ATTEMPTS TOWARDS THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF (-)-CYCLEANINE AND ANTHRAX LETHAL FACTOR INHIBITORS

OTMAN DAKHIL


CENTRE FOR NFLD. STUDIES
MEMORIAL UNIVERSITY
OF NEWFOUNDLAND

Attempts Towards the Enantioselective Total Synthesis of (-)-Cycleanine and Anthrax Lethal Factor Inhibitors

by

Otman Dakhil

(B.Sc., M.Sc.) University of Garyounis,

Benghazi, Libya

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for

the degree of Doctor of Philosophy

Department of Chemistry

Memorial University of Newfoundland

St. John's, Newfoundland and Labrador, Canada

July, 2009

Dedication

To my late father Othman Dakhil

To my mother Om Alaz

To my wife Ainas Bentaher

To my children Mouhab, Dania,

Malak and Malk

Abstract

(-)-Cycleanine is a bisbenzyltetrahydroisoquinoline (BBIQ) member of the large family of tetrahydroisoquinoline (IQ) alkaloids. The aim of the present work is the total synthesis of (-)-cycleanine via a strategy of using differential and selectively protected of gallic acid as the starting material. Subsequent homologation of the carboxyl group of the protected gallic acid intermediate to produce the secondary amine, followed by a Schotten-Baumann reaction and the Bischler-Napieralski cyclization to produce the desired intermediate. The presence of the chosen chiral auxiliary assisted the formation of the desired distereoisomers. Crystals of the key intermediates to the diaryl ether coupling step were collected and the absolute configurations were confirmed based on the X-ray data. Strategies involving the use of a S_NAr reaction and Ullmann reactions on this intermediate were used to form the diaryl ether linkage to produce cycleanine.

Anthrax is an acute transferable disease caused by *Bacillus anthracis, and* the disease is highly lethal in some forms. The design of appropriate anti-toxins to assist in the treatment of the infection in the advanced stages is desirable. A recent study that showed 5-hydroxydopamine derivatives were noncompetitive inhibitors of anthrax lethal factor (LF) encouraged our interest in discovering more potent LF inhibitors that posse a similar polyphenolic design. These studies led us to consider the use of some of the intermediates obtained in the course of the attempts towards the enantioselective synthesis of (-)-cycleanine and of other

BBIQs of interest, for the enantioselective synthesis of some analogues of those LF inhibitors. Precursors for the final targets were prepared and these endeavors are reported in this thesis.

Acknowledgments

I would like to express my deep sense of gratitude, sincerest appreciation and indebtedness to my supervisor Professor Paris E. Georghiou who gave me the chance to work with him and for his constant instruction, assistance, encouragement, inspiration and guidance throughout the period of the research work.

I also thank my supervisory committee members Professor R. W. Davis and Professor D. W. Thompson for their guidance and suggestions. Also, I would like to show my gratitude to Ms. L. Winsor, and Ms. J. Collins for MS spectra and X-ray data.

Much gratitude is also extended to Professor G. Bodwell, Professor S. V. Pansare, Professor Y. Zhao, the entire organic group and the staff in the Chemistry department Ms. M. Flinn and Ms. V. Martin for their enthusiastic and generous help.

I would like to thank my family in Canada, Ainas, Mouhab, Dania, Malak and Malk, and those in Libya for their support and encouragement.

My appreciation is also extended to the Libyan government for the scholarship and to the Libyan embassy staff in Ottawa for their assistance.

Memorial University and the Natural Sciences and Engineering Research Council of Canada (NSERC) are also gratefully appreciated.

Last but not least I am not going to forget my friends who offered me a helping hand throughout my working time, to all of them I express my sincere gratitude.

Table of contents

CHAPTER 1

Total Synthesis of Bisbenzyltetrahydroisoquinoline Alkaloids

CHAPTER 4

Attempts towards the total synthesis of bisbenzyltetrahydroisoquinoline Anthrax lethal Factor Inhibitors

pages

List of Tables

pages

List of Schemes

List of Symbols, Abbreviations and Acronyms

Å	Angstrom units
Aq.	aqueous
APCI-MS	atmospheric pressure chemical ionization mass spectrometry
BBIQ	bisbenzyltetrahydroisoquinolines
BIQ	benzyltetrahydroisoquinolines
Bn	benzyl
BNC	Bischler-Napieralski cyclization
br	broad (in NMR)
CA	Chiral auxiliary
DCC	dicyclohexylcarbodiimide
δ	chemical shift in ppm downfield from tetramethylsilane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Et	ethyl
h	hour
Hz	hertz
J	coupling constant (Hz)
m	multiplet (in NMR)
M^+	molecular ion
Me	methyl
mol equiv	molar equivalent

m.p.	melting point
ms	mass spectrometry
MW	microwave
NBS	N-bromosuccinimiide
NMR	nuclear magnetic resonance
p	*para*
PG	protecting group
Ph	phenyl
PLC	preparative layer chromatography
ppm	parts per million
PSC	Pictet-Spengler cyclization
q	quartet (in NMR)
rt	room temperature
s	singlet (in NMR)
t	triplet (in NMR)
TBDMS	*tert*-butyldimethylsilyl
tert	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMHD	2,2,6,6-tetramethylheptane-3,5-dione
TMS	tetramethysilane (in NMR)

Chapter 1

Introduction

1.1 Definition and classification of alkaloids.

1.1.1 Alkaloids.

Meissner[1] was the first to propose the term 'alkaloids' in 1819. He wrote:

*"To me it seems wholly appropriate to refer to those plant substances currently known not by the name alkalis, **but alkaloids**, since in some of their properties they differ from alkalis considerably, and would thus find their place before the plant acids in the field of plant chemistry."*

The word alkaloid is made up of two words 'alkali', from the Arabic word for 'plant ashes', namely, *"al-qualja" and* '*ειδος*', the Greek word meaning 'similarity'. Thus, alkaloids are naturally-occurring substances with alkali-like characteristics. There are, of course, many other definitions for alkaloids. For example, in 1896, Guareschi[2] wrote the following definition:

"The term 'alkaloids' is applicable to all basic, organic compounds whether obtained either from animal or plant material, or prepared artificially; that is, the expression 'alkaloids' is synonymous with 'organic base' or 'organic alkali'.

Stoll,[3] in 1953, proposed the following shorter definition:

"Nitrogen-containing bases of vegetable origin were grouped together under the label 'alkaloids".

Finally, in his book *"Alkaloids: Nature's Curse or Blessing"* Hesse[4] has collected many of the definitions of alkaloids and summarized them in the following single definition:

> *"Alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character."*

1.1.2 Classification of alkaloids.

In Hesse's excellent recent book[4] on alkaloids, a useful approach to classifying these compounds is outlined and will, in essence, be employed herein. Since a very large number of alkaloids exists, roughly estimated to be in the order of 10,000 compounds isolated and characterized so far, it is difficult to categorize them into specific groups. This difficulty comes about from the broad structural variation which is present in the alkaloids. In order to manage so many different compounds, therefore, it is essential to perform some form of sub-classification.

The standards used for alkaloid classification are: biogenesis, structural relationship, biological origin, and spectroscopic/spectrometric properties. According to those standards, alkaloids are classified into five main classes (see sections 1.1.2.1 to 1.1.2.5). These five classes are further classified into other sub-groups. There are examples for each of the major five classes shown in Figure 1.1.

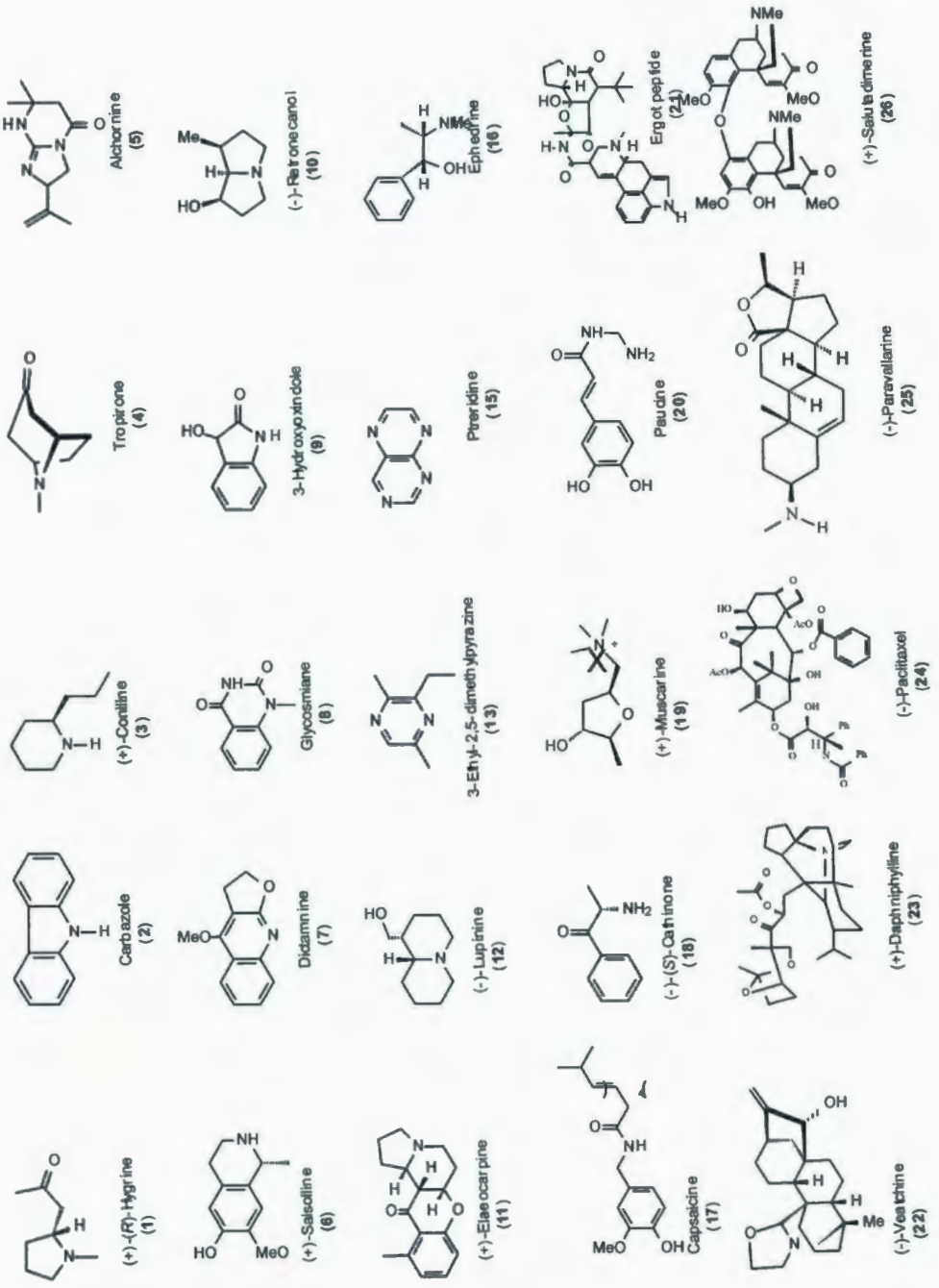


Figure 1.1. Some selected examples of alkaloids.

1.1.2.1 Heterocyclic alkaloids.

The class of heterocyclic alkaloids includes the following examples:

a. Pyrrolidine alkaloids *e.g.* (+)-(*R*)–Hygrine (**1**)

b. Indole alkaloids *e.g.* Carbazole (**2**)

c. Piperidine alkaloids *e.g.* (+)-Coniine (**3**)

d. Tropanes and related bases *e.g.* (+)-Tropinone (**4**)

e. Histamine, imidazole, and guanidine alkaloids *e.g.* Alchornine (**5**)

f. Isoquinoline alkaloids *e.g.* (+)-Salsoline (**6**)

g. Quinoline alkaloids *e.g.* Dictamnine (**7**)

h. Quinazoline alkaloids *e.g.* Glycosmicine (**8**)

i. Benzoxazines and Benzoxazoles *e.g.* 3-Hydroxyoxindole (**9**)

j. Pyrrolizidine alkaloids *e.g.* (-)-Retronecanol (**10**)

k. Indolizidine alkaloids *e.g.* (+)-Elaeocarpine (**11**)

l. Quinolizidine alkaloids *e.g.* (-)-Lupinine (**12**)

m. Pyrazine alkaloids *e.g.* 3-Ethyl-2,5-dimethylpyrazine (**13**)

n. Purine Bases *e.g.* Adenine (**14**)

o. Pteridines *e.g.* Pteridine (**15**)

1.1.2.2 Alkaloids having exocyclic nitrogen atoms.

This class of alkaloids includes the following examples:

a. Phenylalkylamine derivatives *e.g.* (-)-Ephedrine (**16**)

b. Benzylamine- type alkaloids *e.g.* Capsaicine (**17**)

c. Khat *e.g.* (-)-(*S*)-Cathinone (**18**)

d. Muscarines *e.g.* (+)-Muscarine (**19**)

1.1.2.3 Putrescine, Spermidine, and Spermine alkaloids.

An example of this class is Paucine (**20**).

1.1.2.4 Peptide alkaloids.

An example of this class is the ergot peptide alkaloid **21**.

1.1.2.5 Terpene and Steroid alkaloids.

This class of alkaloids includes:

a. Diterpenes *e.g.* (-)-Veatchine (**22**).

b. Daphniphyllum alkaloids *e.g.* (+)-Daphniphylline (**23**)

c. Taxus alkaloids *e.g.* (-)-Paclitaxel (**24**).

d. Steroid alkaloids *e.g.* (-)-Paravallarine (**25**).

1.1.2.6 Dimeric alkaloids.

An example of this class is (+)-Salutadimerine (**26**).

1.2 Definition and classification of BBIQ alkaloids.

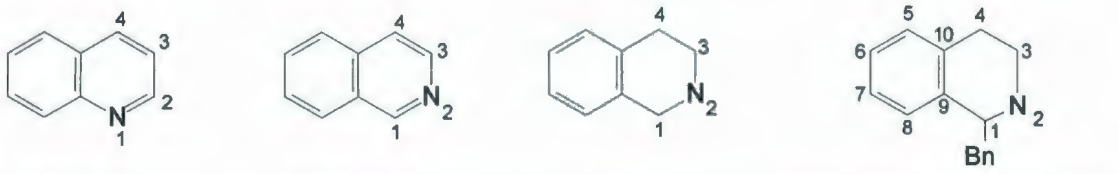


Figure 1.2. Derivation of the term "benzyltetrahydroisoquinoline".

As shown in Figure 1.2, the term benzyltetrahydroisoquinoline ("BIQ") is derived from the term quinoline ("**Q**") which has the nitrogen atom in position 1. Isoquinoline ("**IQ**") has the nitrogen atom at position 2. Reduction of the two double bonds of isoquinoline produces tetrahydroisoquinoline ("**THIQ**"), and finally introduction of a benzyl group to position 1 of ("**THIQ**") leads to an example of BIQ.

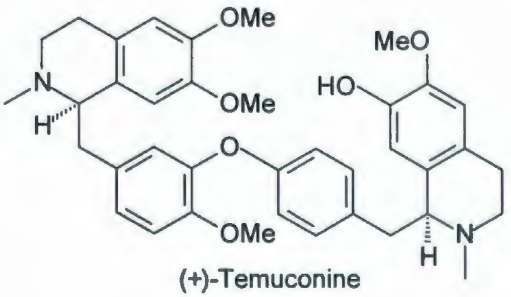
The bisbenzyltetrahydroisoquinoline (BBIQ) family of alkaloids consists of almost 200 members. Two BIQ units are linked together by ether bridges, methylenoxy bridging and/or direct carbon-carbon bonds to form BBIQ alkaloids. Guha[5] and Shamma[6] have classified them into five groups (A-E) and twenty-eight types (I-XXVII) based on four main features:

1. The nature of the bridges: when two benzyl groups link together, this is called a "*tail-to-tail*" linkage. If the link is between one isoquinoline and one benzyl group, it is called a "*head-to-tail*" linkage. However if the link is between two isoquinoline units, it is called a "*head-to-head*" linkage.

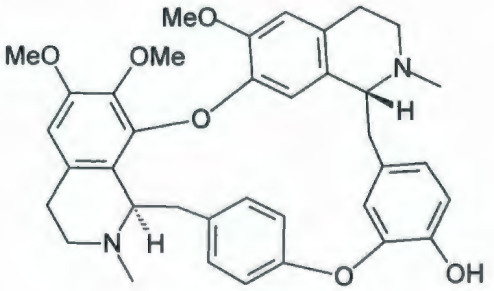
2. The number of the oxygen substituents on the aromatic rings.

3. The number of linkages between the two (BIQ) units.

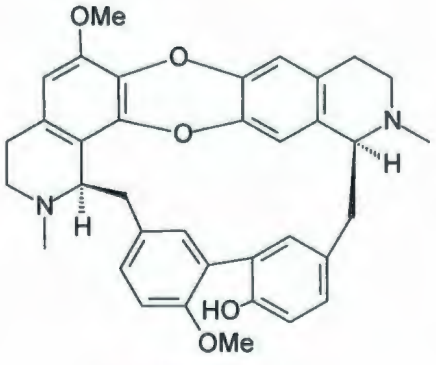
4. The sites at which the bonds exist between the two BIQ units.



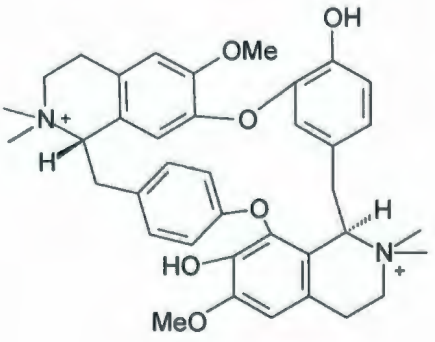
(+)-Temuconine
(27)



(+)-Oxyacanthine
(28)



(+)-Tiliacorine
(29)



(+)-Tubocurarine
(30)

Figure 1.3. Examples of BBIQ alkaloids.

Within the same group, members differ simply in: (1) the nature of the oxygenated substituents (*e.g.* OH, OMe, OCH_2O); (2) the nature of the substituents on the two nitrogen atoms (*e.g.* NH, NMe, Me_2N^+, NO); (3) the degree of unsaturation of the hetero-rings; and/or (4) the stereochemistry of the two asymmetric centers.[5] The simplest representative for BBIQ alkaloids which have a "tail-to-tail" linkage, is (+)-temuconine (**27**, Figure 1.3) which is an example of a "Type I of Group A" according to Guha and Shamma's classification system. (+)-Oxyacanthine (**28**) has both a "head-to-head" and a "tail-to-tail" linkage.

In addition to the two linkages between the two isoquinoline units, (+)-tiliacorine (**29**) has an additional carbon-carbon bond between the two benzyl groups (biphenyl linkage). A "head-to-tail" and "tail-to-head" group is represented by (+)-tubocurarine (**30**). These examples are shown in Figure 1.3.

(+)-Neothalibrine (**31**) and the degradation product **32** of (+)-antioquine (**33**) shown in Figure 1.4 are two representative examples for BBIQ alkaloids which respectively have one diaryl ether linkage and one biphenyl linkage. (+)-Antioquine (**33**), and (-)-limacine (**34**) are examples of BBIQ alkaloids which have two diaryl ether linkages, and one diaryl ether and one biphenyl linkage, respectively.

As shown in Figure 1.4, (+)-Norcocsuline (**35**) and (+)-*N*-methylpachygonamine (**36**) are examples of BBIQ alkaloids respectively having

three diaryl ether linkages, and two diaryl ether linkages, together with one biphenyl.[7]

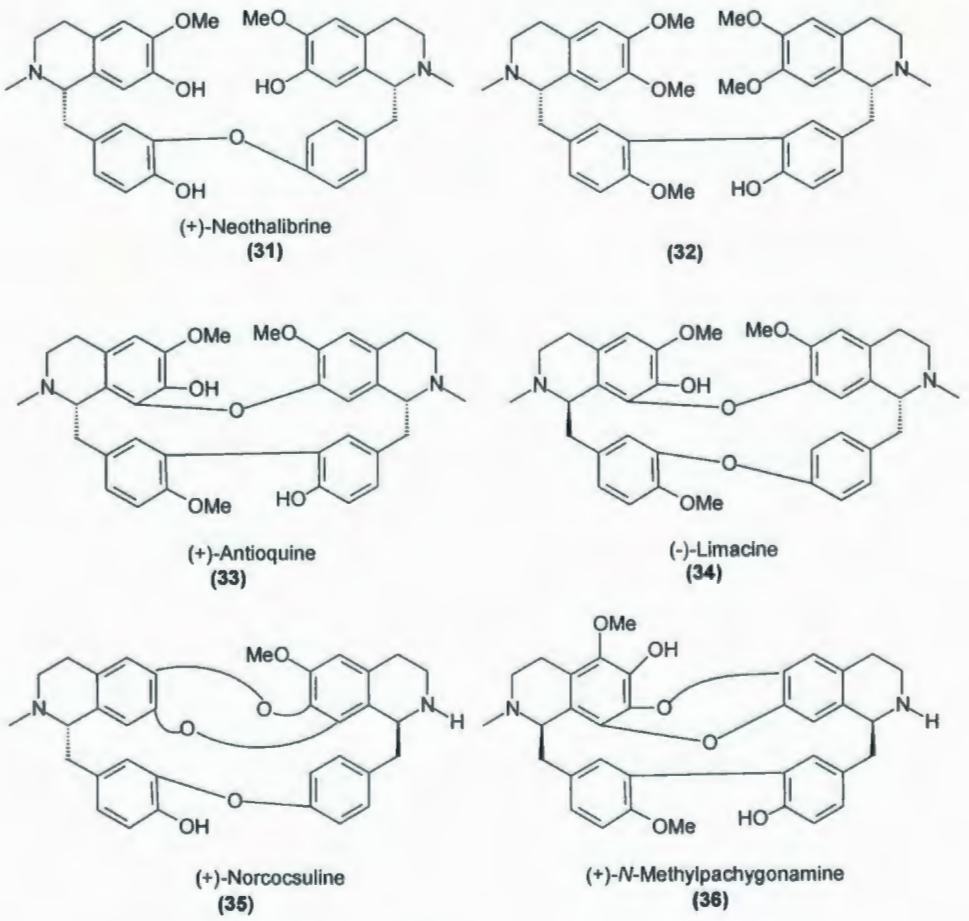


Figure 1.4. Examples of BBIQ alkaloids.

1.3 Biological significance of alkaloids.

1.3.1 Biological activities of alkaloids.

Various specialist literature reviews[8-10] showed that alkaloids exhibit some biological activities such as antifungal activity, protection against UV- irradiation, insecticides, herbicides, and also as feeding deterrents.

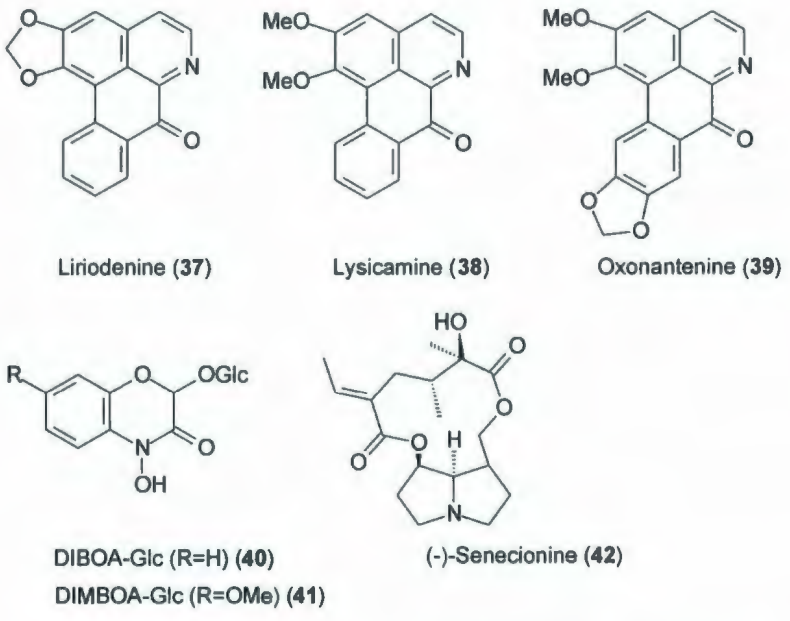


Figure 1.5. Examples of alkaloids which have biological activities.

Some alkaloids work as plant protectors against insect attacks. (-)-Senecionine (**42**), for example, is a highly effective defense for the plants that produce it (Figure 1.5).

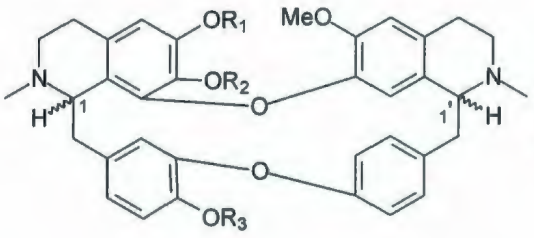
1.3.2 Pharmacological activities of BBIQ alkaloids.

Anti-tumor, anti-inflammatory, antibiotic, anti-hypertensive, and anti-plasmodial are some of the most important known biological activities of BBIQ alkaloids.[11] These are summarized in Table 1.1. Humans have always used drugs containing alkaloids in potions, medicines, poultices and poisons.[12] Table 1.1 shows some selected pharmacological activities of several BBIQ alkaloids.[13]

Table 1.1. Pharmacological activities of some BBIQ alkaloids.

BBIQ alkaloid	Pharmacological Activities
(+)-Oxyacanthine (**28**)	Antioxidant , anti-inflammatory, antiproliferative
(-)-Limacine (**33**)	Antiplasmodial, anti-inflammatory, antioxidant
(+)-Tetrandrine (**43**)	Antiplasmodial, anti-inflammatory
(+)-Fangchinoline (**44**)	Antiplasmodial, anti-inflammatory
(+)-Cepharanthine (**45**)	Anti-inflammatory
(+)-Aromoline (**46**)	Antiplasmodial, anti-inflammatory
(-)-Repandine (**47**)	Antiplasmodial, anti-inflammatory

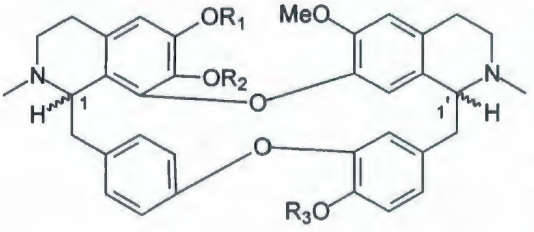
It can be seen that anti-inflammatory activity is common for those compounds and that individual BBIQ alkaloids have several additional pharmacological activities. A large number of studies have been undertaken by researchers to relate the structural features of such BBIQ alkaloids with their pharmacological activities.[14,15] Chirality and substitution patterns have been found to be the most important factors that determine their pharmacological activities.[16,17] Even though the pharmacological activities of the BBIQ alkaloids are assumed to be related to the chirality and the substitution patterns, no firm conclusions have been made about exactly how these features affect these biological activities, given the chemical complexity of living systems.



(33) (-)-(1*R*,1'*R*)-Limacine $R_1=CH_3$, $R_2=H$, $R_3=CH_3$

(43) (+)-(1S,1'S)-Tetrandrine $R_1=CH_3$, $R_2=CH_3$, $R_3=CH_3$

(44) (+)-(1*R*,1'*S*)-Fangchinoline $R_1=CH_3$, $R_2=CH_3$, $R_3=H$



(45) (+)-(1*R*,1'*S*)-Cepharanthine $R_1=CH_3$, $R_2=CH_3$, $R_3=CH_3$

(46) (+)-(1*R*,1'*S*)-Aromoline $R_1=H$, $R_2=CH_3$, $R_3=H$

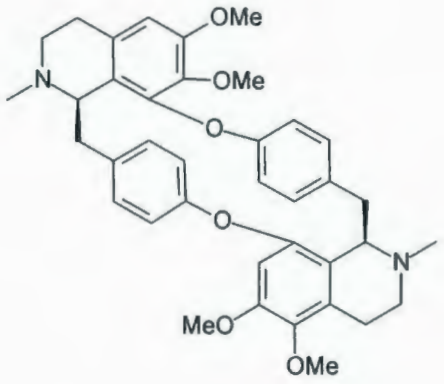
(28) (+)-(1*S*,1' R)-Oxyacanthine $R_1=CH_3$, $R_2=CH_3$, $R_3=H$

(47) (-)-(1*S*,1'*S*)-Repandine $R_1=CH_3$, $R_2=CH_3$, $R_3=H$

Figure 1.6. Examples of alkaloids having pharmacological activities.

1.3.3 Pharmacological activities of cycleanine.

(-)-Cycleanine (**48**) has been found to have diverse pharmacological activities such as antibacterial, antifungal, antiplasmodial, anti-inflammatory, cytotoxic, analgesic, and muscle relaxant properties.[18-22] The pharmacological activities of cycleanine can be traced back to early times in Southern Nigeria and other coastal regions of West Africa, where the natives used the root bark powder of the plant *Synclisia Scarbrida* which contains cycleanine, for medicinal purposes. A recent study[23] revealed that cycleanine has an effect on the central nervous system. However, cycleanine has various other pharmacological activities, and further investigations are required to relate its biological activities with its structural features.



