FURTHER PROGRESS TOWARDS ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE BISBENZYLTETRAHYDROISOQUINOLINE ALKALOID (--)-CYCLEANINE

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FURTHER PROGRESS TOWARDS ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE BISBENZYLTETRAHYDROISOQUINOLINE ALKALOID (-)-CYCLEANINE

by

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Abstract

Bisbenzylisoquinoline (BBIQ) alkaloids are a large group of compounds which outnumber those of most of the other alkaloid families. These compounds occur in many different plants and usually display a variety of pharmacological properties such as antitumor and antibacterial activities. The two benzylisoquinoline subunits in BBIQs can be connected through an oxygen atom or by carbon-carbon linkage. The subunits may have the same or opposite configurations at their asymmetric centres. BBIQs may also contain dihydroisoquinoline or tetrahydroisoquinoline units. A vast number of possible structures may be constructed in this way which make BBIQs very interesting synthetic targets.

In this thesis, the asymmetric synthesis of the BBIQ (-)-cycleanine was attempted. A chiral auxiliary-assisted diastereoselective Bischler-Napieralski cyclization was used to form the two correct tetrahydroisoquinoline subunits. Two different methods of recently reported improved Ullmann coupling methods, namely (a) *N,N*-dimethylglycine-promoted coupling, and (b) 2,2,6,6-tetramethylheptane-3,5-dione-accelerated coupling were first employed to build the framework of the target molecule. The use of a methodology of using a mild S_NAr reaction between phenols and electron-deficient aryl fluorides was also evaluated. In addition, some efforts at making some intermediates for the total synthesis more synthetically accessible are also discussed.

Acknowledgements

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APCI-MS	atmospheric pressure chemical ionization-mass spectrometry
AcOH	acetic acid
BBIQ	bisbenzyltetrahydroisoquinoline
Bn	benzyl
BNC	Bischler-Napieralski cyclization
Boc	*tert*-butoxycarbonyl
CA	chiral auxiliary
Cbz	benzyloxycarbonyl
DCC	dicyclohexylcarbodiimide
DHP	dihydropyran
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDTA	ethylenediaminetetraacetic acid
Et	ethyl
h	hour
i-Pr	isopropyl
LC/MS	liquid chromatography/mass spectrometry
Me	methyl
min	minute(s)
m.p.	melting point

MTBE	methyl t-butyl ether
MW	microwave
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyllithium
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Ph	phenyl
PLC	preparative layer chromatography
PPTS	pyridinium p-toluenesulfonate
PSC	Pictet-Spengler cyclization
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
THP	tetrahydropyran
TMHD	2,2,6,6-tetramethylheptane-3,5-dione

Chapter 1

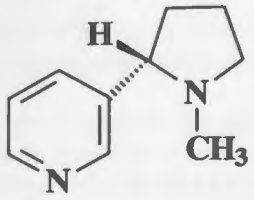
Introduction

1.1 Definition and structural classification of BBIQ alkaloids

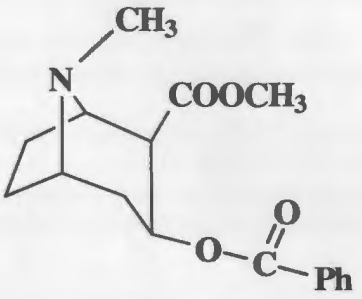
Since ancient times man has utilized alkaloids as medicines, poisons, or as "magical potions". The term "alkaloid" or "alkali-like", was first proposed by W. Meissner in 1818.[1] It is usually applied to basic, nitrogen-containing compounds of plant origin. Two further qualifications are usually added to this definition: alkaloids have complex molecular structures, and they manifest a variety of significant pharmacological activities. When classifying a compound as an alkaloid, its chemical, pharmacological and botanical properties must all be considered. Some well-known alkaloids such as nicotine (**1**), cocaine (**2**), quinine (**3**), and morphine (**4**) are presented in Figure 1.1.[2]

Bisbenzylisoquinoline (BBIQ) alkaloids are a large and diverse group of alkaloids that exist in many plant species, particularly in members of the *Menispermaceae, Berberidaceae, Ranunculaceae, Annonaceae,* and *Monimiaceae.*[3] Many of the plants that contain these compounds enjoy a folkloric reputation as medicines in various cultures. It is believed that some indigenous South American tribes used a BBIQ alkaloid as a component of the arrow poison *Curare.* [4]

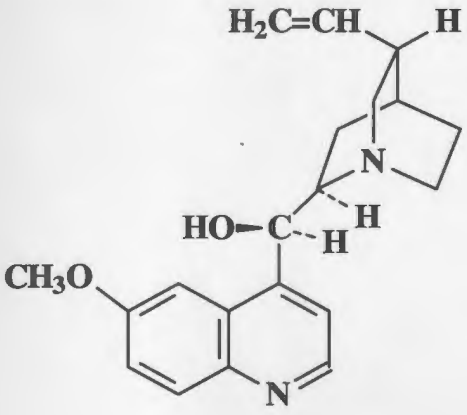
The most obvious structural characteristic of BBIQ alkaloids is that there are two benzylisoquinoline subunits in each molecule. The two benzylisoquinoline subunits can be bound by diaryl ether bridges, by carbon-carbon linkages or by methylene-oxy linkages. When the linkage involves two benzyl groups, it is called a "tail-to-tail" linkage. If the linkage is between one isoquinoline and one benzyl group



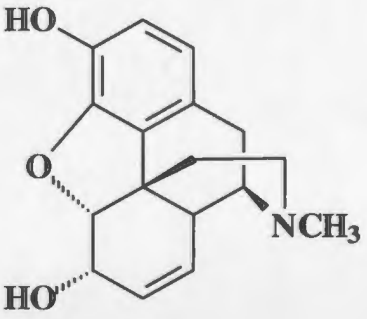
Nicotine (1)



Cocaine (2)



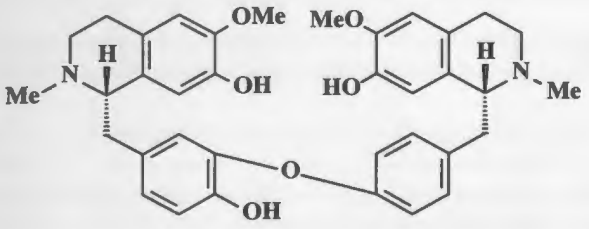
Quinine (3)



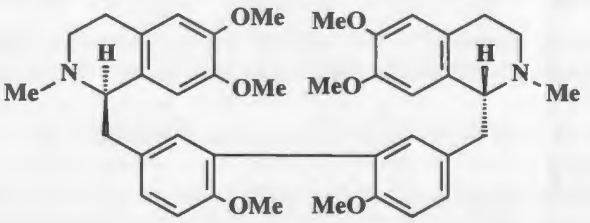
Morphine (4)

Figure 1.1 Some examples of alkaloids

unit, it is called a "head-to-tail" linkage. There may also be different numbers of diaryl ether linkages in different BBIQs. Figure **1.2** shows some BBIQ alkaloids with representative structures.[5] There are examples known with one, *e.g.* **5**; two, *e.g.* **6**; or three, *e.g.* **7,** diaryl ether linkages. There are BBIQs known with only one biphenyl linkage such as **8**. There are also BBIQs known with one diaryl ether linkage and one biphenyl linkage such as **9**. And finally, there are BBIQs known with one diaryl ether linkage, one biphenyl linkage and one methylenedioxy linkage such as **10**. The two coupled isoquinoline subunits may have the same or opposite absolute configurations, and either or both may be isoquinolines, dihydroisoquinolines or tetrahydroisoquinolines.

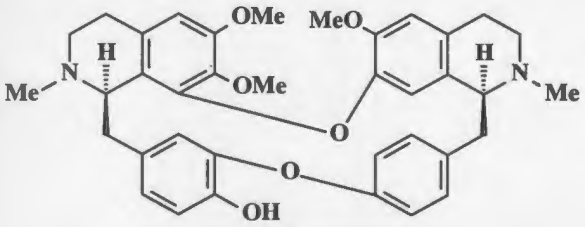


Magnoline (**5**)

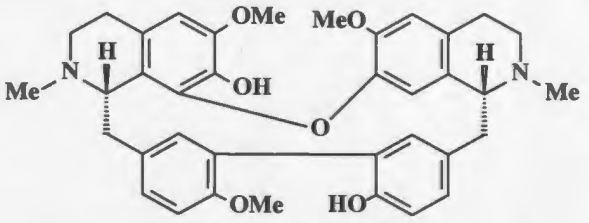


Pisopowine (**8**)

Singly-linked dimers

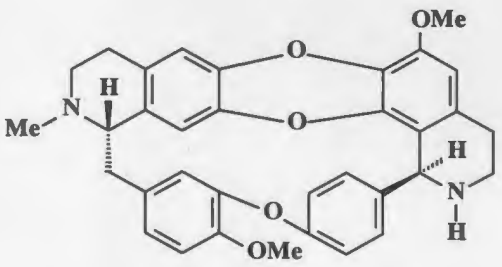


Berbamine (**6**)

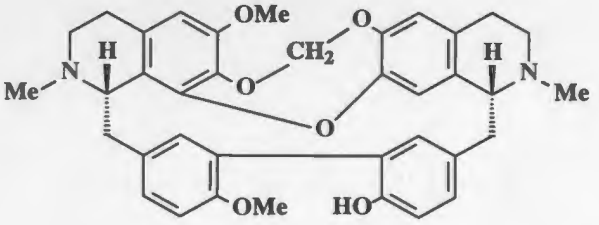


Antioquine (**9**)

Doubly-linked dimers



Trilobine (**7**)



Medelline (**10**)

Triply-linked dimers

Figure 1.2 Some BBIQ alkaloids with different structures

Therefore, a vast number of structures can be constructed in these ways, and up to now a total of at least over 350 BBIQs are known.

1.2 Pharmacological activities of BBIQ alkaloids

The history of alkaloids is almost as old as civilization itself. This can be

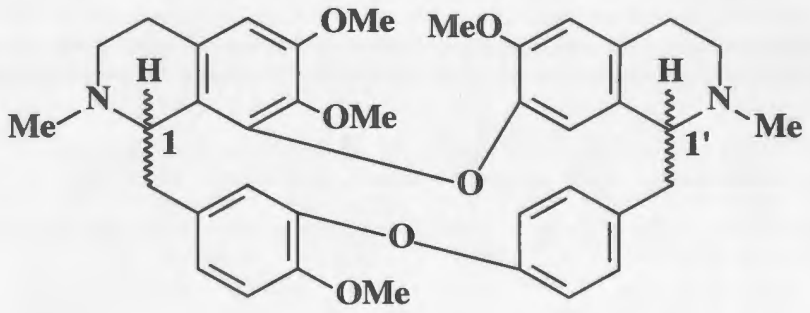
attributed to the pharmacological activities which alkaloids possess. It is said that humankind has used drugs containing alkaloids in potions, medicines, teas, poultices and poisons for over 4000 years.[6] As one of the most important groups in all of the alkaloids, BBIQ alkaloids also have been found to possess various kinds of biological activities such as antimicrobial, anti-arrhythmic, anti-inflammatory, antibiotic, anti-tumor, anti-hypertensive and antiplasmodial activities.[3] Table 1.1 lists some of the pharmacological activities of several BBIQ alkaloids.[7]

Table 1.1 The pharmacological activities of several BBIQ alkaloids

Alkaloids	Pharmacological Activities
Berbamine (**6**)	Antiplasmodial, anti-inflammatory, antioxidant
Cepharanthine (**11**)	Anti-inflammatory, analgesic
Aromoline (**12**)	Anti-inflammatory, antiplasmodial
Tetrandrine (**13**)	Antiplasmodial, anti-inflammatory
Oxyacanthine (**14**)	Anti-inflammatory, antioxidant, antiproliferative
(-)-Repandine (**15**)	Antiplasmodial, anti-inflammatory
Fangchinoline (**16**)	Antiplasmodial, anti-inflammatory

Since the1970s, much work has been conducted with the aim to disclose the relationship between the structural features of BBIQ alkaloids and their pharmacological activities.[8, 9] Some researchers recognized that their pharmacological activities are somewhat dependent on their chirality and their substitution patterns. For example, although (+)-tetrandrine (**13**), (-)-phaeanthine (**17**), and (+)-isotetrandrine (**18**)

(Figure 1.3) have very similar structures, they have quite different pharmacological activities due to their different absolute configurations.[10, 11]



(+)-(1*S*,1′*S*)- Tetrandrine **(13)**

(-)-(1*R*,1′*R*)- Phaeanthine **(17)**

(+)-(1*R*,1′S)- Isotetrandrine **(18)**

Figure 1.3 Structures of (+)-tetrandrine **(13)**, (-)-phaeanthine**(17)**, and (+)-isotetrandrine**(18)**

Although it is presumed that there is a close relationship between the activities of BBIQ alkaloids and their molecular structures, how these structural features of BBIQ alkaloids exactly influence their biological activities still remains unknown.

1.3 Sources of BBIQ alkaloids

1.3.1 Botanical sources

In spite of the large number of BBIQ alkaloids whose structures have been confirmed and whose biological activities have been reported, to date most can only be obtained from their respective plant sources. Usually the nature and the quantities of BBIQ alkaloids found in plants are decided by ecological factors. Different groups of BBIQs are normally found in different genera. In general, several different BBIQ alkaloids are found in a single plant with one being a major component, along with other

minor alkaloids. Furthermore, the relative proportions of one alkaloid in a plant differ in the different parts of the plant.[4] Table 1.2 is a list of some of the botanical sources of some BBIQ alkaloids.

Table 1.2 An outline of the botanical sources of some BBIQ alkaloids

Name of the plant	Plant parts	Alkaloids
T. minus Linn	Above ground parts	Thalmethine (**19**)[12]
	Root	Thalfine (**20**), thalfinine (**21**)[13]
	Whole plant	Thalmine (**22**)[14]
T. patens Oliv	Root and stem	Cocsuline (**23**)[15]
	Leaf	Aromoline (**12**)[16]
C. *pareira Linn*	Whole plant	Cissampareine (**24**)[17]
	Root and leaf	Cycleanine (**25**)[18]
C. leaeba DC	Root	Oxyacanthine (**14**)[19]
	Leaf	Menisarine (**26**)[20]
D. species	Bark	Isotenuipine (**27**)[21]
Heracleum Wallichi	Root	Cycleanine (**25**)[22]
S. tetrandra S. *Moore*	Tuber	Tetrandrine (**13**)[23]

1.3.2 Syntheses of BBIQ alkaloids

Most of the total synthetic work on BBIQ alkaloids was undertaken in the1960s and the early 1970s.[6-9, 24] Among them, the achievements of Tomita's group, Inubushi's group and Kametani's group are well known.[25-35] A brief review of their work done at

that time reveals that two pivotal steps are usually employed for the synthesis of BBIQs: one is the reaction for the formation of the diaryl ether linkage, usually by the classic Ullmann coupling reaction; and the second is the cyclization process for the formation of the isoquinoline subunit, usually by a Bischler-Napieralski cyclization (BNC) or a Pictet-Spengler cyclization (PSC) reaction. However, a review of these two key steps in the work undertaken at that time will will show that the results obtained from both of them are far from ideal. First, the yields obtained from the classic Ullmann coupling were generally quite low, and the reaction conditions were very harsh.[24, 36-38] Secondly, the cyclization process always resulted in the formation of a mixture of stereoisomers which either required a chiral resolution step to isolate, or could not be separated at all.[25, 27-29]

Many new methodologies have been developed to overcome these two problems. For the formation of the diaryl ether linkage, improved Ullmann coupling with high yields and new methodologies involving different mechanisms such as (i) S_NAr reactions; (ii) thallium(III)-mediated oxidative cyclizations;[39, 40] (iii) palladium-catalyzed diaryl ether syntheses; (iv) cycloaddition reactions such as Diels-Alder cycloadditions; and (v) Robinson annulations have been developed.[41-44] At the same time, numerous procedures have been developed to control the diastereoselectivity of the cyclization process while constructing the isoquinoline subunit.[45] One example of such an approach is the first enantioselective total synthesis of (-)-tejedine (**28**) by Wang and Georghiou.[46] (-)-Tejedine is a seco-bisbenzyltetrahydroisoquinoline which was first extracted from *Berberis vulgaris* as a minor component in 1998.[46] In their synthesis, a chiral auxiliary-assisted diastereoselective Bischler-Napieralski cyclization strategy was utilized with

satisfactory results. A mild $Cu(OAc)_2$-mediated diaryl ether coupling methodology which had recently been reported by Evans and Chan[47, 48] was successfully used. Later in this thesis, in order to make the work described for this thesis more understandable, some of these new advances in forming biaryl ether linkages and controlling the stereochemistry during the synthesis of some isoquinolines will be introduced.

1.4 Cycleanine

In 1937, Kondo et al. first isolated cycleanine (**25**) from *Cyclea insularis* (MAKINO) DIELS and *Stephania cepharantha* HAYATA.[49] Later, its exact structure was established and it was found that cycleanine, also called *O,O*-dimethylisochondodendrine, is a C_2-symmetrical compound with two benzyltetrahydroisoquinoline subunits connected by two diaryl ether linkages. It is a "head-to-tail" dimer with the two isoquinolines having the same absolute configuration (Figure 1.4).[50]

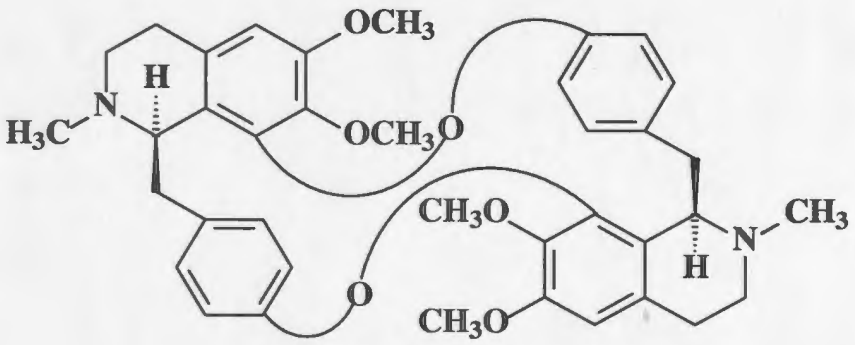


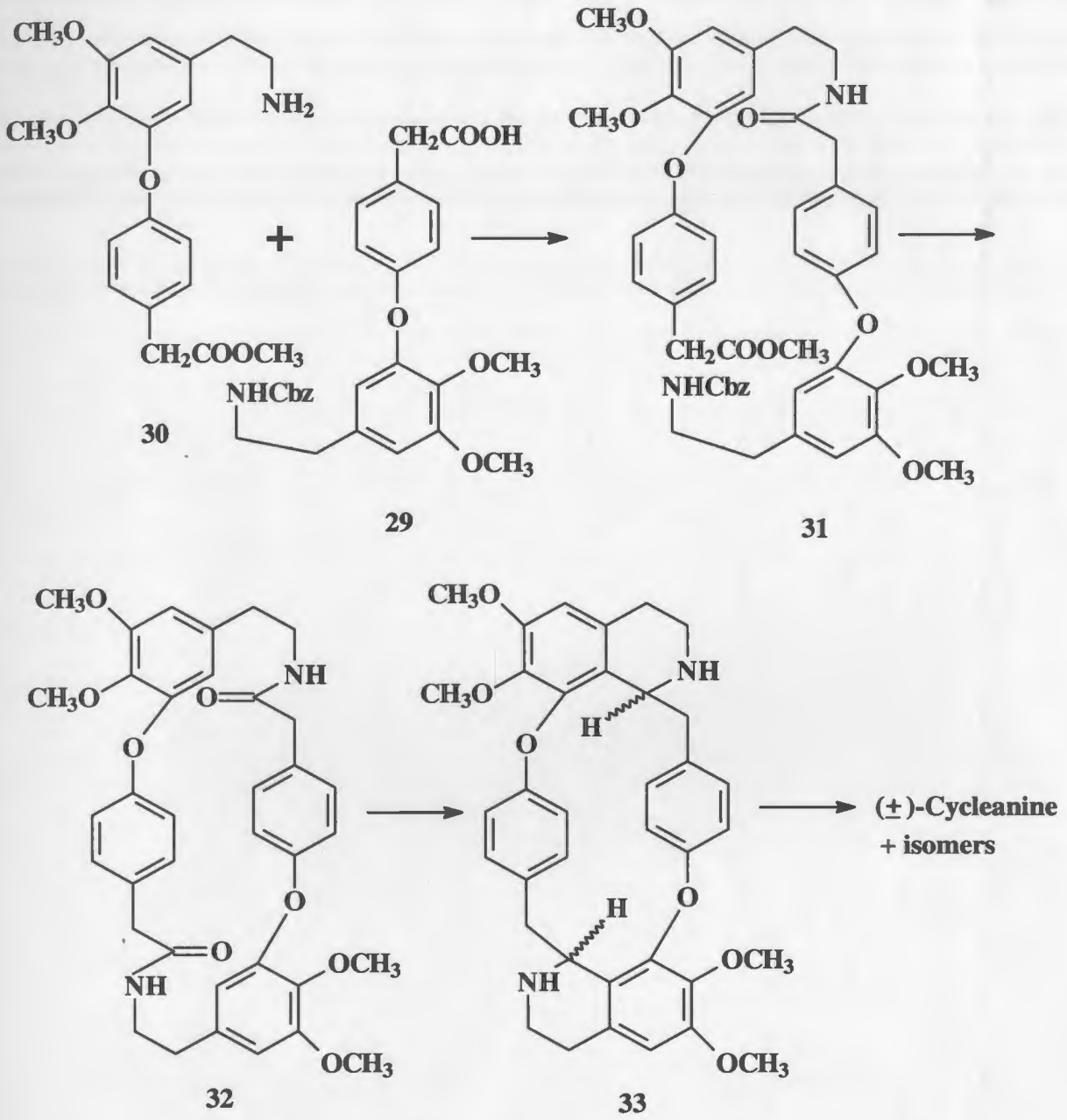
Figure 1.4 (-)-Cycleanine (**25**)

1.4.1 Pharmacological activities of cycleanine

The early evidences of the pharmacological activities of cycleanine can be traced back to ancient Southern Nigeria and other coastal regions of West Africa. At that time, the root bark of the plant *Synclisia scarbrida,* which contained cycleanine, had been used widely as a medicine to treat various ailments such as acute psychosis, dysmenorrhea and to prevent spontaneous abortion. Later, it was found that cycleanine also has analgesic, muscle relaxant and anti-inflammatory activites.[51] Recent investigations have shown that cycleanine has effects on the central nervous system.[52]

1.4.2 Previous synthetic approaches towards cycleanine

Although cycleanine was isolated from plants a long time ago and its structure has also long been established, efficient synthetic approaches to this alkaloid have not yet been achieved.[53-56] The only report on the synthesis of cycleanine was reported by Tomita *et al* in 1966.[53] In this synthetic approach, the reaction of an amino acid derivative (**29**) with methyl ester (**30**) with the aid of DCC in dichoromethane formed the amide **31**, which was further converted to **32** by a series of steps. Bischler-Napieralski cyclization of **32** followed by sodium borohydride reduction in methanol afforded a mixture of tetrahydroisoquinolines **33**. Treatment of **33** with formalin, then with sodium borohydride yielded the *N*-methyl derivatives of (±)-cycleanine along with its isomers (Scheme 1.1). Tomita's approach was not synthetically useful due to the very low overall yield and the formation of a mixture of diastereomers.



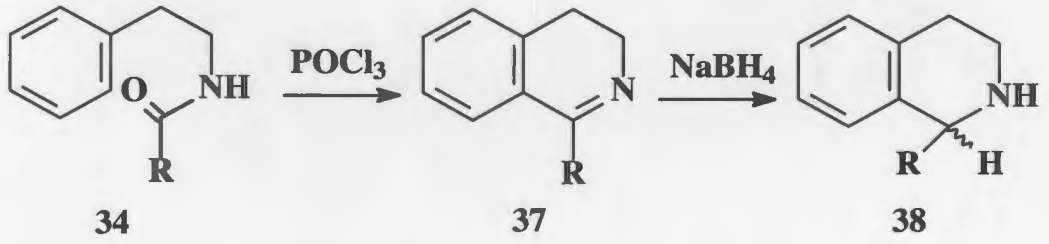
Scheme 1.1

In order to overcome the drawbacks of Tomita's synthesis, Cui and Georghiou[7] initiated a new synthetic effort using a different approach. Although they obtained the tetrahydroisoquinoline subunits with the desired stereochemistry, they did not obtain the desired cyclic product when they tried to combine the two subunits by formation of biaryl

ether linkages.[7] This attempt will be discussed in greater detail in a later section of this thesis.

1.5 Recent advances in the synthesis of isoquinolines

As mentioned previously, BNC and PSC are two classical ways to produce isoquinolines. Both reactions with modifications are still the most frequently employed methodologies for such syntheses but with modifications. The BNC usually commences with refluxing of a mixture of a phenethylamide e.g. **34** and a Lewis acid, most often $POCl_3$, in benzene, which first leads to the dihydroisoquinoline **37**. Compound **37** can be further reduced by $NaBH_4$ to give the tetrahydroisoquinoline **38** (Scheme 1.2).

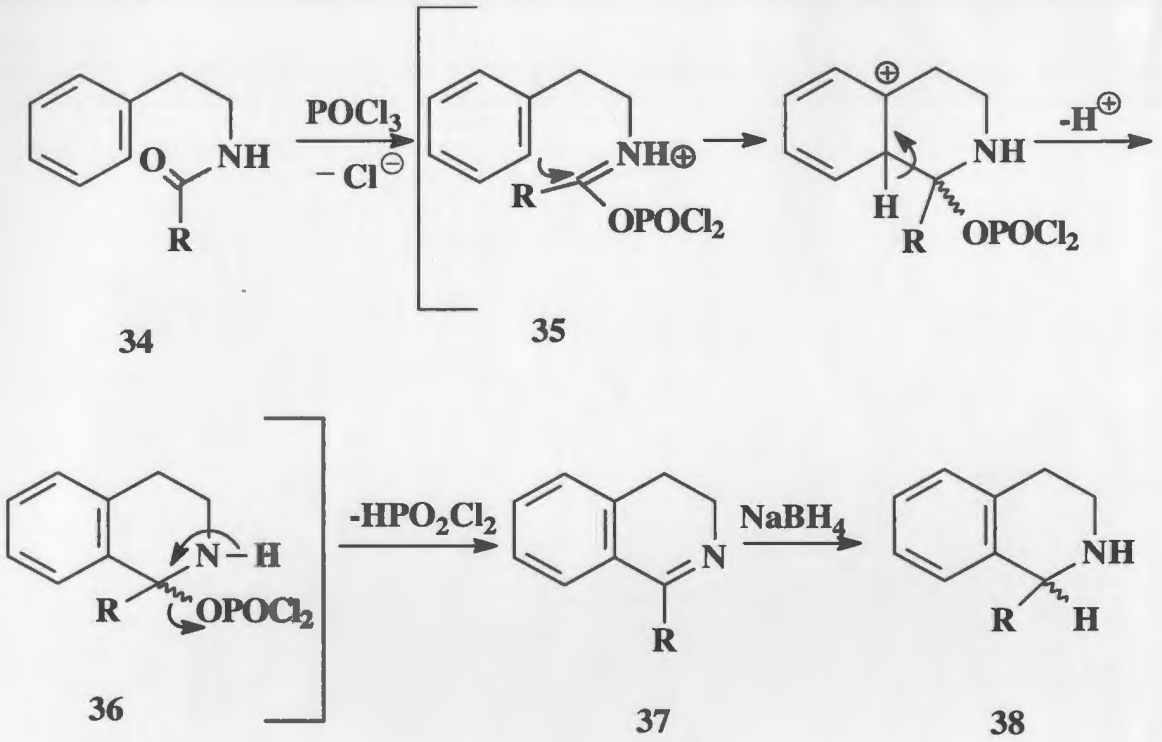


34 **37** **38**

Scheme 1.2

Outlined in Scheme 1.3 is the mechanism for the BNC.[57] The intermediate **35** is first formed between the phenethylamide **34** and the Lewis acid. Electrophilic attack by the aromatic ring followed by re-aromatization leads to intermediate **36**, which then results in the formation of dihydroisoquinoline **37** by elimination of a molecule of HPO_2Cl_2. Reducing this dihydroisoquinoline **37** produces the final tetrahydroisoquinoline **38** usually as a mixture of enantiomers. If the R group in **38** is a benzyl group, the products are benzylisoquinolines. In order to overcome the drawback of the formation of

undesired enantiomers, currently several methodologies have been reported which seem to be promising.

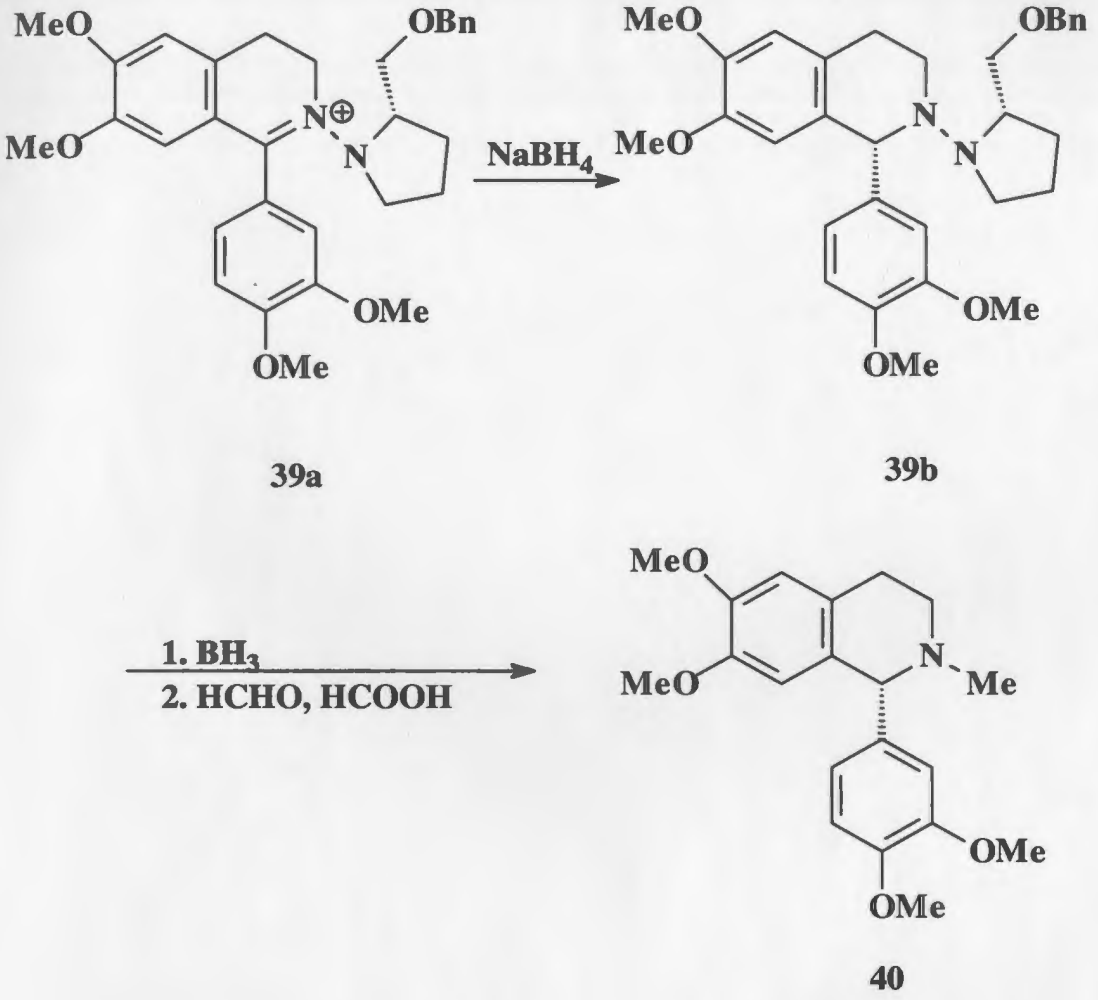


Scheme 1.3

In Scheme 1.4, dihydroisoquinolinium salt **39a** with an incorporated chiral hydrazonium functionality was used as a substrate by Kibayashi et al. in the synthesis of (*R*)-(-)-cryptostyline.[58] Reduction of **39a** by employing $NaBH_4$ followed by two additional steps resulted in the tetrahydro product **40** with excellent enantioselectivity (90-96% ee).

Sodium triacyloxyborohydride **41**, prepared from $NaBH_4$ and *N,N*-phthaloyl-protected (phth) amino acids, was used by Hajipour and Hantehzadeh in the synthesis of benzyltetrahydroisoquinoline (*S*)-(-)-norcryptostyline **40b**.[59] The enantioselectivity

(65-75% ee) increased when the reduction of **40a** was performed in the presence of $ZnCl_2$ (72-87% ee) or carried out under solid-state conditions (83-100% ee) (Scheme 1.5).

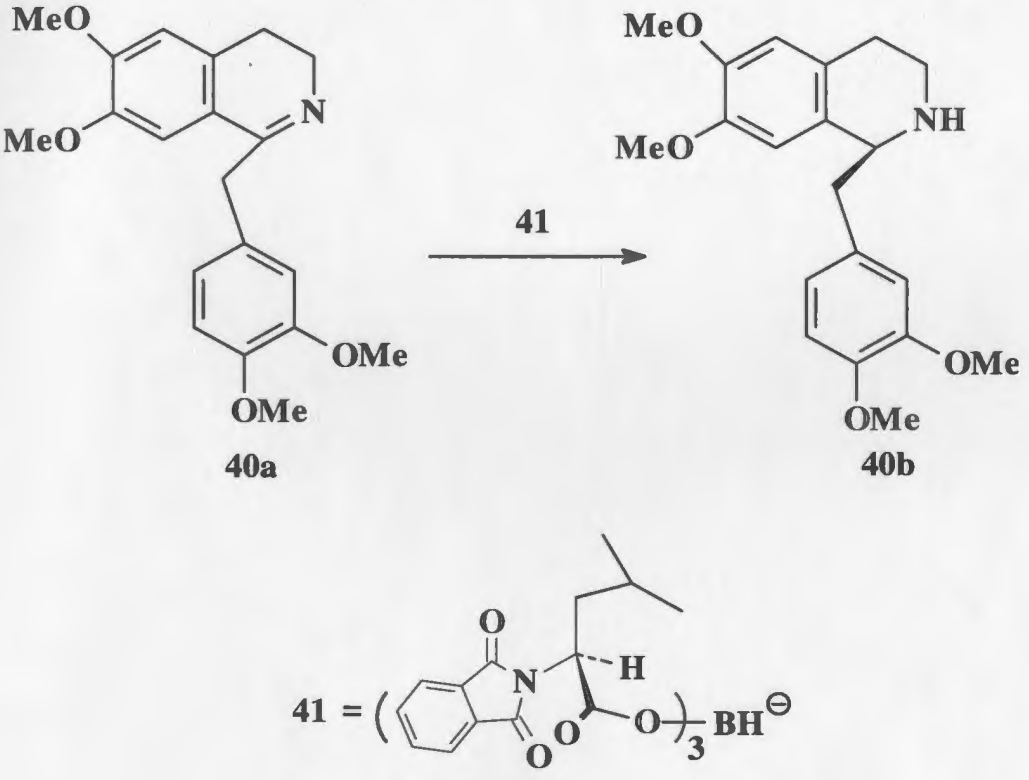


Scheme 1.4

As mentioned before, (-)-tejedine (**28**) has been synthesized enantioselectively in 2002.[46] In that multistep synthesis, (*S*)-α-methylbenzylamine was used as a very efficient chiral auxiliary to control the enantioselectivity of the crucial cyclization step.

The key intermediate **42** was prepared from chiral amine **43** (obtained from

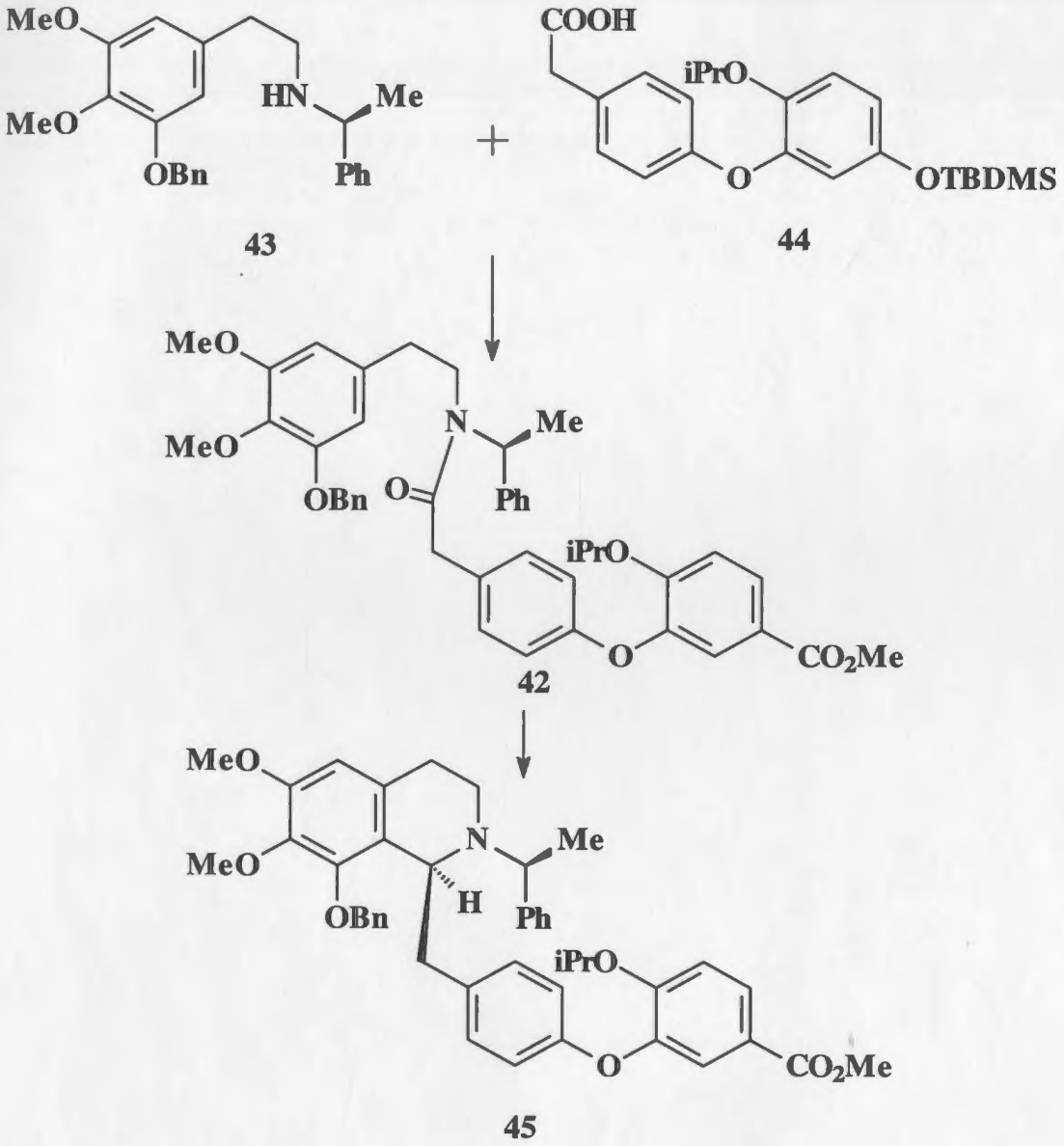
vanillin in 13 synthetic steps) and carboxylic acid **44** (synthesized from 4-hydroxybenzaldehyde in 11 steps). Cyclization of **42** using $POCl_3$ in benzene followed by reduction gave the desired regioisomer of tetrahydroisoquinoline **45** in 40% yield and with 99% de. Then, the synthesis of the final alkaloid (-)-tejedine was completed after an additional series of transformations (Scheme 1.6).



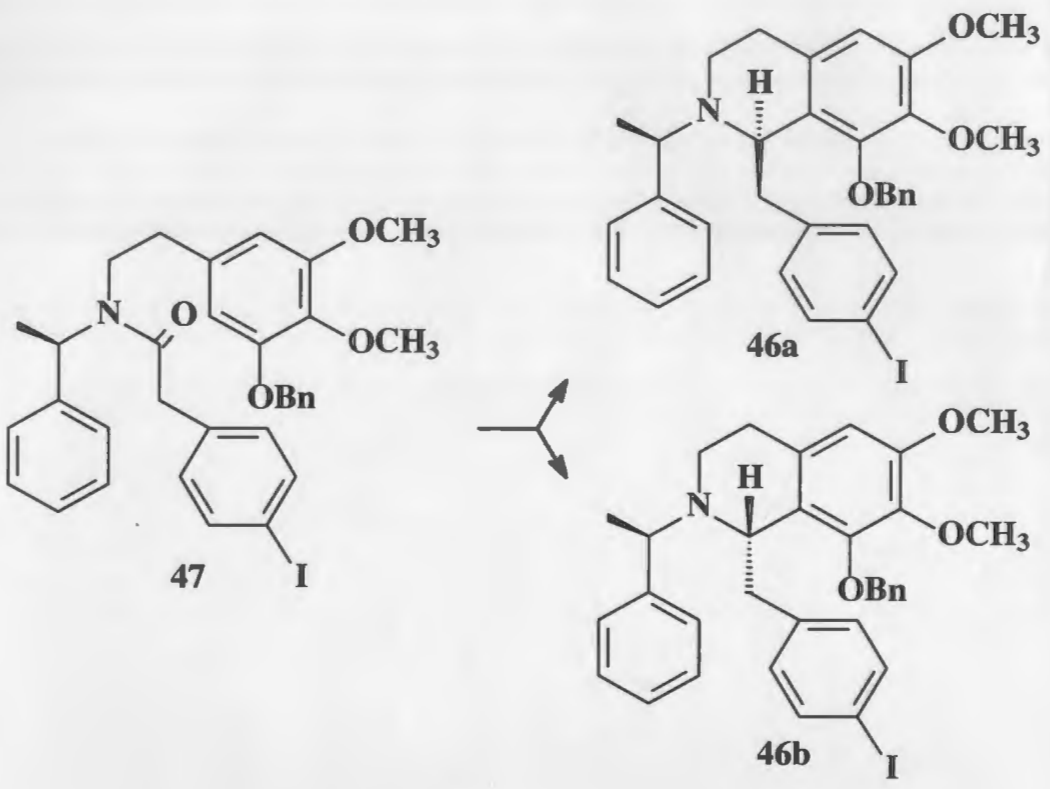
Scheme 1.5

A strategy similar to the above example was developed by Cui and Georghiou when they attempted the synthesis of (-)-cycleanine. In Cui's work, the important intermediate **46a** was prepared from compound **47** by BNC using (*R*)-α-methylbenzyl-amine as a chiral auxiliary. After obtaining an X-ray crystal structure for **46a**, they were

able to verify that the configuration of the asymmetric carbon center in **46a** was correct (Scheme 1.7 and Figure 1.5).[7]



Scheme 1.6



Scheme 1.7

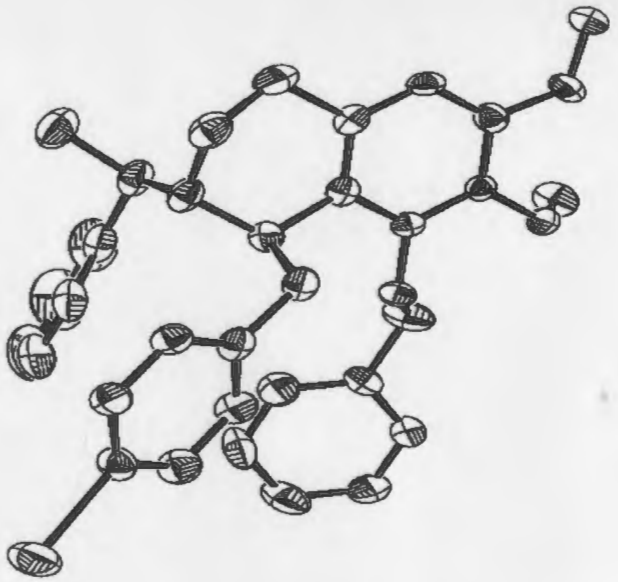
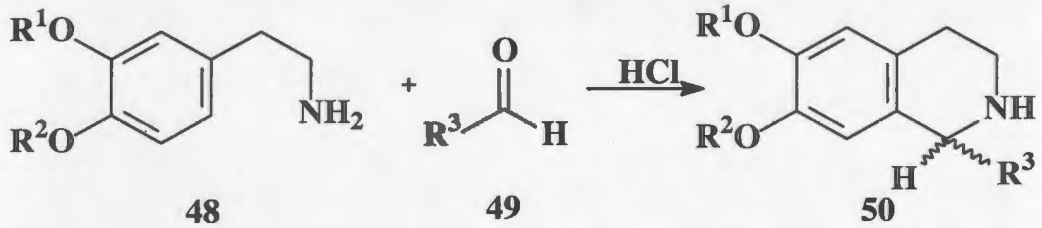


Figure 1.5 The X-ray structure of **46a**[7]

PSC is also a frequently employed way to construct isoquinolines. It involves the condensation of β-arylethylamines, e.g. **48**, with aldehydes, e.g. **49**. In this method the stereogenic center at C_1 is generated during the ring closure in a one-pot process (Scheme 1.8).[60]

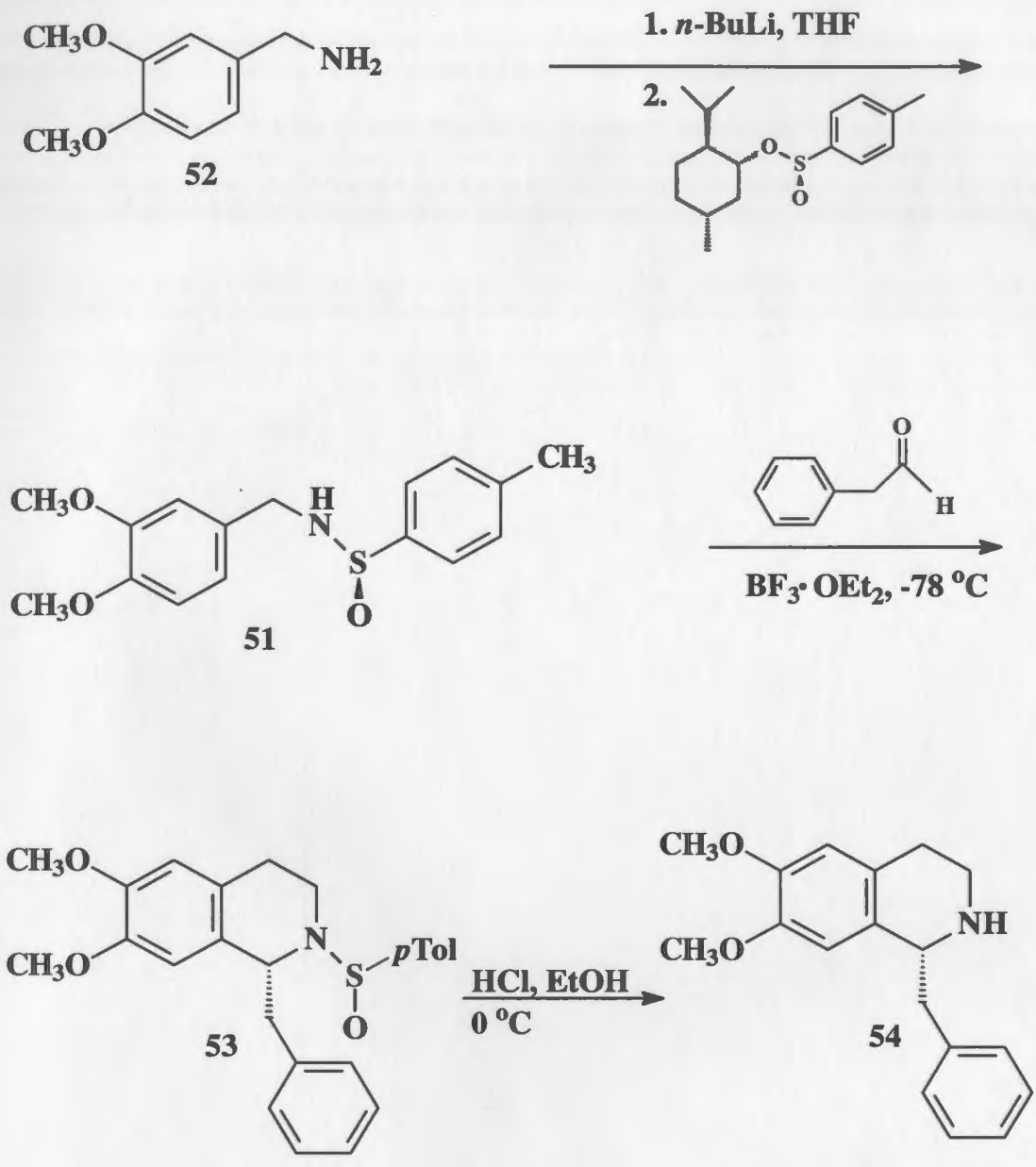


48 **49** **50**

Scheme 1.8

There are several advantages to the use of PSC to construct the framework of isoquinolines, such as the use of milder reaction conditions and the lack of a requirement for a reduction step. Recently, several synthetic methodologies have been developed to control the stereoselectivity of the PSC reaction. In order to effect this, the reaction was usually carried out in an asymmetric manner. The chirality transfer occurred from a chiral auxiliary introduced in either the β-arylethylamine **48** or the aldehyde **49** component, thus involving a stereoselective synthesis.

An example of a stereoselective synthesis of an isoquinoline by PSC has been reported by Gremmen et al. (Scheme 1.9).[61]In this report, *N*-*p*-tolylsulfinylphenylethyl amine **51** was obtained by first treatment of the phenylethylamine **52** with *n*-butyl-lithium and then with a commercially available Andersen reagent, (1*R*,2*S*,5*R*)-menthyl-(*S*)-*p*-toluenesulfinate in 86% yield. A PSC between **51** and

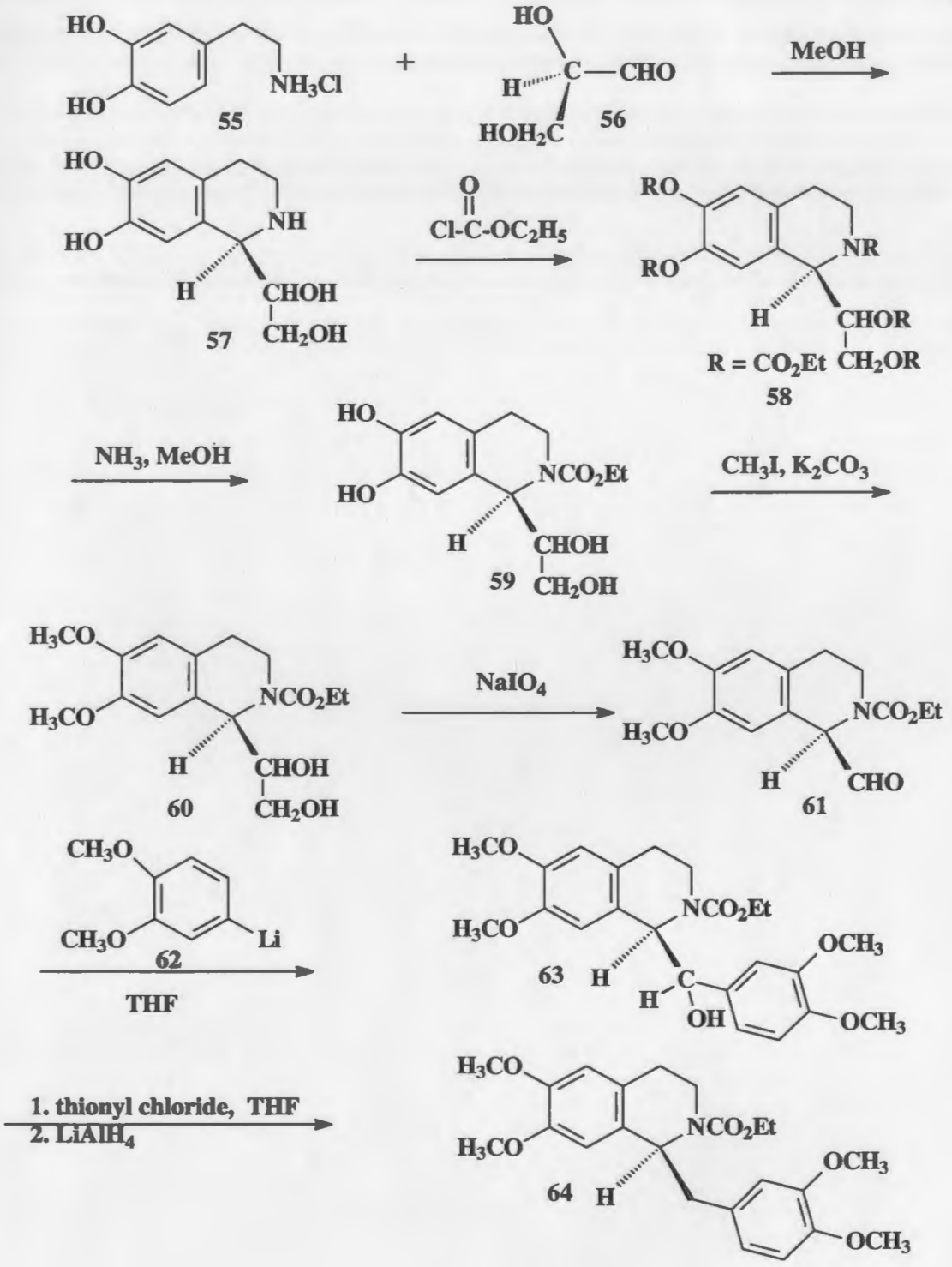


Scheme 1.9

phenylacetaldehyde afforded **53** in 38% yield with excellent diastereopurity. Removal of the chiral auxiliary proceeded without racemization by treatment with HCl in ethanol, at 0 °C, and gave **54** in 90% yield with a 98% ee.

