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THESIS

ASYMMETRIC SYNTHESIS OF (-)-*N*-FORMYLNORNUCIFERINE AND (-)-*N*-FORMYLANNONAINE WITH CARDIOTONIC ACTIVITY

KOMSAN IMPHANBAN

A Thesis Submitted in Partial Fulfillment of
the Requirements for the Degree of
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(-)-*N*-Formylnornuciferine and (-)-*N*-formylannonaine, two aporphine alkaloids isolated from stems of *Tinospora crispa* (Borapet in Thai), showed *in vitro* cardiotonic activity. They exhibited significant increase in force of contraction on atria of isolated rat heart with no change on the rate. Due to very limited amounts of these active compounds isolated from *T. crispa*, the cardiotonic activity evaluation of these compounds is hampered. One way to obtain enough quantities for pharmacological investigation is by chemical synthesis.

(±)-*N*-Formylnornuciferine and (±)-*N*-formylannonaine in racemic form were successfully synthesized by using palladium-catalyzed coupling reaction as a key step. (±)-*N*-Formylnornuciferine was synthesized in 6 steps from homoveratrylamine with an overall yield of 50%, whereas (±)-*N*-formylannonaine was also achieved in 9 steps from dopamine hydrochloride with an overall yield of 30%. Moreover, the enantiopures, (-)-*N*-formylnornuciferine and (-)-*N*-formylannonaine, were synthesized in 50% and 34% overall yield, respectively by asymmetric transfer hydrogenation method using chiral ruthenium complex as a catalyst.

For cardiotonic activity, it was found that the racemic mixture, (±)-*N*-formylnornuciferine and (±)-*N*-formylannonaine, showed the different activity from that of the natural ones, while the enantiopure of these two synthetic alkaloids showed quite similar results to the natural ones isolated from *T. crispa*. From our results, it may be possible to develop these active alkaloids to become a potential cardiotonic drug in the future.

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Student's signature Thesis Advisor's signature

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Komsan Imphanban

April 2009

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LIST OF ABBREVIATIONS

[α]	=	specific rotation
δ	=	chemical shift (ppm)
υ_{max}	=	maximum absorption frequency
Ar	=	aryl
Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl
br s	=	broad singlet
Calcd.	=	calculated
cm^{-1}	=	reciprocal centimeter (wave number)
d	=	doublet
dba	=	dibenzylidene acetone
dd	=	doublet of doublets
ddd	=	doublet of doublet of doublets
de	=	diastereomeric excess
DMA	=	dimethyl acetamide
DME	=	dimethoxy ethane
dppf	=	1,1′-diphenylphosphino ferrocene
ee	=	enantiomeric excess
EI	=	electron impact
Et	=	ethyl
FTIR	=	fourier transform infrared spectroscopy
h	=	hour
HRMS	=	high resolution mass spectroscopy
Hz	=	Hertz
J	=	coupling constant
m	=	multiplet
Me	=	methyl
m.p.	=	melting point
MS	=	mass spectroscopy

LIST OF ABBREVIATIONS (Continued)

m/z	=	a value of mass divided by charge
NMR	=	nuclear magnetic resonance
ppm	=	part per million
rt	=	room temperature
s	=	singlet
t	=	triplet
*t*Bu	=	tertiary butyl

ASYMMETRIC SYNTHESIS OF (-)-*N*-FORMYLNORNUCIFERINE AND (-)-*N*-FORMYLANNONAINE WITH CARDIOTONIC ACTIVITY

INTRODUCTION

Aporphines are a large group of alkaloids, with more than 500 structures reported to date. The general structure and numbering system of aporphine alkaloids are shown in Figure 1.

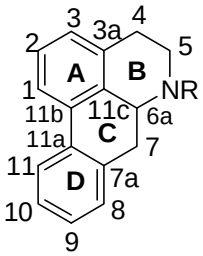
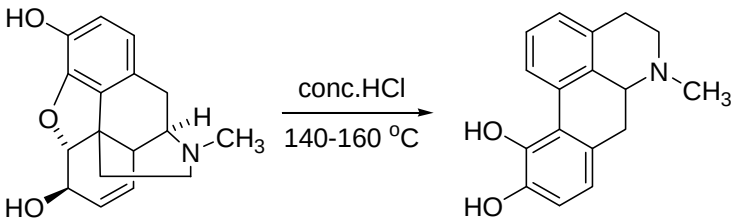


Figure 1 General structure and numbering system of aporphine alkaloids

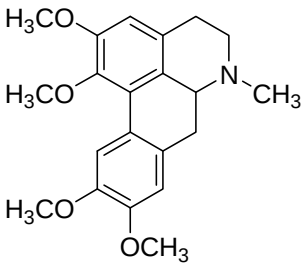
Aporphine alkaloids are widely distributed in many plant species, including *Annonaceae, Lauraceae, Monimiaceae, Menispermaceae, Hernandiaceae, Ranunculaceae* and others. Many members of aporphines demonstrate interesting and assorted biological activities, such as antioxidant, antiplatelet, antitumor, anticonvulsant, antiplasmodial, antineoplastic, antimalarial, antiprotozoal, antipoliovirus, cytotoxic, and antiparkinsonian effects (Zhang *et.al.*, 2007).

At first, in 1869, aporphine alkaloid was obtained by chemical reaction not by isolation. It was found that hot concentrated hydrochloric acid caused rearrangement of morphine (1) to apomorphine (2), which is not a natural product (Matthiesson and Wright, 1869).



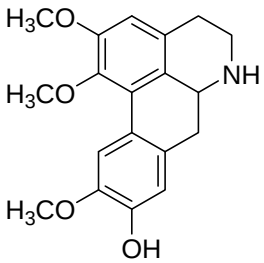
(1) (2)

Glaucine (3), a naturally occurring aporphine alkaloid, was obtained from *Glaucium luteum* (Fischer, 1901). It was subsequently isolated from *Corydalis cava* (Gadamer, 1911), *Corydalis tuber* (Go, 1930), *Dicentra eximia* (Manske, 1933), *Dicentra oregana* (Manske, 1934) and *Glaucium serpieri* (Manske, 1942).

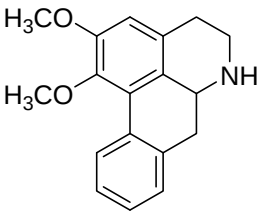


(3)

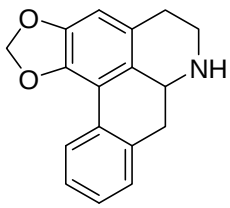
Since glaucine alkaloid (3) was reported, many different analogues of aporphine alkoloids have been isolated from plant sources, such as laurotetanine (4), nornuciferine (5), annonaine (6), boldine (7), domesticine (8), nuciferine (9), laurifoline (10), cocsarmine (11) and xanthoplanine (12).



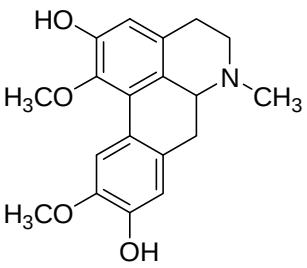
Laurotetanine (4)



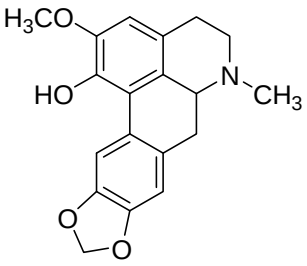
Nornuciferine (5)



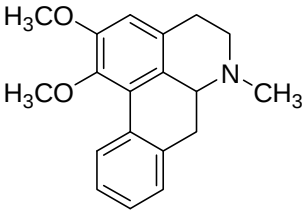
Annonaine (6)



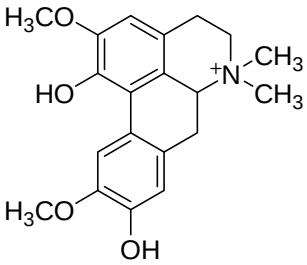
Boldine (7)



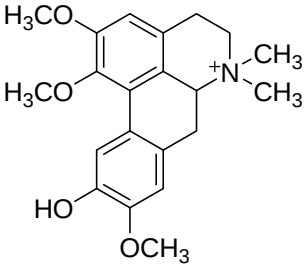
Domesticine (8)



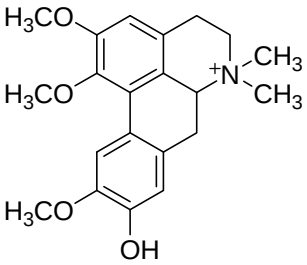
Nuciferine (9)



Laurifoline (10)

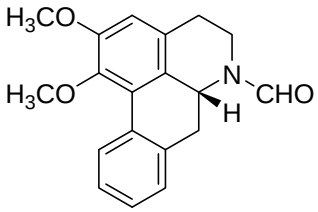


Cocsarmine (11)

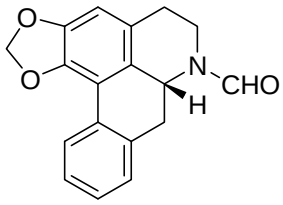


Xanthoplanine (12)

(-)-*N*-Formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b) are one of the naturally occurring aporphine alkaloid types. The structures of them are shown below.



(-)-*N*-Formylnornuciferine (13b)



(-)-*N*-Formylannonaine (14b)

Both compounds were isolated from many plants such as *Hexalobus crispiflorus*, *Guyanese annonaceous*, *Tinospora crispa* and others as shown in Table 1 and 2.

Table 1 *N*-Formylnornuciferine found in plants

Scientific name	Part of plant	Reference
Guyanese annonaceous	Leaves	Cortes *et al*., 1986
Tinospora crispa	Stems	Pachaly *et al*., 1992
		Cavin *et al*., 1998
Piptostigma fugax	Barks and roots	Achenbach and Schwinn, 1995
Piper argyrophylum	Stems	Simonsen *et al*., 1996

Table 2 *N*-Formylannonaine found in plants

Scientific name	Part of plant	Reference
Hexalobus crispiflorus	-	Achenbach *et al*., 1982
Tinospora malabarica	-	Atta-ur-Rehman and Ahmad, 1987
Rollinia mucosa	Barks	Caetano and Dadoun, 1987
Hexalobus monopetalus	Leaves	Fiagbe *et al*., 1988
Tinospora crispa	Stems	Pachaly *et al*., 1992
		Cavin *et al*., 1998
Annona cherimola	Barks	Chen *et al*., 1997
Phoebe formosana	Barks	Chen *et al*., 1997
Annona glabra	Fruits and barks	Chang *et al*., 2000
Magnolia obovata	Leaves	Pyo *et al*., 2003

There have been only few reports published on biological activities of (-)-*N*-formylnornuciferine (13) and (-)-*N*-formylannonaine (14). Cavin *et al*. (1998) showed antioxidant properties of (-)-*N*-formylnornuciferine (1) against DPPH radical, it was proved to be completely inactive.

Pyo *et al.* (2003) reported the inhibitory effects of (-)-*N*-formylannonaine (14) on rat platelet aggregation. The compound showed 220-fold stronger inhibitory effects than acetylsalicylic acid (ASA).

In 2002, Kongkathip and co-workers have found that *Tinospora crispa* extracts showed cardiac contractility (Kongkathip *et al.*, 2002) and in 2007, they isolated two pure active alkaloids, (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b), from the dichloromethane and ethanol extracts, respectively. (-)-*N*-Formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b) showed *in vitro* cardiotonic activity. Both alkaloids exhibited significant increase in the force of contraction on isolated rat heart with no significant change on rate (Kongkathip, 2007a, 2007b, 2007c, 2007d).

Unfortunately, these active compounds were separated from *Tinospora crispa* in very small quantities (0.357 mg% dry weight for (-)-*N*-formylnornuciferine (13b) and 0.084 mg% dry weight for (-)-*N*-formylannonaine (14b). The evaluation of these active alkaloids is hampered by lack of material. At present, one way to obtain enough quantities for pharmacological investigation is by chemical synthesis.

We plan to use two pathways for synthesis of *N*-formylnornuciferine (13) and *N*-formylannonaine (14). The first pathway is intramolecular aryl coupling of benzylisoquinoline. The second pathway is intermolecular of substituted phenylethyl amine and phenyl acetic acid, followed by cyclization to construct aporphine structure.

OBJECTIVES

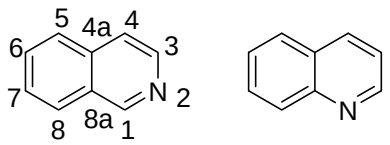
1. To synthesize two aporphine alkaloids, *N*-formylnornuciferine and *N*-formylannonaine.

2. To study cardiotonic activity on *N*-formylnornuciferine and *N*-formylannonaine.

LITERATURE REVIEW

1. Synthesis of Isoquinoline Alkaloids

Isoquinoline (15), a structural isomer of quinoline (16), is benzopyridine composed of a benzene ring fused to a pyridine ring. The numbering system of the isoquinoline nucleus is shown in Figure 2.



(15) (16)

Figure 2 General structure and numbering system of isoquinoline nucleus

Several isoquinoline synthetic methods have been developed due to its skeleton represent as a key intermediate for synthesis of many aporphine alkaloids. The synthetic approaches toward isoquinoline alkaloids and derivatives can be divided systematically into 15 different types (Figure 3), relying on the mode of formation of the heterocyclic ring (1-8 and 15) and the homocyclic ring (9-14) (Figure 3), where the dashed lines indicate bonds being formed. Type 6, 8 and 14 are cycloaddition, while type 15 entails a rearrangement (Grethe, 1981).

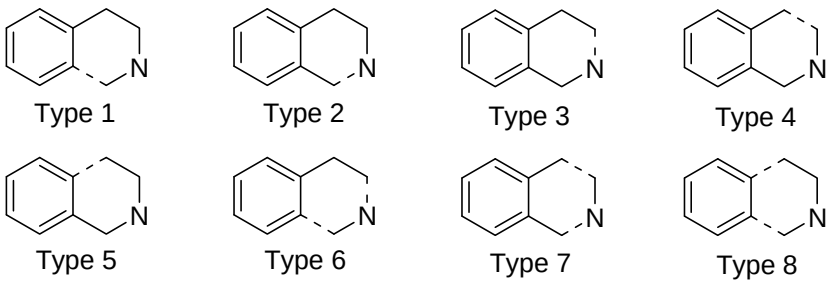


Figure 3 Isoquinoline alkaloid synthetic approaches

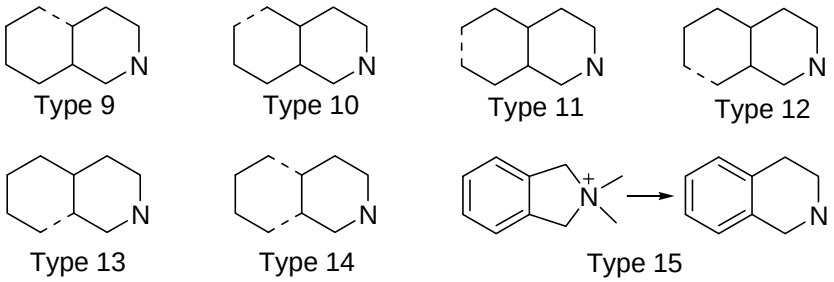
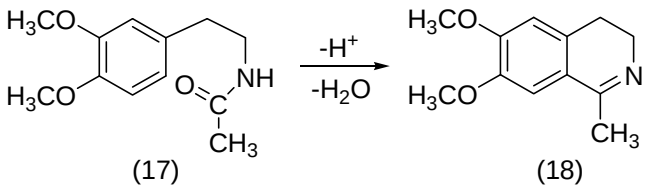


Figure 3 Isoquinoline alkaloid synthetic approaches (Continued)

The classical and important methods of isoquinoline synthesis are the Bischler-Napieralski reaction, the Pictet-Spengler reaction, and the Pomeranz-Frisch reaction. Bischler-Napieralski reaction and Pictet-Spengler reaction belong to type 1 synthesis, involving ring closure between the benzene ring and the carbon atom that forms C-1 of the resulting isoquinoline ring. In addition, the Pomeranz-Fritsch reaction, the ring closing between C-4 and C-4a of the isoquinoline nucleus, is type 5 synthesis.

1.1 The Bischler-Napieralski reaction

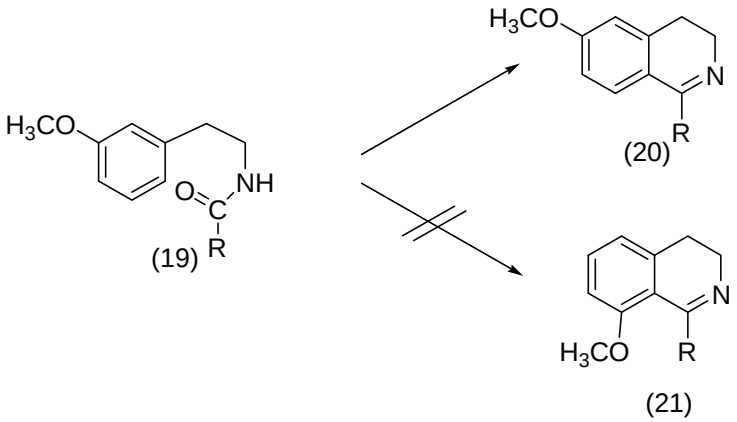
The Bischler-Napieralski reaction is the most valuable and frequently used for the synthesis of isoquinoline compounds. It involves the cyclodehydration of an acyl derivatives of *β*-phenethylamides (17) in the presence of a Lewis acid such as phosphoryl chloride or phosphorus pentoxide in dry inert solvent to afford a 3,4-dihydroisoquinoline (18).



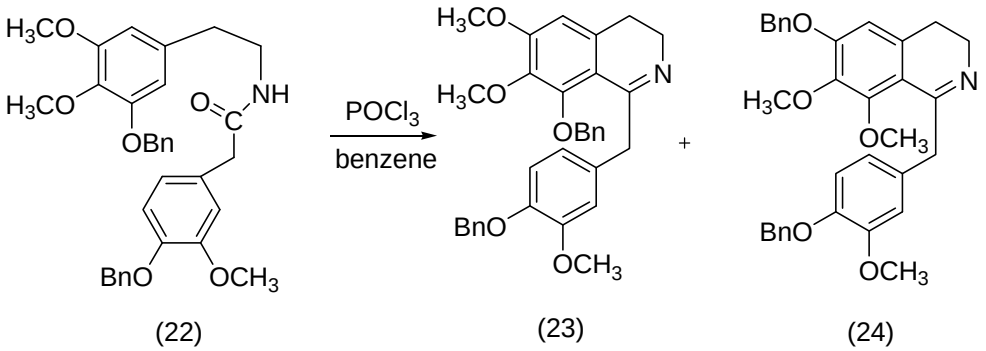
(17) (18)

The cyclization of Bischler-Napieralski reaction could be occurred in more than one direction. For instance, cyclization of *m*-methoxy-*β*-phenylethylamine (19) may be led to either 6-methoxy- or 8-methoxy-3,4-dihydro isoquinoline,

depending on the direction of ring closure. When the *para* position to the methoxy group has no substituent, cyclization preferentially occurs at the *para* to give a 6-methoxy-isoquinoline derivative (20). When the *para* position is blocked, cyclization will proceed to the *otho* position to the methoxy group.



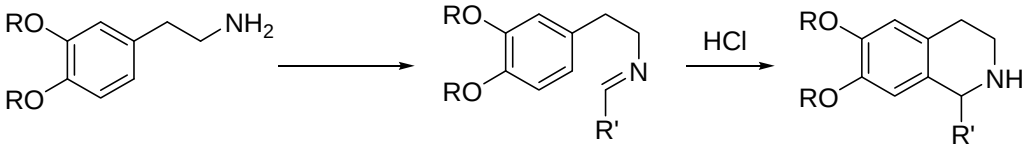
If the both available positions are activated to a similar extent, a mixture of both cyclized products is obtained, as in case of cyclization of *N*-(3-benzyloxy-4,5-dimethoxyphenethyl)-4-benzyloxy-3-methoxyphenylacetamide (22) to the 8-benzyloxy-6,7-dimethoxy- (23) and 6-benzyloxy-7,8-dimethoxy-3,4-dihydroiso quinoline derivative (24).



1.2 The Pictet-Spengler reaction

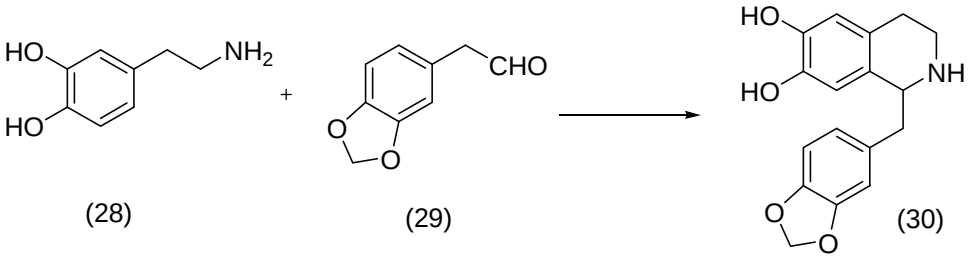
The Pictet-Spengler reaction, one of the special cases of the Mannich reaction, is the condensation of a *β*-arylethylamine with a carbonyl compound to yield 1,2,3,4-tetrahydroisoquinoline.

In 1911, Pictet and Spengler reported the condensation of phenylethylamine (25) with a dimethoxymethane in the presence of concentrated hydrochloric acid to form 1,2,3,4-tetrahydroisoquinoline (27).



(25) (26) (27)

In nature, the use of concentrated hydrochloric acid as a catalyst in preparing tetrahydroisoquinoline was not reasonable, so the condensation under possible physiological condition was examined. In 1934, Schőpf and Bayerle achieved Pictet-Spengler reaction under the same condition in plants. The reaction of *β*-(3,4-dihydroxyphenyl)ethylamine (28) with homopiperonal (29) gave 1,2,3,4-tetrahydro-6,7-dihydroxy-1-piperonylisoquinoline (30) at pH 6 and 25 ^{o}C.

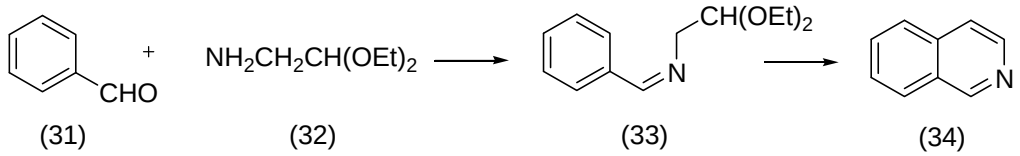


(28) (29) (30)

1.3 The Pomeranz-Fritsch reaction

This reaction, first reported by Pomeranz and Fritsch, has been utilized in the synthesis of a variety of isoquinoline derivatives. Cyclization of benzal

aminoacetal (33) under acid-catalyzed condition resulted in the formation of the expected isoquinoline (34) (Pomeranz, 1893; Fritsch, 1893).



(31) (32) (33) (34)

The process is carried out in two stages; the first involves the formation of the benzalaminoacetal (33), and the second entails the acid-catalyzed cyclization. In the first step, the Schiff base (33) is formed by the condensation of aromatic aldehyde (31) and an aminoacetal (32), and the product can be used in the cyclization step either with or without purification. In the cyclization step, sulfuric acid has been used in concentrations ranging from fuming acid to approximately 70% sulfuric acid or in a mixture with other acidic reagents such as gaseous hydrogen chloride, acetic acid, phosphorous pentoxide and phosphoryl chloride.

2. Synthesis of Aporphine Alkaloids

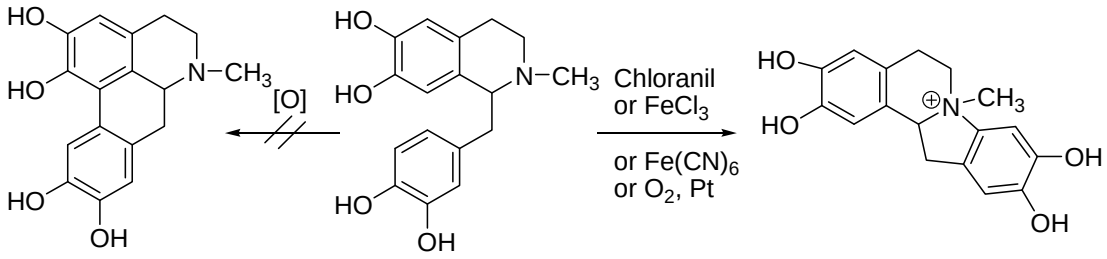
Many synthetic methods for the synthesis of aporphine alkaloids have been developed. Most of the methods follow a biogenetic pathway in which the last step involves the cyclization of a 1-benzylisoquinoline. Some of the widely used benzylisoquinoline cyclization methods are reviewed as follows.

2.1 Phenolic and Non-Phenolic Oxidation

The phenolic oxidation plays an important role in the biogenesis of many natural products. Since 1932, the biogenetical applicability of phenolic oxidation in the synthesis of aporphine alkaloids has been investigated, and the total synthesis of a number of the alkaloids has been achieved using biogenesis-type reaction steps.

The biogenesis of aporphines was first considered by Robinson and Sugasawa. They tried to cyclize the tetrahydrobenzylisoquinoline *N*-methyl

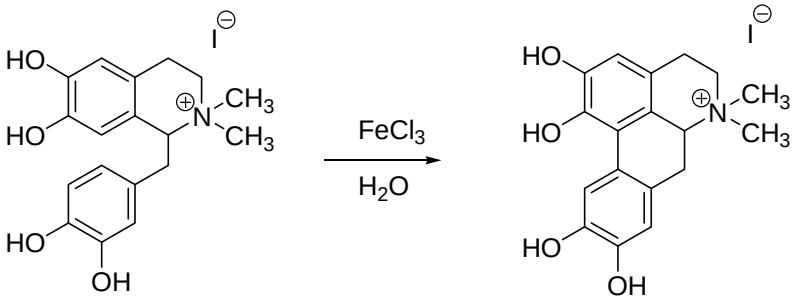
laudanosoline (36) by intramolecular phenolic oxidative coupling as biological synthesis into 1,2,9,10-tetrahydroaporphine (37), but the product was proved to be the dibenzopyrrocoline salt (35) instead (Robinson and Sugasawa, 1932).



(35) (36) (37)

In 1957, Barton and Cohen proposed the theory of phenolic oxidation in the biogenesis that the bond between two aromatic rings of aporphines could be generated by phenolic oxidation of phenolic base. This hypothesis was confirmed by tracer investigation later (Blaschke, 1968).

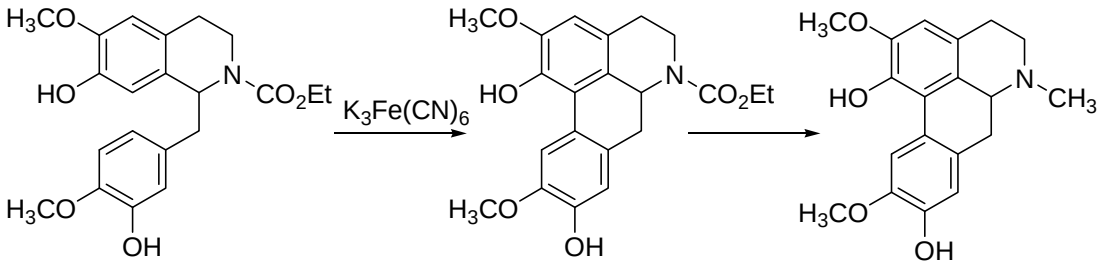
Franck and Schlingloff (1962) accomplished the first *in vitro* chemical synthesis of aporphine *via* direct phenolic oxidation of laudanosoline methiodide (38) with iron (III) chloride to give a quaternary aporphine (39) in 60%.



(38) (39)

Phenolic oxidation of various conditions was studied. Kametani reported the phenolic oxidative coupling of *N*-ethoxycarbonylnorreticuline (40) with potassium ferricyanide in diluted ammonia to give aporphine (41) in 5 to 7% yield, which was

reduced using lithium aluminium hydride to afford isoboldine (42) (Kametani *et al*., 1969).



(40) (41) (42)

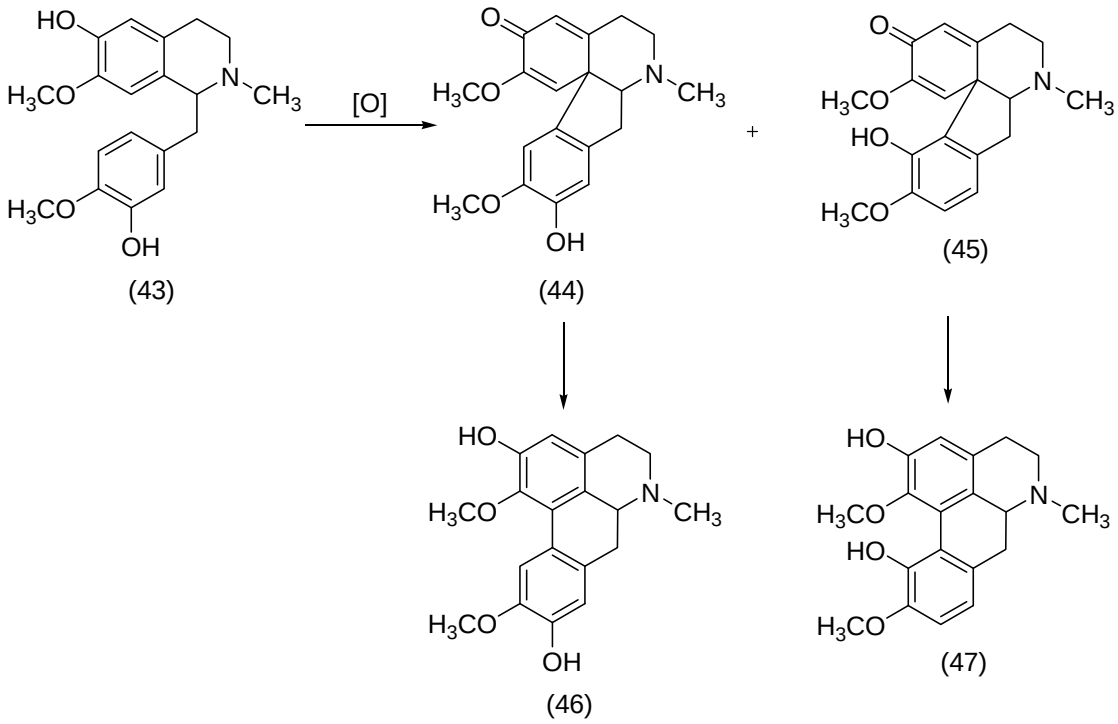
In addition, several oxidizing agents for conversion of reticuline (40) to isoboldine (42) have been studied as shown in Table 3 (Kamitani and Fukumoto, 1972).

Table 3 Reaction conditions for transformation of reticuline (40) into isoboldine (42)

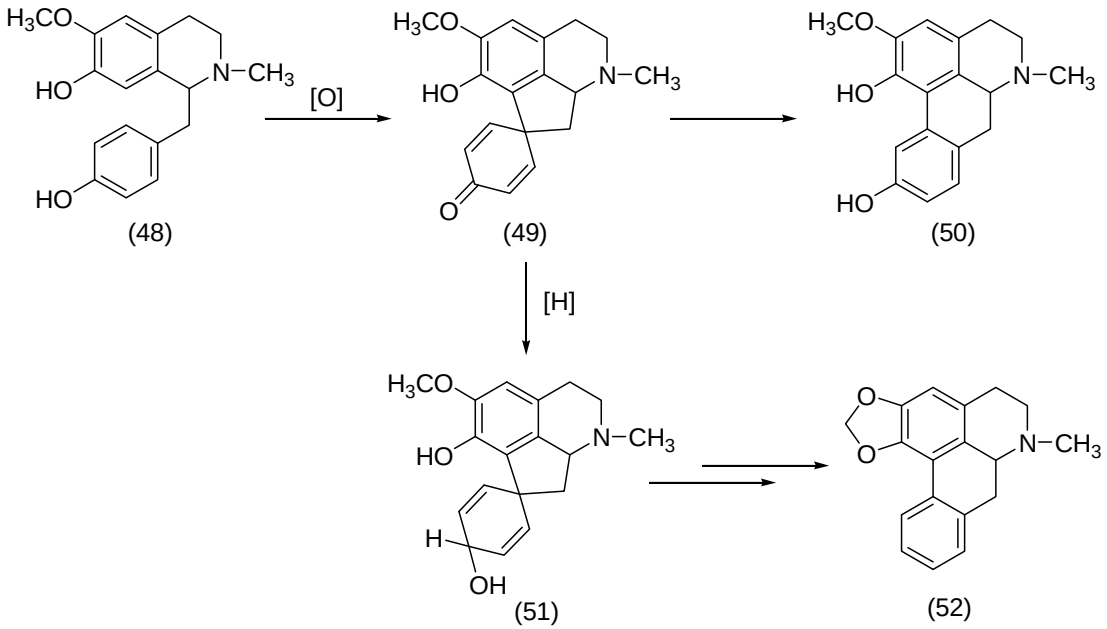
Reagents	Base	Reaction conditions		Yield %
		Temp. (^oC)	Time (h)	
$K_3Fe(CN)_6$	8%$AcONH_4$	-12	14	0.055
$K_3Fe(CN)_6$	0.2 N KH_2PO_4	rt	3	5-6
	0.2 N NaOH			
$K_3Fe(CN)_6$	5% $NaHCO_3$	5-10	0.5	0.4
	5% $NaHCO_3$	rt	1	5
Ag_2CO_3/ celite	-	rt	1.5	3
$VOCl_3$	-	rt	2	+
MnO_2/ SiO_2	-			6

Several aporphine alkaloids were constructed in such a way that their biogenesis by direct phenolic oxidation involves unlikely precursors. By means of tracer experiments, Battersby *et al.* (1971) elucidated a surprising biogenetic route to aporphines (46) and (47). Isoquinoline (43) was not directly converted by phenolic

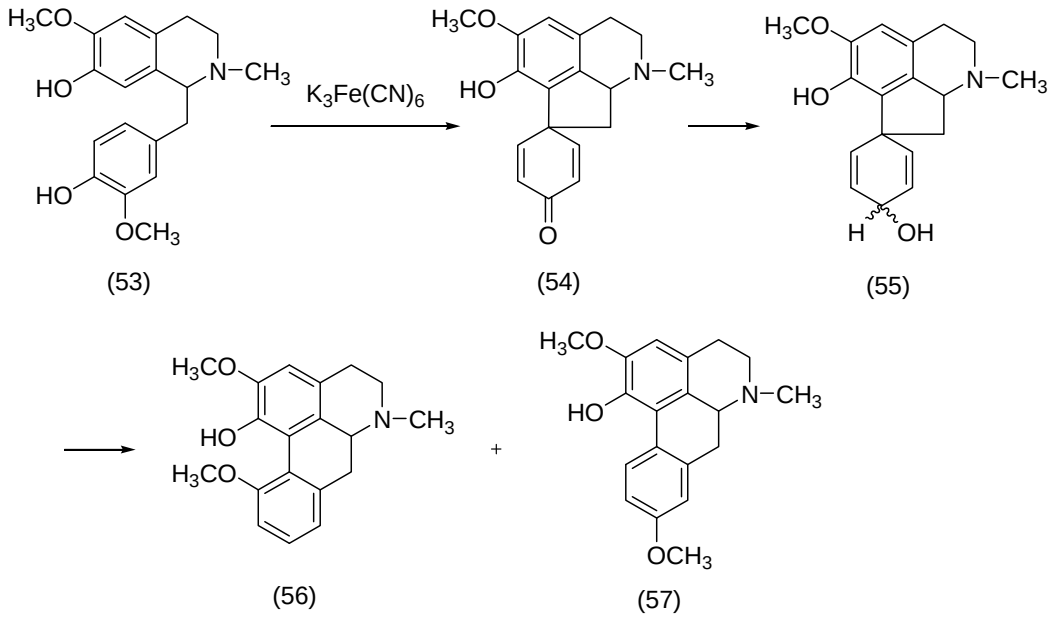
oxidation into aporphines (46 and 47) but was transformed to be dienones (44) and (45). Dienone-phenol rearrangement of dienone (44 and 45) yielded aporphines (46 and 47).



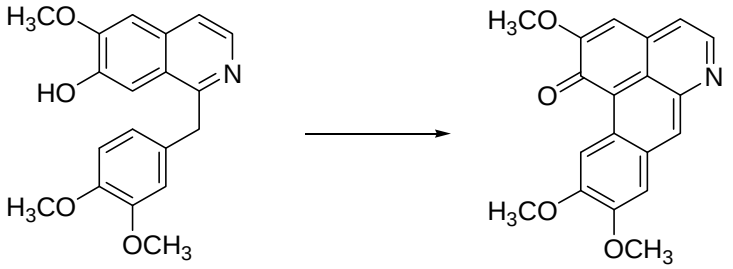
Barton and Cohen (1957) proposed the coupling process of roemerine (50) and anonaine (52). The coclaurine (48) was oxidized to dienone (49), which then underwent dienone-phenol rearrangement to generate anonaine (50). The reduction of dienone (49) to dienol (51), followed by dienol-benzene rearrangement, and would then furnish roemerine (52).



In 1964, Battersby *et al.* first reported the synthesis of aporphines *via* dienol-benzene rearrangement. Orientaline (53) underwent phenolic oxidation with potassium hexacyanoferate (III) in 8% ammonium acetate solution to afford orientalinone (54). Orientalinone (54) was reduced by sodium borohydride to orientalinol (55), followed by dienol-benzene rearrangement to give isothebaine (56) and xylopine-type aporphine (57).



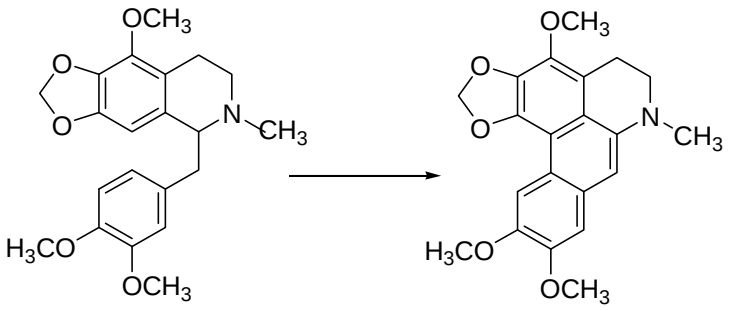
Although diphenolic oxidation plays an important role in aporphine synthesis, it has been also limited by low yield (Kupchan and Liepa, 1973). Kupchan *et al.* reported the conversion of monophenolic benzylisoquinolines (58) in an attempt to develop intramolecular coupling method.



(58) (59)

A variety of oxidizing agents were determined, such as cobalt trihydroxide in 10% sulfuric acid solution, ceric sulfate in 10% sulfuric acid solution, and vanadium oxytrifluoride in trifluoroacetic acid solution. The most effective condition to promote coupling of monophenolic benzylisoquinolines (58) was molybdinum perchlorate in trifluoroacetic acid-chloroform solution (Kupchan *et al.*, 1978).

Nonphenolic oxidative coupling was studied by Taylor *et al.* (1977). Nonphenolic oxidation of *N*-methyltetrahydrobenzylisoquinolines (60) can be performed in good yield using thallium tristrifluoroacetate (TTFA). Thus treatment of the benzylisoquinoline (60) with TTFA at -40 ^{o}C led to a 46% yield of ocoteine (61).



(60) (61)

2.2 Pschorr cyclization

Pschorr reaction was applied to synthesize aporphines by nucleophilic attack of the C-8 on the isoquinoline ring to the aromatic benzyl cation derived from the corresponding diazonium salt.

In 1971, Kametani *et al.* reported the Pschorr cyclization of aminobenzylisoquinoline (62) in acid solution of 10% sodium nitrite gave thalicsimidine (64) *via* diazonium aryl intermediate (63).

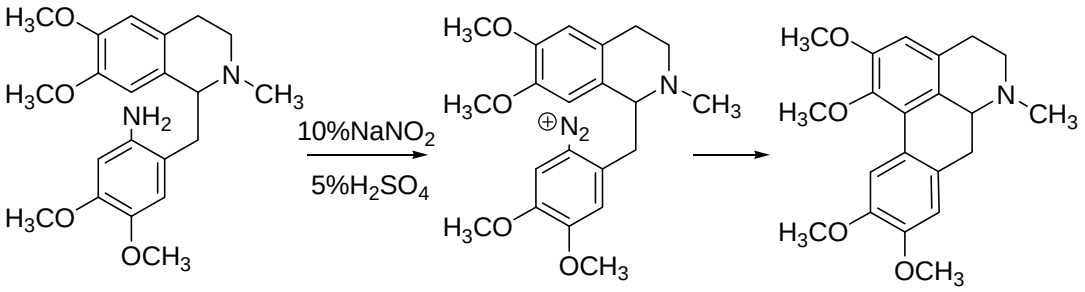
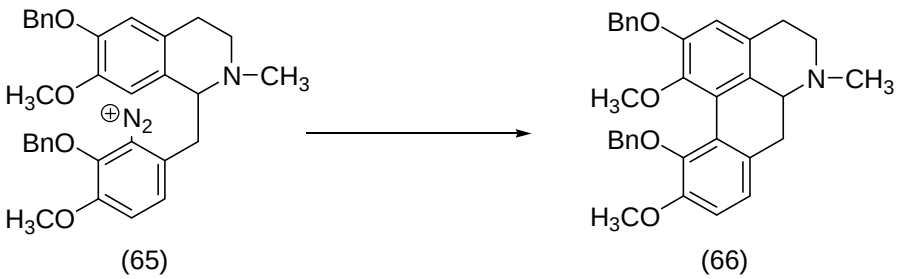
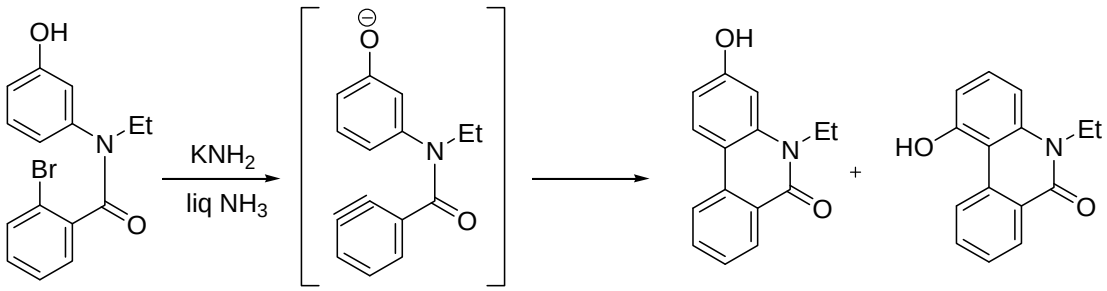


Photo-Pschorr, an improved Pschorr reaction, was used for aporphine preparation. Kametani *et al.* (1971) reported a comparison of thermal and photo-Pschorr methods. For the thermal-Pschorr cyclization, the diazonium isoquinoline (65) was decomposed at 70 ^{o}C in dilute sulfuric acid to give aporphine (66) in 9.1% yield. By the second method, the photolytic decomposition of diazonium (65) yielded aporphine (66) up to 27.2%. A comparison showed clearly that photolytic method is more suitable to prepare the aporphine than the thermal decomposition method.



2.3 Benzyne cycloaddition

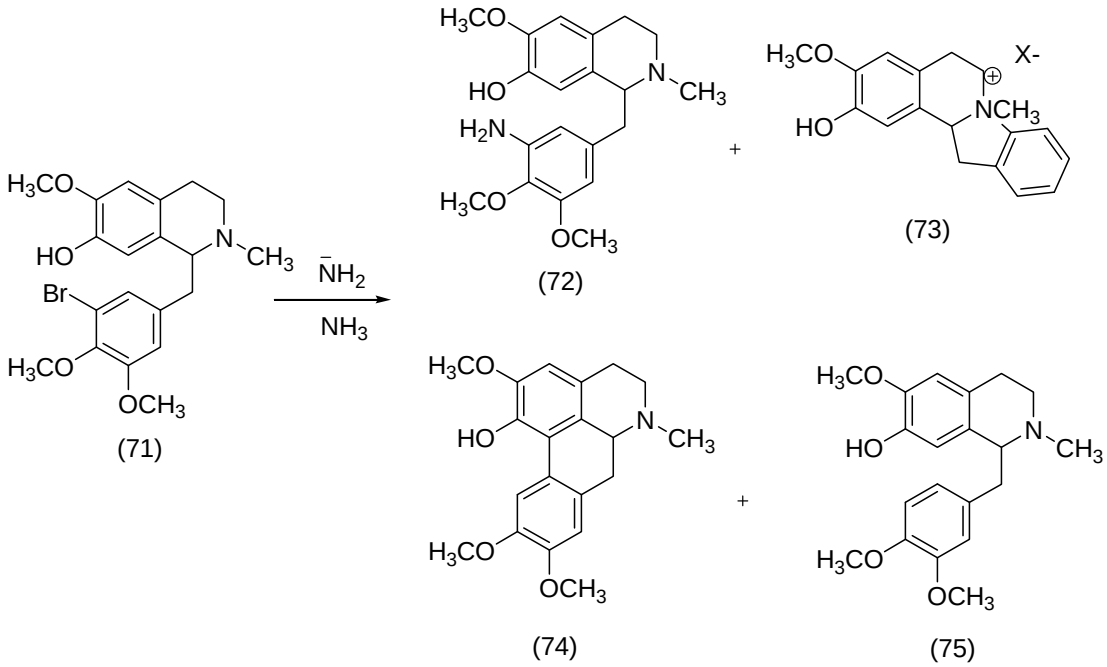
In 1963, Hey *et al.* showed that intramolecular addition of nucleophillic aromatic side-chain to the benzyne intermediate (68) resulted in ring closure.



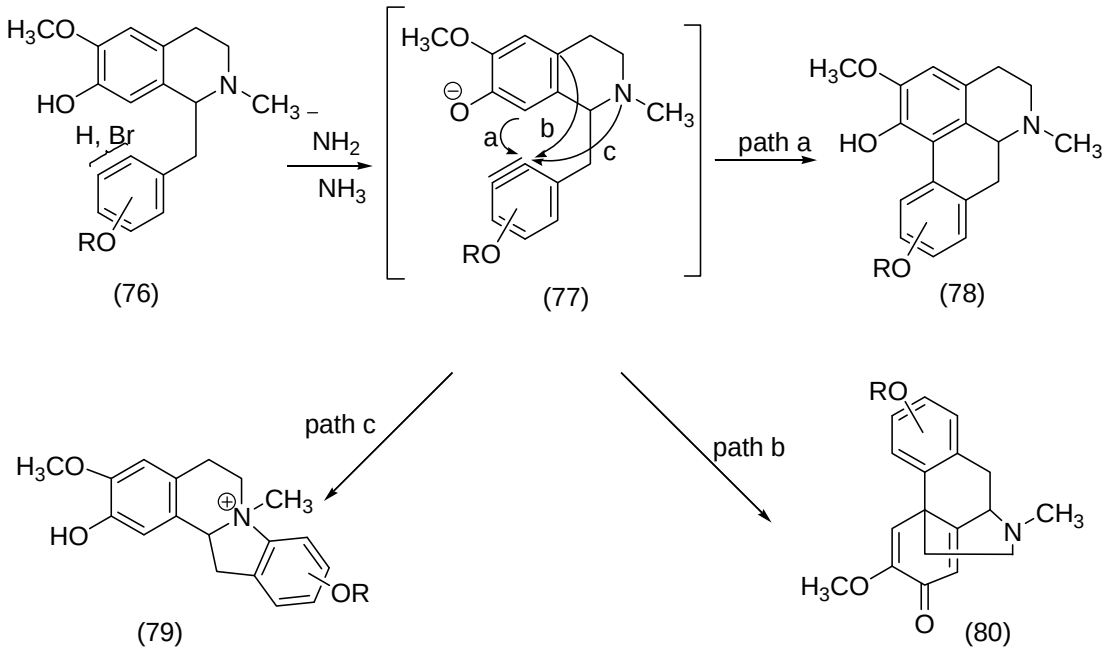
(67) (68) (69) (70)

Several groups have investigated the application of this coupling process to synthesize aporphine alkaloids by using the C-8 on the isoquinoline ring as a nucleophile.

In 1972, Tetsuji *et al.* reported the formation of aporphine by the benzyne reaction. Treatment of phenolic bromobenzylisoquinoline (71) with sodium amide in liquid ammonia afforded thaliporphine (74) as an aporphine alkaloid together with cryptaustoline (74), 1-(3,4-dimethoxybenzyl)- (75) and 1-(2-amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (72).



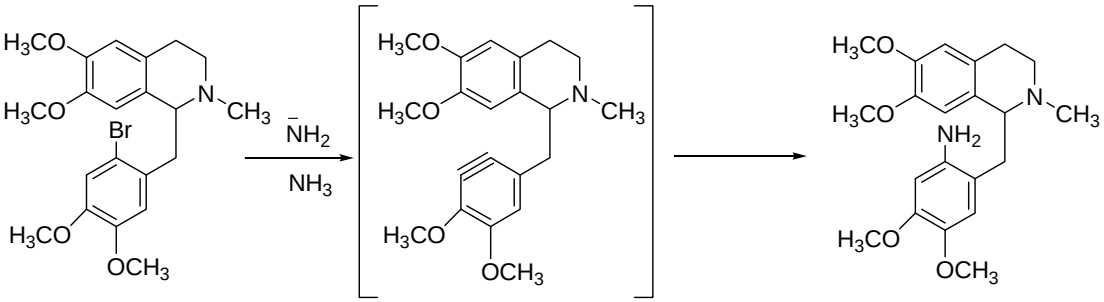
As Tetsuji and other research groups reported (Tetsuji *et al.*, 1972; Kametani *et al.*, 1972; Kametani *et al.*, 1973), more than one product was obtained from the benzyne cyclization process due to the competitive problem.



Only minor amounts of aporphine (78) were obtained by the formation of the primary aromatic amines (path a; the addition of ammonia to the aryne) due to the competition with morphinandienone (80) formation (path b; the *para* attack of the phenoxide on aryne) and the formation of indolizine derivative (79) (path c; the attack of the nucleophillic isoquinoline nitrogen on the aryne).

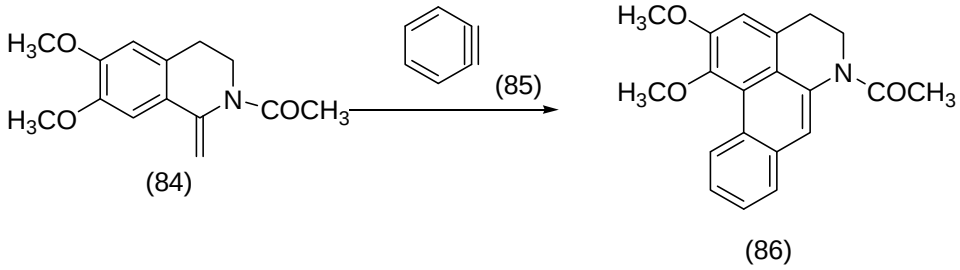
In the most cases the major cyclized products were the indolizine derivatives. Therefore, if the cyclization process is used for synthesis of aporphine, the isoquinoline nitrogen must be protected during the cyclization in order to prevent indolizine formation.

It is necessary to have a phenolic function on ring A of benzylisoquinoline for the construction of aporphine *via* intramolecular benzyne reaction unless the benzylisoquinoline do not undergo the cyclization. For instance, treatment of bromolaudanosine (81) with potassamide in liquid ammonia afforded aminolaudanosine (83) instead of directly converted aporphine product. (Ahmad and Gibson, 1975).



(81) (82) (83)

Generally, intramolecular benzyne cyclization gave aporphinoids in quite low yields. In 1982, intermolecular benzyne cycloaddition (IBC) was developed to synthesize aporphine by using benzyne as dienophile and *N*-protected methylene isoquinoline as diene. Castedo reported the synthesis of dehydroaporphine alkaloid (86) by IBC between benzyne (85) and 1-methylene isoquinoline (84) (Castedo *et al.*, 1982).

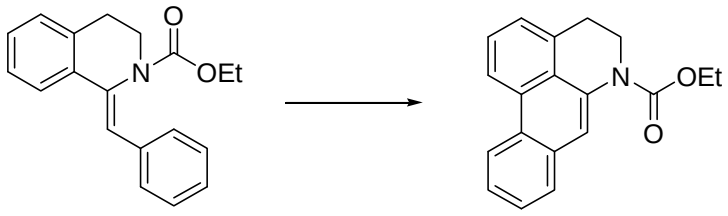


(84) (86)

After Castedo *et al.* completed aporphine construction using the IBC reaction, this cyclization method was applied to synthesize many aporphine-type alkaloids such as dehydronoraporphines, oxoaporphines (Saa *et al.*, 1985) and 13-substituted 8-oxoprotoberberines (Saa *et al.*, 1986).

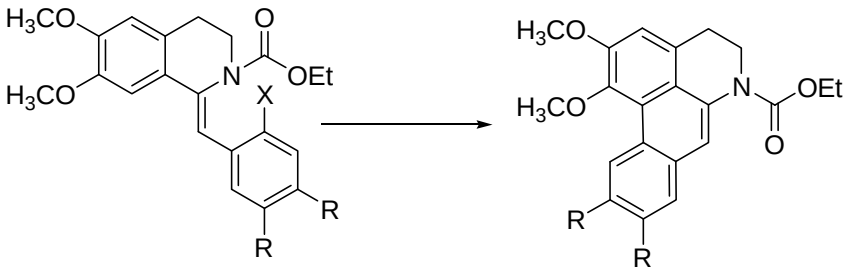
2.4 Photocyclization reaction

In 1966, Cava *et al.* first reported a new synthetic route of aporphine alkaloids by utilizing of enamide photocyclization. Ultraviolet irradiation of benzylidene isoquinoline (87) in ethanol in the presence of iodide as oxidant afforded dehydronornuciferine (88) in 15% yield.



(87) (88)

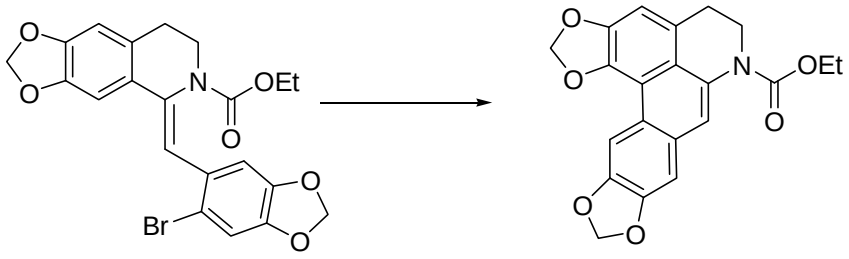
Non oxidative photocyclization of a halogenated stilbene was carried out in 1970. The dehydroaporphines (91 and 92) were synthesized in 32% and 24% yields, respectively by photolysis of halogenated stilbene-type precursor (89 and 90) in the presence of calcium carbonate as an acid scavenger but in an absence of any added oxidants (Cava *et al*., 1970).



89, X = Cl; R = H
90, X = Br; R = OCH3

91, R = H
92, R = OCH3

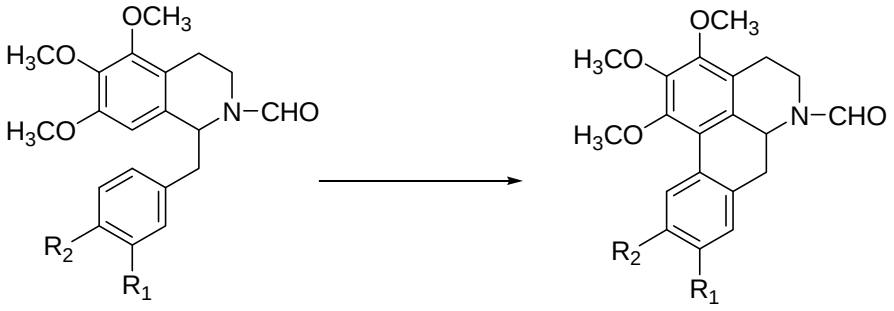
Cava *et al.* (1973) improved non-oxidative photocyclization by substitution of potassium *t*-butoxide for calcium carbonate as the base. The high yield (72%) of dehydroaporphine (94) from benzylidene isoquinoline (93) is achieved by using this condition.



(93) (94)

2.5 Hypervalent iodide

Pingaew and Ruchirawat (2007) reported the synthetic application of [bis(trifluoroacetoxy)iodo] benzene (BTI) for synthesis of aporphine alkaloids. The results showed that it is important to have the alkoxy group at the C-5 position on the tetrahydroisoquinoline nucleous in order to avoid participation of nitrogen free electron pair. Biarylation of **95** and **96** containing 5-alkoxy group with BTI–BF_3.OEt_2 gave *N*-formylaporphine (98 and 99) in 72% and 67% yield, respectively.

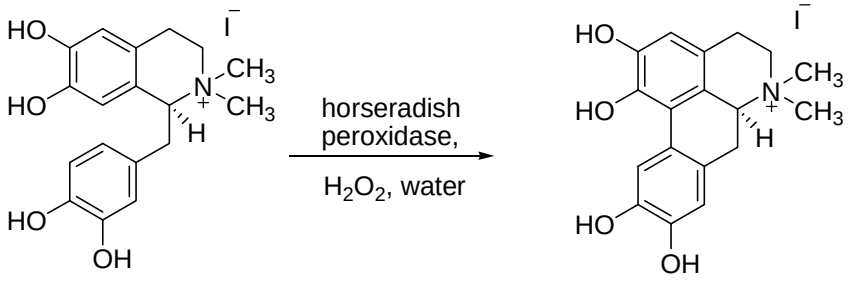


95, R_1=R_2 =OMe
96, R_1=R_2 = OCH_2O

98, R_1=R_2 =OMe
99, R_1=R_2 = OCH_2O

2.6 Enzymatic oxidative coupling

Enzymatic coupling of tetrahydrobenzylisoquinolines was an efficient purely chemical method in the preparation of aporphines. Horseradish peroxidase coupling of (+)-laudanosoline methiodide (100) at neutral pH gave a 60% yield of the corresponding aporphine (101). The reaction proceeds with retention of configuration (Brossi *et al.*, 1973).



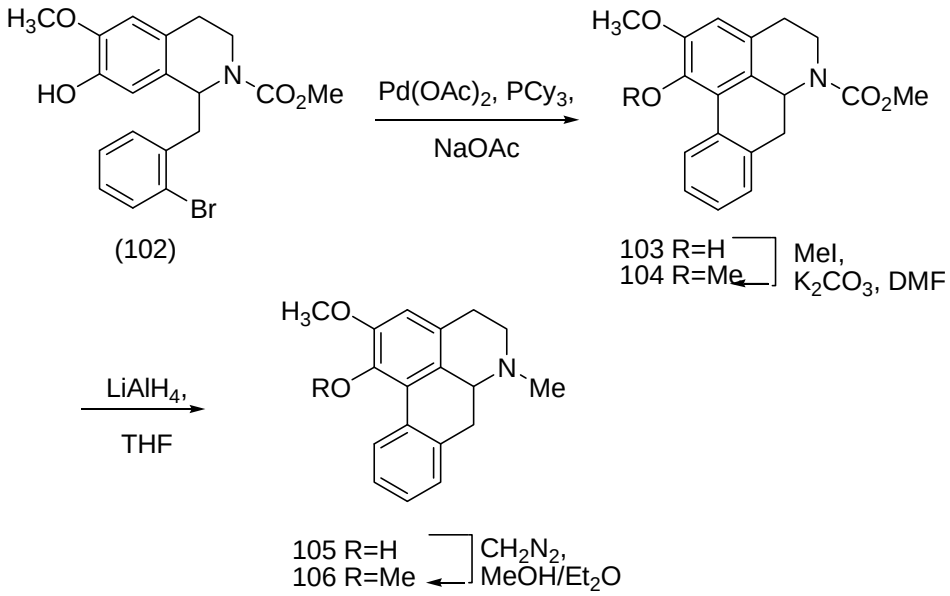
(100) (101)

2.7 Palladium-catalyzed arylation reaction

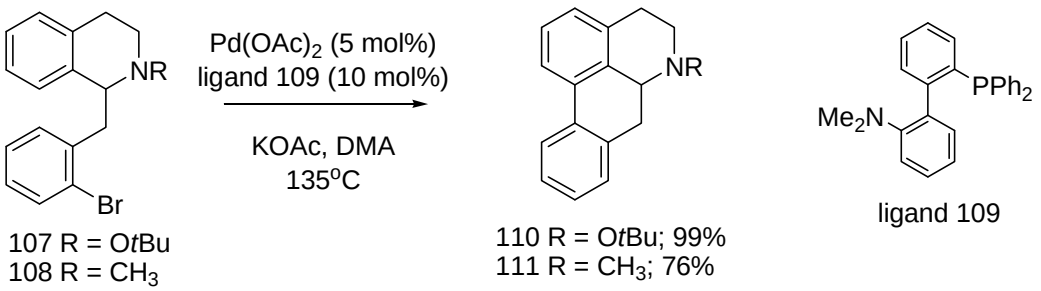
Carbon-carbon bond forming reactions based on transition metal catalysis have been developed as a powerful tool for construction of complex molecules. The most prominent reactions are the reaction catalysed by palladium.

Cuny reported a palladium-mediated intramolecular phenol *ortho*-arylation reaction for aporphine alkaloids construction. This methodology was

employed in the syntheses of two aporphine alkaloids, (±)-lirinidine (105) and (±)-nuciferine (106) (Cuny, 2003).



In 2004, Lafrance *et al*. reported a catalyst system for preparation of aporphine alkaloids (110 and 111) *via* the direct arylation of unactivated substrates (107 and 108). The optimal condition was obtained with 5 mol% $Pd(OAc)_2$, 10 mol% 2-(diphenylphosphino)-2'-(*N,N*-dimethylamino)-biphenyl (109) and 2 equivalents of KOAc in DMA at 135 ^{o}C.

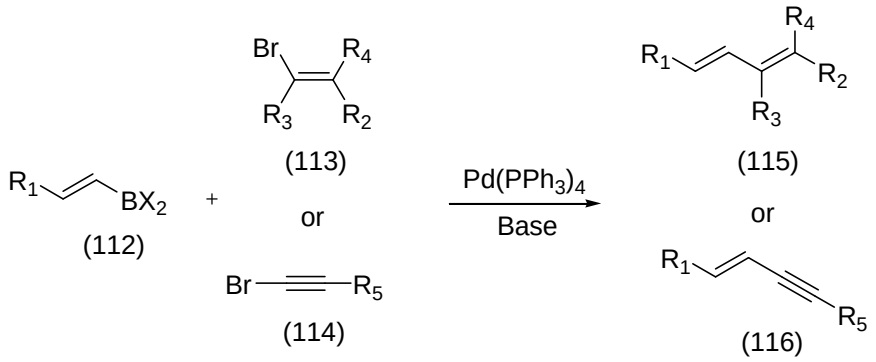


This methodology avoided the need to use activating groups on the arene moiety and high catalyst loading. Moreover, the yield obtained from this method was higher than previous report (Cuny, 2003).

3. Suzuki Reaction

The Suzuki reaction, also known as the Suzuki-Miyaura cross coupling reaction, is broadly defined as the palladium-catalyzed cross coupling of organoboron with organic halides under basic condition.

In 1979, Miyaura *et al.* first published the palladium-mediated coupling of alkenyl (113) or alkynyl (114) halides with alkenylboranes (112) to give corresponding conjugated dienes (115) or enynes (116).

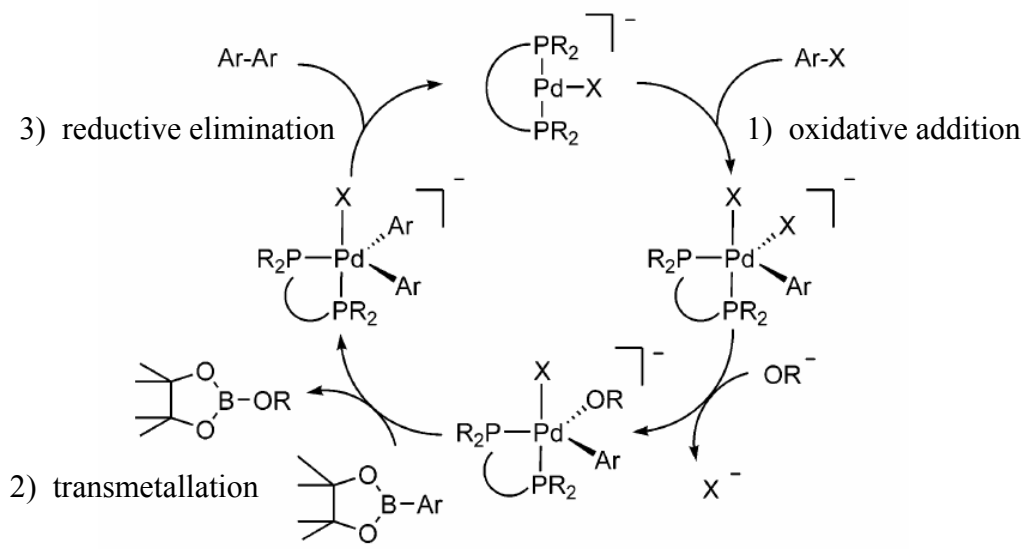


Subsequent research by the Suzuki group and many others resulted in vast improvements in the Suzuki reaction. Recently, it is one of the most reactions in the carbon-carbon bond construction, and in particular biaryl bonds formation.