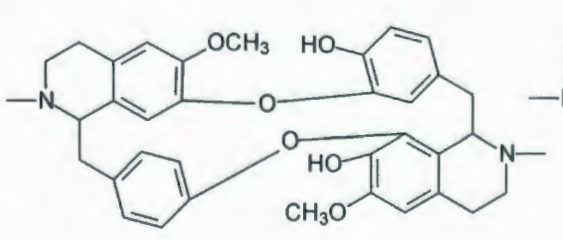
(-)-Cycleanine
(**48**)

Figure 1.7. The structure of (-)-cycleanine.

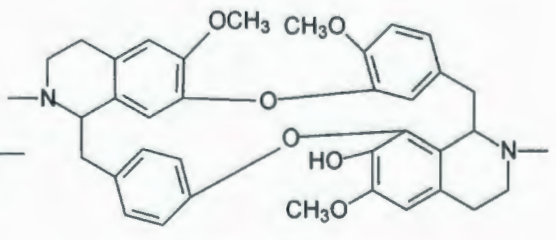
1.4. Sources of BBIQ alkaloids.

1.4.1. Botanical sources of BBIQ alkaloids.

The nature and the quantity of the BBIQ alkaloids in plants are affected by geographical and climatic factors. For instance, *Cissampelos pareira* Linn, from Kashmir produces hayatine (**49**) and hayatinine (**50**) (Figure 1.8), both of the isoquinoline type, whereas the same plant grown in Pilibhit, produces only hayatine. Different groups of BBIQs are normally found in different genera.



Hayatine
(**49**)



Hayatinine
(**50**)

Figure 1.8. The structure of hayatine (**49**) and hayatinine (**50**).

Furthermore, the BBIQs vary in their nature and in their relative proportions in the different parts of plants. For example, leaves of *menispermum canadense* Linn contain no alkaloids, whereas the stem, the roots, and the rhizome contain "Type (I)"[5] alkaloids in which two BIQ units are linked together by a single ether bridge linking the two benzyl groups. Table 1.2 outlines some of the botanical sources of some BBIQ alkaloids.[24]

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

Name of the plant	Alkaloids	Plant parts
T. patens oliv	(+)-aromoline (**46**)	leaf
C. pareira linn	(-)-Cycleanine (**48**)	root and leaf
C. leaeba DC	(+)-Oxyacanthine (**28**)	root
S. tetrandra S. moore	(+)-Tetrandrine (**43**)	tuber
Abuta candicans	(+)-neothalibrine (**31**)	stem
Anisocyclea gradidieri H.Bn	(+)-Norcocsuline (**35**)	stem

1.4.2 Synthetic approaches toward BBIQ alkaloids.

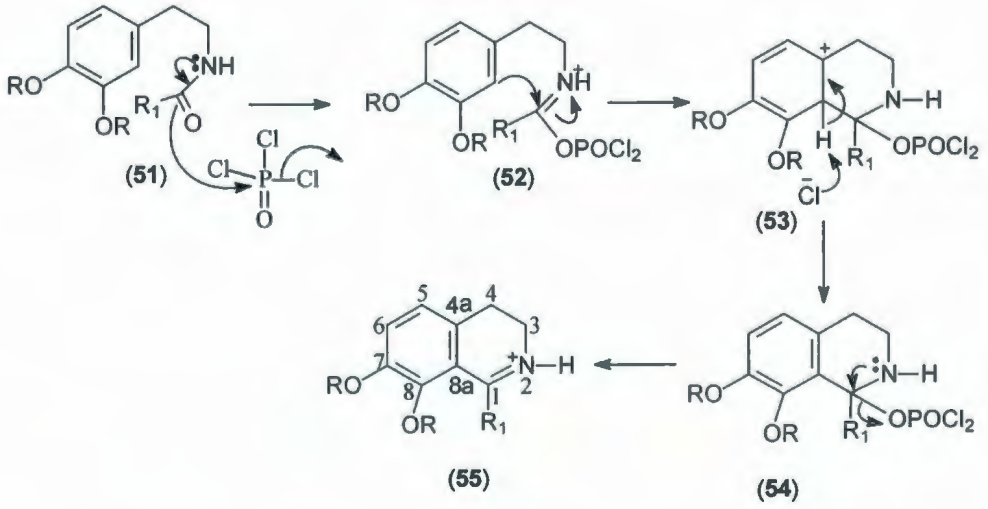
1.4.2.1 Asymmetric synthesis of isoquinoline alkaloids.

There are two major strategies for the asymmetric synthesis of isoquinoline alkaloids: (1) stereochemical modification of the usual, typical methods (i.*e.* sequential Bischler-Napieralski (BN) cyclization/reduction, Pictet-Spengler

cyclization (PSC) and Pomeranz-Fritsch cyclization); and (2) Introduction of nucleophilic or electrophilic carbon units into the C-1 position for C-1 substituted isoquinoline derivatives (the "C-1, C-α connective approach").[25]

In the Bischler-Napieralski reaction[26] a β-arylethylamide is cyclized to a 1-substituted 3,4-dihydroisoquinoline, or, to a corresponding isoquinolinium salt which is reduced in the next step to its 1,2,3,4-tetrahydro-derivative. In this reduction step, a diasteroselective or enantioselective synthesis can be effected.

In 1980, Nagubandi and Fodor [27] proposed a mechanism for the Bischler-Napieralski reaction (Scheme1.1).

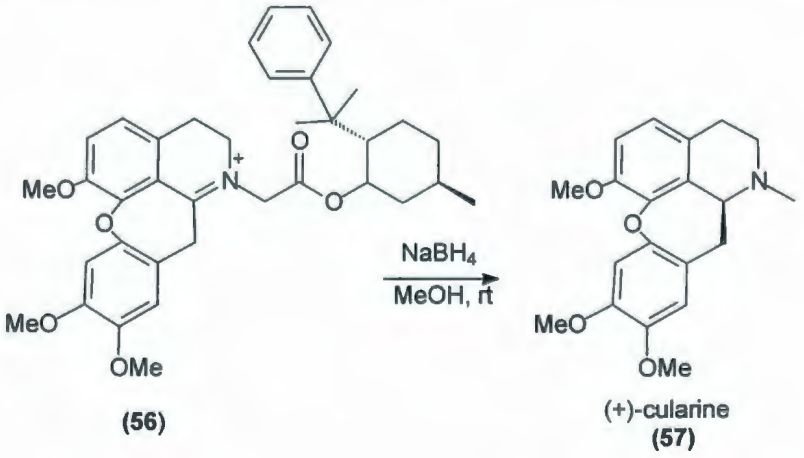


Scheme 1.1. The mechanism of the Bischler-Napieralski reaction.

The Lewis acid initially coordinates with the carbonyl oxygen of the amide **51** and forms the intermediate **52**. Electrophilic attack by the aromatic ring and subsequent re-aromatization results in the formation of the tetrahydroisoquinoline

intermediate **53** and **54**. The resultant iminium ion **55** is reduced by a reducing agent to the corresponding tetrahydroisoquinoline.Satisfactory-to-excellent results have been found when hydride reduction, or catalytic hydrogenation of chiral 1-substituted-3,4-dihydroisoquinolines, or of the corresponding 3,4-dihydroisoquinolinium salts have been used. In some cases a chiral auxiliary can be attached to the imine nitrogen, resulting in subsequent enantioselective reduction as for example in the syntheses described below (Scheme 1.2).

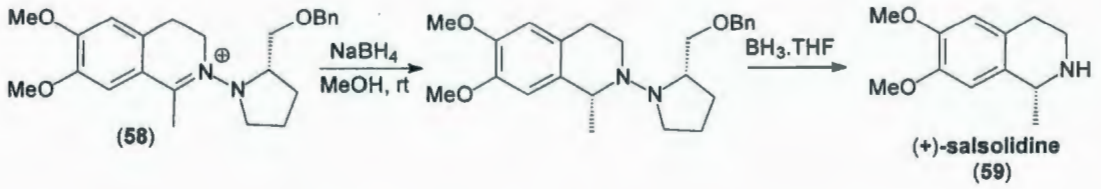
Rodrigues *et al*[28] used the iminium salt **56** as the key intermediate In the synthesis of (+)-cularine (**57**) (Scheme 1.2). The chiral auxiliary was removed by reduction with $NaBH_4$ leading directly to the *N*-methyl derivative.



(56) (+)-cularine **(57)**

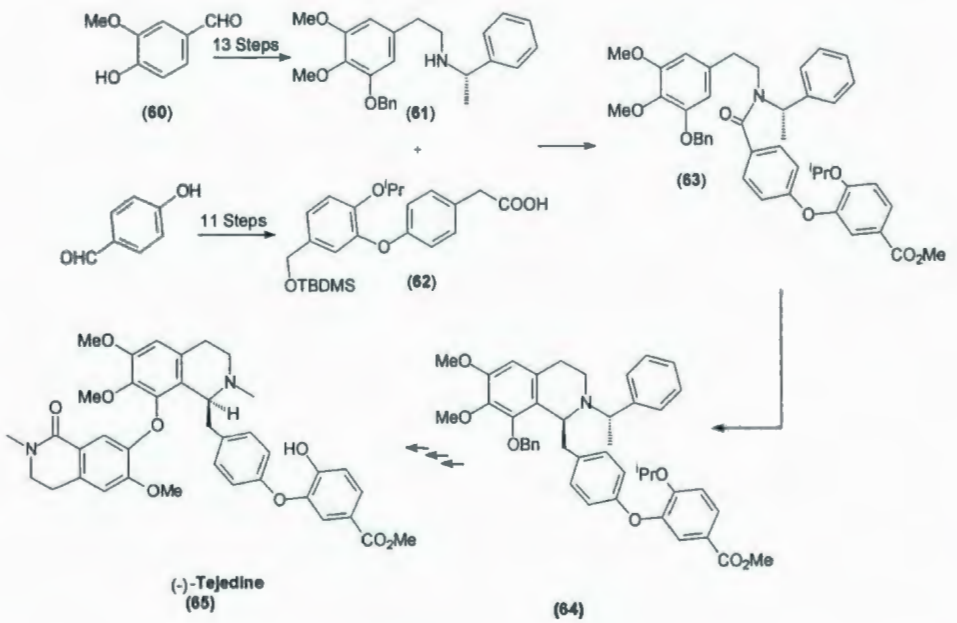
Scheme 1.2. Reduction of **56** to (+)-cularine (**57**).

Kibayashi *et al*[29] used the dihydroisoquinolinium salt **58**, incorporating a chiral hydrazonium functionality, to prepare (+)-salsolidine (**59**) as shown in Scheme 1.3.



Scheme 1.3. Synthesis of (+)-salsolidine from compound **58.**

The steric shielding effect presented by the chiral auxiliary group in both of these two examples, is assumed to account for the asymmetric reduction step by directing the hydride to the imine double bond from the sterically less-shielded face.

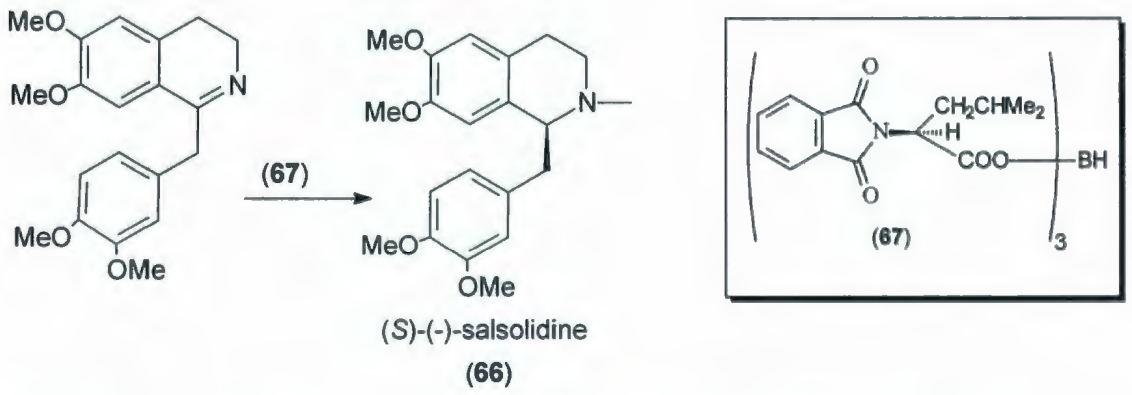


Scheme 1.4. The total synthesis of (-)-tejedine.

The Georghiou group found (*S*)-α-methylbenzylamine to be a very effective chiral auxiliary in the total synthesis of (-)-tejedine[30] (**65**), shown in Scheme 1.4.

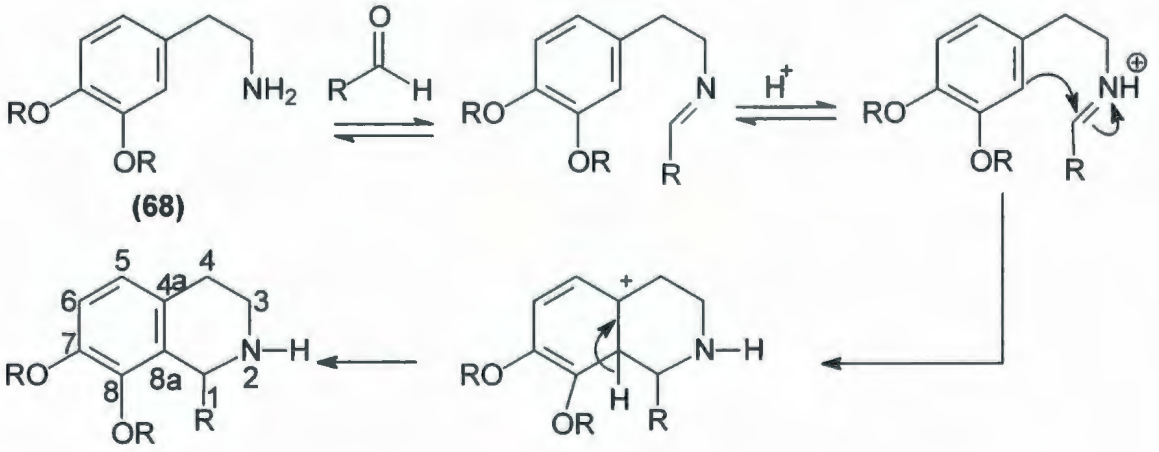
The chiral amine **61** was obtained from vanillin (**60**) in 13 synthetic steps, and the acid **62** was synthesized from 4-hydroxybenzaldehyde in 11 steps. The key intermediate **63** was prepared from the reaction of **61** and **62**. Cyclization of **63** using $POCl_3$ in benzene, followed by reduction, gave the desired tetrahydroisoquinoline regioisomer **64** in 40% yield with 99% *de*.

Chiral hydride reducing agents or chiral catalysis can also be used to accomplish the enantioselective synthesis of isoquinolines via a Bischler-Napieralski cyclization/reduction approach. For example, Hajipour and Hantehzadeh,[31] used sodium triacyloxy borohydride (**67**), prepared from $NaBH_4$ and *N*,*N*-phthaloyl-protected amino acid (Scheme 1.5) in the synthesis of (*S*)-(-)-salsolidine (**66**).The enantioselectivity (65-75% *ee*) increased when the reduction was achieved in the presence of $ZnCl_2$ (72-80% *ee*), or when carried out under solid-state conditions (83-100% *ee*).



Scheme 1.5. Use of chiral triacyloxy borohydrides for reduction of imine intermediate in the synthesis of (*S*)-(-)-salsolidine (**66**).

The Pictet-Spengler cyclization reaction[32] is often the most effective method for constructing tetrahydroisoquinolines. The condensation of β-arylethylamine *e.g.* **68** with an aldehyde or its synthetic equivalent leads to the formation of the stereogenic C-1 center during the ring closure in a one-pot process as shown in Scheme 1.6. The mild reaction conditions and the lack of requirement for subsequent reduction give the Pictet-Spengler method some advantages over the Bischler-Napieralski reaction for the construction of isoquinolines.



Scheme 1.6. Mechanism of the Pictet-Spengler cyclization reaction.

Chiral cyclohexyl-based auxiliaries on compounds **69**[33] and **70**[34] are two examples which were used for the synthesis of **71** and **72** respectively. The two chiral auxiliaries were appended to the amine nitrogen (Figure 1.9). To control the formation of the chiral center at C-1 and to achieve the total synthesis of the alkaloid **76**, a chiral aldehyde was used by Czarnock *et al.*[35] The reaction between **73** and the chiral aldehyde **74** gave **75** in 80% yield (Scheme 1.7).

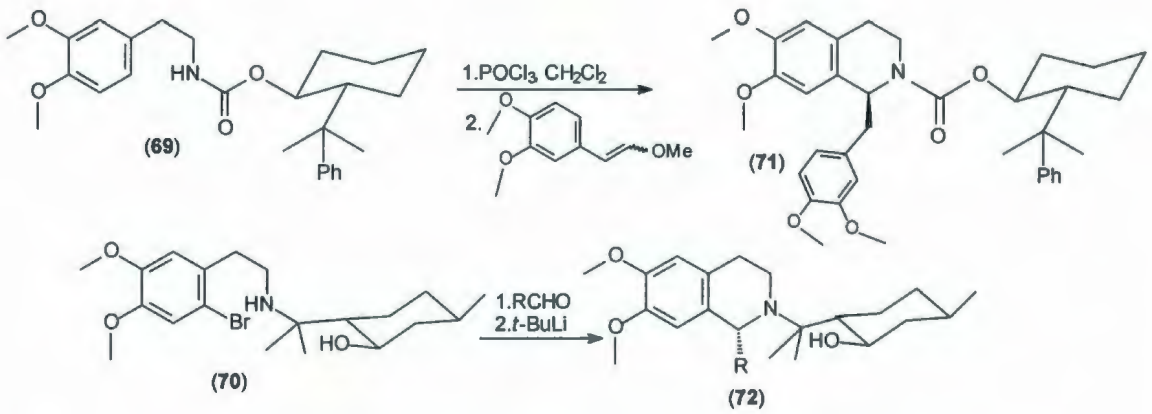
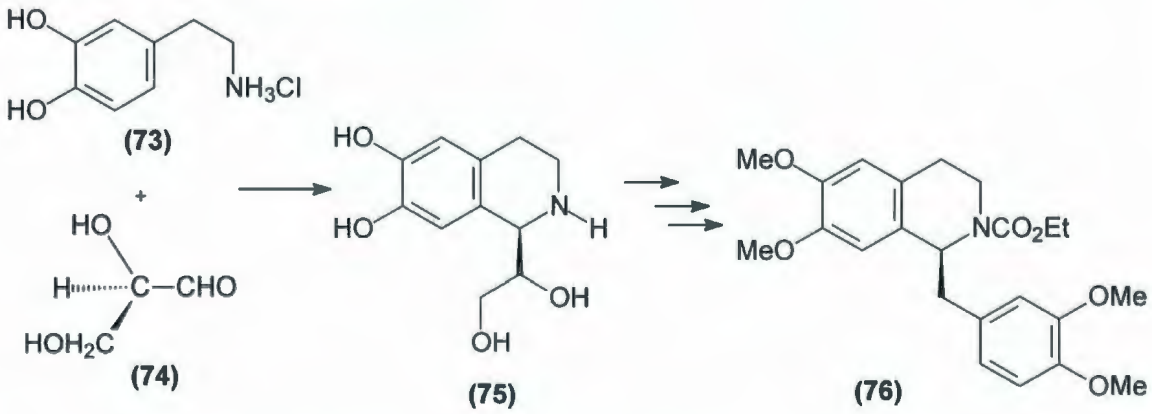


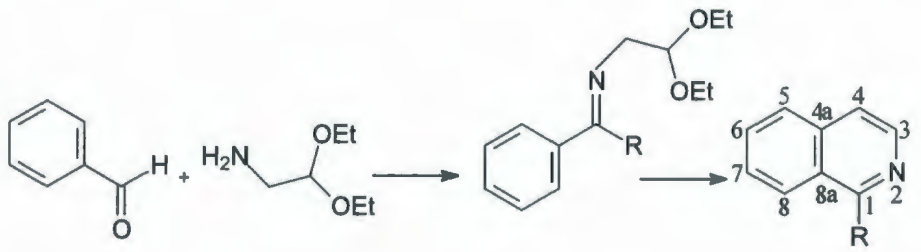
Figure 1.9. Preparing alkaloids **71**, **72** using cyclohexyl-based chiral auxiliaries.

The application of the Pictet-Spengler cyclization methodology in the synthesis of cycleanine was attempted in earlier investigations by Mark Ralph in the Georghiou laboratory.[36]



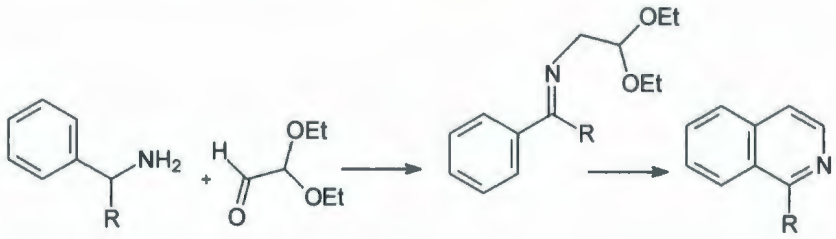
Scheme 1.7. Use of chiral aldehyde to form the desired stereocenter at C-1.

The Pomeranz-Fritsch reaction[37,38] forms the completely aromatic isoqunolines by acid-catalyzed cyclization of benzalaminoacetals prepared from aromatic aldehydes and aminoacetal (Scheme 1.8).



Scheme 1.8. Pomeranz-Fritsch reaction.

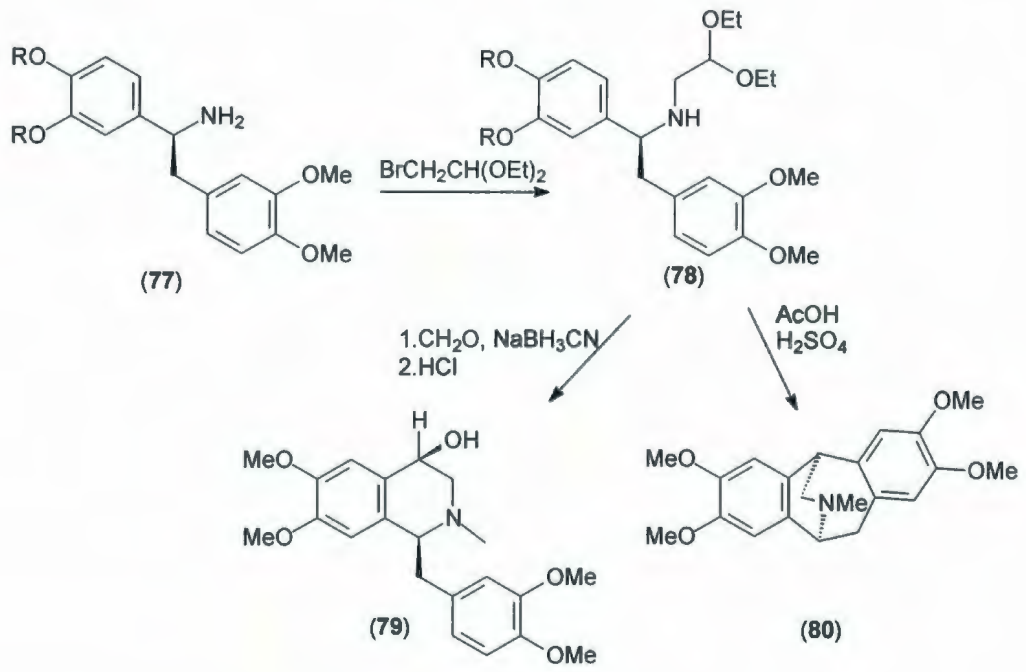
In the Schlittler-Müller modification[39] the starting materials are benzyl amines and glyoxal semiacetal. (Scheme 1.9).



Scheme 1.9 Schlittler-Müller reaction.

O-Methylroemecarine (**79**) and (-)-*O*-methylthalisopavine (**80**) (Scheme 1.10) were constructed in good yields with high enantiomeric purity by *N*-alkylation of benzylamines **77** with bromoacetaldehyde acetal, followed by acid-catalyzed cyclization of the secondary amines **78**.[40]

The three basic methods, described above involve the closure of the six-membered nitrogen-containing rings by the formation of the new bonds between C-8a and C-1 (Bischler-Napieralski, Scheme 1.1), C-8a–C-1 and N-2 (Pictet-Spengler, Scheme 1.6), and C-4 and C-4a (Pomeranz-Fritsch, Scheme 1.8).

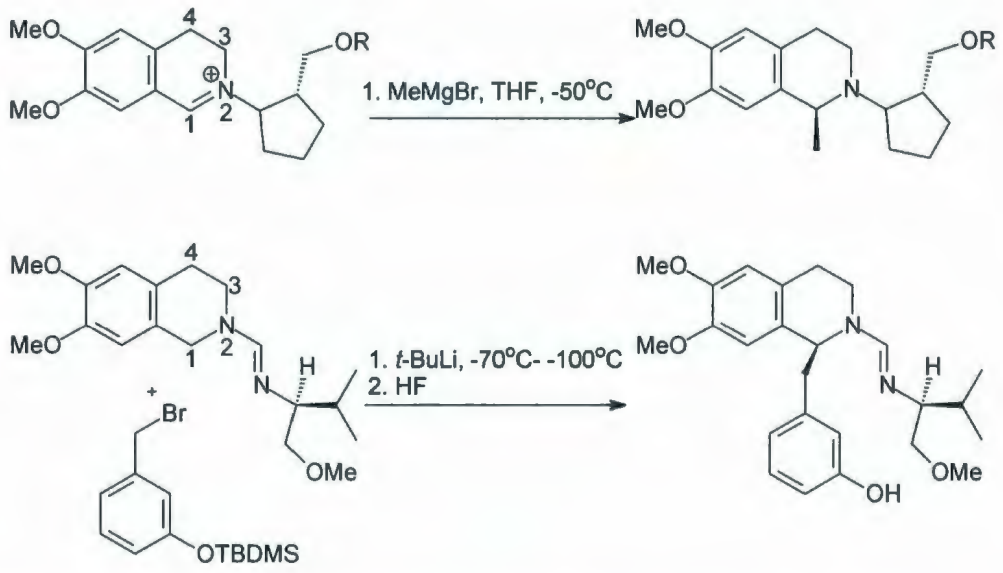


Scheme 1.10. The total synthesis of compounds **79** and **80**.

However, there are other methods which have different strategies for formation of isoquinoline compounds, including hetrocyclic ring closure between the C1-N2 or C3-N2 atoms as well. Introduction of a carbon unit to the C-1 position of the isoquinoline heterocycle has recently been discovered as an alternative to the traditional synthetic methods. To prepare isoquinolines by this methodology, there are two strategies which can be followed, as shown in Scheme 1.11.

The two approaches are: (1) Addition of carbon nucleophiles to isoquinolines, 3,4-dihydroisoquinolines, or to the corresponding isoquinolinium ions,[41] (2) C-alkylation of tetrahydroisoquinoline derivatives with electrophilic carbon reagents,[42] the stereogenic center being created at this stage of the

synthesis. Munchhof and Meyers,[43] have prepared several alkaloids from a common intermediate by the C-1-N-2 connectivity approach,.



Scheme 1.11. Tetrahydroisoquinoline synthesis *Top*: via nucleophilic carbon addition to iminum intermediate; and *Bottom*: via addition to an electrophilic carbon atom.

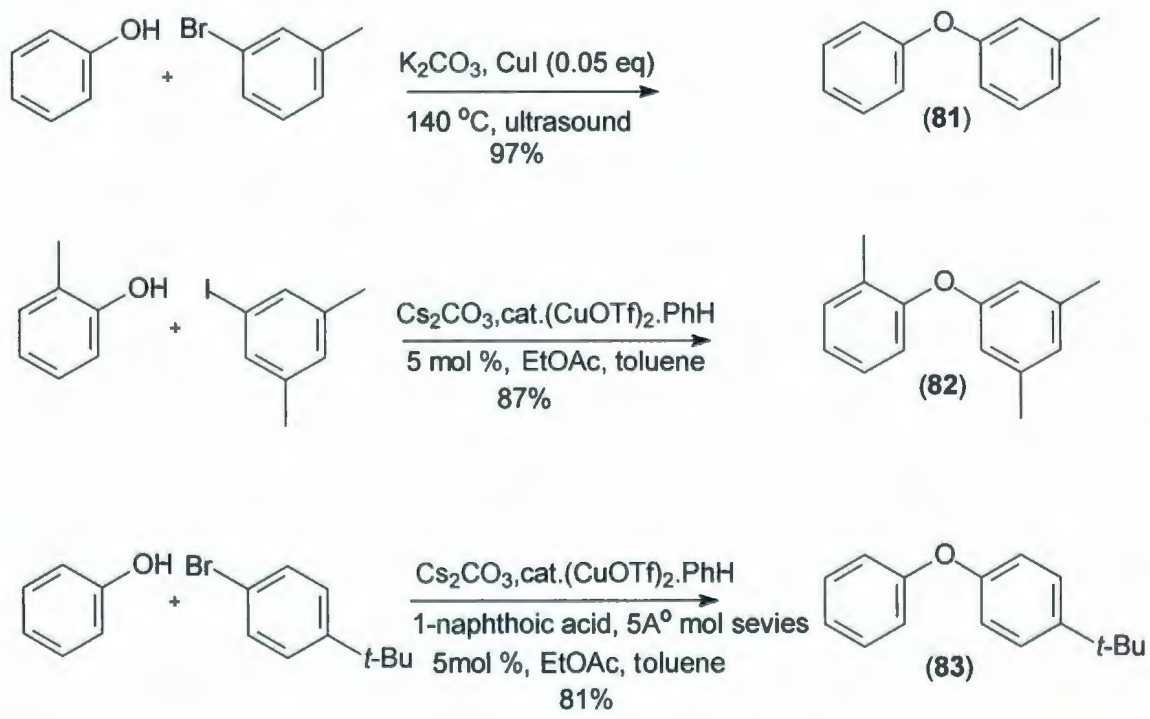
1.4.2.2 Diaryl ether formation.

