amination sequence of electron-rich phenylacetaldehyde **3.40**. From a 'green' chemistry point of view, this approach is attractive. It eliminates the use and generation of hazardous substances such as:

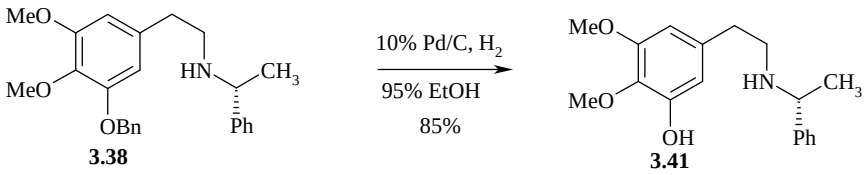
- Corrosive and irritant cyanuric chloride used for preparation of condensing reagent DMTMM.
- Corrosive and irritant thionyl chloride utilised in synthesis of **3.24**.
- Hygroscopic and poisonous sodium cyanide used in the preparation of **3.25**.
- Highly flammable moisture-sensitive reducing reagents BH_3·THF complex and BF_3·OEt_2 which sometimes do not give fully converted amine **3.38**.

This method results in a more efficient process by which less synthetic steps are involved and this reduces the waste associated with the isolation of intermediates involved in Scheme 3.5. Furthermore, less by-products are generated and this leads to higher yields. Formation of phenylacetaldehyde *via* the enol ether was repeated in the preparation of other intermediates of our target compound (See Section 3.4 and Scheme 3.45).



Scheme 3.10: Formation **3.38** based on a Wittig reaction.

Since a phenolic function would be required in the next step to control the regioselectivity during the Pictet-Spengler cyclisation, it was necessary at this point to deprotect the benzyl moiety of **3.38**. Deprotection of the benzyl ether moiety of **3.38** proved to be difficult with Lewis acids such as $FeCl_3$[19] and $TiCl_4$.[20] Catalytic hydrogenolysis would be difficult to conduct since both *O*-debenzylation and *N*-debenzylation occurs under the same conditions.[21,22] However, it is generally assumed that *O*-debenzylation is faster than *N*-debenzylation with hydrogen in the presence of palladium on activated carbon (Pd/C) catalyst. Under controlled conditions (at ambient pressure and temperature), the *O*-benzyl was selectively deprotected furnishing amino alcohol **3.41** in 85% yield after 15 minutes (Scheme 3.11). It should be noted that if the reaction is not monitored carefully (TLC), the *N*-debenzylated product could be isolated (after 20 minutes). The absence of the benzyloxy methylene singlet at δ_H 5.10 in the ^{1}H NMR spectrum of **3.41** as well as the reduced number of aromatic protons at δ_H 7.16-7.19 (5H, m), confirmed the formation of the *O*-deprotected product **3.41** (Plate 2). With the enantiomerically-pure amine prepared, it was viable to proceed to the synthesis of phenylacetaldehyde **3.6** to be used in the subsequent coupling reaction to achieve the desired THIQ. Different synthetic methods for the preparation of phenylacetaldehydes employed in this study are presented in the following paragraphs.



3.38 **3.41**

Scheme 3.11: Selective *O*- vs. *N*-debenzylation.

3.4 Synthesis of phenylacetaldehydes

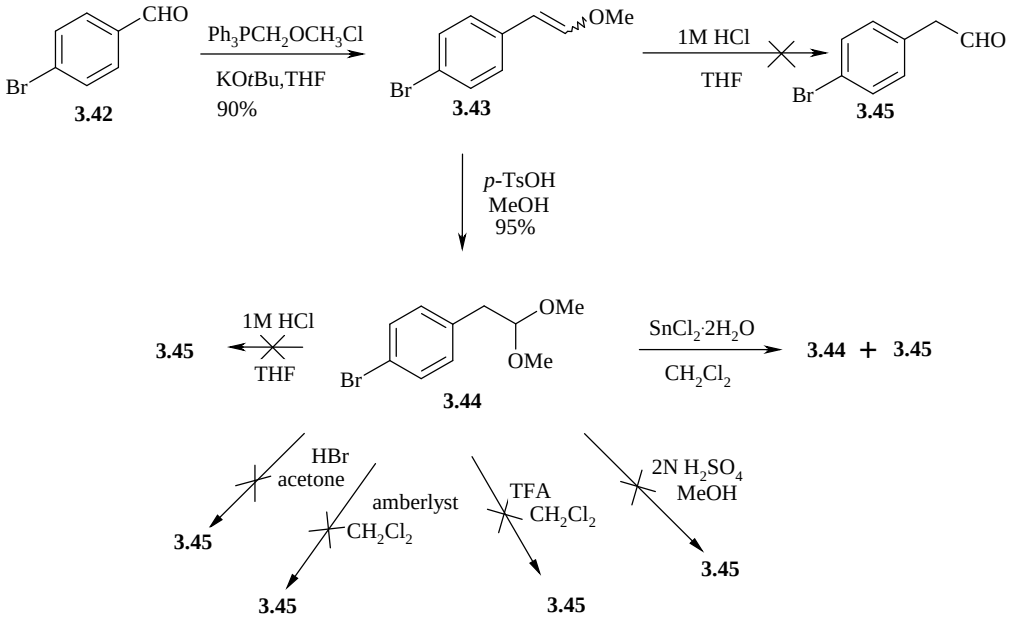
3.4.1 4-Bromophenylacetaldehyde (3.45)

The aldehyde functionality occupies a central position in functional group chemistry and numerous procedures have been introduced to generate this functionality ranging from oxidation of benzylic sites, alcohols, ethers, halides and hydrolysis of acetals. One of the methods chosen for the preparation of the target compound **3.45** is the hydrolysis of an acetal which was prepared from 4-bromobenzaldehyde (**3.42**), following a Wittig-based

strategy.[23] The reaction of 4-bromobenzaldehyde (**3.42)** with (methoxy)triphenylphosphonium chloride gave the enol ether **3.43** in 90% yield. The acid-catalysed hydrolysis of the enol ether **3.43** with HCl did not yield the desired product. It was only after the completion of the synthesis of this series of phenylacetaldehydes, that the reaction conditions described on page 71 were developed, and a longer route was followed for the preparation of these compounds. The enol ether was then treated with *p*-TsOH in methanol to the corresponding dimethyl acetal **3.44** (Scheme 3.12).[24] Different protocols employed for the hydrolysis of the acetal are described below.

3.4.1.1 Hydrolysis of acetal 3.44

Acetals are the most important protecting groups for aldehydes. Regeneration of the parent carbonyl from acetals by hydrolysis is well known. Classically, hydrolysis has been performed in the presence of commonly-used acids such as HCl, H_2SO_4, *p*-TsOH, HBr, TFA, Amberlyst and the Lewis acid tin chloride, to mention a few.



Scheme 3.12: Protocols for the hydrolysis of dimethyl acetal **3.44**.

Partial hydrolysis has been occasionally mentioned as an inconvenience in the chromatography of acetals on wet silica gel.[25] As the method employs a heterogeneous reagent, the removal of reagents by filtration when the transformation is complete, was going to be easy. However, Amberlyst and wet silica proved to be too mild for our

compound since only the starting material was isolated, even after utilising different reaction conditions (different solvents and temperatures). Even with commonly used acids such as HCl, H_2SO_4 and HBr, no reproducible results were obtained and the desired product was isolated in minor quantities (Scheme 3.12).

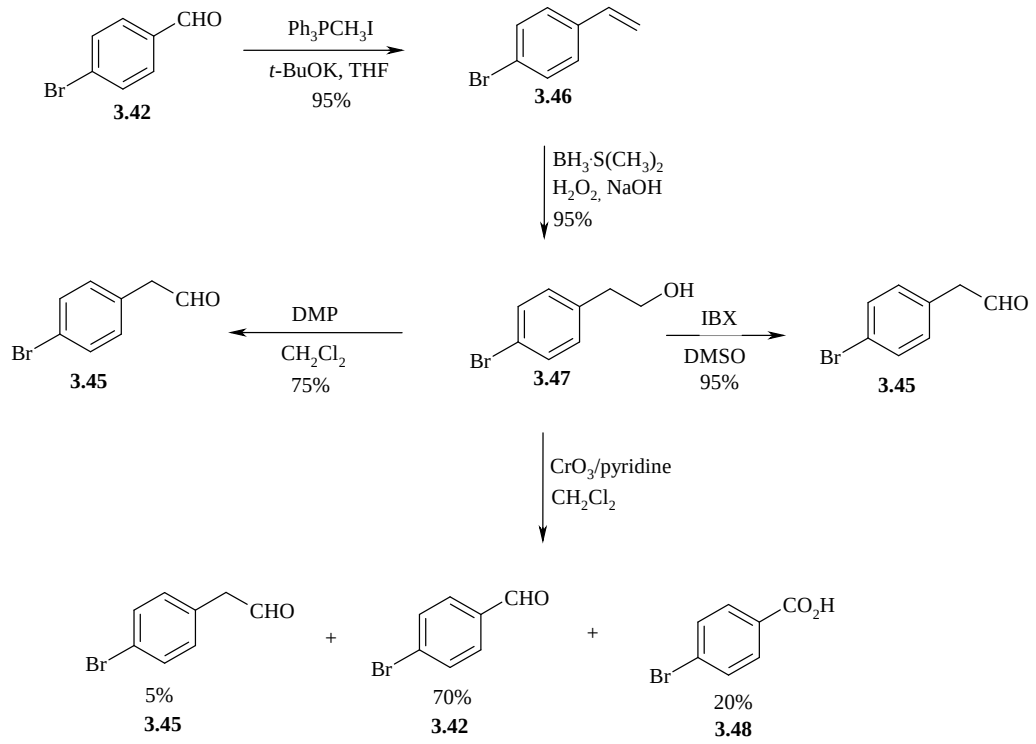
Ford and Roskamp[26] reported the deprotection of acetals using tin dichloride dihydrate ($SnCl_2.2H_2O$) under neutral, even mildly basic, conditions in methylene chloride. Deprotection was tried under the same conditions and 50% of the product was isolated, with the rest being the starting material. This might be due to the reacetalisation of the formed product if the reaction is left for long periods of time. This was inhibited by the addition of sodium bicarbonate, which increased the product formation by only 5%. Addition of naphthalene, which was reported to lower reaction times and improve the yields, resulted in an increase of the yields by 20% (from 50% to 70%).[26] However, chromatographic separation of naphthalene and the product **3.45** was not an easy task because the two compounds have close R_f-values. Taking into account the above-mentioned difficulties to obtain the pure target compound, it was therefore decided to exploit other methods.

3.4.1.2 Oxidation of alcohol 3.47

Oxidation of primary and secondary alcohols to aldehydes can be achieved using a plethora of reagents *(i.e.* $KMnO_4$, MnO_2, CrO_3, SeO_2, Br_2, *etc.*) in stoichiometric amounts. However, precautions must be taken that the aldehyde is not oxidised further to a carboxylic acid. Although many methods using a variety of reagents and conditions have been investigated, the development of selective oxidation using safe, economic and environmentally benign agents remains a critical challenge in organic synthesis. The alcohol **3.47** was prepared from 4-bromobenzaldehyde (**3.42**) *via* a Wittig olefination followed by hydroboration and subsequent oxidation gave the anti-Markovnikov alcohol **3.47** as the major product (Scheme 3.13).

Potentially, two regiochemically different products could be formed by hydroboration of the asymmetrical alkene **3.46**. However, one regioisomer is formed predominantly because boron preferentially adds to the less-substituted carbon to avoid steric hindrance. Furthermore, the high regioselectivity can be explained through the mechanism, the

reaction starts with the interaction of the π-electron pair of the alkene and the electron-deficient *p*-orbital of borane. The transition state with boron at the less-substituted carbon is energetically favoured because the partial positive charge located at the benzylic carbon is better stabilised due to delocalisation. It must be noted that good yields (95%) for the desired anti-Markovnikov product **3.47** were obtained at a low temperature (0 ºC), but an increase in temperature enhanced the formation of the undesired Markovnikov product. Different methods employed for the oxidation of the alcohol are presented below.

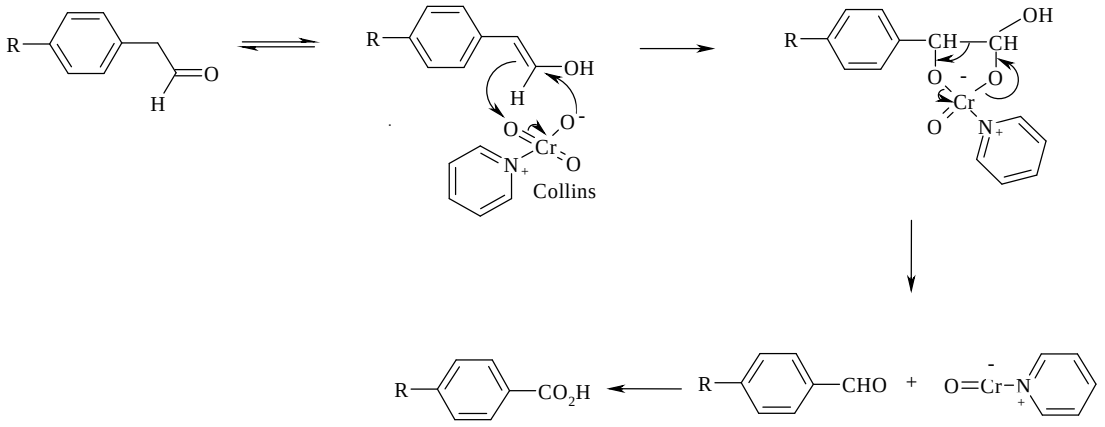


Scheme 3.13: Formation and oxidation of phenethyl alcohol **3.47**.

Collins reagent (CrO_3/pyridine) is one of the most important methods for the preparation of aldehydes.[27] Nevertheless, when the phenethyl alcohol **3.47** was subjected to this oxidation procedure, traces of the desired product **3.45** were obtained along with 4-bromobenzaldehyde (**3.42**) and 4-bromobenzoic acid (**3.48**) (Scheme 3.13).

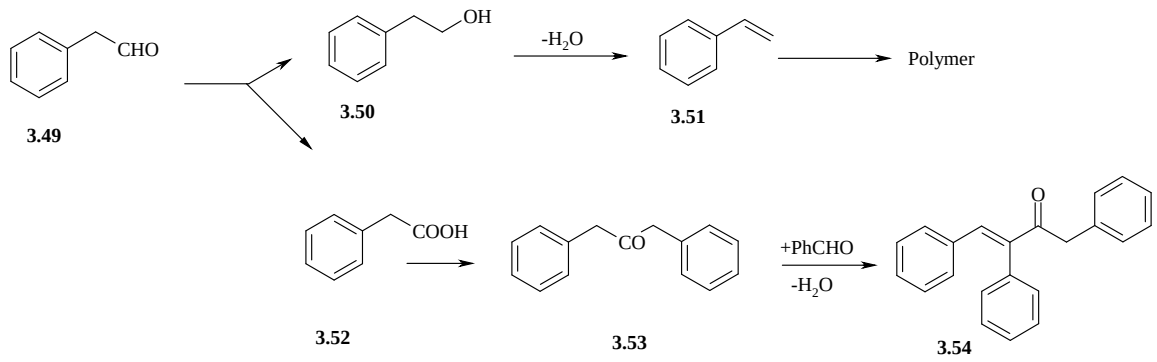
The unexpected formation of these side products can be rationalised in the mechanism proposed below (Scheme 3.14). The desired product was formed initially and then immediately attacked by another molecule of Collins reagent. The key cyclic intermediate

is formed in a concerted mechanism and the subsequent rearrangement ought to proceed efficiently to give benzaldehyde, which could be oxidised further to yield benzoic acid.



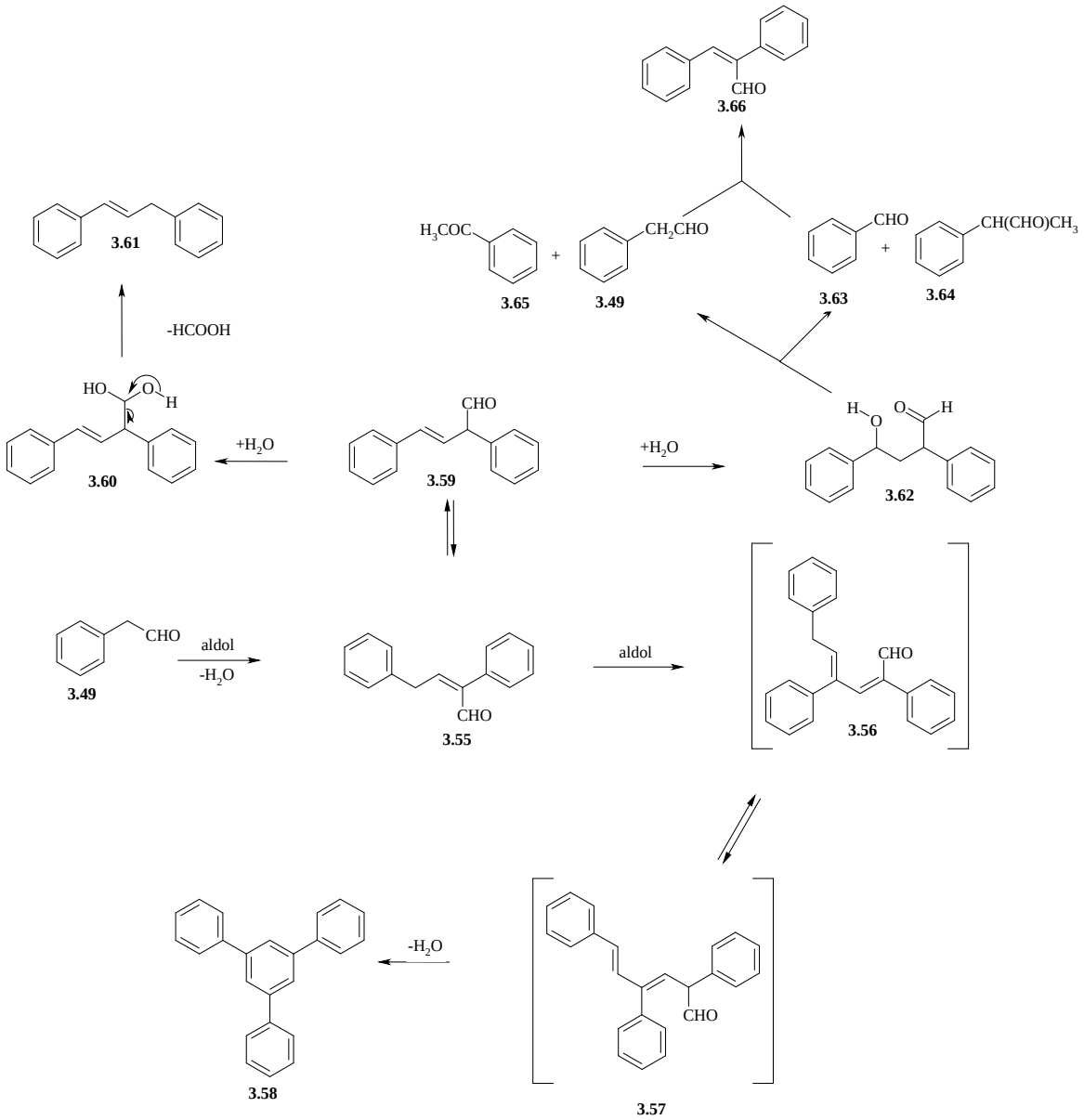
Scheme 3.14: Proposed mechanism for the formation of side products during oxidation using Collins reagent.

Given the general tendency for aldehydes to undergo some degree of aldol self-condensation under basic or acidic conditions, it was not surprising that the highly enolisable arylacetaldehyde gave so many problems. Phenylacetaldehyde is highly reactive in water at higher temperatures, with two major possible pathways which can occur, that is, disproportionation (Scheme 3.15) and condensation pathways (Scheme 3.16).[28] Disproportionation gives phenethyl alcohol (**3.50**) and phenylacetic acid (**3.52**). Dehydration of phenethyl alcohol leads to styrene (**3.51**), which in the presence of heat and acid polymerises to high-molecular weight products. The aldol reaction of dibenzyl ketone (**3.53**) with benzaldehyde produces **3.54**.



Scheme 3.15: Disproportion pathways for phenylacetaldehyde.

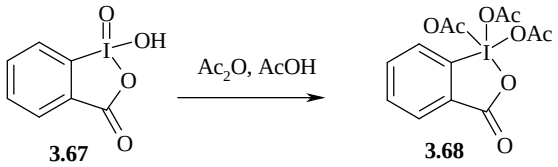
In the condensation pathway (Scheme 3.16), the initial aldol product **3.55** undergoes further aldol condensation to **3.56**, which then closes with concomitant dehydration to form triphenylbenzene (**3.58**) *via* intermediate **3.57**. Rearrangement of the double bond in **3.55** to **3.59** followed by hydration lead to the reactive intermediates **3.60** and **3.62**. Cleavage of formic acid from **3.60** gives 1,3-diphenylpropene (**3.61)**, whereas **3.62** decomposes to either phenylacetaldehyde (**3.49**) and acetophenone (**3.65**) or benzaldehyde (**3.63**) and 2-phenylpropionaldehyde (**3.64**) as the side products. Compound **3.66** is generated *via* aldol condensation of **3.49** and **3.63**.



Scheme 3.16: Condensation pathway for phenylacetaldehyde.

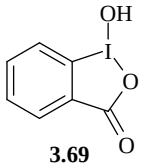
In view of the limited number of arylacetaldehydes available commercially and their high sensitivity to oxidative degradation in the presence of moisture, it was tempting to bypass the actual isolation of these molecules. However, these would be inappropriate since formation of THIQ in the Pictet-Spengler reaction does not utilise the same conditions as formation of arylacetaldehydes.

The use of Dess-Martin periodinane (DMP) (**3.68**) for oxidation gave the desired product **3.45** in 75% yield. However, preparation of DMP (**3.68**) requires an additional two steps with the inert conditions needed for oxidation. *o*-Iodoxybenzoic acid (IBX) (**3.67**) has been widely utilised for the preparation of DMP (**3.68**), a well-known mild oxidant affecting the conversion of alcohols to their corresponding carbonyls (Scheme 3.17).[29] IBX (**3.67**) have initially not been used as a reagent in organic synthesis because of its insolubility in common solvents such as DMF, CH_3CN, $CHCl_3$, CH_2Cl_2, acetone and THF. Moreover, IBX (**3.67**) was not commonly used as an oxidant due to the fact that it was reported to explode on heating. However, it was found that during synthesis of IBX (**3.67**), the sample was contaminated with residual bromine, which contributed significantly to the explosive feature of the sample. In contrast to DMP (**3.68**), IBX (**3.67**) is stable to moisture and the oxidation does not require dry solvents or an inert atmosphere. The successful synthetic use of IBX (**3.67**) as an oxidising agent is carried out in DMSO, the only solvent in which the reagent readily dissolves. In recent years, IBX (**3.67**) has seen a dramatic increase use as a reagent capable of 1) dehydrogenating ketones, aldehydes and silyl enol ethers to their corresponding α,β-unsaturated carbonyl compound,[30,31,32] 2) facilitating cyclisation of functionalised anilide systems to their heterocyclic counterparts[33,34] and 3) oxidation of benzylic sites.[35] Oxidation of phenethyl alcohol **3.47** with IBX gave 4-bromophenylacetaldehyde (**3.45**) in a good yield of 95%. Oxidation with IBX (**3.67**) gives IBA (**3.69**) as a by-product.



3.67 **3.68**

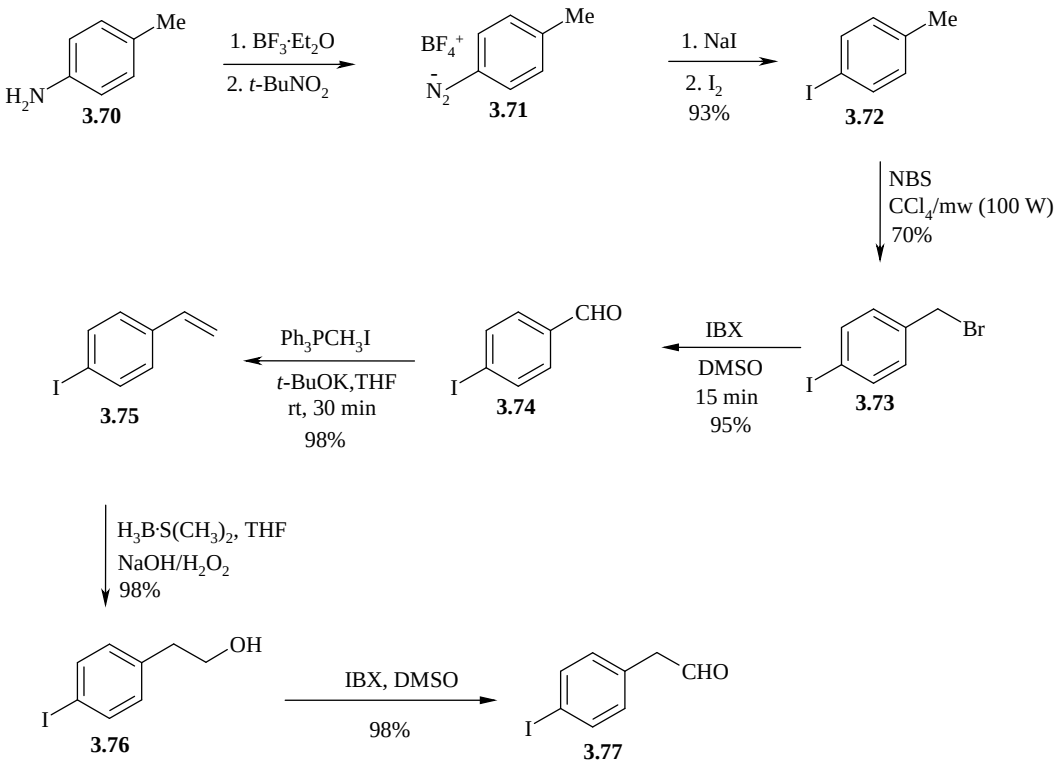
Scheme 3.17: Synthesis of DMP (**3.68**) from IBX (**3.67**).



3.69

3.4.2 4-Iodophenylacetaldehyde (3.77)

Different halo-arenes have been reported to give an array of yields in the formation of diaryl ether linkages. Generally, aryl iodides are more reactive than aryl bromides in the Ullmann reaction to form diaryl ethers. Since we planned to use the Ullmann reaction in the final step of the synthesis of cycleanine (**3.1**), the 4-iodo derivative **3.77** was also synthesised.



Scheme 3.18: Preparation of 4-Iodophenylacetaldehyde (**3.77**) from *p*-toluidine (**3.70**).

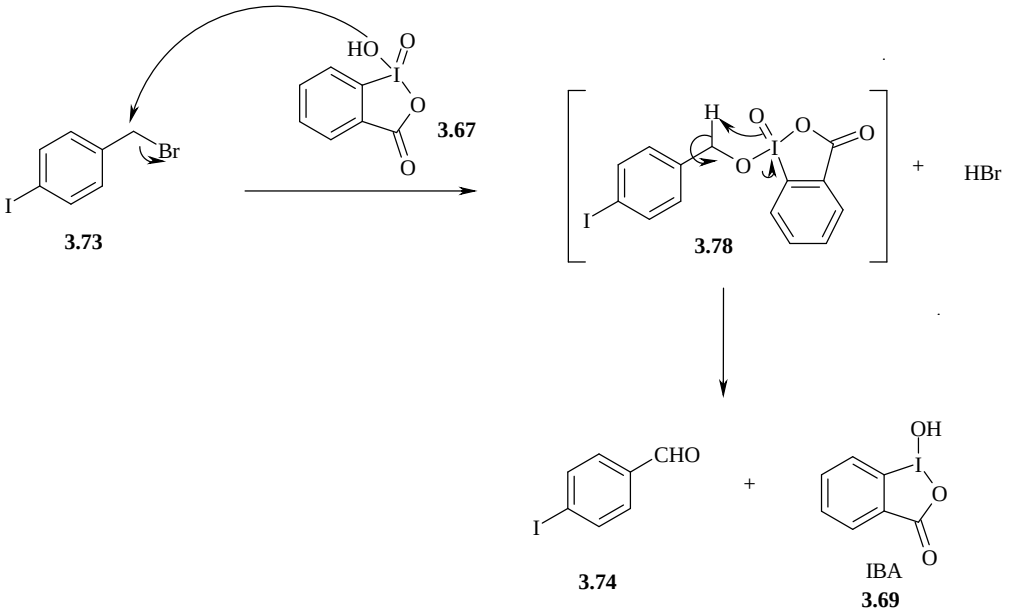
During the preparation of 4-iodophenylacetaldehyde (**3.77**), IBX (**3.67**) was utilised twice in one reaction sequence (Scheme 3.18) and this is an indication of the reagent's versatility and broad potential in further systems. The benzaldehyde **3.74** could be utilised as a starting material. However, this starting material is expensive and we decided to prepare it from the readily available *p*-toluidine (**3.70**). The diazotisation of *p*-toluidine (**3.70**) in anhydrous methylene chloride did not give good results due the low solubility of *p*-toluidine (**3.70**) in the chosen solvent. Changing the solvent to acetone, in the presence of excess boron trifluoride to trap the alcohol and water produced during the reaction, the arenediazonium tetrafluoroborate **3.71** precipitated from the solution as it was formed. The anhydrous tetrafluoroborate salt was obtained by a simple filtration and because it is

sensitive to air, it was immediately iododediazonated with sodium iodide in the presence of a catalytic amount of iodine to give *p*-iodotoluene (**3.72**) in 93% yield.

Chhattise *et al*.[36] reported the benzylic bromination of toluene with NBS as a serendipitous reaction of aromatic ring bromination. Their method was employed, but, since acetonitrile gave the product only after a long reaction time, carbon tetrachloride was opted for as the solvent of choice. The microwave-assisted bromination of *p*-iodotoluene (**3.72**) was completed after 10 minutes without an initiator to give *p*-iodobenzyl bromide (**3.73**) in 70% yield. From a chemistry point of view, NBS offers a major advantage as brominating reagent because the by-product of this reaction is succinimide and it can be easily recovered and recycled to NBS. Portion-wise addition of NBS to this reaction was important since the once-off addition of NBS resulted in a low product yield. It must be noted that during prolonged reaction times, the reaction mixture gradually turned purple as a result of the formation of I_2. This is most likely due to the iodine-bromine exchange which occurred at a slow rate since none of the deiodinated side product was observed. Microwave-assisted α-bromination of *p*-iodotoluene was achieved regioselectively in a short reaction time in a good yield and no side reactions like aromatic bromination or iodine-bromine exchanged were observed.

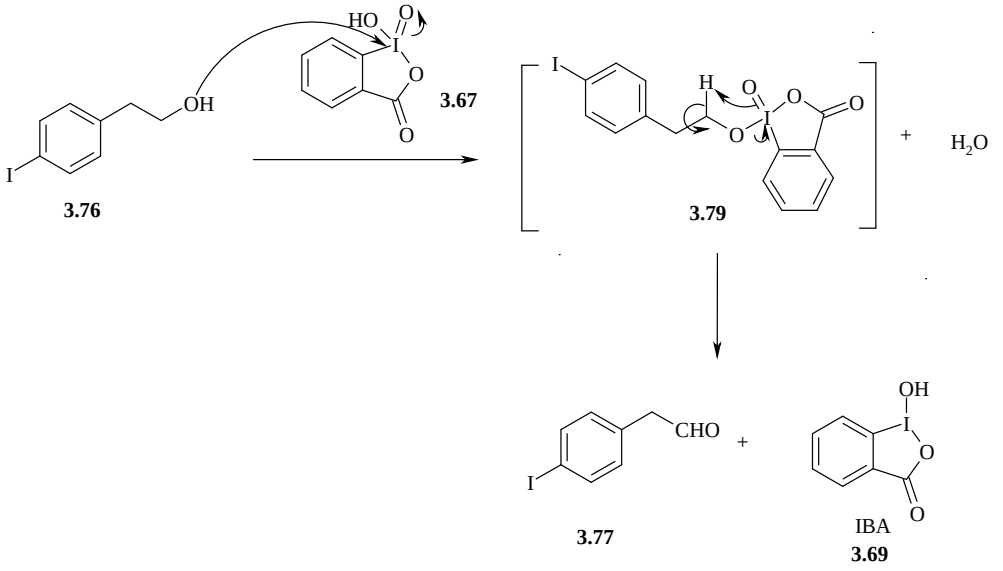
The oxidation of halides to carbonyl compounds can be accomplished by a number of methods, including *N*-alkoxypyridinium salts,[37] $NaIO_4$-DMF[38] and oxodiperoxovanadate.[39] However, most of these methods have disadvantages in terms of acid/base conditions, long reaction times, poor yields, high temperatures, etc. The method reported by Moorthy *et al*.[40] was employed for the oxidation of benzyl bromide **3.73** because IBX was already prepared for oxidation of the phenethyl alcohols. Even though a one-pot bromination-oxidation of iodotoluene was tried, the desired product was achieved in low yields, hence the sequential two-step procedure was followed.

p-Iodobenzyl bromide (**3.73**) was rapidly oxidised to give **3.74** in 95% yield. Oxidation of benzyl bromide **3.73** was faster than oxidation of phenethyl alcohol **3.76** to **3.77** and this is attributed to different mechanisms of oxidations (Scheme 3.19). The first reaction follows a S_N2 mechanism, where the first step is the rate-determining step, and hence the nucleophile is in high concentration, and the leaving group is bromide, which explains why this reaction is fast.



Scheme 3.19: Mechanism for the oxidation of benzyl bromide **3.73** to iodobenzaldehyde **3.74**.

Accordingly, the reaction may lead to the addition product **3.78**, which may subsequently decompose to the aldehyde **3.74** with liberation of IBA (**3.69**). A complication associated with this reaction is the competition IBA (**3.69**) and IBX (**3.67**) for the benzyl halide to form undesirable ethers. This can be avoided by addition of excess IBX (**3.67**), because from the mechanism, one equivalent of IBX (**3.67**) should suffice for the oxidation.

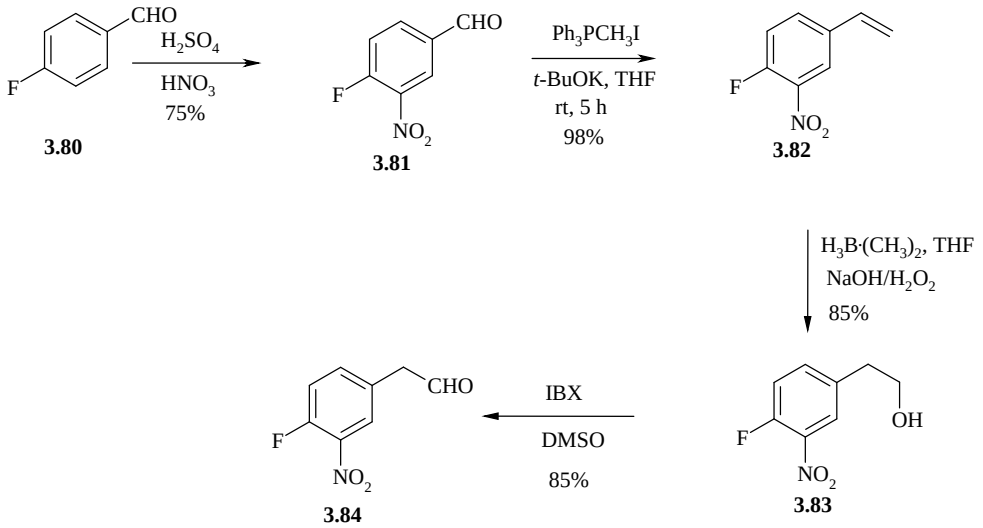


Scheme 3.20: Mechanism for the oxidation of phenethyl alcohol **3.76** to iodophenylacetaldehyde **3.77**.

In the oxidation of the alcohol **3.76** the first step is fast, the subsequent step is the slowest in the sequence and according to the mechanism, the presence of water slows down the forward process (Scheme 3.20).

