PROGRESS TOWARDS ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE BISBENZYLTETRAHYDROISOQUINOLINE ALKALOID (-)- CYCLEANINE AND A NEW APPROACH TO THE SYNTHESES OF SOME ISOQUINOLONES

JIANWEN CUI

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by

Jianwen Cui

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ABSTRACT

Bisbenzylisoquinoline (BBIQ) alkaloids are a very large and structurally diverse family of compounds, which can exist in up to 28 possible types. These compounds have been isolated from a variety of different plant sources and are found to exhibit a multitude of pharmacological properties including antitumor, antimalarial, and antibacterial activities. Variation in the number of oxygen substituents on the aromatic rings present, the number of ether linkages, the nature of the ether bridges and the sites on the two benzylisoquinoline units where the ether or carbon-carbon bonds originate, have made BBIQ's very interesting targets for several synthetic endeavours.

The research described herein focuses on the asymmetric synthesis of the BBIQ (−)-cycleanine, and several other compounds of interest. The mild $Cu(OAc)_2$-promoted diaryl ether formation methodology was applied to construct the target molecule. Crystals of the key precursor to the diaryl ether formation step were obtained and the absolute configuration of a new stereogenic center was established based on the X-ray crystallography analysis. The use of a chiral auxiliary-assisted diastereoselective Bischler-Napieralski cyclization is discussed.

In addition, a new approach to the synthesis of isoquinolones thalifoline, corydaldine and *N*-methylcorydaldine is investigated utilizing the Bischler-Napieralski strategy for the isoquinolines formation. Furthermore, regioselective oxidation of tetrahydroquinolines by using RuO_2-$NaIO_4$ is explored.

ACKNOWLEDGEMENTS

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List of Abbreviations

APCI-MS	atmospheric pressure chemical ionization-mass spectrometry
AcOH	acetic acid
BBIQ	bis(benzyltetrahydroisoquinoline)
BI	benzyltetrahydroisoquinoline
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BNC	Bischler-Napieralski cyclization
CA	chiral auxiliary
Cb_Z	benzyloxycarbonyl
CH_2Cl_2	dichloromethane
DCC	dicyclohexylcarbodiimide
DMAP	4,4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
i-Pr	isopropyl

ISB	iodosylbenzene
LC/MS	liquid chromatography/mass spectrometry
min	minute(s)
Me	methyl
MeOH	methanol
n-BuLi	*n*-butyllithium
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
PLC	preparative layer chromatography
rt	room temperature
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran

CHAPTER 1

INTRODUCTION

1.1 Structures and Sources of BBIQ Alkaloids

Bisbenzyltetrahydroisoquinoline (BBIQ) alkaloids are represented by approximately two hundred compounds, which occur primarily in the Families *Berberidaceae*, *Menispermaceae*, *Monimiaceae* and *Ranunculaceae*.[1] It is believed that one of the earliest applications of a BBIQ alkaloid is as a component of the arrow poison *Curare* used by some indigenous South American tribes.[1] Natural products chemists and pharmacists have been interested in the BBIQ alkaloids because of their diverse structures and varied pharmacological effects. Most of the literature on the BBIQ alkaloids is focused on their sources, structures and pharmacological activities.[1-4]

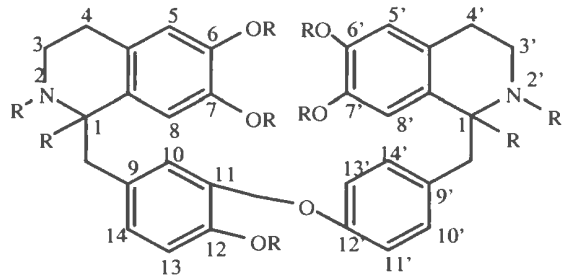
1.1.1 Botanical Source

Ecological factors affect the nature and the quantities of BBIQ alkaloids found in plants. Different groups of BBIQ alkaloids are distributed in different genera, and a single one may contain one major BBIQ alkaloid and some other minor alkaloids. Moreover, the alkaloids vary in their relative proportions in different parts of the plant. For example, in the case of *Mahonia fortunei* Fedde, the trunk is found to contain berbamine and oxyacanthine, but its leaves do not contain any BBIQ alkaloids.[5]

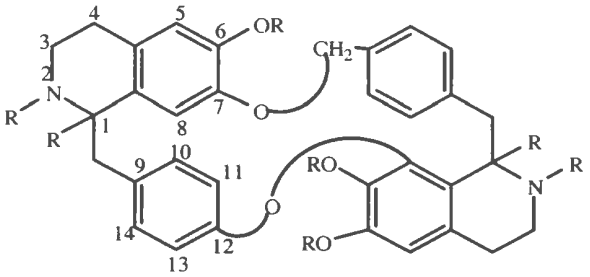
1.1.2 Structure

BBIQ alkaloids are composed of two benzyltetrahydroisoquinoline (BI) units linked by ether bridges. As well, methylenoxy bridging or direct carbon-carbon bonding between the two BI units is also found. According to Guha[1] and Shamma,[6] BBIQ

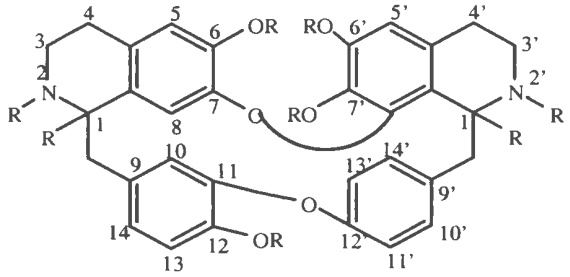
alkaloids are classified into 5 groups and 28 types, based on differences in their structural patterns: (1) the number of oxygen substituents on the aromatic rings; (2) the number of ether linkages; (3) the nature of ether bridges, *viz.*, diphenyl ether or benzylphenyl ether; and (4) the sites on the two BI units at which the ether or the carbon-carbon bond originate.[1] Most types of BBIQ alkaloid belong to groups A, B and C. Groups D and E only contain a few members.



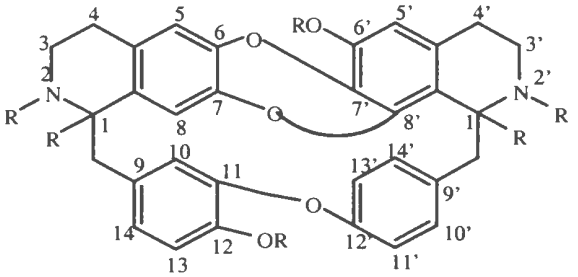
1a: Type I of Group A: one diphenyl ether linkage R=CH_3 or H



1c: Type XXII of Group C: one diphenyl ether and one benzyl phenyl ether linkage R=CH_3 or H



1b: Type VI of Group B: two diphenyl ether linkages R=CH_3 or H



1d: Type XXIII of Group D: three ether linkages R=CH_3 or H

Figure 1. Four structural types of BBIQ alkaloids

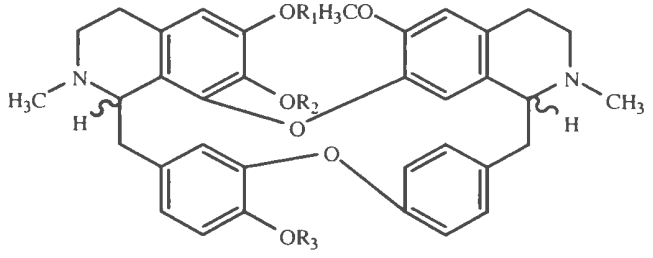
Figure 1 contains four different structures: **1a** according to Guha's classification, is an example of a structural Type I of Group A, and is characterized by one diphenyl ether linkage between the two "tail-to-tail" connecting subunits; **1b** is an example of a structural Type VI of Group B, with two diphenyl ether linkages between the two tetrahydroisoquinoline units, with a "head-to-head" and "tail-to-tail" connecting pattern;

1c is an example of a structural Type XXII of Group C with one diphenyl ether and one benzyl phenyl ether linkage between the two subunits; **1d** is an example of a structural Type XXIII of Group D, with two tetrahydroisoquinoline units connected by three diphenyl ether linkages.

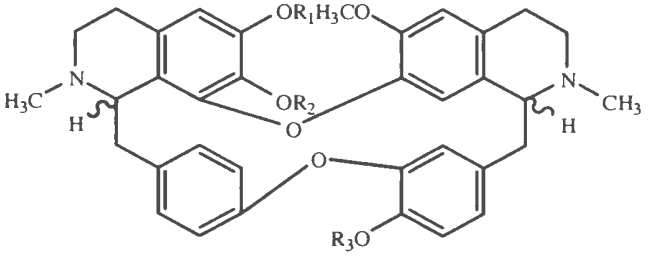
1.2. Pharmacological Activities of BBIQ Alkaloids

BBIQ alkaloids have been widely demonstrated to possess potent biological activities, including anti-tumor, anti-inflammatory, antibiotic, anti-hypertensive and anti-plasmodial activities.[4] The pharmacological activity of several BBIQs is outlined in Table 1, which shows that anti-inflammatory action is common to those compounds and that individual alkaloids usually have multiple pharmacological activities.

BBIQs, therefore, are potentially potent, non-toxic therapeutic agents that inhibit inflammation and biological oxidation.[4] Over the past thirty years, many researchers have tried to reveal the relationship between the structure features of BBIQs and their



1 1*R*,1'*S* - berbamine $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$
4 1*S*,1'*S* - tetrandrine $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$
7 1*S*,1'*S* - fangchinoline $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$



2 1*R*,1'*S* - cepharanthine $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$
3 1*R*,1'*S* - aromoline $R_1 = H$, $R_2 = CH_3$, $R_3 = H$
5 1*S*,1'*R* - oxyacanthine $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$
6 1*S*,1'*S* - repandine $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = H$

pharmacological activities.[2, 24] It was reported by Wright[25] and Galle[26] that chirality and substitution play roles in aiding in the selective interaction with various substrates. Although chirality and substitution patterns are believed to be related to the activities of BBIQs, [25, 26] no conclusions have been made about exactly how these structural features of BBIQs affect their biological activities.

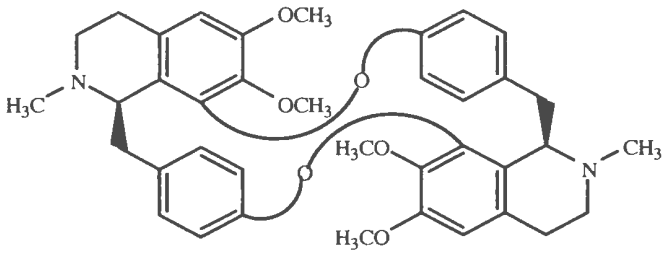
Table 1. Selected pharmacological activities of several BBIQ alkaloids

Alkaloid	Structural Type	Pharmacological Activity
Berbamine (**1**)	VIII	antiplasmodial,[7] anti-inflammatory,[8-11] antiproliferative,[12] antioxidant[13]
Cepharanthine (**2**)	VI	anti-inflammatory,[14] analgesic[15]
Aromoline (**3**)	VI	anti-inflammatory,[16] antiplasmodial[17]
Tetrandrine (**4**)	VIII	inhibition of T-Cell dependant immune responses,[18] antiplasmodial,[19] anti-inflammatory[12, 20-22]
Oxyacanthine (**5**)	VI	anti-inflammatory,[9-11] antioxidant,[13] antiproliferative[12]
(−)-Repandine (**6**)	X	antiplasmodial,[19] anti-inflammatory[9, 14]
Fangchinoline (**7**)	VIII	antiplasmodial, anti-inflammatory[23]

1.3 Syntheses of BBIQs

In spite of the vast literature on the isolation of BBIQs from different parts of plants, their structure determinations and their biological activities, there is relatively little on their syntheses. The complexity of these compounds makes their syntheses a

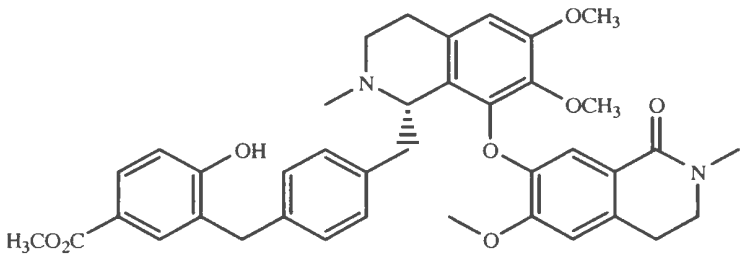
great challenge. Undertaken in the 1960s and early 1970s, the work of the main early researchers on the syntheses of BBIQs, Tomita,[24, 27-29] Inubushi[30] and Kametani,[31-33] was reviewed by Shamma *et al.*[2] The syntheses of oxyacanthine, berbamine and related compounds were reported by Inubushi and Kametani, while Tomita focused on the synthesis of the isochondodendrine type of BBIQ, *e.g.* cycleanine (**8**). Unfortunately,



(−)-Cycleanine (**8**)

each group experienced the same problems associated with regioselectivity, diastereoselectivity and coupling difficulties.

In 2002, Wang and Georghiou[34] completed the first enantioselective total synthesis of (−)-tejedine (**9**), a *seco*-bisbenzyltetrahydroisoquinoline, which was isolated



(−)-Tejedine (**9**)

in 1998 as a minor component from *Berberis vulgaris*.[35] This synthesis was accomplished with four key steps in which a chiral auxiliary-assisted diastereoselective Bischler-Napieralski cyclization (BNC) strategy was employed. A mild $Cu(OAc)_2$-mediated diaryl ether coupling methodology recently developed by Evans[36] and Chan[37] was successfully applied in the (−)-tejedine synthesis. This also formed the main synthetic strategy employed towards the formation of diaryl ethers described in this thesis and will be described in greater detail in the following sections.

1.4 Cycleanine

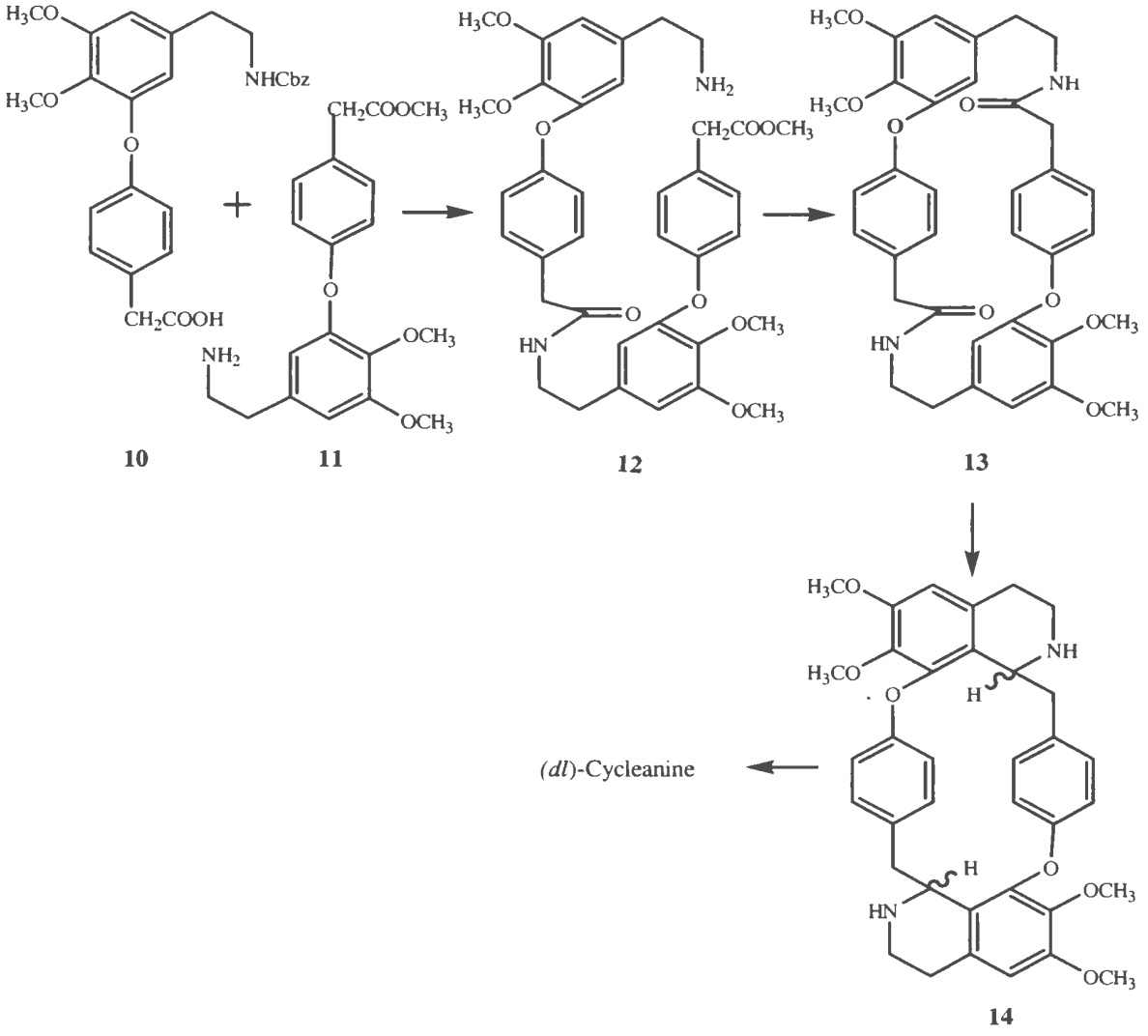
Cycleanine (**8**) (*O*,*O*-dimethylisochondodendrine) is a C_2-symmetrical compound with two benzyltetrahydroisoquinoline units connected by two diaryl ether linkages. It was first isolated from *Cyclea insularis* (MAKINO) DIELS and *Stephania cepharantha* HAYATA in 1937 by Kondo *et al.*[38] Cycleanine is a "head-to-tail" dimer and is a Type XX, Group B, BBIQ.

1.4.1 Pharmacological Activities of Cycleanine

Cycleanine can be obtained from the root bark of the plant *Synclisia scarbrida Miers (Menispermanceae)*, a slender woody creeper found in Southern Nigeria and other coastal regions of West Africa. The root bark is widely used in traditional medicine to treat various ailments such as acute psychosis, dysmenorrhea and threatened abortion. Men in southern Nigeria have been reported to use the root powder also as an aphrodisiac. Cycleanine has also been reported to be an analgesic, muscle relaxant and anti-inflammatory.[15] Wambebe *et al.*[39] evaluated the cycleanine activity in the central nervous system and uterotonic effects. They revealed that cycleanine significantly

reduced spontaneous motor activities (SMA) in a dose-related manner and evoked concentration-dependent contractions that were resistant to atropine but were blocked by salbutamol.

Although further investigations are needed to identify structure–activity relationships for the biological activity of cycleanine, clearly the compound has many

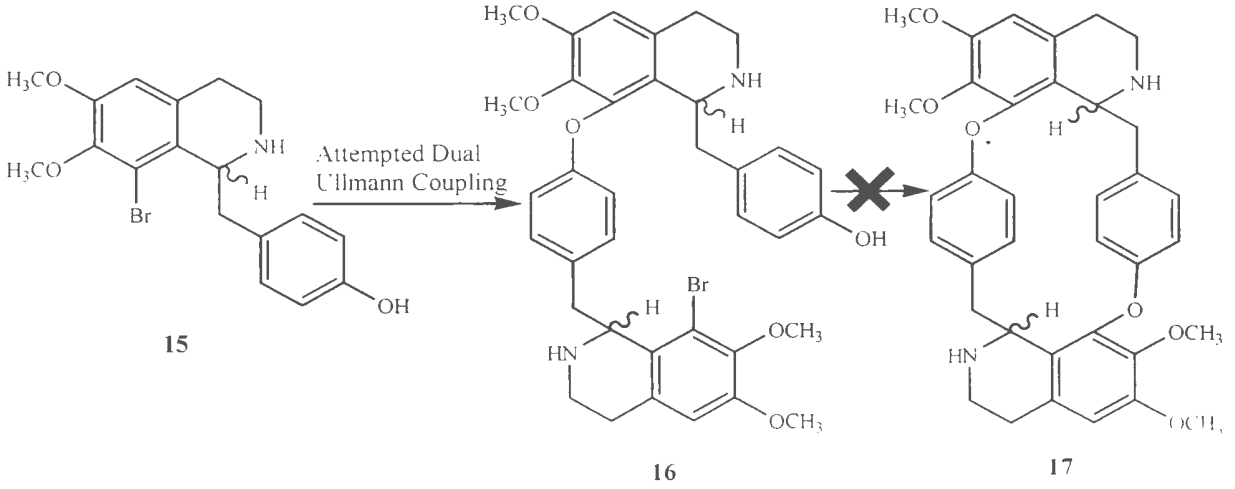


Scheme 1.

properties which make it of pharmacological interest.

1.4.2 Previous Synthetic Approaches towards Cycleanine

Most of the previous synthetic efforts towards cycleanine were made by Tomita, *et al.*[27-29] They completed the first synthesis of *(dl)*-cycleanine in 1966.[28] The outline of their synthesis is displayed in Scheme 1. Condensation between the *N*-Cb_Z carboxylic acid **10** and the methyl ester **11** gave an amide **12** with the aid of dicyclohexylcarbodiimide (DCC) in dichloromethane. Deprotection of the amino group and ester hydrolysis, followed by a second condensation reaction using DCC gave the cyclic diamide **13**. Bischler-Napieralski cyclization (BNC) of the cyclic diamide **13** followed by sodium borohydride reduction gave a mixture of tetrahydroisoquinolines, that after *N*-methylation, produced a mixture of *(dl)*-cycleanine and its regioisomers. This approach was not synthetically useful because of the very low yield of the ring-closure step (<10%), the formation of a mixture of diastereoisomers and the lack of regioselectivity.



Scheme 2.

Tomita's other attempted synthesis of cycleanine, which is shown in Scheme 2, via a dual Ullmann coupling reaction was disappointing.[29] This approach endeavoured to form the dual Ullmann coupling product cyclic diamine **17** from the 8-bromoarmepavine **15**. However, the attempts gave only the linear diamine **16,** which could not be further coupled.

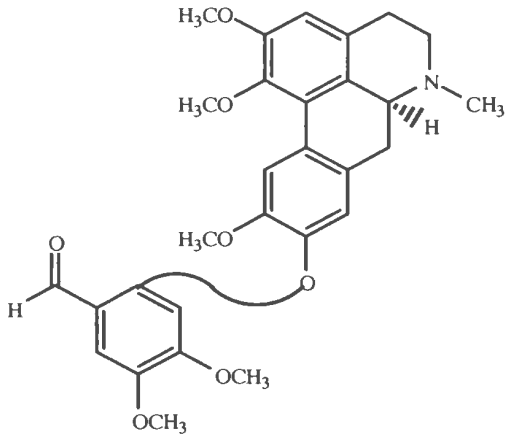
Although the synthesis of this alkaloid was unsuccessful, information gained from the attempted syntheses by Tomita *et al.* was valuable. As a result of their efforts, the main problems associated with the formation of the macrocyclic ether linkages and the determination of the correct regiochemical result from the tetrahydroisoquinoline ring closure were partly solved. With the development of modern synthetic techniques, it was postulated that those difficulties might be overcome more effectively. In this thesis, a $Cu(OAc)_2$-mediated diaryl ether formation methodology is discussed. In order to solve the problem of the regioselectivity, an enantiomerically pure subisoquinoline unit as a precursor of the diaryl ether-macroether ring-closure step was successfully synthesized. This accomplishment could be helpful towards reaching the target molecule in the future.

1.5 Benzyltetrahydroisoquinolones

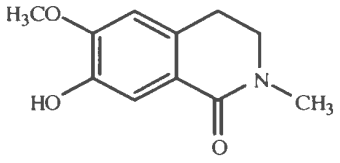
1.5.1 Benzyltetrahydroisoquinolones

Benzyltetrahydroisoquinolones are a group of alkaloids that are present only in minor amounts in certain plants. Since these compounds are minor constituents in sources that produce alkaloids derived from benzyltetrahydroisoquinoline units, their origin is most likely a result of biochemical oxidation of these major products.[40] This hypothesis was presented in Tomita's report.[41, 42] The presence of hernandaline (**18**) and thalifoline

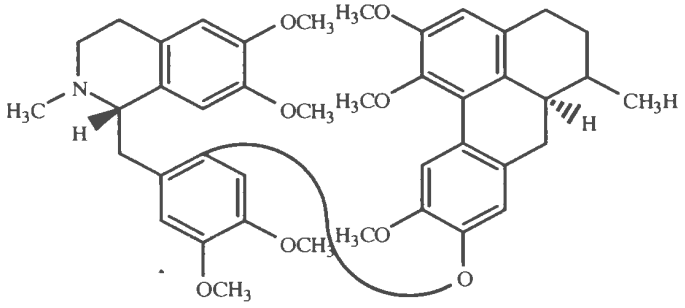
(**19**)[43] in the same plant possibly results from the oxidation of the dimeric benzylisoquinoline-aporphine dimer, thalicarpine (**20**),[41] which is known to occur in the same species.[42] It should not be surprising, therefore, that thalifoline, first isolated from *Thalictrum minus L. Var. adiantifolium Hort* by R. W. Doskotch *et al.* in 1969,[43] was found to be a subunit of (−)-tejedine (**9**).[34]



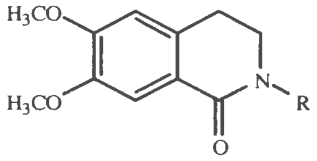
(+)-Hernandaline (**18**)



Thalifoline (**19**)



(+)-Thalicarpine (**20**)



N-Methylcorydaldine (**21**) R=CH_3
Corydaldine (**22**) R=H

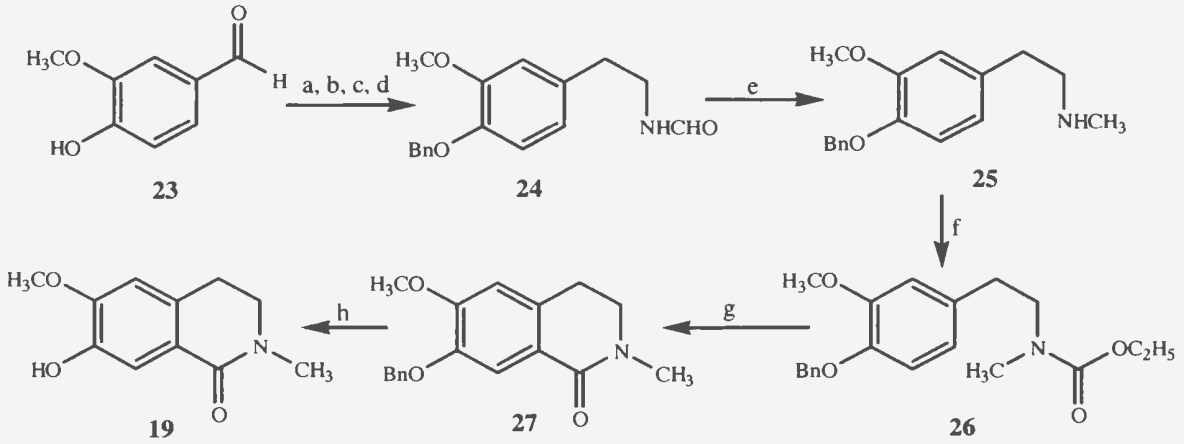
N-Methylcorydaldine (**21**),[44] isolated in 1971 from *Thalictrum fendleri* Engelm. ex Gray, as a colourless oil, was found to be devoid of cytotoxicity when measured by the degree of inhibition of protein synthesis with monolayer KB cell cultures. Corydaldine

(**22**),[45] another member of this small, rare group of isoquinolones, is known to have medicinal importance.[46] No other studies have been reported on the biological activity of these isoquinolone compounds.

Although these isoquinolones are relatively rare compounds and there are only a few reports on their biological activity, it is important to study the syntheses of such compounds using potentially efficient methodologies, which may be used in the syntheses of other BBIQ alkaloids. This thesis will describe approaches towards the syntheses of thalifoline (**19**), *N*-methylcorydaldine (**21**), corydaldine (**22**) and related structures using newly developed selective C-1 oxidation methodologies,[47] which may be applicable to the total syntheses of BBIQs.

1.5.2 Previous Synthetic Approaches towards Isoquinolones

Compared to the great interest in the synthesis of isoquinolines, only a few syntheses of isoquinolones have been reported. It is known that tetrahydrobenzyl-isoquinolines can be oxidized to form isoquinolones using potassium permanganate. Doskotch *et al.*[43] completed a synthesis of thalifoline (**19**) using this methodology in less than 10% overall yield using vanillin (**23**) as the starting material. In 2002, Wang and Georghiou achieved the synthesis of this target molecule efficiently by a multistep synthesis with 37% overall yield.[48] The synthesis is illustrated in Scheme 3.



Conditions: (a) $BnBr/K_2CO_3$, acetone, reflux, 98%; (b) CH_3NO_2/NH_4Ac, CH_3COOH, reflux, 90%; (c) $LiAlH_4$, THF, reflux; (d) $HCOOC_2H_5$, reflux, 78%, two steps; (e) BH_3/THF, BF_3/Et_2O, THF, reflux; (f) 1. $ClCOOC_2H_5$; 2. $NaHCO_3$, CH_2Cl_2-H_2O, 0°C, 60%, two steps; (g) Tf_2O/DMAP, CH_2Cl_2, 0°C, 90%; (h) H_2/Pd/C, methanol, 99%.

Scheme 3.

This approach also started from vanillin (**23**). After six straightforward steps, the key intermediate carbamate **26** was obtained in 41% overall yield. The penultimate step is no doubt the most impressive reaction in the synthesis. Under conditions which employ a combination of trifluoromethanesulfonic anhydride (Tf_2O) and 4-dimethylaminopyridine (DMAP) as discovered by Banwell *et al.*,[49, 50] an efficient cyclization of the carbamate **26** was achieved to afford *O*-benzylthalifoline **27**, which was easily converted to the target molecule **19** by hydrogenolysis.

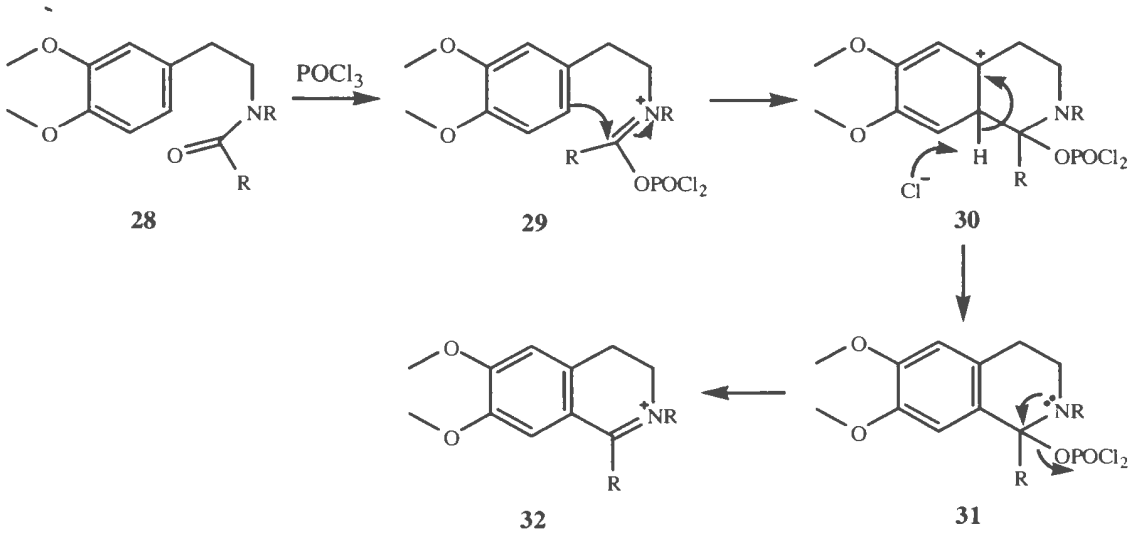
Recently, Huang *et al.*[51] reported oxidation of *N*-methyltetrahydroisoquinolines with iodosylbenzene (ISB) in the presence of a catalytic amount of tetrabutylammonium iodide in various solvents to afford the corresponding amide isoquinolones in almost quantitative yields. Corydaldine (**22**), *N*-methylcorydaldine (**21**) and other iso-quinolones were similarly obtained by oxidation of the corresponding isoquinolines using this procedure, the advantages of which include easy handling of reagents, which have low

toxicity, and the employment of mild conditions. This ISB methodology will be hopefully applied to other BBIQ syntheses.

1.6 Tetrahydroisoquinoline Ring Closure

The Bischler-Napieralski reaction[52] is of great importance in isoquinoline synthesis. This reaction was employed for the construction of isoquinoline rings during the original syntheses of BBIQs. An endocyclic iminium ion is formed under the classic Bischler-Napieralski reaction conditions of refluxing an amide and a Lewis acid (such as $POCl_3$) in benzene. The iminium ion is subsequently reduced by $NaBH_4$ to give the isoquinoline ring.

This currently accepted mechanism, outlined in Scheme 4, was first proposed by Fodor and Nagubandi[53] in 1980. The Lewis acid initially coordinates with the carbonyl oxygen of the amide **28** and forms the intermediate **29**. Electrophilic attack by the aromatic ring and subsequent re-aromatization results in the formation of the



Scheme 4.

tetrahydroisoquinoline intermediates **30** and **31**. The resultant iminium ion **32** is reduced to the corresponding tetrahydroisoquinoline by sodium borohydride.

The presence of an electron-donating group *para* to the site of the ring closure is necessary for the BNC reaction to occur. As a result, there may be more than one ring-closure site if there are two or more electron-donating groups. As well, a bulky group may block ring–closure on a position *ortho* to that group.

Pictet-Spengler[54] and Pomeranz-Fritsch cyclizations[55] have also been employed to construct the six-membered ring. The Pictet-Spengler cyclization has become the most popular method for the construction of six-membered heterocyclic rings because of several advantages, such as the use of milder reaction conditions than the traditional BNC reaction and also the lack of a requirement for a subsequent reduction. Unfortunately, the application of Pictet-Spengler cyclization methodology in an earlier attempt of the synthesis of cycleanine by M. Ralph in the Georghiou laboratory[56] was abandoned due to the failure to obtain the necessary precursor needed for the cyclization step.

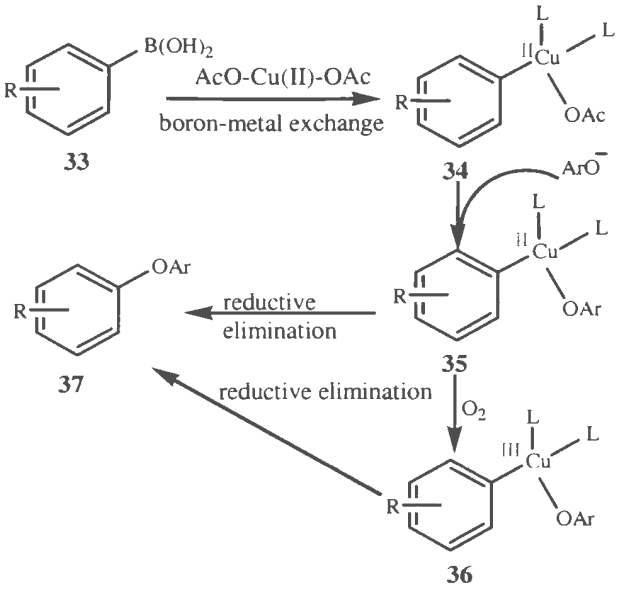
This thesis will describe approaches applied towards the isoquinoline ring closure using BNC methodology. The utilization of a chiral auxiliary to control a chiral centre outcome of a ring-closure step will also be discussed.

1.7 Diaryl Ether Formation

Diaryl ethers are an important class of compounds in pharmaceuticals and organic natural products. A large variety of naturally-occurring and medicinally-important compounds contain a diaryl ether moiety. Among the methods used for the preparation of such diaryl ethers, the classic Ullmann[57] ether synthesis is the most well known.

However, this reaction, in which an aryl bromide or iodide reacts with a phenol under basic conditions in the presence of copper salt catalysts, is often limited by the need to employ harsh reaction conditions and stoichiometric amounts of copper.[57] An improvement to the classic Ullmann ether synthesis has been reported by Buchwald.[58] Recent developments in palladium-catalyzed ether formation reactions have solved certain problems in this area as well.[53] However, at present, copper catalysts still play an important role in industrial applications because of the advantage of their low cost in large-scale reactions.

According to Evans,[36] the addition of powdered 4 Å molecular sieves to the reaction mixture was confirmed to suppress phenol and diphenyl ether formation and increase product yields. It was further noted that a dry and pure oxygen atmosphere was unnecessary, as running the reaction under an ambient condition gave identical results. Although evidence is lacking, the base, triethylamine or pyridine, could have a dual role as both a base and a ligand for the organocopper intermediates. From Evans' observations, pyridine increased the yield of this transformation. Although further studies on the mechanism of this methodology are ongoing, Evans[36] put forth the following preliminary hypothesis. The boron-metal exchange of arylboronic acid **33** with copper acetate can afford arylcopper(II) complex **34**, which reacts with phenoxide ion to form the corresponding arylcopper(II) phenoxide intermediate **35**. This arylcopper(II) phenoxide intermediate **35** can undergo either subsequent reductive elimination to the diaryl ether compound **37** or oxidation to arylcopper(III) phenoxide intermediate **36** prior to elimination to produce product **37** as shown in Scheme 5.

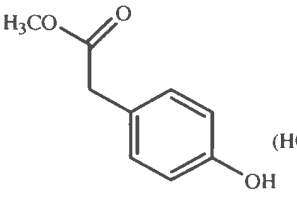
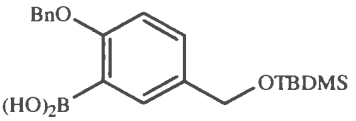
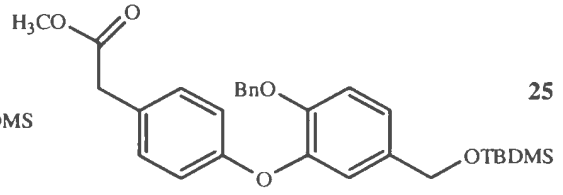
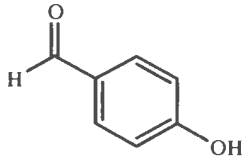
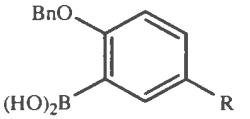
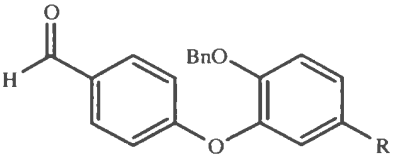
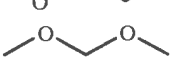
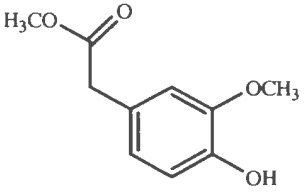
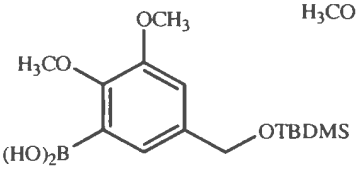
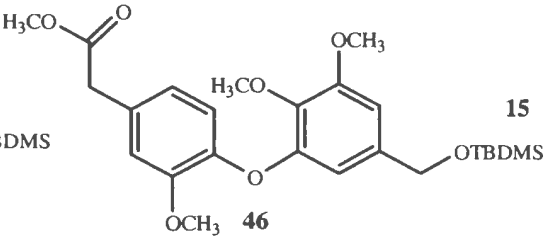
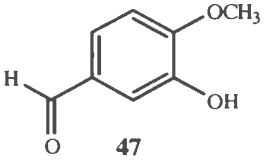
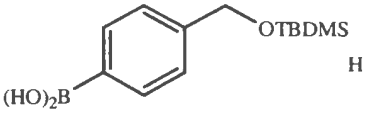
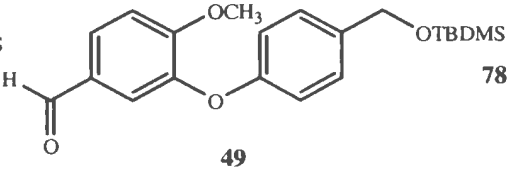
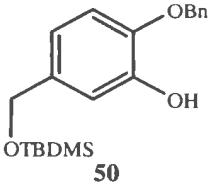
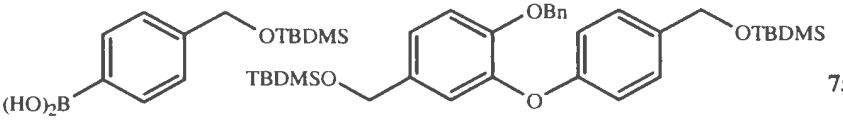
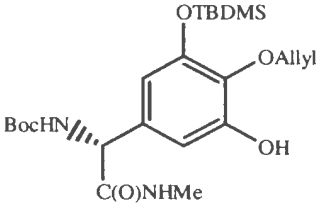
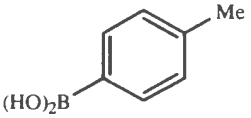
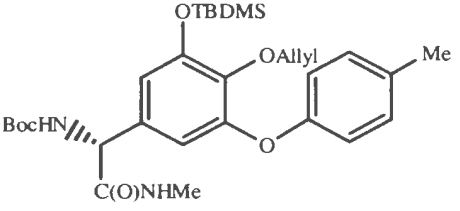


Scheme 5.