The importance of the diaryl ether class of organic compounds comes from their use throughout the polymer and pharmaceutical industries.[44] Some of these compounds have been described as having significant biological activity, such as the natural products of the isodityrosine family and its derivatives (*e.g.* the antibiotic vancomycin and the antitumoral bouvardin).[45] The most straightforward way to synthesize diaryl ethers involves the direct formation of an aryl-oxygen bond from an aryl halide.[46] The copper-mediated arylation of phenols

with aryl halides, discovered by Ullmann in 1904,[47] seems to be the method of choice. This method is often limited due to the need to employ harsh reaction conditions and stoichiometric amounts of copper. Palladium catalysts have been used recently for arylation of phenols or their sodium salts.[48] However, the high cost of palladium and non-commercial specialized phosphine ligands make this method potentially unattractive for large-scale and industrial applications. Therefore, less costly alternatives are needed. Considerable effort has been applied in the past few years toward the discovery of more cost-effective Ullmann *O*-arylation methodologies. For example, Buchwald's group[49] has used copper (II) triflate salts as catalysts to carry out these reactions under milder conditions with a wider variety of substrates in good yields (*e.g.* the formation of **82** Scheme 1.2). Cesium carbonate was shown to be the best base in this system and allows the use of a non-polar solvent (toluene) at reduced reaction temperatures. Addition of a carboxylic acid and molecular sieves was effective in promoting couplings of specific phenols devoid of electron-donating groups to unactivated aryl halides (*e.g.*, the formation of **82**).

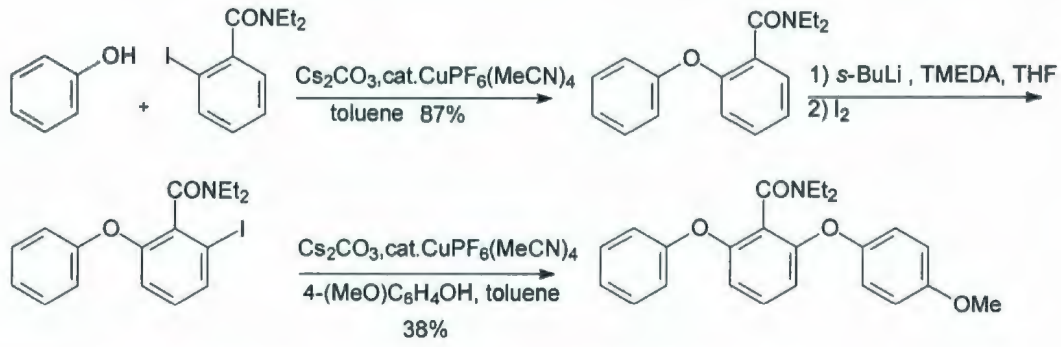
The limitation of these strategies comes from the relatively high cost of copper triflate and its air sensitivity. Pyridine-type ligands, or phosphine-type ligands in catalytic amounts, however have been used recently by a number of groups to accelerate or enhance the Ullmann reaction and to allow it to occur under more moderate conditions.[50] Several investigations have demonstrated that certain additives such as ethylene glycol diacetate,[51a] 8-

hydroxyquinoline,[51b,c] 1-naphthoic acid,[51d] triphenylphosphine[51e] and neocuproine[51f] have been used successfully as promoters. These additives probably act as copper ligands which enhance reaction rates and allow the couplings to be carried out in the presence of reduced amounts of copper, at milder temperatures, or with a larger substrate range.[51] Smith[53] prepared diaryl ethers (*e.g.* the formation of **82**) by using catalytic copper (I) iodide and ultrasound. These reactions were conducted in the absence of solvent and in conjunction with sonication to break up particles of the base and catalyst. By using 2 mol equiv. of phenol, (Scheme 1.12) these reactions afforded diaryl ethers in yields generally greater than under the corresponding classical Ullmann conditions.



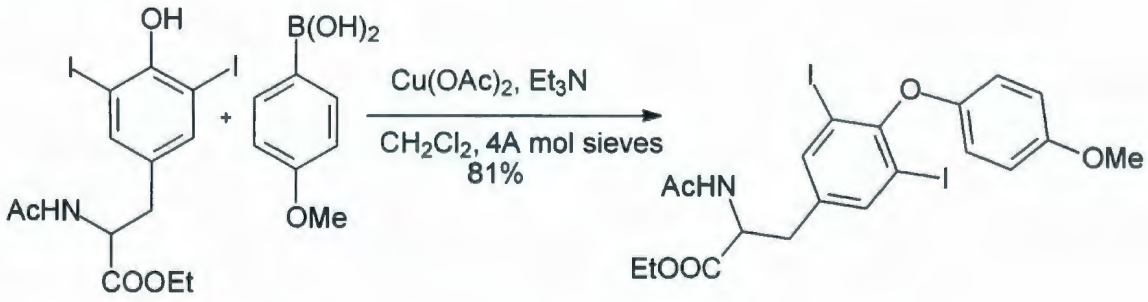
Scheme 1.12. Diaryl ether coupling by using different reagents.

In 1999 Snieckus[54] reported the use of catalytic $CuPF_6(MeCN)_4$ to assist the coupling of phenols to *o*-halo tertiary- and secondary benzamides and sulfonamides. The resulting diaryl ethers may then be submitted to direct *ortho*-metalation, halogenation, and an additional Ullmann ether operation to produce bis- and triarylethers, as shown in Scheme1.13.



Scheme 1.13. Use of $CuPF_6(MeCN)_4$ for diaryl ether coupling.

Chan[55] and Evans[56] have tried the coupling of aryl boronic acids and phenols in copper-mediated synthesis of diaryl ethers. These reactions employ stoichiometric quantities of copper (II) acetate.

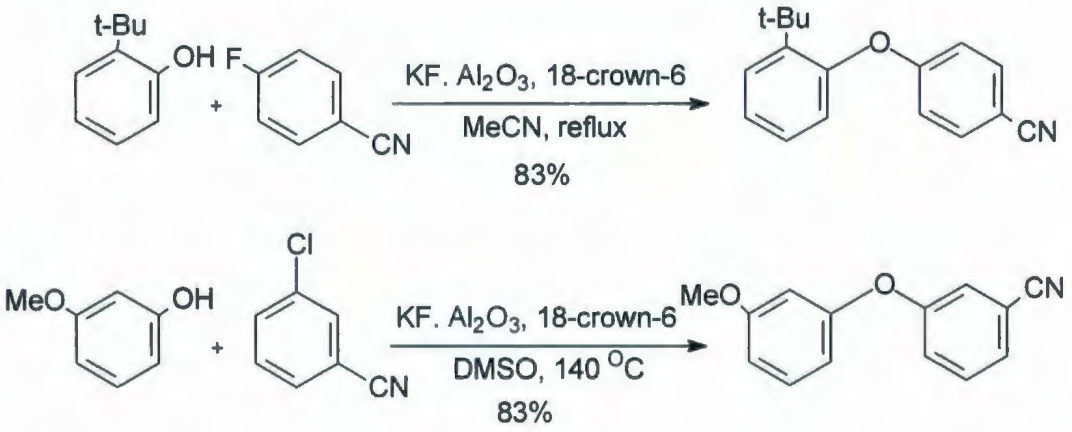


Scheme 1.14. Diaryl ether coupling by using boronic acids.

However, the reaction is conducted at room temperature, tolerates a wide variety of substituents on both fragments, and proceeds in generally high yields (Scheme 1.14). The Ullmann condensation can be enhanced (10 to 15 fold) by using 25 mol% of 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as an additive along with CuCl as catalyst and Cs_2CO_3 as the base. TMHD, which exists as the diketo tautomer under the reaction conditions, forms a co-complex with the copper (I)-phenolate species which kinetically enhances the rate-determining step.[57] He and Wu[58] used a microwave protocol which was developed by Buchwald[49] to enhance the reaction of aryl bromides and iodides with a range of phenols. The same reaction conditions did not work with aryl chlorides since, even after 14 h at 195 °C, mostly unchanged starting materials were recovered. Phosphazene (P_4-*t*-Bu, also known as Schwesinger base) has been used by Palomo *et al*[59] to develop an efficient method for the coupling of aryl halides with phenols. They tried CuI, CuCl, CuBr and $(CuOTf)_2$ C_6H_6 as Cu(I) sources and found that the use of CuBr in a 20 mol % catalytic amount was the best. No reaction was observed when Cu(II) salts were used.

Syntheses of diaryl ethers via nucleophilic substitution on the aromatic ring (S_NAr) reactions were proposed in 1998 as an efficient and alternative method to the Ullmann ether synthesis. These reactions involve the base-mediated addition of a phenol to an appropriate aryl halide. Sawyer *et al*[60] used KF/alumina and 18-crown-6 in acetonitrile or DMSO (Scheme 1.15).

S_NAr reactions can be accelerated by using halo-substituted benzonitriles or nitrobenzenes in refluxing acetonitrile. Even the sterically-crowded nucleophile, 2-*tert*-butylphenol, which is usually unreactive under normal Ullmann conditions, added smoothly to 4-fluorobenzonitrile to give the diaryl ether.



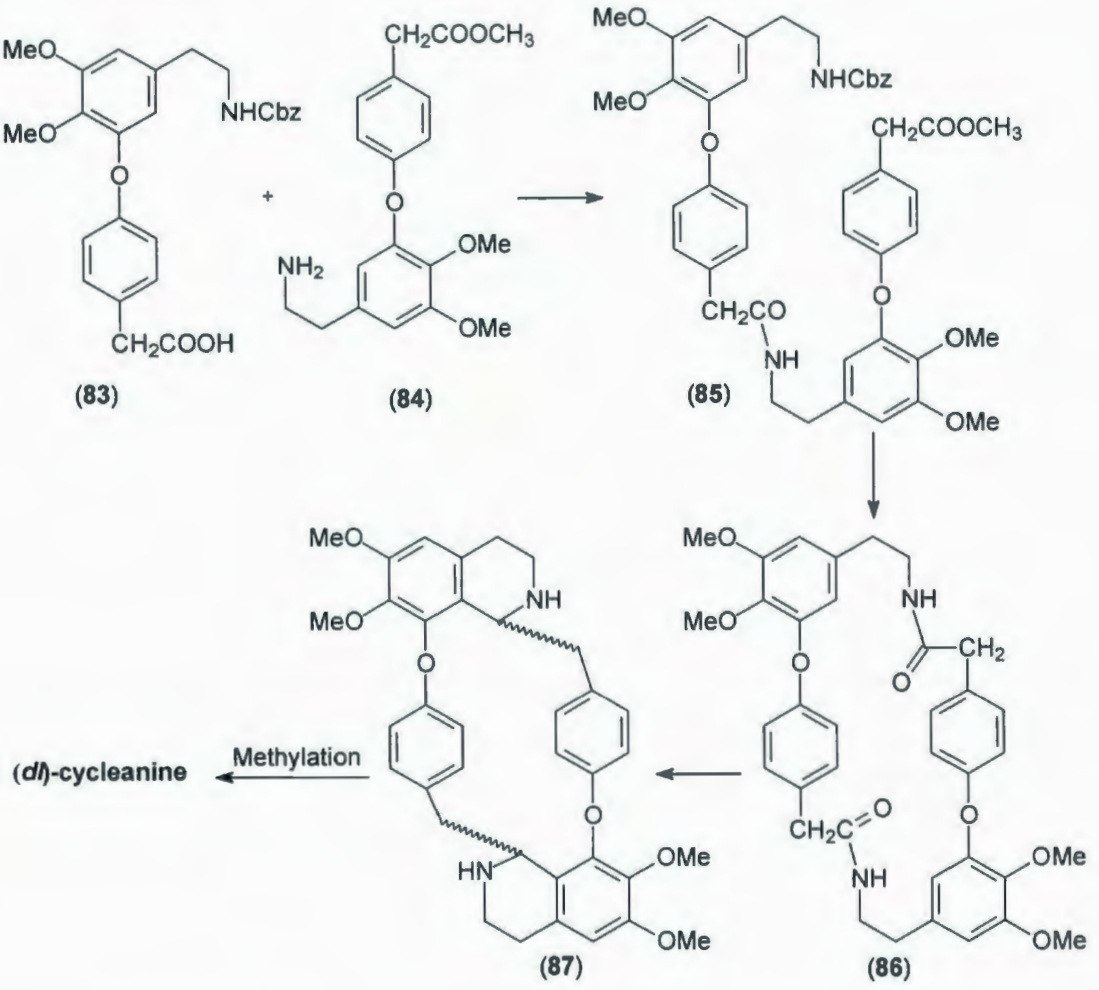
Scheme 1.15. S_NAr-based addition reactions.

S_NAr-based addition reactions have been used by many researchers employing different reaction conditions, for instance KF/Al_2O_3, 18-crown-6, MeCN, reflux;[61] K_2CO_3, dimethylacetamide (DMAC), reflux;[62] NaH, 4 mM in THF[63]; CsF, DMF;[64] and $KHCO_3$, THF.[65]

All of these examples suggest that the use of either improved Ullmann coupling or S_NAr-based reactions are potential approaches to construct the biaryl ether bonds in the target cycleanine molecule. The use of both of these approaches will be presented and described in this thesis.

1.4.2.4 Previous synthetic approaches towards cycleanine.

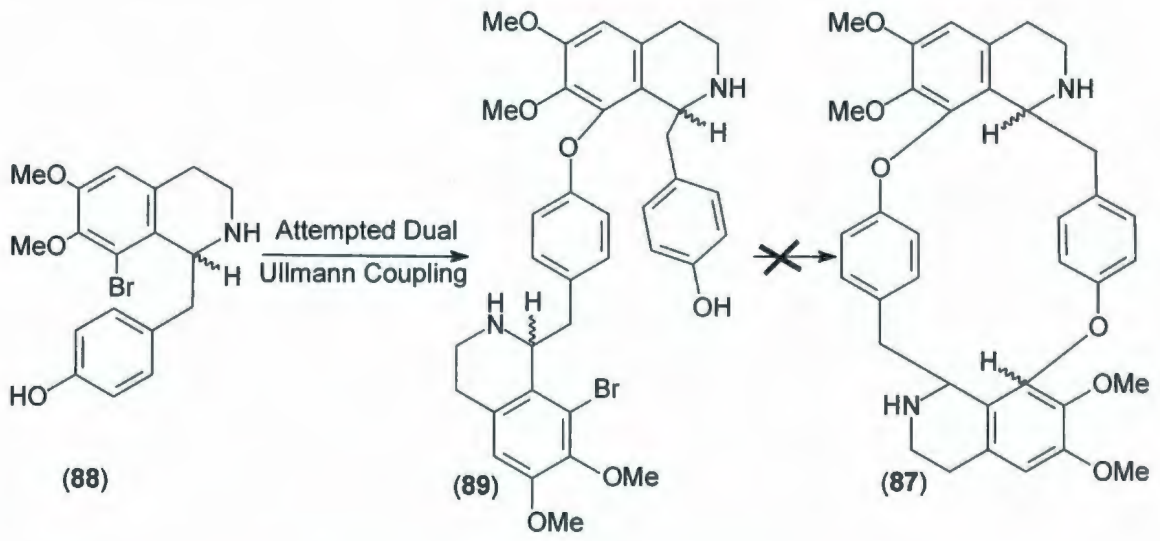
Cycleanine (**48**) (*O,O*-dimethylisochondodendrine) is a C_2-symmetrical compound having two benzyltetrahydroisoquinoline units connected by two biaryl ether linkages. According to the classification of BBIQ alkaloids by Guha[5] and Shamma,[6] cycleanine is a Type XX, Group B "head-to tail" dimer. Even though cycleanine was first isolated from plants in 1937 by Kondo *et al,*[66] to date no successful enantionselective total synthesis has been reported.



Scheme 1.15. First synthetic route of Tomita to prepare cycleanine.

Up to now there have been only two synthetic efforts toward cycleanine which have been reported.[67-70] Both attempts however, were not synthetically useful because of the very low yield and the lack of regioselectivity and stereoselectivity. Tomita *et al*[67-68] completed the first synthesis of (*d,l*)-cycleanine in 1966. As shown in Scheme1.16 in the presence of dicyclohexylcarbodiimide (DCC), carboxylic acid **83** reacted with amine **84** to give the amide **85**. Deprotection of the amino group and ester hydrolysis, followed by a second condensation reaction using DCC afforded the cyclic diamide **86.** Cyclization via the Bischler-Napieralski reaction followed by reduction with sodium borohydride, gave a mixture of tetrahydroisoquinolines **87**. Methylation of the secondary amines in **87** produced a mixture of (*d,l*)-cycleanine. This synthetic approach gave only <10% yield in the ring-closure step as a mixture of diastereoisomers which were not purified.

The second attempt was conducted by the same group.[69-70] As outlined in Scheme 1.16, this attempt depended on a dual Ullmann coupling reaction for compound **88** to form the macrocyclic compound **87**. However, this attempt was unsuccessful since the Ullmann reaction gave only the diamine **89** instead.



Scheme 1.16. The second attempt at the total synthesis of cycleanine

Although this second attempt of the total synthesis of cycleanine was unsuccessful and the first attempt only produced a mixture which included racemic cycleanine, the information gained from the attempted syntheses by Tomita *et al* was significant. Our attempts toward the total synthesis of (-)-cycleanine (**48**) include an extensive study to achieve a regioselective and stereoselective syntheses of several key benzyltetrahydroisoquinoline intermediates. These compounds have been investigated in order to complete the diaryl ether coupling step that leads to our target. In Chapter 2 of this thesis the approach toward the synthesis of (-)-cycleanine (**48**) using two different strategies will be described.

References

1. Meissner, W. *J. Chem. Phys.*, **1819**, *25*, 379.

2. Guareschi, I. "*Einfũhrung in das Stadium der Alkaloids mit besonderer Berũcksichtigung der tigung der vegetabilischen Alkaloids und der Ptomaine*", Gaertners Verlagsbuchhandlung, Handlung, Berlin, **1896.**

3. Stoll. A.; Jucker, '*Alkaloide*', in *Ullmanns encyklopadie der technischen chemie*, 3rd Ed. Vol. 3, 177,**1953.**

4. Manfred. H. "*Alkaloids nature's curse or blessing?*" John Wiley & Sons, Inc. New York, NY., **1981**, PP.1-5.

5. Guha, K. P.; Mukherjee, B. *J. Nat. Prod.*, **1979**, *42*, 1.

6. Shamma, M., Moniot, J. L. *Heterocycles.*, **1976**, *4*, 1817.

7. Schiff, P. L., Jr. *J. Nat. Prod.*, **1997**, *60*, 934.

8. Clark, A. M., Hufford, D. C. *The alkaloids.*, **1992**, *42*, 117.

9. Wink, M. "*Allelochemical Properties, or the Raison d'Etre of Alkaloids", The Alkaloids*, **1993**, *43*, 1.

10. Daly, J. W.; Garraffo, H. M,; Spande, T. F. *The alkaloids,* **1993**, *43*, 185.

11. Schiff, P. L. *J. Nat. Prod.*, **1983**, *46*, 1.

12. Cordell, G. A. "*Introduction to Alkaloids*," John Wiley & Sons, Inc. New York, NY, **981**, pp.1-8.

13. Cui, J. *M. Sc. Thesis*, Memorial University of Newfoundland, **2003**.

14. Shamma, M. in "*The Isoquinoline Alkaloids*," Vol. 25, Academic Press, New York, NY, **1972**,PP. 115-150.

15. Shamma, M.; Monito, J. L. "*Isoquinoline Alkaloids Research*," Plenum Press, New York, NY, **1972- 1977**, pp. 71-100.

16. Wright, J. S.; Johnson, E. R.; Dilabio, G. A. *J. Am. Chem. Soc.*, **2001**, 123, 1173.

17. Galle, V. K.; Bladt, S.; Wagner, H. *Deutsche Apotheker Zeitung*, **1994**, 134, 35.

18. Kambu, K., Eléments de phytothérapie comparée. *Plantes Médicinales Africaines*. CRP, Kinshasa. **1990.**

19.Watanabe, K.; Uramoto, H.; Maeda-Hagiwara, M.; Kikuchi, T. *Arch. Int. Pharmacodyn. Ther.* **1985**, *278*, 53.

20. Likhitwitayawuid, K.; Angerhofer, C. K.; Cordell, G. A.; Pezzuto, J. M. *J. Nat. Prod.* **1993**, *56*, 30–36.

21. Valentin, A.; Benoit-Vical, F.; Moulis, C.; Stanislas, E.; Mallié, M., ;Fournaste, I.; Bastide, J. M. *A. A. C.* **1997,** *41*, 2305.

22. Angerhofer, C. K.; Guinaudeau, H.; Wongpanich, V.; Pezzuto, J. M.; Cordell, G. A. *J. Nat. Prod.* **1999**, *62*, 59.

23. Wambebe, C.; Gamaniel, K.; Akah, P.A.; Kapu, S. D.; Samson, A.; Orisadipe, A. T.; Okogun, J. I. *Ind. J. Pharmacol.*, **1997**, *29*, 5366.

24. Zhou, N. *M. Sc. Thesis*, Memorial University of Newfoundland, **2004**.

25. Chrzanowska. M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

26. Bischler, A.; Napieralski, B. *Ber.***1893**, *26*, 1903.

27. Nagubandi, S.; Fodor, G. *Heterocyclic Chem.* **1980**, *17*, 1457.

28. de Sousa, J. D. F.; Rodrigues, J. A. R. *J. Am. Chem. Soc.* **1994**, *116*, 9745.

29. Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1995**, *36*, 6709

30. Wang, Y.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675.

31. Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475.

32. Pictet, A.; Spengler, T. Ber. **1911**, *44*, 2030.

33. Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*,16327.

34. Pedrosa, R.; Andres, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243.

35. Czarnocki, Z.; Maclean, D. B.; Szarek, W. A. *Can. J. Chem.* **1986**, *64*, 2205.

36. Ralph, M. S. *M.Sc. Thesis*, Memorial University of Newfoundland, **2001**.

37. Pomeranz. C. *Monatsh.* **1893**, *14*, 116.

38. Fritsch. P. *Ber.* **1893**, *26*, 419.

39. Schlittler. E.; Müller. J. *Helv. Chim. Acta.* **1948**, *31*, 914, 1119.

40. Carrillo, L.; Badia, D.; Dominguez, E.; Vicario, J. L.; Tellitu, I. *J. Org. Chem.* **1997**, *62*, 6716.

41. Meyers, A. I.; Nguyen, T. H. *Heterocycles.* **1994**, *39*, 513.

42. Meyers, A. I. *Tetrahedron.* **1992**, *48*, 2589.

43. Munchhof, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607.

44. Theil, F. *Angew. Chem. Int. Ed.* **1999**, 38, 2345.

45. (a) Zhu, J. *Synlett.* **1997**, 133. (b) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544.

46. For reviews, see: (a) Sawyer, J. S. *Tetrahedron.* **2000**, *56*, 5045. (b)Lindley, J. *Tetrahedron.* **1984**, *40*, 1433. (c) Moroz, A. A.; Shvartsberg, M.S. *Russ. Chem. Rev.* **1974**, *43*, 679.

47. (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853. (b) Hassan,J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**,*102*, 1359. (c) Thomas, A. W.; Ley, S. V. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.

48. (a) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J.P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369. (b) Kataoka, N.;Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553. (c) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G.*Tetrahedron Lett.* **2001**, *42*, 8751.

49. Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

50. (a) Gujadhur, R. K.; Bates, C. G.;Venkataraman, D. *Org. Lett.* **2001**, *3*, 4135. (b) Fagan, P. J.; Hauptman,E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

51. (a) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R.P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623. (b) Goodbrand, H. B.; Hu, N.-X.*J. Org. Chem.* **1999**, *64*, 670. (c) Lu, Z.; Twieg, R. J.; Huang, S. D.*Tetrahedron Lett.* **2003**, *44*, 6289.

52. (a) Weingarten, H. *J. Org. Chem.* **1964**, *29*, 3624. (b) Oi, R.;Shimakawa, C.; Takenaka, S. *Chem. Lett.* **1988**, 899. (c) Fagan, P. J.;Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*,5043. (d) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.***1997**, *119*, 10539. (e) Gujadhur, R. K.; Venkataraman, D. *Synth. Commun.***2001**, *31*, 2865. (f) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org.Lett.* **2001**, *3*, 4315.

53. Smith, K.; Jones, D. *J. Chem. Soc. Perkin Trans.* **1992**, *1*, 407.

54. Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org.Chem.* **1999**, *64*, 2986.

55. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P.*Tetrahedron Lett.* **1998**, *39*, 2933.

56. Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937

57. Buck, E .; Song ,Z. J.; Tschaen ,D.; P. G. Dormer, R. P. Volante,P. J. Reider, *Org. Lett.* **2002**, *4*, 1623.

58. He, H.; Wu ,Y. J. *Tetrahedron Lett.* **2003**, *43*, 3445.

59. Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez-Bengoa, E. *Chem.Commun.* **1998**, 2091.

60. Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J. *J. Org. Chem.* **1998**, *63*, 6338.

61. Sawyer, J. S.; Bach, N. J.; Baker, S. R.; Baldwin, R. F.;Borromeo, P. S.; Cockerham, S. L.; Fleisch, J. H.; Floreancig,P.; Froelich, L. L.; Jackson, W. T.; Marder, P.; Palkowitz, J. A.;Roman, C. R.; Saussy Jr, D. L.; Schmittling, E. A.; Silbaugh, S. A.; Spaethe, S. M.; Stengel, P. W.; Sofia, M. J. *J. Med. Chem.* **1995**, *38*, 4411.

62. Yeager, G. W.; Schissel, D. N. *Synthesis.* **1995**, 28.

63. Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, 3938.

64. Carrington, S.; Fairlamb, A. H.; Blagbrough, I. S. *J. Chem.Soc., Chem. Commun.* **1998**, *21*, 2335.

65. Roussi, G.; Zamora, E. G.; Carbonnelle, A.-C.; Beugelmans, R. *Tetrahedron Lett.* **1997**, *38*, 4401.

66. (a) Kondo, H.; Tomita, M.; Uyeo, S. *Ber.*, **1937**, 70B, 1890; (b) Kondo, H.; Tomita, M.; Uyeo, S. *Yakugaku Zasski*, **1942**, *62*, 534.

67. Tomita, M .; Aoyagi, Y.; Sakatani, Y ,; Fujitani, K. *Chem. Pharm. Bull.*, **1967**, *15*,1996.

68. Tomita, M .; Aoyagi, Y.; Sakatani, Y ,; Fujitani, K. *Tetrahedron lett.*, **1966**, *35*, 4243.

69. Tomita, M .; Aoyagi, Y.; Sakatani, Y ,; Fujitani, K. *Chem. Pharm. Bull.*, **1968**, *16*, 56.

70. Tomita, M .; Aoyagi, Y.; Sakatani, Y ,; Fujitani, K. *Chem. Pharm. Bull.*, **1968**, *16*, 62.

Chapter 2

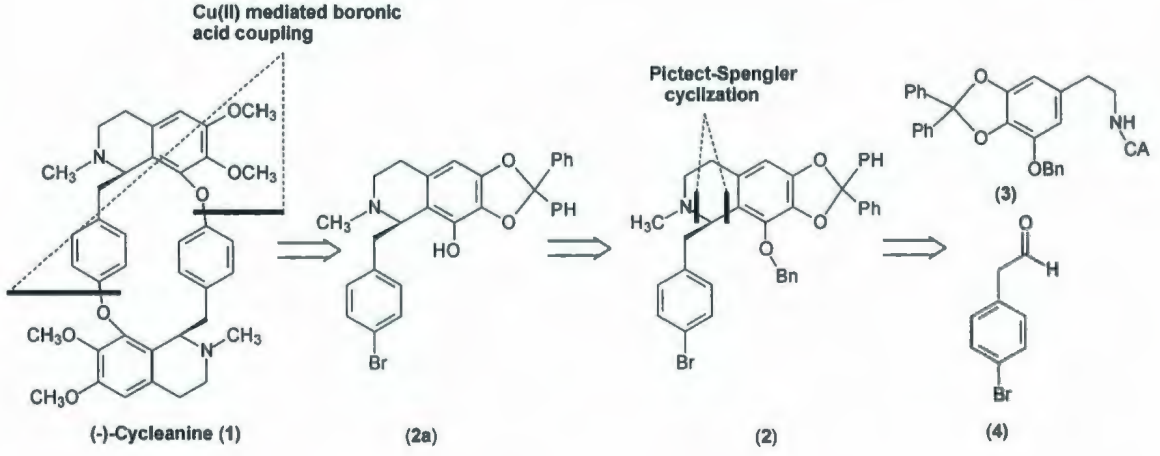
Synthetic Attempts Towards (-)-Cycleanine

2.1 Introduction

The attempted synthesis of (-)-cycleanine (**1**) by the use of two different strategies will be described in this Chapter. The synthesis of **1** has been a long-standing project of the Georghiou group. At this juncture, the previous approaches toward the total synthesis of (-)-cycleanine (**1**) undertaken by Ralph,[1] Cui[2] and Zhou[3] during their M.Sc. studies needs to be reviewed. This is necessary in order to identify the methodologies employed, and the problems encountered by these authors and to place the work described below in context.