3.4.3 4-Fluoro-3-nitrophenylacetaldehyde (3.84)

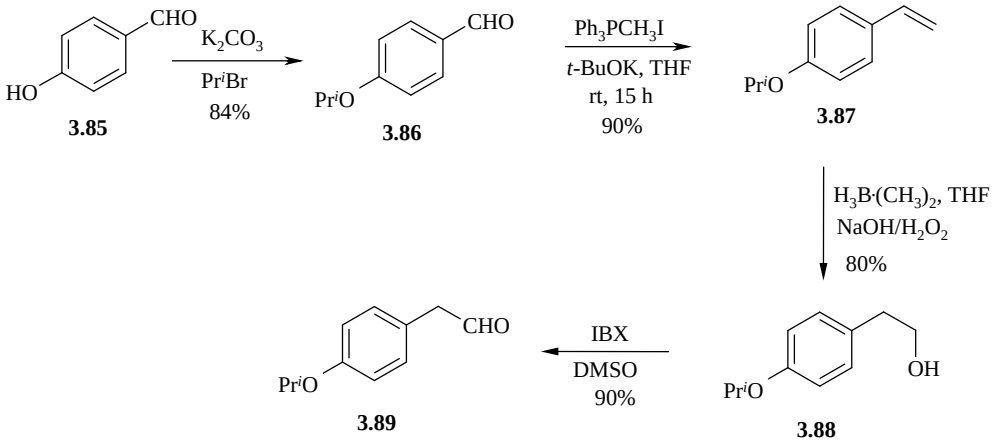
From Scheme 3.1, it was possible to construct a diaryl ether bond from two identical THIQ monomers *via* nucleophilic aromatic substitution (route **f**). However, nucleophilic aromatic substitution will only be possible with an activated 1-benzyl ring of the THIQ. This activated THIQ could be constructed by using an activated arylacetaldehyde during the Pictet-Spengler reaction. For this reason, 3-nitro-4-fluorophenylacetaldehyde (**3.84**) (Scheme 3.21) was prepared to give an activated THIQ in the Pictet-Spengler reaction and this could be used in the nucleophilic aromatic substitution to cycleanine (**3.1**) in a later stage of the total synthesis. Nitration of fluorobenzaldehyde **3.80** afforded a single nitro isomer **3.81** in 75% yield. The position of the nitro group was confirmed by the NOESY correlation between the aldehyde proton to two aromatic protons resonating at δ_H 8.08 (1H, dd, *J* = 2.3, 8.3 Hz, H-6) and 8.52 (1H, d, *J* = 2.3 Hz, H-2). 4-Fluoro-3-nitro styrene (**3.82**) was achieved in 95% yield, but it should be noted that good yields for the Wittig olefination of **3.81** were obtained after long reaction times (5 hours) compared to the bromo- and iodo-vinylbenzenes derivatives and this can be attributed to the presence of the strong electron-withdrawing nitro group. Hydroboration-oxidation of **3.82** to the alcohol **3.83** was achieved in 85% yield, followed by IBX oxidation to **3.84**.



Scheme 3.21: Synthesis of 4-fluoro-3-nitrophenylacetaldehyde (**3.84**).

3.4.4 4-Isopropyloxyphenylacetaldehyde (3.89)

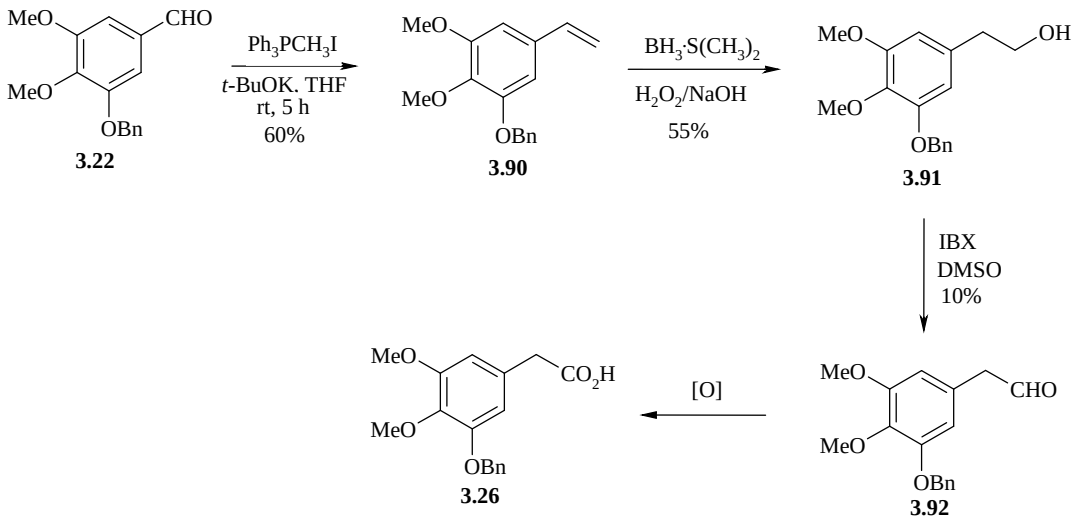
To exploit the scope of substrate effects on the Pictet-Spengler reaction, we decided to prepare the THIQ monomer with the electron-rich 1-benzyl moiety and on this basis 4-isopropyloxyphenylacetaldehyde (**3.89**) was prepared (Scheme 3.22). Formation of **3.89** was initiated by protection of the free hydroxy in **3.85** to **3.86** in 84% yield. The developed protocol for synthesis of phenylacetaldehydes was also used to give 4-isopropyloxyphenylacetaldehyde (**3.89**) in an overall yield of 55% from 4-hydroxybenzaldehyde. Although the reactions performed with the electron-donating isopropyloxy group were sluggish, reasonable yields were obtained. Wittig olefination of **3.86** took 15 hours to afford **3.87** in 90% yield, followed by an overnight hydroboration-oxidation to **3.87** and subsequent IBX oxidation to **3.89** in 90% yield. IBX (**3.70**) oxidised the phenethyl alcohols to aldehydes at room temperature without overoxidation to the carboxylic acids, no starting materials or C-C bond cleavage was observed. For all the products formed (**3.77**, **3.84** and **3.89**), the disappearance of the two triplets due CH_2CH_2OH were evident in the ^1H NMR spectra and the aldehyde triplet signal was apparent in all products formed. The yields for the formation of arylacetaldehydes vary with the halogen used, with the iodo being more reactive and giving higher yield at shorter reaction times (98%, 30 min) followed by bromo (95%, 1.5 h) and the fluoro (85%, 5 h) and with the electron-rich **3.88** reacting slower (90%, 18 h) than the rest of the phenethyl alcohols.



Scheme 3.22: Synthesis 4-isopropyloxyphenylacetaldehyde (**3.89**).

3.4.5 The anticipated synthesis of 3-benzyloxy-4,5-dimethoxyphenylacetic acid (3.26) *via* IBX (3.67) oxidation

The good results obtained in the oxidation of phenethyl alcohols (Scheme 3.12, 3.17, 3.20 and 3.21) encouraged us to attempt the synthesis of phenylacetic acid **3.26** using IBX (**3.70**). Synthesis of the phenylacetic acid was envisaged as indicated in Scheme 3.22. The envisaged synthesis of **3.26** according to Scheme 3.22 promised higher yields and shorter reaction times compared to synthesis of **3.26** following Scheme 3.6. The reaction of phenethyl alcohol **3.91** with IBX (**3.70**) was attempted. However, to our disappointment the oxidation of **3.91** to **3.92** gave the desired product in 10% yield. This could be attributed to coordination of the substrate to IBX (**3.70**), which may undermine the desired reaction course. The phenethyl alcohol **3.91** coordinates to the iodine centre *via* the lone pair of electrons on the ethereal oxygen thus changing the course of the reaction and the desired product is not formed. All reactions performed on **3.22** to **3.91** gave the products in low yields (Scheme 3.23), this could be due to the electron-rich character of subsequent compounds. Compound **3.90** was achieved in 60% yield compared to 95% yield of the iodo derivative **3.77**. Oxidation of **3.90** to **3.91** was obtained in moderate yield of 55%, whereas IBX oxidation gave **3.92** in a very low yield of 10%.



Scheme 3.23: Envisaged synthesis of 3-benzyloxy-4,5-dimethoxyphenylacetic acid (**3.26**) *via* IBX oxidation.

The importance of IBX (**3.67**) methodology stems from the fact that all the above-mentioned transformations are quite general and can be easily applied to a magnitude of synthetic strategies. The mild and chemoselective nature of IBX (**3.67**), coupled with the

high reaction yields that frequently accompany its employment, has rendered this reagent as a unique and powerful tool in chemical synthesis.

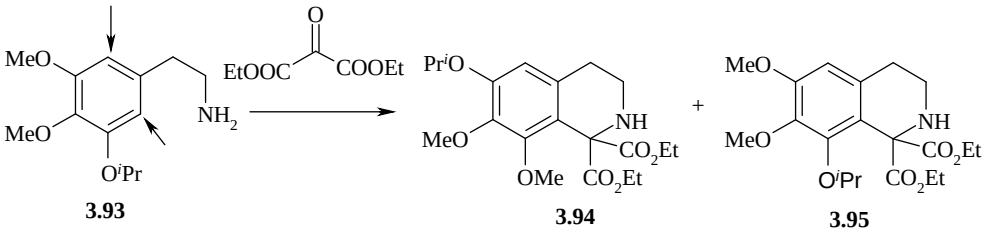
3.5 Regio- and stereoselective synthesis of 1,2,3,4-tetrahydroisoquinoline (THIQ) derivatives.

With the two starting materials **3.41** and different phenylacetaldehydes available for the formation of THIQ, the best conditions for synthesis of THIQ's were investigated. It has been reported that the Pictet-Spengler[41] strategy is the straightforward and synthetically efficient protocol for the synthesis of tetrahydroisoquinoline alkaloids. In this study, the Pictet-Spengler methodology was employed because fewer steps are involved. Though efficient, regioselectivity and stereoselectivity are known to be major drawbacks of the Pictet-Spengler reaction.

Although Pictet and Spengler originally reported the formation of the parent THIQ by heating of a mixture of 2-phenethylamine and formaldehyde in the presence of concentrated hydrochloric acid at reflux (150 ºC), a number of attempts to reproduce the synthesis of the parent THIQ in this prototype reaction have failed. For example, Clemo and Swan[42] reported the formation of large amounts of bis(2-phenylethylamine)methane along with the traces of THIQ under the reaction conditions originally described. The presence of the catalytic amount of the acid facilitates the ring closure in the Pictet-Spengler reaction. The preferred protic acid for the Pictet-Spengler reaction include HCl, formic acid, perchloric acid, phosphoric acid, trifluoroacetic acid (TFA), trifluoromethanesulfonic acid, to mention a few. The reactivity, regio- and stereoselectivity of the Pictet-Spengler reaction depend greatly on the nature of the starting chiral auxiliary amine, the degree of activation of the cyclising benzene ring of the relevant imines as well as the reaction conditions. The following paragraphs details the substrate effects, regio- and stereoselectivity of the products formed by the Pictet-Spengler reaction.

3.5.1 Regioselective analysis.

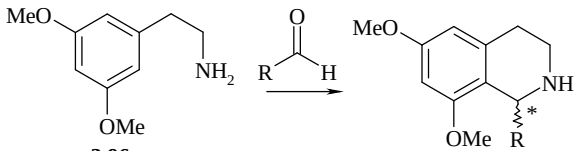
One problem which arises in the application of the Pictet-Spengler reaction is the regiochemical control when there is more than one site for cyclisation (Scheme 3.24). Hence this gives rise to two regioisomers if the site of the closure is not controlled. For example, 3,4,5-trisubsituted β-phenethylamine **3.93** gives **3.94** and **3.95** in 3:2 ratio.[43]



3.93 **3.94** **3.95**

Scheme 3.24: Regioisomers formed in the Pictet-Spengler reaction.

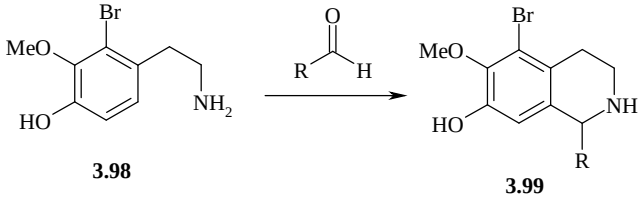
The synthesis of symmetrical THIQ's[44] is well known and in this case the regioselectivity is not important since any site for cyclisation gives the desired product **3.97** as a sole product (Scheme 3.25).



3.96 **3.97**

Scheme 3.25: Synthesis of a symmetric THIQ *via* the Pictet-Spengler reaction.

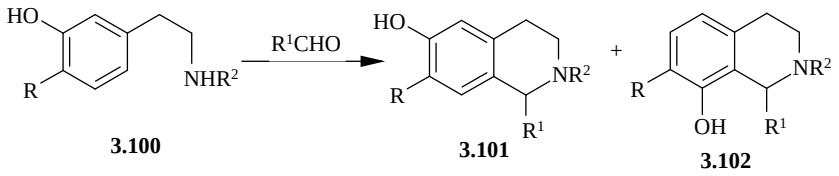
Cho *et al.* [45] employed a halogen blocking group so that cyclisation can be directed to one position (Scheme 3.25), in this case **3.98** gives only **3.99**. However, introduction of the blocking group add two more steps to the total synthesis, that is, addition as well as removal of the blocking group.



3.98 **3.99**

Scheme 3.26: Employment of a blocking group in the Pictet-Spengler reaction.

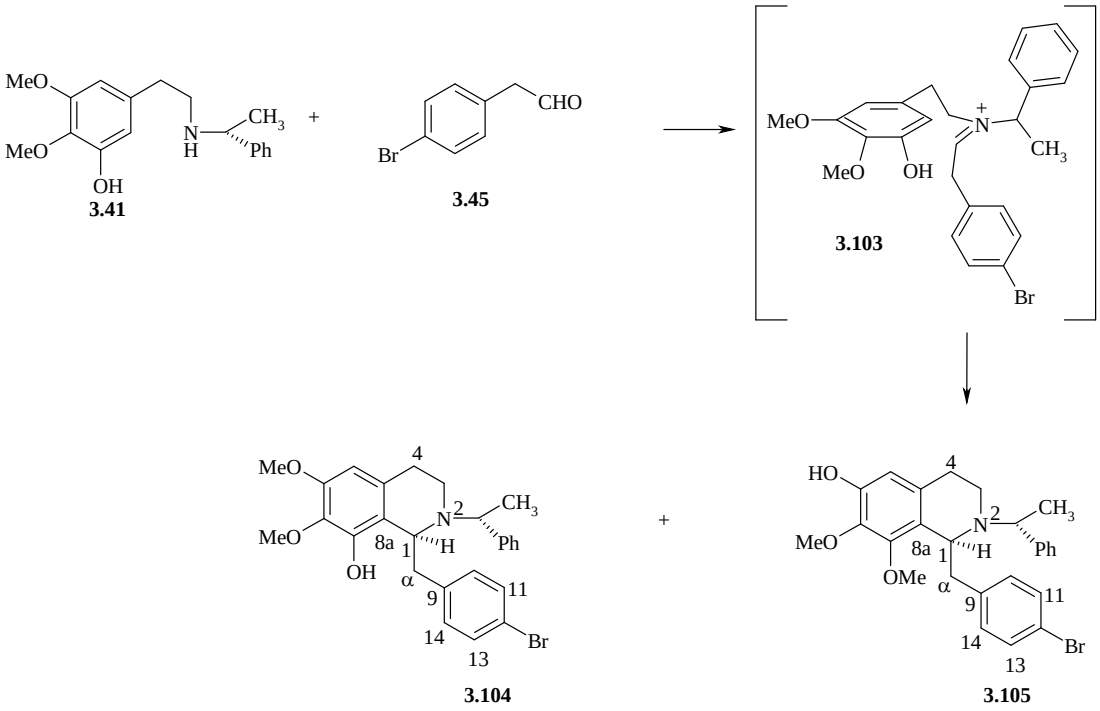
Cyclisation has generally been reported to proceed *para*[46] to the activating 3-alkoxy or 3-hydroxy group, thereby generating 6-alkoxy- or 6-hydroxytetrahydroisoquinolines. For example, condensation of dopamine with formaldehyde proceeds with preferential formation of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline over the 7,8-dihydroxy isomer, due to the pronounced directing effect of the activating OH group to the *para*- rather than *ortho*-position as a result of the steric hindrance. [47] Cyclisation of **3.100** afforded predominantly **3.101** with **3.102** as a minor product (Scheme 3.27).



3.100 **3.101** **3.102**

Scheme 3.27: Directing effect of OH group in the Pictet-Spengler reaction.

Due to the prominent directing effect of a free hydroxyl group, in this study the β-phenethylamine with a free hydroxy group was utilised. In the reaction conditions were optimised by using 4-bromophenylacetaldehyde (**3.6**) because fewer steps are involved during its preparation as compared to the other three arylacetaldehydes. The condensation reaction of β-phenethylamine **3.41** and phenylacetaldehyde **3.45** *via* the imine intermediate **3.103** could form two possible regioisomers **3.104** and **3.105** could form (Scheme 3.28). The predominant formation of the desired regioisomer **3.104** was essential since the separation of the isomers can be a tedious process, especially for large scale preparations.

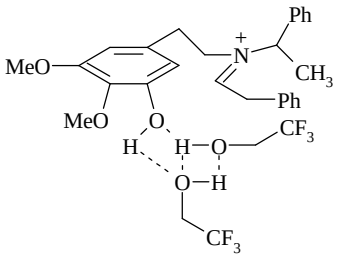


Scheme 3.28: Regioisomers isolated in the Pictet-Spengler reaction between **3.41** and **3.45**.

In this study, CH_2Cl_2 was used as the solvent and HOAc was chosen as the catalyst to promote formation of the iminium cation in the Pictet-Spengler reaction. During the formation of the iminium intermediate, water is also formed and this could slow the formation of the final product. Thus, molecular sieves were added to improve the rate as well as the yields of the reaction. The highly polar 2,2,2-trifluoroethanol (TFE) was also used as a co-solvent. The unique properties brought about by the presence of three fluoro substituents in this solvent were expected to dramatically modify the course of the reaction. The electron-withdrawing character of CF_3 confers high acidity to the hydrogen of the hydroxy group with a pKa value of 12.4. Furthermore, TFE possesses a very strong hydrogen bond donor power ($\alpha = 1.51$). Previously, TFE was used in the Pictet-Spengler reaction to influence the stereochemistry of the reaction, but to the best of our knowledge, this is the first time that it is used to control the regioselectivity of the Pictet-Spengler reaction.[48]

When the amine **3.41** and the aldehyde **3.45** reacted at 25 ºC in the absence of TFE and HOAc, no reaction occurred after 12 hours (Table 3.1, Run 1). Addition of TFE as a co-solvent did not provide the desired product (Table 3.1, Run 2). Addition of a catalytic amount of HOAc (0.01 eq.) and reduction of TFE (CH_2Cl_2:TFE 2:1) at 25 ºC resulted in a

formation of the mixture of the two regioisomers **3.104** and **3.105** in a 1:1 ratio (Table 3.1, Run 3, Plate 3). Reduction of the co-solvent from a 1:1 ratio to a 7:1 (CH_2Cl_2:TFE) ratio and increasing the HOAc (0.1eq.), resulted not only in an increased yield of the reaction, but also to the formation of **3.104** as the major product (Table 3.1, Run 6). The results from runs 3-5 clearly demonstrated that the hydroxy group of the 3,4-dimethoxy ring was activated by the presence of TFE, due to the high hydrogen bond donor ability of TFE and its high ionising power. High concentration of TFE in the reaction mixture (low pH) resulted in cyclisation *para* to the hydroxy group and this is in agreement with results reported by Bates where cyclisation occur exclusively in the *para* position. Furthermore, a high concentration of TFE in the solution can result in the formation of the dimeric TFE complex in the transition state, which will make the *ortho* position to the OH group less accessible for cyclisation due to steric effects (Figure 3.1).



3.106

Figure 3.1: Hydrogen bonding due to the presence of TFE in the Pictet-Spengler reaction.

A decrease in temperature from 25 ºC to 0 ºC resulted in a change in ratio to 1:6, with **3.105** being the major isomer (Table 3.1, Run 5, Plate 4). This indicates that lower temperatures retard cyclisation in the desired position, hence decreased the formation of the desired product. In refluxing CH_2Cl_2 in the presence of molecular sieves and lower amounts of TFE, to our delight the desired regioisomer **3.104** was formed as a major product (Table 3.1, Run 6). Increase in the reaction times from 12 h to 18 h in refluxing CH_2Cl_2 resulted in the formation of **3.104** as a sole product (Table 3.1, Run 7, Plate 5). Overall, under optimised conditions [CH_2Cl_2:TFE = 7:1, HOAc (0.1 eq.), reflux, molecular sieves, 18 h], the desired product **3.104** was obtained in 78% yield. When this reaction mixture was heated for a longer period (24 h) and with a high concentration of HOAc (1 eq.), the yield of the product was decreased from 78% to 45% (Table 3.1, Run 8). This indicated that HOAc rapidly induced the cyclisation and at the same time slowly decomposed the products due to prolonged exposure to the acid (Plate 6). This was also

experienced when product was in contact with $CDCl_3$, which is slightly acidic for a long time. These results suggested that the ratio of regioisomers is thermodynamically rather than kinetically controlled. At this stage, we were not sure what the stereochemistry at C-1 of **3.104** and **3.105** was, but based on results obtained later (Section 3.7), the stereochemistry at C-1 was assigned as *S*.

Table 3.1: Effects of time, temperature and co-solvent on the yields and ratio of the regioisomers of the Pictet-Spengler reaction.

Run	Solvent	Additives	Temp (ºC)	Time	Yield (%)[a]	Ratio (**3.104/3.105**)[b]
1	CH_2Cl_2	-	25	12	-	-
2	CH_2Cl_2/TFE (1:1)	-	25	12	-	-
3	CH_2Cl_2/TFE (2:1)	HOAc (0.01 eq.)	25	12	50	1:1
4	CH_2Cl_2/TFE (2:1)	HOAc (0.1 eq.)	25	12	55	2:3
5	CH_2Cl_2/TFE (2:1)	HOAc (0.1 eq.)	0	12	65	1:6
6	CH_2Cl_2/TFE (7:1)	HOAc (0.1 eq.)	reflux	12	70	4:1
7	CH_2Cl_2/TFE (7:1)	HOAc/ms (0.1 eq.)	reflux	18	78	100:0
8	CH_2Cl_2/TFE (7:1)	HOAc/ms (1 e.q)	reflux	24	45	decomposition

[a]Yields are for isolated products obtained after chromatography (Hexanes/EtOAc)

[b]Ratios were determined by ^{1}H NMR spectroscopic integration

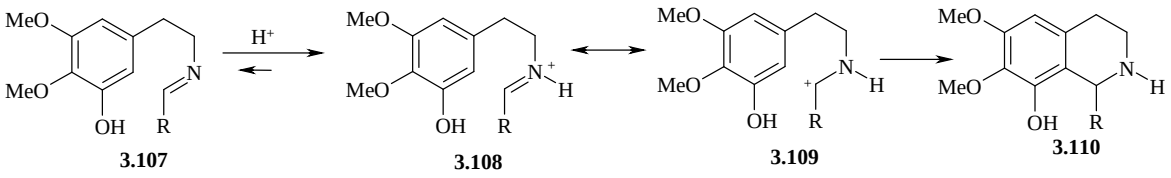
The results achieved are in good agreement with the reported studies by Manabe *et al.*[49] and Eynden *et al.*,[50] but it is important to note that in their case, the formation of one regioisomer was attributed to steric control. Nevertheless, in our investigation the product formed at higher temperature was governed by electronic factors as well as the steric control. *Ortho*-cyclisation may also be favoured by dipolar attraction between the iminium cation and phenolate anion. Looking at the NMR shifts of the different aromatic protons of compound **3.41**, it is apparent that the proton *ortho* to the free hydroxy at δ_H 6.18 (1H, d, J = 1.8, H-6) is more electron-rich than the *para* proton at δ_H 6.33 (1H, d, J = 1.8 Hz, H-2), since it resonates up-field and more energy is needed for cyclisation to occur at H-2.

The ratio of regioisomers **3.104** and **3.105** formed in the Pictet-Spengler reaction depends on the reaction conditions, *i.e.* temperature, the amount of the co-solvent and time as shown in Table 3.1. The reactions conducted under milder conditions gave low regioselectivity, while the reactions under forced conditions showed high regioselectivity, for example, the ratio of **3.104** and **3.105** was 1:1 at 25 ºC and at reflux 100:0. The structures of products **3.104** and **3.105** were determined by spectral analyses (MS, IR, ^{1}H, ^{13}C, NOESY). The ^{1}H NMR of **3.104** exhibited ten aromatic protons, a singlet (H-5) at δ_H 6.22, methine H-1 at δ_H 4.35, two methoxy groups, methine quartet (δ 3.63) and methyl doublet (δ_H 0.96) from the chiral auxiliary and six aliphatic protons (three pairs of methylene protons). The presence of ten aromatic protons instead of five protons in the starting material, methine H-1, splitting patterns of the diastereotopic H-α protons and the methylene protons indicate the presence of the newly chiral centre at C-1 and these corroborate formation of **3.104**. The aromatic region (δ_H 6.22 - 7.45) of the ^{1}H NMR spectrum exhibited two separate spin systems, an AA'BB' and ABC. Analyses of ^{13}C NMR, DEPT and HSQC revealed the presence of two methine, one methyl, three methylene and eight quaternary carbons. The HMBC spectrum permitted the construction of structure showing correlations from H-5 to C-6, C-4, C-4a; H-1 to C-8a, C-6, C-7; H-α to C-1, C-9, C-10; H-10 to C-9, C-11, C-12; H-11 to C-9,C-10, C-12.The assigned structure was also supported by the MS data (*m/z* 482.1333 $[M+H]^{+}$). The difference between **3.104** and **3.105** structures was determined by NOESY. In the NOESY spectrum of **3.104** (Plate 7), the signal of the H-5 singlet at δ_H 6.22 showed a correlation to the C-6 methoxy protons at δ 3.80, whereas for **3.105** no correlation to a methoxy signal was observed. In addition, the methine proton (H-1) of **3.105** appears at higher chemical shifts due to the shielding effect of the methoxy group at C-8.

3.5.2 Effects of substrates

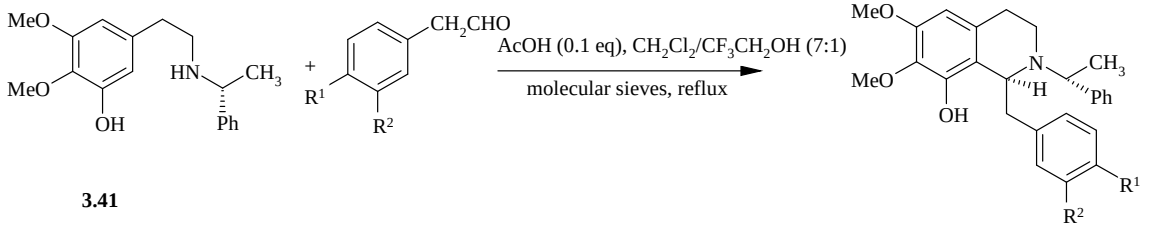
Thus, the general consensus hitherto has been that the Pictet-Spengler cyclisation is sensitive to the aromatic substituents of the 2-arylethylamine moiety of the imine. Furthermore, an electron-donating hydroxy or an alkoxy group at the *para*-position of the cyclisation site, is the minimum requirement for a facile reaction.[51] Because a methoxy group on the aromatic ring is a strong electron-donating group, the imine **3.107**, which bears two methoxy groups, can be regarded as an activated substrate. This imine readily undergoes cyclisation to give the corresponding THIQ **3.110** in a high yield. The imine

3.107 is protonated in HOAc to give the iminium cation **3.108**, which cyclises in the rate-determining step of the reaction to give **3.110** (Scheme 3.29).



Scheme 3.29: Iminium cation formed in the Pictet-Spengler reaction.

The influence of substituents on the phenylacetaldehyde ring was also investigated (Scheme 3.29, Table 3.2). It was noted that the reaction yields increased in the presence of the electron-withdrawing halides by increasing the electrophilicity of the aldehyde. Formation of THIQ **3.113** required longer reaction times and lower yields were obtained in comparison to the THIQ with halides substituents (Table 3.2, Entry 4). Although the phenylacetaldehydes with bromine and iodine substituents did not show a big difference in terms of the yields, the reaction of the bromo derivative took longer than the reaction of the iodo derivative (Entries 1 and 2, Table 3.2). The fluoro-nitro substituents gave lower yield at longer reaction times (Table 3.2, Entry 3) compared to the other two halides.



3.45: R^1 = Br, R^2 = H
3.77: R^1 = I, R^2 = H
3.84: R^1 = F, R^2 = NO_2
3.89: R^1 = O^iPr, R^2 = H

3.104: R^1 = Br, R^2 =H (78%)
3.111: R^1 = I, R^2 = H (80%)
3.112: R^1 = F, R^2 = NO_2 (72%)
3.113: R^1 = O^iPr, R^2 = H (70%)

Scheme 3.30: Effects of R^1 and R^2 substituents on phenylacetaldehyde on the formation of THIQ .

Table 3.2. Effects of R^1 and R^2 substituents on the time and reaction yields of the Pictet-Spengler reaction.

Entry	R^1	R^2	Time (h)	Yield (%)
1	Br	H	18	78
2	I	H	12	80
3	F	NO_2	24	72
4	O^iPr	H	20	70

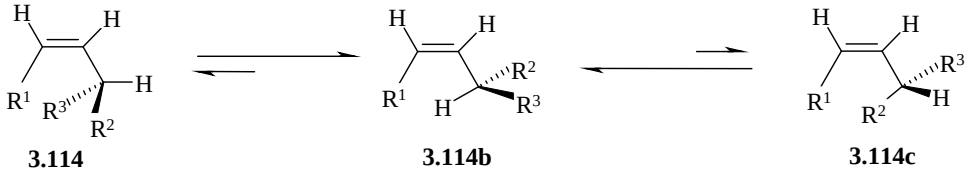
No intermolecular side products were formed since the iminium cation intermediate formed is a weak electrophile and it requires a reactive nucleophile and this favours intramolecular cyclisation to a heterocyclic ring over intermolecular reactions. The Pictet-Spengler cyclisation proceeded exclusively in a 6-*endo* fashion and no products derived from the 5-*exo* alternative were observed. Furthermore none of the uncyclised products were isolated.

3.5.3 Stereochemical and conformational analyses

The use of chiral auxiliaries to control stereochemistry played a major role in the development of stereoselective syntheses for natural products. One way to control the stereochemistry of tetrahydroisoquinolines at C-1 is to incorporate a chiral auxiliary on the nitrogen. Based on results published on the Bischler-Napieralski reaction,[8] we initially anticipated that the chiral auxiliary with a *R*-configuration will result in the *R*-configuration at the new chiral centre.

In a X-ray crystallographic study discussed later (page 107), it was found that the heterocyclic ring of the THIQ has a half-chair conformation, with the substituent (4-bromobenzyl) at C-1 and the bulky benzyl group at nitrogen *trans* to each other. The stereochemistry of the newly formed chiral centre was proven to be *S* from the X-ray structure of compound **3.131**. Compound **3.131** was prepared from isoquinoline **3.104** and, therefore, the stereochemistry at C-1 of **3.104** must also be *S*. Compound **3.104** has two stereocentres and if the Pictet-Spengler reaction was not stereoselective, the result would be a mixture of diastereomers. The NMR spectra of **3.104** clearly showed that it consisted of one diastereomer only and that the reaction proceeded with high stereoselectivity.

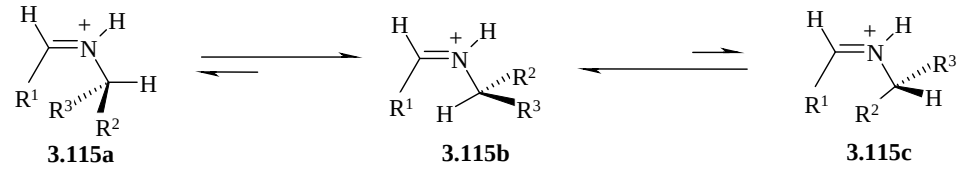
The Bischler-Napieralski reaction gives the same isomer as the starting chiral auxiliary, therefore, the results found from X-ray indicates that different mechanisms are followed during cyclisation when the Pictet-Spengler reaction is employed instead of the Bischler-Napieralski reaction. The stereochemical outcome of the Pictet-Spengler reaction and the Bischler-Napieralski reaction can be explained by Houk's computational studies.[52] Both reactions are cases of an 2-aza-allyl system and Houk's investigation found that for these systems, one conformation is preferred due to allylic 1,3-strain. Thus it is important to predict the conformation of the starting materials.



3.114 **3.114b** **3.114c**

Scheme 3.31: The most stable conformer of open chain allylic system.

For simple alkenes, the preferred conformation is the one with the hydrogen in the plane of the alkene. The relative sizes of the R^2 and R^3 substituents differentiate the diastereotopic faces on the double bond (Scheme 3.31). When R^1 = Me the equilibrium lie in favour of **3.114b** and if R^3 is bigger than R^2, the attack will occur from the less sterically hindered side. For heterosubstituted allylic systems, experimental asymmetric induction and spectroscopic measurements suggest that the conformer **3.115b** is markedly favoured over conformers **3.115a** and **3.115c**, even when R^1 = H (Scheme 3.32)[48].



3.115a **3.115b** **3.115c**

Scheme 3.32: The most stable conformer of heterosubstituted allylic system.

We applied Houk's model to rationalise the stereochemical outcome of the Bischler-Napieralski and the Pictet-Spengler reactions. In these two reactions the reacting prochiral groups and the inducing stereocentres are part of the same molecule. The two entities are separated by two bonds equivalent to 1,3-asymmetric induction. Both these reactions require nucleophilic attack to an imine. Nucleophilic attack on imines, as in the case with carbonyls, follows the Bürgi-Dunitz trajectory,[53] as the nucleophile approaches the C=N

carbon atom, the two alkyl substituents R^2 and R^3 bend away and the C=N distance becomes longer. The nucleophile approaches along a line which is not perpendicular to the C=N but forms an angle of 107° with it (Figure 3.2).

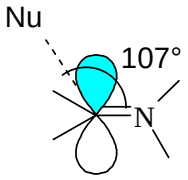
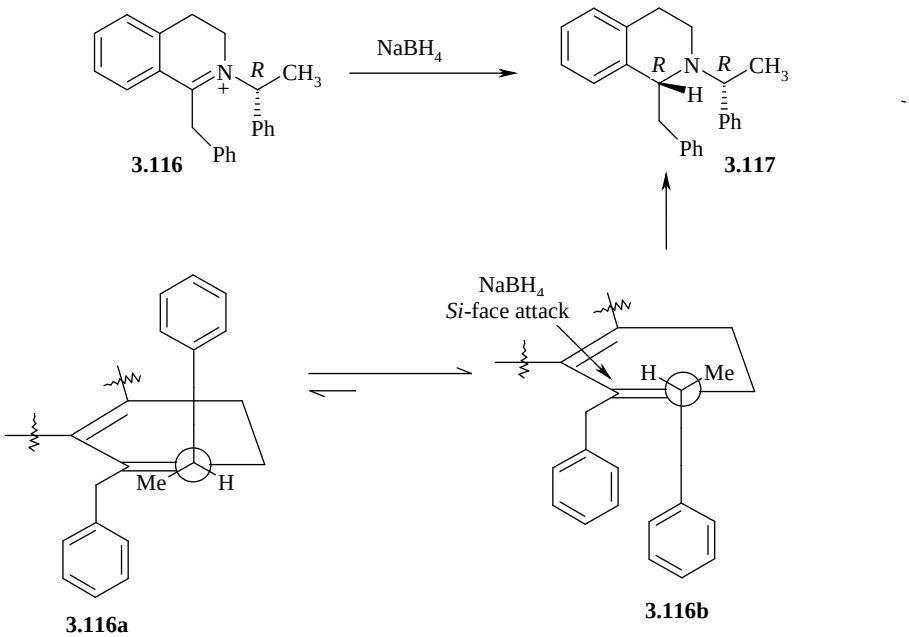


Figure 3.2: Nucleophilic approach to C=N carbon atom.