Evans[36] and Chan[37] explored the use of arylboronic acids to couple with activated phenols through the mediation of $Cu(OAc)_2$. A number of structurally and electronically diverse substrates were evaluated by Evans[36] and Wang.[59] It can be seen from Table 2, that electron-rich phenols underwent arylation most efficiently. Evans also pointed out that generally *ortho*-substituted phenols were arylated in good yields, but that yields were depressed with *ortho*-substituted boronic acids.

Approaches towards the total syntheses of (−)-cycleanine, isoquinolones and related structures using recently developed methodologies are discussed in this thesis. The $Cu(OAc)_2$-mediated diaryl ether formation methodology, which was employed to furnish the diaryl ether ring-closure step, will be discussed in detail. The use of a chiral auxiliary-assisted diastereoselective Bischler-Napieralski cyclization strategy will be also studied in the following section.

Table 2. $Cu(OAc)_2$-mediated diaryl ether formation

Phenol	Boronic acid	Diaryl ether	Yield (%)
 **38**	 **39**	 **40**	**25**
 **41**	 **42 R=** 	 **43 R=** 	**21**
 **44**	 **45**	 **46**	**15**
 **47**	 **48**	 **49**	**78**
 **50**	 **51** **52**		**75**
 **53**	 **54**	 **55**	**81**

CHAPTER 2

Synthetic Efforts towards (−)-Cycleanine

2.1 Introduction

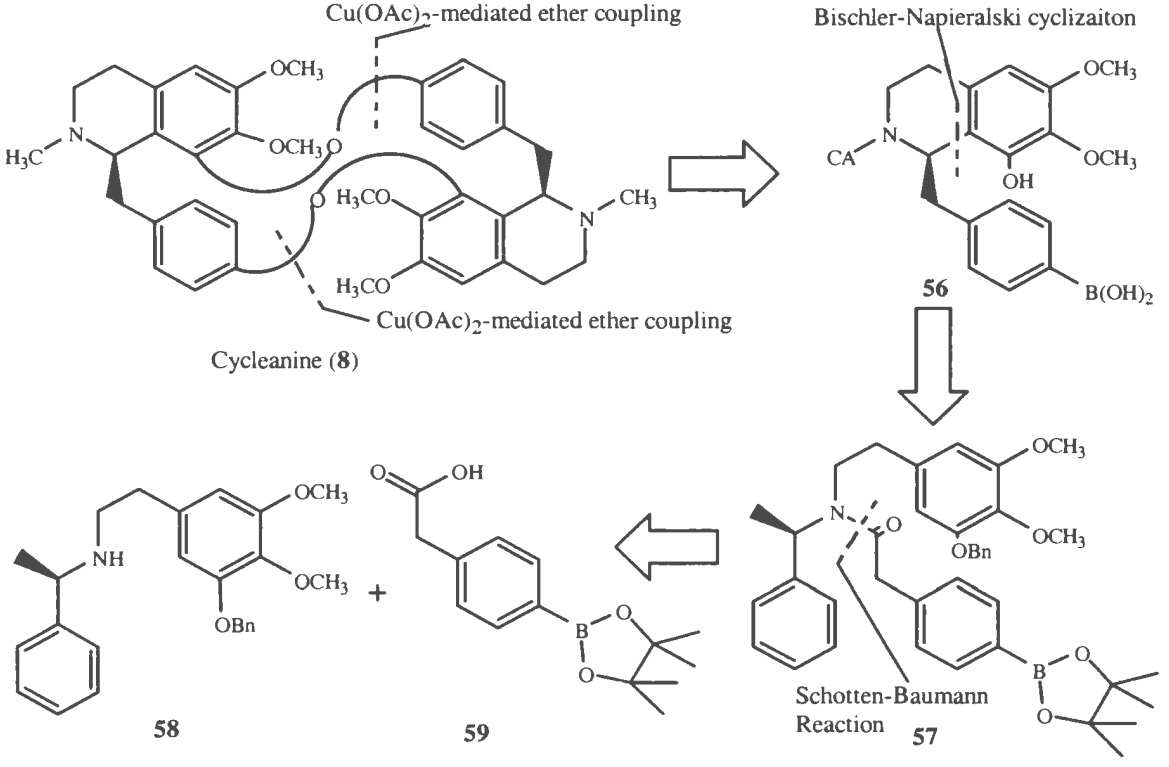
This chapter is focused on the synthesis of (−)-cycleanine (**8**). As described in Chapter 1, (−)-cycleanine (**8**) has a C_2-symmetric structure connected "head-to-tail" by two diaryl ether linkages. Because of cycleanine's particular structure and especially its pharmacological activities,[15, 39] the total synthesis of this BBIQ alkaloid is attractive to both organic chemists and pharmacognosists. However, an enantioselective synthesis of this natural compound has not yet been accomplished. Most of the previous attempts towards this target have been attributed to Tomita *et al.*[26-29] Based on retrosynthetic analysis of (−)-cycleanine and Tomita's synthetic experience, several multistep routes were evaluated towards the target molecule and are described in this thesis.

2.2 Results and Discussion

2.2.1 Initial Proposal For the Synthesis of (−)-Cycleanine

Outlined in Scheme 6 is an initial retrosynthetic analysis for (−)-cycleanine (**8**). The first retrosynthetic cut gives the chiral-auxiliary (CA)-protected boronic acid **56** as a precursor to the $Cu(OAc)_2$-promoted ether coupling step, which is one of the main methodologies applied in this synthesis. In the synthetic direction, BNC of amide **57** would be expected to result in the formation of boronic acid **56** and its regioisomer because there are two sites for the ring-closure step (*para* and *ortho* to the electron-donating benzyloxy group). Structure **57** includes boronate, chiral auxiliary and amide

moieties required for the ring-closure step to the corresponding isoquinoline **56**. A further retrosynthetic cut dissects the amide **57** into the key intermediates: chiral amine **58** and carboxylic acid **59**. These two key intermediates are required for the Schotten-Baumann reaction[60] to afford the amide **57**. At this initial synthetic stage, the synthesis was reduced to the formation of those four key intermediates: boronic acid **56,** boronate **57**, chiral amine **58** and carboxylic acid **59**.



Scheme 6.

In Chapter 1, an alternative ring-closing methodology investigated in the Georghiou laboratory for the formation of the isoquinoline rings was discussed and no satisfactory results were obtained.[56] On the other hand, other methods of ether formation,

including the classic Ullmann coupling,[57-58] were not considered in this particular synthesis due to the disadvantageous reaction conditions which these methods require. In this thesis, discussion will concentrate on the $Cu(OAc)_2$-mediated boronic acid coupling methodology first described by Evans[36] and Chan.[37] In addition, the use of a chiral auxiliary-assisted BNC required for the cyclizaton of **57**, will also be examined.

The effects of some substitutents on the ring-closure step needed to construct compounds **56-59** will also be presented. The role of a chiral auxiliary in controlling the stereoselectivity will be another key point in the following sections. Furthermore, suggested alternative attempts towards the completion of the target molecule will be explored.

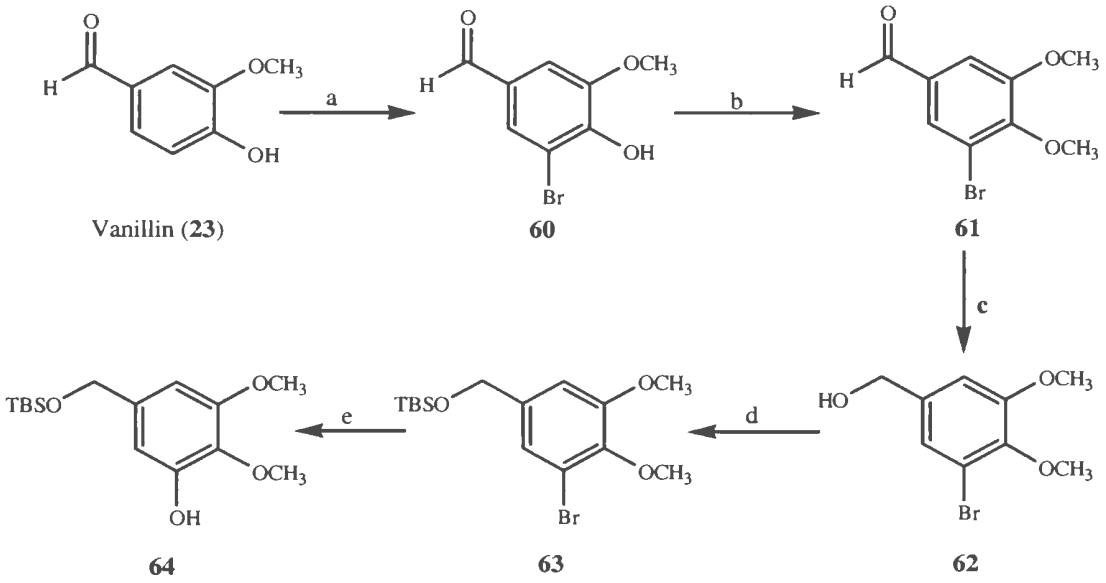
2.2.2 Model Study of Diaryl Ether Formation

As described in Chapter 1, the diaryl ether formation methodology was employed in the synthesis of (−)-tejedine (**9**).[34] The model study of this methodology was explored in the Georghiou laboratory, and it is displayed in Table 2 of Chapter 1. Under diaryl ether formation conditions, only those reactions between boronic acids and *ortho*-substituted phenols afforded the corresponding diaryl ethers with acceptable yields. The yields were very low with *ortho*-substituted boronic acids, as was noted by Evans.[36] When pyridine was the base in these model studies, good yields were obtained. When triethylamine was used as the base, very low yields were obtained. Furthermore, very dilute solutions (0.05 M in reaction solution) were found to be necessary for the diaryl

ether formation to occur efficiently. As described in Evans' report,[36] 4 Å molecular seives were added to the reaction and this helped to increase the reaction yields.

2.2.3 Synthesis of the Key Intermediates 56-58

Vanillin (**23**) was chosen as the starting material for the synthesis of chiral amine **58** since vanillin has substituent groups that are suitable for further functionalization. Protection and deprotection of those functional groups are necessary in this synthesis. The chosen protecting groups should withstand the reaction conditions without



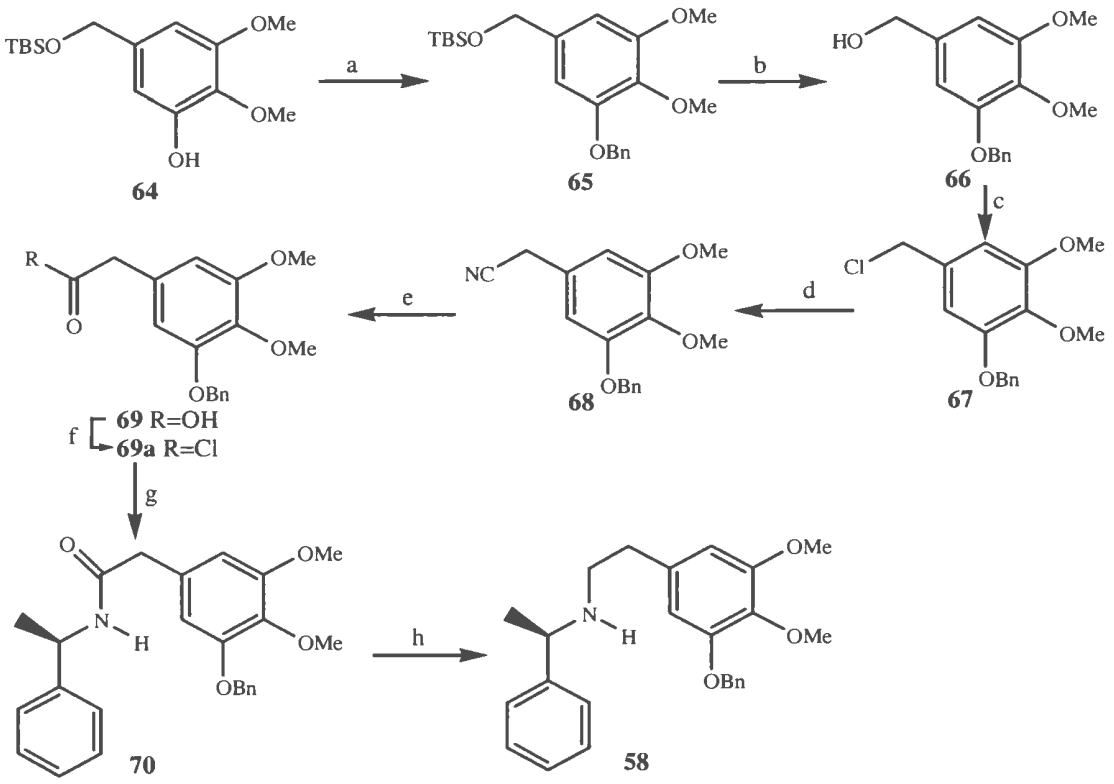
Conditions: a) Br_2, AcOH, 95%; b) Me_2SO_4, NaOH, H_2O, CH_2Cl_2, Adogen 464®, 85%; c) $NaBH_4$, MeOH, THF, 99%; d) TBSCl, imidazole, DMF, rt., 88%; e) 1. *t*-BuLi, then $B(OMe)_3$; 2. -78°C, H_2O_2, 71%.

Scheme 7.

interference with other substituent groups. At the same time, those protecting groups should be easily removed at a later stage. Considering the above, the synthetic routes shown in Schemes 7-10 were designed towards those intermediates.

Because of the *ortho*-directing effect of the hydroxy group on vanillin, the first bromination step gave the desired 5-bromovanillin **60** (95%). Methylation of **60** furnished 5-bromoveratraldehyde **61** (85%). Reduction of the aldehyde moiety of **61** using $NaBH_4$ afforded a primary alcohol **62** (99%). Protection of the hydroxy group in **62** as the TBS ether **63** (88%) was followed by a lithiation-boronation sequence, involving by quenching with trimethyl borate at -78 ^{o}C and finally oxidation using hydrogen peroxide. This resulted in formation of the phenol **64** (71%).

After these five straightforward steps, phenol **64** was converted to the phenylacetic acid **69** in very high overall yields (68%). Protection of the phenol **64** as a benzyl ether **65** was followed by easy removal the TBS group using TBAF to afford the primary alcohol **66** (99%). Reaction of **66** with thionyl chloride produced the chloride **67** in almost quantitative yield. Cyanation gave compound **68** (91%), which was followed by hydrolysis with NaOH/EtOH to form the phenylacetic acid **69** (90%). Studies in the Georghiou laboratory by Dr. Wang found that the commercially available (*R*)-(+)-α-methylbenzylamine to be the most efficient chiral auxiliary to affect a diastereoselective BNC at later steps. A detailed discussion of this reaction will be presented in later sections of this thesis. Reaction of the phenacyl chloride, formed *in situ* from phenylacetic acid **69**, with (*R*)-(+) -α-methylbenzylamine under Schotten-Baumann conditions resulted in the formation of amide **70** (85%), which was reduced to the corresponding chiral amine **58** upon treatment with BH_3/THF and BF_3/Et_2O in refluxing THF. The Schotten-Baumann reaction was employed in this research as the main



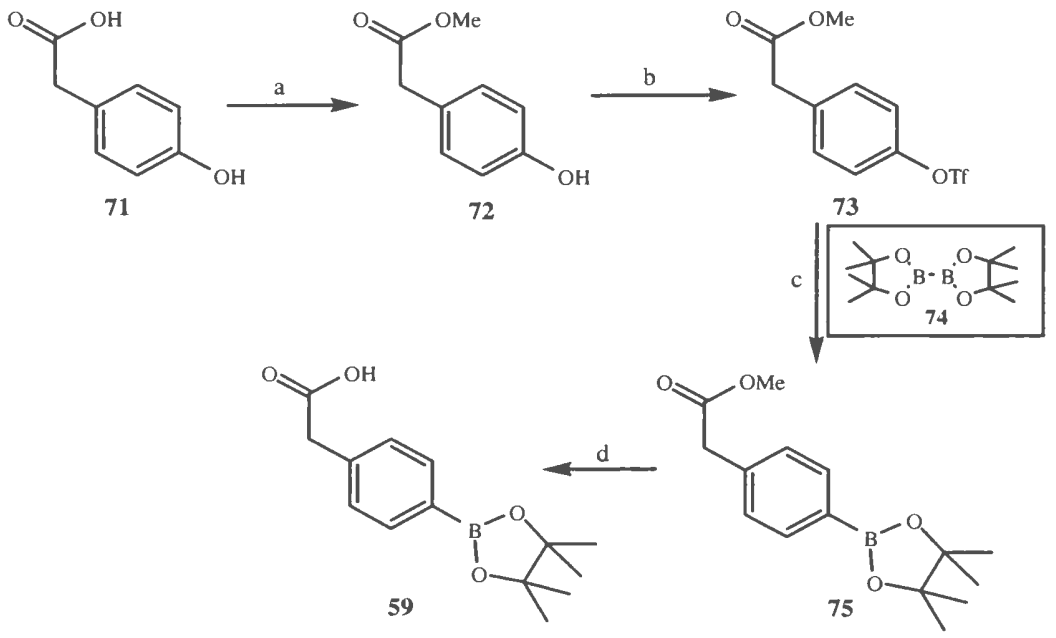
Conditions: a) BnBr, K_2CO_3, acetone, 85%; b) TBAF, THF, 0 °C, 99%; c) $SOCl_2$, benzene, 98%; d) NaCN, DMSO, benzene, 91%; e) 4.0 M NaOH, ethanol, reflux, 90%; f) $(COCl)_2$, benzene, DMF; g) **69a**, (R)-(+)-α-methylbenzylamine, 5% NaOH-CH_2Cl_2, 84%; h) BH_3/THF, BF_3/Et_2O, THF, reflux, 81%.

Scheme 8.

method to construct target amides.

Attention was next directed towards the construction of the key intermediate **59**. The synthesis of **59** is shown in Scheme 9. This synthesis started from 4-hydroxy-phenylacetic acid **71**, which is commercially available. Esterification of the carboxylic acid in refluxing methanol in the present of a catalytic amount of concentrated sulfuric acid gave methyl(4-hydroxyphenyl)acetate **72** (91%). According to published reports,[61] activation of the phenolic group is necessary prior to the palladium-catalyzed borylation

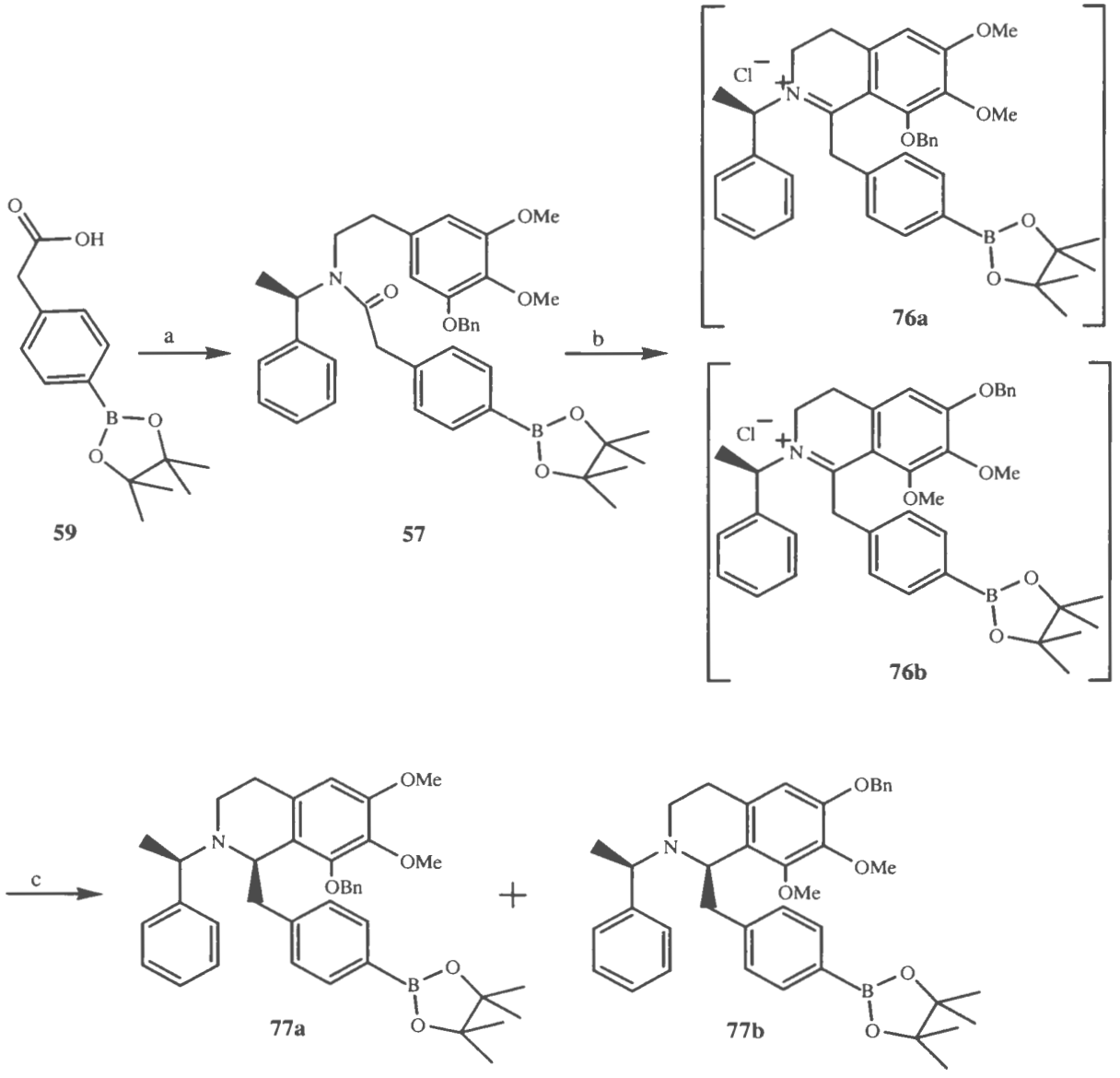
step. Reaction of **72** with Tf_2O at –40 °C in the presence of 2,6-lutidine converted



Conditions: a) MeOH, conc. H_2SO_4, reflux, 90%; b) Tf_2O, 2,6-lutidine, CH_2Cl_2, -40 °C, 83%; c) **74**, $PdCl_2$(dppf), Et_3N, dioxane, 80 °C, 75%; d) LiOH, THF-MeOH-H_2O, 95%.

Scheme 9.

the phenolic group to the triflate **73**, in good yield (83%). [1,1'-Bis-(diphenylphosephino)-ferrocene]dichloropalladium(II) ($PdCl_2$(dppf))-catalyzed coupling of triflate **73** with bis(pinacolato)diboron **74**[62] afforded the boronate acetate **75**. In order to increase the yield from this step, the reaction was repeated under different conditions. Refluxing of the reactants for 5 h at 80 °C in dioxane in the presence of the catalyst with triethylamine as a base was found to be the best set of conditions, the yield being 75%. Hydrolysis of acetate **75** using aqueous lithium hydroxide afforded the key



Conditions: a) $(COCl)_2$, benzene, **58**, aq. 5% NaOH-CH_2Cl_2, 89%; b) $POCl_3$, benzene, reflux; c) $NaBH_4$, MeOH, -78 °C, 88% from **57.**

Scheme 10.

carboxylic acid **59** (95%).

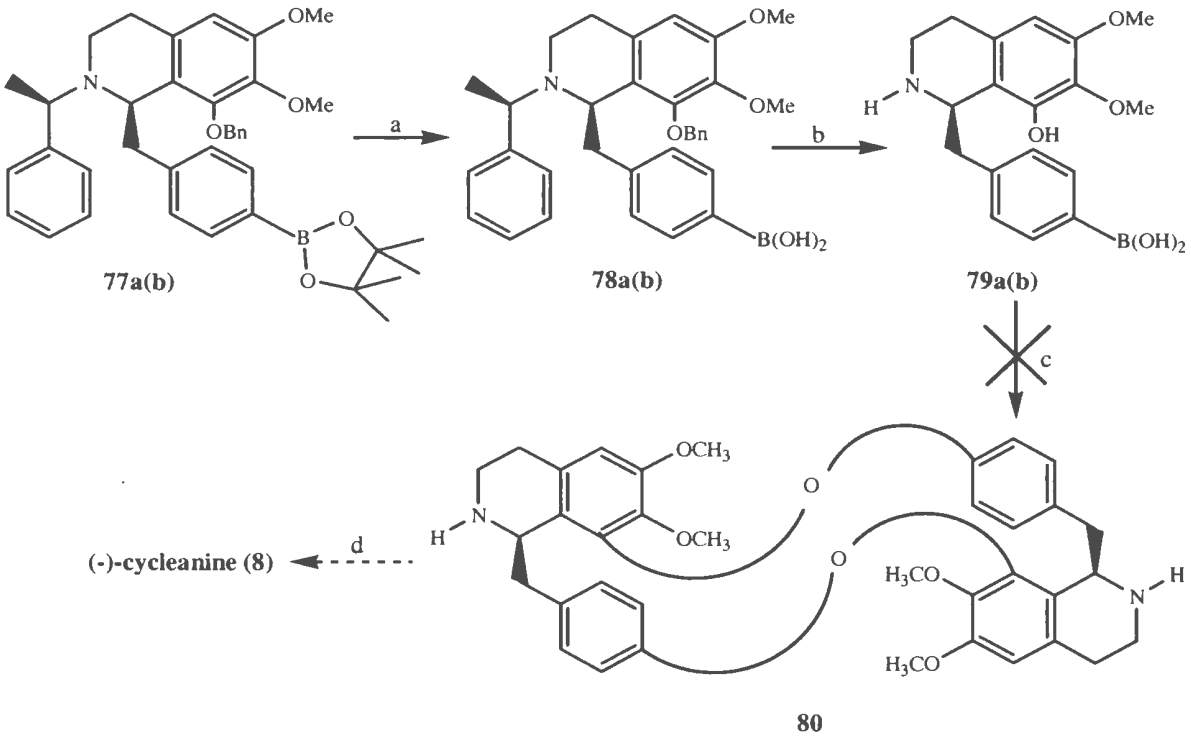
With the two intermediates **58** and **59** on hands, application of Schotten-Baumann reaction conditions smoothly afforded in 89% yield (Scheme 10) amide **57**. As discussed in Chapter 1, the BNC reaction was used to carry out the ring-closure step. Because there are two possible ring-closure sites on the precursor amide **57**, *para* and *ortho* to the benzyloxy group, the BNC step would be expected to proceed via a pair of ring-closure products **76a** and **76b**.

Normal BNC conditions, refluxing the amide **57** with phosphorus oxychloride in anhydrous benzene, resulted in the formation of the iminium salts **76a** and **76b.** These compounds were reduced by using $NaBH_4$ to afford a pair of regioisomers **77a** and **77b**. The chiral auxiliary directed the formation of the new chiral center in these compounds. Presumably, hydride adds to the double bond of the iminium salts **76a** (and **76b**) from the less hindered face in the reduction step. This would be due to the steric hindrance presented by either the methyl or phenyl group of the chiral auxiliary moiety. Difficulties encountered in separating this pair of regioisomers prevented confirmation of this hypothesis. However, the X-ray crystal structure (Figure 2) of a similar ring-closure product **85a** at a later stage, clearly established the configuration of the chiral centers in **85a**, and established that the configuration of the new stereogenic center was the desired one.

The use of either flash column chromatography or preparative layer chromatography did not lead to separation of these regioisomers. As a result of this

difficulty, subsequent research was continued using the mixture of regioisomers.

In order to obtain a boronic acid from the corresponding boronate, Jung and Lazarova's[63] procedure can be applied: reaction of a boronate ester with diethanolamine forms the corresponding cyclic aminoboronate intermediate, which is hydrolyzed *in situ* to give the boronic acid. The above procedure was applied in this research, but it gave a very low yield. In the meantime, an efficient procedure for the same conversion, which is called "trans-boro-esterification" with phenyl boronic acid and treatment with aqueous



Conditions: a) phenylboronic acid, aq. 2.0 M HCl, THF, MeOH, 70%; b) H_2, Pd/C, EtOH-EtOAc-aq. 10% HCl; c) $Cu(OAc)_2$, pyridine, 4 Å molecular sieves, CH_2Cl_2; d) aq. 37% HCHO, $NaBH_3CN$.

Scheme 11.

2.0 M HCl, was reported by Decicco.[64] This procedure was employed to bring about the conversion of boronates **77a(b)** to the mixture of corresponding boronic acids **78a(b)** (70%). The conversion of only one regioisomer **77a** is shown in Scheme 11. Palladium-catalyzed hydrogenolysis smoothly removed in one step both the chiral auxiliary and the benzyl group of the boronic acid **78a**. Since **78a** could not be separated from **78b**, the mixture of phenolic compounds **79a(b)** was used in the homocoupling reaction step.

Using the $Cu(OAc)_2$-mediated coupling reaction conditions, with a stoichiometric amount of $Cu(OAc)_2$, a catalytic amount of pyridine, and 4 Å molecular sieves in very dilute solution (5.0×10^{-3} M solution in CH_2Cl_2), the first coupling attempt did not afford **80**. This is likely because the precursors to the coupling reaction product were a mixture of regioisomers, which should result in the formation of at least four coupling products. Another problem experienced was that the precursor compounds possess a tertiary amine group, a phenolic group and a boronic acid group all of which are polar. As a result, it was very difficult to monitor the reaction.

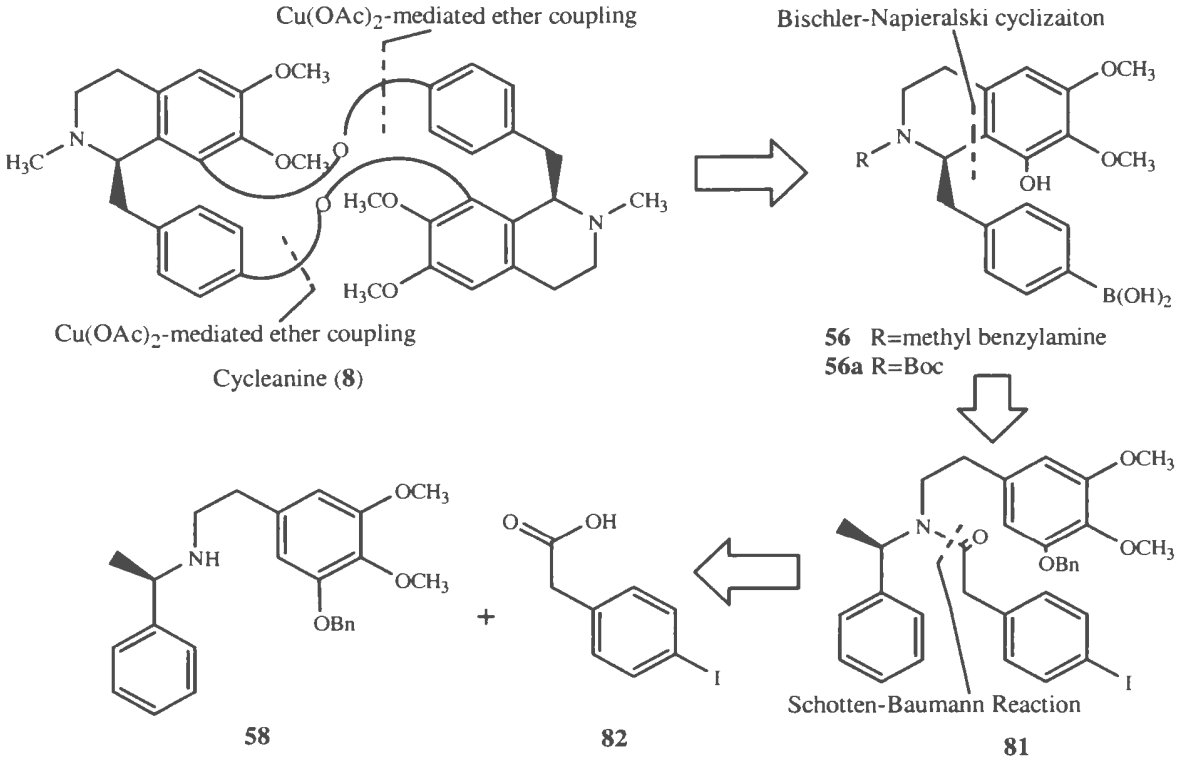
Although the first attempt was not successful, some important information and experience were gained. First, in order to establish the configuration of the ring-closure product isoquinoline **77a**, the separation and the purification of the pair of regioisomers **77a** and **77b** is necessary. Second, suitable modification of the precursor to the final coupling step may be required. For example, the use of a less polar precursor, such as a protected tertiary amine, could increase the success of the coupling reaction. In addition,

because difficulties were experienced in the separation of these regioisomeric compounds (**77a(b), 78a(b)** and **79a(b)**); and because these compounds were not easily prepared on a large scale, the chemistry of these compounds was not explored any further. Similar, but modified, compounds were more fully investigated instead, and these investigations are described in later sections.

2.2.4 First Modified Synthetic Route towards (–)-Cycleanine

As a result of our initial findings, the synthetic route was modified as shown in Scheme 12. This route is similar to the initial retrosynthetic route, but with two important differences. An iodine atom was used instead of the boronate moiety in target intermediates **81** and **82**, which potentially allowed the formation of the boronic acid in a later step. It was hoped that without the boronate moiety present, the regioisomers that resulted from the BNC step might be separated more easily. Furthermore, a *tert*-butoxycarbonyl (Boc) group-protected tertiary amine **56a** should be less polar than the methylated tertiary amine **56**, which could assist the workup step in the subsequent cyclization reaction.

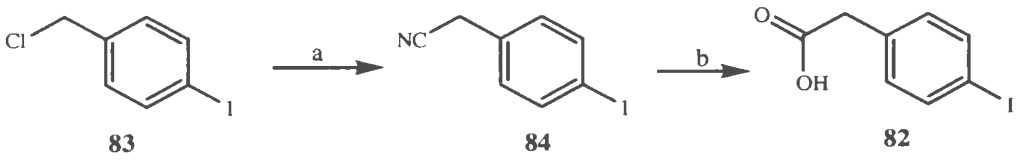
The next focus was the construction of the key intermediates **56**, **56a**, **81** and



Scheme 12.

82. The synthesis of the chiral amine **58** had already been completed in the previous route (Scheme 7). As shown in Scheme 13, the carboxylic acid **82** could be easily constructed from 4-iodobenzylchloride **83** via two straightforward steps. Cyanation of **83**, followed by hydrolysis in aqueous 4.0 M NaOH afforded the carboxylic acid **82** in good yield (84%). It should be mentioned that 4-iodobenzyl chloride **83,** which was synthesized by the Georghiou laboratory via a two-step sequence, can be easily produced from 4-iodobenzaldehyde, a commercially available reagent. Reduction of 4-iodobenzaldehyde using $NaBH_4$ afforded a corresponding primary alcohol, which was chlorinated using $SOCl_2$ to form **83** *in situ*.

Under Schotten-Baumann reaction conditions, **82** was reacted with the chiral amine **58** to form the amide **81** (98%), the precursor required for the BNC reaction. Amide **81** existed as slowly interconverting rotamers and exhibited its clearest ^{1}H NMR



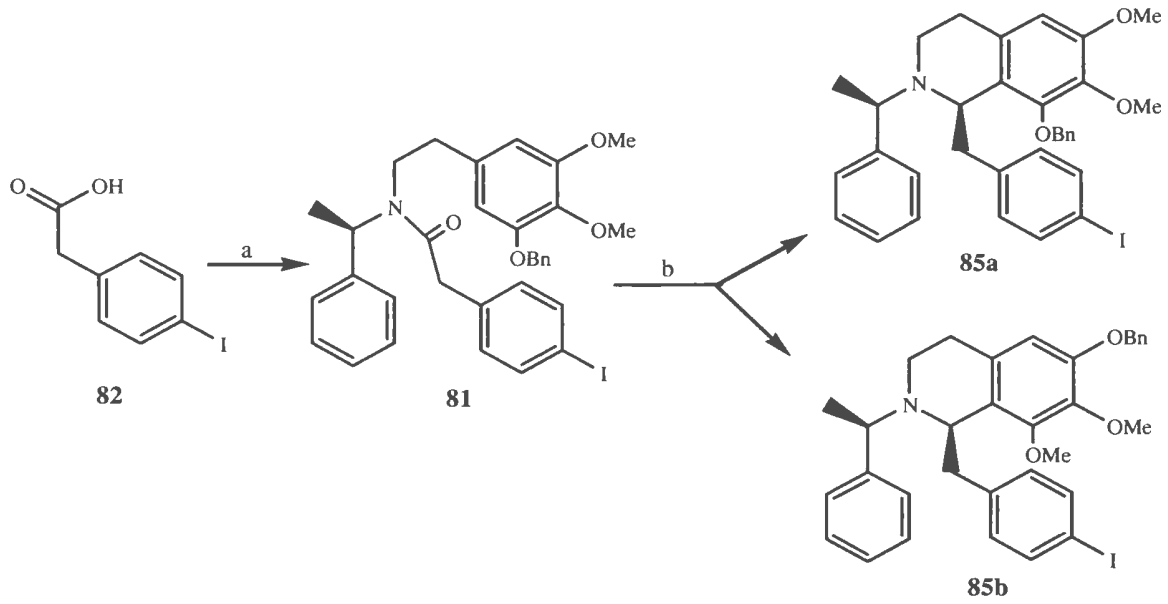
83 **84** **82**

Conditions: a) NaCN, DMSO, benzene, 85%; b) aq. 4.0 M NaOH, EtOH, 84%.

Scheme 13.

spectrum at 100 °C (the compound decomposed above 100 °C). At this temperature most of the protons appeared as single sets of signals.

An efficient route for the formation of the isoquinoline regioisomers **85a(b)** under BNC reaction conditions is shown in Scheme 14. Cyclization of amide **81** under such conditions with $POCl_3$ in benzene was followed by $NaBH_4$ reduction, which afforded a pair of regioisomers **85a** and **85b** in 37 and 40% yields, respectively. At this stage, the pair of regiosomers was successfully separated by flash chromatography and crystals of **85a** suitable for X-ray crystallography were obtained. The regioisomer **85a**, which was required for the synthesis of (−)-cycleanine, was formed in approximately > 90% de, as estimated from its ^{1}H NMR spectrum.



Conditions: a) $(COCl)_2$, benzene, then **58**, aq. 5% NaOH-CH_2Cl_2, 98%; b) 1). $POCl_3$, benzene, reflux; 2). $NaBH_4$, MeOH, -78 °C; 37% for **85a**; 40% for **85b**.

Scheme 14.

Due to the known *R*-configuration of the chiral auxiliary, the X-ray crystal structure[65] (Figure 2) of **85a** could be used to establish that the absolute configuration of the new stereogenic center was the desired one. Unfortunately, efforts towards obtaining suitable crystals of **85b** for X-ray crystallography were not successful. The ^{1}H NMR and NOED spectra of **85a/85b** were also consistent with the proposed structures obtained (Figure 3). From their ^{1}H NMR and NOED spectra, two significant differences between the two compounds **85a** and **85b** were clearly identified.

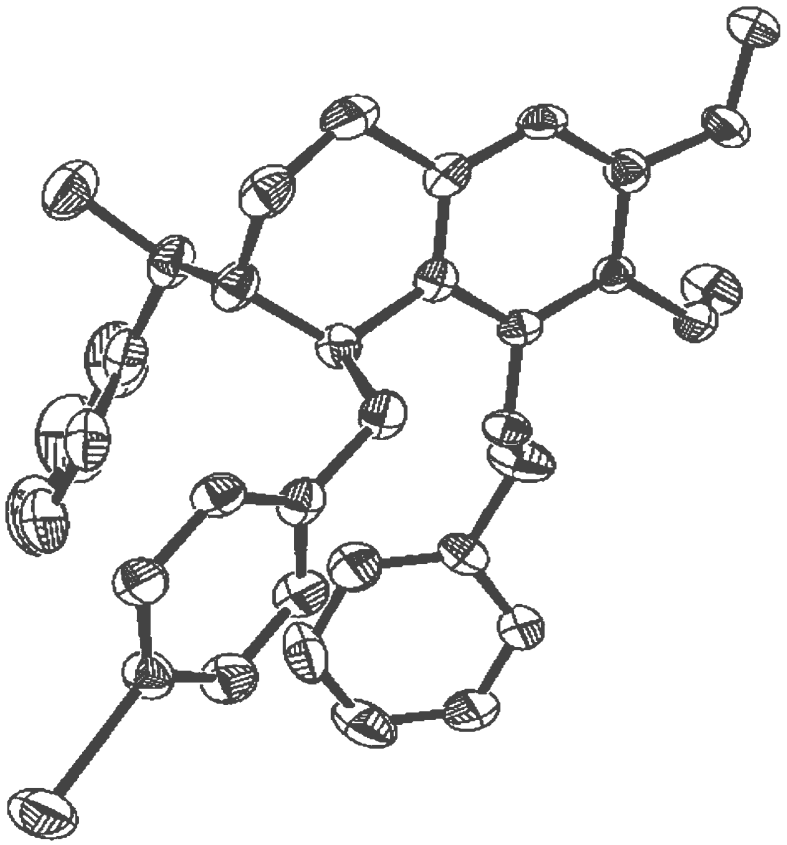


Figure 2. ORTEP Representation of Compound 85a

First, in the ^{1}H NMR spectrum, the signals for Hb and Hb' (diastereotopic) of the benzyl group of **85a** were observed as a well-separated pair of doublets at δ 5.20 and 4.20 (J = 9.7 Hz). The corresponding protons of compound **85b,** however, appeared as a triplet (AB system, J_{AB}=5.4 Hz). Second, for compound **85a,** a NOE could be detected between the aromatic proton Ha and the protons Hc on one of the methoxy groups, but no NOE effect could be observed between the aromatic proton Ha and the protons Hb and Hb' on the benzyl group. However, for compound **85b**, the only NOE observed was that between

the aromatic proton Ha and the protons Hb and Hb' on the benzyl group, and no NOE was observed between the Ha and the protons Hc on the methoxy group.