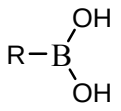
The Suzuki reaction conditions have been developed such that the scope of the reaction has expanded enormously. It is now possible to conduct the reaction at room temperature, using aryl chloride substrate, with extremely low catalyst loading (Barder *et al.*, 2005), under ligand-free condition (Klingensmith and Leadbeater, 2003), in water using microwave irradiation (Leadbeater and Marco, 2002) and in the absence of transition metal catalysts (Leadbeater and Marco, 2003).

Such extensive research into the Suzuki reaction revealed a highly complex reaction mechanism that proceeds through three main steps: 1) the oxidative addition of palladium to the carbon electrophile to form the organo-palladium species; 2) the

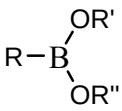
transmetallation of a nucleophillic carbon from boron; 3) the reductive elimination to obtain the desired product and restore the palladium catalyst (Nising *et al.*, 2004).



Boronic acid (117) and boronic ester (118) are important building blocks in the Suzuki-Miyaura coupling reaction. They act as a predominant intermediate in transmetallation of the coupling process. Recently, several procedures for the preparation of organoboron compounds have been reported.



Boronic acid
(117)

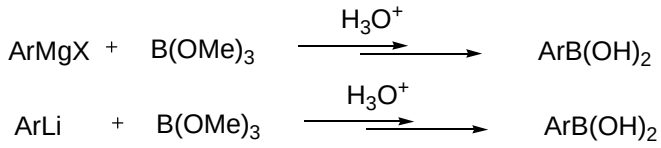


Boronic ester
(boronate ester)
(118)

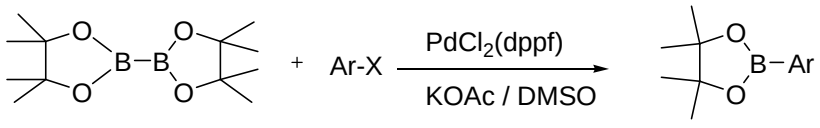
Hydroboration of alkene and alkyne is an established preparative method of alkyl- and alkenylboranes (Tsuji, 2004). Hydroboration proceeds through an *anti*-Markovnikov addition in quantitative yield. The reaction is useful for the synthesis of stereodefined alkenylboronic acid and their ester (Miyaura and Suzuki, 1995).

Arylborane, arylboronic acid and their ester (boronate) are prepared from the aryllithium or Grignard reagent (Tsuji, 2004). An appropriately protected aryl halide

is transformed to aryllithium or Grignard reagent at low temperature, followed by a trialkylborate to quench the organometallic, and finally hydrolysis of the boronic ester with aqueous hydrochloric acid (Miyaura and Suzuki, 1995).

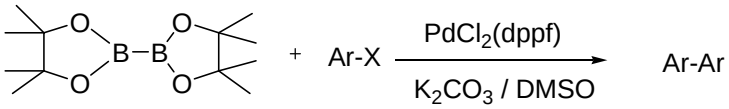


In 1995, Miyaura and Suzuki developed the synthesis of aryl boronates by transition metal catalysis. The palladium-catalyzed coupling reaction of the pinacol ester of diboron (119) and aryl halide (120) for preparing arylboronic ester (121) was reported.



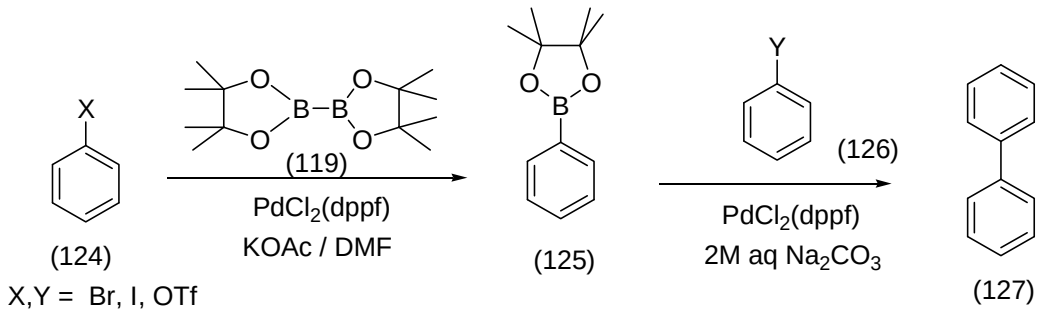
(119) (120) (121)

In the course of optimizing the reactions, Miyaura's group found that the KOAc was the best base in term of yield and selectivity. Stronger bases such as K_3PO_4 and K_2CO_3 afforded the aryl boronate along with substantial amounts of symmetrical biaryl by product (123).

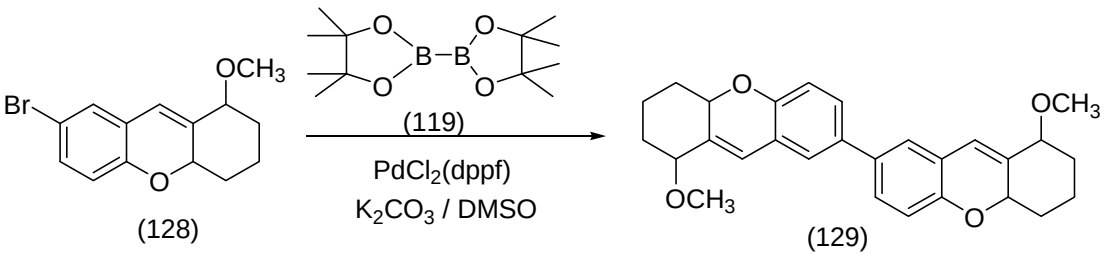


(119) (122) (123)

The reaction using the stronger bases such as K_2CO_3 performs arylboronic ester and immediately continues to a Suzuki coupling step to yield the corresponding biaryl. In 1997, Giroux *et al.* reported a method for a one-pot preparation of biaryl (127) *via* a modified *in situ* Suzuki cross-coupling reaction using diborane (119).

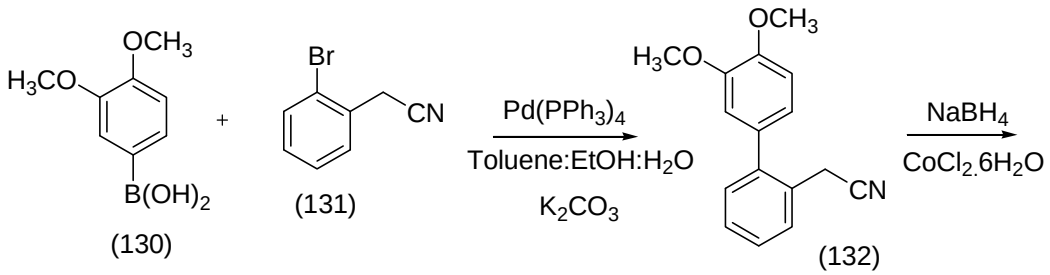


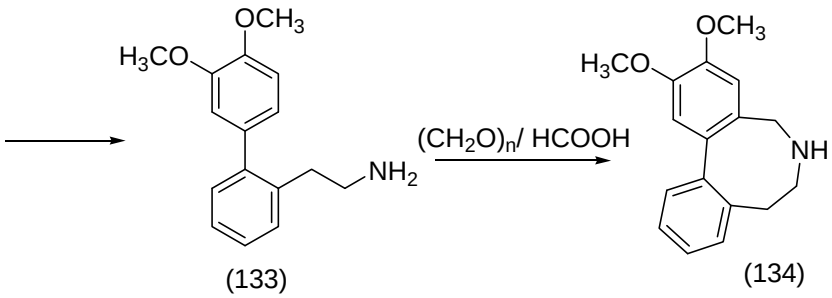
In the following studies, Nising *et al.* optimized the reaction conditions for transforming haloarenes into symmetrical biaryls and first applied one-pot Suzuki reaction to synthesize bisxanthene (129) (Nising *et al.*, 2004).



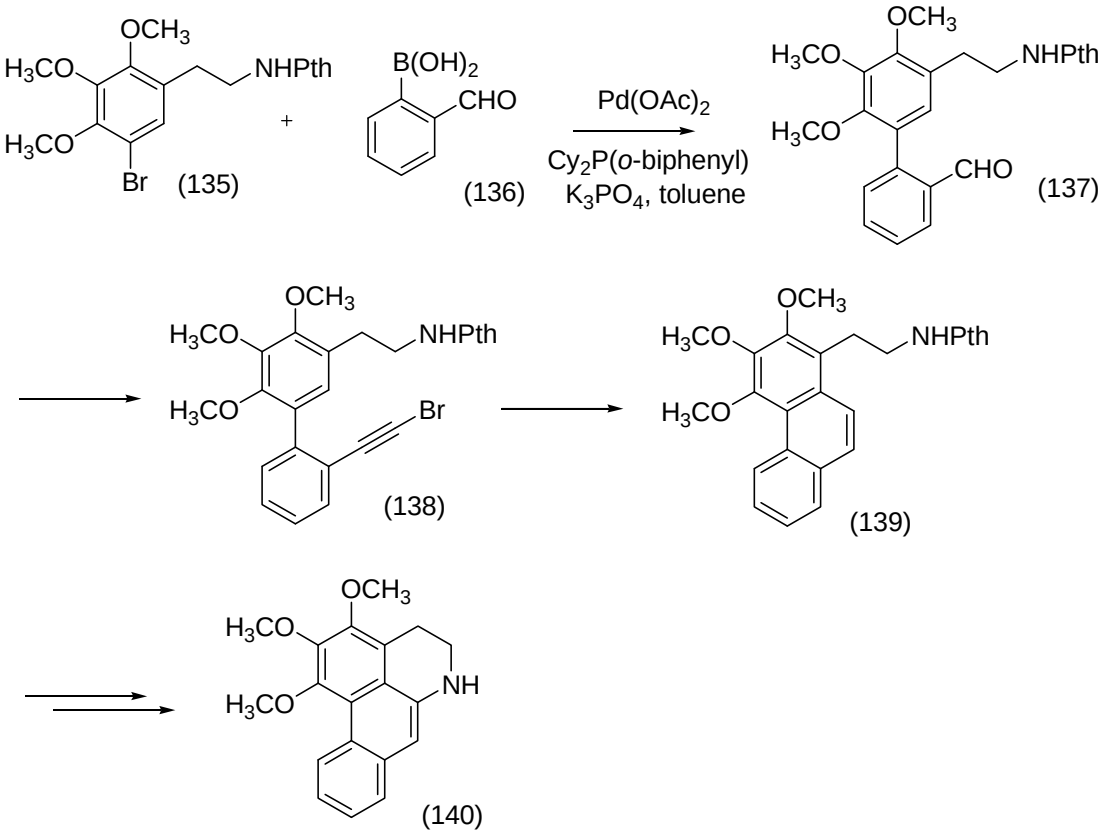
Extensive investigation revealed that the best reaction proceeds in polar solvents such as DMSO, DMF or DMA, while $Pd(OAc)_2$ and $(Ph_3P)_2PdCl_2$ are suitable catalysts to effect the transformation. However, these reaction conditions seem not to be appropriate for every substrate (Tsuji, 2004).

In 2003, Sahakitpichana and Ruchirawata reported an efficient three-step total synthesis of buflavine (134) using Suzuki coupling reaction. Biarylacetonitrile (132) was synthesized using Suzuki coupling, followed by construction of the eight-membered *N*-heterocyclic ring to afford buflavine (134).



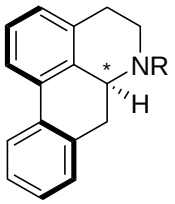


Fürstner and Mamane (2003) reported the synthesis of aporphine skeleton using Suzuki biaryl coupling, followed by cyclization to obtain an aporphine skeleton. Suzuki coupling reaction was performed to give biphenyl carboxaldehyde (137), which was converted to bromoalkyne (138). Carbocyclization of **138** gave phenanthene core (139), followed by intramolecular amination reaction to afford *O*-methyl-dehydroisopiline (140).

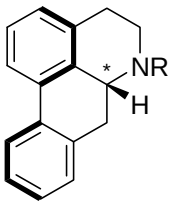


4. Absolute Configuration of Aporphine Alkaloids

The absolute configuration of aporphine alkaloid was first considered by Bentley and Cardwell in term of *α*- or *β*- orientation of the hydrogen atom attached to the asymmetric carbon (C-6a). They found that aporphine alkaloid possessed a permanently twisted biphenyl system and the chirality was determined by the absolute configuration of the asymmetric carbon atom. In terms of the Cahn-Ingold-Prelog convention, the biphenyl system of **141** belongs to (*S*)-series, while the (*R*)-notation must be attributed to the antipode **142** (Bentley and Cardwell, 1955).



(141)



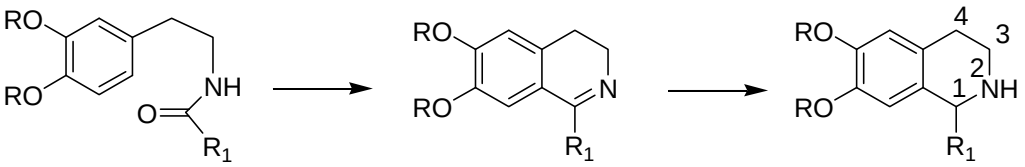
(142)

The absolute configuration of an aporphine may be simply determined by the sign of its specific rotation. If an aporphine is dextrorotatory, the absolute configuration is represented by **141**, while if it is levorotatory, its absolute configuration is as in **142** (Shamma, 1962).

5. Asymmetric Isoquinoline Synthesis

In order to synthesize the chiral aporphine alkaloids, it is important to control the stereogenic center of benzylisoquinoline due to the benzylisoquinoline serving as a key intermediate for aporphine synthesis. The most frequently used strategy for asymmetric synthesis of isoquinoline alkaloids is an asymmetric reduction through a Bischler-Napieralski cyclization.

In the Bischler-Napieralski cyclization, *β*-arylethylamide (143) was cyclized to 1-substitued 3,4-dihydroisoquinoline (144), which was then reduced in the next step to the 1,2,3,4-tetrahydro derivative (145).

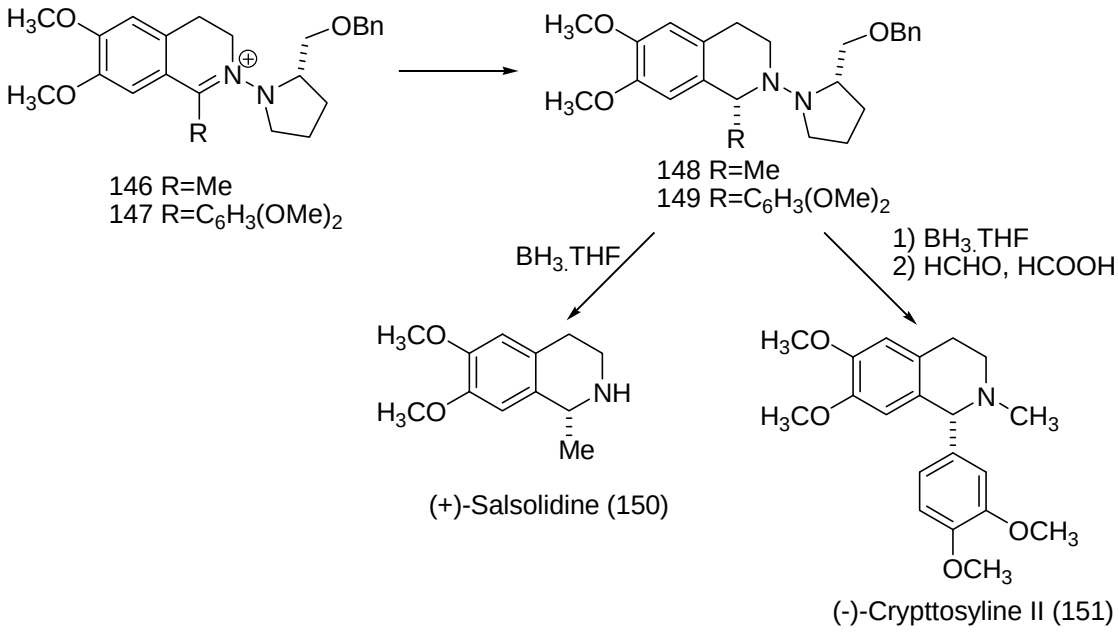


(143) (144) (145)

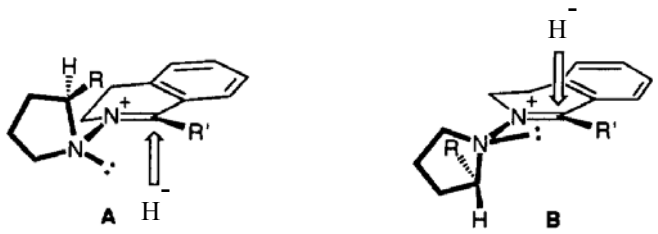
The reduction process is a crucial step for stereochemical outcome of the synthesis because it creates a stereogenic center. Methods to control stereogenic C-1 center of isoquinoline are generally based on two approaches: the transfer of asymmetry from a chiral auxiliary or through chiral reducing agents (Chrzanowska and Rozwadowska, 2004).

5.1 Chiral auxiliary mediated asymmetric synthesis

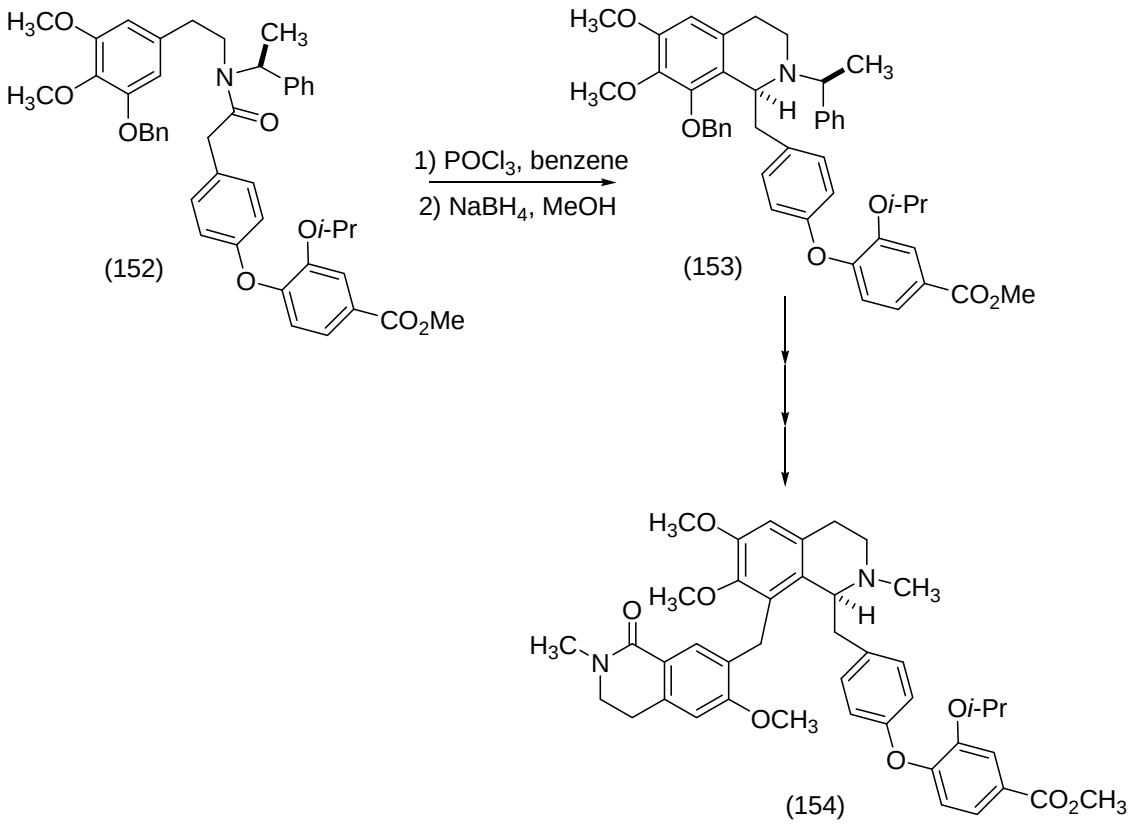
Suzuki *et al.* devised a general procedure for preparing diastereoselective pure of 1-substituted tetrahydroisoquinolines *via* asymmetric addition of hydride to hydrazonium ions. This methodology was applied to asymmetric synthesis of isoquinoline alkaloids, (+)-salsolidine (150) and (-)-crypttosyline II (151). Reduction of **146** and **147** by sodium borohydride afforded tetrahydroisoquinoline (148 and 149) with excellent diastereoselectivity (90-96%). Reductive N-N bond cleavage converted 148 and 149 into (+)-salsolidine (150) and (-)-crypttosyline II (151), respectively (Suzuki *et al*., 1995).



The perpendicular approach of the hydride ion to the azeomethine group should preferably occur from the sterically less shielded bottom face of the favored conformer A leading to isomer **148** and **149**. The alternative conformer B is disfavored because of steric repulsion between the *R* in the pyrrolidine ring and the C-3 methylene group in the dihydroisoquinoline.



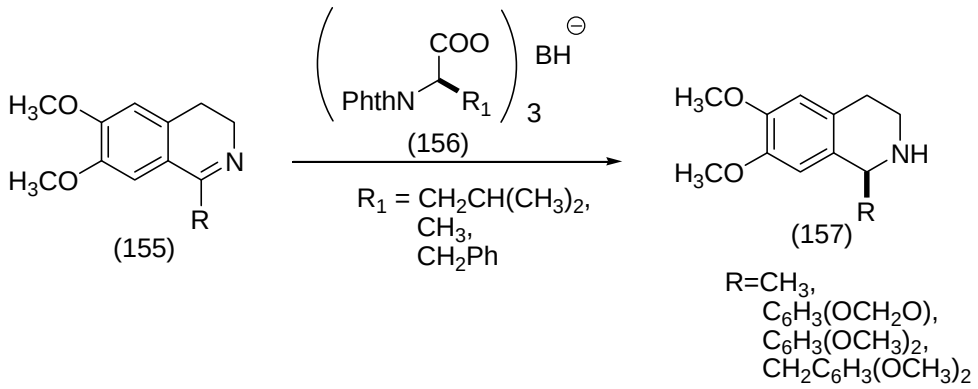
(*S*)-α-Methylbenzylamine was found to be a very efficient chiral auxiliary and was applied in the first enantioselective total synthesis of the (-)-tejedine (154). Cyclization of **152** using Bischler-Napieralski conditions, followed by $NaBH_4$ reduction afforded the desired regioisomer of tetrahydroisoquinoline (153) in 40% yield with 99% de (Wang and Georghiou, 2002).



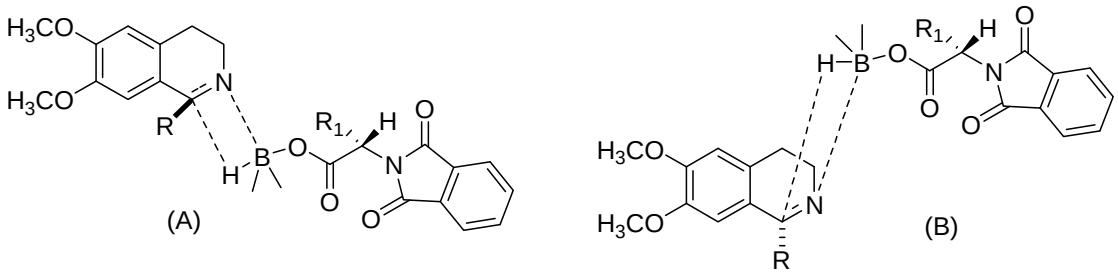
5.2 Reduction by using chiral hydride reducing agents

An alternative approach for synthesis of chiral tetrahydroisoquinolines *via* the Bischler-Napieralski cyclization is based on the use of chiral reducing agents to reduce stereoselectively the C=N bond in 3,4-dihydrointermediate.

Chiral nonracemic asymmetric reducing agents have been used for the reduction of prochiral cyclic imines to the corresponding enantiomerically enriched alkaloids. In 1999, Hajipour and Hantehzadeh reported the asymmetric synthesis of isoquinoline (155) by using chiral sodium triacyloxy borohydrides (156).

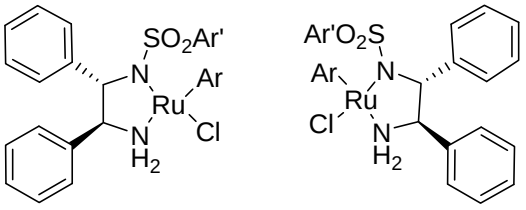


The enantiomeric excess of (*S*)-157 was determined to be 65-75% ee. The (*S*)-selectivity was postulated to arise from preferential transition state A. In the transition state, the *si*-face (transition state B) is more steric hindrance than the *re*-face (transition state A). Therefore, the addition of hydride to the borane-chelated form should occur in the least sterically transition state A of the cyclic imines (Hajipour and Hantehzadeh, 1999).



Catalytic asymmetric transfer hydrogenation has become a useful tool to obtain optically active compounds. The reaction uses inexpensive reagents and is usually easy to perform, compared with the typically used expensive and hazardous reagents such as borane reagents.

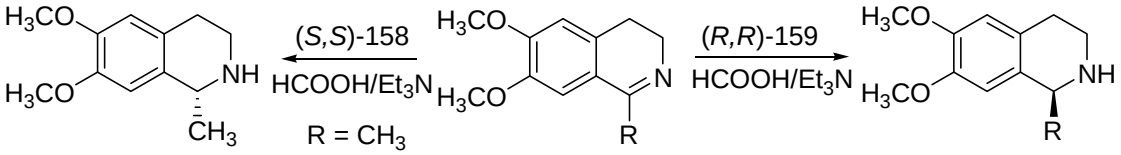
In 1996, the first asymmetric transfer hydrogenation of imine using chiral *N*-sulfonated diamine ruthenium complexes (158 and 159) with formic acid-triethylamine mixture was reported by Noyori *et al*.



(*S*,*S*)-158 (*R*,*R*)-159

Ar = *p*-cymene, benzene, cyclopentadiene
Ar' = 4-MeC_6H_4, 2,4,6-$Me_3C_6H_2$, 1-naphtyl

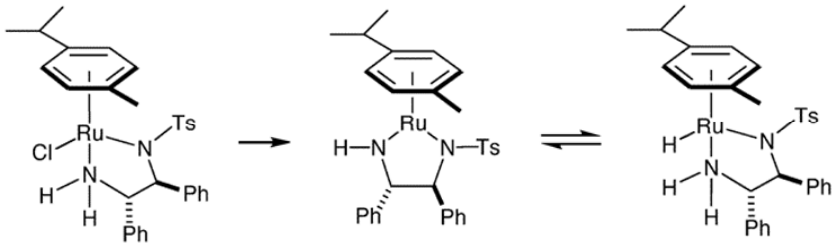
This catalytic method is particularly useful for the enantioselective reduction of cyclic imines to amines. Several isoquinoline alkaloids were prepared in high yield with an enantiomeric excess value ranging from 90% to 95%, starting from cyclic amine 161 (R=CH_3, $CH_2C_6H_3(CH_3)_2$, $(CH_2)_2C_6H_3(OCH_3)_2$ and $C_6H_3(OCH_3)_2$.



(160) (161) (162)

The results showed that the stereochemistry of the catalyst determined stereochemistry of amine products (160 and 162). The amine with (1*R*) isomer (160) was obtained when the (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylamine ((*S*,*S*)-TsDPEN) was applied, whereas the (1*S*) configuration (162) were obtained when (*R*,*R*)-TsDPEN was used (Noyori *et al*, 1996).

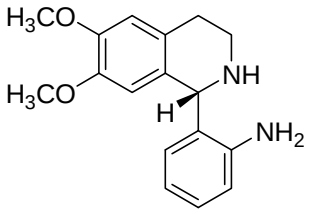
Extensive research in single-crystal X-ray analysis of the catalyst precursor (163), the true catalyst (164) and the reactive intermediate (165) gave much understand in Ru(II)-promoted asymmetric transfer hydrogenation (Haack *et al.*, 1997).



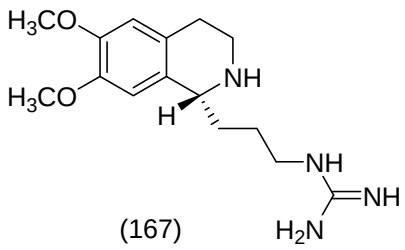
(163) (164) (165)

The true catalyst (163) (16-electron) was formed by treatment of the catalyst precursor (163) (18-electron) with a strong base. The strong base was required for irreversible elimination of HCl. Complex **163** was then shown to form the reactive intermediate (165) as a stable ruthenium hydride on treatment with formic acid.

The same catalytic system has been successful applied to synthesize many tetrahydroisoquinoline in high yield with a high level of enantioselectivity. (*S*)-1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (166) was obtained with 98% ee by using (*S*,*S*)-**158** (Ar = benzene, Ar′= 1-naphthyl) (Vedejs *et al.*, 2009). Moreover, ruthenium complex (*S*,*S*)-**158** was applied to synthesize (+)-crispine E (167) in good yield with 89% ee (Czarnocki *et al.*, 2008).



(166)



(167)

The Ru(II)-promoted asymmetric transfer hydrogenation conditions have been developed to expend the scope of the reaction. For example, Ru (II) catalyst was modified to be a water-soluble catalyst for an asymmetric transfer hydrogenation in water (Wu *et al.*, 2006). In addition, asymmetric transfer hydrogenation over Ru–TsDPEN catalysts supported on siliceous mesocellular foam was studied to employ practical and environmental friendly reaction (Xiaohua and Ying, 2007).

MATERIALS AND METHODS

Materials

Instrument

The following analytical methods were used throughout this work, unless otherwise indicated.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Gemini 300 spectrophotometer. Chemical shifts were recorded as δ values in ppm. Spectra were acquired in $CDCl_3$ unless otherwise stated. The peak due to residual $CHCl_3$ (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C) was used as the internal reference. Coupling constants (*J*) are given in Hz, and multiplicity is defined as follows: br = broad, s = singlet, d = doublet, dd = doublet of doublet, dt = double of triplet, t = triplet, q = quartet, m = multiplet.

Infrared (IR) spectra were recorded in cm^{-1} on a Perkin-Elmer 2000 Fourier transform infrared spectrophotometer at the Chemistry Department, Faculty of Science, Kasetsart University. Samples were analyzed as KBr disks.

Mass spectra (MS) were obtained from Department of Chemistry, Faculty of Science, Mahidol University. Accurate masses (HRMS) were obtained from PERCH Mass Spectrometry Research Laboratory, Department of Chemistry, Faculty of Science, Chiang Mai University.

Melting points (m.p.) were determined on a Mel-Temp electrothermal apparatus at the Chemistry Department, Kasetsart University and are reported uncorrected in ^{o}C.

Specific rotations were determined on a JASCO P-1010 polarimeter at the Chemistry Department, Faculty of Scienece, Silpakorn University.

Chromatographic system

Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatograms were visualized under a 254 nm UV lamp and/or by spraying with a solution of vanillin (3% in ethanol with 3% sulfuric acid) followed by heating.

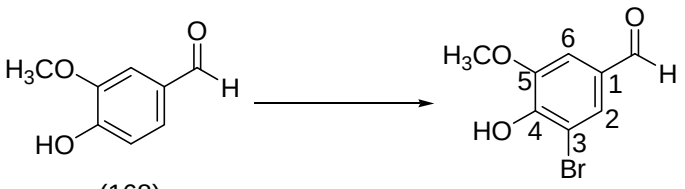
Flash column chromatography was conducted according to the method of Still and co-workers (1978) using silica gel 60 (mesh size 0.040-0.063 mm). Column chromatography was performed on silica gel 60 (70-230 mesh, Merck) and the column was packed by slurry method.

Chemical reagents

Analytical grade solvents and reagents used for synthesis were obtained from local commercial outlets. Dry tetrahydrofuran (THF) was freshly distilled under N_2 from sodium with benzophenone ketyl as an indicator. Dichloromethane was dried over anhydrous calcium chloride and distilled from calcium hydride immediately before use.

Methods

Bromovanillin (169)



(168) (169)

To a cool solution of vanillin (168) (1.5 g, 9.86 mmol) in 3 mL of gracial acetic acid was added rapidly bromine (0.55 mL, 9.86 mmol) in 2 mL of gracial acetic acid. After being stirred at room temperature for 1 h, the reaction mixture was added with water to crystallize the 5-bromovanillin (169) out. Purification by flash column chromatography (40% ethyl acetate/hexane) gave bromovanillin (169) (2.1 g, 95%). Recrystallization of **169** from ethanol gave a white crystal, m.p.163-164 ^{o}C.

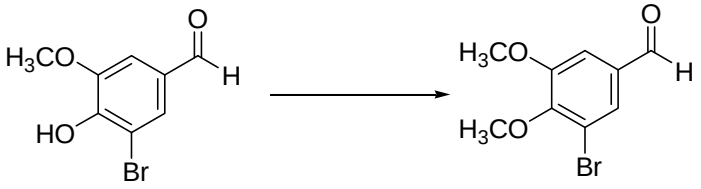
FTIR (KBr), υ_{max}, cm^{-1}: 3298 (O-H), 1675 (C=O), 1590 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.80 (s, 1H, CHO), 7.69 (d, *J*=1.8 Hz, 1H, H-2), 7.43 (d, *J*=1.7 Hz, 1H, H-6), 3.95 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 189.7 (CHO), 150.0 (C-3), 148.8 (C-1), 130.1 (C-5), 128.9 (C-2), 109.4 (C-6), 108.8 (C-4), 56.2 (OCH_3).

MS (EI), *m/z* (relative intensity): 230 (M^+, 100), 229 (82).

3-Bromo-4,5-dimethoxybenzaldehyde (170)



(169) (170)

Method I

To a suspension of bromovanilin (169) (2 g, 8.65 mmol) and potassium carbonate (1.79 g, 12.9 mmol) in acetone (100 mL) was added iodomethane (2.16 mL, 34.51 mmol). After refluxing for 6 h, the reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The combined organic layer was dried over anhydrous sodium sulfate, filterated and evaporated under reduced pressure to dryness. The crude product was further purified by silica gel flash column chromatography with 1:1 dichloromethane: hexane as eluent. The product was a white solid with an isolated yield of 0.96 g, 92%, m.p. 158-159 ^{o}C.

Method II

To a stirred solution of bromovanilin (169) (2 g, 8.65 mmol) in dichloromethane (20 mL) was added dropwise a solution of sodium hydroxide (830 mg, 20.8 mmol) and *n*-butylammonium iodide (3.8 g, 10.4 mmol) in water (20 mL) at room temperature. The iodomethane (0.82 mL, 12.9 mmol) was added to above mixture and then refluxed for 5 h. The reaction mixture was acidified with 10% aqueous hydrochloric acid. The combined organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. Purification by flash chromatography (30% ethyl acetate/hexane) gave 3-bromo-4,5-dimethoxy benzaldehyde (170) (1.93 g, 91%), m.p. 158-159 ^{o}C.

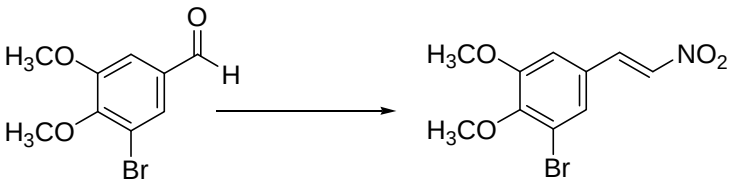
FTIR (KBr), υ_{max}, cm^{-1}: 1675 (C=O), 1590 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.82 (s, 1H, CHO), 7.63 (d, *J*=1.8 Hz, 1H, H-2), 7.37 (d, *J*=1.8 Hz, 1H, H-6), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 189.8 (CHO), 154.2 (C-3), 151.8 (C-1), 133.0 (C-5), 128.7 (C-2), 117.9 (C-4), 110.1 (C-6), 60.8 (OCH_3), 56.2 (OCH_3).

MS (EI), *m/z* (relative intensity): 244 (M^+, 100), 243 (19).

1-Bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171)



(170) (171)

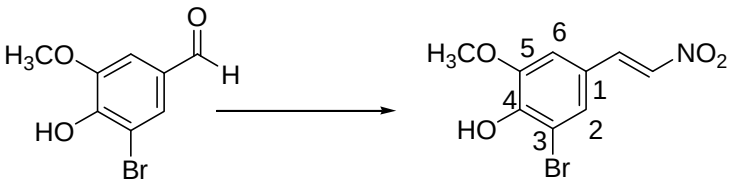
To a suspension of 3-bromo-4,5-dimethoxybenzaldehyde (170) (200 mg, 0.82 mmol) and ammonium acetate (138 mg, 1.79 mmol) in acetic acid (2 mL) was added nitromethane (0.44 mL, 8.17 mmol). After sonication for 9 h, the solid was filtered off and partitioned between ethyl acetate and water. The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. Purification by flash chromatography (5% ethyl acetate/ hexane) gave 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (168 mg, 71%). Recrystallization from ethanol gave **171** as a yellow needle, m.p. 158-159 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1628 (C=C), 1556, 1354 (NO_2).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.80 (d, *J*=13.6, 1H, ArC<u>H</u>=CHNO_2), 7.30 (d, *J*=13.6, 1H, ArCH=C<u>H</u>NO_2), 7.19 (s, 1H, H-2), 6.91 (d, *J*=2.0, 1H, H-6), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 154.0 (C-3), 149.7 (C-1), 137.5 (Ar<u>C</u>H=CHNO$_2$), 137.1 (ArCH=<u>C</u>HNO$_2$), 126.8 (C-5), 126.2 (C-2), 118.4 (C-4), 111.5 (C-6), 60.8 (OCH_3), 56.2 (OCH_3).

2-Bromo-6-methoxy-4-(2-nitrovinyl)phenol (172)



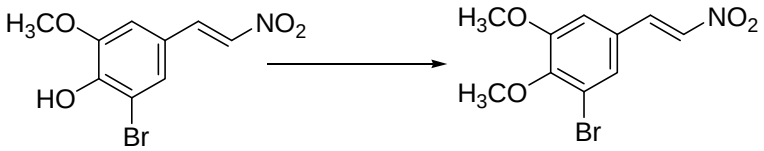
(169) (172)

To a suspension of bromovanilin (169) (330 mg, 1.48 mmol) and ammonium acetate (242 mg, 3.14 mmol) in acetic acid (3 mL) was added nitromethane (0.77 mL, 14.3 mmol). After sonication for 10 h, the solid was filtered off and partitioned between ethyl acetate and water. The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. Purification by flash chromatography (10% ethyl acetate/hexane) gave 2-bromo-6-methoxy-4-(2-nitrovinyl)phenol (172) (331 mg, 68%). Recrystallization from ethanol gave **172** as a yellow needle, m.p. 190-191 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1630 (C=C), 1510, 1347 (NO_2).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.32 (s, 1H, CHO), 8.02 (s, 2H, H-2, H-6), 7.66 (d, *J*=8.0, 1H, ArC<u>H</u>=CHNO$_2$), 7.53 (d, *J*=8.0, 1H, ArCH=C<u>H</u>NO$_2$), 3.99 (s, 3H, OCH_3).

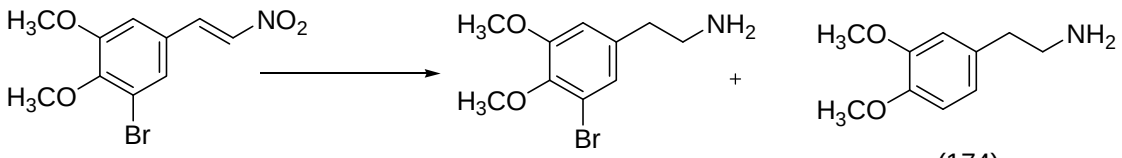
1-Bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171)



(172) (171)

To a solution of 2-bromo-6-methoxy-4-(2-nitrovinyl)phenol (172) (1 g, 3.65 mmol) and potassium carbonate (755 mg, 5.58 mmol) in acetone (40 mL) was added iodomethane (0.91 mL, 34.51 mmol). After refluxing for 6 h, the reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The combined organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to dryness. Purification by flash chromatography (5% ethyl acetate/hexane) gave 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (0.95 g, 90%). Recrystallization from ethanol gave **171** as a yellow needle, m.p. 158-189 ^{o}C.

2-(3-Bromo-4,5-dimethoxyphenyl)ethanamine (173)



(171) (173) (174)

Method I

To a stirred solution of 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (35 mg, 0.12 mmol) in ethyl acetate (1 mL) was added 10% palladium on charcoal (13 mg, 0.01 mmol). The reaction mixture was treated with hydrogen balloon and stirred for 12 h. The mixture was filtered through celite pad and rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure. Analytical TLC on siliga gel (10% ethyl acetate/ hexane) showed only the starting material's spot.

Method II

To a cool suspension of sodium borohydride (360 mg, 9.52 mmol) in tetrahydrofuran (15 mL) was added boron trifluoride diethyl etherate (1.5 mL). After addition, the flask was warmed to room temperature and stirred for 15 min. A solution of 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (300 mg, 1.04 mmol) in 5 mL of tetrahydrofuran was added dropwise, and the reaction mixture was heated at reflux for 6 h. The mixture was cooled to room temperature, quenched carefully by the addition of water (25 mL), acidified with 2 mL of 1 N hydrochloric, and heated at 80–85 ^{o}C for 2 h. After cooling to room temperature, tetrahydrofuran was removed under reduced pressure and the remaining material was washed once with diethyl ether. The aqueous layer was separated, made strongly alkaline with 10% aqueous sodium hydroxide, and extracted with diethyl ether, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure. Analytical TLC on siliga gel (10% ethyl acetate/ hexane) showed indefinite spots.

Method III

Zinc dust (519 mg) and mercuric chloride (22 mg) were stirred in 1 mL of water for 10 min. The water was then decanted and the amalgam was cooled in an ice bath. A solution of 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (100 mg, 0.35 mmol) in methanol (saturated with hydrogen chloride) was added to the amalgum. After addition was complete, the reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into saturated sodium bicarbonate and extracted with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Analytical TLC on siliga gel (10% ethyl acetate/ hexane) showed the starting material spot and indefinite spots.

Method IV

To a cool suspension of lithium aluminium hydride (92 mg, 2.43 mmol) in dry tetrahydrofuran (1 mL) was added 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171) (200 mg, 0.69 mmol) in dry tetrahydrofuran (5 mL). After refluxing for 4 h, the reaction mixture was cooled and added dropwise saturated sodium sulfate. The reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (3% methanol-dichloromethane) to give 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (173) (19 mg, 11%) and 2-(3,4-dimethoxyphenyl)ethanamine (174) (65 mg, 53%).

2-(3-Bromo-4,5-dimethoxyphenyl)ethanamine (173)

FTIR (neat), υ_{max}, cm^{-1}: 3321, 3284 (N-H), 1596, 1566 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.01 (d, *J*=1.9 Hz, 1H, H-2), 6.95 (d, *J*=1.8 Hz, 1H, H-6), 3.84 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.41 (t, *J*=14.7 Hz, 2H, $ArCH_2C\underline{H}_2NH_2$), 2.80 (t, *J*=14.6 Hz, 2H, $ArC\underline{H}_2CH_2NH_2$).

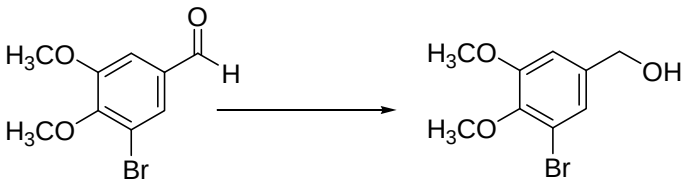
^{13}C NMR ($CDCl_3$, 100 MHz), δ: 154.1 (C-3), 145.2 (C-1), 139.3 (C-5), 125.2 (C-2), 117.1 (C-4), 113.8 (C-6), 60.2 (OCH_3), 56.0 (OCH_3), 53.1 ($CH_2\underline{C}H_2NH_2$), 36.4 ($\underline{C}H_2CH_2NH_2$).

MS (EI), *m/z* (relative intensity): 259 (M^+, 11), 230 (100).

2-(3,4-Dimethoxyphenyl)ethanamine (174)

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.85-6.73 (m, 3H, H-2, H-5, H-6), 3.73 (s, 3H, OCH_3), 3.69 (s. 3H, OCH_3), 3.33 (t, *J*=7.2, 1H, $ArCH_2C\underline{H}_2NH$), 2.84 (t, *J*=7.2, 1H, $ArC\underline{H}_2CH_2NH$).

(3-Bromo-4,5-dimethoxyphenyl)methanol (175)



(170) (175)

To a cool solution of 3-bromo-4,5-dimethoxybenzaldehyde (170) (1 g, 4.08 mmol) in ethanol (12 mL) was added sodium borohydride (160 mg, 4.11 mmol) and stirred at room temperature for 20 min. The ethanol was evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x80 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% ethyl acetate/dichloromethane) to afford product **175** (0.92 g, 91%) as a colourless oil.

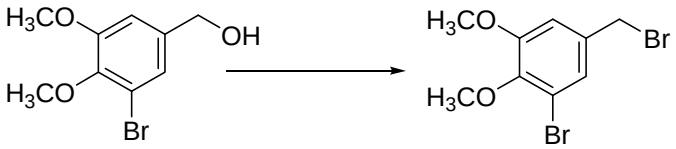
FTIR (neat) υ_{max}, cm^{-1}: 3412 (O-H), 1598, 1570 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.03 (s, 1H, H-2), 6.80 (s, 1H, H-6), 4.53 (s, 2H, Ar$C\underline{H}_2$OH), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 153.6 (C-3), 145.5 (C-1), 138.1 (C-5), 122.8 (C-2), 117.4 (C-4), 110.2 (C-6), 64.3 (Ar$\underline{C}H_2$OH), 60.5 (OCH_3), 57.0 (OCH_3).

MS (EI), *m/z* (relative intensity): 246 (M^+, 100), 231 (18).

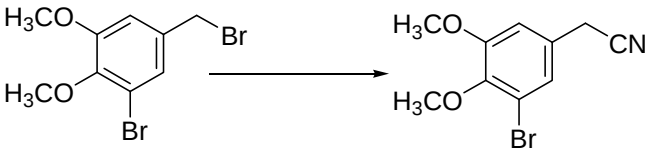
1-Bromo-5-(bromomethyl)-2,3-dimethoxybenzene (176)



(175) (176)

To a solution of (3-bromo-4,5-dimethoxyphenyl)methanol (175) (500 mg, 2.02 mmol) in dichloromethane (4 mL) was added phosphorus tribromide (0.74 mL, 4.04 mmol). After 20 min of stirring at room temperature, the reaction mixture was evaporated under reduced pressure to give the yellow residue which was dissolved in dichloromethane and then added sodium hydrogen carbonate. The precipitate was filtered off through sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was used in the next step without further purification.

2-(3-Bromo-4,5-dimethoxyphenyl)acetonitrile (177)



(176) (177)

Method I

The crude of 1-bromo-5-(bromomethyl)-2,3-dimethoxybenzene (176) and sodium cyanide (86 mg, 1.75 mmol) were mixed in dimethylformamide (20 mL) and stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the residue was partitioned between ether (300 mL) and water (100 mL). The aqueous phase was extracted with ether (100 mL) and the combined organic phase was washed with water, brine and then dried over anhydrous sodium sulfate. After evaporation, the residue was purified by flash column chromatography using

ethyl acetate: hexane (50:50) to give 2-(3-bromo-4,5-dimethoxyphenyl)acetonitrile (177) as a pale-yellow solid (424 mg, 82% (two steps)), m.p. 65-67 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1598, 1570 (C=C), 2250 (C≡N).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.01 (d, *J*=2.08, 1H, H-2), 6.74 (d, *J*=2.08, 1H, H-6), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (s, 1H, Ar$\underline{C}H_2$CN).

^{13}C NMR ($CDCl_3$, 100 MHz), 154.0 (C-3), 140.3 (C-1), 126.7 (C-5), 124.1 (C-2), 117.8 (CN), 118.1 (C-4), 111.3 (C-6), 60.5 (OCH_3), 56.2 (OCH_3), 23.0 (Ar$\underline{C}H_2$CN).

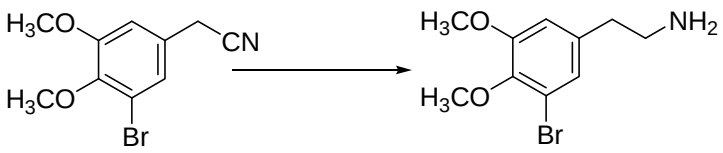
MS (EI), *m/z* (relative intensity): 255 (M^+, 100), 240 (52).

Method II

A 50 mL round bottom flask was charged with 2.0 g (40.8 mmol) of sodium cyanide dissolved in 5 mL of distilled water, and 4.0 g of neutral alumina was added to it in one portion. The water was evaporated under reduced pressure, keeping the bath temperature below 65 ^{o}C. Impregnated alumina was then dried and ready to use.

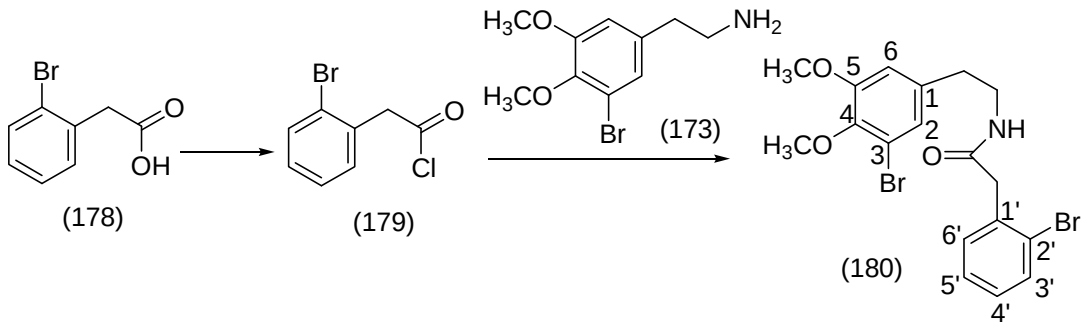
To a solution of 1-bromo-5-(bromomethyl)-2,3-dimethoxybenzene (176) in toluene (10 mL) was added sodium cyanide onto alumina (6.01 g). After refluxing for 3 h, a mixture was cooled to room temperature, filtered through celite and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate: hexane (50:50) to give 2-(3-bromo-4,5-dimethoxyphenyl)acetonitrile (177) as a pale-yellow solid (439 mg, 85% (two steps)), m.p. 65-67^{o}C.

2-(3-Bromo-4,5-dimethoxyphenyl)ethanamine (173)



To a cool solution (0 ^{o}C) of 2-(3-bromo-4,5-dimethoxyphenyl)acetonitrile (177) (100 mg, 0.39 mmol) in dry tetrahydrofuran (1 mL) was added dropwise a 1 M borane tetrahydrofuran complex solution (1.17 mL, 1.17 mmol) in tetrahydrofuran. The resultant mixture was refluxed under nitrogen atmosphere for 12 h and then cooled to 0 ^{o}C. After the solution was cooled, the methanol (5 mL) was added cautiously to quench the reaction. The mixture was concentrated under reduced pressure to be oil. The oil was dissolved in methanol (5 mL) and reconcentrated under reduced pressure (that process was repeated two more times). The resulting residue was purified by flash column chromatography using methanol-dichloromethane (4:96) to give 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (173) as a yellow oil (83 mg, 82%).

***N*-(3-Bromo-4,5-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (180)**



A solution of phenylacetic acid (178) (580 mg, 2.70 mmol), oxalyl chloride (0.35 mL, 4.08 mmol) and a catalytic amount of dimethylformamide (3 drops) in benzene (6 mL) was stirred at room temperature. After 2 h, the solvent was removed

to give the phenylacetyl chloride (179) which was used in the next step without purification.

The resulting acid chloride (179) in dichloromethane was added to a mixture of 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (173) (700 mg, 2.70 mmol) and sodium carbonate (349 mg, 3.24 mmol) in dichloromethane (3 mL) and water (3 mL). The reaction mixture was stirred at room temperature for 2 h. Layers were separated and the aqueous layer was extracted with dichloromethane (300 mL). The combined organic phase was washed with water (200 mL), brined (200 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethanol to give *N*-(3-bromo-4,5-dimethoxyphenethyl)-2-(2-bromophenyl) acetamide (180) as a white crystal (1.15 g, 93%), m.p. 134-135 ^{o}C.

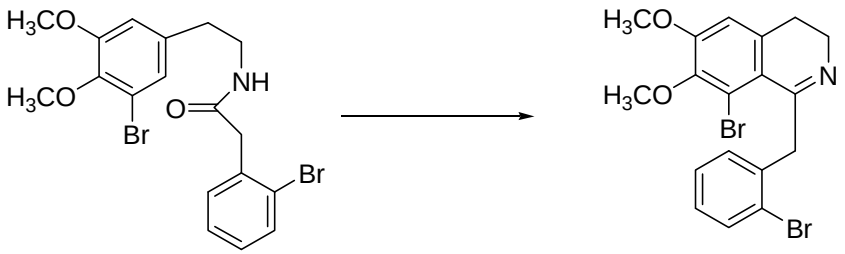
FTIR (KBr), υ_{max}, cm^{-1}: 3291 (N-H), 1646 (C=O), 1553 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.49 (d, *J*=7.8 Hz, 1H, H-3'), 7.22-7.21 (m, 2H, H-4', H-6'), 7.08 (m, 1H, H-5'), 6.78 (d, *J*=1.9 Hz, 1H, H-2), 6.54 (d, *J*=1.8 Hz, 1H, H-6), 5.34 (br s, 1H, NH), 3.75 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.61 (s, 2H, Ar$\underline{C}H_2$CO), 3.40 (dd, *J*=12.9, 6.8 Hz, 2H, Ar$CH_2C\underline{H}_2NH_2$), 2.62 (t, *J*=6.8 Hz, 2H, Ar$\underline{C}H_2CH_2NH_2$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 169.6 (C=O), 153.7 (C-3), 145.1 (C-1), 135.8 (C-5), 134.6 (C-2'), 133.1 (C-3'), 131.6 (C-4'), 129.2 (C-5'), 128.0 (C-6'), 124.9 (C-1'), 124.6 (C-2), 117.5 (C-4), 112.1 (C-6), 60.5 (OCH_3), 56.1 (OCH_3), 44.0 (Ar'$\underline{C}H_2$CONH), 40.7 (Ar$CH_2\underline{C}H_2$NH), 34.9 (Ar$\underline{C}H_2CH_2$NH).

MS (EI), *m/z* (relative intensity): 457 (M^+, 4), 242 (100), 207 (80).

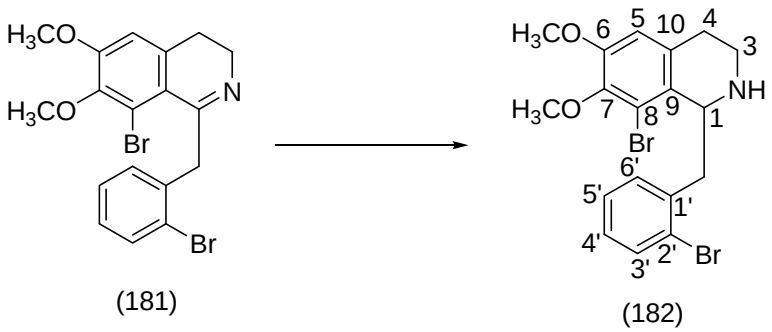
1-(2-Bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (181)



(180) (181)

Phosphorus oxychloride (0.16 mL, 0.87 mmol) was added dropwise into a cool solution of *N*-(3-bromo-4,5-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (180) (100 mg, 0.22 mmol) in dry dichloromethane (2 mL). The reaction mixture was refluxed under nitrogen atmosphere for 12 h. After cooling to 0 ^{o}C, a cool solution was carefully added 10% sodium hydroxide and extracted with dichloromethane (3x100 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxy isoquinoline (181) which was used in the next step without further purification.

1-(2-Bromobenzyl)-8-bromo-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (182)



(181) (182)

A cool solution (0 ^{o}C) of crude 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (181) in methanol (2 mL) was slowly added sodium borohydride (11 mg, 0.28 mmol) and stirred at room temperature for 2 h. A cool reaction mixture was added with brine solution and extracted with dichloromethane

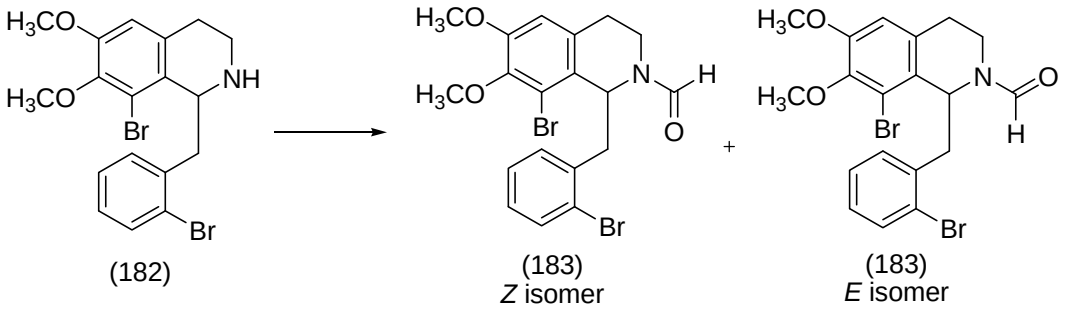
(3x100 mL). The organic layer was separated and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using methanol-dichloromethane (0.5:99.5) to give 1-(2-bromobenzyl)-8-bromo-1,2,3,4-tetrahydro-6,7-dimethoxy isoquinoline (182) as a yellow liquid (66 mg, 68 % (two step)).

FTIR (neat), υ_{max}, cm^{-1}: 3437 (N-H), 1595, 1561 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.53-7.48 (m, 2H, H-3', H-6'), 7.24 (dd, *J*=7.5, 1.3 Hz, 1H, H-4'), 7.02 (dd, *J*=7.6, 1.7 Hz, 1H, H-5'), 6.58 (s, 1H, H-5), 4.41 (dd, *J*=10.3, 3.7, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.35 (ddd, *J*=11.9, 11.9, 4.8 Hz 1H, H-3), 3.21 (dd, *J*=14.5, 3.7 Hz, 1H, ArC$\underline{H}_2$CHNH), 3.14 (dd, *J*=14.5, 10.3 Hz, 1H, ArC$\underline{H}_2$CHNH), 2.94-2.88 (m, 1H, H-3), 2.85-2.77 (m, 1H, H-4), 2.67-2.61 (m, 1H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 151.8 (C-8), 144.7 (C-10), 139.4 (C-6), 132.9 (C-3'), 132.2 (C-2'), 130.7 (C-4'), 130.6 (C-9), 128.0 (C-5'), 127.6 (C-6'), 125.2 (C-1'), 118.7 (C-7), 112.5 (C-5), 60.5 (C-1), 56.4 (OCH_3), 56.0 (OCH_3), 43.0 (Ar'$\underline{C}H_2$CH) 37.7 (C-3), 29.2 (C-4).

1-(2-Bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (183)



A solution of 1-(2-bromobenzyl)-8-bromo-1,2,3,4-tetrahydro-6,7-dimethoxy isoquinoline (182) (170 mg, 0.38 mmol) in ethyl formate (2 mL) was heated to 60 °C.

After 3 h, ethyl formate was removed under reduced pressure to give crude product. Purification of crude product by flash chromatography using methanol-dichloromethane (1:99) afforded 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyiso quinoline-2(1H)-carbaldehyde (183) (150 mg, 85%) as a pale-yellow liquid.

FTIR (neat), υ_{max}, cm^{-1}: 1654 (C=O), 1561 (C=C).

H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.58 (s, 1H, CHO), 7.48 (dd, *J*=8.0, 1.2 Hz, 1H, H-3'), 7.30 (dd, *J*=7.7, 1.7 Hz, 1H, H-6'), 7.22 (ddd, *J*=7.6, 7.5, 1.2 Hz, 1H, H-5'), 7.05 (ddd, *J*=7.7, 7.5, 1.7 Hz, 1H, H-4'), 6.65 (s, 1H, H-5), 4.99 (dd, *J*=10.1, 3.8 Hz, 1H, H-1), 4.07-3.97 (m, 1H, H-3), 3.82 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.51-3.47 (m, 1H, H-3), 3.33 (dd, *J*=14.1, 3.8 Hz, 1H, Ar$C\underline{H}_2$CHNH), 3.09 (dd, *J*=14.1, 10.1 Hz, 1H, Ar$C\underline{H}_2$CHNH), 2.90-2.87 (m, 2H, H-4).

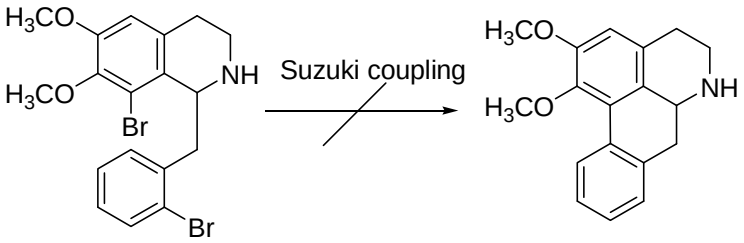
Minor isomer (*Z* isomer) δ: 7.91 (s, 1H, CHO), 7.51-7.49 (dd, *J*=7.7, 1.7 Hz, 1H, H-6'), 7.41 (dd, *J*=8.0, 1.2 Hz, 1H, H-3'), 7.19-7.18 (m, 1H, H-5'), 6.95 (ddd, *J*=7.7, 7.6, 1.7 Hz, 1H, H-4'), 6.56 (s, 1H, H-5), 5.88 (dd, *J*=10.1, 3.8 Hz, 1H, H-1), 4.07-3.97 (m, 1H, H-3), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.51-3.47 (m, 1H, H-3), 3.42 (dd, *J*=14.7, 3.8 Hz, 1H, Ar$C\underline{H}_2$CHNH), 3.18 (dd, *J*=14.7, 10.1 Hz, 1H, Ar$C\underline{H}_2$CHNH), 2.93-2,91 (m, 1H, H-4), 2.81-2.80 (m, 1H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) δ: 161.1 (CHO), 152.5 (C-7), 145.1 (C-6), 136.9 (C-2'), 133.2 (C-3'), 131.7 (C-6'), 131.0 (C-8), 128.7 (C-4'), 127.8 (C-5'), 128.7 (C-1'), 128.0 (C-9), 127.7 (C-10), 124.9 (C-9), 112.0 (C-5), 60.5 (OCH_3), 58.1 (C-1), 56.0 (OCH_3), 39.7 (C-4), 35.7 (C-3), 27.6 (Ar$\underline{C}H_2$CHNH).

Minor isomer (*Z* isomer) *δ*: 161.0 (CHO), 152.3 (C-7), 145.1 (C-6), 136.9 (C-2'), 132.4 (C-3'), 131.3 (C-6'), 130.8 (C-8), 128.2 (C-4'),127.9 (C-5'), 127.3 (C-1'), 127.9 (C-9), 127.3 (C-10), 124.7 (C-9), 111.9 (C-5), 60.5 (OCH_3), 56.0 (OCH_3), 51.5 (C-1), 40.1 (C-4), 37.9 (C-3), 29.3 (Ar$\underline{C}H_2$CHNH).

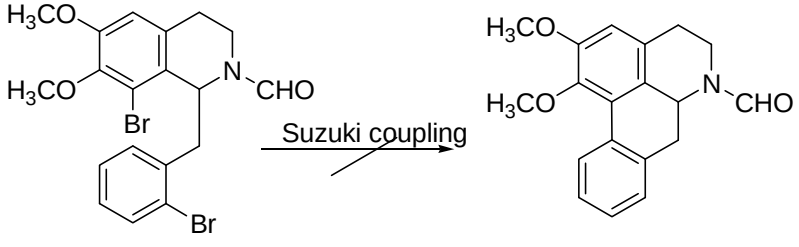
Nuciferine (184)



(182) (184)

A dry three-necked flask, equipped with a magnetic stirring bar, septum, and condenser with an nitrogen inlet-outlet was charged with [1,1'-bis(diphenyl phosphino)ferrocene] dichloropalladium (1 mg, 0.002 mmol), bis(pinacolato)diboron (16 mg, 0.068 mmol), sodium acetate (15 mg, 0.186 mmol) and 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (182). The flask was flushed with nitrogen and then dimethylformamide (1 mL) was added. After heated at 80 °C for 2 h, the reaction was cooled to room temperature and added sodium carbonate solution. The mixture was heated for 12 h at 80 ^{o}C, then was filtered through celite pad, and the solvent was evaporated under reduced pressure. Analytical TLC on siliga gel (50% ethyl acetate/ hexane) showed indefinite spots.