The Bischler-Napieralski reaction entails formation of a new stereocentre on a cyclic six-membered ring substrate (Scheme 3.33). Since the C=N double bond is set in a rigid six-membered ring, only two rotations are possible for this structure: 1) rotation around C-N bond linking the N to the stereogenic centre and 2) rotation around C-C bond linking the stereocentre and the aromatic moiety. This conformational rigidity ensures the high levels of stereocontrol. The mechanism accounting for this success is the stereocontrolled formation of the iminium ion-borohydride ion pair prior to reduction, followed by the hydride ion attack of the activated iminium moiety with the generation of the new chiral centre in **3.117** (Scheme 3.33).[54]

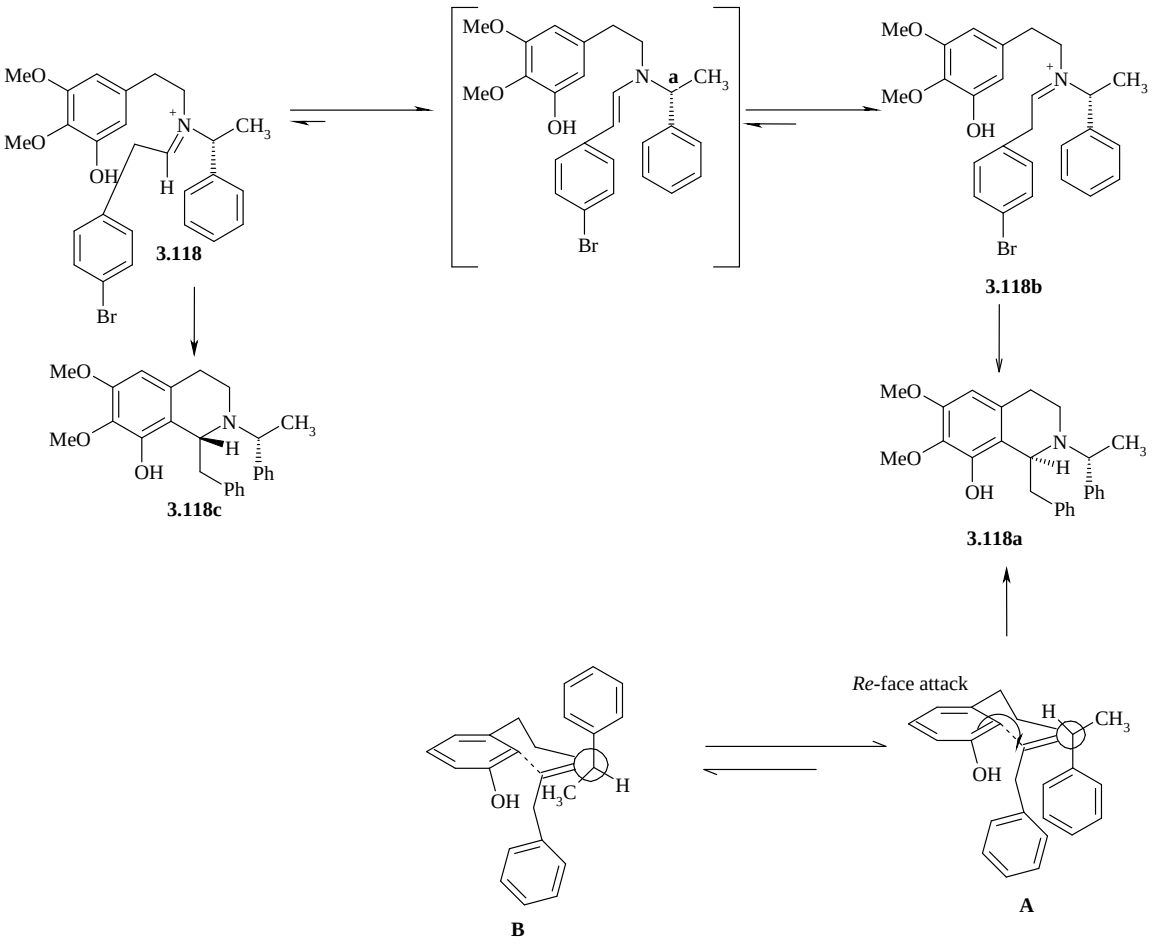


Scheme 3.33: Diastereoselective synthesis of THIQ **3.117** *via* the Bischler-Napieralski reaction.

The single stereogenic centre appended to the nitrogen atom controls the effectiveness of the asymmetric induction by creating different steric environments at the two diastereofaces of the iminium. The *R*-diastereomer was postulated to arise from transition state of the **3.116b** which is more stable than **3.116a** favouring a *si*-attack by a hydride ion. The *si*-face is the least hindered face and in this conformer 1,3-allylic strain is minimised. The attack from the *si*-face will lead to the *R*-benzyltetrahydroisoquinoline.

The Pictet-Spengler reaction represents asymmetric induction of an open chain allylic system. For the efficient asymmetric induction in the open-chain situations, two conditions have to be met. Firstly, the number of energetically favourable conformations of the bonds connecting the prochiral group and the inducing stereogenic centre has to be restricted so that one conformation is available in the transition state. Secondly, in this conformation the different groups on the stereogenic centre must differentiate the diastereotopic faces of the reacting prochiral group. This differentiation can be accomplished by using a large group at the controlling stereocentre that shields the approach on one side of the prochiral group. The main aim is to control the conformation around the bond between the inducing centre and the reacting prochiral C=N group, e.g. around **a 3.118b** and to control the geometry of the C=N bond.

The preference for the formation of diastereomer **3.104** by Pictet-Spengler cyclisation of iminium **3.118b** was not consistent with the stereoselective outcome of Pictet-Spengler reaction reported previously.[55] Therefore, an effort was made to rationalise these findings. Scheme 3.34 depicts two possible diastereoisomers that can be formed depending on the faces exposed. The iminium cation can adopt the *E*-**3.118** or the *Z*-**3.118a** configuration *via* the enamine intermediate and when discussing the stereochemical outcome of Pictet-Spengler cyclisation both isomers must be considered. Normally the *E*-isomer is more stable than the *Z*-isomer. For the *E*-isomer, the attack will be from the *si*-face and this will result in the *R*-configuration at the newly formed stereogenic centre of compound **3.118c**, which is not the isolated isomer. However, from the results obtained, it was clear that the Pictet-Spengler cyclisation proceeded *via* the *Z*-isomer. We propose that the presence of TFE influences the reaction selectivity by forming a coordinated TFE complex (Figure 3.1), which will prevent formation of the *E*-isomer in the transition state. This change in selectivity in the presence of TFE was also observed by Zhu and co-workers[48] in the synthesis of ecteinascidin.



Scheme 3.34: Mechanism for the diastereoselective synthesis of THIQ **3.118a** *via* the Pictet-Spengler reaction.

The preferential formation of isomer **3.118a** was rationalised according to Houk's model. According to Houk's model the allylic hydrogen of the chiral auxiliary will be in the same plane as the C=N bond as in conformer **A**. It must be noted that molecule **3.118b** is not frozen in conformer **A** and changes in the rotation around bond **b** is possible to form conformer **B**. However, conformer **B** is destabilised by allylic 1,3-strain[56] (C-Me bond eclipsing the double bond). The difference in population of the conformers **A** and **B** is a significant factor affecting the level of asymmetric induction of this reaction and this favours the *re*-attack resulting in the *S*-isomer as the major product and the results indicates that the reaction proceed from the *Z*-isomer of the starting material.

3.5.4 Conclusion

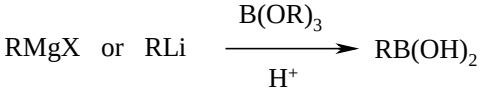
We have described a highly efficient regioselective and stereoselective synthesis of THIQ derivatives using the *N*-phenethyl chiral auxiliary to control the stereochemistry and the hydroxy group to control regiochemistry of the Pictet-Spengler reaction. The mechanism was proposed in order to account for the stereochemical outcome of the Pictet-Spengler cyclisation. Effects of substrates on the reaction yield were examined and it was found that electron-rich substrates react slowly giving lower yields compared to electron-deficient phenylacetaldehydes. The ease of formation of enantiomerically pure β-phenethylamine **3.22** combined with the ability to synthesise phenylacetaldehydes with a variety of substituents, makes this method efficient for the preparation of other THIQ's. Moreover, both the *R* and *S* isomers of THIQ are found in naturally occurring biological active alkaloids, therefore, our study proposes a solution to the highly stereoselective synthesis of both isomers. Also, our study compares favourably with previous methods in terms of efficiency and potential scope.

3.6 Synthesis of boronic acid 3.10

The substitution of an aryl halide by a nucleophile that takes place with catalysis by a transition-metal complex is generally referred to as a cross-coupling reaction if it follows the mechanistic course of oxidative addition, transmetallation and reductive elimination. The Suzuki-Miyaura cross-coupling reaction is one of the most versatile procedures developed in the 20th century.[57] Since its discovery many improvements have been made, for example, Evans *et al.*[58] reported a useful boronic acid phenol cross-coupling that expand the versatility of the Suzuki coupling reaction. The chemistry of boronic acids continues to be a growth area in synthetic methodology. Arylboronic acids are useful in synthesis by coupling reactions with phenols,[59] amines,[60] amides and imides,[61] and *N*-heterocycles[62,63] to give the corresponding *O*- or *N*-arylated products.

The remarkably simple resolution by Evans *et al.*[58] allows formation of diaryl ethers from phenols and boronic acids catalysed by Cu(II) acetate at ambient temperature. Since the target compound cycleanine (**3.1**) comprises two asymmetric centres, it was envisaged that the centres could be inert to these reaction conditions. The mild reaction conditions of this method prompted us to use it, therefore, it was necessary to prepare an arylboronic acid. A

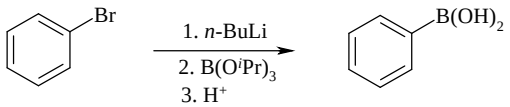
typical preparation of an arylboronic acid involves a reaction between an organoborate and an organometal (Li or Mg), usually prepared by magnesium insertion or lithium-halogen exchange (LHE) of the corresponding aryl halides (Scheme 3.35).[64] Both methods were employed in this study.



Scheme 3.35: Preparation of boronic acids by magnesium insertion or lithium-halogen exchange.

3.6.1 Lithium-Halogen Exchange (LHE)

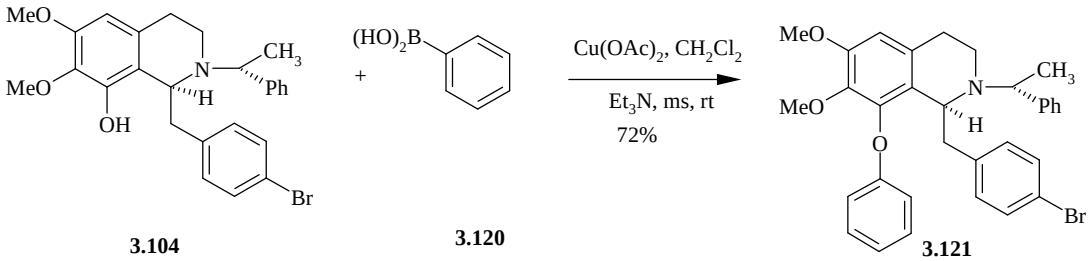
The LHE reaction, discovered by Wittig *et al.*[65] and Gilman co-workers[66] is the most versatile method used to generate organolithium compounds. The LHE reaction provides access to many unstable organolithium intermediates because it is rapid even at low temperatures (lower than -70 ºC). Bromobenzene (**3.119**) was used in a model reaction as a unsubstituted aryl halide. Conventional protocol was employed, that is bromobenzene (**3.119**) was treated with *n*-butyllithium at -78 ºC followed by triisopropyl borate and then acid hydrolysis to give boronic acid **3.120** in 50% yield (Scheme 3.36).



3.119 **3.120**

Scheme 3.36: Formation of phenylboronic acid (**3.118**) from bromobenzene *via* LHE.

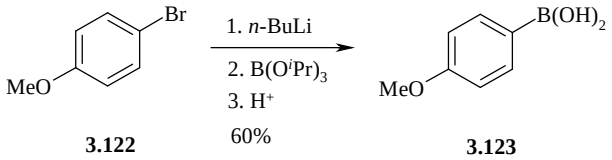
The resultant phenylboronic acid (**3.120**) was then coupled with the THIQ **3.104** to yield the diaryl ether **3.121** in 72% yield (Scheme 3.36).



3.104 **3.120** **3.121**

Scheme 3.37: Formation of diaryl ether **3.121** *via* boronic acid coupling.

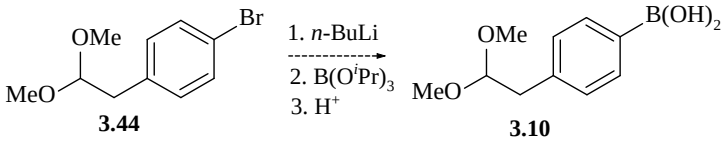
While optimising the reaction conditions, we were interested to see the effects of substituents on the benzene ring since the targeted diaryl ether **3.11** is *para*-substituted. For this reason, 4-bromoanisole (**3.122**) was subjected to the same reaction conditions and to our delight the yields were improved from 50% in bromobenzene (**3.119**) to 60% in 4-bromoanisole (**3.122**) and it was envisaged that the same conditions could be used for our target compound **3.8 (**Scheme 3.38).



3.122 **3.123**

Scheme 3.38: Formation of boronic acid from bromoanisole (**3.123**) *via* lithium-halogen exchange.

The reaction of 1-bromo-4-(2,2-dimethoxyethyl)benzene (**3.44**) with BuLi and $B(OMe)_3$ followed by acid quench and aqueous workup with concomitant deprotection of the dimethoxyethyl group did not give the desired product **3.10** and only non-identifiable mixture of products were isolated (Scheme 3.39).



3.44 **3.10**

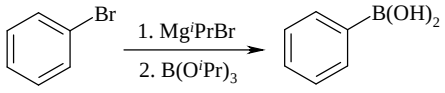
Scheme 3.39: Formation of boronic acid from 1-bromo-4-(2,2-dimethoxyethyl)benzene (**3.44**) *via* lithium-halogen exchange.

Li *et al.*[67] reported that the order of addition of the reagents was the key to a successful preparation of arylboronic acids. The addition procedure was reversed, and 1-bromo-4-(2,2-dimethoxyethyl)benzene (**3.44**) was added to a solution of *n*-BuLi followed by addition of $B(OMe)_3$. The boronate ester was even changed to triisopropyl borate with no success. Furthermore, the sequence was changed again where *n*-BuLi was added to a solution of 1-bromo-4-(2,2-dimethoxyethyl)benzene (**3.44**) and $B(O^iPr)_3$ followed by acid quenching, but this also did not give better results. The activating ability of the methoxy group with bromoanisole can be explained in terms of the inductive effect but for the dimethoxyethyl group this is not obvious as its electronegative properties are weak. It should be noted that BuLi/THF deprotonates acidic hydrogens faster than bromine-lithium exchange and this could be the reason for isolation of non-identifiable products. Although

halogen-lithium exchange is reported to be an excellent method for the preparation of organolithium compounds, which readily undergo transmetallation to provide a variety of organometallic reagents, this protocol did not work well for the preparation of the target compound **3.11** and an alternative method was employed.

3.6.2 Preparation of arylmagnesium reagents

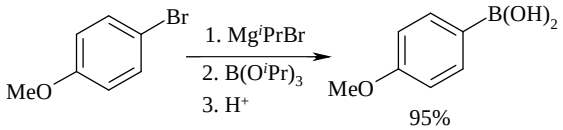
Organomagnesium reagents first prepared by Grignard over 100 years ago, still occupy a central place in organic chemistry and have excellent reactivity towards a wide range of electrophiles. The most common method used to prepare organomagnesium compounds is the direct reaction of magnesium metal with organic halides. The reactivity of organomagnesium reagent is strongly dependent on the reaction temperature Thus performing the halogen-magnesium exchange at temperatures below 0 ºC has the potential for the preparation of organometallic reagents that contain reactive functional groups.



3.119 **3.120**

Scheme 3.40: Formation of phenylboronic acid from bromobenzene *via* the Grignard reaction.

Although slower than I/Mg, Br/Mg exchange is sufficiently fast below 0 ^oC for the preparation of functionalised aryl magnesium bromides that bear electron-withdrawing groups. Therefore Br/Mg exchange is suitable for the preparation of Grignard reagents that contain sensitive functional groups. The exchange rate depends strongly on the electron density of the aromatic ring.

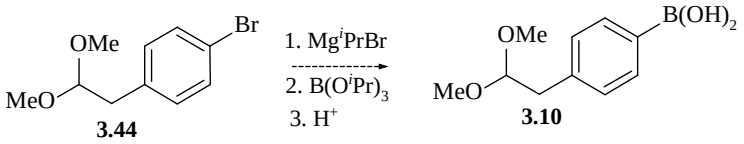


3.122 **3.123**

Scheme 3.41: Formation of boronic acid from bromoanisole *via* the Grignard reaction.

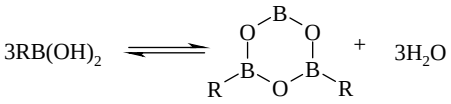
Model reactions on bromobenzene (**3.119**) and bromoanisole (**3.122**) with magnesium triisopropyl bromide produced better yields of **3.120** (70%) and **3.123** (95%), respectively

(Schemes 3.40 and 3.41). Nonetheless, these reaction conditions failed to produce **3.10** (Scheme 3.42).



Scheme 3.42: Formation of boronic acid from 4-bromo-1-(dimethoxymethyl)benzene *via* the Grignard reaction.

Even though the organoboranes give promising results, many of these reagents are difficult to purify because they are waxy solids. The situation is complicated by the formation of trimeric cyclic anhydrides (boroxines).



This equilibrium has no bearing on the coupling process, but it can influence the reaction stoichiometry, since it is difficult to determine the concentration of boronic acid versus boroxine in a mixture and there is no simple assay to assess the amount of total boronic acid available. Consequently, many literature protocols employ excess boronic acid to ensure a complete conversion of the electrophilic component of the reaction, clearly an inefficient use, of what might be the most expensive component of the reactions. Moreover, as Brönsted acids, boronic acids react readily with a variety of bases and nucleophiles, and because of their electron-deficient character are easily oxidised.

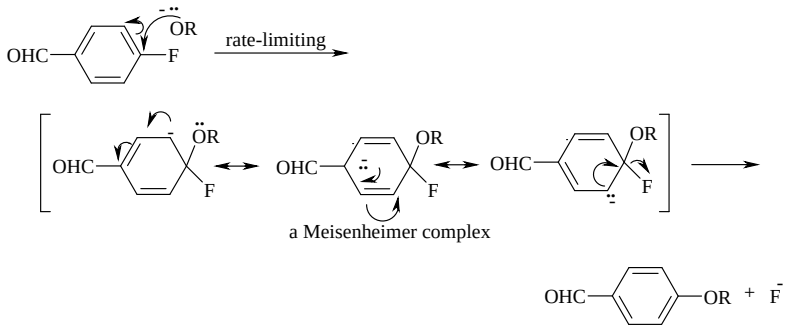
Because many organic functional group transformations involve bases, nucleophiles and oxidants, we sought to look for an alternative procedure for the formation of the diaryl ether. These factors together with the difficulty in the preparation of this reagent, led us to consider nucleophilic aromatic substitution as a possible method for the diaryl ether synthesis. Moreover, successful use of IBX in oxidation reactions and frustrations encountered during formation of the diaryl ether bond using boronic acids, led to reconsideration of our synthetic plans where S_NAr was considered to be the solution to the frustrations.

3.7 Formation of diaryl ether 3.131 *via* nucleophilic aromatic substitution

A number of years ago intensive studies on diaryl ether synthesis involved nucleophilic S_NAr reactions of activated aryl halides were carried out, but due to the success of palladium, copper and boronic acid mediated chemistry, the progress in this field has slowed down. Despite that, some new extensions of the classical nucleophilic aromatic substitution methods to diaryl ethers have been developed. Aryl halides that have one or more strongly electronegative groups (nitro, methylcarbonyl) *para* or *ortho* to the halogen are considered to be activated and undergo nucleophilic substitution with phenols under relatively mild conditions.

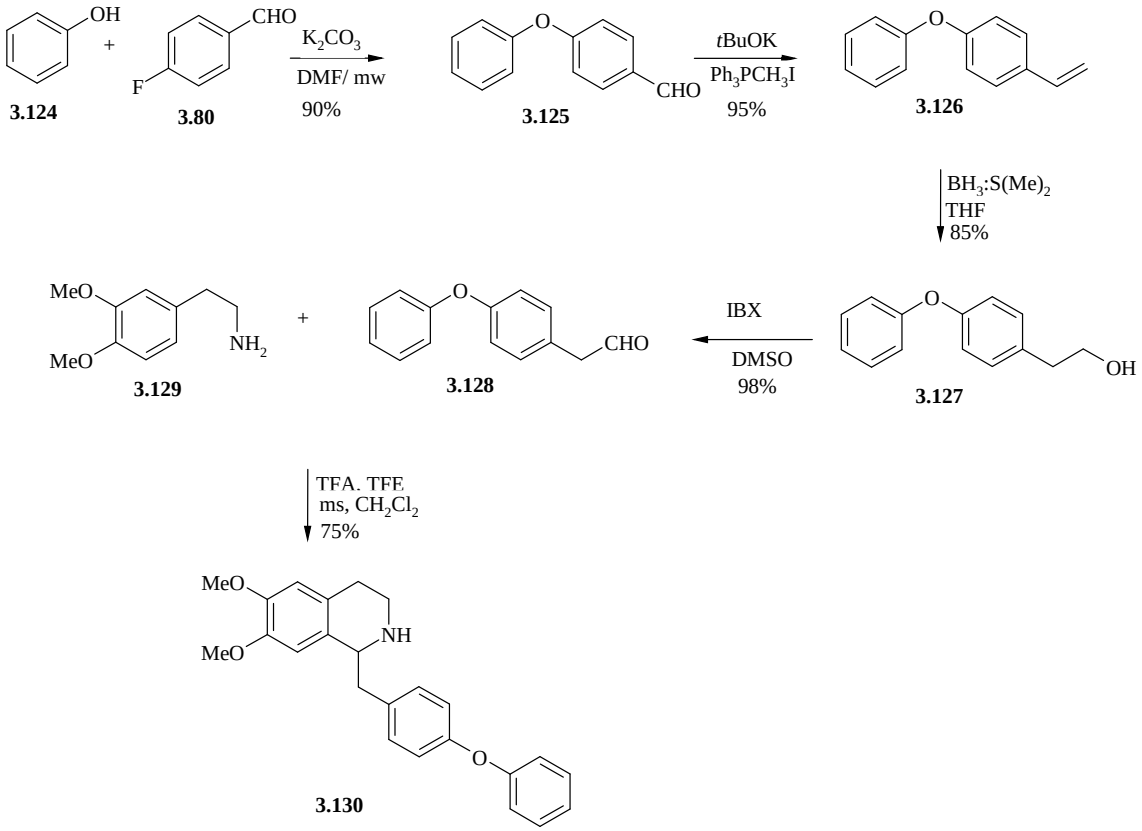
Microwave irradiation has become increasingly popular in recent years to improve the yield and shorten reaction times in a variety of reactions. Wang and co-workers[68] developed a convenient microwave-assisted version of diaryl ether synthesis from electron-deficient phenols and aryl halides. This technology has also been explored for nucleophilic substitution of haloheterocycles with sodium phenoxide on pyridine, quinoline, isoquinoline, pyrazine and pyrimidine systems by Cherng.[69]

Aryl halides do not undergo nucleophilic substitution reactions by S_N1 and S_N2 mechanisms, instead certain aryl halides do undergo nucleophilic substitution by nucleophilic aromatic substitution, where substitution occurs at a carbon of an aromatic ring by a nucleophilic mechanism. In our study, we employed fluorobenzaldehyde (**3.80**) as an aryl halide because the fluorides are the most reactive substrates in nucleophilic aromatic substitution. The mechanism of this reaction is illustrated in Scheme 3.43. The electron-withdrawing aldehyde group *para* to the halide accelerates the reaction because the transition state resembles the Meisenheimer complex and this aldehyde also stabilises this complex by resonance. Fluorine also stabilises the negative charge by its electron-withdrawing polar effect, which is greater than the polar effect of other halogens. The loss of the halide is not rate limiting and thus the leaving-group ability does not determine the reaction rate.



Scheme 3.43: Mechanism of the nucleophilic aromatic substitution reaction.

Prior to coupling of THIQ **3.104** with aryl fluoride **3.80**, the reaction conditions were optimised with the model reaction of phenol (**3.124)** and fluorobenzaldehyde (**3.80**). The model reactions illustrated in the Scheme 3.44 below gave good yields, and better reaction conditions were formulated. Nucleophilic aromatic substitution between **3.80** and **3.124** gave **3.125**, which was homologated *via* Wittig olefination to **3.126** followed by hydroboration-oxidation to **3.127** and a subsequent IBX oxidation afforded **3.128**, which was condensed with **3.129** under Pictet-Spengler conditions to afford the desired product in the overall yield of 53%.



Scheme 3.44: Model reaction for the formation of the diaryl ether and subsequent reactions.

The structures of all the compounds were confirmed by NMR, IR and MS. Nine aromatic protons in the ^{1}H NMR spectrum as well as MS data (*m/z* 199.0759 $[M+H]^+$) confirmed the formation of **3.125**. The absence of the aldehyde proton at δ_H 9.85 and the presence of the vinyl protons at δ_H 5.19 and 5.65 in the ^{1}H NMR spectrum proved the formation of **3.126**. The ^{1}H NMR spectrum of **3.127** exhibited two triplets at δ_H 2.79 (2H) and δ_H 3.85 (2H) and MS data (*m/z* 215.1073 $[M+H]^+$) and these correlate to the structure of **3.127**. The presence of the doublet at δ_H 3.59 (2H) and the triplet at δ_H 9.67 (1H) in the ^{1}H NMR spectrum as well as carbonyl carbon at δ_C 199.2 in the ^{13}C NMR spectrum confirmed formation of **3.128**. The results of ^{1}H NMR spectroscopic analysis are consistent with the structure of compound **3.130**. The aromatic region (δ_H 5.99-7.35) of the ^{1}H NMR spectrum exhibits two separate spin systems, an AA'BB' and ABC. Analyses of ^{13}C NMR, DEPT and HSQC reveal the presence of one methine, three methylene and seven quaternary carbons. The HMBC spectrum permitted the construction of structure showing correlations from H-5 to C-6, C-4, C-4a; H-8 to C-8a, C-1, C-6, C-7; H-α to C-1, C-9, C-10; H-10 to C-9, C-11, C-12. H-5 and H-8 were differentiated on the basis of nOe analysis. A NOESY correlation between H-5 and H-4 and one methoxy protons is observed and for H-8 there is a correlation only to the methoxy protons. The MS data (*m/z* 376.1913 $[M+H]^+$) corroborate formation of compound **3.130**.

Prompted by above-mentioned promising results, we coupled our electron-rich THIQ **3.104** with the electron-poor aryl fluoride **3.80** under microwave conditions [CEM, Discover®, at 100 W (100 ºC)] in the presence of K_2CO_3 in DMF for 15 minutes gave **3.131** in 85% yield. The presence of the singlet signal at δ_H 9.88 in the ^{1}H NMR spectrum and the carbonyl carbon at δ_C 190.7 in the ^{13}C NMR, together with the IR signal at 34796 cm^{-1} revealed the presence of the aldehyde in compound **3.131** (Plate 8). The MS (*m/z* 586.1594 $[M+H]^+$) data corroborated formation of **3.131**. The phenol **3.104** showed good tolerance in the coupling process since the product was obtained in high yield (85%) without epimerisation along with 10% starting aryl halide (Plate 8). In a control experiment, the same reaction mixture was heated at 120 ^{o}C overnight using an oil bath and the product was obtained in 60% yield with 20% starting phenol and 10% starting aryl halide as well as other minor diastereomers present. This observation demonstrates the advantage of microwave radiation over conventional heating techniques. The chosen aryl halide is readily available commercial, and proved to be the good reagent because for S_NAr reactions, electron-poor fluorides are considered the most reactive. Two noteworthy trends

are apparent. Firstly, reaction under microwave condition give higher yields at shorter reaction times compared to the bench-top reaction. Secondly, microwave conditions afforded only one diastereomer. In summary, microwave heating can be quite effective in improving the yields and decreasing the reaction times of S_NAr ether synthesis.

Until this point, the absolute stereochemistry at C-1 for THIQ was not known since attempts to recrystallise THIQ monomers were unsuccessful. This necessitated the recrystallisation of the intermediates in order to determine the absolute stereochemistry. However, recrystallisation of diaryl ether **3.131** in chloroform afforded colourless crystals which were suitable for X-ray diffractrometry. The crystal structure of **3.131** confirmed the stereochemistry of the newly formed chiral centre (Figs 3.3 and 3.4).

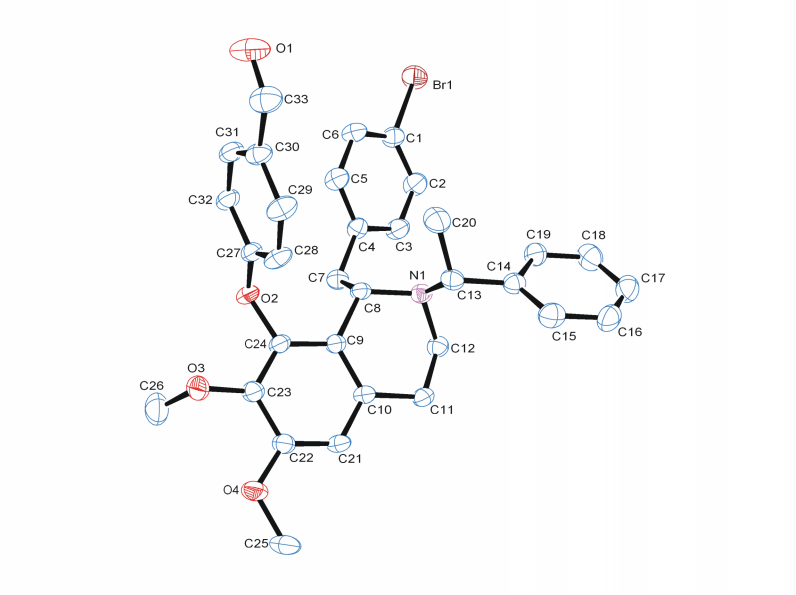


Figure 3.3: Thermal ellipsoid plot for the 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.131**) (50% probability level), with H atoms not labelled for clarity.

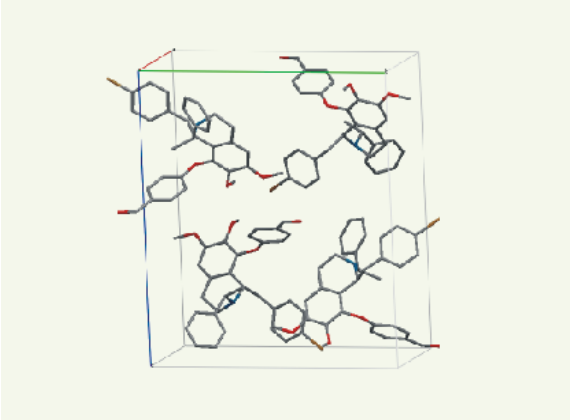
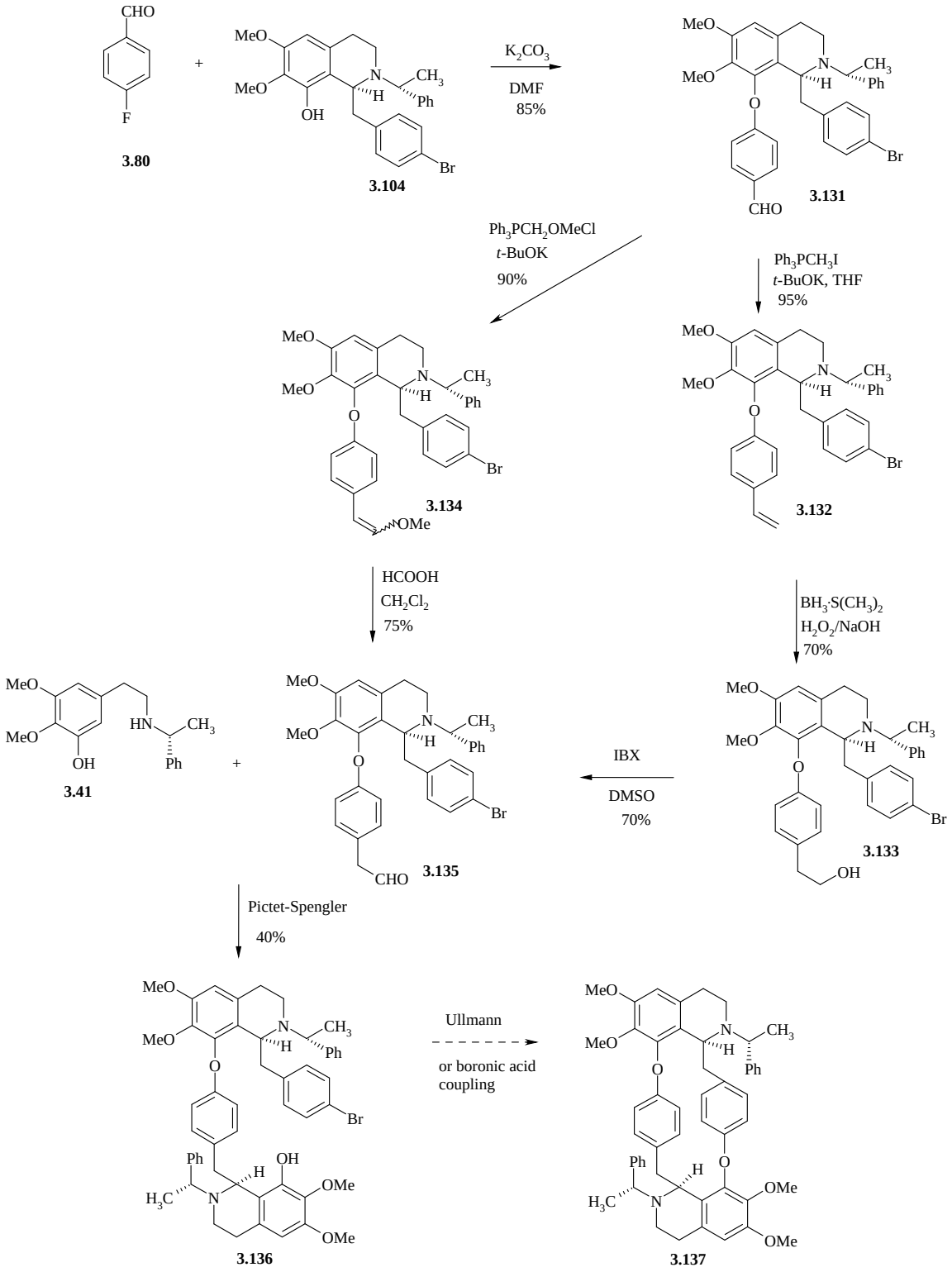


Figure 3.4: Unit cell contents

The X-ray structure is summarised as follows: Orthorhombic, $P2_12_12_1$, a = 8.166 (5) Å, b = 17.376 (5) Å, c = 20.387 (5) Å, V = 2893 (2) Å3, Z = 4, μ = 1.46 mm^{-1}, T = 293 K. In the crystal structure of **3.131** one crystallographically independent molecule is found in the asymmetric unit. The crystal structure contains no short van der Waals contacts less than the sum of the van der Waals radii. However, the crystal packing is loosely stabilised by a single intermolecular O···H—C interaction between adjacent molecules [O···H—C distance of 2.65 (1) Å]. The heterocyclic ring adopts a half chair conformation with the N1-benzyl moiety in an equatorial and C1 benzyl with *p*-bromine in an axial position. The adopted conformer shifts C3 out of the plane by 0.317 (3) Å, hence minimises the $A^{1,3}$ strain between the axial methine proton at C1 and the equatorial methylene proton at C3. The N1-benzyl moiety deviates from planarity by −0.341 (2) Å. The endocyclic torsion angle C1-C8a-C4a-C4 is 3.0 (4)° but C4a-C8a-C1-N1 is −19.1 (4)° which is constricted, most likely this is related to the substitution pattern on C1 and N1, the two bulky benzyl groups play a role in this respect. The remaining torsion angles are consistent with the half-chair conformation. The crystal structure, in accordance with conclusions from NMR interpretations, confirmed the absolute configuration of the two chiral centres C1 and the incorporated chiral auxiliary as *S* and *R*, respectively, with heterocyclic ring adopting the half-chair conformation.