2.1.1 Review of synthetic studies previously conducted.

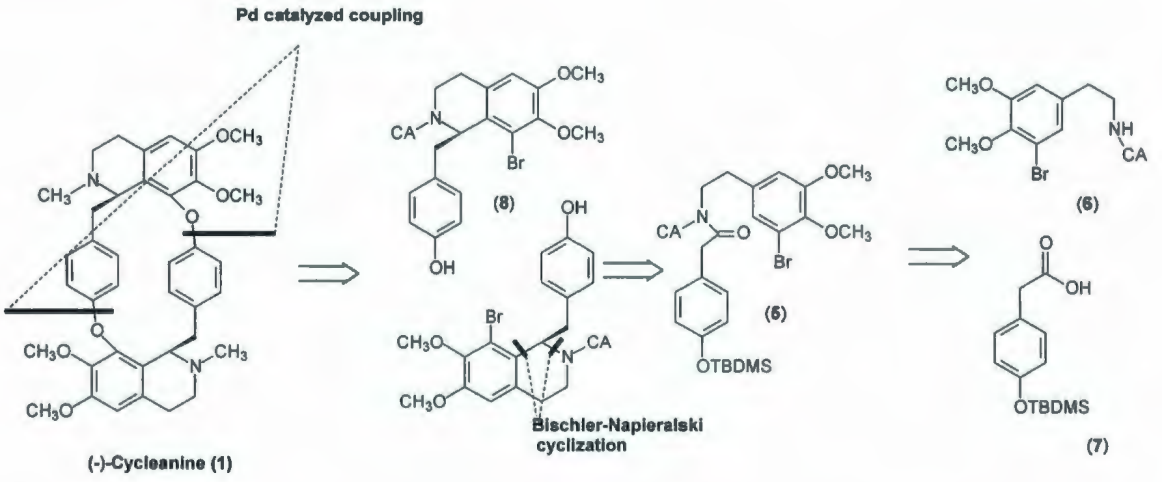
2.1.1,1 Ralph's synthetic studies.



Scheme 2.1. Ralph's first retrosynthetic approach toward (-)-cycleanine.

The first of these studies conducted in the Georghiou lab[1] in 2001 by M. Ralph.[1] The retrosynthetic analysis of the target **1**, (Scheme 2.1) suggested that the Pictet-Spengler cyclization methodology is one route that may be successfull. It was therefore first used to synthesize compound **2,** an important precursor compound in this approach towards the synthesis of (-)-cycleanine.

Ralph was unable to obtain the free hydroxyl compound **2a** derived from the key intermediate, 8-benzyloxy-1-(4-bromo-benzyloxy)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**), via the Pictet-Spengler cyclization of **3** and **4.** Attention, therefore, was next given to the application of a Bischler-Napieralski cyclization methodology.



Scheme 2.2. Ralph's second retrosynthetic approach toward (-)-cycleanine.

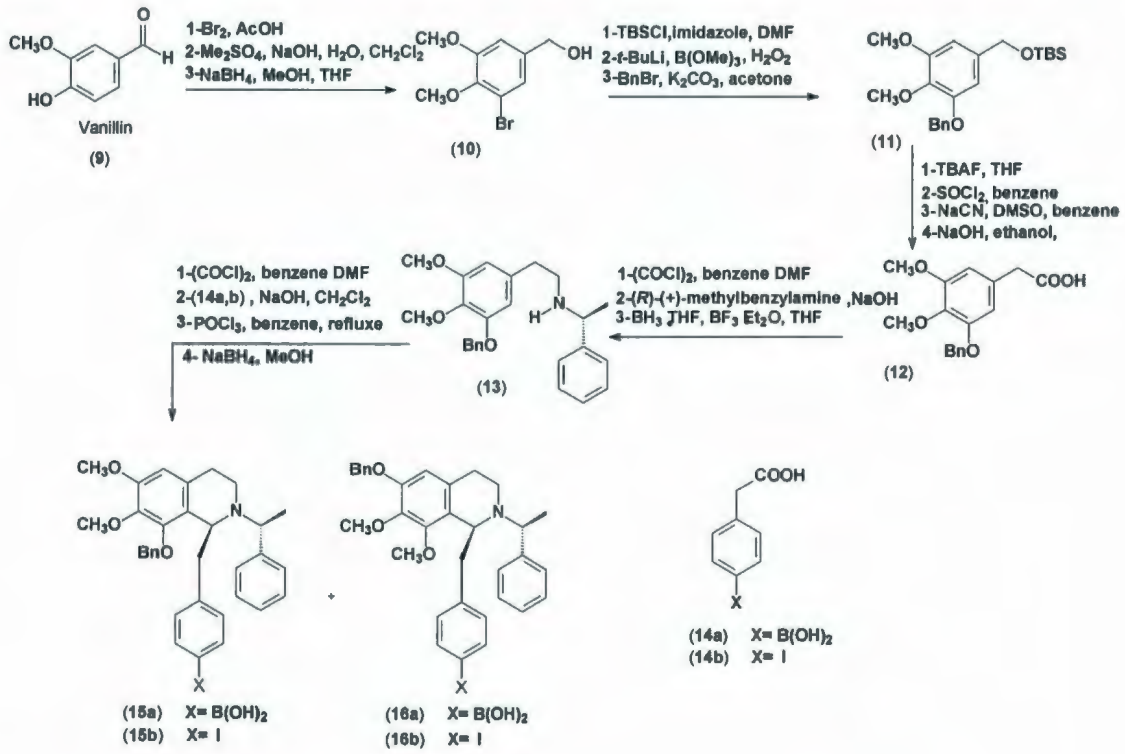
The retrosynthetic analysis shown in Scheme 2.2, provided a second approach toward **1** using a Bischler-Napieralski cyclization (BNC) methodology. This approach targeted the preparation of the key intermediate **5** by using the

secondary amine, *N*-[(*R*)-methylbenzyl]-(5-bromo-3,4-dimethoxy)phenylethanamine (**6**) and carboxylic acid **7**. Application of BNC conditions to the intermediate **5** successfully gave the benzyltetrahydroisoquinoline **8**. However, because this cyclization step gave a very low yield in his preliminary experiments, and due to his M.Sc. program time constraints, no further investigations were conducted by Ralph using this BNC approach.

2.1.1.2 Cui's synthetic studies.

In the second study which was undertaken in 2003 by Jianwen Cui[2], vanillin (**9**) was chosen as the starting material. The synthetic analysis presented in Scheme 2.3, shows that bromination, methylation and reduction of vanillin could lead to 3-bromo-4,5-dimethoxy-phenylmethanol (**10**). The hydroxy group in **10** was first protected as the *tert*-butyldimethylsilyl (TBDMS) ether to form (3-benzyloxy-4,5-dimethoxy-benzyloxy)-*t*-butyldimethylsilane (**11**). *t*-BuLi in the presence of $B(OMe)_3$ and H_2O_2 was used to convert the bromide to a phenolic hydroxyl group, which was then subsequently protected as its benzyl ether. The aryl acetic acid **12** was then obtained by removal of the TBDMS protecting group, followed by chlorination with $SOCl_2$ in benzene, cyanation with NaCN in DMSO-benzene, and subsequent hydrolysis. Because (*R*)-(α)-methylbenzylamine was demonstrated to be a convenient reagent in the enantioselective total synthesis of (-)-tejedine,[4] it was chosen to be the chiral auxiliary in Cui's attempt toward the total synthesis of (-)-cycleanine. The Introduction of the chiral auxiliary to **12,** via a Schotten-Baumann reaction, was followed by reduction of the carbonyl group

to furnish the secondary amino compound **13**. A Schotten-Baumann reaction was used again with **14a** or **14b** followed by a BNC reaction to provide the respective benzyltetrahydroisoquinolines **15a**, or **15b**, and **16a**, or **16a**.



Scheme 2.3. Cui's attempt toward the synthesis of (-)-cycleanine.

After re-evaluation of this work, three drawbacks were noted: (1) The neccessity of creating a new hydroxy group demanded two additional steps. A starting material therefore, with three hydroxy groups already present could have some advantages; (2) Using an expensive protecting group (TBDMSCl) could be disadvantageous in a larger-scale synthesis; (3) Separation of the two isomers

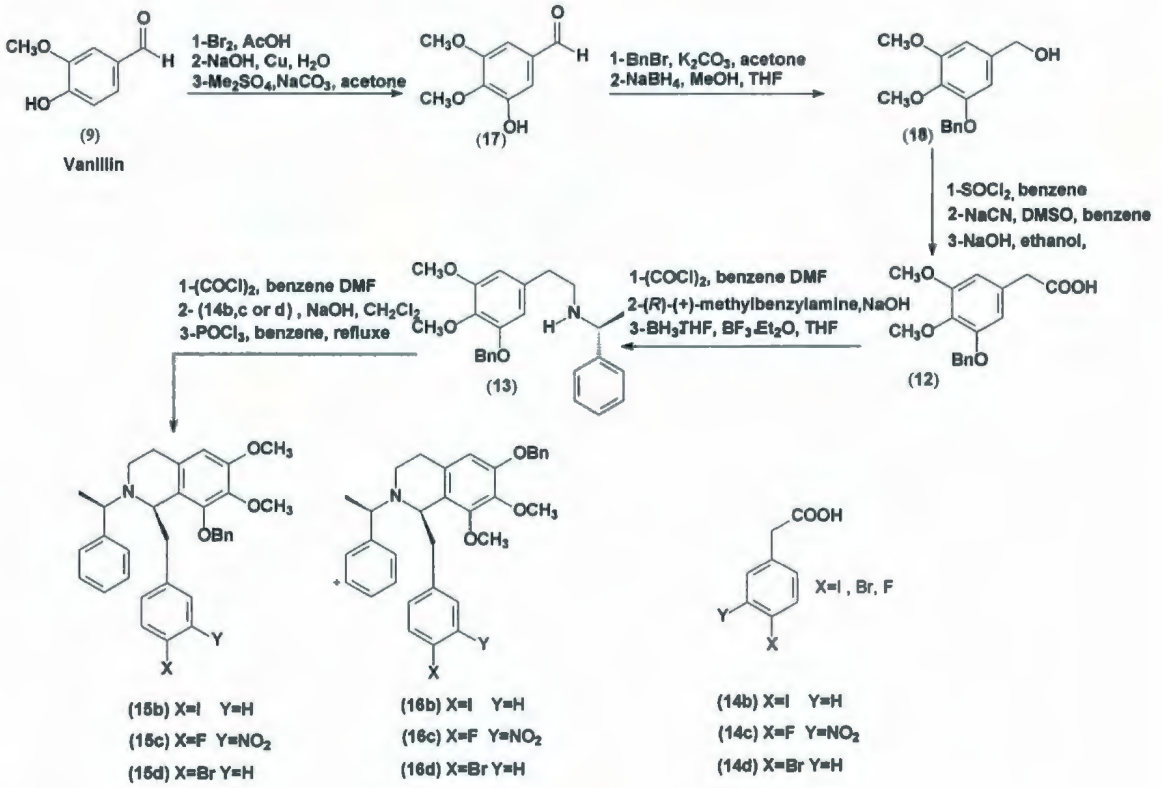
which were generated in the BNC step is not an easy task, in addition to the low yields obtained of the desired compound.

Despite these experimental difficulties, the methodology employed was seen to be a useful route towards the total synthesis of cycleanine. However, the problems encountered described above, coupled to the very small amounts of the precursors obtained for the biaryl ether formation step and his time constraints, a systematic investigation by Cui for the last steps required to produce the target compound was precluded.

2.1.1.3 Zhou's synthetic studies.

In the third study,[3] vanillin was again chosen as a starting material. Zhou followed almost the same strategy as Cui but with some variations, as shown in Scheme 2.4. Vanillin was mono-brominated followed by conversion of the bromide to a hydroxyl group with Cu/NaOH, instead of via the *t*-BuLi/$B(OMe)_3$ sequence used in Scheme 2.3. Mono methylation of the C-4 hydroxyl followed by sequential benzylation and reduction of the aldehyde group afforded **18**. The carboxylic acid **12** was then prepared in three steps. Conversion of **12** to the chiral auxiliary-protected secondary amine **13** was achieved via a Schotten-Baumann reaction and subsequent reduction of the precursor amide using $BH_3/BF_3{\cdot}Et_2O$. In order to prepare the key benzyltetrahydroisoquinoline intermediates **15b-d** and **16b-d**, the corresponding carboxylic acids **14b-d** respectively were introduced to compound **13** each via a Schotten-Baumann

reaction, followed by a BNC reaction. The lack of regioselectivity in the BNC step however was a major impediment that prevented successful completion of the synthesis of (-)-cycleanine by Zhou.



Scheme 2.4. Zhou's approach toward the synthesis of (-)-cycleanine.

2.2 Results and Discussion.

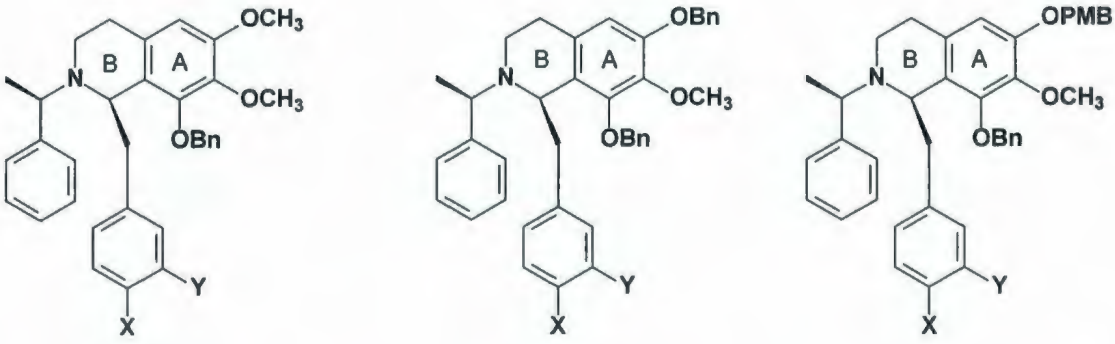
Cycleanine has been shown to be biologically-active with potential pharmacological applications. For further studies, a relatively inexpensive and concise process for producing the required starting materials and intermediates which could also allow for structural modifications as well would represent a

major contribution. Two different enantioselective synthetic strategies were examined in this work and are described in the following sections.

2.2.1 Attempts toward the total synthesis of (-)-cycleanine.

2.2.1.1 Preparation of the intermediates 15b-d, 19a-c and 20a-c.

The benzyltetrahydroisoquinolines **15b-d**, **19a-c** and **20a-c** (Figure 2.1) were targeted as potential precursors to achieve the synthesis of (-)-cycleanine (**1**).



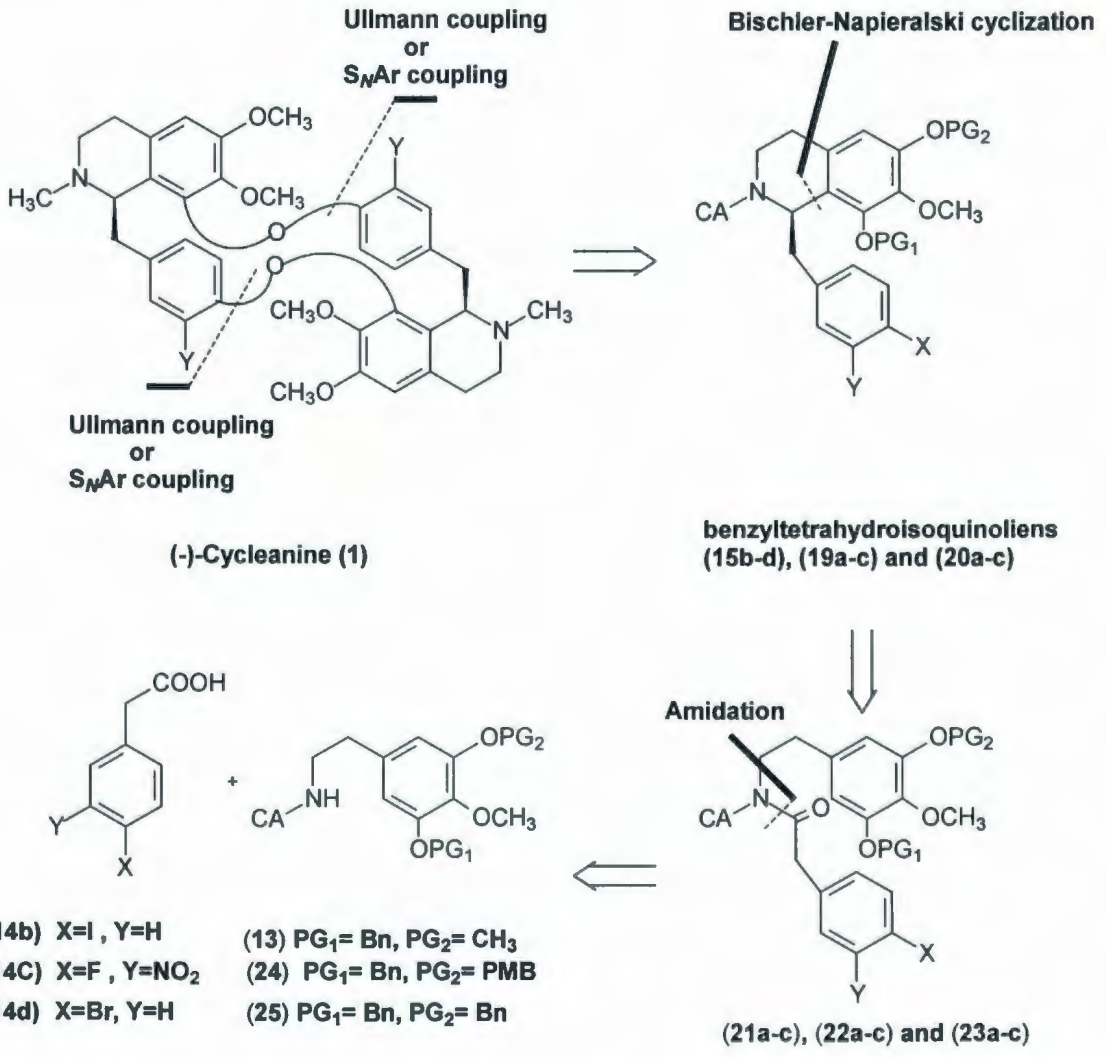
(15b) X= I, Y=H
(15c) X= F, Y=NO_2
(15d) X= Br, Y=H

(19a) X= I, Y=H
(19b) X= F, Y=NO_2
(19c) X= Br, Y=H

(20a) X= I, Y=H
(20b) X= F, Y=NO_2
(20c) X= Br, Y=H

Figure 2.1. Benzyltetrahydroisoquinolines **15b-d, 19a-c** and **20a-c.**

As described in Chapter 1, (-)-cycleanine (**1**) has a C_2-symmetric structure and is connected in a "head-to-tail" fashion by two diaryl ether linkages. The retrosynthetic approaches which were employed in the present study to achieve its total synthesis are outlined in Scheme 2.5.



Scheme 2.5. Retrosynthetic analysis for the preparation of (-)-cycleanine via precursors **15b-d**, **19a-c** and **20a-c**.

Scheme 2.5 shows that there are at least four synthetic challenges needed to be overcome in order to complete the total synthesis of (-)-cycleanine (**1**). These include:

1. What is the appropriate starting material which is suitable for preparation of the precursors **13**, **24** and **25**?

2. How can the regioselective cyclization steps be accomplished with acceptable yields?

3. How can the desired stereocenter on **15b-d**, **19a-c** and **20a-c** be created with high enantioselectivity?

4. What is the best methodology to accomplish the diaryl ether coupling step?

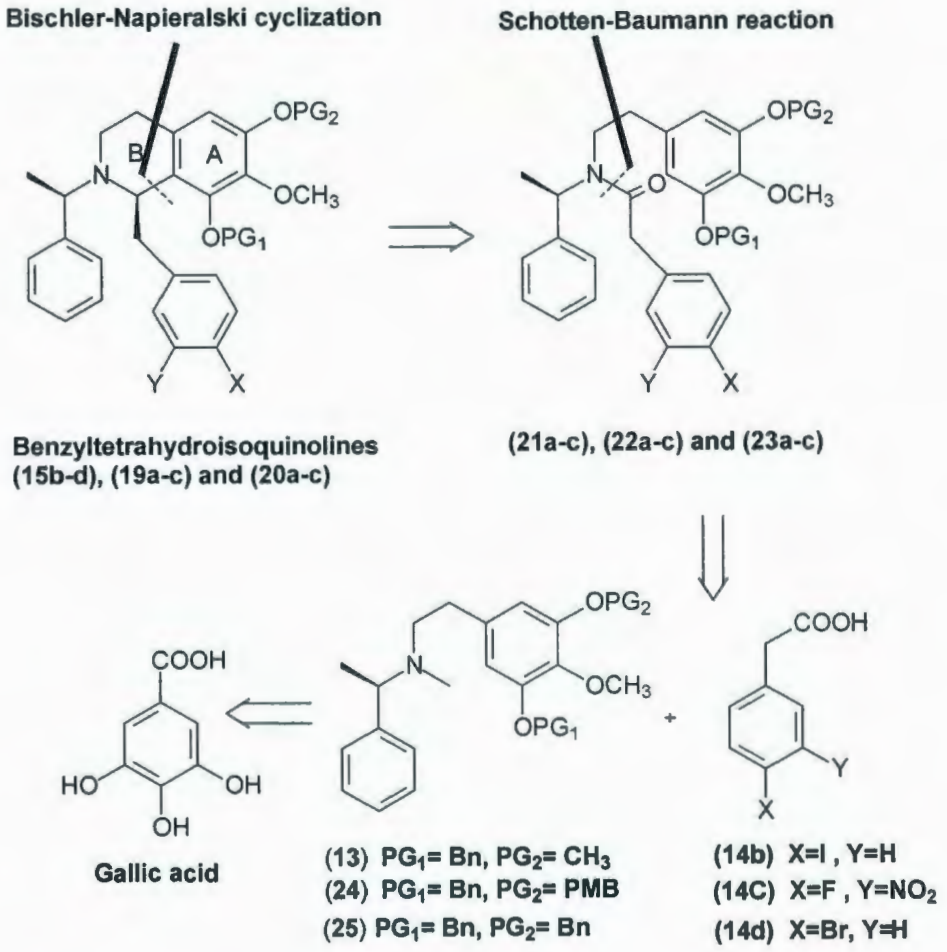
The answers to questions 1, 2 and 3 are presented below with the assistance of Scheme 2.6. However, the last problem, namely, the diaryl coupling will be addressed in a later section.

2.2.1.2 The retrosynthetic analysis for the synthesis of benzyltetrahydroisoquinolines 15b-d, 19a-c and 20a-c.

Even though the previous attempts did not reach the final target, they provided very valuable guidance. From those attempts it was evident that there were some drawbacks to the approaches which have been tried, and thus needed to be avoided as much as possible. At the same time, attention has been paid in order to benefit from those steps which were useful and constructive.

As outlined in Scheme 2.6, gallic acid provides an answer to the first question noted above for three reasons: (i) It is a reasonably cheap starting material; (ii) It has three hydroxyl groups which can be selectively protected in order to build the key intermediates **13**, **24** and **25**; and (iii) It has a carboxylic acid group which can be utilized to assemble ring **B** on **15b-d**, **19a-c** and **20a-c**.

The plan for the synthesis of compounds **15b-d**, **19a-c** and **20a-c** was then to first employ a Schotten-Baumann reaction using secondary amines **13**, **24** and **25** with **14b-d**, respectively, followed by Bischler-Napieralski cyclizations. Selective protection of each of the three hydroxyl groups on the gallic acid, and elaboration of the carboxylic acid functional group to a chain- extended secondary amine lead to compounds **13**, **24** and **25**. The synthesis of the carboxylic acids **14b**, **14c** and **14d** are discussed in later paragraphs.



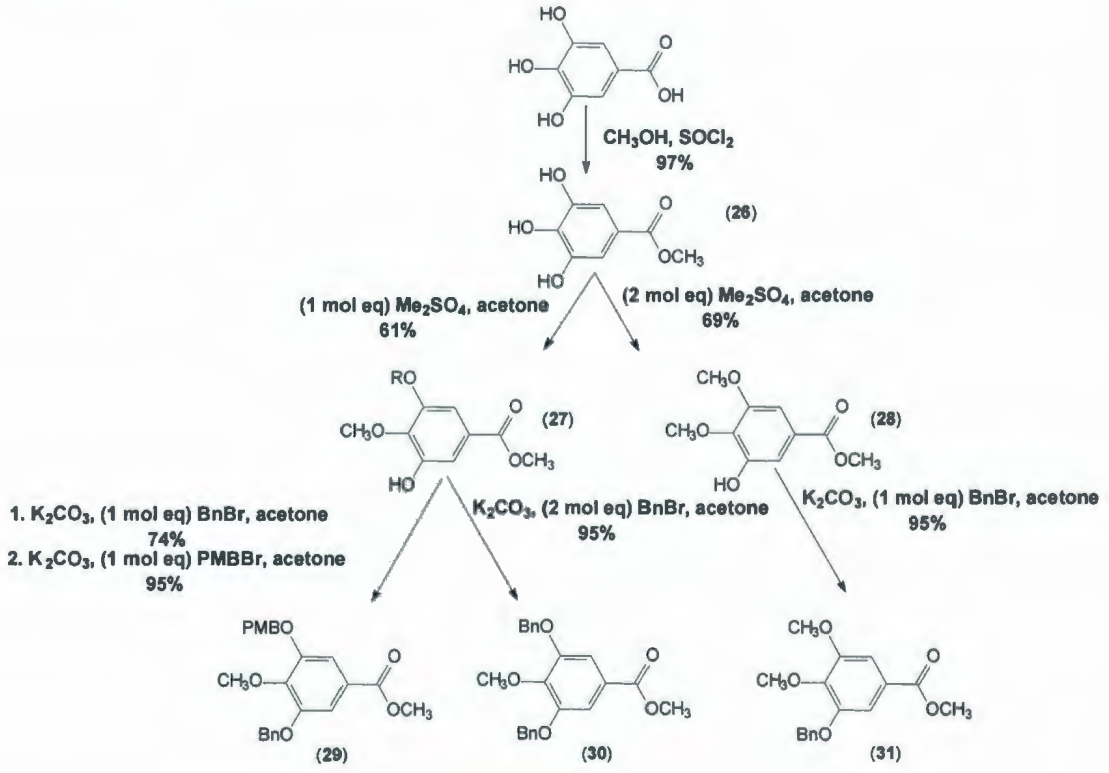
Scheme 2.6 The retrosynthetic analysis of **15b-d**, **19a-c** and **20a-c**.

In the previous attempts toward the synthesis of cycleanine, the introduction of the hydroxyl group into the aromatic ring was one of the drawbacks. Gallic acid however possesses three hydroxyl groups and thus two steps could be eliminated from the synthesis. Benzyl bromide and *para*-methoxy benzyl bromide (PMBBr) were utilized to protect two of the hydroxyl groups on gallic acid, thus producing the intermediates needed for **13**, **24** or **25**. To investigate the Bischler-Napieralski cyclization step and improve the yields obtained in this step, three strategies were decided upon: (i) To protect one of *meta*-hydroxyl groups as its benzyl ether and convert the others to methoxys; or (ii) To protect one *meta*-hydroxyl as its benzyl ether and the other *meta* hydroxyl as its PMB ether and convert the remaining one to a methoxy group; or (iii) To protect both of the two *meta*-hydroxyl groups as the benzyl ether and the remaining one as its methoxy ether. Subsequent to forming the BNC steps comparison was made to establish which approach gave a higher yield of the desired intermediates benzyltetrahydroisoquinoline **15b-d**, **19a-c** and **20a-c**.