Another interesting example of stereoselective PSC uses a chiral aldehyde to control the formation of the asymmetric carbon center (Scheme 1.10). The PSC between **55** and **56** in boiling MeOH gave **57** in a yield of approximately 80%. Treatment of **57** with an excess of ethyl chloroformate afforded **58** (56%). Subjecting **58** to methanolic ammonia removed both carbonic ester functions, and afforded **59** in a yield of 93%. Methylation of **59** at the phenolic hydroxyls with iodomethane in the presence of K_2CO_3 gave **60** in 86% yield. Aldehyde **61** was obtained through oxidation of **60** with sodium periodate (93%). Treatment **61** with **62** in THF gave **63** in 64% yield. Finally, treating **63** first with $SOCl_2$, and then with $LiAlH_4$, in an one-pot reaction afforded the benzyltetrahydroisoquinoline **64** in 88% yield.[62]

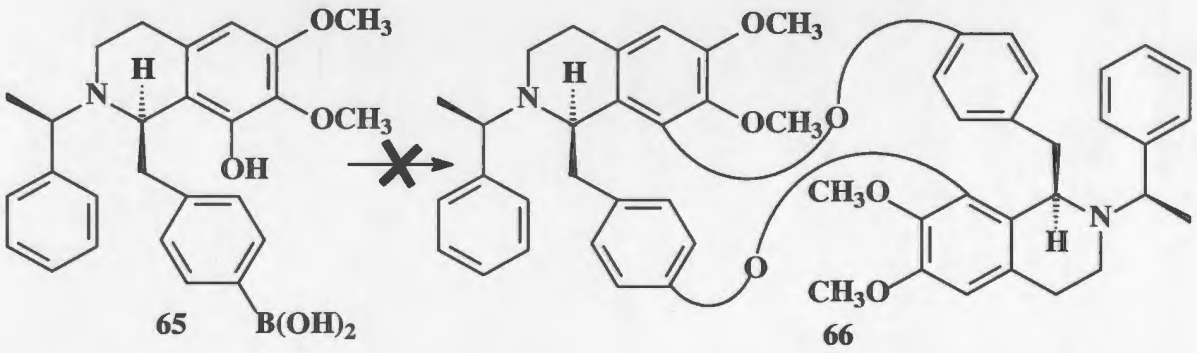
Unfortunately, due to the unsuccessful attempts to obtain the necessary precursor for the cyclization, the application of PSC methodology in an earlier effort for the synthesis of cycleanine by M. Ralph in the Georghiou laboratory was abandoned.[63] As a result, only BNC was selected as the strategy to build the benzylisoquinoline subunits for the final target molecule cycleanine in this thesis.


HO
HO
NH3Cl
55
+
HO
H
C
CHO
HOH2C
56
MeOH
HO
HO
NH
H
CHOH
CH2OH
57
O
Cl-C-OC2H5
RO
RO
NR
H
CHOR
R = CO2Et CH2OR
58
NH3, MeOH
HO
HO
NCO2Et
H
CHOH
CH2OH
59
CH3I, K2CO3
H3CO
H3CO
NCO2Et
H
CHOH
CH2OH
60
NaIO4
H3CO
H3CO
NCO2Et
H
CHO
61
CH3O
CH3O
Li
62
THF
H3CO
H3CO
NCO2Et
63
H
C
H
OH
OCH3
OCH3
1. thionyl chloride, THF
2. LiAlH4
H3CO
H3CO
NCO2Et
64
H
OCH3
OCH3

Scheme 1.10

1.6 Recent developments in the formation of Diaryl ethers

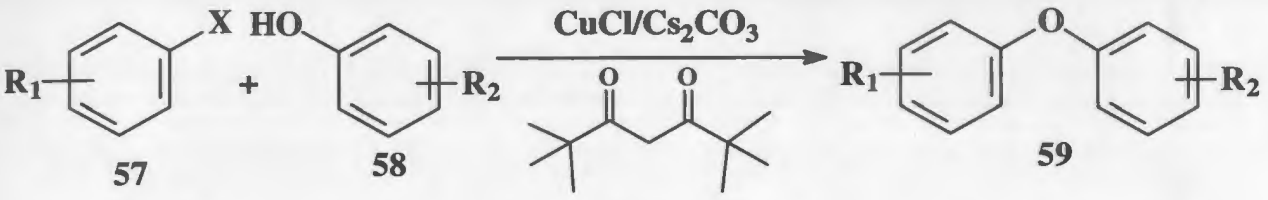
A mild $Cu(OAc)_2$-mediated diaryl ether coupling methodology recently reported by Evans[47] and Chan[48] was successfully used by Wang and Georghiou in their enantioselective total synthesis of (-)-tejedine.[46] This methodology for the diaryl ether cross coupling employs $Cu(OAc)_2$ in the presence of triethylamine at room temperature. Cui also employed this method to build the diaryl ether bonds in his attempts to synthesize cycleanine. However, when he used the correct regioisomer **65** for the homocoupling reaction for constructing the macrocyclic dimer **66**, he reported that the reaction failed to produce the desired product (Scheme 1.11).[7] Therefore, the focus of the research described in this thesis was on the use of alternative methods.



Scheme 1.11

In 2002, an improved version of Ullmann coupling was reported by Buck et al.[64] In this report, 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) was found to accelerate greatly the normally difficult Ullmann coupling reaction, and allowing it occur at more moderate temperatures. In the presence of TMHD, aryl halides **67** and phenols **68** were

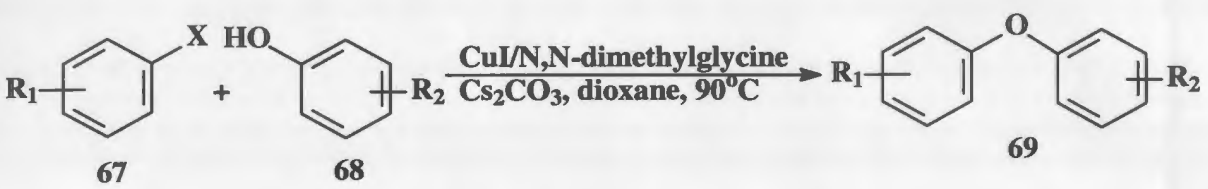
shown to form ethers **69** in NMP with cesium carbonate as base and CuCl as the catalyst (Scheme 1.12).



Scheme 1.12

The reaction was also shown to tolerate electron-rich aryl bromides and electron-neutral or poor phenols. This represents a significant improvement over the classical conditions, which generally do not work with aryl halides with strong electron-donating groups and phenols with electron-withdrawing groups. As a general procedure, the aryl halide, the phenol, TMHD, and cesium carbonate were added to anhydrous NMP. To this mixture was added CuCl. This mixture was then heated under nitrogen to 120 °C. After completion of the reaction, the reaction mixture was diluted with MTBE and filtered. The filtrate was washed with aqueous acid, followed by base, and then the desired product was isolated by column chromatography, or by direct crystallization. According to the authors, the formation of a complex involving the Cu(I), diketone as well as the phenolate presumably accelerated the rate-determining step.[64]

In 2004, a similarly interesting development in Ullmann coupling methodology was reported by Ma et al.[65] In this report, the diaryl ether syntheses were performed at even lower temperature by using either aryl iodides or aryl bromides as the substrates with phenols in the presence of *N,N*-dimethylglycine (Scheme 1.13).

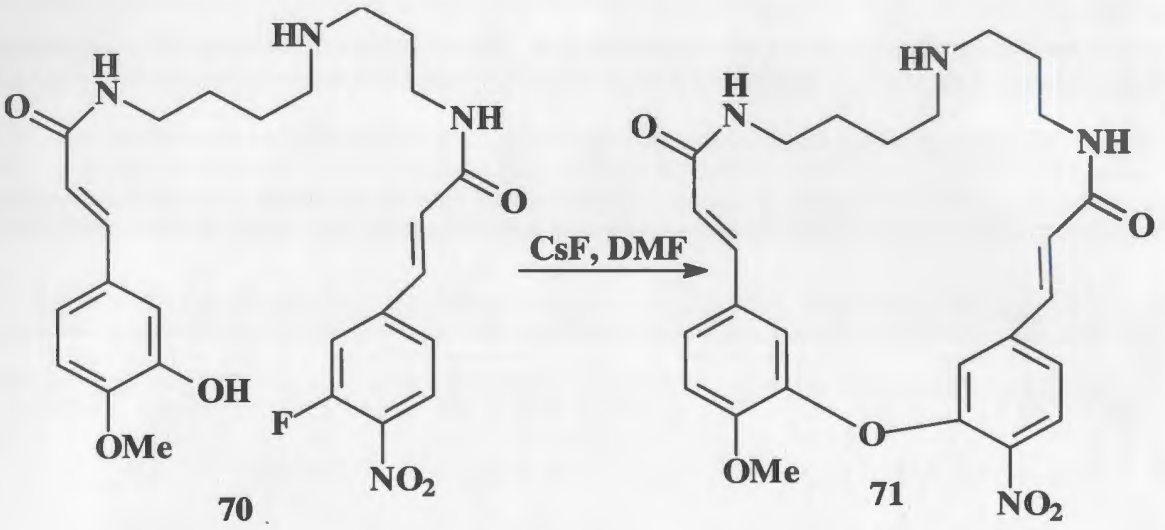


Scheme 1.13

In this methodology, aryl iodides or aryl bromides with different substituents such as alkoxy, amino, fluoro, nitro, carbonyl or cyano groups, can tolerate the reaction conditions. As a result, this method potentially can also be employed for the synthesis of more complex diaryl ethers such as those are found in some natural products.

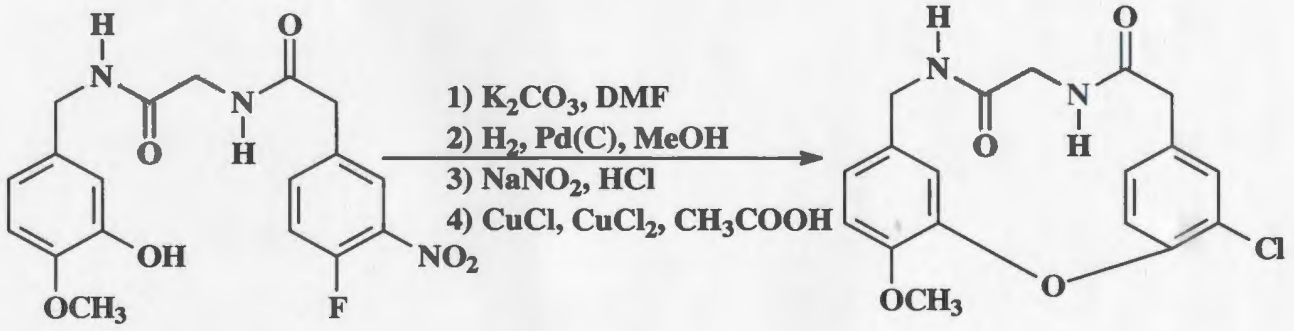
In addition to the methods above, which are simple variations on the classic Ullmann coupling, another very interesting method for diaryl ether synthesis is the use of a S_NAr reaction.

An example from the Carrington group illustrates the nature of this kind of S_NAr reaction for forming diaryl ether bonds.[66] In this example, compound **70** was successfully cyclized in relative high yield to the macrocycle **71**, an intermediate for the synthesis of the naturally occurring 23-membered polyamine lactam alkaloid cadabicine (Scheme 1.14).



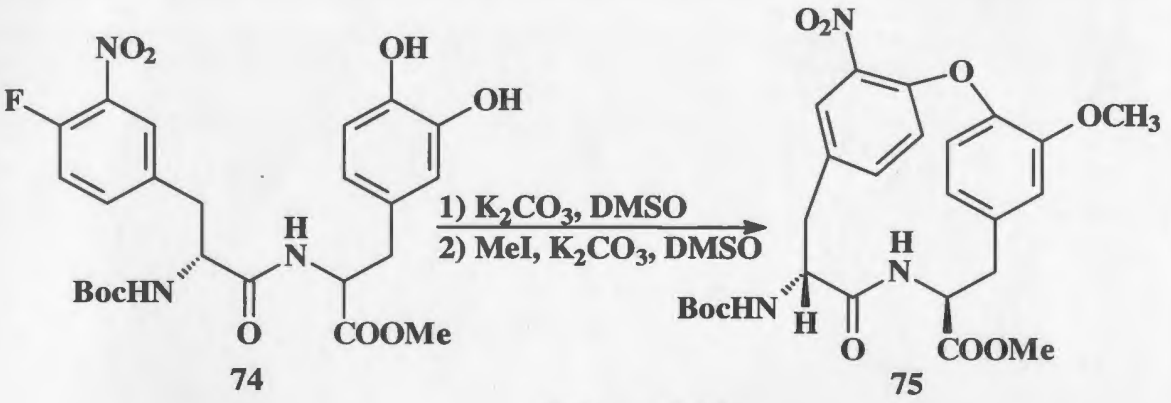
Scheme 1.14

Using a similar strategy, compound **72** was cyclized to a mixture of atropisomers that was subsequently reduced via two further operations to the 15-membered macrocycle **73**, which was an important intermediate for the synthesis of the antiviral/antibacterial agents, kistamicins A and B (Scheme 1.15).[67]

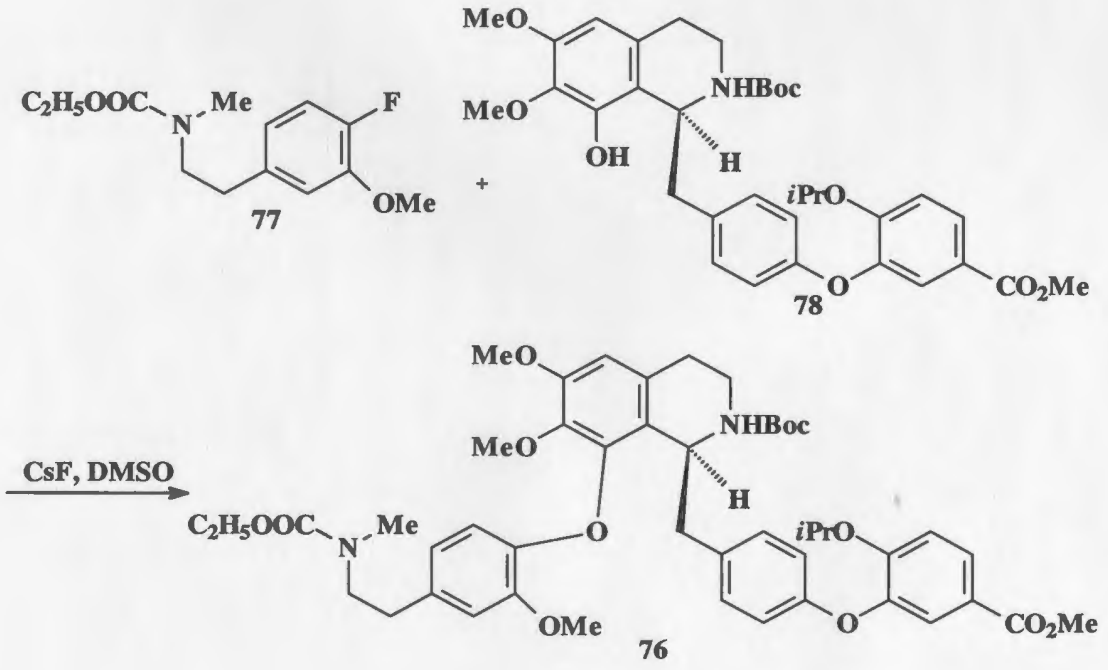


Scheme 1.15

Recently, Zhu et al. have used K_2CO_3 as the base, to convert compound **74** to **75** in 45% yield over two steps when they attempted to synthesize RA-VII, a natural product with potent antitumor activity (Scheme 1.16).[68]



Scheme 1.16



Scheme 1.17

In their synthesis of (-)-tejedine, Wang and Georghiou prepared the important intermediate compound **76** by a base-mediated S_NAr reaction between compound **77** and **78** (Scheme 1.17).[46]

From all of the examples described above, it is easy to realize that the use of either improved Ullmann coupling methodologies or S_NAr-based reactions are potential ways to construct the biaryl ether bonds in the target molecule cycleanine. The use of both of these approaches will be discussed in this thesis.

Chapter 2

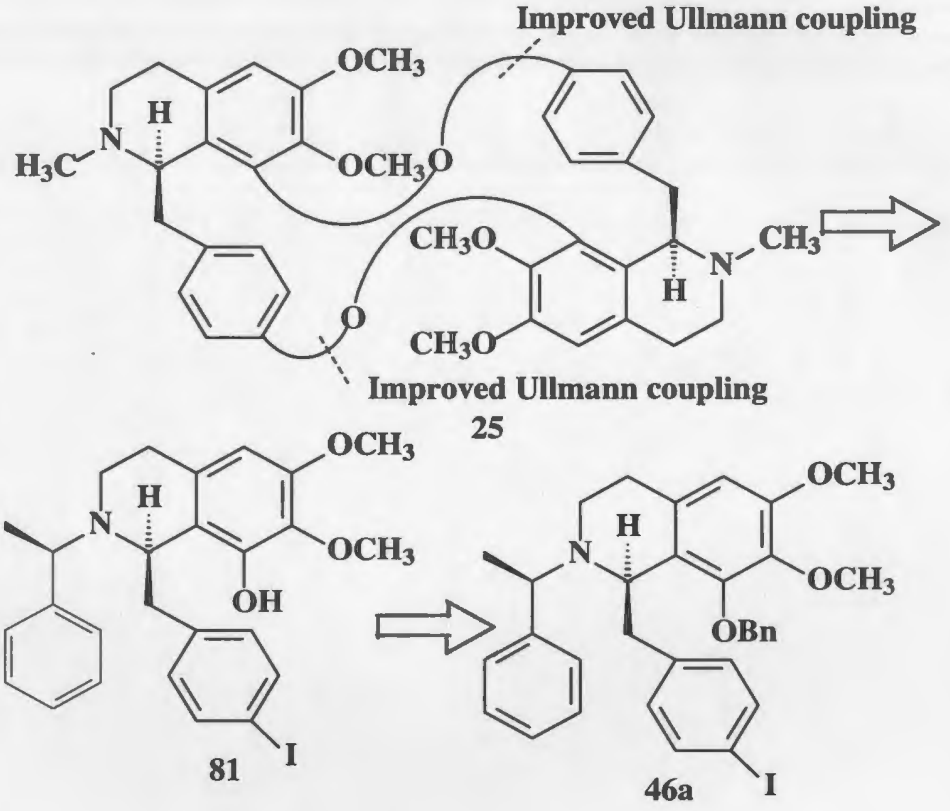
Synthesis of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (79) and 4-iodophenylacetic acid (80)

2.1 Introduction

In chapter 1 were outlined a brief description of cycleanine, endeavors previously reported toward its synthesis, and a brief review of some recently developed methodologies with potential application for its synthesis. In this chapter and the next the synthetic efforts toward cycleanine conducted by this author will be described. From Chapter 1 we have noted that usually there are two key steps for preparing BBIQ alkaloids such as cycleanine: (i) the stereoselective tetrahydroisoquinoline ring formation, and (ii) the efficient formation of diaryl ether linkages. One of these two problems had previously been resolved by Georghiou's group: the tetrahydroisoquinoline subunit needed for cycleanine had been synthesized with well-controlled stereoselectivity as shown in their synthesis of tejedine.

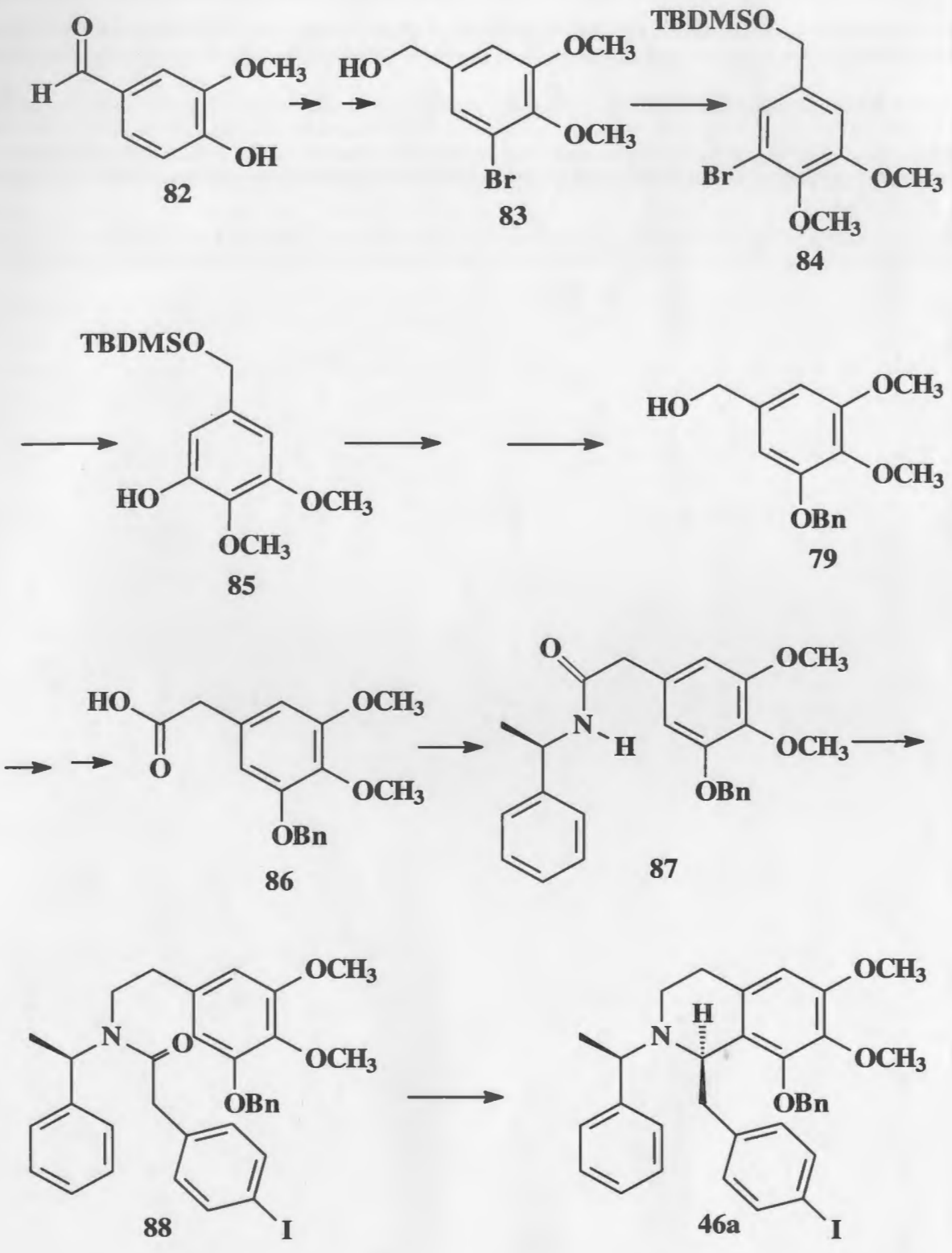
The remaining task was to find a suitable method to construct the diaryl ether linkages. The improved Ullmann coupling reactions or a S_NAr reaction are potential methodologies which could be used for the formation of diaryl ether linkages in cycleanine. As a result of all of these considerations, an initial retrosynthetic analysis for (-)-cycleanine using improved Ullmannn coupling was considered (Scheme 2.1). If such a coupling methodology were employed, the correct precursor for (-) cycleanine should be **81,** in which both halide and phenolic hydroxy groups are present. Compound **81**

should be readily derived from **46a**, which had been synthesized previously in the Georghiou laboratory by using vanillin as a starting material.



Scheme 2.1

Outlined in Scheme 2.2 is the strategy employed in the synthesis of **46a** by Cui.[7] Vanillin (**82**) was first converted to compound **83** by bromination and reduction. Then in order to obtain compound **79**, the hydroxy group on **83** was protected as the *tert*-butyldimethylsilyl (TBDMS) ether to give **84**. After **84**was converted to the phenol **85**, the TBDMS group was removed to afford the benzyl ether **79**. After several more steps, the arylacetic acid **86** was obtained. After this, the chiral auxiliary group was introduced into **86** via the corresponding acid chloride to form compound **87**. Amide **88** was


O
H
OCH3
OH
82
HO
OCH3
OCH3
Br
83
TBDMSO
Br
OCH3
OCH3
84
TBDMSO
HO
OCH3
OCH3
85
HO
OCH3
OCH3
OBn
79
HO
O
OCH3
OCH3
OBn
86
O
N
H
OCH3
OCH3
OBn
87
N
O
OCH3
OCH3
OBn
88
I
N
H
OCH3
OCH3
OBn
46a
I

Scheme 2.2

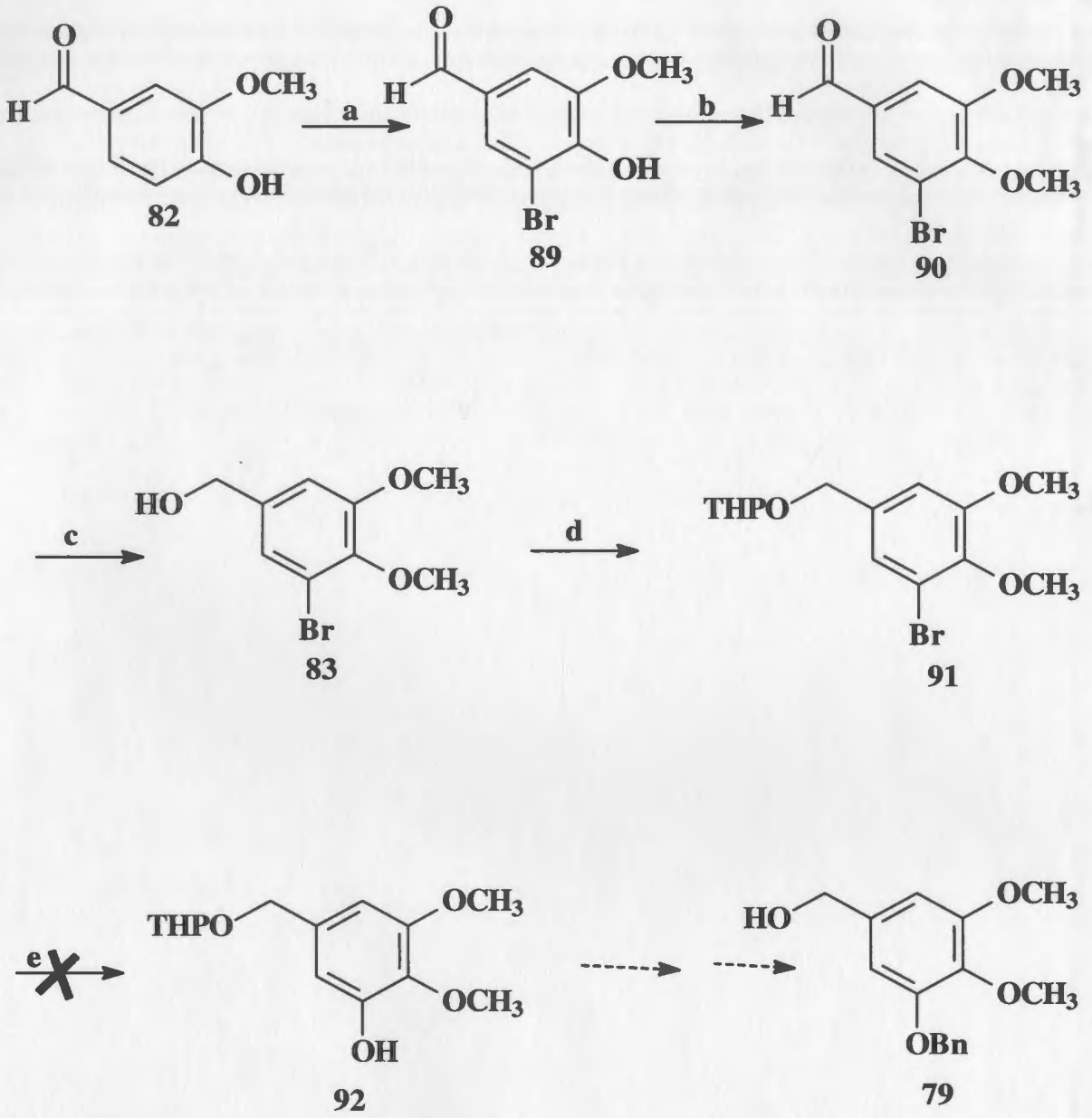
synthesized from **87** first by reducing the amide group with BH_3 followed by a Schotten-Baumann reaction. Compound **88** was the precursor for the required BNC, which provided **46a**. However, re-evaluation of this work for the current research revealed two drawbacks: (1) An additional protection step for forming **84** was used, and the protecting reagent, TBDMSCl, is expensive; and (2) an indirect bromine-hydroxyl exchange from compound **84** to form **85** needed to be accomplished by a lithiation-boronation sequence which was also demanding and expensive. Of course, if they were involved for only a short synthetic route, these problems would not necessarily be serious. But for the synthesis of a complex compound such as cycleanine, they cannot be ignored. In the previous synthetic effort by Cui, the failure to complete the synthesis of cycleanine can also be attributed in part to a failure to resolve these two problems. This previous effort was already very close to the final target molecule, but since there were insufficient amounts of the precursors to allow a systematic investigation of the key birayl ether formation step, the ultimate target was not eventually obtained. Since cycleanine demonstrates various pharmacological activities, there is the potential that this compound may be of pharmaceutical interest. This also makes it meaningful to establish a relatively cheap and concise process for producing the required starting materials and the intermediates. It is because of all of these reasons that the major focus of this chapter is mainly given to the synthesis of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**79**), a simple-looking, but very important, intermediate that is essential for the total synthesis of cycleanine.

2.2 Results and discussion

2.2.1 Synthesis of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (79)

2.2.1.1 First attempt using THP-protected vanillin as starting material

The first attempted improvement for the synthesis of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**79**) was tried by using a less expensive protecting group for the phenolic hydroxy group instead of the more expensive TDMSCl. The main consideration for choosing a protecting group is that it should withstand the subsequent reaction conditions, it should not interfere with other substituents on this molecule, and it should be easily removed at a later stage.[69] Based on these considerations and also on our previous experience, a synthetic pathway toward compound **79** employing THP as protecting group, as outlined in Scheme 2.3, was first employed. Bromination of vanillin produced the desired 5-bromovanillin (**89**) in 95% yield, under the *ortho*-directing effect of the hydroxy group on vanillin (**82**). Compound **90** was produced by methylation of **89** (99%). Reduction of the aldehyde moiety of **90** with $NaBH_4$ gave the 5-bromo-3,4-dimethoxybenzyl alcohol (**83**) in a yield of 99%. At this stage, the hydroxy group was protected as the THP ether **91** in a very high yield (96%) by the reaction of **83** with DHP using PPTS as the catalyst. The key step of converting the bromo group to a phenolic hydroxy group by a lithiation-boronation-oxidation sequence was then conducted. However, when the same procedure, which was used by Cui, was employed with THP-protected **91,** the desired compound **92** was not obtained, but most of the starting material was recovered.

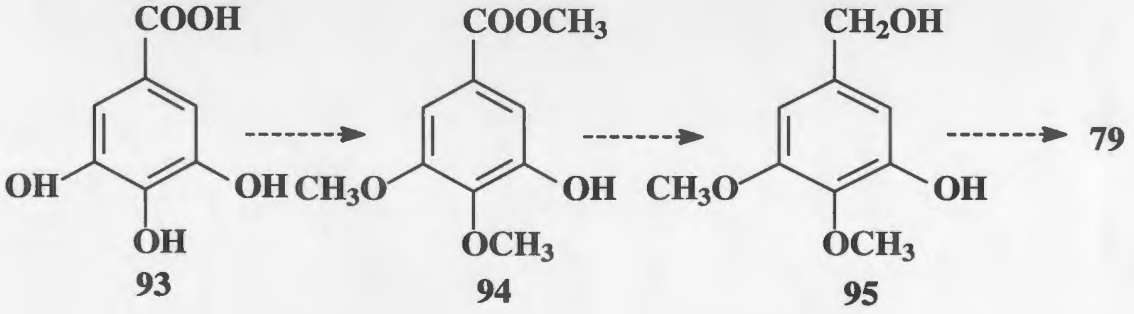


Conditions: a) Br_2, AcOH, 95%; b) Me_2SO_4, NaOH, H_2O, CH_2Cl_2, Adogen 464®, 99%; c) $NaBH_4$, MeOH, THF, 99%; d) DHP, PPTS, CH_2Cl_2, 96%; e) n-butyllithium, $B(OCH_3)_3$, H_2O_2.

Scheme 2.3

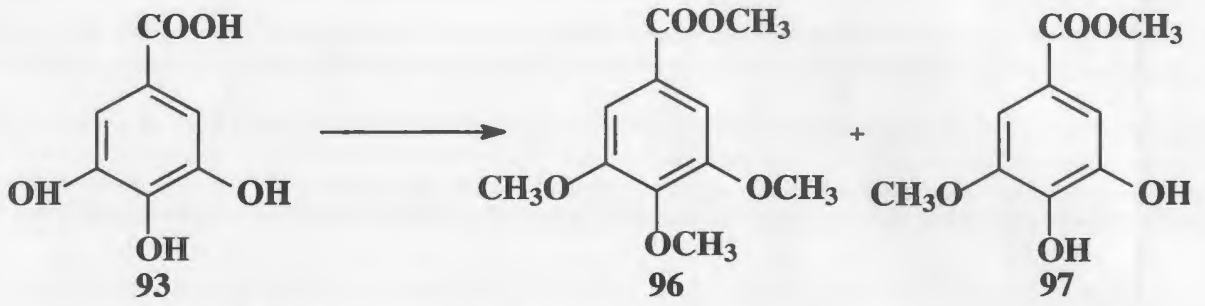
2.2.1.2 Attempted synthesis of 79 using gallic acid as the starting material

As a result of the unsuccessful attempt at using THP as a protecting group to form **92**, the second approach for the synthesis of 5-benzoxy-3,4-dimethoxybenzyl alcohol (**79**) was attempted. This time gallic acid (**93**) was selected as a starting material (Scheme 2.4). The planned approach was that gallic acid could be selectively methylated to form compound **94**. If **94** could be obtained, then treating it with a suitable reducing reagent should easily afford compound **95**. Although there are two hydroxy groups in **95**, it should be easy to convert it to 5-benzoxy-3,4-dimethoxybenzyl alcohol (**79**) by a selective benzylation due to the more acidic character of the phenolic hydroxy than that of the alcoholic hydroxy group.



Schenme 2.4

However, it was found that after gallic acid (**93**) was treated with dimethyl sulfate in a mixture of CH_2Cl_2 and aqueous NaOH containing phase-transfer catalyst, Adogen®, methyl 3,4,5-trimethoxybenzoate (**96**) and methyl 3,4-dihydroxy-5-methoxybenzoate (**97**) were both obtained in yields of only 14% (Scheme 2.5).

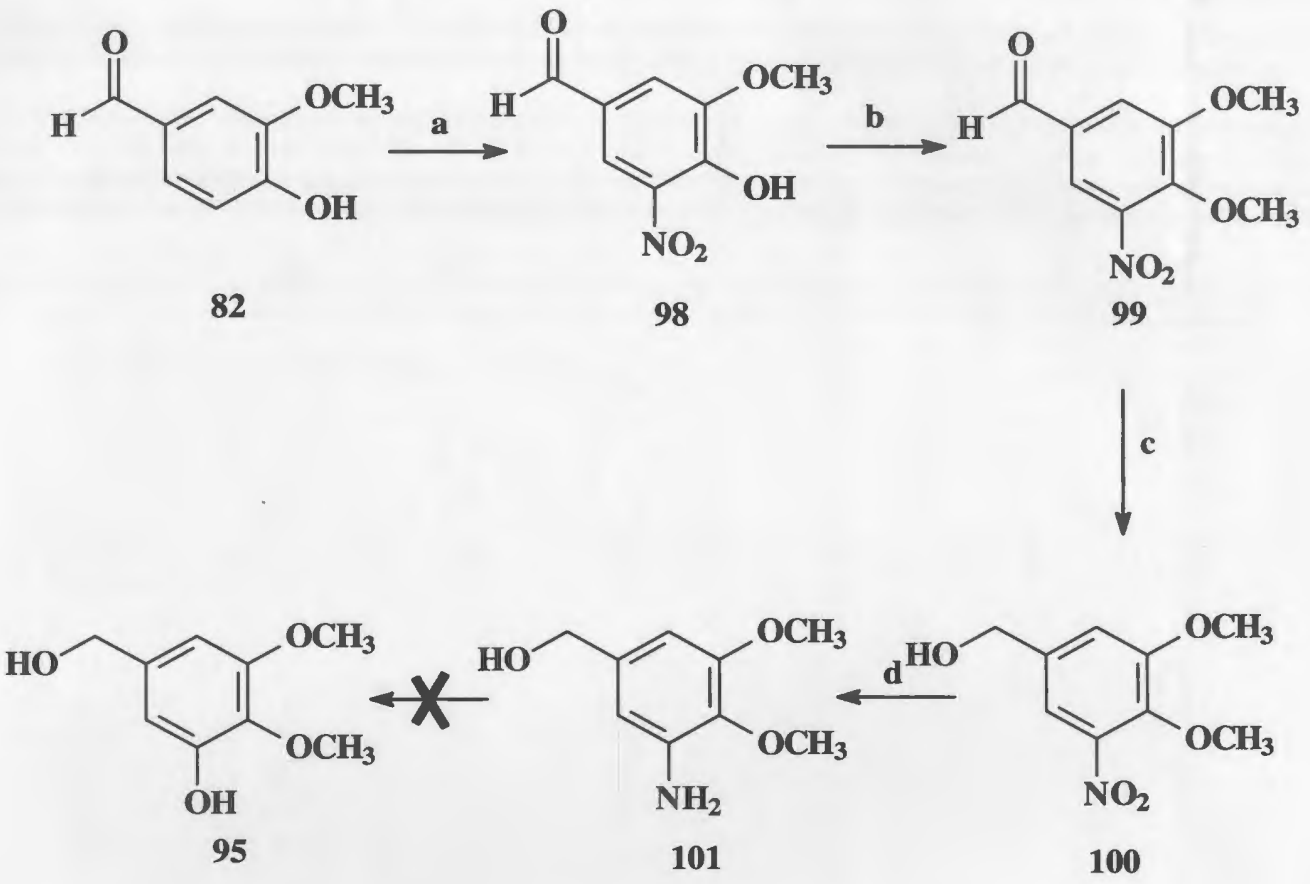


Conditions: $(CH_3)_2SO_4$, H_2O, CH_2Cl_2, NaOH, Adogen®, yield 14 % of **96** and 14 % of **97**.

Scheme 2.5

2.2.1.3 Diazotization approach using vanillin (67) as the starting material

The third approach examined for the synthesis of **79** is outlined in Sheme 2.6. In this approach vanillin (**82**) was employed once again as the starting material, but the key step of introducing the hydroxy group was planned by using a diazotization reaction sequence. Thus, subjecting vanillin (**82**) with fuming HNO_3 in glacial acetic acid afforded compound **98** (76%). Following the method of Sato et al.,[70] methylation of the potassium salt of **98** with dimethyl sulfate produced 3,4-dimethoxy-5-nitrobenzaldehyde (**99**) in a yield of 91%. It was expected that a direct reduction of the nitro group followed by a diazotization reaction would introduce the hydroxyl group onto the aromatic ring. However, considering the aldehyde moiety in **99** would not survive the relatively harsh diazotization reaction conditions, **99** was first converted to **100** and then to 5-amino-3,4-dimethoxybenzyl alcohol (**101**) by two successive reduction steps in 85% and 75% yields, respectively. With compound **101** in hand, the diazotization reaction was conducted. However when **101** was treated with HNO_2 in an acidic medium, a product was produced which could not be analyzed by either NMR or GC-MS. The failure of this



Conditions: a) HNO_3, AcOH, 76%; b) $(MeO)_2SO_4$, xylene, 91%; c) $NaBH_4$, THF, 85%; d) H_2, Pd/C, 75%; e) $NaNO_2$, H_2SO_4

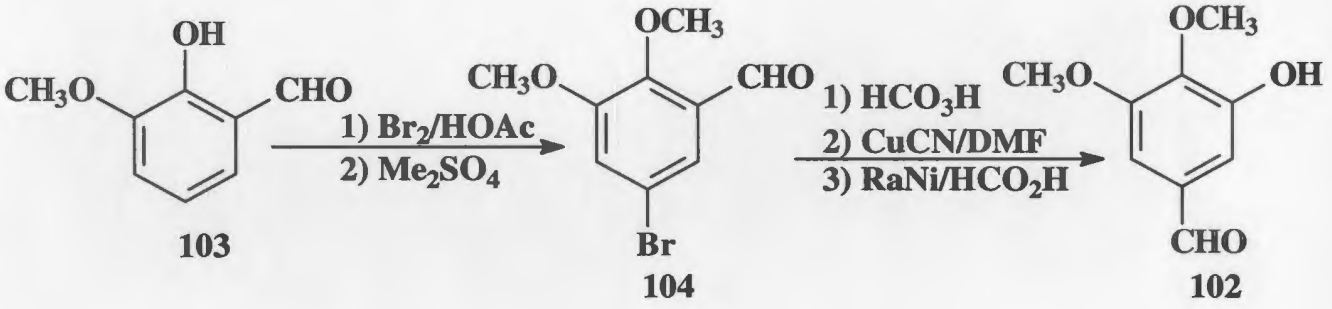
Scheme 2.6

reaction to afford the desired **95** is most probably due to the fact that the primary alcohol group was not protected. No protecting groups, however, were examined.

2.2.1.4 Some literature reports concerning the introduction of a hydroxyl group onto an aromatic ring

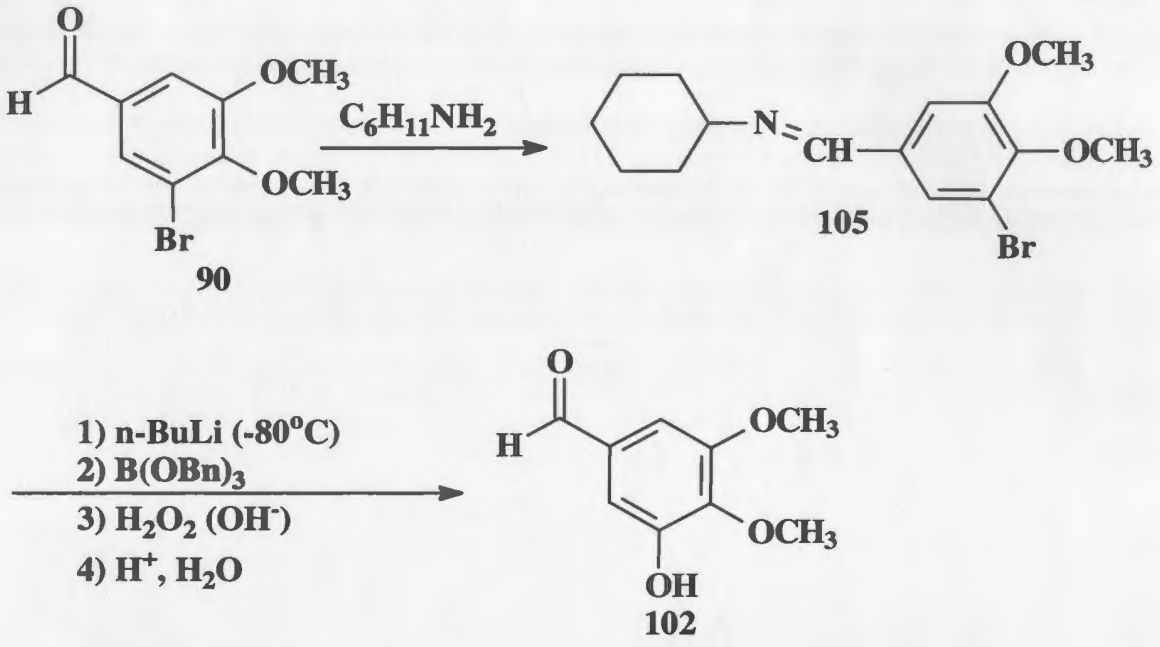
Because all attempts failed to afford **79**, an extensive review of the relevant literature was undertaken to find a more practical methodology for the synthesis of **79**. In 1983, Linuma *et al* had described an indirect route to introduce a hydroxy group onto a aromatic ring.[71] In their route, 3,4-dimethoxy-5-hydroxy-benzaldehyde (**102**) was

prepared by using *o*-vanillin (**103**) as starting material. The process involved five steps, with an overall yield of approximately 20% (Scheme 2.7). The key reactions in this route are a Baeyer-Villiger reacton with peroxyformic acid, followed by a Rosenmund-Von Braun cyanation with cuprous cyanide at 200°C. The interesting aspect of this example is that the final product **102** is the direct precursor of our desired compound **79**. The above reaction sequence, however, was deemed undesirable due to the low overall yields obtained and harsh reaction conditions.



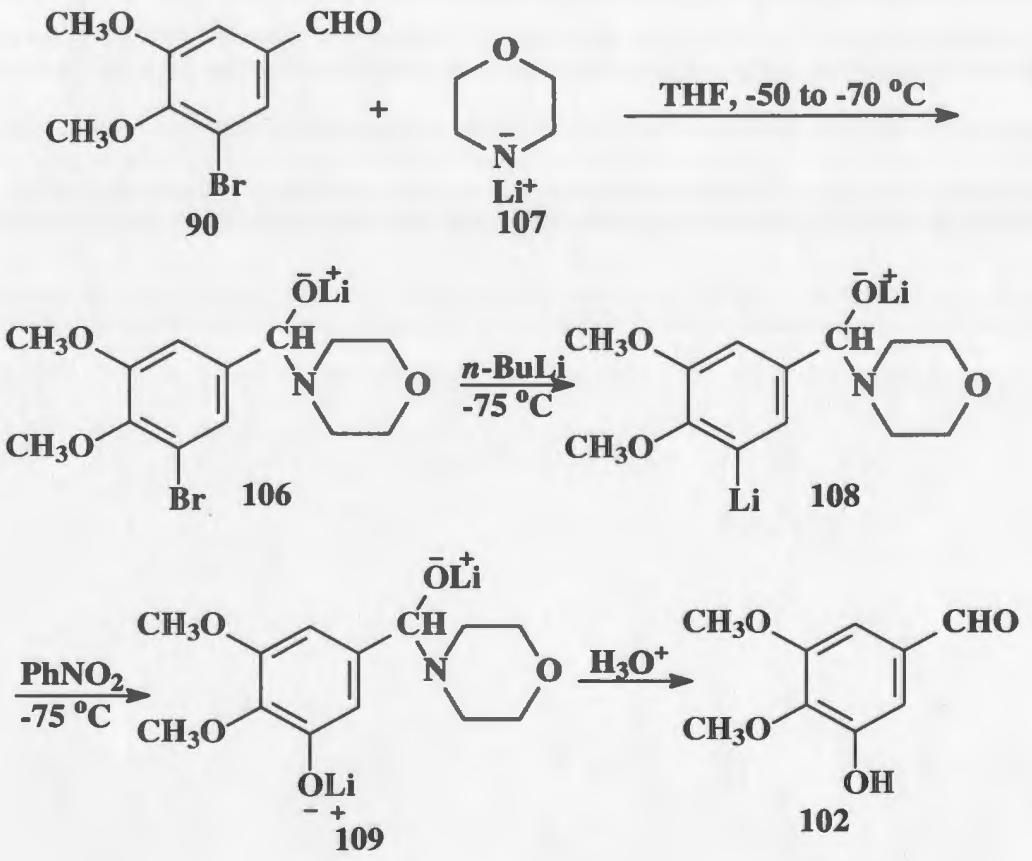
Scheme 2.7

A synthesis of hydroxybenzaldehyde **102** from bromobenzaldehyde **90** via lithiated Schiff's bases had been reported by Jacob and Shulgin when they attempted the synthesis of 5-hydroxypiperonal and related compounds (Scheme 2.8).[72] In their report, a procedure for the replacement of a bromine with a hydroxyl group in the readily available bromobenzaldehyde **90** was successfully performed using the Schiff's base, **105**, to protect the aldehyde group.



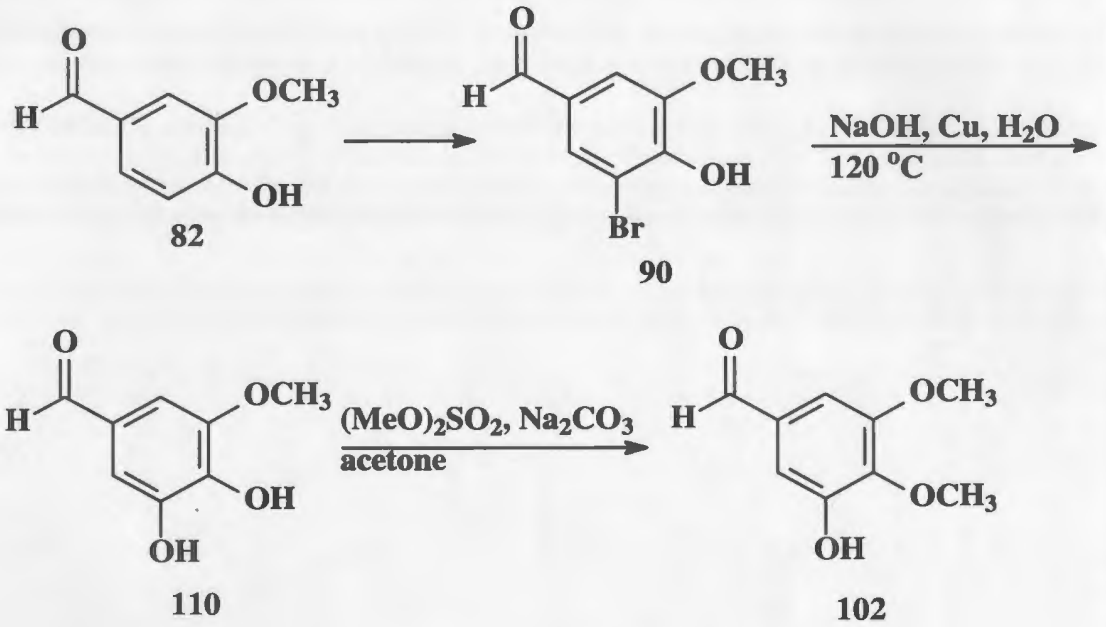
Scheme 2.8

In a similar report, **102** was synthesized from bromobenzaldehyde **90** via the reaction of *in situ*-generated, lithiated α-morpholinobenzyl alkoxide **106** with nitrobenzene.[73] The detailed process is outlined in Scheme 2.9. The aldehyde functional group of **90** was protected *in situ* by reacting **90** at –50 °C with lithium morpholide **107** to give **106**. The lithiated morpholinoalkoxide **108** was generated by reacting **106** with *n*-BuLi at –75 °C. Reaction of **108** with nitrobenzene for 4 h at –75 °C first gave **109** followed by an acidic workup to furnish the desired **102** in 55% yield.