The intermediate **3.135** was assembled from **3.131** in three steps, following protocols developed in the course of the synthesis of the above-mentioned compound **3.130**. Wittig olefination of **3.131** to **3.132** followed by boron oxidation to **3.133** and the subsequent IBX oxidation gave the desired **3.134** in the overall yield of 46% yield (Scheme 3.44). Alternatively, **3.135** was achieved *via* formation of the enol ether **3.134** in 68%, and this method provides a better option for synthesis of macrocyclic phenylacetaldehydes in excellent yield. The structures of intermediates **3.132**, **3.133**, **3.134** and **3.135** were readily determined by MS, IR, ^{1}H- and ^{13}C- NMR analyses. The MS (*m/z* 584.1801 $[M+H]^+$) data established the molecular formula of compound **3.132** as $C_{34}H_{34}{}^{79}BrNO_3$. The aromatic region of ^{1}H NMR spectrum exhibits two AA'BB' spin systems and a singlet of one proton of H-5. The presence of the vinyl protons at δ_H 5.19 and 5.62 confirmed formation of **3.132**.



Scheme 3.45: Redesigning the synthetic plan according to nucleophilic aromatic substitution.

The ^{1}H NMR spectrum of **3.133** exhibited one triplet of two protons at δ_H 3.71 and second triplet overlapping with H-α, H-3 and H-4 at δ_H 2.72-2.92. The broad OH signal in the IR

spectrum at 3429 cm^{-1} is consistent with the structure of compound **3.133**. Compound **3.134** was obtained as a yellow oil, $[\alpha]_D^{25}$ = + 33.4 (*c* = 1.1, $CHCl_3$). The presence of the extra methoxy protons at δ_H 3.68 as well as two *cis* protons at δ_H 5.20 and 6.19 (*J* = 10.5 Hz) and two *trans* protons at δ_H 5.80 and 6.95 (*J* = 16.9 Hz) in the ^1H NMR spectrum (Plate 9) as well as the MS (*m/z* 612.1750 $[M+H]^+$) data are in agreement with the structure of **3.134**. The presence of the triplet at δ_H 9.85 in the ^1H NMR spectrum (Plate 10) and the carbonyl carbon at δ_C 199.9 in the ^{13}C NMR, together with the IR signal at 3496 cm^{-1} revealed the presence of the aldehyde in compound **3.135**. The MS (*m/z* 601.1750 $[M+H]^+$) data corroborated formation of **3.135**. The key coupling of **3.41** and **3.135** forming of the second THIQ moiety *via* the Pictet-Spengler reaction gave the desired **3.136** in low yields due to the formation of other side products. In part, this may be attributed to the slower reaction of **3.41** with **3.135** due to the increased electrondensity on the phenylacetaldehyde, resulting from the *p*-phenoxy substituent. Furthermore, these disappointing results may be due to the previously reported instability of the phenacetylaldehyde which may undergo disproportionation reactions to yield the phenylacetic acid and phenethyl alcohol in the presence of acid. In addition, during the synthesis of the THIQ monomer, it was found that prolonged contact of the THIQ with the acid resulted in the decomposition of the product.

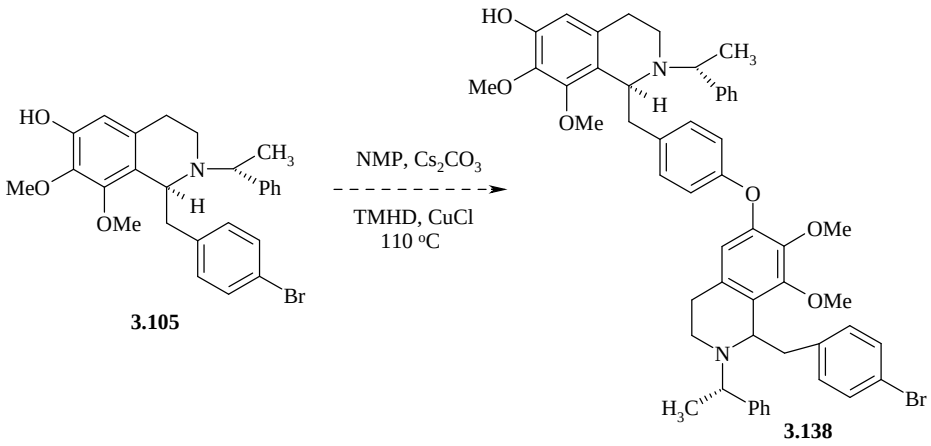
In designing a macrocyclisation method, we sought to address the following issues:

- Increasing the yield of cyclisation product
- Avoiding the harsh conditions
- Enhancing the versatility (flexibility) of cyclisation procedure
- Prevent epimerisation during the ring-closure process

Cyclisation is usually disfavoured because of loss of entropy and of strain associated with the ring formation.

To investigate the macrocyclisation method, a model reaction was carried out. The reaction relies on the intermolecular Ullmann condensation of the side product **3.105** since it resembles the THIQ **3.104**. However, this reaction was troublesome and resulted in decomposition of the material (Scheme 3.46). Although the Ullmann reaction on the odel compound **3.105** was not successful, we decided to use the actual intermediate **3.136** to close the ring. The model reaction on **3.105** entailed an intermolecular reaction. Since

intramolecular reactions are often easier to accomplish than the intermolecular reactions, there was a chance that intramolecular Ullmann reaction on **3.136** might succeed. The intermediate **3.136** was subjected to the modified Ullmann coupling conditions, where **3.136** was heated at 110 ºC in NMP, using CuCl and TMHD as catalysts and Cs_2CO_3 as a base, but to our disappointment the starting material decomposed and only unidentifiable products were isolated. Due to time constraints, we could not synthesise more of **3.136** in order to find the suitable reaction conditions for macrocyclisation to **3.137**, and this will be pursued further in our laboratories since synthesis of BBIQ is an ongoing research within our group.



Scheme 3.46: Model reaction for coupling *via* the Ullmann condensation reaction.

In summary, we successfully synthesised a bisbenzyltetrahydroisoquinoline **3.136** in 13 steps employing vanillin as the starting material. Our synthesis features the regio- and the diastereoselective synthesis of a THIQ by Pictet-Spengler cyclisation. The stereochemistry of the newly-formed chiral centre at C-1 was established by the X-ray structure of **3.131** prepared by the efficient microwave-assisted S_NAr reaction. The developed Wittig homologation used in formation of **3.22** and the Pictet-Spengler reaction used in the synthesis of THIQ's were employed to form a bisbenzyltetrahydroisoquinoline **3.136**. Although we failed to form the final diaryl ether bond, the developed synthetic strategy can also be employed in the construction of other complex intermediates in the synthesis of natural products containing diaryl ethers. The use of the Wittig and Pictet-Spengler reactions more than once using the same materials and conditions renders our total synthesis efficient and practical.

3.9 References

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Table 3.3: Crystal data and structure refinement of 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

Description	Planar, colourless
Molecular formula	$C_{33}H_{32}BrNO_4$
Formula weight	586.49
Temperature	T = 293 K
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Hall symbol	P2ac2ab
Unit cell dimensions	a = 8.166 (5) Å μ = 1.46 mm−1
	b = 17.376 (5) Å
	c = 20.387 (5) Å 0.50 × 0.35 × 0.35 mm
Volume	V = 2893 (2) Å3
Z	4
Density (calculated)	1.347mg/m^3
Absorption coefficient	1.46
Crystal size	0.50 × 0.35 × 0.35 mm
θ Range for data collection	2.7-32.0°
Reflections collected	9093
Independent reflections	9093
Refinement method	Full-matrix least squares F^2
Goodness-of-fit-on F^2	0.104
Largest diff. peak and hole	0.22 and -0.43 e $Å^{-3}$

Table 3.4: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

	x	y	z	Uiso*/Ueq
C1	1.2059 (3)	0.26161 (14)	0.26842 (13)	0.0383 (6)
C008	1.3011 (3)	0.24389 (14)	0.32427 (13)	0.0413 (6)
C009	0.8383 (3)	0.23449 (15)	0.21565 (13)	0.0434 (7)
H009	0.8480	0.2738	0.2499	0.052*
C010	0.9876 (4)	0.03463 (14)	0.43606 (12)	0.0498 (7)
C011	1.1326 (3)	0.19768 (14)	0.22679 (13)	0.0393 (6)
H011	1.0843	0.1600	0.2569	0.047*
C012	1.0531 (3)	0.29478 (14)	0.14837 (13)	0.0429 (7)
H01A	0.9689	0.3095	0.1172	0.051*
H01B	1.1519	0.2834	0.1238	0.051*
C013	1.1236 (4)	0.00251 (16)	0.40727 (14)	0.0534 (7)
H013	1.1382	-0.0505	0.4091	0.064*
C014	1.2163 (3)	0.12642 (15)	0.37331 (12)	0.0412 (6)
C015	1.3705 (3)	0.29928 (15)	0.36329 (13)	0.0445 (7)
C016	1.0865 (3)	0.36231 (14)	0.19415 (13)	0.0439 (6)
H01C	1.1432	0.4024	0.1701	0.053*
H01D	0.9831	0.3833	0.2093	0.053*
C017	1.2630 (3)	0.15534 (15)	0.18634 (15)	0.0482 (7)
H01E	1.3117	0.1913	0.1556	0.058*
H01F	1.3488	0.1377	0.2156	0.058*
C018	1.1690 (4)	0.01789 (16)	0.17826 (14)	0.0521 (7)
H018	1.1896	0.0129	0.2229	0.062*
C019	0.9707 (4)	0.11386 (15)	0.43467 (14)	0.0586 (8)
H019	0.8815	0.1365	0.4554	0.070*
C020	1.0840 (4)	0.16022 (16)	0.40296 (14)	0.0544 (8)
H020	1.0704	0.2133	0.4018	0.065*
C021	1.2377 (4)	0.04652 (14)	0.37604 (14)	0.0484 (7)
H021	1.3288	0.0237	0.3567	0.058*
C022	1.1886 (3)	0.33920 (15)	0.25280 (12)	0.0386 (6)

Table 3.4 (continued): Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($Å^2$) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

C023	0.7151 (3)	0.26126 (15)	0.16526 (13)	0.0433 (6)
C024	1.2612 (3)	0.39548 (14)	0.29113 (13)	0.0447 (7)
H024	1.2482	0.4469	0.2795	0.054*
C025	1.3524 (3)	0.37742 (16)	0.34602 (13)	0.0451 (6)
C026	1.1968 (3)	0.08759 (15)	0.14888 (13)	0.0421 (6)
C027	0.6956 (3)	0.22157 (17)	0.10664 (14)	0.0511 (7)
H027	0.7595	0.1784	0.0983	0.061*
C028	1.1591 (4)	0.09358 (17)	0.08228 (14)	0.0557 (7)
H028	1.1744	0.1405	0.0612	0.067*
C029	0.5057 (4)	0.34958 (18)	0.12872 (19)	0.0696 (9)
H029	0.4420	0.3930	0.1364	0.083*
C030	0.6183 (4)	0.32544 (17)	0.17611 (17)	0.0582 (8)
H030	0.6283	0.3527	0.2152	0.070*
C031	1.4057 (4)	0.50843 (16)	0.37079 (16)	0.0648 (9)
H03A	1.4464	0.5171	0.3272	0.097*
H03B	1.4665	0.5393	0.4013	0.097*
H03C	1.2920	0.5223	0.3727	0.097*
C032	0.4886 (4)	0.3103 (2)	0.07177 (18)	0.0708 (9)
H032	0.4141	0.3268	0.0403	0.085*
C033	1.1108 (4)	-0.04590 (16)	0.14387 (14)	0.0498 (7)
H033	1.0952	-0.0929	0.1647	0.060*
C034	1.0996 (4)	0.03167 (16)	0.04670 (14)	0.0569 (8)
H034	1.0753	0.0366	0.0023	0.068*
C035	1.0774 (3)	-0.03722 (15)	0.07863 (15)	0.0475 (7)
C036	0.5828 (4)	0.2454 (2)	0.06072 (15)	0.0645 (9)
H036	0.5699	0.2177	0.0220	0.077*
C037	1.6224 (4)	0.2802 (2)	0.41653 (19)	0.0833 (11)
H03D	1.6589	0.2449	0.3834	0.125*
H03E	1.6676	0.2654	0.4581	0.125*

Table 3.4 (continued): Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

H03F	1.6581	0.3312	0.4057	0.125*
C038	0.8604 (5)	-0.0128 (2)	0.46706 (17)	0.0701 (9)
C039	0.7805 (4)	0.1591 (2)	0.24695 (16)	0.0665 (9)
H03G	0.7958	0.1176	0.2165	0.100*
H03H	0.6665	0.1632	0.2580	0.100*
H03I	0.8429	0.1493	0.2860	0.100*
N1	1.0000 (3)	0.22487 (10)	0.18308 (9)	0.0387 (4)
O1	0.8586 (3)	-0.08179 (14)	0.46942 (11)	0.0860 (8)
O002	1.3324 (2)	0.16681 (10)	0.33938 (9)	0.0472 (5)
O003	1.4509 (2)	0.27856 (11)	0.42008 (9)	0.0558 (5)
O004	1.4237 (2)	0.42944 (10)	0.38719 (9)	0.0586 (5)
Br01	1.00439 (4)	-0.124178 (17)	0.028924 (16)	0.07177 (12)
H100	0.772 (4)	0.0128 (18)	0.4850 (16)	0.076 (12)*

Table 3.5: Atomic displacement parameters (Å^2) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

	*U*11	*U*22	*U*33	*U*12	*U*13	*U*23
C1	0.0399 (14)	0.0337 (14)	0.0412 (15)	-0.0009 (12)	-0.0015 (12)	0.0009 (11)
C008	0.0469 (15)	0.0301 (14)	0.0468 (16)	-0.0003 (12)	-0.0020 (13)	0.0020 (12)
C009	0.0450 (16)	0.0443 (16)	0.0410 (16)	-0.0039 (13)	0.0003 (13)	-0.0091 (12)
C010	0.0643 (18)	0.0427 (14)	0.0425 (15)	-0.0088 (17)	0.0007 (16)	0.0014 (11)
C011	0.0413 (14)	0.0330 (14)	0.0437 (16)	-0.0016 (12)	-0.0028 (13)	-0.0020 (12)
C012	0.0417 (15)	0.0456 (16)	0.0414 (15)	0.0002 (12)	0.0015 (12)	0.0046 (12)
C013	0.072 (2)	0.0317 (14)	0.0561 (19)	-0.0027 (15)	-0.0105 (17)	0.0015 (14)
C014	0.0492 (15)	0.0343 (13)	0.0401 (15)	-0.0031 (14)	-0.0086 (13)	0.0030 (12)
C015	0.0533 (16)	0.0415 (16)	0.0387 (16)	-0.0033 (13)	-0.0048 (14)	0.0014 (12)
C016	0.0481 (15)	0.0371 (15)	0.0465 (16)	-0.0017 (12)	-0.0037 (13)	0.0065 (12)
C017	0.0474 (16)	0.0410 (15)	0.0561 (18)	0.0025 (13)	-0.0026 (14)	-0.0050 (13)

C018	0.067 (2)	0.0489 (18)	0.0402 (16)	0.0031 (15)	0.0020 (15)	-0.0006 (13)
C019	0.072 (2)	0.0481 (17)	0.0559 (18)	0.0038 (17)	0.0169 (16)	0.0050 (13)
C020	0.077 (2)	0.0326 (15)	0.0533 (19)	0.0056 (15)	0.0050 (16)	-0.0019 (13)
C021	0.0574 (17)	0.0321 (15)	0.0558 (18)	0.0034 (14)	-0.0059 (15)	0.0002 (13)
C022	0.0421 (15)	0.0338 (14)	0.0401 (16)	-0.0028 (12)	0.0023 (12)	0.0003 (11)
C023	0.0383 (14)	0.0454 (16)	0.0464 (16)	-0.0015 (13)	0.0046 (13)	-0.0004 (13)
C024	0.0528 (17)	0.0298 (14)	0.0517 (18)	-0.0044 (12)	0.0025 (14)	0.0027 (12)
C025	0.0494 (15)	0.0406 (15)	0.0453 (16)	-0.0072 (14)	-0.0021 (13)	-0.0019 (13)
C026	0.0412 (15)	0.0405 (15)	0.0446 (17)	0.0083 (13)	0.0032 (13)	-0.0052 (12)
C027	0.0506 (16)	0.0541 (17)	0.0486 (18)	0.0023 (14)	-0.0036 (14)	0.0000 (14)
C028	0.072 (2)	0.0431 (16)	0.0521 (18)	-0.0026 (15)	-0.0032 (17)	0.0024 (14)
C029	0.0439 (16)	0.0647 (19)	0.100 (3)	0.0100 (19)	0.005 (2)	0.0195 (19)
C030	0.0515 (18)	0.0575 (19)	0.066 (2)	0.0027 (16)	0.0107 (17)	-0.0059 (16)
C031	0.079 (2)	0.0435 (18)	0.072 (2)	-0.0247 (16)	0.0004 (18)	-0.0082 (15)
C032	0.0506 (18)	0.084 (2)	0.078 (2)	-0.004 (2)	-0.006 (2)	0.033 (2)
C033	0.0646 (18)	0.0366 (16)	0.0481 (18)	-0.0007 (14)	0.0050 (15)	0.0017 (13)
C034	0.077 (2)	0.0496 (18)	0.0441 (18)	0.0045 (16)	-0.0075 (16)	-0.0037 (14)
C035	0.0489 (15)	0.0386 (15)	0.0551 (18)	0.0073 (13)	-0.0011 (14)	-0.0116 (13)
C036	0.0632 (18)	0.083 (2)	0.0474 (19)	-0.0104 (19)	-0.0061 (17)	0.0018 (17)
C037	0.060 (2)	0.110 (3)	0.079 (3)	-0.002 (2)	-0.015 (2)	0.024 (2)
C038	0.092 (3)	0.066 (2)	0.053 (2)	-0.008 (2)	0.009 (2)	0.0034 (18)
C039	0.0524 (19)	0.083 (2)	0.064 (2)	-0.0160 (18)	0.0008 (16)	0.0142 (17)
N1	0.0378 (10)	0.0391 (10)	0.0392 (11)	-0.0004 (12)	0.0001 (12)	-0.0020 (8)
O1	0.125 (2)	0.0548 (14)	0.0783 (16)	-0.0319 (14)	0.0235 (16)	-0.0042 (13)
O002	0.0477 (11)	0.0322 (10)	0.0618 (12)	0.0008 (9)	-0.0013 (10)	0.0072 (9)
O003	0.0666 (13)	0.0612 (12)	0.0395 (11)	-0.0115 (10)	-0.0128 (10)	0.0073 (9)
O004	0.0757 (13)	0.0409 (11)	0.0593 (13)	-0.0134 (10)	-0.0136 (11)	-0.0067 (9)
Br01	0.0784 (2)	0.05399 (18)	0.0829 (2)	-0.0007 (2)	-0.0145 (2)	-0.02055 (15)

Table 3.6: Geometric parameters (Å, °) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

C1-C022	1.393 (3)	C021-H021	0.9300
C1-C008	1.413 (4)	C022-C024	1.385 (4)
C1-C011	1.521 (3)	C023-C030	1.385 (4)
C008-C015	1.372 (4)	C023-C027	1.389 (4)
C008-O002	1.398 (3)	C024-C025	1.380 (4)
C009-N1	1.488 (3)	C024-H024	0.9300
C009-C023	1.511 (4)	C025-O004	1.364 (3)
C009-C039	1.531 (4)	C026-C028	1.396 (4)
C009-H009	0.9800	C027-C036	1.377 (4)
C010-C013	1.375 (4)	C027-H027	0.9300
C010-C019	1.384 (4)	C028-C034	1.386 (4)
C010-C038	1.469 (4)	C028-H028	0.9300
C011-N1	1.479 (3)	C029-C032	1.354 (4)
C011-C017	1.535 (4)	C029-C030	1.398 (4)
C011-H011	0.9800	C029-H029	0.9300
C012-N1	1.471 (3)	C030-H030	0.9300
C012-C016	1.524 (3)	C031-O004	1.420 (3)
C012-H01A	0.9700	C031-H03A	0.9600
C012-H01B	0.9700	C031-H03B	0.9600
C013-C021	1.363 (4)	C031-H03C	0.9600
C013-H013	0.9300	C032-C036	1.384 (4)
C014-O002	1.368 (3)	C032-H032	0.9300
C014-C020	1.370 (4)	C033-C035	1.366 (4)
C014-C021	1.400 (3)	C033-H033	0.9300
C015-O003	1.379 (3)	C034-C035	1.375 (4)
C015-C025	1.410 (4)	C034-H034	0.9300
C016-C022	1.512 (4)	C035-Br01	1.914 (3)
C016-H01C	0.9700	C036-H036	0.9300
C016-H01D	0.9700	C037-O003	1.403 (4)
C017-C026	1.503 (4)	C037-H03D	0.9600

Table 3.6 (continued): Geometric parameters (Å, °) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

C017-H01E	0.9700	C037-H03E	0.9600
C017-H01F	0.9700	C037-H03F	0.9600
C018-C026	1.370 (4)	C038-O1	1.200 (4)
C018-C033	1.395 (4)	C038-H100	0.92 (3)
C018-H018	0.9300	C039-H03G	0.9600
C019-C020	1.387 (4)	C039-H03H	0.9600
C019-H019	0.9300	C039-H03I	0.9600
C022-C1-C008	116.8 (2)	C027-C023-C009	120.6 (3)
C022-C1-C011	122.7 (2)	C025-C024-C022	121.9 (2)
C008-C1-C011	120.5 (2)	C025-C024-H024	119.1
C015-C008-O002	118.0 (2)	C022-C024-H024	119.1
C015-C008-C1	122.8 (2)	O004-C025-C024	125.3 (3)
O002-C008-C1	119.2 (2)	O004-C025-C015	116.1 (2)
N1-C009-C023	108.8 (2)	C024-C025-C015	118.5 (2)
N1-C009-C039	111.3 (2)	C018-C026-C028	117.0 (3)
C023-C009-C039	110.0 (2)	C018-C026-C017	122.0 (2)
N1-C009-H009	108.9	C028-C026-C017	121.0 (3)
C023-C009-H009	108.9	C036-C027-C023	120.8 (3)
C039-C009-H009	108.9	C036-C027-H027	119.6
C013-C010-C019	118.4 (3)	C023-C027-H027	119.6
C013-C010-C038	121.8 (3)	C034-C028-C026	121.9 (3)
C019-C010-C038	119.8 (3)	C034-C028-H028	119.0
N1-C011-C1	113.0 (2)	C026-C028-H028	119.0
N1-C011-C017	109.7 (2)	C032-C029-C030	120.6 (3)
C1-C011-C017	112.1 (2)	C032-C029-H029	119.7
N1-C011-H011	107.2	C030-C029-H029	119.7
C1-C011-H011	107.2	C023-C030-C029	120.4 (3)
C017-C011-H011	107.2	C023-C030-H030	119.8
N1-C012-C016	113.2 (2)	C029-C030-H030	119.8

Table 3.6 (continued): Geometric parameters (Å, °) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

N1-C012-H01A	108.9	O004-C031-H03A	109.5
C016-C012-H01A	108.9	O004-C031-H03B	109.5
N1-C012-H01B	108.9	H03A-C031-H03B	109.5
C016-C012-H01B	108.9	O004-C031-H03C	109.5
H01A-C012-H01B	107.8	H03A-C031-H03C	109.5
C021-C013-C010	121.6 (3)	H03B-C031-H03C	109.5
C021-C013-H013	119.2	C029-C032-C036	119.5 (3)
C010-C013-H013	119.2	C029-C032-H032	120.2
O002-C014-C020	123.3 (2)	C036-C032-H032	120.2
O002-C014-C021	116.3 (2)	C035-C033-C018	118.0 (3)
C020-C014-C021	120.4 (3)	C035-C033-H033	121.0
C008-C015-O003	120.0 (2)	C018-C033-H033	121.0
C008-C015-C025	119.2 (2)	C035-C034-C028	118.3 (3)
O003-C015-C025	120.7 (2)	C035-C034-H034	120.8
C022-C016-C012	112.3 (2)	C028-C034-H034	120.8
C022-C016-H01C	109.2	C033-C035-C034	122.1 (3)
C012-C016-H01C	109.2	C033-C035-Br01	119.4 (2)
C022-C016-H01D	09.2	C034-C035-Br01	118.5 (2)
C012-C016-H01D	109.2	C027-C036-C032	120.4 (3)
H01C-C016-H01D	107.9	C027-C036-H036	119.8
C026-C017-C011	113.5 (2)	C032-C036-H036	119.8
C026-C017-H01E	108.9	O003-C037-H03D	109.5
C011-C017-H01E	108.9	O003-C037-H03E	109.5
C026-C017-H01F	108.9	H03D-C037-H03E	109.5
C011-C017-H01F	108.9	O003-C037-H03F	109.5
H01E-C017-H01F	107.7	H03D-C037-H03F	109.5
C026-C018-C033	122.6 (3)	H03E-C037-H03F	109.5
C026-C018-H018	118.7	O1-C038-C010	125.9 (4)
C033-C018-H018	118.7	O1-C038-H100	117 (2)
C010-C019-C020	121.4 (3)	C010-C038-H100	117 (2)

Table 3.6 (continued): Geometric parameters (Å, °) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

C010-C019-H019	119.3	C009-C039-H03G	109.5
C020-C019-H019	119.3	C009-C039-H03H	109.5
C014-C020-C019	118.9 (3)	H03G-C039-H03H	109.5
C014-C020-H020	120.6	C009-C039-H03I	109.5
C019-C020-H020	120.6	H03G-C039-H03I	109.5
C013-C021-C014	119.3 (3)	H03H-C039-H03I	109.5
C013-C021-H021	120.3	C012-N1-C011	109.8 (2)
C014-C021-H021	120.3	C012-N1-C009	112.54 (19)
C024-C022-C1	120.7 (2)	C011-N1-C009	114.62 (19)
C024-C022-C016	119.7 (2)	C014-O002-C008	118.4 (2)
C1-C022-C016	119.6 (2)	C015-O003-C037	115.3 (3)
C030-C023-C027	118.2 (3)	C025-O004-C031	116.8 (2)
C022-C1-C008-C015	1.9 (4)	O003-C015-C025-C024	-175.6 (2)
C011-C1-C008-C015	179.7 (2)	C033-C018-C026-C028	2.1 (4)
C022-C1-C008-O002	-175.3 (2)	C033-C018-C026-C017	-178.7 (2)
C011-C1-C008-O002	2.5 (4)	C011-C017-C026-C018	-79.8 (3)
C022-C1-C011-N1	-19.1 (4)	C011-C017-C026-C028	99.4
C008-C1-C011-N1	163.2 (2)	C030-C023-C027-C036	-0.1 (4)
C022-C1-C011-C017	105.5 (3)	C009-C023-C027-C036	179.6 (3)
C008-C1-C011-C017	-72.2 (3)	C018-C026-C028-C034	-1.4 (4)
C019-C010-C013-C021	-2.1 (4)	C017-C026-C028-C034	179.4 (3)
C038-C010-C013-C021	177.1 (3)	C027-C023-C030-C029	-0.7 (4)
O002-C008-C015-O003	-8.0 (4)	C009-C023-C030-C029	179.6 (3)
C1-C008-C015-O003	174.7 (2)	C032-C029-C030-C023	0.5 (5)
O002-C008-C015-C025	174.7 (2)	C030-C029-C032-C036	0.4 (5)
C1-C008-C015-C025	-2.6 (4)	C026-C018-C033-C035	-1.5 (5)
N1-C012-C016-C022	46.4 (3)	C026-C028-C034-C035	0.1 (4)
N1-C011-C017-C026	-58.3 (3)	C018-C033-C035-C034	0.1 (4)
C1-C011-C017-C026	175.2 (2)	C018-C033-C035-Br01	177.9 (2)

Table 3.6 (continued): Geometric parameters (Å, °) for 4-[1-(4-bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.124**).

C013-C010-C019-C020	2.5 (4)	C028-C034-C035-C033	0.5 (4)
C038-C010-C019-C020	-176.7 (3)	C028-C034-C035-Br01	-177.3 (2)
O002-C014-C020-C019	178.2 (2)	C023-C027-C036-C032	1.1 (4)
C021-C014-C020-C019	-1.1 (4)	C029-C032-C036-C027	-1.3 (5)
C010-C019-C020-C014	-0.9 (4)	C013-C010-C038-O1	-1.8 (5)
C010-C013-C021-C014	0.2 (4)	C019-C010-C038-O1	177.4 (3)
O002-C014-C021-C013	-177.9 (2)	C016-C012-N1-C011	-63.4 (3)
C020-C014-C021-C013	1.4 (4)	C016-C012-N1-C009	65.5 (3)
C008-C1-C022-C024	-0.5 (4)	C1-C011-N1-C012	47.7 (3)
C011-C1-C022-C024	-178.2 (2)	C017-C011-N1-C012	-78.2 (2)
C008-C1-C022-C016	-179.2 (2)	C1-C011-N1-C009	-80.1 (3)
C011-C1-C022-C016	3.0 (4)	C017-C011-N1-C009	154.00 (19)
C012-C016-C022-C024	165.4 (2)	C023-C009-N1-C012	54.4 (3)
C012-C016-C022-C1	-15.8 (3)	C039-C009-N1-C012	175.8 (2)
N1-C009-C023-C030	-128.3 (2)	C023-C009-N1-C011	-179.2 (2)
C039-C009-C023-C030	109.6 (3)	C039-C009-N1-C011	-57.9 (3)
N1-C009-C023-C027	52.0 (3)	C020-C014-O002-C008	-11.5 (4)
C039-C009-C023-C027	-70.1 (3)	C021-C014-O002-C008	167.8 (2)
C1-C022-C024-C025	-0.3 (4)	C015-C008-O002-C014	99.6 (3)
C016-C022-C024-C025	178.5 (2)	C1-C008-O002-C014	-83.0 (3)
C022-C024-C025-O004	-178.0 (2)	C008-C015-O003-C037	103.5 (3)
C022-C024-C025-C015	-0.4 (4)	C025-C015-O003-C037	-79.2 (3)
C008-C015-C025-O004	179.6 (2)	C024-C025-O004-C031	-1.8 (4)
O003-C015-C025-O004	2.3 (4)	C015-C025-004-C031	-179.6 (2)
C008-C015-C025-C024	1.7 (4)		

Hydrogen-bond geometry (Å, °)

D—H···A D—H H···A D···A D–H···A

C036—H036···O1i 0.93 2.66 3.432 (5) 141 (1)

Symmetry codes: (i) −x+3/2, −y, z−1/2.

CHAPTER 4

Conclusions and Future Work

4.1 Conclusions

In this study, we have been able to

- Develop a concise route for the synthesis of a β-phenethylamine derivative containing a chiral auxiliary
- Prepare a series of phenylacetaldehydes in high yields
- Develop reaction conditions to control the regioselectivity and diastereoselectivity of the Pictet-Spengler reaction
- Provide proof for the stereochemistry of the prepared benzyltetrahydroisoquinoline by X-ray crystallography
- Form a diaryl ether from the parent tetrahydroisoquinoline by a microwave-assisted S_NAr reaction
- Prepare bisbenzyltetrahydroisoquinoline **3.136**.

We have developed a novel procedure for the synthesis of an enantiomerically-pure β-phenethylamine derivative, which comprise carbon homologation of the aldehyde **3.22** by a Wittig reaction, followed by hydrolysis of enol ether **3.39** to phenylacetaldehyde **3.40**, and a subsequent reductive amination to **3.41**. This method proved to be an efficient approach since it reduces the steps and hazardous wastes associated with the isolation of intermediates involved in standard procedures and high yields are obtained. In order to control the regioselectivity of Pictet-Spengler reaction in the formation of THIQ **3.104**, the C-3 hydroxy group was strategically position in **3.41** to facilitate the ring closure in the *ortho*-position and to control stereochemistry, a chiral auxiliary was embedded on the nitrogen of β-phenethylamine. A variety of phenylacetaldehyde, reaction partners of β-phenethylamine for the Pictet-Spengler reaction, were prepared with the yields varying according to substituents. Phenylacetyladehydes with bromo- and iodo-substituents were prepared in higher yields at shorter reaction times (95% and 98%, respectively) as compared to the fluoro and electron-rich substrates, which were formed with longer

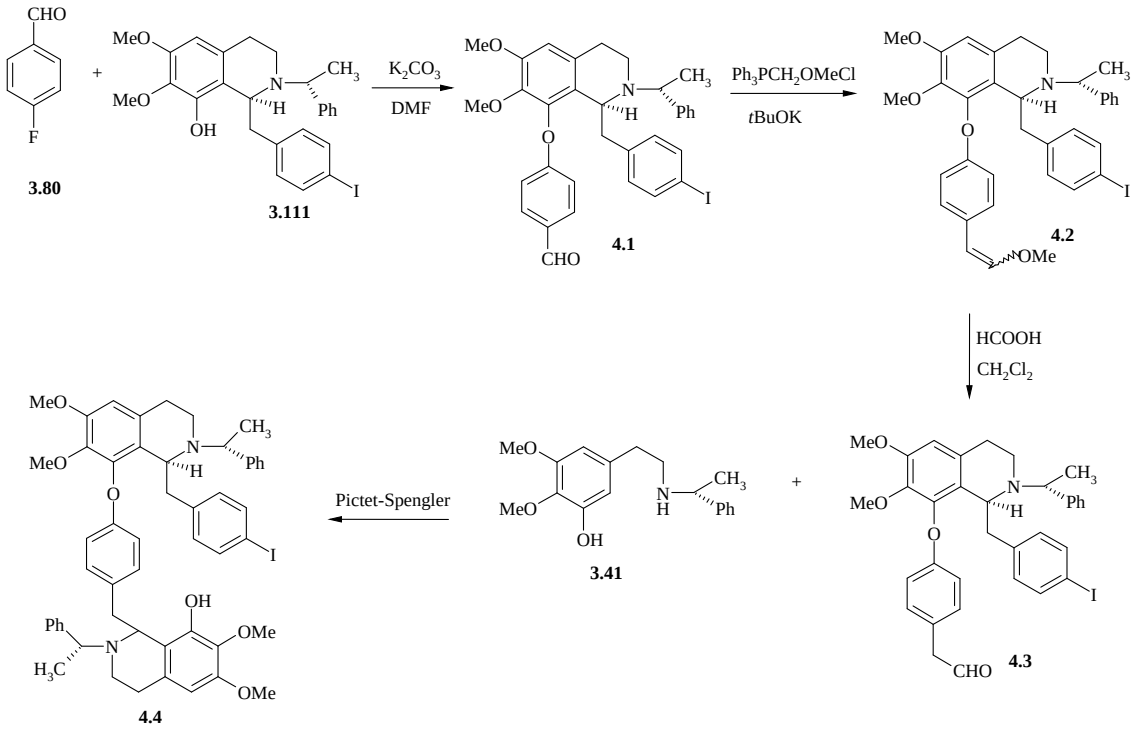
reaction times but with high yield (85% and 90%). The ease of formation of enantiomerically pure β-phenethylamine **3.22** combined with the ability to synthesise phenylacetaldehydes with a variety of substituents, makes the Pictet-Spengler reaction efficient for the preparation of other THIQ's.

The reaction conditions to control the regioselectivity and diastereoselectivity of the Pictet-Spengler reaction were developed. High yields in short reaction times were obtained. However, the highly selective formation of the desired isomer **3.104** was not straightforward. The electronic and steric properties of the β-phenethylamine and phenylacetaldehyde reaction partners have been examined extensively in order to provide an efficient cyclisation towards the THIQ's. The stereochemistry of the newly chiral centre at C-1 was established by the X-ray structure of **3.131** prepared from the parent THIQ **3.104** and a mechanism was proposed for the stereochemical outcome of the Pictet-Spengler reaction. In most cases, starting materials were efficiently prepared using well-known reactions in a limited number of steps from commercially available reagents. Various functional groups are tolerated in subsequent reactions. THIQ monomers have shown to have an MDR activity[1] which was the original motivation for total synthesis of cycleanine (**3.1**). If interesting products can be formed in synthetically useful yields and diastereomeric ratios, this methodology can be extended to the formation of other THIQ's of biological importance.