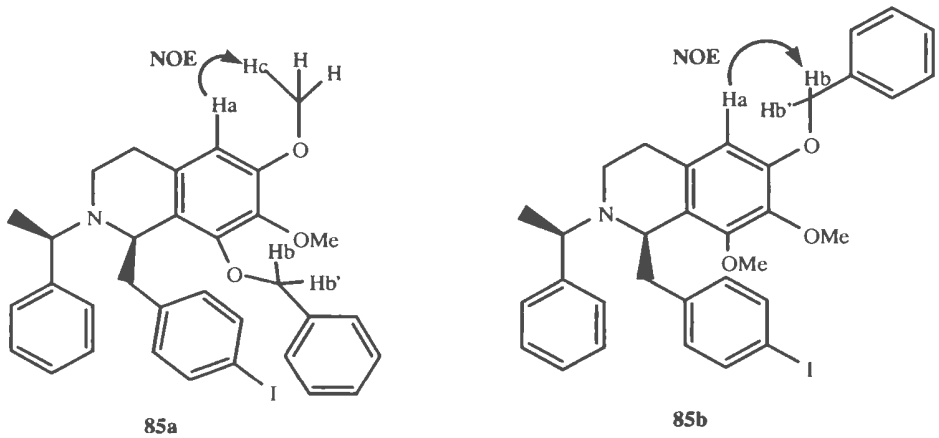
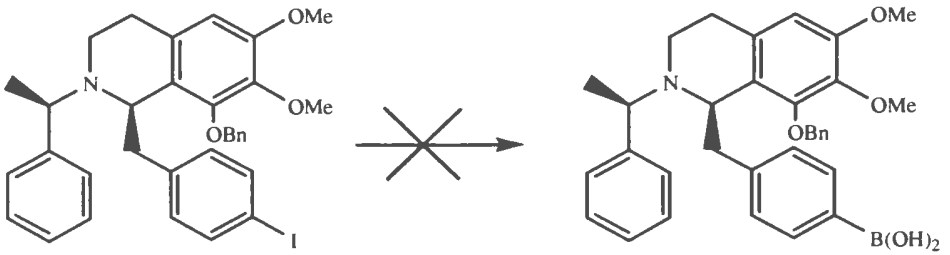


Figure 3. Structures of 85a and 85b

With enantiomerically pure iodotetrahydroisoquinoline **85a** in hand, the conversion to its corresponding boronate **77a** and the boronic acid **56** was attempted. The procedure that was first attempted for this transformation was a modification of the procedure of an iodine-magnesium exchange reaction reported by Knochel.[66] In his report, transmetallation with a Grignard reagent followed by quenching with trimethyl borate and then hydrolysis with aqueous HCl accomplished the conversion from an iodide to its corresponding boronic acid. However, the same iodine-magnesium exchange procedure (Scheme 15) applied in this research failed to convert **85a** into **78a**. Surprisingly, all of the starting material was recovered.

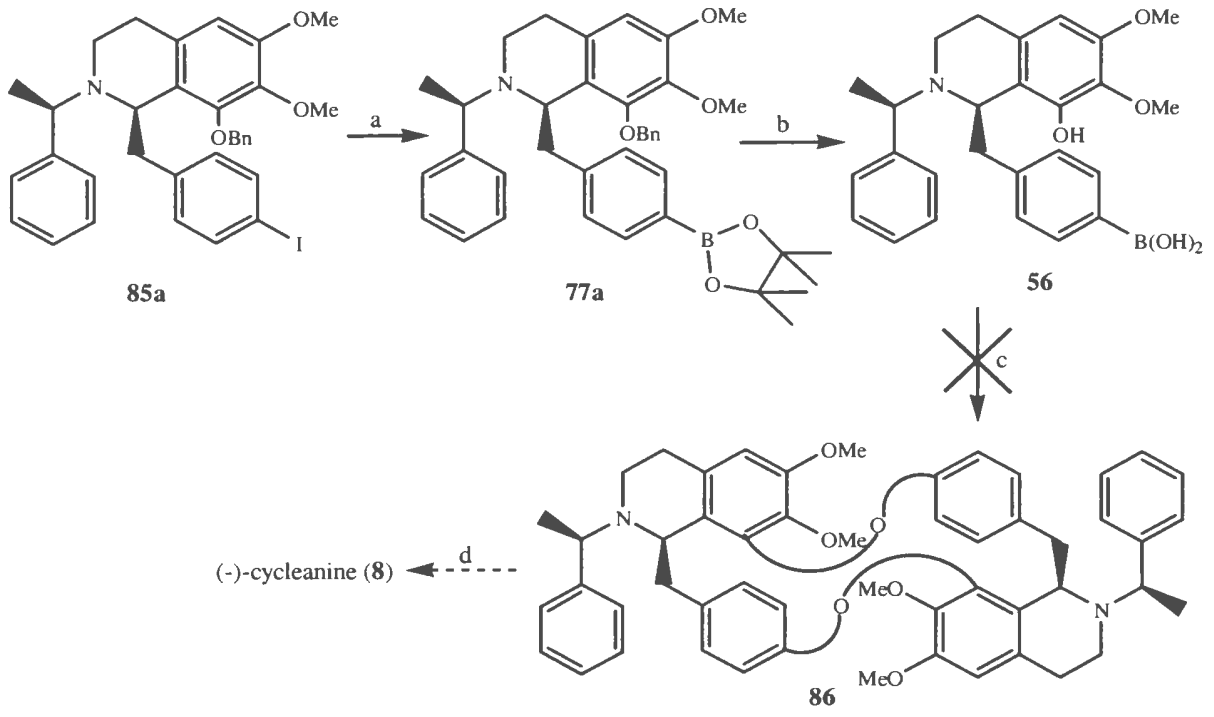


85a **78a**

Condition: 1). *i*-PrMgCl/THF, -60 °C to -40 °C; 2) $B(OMe)_3$, -50 °C to -60 °C; 3). aq. 2.0 M HCl, H_2O.

Scheme 15.

Based on this, a combination of $PdCl_2$(dppf)-catalyzed borylation and the subsequent trans-boro-esterification reported by Decicco[64] was employed to complete the formation of boronic acid **56** in two steps (Scheme 16). The first step resulted in the formation of the corresponding boronate **77a** and the second step efficiently completed the construction of the boronic acid **56**, a key precursor of the next homocoupling step, as well as simultaneously removing the benzyl group of **77a** to form the phenolic group. However, the subsequent homocoupling reaction of the boronic acid **56** in the presence of $Cu(OAc)_2$ was not successful, and the mass spectrum of the resulting product mixture was inconclusive. No additional spectroscopic evidence could be obtained because of an insufficient quantity of the sample.

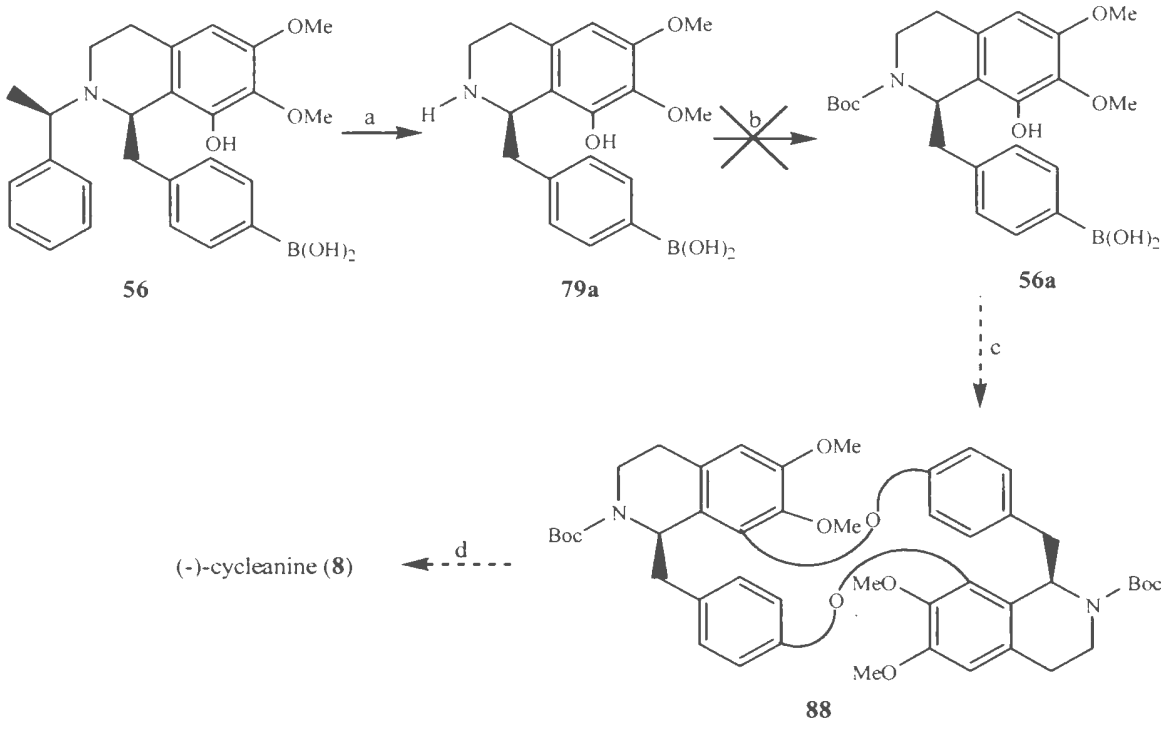


85a 77a 56 86

Conditions: a) $PdCl_2(dppf)$, DMSO, KOAc, **74**, 68%; b) phenylboronic acid, conc. HCl (aq.), MeOH, reflux, 68%; c) $Cu(OAc)_2$, pyridine, 4 Å molecular seives; d) 1. H_2, Pd/C; 2. HCHO, MeCN, $NaBH_3CN$.

Scheme 16.

Another strategy towards (−)-cycleanine involved producing the Boc-protected amine **56a** as the precursor to the coupling step (Scheme 17). However, the synthesis of **56a** could not be achieved. Palladium-catalyzed hydrogenolysis removed the chiral auxiliary group to afford the tertiary amine **79a**. It was hoped that this could be protected with a Boc group to form the carbamate **56a**. The tertiary amine **79a,** however, was difficult to purify due to the polarity of the compound, and as a result, unequivocal formation of the desired carbamate was not achieved by this route. The synthetic scheme envisioned in Scheme 17 was therefore abandoned.



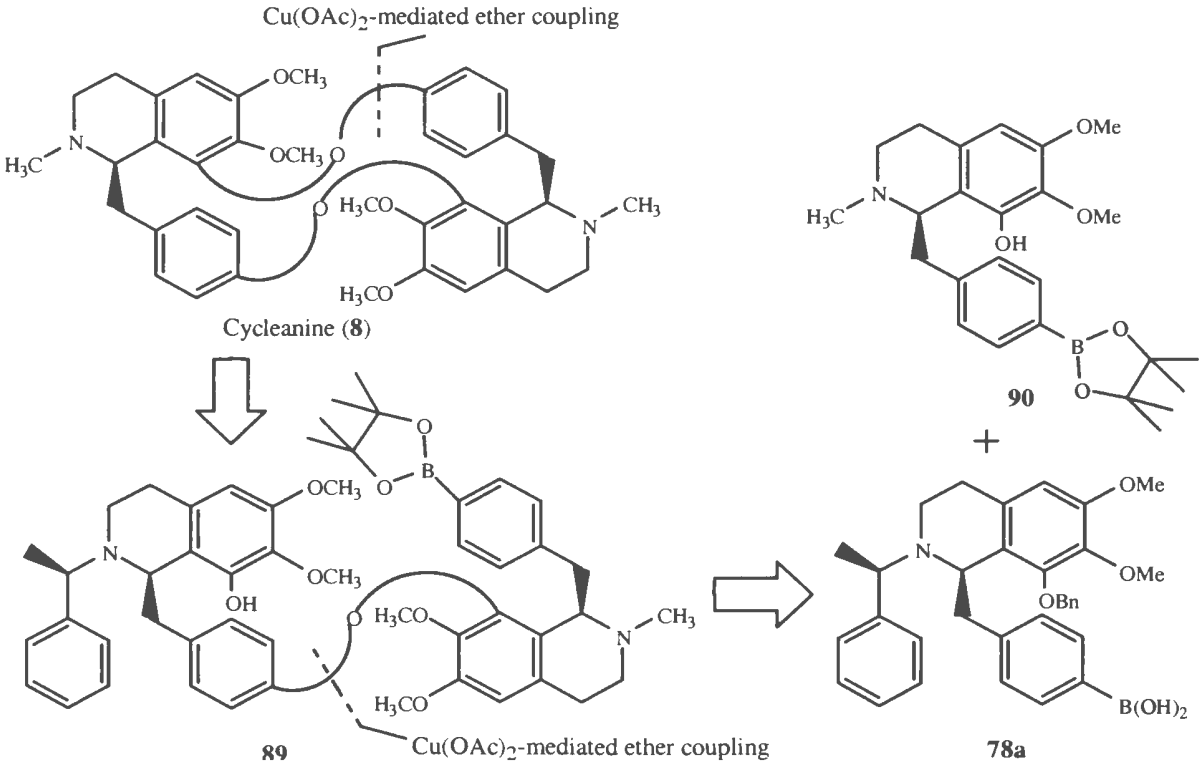
Conditions: a) H_2, Pd/C, EtOH-EtOAc-aq. 10% HCl; b) Boc_2O, THF, Et_3N, -78 °C to rt.; c) $Cu(OAc)_2$, pyridine, 4 Å , CH_2Cl_2; d) 1. TFA, THF; 2. HCHO, MeCN, $NaBH_3CN$.

Scheme 17.

2.2.5 Second Modified Synthetic Route towards (−)-Cycleanine

All of the previous efforts towards the target molecule were based on a homocoupling of an isoquinoline subunit precursor. Although the enantiomerically pure isoquinoline subunits were obtained, the key coupling step of these subunits using the $Cu(OAc)_2$-mediated diaryl ether formation methodology remained unsuccessful. Considering the polarity of the precursors and the requirements for the coupling reaction conditions, such as the concentration of the reactants, the length of reaction time and even the molar ratio among those reactants, the two diaryl ether linkages are difficult to form in such a coupling reaction. In addition, the possibilities that not just the single desired

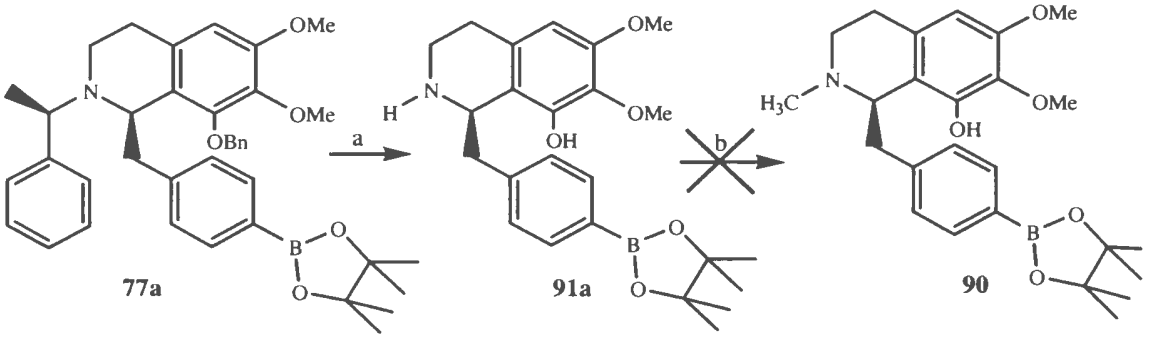
diaryl ether linkage could be formed, but that also other undesired ether linkages could be formed between the isoquinoline subunits made the coupling reaction even more potentially complex. Thus, a different synthetic route was proposed for the synthesis of (−)-cycleanine. The retrosynthetic analysis of this new approach is outlined in Scheme 18. Based on this retrosynthetic analysis, the formation of the two precursor subunits **78a**



Scheme 18.

and **90** was explored. From previous efforts (Scheme 11), it was found that **78a** can be produced from the corresponding boronate tetrahydroisoquinoline **77a** via a trans-boro-esterification with phenyl boronic acid and aqueous 2.0 M HCl. Thus, this new approach focused on the formation of the other key intermediate **90**. Unfortunately, methylation of

the tertiary amine **91a** failed (Scheme 19), perhaps for the same reason(s) that led to the failure to obtain the Boc-protected tertiary amine **56a** (Scheme 17). However, although the methylation or Boc-protection of the tertiary amine steps failed in the hands of this author without further exploring the reaction conditions, it is felt that this stepwise diaryl ether formation proposal is still viable, and needs further study.



Conditions: a) H_2, Pd/C, EtOH-EtOAc-aq. 10% HCl; b) HCHO, MeCN, $NaBH_3CN$.

Scheme 19.

2.3 Summary

Although the goal of completing the total synthesis of (−)-cycleanine (**8**) was not achieved, the information presented in this thesis does offer promise for future endeavours. The difficulties experienced in the synthetic efforts have been discussed. Such information could lead to the modification of existing synthetic proposal, thus providing a important foundation for future success.

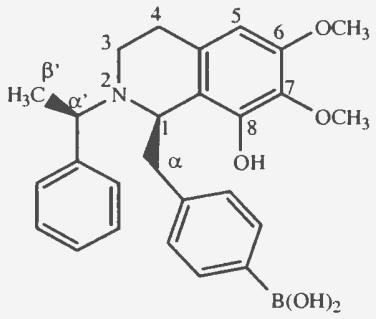
2.4 Experimental

General

Flash column chromatography was performed using 240-400 mesh silical gel and preparative layer (1 mm) chromatography (PLC) was conducted using 60 mesh silica gel. All solvents and reagents used were either of the highest commercial grade available/or were redistilled (CH_2Cl_2, hexane, and benzene distilled over CaH_2, $CHCl_3$ distilled over P_4O_{10}). ^1H and ^{13}C NMR spectra were obtained on a General Electric GE-300 NB spectrometer at 300 MHz in $CDCl_3$ unless otherwise specified, and shifts are relative to an internal trimethylsilane signal. Some of the NMR data were obtained on the Bruker Advance 500 MHz instrument with a TXI inverse-detect gradient probe and these data are designated in the experimental section. The following abbreviations are used in description in the ^1H NMR: 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 when the spectral data of compounds were obtained from mixtures. NMR free induction decay data were processed using WinNuts (Acorn NMR software). 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*) unless mass data obtained from Atmospheric Pressure Chemical Ionization-Mass Spectrometry (APCI-MS), which are described as APCI-MS

(*m/z*). Melting points (m.p.) were determined using a Fisher-Johns hot stage apparatus and are uncorrected.

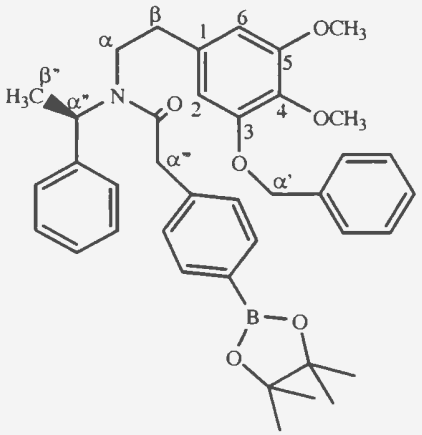
1-(*R*)-(4-Dihydroxyborylbenzyl)-*N*-[(*R*)-α-methylbenzyl]- 6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (56)



To a solution of **77a** (47 mg, 0.076 mmol) in THF (6.0 mL), were added MeOH (2.0 mL), aqueous concentrated HCl (9.4 mL) and phenylboronic acid (19 mg, 0.16 mmol). After refluxing for 6 h, the solvent was removed by a rotary evaporator and the resultant mixture was neutralized by using 6.0 M NaOH (3.0 mL) and aqueous saturated $NaHCO_3$ (5.0 mL) subsequently. The mixture was added EtOAc (15 mL) and transfer to a separatory funnel. The aqueous layers were re-extracted with EtOAc (10 mL x 3) and the combined organic layers were washed with water (10 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was redissolved in CH_2Cl_2 and purified with preparative chromatography (10% MeOH/CH_2Cl_2) to afford **56** (27 mg, 68%) as a colorless oil; ^{1}H NMR (500 MHz): δ 8.16-5.78 (m, 10H, Ar-H), 4.05 (m, 1H, H-3), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.66 (m, 1H, H-α'), 3.47 (m, 1H, H-3), 3.30 (m, 1H, H-4), 3.04 (m, 1H, H-4), 2.90 (m, 2H, H-α), 2.41 (m, 1H, H-1), 1.24 (m, 3H, H-β'); APCI-MS (*m/z*): 448.20 (M^++2, 26), 420.20 (100).

***N*-((*R*)-α-Methylbenzyl)-*N*-((3-benzyloxy-4,5-dimethoxy)phenethyl)-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)]phenylacetamide (57)**

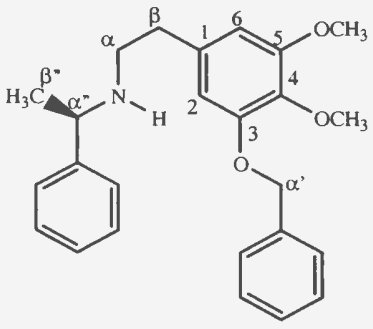
To a stirred solution of oxalyl chloride (0.070 mL, 0.40 mmol) in anhydrous benzene (10 mL) were added **59** (76 mg, 0.29 mmol) and DMF (3 drops). The mixture was stirred



until the evolution of gas ceased. The benzene was then evaporated to give crude acid chloride, which was used directly in the next step.

The acid chloride was re-dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution, a stirred mixture of **58** (110 mg, 0.29 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 5.0 mL) was added. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (5.0 mL x 3), washed with water (5.0 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford amide **57** (170 mg, 89%) as a viscous oil; ^{1}H NMR (500 MHz, toluene-d_8, 373 K): δ 6.96-7.91 (m, 14H, Ar-H), 6.27 (s, 1H, H-2), 6.19 (s, 1H, H-6), 4.89 (s, 2H, H-α"), 3.74 (s, 3H, OCH_3), 3.63 (m, 3H, H-α", H-α"'), 3.52 (s, 3H, OCH_3), 3.21 (m, 2H, H-α), 2.59 (s, 1H, H-β), 2.30 (s, 1H, H-β), 1.25 (d, *J*=6.4 Hz, 3H, β"-CH_3), 1.15 (s, 12H, CH_3); APCI-MS (*m/z*) 636.35 (M^++2, 100).

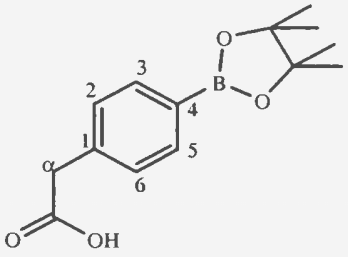
***N*-((*R*)-α-Methylbenzyl)-(3-benzyloxy-4,5-dimethoxy)phenylacetamine (58)**



To a solution of chiral amide **70** (180 mg, 0.45 mmol) in anhydrous THF (10 mL) was added BF_3/Et_2O (0.030 mL, 0.20 mmol) under argon. The mixture was heated to gentle reflux and BH_3/THF (1.0 M solution in THF, 1.3 mL, 1.1 mmol) was then added dropwise. The reaction mixture was refluxed for 2 h, and then the reaction mixture was cooled to 0 °C and aqueous 20% HCl

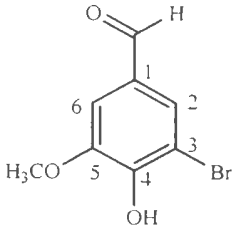
(20 mL) was added to the mixture. The reaction which was stirred at 0 °C for 1 h and then at room temperature overnight, was basified to pH =13 with aqueous 50% KOH solution. The mixture was then extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water (20 mL x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **58** (140 mg, 81%) as a colorless oil, which was pure enough to be used directly in the next step; ^{1}H NMR: δ 7.58-7.36 (m, 10H, Ar-H), 6.55 (d, *J*=1.6 Hz, 1H, H-2), 6.50 (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), 1.32 (d, *J*=6.5 Hz, 3H, H-β"); APCI-MS: 392.20 (M^++1, 100).

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenylacetic acid (59)



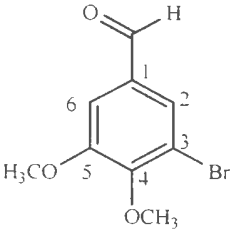
To a solution of **75** (160 mg, 0.59 mmol) in MeOH-THF-H_2O (5.0 mL, 1:3:1) was added powdered LiOH (36 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with water, neutralized with aqueous 10% HCl and extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with brine (2 x 5.0 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated. A white foam was obtained which was purified by preparative TLC (50% EtOAc/hexane) to give **59** (150 mg, 95%) as a white powder; ^{1}H NMR (500 MHz): δ 7.79 (d, *J*=7.6 Hz, 2H, H-2, H-6), 7.30 (d, *J*=7.6 Hz, 2H, H-3, H-5), 3.67 (s, 2H, H-α), 1.33 (s, 12H, CH_3); ^{13}C NMR: δ 175.4, 136.6, 135.3, 128.9, 84.0, 69.3, 41.1, 25.1; MS (*m/z*): 261 (M^+, 34), 247 (46), 163 (100), 91(16).

3-Bromo-4-hydroxy-5-methoxybenzaldehyde (60)



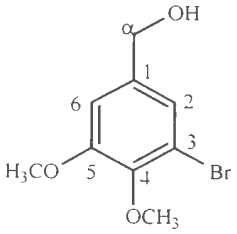
Bromine (11 mL, 0.22 mol) was added dropwised to a solution of vanillin **23** (30 g, 0.20 mol) in glacial acetic acid (100 mL). After stirring for 1 h, the reaction mixture was diluted with ice-water (400 mL), the resulting precipitate was filtered, washed with water (50 mL x 2), and dried over P_2O_5 under reduced pressure to give **60** as a colorless solid (44 g, 95%); m.p. 162.0-162.5 °C (Lit.,[67] 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 (61)



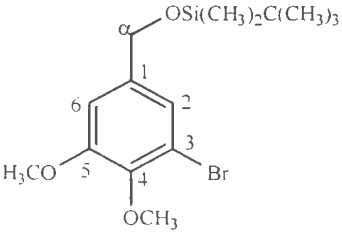
A mixture of **60** (44 g, 0.19 mol), sodium hydroxide (20 g, 0.50 mol), dimethyl sulfate (30 mL, 0.18 mol), Adogen 464® (5.0 mL), water (350 mL) and CH_2Cl_2 (350 mL) was vigorously stirred at room temperature. After 16 h, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined CH_2Cl_2 extracts were thoroughly washed with aqueous ammonium hydroxide (30 mL of 30% NH_3 (aq.) diluted to 100 mL with water), water (100 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated to give an oily residue. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **61** as a colorless solid (39 g, 85%); m. p. 62-63 °C.(Lit.,[68] m.p. 63-64 °C.); ^{1}H NMR: δ 9.85 (s, 1H, CHO), 7.65 (d, *J*=1.9 Hz, 1H, H-2), 7.39 (d, *J*=1.9 Hz, 1H, H-6), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3).

3-Bromo-4,5-dimethoxybenzyl alcohol (62)



To a solution of **61** (39 g, 0.16 mol) in MeOH (150 mL) and THF (150 mL) was added $NaBH_4$ (3.0 g, 0.080 mol) in portions over a period of 3 h. The solution was stirred at room temperature for 11 h, followed by removal of the solvent on a rotary evaporator. The yellow solid was dissolved with aqueous 10% HCl (100 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers were washed with brine (3 x 50 mL), 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 (40 g, 99%): ^{1}H NMR: δ 7.05 (d, *J*=1.8 Hz, 1H, H-2), 6.82 (d, *J*=1.8 Hz, 1H, H-6), 4.53 (s, 2H, H-α), 3.82 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.02 (s, 1H, OH); MS (*m/z*): 248 (M^++2, 98), 246 (M^+, 100), 231 (15), 96 (57), 84 (12).

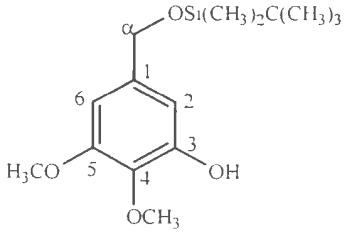
1-*tert*-Butyldimethylsilyl-3-bromo-4,5-dimethoxybenzyl ether (63)



To a cooled (0 °C) solution of **62** (40 g, 0.16 mol) and imidazole (11 g, 0.16 mol) in anhydrous DMF (80 mL) was added *tert*-butyldimethylsilyl chloride (29 g, 0.19 mol). After stirring for 48 h at room temperature, the reaction mixture was quenched by adding water (50 mL), and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (50 mL x 3), and brine (20 mL x 2), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (20% EtOAc/hexane) to afford **63** (51 g, 88%) as a yellow

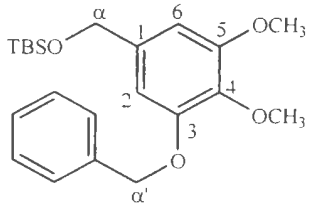
oil; ^{1}H NMR: δ 6.98 (d, *J*=1.9 Hz, 1H, H-2), 6.79 (s, *J*=1.9 Hz, 1H, H-6), 4.57 (s, 2H, H-α), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 0.87 (s, 9H, C-CH_3), 0.19 (s, 6H, Si-CH_3); MS (*m/z*): 360 (M^+, 5), 362 (M^++2, 5).

1-*tert*-Butyldimethylsilyl-3-hydroxy-4,5-dimethoxybenzyl ether (64)



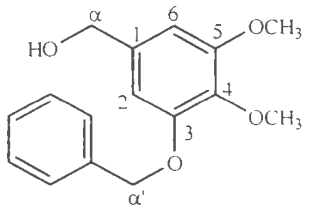
t-Butyllithium (1.6 M in hexane, 23 mL, 0.040 mol) was added dropwise to a solution of **63** (18 g, 0.030 mol) in anhydrous THF (300 mL), under argon at -78 °C. After stirring for 0.5 h, to the reaction mixture was then added dropwise $B(OCH_3)_3$ (4.4 mL, 0.040 mol), and the mixture allowed to warm to room temperature overnight. Hydrogen peroxide aqueous solution (37%, 100 mL) was then added and the resulting mixture was stirred for 12 h. The reaction was quenched with aqueous 1.0 M HCl (20 mL), and the mixture was concentrated *in vacuo* to give a residue. Water (20 mL) was added to the residue and the mixture was extracted with ethyl acetate (20 mL x 3), washed with water (30 mL x 3), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (5% EtOAc/hexane) to afford **64** (10 g, 71%) as a colorless oil; ^{1}H NMR: δ 6.55 (d, *J*=1.7 Hz, 1H, H-2), 6.50 (d, *J*=1.7 Hz, 1H, H-6), 5.90 (s, 1H, OH), 4.64 (s, 2H, H-α), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 0.93 (s, 9H, C-CH_3), 0.10 (s, 6H, Si-CH_3); ^{13}C NMR: δ 152.4, 149.3, 138.0, 126.5, 105.6, 101.9, 64.9, 61.2, 55.9, 26.2, 18.6, -5.1; MS (*m/z*): 297 (M^+, 5), 241 (100), 167 (83), 75 (13).

1–*tert*-Butyldimethylsilyl-3-benzyloxy-4,5-dimethoxybenzyl ether (65)



To a suspension of anhydrous potassium carbonate (25 g, 0.18 mol) in acetone (300 mL) was added **64** (9.8 g, 0.030 mol) and benzyl bomide (7.3 mL, 0.050 mol). After being refluxed for 4 h, the reaction mixture was filtered and concentrated *in vacuo*. Water (20 mL) was added and the mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic extracts were washed with water (15 mL x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (5% EtOAc/hexane) to afford **65** (11 g, 85%) as a colorless oil; ^{1}H NMR: δ 7.29-7.45 (m, 5H, Ar-H), 6.59 (b, 1H, H-2), 6.57 (b, 1H, H-6), 5.14 (s, 2H, H-α'), 4.64 (s, 2H, H-α), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 0.93 (s, 9H, C-CH_3), 0.07 (s, 6H, Si-CH_3); ^{13}C NMR: δ 153.5, 152.5, 137.5, 137.4, 137.3, 128.7, 127.9, 127.3, 105.1, 103.3, 71.1, 65.0, 61.1, 56.2, 26.1, 18.6, -5.1; MS (*m/z*): 388 (M^++1, 25), 330 (34), 257 (100), 91 (99), 73 (30).

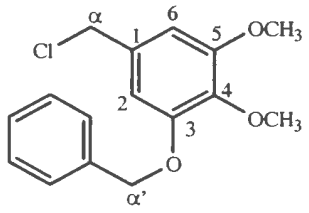
3-Benzyloxy-4,5-dimethoxybenzyl alcohol (66)



To a cooled (0 °C) solution of **65** (3.5 g, 9.0 mmol) in THF (100 mL) was added tetrabutylammonium fluoride (21 mL, 18 mmol, 1.0 M in THF). After stirring for 2 h at 0 °C, the reaction was quenched by addition of water (30 mL), and then the mixture was extracted with ethyl acetate (25 mL x 3). The combined organic layers were washed with water (15 mL x 3), brine (10 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the

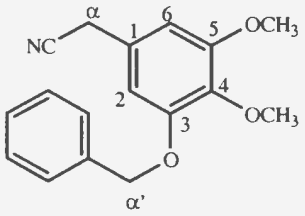
solvent was evaporated. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **66** (2.5 g, 99%) as a colorless oil; ^{1}H NMR (500 MHz): δ 7.26-7.40 (m, 5H, Ar-H), 6.62 (s, 1H, H-2), 6.59 (s, 1H, H-6), 5.11 (s, 2H, H-α'), 4.56 (s, 2H, H-α), 3.86 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 2.03 (s, 1H, OH); ^{13}C NMR: δ 153.7, 152.6, 138.2, 137.3, 136.8, 128.7, 128.0, 127.4, 106.1, 104.4, 71.2, 65.5, 61.1, 56.3; MS (*m/z*): 274 (M^+, 1), 142 (100), 91(56).

3-Benzyloxy-4,5-dimethoxybenzyl chloride (67)



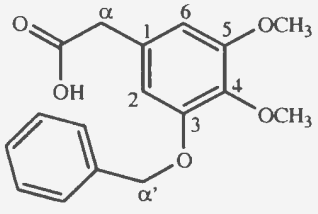
To a solution of **66** (2.2 g, 7.9 mmol) in anhydrous benzene (50 mL) was added dropwise thionyl chloride (1.1 mL, 11 mmol). After stirring at room temperature overnight, the reaction was quenched by addition of water (20 mL), and the mixture was extracted with ethyl acetate (15 mL x 3). The combined extracts were washed with aqueous saturated $NaHCO_3$ (10 mL x 3), water (20 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford a colorless oil **67** (2.4 g, 98%) which was directly used in the following step; ^{1}H NMR: δ 7.32-7.47 (m, 5H, Ar-H), 6.66 (d, *J*=1.9 Hz, 1H, H-2), 6.62 (d, *J*=1.9 Hz, 1H, H-6), 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 (68)



To the solution of **67** (2.2 g, 7.1 mmol) in DMSO (1.3 mL) and benzene (0.65 mL) was added NaCN powder (0.92 g, 18 mmol) in 3 portions. After stirring for 2 h at room temperature, the reaction mixture was poured into water (10 mL) and extracted with benzene (10 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **68** (1.8 g, 91%) as a colorless oil; ^{1}H NMR (500 MHz): δ 7.31-7.45 (m, 5H, Ar-H), 6.57 (s, 1H, H-2), 6.53 (s, 1H, H-6), 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, 10), 177 (24), 91 (100).

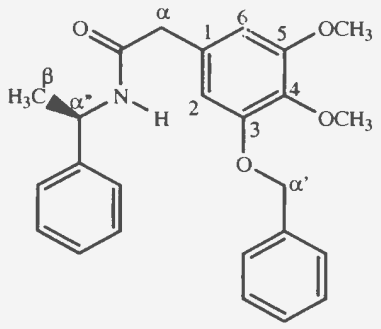
3-Benzyloxy-4, 5-dimethoxybenzoic acid (69)



A solution of **68** (1.4 g, 4.9 mmol) in ethanol (25 mL) and aqueous 4.0 M NaOH (2.0 mL) was heated at reflux for 20 h. The reaction mixture was then cooled to room temperature and diluted with water (10 mL) and then washed with CH_2Cl_2 (15 mL x 3). The aqueous layer was separated, acidified with aqueous concentrated HCl to pH = 1 and re-extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were washed with brine (15 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to give **69** (1.4 g, 90%) as a white solid, which was used directly in the

next step; ^{1}H NMR (500 MHz): δ 7.28-7.44 (m, 5H, Ar-H), 6.56 (d, 1H, *J*=1.5 Hz, H-2), 6.51 (d, 1H, *J*=1.5 Hz, H-6), 5.11 (s, 2H, H-α'), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.54 (s, 2H, H-α); ^{13}C NMR: δ 177.6, 153.7, 152.7, 138.3, 137.2, 128.8, 128.7, 128.1, 127.6, 108.9, 107.1, 71.4, 61.1, 56.4, 41.4; MS (*m/z*): 301 (M^+, 6), 196 (16), 151 (32), 91 (22), 84 (100), 47 (24).

***N*-((*R*)-α-Methylbenzyl)-(3-benzyloxy-4,5-dimethoxy)phenylacetamide (70)**

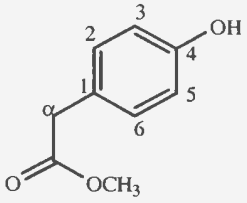


To a stirred solution of oxalyl chloride (0.11 mL, 1.3 mmol) in anhydrous benzene (10 mL) were added **69** (250 mg, 0.84 mmol) in one batch and DMF (2 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give crude acid chloride **69a**, which was used directly in the next step.

The crude acid chloride **69a** was re-dissolved in CH_2Cl_2 (2.0 mL) at 0 °C and the resulting solution was dropwise added to a stirred mixture of (*R*)-α-methylbenzylamine (0.17 mL, 1.0 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 5 mL). After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (10 mL x 3), washed with water (15 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford amide **70** (280 mg, 84%) as a viscous oil; ^{1}H NMR (500 MHz): δ 7.42-7.17 (m, 10H, Ar-H), 6.48 (d, *J*=0.6 Hz, 1H, H-2), 6.44 (d, *J*=0.6 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,

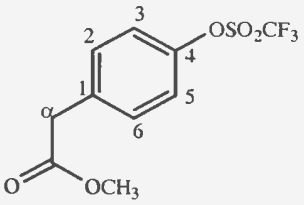
3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.47 (s, 2H, H-α), 1.38 (d, *J*=8.3 Hz, 3H, β-CH_3); ^{13}C NMR: δ 170.0, 153.9, 152.9, 143.4, 138.2, 137.1, 130.5, 128.8, 128.7, 128.1, 127.6, 127.4, 126.2, 108.8, 106.9, 71.3, 61.1, 56.4, 48.9, 44.3, 21.9; MS (*m/z*): 404 (M^+, 36), 300 (7), 257 (10), 151 (17), 105 (99), 91 (100).

Methyl 4-hydroxyphenylacetate (72)



To methanol (50 mL), which was pre-cooled to -10 °C, was added dropwise thionyl chloride (4.4 mL, 0.060 mol). 4-Hydroxyphenyl-acetic acid **71** (6.1 g, 0.040 mol) was then added in one batch. The cooling bath was removed, and the mixture was refluxed for 3 h. The reaction was quenched by addition of water (30 mL), and then the mixture was extracted with ethyl acetate (20 mL × 3). The combined organic phases were washed with water (20 mL x 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **72** (5.9 g, 90%) as a colorless oil; ^1H NMR: δ 7.16 (d, *J*=8.0 Hz, 2H, H-2, H-6), 6.78 (d, *J*=8.0 Hz, 2H, H-3, H-5), 5.52 (s, 1H, OH, D_2O exchangeable), 3.70 (s, 3H, $COOCH_3$), 3.56 (s, 2H, H-α).

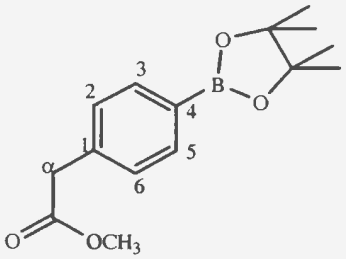
Methyl 4-(trifluoromethanesulfonato)phenylacetate (73)



To a solution of methyl 4-hydroxyphenylacetate **72** (5.8 g, 0.035 mol) and 2,6-lutidine (16 mL, 0.14 mol) in CH_2Cl_2 (100 mL), which was pre-cooled to -40 °C (dry ice in acetone), was added dropwise trifloromethanesulfonic anhydride (Tf_2O, 12 mL, 0.070 mol). After stirring for 2 h, the reaction was added water (40 mL) and the mixture was

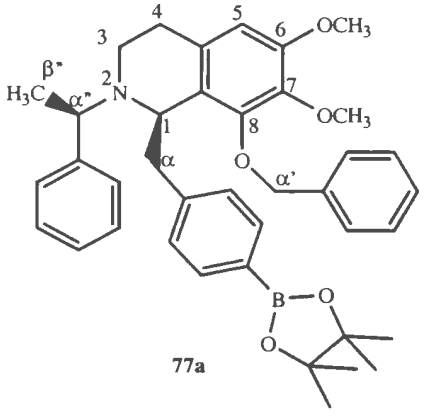
extracted with EtOAc (30 mL x 3). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (5% EtOAc/hexane) to afford compound **73** (8.7 g, 83%) as a colorless oil; ^{1}H NMR: δ 7.49 (d, *J*=8.0 Hz, 2H, H-2, H-6), 7.35 (d, *J*=8.0 Hz, 2H, H-3, H-5), 3.81 (s, 3H, $COOCH_3$), 3.76 (s, 2H, H-α).

