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Obinna Osuji

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# THÈSE

PRÉSENTÉE A

**L'UNIVERSITÉ DE BORDEAUX**

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES

POUR L'OBTENTION DU GRADE DE DOCTEUR

SPÉCIALITÉ : CHIMIE ORGANIQUE

Par

Obinna Uchechukwu OSUJI

## **TOWARD THE TOTAL SYNTHESIS OF BBIQ ALKALOIDS: THE TRILOBINE**

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Soutenue le: 19 Novembre 2020

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## **DEDICATION**

This research work is dedicated to Chimamanda, Munachisom, and Chibuikem with special thanks and love to Chizoba Obinna Osuji, wife, friend, and companion. And to the members of my family; for their prayers, unconditional love, and moral support, which has allowed me to complete this great landmark in my career.

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## RÉSUMÉ

BisBenzyl-tetrahydroIsoQuinolin (BBIQ) est une famille très importante de molécules, de par leur nombre, mais aussi du point de vue de leurs activités pharmacologiques. La trilobine et l'isotrilobine (son homologue N-méthylé) font partie de cette famille des BBIQ qui sont classées en différentes sous-classes, ces composés sont des BBIQ de type XXIII, *i.e.* avec trois ponts diaryléthers, reliant les deux benzylisoquinolines d'une manière tête-à-tête, avec un système dibenzodioxiranne. Initialement, la trilobine montrait des activités antiparasitaires (*leishmania sp.*, *trypanosoma cruzi*, *plasmodium falciparum*, . . .), puis des études avaient montré d'autres intérêts avec des activités biologiques anti-protazoaires, anti-inflammatoire et anti-tumorale.<sup>1</sup> Plus récemment, ils ont été évalués en tant que régulateur épigénétique avec des activités d'inhibition des méthyltransférases d'ADN (DNMTs).<sup>2</sup>

Ces produits naturels ont été extraits des parties aériennes de *Cocculus hirsutus*, (Menispermaceae)<sup>3</sup> et des travaux de dérivatization ont été entrepris, mais sans amélioration notable des activités biologiques. La synthèse totale de la trilobine a été rapportée en 1976<sup>4</sup>, mais un grand nombre de challenges persistent pour améliorer cette synthèse ayant un grand nombre d'étapes et de très faibles rendements.

Le but de cette thèse est d'étudier une nouvelle voie de synthèse, courte, efficace et flexible pour permettre la préparation de molécules naturelles mais également d'analogues, par modifications des substituants, de la taille et la nature des cycles.

La synthèse a été menée avec deux étapes clés : l'une est la synthèse des isoquinolines par réaction Pictet-Spengler ou Bischler-Napielralski, en utilisant la dopamine et des acides phénylacétique convenablement substitués. Le but est de protéger les hydroxyles et l'amine, et de permettre la cyclisation en tetrahydroisoquinoline par réaction de Pictet-Spengler. La seconde réaction-clé est la formation de parties diaryléthers réalisée par des réactions de type Ullmann catalysées par des sels de cuivre comme  $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ . Le système dibenzodioxiranne a été formé avec  $\text{K}_2\text{CO}_3$  dans le DMF, avec un excellent rendement.

Le but de ces travaux de recherche est de développer une voie de synthèse, efficace, avec le moins d'étapes possible pour ces structures dimériques et permettre l'accès à des substances biologiquement actives, et à des analogues par modifications des substituants des noyaux aromatiques, et par la taille et la nature du macrocycle.

---

<sup>1</sup> A. Fournet, A. Rojas de Arias, M. E. Ferreira, H. Nakayama, S. Torres de Ortiz, A. Schinini, M. Samudio, N. Vera de Bilbao, M. Lavault, F. Bonté, *Int. J. Antimicrob. Agents*, **2000**, *13*, 189 – 195.

<sup>2</sup> L. Halby; Y. Menon; E B. Kaloun; C. Long; P.B. Arimondo, *PCT Int. Appl.*, **2017**, WO 2017055633.

<sup>3</sup> Y. Menon, C. Long, F. Sautel, P.B. Arimondo, *PCT Int. Appl.*, **2017**, WO 2017055632.

<sup>4</sup> a) Y. Inubushi, Y. Ito, Y. Masaki, T. Ibuka, *Tetrahedron Lett.*, **1976**, *33*, 2857-2860.

b) Y. Inubushi, Y. Ito, Y. Masaki, T. Ibuka, *Chem. Pharm. Bull.*, **1977**, *25*(7), 1636-1644.

## **RÉSUMÉ (in english)**

BisBenzyl-tetrahydroIsoQuinoline (BBIQ) is a family of very important molecules with a great potency from a pharmacological point of view. So, the Trilobine and Isotrilobine (its *N*-methylated homologue) take part to this family of BBIQ, and are classified in different sub-class. These two are BBIQ type XXIII, *i.e.* with three etheral bonds linking the aromatic rings in a head-to-head manner, with a dioxiran system. Initially, trilobine has shown antiparasitic activities (*leishmania sp.*, *trypanosoma cruzi*, *plasmodium falciparum*, . . .) then, studies have shown that has the ability to demonstrate other biological activities in anti-protozoal, anti-inflammatory and, anti-tumour<sup>1</sup>. More recently, they were evaluated as epigenetic regulator with inhibition of DNA methyltransferase (DNMTs) inhibitors<sup>2</sup>.

These natural alkaloids, have been extracted from aerial parts of *Cocculus hirsutus* (menispermaceae),<sup>3</sup> and derivatisation program has been already engaged for preparation of derivatives, but without really improvement of the biological activities. The total synthesis of trilobine was first reported in 1976<sup>4</sup> and several number of challenges and some disadvantages still exist such as tedious reaction conditions, low yields, and multiple sequences.

This synthetic route will use two main key steps, the tetrahydroisoquinoline synthesis using Pictet-Spengler or Bischler-Napieralski reaction, and the formation of diaryl etheral bonds by metalcatalysed Ullman or Ullman-type coupling reaction, catalyzed by a copper salt such as Cu(MeCN)<sub>4</sub>PF<sub>6</sub>. However, we also engaged in the formation of dibenzo-*p*-dioxine compound with K<sub>2</sub>CO<sub>3</sub>/ DMF instead of metalcatalyzed salt and it gave excellent yield. The target in this research is to develop a synthetic strategy that is efficient in having a short route for dimeric structure and provide access to diverse bioactive principles and its analogues.

The goal of this research was geared towards the study of a new synthetic route, short, efficient, and flexible, which will enable us to prepare the natural molecules with different analogues on it through the modification of the aromatic substituents, and the size and nature of the macrocycle.



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## ABBREVIATIONS

Ac	Acetyl
AcOH	Acetic acid
MeCN	Acetonitrile
aq	Aqueous
Ar	Aromatic
BBIQ	BisBenzyltetrahydroIsoQuinoline
BF <sub>3</sub> -OEt <sub>2</sub>	Boron trifluoride etherate
BH <sub>3</sub> -THF	Boron tetrahydrofuran
Bn	Benzyl
Boc	Di-tert-butyloxydicarbonate
Br <sub>2</sub>	Bromine
Cbz	Carboxybenzyl
CHCl <sub>3</sub>	Chloroform
(COCl) <sub>2</sub>	Oxalyl chloride
Cq	Quaternary carbon
Cs <sub>2</sub> CO <sub>3</sub>	Caesium carbonate
Cu(MeCN) <sub>4</sub> .PF <sub>6</sub>	Tetrakis(acetonitrile) copper (I) hexafluorophosphate
Cy	Cyclohexane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
Dibal-H	Diisobutylaluminium hydride
Me <sub>2</sub> CO <sub>3</sub>	Dimethyl carbonate
DMF	Dimethyl formamide
Me <sub>2</sub> SO <sub>4</sub>	Dimethyl sulfate
DMSO	Dimethyl sulfoxide
d	Doublet
dd	doublet of doublet
EtOH	Ethanol
Et <sub>3</sub> N	Triethylamine
Et <sub>2</sub> O	Diethyl ether

EtOAc	Ethylacetate
eq.	Equivalent
FTIR	Fourier Transform Infrared
g	Gram
h	Hour
H <sub>2</sub> SO <sub>4</sub>	Sulphuric acid
HBTU	2(1H-benzotriazol-1-yl)-1, 1, 3, 3-tetramethyl uranium hexafluorophosphate
HCHO	Formaldehyde
HCO <sub>2</sub> H	Formic acid
HRMS	High resolution mass spectrometry
IBX	2-iodoxybenzoic acid
J	constant coupling
KI	Potassium iodide
KMnO <sub>4</sub>	Potassium permanganate
K <sub>2</sub> CO <sub>3</sub>	Potassium carbonate
LiAlH <sub>4</sub>	Lithium aluminium hydride
LiOH	Lithium hydroxide
m	Multiplet
mg	Milligram
mmol	Millimole
M	Concentration (mole per litre)
Me	Methyl
MeOH	Methanol
MeI	Methyl iodide
MeNO <sub>2</sub>	Nitromethane
MHz	Mega Hertz
MS	Molecular sieves
MW	Molecular weight
NaBH <sub>4</sub>	Sodium borohydride
NaCl	Sodium chloride
NaH	Sodium hydride
NaHCO <sub>3</sub>	Sodium bicarbonate

NaIO <sub>4</sub>	Sodium periodate
NaOH	Sodium hydroxide
Na <sub>2</sub> SO <sub>4</sub>	Sodium sulphate
Na <sub>2</sub> SO <sub>3</sub>	Sodium sulphite
NIS	N-iodosuccinimide
NH <sub>4</sub> OAc	Ammonium acetate
NH <sub>4</sub> OH	Ammonium hydroxide
NMP	1-methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
N <sub>2</sub> H <sub>4</sub>	Hydrazine
PCC	Pyridium Chloro Chromate
Ph	Phenyl
POCl <sub>3</sub>	Phosphorus oxychloride
PPh <sub>3</sub>	Triphenylphosphine
PTSA	<i>para</i> -toluenesulfonic acid
ppm	Part per million
py	Pyridine
q	Quadruplet
R <sub>f</sub>	Retention factor
rt	Room temperature
THF	Tetrahydrofuran
s	Singlet
SO <sub>2</sub> Cl <sub>2</sub>	Sulfuryl chloride
SOCl <sub>2</sub>	Thionyl chloride
t	Triplet
TFA	TriFluoroacetic Acid
TLC	Thin Layer Chromatography
TMHD	2,2,6,6-tetramethyl-3,5-heptanedione





## PREAMBLE

The project of total synthesis of trilobine and isotriloquine was engaged some years ago, in Toulouse in the former CNRS and the Institut de Recherche Pierre Fabre joint unit USR 3388 ETaC, Epigenetics, and Targeting of Cancer. Working for one part in isolation and characterization of natural products from natural resources and for another part in chemical modifications of these natural substances, the main goal of this unit was to develop new biological active molecules (mainly for Oncology or Central Nervous System) based on Natural Substances. Several High Throughput Screening campaigns allowed to identify “hits” active on different pharmaceutical targets. One of this campaign looked for identifying epigenetic modulators, as inhibitors of DNA methyltransferase. During this campaign, trilobine and its homologue, the isotriloquine, (Figure 1) were found to have interesting activity towards these methyltransferases, and it was decided to develop a project for the preparation of these molecules by total synthesis, in addition to a program of derivatization by semisynthesis from natural trilobine. Results for the semisynthesis program was already published<sup>2</sup>. The total synthesis program was initiated with the work of Alexis Prieto<sup>5</sup>, a master student.

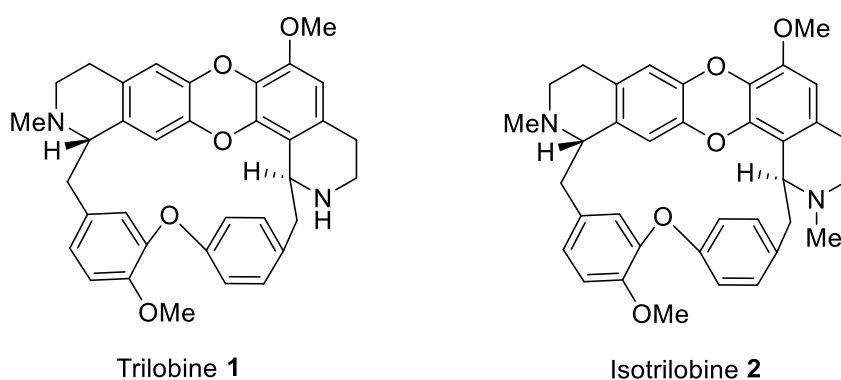


Figure 1 : Structure of trilobine and isotriloquine

For our part, trilobine, isotriloquine and several other related alkaloids were isolated from roots of a Menispermaceae, *Cocculus hirsutus*, with a yield of 100 mg per kilo (and 125 mg per kilo for isotriloquine).

Due to low possibilities for modulation anchorage, only one nitrogen is free for modifications, the derivatization program failed to improve the potency of this series, and the total synthesis becomes more and more relevant for the obtention of biologically active molecules from natural substances.

In 2016, the collaboration between Pierre Fabre Laboratories and the CNRS took a new direction and some projects dealing with chemical modulation of natural substances, including “Total synthesis of Trilobine” were moved to Bordeaux, with the move of Frédéric CANTAGREL from Toulouse to Institut des Sciences Moléculaire, at Université de Bordeaux.

<sup>2</sup> L. Halby, Y. Menon, El B. Kaloun, C. Long, P. B. Arimondo; PCT Int. Appl., **2017**, WO 2017055633 A1 20170406.

<sup>5</sup> Present address, Institut Charles Gerhardt Montpellier, UMR 5253.



## INTRODUCTION

### A. Generality on medicinal plants

Natural products are any substance(s) produced by a living organism that are found in nature. They have pharmacological or biological activities because humans relied much on it for their basic needs either as poison, medicine, or food throughout their existence. Plants play an important role in natural products and they have been characterized according to their (primary or secondary) metabolites<sup>6</sup>.

Medicinal plants are of great value in the field of treatment and cure of diseases in mankind, as most herbs demonstrates great versatility in the health care system. It has now been universally accepted that herbal medicines are used in curing many complex diseases. Especially, the developing countries employ their indigenous herbs practices to cure their prevailing illness based on its method of applications<sup>7</sup>.

The use of medicinal plants for the benefit of mankind has long been sought and it is on the increase day by day. However, the taxonomy of a plant is very essential to understand its communities based on origin and how they are related to each other<sup>8</sup>. Their exploitation has been increasing, once they are recognized as rich sources of natural products with a huge variety of chemical constituents and the most developed specimens of the plant kingdom help to play an important role in the benefit of mankind's health system<sup>9</sup>.

The idea of morphological classification and chemical profile of plants is considered a useful tool towards the characterization and determination of plant families across their chemotaxonomic profile<sup>10</sup>. Secondary metabolites are compounds that perform non-essential functions in plants and are used for protection and defense against predators and pathogens. They are compounds of restricted occurrence and are very useful in chemotaxonomic classification<sup>11</sup>.

Recently, the increase in the studies related to chemotaxonomy is mainly due to the advance of analytical techniques that can detect even traces of chemical compounds and the findings related to this chemotaxonomy are useful for taxonomist, phytochemists, and pharmacologists to solve possible problems.

### B. About alkaloids

In 1819, a German pharmacist, Carl Friedrich Wilhelm. Meißner, laid the foundation of alkaloids chemistry, even if alkaloids-containing plants were known since the early time of Ancient History, attested by Sumerian cuneiform tablets. The name comes from the Medieval Latin *alkali*, himself

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<sup>6</sup> N. B. S. Deus and M. H. Zenk. *Planta Med.* **1982**, 50(5), 427-431.

<sup>7</sup> S.S. Agarwal and M. Paridhavi. *Herbal drug technology*, **2007**, 1 – 3. 1<sup>st</sup> ed. University Press India. Hyderabad;

<sup>8</sup> M. Wink. *Medicines*, **2015**, 2, 251-286.

<sup>9</sup> A. Misra, S. Srivastava. *J. Pharmacogn Nat. Prod.* **2016**, 2, 4-9.

<sup>10</sup> J. M. Hagel, R. Mandal, B. Han, J. Han, D. R. Dinsmore, C. H. Borchers, D. S. Wishart, P. J. Facchini. *Plant Biol.* **2015**, 15, 220-228.

<sup>11</sup> D. K. Liscombe, B. P. MacLeod, N. Loukanina, O. I. Nandi, P. J. Facchini. *Phytochemistry*, **2005**, 66(20), 2500-2520.

coming from the Arabic القالي (*al qaly* which mean “soda”), and the Greek suffix εἶδος (“oid” which means “with the form of”).

Meißner defined it as basic nitrogenous compound of plant origin, which has a complex molecular structure and many pharmacological activities. By the same time, Pierre-Joseph Pelletier isolated alkaloids (with Joseph Bienaimé Caventou) like Strychnino - (1818)(Figure 2– page 14), quinine **4** (1820) (Figure 2– page 14), caffeine **10** (1820)( Figure 4 – page 14) and he defined alkaloids as a cyclic compound containing nitrogen in negative oxidation state which is limited in distribution in the living organism.

The first total synthesis of an alkaloid was the work of Albert Ladenburg in his laboratory, in Kiel, in 1886. Before he had already prepared coniine **11** (in his racemic form - Figure 4 – page 14) from acetaldehyde and 2-methylpyridine<sup>12</sup>, and redefined alkaloids as natural plant compounds that have basic characters and contain at least one nitrogen atom in a heterocyclic ring and they are having biological activities.

Although it is still difficult to define alkaloids, so alkaloids are biologically active basic nitrogenous secondary metabolite obtained from natural resources, mostly optically active and possessing nitrogen, often within a heterocyclic ring, as their structural unit<sup>13</sup>. The “official” definition given by IUPAC is: “*Basic nitrogen compounds (mostly heterocyclic) occurring mostly in the plant kingdom (but not excluding those of animal origin). Amino acids, peptides, proteins, nucleotides, nucleic acids, amino sugars and antibiotics are not normally regarded as alkaloids. By extension, certain neutral compounds biogenetically related to basic alkaloids are included.*”<sup>14</sup>

Alkaloids can be localized in leaves, seeds, or roots of the plants which vary widely depending on the species and its organ, the vegetation period of the plant and the environmental conditions such as climate, soil, humidity and others. The natural organism with single alkaloids is rare in instances because most of them come in mixture form with a wide varies of components as most plants are usually found as salts of various organic and mineral acids.<sup>15</sup>

Probably, over 10000 compounds of alkaloids properties are known to comprise the largest single class of plants secondary metabolites (more and more are often called specific metabolites, in reference to their specific actions in the plant). They possess important biological properties and with the advances in technology, the structural diversity of this secondary/specific metabolites have become the target of a constant investigation by researchers around the globe.<sup>16</sup>

### 1. Extraction of alkaloids:

Extraction of bioactive alkaloids from plant is one of the fundamental and crucial step before any applications. Nowadays, conventional organic solvents (e.g. methanol, alcohol, ethyl acetate, acetone, and chloroform) have been widely used in the extraction of alkaloids from plant materials. Nonetheless, most of these solvents show many intrinsic drawbacks such as environmental pollution,

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<sup>12</sup> A. Ladenburg; *Ber. Dtsch. Chem. Ges.*, **1886**, 19(1), 439 – 441.

<sup>13</sup> R. Hegnauer. *Phytochemistry*, **1988**, 27(8), 2423 – 2427.

<sup>14</sup> *Pure & App. Chem.* **1995**, 67, 1307 – 1375.

<sup>15</sup> R. H. F. Manske, and H. L. Holmes: *The alkaloids*, **1958**, 1 – 8.m

<sup>16</sup> I. Umadevi, M. Daniel, S.D. Sabnis. *Advances in Biosciences.* **1988**, 7(1), 79 – 87.

high toxicity and cost<sup>17</sup>. Although the extraction media of the natural product proved to be of novel high-efficiency, which is of great interest in the type of bioactive compound extracted as it may help to prevent various diseases because they possess important biological properties like anti-inflammation, anti-depression, anti-oxidant, anti-diabetic<sup>18</sup> and so on. For example, most of the bisbenzyltetrahydroisoquinoline alkaloids (BBIQs) isolated from *Stephania tetrandra*, have recently been found to exert inhibiting release of histamine, and reducing myocardial oxygen consumption<sup>19</sup>. For our part, extraction of alkaloids (BBIQs and THIQs) was performed from *Cocculus hirsutus* by Long *et al.*<sup>20</sup>

## 2. Classification of alkaloids

The chemical, pharmacological and botanical properties must all be considered in classifying a compound as an alkaloid since the plant species are in the same family often produce bases with a similar biogenetic structure that are convenient with their origin and structure type. Based on this knowledge and speculation, alkaloids are grouped into three main classes<sup>20,21</sup>;

### a. True alkaloids

True alkaloids are compounds in which the nitrogen-containing heterocyclic system is derived from amino acid and are highly active substances with biological activity even in low doses. They appear as a white solid with a bitter taste with some exceptions like nicotine **3**, which is a brown liquid, and the alkaloids are water-soluble salts. True alkaloids occur in the plant either as a free-state, salts or N-oxide. They occur in a limited number of species and families in which decarboxylated amino acid is condensed with a non-nitrogenous structural moiety. Examples of true alkaloids includes biologically active alkaloids as quinine **4**, strychnine **5**, morphine **6** and others (Figure 2).

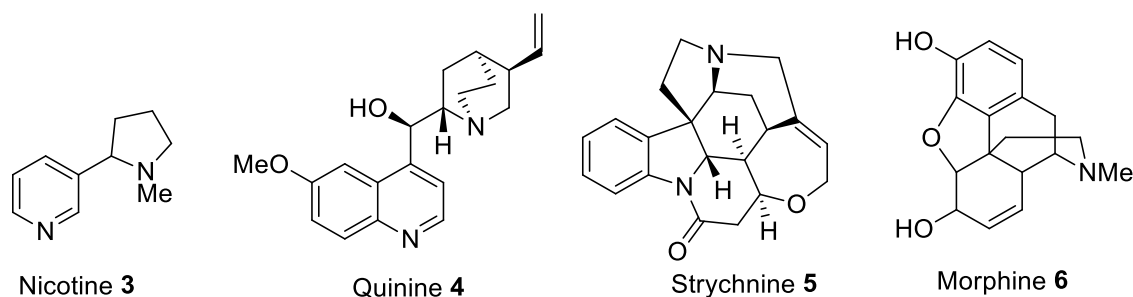


Figure 2 : Example of true alkaloids

<sup>17</sup> L. Duan, W. H. Zhang, Z. H. Zhang, E. H. Liu, L. Guo. *Microchem. J.* **2019**, *145*, 180 – 186.

<sup>18</sup> (a) L. B. Pagliosa, S. C. Monteiro, K. B. Silva, J. P. De Andrade, J. Dutilh, J. Bastida, M. Cammarota, J. A. Zuanazzi. *Phytomedicine* **2010**, *17*, 698 – 701. (b) M. T. H. Anna, J. K. Karamyan. *Chem. Rev.* **2010**, *110*(8), 4489 – 4497. (c) H. F. Zhang, L. J. Shi, G. Y. Song, Z. G. Cai, C. Wang, R. J. An. *Food Chem. Toxicol.* **2013**, *55*, 70 – 77.

<sup>19</sup> L. Liu, S. Li, Z. Chen. *J. Pharm. Biomed. Anal.* **2012**, *61*, 252 – 255.

<sup>3</sup> Y. Menon, C. Long, F. Sautel, P.B. Arimondo, *PCT Int. Appl.*, **2017**, WO 2017055632.

<sup>20</sup> T. Robinson. in *The Biochemistry of Alkaloids*, 2nd edn. Springer, New York. **1981**, chap 1, pp 20 – 34.

<sup>21</sup> T. Aniszewski. *Alkaloids-Chem. Bio. and Appl.* Elsevier 2<sup>nd</sup> ed. **2005**: 1 – 15.

### b. Proto alkaloids

Proto alkaloids are like true alkaloids, derived from amino acid but they do not contain any heterocyclic system. They are those with a closed ring, being perfect but structurally simple alkaloids in the minority of all alkaloids for example dopamine **7** ephedrine **8**, mescaline **9**, and others.

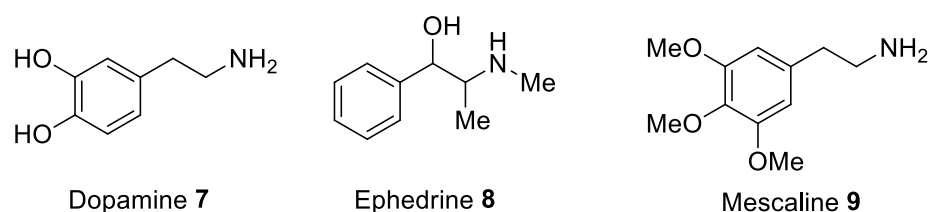


Figure 3 : Example of proto alkaloids

### c. Pseudo alkaloids

Pseudo alkaloids are apparently unrelated to amino acid but they contain nitrogen molecules in their heterocyclic ring system. For example, caffeine **10**, coniine **11**, purine **12**, and others

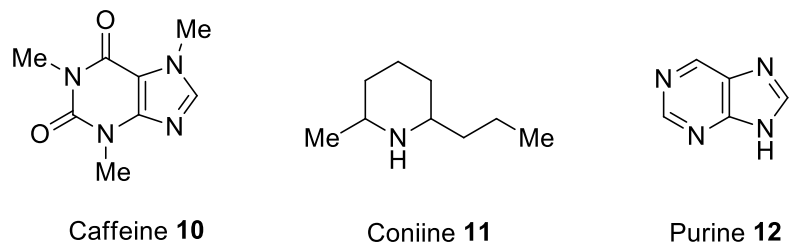


Figure 4 : Example of pseudo alkaloids

## 3. Alkaloids in nature

Alkaloids are basic in nature and form water soluble salts with mineral acids. The degree of basicity varies considerably, depending on the structure of the molecules and the presence or location of the functional groups as most of the alkaloids are crystalline solids and are bitter in taste. Alkaloids are colourless, crystalline compounds but some exceptions are in liquid form like the nicotine. Nicotine **3** is a hygroscopic oil liquid and miscible with water in its base as well as its salt form. It possesses two nitrogenous ring systems: one is pyridine and the other is a pyrrolidine ring system with a potent nerve poison. In lower concentration, nicotine is a stimulant *i.e.* it increases activity, alertness, and memory, which is one of the factors that contribute to the dependence-forming properties of tobacco smoking. While high doses can cause nausea and vomiting. However, the

following table shows different major types of alkaloids, their generic skeletons, and specific examples<sup>22,23</sup>.

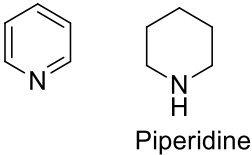
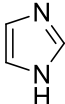
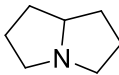
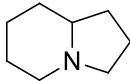
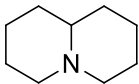
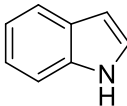
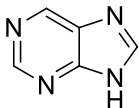
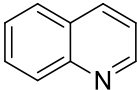
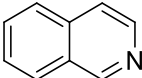
Class	Generic structure	Example
Pyridine and (Nicotinic acid derived)	 Pyridine: <chem>C1=CC=NC=C1</chem> Piperidine: <chem>C1CCNCC1</chem>	Nicotine, Piperine Coniine
Imidazole (Histidine derived)	 Imidazole: <chem>C1=CN=CN1</chem>	Histamine and Pilocarpine
Pyrrolizidines (Ornithine derived)	 Pyrrolizidine: <chem>C1CCN(C1)C2CC2</chem>	Echimidine and Symphitine
Indolizidines (Lysine derived)	 Indolizidine: <chem>C1CCN(C1)C2CC2</chem>	Swainsonine and Castanospermine
Quinolizidine (Lysine derived)	 Quinolizidine: <chem>C1CCN(C1)C2CC2</chem>	Cytisine Lupanine
Indole (Tryptophan derived)	 Indole: <chem>C1=CC=C2C(=C1)C=CN2</chem>	Ergotamine
Purine (Xanthosine derived)	 Purine: <chem>C1=NC2=C(N1)N=CN=C2</chem>	Caffeine, Theobromine
Quinoline (Tryptophan derived)	 Quinoline: <chem>C1=CC=C2C=CC=NC2=C1</chem>	Quinine Quinidine, Cinchonine
Isoquinoline (Tyrosine derived)	 Isoquinoline: <chem>C1=CC=C2C=CC=N2C=C1</chem>	Morphine, Berberine Papaverine, Codeine

Table 1 : Examples of true (or not) alkaloid skeletons.

<sup>22</sup> Z. Řeháček and P. Sajdl. *Ergot Alkaloids: Chemistry, bio effects, biotech.* **1990**, pp.383.

<sup>23</sup> S. D. Sarker and L. Nahar. *Organic and Nat. Prod. Chem.* John Wiley & Sons Ltd, **2007**, 289 – 292.

## C. The BBIQ alkaloids

### 1. The THIQ alkaloids

Simple isoquinoline alkaloids are known to have only one aromatic nucleus and no other cyclic structure except a methylenedioxy substituent, which is mostly derived from only one aromatic amino acid residue like tyrosine moiety. Some families like the Cactaceae, Chenopodiaceae and Fabaceae are known to produce simple isoquinoline alkaloids<sup>24</sup> contrary to Menispermaceae, Monimiaceae where the majority of isoquinoline alkaloids are dimers.

However, the formation of isoquinoline **13** alkaloids usually involves the amine and aldehyde in which several compounds can serve as precursors in specific instances, while the tetrahydroisoquinoline **14** alkaloids are widespread across almost all the families that possess isoquinoline alkaloids<sup>25</sup> (Figure 5).

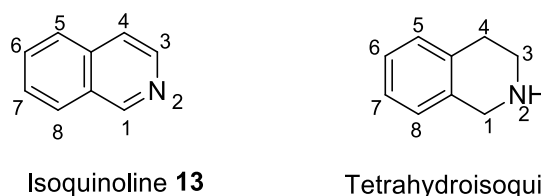


Figure 5 : Skeletal structure and numeration of isoquinoline alkaloids

#### a. Benzyltetrahydroisoquinoline alkaloids:

Some of the benzylisoquinoline **15** like papaverine and benzyltetrahydroisoquinoline alkaloids have gained importance as clinical agents. The majority of benzyltetrahydroisoquinoline **16** alkaloids are isolated from plants with oxygen substituents in 6- and 7-positions, and also in 8-, 11- and 12- positions. This is a characteristic of a large group of isoquinolines that arise biogenetically from benzyltetrahydroisoquinoline precursors<sup>26</sup>. Benzyltetrahydroisoquinoline alkaloids have been observed in plants from the families Berberidaecae, Fumariaceae, Papaveraceae, Ranunculaceae, and Rhamnaceae<sup>27</sup> (Figure 6).

<sup>24</sup> M. D. Menachery, G. L. Lavanier, M. L. Wetherley, H. Guinaudeau and M. Shamma. *J. Nat Prod.* **1986**, 49(5), 745.

<sup>25</sup> D. S. Seigler. *Plant Secondary Metabolism*, **1998**, 579 – 614.

<sup>26</sup> K.W. Bentley. *The Isoquinoline Alkaloids*. **1965**, 41 – 59.

<sup>27</sup> A. Brossi and G. A. Cordell. *The alkaloids: Chemistry and Pharmacology*. **1992**, 41, 6 – 12.



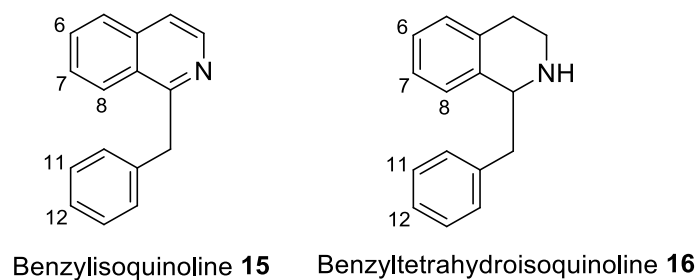


Figure 6 : Skeletal structure of benzyltetrahydroisoquinoline alkaloids

### b. Structures

The bisbenzyltetrahydroisoquinoline alkaloids are structurally constructed from two monomeric benzyltetrahydroisoquinoline units (THIQ) joined by one or more ether bridges. The substituent on the aromatic rings may be hydroxyl (OH) or methoxy (OMe) or methylenedioxy (OCH<sub>2</sub>O) groups. The complexity of bisbenzyltetrahydroisoquinoline alkaloids is the two asymmetric centres, which can be in *R* or *S* configuration. However, these have been a challenge in the identification of new bisbenzyltetrahydroisoquinoline given to the degree of variation of structural features differing in oxidation state or the degree of substitution of the two nitrogen atom (imine, NH, NMe, or quaternary amine)<sup>28,29,26</sup> (Figure 7).

<sup>28</sup> K. P. Guha, P. C. Das, B. Mukherjee, R. Mukherjee, G. P. Juneau, N. S. Bhacca. *Tetrahedron Lett.* **1978**, 17(47), 4241 – 4244.

<sup>29</sup> K. P. Guha, B. Mukherjee, R. Mukherjee. *J. Nat Prod.* **1979**, 42(1), 1 – 84.

<sup>26</sup> K.W. Bentley. *The Isoquinoline Alkaloids.* **1965**, 41 – 59.

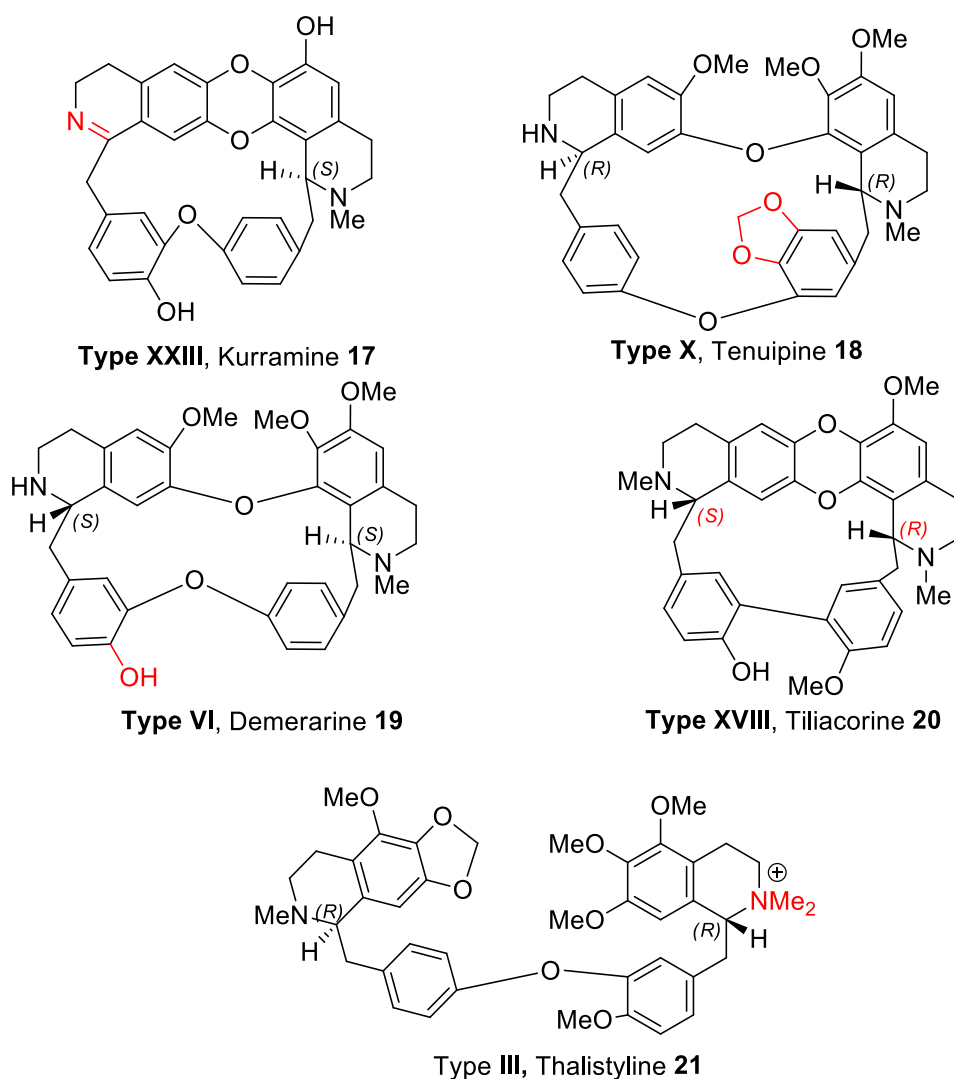


Figure 7 : Structural types of bisbenzyltetrahydroisoquinoline alkaloids

However, over hundreds of bisbenzyltetrahydroisoquinoline alkaloids are known and the two benzyltetrahydroisoquinoline units may be bonded together by one, two or three diaryl ether linkages. When only one diaryl ether linkage is present, the bond involved tail-to-tail or head-to-tail coupling but not head-to-head coupling. If the linkage is two or three diaryl ether, the benzyltetrahydroisoquinoline units can be bonded either head-to-head or head-to-tail, which makes the diversity in the structures of bisbenzyltetrahydroisoquinoline alkaloids, coupled with their known or potential pharmacological activities that have stimulated substantial interest in their synthesis. The consideration of the head and tail nomination will be explained in the next part.

#### b. Numerotation

The bisbenzyltetrahydroisoquinoline alkaloids are structurally constructed of two monomeric benzyltetrahydroisoquinoline unit joined by one or more ether bridges. More so the direct carbon-to-carbon biphenyl and methylenedioxy linkages are also found in some of these units. The bisbenzyltetrahydroisoquinolines have six rings (A, B, C, A', B', C') which numbers the skeleton of

the alkaloid structure. The tetrahydroisoquinoline portion is considered as the ‘head’ of the monomer because they contain rings A and B. as the ring A tends to possess an unsaturated aromatic ring system with two, three or more oxygenated substituents, and ring B possess secondary, tertiary or quaternary amine which sometimes varies with both saturated and unsaturated aromatic system. While the benzyl portion is considered as ‘the tail’ of the monomer with the ring C because it has only one ring with one or two substituents. The numbering of bisbenzyltetrahydroisoquinoline skeleton is generally represented by the structure, shown in Figure 8.<sup>30</sup>

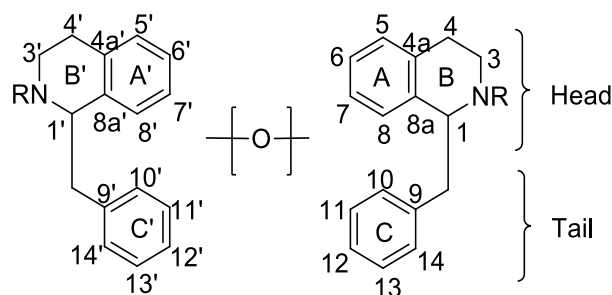


Figure 8 : Numbering of bisbenzyltetrahydroisoquinoline alkaloids

### c. Biosynthesis

Biosynthesis is the experimental study of the formation of a secondary metabolite which starts from the hypothetical speculation on the precursor product and this tends to relate with the biosynthetic pathway. Most alkaloids of Menispermaceae are isoquinoline type derived from benzyltetrahydroisoquinoline which originated from tyrosine<sup>31</sup>. Over the past decades, biogenesis has proved to be a very interesting and fruitful area of organic chemistry. However, the Menispermaceae family have the isoquinoline type that form the tetrahydroisoquinoline alkaloids which originated from the tyrosine<sup>32</sup>.

Isoquinoline alkaloids are derived from benzyltetrahydroisoquinoline. The initial reaction in benzyltetrahydroisoquinoline biosynthesis is a condensation of two aromatic units; both derived from tyrosine or dopamine, and hydroxyphenylacetaldehyde.

However, Schumacher *et al.*,<sup>33</sup> proved by the discovery of a novel enzyme named norlaudanosoline synthase, that route **I** is a real pathway of benzyltetrahydroisoquinoline biosynthesis and that the previously postulated intermediate norlaudanosoline-1-carboxylic **27** is probably an artefact (Scheme 1).

In a more modified step, when (*S*)-tyrosine **22** involved the enzyme of decarboxylase it forms tyramine **29** which was hydrolyase at meta-position to form the dopamine **7** compound. On the other hand, the same tyrosine **22**, lyase to forms the *p*-hydroxyphenyl pyruvate **30**, which was further decarboxylase to afford the *p*-hydroxyphenyl aldehyde **31**. The experimental precursor and cell

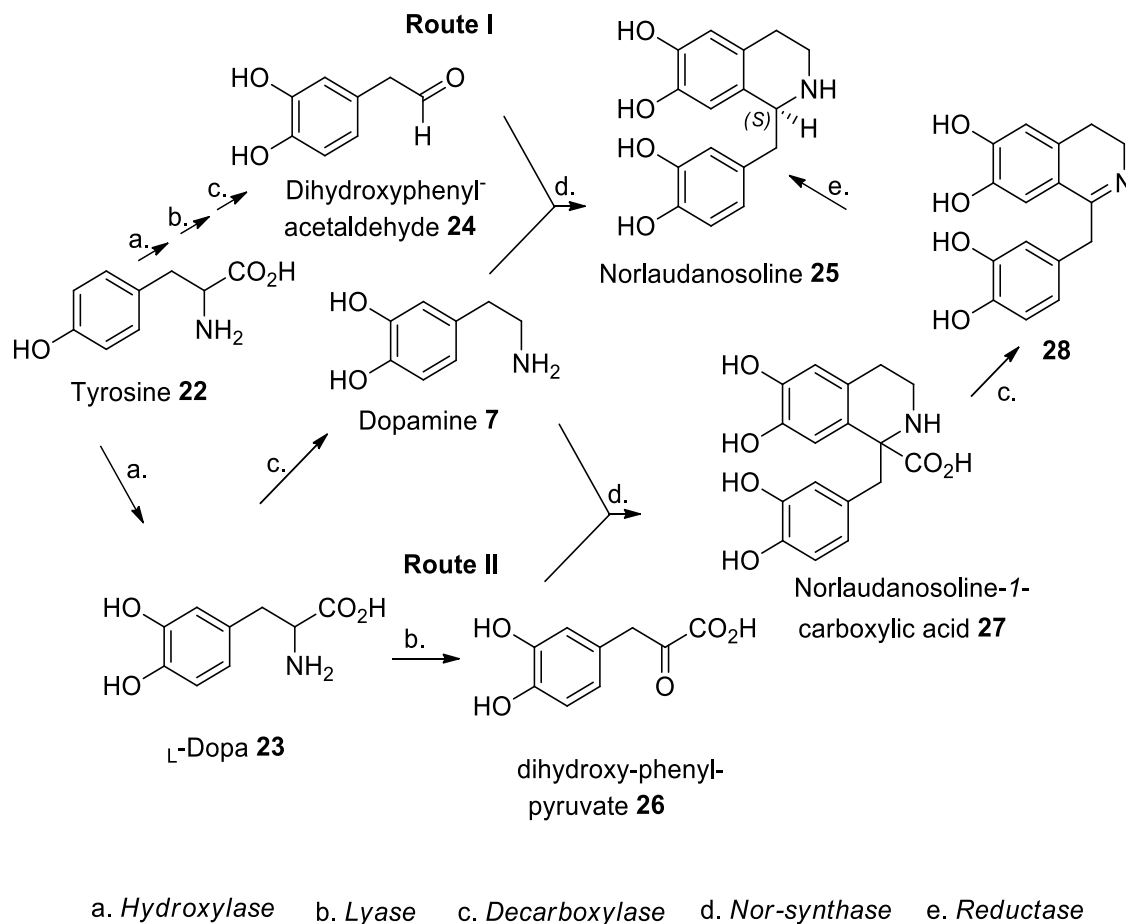
<sup>30</sup> P. L. Schiff Jr. *J. Nat Prod.* **1983**, 46(1), 1 – 43.

<sup>31</sup> T. Robinson. in *The Biochemistry of Alkaloids*, 2nd ed. Springer, New York. **1981**, chap 1, pp 54 – 55.

<sup>32</sup> D.S. Bhakuni, V.M. Labroo, A.N. Singh, R.S. Kapil. *J. Chem. Soc. Perkin Trans.*, **1979**, 1, 121 – 125.

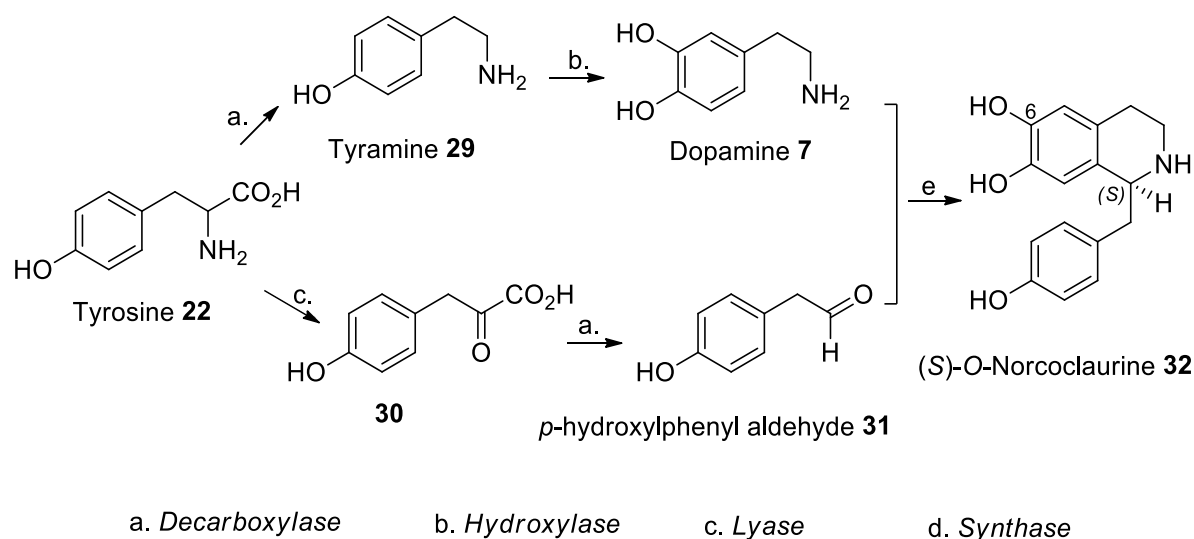
<sup>33</sup> H. M. Schumacher, M. Ruffer, N. Nagakura, M. H. Zenk. *Planta Med.* **1983**, 48, 212 – 220.

cultures showed that condensation between dopamine **7** and *p*-hydroxyphenyl aldehyde **31** form the first alkaloid intermediate (*S*)-norcoclaurine **32** which is an intermediate of bisbenzyltetrahydroisoquinoline isoquinolinealkaloids<sup>3431</sup> (Scheme 2).



Scheme 1 : Two putative biosynthetic routes to norlaudanosoline skeleton by Schumacher *et al*

<sup>34</sup> E. J. Lee, P. J. Facchini. *Plant Physiology*, **2011**, 157(3), 1067 – 1078.



Scheme 2 : Biosynthesis of norcoclaurine from tyrosine

It is known that (S)-coclaurine can be converted into its epimer **33b** (also called sanjoinine K) via the imine by oxidation-reduction process<sup>35</sup>; the same transformation was described more accurately for reticuline by Facchini *et al.* They have shown that the inversion is catalyzed by 1,2-dehydroreticuline synthase (DRS) and 1,2-dehydroreticuline reductase (DRR).<sup>36</sup>

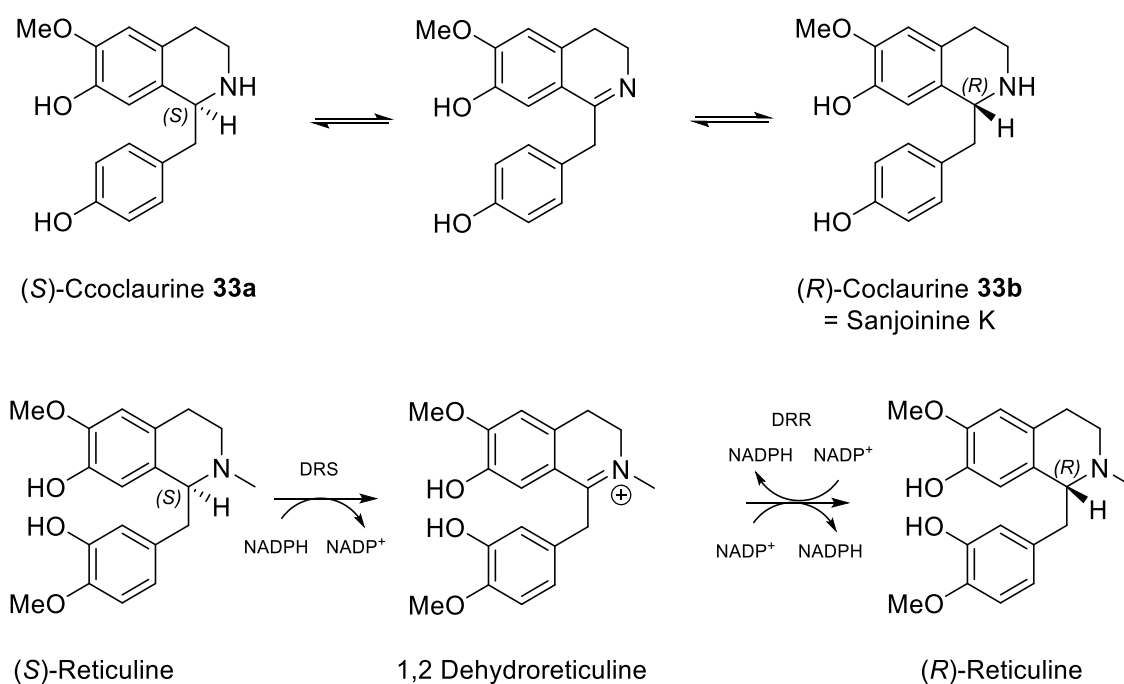
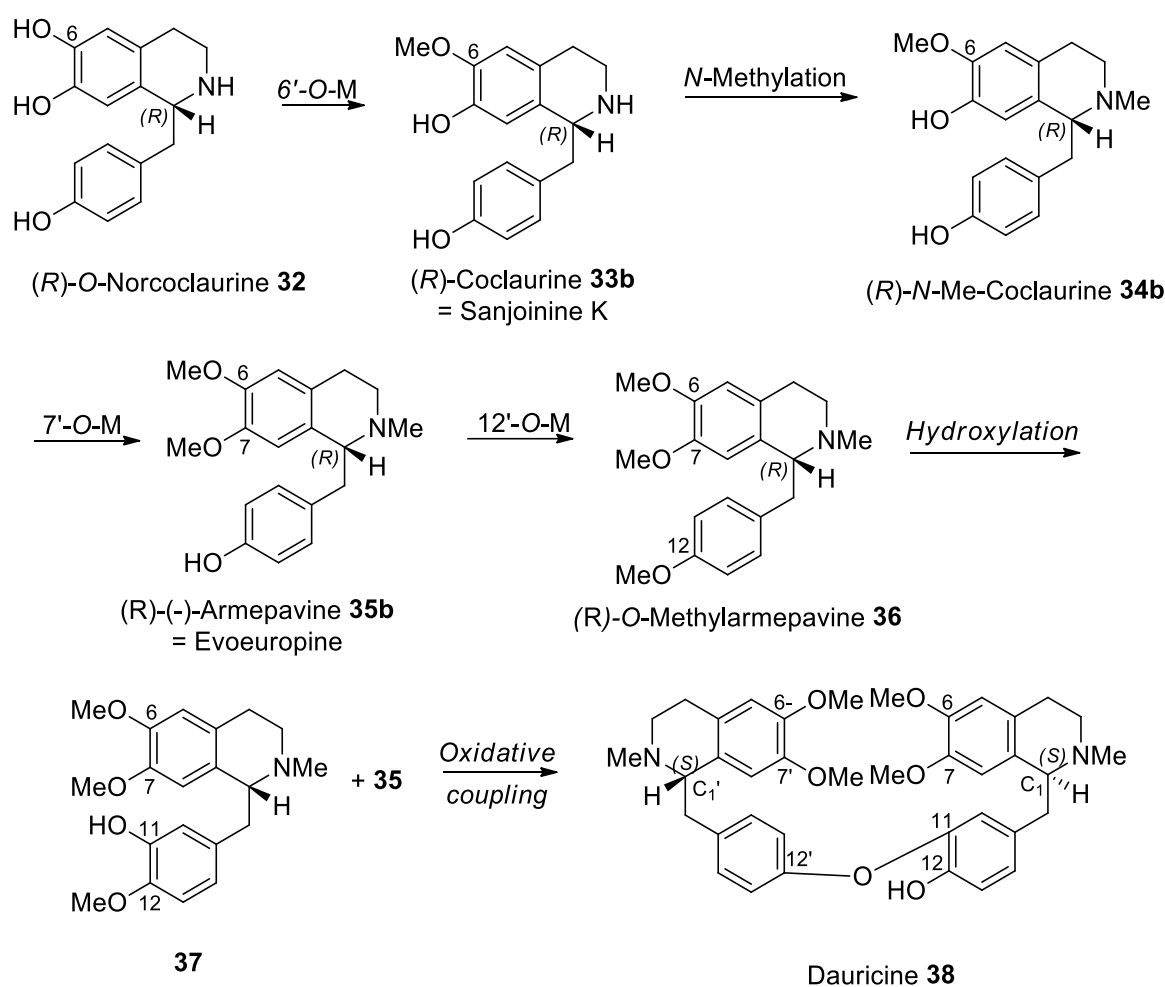


Figure 9 : Stereochemical inversion of coclaurine and reticuline

<sup>35</sup> C. Weber, T. Opatz; *Alkaloids* (San Diego, CA, United States), **2019**, 81, 1-114.

<sup>36</sup> S.C. Farrow, J.M. Hagel, G.A.W. Beaudoin, D.C. Burns, P.J. Facchini, *Nature Chemical Biology* **2015**, 11, 728 – 732.

The (*R*)-norcoclaurine **32** can be changed to (*R*)-coclaurine **33b** simple by *O*-methylation of the hydroxyl group at position 6. The (*R*)-coclaurine **33b** can undergo triple methylation at secondary amine, 7' and 12'-positions of the aromatic system to form (*O*)-methylarmepavine **36**, and when hydrolyzed, compound **37** is obtained. When two units of tetrahydroisoquinoline moieties of **35** and **37** are combined through an oxidative reaction, there's a formation of diaryl ether bridges like dauricine **38**. However, the dimerization of one, two or three oxidative couplings can form the bisbenzyltetrahydroisoquinoline alkaloids and these sequences are often initiated from tyrosine<sup>31</sup> (Scheme 3).



Scheme 3 : Biosynthesis of dauricine from (*R*)-norcoclaurine

## 2. Dimerization of THIQ

### a. Dimerization process

Bisbenzyltetrahydroisoquinoline (BBIQs) alkaloids belong to the very large isoquinoline alkaloid family consisting of two benzyltetrahydroisoquinoline parts linked through diphenyl ether,

benzyl phenyl ether, or biphenyl bonds<sup>26</sup>. The bisbenzylisoquinoline alkaloids are mostly found in the Menispermaceae, Berberidaceae, Lauraceae, and Ranunculaceae families and these plants preferably grow in tropical and subtropical regions. The most prodigious source of these alkaloids is plants of Menispermaceae family which the genus *Cyclea* is known to be the richest source of alkaloids isolated<sup>29,37</sup>.

So far, over 500 benzyltetrahydroisoquinoline dimers are been characterized and the alkaloids that occur in a plant of menispermaceae family are been subjected to several reviews from their botanical point of precept<sup>38</sup>. The position and the number of ether linkages in the molecule have served as a convenient criteria for the classification of these alkaloids into subgroups. Based on the differences of aromatic oxygen substituents, the number of linkages, types, and ether bridges play an important role in classifying the bisbenzyltetrahydroisoquinoline alkaloids. To understand the clarity of atom on bisbenzyltetrahydroisoquinoline alkaloids, the priority is referred to as the hemisphere which is separated by a hyphen such that each diaryl ether linkage has a symbol of \*, + and # symbols. There is a need to expatiate the tetrahydro-, dihydro- or fully aromatic isoquinoline moiety even when it does not give more information about the stereochemistry of the stereogenic centre at C-1 and C-1' or pattern with *N* or *O*- methylation. The more highly oxygenated benzyltetrahydroisoquinoline half constitutes the right-hand side C-1 of the dimer and is listed first while the prime (C-1') constitutes the less oxygenated molecule on the left-hand side.

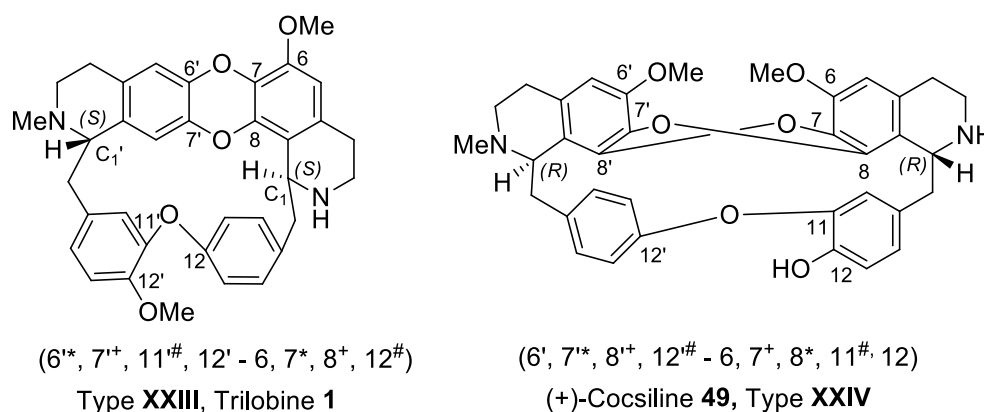


Figure 10 : Numerotation of BBIQ

These distinguishable patterns used in interpreting the nomenclature and data of a bisbenzyltetrahydroisoquinoline molecules which are very essential not necessarily to classify the systematic part but it acknowledge a uniform rule that allows the phrase of a compound since their labelling is handled individually. Moreover, the use of number and symbol to systematically explain

<sup>26</sup> K.W. Bentley. *The Isoquinoline Alkaloids*. **1965**, 41 – 59.

<sup>29</sup> K. P. Guha, B. Mukherjee, R. Mukherjee. *J. Nat. Prod.* **1979**, 42(1), 1 – 84.

<sup>37</sup> M. Tamura, In *Flowering Plants – Dicotyledons: Magnoliid, Hamamelid and Caryophyllid Families*; K. Kubitzki, J.G. Rohwer, V. Bittrich. Springer: Berlin, Heidelberg, **1993**, 563 – 583.

<sup>38</sup> E. Vasconcelos Leitao da-Cunha, A.I. Gray. In *The Alkaloids 54*, J.M. Barbosa-Filho, G.A. Cordell. Academic Press: New York, **2000**, 1 – 190.

each half of the dimer concerning its oxygenation pattern on both the type(s) and position of the coupled compound<sup>30,31,39</sup>.