Despite the unsuccessful macrocyclisation of compound **3.136**, some progress was made in the right direction. The microwave-assisted S_NAr formation of diaryl ether **3.131**, using a reactive aryl fluoride and the electron-rich phenol **3.104** was achieved in high yields and short reaction times without racemisation of the product. Recrystallisation of diaryl ether **3.131** afforded colourless crystals which were suitable for X-ray diffractrometry and the crystal structure of **3.126** established the stereochemistry of C-1 in **3.104**. The developed C-C Wittig homologation and the Pictet-Spengler reaction used in the previous steps were employed to form a bisbenzyltetrahydroisoquinoline **3.136** in low yields due to the thermolability of phenylacetaldehydes in acid conditions. The intramolecular Ullmann reaction of **3.136** to **3.137** was unsuccessful.

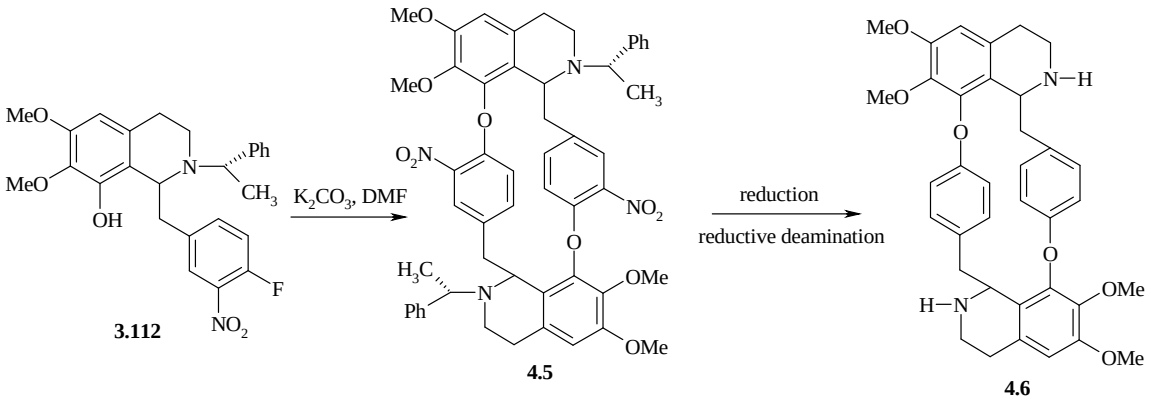
4.2 Future Work

Future efforts should be concentrated toward the synthesis of precursors with iodo substituents, since molecules with iodo group are reported to be more reactive in coupling reactions to form diaryl ethers (Scheme 4.1). The developed methods can be used to form the intermediates to cycleanine (**3.1**) and iodo derivatives assure high yields and short reaction times as was observed in the formation of phenylacetaldehyde and the subsequent THIQ **3.111**.



Scheme 4.1: Proposed reaction for coupling *via* the Ullmann coupling method.

Alternatively, the approach to cycleanine (**3.1**) can be achieved *via* a S_NAr coupling reaction in a one-pot reaction (Scheme 4.2). The readily prepared THIQ **3.112** with the nitro-activating group can undergo a facile intramolecular S_NAr to provide a macrocyclic precursor **4.5**, which can be easily reduced to **4.6** and *N*-methylated to the target cycleanine (**3.1**).



Scheme 4.2: Proposed reaction for coupling *via* the nucleophilic aromatic substitution.

The most striking feature of our approach towards total synthesis of cycleanine (**3.1**) is its reliance on only the simplest of reagents to carry out what seemed to be rather complex chemical transformations. We managed to overcome the daunting regiochemical and stereochemical problems associated with the synthesis of cycleanine (**3.1**), and the only pending issue is formation of the macrocyclic ring. These challenges give impetus to the development of new synthetic technologies and strategies to address stereocontrol and macrocyclisation problems. Total synthesis of cycleanine (**3.1**) provided a tough challenge and synthetic methods developed here can be used by those who wish to continue with the synthesis of BBIQ's.

4.3 Reference

1. L. Xue, M. Sun, T. Min, C. Zhang and H. Sun, *Lett. Drug Des Discov*., **2009**, *6*, 387-392.

CHAPTER 5

Experimental

5.1 General

Reactions requiring anhydrous conditions were performed under nitrogen using clean oven-dried glassware. All reagents were purchased from FLUKA, ALDRICH or MERCK and used without further purification, unless otherwise specified. Anhydrous solvents were obtained from a Pure-Solv Solvent Purification System supplied by Innovative Technology, Inc. This system removes water and oxygen to produce dry deoxygenated high-purity solvent, by passing room temperature solvents through columns containing activated alumina and copper under low nitrogen pressure to remove trace impurities.

A chromatotron (model 7924, Harrison Research) was used for centrifugal chromatography. Flash column chromatography was performed on a glass column (5 cm diameter) charged with 100 g of Merck Kieselgel 60 (230-400 mesh) for every 1 g of the crude material. The crude product was dissolved in a minimum of the appropriate solvent, applied to the column and eluted with the solvent of choice. Qualitative thin-layer chromatography (TLC) was performed on pre-coated Merck plastic sheets (silica gel $PF_{254,}$ 0.25 mm). After development, compounds were detected under UV (254 nm) followed by staining the plates with vanillin-H_2SO_4 or iodine. Yields reported refer to isolated material determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC), unless specified otherwise in the text.

All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 at 30 ºC. Chemical shifts are reported in ppm relative to residual solvent peak [$CDCl_3$ 7.26 ppm (^{1}H) and 77.0 ppm (^{13}C), or CD_3OD, 3.31 ppm (^{1}H) and 49 ppm (^{13}C) or DMSO-d_6, 2.5 ppm (^{1}H) and 39.5 ppm (^{13}C)]. Structures were determined by analysis of 2D (HSQC, HMBC, COSY) and nuclear Overhauser effect (NOE) spectroscopy. All high-resolution mass spectroscopic data were collected on a TOF Waters LCT Premier mass spectrometer using electrospray ionisation in the positive or negative mode. Infrared (IR) spectra were recorded neat on a Bruker Alpha FT-IR spectrometer. Melting points were measured on

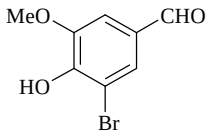
Kofler hot-stage melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin Elmer polarimeter with a cuvette of 1 cm path length.

Table 5.1: Abbreviations used in describing ^{1}H NMR signal multiplicities.

Abbreviation	Signal multiplicity	Abbreviation	Signal multiplicity
s	singlet	dd	doublet of doublets
d	doublet	br	broadened
t	triplet	*eq*	equatorial
m	multiplet	*ax*	axial
q	quartet	ddd	doublet of doublet of doublets

5.2 Synthetic procedures

5.2.1 3-Bromo-4-hydroxy-5-methoxybenzaldehyde (3.13)



A mixture of Br_2 (7.4 ml, 60 mmol) in glacial acetic (25 ml) was added dropwise to a stirred solution of vanillin (20.0 g, 130 mmol) in glacial acetic acid (160 ml) over a period of 20 min. The reaction was stirred for 1 h and monitored by TLC. The precipitate formed during the process was filtered and washed several times with water to give a yellow powder. The dried powder was recrystallised to give bromovanillin (**3.13**) (24.9 g, 93%) as white crystals (from ethanol), m.p. 164-165 ºC (lit.[1] 163-164 ºC).

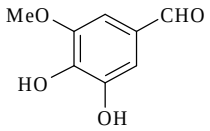
^{1}H NMR ($CDCl_3$): δ_H 3.98 (3H, s, OC<u>H</u>$_3$), 6.54 (1H, s, br, OH), 7.36 (1H, d, *J* = 1.5 Hz, H-6), 7.64 (1H, d, *J* = 1.5 Hz, H-2), 9.79 (1H, s, C<u>H</u>O).

^{13}C NMR ($CDCl_3$): δ_C 56.2 (OCH_3), 107.9, 108.1, 130.0, 130.1, 147.6, 148.8 (6 x ArC), 189.6 (CHO).

HRESIMS (negative ionisation mode), *m/z* found 228.9491 $[M-H]^-$, calculated for $C_8H_7{}^{79}BrO_3$ 228.9500.

IR: υ_{max} (neat)/cm^{-1}: 3507, 3168, 1661, 1583, 1460, 1426, 1295, 1258, 1149, 1014, 949, 854, 792.

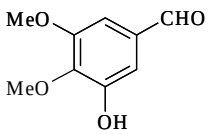
5.2.2 3,4-Dihydroxy-5-methoxybenzaldehyde (3.14)



A mixture of bromovanillin (**3.13**) (25.0 g, 109 mmol), NaOH (28.6 g, 700 mmol) and copper powder (2.6 g, 41 mmol) in H_2O (100 ml) were refluxed for 24 h. Sodium hydrogenphosphate (9.2 g, 65 mmol) was added during the last hour of reflux, and the mixture was cooled to room temperature, filtered to remove the precipitate of cupric hydrogenphosphate and acidified with HCl. The mixture was extracted with EtOAc (3 x 50 ml) and the combined organic layers were stirred with activated carbon and filtered. The filtrate was washed with a saturated EDTA solution followed by brine, water and dried ($MgSO_4$). The EtOAc layer was concentrated to give 3,4-dihydroxy-5-methoxybenzaldehyde as a solid product (11.8 g, 65%). The crude product was recrystallised from toluene as brownish crystals, m.p. 133-135 ºC (lit.[2] 132-133 ºC).

^{1}H NMR ($CDCl_3$): δ_H 3.96 (3H, s, OC<u>H</u>$_3$), 5.44 (1H, s, br, OH), 5.94 (1H, s, br, OH), 7.08 (1H, d, *J* = 1.5 Hz, H-6), 7.14 (1H, d, *J* = 1.5 Hz, H-2), 9.78 (1H, s, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 56.6 (OCH_3), 107.9, 108.1, 130.0, 130.1, 147.6, 148.8 (6 x ArC) 189.7 (CHO).
HRESIMS (negative ionisation mode), *m/z* found 167.0423 $[M-H]^-$, calculated for $C_8H_7O_4$ 167.0422.
IR: υ_{max} (neat)/cm^{-1} 3504, 3093, 1725, 1655, 1595, 1511, 1468, 1343, 1296, 1261, 1192, 1166, 1155, 1136, 1086, 1003, 947, 856, 839, 714, 682.

5.2.3 3-Hydroxy-4,5-dimethoxybenzaldehyde (3.21)

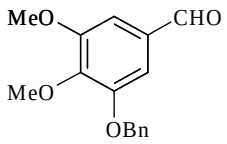


The mixture of 3,4-dihydroxy-5-methoxybenzaldehyde (**3.14**) (20.0 g, 119 mmol), dimethyl sulfate (11.3 ml, 119 mmol), sodium carbonate (13.9 g, 130.8 mmol) in acetone

(100 ml) were heated at reflux for 4 h. The reaction mixture was then cooled to room temperature and filtered. The acetone was removed under vacuum and the reaction mixture was poured into water and extracted with EtOAc. The EtOAc layer was washed with brine, water and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum afforded **3.21** (16.2 g, 75%) as a yellowish solid. The product was recrystallised from toluene:heptane (2:1) and 3-hydroxy-4,5-dimethoxybenzaldehyde (**3.21**) was obtained as yellowish crystals with m.p. 65-66 ºC (lit.[2] 64-65 ºC).

^{1}H NMR ($CDCl_3$): δ_H 3.93 (3H, s, OC<u>H</u>$_3$), 4.00 (3H, s, OC<u>H</u>$_3$), 5.93 (1H, s, O<u>H</u>), 7.06 (1H, d, *J* = 2.0 Hz, H-6), 7.12 (1H, d, *J* = 2.3 Hz, H-2), 9.87 (1H, s, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 55.9 (OCH_3), 60.8 (OCH_3), 103.7, 111.6, 131.9, 140.1, 149.7, 152.7 (6 x ArC) and 191.4 (CHO).
HRESIMS (positive ionisation mode), *m/z* found 205.0476 $[M+Na]^+$, calculated for $C_9H_{10}O_4$ 205.0477.
IR: υ_{max} (neat)/cm^{-1}: 3507, 3310, 2249, 1720, 1676, 1611, 1584, 1351, 1234, 1131, 1100, 977, 943, 836, 757, 698.

5.2.4 3-Benzyloxy-4,5-dimethoxybenzaldehyde (3.22)



To a solution of **3.21** (12.0 g, 65.9 mmol) in abs. EtOH (10 ml) were added K_2CO_3 (10.1 g, 73.2 mmol) and KI (43.8 g, 264 mmol). Freshly distilled benzyl chloride (9.3 ml, 73.1 mmol) was added dropwise and the resulting suspension was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature and water was added. After evaporation of EtOH under vacuum, the solution was poured into 2 M NaOH solution (30 ml). The aqueous solution was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated under reduced pressure to yield **3.22** (17.6 g, 98%) as pale yellow crystals (from petroleum ether) m.p. 52-53 ºC (lit.[3] 50-51 ºC).

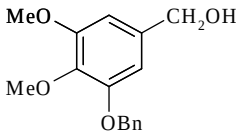
^{1}H NMR ($CDCl_3$): δ_H: 3.93 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.19 (2H, s, OCH_2Ph), 7.14 (1H, d, *J* = 1.5 Hz, H-6), 7.17 (1H, d, *J* = 1.5 Hz, H-2), 7.33-7.46 (5H, m, ArH), 9.64 (1H, s, CHO).

^{13}C NMR ($CDCl_3$): δ_C: 56.3 (OCH_3), 61.0 (OCH_3), 71.2 (OCH_2), 106.6, 109.2, 127.3 (2C), 128.1, 128.6 (2C), 131.6 (2C), 136.4, 152.6, 153.8 (12ArC) and 190.9 (CHO).

HRESIMS (positive ionisation mode), *m/z* found 295.0947 $[M+Na]^+$, calculated for $C_{16}H_{16}O_4$ 295.0946.

IR: υ_{max} (neat)/cm^{-1}: 3030, 2955, 2245, 1725, 1684, 1500, 1325, 1230, 1112, 877, 989, 725.

5.2.5 3-Benzyloxy-4,5-dimethoxybenzyl alcohol (3.23)



To the well-stirred solution of benzaldehyde **3.22** (20.0 g, 73 mmol) in EtOH (100 ml), $NaBH_4$ (8.3 g, 220 mmol) was slowly added at 0 ^{o}C. After stirring for 1.5 h, the excess $NaBH_4$ was destroyed by careful addition of 10% HCl. EtOH was evaporated and the residue extracted with EtOAc. The EtOAc layer was washed with saturated solution of $NaHCO_3$ and water, dried over $MgSO_4$ and concentrated under vacuum to afford pure benzyl alcohol **3.23** (19.2 g, 96%) as an oily substance.

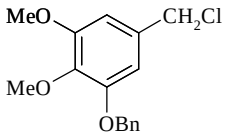
^{1}H NMR ($CDCl_3$): δ_H 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.53 (2H, s, CH_2OH), 5.07 (2H, s, OCH_2Ph), 6.56 (1H, d, *J* = 1.7 Hz, H-6), 6.60 (1H, d, *J* = 1.7 Hz, H-2), 7.28-7.42 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ_C 55.9 (OCH_3), 60.7 (OCH_3), 65.1 (CH_2OH), 70.8 (OCH_2), 104.0, 106.2, 127.1 (2C), 127.7, 128.4 (2C), 136.6, 136.9 (2C), 152.3, 153.3 (12 x ArC).

HRESIMS (positive ionisation mode), *m/z* found 297.1104 $[M+Na]^+$, calculated for $C_{16}H_{18}O_4$ 297.1103.

IR: υ_{max} (neat)/cm^{-1}: 3427, 3028, 2938, 1591, 1503, 1453, 1429, 1233, 1114, 1065, 1007, 957, 837, 737, 694.

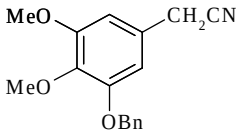
5.2.6 3-Benzyloxy-4,5-dimethoxybenzyl chloride (3.24)



Thionyl chloride (26.0 g, 218 mmol) in anhydrous $CHCl_3$ (15 ml) was added to the solution of alcohol **3.23** (20.0 g, 73 mmol) in anhydrous $CHCl_3$ (25 ml) at 0 ºC. The solution was stirred for 1 h at the same temperature, poured into ice and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with saturated $NaHCO_3$ solution, brine, water and evaporated. Flash column chromatography (hexanes:EtOAc, 8:2) gave benzyl chloride **3.24** (18.1 g, 85%) as pale yellow crystals from petroleum ether m.p. 68-69 ºC (lit.[4] 67-68 ºC).

^{1}H NMR ($CDCl_3$): δ_H 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.51 (2H, s, CH_2Cl), 5.13 (2H, s, $OC\underline{H}_2Ph$), 6.63 (1H, d, *J* = 1.8 Hz, H-6), 6.67 (1H, d, *J* = 1.8 Hz, H-2), 7.32-7.46 (5H, m, ArH).
^{13}C NMR ($CDCl_3$): δ_C 44.6 (CH_2Cl), 56.0 ($O\underline{C}H_3$), 60.7 ($O\underline{C}H_3$), 71.0 ($O\underline{C}H_2$), 105.9, 107.7, 127.2 (2C), 127.8, 128.4 (2C), 132.7 (2C), 136.8, 152.3, 153.4 (12ArC).
HRESIMS (positive ionisation mode), *m/z* found 315.0767 $[M+Na]^+$, calculated for $C_{16}H_{17}O_3Cl$ 315.0766.
IR: υ_{max} (neat)/cm^{-1}: 3030, 2848, 1597, 1589, 1419, 1329, 1237, 1116, 992, 692, 658.

5.2.7 3-Benzyloxy-4,5-dimethoxyphenylacetonitrile (3.25)



A mixture of benzyl chloride **3.24** (15.0 g, 54 mmol) and sodium cyanide (13.3 g, 271 mmol) in dimethyl sulfoxide (50 ml) were heated at 80 ^{o}C for 5 h. The reaction mixture was poured into water and extracted with EtOAc. The EtOAc extract was washed several times with water, brine, evaporated and subjected to flash column chromatography (hexanes:EtOAc, 7:3) to give phenylacetonitrile **3.25** (10.8 g, 70%) as a yellowish oil.

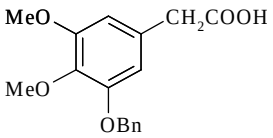
^{1}H NMR ($CDCl_3$): δ_H 3.64 (2H, s, CH_2CN), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.12 (2H, s, OCH_2Ph), 6.52 (1H, d, *J* = 1.8 Hz, H-6), 6.57 (1H, d, *J* = 1.8 Hz, H-2), 7.31-7.45 (5H, m, ArH).

^{13}C NMR ($CDCl_3$): δ_C 23.5 (CH_2CN), 56.1 (OCH_3), 60.8 (OCH_3), 71.1 (OCH_2), 105.2, 107.1, 117.7, 125.1, 127.2 (2C), 127.9, 128.5 (2C), 136.6, 138.1, 152.6, 153.7 (13C, 12ArC and CN).

HRESIMS (positive ionisation mode), *m/z* found 306.1109 $[M+Na]^+$, calculated for $C_{17}H_{17}O_3N$ 306.1106.

IR: υ_{max} (neat)/cm^{-1} 3020, 2938, 2233, 1591, 1505, 1453, 1429, 1334, 1235, 1112, 1002, 919, 819, 737, 697.

4.2.8 3-Benzyloxy-4,5-dimethoxyphenylacetic acid (3.26)



To the solution of phenylacetonitrile **3.25** (10.0 g, 35 mmol) in MeOH (100 ml) was added 25% aq NaOH (35 ml) and the reaction was refluxed until the evolution of ammonia has ceased (pH paper, 24 h). The mixture was concentrated under vacuum and the aqueous residue was washed with ether. The aqueous layer was acidified with 15% aq HCl and extracted with EtOAc. The EtOAc extract was washed with brine, water and evaporated to give the acid **3.26** as colourless crystals (9.8 g, 92%), m.p. 108-110 ºC (from toluene-light petroleum) (lit.[5] 108-109 ºC).

^{1}H NMR ($CDCl_3$): δ_H 3.54 (2H, s, CH_2COOH), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.11 (2H, s, OCH_2Ph), 6.51 (1H, d, *J* = 1.9 Hz, H-6), 6.56 (1H, d, *J* = 1.9 Hz, H-2), 7.31-7.43 (5H, m, ArH).

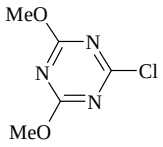
^{13}C NMR ($CDCl_3$): δ_C 41.2 (CH_2CO_2H) 56.1 (OCH_3), 60.8 (OCH_3), 71.2 (OCH_2), 106.8, 108.6, 127.3 (3C), 127.8, 128.5 (3C), 136.9, 152.4, 153.4 (12ArC) and 178.6 (CO_2H).

HRESIMS (negative ionisation mode), *m/z* found 301.1077 $[M-H]^-$, calculated for $C_{17}H_{18}O_5$ 301.1075.

IR: υ_{max} (neat)/cm^{-1} 3030, 2944, 2631, 2248, 1707, 1685, 1591, 1456, 1332, 1317, 1233, 1179, 1149, 1110, 1026, 1002, 737.

52.9 Synthesis of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) (3.30)

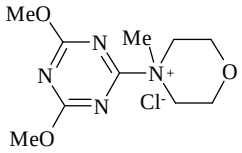
5.2.9.1 2-Chloro-4,6-dimethoxy-1,3,5-triazine (3.28)



$NaHCO_3$ (8.5 g, 0.1 mol) followed by 2,4,6-trichloro-1,3,5-triazine (**3.27**) (9.3 g, 0.05 mol) were added to the solution of MeOH (28 ml) and H_2O (2.5 ml) at 0 ºC. The reaction mixture was stirred for 1 h at room and as the temperature raised, CO_2 evolved. After evolution of CO_2 has ceased, the mixture was refluxed for 30 min and then cooled to room temperature. Water (100 ml) was added to the white precipitate formed, filtered, washed with water and dried in *vacuo* to give CMDT (**3.28**) as white crystals (6.5 g, 74%) m.p. 73-74 ºC (from H_2O) (lit.[6] 72-76 ºC).

^{1}H NMR (CD_3OD): δ_H 4.08 (6H, s, OCH_3).

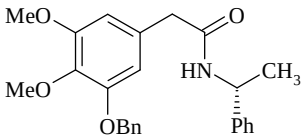
5.2.9.2 DMTMM (3.30)



N-methylmorpholine (NMM) (**3.29**) (2.85 ml, 26 mmol) was added dropwise to a solution of **3.28** (5.0 g, 28 mmol) in THF (80 ml) at room temperature. After stirring for 30 min at room temperature, the white solid formed was filtered and washed with THF (2 x 50 ml) and dried in vacuo to give DMTMM (**3.30**) (100%, 7.15 g) m.p. 117 ºC (from THF) (lit.[7] 116 ºC).

^{1}H NMR (CD_3OD): δ_H 3.56 (3H, s, $NC\underline{H}_3$), 3.88 (4H, m, $C\underline{H}_2$), 4.09 (2H, m, $C\underline{H}_2$), 4.20 (6H, s, OCH_3) and 4.55 (2H, m, $C\underline{H}_2$).

5.2.10 (*R*)-2-(3-Benzyloxy-4,5-dimethoxyphenyl)-*N*-(1-phenylethyl)acetamide (3.37)



To a solution of (*R*)-(-)-1-phenylethylamine (**3.36**) [(0.4 ml, 33 mmol), $[\alpha]_D^{25}$ = + 35.3 (*c* = 1.1) in MeOH)] and phenylacetic acid **3.26** (7.0 g, 23 mmol) in CH_3OH:H_2O (10:1, 50 ml) was added DMTMM (23 mmol) and the mixture was stirred overnight at room temperature. The resulting residue was poured into water and extracted with ether. The ether layer was washed successively with saturated Na_2CO_3, water, 10% aq. HCl, water and brine, and dried ($MgSO_4$). Evaporation of the solvent afforded amide **3.37** (9.1 g, 98%) as a white solid.

^{1}H NMR ($CDCl_3$): δ_H 1.38 (3H, d, *J* = 6.9 Hz, CHC<u>H</u>$_3$), 3.47 (2H, s, C<u>H</u>$_2$CO), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.08 (2H, s, OC<u>H</u>$_2$Ph), 5.09 (1H, q, *J* = 6.9 Hz, C<u>H</u>CH$_3$), 5.62 (1H, br d, NH), 6.44 (1H, d, *J* = 1.8 Hz, H-6), 6.48 (1H, d, *J* = 1.8 Hz, H-2), 7.19-7.40 (10H, m, ArH).

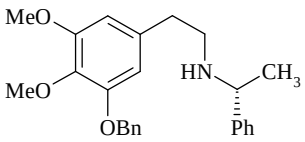
^{13}C NMR ($CDCl_3$): δ_C 21.6 (<u>C</u>H$_3$CH), 44.0 (C<u>H</u>$_2$CO) 48.6 (<u>C</u>HNH), 56.1 (OCH_3), 60.8 (OCH_3), 71.0 (O<u>C</u>H$_2$Ph), 106.4, 108.4, 125.9 (3C), 127.1 (3C), 127.3, 127.9, 128.5 (3C), 130.2, 136.8, 143.0, 152.5, 153.6 (18ArC) and 169.8 (<u>C</u>O).

HRESIMS (positive ionisation mode), *m/z* found 428.1840 $[M+Na]^+$, calculated for $C_{25}H_{27}O_4N$ 428.1838.

IR: υ_{max} (neat)/cm^{-1} 3635, 3025, 2960, 2644, 2178, 1677, 1643, 1231, 1111, 1007, 989, 739, 696.

$[\alpha]_D^{25}$ = + 42.4 (*c* = 1.1, MeOH).

5.2.11 (*R*)-*N*-[2-(3-Benzyloxy-4,5-dimethoxyphenyl)ethyl]-1-phenylethylamine (3.38)



Method A: Reduction of **3.37**

$BF_3{\cdot}Et_2O$ (12.9 g, 91 mmol) complex was slowly added to a solution of acetamide **3.37** (8.0 g, 20 mmol) in anhydrous THF (25 ml) followed by the addition of $BH_3{\cdot}THF$ (1 M, 1.8 g, 120 mmol) complex at room temperature, and the reaction mixture was refluxed for 1 h. After cooling the mixture to room temperature, the excess reagents were decomposed with 6 N HCl. The aqueous solution was washed with EtOAc, basified with 10% KOH and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with water and evaporated to give amine **3.38** (4.6 g, 60%) as an oily substance.

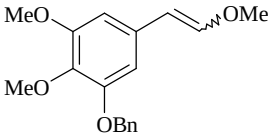
Method B: Condensation with **3.36** followed by in situ reduction.

A solution of (*R*)-(-)-1-phenylethylamine (**3.36**) [(0.13 ml, 10.5 mmol), $[\alpha]_D^{25}$ = + 35.3 (*c* = 1.1) in MeOH)] was gradually added to a solution of phenylacetaldehyde **3.40** (3.0 g, 10.5 mmol) in CH_3OH (30 ml) cooled with ice and the mixture was stirred overnight at room temperature. Sodium borohydride (0.34 g, 10.5 mmol) was gradually added with cooling, and the mixture was then stirred for 3 h at room temperature and then added to aqueous sodium hydrogen carbonate (20 ml). Methanol was removed under reduced pressure and the resulting residue was poured into water and extracted with ether. The ether layer was washed successively with water and brine, and dried ($MgSO_4$). Evaporation of the solvent afforded amine **3.38** (3.9 g, 95%) as an oily substance.

^{1}H NMR ($CDCl_3$): δ_H 1.34 (3H, d, *J* = 6.9 Hz, CHC<u>H</u>$_3$), 1.71 (1H, br d, NH), 2.70-2.74 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$NH), 3.76 (1H, q, *J* = 6.9 Hz, C<u>H</u>CH$_3$), 3.81 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.10 (2H, s, OC<u>H</u>$_2$Ph), 6.41 (1H, d, *J* = 1.8 Hz, H-6), 6.47 (1H, d, *J* = 1.8 Hz, H-2), 7.23-7.46 (10H, m, ArH).

^{13}C NMR ($CDCl_3$): δ_C 23.9 ($\underline{C}H_3CH$), 36.2 ($\underline{C}H_2CH_2NH$), 48.3 ($CH_2\underline{C}H_2NH$), 55.7 (OCH_3), 55.8 ($\underline{C}HNH$), 60.5 (OCH_3), 70.4 ($O\underline{C}H_2Ph$), 105.8, 107.6, 126.2 (2C), 126.5, 126.9 (2C), 127.4, 128.0 (2C), 128.1 (3C), 135.3, 136.9, 145.2, 151.9, 153.0 (18ArC).
HRESIMS (positive ionisation mode), *m/z* found 414.2047 $[M+Na]^+$, calculated for $C_{25}H_{29}O_3N$ 414.2045.
IR: υ_{max} (neat)/cm^{-1} 3439, 2918, 1643, 1587, 1505, 1451, 1427, 1332, 1233, 1114, 1028, 1007, 989, 761, 735, 697.
$[\alpha]_D^{25}$ = + 55,3 (*c* = 1.3, CH_3Cl).

5.2.12 1-(Benzyloxy)-2,3-dimethoxy-5-(2-methoxyethenyl)benzene (3.39)

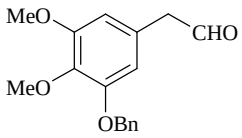


To a suspension of (methoxymethyl)triphenylphosphonium chloride (7.3 g, 21.3 mmol) in dry THF (10 ml), *t*-BuOK (3.3 g, 29.7 mmol) was added at 0 ^{0}C for 15 min. Then benzaldehyde **3.22** (5 g, 16.9 mmol) was added and stirred for 8 h. The reaction mixture was concentrated under vacuum and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layer was washed with water and brine, dried and concentrated under vacuum. Flash column chromatography (hexanes:EtOAc, 7:3) gave **3.39** (4.2 g, 90%) as a yellow oil.

^{1}H NMR ($CDCl_3$): δ_H^{1}H NMR ($CDCl_3$): δ_H: 3.31 (3H, s, OCH_3 *trans*), 3.75 (3H, s, OCH_3 *cis*), 3.86 (12H, s, 4 x OCH_3), 5.13 (4H, s, 2 x $O\underline{C}H_2Ph$), 5.73 (1H, d, *J* = 13.0 Hz *trans*), 6.07 (1H, d, *J* = 7.2 Hz *cis*), 6.47 (1H, d, *J* = 1.7 Hz, H-6), 6.84 (1H, d, *J* = 1.7 Hz, H-2), 6.93 (2H, m, ArH) 7.32-7.46 (10H, m, ArH),
^{13}C NMR ($CDCl_3$): δ_C 56.0 ($O\underline{C}H_3$ *trans*), 56.1 ($O\underline{C}H_3$ *cis*), 55.4 ($O\underline{C}H_3$), 60.7 ($O\underline{C}H_3$), 60.9 ($O\underline{C}H_3$), 61.0 (OCH_3), 71.1 ($O\underline{C}H_2$ *trans*), 71.2 ($O\underline{C}H_2$ *cis*), 102.9, 104.8, 105.1, 105.6, 106.1, 107.9, 127.2 (2C), 127.4 (2C), 127.7, 127.8, 128.4 (2C), 128.5 (2C), 131.5, 132.1, 137.2, 137.3 (2C), 137.5, 147.5, 148.6, 152.1, 152.6, 153.0 and 153.4.
HRESIMS (positive ionisation mode), *m/z* found 300.1259 $[M+Na]^+$, calculated for $C_{18}H_{20}O_4$ 323.1256.

IR: υ_{max} (neat)/cm^{-1}: 3028, 2938, 1591, 1503, 1453, 1429, 1233, 1114, 1065, 1007, 957, 837, 737, 694.

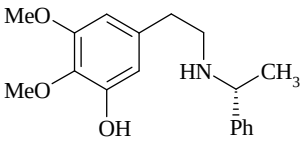
5.2.13 3-Benzyloxy-4,5-dimethoxyphenylacetaldehyde (3.40)



Formic acid (10 ml) was added to a solution of **3.39** (4.5 g, 14.9 mmol) in CH_2Cl_2 (30 ml) The reaction mixture was stirred for 48 hr at the room temperature, then diluted with water followed by the extraction with CH_2Cl_2, the organic layer was washed several times with water and concentrated to give **3.40** (3.1 g, 80%) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ_H^{1}H NMR ($CDCl_3$): δ_H: 3.57 (2H, d, *J* = 2.4 Hz, C$\underline{H_2}$CHO), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.11 (2H, s, OC$\underline{H_2}$Ph), 6.42 (1H, d, *J* = 1.7 Hz, H-6), 6.46 (1H, d, *J* = 1.7 Hz, H-2), 7.29-7.44 (5H, m, ArH), 9.68 (1H, t, *J* = 2.4 Hz, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 50.6 ($\underline{C}H_2$CHO), 56.2 (O$\underline{C}H_2$), 60.9 (O$\underline{C}H_3$), 71.3 (O$\underline{C}H_3$), 107.1, 109.1, 127.2 (2C), 127.3, 127.9, 128.5 (2C), 136.9, 138.3, 152.8, 153.9 and 199 (CHO).
HRESIMS (positive ionisation mode), *m/z* found 309.1105 $[M+Na]^+$, calculated for $C_{17}H_{18}O_4$ 309.1103.
IR: υ_{max} (neat)/cm^{-1}: 3425, 3144, 2890, 1517, 1437, 1419, 1233, 1111, 1067, 955, 837, 694.

5.2.14 (*R*)-*N*-[2-(3-Hydroxy-4,5-dimethoxyphenyl)ethyl]-1-phenylethylamine (3.41)

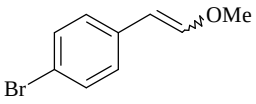


To a solution of **3.38** (4.5 g, 12 mmol) in 95% EtOH (20 ml) was added 10% Pd/C (2.0 g, 19 mmol) and the mixture was hydrogenated at atmospheric pressure at room temperature for 30 min. The mixture was filtered through a pad of celite and the filtrate was

concentrated. The residue was purified by column chromatography (hexanes:EtOAc, 9:1) to afford **3.41** (3.07 g, 85%) as a brown oil.

^{1}H NMR ($CDCl_3$): δ_H 1.35 (3H, d, *J* = 6.7 Hz, CHC<u>H</u>$_3$), 2.66-2.68 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$NH), 3.76 (1H, q, *J* = 6.9 Hz, C<u>H</u>CH$_3$), 3.76 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.23 (1H, d, *J* = 1.8 Hz, H-6), 6.39 (1H, d, *J* = 1.8 Hz, H-2), 7.24-7.30 (5H, m, ArH).
^{13}C NMR ($CDCl_3$): δ_C 23.8 (<u>C</u>H$_3$CH), 36.0 (<u>C</u>H$_2$CH$_2$NH), 48.4 (CH$_2$<u>C</u>H$_2$NH), 55.7 (OCH_3), 58.1 (<u>C</u>HNH), 60.7 (OCH_3), 104.2, 108.5, 126.5, 126.9, 128.4 (2C), 134.0, 135.8, 149.4, 152.4 (10ArC).
HRESIMS (positive ionisation mode), *m/z* found 302.1757 $[M+H]^+$, calculated for 302.1756.
IR: υ_{max} (neat)/cm^{-1} 3591, 3459, 3188, 2987, 1643, 1595, 1468, 1433, 1239, 1111,1084, 983, 834, 780, 739, 696, 677.
$[\alpha]_D^{25}$ = + 22.2 (*c* = 1.2, MeOH).

5.2.15 4-(2-Methoxyethenyl)-1-bromobenzene (3.43)



To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.2 g, 3.4 mmol) in dry THF (10 ml), *t*-BuOK (0.46 g, 4.09 mmol) was added at 0 ^{0}C for 15 min. Then 4-bromobenzaldehyde (0.5 g, 2.7 mmol) was added and stirred for 15 min. The reaction mixture was concentrated under vacuum and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layer was washed with water and brine, dried and concentrated under vacuum. Flash column chromatography (hexanes:EtOAc, 7:3) gave **3.43** as a mixture of the *cis* and *trans* isomers (0.52 g, 90%) as a yellow oil.