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylacetate (75)

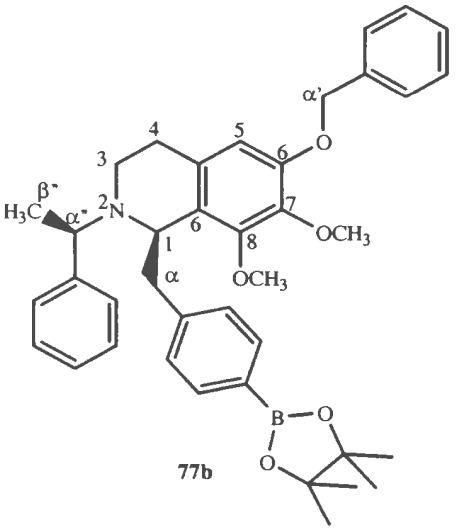


A flask maintained under argon was charged with [1,1'-bis-(diphenylphosphino)ferrocene]dichloropalladium(II) (270 mg, 0.34 mmol), Et_3N (4.2 mL) and bis(pinacolato)diboron (28 mg, 110 mmol) in dioxane (50 mL). Compound **73** (3.0 g, 100 mmol) was added to the mixture. After stirring at 80 °C for 5 h, the reaction was diluted with benzene (50 mL) and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with benzene (20 mL x 2) and the combined organic layers were washed with brine (20 mL x 3), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (10% EtOAc/hexane) to afford **75** (2.1 g, 75%) as a colorless oil; ^{1}H NMR (500 MHz): δ 7.78 (d, *J*=7.8 Hz, 2H, H-2, H-6), 7.29 (d, *J*=7.8 Hz, 2H, H-3, H-5), 3.67 (s, 3H, $COOCH_3$), 3.63 (s, 2H, H-α), 1.33 (s, 12H, CH_3); ^{13}C NMR: δ 171.8, 137.2, 135.2, 128.8, 83.9, 68.0, 52.2, 41.5, 24.9; MS (*m/z*): 276 (M^++1, 6), 261 (7), 190 (11), 177 (16), 91 (49), 84 (100).

1-(*R*)-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl]-*N*-((*R*)-α-methylbenzyl)-6,7-dimethoxy-8-benzyloxy-1,2,3,4-tetrahydroisoquinoline (77a) and **1-(*R*)-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-((*R*)-α-methylbenzyl)-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (77b)**



77a

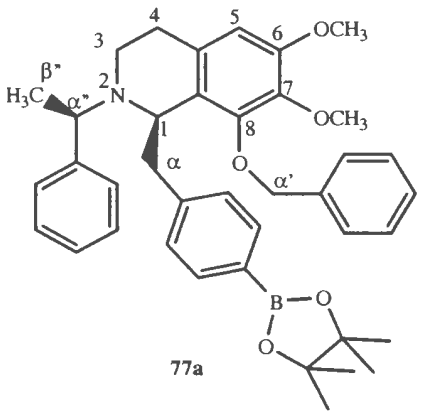


77b

Compound **57** (190 mg, 0.31 mmol), $POCl_3$ (1.0 mL) and benzene (3.0 mL) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 8 h, the solvent was evaporated on a rotary evaporator and the residual $POCl_3$ was evaporated 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 $NaBH_4$ (58 mg, 1.5 mmol) in five portions over a period of 5 h. The reaction was quenched through the addition of aqueous 10% HCl (10 mL), and the mixture was stirred at room temperature for 10 min. The MeOH was evaporated on a rotary evaportator, and 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 further

extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (3 x 5.0 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to give a mixture of regioisomers **77a** and **77b** (170 mg, 88%) as a colorless oil. Column chromatography or preparative TLC failed to separate this pair of regioisomers. Therefore, ^{1}H NMR spectra of **77a/77b** could not be obtained separately. However, because it is a pair of regioisomers, **77a** and **77b** have the same molecular mass. APCI-MS (*m/z*) (**77a/b**): 620.25 (M^++2, 100).

1-(*R*)-4-(4,4, 5, 5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-[(*R*)-α-methylbenzyl]- 6,7-dimethoxy-8-benzyloxy-2,3,4-tetrahydroisoquinoline (77a)

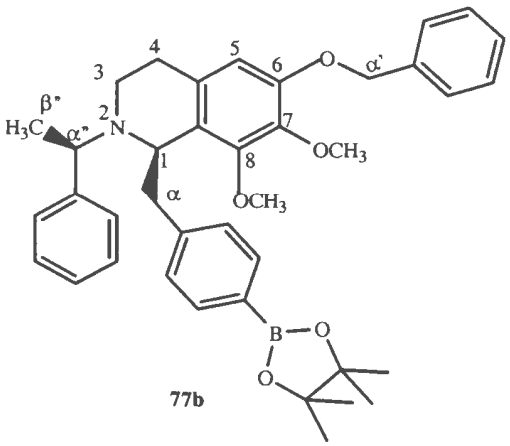


77a

To a solution of compound **85a** (300 mg, 0.49 mmol) in 10 mL of DMSO, bis(pinacolato)diboron (140 mg, 0.55 mmol), KOAc (152 mg, 1.5 mmol) and $PdCl_2$(dppf) (30 mg, 0.015 mmol) were added under argon. The reaction mixture was stirred at 80 °C for 6 h followed by the addition of water (10 mL). The aqueous layers were extracted with EtOAc (10 mL x 3). The combined organic layers were washed with water (5.0 mL x 3), brine (5.0 mL x 2), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by preparative chromatography (5% EtOAc/hexane with 0.4% Et_3N) to give **77a** (210 mg, 68%) as a colorless powder; ^{1}H NMR (500 MHz): δ 7.60-6.63 (m, 14H, Ar-H), 6.50 (s, 1H, H-5), 5.13 (d, *J*=9.7 Hz, 1H, H-α'), 4.23 (d,

J=9.7 Hz, 1H, H-α'), 3.89 (m, 7H, OCH_3, H-3), 3.57 (m, 2H, H-α", H-3), 3.36 (m, 1H, H-4), 2.95 (m, 1H, H-4), 2.77 (m, 2H, H-α), 2.44 (d, *J*=4.6 Hz, 1H, H-1), 1.39 (d, *J*=1.7 Hz, 12H, $BO(CH_3)_4$), 1.23 (m, 3H, H-β"); ^{13}C NMR: δ 151.9, 150.6, 146.3, 144.3, 140.7, 137.3, 134.2, 130.9, 130.8, 129.7, 129.3, 128.5, 128.4, 128.3, 127.5, 126.5, 124.6, 107.9, 83.7, 75.6, 61.1, 58.9, 56.7, 56.1, 41.3, 38.4, 25.1, 25.0, 22.9, 22.4; APCI-MS (*m/z*): 620.30 (M^++1, 100), 619.30 (M^+, 25).

1-(*R*)-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (77b)

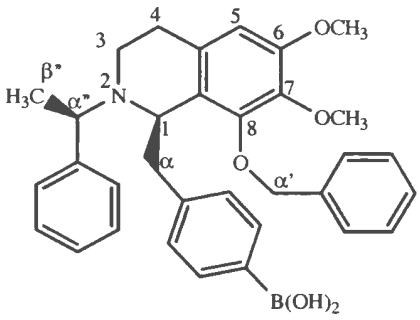


77b

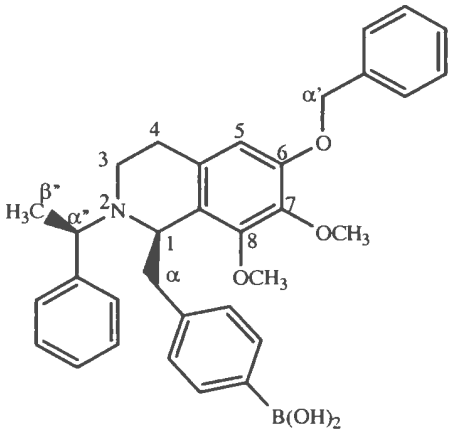
Via a similar procedure as was used with **85a** to afford **77a,** compound **77b** (22 mg, 63%) was obtained from **85b** (35 mg, 0.057 mmol); ^1H NMR (500 MHz): δ 7.68-6.67 (m, 14H, Ar-H), 6.51 (s, 1H, H-5), 5.09 (t, J_{AB}=5.4 Hz, 2H, H-α'), 3. 87 (s, 3H, OCH_3), 3.82 (m, 1H, H-3), 3.66 (s, 3H, OCH_3), 3.55 (q, *J*=6.4 Hz, 1H, H-α"), 3.44 (m, 1H, H-3), 3.28 (m, 1H, H-4), 2.85 (m, 3H, H-4, H-α), 2.36 (d, *J*=4.5 Hz, 1H, H-1), 1.38 (s, 12H, $BO(CH_3)_3$),1.22 (d, *J*=7.0 Hz, 3H, H-β"); APCI-MS (*m/z*): 620.35 (M^++1, 100), 619.35 (M^+, 27).

1-(*R*)-(4-Dihydroxyborylbenzyl)-*N*-[(*R*)-α-methylbenzyl]-6,7-dimethoxy-8-benzyloxy-1,2,3,4-tetrahydroisoquinoline (78a) and

1-(*R*)-(4-Dihydroxyborylbenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy –1,2,3,4-tetrahydroisoquinoline (78b)



78a



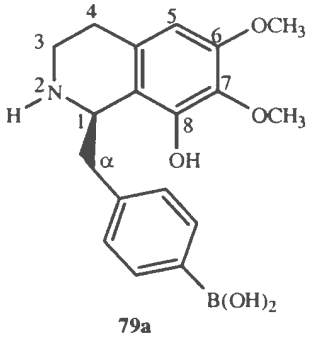
78b

Aqueous 2.0 M HCl (9.4 mL) and phenylboronic acid (19 mg, 0.16 mmol) were added to a mixture of **77a** and **77b** (51 mg, 0.082 mmol) in THF (6.0 mL) and MeOH (2.0 mL). After stirring for 16 h at room temperature, the reaction was quenched with the addition of water (5.0 mL). The solvent was removed by a rotary evaporator and the resultant mixture was extracted with EtOAc (15 mL). The aqueous layer was re-extracted with EtOAc (5.0 x 3 mL) and the combined organic layers were washed sequentially with aqueous saturated $NaHCO_3$ (5.0 mL), brine (5.0 mL) and dried over $MgSO_4$. After filtration and removal of solvent in *vacuo*, the residue was purified by flash column chromatography (50% EtOAc/hexane) to give a pair of regioisomers **78a** and **78b** (31

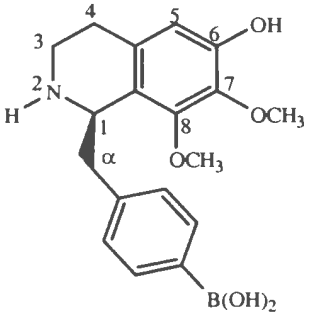
mg, 70%) as a colorless oil. Column chromatography or preparative TLC failed to separate this mixture. APCI-MS (*m/z*) (**78a/b**): 538.20 (M^++2, 100).

1-(*R*)-(4-Dihydroxyborylbenzyl)-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydro-isoquinoline (79a) and

1-(*R*)-(4-Dihydroxyborylbenzyl)-7,8-dimethoxy-6-hydroxy-1,2,3,4-tetrahydro-isoquinoline (79b)



79a

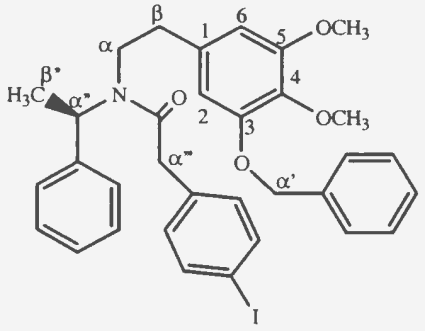


79b

To a mixture of **78a** and **78b** (20 mg, 0.037 mmol) in EtOAc (1.0 mL) and EtOH (3.0 mL) was added aqueous 10% HCl (0.20 mL). The resulting mixture was hydrogenolyzed using 10% Pd/C (20 mg) catalyst for 15 h, with stirring. Filtration over Celite followed by evaporation of the solvent afforded a residue. The residue was added water (5.0 mL) and CH_2Cl_2 (5.0 mL), and the mixture was basified to pH = 8 with aqueous saturated $NaHCO_3$ and transferred to a separatory funnel. The aqueous layer was re-extracted with CH_2Cl_2 (5.0 mL x 3). The combined organic layers were washed with brine (5.0 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. This residue, as a mixture of **79a** and **79b**, was used directly in the next step without purification. ^{1}H NMR

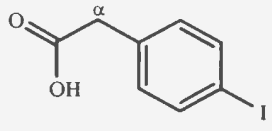
spectrum showed a mixture of this pair of regioisomers, however, ^{1}H NMR spectra of **79a/b** could not be obtained separately due to separation difficulties. APCI-MS (*m/z*) (**79a/b**): 344.10 (M^++2, 19).

***N*-[(*R*)-α-Methylbenzyl]-*N*-[(3-benzyloxy-4,5-dimethoxy)phenethyl]-4-iodophenyl acetamide (81)**



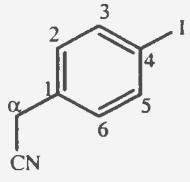
To a solution of oxalyl chloride (0.25 mL, 1.4 mmol) in dry benzene (20 mL) were added **82** (0.60 g, 2.3 mmol) and DMF (2 drops). The mixture was stirred until the evolution of gas ceased. The benzene was removed by rotary evaporation to give an acid chloride. The acid chloride was re-dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution, a mixture of **58** (660 mg, 1.7 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 10 mL) was added. After stirring at room temperature for 1 h, the mixture was extracted with chloroform (5.0 mL x 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 **81** (1.1 g, 98%) as a viscous oil; ^{1}H NMR (500 MHz, toluene-d_8, 373 K, mixture of rotamers): δ 7.44-6.20 (m, 16H, Ar-H), 5.34 (bs, 1H, H-α''), 4.89 (s, 2H, H-α'), 3.75 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3), 3.43 (s, 2H, H-α''), 3.20 (m, 2H, H-α, H-β), 2.58 (bs, 1H, H-α), 2.31 (bs, 1H, H-β), 1.25 (d, *J*=6.9 Hz, 3H, H-β''); MS (*m/z*): 636 (M^++2, 10), 271 (27), 270 (92), 217 (13), 105 (100), 91 (81).

4-Iodophenylacetic acid (82)



A mixture of **84** (3.4 g, 14 mmol) in ethanol (100 mL) and 4.0 M NaOH (20 mL) was heated at reflux for 20 h. The reaction mixture was then cooled to room temperature and diluted with additon of water (30 mL). The mixture was extracted with CH_2Cl_2 (15 mL x 3). The aqueous layer was acidified with aqueous concentrated HCl to pH = 1 and re-extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated in *vacuo* to give **82** (3.1 g, 84%) as a white solid; ^{1}H NMR (500 MHz): δ 11.01 (bs, 1H, COOH), 7.67 (d, *J*=8.2 Hz, 2H, H-2, H-6), 7.03 (d, *J*=8.2 Hz, 2H, H-3, H-5), 3.59 (s, 2H, H-α); ^{13}C NMR: δ 176.9, 137.9, 132.9, 131.6, 93.2, 40.6; MS (*m/z*): 261 (M^+, 93), 217 (100), 91 (21).

4-Iodophenylacetonitrile (84)



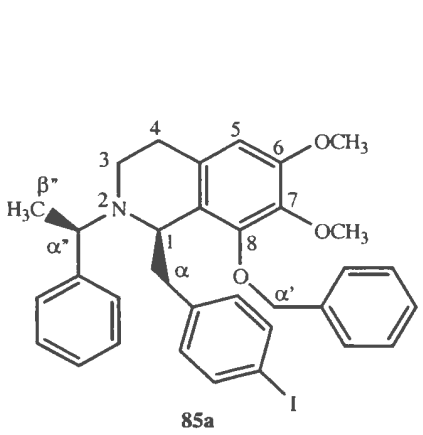
To a solution of 4-iodobenzyl chloride (**83**) (4.3 g, 17 mmol) in DMSO (20 mL) and benzene (30 mL) was added NaCN powder (2.1 g, 42 mmol) in 3 portions. After stirring for 2 h at room temperature, the reaction was poured into water (15 mL) and the mixture was extracted with benzene (10 mL x 3). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated in *vacuo* to give a residue that was purified by flash column chromatography (10% EtOAc/hexane) to afford **84** (3.5 g, 85%) as a white powder; ^{1}H NMR (500 MHz): δ 7.72 (d, *J*=8.3 Hz, 2H, H-2,

H-6), 7.08 (d, *J*=8.3 Hz, 2H, H-3, H-5), 3.69 (s, 2H, H-α); ^{13}C NMR: δ 138.5, 129.9, 129.8, 117.4, 93.8, 23.5; MS (*m/z*): 243 (M^++1, 100), 116 (88), 89 (42).

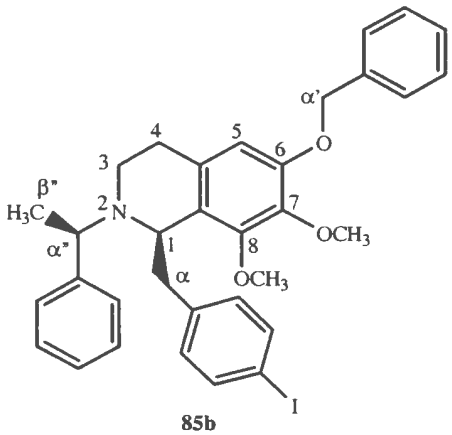
1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-8-benzyloxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (85a) and

1-(*R*)-(4-Iodobenzyl)-*N*-[(*R*)-α-methylbenzyl]-6-benzyloxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (85b)

Compound **81** (0.99 g, 1.6 mmol), $POCl_3$ (6.0 mL) and benzene (17 mL) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 5 h, the



85a



85b

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 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 (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 x 5.0 mL). The combined organic layers were washed with brine (2 x 5.0 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 give compounds **85a** (370 mg, 37%) as a colorless oil and **85b** (400 mg, 40%) also as a colorless oil; **85a:** ^{1}H NMR (500 MHz): δ 7.39-6.47 (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 (d, *J*=4.5 Hz, 1H, H-1), 1.25 (d, *J*=7.3 Hz, 3H, H-β"); ^{13}C NMR: δ 152.1, 150.6, 146.4, 140.8, 137.3, 136.6, 132.4, 130.8, 129.5, 128.6, 128.5, 128.3, 127.4, 126.6, 124.2, 107.8, 90.6, 75.7, 61.2, 58.9, 57.2, 56.2, 40.7, 38.5, 31.1, 23.0, 22.4; APCI-MS (*m/z*): 620.05 (M^++1, 100);

85b: ^{1}H NMR (500 MHz): δ 7.53-6.66 (m, 14H, Ar-H), 6.51 (s, 1H, H-5), 5.10 (t, J_{AB}=5.4 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 (d, *J*=3.7 Hz, 1H, H-1), 1.23 (d, *J*=4.3 Hz, 3H, H-β");

APCI-MS (*m/z*): 620.15 (M^++1, 100).

Chapter 3

Syntheses of Isoquinolones

3.1 Introduction

The work presented in this section deals with a route to the syntheses of thalifoline (**19**), *N*-methylcorydaldine (**21**), corydaldine (**22**) and some other tetrahydro-isoquinolone analogues. As described in Chapter 1, an efficient synthetic route towards thalifoline was accomplished by Wang and Georghiou.[48] In addition, a different approach involving oxidation of *N*-methyltetrahydroisoquinolines to afford the corresponding amide tetrahydroisoquinilones using iodosylbenzene (ISB) was recently reported by Huang *et al.*[51] in 2002. Schultz reported on the use of RuO_2-$NaIO_4$ as an oxidant[47] describing its advantages, such as ease of handling with other reagents, and the use of mild reaction conditions. In this section, the research described is focused on the use of similar oxidation methodology to those of Huang, but using RuO_2-$NaIO_4$ as oxidation reagent.

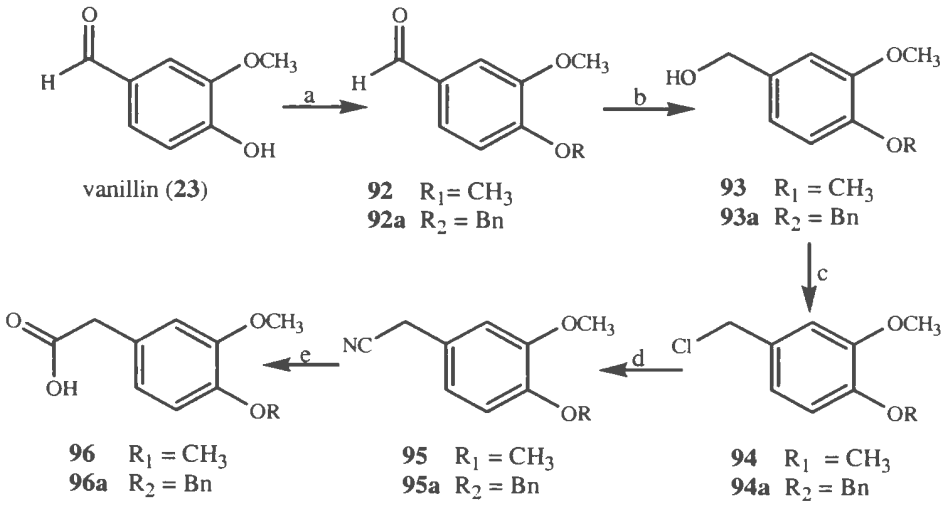
3.2 Results and Discussion

3.2.1 Attempts towards the Synthesis of *N*-Methylcorydaldine (21)

Retrosynthetic analysis of target tetrahydroisoquinolones **19**, **21** and **22** suggested approaches for their syntheses. From the efforts towards the synthesis of (−)-cycleanine (**8**) described in the previous chapters, it is clearly evident that the tetrahydroisoqinoline rings could be easily formed from the corresponding amides via the Bischler-Napieralski

cyclization reaction. It was postulated that after the formation of the isoquinoline rings, oxidation using RuO_2-$NaIO_4$ as a reagent would result in the desired isoquinolones.

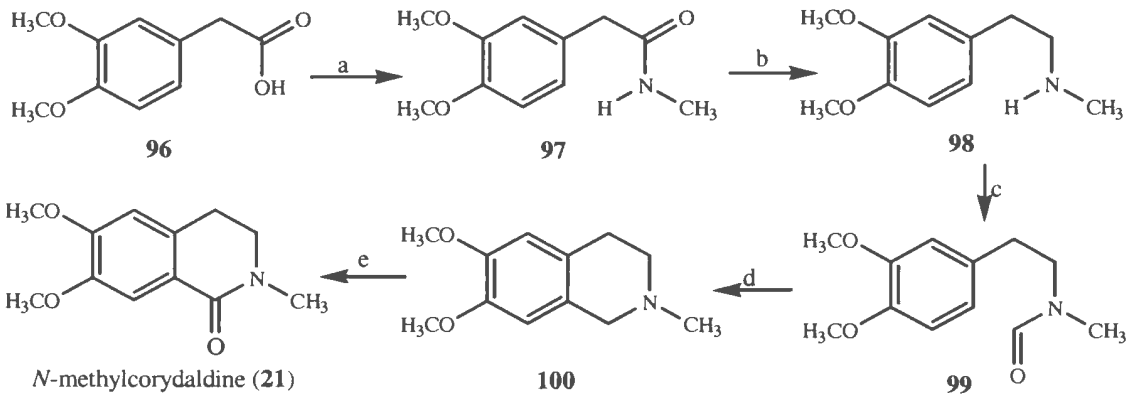
As shown in Scheme 20, the synthesis started from vanillin (**23**). Methylation (or benzylation) of the phenolic group of vanillin (**23**) afforded the methylated vanillin **92** (or the benzyl ether **92a**), which were both reduced, usually with quantitative yield, to the corresponding alcohols **93** (and **93a**) using $NaBH_4$. Chlorination, cyanation, and then hydrolysis of the resulting primary nitriles **95** (and **95a**) completed the formation of the respective carboxylic acids **96** (and **96a**). Although it took five steps to produce the two target intermediates **96** and **96a**, all of these steps gave very high yields. It should be mentioned that these two compounds were used as starting materials in the work



Conditions: a) **92**: Me_2SO_4, NaOH, H_2O, CH_2Cl_2, Adogen 464®; **92a**: BnBr, K_2CO_3, reflux in acetone; b) $NaBH_4$, MeOH, THF; c) $SOCl_2$, benzene; d) NaCN, DMSO, benzene; e) aq. 4.0 M NaOH, ethanol, reflux.

Scheme 20.

described in this thesis because they were commonly used and shared in the Georghiou laboratory.



Condition: (a) $(COCl)_2$, benzene, DMF, then methylamine, aq. 5% NaOH-CH_2Cl_2, 77%; (b) BH_3/THF, BF_3/Et_2O, then aq. 20% HCl, 84%; (c) Ac_2O/HCOOH, 80%; (d) $POCl_3$, reflux in benzene; $NaBH_4$, MeOH, 88%; (e) PCC, CH_2Cl_2, very low yield.

Scheme 21.

The synthesis of *N*-methylcorydaldine (**21**) is outlined in Scheme 21. Acid **96** reacted with oxalyl chloride to afford the acid chloride, which then reacted *in situ* with methylamine to furnish the amide **97** under the usual Schotten-Baumann conditions. In the presence of borane and boron trifluoride, the amide **97** was reduced to the amine **98** (84%), which could be acylated to afford the desired amide **99** (80%). Bischler-Napieralski cyclization of **99** afforded **100** in good yield (88%). As a key intermediate in this synthesis, the *N*-methylisoquinoline **100** was completed in four steps in an overall yield of 46%.

It was at this stage that different oxidation methodologies could be investigated

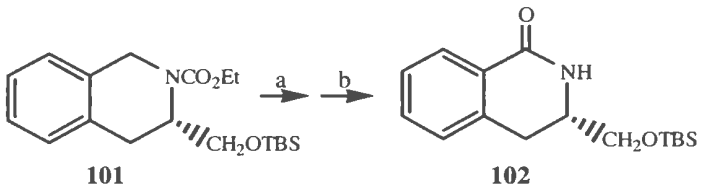
for the formation of the tetrahydroisoquinolone **21**. For this particular synthetic target, the research presented here will concentrate on the C-1 regioselective oxidation of the tetrahydroisoquinolines using RuO_2-$NaIO_4$ and other oxidation reagents, such as pyridinium chlorochromate (PCC) and the Dess-Martin periodinane.[68]

The selective oxidation of isoquinoline **100**, posed significant difficulty. The use of RuO_2-$NaIO_4$ reagents was disappointing. This oxidation procedure resulted in a mixture, which could not be separated. Oxidation of C-1 of isoquinoline **100** requires a regioselective oxidant since there is another methylene group and a methyl group adjacent to the nitrogen atom. RuO_2-$NaIO_4$ is a very strong oxidizing reagent, which might oxidize these other positions that are adjacent to the nitrogen atom and benzylic position, in addition to the desired C-1, resulting a mixture of oxidation products. The use of the alternative reagents, PCC and the Dess-Martin reagent, was also evaluated. Although no target compound was obtained from the Dess-Martin periodinane oxidation reaction, the PCC oxidation of the isoquinoline **100** afforded a very small amount of the target molecule *N*-methylcorydaldine (**21**). The structures of other two unknown products were hard to be determined. The PCC oxidation result verified the previous speculation, but unfortunately, the yield from this reaction was very low.

The experimental results showed that the success of the final oxidation step is related to the selection of the appropriate reagent. Although a positive result was obtained from the oxidation reaction with PCC, none of the oxidation reagents that were tried gave satisfactory results. Attention was therefore directed towards modification of the

precursor.

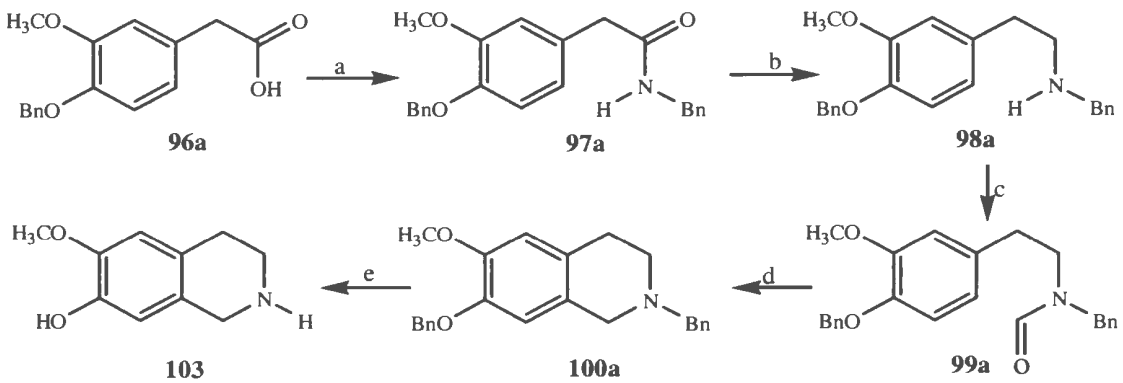
3.2.2 Attempts towards the Syntheses of Thalifoline (19) and Corydaldine (22)



101 **102**

Conditions: a) RuO_2 (cat.), $NaIO_4$, CH_3CN; b) NaOMe, MeOH; 75% for two steps.

Scheme 22.



96a **97a** **98a** **99a** **100a** **103**

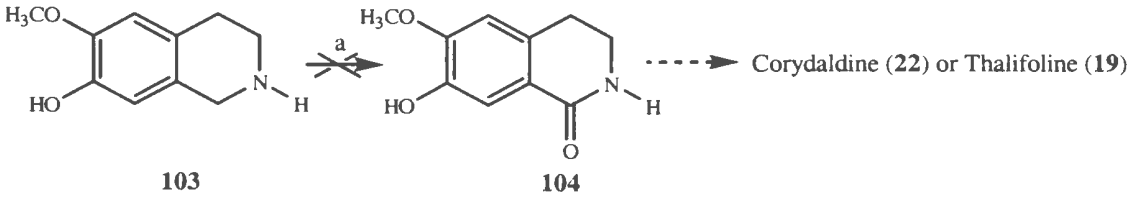
Condition: (a) $(COCl)_2$, benzene, DMF, then benzylamine, aq. 5% NaOH-CH_2Cl_2, 77%; (b) BH_3/THF, BF_3/Et_2O, then aq. 20% HCl, 84%; (c) Ac_2O/HCOOH, 80%; (d) $POCl_3$, reflux in benzene; $NaBH_4$, MeOH, 88%; (e) H_2, Pd/C, ethanol, rt, 12h, 89%.

Scheme 23.

As reported by Schultz,[47] a carbamate **101** could be easily selectively oxidized to its corresponding compound **102** in high yield (75% for two steps) using RuO_2-$NaIO_4$ system (Scheme 22). Based on this, attention was turned to the modification of the precursor to the oxidation step. A carbamate was chosen as the oxidation precursor. The modified synthetic route is shown in Schemes 23-25. Synthesis of the isoquinoline **103** was achieved in good yields. Carboxylic acid **96a** was chosen as the starting material.

The synthesis of **96a,** another compound shared in the Georghiou laboratory and easily synthesized from vanillin (**23**), was shown previously in Scheme 20.

Carboxylic acid **96a,** after conversion to the corresponding acid chloride, afforded the amide **97a** using typical Schotten-Baumann conditions with benzylamine (77%). The amide **97a** was reduced to the amine **98a** using BH_3/THF and BF_3/Et_2O (84%). Acylation of amine **98a** in HCO_2H/Ac_2O formed amide **99a** (80%), which afforded the cyclic benzyl amine **100a** (88%) via BNC reaction, followed by the reduction using $NaBH_4$. Palladium-catalyzed hydrogenolysis of **100a** removed the two benzyl groups to afford the key compound **103** in high yield (89%). The direct oxidation of the intermediate **103** however, also did not give a satisfactory result (Scheme 24). As a result, further exploration of the syntheses of corydadine (**22**) and thalifoline (**19**) from **104** was



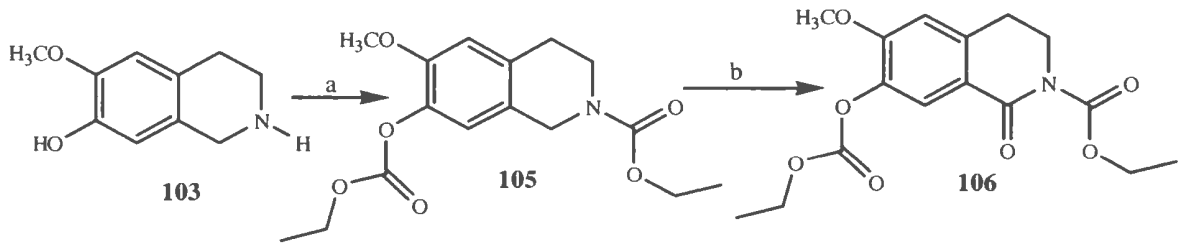
103 **104**

Condition: a) RuO_2-$NaIO_4$, CH_3CN-CCl_4-H_2O.

Scheme 24.

abandoned.

Based on the report of Schultz,[47] attention was next turned towards the conversion of the tertiary amine **103** to the corresponding carbamate. As shown in Scheme 25, the phenolic group of **103** also became derivatized and resulted in a carbamate-carbonate analogue **105**. Oxidation of **105** with RuO_2-$NaIO_4$ gave a very clean reaction, which afforded isoquinolone **106** in acceptable yield (68%). Due to time constraints, our



Conditions: (a) ClCOOEt, aq. $NaHCO_3$, 85%; (b) RuO_2-$NaIO_4$, CH_3CN-CCl_4-H_2O, 68%.

Scheme 25.

research in this area ceased at this stage, but it is apparent that thalifoline (**19**) and corydaldine (**22**) could be easily prepared from compound **106**.

3.3 Summary

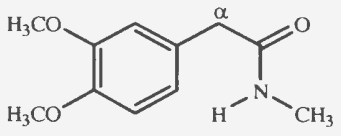
Although the goals of synthesizing thalifoline (**19**) and corydaldine (**22**) were not achieved, *N*-methylcorydaldine (**21**) was synthesized, albeit in very low yield. Oxidation of the carbamate-carbonate **105** afforded the corresponding isoquinolone **106** in acceptable yield using RuO_2-$NaIO_4$. The difficulties that have been identified in these synthetic trials are related to the selection of the oxidation reagents and the nature of the precursor to the oxidation step. Such information will lead to the modification of future synthetic proposals and will be important for future endeavors.

3.4 Experimental

General

Flash column chromatography was performed using 240-400 mesh silical gel and preparative layer (1 mm) chromatography (PLC) was conducted using 60 mesh silica gel. All solvents and reagents used were either of the highest commercial grade available from Sigma-Aldrich and/or were redistilled (CH_2Cl_2, hexane, and benzene distilled over CaH_2, $CHCl_3$ distilled over P_4O_{10}). ^1H and ^{13}C NMR spectra were obtained on a General Electric GE-300 NB spectrometer at 300 MHz in $CDCl_3$ unless otherwise specified and shifts are relative to an internal trimethylsilane signal. Some of the NMR data were obtained on the Bruker Advance 500 MHz instrument with a TXI inverse-detect gradient probe, and these data are designated in the experimental section. The following abbreviations are used in the description in the ^1H NMR: 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 when the spectral data of compounds were obtained from mixtures. NMR free induction decay data were processed using WinNuts (Acorn NMR software). Low resolution mass spectral data were obtained from the V.G. Micromass 7070HS instrument.

***N*-Methyl-3, 4-dimethoxyphenylacetamide (97)**



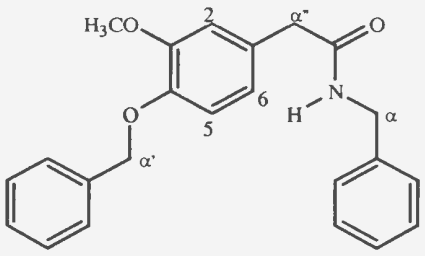
To a stirred solution of oxalyl chloride (1.1 mL, 5.8 mmol) in anhydrous benzene (50 mL) were added compound **96** (2.0 g, 10 mmol) and DMF (2 drops). The reaction was stirred until the evolution of gas ceased. The benzene was removed by rotary evaporation to give the corresponding acid chloride, which was used directly in the next step.

The acid chloride was re-dissolved in CH_2Cl_2 (10 mL) at 0 °C. To this solution, a stirred mixture of methylamine (0.38 g, 12 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 10 mL) was added. After stirring at room temperature for 1 h, the reaction mixture was extracted by using chloroform (10 mL x 3). The organic layers were washed with water (15 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (35% EtOAc/hexane) to afford the amide **97** (1.6 g, 77%) as a colorless oil; ^{1}H NMR: δ 6.86-6.77 (m, 3H, Ar-H), 5.55 (bs, 1H, N-H), 3.88 (s, 6H, OCH_3), 3.52 (s, 2H, H-α), 2.76 (d, N-CH_3); ^{13}C NMR: δ 172.5, 149.7, 148.8, 127.7, 122.1, 113.0, 112.0, 60.5, 56.3, 43.6, 26.9; MS (*m/z*): 209 (M^++1, 41), 151 (100), 91 (35).

***N*-Benzyl-(3-methoxy-4-benzoxyl)phenylacetamide (97a)**

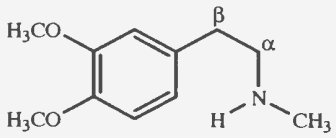
To a stirred solution of oxalyl chloride (1.1 mL, 5.8 mmol) in anhydrous benzene (50 mL) were added compound **96a** (2.1 g, 7.7 mmol) and DMF (2 drops). The reaction was stirred until the evolution of gas ceased. And then benzene was removed by rotary evaporation to give acid chloride, which was used directly in the next step.

The acid chloride was re-dissolved in CH_2Cl_2 (10 mL) at 0 °C. To above solution, a



stirred mixture of benzylamine (1 mL, 9.2 mmol) and CH_2Cl_2-aqueous 5% NaOH (1:1.5, 10 mL) was added dropwise. After stirring at room temperature for 1 h, the reaction mixture was extracted by using chloroform (10 mL x 3). The organic layers were washed with water (15 mL x 2), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (35% EtOAc/hexane) to afford the amide **97a** (2.1 g, 77%) as a colorless oil; ^{1}H NMR: δ 7.52-7.11 (m, 10H, Ar-H), 6.78 (m, 3H, H-2, H-5, H-6), 5.81 (bs, 1H, N-H), 5.13 (s, 2H, H-α"), 4.39 (s, 2H, H-α'), 3.85 (s, 3H, -OCH_3), 3.55 (s, 2H, H-α); MS (*m/z*): 365 (M^+, 5), 91 (100).

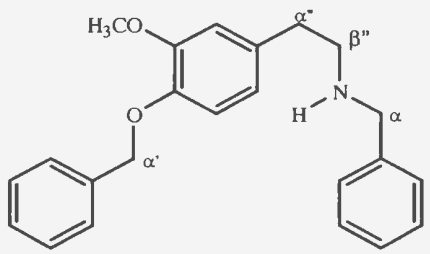
_N_-Methyl-3, 4-dimethoxyphenylacetamine (98)



To a solution of amide **97** (1.3 g, 6.1 mmol) in anhydrous THF (20 mL) was added BF_3/Et_2O (0.32 mL, 2.5 mmol) under argon. The mixture was heated to gentle reflux and then added BH_3/THF (1.0 M solution in THF, 15 mL, 15 mmol) dropwise. The reaction mixture was refluxed for 2 h and then cooled to 0 °C. Aqueous 20% HCl (15 mL) was added to the mixture and it was stirred at 0 °C for 1 h and then at room temperature for overnight. The reaction mixture was basified with aqueous 50% KOH solution and extracted with CH_2Cl_2 (10 mL x 3). The combined organic layers were washed with water (20 mL x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **98** (1.0 g, 84%) as a colorless oil, which was pure enough to be used in the next step without

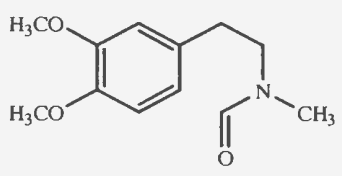
purification. ^{1}H NMR: δ 6.84-6.74 (m, 3H, Ar-H), 4.81 (bs, 1H, N-H), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 2.80 (m, 4H, H-α, H-β), 2.45 (s, 3H, N-CH_3).

_N_-Benzyl-(3-methoxy-4-benzoxyl)phenylethylamine (98a)



To a solution of amide **97a** (1.5 g, 4.2 mmol) in anhydrous THF (20 mL) was added BF_3/Et_2O (0.54 mL, 2.5 mmol) under argon. The mixture was heated to gentle reflux and then added dropwise BH_3/THF (1.0 M solution in THF, 14 mL, 14 mmol). The reaction mixture was refluxed for 2 h and then cooled to 0 °C. Aqueous 20% HCl (15 mL) was added to the mixture and it was stirred at 0 °C for 1 h, and then at room temperature for overnight. The reaction mixture was basified with aqueous 50% KOH solution and extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with water (20 mL x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **98a** (1.2 g, 84%) as a colorless oil, which was pure enough to be used in the next step without purification.