### 3. The Shamma-Moniot nomenclature

Regards to the number of BBIQs described, and moreover regards to the diversity of their structures, it became pertinent to create a specific classification for these dimeric compounds. In 1976, Maurice Shamma and Jérôme Moniot have presented a classification of these BisBenzyltetrahydroIsoQuinoline, and this classification is still ongoing, nowadays. After them, several authors and first of all Paul L. Schiff Jr. have enriched it and many reviews were published<sup>Error! Bookmark not defined., 40, 41</sup>. A recent and almost exhaustive description of all these types was published in 2019 by Weber and Opatz.<sup>35</sup>

#### a. Etheral connection

The simplest link between two benzyltetrahydroisoquinoline, is an ether bond, so the first groups of this subdivision (type **I** to type **III**) described BBIQ with one ethereal link, and all of them are connected by the tail, *i.e.* by the benzyl moiety, and never by the isoquinolines moiety. The differentiation between these isoquinolines is the oxidation level of aromatic rings and the position of the ethereal bond. Thus, type **VI** to **XVII** are dedicated to BBIQ with two ether bridges, one which link the two benzyl moiety and the second bridge connecting the two isoquinolines. Finally, type **XXIII**, **XXIV**, and **XXVIII**, for BBIQ contain 3 ethereal bridges, with two for the connection between the isoquinolines. As molecules are isolated and characterized, this classification is continuing to be incremented, this is the reason why the continuum if the numeration is not in the following. Usually, the numeration begins with molecules possessing a single bond to finish with molecules which isoquinoline moiety is connected with three bridges. It is also for that reason, that sometimes, authors create type **Ia** to a make distinction with normal **type I**. The difference is just an additional hydroxyl group in position 5, but one more time because the first compound with this over oxidation was isolated after the establishment of the classification, it was not possible to change numeration, and the creation of an extension of type **I** appears to be the simplest. This is also the same case for type **XII/XIIa**, for type **XXIII/XXIIIa**. When compounds with and without oxidation in this position 5 were already discovered before 1976, two different types were created and it is the case for type **VI** and type **VII** (see Table 2).

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<sup>30</sup> P. L. Schiff Jr. *J. Nat Prod.* **1983**, 46(1), 1 – 43.

<sup>31</sup> T. Robinson. in *The Biochemistry of Alkaloids*, 2nd edn. Springer, New York. **1981**, chap 1, pp 54 – 55.

<sup>39</sup> J. M. Barbosa-Filho, E. V. L. Da-Cunha and A. I. Gray. *The Alkaloids.* **2000**, 54, 13 – 14.

<sup>29</sup> K. P. Guha, B. Mukherjee, R. Mukherjee. *J. Nat Prod.* **1979**, 42(1), 1 – 84.

<sup>40</sup> P. L. Schiff Jr. *J. Nat Prod.* **1991**, 54(3), 645 – 749.

<sup>41</sup> P. L. Schiff Jr. *J. Nat Prod.* **1997**, 60(9), 934 – 953.

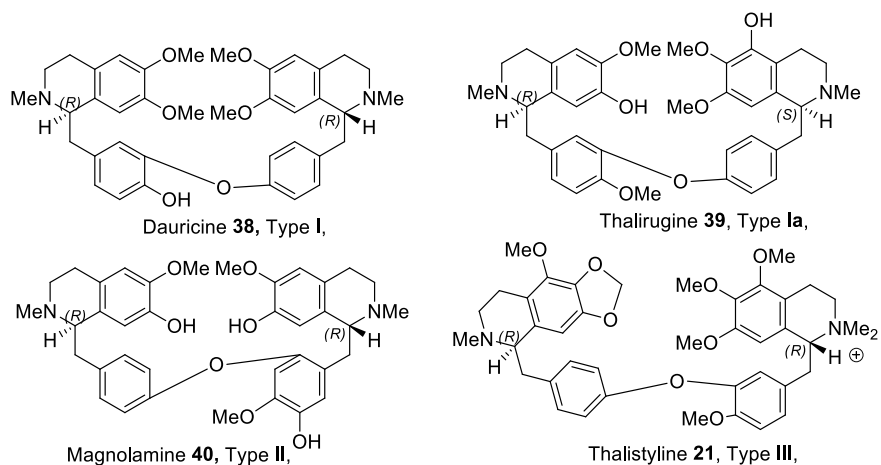
<sup>35</sup> C. Weber, T. Opatz; *Alkaloids* (San Diego, CA, United States), **2019**, 81, 1-114.



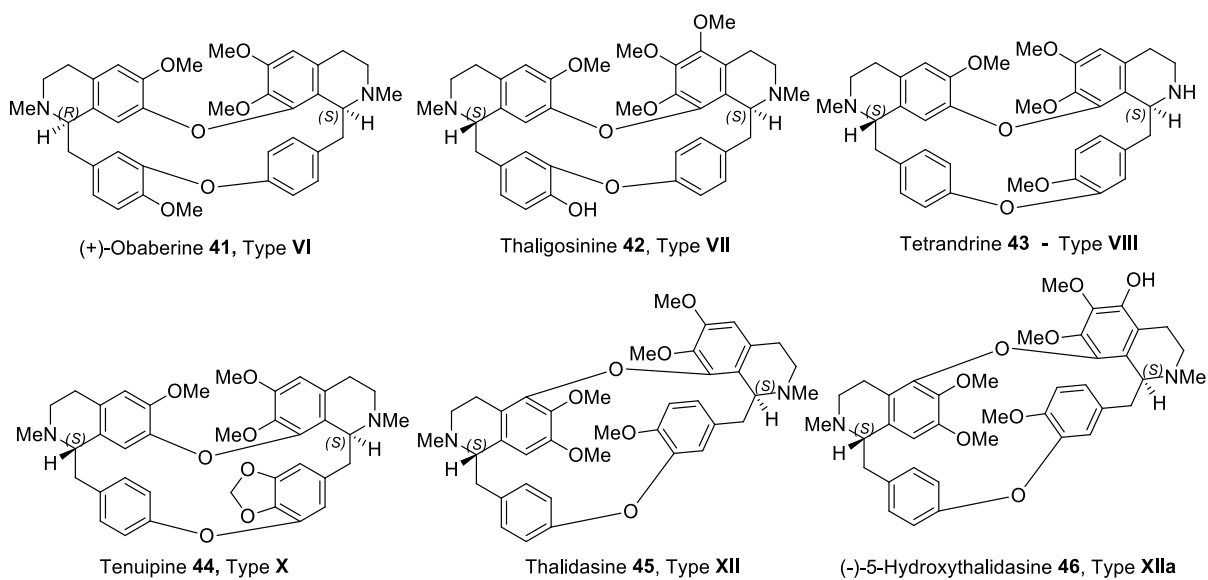
Table 2 : The Shamma-Moniot classification: ethereal head-to-head links

Head-to-Head / Tail-to-Tail

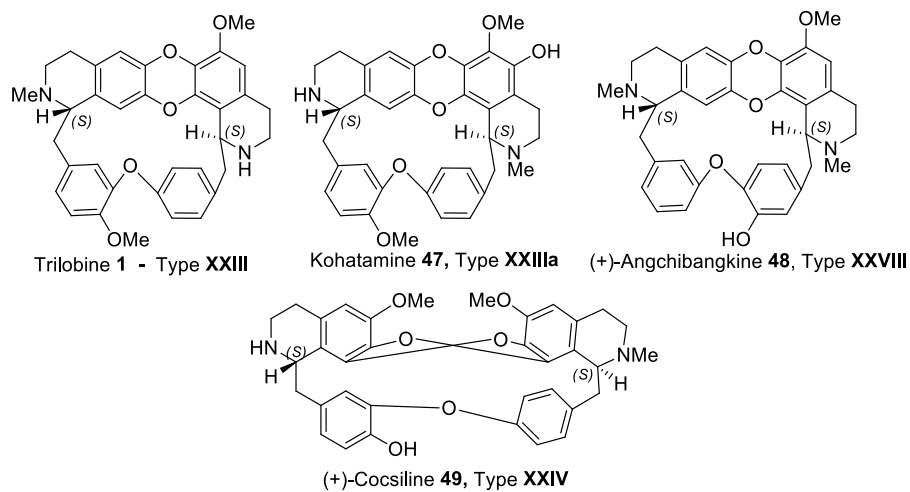
1 link tail-to-tail



1 link tail-to-tail  
1 link head-to-head



1 link tail-to-tail  
2 link head-to-head

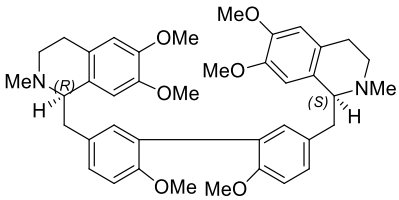
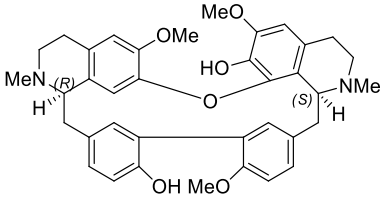
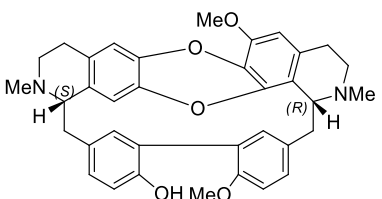
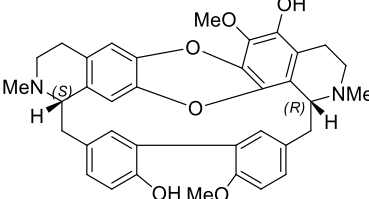


b. Aryl-aryl link

As already mentioned, numeration of subgroups type of BBIQ Shamma-Moniot classification depends on the order of isolation and characterization of natural BBIQ and not with any relation with the structure. Thus, concerning the third group where THIQ is connected with one no-etheral bridge but an aryl-aryl one, compounds with this single carbon-carbon bond are classified as type **XXVII**, while compound as cordobine with one aryl-aryl bond and an etheral bridge are classified as type **IV**. All compounds classified in type **XXVII**, *i.e.* pisopowine and analogues, were isolated from *Popovia pisocarpa*, an Annonaceae, by Cavé *et al.* in 1986, and so 10 years after the introduction of the classification by Shamma and Moniot, for that reason these molecules with a simple link are classified with a “high” number. This aryl-aryl link only occurs for the benzyl moiety and never, up to now, to connect the isoquinoline moieties

Type **XVIII** and **XIX** are dealing with compounds which possesses a dioxin system in addition to this aryl-aryl bond (Table 3).

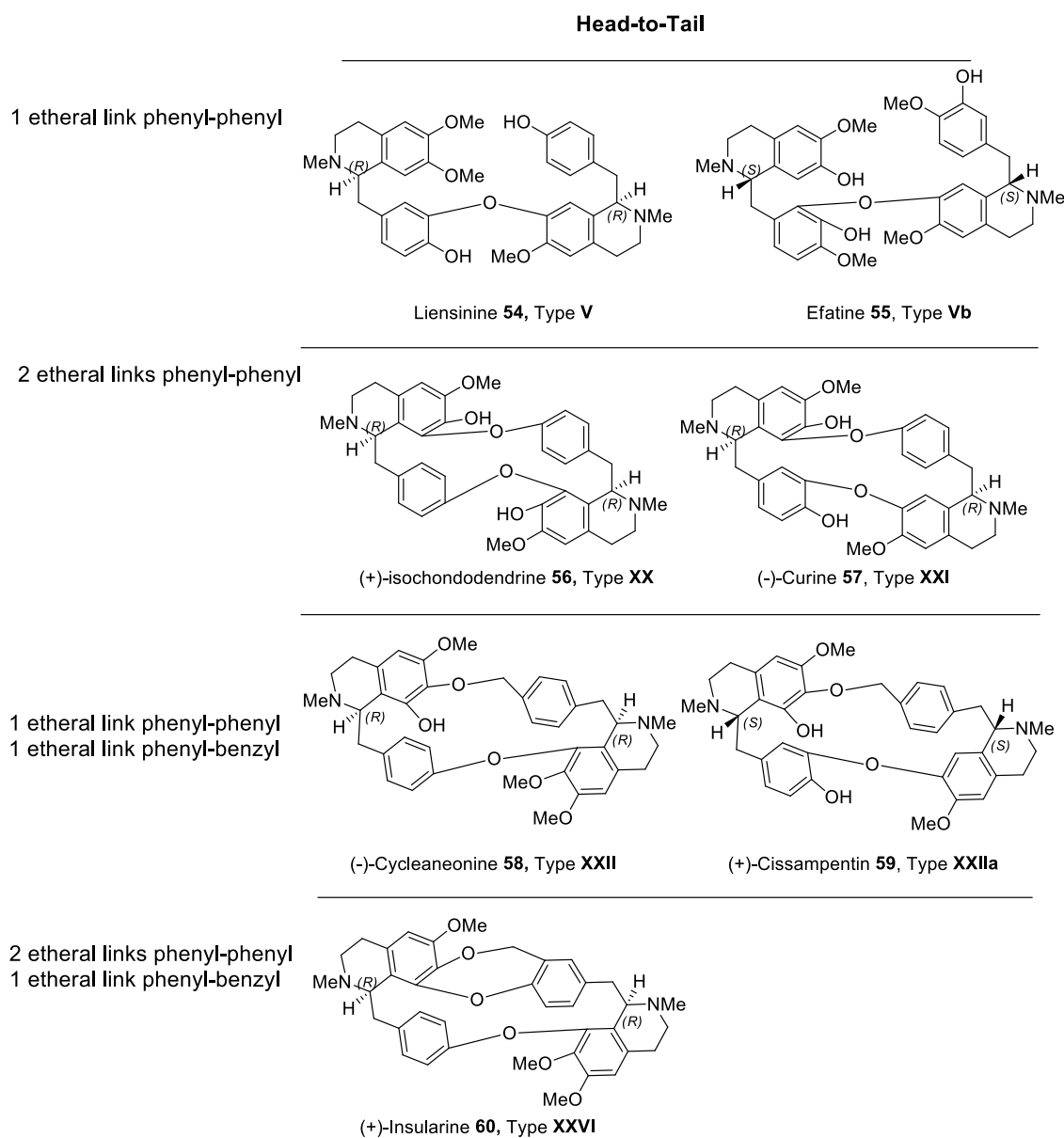
Table 3 : The Shamma-Moniot classification: aryl-aryl links

	Aryl-Aryl link
1 link phenyl-phenyl tail-to-tail	 <p style="text-align: center;">(-)-Pisopowine <b>50</b>, type <b>XXVII</b></p>
1 link phenyl-phenyl tail-to-tail 1 etheral links phenyl-phenyl head-to-head	 <p style="text-align: center;">(-)-Cordobine <b>51</b>, Type <b>IV</b>,</p>
1 link phenyl-phenyl tail-to-tail 2 etheral links phenyl-phenyl head-to-head	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>Tiliacorine <b>52</b>, Type <b>XVIII</b>,</p> </div> <div style="text-align: center;">  <p>(+) - Yanangine <b>53</b>, Type <b>XIX</b></p> </div> </div>

### c. Head-to-tail connection

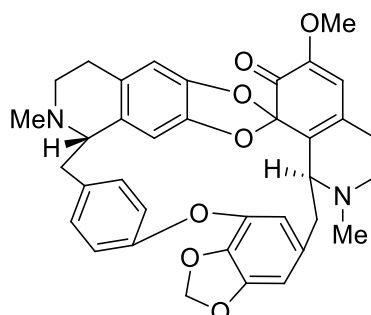
The dimerization process of two THIQ can also lead to other types of dimeric compounds, by a head-to-tail junction. Thus, a tetrahydroisoquinoline of the first THIQ is connected to the benzyl of the second one, and not to the second isoquinoline moiety. This is especially the case for a very well-known family of natural poisons, the curare. In fact, curare is a generic name for highly poisonous substances mainly extracted from Menispermaceae *Chondodendron tomentosum* and from the Loganiaceae *Strychnos toxifera*. The molecule known as curare is curine, which is a type **XXI** BBIQ alkaloid, and it is used in the clinic as its ammonium salt under the name of Tubocurarine. One specificity of this subgroup, is the presence in some types of a phenyl-benzyl ether bridge instead of a classical phenyl-phenyl ethereal bridge, as in type **XXII**, **XXIIa** and **XXVI** (see table Table 4).

Table 4 : The Shamma-Moniot classification: head-to-tail links



d. Other original subclass

Other original BBIQ were isolated, and molecules classed in type **XXV** are interesting examples. The connection between the two isoquinolines forms a keto acetal.



Repanduline **61**, Type **XXV**

Figure 11 : structure of repanduline

Newly, in 2015, A. Giannis *et al.* isolated new BBIQs with head-to-tail connections, without known subgroup, and moreover they described a really new type of BBIQ with on the same molecule head-to-tail connections and an aryl-aryl link<sup>42</sup> (compound **64** in Figure 12). In 2018, Menéndez-Perdomo and Facchini had isolated a head-to-tail BBIQ, Nelumborine **67**<sup>43</sup>, classified in type **XXXI**, with a single aryl-aryl bond, related to compound **64** described by Giannis but without the ethereal link (Figure 13). For the moment, some newly isolated compounds are not classed in subgroups BBIQs type and even were not to be named (it is the case for compounds **62-66** isolated by Giannis *et al.*) but the community will probably create a new type, as it is done regularly.

<sup>42</sup> G.R. Malca Garcia, L. Hennig, I.V. Shelukhina, D.S. Kudryavtsev, R.W. Bussmann, V.I. Tselin, A. Giannis ; *J. Nat. Prod.* **2015**, 78(11), 2537 – 2544.

<sup>43</sup> I.M. Menéndez-Perdomo, P.J. Facchini, *Molecules*, **2018**, 23(11), 2899 – 2915.

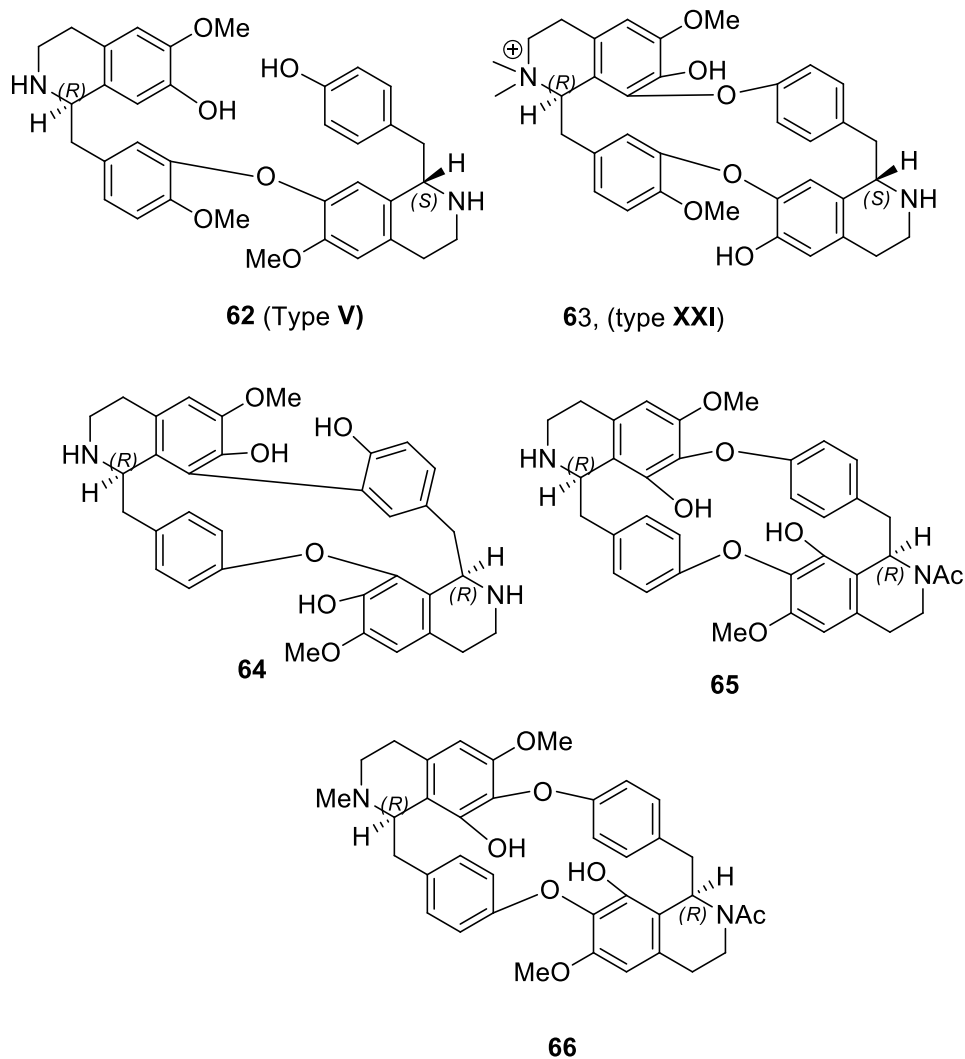


Figure 12 : Structure of BBIQ isolated by Giannis *et al.*

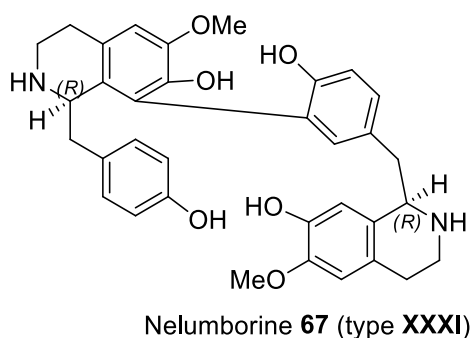


Figure 13 : Structure of Nelumborine

Since the earliest commercial drug preparation, natural product chemist and pharmacognosists have been interested in the bisbenzyltetrahydroisoquinoline alkaloids because of their diverse formulations and varied pharmacological effects. The Shamma-Moniot reported the chemical aspects

of this field and has intensified the long-felt need for a glossary of these alkaloids containing all information necessary for a natural product chemist searching for new BBIQ alkaloids. However, the BBIQ alkaloids are built up of two benzyltetrahydroisoquinoline unit linked by ether bridges, methylenedioxy bridges, or direct carbon-to-carbon bonds.

#### 4. Biological activity / pharmacology of BBIQ

The number of publications concerning the pharmacological activities of bisbenzyltetrahydroisoquinoline alkaloids has largely increased over the past years to the extent that a single plant with secondary metabolites are extracted and were evaluated for a new application area which may add to those known from the traditional medicines<sup>44</sup>.

Recently, bisbenzylisoquinoline alkaloids were found to have wide biological activities including antioxidant, cardiovascular effects such as antihypertensive and antiarrhythmic actions<sup>45</sup>, reversing the multidrug resistance (MDR) effect of human carcinomas, anti-HIV and as anti-tuberculosis agents towards multidrug resistant<sup>46,47</sup>.

The curares are isolated from *Chondodendron* species (Menispermaceae) and curine is the most active constituent of the mixture which is known as arrow poison used by South American Indians. When injected into the bloodstream, it quickly blocks the neuromuscular action so that respiration ceases and death occurs. Actually, the curare alkaloids bind readily to the active site of the receptor for acetylcholine (Ach) at the neuromuscular junction, blocking the nerve impulse from being sent to the skeletal muscles which will effectively paralyze the muscles of the body<sup>48</sup>.

The tetrandrine, dauricine, daurisolone, and neferine are BBIQ alkaloids that have shown cardiovascular pharmacological effects and the mechanism of actions of these compounds was reviewed<sup>49</sup>. The antihypertensive effects of tetrandrine have been demonstrated in experimental hypertensive animals and patients because when calcium is added, it antagonizes the effect of tetrandrine in the interaction with the *M*-receptors, which means it can also be used as an antimalarial study based on *in vitro* culture of both chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*, this also showed that the antiarrhythmic effect of daurisolone is more potent than that of dauricine. Tetrandrine has a potential therapeutic value to prevent excess scarring in a patient with severe conjunctival inflammation. It has anti-inflammatory, immunologic, and antiallergenic effects. It inhibits the degranulation of mast cells. This action makes tetrandrine and related compounds are potentially useful in the treatment of lung silicosis, rheumatoid arthritis.<sup>50</sup>

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<sup>44</sup> A.L. Otshudi, S. Apers, L. Pieters, M. Claeys, C. Pannecouque, E. De Clercq, A. Van Zeebroeck, S. Lauwers, M. Frederich, A. Foriers. *J. Ethnopharmacol.* **2005**, 102(1), 89 – 94.

<sup>45</sup> J. Tabeshpour, M. Imenshahidi, H. Hosseinzadeh. *Iran J. Basic Med. Sci.* **2017**, 20(5), 557 – 568

<sup>46</sup> Y. Kashiwada, A. Aoshima, Y. Ikeshiro, Y.P. Chen, H. Furukawa, M. Itoigawa, T. Fujioka, K. Mihashi, L.M. Cosentino, S.L. Morris-Natschke, K.H. Lee. *Bioorg. Med. Chem.* **2005**, 13(2), 443 – 448.

<sup>47</sup> S.Sureram, S.P. Senadeera, P. Hongmanee, C. Mahidol, S. Ruchirawat, P. Kittakoop. *Bioorg. Med. Chem. Lett.* **2012**, 22(8), 2902 – 2905.

<sup>48</sup> J. D. Dutscher. *J. Am. Chem. Soc.* **1952**, 74(13), 2221.

<sup>49</sup> J.Q. Qian. *Acta Pharmacol. Sin.* **2002**, 23(12), 1086 – 1092

<sup>50</sup> C.Y. Kwan, F. I. Achike. *Acta Pharmacol. Sin.* **2002**, 23(12), 1057 – 1068.

a. Antiparasitic activities of bisbenzylisoquinoline alkaloid:

A large number of antimalarial compounds with a wide variety of structures have been isolated from plants, and they can play an important role in the development of new antimalarial drugs using a template designed by ethnopharmacological researchers as this gave a promising pathway to plant metabolites and also to improve on the new properties<sup>51</sup>. Malaria is a mosquito-borne infectious disease caused by eukaryotic parasitic protozoans of the genus *Plasmodium*; typical symptoms include fever, fatigue, vomiting, and headaches. The disease is widespread throughout tropical and subtropical regions like Africa, Asia and South America, as it remains one of the major infectious diseases that threaten human lives. The quinine **4** and quinidine **68** were isolated from the bark of the cinchona tree which was the first effective antimalarial medicines and were used for centuries until chloroquine **69** was discovered in the 1940s. However, chloroquine is more effective for all types of malaria with fewer side effects until a resistant strain started to emerge in the 1960s, so other antimalarial agents with similar heterocyclic ring structures were developed afterward include mefloquinone **71** and mepacrine **72**<sup>52,53</sup> (Figure 14).

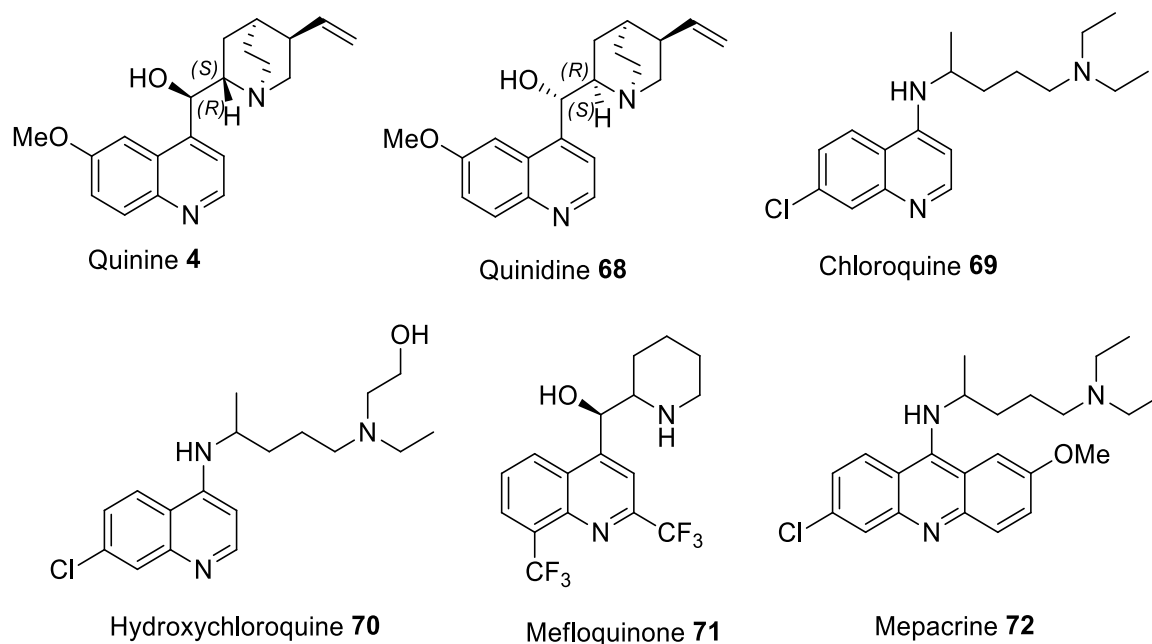


Figure 14 : Malaria chemotherapeutics

A new type of antimalarial agent artemisinin was isolated in 1972 from the traditional Chinese medicinal plants, *Artemisia annua* (Asteraceae), which has been used for the treatment of fever and malaria since ancient times. Unlike most of the conventional antimalarial agents, artemisinin is a sesquiterpene lactone peroxide without a heterocyclic aromatic ring and was found to be more effective in treating malaria without obvious side effect. Because of its low solubility in both oil and water and its biotransformation, it is difficult to administer. Thus, many semisynthetic derivatives of

<sup>51</sup> J. Bero, M. Frederich, J. Quetin-Leclercq. *J. Pharm. Pharmacol.* **2009**, *61*, 1401 – 1433.

<sup>52</sup> M. Schlitzer. *ChemMedChem.* **2007**, *2*(7), 944 – 986.

<sup>53</sup> D. Chaturvedi, A. Goswami, P. P. Saikia, N. C. Barua and P. G. Rao. *Chem. Soc. Rev.* **2010**, *39*, 435 – 454.

artemisinin **73** have been synthesized including dihydroartemisinin **74**, artesunate **75**, artemether **76**, and artemisone **77**. Among these derivatives, artesunate **75** is commonly used in antimalarial combination therapy at the present time<sup>53</sup> (Figure 15).

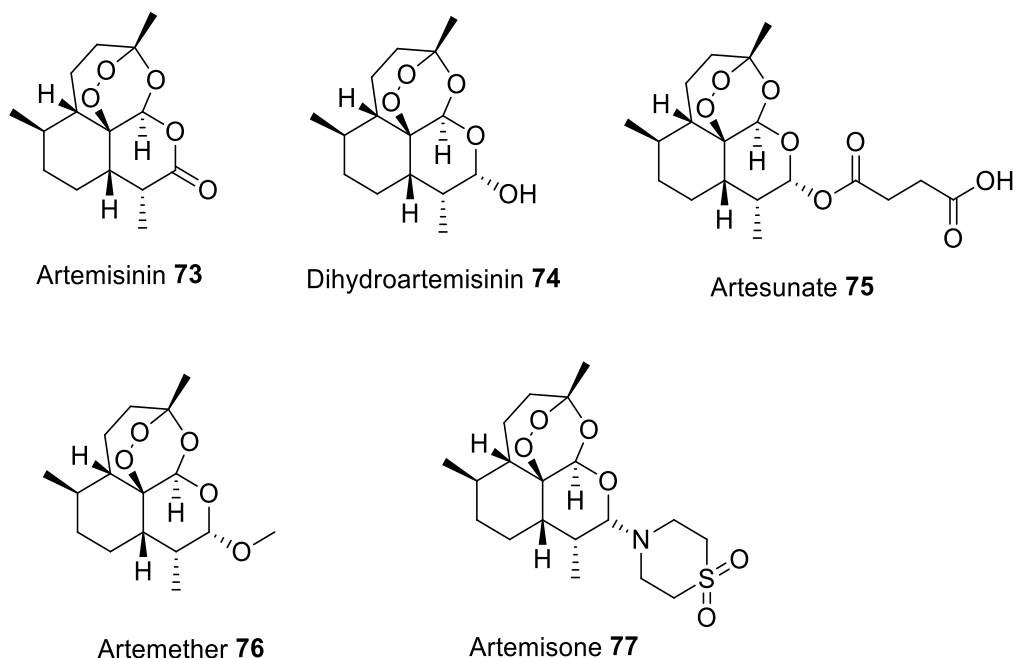


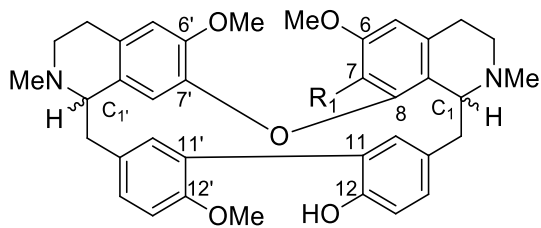
Figure 15 : A novel drug of malarial by Chaturvedi *et al.*

So, Del Rayo Camacho *et al.*<sup>54</sup> reported the *in vitro* activity of *Triclisia patens* and some BBIQ alkaloids against *Leishmania donovani* and *Trypanosoma brucei* which was aimed to improve the understanding and structural requirement for the antiprotozoal effects of plant secondary metabolites. In assessing the relationship on the antitrypanosomal structure-activity, it can be observed that the substituents present in each monomeric half of the molecule may influence antitrypanosomal activity. This means a comparison of the phenolic alkaloids tiliageine **79** with its methyl ether funiferine **78** suggests that the presence of a phenolic hydroxyl group results in a decrease in activity. It can also be seen that most active bisbenzylisoquinoline alkaloids ( $IC_{50} < 10 \mu\text{g/ml}$ ) for example, isotetrandrine **85**, isotrilobine **2** and trilobine **1** had similar antiprotozoal activities against *L. donovani* and *T. brucei*. This could be explained by the fact that *Leishmania* and *Trypanosoma* species possess several molecular and biochemical features that are unique to the kinetoplastid order. In contrast, funiferine **78**, and tiliageine **79** showed a selective activity towards *L. donovani* promastigotes, whilst the daphnoline **81**, phaeanthine **84**, berbamine **87** and trilobine **1** displayed selective activity against *T. brucei* (Figure 16).

<sup>53</sup> D. Chaturvedi, A. Goswami, P. P. Saikia, N. C. Barua and P. G. Rao. *Chem. Soc. Rev.* **2010**, *39*, 435 – 454.

<sup>54</sup> M. Del Rayo Camacho, J. D. Phillipson, S. L. Croft, P. Rock, S. J. Marshall and P. L. Schiff Jr. *Phytother. Res.* **2002**, *16*(5), 432 – 436.



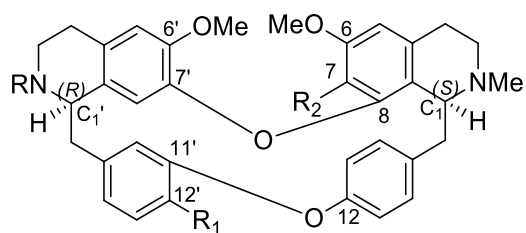


Type IV

R<sub>1</sub>

Funiferine **78**, C<sub>1</sub>-(S), C<sub>1'</sub>-(R), OMe

Tiliageine **79**, C<sub>1</sub>-(S), C<sub>1'</sub>-(R), OH



Type VI

R

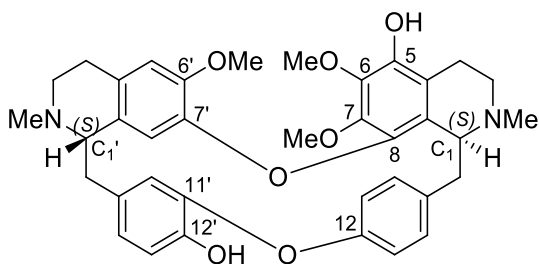
R<sub>1</sub>

R<sub>2</sub>

Aromonline **80**, C<sub>1</sub>-(S), C<sub>1'</sub>-(R), Me OH OH

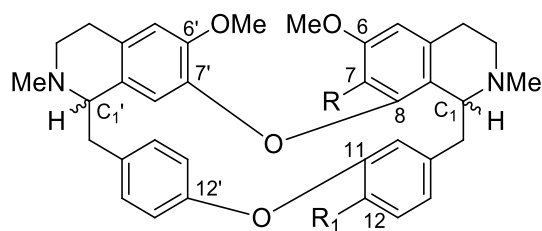
Daphnoline **81** C<sub>1</sub>-(S), C<sub>1'</sub>-(R), H OH OH

Oxyacanthine **82** C<sub>1</sub>-(S), C<sub>1'</sub>-(R), Me OH OMe



Type VII

Thalisopidine **83** C<sub>1</sub>-(S), C<sub>1'</sub>-(S),



Type VIII

R

R<sub>1</sub>

Phaeanthine **84** C<sub>1</sub>-(R), C<sub>1'</sub>-(R),

OMe

OMe

Isotetrandrine **85** C<sub>1</sub>-(R), C<sub>1'</sub>-(S),

OMe

OMe

Fangchinoline **86** C<sub>1</sub>-(S), C<sub>1'</sub>-(S),

OH

OMe

Berbamine **87** C<sub>1</sub>-(R), C<sub>1'</sub>-(S),

OMe

OH

Obamegine **88** C<sub>1</sub>-(R), C<sub>1'</sub>-(S),

OH

OH

Figure 16 : Structures of bisbenzyltetrahydroisoquinoline by Camelo *et al.*



## CHAPTER 1 : COCCULUS HIRSUTUS AND TRILOBINE / ISOTRILOBINE

### A. *Cocculus hirsutus*

#### 1. *Ethnopharmacology*

Herbal medicine is a major remedy in the traditional system that have been used in medical practices since antiquity and the practice continues to date because of its biomedical benefits as well as the place in cultural believes in many parts of the world which have greatly contributed to the maintaining of human health. Presently the world population depends on the plant-derived medicine for the first line of primary health care alleviation because it has no side effects<sup>55</sup>.

Most medicinal plants are important for pharmacological research and drug development, not only when plant constituents are used directly as therapeutic agents, but also as starting materials for the synthesis of drugs or as models for pharmacologically active compounds. The presence of radical scavenging potential in the plant helps us to understand that the plant possess bioactivity and some underlying molecule responsible for its activities.<sup>56</sup>

*Cocculus hirsutus* (L.) Diels (common name ink berry) is an important medicinal plant belonging to the family Menispermaceae (the moon seed). They contain about 70 genera and more than 450 species, they grow mostly in a dry region of entire tropical Africa and Asia with their name distributed across the sphere<sup>57</sup>. This plant has an excellent ethnomedicinal potential to cure several ailments such as alleviating burning, sensation in eyes, taste, healing wounds in very less time. The roots, leaves, and fruits have immense medical properties to cure numerous diseases in an efficient manner.



Figure 17 : *Cocculus hirsutus* plant and Raw & ripened fruits by Dinesh Valke photo

#### 2. *Ethnomedicinal use of C. hirsutus plant:*

The bioactive compounds produced during secondary metabolism are usually responsible for the biological properties of plant species used throughout the globe for various purposes, including the treatment of infectious diseases. *Cocculus hirsutus* is an important species of flowering plant

<sup>55</sup> V. Steenkamp, E. Mathivha, M. C. Gouws, C. E. J. Van Rensburg, *S. Afri. J. Ethnopharmacol*, **2004**, 95(2-3), 353 – 357.

<sup>56</sup> J. B. Harbone. *Phytochemical method*, **1984**, 100 – 101.

<sup>57</sup> V.U. Ahmad, T. Rasheed. *J. Chem Soc Pak*. **1986**, 8(4), 537 – 540

belonging to family Menispermaceae. *C. hirsutus* is a widely used medicinal plant in famine food and pharmaceutical industries. Merchant *et al*<sup>58</sup> reported the ethnomedicinal value of *C. hirsutus*, which are used both for internal as well as external purposes. When the juice of the roots is mixed along with half spoon of sugar, it treats excessive body heat. While, the decoction of the roots, dried ginger, and long pepper is given along with milk to treat rheumatic pains, joint pains, diuretic, malaria, etc.

Also, the roots are used for the antidote of snake bites. The juicy extract of the leaves is used to treat eye disease and soothing skin in eczema. However, if the extract of the mucilaginous leaves is taken along with water continuously for 2 – 3 days, it cures dysentery, urinary problem, and tongue sore<sup>59</sup>.

## B. Pharmacology

The *C. hirsutus* a useful agent of antimicrobial properties because it prevents infections, this may be a result of the phenolic compound presence and the tannins which acts as astringent that helps to heal wounds and ulcer<sup>60</sup>.

### 1. Anti-inflammatory and analgesic activities of *C. hirsutus*

The inflammation and pains are the most common health challenges treated with traditional remedies mainly the medicinal plant which provides relief symptoms with very little side effect when compare with chemical therapeutics. Sengottuvelu *et al.*<sup>61</sup> reported the analgesic and anti-inflammatory activity of *C. hirsutus* in both *in vitro* and *in vivo* analysis.

They used the human red blood cell (HRBC) membrane stabilization method for the *in vitro* anti-inflammatory activity and the induced granuloma in mice. From the phytochemical test, it showed the presence of phenolic compounds in methanolic extract of *C. hirsutus* which might suppress the formation of prostaglandin and bradykinins. More so if the noxious stimuli are depressed, it will reduce the number of writhes (peripheral effects) in animals and these writhing induced are due to the sensitization of nociceptors by prostaglandins.

The treatment with methanolic extract of *C. hirsutus* leaves at doses of 100 and 200 mg/kg reduced the number of writhes (45.51% protection and 64.5% protection) respectively. And among the two doses, 200 mg/kg showed a slightly lower analgesic activity than the standard drug indomethacin (70.5% protection) which showed the onset writhing was delayed and the duration of writhing was shortened.

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<sup>58</sup> J.R. Merchant, R.M. Naik, S.N. Hirwe. *J. India Chem. Soc.* **1962**, 39, 411 – 416.

<sup>59</sup> J.E. Caius. *The medicinal and poisonous plants of India*, Jodhpur, scientific publisher; **1986**, 166 – 171.

<sup>60</sup> T.K Chatterjee. *Herbal options*, 1<sup>st</sup> ed M/s Eastern Traders, Calcutta; **1996**, 157 – 178.

<sup>61</sup> S. Sengottuvelu, K. Rajesh, S. H. Sherief, R. Duraisami, M. Vasudevan, J. Nandhakumar, D. Karthikeyan and T. Sivakumar. *J. Res. Educ. Indian Med.* **2012**, 18(3), 175 – 182.

The same extracts showed significant anti-inflammatory activity in a concentration-dependent manner. The methanolic extract at 200 mg/ml concentration showed 53.7% protection of HRBC in hypotonic solution when compared with the standard Diclofenac which showed 65.2% protection.

After 6 days, the mean dry weight of granulomatous tissue surrounding the threads was significantly lower for the group treated with *C. hirsutus* extract as compared to the control group. The results indicate that *C. hirsutus* at the dose level of 100 mg/kg and 200 mg/kg produced a significant decrease weight of 57.4% inhibition and 68.3% inhibition as compared to the standard drug Naproxen 76.0% inhibition. From their results, they conclude that the methanolic extract of *C. hirsutus* possesses analgesic and anti-inflammatory activity.

## 2. Antibacterial activity:

The emergence of antibacterial resistance among bacteria has induced a compulsory need to search and identify newer novel, and safer antibacterial agents.<sup>62</sup> Over the past decades, intensive efforts have been made to discover clinical importance of antibacterial drugs of which 50% of all modern drugs are of natural product origin<sup>63</sup>.

Kalirajan *et al.*<sup>64</sup> tried to analyze the antibacterial activity of the leaves of *C. hirsutus* using methanolic and aqueous extract fractions for the *in-vivo* and *in-vitro* study against five pathogenic bacteria (*Pseudomonas fluorescens*, *Escherichia coli*, *Klebsilla pneumonia*, *Sphylococcus aureus*, and *Vibrio Cholerae*). According to their report, methanolic and aqueous extracts of *C. hirsutus* are the same level of activity than pure Streptomycin, they use as control.

The chloroform fraction extracted from the root of *C. hirsutus* showed maximum inhibition zone against pathogenic bacteria *Pseudomonas aeruginosa* and *Bacillus cereus* compare to *Staphylococcus aureus*, and no activity against *Escherichia coli* or *Klebsilla pneumonia*. The ethanolic or aqueous extracts also had no activity against all of these five stains.<sup>65</sup>

## 3. Antidiabetic activity:

In 2007, Sangameswaran and Jayakar<sup>66</sup> reported the antidiabetic activity of the alcoholic leave extract of *C.hirsutus* on animals using rats in their study. The effect of *C. hirsutus* extracts showed a significant decrease in the blood glucose level to 165 mg/ 100 ml on long term treatment of 15 days, model at the doses of 400 and 800 mg/kg. Thus, the treatment restored the serum glucose levels almost nearer to normal values when compared with the glibenclamide as a standard. However, they also observed an increase in body weight of the animal (rats) after treatment unlike when the standard glibenclamide was used, probably the improvement in insulin secretion and glycemic control assisted to prevent loss of the body weight.

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<sup>62</sup> J. M. Sashikumar, M. Remya, K. Janaradhanan. *Asian J. Microb. Biotech.* **2003**, 5(2), 183 – 185.

<sup>63</sup> A. D. Ates. *Turkish J. Bio.* **2003**, 27, 157 – 162.

<sup>64</sup> A. Kalirajan, J. M. Savarimuthu, A.J.A. Ranjit singh, C. Padmalatha. *Int'l J. Appl. Bio. and Pharm. Techno.* **2012**, 3(2), 63 – 67.

<sup>65</sup> R. Jeyachandran, A. Maheshn L. Cindrella and X. Baskaran. *J. Plant Sci.*, **2008**, 3(2), 194 – 198.

<sup>66</sup> B. Sangameswaran and B. Jayakar. *Afri. J. Biotech.* **2007**, 6(10), 1212 – 1216.

#### 4. Antioxidant activity

In a step in this direction, we evaluated antioxidant potency of the ethanol extract on the aerial parts of *Cocculus hirsutus* Diels. The extract was investigated for its free radical scavenging action towards 1,1-Diphenyl-2-picryl hydrazyl (DPPH), nitric oxide (NO), superoxide and hydroxyl radicals and found that the ethanol extract shows promising free radical scavenging activity in dose-dependent manner. This antioxidant potency maybe related to the presence of antioxidant vitamins and phenolic compounds present in the extract. These results against free radical-mediated diseases clearly indicate that *C. hirsutus* Diel is effective

#### C. Natural Substances in *Cocculus hirsutus*.

Das *et al*<sup>67</sup> reported that many scientists had carried out research on the chemical composition of *C. hirsutus* to contain essential oil,  $\beta$ -sitosterol, glycoside, tannins, and alkaloids. More so, Khushboo *et al.*<sup>68</sup> reported the preliminary phytochemical analysis of *C. hirsutus* leaves to have flavonoids, phenolics, saponins steroids, and tannins. The phytoconstituents exhibit a great deal of medicinal importance like terpenoids which act as antibacterial, anti-inflammatory, and antioxidant activity. The presence of phenolic components may act as antioxidant, and antimicrobial activity. Many flavonoids are shown to have antioxidant, free radical scavenging capacity, prevents coronary heart disease, anti-inflammatory, anticancer, and anti arthristis as this phytoconstituent can be used as a major tool for producing a quality control profile for a drug.

Another reviewer Bhavna and Bothara<sup>69</sup> reported the phytochemical constituents of *C. hirsutus* leaves to contain D-Trilobine **1**, Isotrilobine **2**, DL-Coclaurine **33** or **33b**, and different sterols **89** (Figure 18), while Cohirsianine **90**<sup>70</sup>, Jamtinine **91**<sup>71</sup> Haiderine **92**<sup>72</sup>, Cohirsine **93**<sup>73</sup>, Shaheenine **94**<sup>74</sup>, Hirsutine **95**<sup>75</sup> and Cohirstinine **96**<sup>76</sup> were extracted from stem and roots (Figure 19).

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<sup>67</sup> P. K. Das, V. Nath, K. D. Gode and A. K. Sanyal. *Ind. J. Med Res.* **1964**, 52, 300 – 307.

<sup>68</sup> J. Khushboo, B. Dhara, D. Bhavita, P. Sonal, Z. Maitreyi. *Int J. Pharm. Sci. Res.* **2016**, 38(1), 165 – 170.

<sup>69</sup> H. M. Bhavna, S. B. Bothara. *Int'l J. Pharm Sci Res.* **2011**, 7(1), 108 – 112.

<sup>70</sup> V.U. Ahmad, T. Rasheed., S. Iqbal. *Phytochemistry*, **1991**, 30(4), 1350 – 1351.

<sup>71</sup> V.U. Ahmad, S. Iqbal. *Phytochemistry*, **1993**, 33(3), 735 – 736.

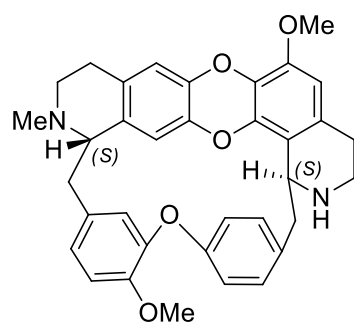
<sup>72</sup> V.U. Ahmad, S. Iqbal. *Nat. Prod. Lett.* **1993**, 2(2), 105 – 109.

<sup>73</sup> V.U. Ahmad, A. U. Rahman, T. Rasheed, H.-u-Rehman *Heterocycles*, **1987**, 26(5), 1251 – 1255.

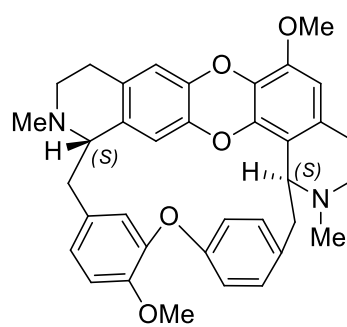
<sup>74</sup> T. Rasheed, M. N. I. Khan, S. S. Zhadi, S. Durrani. *Fitoterapia*, **1991**, 62(2), 157 – 158.

<sup>75</sup> T. Rasheed, M. N. I. Khan, S. S. Zhadi, S. Durrani, *J. Nat. Prod.* **1991**, 54(2), 582-584 1350 – 1351.

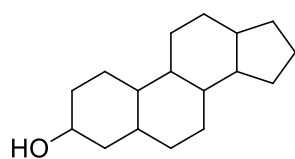
<sup>76</sup> V.U. Ahmad, S. Iqbal. *Fitoterapia*, **1992**, 63(4), 308 – 310.



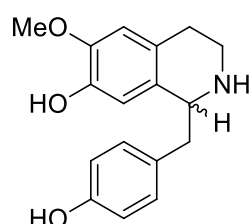
Trilobine **1**



Isotrilobine **2**



Sterols **89**



Coclaurine **33 or 33b**

Figure 18 : Structure of isolated phytoconstituents from the leaves of *C. hirsutus*

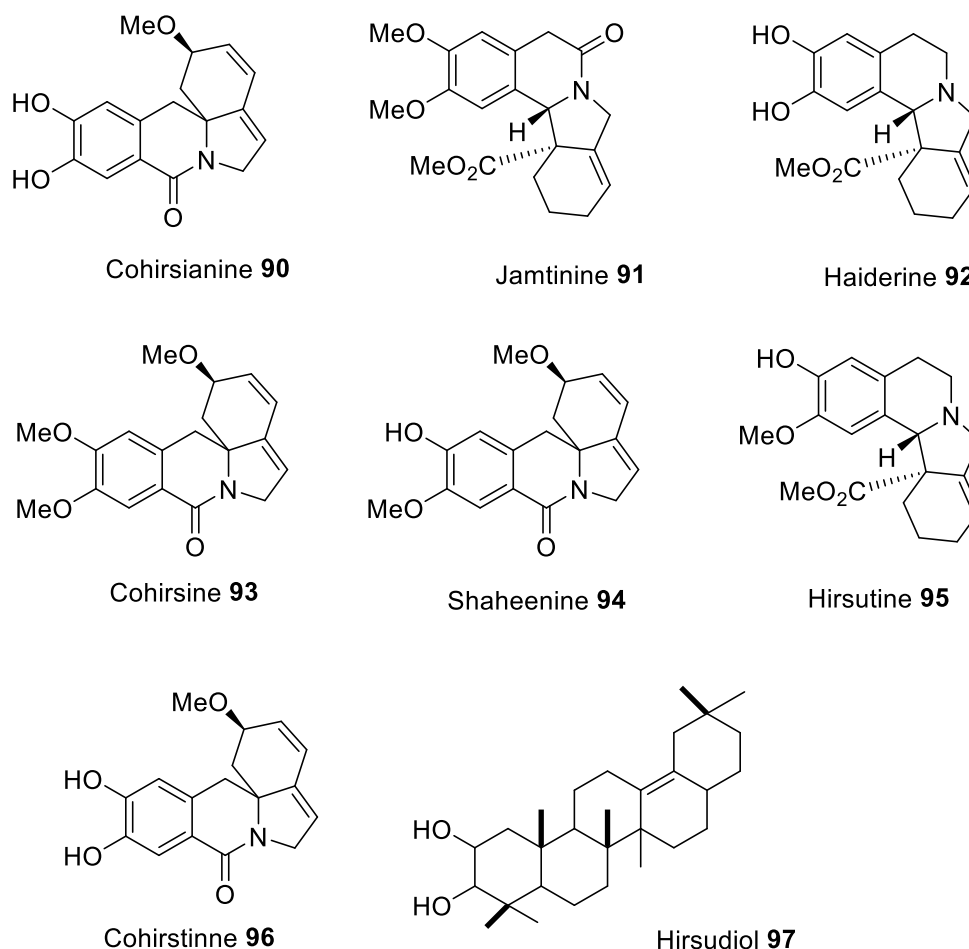


Figure 19 : Structure of isolated phytoconstituents from the stems and roots of *C. hirsutus*

## D. New interest of cancer therapy

### 1. Natural products in cancer therapy

Cancer is one of the leading causes of death in the world. According to the statistical data from the World Cancer Report, about 8.2 million people died because of cancer in 2012 which means 22,500 death per day, among them about 62% are from developing countries and 38% are from developed countries. So if this rate continues, 17.5 million cancer deaths per year can be predicted by 2050<sup>77,78</sup>.

In the 1950s, scientist began the search for anticancer agent from plant and the vinca alkaloids were discovered as the first natural products entering clinical use as an important class of anticancer agents. The vinca alkaloids are series of compounds composed of indole and indoline subunits isolated from *Catharanthus roseus* (L) (Apocynaceae family). After the success of the first clinical trials in the 1960s, clinicians started to use these called vinca alkaloids to treat different types of cancer, they were given the trade names of Velban®, Velbe®, and Oncovin®. Although some

<sup>77</sup> Global cancer facts and figures. *Am. Cancer Soc. Atlanta* 2007.

<sup>78</sup> B. W. Stewart and C. P. Wild. *World cancer report*, 2014. IARC Nonserial 2014.



analogues of the vinca alkaloids have been synthesized and then entered into clinical use including<sup>79</sup> vindesine **98**, vinorelbine **99**, and vinflunine **100** (Figure 20).

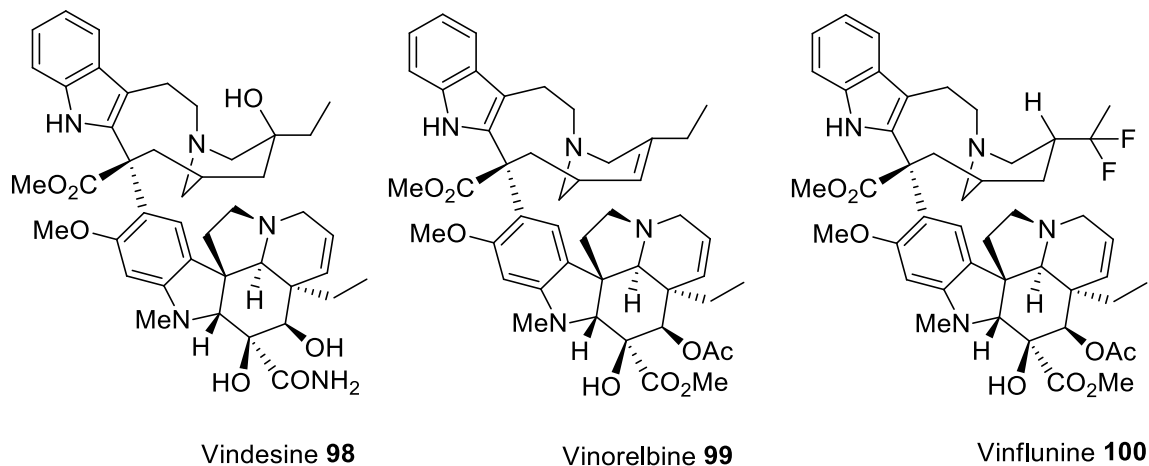


Figure 20 : Anticancer drug from vinca alkaloids

Taxol (paclitaxel) **101**, an active component extracted from the bark of *Taxus brevifolia* is used for years but overcame allergic reaction by using a lengthened infusion period and premedication. Nevertheless, taxol was approved by the FDA for the treatment of ovarian and breast cancer in 1992 and 1994<sup>80</sup>, because it was the first very active to treat these cancers. The semisynthetic analogue docetaxel **102** showed better activities in some assays than taxol **101** and was approved by FDA in 1995<sup>81</sup>.

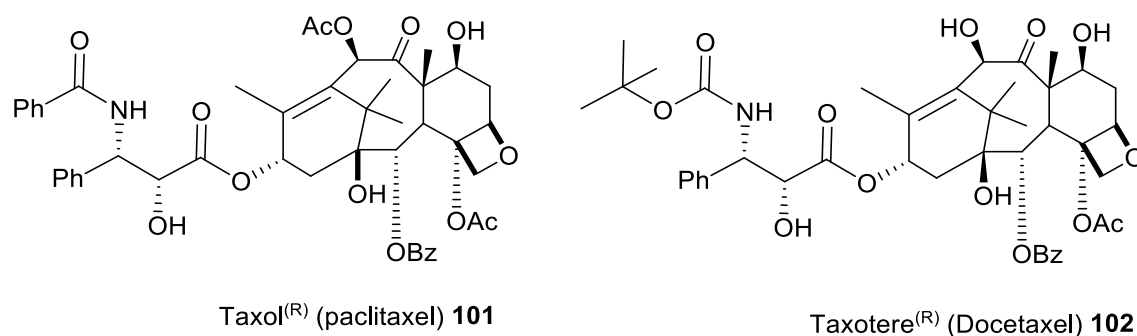


Figure 21 : Anti-cancer drug from Taxol

<sup>79</sup> J. Fahy, A. Duflos, J. P. Ribet, J. C. Jacquesy, C. Berrier, M. P. Jouannetaud, F. Zunino. *J. Am. Chem. Soc.* **1997**, *119*(36), 8576 – 8577.