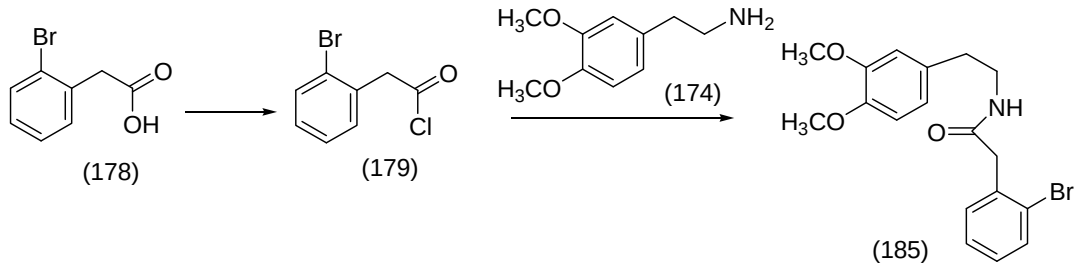
***N*-Formylnornuciferine (13a)**



(183) (13a)

A mixture of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxy isoquinoline-2(1H)-carbaldehyde (183) (30 mg, 0.06 mmol), bis(pinacolato)diboron (0.8 mg, 0.03 mmol), [1,1'-bis(diphenyl phosphino)ferrocene] dichloropalladium (0.2 mg, 0.002 mmol), potassium carbonate (26 mg, 0.19 mmol) in dimethyl sulfoxide (1 mL) under nitrogen atmosphere was heated at 80 ^{o}C for 8 h. After cooling to room temperature, the reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. Analytical TLC on siliga gel (50% ethyl acetate/ hexane) showed only a starting material's spot.

_N_-(3,4-Dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185)



A solution of 2-bromophenylacetic acid (178) (643 mg, 2.99 mmol), oxalyl chloride (0.6 mL, 4.48 mmol) and a catalytic amount of dimethylformamide (3 drops) in benzene (6 mL) was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure to give bromophenylacetyl chloride (179) which was used in the next step without further purification.

The resulting acid chloride (179) in dichloromethane (3 mL) was added to a mixture of homoveratylamine (174) (500 mg, 2.99 mmol) and sodium carbonate (380 mg, 3.59 mmol) in dichloromethane (3 mL) and water (3 mL). The reaction mixture was stirred at room temperature for 2 h. Layers were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic phase was washed with water, brined, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from ethanol to give *N*-(3,4-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185) (1.03 g, 91%) as a white needle crystal, m.p. 126-128 ^{o}C.

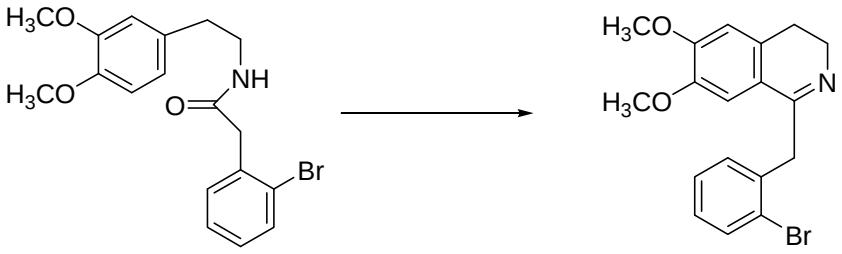
FTIR (KBr), υ_{max}, cm^{-1}: 3309 (N-H), 1647 (C=O), 1546 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.46 (d, *J*=8.2, 1H, H-3'), 7.20-7.18 (m, 2H, H-6', H-4'), 7.08-7.04 (m, 1H, H-5'), 6.64 (d, *J*=8.1 Hz, 1H, H-5), 6,56 (d, *J*=2.0 Hz, 1H, H-2), 6.52 (dd, *J*=8.1, 2.0 Hz, 1H, H-6), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.58 (s, 2H, Ar$\underline{C}H_2$CO), 3.39 (dd, *J*=12.8, 6.9 Hz, 2H, $ArCH_2C\underline{H}_2NH_2$), 2.63 (t, *J*=6.9 Hz, 2H, Ar$\underline{C}H_2CH_2NH_2$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 169.4 (C=O), 149.0, 147.6 (C-3, C-4), 134.7 (C-2'), 133.0 (C-3'), 131.6 (C-4'), 131.0 (C-1'), 129.0 (C-5'), 127.9 (C-6'), 124.9 (C-1), 120.5 (C-6), 111.8 (C-2), 111.3 (C-5), 55.9 (OCH_3), 55.8 (OCH_3), 44.0 (Ar$\underline{C}H_2$CO), 40.7 ($ArCH_2\underline{C}H_2NH_2$), 34.9 (Ar$\underline{C}H_2CH_2NH_2$).

MS (EI), *m/z* (relative intensity): 377 (8), 164 (100), 151 (11).

1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (186)

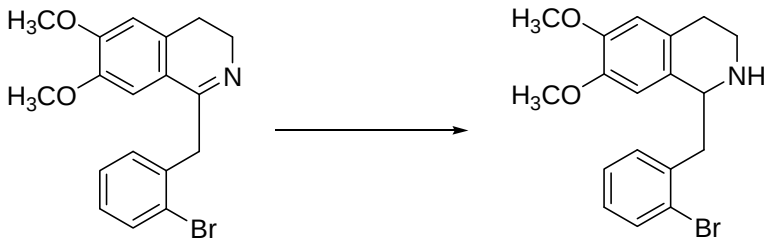


(185) (186)

Phosphorus oxychloride (0.48 mL, 5.29 mmol) was added dropwise into a cool solution of *N*-(3,4-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185) (500 mg, 1.32 mmol) in dry dichloromethane (6 mL). The reaction mixture was refluxed under nitrogen atmosphere for 4 h. After cooling to 0 ^{o}C, a cool solution was carefully added 10% sodium hydroxide and extracted with dichloromethane (3x100 mL).The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product of 1-(2-

bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (186) which was used in the next step without further purification.

1-(2-Bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (187)



(186) (187)

To a cool solution (0 ^{o}C) of crude product of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (188) in methanol (6 mL) was slowly added sodium borohydride (65 mg, 1.71 mmol) and stirred at room temperature for 2 h. A cool reaction mixture was added with brine and extracted with dichloromethane (3x50 ml). The organic layer was separated and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography using methanol-dichloromethane (3:97) to give 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (187) (0.39 g, 83% (two steps)) as a yellow liquid.

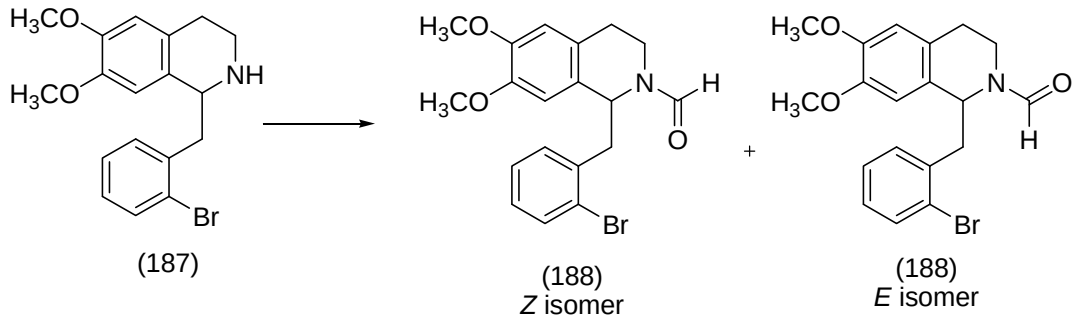
FTIR (neat), υ_{max}, cm^{-1}: 3437 (N-H), 1595, 1561 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.51 (d, *J*=8.0 Hz, 1H, H-3'), 7.20-7.18 (m, 2H, H-5', H-6'), 7.04 (ddd, *J*=8.0, 4.6, 4.6 Hz, 1H, H-4'), 6.59 (s, 1H, H-8), 6.52 (s, 1H, H-5), 4.21 (dd, *J*=9.6, 4.2 Hz, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.28 (dd, *J*= 13.6, 4.2 Hz, 1H, ArC$\underline{H_2}$CHNH), 3.19 (dt, *J*= 12.4, 6.0 Hz, 1H, H-3), 2.96 (dd, *J*= 13.5, 9.6 Hz, 1H, ArC$\underline{H_2}$CHNH), 2.91 (dd, *J*= 12.3, 5.4 Hz, 1H, H-3), 2.69 (t, *J*=5.9 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 147.6, 147.1 (C-6, C-7), 138.6 (C-2'), 133.0 (C-3'), 132.0 (C-6'), 130.0 (C-1'), 128.2 (C-4'), 127.4 (C-5'), 126.9 (C-9), 124.9 (C-10), 111.7 (C-5), 109.7 (C-8), 55.8 (OCH_3), 55.8 (OCH_3), 54.8 (C-1), 43.0 (Ar<u>C</u>H_2CHNH), 39.8 (C-3), 29.1 (C-4).

HRMS calcd, for $C_{18}H_{21}NO_2Br$: 362.0756, Found 362.0757.

1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (188)



A solution of 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyiso quinoline (187) (300 mg, 0.828 mmol) in ethyl formate (2.78 mL) was heated to 60 °C. After 3 h, ethyl formate was removed under reduced pressure to give crude product. Purification of crude product by flash chromatography using ethyl acetate-hexane (40:60) gave 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-car baldehyde (188) (0.32 g, 85%) as a white solid. Recrystallization of compound **188** from ethanol gave a white crystal with m.p. 133-134 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1654 (C=O), 1520 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.53 (dd, *J*=7.6, 1.2 Hz, 1H, H-3'), 7.50 (s, 1H, CHO), 7.18 (ddd, *J*=7.6, 7.5, 1.2 Hz, 1H, H-5'), 7.07 (ddd, *J*=7.6, 7.6, 1.7 Hz, 1H, H-4'), 6.96 (dd, *J*=7.5, 1.7 Hz, 1H, H-6'), 6.65 (s, 1H, H-8), 6.56 (s, 1H, H-5), 4.71 (dd,

J=10.2, 4.0 Hz, 1H, H-1), 4.43 (ddd, *J*=13.2, 6.2, 2.3 Hz, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.27 (dd, *J*=13.9, 4.0 Hz, 1H, Ar$C\underline{H}_2$CHNH), 3.17 (ddd, *J*=13.2, 11.4, 4.8 Hz, 1H, H-3), 3.02 (dd, *J*=13.9, 10.2 Hz, 1H, Ar$C\underline{H}_2$CHNH), 2.81 (dd, *J*=11.4, 6.2 Hz, 1H, H-4), 2.70 (dd, *J*=4.8, 2.3 Hz, 1H, H-4).

Minor isomer (*Z* isomer) *δ*: 7.98 (s, 1H, CHO), 7.74 (dd, *J*=8.0, 1.1 Hz, 1H, H-3'), 7.17 (ddd, *J*=7.6, 6.8, 1.1 Hz, 1H, H-5'), 7.11 (dd, *J*=7.6, 2.2 Hz, 1H, H-6'), 7.01 (ddd, *J*=8.0, 6.8, 2.2 Hz, 1H, H-4'), 6.49 (s, 1H, H-8), 6.34 (s, 1H, H-5), 5.59 (dd, *J*=8.4, 6.0 Hz, 1H, H-1), 3.77 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.62-3.58 (m, 2H, H-3), 3.26 (dd, *J*=13.7, 6.0 Hz, 1H, Ar$C\underline{H}_2$CHNH), 3.08 (dd, *J*=13.7, 8.5 Hz, 1H, Ar$C\underline{H}_2$CHNH), 2.85 (dd, *J*=11.3, 6.2 Hz, 1H, H-4), 2.65 (dd, *J*=4.7, 2.3 Hz, 1H, H-4).

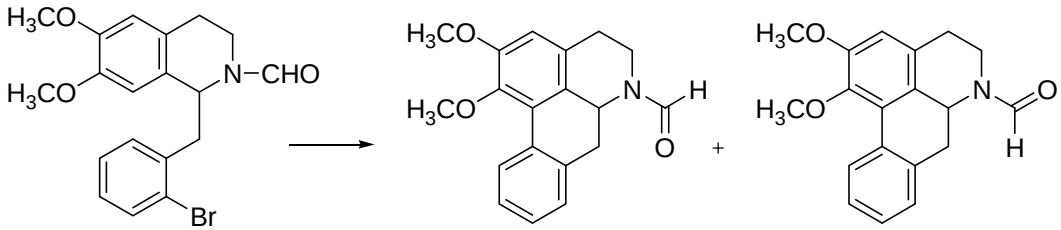
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) *δ*: 161.2 (CHO), 148.3, 147.6 (C-6, C-7), 136.6 (C-2'), 133.0 (C-3'), 132.1 (C-6'), 128.9 (C-4'), 127.8 (C-5'), 127.3 (C-1'), 125.9 (C-9), 124.4 (C-10), 111.5 (C-5), 109.7 (C-8), 56.5 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 43.4 (Ar$\underline{C}H_2$CHNH), 34.3 (C-3), 27.6 (C-4).

Minor isomer (*Z* isomer) *δ*: 161.2 (CHO), 148.0, 147.4 (C-6, C-7), 137.1 (C-2'), 132.7 (C-3'), 131.6 (C-6'), 128.3 (C-4'), 127.2 (C-5'), 127.0 (C-1'), 125.3 (C-9), 124.9 (C-10), 111.2 (C-8), 110.2 (C-5), 55.8 (OCH_3), 55.7 (OCH_3), 50.8 (C-1), 41.6 (Ar$\underline{C}H_2$CHNH), 40.3 (C-3), 29.1 (C-4).

HRMS calcd, for $C_{19}H_{21}NO_3Br$: 390.0705, Found 390.0705.

(±)-*N*-Formylnornuciferine (13a)



A mixture of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (188) (50 mg, 0.128 mmol), tricyclohexylphosphine (36 mg, 0.128 mmol), sodium acetate (33 mg, 0.410 mmol) and palladium acetate (14 mg, 0.064 mmol) in dimethylacetamide (1 mL) under nitrogen atmosphere was heated at 110 ^{o}C for 24 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (40:60) and then was recrystallized from methanol to give *N*-formylnornuciferine (13a) (28 mg, 78%) as a colorless crystal, m.p. 222-224 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1668 (C=O), 1587 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*Z* isomer) δ: 8.35 (d, *J*=8.0 Hz, 1H, H-11), 8.19 (s, 1H, CHO), 7.31-7.15 (m, 3H, H-10, H-9, H-8), 6.59 (s, 1H, H-3), 4.86 (dd, *J*=13.9, 4.2 Hz, 1H, H-6a), 3.83 (s, 3H, OCH_3), 3.75 (ddd, *J*=12.7, 4.6, 1.8 Hz, 1H, H-5), 3.60 (s, 3H, OCH_3), 3.35 (ddd, *J*=12.7, 12.4, 2.8 Hz, 1H, H-5), 3.05 (dd, *J*=13.7, 4.2 Hz, 1H, H-7), 2.89-2.66 (m, 3H, H-4, H-4, H-7).

Minor isomer (*E* isomer) δ: 8.37 (d, *J*=8.0 Hz, 1H, H-11), 8.32 (s, 1H, CHO), 7.31-7.15 (m, 3H, H-10, H-9, H-8), 6.62 (s, 1H, H-3), 4.43 (dd, *J*=14.2, 4.0 Hz, 1H, H-6a), 4.35 (ddd, *J*=12.7, 4.6, 3.6 Hz, 1H, H-5), 3.84 (s, 3H, OCH_3), 3.60 (s, 3H,

OCH_3), 3.14 (ddd, *J*=12.7, 10.4, 3.7 Hz, 1H, H-5), 3.12-3.03 (m, 1H, H-7), 2.89-2.66 (m, 3H, H-4, H-4, H-7).

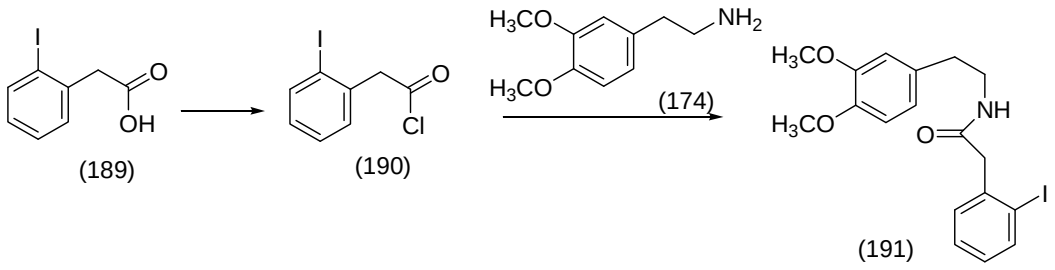
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*Z* isomer) δ: 162.1 (CHO), 152.4 (C-2), 146.0 (C-1), 136.1 (C-7a), 131.5 (C-11a), 128.6 (C-11c), 128.6 (C-8), 128.4 (C-11), 127.9 (C-11b), 127.8 (C-9), 127.1 (C-10), 125.3 (C-3a), 111.5 (C-3), 60.0 (OCH_3), 56.0 (OCH_3), 49.4 (C-6a), 42.0 (C-5), 34.1 (C-7), 31.0 (C-4).

Minor isomer (*Z* isomer) δ: 161.9 (CHO), 152.6 (C-2), 145.8 (C-1), 135.4 (C-7a), 131.6 (C-11a), 129.5 (C-11c), 128.7 (C-11), 128.2 (C-8), 127.9 (C-9), 127.5 (C-10), 127.4 (C-11b), 124.8 (C-3a), 111.8 (C-3), 60.1 (OCH_3), 56.0 (OCH_3), 53.5 (C-6a), 37.9 (C-7), 36.1 (C-5), 29.6 (C-4).

MS (EI), *m/z* (relative intensity): 309 (59), 252 (20), 264 (22), 251 (100)

***N*-(3,4-Dimethoxyphenethyl)-2-(2-iodophenyl)acetamide (191)**



A solution of 2-iodophenylacetic acid (189) (723 mg, 2.76 mmol), oxalyl chloride (0.6 mL, 4.14 mmol) and a catalytic amount of dimethylformamide (3 drops) in benzene (6 mL) was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure to give iodophenylacetyl chloride (190) which was used in the next step without further purification.

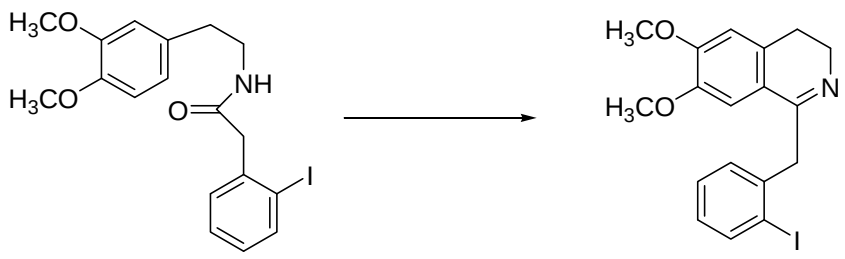
The resulting acid chloride (190) in 3 mL of dichloromethane was added to a mixture of homoveratylamine (174) (500 mg, 2.76 mmol) and sodium carbonate (350 mg) in dichloromethane (3 mL) and water (3 mL). The reaction mixture was stirred at room temperature for 2 h. Layer were separated and the aqueous layer was extracted with dichloromethane (3x50 mL). The combined organic phase was washed with water, brined, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was recrystallized from ethanol to give *N*-(3,4-dimethoxyphenethyl)-2-(2-iodophenyl)acetamide (191) (1.09 g, 92%) as a white needle, m.p. 139-140 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 3309 (N-H), 1647 (C=O), 1546 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.75 (dd, *J*=7.9, 1.2 Hz, 1H, H-3'), 7.23 (ddd, *J*=14.6, 7.6, 1.2 Hz, 1H, H-6'), 7.19 (dd, *J*=7.6, 2.0 Hz, 1H, H-4'), 6.89 (ddd, *J*=14.9, 7.9, 2.0 Hz, 1H, H-5'), 6.64 (d, *J*=8.1 Hz, 1H, H-5), 6.56 (d, *J*=1.9 Hz, 1H, H-2), 6.51 (dd, *J*=8.1, 1.9 Hz, 1H, H-6), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.61 (Ar$\underline{C}H_2$CO, s, 2H), 3.40 (dd, *J*=12.9, 6.8 Hz, 2H, $ArCH_2C\underline{H}_2NH_2$), 2.64 (t, *J*=6.8 Hz, 2H, Ar$\underline{C}H_2CH_2NH_2$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 169.4 (C=O), 149.0, 147.6 (C-3, C- 4), 139.8 (C-3'), 138.2 (C-2'), 131.0 (C-1'), 130.8 (C-4'), 129.1 (C-5'), 126.8 (C-6'), 120.6 (C-6), 111.8 (C-2), 111.4 (C-5), 101.1 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 48.6 (Ar$\underline{C}H_2$CO), 40.8 ($ArCH_2\underline{C}H_2NH_2$), 34.9 (Ar$\underline{C}H_2CH_2NH_2$).

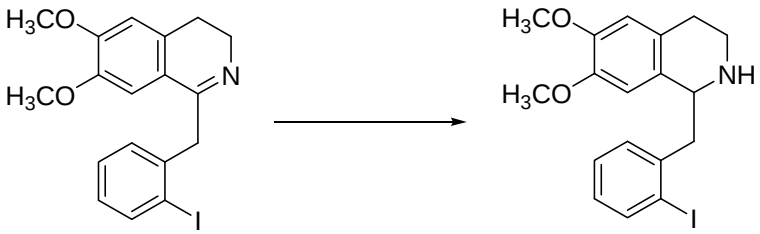
1-(2-Iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (192)



(191) (192)

Phosphorus oxychloride (0.43 mL, 4.70 mmol) was added dropwise into a cool solution of *N*-(3,4-dimethoxyphenethyl)-2-(2-iodophenyl)acetamide (191) (500 mg, 1.18 mmol) in dry dichloromethane (6 mL). The reaction mixture was refluxed under nitrogen atmosphere for 4 h. After cooling to 0 ^{o}C, a cool solution was carefully added 10% sodium hydroxide and extracted with dichloromethane (3x100 mL).The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product of 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (192) which was used in the next step without further purification.

1-(2-Iodobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (193)



(192) (193)

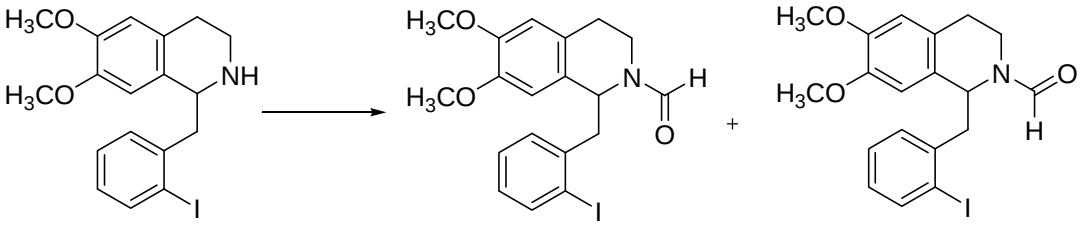
A cool solution (0 ^{o}C) of crude product of 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (192) in methanol (6 mL) was slowly added sodium borohydride (58 mg, 1.53 mmol) and stirred at room temperature for 2 h. A cool reaction mixture was added with brine and extracted with dichloromethane (3x100 ml). The organic layer was separated and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using methanol-dichloromethane (3:97) to give 1-(2-iodobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (193) (0.35 g, 81% (two steps)) as a yellow liquid.

FTIR (neat), υ_{max}, cm^{-1}: 3437 (N-H), 1595, 1561 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.51 (dd, *J*=7.5, 1.2 Hz, 1H, H-3'), 7.24 (ddd, *J*=7.5, 7.5, 1.2 Hz, 1H, H-5'), 7.18 (dd, *J*=7.5, 1.9 Hz, 1H, H-6'), 6.87 (ddd, *J*=7.5, 7.5, 1.9 Hz, 1H, H-4'), 6.64 (s, 1H, H-8), 6.52 (s, 1H, H-5), 4.21 (dd, *J*=9.6, 4.4 Hz, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.22 (dd, *J*=13.7, 4.8 Hz, 1H, ArC$\underline{H_2}$CHNH), 3.20 (dd, *J*=12.4, 6.1 Hz, 1H, H-3), 3.02 (dd, *J*=13.6, 9.6 Hz, 1H, ArC$\underline{H_2}$CHNH), 2.95 (dt, *J*=12.3, 5.5 Hz, 1H, H-3), 2.73 (t, *J*=5.8 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 147.7, 147.1 (C-6, C-7), 141.5 (C-2'), 139.7 (C-3'), 131.3 (C-6'), 129.4 (C-1'), 128.4 (C-4'), 128.3 (C-5'), 126.7 (C-9), 111.7 (C-5), 109.8 (C-8), 101.2 (C-10), 55.8 (OCH_3), 55.8 (OCH_3), 54.8 (C-1), 47.0 (Ar$\underline{C}H_2$CHNH), 39.8 (C-3), 28.9 (C-4).

1-(2-Iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (194)



To a solution of 1-(2-iodobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyiso quinoline (193) (300 mg, 0.733 mmol) in ethyl formate (2.45 mL) was heated to 60 °C. After 3 h, ethyl formate was removed to give crude product. Purification was done by flash chromatography using ethyl acetate-hexane (40:60) to give 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (194) (0.26 g, 81%) as an orange liquid.

FTIR (neat), υ_{max}, cm^{-1}: 1656 (C=O), 1524 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) *δ*: 7.81 (dd, *J*=7.6, 1.2 Hz, 1H, H-3'), 7.48 (s, 1H, CHO), 7.21 (ddd, *J*=7.6, 7.6, 1.2 Hz, 1H, H-5'), 6.93 (dd, *J*=7.6, 1.6 Hz, 1H, H-6'), 6.88 (ddd, *J*=7.6, 7.6, 1.6 Hz, 1H, H-4'), 6.71 (s, 1H, H-8), 6.56 (s, 1H, H-5), 4.70 (dd, *J*=10.1, 4.0 Hz, 1H, H-1), 4.45 (ddd, *J*=13.2, 6.2, 2.2 Hz, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.23-3.04 (m, 3H, H-3, Ar$C\underline{H}_2$CHNH, Ar$C\underline{H}_2$CHNH), 2.89-2.80 (m, 2H, H-4).

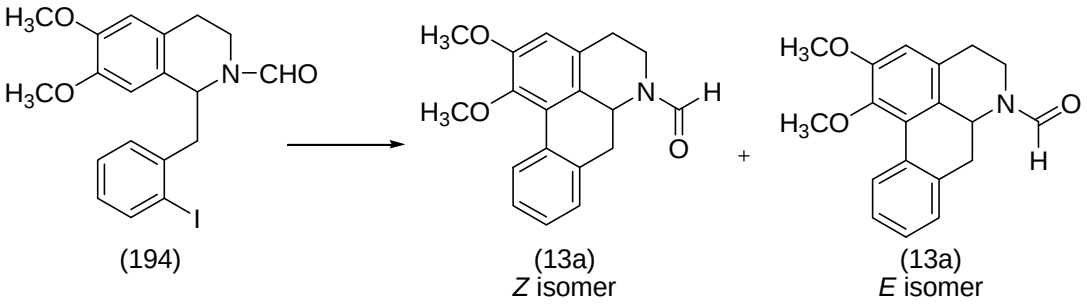
Minor isomer (*Z* isomer) *δ*: 7.99 (s, 1H, CHO), 7.73 (dd, *J*=7.6, 1.2 Hz, 1H, H-3'), 7.17 (ddd, *J*=7.6, 7.6, 1.1 Hz, 1H, H-5'), 7.11 (dd, *J*=7.6, 1.6 Hz, 1H, H-6'), 6.83 (ddd, *J*=7.6, 7.6, 1.6 Hz, 1H, H-4'), 6.50 (s, 1H, H-8), 6.37 (s, 1H, H-5), 5.58 (dd, *J*=8.3, 6.2 Hz, 1H, H-1), 3.77 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.64-3.61 (m, 2H, H-3), 3.60 (s, 3H, OCH_3), 3.23-3.04 (m, 2H, Ar$C\underline{H}_2$CHNH), 2.89-2.80 (m, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) *δ*: 161.2 (CHO), 148.3, 147.6 (C-6, C-7), 139.8 (C-2'), 139.7 (C-3'), 131.5 (C-6'), 129.0 (C-4'), 128.4 (C-5'), 128.1 (C-1), 125.9 (C-9), 111.2 (C-10), 110.2 (C-8), 100.4 (C-5), 56.5 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 47.4 (Ar$\underline{C}H_2$CHNH), 34.3 (C-3), 27.6 (C-4).

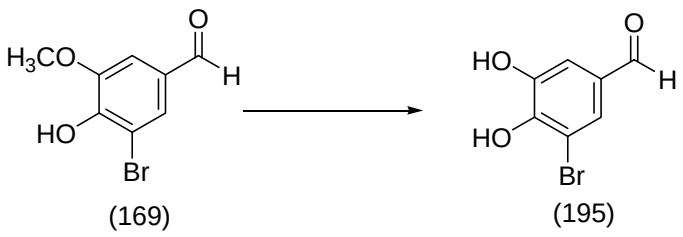
Minor isomer (*Z* isomer) *δ*: 161.2 (CHO), 148.0, 147.4 (C-6, C-7), 140.4 (C-2'), 139.4 (C-3'), 130.7 (C-6'), 128.6 (C-4'), 127.1 (C-5'), 126.8 (C-1'), 125.0 (C-9), 111.4 (C-10), 109.7 (C-8), 101.8 (C-5), 55.8 (OCH_3), 55.6 (OCH_3), 50.9 (C-1), 46.0 (Ar$\underline{C}H_2$CHNH), 40.4 (C-3), 29.1 (C-4).

(±)-*N*-Formylnornuciferine (13a)



A mixture of 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (194) (50 mg, 0.140 mmol), tricyclohexylphosphine (32 mg, 0.140 mmol), sodium acetate (30 mg, 0.366 mmol) and palladium acetate (12 mg, 0.057 mmol) in *N,N*-dimethylacetamide (1 mL) under nitrogen atmosphere was heated at 110 ^{o}C for 24 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate-hexane (40:60) and then was recrystallized from methanol to give *N*-formylnornuciferine (13a) (23 mg, 71%) as a colorless crystal, m.p. 222-224 ^{o}C.

3-Bromo-4,5-dihydroxybenzaldehyde (195)



Method I

To a stirred solution of bromovanilin (169) (100 mg, 0.43 mmol) in dichloromethane was added aluminium chloride (80 mg, 0.61 mmol) and then added dropwise pyridine (0.15 mL). After refluxing for 7 h, the reaction mixture was cooled

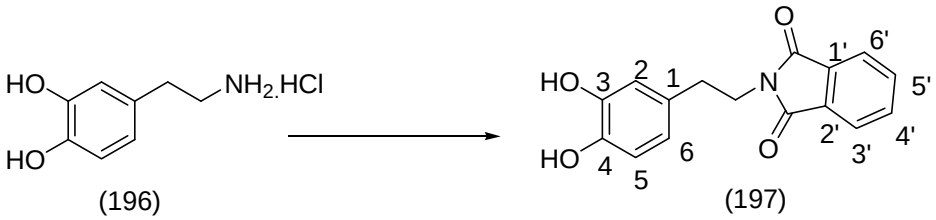
down and concentrated under reduced pressure. A cool reaction mixture was added with brine and extracted with dichloromethane (3x100 mL). The organic layer was separated and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (80:20) to give 3-bromo-4,5-dihydroxybenzaldehyde (195) (60 mg, 59 %) as a white solid.

^{1}H NMR (acetone-d6, 400 MHz), δ: 9.78 (s, 1H, CHO), 7.37 (s, 1H, H-6), 7.61 (s, 1H, H-2).

Method II

A stirred solution of bromovanilin (169) (50 mg, 0.20 mmol), in anhydrous dichloromethane (5 mL) was cooled to -78 ^{o}C under nitrogen atmosphere. A 1 M solution of boron tribromide in dichloromethane (0.12 mL, 0.82 mmol) was slowly added *via* syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was cooled and carefully quenched with methanol (5 mL). The solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (80:20) to give 3-bromo-4,5-dihydroxybenzaldehyde (195) (31 mg, 63 %) as a white solid.

2-(3,4-Dihydroxyphenethyl)isoindoline-1,3-dione (197)



A mixture of dopamine hydrochloride (196) (100 mg, 0.53 mmol), phthalic anhydride (156 mg, 1.05 mmol), and acetic acid (1.5 mL) was heated at reflux under vigorous stirring for 4 h. The mixture was cooled to 0 ^{o}C, and 0.5 mL of distillated

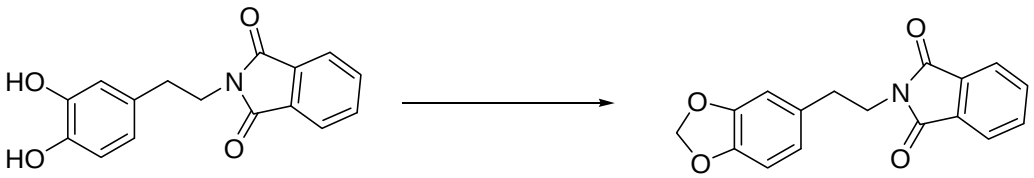
water was added. The precipitate was collected and vacuum dried to afford 2-(3,4-dihydroxyphenethyl) isoindoline-1,3-dione (197) (138 mg, 93 %) which was recrystallized from hexane/ ethyl acetate to give a pale-yellow needle with m.p. 135-136 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 3009 (N-H), 1684 (C=O), 1586 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.81 (s, 4H, H-3', H4', H-5', H-6'), 7.72 (s, 1H, OH), 7.65 (s, 1H, OH), 6.74 (d, J = 2.1 Hz, 1H, H-2), 6.70 (d, J = 8.0 Hz, 1H, H-5), 6.55 (dd, J = 2.1, 8.0 Hz, 1H, H-6), 5.82 (s, 2H, OC$\underline{H_2}$O), 3.81 (t, J = 7.5 Hz , 2H, ArCH$_2$C$\underline{H_2}$N), 2.83 (t, J = 7.5 Hz, ArC$\underline{H_2}$CH$_2$N, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 168.3 (C=O), 145.6, 144.2 (C-3, C-4), 134.6 (C-3', C-6'), 134.6 (C-1), 132.7, 130.6 (C-1', C-2'), 123.3, 123.3 (C-4', C-5'), 120.6 (C-6), 116.3 (C-2), 115.8 (C-5), 39.8 (ArCH$_2$$\underline{C}H_2$N), 34.1 (Ar$\underline{C}H_2CH_2$N).

2-(2-(Benzo[d][1,3]dioxol-6-yl)ethyl)isoindoline-1,3-dione (198)



(197) (198)

To a stirred suspension of 2-(3,4-dihydroxyphenethyl)isoindoline-1,3-dione (197) (50 mg, 0.18 mmol) and cesium carbonate (230 mg, 0.70 mmol) in dimethylformamide (1 mL) was added dibromomethane (0.04 mL) and the resulting suspension was stirred at room temperature for 1 h. The reaction mixture was poured into water (10 mL) and extracted with dichloromethane (3x10 mL). The combined organic layer was washed with water (10 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. Chromatography (silica gel, elution with 10% ethyl acetate, hexane) provided 42 mg (82%) of 2-(2-(benzo[d][1,3]dioxol-

6-yl)ethyl)isoindoline-1,3-dione (198) as a white solid. Recrystallization of **198** from ethyl acetate/ hexane gave a white crystal with m.p. 141-142 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1707 (C=O), 1492 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.76 (dd, J = 3.0, 5.4 Hz, 2H, H-4', H-5'), 7.63 (dd, J = 3.0, 5.4 Hz, 2H, H-3', H-6'), 6.68 (d, J = 1.6 Hz, 1H, H-2), 6.64 (d, J = 7.8 Hz, 1H, H-5), 6.60 (dd, J = 1.6, 7.8 Hz, 1H, H-6), 5.82 (s, 1H, OCH_2O), 3.80 (t, J =7.6 Hz, 2H, $ArCH_2C\underline{H}_2N$), 2.83 (t, J =7.6 Hz, 2H, $ArC\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 168.1 (C=O), 147.6, 146.1 (C-3, C-4), 133.8, 133.8 (C-3', C-6'), 133.8 (C-1), 132.0, 131.7 (C-1', C-2'), 123.1, 123.1 (C-4', C-5'), 121.7 (C-6), 109.2 (C-2), 108.2 (C-5), 100.8 (OCH_2O), 39.4 ($ArCH_2\underline{C}H_2N$), 34.2 ($Ar\underline{C}H_2CH_2N$).

HRMS calcd, for $C_{17}H_{13}NO_4Na$: 318.0742, Found 318.0739.

2-(Benzo[1,3]dioxol-6-yl)ethanamine (199)

(198) (199)

A mixture of 2-(benzo[d][1,3]dioxol-6-yl)ethanamine (198) (50 mg, 0.17 mmol) and 65% hydrazine monohydrate (0.03 ml, 0.71 mmol) in methanol (1 mL) was stirred at room temperature for 30 min. The reaction was evaporated under reduced pressure to give an oily white solid, which was transferred to a separatory funnel and partitioned in ether (10 mL) and water (10 mL). The aqueous phase was separated and extracted with ether (3x10 mL) and the combined organic phases were washed with water, brine and then dried over sodium sulfate. After purification by

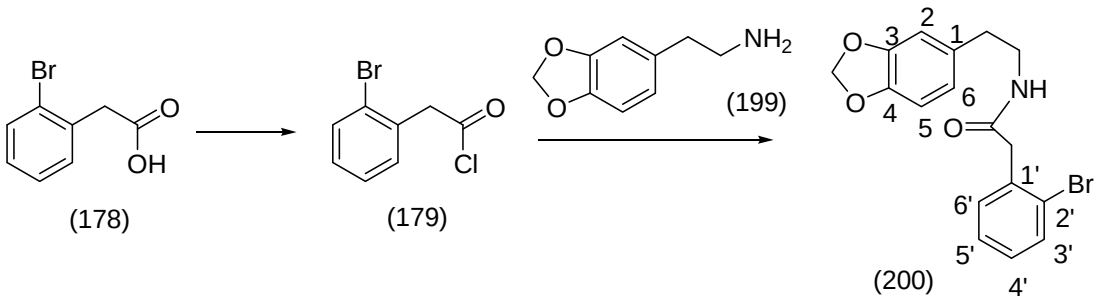
flash column chromatography using methanol-dichloromethane (5:95), 2-(benzo[1,3] dioxol-6-yl)ethanamine (199) was obtained as a pale yellow oil (22 mg, 81%).

FTIR (neat), υ_{max}, cm^{-1}: 3424, 3416 (N-H), 1507 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.67 (d, J = 7.8 Hz, 1H, H-5), 6.62 (d, J = 1.6 Hz, 1H, H-2), 6.57 (dd, J = 7.8, 1.6 Hz, 1H, H-6), 5.82 (d, J = 1.7 Hz, 2H, OCH_2O), 2.85 (t, J = 6.8 Hz, 2H, $ArCH_2C\underline{H}_2N$), 2.59 (t, J = 6.8 Hz, 2H, $ArC\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 147.5, 145.8 (C-3, C-4), 133.1 (C-1), 121.5 (C-2), 108.9 (C-5), 108.1 (C-6), 100.1 (OCH_2O), 43.2 ($ArCH_2\underline{C}H_2N$), 38.9 ($Ar\underline{C}H_2CH_2N$).

_N_-(2-(Benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromophenyl)acetamide (200)



A solution of 2-bromophenylacetic acid (178) (38 mg, 0.18 mmol), oxalyl chloride (0.04 mL, 0.27 mmol) and a catalytic amount of dimethylformamide (1 drop) in benzene (1 mL) was stirred at room temperature. After 2 h, the solvent was removed under reduced pressure to give 2-bromophenylacetyl chloride (179) which was used in the next step without further purification.

The resulting acid chloride (179) in dichloromethane was added to a mixture of 2-(benzo[d][1,3]dioxol-6-yl)ethanamine (199) (30 mg, 0.18 mmol) and sodium carbonate (23 mg, 0.22 mmol) in dichloromethane (1 mL) and water (1 mL). The reaction mixture was stirred at room temperature for 4 h. Organic layer was separated

and the aqueous layer was extracted with dichloromethane (3x10 mL). The combined organic phase was washed with water, brined, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was recrystallized from ethanol to give *N*-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromophenyl)acetamide (200) (61 mg, 93%) as a white needle; m.p. 131-132 ^{o}C.

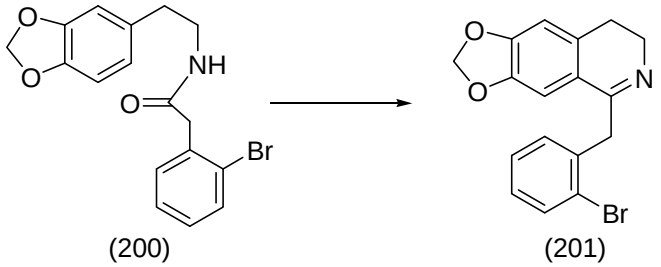
FTIR (KBr), υ_{max}, cm^{-1}: 3288 (N-H), 1638 (C=O), 1547 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.49 (d, J = 8.2 Hz, 1H, H-3'), 7.21-7.19 (m, 2H, H-5', H-6'), 7.09-7.04 (m, 1H, H-4'), 6.58 (d, J = 7.8 Hz, 1H, H-6), 6.48 (d, J = 1.7 Hz, 1H, H-2), 6.41 (dd, J = 7.8, 1.7 Hz, 1H, H-5), 5.83 (s, 2H, OCH_2O), 5.40 (bs, 1H, NH), 3.60 (s, 2H, Ar'C$\underline{H}_2$CO), 3.36 (dt, J = 6.6, 6.0 Hz, 2H, $ArCH_2C\underline{H}_2N$), 2.59 (t, J = 6.8 Hz, 2H, $ArC\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 169.4 (C=O), 147.1, 146.1 (C-3, C-4), 134.7 (C-2'), 133.1 (C-3'), 132.3 (C-1'), 131.6 (C-5'), 129.0 (C-4'), 127.9 (C-6'), 124.9 (C-1), 121.5 (C-5), 108.9 (C-2), 108.2 (C-6), 100.8 (OCH_2O), 43.9 (Ar'$\underline{C}H_2$CO), 40.8 ($ArCH_2\underline{C}H_2N$), 35.1 ($Ar\underline{C}H_2CH_2N$).

HRMS calcd, for $C_{17}H_{17}NO_3Br$: 362.0392, Found 362.0396.

5-(2-Bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (201)

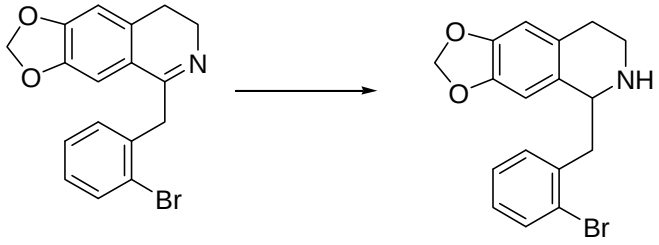


(200) (201)

A cool solution of the *N*-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromo phenyl)acetamide (200) (200 mg, 0.55 mmol) in dry dichloromethane (3 mL) was

treated with phosphorus oxychloride (0.20 mL, 2.21 mmol) and refluxed for 5 h. The reaction mixture was made basic (10% aqueous sodium hydroxide), and extracted with dichloromethane. The organic phase was washed with water, dried with anhydrous sodium sulfate, and concentrated under reduced pressure to give crude 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (201) as a yellow oil. This residue was used in the next step without further purification.

5-(2-Bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (202)



(201) (202)

To a cool solution (0 ^{o}C) of crude product of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (201) in methanol (3 ml) was slowly added sodium borohydride (42 mg, 1.11 mmol) and stirred at room temperature for 2 h. A cool reaction mixture was added with brine and extracted with dichloromethane (3x10 ml). The organic layer was separated and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure. The residue was purified by flash column chromatography using methanol-dichloromethane (3:97) to give 5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (202) (144 mg) (76%) as a yellow liquid.

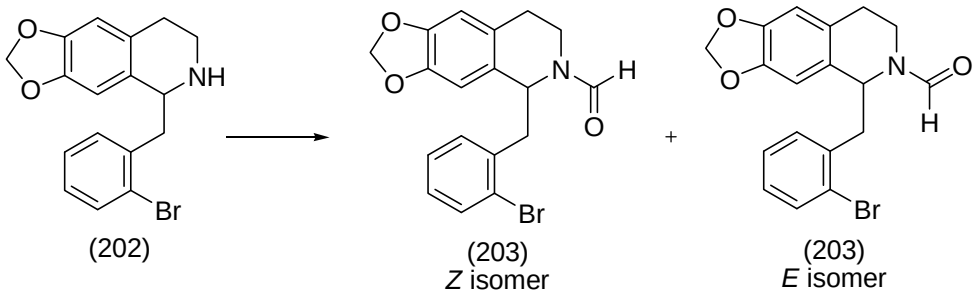
FTIR (neat), υ_{max}, cm^{-1}: 3446 (N-H), 1477 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.52 (d, *J*=7.7 Hz, 1H, H-3'), 7.21-7.20 (m, 2H, H-5', H-6'), 7.08-7.04 (m, 1H, H-4'), 6.76 (s, 1H, H-8), 6.51 (s, 1H, H-5), 5.84 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.84 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.16 (dd , *J*=10.3, 3.2

Hz, 1H, H-1), 3.27 (dd, *J*=13.7, 3.2 Hz, 1H, ArC<u>H</u>$_2$CHNH), 3.19-3.13 (m, 1H, H-3), 2.91-2.84 (m, 2H, Ar'C<u>H</u>$_2$CHNH, H-3), 2.67 (t, *J*= 5.7 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 145.9, 145.7, (C-6), (C-7), 138.7 (C-2'), 133.1 (C-3'), 131.9 (C-6'), 131.7 (C-1'), 128.2 (C-9), 128.2 (C-4'), 127.4 (C-5'), 124.8 (C-10), 108.8 (C-5), 106.5 (C-8), 100.6 (OCH_2O), 55.2 (C-1), 43.0 (Ar<u>C</u>H$_2$CHNH), 39.9 (C-3), 29.9 (C-4).

5-(2-Bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carbaldehyde (203)



A mixture of 5-(2-bromobenzyl)-5,6,7,8 -tetrahydro- [1,3] dioxolo [4,5-g] isoquinoline (202) (15 mg, 0.04 mmol) and ethylformate (1 mL) was heated at reflux. After 3 h, ethylformate was removed by distillation to give crude product. Purification was done by flash chromatography using ethyl acetate-hexane (30%) to give 5- (2-bromobenzyl)- 7,8- dihydro- [1,3] dioxolo [4,5-g] isoquinoline- 6 (5H) - carbaldehyde (203) (13 mg, 82%) as a white solid.

FTIR (KBr), υ_{max}, cm^{-1}: 1655 (C=O), 1476 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.92 (s, 1H, CHO), 7.47 (dd, *J*=7.9, 1.1 Hz, 1H, H-3'), 7.12 (dd, *J*=7.3, 1.2 Hz, 1H, H-5'), 7.04 (dd, *J*=7.2, 1.7 Hz, 1H, H-6'), 7.00 (dd, *J*=7.6, 1.8 Hz, 1H, H-4'), 6.57 (s, 1H, H-8), 6.48 (s, 1H, H-5), 5.86 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.84 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.68 (dd, *J*=10.7, 3.5 Hz, 1H, H-1),

3.57 (m, 2H, H-3), 3.27 (dd, *J*=14.0, 4.7 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.03 (dd, *J*=13.9, 9.4 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.83 (dd, *J*=11.3, 6.2 Hz, 1H, H-4), 2.64 (dd, *J*=4.6, 2.7 Hz, 1H, H-4).

Minor isomer (*Z* isomer) δ: 7.54 (dd, *J*=7.8, 1.3 Hz, 1H, H-3') 7.39 (s, 1H, CHO), 7.19 (dd, *J*=7.5, 1.2 Hz, 1H, H-5'), 7.08 (dd, *J*=7.8, 1.7 Hz, 1H, H-6'), 6.96 (dd, *J*=7.5, 1.7 Hz, 1H, H-4'), 6.76 (s, 1H, H-8), 6.54 (s, 1H, H-5), 5.88 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.87 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.59 (dd, *J*=9.8, 4.9 Hz, 1H, H-1), 4.40 (ddd, *J*= 13.1, 6.2, 2.5 Hz, 1H, H-3), 3.24 (dd, *J*=14.0, 3.5 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.14 (ddd, *J*= 13.2, 11.3, 4.8 Hz, 1H, H-3), 2.98 (dd, *J*=14.0, 10.9 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.78 (dd, *J*=11.2, 6.2 Hz, 1H, H-4), 2.68 (dd, *J*=4.6, 2.7 Hz, 1H, H-4).

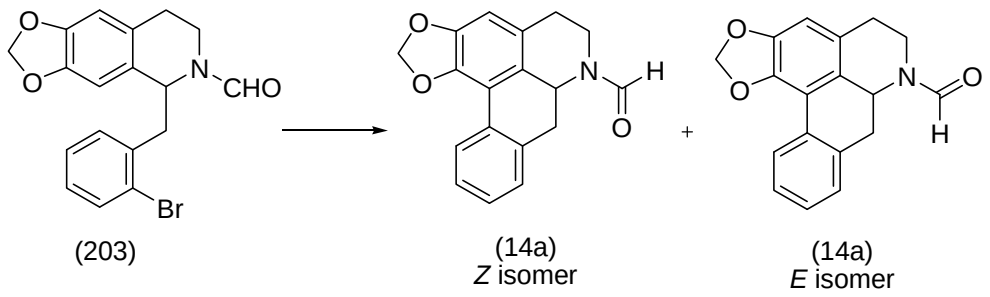
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) δ: 161.1 (CHO), 146.7 (C-2'), 146.4 (C-6), 136.9 (C-7), 132.8 (C-3'), 131.4 (C-6'), 128.5 (C-1'), 128.4 (C-4'), 127.2 (C-5'), 126.2 (C-9), 125.2 (C-10), 108.4 (C-8), 107.2 (C-5), 100.9 (O$\underline{C}H_2$O), 51.0 (C-1), 41.9 (Ar$\underline{C}H_2$CHNH), 40.1 (C-3), 29.7 (C-4).

Minor isomer (*Z* isomer) δ: 161.2 (CHO), 146.9 (C-2'), 146.4 (C-6), 136.5 (C-7), 133.2 (C-3'), 132.1 (C-6'), 129.1 (C-4'), 128.5 (C-1'), 127.9 (C-5'), 127.2 (C-9), 124.4 (C-10), 108.7 (C-8), 106.6 (C-5), 101.1 (O$\underline{C}H_2$O), 56.8 (C-1), 43.3 (Ar$\underline{C}H_2$CHNH), 34.2 (C-3), 28.1 (C-4).

HRMS calcd, for $C_{18}H_{16}NO_3NaBr$: 396.0211, Found 396.0211.

(±)-*N*-Formylannonaine (14a)



A mixture of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carbaldehyde (203) (40 mg, 0.11 mmol), tricyclohexylphosphine (30 mg, 0.11 mmol), sodium acetate (28 mg, 0.34 mmol) and palladium acetate (12 mg, 0.05 mmol) in *N,N*-dimethylacetamide (1 mL) under nitrogen atmosphere was heated at 110 ^{o}C for 24 h. After cooling to room temperature, the reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (40:60) and then was recrystallized from ethanol to give *N*-formylannonaine (14a) (27 mg, 85%) as a colorless crystal; m.p. 218-219 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1659 (C=O), 1457 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*Z* isomer) δ: 8.19 (s, 1H, CHO), 8.02 (d, *J*= 7.8 Hz, 1H, H-11), 7.23-7.18 (m, 3.0 H, H-10, H-9, H-8), 6.51 (s, 1H, H-3), 6.04 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.91 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.98 (dd, *J*= 14.0, 4.4 Hz, 1H, H-6a), 3.75 (ddd, *J*= 12.7, 4.5, 1.8 Hz, 1H, H-5), 3.33 (ddd, *J*=12.4, 12.4, 2.9 Hz, 1H, H-5), 3.16 (dd, *J*= 14.0, 4.4 Hz, 1H, H-7), 2.85-2.61 (m, 3.0 H, H-4, H-4, H-7).

Minor isomer (*E* isomer) δ: 8.32 (s, 1H, CHO), 8.04 (d, *J*= 7.8 Hz, 1H, H-11), 7.23-7.18 (m, 3H, H-10, H-9, H-8), 6.54 (s, 1H, H-3), 6.04 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.91 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.55 (dd, *J*=14.2, 4.2, Hz, 1H, H-6a), 4.40

(ddd, *J*=12.6, 4.5, 3.1 Hz, 1H, H-5), 3.58-3.55 (m, 2H, H-3), 3.11-3.01 (m, 1H, 1H, H-7, H-5), 2.85-2.61 (m, 3H, H-4, H-4, H-7).

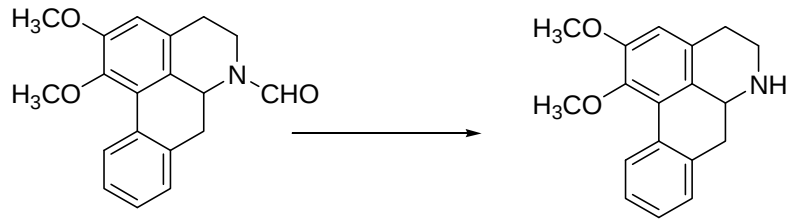
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*Z* isomer) *δ*: 162.1 (C-12), 147.1 (C-2), 143.3 (C-1), 135.1 (C-7a), 128.8 (C-8), 127.9 (C-9), 127.1 (C-10), 127.1 (C-11), 126.6 (C-3a), 124.7 (C-11c), 117.4 (C11b), 107.5 (C-3), 101.0 (OCH_2O), 49.4 (C-6a), 42.2 (C-5), 33.5 (C-7), 31.0 (C-4).

Minor isomer (*E* isomer) *δ*: 162.0 (C-12), 147.1 (C-2), 143.3 (C-1), 135.1 (C-7a), 128.4 (C-8), 128.0 (C-9), 127.5 (C-3a), 127.4 (C-10), 127.1 (C-11), 124.6 (C-11c), 117.4 (C11b), 107.9 (C-3), 101.1 (OCH_2O), 53.3 (C-6a), 37.7 (C-7), 36.2 (C-5), 29.7 (C-4).

HRMS calcd, for $C_{18}H_{15}NO_3Na$: 316.0950, Found 316.0951.

Nuciferine (184)



N-Formylnornuciferine (13) Nuciferine (184)

To a solution of *N*-formylnornuciferine (13) (10 mg, 0.03 mmol) in methanol (0.5 mL) was added saturated hydrogen chloride in methanol (0.06 mL) and refluxed for 13 h. The mixture was concentrated under reduced pressure, and the residue was extracted with dichloromethane. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting

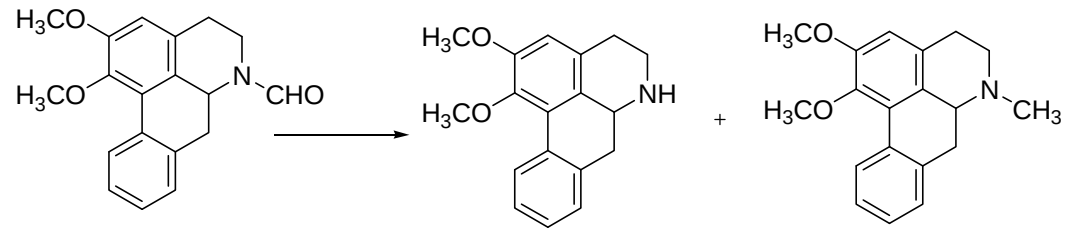
with 5:95 methanol: dichloromethane to provide nuciferine (184) (8 mg, 89%) as a colorless oil.

FTIR (neat), υ_{max}, cm^{-1}: 3380 (N-H), 1420 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.31 (d, *J*=7.9 Hz, 1H, H-11), 7.23 (ddd, *J*=7.8, 6.7, 2.4 Hz, 1H, H-10), 7.16-7.12 (m, 1H, H-9, H-8), 6.57 (s, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.77 (dd, *J*=13.7, 4.7 Hz, 1H, C-6a), 3.59 (s, 3H, OCH_3), 3.33-3.30 (m, 1H, H-5), 2.96-2.94 (m, 2H, H-5, H-4), 2.79 (dd, *J*=13.8, 4.7 Hz, 1H, H-7), 2.69 (d, *J*=13.7 Hz, 1H, H-7), 2.65-2.62 (m, 1H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 152.2 (C-2), 145.2 (C-1), 136.1 (C-7a), 132.2 (C-11a), 128.8 (C-11c), 128.8 (C-11b), 128.4 (C-8), 127.7 (C-9), 127.4 (C-11), 127.0 (C-10), 126.5 (C-3a), 111.8 (C-3), 60.2 (OCH_3), 55.9 (OCH_3), 53.5 (C-6a), 43.1 (C-5), 37.4 (C-7), 29.1 (C-4).

Nuciferine (184) and nornuciferine (204)



N-Formylnornuciferine (13a) Nuciferine (184) Nornuciferine (204)

Method I

To a suspension of lithium aluminium hydride (33 mg, 0.87 mmol) in tetrahydrofuran (1 mL) was added a mixture of *N*-formylnornuciferine (13a) (60 mg, 0.19 mmol) in tetrahydrofuran (2 mL) under nitrogen atmosphere at -78^{o}C. After the mixture was stirred for 2 h at room temperature, a suspension was carefully added saturated potassium carbonate solution (0.1 mL) and extracted with diethyl ether

(3x100 ml). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. Purification of crude product by flash chromatography using methanol-dichloromethane (4:96) afforded nuciferine (184) as a colourless oil (46 mg, 86%) and nornuciferine (204) as a white solid (6 mg, 11%), m.p. 133-134 ^{o}C.

Method II

To a stirred suspension of lithium aluminium hydride (33 mg, 0.87 mmol) in dry tetrahydrofuran (1 mL) was added a mixture of *N*-formylnornuciferine (13a) (60 mg, 0.19 mmol) in dry tetrahydrofuran (2 mL) under nitrogen atmosphere at 0 ^{o}C. After 1 h of reflux, the mixture was allowed to cool to room temperature and was added saturated potassium carbonate solution (0.1 mL). The mixture was extracted with diethyl ether and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (4:96 methanol: dichloromethane) to provide nornuciferine (204) as a colourless oil 44 mg, 78%), m.p. 133-134 ^{o}C.

Noruciferine (204)

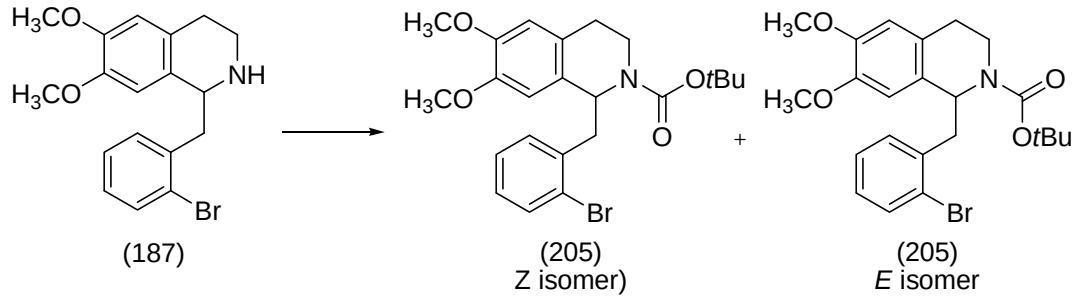
FTIR (KBr), υ_{max}, cm^{-1}: 1449 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.28 (dd, *J*=7.8, 1.0 Hz, 1H, H-11), 7.23 (dddd, *J*=7.8, 7.4, 2.0 0.9 Hz, 1H, H-10), 7.19-7.16 (m, 1H, H-9), 7.14 (dd, *J*=7.4, 1.2 Hz, 1H, H-8), 6.55 (s, 1H, H-3), 3.80 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.08 (ddd, *J*=16.0, 12.0, 6.0 Hz, 1H, H-4), 3.01 (dd, *J*=13.5, 4.0 Hz, 1H, H-7), 2.97 (dd, *J*=12.0, 6.0 1.4 Hz, 1H, H-5), 2.93 (dd, *J*=13.5, 4.0 Hz, 1H, H-6a), 2.60 (dd, *J*=16.0, 4.0 Hz, 1H, H-4), 2.53 (dd, *J*=13.5, 13.5 Hz, 1H, H-7), 2.46 (s, 3H, N-CH_3), 2.42 (ddd, *J*=12.0, 12.0, 4.0 Hz, 1H, H-5).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 151.9 (C-2), 145.1 (C-1), 136.4 (C-7a), 132.1 (C-11a), 128.7 (C-11c), 128.3 (C-8), 127.9 (C-11b), 127.8 (C-9), 127.3 (C-11), 126.9 (C-3a), 126.8 (C-10), 111.2 (C-3), 62.3 (C-6a), 60.2 (OCH_3), 55.8 (OCH_3), 53.2 (C-5), 43.9 (N-CH_3), 35.1 (C-7), 29.2 (C-4).

HRMS calcd, for $C_{19}H_{22}NO_2$: 296.1651, Found 296.1652.

1-(2-Bromobenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (205)



To a cool (0 ^oC) solution of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxy isoquinoline (187) (20 mg, 0.05 mmol) in tetrahydrofuran (0.5 mL) was added 1N sodium hydroxide solution (0.11 mL). Di-*tert*-butylcarbonate (12 mg, 0.05 mmol) was added to the above solution and stirring was continued for 30 min at 0 ^oC. The reaction mixture was stirred at room temperature for 1 h. The organic solvent was stripped in vacuum and the aqueous residue was diluted with water (10 mL). The cloudy solution was extracted with dichloromethane (3x20 mL). The organic extract was dried over anhydrous sodium sulfate, filtrated and concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with 15:85 ethyl acetate: hexane. Recrystallization from ethanol gave 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (205) (21 mg, 82%) as a white crystal with m.p. 110-111^oC.

FTIR (KBr), υ_{max}, cm^{-1}: 1689 (C=O), 1419 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.50 (dd, *J*=7.9, 0.8 Hz, 1H, H-3'), 7.15 (ddd, *J*=7.4, 7.4, 1.0 Hz, 1H, H-5'), 7.05 (ddd, *J*=7.7, 7.7, 1.5 Hz, 1H, H-4'), 7.01 (dd, *J*=7.4, 1.5 Hz, 1H, H-6'), 6.73 (s, 1H, H-8), 6.55 (s, 1H, H-5), 5.29 (dd, *J*=10.6, 3.3 Hz, 1H, H-1), 4.30 (dd, *J*=12.2, 4.8 Hz, 1H, H-3), 3.79 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.25-3.18 (m, 2H, Ar'C$\underline{H}_2$CHNH, H-3), 2.92 (dd, *J*=13.6, 10.8 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.83 (dd, *J*=11.4, 5.9 Hz, 1H, H-4), 2.61-2.56 (m, 1H, H-4), 1.04 (s, 9H, BOC(CH_3)).

Minor isomer (*Z* isomer) δ: 7.43 (d, *J*=8.0 Hz, 1H, H- 3'), 7.17-6.97 (m, 3H, H-6', H-5', H-4'), 6.51 (s, 1H, H-8), 6.37 (s, 1H, H-5), 5.34 (d, *J*=6.0Hz, 1H, H-1), 3.76 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.36 (dd, *J*=13.7, 6.0 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.05 (dd, *J*=13.2, 8.2 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.76-2.70 (m, 1H, H-3), 2.61-2.56 (m, 1H, H-4), 1.28 (s, 9H, BOC(CH_3)).