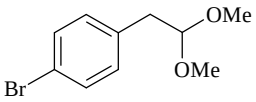
^{1}H NMR ($CDCl_3$): δ_H 3.68 (3H, s, OCH_3 *trans*), 3.78 (3H, s, OCH_3 *cis*), 5.17 (1H, d, *J* =7.0 Hz *cis,*), 5.74 (1H, d, *J* = 13.0 Hz *trans*), 6.16 (1H, d, *J* = 7.0 Hz cis), 7.03 (1H, d, *J* = 13.0 Hz *trans*), 7.09 (2H, d, *J* = 8.5 Hz, H-2,6), 7.36-7.40 (4H, m) and 7.44 (2H, d, *J* = 8.5 Hz, H-3,5).

^{13}C NMR ($CDCl_3$): δ_C 56.5 (OCH_3), 60.7 (OCH_3), 103.9 ($\underline{C}H(OCH_3)$) 104.5 ($\underline{C}HOCH_3$), 118.8 ($\underline{C}H_2CHOCH_3$), 119.0 ($\underline{C}H_2CHOCH_3$), 126.5 (2C), 129.6 (2C), 131.1 (2C), 131.5 (2C), 134.7, 135.3, 148.4, 149.2 (12ArC).

HRESIMS (positive ionisation mode), *m/z* found 212.9916 $[M+H]^+$, calculated for $C_9H_9{}^{79}BrO$ 212.9915.

IR: υ_{max} (neat)/cm^{-1} 3013, 2931, 1649, 1638, 1509, 1408, 1240, 1153, 1123, 1006, 931, 832, 716, 694.

5.2.16 1-bromo-4-(2,2-dimethoxyethyl)benzene (**3.44**)



The solution of **3.43** (0.12 g, 0.55 mmol), *p*-TsOH (0.11g, 0.55 mmol), and molecular sieves (0.1g) in MeOH were heated under reflux for 3 h. The reaction mixture was poured into water and extracted with EtOAc. The EtOAc extract was washed with water, brine and evaporated to give **3.44** (0.12 g, 95%) as bright yellow oil.

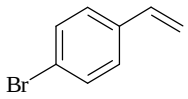
^{1}H NMR ($CDCl_3$): δ_H 2.85 (2H, d, $C\underline{H}(OCH_3)_2$, *J* = 5.6 Hz), 3.33 (6H, s, $CH(OC\underline{H}_3)_2$), 4.45 (1H, t, $C\underline{H}_2CH(OCH_3)_2$, *J* = 7.0 Hz,), 7.11 (2H, d, *J* = 8.3 Hz, H-2,6), 7.40 (2H, d, *J* = 8.3 Hz, H-3,5).

^{13}C NMR ($CDCl_3$): δ_C 38.9 ($\underline{C}H(OCH_3)_2$), 53.3 (2C, ($O\underline{C}H_3)_2$), 104.8 ($\underline{C}H_2CH$), 120.1, (C-1), 131.0 (2C, C-2,6), 131.2.1 (2C, C3,5), 135.8 (C-4).

HRESIMS (positive ionisation mode), *m/z* found 244.0099 $[M+H]^+$, calculated for $C_{10}H_{12}O_2{}^{79}Br$ 244.0098.

IR: υ_{max} (neat)/cm^{-1} 3020, 2923, 2858, 1737, 1459, 1242, 1196, 1171, 1030, 979, 832, 755, 680.

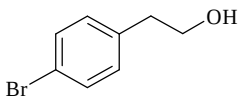
5.2.17 1-Bromo-4-vinylbenzene (3.46)



t-BuOK (1.9 g, 16.7 mmol) was added at 0 ^{o}C to a suspension of triphenylphosphonium methyl iodide (5.2 g, 13.9 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of 4-bromobenzaldehyde (2.0 g, 10.8 mmol) in dry THF (5ml). The mixture was stirred at room temperature for 1h (TLC). The reaction mixture was concentrated under vacuum and partitioned between water and Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 95:5) gave **3.46** as a colorless oil (1.9 g, 95% yield).

^{1}H NMR ($CDCl_3$): δ_H 5.29 (1H, d, *J* = 10.8 Hz C$\underline{H}_2$CH, *cis*), 5.76 (1H, d, *J* = 17.1 Hz C$\underline{H}_2$CH, *trans*), 6.67 (1H, dd, *J* = 17.1, 10.8 Hz $CH_2C\underline{H}$), 7.28 (2H, d, *J* = 8.4 Hz, H-2,6) 7.46 (2H, d, *J* = 8.4 Hz, H-3,5 ArH).
^{13}C NMR ($CDCl_3$): δ_C 114.5 (CH$\underline{C}H_2$), 121.6 (C-1), 127.8 (2C, C-2,6), 131.6 (2C, C-3,5), 135.8 ($\underline{C}HCH_2$) and 136.5 (C-4).
HRESIMS (positive ionisation mode), *m/z* found 182.9809 $[M+H]^{+}$, calculated for $C_8H_7O^{79}Br$ 182.9809.
IR: υ_{max} (neat)/cm^{-1} 2922, 2849, 1530, 1487, 1453, 1373, 1246, 1072, 1009, 822, 675.

5.2.18 2-(1,4-Bromophenyl)ethanol (3.47)

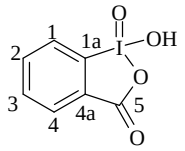


$BH_3{\cdot}S(CH_3)_2$ (5.5 mmol, 5M) was added at 0 ºC to a solution of **3.46** (1.0 g, 5.4 mmol) in dry THF (10ml), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (15.2 mmol) were added dropwise over 30 min, then stirred at room temperature for 3 h. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the

organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.47** as colourless oil in (1.0 g, 95%).

^{1}H NMR ($CDCl_3$): δ_H 2.50 (1H, s, br, OH), 2.77 (2H, t, *J* = 6.6 Hz C$\underline{H}_2$CH_2OH), 3.76 (2H, t, *J* = 6.6 Hz CH_2C$\underline{H}_2$OH), 7.08 (2H, d, *J* = 8.4 Hz, H-2,6), 7.41 (2H, d, *J* = 8.4 Hz, H-3,5).
^{13}C NMR ($CDCl_3$): δ_C 38.5 ($\underline{C}H_2CH_2OH$), 63.5 ($CH_2\underline{C}H_2OH$), 120.2 (C-1), 130.8 (2C, C-2,6), 131.6 (2C, C-3,5) and 137.7 (C-4).
HRESIMS (positive ionisation mode), *m/z* found 200.9917 $[M+H]^+$, calculated for $C_8H_7O^{79}Br$ 200.9915.
IR: υ_{max} (neat)/cm^{-1} 3371, 2938, 1675, 1525, 1487, 1349, 1317, 1143, 1071, 1043, 953, 804, 722, 675.

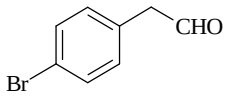
5.2.19 *o*-Iodoxybenzoic acid (IBX) (3.67)



Potassium bromate (4.0 g, 24 mmol) was added over 0.5 h to a vigorously stirred mixture of 2-iodobenzoic acid (4.0 g, 16 mmol) in H_2SO_4 (2M, 38 ml) cooled to 55 ºC in an ice bath. The reaction mixture was stirred for 3.5 h at 65 ºC, and then cooled and filtered. The white precipitate formed was washed with H_2O (500 ml) followed by cold ethanol (500 ml) to give a white powder. The product was recrystallised from ethanol and IBX (**3.67**) was obtained as white crystals (3.9 g, 88%) with m.p. 232-233 ºC (lit.[2] 233 ºC).[8]

^{1}H NMR (DMSO): δ_H 7.84 (1H, t, *J* = 8.3 Hz, H-3), 7.98 (1H, t, *J* = 8.3 Hz, H-2), 8.02 (1H, d, *J* = 12.8 Hz H-4), 8.14 (1H, d, J = 12.8 Hz, H-1).
^{13}C NMR (DMSO): δ_C 125.5 (C-1), 130.6 (C-4), 131.6 (C-4a), 134.9 (C-3), 134.9 (C-2), 147.0 (C-1a) and 168.0 (C-5).
HRESIMS (negative ionisation mode), *m/z* found 278.9154 $[M+H]^-$, calculated for $C_7H_4O_6I$ 278,9154.
IR: υ_{max} (neat)/cm^{-1} 3358, 2979, 1591, 1476, 1245, 1170, 1078, 1040, 930, 755, 694, 653.

5.2.20 4-Bromophenylacetaldehyde (**3.45**)



Method A: Oxidation of **3.47**

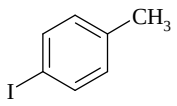
IBX (**3.67**) (1.4 g, 5 mmol) was dissolved in DMSO (20ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.47** (0.85 g, 4.3 mmol) dissolved in DMSO (5ml) was added and the reaction was stirred at rt for 1.5 h (TLC). Upon completion of the reaction the mixture was diluted with water followed by the extraction with EtOAc, the organic layer was washed several times with water and concentrated to a give the desired product. Compound **3.45** was isolated as a colourless oil (0.81 g, 95% yield).

Method B: Hydrolysis of **3.43**

Formic acid (10 ml) was added to a solution of **3.43** (0.50 g, 2.4 mmol) in CH_2Cl_2 (30 ml) The reaction mixture was stirred for 48 hr at the room temperature, then diluted with water followed by the extraction with CH_2Cl_2, the organic layer was washed several times with water and concentrated to give **3.45** (0.44 g, 95%) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ_H 3.66 (2H, d, *J* = 2.4 Hz, C$\underline{H}_2$CHO), 7.10 (2H, d, *J* = 8.2 Hz, H-2,6), 7.49 (2H, d, *J* = 8.2 Hz, H-3,5), 9.74 (1H, t, *J* = 2.4 Hz, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 49.7 ($\underline{C}H_2$CHO), 121.5 (C-1), 130. 7 (C-4), 131.2 (C-2,6), 132.1 (C-3,5 ArC) and 198.5 ($\underline{C}$HO).
HRESIMS (positive ionisation mode), *m/z* found 198.9757 $[M+H]^+$, calculated for $C_8H_7O^{79}Br$ 198.9758.
IR: υ_{max} (neat)/cm^{-1} 3289, 2938, 1705, 1586, 1487, 1436, 1345, 1168, 1069, 1050, 942, 806, 757, 694, 651.

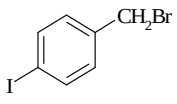
5.2.21 4-Iodotoluene (3.72)



A solution of *p*-toluidine (10.0 g, 93 mmol) in dry ether (10 ml) was added dropwise to $BF_3 \cdot Et_2O$ (52.0 g, 373 mmol) chilled in dry acetone (-15 ºC) under nitrogen, followed by addition of a solution of *tert*-butylnitrite (16.0 g, 163 mmol) in dry ether (10ml) over a period of 30 min. The chilled mixture was stirred an additional 10 min, and the cold bath was allowed to warm to 5 ºC over 20 min. Diethyl ether was added to the chilled precipitate formed during the process and the solid product was filtered and washed several times with chilled Et_2O and air-dried to give diazonium salt **3.71**. A solution of diazonium salt **3.71** (8.0 g, 40 mmol) in CH_3CN was then added dropwise to the solution of NaI (6.0 g, 45 mmol) and I_2 (1 g, 4 mmol) in CH_3CN. The mixture was then stirred at rt for 1 h, then $Na_2S_2O_3$ (2 M, 20 ml) was added to the mixture. The resultant solution was extracted with CH_2Cl_2 (3 x 25 ml) and the organic phase was washed with brine and dried over Na_2SO_2. The crude product was purified by column chromatography with (hexanes:EtOAc, 8:2) to give *p*-iodotoluene (**3.72**) (8.7 g, 93%) as a yellow powder.

^{1}H NMR ($CDCl_3$): δ_H 2.45 (C<u>H</u>$_3$), 6.93 (2H, d, *J* = 8.5 Hz, H-2,6), 7.61 (2H, d, *J* = 8.5 Hz, H-3,5).
^{13}C NMR ($CDCl_3$): δ_C 21.3 (<u>C</u>H$_3$), 94.9 (C-1), 130.7 (2C, C-2,6), 136.9 (C-4), 137.9 (2C, C-3,5).
HRESIMS (positive ionisation mode), *m/z* found 232.9464 $[M+H]^+$, calculated for C_7H_5OI 232.9463.
IR: υ_{max} (neat)/cm^{-1} 3030, 29234, 2850, 1660, 1461, 1364, 1301, 1255, 1055, 979, 673.

5.2.22 4-Iodobenzyl bromide (3.73)

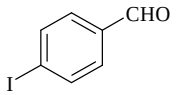


NBS was added in 3 equal portions (3 x 0.8 g, 14 mmol) over 10 minutes to a solution of *p*-iodotoluene (3.1 g, 14 mmol) in refluxing CCl_4 (30 ml) under incandescent irradiation

(100W). The mixture was cooled to rt and filtered and washed twice with hexane to give *p*-iodobenzyl bromide (**3.73**) (2.9 g, 70%) white crystals (from hexane) m.p. 77-79 ºC (lit.[9] 78.5-79.5 ºC).

^{1}H NMR ($CDCl_3$): δ_H 4.44 (2H, s, C$\underline{H}_2$), 7.15 (2H, d, *J* = 8.5 Hz, H-2,6), 7.69 (2H, d, *J* = 8.5 Hz, H-3,5).
^{13}C NMR ($CDCl_3$): δ_C 32.4 ($\underline{C}H_2Br$), 94.1 (C-1), 130.8 (2C, C-2,6), 137.4 (C-4), 137.5 (2C, C-3,5).
HRESIMS (positive ionisation mode), *m/z* found 296.8776 $[M+H]^+$ calculated for C_7H_6IBr 296.8775.
IR: υ_{max} (neat)/cm^{-1} 3025, 2942, 1643, 1457, 1231, 1128, 1005, 989, 871, 822, 739, 710, 668.

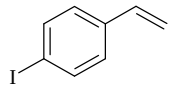
5.2.23 4-Iodobenzaldehyde (3.74)



IBX (**3.67**) (4.8 g, 17 mmol) was dissolved in DMSO (10 ml) and the dissolution of IBX (**3.67**) required 10-15 min. Benzyl bromide **3.73** (1.7 g, 5.6 mmol) dissolved in DMSO (5 ml) was added to the reaction mixture and stirred at room temperature for 15 min (TLC). Upon completion of the reaction the mixture was diluted with water followed by the extraction with ethyl acetate, the organic layer was washed several times with water and concentrated to a white solid, recrystallised from ethanol m.p. 76-78 ºC (lit.[10] 76-77 ºC) to give **3.74** (1.2 g, 95% yield) as white crystals.

^{1}H NMR ($CDCl_3$): δ_H 7.15 (2H, d, *J* = 8.3 Hz, H-2,6), 7.69 (2H, d, *J* = 8.3 Hz, H-3,5) 9.98 (1H, s, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 102.7 (C-1), 130.7 (2C, C-2,6), 135.6 (C-4), 138.4 (2C, C-3,5), 191.4 (CHO).
HRESIMS (positive ionisation mode), *m/z* found 232.9464 $[M+H]^+$, calculated for C_7H_5OI 232.9463.
IR: υ_{max} (neat)/cm^{-1} 3029, 2944, 2850, 1705, 1660, 1476, 1395, 1301, 1265, 1054, 980, 675.

5.2.24 1-Iodo-4-vinylbenzene (3.75)



t-BuOK (0.93 g, 8.35 mmol) was added at 0 ^{o}C to a suspension of triphenylphosphonium methyl iodide (2.6 g, 6.95 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of 4-iodobenzaldehyde (**3.74)** (1.3 g, 5.4 mmol) in dry THF (5ml). The mixture was stirred at room temperature for 30 minutes (TLC). The reaction mixture was concentrated under vacuum and partitioned between water and Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 95:5) gave **3.75** (1.2 g, 98%) yield as a yellowish oil.

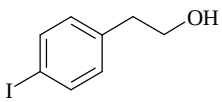
^{1}H NMR (CDCl3): δ_H 5.17 (1H, d, *J* = 10.6 Hz, *cis* C$\underline{H}_2$CH), 5.66 (1H, d, *J* = 17.5 Hz, *trans* C$\underline{H}_2$CH), 6.55 (1H, dd, *J* = 17.5, 10.6 Hz $CH_2C\underline{H}$), 7.05 (2H, d, *J* = 8.4 Hz, H-2,6), 7.56 (2H, d, *J* = 8.4 Hz, H-3,5).

^{13}C NMR ($CDCl_3$): δ_C 114.2 (CH$\underline{C}H_2$), 120.3 (C-1), 127.2 (2C, C-2,6), 130.9 (2C, C-3,5), 135.1 ($\underline{C}HCH_2$) and 136.2 (C-4).

HRESIMS (positive ionisation mode), *m/z* found 230.9671 $[M+H]^+$, calculated for C_8H_7I 230.9670.

IR: υ_{max} (neat)/cm^{-1} 3051, 2877, 1701, 1690, 1582, 1483, 1245, 1169, 1117, 1089, 1058, 975, 811, 753, 692.

5.2.25 2-(1,4-Iodophenyl)ethanol (3.76)

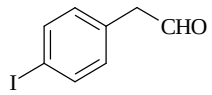


$BH_3{\cdot}S(CH_3)_2$ (5.5 mmol, 5M) was added at 0 ºC to a solution of **3.75** (1.2 g, 5.4 mmol) in dry THF (10ml), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (15.2 mmol) were added dropwise over 30 min, then stirred at 0 ºC for 3 h. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was

washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.76** (1.3 g, 98%) yield as a colourless oil.

^{1}H NMR ($CDCl_3$): δ_H 2.82 (2H, t, *J* = 6.5 Hz, C$\underline{H}_2$CH$_2$OH), 3.85 (2H, t, *J* = 6.5 Hz, CH$_2$C$\underline{H}_2$OH), 7.00 (2H, d, *J* = 8.2 Hz, H-2,6), 7.65 (2H, d, *J* = 8.2 Hz, H-3,5).
^{13}C NMR ($CDCl_3$): δ_C 38.7 ($\underline{C}$H$_2$CH$_2$OH), 63.3 (CH$_2\underline{C}$H$_2$OH), 91.6 (C-1), 131.1 (2C, C-2,6), 137.6 (2C, C-3,5) and 138.3 (C-4).
HRESIMS (positive ionisation mode), *m/z* found 248.9776 $[M+H]^+$, calculated for C_8H_7OI 248.9776.
IR: υ_{max} (neat)/cm^{-1} 3297, 2930, 1756, 1651, 1483, 1231, 1002, 989, 830, 800, 768, 739, 669, 656.

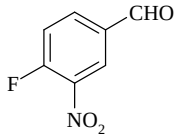
5.2.26 4-Iodophenylacetaldehyde (3.77)



IBX (**3.67**) (1.4 g, 5 mmol) was dissolved in DMSO (20ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.76** (1.1 g, 4.3 mmol) dissolved in DMSO (5ml) was added and the reaction was stirred at room temperature for 30 minutes (TLC). The reaction mixture was diluted with water followed by the extraction with EtOAc, the organic layer was washed several times with water and concentrated to a give the desired product. Compound **3.77** was isolated as a yellow oil (1.1 g, 98% yield).

^{1}H NMR ($CDCl_3$): δ_H 3.64 (2H, d, *J* = 2.4 Hz, C$\underline{H}_2$CHO), 7.03 (2H, d, *J* = 8.6 Hz, H-2,6), 7.41 (2H, d, *J* = 8.6 Hz, H-3,5) and 9.72 (1H, t, *J* = 2.4 Hz, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 49.5 ($\underline{C}$H$_2$CHO), 121.3 (C-1), 129.9 (C-4), 131.9 (C-2,6), 132.0 (C-3,5) and 199.5 ($\underline{C}$HO).
HRESIMS (positive ionisation mode), *m/z* found 246.9618 $[M+H]^+$, calculated for C_8H_7OI 246.9619.
IR: υ_{max} (neat)/cm^{-1} 3277, 2935, 1715, 1577, 1490, 1430, 1380, 1188, 1049, 1065, 925, 811, 766, 685, 642.

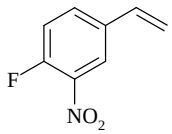
5.2.27 4-Fluoro-3-nitrobenzaldehyde (3.81)



A mixture of H_2SO_4 (c) (20 ml) and nitrite free HNO_3 (2.7 ml) cooled to -5 ºC, were treated dropwise with *para*-fluorobenzaldehyde (**3.80**) (5.0 g, 40.2 mmol) with the temperature kept below 5 ºC. The mixture was allowed to stand for 48 hours at room temperature, then poured on ice (500 g) and the precipitate formed was filtered to yield **3.81** (5.1 g, 75%) yield as yellowish solid, which was recrystallised (from Et_2O) to give yellow crystals m.p. 46-47 ºC (lit.[11] 46.5 ºC).

^{1}H NMR ($CDCl_3$): δ_H 7.32 (1H, d, *J* = 8.3 Hz, H-5), 8.08 (1H, dd, *J* = 2.3, 8.3 Hz, H-6), 8.52 (1H, d, *J* = 2.3 Hz, H-2), 9.95 (1H, s, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 117.3 (C-5), 125.6 (C-2), 133.7 (C-1), 140.1 (C-3), 138.5 (C-6), 163.8 (C-4) and 191.4 (<u>C</u>HO).
HRESIMS (positive ionisation mode), *m/z* found 170.0253 $[M+H]^+$, calculated for $C_7H_4NO_3F$ 170.0254.
IR: υ_{max} (neat)/cm^{-1} 3279, 2940, 1725, 1565, 1490, 1236, 1197, 1169, 1095, 1045, 816, 777, 679.

5.2.28 1-Fluoro-2-nitro-4-vinylbenzene (3.82)

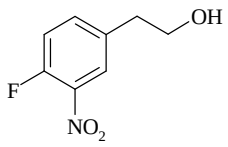


t-BuOK (1.9 g, 16.7 mmol) was added at 0 ºC to a suspension of triphenylphosphonium methyl iodide (5.2 g, 13.9 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of 4-fluoro-3-nitrobenzaldehyde **(3.81)** (1.8 g, 10.8 mmol) in dry THF (5ml). The mixture was stirred at room temperature for 5 h (TLC). Upon completion of the reaction the mixture was concentrated under vacuum and partitioned between water and Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$ and

concentrated. Purification by column chromatography (hexanes:EtOAc, 95:5) gave **3.82** (1.7 g, 98%) as a yellowish oil.

^{1}H NMR ($CDCl_3$): δ_H 5.35 (1H, d, *J* = 10.8 Hz, C$\underline{H}_2$CH, *cis*), 5.87 (1H, d, *J* = 17.1 Hz, C$\underline{H}_2$CH, *trans*), 6.77 (1H, dd, *J* = 17.1, 10.8 Hz $CH_2C\underline{H}$), 7.09 (1H, d, *J* = 8.3 Hz, H-5), 7.29 (1H, dd, *J* = 2.3, 8.3 Hz, H-6), 7.89 (1H, d, *J* = 2.3 Hz, H-2).
^{13}C NMR ($CDCl_3$): δ_C 114.7 (CH$\underline{C}H_2$), 121.8 (C-1), 127.8 (C-5), 131.9 (C-6), 133. 2 (C-2), 135.9 ($\underline{C}HCH_2$) and 136.9 (C-4).
HRESIMS (positive ionisation mode), *m/z* found 168.0461 $[M+H]^+$, calculated for $C_8H_6NO_2F$ 168.0460.
IR: υ_{max} (neat)/cm^{-1} 2937, 1615, 1535, 1495, 1339, 1240, 1170, 1154, 1080, 1051, 825, 752, 672.

5.2.29 4-(Fluoro-2-nitrophenyl)ethanol (3.83)

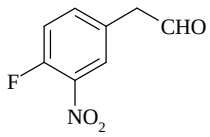


$BH_3{\cdot}S(CH_3)_2$ (5.5 mmol, 5M) was added at 0 ºC to a solution of **3.82** (0.90 g, 5.4 mmol) in dry THF (10 ml), and stirred for 4 h at room temperature. The mixture was cooled to 0ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (15.2 mmol) were added dropwise over 30 min, then stirred for 8 h at 0 ºC. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.83** (0.85 g, 85%) yield as a colourless oil.

^{1}H NMR ($CDCl_3$): δ_H 2.77 (2H, t, *J* = 6.3 Hz, C$\underline{H}_2CH_2OH$), 3.79 (2H, t, *J* = 6.3 Hz, $CH_2C\underline{H}_2OH$), 7.06 (1H, d, *J* = 8.3 Hz, H-5), 7.25 (1H, dd, *J* = 2.3, 8.3 Hz, H-6), 7.51 (1H, d, *J* = 2.3 Hz, H-2).
^{13}C NMR ($CDCl_3$): δ_C 38.8 ($\underline{C}H_2CH_2OH$), 63.7 ($CH_2\underline{C}H_2OH$), 116.9 (C-5), 124.2 (C-2), 133.5 (C-3), 134.8 (C-6), 135.6 (C-1) and 157.7 (C-4).
HRESIMS (positive ionisation mode), *m/z* found 186.0567 $[M+H]^+$, calculated for $C_8H_8NO_3F$ 186.0566.

IR: υ_{max} (neat)/cm^{-1} 3340, 2931, 1612, 1530, 1498, 1347, 1246, 1175, 1164, 1082, 1043, 830, 815, 765, 668.

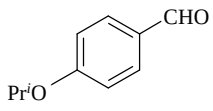
5.2.30 4-Fluoro-3-nitrophenylacetaldehyde (3.84)



IBX (**3.67**) (1.4 g, 5 mmol) was dissolved in DMSO (20ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.83** (0.80 g, 4.3 mmol) dissolved in DMSO (5 ml) was added and the reaction was stirred at room temperature for 5 h (TLC). Upon completion of the reaction the mixture was diluted with water followed by the extraction with EtOAc, the organic layer was washed several times with water and concentrated to a give the desired product. Compound **3.84** was isolated as a yellow oil (0.67 g, 85%).

^{1}H NMR ($CDCl_3$): δ_H 3.66 (2H, d, *J* = 2.4 Hz, C<u>H</u>$_2$CHO), 7.13 (1H, d, *J* = 8.4 Hz, H-5), 7.21 (1H, dd, *J* = 2.4, 8.4 Hz, H-6), 7.51 (1H, d, *J* = 2.4 Hz, H-2), 9.71 (1H, t, *J* = 2.4, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 49.9 (<u>C</u>H$_2$CHO), 117.3 (C-5), 126.2 (C-2), 132.1 (C-1), 135.9 (C-3), 138.9 (C-6), 156.8 (C-4) and 199.7 (<u>C</u>HO).
HRESIMS (positive ionisation mode), *m/z* found 184.0409 $[M+H]^+$, calculated for $C_8H_6NO_3F$ 184.0409.
IR: υ_{max} (neat)/cm^{-1} 3277, 2935, 1715, 1545, 1488, 1349, 1246, 1177, 1169, 1075, 1045, 825, 767, 669.

5.2.31 4-Isopropyloxybenzaldehyde (3.86)

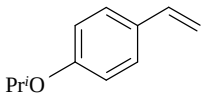


To a mixture of 4-hydroxybenzaldehyde (6.5 g, 53.2 mmol) in dry DMF (20 ml) were added K_2CO_3 (14.7 g, 106.5 mmol). Freshly distilled isopropyl bromide (16.9 ml, 186.3 mmol) was added dropwise and the resulting suspension was stirred at room temperature

for 19 h. After evaporation of DMF under vacuum, the solution was poured into 2M HCl solution (30 ml). The aqueous solution was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were concentrated under reduced pressure to yield **3.86** (8.4 g, 84%) as yellow oil.

^{1}H NMR ($CDCl_3$/ CD_3OD) δ_H: 1.31 (6H, d, *J* = 6.2 Hz, CHC$\underline{H_3}$C$\underline{H_3}$), 4.62 (1H, m, OC$\underline{H}$), 6.92 (2H, d, *J* = 8.8 Hz, H-3,5), 7.76 (2H, d, *J* = 8.8 Hz, H-2,6), 9.76.17 (1H, s, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 21.1 (2C, $\underline{C}H_3\underline{C}H_3$), 69.9 (O$\underline{C}$H), 115.1 (2C, C-3,5), 128.8 (C-1), 131.6 (2C, C-2,6), 162.9 (C-4) 190.9 ($\underline{C}$HO).
HRESIMS (positive ionisation mode), *m/z*) found 187.0737 $[M+Na]^+$, calculated for $C_{10}H_{12}O_2$ 187.0735.
IR: υ_{max} (neat)/cm^{-1} 3020, 1715, 1686, 1597, 1573, 1252, 1216, 1177, 1156, 1115, 1100, 947, 830, 739, 696.

5.2.32 1-Isopropyloxy-4-vinylbenzene (3.87)



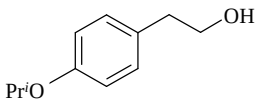
t-BuOK (1.9 g, 16.7 mmol) was added at 0 ^oC to a suspension of triphenylphosphonium methyl iodide (5.2 g, 13.9 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of *p*-Isopropyloxybenzaldehyde (**3.86**) (1.8 g, 10.8 mmol) in dry THF (5ml). The mixture was stirred at room temperature for 15 h (TLC). Upon completion of the reaction the mixture was concentrated under vacuum and partitioned between water and Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 95:5) gave **3.87** (1.6 g, 90%) as a colourless oil.

^{1}H NMR ($CDCl_3$/ CD_3OD): δ_H 1.28 (6H, d, *J* = 6.2 Hz, CHC$\underline{H_3}$C$\underline{H_3}$), 4.59 (1H, m, OC$\underline{H}$), 5.28 (1H, d, *J* = 10.5 Hz, C$\underline{H_2}$CH, *cis*), 5.79 (1H, d, *J* = 17.3 Hz, C$\underline{H_2}$CH, *trans*), 6.48 (1H, dd, *J* = 17.3, 10.5 Hz $CH_2C\underline{H}$), 6.77 (2H, d, *J* = 8.5 H-2,6), 7.58 (2H, d, *J* = 8.5 Hz, H-3,5).
^{13}C NMR ($CDCl_3$): δ_C 20.9 (2C, $\underline{C}H_3\underline{C}H_3$), 69.5 (O$\underline{C}$H), 114.2 (CH$\underline{C}H_2$), 115.1 (2C, C-3,5), 128.5 (2C, C-2,6) and 134.8 ($\underline{C}HCH_2$).

HRESIMS (positive ionisation mode), *m/z* found 163.1124 $[M+H]^+$, calculated for $C_{11}H_{14}O$ 163.1122.

IR: υ_{max} (neat)/cm^{-1} 3023, 1677, 1589, 1575, 1240, 1166, 1145, 1120, 945, 825, 732, 693.

5.2.33 2-(4-Isopropyloxyphenyl)ethanol (3.88)



$BH_3{\cdot}S(CH_3)_2$ (5.5 mmol, 5M) was added at 0 ºC to a solution of **3.87** (0.80 g, 5.4 mmol) in dry THF (10ml), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (15.2 mmol) were added dropwise over 30 min, then stirred overnight at 0 ºC. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.88** (0.78 g, 92%) as a colourless oil.

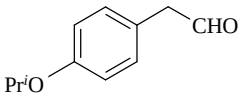
^{1}H NMR ($CDCl_3$): δ_H 1.33 (6H, d, *J* = 6.0 Hz, CHC<u>H</u>$_3$C<u>H</u>$_3$), 2.74 (2H, t, *J* = 6.4 Hz, C<u>H</u>$_2$CH$_2$OH), 3.73 (2H, t, *J* = 6.4 Hz, CH$_2$C<u>H</u>$_2$OH), 4.52 (1H, m, OC<u>H</u>), 6.75 (2H, d, *J* = 8.6 Hz, H-3,5), 7.46 (2H, d, *J* = 8.6 Hz, H-2,6).

^{13}C NMR ($CDCl_3$): δ_C 21.9 (2C, <u>C</u>H$_3$<u>C</u>H$_3$), 38.4 (<u>C</u>H$_2$CH$_2$OH), 64.6 (CH$_2$<u>C</u>H$_2$OH), 69.8 (2C, O<u>C</u>H), 115.8 (2C, C-3,5), 128.5 (2C, C-2,6), 132.8 (C-1), 157.2 (C-4).

HRESIMS (positive ionisation mode), *m/z* found 181.1229 $[M+Na]^+$, calculated for $C_{11}H_{16}O_2$ 181.1228.

IR: υ_{max} (neat)/cm^{-1} 3471, 3025, 2960, 1643, 1507, 1237, 1179, 1169, 1117, 1006, 953, 824, 739, 696.

5.2.34 4-Isopropyloxyphenylacetaldehyde (3.89)

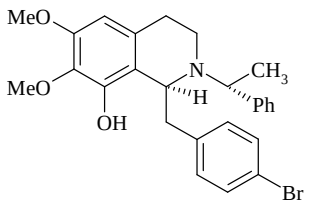


IBX (**3.67**) (1.4 g, 5 mmol) was dissolved in DMSO (20ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.88** (0.68 g, 4.3 mmol) dissolved in DMSO (5ml) was added, and the reaction was stirred at room temperature for 18 h. The reaction mixture was diluted with water followed by the extraction with EtOAc, the organic layer

was washed several times with water and concentrated to a give the desired product. Compound **3.89** was isolated as a yellowish oil (0.69 g, 90%).

^{1}H NMR ($CDCl_3$): δ_H 1.27 (6H, d, *J* = 9.1 Hz, CH(C<u>H</u>$_3$)$_2$), 3.58 (2H, d, *J* = 2.4 Hz, C<u>H</u>$_2$CHO), 4.51 (1H, m, C<u>H</u>(CH$_3$)$_2$), 6.83 (2H, d, *J* = 8.6 Hz, H-3,5), 6.95 (2H, d, *J* = 8.6 Hz, H-2,6), 9.70 (1H, t, *J* = 2.4 Hz, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 21.8 (2C, CH(<u>C</u>H$_3$)$_2$), 49.7 (<u>C</u>H$_2$CHO), 69.9 (<u>C</u>H(CH$_3$)$_2$), 116.5 (2C, C-3,5), 123.5 (C-1), (2C, C-2,6), 157.5 (C-4) and 199.8 (<u>C</u>HO).
HRESIMS (positive ionisation mode), *m/z* found 179.1072 $[M+H]^+$, calculated for $C_{11}H_{14}O_2$ 179.1072.
IR: υ_{max} (neat)/cm^{-1} 3277, 2935, 1715, 1592, 1460, 1425, 1365, 1168, 1072, 1055, 930, 815, 765, 684, 644.

5.2.35 (1*S*)-1-(4-Bromobenzyl) -6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-ol (3.104)



To a solution of amine alcohol **3.41** (1.2 g, 4.05 mmol), phenylacetaldehyde **3.45** (0.7 g, 3.5 mmol), 3 Å molecular sieves (1.0 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (0.1 eq.) was added dropwise. The reaction was refluxed for 18 h and upon completion of the reaction the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.104** (1.3 g, 78%) as yellow solid.

^{1}H NMR ($CDCl_3$): δ_H 0.96 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$), 2.16 (1H, dd, *J* =13.5, 3.2 Hz, H-4*eq*), 2.68-3.20 (3H, m, H-α, H-3, H-4), 3.05 (1H, dd, *J* = 2.4, 10.4 Hz, H-α), 3.18 (1H, ddd, *J* = 3.2, 11.1, 13.2, Hz, H-3*eq*), 3.63 (1H, q, *J* = 6.4 Hz, C<u>H</u>CH$_3$), 3.65 (3H, s, 7-OCH$_3$), 3.80 (3H, s, 6-OCH$_3$), 4.35 (1H, dd, *J* = 3.8 Hz, 10.4, H-1), 5.93 (1H, s, OH), 6.22 (1H, s, H-5), 7.14 (2H, d, *J* =8.4 Hz, H-11,13), 7.23-7.25 (5H, m, ArH), 7.45 (2H, d, *J* = 8.4, H-10,14).