2.2.1.3 Synthesis of the benzyltetrahydroisoquinolines 15b-d, 19a-c and 20a-c.

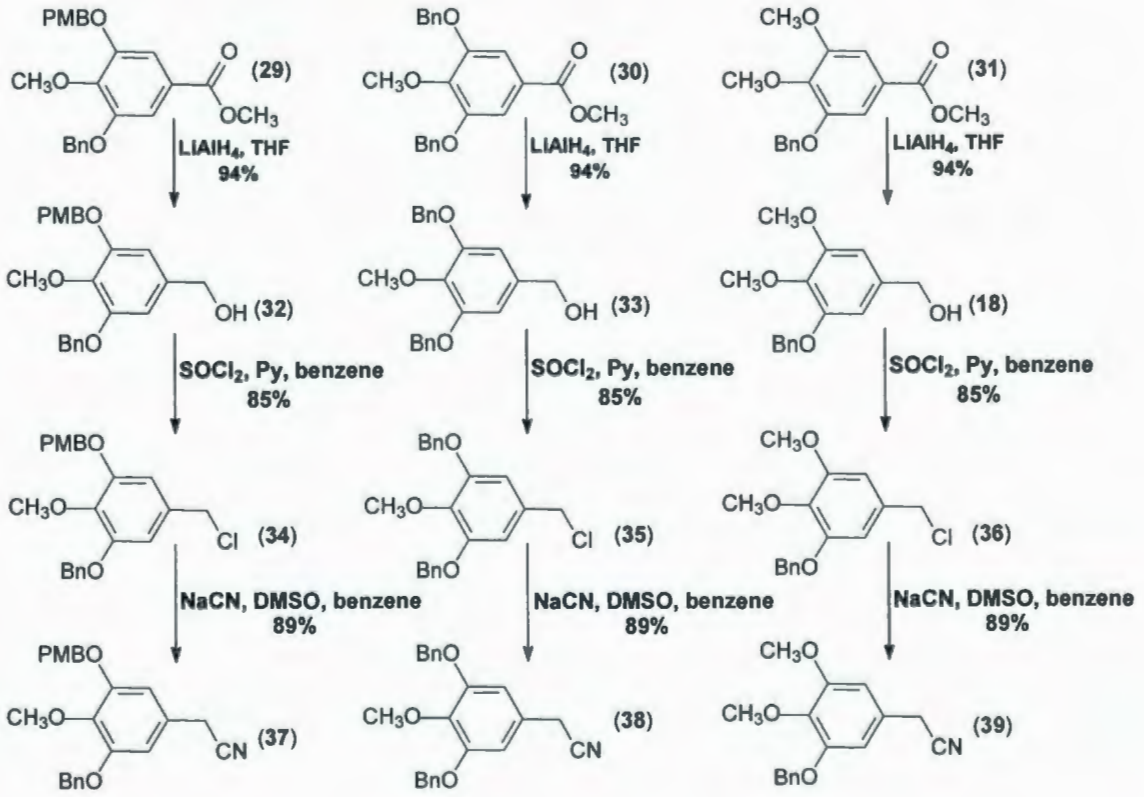
As shown in Scheme 2.7, the first step using the strategy presented in Scheme 2.6 is the esterfication of gallic acid by MeOH and $SOCl_2$ to form methyl gallate (**26**) (95% yield). Methyl-3,5-dihydroxy-4-methoxygallate (**27** R=H) and methyl-3-hydroxy-4,5-dimethoxygallate (**28**) are formed in yields of 61% and 69 % respectively by treating compound **26** respectively with 1 or 2 (mol equiv) of

dimethyl sulfate[5] and potassium carbonate in acetone. Selective mono-methylation of the C-4 hydroxyl in greater than 61% yield was not achievable. After several conditions were tried, it was found that the yield could be increased to 61% by decreasing the dimethyl sulfate addition time and cooling the reaction temperature to 0 °C during the addition. Treatment of compound **27** (R=H) with 1 (mol equiv) benzyl bromide, to form **27** (R=CH_3) and then with 1 (mol equiv) PMBBr in the presence of K_2CO_3 and acetone[5] afforded methyl-3-benzyloxy-4-methoxy-5-(4-methoxy-benzyloxy)gallate (**29**) in 70.3% yield. Treating **27** with 2 (mol equiv) BnBr in the presence of K_2CO_3 and acetone furnished methyl-3,5-dibenzyloxy-4-methoxy-gallate (**30**) in 95% yield.



Scheme 2.7. Synthesis of intermediates **29**, **30** and **31**.

Treatment of **28** with stoichiometric amounts of BnBr and K_2CO_3 in acetone provided the dimethoxylated **31** in 95% yield. As summarized in Scheme 2.8, preparation of the three intermediates, 2-(3-benzyloxy-4-methoxy-5-(4-methoxy-benzyloxy)phenyl acetonitrile (**37**), 2-(3,5-dibenzyloxy)-4-methoxy-phenyl acetonitrile (**38**) and 2-(3-benzyloxy-4,5-dimethoxyphenyl) acetonitrile (**39**) from compounds **29-31**, respectively was each achieved in three steps.

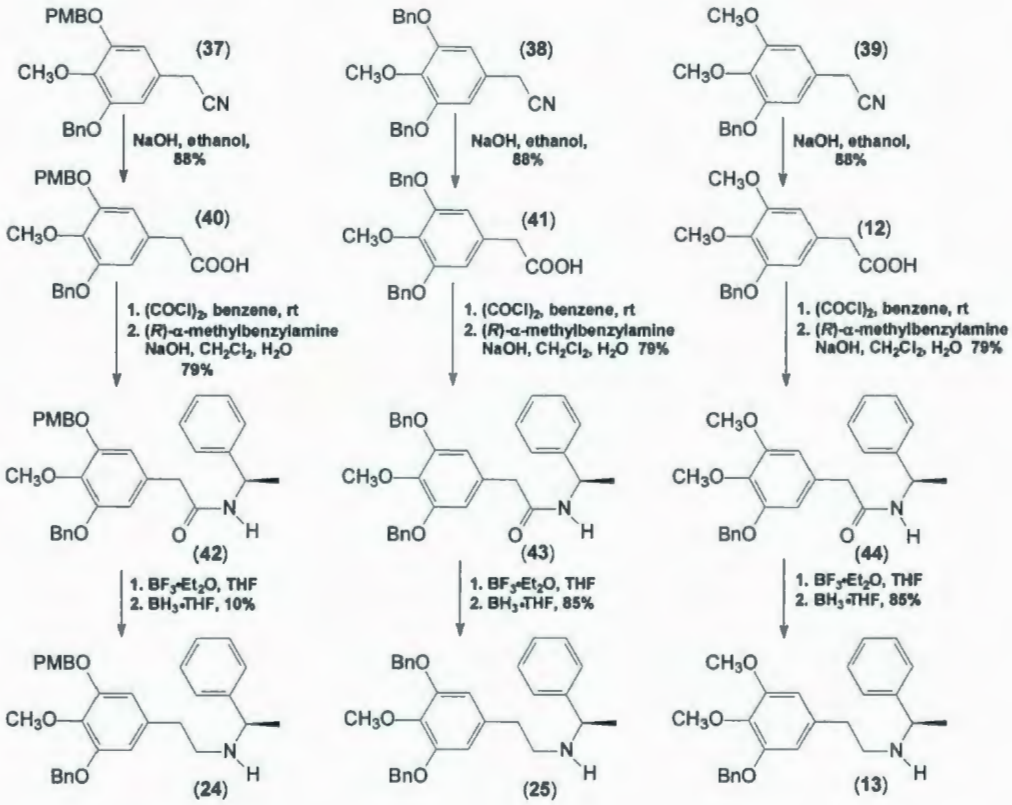


Scheme 2.8. Synthesis of intermediates **37**, **38** and **39**.

First, reduction of the ester groups of compounds **29, 30** and **31** by lithium aluminum hydride provided the corresponding compounds 3-benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)benzyl alcohol (**32**), 3,5-dibenzyloxy-4-

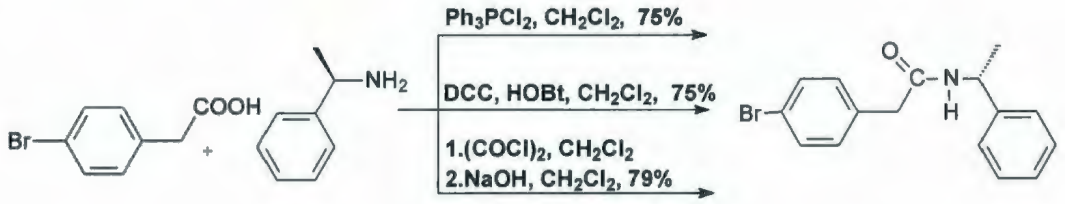
methoxybenzyl alcohol (**33**), and 3-benzyloxy-4,5-dimethoxybenzyl alcohol (**18**), each in almost the same yields (94%). Next, using $SOCl_2$ in the presence of pyridine and benzene converted compounds **32, 33** and **18** to the corresponding chlorides namely 3-benzyloxy-4-methoxy-5-(4-methoxy-benzyloxy)benzyl chloride (**34**), 3,5-dibenzyloxy-4-methoxybenzyl chloride (**35**) and 3-benzyloxy-4,5-dimethoxy- benzyl chloride (**36**). Finally, the cyanation of **34-36** to form compounds **37-39** respectively each in 89% yields was achieved using NaCN in dimethyl sulfoxide and benzene. It was found that the benzyl chlorides compounds **34-36** needed to be very dry, and that the addition of the NaCN must added in small portions, otherwise, oily products with difficulty to purify were formed. Scheme 2.9 shows the conversion of compounds **37-39** to the corresponding secondary amines on compounds **24, 25** and **13.**

The third question posed previously will now be addressed. There are many different strategies or methods available to produce the desired stereogenic centers on organic compounds. One of the most common methods is by using a chiral auxiliary. For the total synthesis of (-)-tejedine,[4] several chiral auxiliaries were investigated to achieve this task. (*R*)-α-methylbenzylamine was found to be the best chiral auxiliary to use in order to realize the required target compounds. The same chiral auxiliary was therefore used in the syntheses of tetrahydroisoquinolines **15b-d**, **19a-c** and **20a-c**.



Scheme 2.9. Syntheses of intermediates **24**, **25** and **13**.

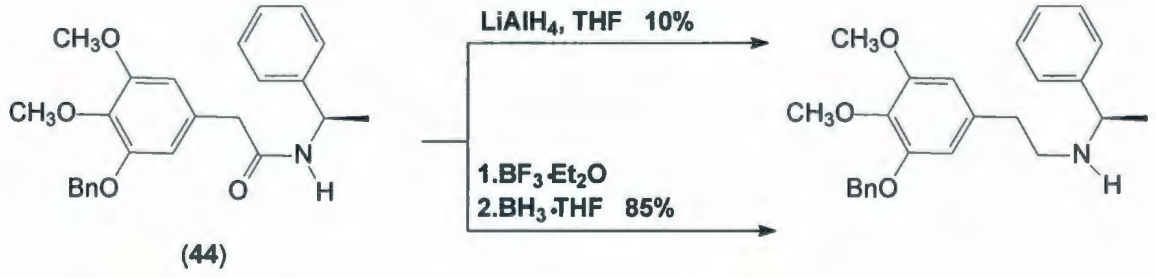
This chiral auxiliary afforded excellent results in the present study. Scheme 2.9 shows the hydrolysis of the cyano groups on compounds **37**-**39** in basic media using NaOH and ethanol, to produce, after acidification, the corresponding carboxylic acids 3-benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)-benzoic acid (**40**), 3,5-dibenzyloxy-4-methoxy benzoic acid (**41**) and 3-benzyl-oxy-4,5-dimethoxybenzoic acid (**12**) each in 88% yields. Before introducing the chiral auxiliary to compounds **40**, **41** and **12**, model reactions as outlined in Scheme 2.10 were first evaluated in order to determine which method afforded the best results for amide formation.



Scheme 2.10. Model reactions for introducing the chiral auxiliary group.

As outlined in Scheme 2.10, the model reactions were used on *p*-bromophenylacetic acid and the chiral auxiliary by using three different methods: (i) Oxalyl chloride conversion of the carboxylic acid to the acid chloride, followed by a Schotten Baumann reaction; (ii) Use of dicyclohexylcarbodiimide (DCC), in the presence of 1-hydroxybenzotriazole (HOBt);[6] and (iii) use of dichlorotriphenylphosphorane (Ph_3PCl_2) reagent[7] in CH_2Cl_2 to form the acid chloride *in situ*. The three methods provided almost the same yields of chiral-auxiliary-functionalized amide. Even though dealing with oxalyl chloride makes the Schotten-Baumann procedure the most demanding technique of these three methods, it was chosen as the method for introducing the chiral auxiliary to compounds **40, 41**, and **12** because the subsequent purification step proved to be the simplest of the three. The amides *N*-((*R*)-α-methylbenzyl)-(3-benzyloxy-4-methoxy-5-(4-methoxy-benzyloxy) phenylacetamide (**42**), *N*-((*R*)-α-methylbenzyl)-(3,5-dibenzyloxy-4-methoxy) phenylacetamide (**43**) and *N*-((*R*)-α-methylbenzyl)-(3-benzyloxy-4,5-dimethoxy) phenylacetamide (**44**) were synthesized in approximately 10% and 85% yields, respectively.

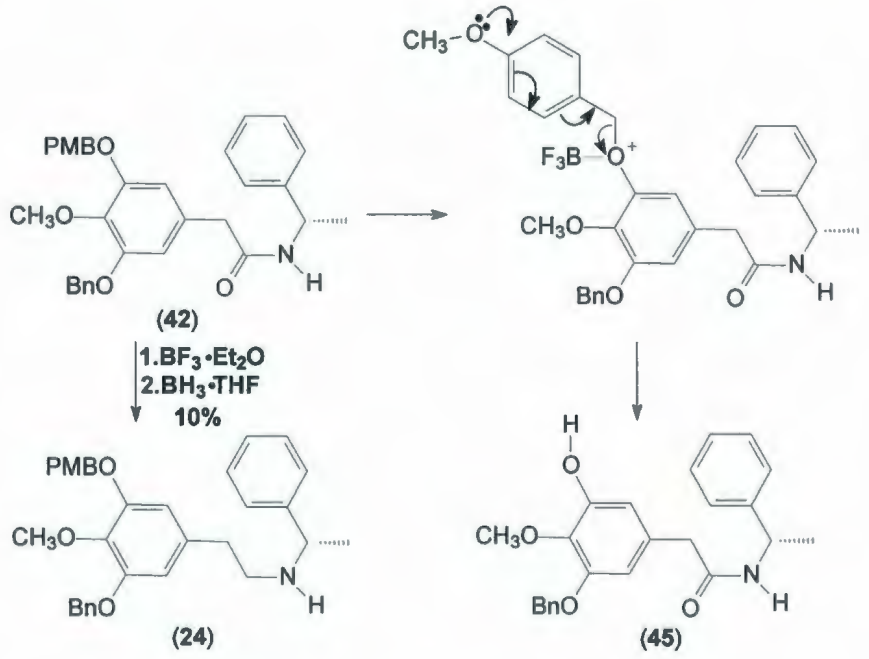
Conditions for the optimal reductions of the secondary amides to the corresponding secondary amines were evaluated using two different methods summarized in Scheme 2.11. Even though use of $LiAlH_4$ in THF has been reported as being a successful reagent for reduction of an amide group,[8] attempts in our hands did not meet with great success. Using borane tetrahydrofuran complex (BH_3·THF) and catalytic amounts of boron trifluoride etherate ($BF_3 \cdot Et_2O$) however, produced the desired product in 85% yield.



Scheme 2.11. Reduction of the amide group using two different methods.

Interestingly, reduction of the three different amides with BH_3·THF did not provide the same yields. While the reduction yield of compounds **43** and **44** were both approximately 85%, the reduction yield of compound **42** was only 10%. As outlined in Scheme 2.12 the major product was compound **45** instead of the desired product **24**. The proposed mechanism of this deprotection of PMB ether is illustrated in Scheme 2.12.[9,10] Boron trifluoride can co-ordinate with the PMB ether oxygen atom, after that, an electronic delocalization takes place to release the parent phenol. The boron trifluoride can also be attacked by the benzyl ether oxygen. Nevertheless, the lack of a *p*-methoxy group on the benzyl protecting

group makes this kind of electronic delocalization ineffective in the case of a simple benzyl group. Therefore, some Lewis acids can be utilized for selectively removing of the PMB protecting group in the presence of a benzyl protecting group.

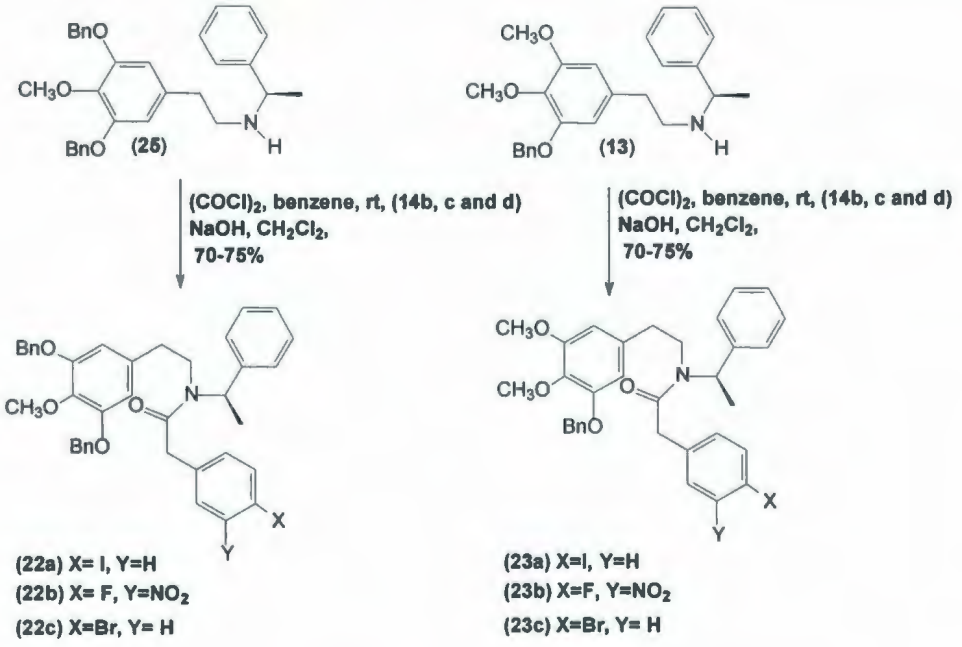


Scheme 2.12. Proposed mechanism of cleavage of PMB-protecting group by $BF_3 \cdot Et_2O$.

Since the yield of the transformation from the secondary amide **42** to the secondary amine **24** was very low, no further investigations were conducted on **24**. Instead, amide **45** was re-protected with a benzyl group to produce the di-benzylated secondary amide **43**. Attention was concentrated on the remaining secondary amines **25** and **13**. Since compounds **25** and **13** were on hand,

Schotten-Baumann conditions were again applied to obtain the tertiary amides **22a-c** and **23a-c** respectively, in 72-75% yields (Scheme 2.13).

Before proceeding to the next steps, the strategies for preparing the carboxylic acids **14b-d** have to be revealed first. As mentioned in Chapter 1, there are two major methodologies to achieve the diaryl ether coupling reactions: (i) Ullmann reactions, and (ii) S_NAr reactions.

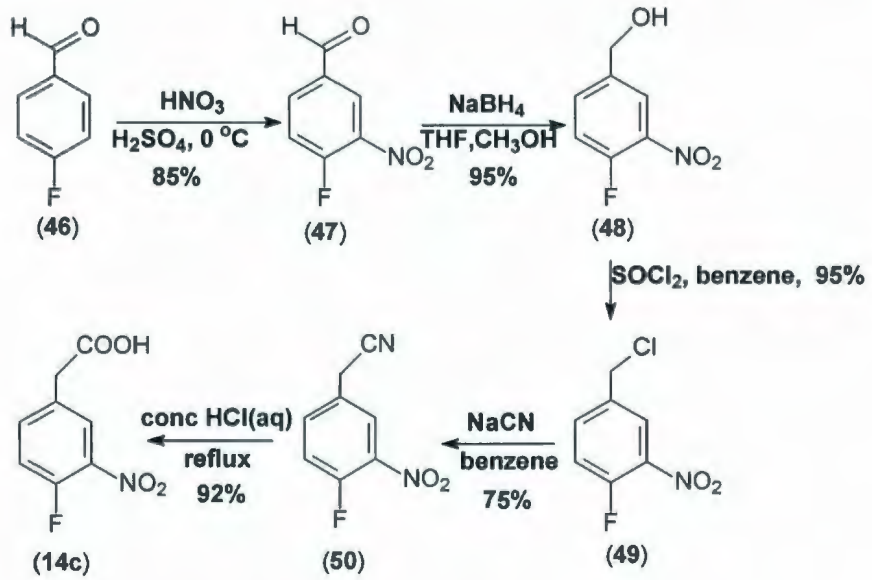


Scheme 2.13. Preparation of the tertiary amides **22a-c** and **23a-c**.

One of the requirements of the Ullmann reaction is the presence of a good leaving group on the aromatic ring such as Br, I, or $B(OH)_2$. However, part of the requirements of the S_NAr reactions is the presence of a good electron-withdrawing group on the aromatic ring. In attempts to investigate which strategy

would give better results in the diaryl ether coupling step, three different carboxylic acids were prepared: **14c** which was utilized for the S_NAr reaction, and **14b** and **14d** which were utilized in the Ullmann reactions. As illustrated in Scheme 2.14, 4-fluoro-3-nitrophenylacetic acid was prepared in five steps. A previous study[11] has shown that the presence of a nitro group ortho to a fluoride group facilities the nucleophilic substitution of the fluoride on the aromatic ring (S_NAr).

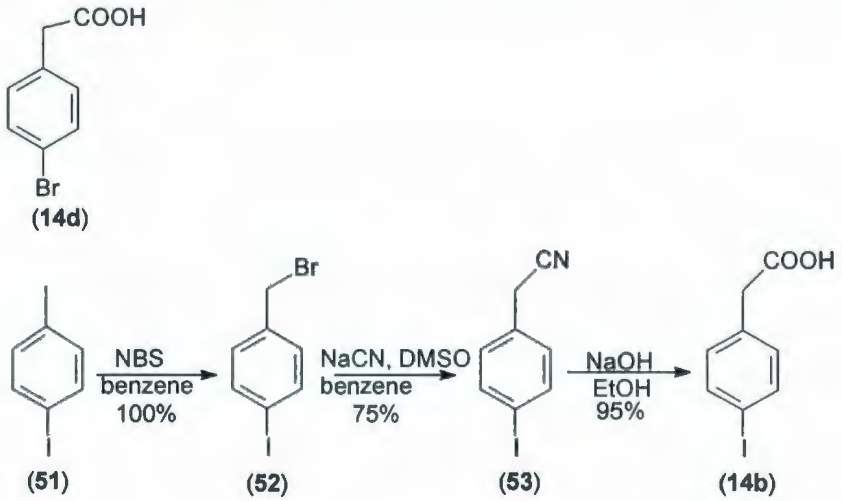
Scheme 2.14 commences with the nitration of the commercially-available starting material 4-fluorobenzaldehyde (**46**) using a mixture of HNO_3 and H_2SO_4 to produce 4-fluoro-3-nitrobenzaldehyde (**47**) in 85% yield. Reduction of the aldehyde group to the corresponding primary alcohol was accomplished using sodium borohydride to furnish 4-fluoro-3-nitrobenzyl alcohol (**48**) in 95% yields.



Scheme 2.14. Preparation of the carboxylic acid **14c.**

Conversion of the primary hydroxyl group using $SOCl_2$ in benzene furnished 4-fluoro-3-nitrobenzyl chloride (**49**) in 95% yields. Cyanation of **49** using sodium cyanide gave 4-fluoro-3-nitrophenyl acetonitrile (**50**) in 75% yields. Finally, hydrolysis of the cyano group in acidic media using aqueous concentrated HCl under reflux conditions gave the desired carboxylic acid **14c** in 92% yields.

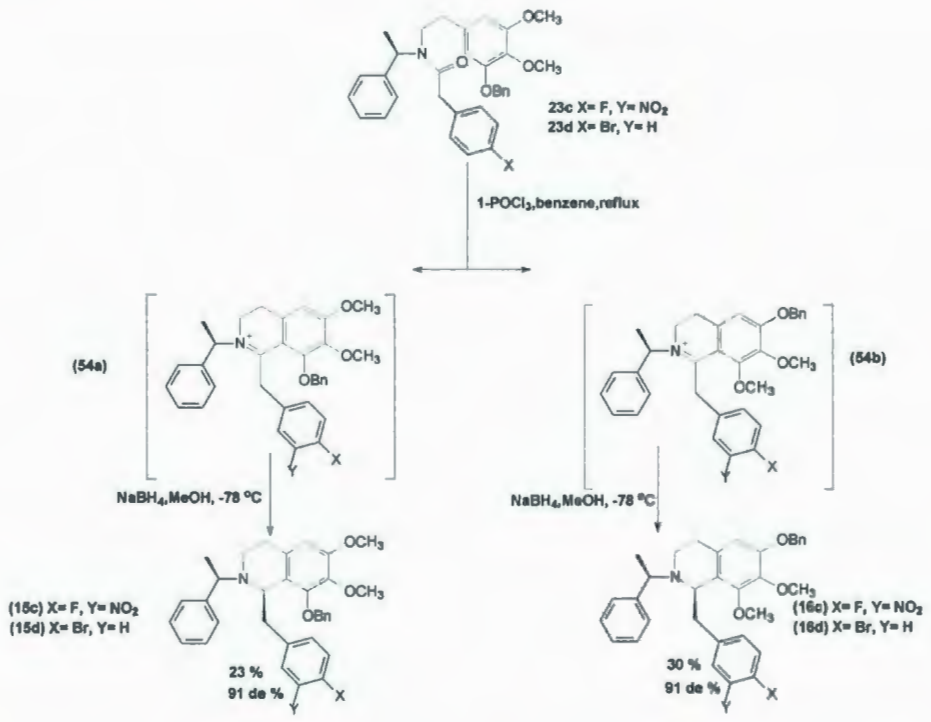
p-Bromophenylacetic acid (**14d**) is commercially available, but *p*-iodophenyl acetic acid (**14b**) was synthesized in three steps as shown in Scheme 2.15. Treatment of the starting material, *p*-iodotoluene (**51**) with *N*-bromosuccinimide (NBS) lead to the formation of *p*-iodobenzylbromide (**52**) in quantitative yields. Cyanation followed by hydrolysis of compound **52** gave *P*-iodophenyl acetonitrile (**53**) and *p*-iodophenylacetic acid (**14b**) respectively.



Scheme 2.15. Preparation of the carboxylic acid **14b.**

Extensive investigations were conducted in order to explore whether compounds **22a, 22b** and **22c**, which each have two protecting groups or compounds **23a**, **23b**, and **23c**, which each have a single protecting group gave better results in the BNC step.

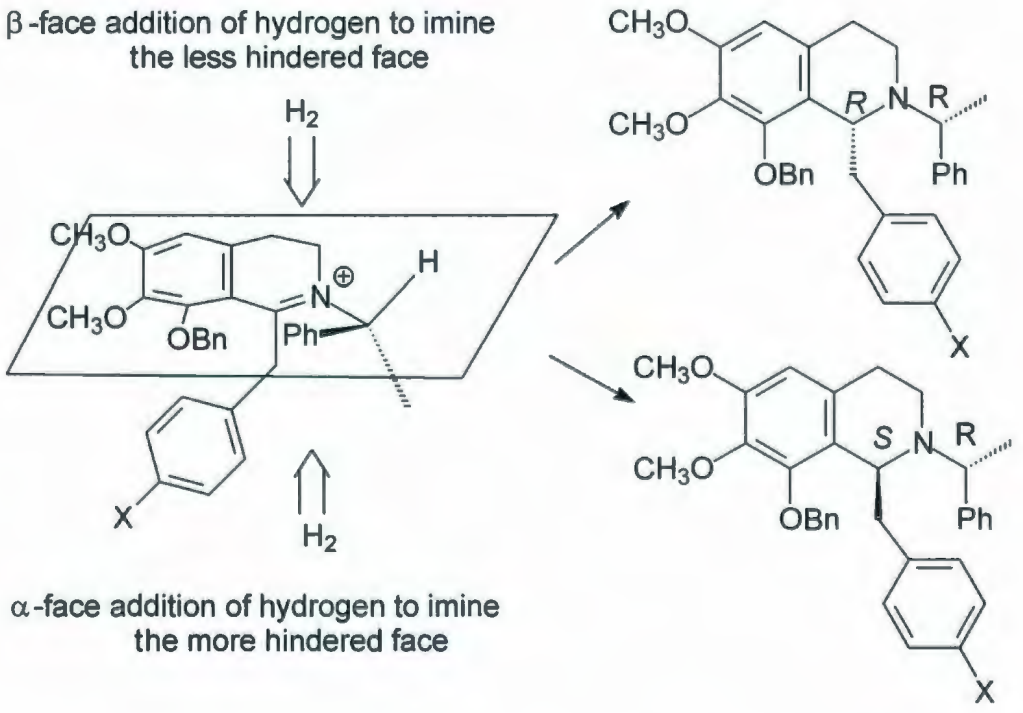
Application of BNC conditions therefore on compounds **23c,** and **23d** each formed two regioisomers **15c** and **16c**; and **15d** and **16d,** respectively (Scheme 2.16). Since there are two promising ringclosure sites, *ortho* and *para* to the benzyloxy group, on each of the amides **23c,** and **23d**, the BNC step would be predicted to produce two ring closure products



Scheme 2.16. Preparation of the benzyltetrahydroisoquinolines **15c, d** and **16c, d.**

After heating the amides **23a,** and **23c** with phosphorus oxychloride in anhydrous benzene for 6 h at reflux, the resulting mixture of iminium salts **54a,** and **54b** were reduced by sodium borohydride to produce two regioisomers **15b** and **15d;** and **16bc** and **16d** for each pair in 23%, 91de% and 30%, 91de% yields, respectively. The desired regioisomers **15c-d** were produced in > 91% de, as calculated approximately from their ^{1}HNMR spectra.