<sup>80</sup> Y. Ito, N. Horikoshi, T. Watanabe, Y. Sasaki, T. Tominaga, T. Okawa, T. Tabei, Y. Kuraishi, K. Tamura, R. Abe, M. Kitajima, S. Yamaguchi, T. Kobayashi, H. Koyama, K. Orita, S. Takashima, Y. Nomura, M. Ogawa. *Invest. New Drugs*, **1998**, *16*, 183 – 190.

<sup>81</sup> M. C. Bissery, G. Nohynek, G. J. Sanderink, F. Lavelle. *Anti-Cancer Drugs*, **1995**, *6*, 339 – 368.

Another important anticancer natural product is podophyllotoxin **103** which was first isolated in 1880 from an alcoholic extract of *Podophyllum* (Podophyllaceae family) and it is a major component of podophyllin (Figure 22) which was found to inhibit mitotic spindle assembly. Although its side effect stopped its antitumor study. Fortunately, the synthesized podophyllotoxin glycoside as the etoposide **104** which entered into clinical use as an effective anticancer drug<sup>82</sup>. Later on, FDA approved etoposide drug for testicular cancer treatment.

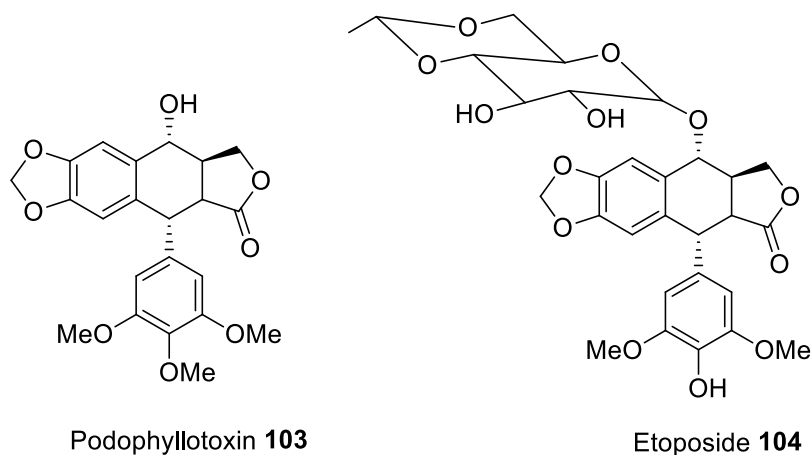


Figure 22 : Anticancer drug from podophyllotoxine alkaloids by Canel *et al*

All these natural products had represented important milestones in the anti-cancer drugs development with their specific mode of action, and BBIQs extracted from Menispermaceae such as trilobine and isotrilobine may represent the next one with development of knowledge in the epigenetic field.

## E. Trilobine and isotrilobine

### 1. History.

The first evocation of Trilobine or Isotrilobine dates from the 1920s. At that time, Kondo and Nakazato have isolated alkaloids from *Cocculus trilobus*, and they named it trilobine<sup>83</sup> but with a wrong structure. Two years later, the same group isolated a second alkaloid from the same *Cocculus trilobus*, and called it homotrilobine because of its additional methyl<sup>84</sup>. The same compounds were then also isolated from *Cocculus sarmentosus*.<sup>85</sup>

<sup>82</sup> C. Canel, R. M. Moraes, F. E. Dayan, D. Ferreira. *Phytochemistry*, **2000**, 54(2), 115 – 120.

<sup>83</sup> H. Kondo, T. Nakazato, *Yakugaku Zasshi.*, **1924**, (511), 691 – 692.

<sup>84</sup> T. Nakazato, *Yakugaku Zasshi.*, **1926**, (532), 461 – 462.

<sup>85</sup> H. Kondo, M. Tomita, *Yakugaku Zasshi.*, **1927**, (542), 265 – 278.

In 1932, Franz Faltis corrected the structure<sup>86</sup> to a dimeric molecule, but with a wrong position for the methoxy group in position 8' instead of position 5. Finally, after different publications, the definitive correct structure, with stereochemical configurations was established in 1962.<sup>87</sup>

## 2. Botanical and phytochemistry clarification

Usually, natural products are named with respect to the name of the plant from which they were isolated. So, naturally, when Kondo and Nakazato isolated alkaloids from *Cocculus trilobus*, they gave the name Trilobine. Then, they gave the name homotrilobine to the second alkaloids they isolated with an additional methyl. Unfortunately, in 1992, an American group had isolated a highly cytotoxic acetogenin from an Annonaceae *Asimina triloba*,<sup>88</sup> and gave the name trilobin **105** (without a terminal “e”) to this molecule, which has no relation at all to the trilobine **1** (with a terminal “e”) from Menispermaceae *Cocculus sp.* (Figure 23).

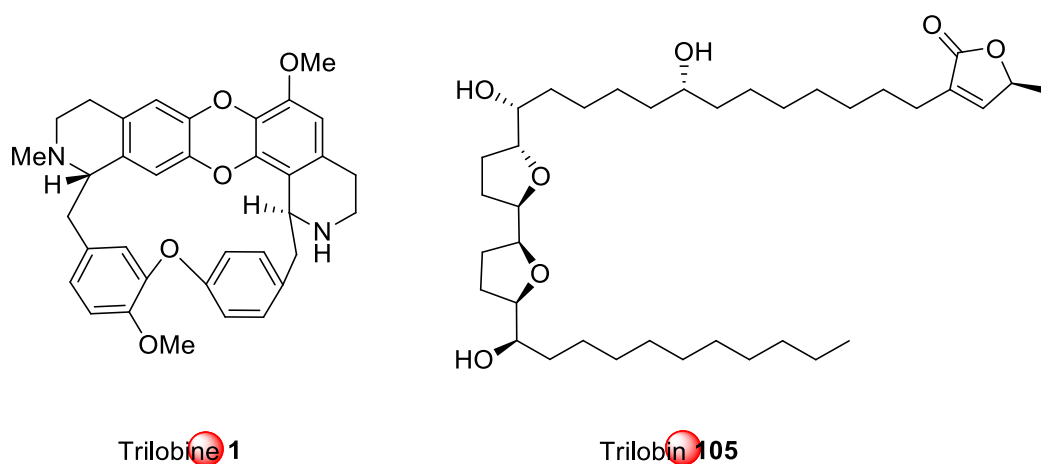


Figure 23 Trilobine and Trilobin

Many plant species have “trilobus” as qualification that just means these plants are three-lobes leaves plants. It is not a problem for botanists, because plants are named with a genus name and with a species name, but it becomes problematic in chemistry when molecules are named with only one appellation. The opposite is also known, when a molecule is isolated separately from different plant and is named differently, and a single molecule finishes with two (or even more) different names. This is a real problem to which we have to pay close attention, and discussed in default to solve it.<sup>89</sup>

<sup>86</sup> F. Faltis, *Justus Liebig Ann.*, **1932**, 301-302.

<sup>87</sup> Y. Inubushi, K-I. Nomura, *Tetrahedron Lett.* **1962**, 24(3), 1133 – 1136.

<sup>88</sup> G. Zhao, Y. Hui, J.K. Rupprecht, J.L. McLaughlin, K.V. Wood, *J. Nat. Prod.* **1992**, 55(3), 347 – 356.

<sup>89</sup> C. Lavaud, G. Massiot, *Phytochemistry* **2016**, 131, 7 – 8.

### 3. First Synthesis of trilobine and related compounds

In 1962, Inubushi and Nomura were first to report the structure of trilobine and isotrilobine which were been isolated from *C. trilobus* DC.<sup>87</sup> Although, the stereochemical configuration of asymmetric centers and the secondary nitrogen were undermining the reductive fission with sodium in liquid ammonia by which the steric configuration of most bisbenzylisoquinoline alkaloids was decisively used even when this condition didn't give favourable result because of the presence of the dibenzo-*p*-dioxin system.

Then, some Japanese researcher Inubushi *et al.*<sup>90</sup> reported the first total synthesis of trilobine **1** and obaberine **41** alkaloids. They started by synthesizing the benzyl-8-bromo-N-norarmepavine **110** from the condensation of *p*-benzyloxyphenyl acetic acid **106** and 3-bromo-4,5-dimethoxyphenethylamine **107** to form amide **108**. The compound amide **108** was subjected to Bischler-Napieralski reaction to form the cyclized imine **109** and then reduced with NaBH<sub>4</sub> to afford **110** (Scheme 4).

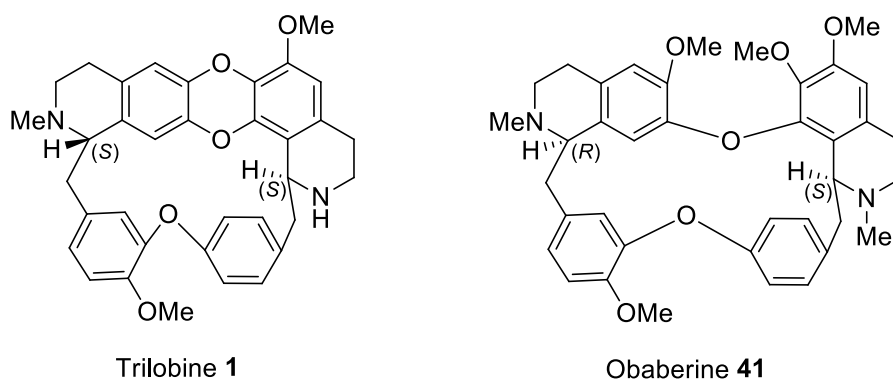
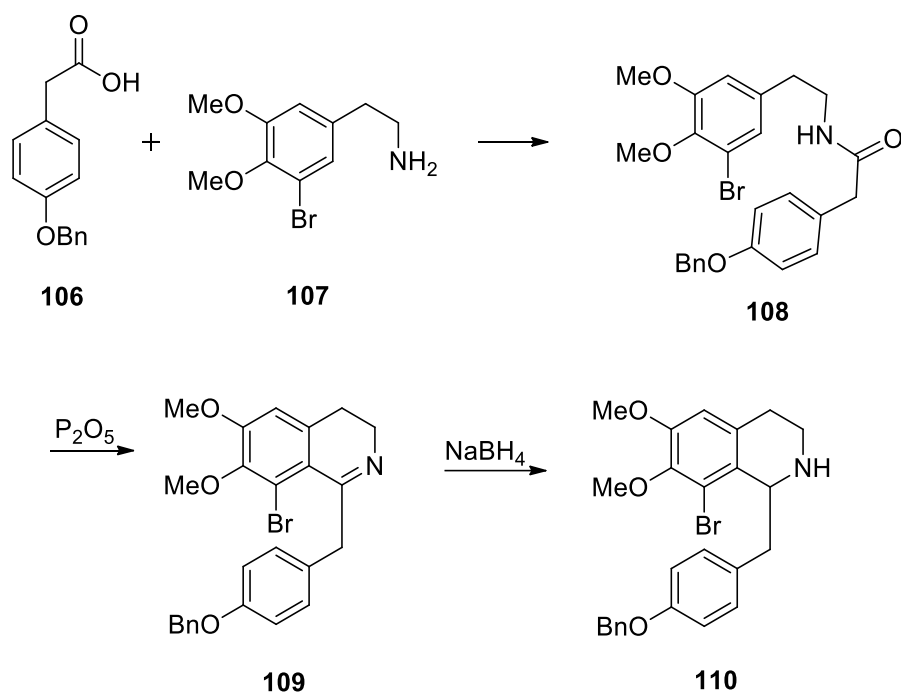


Figure 24 : Structure of Trilobine **1** and Obaberine **41**

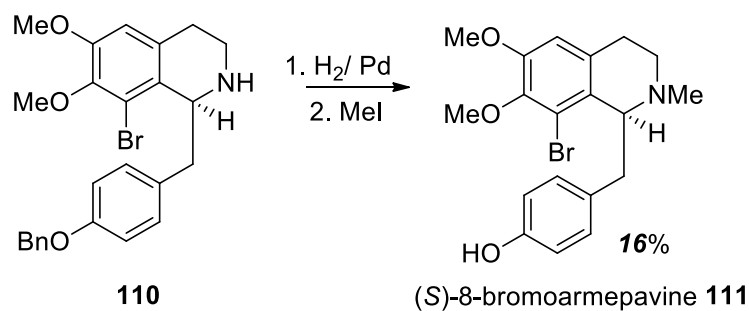
<sup>87</sup> Y. Inubushi, K-I. Nomura, *Tetrahedron Lett.* **1962**, 24(3), 1133 – 1136.

<sup>90</sup> a) Y. Inubushi, Y. Ito, Y. Masaki and T. Ibuka. *Tetrahedron Lett.* **1976**, 33, 2857 – 2860. b) Y. Inubushi, Y. Ito, Y. Masaki and T. Ibuka. *Chem. Pharm. Bull.* **1977**, 25, 1636 – 1644.



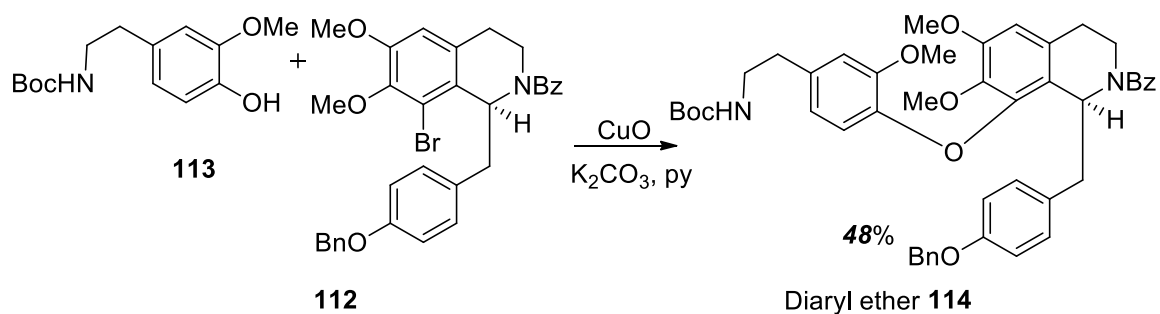
Scheme 4 : Synthetic route of cyclization by Inubushi *et al*

The compound **110** was resolved via its *N*-acetyl-*L*-leucine salt and the absolute configuration and optical purity of the resolved free base were converted into (*S*)-8-bromo-armepavine **111** (16% yield, Scheme 5), to be compared to the compound of the bromation of natural armepavine.



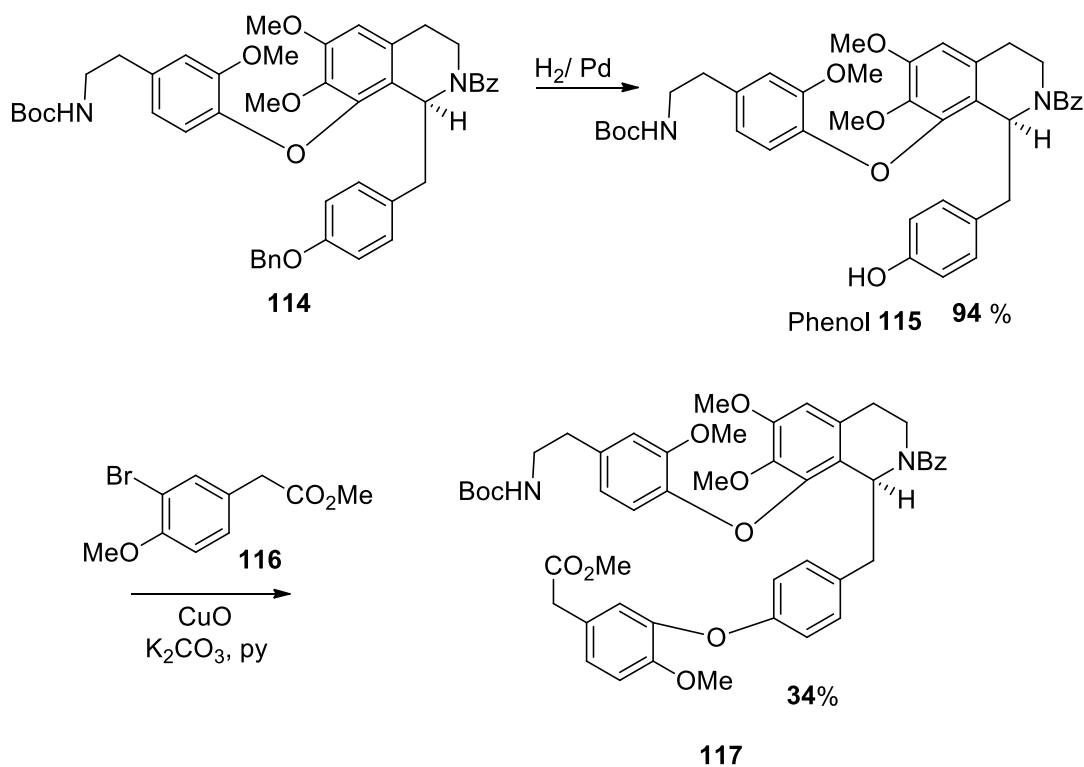
Scheme 5 : Synthesis of bromoarmepavine by Inubushi *et al*

The compound **111** was protected with benzoyl group to give the compound **112** which enabled the condensation by Ullmann reaction on *N*-*t*-butoxycarbonyl-3-methoxy-4-hydroxyphenylethylamine **113** since the Boc group is unstable under Ullmann reaction to give diphenyl ether **114** in 48% yield (Scheme 6).



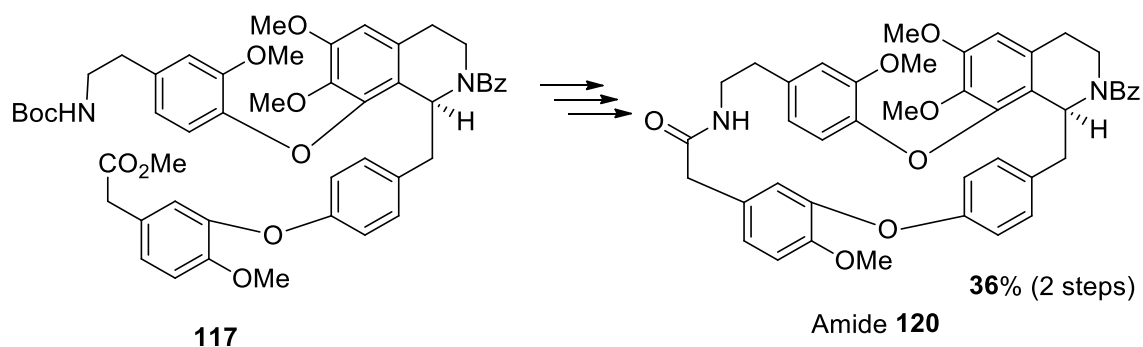
Scheme 6 : Ullmann type reaction

Hydrogenolysis of **114** on Pd catalyst gave the phenol **115** and the condensation by Ullmann reaction with methyl 3-bromo-4-methoxyphenyl acetate **116**, afforded compound **117** in 34% yield (Scheme 7).



Scheme 7 : Hydrogenolysis/ Ullmann reaction

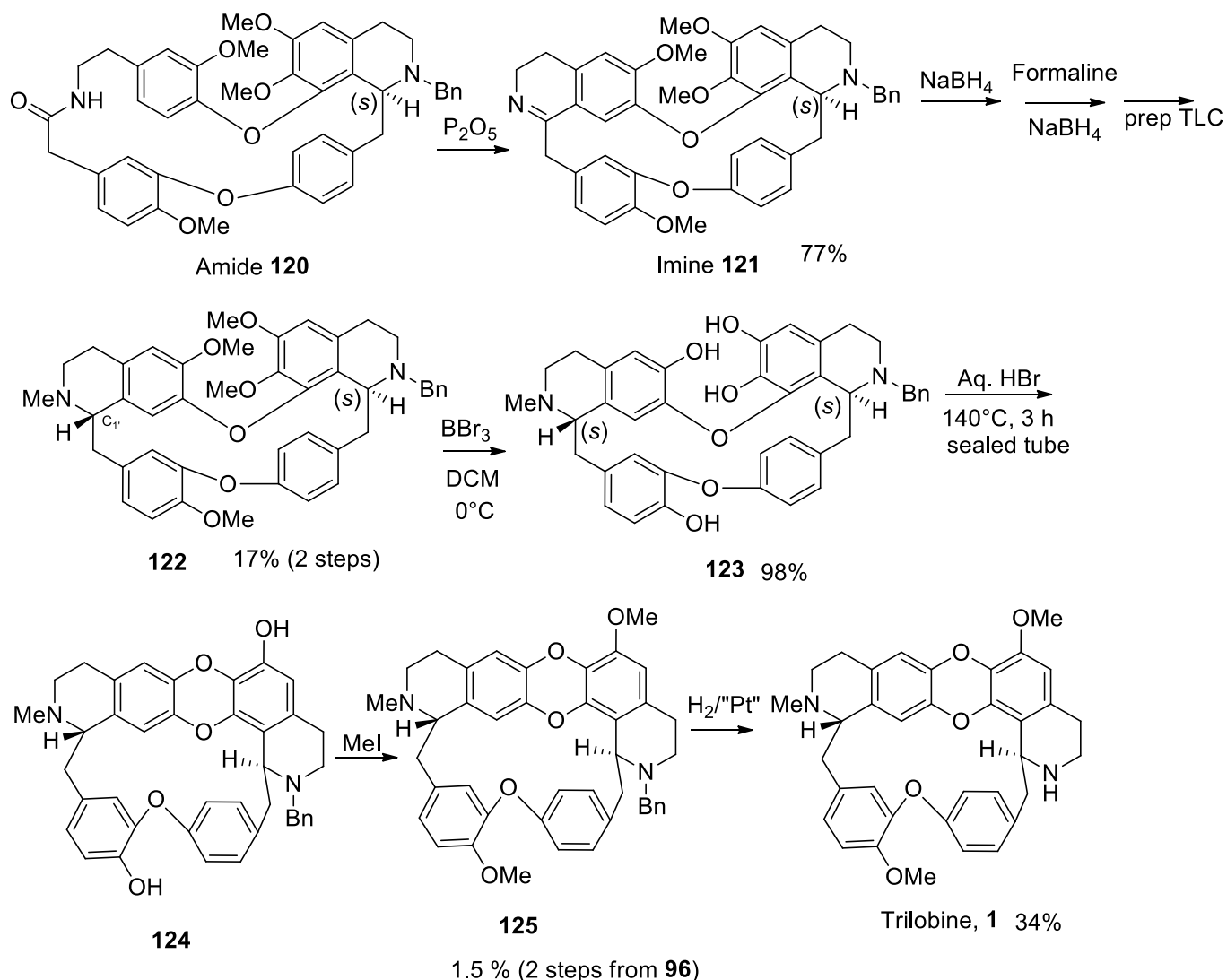
The compound **117** was hydrolyzed by alkali to form a free acid which was converted into its *p*-nitrophenyl ester with *p*-nitrophenol in the presence of dicyclohexycarbodiimide (DCC) and removal of *N-t*-Boc with trifluoroacetic acid gave *p*-nitrophenyl ester phenethylammonium trifluoroacetate and was then cyclized to form the amide **120** in 36% yield (Scheme 8).



Scheme 8 : Hydrolysis/ amide reaction

With the Bischler-Napieralski reaction, the cyclization of the amide **120** affords the imine **121** and in such subjected to reduction with  $\text{NaBH}_4$  gave a diastereoisomeric mixture. Both diastereoisomers were separated by preparative TLC, and the expected compound **122**, was obtained in only 17% yield. This diastereoisomeric compound ( $\text{C1}'$ :  $\alpha$ -H) was isolated in 43 % yield. **122** was then treated with  $\text{BBr}_3$  in DCM at  $0^\circ\text{C}$  to form the per-*O*-demethylated compound **123**. The next stage is the construction of the dibenzo-*p*-dioxin nucleus with a saturated solution of HBr heated in a sealed tube at  $140^\circ\text{C}$  for 3 hrs to afford the compound **124** and methylation with diazomethane provided **125**, and on hydrogenolysis with platinum catalyst gave trilobine **1** (Scheme 9). The Isotrilobine is then directly obtained from trilobine by classical Eschweiler-Clark reaction <sup>91</sup>

<sup>91</sup> M. Tomita; Y. Inubushi, *Pharm. Bull.*, **1955**, 3(1), 7-11.



Scheme 9 : Synthesis of trilobine alkaloids

Although, their synthetic report showed that the structural feature of trilobine and isotrilobine alkaloids, both possess a dibenzo-*p*-dioxin nucleus, which is usually formed by Ullmann type of reactions. Their synthesis involved multiple steps, dramatically low yield, and unsymmetrically substituted derivatives. We aim to improve on the synthesis of this trilobine and isotrilobine alkaloids in our research study.

With respect to the very poor global yield of this synthesis (less than 0.00005 %), it cannot be possible to use it to be able to prepare trilobine and analogues, and we need to rethink all the strategy to improve this synthesis.

Our objective of this research comprised two distinct parts. The first is to develop a synthetic strategy that will be more efficient to provide the access to the dimeric structure in a shorter route. And secondly, to access the diverse bioactive compound of each molecule in other to validate its efficacy and medicinal used.



Since herbal plants have been consumed by men for their purported or documented health benefits; even during an era when their phytochemical constituent were not known. However, in recent times, scientific studies are beginning to confirm or refute quite a number of claims and assertions; by isolating, characterizing, identifying, and classifying the various secondary metabolites responsible for their actions. Also, factors that may be responsible for certain deleterious effects of herbal beverages are being identified. As of present, there is incontrovertible scientific evidence that herbal plants are a rich source of phytochemicals that possess a myriad of health benefits; including the prevention or management of central nervous systems (CNS) disorders such as mood, anxiety-related, or neurodegenerative disorders.

The aim of this research work is to contribute to the existing body of knowledge about trilobine (*C. hirsutus*) as medicinal plants. Medicinal plants are used to cure diseases and several modern research have shown that the therapy of using plants is better than chemicals, by being safer besides having the synergistic effect of their active ingredient and presence of certain minerals.

Although, there is still a large number of medicinal plants in which the active constituents have not yet been investigated even though their effect is established by folklore and traditional system of medicine. So many reviews on the medicinal values of *C. hirsutus* showed that it possesses various therapeutic properties. Taking into consideration the reported pharmacological actions and the traditional claims of *C. hirsutus*, we planned to achieve the below objectives.

We are looking for other syntheses of BBIQ derivative and to study them, to find a better solution for the synthesis of trilobine than the one presented, in 1977, by Inubushi and his group.



## CHAPTER 2 : CHEMISTRY AND SYNTHESIS OF BBIQ ALKALOIDS

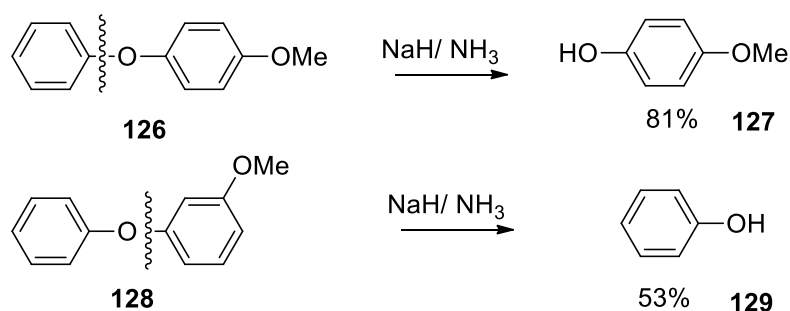
As just describe in the precedent chapter, the total synthesis of trilobine described up to now is not satisfactory. Some steps were very problematic, and the development of a new and efficient synthesis presupposes certain changes in protocol or pathway of these problematic steps. We are to focus then, by looking at all synthesis described for other BBIQ, and not from the type **XXIII** subgroup.

### A. Elucidation of dimers:

The bisbenzyltetrahydroisoquinoline alkaloids comprise of over thirty subtypes which possesses structures containing two benzyltetrahydroisoquinoline nuclei joined by one, two, or three ether linkages. They occur in plants of Menispermaceae and other related families which include genera *Berberis*, *Magnolia*, and various species. The position and the number of ether linkages in the molecule have served as convenient criteria for the classification of these alkaloids into subgroups.

#### 1. Diaryl ether cleavage:

In 1937, Sartoretto and Sowa<sup>92</sup> reported on the cleavage of diaryl ethers with sodium in liquid ammonia which was used before the advent of chromatography as a standard laboratory tool for the reaction. The simple mechanism for the reductive cleavage of diaryl ether is that the metal in liquid ammonia system is a rich source of electrons because the successive steps involves the addition of an electron to form an anion radical followed by protonation with the ammonia which acts as the proton source (Scheme 10).



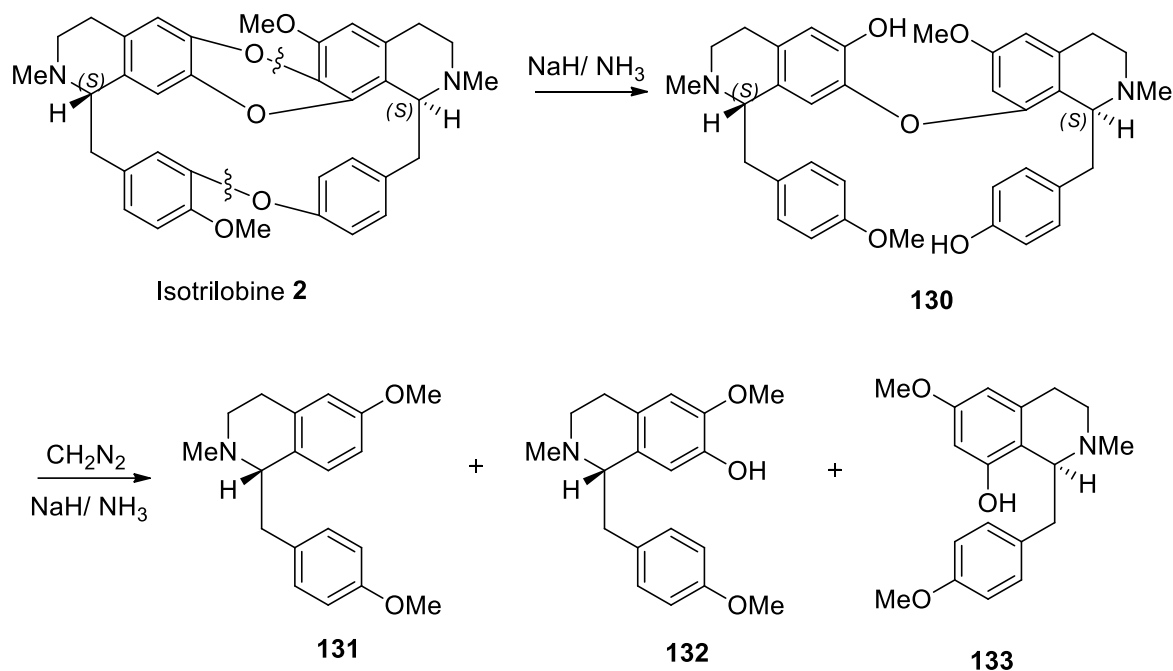
Scheme 10 : Cleavage of diaryl ether by Sartoretto and Sowa

Cleavage of bisbenzyltetrahydroisoquinoline was believed to be a rich source of electrons to the system which forms an ion radical that is protonated by the ammonia prior to the cleavage. It was not until 1951 when Tomita *et al.*<sup>93</sup> applied this reaction to the isotrilobine **2** in the determination of the steric configuration of two asymmetric centres in bisbenzyltetrahydroisoquinoline alkaloids.

<sup>92</sup> P. A. Sartoretto, F. J. Sowa. *J. Am. Chem. Soc.* **1937**, 59(4), 603 – 606.

<sup>93</sup> M. Tomita, E. Fujita, F. Murai. *J. Pharm Soc. Jpn.* **1951**, 71(10), 1035 – 1039.

Since that time, this reaction has been utilized on different bisbenzyltetrahydroisoquinoline alkaloids and remain a useful method to elucidate the structure of dimers (Scheme 11).



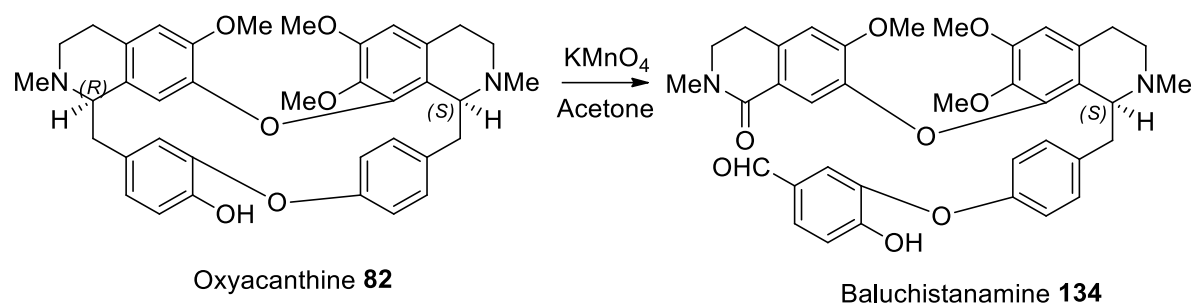
Scheme 11 : Cleavage of bisbenzyltetrahydroisoquinoline alkaloid by Tomita *et al*

## 2. Potassium Permanganate Oxidation:

The oxidation with potassium permanganate in aqueous acidic solutions has been used to determine the nature and substitution of the “south” part (bisbenzyl part) of various bisbenzyltetrahydroisoquinoline alkaloids. Shamma *et al.*<sup>94</sup> reported that oxyacanthine **82** could be converted to baluchistanamine **134** by treating with potassium permanganate in acetone and it is necessary to alkylate phenolic groups of the molecule prior to oxidation so that the dimeric nature of the product is not lost during phenolic oxidation. However, similar structural bisbenzyltetrahydroisoquinoline alkaloids underwent oxidation in an analogue manner which was formed by cleavage at the benzylic bond of isoquinoline moiety unsubstituted at C-8' or C-8<sup>95</sup> (Scheme 12).

<sup>94</sup> M. Shamma, J. E. Foy, G. A. Miana. *J. Am. Chem. Soc.* **1974**, 96(25), 7809 – 7811.

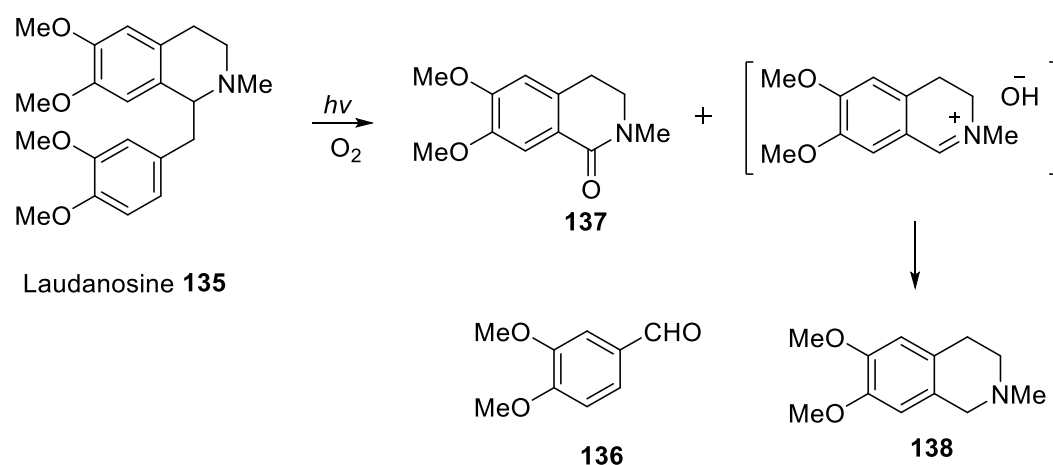
<sup>95</sup> J. E. Leet, S. F. Hussain, R. D. Minard, M. Shamma. *Heterocycles*, **1982**, 19(12), 2355 – 2360.



Scheme 12 : Oxidation of bisbenzyltetrahydroisoquinoline alkaloids by Shamma *et al*

### 3. Photo-oxidation:

In 1971 Bick *et al.*<sup>96</sup> reported the use of photo-oxidative cleavage reaction in some benzyltetrahydroisoquinoline based alkaloids that are useful in the structural studies of bisbenzyltetrahydroisoquinoline alkaloids. The laudanosine **135** under ultraviolet irradiation in the presence of oxygen, gave mostly 3,4-dimethoxybenzaldehyde **136** in 67%, followed by 3,4-dimethoxyterahydroisoquinolone **137** in 45% and the carbinoamine, which was reduced with sodium borohydride to afford 3,4-dimethoxytetrahydroisoquinoline **138** (Scheme 13).

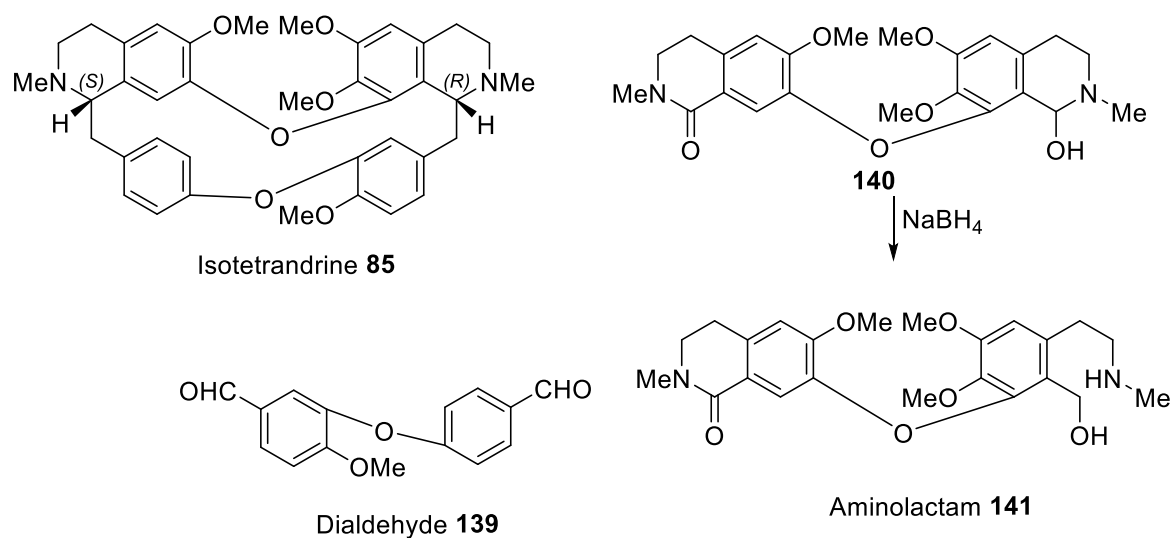


Scheme 13: Photo-oxidative cleavage reaction of benzyltetrahydroisoquinoline alkaloids by Bick *et al*

According to them, this method has had only limited success when applied to the more complicated bisbenzyltetrahydroisoquinoline alkaloids. So they tried an example of isotetrandrine **85** alkaloids in the presence of oxygen which gave the dialdehyde **139** in 50% as the major product and amide-carbinolamine intermediate **140**, isolated after reduction and its ready dehydration gave aminolactam **141** in 30%. However, this reaction was of great importance in the determination of the dibenzo-*p*-dioxine structure of bisbenzyltetrahydroisoquinoline alkaloids. So, the emergence of

<sup>96</sup> I. R. C. Bick, J. B. Bremner, P. Wiriyachitra. *Tetrahedron Lett.* **1971**, 12(50), 4795 – 4797.

oxidative photolysis is still an alternate to Na/NH<sub>3</sub> cleavage in the elucidation of the structure of bisbenzyltetrahydroisoquinoline alkaloids by conversion of simpler products (Scheme 14).



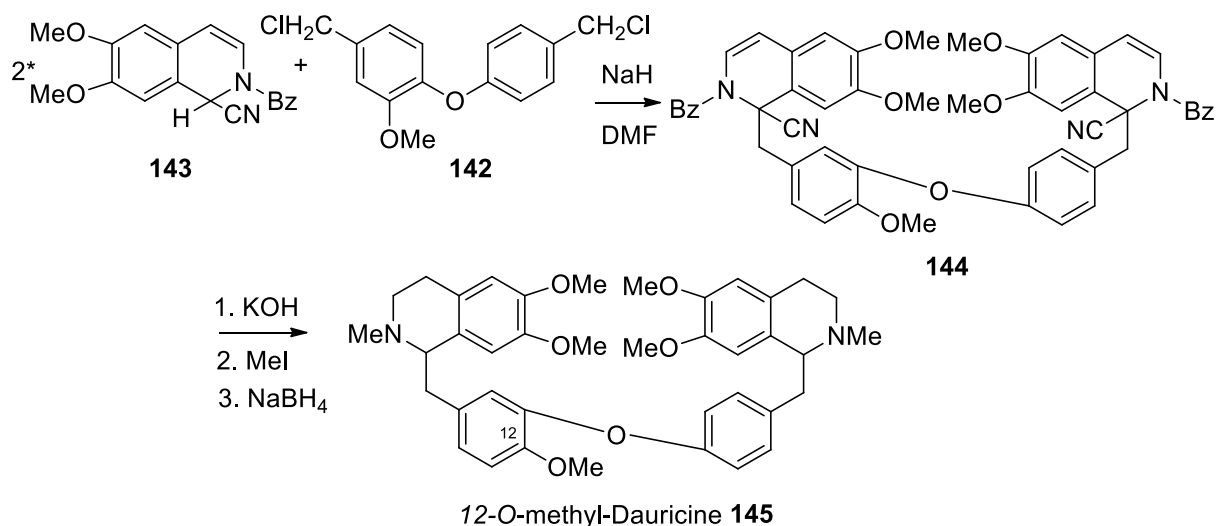
Scheme 14 : Photolysis of bisbenzyltetrahydroisoquinoline alkaloids by Bick *et al.*

#### 4. With Reissert condensation:

In 1905<sup>97</sup> Arnold Reissert discovered that quinolone or isoquinoline could react with benzoyl chloride in the presence of aqueous potassium cyanide to form the resulting 1,2-dihydro-1-benzoyl-2-cyanoquinoline which was later named Reissert compounds and it became a versatile tool for different synthetic applications. However, Blasko *et al.*<sup>98</sup> reported the synthetic work of bisbenzylisoquinoline-type alkaloids by alkylation of the anion of isoquinoline with bifunctional diaryl ether **142**. The sequence involving diaryl ether **142** and the Reissert **143** derivatives afford bisbenzylisoquinoline **144**. The quaternarization of deprotected **144** with methyl iodide and subsequent sodium borohydride reduction gave *O*-Methylauricine **145** in racemic form (Scheme 15).

<sup>97</sup> A. Reissert, *Chem. Ber.* **1905**, 38, 1603-1614.

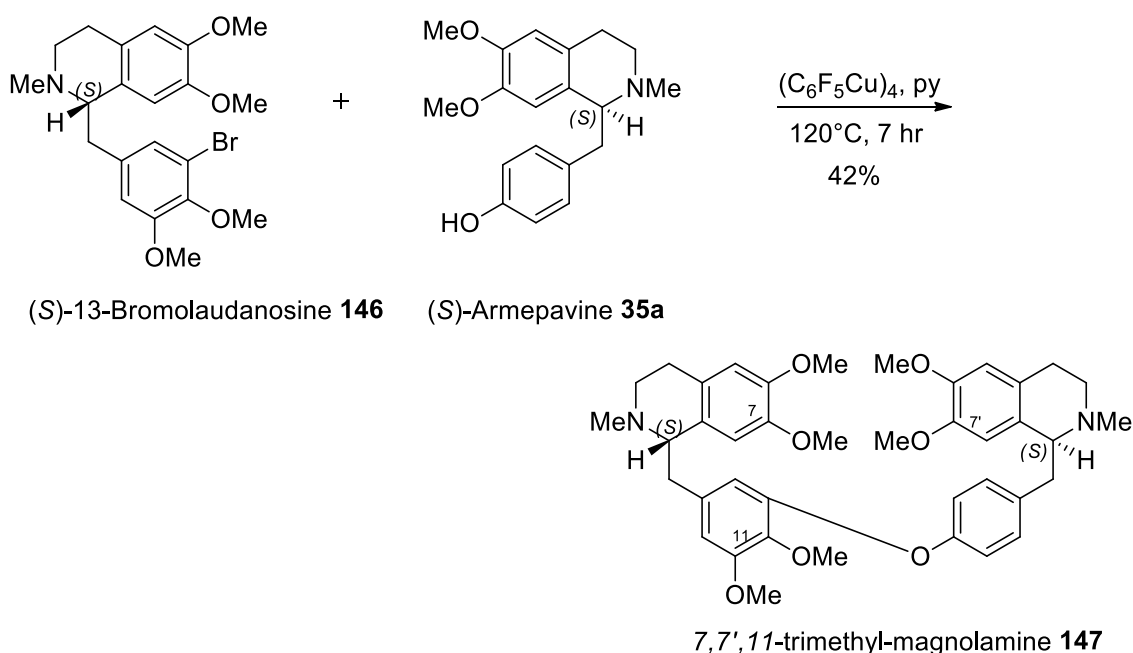
<sup>98</sup> G. Blasko, P. Kerekes and S. Makleit, *Alkaloids*, (Academic Press) **1987**, 31, 1 – 28.



Scheme 15 : BBIQ synthesis by Reissert condensation.

### 5. Ullmann-type reaction:

The classical Ullmann-type synthesis of a bisbenzyltetrahydroisoquinoline alkaloids involves the direct coupling of a phenolic benzyltetrahydroisoquinoline with a halogenated in the presence of copper or one of its salts or oxides. The advantage of this approach is that the two halves of the dimers may be prepared, separated as pure enantiomers before the final coupling step although the yield is very low. The condensation of an equimolar amount of (*S*)-5'- bromolaudanosine **146** with (*S*)-armepavine **35a** in pyridine in the presence of pentafluorophenyl copper gave *O*-trimethylmagnolamine **147** in 42% yield (Scheme 16).



Scheme 16 : Ullmann type of reaction

## B. Synthesis of bisbenzyltetrahydroisoquinoline alkaloids containing one diphenyl ether link:

The simplest bisbenzyltetrahydroisoquinoline alkaloids are bases of mono ether type – dauricine (**type I**) and liensinine (**type V**) were aimed at the first synthetic attempts. There exist two fundamental synthetic routes to such alkaloids from substituted diphenyl ethers by the addition of appropriate isoquinoline fragments using the known classical method (Pictet-Spengler or Bischler-Napieralski reactions) and linking substituted benzyloisoquinoline bases by means of ether bridges.

### 1. Dauricine (Type I)

Dauricine is one of the alkaloids of Menispermaceae plant isolated from *Menispermum dauricum* DC by Kondo and Narita in 1927 and later in 1943, Manske also isolated it from *Menispermum canadense* L<sup>99</sup>. Kondo and Narita used a chemical methods to assign the structure of dauricine and Tomita *et al.*<sup>100</sup> stated that *O*-methyldauricine **145** was synthesized by Ullmann reaction of armepavine **35** and 3'-bromo-armepavine **148**.

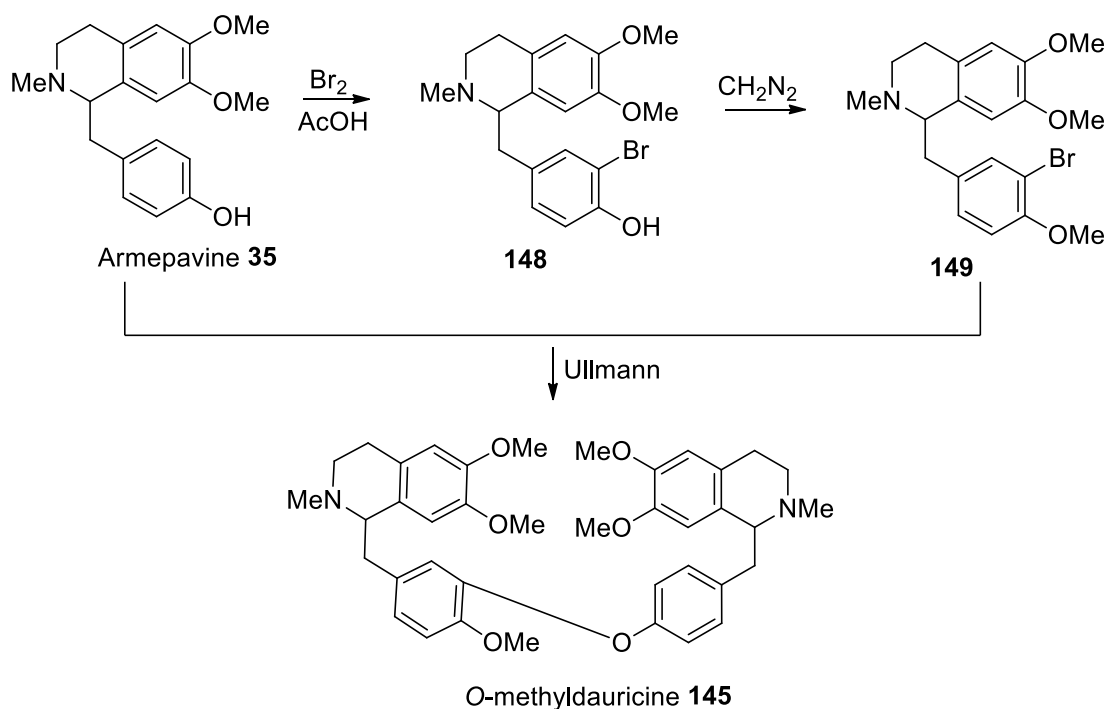
The starting material for the first clean optically active of armepavine **35** was engaged into bromination with acetic acid to form bromo-armepavine **148** and then methylated to afford the bromo-*O*-methylarmepavine **149**. So, armepavine **35** and compound **149** were heated (190-200°C) in presence of potassium methanolate and a mixture of copper powder and cupric acetate to afford the *O*-methyldauricine **145** (Scheme 17).

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<sup>99</sup> H. Kondo, Z. Narita. *Yakugaku Zasshi* **1927**, (542), 279 – 280. (b) R. H. F. Manske. *Can. J; Research*, **1943**, 21B, 17 – 20.

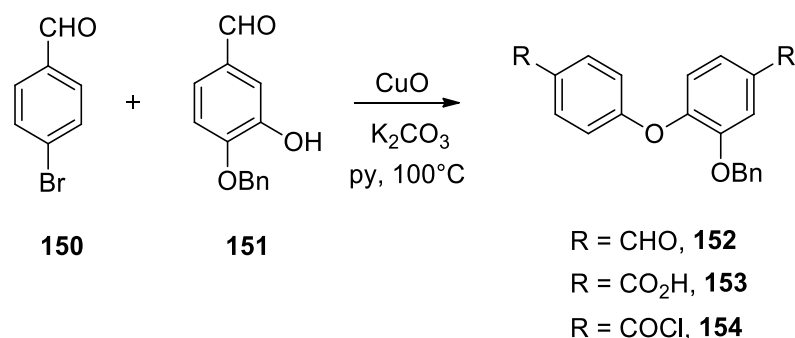
<sup>100</sup> M. Tomita, K. Ito, H. Yamaguchi. *Pharm. Bull.* **1955**, 3(6), 449 – 453.





Scheme 17 : Synthesis of O-methyldauricine alkaloids by Tomita *et al.*

However, Kametani and Fukumoto<sup>101</sup> reported the total synthesis through the cyclization of the diamide in order to obtain the corresponding isoquinoline and its methiodide form – the dauricine. They started by Ullmann reaction of 4-bromobenzaldehyde **150** with 4-benzylprotocatechuic aldehyde **151** to yield to 2-benzyloxy-4',5'-diformyldiphenyl ether **152**, and the oxidation of diphenyl ether **152** gave the corresponding dicarboxylic acid **153**, such that the chlorination of the acid with thionyl chloride form acid chloride **154** (Scheme 18).

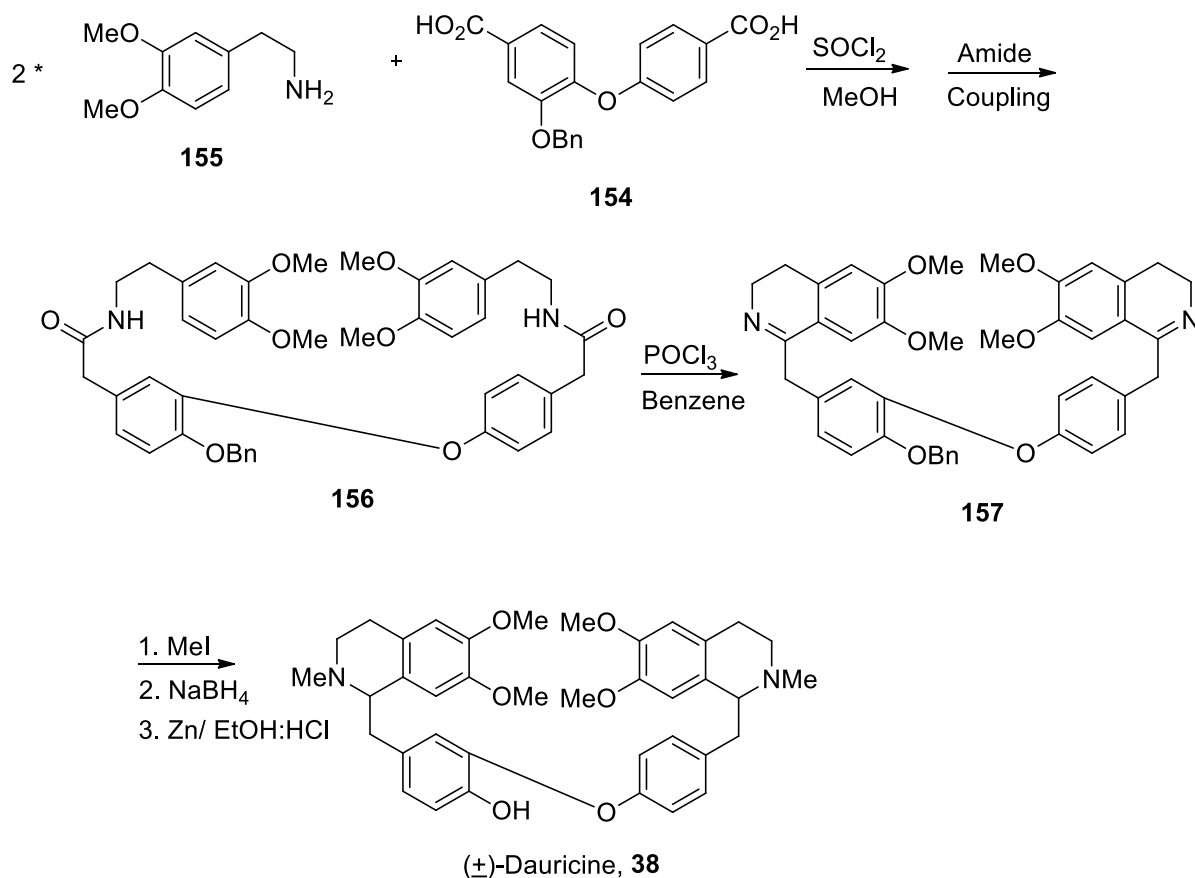


Scheme 18 : Diaryl ether formation

The dimethyl-dopamine **155** was treated under Schotten-Baumann conditions with the derivative of the diacid **154** afforded the amide **156**. The Bischler-Napieralski cyclization of the amide **156** afforded the isoquinoline **157** derivative. The reduction the methiodide derivative of **157**, follow

<sup>101</sup> T. Kametani, K. Fukumoto, *Tetrahedron Lett.* **1964**, 5(38), 2771 – 2775.

by débenzylation with zinc dust and ethanol-concentrated hydrochloric acid (1:1) afforded a mixture of (+) dauricine **38** and its diastereoisomer (Scheme 19).



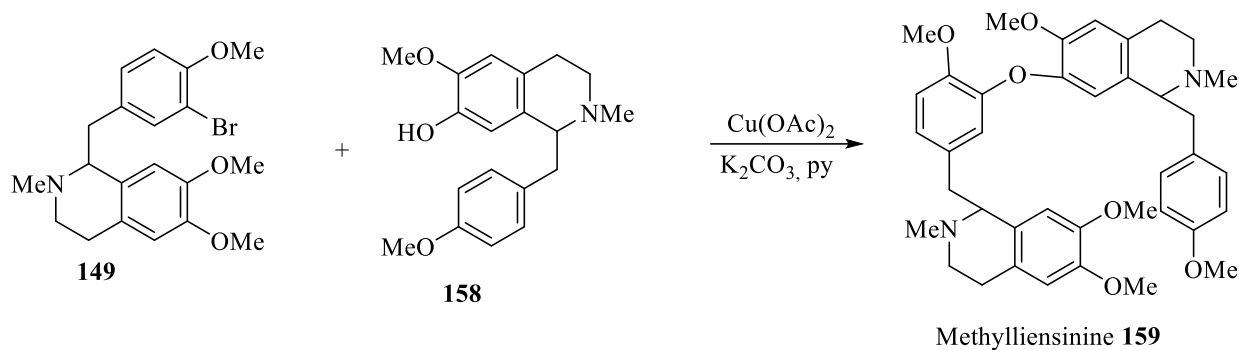
Scheme 19 : Synthesis of dauricine by Kametani and Fukumoto

## 2. *Liensinines (Type V)*

In 1966 Kametani *et al* reported the total synthesis of diastereoisomeric mixture of liensinine which was extensive degradative work on the liensinine alkaloids (**Type V**) with the composition of  $C_{37}H_{42}O_6N_2$  that was isolated from the seed of *Nelumbo nucifera* Gaertn (also called sacred lotus)<sup>102</sup>. The result showed that the structure had a mixture of diastereoisomer that could not be readily separated. The reaction was carried out with *O*-methyl-Coclaurine **158**, prepared by Bischler-Napieralski reaction, and then condensed by Ullmann type reaction with 3'-bromo-armepavine **149** to afford the diastereoisomeric mixture of methyl liensinine **159** which is not separable<sup>103</sup> (Scheme 20)

<sup>102</sup> T-y Chao, Y-l. Chou, T.-t. Young, T.-q. Chou, *Sci. Sin.*, **1962**, *11*, 215-219.

<sup>103</sup> T. Kametani, S. Takano, K. Masuko, F. Sasaki. *Chem. Pharm. Bull.*, **1966**, *14*(1), 67 – 72.



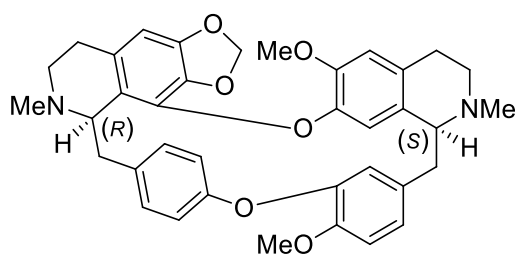
Scheme 20 : Synthesis of Liensinine by Kametani *et al.*

### C. Synthesis of bisbenzylisoquinoline alkaloids containing two diphenyl ether link:

This group of alkaloids that are formed in plants by enzymatic double dehydrogenation of two molecules of coclaurine and its derivatives differing in the location of the ether.