Scheme 2.9

In each of these methodologies an inexpensive method was employed for protection the aldehyde group which otherwise would have affected the lithium-halogen exchange step. However, both methods outlined above employed a lithiation, boronation and peroxidation process which is difficult to conduct on large scale. Fortunately, this problem was resolved very well by the report of a procedure by Ellis and Lenger for a synthesis of **102**.[74] The actual process also included a step of converting a bromo group to a hydroxy group, but here the change was accomplished by a direct hydrolysis, by treating **90** with an aqueous solution of NaOH in the presence of three mole % of copper powder, at refluxing temperature. This process produced **110** in 70%



Scheme 2.10

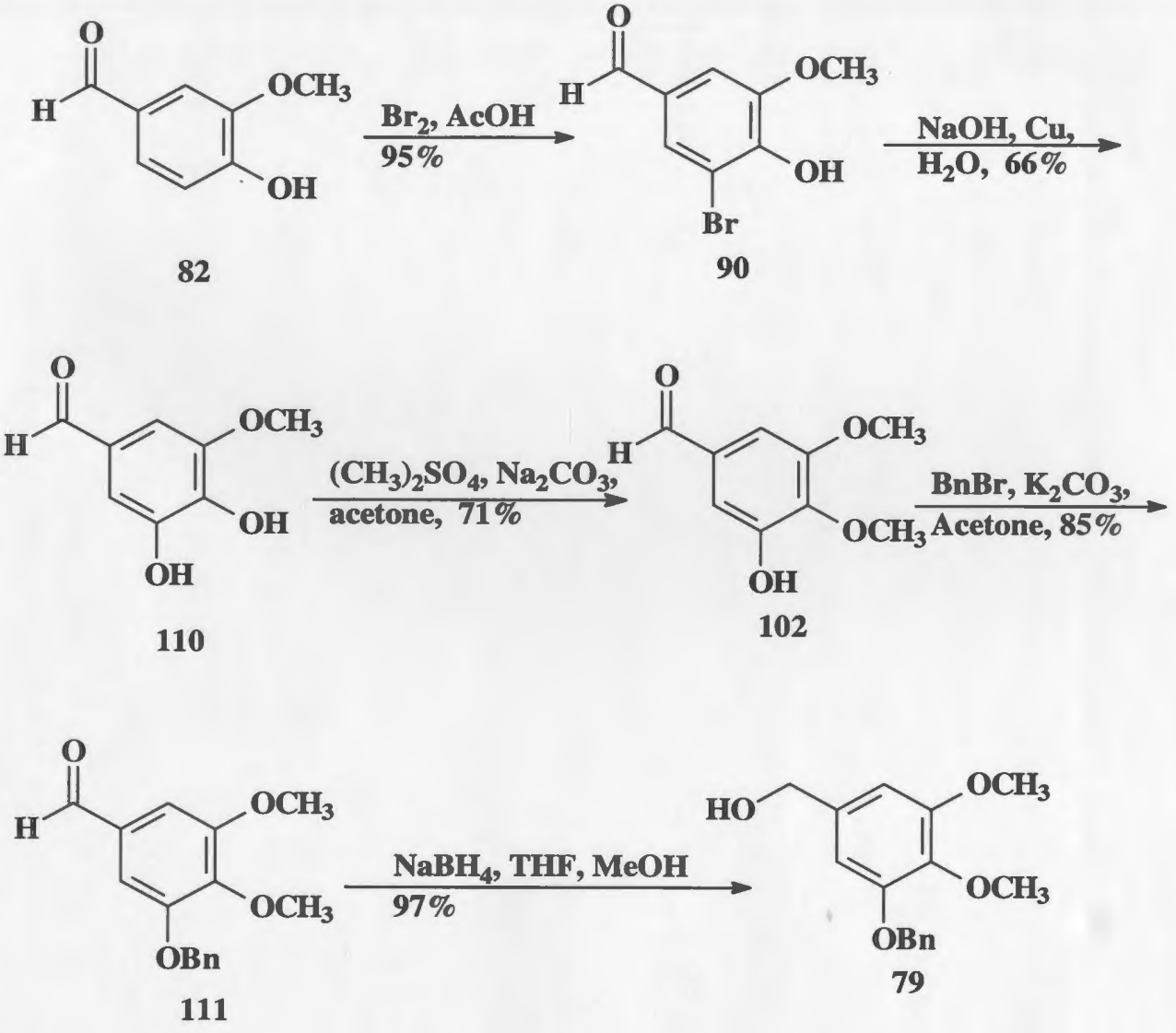
yield. After this, compound **110** was converted to **102** by a selective methylation (Scheme 2.10).

Obviously, the step of changing 5-bromovanillin (**90**) to 5-hydroxyvanillin (**102**) by hydrolysis using this methodology is a great advance over all prior reports. It is very economical and also extremely practical for large-scale synthesis due to the minimum of manipulative steps.

2.2.1.5 Methodology eventually adopted for synthesizing 3-benzyloxy-4,5-dimethoxybenzyl alcohol (79)

With all the above reports in mind, and also based on the previous work in our laboratory, an economical and practical synthetic pathway to **79** was eventually designed. Scheme 2.11 is the route employed. Compound **90** was obtained as previously described. Treating **90** by employing the methodology of Ellis indeed gave the desired precursor compound **110** in the reported yield of 66%. Selective methylation of **110**

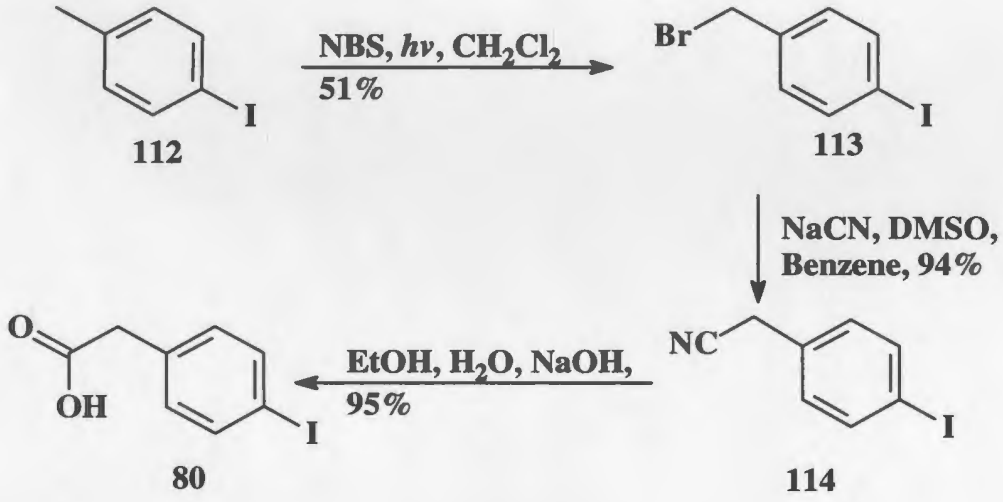
produced compound **102** in an acceptable yield. Reaction of **102** with benzyl bromide in the presence of potassium carbonate produced 3-benzyloxy-4,5-dimethoxybenzaldehyde (**111**) in 85% yield. The desired 3-benzyloxy-4,5- dimethoxybenzyl alcohol (**79**) was obtained in 97% yield by reduction of **111** with $NaBH_4$.



Scheme 2.11

2.2.2 Synthesis of 4-iodophenylacetic acid (65)

Although the synthesis of **79** had required much of the research effort that is described in this thesis, the synthesis of 4-iodophenylacetic acid (**80**) was accomplished in a relatively smooth way with a small modification of the methodology developed by Cui and Georghiou (Scheme 2.12).[7] Using 4-iodotoluene (**112**) as starting material, **113** was produced by utilizing a radical reaction with NBS as the bromination reagent (51%). Treating **113** with NaCN in DMSO resulted in the formation of 4-iodophenylacetonitrile (**114**) in a 94% yield. The desired 4-iodophenylacetic acid (**80**) was then obtained in a 95% yield by base-mediated hydrolysis of **114**.



Scheme 2.12

2.3 Summary

Two intermediates required for the total synthesis of cycleanine, 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**79**) and 4-iodophenylacetic acid (**80**) were prepared in synthetically useful yields. In particular, the synthesis of 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**79**) required a great amount of time and effort. At first it

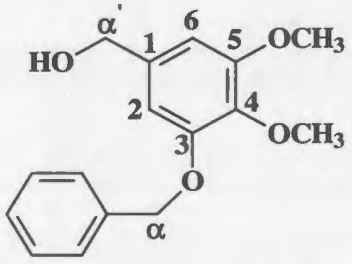
seems unworthy to take such great pains for the synthesis of such a simple compound as **79**. However, although these compounds are structurally simple and probably many different methodologies may be chosen to produce them, they may not be easy to synthesize in an economical and practical way. On the other hand, if these simple compounds are used as synthetic intermediates for the beginning stages of a lengthy total synthesis, such as the synthesis of cycleanine, contemplated in this thesis, the development of economical and practical ways for preparing them is really crucial to the final success. With all these considerations in mind, therefore, it should be recognized that the effort expended for preparing these intermediates in an efficient manner was a worthwhile endeavour.

2.4 Experimental

General

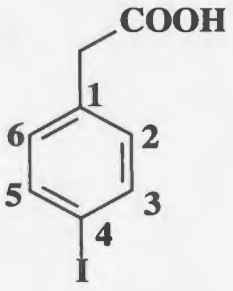
Flash column chromatography was performed using 240-400 mesh silica gel and preparative layer (1 mm) chromatography (PLC) was conducted using 60 mesh silica gel. All solvents and reagents were either of the highest commercial grade available or were redistilled (CH_2Cl_2, hexane, and benzene distilled over CaH_2). ^1H and ^{13}C NMR spectra were obtained on the Bruker Avance 500 MHz instrument with a TXI inverse-detection gradient probe in $CDCl_3$ unless otherwise specified, and shifts are relative to an internal tetramethylsilane signal. The following abbreviations are used in descriptions of the ^1H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). The ^{13}C NMR spectra shifts were measured relative to the solvent. Overlap may have prevented the reporting of all resonances. Low-resolution mass spectral data were obtained from the V.G. Micromass 7070HS instrument or obtained from Atmospheric Pressure Chemical Ionization-Mass Spectrometry (APCI-MS). Mass spectral data and intensity (%) are described as MS (*m/z*) or APCI-MS (*m/z*). Melting points (m.p.) were determined using a Fisher-Johns hot stage apparatus, and are uncorrected.

3-Benzyloxy-4,5-dimethoxybenzyl alcohol (79)



To a solution of **111** (2.3 g, 8.6 mmol) in MeOH (20 mL) and THF (20 mL) was added $NaBH_4$ (0.18 g, 4.8 mmol) in three portions over a period of 1.5 h. The mixture was stirred at room temperature for 15 h before by removal of the solvent on a rotary evaporator. The yellow residue obtained was dissolved in aqueous 10% HCl (20 mL), the solution was transferred to a separatory funnel and the mixture was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over $MgSO_4$, filtered and the solvent was evaporated to give **79** as a yellow oil (2.3 g, 97%). The product was pure enough to be used in the next step without further purification; ^1H NMR (500 MHz): δ 7.31-7.45 (m, 5H, Ar-H), 6.64 (s, 1H, H-6), 6.61 (s, 1H, H-2), 5.13 (s, 2H, H-α), 4.59 (s, 2H, H-α'), 3.87 (s, 6H, OCH_3); MS (*m/z*): 274 (M^+, 30), 243 (2), 91 (100).

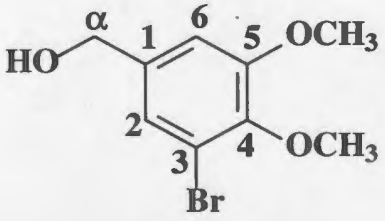
4-Iodophenylacetic acid (80)



A mixture of **114** (7.5 g, 31 mmol) in 95% ethanol (150 mL) and aqueous 6.0 M NaOH (30 mL) was heated at reflux for 16 h. The reaction mixture was then cooled to room temperature and the ethanol was removed on a rotary evaporator. Water (80 mL) was added, and the mixture was extracted with CH_2Cl_2 (30 mL × 3) to remove any remaining starting material. The aqueous layer was acidified with aqueous concentrated HCl to pH = 1 and was re-extracted with CH_2Cl_2 (40

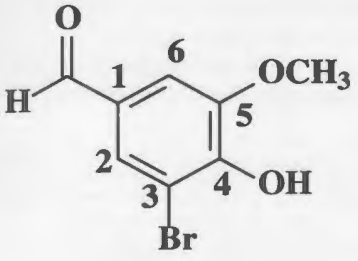
mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated on a rotary evaporator to give **80** (7.7 g, 95%) as a white solid. The product was used in the next step without purification; ^{1}H NMR: δ 7.67 (d, J = 8.0 Hz, 2H, H-2, H-6), 7.04 (d, J = 8.0 Hz, 2H, H-3, H-5), 3.60 (s, 2H, -CH_2-).

3-Bromo-4,5-dimethoxybenzyl alcohol (83)



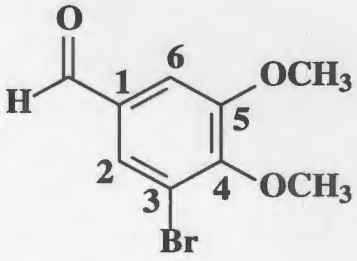
To a solution of **90** (20 g, 80 mmol) in MeOH (75 mL) and THF (75 mL) was added $NaBH_4$ (1.6 g, 40 mmol) in portions over a period of 1.5 h. The solution was stirred at room temperature for 11 h, before removal of the solvent on a rotary evaporator. The yellow solid was dissolved with aqueous 10% HCl (80 mL), and the solution was transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (30 mL × 3) and the combined organic layers were washed with brine (40 mL × 2), dried over $MgSO_4$, filtered, and the solvent was evaporated to give a yellow-tinted oil. The product was used in the next step without purification (21 g, 99%); ^{1}H NMR: δ 7.12 (d, J = 2.0 Hz, 1H, H-2), 6.89 (d, J = 1.5 Hz, 1H, H-6), 4.62 (d, J = 6 Hz, 2H, H-α), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); MS (*m/z*): 248 (M^++2, 98), 246 (M^+, 100), 231 (15), 96 (98), 84 (12).

3-Bromo-4-hydroxy-5-methoxybenzaldehyde (89)



Bromine (11 mL, 34 g, 0.22 mol) was added dropwise to a solution of vanillin **23** (30 g, 0.20 mol) in glacial acetic acid (140 mL). After stirring for 2 h, the reaction mixture was diluted with ice-water (400 mL). The resulting precipitate was filtered, washed with water (50 mL × 2), and dried over P_2O_5 under reduced pressure to give **89** as a white solid (44 g, 95%); m. p. 162-64 °C (lit.[73] m.p. 164-166 °C); ^{1}H NMR: δ 9.79 (s, 1H, CHO), 7.65 (d, J = 1.8 Hz, 1H, H-2), 7.37 (d, J = 1.8 Hz, 1H, H-6), 6.57 (s, 1H, OH), 3.99 (s, 3H, OCH_3).

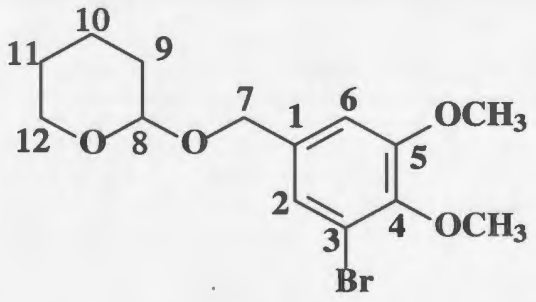
3-Bromo-4,5-dimethoxybenzaldehyde (90)



A mixture of **89** (42 g, 0.18 mol), sodium hydroxide (20 g, 0.50 mol), dimethyl sulfate (30 mL, 0.18 mol), Adogen 464® (5.0 mL), water (350 mL) and CH_2Cl_2 (350 mL) was vigorously stirred at room temperature. After 17 h, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined CH_2Cl_2 extracts were thoroughly washed with aqueous ammonium hydroxide (30 mL of 30% NH_3 (aq.) diluted to 130 mL with water), water (100 mL), dried over $MgSO_4$, and filtered, and the solvent was evaporated to give an oily residue. The residue was purified by column chromatography (10% EtOAc/hexane) to afford **90** as a colorless solid (44 g, 99%); m. p. 58-60 °C (lit.[70] m.p. 63-64 °C.); ^{1}H NMR: δ 9.85 (s, 1H, CHO), 7.65 (d, J = 1.5 Hz, 1H, H-2), 7.39 (d, J = 1.5 Hz, 1H, H-6), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); MS (*m/z*): 246 (M^++2, 98),

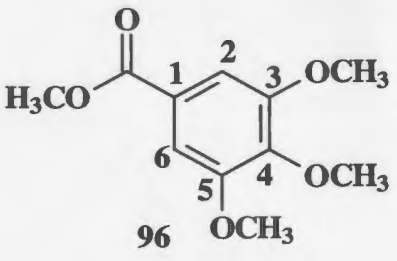
244 (M^+, 100), 173 (18), 94 (50).

3-Bromo-1,2-dimethoxy-5-(tetrahydropyranyloxy)methyl benzene (91)

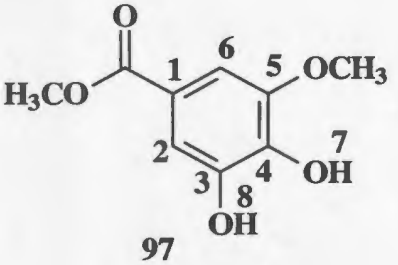


A mixture of **83** (4.4 g, 18 mmol), DHP (3.0 g, 35 mmol), PPTS (0.50 g, 5.9 mmol) in CH_2Cl_2 (30 mL) was stirred at a reflux temperature. After 2 h, the reaction mixture was diluted with diethyl ether (30 mL), washed with aqueous saturated $NaHCO_3$ (30 mL), brine (30 mL), water (30 mL) and dried over $MgSO_4$, filtered, and the solvent was evaporated to afford **91** as a yellow-tinted oil (5.7 g, 96%). The product was used in the next step without purification; ^{1}H NMR: δ 7.14 (s, 1H, H-2), 6.87 (s, 1H, H-6), 4.69 (m, 1H, H-8), 4.69 (d, 1H, J = 12Hz, H-7), 4.41(d, 1H, J = 12Hz, H-7), 3.54-3.57 (m, 1H, H-12), 3.87 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.54-3.58 (m, 1H, H-12), 1.54-1.90 (m, 6H, H-9, H-10, H-11); ^{13}C NMR: δ 153.8, 145.9, 135.6, 124.1, 117.7, 111.4, 98.0, 68.2, 62.5, 60.7, 56.2, 30.7, 25.6, 19.6; MS (*m/z*): 332 (M^++2, 10), 330 (M^+, 10), 246 (8), 231 (100), 151 (81), 85 (35).

Methyl 3,4,5-trimethoxybenzoate (96) and methyl 3,4-dihydroxy-5-methoxybenzoate (97)



96

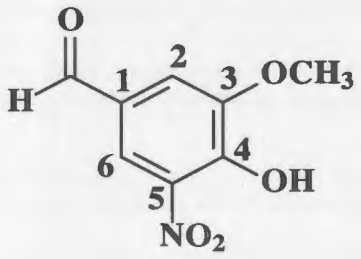


97

A mixture of gallic acid (0.50 g, 2.9 mmol), sodium hydroxide (0.35 g, 8.8 mmol), dimethyl sulfate (0.74 mL, 7.8 mmol), phase-transfer catalyst Adogen 464® (1 drop), CH_2Cl_2 (15 mL), and water (15 mL) was stirred at room temperature. After 7h, aqueous 5% NaOH (10 mL) was added. The organic layer was isolated and the aqueous layer was extracted with diethyl ether (20 mL × 2). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by column chromaography using ethyl acetate-hexane (3:7) as an eluent to afford **96** as a white solid (90 mg, 14%); ^{1}H NMR: δ 7.30 (s, 2H, H-2, H-6), 3.91 (s, 12H, OCH_3); MS (m/z): 226 (M^+, 100), 211 (65), 155 (50), 125 (30), 66 (45).

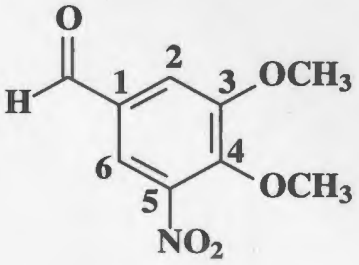
The aqueous layer was acidified with aqueous concentrated HCl to pH = 1, then it was extracted with diethyl ether (20 mL × 2), washed with water, dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by column chromatography (50% EtOAc/hexane) to give **97** as a grey-yellow solid (82 mg, 14%); ^{1}H NMR: δ 9.52 (s, 1H, OH), 7.11 (d, J = 1.5Hz, 1H, H-2), 7.04 (d, J = 1.5 Hz, 1H, H-6), 3.80 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.33 (s, 1H, OH); ^{13}C NMR: δ 167.9, 153.7, 151.2, 141.1, 126.6, 111.7, 105.3, 60.8, 56.6; MS (*m/z*): 198 (M^+, 100), 183 (75), 155 (12), 127 (45), 81 (16), 67 (20).

4-Hydroxy-3-methoxy-5-nitrobenzaldehyde (98)



To a solution of vanillin in glacial acetic acid (20 g, 150 mL) was added fuming nitric acid (8 mL) dropwise while keeping the temperature around 15 °C. After the addition of HNO_3, the reaction mixture was filtered. The solid was washed with cool methanol (10 mL) and then dried in air to afford **98** as a green-yellow solid (19 g, 76%); m. p. 174-175 °C (lit.[74] m.p. 175-176 °C); ^{1}H NMR: δ 9.91 (s, 1H, CHO), 8.24 (d, J = 1.5, 1H, H-6), 7.66 (d, J = 1.5, 1H, H-2), 4.04 (s, 3H, OCH_3), 1.55 (s, 1H, OH); MS (*m/z*): 197 (M^+, 100), 182 (55), 149 (35), 135 (46), 79 (75), 51(81).

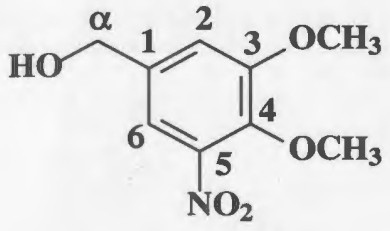
3,4-Dimethoxy-5-nitrobenzaldehyde (99)



Compound **98** was heated on a steam bath with 1 eq of aqueous 1M KOH. The resultant clear solution was allowed to cool, and the precipitated potassium salt was filtered and dried. A mixture of the well-dried 5-nitrovanillin salt, and dimethyl sulfate (0.30 mL, 3.2 mmol) in xylene (30 mL) was stirred at 125 °C for 4 h. After the reaction cooled down, aqueous 5% KOH (15 mL) was added. The mixture was filtered. Diethyl ether (15 mL) was added to the filtrate, and the organic layer was separated. The aqueous layer was extracted with diethyl ether (15 mL). The combined organic layers were washed with water (15 mL), dried over $MgSO_4$, and concentrated to afford **99** as yellow solid (0.51 g, 91%) which was crystallized from 60% aqueous EtOH; m. p. 87-88 °C (lit.[68] m.p. 90-91 °C.); ^{1}H NMR: δ 9.92 (s, 1H,

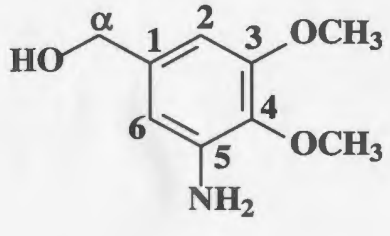
CHO), 7.84 (s, 1H, H-6), 7.63 (s, 1H, H-2), 4.08 (s, 3H, OCH_3), 4.00 (s, 1H, OCH_3); MS (*m/z*): 211 (M^+, 100), 164 (45), 135 (47), 77 (79), 51(53).

3,4-Dimethoxy-5-nitrobenzyl alcohol (100)



A solution of **99** (3.7 g, 18 mmol) in THF (15 mL) was added dropwise into a suspension of $NaBH_4$ (1.4 g, 36 mmol) in THF (15 mL). After the addition, the reaction was allowed to proceed for an additional 1 h. The excess $NaBH_4$ was destroyed by addition of water (15 mL) and a few NaH_2PO_4 crystals. The THF and water were removed on a rotary evaporator. Water (15 mL) was added to the residue, and the resulting mixture was extracted with diethyl ether (15 mL × 3). The combined ether layers were washed with brine, dried over $CaCl_2$, filtered and the solvent was evaporated. The residue was purified by column chromatography (ethyl acetate/hexane = 1:1) to afford **100** as a yellow solid (3.3 g, 85%); ^{1}H NMR: δ 7.31 (s, 1H, H-6), 7.16 (s, 1H, H-2), 4.70 (d, J = 5.2 Hz, 2H, H- α), 3.97 (s, 1H, OCH_3), 3.94 (s, 1H, OCH_3); MS (*m/z*): 213 (M^+, 100), 166 (25), 137 (25), 77 (31), 53(30).

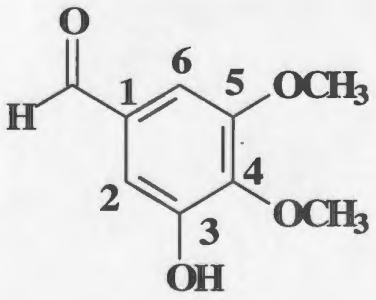
5-Amino -3,4-dimethoxybenzyl alcohol (101)



Hydrogen gas was added to a mixture of **100** (3.2 g, 0.015 mmol), 10% Pd/C (0.15 g) in anhydrous methanol (30 mL) at atmospheric pressure. After stirring at room temperature for 4.5 h, the mixture was filtered and concentrated to a red oil. Purifying this red oil by column

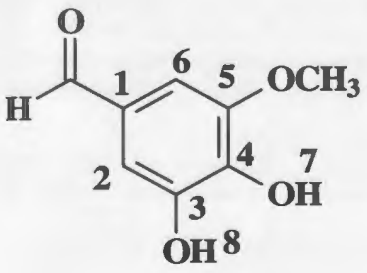
chromatography (EtOAc/hexane =1:1) afforded **101** (2.1 g, 75%) as yellow solid; ^{1}H NMR: δ 6.39 (s, 1H, H-2), 6.37 (s, 1H, H-6), 4.54 (s, 2H, H-α), 3.85 (s, 1H, OCH_3), 3.81 (s, 1H, OCH_3); MS (*m/z*): 183 (M^+, 100), 168 (89), 108 (49), 80 (52), 53 (24).

4,5-Dimethoxy-3-hydroxybenzaldehyde (102)



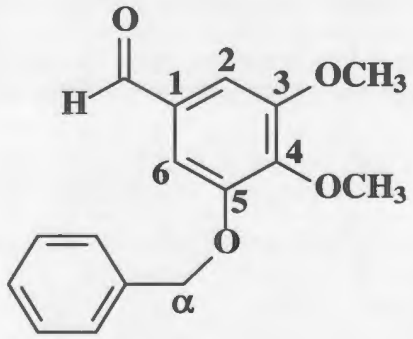
Compound **110** (10 g, 60 mmol), dimethyl sulfate (7.5 g, 60 mmol) and sodium carbonate (7.0 g, 66 mmol) were added into acetone (200 mL). The reaction mixture was heated at reflux for 4.5 h and then cooled to room temperature. After filtering to remove inorganic salts, the acetone was evaporated. To the residue was added water (20 mL) and CH_2Cl_2 (20 mL). The resulting mixture was acidified to pH = 1 with aqueous concentrated HCl. The organic layer was isolated and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were washed with brine, dried over $MgSO_4$ and filtered. After the CH_2Cl_2 was evaporated on a rotary evaporator, the red oil obtained was purified by column chromatography (EtOAc/hexane = 3:7) to afford **102** as a white solid (7.6 g, 71%); m. p. 59-60 °C (lit.[72] m.p. 64-65 °C); ^{1}H NMR (DMSO): δ 9.80 (s, 1H, CHO), 9.74 (s, 1H, OH), 7.06 (s, 1H, H-2), 7.05 (s, 1H, H-6), 3.84 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3); MS (*m/z*): 182 (M^+, 100), 167 (38), 111 (30), 96 (28), 65 (25).

3,4-Dihydroxy-5-methoxybenzaldehyde (110)



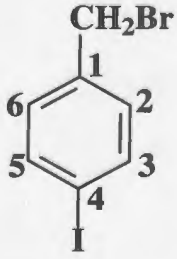
Compound **90** (20 g, 90 mmol), sodium hydroxide (25 g, 0.61 mol) and copper powder (0.10 g, 1.6 mmol) were combined as a slurry in 0.30 L water. The reaction mixture was heated at reflux for 26 h. Sodium hydrogen phosphate (0.45 g, 3.2 mmol) was added for the last 0.5 h of reflux. The reaction was then cooled to 50 °C, filtered to remove the precipitate of cupric hydrogen phosphate and the filtrate was acidified with aqueous concentrated hydrochloric acid (46 g). The reaction mixture was placed in a continuous extractor and extracted with ethyl acetate (0.30 L). The ethyl acetate solution was stirred with activated carbon and filtered. The filtrate was washed with saturated aqueous EDTA solution followed by brine solution. The organic solution was then dried over $MgSO_4$ and filtered and the solvent evaporated to afford a solid. The crude product was dissolved in boiling toluene (0.20 L), treated with activated charcoal, filtered, cooled and allowed to crystallize to yield **110** as a grey solid (8.8 g, 66%); m. p. 129-130 °C (lit.[72] m.p. 132-133 °C.); ^{1}H NMR (DMSO): δ 9.70 (s, 1H, CHO), 9.49 (s, 1H, OH), 9.43 (s, 1H, OH), 7.03 (d, J = 1.5Hz, 1H, H-2), 7.37 (d, J = 1.5Hz, 1H, H-6), 6.47 (s, 1H, H-8), 3.98 (s, 3H, OCH_3); MS (*m/z*): 168 (M^+, 100), 125 (30), 97 (41), 51 (29).

3-Benzoxy-4,5-dimethoxybenzaldehyde (111)



To a suspension of anhydrous potassium carbonate (9.8 g, 71 mmol) in acetone (80 mL) was added **102** (2.0 g, 10 mmol) and benzyl bromide (2.2 mL, 20 mmol). After heating at reflux for 5 h, the reaction mixture was cooled, filtered and concentrated on a rotary evaporator, to the residue 20 mL aqueous 5% NaOH was added and the mixture was extracted with CH_2CL_2 (25 mL × 2). The combined organic extracts was washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated on a rotary evaporator. The residue was purified by column chromatography (EtOAc/hexane = 15:85) to afford **111** as a white solid (2.5 g, 85%); ^{1}H NMR: δ 9.84 (s, 1H, CHO), 7.33-7.47 (m, 5H, Ar-H), 7.17 (s, 1H, H-6), 7.15 (s, 1H, H-2), 5.21 (s, 2H, H-α), 3.96 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3); MS (*m/z*): 272 (M^+, 15), 244 (3), 181 (5), 91 (100), 65 (16).

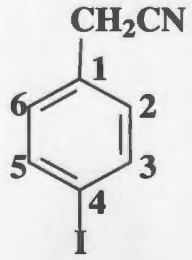
4-Iodobenzyl bromide (113)



To CH_2Cl_2 (6 mL) was added **112** (0.50 g, 2.3 mmol), NBS (0.45 g, 2.5 mmol) and a few crystals of dibenzoyl peroxide. The mixture was stirred under the light of a 100-watt lamp at a gentle reflux. After 1 h, the reaction was stopped. Brine (4 mL) with KI (0.13 g) was added to the reaction mixture. Then aqueous $Na_2S_2O_3$ solution (10 mL) was added to remove the produced I_2. After this, the organic layer was separated and the aqueous layer was extracted by CH_2Cl_2 (4 mL×3). The combined organic layers were

washed by brine (4 mL), dried with $MgSO_4$, filtered and the solvent was evaporated to give crude **113** which was purified by recrystallization by using EtOH to afford **113** as white solid (0.35 g, 51%); m. p. 77-78 °C (lit.[75] m.p. 78-79 °C.); ^{1}H NMR: δ 7.68 (d, *J*=8.5 Hz, 2H, H-2, H-6), 7.14 (d, *J*=8.5 Hz, 2H, H-3, H-5), 4.42 (s, 2H, -CH_2Br); MS (*m/z*): 298 (M^++1, 10), 296 (M^+-1, 9), 217 (100), 127 (41), 90 (74), 63 (43).

4-Iodophenylacetonitrile (114)



To a solution of 4-iodobenzyl bromide (**113**) (9.8 g, 33 mmol) in DMSO (40 mL) and benzene (60 mL) was added NaCN powder (4.2 g, 86 mmol) in four portions. After stirring for 3 h at room temperature, the reaction was poured into water (50 mL) and the mixture was extracted with benzene (40 mL × 3). The combined organic layers were washed with brine (30 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated in *vacuo* to afford **114** (7.5 g, 94%) as a white powder. The product was used in the next step without purification; ^{1}H NMR: δ 7.72 (d, *J*=8.0 Hz, 2H, H-2, H-6), 7.08 (d, *J*=8.0 Hz, 2H, H-3, H-5), 3.69 (s, 2H, -CH_2CN); MS (*m/z*): 243 (M^++1, 100), 116 (98), 89 (50).

Chapter 3

Synthetic efforts towards (-)-cycleanine

3.1 Introduction

As indicated in Chapter 1, the work described in this thesis is a continuation of the efforts of the previous work conducted in the Georghiou group on the synthesis of (-)- cycleanine (**25**). The successful aspects of the previous work were retained and continued and the unsatisfactory aspects were improved or replaced by newer and improved methodologies.

In Chapter 2, the preparation of the two intermediates **79** and **80** needed in relatively large amounts to explore the synthesis of the tetrahydroisoquinoline subunits of (-)-cycleanine had been accomplished with fairly satisfactory results. With these two important precursors in hand, the tetrahydroisoquinoline subunits **46a** can be synthesized by following the methodology previously developed by Cui and Georghiou (Scheme 2.2). In this chapter, the major attention will be focused on the attempts to connect the two tetrahydroisoquinoline subunits **46a** by forming the diaryl ether linkages.

3.2 Results and discussion

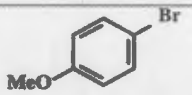
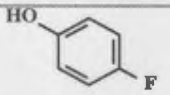
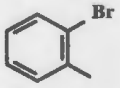
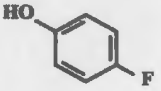
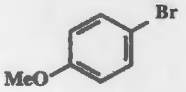
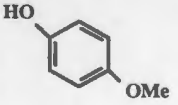
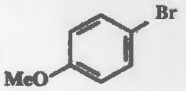
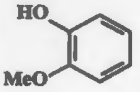
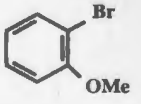
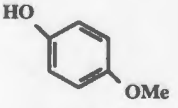
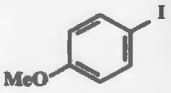
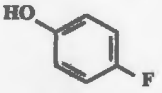
3.2.1 First attempts towards (-)-cycleanine by improved Ullmann coupling reaction

The first attempt towards (-)-cycleanine using improved Ullmann coupling reaction conditions in this thesis were based upon Buck's and Ma's methodologies which have been described in Chapter 1 and were shown in Schemes 1.12 and 1.13 [64, 65]

The reasons for selecting these two methodologies are that, besides the various advantages which they offer and which have been discussed before, in some entries of

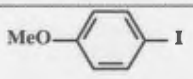
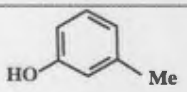
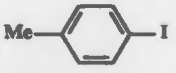
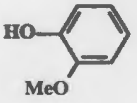
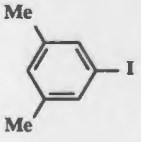
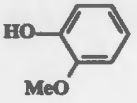
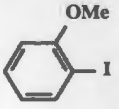
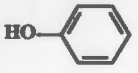
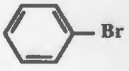
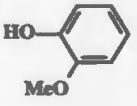
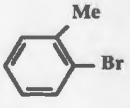
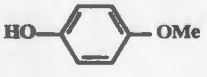
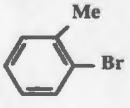
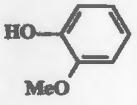
coupling reactions in the two original published reports, the structures of the phenols and biaryl halides used have much similarity with the precursors for forming the two diaryl ether linkages in (-)-cycleanine (Table 3.1 and Table 3.2). In the initial retrosynthetic analysis described in Chapter 2 (Scheme 2.1), compound **81** will be used as the precursor to construct the framework of (-)-cycleanine through the improved Ullmann coupling reactions. In compound **81**, the hydroxyl group is located on the same aromatic ring as the two methoxyl groups which are *o*- and *m*- to the hydroxy group. As for the iodo

Table 3.1 Ullmann coupling in the presence of 2,2,6,6-tetramethylheptane-3,5- dione[64]

Entry	Ar-X	ArOH	Isolated yield %
1			55
2			85
3			77
4			66
5			76
6			68

group, it is on the benzyl group of the benzylisoquinoline subunit, with a methylene group *para* to it. So if the structure of this benzylisoquinoline is compared with the entries outlined in Table 3.1 and Table 3.2, two molecules of compound **81** should be easy be connect by forming diaryl ether linkages using the newer Ullmann coupling procedure. The first attempts at the synthesis of (-)-cycleanine were undertaken using modified Ullmann coupling conditions.

Table 3.2 Coupling reaction of aryl halides with phenols under CuI and *N,N*-dimethylglycine catalysis[65]

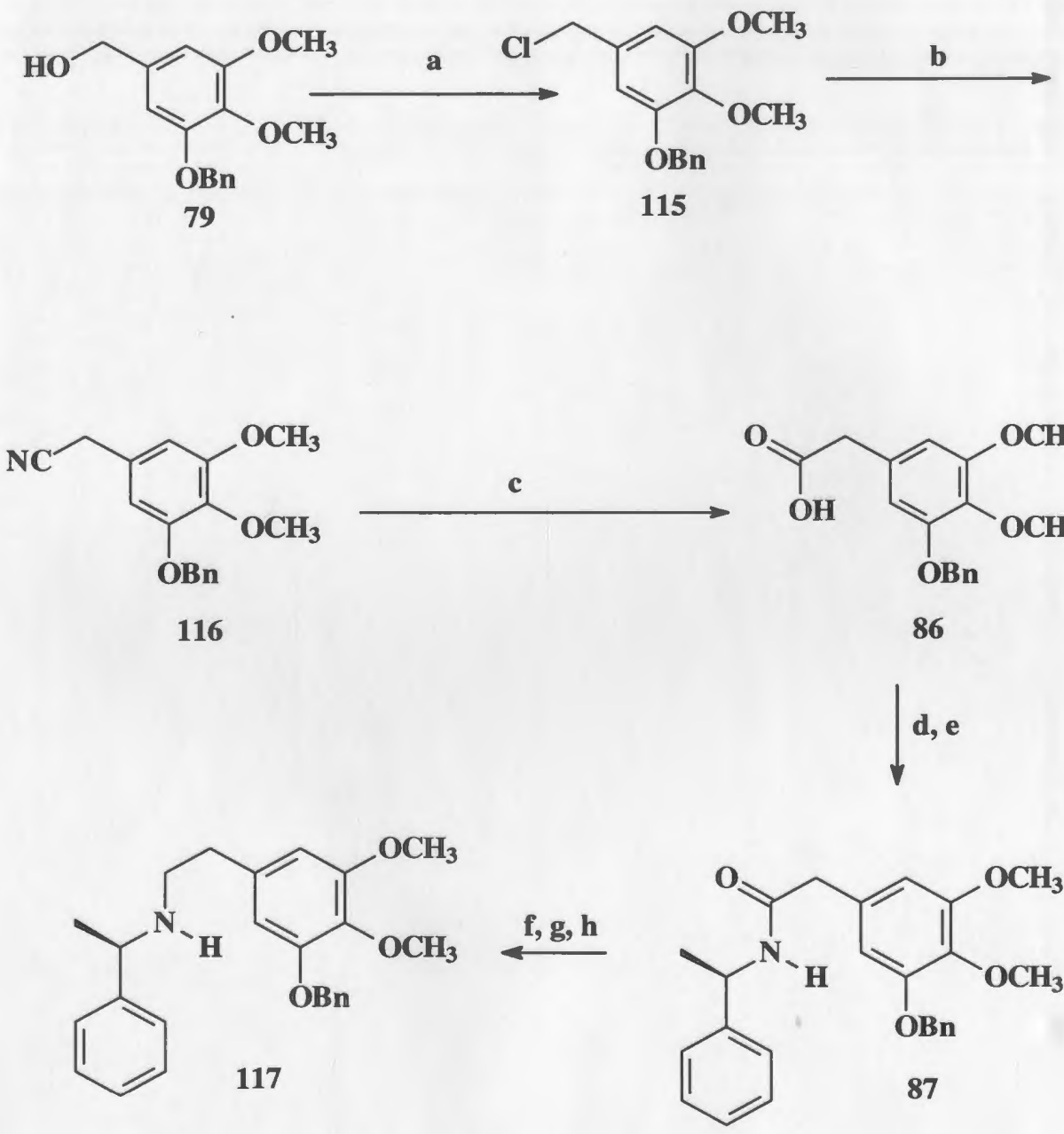
Entries	Aryl halides	Phenols	Yield (%)
1			89
2			74
3			82
4			80
5			83
6			75
7			64

3.2.1.1 Synthesis of the tetrahydroisoquinoline

Outlined in Scheme 3.1 and Scheme 3.2 are the synthetic approaches for the benzylisoquinoline subunit which are based on the previous work in the Georghiou laboratory.[7]

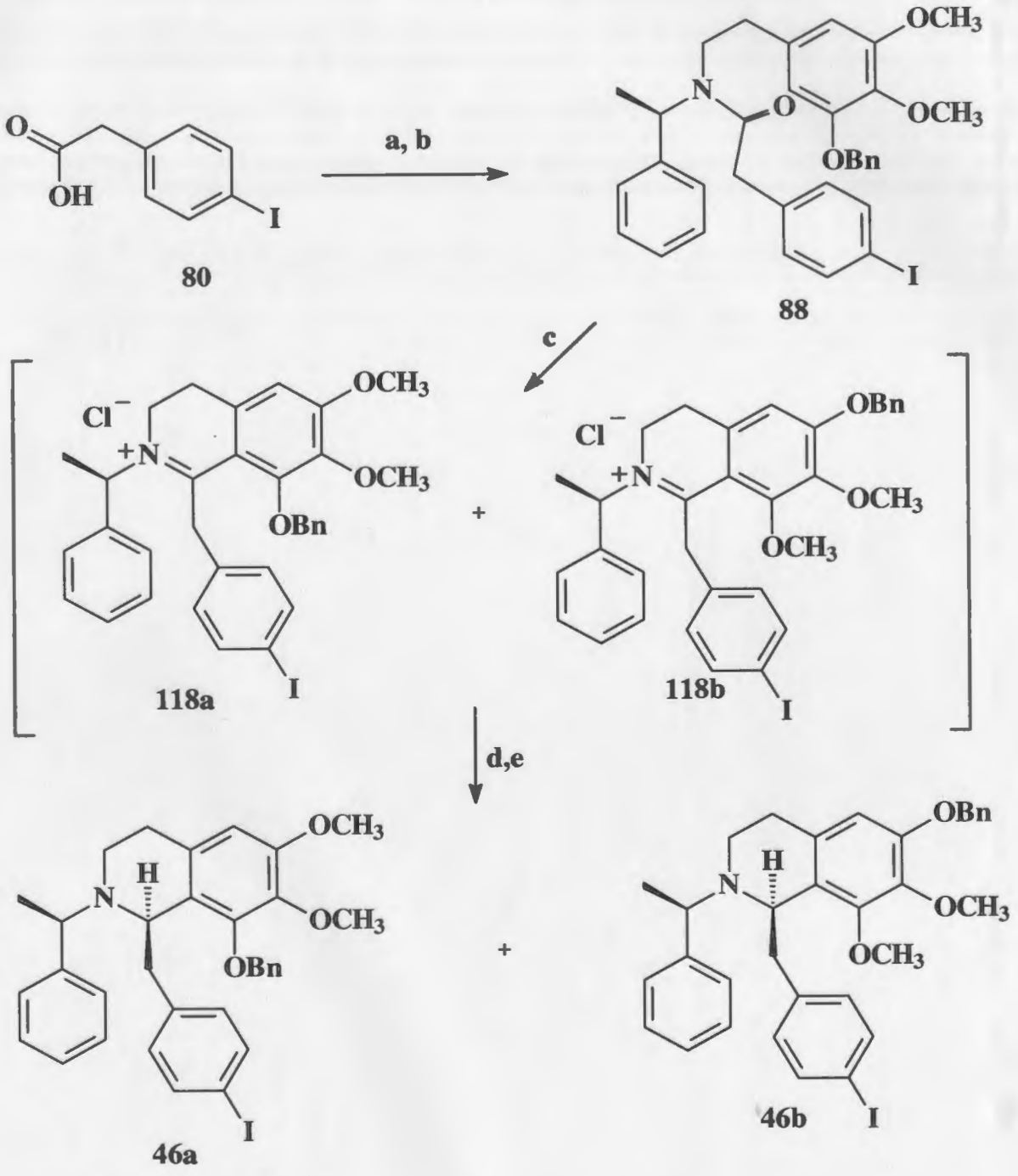
Treating 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**79**) with $SOCl_2$ gave the benzyl chloride **115** in a yield of 94%. Subjecting **115** to NaCN in DMSO produced 3-benzyloxy-4,5-dimethoxyphenylacetonitrile (**116**) (99%). Hydrolysis of **116** in NaOH/EtOH afforded the phenylacetic acid **86** (54%). At this stage the chiral auxiliary was introduced. Treatment of **86** with oxalyl chloride followed by reaction of the resulting acid chloride with (*R*)-(+)-α- methylbenzylamine under Schotten-Baumann conditions resulted in the formation of amide **87** (97%). This amide was reduced to the corresponding chiral amine **117** by treating it with B_2H_6•THF and BF_3•Et_2O in refluxing THF followed by the usual work-up.

With compound **117** in hand, amide **88** was synthesized by employing another Schotten-Baumann reaction utilizing compound **80**. Since two possible ring-closure sites, *para* and *ortho* to the benzyloxy group, are presented on the precursor amide **88**, the BNC step would be anticipated to lead to a pair of ring-closure products **46a** and **46b**. Under normal BNC conditions, the iminium salts **118a** and **118b** were formed by refluxing the amide **88** with phosphorus oxychloride in anhydrous benzene. The mixture of the two iminium salts was reduced with $NaBH_4$ which resulted in the formation of a pair of regioisomers **46a** and **46b.**



Conditions: a) $SOCl_2$, benzene, 94%; b) NaCN, DMSO, benzene, 99%; c) NaOH, EtOH, H_2O, 54%; d) oxalyl chloride, benzene; e) (*R*)-(+)-α-methylbenzylamine, 8% aqueous NaOH, 97%; f) B_2H_6•THF, BF_3•Et_2O, THF; g) aqueous HCl; h) 50% KOH, 99%.

Scheme 3.1



Conditions: a) oxalyl chloride, benzene; b) **117**, NaOH, CH_2Cl_2, H_2O, 91%; c) $POCl_3$, benzene, reflux; d) $NaBH_4$, MeOH, -78 °C; e) aqueous HCl, 21% of **46a** and 26% of **46b**.

Scheme 3.2

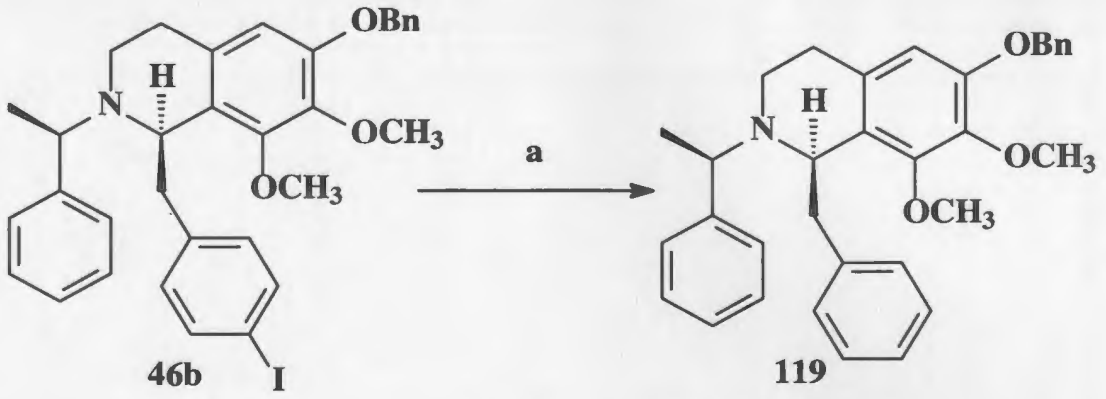
Finally, **46a** and **46b** were separated by column chromatography as pure compounds in the relatively low yields of 21% and 26%, respectively, based upon the amount of **88** used. Obviously, a 47% overall yield for this BNC reaction was not an ideal result for such a long synthetic pathway as envisioned in this thesis, especially considering the fact that the products were a pair of regioisomers, one of which was not of further use. In order to increase the yield of this BNC reaction, several methods, such as employing MeCN and toluene as solvent, or utilizing P_2O_5 as catalyst, were tried, but none of them gave higher yields. Because of this low yield from the BNC reactions, all of the later steps in the synthesis were negatively affected due to limited amounts of precursor compounds. This will be discussed further in the later sections of this thesis.

3.2.1.2 Use of improved Ullmann coupling reactions to form the diaryl ether linkages in (-)-cycleanine

Although the yield of the BNC reaction was somewhat low, it provided the desired enantiomeric and regioisomeric iodotetrahydroisoquinolines **46a** and **46b**. The significance of this is that with these compounds in hand, just by removing the protecting benzyl group , the originally designed Ullmann coupling reaction for forming the framework of (-)-cycleanine (Scheme 2.1) could be attempted.

Initially, it was thought that the debenzylation process would be relatively simple and, according to numerous literature reports, a Pd/C catalyzed hydrogenolysis could accomplish this in a fairly high yield.[78-81] However, when compound **46b** was used as a model and subjected to the hydrogenolysis conditions, it did not give the expected phenolic compound. What was formed instead was compound **119** (Scheme 3.3). Thus,

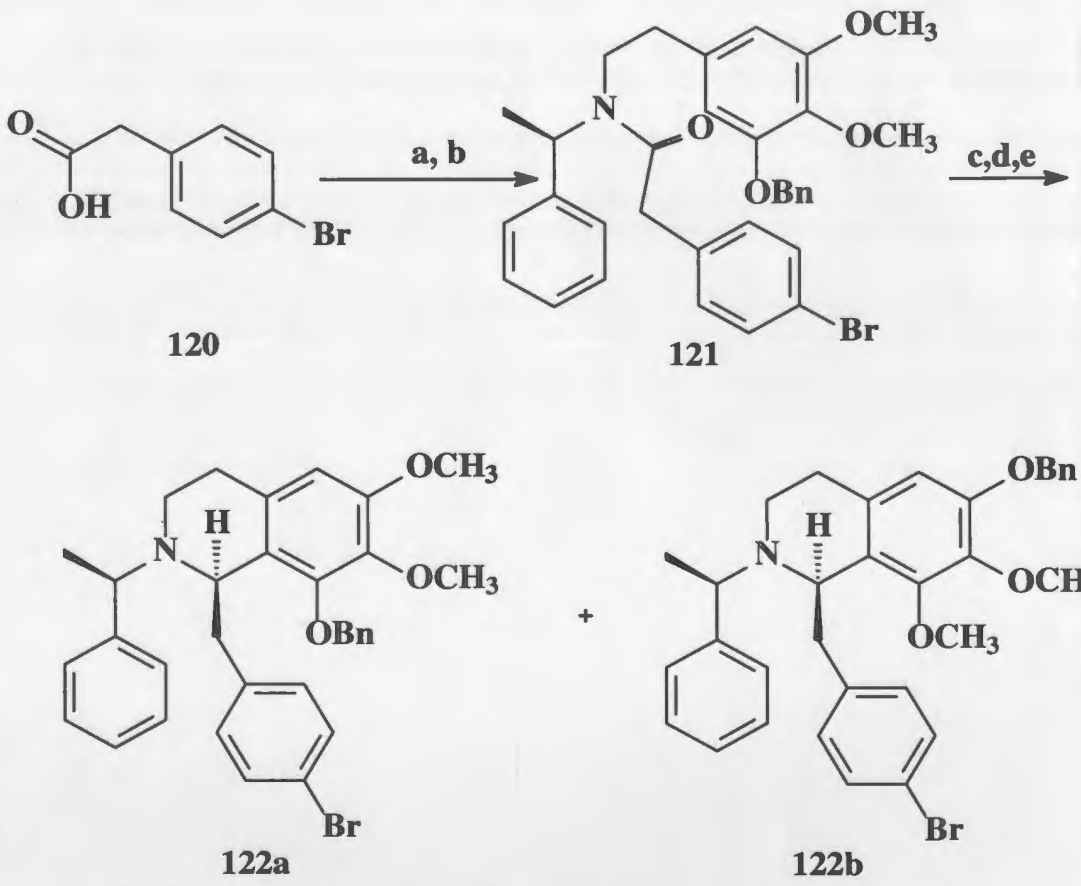
hydrogenolysis removed the iodo group more rapidly than the benzyl group. As a result of this finding, hydrogenolysis of compound **46a** itself was not attempted in order to save the valuable regioisomer for other attempts.



Conditions: a) H_2, Pd/C, MeOH, 84%.