The presence of the chiral auxiliary most probably causes the reduction to occur from the less-hindered face (*Re*-face) to produce the desired stereogenic center.[12] This would be as a result of the steric hindrance offered by the phenyl and benzyl groups of the chiral auxiliary moiety (Scheme 2.17).



Scheme 2.17. Effect of the chiral auxiliary on the direction of the reduction.

The cyclization to the site *para* to the benzyloxy group was preferred to that of the *ortho* site due to the steric hinderance offered by the benzyloxy group, the yields of compound **16b** and **d** were higher than those of compound **15b** and **15d**. The chromatographic purification of each of the regioisomers was not easily achieved, since their properties are very similar to each other. Three successive columns chromatographic separation were needed.

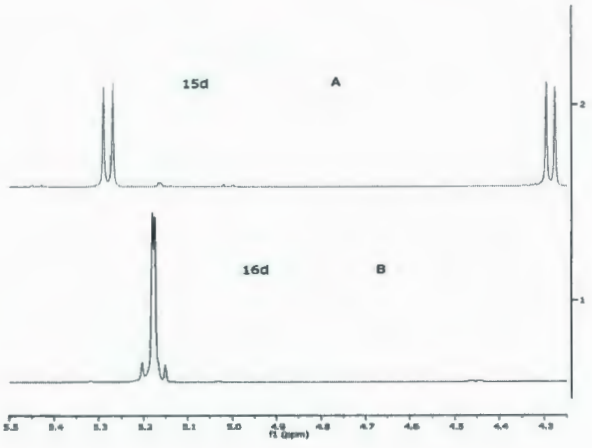


Figure 2.2. (*A*): H_a and H_b ^1H NMR shifts of compound **15d**; (*B*): H_a and H_b ^1H NMR shifts of compound **16d**.

Distinguishing between each of two regioisomers was achieved using two different techniques. First; the ^1H NMR spectra of the benzyltetrahydroisoquinoline **15d** shows two doublet signals at δ=5.12 and 4.20 ppm (J_{AX} = 9.7*Hz*) (Figure 2.2 A) which is a first-order splitting pattern. These two signals belong to protons H_a, and H_b, on the benzyl group. The two protons have different chemical shifts, because they are influenced unequally by the adjacent

p-bromobenzyl group. Since there is no direct influence of the *p*-bromobenzyl group on protons H_a and H_b for compound **16d** the two protons appear at δ= 5.19 and 5.15 ppm (J_{AB} =5 Hz), which is a second-order splitting pattern (Figure 2.1B). Second, X-ray crystallography[13] (Figure 2.3) confirms the ring closure site and the desired stereogenic center of compound **15d**.

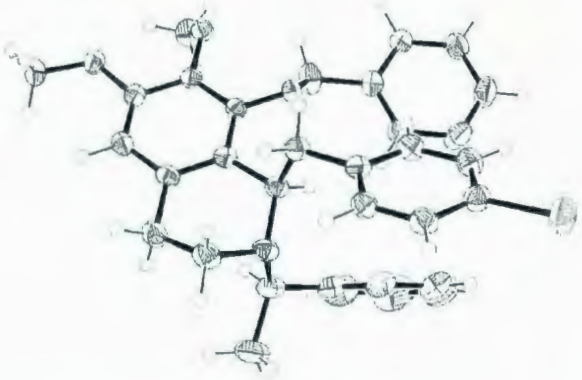
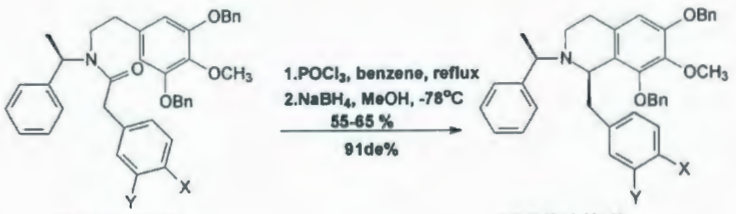


Figure 2.3. The X-ray crystallographic structure of compound **15d.**

Applying the BNC conditions to compounds **22a-c** resulted in the formation of benzyltetrahydroisoquinolines **19a-c** in 55-65% yields and in > 91% de, as calculated approximately from their ^{1}HNMR spectra.



Scheme 2.18. Preparation of the intermediates **19a-c.**

As shown in Figure 2.4, the X-ray crystal structure of compound[14] **19c** shows the desired stereogenic center. Unfortunately, attempts to crystallize compounds **19a** and **19b** did not meet with similar success.

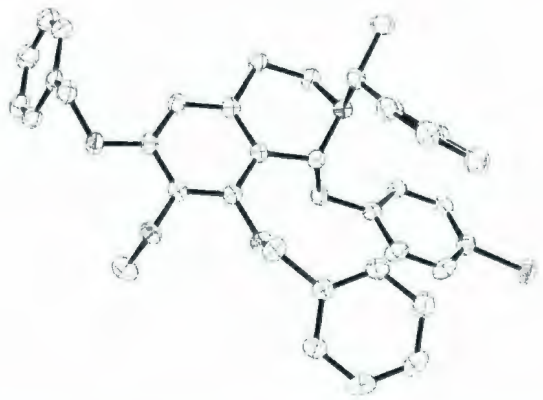
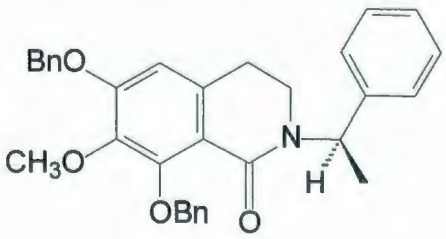
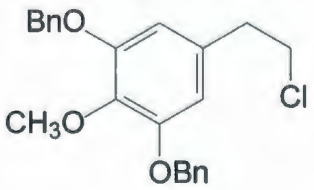


Figure 2.4. The crystallographic structure of compound **19c**.

Moreover, two side-products **55** which was obtained in 5% yield and **56** which was obtained 10% yield were separated after the application of BNC step on compound **22b** (Figure 2.5).



(55)



(56)

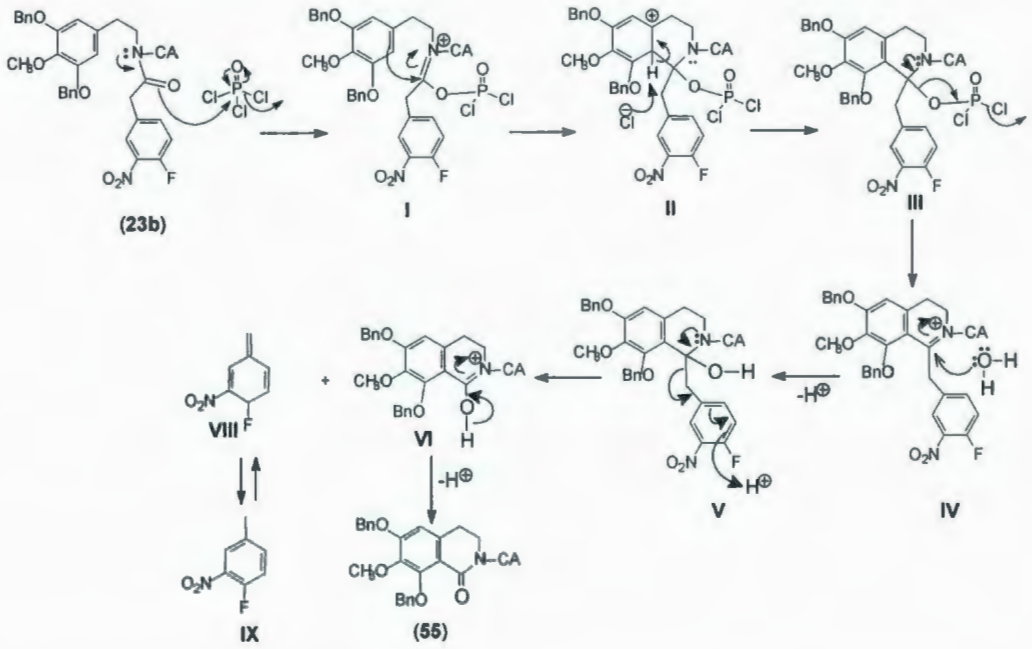
Figure 2.5. The two-side products **55** and **56.**

X-ray crystallography[15] for compound **56** established the structure of this compound (Figure 2.6).

Figure 2.6 The crystallographic structure of compound **56.**

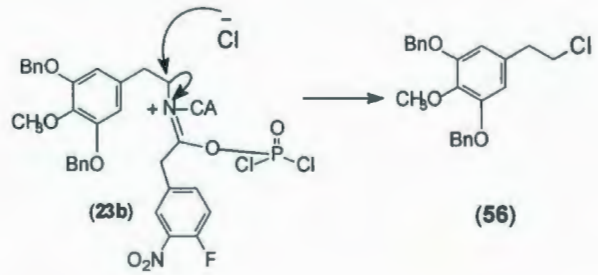
Before continuing the description on the synthetic endeavors, two observations will be elaborated upon. First, the proposed mechanisms of formation of compounds **55** and **56** from compound **22b**, will be presented with the assistance of Schemes 2.19 and 2.20.

As shown in Scheme 2.19, intermediates **I-IV** are formed via the standard BNC process. However, it is presumed that intermediate **IV** undergoes a hydrolysis reaction instead of the usual $NaBH_4$ reduction that forms the corresponding benzyltetrahydroisoquinoline **19b**. This hydrolysis can be envisioned to form isoquinoline **55** via intermediates **V-VI**. Presumably, the more stable aromatic form, **IX**, is formed via tautomerization of **VIII**. The lone pair electrons on the nitrogen atom of compound **V** delocalized to form the intermediates **VIII** and **VI**. Compound **55** can be formed by de-protonation from the intermediate **VI**.



Scheme 2.19. Proposed mechanism of formation of compound **55.**

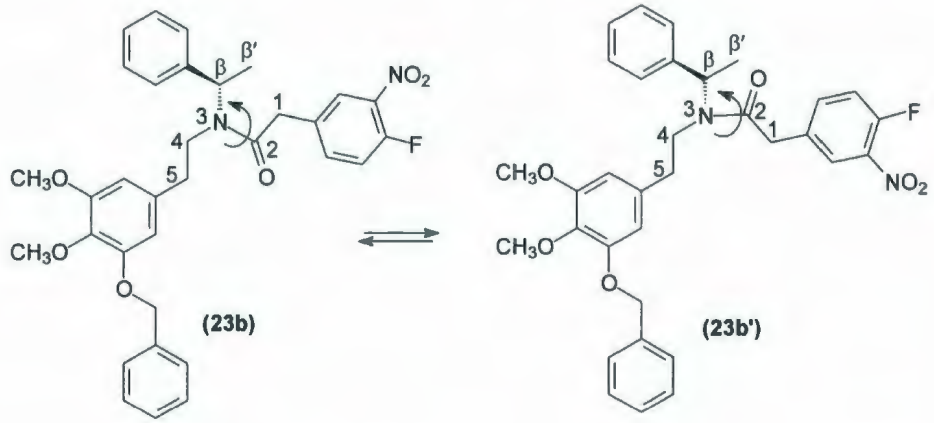
The proposed mechanism of formation of compound **56** is illustrated in Scheme 2.20. A chloride ion presumably displaced the amide group which could have been assisted by the $POCl_3$ as shown, to form **56**.[16]



Scheme 2.20. Proposed mechanism of formation of compound **56**.

Secondly, the ^{1}H- and ^{13}C-NMR spectra in $CDCl_3$ of compounds **22a-c** and **23a-c** showed a doubling of the majority of the signals. Several studies[17-20]

reported that the presence of the amide bond in some tetrahydroisoquinolines results in the formation of rotamers. As shown in Scheme 2.21, rotation about the amide bond of compound **23b** leads to interconversion of the two rotamers **23b** and **23b'** which is sufficiently slow on the NMR time scale, and as a result, the ^{1}H- and ^{13}C-NMR signals are duplicated.



Scheme 2.21. The structure of the two rotamers **23b** and **23b'**.

Using the ^{1}H-NMR spectrum of **23b** in $CDCl_3$ (Figure 2.7) as an example, the H-β' signals appeared as two doublets at δ 1.62-1.49 ppm, while the two methoxy groups appear as four singlets at δ 3.91-3.78 ppm. Furthermore, the integration of the signals obtained from the ^{1}H-NMR spectra under ambient NMR conditions reveals that the two rotational conformers are present in a ratio ≈ 1:1.8 (in $CDCl_3$).

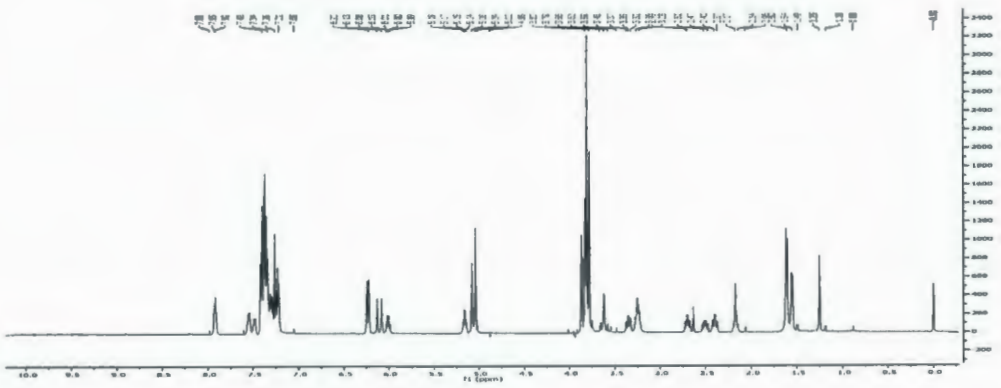
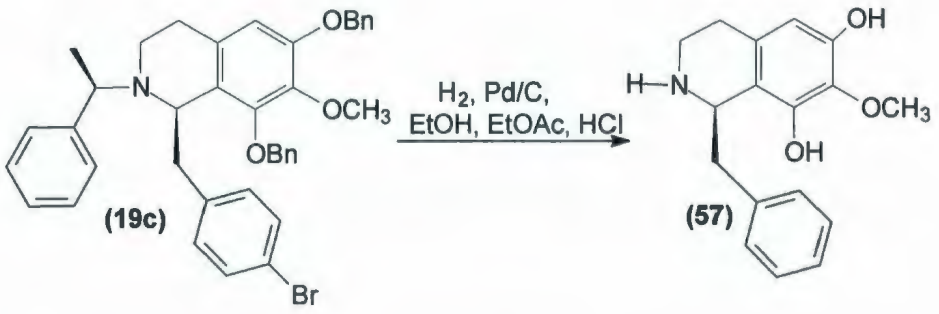


Figure 2.7. The ^{1}H-NMR spectrum of **23b**.

2.2.1.4 Attempts at the diaryl ether coupling.

2.2.1.4.1 The formation of compounds 58a-c.

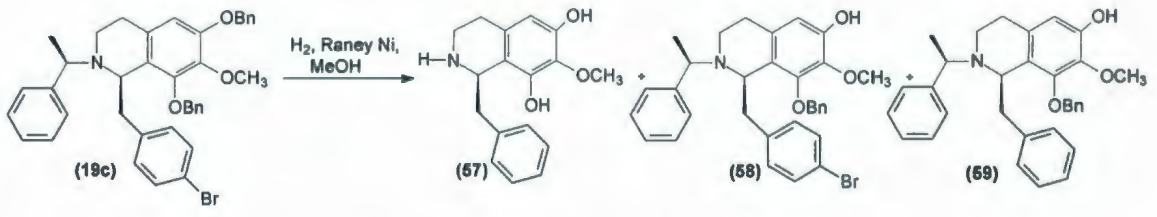
In order to effect the diaryl ether coupling steps, the benzyl groups need first to be removed from compounds **15a-c** and **19a-c**. The most common method to cleave benzyl groups in general, is via Pd/C-catalyzed hydrogenolysis.[21-23] In order to test the hydrogenolysis conditions required for our compounds, compound **19c** was first utilized. A mixture of **19c**, 10% Pd/C, ethanol, EtOAc and $HCl_{(aq)}$, was stirred for 24h under H_2. However, these conditions did not give the desired de-benzylated product. 1-Benzyl-6,8-dihydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (**57**) was formed instead, in which the bromine, the chiral auxiliary, and both benzyl groups were removed (Scheme 2.22).



Scheme 2.22. Hydrogenation of Compound **19c**.

A study in 2006[24] showed that selective de-benzylation in the presence of a halogen group can be achieved using Raney nickel in MeOH. However, when similar conditions were employed on compound **19c**, compound **57** was again produced, this time in 19% yield, along with compounds **58** in 33 %, and **59** in 30 % yields, respectively (Scheme 2.23).

From the results of the previous two hydrogenation conditions it was presumed that, since the benzyl group on C-5 is sterically hindered, the bromide aryl is more susceptible for hydrogenolysis. Consequently, attention was paid to milder hydrogenation conditions or a different debenzylation method.



Scheme 2.23. Hydrogenation of Compound **19c**.

Even though compound **57** is not the desired product it is nevertheless of interest. Many recent reports[25-27] have identified that, 1-benzyl-1,2,3,4-tetrahydroisoquinoline and some of its derivatives, for example, papaverine (**60**), 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**61**), 1-(3',4'-dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (**62**), and 1-(3',4'-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**63**), are endogenous neurotoxins that have been proposed as etiological factors for Parkinson's disease[28] (Figure 2.8). Further investigation needs to be done on compound **57** to establish whether it too, could be a potential endogenous or exogenous neurotoxin.

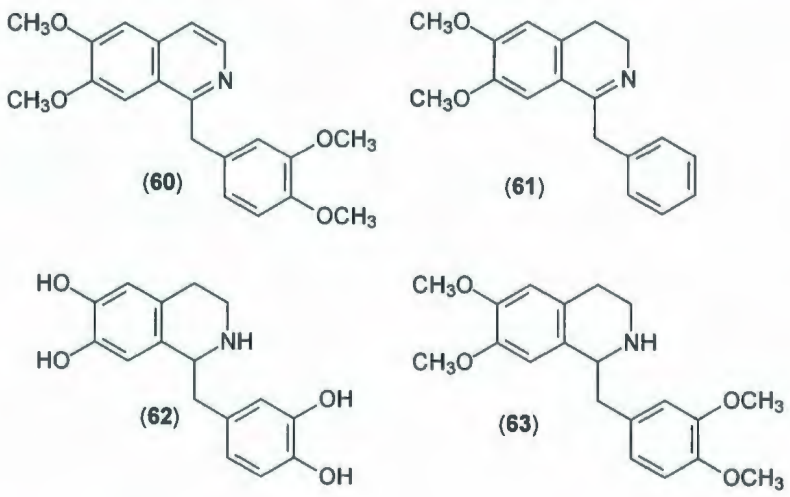
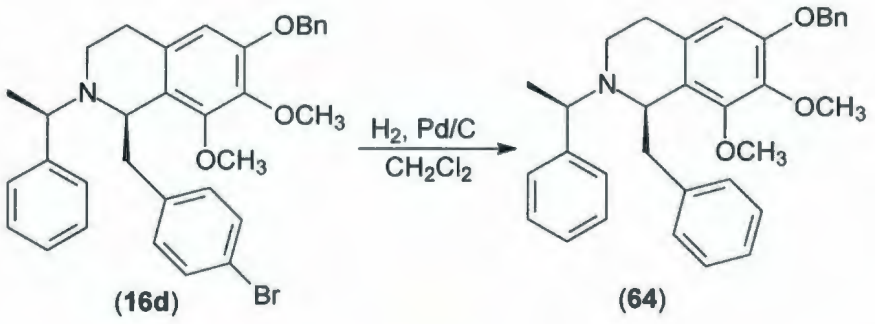


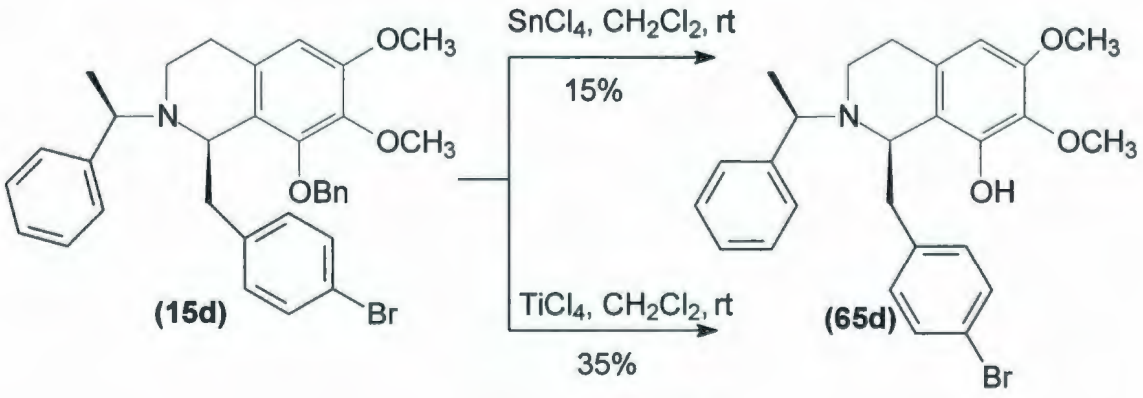
Figure 2.8. The structures of **60** - **63**.

Using milder hydrogenation conditions (H_2, Pd/C in CH_2Cl_2) on **16d** led to the formation of only **64**, in which the bromine was removed, together with unreacted starting material (Scheme 2.24).



Scheme 2.24. Reduction of **16d** via Pd/C catalyzed hydrogenolysis conditions.

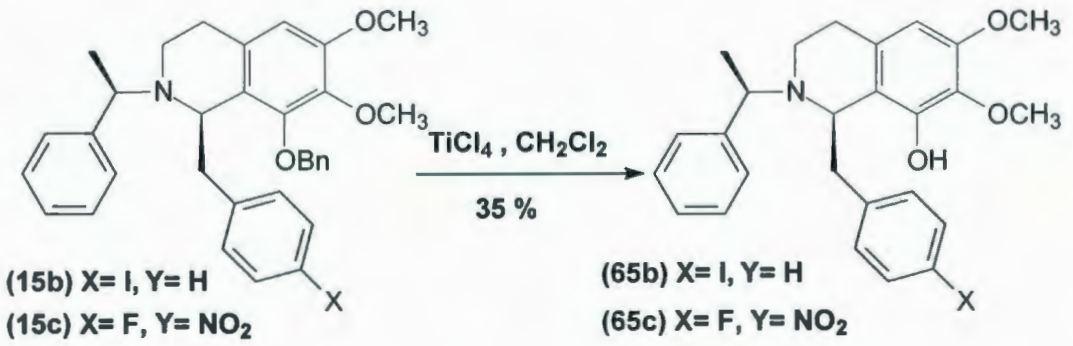
Attention was then directed towards an alternative mild-condition method to achieve the debenzylation. Many studies[19-34] have reported that Lewis acids [*e.g.* titanium tetrachloride ($TiCl_4$) or tin tetrachloride ($SnCl_4$)] can be utilized at room temperature to cleave a benzyl group.



Scheme 2.25. Debenzylation of **15d** via $SnCl_4$ and $TiCl_4$.

When compound **15d** was stirred with $SnCl_4$ for 48 h however, only a 15 % yield of the desired phenolic compound **65c** was obtained (Scheme 2.25). Even though the reaction was conducted under relatively mild conditions, only 20% of

unreacted starting material was recovered. Reaction of compound **15d** with $TiCl_4$ under the same conditions that were used with $SnCl_4$, increased the yield of **65** to 35 %.



(15b) X= I, Y= H
(15c) X= F, Y= NO_2

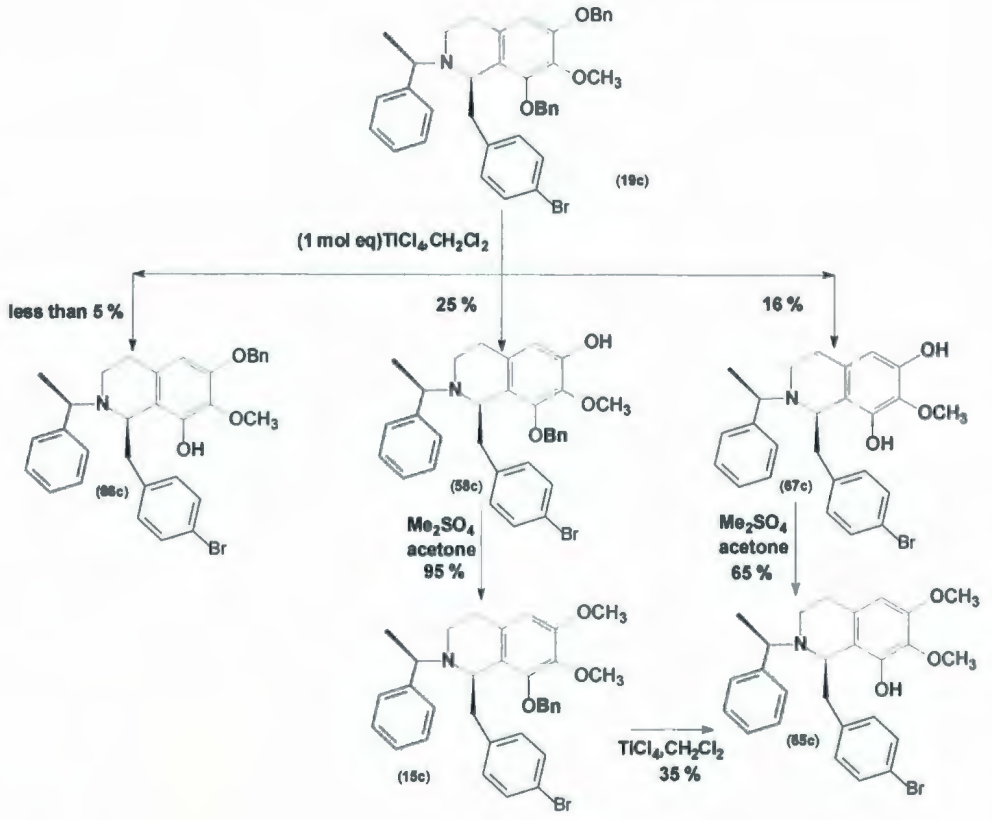
(65b) X= I, Y= H
(65c) X= F, Y= NO_2

Scheme 2.26. Reduction of **15b** and **15c**.

As with $SnCl_4$, only a small amount of the starting material was recovered and the rest was a brown intractable residue (Scheme 2.25). Since the $TiCl_4$ conditions afforded the desired phenolic compound the same conditions were employed with compounds **15b** and **15c** to give compounds **65b** and **65c**, respectively (Scheme 2.26).

It was expected that since in the case of compounds **19a-c** each contains two benzyl groups that the debenzylation steps would result in more complex results. As shown in Scheme 2.27, the desired selective mono-debenzylation for compounds **19c** by using 1 mol eq of $TiCl_4$ in CH_2Cl_2 was unachievable.

However, the steric hinderance around the C-8 benzyloxy group presumably could again (Scheme 2.23) account for the reduced the yield of **66c** to less than 5%.

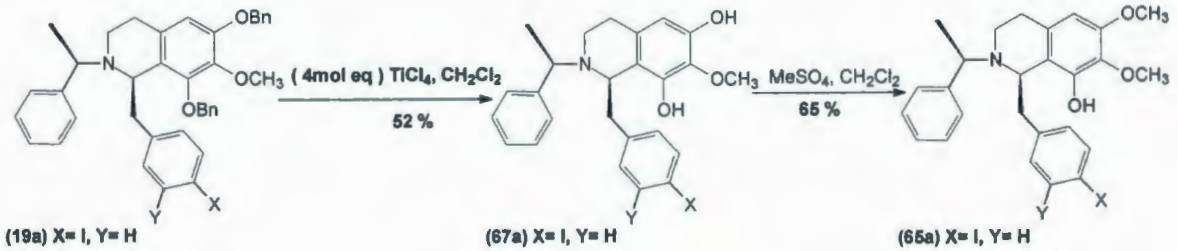


Scheme 2.27. Reduction of **19c** via $TiCl_4$-mediated debenzylation.

On the other hand, because the benzyloxy group on C-6 was more accessible, compound **58c** was formed in 25% yields. Compound **67c** in which the two benzyl groups on **19c** were removed, was formed in 16% yield. The desired intermediate **65c** was nevertheless prepared from compound **58c** by methylation of the C-6 hydroxy group with dimethyl sulfate to produce compound

15c in 95% yields, followed by debenzylation. However, the C-6 hydroxy group of compound **67c** was methylated to form **65c** in 65% yields.

Increasing the number of molar equivalents of $TiCl_4$ in the reacton elevated the yields of **67a-c** to ~52 %. When methylated, **67a-c** formed **65a-c** in ~34 % yields from **19a-c** (Scheme 2.28).