#### 1. Cepharanthine alkaloids (Type VI):

Cepharanthine is a member of bisbenzylisoquinoline alkaloids that possess a unique structural feature with the methylenedioxy group on its tetrahydroisoquinoline nucleus. Cepharanthine **160** is an ether-soluble, optically active, non-phenolic, amorphous tertiary base which can only be crystallized from benzene as the benzene adduct. It was earlier believed that this alkaloid ( $C_{37}H_{38}O_6N_2$ ) contained three methoxyl groups and three oxygen bridges in the molecule, but careful functional group determination<sup>104</sup> showed that there are two methoxy groups, two ether bridges, and one methylenedioxy group (Figure 25).



Cepharanthine **160**

Figure 25 : Cepharanthine structure

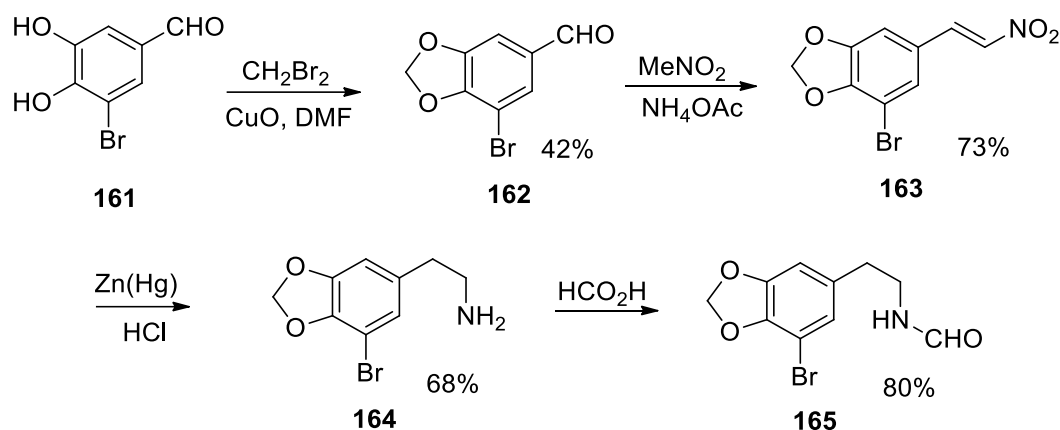
This natural product is mainly isolated from *Stephania cepharantha* Hayata and the structure was later elucidated<sup>105</sup>. Although, the attempt to synthesize this alkaloid remained unsuccessful until

<sup>104</sup> (a) H. Kondo and M. Tomita. *J. Pharm. Soc. Jpn.* **1939**, 59, 207 – 209; (b) *Chem. Abstr.*, **1940**, 34, 7530 – 7533.

<sup>105</sup> H. Kondo, Y. Yamamoto, I. Keimatsu. *J. Pharm. Soc. Jpn.* **1934**, 54, 620 – 633; M. Tomita, Y. Sasaki. *Chem. Pharm. Bull. Tokyo.* **1953**, 1(1), 105 – 109.

M. Tomita *et al.* reported its first synthesis<sup>106</sup> through Bischler-Napieralski reaction. The preparation of 5-bromohomopiperonylamine **164** was performed starting from 5-bromoprotocatechic aldehyde **161**.

The methylenation of **161** with methylene bromide in DMF under the presence of a catalyst CuO<sup>107</sup> afforded **162** that was condensed by Henry's reaction to form the nitrostyrene **163** on further reduction under Clemmensen condition gave the corresponding amine **164** though the amino function was protected with formic acid that resulted in the *N*-formyl derivatives **165** (Scheme 21).

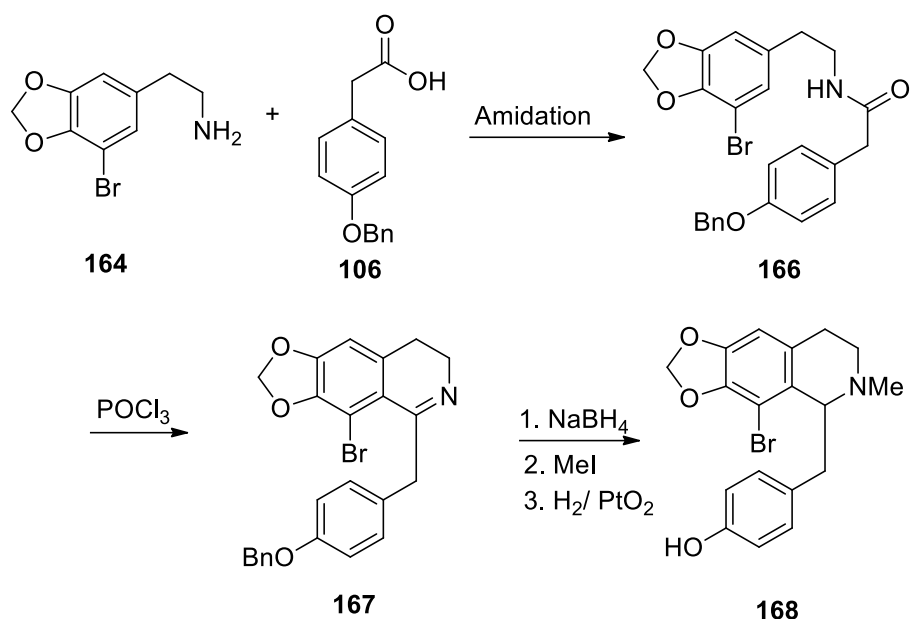


Scheme 21 : Synthesis of bromoarylamine derivatives by Tomita *et al.*

The tetrahydroisoquinoline derivative **168** was obtained by condensation of **164** with **106** by the classic method to form amide **166**. The amide **166** was cyclized by Bischler-Napieralski to form imine **167** and it was subsequently, reduced with NaBH<sub>4</sub> to afford **168** (Scheme 22).

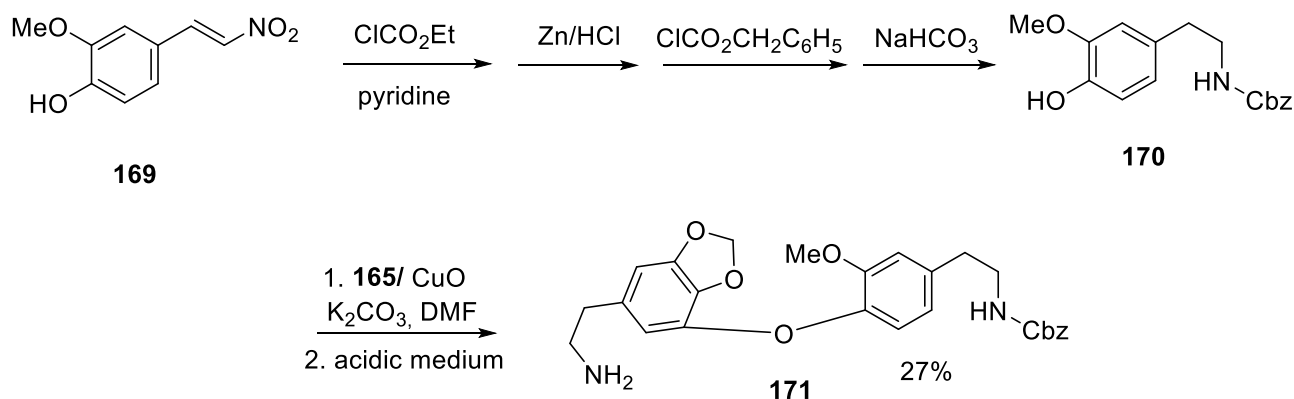
<sup>106</sup> M. Tomita, K. Fujitani, Y. Aoyagi. *Tetrahedron Lett.* **1967**, 8(13), 1201 – 1206.

<sup>107</sup> M.P. Cava, A.Afzali. *J. Org. Chem.* **1975**, 40(11), 1553 – 1556.



Scheme 22 : Synthesis of 8'-bromo-tetrahydroisoquinoline by Tomita *et al.*

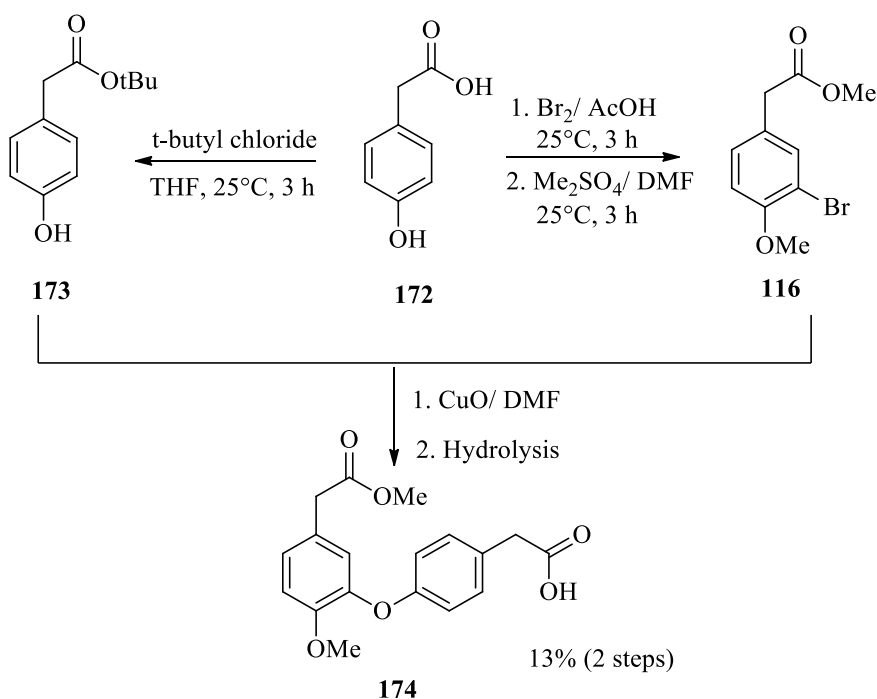
On the other hand, the hydroxy function of the nitrostyrene **169** was protected with ethylchloroformate and then reduce under Clemmensen condition to yield to phenethyl derivative. Then, the amino group was protected as carbobenzoxy derivative and phenol was selectively deprotected by aqueous sodium bicarbonate to form **170**. Its condensed with **165** was performed by Ullmann reaction with cupric oxide as catalyst and the formyl group was remove by hydrochloric acid in methaznol, yielded to **171** in 27% yield for the two last step (Scheme 23).



Scheme 23 : Synthesis of diphenyl ether by Tomita *et al.*

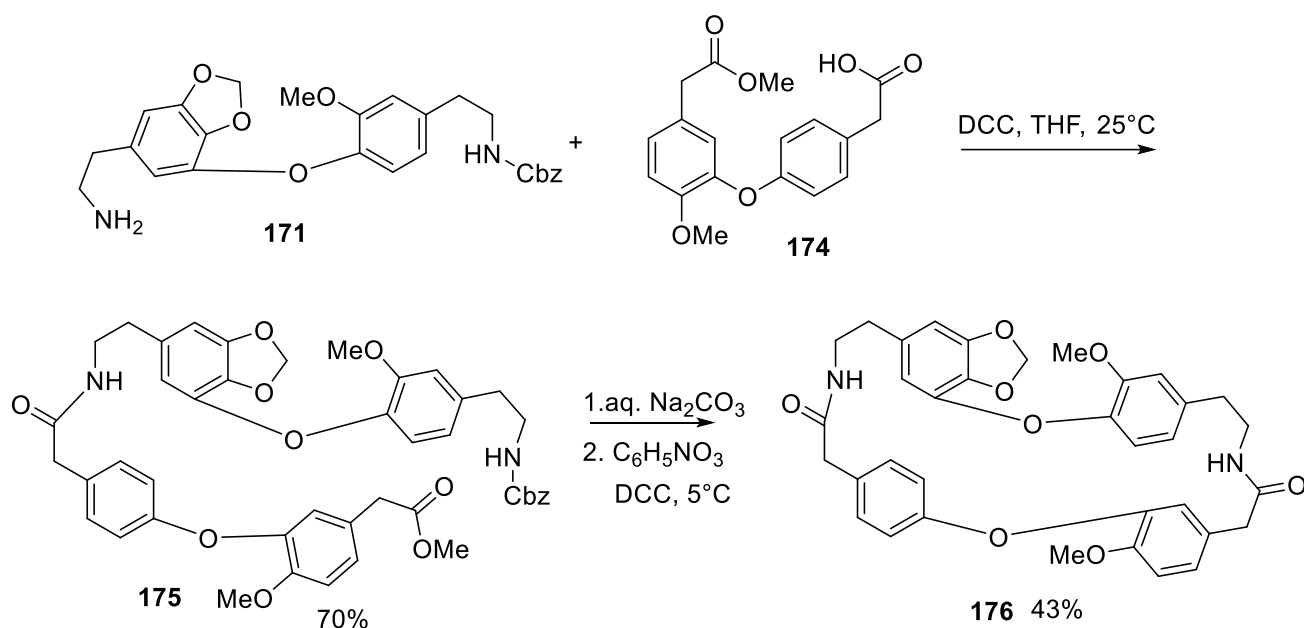
With the northern part of their synthesis in hand, they tried to synthesize the south part that formed the intermediate of cyclobisamide **176** through the diphenyl ether diacetic acid mono-ester **174**. This was prepared with *p*-hydroxyphenyl acetic acid **172** which was first brominated and then methylated to form **116**. The same acid **172** was converted to the tert-butyl ester **173**. The use of different protecting groups on the acid was to have a selective removal of the protective group through

the acidic medium. Thereafter, Ullmann condensation was performed to form, after hydrolysis of the tertbutyl group, the corresponding **174** but only in with 13% yield for these two steps (Scheme 24).



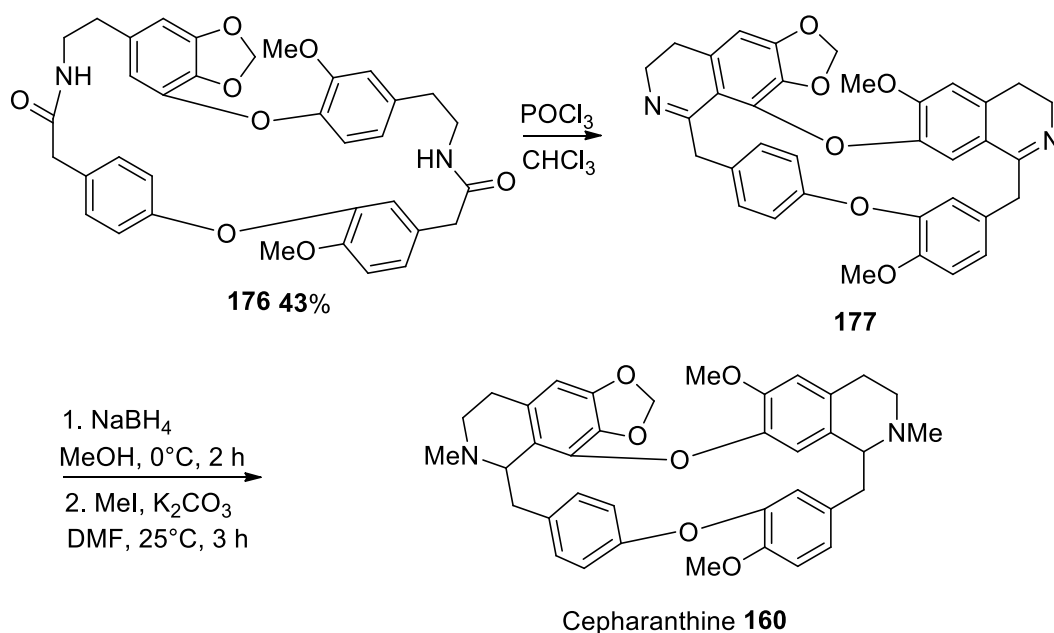
Scheme 24 : Synthesis of diphenyl ether diacetic acid mono-ester by Tomita *et al.*

Then condensation of amine **171** and diphenyl ether diacetic acid mono-ester **174** with the aid of dicyclohexyl carbodiimide in methylene chloride gave the amide **175** in 70 % in yield and the resulted amide **175** was hydrolyzed with sodium carbonate to the corresponding carboxylic acid, activated as *p*-nitrophenyl ester and then cyclized to afford the cyclobisamide **176** in 43% yield (Scheme 25)



Scheme 25 : Cyclobisamide by Tomita *et al.*

Bischler-Napieralski reaction of the cyclobisamide **176** with  $\text{POCl}_3$  in chloroform gave a mixture of 3,4-dihydroisoquinoline **177** with two spots on the thin layer chromatography. This mixture was hydrogenated over a platinum catalysts to avoid the ready oxidation with atmospheric oxygen and the product was reduced with sodium borohydride to afford a mixture of *N*-methyltetrahydroisoquinolines **160**. These products were separated and purified with a preparative TLC and column chromatography on alumina, the  $R_f$  value and NMR data of the synthesized molecule was identical with natural cepharanthine **160** (Scheme 26).



Scheme 26 : Synthesis of Cepharanthine by Tomita *et al.*

However, the cepharanthine drug is mostly used in Japan since the 1950s to treat acute and chronic diseases like leukopenia, snake bite and others. It is approved for human use in the large class of bisbenzyltetrahydroisoquinoline alkaloids, as it is mainly isolated from the plant *Stephanta cephalantha* Hayata. They tend to exhibit multiple pharmacological properties like antioxidant, anti-inflammatory, anticancer, antiviral, and antiparasitic properties<sup>108</sup>.

## 2. Tetrandrine (Type VIII)

Tomita *et al*<sup>106, 109</sup> made an attempt to accomplish the total synthesis of alkaloids possessing two asymmetric centers in the oxyacanthine **82** – berbamine **87** series of bisbenzyltetrahydroisoquinoline alkaloids, but unforeseen complication prevented the completion of the synthesis except for the cepharanthine (racemic). But in 1968, Inubushi *et al*<sup>110</sup> were able to report the first total synthesis of the optically active alkaloids: tetrandrine, isotetrandrine **85** and phaeanthine **84**.

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<sup>108</sup> C. Bailly. *Phytomedicine*, **2019**, 62, 152956 – 152968.

<sup>106</sup> M. Tomita, K. Fujitani, Y. Aoyagi. *Tetrahedron Lett.* **1967**, 8(13), 1201 – 1206.

<sup>109</sup> M. Tomita, K. Fujitani, Y. Aoyagi, Y. Kajita. *Chem. Pharm. Bull. Tokyo.* **1968**, 16(2), 217 – 226.

<sup>110</sup> Y. Inubushi, Y. Masaki, S. Matsumoto, F. Takami. *Tetrahedron Lett.* **1968**, 9(30), 3399 – 3402.



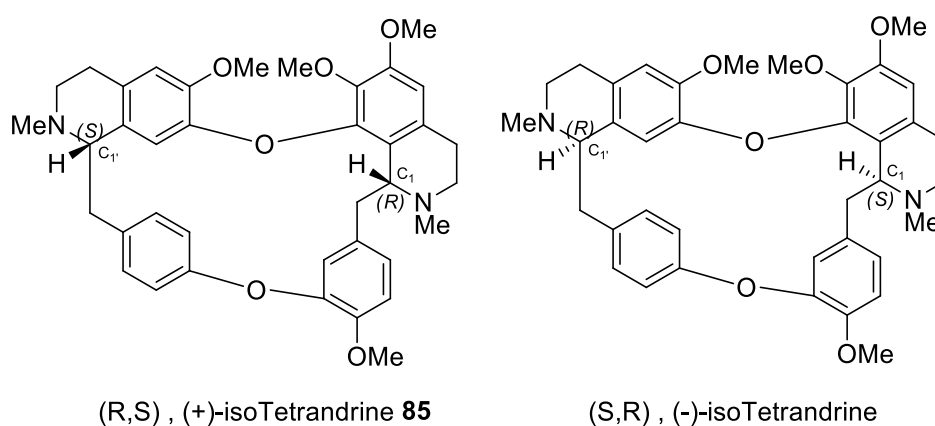
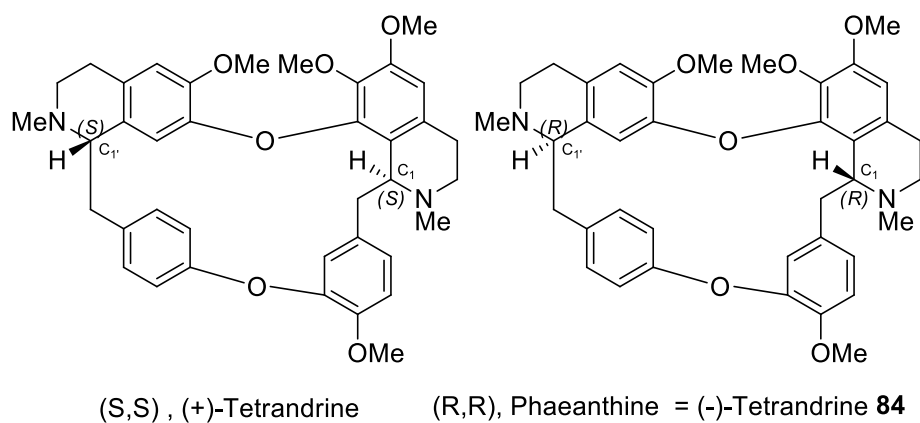
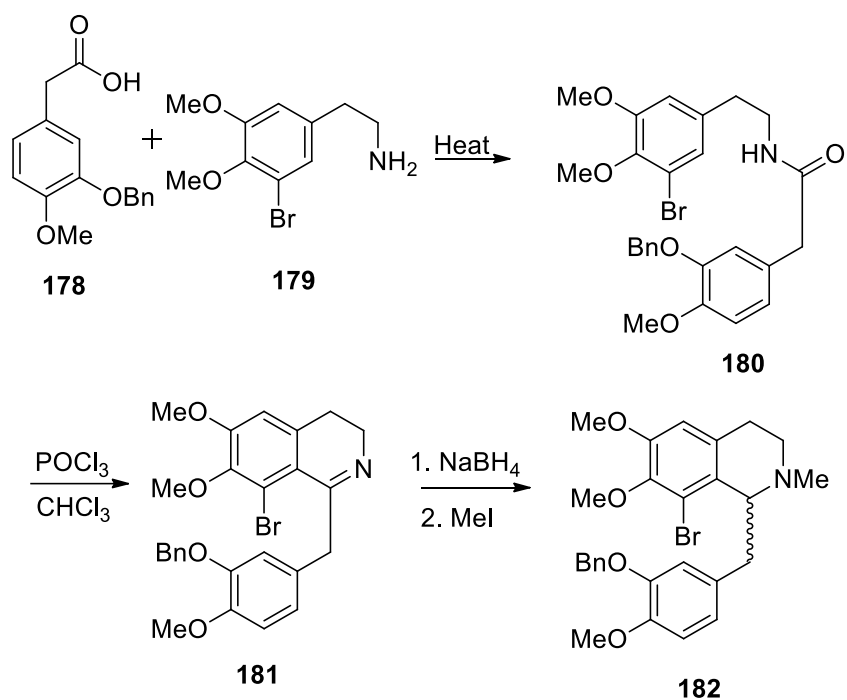


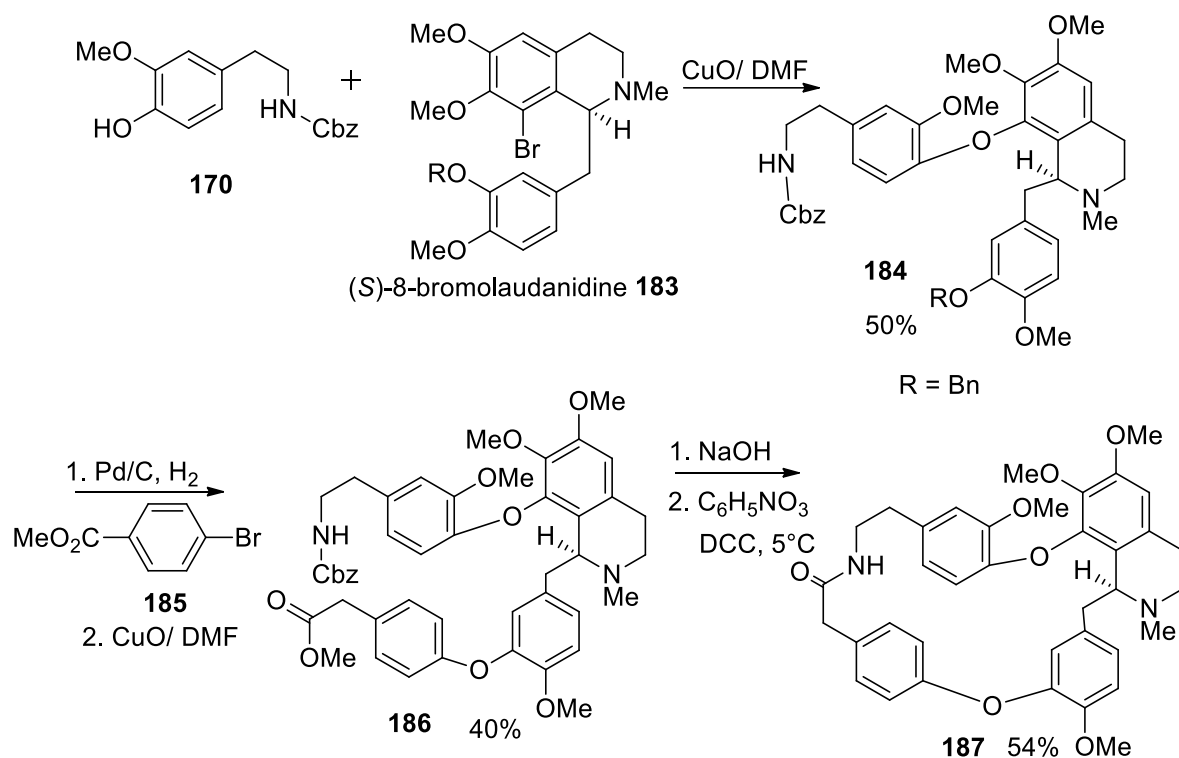
Figure 26 : Structure type **VIII** BBIQs

The starting material for their synthesis, *O*-benzyl-8-bromolaudanine **182** (racemic mixture) was obtained from *O*-benzylhomoisovanillic acid **178** and 3-bromo-4,5-dimethoxyphenylethylamine **179** via Bischler-Napieralski reaction (Scheme 27).



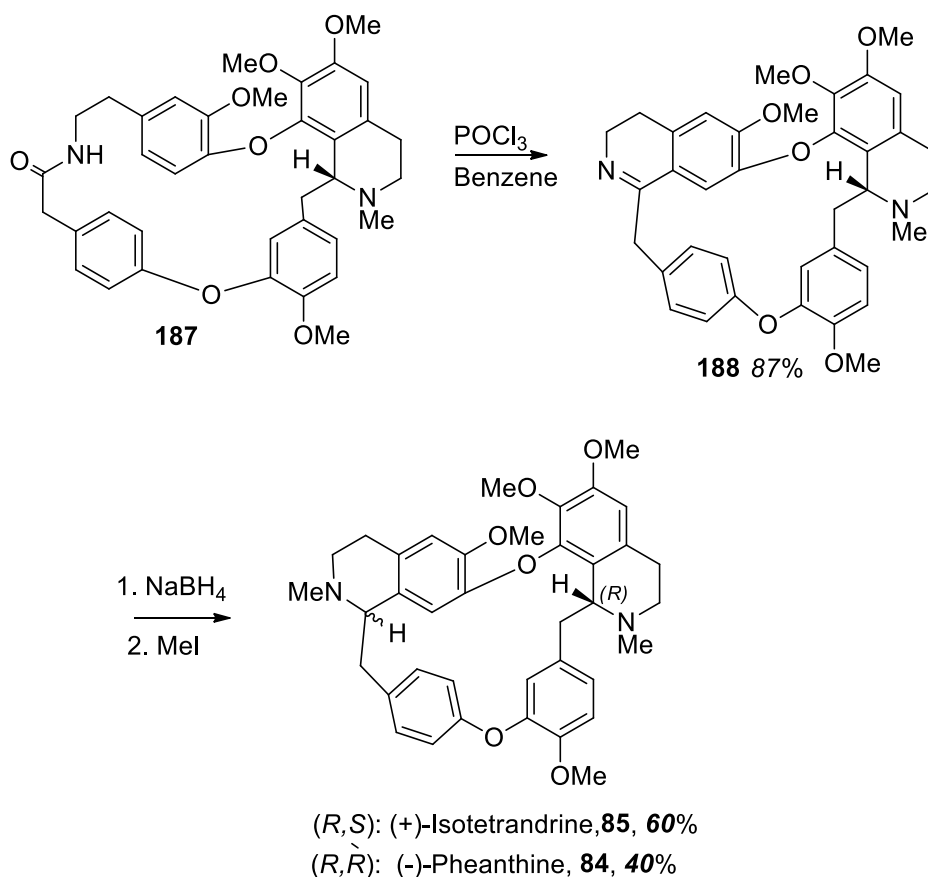
Scheme 27 : Synthesis of tetrahydroisoquinoline alkaloids by Inubushi *et al*

The tetrahydroisoquinoline **182** derivatives were resolved into its optical antipodes by means of (+)-tartaric acid. The Ullmann condensation of (*S*)-8-bromo-laudanidine **183** with *N*-*t*-butoxycarbonyl phenylethylamine **170** afforded a diphenyl ether **184** in 50% yield. After hydrolysis, followed by Ullmann condensation with methyl *p*-bromophenylacetate **185** gave *N*-*t*-butoxycarbonyl-carboxylic acid methyl ester **186** in 40% yield, the protecting group in the diphenyl ether was removed and then condensed to form cycloamide **187** in 54% yield (Scheme 28).



Scheme 28 : Ullmann-type/ Hydrolysis reaction by Inubushi *et al.*

The Bischler-Napieralski reaction of the cycloamide **187** afforded the dihydroisoquinoline **188** derivatives. The direction of this reaction can be ultimately settled by the identification of the final product of isotetrandrine and peganthine. The reduction of the dihydroisoquinoline **188** with  $\text{NaBH}_4$  followed by N-methylation gave a mixture of isotetrandrine **85** in 60% and peganthine **84** in 40%. Thus, the ratio of these two alkaloids in the mixture was estimated by comparing the NMR spectrum of the two mixed with the natural products respectively. Although, the separation of each diastereoisomer from the **188** was effected by the aid of different solubilities of **85** and **84** picrates as the less soluble **84** picrate tends to crystallize and the solution removed from crystallization contained mainly isotetrandrine **85** (Scheme 29).



Scheme 29 : Synthesis of Isotetrandrine and Pheanthine alkaloids by Inubushi *et al.*

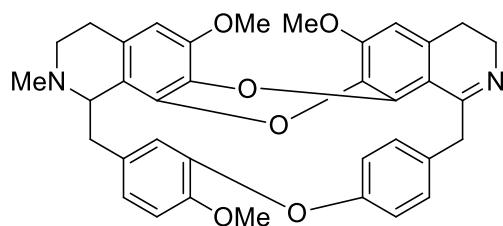
#### D. Synthesis of some bisbenzyltetrahydroisoquinoline alkaloids containing three diphenyl ether link:

This group of bisbenzylisoquinoline alkaloids possesses a structure that includes three oxygen bridges consisting of one diphenyl ether linkage and a diphenylene dioxide ring. These alkaloids may be considered as the off-springs of coclaurine and of the oxyacanthine-berbamine series. WE had already presented, in chapter 1, the total synthesis of Trilobine and Isotrilobine with all its flaws, and to improved it, we have to look carefully the synthesis described for others BBIQ type **XXIII** with the three ethereal ether bridge linkage.

##### 1. Methyldihydromenisarine (Type XXIV)

In the preparation of a bisbenzyltetrahydroisoquinoline alkaloids with three diphenyl ether linkages, an Ullmann reaction was used to build the important symmetrical diamine which incorporates the diphenylene dioxide bridge. Menisarine is an alkaloid isolated from *Cocculus*

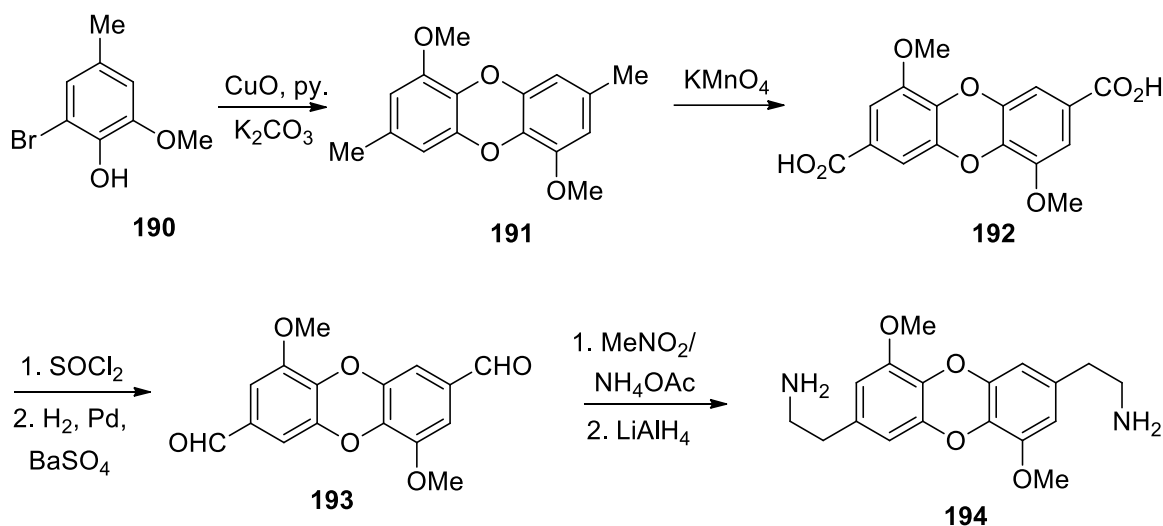
*sarmentosus* Diels a member of Menispermaceae. Tomita *et al.*<sup>111</sup> proposed by degradation reactions the structure of menisarine **189** (Figure 27).



Menisarine **189**

Figure 27 : Structure of menisarine

The first stage of the synthesis concerned the preparation of the diamine **194** which was carried out by double Ullmann with the starting material of **190** as shown in (Scheme 30)<sup>112</sup>.

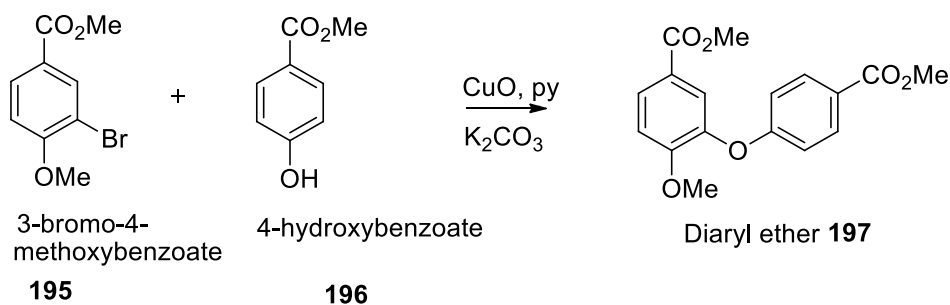


Scheme 30 : Synthesis of bisphenylethylamine structure by Tomita *et al.*

While the half of the molecule was prepared using double Arndt-Eistert reaction on diarylether **197**, prepared by Ullmann coupling of 3-bromo-4-methoxybenzoate **195** and 4-hydroxybenzoate **196** (Scheme 31).

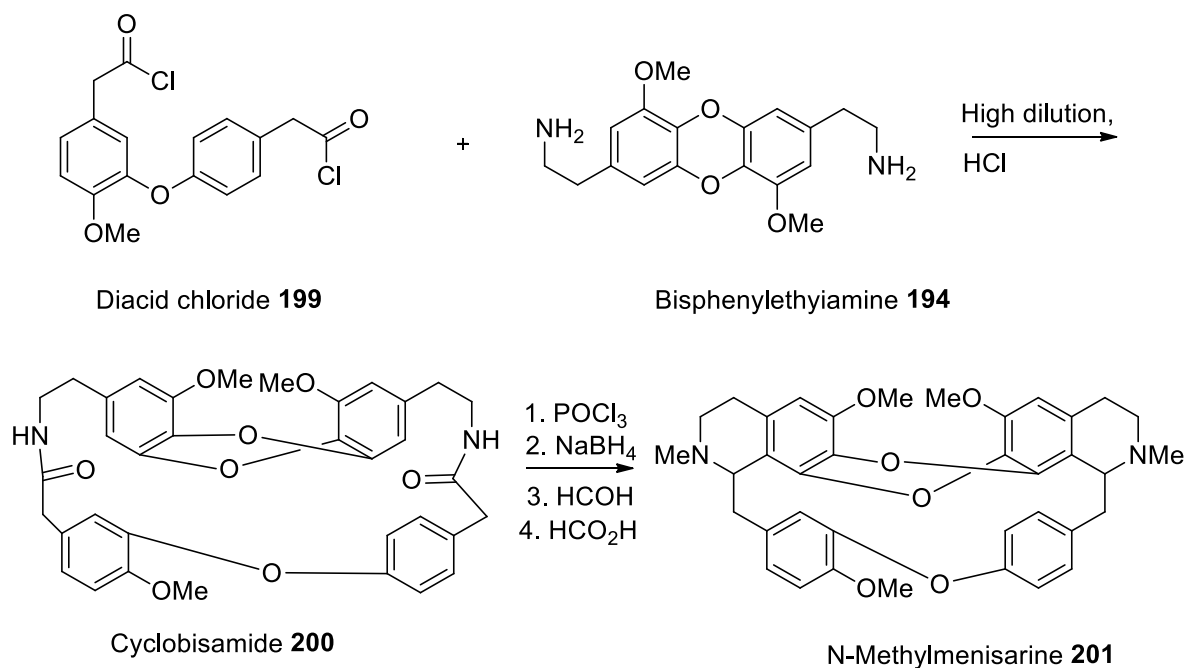
<sup>111</sup> M. Tomita, S. Ueda, A. Teraoka. *Tetrahedron Lett.* **1962**, 3(14), 635 – 636.

<sup>112</sup> S. Ueda, *J. Pharm. Soc. Japan* **1962**, 82(5), 714 – 715.



Scheme 31 : Synthesis of diphenyl ether diacetic acid

The condensation of the diacyl chloride **199** with the diamine **194** at high dilution yielded to diamide **200**, then followed by Bischler-Napieralski reaction and finally *N*-methylmenisarine **201** was obtained after methylation of the two nitrogen by classic Eschweiler-Clarke reaction (Scheme 32).

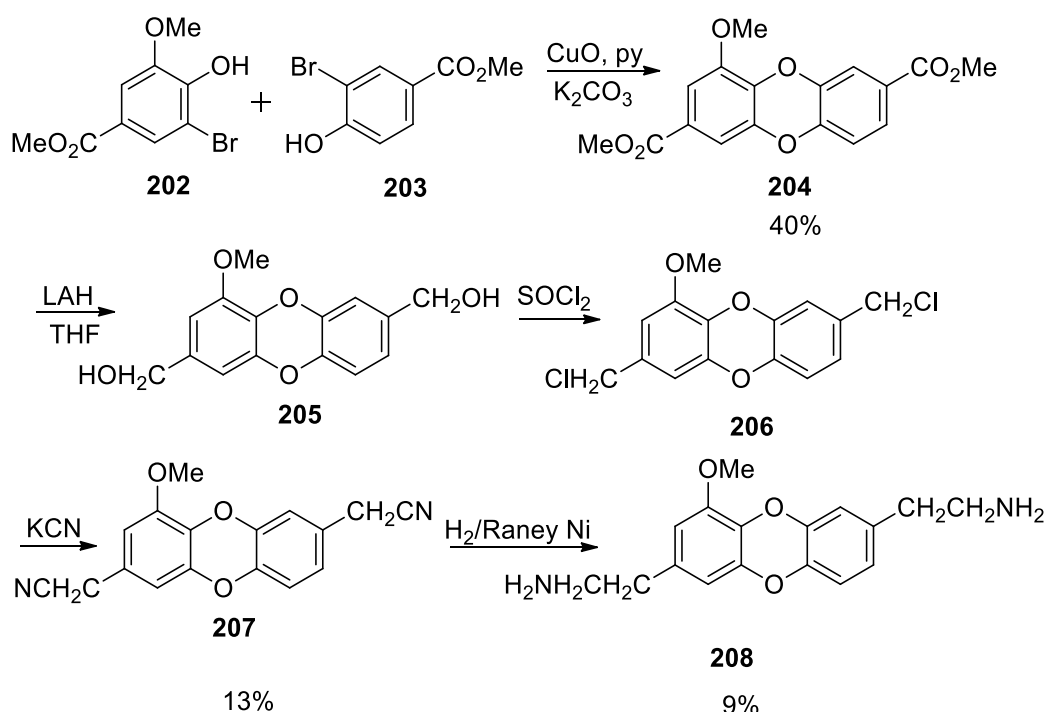


Scheme 32 : Synthesis of methylmenisarine

## 2. *Tiliacorine* (Type XVIII)

In 1971, Anjaneyulu *et al*<sup>113</sup> reported the synthesis of diastereoisomer tiliacorinine alkaloids which were isolated from *Tiliacora racemose* Colebr, and the structure has been assigned on the basis of extensive degradation. The unique feature of this alkaloids is that it has two diaryl ether linkages and one aryl-to-aryl linkage which are mostly member of bisbenzyltetrahydroisoquinoline alkaloids.

An Ullmann reaction between the 5-bromovanillate **202** and methyl-3-bromo-4-hydroxybenzoate **203** to yield all the three possible dicarbomethoxy-dibenzo-*p*-dioxins **204** in 40% yield, which was separated by chromatography<sup>114</sup>. The diester **204** was reduced with LAH in THF to form diol **205** which was then converted with thionyl chloride to afford the dichloride **206** and was treated with KCN to form dinitrile **207** in 13% yield which was equally reduced in the presence of Raney nickel to afford the bisphenylethylamine **208** in 9% yield (Scheme 33).



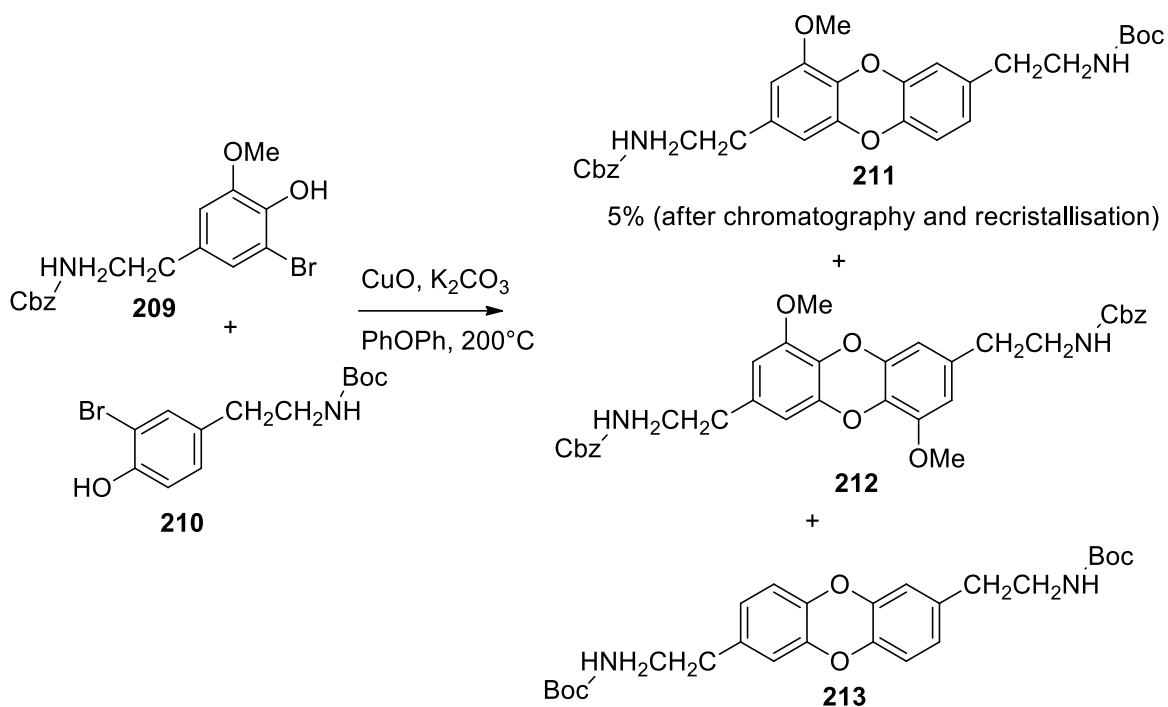
Scheme 33 : Synthesis of dibenzo-*p*-dioxin by Anjaneyulu *et al*.

The same trouble of non-selective double Ullmann cross-coupling observed by Anjaneyulu *et al*. for the preparation of dibenzo-dioxin **204**, was also observed by Pachaly and Schäfer, when they try to form dioxin using two different bromo-hydroxy phenethylamines (Scheme 34) for their synthesis of tiliacorine.<sup>115</sup>

<sup>113</sup> B. Anjaneyulu, T. R. Govindachari and N. Viswanathan. *Tetrahedron*, **1971**, 27(2), 439 – 443.

<sup>114</sup> (a) M. Tomita, S. Ueda. *J. Pharm. Soc. Jpn.* **1958**, 78(6), 676 – 679; (b) *Chem. Abstr.*, **1958**, 52, 18422 – 18428.

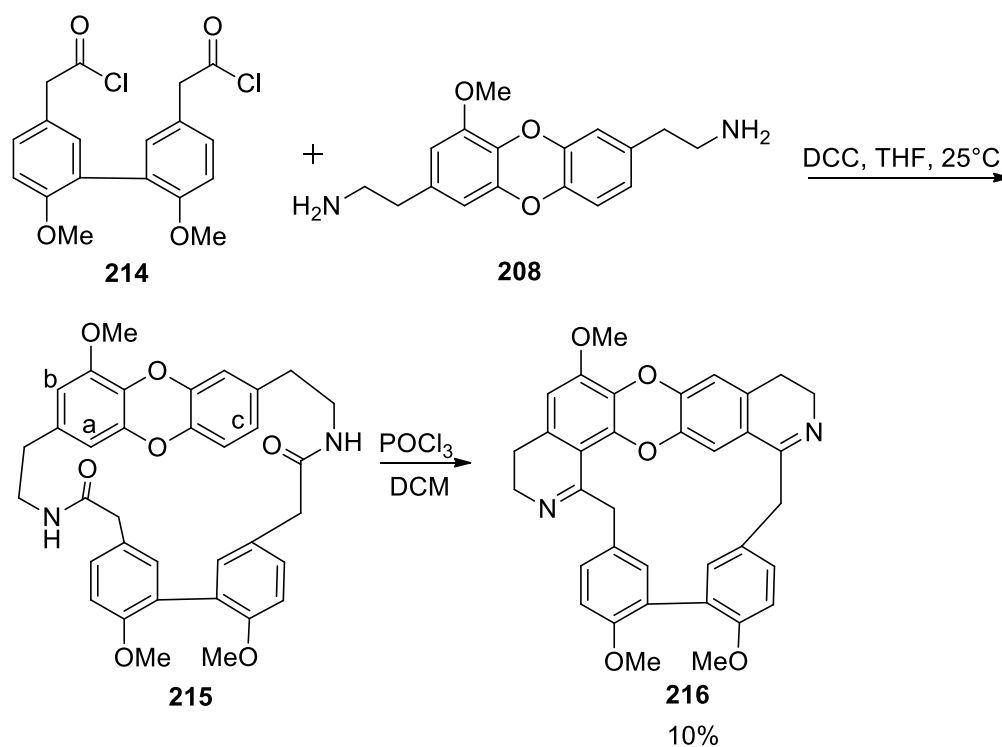
<sup>115</sup> P. Pachaly, M. Schäfer; *Arch. Pharm.* **1989**, 322, 477 – 482.



Scheme 34 : Synthesis of dibenzo-*p*-dioxin by Pachaly *et al.*

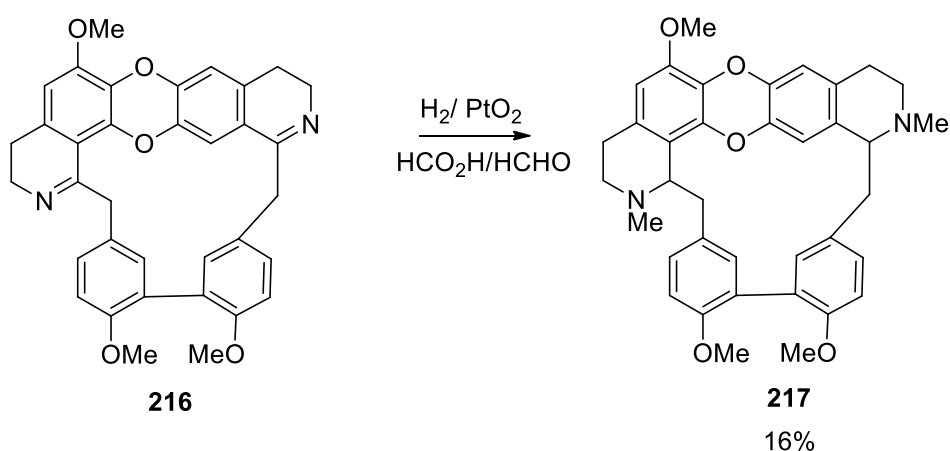
The bisamine **208** was condensed with the diacid chloride **214** of 2,2'-dimethoxy-diphenyl-5,5'-diacetic acid in DCM in the presence of base under high dilution condition to yield bisamide **215** in 38% yield. Bischler-Napieralski cyclization of **216** was expected to result in the cyclization at both sides of the molecules simultaneously (Scheme 35).





Scheme 35 : Bischler-Napieralski reduction by Anjaneyulu *et al.*

In this cyclization, the methoxyl bearing benzene ring was preferred rather than the analogy with the amide used for the synthesis of N-methyldihydromenisarine whereas the cyclization of the other benzene ring took place as it is observed under drastic conditions to afford dihydroisoquinoline **216** in 10% yield, such that its relative flexibility depends on the difference on their comparison. The compound **216** without purification, was reduced in the presence of Adams catalyst to yield a diastereoisomer and on methylation under Eschweiler-Clarke conditions (formaldehyde and formic acid) formed a diastereoisomeric mixture of racemic *O*-methyltiliacorine **217** in 16% yield (Scheme 36).



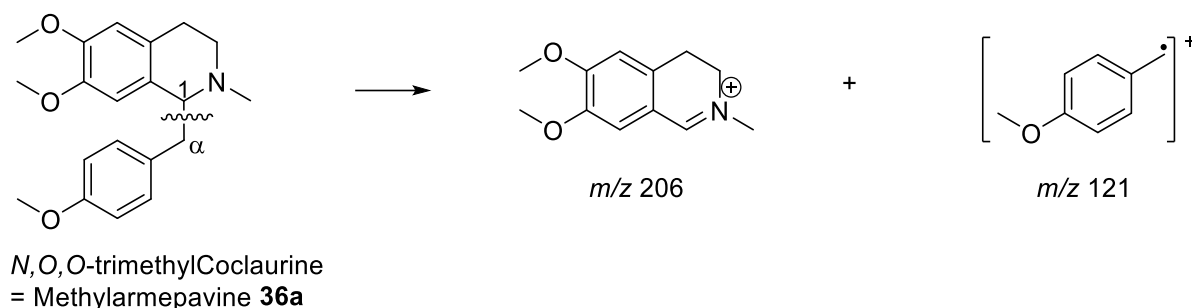
Scheme 36 : Methytiliacorine synthesis by Anjaneyulu *et al.*

One more time, for the synthesis of tiliacorine, these authors, Anjaneyulu, and Pachaly as well, have preferred Bishler-Napieralski reaction compare to Pictet-Spengler, even if the yield obtained is very low and non-selective.

### E. Spectral analysis of bisbenzyltetrahydroisoquinoline alkaloids

The elucidation of the structure of benzyltetrahydroisoquinoline alkaloids may be facilitated with the assistance of the following spectra analysis like the mass spectroscopy, nuclear magnetic resonance, X-ray analysis, UV spectroscopy.

In mass spectroscopy, the main cleavage that the Coclaurine alkaloid undergoes is at C-1 to C- $\alpha$  bond, which is doubly benzylic and also adjacent to the nitrogen atom. The base peak and intense peaks differ due to the loss of the methyl group from the base ion. Since the charge prefers to remain on the nitrogen atom, the ion representing the C ring of the molecule shows up only as a minor peak<sup>116</sup> (Scheme 37).

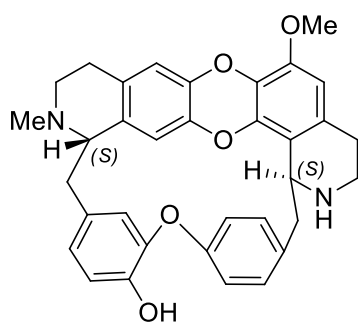


Scheme 37 : Mass spectroscopy of coclaurine alkaloid

Although, David G.I. Kingston reported the X-ray study of alkaloids isolated from *Anisocycla grandidieri* (Menispermaceae), and which was revealed by the crystal analysis to be the cocsuline **218**. The C-6 methoxyl points away from the C-7 hydroxyl and the C-1 hydrogen is beta. The ring C plane is nearly perpendicular to the mean plane of tetrahydroisoquinoline ring system. Since the nitrogen is secondary, ring C lies on the nitrogen side<sup>117</sup> (Figure 28).

<sup>116</sup> M. Tomita, H. Furukawa, T. Kikuchi, A. Kato, T. Ibuka. *Chem. Pharm. Bull.*, **1966**, *14*, 232 – 237.

<sup>117</sup> Y.Liu, L. Harinantenaina, P.J. Brodie, C. Slebodnick, M.W. Callmander, R. RAKotondrajaona, E. Rakotobe, V.E. Rsamison, K. TenDyke, Y. Shen, D.G.I. Kingston, *Magn. Reson. Chem.* **2013**, *51*, 574 – 579.



Cocculine **218**

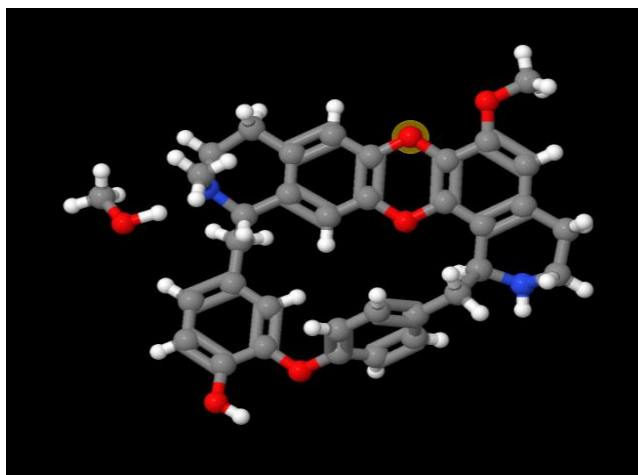


Figure 28 : X-ray of *N*-Cocculine **218** (type **XXIII**) by Kinston *et al.*

Mass spectroscopy provides useful information for the structural elucidation of *dimeric* benzyltetrahydroisoquinoline alkaloids and the fragmentation pattern. For example, the fragmentation pattern of tetrandrine alkaloids in which the doubly charged ion  $m/e$  198 is the base peak and these ions can lose the elements of dimethyl ether to form the  $m/e$  175 peaks. Isotetrandrine **85** also shows a weak but characteristic peak at  $m/e$  (191 – 137) (Figure 29).

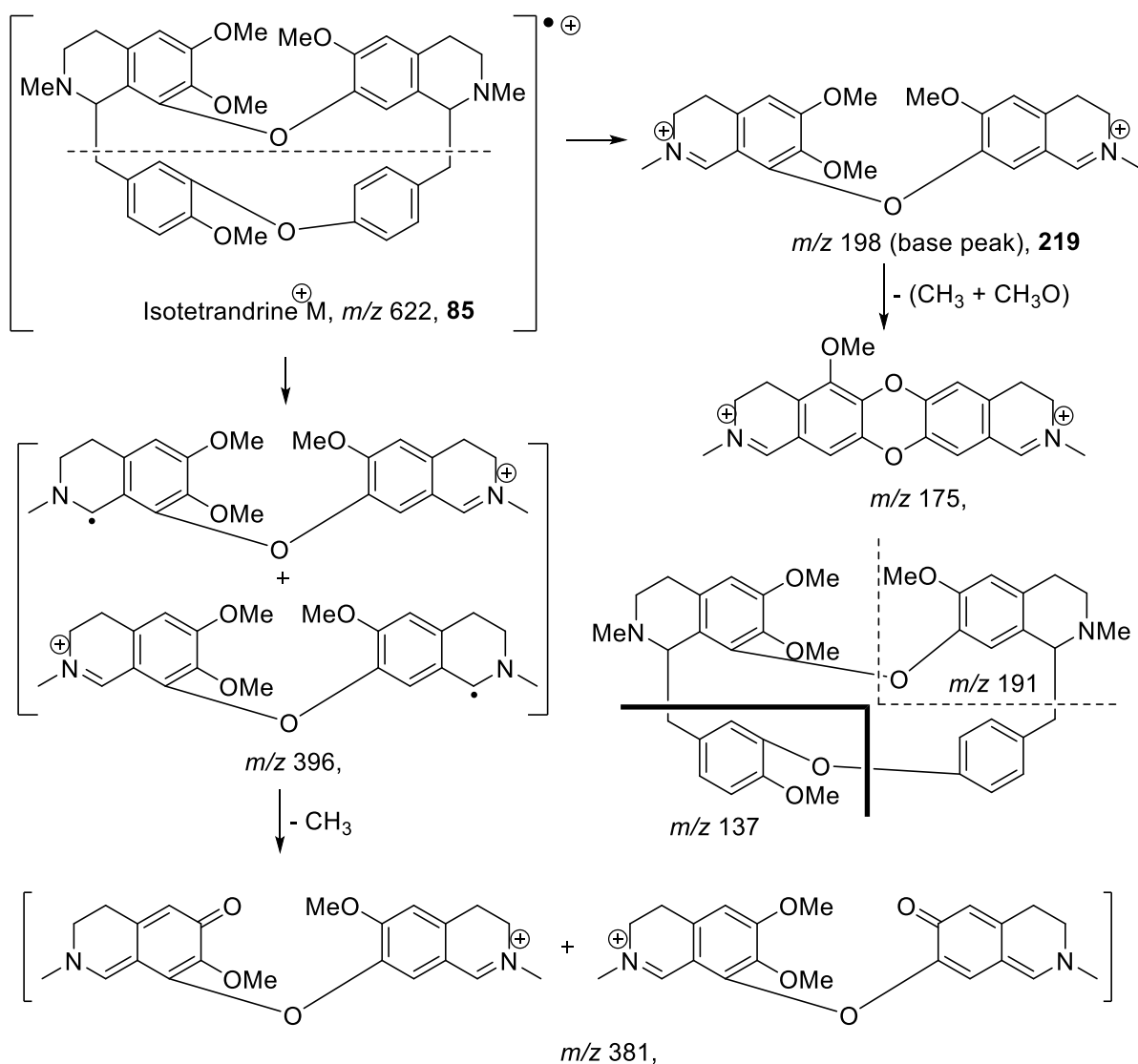
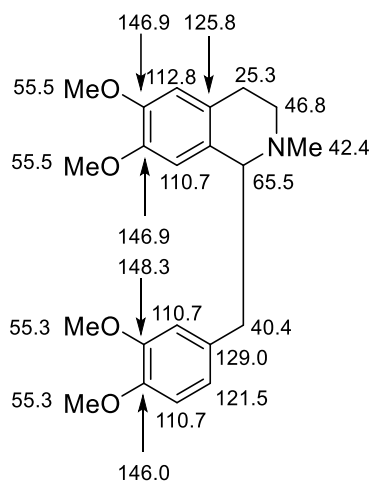


Figure 29 : mass spectra of isotetrandrine by Tomita *et al*

The NMR spectroscopy has been firmly established that in most *N*-methylbenzyltetrahydroisoquinolines, rings A and C lie on the same side of the molecules, while the ring C is preferentially located on the same side as the tertiary or quaternary nitrogen. For example, the laudanosine in  $\text{CDCl}_3$ , H-5 is at  $\delta$  7.68 and H-8 is at  $\delta$  7.49. The C-6 and C-7 methoxys are found at  $\delta$  4.12 and  $\delta$  4.00 respectively. In most cases, minor differences in chemical shifts appear if an additional methoxyl is present at C-8. While the  $^{13}\text{C}$  chemical shift has been assigned and will be noted that the C-6' signal comes at 121.5 ppm since this carbon atom is deshielded with respect to its ortho and meta methane neighbors by its lacking the strongly shielding influence of ortho and methoxy groups<sup>118,119</sup>(Figure 30).