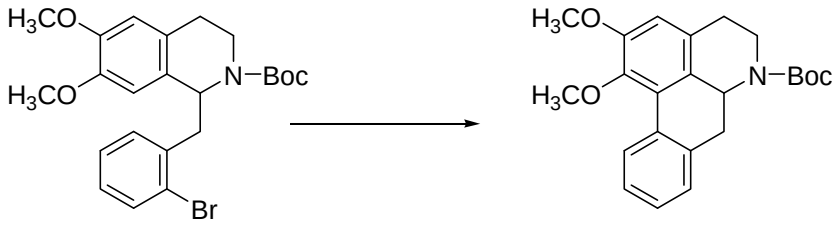
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) δ: 154.2 (BOC (C=O)), 147.9, 147.4 (C-7, C-6), 138.2 (C-2'), 132.5 (C-3'), 131.9 (C-6'), 128.9 (C-1'), 128.2 (C-4'), 127.5 (C-5'), 126.5 (C-9), 125.2 (C-10), 111.5 (C-8), 109.9 (C-5), 79.4 (BOC (Cq)), 55.9 (OCH_3), 55.9 (OCH_3), 53.7 (C-1), 42.7 (Ar'$\underline{C}H_2$CHNH), 36.2 (C-3), 28.3 (C-4), 27.9 (BOC (CH_3)).

Minor isomer (*Z* isomer) δ: 154.3 (BOC (C=O)), 147.9, 147.5 (C-7, C-6), 138.1 (C-2'), 131.6 (C-3'), 131.6 (C-6'), 128.8 (C-1'), 127.9 (C-4'), 127.1 (C-5'), 126.4 (C-9), 125.4 (C-10), 111.1 (C-8), 110.3 (C-5), 79.3 (BOC (Cq)), 55.8 (OCH_3), 55.8 (OCH_3), 53.8 (C-1), 41.9 (Ar'$\underline{C}H_2$CHNH), 38.8 (C-3), 28.3 (C-4), 28.1 (BOC (CH_3)).

HRMS calcd, for $C_{23}H_{30}NO_4NaBr$: 486.1256, Found 486.1257.

1-(1,2-Dimethoxy)-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester (206)



(205) (206)

A dry three-necked flask, equipped with a magnetic stirring bar, septum, and condenser with an nitrogen inlet-outlet was charged with palladium acetate (14 mg, 0.06 mmol), sodium acetate (34 mg, 0.41 mmol), tricyclohexylphosphine (36 mg, 0.13 mmol), and 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (205) (60 mg, 0.13 mmol). The flask was flushed with nitrogen and dimethylacetamide (2 mL) was added. The reaction mixture was heated to 110 °C and stirred with gentle reflux for 14 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (20:80) and then was recrystallized from methanol to 1-(1,2-dimethoxy)-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester (206) (44 mg, 85%) as a colorless crystal, m.p. 156-158 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1689 (C=O), 1410 (C=C).

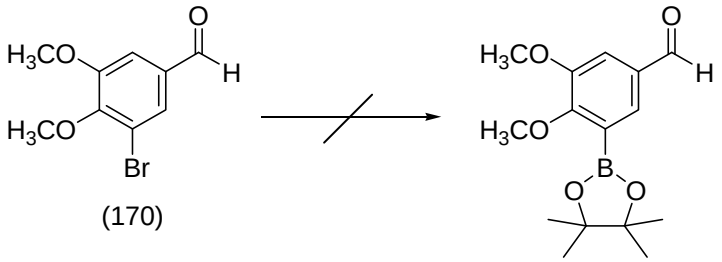
^{1}H NMR ($CDCl_3$, 400 MHz), δ: 8.35 (d, J=7.8Hz, 1H, H-11), 7.25-7.13 (m, 3H, H-10, H-9, H-8), 6.59 (s, 1H, H-3), 4.58 (d, J=14.0 Hz, 1H, H-6a), 4.33 (d, J=11.0 Hz, 1H, H-5), 3.81 (s. 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.91-2.71 (m, 4H, H-7, H-7, H-5, H-4), 2.59-2.55 (m, 1H, H-4), 1.41 (s, 9H, Boc(CH_3)).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 154.5 (BOC (C=O)), 151.9 (C-2), 145.6 (C-1), 136.9 (C-7a), 131.7 (C-11a), 129.8 (C-11c), 128.4 (C-11), 128.0 (C-9), 127.6 (C-

8), 127.5 (C-11b), 126.9 (C-3a), 126.5 (C-10), 111.4 (C-3), 79.8 (BOC (Cq)), 59.9 (OCH_3), 55.9 (OCH_3), 51.6 (C-6), 38.2 (C-5), 35.3 (C-7), 30.4 (C-4), 28.5 (BOC (CH_3)).

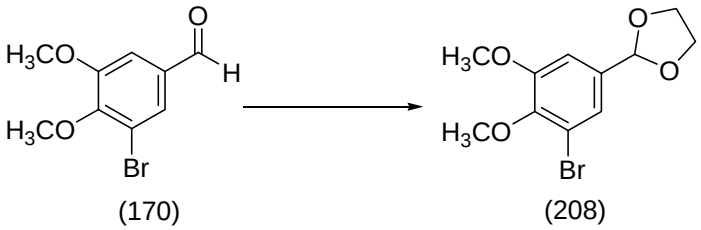
HRMS calcd, for $C_{23}H_{27}NO_4Na$: 404.1838, Found 404.1832.

3,4-Dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (207)



A mixture of 3-bromo-4,5-dimethoxybenzaldehyde (170) (50 mg, 0.20 mmol), bis(pinacolato)diboron (24 mg, 0.10 mmol), [1,1'-bis(diphenyl phosphino)ferrocene] dichloropalladium (3 mg, 0.004 mmol), potassium carbonate (84 mg, 0.61 mmol) in dimethyl sulfoxide (1 ml) under nitrogen atmosphere was stirred at room temperature for 12 h. The reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. Analytical TLC on siliga gel (20% ethyl acetate/ hexane) showed only the starting material's spot.

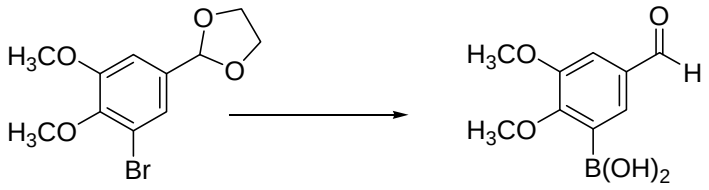
2-(3-Bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (208)



To a solution of 3-bromo-4,5-dimethoxybenzaldehyde (170) (200 mg, 0.82 mmol) in dichloromethane (5 mL) was added ethylene glycol (1.8 mL, 32.6 mmol), triethylorthoformate (1.1 mL, 6.12 mol) and *p*-toluenesulfonic acid (0.02 mL, 0.08 mmol), respectively. After 1 h of stirring, the reaction mixture was basified by adding triethylamine. The mixture was extracted with dichloromethane and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5:95 ethyl acetate: hexane) to provide 2-(3-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (210) (211 mg, 89%) as a colourless gum.

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.80 (d, J=2.0 Hz, 1H, H-2), 7.47 (d, J=2.0 Hz, 1H, H-6), 4.39 (t, J=4.6 Hz, 2H, CH_2O), 3.89 (t, J=4.6 Hz, 2H, CH_2O), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3).

5-Formyl-2,3-dimethoxyphenylboronic acid (209)



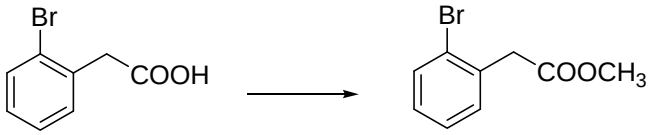
(208) (209)

A solution of 1.6 M *n*-butyllithium in hexane (0.13 mL, 0.21 mmol) was added dropwise to a solution of 2-(3-bromo-4,5-dimethoxyphenyl)-1,3-dioxolane (208) (50 mg, 0.17 mmol) in tetrahydrofuran (2 mL) at -78 ^oC under nitrogen atmosphere. After stirring for 1 h, trimethoxyborane (0.04 mL, 0.35 mmol) was added and the reaction mixture was left overnight at room temperature. Then, it was cooled to 0 ^oC, 2 M hydrochloric acid was added, and the mixture was stirred for 12 h at room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3x10 mL). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15:85

ethyl acetate: hexane) to provide 5-formyl-2,3-dimethoxyphenylboronic acid (209) (24 mg, 64%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.87 (s, 1H, CHO), 7.86 (d, J=2.0 Hz, 1H, H-2), 7.50 (d, J=2.0 Hz, 1H, H-6), 5.89 (br s, 2H, OH), 3.98 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).

Methyl 2-(2-bromophenyl)acetate (210)

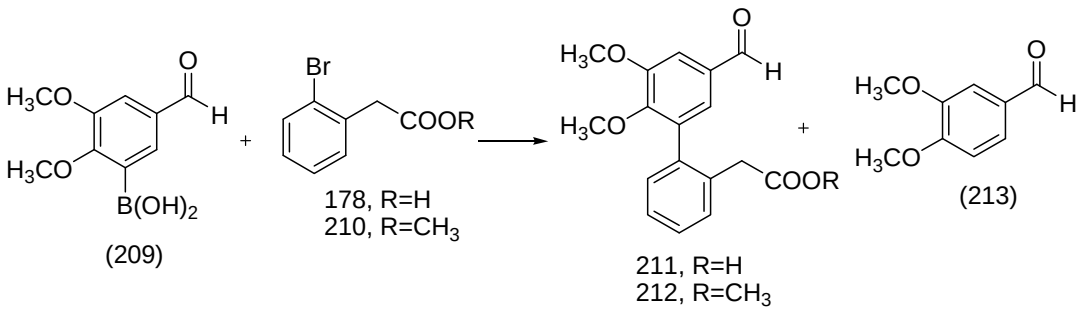


(178) (210)

To a suspension of 2-(2-bromo phenyl)acetic acid (178) (100 mg, 0.46 mmol) and potassium carbonate (78 mg, 0.69 mmol) in acetone (1 mL) was added iodomethane (0.04 mL, 0.68 mmol). After refluxing for 5 h, the reaction mixture was cooled to room temperature and was concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The combined organic layer was dried over anhydrous sodium sulfate, filterated and evaporated under reduced pressure to dryness. The crude product was further purified by silica gel flash column chromatography with 5:95 ethyl acetate: hexane as eluent. The product was a white solid with an isolated yield of 100 mg, 94%.

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.51 (d, J=8.4 Hz, H-3), 7.24-7.20 (m, 2H, H-4, H-5), 7.11-7.06 (m, 1H, H-6), 3.78 (s, 3H, $COOCH_3$), 3.67 (s, 3H, OCH_3).

2,3-Dimethoxy-5-benzaldehyde-1,1'-biphenyl-2'-carboxylate ester (213 or 214)



Method I

A solution of 5-formyl-2,3-dimethoxyphenylboronic acid (209) (20 mg, 0.09 mmol) in mixture of dimethoxy ethane (1 mL), was introduced *via* a syringe in a two-necked round bottomed flask containing sodium carbonate (9 mg, 0.09 mmol), tris(dibenzylideneacetone)dipalladium (5 mg, 0.0006 mmol) and 2-(2-bromo phenyl)acetic acid (178) (6 mg, 0.03 mmol). After stirring at reflux for 4 h, the mixture was filtration over celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15:85 ethyl acetate: hexane) to provide 3,4-dimethoxybenzaldehyde (213) (9 mg, 65%).

3,4-Dimethoxybenzaldehyde (213)

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.82 (s, 1H, CHO), 7.43 (dd, *J*=8.2, 1.8 Hz, H-2), 7.38 (d, *J*=1.8 Hz, H-6), 6.95 (d, *J*=8.2 Hz, H-3), 3.94 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3).

Method II

A mixture of 5-formyl-2,3-dimethoxyphenylboronic acid (209) (15 mg, 0.06 mmol), 2-(2-bromophenyl)acetic acid (178) (5 mg, 0.02 mmol), tetrakis (triphenylphosphine)palladium (0.5 mg, 0.0004 mmol) and sodium carbonate (7 mg, 0.06 mmol) in a mixture of ethanol/dimethoxyethane (0.5 mL/0.5 mL) under nitrogen

atmosphere was refluxed for 4 h. The reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (15:85 ethyl acetate: hexane) to provide 3,4-dimethoxybenzaldehyde (213) (6 mg, 63%).

Method III

A solution of 5-formyl-2,3-dimethoxyphenylboronic acid (209) (30 mg, 0.13 mmol) in mixture of ethanol/ dimethoxy ethane (1mL/1 mL), was introduced *via* a syringe in a two-necked round bottomed flask containing sodium hydroxide (7 mg, 0.16 mmol), tetrakis(triphenylphosphine)palladium (0.5 mg, 0.0004 mmol) and 2-(2-bromophenyl)acetic acid (178) (10 mg, 0.04 mmol). After stirring at room temterature for 4 h, the mixture was filtration over celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15:85 ethyl acetate: hexane) to provide 3,4-dimethoxybenzaldehyde (213) (9 mg, 42%) and 5-formyl-2,3-dimethoxyphenylboronic acid (209) (2 mg, 11%).

Method IV

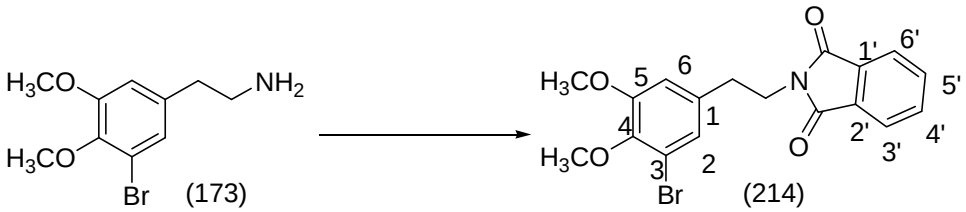
A solution of 5-formyl-2,3-dimethoxyphenylboronic acid (209) (30 mg, 0.13 mmol) in mixture of ethanol/ dimethoxy ethane (1 mL/1 mL), was introduced *via* a syringe in a two-necked round bottomed flask containing cesium carbonate (44 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium (1 mg, 0.0009 mmol) and 2-(2-bromophenyl)acetic acid (178) (9 mg, 0.04 mmol). After stirring at room temterature for 4 h, the mixture was filtration over celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15:85 ethyl acetate: hexane) to provide 3,4-dimethoxybenzaldehyde (213) (15 mg, 71%).

Method V

A solution of 5-formyl-2,3-dimethoxyphenylboronic acid (209) (20 mg, 0.09 mmol) in carefully degassed ethanol (1 mL), was introduced *via* a syringe in a two-

necked round bottom flask containing sodium carbonate (9 mg, 0.09 mmol), tetrakis(triphenylphosphine)palladium (0.6 mg, 0.0006 mmol) and methyl 2-(2-bromophenyl)acetate (210) (6 mg, 0.03 mmol). After stirring at reflux for 6 h, the mixture was filtration over celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10:90 ethyl acetate: hexane) to provide 3,4-dimethoxybenzaldehyde (213) (9 mg, 62%).

2-(3-Bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione (214)



A mixture of 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (173) (100 mg, 0.39 mmol), phthalic anhydride (114 mg, 0.77 mmol), and acetic acid (1 mL) was heated at reflux under vigorous stirring for 7 h. The mixture was cooled to 0 ^{o}C, and 0.5 mL of distillated water was added. The precipitate was collected and vacuum dried to afford 2-(3-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione (214) (135 mg, 89 %) which was reprecipitated again from hexane/ ethyl acetate to give a white solid with m.p.130-131 ^{o}C.

FTIR (KBr), υ_{max}, cm^{-1}: 1710 (C=O), 1564 (C=C).

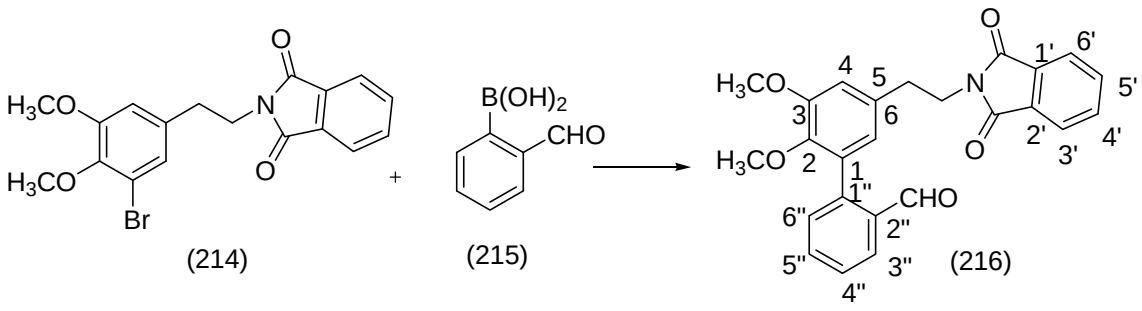
^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.76 (dd, *J*=3.0, 5.4 Hz, 2H, H-4', H-5'), 7.63 (dd, *J*=5.4, 3.0 Hz, 2H, H-3', H-6'), 6.95 (d, *J*=2.0 Hz, 1H, H-2), 6.67 (d, *J*=2.0 Hz, 1H, H-6), 3.83 (t, *J*=7.8 Hz, 2H, $ArCH_2C\underline{H}_2N$), 3.75 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 2.84 (t, *J*=7.8 Hz, 2H, $ArC\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 168.1 (C=O), 152.7 (C-3), 144.5 (C-1), 134.4 (C-5), 133.8 (C-3', C-6'), 119.6 (C-2), 124.4 (C-1', C-2'), 122.8 (C-4', C-5'),

117.8 (C-4), 112.3 (C-6), 61.4 (OCH_3), 56.1 (OCH_3), 38.4 ($ArCH_2\underline{C}H_2N$), 33.8 ($Ar\underline{C}H_2CH_2N$).

HRMS calcd, for $C_{18}H_{16}NO_4NaBr$: 412.0160, Found 412.0157.

2,3-Dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-carbox aldehyde (216)



Method I

To a solution of palladium triphenylphosphine (6 mg, 0.005 mmol) and 2-(3-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione (214) (50 mg, 0.13 mmol) in dimethoxyethane (1 mL) was added 1.8 M sodium carbonate (0.13 mL). After stirring at room temterature for 5 min, a solution of 2-formylphenylboronic acid (215) (17 mg, 0.12 mmol) in dimethoxyethane (1 mL) was added to a reaction. The mixture was heated to 95 ^oC for 5h. After reaction was cooled to room temperature, the mixture was added ammonium chloride solution and extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5:95 ethyl acetate: hexane) to provide starting material (214) (21 mg, 42%).

Method II

A mixture of 2-(3-bromo-4,5-dimethoxyphenethyl)isoindoline-1,3-dione (214) (300 mg, 0.77 mmol), tricyclohexylphosphine (8 mg, 0.04 mmol), palladium acetate (2 mg, 0.02 mmol), 2-formylphenylboronic acid (215) (142 mg, 0.95 mmol), potassium phosphate (229 mg, 1.53 mmol) in toluene (10 mL) under nitrogen atmosphere was heated at 110 ^{o}C for 24 h. After cooling to room temperature, the reaction mixture was filtered through celite pad and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (15:85) to give 2,3-dimethoxy-5-((2-phenylethyl) isoindole-1,3-dione)-1,1'-biphenyl-2'-carbox aldehyde (216) (272 mg, 85%) as a pale-yellow gum.

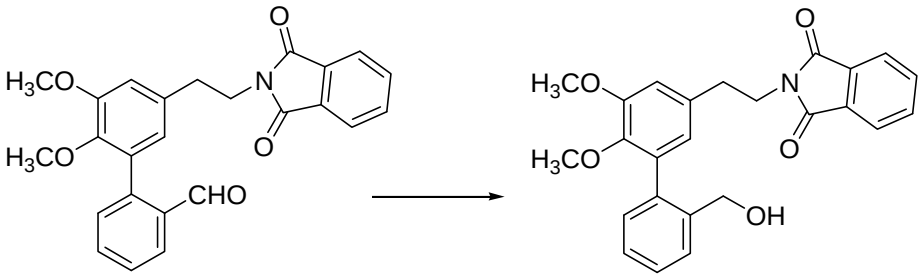
FTIR (neat), υ_{max}, cm^{-1}: 1713 (C=O), 1585 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.64 (d, *J*=0.7 Hz, 1H, CHO), 7.86 (dd, *J*=7.8, 1.3 Hz, 1H, H-6"), 7.69 (dd, *J* = 3.0, 5.4 Hz, 2H, H-4', H-5'), 7.59 (dd, *J* = 5.4, 3.0 Hz, 2H, H-3', H-6'), 7.47 (ddd, *J*=7.5, 7.5, 1.4 Hz, 1H, H-4"), 7.35 (ddd, *J*=7.8, 7.5, 1.0 Hz, 1H, H-5"), 7.17 (dd, *J*=7.5, 0.7 Hz, 1H, H-3"), 6.77 (d, *J* = 2.0 Hz, 1H, H-6), 6.64 (d, *J* = 2.0 Hz, 1H, H-4), 3.87 (t, *J* =7.8 Hz, 2H, $ArCH_2C\underline{H}_2N$), 3.73 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 2.90 (t, *J* =7.8 Hz, 2H, $ArC\underline{H}_2CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 191.8 (CHO), 167.9 (C=O), 152.3 (Cq aromatic), 144.9 (Cq aromatic), 141.1 (Cq aromatic), 134.0 (Cq aromatic), 133.8 (C-3', C-6'), 133.5 (Cq aromatic), 133.1 (C-4"), 131.8 (Cq aromatic), 131.7 (Cq aromatic), 130.7 (C-3"), 127.6 (C-5"), 126.5 (C-6"), 123.0 (C-6), 122.9 (C-4', C5'), 113.1 (C-4), 60.1 (OCH_3), 55.7 (OCH_3), 38.8 ($ArCH_2\underline{C}H_2N$), 33.9 ($Ar\underline{C}H_2CH_2N$).

HRMS calcd, for $C_{25}H_{21}NO_5Na$: 438.1317, Found 438.1309.

2,3-Dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-benzyl alcohol (217)



To a suspended solution of sodium cyanoborohydride (18 mg, 0.09 mmol) and zinc chloride (6 mg, 0.04 mmol) in diethyl ether (1 mL) at room temperature was added 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-carbox aldehyde (216) (30 mg, 0.07 mmol). The reaction mixture was stirred at room temperature for 4 h and diluted with diethyl ether (10 mL). The mixture was extracted with diethyl ether and the combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20:80 ethyl acetate: hexane) to provide 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-benzyl alcohol (219) as a white solid (25 mg, 86%). Recrystallization of compound **217** from ethyl acetate/ hexane gave a white crystal with m.p. 101-102 ^{o}C.

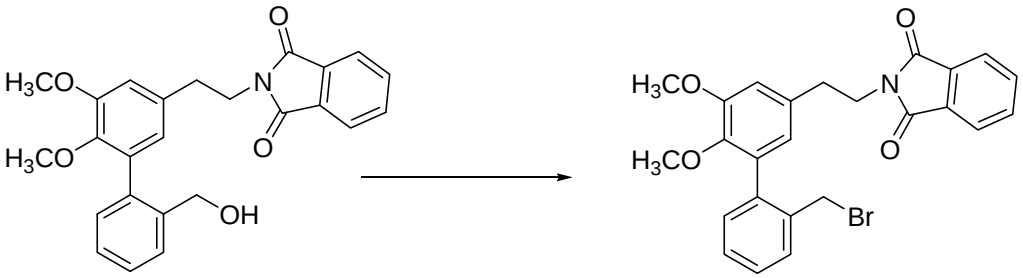
FTIR (KBr), υ_{max}, cm^{-1}: 3421 (O-H), 1713 (C=O), 1580 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.75-7.72 (m, 2H, H-4', H-5'), 7.63-7.61 (m, 2H, H-3', H-6'), 7.42 (d, *J*=7.5 Hz, 1H, H-6"), 7.29 (ddd, *J*=7.5, 7.5, 1.4 Hz, 1H, H-5"), 7.21 (ddd, *J*=7.5, 7.5, 1.4 Hz, 1H, H-4"), 7.02 (d, *J*=7.5, 1H, H-3"), 6.71 (d, *J*=1.9, 1H, H-6)**.** 6.57 (d, *J*=1.9, 1H, H-4), 4.23 (s, 2H, C$\underline{H}_2$OH), 3.87 (t, *J*=7.7 Hz, 2H, ArCH$_2$C$\underline{H}_2$N), 3.74 (s, 3H, OCH_3), 3.34 (s, 3H, OCH_3), 2.89 (t, *J*=7.7 Hz, 2H, ArC$\underline{H}_2$CH$_2$N).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 168.1 (C=O), 152.3 (Cq aromatic), 144.6 (Cq aromatic), 139.2 (Cq aromatic), 136.9 (Cq aromatic), 135.3 (Cq aromatic), 134.2 (Cq aromatic), 133.9 (C-3', C-6'), 131.9 (Cq aromatic), 129.6 (C-3"), 129.2 (C-6"), 128.0 (C-5"), 127.3 (C-4"), 123.2 (C-4), 123.1 (C-4', C-5'), 112.3 (C-6), 63.6 ($\underline{C}H_2OH$), 60.7 (OCH_3), 55.7 (OCH_3), 39.0 ($ArCH_2\underline{C}H_2N$), 34.1 ($Ar\underline{C}H_2CH_2N$).

HRMS calcd, for $C_{25}H_{23}NO_5Na$: 440.1474, Found 440.1474.

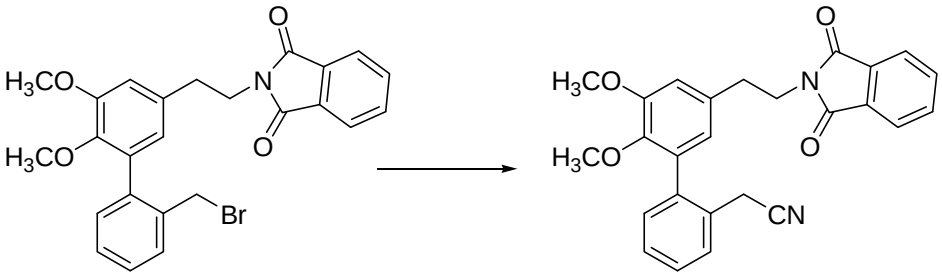
2,3-Dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-benzyl bromide (218)



(217) (218)

To a solution of 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-benzyl alcohol (217) (15 mg, 0.04 mmol) in dichloromethane (1 mL) was added phosphorus tribromide (0.01 mL, 0.07 mmol). After 20 min of stirring at room temperature, the reaction mixture was evaporated under reduced pressure to give the yellow residue which was dissolved in dichloromethane and then sodium hydrogen carbonate was added. The precipitate was filtered off through sodium sulfate pad, and the solvent was evaporated under reduced pressure. The residue was used in the next step without further purification.

2,3-Dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-phenyl acetonitrile (219)



(218) (219)

The crude of 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-benzyl bromide (218) and sodium cyanide (2 mg, 0.04 mmol) were mixed in dimethylformamide (1 mL) and stirred at room temperature for 1 h. The solvent was then removed under reduced pressure and the residue was partitioned between ether (30 mL) and water (10 mL). The aqueous phase was extracted with ether (10 mL) and the combined organic phase was washed with water, brine and then dried over anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by flash column chromatography using ethyl acetate: hexane (20:80) to give 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-phenylaceto nitrile (219) as a white solid (13 mg, 81% (two steps)). Recrystallization of compound **219** from ethyl acetate/ hexane gave a white crystal with m.p.141-142 ^{o}C.

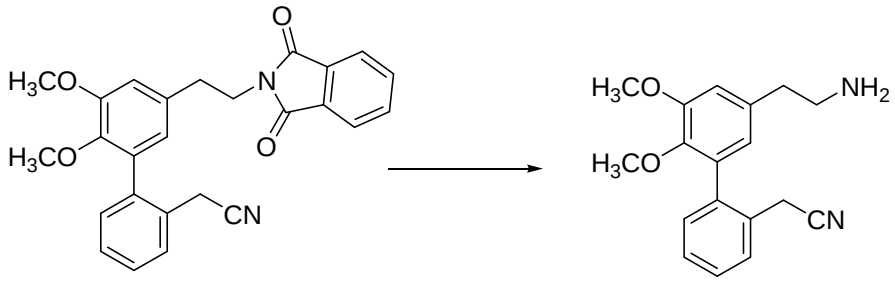
FTIR (KBr), υ_{max}, cm^{-1}: 1707 (C=O), 1586 (C=C), 2244 (C≡N).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.75 (dd, *J* = 3.0, 5.4 Hz, 2H, H-4', H-5'), 7.64 (dd, *J* = 3.0, 5.4 Hz, 2H, H-3', H-6'), 7.48 (dd, *J*=7.5, 0.5 Hz, 1H, C-6"), 7.32 (dd, *J*=7.5, 7.5, 1.4 Hz, 1H, H-5"), 7.25 (dd, *J*=7.5, 7.5, 1.4 Hz, 1H, H-4"), 7.09 (dd, *J*=7.5, 1.4, 1H, H-3"), 6.74 (d, *J*=2.0, 1H, H-6), 6.55 (d, *J*=2.0, 1H, H-4), 3.89 (t, *J*=7.6 Hz, 2H, $ArCH_2C\underline{H_2}N$), 3.76 (s, 3H, OCH_3), 3.67 (d, *J*=19.0 Hz, 1H, $C\underline{H_2}CN$), 3.35 (s, 3H, OCH_3), 3.33 (d, *J*=19.0 Hz, 1H, $C\underline{H_2}CN$), 2.91 (t, *J*=7.6 Hz, 2H, $ArC\underline{H_2}CH_2N$).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 168.1 (C=O), 152.6 (Cq aromatic), 144.7 (Cq aromatic), 137.5 (Cq aromatic),137.5 (Cq aromatic), 134.5 (Cq aromatic), 134.0 (C-3', C-6'), 133.9 (Cq aromatic), 131.9 (Cq aromatic), 130.2 (C-3"), 129.1 (Cq aromatic), 128.2 (C-5"), 127.8 (C-6"), 127.6 (C-4"), 123.2 (C-4', C-5'), 122.9 (C-6). 118.4 (Cq aromatic), 112.8 (C-4), 60.7 (OCH_3), 55.8 (OCH_3), 39.1 ($ArCH_2\underline{C}H_2N$), 34.2 ($Ar\underline{C}H_2CH_2N$), 21.7 ($\underline{C}H_2CN$).

HRMS calcd, for $C_{26}H_{22}N_2O_4Na$: 449.1477, Found 449.1477.

2,3-Dimethoxy-5-(2-aminoethyl)-1,1'-biphenyl-2'-phenylacetonitrile (220)



(219) (220)

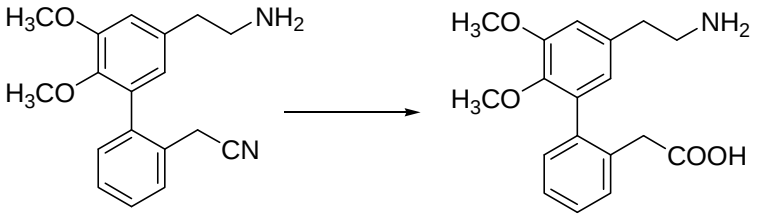
A mixture of 2,3-dimethoxy-5-((2-phenylethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-phenyl acetonitrile (219) (40 mg, 0.09 mmol) and 65% hydrazine monohydrate (0.002 ml, 0.38 mmol) in methanol (1 mL) was stirred at room temperature for 1 h. The reaction was evaporated in *vacuo* to give an oily white solid, which was transferred to a separatory funnel and partitioned in ether (10 mL) and water (10 mL). The aqueous phase was separated and extracted with ether (10x3 mL) and the combined organic phases were washed with water, brine and then dried over sodium sulfate. After removal of solvent and purification by flash column chromatography using methanol-dichloromethane (10:90), 2,3-dimethoxy-5-(2-aminoethyl)-1,1'-biphenyl-2'-phenyl acetonitrile (220) was obtained as a pale yellow oil (22 mg, 83%).

FTIR (neat), υ_{max}, cm^{-1}: 3462 (N-H), 1586 (C=C), 2238 (C≡N).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.45 (dd, *J*=7.5, 1.7 Hz, 1H, H-6”), 7.32 (dd, *J*=7.5, 7.5, 1.7 Hz, 1H, H-5”), 7.29 (dd, *J*=7.5, 7.5, 1.7 Hz, 1H, H-4”), 7.21 (dd, *J*=7.5, 1.4, 1H, H-3”), 6.75 (d, *J*=2.0, 1H, H-6), 6.56 (d, *J*=2.0, 1H, H-4), 3.83 (s, 3H, OCH_3), 3.68 (d, *J*=18.7 Hz, 1H, $C\underline{H}_2CN$), 3.48 (d, *J*=18.7 Hz, 1H, $C\underline{H}_2CN$), 3.37 (s, 3H, OCH_3), 2.95 (t, *J*=6.8 Hz, 2H, $ArCH_2C\underline{H}_2N$), 2.71 (t, *J*=6.8 Hz, 2H, $ArC\underline{H}_2CH_2N$), 2.34 (br s, 2H, NH_2).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 144.4 (Cq aromatic), 137.8 (Cq aromatic), 136.0 (Cq aromatic), 133.8 (Cq aromatic), 130.3 (C-3), 129.2 (Cq aromatic), 128.2 (C-5), 128.1 (C-4), 127.8 (C-6), 122.8 (C-6), 118.3 (Cq aromatic), 112.7 (C-4), 60.7 (OCH_3), 55.9 (OCH_3), 43.0 ($ArCH_2\underline{C}H_2N$), 38.9 ($Ar\underline{C}H_2CH_2N$), 21.9 ($\underline{C}H_2CN$).

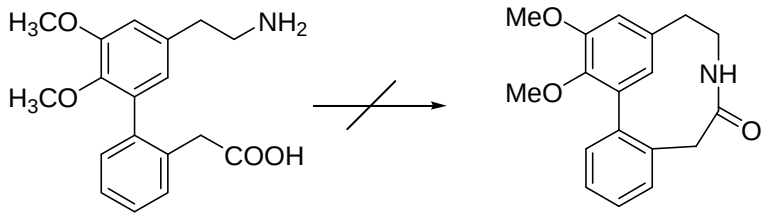
2,3-Dimethoxy-5-(2-aminoethyl)-1,1’-biphenyl-2’-phenylacetic acid (221)



(220) (221)

To a suspension of 2,3-dimethoxy-5-(2-aminoethyl)-1,1’-biphenyl-2’-phenyl acetonitrile (220) (10 mg, 0.03 mmol) in mixture of methanol/water (0.5 mL/0.25 mL) was added sodium hydroxide (13 mg, 0.34 mmol). After the mixture was refluxed for 2 h., saturated sodium hydrogen carbonate was added to the reaction. The mixture was extracted with ethyl acetate (3x10 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was used in the next step without futher purification.

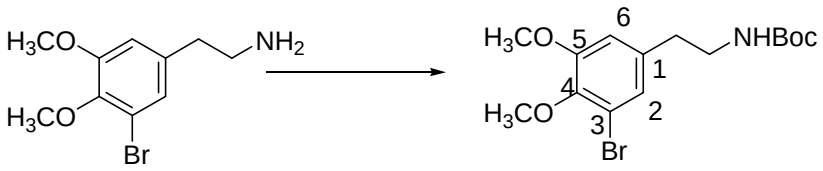
2,3-Dimethoxy-5-(2-aminoethyl)-1,1'-biphenyl-2'- phenylacetamide (222)



(221) (222)

A solution of crude product of 2,3-dimethoxy-5-(2-aminoethyl)-1,1'-biphenyl-2'-phenylacetic acid (221) in toluene was refluxed for 12 h. After the mixture was cooled to room temperature, the solvent was removed and extracted with ethyl acetate (3x10 mL). The organic extract was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Analytical TLC on siliga gel (15% ethyl acetate/ hexane) showed indefinite spots, implying decomposition of starting material.

***Tert*-butyl 3-bromo-4,5-dimethoxyphenethylcarbamate (223)**



(173) (223)

To a cool (0 ^{o}C) solution of 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (173) (400 mg, 1.54 mmol) in tetrahydrofuran (10 mL) was added 1N sodium hydroxide solution (3 mL). Di-tertbutylcarbonate (337 mg, 1.54 mmol) was added to the solution and stirring was continued for 30 min at 0 ^{o}C. The reaction mixture was stirred at room temperature for 2 h. The organic solvent was removed under reduced pressure and the aqueous residue was diluted with water (20 mL). The cloudy solution was extracted with dichloromethane (3x50 mL). The organic extract was dried over anhydrous sodium sulfate, evaporated under reduced pressure. The crude product was purified by flash column chromatography eluting with 10:90 ethyl acetate: hexane to

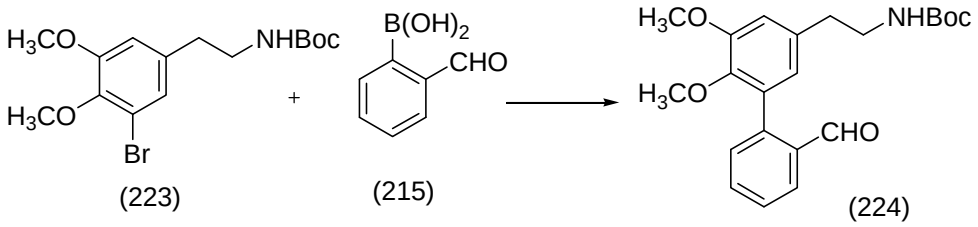
afford *tert*-butyl 3-bromo-4,5-dimethoxyphenethylcarbamate (223) (471 mg, 85%). Recrystallization of compound **223** from ethyl acetate/ hexane gave a white crystal with m.p. 101-102 ^{o}C

FTIR (KBr), υ_{max}, cm^{-1}: 3387 (N-H), 1701 (C=O), 1568 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.88 (s, 1H, H-2), 6,61 (s, 1H, H-6), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.29-3.24 (m, 2H, $ArCH_2C\underline{H}_2NH$), 2.64 (t, *J*=7.0 Hz, $ArC\underline{H}_2CH_2NH$), 1.37 (s, 9H, Boc(CH_3)).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 155.8 (Boc(C=O)), 153.5 (C-3), 144.9 (C-1), 136.2 (C-5), 124.6 (C-2), 117.4 (C-4), 112.2 (C-6), 79.2 (Boc(Cq)), 60.4 (OCH_3), 55.9 (OCH_3), 41.5 ($Ar\underline{C}H_2CH_2NH$), 35.7 ($ArCH_2\underline{C}H_2NH$), 28.3 (Boc(CH_3)).

2,3-Dimethoxy-5-(*tert*-butyl(2-phenylethyl)carbamate)-1,1'-biphenyl-2'-carbox aldehyde (224)



A dry three-necked flask, equipped with a magnetic stirring bar, septum, and condenser with an nitrogen inlet-outlet was charged with palladium acetate (2 mg, 0.02 mmol), 2-formylphenylboronic acid (215) (142 mg, 0.95 mmol), potassium phosphate (200 mg, 0.95 mmol), tricyclohexylphosphine (5 mg, 0.02 mmol) and *tert*-butyl 3-bromo-4,5-dimethoxyphenethylcarbamate (223) (170 mg, 0.47 mmol). The flask was flushed with nitrogen and toluene (2 mL) was added. The reaction mixture was heated to 110 °C and stirred with gentle reflux for 14 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl

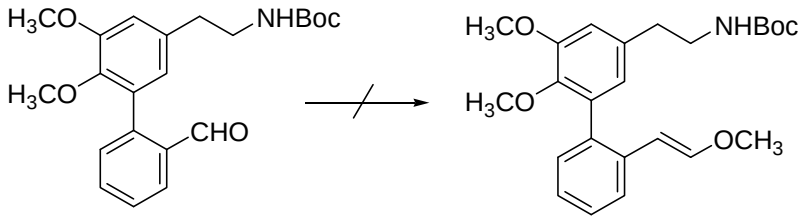
acetate-hexane (3:97) to give 2,3-dimethoxy-5-(*tert*-butyl(2-phenylethyl)carbamate)-1,1'-biphenyl-2'-carboxaldehyde (224) (121 mg, 67%) as a pale-yellow liquid.

FTIR (neat), υ_{max}, cm^{-1}: 3445 (N-H), 1697 (C=O), 1585 (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 9.77 (d, *J*=0.8 Hz, 1H, CHO), 7.93 (dd, *J*=7.8, 1.3 Hz, 1H, C-6'), 7.56 (ddd, *J*=7.5, 7.5, 1.4 Hz, 1H, C-4'), 7.43 (ddd, *J*=7.8, 7.5, 1.0 Hz, 1H, C-5'), 7.31 (dd, *J*=7.5, 0.8 Hz, 1H, C-3'), 6.77 (d, *J*=1.9 Hz, 1H, H-4), 6.64 (d, *J*=1.9 Hz, 1H, H-6), 3.84 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.34-3.31 (m, 2H, $ArC\underline{H}_2CH_2NH$), 2.73 (t , *J*=7.1 Hz, 2H, $ArCH_2C\underline{H}_2NH$), 1.36 (Boc(CH_3)).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 192.0 (CHO), 155.8 (Boc(C=O)), 152.4 (Cq aromatic), 144.8 (Cq aromatic), 141.2 (Cq aromatic), 135.1 (Cq aromatic), 133.6 (Cq aromatic), 133.2 (C-4'), 131.9 (Cq aromatic), 130.9 (C-5'), 127.7 (C-3'), 126.7 (C-6'), 123.1 (C-6), 113.1 (C-4), 60.2 (OCH_3), 55.8 (OCH_3), 41.7 ($Ar\underline{C}H_2CH_2NH$), 35.8 ($ArCH_2\underline{C}H_2NH$), 28.3 (Boc(CH_3)).

2,3-Dimethoxy-5-(tert-butyl(2-phenylethyl)carbamate)-1,1'-biphenyl-2'-methoxyvinylbenzene (225)

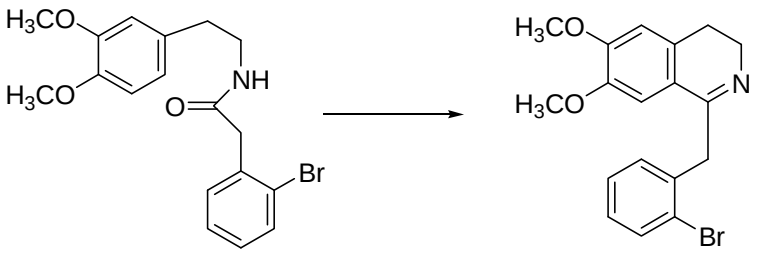


(224) (225)

A solution of (methoxymethyl)triphenylphosphonium chloride (14 mg, 0.43 mmol) in anhydrous tetrahydrofuran (1 mL) at 0 °C was treated dropwise with a solution of potassium *tert*-butoxide (46 mg, 0.40 mmol) in anhydrous tetrahydrofuran (1 mL). The resultant mixture was warmed to room temperature and stirred under nitrogen atmosphere for 30 min, then treated with a solution of 2,3-dimethoxy-5-(*tert*-

butyl(2-phenylethyl)carbamate)-1,1'-biphenyl-2'-carboxaldehyde (224) (50 mg, 0.20 mmol) in anhydrous tetrahydrofuran (1 mL) and stirred at room temperature under nitrogen atmosphere for 24 h. The reaction was quenched by the addition of brine (5 mL), extracted with ethyl acetate (3×5 mL), and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (10:90) to recover a starting material.

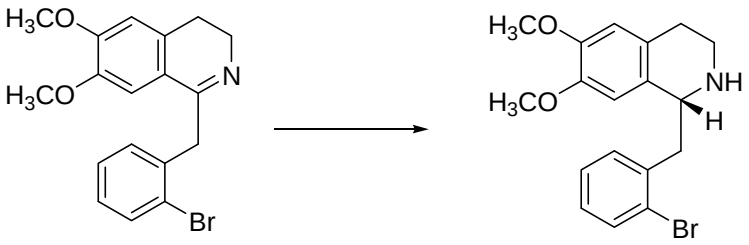
1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (186)



(185) (186)

Phosphorus oxychloride (0.05 mL, 0.53 mmol) was added dropwise into a cold solution of *N*-(3,4-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185) (50 mg, 0.13 mmol) in dry dichloromethane (6 mL). The reaction mixture was refluxed under nitrogen atmosphere for 4 h. After cooling to 0 ^{o}C, a cold solution was carefully added 10% sodium hydroxide and extracted with dichloromethane (3x100 mL).The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (186) which was used in the next step without further purification.

(*R*)-1-(2-Bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (226)



(186) (226)

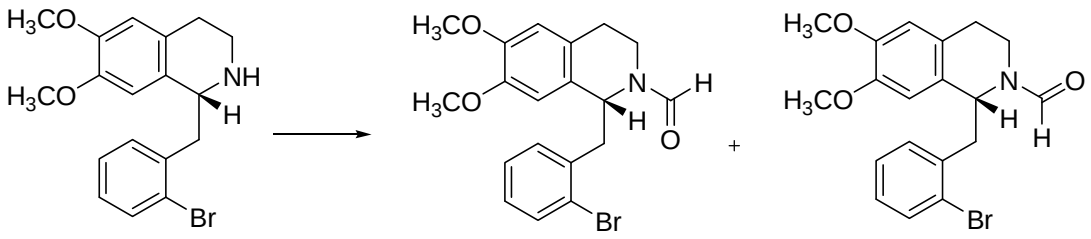
To a solution of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (186) in acetronitrile was added an azeotropic mixture of formic acid and triethylamine (5:2, 0.14 mL), followed by the addition of the pre-formed catalyst, a mixture of $[RuCl_2(p\text{-cymene})]_2$ (5 mg, 0.008 mmol) and (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-toluoylsulfonyl)ethlylamine (6 mg, 0.002 mmol) in 1 mL of acetronitrile. The mixture was then stirred at room temperature for 12 h. After evaporation of the solvent, the residue was basified by addition of aqueous sodium carbonate and extracted with dichloromethane. The combined organic phase was washed with water, brined, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was further purified by silica gel flash column chromatography with 2:98 methanol: dichloromethan as eluent. The product was a pale-yellow liquid with an isolated yield 38 mg, 82% (two steps), $[\alpha]_D$: -27.3^o ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.53 (d, *J*=7.9 Hz, 1H, H-3'), 7.51 (d, *J*=4.0 Hz, 1H, H-5'), 7.19 (d, *J*=4.0 Hz, 1H, H-6'), 7.04 (ddd, *J*=8.1, 4.6, 4.6 Hz, 1H, H-4'), 6.59 (s, 1H, H-8), 6.53 (s, 1H, H-5), 4.24 (dd, *J*=9.7, 4.5 Hz, 1H, H-1), 3.79 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.28 (dd, *J*= 13.6, 4.2 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.19 (ddd, *J*= 12.4, 12.3, 6.0 Hz, 1H, H-3), 2.96 (dd, *J*= 13.6, 9.7 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.91 (dd, *J*= 12.3, 5.4 Hz, 1H, H-3), 2.69 (dd, *J*=5.8, 5.7 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 147.6, 147.1 (C-7, C-6), 138.8 (C-2'), 133.0 (C-3'), 132.0 (C-6'), 130.5 (C-1'), 128.2 (C-4'), 127.4 (C-5'), 127.2 (C-9), 124.9

(C-10), 111.7 (C-5), 109.7 (C-8), 55.9 (OCH_3), 55.8 (OCH_3), 54.9 (C-1), 43.2 (Ar'$\underline{C}H_2$CHNH), 40.0 (C-3), 29.4 (C-4).

(*R*)-1-(2-Bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (227)



To a solution of (*R*)-1-(2-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy isoquinoline (226) (300 mg, 0.83 mmol) in ethyl formate (10 ml) was heated to 50 °C. After 4 h, ethyl formate was removed to give crude product. Purification was done by flash chromatography using ethyl acetate-hexane (30:70) to give (*R*)-1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (229) (0.32 g, 85%) which was recrystallized with ethyl acetate/hexane to give a white crystal, m.p. 156-157 ^{o}C, $[\alpha]_D$: -86.8 ^{o} ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.54 (dd, *J*=8.0, 1.2 Hz, 1H, H-3'), 7.50 (s, 1H, CHO), 7.18 (ddd, *J*=7.6, 7.5, 1.3 Hz, 1H, H-5'), 7.07 (ddd, *J*=7.7, 7.6, 1.7 Hz, 1H, H-4'), 6.96 (dd, *J*=7.5, 1.7 Hz, 1H, H-6'), 6.66 (s, 1H, H-5), 6.56 (s, 1H, H-8), 4.71 (dd, *J*=10.2, 4.0 Hz, 1H, H-1), 4.45 (ddd, *J*=13.2, 6.2, 2.2 Hz, 1H, H-3), 3.81 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.27 (dd, *J*=13.9, 4.0 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.17 (ddd, *J*=13.1, 11.5, 4.8 Hz, 1H, H-3), 3.02 (dd, *J*=13.9, 10.2 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.82 (dd, *J*=11.1, 6.1 Hz, 1H, H-4), 2.71 (dd, *J*=4.7, 2.3 Hz, 1H, H-4).

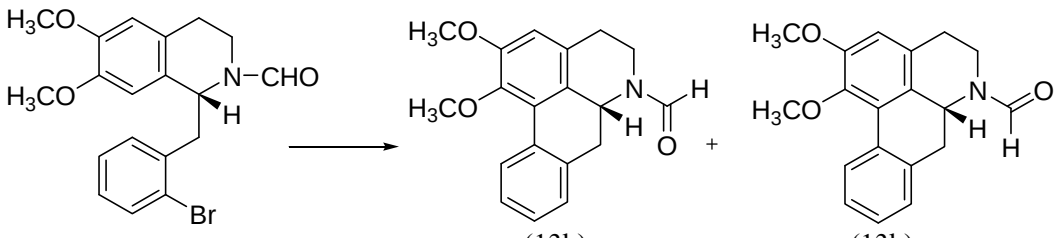
Minor isomer (*Z* isomer) *δ*: 7.98 (s, 1H, CHO), 7.74 (dd, *J*=8.0, 1.2 Hz, 1H, H-3'), 7.17 (dd, *J*= 6.8, 1.1 Hz, 1H, H-5'), 7.11 (dd, *J*=7.6, 2.3 Hz, 1H, H-6'), 7.01 (ddd, *J*=8.0, 6.9, 2.2 Hz, 1H, H-4'), 6.50 (s, 1H, H-5), 6.35 (s, 1H, H-8), 5.61 (dd, *J*=8.2, 6.0 Hz, 1H, H-1), 3.78 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.62-3.59 (m, 2H, H-3), 3.26 (dd, *J*=13.7, 6.0 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.09 (dd, *J*=13.6, 8.5 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.86 (dd, *J*=11.4, 6.3 Hz, 1H, H-4), 2.67 (dd, *J*=4.7, 2.3 Hz, 1H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) *δ*: 161.2 (CHO), 148.4, 147.6 (C-7, C-6), 136.7 (C-2'), 133.2 (C-3'), 132.2 (C-6'), 129.0 (C-4'), 127.9 (C-5'), 127.3 (C-1'), 124.5 (C-9), 120.0 (C-10), 111.5 (C-5), 109.7 (C-8), 56.6 (C-1), 56.0 55.9 (OCH_3, OCH_3), 43.5 Ar'$\underline{C}H_2$CHNH), 34.3 (C-3), 27.7 (C-4).

Minor isomer (*Z* isomer) *δ*: 161.2 (CHO), 148.0, 147.4 (C-7, C-6,), 137.2 (C-2'), 132.7 (C-3'), 131.7 (C-6'), 128.4 (C-4'), 127.2 (C-5'), 127.0 (C-1'), 125.4 (C-9), 125.0 (C-10), 111.3 (C-8), 110.2 (C-5), 55.9, 55.8 (OCH_3, OCH_3), 50.8 (C-1), 41.7 (Ar'$\underline{C}H_2$CHNH), 40.3 (C-3), 29.2 (C-4).

(-)-*N*-Formylnornuciferine (13b)



A mixture of (*R*)-1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (227) (50 mg, 0.128 mmol), tricyclohexylphosphine (36 mg, 0.128 mmol), sodium acetate (33 mg, 0.410 mmol) and palladium acetate (14 mg,

0.064 mmol) in dimethylacetamide (1 mL) under a nitrogen atmosphere was heat at 110 ^{o}C for 14 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (40:60) and then was recrystallized from methanol to give (-)-*N*-formylnornuciferine (13b) (28mg, 78%) as a colorless crystal, m.p. 154-155 ^{o}C, $[\alpha]_D$:-315.7^{o} ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*Z* isomer) δ: 8.35 (d, *J*=8.0 Hz, 1H, H-11), 8.19 (s, 1H, CHO), 7.31-7.15 (m, 3H, H-10, H-9, H-8), 6.59 (s, 1H, H-3), 4.86 (dd, *J*=13.9, 4.1 Hz, 1H, H-6a), 3.83 (s, 3H, OCH_3), 3.75 (ddd, *J*=12.7, 4.6, 1.8 Hz, 1H, H-5), 3.60 (s, 3H, OCH_3), 3.34 (ddd, *J*=12.5, 12.5, 2.8 Hz, 1H, H-5), 3.05 (dd, *J*=13.9, 4.2 Hz, 1H, H-7), 2.89-2.66 (m, 3H, H-7, H-4, H-4).

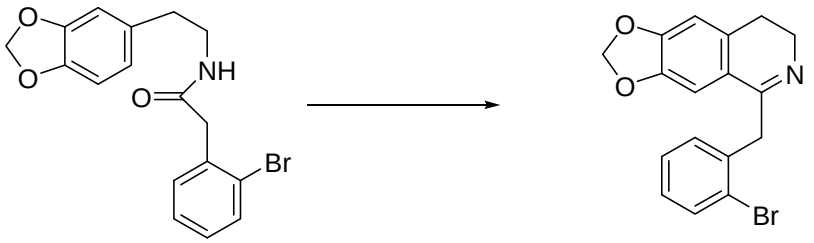
Minor isomer (*E* isomer) δ: 8.36 (d, *J*=7.9 Hz, 1H, H-11), 8.31 (s, 1H, CHO), 7.31-7.15 (m, 3H, H-10, H-9, H-8), 6.62 (s, 1H, H-3), 4.43 (dd, *J*=14.3, 4.0 Hz, 1H, H-6a), 4.35 (ddd, *J*=12.7, 4.6, 3.6 Hz, 1H, H-5), 3.83 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.14 (ddd, *J*=12.7, 10.4, 3.7 Hz, 1H, H-5), 3.12-3.03 (m, 1H, H-7), 2.89-2.66 (m, 3H, H-7, H-4, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*Z* isomer) δ: 162.1 (CHO), 152.4 (C-2), 146.0 (C-1), 136.1 (C-7a), 131.5 (C-11a), 128.6 (C-11c), 128.6 (C-8), 128.4 (C-11), 127.9 (C-11b), 127.8 (C-9), 127.1 (C-10), 125.3 (C-3a), 111.5 (C-3), 60.0 (OCH_3), 56.0 (OCH_3), 49.4 (C-6a), 42.0 (C-5), 34.1 (C-7), 31.0 (C-4).

Minor isomer (*E* isomer) δ: 161.9 (CHO), 152.6 (C-2), 145.8 (C-1), 135.4 (C-7a), 131.6 (C-11a), 129.5 (C-11c), 128.7 (C-11), 128.2 (C-8), 127.9 (C-9), 127.5 (C-10), 127.4 (C-11b), 124.8 (C-3a), 111.8 (C-3), 60.1 (OCH_3), 56.0 (OCH_3), 53.5 (C-6a), 37.9 (C-7), 36.1 (C-5), 29.6 (C-4).

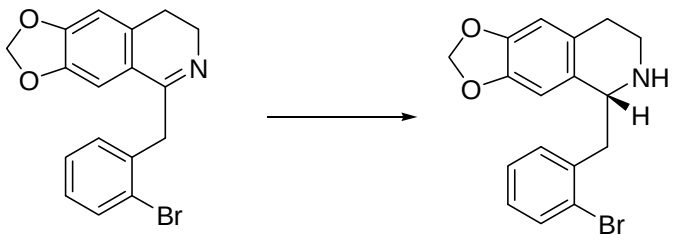
5-(2-Bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (201)



(200) (201)

Phosphorus oxychloride (1.01 mL, 11.05 mmol) was added dropwise into a cold solution of *N*-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromophenyl)acetamide (200) (1 g, 2.76 mmol) in dry dichloromethane (20 mL). The reaction mixture was refluxed under nitrogen atmosphere for 4 h. After cooling to 0 ^{o}C, a cold solution was carefully added 10% sodium hydroxide and extracted with dichloromethane (3x300 ml). The combined organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (201) which was used in the next step without further purification.

1-((*R*)-5-(2-Bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (228)



(201) (228)

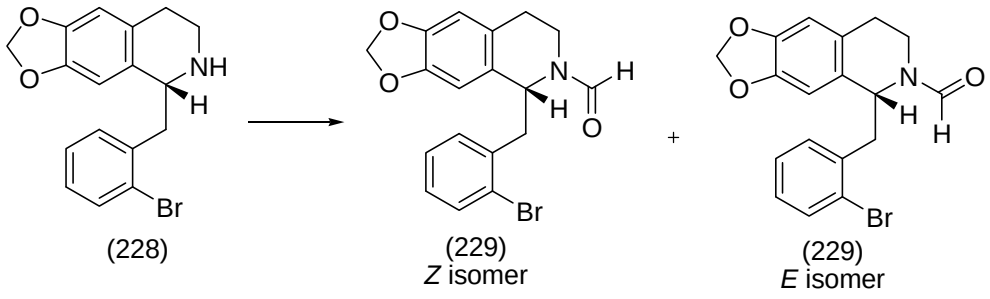
To a solution of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g] isoquinoline (201) in 20 mL of acetronitrile was added an azeotropic mixture of formic acid and triethylamine (5:2, 1.45 mL), followed by the addition of the pre-formed catalyst, a mixture of $[RuCl_2(p\text{-cymene})]_2$ (11 mg, 0.02 mmol) and (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-toluoylsulfonyl)ethlylamine (13 mg, 0.04 mmol) in 10 mL of

acetronitrile. The mixture was then stirred at room temperature for 12 h. After evaporation of the solvent, the residue was basified by addition of aqueous sodium carbonate and extracted with dichloromethane. The combined organic phase was washed with water (100 ml), brined (50 ml), dried with anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was further purified by silica gel flash column chromatography with 2:98 methanol: dichloromethane as eluent. The product was a white solid with an isolated yield 0.80 g, 84% (two steps) which was recrystallized from ethyl acetate/hexane to give a white crystal, m.p. 121-122 ^{o}C, $[\alpha]_D$: -28.3 ^{o} ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz), δ: 7.51 (d, *J*=7.8 Hz, 1H, H-3'), 7.20-7.17 (m, 2H, H-6', H-5'), 7.06-7.02 (ddd, *J*=8.0, 5.0, 4.0 Hz, 1H, H-4'), 6.75 (s, 1H, H-8), 6.50 (s, 1H, H-5), 5.83 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.82 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.16 (dd , *J*=10.4, 3.2 Hz, 1H, H-1), 3.27 (dd, *J*=13.7, 3.2 Hz, 1H, Ar'C$\underline{H_2}$CHNH), 3.14 (ddd, *J*=13.3, 6.8, 5.6 Hz, 1H, H-3), 2.86 (dd, *J*=13.7, 8.4 Hz, 1H, Ar'C$\underline{H_2}$CHNH), 2.85 (dd, *J*=12.1, 5.6 Hz, 1H, H-3), 2.67 (dd, *J*=6.1, 5.8 Hz, 2H, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz), δ: 145.9, 145.7 (C-7, C-6), 138.7 (C-2'), 133.0 (C-3'), 131.9 (C-6'), 131.7 (C-1'), 128.2 (C-9), 128.2 (C-4'), 127.4 (C-5'), 124.8 (C-10), 108.8 (C-5), 106.5 (C-8), 100.6 (OCH_2O), 55.2 (C-1), 43.0 (Ar'C$\underline{H_2}$CHNH), 39.9 (C-3), 29.9 (C-4).

(*R*)-5-(2-Bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6(5H)-carbaldehyde (229)



To a solution of 1-((*R*)-5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo [4,5-g]isoquinoline (228) (300 mg, 0.828 mmol) in ethyl formate (10 mL) was heated to 50 °C. After 5 h, ethyl formate was removed to give crude product. Purification was done by flash chromatography using ethyl acetate-hexane (25:75) to give (*R*)-5-(2-bromobenzyl)-7,8-dihydro-[1,3] dioxolo [4,5-g] isoquinoline-6 (5H) -carbaldehyde (229) (0.32 g, 85%) which was recrystallized from ethyl acetate/hexane to give a white crystal, m.p. 154-155 ^{o}C, $[\alpha]_D$: -88.5 ^{o} ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*E* isomer) δ: 7.53 (dd, *J*=8.0, 1.2 Hz, 1H, H-3') 7.39 (s, 1H, CHO), 7.19 (dd, *J*=7.5, 1.2 Hz, 1H, H-5'), 7.08 (dd, *J*=7.7, 1.7 Hz, 1H, H-6'), 6.96 (dd, *J*=7.5, 1.7 Hz, 1H, H-4'), 6.76 (s, 1H, H-8), 6.54 (s, 1H, H-5), 5.88 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.87 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.68 (dd, *J*=10.7, 3.4 Hz, 1H, H-1), 4.40 (ddd, *J*= 13.1, 6.2, 2.6 Hz, 1H, H-3), 3.24 (dd, *J*=14.0, 3.4 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.14 (ddd, *J*= 13.2, 11.3, 4.8 Hz, 1H, H-3), 2.98 (dd, *J*=14.0, 10.7 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.78 (dd, *J*=11.3, 6.2 Hz, 1H, H-4), 2.68 (dd, *J*=4.8, 2.6 Hz, 1H, H-4).

Minor isomer (*Z* isomer) δ: 7.92 (s, 1H, CHO), 7.46 (dd, *J*=7.9, 1.2 Hz, 1H, H-3'), 7.12 (dd, *J*=7.3, 1.2 Hz, 1H, H-5'), 7.04 (dd, *J*=8.0, 1.8 Hz, 1H, H-6'), 7.00 (dd, *J*=7.6, 1.8 Hz, 1H, H-4'), 6.57 (s, 1H, H-8), 6.48 (s, 1H, H-5), 5.86 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.84 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.59 (dd, *J*=9.4, 4.7 Hz, 1H, H-1), 3.57-3.54 (m, 2H, H-3), 3.27 (dd, *J*=14.0, 4.7 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 3.03 (dd, *J*=14.0, 9.4 Hz, 1H, Ar'C$\underline{H}_2$CHNH), 2.83 (dd, *J*=11.4, 6.2 Hz, 1H, H-4), 2.64 (dd, *J*=4.6, 2.7 Hz, 1H, H-4).

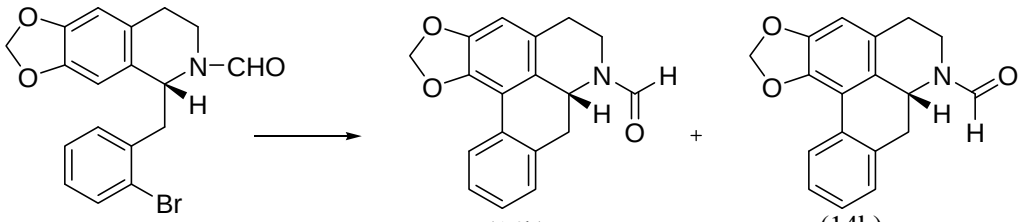
^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*E* isomer) δ: 161.2 (CHO), 147.0 (C-2'), 146.4 (C-6), 136.5 (C-7), 133.2 (C-3'), 132.1 (C-6'), 129.0 (C-4'), 128.5 (C-1'), 127.9 (C-5'), 127.2 (C-

9), 124.4 (C-10), 108.7 (C-8), 106.6 (C-5), 101.1 (O<u>C</u>H$_2$O), 56.8 (C-1), 43.3 (Ar'<u>C</u>H$_2$CHNH), 34.2 (C-3), 28.1 (C-4).

Minor isomer (*Z* isomer) δ: 161.1 (CHO), 146.7 (C-2'), 146.4 (C-6), 136.9 (C-7), 132.8 (C-3'), 131.4 (C-6'), 128.5 (C-1'), 128.4 (C-4'), 127.2 (C-5'), 126.2 (C-9), 125.2 (C-10), 108.4 (C-8), 107.2 (C-5), 100.9 (O<u>C</u>H$_2$O), 51.0 (C-1), 41.9 (Ar'<u>C</u>H$_2$CHNH), 40.1 (C-3), 29.7 (C-4).