(19a) X= I, Y= H
(19b) X= F, Y= NO_2
(19c) X= Br, Y= H

(67a) X= I, Y= H
(67b) X= F, Y= NO_2
(67c) X= Br, Y= H

(65a) X= I, Y= H
(65b) X= F, Y= NO_2
(65c) X= Br, Y= H

Scheme 2.28. Reduction of **19a-c** via 4 mol equivalent of $TiCl_4$.

In order to assign some ^{1}H-NMR signals in the spectra of intermediates that were produced after the BNC step, 2-D correlation spectroscopy (COSY) experiments were conducted. For compound **58b**, as shown in Figure 2.9, for example, there is a cross-peak correlation between the signals at δ 1.31 and 3.68 ppm. These two signals are attributed to the protons on C-β' and C-β, respectively. Furthermore, there is a cross-peak correlation between the signals at δ 2.58 and 3.43 ppm, which are attributed to the protons on C-α' and C-1, respectively. There is also a cross-peak correlation between signals at δ 2.44, 2.95, and 3.46 ppm. These signals are attributed to the protons on C-3 and C-4.

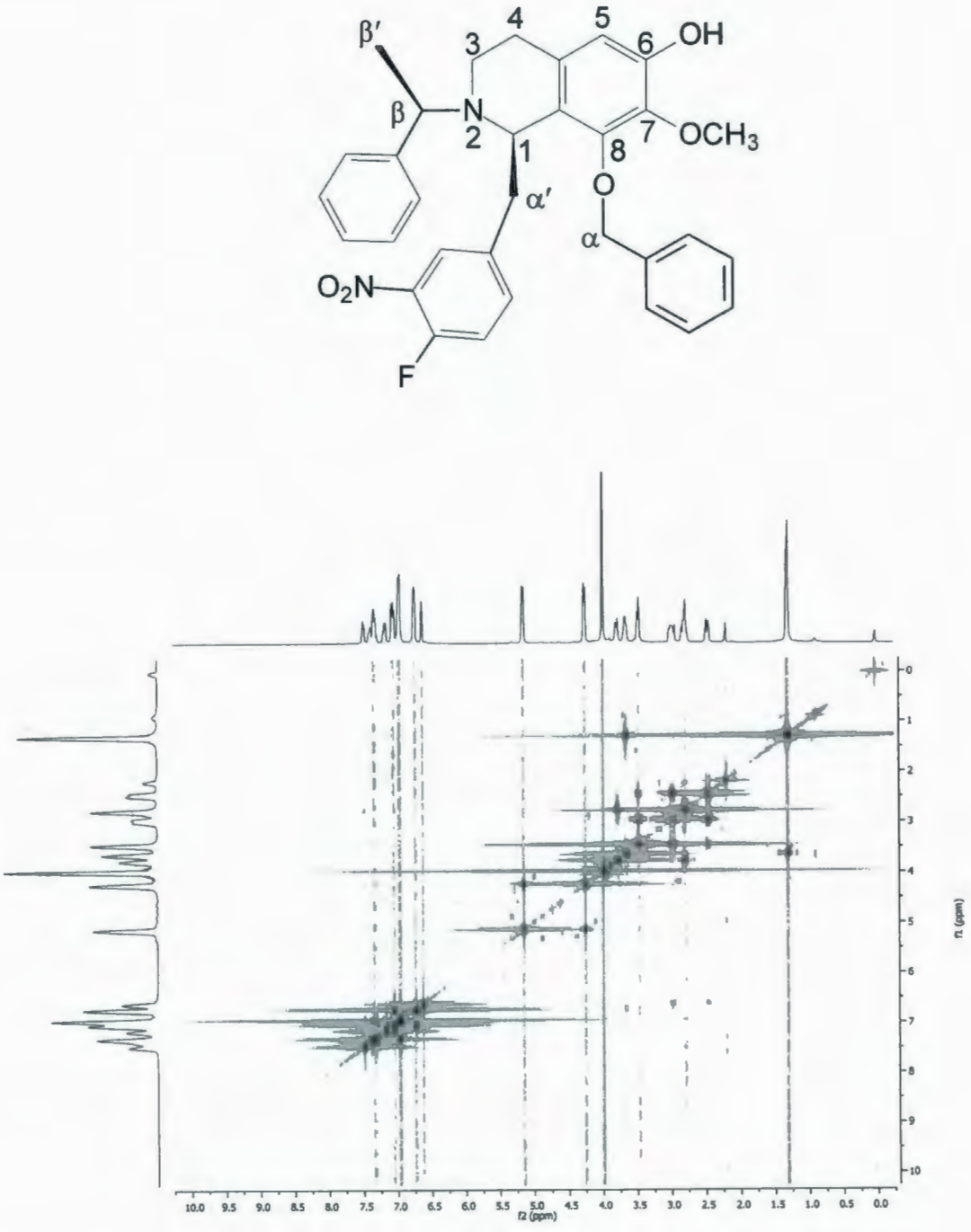


Figure 2.9. The structure and COSY spectrum of compound **58b**.

The NOESY spectra showed a NOE between H_5 and the two protons of the benzyl group for compound **66b**. This effect was not shown in **58b** in which there is a NOE between the two protons of the benzyl group and Hα' (Figure 2.3).

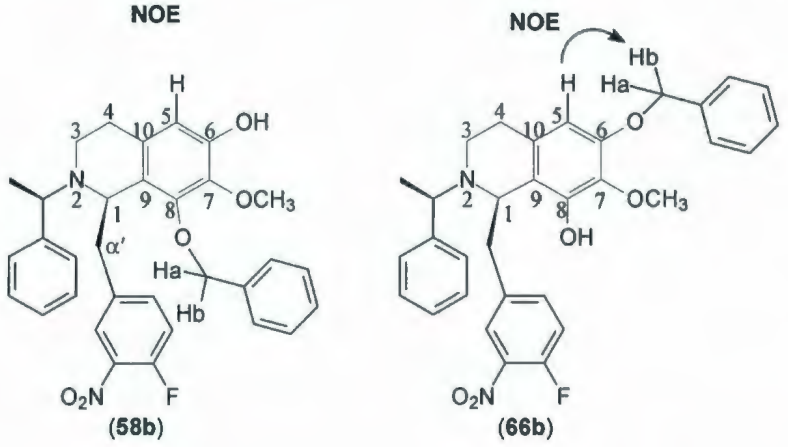
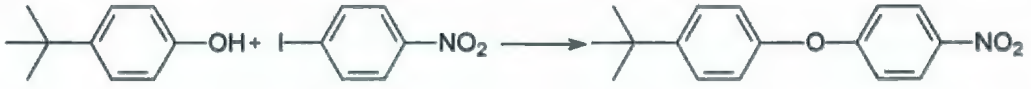


Figure 2.10. NOED used to distinguish between regioisomers **58b** and **66b.**

2.2.1.4.2 The first attempt toward the diaryl ether coupling via the improved Ullmann coupling approach.

With enantiomerically-pure benzyltetrahydroisoquinolines **65a-c** in hand, the corresponding diaryl ether couplings were attempted. As mentioned in a previous section, there are two major approaches to achieve diary ether coupling, namely Ullmann coupling and S_NAr reactions.



Scheme 2.29. A model reaction for the Ullmann reaction.

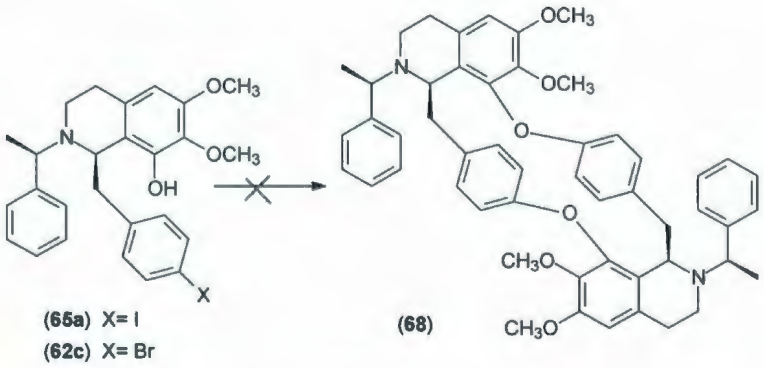
Table 2.1. Yields of the diaryl ether products (Scheme 2.29) using different Ullmann coupling conditions.

Conditions	Yields%
Cs_2CO_3, 0.25 mol% ($CuOTf)_2$. PhH, toluene, 5 mol% EtOAc, 1-naphthoic acid, 96 °C	66%
Cs_2CO_3, 0.25 mol% CuCl, toluene, 5 mol% EtOAc, 1-naphthoic acid, 96 °C	33%
CsF, 0.25 mol% ($CuOTf)_2$. PhH, toluene, 5 mol% EtOAc, 1-naphthoic acid, 96 °C	35%
BaO, $CuCl_2$, DMF, 115 °C	54%
Cs_2CO_3, CuCl, TMHD, 120 °C	70%
Cs_2CO_3, CuI, N,N-dimethyl glycine, dioxane, 90 °C	64%

In order to experiment with different Ullmann reaction conditions and to test the reactivity of the reagents used in those experiments, and also to save the valuable intermediates **65a-c**, model reactions were first conducted (Scheme 2.29). Six different conditions were tried to determine which method afforded the best results.[35-38] As shown in Table 2.1, the yields of 4-nitrophenyl-4-*t*-butylphenyl ether varied under all the conditions examined. Since the procedure

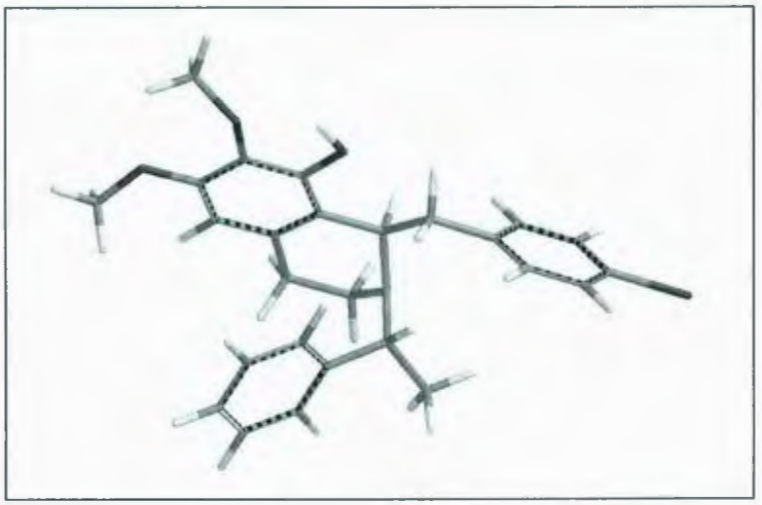
in which CuCl was used with Cs_2CO_3 in the presence of a catalytic amount of 2,2,6,6-tetramethylheptane-3,5-dione (TMHD), as reported by Song and co-workers,[37] and which afforded the highest yield, it was tried first with **65a** and **65c**.

After stirring either of **65a** and **65c** with Cs_2CO_3, CuCl and TMHD at 120°C for 96 h, no changes in the starting materials were observed (Scheme 2.30), and only unreacted starting materials were recovered. Attention was then directed to the use of other procedures. However, none of these approaches gave the desired product **68**.



Scheme 2.30. The first attempts via Cs_2CO_3 / CuCl / TMHD Ullmann reaction conditions.

In order to try to ascertain factors which could be responsible for the unreactivity of the intermediates **65a** and **65c** a molecular mechanics modeling study was conducted.



Figur 2.11. The structure of compound **65c** generated by Spartan' 08.

As shown in Figure 2.11, the *p*-bromobenzyl and the chiral auxiliary moieties shield the top and bottom faces of the intermediate **65c** and presumably, also, of **65a**. These steric effects could consequently inhibit the hydroxyl group of a reacting partner in the homodiaryl ether coupling step from displacing the halide of the other partner.

The optimal way to decrease these steric effects could conceivably be to first remove the chiral auxiliary group. Unfortunately, the chiral auxiliary is removed under the same hydrogenation conditions which remove the halide group as well, and selective removal conditions would be necessary to establish first.

2.2.1.4.3 The second attempt toward the diaryl ether coupling via the S_NAr.

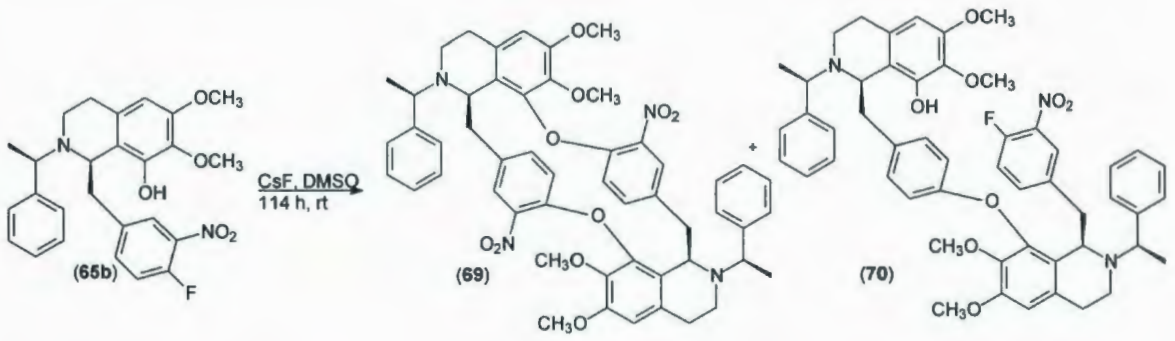
Attention was then directed to the S_NAr approach. As mentioned in previous sections, the presence of a nitro group *ortho* or *para* to the halide(s)

enhances the direct nucleophilic substitution coupling reactions. Such an approach has been successfully utilized recently by using different reagents; for instance: KF/Al_2O_3, 18-crown-6, MeCN, reflux;[39] K_2CO_3, dimethylacetamide (DMAC), reflux;[40] NaH, 4 mM in THF;[41] CsF, DMSO;[42] and $KHCO_3$, THF.[43]

Since positive results were obtained in the synthesis of (-)-tejedine with CsF in DMSO,[42] these conditions were used first. During 144 h of stirring of compound **65b** with CsF in DMSO at room temperature, the reaction was monitored by TLC and HPLC techniques. After 48 h, monitoring of the reaction showed the presence of some new small spots on the TLC. The reaction was stirred for 6 days in total, after which work-up afforded a brown residue. HPLC-ms analysis of this residue suggested the presence of compound **69** and **70**. (Scheme 2.31) as indicated by peaks corresponding to 893.01 and 913.01. Unfortunately, attempts towards the purification of either of these compounds did not meet with success, and no further characterizations could be made.

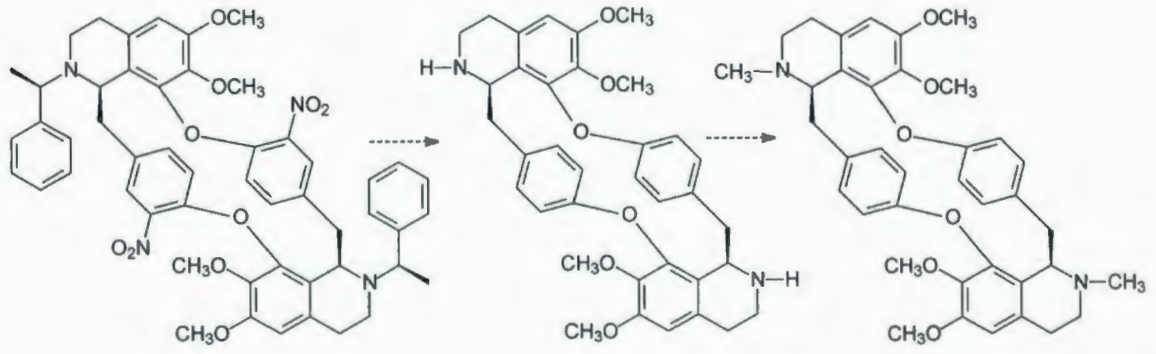
Even though compounds **69** and **70** could not be completely characterized via the previous procedure, the S_NAr-based approach showed some promising results for forming the diaryl ether linkages needed for the target compound, (-)-cycleanine.

Other conditions were employed with compound **65b,** such as K_2CO_3, THF, 18-C-6,[44] K_2CO_3, CH_3CN, 18-C-6,[45] and 0.5 mol% Pd_2dba_3, 2.0% mol *t*-Bu_3P, K_3PO_3 (3 eq) in dioxane,[46] respectively.



Scheme 2.31. The diaryl ether coupling of compound **65b**.

However, none of these methods gave the desired product. Approximately 80 % of the starting material was recovered in each experiment. Therefore, the subsequent steps (Scheme 2.32) such as removing the nitro and chiral auxiliary groups, and the introduction of the methyl group to the secondary amine were not completed.



Scheme 2.32.

2.3 Summary and conclusions.

After re-evaluation of the BNC steps using compounds **22a-c** and **23a-c**, and debenzylation of compounds **15a-c**, **16a-c**, and **19a-c**, three significant observations were concluded: (i) the presence of two similar protecting groups along with a suitable chiral auxiliary on compounds **22a-c** produced stereoselective isomers with acceptable yields in the BNC step; (ii) the presence of one protecting group on compounds **23a-c** produced two hard-to-separate regioisomers. (iii) after the BNC, the debenzylation and the methylation steps, the final yields of the desired intermediates **65a-c** via the use of two similar protecting groups in the starting materials **22a-c** were ≈ 22% however, while the final yields for the same steps but different protecting groups as in **23a-c** were ≈ 5%, as well as having the disadvantage of having to separate regioisomers.

As a conclusion, the use of intermediates **22a-c**, having similar protecting groups, was a successful approach to improve the yields of the BNC step. Moreover, the drawback of forming two regioisomers that faced the previous students in Georghiou group during their attempts toward the total synthesis of (-)-cycleanine was avoided.

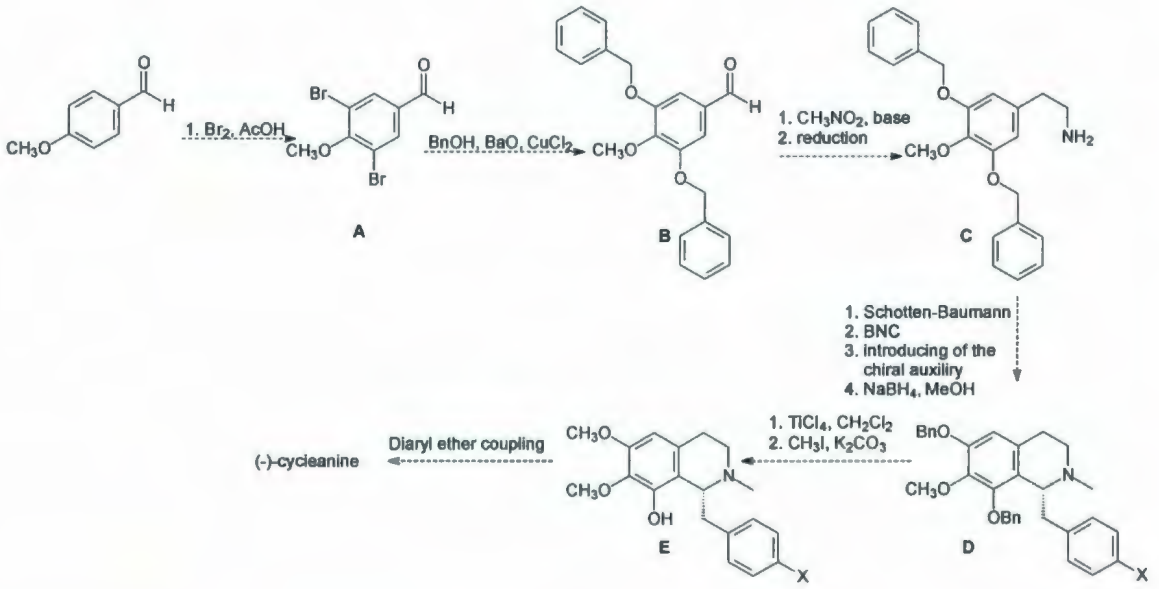
The enantioselective homo-aryl ether coupling synthesis of (-)-cycleanine was attempted via two different approaches namely: (1) the improved Ullmann approach using **65a** which has a free hydroxyl group and an iodide, with **65c** which has a free hydroxyl group and a bromide; and (2) the S_NAr approach using

65b which has a free hydroxyl group, a fluoride and a nitro group *ortho* to the fluoride. However, neither of these two approaches gave a satisfactory result. This auther suggests that the total synthesis of (-)-cycleanine is still achievable if the intermediate benzyltetrahydroisoquinolines that are used as precursors can be prepared by shorter routes and in higher yields, and if the steric-hindering effect around the nucleophile and the electrophile can be decreased.

2.4 Proposal for future endeavours toward the total synthesis of (-)-cycleanine.

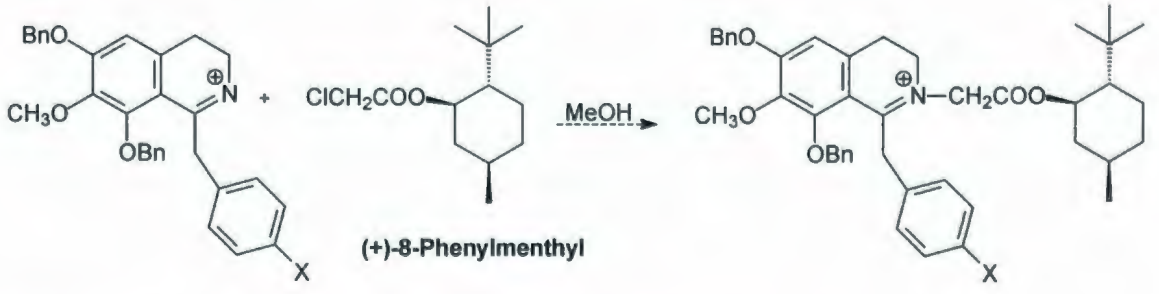
The procedure outlined below in Scheme 2.33 involves ten steps to achieve the total synthesis of (-)-cycleanine. As shown is Scheme 2.33, this proposal commences with di-bromination of the commercially-available *p*-methoxybenzaldehyde to form compound **A**. Due to the *meta*-orientation of the aldehyde group on the starting material this step always gives very high yields.

Substitution of the two bromines on **A** to form the corresponding benzyloxy groups provides compound **B**,[36] with the subsequent step being the well-known Henry reaction.[47] Addition of nitro methane to the aldehyde in the presence of a base, followed by reduction leads to a primary amine. The Schotten-Baumann reaction, then BNC leads to the formation of **D**. The chiral auxiliary, which is proposed in this approach is one reported by Rodrigues *et al.* in 1994.[48] This chiral auxiliary is introduced by reaction of the imine with (+)-8-phenylmenthyl chloroacetate, in methanol (Scheme 2.34).



Scheme 2.33. A proposed procedure for the total synthesis of (-)-cycleanine.

Introduction of the chiral auxiliary followed by addition of $NaBH_4$ leads to the reduction from the desired side, removal of the chiral auxiliary group and methylation of the nitrogen atom in the same step form the required isomer enantioselectively. (+)-8-Phenylmenthyl group anticipated to shield one side of the dihydroisoquinoline much more efficiently than the other (Scheme 2.34).



Scheme 2.34. The structure of the proposed chiral auxiliary.

Debenzylation of compound **D** followed by methylation leads to the desired precursor **E**. Preparation of **E** in nine steps, and without the chiral auxiliary, should increase the yields of the intermediates and decrease the potential steric effect around the nucleophilic hydroxyl group which would potentially enhance the possibility of effecting the diaryl ether coupling.

References of chapter 2

1 Ralph, M. S. *M.Sc. Thesis*, Memorial University of Newfoundland, **2001.**

2 Cui, J. *M. Sc. Thesis*, Memorial University of Newfoundland, **2003**.

3 Zhou, N. *M. Sc. Thesis*, Memorial University of Newfoundland, **2004**.4 Manfred. H. "*Alkaloids nature's curse or blessing?*" John Wiley & Sons, Inc. New York, NY, **1981**, pp.1-5.

4 Wang, Y.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675.

5 Lihua. Y.; Adam. R.; Sanford. W.; Aimin. Z.; Jin. Z.; Huaqiang. Z.; Kazuhiro.; Minfeng. L.; Joseph. S.; Bing. G. *J. Org. Chem.*, **2005**, *70* (26), 10660.

6 Louis A. *J. Am. Chem. Soc.* **1993**, *115* (10), 4397.

7 Kosuke. K,; Kanako. S,; Miho. O.; Shiho. Y.; Reiko. S.; Norio. I.; Hyuma. M.; Takako. K.; Masahide. T.; Isao. A. *J. Molstruc.* **2008**. *891* 346.

8 Munchhof, M.; Meyers. A. I. *J. Org. Chem.* **1996**, *61*, 460

9 Anna. C.; Enrico. M.; Elisabetta. T.; Giuseppe. B.; Maria. C.; Marcella. Bosco.; Letizia. S. *J. Org. Chem.*, **1999**, 64 (15), 5696.

10 Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A.; Vijaykumar, D. *J. Org. Chem.* **1995**, *60*, 5961.

11 Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2717.

12 Thomas. C.; Mohamed. E.; Vijay. N. *J. Org. Chem.* **2008**, *73* (4), pp 1297.

13. $C_{33}H_{34}BrNO_3$, orthorhombic, space group $P2_12_12_1$ (#19), a = 9.5724 (7) Å, b = 15.0460 (13) Å, c = 19.8821 (15) Å, V = 2863.5 (4) Å^3, Z = 4, D_{calcd} = 1.328 g/cm^3. The data were collected at a temperature of -120 ± 1 °C to $2\Theta_{max}$ 61.8°. All measurement were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation (λ = 0.71070 Å). A total of 12438 reflections were measured, of which 43633 (R_{int} = 0.033) were unique. The final cycle of full-matrix least-squares on F^2 was based on 5942 observed

reflections ($I > 2.00\sigma(I)$) and 346 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.0334$, $R_w = 0.0842$, $GOF = 1.070$.

14. $C_{39}H_{38}BrNO_3$, monoclinic, space group $P2_1$ (#4), $a = 9.942$ (3) Å, $b = 14.329$ (4) Å, $c = 11.959$ (4) Å, $V = 1610.3$ (8) Å^3, $Z = 2$, $D_{calcd} = 1.338$ g/ cm^3. The data were collected at a temperature of -150 ± 1 °C to $2\Theta_{max}$ 61.8°. All measurements were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation (λ = 0.71075 Å). A total of 27462 reflections were measured of which 6644 ($R_{int} = 0.041$) were unique. The final cycle of full-matrix least-squares on F^2 was based on 6644 observed reflections ($I > 2.00\sigma(I)$) and 398 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.0325$, $R_w = 0.0779$, $GOF = 1.063$.

15. $C_{23}H_{23}ClO_3$, orthorhombic, space group $P2_12_12_1$ (#19), $a = 9.9044$ (15) Å, $b = 9.9376$ (15) Å, $c = 19.755$ (3) Å, $V = 1944.4$ (5) Å^3, $Z = 4$, Dcalcd = 1.308 g/ cm^3. The data were collected at a temperature of -135 ± °C to $2\Theta_{max}$ 61.5°. All measurements were made on a Rigaku Saturn CCD area detector with graphite monochromated Mo-Kα radiation (λ = 0.71075 Å). A total of 17397 reflections were measured of which 3991 ($R_{int} = 0.026$) were unique. The final cycle of full-matrix least-squares on F^2 was based on 3991 observed reflections ($I > 2.00\sigma(I)$) and 246 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = 0.0358$, $R_w = 0.0911$, $GOF = 1.060$.

16. Sotomayor, N.; Esther Domı´nguez, E.; Lete, E. *J. Org. Chem.*, **1996**, *61*, 4062.

17. Novruz, G.; Evgeniy, M.; Dennis, H.; Magn, R. *Chem.*, **2004**, *42*, 39.

18. Petr, J.; Vladimir, M.; Petr, N.; Vladimir, W.; Marketa, S. *Molecules.*, **2007**, *12*, 1064.

19. Al-Showiman, S.; Jennings, W. *J. Org. Chem.*, **1978**, *43*, 3335.

20. Schmidt, O. T.; Schmadel, H. *Annalen.*, **1961**, *649*, 149.

21. Baker, W.; Godsell, J. A.; Mcomie, J. F. W.; Ulbricht, T. L. V. *J. Chem. Soc.*, **1953**, 4085.

22. Felix, A. M.; Heimer, E. P.; Lambros, T. J. *J. Org. Chem.,* **1978**, *43*, 4194.

23. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron. Lett.*,**1997**, *38*, 8101.