<sup>118</sup> T. Tomimatsu, S. Yamada, R. Yuasa, *J. Pharma. Soc. Jpn.* **1977**, 97(2), 217 – 222.

<sup>119</sup> D. W. Hughes and D. B. Maclean, *The Alkaloids*, **1981**, 23, 219 – 225.



Laudanosine **135**

Figure 30 : NMR spectroscopy of Laudanosine alkaloids

The bisbenzyltetrahydroisoquinoline alkaloids are isolated from plant extracts containing mixtures of different alkaloid classes which varies from the degree of structural complexity and it is usually accompanied by other alkaloids families of isoquinoline like the benzyltetrahydroisoquinolines, morphinane, berberines, or aporphines, though they all emerged from the same biochemical precursors<sup>120</sup>.

To successfully separate the alkaloids mixtures of bisbenzyltetrahydroisoquinoline, a preparative process was carried out in multiple extractions by using solvents of different polarities and pH values. As the final purification is achieved by chromatography ranging from thin-layer chromatography, which in most cases is replaced by automated high-pressure chromatography and the still standard for cleaning is column chromatography<sup>121</sup>.

Thus, on elucidating the structure of the compounds, analytical spectroscopy has been used such as UV, IR, NMR, and MS that serve as a standard in past decades and as well replace the classical method of degradation and derivatization. Although a complete  $^1\text{H}$  and  $^{13}\text{C}$  NMR data sets for many bisbenzyltetrahydroisoquinoline alkaloids characterized in the past century are still lacking. In many cases, the interpretation of  $^1\text{H}$  NMR data of unknown molecules relied on the standard work of Guinaudeau and Shamma, on the spectral characteristics of tail-to-tail connected bisbenzylisoquinoline, or on comparisons with related substances. Only in very few cases, absolute configurations were determined by X-ray crystallographic analysis<sup>122</sup>.

For analytical purposes and in particular, for the separation, determination, and quantification of alkaloids in plant extracts for medical applications, HPLC methods proved to be a powerful tool. The bisbenzyltetrahydroisoquinoline mixtures with up to 15 compounds can be separated after the evaluation of various solid-phase materials and optimization with acidic or basic buffer systems<sup>123</sup>. Moyer 2004, detailed more look into the complex alkaloid compositions that allow the combinations

<sup>120</sup> J. Ziegler, M.L. Diaz-Chavez, R. Kramell, C. Ammer, T.M. Kutchan. *Planta* **2005**, 222, 458 – 471.

<sup>121</sup> S.W. Sun, S.S. Lee, A.C. Wu, C.K. Chen. *J. Chromatogr. A*. **1998**, 799(1-2), 337 – 342.

<sup>122</sup> H. Guinaudeau, A.J. Freyer, M. Shamma. *Nat. Prod. Rep.* **1986**, 3, 477 – 488.

<sup>123</sup> J.N. Tshibangu, A.D. Wright, G.M. Konig. *Phytochem. Anal.* **2003**, 14(1), 13 – 22.

of LC with MS analyses which established a library with the MS fragmentation pattern of 20 alkaloids belonging to 10 different bisbenzyltetrahydroisoquinoline types<sup>124</sup>.

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<sup>124</sup> W.N. Wu, M.D. Moyer. *J. Pharm. Biomed. Anal.* **2004**, *34*, 53 – 66.

## CHAPTER 3 : RESULTS AND DISCUSSIONS

As already presented in the preamble, the project of total synthesis started some years ago, in Toulouse. The first biological results of trilobine and isotriloquine as epigenetic modulators were very encouraging, but unfortunately the structures we were able to prepare in a derivatization program from natural trilobine never improve enough of these results.<sup>Error! Bookmark not defined.</sup> The only opportunity we had to find a “drug candidate” was to develop a synthesis, efficient and flexible enough to be able to have access to unnatural BBIQ type **XXIII**, and thus to have access and propose new biologically active molecules against cancer.

### A. Retrosynthesis

The retrosynthesis analysis of trilobine and isotriloquine alkaloids could be accessed from connection of four synthon, two arylacetic acid derivatives and two phenethylamine. The two isoquinoline moieties should be prepared using Pictet-Spengler or Bischler-Napieralski reaction (**Error! Reference source not found.**). The final step should be this macrocyclisation reaction by the formation of the dioxiran system. This dioxiran system have to be install by reaction of a catechol derivative and a dihalogeno substrate, at the end of the synthesis to avoid problem in the regioselectivity of this double reaction as already discussed in chapter 2.

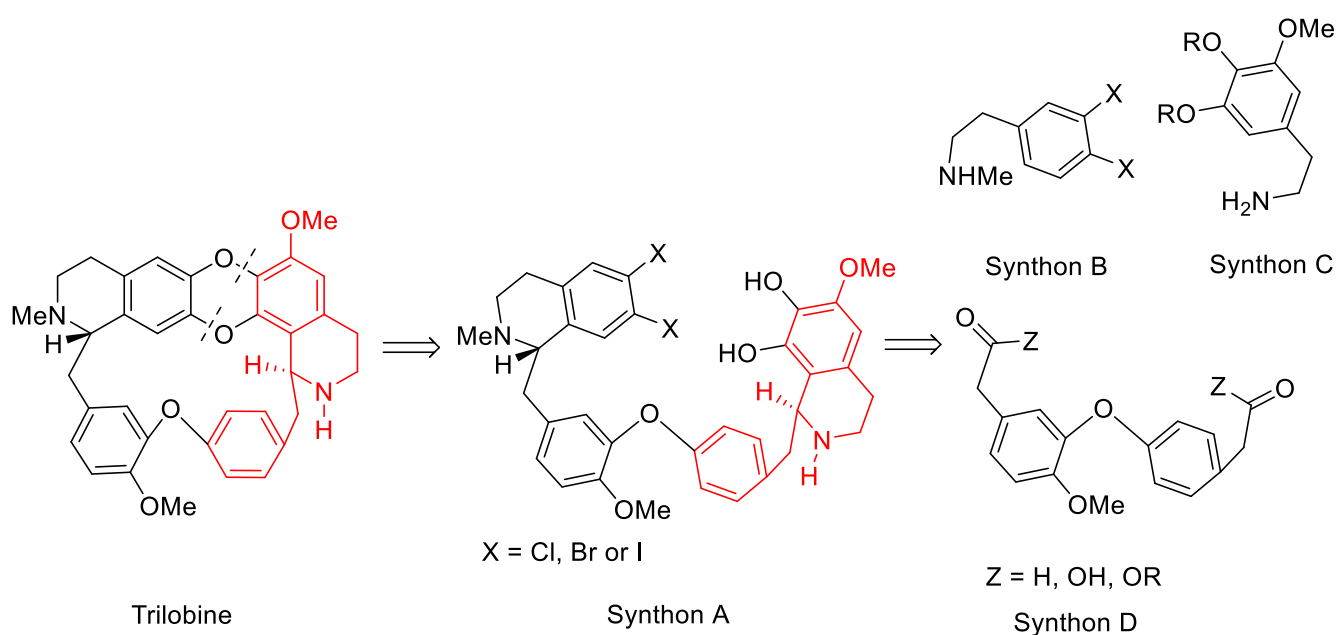
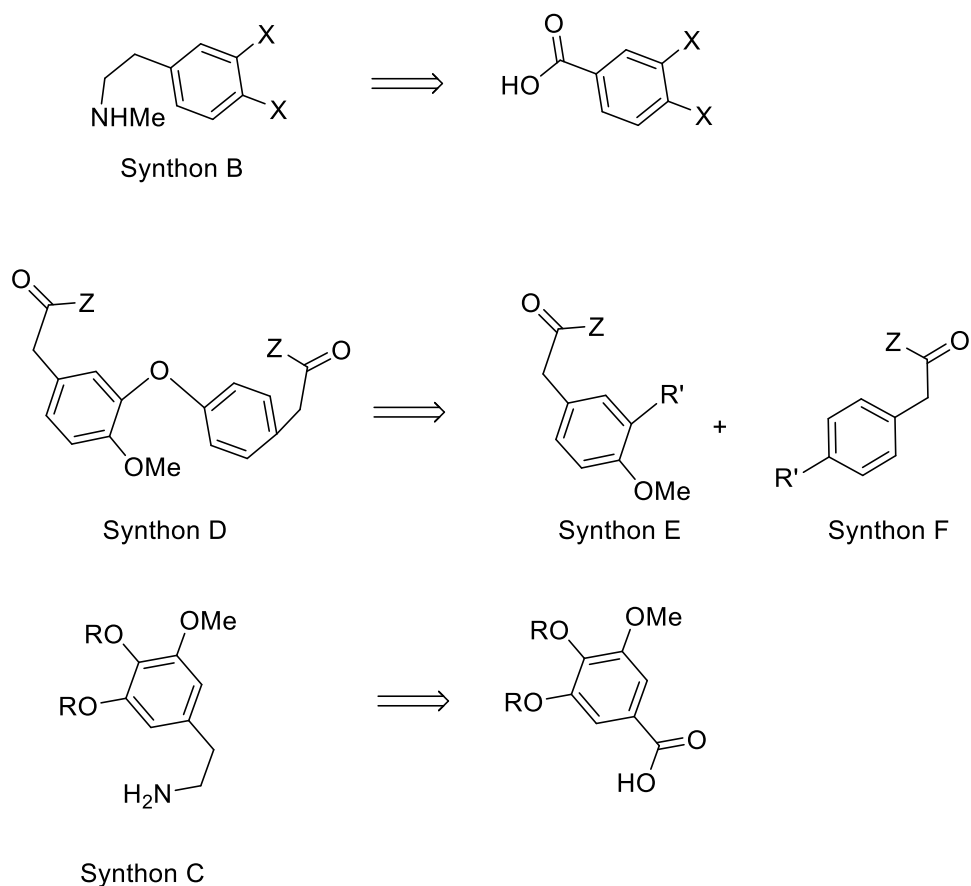


Figure 31 : Retrosynthesis of trilobine and isotriloquine alkaloids

Both phenethylamine, (Synthon B and C) should come from homologation process of benzoic derivative, by a Henry reaction followed by reduction of the double bond and the nitro group. The diaryl ether, synthon D, should come from a Ullman o Ullman type reaction between a phenol and an halogenoaryl derivative (Scheme 38).



Scheme 38 : Preparation of synthons for trilobine synthesis

## B. Previous work

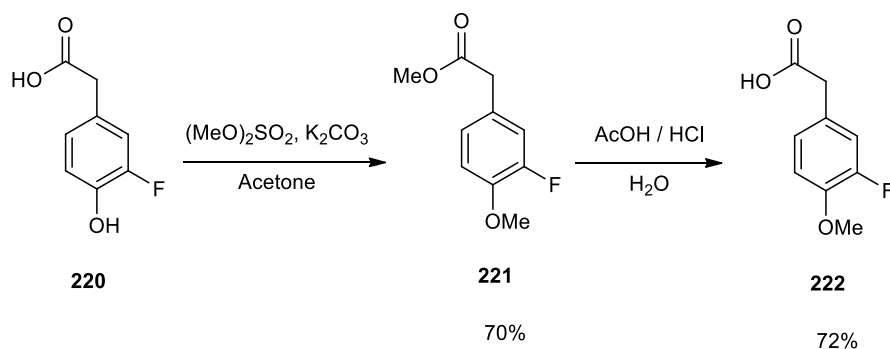
As shown before, there are no very efficient conditions for Ullman-type coupling and some gave very low yields of diaryl ether. So, we looked for other methods to prepare such ethereal compounds, in particular, the aromatic nucleophilic substitution with fluoroarene or metallo catalyzed reaction (other than Ullmann-type coupling).

### 1. Nucleophilic Aromatic Substitution

The sequence<sup>125</sup> starts using 3-fluoro-4-hydroxy-phenyl acetic acid **220**, which is protected as methyl ester and methyl ether in one step and dimethylsulfate with potassium carbonate in acetone. The resulting ester **221** can be hydrolyzed by hydrochloric acid to afford free acid **222**

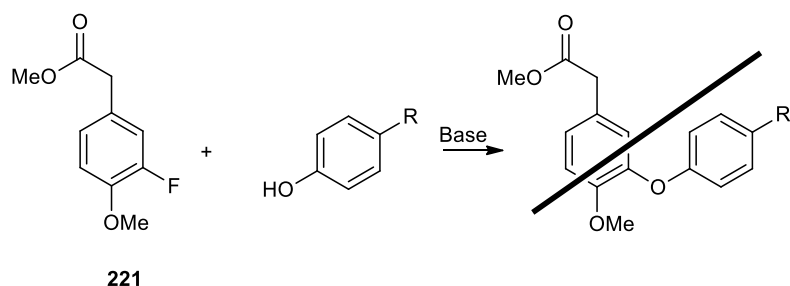
<sup>125</sup> A. Prieto., P.B. Arimondo; F. Cantagrel; *unpublished results*





Scheme 39 : synthesis of fluorinated derivatives

Several attempts were engaged to perform the nucleophilic substitution of the fluorine atom by a hydroxyl functional group using classic procedure *i.e.* by heating the two reagents in DMF with base. Several bases were used, carbonate or hydroxide, but no simple coupling product was obtained. The crude reaction mixture we were able to recuperate showed a large variety of compounds, from degradation product to oligomers and we had to conclude that the high reactivity of benzylic position in such substrate as compound **221** prohibited this pathway.

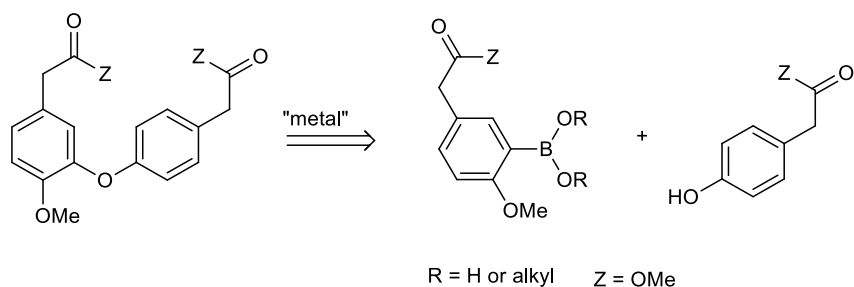


Scheme 40 : Aromatic nucleophilic substitution reaction

We then turned our attention to metallocatalyzed coupling reactions.

## 2. Metal catalyzed diarylether coupling reaction.

As an alternative to the nucleophilic aromatic substitution, we turn our effort to the metal catalyzed coupling reaction for the preparation of our diaryl ether moiety. Borylated derivatives are often used for such reaction, and former works from the lab were already done.

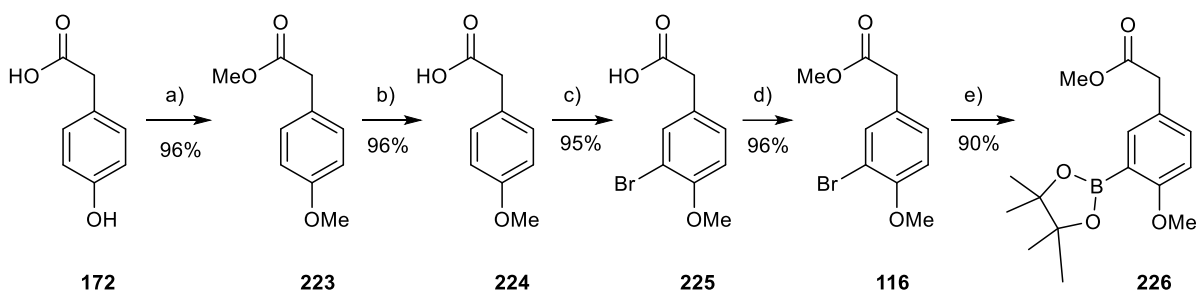


Scheme 41 : Retrosynthetic scheme for diaryl ether synthesis from arylboronic acid.

a. Reaction catalyzed by palladium.

The coupling reaction mediated by palladium is a Suzuki type reaction but using a phenolate as ligand, which is able to react with the aryl moiety during the reductive elimination step to form a diaryl ether. The preparation of the borylated partner was already described by Ghosh *et al.* in a 5 steps sequence from commercially available 4-hydroxyphenylacetic acid with a 75% overall yield.<sup>126</sup> Later, two other groups used the Ghosh's sequence to prepare the same compound **226** but with lower efficiency for the borylation step. Scott in 2011 obtained less than 80%<sup>127</sup> and Yokokawa in 2016 only 60%.<sup>128</sup>

Ghosh *et al.*



Reagents and conditions: (a) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone, 25 °C, 12 h; (b) LiOH, MeOH, H<sub>2</sub>O, 25 °C, 30 min; (c) Br<sub>2</sub>, AcOH, 25 °C, 17 h; (d) Me<sub>2</sub>SO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone, 25 °C, 3 h; (e) bis(pinacolato)diboron, KOAc, PdCl<sub>2</sub>(dppf), DME, 110 °C, 18 h.

Scheme 42 : Synthesis of aryl boronic acid by Ghosh *et al.*

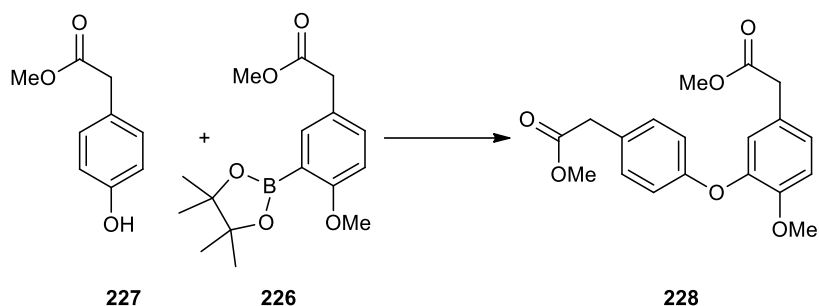
Precedent students in the group tried to reproduce the same sequence using the same protocols described. Unfortunately, in their hands, the result for the borylation reaction was much closer to the one of Yokokawa than the one of Ghosh. Nevertheless, the borylated compounds **226** were engaged

<sup>126</sup> Ghosh, S., Kumar, A.S., Mehta, G.N.; Soundararajan, R.; *Synthesis*, **2009**, (19), 3322-3326.

<sup>127</sup> Scott, J.M., Baccei, C., Bain, G.; Broadhead, A., Evans, J. F., Fagan, P., Hutchinson, J. H., King, C., Lorrain, D. S., Lee, C., Prasit, P., Prodanovich, P., Santini, A., Stearns, B. A., *Bioorg. Med. Chem. Lett.* **2011**, 21(21), 6608-6612.

<sup>128</sup> Yokokawa, F., Nilar, S., Noble, C. G., Pheng Lim, S., Rao, R., Tania, S., Wang, G., Lee, G., Hunziker, J., Karuna, R., Manjunatha, U., Shi, P.-Y., Smith, P.W., *J. Med. Chem.* **2016**, 59(8), 3935-3952.

in a coupling reaction with the hydroxyphenylacetate **227**. Different conditions were used using a different sources of palladium, ligands, but yields in compound **228** were never up to 55-60%.



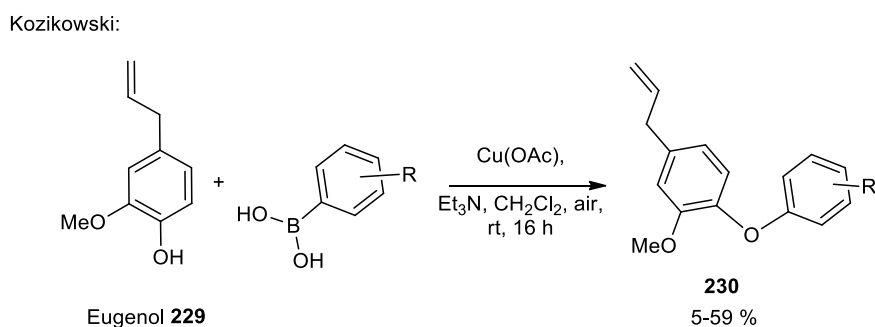
Scheme 43 : Scheme for coupling of arylboronic acid with palladium.

At that time, these yields for borylation reactions and coupling reactions were judged too low to propose an efficient preparation of substrates, so an alternatives with higher yield were looked after.

#### b. Reaction catalyzed by copper.

Instead of palladium, copper salt was also described to perform this coupling between phenol and a borylated aryl derivatives. Most of the examples reported in the literature described intramolecular coupling, but some examples also shows intermolecular cross-coupling.

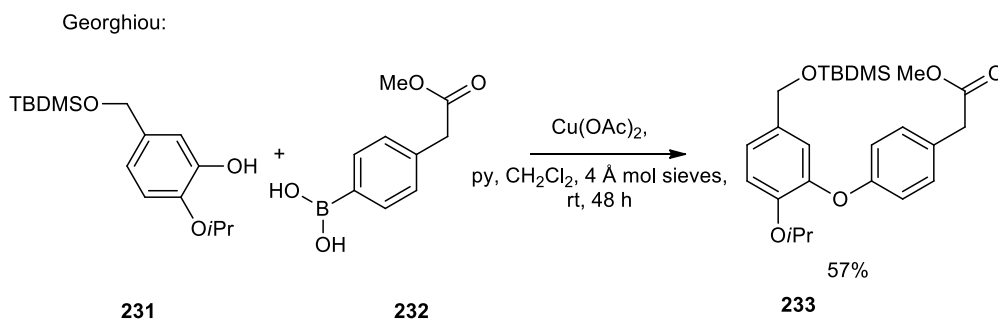
For example, Kozikowski and co-workers described the coupling between arylboronic acid and eugenol **229** (or  $\beta$ - $\gamma$  dihydroeugenol) mediated by cuprous acetate with variable efficiency depending of the substituent on aromatic boronic acid<sup>129</sup>.



Scheme 44 : Copper catalyzed coupling reaction of arylboronic acid and eugenol

<sup>129</sup> Suresh K. Tipparaju, S.K.; Mulhearn, D.C.; Klein, G.M.; Chen, Y.; Tapadar, S.; Bishop, M.H.; Yang, S.; Chen, J.; Ghassemi, M.; Santarsiero, B.D.; Cook, J.L.; Johlf, M.; Mesecar, A.D.; Johnson, M.E.; Kozikowski A.P. *ChemMedChem*. **2008**, 3(8), 1250 – 1268.

Another example was presented by Georghiou and coll. for the elaboration of the synthesis of (-)-tejedine, a minor seco-bisbenzotetrahydroisoquinoline alkaloid (a **type VI BBIQ**) in *Berberis vulgaris* (berberidaceae), they used cupric acetate with pyridine for the coupling of an arylboronic acid with a disubstituted phenol with a 57% yield<sup>130</sup>.



Scheme 45 : Copper catalyzed coupling reaction of arylboronic acid

With regards to the yield obtained by all of those groups, not better and even worse than those we have obtained with palladium, investigations with arylboronic acid were discarded and even more with the comments Evans did after his study of coupling arylboronic with activated phenol<sup>131</sup>. Evans underlines the fact that if *ortho*-substituted phenol reacts with good yield, it is the opposite of *ortho*-substituted boronic acids. In our case, this is an undesired limitation. Finally, without better results than those given by Ullman-type reaction, we decided to study and improve the known and described conditions.

## C. “North part” of Trilobine

### 1. *Dibenzo-p-dioxiran system*

As we had already presented in precedent chapters, several sequences for the formation of dibenzodioxiran system. Two main ways lead to this system; double Ullmann-type coupling reaction or double aromatic nucleophilic substitution reaction.

<sup>130</sup> Wang, Y-C. ; Georghiou, P.E., *Org. Lett.* **2002**, 4(16), 2675 – 2678.

<sup>131</sup> Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, 39(19), 2937 – 2740.

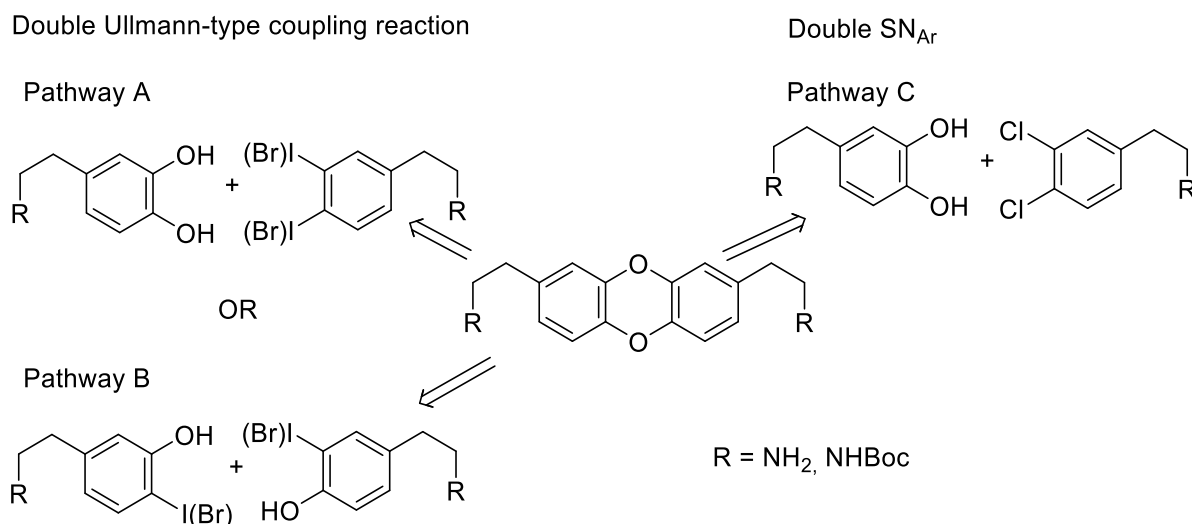
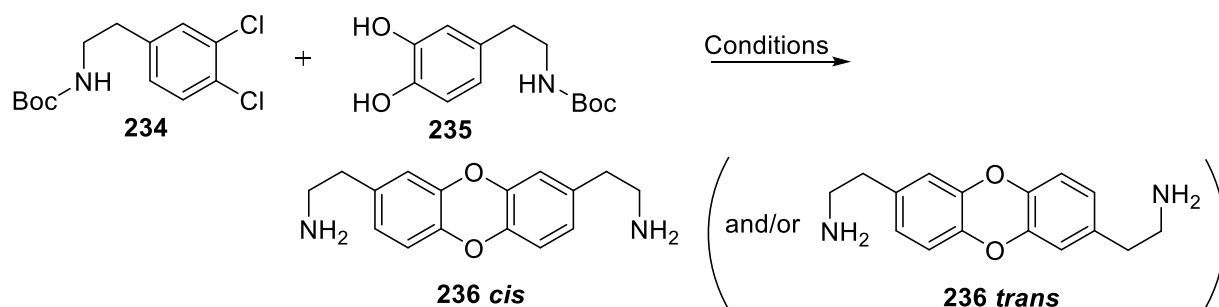


Figure 32 : Strategies for dibenzodioxiran system synthesis

None of the two Ullmann-type coupling reaction pathways were satisfactory, as regards to all procedures described in the literature and presented in chapters 1 and 2. Yields of the coupling are often low and selectivities are not good at all. So, in our part we looked for the third pathway, with double aromatic nucleophilic substitution. As preparative work, we checked if this reaction was effective or not. Thus, we engaged protected N-Boc dopamine **235** and protected N-Boc dichlorophenylethylamine **234** in typical conditions and obtained the desired dibenzo-*p*-dioxiran system in 68% yield as shown in table 5. Because of symmetry, we can not be sure we did not obtain mixture of “*cis*” and “*trans*” regioisomer, while NMR spectra are not distinguishable, and of course even less mass spectra. Only X-ray analysis would give clues, but only in a lonely crystal.



Scheme 46 : Synthesis of dibenzo-*p*-dioxiran system

Table 5 : optimization condition of green synthesis

Entry	Base	Solvent	Time	Temp (°C)	Yield (%)
1.	K <sub>2</sub> CO <sub>3</sub>	DMSO	48 h	120	21
2.	K <sub>2</sub> CO <sub>3</sub>	DMF	48 h	120	68

We did not optimized this reaction. At this stage, our goal was to check the feasibility. In our strategy, this reaction for the formation of the dibenzo-*p*-dioxiran system is planned to be the last critical step, after the formation by cyclization of the two tetrahydroisoquinoline. So, we hope that an intramolecular process will limit the regioselectivity problem.

We need now to develop the preparation of the two phenethylamine, and study the tetrahydroisoquinoline cyclization process.

## 2. Dihalogeno-phenethylamine:

One of the classical pathways to access to the benzyltetrahydroisoquinoline alkaloids is the Bischler-Napieralski<sup>132</sup> intramolecular condensation or Pictet-Spengler reaction.<sup>133</sup> As shown in precedent chapters, the majority of authors prefer the Bischler-Napieralski cyclization as one of the choice methods used for the preparation of simple benzyltetrahydroisoquinolines, through an amide formation obtained from the substituted phenethylamine and acid.

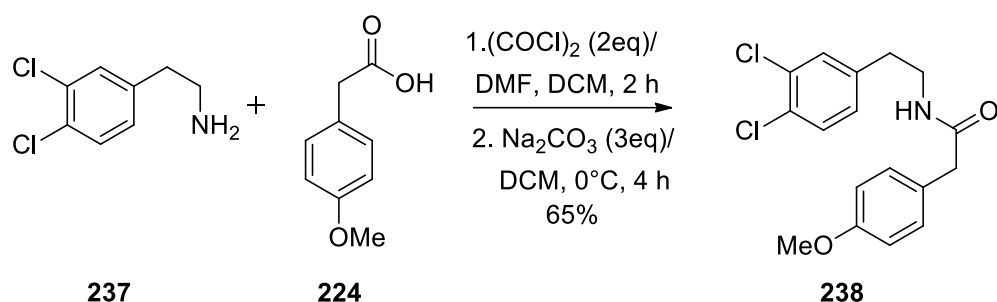
We advance our synthesis to form a monomer of benzyltetrahydroisoquinoline derivative. So, we activated the compound **224** with oxalyl chloride in a catalytic amount of DMF in DCM for 2 hrs into acid chloride and without purification, the commercial available dichlorophenethylamine **237** was added to the mixture to stirred at 0°C for 4 hrs<sup>134</sup>, to form the key amide **238** intermediate in 65% yield (Scheme 47).

It is obvious that the Bischler-Napieralski intramolecular condensation can be performed with this intermediate of the amide to afford the benzyltetrahydroisoquinoline alkaloids.

<sup>132</sup> W. M. Whaley, T. R. Govindachari. *Org. React.* **1951**, 6, 151-190.

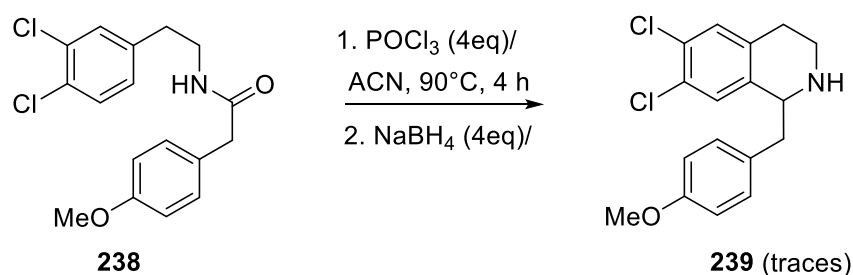
<sup>133</sup> W. M. Whaley, T. R. Govindachari. *Org. React.* **1951**, 6, 74-150.

<sup>134</sup> K. Tangdenpaisal, R. Worayuthakarn, S. Karnkla, P. Ploypradith, P. Intachote, S-. Sengsai, B. Saimanee, S. Ruchirawat, M. Chittchang. *Chem. Asian J.* **2015**, 10(4), 925-937.



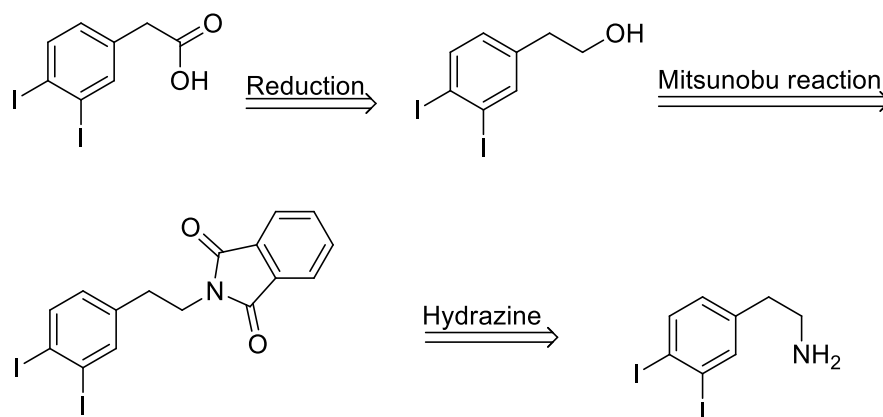
Scheme 47 : Synthesis of amide **238**

Having the amide **238** in hand, we condensed it intramolecularly with  $\text{POCl}_3$ , in acetonitrile under stirring at  $90^\circ\text{C}$  for 4 hrs which is known as Bischler-Napieralski reaction to form the iminium salt. On reduction with  $\text{NaBH}_4$ , at  $0^\circ\text{C}$  for 4 hrs, the compound could not be isolated properly. But we observed a traces of two singlet which differs from the three spin system of the amide. Because it was carried out on low scale medium, it was difficult to purify the compound **239** after several attempts (Scheme 48).



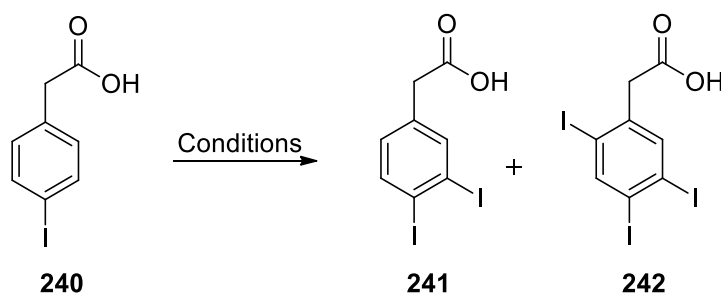
Scheme 48 : Bischler-Napieralski reaction of **238**

Unfortunately, it was not possible to investigate this transformation more ahead because of restriction policies of the chemical company which supplies the starting dichlorophenethylamine **237** at an affordable price. We sought alternative routes to overcome our problem and that was to develop the different monomer of phenylethylamine derivatives with diiodo substrates, it will give a better formation of dibenzo-*p*-dioxine nucleus. Iodide is a preferred choice of Ullmann type coupling because it's stable and more reactive under Ullmann conditions than the other halide compounds.



Scheme 49 : Retrosynthesis analysis of diiodophenylethylamine relying on 4-iodophenyl acetic acid

Therefore, the 4-iodophenyl acetic acid **240** was used as a starting material and submitted to Kraszkiewicz procedure<sup>135</sup> to afford the corresponding 3,4-diiodophenyl acetic acid **241**. Unfortunately, the reaction was over iodinated and the attempt to separate these two molecules became impossible to accomplish. Several conditions were tried as shown on Scheme 50 and Table 6, but none of them gave selectively diiodinated compound **242**.



Scheme 50 : Direct diiodination

Table 6 : Various condition of direct double iodination of aryl acetic acid

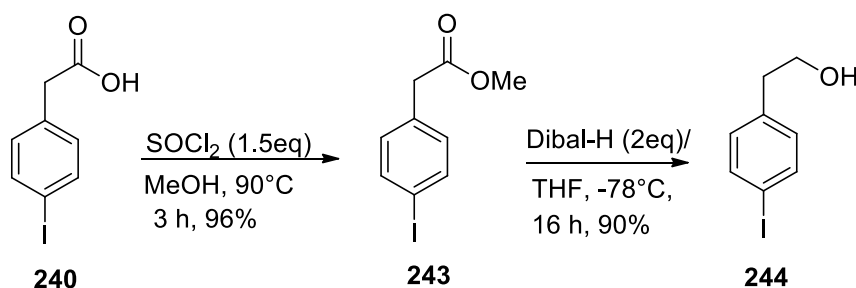
Entry	Halide	Solvent	Time	Temp	Yield	Ration ( <b>241:242</b> )
a.	NaIO <sub>4</sub> / KI (3eq)	Conc. H <sub>2</sub> SO <sub>4</sub>	4 h	25°C	69 % (recryst CCl <sub>4</sub> ) Over I <sub>2</sub>	87:13
b.	NaIO <sub>4</sub> / KI (3.5eq)	Conc. H <sub>2</sub> SO <sub>4</sub>	4 h	25°C	43 % (recryst CCl <sub>4</sub> ) Over I <sub>2</sub>	77:23
c.	NaIO <sub>4</sub> / KI (3eq)	Conc. H <sub>2</sub> SO <sub>4</sub>	3 h	25°C	70 % (recryst CCl <sub>4</sub> ) Over I <sub>2</sub>	90:10

<sup>135</sup> L. Kraszkiewicz, M. Sosnowski, L. Skulski. *Tetrahedron*, **2004**, 60(41), 9113 – 9119.



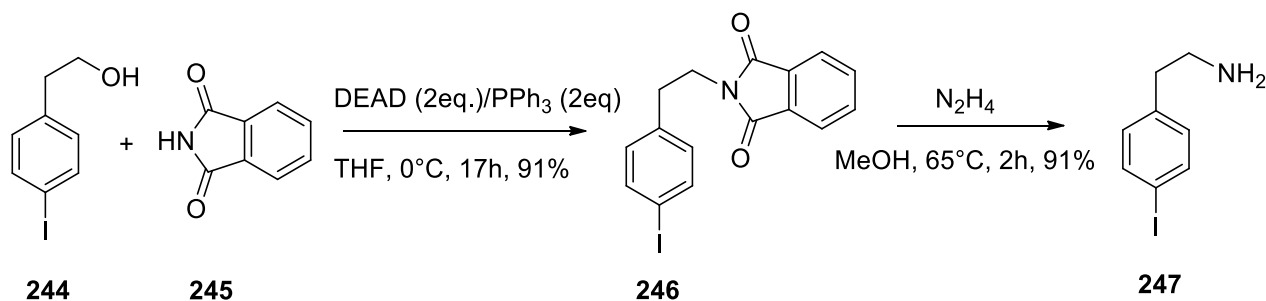
d.	NaIO <sub>4</sub> / KI (3eq)	Conc. H <sub>2</sub> SO <sub>4</sub>	3 h	25°C	71 % (recryst C <sub>2</sub> H <sub>2</sub> Cl <sub>6</sub> ) Over I <sub>2</sub>	89:11
e.	NIS (1.2eq)	DCM	3 h	25°C	No conv.	No conv.
f.	NIS (1.2 eq)/ TsOH	ACN	3 h	25°C	No conv.	No conv.
g.	ICl (1.1eq)	AcOH	48 h	50°C	No conv.	No conv.

Based on these challenges and difficulties encountered to obtain the iodinated compound **241** directly from **240** we proceed further to performed iodination reaction on nonbenzylic substrate. **240** was thus, reduce into alcohol **244**, via reaction of DiBAL-H on corresponding methylester **243**. (Scheme 51).



Scheme 51 : Reduction of Ester **243**

With 4-iodophenyl alcohol compound **244** in hands, the Mitsunobu reaction with phthalimide **245** as nucleophile was attempted. The reaction worked very well and we isolated the compound **246** in 91% yield. We checked first the effectiveness of hydrazine to liberate the free amine.<sup>136</sup> On the completion reaction mixture, 4-iodophenylethylamine **247** was obtained in 91% yield (Scheme 52).

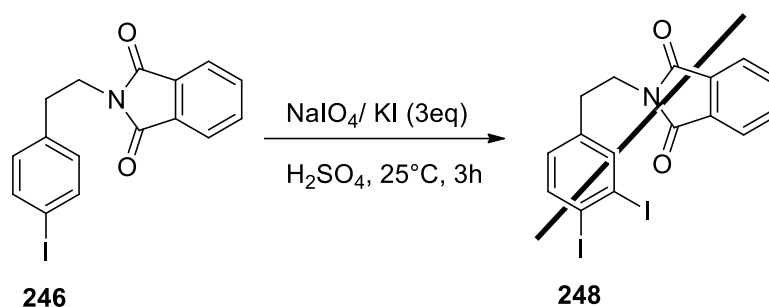


Scheme 52 : 4-iodophenylethylamine **247**

<sup>136</sup> T. Kanamori, K. Kuwayama, K. Tsujikawa, H. Miyaguchi, Y. T. Iwata, H. Inoue. *J. Forensic Sci.* **2011**, 56(5), 1319-1323.

After checking that, we were able to regenerate iodophenethylamine derivative **247** from phthalimide **246**, we looked after conditions for the monoiodination of **246**.

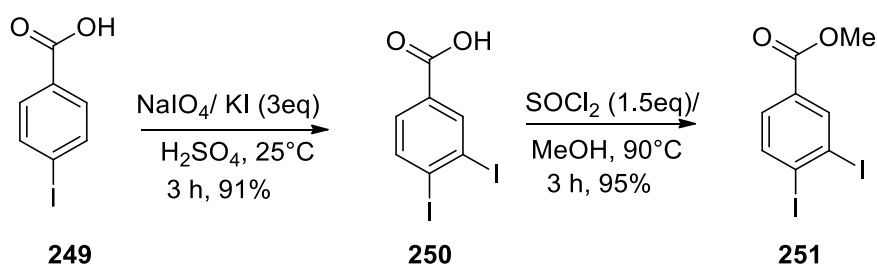
So, we engaged it into oxidative iodination using the Kraszkiewicz *et al.*, method which we have used in our previous experimental procedure to form compound **241**. Unfortunately, the reaction was not successful rather the product got destroyed after the workup. Probably, the condition was too harsh (Scheme 53).



Scheme 53 : Iodination of compound **246**

Since achieving the diiodophenylethylamine with the above sequence may not be possible. We have to resolve to another approach and this time around, we used the commercially available 4-iodobenzoic acid **249**. Even though it involves multiple steps to get the diiodo compound but it will form a better yield on Ullmann reaction of dibenzo-*p*-dioxin nucleus.

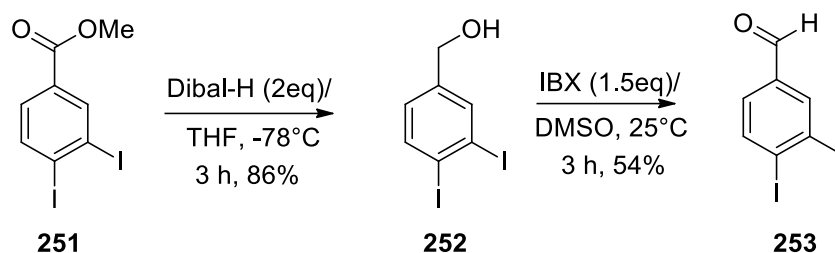
So we engaged compound **249** according to Kraszkiewicz *et al.*<sup>135</sup> method which has been used in our previous experimental procedure. The reaction worked very well and it was recrystallized with  $\text{CCl}_4$  to form 3,4-diiodobenzoic acid **250** in 91% yield without any over iodination and subsequently, we subjected **250** with thionyl chloride in MeOH to form methyl-3,4-diiodobenzoate **251** in 95% yield (Scheme 54).



Scheme 54 : Double iodinated ester **251**

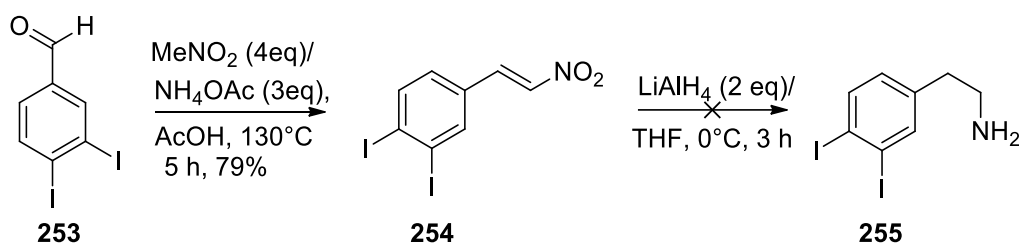
This diiodobenzoate **251** was reduced with Dibal-H and gave the diiodo alcohol **252** in 86% yield. This alcohol **252** was oxidized with IBX according to Nadkarni *et al.*<sup>137</sup> and we obtained the diiodobenzaldehyde **253** in 54% yield (Scheme 55).

<sup>137</sup> D.H. Nadkarni, S. Murugesan, S.E. Velu.. *Tetrahedron* **2013**, 69(20), 4105 – 4113.



Scheme 55 : Double iodinated aldehyde **253**

We also tried to transform the 3,4-diiodobenzaldehyde **253** using Henry's reaction which is a well-known classic reaction with MeNO<sub>2</sub> in the presence of NH<sub>4</sub>OAc in acetic acid. The reaction gave the corresponding 3,4-diiodobenzene nitrostyrene **254** in 79% yield and the 3,4-diiodobenzene nitrostyrene **254** was then reduced with LAH in THF. Unfortunately, we could not obtain the 3,4-diiodophenylethylamine **255** product in a purified form (Scheme 56).

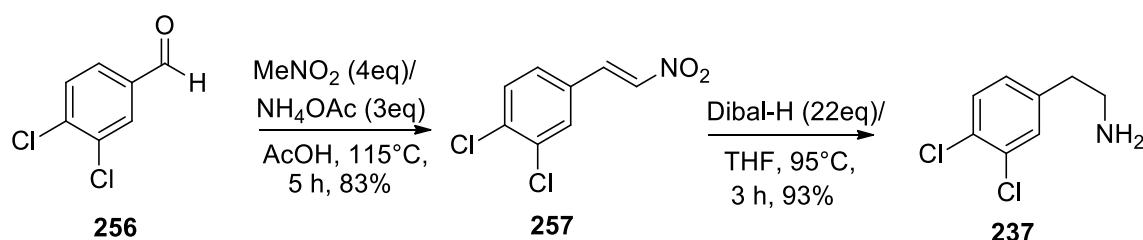


Scheme 56 : Diiodinated phenethylamine **255**

With these disappointing results from 3,4-diiodophenylethylamine **255** approaches, we were motivated to find another procedure to circumvent the use of diiodophenethylamine. Thus, it was envisioned that 3,4-dichlorobenzaldehyde **256** could be an attractive equivalent for the above diiodophenylethylamine compound and could be used to give rapid access to trilobine.

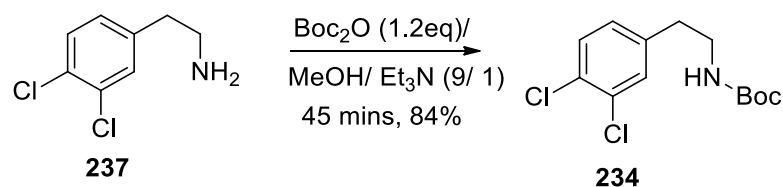
So, the dichlorobenzaldehyde **256** was engaged into Henry's type of reaction, interestingly we obtain the corresponding dichloronitrostyrene **257** in 83% yield. Although the similar challenge we encountered on diiodophenylethylamine **254** came up, the Petersen *et al.* method<sup>138</sup> with Dibal-H in THF. We were able to resolve the problem through the conversion of the 3,4-dichloronitrostyrene **257** into 3,4-dichlorophenylethylamine **237** in 93% yield (Scheme 57).

<sup>138</sup> S. Leth-Petersen, I. N. Petersen, A. A. Jesen, C. Bundgaard, M. Baek, J. Kehler, J. L. Kristensen. *Chem. Neurosci.* **2016**, 7(11), 1614 – 1619.



Scheme 57 : Synthesis of dichlorophenylethylamine **237**

The crude dichlorophenylethylamine **237** had some residues of Dibal-H and it was challenging to get it purified by column chromatography in a pure form. Due to high polarity and some instability of free amine **237** during purification process, we decided to protect it directly by Boc derivative. This reaction worked very well and it was easier to purify by column chromatography to form the corresponding N-Boc-3,4-dichlorophenylethylamine **234** in 84% yield (Scheme 58).



Scheme 58 : Protection of dichlorophenylethylamine **237**

Concerning the problem of commercially affordable supply of dichlorophenethyl amine **237**, with this sequence, we were now able to focus our attention on the intramolecular cyclization for tetrahydroisoquinoline alkaloids. This approach would provide general and straightforward access to preparing amine and aldehyde which is an entry to the natural product of trilobine **1** or isotrilobine **2**. But, we also need to study cyclization process, inefficiency and in regioselectivity, with di- and trihydroxy phenethylamine derived from dopamine and gallic acid.

## D. Tetrahydroisoquinoline synthesis

### a. Dopamine approach

To take the advantage of cyclization process in constructing benzyltetrahydroisoquinoline derivatives, we adapted our proposed retrosynthetic analysis using dopamine hydrochloride salt **7\*HCl** and any synthesized simple building block of the molecule, which could finally be cyclized with  $\text{BF}_3\text{-OEt}_2$ . After the construction, the obtained benzyltetrahydroisoquinoline compound could then be used to form the coupling of dibenzo-*p*-dioxin nucleus and diaryl ether through Ullmann type reaction. Hopefully, the trilobine or isotrilobine compound could be accomplished by this process.

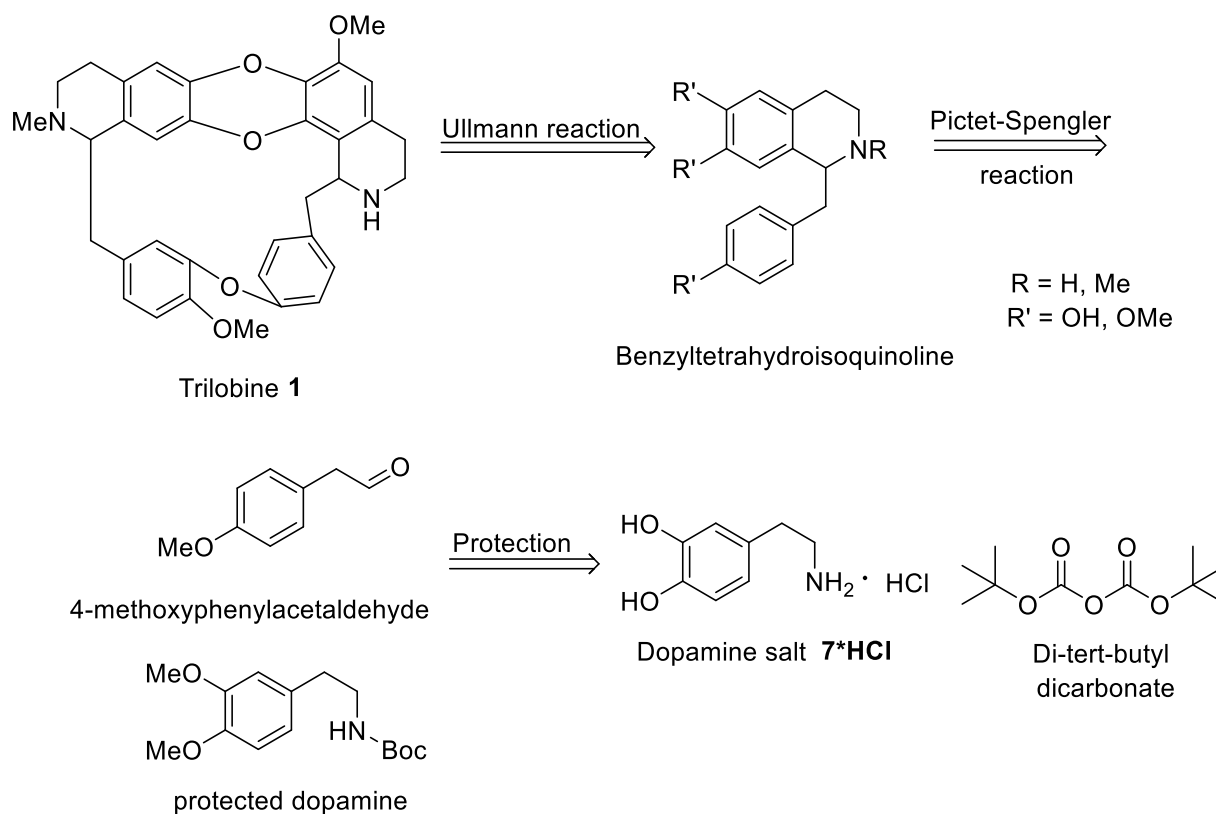


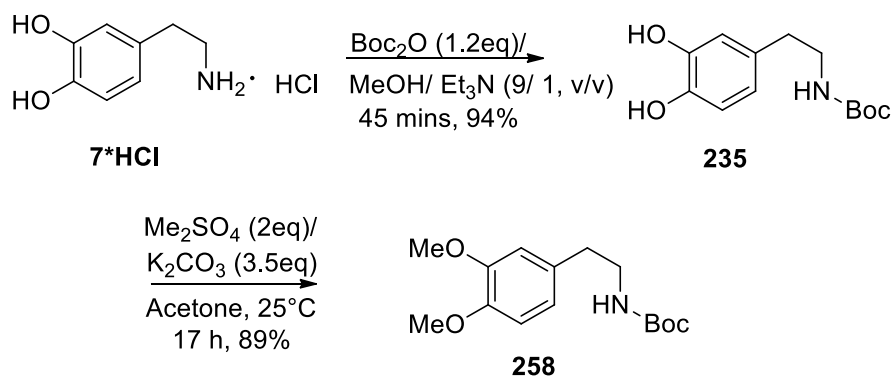
Figure 33 : Retrosynthesis analysis of benzyltetrahydroisoquinoline alkaloid

Dopamine is known for its therapeutic effect in the treatment of Parkinson's disease which makes it interesting in both biological and medicinal fields. More so the synthetic organic chemist have regarded it as a useful building block to design and synthesize some biological active compound because it possesses an amino group and catechol moiety<sup>139</sup>.

The dopamine hydrochloride **7\*HCl** was protected with boc according to M. Sani *et al.*<sup>140</sup> method. The reaction worked well and formed the desired product of dopamine with boc **235** in 94% yield. Then, it was reacted with dimethyl sulfate in the presence of  $K_2CO_3$  as the base, and on the completion, it was isolated to form the compound **258** in 88% yield (Scheme 59).

<sup>139</sup> Y. Kotake, Y. Tasaki, Y. Makino, S. Ohita and M. Hirobe. *J. Neurochem.* **1995**, 65(6), 2633 – 2638.

<sup>140</sup> M. Sani, A. Volonoterio, M. Zanda. *ChemMedChem.* **2007**, 2(12), 1696-1700.



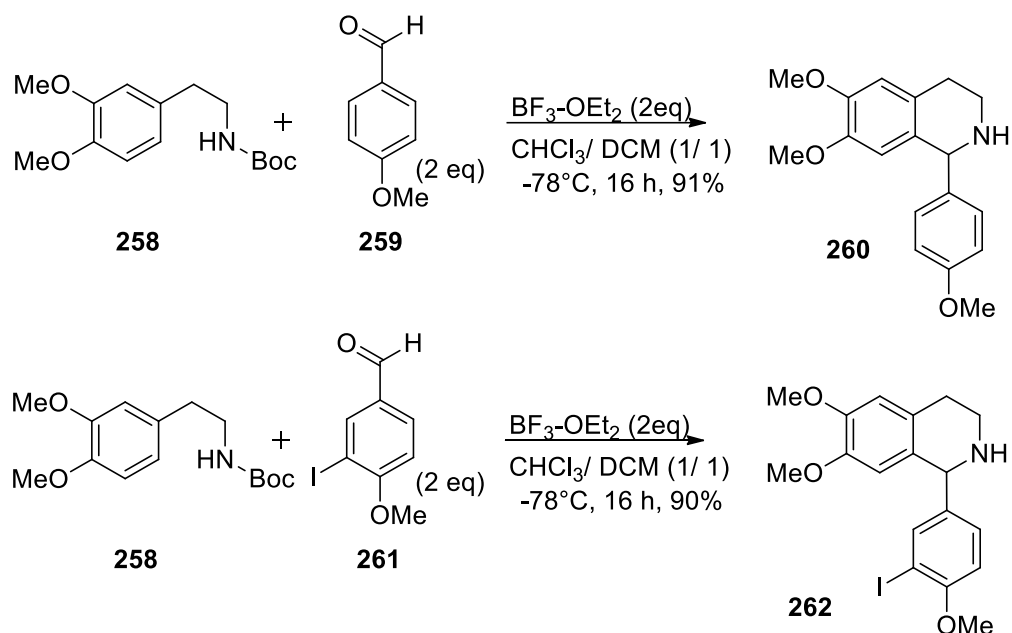
Scheme 59 : Synthesis of dimethoxyphenylethylamine **258**

Now, we tried to engage 3,4-dimethoxyphenylethylamine protected with boc **258** with *p*-anisaldehyde **259** to form a cyclization in the presence of an acidic medium and this can be achieved by Pictet-Spengler type reaction. The Pictet-Spengler reaction is a well-known type of reaction that involves the condensation of tetrahydroisoquinoline skeleton mostly present in many molecules of physiological and therapeutic use<sup>141</sup>.