Scheme 3.3

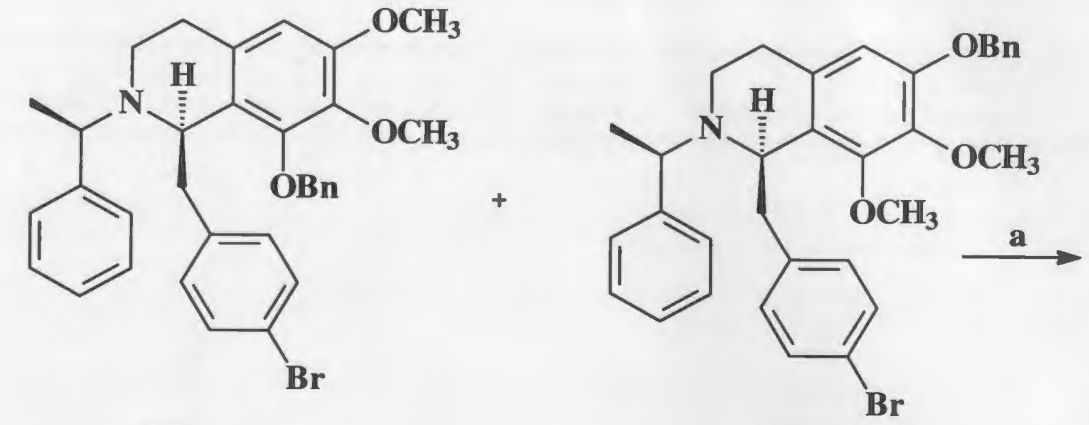
A new synthetic route (Scheme 3.4) was therefore devised with the intent to acquire the correct precursor required for the Ullmann coupling reactions. This pathway was similar to that for the synthesis of compound **46a** but with one difference: a commercially available carboxylic acid **120** could be used instead of compound **80**. Thus, **120** was first treated with oxalyl chloride in benzene then with **117** under Schotten-Baumann reaction conditions to form the BNC precursor **121**. Using a normal BNC reaction, the two benzyltetrahydroisoquinolines **122a** and **122b** were produced in yields of 23% and 23%, respectively. The stereochemistry of these two compounds was presumed to be as depicted, based upon the fact that they had fairly similar NMR spectra with those of compounds **46a** and **46b**.



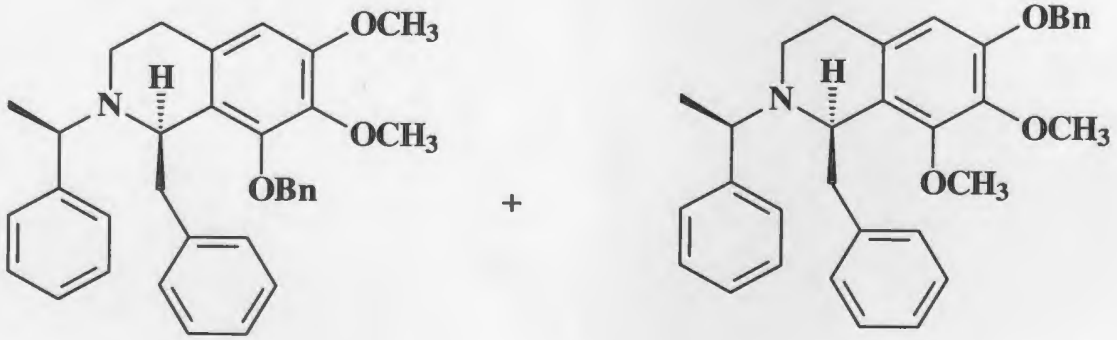
Conditions: a) oxalyl chloride, benzene; b) **117**, NaOH, CH_2Cl_2, H_2O, 91%; c) $POCl_3$,benzene, reflux; d) $NaBH_4$, MeOH, -78 °C; e) aqueous HCl, 23% of **122a** and 23% of **122b**.

Scheme 3.4

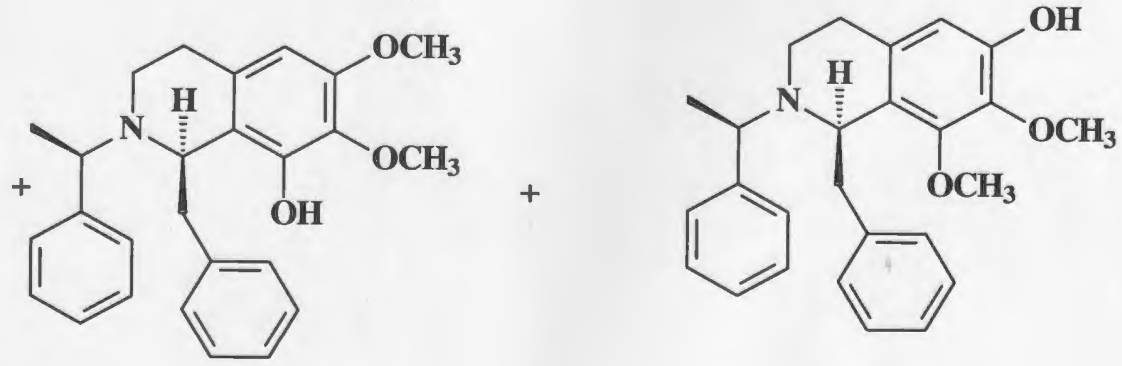
The reason for replacing the iodine atom with a bromine atom in the benzylic phenyl unit is that a carbon-bromine bond is stronger than a carbon-iodine bond. It was anticipated that the bromine atom would survive the hydrogenolysis conditions necessary for the removal of the benzylic ether protecting groups in **122a** or **122b**. However, when the mixture of compounds **122a** and **122b** in methanol was treated with H_2 in the presence of Pd/C catalyst, four possible products **123a**, **123b**, **124a**, and **124b** were found in the mixture of crude products when analyzed by APIC-MS (Scheme 3.5). As a result, attempts to remove the benzyl group by hydrogenolysis had to be abandoned.



122a + 122b



123a + 123b

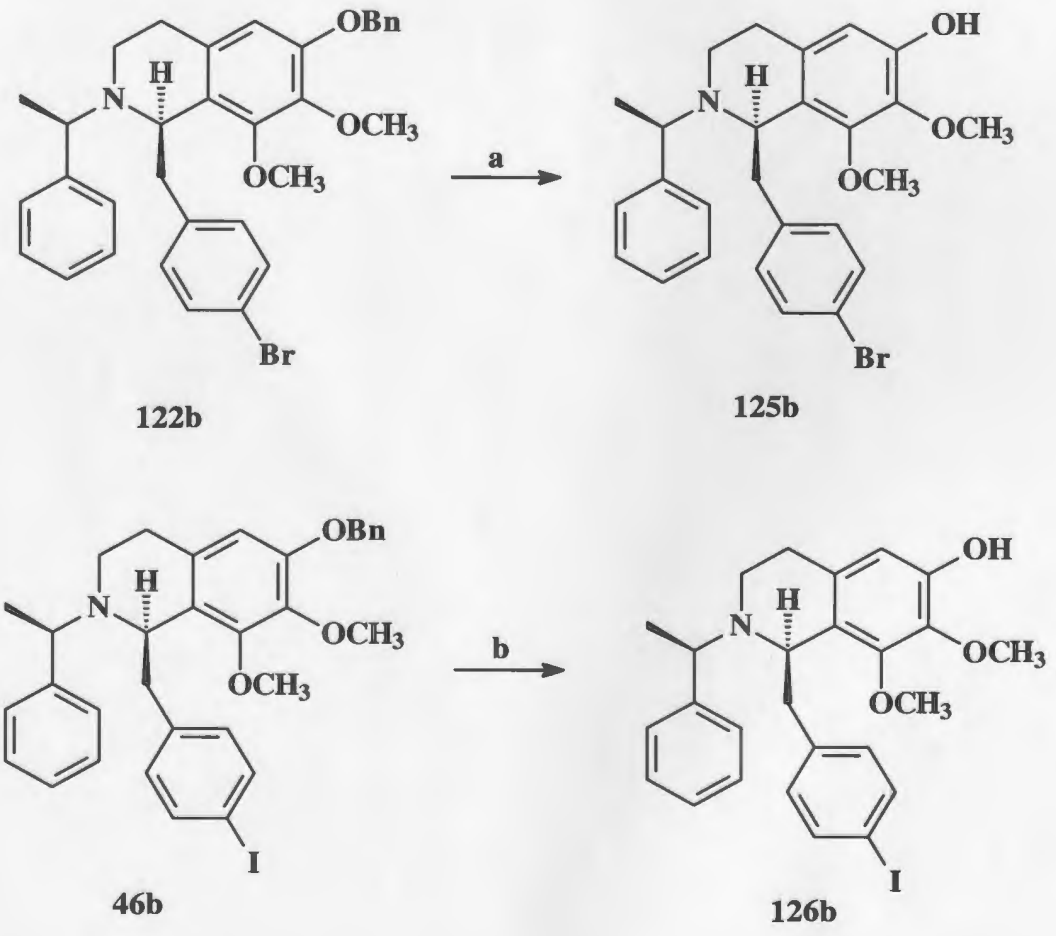


124a + 124b

Conditions: a) H_2, Pd/C, MeOH

Scheme 3.5

According to many literature reports, acids, including both Brønsted acids and Lewis acids, have also frequently been used to realize the debenzylation process.[82-85] For our research, considering that the other groups present including the chiral auxiliary may be sensitive to the harsh reaction conditions when Brnøsted acids are utilized, a debenzylation procedure developed by Hori and Mukai's group[86, 87] utilizing the Lewis acids $SnCl_4$ or $TiCl_4$ was applied. First, with compounds **122b** and **46b** in model studies,



122b **125b**

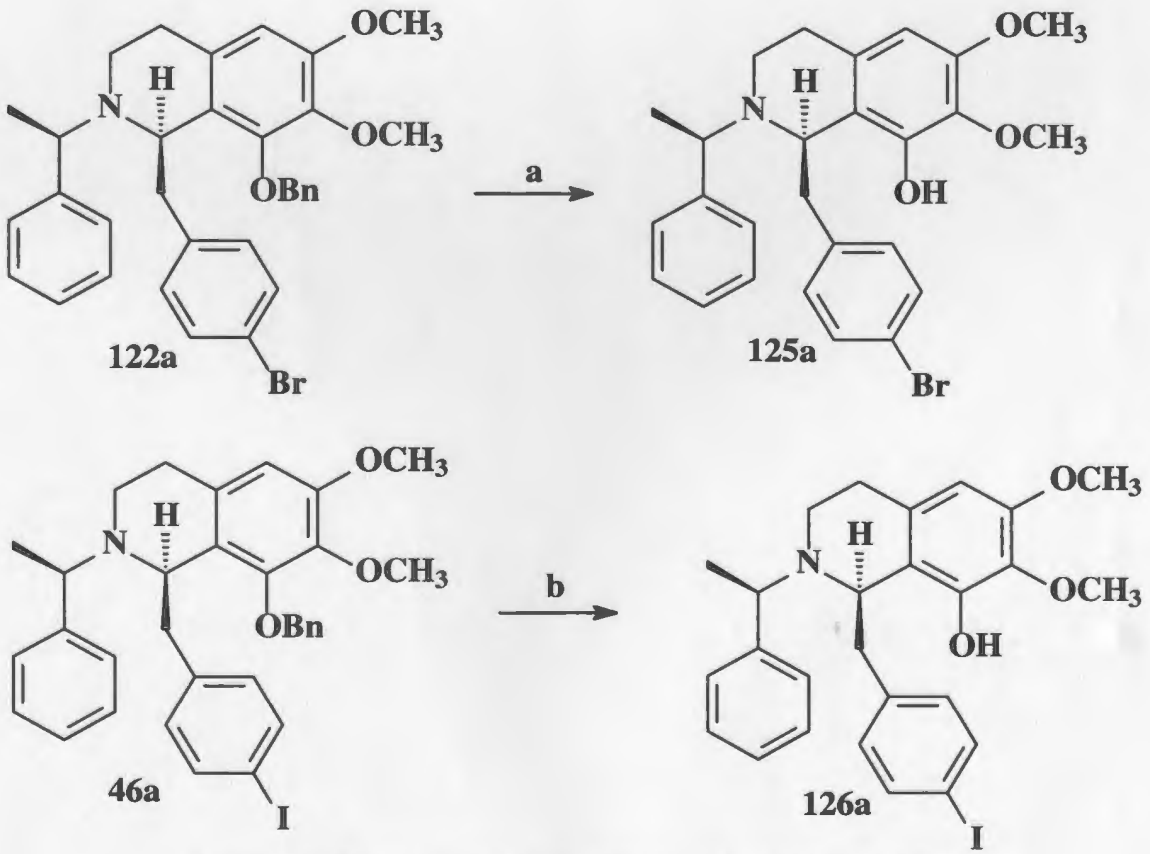
46b **126b**

Conditions: a) $SnCl_4$, CH_2Cl_2, rt, 34%; b) $SnCl_4$, CH_2Cl_2, rt, 57%.

Scheme 3.6

it was found that they did produce the corresponding desired products **125b** and **126b** when subjected to $SnCl_4$ in anhydrous CH_2Cl_2 (Scheme 3.6).

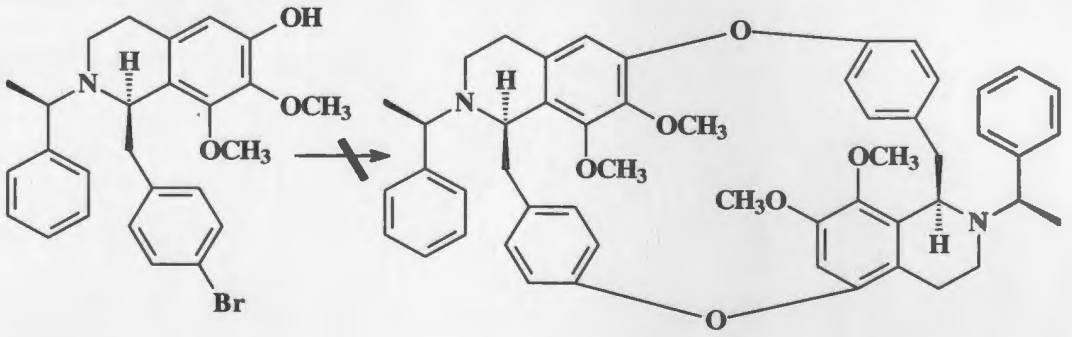
The desired reactions were therefore then conducted by treating the desired regioisomers **122a** and **46a** under the same conditions with $SnCl_4$ and $TiCl_4$ in anhydrous CH_2Cl_2 at room temperature. These reactions produced compound **125a** and **126a** respectively (Scheme 3.7). After successfully finding a suitable method to remove selectively the benzyl protecting group, the work in the next stage was concerned with the formation of the diaryl ether linkages by Ullmann couplings.



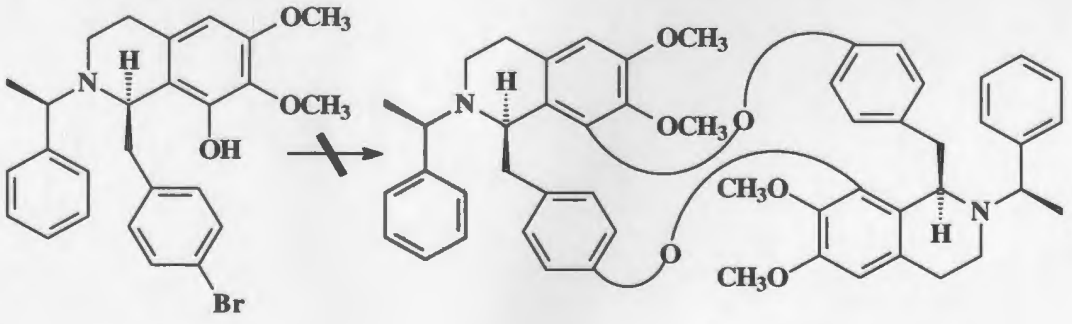
Conditions: a) $SnCl_4$, CH_2Cl_2, rt, 43%; b) $TiCl_4$, CH_2Cl_2, rt, 64%

Scheme 3.7

Both Buck's TMHD-accelerated Ullmann coupling and Ma's *N,N*-dimethyl glycine-promoted Ullmann coupling procedures were potential methodologies for the formation of diaryl ether linkages for the framework of (-)-cycleanine. Considering the lower reaction temperature used, Ma's method was first attempted using compounds **125a** and **125b** as reactants. A mixture of **125b** or **125a**, Cs_2CO_3, copper catalyst,



125b **127b**



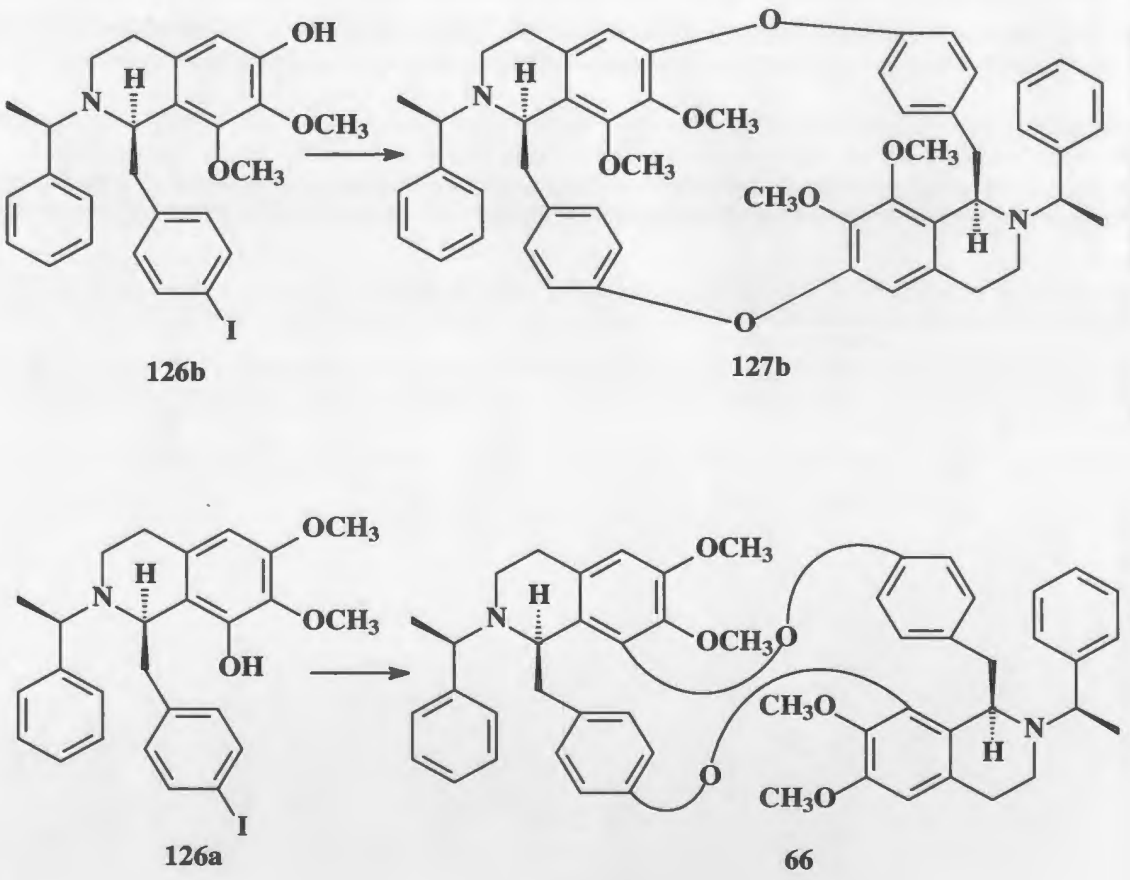
125a **66**

Conditions: Cs_2CO_3, CuI, *N,N*-dimethyl glycine, dioxane 90 °C, 35h.

Scheme 3.8

N,N-dimethylglycine and anhydrous dioxane was heated at 90 °C under a nitrogen atmosphere for 35 h. However, this procedure failed to produce the desired products **127b** and **66** and only unreacted starting material was recovered (Scheme 3.8). Therefore, attention was directed to Buck's method using the aryl iodides **126b** and **126a** as substrates.

According to the reported general procedure, cesium carbonate, model compound **126b** or compound **126a**, TMHD, and CuCl was added to anhydrous NMP, And the mixture was warmed to 120 °C under nitrogen . After 24 h, the mixture was cooled to room temperature, diluted with ethyl acetate and the resulting mixture was worked up in the usual manner to give a dark red oil. Analysis of this red oil by APCI-MS revealed the presence of coupled products **127b** and **66** (Scheme 3.9). Nevertheless, subsequent attempts at purification of these products were unsuccessful. There are two factors that could be responsible for this: (i) a suitable solvent system for chromatographic separation was not found, and; (ii) it could also be that the actual yields of **127b** or **66** were very low since APCI-MS does not give quantitative results about the reaction without any prior calibration with authentic standards. Of course, the very small reaction scale used and the nature of the Ullmann coupling itself also caused difficulties in the isolation process for these structurally complex compounds. As a result of these difficulties, the following steps such as converting the chiral auxiliary group to a methyl group for the final product (-)-cycleanine could not be carried out.



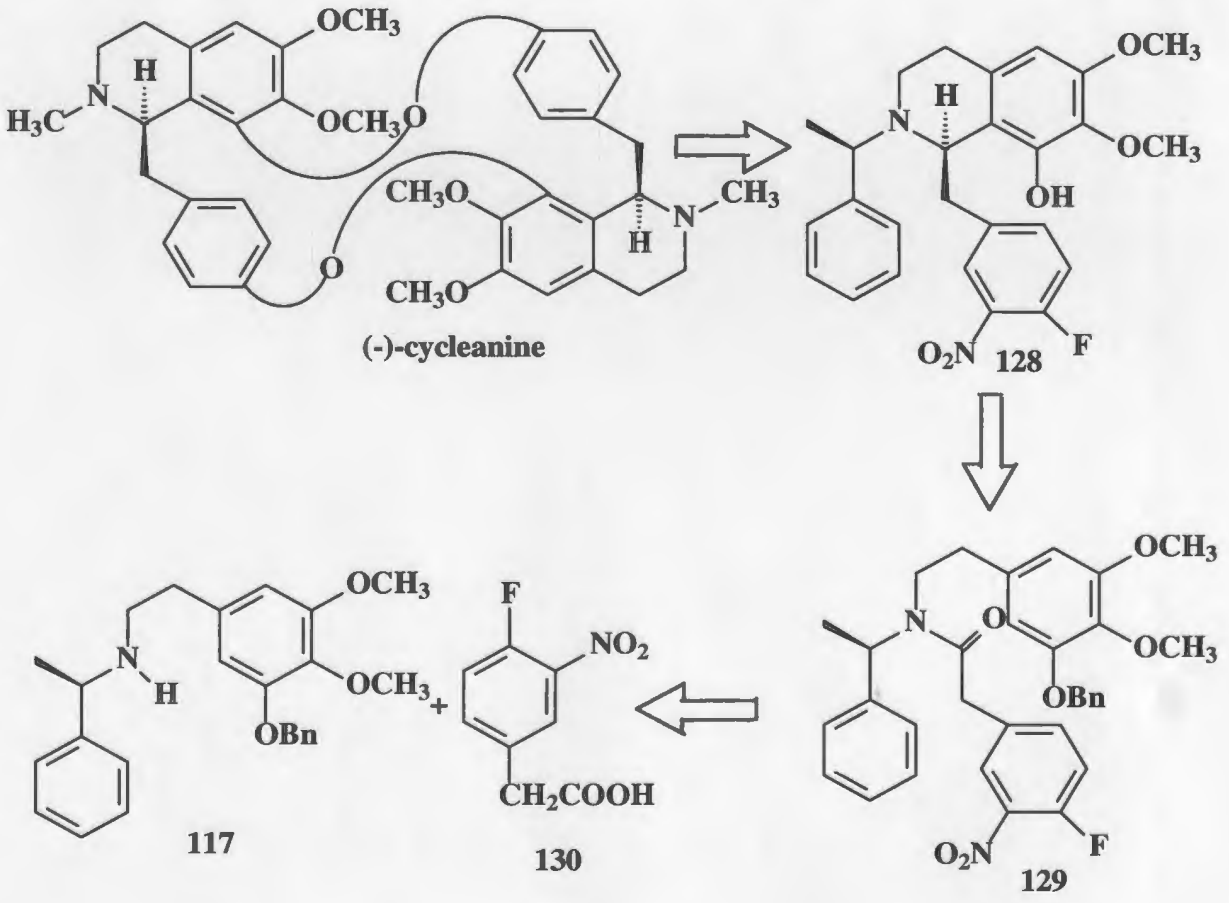
Conditions: Cs_2CO_3, CuCl, TMHD, NMP, 120 °C, 24h.

Scheme 3.9

Usually, the outcome of Ullmann coupling is affected by many factors such as the concentration of substrate, the ratio of copper catalyst to the aryl halide, and also the temperature of the reaction.[88] A further study by experimenting with these reaction parameters with our system could result in a better outcome. However, due to the difficulty in obtaining sufficient amounts of starting material as a result of the low yields obtained from the earlier BNC reaction, a more systemic study could not be conducted within a reasonable time frame available to this author. In the next section of this chapter, the attempts at connecting the two benzylisoquinoline subunits using a S_NAr-based reaction will be discussed.

3.2.2 Second synthetic effort towards (-)-cycleanine by S_NAr-based reaction

The S_NAr-based reaction for biaryl ether formation involves a direct nucleophilic coupling of phenols to electron-deficient aryl halides. Nucleophilic substitution attack on an electron-rich aromatic ring is expected to be very slow under the normal S_NAr reaction conditions. An electron-withdrawing group such as a nitro group is usually needed on the *ortho* or *para* position to the group which will be replaced. With these considerations in mind and also based on the work described previously, a retrosynthetic analysis for (-)-cycleanine by using a S_NAr-based reaction was devised as shown in Scheme 3.10.

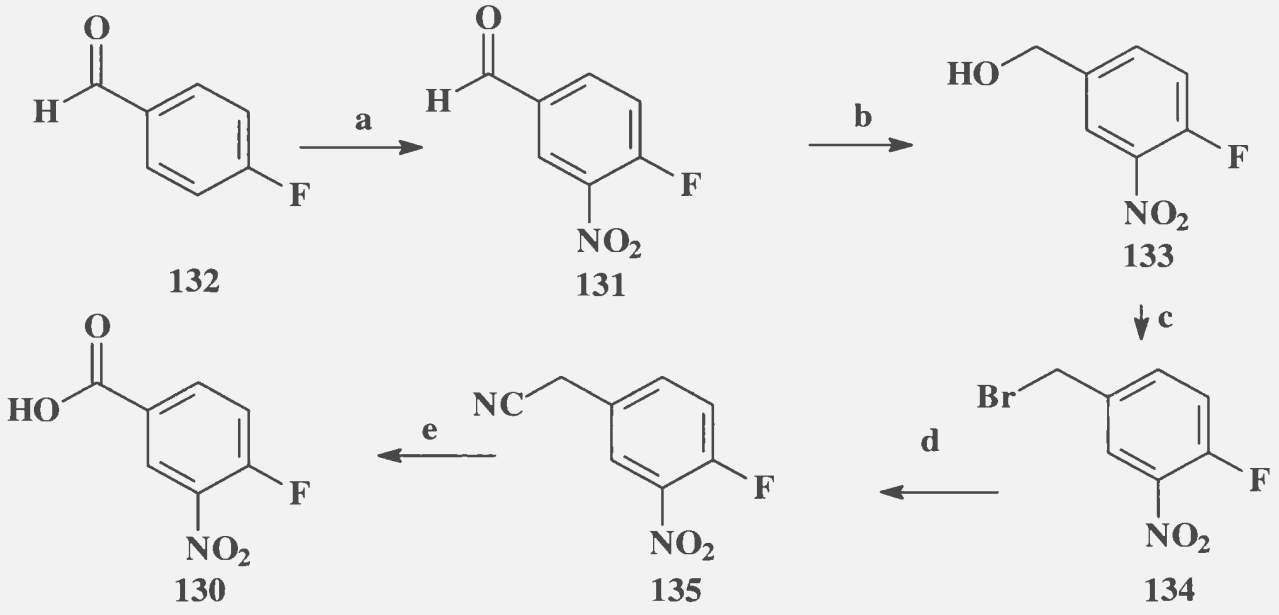


Scheme 3.10

In this retrosynthetic analysis, the basic framework of (-)-cycleanine was designed to be obtained by a S_NAr-based coupling of **128**. A BNC reaction of amide **129** should lead to **128**. Finally, a Schotten-Baumann reaction between **117** and **130** could form **129**. Compound **117** had been synthesized previously as described in the early part of this thesis (Scheme 3.1). The synthesis of compound **130** could be achieved using 4-fluorobenzaldehyde (**132**) and the procedure will be described in the following Section 3.2.2.1.

3.2.2.1 Synthesis of the fluorobenzylisoquinoline subunit

The synthesis of the fluorobenzylisoquinoline subunit commenced with the preparation of compound **130** (Scheme 3.11). First, 4-fluoro-3-nitrobenzaldehyde (**131**)



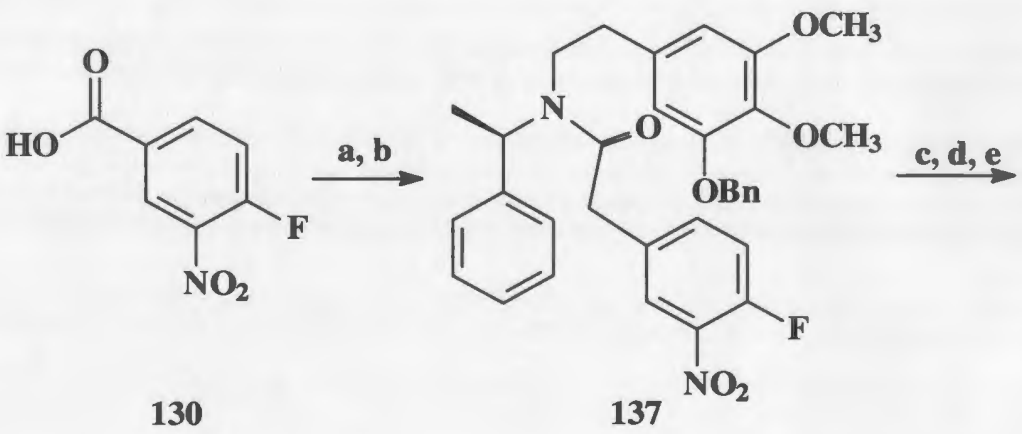
132 131 133 134 135 130

Conditions: a) HNO_3, H_2SO_4, 0 °C, 74%; b) $NaBH_4$, THF, CH_3OH, 84%; c) PBr_3, CH_2Cl_2, 0 °C, 51%; d) Et_4NCN, CH_3CN, 43%; e) aq. conc. HCl, reflux, 95%.

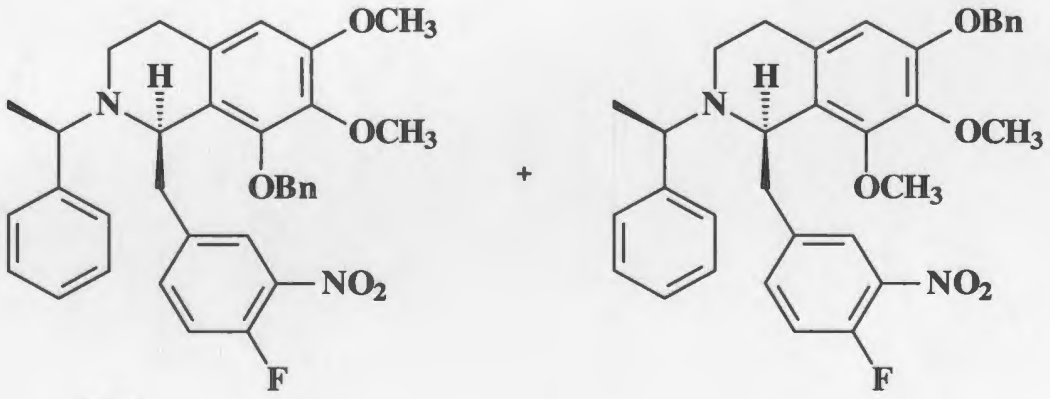
Scheme 3.11

was obtained by nitration of **132** using a mixture of HNO_3 and H_2SO_4 (74%). Reduction of compound **131** with sodium borohydride produced the primary alcohol **133** in 84% yield. Subjecting **133** to PBr_3 in dichloromethane at low temperature afforded 4-fluoro-3-nitrobenzyl bromide (**134**) in 51% yield which, after cyanation with Et_4NCN in acetonitrile, formed **135** (43%). Then, a simple hydrolysis of **135** in aqueous concentrated HCl at refluxing temperature afforded the desired 4-fluoro-3-nitrophenylacetic acid (**130**).

After the carboxylic acid **130** was obtained, the subsequent work was to synthesize the fluorobenzylisoquinoline subunit **136a**. This was accomplished using the same methodology that was used for compound **46a** and **122a** described earlier. Treating **130** with oxalyl chloride led to the respective acid chloride, then the chiral auxiliary was introduced by a reaction between the acid chloride with (*R*)-α- methylbenzylamine which produced the amide **137** (74%). After this, BNC reaction with **137** as substrate produced the two regioisomers **136a** and **136b** in yields of 21% and 30%, respectively (Scheme 3.12).



130 137



136a 136b

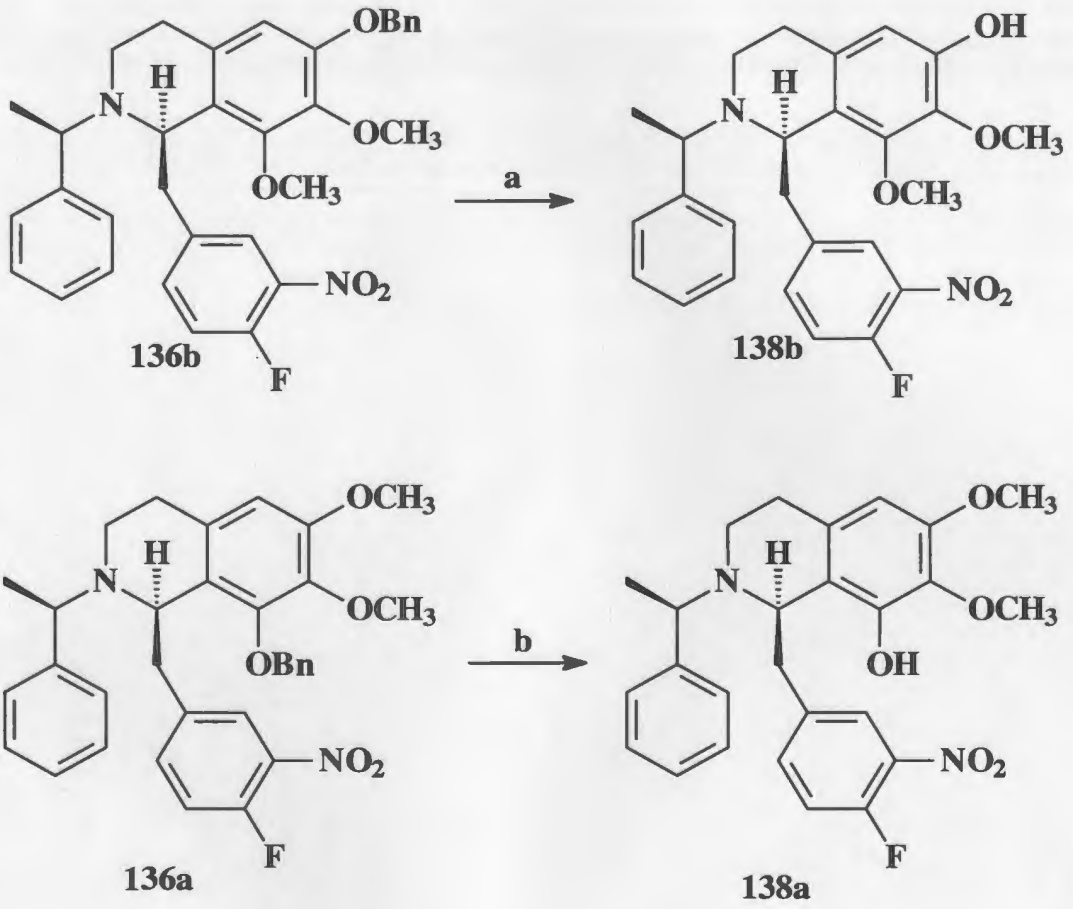
Conditions: a) oxalyl chloride, benzene; b) **117**, NaOH, CH_2Cl_2, H_2O, 74%; c) $POCl_3$, benzene, reflux; d) $NaBH_4$, MeOH, -78 °C; e) aqueous HCl, 21% **136a** and 30% **136b**.

Scheme 3.12

3.2.2.2 Use of a S_NAr-based reaction to build the framework of (-)-cycleanine

With pure fluorotetrahydroisoquinoline **136a** and **136b** in hand, attention was then focused on conducting the S_NAr-based reaction to construct the (-)-cycleanine framework. In order to do this, **136b**, which was utilized as a model compound as before,

and **136a** were first treated with $TiCl_4$ which, as expected, led to **138b** and **138a** respectively, in average yields of 61% and 57% (Scheme 3.13).

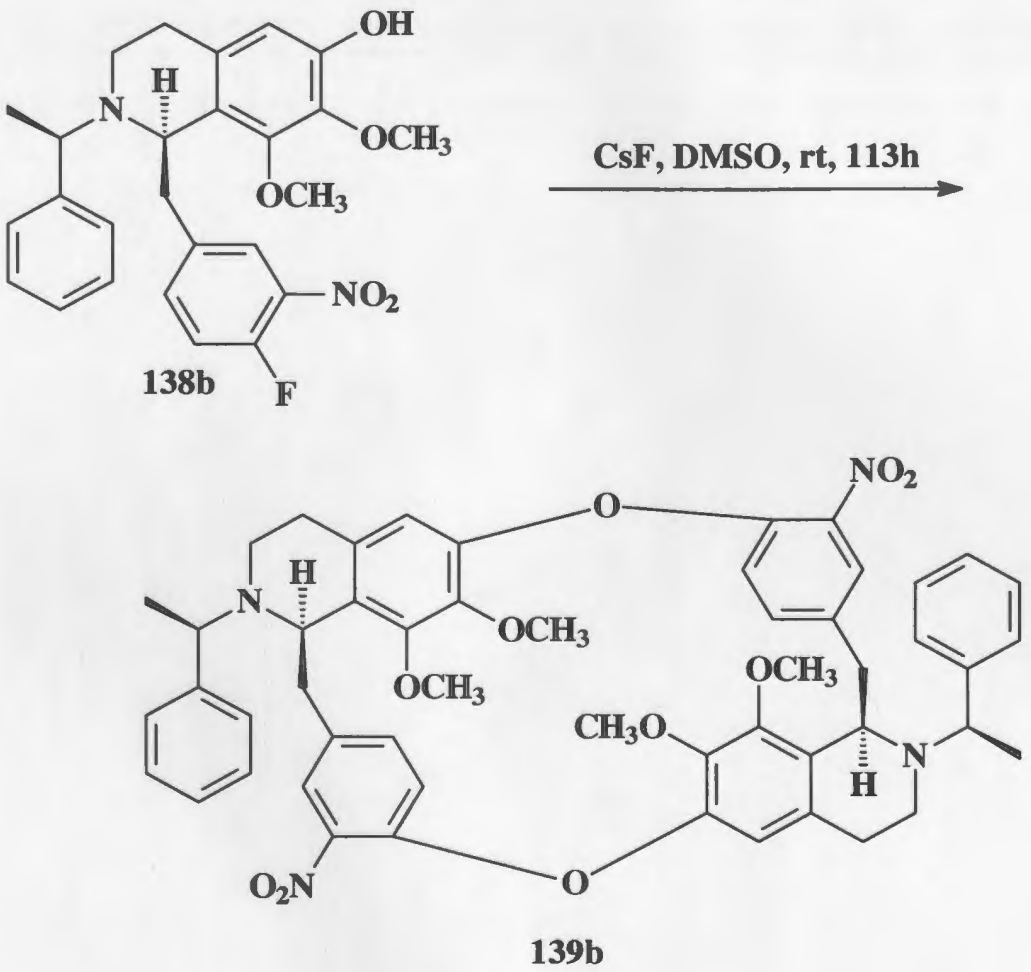


Conditions: a) $TiCl_4$, CH_2Cl_2, 5 h, 61%; b) $TiCl_4$, CH_2Cl_2, 5 h, 57%.

Scheme 3.13

The S_NAr reaction, as discussed before, is usually conducted with bases such as $NaCO_3$, K_2CO_3, and CsF in aprotic media such as DMF or DMSO. In this research, to affect the coupling process of building the skeleton of (-)-cycleanine, CsF in DMSO was used, based on the results obtained in the synthesis of (-)-tejedine.[46] In order not to waste the valuable compound **138a**, compound **138b** was first used to conduct model studies for the coupling reaction (Scheme 3.14). Thus, compound **138b** was stirred with CsF in

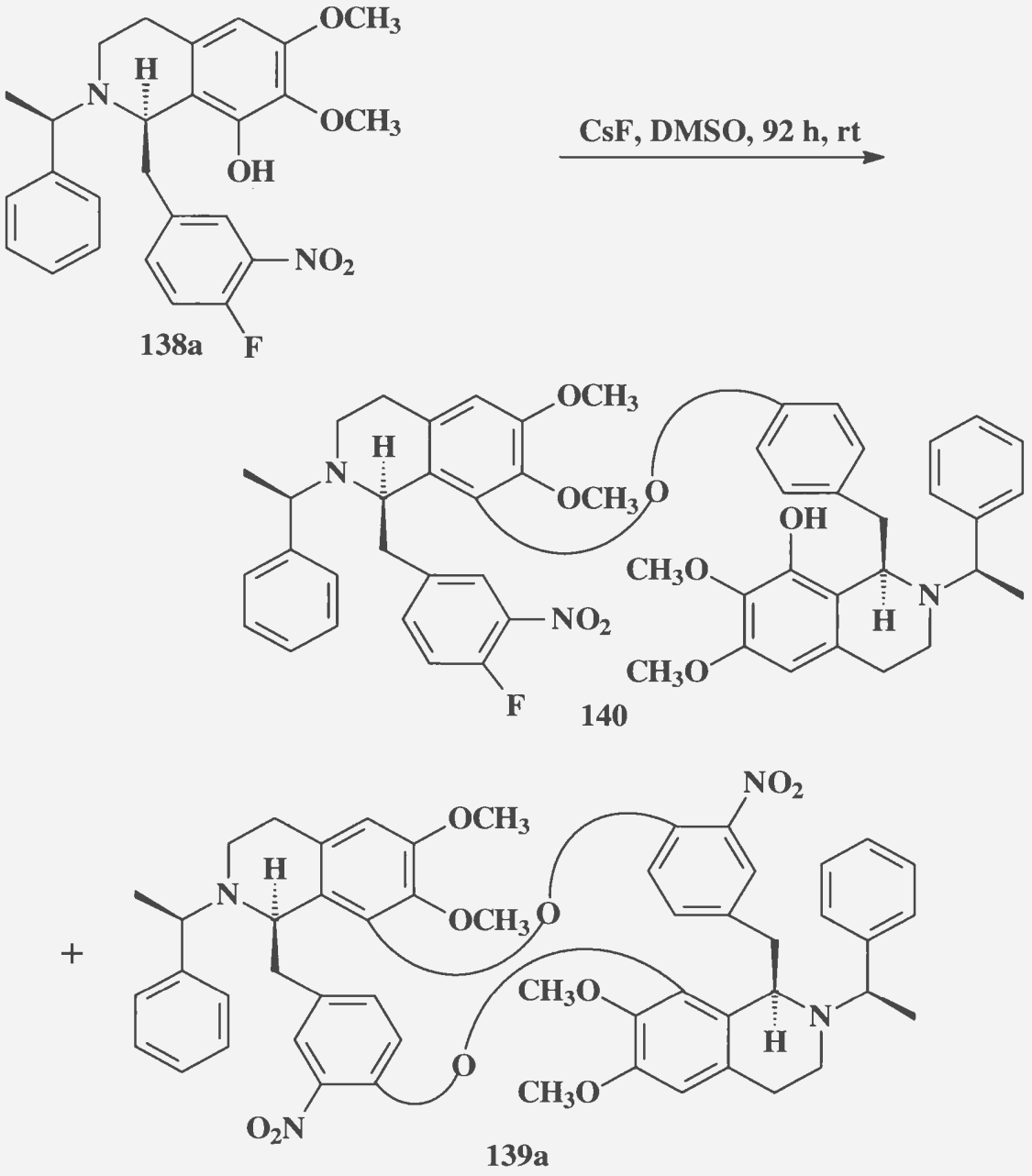
DMSO at room temperature under argon for 113 h. The reaction was worked up in the usual way to form a red residue. Although APCI-MS revealed the presence of the expected dimer **139b**, it could not be separated or purified.



Scheme 3.14

Although pure **139b** was not obtained from this model reaction, it still showed that the S_NAr-based procedure could potentially be a effective method for forming the diaryl ether linkages for the final target compound (-)-cycleanine. Therefore, the coupling

reaction with the desired precursor was attempted next by employing the same procedure as the model reaction. When the reaction was finished after a reaction time of 92 h and worked up as before, the crude product was checked by APCI-MS. This time, two mass



Scheme 3.15

peaks were found, one corresponding to the ring dimer **139a**, the other corresponding to the linear dimer **140** (Scheme 3.15). But just as before, all of the efforts attempted for isolating these products from the mixture failed. The subsequent steps such as removing the nitro and the chiral auxiliary groups, and the introduction of the methyl groups to the nitrogen atoms was therefore not be performed although these steps may have led to products which could be separable.

Thus, as with the improved Ullmann coupling reaction, S_NAr-based reactions also did not afford the desired products. However, if the results of the S_NAr reaction are compared, they still provide some useful information. The model coupling reaction with **138b** via S_NAr reaction only produced a macrocyclic product with no linear dimer remaining in the crude reaction product according to APCI-MS. However, the coupling reaction of **138a** using the same reaction conditions formed both linear dimer **140** and the macrocyclic dimer **139a**. If the abundance of the M^+ ion is used as a reference peak in the MS for determining the ratio of product amounts, the linear dimer **140** appears to be formed in a greater amount than the macrocyclic product **139a**. The macrocyclic dimer **139b** (Scheme 3.15) formed by the homocoupling of **138b** contains a 22-membered ring, whereas the dimer **139a** (Scheme 3.16) formed from the homocoupling of reaction of **138a** contains only an 18-membered ring. This meant that in the S_NAr-based reaction once the linear dimer of **138b** was formed, it would undergo intramolecular ring closure to form the 22-membered macrocyclic product **139b** relatively easily because of the relatively larger ring size. However, in case of **138a**, possibly due to the constraints of the smaller 18-membered macrocycle, it is difficult to

form **139a** from the linear dimer **140**. This experiment needs to be further evaluated in the future in order to ascertain whether re-subjecting the product mixture to the reaction conditions would result in a changed **139a** to **140** ratio. Of course, although the coupling of **138a** using the S_NAr-based reaction approach seemed to more easily give **140**, it does not mean that this methodology is completely unsuitable for synthesizing the target (-)-cycleanine. As was discussed before, there are various factors which can affect the result of this coupling reaction. Since the MS data suggests that the desired dimer **139a** formed, a more systematic investigation of this reaction could possibly lead successfully to the desired synthesis of (-)-cycleanine.

3.3 Summary and conclusions

In this chapter, an enantioselective synthesis of (-)-cycleanine was attempted. Both the improved Ullmann coupling methodologies and a S_NAr-based aryl ether reaction were used to build the basic skeleton of the target molecule. However, neither of these two key reactions provided a satisfactory result. From the experience of this author, it is felt that both methods are still viable for synthesizing (-)-cycleanine, although the S_NAr reaction appears to be more viable if the mild reaction conditions and the simplicity of isolating the product are considered. It is also felt by the author that the synthesis of the benzylisoquinoline subunit should also be given more attention. Although the BNC reaction in this thesis resulted in the desired product with correct stereochemist-ry, its low yield and lack of regioselectivity limited the experiments which could be undertaken in the subsequent steps.

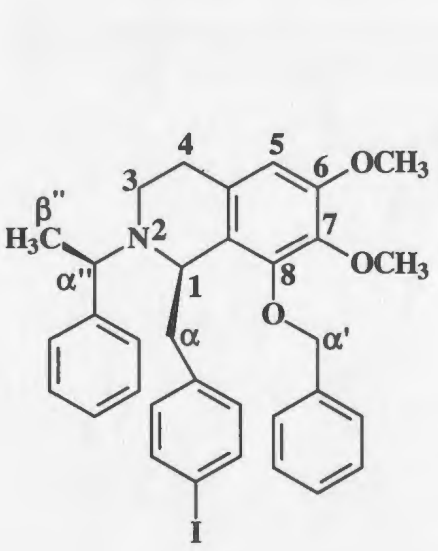
3.4 Experimental

General

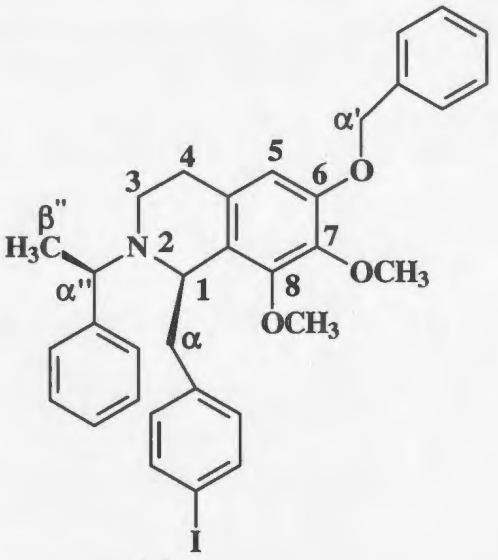
Flash column chromatography was performed using 240-400 mesh silica gel and preparative layer (1 mm) chromatography (PLC) was conducted using 60 mesh silica gel. All solvents and reagents were either of the highest commercial grade available or were redistilled (CH_2Cl_2, hexane, and benzene distilled over CaH_2). ^1H and ^{13}C NMR spectra were obtained on the Bruker Avance 500 MHz instrument with a TXI inverse-detection gradient probe in $CDCl_3$ unless otherwise specified, and shifts are relative to an internal tetramethylsilane signal. The following abbreviations are used in descriptions of in the ^1H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). The ^{13}C NMR spectra shifts were measured relative to the solvent. Overlap may have prevented the reporting of all resonances. Low-resolution mass spectral data were obtained from the V.G. Micromass 7070HS instrument or obtained from Atmospheric Pressure Chemical Ionization-Mass Spectrometry (APCI-MS). Mass spectral data and intensity (%) are described as MS (*m/z*) or APCI-MS (*m/z*). Melting points (m.p.) were determined using a Fisher-Johns hot stage apparatus and are uncorrected.

1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (46a) and

1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (46b)



46a



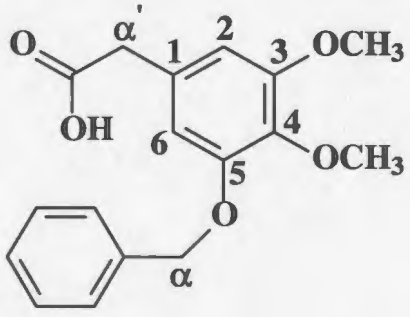
46b

Compound **88** (0.99 g, 1.6 mmol), $POCl_3$ (6.0 mL) and benzene (17 mL) were combined under an atmosphere of argon and the mixture was brought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (7.0 mL) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.30 g, 7.9 mmol) in five portions over 3 h. The reaction was quenched by the addition of aqueous 10% HCl (10 mL), and the mixture was stirred at room temperature for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (15 mL) and transferred to a separatory funnel

containing H_2O (5.0 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3). The combined organic layers were washed with brine (5.0 mL × 2), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by column chromatography (30% EtOAc/hexane) to give compounds **46a** (120 mg, 21% based on used **88**) as a colorless oil , **46b** (150 mg, 26% based on used **88**) also as a colorless oil and recovered **88** (400 mg); **46a:** ^{1}H NMR (500 MHz): δ 7.41-6.47 (m, 15H, Ar-H), 5.20 (d, J = 9.7 Hz, 1H, H-α'), 4.20 (d, J = 9.7 Hz, 1H, H-α'), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.73 (m, 1H, H-3), 3.60 (q, J = 7.3 Hz, 1H, H-α"), 3.50 (m, 1H, H-3), 3.39 (d, J = 6.0 Hz, 1H, H-4), 2.96 (m, 1H, H-4), 2.65 (d, J = 4.5 Hz, 2H, H-α), 2.43 (dd, J = 4.5 Hz, J = 17 Hz, 1H, H-1), 1.25 (d, J = 7.3 Hz, 3H, H-β");

46b: ^{1}H NMR (500 MHz): δ 7.53-6.66 (m, 14H, Ar-H), 6.51 (s, 1H, H-5), 5.10 (d, J = 1.5 Hz, 2H, H-α'), 3.87 (s, 3H, OCH_3), 3.67 (m, 4H, H-3, OCH_3), 3.53 (q, J = 6.4 Hz, 1H, H-α"), 3.45 (m, 1H, H-3), 3.33 (m, 1H, H-4), 2.87 (m, 1H, H-4), 2.69 (m, 2H, H-α), 2.36 (dd, J = 4 Hz, J = 7.5 Hz, 1H, H-1), 1.23 (d, J = 4.3 Hz, 3H, H-β").