(-)-*N*-Formylannonaine (14b)



A mixture of (*R*)-5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]iso quinoline-6(5H)-carbaldehyde (229) (300 mg, 0.80 mmol), tricyclohexylphosphine (225 mg, 0.80 mmol), sodium acetate (211 mg, 2.57 mmol) and palladium acetate (90 mg, 0.40 mmol) in dimethylacetamide (10 mL) under a nitrogen atmosphere was heat at 110^{o}C for 12 h. The reaction mixture was filtered through celite pad, and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography using ethyl acetate-hexane (30:70) and then was recrystallized from methanol to give (-)-*N*-formylannonaine (14b) (210 mg, 84%) as a white crystal, m.p. 234-236 ^{o}C, $[\alpha]_D$:-189.0 ^{o} ($CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz),

Major isomer (*Z* isomer) δ: 8.18 (s, 1H, CHO), 8.02 (d, *J*= 7.8 Hz, 1H, H-11), 7.29-7.14 (m, 3.0 H, H-10, H-9, H-8), 6.49 (s, 1H, H-3), 6.01 (d, *J*=1.4 Hz, 1H, OCH$_2$O), 5.89 (d, *J*=1.4 Hz, 1H, OCH$_2$O), 4.98 (dd, *J*= 14.0, 4.4 Hz, 1H, H-6a), 3.75

(ddd, *J*= 12.5, 4.6, 1.9 Hz, 1H, H-5), 3.33 (ddd, *J*=12.5, 12.5, 2.9 Hz, 1H, H-5), 3.16 (dd, *J*= 14.0, 4.4 Hz, 1H, H-7), 2.85-2.61 (m, 3H, H-7, H-4, H-4).

Minor isomer (*E* isomer) *δ*: 8.31 (s, 1H, CHO), 8.03 (d, *J*= 7.6 Hz, 1H, H-11), 7.29-7.14 (m, 3H, H-10, H-9, H-8), 6.52 (s, 1H, H-3), 6.02 (d, *J*=1.4 Hz, 1H, OCH_2O), 5.89 (d, *J*=1.4 Hz, 1H, OCH_2O), 4.55 (dd, *J*=14.4, 4.3 Hz, 1H, H-6a), 4.40 (ddd, *J*=12.7, 4.6, 3.2 Hz, 1H, H-5), 3.11-3.01 (m, 2H, H-7, H-5), 2.85-2.61 (m, 3H, H-7, H-4, H-4).

^{13}C NMR ($CDCl_3$, 100 MHz),

Major isomer (*Z* isomer) *δ*: 162.1 (CHO), 147.1 (C-2), 143.3 (C-1), 135.1 (C-7a), 130.4 (C-11a), 128.8 (C-8), 127.9 (C-9), 127.1 (C-10), 127.1 (C-11), 126.6 (C-3a), 124.7 (C-11c), 117.4 (C-11b), 107.5 (C-3), 101.0 (OCH_2O), 49.4 (C-6a), 42.2 (C-5), 33.5 (C-7), 31.0 (C-4).

Minor isomer (*E* isomer) *δ*: 162.0 (CHO), 147.1 (C-2), 143.3 (C-1), 135.1 (C-7a), 130.6 (C-11a), 128.4 (C-8), 128.0 (C-9), 127.5 (C-3a), 127.4 (C-10), 127.1 (C-11), 124.6 (C-11c), 117.4 (C-11b), 107.9 (C-3), 101.1 (OCH_2O), 53.3 (C-6a), 37.7 (C-7), 36.2 (C-5), 29.7 (C-4).

***In vitro* cardiotonic testing**

The cardiotonic testing was done by Associate Professor Dr. Prasan Dhumma-upakorn and Rungnapa Mesripong, Department of Pharmacology, Faculty of Pharmaceutical Sciences, Huachiew Chalermprakiet University.

Male Wistar rats weighting 250-300 g were killed by a sharp blow on the head and exsanguination. The heart was quickly excised, placed and swirled for a few seconds in a beaker containing Krebs-Henselet solution (Composition (mM): NaCl 118.1, KCl 4.7, $CaCl_2$ 1.8, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25.0; glucose 5.8, pH 7.4) and gassed with carbogen (95% O_2 and 5% CO_2), then transferred to a petri dish containing Krebs-Henselet solution. The atria were dissected out and cut into right and left sides. They were then mounted in an organ-bath containing 20 mL of Krebs-Henselet solution gassed with carbogen and kept at 37 ^{0}C. The right atria, which beat spontaneously, were allowed to equilibrate until stable rate was observed. The left atria were electrically stimulated with square wave pulse (5 V strength and 5 ms duration) to beat at a constant rate of 250 per min. Force of contraction and rate were recorded with isomeric force transducer (Mac Lab) connected to Mac Lab Bridge Amplifier and the results were recorded or printed by Macintosh LC 457 microcomputer.

The test compound was dissolved in dimethylsulfoxide (1 mg/ 0.5 mL). This solution (10-20 μL) was administrated to the organ bath. After 30 min, the force of contraction and heart rate were recorded for 30-45 min.

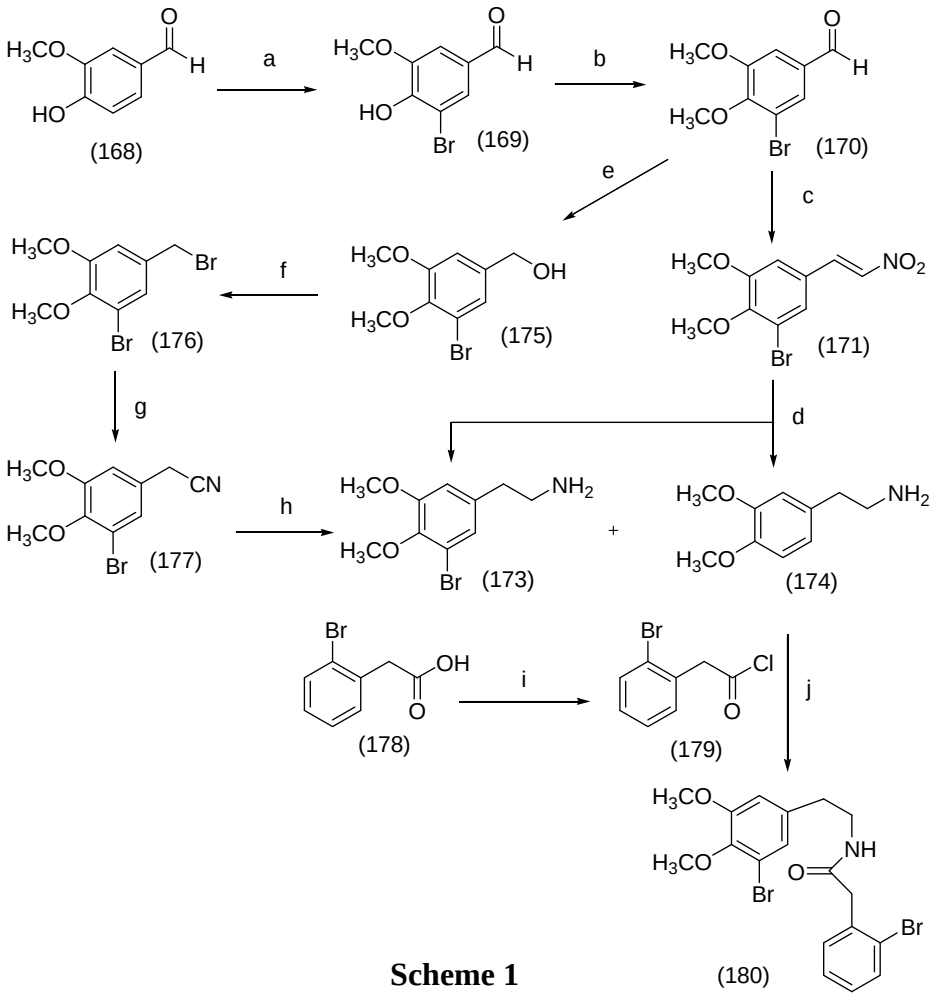
RESULTS AND DISCUSSION

Results

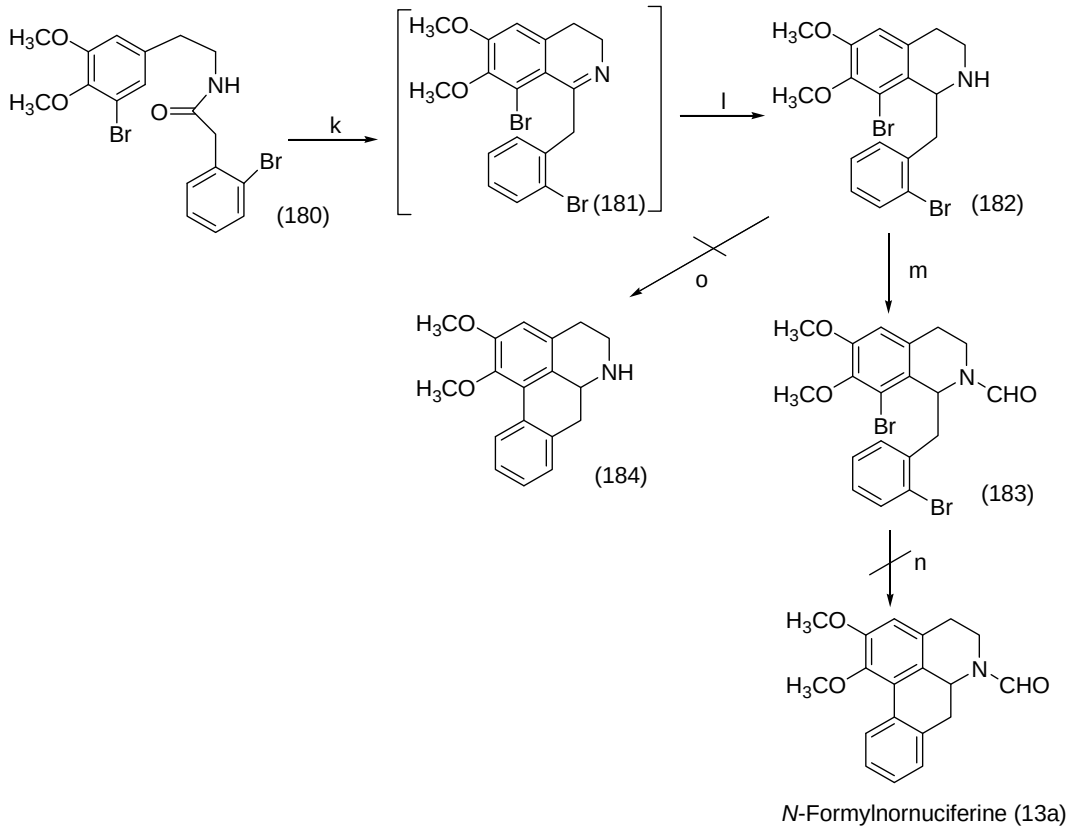
1. The First Synthetic Strategy

1.1 An attempt to synthesize *N*-formylnornuciferine (13a) *via* intramolecular Suzuki coupling reaction

An attempt to synthesize *N*-formylnornuciferine (13a) from a commercially available vanillin (168) was studied by using intramolecular Suzuki coupling reaction as a key step (Scheme 1).



Scheme 1



Scheme 1 (Continued)

Reagents and conditions

a) Br_2, CH_3COOH, rt, 1 h, 92%

b) i) CH_3I, K_2CO_3, acetone, reflux, 8 h, 92%

ii) CH_3I, NaOH, Bu_4NI, CH_2Cl_2, H_2O, reflux, 4 h, 91%

c) CH_3COONH_4, CH_3NO_2, CH_3COOH, sonication, 71%

d) Reduction condition (table 4)

e) $NaBH_4$, EtOH, rt, 20 min, 91%

f) PBr_3, CH_2Cl_2, rt, 20 min

g) i) NaCN, DMF, rt, 1 h, 82% (two steps)

ii) NaCN/ alumina, toluene, reflux, 85% (two steps)

h) BH_3.THF (1M in THF), THF, reflux, 12 h, 82%

i) $(COCl)_2$, DMF (cat.), benzene, rt, 2 h

j) Acid chloride (179), Na_2CO_3, 1:1 v/v CH_2Cl_2:H_2O, rt, 5 h, 93%

k) $POCl_3$, CH_2Cl_2, reflux, 12 h

l) $NaBH_4$, MeOH, rt, 2 h, 68% (two steps)

m) HCOOEt, reflux, 4 h, 85%

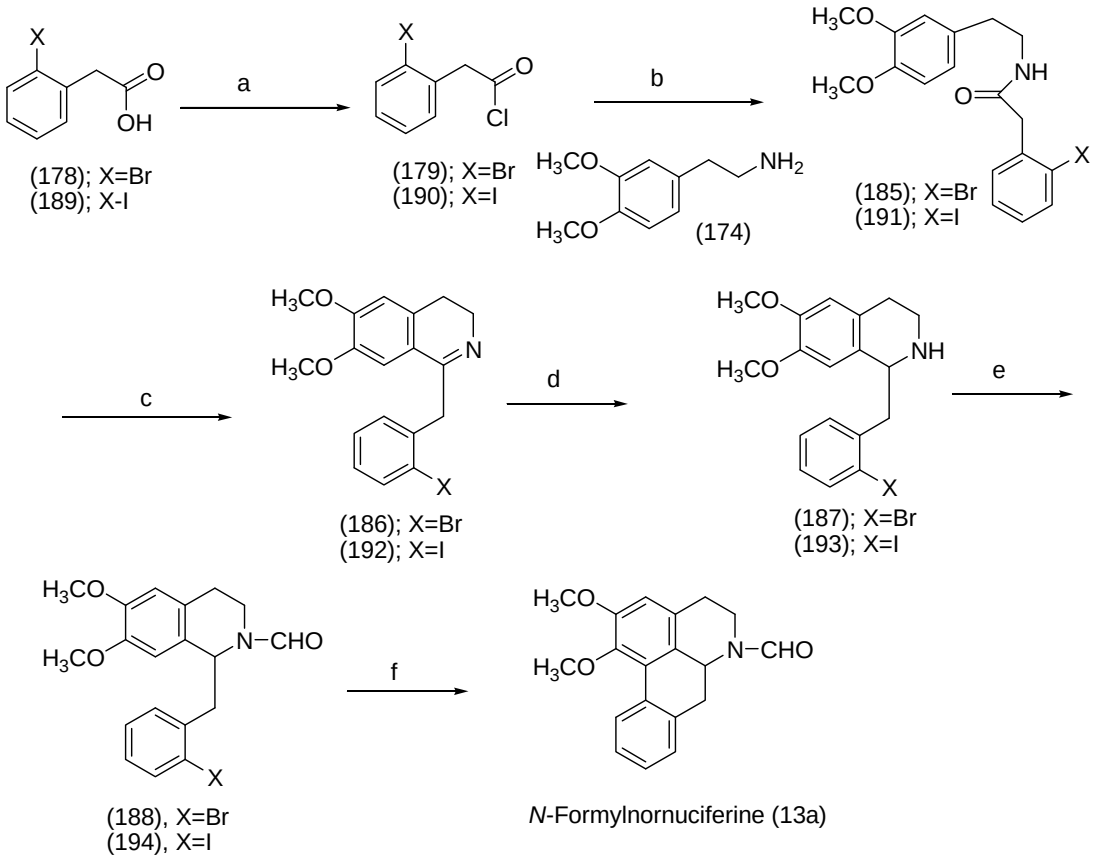
n) $PdCl_2$(dppf), K_2CO_3, DMSO

o) i) $PdCl_2$(dppf), NaOAc, DMF

ii) $PdCl_2$(dppf), 2M Na_2CO_3, DMF

1.2 Synthesis of (±)-*N*-formylnornuciferine (13a) *via* palladium-catalyzed coupling reaction

(±)-*N*-Formylnornuciferine (13a) was synthesized from homoveratryl amine (174) *via* palladium-catalyzed coupling reaction as illustrated in Scheme 2.



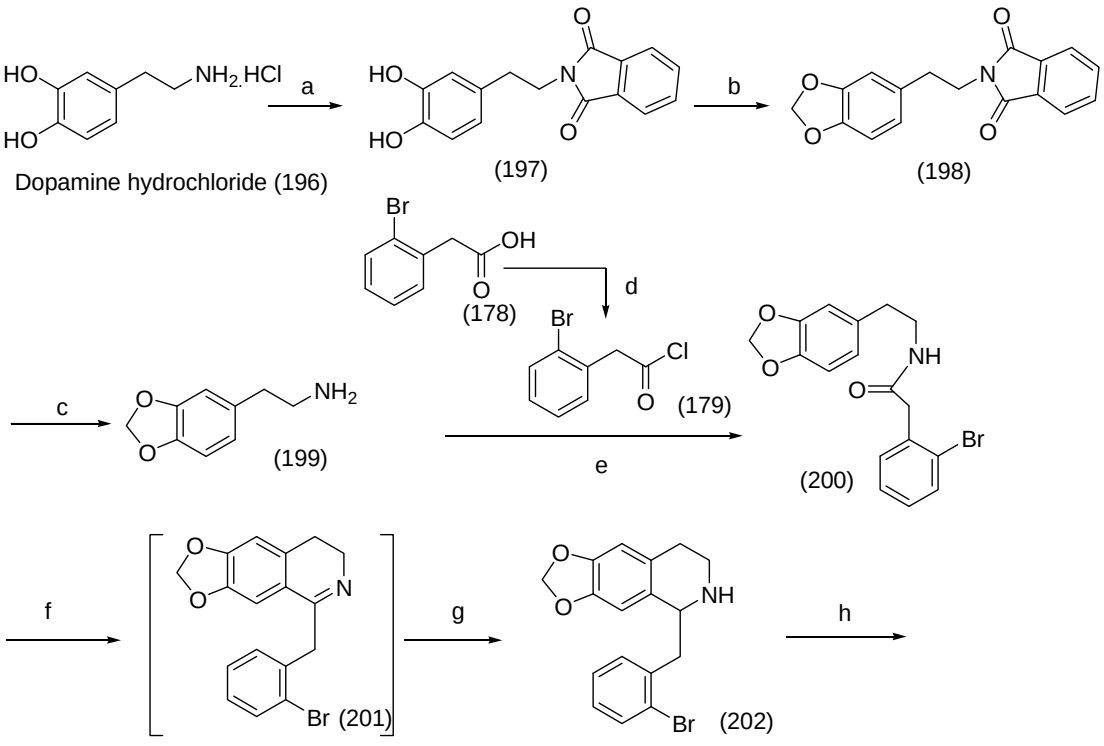
Scheme 2

Reagents and conditions:

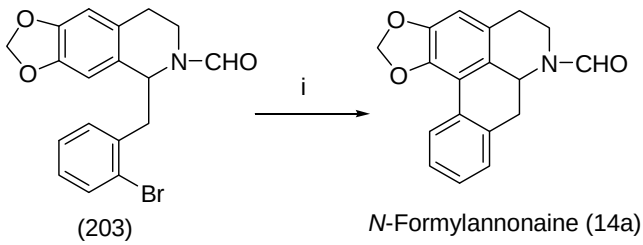
a) $(COCl)_2$, DMF (cat.), benzene, rt, 2 h
b) Homoveratrylamine (174), Na_2CO_3, 1:1 v/v CH_2Cl_2:H_2O, rt, 3h, (5a=91%, 5b=92%) (two steps)
c) $POCl_3$, CH_2Cl_2, reflux, 4 h
d) $NaBH_4$, MeOH, rt, 2 h, (7a=83%, 7b=81%) (two steps)
e) HCOOEt, reflux, 3 h, (8a=85%, 8b=81%)
f) $Pd(OAc)_2$, PCy_3, NaOAc, DMA, 110°C, 14 h, (I=78%, Br=71%)

1.3 Synthesis of (±)-*N*-formylannonaine (14a) *via* palladium-catalyzed coupling reaction

Synthesis of (±)-*N*-formylannonaine (14a) starting from dopamine hydrochloride (196) *via* palladium-catalyzed reaction was shown in Scheme 3.



Scheme 3



(203) *N*-Formylannonaine (14a)

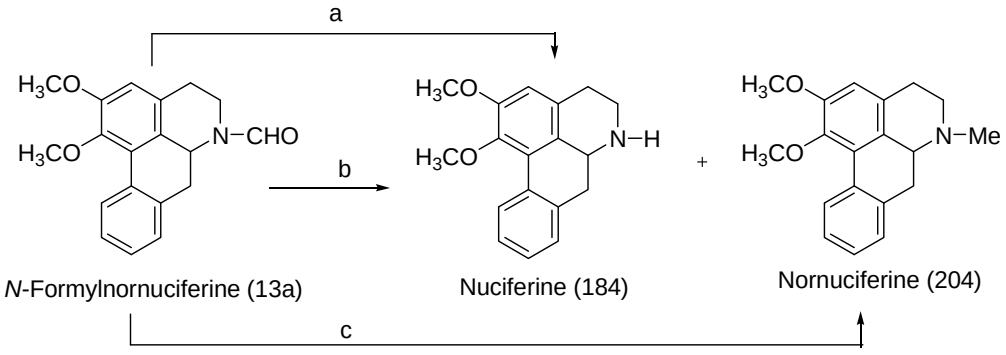
Scheme 3 (Continued)

Reagents and conditions:

a) Phthalic anhydride, CH_3COOH, reflux, 4 h, 93%
b) Br_2CH_2, Cs_2CO_3, DMF, rt, 1 h, 82%
c) 65% $NH_2NH_2.H_2O$, MeOH, rt, 30 min, 81%
d) $(COCl)_2$, DMF (cat.), benzene, rt, 2 h
e) Acid chloride (179), Na_2CO_3, 1:1 v/v CH_2Cl_2:H_2O, rt, 4 h, 93%
f) $POCl_3$, CH_2Cl_2, reflux, 5 h
g) $NaBH_4$, MeOH, rt, 2 h, 76% (two steps)
h) HCOOEt, reflux, 3 h, 82%
i) $Pd(OAc)_2$, PCy_3, NaOAc, DMA, 110°C, 24 h, 85%

1.4 Synthesis of *N*-formylnornuciferine analogues

Nuciferine (184) and nornuciferine (204) were synthesized from *N*-formylnornuciferine (13a) as illustrated in Scheme 4.



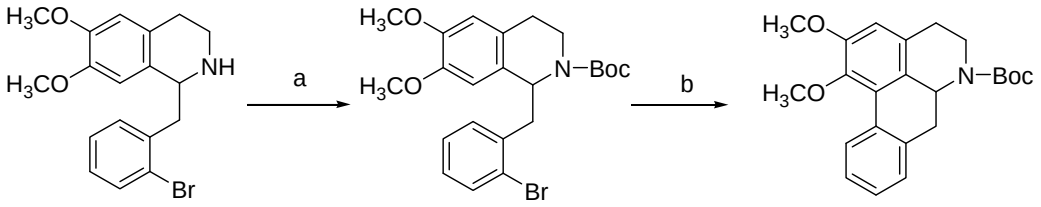
N-Formylnornuciferine (13a) Nuciferine (184) Nornuciferine (204)

Scheme 4

Reagents and conditions:

a) sat. HCl/MeOH, reflux, 13 h, 89%
b) $LiAlH_4$, THF, rt, 2 h, **184**, 86% and **204**, 11%
c) $LiAlH_4$, THF, reflux, 1 h, 78%

Synthesis of 1-(1,2-dimethoxy)-4,5,6a,7-tetrahydro-dibenzoquino line-6-carboxylic acid *tert*-butyl ester (206) starting from benzylisoquinoline (187) was showed in Scheme 5.



(187) (205) (206)

Scheme 5

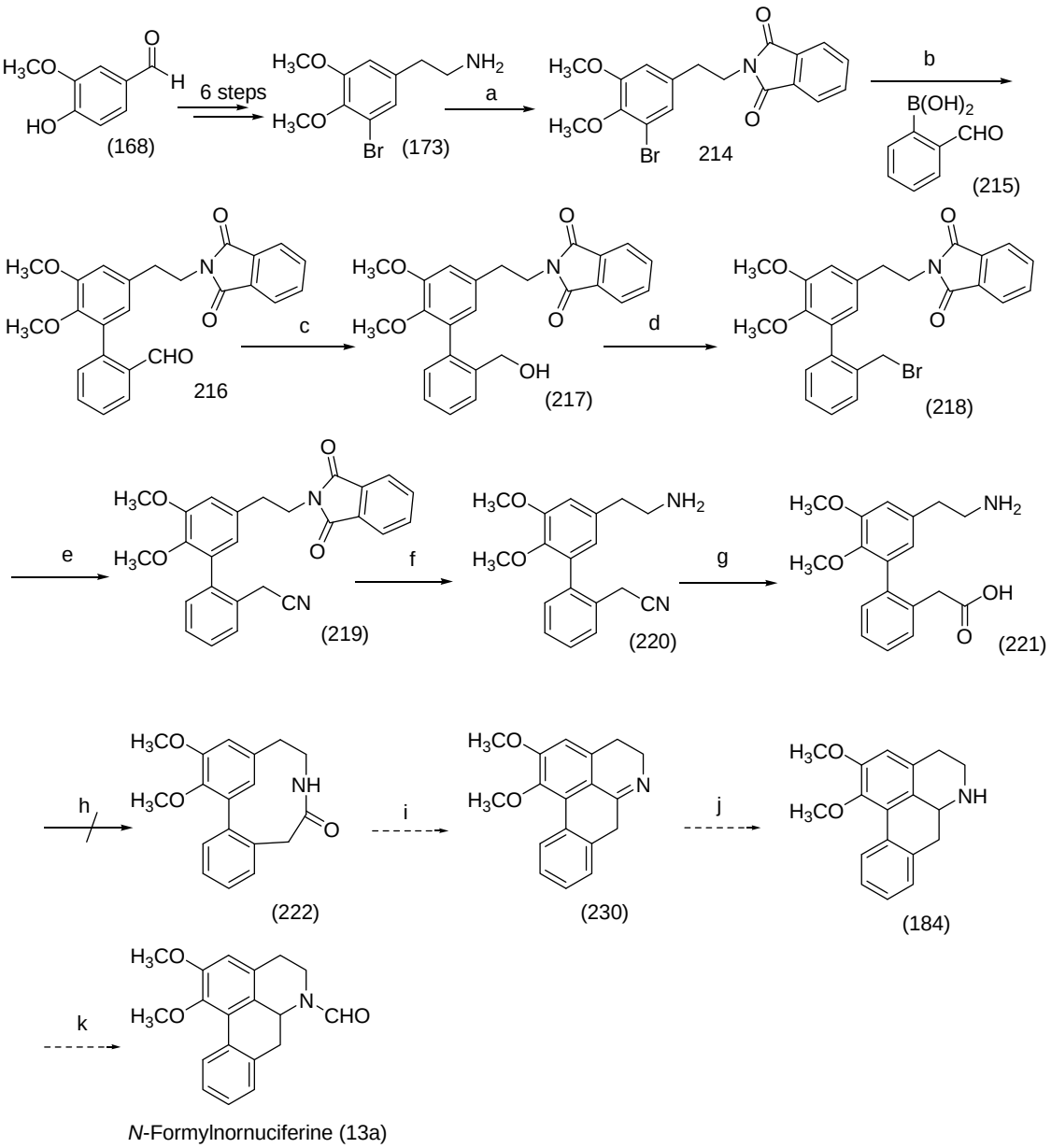
Reagents and conditions:

a) Boc_2O, 1N NaOH, THF, rt, 1 h, 82%
b) $Pd(OAc)_2$, PCy_3, NaOAc, DMA, 110°C, 14 h, 85%

2. The Second Synthetic Strategy

2.1 An attempt to synthesize (±)-*N*-formylnornuciferine (13a) *via* intermolecular Suzuki coupling reaction and Bischler-Napieralski reaction.

An attempt to synthesize (±)-*N*-formylnornuciferine (13a) from a commercially available vanillin (168) was studied by using intermolecular Suzuki coupling reaction and Bischler-Napieralski reaction as key steps (Scheme 6).



Scheme 6

Reagents and conditions

a) Phthalic anhydride, CH_3COOH, reflux, 7 h, 89 %

b) 2-Formylphenylboronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, toluene, 110°C, 24 h, 85%

c) $NaBH_3(CN)$, $ZnCl_2$, Et_2O, rt, 4 h, 86%

d) PBr_3, CH_2Cl_2, rt, 20 min

e) NaCN, DMF, rt, 1 h, 81% (two steps)

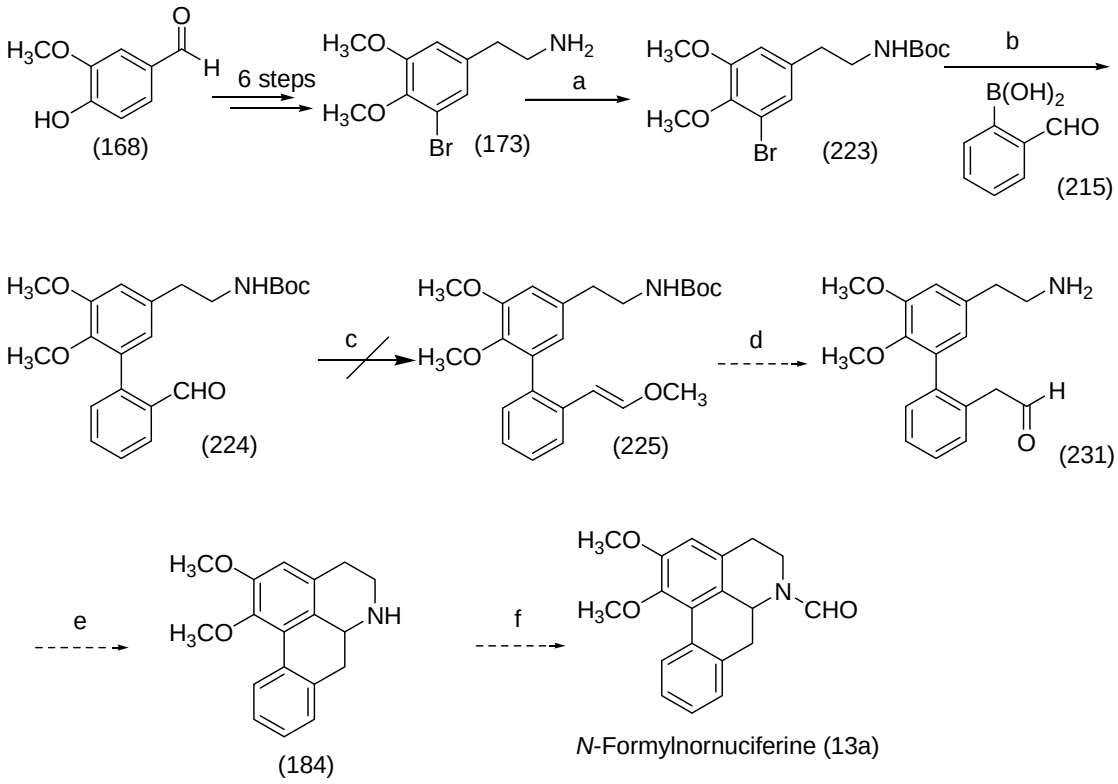
f) 65% $NH_2NH_2.H_2O$, MeOH, rt, 1 h, 83%

g) NaOH, MeOH/H_2O, reflux, 2 h

h) Toluene, reflux, 24 h

2.2 An attempt to synthesize (±)-*N*-formylnornuciferine (13a) *via* intermolecular Suzuki coupling reaction and Pictet-Spengler reaction.

An attempt to synthesize (±)-*N*-formylnornuciferine (13a) from a commercially available vanillin (168) was studied by using intermolecular Suzuki coupling reaction and Pictet-Spengler reaction as key steps (Scheme 7).



Scheme 7

Reagents and conditions

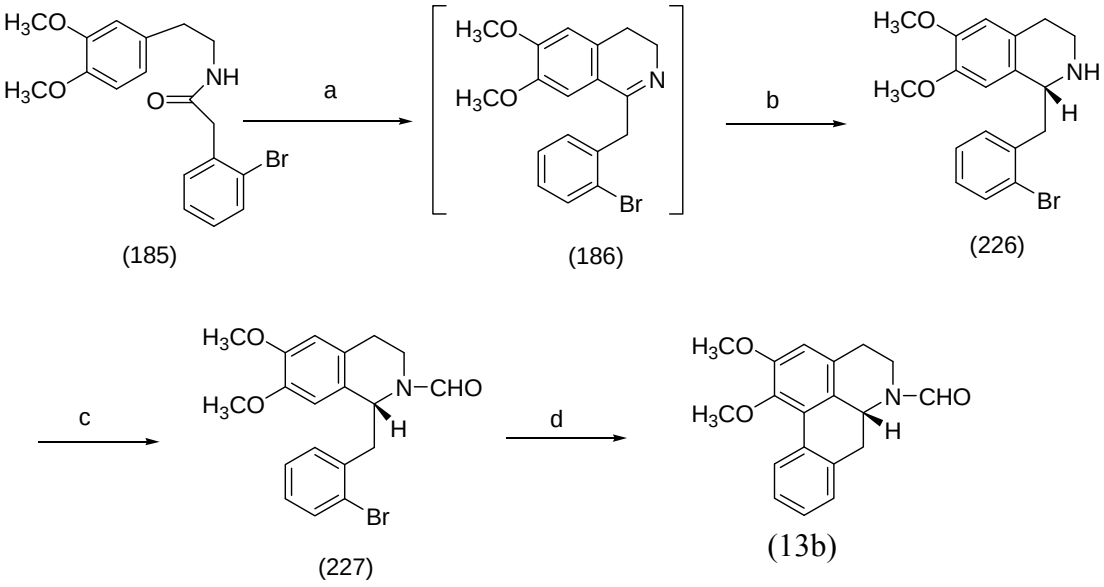
a) Boc_2O, 1N NaOH, THF, rt, 2 h, 85%

b) 2-Formylphenylboronic acid, $Pd(OAc)_2$, PCy_3, K_3PO_4, toluene, 110°C, 14 h, 67%

c) $Ph_3PCH_2OCH_3Cl$, *t*-BuOK, THF, rt, 24 h

3. Asymmetric Synthesis of (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formyl annonaine (14b)

Asymmetric synthesis of (-)-*N*-formylnornuciferine (13b) using asymmetric transfer hydrogenation as a key reaction was illustrated in Scheme 8.



(185) (186) (226) (227) (13b)

Scheme 8

Reagents and conditions:

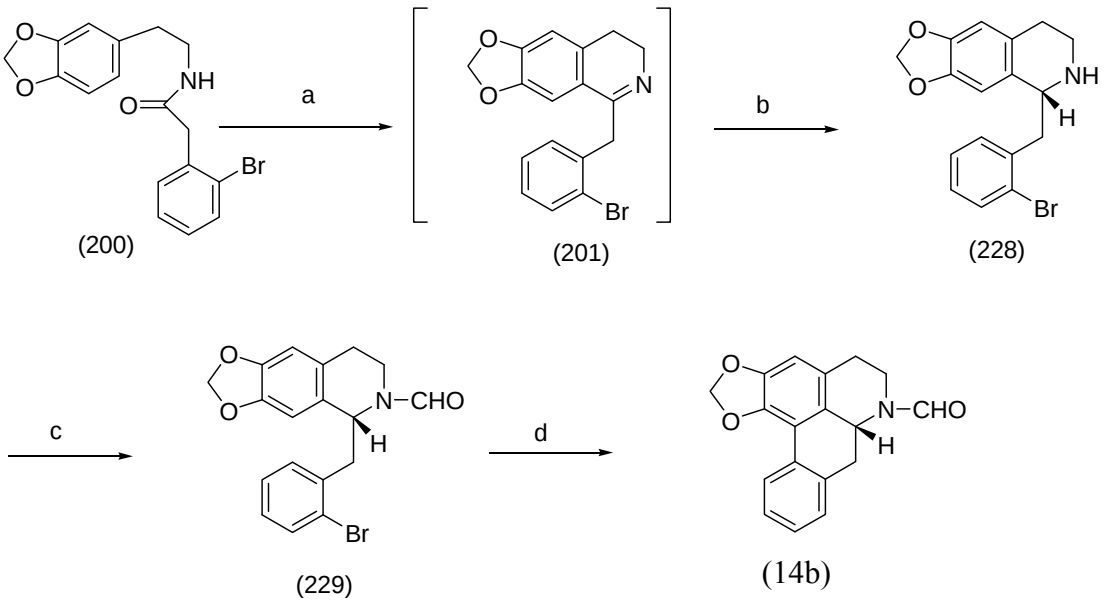
a) $POCl_3$, CH_2Cl_2, reflux, 4 h

b) $[RuCl_2(p\text{-cymene})]_2$, (*S,S*)-TsDPEN, 5:2 HCOOH:Et_3N, CH_3CN, rt, 12 h, 82% (two steps)

c) HCOOEt, reflux, 4 h, 85%

d) $Pd(OAc)_2$, PCy_3, NaOAc, DMA, 110^oC, 14 h, 78%

Asymmetric synthesis of (-)-*N*-formylanonaine (14b) using asymmetric transfer hydrogenation as a key reaction was showed in Scheme 9.



Scheme 9

Reagents and conditions:

a) $POCl_3$, CH_2Cl_2, reflux, 4 h

b) $[RuCl_2(p\text{-cymene})]_2$, (*S,S*)-TsDPEN, 5:2 HCOOH:Et_3N, CH_3CN, rt, 12 h, 84% (two steps)

c) HCOOEt, reflux, 5 h, 85%

d) $Pd(OAc)_2$, PCy_3, NaOAc, DMA, 110^oC, 12 h, 84%

4. Cardiotonic activity testing

N-Formylnornuciferine (13) and *N*-formylannonaine (14) in racemic mixture and single enantiomer forms were evaluated for *in vitro* cardiac contractility. The results were shown in figure below.

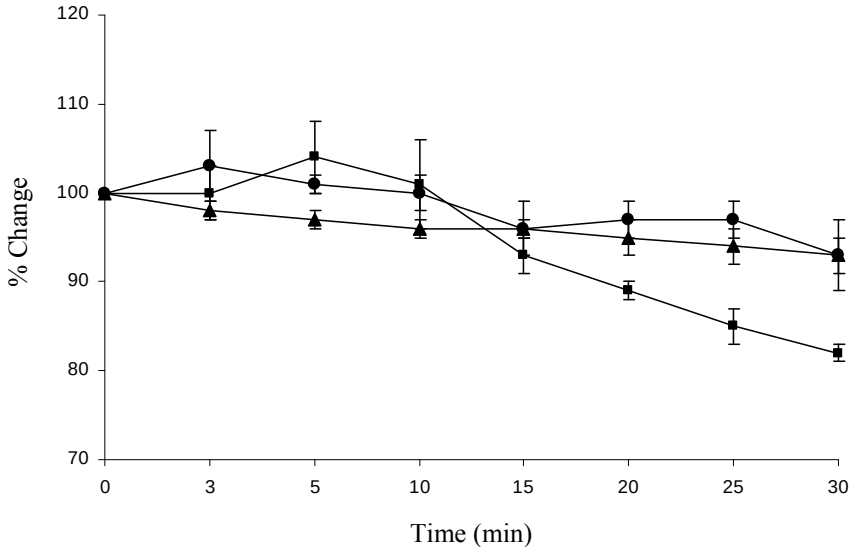


Figure 4 Cardiotonic effects of (±)-*N*-formylnornuciferine (13a) as a racemic mixture on the isolated rat heart; right force (●); left force (■); heart rate (▲)

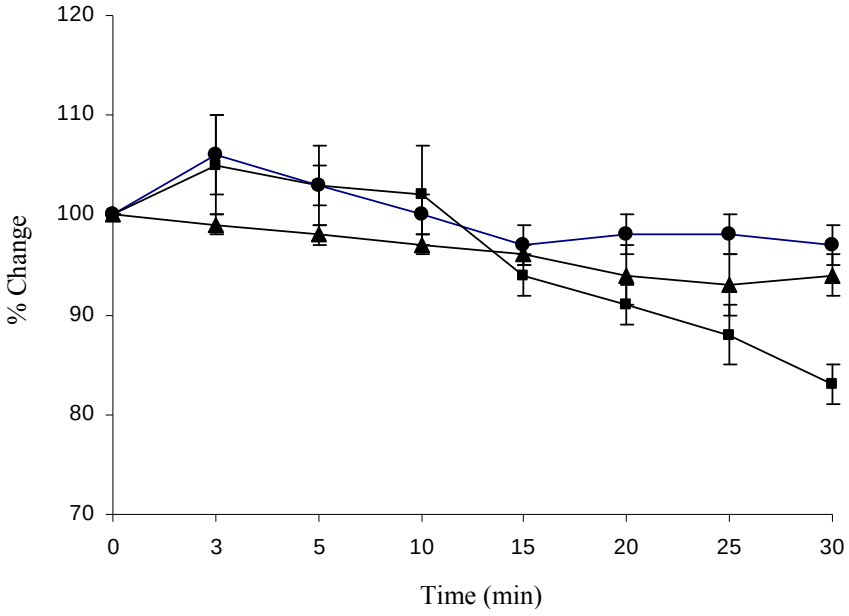


Figure 5 Cardiotonic effects of (±)-*N*-formylannonaine (14a) as a racemic mixture on the isolated rat heart; right force (●); left force (■); heart rate (▲)

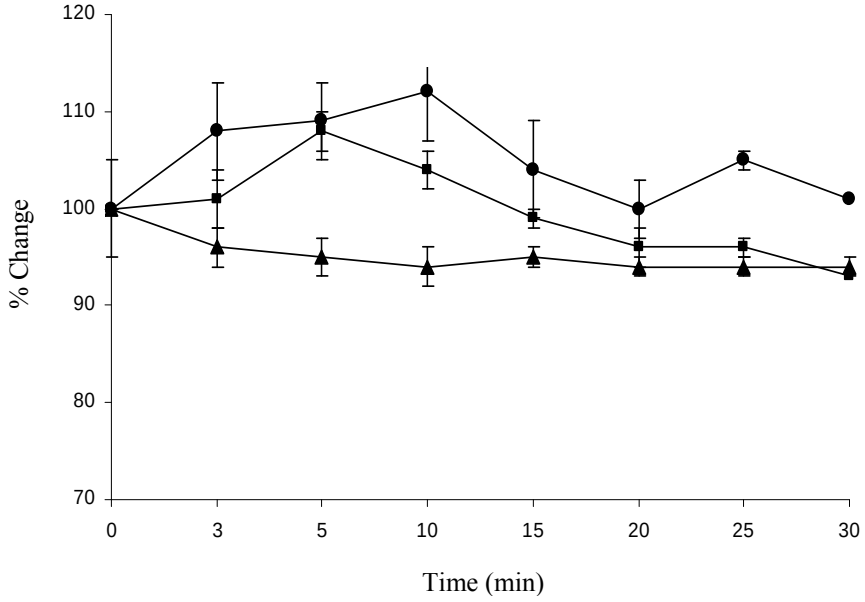


Figure 6 Cardiotonic effects of (-)-*N*-formylnornuciferine (13b) as a single enantiomer on the isolated rat heart; right force (●); left force (■); heart rate (▲)

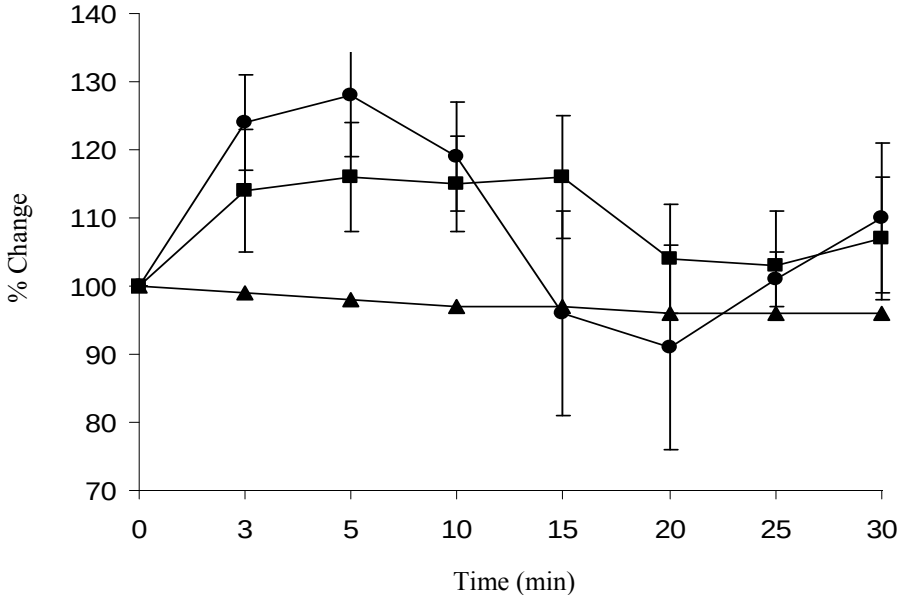
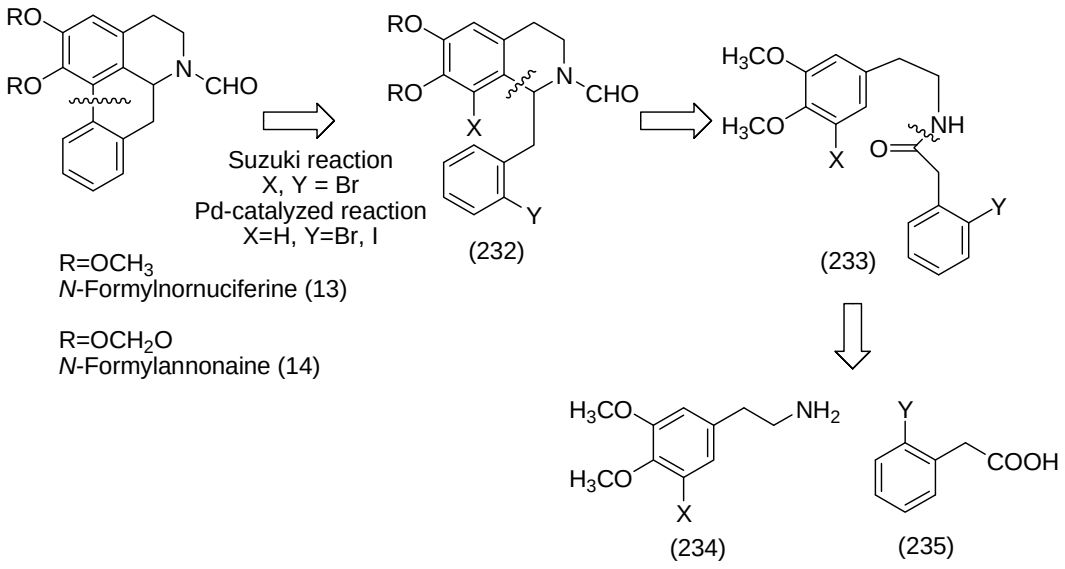


Figure 7 Cardiotonic effects of (-)-*N*-formylannonaine (14b) as a single enantiomer on the isolated rat heart; right force (●); left force (■); heart rate (▲)

Discussion

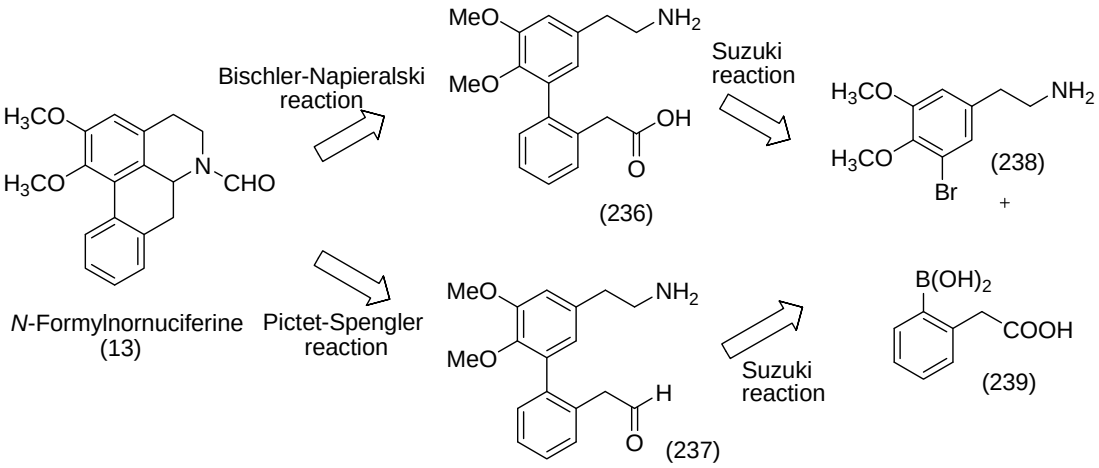
In this thesis work, the synthetic approach to access two aporphine alkaloids, *N*-formylnornuciferine and *N*-formylannonaine was divided into two pathways. The first pathway followed a biogenetic pathway that utilized the cyclization of a benzylisoquinoline in the last step. The second pathway was involved in the intermolecular arylation in the first step, followed by cyclization to construct aporphine skeleton.

The retrosynthetic analysis of the first approach was illustrated in Scheme 10. Aporphines **13** and **14** would be obtained from arylation reaction of 1-benzylisoquinoline (232). The arylation reaction that we desired to study was either intramolecular Suzuki coupling or palladium-catalyzed coupling reaction. For the Suzuki coupling reaction, the bromide (Y) of isoquinoline (232) was transformed *in situ* to boronate ester and subsequently coupled to give aporphine molecule. The benzylisoquinoline (232) could be obtained from Bischler-Napieralski reaction of phenethylamide (233), derived from amide formation between phenethylamine (234) and phenylacetic acid (235).



Scheme 10

The retrosynthetic analysis of the second approach was shown in Scheme 11. Aporphine skeleton (13) could be obtained from Bischler-Napieralski or Pictet-Spengler reaction of the biphenyl phenylacetic acid (236) or biphenyl phenyl acetaldehyde (237), respectively. The biphenyls (236 and 237) could be prepared from intermolecular Suzuki coupling reaction of phenethylamine (238) and boronic acid (239).



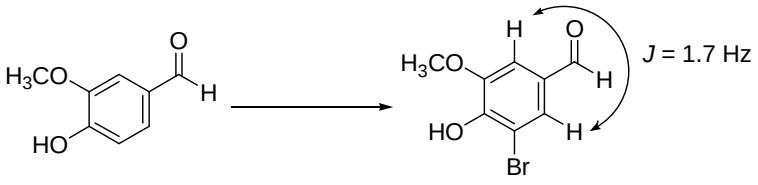
Scheme 11

1. The First Synthetic Strategy

1.1 Synthesis of (±)-*N*-formylnornuciferine (13a)

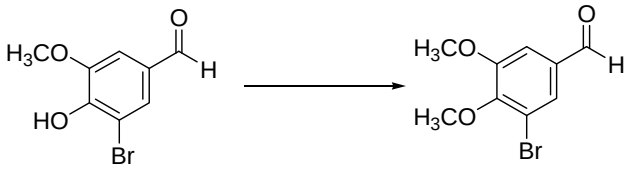
As described in Scheme 1, (±)-*N*-formylnornuciferine (13a) could be synthesized from a commercially available vanillin (168) *via* intramolecular Suzuki coupling reaction as a key step.

The bromovanillin (169) was obtained in high yield from bromination of vanillin (168) without a regioselectivity problem. The ^{1}H NMR spectrum of **169** showed clearly that the bromination occurred only at the *otho* position of strongly activating hydroxy group. The spectrum showed doublet signal at δ 7.69 and 7.43 with J=1.7 Hz indicated the *meta* interaction (^{4}J=1-3 Hz) of CH aromatic ring.



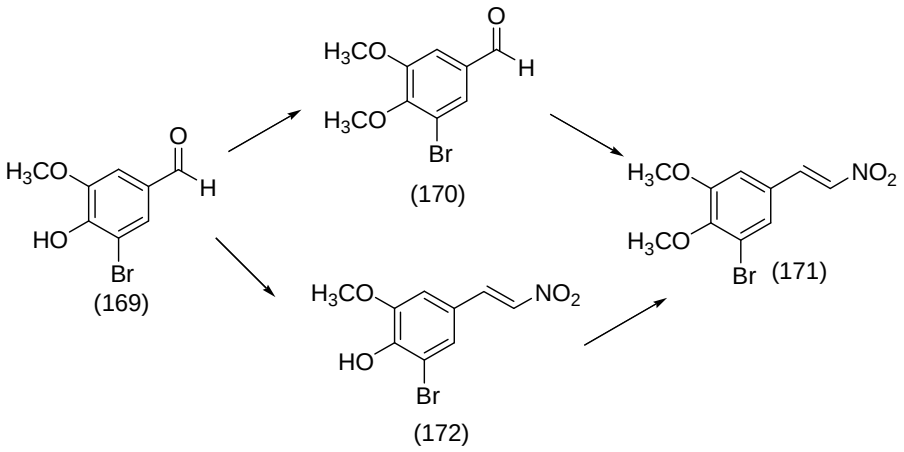
(168) (16)

Methylation conditions of bromovanillin (169) to 3-bromo-4,5-dimethoxybenzaldehyde (170) were investigated. The first condition utilized 4 equivalents of methyl iodide and 1.5 equivalents of potassium carbonate in acetone under reflux to give **170** in 92% yield. However, in order to reduce the amount of methyl iodide used in the reaction, stronger base (sodium hydroxide) in the presence of *n*-butylammonium iodide as a phase transfer catalyst were used. Only 1.5 equivalents of methyl iodide were used in this reaction condition to afford compound **170** in 91% yield.



(169) (170)

Aldol condensation of benzaldehyde (170) by sonication with nitromethane and ammonium acetate in acetic acid yielded nitrostyrene (171). In addition, nitrostyrene (171) was synthesized from benzaldehyde (169) by changing the order of the reaction sequence. Benzaldehyde (169) was first transformed to nitrostyrene (172), followed by methylation to afford nitrostyrene (171) with no significant change in yield.



Many reaction conditions for the reduction of nitrostyrene (171) to phenethylamine (173) were explored. The results were shown in Table 4. Most of the reduction conditions used did not give a desired amine product (173). Only one case (entry 4), small amount of the desired amine (173) was obtained and the major product was a debrominated compound (174).

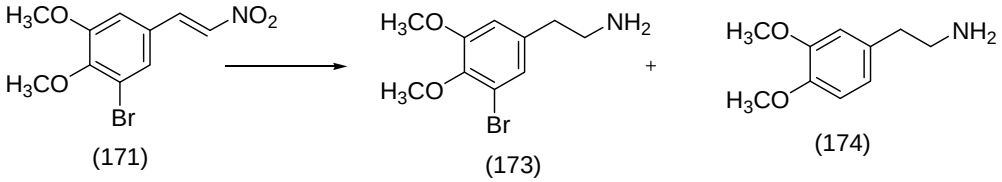
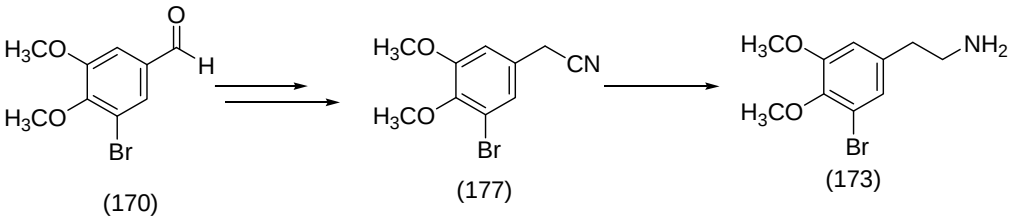


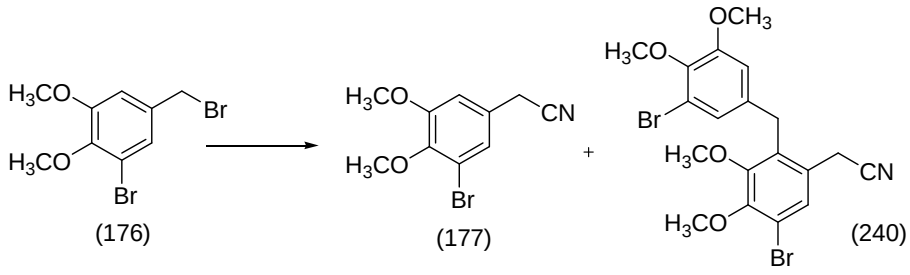
Table 4 Reduction conditions of **171**

Entry	Reagents	Results
1	10% Pd-C, H_2, ethyl acetate	No reaction and starting material recovered
2	$NaBH_4$, BF_3-Et_2O, THF	Unknown product
3	Zn, $HgCl_2$, MeOH-HCl	Starting material recovered and unknown product
4	$LiAlH_4$, THF	**173** (11%) and **174** (53%)

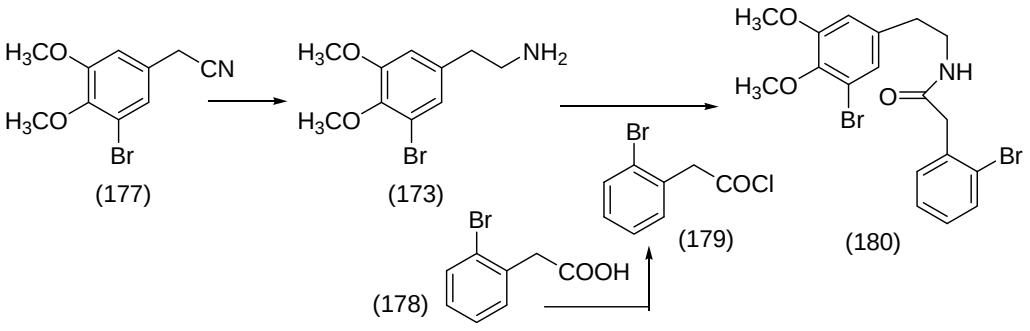
As described above, the reduction of nitrostyrene in several conditions did not give a desired product or the product (173) was obtained in very low yield. Therefore, we had to change our synthetic pathway to synthesize phenylacetonitrile (177) and then transformed the cyanide group of **177** to amino group (Scheme 1).



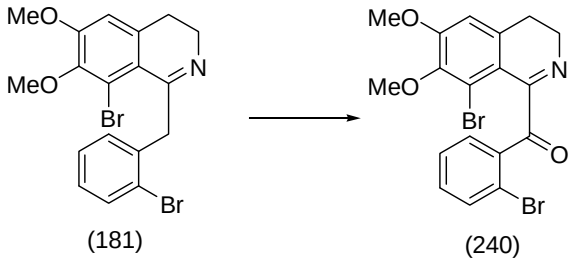
Nucleophillic substitution of bromide by cyanide was studied. Two substitution conditions using sodium cyanide in dimethylformamide and sodium cyanide onto aluminar in toluene were investigated to transform **176** to **177**. It was found that when the reaction was carried out in small amount of solvent, the side coupling product (240) was obtained.



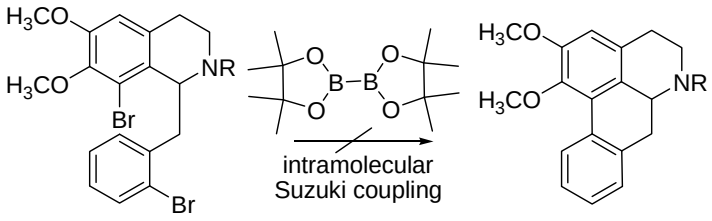
The bromo phenethylamine (173) was successfully prepared from the reduction of the corresponding phenyl acetonitrile (177) with borane tetrahydrofuran complex. Condensation of phenylacetyl chloride (179), derived from phenylacetic acid (178) with **173** gave phenylacetamide (180) in 93% yield (two steps).



Bischler-Napieralski reaction of **180** was performed in the presence of phosphorus oxychloride in dichloromethane to afford 3,4-dihydroisoquinoline (181). The dihydroisoquinoline (181) is not stable. It can be easily oxidized by air to give the corresponding ketone (240). Therefore, the synthesized dihydroisoquinolines were converted to 1,2,3,4-tetrahydroisoquinoline without prior purification.



Intramolecular Suzuki coupling conditions of benzylisoquinoline (182, 183) to aporphine skeletons (184, 13a) were studied (Table 5). The condition in entry 1 using two steps reaction, the first step involved the formation of aryl boronate ester from one of aromatic bromide using sodium acetate as base and the second step was Suzuki coupling between generated aryl boronate ester and another aryl halide under stronger basic condition (potassium carbonate). The results in entry 1 showed this condition afforded a complex mixture. The condition in entry 2 was a biaryl coupling *via* one-pot Suzuki reaction using potassium carbonate as base which was a protocol published by Miyaura. This process also showed no reaction occurred and only starting material was recovered.



(182); R=H
(183); R=CHO

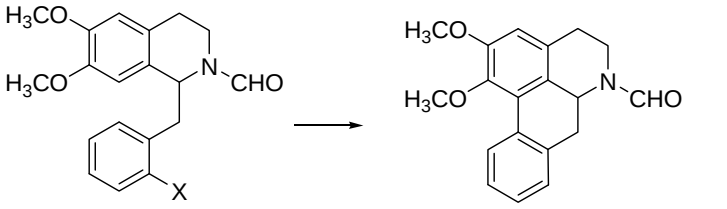
(184); R=H
(13a); R=CHO

Table 5 Intramolecular Suzuki coupling condition

Entry	R	Pd	Base	Solvent	Results
1	H	i) $PdCl_2$(dppf)	NaOAc	DMF	
		ii) $PdCl_2$(dppf)	2M $NaCO_3$	DMF	Unknown product
2	CHO	$PdCl_2$(dppf)	K_2CO_3	DMSO	No reaction and starting material recovered

The unsuccessful cyclization of **182** and **183** *via* intramolecular Suzuki coupling led us to consider another reaction condition. Inspired by the intramolecular *ortho*-arylation to synthesis of aporphine alkaloids by Cuny (Cuny, 2003), we applied this methodology to cyclize *N*-formyl benzylisoquinoline (188 and 194).

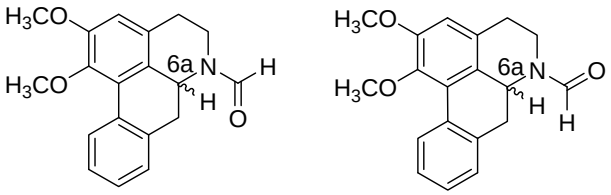
In Scheme 2, benzylisoquinolines (188 and 194) were prepared from homoveratrylamine (174) and halophenylacetic acid (178 and 189) by using similar conditions for the synthesis of benzylisoquinoline (183) (Scheme 1). The palladium-catalyzed cyclization of *N*-formyl benzylisoquinoline (188 and 194) was performed using the condition reported by Cuny. The suitable condition, palladium acetate, triphenylphosphine and anhydrous sodium acetate in dimethylacetamide, was used to obtain (±)-*N*-formylnornuciferine (13a) in high yield.



(188); X= Br
(194); X=I

(±)-*N*-Fromylnoenuciferine (13a)

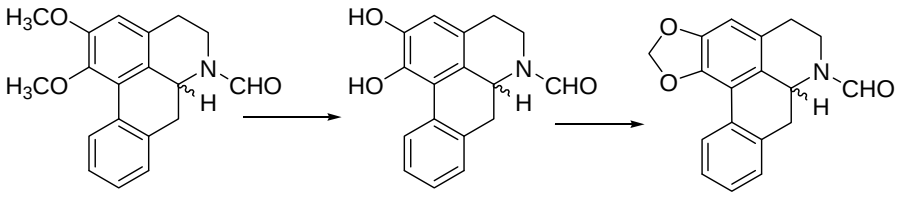
The spectral data of (±)-*N*-formylnornuciferine (13a) were identical with the previous reported data of (-)-*N*-formylnornuciferine (Pachaly *et al*., 1992). The ^{1}H NMR spectrum exhibited two sets of signals of two rotational isomers in the ratio of 1.7: 1 (*Z*-: *E*-) due to the restricted rotation of the N-CHO group. The ^{1}H NMR spectrum of (±)-*N*-formylnornuciferine (13a) in $CDCl_3$ showed two sets of signals of H-6a as doublet of doublets at δ 4.86 and 4.43 that indicated the presence of two rotational isomers. The signal of *Z* isomer should be observed at higher field than *E* isomer due to the shielding of carbonyl anisotropy. Therefore, the signals at 4.86 and 4.43 were assigned to H-6a of *Z*- and *E*- isomer, respectively.



(*Z*) (*E*)

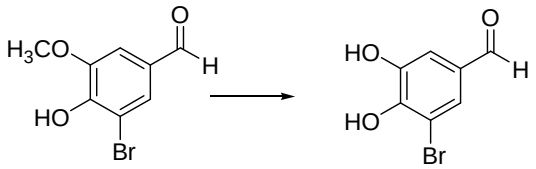
1.2 Synthesis of (±)-*N*-formylannonaine (14a)

Our initial plan for the synthesis of (±)-*N*-formylannonaine (14a) was desired to synthesize from (±)-*N*-formylnornuciferine (13a) by demethylation and methyleneation, respectively.