We used the protected dopamine with boc **258** and commercial *p*-anisaldehyde **259** as a model for the cyclization process of the aromatic ring system with  $\text{BF}_3\text{-Et}_2$ . The reaction worked very well and it was isolated to form the compound **260** in 91% yield.

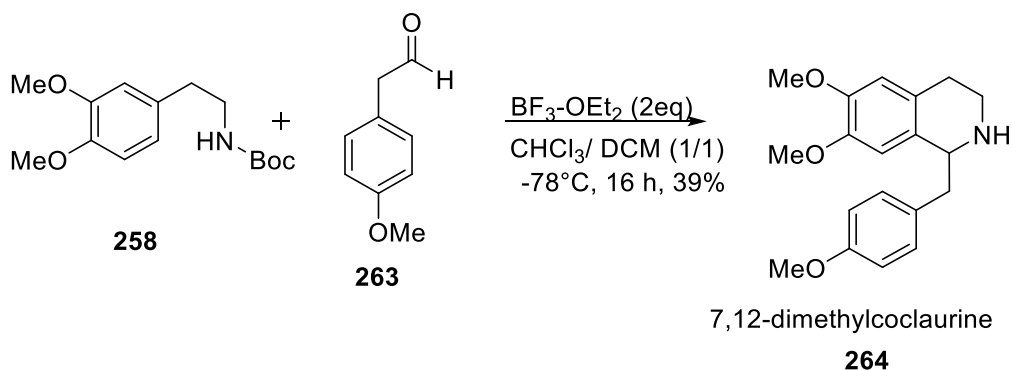
Subsequently, we tried the same condition on protected dopamine with boc **258** and our synthesized 3-iodo-4-methoxybenzaldehyde **261**. The corresponding compound **262** was obtained in 90% yield (Scheme 60)

<sup>141</sup> J. Stockigi, A. P. Antonchick, F. Wu, H. Waldmann. *Angew. Chem. Int. Ed. Engl.*, **2011**, 50(37), 8538 – 8564.



Scheme 60 : Pictet-Spengler reaction of **258** with *p*-anisaldehyde and *m*-iodo-*p*-anisaldehyde

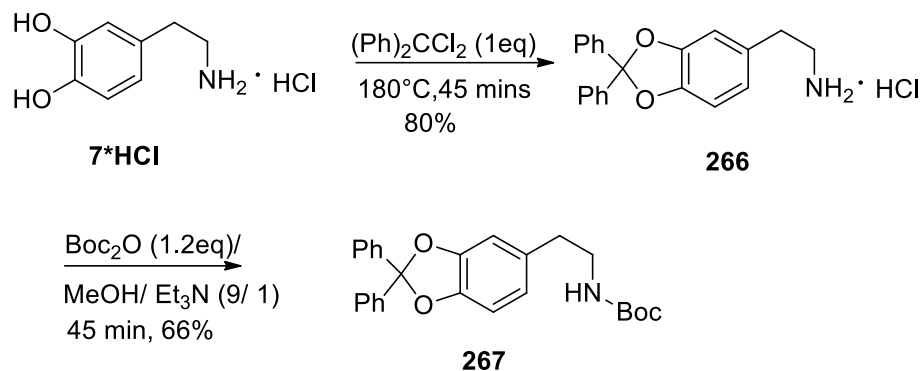
The same condition reaction was tried on protected dopamine with boc **258** using a building block of 4-methoxyphenyl acetaldehyde **263**. The reaction worked and 7,12-dimethylcoclaurine **264** was obtained in 39% yield. Although the yield was low when compared to reactions of Scheme 60. Maybe the acetaldehyde is more reactive or less stable because benzyl positions under these reaction condition than the benzaldehyde (Scheme 61).



Scheme 61 : Pictet-Spengler reaction of protected dopamine **258** with arylacetaldehyde **263**

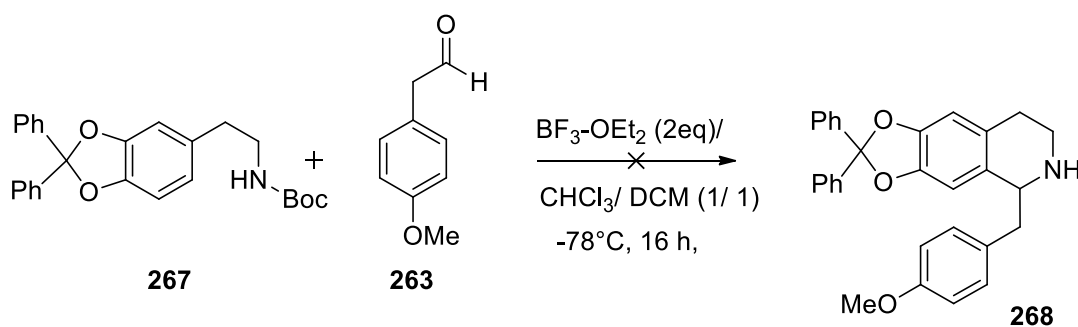
The preparation of natural substance dimethylcoclaurine **264** validate this sequence, but to continue the synthesis toward trilobine, we need to change protecting group since it is not possible to perform selective demethylation of benzyl methoxy group without reaction on the dimethoxy system on isoquinoline moiety.

Thus, with dopamine hydrochloride salt **7\*HCl** in hand, we treat it directly with diphenyldichloromethane according to Takaoka *et al.*<sup>142</sup> and it affords the corresponding **266** in 80% yield and this product can easily be deprotected by hydrolysis under acidic condition<sup>143</sup>. Moreover, we proceed further to protect the free amine of diphenyl dopamine **266** with boc as reported in our previous experimental procedure to form the compound **267** in 66% yield (Scheme 62).



Scheme 62 : Protection of dopamine with boc

Now, we tried to cyclize the protected diphenyl group on dopamine compound **267** and our synthesized 4-methoxyphenyl acetaldehyde **263** under the same condition of acid catalyzed condensation with  $\text{BF}_3\text{-Et}_2\text{O}$ . The expected formation of a benzyltetrahydroisoquinoline **268** was unsuccessful. Probably the deprotection of diphenyl groups occurs in the reaction mixture since it is acid sensitive and the by-product may have complexed with the desired product making it difficult to isolate them (Scheme 63).



Scheme 63 : Pictet-Spengler reaction of **267**

Having the methodology for the preparation of tetrahydroisoquinoline in hands, we now turn our attention to trioxygenated substrate instead of the two oxygenated dopamine. Gallic acid is the starting material of choice, since its transformation to phenethylamine derivative can be performed using the Henry reaction/reduction sequence, we have already used with halogenated benzoic acids.

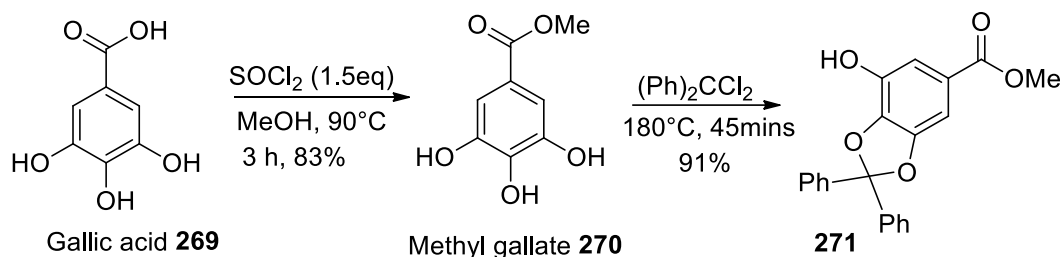
<sup>142</sup> S. Takaoka, N. Takaoka, Y. Minoshima, J. Huang, M. Kubo, K. Harada, H. Hioki, Y. Fukuyama. *Tetrahedron*, **2009**, 65(40), 8354–8361.

<sup>143</sup> L. Jurd. *J. Am. Chem. Soc.* **1959**, 81(17), 4606–4610.



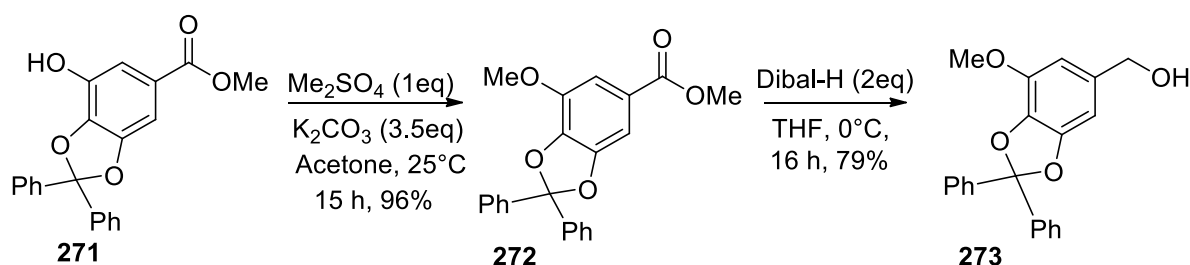
## b. Gallic acid approach

The synthesis of trioxygenated phenethylamine began by protection reaction of the cheap commercially available gallic acid **269**. The Fischer esterification was performed to form methyl gallate **270** in 83% yield. The methyl gallate **270** react with diphenyldichloromethane according to Takaoka *et al.*<sup>142</sup> and it gave the promising bisprotected **271** in 91% yield (Scheme 64).



Scheme 64 : Protection of methyl gallate

Subsequently, compound **271** was methylated using M. Sani *et al.*<sup>144</sup> method and the reaction mixture worked very well to form compound **272** in 96% yield. Then, the compound **272** was reduced with Dibal-H to afford the corresponding alcohol **273** in 79% yield (Scheme 65).

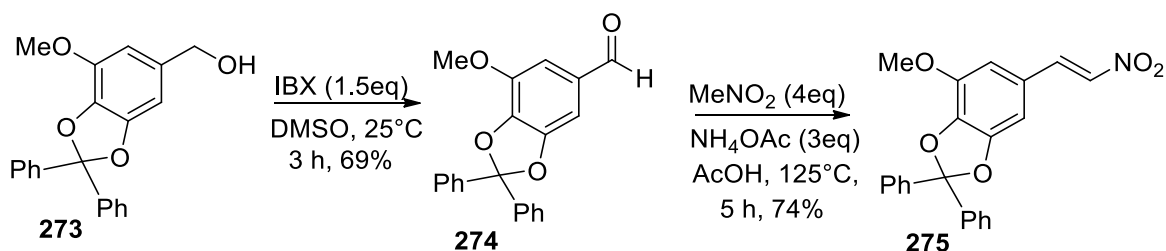


Scheme 65 : Reduction of gallate

Alcohol **273** was oxidized with IBX in DMSO to obtain the aldehyde **274** in 69% yield. We then transformed the **274** by Henry's reaction according to our previously used experimental procedure with MeNO<sub>2</sub> in the presence of NH<sub>4</sub>OAc in acetic acid. On completion of the reaction, the desired nitrostyrene compound **275** was isolated in 74% yield (Scheme 66).

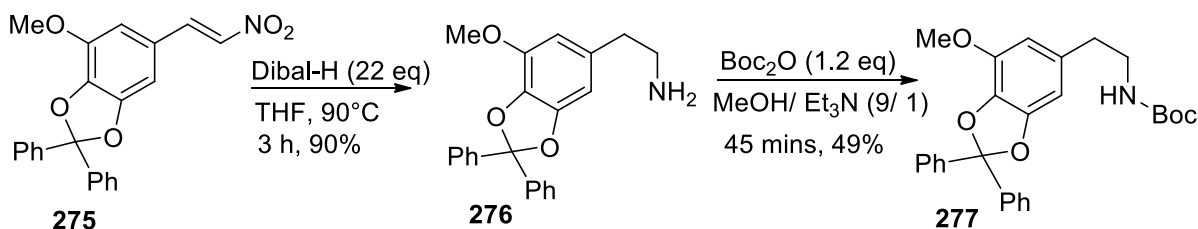
<sup>142</sup> S. Takaoka, N. Takaoka, Y. Minoshima, J. Huang, M. Kubo, K. Harada, H. Hioki, Y. Fukuyama. *Tetrahedron*, **2009**, 65(40), 8354–8361.

<sup>144</sup> M. Sani, A. Volonoterio, M. Zanda. *Chem.Med.Chem.* **2007**, 2, 496 – 504.



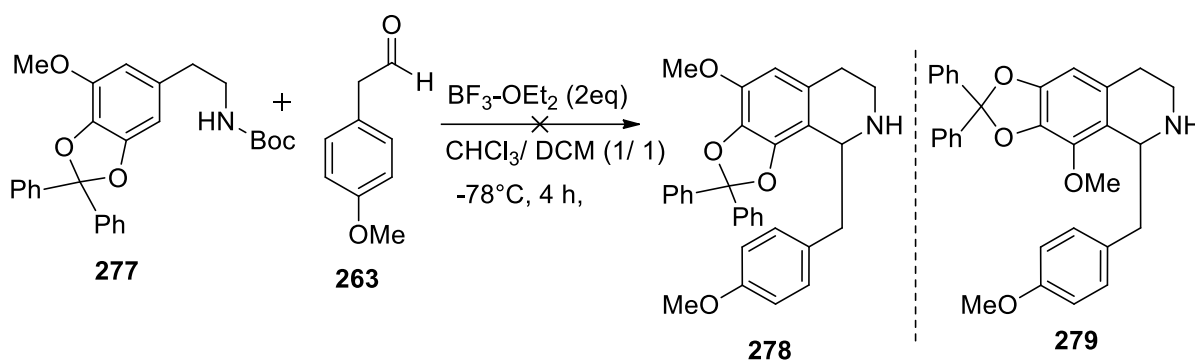
Scheme 66 : Formation of nitrostyrene **275**

We tried to reduce the nitrostyrene compound **275** with Dibal-H, according to Leth-Petersen *et al.*<sup>138</sup> method to form the corresponding amine **276** in 90% yield. Although, the crude product still had some residues of by-products from the reaction mixture and the attempt to possibly isolate it in pure form as the free amine became hard due to the compound **276** easily decomposed on silica gel column chromatography. To avoid this, we protected directly the crude product **276** as boc derivative, which is much easier to purify. The compound **277** was obtained in 49% yield, for these two steps (Scheme 67).



Scheme 67 : Synthesis and Protection phenylethylamine **277**

With the compound **277** in hand, the Pictet-Spengler reaction with 4-methoxyphenyl acetaldehyde **263** was also tried on the same condition but in a different time interval which is aim to form a cyclized benzyltetrahydroisoquinoline compound. Unfortunately, the reaction mixture didn't work out again because the multiple products was difficult to isolate (Scheme 68).

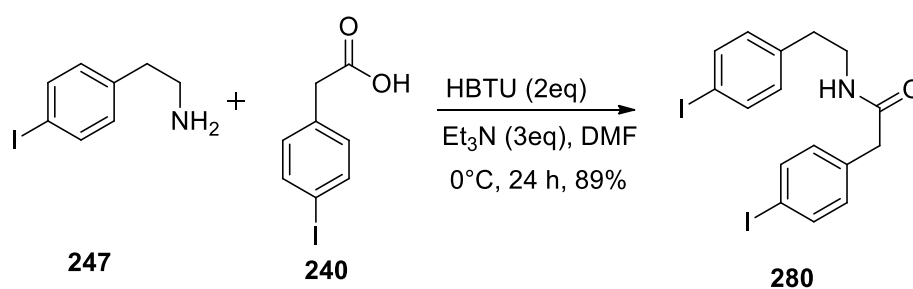


Scheme 68 : Pictet-Spengler reaction of **277**

We understand that with diphenyl protection in both dopamine and gallate, it was always difficult to perform the intramolecular cyclization by Pictet-Spengler reaction because the diphenyl molecule is sensitive to acidic medium. However, we have to engage the diphenyl protection of gallate by Bischler-Napieralski reaction to ascertain if the same challenge.

### c. Iodophenylethylamine approach

Although the Tangdenpaisal *et al.*<sup>134</sup> method used earlier in our experiment gave us a good yield, it is moisture sensitive and so we sought for another method free from previous challenge. Since the acid chloride compound is moisture sensitivity. We found out that Cox *et al.*<sup>145</sup> could actually work well on one spot condition to form the amide which will enable the intramolecular cyclization reaction. So we engaged 4-iodophenylethylamine **247** to react with 4-iodophenyl acetic acid **240** in the presence of HBTU and  $\text{Et}_3\text{N}$  as a base in DMF at  $0^\circ\text{C}$  for 24 hours. The reaction worked very well and we isolated the amide compound **280** in 89% yield (Scheme 69).



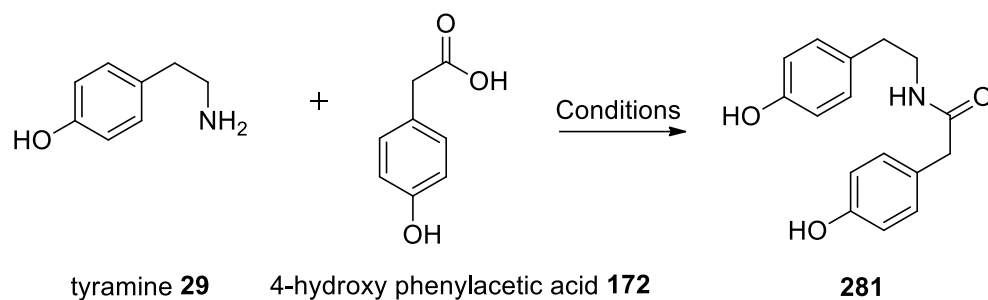
Scheme 69 : Amide reaction from iodophenylethylamine

We tried a model with a free hydroxyl group, using the commercially available tyramine **29** and 4-hydroxyphenyl acetic acid **172** respectively to react under the same condition of Cox *et al.*

<sup>134</sup> K. Tangdenpaisal, R. Worayuthakarn, S. Karnkla, P. Ploypradith, P. Intachote, S.-. Sengsai, B. Saimanee, S. Ruchirawat, M. Chittchang. *Chem. Asian J.* **2015**, 10(4), 925 – 937.

<sup>145</sup> J. B. Cox, A. Kimishima, J. L. Wood. *J. Am. Chem. Soc.* **2019**, 141(1), 25 – 28.

Unfortunately this reaction didn't work, probably the free hydroxyl group complexed with the HBTU reagent in the medium and it resulted to a mixtures of multiple compounds that was very difficult to isolate. To overcome this problem, we found out that the report of Valpuesta *et al.*<sup>146</sup> which they developed in their synthesis could actually solve our problem. So we tried their procedure with the tyramine **29** and the 4-hydroxyphenyl acetic acid **172** was heated and the reaction worked very well and we isolated the amide compound **281** in 89% yield (Scheme 70).



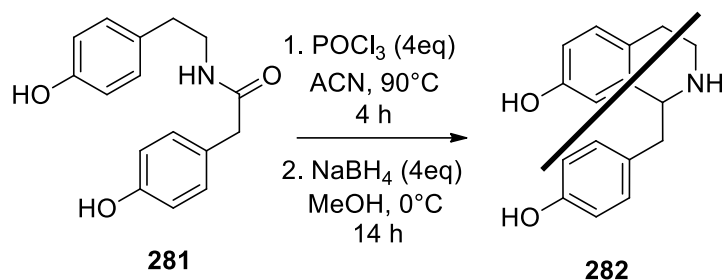
Scheme 70 : Amide reaction from tyramine

Table 7 : Conditions for amide reaction

Entry	Conditions	Time	Temp.	Yield
1.	HBTU (2eq)/ Et <sub>3</sub> N (3eq), DMF	24 h	0°C	0
2.	Heat	2 h	180°C	89%

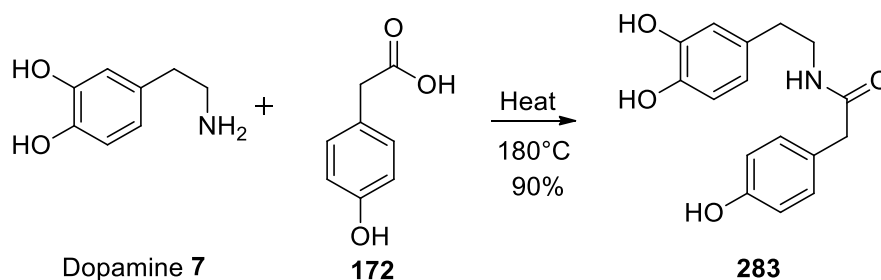
We subjected the amide compound **281** as a model to a Bischler-Napieralski intramolecular condensation reaction through POCl<sub>3</sub> in acetonitrile, but TLC control of the reaction showed multiple spots. After reduction with NaBH<sub>4</sub>, it was very difficult to isolate anything from the mixture, maybe the free hydroxyl group could have affected the cyclization process by reacting with the POCl<sub>3</sub> reagent in the medium (Scheme 71)

<sup>146</sup> M. Valpuesta, M. Ariza, A. Diaz, G. Torres, R. Suau. *Eur. J. Org. Chem.* **2010**, (4), 638–645.



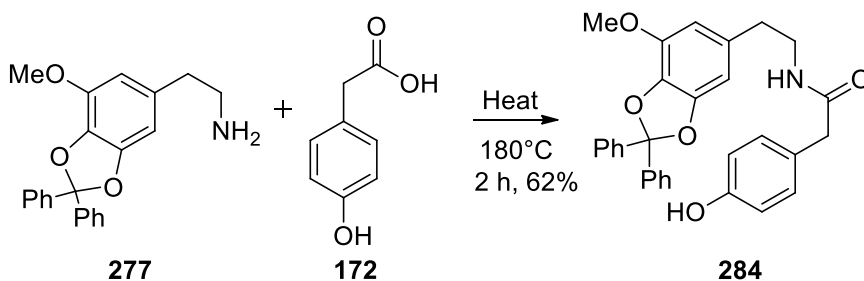
Scheme 71 : Bischler-Napieralski reaction

However, we engaged dopamine **7** and 4-hydroxyphenyl acetic acid **172** by the same method<sup>146</sup>, the reaction worked very well and we isolated the amide compound **283** in 90% yield (Scheme 72). We find out this approach is more efficient and convenient, because no reagent or an activating agent is required and no side product is formed. Since our previous attempt to cyclized free hydroxyl compound using Bischler-Napieralski reaction didn't work, so we never bothered to engage **283** into it. Rather, we coupled the amide compound **283** and a monomer of halide substrates of amide into diaryl ether formation using Ullmann type reaction.



Scheme 72 : Synthesis of amide coupling of dopamine

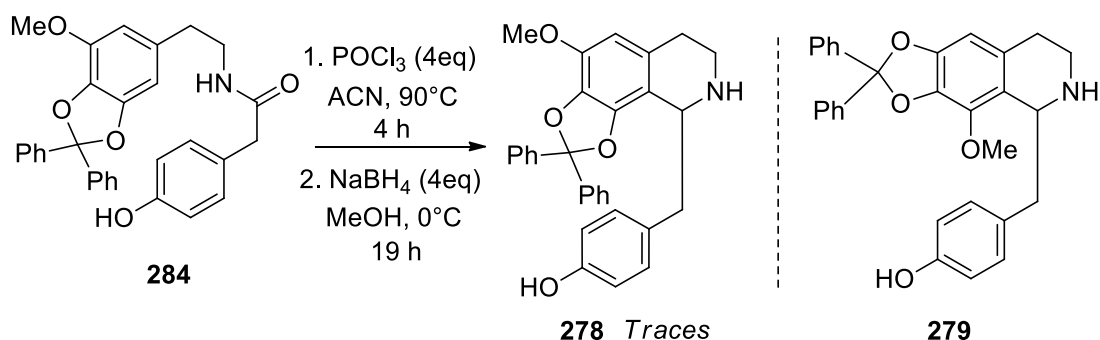
With these promising results, we extend Valpuesta *et al.*<sup>146</sup> method to phenethylamine compound **277** and 4-hydroxyphenyl acetic acid **172**. These gave us the desired amide compound **284** in 62% yield without any side reaction (Scheme 73).



Scheme 73 : Synthesis of amide coupling

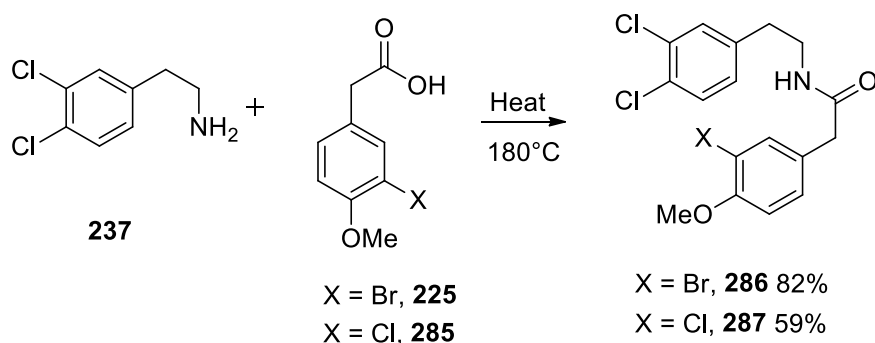
Therefore, the amide compound **284** was engaged into a Bischler-Napieralski reaction, which is usually mediated by  $\text{POCl}_3$  in acetonitrile. The reaction formed an intermediate imine compound

and it was subsequently reduced with NaBH<sub>4</sub>. We obtained traces of compound **278** of benzyltetrahydroisoquinoline in a complex mixture that was very difficult to separate (Scheme 74).



Scheme 74 : Bischler-Napieralski reaction of **284**

From the aforementioned reactions, Valpuesta *et al*<sup>146</sup>. method proved to be more efficient and convenient which proved to be compatible with amide reaction. Based on these premises, we decide to engage the 3,4-dichlorophenylethylamine **237** with different halide substrates of 4-methoxyphenyl acetic acid (**225** and **285**) and it gave us the corresponding amide compound of **286** and **287** in 82% and 59% yield respectively (Scheme 75).



Scheme 75 : Synthesis of amide coupling

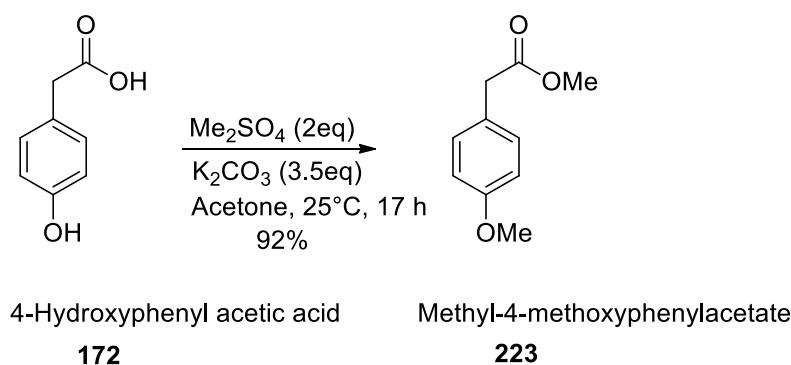
We have now in hands, the two phenethylamine; the catechol on the one hand, and the dichlorophenyl on another hand. We knew that it is possible to perform a reaction between them to form the dibenzo-dioxiran system, and we began to study the cyclization process via Bischler-Napieralski or Pictet-Spengler reaction. The last point to be solved is the formation of diaryl ether moiety corresponding to the “south part” of the trilobine, correctly functionalized *i.e.* with two masked aldehydes which will need to be regenerated separately.

## E. Synthons for “south” part of trilobine

As the aromatic nucleophilic substitution can't be efficient, we turned our attention to other halogenated substrate and replaced the fluorine with iodine, bromine, or chlorine.

The first attempt is synthesizing the latter synthon with the commercially available 4-hydroxyphenyl acetic acid **172**. It reacted with dimethyl sulfate in the presence of potassium carbonate according to M. Sani *et al.*<sup>140</sup> to yield to bisprotected compound **223** in excellent yield.

When we tried to increase on a large scale, we had the challenge of isolating the product from column chromatography because of the sulphate residues in the compound and this made us use Kugelrohr distillation which is more efficient to remove the sulphate residues but may not be a convenience for large scale production. We sourced alternate methylation reagent and we tried dimethyl carbonate under the same method. This time around, it was easier to purify even on a large scale because the by-product is carbon dioxide and it is volatile, but the yield is slightly lower if compared with dimethyl sulphate (Scheme 76)



Scheme 76 : Methylation of acid

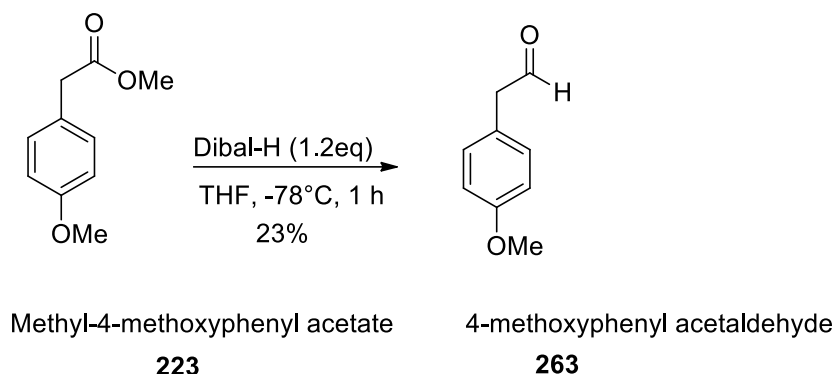
Table 8 : Conditions of large scale methylation of 4-hydroxyphenylacetic acid.

Entry	Reactant	Base	Solvent	Time (h)	Temp (°C)	Yield (%)
1 g	Me <sub>2</sub> SO <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	17 h	25	96
2 g	Me <sub>2</sub> SO <sub>4</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	17 h	25	92
5 g	Me <sub>2</sub> CO <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	17 h	25	89
10 g	Me <sub>2</sub> CO <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	17 h	25	88
12 g	Me <sub>2</sub> CO <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	Acetone	17 h	25	81

So the methyl-4-methoxyphenyl acetate **223** was allowed to undergo a reduction reaction<sup>147</sup> using diisobutylaluminium hydride (1 M, Dibal-H) in THF for 1 hr at -78°C, to afford the

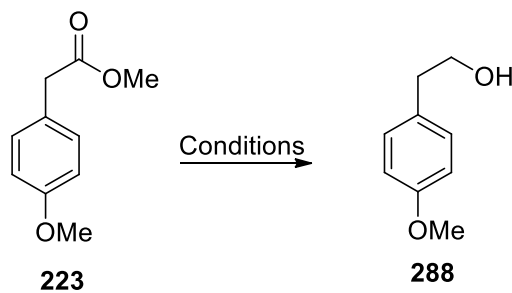
<sup>147</sup> N. J. Race, A. Faulkner, G. Fumagalli, T. Yamauchi, J. S. Scott, M. Rydén-Landergren, H. A. Sparkes, J. F. Bower. *Chem. Sci.* **2017**, (8), 1981 – 1985.

corresponding aldehyde **263** in 23% yield. The product was very difficult to isolate because it degrades on silica gel during column chromatography (Scheme 77).



Scheme 77 : Dibal-H reduction of ester.

We engage methyl-4-methoxyphenyl acetate **223** in a mild reduction process with NaBH<sub>4</sub> in THF to reflux at 65°C for overnight. Unfortunately, all the starting material was not consumed rather it gave alcohol of 42% yield **288** and 56% yield of starting material **223**. Since this method isn't given complete conversion, we performed then, the reduction of **223** using Dibal-H at -78°C for overnight and thus a complete conversion was obtained and the alcohol **288** was formed in 98% yield (Scheme 78).



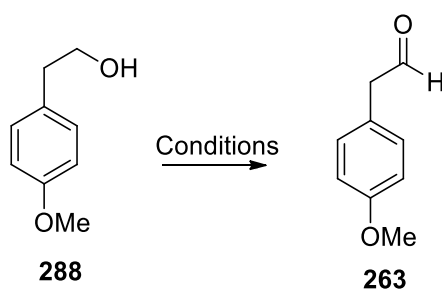
Scheme 78 : Reduction of ester **223**

Table 9 : Reduction of esters **223**

Entry	Reagent	Solvent	Time	Temp	Yield
1.	NaBH <sub>4</sub> (4eq)	THF	17 h	65°C	42%
2.	Dibal-H (2.5eq)	THF	17 h	-78°C	96%



With this alcohol **288** in hand, we oxidized it with pyridium chlorochromate (PCC) as a reported method by Pedrosa *et al.*<sup>148</sup> in DCM at 50°C for 4 hrs. There was some trouble in the purification process from the column chromatography probably the mixture was sensitivity to the silica gel even though we obtain the aldehyde **263** in 44% yield, but there are still some impurities in the compound. So we sought another method and found the report of Nadkarni, *et al.*<sup>137</sup> with IBX which is a powerful oxidizing agent. The reaction worked well and we isolated the aldehyde **263** in 64% yield in pure form (Scheme 79).



Scheme 79 : Oxidation of alcohol **237**

Table 10 : Oxidation of alcohol **288**

Entry	Reagent	Solvent	Time	Temp	Yield
1.	NaOAc (2eq)/ PCC (2eq)	DCM	4 h	65°C	44%
2.	IBX (1.5eq)	DMSO	3 h	25°C	64%

With this methodology in hand, there's a need to have substrates of either halide or hydroxyl group in the aromatic ring system, as the first partner for Ullmann-type coupling reaction. The goal is to be able to synthesize the south part of our molecule and this will require the incorporation of mono-halogenated substrates into the aromatic ring system which will enhance the coupling of the diaryl ether.

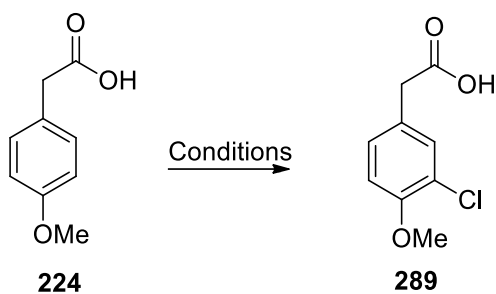
With the 4-methoxyphenyl acetic acid **224** obtained by saponification of the corresponding ester (as already shown in Scheme 42) in hand, we engage it with oxone as oxidant and saturated NaCl according to M. Antonello *et al.*<sup>149</sup>. Unfortunately, the reaction was unsuccessful. Probably, the compound is not compatible with the oxidant reagent. Thus, we sought for a more efficient method to achieve this and the report by G. Yu *et al.*<sup>150</sup> with sulfonyl chloride in a polar protic solvent (AcOH) at room temperature for 3 hrs gave us a direct mono-chlorination of electron-rich aryl compound **289** in 94% yield (Scheme 80).

<sup>148</sup> R. Pedrosa, C. Andres, J.M. Iglesias. *J. Org. Chem.* **2001**, 66(1), 234 – 250.

<sup>137</sup> D.H. Nadkarni, S. Murugesan, S.E. Velu.. *Tetrahedron* **2013**, 69(20), 4105 – 4113.

<sup>149</sup> M. Antonello, S. Massa, S. Valente, S. Simeoni, R. Ragno, P. Bottoni, R. Scatena, G. Brosch. *ChemMedChem.* **2006**, 1(2), 225 – 237.

<sup>150</sup> G. Yu, H. J. Mason, K. Galdi, X. Wu, L. Cornelius, N. Zhao, M. Witkus, W. R. Ewing, J. E. Macor. *Synthesis*, **2003**, 3, 403 – 407.

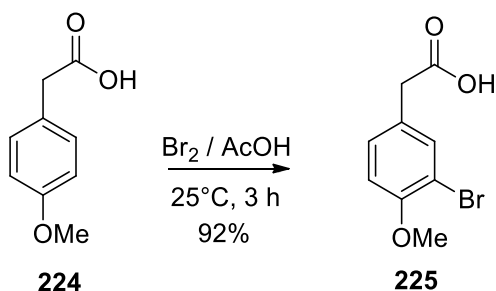


Scheme 80 : Direct mono-chlorination of **224**

Table 11 : Direct mono-chlorination of **227**

Entry	Reagent	Solvent	Time	Temp	Yield
1.	Oxone (1.1eq)/ NaCl	Acetone	6 h	25°C	0
2.	SO <sub>2</sub> Cl <sub>2</sub> (1.1eq)	AcOH	3 h	25°C	94%

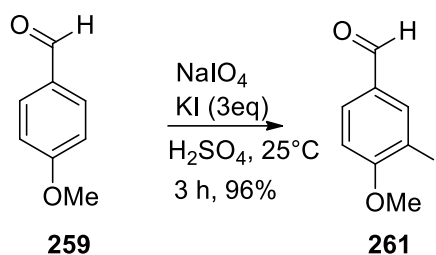
For the preparation of brominated compound, we reproduced the reaction described with very classic conditions using bromine in acetic acid.



Scheme 81 : Bromination of acid **224**

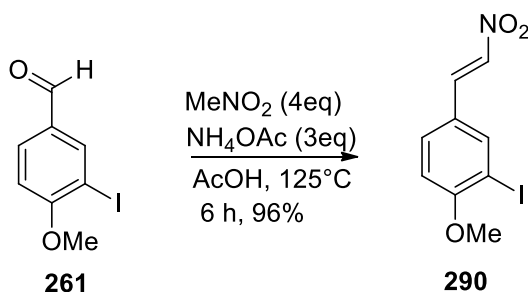
The bromination of acid **224** gave good results but the iodination of the same substrate **224** was more problematic and yielded to inseparable mixture of mono and di-iodinated compound.

We changed our starting material to commercial *p*-anisaldehyde **259**, which was synthesized according to Kraszkiwicz *et al.*<sup>135</sup> method. After complete reaction, the only mono-iodinated **261** was isolated in 96% yield (Scheme 82).



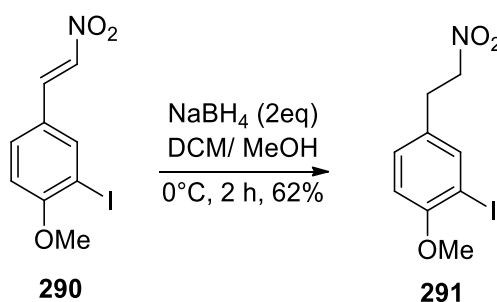
Scheme 82 : Iodination of aldehyde **261**

With compound **261** in hand, we transformed it into nitrostyrene compound using Henry's reaction<sup>151</sup>. On the completion of the reaction, it was isolated and the corresponding nitrostyrene **290** was formed in excellent yield (96%, Scheme 83)



Scheme 83 : Henry's reaction of aldehyde **261**

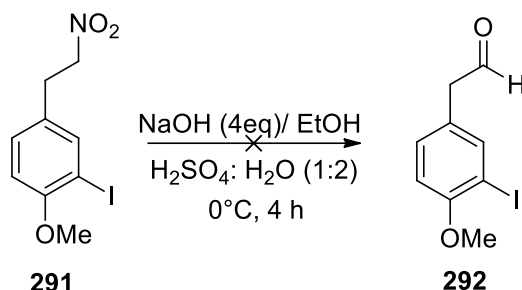
So the nitrostyrene **290** compound was further reduced with  $\text{NaBH}_4$ . and saturated nitro compound **291** was obtained in 62% yield (Scheme 84).



Scheme 84 : Selective reduction of nitrostyrene **291**

<sup>151</sup> A. Bermejo, I. Andreu, F. Suvire, S. Léonce, D. H. Caignard, P. Renard, A. Pierré, R. D. Enriz, D. Cortes, N. J. Cabedo. *J. Med. Chem.* **2002**, 45(23), 5058 – 5068.

Having the saturated nitro compound **291** in hand, we tried the Nef-type reaction<sup>152</sup> which was expected to transform the nitro group into a carbonyl group under the acidic condition to form the aldehyde **292**. But this reaction was unsuccessful, maybe the by-product of nitrous oxide causes the desired product to degrade in the reaction process (Scheme 85).



Scheme 85 : Formation of aryl aldehyde by Nef-type reaction

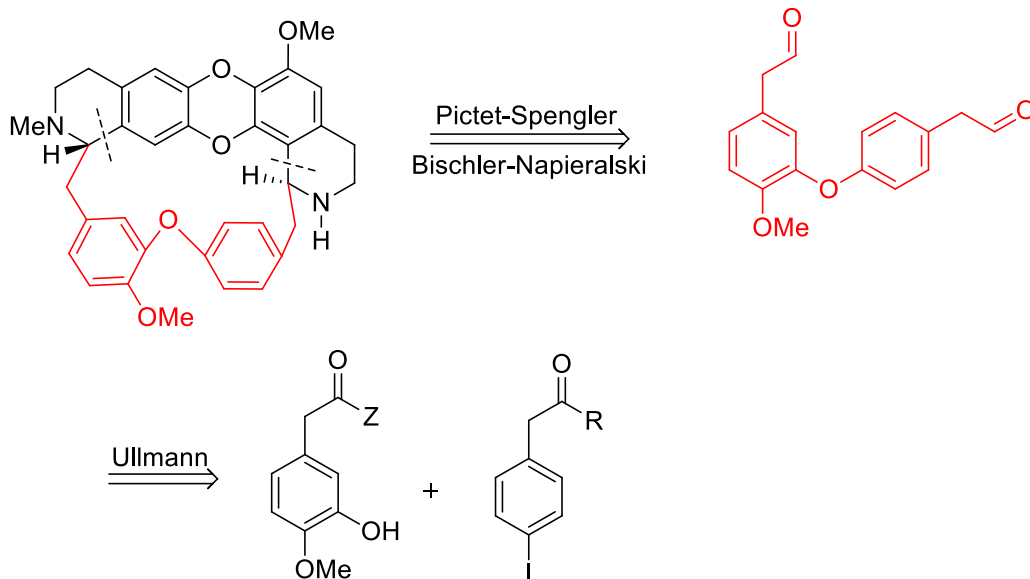
After several attempts trying to obtain the iodinated partner for Ullmann-type coupling reaction, we were a bit disappointed not to be able to obtain it by an efficient method, and on a large scale. We stopped our investigations here, considering and hoping that the brominated phenylacetate will be reactive enough under copper catalysis to form our desired diaryl ether synthon for the “South part” of the trilobine.

#### 1) South part of trilobine

We proposed the retrosynthesis analysis of the southern part of trilobine and the need is to establish discrimination of the two functions of aldehyde and/or acid for Pictet-Spengler and/or Bischler-Napieralski reaction respectively. The importance of this step is to enable us to perform the two cyclization reactions sequentially and to avoid the formation of the mixture which is always more complicated to purify.

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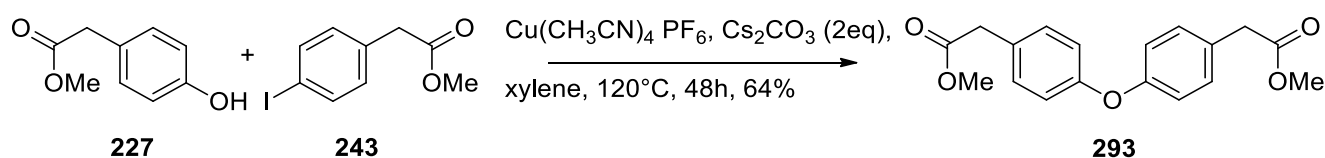
<sup>152</sup> (a) W. E. Noland. *Chem. Rev.*, **1955**, 55(1), 137 – 155; (b) R. Ballini, M. Petrini. *Tetrahedron*, **2004**, 60(5), 1017 – 1047; (c) C. F. Chang, C. Y. Huang, Y. C. Huang, K. Y. Lin, Y. J. Lee and C. J. Wang. *Syn. Comm.* **2010**, 40(23), 3452 – 3466.



Scheme 86 : Retrosynthesis of the southern part of diaryl ether.

#### d. Preliminary studies

As a model for our diaryl ether, we first tried to couple simple substrate such as phenol **227** and iodoaryl **243**. Numerous cupric or cuprous salt were tried, and all results were more or less the same. No drastic difference was observed, except with tetrakis(acetonitrile)copper hexafluorophosphate, where the crude reaction mixture is cleaner and easier to purify. Yields is also slightly higher.

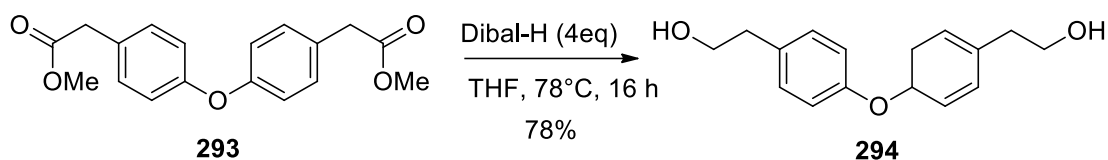


Scheme 87 : Ullmann type reaction for diaryl ether **293**

We use a complex made in the group. The preparation of this cuprous complex is well described in the literature<sup>153</sup>, and simple by the addition of hexafluorophosphoric acid to acetonitrile solution of cuprous oxide.

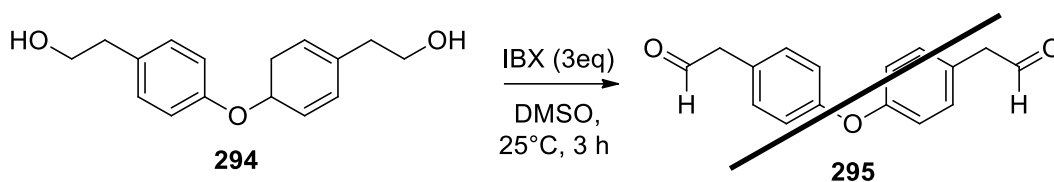
With this diaryl ether compound in hand, it will give access to two possible ways of cyclization either with Bischler-Napieralski or Pictet-Spengler type reactions. So we further reduced the diaryl ether **293** compounds with Dibal-H in THF and it gave the diaryl ether alcohol of compound **294** in 78% yield (Scheme 88)

<sup>153</sup> G. J. Kubas, *Inorg. Synth.*, **1979**, vol XIX, exp 18, 90 – 92, Ed. D.F. Shriver.



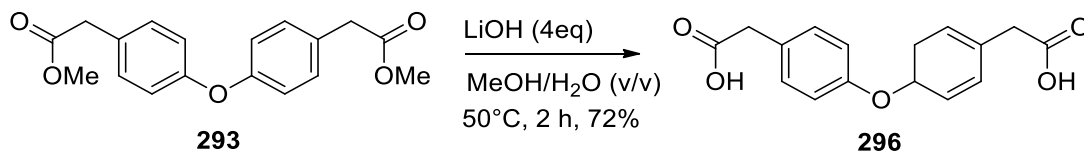
Scheme 88 : Reduction reaction

So, we tried to oxidize the alcohol compound **294** with IBX in DMSO. Unfortunately, we couldn't properly isolate the aldehyde compound **295** from column chromatography (Scheme 89).



Scheme 89 : Oxidation reaction

Therefore, we tried to engage the diaryl ether compound **293** to saponification under the basic condition and the reaction condition was carried out in the same manner with our previous experiment on saponification and it gave us the acid compound **296** in 72% yield (Scheme 90).

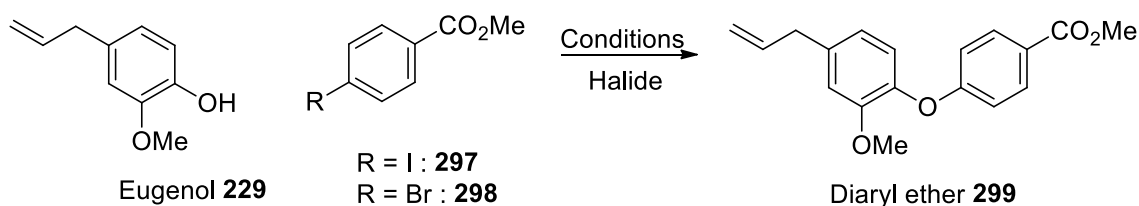


Scheme 90 : Hydrolysis of diaryl ether

#### e. Using eugenol as a model

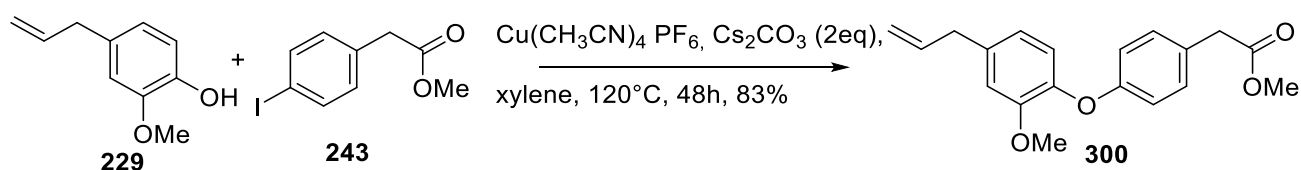
Therefore, our approach started with the commercial available eugenol **229** (as a model) and 4-iodobenzoate **297** or 4-bromobenzoate **298** in the presence of tetrakis(acetonitrile)copper (I) hexafluorophosphate and caesium carbonate as the base in xylene to give the desired diaryl ether **299** compounds in 65% yield. It is worth noticing that the tetrakis(acetonitrile)copper (I) hexafluorophosphate used is very essential for the efficiency and yield of this reaction. On changing the halide substrates to bromine, the yield reduced to 39% so we understand that the iodide gives a better yield of Ullmann coupling with a copper salt. When we changed our solvent to DMSO, we had a lower yield of 21%.

Table 12 : Ullmann type coupling conditions of halobenzoate



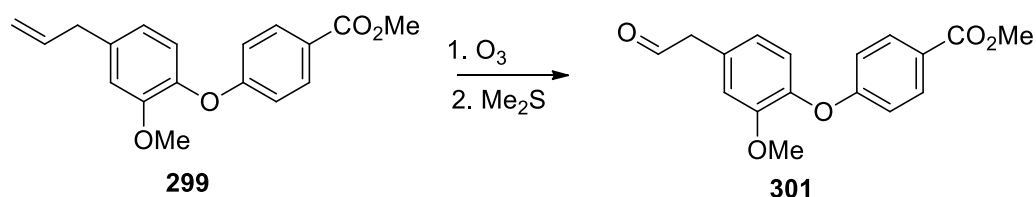
Entry	Catalyst	Halide	Yield
1.	Cu(MeCN) <sub>4</sub> .PF <sub>6</sub> (0.1eq), Cs <sub>2</sub> CO <sub>3</sub> (2eq), xylene 120°C, 6 days		65
2.	Cu(MeCN) <sub>4</sub> .PF <sub>6</sub> (0.1eq), Cs <sub>2</sub> CO <sub>3</sub> (2eq), xylene 120°C, 6 days		39
3.	Cu(MeCN) <sub>4</sub> .PF <sub>6</sub> (0.1eq), Cs <sub>2</sub> CO <sub>3</sub> (2eq), DMSO 120°C, 2 days		21
4.	CuI, (0.1eq), TMHD (0.5eq) Cs <sub>2</sub> CO <sub>3</sub> (2eq), NMP 150°C, 2 days		0

We also engaged methyl-4-iodophenyl acetate **243** with eugenol **229** under the same protocol and a promising diaryl ether **300** compound was formed in 83% yield (Scheme 91).



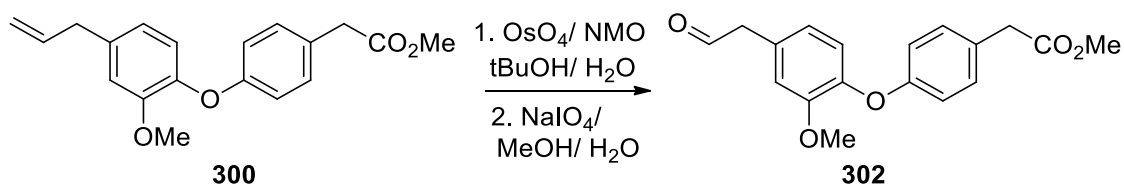
Scheme 91 : Ullmann type coupling of iodophenylacetic ester

With the diaryl ethers in hand, we engaged them in ozonolysis reaction for the oxidative cleavage of alkene into an aldehyde. We first tried with compound **299** to obtain aldehyde **301** and this reaction was performed with oxygen and dimethyl sulphide. Unfortunately, the desired aldehyde couldn't be isolated in pure form because it was difficult to separate it from the by-product, even after several attempts and several conditions on column chromatography (Scheme 92).



Scheme 92 : Ozonolysis reaction

So we sought for another method that could be used for the oxidative cleavage of alkene and the report of Dittrich *et al*<sup>154</sup> was applied on the allylic aryl compound **300** to dihydroxylate it with catalytic osmium tetroxide to form diol, followed by periodate cleavage. Unfortunately, the desired aldehyde **302** could not be isolated rather the traces were observed from the NMR spectra (Scheme 93)



Scheme 93 : Osmium reaction

Even if we managed to improve the Ullmann-type coupling, this sequence needs further works to be able to discriminate properly both “masked” aldehyde, and optimized the preparation of aldehyde **302**, and engaged it in a Pictet-Spengler cyclization. We plan to do this using the “real” south part of the Trilobine, *e.i.* with a *meta-para* connection.

### 3. For the “real” south part of Trilobine

After the optimization of the Ullmann-type coupling with eugenol, we were committed to the preparation of the “south part” we need for Trilobine. The aryl moiety we need should have the free hydroxyl group in *meta* position with respect to the alkyl chain.

<sup>154</sup> N. Dittrich, L. I. Pikkington, E. Leung, D. Barker; *Tetrahedron*, **2017**, 73(14), 1881 – 1894.



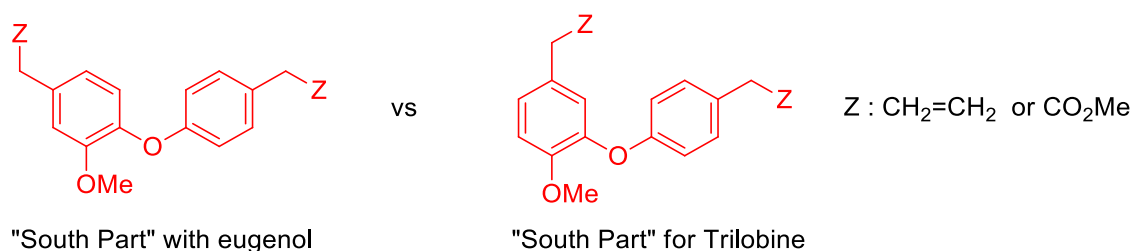


Figure 34 : « South part » for Trilobine

The retrosynthesis of this “south part” is based on Ullmann-type coupling. We still considered that allyl and ester are best groups as masked aldehyde, and can give back the aldehyde function we need for Pictet-Spengler cyclisation. Moreover, the ester can also give easily an acid function if Pictet-Spengler reaction failed, and if Bischler-Napieralski reaction is necessary for one of the isoquinoline moiety preparation. We found that it will be easy to prepare the less substituted aryl with the allyl group. Two different schemes are possible, as we have to use one phenol and one iodoaryl, and both can be substituted by the methoxy group.

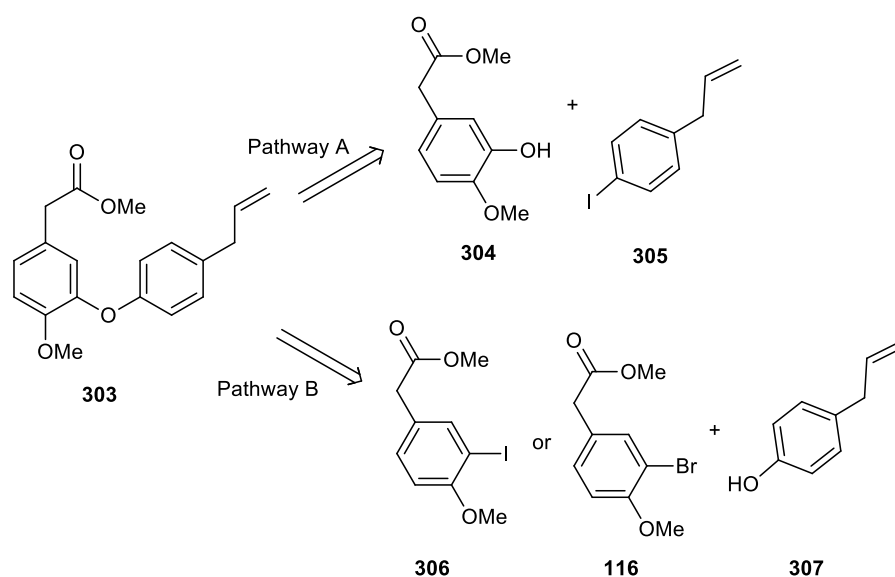


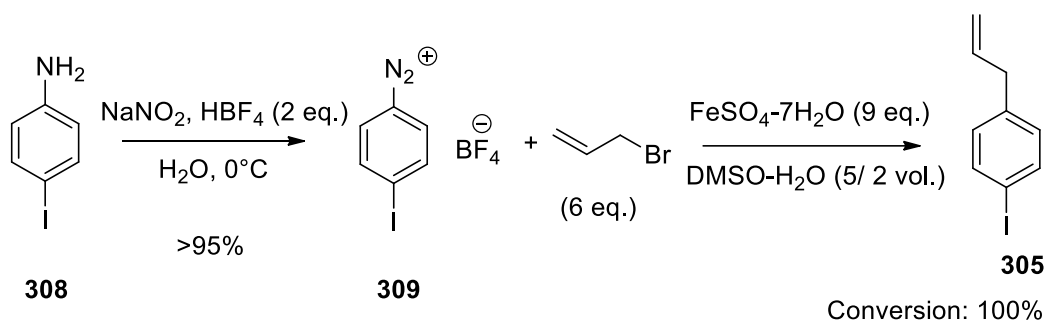
Figure 35 : Retrosynthetic scheme for the south part of Trilobine

a. Preparation of 4-allyl iodobenzene.

The synthesis of the 4-allyl iodobenzene **305** began by the formation of the diazonium salt of the iodoaniline **308**. Allylation of diazonium salt was performed using allyl bromide in the presence of ferrous salt, in a mixture of DMSO and water<sup>155</sup>. Unfortunately, even if conversion is complete,

<sup>155</sup> M.R. Heinrich, O. Blank, D. Ullrich, M. Kirschstein. *J. Org. Chem.* **2007**, 72(25), 9609 – 9616.