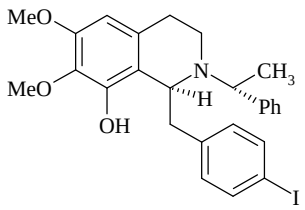
^{13}C NMR ($CDCl_3$): δ_C 22.4, 22.6, 31.8, 39.6, 53.8, 55.6, 57.7, 61.1, 103.7, 117.9, 119.4, 126.7, 127.3, 128.3, 130.7 (2C), 131.1, 131.6 (2C), 132.1 (2C), 133.4, 140.8, 146.3, 145.7, 150.5.

HRESIMS (positive ionisation mode), *m/z* found 482.1333 $[M+H]^+$, calculated for $C_{26}H_{28}{}^{79}BrNO_3$ 482.1331.

IR: υ_{max} (neat)/cm^{-1} 3591, 3459, 3188, 2987, 2931, 2845, 1678, 1658, 1602, 1562, 1489, 1366, 1258, 1233, 1153, 1120 and 1051.

$[\alpha]_D^{25}$ = + 55.6 (*c* = 1.2, $CHCl_3$).

5.2.36 (1*S*)-1-(4-Iodobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-ol (3.111)



To a solution of amine alcohol **3.41** (1.4 g, 4.7 mmol), phenylacetaldehyde **3.79** (0.7 g, 2.8 mmol), 3 Å molecular sieves (1.0 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (0.1 eq.) was added dropwise. The reaction was refluxed for 12 h and upon completion of the reaction the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.111** (1.2 g, 80%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ_H 0.98 (3H, d, *J* = 6.4 Hz, CHC$\underline{H}_3$), 2.21 (1H, dd, *J* =13.5, 3.2 Hz, H-4*eq*), 2.71-3.29 (3H, m, H-α, H-3, H-4), 3.12 (1H, dd, *J* = 2.8, 10.3, Hz, H- α), 3.25 (1H, ddd, *J* = 3.2, 11.1, 13.2, Hz, H-3*eq*), 3.66 (1H, q, *J* = 6.4 Hz, C$\underline{H}$CH$_3$), 3.70 (3H, s, 7-OCH$_3$), 3.92 (3H, s, 6-OCH$_3$), 4.38 (1H, dd, *J* = 2.8 Hz, 10.3, H-1), 5.97 (1H, s, OH), 6.29 (1H, s, H-5), 7.20 (2H, d, *J* =8.5 Hz, H-11,13), 7.43-7.65 (5H, m, ArH), 7.45 (2H, d, *J* = 8.5, H-10,14).

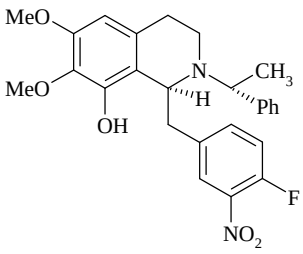
^{13}C NMR ($CDCl_3$): δ_C 22.7, 23.0, 31.9, 39.9, 54.1, 56.2, 57.9, 61.9, 104.2, 118.2, 119.9, 127.2, 127.9, 128.8, 131.5 (2C), 131.9, 131.8 (2C), 132.9 (2C), 133.8, 141.2, 146.9, 148.2, 151.1.

HRESIMS (positive ionisation mode), *m/z* found 530.1193 $[M+H]^+$, calculated for $C_{26}H_{28}NO_3I$ 530.1192.

IR: υ_{max} (neat)/cm^{-1} 3585, 3427, 3190, 2968, 2850, 1670, 1602, 1555, 1470, 1390, 1245, 1175 and 1025.

$[\alpha]_D^{25}$ = + 59.8 (*c* = 1.1, $CHCl_3$).

5.2.37 (1*S*)-1-(4-Fluoro-3-nitro-benzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-ol (3.112)



To a solution of amine alcohol **3.41** (1.3 g, 4.4 mmol), phenylacetaldehyde **3.84** (0.70 g, 3.8 mmol), 3 Å molecular sieves (1.0 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (0.1 eq.) was added dropwise. The reaction was refluxed for 20 h and upon completion of the reaction the mixture diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.112** (1.3 g, 72%) as a yellow oil.

^{1}H NMR ($CDCl_3$): δ_H: 0.98 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$), 2.20 (1H, dd, *J* =13.5, 3.2 Hz, H-4*eq*), 2.71-3.25 (3H, m, H-α, H-3, H-4), 3.12 (1H, dd, *J* = 3.6, 10.3, Hz, H- α), 3.25 (1H, ddd, *J* = 3.2, 11.1, 13.2, Hz, H-3*eq*), 3.66 (1H, q, *J* = 6.4 Hz, C<u>H</u>CH$_3$), 3.71 (3H, s, 7-OCH_3), 3.84 (3H, s, 6-OCH_3), 4.37 (1H, dd, *J* = 3.6, 10.3 Hz, H-1), 5.96 (1H, s, OH), 6.26 (1H, s, H-5), 7.16 (1H, d, *J* = 8.4 Hz, H-10), 7.26-7.31 (5H, m, ArH), 7.45 (1H, dd, *J* = 2.4, 8.4 Hz, H-14) 7.13 (1H, d, *J* = 8.4 Hz, H-11).

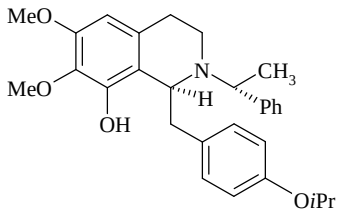
^{13}C NMR ($CDCl_3$): δ_C 22.6, 32.3, 41.3, 45.7, 53.2, 53.9, 55.6, 61.2, 104.9, 116.9, 117.5, 124.5, 127.3, 128.9, 130.9 (2C), 131.5, 131.9 (2C), 132.4 (2C), 133.9, 139.7, 145.7, 146.3, 151.3.

HRESIMS (positive ionisation mode), *m/z* found 467.1948 $[M+H]^+$, calculated for $C_{26}H_{27}NO_5F$ 467.1947.

IR: υ_{max} (neat)/cm^{-1} 3496, 2944, 3188, 2987, 2865, 1615, 1589, 1505, 1453, 1362, 1235, 1186, 1119, 1069, 908, 820, 729, 699.

$[\alpha]_D^{25}$ = + 52.5 (*c* = 1.3, $CHCl_3$).

5.2.38 (1*S*)-1-(4-Isopropoxybenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-ol (3.113)



To a solution of amine alcohol **3.41** (1.2 g, 3.9 mmol), phenylacetaldehyde **3.89** (0.60 g, 3.4 mmol), 3 Å molecular sieves (1.0 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (0.1 eq.) was added dropwise. The reaction was refluxed for 24 h and diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.113** as pale yellow oil (1.1 g, 70%).

^{1}H NMR ($CDCl_3$): δ_H 0.95 (3H, d, *J* = 6.5 Hz, CHC$\underline{H}_3$), 1.35 (6H, d, *J* = 6.1Hz, CH(C$\underline{H}_3$)$_2$), 2.13 (1H, dd, *J* =13.4, 3.3 Hz, H-4*eq*), 2.59-3.17 (3H, m, H-α, H-3, H-4), 3.09 (1H, dd, *J* = 3.5, 10.6, Hz, H- α), 3.22 (1H, ddd, *J* = 3.3, 11.1, 13.4, Hz, H-3*eq*), 3.65 (1H, q, *J* = 6.9 Hz, C$\underline{H}$CH$_3$), 3.80 (3H, s, OCH$_3$), 3.91 (3H, s, OCH$_3$), 4.38 (1H, dd, *J* = 3.5, 10.6 Hz, H-1), 4.57 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 5.91 (1H, s, H-5 or H-8), 6.22 (1H, s, H-5 or H-8), 6.88 (2H, d, *J* = 8.6, H-10,14), 7.16-7.22 (5H, m, ArH) and 7.27 (2H, d, *J* = 8.6 Hz, H-11,13).

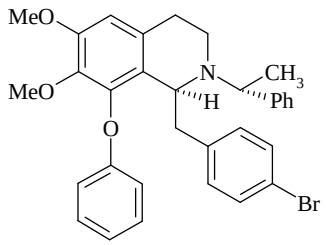
^{13}C NMR ($CDCl_3$): δ_C 22.5 [OCH(C$\underline{H}_3$)$_2$], 22.5 (CHC$\underline{H}_3$), 22.6 (C-4), 39.3 (C-α), 39.4 (C-3), 53.9 (C-1), 55.6 (OC$\underline{H}_3$), 57.7 (NC$\underline{H}$Ph), 61.0 (OC$\underline{H}_3$), 70.0 [OC$\underline{H}$(CH$_3$)$_2$], 103.5 (C-5), 115.2 (C-10,14), 118.3 (C-8a), 125.7 -128.3 (C-Ph), 130.6 (C-11,13), 131.1 (C-9), 133.3 (C-4a), 134.1 (quaternary on Ph), 147.3 (C-8), 146.7 (C-7), 150.4 (C-6), 155.9 (C-12).

HRESIMS (positive ionisation mode), *m/z* found 462.2645 $[M+H]^+$, calculated for $C_{29}H_{35}O_4N$ 462.2644.

IR: υ_{max} (neat)/cm^{-1} 3582, 3466, 3125, 2965, 2849, 1643, 1655, 1613, 1566, 1231, 1113, 1061, 977, 743, 695.

$[\alpha]_D^{25}$ = + 63.5 (*c* = 1.0, $CHCl_3$).

5.2.39 (1*S*)-1-(4-bromobenzyl)-6,7-dimethoxy-8-phenoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (3.121)



A mixture of phenol **3.104** (0.2 g, 0.41 mmol), $Cu(OAc)_2$ (75 mg, 0.41 mmol), arylboronic acid (0.15 g, 1.2 mmol) and powdered 4 Å molecular sieves (100 mg) were dissolved in CH_2Cl_2, and Et_3N (2.07 mmol, 0.29 ml) was added. The resulting coloured heterogeneous mixture was stirred for 18 h at 25 °C, then filtered and separated by flash chromatography (hexanes:EtOAc, 9:1) to afford **3.121** (0.16 g, 72%) as a colourless oil.

^{1}H NMR ($CDCl_3$): δ_H 0.77 (3H, d, *J* = 6.5 Hz, CHC<u>H</u>$_3$), 2.29 (1H, dd, *J* =16.5, 4.2 Hz, H-4), 2.72-2.91 (4H, m, 2x H-α, H-3, H-4), 3.19 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.61 (1H, q, *J* = 6.5 Hz, C<u>H</u>CH$_3$), 3.59 (3H, s, 7-OCH$_3$), 3.78 (3H, s, 6-OCH$_3$), 4.01 (1H, t, *J* = 5.3, 7.8, H-1), 6.51 (1H, s, H-5), 7.00-7.08 (6H, m, ArH), 7.18 (3H, ArH), 7.36 (2H, d, *J* = 8.3), 7.83 (2H, d, *J* = 8.5 Hz).

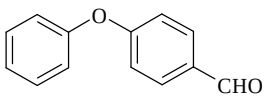
^{13}C NMR ($CDCl_3$): δ_C 21.4, 22.3, 30.7, 38.9, 40.2, 53.3, 55.8, 57.9, 60.3, 109.7, 115.1 (2C), 119.1, 123.8, 126.4, 126.8 (2C), 128.1 (2C), 130.5 (2C), 131.0, 131.1 (2C), 131.5, 131.9, 135.6, 139.8, 144.4, 145.7, 152.2 and 162.5.

HRESIMS (positive ionisation mode), *m/z* found 558.1645 $[M+H]^+$, calculated for $C_{32}H_{32}{}^{79}BrNO_3$ 558.1643.

IR: υ_{max} (neat)/cm^{-1} (ATR platinum gold) 2955, 2875, 1687, 1615, 1591, 1507, 1470, 1391, 1275, 1157 and 1071.

$[\alpha]_D^{25}$ = + 17.2 (*c* = 1.1, MeOH).

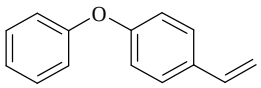
5.2.40 1-Phenoxy-4-benzaldehyde (3.125)



The mixture of *p*-fluorobenzaldehyde (**3.80**) (5.0 g, 40 mmol), phenol (**3.124**) (3.5 g, 40 mmol) and K_2CO_3 (0.8 mmol) were dissolved in DMF (10 ml) and heated at reflux for 1 h under microwave (100 °C). The reaction ws then cooled to room temperature filtered and acidified with HCl (pH indicator). The reaction mixture was extracted with EtOAc (3 x 50 ml), washed with brine and concentrated to a crude solid. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.125** (7.2 g, 90%) yield as a white solid.

^{1}H NMR ($CDCl_3$): δ_H 7.00 (2H, d, *J* = 8.7 Hz), 7.02 (1H, d, *J* = 7.8 Hz), 7.16 (2H, t, *J* = 7.8 Hz) 7.34 (2H, t, *J* = 7.8 Hz), 7.76 (2H, d, *J* = 8.7 Hz), 9.85 (1H, s, C<u>H</u>O).
^{13}C NMR ($CDCl_3$): δ_C 117.6 (2C), 120.4 (2C), 124.9 (2C), 130.1, 131.3, 131.9 (2C), 155.1, 163.2, 190.7 (CHO).
HRESIMS (positive ionisation mode), *m/z* found 199.0759 $[M+H]^+$, calculated for $C_{13}H_{10}O_2$ 199.0759.
IR: υ_{max} (neat)/cm^{-1} 3421, 2845, 1725, 1688, 1606, 1586, 1505, 1489, 1423, 1287, 1242, 1197, 873 and 686.

5.2.41 1-Phenoxy-4-vinylbenzene (3.126)



t-BuOK (1.9 g, 16.7 mmol) was added at 0 ^oC to a suspension of triphenylphosphonium methyl iodide (5.2 g, 13.9 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of **3.125** (2.2 g, 10.8 mmol) in dry THF (5ml). The mixture was stirred at room temperature for 15 h (TLC). Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography gave **3.126** (2.0 g, 95%) as a yellow oil.

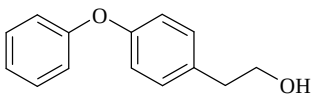
^{1}H NMR ($CDCl_3$): δ_H 5.19 (1H, d, *J* = 10.4 Hz, *cis* C$\underline{H}_2$CH), 5.65 (1H, d, *J* = 17.4 Hz, *trans* C$\underline{H}_2$CH), 6.64 (1H, dd, *J* = 17.4, 10.4 Hz $CH_2C\underline{H}$), 6.89 (2H, d, *J* = 8.3 Hz ArH), 6.95 (2H, d, *J* = 8.4 Hz ArH),7.02 (2H, d, *J* = 8.6 Hz ArH), 7.21 (2H, d, *J* = 8.5 Hz ArH

^{13}C NMR ($CDCl_3$): δ_C 112.6, 117.2 (2C), 120.4 (2C), 125.6 (2C), 128.8, 131.2, 131.9 (2C), 135.8, 155.1 and 156.5.

HRESIMS (positive ionisation mode), *m/z* found 199.0967 $[M+H]^+$, calculated for $C_{14}H_{12}O$ 197.0966.

IR: υ_{max} (neat)/cm^{-1}: 3048, 2931, 1690, 1589, 1485, 1436, 1237, 1181, 1095, 994, 873, 748 and 686.

5.2.42 2-(4-Phenoxyphenyl)ethanol (3.127)



$BH_3{\cdot}S(CH_3)_2$ (5.5 mmol, 5M) was added at 0 ºC to a solution of **3.126** (1.1 g, 5.4 mmol) in dry THF (10ml), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (15.2 mmol) were added dropwise over 30 min, then stirred overnight at 0 ºC. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 8:2) gave **3.127** (0.99 g, 85%) as a colourless oil.

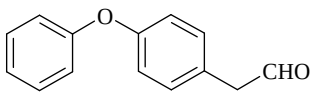
^{1}H NMR ($CDCl_3$): δ_H 2.79 (2H, t, *J* = 6.6 Hz C$\underline{H}_2$$CH_2$OH), 3.85 (2H, t, *J* = 6.6 Hz, CH_2C$\underline{H}_2$OH), 6.99 (2H, d, *J* = 8.6 Hz), 7.01 (1H, d, *J* = 7.8 Hz), 7.14 (2H, t, *J* = 7.8 Hz) 7.20 (2H, t, *J* = 7.8 Hz), 7.35 (2H, d, *J* = 8.6 Hz).

^{13}C NMR ($CDCl_3$): δ_C 38.5, 65.3, 117.1 (2C), 121.4 (2C), 125.3 (2C), 130.1, 131.3, 131.9 (2C), 153.1 and 156.9.

HRESIMS (positive ionisation mode), *m/z* found 215.1073 $[M+H]^+$, calculated for $C_{14}H_{14}O_2$ 215.1072.

IR: υ_{max} (neat)/cm^{-1} 2931, 2845, 1725, 1688, 1606, 1586, 1505, 1489, 1423, 1287, 1242, 1197, 873 and 686.

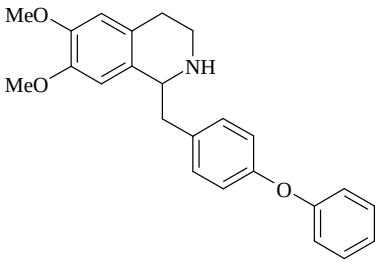
5.2.43 2-(4-Phenoxyphenyl)acetaldehyde (3.128)



IBX (**3.67**) (5 mmol) was dissolved in DMSO (20ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.127** (0.68 g, 4.3 mmol) dissolved in DMSO (5ml) was added, and the reaction was stirred at room temperature for 12 h monitored by TLC. Upon completion of the reaction the mixture was diluted with water followed by the extraction with EtOAc, the organic layer was washed several times with water and concentrated to a give the desired product. Compound **3.128** was isolated as a yellow solid (0.90 g, 98%).

^{1}H NMR ($CDCl_3$): δ_H 3.59 (2H, d, J = 2.2 Hz, C$\underline{H}_2$CHO), 6.91-6.94 (3H, m, ArH), 7.01-7.11 (3H, m, ArH), 7.22-7.28 (3H, m, ArH), 9.67 (1H, t, J = 2.5 Hz, C$\underline{H}$O).
^{13}C NMR ($CDCl_3$): δ_C 49.7, 118.6 (2C), 119.2 (2C), 123.4, 126.5, 129.8 (2C), 130.9 (2C), 156.7, 157.0 and 199.2 (CHO).
HRESIMS (positive ionisation mode), *m/z* found 213.0916 $[M+H]^+$, calculated for $C_{14}H_{12}O_2$ 213.0915.
IR: υ_{max} (neat)/cm^{-1} 2923, 2852, 1731, 1685, 1611, 1581, 1512, 1482, 1422, 1290, 1237, 1196, 1153, 1070, 933, 873 and 688.

5.2.44 6,7-Dimethoxy-1-(4-phenoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (3.130)

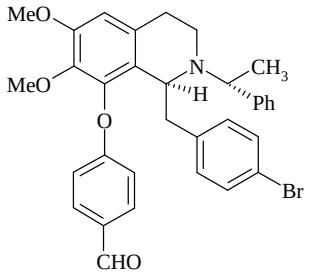


To a solution of 3,4-dimethoxyphenethylamine (**3.129**) (0.79 g, 4.3 mmol), phenylacetaldehyde **3.128** (0.80 g, 3.8 mmol) and the 3 Å molecular sieves (1.0 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (25 mmol) was added

dropwise. The reaction was refluxed for 18 h and upon completion of the reaction the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.130** (1.1 g, 75%) as yellow solid.

^{1}H NMR ($CDCl_3$): δ_H 2.16 (1H, dd, *J* =13.5, 3.2 Hz, H-4*eq*), 2.68-3.20 (3H, m, H-α, H-3, H-4), 3.05 (1H, dd, *J* = 2.4, 10.4, Hz, H- α), 3.18 (1H, ddd, *J* = 3.2, 11.1, 13.2, Hz, H-3*eq*), 3.65 (3H, s, 7-OCH_3), 3.80 (3H, s, 6-OCH_3), 4.35 (1H, dd, *J* = 2.8, 10.4 Hz, H-1), 5.99 (1H, s), 6.31 (1H, s), 6.99 (2H, d, *J* = 8.6), 7.01 (1H, d, *J* = 7.8), 7.14 (2H, t, *J* = 7.8 Hz) 7.20 (2H, t, *J* = 7.8 Hz), 7.35 (2H, d, *J* = 8.6 Hz).
^{13}C NMR ($CDCl_3$): δ_C 23.7, 24.5, 32.5, 40.6, 56.2, 59.4, 117.1 (2C), 121.4 (2C), 125.3 (2C), 126.9, 127.8, 128.6, 130.9 (2C), 132.1, 133.7 (2C), 141.2, 146.9, 153.1 and 156.9.
HRESIMS (positive ionisation mode), *m/z* found 376.1913 $[M+H]^+$, calculated for $C_{24}H_{25}O_4N$ 376.1912.
IR: υ_{max} (neat)/cm^{-1} 2944, 2845, 1662, 1589, 1503, 1487, 1466, 1231, 1199, 1164, 1071, 1011, 871, 839 and 692.

5.2.45 4-[(1*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-yl]oxy]benzaldehyde (3.131)



The mixture of *p*-fluorobenzaldehyde (**3.80**) (0.15 g, 1.24 mmol), phenol **3.104** (0.60 g, 1.24 mmol) and K_2CO_3 (0.8 mmol) were dissolved in DMF (10 ml) and heated at reflux for 1 h under microwave (100 °C). The reaction was then cooled to room temperature filtered and acidified with HCl (pH indicator). The reaction mixture was extracted with EtOAc (3 x 50 ml) was washed with brine and concentrated to a crude solid. Purification by column chromatography gave **3.131** (0.62 g, 85%) as colorless crystals from chloroform m.p. 145-146 ºC.

^{1}H NMR ($CDCl_3$): δ_H 0.79 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$), 2.31 (1H, dd, *J* =16.8, 4.4, H-4), 2.74-2.93 (4H, m, 2x H-α, H-3, H-4), 3.22 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.63 (1H, q, *J* = 6.4 Hz, C<u>H</u>CH$_3$), 3.60 (3H, s, 7-OCH$_3$), 3.81 (3H, s, 6-OCH$_3$), 4.04 (1H, t, *J* = 5.3, 7.8), 6.53 (1H, s, H-5), 7.01-7.09 (6H, m, ArH), 7.20 (3H, ArH), 7.39 (2H, d, *J* = 8.1), 7.86 (2H, d, *J* = 8.6 Hz) and 9.88 (1H, s, CHO).

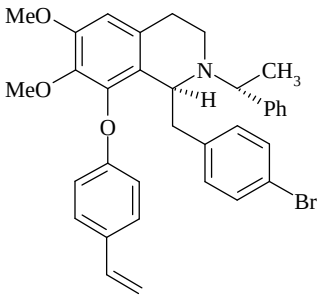
^{13}C NMR ($CDCl_3$): δ_C 21.9, 22.8, 31.9, 39.4, 40.4, 53.9, 56.0, 58.0, 60.9, 110.0, 115.3 (2C), 119.6, 124.1, 126.8, 127.1 (2C), 128.3 (2C), 130.7 (2C), 131.1, 131.3 (2C), 131.6, 132.1 (2C), 139.8, 144.4, 145.7, 152.2, 163.0 and 190.7.

HRESIMS (positive ionisation mode), *m/z* found 586.1594 $[M+H]^+$, calculated for $C_{33}H_{32}{}^{79}BrNO_4$ 586.1593.

IR: υ_{max} (neat)/cm^{-1} (ATR platinum gold) 3479, 2952, 2922, 2855, 1727, 1698, 1686, 1612, 1601, 1582, 1500, 1459, 1377, 1278, 1231, 1157, 1119 and 1071.

$[\alpha]_D^{25}$ = + 20.3 (*c* = 1.1, MeOH).

5.2.46 (1*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-8-(4-vinylphenoxy)-1,2,3,4-tetrahydroisoquinoline (3.132)



t-BuOK (187 mg, 1.67 mmol) was added at 0 ^{o}C to a suspension of triphenylphosphonium methyl iodide (519 mg, 1.39 mmol) in dry THF (10 ml), and stirred for 15 min followed by addition of a solution of 4-[1-(4-Bromobenzyl)-6,7-dimethoxy-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-8-yloxy]benzaldehyde (**3.131**) (0.6 g, 1.08 mmol) in dry THF (5ml). The mixture was stirred at 0 ^{o}C for 12 h (TLC). Upon completion of the reaction the mixture was concentrated under vacuum and partitioned between water and Et_2O. The organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Purification by column chromatography (hexanes:EtOAc, 95:5) gave **3.132** (0.59 g, 95%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ_H 0.80 (3H, d, *J* = 6.3Hz, CHC<u>H</u>$_3$), 2.33 (1H, dd, *J* =16.6, 4.2 Hz, H-4), 2.76-2.96 (4H, m, 2x H-α, H-3, H-4), 3.25 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.69 (1H, q, *J* = 6.3 Hz, C<u>H</u>CH$_3$), 3.63 (3H, s, 7-OCH$_3$), 3.84 (3H, s, 6-OCH$_3$), 4.08 (1H, t, *J* = 5.3, 7.8 Hz, H-1), 5.19 (1H, d, *J* = 10.5 Hz C<u>H</u>$_2$CH, *cis*), 5.62 (1H, d, *J* = 16.9 Hz C<u>H</u>$_2$CH, *trans*), 6.59 (1H, dd, *J* = 16.9, 10.5 Hz CH$_2$C<u>H</u>), 6.61 (1H, s, H-5), 7.09-7.17 (6H, m, ArH), 7.25 (3H, ArH), 7.40 (4H, m, ArH).

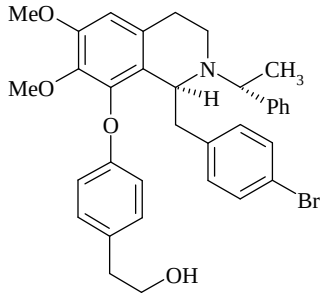
^{13}C NMR ($CDCl_3$): δ_C 21.7, 22.9, 32.3, 39.6, 40.4, 53.9, 56.0, 58.0, 60.9, 109.8, 114.6, 115.2 (2C), 119.8, 124.6, 126.9, 127.5 (2C), 128.6 (2C), 129.7 (2C), 131.3, 131.5 (2C), 131.7, 132.4 (2C), 135.9, 140.1, 142.9, 145.9, 152.4 and 163.0.

HRESIMS (positive ionisation mode), *m/z* found 584.1801 $[M+H]^+$, calculated for $C_{34}H_{34}{}^{79}BrNO_3$ 584.1800.

IR: υ_{max} (neat)/cm^{-1} 2931, 1602, 1503, 1490, 1462, 1345, 1278, 1166, 1112, 1071, 987, 835, 765 and 699.

$[\alpha]_D{}^{25}$ = + 63.3 (*c* = 1.1, $CHCl_3$).

5.2.47 2-[4-[[(1*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-yl]oxy]phenyl]ethanol (3.133)



$BH_3{\cdot}S(CH_3)_2$ (0.91 mmol, 5M) was added at 0 ºC to a solution of **3.132** (0.52 g, 0.9 mmol) in dry THF (10ml), and stirred for 4 h at room temperature. The mixture was cooled to 0 ºC and the solution of NaOH (10.0 mmol) in EtOH/H_2O (2:1, 30 ml) followed by H_2O_2 (2.5 mmol) were added dropwise over 30 min, then stirred overnight at 0 ºC. Upon completion of the reaction the mixture was extracted with EtOAc (3 x 30 ml) and the organic layer was washed with water, brine and dried over $MgSO_4$ and concentrated. Compound **3.133** was isolated after chromatography (hexanes:EtOAc, 8:2) as a colourless liquid (0.36 g, 70%).

^{1}H NMR ($CDCl_3$): δ_H 0.78 (3H, d, *J* = 6.3Hz, CHC<u>H</u>$_3$), 2.30 (1H, dd, *J* =16.6, 4.2 Hz, H-4), 2.72-2.92 (6H, m, 2x H-α, H-3, H-4, C<u>H</u>$_2$CH$_2$OH), 3.23 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.65 (1H, q, *J* = 6.3 Hz, C<u>H</u>CH$_3$), 3.71 (2H, t, *J* = 6.3 Hz, CH$_2$C<u>H</u>$_2$OH), 3.76 (3H, s, 7-OCH$_3$), 3.90 (3H, s, 6-OCH$_3$), 4.20 (1H, t, *J* = 5.3, 7.8, H-1), 6.60 (1H, s, H-5), 7.04-7.11 (6H, m, ArH), 7.19 (3H, ArH), 7.35-44 (4H, m, ArH).

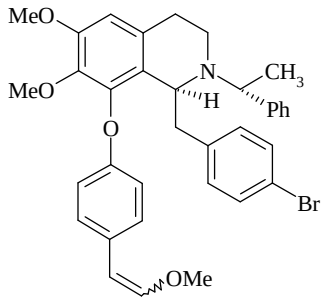
^{13}C NMR ($CDCl_3$): δ_C 21.6, 32.4, 38.5, 40.5, 46.5, 53.7, 53.9, 58.0, 60.6, 62.8, 109.5, 114.2, 114.9 (2C), 119.5, 124.2, 126.5, 127.3 (2C), 128.2 (2C), 129.3 (2C), 131.1, 131.3 (2C), 131.5, 132.2 (2C), 135.7, 139.7, 142.5, 145.3 and 152.2.

HRESIMS (positive ionisation mode), *m/z* found 602.1906 $[M+H]^+$, calculated for $C_{34}H_{36}{}^{79}BrNO_4$ 602.1905.

IR: υ_{max} (neat)/cm^{-1} 3429, 2938, 1604, 1503, 1490, 1462, 1347, 1276, 1168, 1119, 1071, 989, 824, 774 and 701.

$[\alpha]_D^{25}$ = + 40.8 (*c* = 1.0, $CHCl_3$).

5.2.48 (1*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-8-[4-(2-methoxyvinyl)phenoxy]-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (3.134)



To a suspension of (methoxymethyl)triphenylphosphonium chloride (1.2 g, 3.7 mmol) in dry THF (10 ml) *t*-BuOK (0.49 g, 4.4 mmol) was added at 0 ^{o}C for 15 min. Then **3.131** (0.54 g, 0.92 mmol) in dry THF (5 ml) was added, the reaction mixture was stirred for 1 h at rt. Upon completion of the reaction the mixture was concentrated under vacuum and partitioned between water and Et_2O. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layer was washed with water and brine, dried and concentrated under vacuum. Flash column chromatography (hexanes:EtOAc, 7:3) gave **3.134** (0.51 g, 90%) as a yellow oil.

^{1}H NMR ($CDCl_3$): δ_H 0.76 (3H, d, *J* = 6.3 Hz, CHC<u>H</u>$_3$), 2.26 (1H, dd, *J* =16.6, 4.2, H-4), 2.72 (1H, dd, *J* = 5.6, 14.1 Hz, H-3), 2.80-2.86 (2H, m, H-α, H-4), 3.01 (1H, dd, *J* = 5.6, 10.4, H-α), 3.22 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.62 (1H, q, *J* = 6.3 Hz, C<u>H</u>CH$_3$), 3.68 (3H, s, OCH$_3$), 3.74 (3H, s, 7-OCH$_3$), 3.89 (3H, s, 6-OCH$_3$), 4.20 (1H, dd, *J* = 2.78, 7.8), 5.20 (1H, d, *J* = 10.5 Hz, C<u>H</u>OMe, *cis*), 5.80 (1H, d, *J* = 16.9 Hz, C<u>H</u>OMe, *trans*), 6.19 (1H, d, *J* = 10.5 Hz, C<u>H</u>CHOMe, *cis*), 6.59 (1H, dd, *J* = 16.9, 10.5 Hz, CH$_2$C<u>H</u>), 6.58 (1H, s, H-5), 6.86 (2H, m, ArH), 6.95 (1H, d, *J* = 16.9 Hz C<u>H</u>OMe, *trans*), 7.08-7.21 (8H, m, ArH), 7.39 (2H, ArH), 7.53 (1H, ArH).

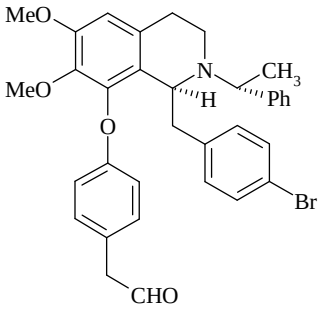
^{13}C NMR ($CDCl_3$): δ_C 22.0, 22.6, 32.5, 39.4, 40.4, 53.8, 56.0, 56.5, 57.9, 60.5, 60.7, 104.5, 105.2, 109.4, 114.5, 115.0 (2C), 119.4, 124.8, 126.3, 127.1 (2C), 128.2 (2C), 129.5 (2C), 130.5, 131.1, 131.4, 135.9, 140.2, 142.9, 145.2, 147.9, 152.1, 156.2 and 156.5.

HRESIMS (positive ionisation mode), *m/z* found 612.1750 $[M+H]^+$, calculated for $C_{35}H_{34}O^{79}BrNO_4$ 612.1749.

IR: υ_{max} (neat)/cm^{-1} 2933, 1608, 1505, 1497, 1465, 1335, 1268, 1177, 1118, 1070, 966, 833 and 701.

$[\alpha]_D^{25}$ = + 33.4 (*c* = 1.1, $CHCl_3$).

5.2.49 2-[4-[[(1*S*)-1-(4-Bromobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-yl]oxy]phenyl]acetaldehyde (3.135)



Method 1:

IBX (**3.67**) (0.15 g, 0.57 mmol) was dissolved in DMSO (10ml) and the dissolution of IBX (**3.67**) required 10-15 min. The phenylethanol **3.133** (0.34 g, 0.57 mmol) dissolved in DMSO (5ml) was added and the reaction was stirred at room temperature for 15 h monitored by TLC. The reaction was diluted with water followed by the extraction with

EtOAc, the organic layer was washed several times with water and concentrated to a give the desired product. Compound **3.135** was isolated as a colourless solid (0.24 g, 70%).

Method 2: Hydrolysis of **3.134**

Formic acid (3 ml) was added to a solution of **3.134** (0.1 g, 0.16 mmol) in CH_2Cl_2 (10 ml) The reaction mixture was stirred for 48 hr at the room temperature, then diluted with water followed by the extraction with CH_2Cl_2, the organic layer was washed several times with water and concentrated to give **3.135** (76 mg, 75%) as a colourless solid.

^{1}H NMR ($CDCl_3$): δ_H 0.80 (3H, d, *J* = 6.4 Hz, CHC$\underline{H}_3$), 2.32 (1H, dd, *J* =16.8, 4.4 Hz, H-4), 2.76-2.93 (4H, m, 2x H-α, H-3, H-4), 3.22 (1H, dt, *J* = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.59-363 (3H, m, C$\underline{H}_2$CHO, C$\underline{H}$CH$_3$), 3.62 (3H, s, 7-OCH$_3$), 3.83 (3H, s, 6-OCH$_3$), 4.19 (1H, d, *J* = 5.3, 7.8 Hz), 6.52 (1H, s, H-5), 6.98-7.12 (11H, m, ArH), 7.45 (2H, ArH), 9.85 (1H, t, *J* = 2.4 Hz, CHO).

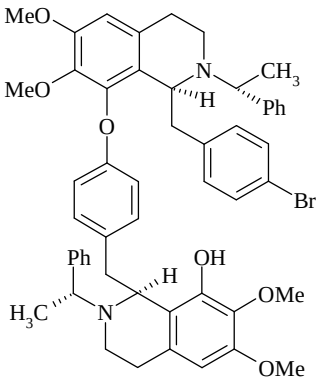
^{13}C NMR ($CDCl_3$): δ_C 21.9, 22.6, 39.4, 40.4, 53.9, 56.0, 57.9, 60.5, 60.7, 104.5, 109.4, 114.5, 115.0 (2C), 119.4, 126.3, 127.1 (2C), 128.2 (2C), 129.5 (2C), 130.6, 131.1, 131.4, 135.9, 140.3, 143.1, 144.9, 148.2, 152.1, 156.2, 156.5 and 199.9.

HRESIMS (positive ionisation mode), *m/z* found 601.1750 $[M+H]^+$, calculated for $C_{34}H_{34}{}^{79}BrNO_4$ 601.1749.

IR: υ_{max} (neat)/cm^{-1} 3496, 2923, 2852, 1731, 1685, 1611, 1581, 1512, 1482, 1422, 1290, 1237, 1196, 1153, 1070, 933, 873 and 688.