N-formylnornuciferine (13a) (242) *N*-formylannonaine (14a)

Before the synthesis of (±)-*N*-formylannonaine (14a) from (±)-*N*-formylnornuciferine (13a) was started, we had studied the demethylation conditions of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (195) as a model reaction (Table 6).



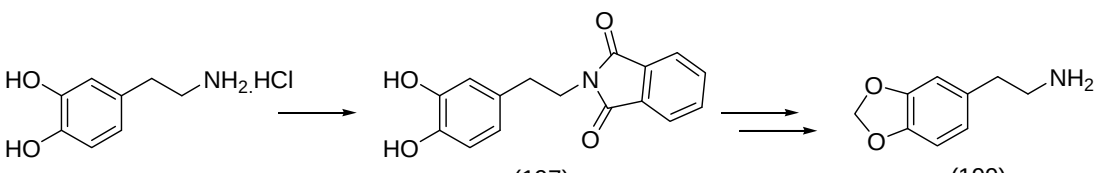
(169) (195)

Table 6 Demethylation conditions of **169**

Entry	Condition	Results
1	$AlCl_3$, Pyridine, CH_2Cl_2, reflux	**195** (59 %) and **169** (18%)
2	BBr_3, CH_2Cl_2, -78 ^oC to rt	**195** (63%) and **169** (11%)

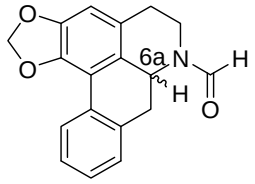
The best condition for demethylation of 3-bromo-4-hydroxy-5-methoxybenzaldehyde (169) (entry 2) was boron tribromide in dichloromethane. This condition gave **195** in moderate yield (63%) together with 11% of recover starting material. This condition was applied for demethylation of (±)-*N*-formylnornuciferine (13a). However, it was found that only low yield (24%) of the desired product (242) and 51% of recovered starting compound was obtained. Therefore, we turned our attention to synthesize (±)-*N*-formylannonaine (13a) by the same synthetic strategy as utilizing for (±)-*N*-formylnornuciferine (13a) (Scheme 3).

The commercially available dopamine hydrochloride (196) was selected as starting material for synthesis of (±)-*N*-formylannonaine (14a). Before introducing methylene to dihydroxy group, it is importance to protect primary amine. Protection of dopamine hydrochloride (196) was carried out by refluxing with phthalic anhydride in acetic acid to give phthalimide (197). Methylenation of compound **197** followed by deprotection of phthalimide afforded phenethylamine (199) which was used as a key intermediate for the synthesis of (±)-*N*-formylannonaine (14a).

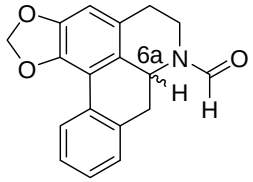


Dopamine hydrochloride (196) (197) (199)

The synthesis of (±)-*N*-formylannonaine (14a) was accomplished in 6 steps from phenethylamine (199) as shown in Scheme 3. The spectral data of (±)-*N*-formylannonaine (14) were in agreement with the literature report (Pachaly *et al*., 1992). The ^{1}H NMR and ^{13}C NMR spectral data exhibited two sets of signals of two rotational isomers in the ratio of 2.5: 1 (*Z*-: *E*-). The *Z*- and *E*- isomers were identified by H-6a signals of ^{1}H NMR at δ 4.98 and 4.55, respectively.



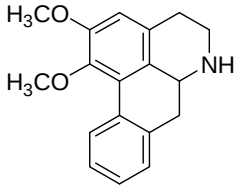
(*Z*)



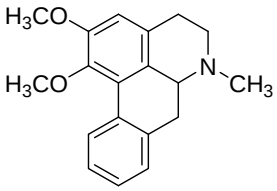
(*E*)

1.3 Synthesis of (±)-*N*-formylnornuciferine analogues

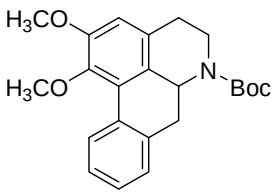
Three analogues of (±)-*N*-formylnornuciferine analogues, nuciferine (184), nornuciferine (204) and 1-(1,2-di1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid tert-butyl ester (206), were synthesized (Scheme 4 and 5).



Nuciferine (184)



Nornuciferine (204)



(206)

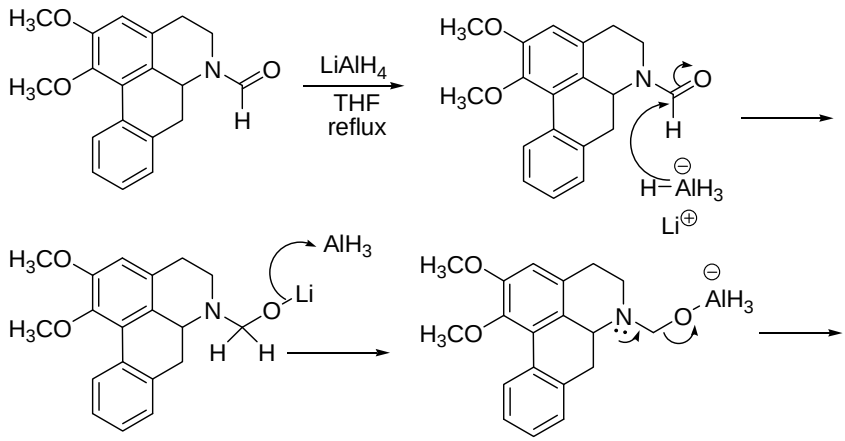
(±)-*N*-Formylnornuciferine (13a) was converted to nuciferine (184) and nornuciferine (204) by either acid hydrolysis or reduction of the N-CHO functional group (Scheme 4). The results were showed in Table 7.

Table 7 Conversion conditions of *N*-formylnornuciferine (13a) to nuciferine (184) and nornuciferine (204)

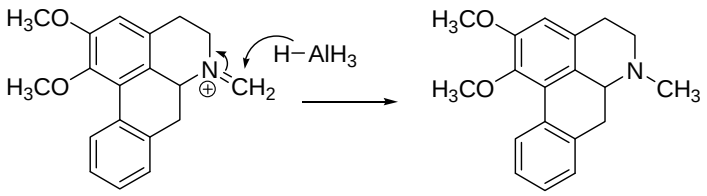
Entry	Reagents	Condition	Nuciferine (184) (%yield)	Nornuciferine (204) (%yield)
1	sat. HCl/ MeOH,	reflux	89%	-
2	$LiAlH_4$, dry THF	-78 ^oC to rt	86%	11%
3	$LiAlH_4$, dry THF	reflux	-	78%

By acid hydrolysis using methanol saturated hydrogen chloride under reflux condition (entry 1), (±)-*N*-formylnornuciferine (13a) was converted to nuciferine (184) in 89% yield. Reduction of (±)-*N*-formylnornuciferine (13) with lithium aluminium hydride at -78 ^oC to room temperature gave 86% of nuciferine (184) and 11% of nornuciferine (204), whereas under refluxing condition in anhydrous tetrahydrofuran afforded only nornuciferine (204) in 78%.

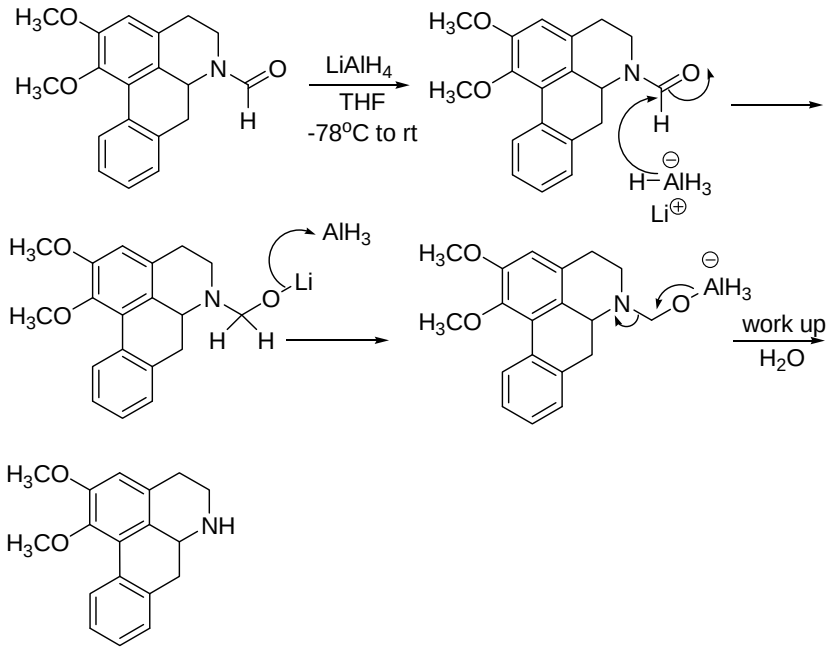
With different results from the reaction using lithium aluminium hydride, the plausible mechanisms were proposed as shown in Scheme 12 and 13.



Scheme 12 The plausible mechanism for conversion of *N*-formylnornuciferine (13a) to nornuciferine (204) by using lithium aluminium hydride

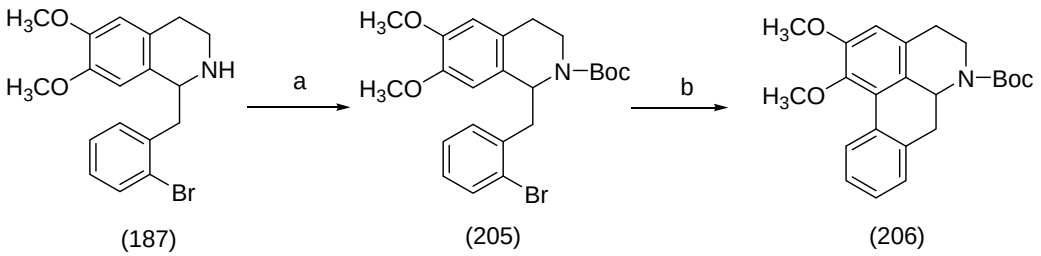


Scheme 12 (Continued)



Scheme 13 The plausible mechanism for conversion of *N*-formylnornuciferine (13a) to nuciferine (184) by using lithium aluminium hydride

In addition, 1-(1,2-di1,2-dimethoxy-4,5,6a,7-tetrahydro-dibenzoquino line-6-carboxylic acid tert-butyl ester (206) was obtained from benzylisoquinoline (187) through benzylisoquinoline **205**. The ^{1}H NMR and ^{13}C NMR spectral data of isoquinoline (205) exhibited two sets of signals of two rotational isomers in the ratio of 4: 1 (*Z*-: *E*-), while spectral data of the aporphine (206) showed only one set of signals.

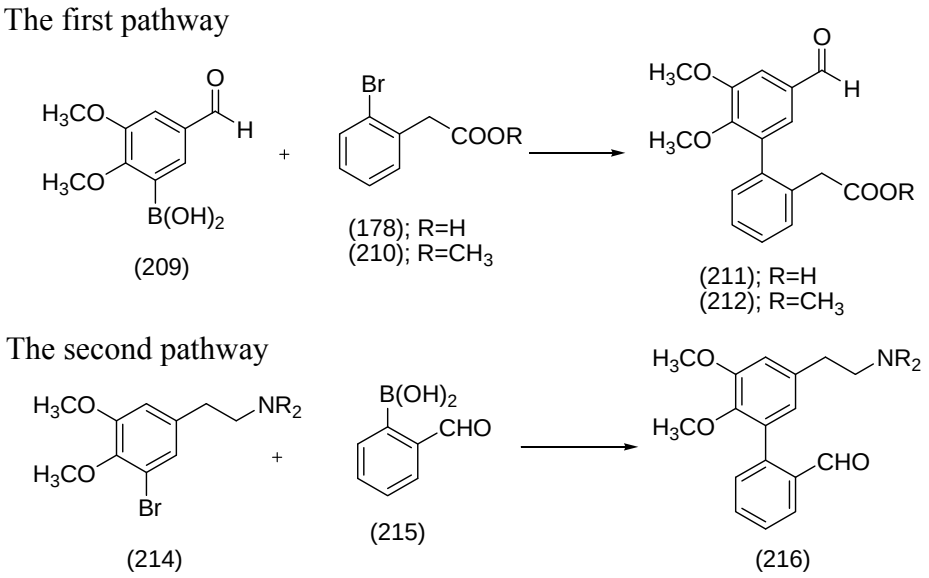


(187) (205) (206)

2. The Second Synthetic Strategy

With no success in the previous strategy utilizing intramolecular Suzuki reaction, we decided to perform the synthesis using intermolecular Suzuki coupling reaction. The Suzuki reaction was used to synthesize biaryl rings A and D of aporphine skeleton. Subsequently cyclization of the biaryl by using Bischler-Napieralski or Pictet-Spengler reaction condition should give an aporphine alkaloid.

Intermolecular Suzuki coupling was studied in two pathways as shown in Scheme 14. The first pathway used ring A in aporphine system as arylboronic acid, whereas the second pathway used ring D as arylboronic acid.



(209) (214) (215) (216)

Scheme 14

The first pathway, the upper aromatic ring was desired to be arylboronic acid (209) or aryl boronate ester (207) for coupling with aryl halide (178 and 210). The arylboronic acid (209) was successfully prepared from boronation of dioxolane (208), followed by acid hydrolysis, whereas the synthesis of the corresponding ester from palladium catalyzed coupling reaction of 3-bromobenzaldehyde (170) and bis(pinacolato)diboron was unsuccessful.

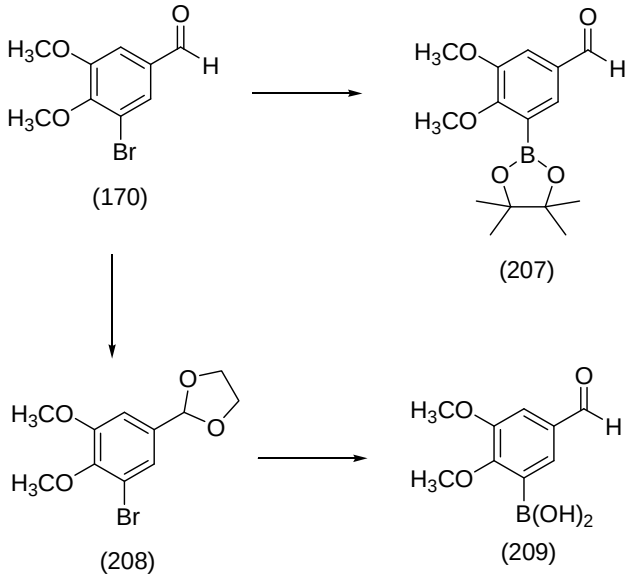


Table 8 Preparation condition of boronic acid (207 and 209)

Entry	Reagents	Results
1	$PdCl_2dppf$, pinacol diboron, K_2CO_3, DMSO	No reaction and starting material recovered
2	i) n-BuLi, $B(OCH)_3$, THF ii) 2M HCl	**209** (61%, 2 steps)

The intermolecular Suzuki coupling between arylboronic acid (209) and aryl halide (178 and 210) was studied using various conditions (Table 9). All conditions did not provide a desired coupling product (211 and 212) but afforded a hydrogen substitution of aromatic ring (213) instead.

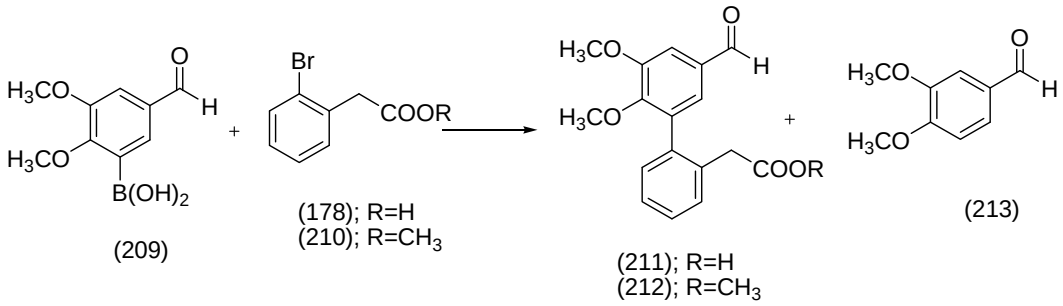


Table 9 Intermolecular Suzuki coupling condition for the first pathway

Entry	R	Pd	Base	Solvent	Results
1	H	$Pd_2(dba)_3$	Na_2CO_3	DME	**213** (65%)
2	H	$Pd(PPh_3)_4$	Na_2CO_3	EtOH/DME	**213** (63%)
3	H	$Pd(PPh_3)_4$	NaOH	EtOH/DME	**213** (42%), **178** (11%)
4	H	$Pd(PPh_3)_4$	Cs_2CO_3	EtOH/DME	**213** (68%)
5	CH_3	$Pd(PPh_3)_4$	Na_2CO_3	EtOH	**213** (62%)

With unsuccessful coupling in the first pathway, the second pathway was emerged to study intermolecular Suzuki coupling as shown in Table 10. In this pathway, the coupling between aryl bromide (214) and 2-formylphenyl boronic acid (215) was studied in two conditions as shown in Table 10.

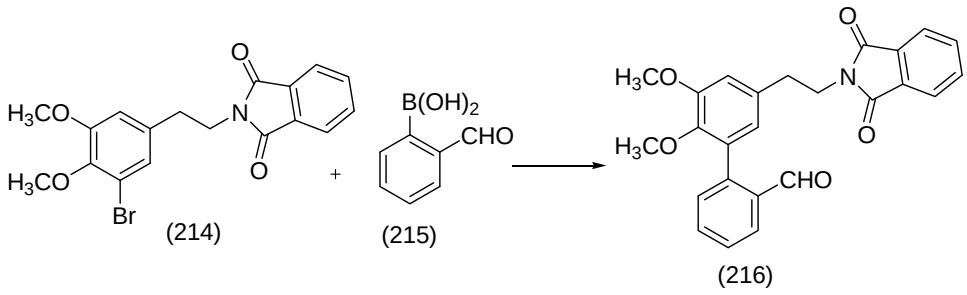
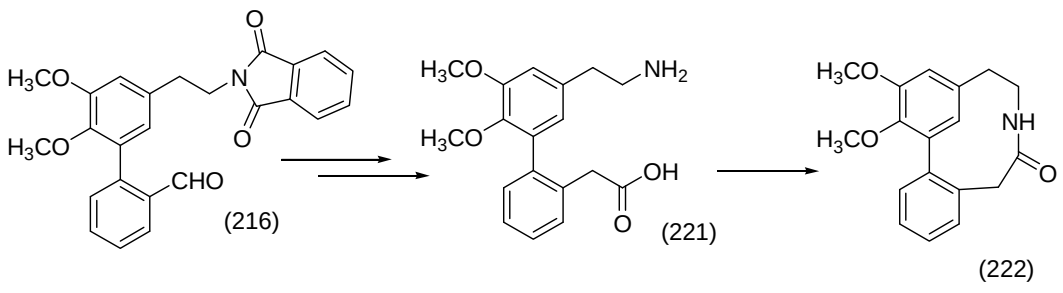


Table 10 Intermolecular Suzuki coupling condition for the second pathway

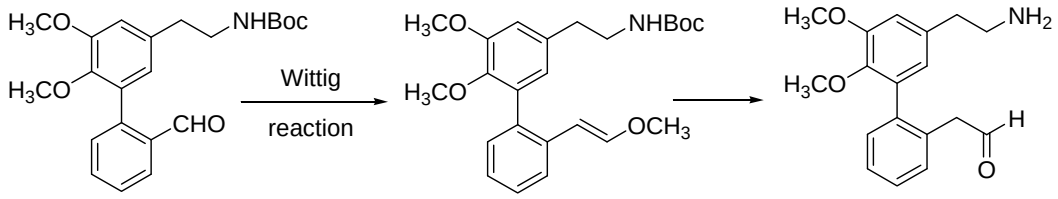
Entry	Pd	Base	Additive	Solvent	Results
1	$Pd(PPh_3)_4$	1.8M Na_2CO_3	-	DME	No reaction and starting material recovered
2	$Pd(OAc)_2$	K_3PO_4	PCy_3	Toluene	82%

By using tetrakis(triphenyl phosphine)palladium and sodium carbonate in dimethoxyethane (entry 1) did not afford the product (216). The suitable condition was in entry 2 using palladium acetate and potassium phosphate in toluene gave desired coupling biaryl product (216). However, the starting material was not completely converted to the product (216) when 1.5 equivalents of 2-formylphenyl boronic acid were used. The condition was optimized by using 2.0 equivalents of 2-formylphenylboronic acid, the reaction showed a complete conversion of starting material to give 82% of the product (216).

After success in the synthesis of biaryl (216) *via* intermolecular Suzuki coupling, the synthesis was continued to construct the aporphine skeleton *via* Bischler-Napieralski reaction. To study Bischler-Napieralski reaction, cyclic amide (222) could be prepared by condensation of biaryl amino carboxylic (221) which was synthesized from biaryl carboxaldehyde (216). However, intramolecular condensation of biaryl amine (221) to amide (222) in refluxing toluene was unsuccessful. Decomposition of the reduction was obtained after refluxing for 12 hours.



Since the Bischler-Napieralski reaction was failed, we turned our attention to construct the aporphine skeleton *via* Pictet-Spengler reaction (Scheme 7). To perform the Pictet-Spengler reaction, the intermediate (231) must be prepared. *Tert*-butyl carbamate was selected to protect primary amine since it could be simultaneously removed when methoxyetene group was hydrolyzed to aldehyde by acid.



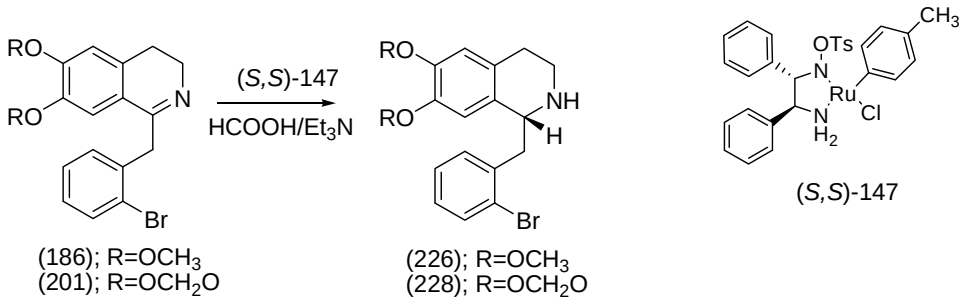
(224) (225) (231)

For Wittig reaction, we faced the problem with forming methoxyetene (225). The problem might occur in the phosphonium ylides generation step. As Li and Castle reported, to generate ylide, a solution of phosphonium chloride in tetrahydrofuran at 0 °C was added dropwise with a solution of potassium *tert*-butoxide in tetrahydrofuran. We tried to using this method and found that the potassium *tert*-butoxide did not dissolve in tetrahydrofuran. Then, we tried to add the suspension to a solution of phosphonium chloride in tetrahydrofuran, followed by adding a solution of starting material in tetrahydrofuran to the reaction mixture. Finally, we found that no reaction occurred and only starting material was recovered. The problem might cause by incomplete reaction in the generation of the ylide.

3. Asymmetric Synthesis of (-)-*N*-Formylnornuciferine (13b) and (-)-*N*-Formyl anonaine (14b)

Inspired by Noyori's work, we applied his protocol to synthesize our tetrahydroisoquinolines (226 and 228). The suitable reagents and condition were $[RuCl_2(p\text{-cymene})]_2$, (1*S*,2*S*)-1,2-diphenyl-*N*-(*p*-toluoylsulfonyl) ethlylamine and azeotropic mixture of formic acid and triethylamine (5:2) in acetronitrile. The (*S*,*S*)-TsDPEN was selected in order to form (*S,S*)-Ru complex which can catalyze the

reaction to produce a 1,2,3,4-tetrahydroisoquinoline with *R* configuration at C-6a as shown below.



(186); R=OCH_3
(201); R=OCH_2O

(226); R=OCH_3
(228); R=OCH_2O

The azeotropic mixture of formic acid and triethylamine (5:2) used in the reaction was not exactly 5:2 v/v, but it meant a liquid mixture of formic acid and triethylamine that retained the same composition (5:2) in the vapor state as in the liquid state during distillation under a certain pressure. This mixture was very crucial for the successful of the asymmetric transfer hydrogenation under Noyori's reaction condition.

Asymmetric transfer hydrogenation of **186** and **201** gave tetrahydro isoquinolines **226** and **228**, respectively in high yield. The configuration of both compounds was assigned by optical rotation measurement (Table 11). With the successful synthesis of (*R*)-**226** and (*R*)-**228** led to accomplish the asymmetric synthesis of both (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b), respectively (Scheme 8 and 9).

The optical rotation of the synthesized compounds was determined as shown in Table 11. The results showed clearly that the non-asymmetric reduction of the dihydroisoqunolines (186 and 201) using sodium borohydride afforded the corresponding of **187** and **202** as a racemic mixture with the same value of optical rotation ($[\alpha]^{27}_D$=0.07), whereas asymmetric transfer hydrogenation using Noyori's condition gave products (226 and 228) as a single enantiomer with $[\alpha]^{27}_D$ -27.33 and -28.30, respectively.

Table 11 Optical rotation of tetrahydroisoquinolines and aporphines

Entry	Non-asymmetric synthesis				Asymmetric synthesis			
	Cpd.	Conc. (ppm)	Temp. (^oC)	$[\alpha]_D$	Cpd.	Conc. (ppm)	Temp. (^oC)	$[\alpha]_D$
1	**187**	1.3	27.1	+0.07	**226**	0.2	27.4	-27.33
2	**188**	0.9	27.7	+0.77	**227**	0.5	27.5	-86.80
3	**13a**	1.1	27.7	+0.18	**13b**	0.4	27.8	-315.75
4	**202**	4.1	26.7	+0.07	**228**	2.0	26.7	-28.30
5	**203**	1.6	26.8	+0.81	**229**	2.0	26.8	-88.500
6	**14a**	0.4	27.0	0.00	**14b**	0.4	27.0	-189.00

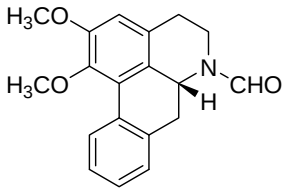
4. Cardiotonic Activity Testing

The racemic mixture of *N*-formylnornuciferine (13) and *N*-formylannonaine (14) were tested for cardiotonic activity on isolated rat heart. The results showed that their activities were not the same as activities of the natural ones isolated from *Tinospora crispa* (Sunthikawinsakul, 2005).

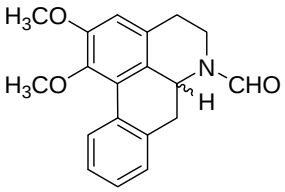
(-)-*N*-Formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b), isolated from *T. crispa*, exhibited significant increase in force of contraction on atrium of isolated rat heart with no change on the rate (Sunthikawinsakul, 2005). Whereas, the racemic mixture of (±)-*N*-formylnornuciferine (13a) and (±)-*N*-formylannonaine (14a), obtained from the synthesis, showed a decrease in the force of contraction on atrium with a small decrease in the heart rate (Figure 4 and 5). Moreover, (±)-*N*-formylnornuciferine (13a) produced slight reduction on the force of contraction and significant reduction on the conduction until stop beating (Appendix Figure 87).

The difference of the activities might be resulted from the fact that the synthesis compound contained a racemic mixture of (±)-*N*-formylnornuciferine (13a) and (±)-*N*-formylannonaine (14a). Whereas, these two alkaloids isolated from *T.*

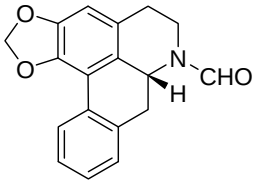
crispa were a single enantiomer of (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b) (Figure 8).



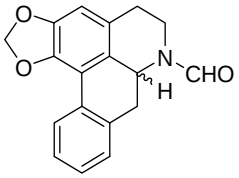
(-)-*N*-Formylnornuciferine (13b)
from *T*. crispa



(±)-*N*-Formylnornuciferine (13a)
from synthesis



(-)-*N*-Formylannonaine (14b)
from *T*. crispa



(±)-*N*-Formylannonaine (14a)
from synthesis

Figure 8 Structure of (-)-*N*-formylnornuciferine (13b), (±)-*N*- formylnornuciferine (13a), (-)-*N*-formylannonaine (14b) and (±)-*N*-formylannonaine (14a)

To prove our hypothesis, asymmetric synthesis were conducted by using asymmetric transfer hydrogenation of the corresponding isoquinoline to provide (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b) with *R* configuration of C-6a. The test results of (-)-*N*-formylnornuciferine (13b) and (-)-*N*-formylannonaine (14b) showed that these alkaloids exhibited significant increase on atrium of isolated heart with no change on the rate which was similar to those isolated from *T. crispa* (Figure 6 and 7).

CONCLUSION

The synthesis of two aporphine alkaloids, (±)-*N*-formylnornuciferine and (±)-*N*-formylannonaine were accomplished *via* palladium-catalyzed coupling reaction as a key step. (±)-*N*-Formylnornuciferine was obtained in 6 steps from a commercially available homoveratrylamine with an overall yield of 50%, whereas (±)-*N*-formylannonaine was also achieved in 9 steps from a dopamine hydrochloride with an overall yield of 30%.

In addition, asymmetric transfer hydrogenation of dihydroisoquinoline intermediates to afford the corresponding enantiopures was investigated. (-)-*N*-Formylnornuciferine and (-)-*N*-formylannonaine, the single enantiomers were successful synthesized in 50% and 34% overall yield, respectively by catalytic asymmetric transfer hydrogenation method using $[RuCl_2(p\text{-cymene})]_2$, (*S*,*S*)-TsDPEN chiral ligand and azeotropic mixture of formic acid and triethylamine as a catalyst system.

Both *N*-formylnornuciferine and *N*-formylannonaine in racemic form and enantiopure were evaluated for cardiotonic activity. The results showed that the synthetic alkaloids in racemic form exhibited difference activity to the natural ones. The synthetic compounds produced decrease on heart rate, while the natural ones exhibited a significant increase in force of contraction with no change on the rate. However, the evaluation of cardiotonic activity of the enantiopure compounds showed that the cardiac contractility and heart rate test of these compounds were very similar to that of the natural ones.

With our synthetic strategy for synthesis of *N*-formylnornuciferine and *N*-formylannonaine, we hope that further cardiotonic activity elucidation will be more efficient. Moreover, it may be possible to develop these active alkaloids to become a potential cardiotonic drug in the future.

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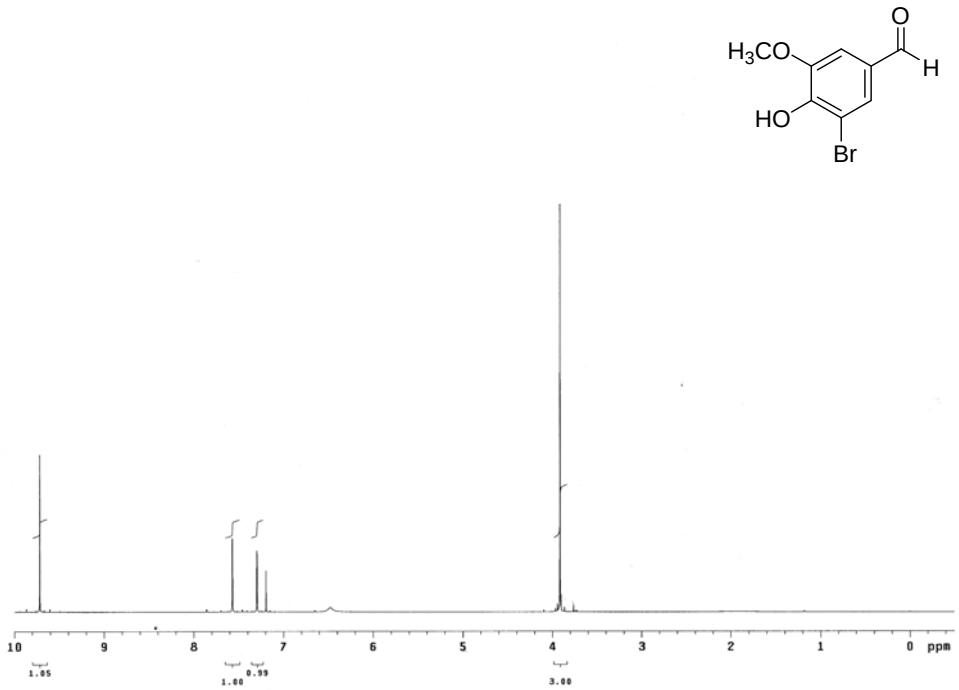
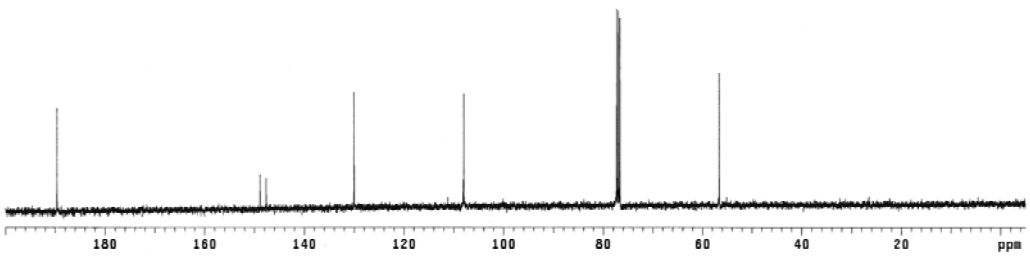
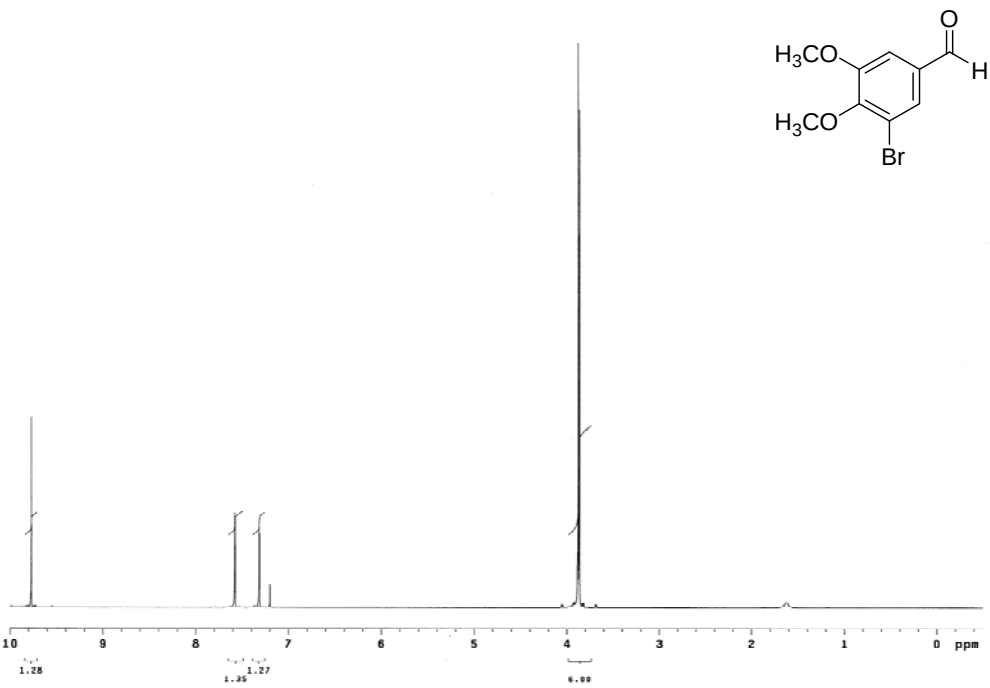
APPENDIX



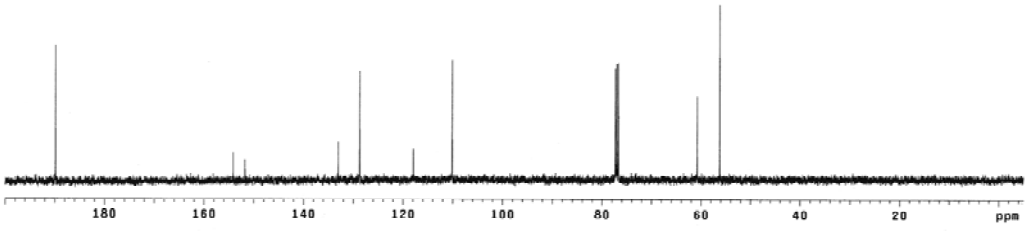
Appendix Figure 1 400 MHz ^{1}H NMR spectrum of 5-bromovanillin (168)



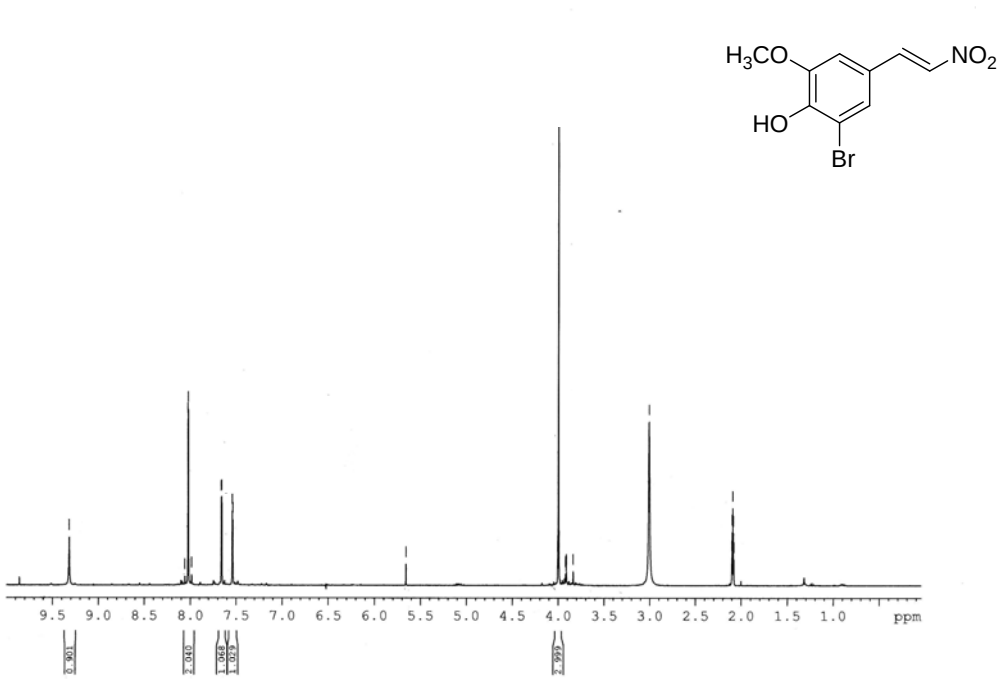
Appendix Figure 2 100 MHz ^{13}C NMR spectrum of 5-bromovanillin (168)



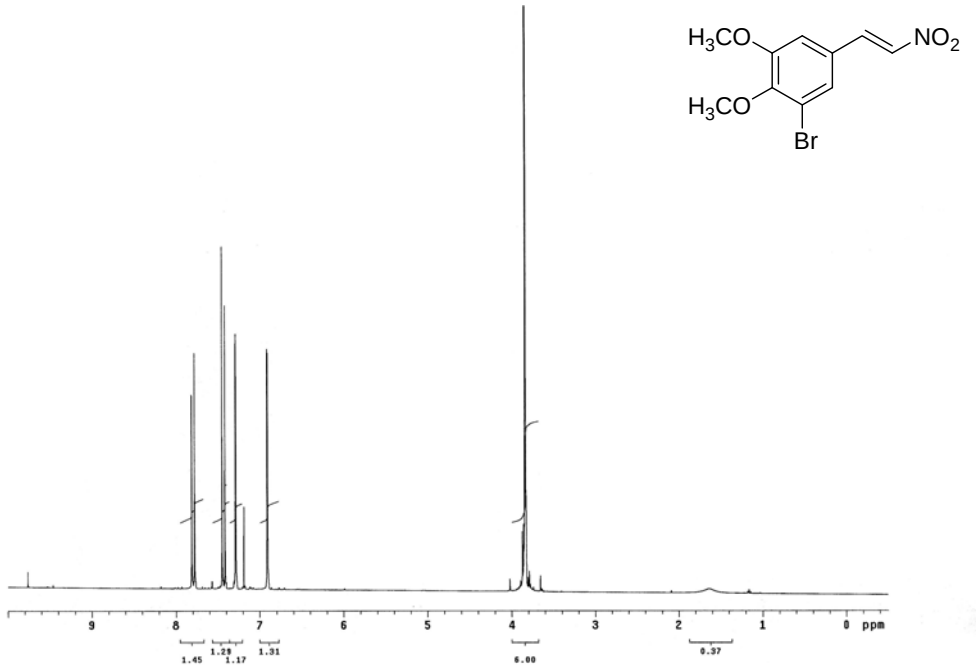
Appendix Figure 3 400 MHz ^{1}H NMR spectrum of 3-bromo-4,5-dimethoxy benzaldehyde (169)



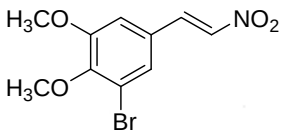
Appendix Figure 4 100 MHz ^{13}C NMR spectrum of 3-bromo-4,5-dimethoxy benzaldehyde (169)

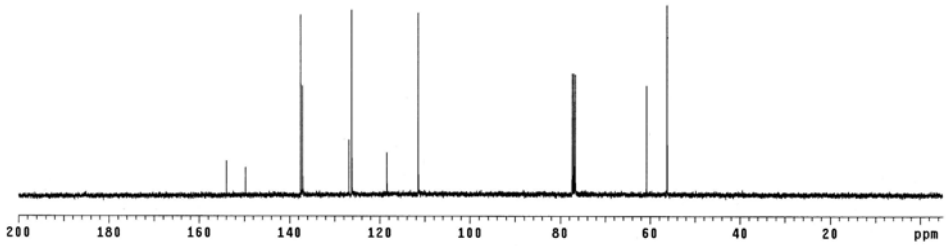


Appendix Figure 5 400 MHz ^{1}H NMR spectrum of 2-bromo-6-methoxy-4-(2-nitro vinyl)phenol (172)

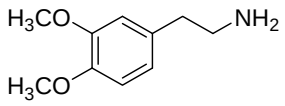


Appendix Figure 6 400 MHz ^{1}H NMR spectrum of 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171)

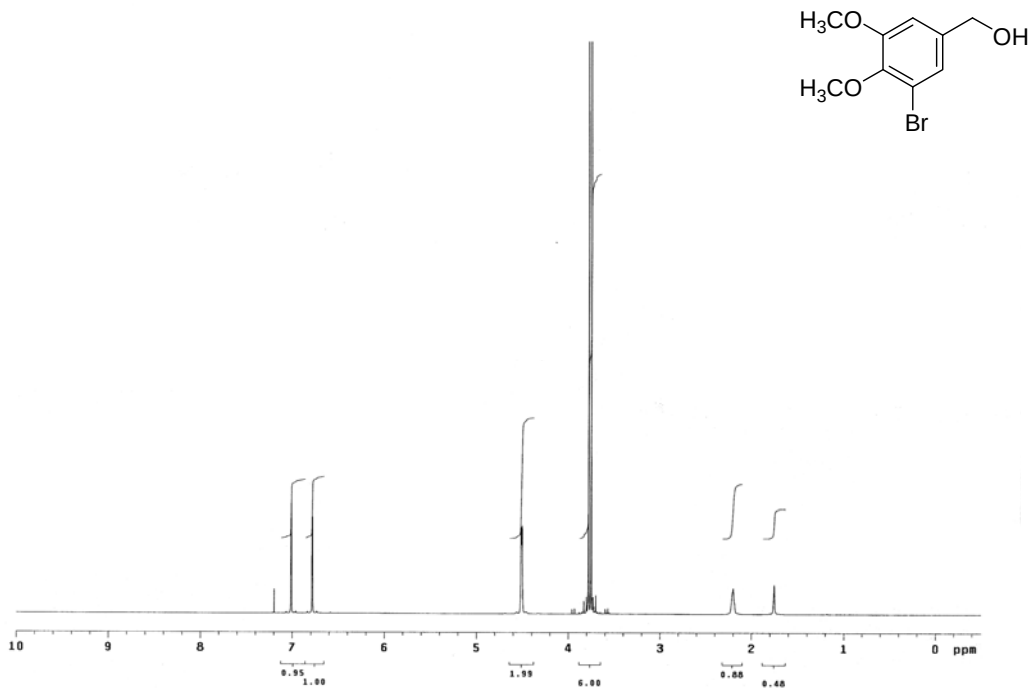




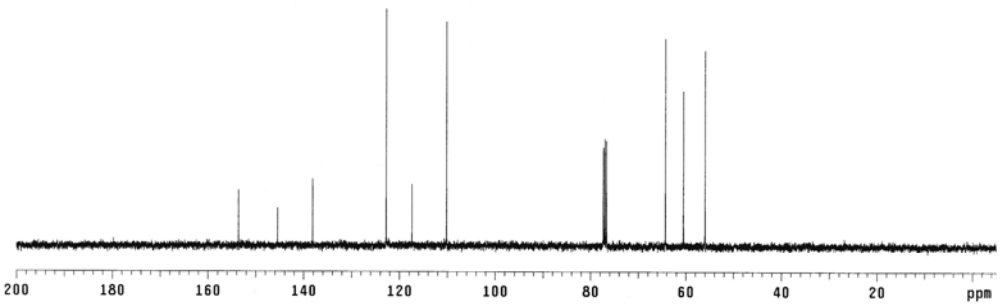
Appendix Figure 7 100 MHz ^{13}C NMR spectrum of 1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (171)



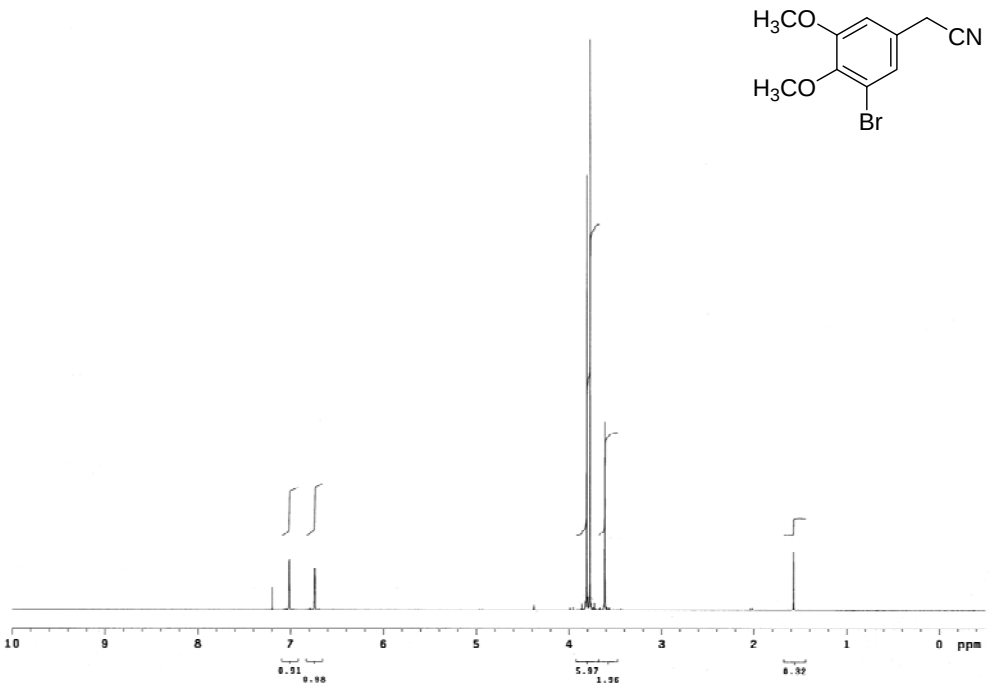
Appendix Figure 8 400 MHz ^{1}H NMR spectrum of 2-(3,4-dimethoxyphenyl) ethanamine (174)



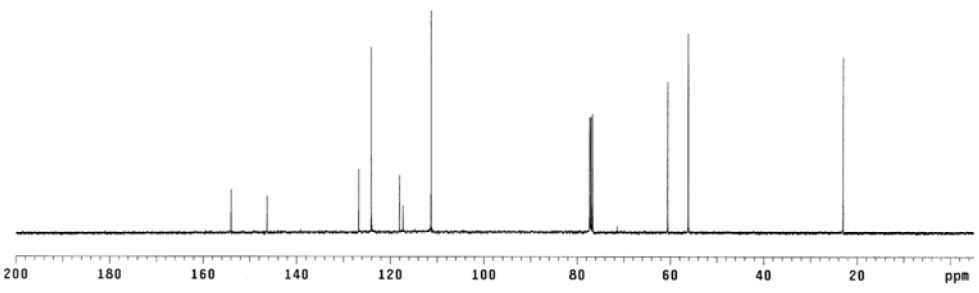
Appendix Figure 9 400 MHz ^{1}H NMR spectrum of (3-bromo-4,5-dimethoxy phenyl) methanol (175)



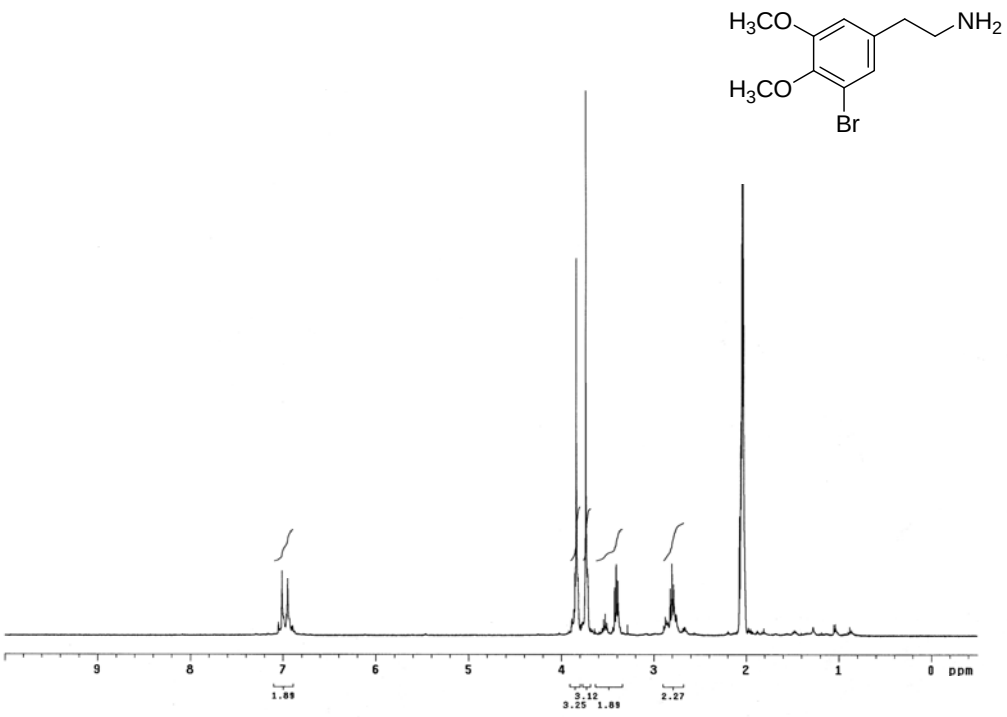
Appendix Figure 10 100 MHz ^{13}C NMR spectrum of (3-bromo-4,5-dimethoxy phenyl) methanol (175)



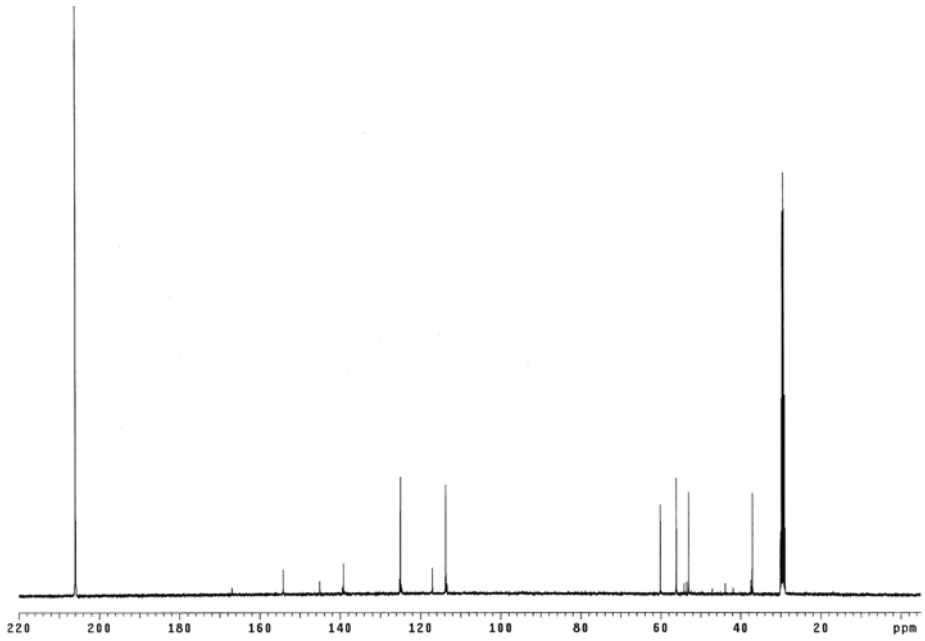
Appendix Figure 11 400 MHz ^{1}H NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenyl)acetonitrile (177)



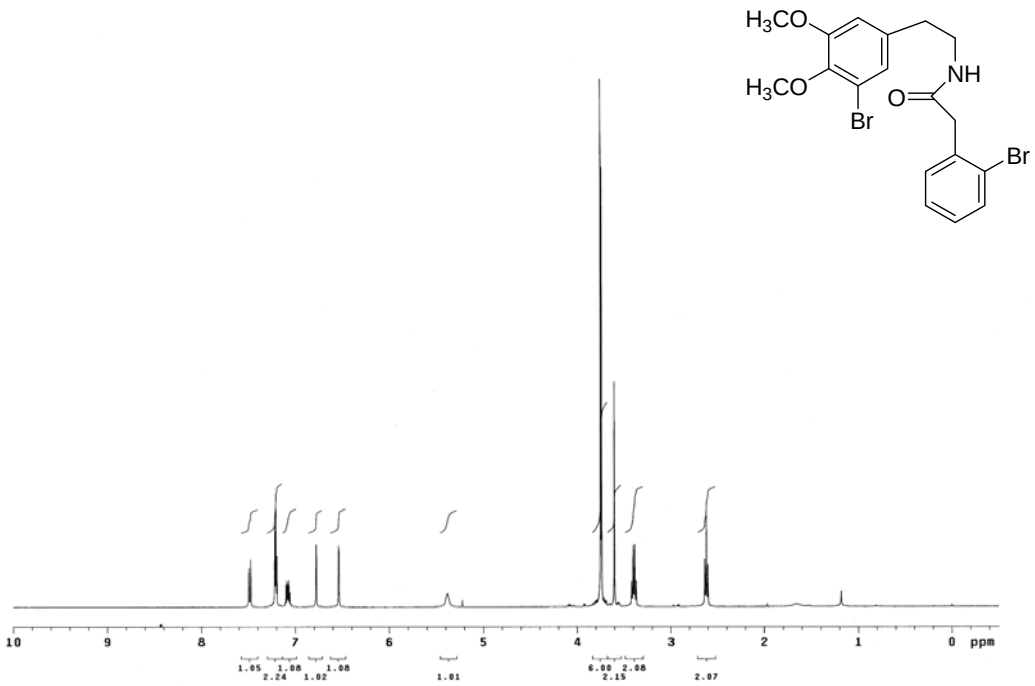
Appendix Figure 12 100 MHz ^{13}C NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenyl)acetonitrile (177)



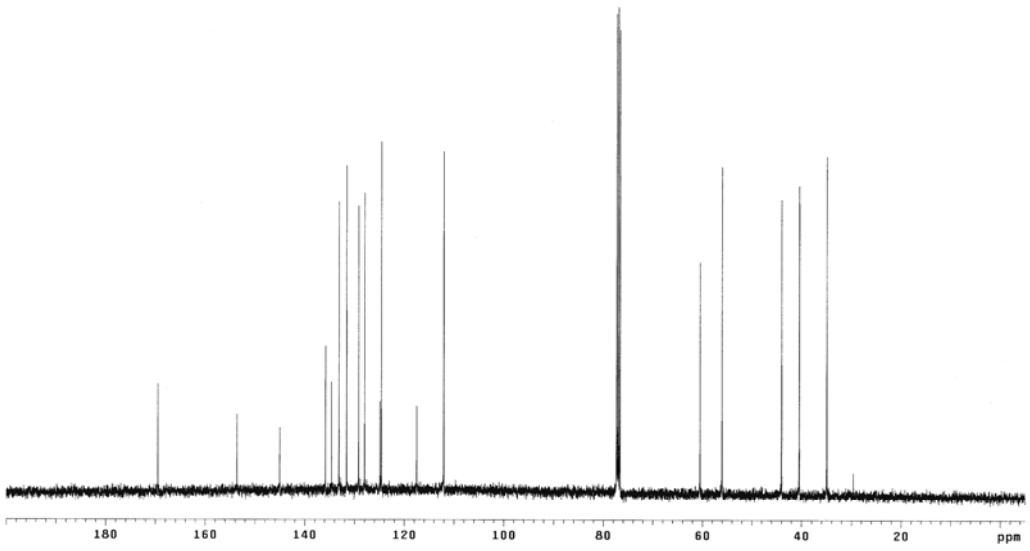
Appendix Figure 13 400 MHz ^{1}H NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenyl)ethanamine (173)



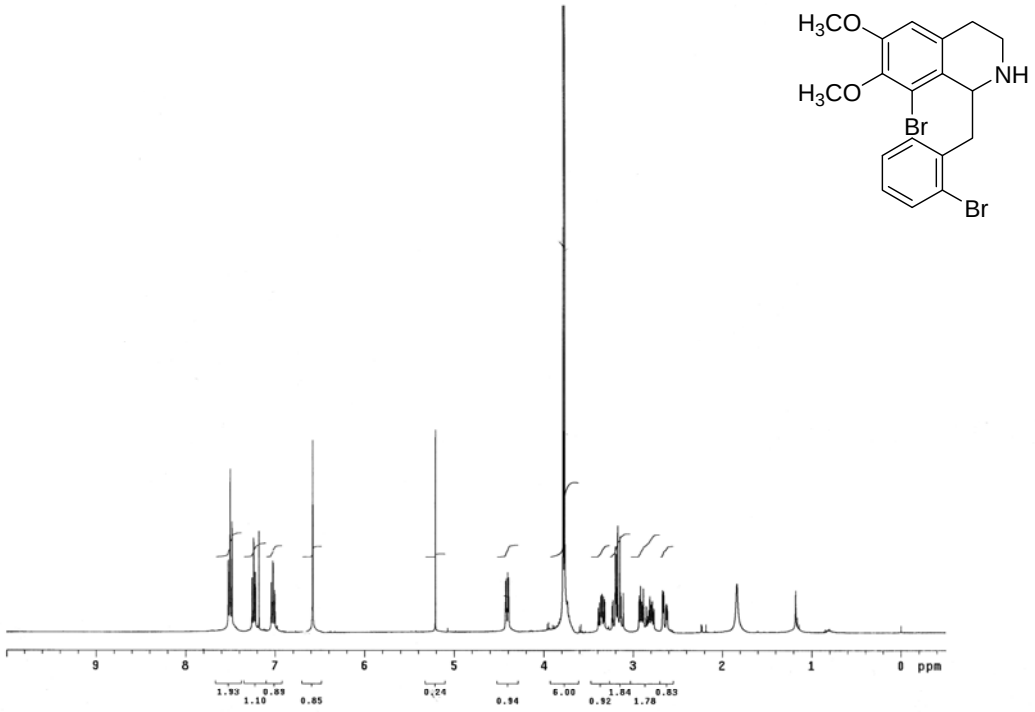
Appendix Figure 14 100 MHz ^{13}C NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenyl)ethanamine (173)



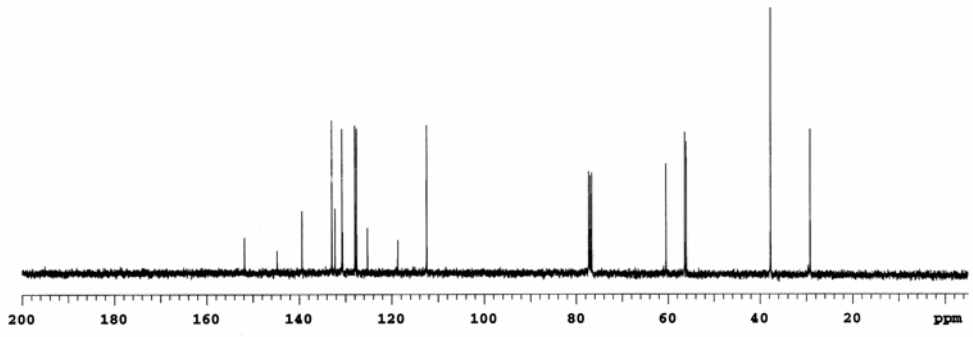
Appendix Figure 15 400 MHz ^{1}H NMR spectrum of *N*-(3-bromo-4,5-dimethoxy phenethyl)-2-(2-bromophenyl)acetamide (180)



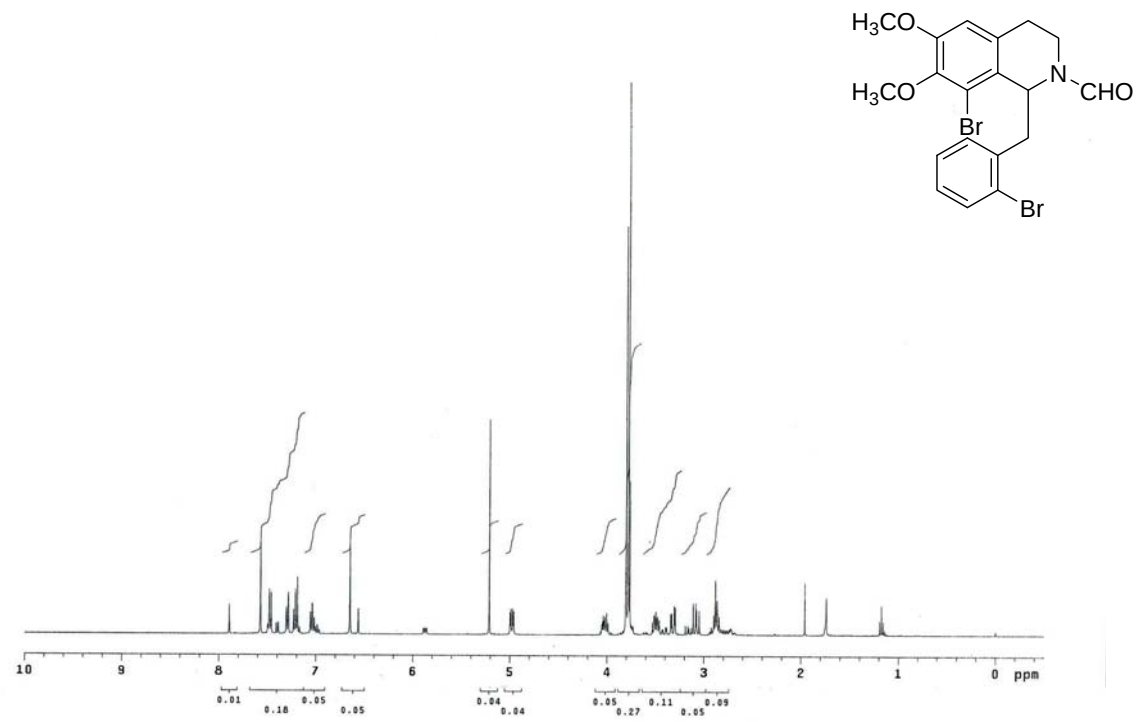
Appendix Figure 16 100 MHz ^{13}C NMR spectrum of *N*-(3-bromo-4,5-dimethoxy phenethyl)-2-(2-bromophenyl)acetamide (180)



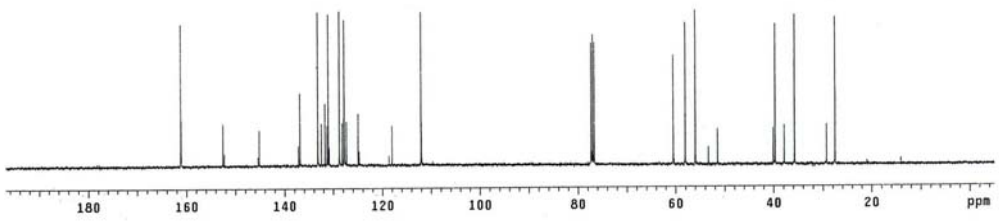
Appendix Figure 17 400 MHz ^{1}H NMR spectrum of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (182)