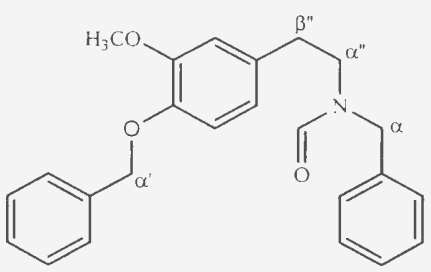
_N_-Methyl-_N_-2-(3,4-dimethoxy)phenylethylformamide (99)



To compound **98** (0.40 g, 2.1 mmol) in a 15 mL flask was added a mixture of HCO_2H and Ac_2O (5.0 mL, 1:1) under argon. After stirring overnight at room temperature, the reaction was diluted with the addition of water (5.0 mL). Then the mixture was extracted with EtOAc (5.0 mL x 2). The organic layers were combined and washed with brine (10 mL x 2), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The

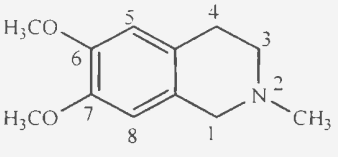
residue was purified by flash column chromatography (50% EtOAc/hexane) to afford **99** (350 mg, 80%) as a colorless oil, which was used directly in the next step.

_N_-Benzyl-_N_-[2-(3-methoxy-4-benzoxyl)phenylethylformamide (99a)



To a compound **98a** (0.40 g, 1.2 mmol) in a 15 mL flask was added a mixture of HCO_2H and Ac_2O (5.0 mL, 1:1) under argon. After stirring overnight at room temperature, the reaction was diluted with the addition of water (5 mL). The mixture was extracted with EtOAc (5 mL x 2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to afford **99a** (347 mg, 80%) as a colorless oil, which was used directly in the next step. MS (*m/z*): 375 (M^++2, 2), 240 (25), 91 (100).

6,7-Dimethoxy-_N_-methyltetrahydroisoquinoline (100)

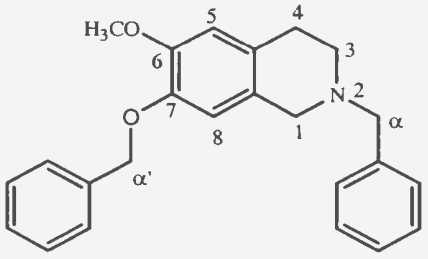


Compound **99** (300 mg, 1.4 mmol), $POCl_3$ (1.0 mL) and benzene (10 mL) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 8 h, the solvent was evaporated on a rotary evaporator and the residual $POCl_3$ was evaporated on a vacuum pump for 1 h.

The residue was re-dissolved in MeOH (10 mL), and the solution was cooled to -78 °C in a dry ice/acetone bath. To this solution was added $NaBH_4$ (40 mg, 1.0 mmol) in five portions over a period of 5 h. The reaction was then quenched by the addition of aqueous 10% HCl (10 mL) and stirred at room temperature for 10 min. The MeOH was

evaporated on a rotary evaporator, and 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 extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with brine (3 x 5.0 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to give **100** (240 mg, 88%) as a colorless oil; ^{1}H NMR: δ 6.59 (s, 1H, H-8), 6.51 (s, 1H, H-5), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.50 (s, 2H, H-1), 2.85 (t, *J*=6.0 Hz, 2H, H-3), 2.66 (t, *J*=6.0 Hz, 2H, H-4), 2.44 (s, 3H, N-CH_3); MS (*m/z*): 206 (M^+, 68), 164 (100), 121 (22), 58 (62).

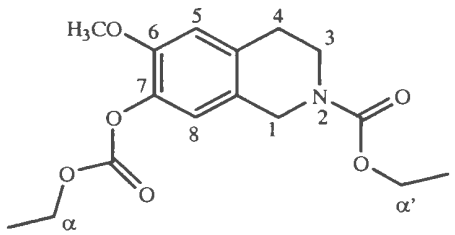
_N_-Benzyl-(6-methoxy-7-benzoxyl)-1,2,3,4-tetrahydroisoquinoline (100a)



Compound **99a** (1.2 g, 3.2 mmol), $POCl_3$ (1.0 mL) and benzene (20 mL) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 8 h, the solvent was evaporated on a rotary evaporator and the residual $POCl_3$ was evaporated on a vacuum pump for an 1 h. The residue was re-dissolved in MeOH (10 mL), and the solution was cooled to -78 °C in a dry ice/acetone bath. To this solution was added $NaBH_4$ (58 mg, 1.5 mmol) in five portions over a period of 5 h. The reaction was then quenched by the addition of aqueous 10% HCl (10 mL) and stirred at room temperature for 10 min. The MeOH was evaporated on a rotary evaporator and the residue was re-dissolved in CH_2Cl_2 (15 mL) and transferred to a separatory funnel containing H_2O (5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were washed with

brine (3 x 5 mL), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to give **100a** (1.3 g, 88%) as a colorless oil; ^{1}H NMR: δ 7.42-7.20 (m, 10H, Ar-H), 6.62 (s, 1H, H-5), 6.51 (s, 1H, H-8), 5.07 (s, 2H, H-α'), 3.84 (s, 3H, OCH_3), 3.65 (s, 2H, H-1), 3.49 (s, 2H, H-α), 2.81 (t, *J*=5.5 Hz, 2H, H-4), 2.70 (t, *J*=5.5 Hz, 2H, H-3).

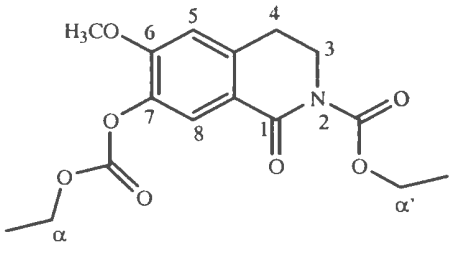
***N*-Ethylcarbonyl-7-ethoxycarbonyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (105)**



To a solution of **103** (0.56 g, 3.1 mmol) in CH_2Cl_2 (10 mL), aqueous saturated solution of $NaHCO_3$ (10 mL) was added. The resulting two-phase mixture was stirred vigorously at 0 °C for 0.5 h, and then ethyl chloroformate (1.2 mL, 9.3 mmol) was added to the mixture dropwise. The reaction mixture was warmed to room temperature and stirred over 3 h. The organic layer was separated. The aqueous phase was extracted using CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with water (5 mL x 2), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by flash column chromatography (50% EtOAc/hexane) to give **105** (0.86 g, 85%) as a colorless oil; ^{1}H NMR: δ 6.78 (s, 1H, H-5), 6.64 (s, 1H, H-8), 4.44 (s, 2H, H-1), 4.20 (q, *J*=7.0 Hz, 2H, H-α), 4.08 (q, *J*=7.0 Hz, 4H, H-α'), 3.72 (s, 3H, OCH_3), 3.58 (bs, 2H, H-4), 2.71 (s, 2H, H-3), 1.30 (t, *J*=7.0 Hz, 3H, α-CH_3), 1.19 (t, *J*=7.0 Hz, 3H, α'-CH_3); ^{13}C NMR: δ 155.9,

153.8, 149.9, 138.9, 133.6, 126.0 (b), 120.4, 113.1, 65.2, 61.8, 56.3, 45.3, 41.5 (b), 28.7 (b), 15.1, 14.5; MS (*m/z*): 323 (M^+, 8), 294 (96), 222 (100).

_N_-Ethylcarbonyl-7-ethoxycarbonyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinolone (106)

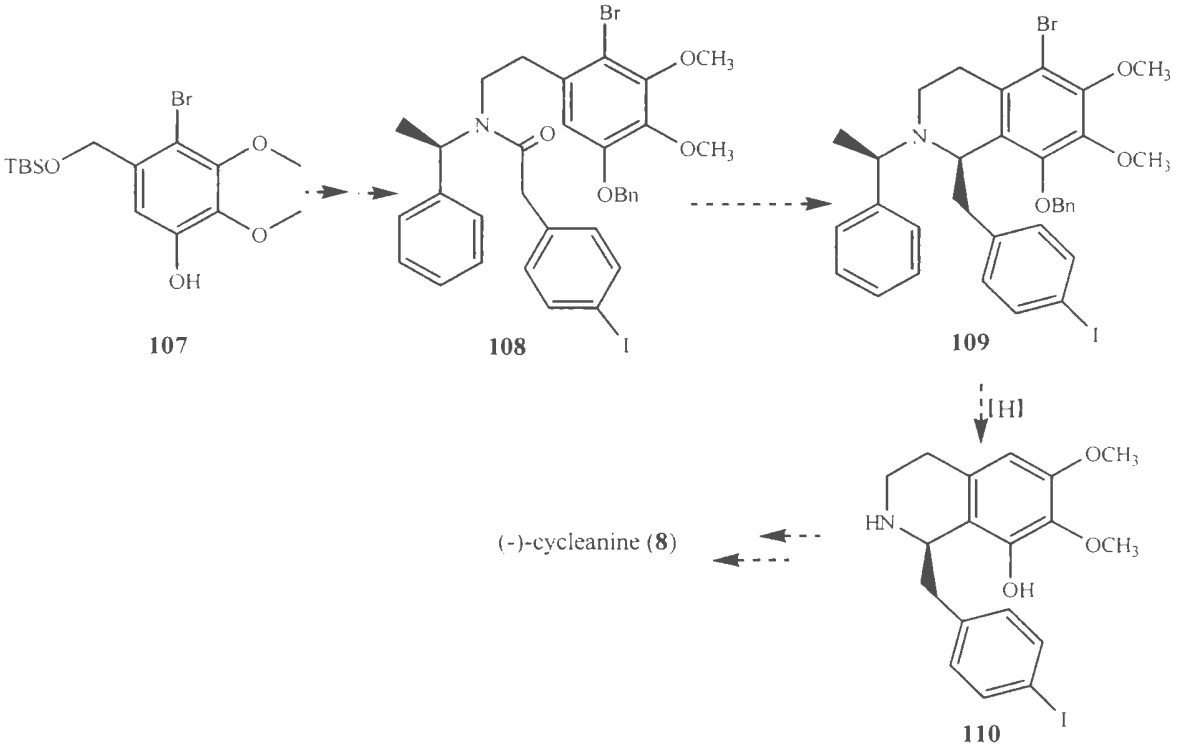


To a mixture of **105** (120 mg, 0.37 mmol) and $NaIO_4$ (340 mg, 1.5 mmol) in CCl_4-CH_3CN-H_2O (1:1:1.5, 5.0 mL), RuO_2 (1.2 mg, 2.2 mol%) was added at once. The reaction mixture was stirred for 3 h at room temperature, and then CH_2Cl_2 (5.0 mL) and H_2O (5.0 mL) were added to the mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layers were washed with water (5.0 mL x 2), dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by preparative TLC (50%, EtOAc/hexane) to give **106** (85 mg, 68%) as a colorless oil; ^1H NMR: δ 7.94 (s, 1H, H-5), 6.77 (s, 1H, H-8), 4.38 (q, *J*=6.9 Hz, 2H, H-α), 4.33 (q, *J*=6.9 Hz, 2H, H-α'), 4.09 (t, *J*=5.1 Hz, 2H, H-4), 3.01 (t, *J*=5.1 Hz, 2H, H-3), 1.36 (m, 6H, α-CH_3, α'-CH_3); ^{13}C NMR: δ 162.8, 155.2, 154.7, 153.1, 139.8, 139.4, 123.9, 121.9, 110.9, 65.3, 63.4, 56.3, 44.6, 28.5, 14.4, 14.2; MS (*m/z*): 338 (M^+, 3), 265 (21), 164 (25), 136 (19), 29 (100).

Chapter 4

Future Work

4.1 Further Studies of the Selective Formation of the Ring-Closure Products via BNC Reaction



Scheme 26.

From the previous studies reported herein, the BNC reaction of compounds **57** or **81** always resulted in the formation of a pair of regioisomers because of the presence of two available ring-closure sites. As a result, lower yields of the target ring-closure products would result, and this also makes separation of the resulting pair of regioisomers difficult. A possible solution to this problem would involve blocking the undesired closure site of the precursor, e.g. **107** and **108**, which could result in a unique target ring-

closure product, e.g. **109** (Scheme 26). The blocking group should survive the BNC reaction conditions and the subsequent procedures. Furthermore, the blocking group should also be removed easily at a later stage, in a selective manner.

With the above considerations, a bromine atom was considered to be a suitable blocking group. This proposal is briefly outlined in Scheme 26. The advantage of this proposal is that the chiral auxiliary, the benzyl group and the blocking group of **109** all could be removed simultaneously in a later Pd/C-catalyzed hydrogenolysis step to afford the key intermediate **110**. However, additional research was not undertaken into exploring the stability of the bromine atom in the BNC and subsequent steps.

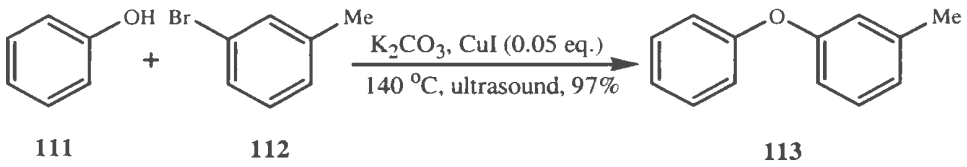
4.2 Further Proposal for the Diaryl Ether Formation Step

Thus far, attempts at the synthesis of the diaryl-ether linkages required to construct the macrocycle of cycleanine (**8**) resulted in failure. However, it should be pointed out that a much effort is currently devoted by many research groups to develop better methods for the synthesis of diaryl ethers in searching for new synthetic routes to a wide range of biologically active compounds. However, due to time constraints, only the $Cu(OAc)_2$-mediated diaryl ether formation methodology was explored for this thesis.

4.2.1 Further Examination of Ullmann Ether Synthesis

As an example of a modification to the classical Ullmann methods, the procedure developed by Smith[69] involving the use of catalytic copper(I) iodide and ultrasound gives better yields of diaryl ethers at lower temperature (Scheme 27). Future attempts into

exploring the formation of the macrocyclization strategies for the synthesis of diaryl ether with the use of this Ullmann methodology could be focused on varying reaction conditions, such as reaction temperature, reaction time or varying the amounts and/or nature of the catalyst.

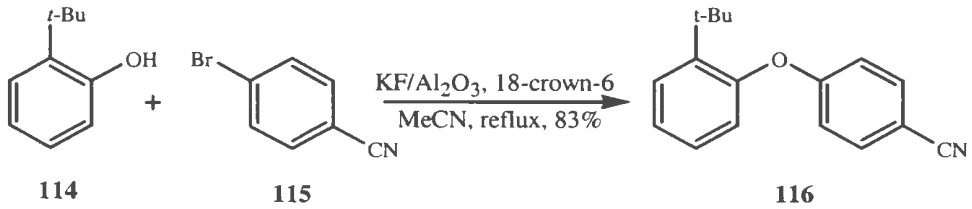


111 112 113

Scheme 27.

4.2.2 Further Examination of S_NAr-based Diaryl Ether Formation Reaction

An example from the Sawyer[70] group illustrates that even the sterically crowded nucleophile 2-*tert*-butylphenol, which is usually unreactive under normal Ulllmann conditions, added smoothly to 4-bromobenzonitrile to give diaryl ether **116** (Scheme 28).

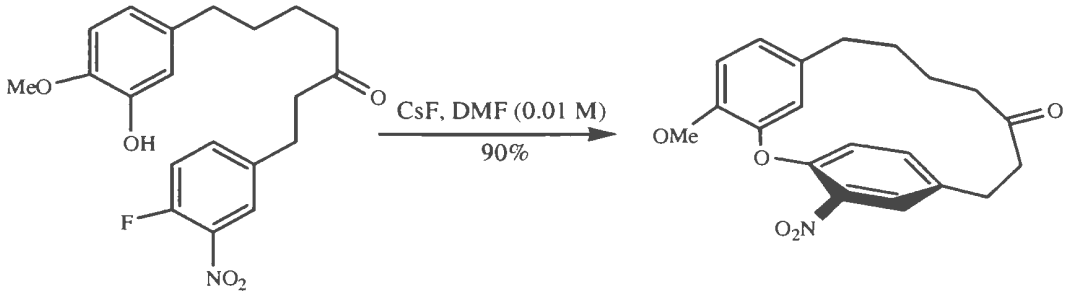


114 115 116

Scheme 28.

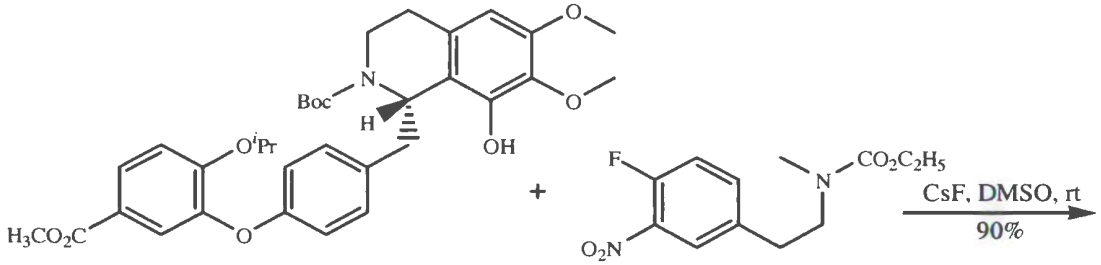
Another example from Zhu[71] shows an efficient intramolecular S_NAr macrocyclization approach (Scheme 29). Similarly, Wang[34] used a base-mediated S_NAr coupling for construction of the diaryl ether key synthetic intermediate **121** in his synthesis of (−)-tejedine (Scheme 30). The *ortho*-nitroarylfluoride **120** reacted with phenol **119** to afford a

diaryl ether compound **121** in a very high yield (90%) using CsF in DMSO at room temperature.

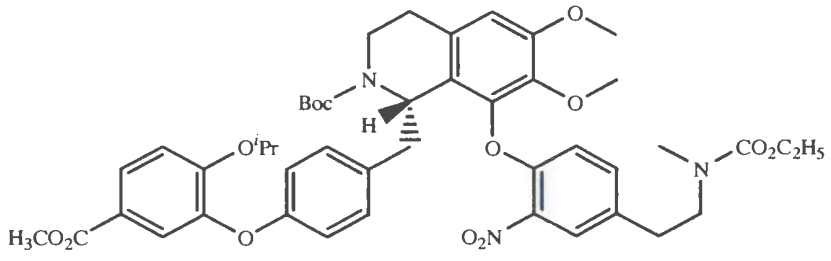


117 **118**

Scheme 29.



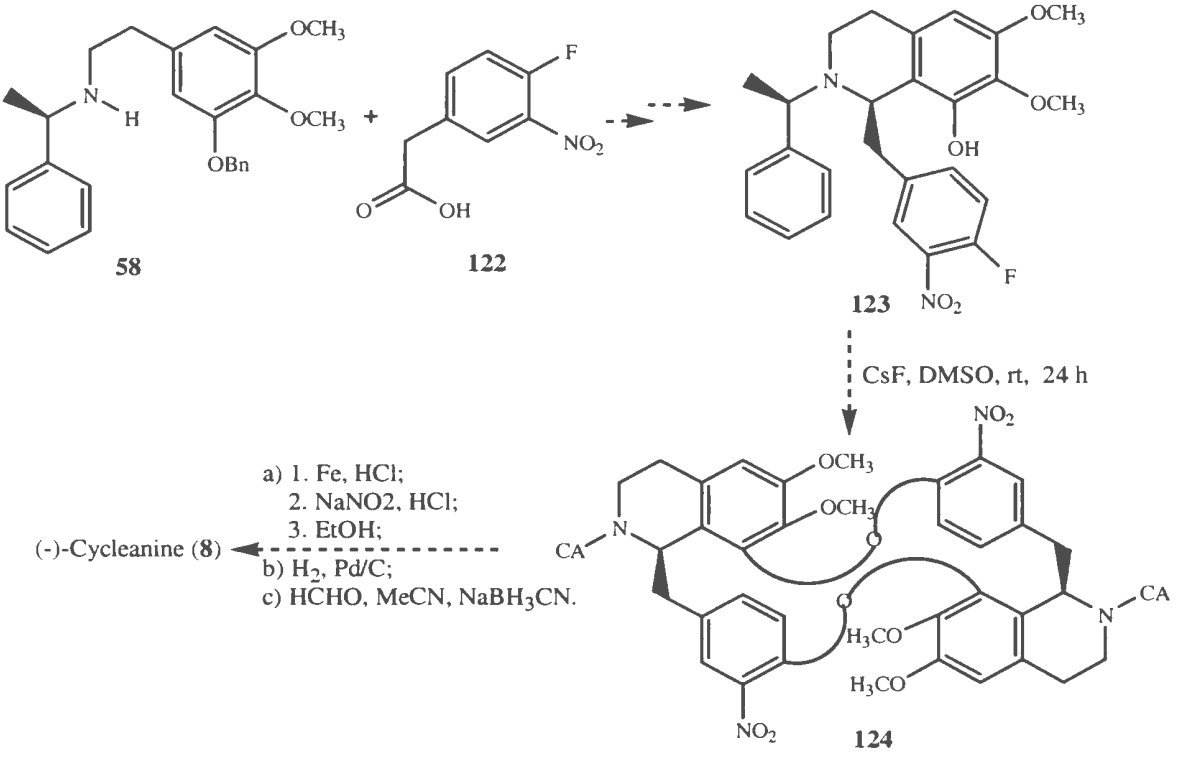
119 **120**



121

Scheme 30.

Future attemps to form the diaryl-ether linkages in the synthesis of cycleanine should evaluate the application of a similar base-mediated S_NAr coupling methodology to



Scheme 31.

that which has been demonstrated to be effective in the synthesis of (−)-tejedine. Success utilizing this methodology would result in the completion of the target molecule, which is outlined in Scheme 31. Upon application of the Schotten-Baumann reaction conditions, chiral amine **58** and carboxylic acid **121** could afford a key intermediate **123**, a precursor for the desired diaryl ether coupling reaction. Under S_NAr coupling reaction conditions, a homocoupling reaction of **123** could complete the key intermediate **124**. Selective removal of the nitro group and the chiral auxiliary of **124** and followed by methylation could afford the target compound (−)-cycleanine (**8**). It should be pointed out that **122**

could be synthesized from 4-fluoro-3-nitrophenylacetonitrile, a commercially available compound.

However, because an *ortho*-substituted electron-withdrawing group is necessary to activate the aryl fluoride, experimentation to evaluate selective removal of the electron-withdrawing group (e.g. $-NO_2$) will require attention. Therefore, model studies on the coupling reaction of aryl fluorides bearing *ortho*-substituted electron-withdrawing groups need to be evaluated.

4.3 Future Proposals for Improvement in Construction of the Tetrahydro-isoquinolones

It should be considered that any current or future progress towards the syntheses of tetrahydroisoquinolones can also be of help in designing syntheses of BBIQs. The selective oxidation of tetrahydroisoquinolines was based on the selection of appropriate oxidation reagent and modification of the precursor to the oxidation step. It is reasonable to consider that future endeavors towards the syntheses of tetrahydroisoquinolones or BBIQs containing tetrahydroisoquinolone unit will be focused around these two particular aspects.

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(65) $C_{33}H_{34}NO_3I$: orthorhombic, space group $P2_12_12_1$ (#19), a = 9.6846 (5) Å, b = 15.1384 (8) Å, C = 19.931(1) Å, V = 2922.1(2) Å^3, Z = 4, D_{caclcd} = 1.408 g/ cm^3. Intensity data were measured at –80±10 °C on a Bruker P4/CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) to $2\theta_{max}$ 52.8°. A

total of 21129 reflections were measured of which 5978 (R_{int} = 0.065) were unique. The final cycle of full-matrix least-squares refinement of F was based on 4784 observed reflections ($I > 2.00\sigma(I)$) and 343 variable parameters and converged with unweighted and weighted agreement factors of: R_1 = 0.047, R_w = 0.100, GOF = 1.05. We thank David O. Miller, X-ray Crystallography Unit, Department of Chemistry, Memorial University of Newfoundland for these measurements. And also, we acknowledge Dr. Bob McDonald, University of Alberta for data collection.

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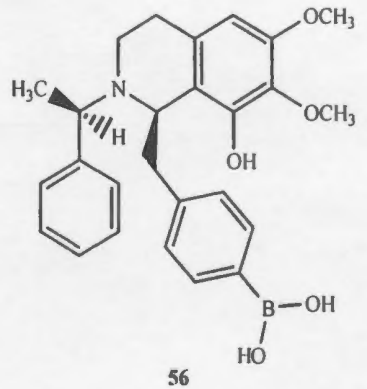

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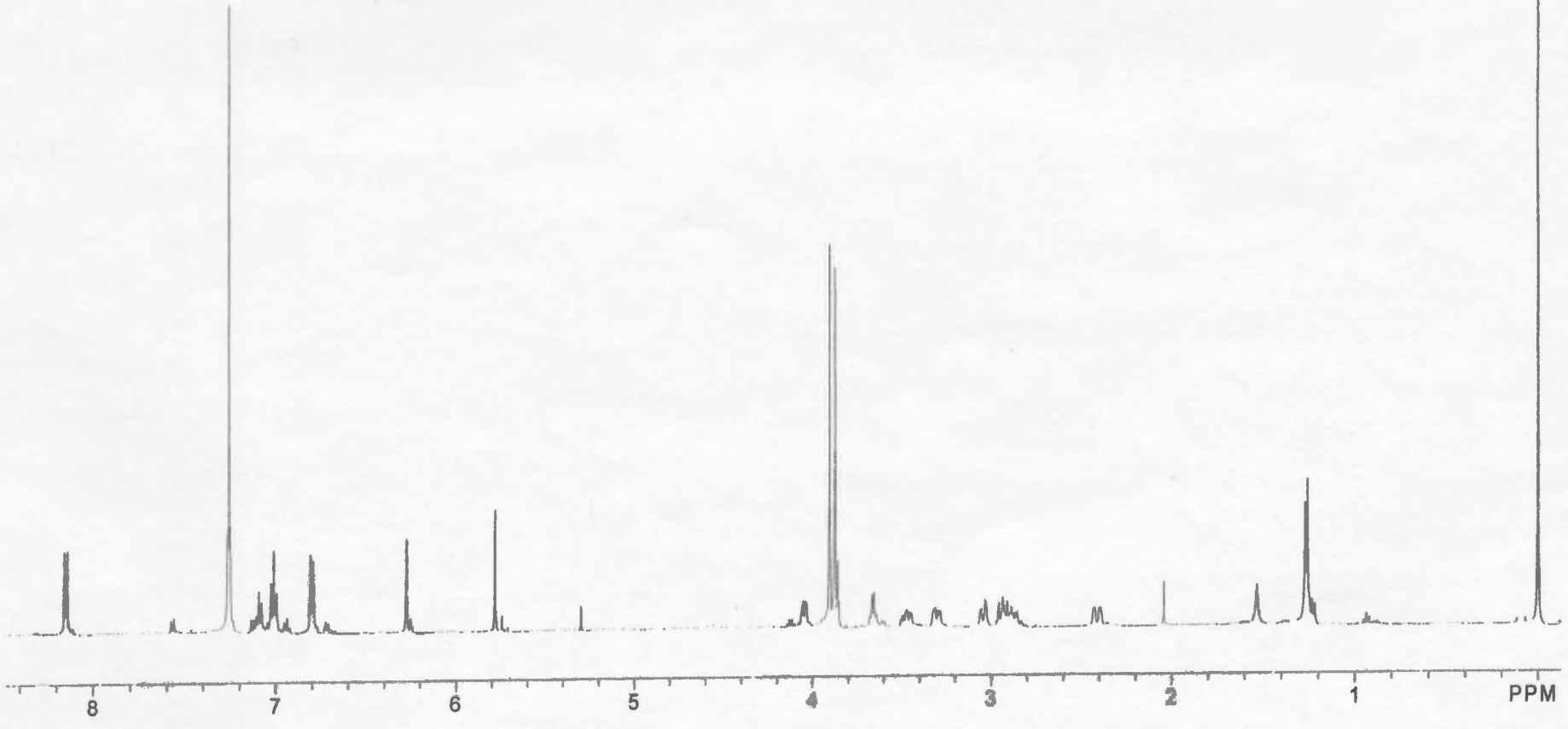

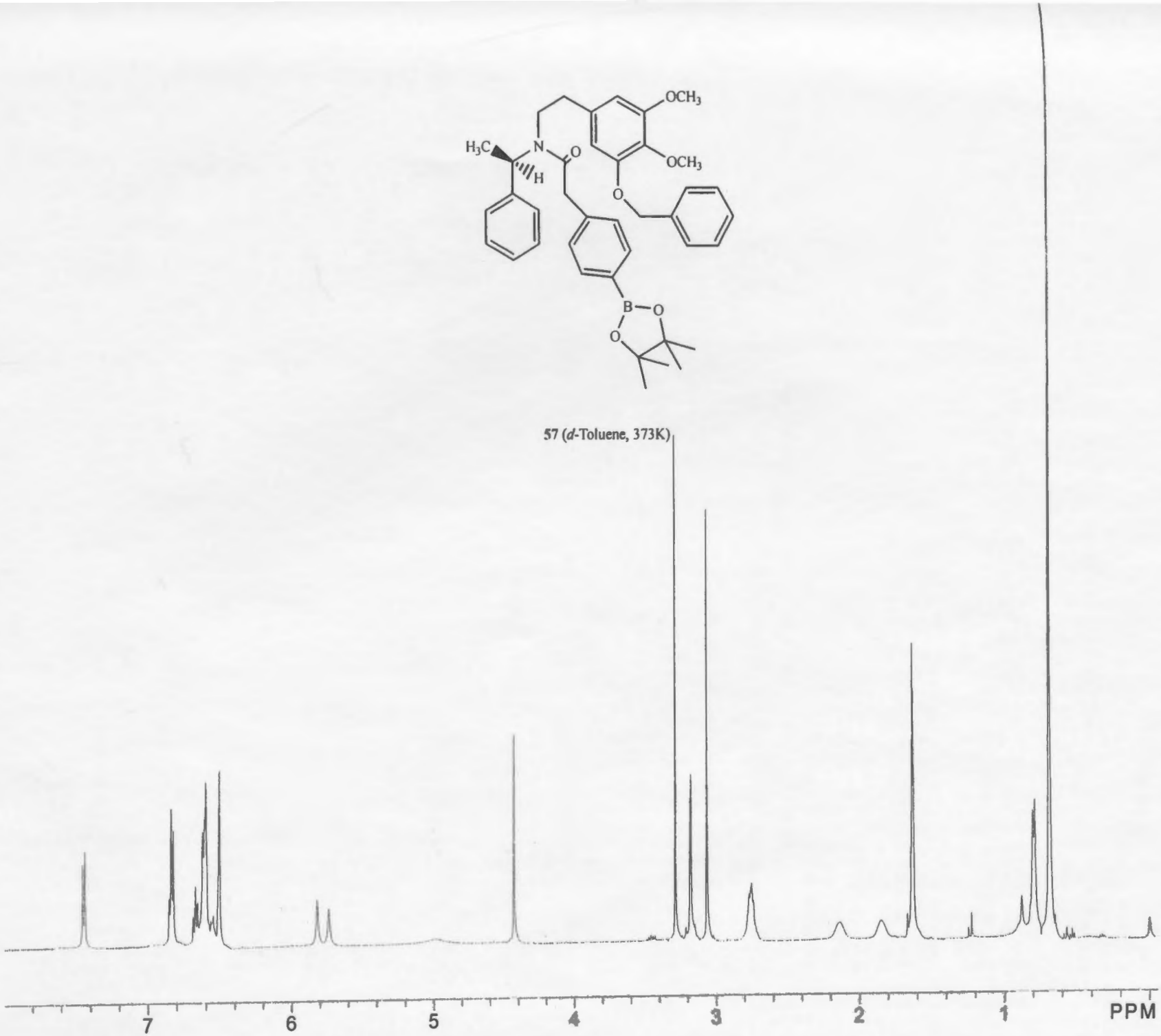
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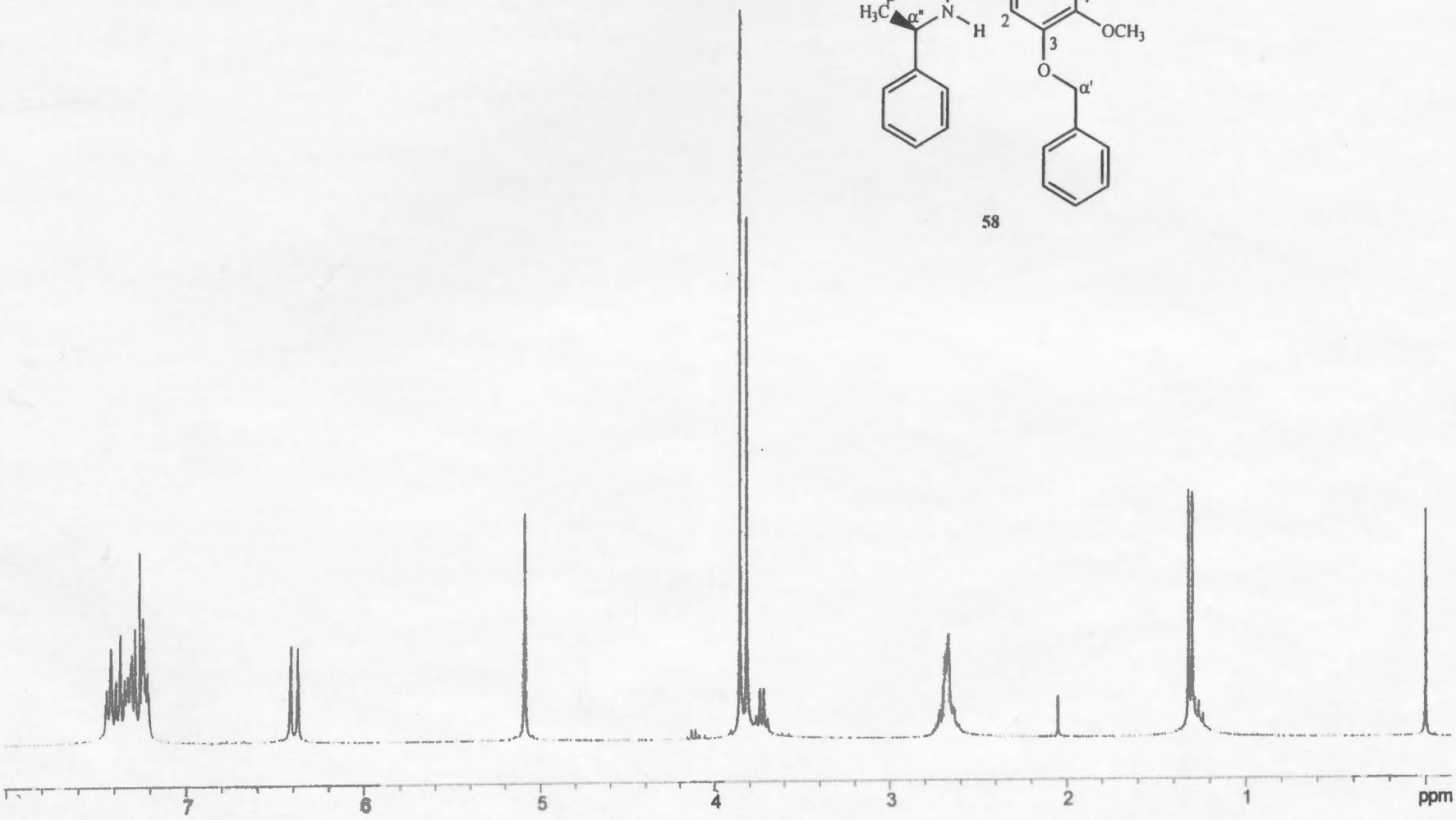
OCH3
H3C
N
O
H
O
B
O
O
57 (d-Toluene, 373K)
7
6
5
4
3
2
1
PPM



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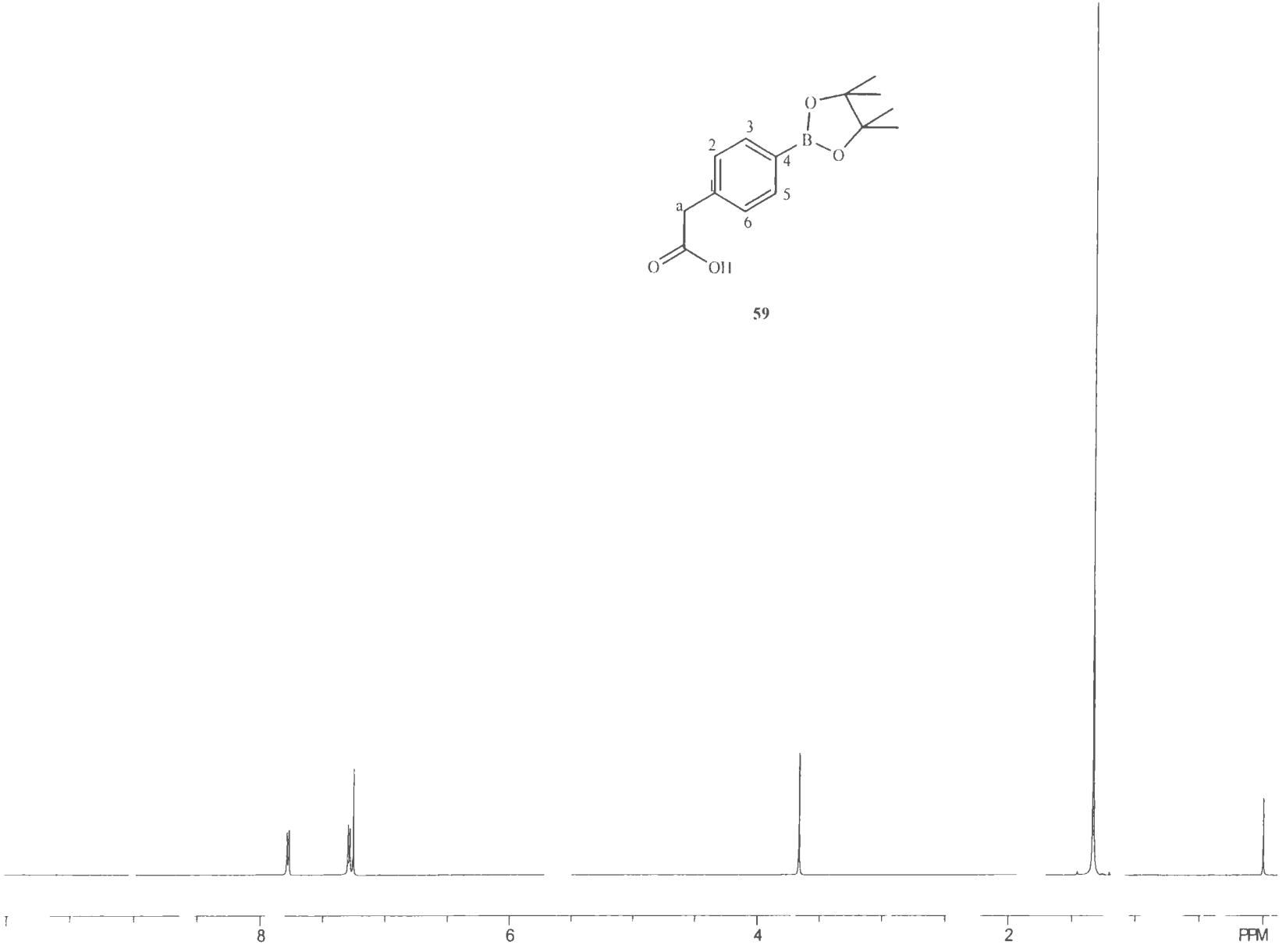

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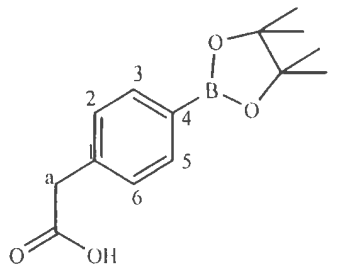

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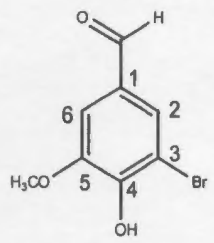