$[\alpha]_D^{25}$ = + 7.6 (*c* = 1.0, $CHCl_3$).

5.2.50 (1*S*)-1-[[4-[[(1*S*)-1-(4-bromobenzyl)-6,7-dimethoxy-*N*-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-yl]oxy]phenyl]methyl]-6,7-dimethoxy-2-[(1*R*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-8-ol (3.136)



To a solution of amine alcohol **3.41** (0.18 g, 0.58 mmol), phenylacetaldehyde **3.135** (0.3 g, 0.50 mmol), 3 Å molecular sieves (0.1 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (7:1, v/v, 20 ml), acetic acid (0.1 eq.) was added dropwise. The reaction was refluxed for 18 h and upon completion of the reaction the mixture was diluted with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (hexanes:EtOAc, 9:1) to give **3.136** as a colourless solid (0.12 g, 40%).

^{1}H NMR ($CDCl_3$): δ_H 0.78 (6H, d, J = 6.3 Hz, 2 x CHC$\underline{H}_3$), 2.13 (2H, m, H-3, H-4), 2.30 (1H, dd, J =16.6, 4.2 Hz, H-4), 2.25-2.45 (4H, m, 2x H-α, H-3, H-4), 2.72-2.92 (4H, m, 2x H-α, H-3, H-4), 3.23 (1H, dt, J = 13.6, 11.7, 5.0, 2.0 Hz, H-3), 3.65 (2H, q, J = 6.3 Hz, 2 x C$\underline{H}$CH$_3$), 3.65 (3H, s, OCH$_3$), 3.76 (3H, s, OCH$_3$), 3.85 (3H, s, OCH$_3$), 3.90 (3H, s, OCH$_3$), 4.18 (1H, t, J = 5.3, 7.8), 4.20 (1H, t, J = 5.3, 7.8 Hz, H-1), 6.54 (1H, s, ArH), 6.60 (1H, s, ArH), 6.79 (2H, d J = 8.4 Hz), 7.04-7.11 (6H, m, ArH), 7.16 (6H, m, ArH), 7.19 (3H, ArH), 7.35-44 (2H, m, ArH).

^{13}C NMR ($CDCl_3$): δ_C 31.8, 32.4, 37.8, 38.5, 45.7, 52.9, 53.7, 53.9, 54.3, 57.3, 58.0, 60.6, 61.7, 62.8, 108.6, 109.2, 113.9, 114.2, 115.3 (2C), 118.6, 119.5, 123.9, 124.2, 126.0, 126.5, 127.0, 127.3 (2C), 127.9, 128.2 (2C), 128.9 (2C), 129.3 (2C), 129.9, 131.1 (2C), 131.3, 131.5, 131.9 (2C), 132.2 (2C), 134.9, 135.7, 137.3, 138.3, 139.7, 142.5, 145.3.

5.3 References

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Appendix: NMR spectra of selected compounds

Plate 1: ^{1}H NMR spectrum of compound 3.26.

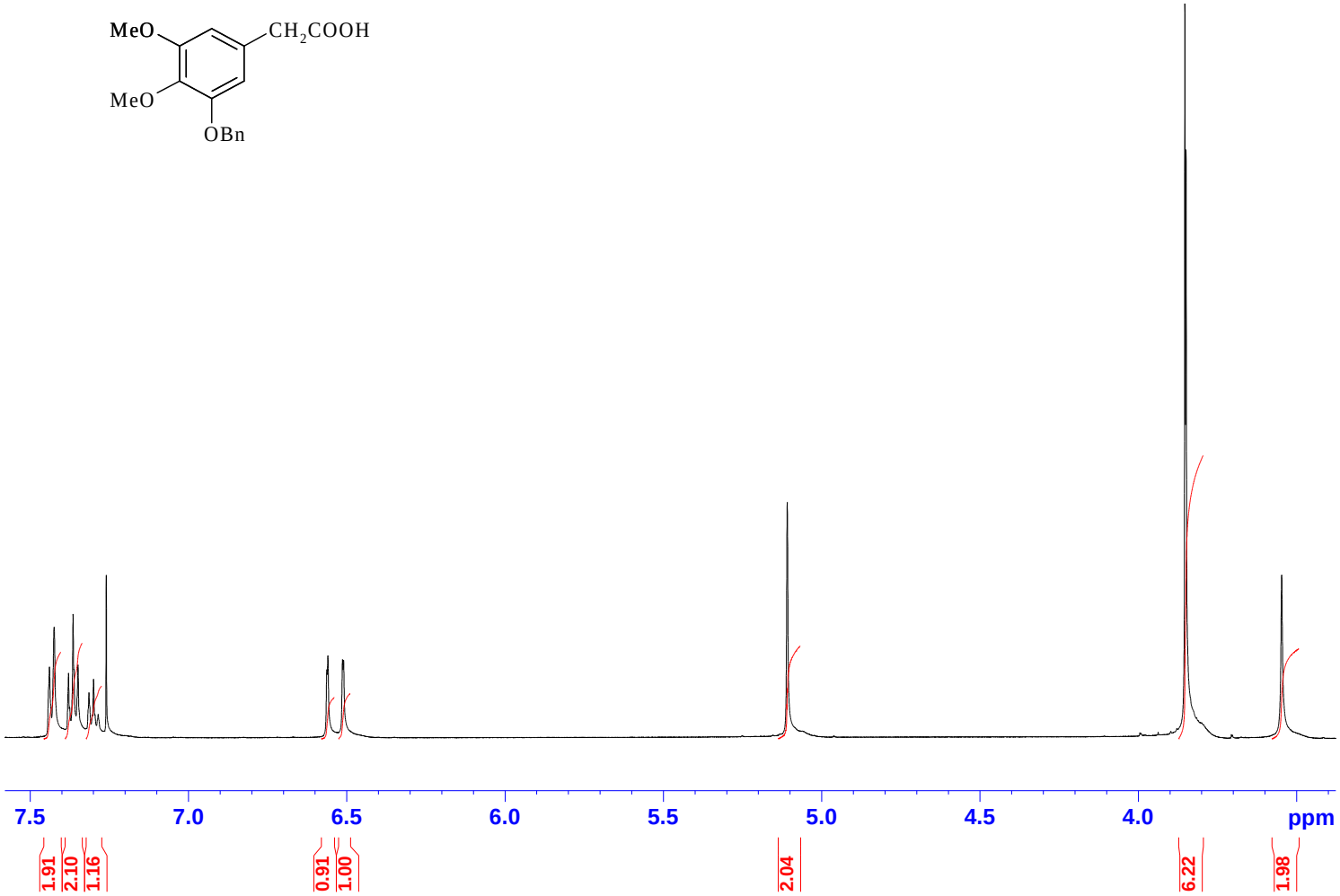

Plate 2: ^{1}H NMR spectrum of compound 3.41.

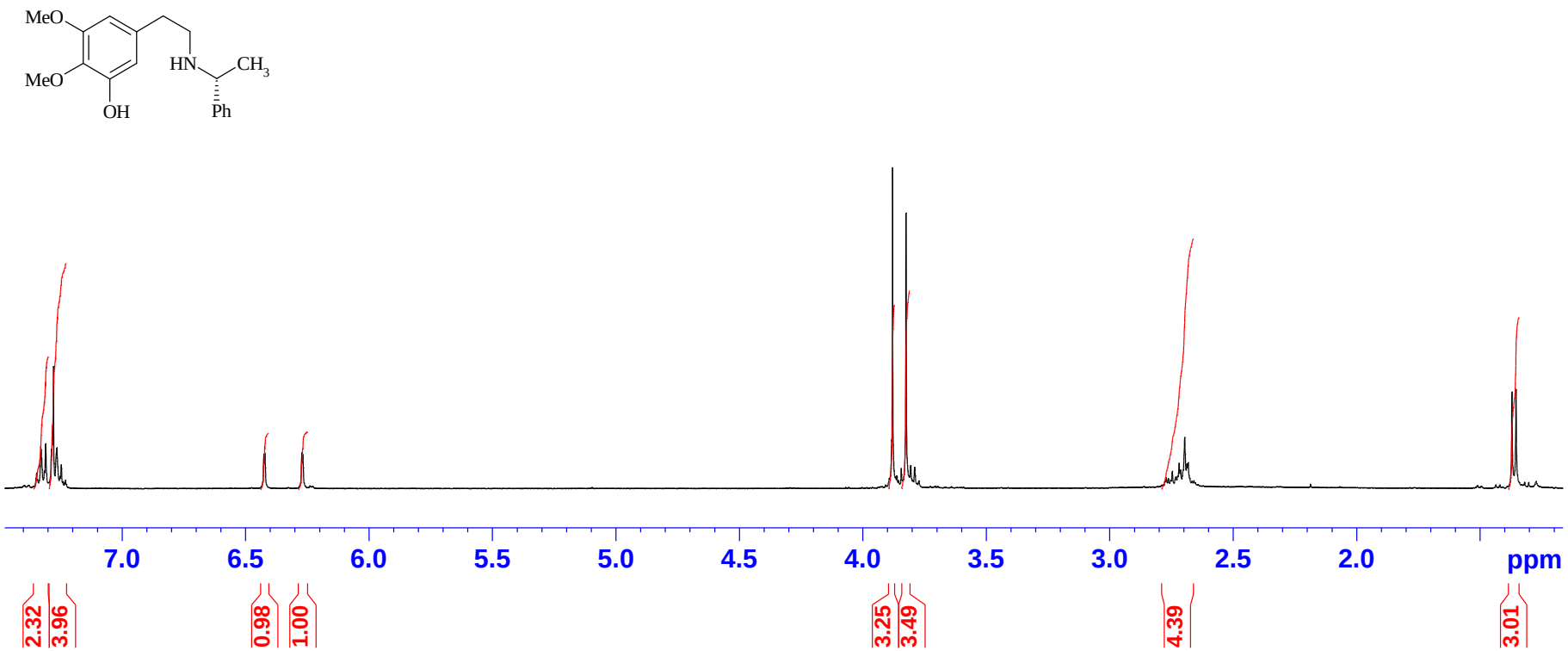

Plate 3: ^{1}H NMR spectrum of a mixture of regioisomers.

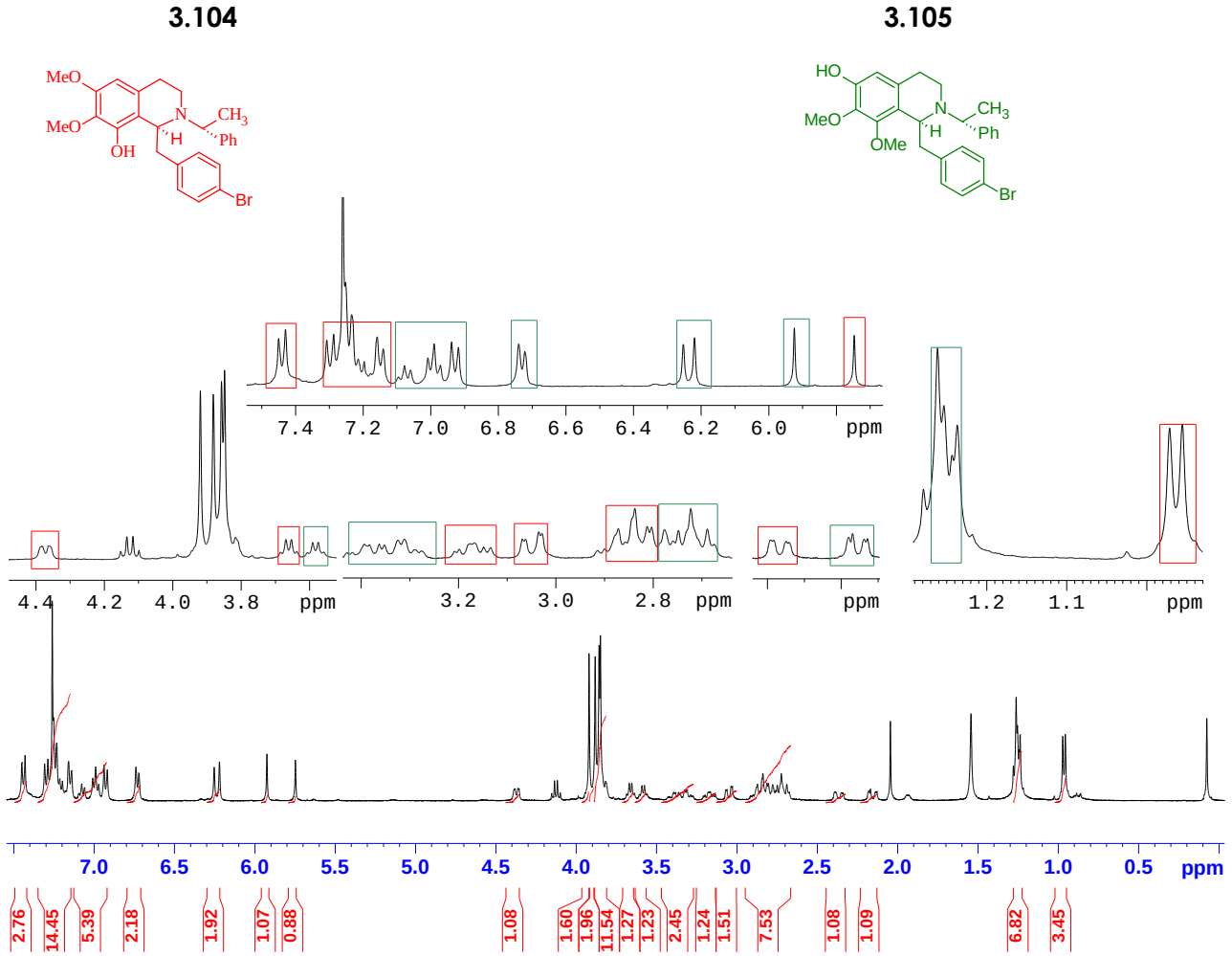

Plate 4: ^{1}H NMR spectrum of compound 3.105 as a major isomer.

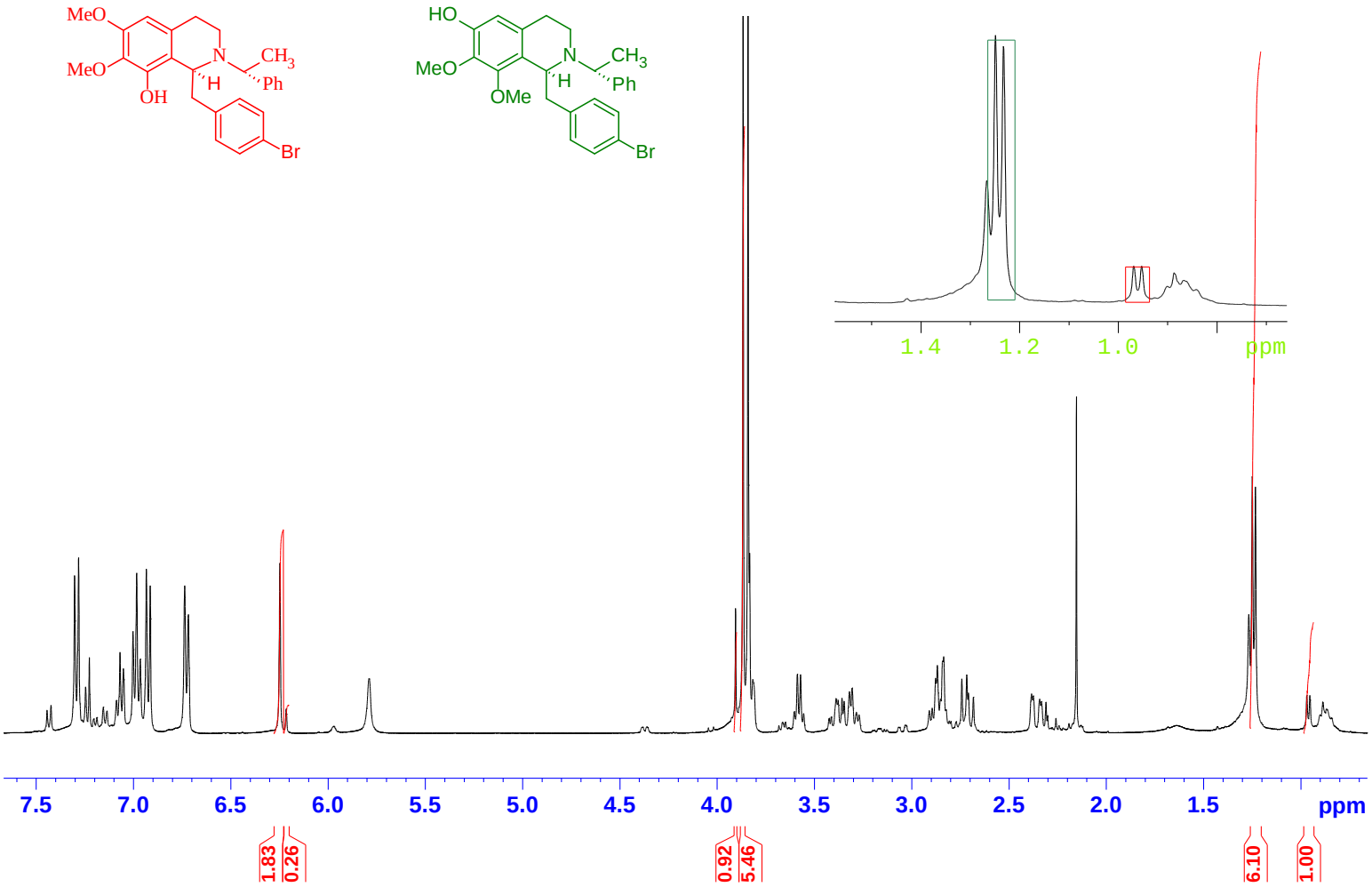

Plate 5: 1H NMR spectrum of compound 3.104.

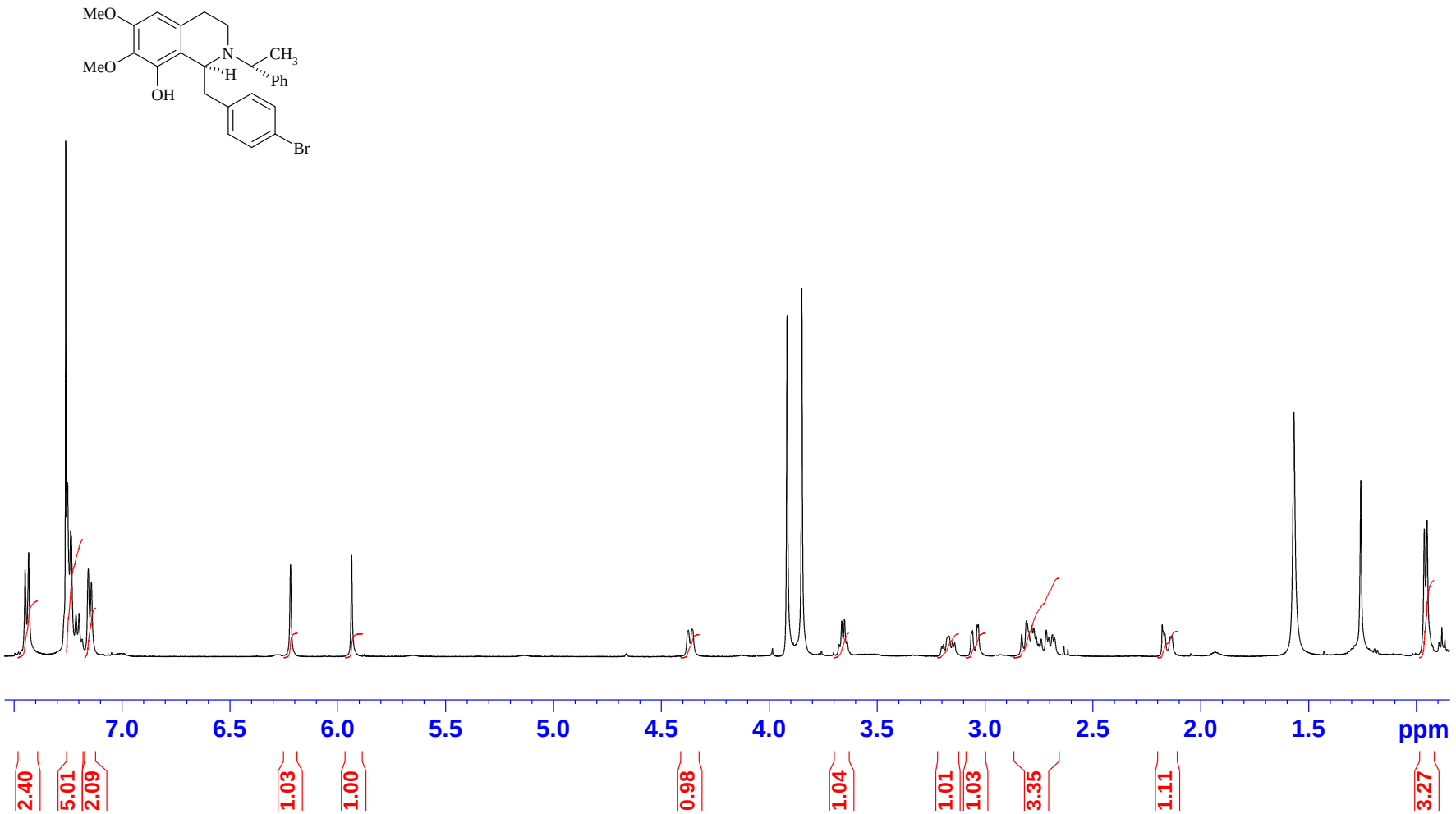

Plate 6: 1H NMR spectrum showing decomposition of compound 3.104.

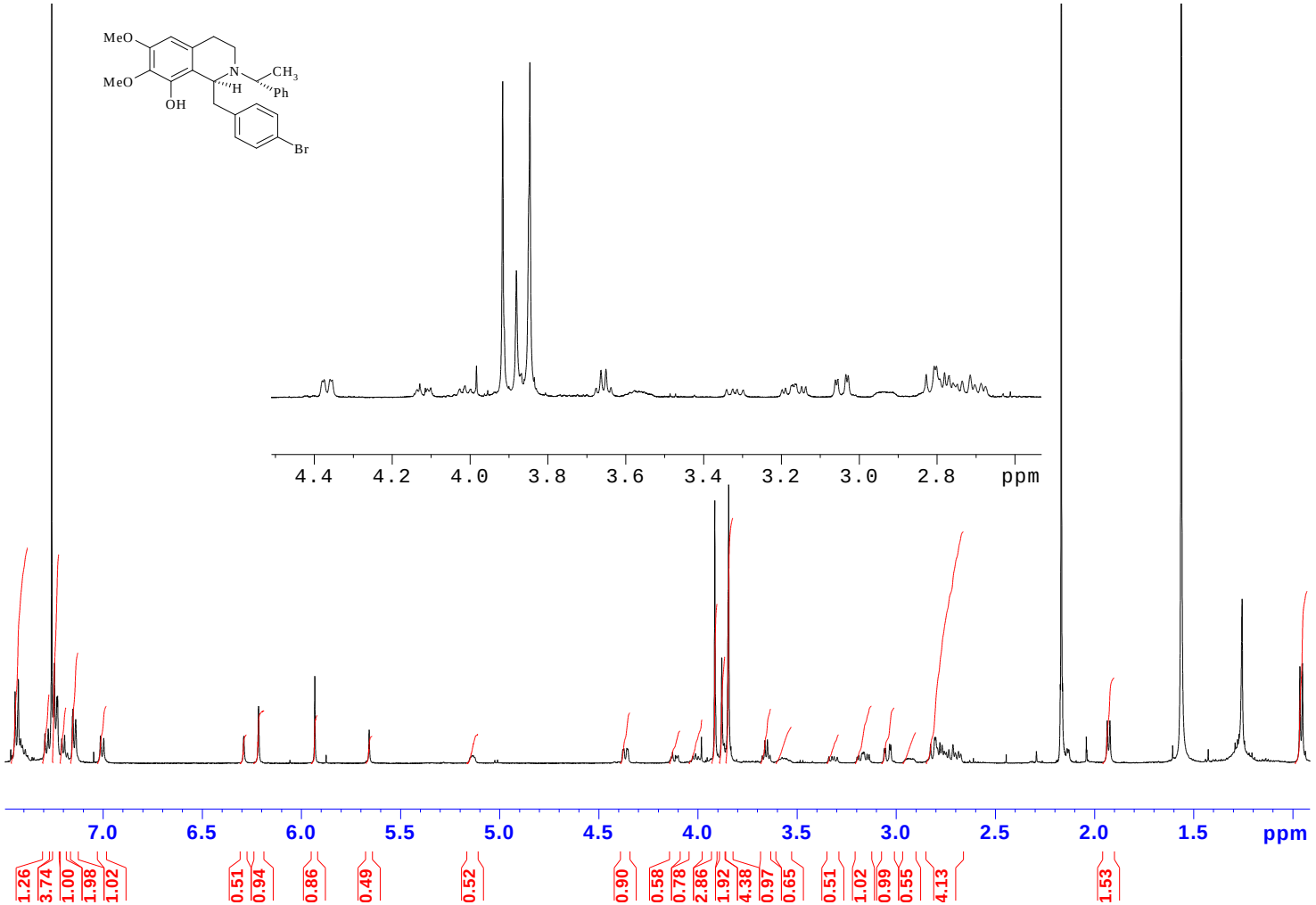

Plate 7: NOESY spectrum of 3.104.

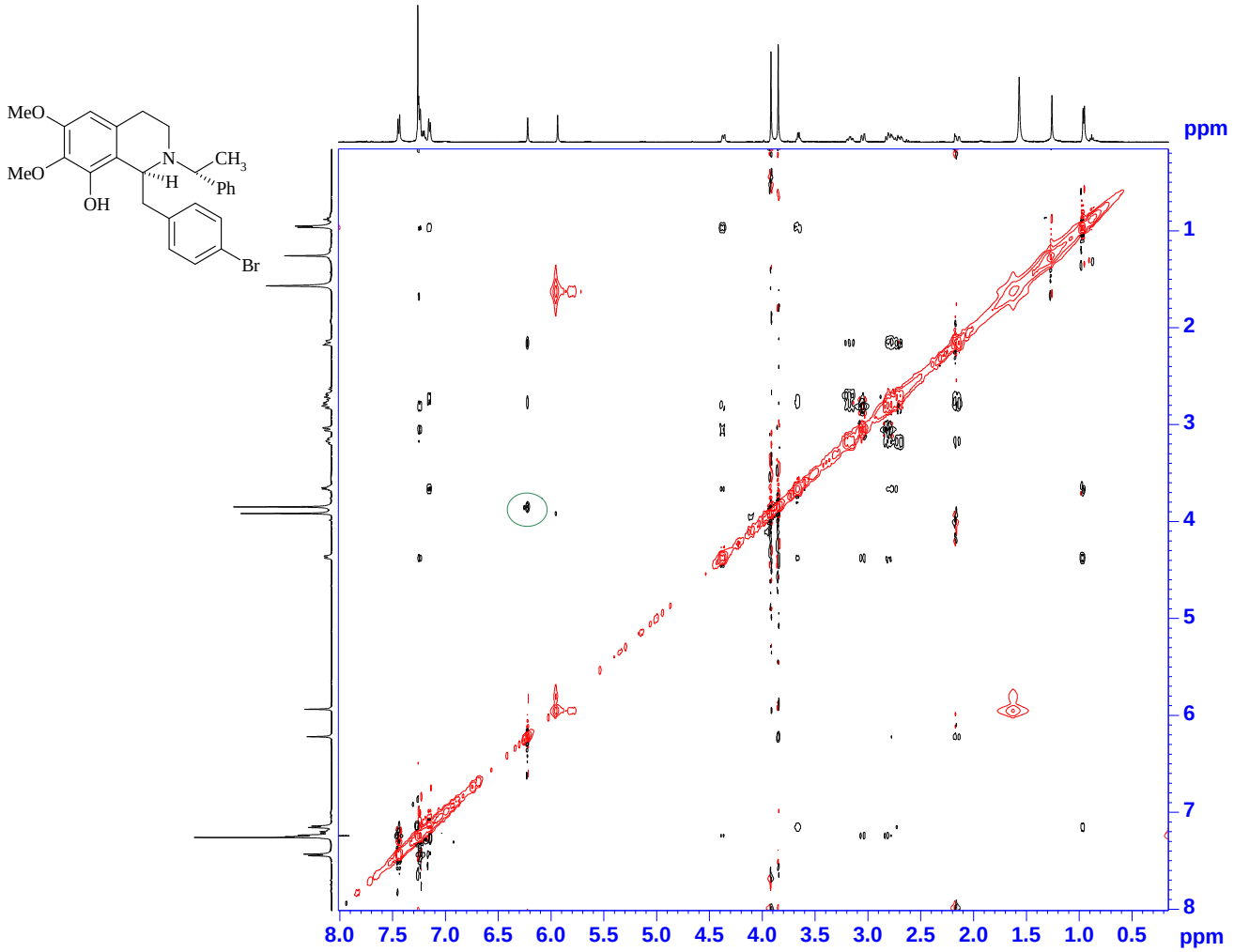

Plate 8: ^{1}H NMR spectrum of 3.131.

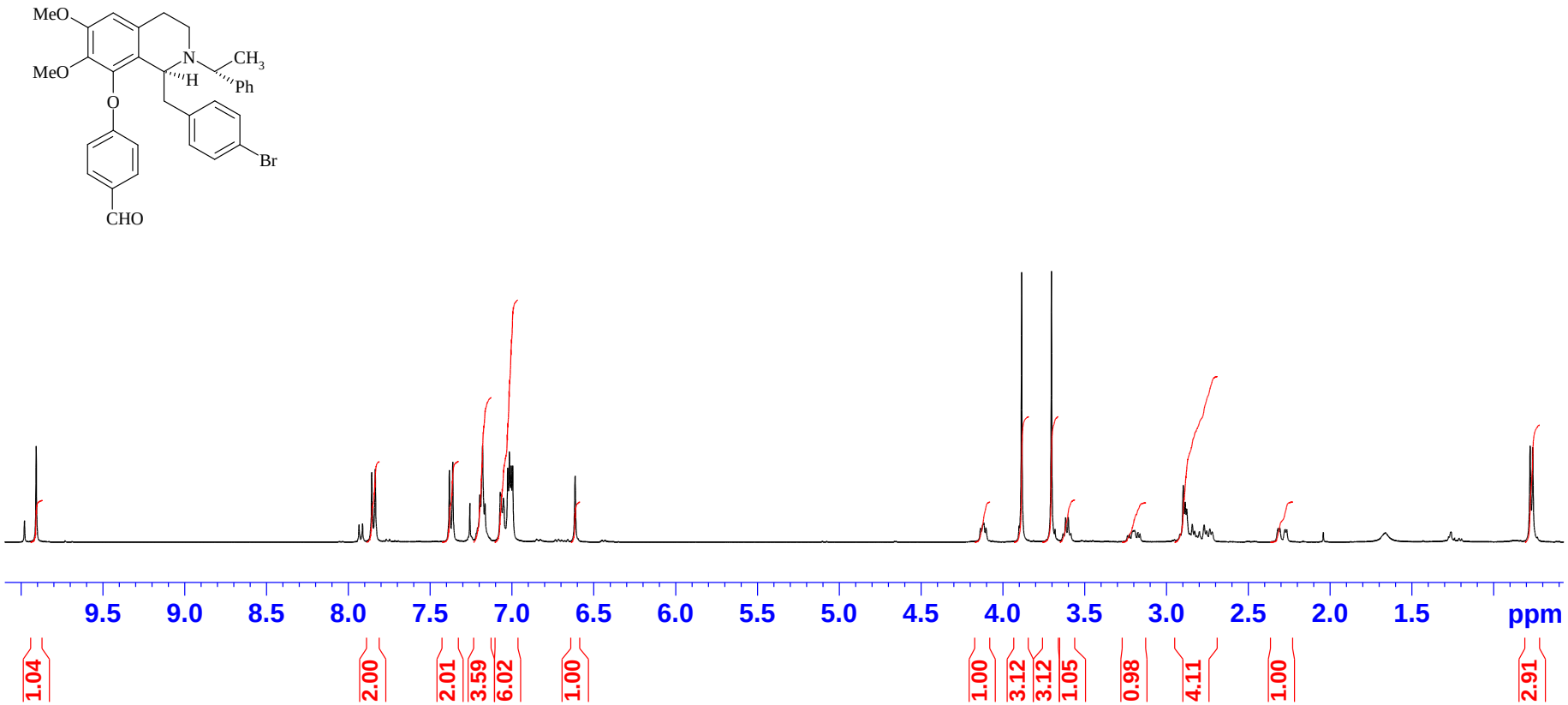

Plate 9: ^{1}H NMR spectrum of 3.134.

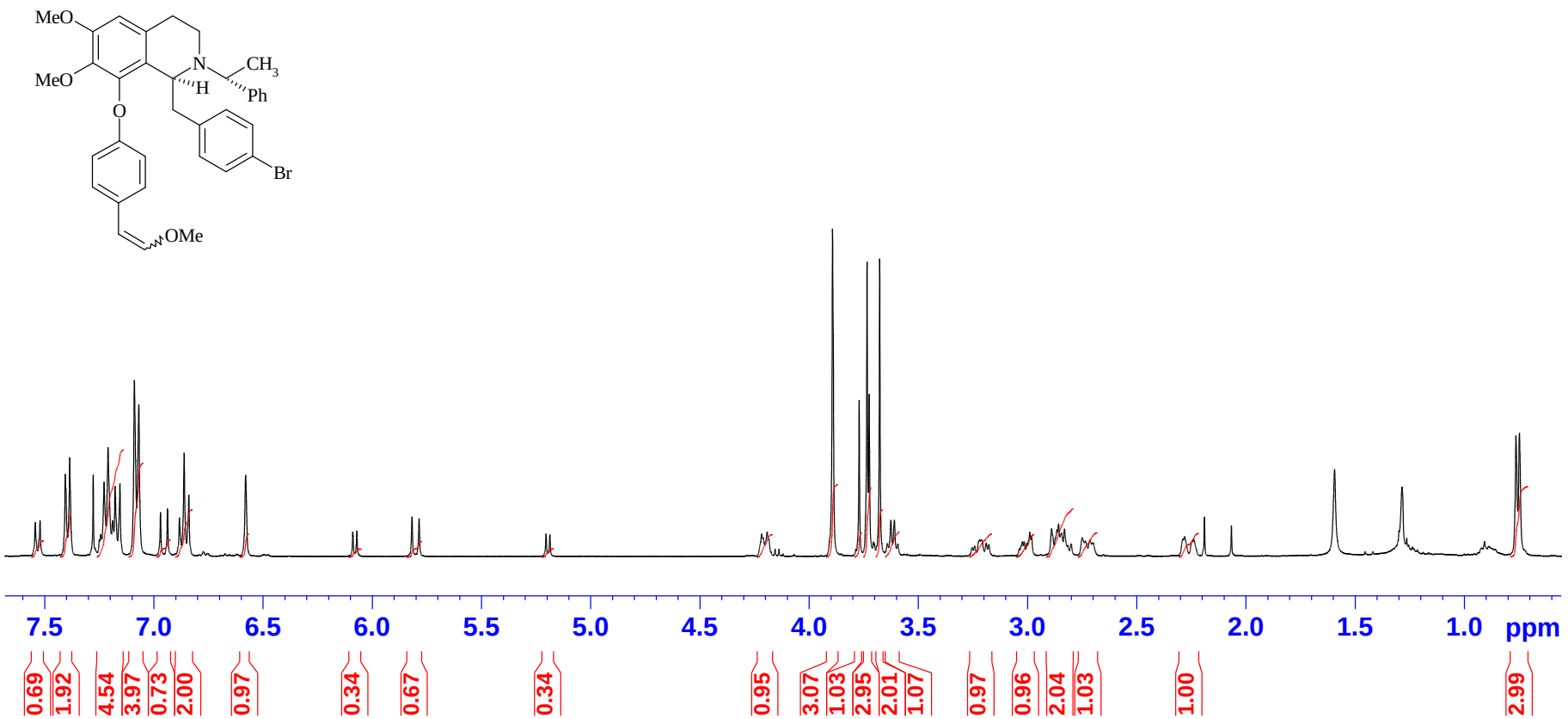

Plate 10: ^{1}H NMR spectrum of 3.135.