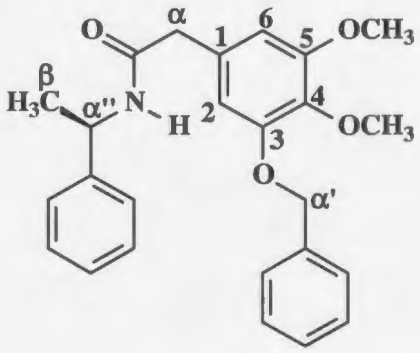
3-Benzyloxy-4, 5-dimethoxybenzoic acid (86)



A solution of **116** (2.0 g, 7.1 mmol) in 95% ethanol (30 mL) and aqueous 4.0 M NaOH (3.5 mL) was heated at reflux for 20 h. The reaction mixture was then cooled to rt and the ethanol was removed on a rotary evaporator. Water (20 mL) was added and the mixture was extracted first with CH_2Cl_2 (15 mL × 3) to remove the remaining starting material **116**. Then the aqueous layer was acidified with

aqueous concentrated HCl to pH = 1 and re-extracted with CH_2Cl_2 (5 mL × 3). The combined organic extracts were washed with brine (15 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to give crude **86**, which was further purified by column chromatography (ethyl acetate/hexane = 1:5) to give **86** (1.2 g, 54%) as a yellow solid; ^{1}H NMR: δ 7.30-7.7.46 (m, 5H, Ar-H), 6.56 (s, 1H, H-2), 6.51 (s, 1H, H-6), 5.11 (s, 2H, H-α), 3.85 (s, 6H, OCH_3), 3.55 (s, 2H, H-α'); MS (*m/z*): 302 (M^+, 18), 91 (100).

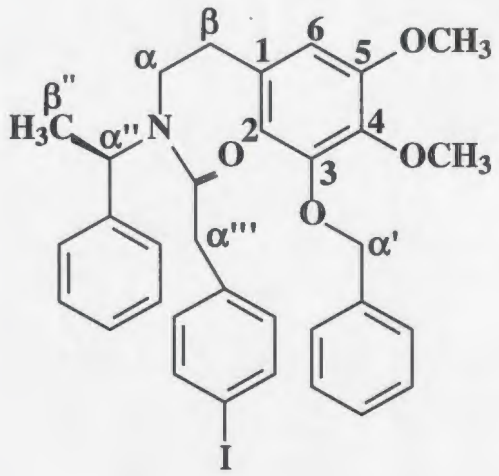
_N_-((_R_)-α-Methylbenzyl)-(3-benzyloxy-4,5-dimethoxy)phenylacetamide (87)



To a stirred solution of oxalyl chloride (0.87 mL, 10 mmol) in anhydrous benzene (30 mL) were added **86** (2.0 g, 6.7 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **86**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (15 mL) at 0 °C and the resulting solution was added dropwise to a stirred mixture of (*R*)-α-methylbenzylamine (1.4 mL, 7.9 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 30 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (30 mL × 3), washed with water (20 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by column chromatography (30% EtOAc/hexane) to afford amide **87** (2.6 g, 97%) as a viscous oil; ^{1}H NMR: δ 7.42-7.17 (m, 10H, Ar-H), 6.48 (d, J = 1.5 Hz, 1H, H-2), 6.44 (d,

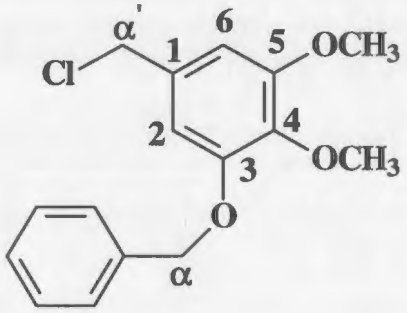
J = 1.5 Hz, 1H, H-6), 5.62 (d, J = 8.3 Hz, 1H, N-H), 5.11 (q, J = 8.3 Hz, 1H, H-α''), 5.08 (s, 2H, H-α'), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.47 (s, 2H, H-α), 1.38 (d, J = 8.3 Hz, 3H, β-CH_3); MS (*m/z*): 405 (M^+, 46), 300 (7), 257 (8), 105 (98), 91 (100).

_N_-[(_R_)-α-Methylbenzyl]-_N_-[(3-benzyloxy-4,5-dimethoxy)phenethyl]-4-iodophenyl acetamide (88)



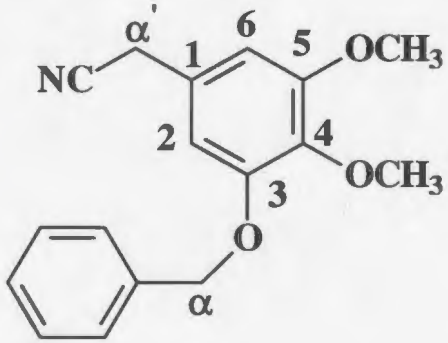
To a solution of oxalyl chloride (0.08 mL, 0.45 mmol) in dry benzene (6.4 mL) were added **80** (0.20 g, 0.73 mmol) and DMF (1 drop). The mixture was stirred until the evolution of gas ceased. The benzene was removed by rotary evaporation to give the crude acid chloride. The acid chloride was re-dissolved in CH_2Cl_2 (3 mL) at 0 °C. Then it was added to a stirred mixture of **117** (210 mg, 0.54 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 4.0 mL) at 0 °C. After stirring at room temperature for 1 h, the mixture was extracted with chloroform (5.0 mL × 3). The combined extracts were washed with water (5.0 mL × 2), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford **88** (0.31 g, 91%) as a viscous oil; The ^1H NMR spectrum of **88** was identical to that reported by Cui.[7]

3-Benzyloxy-4,5-dimethoxybenzyl chloride (115)



To a solution of **79** (2.3 g, 8.7 mmol) in anhydrous benzene (30 mL) thionyl chloride (1.6 mL, 18 mmol) was added dropwise. After stirring at room temperature for 18 h, the reaction was quenched by addition of water (15 mL), and the mixture was extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with aqueous saturated $NaHCO_3$ (10 mL × 2), water (15 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford . **115** as a colorless oil of (2.3 g, 94%) which was directly used in the subsequent step: ^{1}H NMR: δ 7.32-7.47 (m, 5H, Ar-H), 6.66 (d, *J* = 1.9 Hz, 1H, H-6), 6.62 (d, *J* = 1.9 Hz, 1H, H-2), 5.13 (s, 2H, H-α), 4.51 (s, 2H, H-α'), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); MS (*m/z*): 292 (M^+, 13), 91 (100).

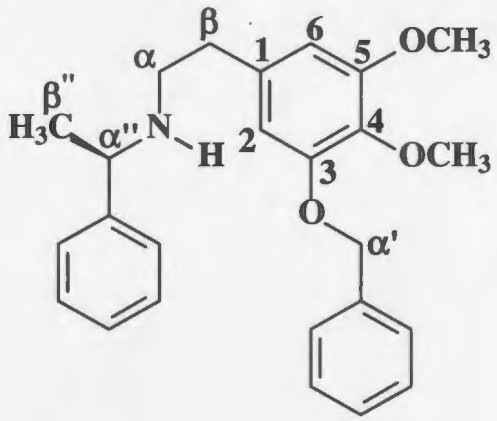
3-Benzyloxy-4,5-dimethoxyphenylacetonitrile (116)



To a solution of **115** (15 g, 51 mmol) in DMSO (9.5 mL) and benzene (4.4 mL) was added powdered NaCN (6.3 g, 18 mmol) in 3 portions. After stirring for 2 h at room temperature, the reaction mixture was poured into water (40 mL) and extracted with benzene (40 mL x 3). The combined organic layers were washed with brine (30 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **116** as a colorless oil (14 g, 99%) which was directly

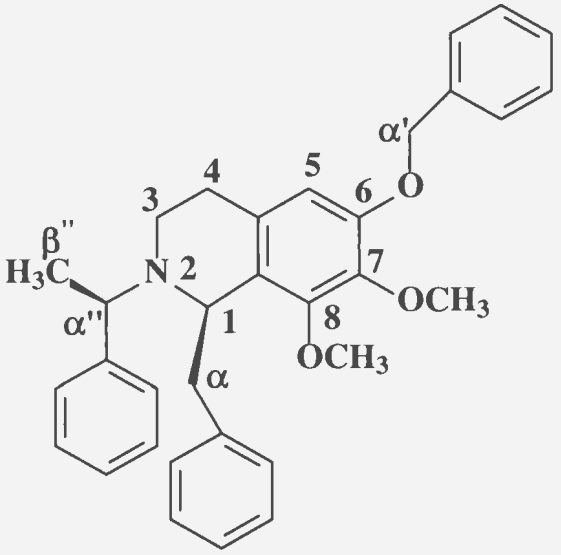
used in the next step;[1]H NMR: δ 7.31-7.45 (m, 5H, Ar-H), 6.57 (s, 1H, H-6), 6.53 (s, 1H, H-2), 5.13 (s, 2H, H-α), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.66 (s, 2H, H-α'); ^{13}C NMR: δ 154.0, 153.2, 138.9, 136.9, 128.8, 128.3, 127.5, 125.4, 118.0, 107.6, 105.7, 71.5, 61.2, 56.5, 24.0; MS (*m/z*): 283 (M^++1, 24), 91 (100).

***N*-((*R*)-α-Methylbenzyl)-(3-benzyloxy-4,5-dimethoxy)phenethylamine (117)**



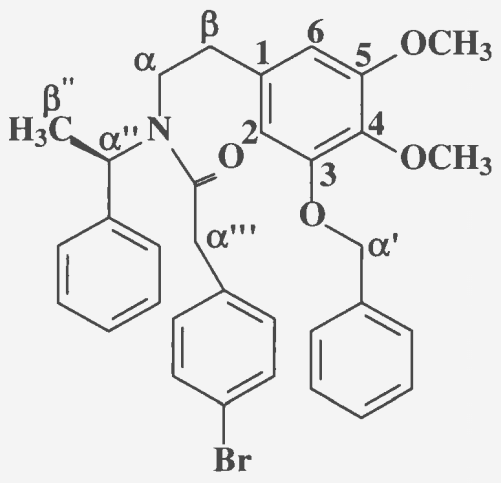
To a solution of chiral amide **87** (960 mg, 2.4 mmol) in anhydrous THF (30 mL) under argon was added BF_3/Et_2O (0.16 mL, 1.1 mmol). The mixture was heated to gentle reflux and BH_3/THF (1.0 M solution in THF, 6.7 mL, 6.0 mmol) was then added dropwise. The reaction mixture was refluxed for 2 h, then cooled to 0 °C and aqueous 20% HCl (50 mL) was added to the mixture. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature overnight, and then it was basified to pH = 13 with aqueous 50% KOH solution. The mixture was then extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with water (20 mL × 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **117** (930 mg, 99%) as a colorless oil, which was pure enough to be used directly in the next step; ^1H NMR: δ 7.21-7.44 (m, 10H, Ar-H), 6.41 (d, J = 1.6 Hz, 1H, H-2), 6.37 (d, J = 1.6 Hz, 1H, H-6), 5.08 (s, 2H, H-α'), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.74 (m, 1H, H-α''), 2.69 (m, 4H, H-α, H-β), 1.31 (d, J = 6.5 Hz, 3H, H-β''); APCI-MS: 392.20 (M^++1, 100).

1-(*R*)-(4-Benzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetra-hydroisoquinoline (119)



To anhydrous methanol (5.0 mL) was added **46b** (0.10 g, 0.16 mmol) and 10% Pd/C catalyst (30 mg). The mixture was stirred under H_2 at atmospheric pressure (maintained using a balloon) for 4 h. The Pd/C catalyst was removed by filtration and the solvent was removed on a rotary evaporator. The residue obtained was purified by column chromatography ($CHCl_3$:MeOH:NH_4OH = 9:1:0.1) to afford **119** as a colorless oil (66 mg, 84%); ^1H NMR: δ 7.48-6.66 (m, 15H, Ar-H), 6.51 (s, 1H, H-5), 5.09 (s, 2H, H-α'), 3.87 (s, 3H, OCH_3), 3.80 (m, 1H, H-3), 3.66 (s, 3H, OCH_3), 3.56 (q, J = 6.4 Hz, 1H, H-α''), 3.48 (m, 1H, H-3), 3.31 (m, 1H, H-4), 2.90 (m, 1H, H-4), 2.80 (m, 2H, H-α), 2.37 (dd, J = 4.5 Hz, J = 17.5 Hz, 1H, H-1), 1.22 (d, J = 6.0 Hz, 3H, H-β''); ^{13}C NMR: 151.6, 151.2, 146.1, 141.1, 140.9, 137.5, 136.8, 132.1, 130.7, 129.9, 129.8, 128.7, 128.3, 128.1 128.0, 127.9 , 127.8, 127.5, 127.4, 127.3, 126.3, 125.6, 125.1, 109.4, 71.1, 61.1, 60.7, 58.9, 56.6, 41.5, 38.6, 22.7, 22.4; APCI-MS (*m/z*): 494.2 (M^++1, 100).

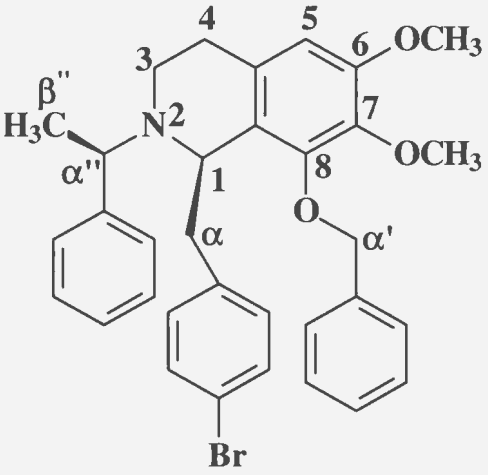
_N_-[(_R_)-α-Methylbenzyl]-_N_-[(3-benzyloxy-4,5-dimethoxy)phenethyl]-4-bromophenyl acetamide (121)



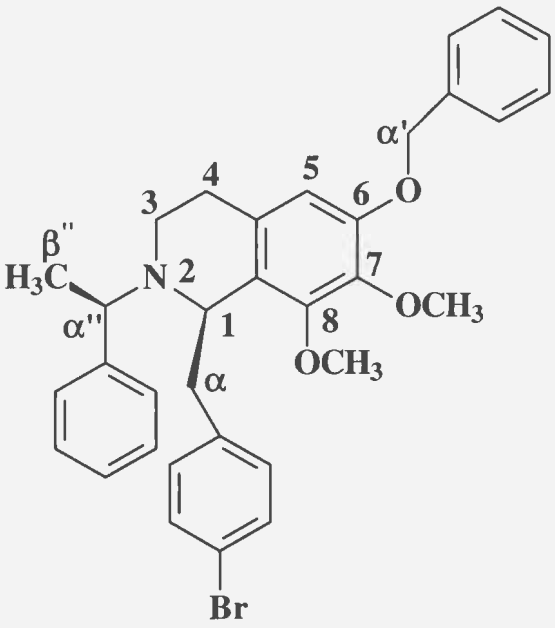
To a solution of oxalyl chloride (0.28 mL, 1.5 mmol) in anhydrous benzene (30 mL) were added **120** (0.54 g, 2.5 mmol) and DMF (3 drops). The mixture was stirred for 0.5 h. The benzene was removed on a rotary evaporator to afford the acid chloride which was immediately redissolved in CH_2Cl_2 (20 mL) at 0 °C. The solution was added to a stirred mixture of **117** (1.6 mg, 4.0 mmol) and CH_2Cl_2- aqueous 5% NaOH (1:1.5, 20 mL). After stirring at room temperature for 1 h, the mixture was extracted with chloroform (10 mL × 3). The combined extracts were washed with water (15 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford **121** (2.2 g, 91%) as a viscous oil; The ^{1}H NMR spectrum of **121** was similar to that of compound **88** described earlier in this thesis. APCI-MS (*m/z*): 590.1 (M^++1, 100); 588.1 (M^+-1, 98).

1-(*R*)-(4-Bromobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (122a) and

1-(*R*)-(4-bromobenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (122b)



122a



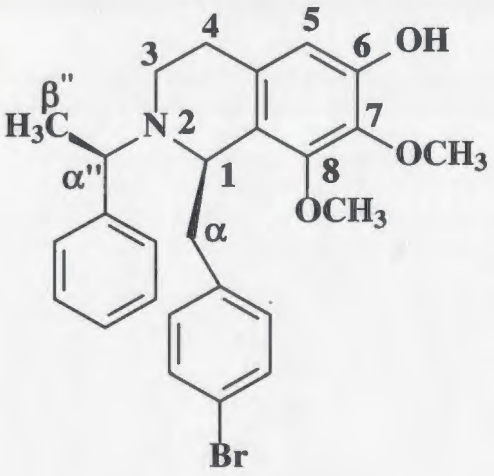
122b

Compound **121** (0.18 g, 0.31 mmol), $POCl_3$ (2.5 mL) and CH_3CN (5 mL) were combined under an atmosphere of argon and brought to a gentle reflux. After approximately 6 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (5.0 mL) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.10 g, 2.8 mmol) in two portions over 4 h. The reaction was quenched through the addition of aqueous 10% HCl (10 mL), and the mixture was stirred at room temperature for 30 min.

The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (10 mL) and transferred to a separatory funnel containing H_2O (5.0 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (5.0 mL × 3). The combined organic layers were washed with brine (5.0 mL × 2), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by PLC (30% EtOAc/hexane) to give compounds **122a** (41 mg, 23%) as a colorless oil , **122b** (39 mg, 23%) also as a colorless oil; **122a:** ^{1}H NMR: δ 7.33-6.50 (m, 15H, Ar-H), 5.19 (d, J = 10 Hz, 1H, H-α'), 4.20 (d, J = 10 Hz, 1H, H-α'), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.73 (m, 1H, H-3), 3.60 (q, J = 7.3 Hz, 1H, H-α"), 3.48 (m, 1H, H-3), 3.39 (d, J = 6.0 Hz, 1H, H-4), 2.95 (m, 1H, H-4), 2.66 (d, J = 4.5 Hz, 2H, H-α), 2.43 (dd, J = 5.0 Hz, J = 16.5 Hz, 1H, H-1), 1.26 (d, J = 7.3 Hz, 3H, H-β"); ^{13}C NMR: δ 152.1, 150.6, 146.4, 140.6, 139.9, 137.2, 131.9, 130.8, 130.5, 129.5, 128.5, 128.4, 128.3, 127.3, 126.6, 124.2, 119.3, 107.7, 75.6, 61.1, 58.9, 57.1, 56.1, 40.5, 38.5, 23.1, 22.9, 22.3.

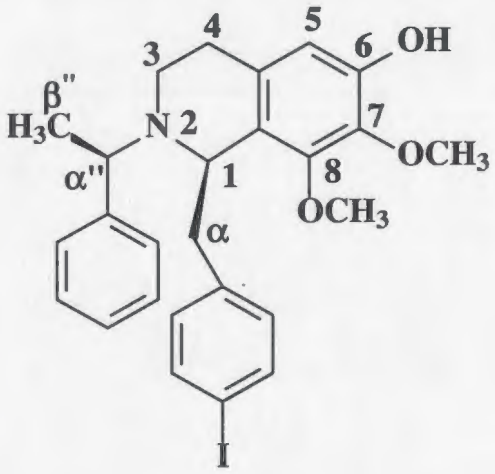
122b: ^{1}H NMR (500 MHz): δ 7.35-6.51 (m, 14H, Ar-H), 6.23 (s, 1H, H-5), 5.10 (d, J = 2.0 Hz, 2H, H-α'), 3.87 (s, 3H, OCH_3), 3.68 (m, 4H, H-3, OCH_3), 3.53 (q, J = 6.4 Hz, 1H, H-α"), 3.45 (m, 1H, H-3), 3.33 (m, 1H, H-4), 2.87 (m, 1H, H-4), 2.69 (m, 2H, H-α), 2.36 (dd, J = 3.7 Hz, J = 17.5 Hz, 1H, H-1), 1.23 (d, J = 4.3 Hz, 3H, H-β"); ^{13}C NMR: δ 151.5, 151.3, 145.9, 140.9, 140.3, 137.4, 131.7, 130.8, 130.7, 128.7, 128.1, 127.5, 127.4, 126.5, 124.6, 119.4, 109.4, 71.1, 61.1, 60.7, 58.8, 56.6, 40.8, 38.6, 22.6, 22.3; APCI-MS (*m/z*): 574.2 (M^++1, 100), 572.2 (M^+-1, 96).

1-(*R*)-(4-Bromobenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (125b)



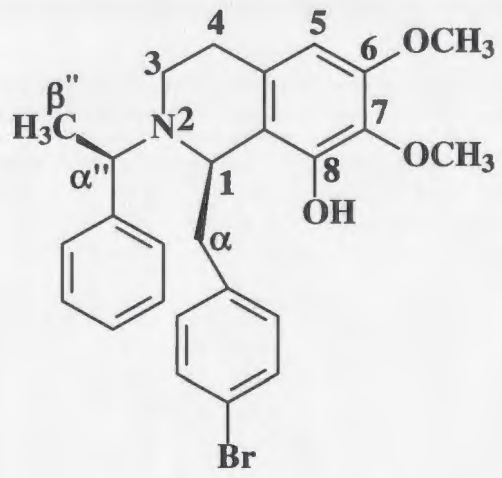
To a solution of **122b** (108 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $SnCl_4$ (0.10 mL) at room temperature. After stirring for 7 h, the reaction solution was poured into cold aqueous saturated $NaHCO_3$. The combined mixture was filtered through a pad of Celite, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The obtained residue was purified by PLC (EtOAc/hexane = 2:8) to give **125b** as a syrup (31 mg, 34%); ^{1}H NMR (500 MHz): δ 7.33-6.68 (m, 9H, Ar-H), 6.51 (s, 1H, H-5), 5.62 (bs, 1H, OH), 3.87 (s, 3H, OCH_3), 3.68 (m, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.52 (q, J = 6.4 Hz, 1H, H-α"), 3.42 (m, 1H, H-3), 3.33 (m, 1H, H-4), 2.87 (m, 1H, H-4), 2.62 (m, 2H, H-α), 2.38 (dd, J = 3.7 Hz, J = 14.5 Hz, 1H, H-1), 1.23 (d, J = 4.3 Hz, 3H, H-β"); ^{13}C NMR: δ 150.3, 147.9, 146.0, 140.2, 138.0, 131.7, 131.5, 130.8, 128.1, 127.4, 126.6, 123.4, 119.4, 110.3, 60.9, 60.2, 58.9, 56.5, 41.1, 38.6, 22.3.

1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (126b)



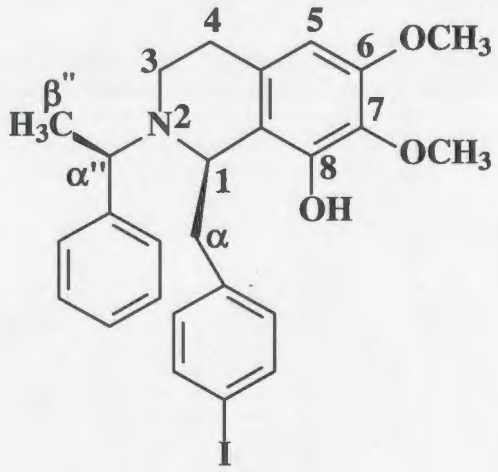
To a solution of **46b** (55 mg, 0.089 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added $SnCl_4$ (0.1 mL) at room temperature. After stirring for 7.5 h, the reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and then the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue was further purified by PLC (EtOAc/hexane = 3:7) to give **126b** as a syrup (27 mg, 57%); ^{1}H NMR: δ 7.53-6.66 (m, 9H, Ar-H), 6.51 (s, 1H, H-5), 5.57 (bs, 1H, OH), 3.86 (s, 3H, OCH_3), 3.67 (m, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.53 (q, J = 6.4 Hz, 1H, H-α"), 3.41 (m, 1H, H-3), 3.33 (m, 1H, H-4), 2.87 (m, 1H, H-4), 2.69 (m, 2H, H-α), 2.36 (dd, J = 4.0 Hz, J = 16.5 Hz, 1H, H-1), 1.23 (d, J = 4.3 Hz, 3H, H-β"); ^{13}C NMR: δ 147.9, 146.1, 140.9, 138.0, 136.8, 132.1, 128.1, 127.4, 126.6, 123.5, 110.3, 90.7, 77.3, 77.2, 76.8, 76.7, 60.9, 58.9, 56.6, 41.2, 38.6, 22.4, 22.3; APCI-MS (*m/z*): 530.0 (M^++1, 100).

1-(*R*)-(4-Bromobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (125a)



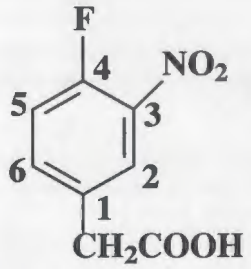
To a solution of **122a** (160 mg, 0.28 mmol) in anhydrous CH_2Cl_2 (20 mL) was added $SnCl_4$ (0.15 mL) at room temperature. After stirring for 4 h, the reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and then the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were washed with brine (10 mL × 2), dried by $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The obtained residue was further purified by PLC (EtOAc/hexane = 2:8) to give **125a** as a viscous oil (40 mg, 43% based on used **122a**) and recovered **122a** (50 mg); ^{1}H NMR: δ 7.31-6.71 (m, 9H, Ar-H), 6.25 (s, 1H, H-5), 5.75 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.81 (m, 1H, H-3), 3.58 (q, J = 6.4 Hz, 1H, H-α"), 3.39 (m, 1H, H-3), 3.31 (m, 1H, H-4), 2.85 (m, 1H, H-4), 2.71 (m, 2H, H-α), 2.36 (dd, J = 4.5 Hz, J = 16.5 Hz, 1H, H-1), 1.23 (d, J = 4.3 Hz, 3H, H-β"); ^{13}C NMR: δ 150.6, 146.8, 146.0, 140.3, 133.5, 132.6, 131.8, 131.1, 130.8, 128.1, 127.4, 126.4, 119.4, 117.9, 117.4, 103.7, 61.2, 58.9, 56.4, 55.9, 39.6, 38.9, 23.1, 22.1; APCI-MS (*m/z*): 484.1 (M^++1, 100).

1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (126a)



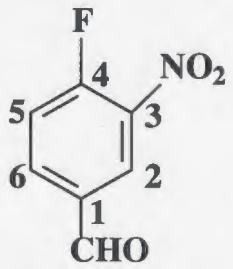
To a solution of **46a** (84 mg, 0.14 mmol) in dry CH_2Cl_2 (10 mL) was added $TiCl_4$ (0.1 mL) at room temperature. After stirring for 5 hours, the reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (5.0 mL × 2). The combined organic layers were washed with brine (5.0 mL × 2), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by PLC (EtOAc/hexane = 3:7) to give **126a** as a syrup (46 mg, 64%); ^{1}H NMR: δ 7.50-6.70 (m, 9H, Ar-H), 6.25 (s, 1H, H-5), 5.75 (s, 1H, OH), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.81 (m, 1H, H-3), 3.57 (q, J = 6.4 Hz, 1H, H-α"), 3.39 (m, 1H, H-3), 3.31 (m, 1H, H-4), 2.87 (m, 1H, H-4), 2.69 (m, 2H, H-α), 2.36 (dd, J = 4.0 Hz, J = 17 Hz, 1H, H-1), 1.24 (d, J = 4.3 Hz, 3H, H-β"); ^{13}C NMR: δ 150.6, 146.8, 146.0, 140.3, 133.5, 132.6, 131.8, 131.2, 130.8, 128.1, 127.4, 126.4, 119.4, 117.9, 117.4, 103.7, 61.2, 58.9, 56.4, 55.9, 39.6, 38.9, 23.1, 22.1; APCI-MS (*m/z*): 530.1 (M^++1, 100).

4-Fluoro-3-nitrophenylacetic acid (130)



To a flask was first added **135** (0.60 g, 3.3 mmol) then concentrated hydrochloric acid (10 mL). The reaction mixture was heated at reflux overnight, then cooled to room temperature. Water (10 mL) was added, followed by extraction with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography (30% ethyl acetate in hexane) to give **130** as white solid (0.62 g, 95%); ^{1}H NMR: δ 8.01 (dd, J = 2.1, 7.2, 1H, H-2), 7.55-7.58 (m, 1H, H-5), 7.29 (dd, *J* = 8.7, 10.5 Hz, 1H, H-6), 3.74 (s, 2H, -CH_2-); MS (*m/z*): 199 (M^+, 100), 154 (99), 122(77), 108 (99), 97 (48), 77 (50).

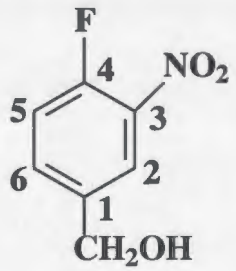
4-Fluoro-3-nitrobenzaldehyde (131)



To a solution of 4-fluorobenzaldehyde (**132**) (3.9 g, 32 mmol) in concentrated sulfuric acid (15 mL) at 0 °C was added 70% nitric acid (2.1 mL) slowly. The resulting reaction mixture was stirred under Argon for 2 h and then was poured into ice water (100 mL), and extracted with benzene (30 mL × 3). The combined benzene extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The residue was purified by column chromatography (EtOAc/hexane = 5:95) to afford **131** (3.9 g, 74%) as white solid; ^{1}H NMR: δ 10.04 (s, 1H, CHO), 8.61 (dd, *J* = 2.1, 7.2 Hz, 1H, H-2), 8.21 (m, 1H, H-6), 7.51 (dd, *J* = 8.3, *J* =

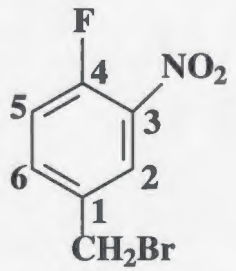
9.3, 1H, H-5); MS (*m/z*): 169 (M^+, 97), 168 (100), 122(55), 94 (56), 75 (97).

4-Fluoro-3-nitrobenzyl alcohol (133)



To a solution of **131** (3.8 g, 22 mmol) in THF (20 mL) and methanol (20 mL) was added sodium borohydride (0.50 g, 13 mmol) in portions. The reaction mixture was stirred for 2 h, and then concentrated to give a residue which then was dissolved in CH_2Cl_2 (20 mL) and water (20 mL) containing aqueous 1M HCl solution (12 mL). The organic phase washed with water, dried over anhydrous $MgSO_4$. Then the solvent was removed to yield a yellowish oil. It was purified by column chromatography (silica gel, 20% EtOAc in hexane) to afford **133** as yellowish oil (3.2 g, 84%); ^{1}H NMR: δ 8.07 (dd, J = 1.5, 7.0, 1H, H-2), 7.63 (m, 1H, H-5), 7.29 (dd, *J* = 8.7, 10.5 Hz, 1H, H-6), 4.77 (s, 2H, -CH_2-), 2.18 (bs, 1H, OH); MS (*m/z*): 171 (M^+, 78), 154 (30), 125 (99), 107 (86), 95 (100), 75 (73).

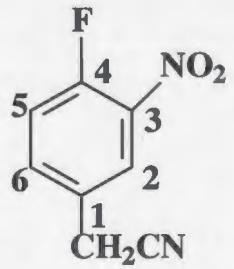
4-Fluoro-3-nitrobenzyl bromide (134)



To a solution of 4-fluoro-3-nitrobenzyl alcohol (**133**) (22 g, 0.13 mol) in CH_2Cl_2 (400 mL), PBr_3 (10 mL, 0.12 mol) was added dropwise under 0 °C. After 3 h of stirring at 0 °C, the reaction mixture was quenched by addition of water, the organic phase was washed with aqueous $NaHCO_3$, water, dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The crude product was purified by column chromatography (ethyl acetate:hexane = 2:8) to afford **134** as a clourless solid (17 g, 51%); ^{1}H NMR: δ 8.10 (dd, J = 2.0, 7.2, 1H, H-2), 7.67 (dddd, *J* =

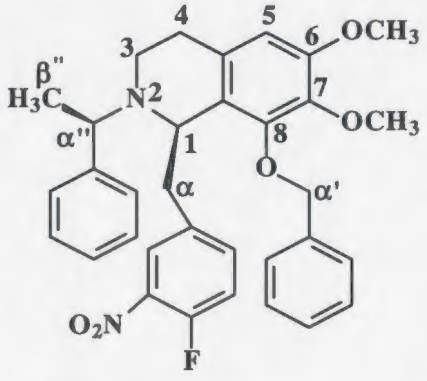
2.1, 4.2, 8.7 Hz, 1H, H-5), 7.29 (dd, *J* = 8.4, 10.6 Hz, 1H, H-6), 4.48 (s, 2H, -CH_2-); MS (*m/z*): 235 (M^+ +2, 3), 233 (M^+ -1, 3), 154 (99), 108 (100), 96 (23), 81 (28).

4-Fluoro-3-nitrophenylacetonitrile (135)

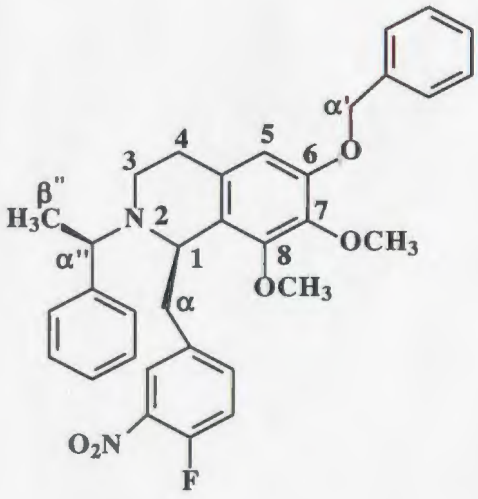


To a solution of **134** (1.8 g, 7.7 mmol) in MeCN (30 mL) was added Et_4NCN (1.6 g, 9.6 mmol). The resulting deep green solution was stirred at room temperature for 5 h. The solvent was removed on a rotary evaporator, and the residue was purified by column chromatography (EtOAc:hexane = 3:7) to give **135** as red oil (0.61 g, 43%); ^{1}H NMR: δ 8.06 (dd, J = 2.1, 7.2, 1H, H-2), 7.64-7.67 (m, 1H, H-6), 7.36 (dd, *J* = 8.7, 10.5 Hz, 1H, H-5), 3.84 (s, 2H, -CH_2-); MS (*m/z*): 180 (M^+, 100), 134 (80), 122(77), 107 (99), 95 (74), 81 (50).

1-(*R*)-(4-Fluoro-3-nitrobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-benzyloxy-6,7-dimethoxy-1,2,3,4- tetrahydroisoquinoline (136a) and **1-(*R*)-(4-fluoro-3-nitrobenzyl) -*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (136b)**



136a

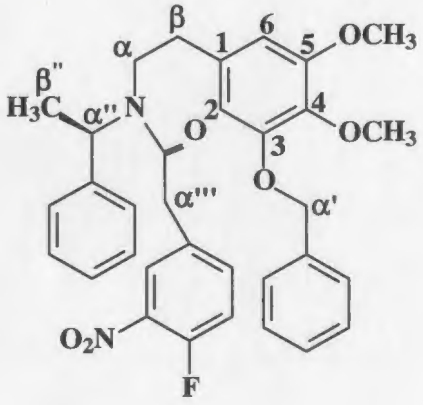


136b

Compound **137** (0.14 g, 0.31 mmol), $POCl_3$ (3.0 mL) and benzene (10 mL) were combined under an atmosphere of argon and the mixture was brought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (5.0 mL) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (80 mg, 2.1 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (10 mL), and the mixture was stirred at room temperature for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (10 mL) and transferred to a separatory funnel containing H_2O (5.0 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (5.0 mL × 3). The combined organic layers were washed with brine (5.0 mL × 2), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by PLC (30% EtOAc/hexane) to give compounds **136a** (28 mg, 21%) as a colorless oil , **136b** (41 mg, 30%) also as a colorless oil; **136a:** ^{1}H NMR (500 MHz): δ 7.47-6.51 (m, 14H, Ar-H), 5.22 (d, J = 9.7 Hz, 1H, H-α'), 4.28 (d, J = 9.4 Hz, 1H, H-α'), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.73 (m, 1H, H-3), 3.60 (q, J = 7.3 Hz, 1H, H-α"), 3.45 (m, 1H, H-3), 3.44 (d, J = 2.0 Hz, 1H, H-4), 2.96 (m, 1H, H-4), 2.75 (d, J = 4.2 Hz, 2H, H-α), 2.45 (d, J = 4.8 Hz, 1H, H-1), 1.28 (d, J = 7.0 Hz, 3H, H-β"); ^{13}C NMR: δ 155.0, 152.9, 152.4, 150.5, 145.9, 140.7, 138.0, 137.9, 137.2, 137.1, 137.0, 130.8, 129.3, 128.7, 128.5, 128.3, 127.4, 127.0, 126.8, 126.7, 123.3, 117.0, 116.9, 107.9, 75.7, 61.2, 60.6, 58.8, 56.7, 56.1, 39.9, 38.6, 22.5; APCI-MS (*m/z*): 557.3 (M^++1, 100);

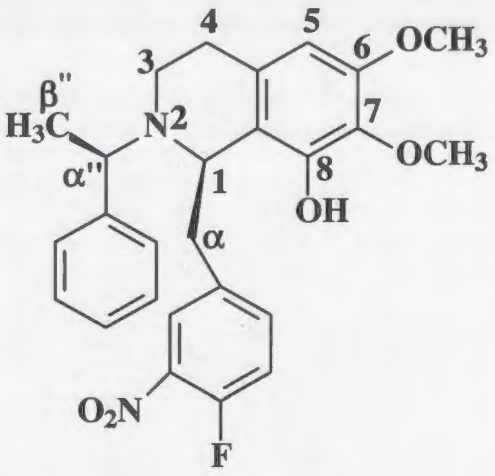
136b: ^{1}H NMR (500 MHz): δ 7.65-6.68 (m, 13H, Ar-H), 6.53 (s, 1H, H-5), 5.10 (d, *J* = 5.4 Hz, 2H, H-α'), 3.88 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.68 (d, J = 7.5Hz, 1H, H-3), 3.53 (q, *J* = 6.4 Hz, 1H, H-α''), 3.39 (m, 1H, H-3), 3.38 (m, 1H, H-4), 2.88 (m, 1H, H-4), 2.78 (m, 2H, H-α), 2.37 (d, *J* = 15 Hz, 1H, H-1), 1.26 (d, *J* = 4.3 Hz, 3H, H-β''); ^{13}C NMR: δ 151.4, 140.9, 137.2, 128.8, 128.2, 127.5, 127.4, 126.7, 126.6, 117.4, 117.2, 109.3, 71.1, 61.1, 60.8, 56.8, 40.1, 22.5; APCI-MS (*m/z*): 557.3 (M^++1, 100).

***N*-[(*R*)-α-Methylbenzyl]-*N*-[(3-benzyloxy-4,5-dimethoxy)phenethyl]-4-fluoro-3-nitrophenyl acetamide (137)**



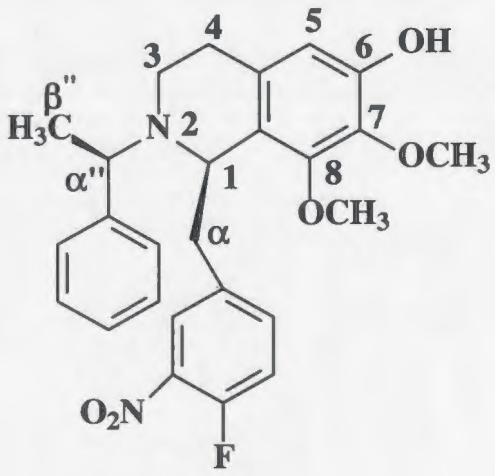
To a solution of oxalyl chloride (0.30 mL, 1.7 mmol) in anhydrous benzene (25 mL) were added **130** (0.62 g, 3.1 mmol) and DMF (2 drops). The mixture was stirred for 0.5 h. The benzene was removed by rotary evaporation to give the acid chloride which was redissolved in CH_2Cl_2 (12 mL) at 0 °C. This solution was added to a stirred mixture of **117** (0.80 g, 2.0 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 12 mL). After stirring at room temperature for 1 h, the mixture was extracted with chloroform. The combined extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by column chromatography (30% EtOAc/hexane) to afford **137** (0.86 g, 74%) as a viscous oil; since this product is a mixture of rotamers, its ^{1}H NMR spectrum was too complex to characterize. APCI-MS (*m/z*): 573.3.1 (M^++1, 100).

1-(*R*)-(4-Fluoro-3-nitrobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (138a)



To a solution of **136a** (21 mg, 0.040 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added $TiCl_4$ (0.050 mL) at room temperature. After stirring for 5 hours, the reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered using a Celite pad, and then organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (5.0 mL × 2). The combined organic layers were washed with brine (5.0 mL × 2), dried by $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue was purified by PLC (MeOH/$CHCl_3$ = 3:7) to give **138a** as a viscous oil (10 mg, 57%); ^{1}H NMR: δ 7.67-6.71 (m, 8H, Ar-H), 6.27 (s, 1H, H-5), 5.83 (s, 1H, OH), 3.90 (s, 3H, OCH_3), 3.86 (s, 1H, OCH_3), 3.79 (m, 1H, H-3), 3.56 (q, J = 6.4 Hz, 1H, H-α"), 3.37 (m, 1H, H-3), 3.35 (m, 1H, H-4), 2.90 (m, 2H, H-α), 2.75 (m, 1H, H-4), 2.37 (d, J = 17 Hz, 1H, H-1), 1.27 (d, J = 7.5 Hz, 3H, H-β"); APCI-MS (*m/z*): 467.1 (M^++1, 100).

1-(*R*)-(4-Fluoro-3-nitrobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (138b)



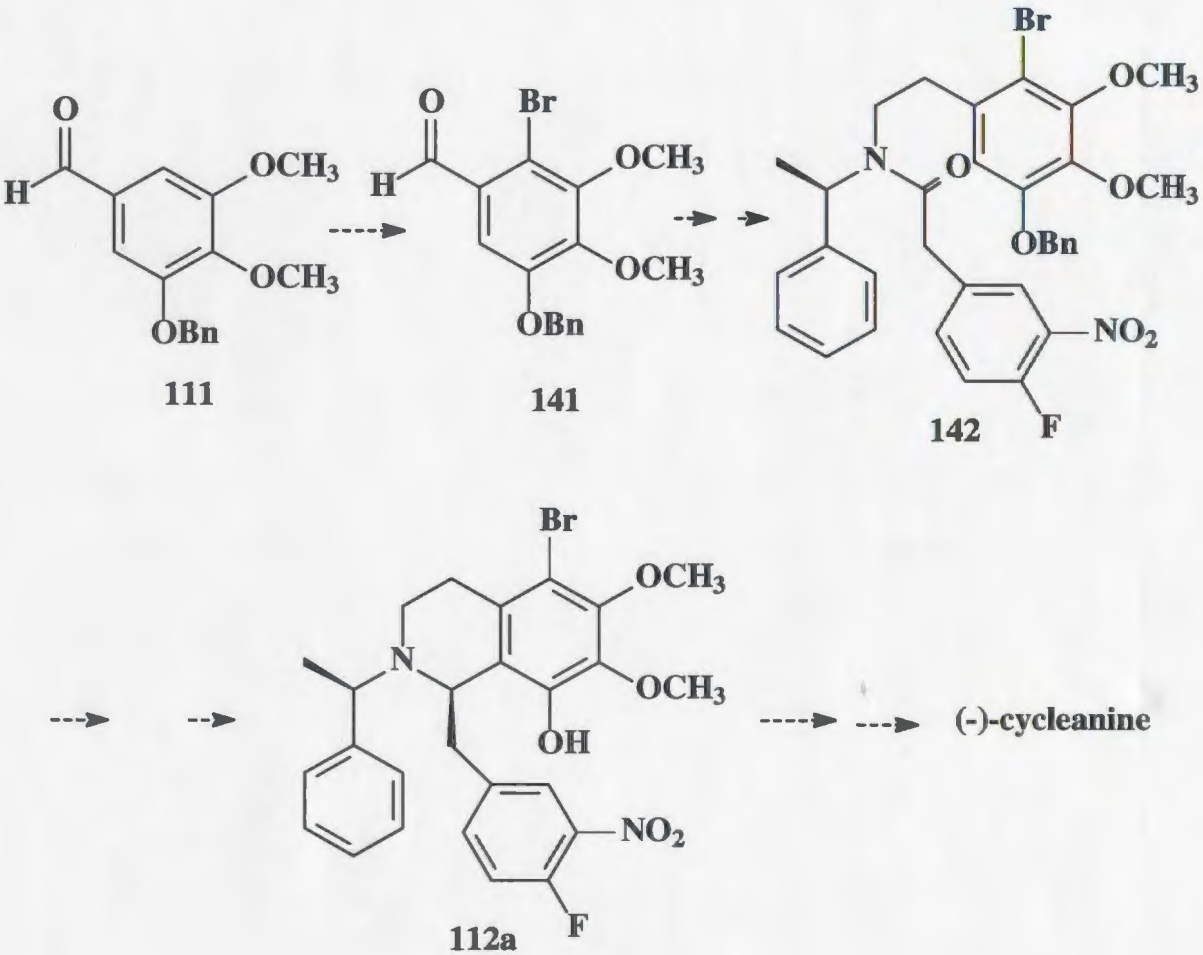
To a solution of **136b** (27 mg, 0.050 mmol) in anhydrous CH_2Cl_2 (5.0 mL) was added $TiCl_4$ (0.050 mL) at room temperature. After stirring for 5 h, the reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and then the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (5.0 mL × 2). The combined organic layers were washed with brine (5.0 mL × 2), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue was further purified by PLC (EtOAc/hexane = 3:7) to give **138b** as a viscous oil (14 mg, 61%); ^{1}H NMR: δ 7.63-6.68 (m, 8H, Ar-H), 6.53 (s, 1H, H-5), 5.61 (bs, 1H, OH), 3.88 (s, 3H, OCH_3), 3.67 (s, 3H, H-3, OCH_3), 3.65 (m, 1H, H-3), 3.53 (q, J = 6.4 Hz, 1H, H-α"), 3.38 (m, 1H, H-3), 3.36 (m, 1H, H-4), 2.88 (m, 1H, H-4), 2.78 (m, 2H, H-α), 2.38 (d, J = 18 Hz, 1H, H-1), 1.27 (d, J = 6.5 Hz, 3H, H-β"); APCI-MS (*m/z*): 467.1 (M^++1, 100).

Chapter 4

Future work

4.1 Further studies of the formation of the benzylisoquinoline subunit

All of the BNC reactions described in this work resulted in low yields. This was mainly because a mixture of regioisomers can be produced when there are two available ring-closure sites. Consequently, the difficulty in achieving the total synthesis increased due to the effort required for the separation of the two regioisomers. In order to

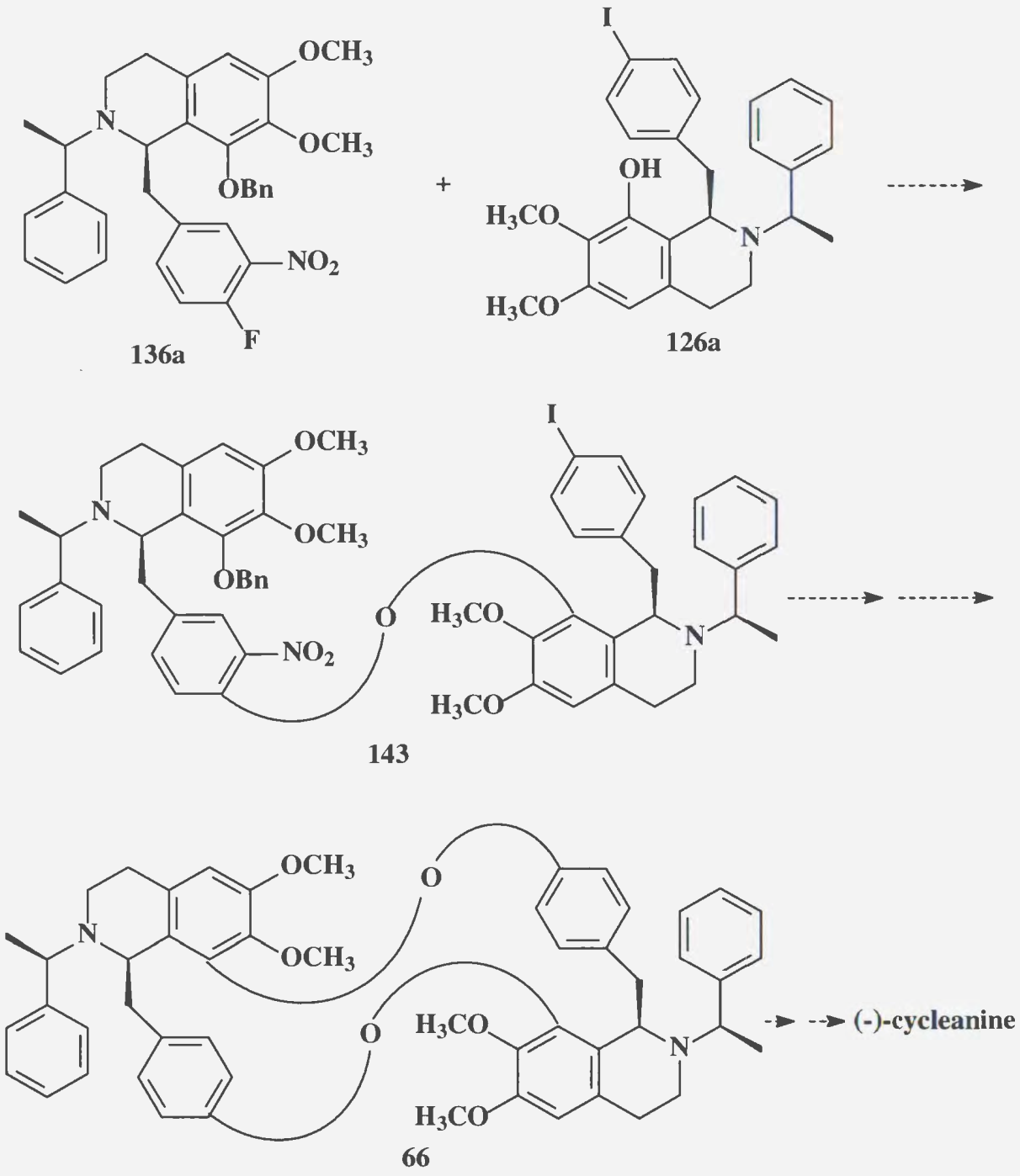


Scheme 4.1

circumvent this problem, the use of a blocking group may possibly prevent the formation of the undesired regioisomer. This blocking group must be robust enough to survive all of the reaction conditions used, and be easily and selectively removed at a later stage. With the above considerations in mind, a bromine atom, for example, could be used as a blocking group. Briefly outlined in Scheme 4.1 is one such proposal. In this scheme, the nitro group is introduced into compound **111**, which can subsequently be removed via a diazotization reaction.

4.2 Further proposal for the formation of diaryl ether linkages by heterocoupling

So far, all efforts towards the synthesis of the diaryl ether linkages with the aim to build the macrocyle of (-)-cycleanine were approached by a homocoupling strategy using either improved Ullmann coupling or S_NAr reactions. It is proposed that heterocoupling using both Ullmann coupling and a S_NAr reaction might possibly yield the desired product as shown in Scheme 4.2. Reaction of **136a** with **126a** could lead to **143**, which, after removal of the benzyl and nitro groups, could be subjected to Ullmann reaction conditions to give the key intermediate **66**. Two successive steps including removing the chiral auxiliary group and introducing the methyl group on to the nitrogen atom will produce the desired final product (-)-cycleanine.



Scheme 4.2

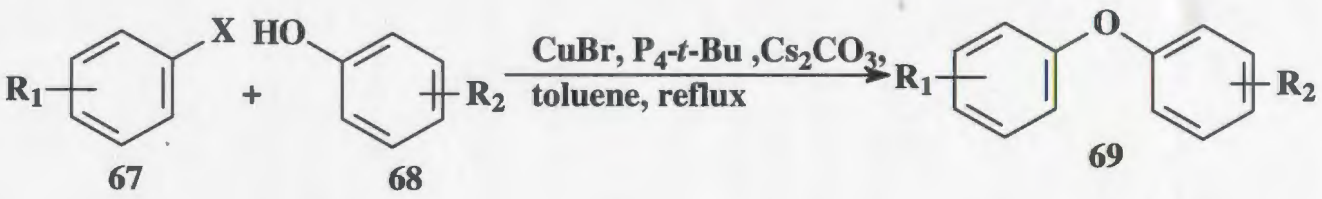
4.3 Further proposal for the diaryl ether formation step

The results obtained during this research demonstrated that the diaryl ether formation step using either the Ullmann coupling or the S_NAr reaction did not produce

ideal results. However, this does not mean these two methodologies are completely untenable. A systematic study was not done due to time constraints. Since various reaction conditions may affect the outcome of such complex coupling reactions, such a systematic study is necessary. Of course, this systemic study should not be limited to only using the same methodologies described in the previous chapters of this thesis.

For the S_NAr reaction, in this research CsF was selected as the base and DMSO was chosen as the reaction solvent. As mentioned before, both the base and the solvent are important factors which could affect the result of such reacton. So, besides CsF and DMSO, the use of other bases such as Na_2CO_3, $K2_CO_3$ and reaction solvents such as DMF could be also attempted.