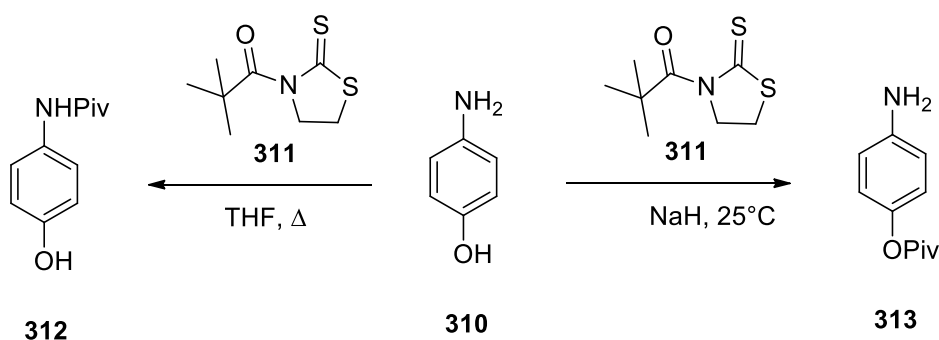
the crude mixture couldn't be purified due to a very low polarity, and by-product couldn't be separated to the desired iodo allyl compound **305**<sup>156</sup>.



Scheme 94 : Synthesis of 4-allyl-iodobenzene **305**

b. Preparation of allyl phenol.

So, we decide to invert the substituents and to prepare hydroxyl allylbenzene **307**<sup>157</sup> and an iodo phenylacetate **306** which supports the pending methoxy group. This is supposed to be formed by halogenation of methoxyphenylacetic acid. The brominated derivative **116** is easier to obtain in pure form, as we have already discussed. The preparation of the 4-allyl phenol **307** was done following the same sequence as for **305** *i.e.* using Heinrich allylation<sup>155</sup> procedure with ferrous salt. We need for that to use amino phenol **310** as a starting material, and we need to protect the hydroxyl group before the formation of the diazonium salt. In 1995, Dai *et al.* published the selective protection of aminophenol of the nitrogen or of the oxygen, depending on the use or not of a base and using 3-acetyl-1,3-thiazolidine-2-thione **311** as acylating agent<sup>158</sup> (Scheme 95)



Scheme 95 : Selective protection of aminophenol

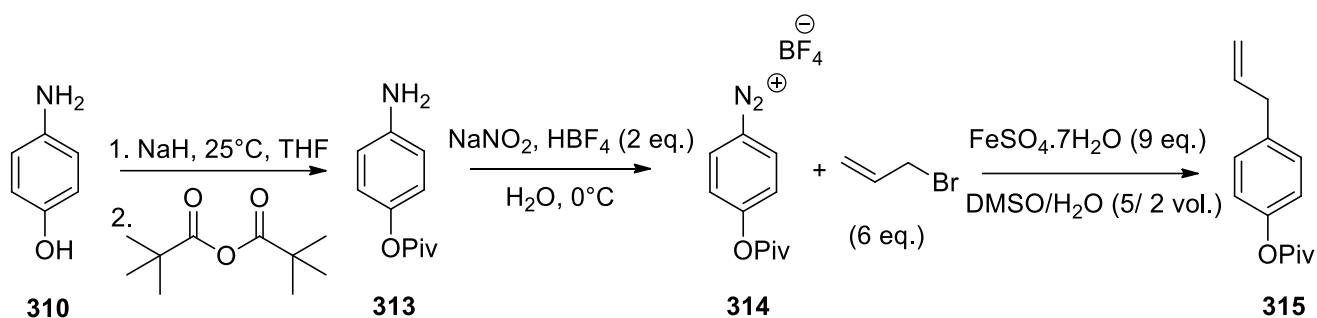
<sup>155</sup> M.R. Heinrich, O. Blank, D. Ullrich, M. Kirschstein. *J. Org. Chem.* **2007**, 72(25), 9609 – 9616.

<sup>156</sup> In collaboration with of Benjamin Roger, M1 student.

<sup>157</sup> In collaboration with of Vincent Cambriel, L3 student

<sup>158</sup> W-M. Dai, Y.K. Cheung, K.W. Tang, P.Y. Choi, S.L. Chung; *Tetrahedron*, **1995**, 51, 12263 – 12276.

The results were not as selective as they described, furthermore the preparation of the acylating agent **311** was not so easy. We finally found that the simple use of NaH and pivalic anhydride give a good results, without any reaction on the nitrogen if we use an excess of sodium hydride and if we allow enough time the aminophenol and the base under stirring before the addition of the pivalic anhydride. The *O*-Piv aminophenol can be obtained with nearly quantitative yield in a 10g scale. After that, the same sequence that we use for iodoaniline **308** is engaged (Scheme 96). The reaction is not clean as the one observe for the iodoaniline, and little amount of a by-product is observed which was not possible to eliminate.

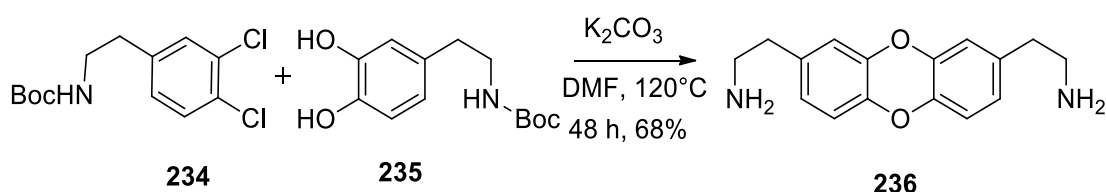


Scheme 96 : Synthesis of allyl-phenol **315**

To finish this sequence, the protected phenol **315** has to be deprotected into free phenol **307**, and have to be engaged in a Ullmann-type reaction with bromo derivative **116** (easier to prepare than the iodo counterpart) to conduct the expected diaryl ether **303**. Moreover, we need to scale up these three steps (diazonium salt formation, allylation and deprotection) and optimized the purifications process of these steps to be able to study effectively the Ullmann type coupling reaction with these substrates, and after that the oxidative cleavage of the allyl group into aldehyde.

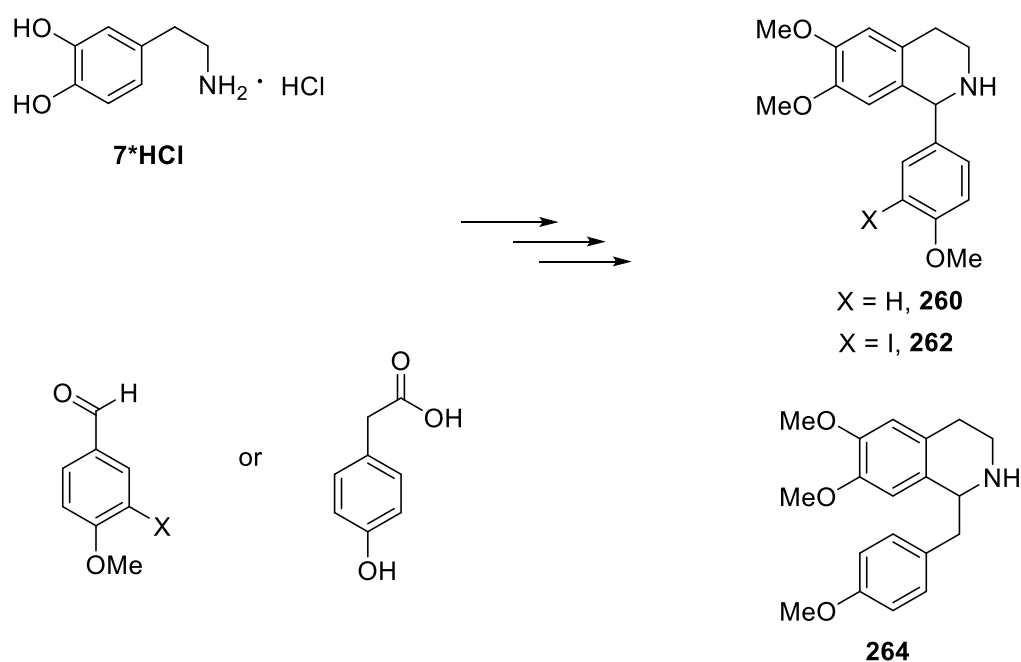
## CONCLUSION

During the course of the total synthesis of trilobine, the monomeric unit of benzyltetrahydroisoquinoline alkaloids was accessed through short sequences of the reaction from commercially available and inexpensive starting materials. From this process, different approaches were developed to access the benzyltetrahydroisoquinoline compound. The first aspect was through the Pictet-Spengler reaction, which worked well with the same protecting group of methoxy but showed some limitations on the regioselective aspect because it always reacts in the process of intramolecular cyclization.



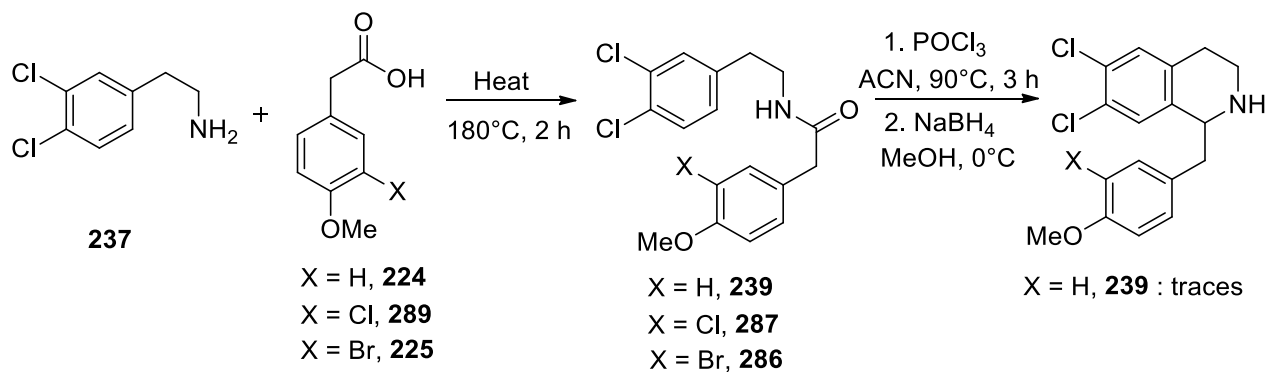
Scheme 97 : Synthesis of dibenzo-p-dioxiran system

During the course of the total synthesis of Trilobine compound, the monomeric unit of benzyltetrahydroisoquinoline alkaloids was accessed through short sequences of the reaction from commercially available and inexpensive starting materials. From this process, different approaches were developed to access the benzyltetrahydroisoquinoline compound.



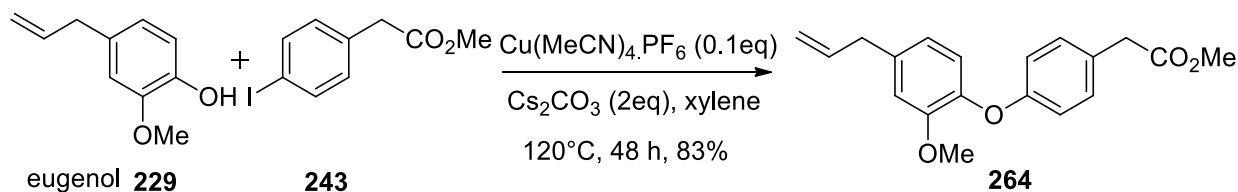
Scheme 98 : Synthesis of THIQ via Pictet-Spengler reaction

Relying on the efficiency of compound **286**, we developed the polychloroamide compound in order to access the polyhalide monomeric unit of Trilobine, which was unable to complete due to global pandemic holiday. However, the Bischler-Napieralski reaction gave access to the intramolecular cyclization of benzyltetrahydroisquinoline compound but only as traces, and more needs to improve this sequence.



Scheme 99 Bischler-Napieralski on dichlorophenethylamine

Our efforts to access the south part of diaryl ether through Ullmann type reaction gave a promising result but to have a selective diaryl ether compound proved to be impossible under oxidative cleavage tested thus preventing us from obtaining the desired trilobine fragment.

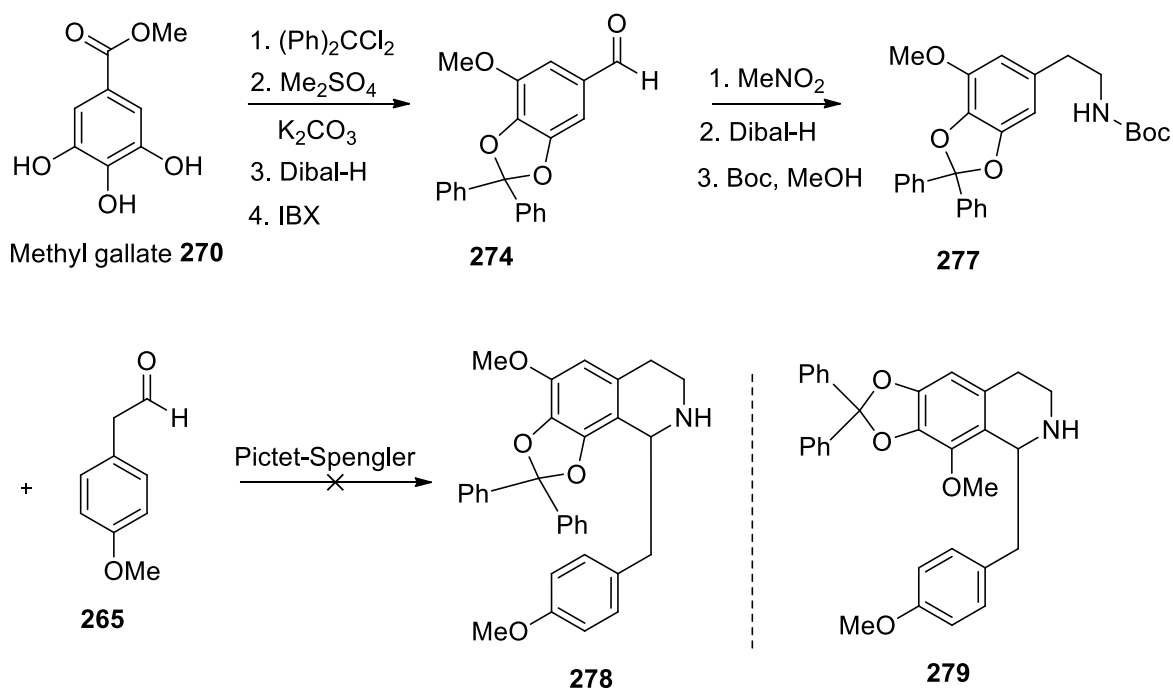


Scheme 100 : Scheme 91 : Ullmann type coupling of iodophenylacetic ester

## A. Perspectives

### 1. Regioselectivity study of Pictet-Spengler / Bishler-Napieralski

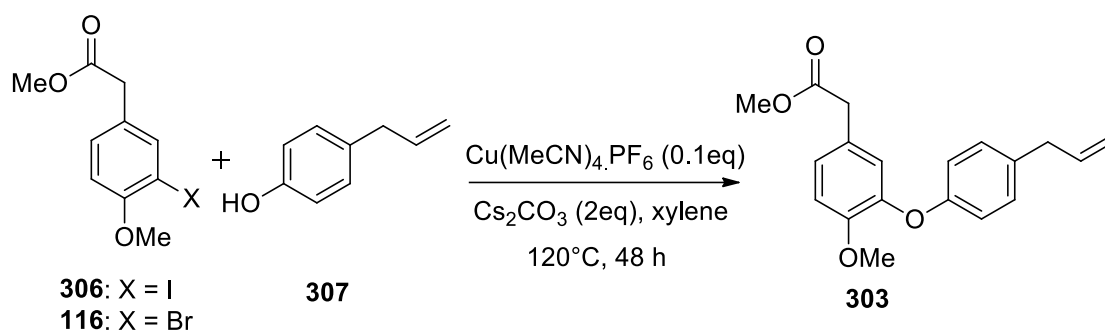
The first aspect was through the Pictet-Spengler reaction, which worked well with the same protecting group of methoxy but showed some limitations on the regioselective aspect because it always reacts in the process of intramolecular cyclization.



Scheme 101 : Regioselective intramolecular cyclization by Pictet-Spengler type

### 2. Optimization of Ullmann-type coupling reaction

Our efforts to access the south part of diaryl ether through Ullmann type reaction gave a promising result but to have a selective diaryl ether compound proved to be impossible under oxidative cleavage tested thus preventing us from obtaining the desired Trilobine fragment. For the preparation of the “south part” of trilobine we need to improve the preparation of allylphenol **307** and study the Ullmann type coupling with these two synthons.



After that, we need to study the oxidative cleavage, with ozonolysis or with OsO<sub>4</sub>/NaIO<sub>4</sub>.

### 3. Transformation of allyl into aldehyde

Depending on the results of the precedent study concerning tetrahydroisoquinoline preparation, we need to establish discrimination of the two functions as aldehyde and/or acid for Pictet-Spengler and/or Bischler-Napieralski respectively. The importance is to be able to perform the two cyclization reactions sequentially to avoid the formation of mixture which is always more complicated to purify. So the preparation of this will give access to the normal and analogue aspect of trilobine compound.

## EXPERIMENTAL PART

### A. General experimental:

Chemicals and solvents were purchased from Sigma Aldrich, Alfa Aesar, Strem Chemicals or TCI and used as received without further purification. Proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were acquired using Bruker Advance III 300 MHz or 400 MHz spectrometers. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak<sup>159</sup>. Coupling constants ( $J$ ) are reported in Hz. Multiplicities are reported using the following abbreviations:  $s$  = singlet;  $d$  = doublet;  $t$  = triplet;  $q$  = quartet;  $m$  = multiplet (range of multiplet is given). Carbon nuclear magnetic resonance ( $^{13}\text{C}$  NMR) spectra were acquired using Bruker Ascend 75MHz or 101 MHz spectrometers. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak. High resolution mass spectra (HRMS) were recorded using a Bruker maXis Impact TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Fourier transform infrared (FT-IR) spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Analytical thin layer chromatography was performed on pre-coated 250 mm layer thickness silica gel 60 F254 plates (EMD Chemicals Inc). Visualization was performed by ultraviolet light and/or by staining with potassium permanganate or *p*-anisaldehyde. Purifications by column chromatography were performed using standard column chromatography using silica gel (40-63  $\mu\text{m}$ , 230-400 mesh).

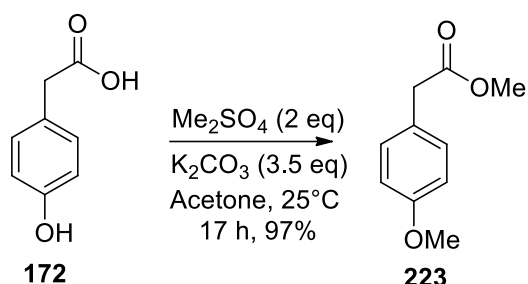
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<sup>159</sup> G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg. *Organometallics* **2010**, 29(9), 2176 – 2179.



## B. Characterizations of synthesized compounds

### Methyl-4-methoxyphenyl acetate (223)



To a mixture of compound **172** (2.0 g, 13.15 mmol), K<sub>2</sub>CO<sub>3</sub> (6.4 g, 46.0 mmol) in acetone (40 ml), Me<sub>2</sub>SO<sub>4</sub> (2.5 ml, 26.29mmol) was added, and the mixture was stirred overnight at 25°C. The reaction mixture was monitored by TLC silica gel with Cy/EtOAc : 8/2) on the complete conversion of the starting material, and filter through celite<sup>®</sup> with EtOAc. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and purified by chromatography over silica gel column to yield to a clear orange oil (2.3 g, **97%**).

R<sub>f</sub> = 0.47 (Cy/ EtOAc: 90/10)

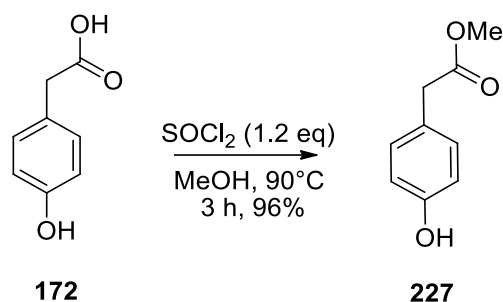
IR v<sub>max</sub> (cm<sup>-1</sup>) = 2998, 1738, 1613, 1437.29, 1301

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ (ppm) = 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.57 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 172.4 (CO), 158.7 (C<sub>q</sub>), 130.3 (2\*CH), 126.1 (C<sub>q</sub>), 114.2 (2\*CH), 55.3 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 40.3 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>10</sub>H<sub>12</sub>O<sub>3</sub> [ESI]<sup>+</sup>: 203.06769, found: 203.06787

### 4-hydroxyphenyl acetate (227)



From the commercially available  $\text{C}_8\text{H}_8\text{O}_3$  (5.0 g, 32.99 mmol) in MeOH (40 ml) and slow addition of  $\text{SOCl}_2$  (3.0 ml, 39.59 mmol) to stir at  $90^\circ\text{C}$  for 3 hours. Then, the reaction mixture was monitored by TLC silica gel with (Cy/ EtOAc; 8/2). On the complete conversion of the starting materials, without extraction it was evaporated as solution of  $\text{NaHCO}_3$  was added and extracted with EtOAc. The organic phase was washed with brine, anhydrous  $\text{Na}_2\text{SO}_4$  and reduced under pressure, and the crude mixture was further purified by column chromatography to obtain a white solid (5.3 g, 96%).

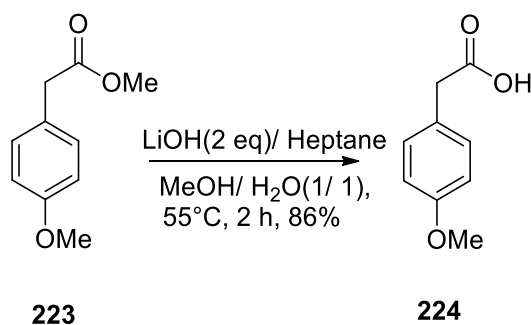
$R_f = 0.64$  (Cy/EtOAc; 85/15)

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3376 (OH), 1720 (C=O), 1615 (C=C), 1444 ( $\text{CH}_2$ ), 1348 (C-O), 1233 ( $\text{CH}_3$ ).

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.13 (d,  $J = 8.5$  Hz, 2H), 6.76 (d,  $J = 8.5$  Hz, 2H), 3.70 (d,  $J = 1.6$  Hz, 3H), 3.56 (s, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 172.8 (CO), 154.9 (Cq), 130.6 (2C), 125.8 (Cq), 115.5 (2C), 52.1 ( $\text{CH}_3$ ), 40.9 ( $\text{CH}_2$ ).

#### 4-methoxyphenyl acetic acid (224)



To the mixture of compound **223** (2.1 g, 11.78 mmol) in 10 ml of MeOH/ $\text{H}_2\text{O}$  (1/1) was added LiOH (1.0g, 23.56 mmol) and the reaction was stirred at  $55^\circ\text{C}$  for an hour. Then, heptane (10ml) was added and the stirring was kept for an additional hour. The reaction mixture was monitored by TLC silica gel with (DCM/MeOH : 9/1) on the complete conversion of the starting material, it was quenched and separated from it aqueous layer. While, the organic phase was acidified with 10% citric

acid to a pH 4 and was further extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford white solid (1.7 g, 86%).

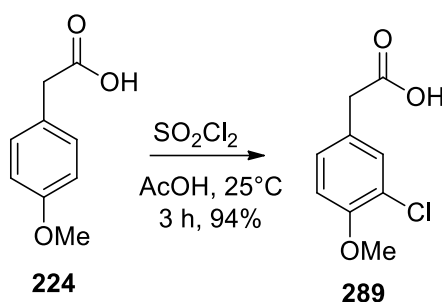
R<sub>f</sub> = 0.78 (EtOAc, 100%)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.20 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.59 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 178.1 (CO<sub>2</sub>H), 158.8 (C<sub>q</sub>), 130.4 (2\*CH), 125.3 (C<sub>q</sub>), 114.1 (2\*CH), 55.3 (CH<sub>3</sub>), 40.3 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>9</sub>H<sub>9</sub>O<sub>3</sub> [ESI]<sup>-</sup>: 165.05555, found: 165.05572

### **3-chloro-4-methoxyphenyl acetic acid (289)**



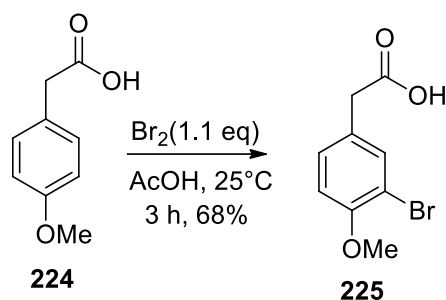
A mixture of acid **224** (0.31 g, 1.84 mmol) in AcOH (1 ml) was stirred for 10 min and SO<sub>2</sub>Cl<sub>2</sub> (0.2 ml, 1.84 mmol) was added dropwise to continue stirring at 25°C for 3 hours. The reaction mixture was monitored by TLC silica gel with EtOAc (100%), on complete conversion of the starting material. The solvent was then evaporated under reduced pressure, and NaHCO<sub>3</sub> was added at 0°C for neutralisation, followed by excess of a 5% solution of Na<sub>2</sub>SO<sub>3</sub> at the same temperature. The precipitate was washed with ice H<sub>2</sub>O, dried overnight on sintered – glass and recrystallized from DCM to form white solid (0.35 g, 94%).

R<sub>f</sub> = 0.22 (EtOAc, 100%)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.31 (d, *J* = 2.2 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.58 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 176.1 (CO<sub>2</sub>H), 131.4 (C<sub>q</sub>), 130.4 (CH), 128.6 (C-Cl), 126.2 (CH), 114.1 (C<sub>q</sub>), 112.2 (CH), 56.2 (CH<sub>3</sub>), 39.6 (CH<sub>2</sub>).

### 3-bromo-4-methoxyphenyl acetic acid (225)



A mixture of acid **224** (1.04 g, 6.24 mmol) in AcOH (2 ml) was stirred for 10 min and Br<sub>2</sub> (0.8 ml, 6.86 mmol) was added dropwise to continue stirring at 25°C for 3 hours. The reaction mixture was monitored by TLC silica gel with EtOAc (100%), on complete conversion of the starting material, it was quenched with a solution of 5% Na<sub>2</sub>SO<sub>3</sub> at 0°C. The precipitate was washed with ice H<sub>2</sub>O, dried overnight on sintered – glass and recrystallized with DCM to form white solid (0.95 g, 63%).

R<sub>f</sub> = 0.21 (EtOAc, 100%)

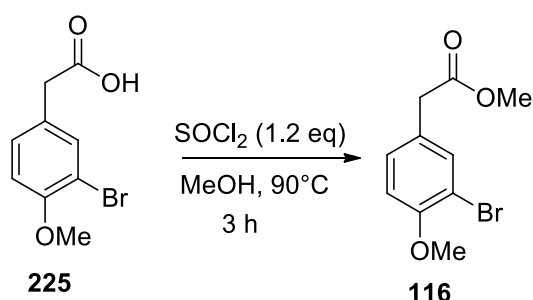
IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3029, 1712, 1502, 1401, 1234, 1054, 590

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.48 (d, *J* = 2.2 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.58 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 177.6 (CO<sub>2</sub>H), 155.2 (C<sub>q</sub>), 134.2 (CH), 133.6 (C<sub>q</sub>), 129.5 (CH), 126.7 (C<sub>q</sub>), 111.8 (CH), 56.3 (CH<sub>3</sub>), 39.6 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>9</sub>H<sub>8</sub>O<sub>3</sub>Br [ESI]<sup>-</sup>: 242.96617, found: 242.96623

### 3-bromo-4-methoxyphenyl acetate (116)



SOCl<sub>2</sub> (0.4 ml, 5.77 mmol) was slowly added to a mixture of acid **225** (1.18 g, 4.81 mmol) in MeOH (10 ml) and the mixture was stirred for 3 hours at 90°C. The reaction mixture was monitored by TLC (Cy/EtOAc : 8/2) on complete conversion of the starting material, and solvents were evaporated. A solution of NaHCO<sub>3</sub> was added for neutralisation and then compound was extracted with DCM. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under

reduced pressure. Purification by chromatography over silica gel column yielded to an orange oil (1.24 g, **99%**).

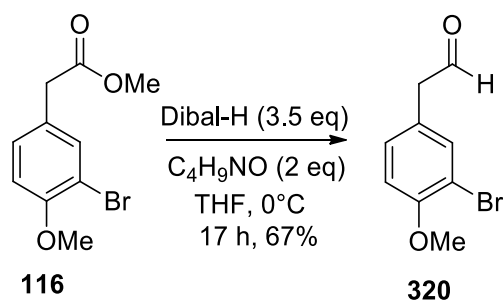
R<sub>f</sub> = 0.58 (Cy/EtOAc ; 90/10)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.47 (d, *J* = 2.2 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.70 (s, 3H), 3.54 (s, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 171.8 (CO), 155.1 (C<sub>q</sub>), 134.1 (CH), 129.3 (C<sub>q</sub>), 127.5 (CH), 111.9 (C<sub>q</sub>), 111.6 (CH), 56.3 (CH<sub>3</sub>), 52.1 (CH<sub>3</sub>), 39.8 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>10</sub>H<sub>11</sub>BrO<sub>3</sub> [ESI]<sup>-</sup>: 257.98920, found: 257.98916

### **3-bromo-4-methoxyphenyl aldehyde (320)**



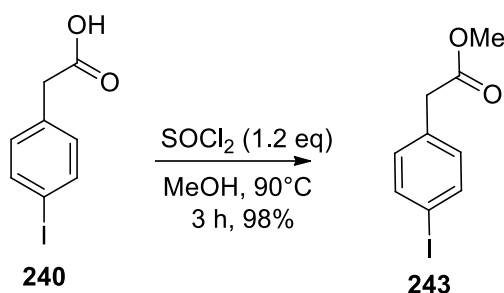
To a solution of morpholine (0.4 ml, 4.9 mmol) in THF (10 ml) was added Dibal-H (1M THF; 9.0 ml, 9.0 mmol) and stirred at 0°C for 3 hrs. Then, the solution C<sub>10</sub>H<sub>11</sub>BrO<sub>3</sub> (0.64 g, 2.45 mmol) was added dropwise to the mixture at 0°C to continue stirring overnight. The reaction mixture was monitored by TLC (Cy/ EtOAc; 8/2) on complete conversion of the starting material, it was quenched with 1N HCl and extracted with EtOAc, then treat with brine, Na<sub>2</sub>SO<sub>4</sub> and reduced under pressure. The crude mixture was further purified by column chromatography to form white solid (0.38 g, **67%**).

R<sub>f</sub> = 0.59 (Cy/EtOAc: 85/15)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.73 (t, *J* = 2.2 Hz, 1H), 7.41 (d, *J* = 2.2 Hz, 1H), 7.12 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.62 (d, *J* = 2.2 Hz, 2H).

HRMS *m/z* calcd for C<sub>10</sub>H<sub>9</sub>BrO<sub>2</sub> [ESI]<sup>-</sup>: 227.97861, found: 227.97859

### **4-iodophenyl acetate (243)**



SOCl<sub>2</sub> (2.0 ml, 22.91 mmol) was slowly added to a mixture of acid **240** (5.01 g, 19.08 mmol) in MeOH (40 ml) and the mixture was stirred for 3 hours at 90°C. The reaction mixture was monitored by TLC (Cy/EtOAc: 8/2) on complete conversion of the starting material, and solvents were evaporated, A solution of NaHCO<sub>3</sub> was added to neutralised and then compound was extracted with EtOAc. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. Purification by chromatography over silica gel column yielded to an orange oil (5.21 g, **98%**).

R<sub>f</sub> = 0.7 (Cy/EtOAc; 90/10)

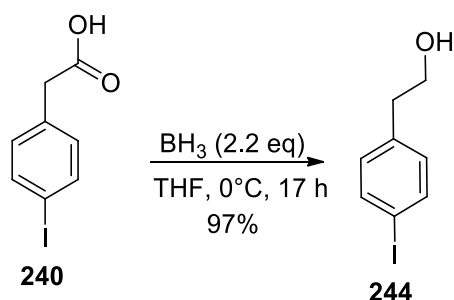
IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3024.20, 1737.24, 1628.03, 1435.05, 1253.54, 485.41

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.67 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 3.71 (s, 3H), 3.59 (s, 2H).

<sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>) δ (ppm): 171.4 (CO), 137.7 (2\*CH), 133.6 (Cq), 131.3 (2\*CH), 92.6 (Cq), 52.2 (CH<sub>3</sub>), 40.6 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>9</sub>H<sub>9</sub>O<sub>2</sub>I: [ESI]<sup>+</sup>: 298.95382, found: 298.95394

#### 4-iodophenyl alcohol (244)



To a solution of acid **240** (1.57 g, 5.99 mmol) in THF (15 ml), 13 ml of a 1M solution of borane in THF (13 mmol) was added at 0°C and the mixture was stirred overnight. The reaction was monitored by TLC, quenched with H<sub>2</sub>O and extracted with EtOAc, the organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure and recrystallized from EtOH to form white solid (1.44 g, **97%**).

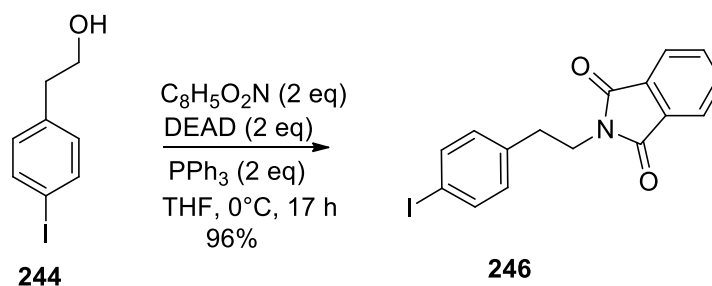
R<sub>f</sub> = 0.26 (EtOAc 100%)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.69 – 7.55 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 3.84 (t, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 6.5 Hz, 2H).

<sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>) δ (ppm): 138.2 (2\*CH), 137.6 (C<sub>q</sub>), 131.1 (2\*CH), 91.7 (C<sub>q</sub>), 63.4 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>8</sub>H<sub>9</sub>IO: [ESI]<sup>+</sup>: 247.96943, found: 247.96981

### 4-iodophenyl phthalimide (246)



To a solution of alcohol **244** (1.82 g, 7.36 mmol) in THF (15 ml) were added P(Ph)<sub>3</sub> (3.86 g, 14.73 mmol) and phthalimide (2.17 g, 14.73 mmol) and the mixture was stirred 10 minutes at 0°C. Then, DEAD (2.56 g, 14.73 mmol) was added dropwise and the reaction was stirred overnight and quenched with water. Products were extracted with DCM, and organics phases were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduce pressure. Recrystallisation from EtOH give phthalimide **246** (2.67 g, **96%**).

R<sub>f</sub> = 0.59 (Cy/EtOAc; 90/10)

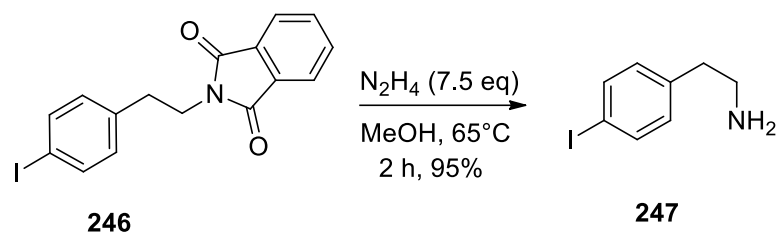
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.83 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 3.94 – 3.86 (m, 2H), 2.98 – 2.90 (m, 2H).

2\*

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 168.1 (2\*CO), 160.3 (2\*C<sub>q</sub>), 137.6 (2\*CH), 134.0 (2\*CH), 132.0 (C<sub>q</sub>), 130.9 (2\*CH), 123.3 (2\*CH), 92.0 (C<sub>q</sub>), 65.5 (CH<sub>2</sub>), 14.1 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>17</sub>H<sub>16</sub>INO<sub>3</sub>: [ESI]<sup>+</sup>: 432.00602, found: 432.00671

### 4-iodophenylethylamine (247)



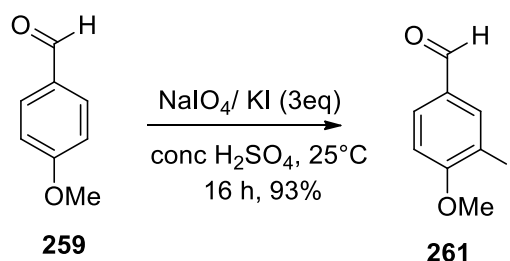
To a solution of compound **246** (2.45 g, 6.51 mmol) in MeOH (2 ml),  $\text{N}_2\text{H}_4$  (1.5 ml, 48.72 mmol) was added and the mixture was heated at  $65^\circ\text{C}$  for 2 h. The reaction was monitored by TLC (DCM/MeOH : 9/1), evaporated to dryness to form white solid colour (1.53 g, **95%**)

$R_f = 0.21$  (DCM/MeOH : 95/5)

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.62 (d,  $J = 8.2$  Hz, 2H), 6.96 (d,  $J = 8.2$  Hz, 2H), 2.96 (t,  $J = 6.9$  Hz, 2H), 2.70 (t,  $J = 6.8$  Hz, 2H).

HRMS  $m/z$  calcd for  $\text{C}_8\text{H}_{11}\text{NI}$ :  $[\text{ESI}]^+$ : 247.99280, found: 247.99307

### 3-iodo-4-methoxybenzaldehyde (261)



$\text{NaIO}_4$  (0.61 g, 2.81 mmol) and  $\text{KI}$  (1.4 g, 8.43 mmol) were added slowly to concentrated  $\text{H}_2\text{SO}_4$  (95%, 30 ml) under stirring at  $25^\circ\text{C}$  and the mixture was stirred for 45 mins forming a dark brown solution. Then, a commercial *p*-anisaldehyde (1.2 ml, 10.0 mmol) was added dropwise to the stirring solution for overnight. The mixture was slowly poured into a stirred ice  $\text{H}_2\text{O}$ , the crude was collected by filtration with continuous washing with  $\text{H}_2\text{O}$  until the filtrate were neutral. Dried on sintered glass and it forms light-brown solid (2.42 g, **93%**).

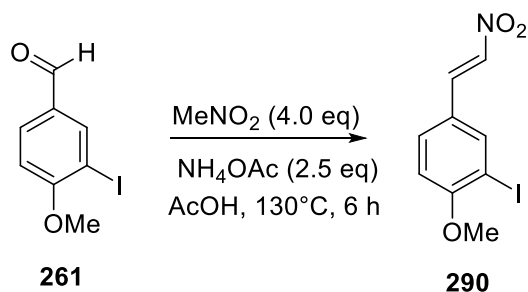
$R_f = 0.49$  (Cy/EtOAc; 80/20)

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 9.82 (s, 1H), 8.31 (d,  $J = 2.0$  Hz, 1H), 7.86 (dd,  $J = 8.5, 2.0$  Hz, 1H), 6.92 (d,  $J = 8.5$  Hz, 1H), 3.98 (s, 3H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 189.4 (CO), 162.8 (CO), 141.1 (CH), 132.1 (Cq), 131.4 (CH), 110.6 (CH), 86.5 (I), 56.8 ( $\text{CH}_3$ )



### 3-iodo-4-methoxybenzy- $\beta$ -nitrostyrene (290)



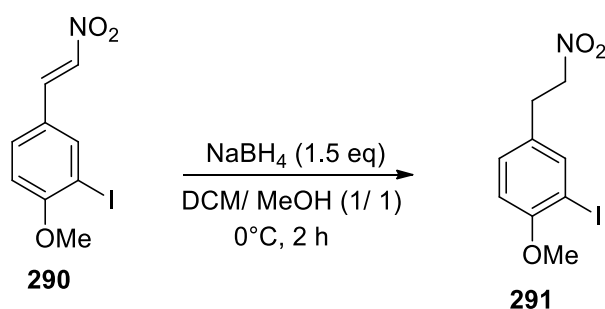
A solution of aldehyde **261** (0.58 g, 2.23 mmol) and  $\text{NH}_4\text{OAc}$  (0.43 g, 5.53 mmol) in  $\text{AcOH}$  (10 ml) was stirred for 10 mins at  $25^\circ\text{C}$ , then  $\text{MeNO}_2$  (0.5 ml, 8.92 mmol) was added and the mixture was heated at  $125^\circ\text{C}$  for 3 h. The reaction was monitored by TLC (Cy/DCM : 8/2), quenched in ice bath by adding water and extract with DCM. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to a yellow solid (0.66 g, **96%**).

$R_f = 0.60$  (Cy/DCM : 80/20)

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.99 (d,  $J = 2.2$  Hz, 1H), 7.89 (d,  $J = 13.6$  Hz, 1H), 7.56 – 7.46 (m, 2H), 6.87 (d,  $J = 8.6$  Hz, 1H), 3.95 (s, 3H).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{O}_5$  [ESI] $^-$ : 304.95408, found: 304.95489

### 3-iodo-4-methoxyethylnitrobenzene (291)



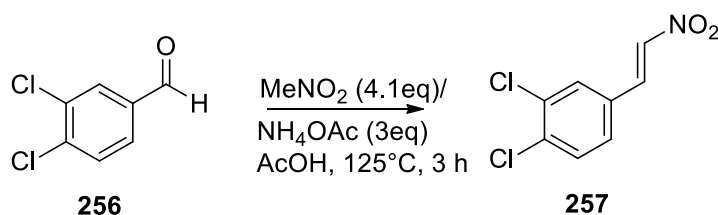
To a solution of **290** (0.42 g, 1.36 mmol) in 10 ml of a mixture of  $\text{DCM}/\text{MeOH}$  (1/1) at  $0^\circ\text{C}$ , was slowly added  $\text{NaBH}_4$  (0.077 g, 2.046 mmol) and the reaction was stirred for 2 h. The reaction was monitored by TLC (Cy/DCM : 8/2), quenched in ice bath by addition of water and extracted with DCM. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced

pressure, and purified by chromatography over silica gel column yielded to a yellow solid (0.26 g, **62%**).

R<sub>f</sub> = 0.56 (Cy/ DCM; 80/20)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 2.2 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 4.57 (t, *J* = 7.3 Hz, 2H), 3.86 (s, 3H), 3.23 (t, *J* = 7.3 Hz, 2H).

### 3,4-dichlorophenyl-β-nitrostyrene (257)



A solution of aldehyde **256** (0.64 g, 3.65 mmol) and NH<sub>4</sub>OAc (0.84 g, 10.94 mmol) in AcOH (10 ml) was stirred for 10 mins at 25°C, then follow by addition of MeNO<sub>2</sub> (0.8 ml, 14.96 mmol) to reflux at 125°C for 3 h. Monitored by TLC (Cy: DCM; 8:2), quenched in ice bath by adding water and extract with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to a yellow solid (0.72 g, **90%**).

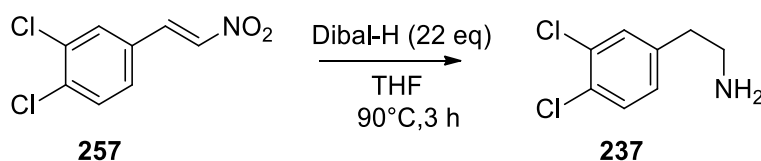
R<sub>f</sub> = 0.7 (Cy/DCM; 80/20)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.91 (d, *J* = 13.7 Hz, 1H), 7.64 (d, *J* = 2.1 Hz, 1H), 7.56 (d, *J* = 3.9 Hz, 1H), 7.53 (d, *J* = 1.4 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.1 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ(ppm): 138.3 (C<sub>q</sub>), 136.4 (CH), 134.0 (C<sub>q</sub>), 131.5 (CH), 130.6 (CH), 130.0 (C<sub>q</sub>), 127.9 (CH), 111.5 (CH).

HRMS *m/z* calcd for C<sub>8</sub>H<sub>5</sub>Cl<sub>2</sub>O<sub>2</sub>N [ESI]<sup>+</sup>: 216.9673, found: 216.9619

### 3,4-dichlorophenylethylamine (237)



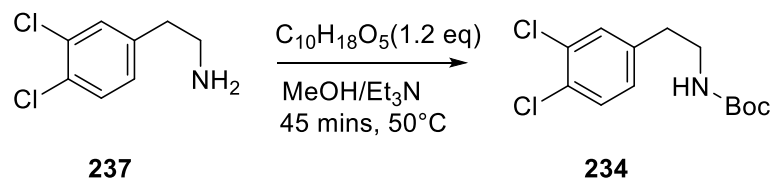
A 1M solution of DiBAL-H (16 ml, 16 mmol) in THF (15 ml) was heated to reflux under nitrogen, then a solution of compound  $C_8H_5Cl_2NO_2$  (153 mg, 0.702 mmol) in THF (15 ml) was slowly added to the reaction mixture and kept to reflux for 3 h. The reaction was quenched in the following: brought to  $-78^\circ C$  and slowly add  $H_2O$  (2 ml) and stir for 10 mins, the cooling bath was removed and aqueous. 5% NaOH (2 ml) was added. More  $H_2O$  (2 ml) and diethyl ether were added to keep the reaction stirring and excess dried  $Na_2SO_4$  was added to form cake which was filtered and wash with diethyl ether to form light-brown oil (129 mg, **97%**).

Rf = 0.21 (EtOAc 100%)

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.41 (d,  $J = 8.2$  Hz, 1H), 7.34 (d,  $J = 2.0$  Hz, 1H), 7.08 (dd,  $J = 8.2, 2.1$  Hz, 1H), 3.00 (t,  $J = 6.8$  Hz, 2H), 2.75 (t,  $J = 6.8$  Hz, 2H).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  (ppm): 143.9 (Cq), 137.8 (Cq), 137.7 (Cq), 131.9 (CH), 131.0 (CH), 121.2 (CH), 39.9 ( $CH_2$ ), 25.4 ( $CH_2$ ).

### **N-Boc-3,4-dichlorophenylethylamine (234)**

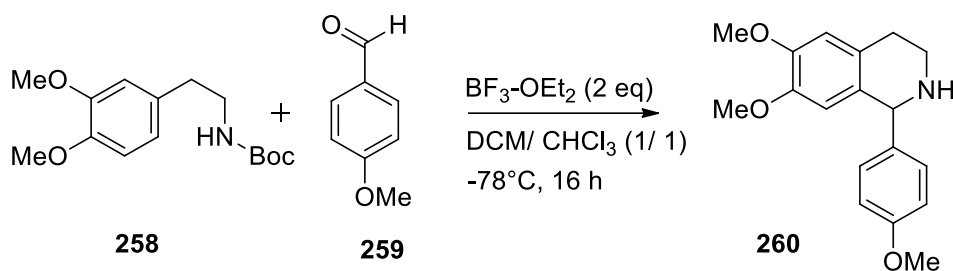


A mixture of 3,4-dichlorophenylethylamine **237** (1.0 g, 5.26 mmol) and di-tert-butyl dicarbonate (1.37 g, 6.31 mmol) in MeOH/ $Et_3N$  (9:1) were heated to reflux for 45 mins. The reaction was monitored by TLC, quenched with water and concentrated. The residue was treated with 1N HCl to pH 2, then extracted with DCM, and the organic layer was washed with brine, dried over  $Na_2SO_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to a white solid colour (1.45 g, **95%**).

Rf = 0.45 (Cy/EtOAc : 90/10)

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  7.41 (d,  $J = 8.2$  Hz, 1H), 7.33 (d,  $J = 2.0$  Hz, 1H), 7.07 (dd,  $J = 8.2, 2.0$  Hz, 1H), 3.39 (dd,  $J = 13.4, 6.7$  Hz, 2H), 2.80 (t,  $J = 7.0$  Hz, 2H), 1.48 (s, 9H).

### 7,12-dimethyl-15-Nor-coclaurine (260)



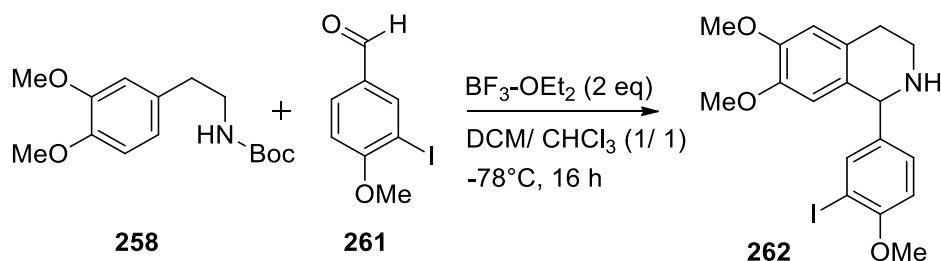
To a solution of compound **258** (0.061 g, 0.22 mmol) and aldehyde **259** (0.05 ml, 0.43 mmol) in 10 ml of  $\text{DCM/CHCl}_3$  (1/1) and was slowly added  $\text{BF}_3\text{-OEt}_2$  (0.05 ml, 0.43 mmol) at  $-78^\circ\text{C}$  and the mixture was stirred overnight. The reaction was monitored by TLC ( $\text{DCM/MeOH}$  : 9/1), quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  and extracted with  $\text{EtOAc}$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to an orange solid (0.059 g, **91%**).

$R_f = 0.25$  ( $\text{DCM/MeOH}$  : 95/5)

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J = 8.8$  Hz, 2H), 6.92 (d,  $J = 8.8$  Hz, 2H), 6.68 (s, 1H), 6.30 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 3.53 (s, 1H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 160.7 (Cq), 149.4 (Cq), 148.4 (Cq), 131.5 (CH), 127.8 (Cq), 124.3 (Cq), 122.4 (Cq), 114.6 (CH), 110.5 (CH), 59.0 (CH), 56.1 (2\* $\text{CH}_3$ ), 55.4 ( $\text{CH}_3$ ), 39.5 ( $\text{CH}_2$ ), 25.0 ( $\text{CH}_2$ ).

### 3-iodo-7,12-dimethyl-15-Nor-coclaurine (262)



To a solution of compound **258** (0.24 g, 0.88 mmol) and aldehyde **261** (0.46 g, 1.74 mmol) in 10 ml of  $\text{DCM/CHCl}_3$  (1/1) and was slowly added  $\text{BF}_3\text{-OEt}_2$  (0.2 ml, 1.74 mmol) at  $-78^\circ\text{C}$  and the mixture was stirred overnight. The reaction was monitored by TLC ( $\text{DCM/MeOH}$  : 9/1), quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  and extracted with  $\text{EtOAc}$ . The organic layer was

washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to an orange solid (0.29 g, **78%**).

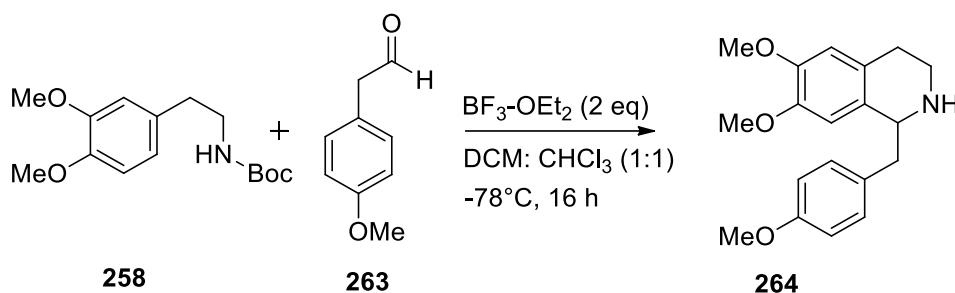
$R_f = 0.27$  (DCM/MeOH : 95/5)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.71 (d,  $J = 2.1$  Hz, 1H), 7.21 (dd,  $J = 8.4, 2.1$  Hz, 1H), 6.79 (d,  $J = 8.4$  Hz, 1H), 6.65 (s, 1H), 6.26 (s, 1H), 3.90 (d,  $J = 1.3$  Hz, 6H), 3.69 (s, 3H), 3.29 – 3.12 (m, 1H), 3.12 – 2.87 (m, 2H), 2.85 – 2.67 (m, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 157.8 (Cq), 148.1 (Cq), 147.4 (Cq), 140.1 (CH), 136.9b (Cq), 130.6 (CH), 126.9 (Cq), 111.4 (CH), 110.8 (CH), 110.7 (CH), 85.9 (Cq), 61.8 (Cq-I), 59.6 (CH), 56.4 ( $\text{CH}_3$ ), 56.0 ( $\text{CH}_3$ ), 55.9 ( $\text{CH}_3$ ), 41.1 ( $\text{CH}_2$ ), 28.2 ( $\text{CH}_2$ ).

HRMS  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{O}_3\text{NI}$  [ESI] $^+$ : 426.05561, found: 426.05606

### 7,12-dimethyl-coclaurine (264)



To a solution of compound **258** (0.24 g, 0.85 mmol) and aldehyde **261** (0.26 g, 1.71 mmol) in 10 ml of DCM/ $\text{CHCl}_3$  (1/1) and was slowly added  $\text{BF}_3\text{-OEt}_2$  (0.22 ml, 1.71 mmol) at  $-78^\circ\text{C}$  and the mixture was stirred overnight. The reaction was monitored by TLC (DCM/MeOH : 9/1), quenched with a saturated aqueous solution of  $\text{NaHCO}_3$  and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to an orange solid (0.101 g, **39%**).

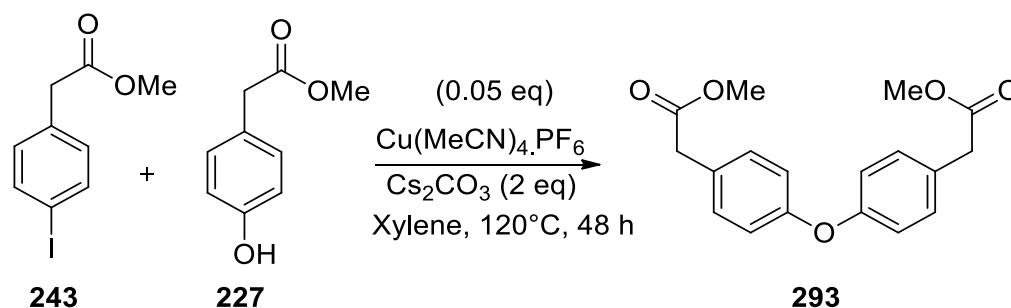
$R_f = 0.34$  (DCM: MeOH; 95:5)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.26 (d,  $J = 8.8$  Hz, 2H), 6.92 (d,  $J = 8.8$  Hz, 2H), 6.68 (s, 1H), 6.30 (s, 1H), 3.92 (s, 3H), 3.84 (s, 3H), 3.71 (s, 3H), 3.53 (s, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 159.0 (Cq), 148.8 (Cq), 147.5 (Cq), 133.3 (CH), 131.1 (CH), 130.1 (CH), 128.4 (CH), 127.1 (Cq), 123.4 (Cq), 122.9 (Cq), 114.4 (CH), 111.2 (CH), 109.8 (CH), 55.9 (CH), 55.8 ( $\text{CH}_3$ ), 55.6 ( $\text{CH}_3$ ), 55.3 ( $\text{CH}_3$ ), 40.0 ( $\text{CH}_2$ ), 39.1 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ).

HRMS  $m/z$  calcd for  $C_{19}H_{24}O_3N$  [ESI]<sup>+</sup>: 314.17469, found: 314.17507

### Diphenyl ether acetate (293)



A mixture of compounds **243** (2.8 g, 10.15 mmol), **227** (2.5 g, 15.22 mmol), with  $Cs_2CO_3$  (6.6 g, 20.29 mmol) and 5 mol% of  $Cu(MeCN)_4.PF_6$  (0.189 g, 0.507 mmol) in xylene (1.4 ml) was heated at 150°C for 6 days. The reaction was monitored by TLC(Cy/EtOAc: 8/2), quenched and concentrated. . The residu was purified by chromatography over silica gel column yielded to a brown solid (2.05 g, **64%**).

Rf = 0.25 (Cy/EtOAc : 85/15)

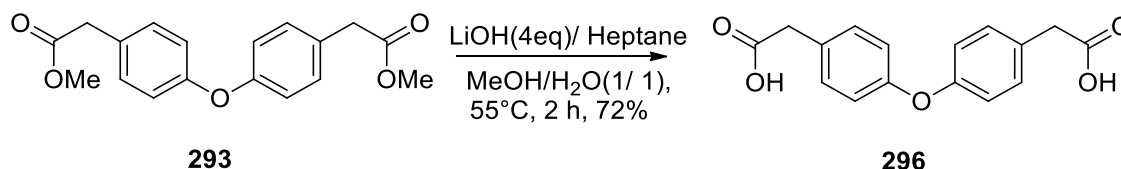
IR  $\nu_{max}$  (cm<sup>-1</sup>) = 3395, 1722, 1516, 1420, 1228, 1167

<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.21 (d,  $J$  = 8.8 Hz, 4H), 7.05 (d,  $J$  = 8.7 Hz, 4H), 3.68 (s, 6H), 3.57 (s, 4H).

<sup>13</sup>C NMR (75 MHz,  $CDCl_3$ )  $\delta$  (ppm): 172.2 (CO), 156.1 (Cq), 130.4 (CH), 127.9 (Cq), 116.6 (CH), 52.0 (CH<sub>3</sub>), 40.4 (CH<sub>2</sub>).

HRMS  $m/z$  calcd for  $C_{18}H_{18}O_5$ : [ESI]<sup>+</sup>: 337.10464, found: 337.10394

### Diphenyl ether acetic acid (296)



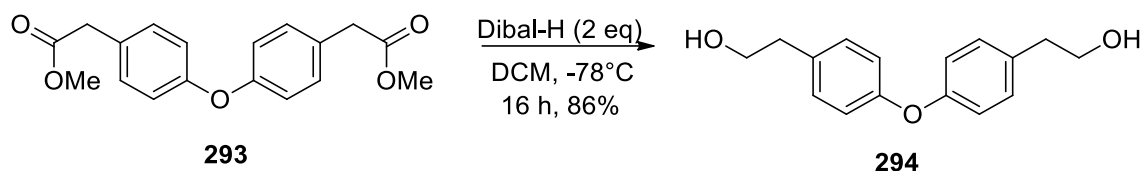
To a solution of compound **293** (0.34 g, 1.09 mmol) in 10 ml of MeOH/H<sub>2</sub>O (1/1) was added LiOH (0.18 g, 4.39 mmol) and the mixture was stirred at 55°C for an hour. Then, heptane (10ml) was added and the reaction was kept stirring for another hour. The reaction mixture was monitored by TLC with (DCM/MeOH : 9/1) on the complete conversion of the starting material, it was quenched and separated from its aqueous layer. While, the organic phase was acidified with 10% citric acid to a pH 4 and was further extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford white solid (0.23 g, 72%).

R<sub>f</sub> = 0.38 (EtOAc 100%)

IR ν<sub>max</sub> (cm<sup>-1</sup>) = 2921, 1702, 1515, 1442, 1211

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.16 (d, *J* = 8.6 Hz, 4H), 6.80 (d, *J* = 8.6 Hz, 4H), 3.59 (s, 4H).