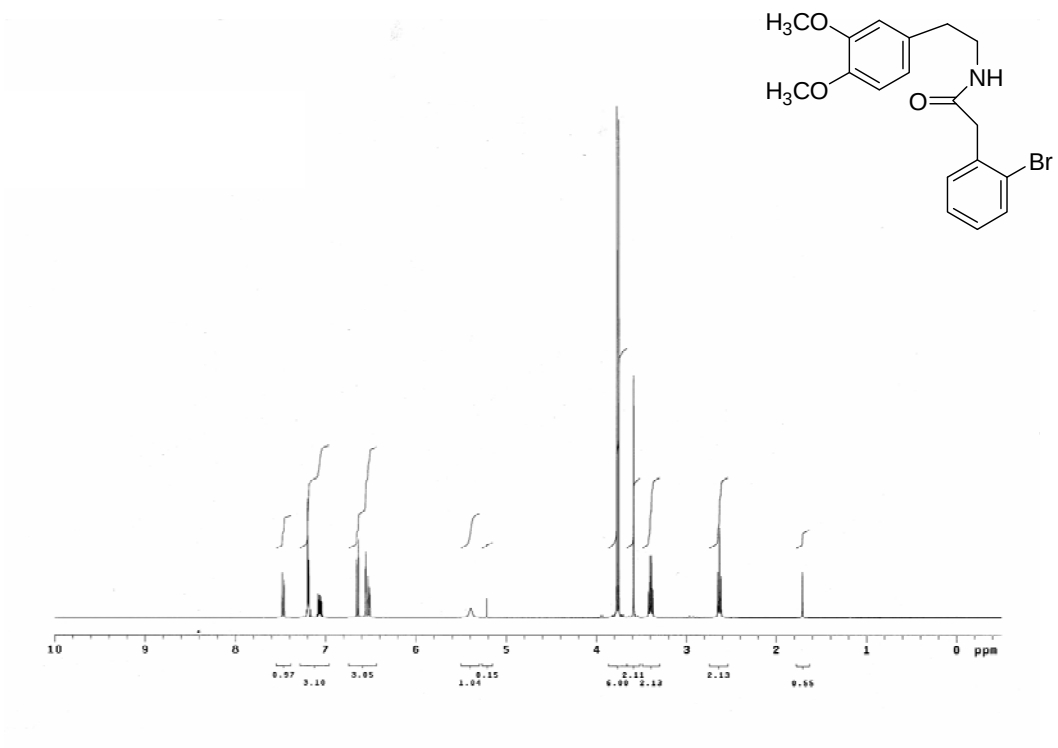
Appendix Figure 18 100 MHz ^{13}C NMR spectrum of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline (182)



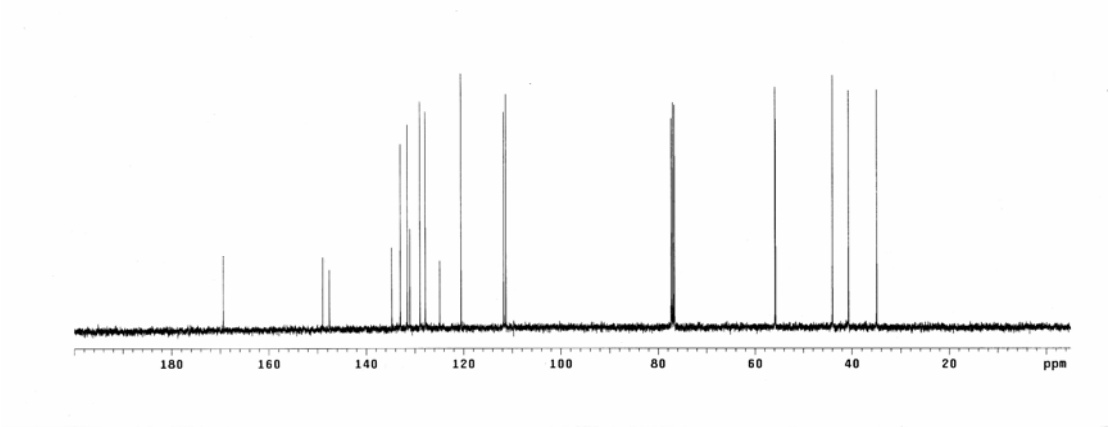
Appendix Figure 19 400 MHz ^{1}H NMR spectrum of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (183)



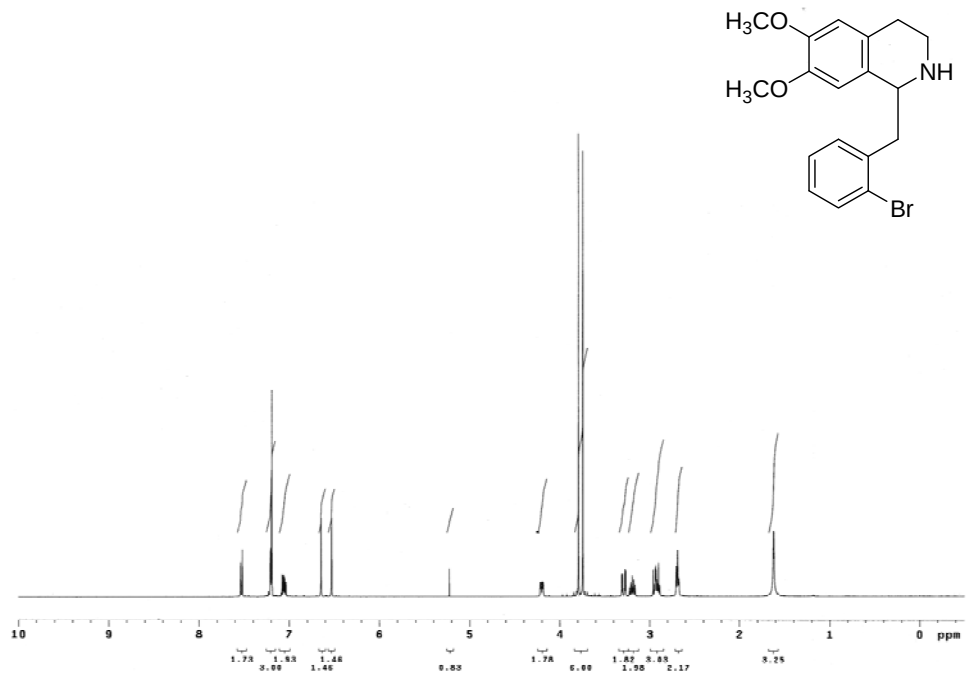
Appendix Figure 20 100 MHz ^{13}C NMR spectrum of 1-(2-bromobenzyl)-8-bromo-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (183)



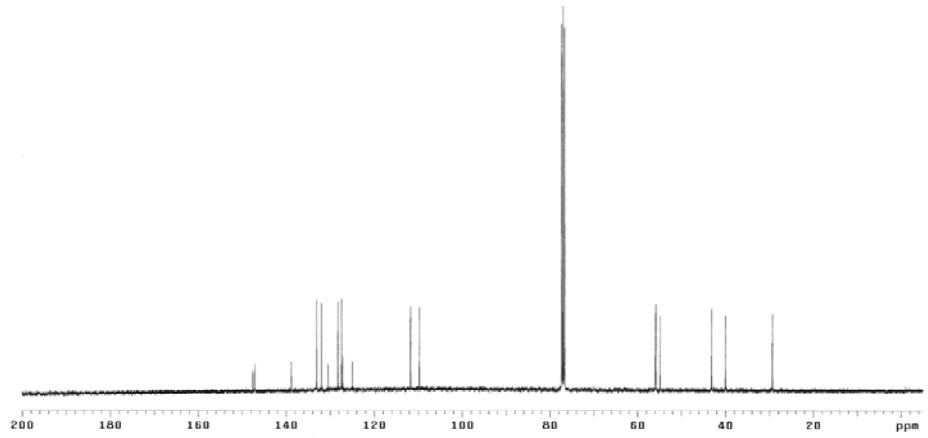
Appendix Figure 21 400 MHz ^{1}H NMR spectrum of *N*-(3,4-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185)



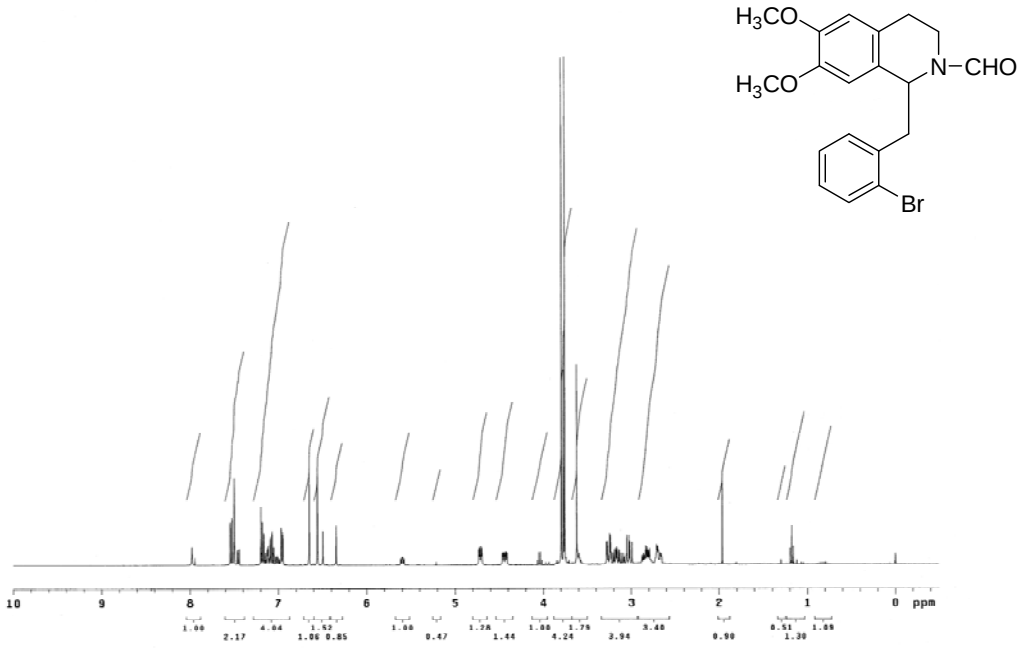
Appendix Figure 22 100 MHz ^{13}C NMR spectrum of *N*-(3,4-dimethoxyphenethyl)-2-(2-bromophenyl)acetamide (185)



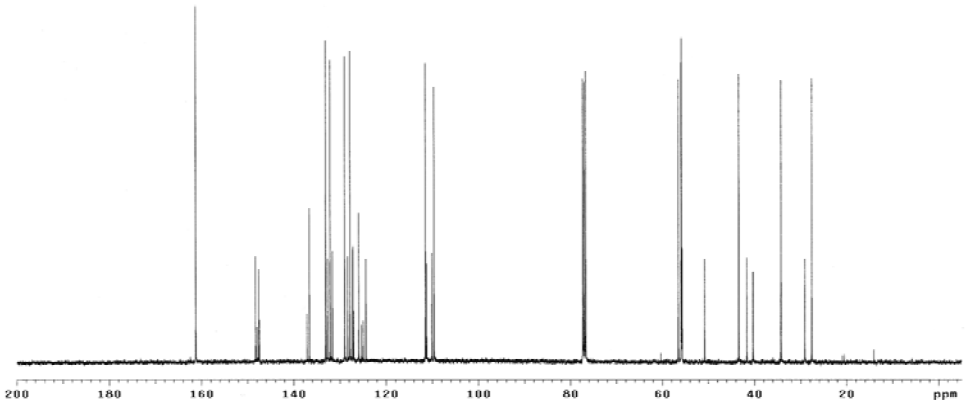
Appendix Figure 23 400 MHz ^{1}H NMR spectrum of 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (187)



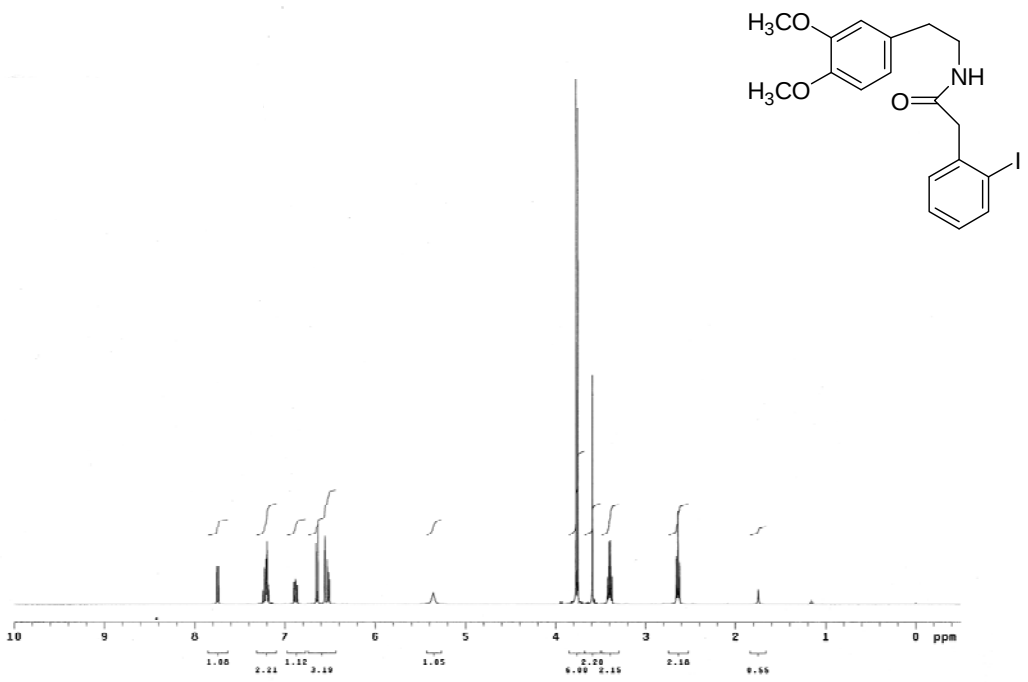
Appendix Figure 24 100 MHz ^{13}C NMR spectrum of 1-(2-bromobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (187)



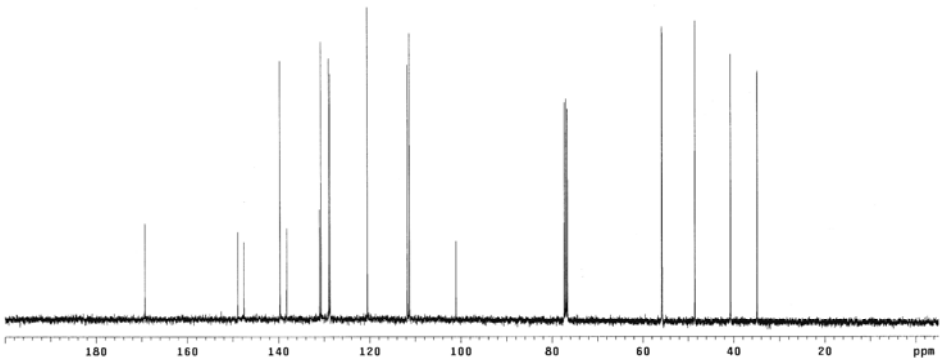
Appendix Figure 25 400 MHz ^{1}H NMR spectrum of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (188)



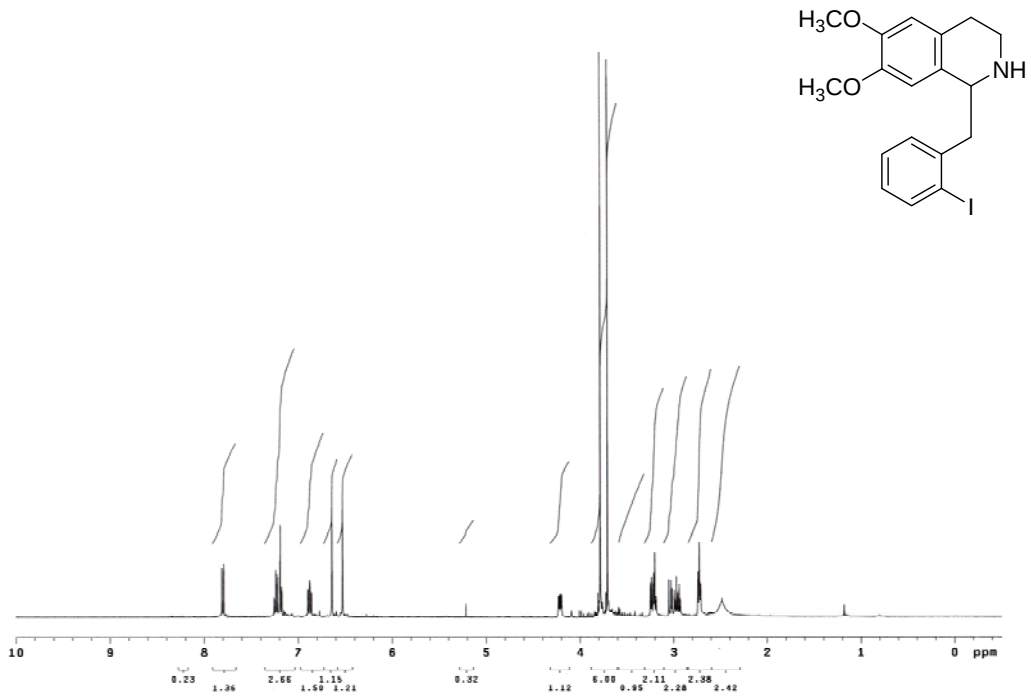
Appendix Figure 26 100 MHz ^{13}C NMR spectrum of 1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (188)



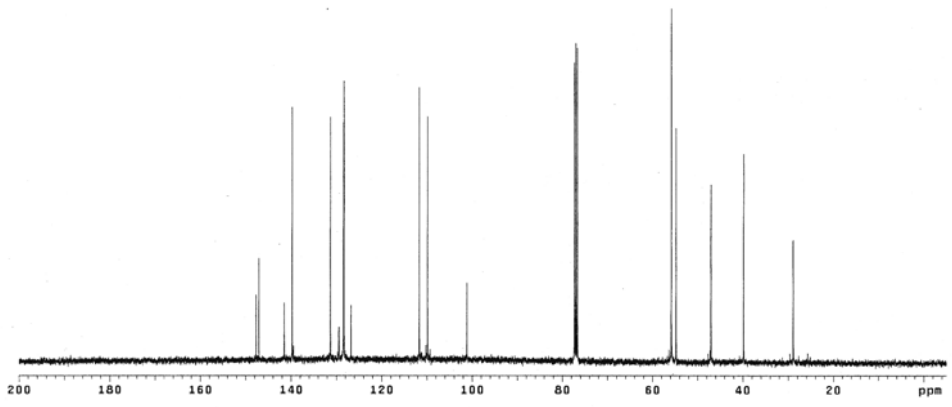
Appendix Figure 27 400 MHz ^{1}H NMR spectrum of *N*-(3,4-dimethoxyphenethyl)-2-(2-iodoophenyl)acetamide (191)



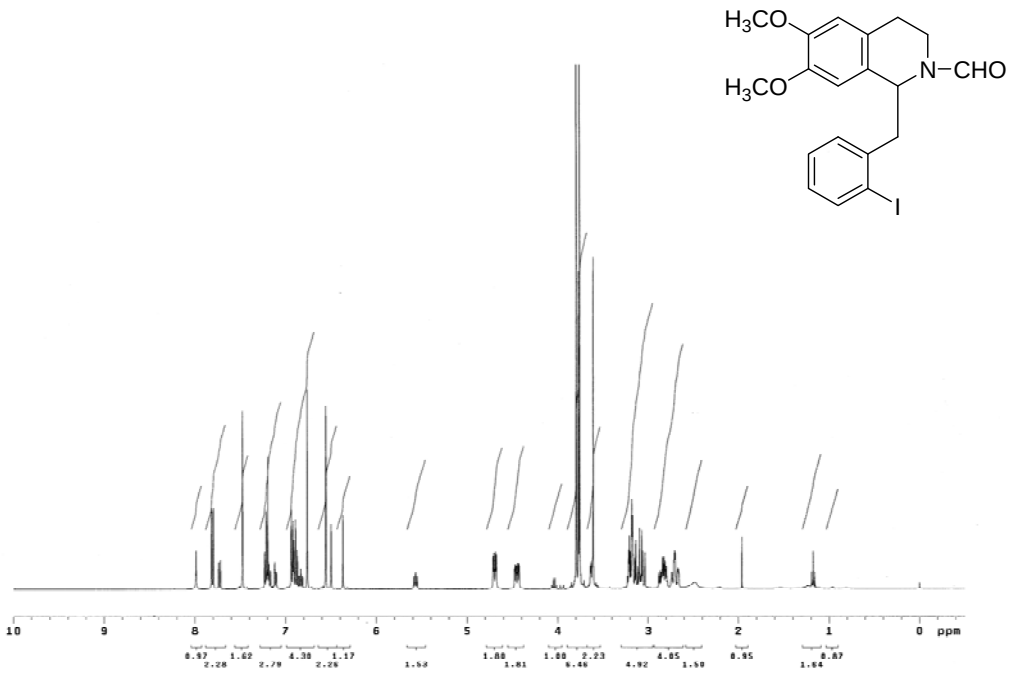
Appendix Figure 28 100 MHz ^{13}C NMR spectrum of *N*-(3,4-dimethoxyphenethyl)-2-(2-iodoophenyl)acetamide (191)



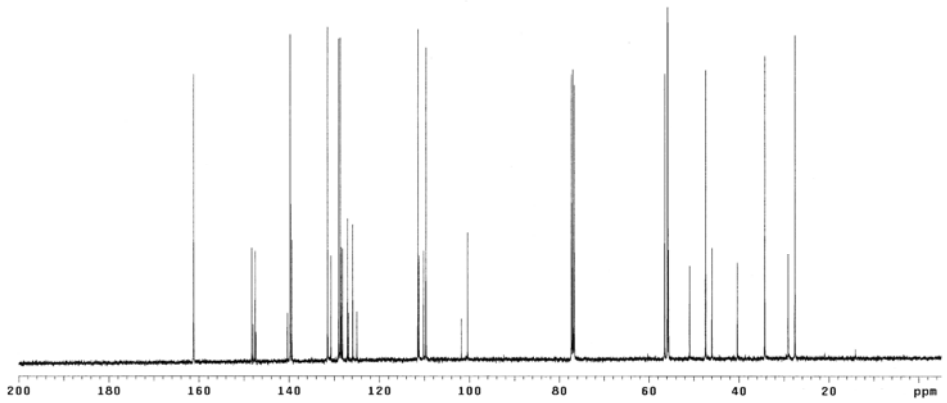
Appendix Figure 29 400 MHz ^{1}H NMR spectrum of 1-(2-iodobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (193)



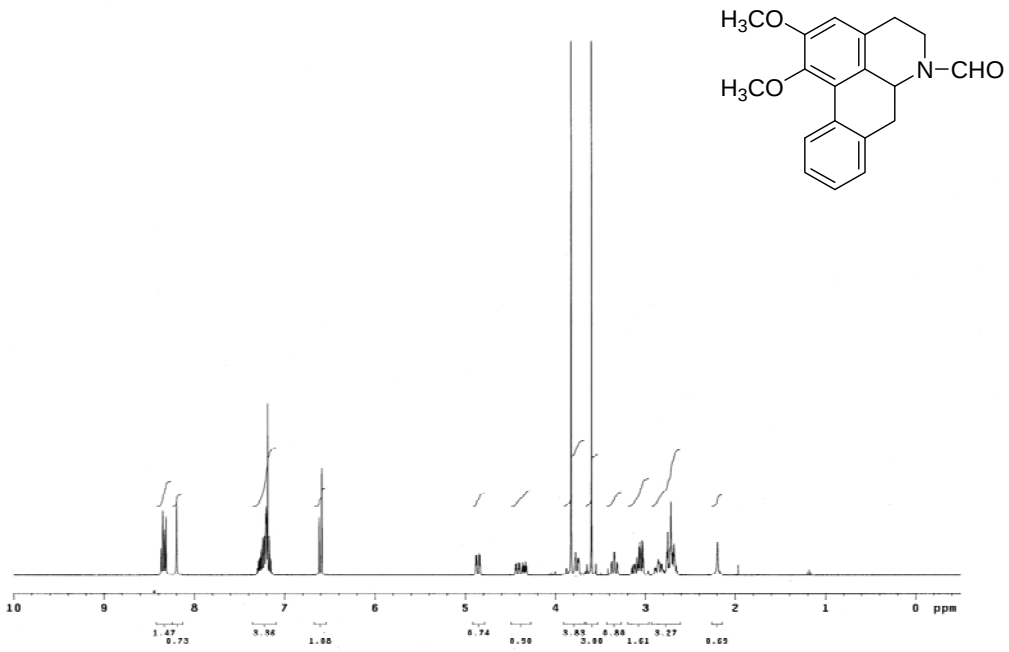
Appendix Figure 30 100 MHz ^{13}C NMR spectrum of 1-(2-iodobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (193)



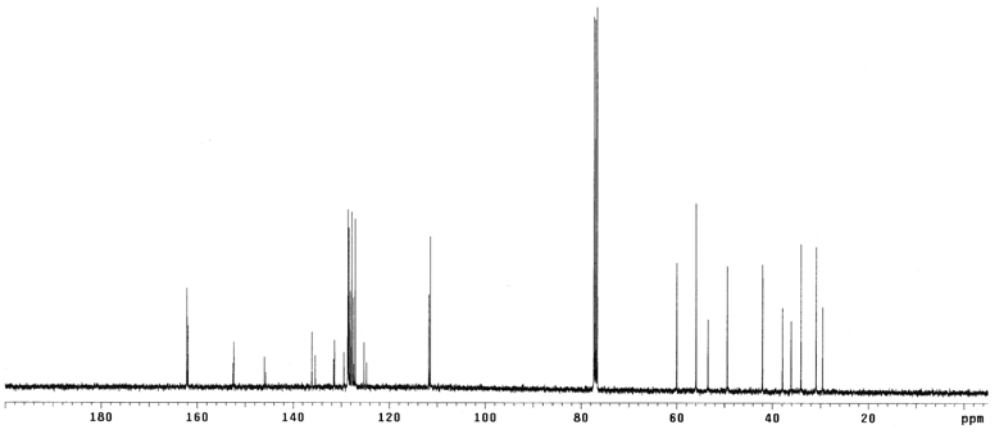
Appendix Figure 31 400 MHz ^{1}H NMR spectrum of 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (194)



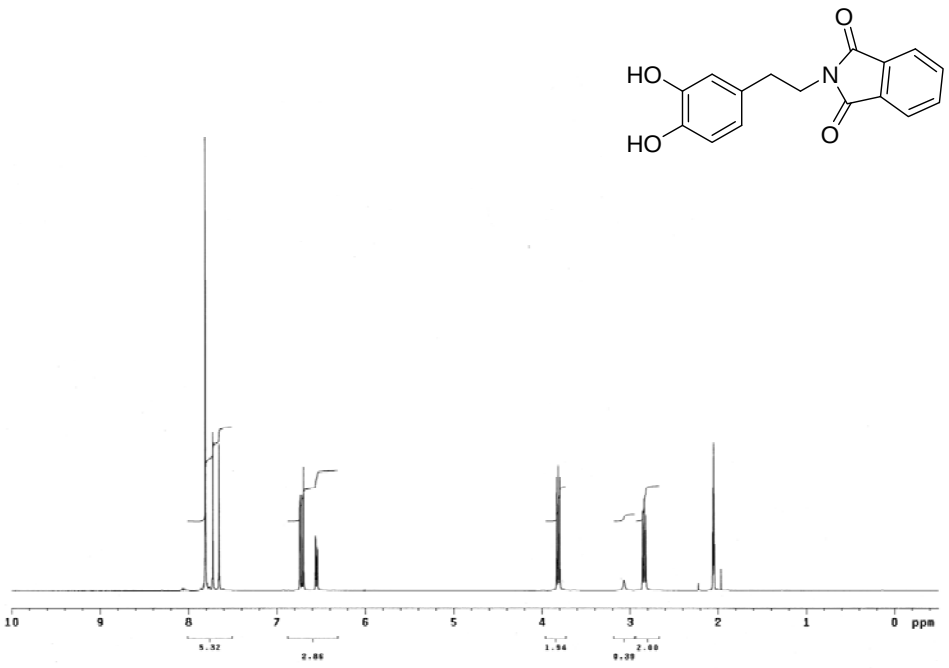
Appendix Figure 32 100 MHz ^{13}C NMR spectrum of 1-(2-iodobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2-carbaldehyde (194)



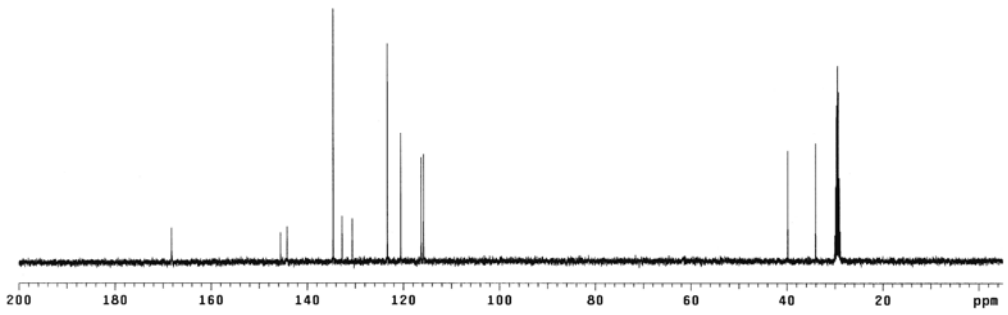
Appendix Figure 33 400 MHz ^{1}H NMR spectrum of (±)-*N*-formylnornuciferine (13a)



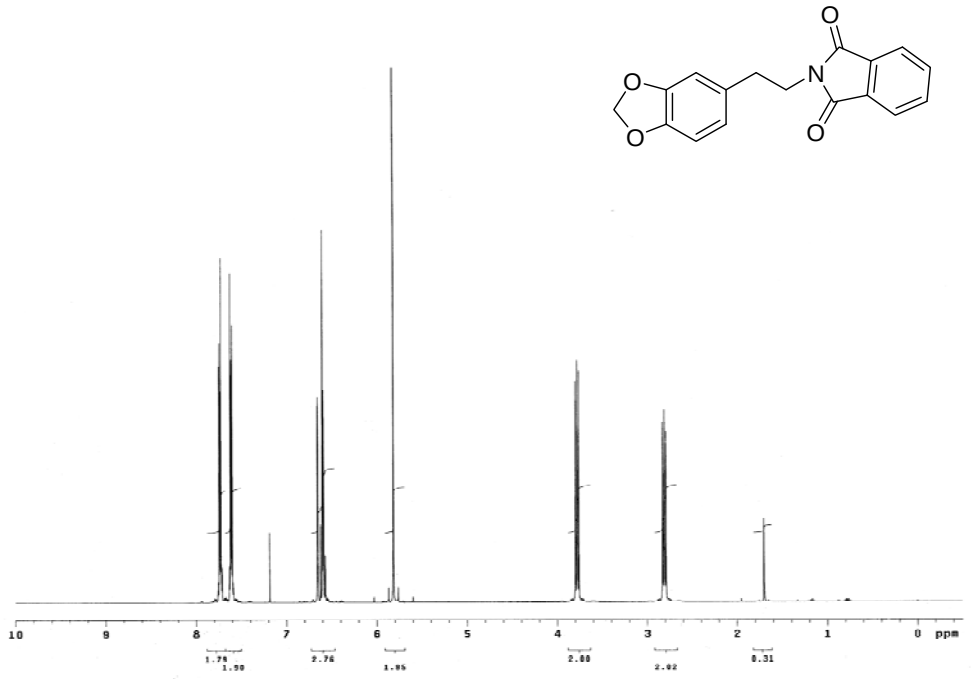
Appendix Figure 34 100 MHz ^{13}C NMR spectrum of (±)-*N*-formylnornuciferine (13a)



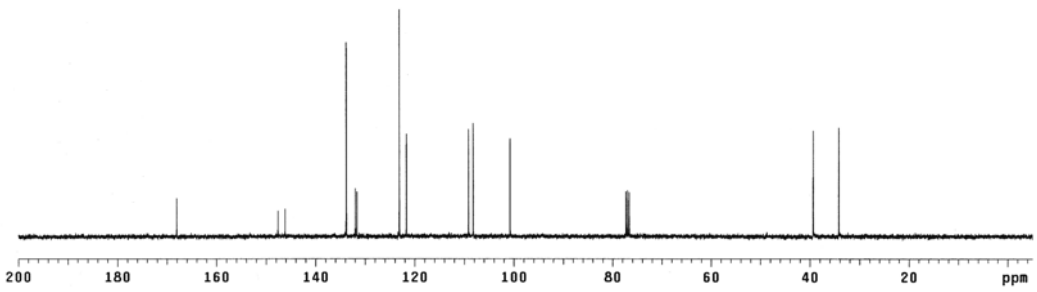
Appendix Figure 35 400 MHz ^{1}H NMR spectrum of 2-(3,4-dihydroxyphenethyl) isoindoline-1,3-dione (197)



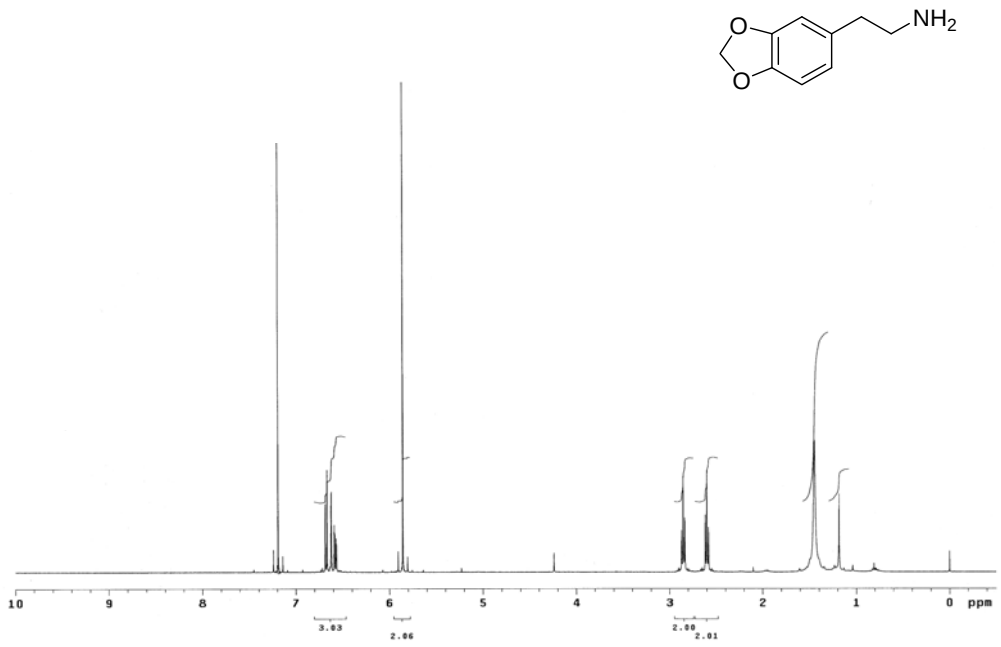
Appendix Figure 36 100 MHz ^{13}C NMR spectrum of 2-(3,4-dihydroxyphenethyl) isoindoline-1,3-dione (197)



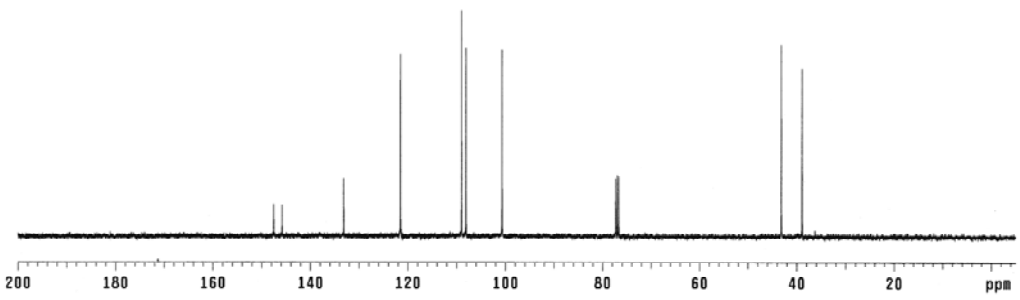
Appendix Figure 37 400 MHz ^{1}H NMR spectrum of 2-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)isoindoline-1,3-dione (198)



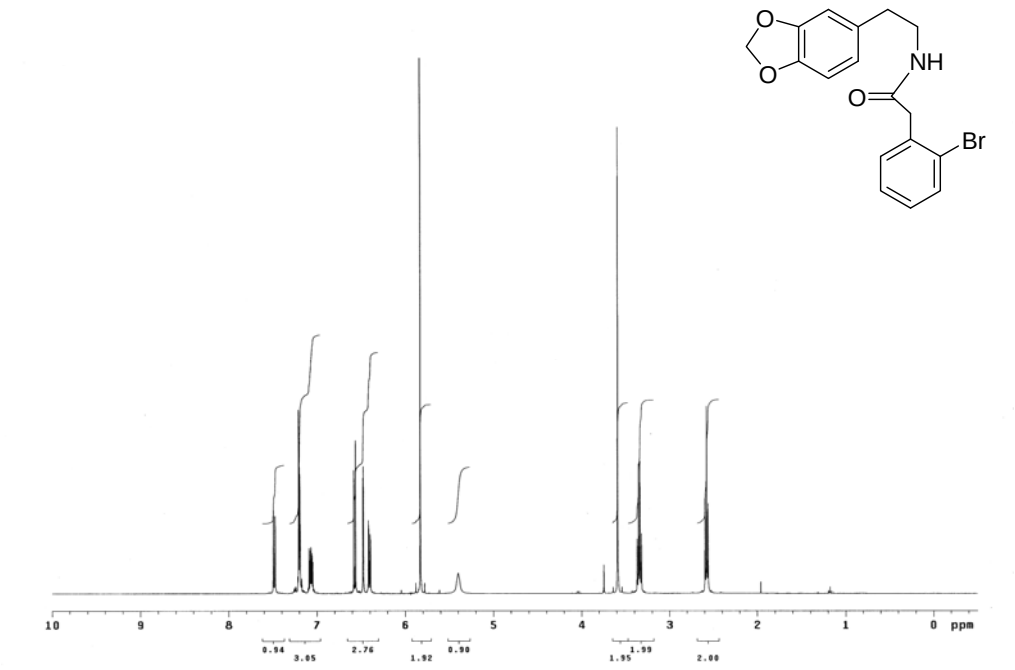
Appendix Figure 38 100 MHz ^{13}C NMR spectrum of 2-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)isoindoline-1,3-dione (198)



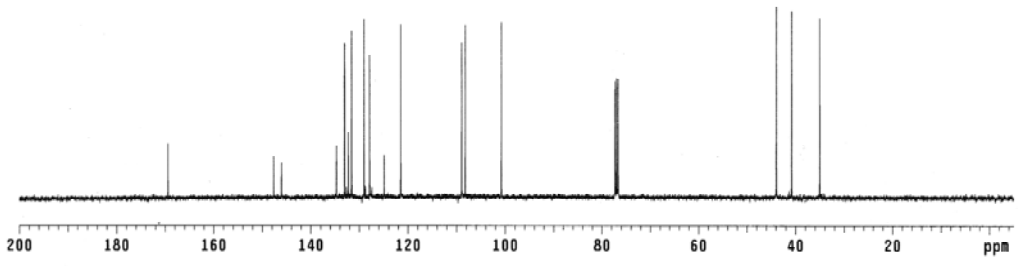
Appendix Figure 39 400 MHz ^{1}H NMR spectrum of 2-(benzo[d][1,3]dioxol-6-yl)ethanamine (199)



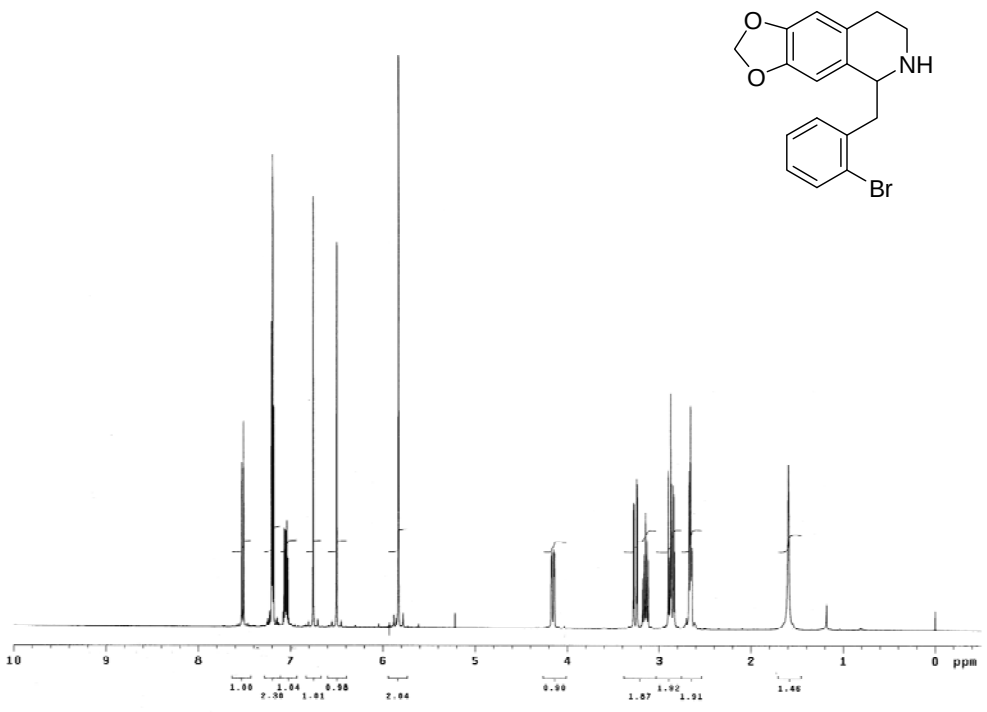
Appendix Figure 40 100 MHz ^{13}C NMR spectrum of 2-(benzo[d][1,3]dioxol-6-yl)ethanamine (199)



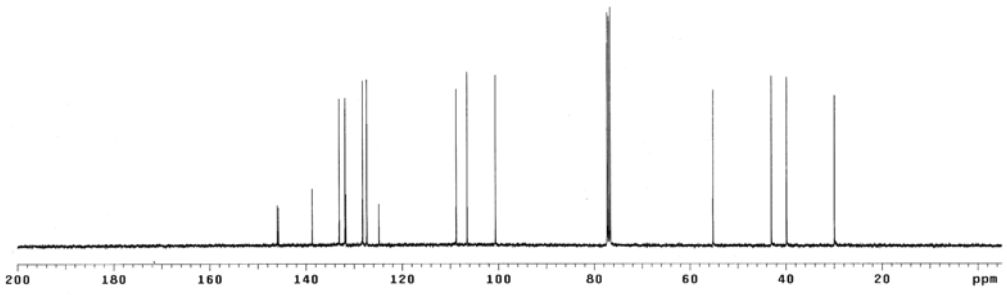
Appendix Figure 41 400 MHz ^{1}H NMR spectrum of *N*-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromophenyl)acetamide (200)



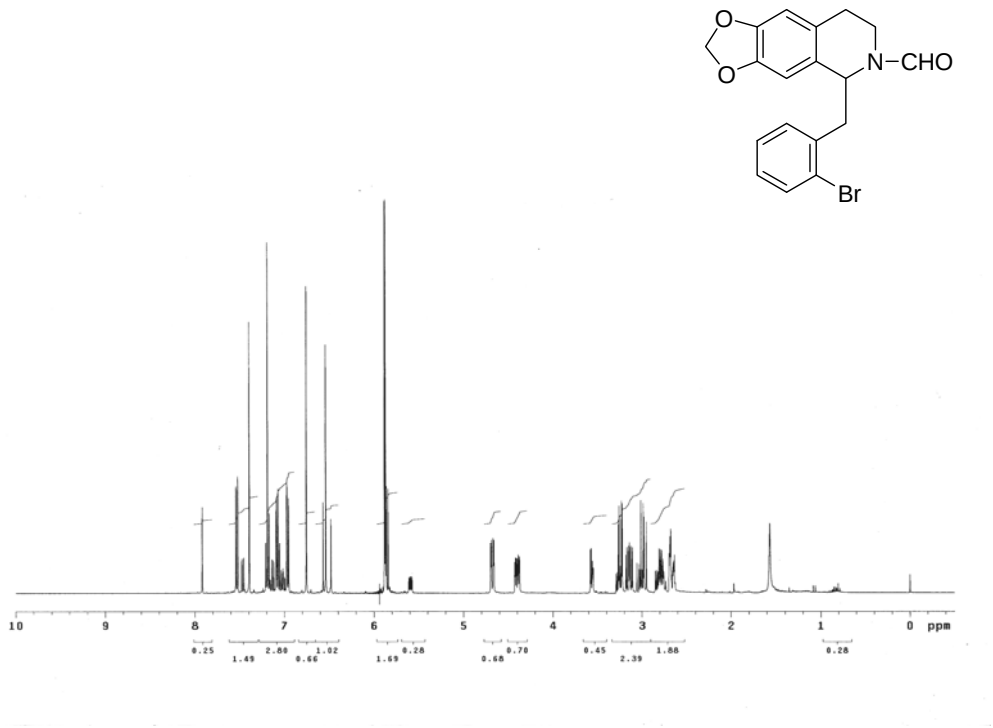
Appendix Figure 42 100 MHz ^{13}C NMR spectrum of *N*-(2-(benzo[d][1,3]dioxol-6-yl)ethyl)-2-(2-bromophenyl)acetamide (200)



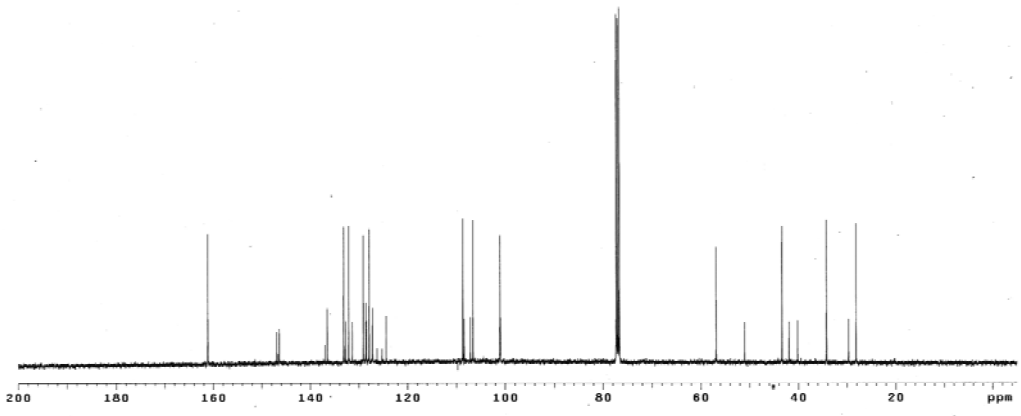
Appendix Figure 43 400 MHz ^{1}H NMR spectrum of 5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (202)



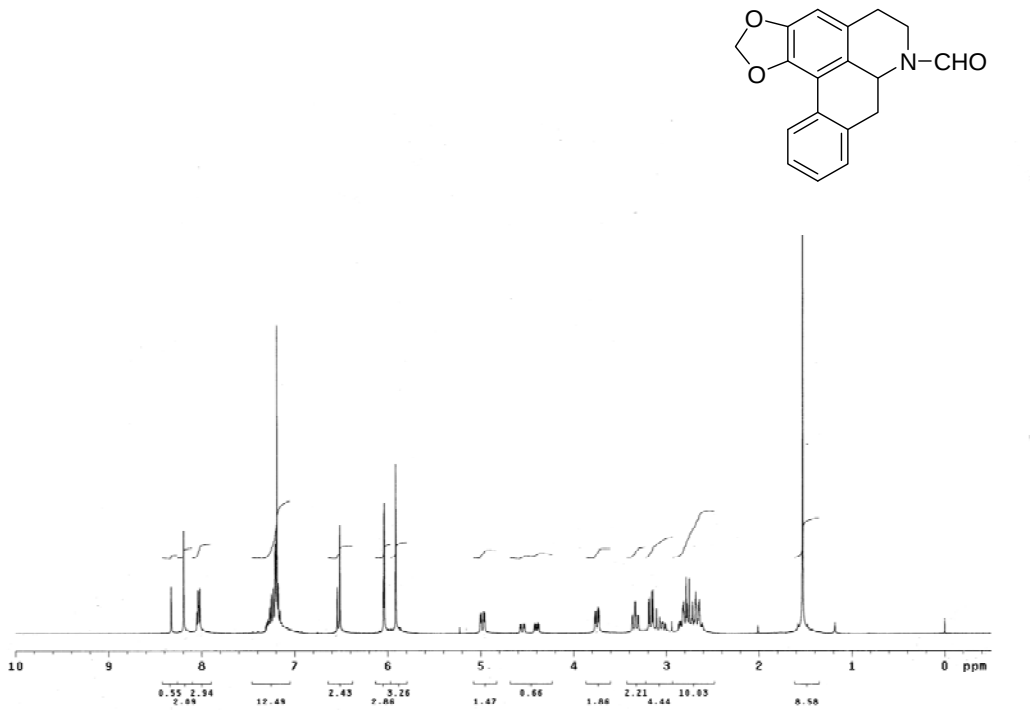
Appendix Figure 44 100 MHz ^{13}C NMR spectrum of 5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (202)



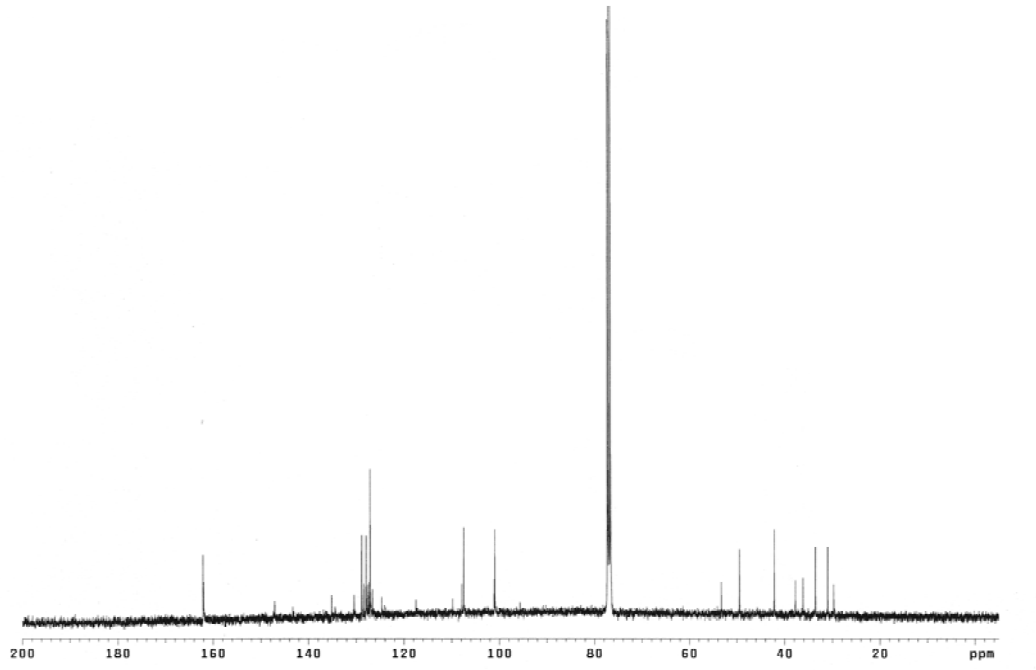
Appendix Figure 45 400 MHz ^{1}H NMR spectrum of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6-carbaldehyde (203)



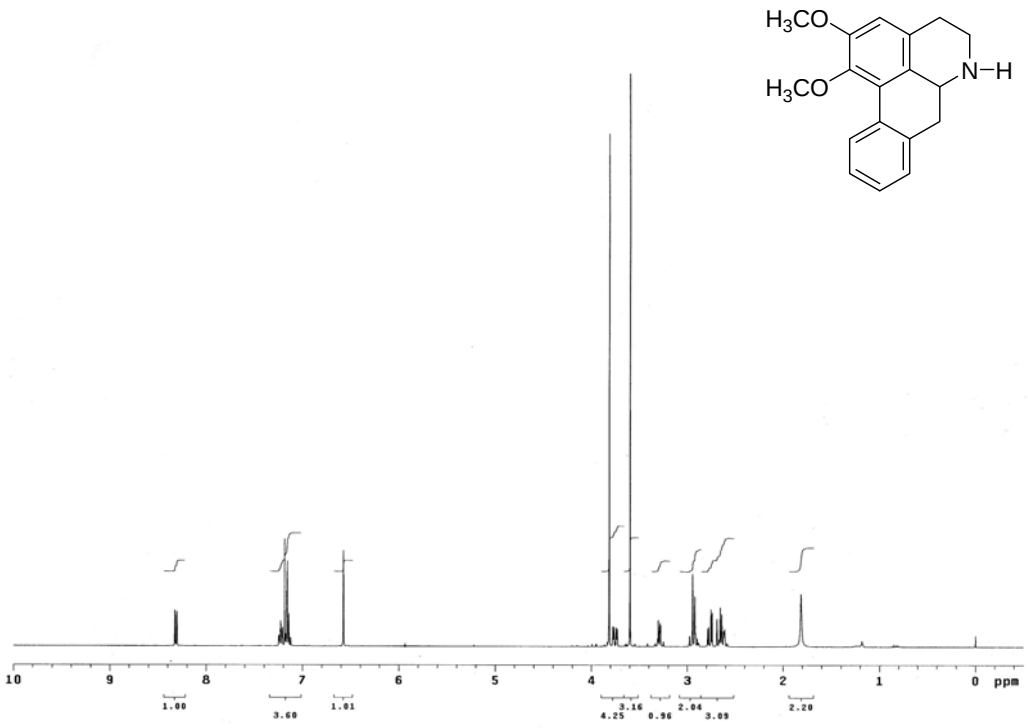
Appendix Figure 46 100 MHz ^{13}C NMR spectrum of 5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6-carbaldehyde (203)



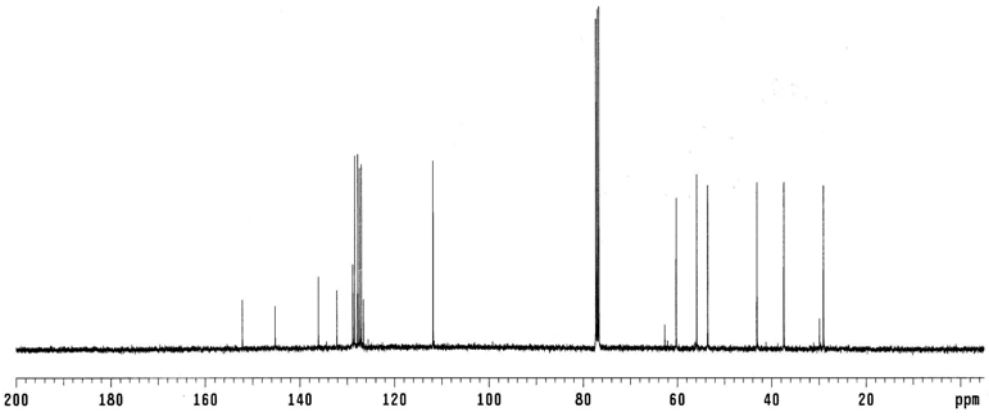
Appendix Figure 47 400 MHz ^{1}H NMR spectrum of (±)-*N*-formylannonaine (14a)



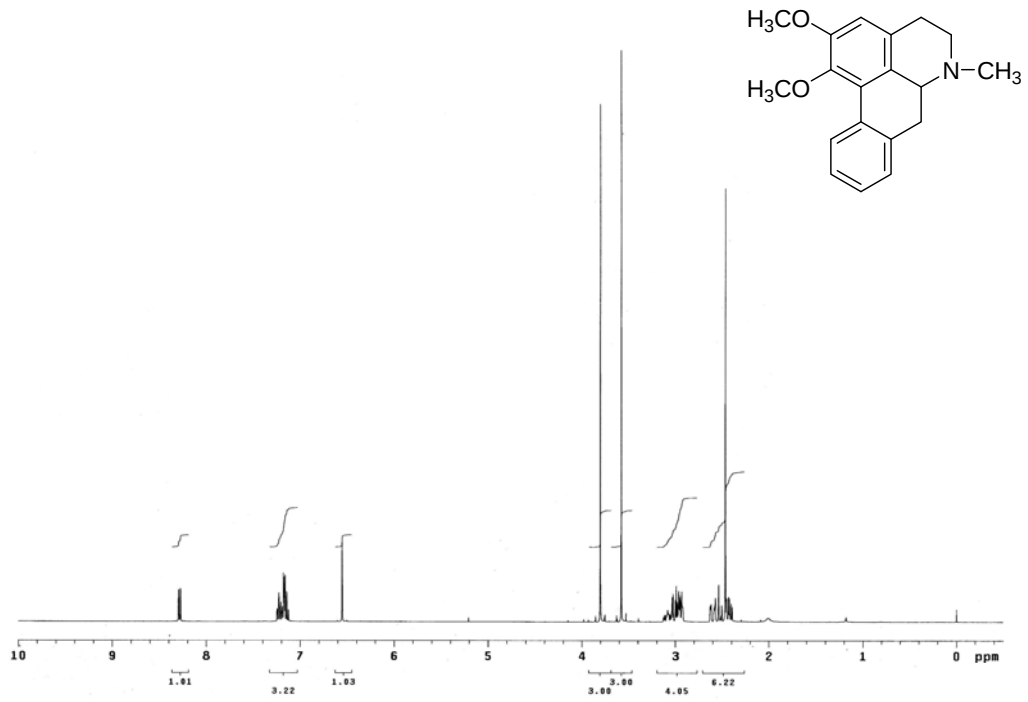
Appendix Figure 48 100 MHz ^{13}C NMR spectrum of (±)-*N*-formylannonaine (14a)



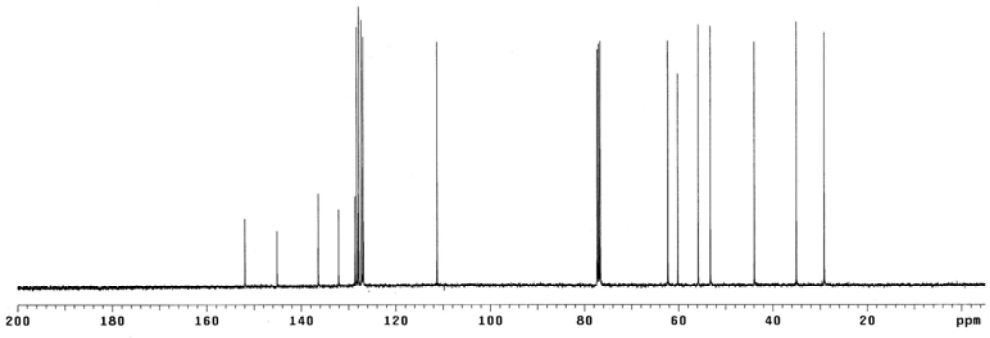
Appendix Figure 49 400 MHz ^{1}H NMR spectrum of nuciferine (184)



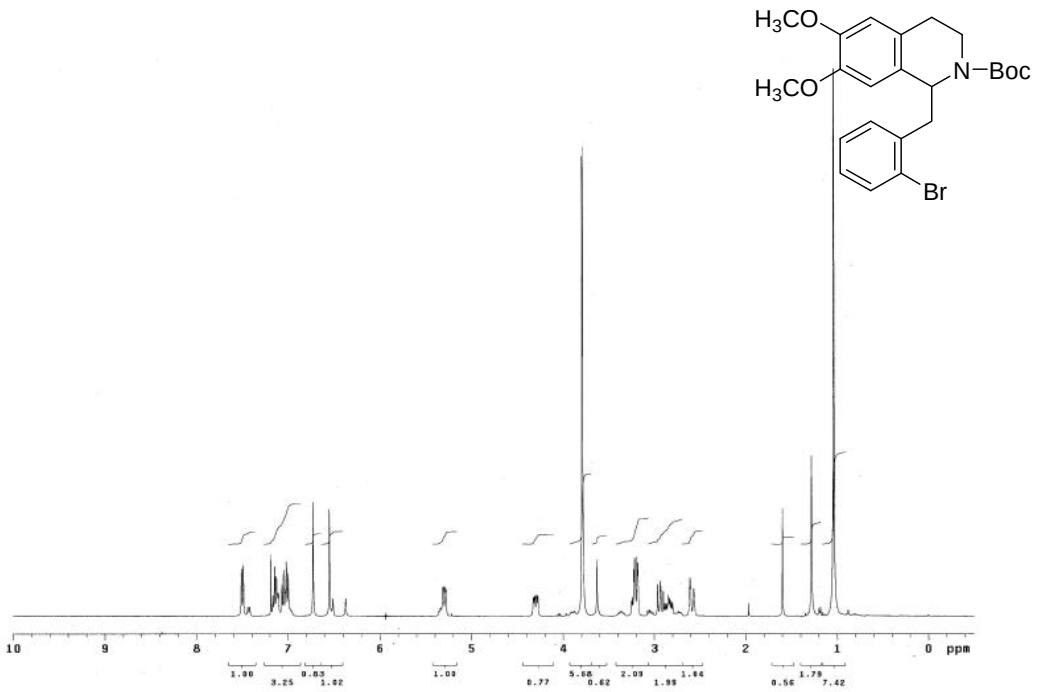
Appendix Figure 50 100 MHz ^{13}C NMR spectrum of nuciferine (184)



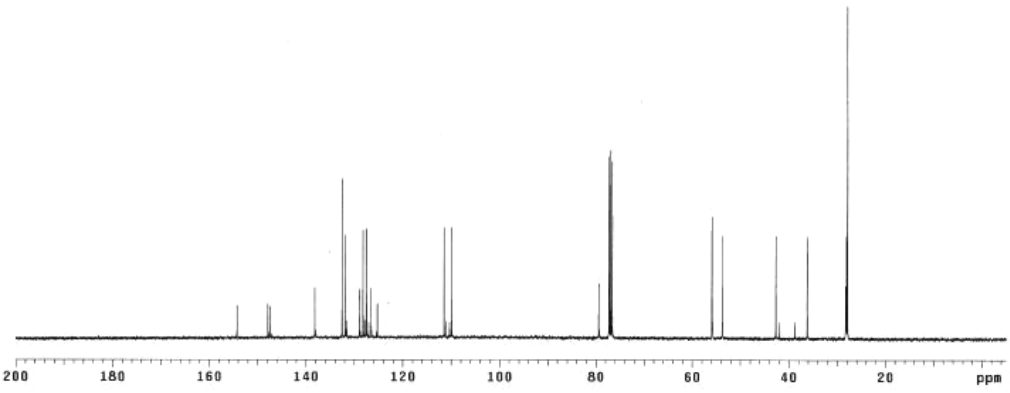
Appendix Figure 51 400 MHz ^{1}H NMR spectrum of nornuciferine (204)



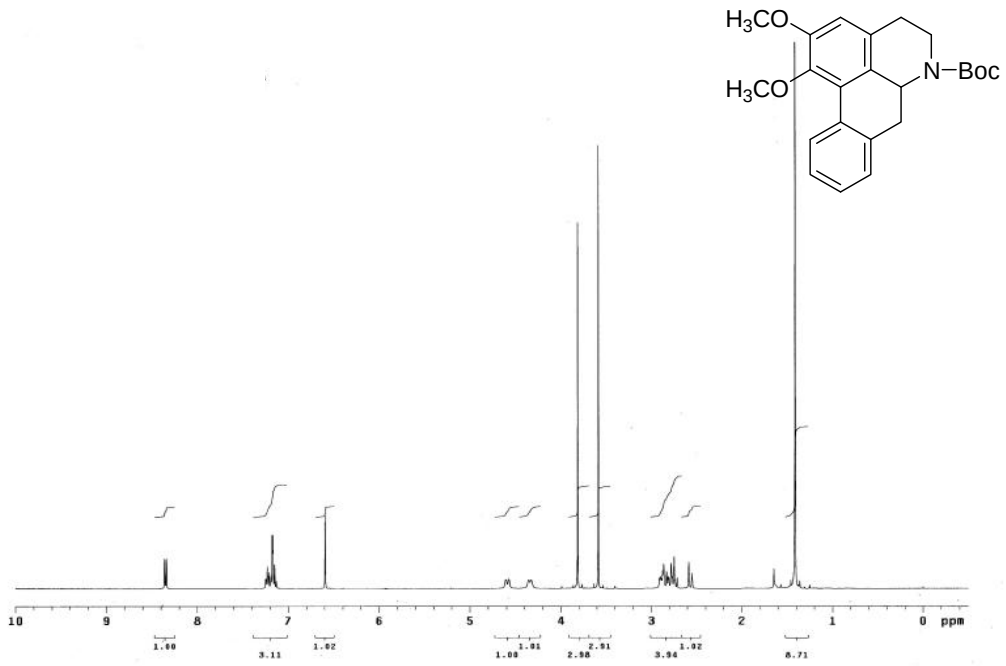
Appendix Figure 52 100 MHz ^{13}C NMR spectrum of nornuciferine (204)