For the improved Ullmann coupling, only Ma and Buck's methodologies were employed in this thesis. Currently, many research groups are working on developing better methods for the synthesis of diaryl ethers in order to find new synthetic routes for a wide range of biologically active compounds. For example, a procedure developed by Palomo involving the use of catalytic P_4-*t*-Bu base gives better yields of diaryl ethers at lower temperatures than the traditional Ullmann coupling (Scheme 4.3).[89]



Scheme 4.3

Another interesting example was reported by Li et al. where the traditional Ullmann coupling reaction was accelerated greatly using a microwave process (Scheme 4.4).[90]

Scheme 4.4

Obviously, these newer methodologies can also potentially be applied in the synthesis of (-)-cycleanine.

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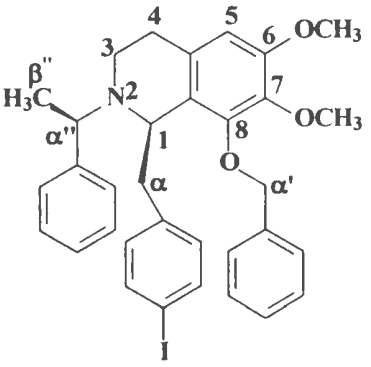
Appendix

^{1}H and ^{13}C NMR Spectra



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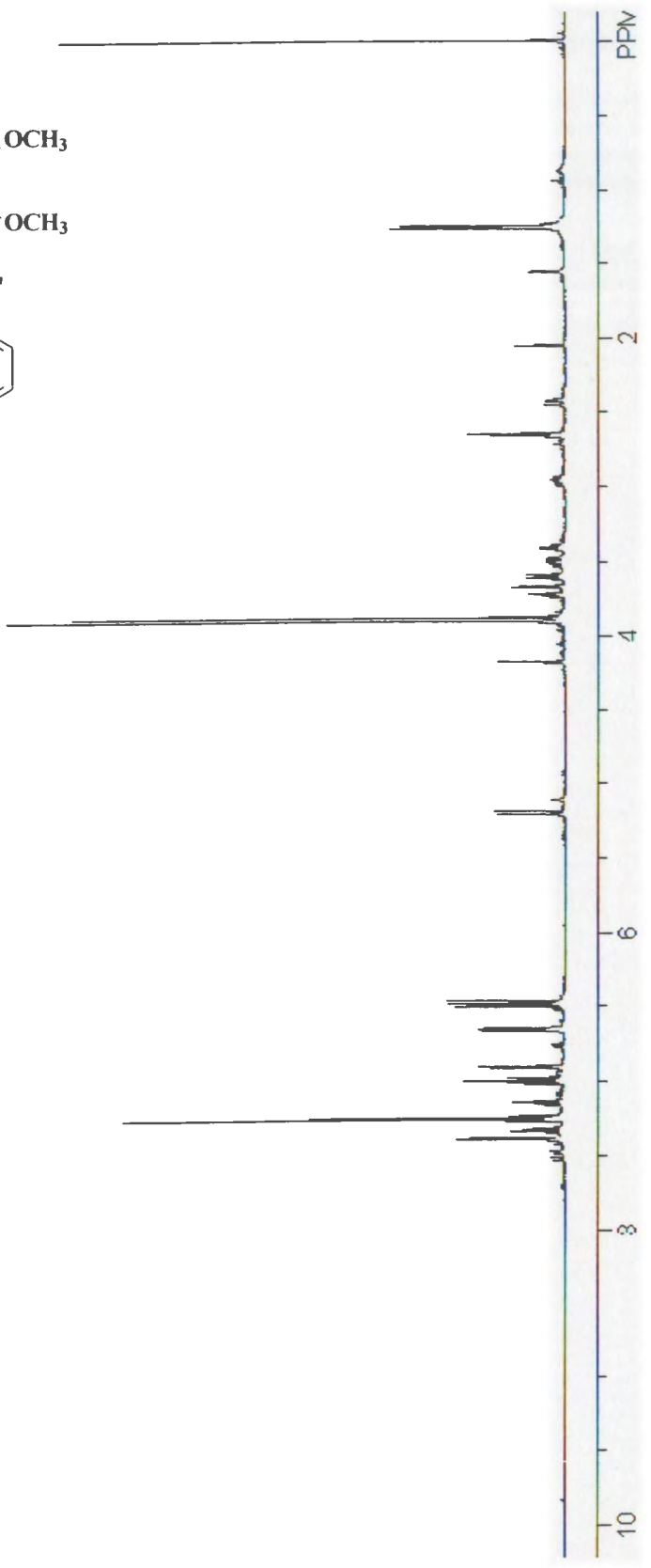

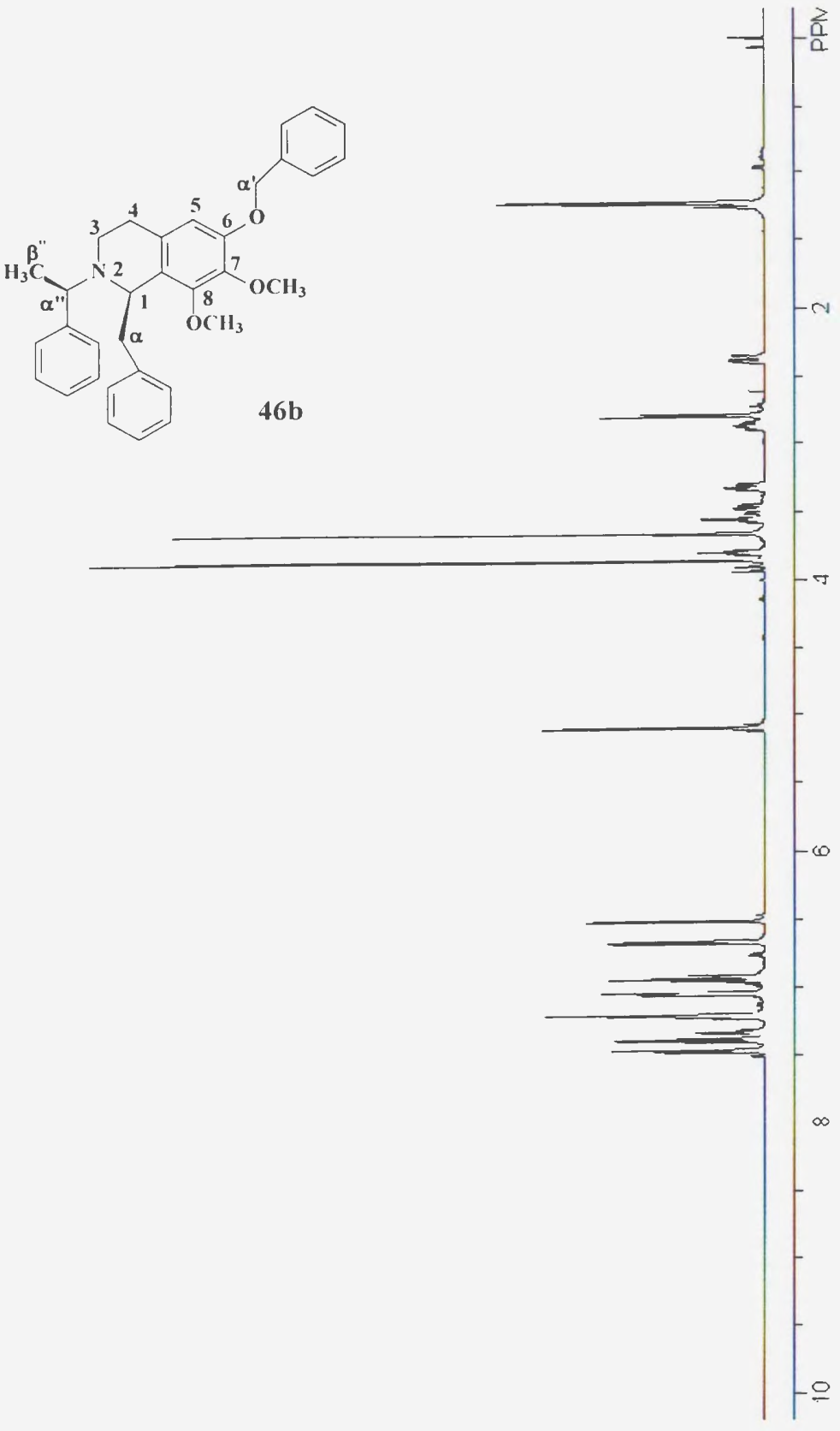

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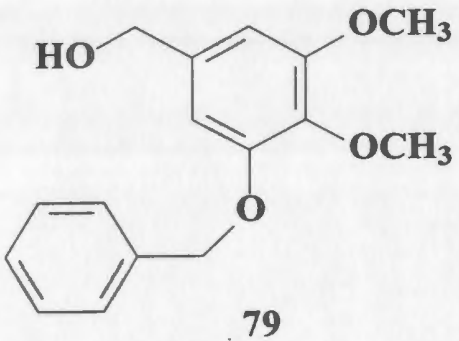

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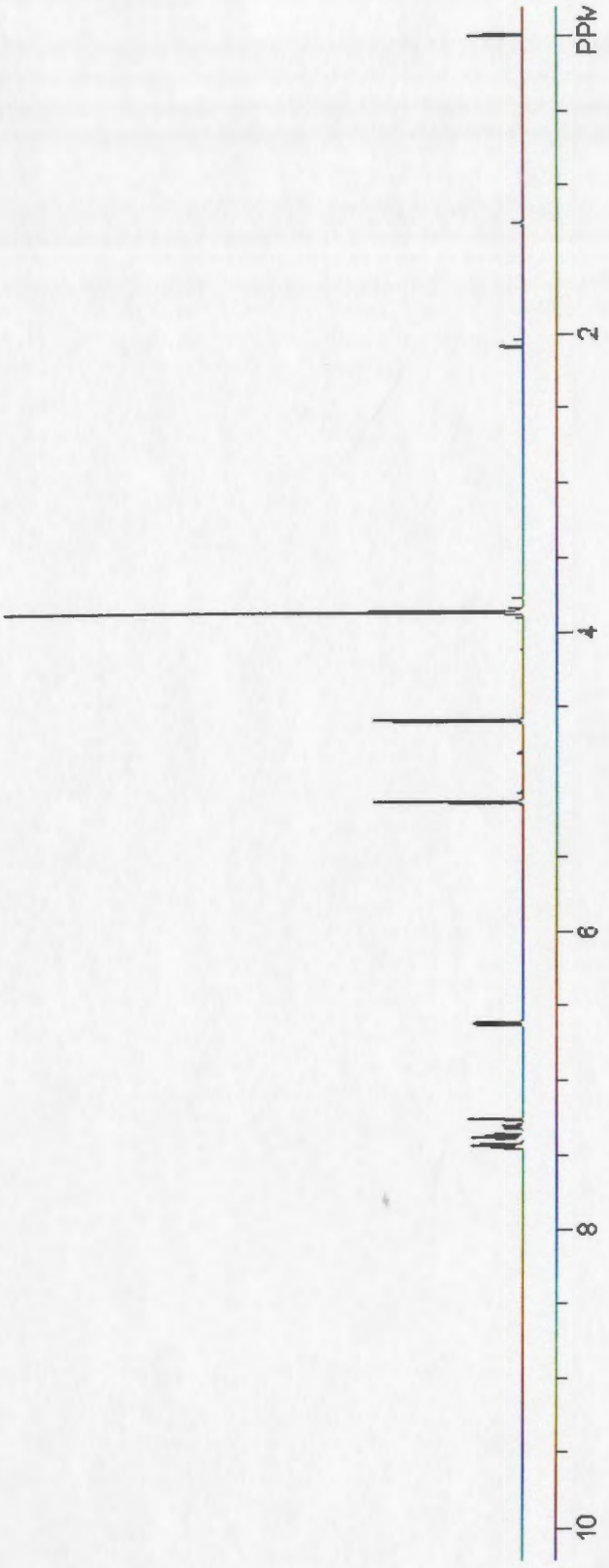

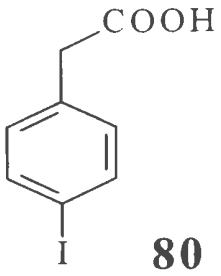

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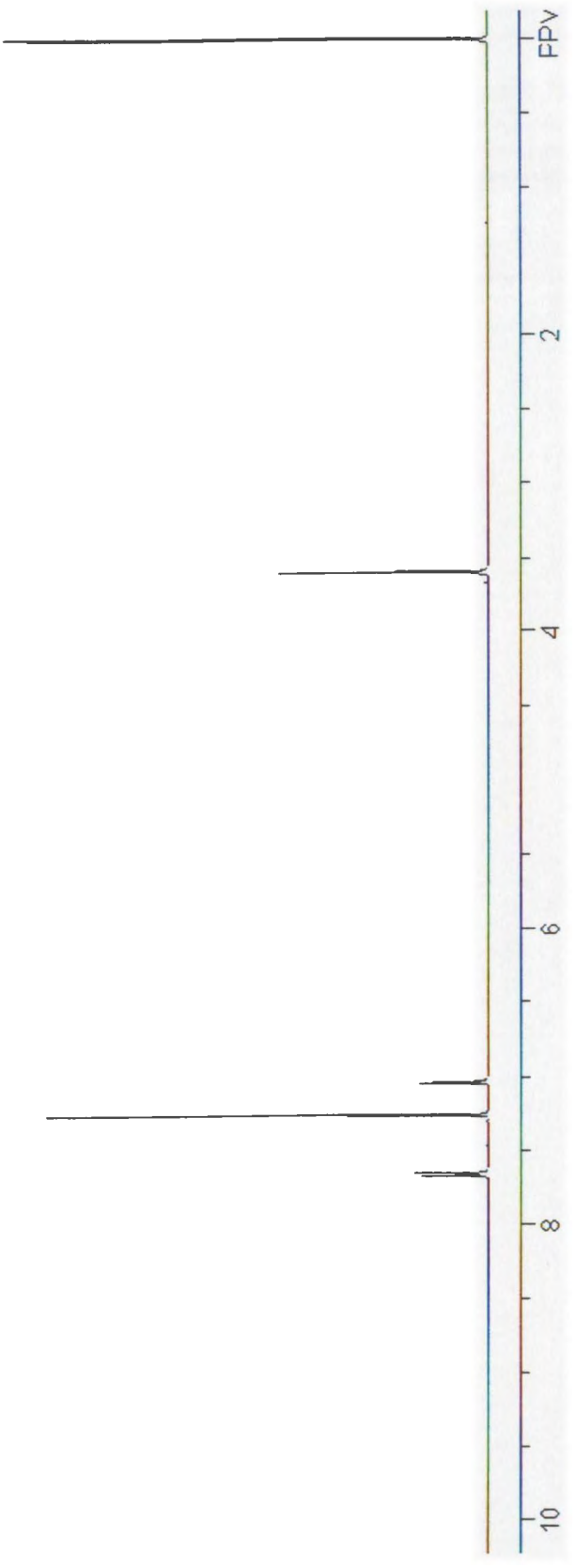

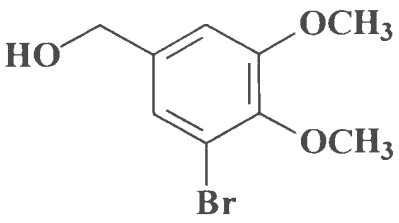

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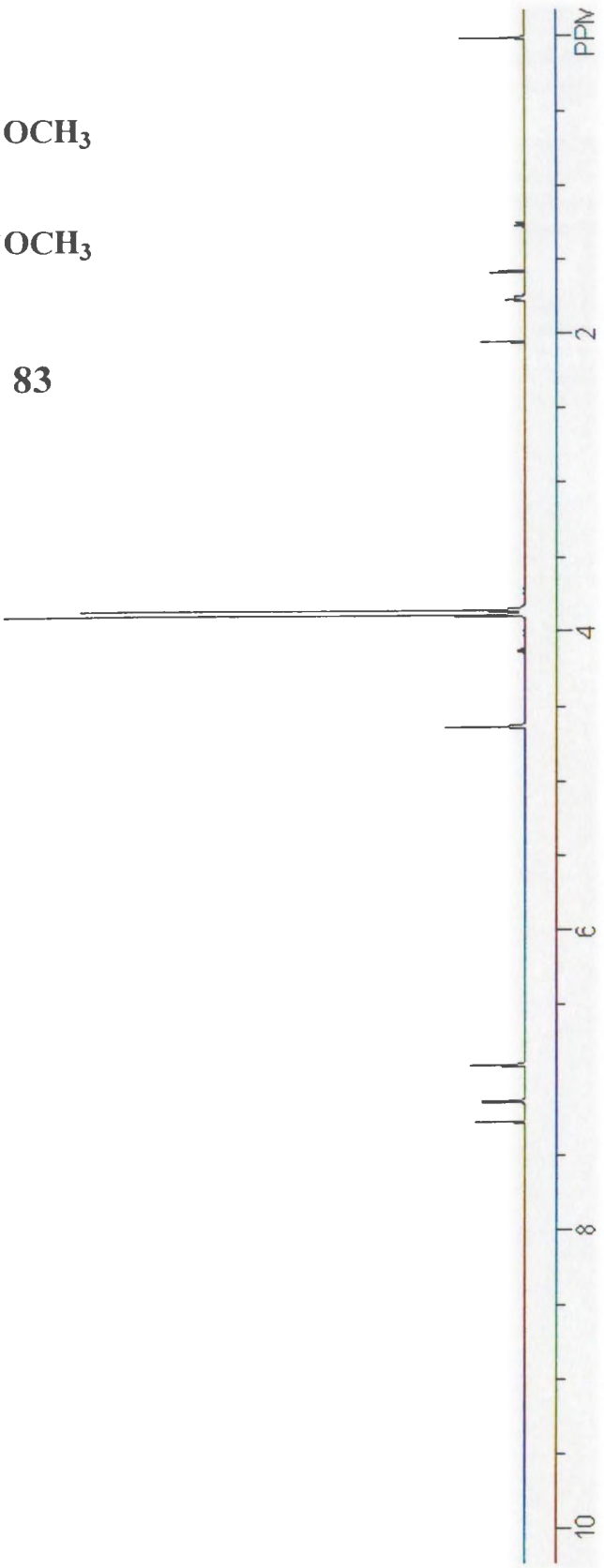

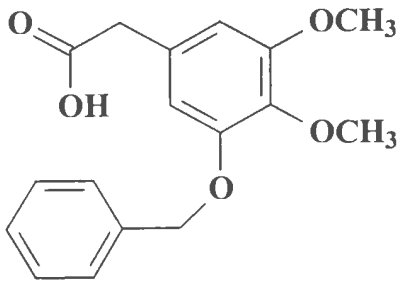

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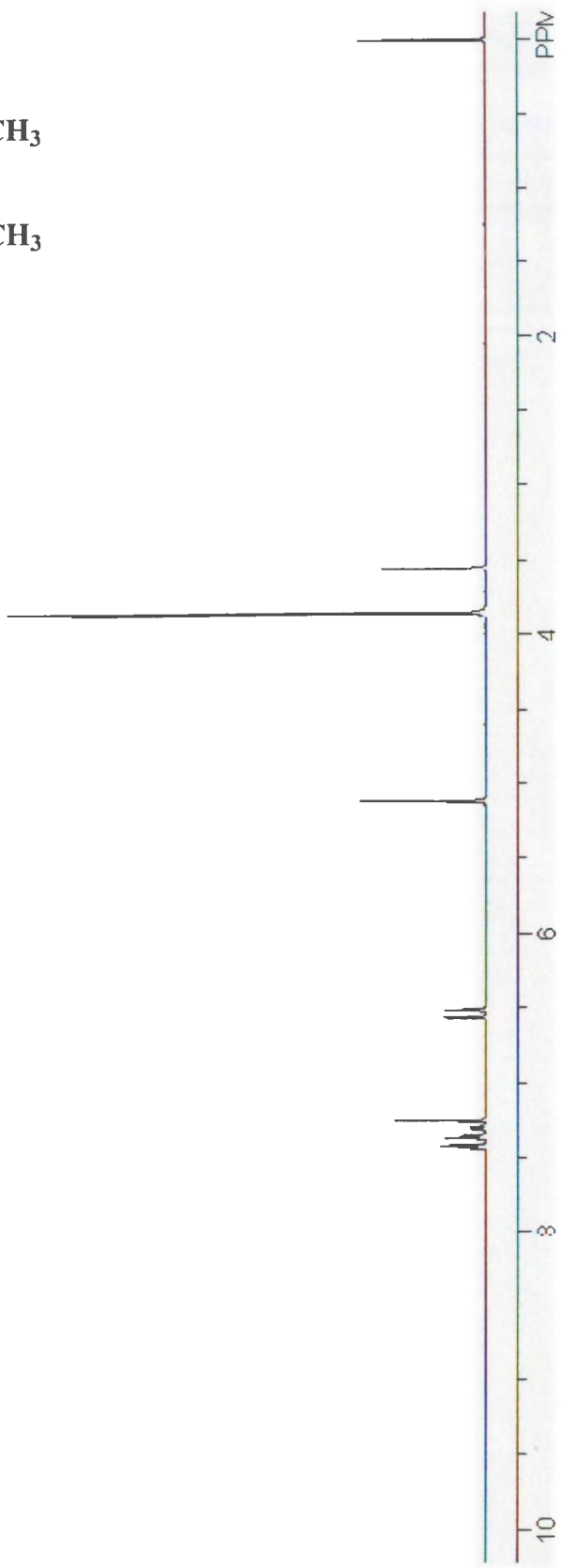

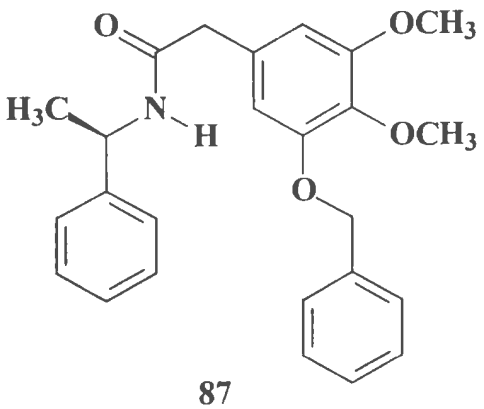

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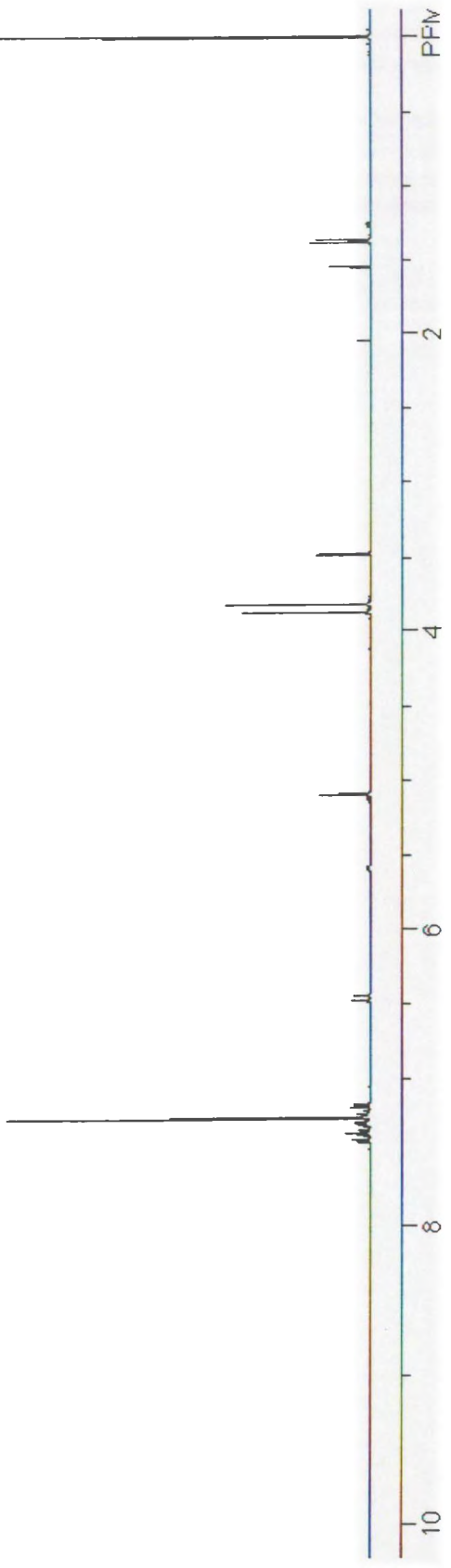

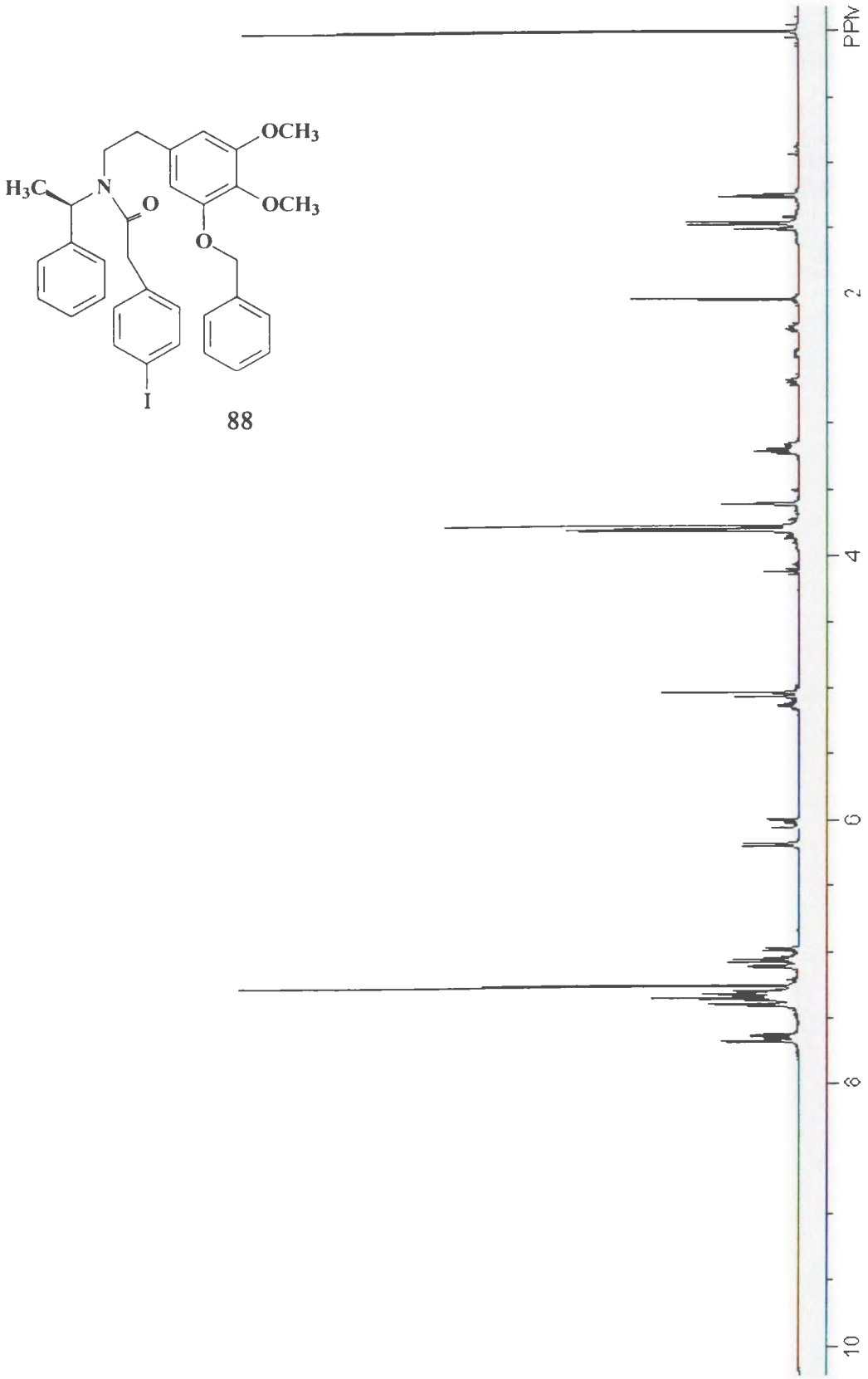

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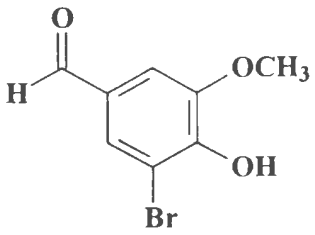

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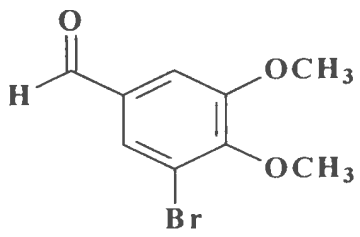

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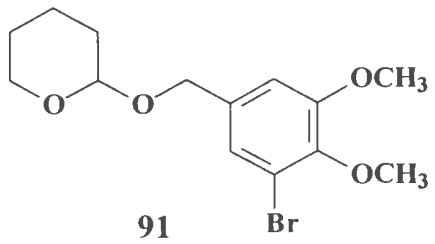

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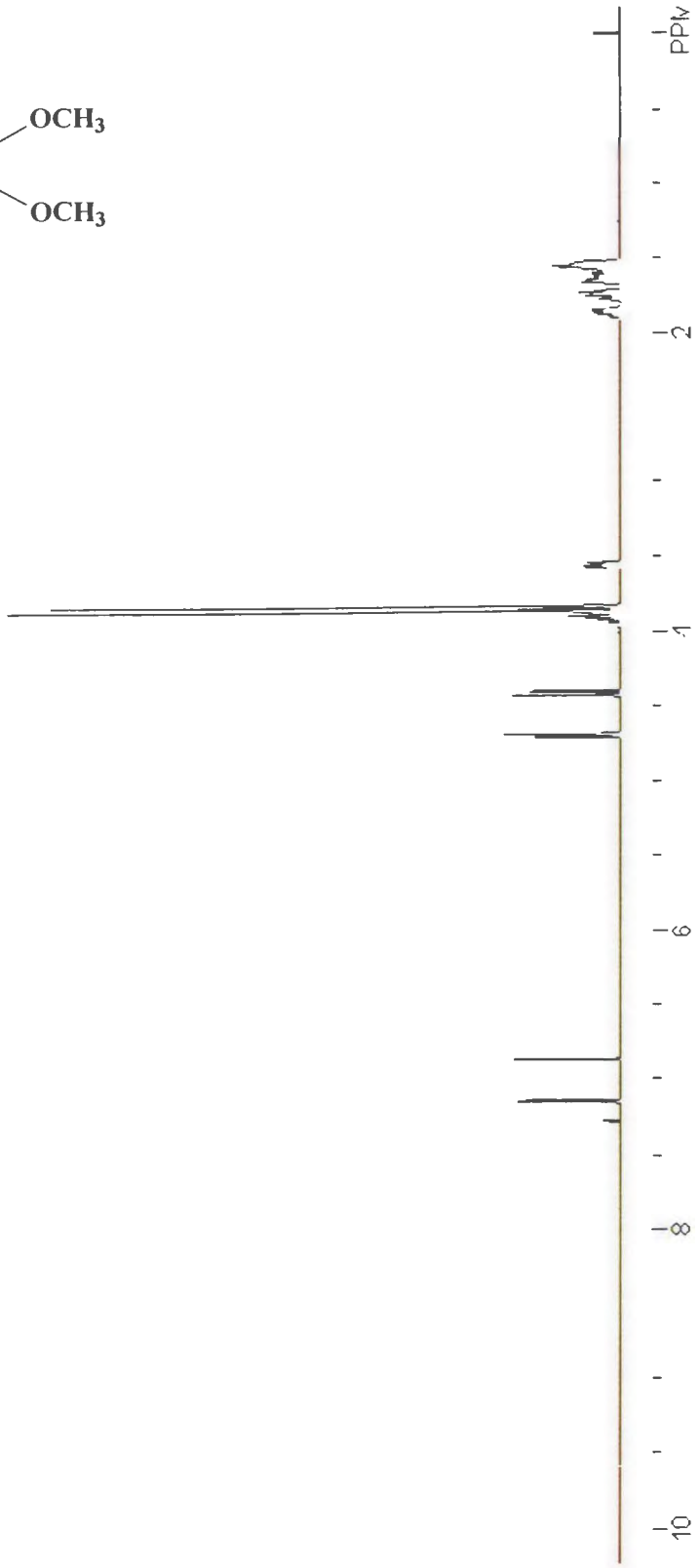

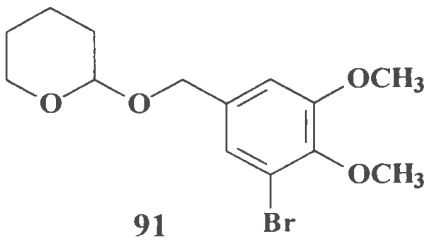

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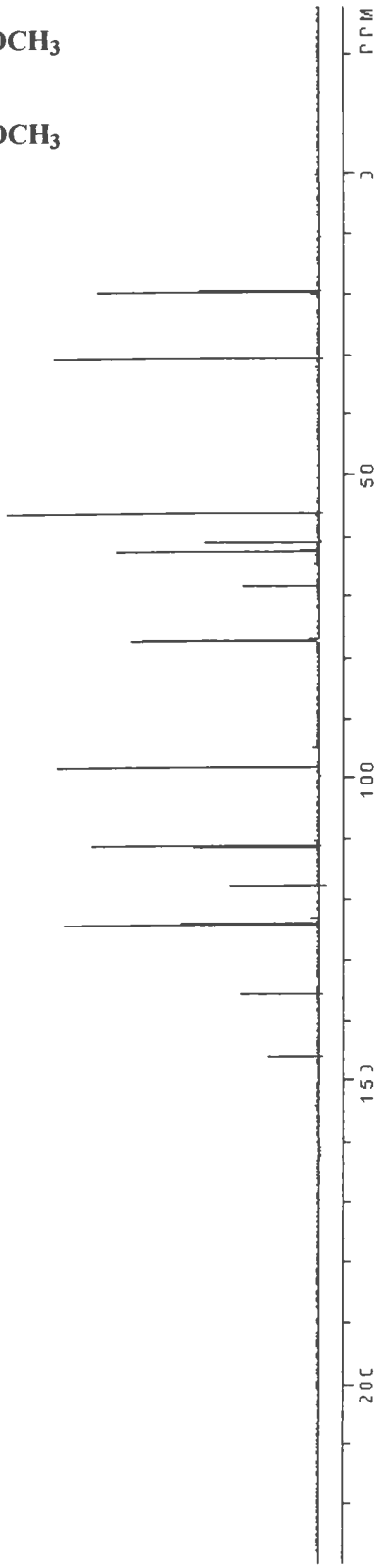

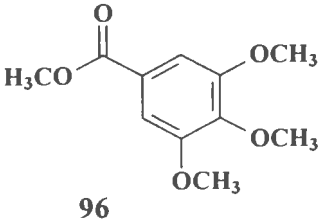

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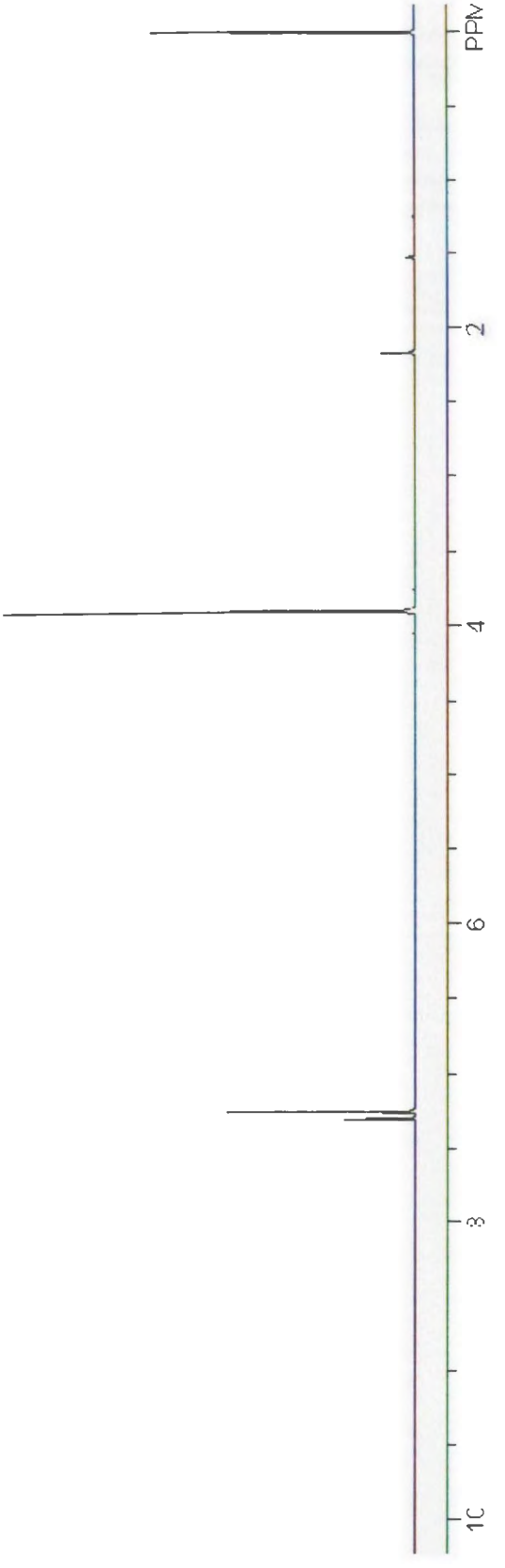

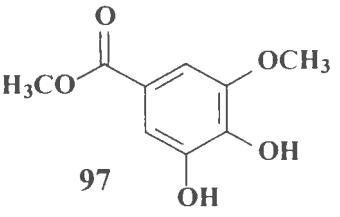

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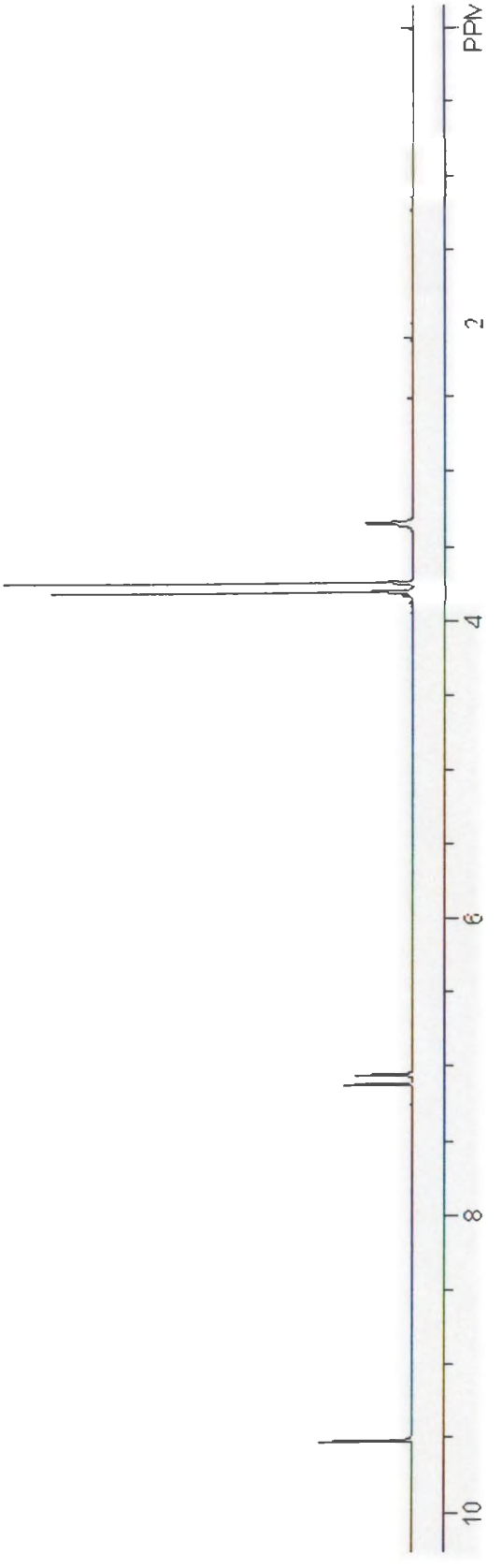

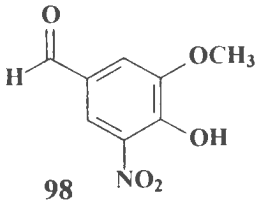

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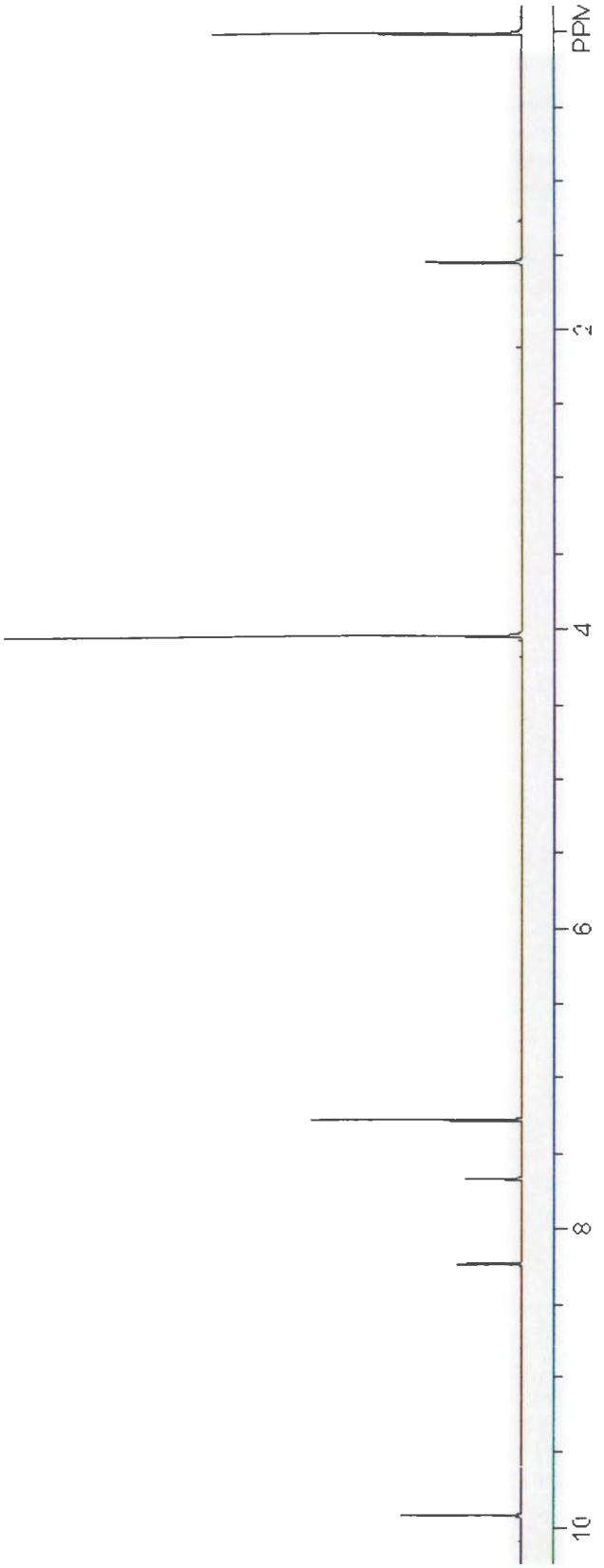

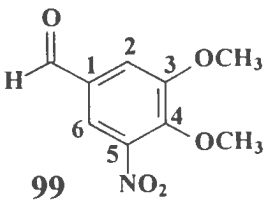

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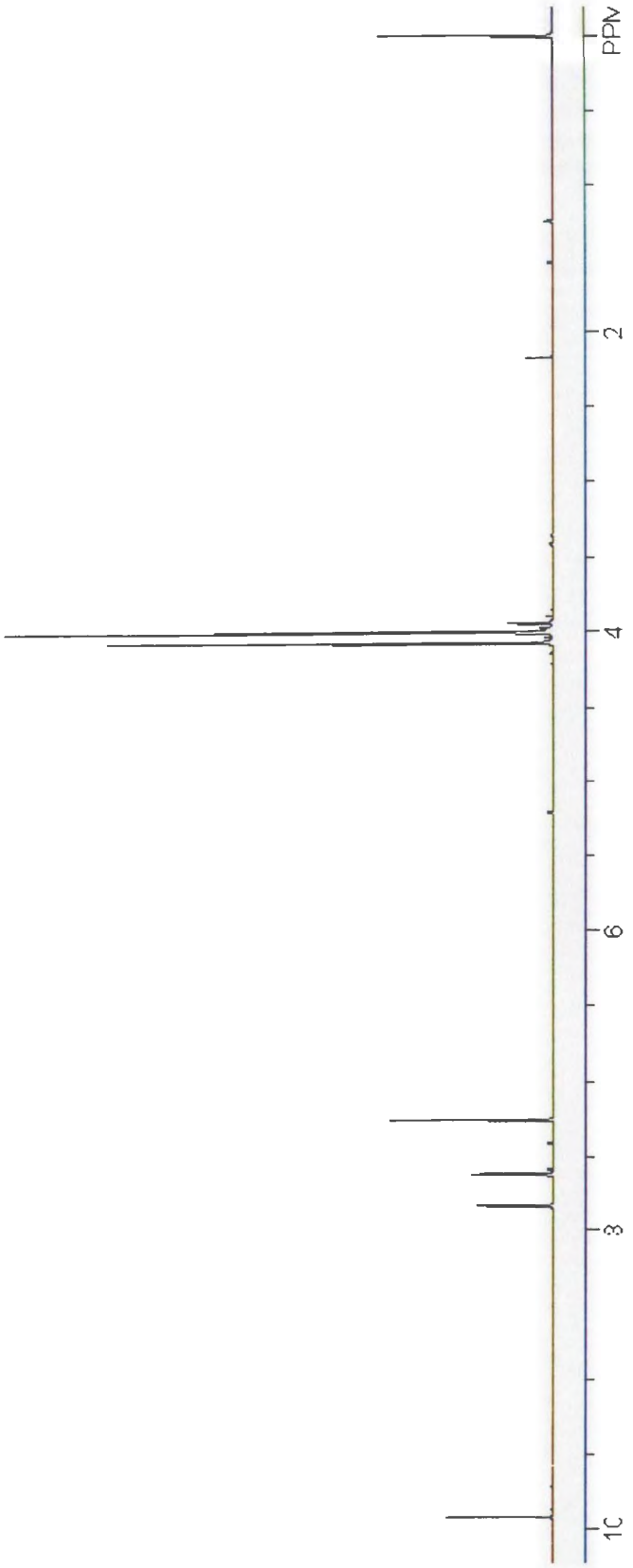

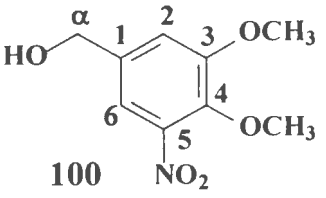

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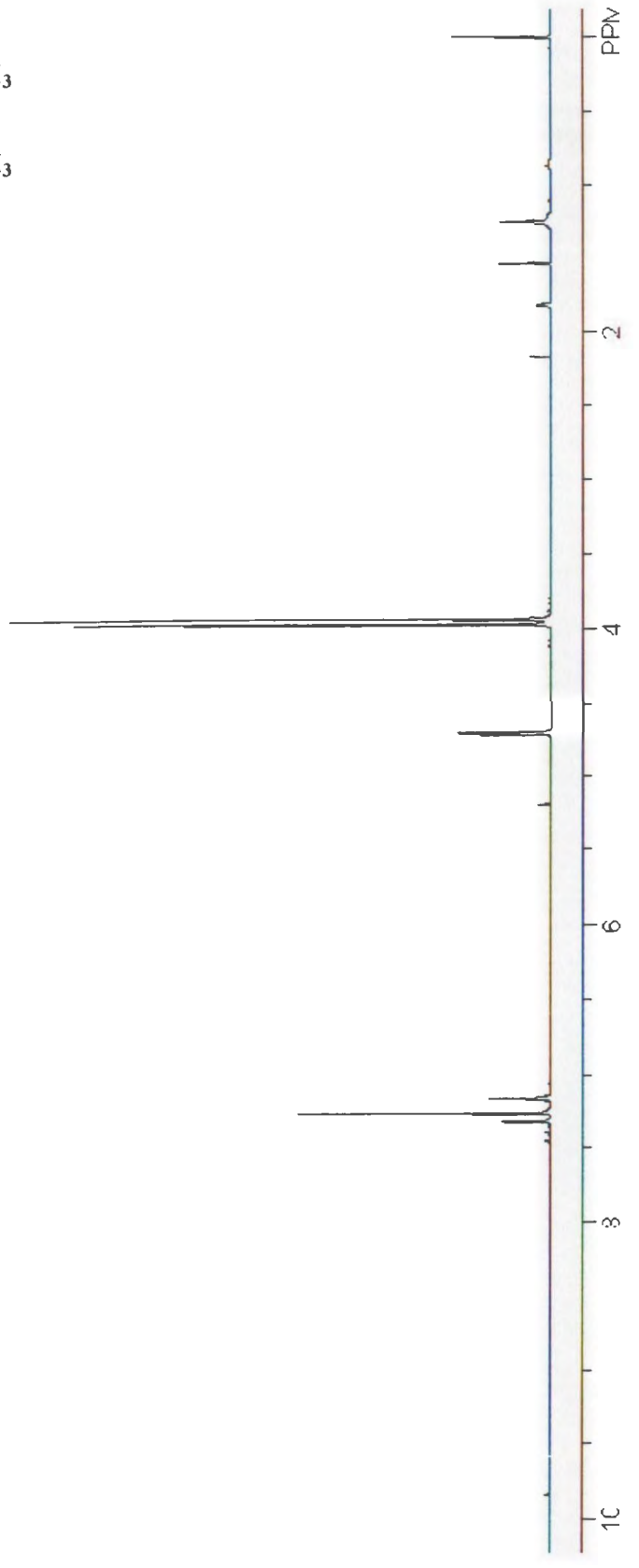

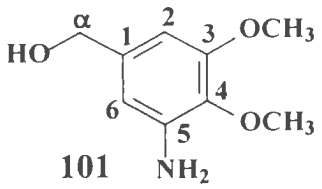

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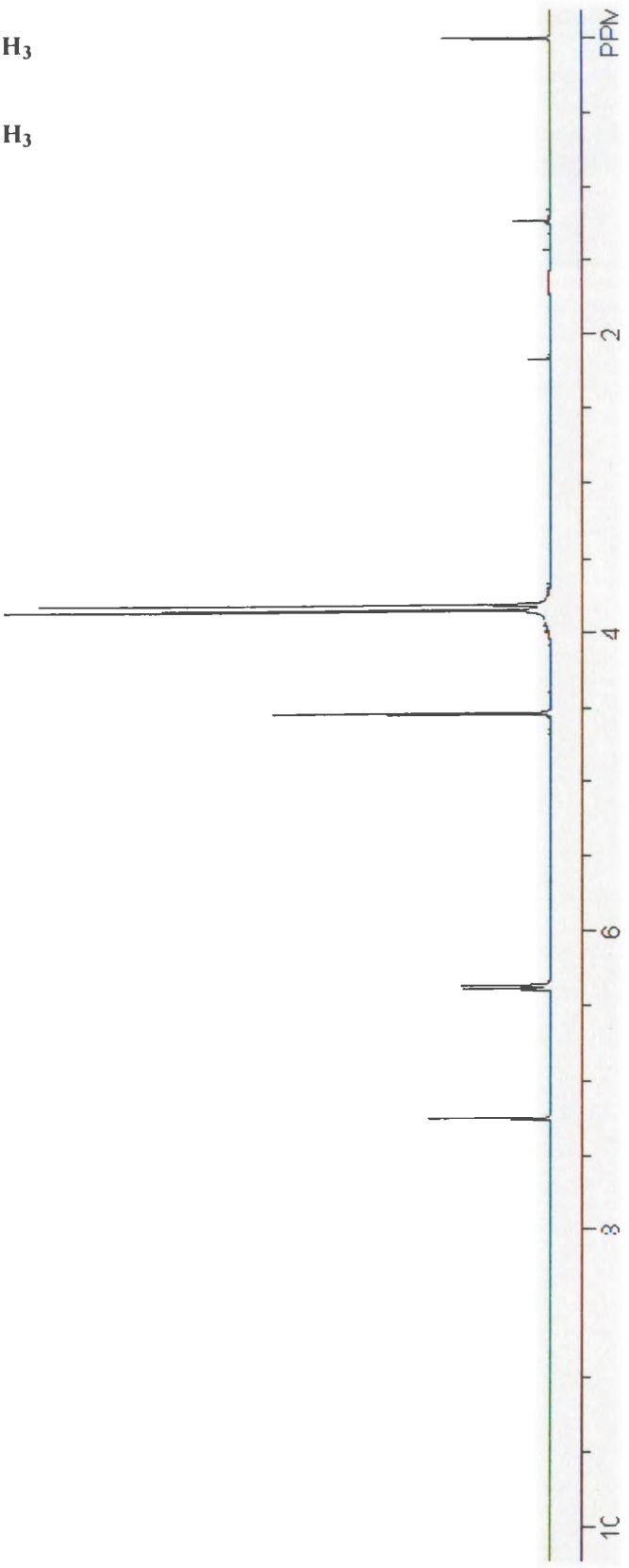