### Diphenyl ether alcohol (294)



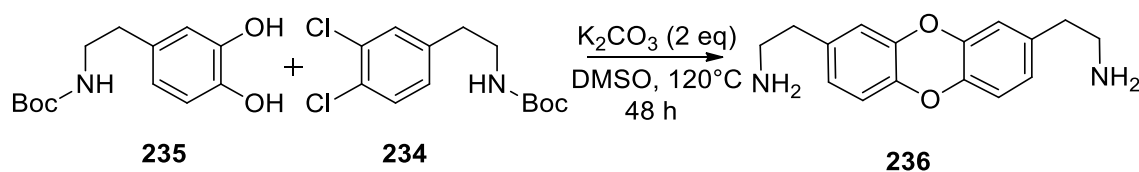
To the mixture of C<sub>18</sub>H<sub>20</sub>O<sub>5</sub> (0.29 g, 0.925 mmol) in THF (10 ml) brought to -78°C, DiBAL-H (1M; 3.0 ml, 1.25 mmol) was slowly added and the reaction was stirred overnight. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched with 1N HCl and extracted with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and purified by chromatography over silica gel column to yield to an orange- brown gummy solid (0.21 g, 86%).

R<sub>f</sub> = 0.25 (Cy/EtOAc : 85/15)

IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3122, 2921, 1596, 1444, 1227

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.12 – 7.07 (m, 4H), 6.80 – 6.76 (m, 4H), 3.83 (t, *J* = 6.5 Hz, 4H), 2.81 (t, *J* = 6.5 Hz, 4H).

### Dibenzo-*p*-dioxine nucleus phenylethylamine (236)



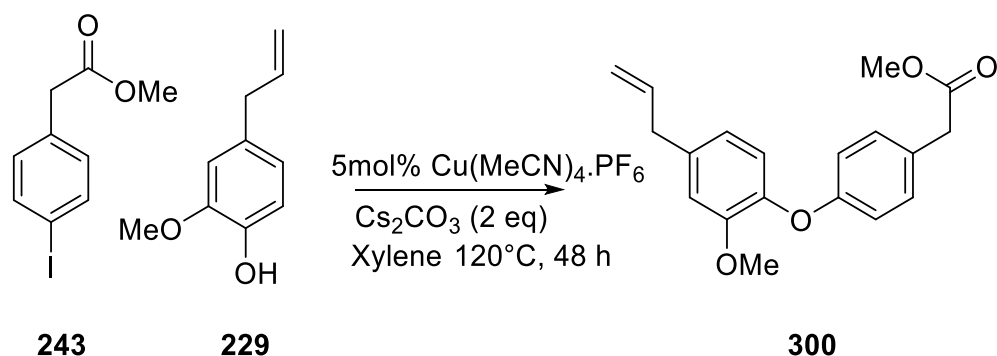
A mixture of compound **234** (86 mg, 0.30 mmol), compound **235** (0.75 mg, 0.30 mmol) and  $\text{K}_2\text{CO}_3$  (82 mg, 0.60 mmol) in DMF (1.5 ml) was heated to reflux at  $180^\circ\text{C}$  for 24 h. Monitored by TLC (DCM/MeOH : 9/1), quenched with  $\text{H}_2\text{O}$  and extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and purified by chromatography over silica gel column to yield to 61 mg (21%) of compound **236**

Rf = 0.25 (DCM/MeOH : 90/10)

IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3305, 2925, 1620, 1468, 1131

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.37 (d,  $J$  = 8.2 Hz, 2H), 7.27 (d,  $J$  = 2.0 Hz, 2H), 7.02 (dd,  $J$  = 8.2, 2.0 Hz, 2H), 3.40 (t,  $J$  = 6.9 Hz, 4H), 2.77 (t,  $J$  = 6.9 Hz, 4H).

### Compound 300



A mixture of compounds **243** (0.199 g, 0.72 mmol), **229** (0.177 mg, 1.08 mmol), with  $\text{Cs}_2\text{CO}_3$  (0.47 g, 1.44 mmol) and 5 mol% of  $\text{Cu}(\text{MeCN})_4\cdot\text{PF}_6$  (0.014 g, 0.036 mmol) in xylene (0.8 ml) was heated at  $120^\circ\text{C}$  for 48 hours. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched with water and extracted with EtOAc and concentrated. The residue was purified by chromatography over silica gel column yielded to a brown gum (0.19 g, **83%**).

Rf = 0.28 (Cy/EtOAc : 85/15)

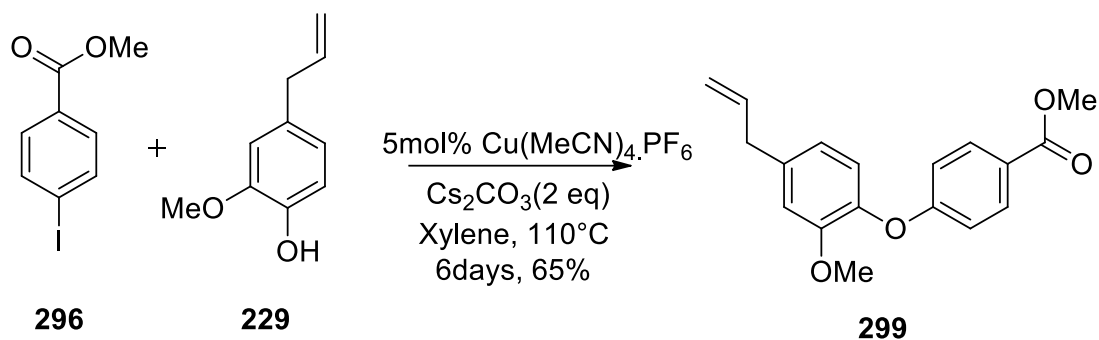
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3062, 1711, 1504, 1419, 1226

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.23 – 7.14 (m, 2H), 6.93 – 6.85 (m, 3H), 6.82 (d,  $J$  = 1.9 Hz, 1H), 6.74 (dd,  $J$  = 8.1, 2.0 Hz, 1H), 5.99 (ddt,  $J$  = 16.9, 10.2, 6.7 Hz, 1H), 5.15 – 5.08 (m, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 3.39 (d,  $J$  = 6.7 Hz, 2H).

$^{13}\text{C}$  NMR (76 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 157.8 (CO), 137.2 (s), 130.4 (s), 126.88 (s), 124.5 (s), 121.4 (CH), 121.0 (CH), 119.9 (CH), 119.3 (CH), 116.9 (CH), 116.0 ( $\text{CH}_2$ ), 113.2 (CH), 55.9 ( $\text{CH}_3$ ), 40.0 ( $\text{CH}_2$ ).



### Diphenyl ether (299)



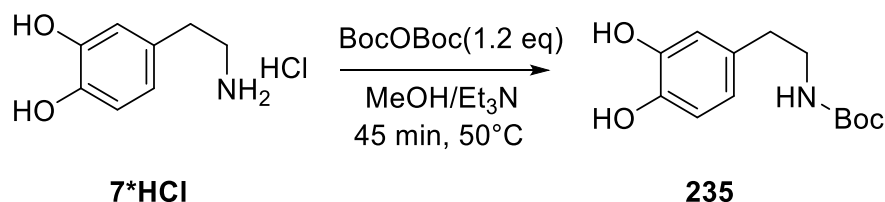
A mixture of compounds **296** (0.15 g, 0.57 mmol), **229** (0.701 mg, 1.08 mmol), with  $\text{Cs}_2\text{CO}_3$  (0.37 g, 1.14 mmol) and 5 mol% of  $\text{Cu}(\text{MeCN})_4 \cdot \text{PF}_6$  (0.011 g, 0.028 mmol) in xylene (0.8 ml) was heated at  $120^\circ\text{C}$  for 8 days. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched with water and extracted with EtOAc and concentrated. The residue was purified by chromatography over silica gel column yielded to a brown gum (0.11 g, **65%**).

Rf = 0.26 (Cy/ EtOAc; 85/15)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 8.00 – 7.92 (m, 2H), 6.99 (d,  $J = 8.0$  Hz, 1H), 6.94 – 6.86 (m, 2H), 6.86 – 6.76 (m, 2H), 6.00 (ddt,  $J = 17.0, 10.2, 6.7$  Hz, 1H), 5.19 – 5.09 (m, 2H), 3.87 (d,  $J = 4.5$  Hz, 3H), 3.77 (s, 3H), 3.41 (d,  $J = 6.7$  Hz, 2H).

$^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 138.4 (CO), 137.2 ( $\text{CH}_2$ ), 131.7 (Cq), 123.9 (Cq), 122.3 (CH), 121.1 (CH), 120.2 (CH), 116.4 ( $\text{CH}_2$ ), 113.4 (CH), 55.0 ( $\text{CH}_3$ ), 52.1 ( $\text{CH}_3$ ), 40.2 ( $\text{CH}_2$ ), 29.8 (s).

### N-Boc dopamine (235)



A solution of dopamine chlorhydrate **7\*HCl** (4.01 g, 21.15 mmol) and di-tert-butyl dicarbonate (5.54 g, 25.37 mmol) in MeOH/ $\text{Et}_3\text{N}$  (9/1) was heated to reflux for 45 mins. The reaction

was monitored by TLC (DCM/MeOH : 9/1), quenched with water and concentrated under reduced pressure. The residue was treated with 1N HCl to pH 2, then extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by chromatography over silica gel column to yield to a white solid (5.03 g, **94%**).

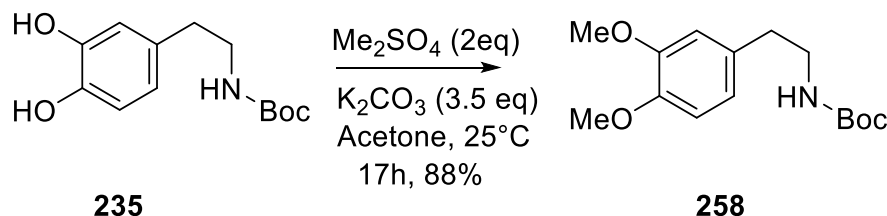
R<sub>f</sub> = 0.65 (DCM/MeOH : 95/5)

IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3366, 2978, 1682, 1447

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.78 (d, *J* = 8.0 Hz, 1H), 6.69 (s, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 3.31 (d, *J* = 6.2 Hz, 2H), 2.64 (t, *J* = 6.9 Hz, 2H), 1.44 (s, 9H).

HRMS *m/z* calcd for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>N [ESI]<sup>-</sup>: 252.12389, found: 252.12413

### **N-boc-3,4-dimethoxyphenylethylamine (258)**



A mixture of compound **235** (3.8 g, 15.02 mmol), K<sub>2</sub>CO<sub>3</sub> (7.26 g, 52.51 mmol) and C<sub>2</sub>H<sub>6</sub>SO<sub>4</sub> (2.8 ml, 30.01 mmol) in acetone (30 ml) were stirred overnight at 25°C. The reaction was monitored by TLC (Cy/EtOAc : 8/2), filtered through Celite<sup>®</sup> with EtOAc. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and was purified by chromatography over silica gel column to yield to a white solid (3.72 g, **88%**).

R<sub>f</sub> = 0.54 (Cy/EtOAc : 90/10)

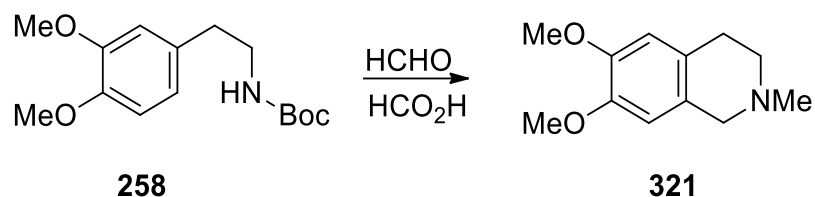
IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3374, 2975, 2836, 1608, 1142.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.85 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 1.9 Hz, 1H), 6.75 (s, 1H), 3.90 (d, *J* = 3.2 Hz, 6H), 3.39 (dd, *J* = 13.1, 6.6 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H), 1.47 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.9 (CO), 149.0 (OCH<sub>3</sub>), 147.6 (C<sub>q</sub>), 131.5 (C<sub>q</sub>), 120.7 (CH), 112.0 (CH), 111.4 (CH), 55.9 (CH<sub>3</sub>), 41.9 (CH<sub>2</sub>), 35.8 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>).

HRMS *m/z* calcd for C<sub>15</sub>H<sub>23</sub>O<sub>4</sub>N [ESI+Na]<sup>+</sup>: 304.15149, found: 304.15193

### **6,7-dimethoxyphenyltetrahydroisoquinoline (321)**

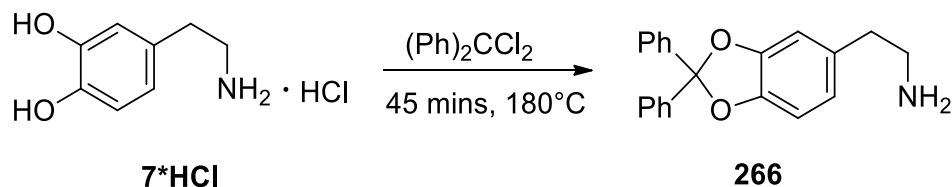


To a solution, cooled with an ice bath, of compound **258** (0.98 g, 3.48 mmol) and paraformaldehyde (0.314 g, 10.463 mmol), HCO<sub>2</sub>H (1 ml) was slowly added and the reaction mixture was heated to reflux for 48 h. The reaction was monitored by TLC (DCM/MeOH : 9/1), quenched with solid Na<sub>2</sub>CO<sub>3</sub> to a basified to pH 10 and extracted with DCM, brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purification by chromatography over silica gel column yield to a brown solid (0.773 g, **87%**).

R<sub>f</sub> = 0.25 (DCM/ MeOH; 90/10)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.60 (s, 1H), 6.51 (s, 1H), 3.84 (d, *J* = 3.0 Hz, 6H), 3.56 (s, 2H), 2.87 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 5.9 Hz, 2H), 2.48 (s, 3H).

### 2,2-diphenyl-1,3-benzodioxole-6-ethylamine (266)

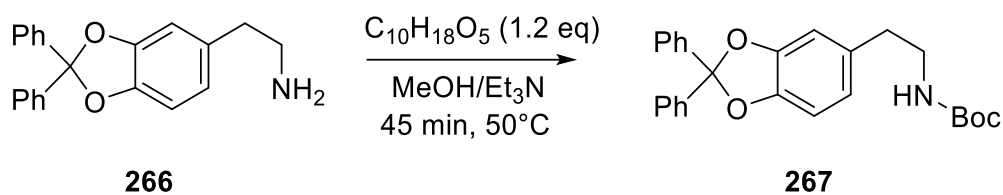


An intimate mixture of dopamine chlorhydrate **270** (1.01 g, 5.28 mmol) and α,α-dichlorodiphenylmethane (1.0 ml, 5.28 mmol) was heated for 45 min at 180°C . Allow to cool and recrystallization in benzene, yield to a white solid (1.66 g, **97%**).

R<sub>f</sub> = 0.38 (DCM/ MeOH; 95/5)

<sup>1</sup>H NMR (300 MHz, DMSO) δ 7.57 – 7.51 (m, 4H), 7.44 (m, 6H), 7.02 – 6.94 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 2.99 (d, *J* = 7.8 Hz, 2H), 2.79 (s, 2H).

### N- boc-2,2-diphenyl-1,3-benzodioxole-6-ethylamine (267)



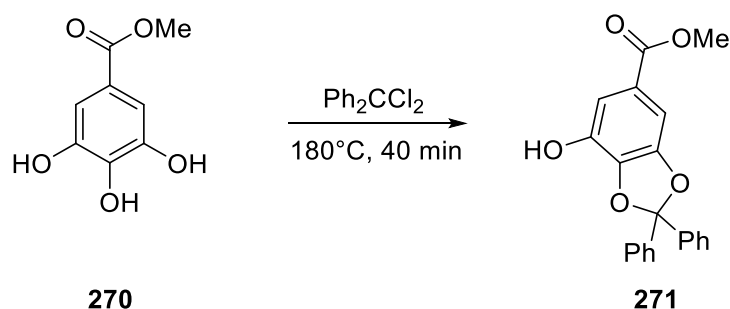
A mixture of compound **266** (0.53 g, 1.66 mmol) and di-tert-butyl dicarbonate (0.45 g, 2.08 mmol) in MeOH/Et<sub>3</sub>N (9:1) was heated to reflux for 45 mins. The reaction was monitored by TLC (DCM/MeOH : 9/1), quenched with water and concentrated under reduced pressure. The residue was treated with 1N HCl to pH 2, then extracted with EtOAc, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated and purified by chromatography over silica gel column to yield to a white solid (0.59 g, **66%**).

R<sub>f</sub> = 0.58 (Cy/EtOAc : 95/5)

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 7.60 (m, 4H), 7.44 – 7.37 (m, 6H), 6.82 (d, *J* = 7.9 Hz, 1H), 6.75 (s, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.13 (dd, *J* = 14.6, 7.3 Hz, 2H), 2.72 (t, *J* = 6.7 Hz, 2H), 1.45 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 155.9 (Cq), 147.4 (Cq), 145.8 (Cq), 140.4 (Cq), 129.1 (2\*CH), 128.3 (4\*CH), 126.3 (4\*CH), 121.7 (CH), 46.2 (CH<sub>2</sub>), 36.0 (CH<sub>2</sub>), 28.4 (3\*CH<sub>3</sub>).

### 7-hydroxy-2,2-diphenyl-1,3-benzodioxole-5-carboxylate (271)



An intimate mixture of methyl gallate **270** (3.05 g, 16.54 mmol) and α,α-dichlorodiphenylmethane (3.0 ml, 16.54 mmol) was heated for 20 min at 180°C. After cooling, mixture was triturated and precipitate from benzene, yielded to a white solid (1.66 g, **97%**).

R<sub>f</sub> = 0.26 (Cy/EtOAc : 8/2)

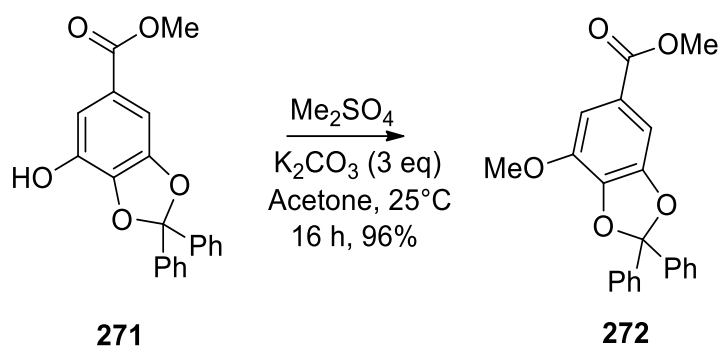
IR ν<sub>max</sub> (cm<sup>-1</sup>) = 3383, 1695, 1517, 1439, 1260.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.59 – 7.54 (m, 4H), 7.73-7.39 (m, 6H), 7.22 (d, *J* = 1.5 Hz, 1H), 7.01 (d, *J* = 1.5 Hz, 1H), 3.86 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.6 (CO), 148.3 (Cq), 139.7 (Cq), 139.1 (Cq), 138.1 (Cq), 129.4 (CH), 128.4 (Cq), 126.3 (CH), 124.4 (CH), 118.8 (CH), 114.0 (Cq), 103.4 (CH), 52.2 ( $\text{CH}_3$ ).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{15}\text{O}_5$  [ESI] $^+$ : 347.09187, found: 347.09250

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-acetate (272)



To a mixture of compound **271** (5.57 g, 16 mmol) in acetone (50 ml) were added  $\text{K}_2\text{CO}_3$  (7.73 g, 55.9 mmol) and  $\text{Me}_2\text{SO}_4$  (1.5 ml, 16 mmol) and the reaction was stirred at  $25^\circ\text{C}$  for 16 h. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched and filtered through a pad celite and wash with EtOAc, the organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure and purified by chromatography over silica gel column to yield to a white solid (5.57 g, **96%**).

$R_f$  = 0.46 (Cy/EtOAc : 90/10)

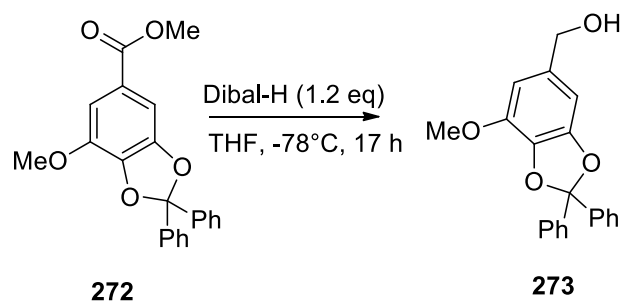
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = , 1718, 1634, 1435, 1331, 1124

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.61 – 7.56 (m, 4H), 7.37 (dd,  $J$  = 5.1, 1.8 Hz, 6H), 7.32 (d,  $J$  = 1.4 Hz, 1H), 7.28 (d,  $J$  = 1.4 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 166.6 (CO), 148.3 (COH), 143.3 (Cq), 139.8 (Cq), 139.7 (Cq), 139.3 (Cq), 129.4 (2\*CH), 128.4 (4\*CH), 126.3 (4\*CH), 124.4 (Cq), 118.7 (Cq), 110.0 (CH), 104.1 (CH), 56.7 ( $\text{CH}_3$ ), 52.3 ( $\text{CH}_3$ ).

HRMS  $m/z$  calcd for  $\text{C}_{22}\text{H}_{18}\text{O}_5$  [ESI] $^+$ : 385.10428, found: 385.10464

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-alcohol (273)



To a mixture of compound **272** (5.36 g, 14.81 mmol) in THF (20 ml) under nitrogen was brought to  $-78^{\circ}\text{C}$  and Dibal-H (1.0M; 18.0 ml, 18mmol) was added dropwise and the reaction was stirred overnight. Monitored by TLC (Cy/EtOAc : 8/2), quenched at  $0^{\circ}\text{C}$  by slowly addition of water. Then, extracted with EtOAc and the organic layer was washed with water, brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure, and purified by chromatography over silica gel column yielded to a white solid (3.89 g, **79%**).

R<sub>f</sub> = 0.26 (Cy/EtOAc : 85/15)

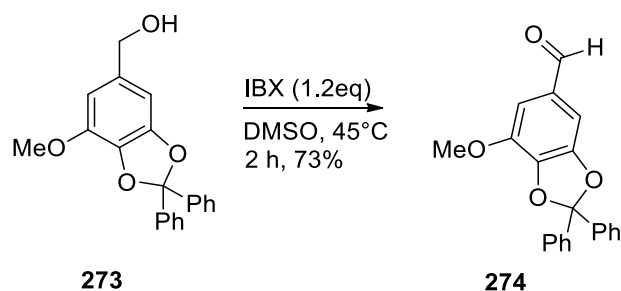
IR  $\nu_{\text{max}}$  ( $\text{cm}^{-1}$ ) = 3367, 2939, 1635, 1450, 1323, 1212

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.63 – 7.56 (m, 4H), 7.39 – 7.33 (m, 6H), 6.61 (d,  $J = 1.4$  Hz, 1H), 6.55 (d,  $J = 1.3$  Hz, 1H), 4.56 (d,  $J = 4.9$  Hz, 2H), 3.93 (s, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 148.5 (Cq), 143.6 (Cq), 140.1 (Cq), 135.7 (2\*Cq), 134.5 (Cq), 129.1 (2\*CH), 128.2 (4\*CH), 126.4 (4\*CH), 117.4 (Cq), 106.6 (CH), 101.4 (CH), 65.5 ( $\text{CH}_2$ ), 56.6 ( $\text{CH}_3$ ).

HRMS  $m/z$  calcd for  $\text{C}_{21}\text{H}_{18}\text{O}_4$  [ESI]<sup>+</sup>: 357.10931, found: 357.10973

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-aldehyde (274)



To a solution of compound **273** (3.89 g, 11.62 mmol) in DMSO (1 ml) was added IBX (4.89 g, 17.43 mmol) and the mixture was stirred at 45°C for 2 h. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched with water and filtered with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure, which was further purified by chromatography over silica gel column to yield to a white solid (2.81 g **73%**).

R<sub>f</sub> = 0.53 (Cy/EtOAc : 90/10)

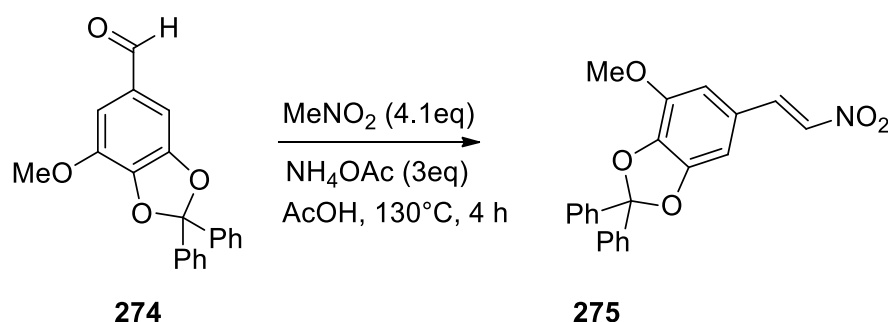
IR ν<sub>max</sub> (cm<sup>-1</sup>) = 2844, 1691, 1507, 1326, 1128

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 9.78 (s, 1H), 7.59 (ddd, *J* = 6.9, 3.3, 1.5 Hz, 4H), 7.41 – 7.36 (m, 6H), 7.12 (dd, *J* = 3.4, 1.4 Hz, 2H), 3.98 (s, 3H).

<sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>) δ (ppm): 190.2 (CHO), 139.3 (Cq), 131.7 (Cq), 129.4 (2\*Cq), 128.3 (4\*Cq), 126.3 (4\*Cq), 110.2 (CH), 103.8 (CH), 56.6 (CH<sub>3</sub>).

HRMS *m/z* calcd for C<sub>21</sub>H<sub>17</sub>O<sub>4</sub> [ESI]<sup>+</sup>: 356.09743, found: 356.10079

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-nitrostyrene (275)



A solution of compound **274** (2.52 g, 7.58 mmol) and NH<sub>4</sub>OAc (1.75 g, 22.74 mmol) in AcOH (20 ml) was stir for 10 min at 25°C, then nitromethane (1.6 ml, 31.0743 mmol) was added, and the mixture was heated to reflux at 130°C for 4 h. The reaction is monitored by TLC (Cy/DCM : 8/2), cooled with ice bath and quenched with water, extracted with DCM. The organic phases was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure and purified by chromatography over silica gel column to yield to a yellow solid (2.094 g **74%**).

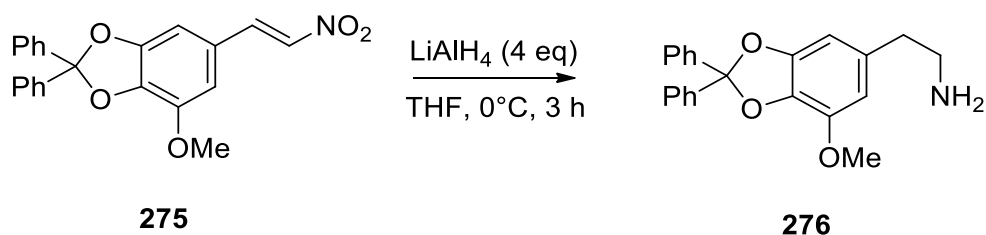
R<sub>f</sub> = 0.49 (Cy/DCM : 80/20)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.89 (d, *J* = 13.5 Hz, 1H), 7.59 – 7.55 (m, 4H), 7.46 (d, *J* = 13.5 Hz, 1H), 7.39 (dd, *J* = 4.1, 2.5 Hz, 6H), 6.81 (d, *J* = 1.5 Hz, 1H), 6.72 (d, *J* = 1.5 Hz, 1H), 3.96 (s, 3H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 149.3 (Cq), 144.0 (Cq), 139.3 (2\*Cq), 135.6 (Cq), 129.5 (2\*Cq), 128.4 (4\*CH), 126.3 (4\*CH), 124.4 (Cq), 118.8 (CH), 111.0 (CH), 102.4 (CH), 56.9 (CH<sub>3</sub>).

HRMS  $m/z$  calcd for  $C_{22}H_{17}O_5N$  [ESI]<sup>+</sup>: 398.09984, found: 399.09989

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-ethanamine (276)



Compound **275** (1.74 g, 4.64 mmol) and  $LiAlH_4$  (0.704 g, 18.56 mmol) in dry THF (10 ml) were stirred at 0°C for 3 h. The reaction was monitored by TLC (DCM/MeOH : 9/1), quenched with  $H_2O$  and extracted with EtOAc. Organic phases were washed with brine, dried over  $Na_2SO_4$  and concentrated to form light yellow oily (1.55 g, **96%**).

$R_f = 0.24$  (DCM/MeOH : 9/1)

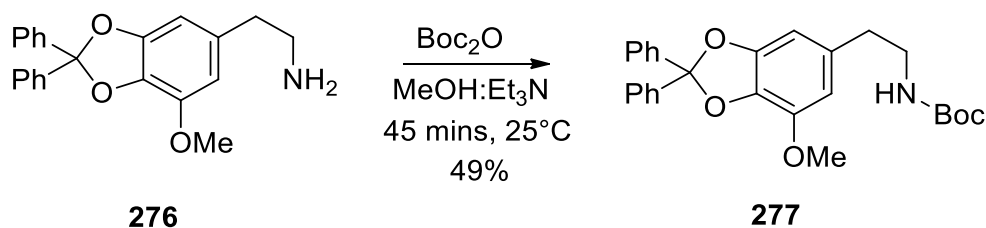
IR  $\nu_{max}$  ( $cm^{-1}$ ) = 3303, 1634, 1451, 1364, 1022.

$^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  (ppm): 7.59 (dd,  $J = 5.1, 1.7$  Hz, 4H), 7.35 (dd,  $J = 5.2, 2.0$  Hz, 6H), 6.44 (d,  $J = 1.4$  Hz, 1H), 6.35 (d,  $J = 1.3$  Hz, 1 H), 3.92 (s, 3H), 2.91 (t,  $J = 6.8$  Hz, 2H), 2.64 (t,  $J = 6.7$  Hz, 2H).

$^{13}C$  NMR (75 MHz,  $CDCl_3$ )  $\delta$  (ppm): 148.4 (Cq), 143.3 (Cq), 140.3 (Cq), 134.3 (Cq), 133.4 (Cq), 129.1 (2\*CH), 128.3 (4\*Cq), 126.5 (4\*CH), 117..2 (Cq), 108.3 (CH), 102.8 (CH), 56.7 (CH<sub>3</sub>), 43.6 (CH<sub>2</sub>), 40.2 (CH<sub>2</sub>).

HRMS  $m/z$  calcd for  $C_{22}H_{22}O_3N$  [ESI]<sup>+</sup>: 348.15855, found: 348.15942

### N-Boc,7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-ethanamine (277)





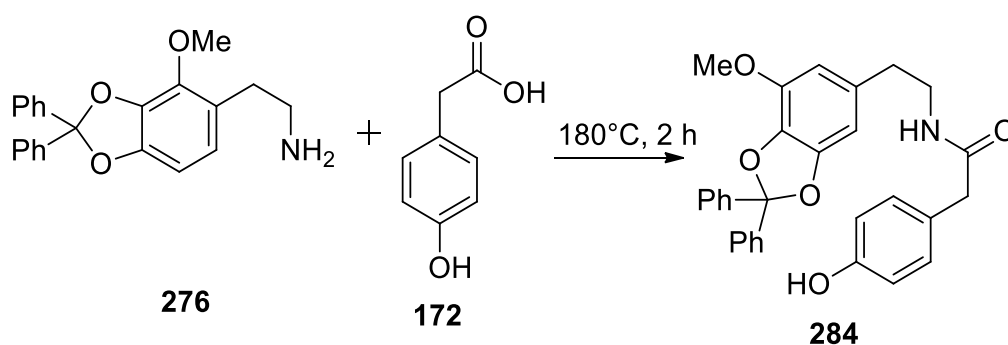
A solution of amine **276** (0.34 g, 0.99 mmol) and di-tert-butyl dicarbonate (0.26 g, 1.19 mmol) in a mixture of MeOH and Et<sub>3</sub>N (9/1) was heated to reflux for 45 min. The reaction was monitored by TLC (Cy/EtOAc : 8/2), and concentrated. The residue was treated with 1N HCl to pH 2 then extracted with DCM, brine dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated and purified by chromatography over silica gel column to yield to a white solid (0.199 g, **46%**).

R<sub>f</sub> = 0.56 (DCM/MeOH : 95/5)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.61 – 7.58 (m, 4H), 7.36 (dd, *J* = 5.1, 2.0 Hz, 6H), 6.42 (d, *J* = 1.3 Hz, 1H), 6.33 (s, 1H), 3.91 (s, 3H), 3.31 (d, *J* = 6.4 Hz, 2H), 2.68 (t, *J* = 6.9 Hz, 2H), 1.42 (s, 9H).

HRMS *m/z* calcd for C<sub>27</sub>H<sub>30</sub>O<sub>5</sub>N [ESI]<sup>+</sup>: 448.21182, found: 448.21185

### 7-methoxy-2,2-diphenyl-1,3-benzodioxole-5-amide (284)



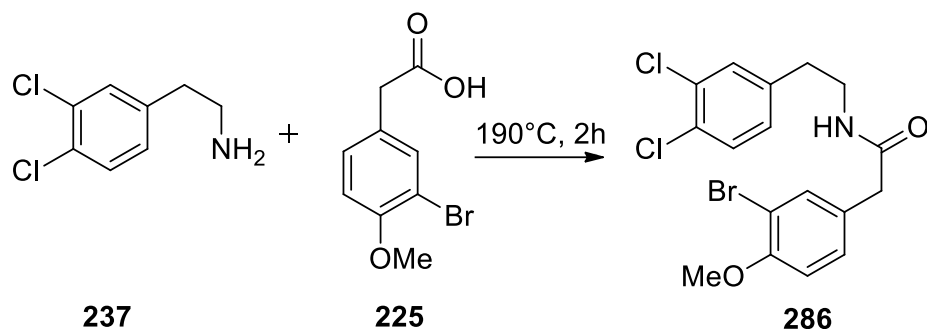
Mixture of amine **276** (0.51 g, 1.47 mmol) and acid **172** (0.22 g, 1.47 mmol) was heated neat for 2 hours at 190°C. The reaction was purified by chromatography over silica gel column, yielded a brown sticky gum (0.44 g, **62%**).

R<sub>f</sub> = 0.37 (DCM/ MeOH; 95/5)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.61 (dd, *J* = 7.5, 2.2 Hz, 4H), 7.40 – 7.36 (m, 6H), 6.92 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.5 Hz, 2H), 6.23 (dd, *J* = 20.4, 1.4 Hz, 2H), 3.87 (s, 3H), 3.40 (dd, *J* = 12.0, 5.7 Hz, 4H), 2.62 (t, *J* = 6.7 Hz, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ = 171.9 (CO), 155.2 (CO), 148.8 (Cq), 143.7 (Cq), 140.6 (Cq), 133.1 (CO), 130.9 (CH), 129.4 (CH), 128.5 (CH), 126.6 (CH), 116.1 (CH), 108.2 (CH), 102.8 (CH), 56.9 (CH<sub>3</sub>), 43.1 (CH<sub>2</sub>), 40.8 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>),

### 3,4-dichloro-3'-bromo-4'-methoxyphenylethylamide (286)



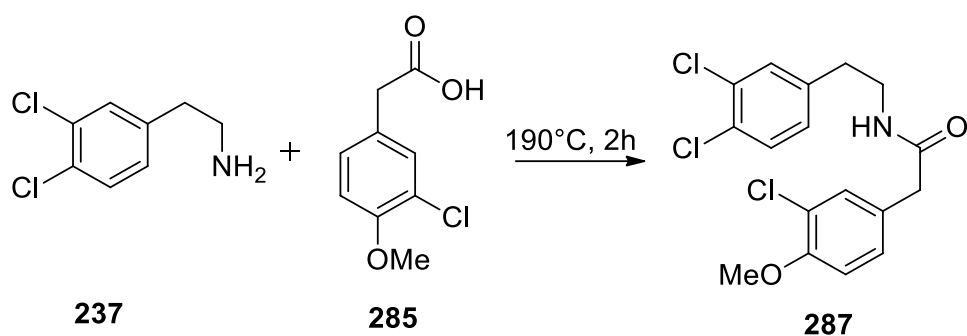
Mixture of dichlorophenethylamine **237** (0.38 g, 2.23 mmol) and acid **287** 0.55 g, 2.23 mmol) was heated neat for 2 hours at 190°C. The reaction was purified by chromatography over silica gel column, yielded a brown solid (0.76 g, **82%**).

R<sub>f</sub> = 0.35 (Cy: EtOAc; 90:10)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.37 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.89 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.45 (p, *J* = 6.7 Hz, 4H), 2.72 (t, *J* = 6.8 Hz, 2H).

<sup>13</sup>C NMR (76 MHz, CDCl<sub>3</sub>) δ = 170.7 (CO), 155.3 (CO), 138.9 (C<sub>q</sub>), 134.3 (CH), 132.5 (C<sub>q</sub>), 130.7 (CH), 130.5 (CH), 129.6 (CH), 128.9 (CH), 128.0 (C<sub>q</sub>), 112.3 (CH), 112.2, 56.3 (CH<sub>3</sub>), 42.4 (CH<sub>2</sub>), 40.4 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>).

### 3,3',4-trichloro-4'-methoxyphenylethylamide (287)



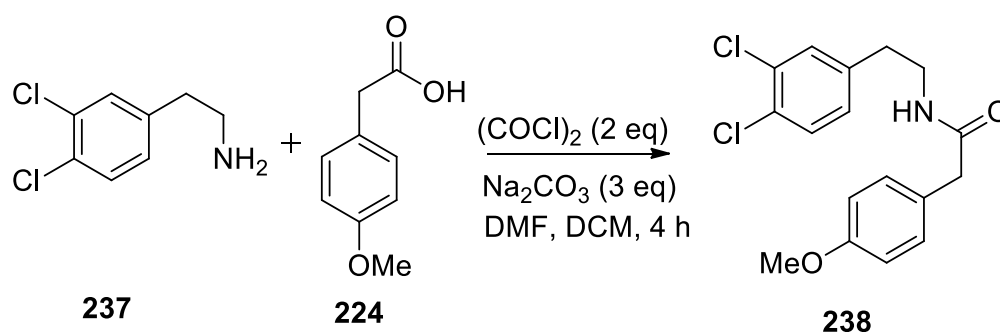
Mixture of dichlorophenethylamine **237** (0.14 g, 0.85 mmol) and acid **287** (0.17 g, 0.85 mmol) was heated neat for 2 hours at 190°C. The reaction was purified by chromatography over silica gel column, yielded a brown solid (0.19 g, **59%**).

R<sub>f</sub> = 0.38 (Cy/ EtOAc; 90/10)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.32 (d, *J* = 8.1 Hz, 2H), 7.19 (dd, *J* = 7.6, 2.1 Hz, 2H), 7.02 (dd, *J* = 8.4, 2.2 Hz, 2H), 6.92 – 6.83 (m, 3H), 3.91 (s, 3H), 3.48 – 3.41 (m, 4H), 2.72 (t, *J* = 6.9 Hz, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 170.9 (CO), 154.41 (CO), 139.0 (Cq), 131.1 (Cq), 130.7 (CH), 130.5 (CH), 128.7 (Cl), 128.2 (Cl), 127.5 (CH), 116.1 (Cl), 115.7 (CH), 114.5 (CH), 112.4 (CH), 56.2 (CH<sub>3</sub>), 42.5 (CH<sub>2</sub>), 40.4 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>).

### 3,4-dichloro-4'-methoxyphenylethylamide (238)



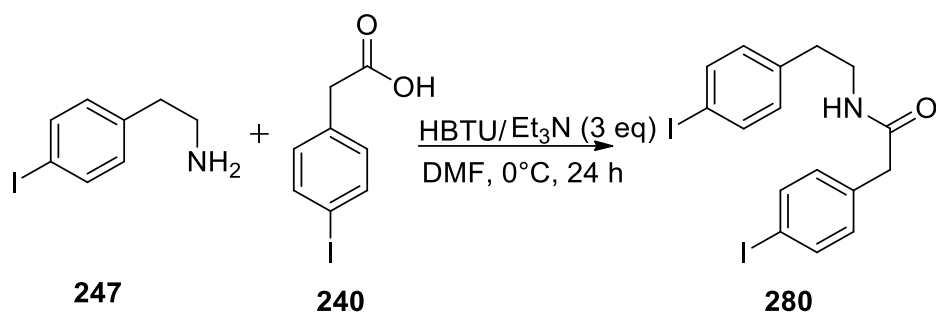
To a solution of **224** (0.083 g, 0.503 mmol) in DCM (1.0 ml) was added oxalyl chloride (0.065 ml, 0.75 mmol) and 3 drops of DMF, and the mixture was stirred at 25°C for 2 h. Then, dichlorophenethylamine **237** C<sub>8</sub>H<sub>9</sub>Cl<sub>2</sub>N (0.095 g, 0.503 mmol) and Na<sub>2</sub>CO<sub>3</sub> (0.159 g, 1.501 mmol) were added, and mixture was stirred for additional 2 h, monitored by TLC, quenched with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Organic phases were washed with brine; dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, and purification over silica gel column yielded to a brown solid (0.104 g, **65%**).

R<sub>f</sub> = 0.38 (Cy/ EtOAc; 90/10)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.29 (d, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.90 – 6.83 (m, 3H), 3.81 (s, 3H), 3.48 (s, 2H), 3.42 (q, *J* = 6.7 Hz, 2H), 2.69 (t, *J* = 6.8 Hz, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 171.5 (CO), 159.0 (CO), 139.0 (Q), 132.4, 130.7, 130.5 (Cq), 130.5 (Cq), 128.2 (CH), 126.5 (CH), 114.5 (CH), 55.3 (CH<sub>3</sub>), 42.9 (CH<sub>2</sub>), 40.3 (CH<sub>2</sub>), 34.7 (CH<sub>2</sub>).

### 4,4'-diiodophenylamide (280)



To a solution of compounds **247** (0.21 g, 0.86 mmol), **240** (0.22 g, 0.86 mmol) and HBTU (0.33 g, 0.86 mmol) in DMF (2.0 ml) and stirred at 0°C. Then, Et<sub>3</sub>N (0.4 ml, 2.57 mmol) was slowly added at 0°C and the reaction was kept under stirring 24 h. The reaction was monitored by TLC (DCM/MeOH : 9/1), quenched with water and evaporated to dryness, then the residue was diluted with H<sub>2</sub>O and extracted with EtOAc. The organic phase was washed treated with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated which was further purified by chromatography over silica gel column, yielded to a white solid (0.37 g, **89%**).

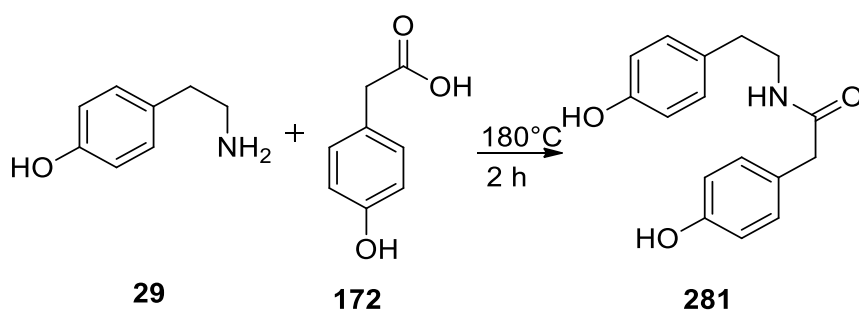
R<sub>f</sub> = 0.55 (DCM/ MeOH; 95/5)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.70 – 7.65 (m, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 3.50 – 3.41 (m, 4H), 2.70 (t, *J* = 6.8 Hz, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 170.3 (CO), 138.1 (CH), 137.7 (CH), 134.8 (Cq), 131.3 (Cq), 96.7, 43.8 (CH<sub>2</sub>), 40.5 (CH<sub>2</sub>), 34.9 (CH<sub>2</sub>).

HRMS *m/z* calcd for C<sub>16</sub>H<sub>15</sub>ON<sub>2</sub> [ESI]<sup>+</sup>: 513.91352, found: 513.91267

#### 4,4'-dihydroxyphenylamide (281)



Mixture of tyramine **29** (0.37 g, 2.69 mmol) and hydroxyphenylacetic acid **172** (0.41 g, 2.69 mmol) is heated neat for 2 hours at 190°C. The reaction was quenched and purified by chromatography over silica gel column, yielded a brown sticky gum (0.59 g, **89%**).

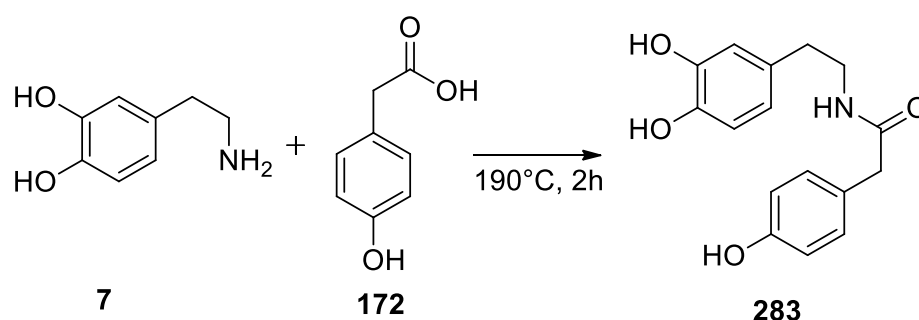
R<sub>f</sub> = 0.55 (DCM/MeOH : 95/5)

$^1\text{H}$  NMR (300 MHz, DMSO)  $\delta$  (ppm): 7.00 (d,  $J = 8.5$  Hz, 2H), 6.94 (d,  $J = 8.4$  Hz, 2H), 6.70 – 6.62 (m, 4H), 3.24 (s, 2H), 3.22 – 3.13 (m, 2H), 2.56 (t,  $J = 7.3$  Hz, 2H).

$^{13}\text{C}$  NMR (75 MHz, DMSO)  $\delta$  (ppm): 171.0 (CO), 156.3 (Cq), 156.0 (Cq), 130.3 (2\*CH), 129.9 (2\*CH), 127.0 (Cq), 115.5 (2\*CH), 115.4 (2\*CH), 42.1 (CH<sub>2</sub>), 34.74 (CH<sub>2</sub>).

HRMS  $m/z$  calcd for C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub> [ESI]<sup>-</sup>: 270.11350, found: 270.11357

### 3,4,4'-trihydroxyphenylamide (283)



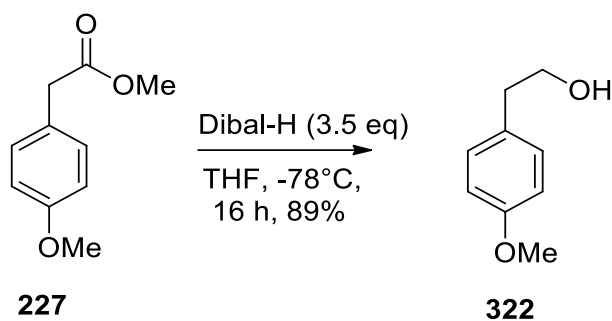
From the compound C<sub>8</sub>H<sub>12</sub>N (0.61 g, 3.99 mmol) and C<sub>8</sub>H<sub>8</sub>O<sub>3</sub> (0.61 g, 3.99 mmol) heated at 190°C for 2 hours. Quenched and purified by column chromatography to form brown sticky gum (0.916 g, **80%**).

R<sub>f</sub> = 0.55 (DCM/ MeOH; 95/5)

$^1\text{H}$  NMR (300 MHz, MeOD)  $\delta$  (ppm): 7.03 (d,  $J = 8.6$  Hz, 2H), 6.71 (d,  $J = 8.6$  Hz, 2H), 6.65 (d,  $J = 8.0$  Hz, 1H), 6.61 (d,  $J = 2.0$  Hz, 1H), 6.45 (dd,  $J = 8.0, 2.1$  Hz, 1H), 3.33 (m, 4H), 2.60 (t,  $J = 7.2$  Hz, 2H).

$^{13}\text{C}$  NMR (75 MHz, MeOD)  $\delta$  (ppm): 174.6 (CO), 157.4 (Cq), 146.2 (Cq), 144.8 (Cq), 131.9 (Cq), 131.1 (2\*CH), 127.5 (CH), 121.1 (CH), 116.8 (CH), 116.3 (2\*CH), 43.1(CH<sub>2</sub>), 42.3 (CH<sub>2</sub>), 35.7 (CH<sub>2</sub>).

### 4-methoxyphenyl alcohol (322)



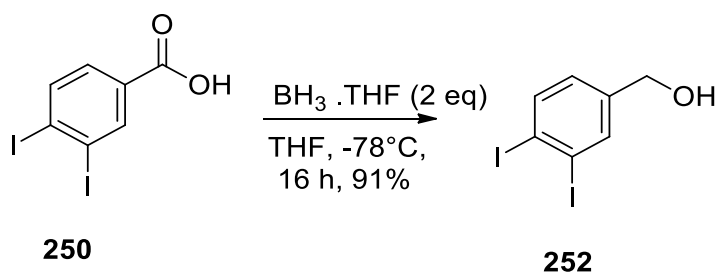
To a solution of ester **227** (1.0 g, 5.61 mmol) in THF (10 ml) at  $-78^\circ\text{C}$ , was added slowly 13 ml of a 1M solution of DIBAL in THF (1M; 13.0 ml, 13 mmol) and the reaction was stirred overnight. Monitored by TLC (Cy/EtOAc : 8/2), quenched with 1N HCl and extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$  and concentrate under reduced pressure, and was further purified by chromatography on silica gel column, yielded to a white solid (0.76 g, **89%**).

$R_f = 0.26$  (Cy/ EtOAc; 90/10)

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.15 (d,  $J = 8.7$  Hz, 2H), 6.86 (d,  $J = 8.7$  Hz, 2H), 3.83 (d,  $J = 3.9$  Hz, 2H), 3.80 (s, 3H), 2.82 (t,  $J = 6.5$  Hz, 2H).

$^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 158.3 (CO), 130.4 (Cq), 123.0 (CH), 114.1 (CH), 63.9 ( $\text{CH}_2$ ), 55.3 ( $\text{CH}_3$ ), 38.3 ( $\text{CH}_2$ ).

### 3,4-diiodobenzyl alcohol (252)



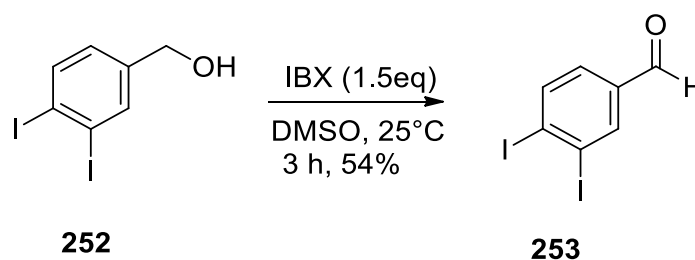
To a solution of acid **250** (3.0 g, 8.023 mmol) in THF (20 ml) at  $-78^\circ\text{C}$  and a 1M solution of borane tetrahydrofuran complex (1M; 17.0 ml, 17 mmol) was slowly added and the mixture was stirred overnight. The reaction was monitored by TLC (Cy/EtOAc : 8/2), quenched slowly with water and extracted with DCM. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , concentrated under reduced pressure, and was further purified by chromatography on silica gel column, yielded to a white solid (2.63 g, **91%**).

$R_f = 0.25$  (Cy/ EtOAc; 90/10)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (d,  $J = 2.0$  Hz, 1H), 7.84 (d,  $J = 8.1$  Hz, 1H), 7.04 (dd,  $J = 8.1, 2.0$  Hz, 1H), 4.61 (s, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 142.4 (CH), 139.4 (Cq), 137.7 (CH), 127.7 (CH), 108.0, 106.4, 63.74 ( $\text{CH}_2$ )

### 3,4-diiodobenzaldehyde (253)



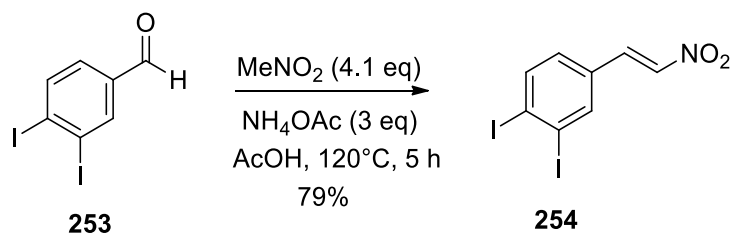
A suspension of alcohol **252** (2.0 g, 5.56 mmol) and IBX (2.33 g, 8.33 mmol) in DMSO, was stirred for 5 h. The reaction is monitored by TLC (Cy/EtOAc : 80/20), quenched and filtered with EtOAc, and the organic phase was treated with brine,  $\text{Na}_2\text{SO}_4$  and evaporated under reduced pressure, and then purified by chromatography on silica gel column to yield to a white solid (1.39 g, **54%**).

$R_f = 0.47$  (Cy/ EtOAc; 90/10)

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.88 (s, 1H), 8.30 (d,  $J = 1.9$  Hz, 1H), 8.07 (d,  $J = 8.1$  Hz, 1H), 7.51 (dd,  $J = 8.1, 1.9$  Hz, 1H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 190.0 (CO), 140.2 (CH), 140.1 (CH), 136.9 (Cq), 129.1 (CH), 116.6, 108.9

### 3-iodo-4-methoxybenzy- $\beta$ -nitrostyrene (254)



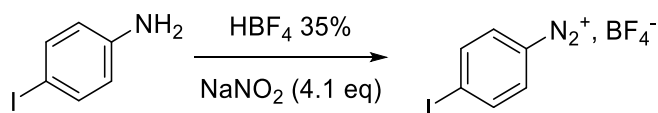
A solution of aldehyde **253** (0.71 g, 1.984 mmol) and NH<sub>4</sub>OAc (0.51 g, 6.577 mmol) in AcOH (10 ml) was stirred for 10 min at 25°C, then MeNO<sub>2</sub> (0.5 ml, 7.934 mmol) is added, and the mixture was heated at 130°C for 5 h. The reaction Monitored by TLC (Cy/DCM : 8/2), quenched in ice bath by adding water and extract with DCM. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure, and purified by chromatography on silica gel column to yield a yellow solid (0.62 g, **79%**).

R<sub>f</sub> = 0.61 (Cy/ DCM; 80/20)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 8.02 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 13.7 Hz, 1H), 7.56 (d, *J* = 13.7 Hz, 1H), 7.19 (dd, *J* = 8.2, 2.1 Hz, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 141.8 (CH), 138.7 (CH), 138.2 (CH), 136.4 (Cq), 131.2 (CH), 130.4 (CH), 112.6, 109.3

### Tetrafluoroborate 4-iodo-benzodiazonium (309)

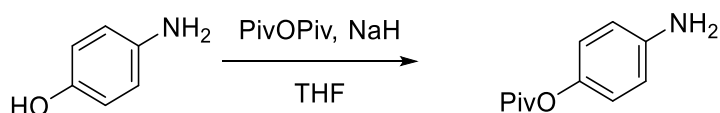


Tetrafluoroboric acid (35% in water) is added to a solution of iodoaniline **270** (8.73g, 0.04 mmol) in water (36ml) at 0°C. The reaction mixture is vigorously stirring during 10min at that temperature, and a solution of sodium nitrite (2.75g, 0.04 mmol) in water (7ml) is added. After 5 min stirring at 0°C, solid is filtered rapidly, and as cold as possible.

Recrystallisation in acetone-ether mixture allowed collecting 12.5 g of the diazonium salt **271** in almost quantitative yield.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ (ppm): 8.43 (d, *J* = 9 Hz, 2H), 8.34 (d, *J* = 9 Hz, 2H)

### O-Piv-4-aminophenol (313)



10 g of aminophenol (92 mmol) are dissolved in 400ml of dried THF, and 1 equivalent of sodium hydride 90% (2.44 g) is added by little portion. The mixture is kept under stirring 1 hour, and



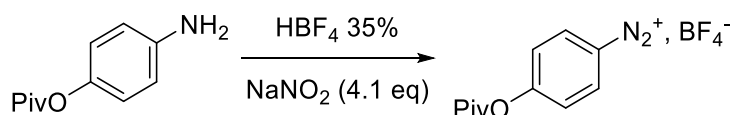
then pivalic anhydride (17,1g) is diluted in 36 ml of dried THF and added and kept under vigorous stirring overnight. Some mineral charcoal is added, filtered off, and the filtrate is concentrated under vacuum. Recrystallisation in ethanol give 17.2g (97%) of protected aminophenol.

R<sub>f</sub> = 0.82 (DCM/MeOH: 80/20)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 6.81 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 2H), 3.85 (br s, 2H), 1.34 (s, 9H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 177.7 (CO), 143.7 (Q), 143.6 (Q), 122.2 (CH), 115.9 (CH), 39.1 (Q), 27.3 (CH<sub>3</sub>).

### Tetrafluoroborate 4-*O*-Piv-benzodiazonium (314)

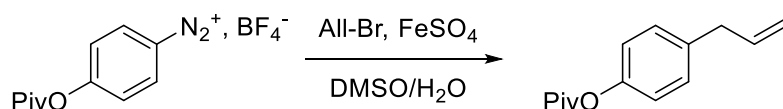


0.4 ml Tetrafluoroboric acid (35% in water) is added to a solution of *O*-Piv-4-aminophenol (0.6g, 3.1 mmol) in water (36ml) at 0°C. The reaction mixture is vigorously stirring during 10min at that temperature, and a solution of sodium nitrite (235.6 mg, 3.4 mmol) in water (0.7ml) is added. After 5 min stirring at 0°C, solid is filtered rapidly, and as cold as possible.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ (ppm): 8.76 (d, *J* = 9.3 Hz, 2H), 7.81 (d, *J* = 9.3 Hz, 2H), 1.33 (s, 9H).

HRMS *m/z* calcd for C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub> [M]: 205.09715, found: 205.09692

### 4-*O*-Piv-allylbenzene (315)



To a solution of ferrous sulphate (2.58 g (9.27 mmol, 9 eq.) and allyl bromide (0.748 g, 6.2 mmol, 6 eq.) in 3 ml of DMSO/H<sub>2</sub>O (5/2) are added dropwise a solution of 300mg of Tetrafluoroborate 4-*O*-Piv-benzodiazonium (1.03 mmol) in 1.5 ml of a mixture (5/2) of DMSO/H<sub>2</sub>O. After 2h stirring, water is added and the reaction mixture is extracted three times with ether. The combined organic layers are washed with brine, dried over sodium sulfate, and solvent is evaporated. Chromatography on silica gel (2-5% ethylacetate in cyclohexane) gives 63 mg (30%) of desired *O*-Piv-allylbenzene.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ (ppm): 7.21 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.96 (ddt, *J* = 16.9, 10.1, 6.8 Hz, 1H), 5.11 – 5.04 (m, 2H), 3.37 (d, *J* = 6.7 Hz, 2H), 1.29 (s, 9H).

HRMS *m/z* calcd for C<sub>16</sub>H<sub>16</sub>NO<sub>3</sub> [M]: 205.09715, found: 205.09692.