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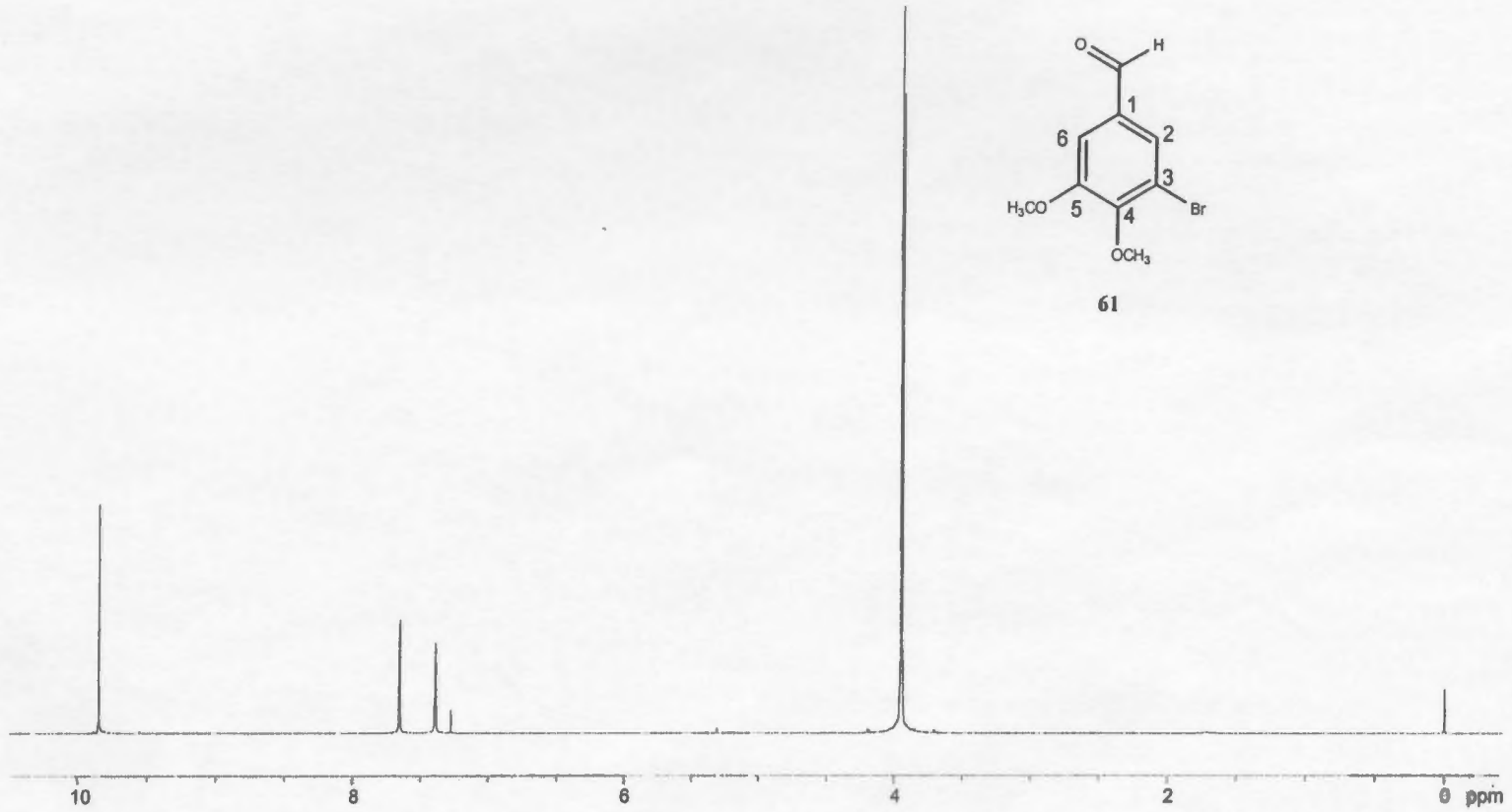

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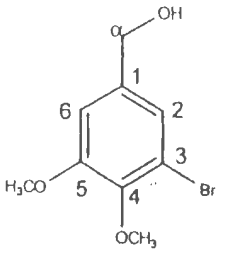

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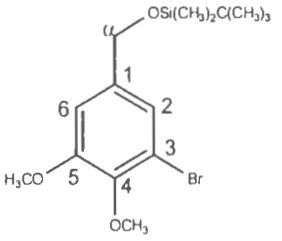
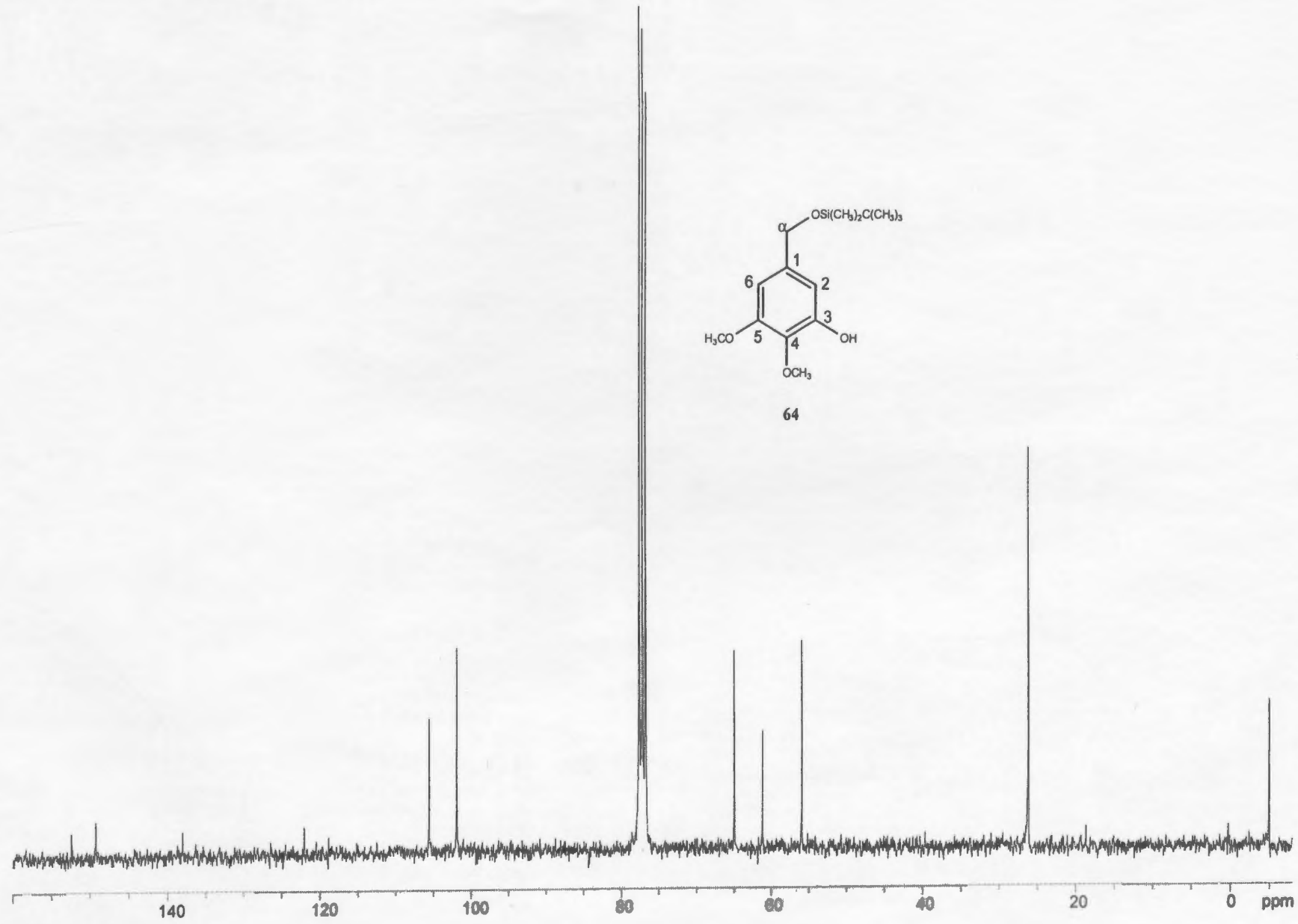


63

OSi(CH3)2C(CH3)3
α
1
2
3
OH
4
OCH3
5
H3CO
6
64
ppm
1
2
3
4
5
6
7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α
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3
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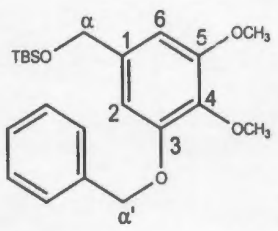
5
6
H3CO
OH
OCH3
140
120
100
80
60
40
20
0
ppm

64



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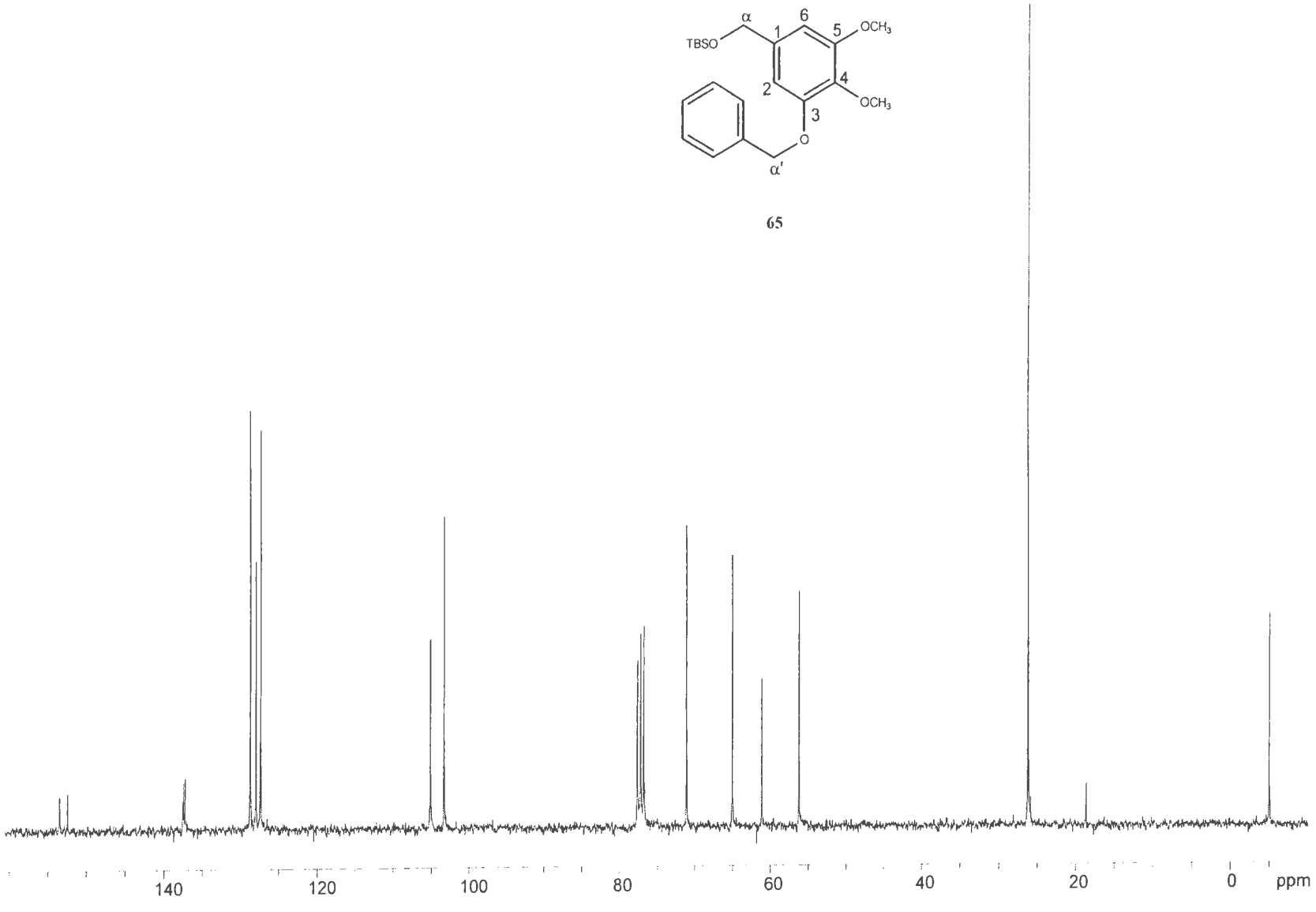

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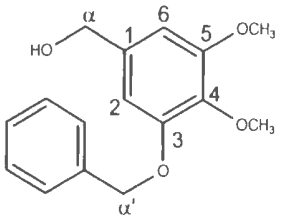

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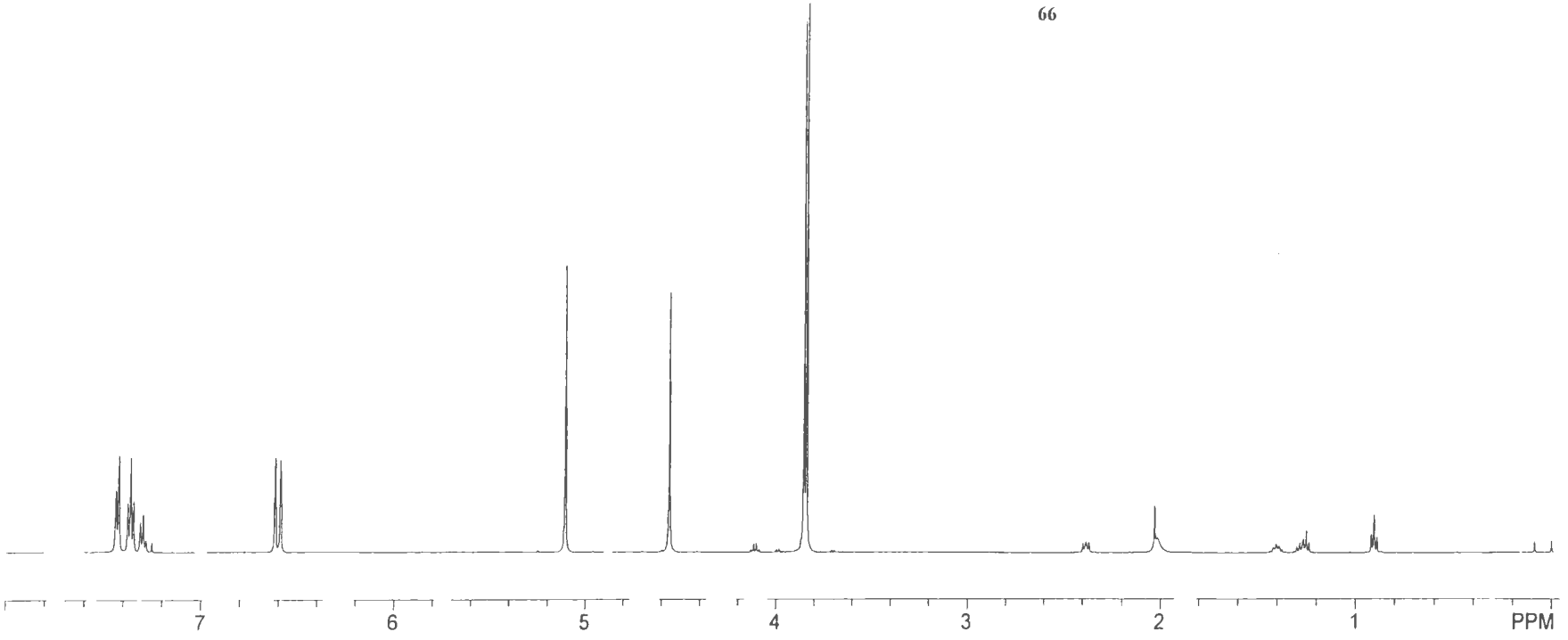

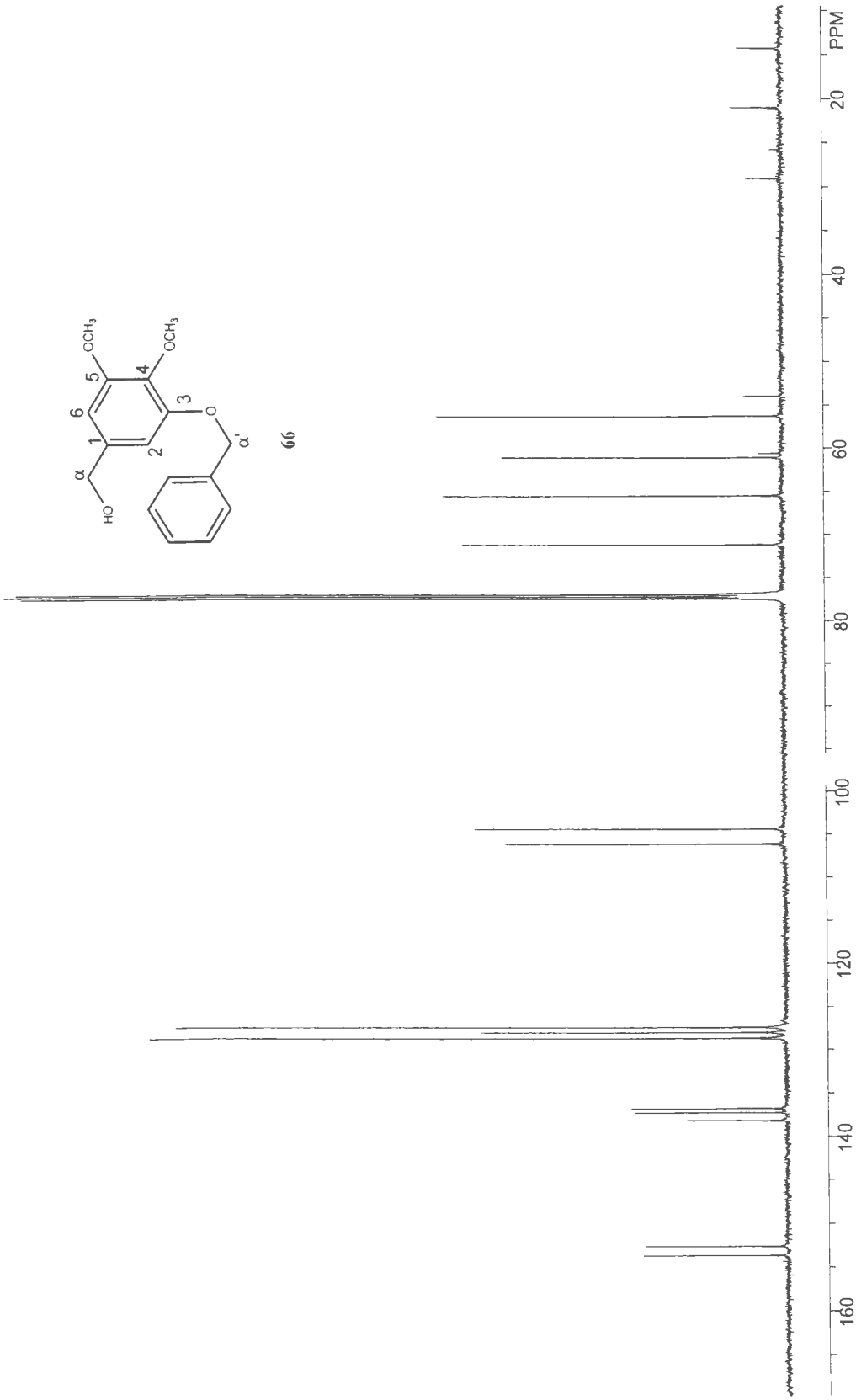

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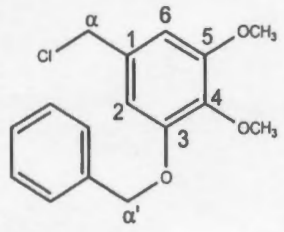

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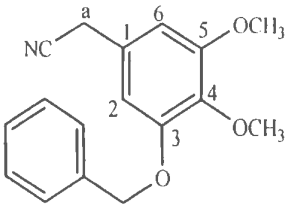

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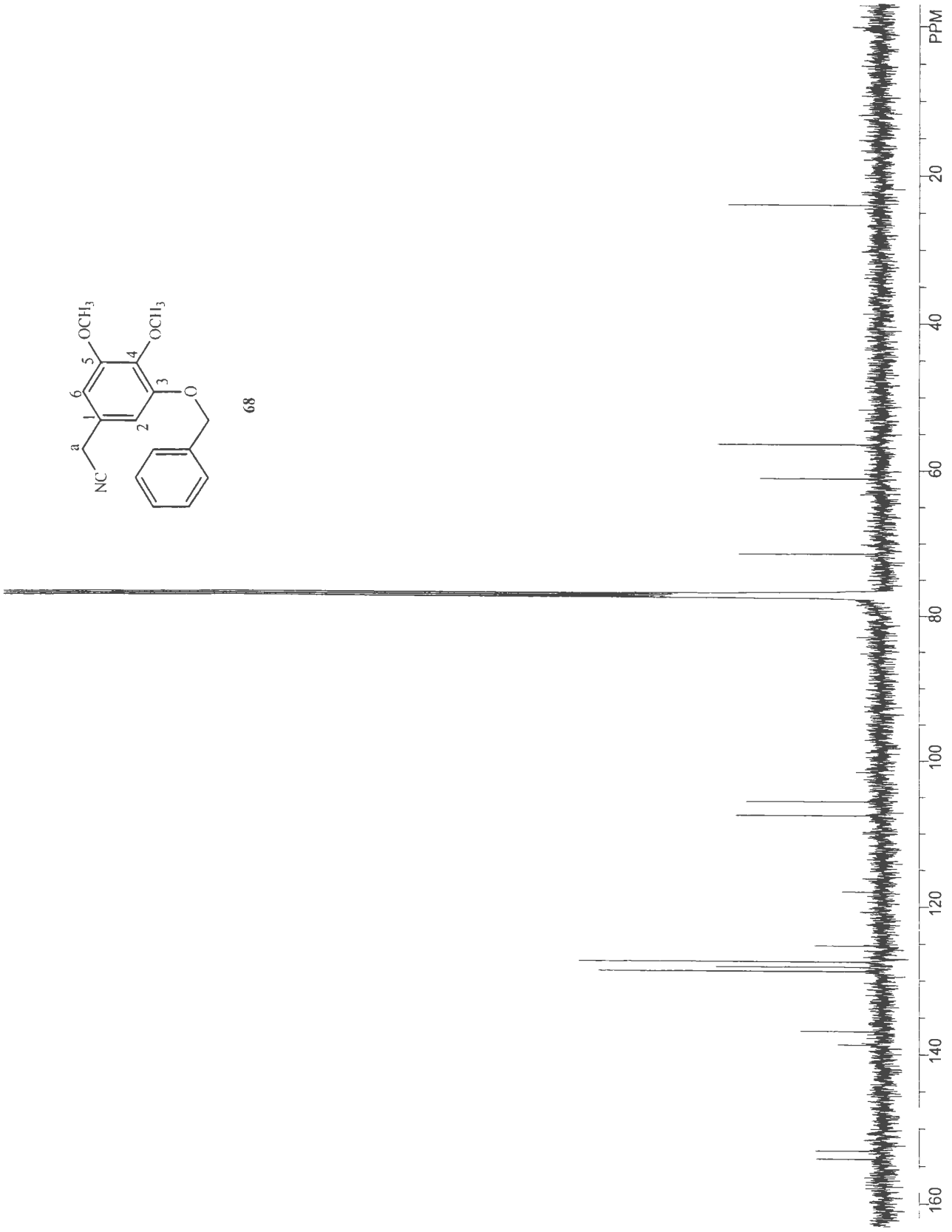
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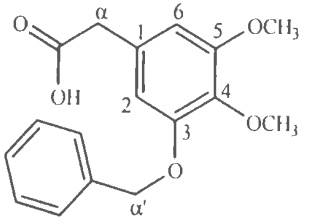
OCH3
5
4
6
3
1
2
a
NC
O
68
PPM
160
140
120
100
80
60
40
20



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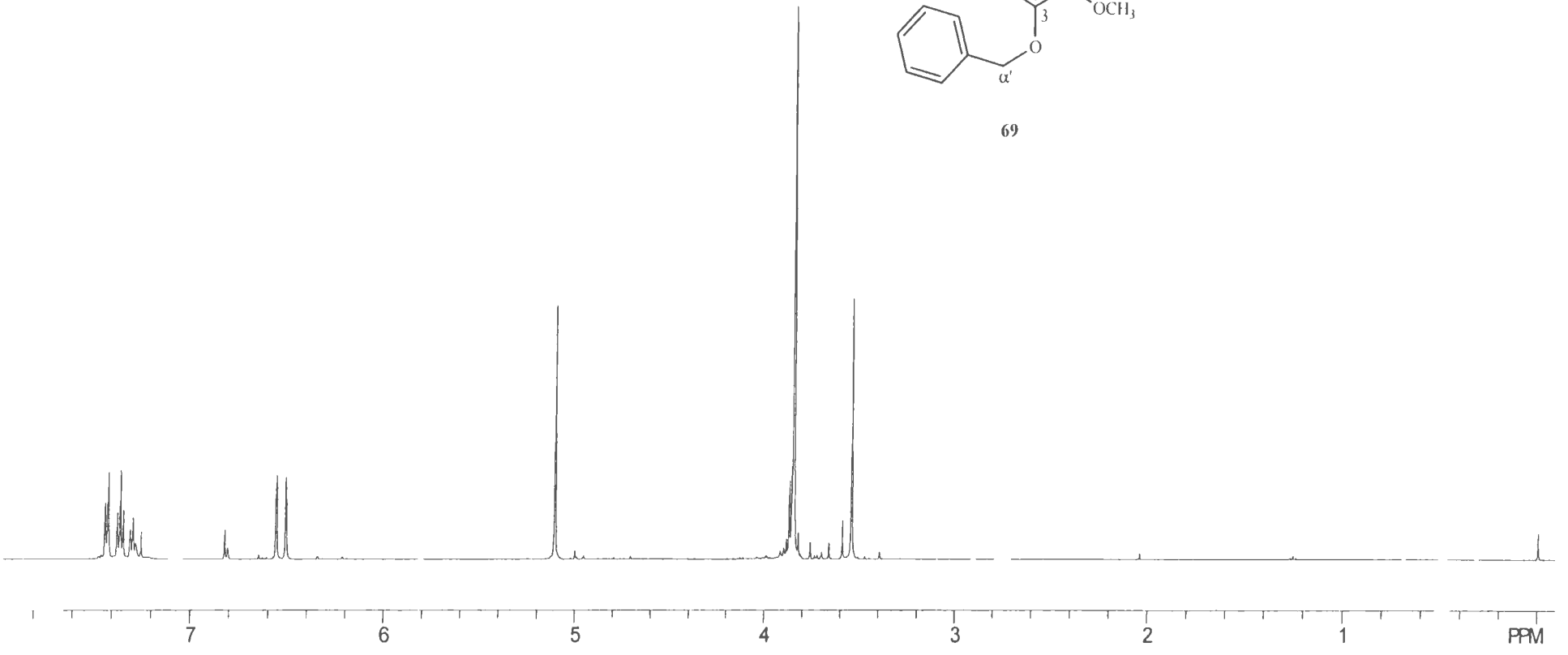

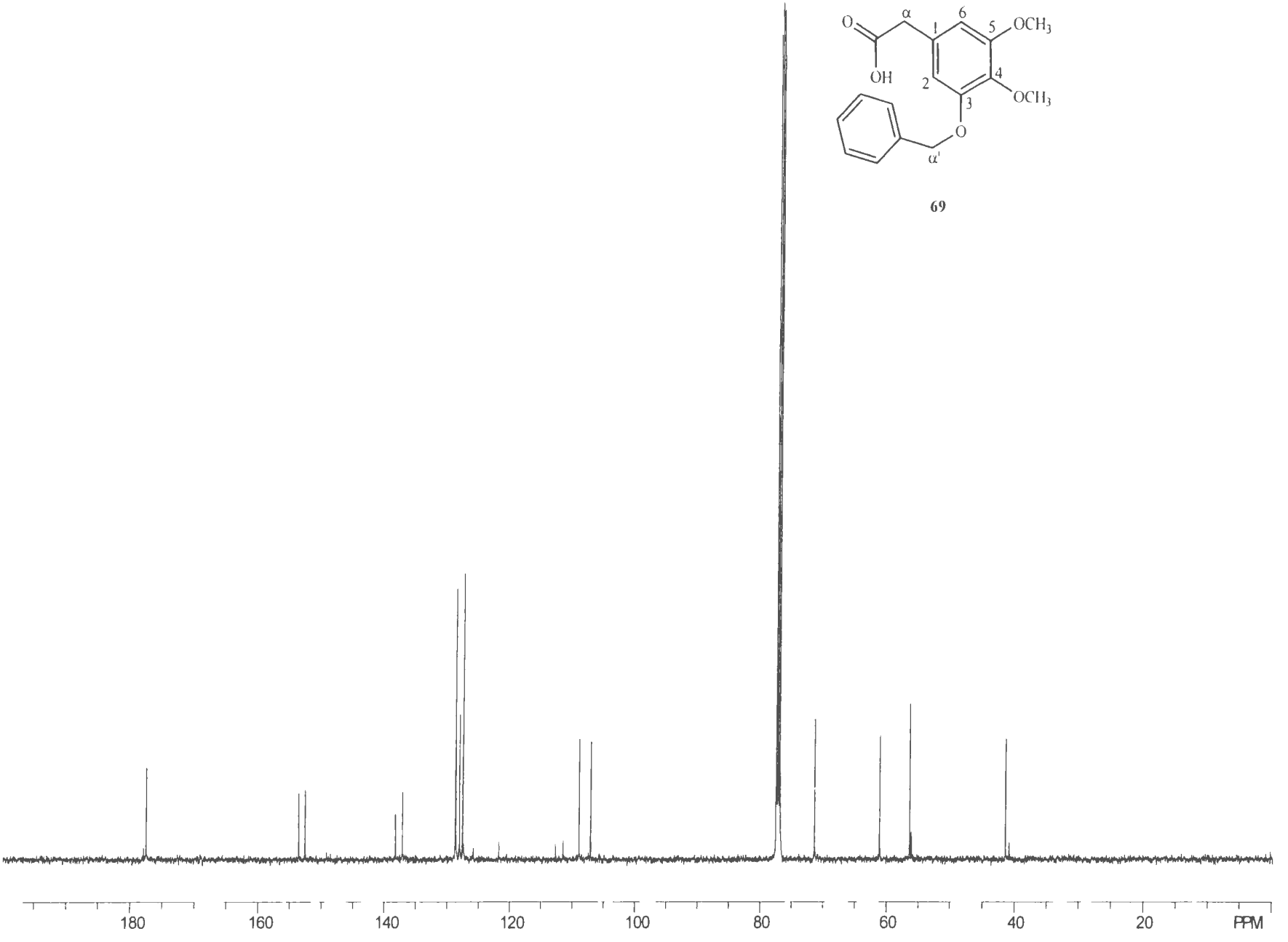

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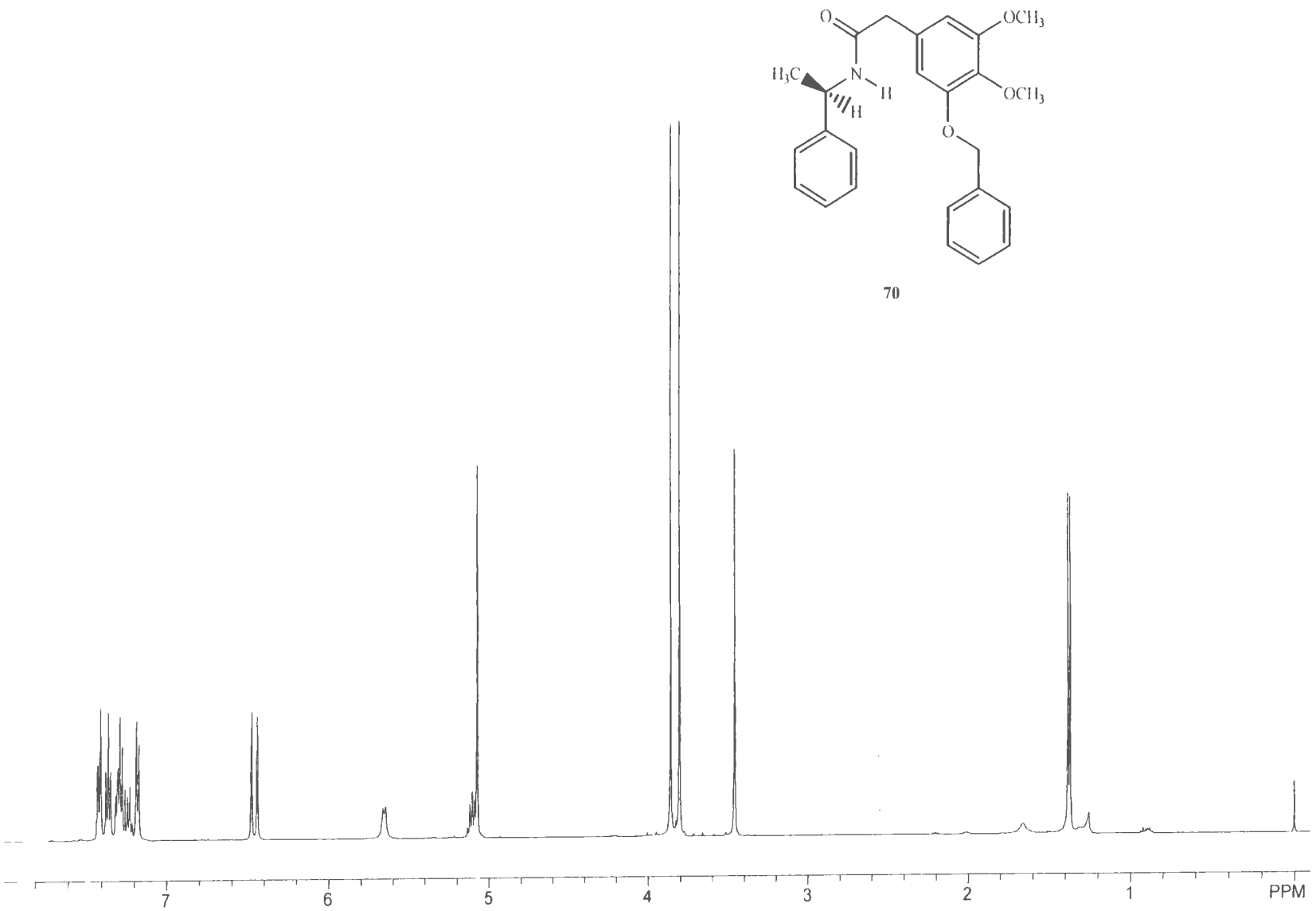

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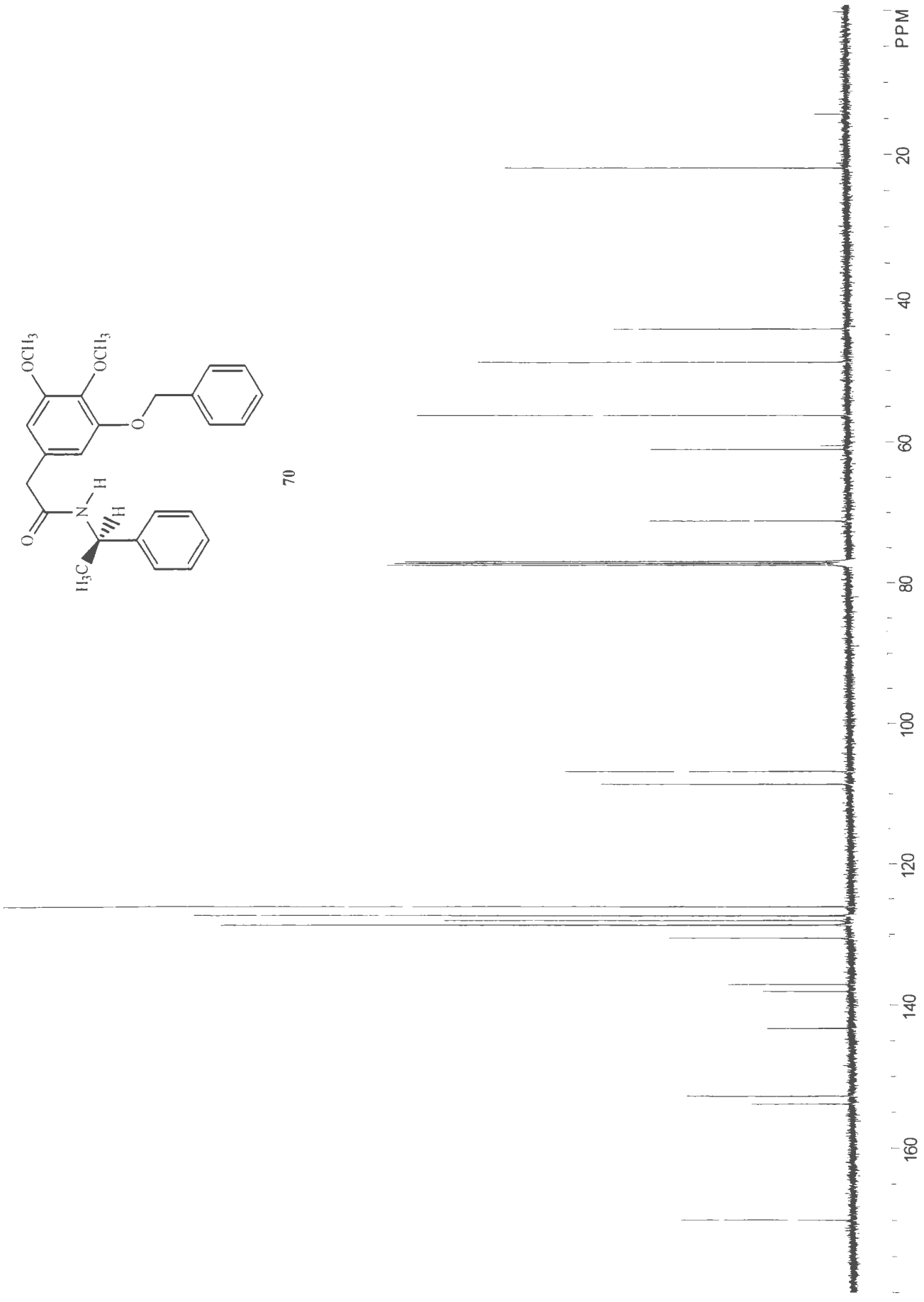
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PPM
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80
100
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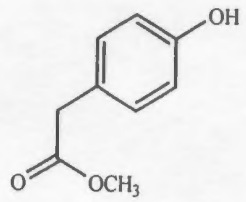
160



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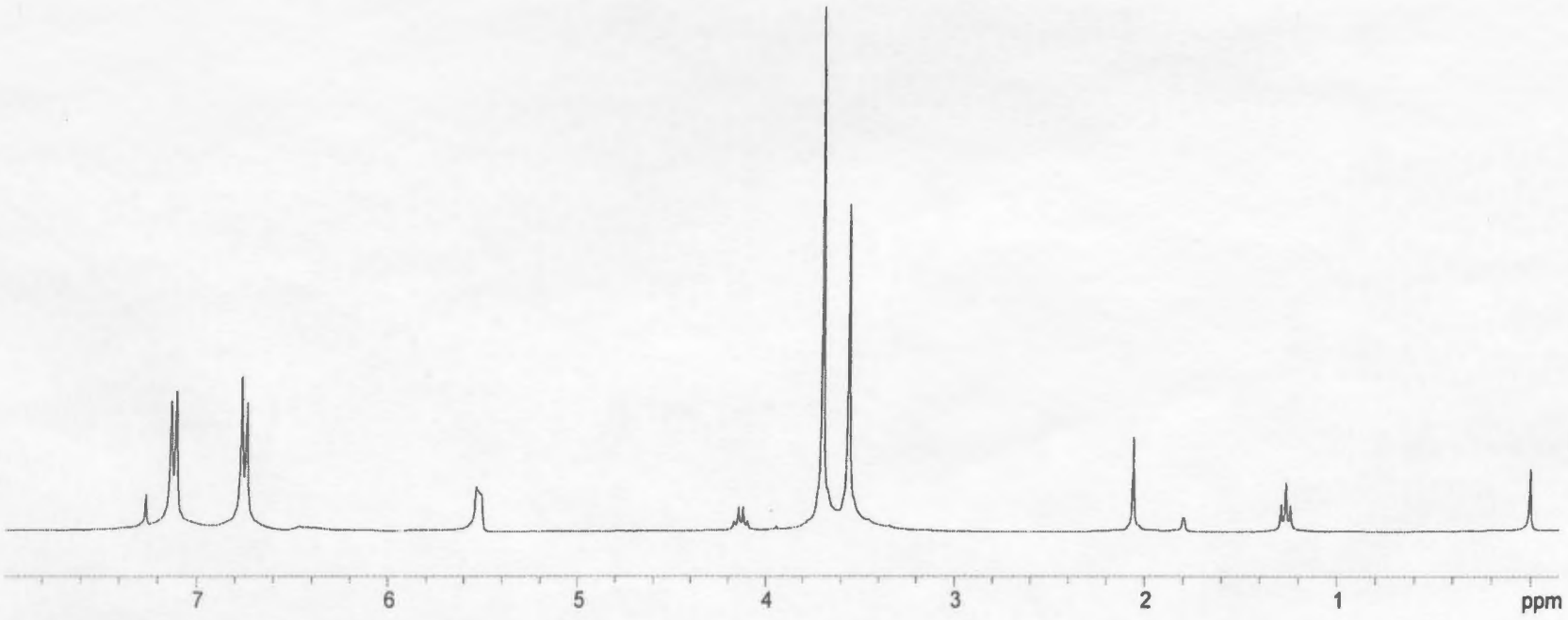