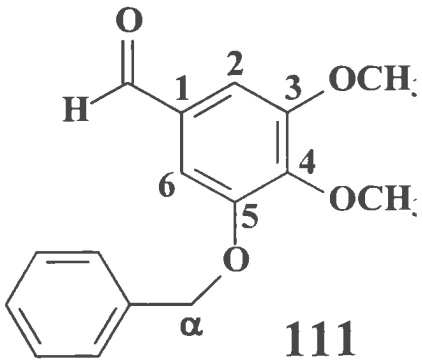

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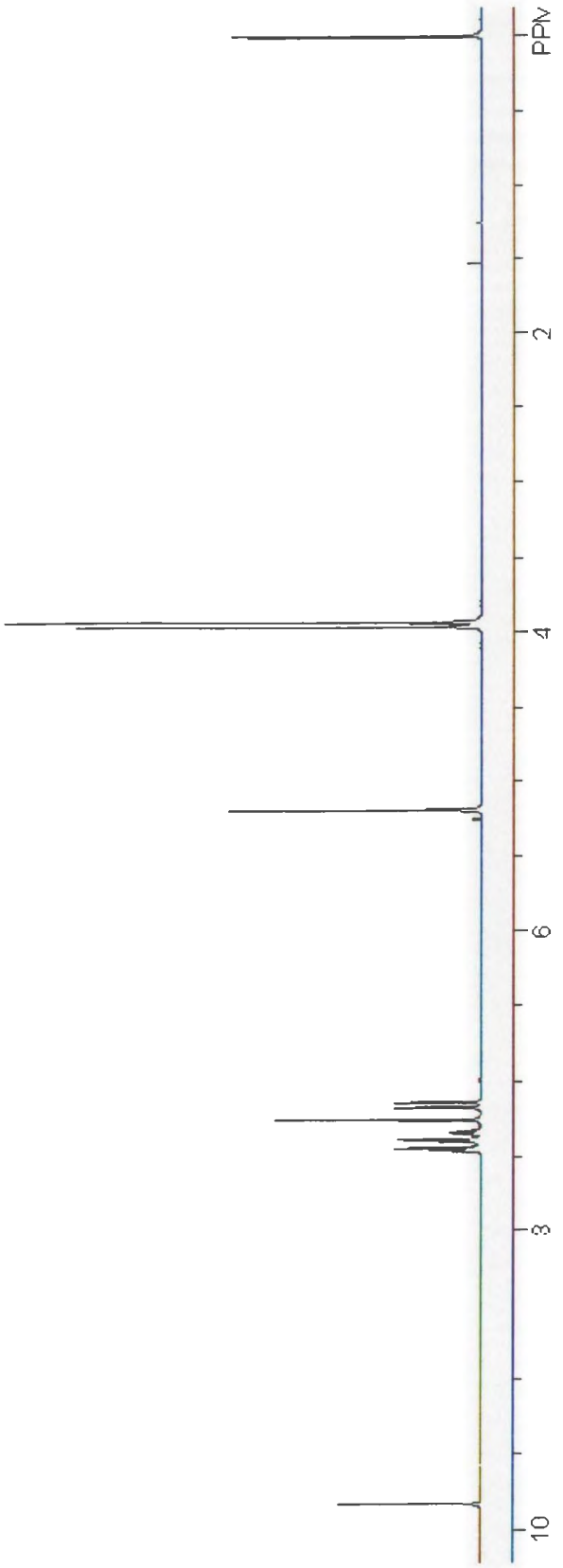

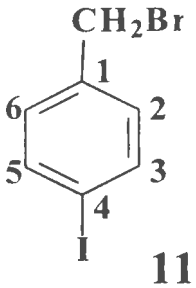

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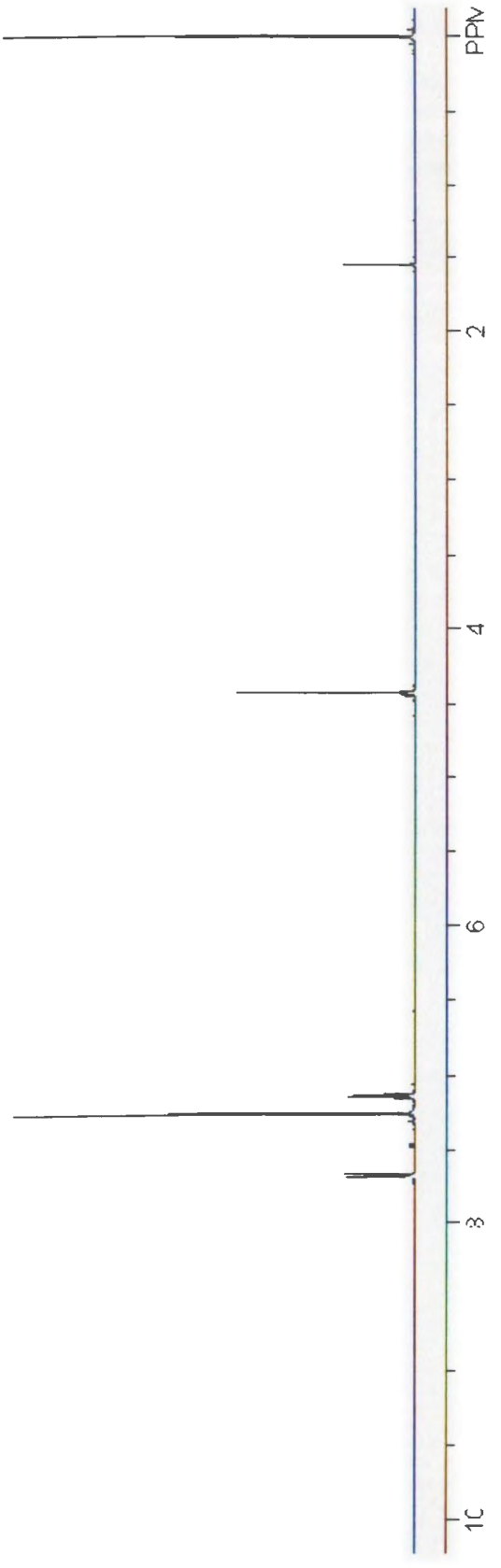

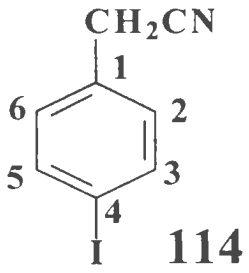

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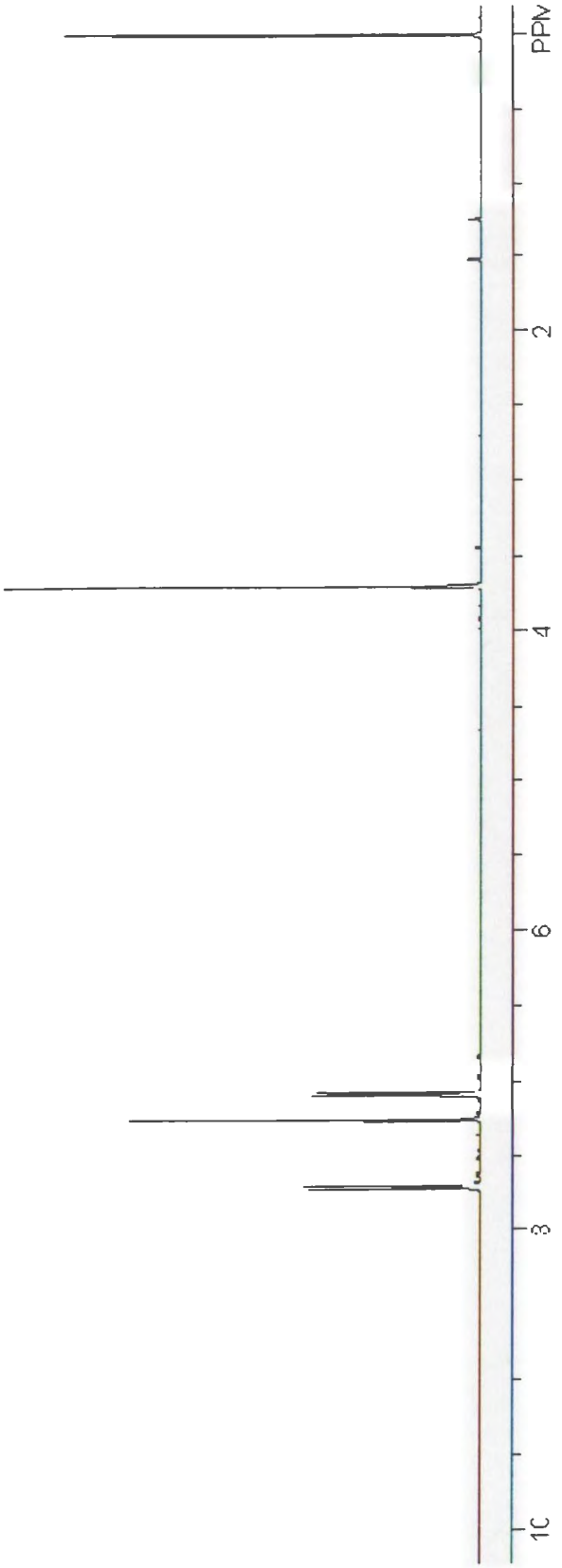

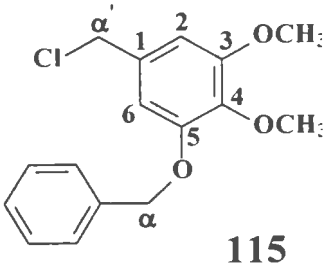

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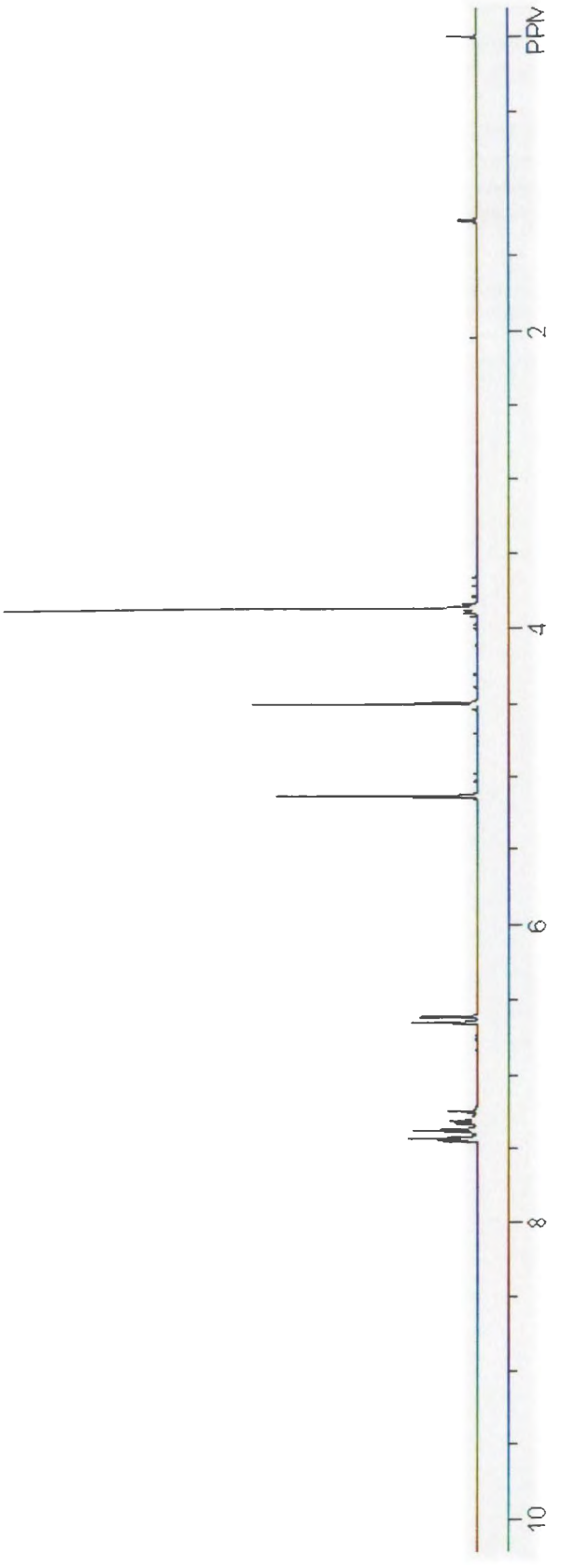

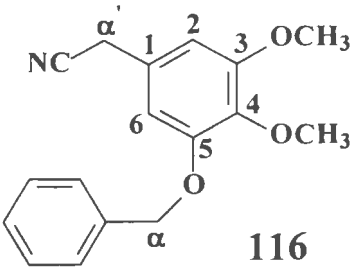

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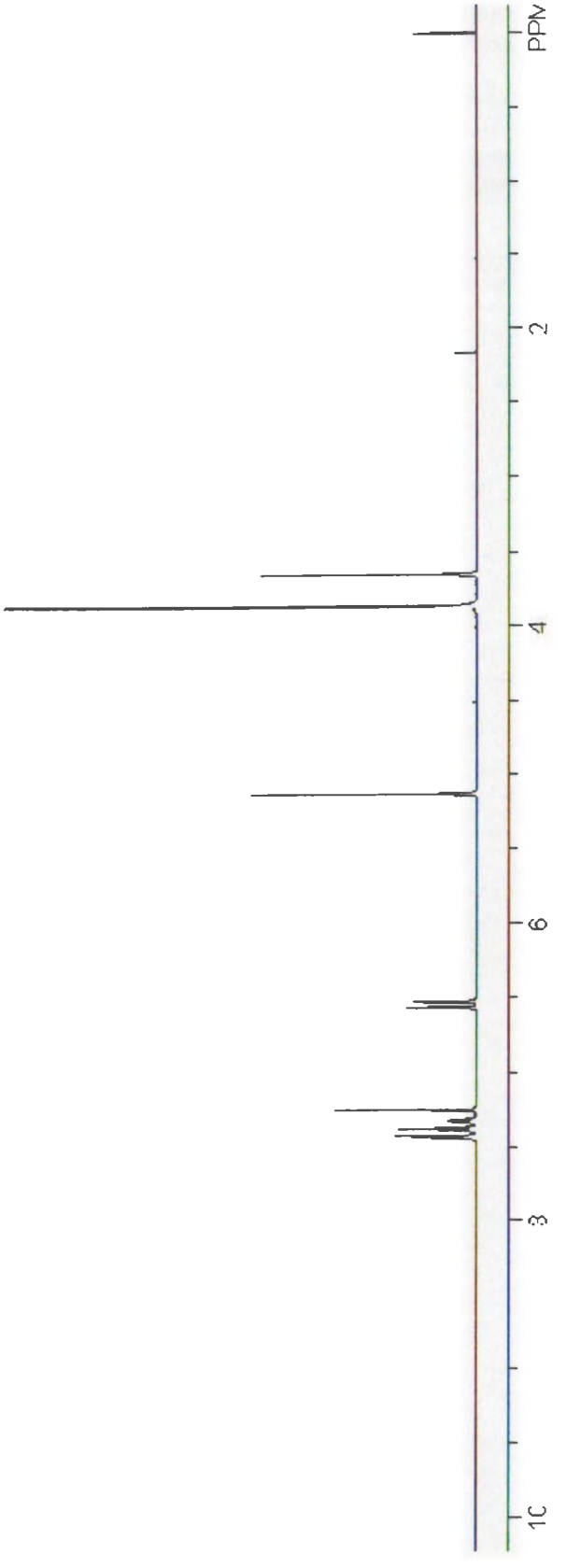

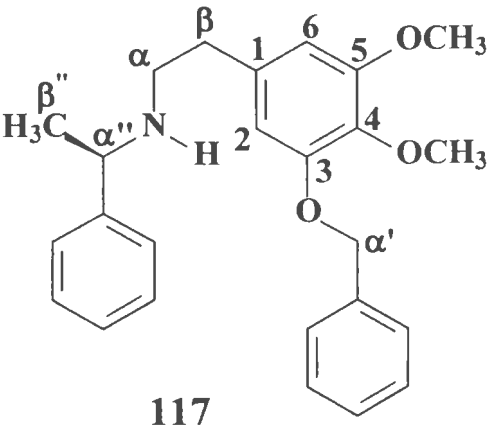

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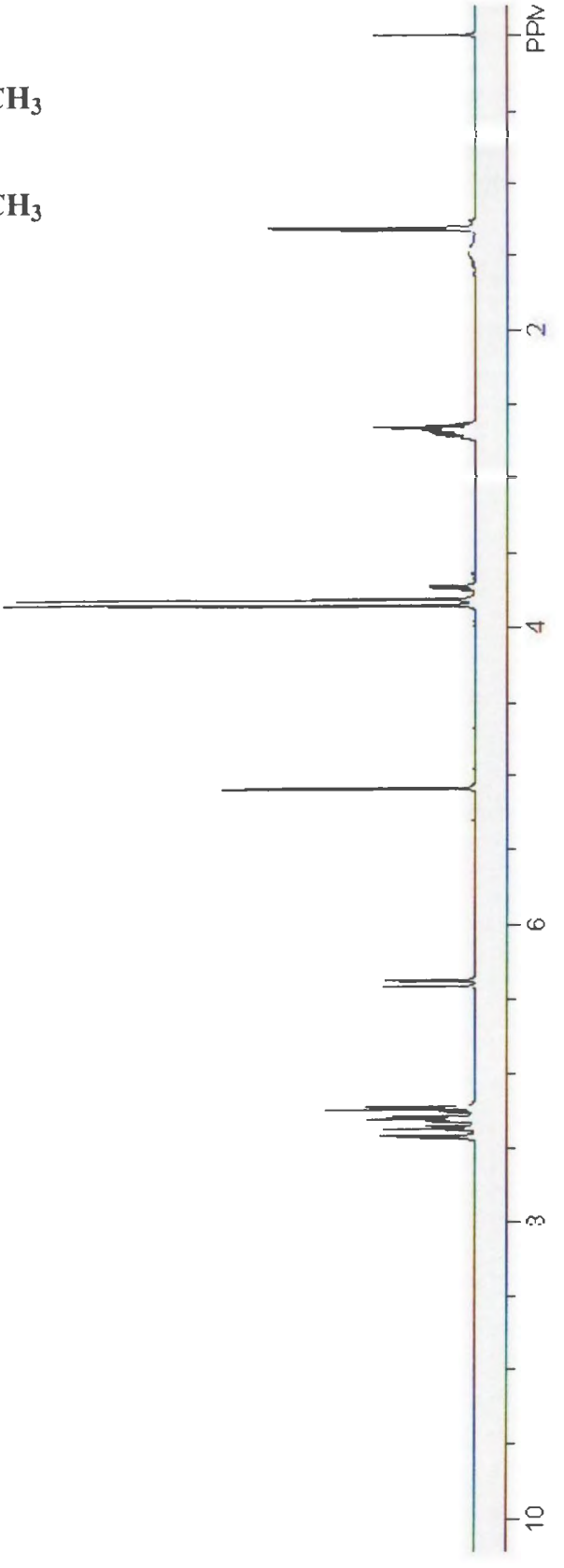

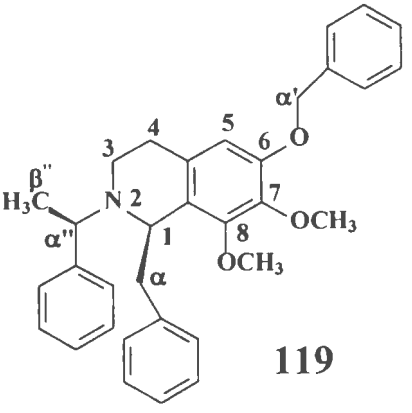

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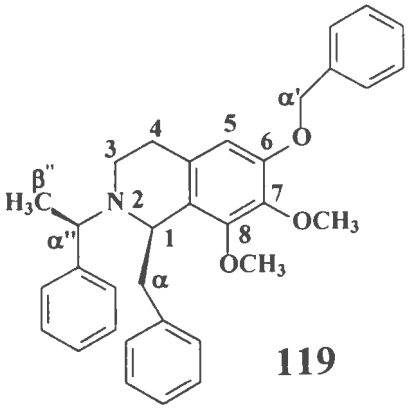

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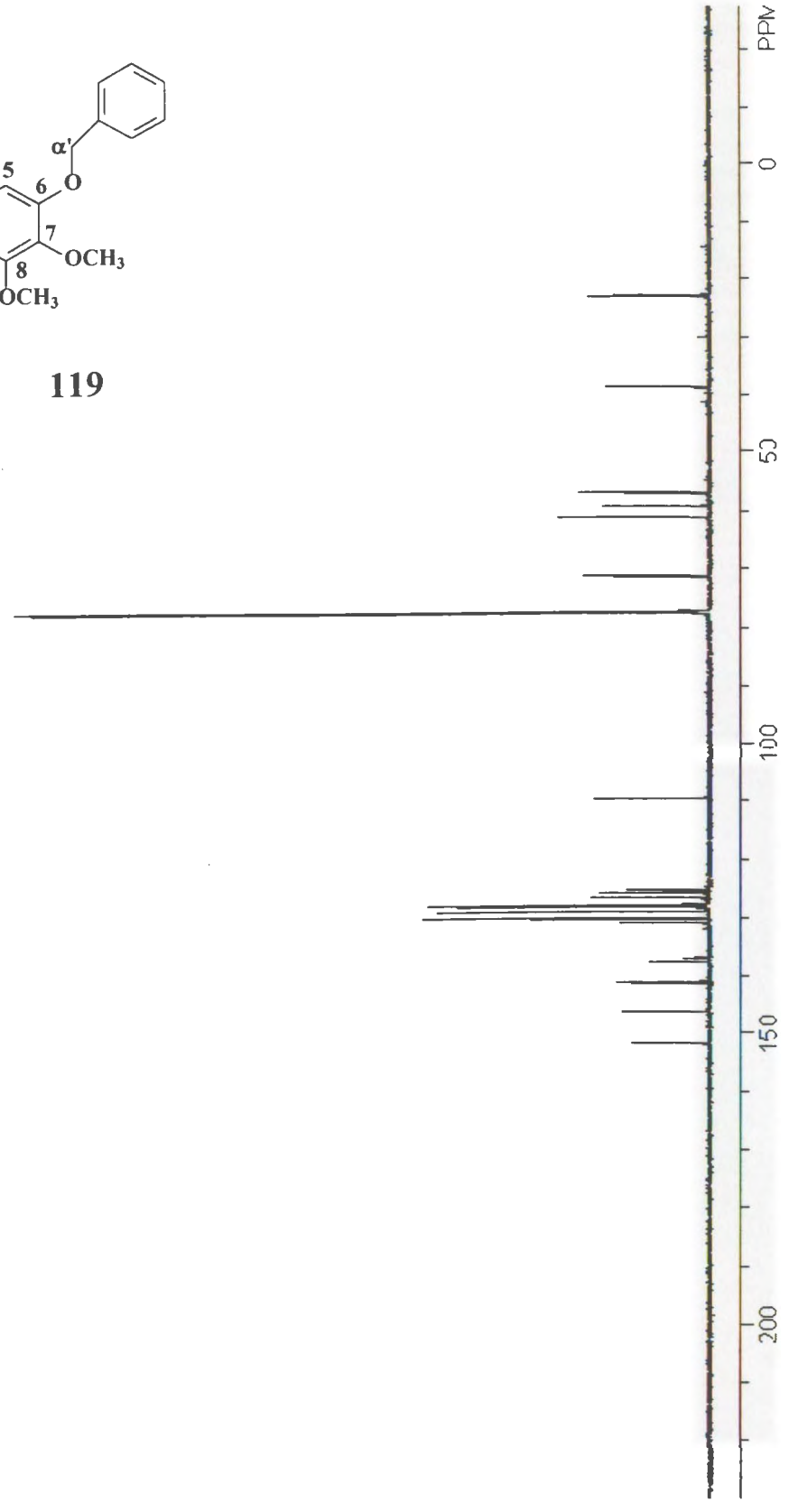

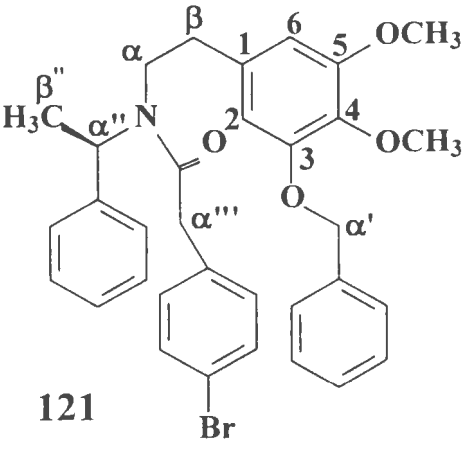

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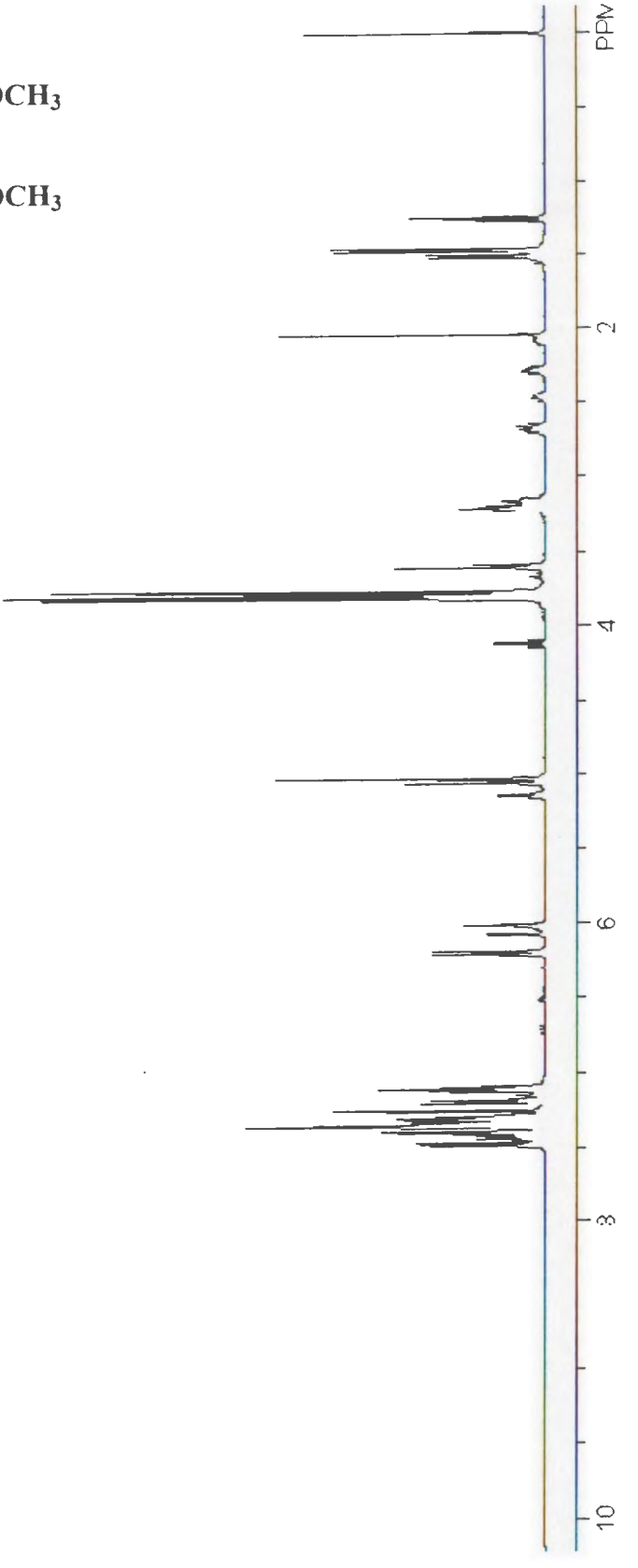
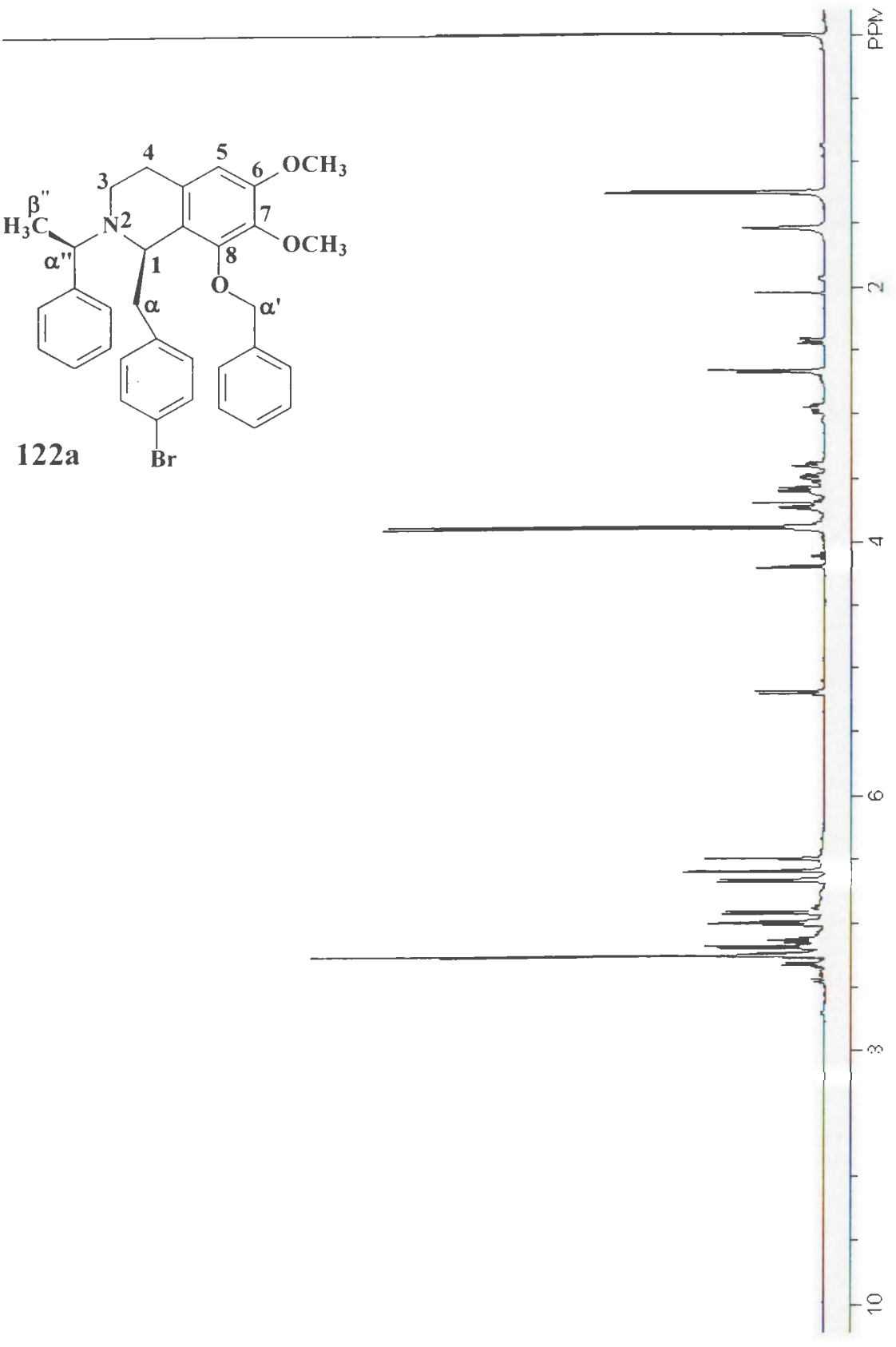
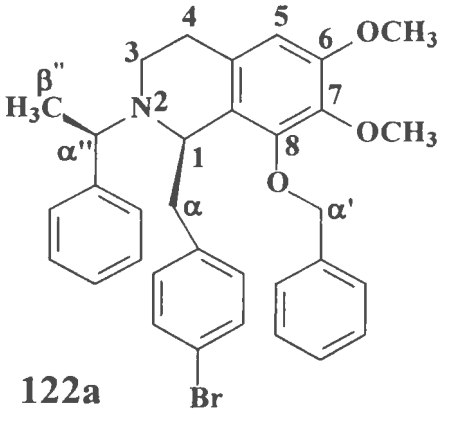
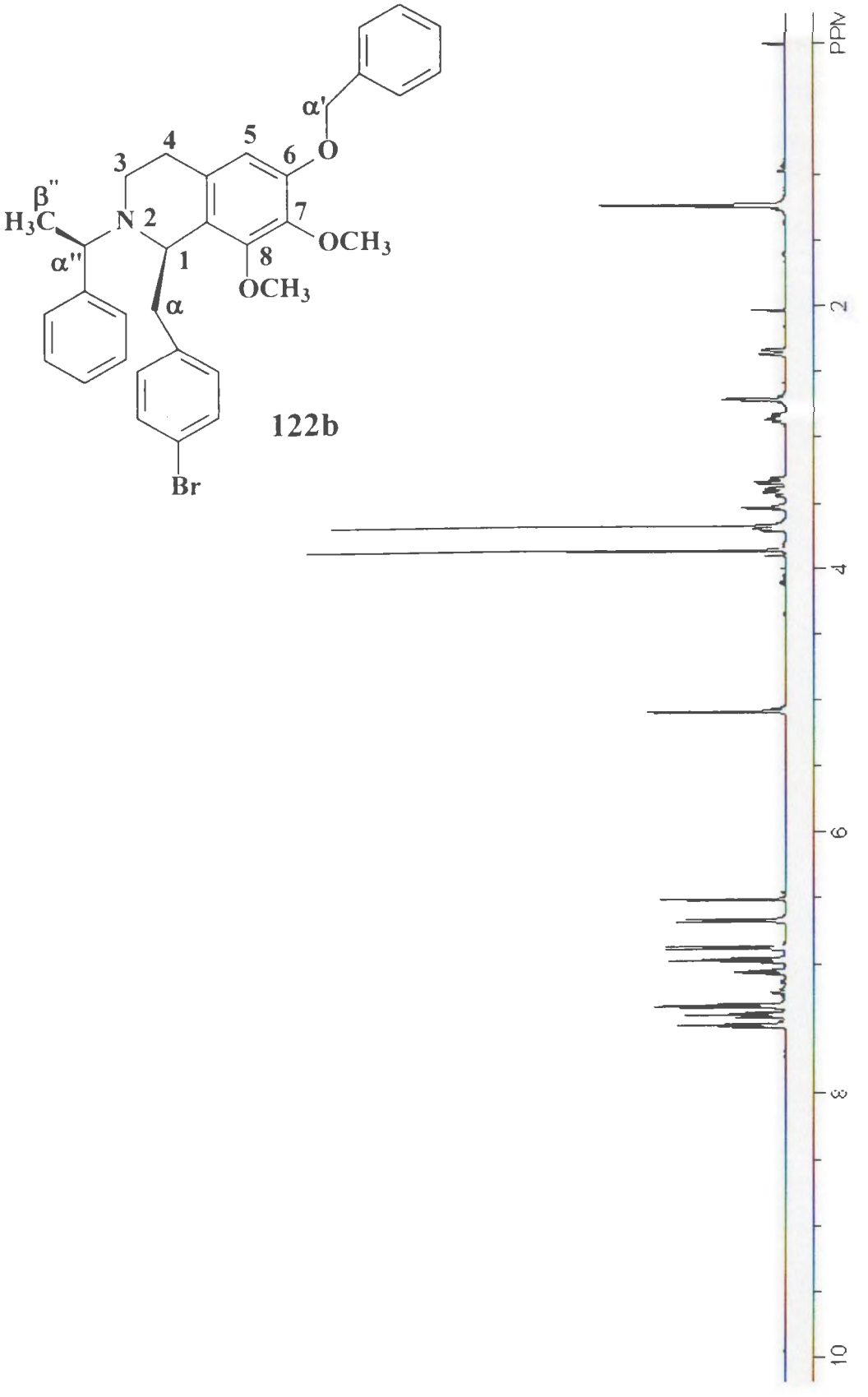