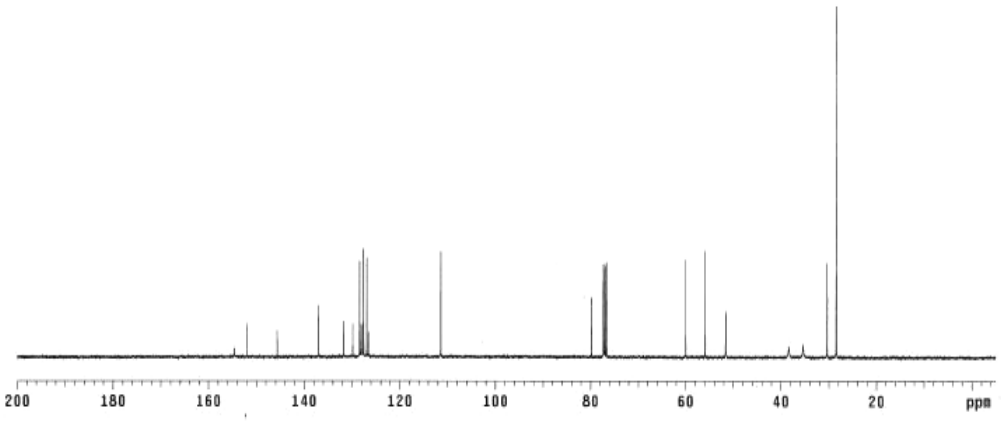
Appendix Figure 53 400 MHz ^{1}H NMR spectrum of 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2-carboxylic acid *tert*-butyl ester (205)



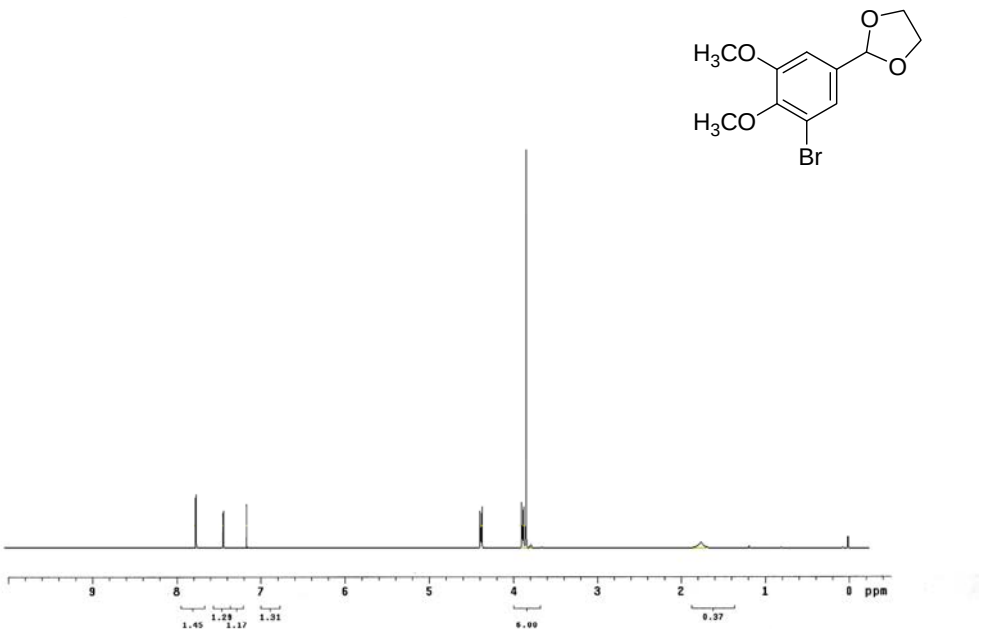
Appendix Figure 54 100 MHz ^{13}C NMR spectrum of 1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2-carboxylic acid *tert*-butyl ester (205)



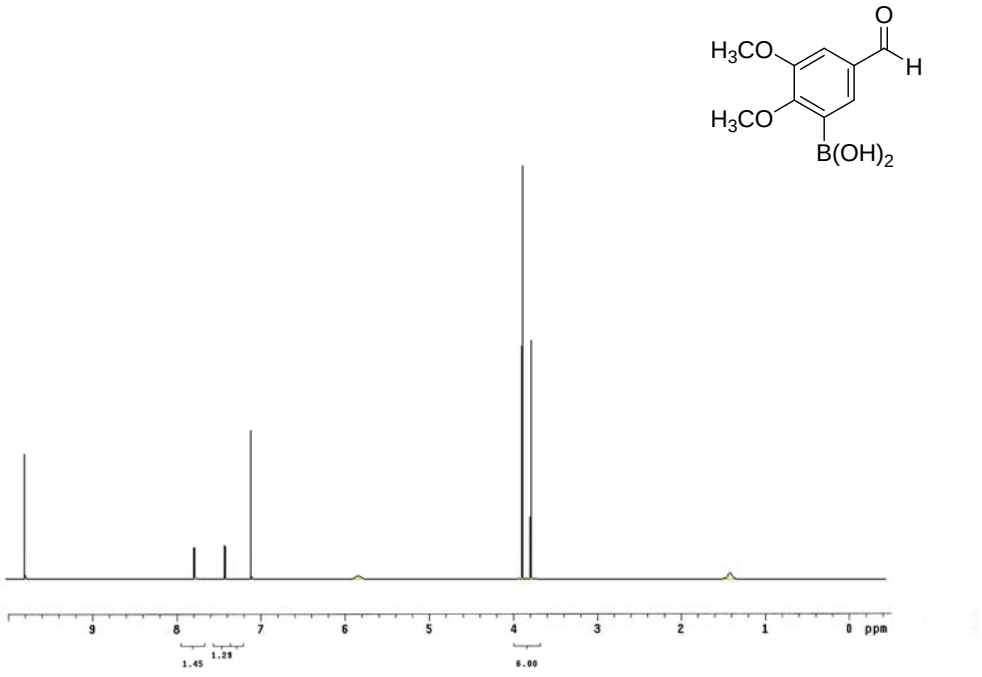
Appendix Figure 55 400 MHz ^{1}H NMR spectrum of 1-(1,2-di1,2-dimethoxy)-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid *tert*-butylester (206)



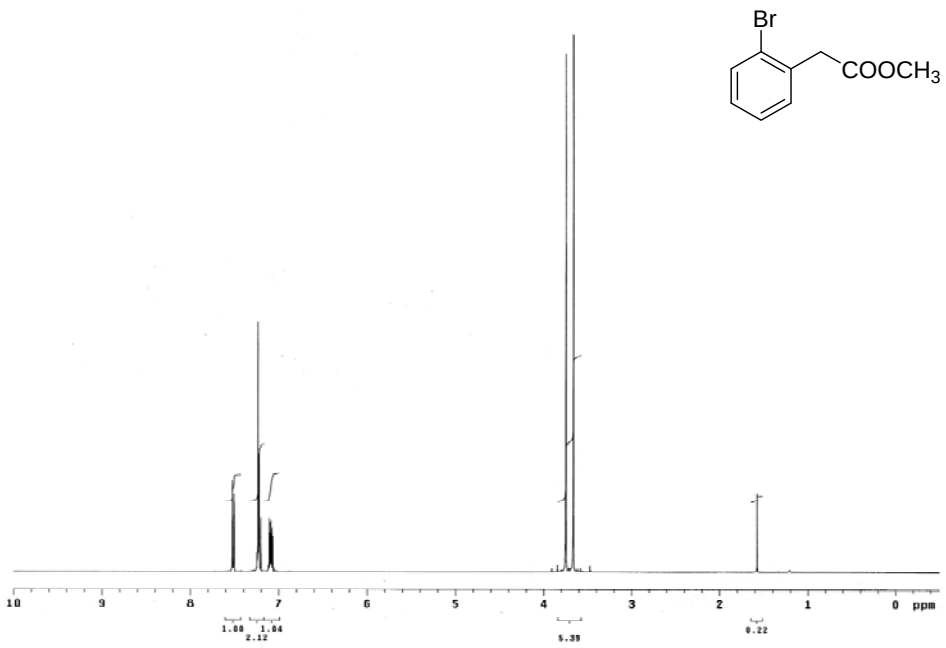
Appendix Figure 56 100 MHz ^{13}C NMR spectrum of 1-(1,2-di1,2-dimethoxy)-4,5,6a,7-tetrahydro-dibenzoquinoline-6-carboxylic acid *tert*-butyl ester (206)



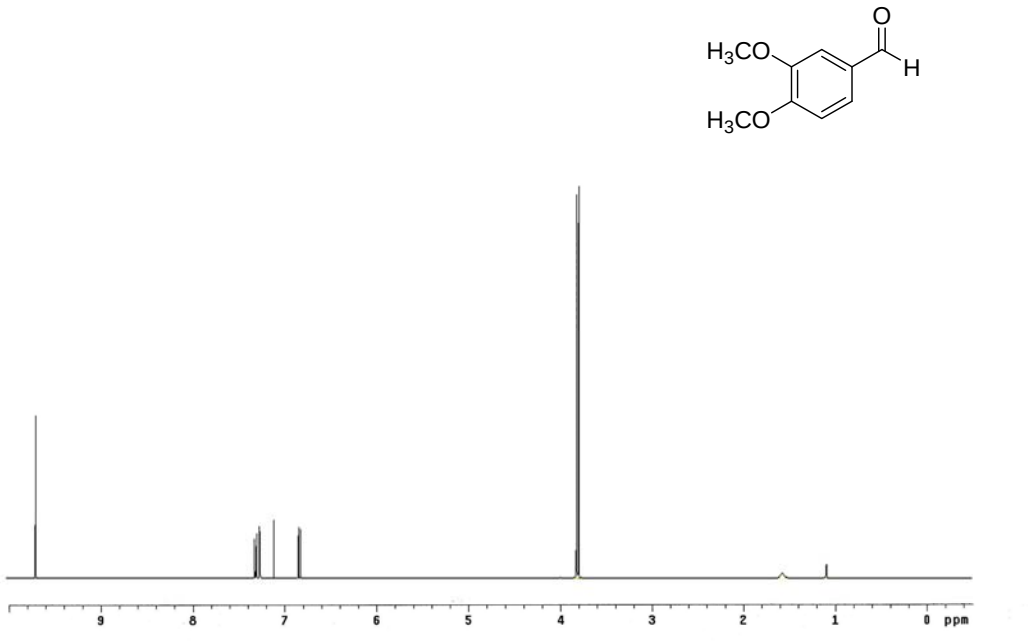
Appendix Figure 57 400 MHz ^{1}H NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenyl)-1,3-dioxolane (208)



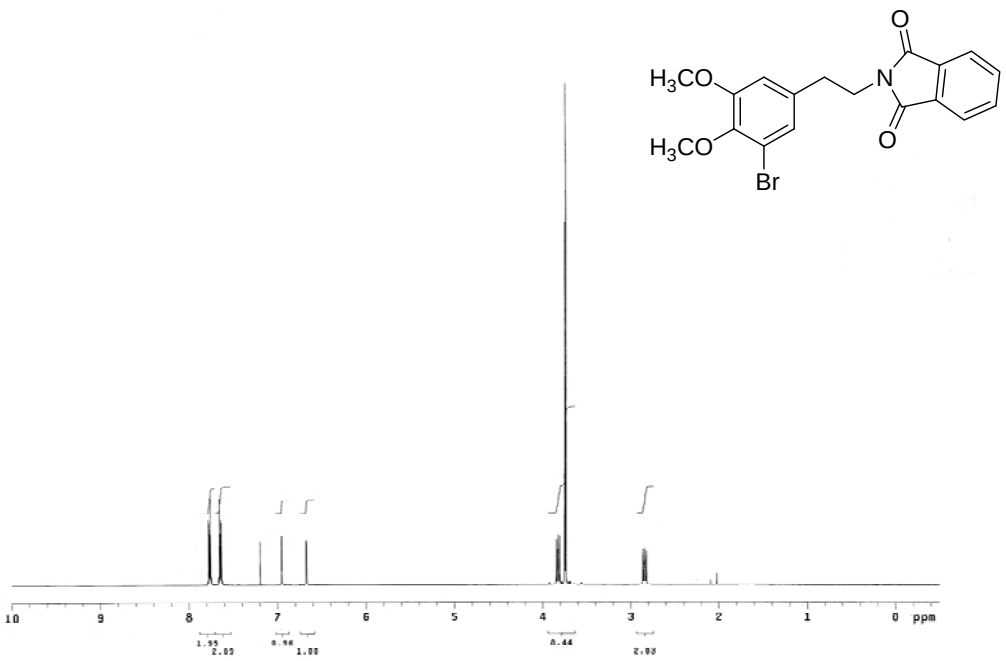
Appendix Figure 58 400 MHz ^{1}H NMR spectrum of 5-formyl-2,3-dimethoxy phenylboronic acid (209)



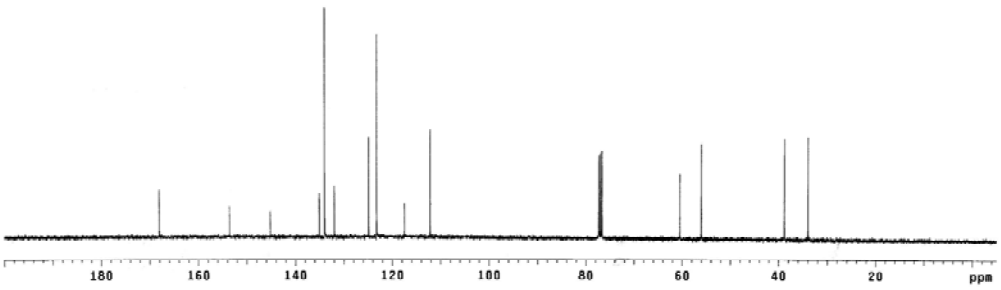
Appendix Figure 59 400 MHz ^{1}H NMR spectrum of methyl 2-(2-bromophenyl) acetate (210)



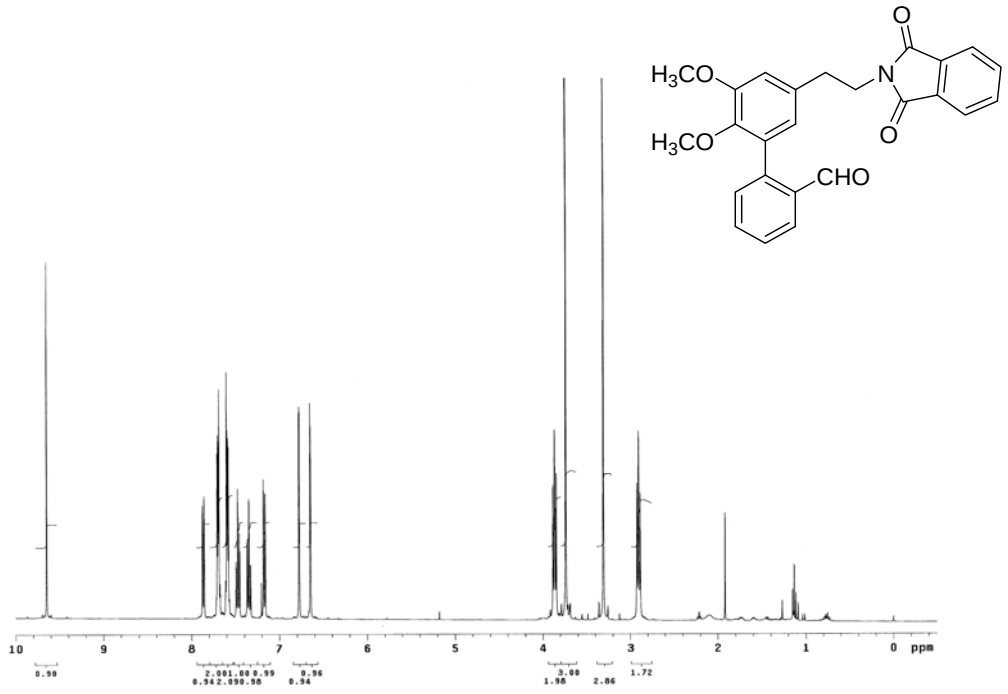
Appendix Figure 60 400 MHz ^{1}H NMR spectrum of 3,4-dimethoxybenzaldehyde (213)



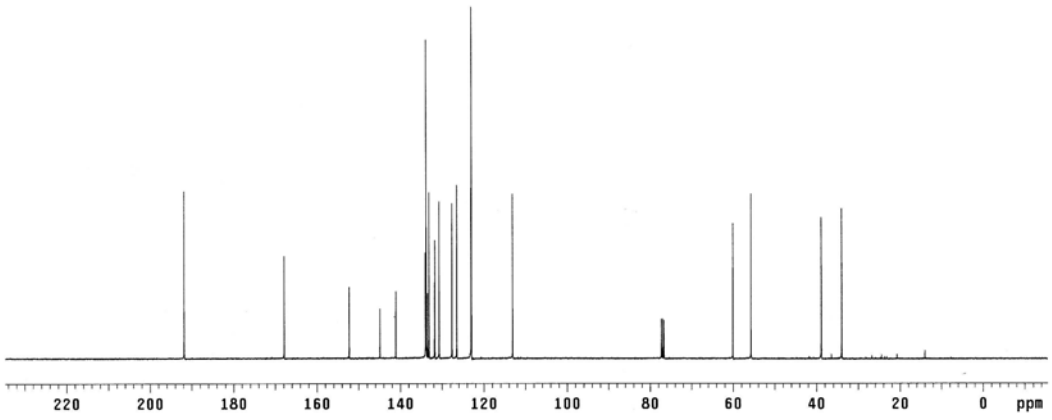
Appendix Figure 61 400 MHz ^{1}H NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenethyl)isoindoline-1,3-dione (214)



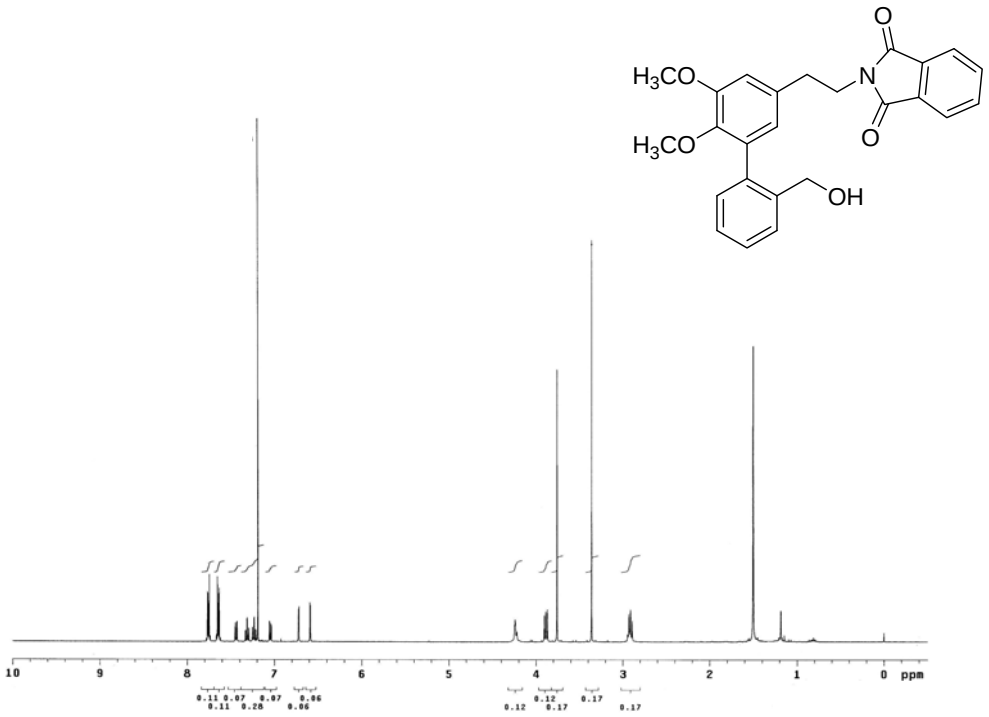
Appendix Figure 62 100 MHz ^{13}C NMR spectrum of 2-(3-bromo-4,5-dimethoxy phenethyl)isoindoline-1,3-dione (214)



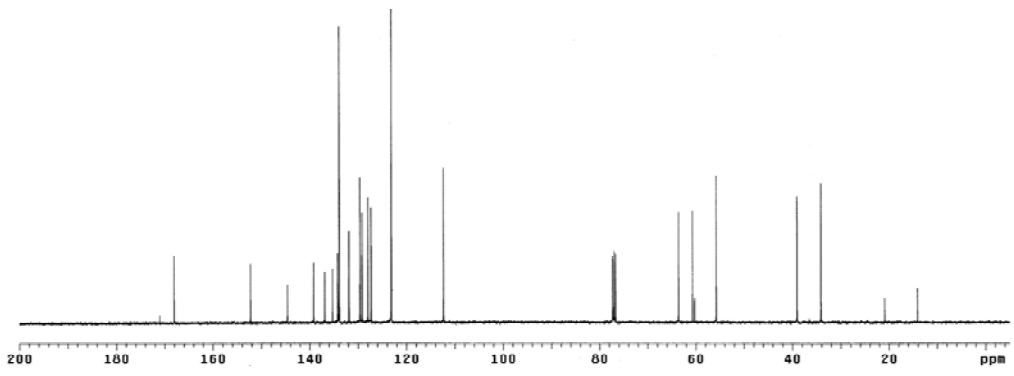
Appendix Figure 63 400 MHz ^{1}H NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1′-biphenyl-2′-carboxaldehyde (216)



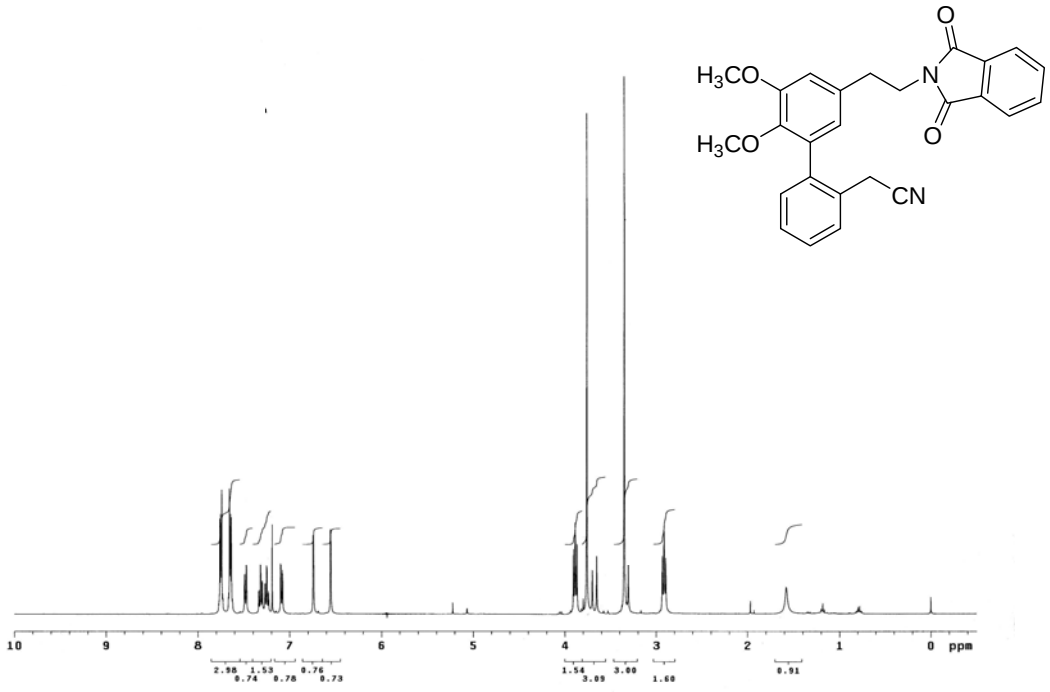
Appendix Figure 64 100 MHz ^{13}C NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1′-biphenyl-2′-carboxaldehyde (216)



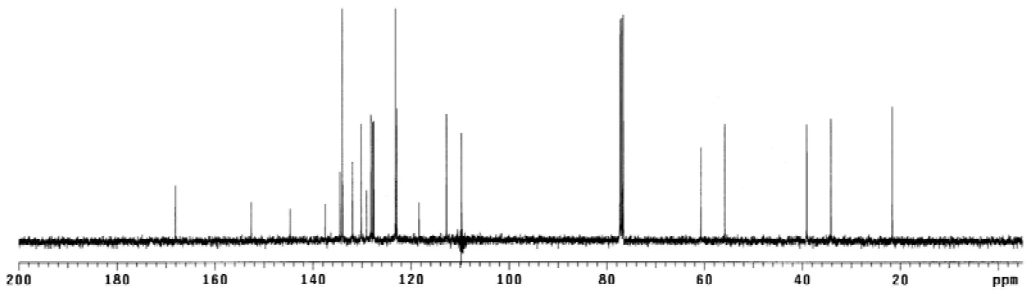
Appendix Figure 65 400 MHz ^{1}H NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1′-biphenyl-2′-benzyl alcohol (217)



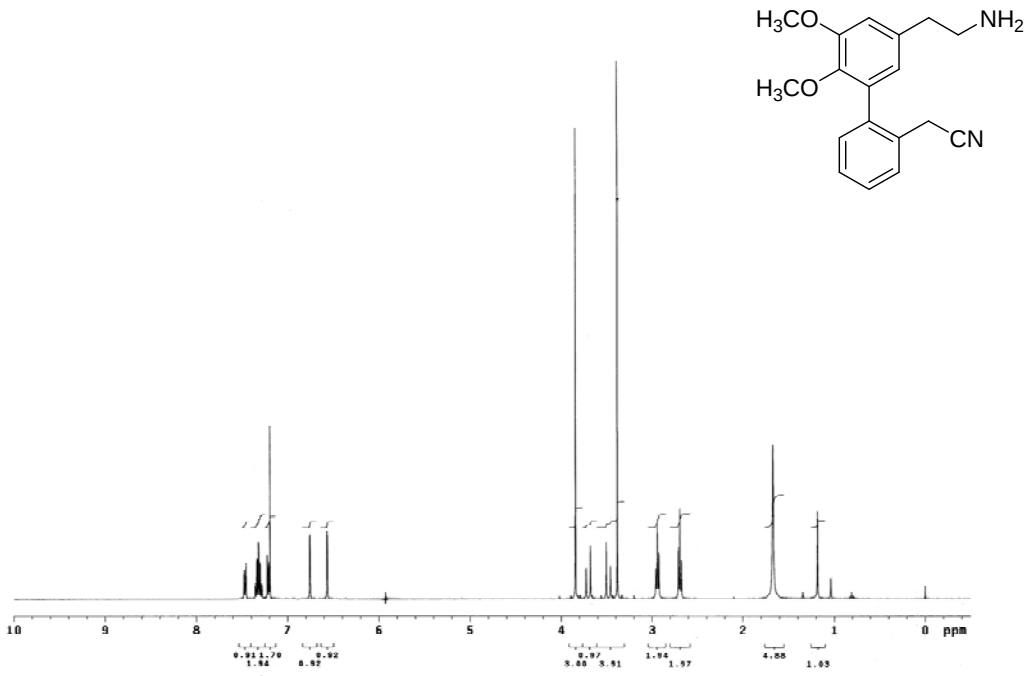
Appendix Figure 66 100 MHz ^{13}C NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1′-biphenyl-2′-benzyl alcohol (217)



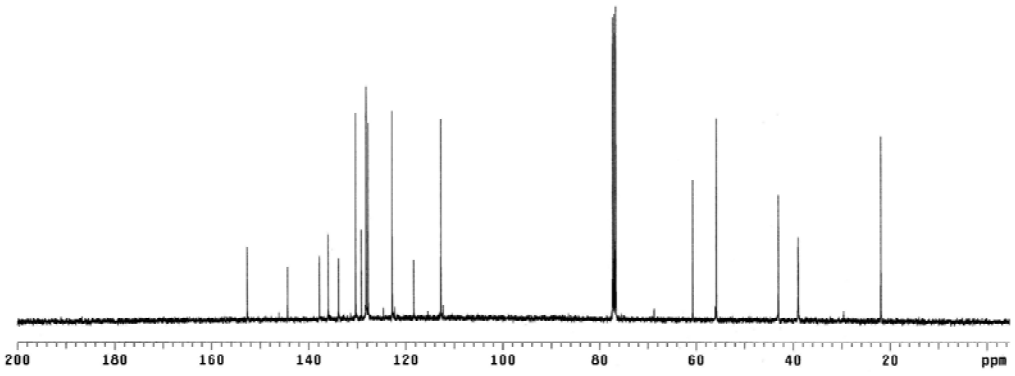
Appendix Figure 67 400 MHz ^{1}H NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1'-biphenyl-2'-phenylacetonitrile (219)



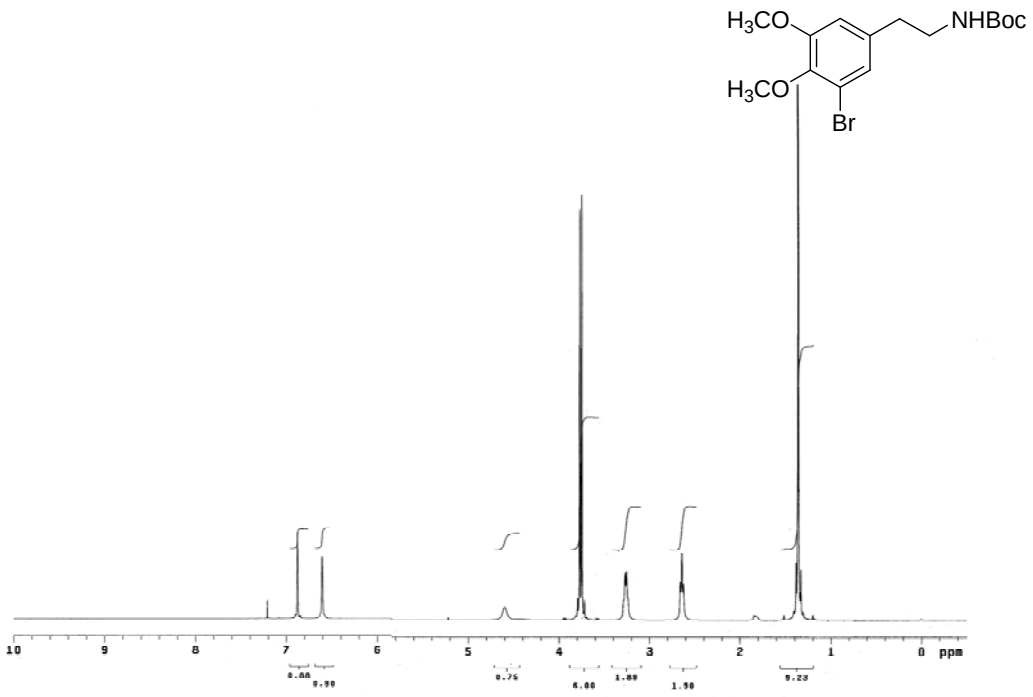
Appendix Figure 68 100 MHz ^{13}C NMR spectrum of 2,3-dimethoxy-5-((2-phenyl ethyl)isoindole-1,3-dione)-1,1′-biphenyl-2′-phenylacetonitrile (219)



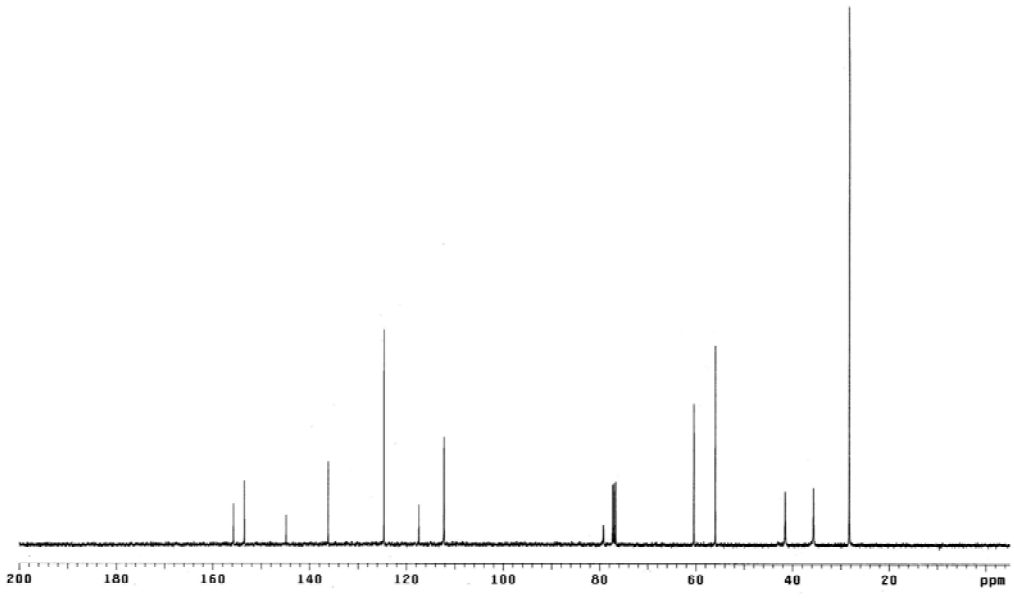
Appendix Figure 69 400 MHz ^{1}H NMR spectrum of 2,3-dimethoxy-5-(2-amino ethyl)-1,ɪ-biphenyl-2′-phenylacetonitrile (220)



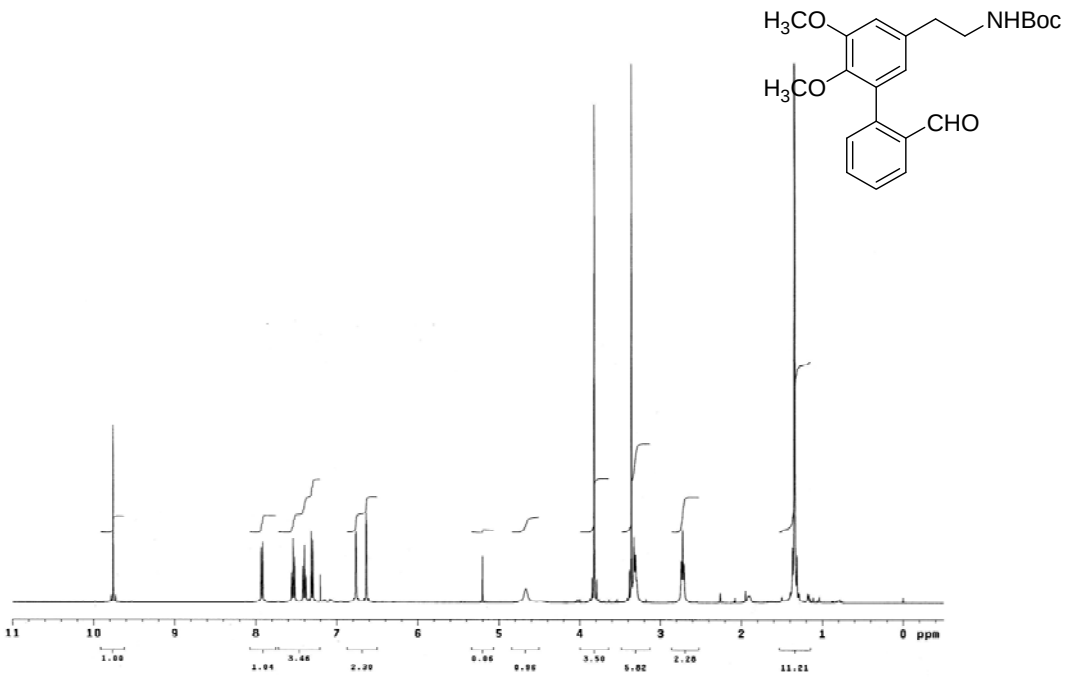
Appendix Figure 70 100 MHz ^{13}C NMR spectrum of 2,3-dimethoxy-5-(2-amino ethyl)-1,1′-biphenyl-2′-phenylacetonitrile (220)



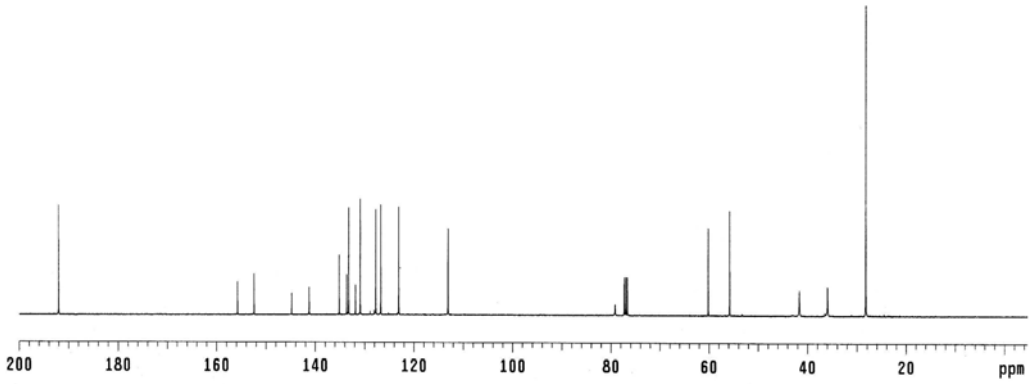
Appendix Figure 71 400 MHz ^{1}H NMR spectrum of *tert*-butyl 3-bromo-4,5-dimethoxyphenethylcarbamate (223)



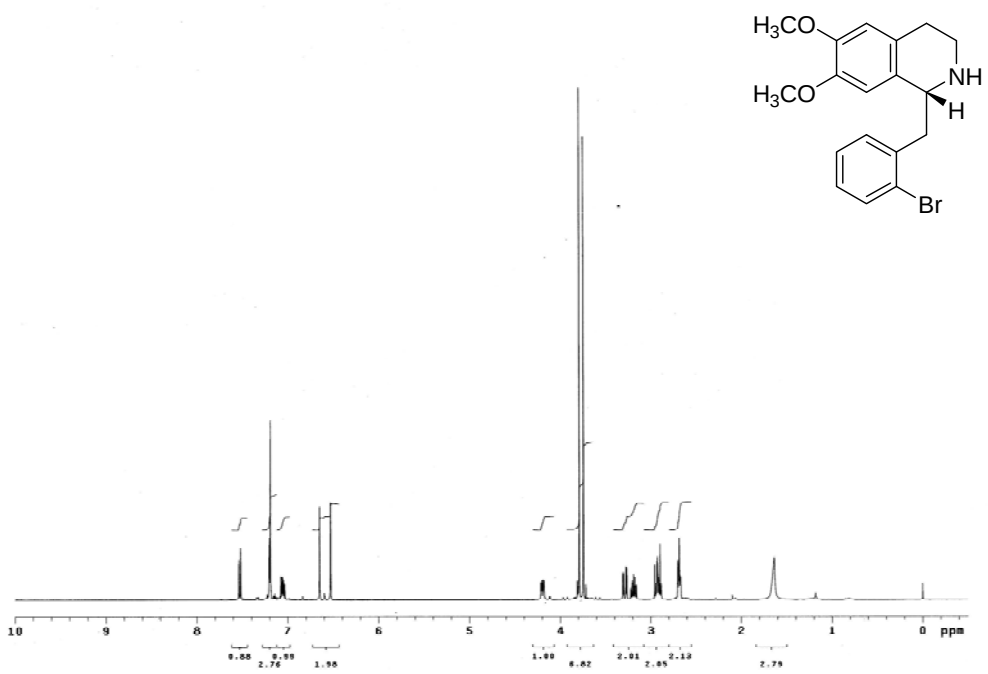
Appendix Figure 72 100 MHz ^{13}C NMR spectrum of *tert*-butyl 3-bromo-4,5-dimethoxyphenethylcarbamate (223)



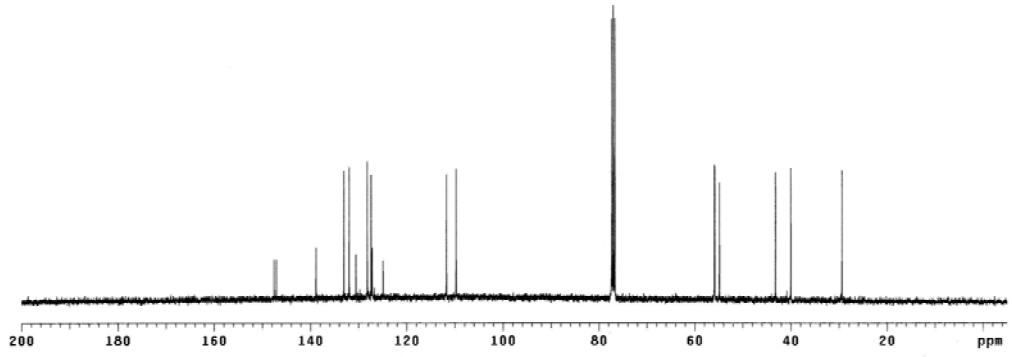
Appendix Figure 73 400 MHz ^{1}H NMR spectrum of 2,3-dimethoxy-5-(*tert*-butyl(2-phenylethyl)carbamate)-1,1′-biphenyl-2 ′-carboxaldehyde (224)



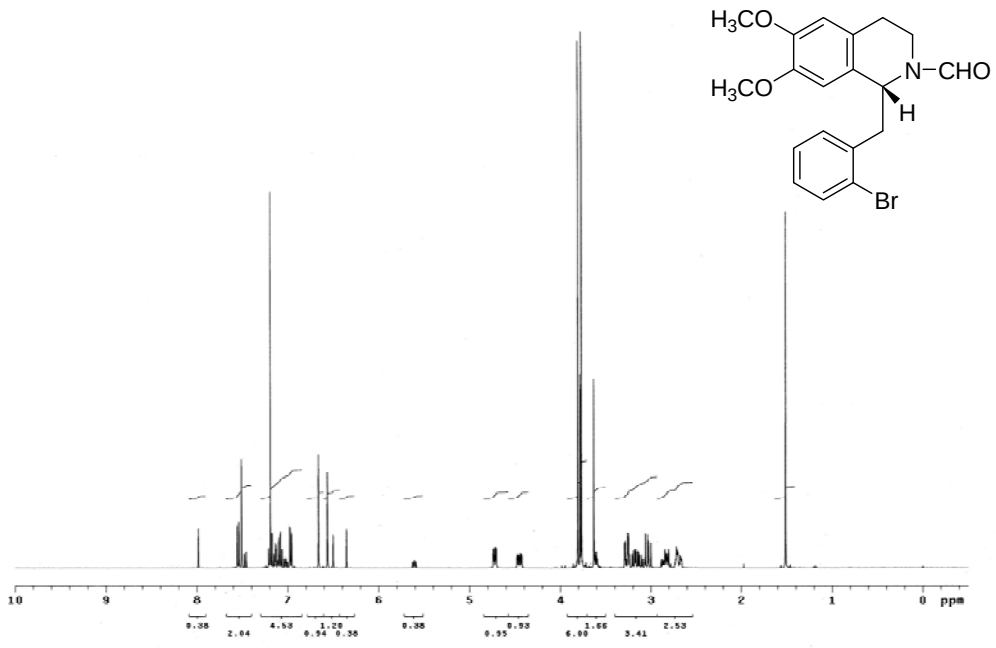
Appendix Figure 74 100 MHz ^{13}C NMR spectrum of 2,3-dimethoxy-5-(*tert*-butyl(2-phenylethyl)carbamate)-1,1′-biphenyl-2′-carboxaldehyde (224)



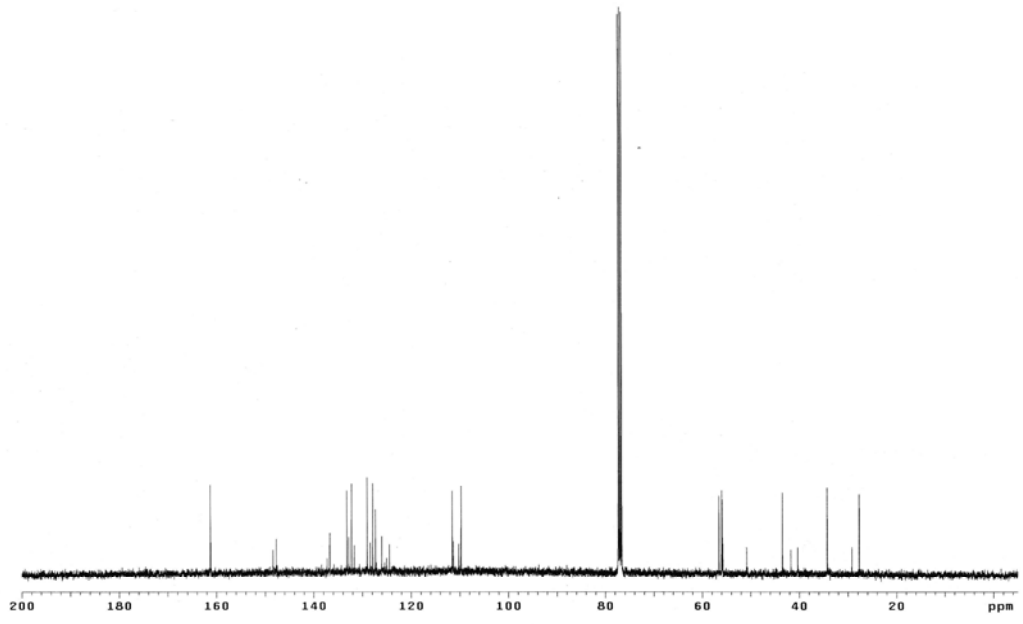
Appendix Figure 75 400 MHz ^{1}H NMR spectrum of (*R*)-1-(2-bromobenzyl)-1,2,3,4 tetrahydro-6,7-dimethoxyisoquinoline (226)



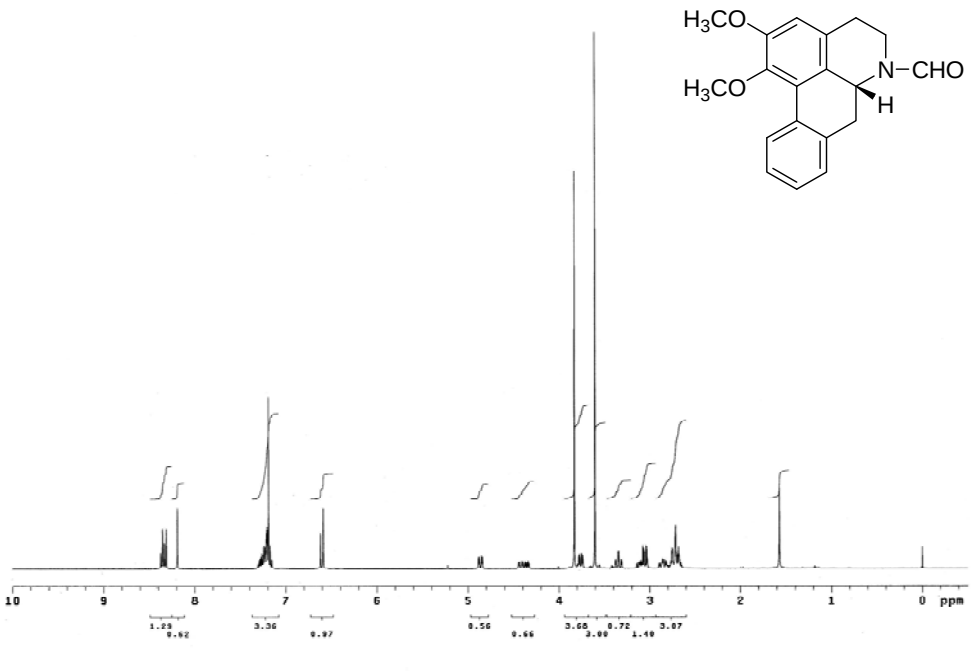
Appendix Figure 76 100 MHz ^{13}C NMR spectrum of (*R*)-1-(2-bromobenzyl)-1,2,3,4 tetrahydro-6,7-dimethoxyisoquinoline (226)



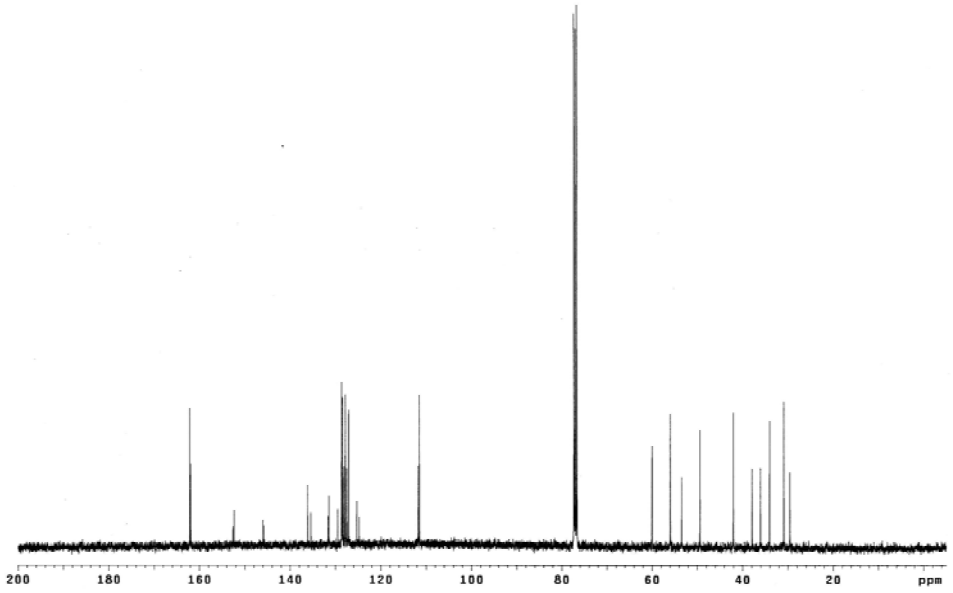
Appendix Figure 77 400 MHz ^{1}H NMR spectrum of (*R*)-1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (227)



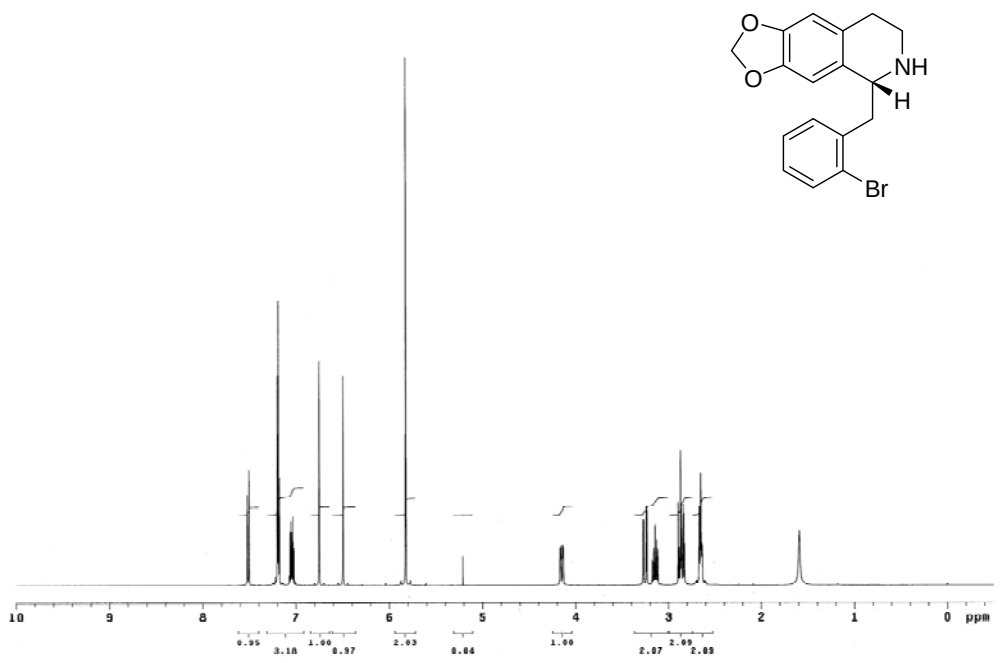
Appendix Figure 78 100 MHz ^{13}C NMR spectrum (*R*)-1-(2-bromobenzyl)-3,4-dihydro-6,7-dimethoxyisoquinoline-2(1H)-carbaldehyde (227)



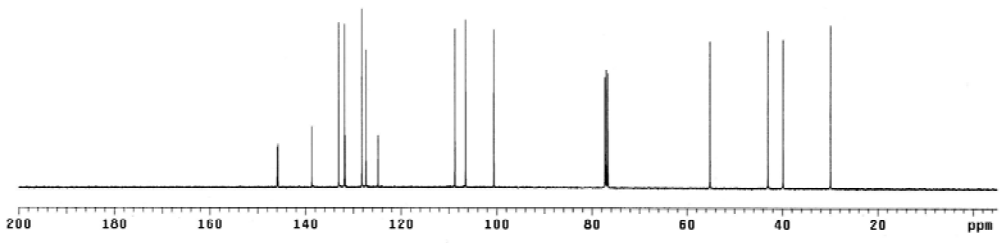
Appendix Figure 79 400 MHz ^{1}H NMR spectrum of (-)-*N*-formylnornuciferine (13b)



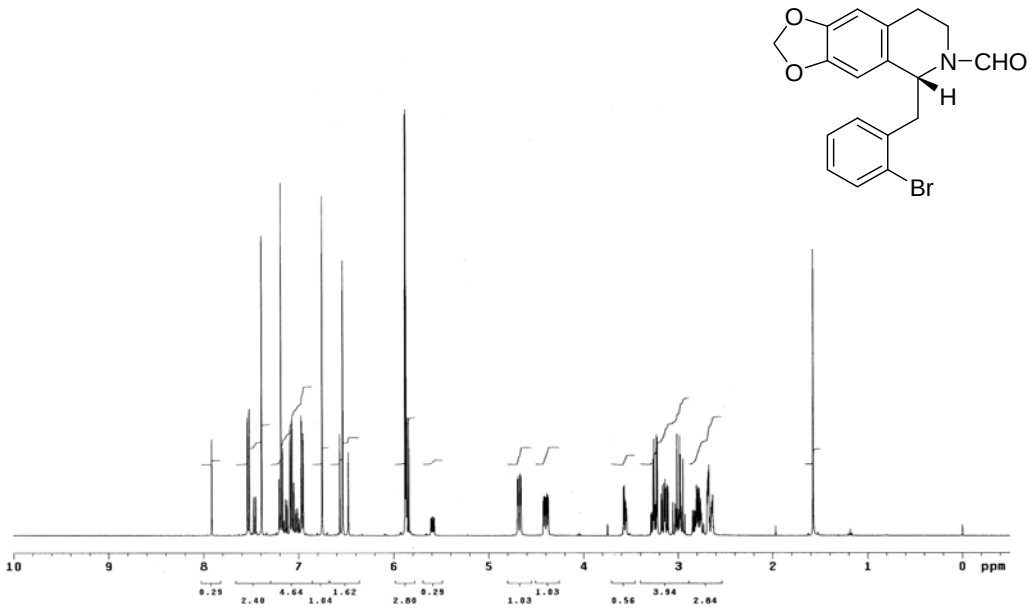
Appendix Figure 80 100 MHz ^{13}C NMR spectrum of (-)-*N*-formylnornuciferine (13b)



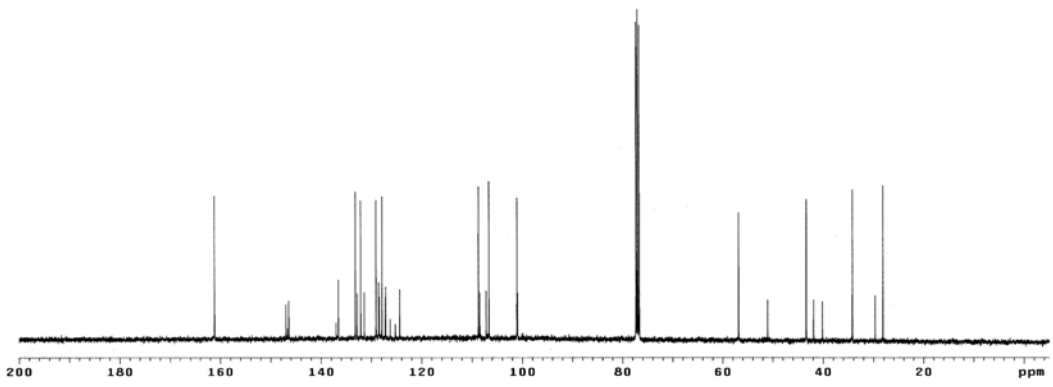
Appendix Figure 81 400 MHz ^{1}H NMR spectrum of 1-((*R*)-5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (228)



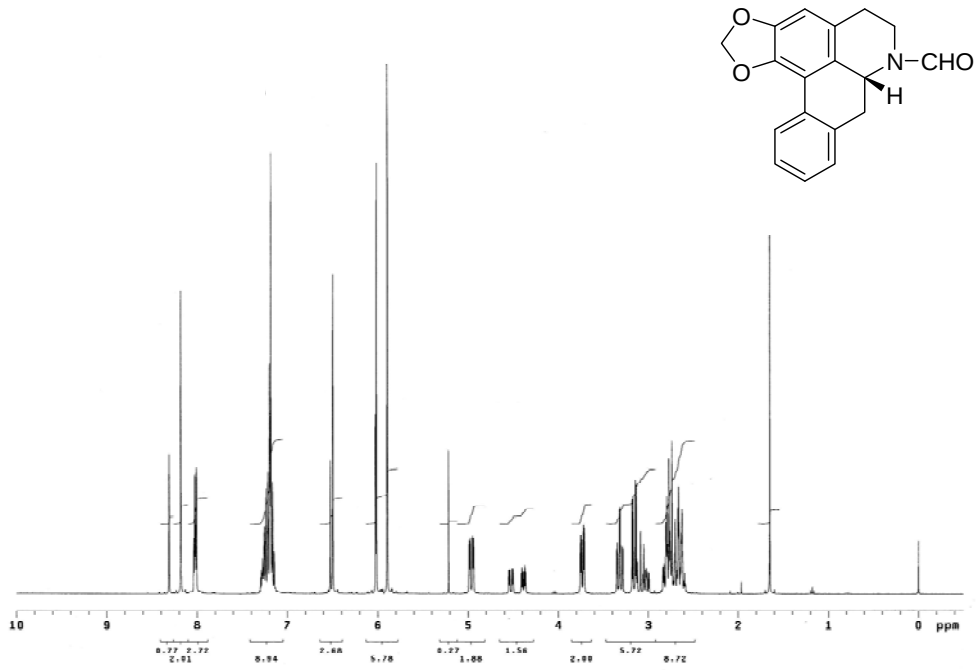
Appendix Figure 82 100 MHz ^{13}C NMR spectrum of 1-((*R*)-5-(2-bromobenzyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (228)



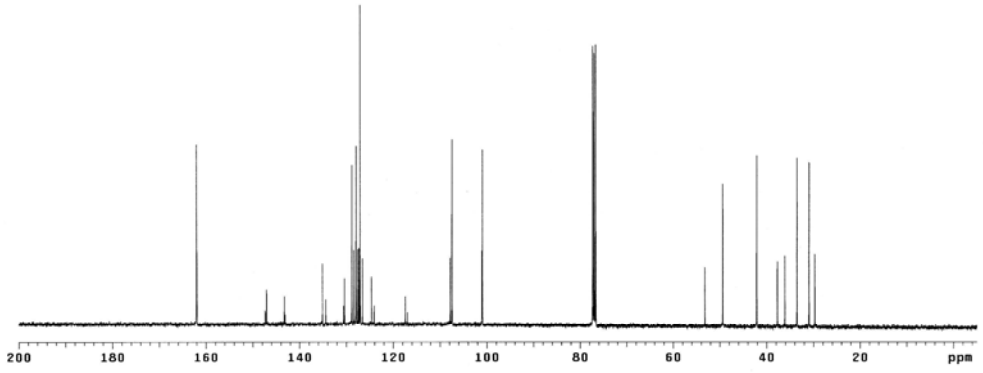
Appendix Figure 83 400 MHz ^{1}H NMR spectrum of (*R*)-5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6-carbaldehyde (229)



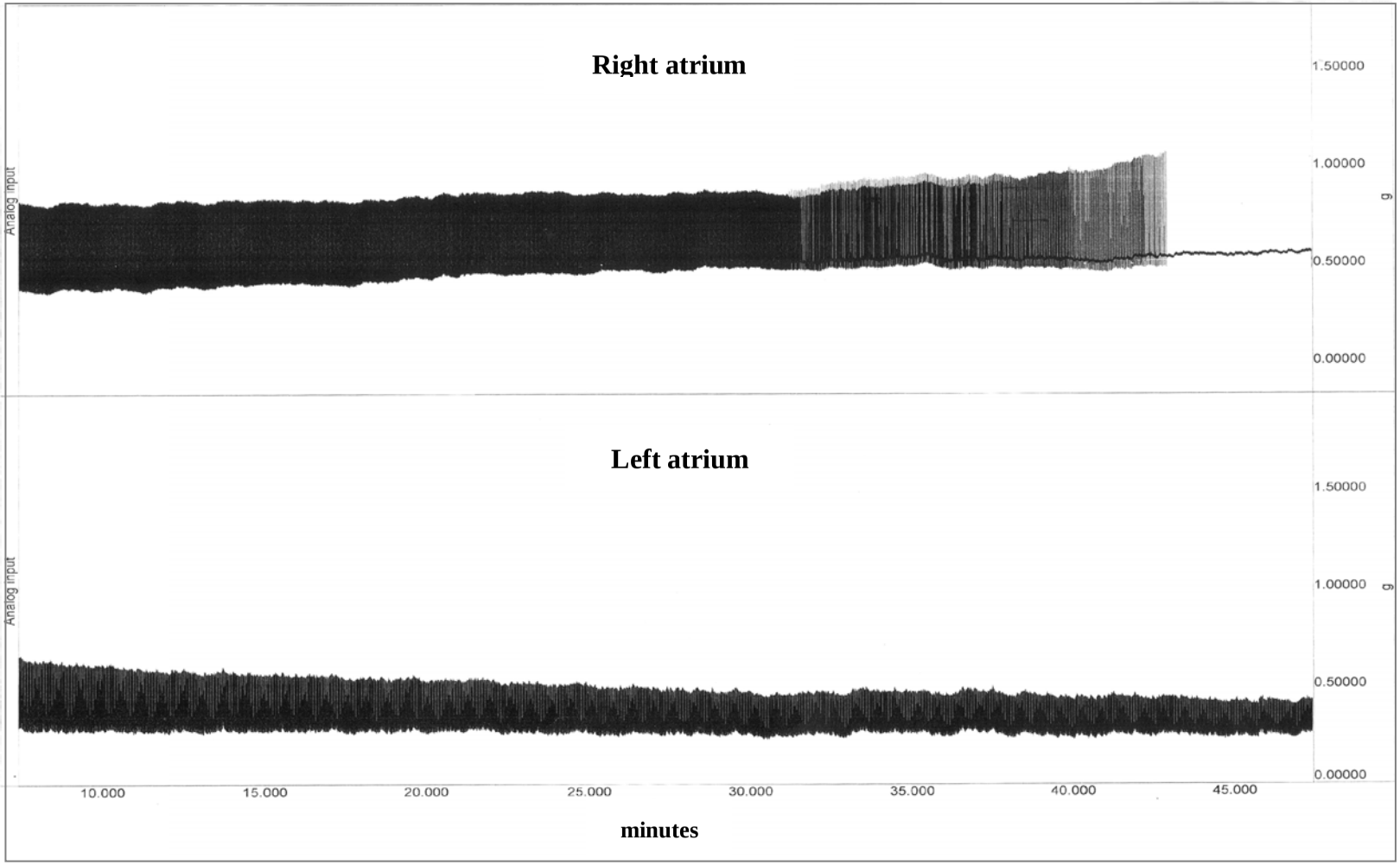
Appendix Figure 84 100 MHz ^{13}C NMR spectrum of (*R*)-5-(2-bromobenzyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline-6-carbaldehyde (229)



Appendix Figure 85 400 MHz ^{1}H NMR spectrum of (-)-*N*-formylannonaine (14b)



Appendix Figure 86 100 MHz ^{13}C NMR spectrum of (-)-*N*-formylannonaine (14b)



Appendix Figure 87 Cardiotonic effects of (±)-*N*-formylnornuciferine (13a) as a racemic mixture on the right and left atria

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: Pure and Applied Chemistry International conference, January 14-16, 2009
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