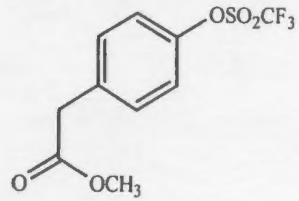

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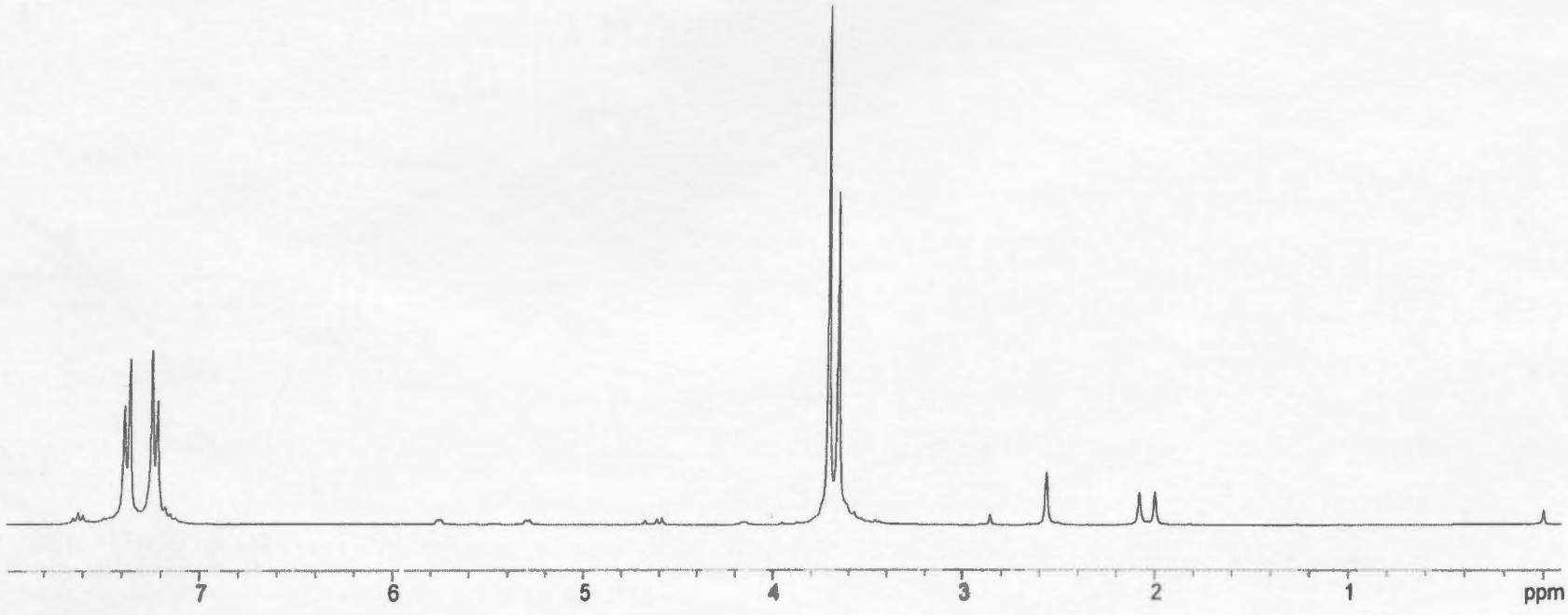

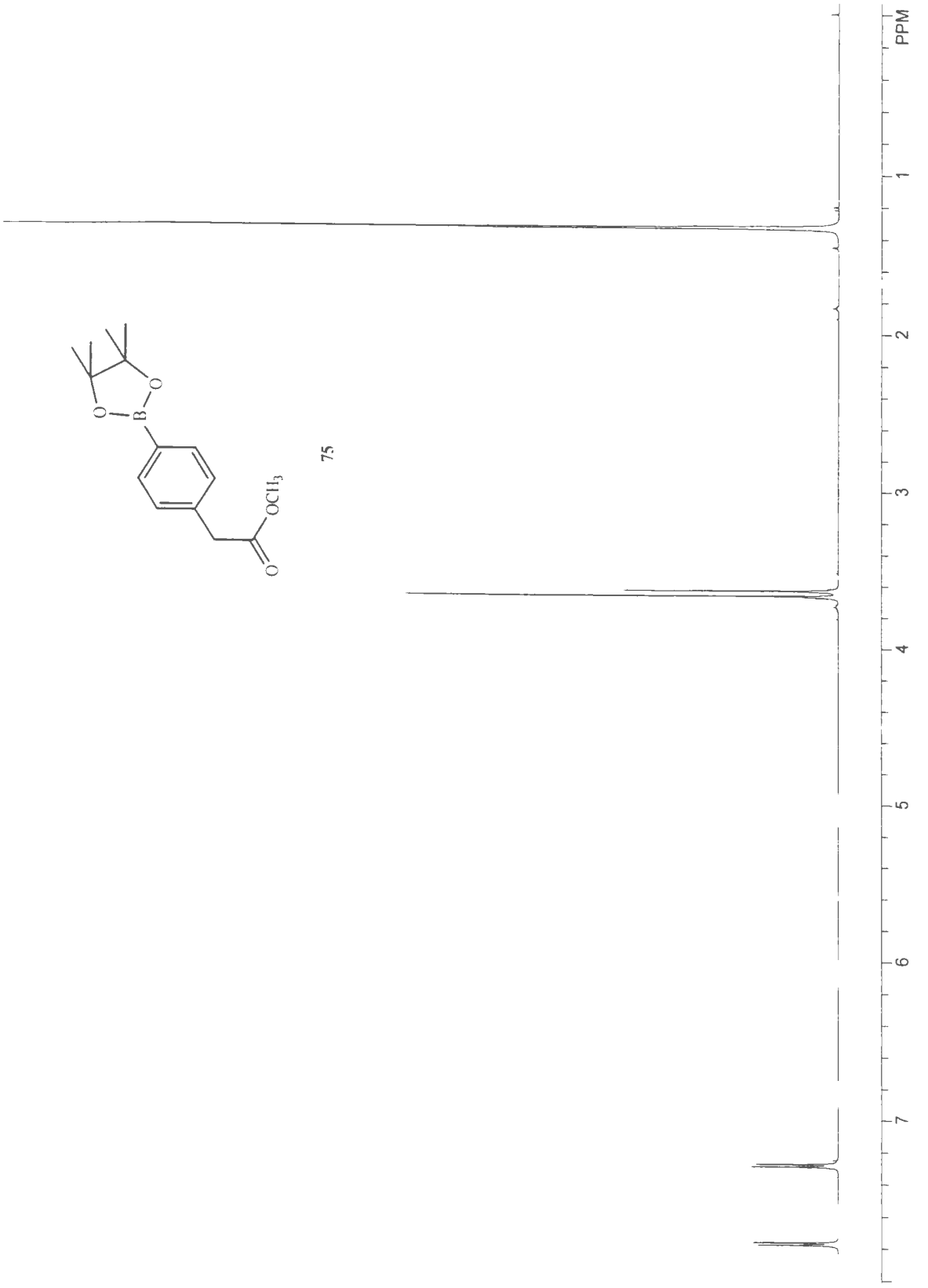

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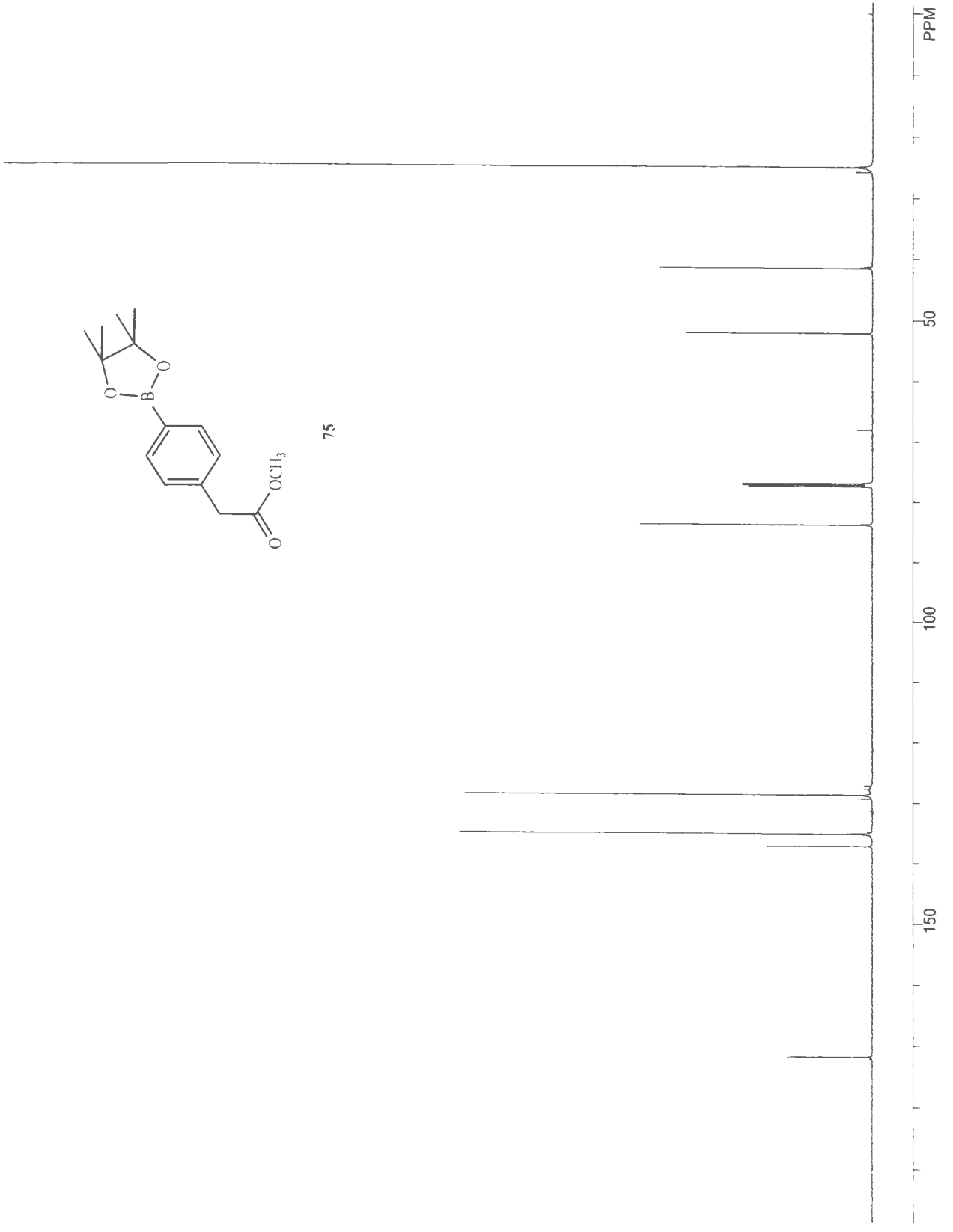
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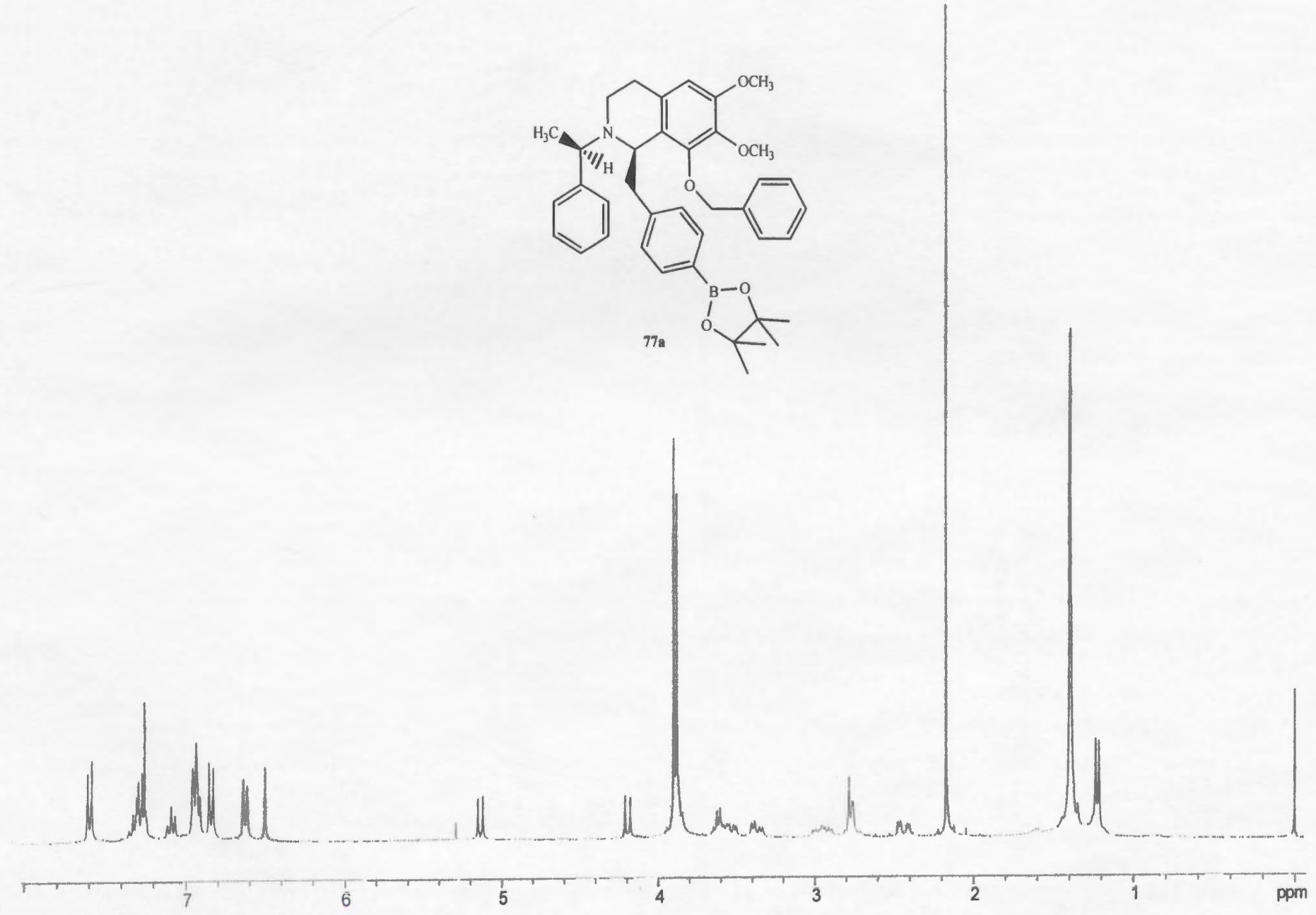
PPM
150
100
50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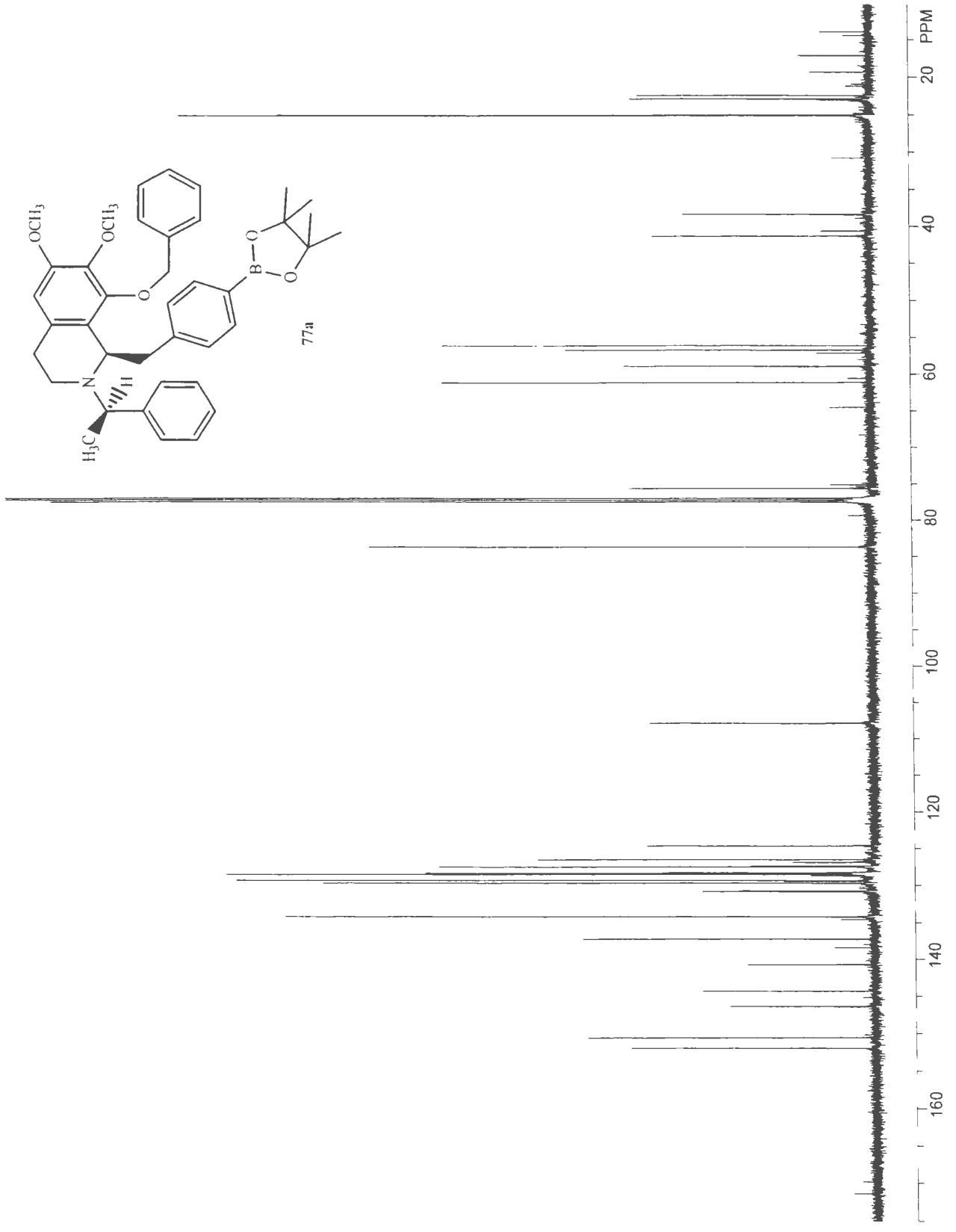
B
O
O
77a
7
6
5
4
3
2
1
ppm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PPM
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100
120
140
160

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N
H
H3C
77b
PPM
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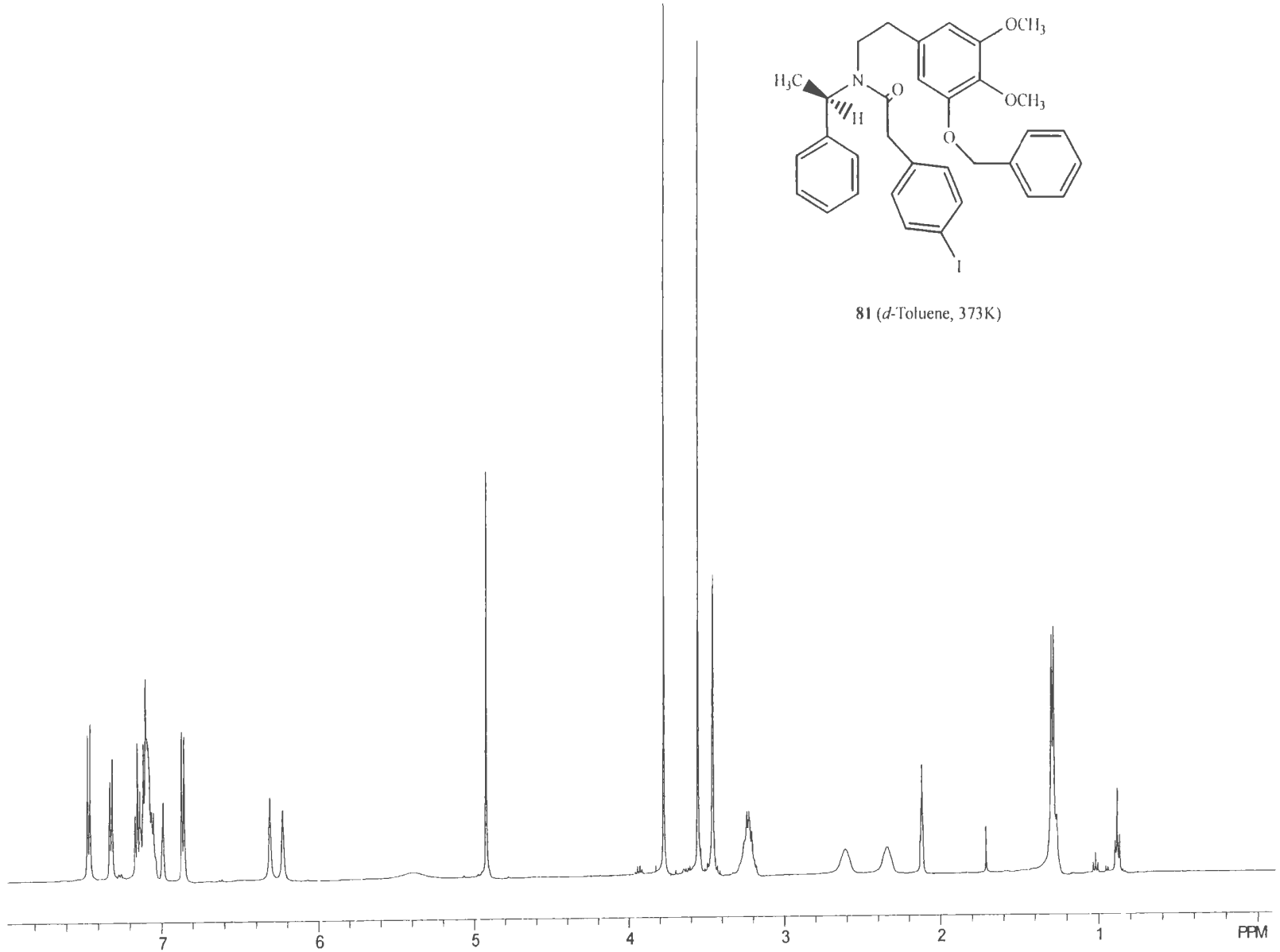
4
5
6
7



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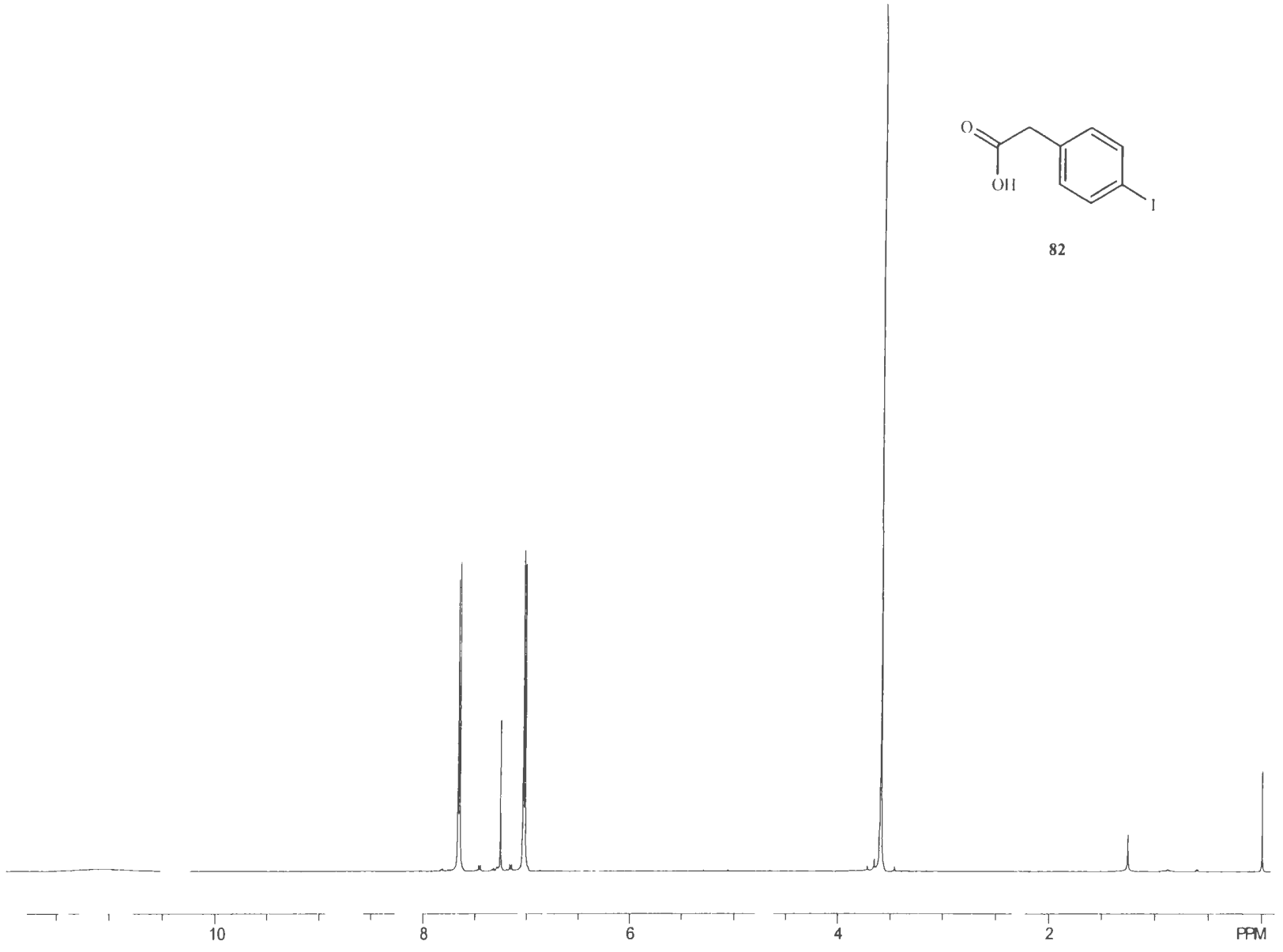
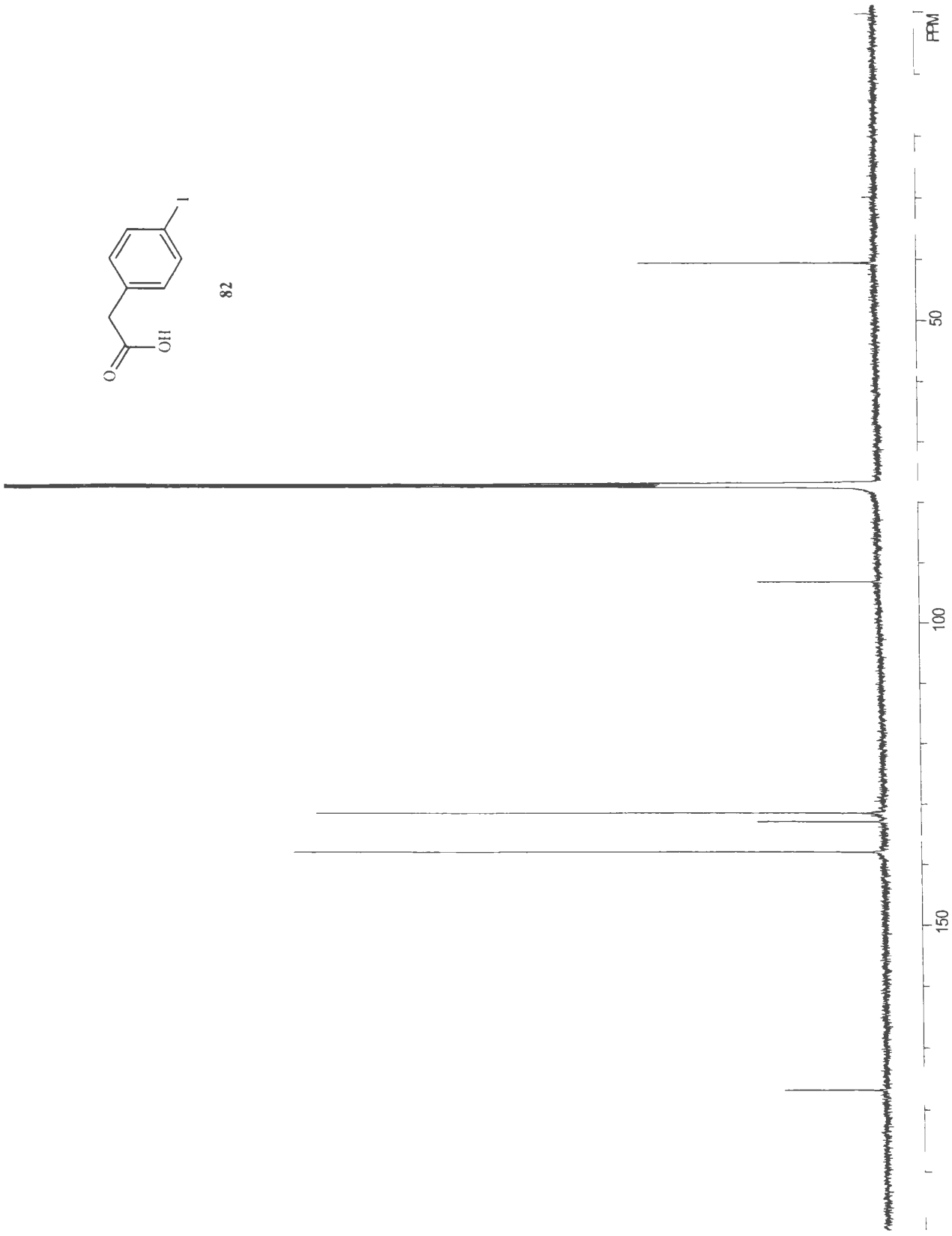


82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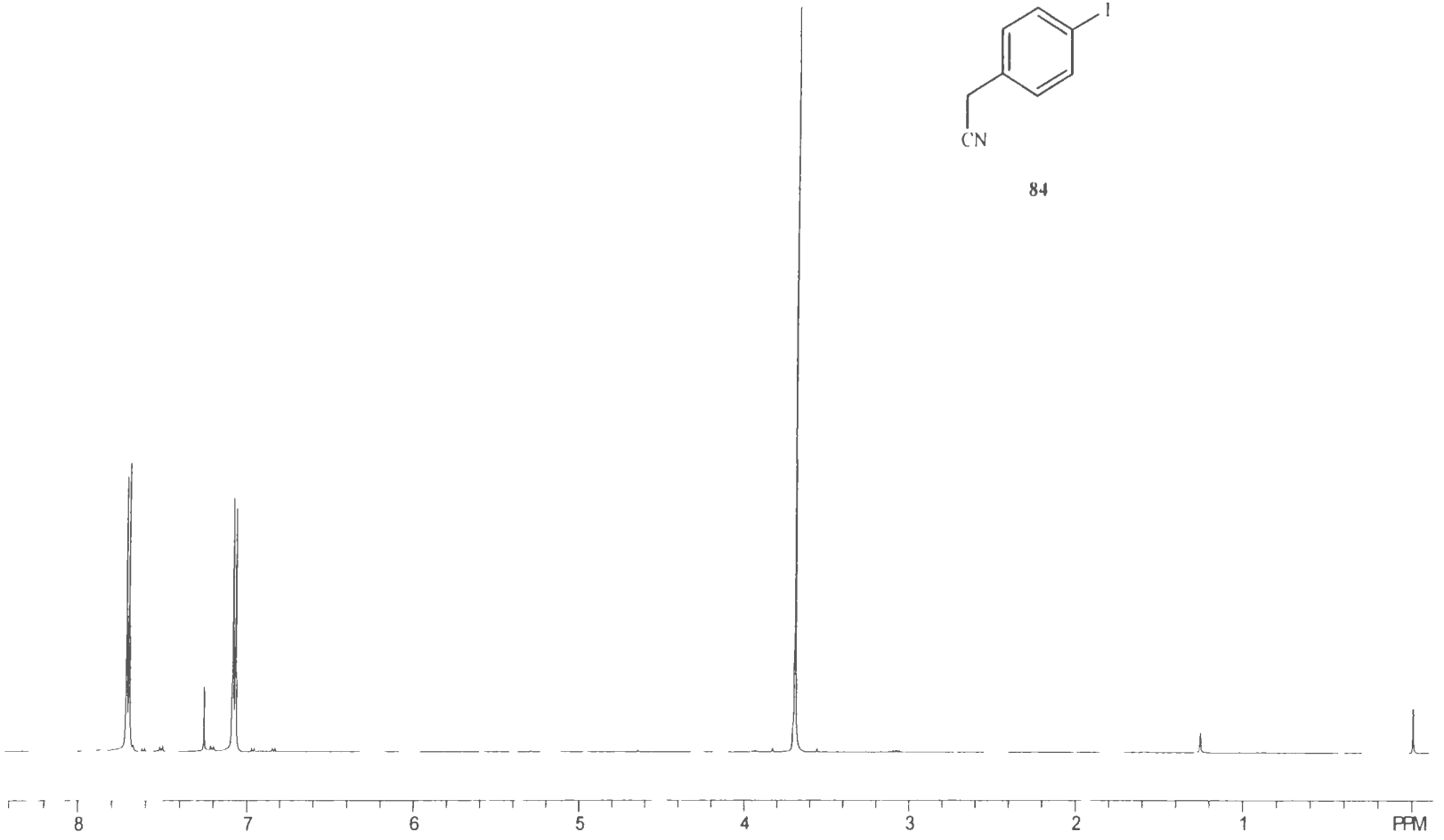
OH
O
82
PPM
50
100
150



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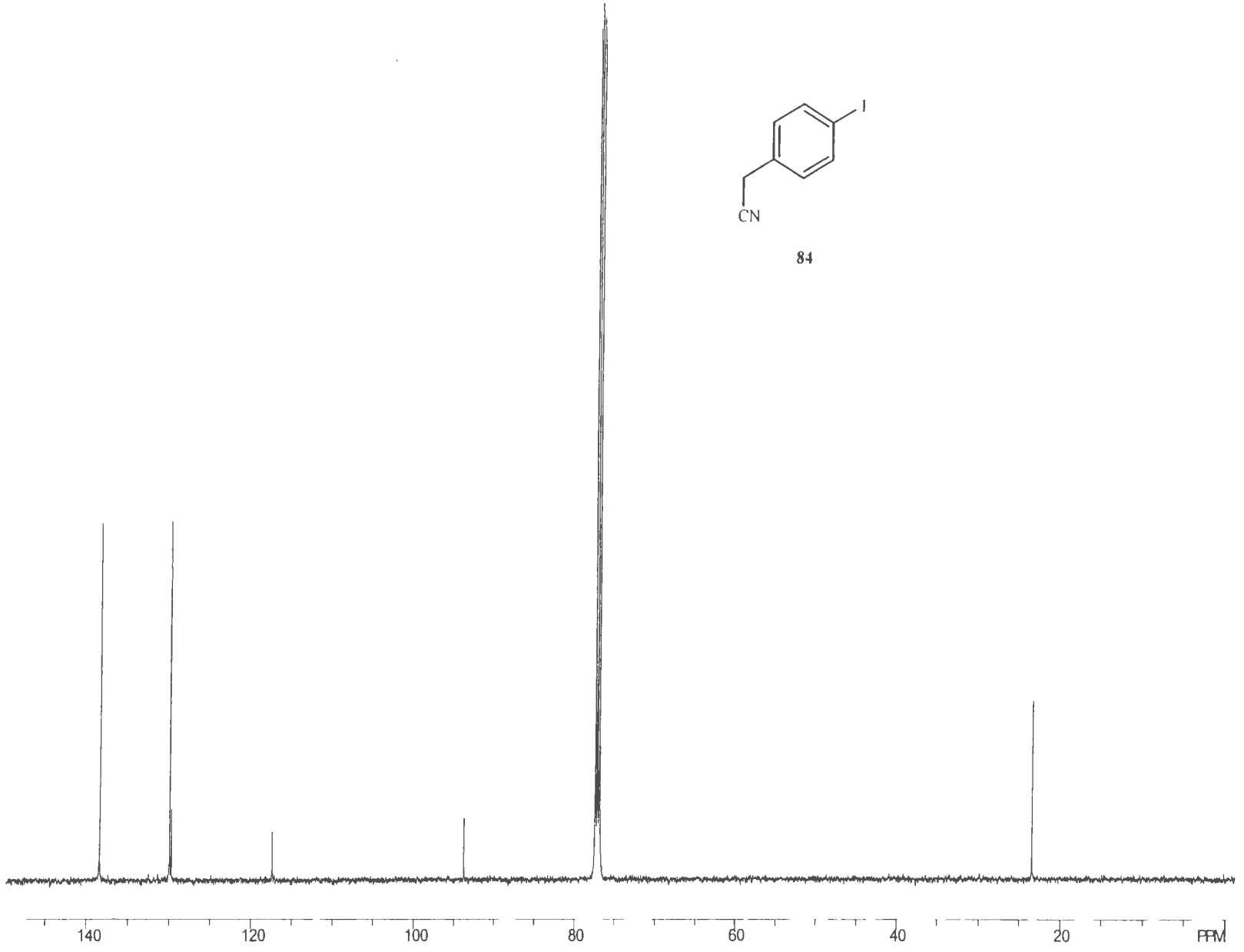

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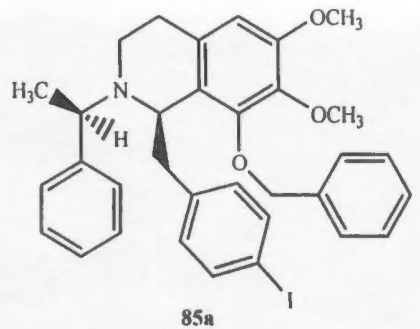
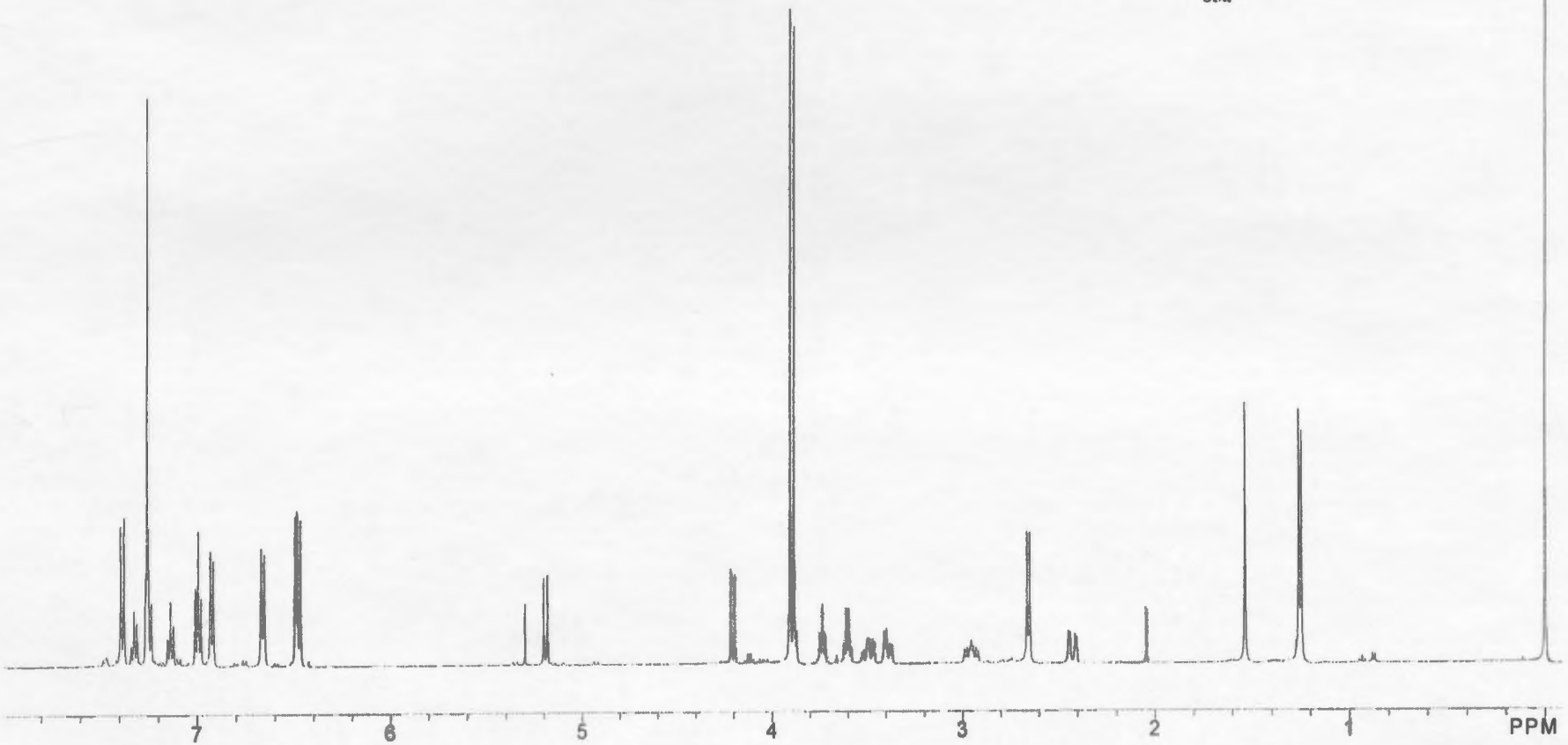
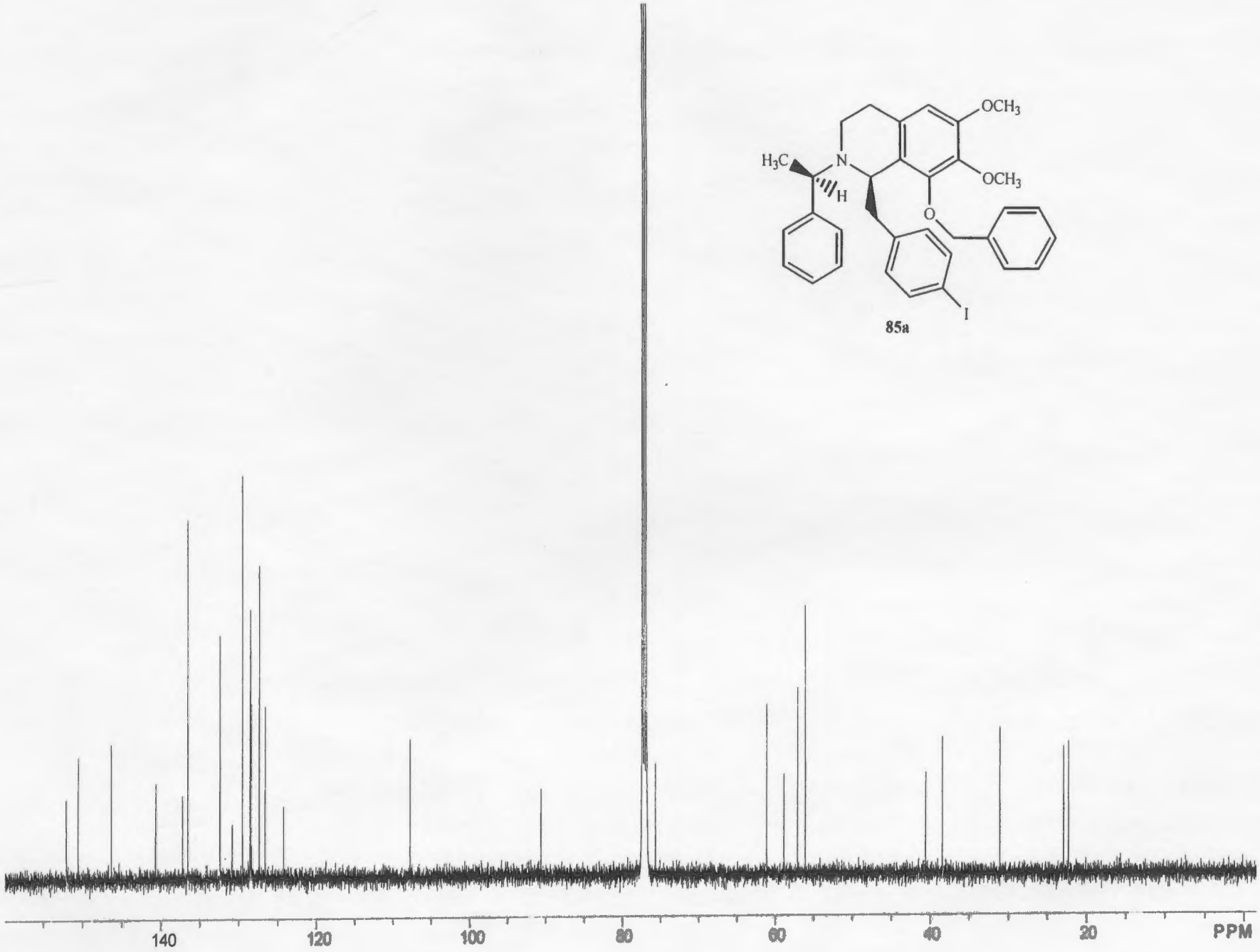