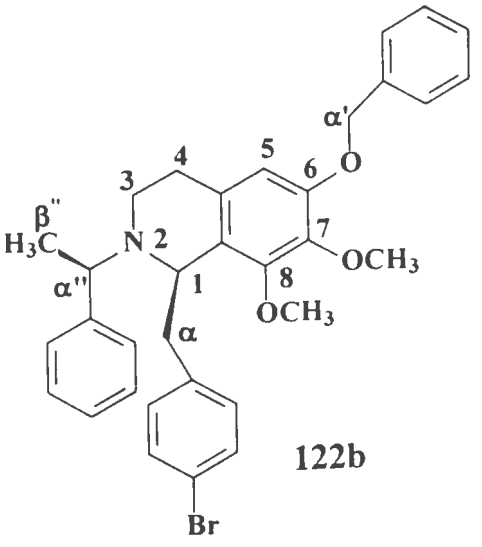


122a

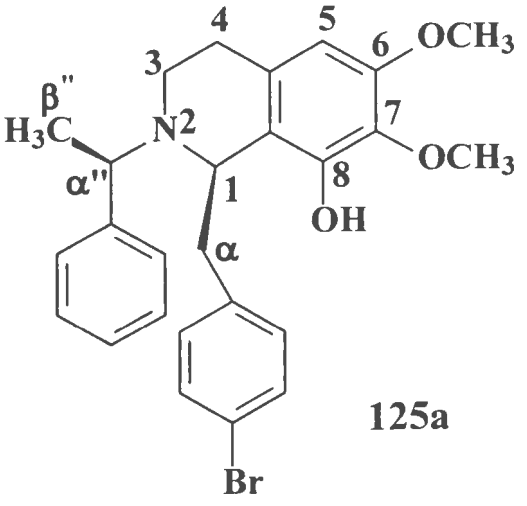


122a

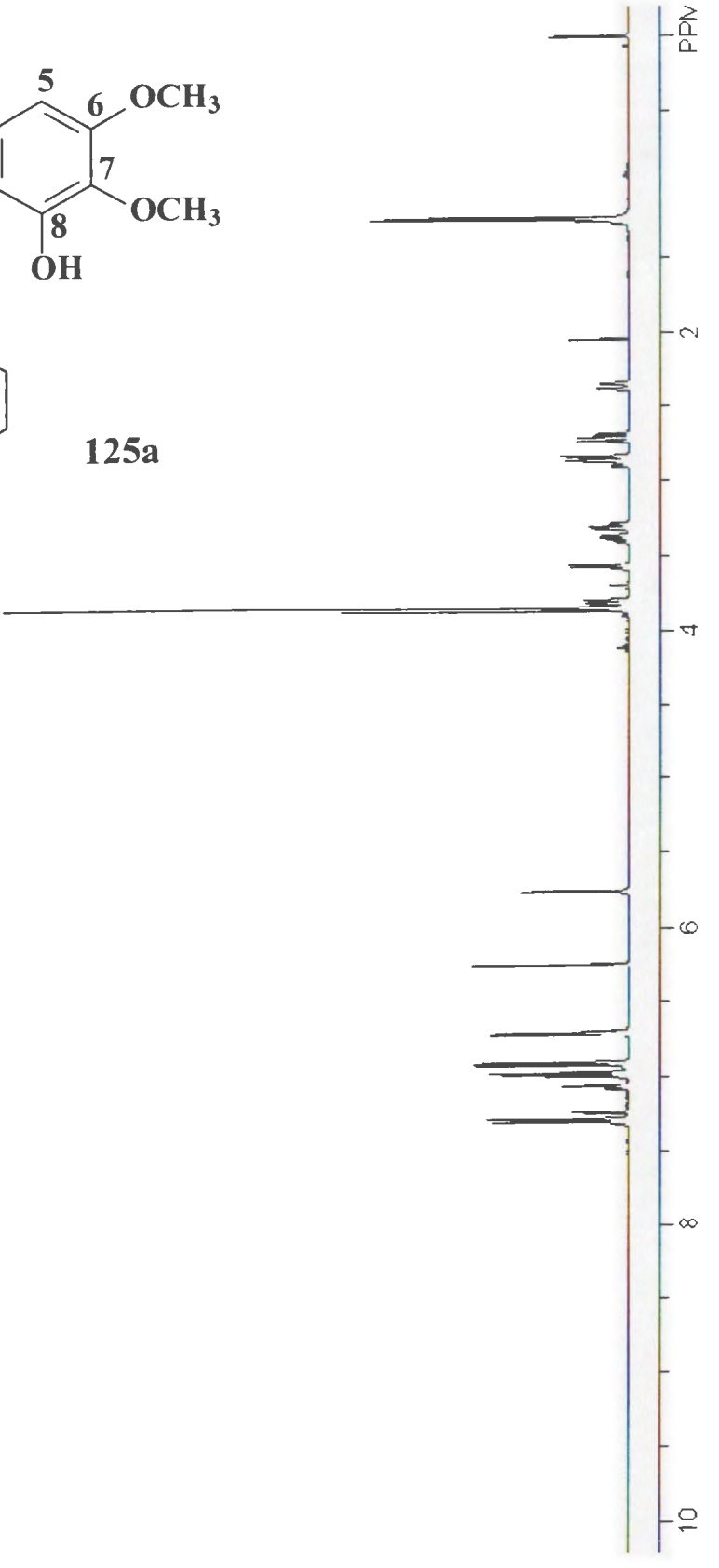

α'
O
6
5
4
3
β''
H3C
N
2
7
OCH3
α''
1
8
OCH3
α
Br
122b
PPM
2
4
6
8
10

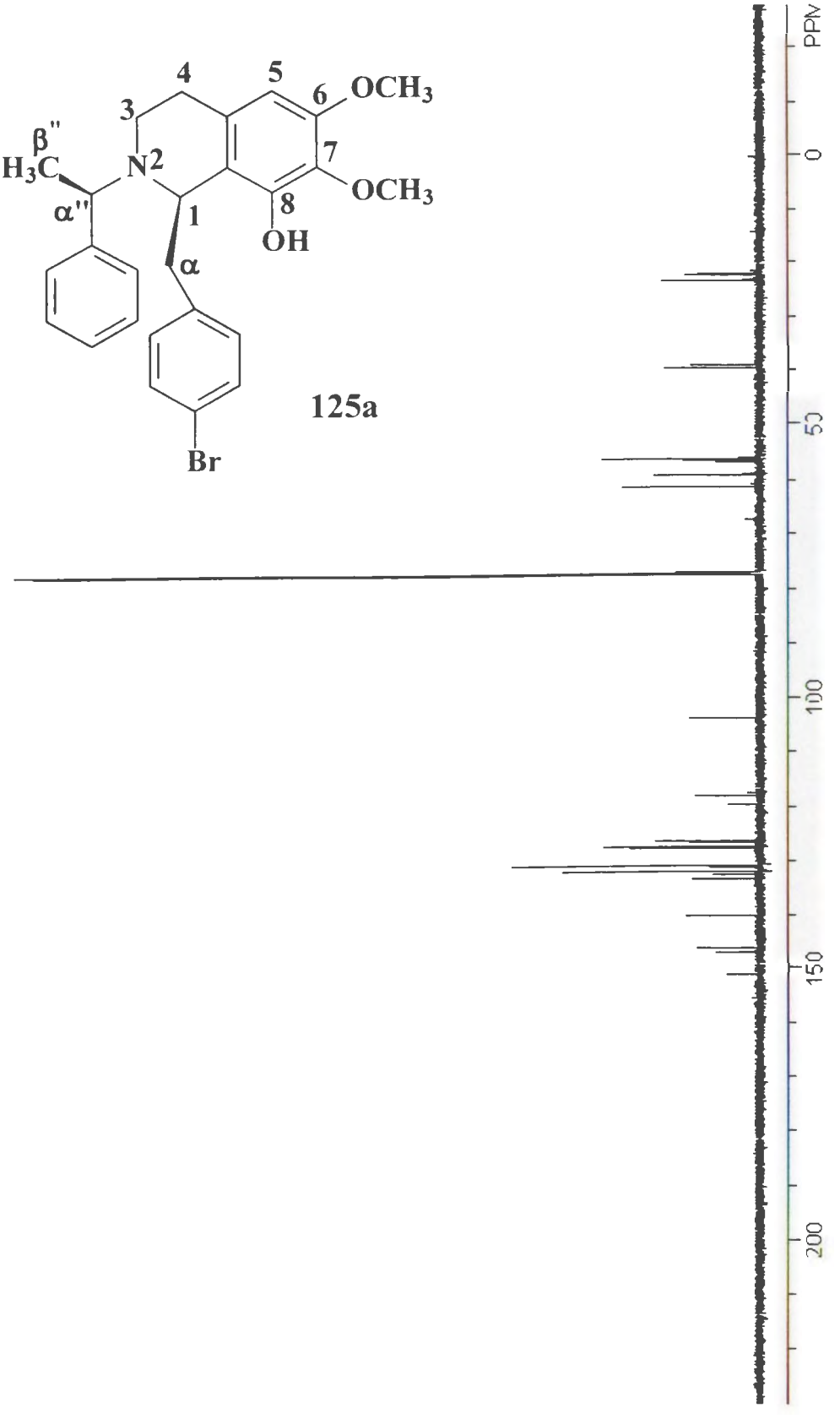


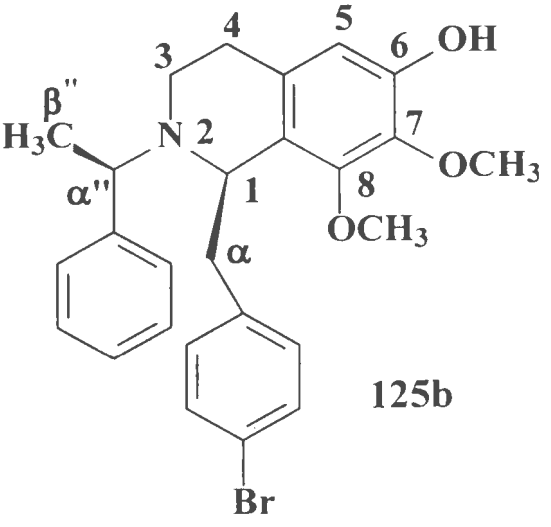
122b



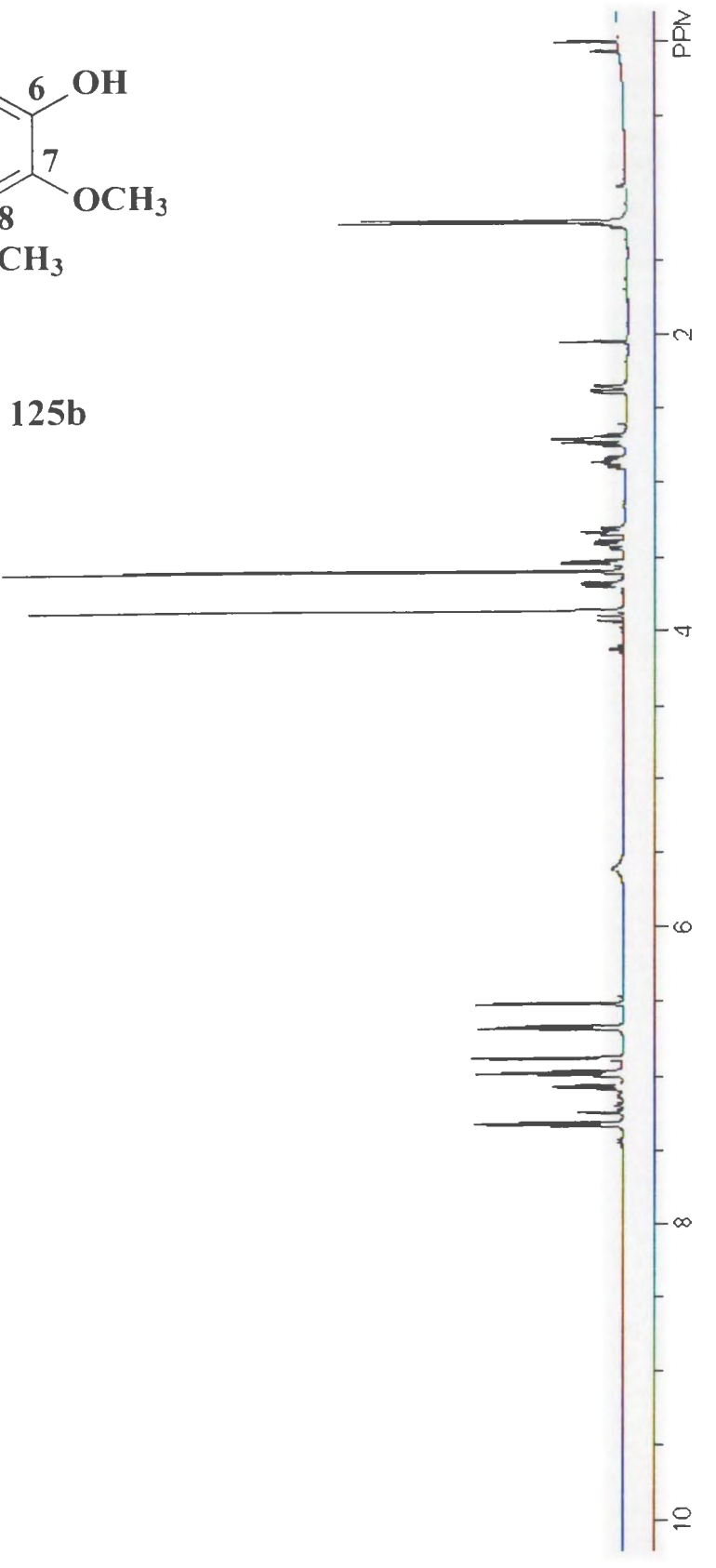
125a

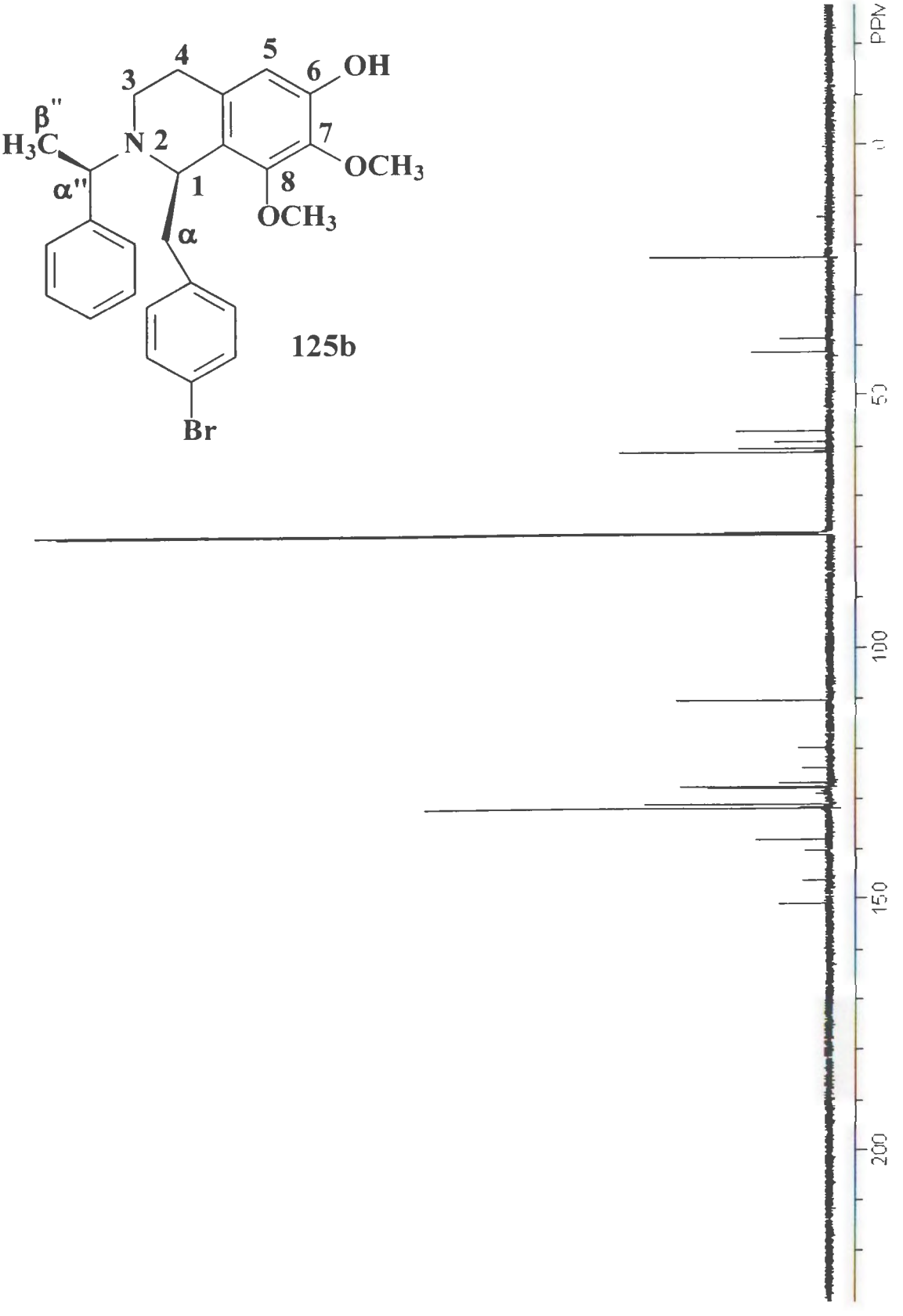


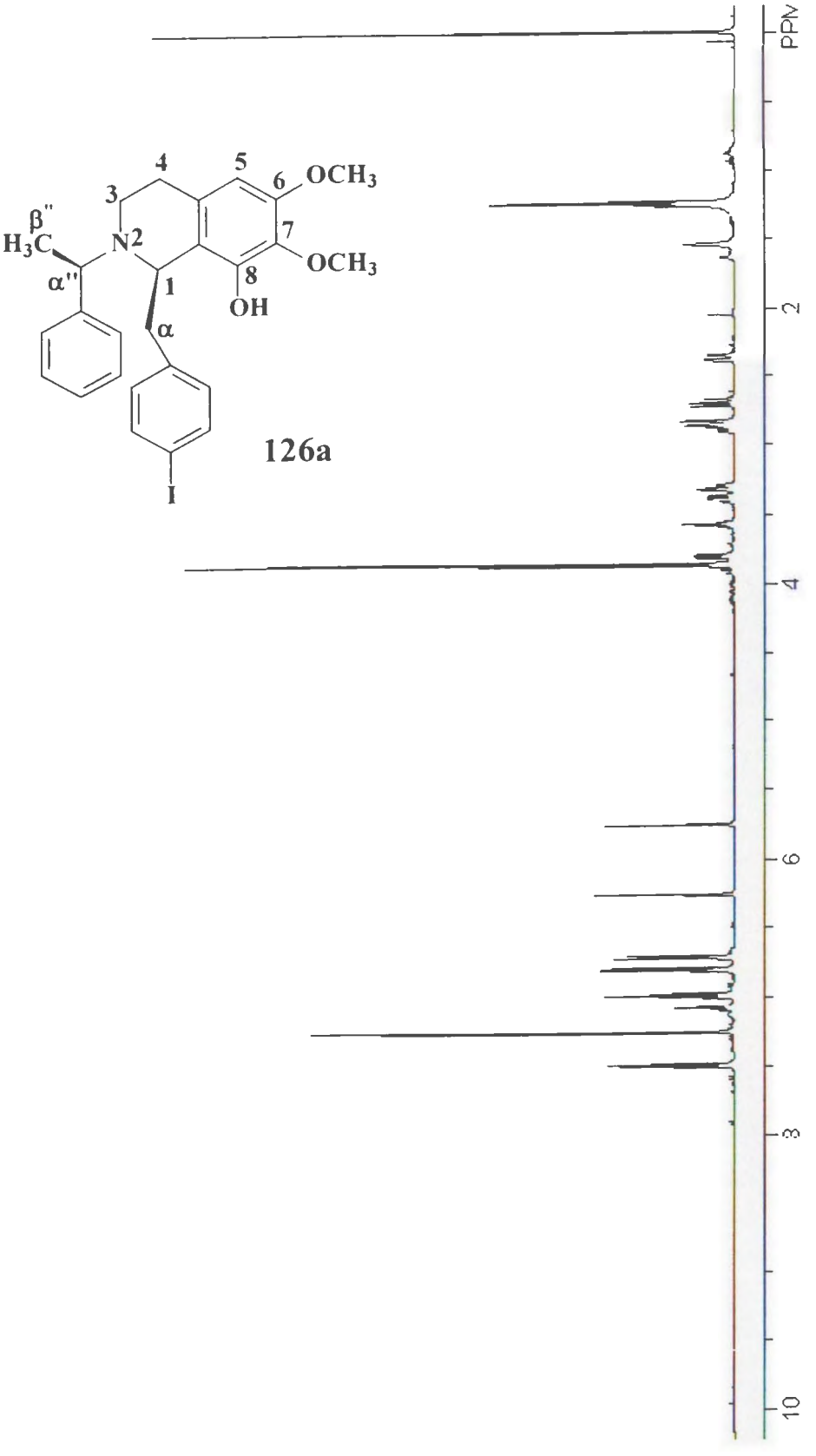

4
5
6
OCH3
3
β"
H3C
N2
7
OCH3
α"
1
8
OH
α
Br
125a
PPM
0
50
100
150
200

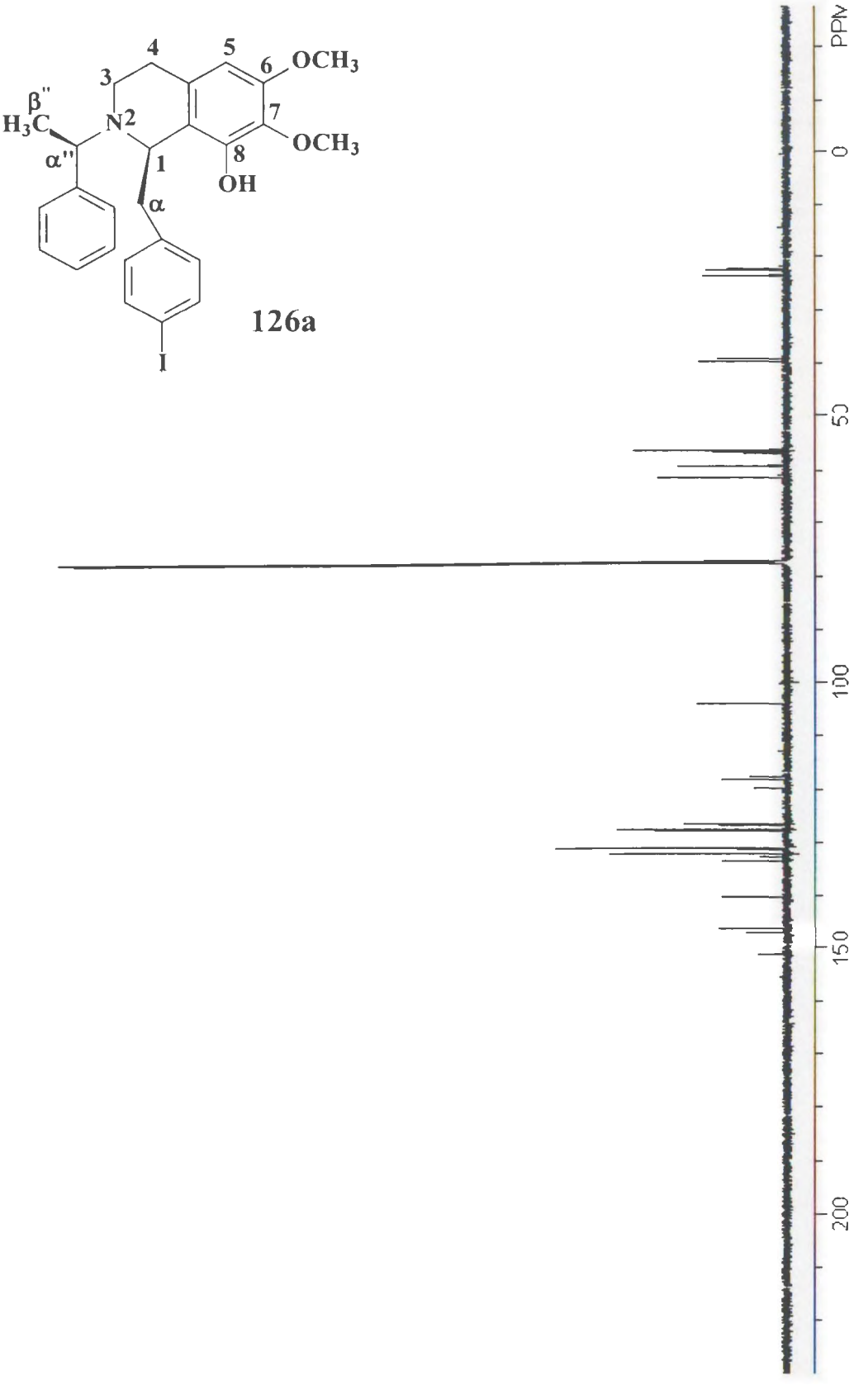


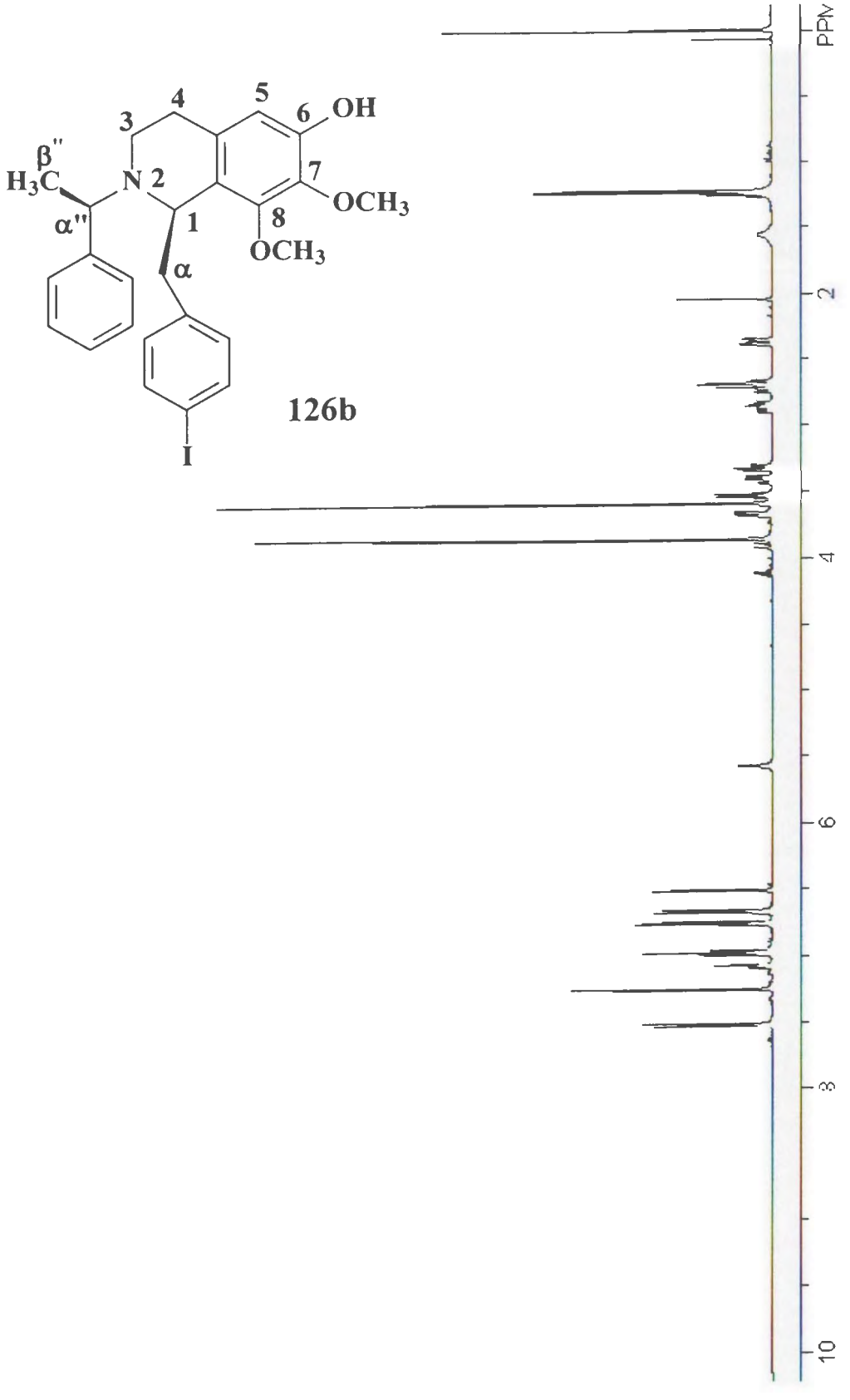
125b

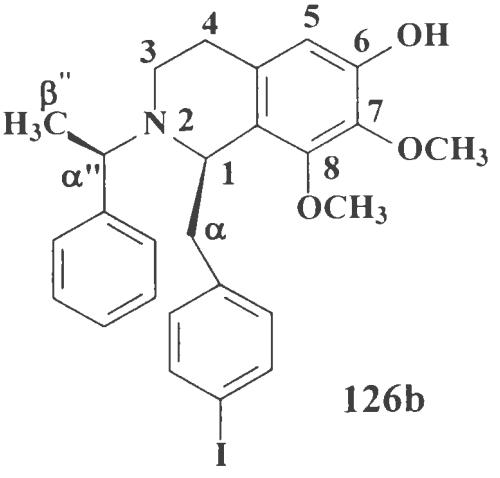



4
5
3
6
OH
β"
H3C
N 2
7
OCH3
α"
1
8
OCH3
α
125b
Br
PPM
50
100
150
200

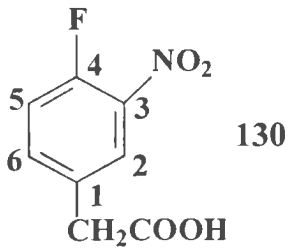

4
5
6
OCH3
3
β"
H3C
N2
7
OCH3
α"
1
8
OH
α
I
126a
PPM
2
4
6
3
10


4
5
6
OCH3
3
β"
H3C
N2
7
OCH3
α"
1
8
OH
α
I
126a
PPM
0
50
100
150
200

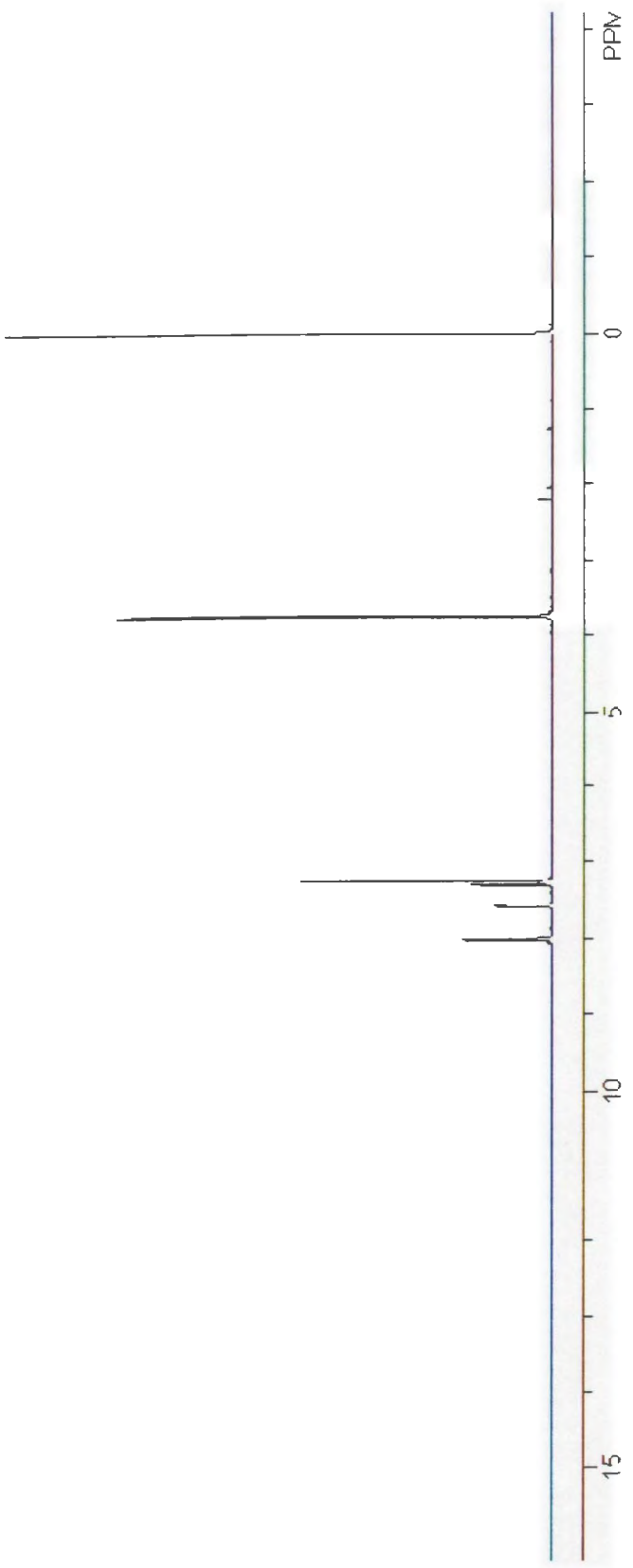

4
5
6
OH
3
β''
H3C
N
2
7
OCH3
α''
1
8
OCH3
α
I
126b
PPM
2
4
6
8
10

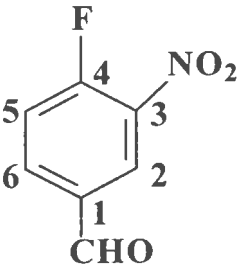


126b

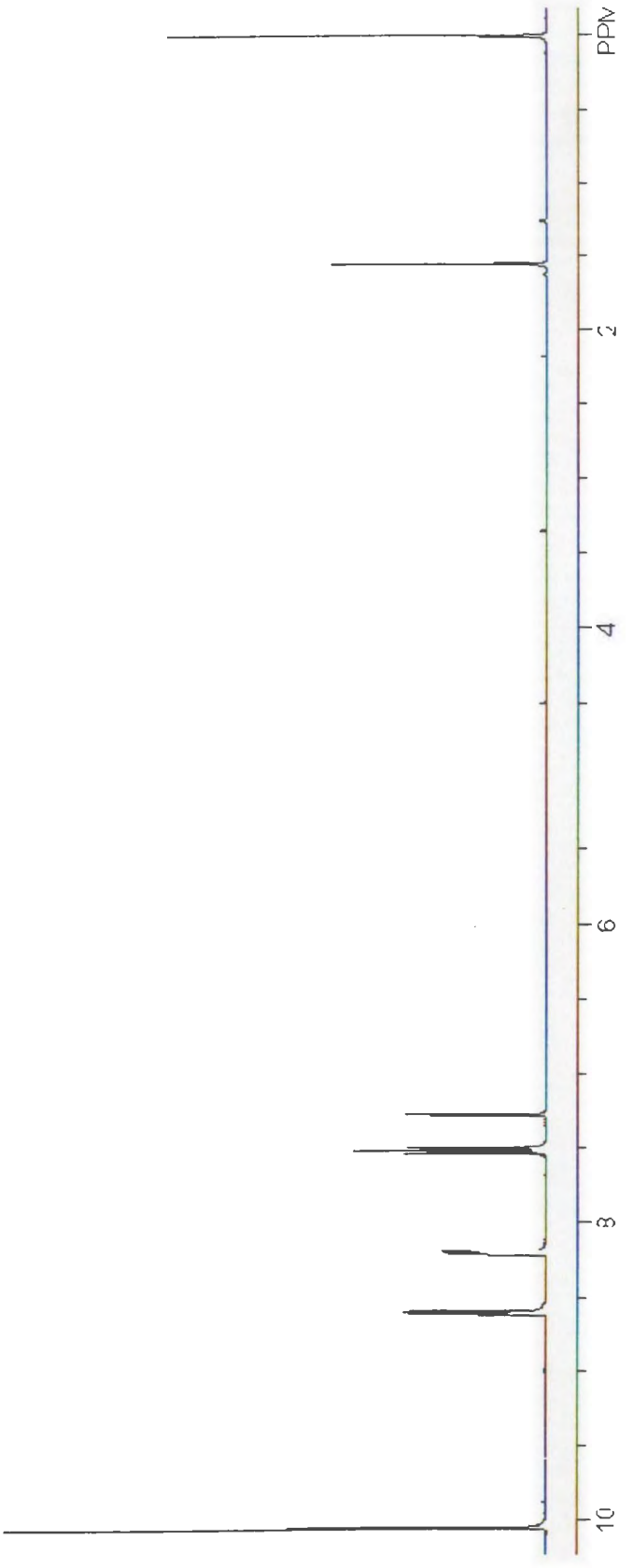


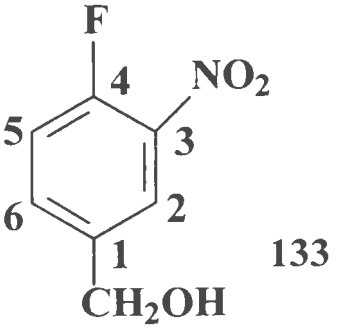
130



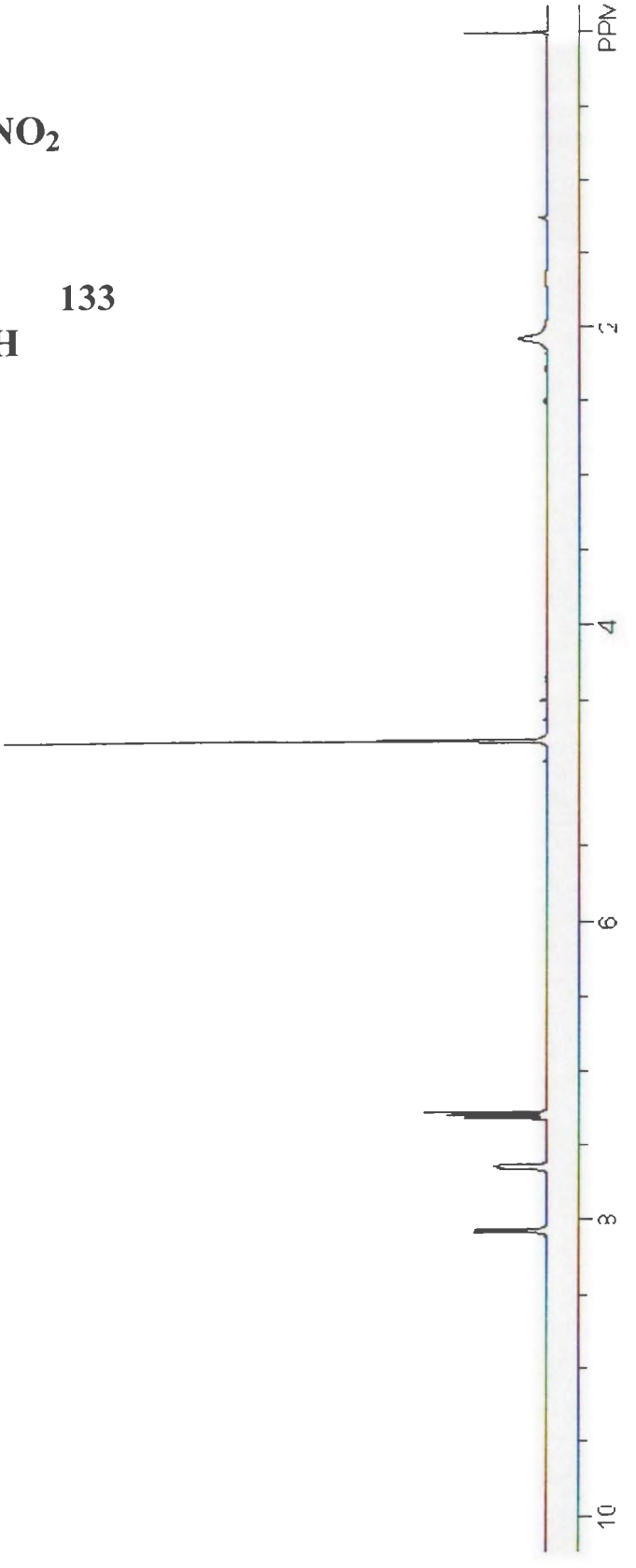


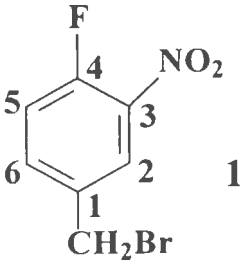
131



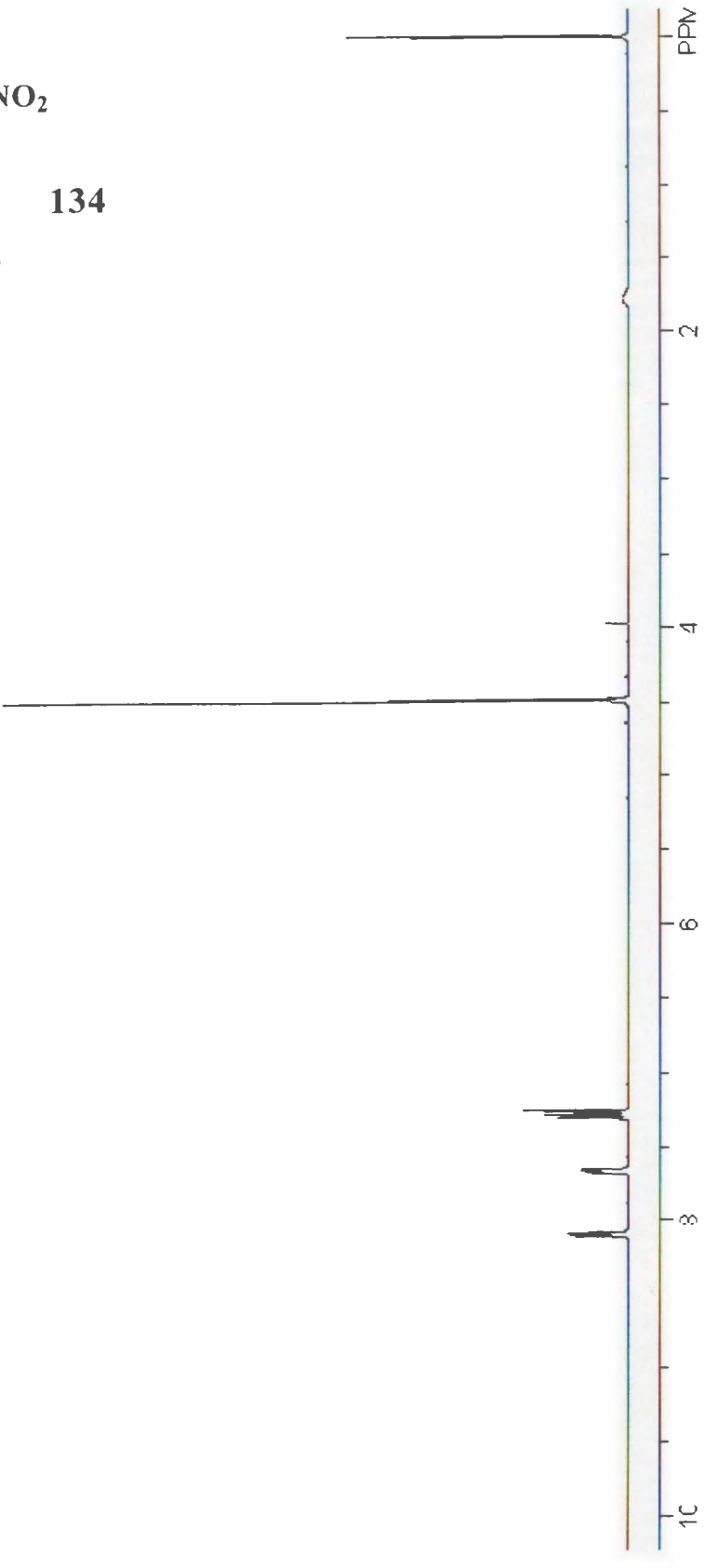


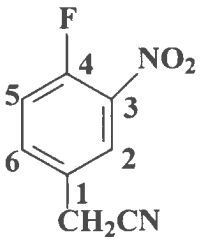
133



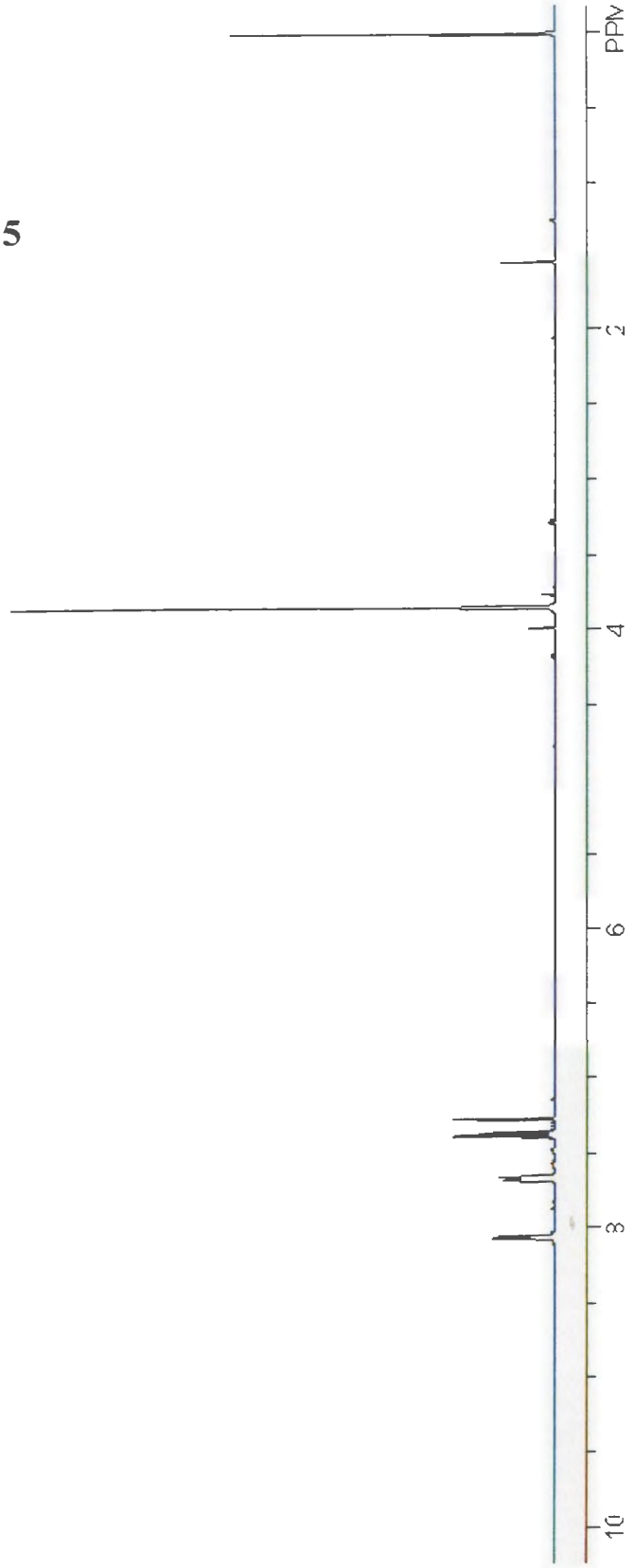


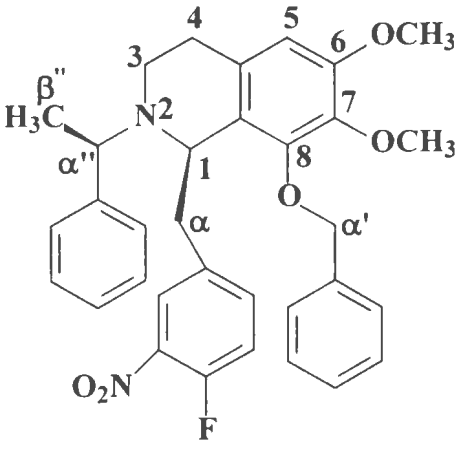
134



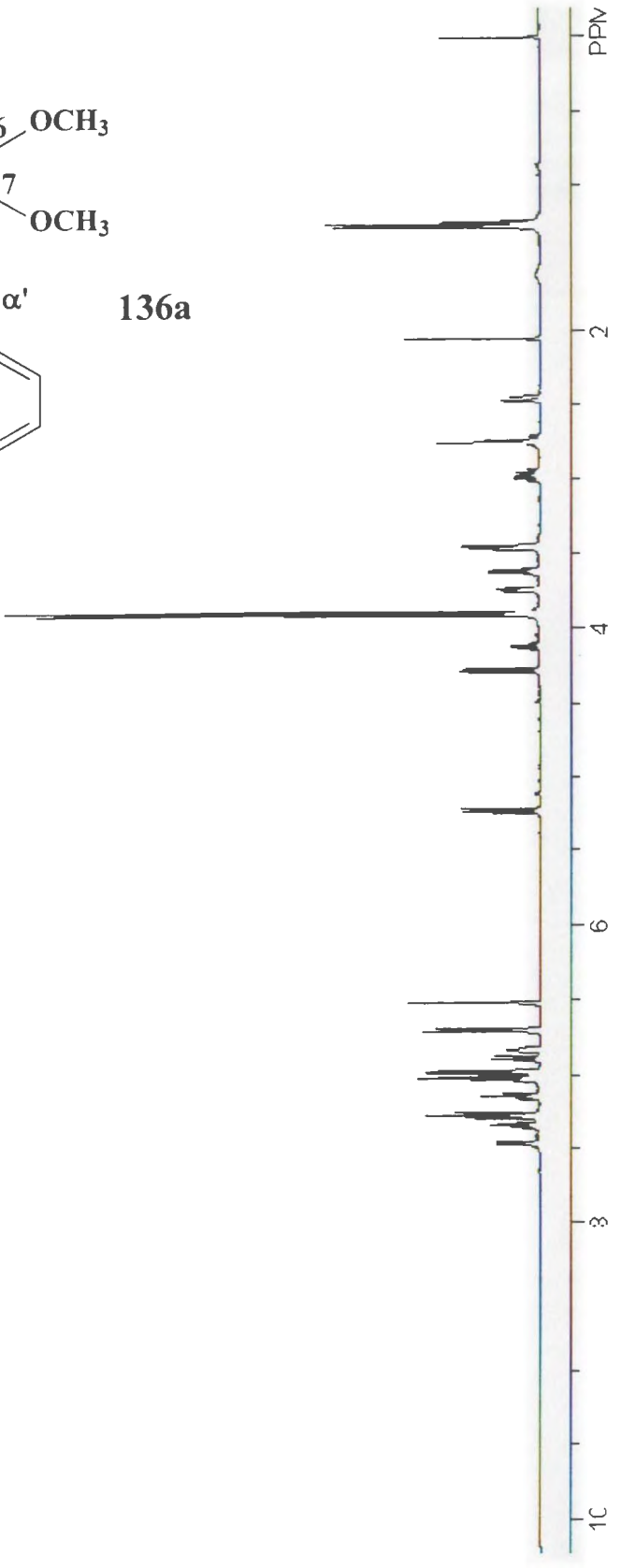


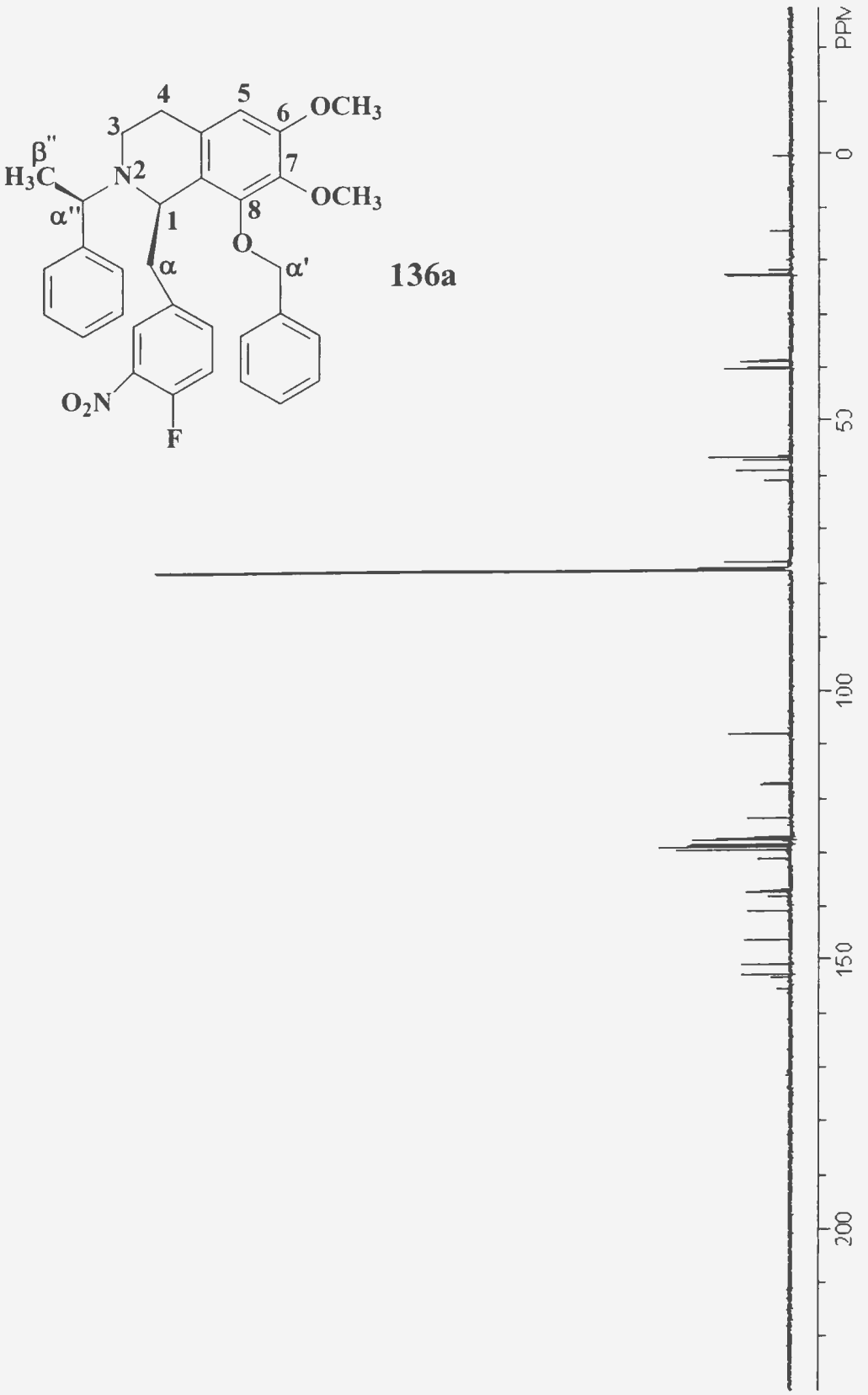
135



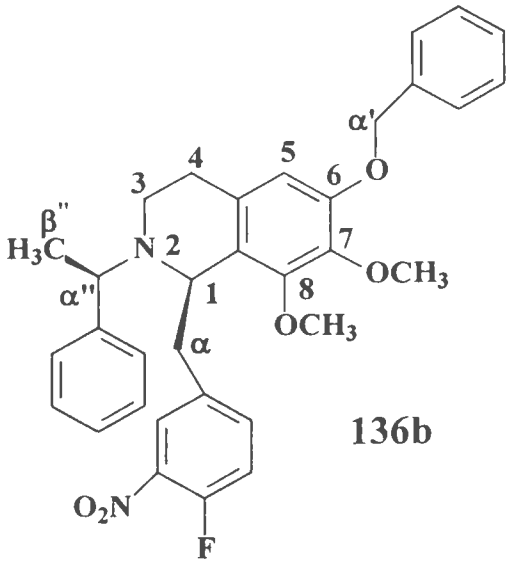


136a

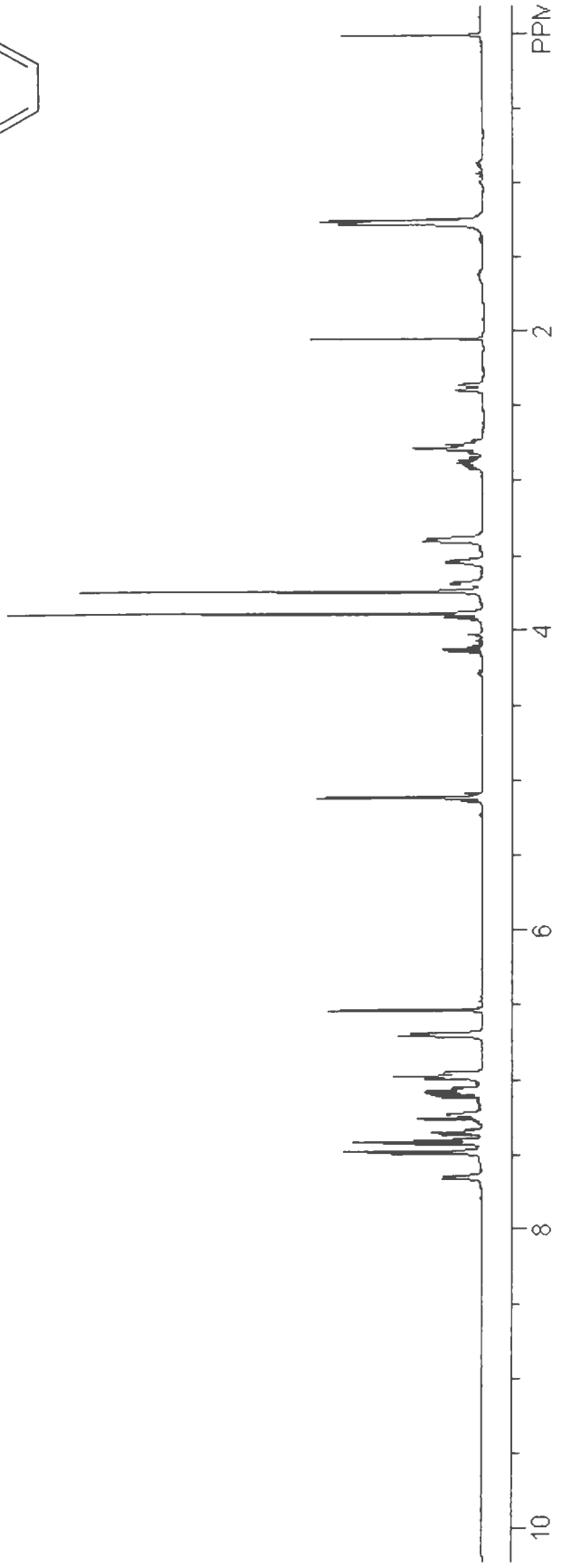


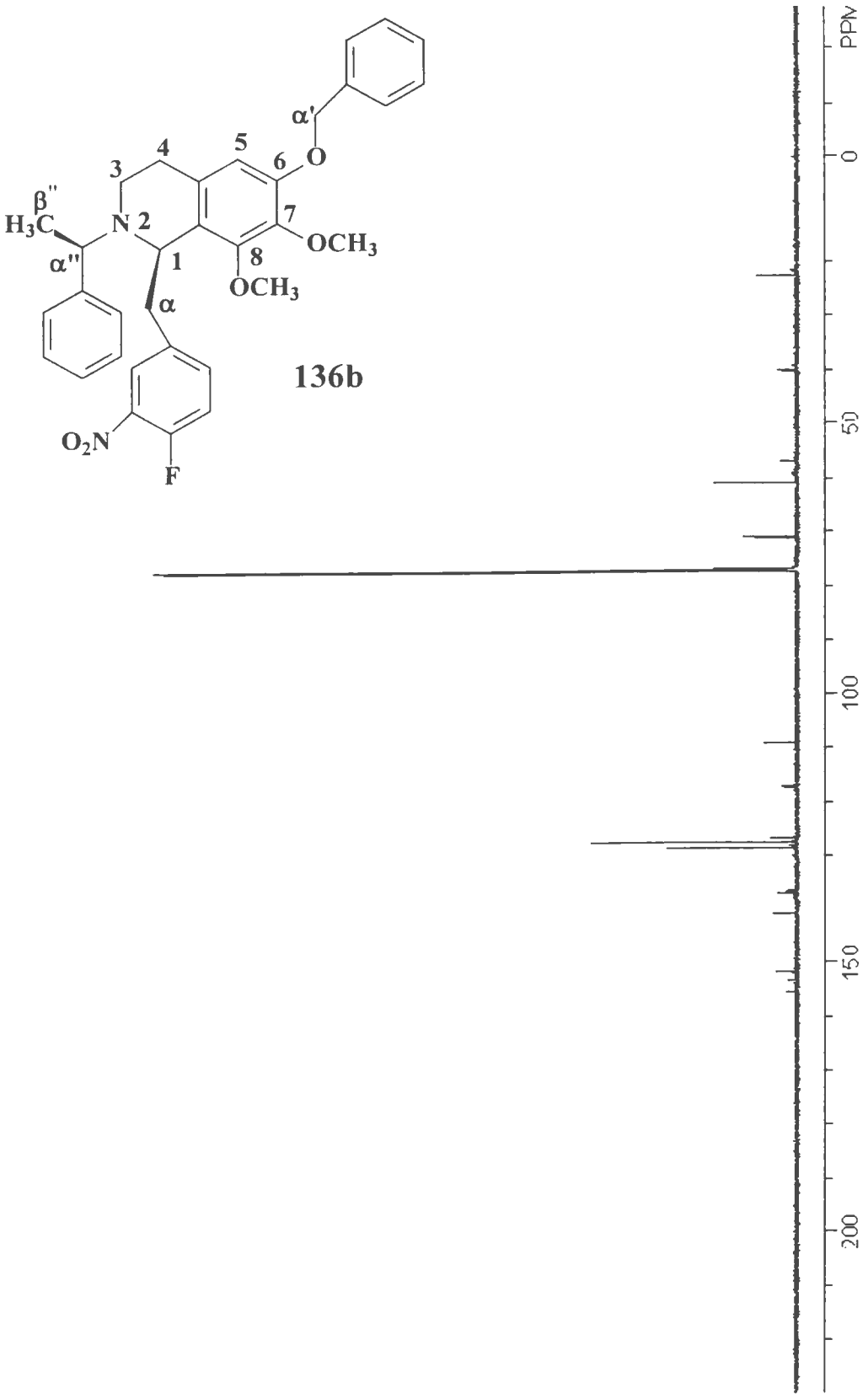


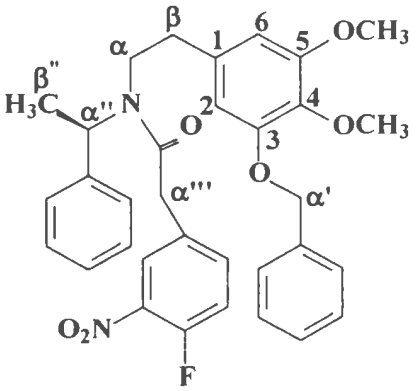
136a



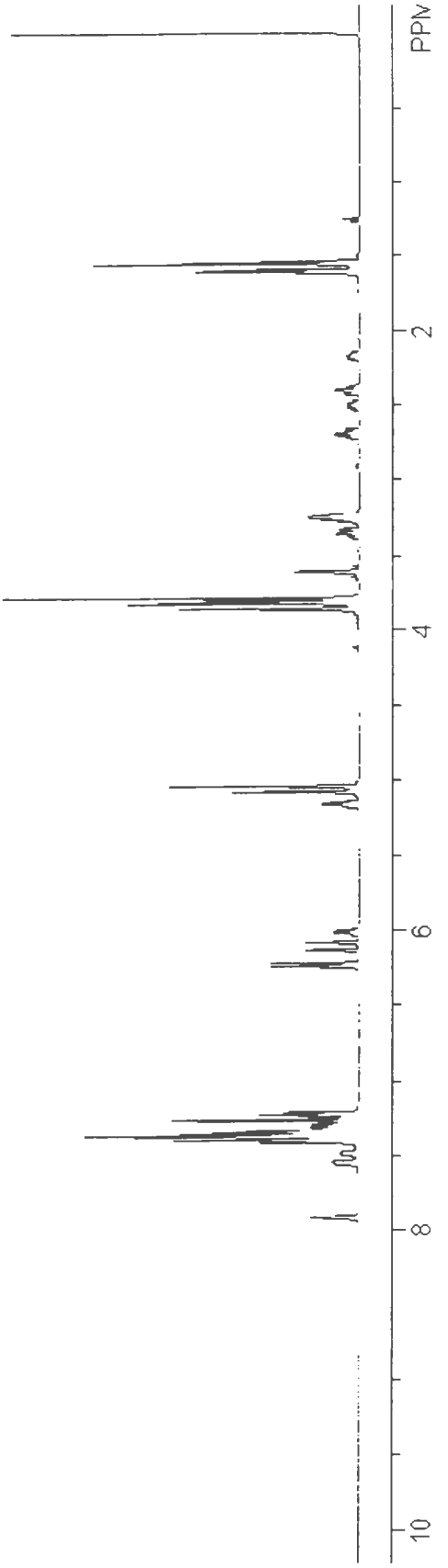
136b

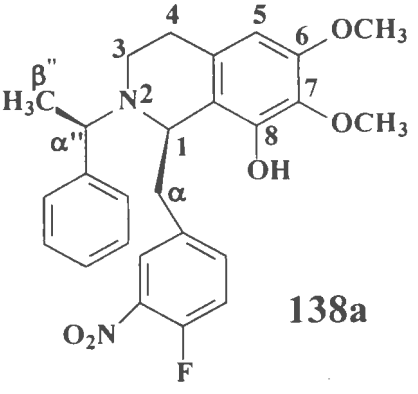



α'
O
6
5
4
3
β''
H3C
N
2
7
OCH3
α''
1
8
OCH3
α
O2N
F
136b
PPM
0
50
100
150
200

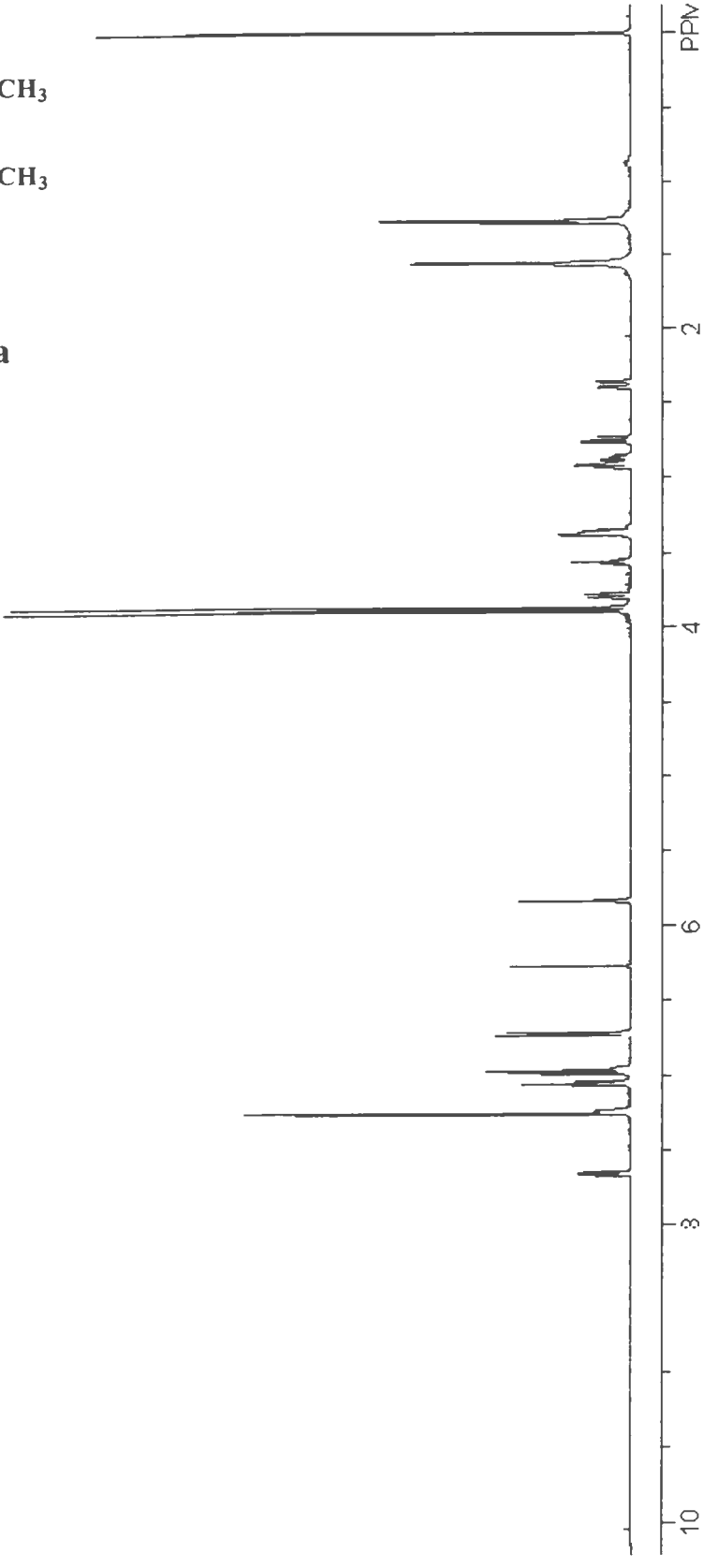


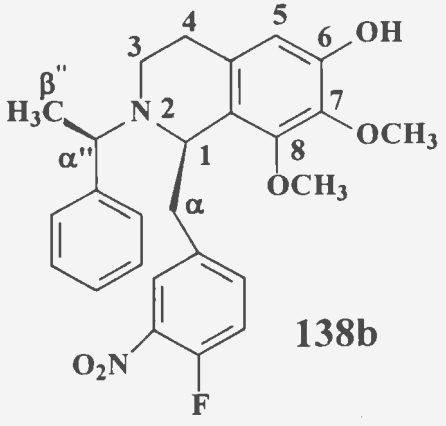
137





138a





138b