85a





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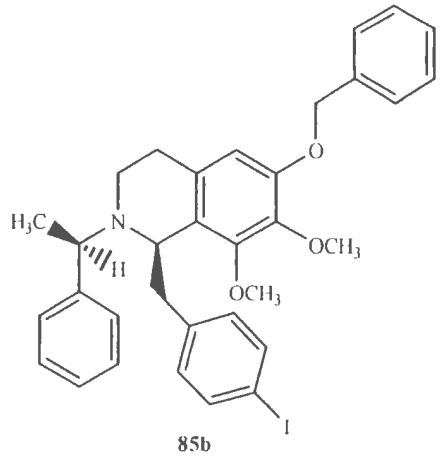

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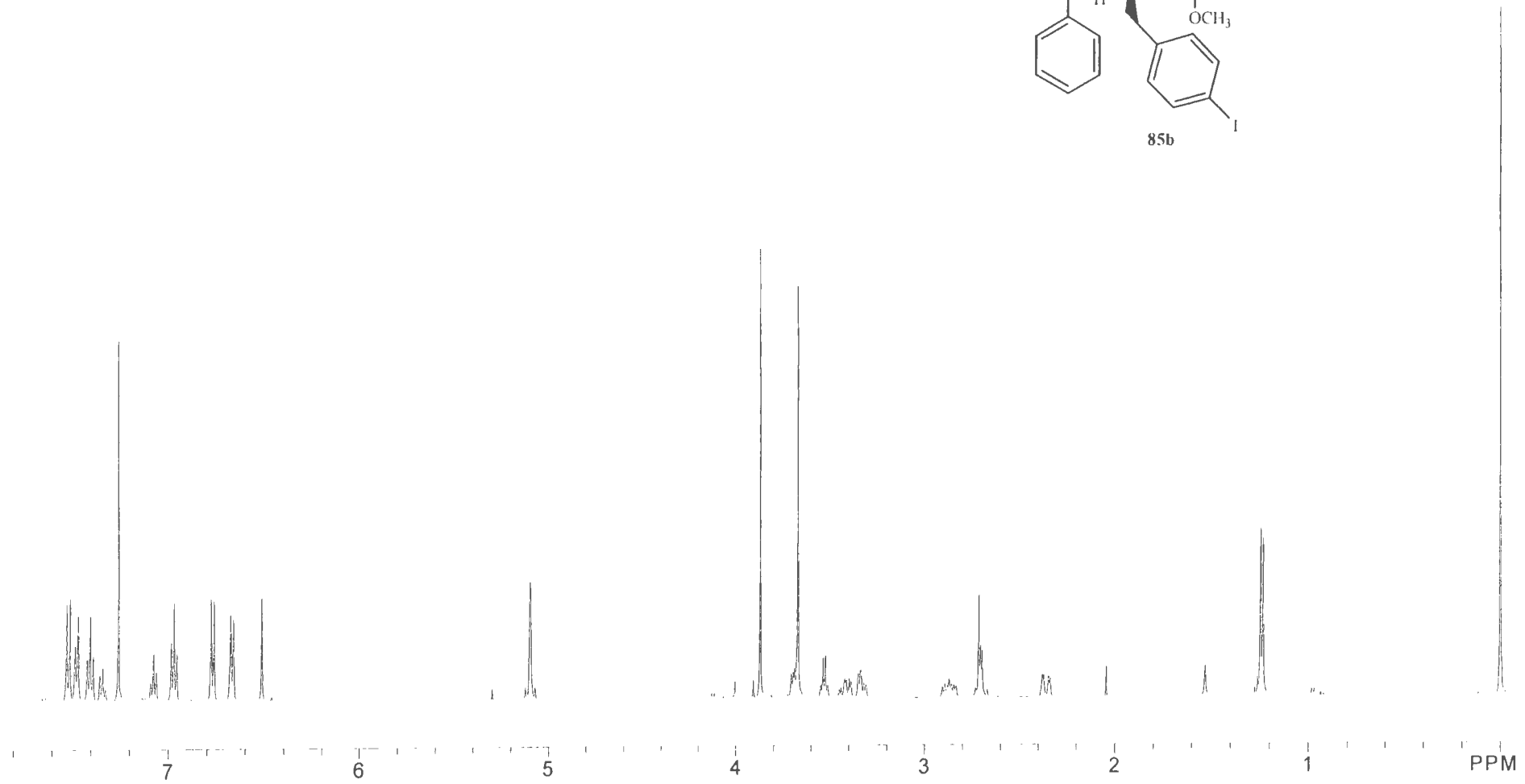

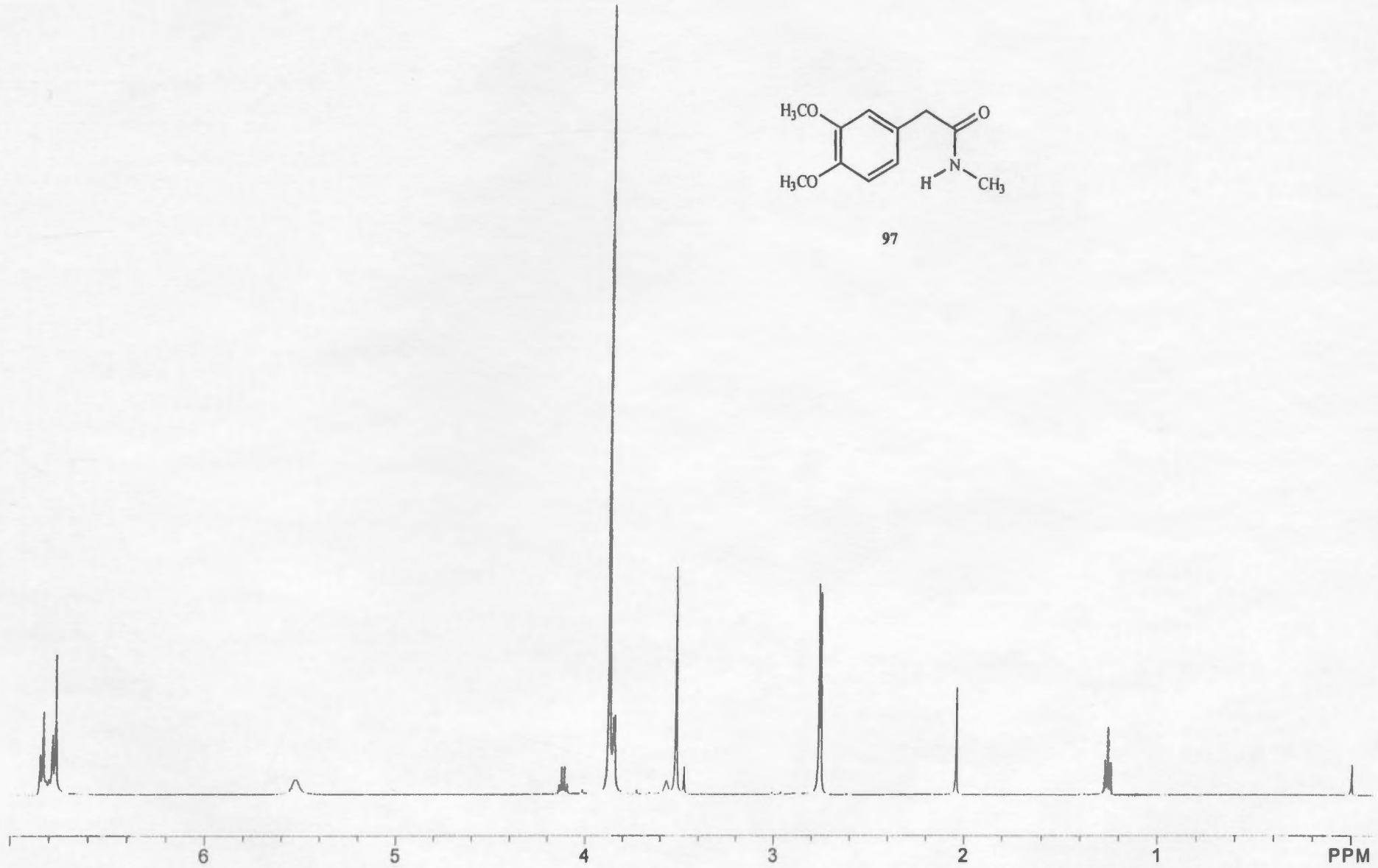

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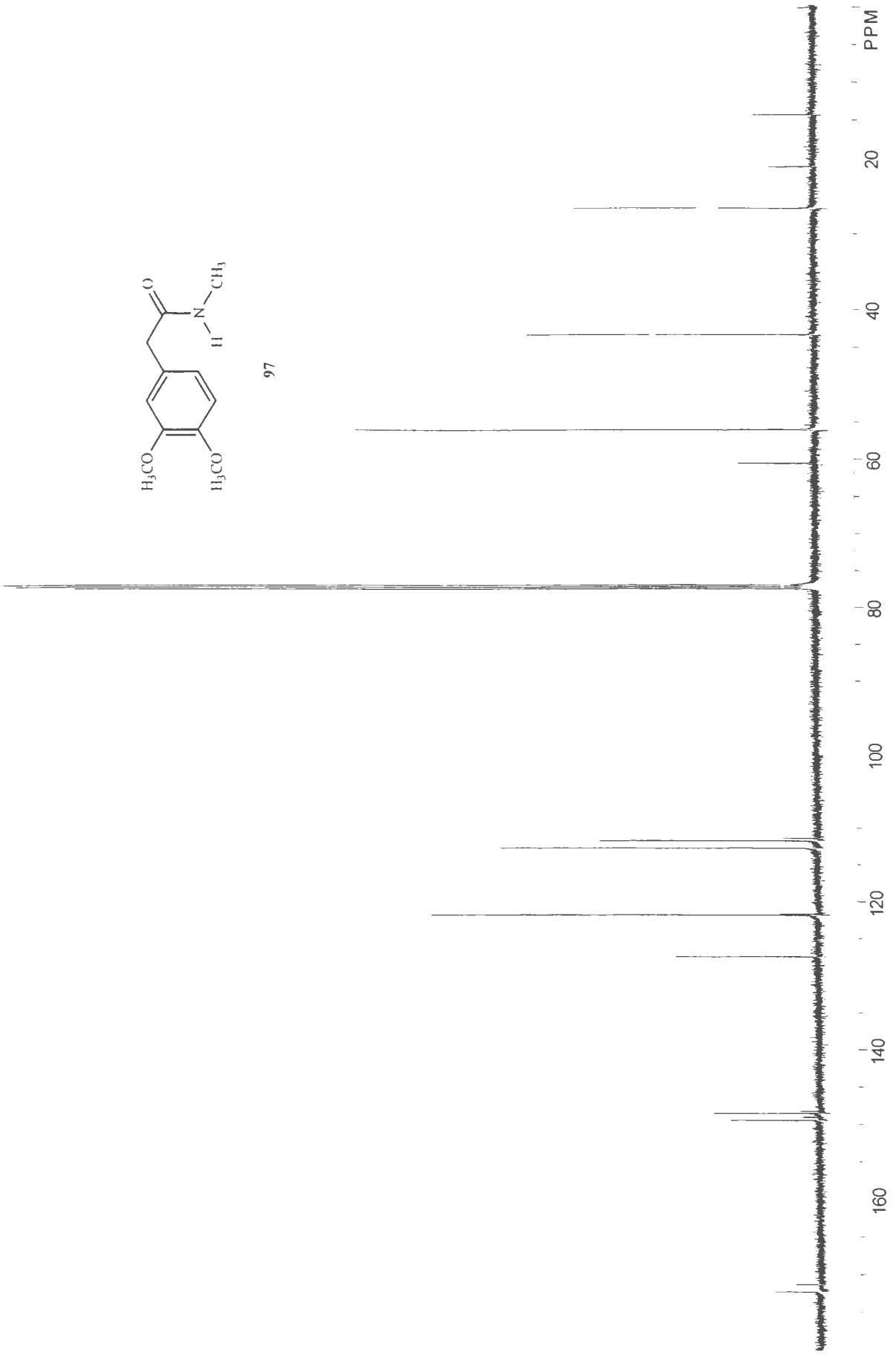
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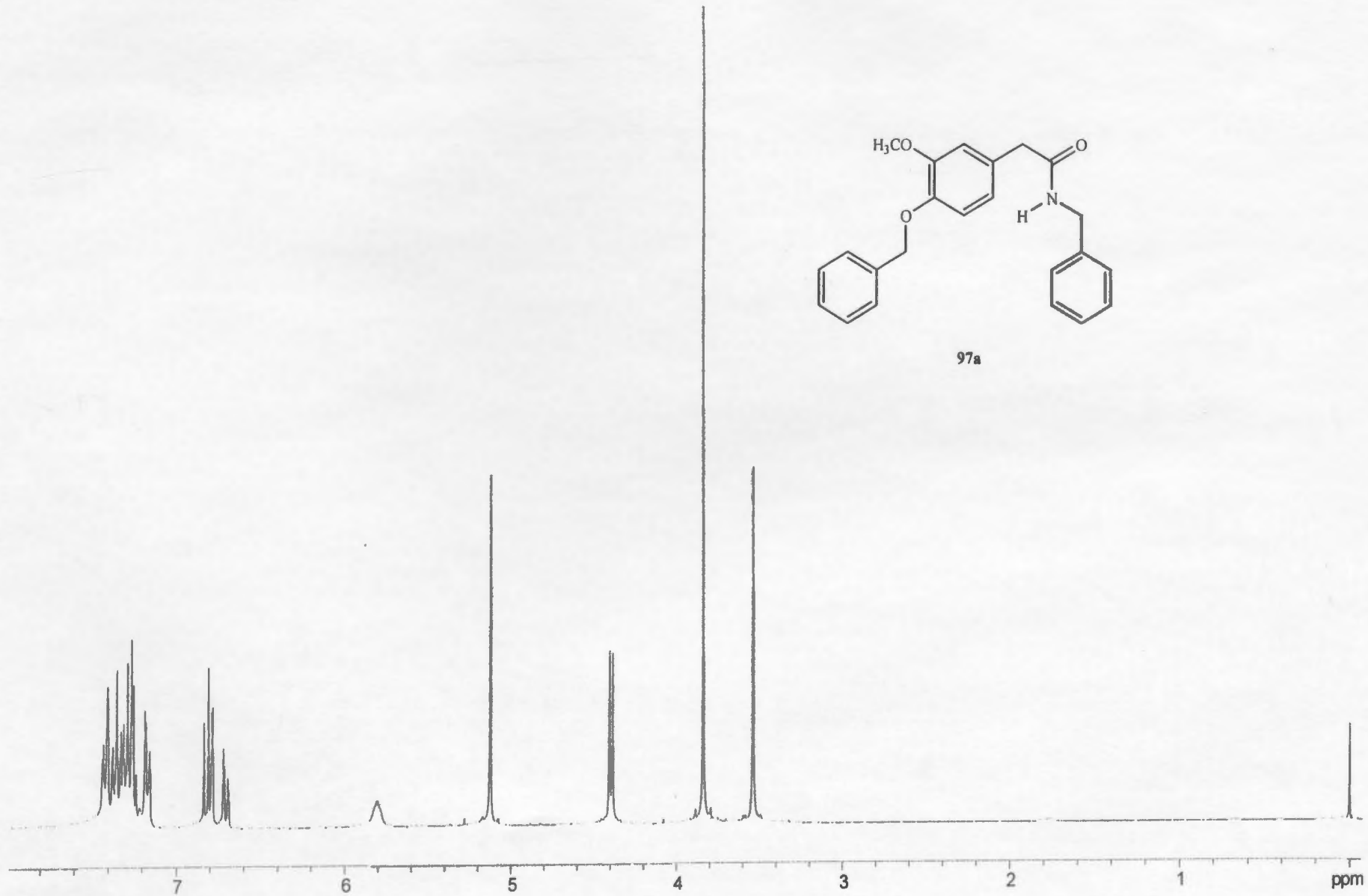

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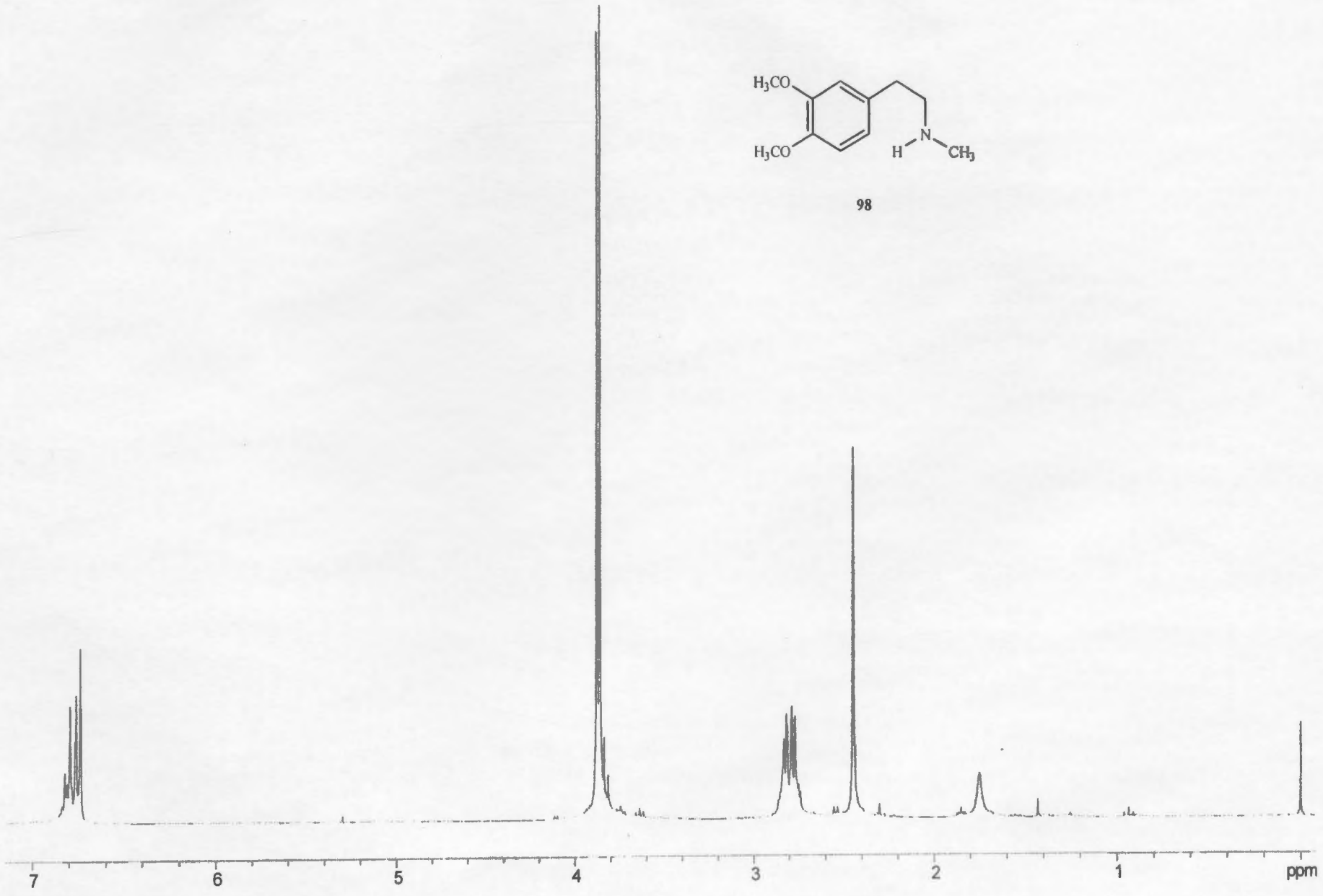

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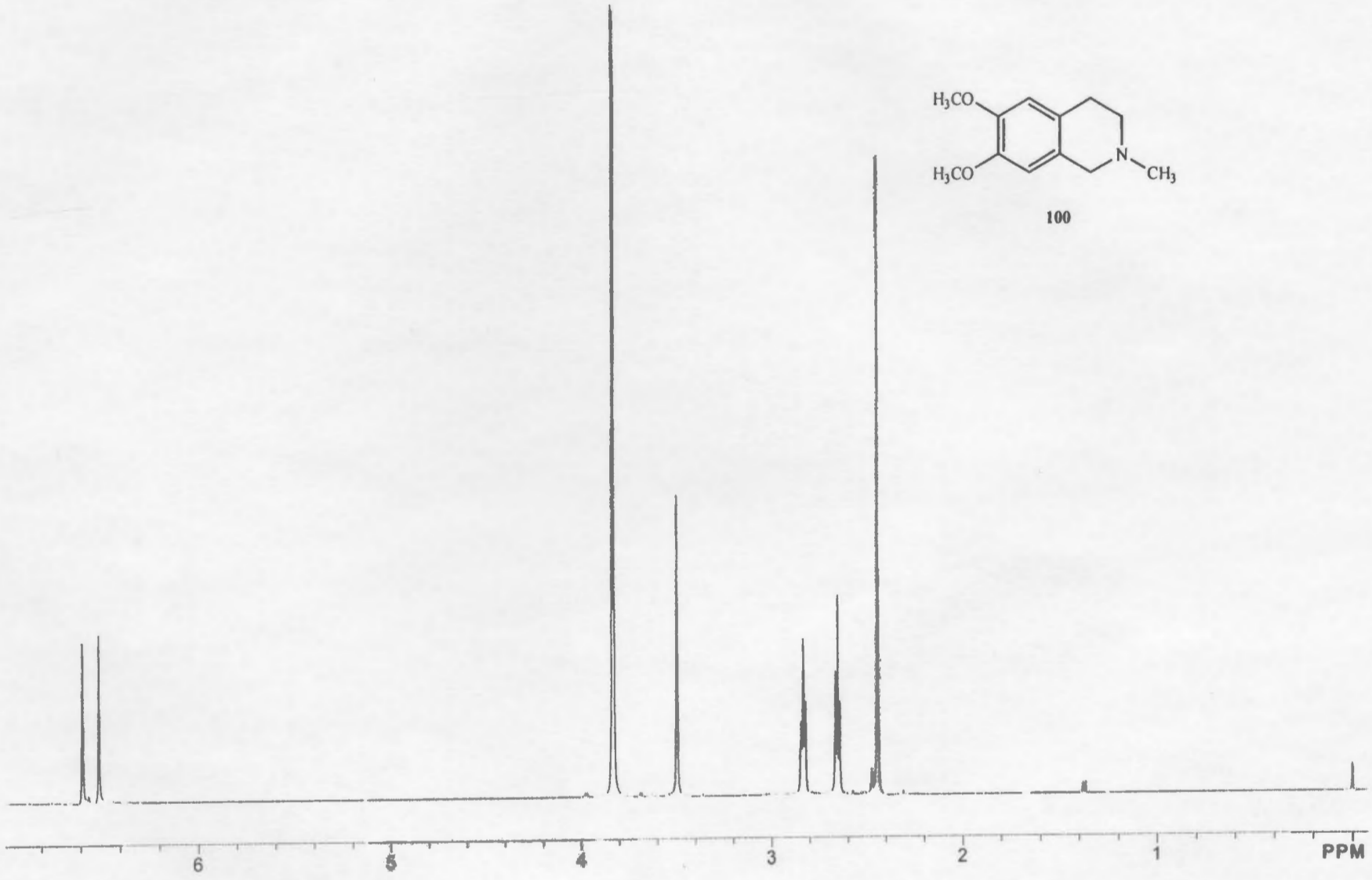

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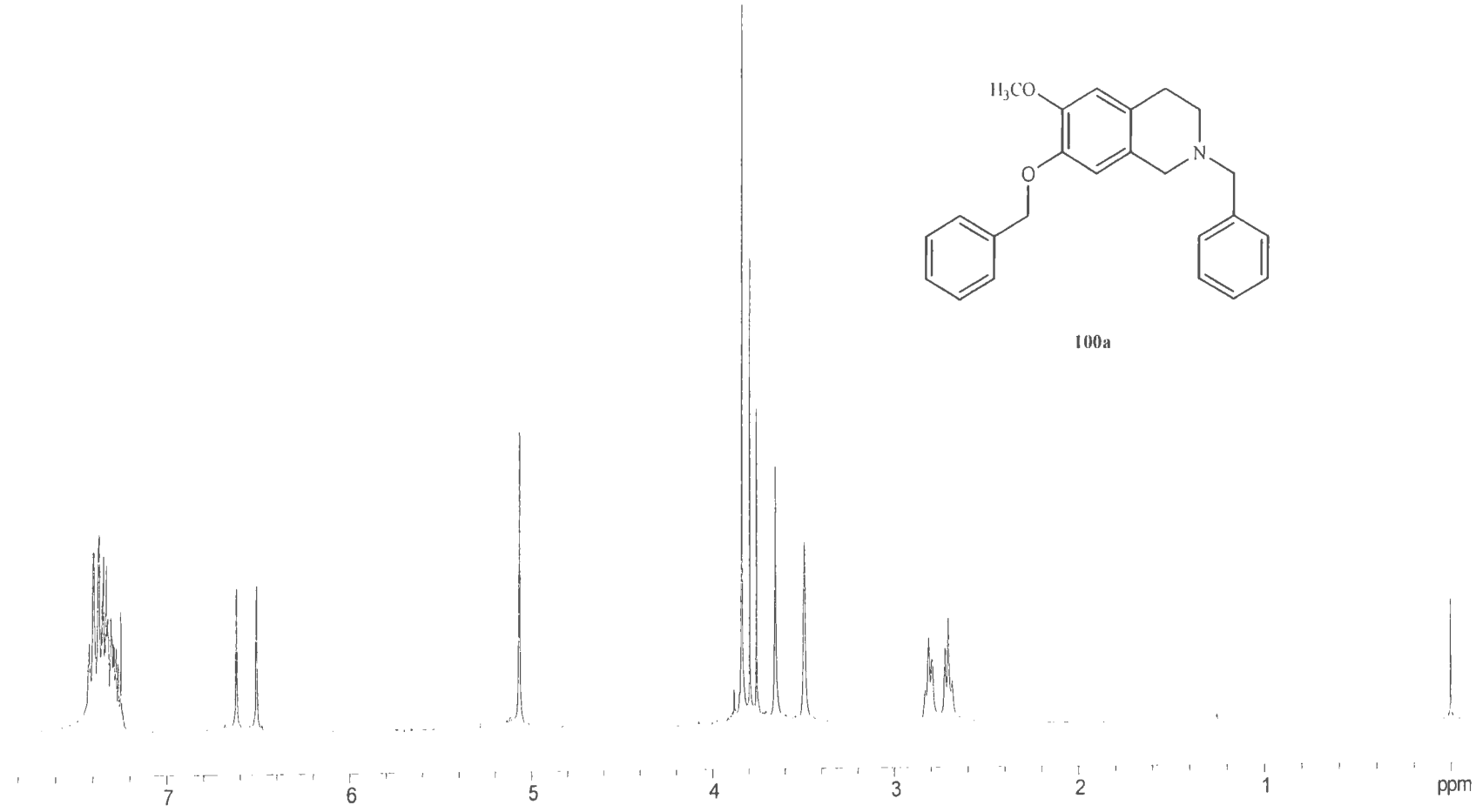

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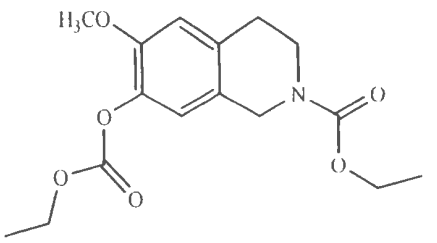

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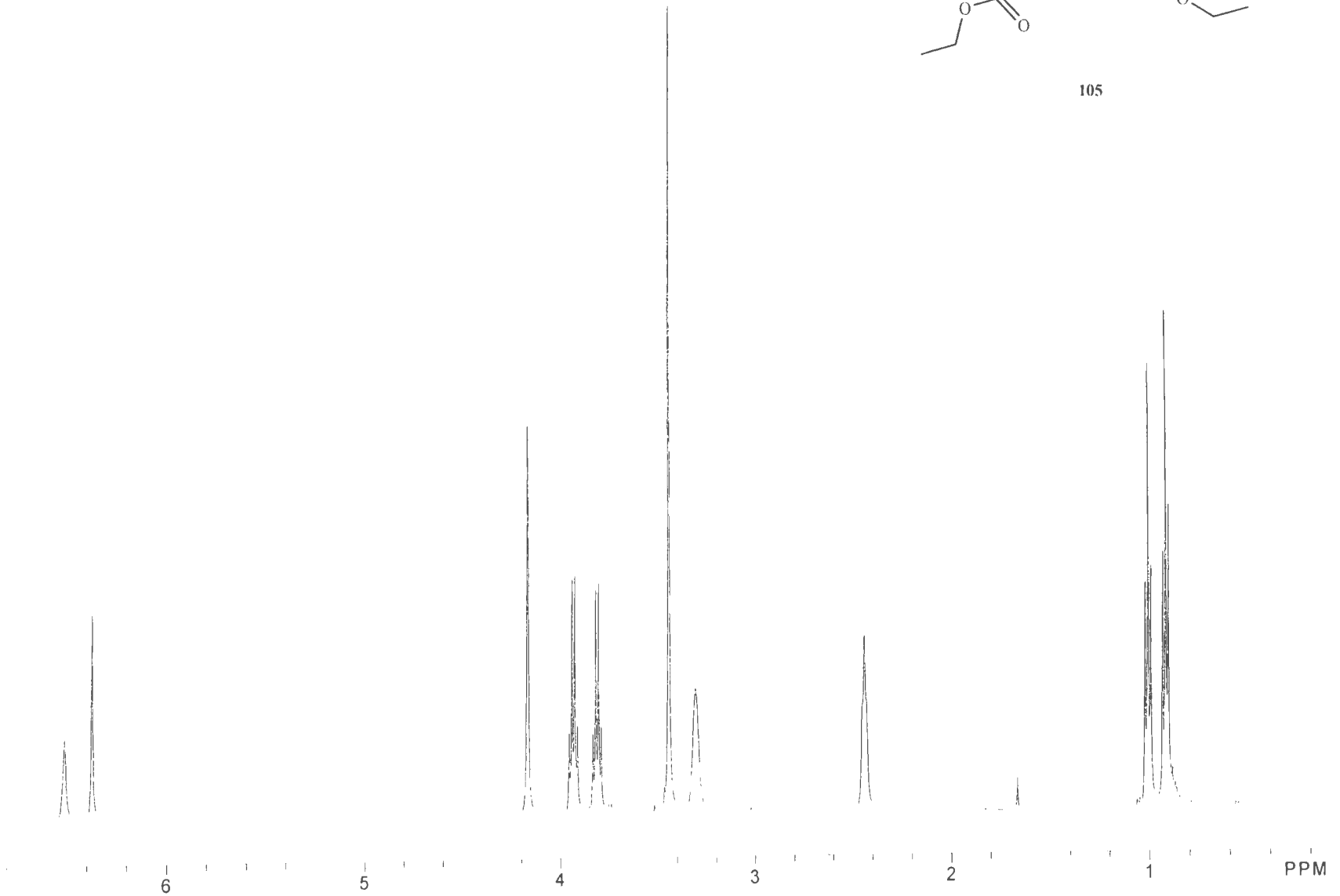

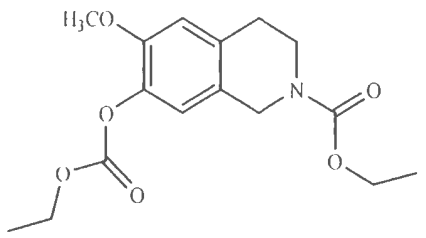

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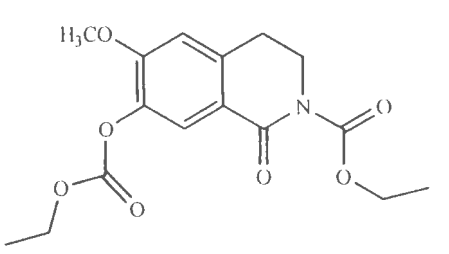

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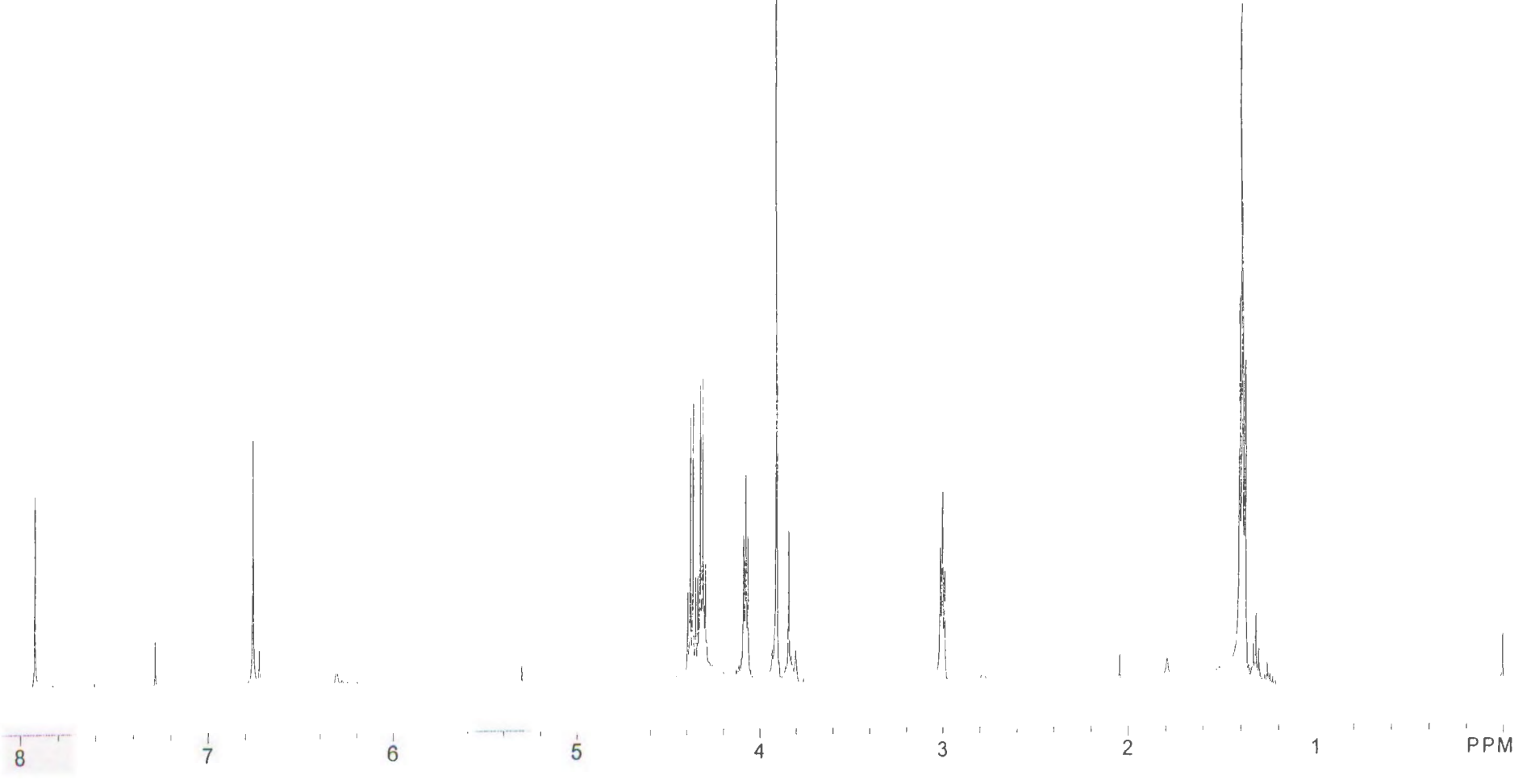

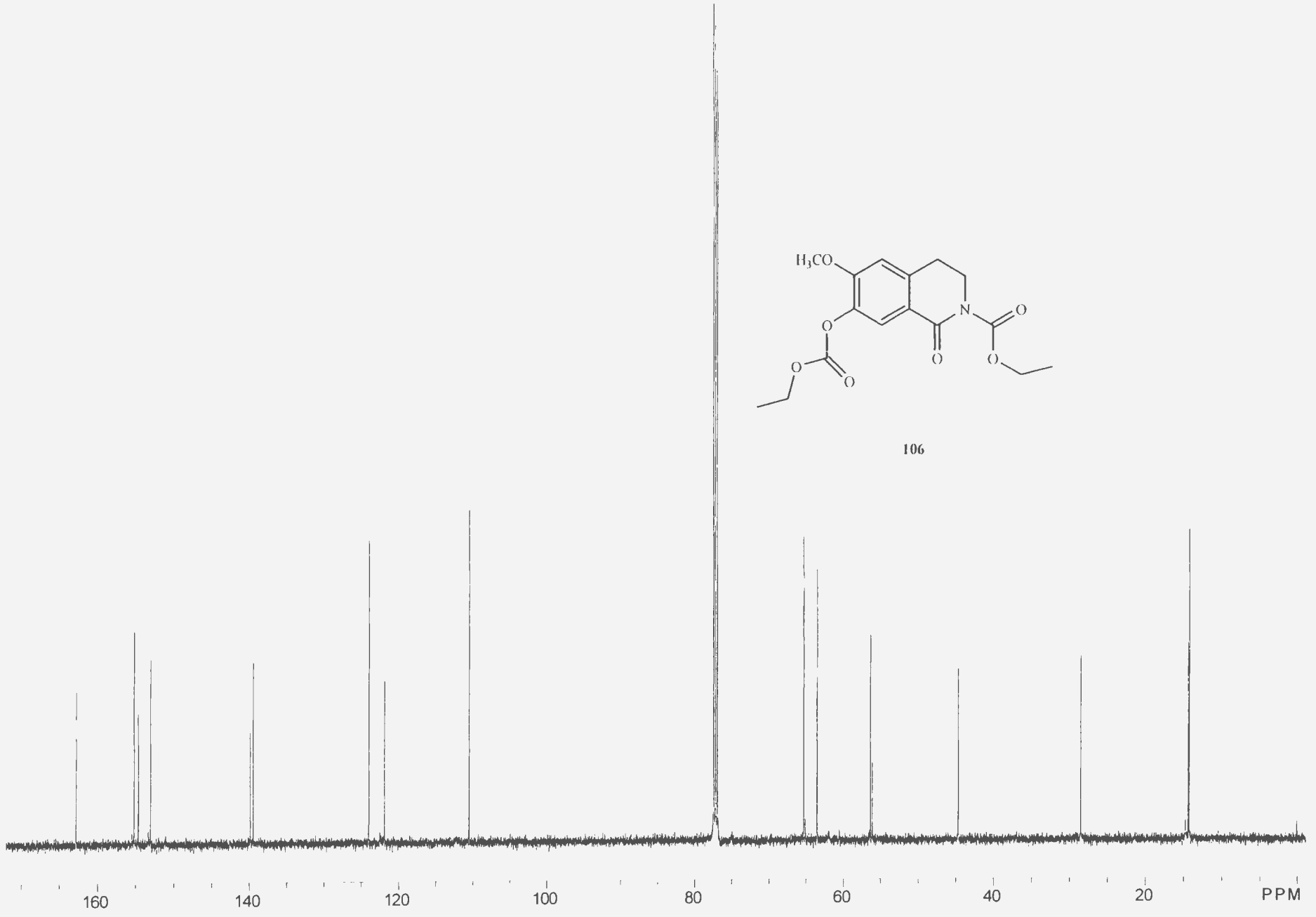

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