24. Crowley, B. M.; Boger, L. D. *J. Am. Chem. Soc.* **2006**, *128*, 2885.

25. Shavali. S.; Ebadi. M. *NeuroToxicology.* ***2003***, *24*, 417.

26. Kotake . Y. *Neuroscience.* **2003**, *117*, 63.

27. Storch. A *et al. Bio. Pharm.* **2002**, *63*, 909.

28. McNaught. K. St. P. *et al. Bio. Chem. Pharm.* **1998**, *56*, 921.

29. Geissman, T. A.; Moje, W. *J. Am. Chem.,* **1951**, *73*, 5765.

30. Dreyer, D. L. *J. Org. Chem.,* **1970**, *35*, 3294.

31. Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

32. Baldwin, J. E.; Haraldsson, G. G. *Acta. Chem. Scand. Ser. B. B40*, **1986,** 400.

33. Hori, H.; Nishida, Y.; Ohrui, H.; Megure, H. *J. Org. Chem.,* **1989**, *54*, 1346.

34. Mukai, C.; Hirai, S.; Hanaoka, M. *J. Org. Chem.,* **1997**, *62*, 6619.

35. Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539.

36. Torii, S.; Tanaka. H.; Siroi, T.; Akada, M. *J. Org. Chem.* **1979**, *44*, 3305.

37. Buck, E.; Song, J. Z.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4,* 1623.

38. Ma, D.; Cai, Q.; Zhang, H. *J. Org. Lett.* **2003**, *5*, 2453.

39. Sawyer, J. S.; Bach, N. J.; Baker, S. R.; Baldwin, R. F.;Borromeo, P. S.; Cockerham, S. L.; Fleisch, J. H.; Floreancig,P.; Froelich, L. L.; Jackson, W. T.; Marder, P.; Palkowitz, J. A.;Roman, C. R.; Saussy Jr, D. L.; Schmittling, E. A.; Silbaugh, S. A.; Spaethe, S. M.; Stengel, P. W.; Sofia, M. J. *J. Med. Chem.* **1995**, *38*, 4411.

40. Yeager, G. W.; Schissel, D. N. *Synthesis* ,**1995**, *28*.

41. Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, 3938.

42. Nicolaou, K. C.; Takayanagi, M.; Jain, N. F.; Natarajan, S.; Koumbis, A. E.; Bando, T.; Ramanjulu, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2717-2719.

43. Roussi, G.; Zamora, E. G.; Carbonnelle, A.-C.; Beugelmans, R. *Tetrahedron Lett.***1997**, *38*, 4401.

44. Neuville, L.; Bois-Choussy, M.; Zhu, J. *Tetrahedron Lett.* **2000**, *41*, 1747.

45.

46. Chen. G.; Chan, C. A.; Kwong. F. *Tetrahedron. Lett.* **2007**, *48*, 473.

47. Heffner, R. J.; Jiang, J.; Joullie, M. M. *J. Am. Chem. Soc.* **1992,** *114*, 10181.

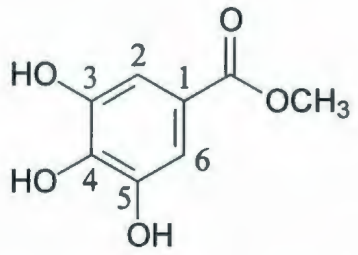
48. de Sousa, J. D. F.; Rodrigues, J. A. R.; Abramovitch. R. A. *J. Am. Chem. Soc.* **1994**, *116*, 9745.

Experimental

General

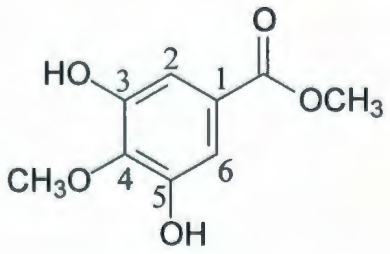
Flash column chromatography was performed using 240-400 mesh silica gel and preparative layer (1mm) chromatography (PLC) was conducted using 60 Å mesh silica gel. All solvents and reagents used were either of the highest commercial grade available or were redistilled (CH_2Cl_2, hexane, and benzene distilled over CaH_2; MeOH was dried over Mg and I_2). ^1H and ^{13}C NMR spectra were obtained on the Bruker Advance 500 MHz instrument with a TXI inverse-detect gradient probe in $CDCl_3$ unless otherwise specified, and shifts are relative to an internal tetramethylsilane signal. The following abbreviations are used in descriptions of the ^1H NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple) and b (broad). The ^1H and ^{13}C NMR spectra chemical shifts were measured relative to the solvent. Overlap may have prevented the reporting of all resonances. Low–resolution mass spectral data were obtained from the V.G. Micromass 7070HS instrument or obtained from Atmospheric Pressure Chemical Ionization-Mass Spectrometry (APCI-MS). Mass spectral data and intensity (%) are described as MS (*m/z*) unless mass data were 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.

Methyl gallate (26).



To a solution of gallic acid (12 g, 71 mmol) in methanol (200 ml) was added drop-wise $SOCl_2$ (5.6 ml, 78 mmol) at 0 °C. The solution was allowed to warm to rt before it was heated at reflux for 2 h. The reddish-brown solution was cooled to rt and 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 × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **26** (13 g, 97%) as a colourless solid; m.p 204-205 °C. ^1H NMR (MeOD): δ 7.05 (s, 2H, H-2, H-6), 4.87 (s, 3H, OH), 3.81 (s, 3H, OCH_3); ^{13}C NMR δ 166.7, 148.87, 138.39, 126.21, 110.00, 61.08; MS (*m/z, %*): 185 (M^++1, 1), 184 (M^+, 5), 183 (M^+ -1, 100), 167 (4), 166 (30), 153 (4).

Methyl-3,5-dihydroxy-4-methoxygallate (27).

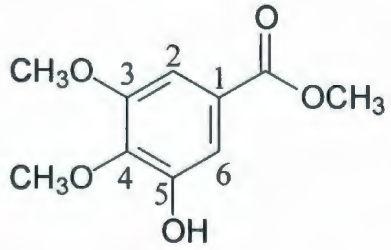


A mixture of **26** (10 g, 54 mmol), potassium carbonate (6.7 g, 49 mmol), dimethyl sulfate (4.6 ml, 49 mmol) in water-free acetone (150 ml) stirred at rt for 2

h. The solution was diluted 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 × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **27** (6.7 g, 61%) as a colourless solid; m.p 149-150 °C.

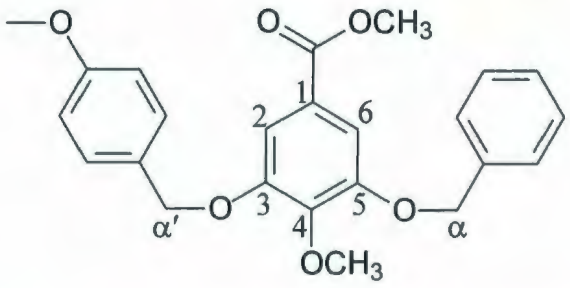
^{1}H NMR: δ 7.25 (s, 2H, H-6, H-2), 5.62 (s, 2H, OH), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); ^{13}C NMR: δ 166.76, 148.87, 138.39, 126.21, 110.00, 61.08, 52.62; MS(*m/z*): 198 (M^+ +1, 1), 197 (M^+, 5), 196 (M^+-1, 100), 182 (4), 181 (30), 166 (4).

Methyl 3-hydroxy-4,5-dimethoxy gallate (28).



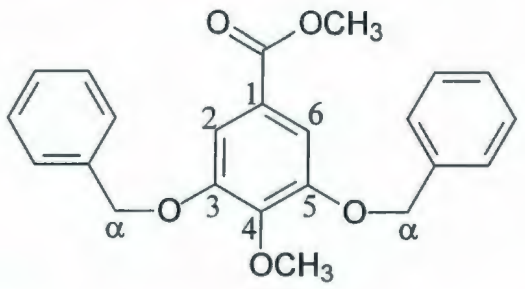
A mixture of **26** (9.1 g, 49 mmol), potassium carbonate (14 g, 98 mmol), dimethyl sulfate (9.2 ml, 98 mmol) in water-free acetone (150 ml) stirred at rt for 3 h. The solution was diluted by addition of water (30 ml), and then the mixture was extracted with ethyl acetate (20 ml × 3). The combined organic phases were washed with water (20 ml × 3), dried over $MgSO_4$, filtered, and then the solvent was evaporated to give **28** (7.3 g, 69%) as a colourless solid; m.p 76-77 °C. ^{1}H NMR: δ 7.30 (d, *J*= 5 Hz, 1H, H-6), 7.20 (d, *J*= 5 Hz, 1H, H-2), 3.95 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3); ^{13}C NMR: δ 166.88, 152.13, 149.18, 139.88, 125.83, 110.10, 105.88, 61.18, 56.23, 52.52; MS(*m/z*): 213 (M^++1, 1), 212 (M^+, 5), 211 (M^+-1, 100), 197 (4), 196 (30), 181 (4).

Methyl 3-benzyloxy-4-methoxy-5-(4-methoxybenzyloxy) benzoate (29).



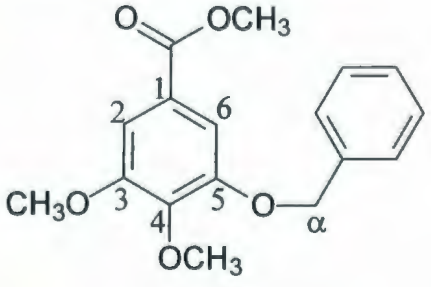
Methyl-3-benzyloxy-5-hydroxy-4-methoxy benzoate (**27a**) was prepared in 74 % yield by the reaction of **27** (10 g, 51 mmol) with benzyl bromide (8.7 g, 51 mmol) in the presence of potassium carbonate (7.1 g, 51 mmol) in acetone. A mixture of **27a** (12 g, 42 mmol) potassium carbonate (5.8 g, 42 mmol), *p*-methoxybenzyl bromide (PMBBr) (7.3 ml, 50 mmol) in anhydrous acetone (150 ml) was stirred at rt for 48 h. The solution was diluted by addition of water (30 ml), and then was extracted with ethyl acetate (20 ml × 3). The combined organic phases were washed with water (20 ml × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **29** (16 g, 93%) as colourless solid; m.p. 116-117 °C; ^{1}H NMR: δ 7.45 (m, 9H, Ar-H), 6.97 (s, 1H, H-2), 6.95 (s, 1H, H-6), 5.20 (s, 2H, H-α), 5.12 (s, 2H, H- α'), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3) 3.80 (s, 3H, OCH_3); ^{13}C NMR: δ 166.79, 159.64, 152.37, 150.58, 143.89, 136.90, 128.74, 128.61, 127.57, 125.10, 114.17, 109.63, 109.40, 71.39, 71.21, 61.13, 55.42, 52.39; MS(*m/z*): 407 (M^+,100), 375 (4), 361 (10), 302 (95), 241 (25), 211 (15), 121 (65).

Methyl 3,5-dibenzyloxy-4-methoxybenzoate (30).



A mixture of **27** (10 g, 51 mmol), potassium carbonate (149 g, 101 mmol), benzyl bromide (11.8 ml, 101 mmol) in anhydrous acetone (150 ml) was stirred at rt for 8 h. The solution was diluted by addition of water (30 ml), and then was extracted with ethyl acetate (20 ml × 3). The combined organic phases were washed with water (20 ml × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **30** (18 g, 95%) as a colourless solid; m.p. 119-120 °C; ^{1}H NMR: δ 7.47-7.31 (m, 12H, Ar-H), 5.16 (s, 4H, H-α), 3.93 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR: δ 166.73, 152.54, 143.90, 136.94, 128.77, 128.21, 127.61, 125.04, 109.44, 71.19, 61.05, 52.33.

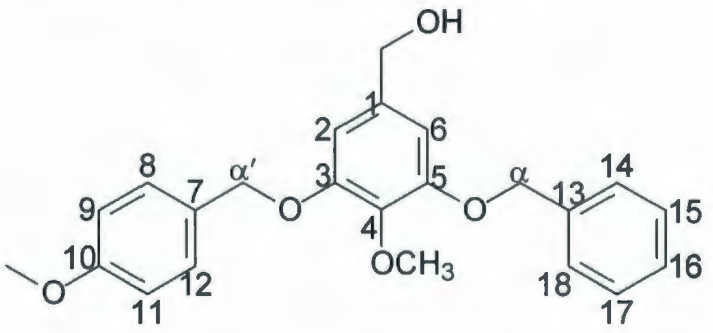
Methyl-3-benzyloxy-4, 5-dimethoxybenzoate (31).



A mixture of **28** (10 g, 47 mmol), potassium carbonate (6.5 g, 47 mmol), benzyl bromide (5.5 ml, 47 mmol) in anhydrous acetone (150 ml) was stirred at rt

for 8 h. The solution was diluted by addition of water (30 ml), and then was extracted with ethyl acetate (20 ml × 3). The combined organic phases were washed with water (20 ml × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated to give **31** (14 g, 95%) as colourless solid; m.p 74-75 °C. ^{1}H NMR: δ 7.49-7.29 (m, 7H, Ar-H), 5.19 (s, 2H, H-α), 3.95 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3); ^{13}C NMR: δ 166.93, 153.35, 152.25, 143.16, 136.90, 128.81, 128.28, 127.72, 125.30, 109.23, 107.34, 71.44, 61.21, 56.48, 52.41; MS (*m/z*): 302 (M^+, 62), 271 (18), 243 (5), 211 (10), 155 (15), 91 (100).

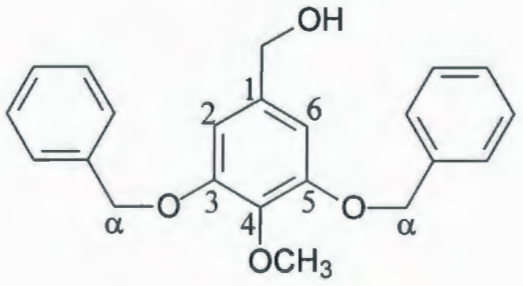
3-Benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)-phenylmethanol (32).



To a suspension of $LiAlH_4$ (1.1 g, 29 mmol) in THF (30 ml) was added a solution of compound **29** (10 g, 25 mmol) in THF (75 ml). The solution was stirred under an argon atmosphere for 4 h. The resulting grey solution was quenched with aqueous 10% HCl, filtered and dissolved in EtOAc (100 ml). The aqueous layer was separated and re-extracted with EtOAc (3 × 15 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$ filtered and the solvent was evaporated to afford **32** (8.8 g, 94 %) as colourless solid, m.p. 112-113 °C.; ^{1}H NMR: δ 7.46-7.30 (m, 7H, Ar-H), 6.91 (d, *J*=10 Hz 2H, H-9, H-11),

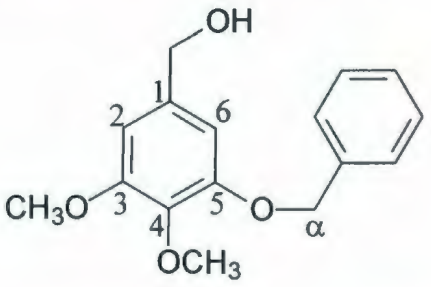
6.66 (d, *J*=5 Hz 2H, H-2, H-6), 5.13 (s, 2H, H-α), 5.06 (s, 2H, H-α'), 4.56 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.05 (s, 1H, OH); ^{13}C NMR: δ 159.52, 152.96, 152.82, 139.11, 137.28, 136.60, 129.20, 128.73, 128.03, 127.41, 114.13, 106.87, 106.65, 71.29, 71.12, 65.54, 61.09, 55.46; MS (*m/z*): 380 (M^+, 1), 379.1 (5), 364.3 (26), 363 (100).

3,5-Dibenzyloxy-4-methoxyphenyl methanol (33).



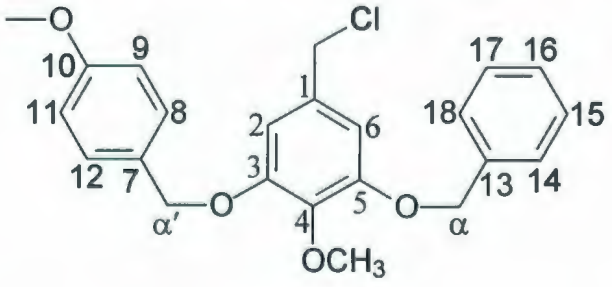
To a suspension of $LiAlH_4$ (1.2g, 32 mmol) in THF (30 ml) was added a solution of compound **30** (10 g, 26 mmol) in THF (75 ml). The solution was stirred under an argon atmosphere for 4 h. The resulting grey solution was quenched with aqueous 10% HCl, filtered and dissolved in EtOAc (100 ml). The aqueous layer was separated and extracted with EtOAc (3 × 15 ml). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and the solvent was then evaporated to afford **33** (8.8 g, 94%) as a colourless solid; m.p. 104-105 °C; ^1H NMR: δ 7.45-7.31 (m, 10H, Ar-H), 6.65 (s, 2H, H-2, H-6), 5.13 (s, 4H, H-α), 4.54 (d, *J*=5 Hz, 2H, CH_2), 3.89 (s, 3H, OCH_3); ^{13}C NMR: δ 152.94, 137.37, 128.79, 128.15, 127.50, 106.77, 71.57, 65.82, 61.22; MS(*m/z*): 351.2 (M^+, 1), 334.2 (25), 333.3 (100), 241(5).

3-Benzyloxy-4,5-dimethoxyphenyl methanol (18).



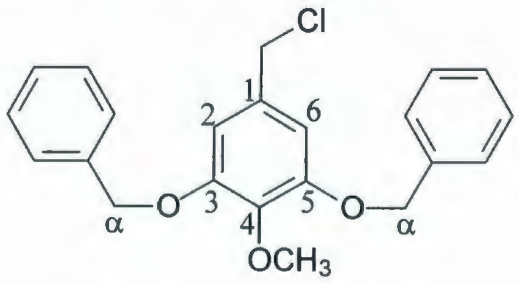
To a suspension of $LiAlH_4$ (1.6 g, 43 mmol) in THF (30 ml) was added a solution of **31** (10 g, 33 mmol) in THF (75 ml). The solution was stirred under an argon atmosphere for 4 h. The resulting grey solution was quenched with aqueous 10% HCl, filtered and dissolved in EtOAc (100 ml). The aqueous layer was separated and extracted with EtOAc (3 × 15ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvent was then evaporated to afford **18** (8.7 g, 94%) as a yellow oil. ^1H NMR: δ 7.40-7.25 (m, 5H, Ar-H), 6.58 (d, *J*=5 Hz, 1H, H-6), 6.53 (d, *J*=5 Hz, 1H, H-2), 5.03 (s, 2H, H-α), 4.49 (d, *J*=5 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR: δ 153.45, 152.40, 137.75, 137.13, 136.39, 128.53, 127.90, 127.29, 105.88, 104.14, 71.02, 65.02, 60.99, 56.14; MS(*m/z*): 274 (M^+, 1), 142 (100), 91 (56).

3-Benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)-benzyl chloride (34).



To a solution of **32** (10 g, 26 mmol), pyridine (1.3 ml, 26 mmol) in anhydrous benzene (75 ml) was added thionyl chloride dropwise (1.9 ml, 26 mmol). After stirring at rt for 2 h, the reaction was quenched by addition of water (25 ml), and the mixture was extracted with ethyl acetate (20 ml × 3).The combined extracts were washed with aqueous saturated $NaHCO_3$ (10 ml × 3), water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **34** (8.9 g, 85 %) as a colourless solid m.p. 76-77 °C. ^1H NMR: δ 7.45-7.30 (m, 7H, Ar-H), 6.91 (d, *J*=5 Hz 2H, H-9, H-11), 6.67 (d, *J*=5 Hz 2H, H-2, H-6), 5.13 (s, 2H, H-α), 5.06 (s, 2H, H-ά), 4.47 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3); ^{13}C NMR: δ 159.86 153.14, 153.1, 140.17, 137.39, 133.07, 129.50, 128.34, 127.73, 114.38, 109.01, 108.78, 71.65, 71.51, 61.26, 55.45, 47.08; MS(*m/z*): 398.88 (M^+, 19), 379.1 (5), 364.3 (26), 363 (100).

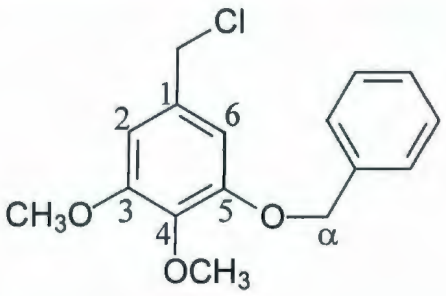
3,5-Dibenzyloxy-4-methoxybenzyl chloride (35).



To a solution of **33** (10 g, 29 mmol), pyridine (1.4 ml, 29 mmol) in anhydrous benzene (75 ml) was added thionyl chloride dropwise (2.1 ml, 29 mmol). After stirring at rt for 2 h, the reaction was quenched by the addition of water (25 ml), and the mixture was extracted with ethyl acetate (20 ml × 3). The combined extracts were washed with aqueous saturated $NaHCO_3$ (10 ml × 3),

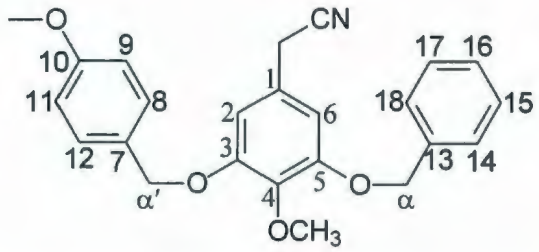
water (20 ml × 3) dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated to afford **35** (9.1 g, 85 %) as a colourless solid, m.p. 79-81 °C; ^1H NMR: δ 7.46-7.30 (m, 10H, Ar-H), 6.68 (s, 2H, H-2, H-6), 5.14 (s, 4H, H-α), 4.47 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3); ^{13}C NMR: δ 152.88, 139.85, 137.14, 132.87, 128.72, 128.10, 127.43, 108.62, 71.44, 61.15, 46.85; MS(*m/z*): 368.85 (M^+,1), 333.1 (100), 241 (10), 91(10).

3-Benzyloxy-4,5-dimethoxybenzyl chloride (36).



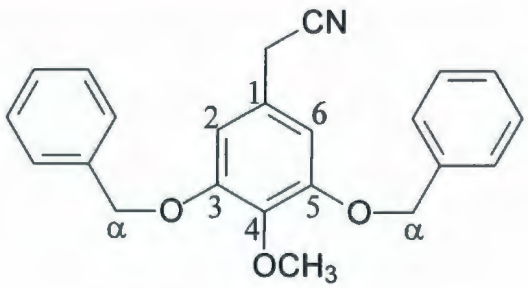
To a solution of **18** (16 g, 57 mmol), pyridine (2.9 ml, 57 mmol) in anhydrous benzene (75 ml) was added thionyl chloride dropwise (4.2 ml, 57 mmol). After stirring at rt for 2 h, the reaction was quenched by addition of water (25 ml), and the mixture was extracted with ethyl acetate (20 ml × 3).The combined extracts were washed with aqueous saturated $NaHCO_3$ (10 ml × 3), water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **36** (14 g, 85 %) as a colourless solid, m.p 83-84 °C. ^1H NMR: δ 7.45-7.31 (m, 5H, Ar-H), 6.66 (d, *J*= 5 Hz, 1H, H-6), 6.62 (d, *J*= 5 Hz, 1H, H-2), 5.12 (s, 2H, H-α), 4.51 (s, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); MS (*m/z*): 292 (M^+, 13), 91 (100).

3-Benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)phenyl acetonitrile (37).



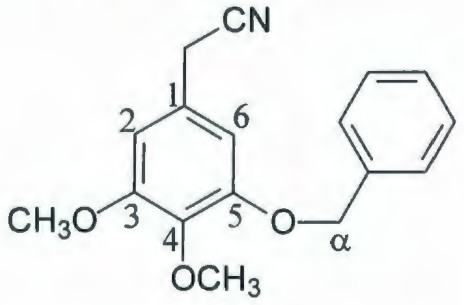
To a solution of **34** (6.1 g, 15 mmol) in DMSO (20 ml) and benzene (15 ml) was added NaCN (0.74 g, 15 mmol) powder in 3 portions. After stirring for 2 h at rt, the reaction mixture was poured into water (40 ml) and extracted with benzene (40 ml × 3).The combined organic layers were washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **37** (5.3 g, 89%) as a colourless solid, m.p 99-100 °C . ^{1}H NMR: δ 7.45-7.30 (m, 7H, Ar-H), 6.95 (d, *J*=10 Hz, 2H, H-9, H-11), 6.61 (d, *J*=10 Hz, 2H, H-2, H-6), 5.16 (s, 2H, H-α), 5.09 (s, 2H, H-ά), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3)), 3.66 (s, 2H, CH_2); ^{13}C NMR: δ 159.69 153.16, 139.66, 136.98, 128.76, 128.17, 127.45, 125.17, 117.94, 114.21, 108.15, 107.88, 71.48, 71.30, 61.09, 55.49, 23.90; MS(*m/z*): 388.88 (M^+, 35), 361.1 (15), 331.1 (6), 241.1 (13), 221 (25), 121 (100).

3,5-Dibenzyloxy-4-methoxyphenyl acetonitrile (38).



To a solution of **35** (9.1 g, 24 mmol) in DMSO (20 ml) and benzene (15 ml) was added NaCN (1.2 g, 24 mmol) powder in 3 portions. After stirring for 2 h at rt, the reaction mixture was poured into water (40 ml) and extracted with benzene (40 ml × 3). The combined organic layers were washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **38** (8.7 g, 91%) as a colourless oil. ^{1}H NMR: δ 7.46-7.30 (m, 10H, Ar-H), 6.58 (s, 2H, H-2, H-6), 5.13 (s, 4H, H-α), 3.89 (s, 3H, OCH_3), 3.61 (s, 2H, H-β); ^{13}C NMR: δ 153.15, 139.23, 136.80, 128.80, 128.22, 127.49, 125.28, 117.54, 107.95, 71.71, 61.04, 23.68; MS(*m/z*): 358.1 (M^+, 5), 333.1 (100), 282 (15), 181,1 (5), 91 (18).

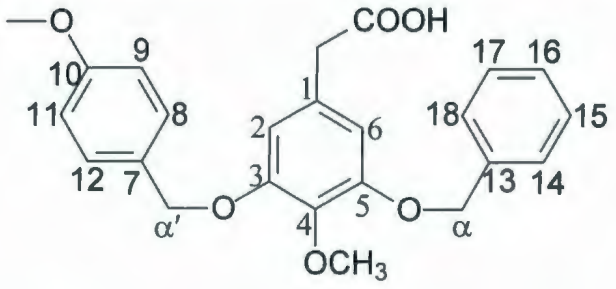
3-Benzyloxy-4, 5-dimethoxyphenylacetonitrile (39).



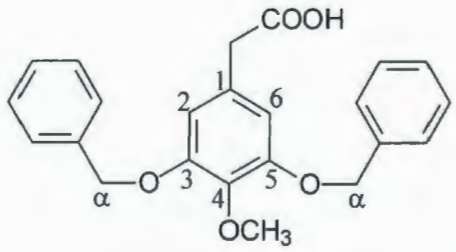
To a solution of **36** (8.2 g, 27 mmol) in DMSO (20 ml) and benzene (15 ml) was added NaCN (1.3 g, 27 mmol) powder in 3 portions. After stirring for 2 h at rt, the reaction mixture was poured into water (40 ml) and extracted with benzene (40 ml × 3). The combined organic layers were washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **39** (6.9 g, 89%) as a colourless solid, m.p 56-57 °C. ^{1}H NMR: δ 7.45-7.30 (m,

5H, Ar-H), 6.57(d, *J*=5 Hz, 1H, H-6), 6.53(d, *J*=5 Hz 1H, H-2), 5.13(s, 2H, H-α), 3.87(s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.64(s, 2H, CH_2); ^{13}C NMR: δ 154.09, 153.00, 138.72, 136.93, 128.76, 128.18, 127.48, 125.36, 118.0, 107.56, 105.64, 71.47, 61.07, 56.40, 24.0; MS(*m/z*): 283 (M^++1, 24), 91 (100).

3-Benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)phenylacetic acid (40).

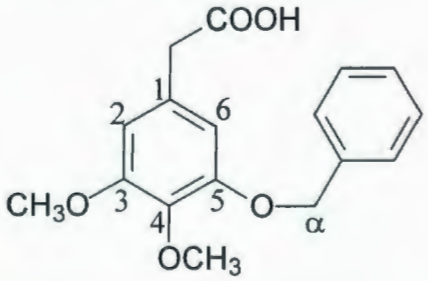


A solution of **37** (5.2 g, 12 mmol) in 95% ethanol (40 ml) and aqueous 4.0 M NaOH (7.0 ml) was heated at reflux for 20 h. The reaction mixture was cooled to rt and then acidified with aqueous concentrated HCl to pH=1, to give a precipitate which was then filtered and washed with water to afford **40** as a yellow solid (4.8 g, 88 %), m.p. 139-141 °C; ^1H NMR: δ 7.49-7.32 (m, 7H, Ar-H), 6.93 (d, *J*=5 Hz, 2H, H-9, H-11), 6.64 (d, *J*=5 Hz, 2H, H-2, H-6), 5.14 (s, 2H, H-α), 5.07 (s, 2H, H-α'), 3.91 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3) ,3.56 (s, 2H, CH_2); ^{13}C NMR: δ 177.57, 159.39, 152.59, 138.83, 137.21, 129.21, 128.58, 127.94, 127.45, 113.98, 109.40, 109.25, 71.26, 71.10, 60.91, 55.29, 41.24; MS (*m/z*): 408.1 (M^++1, 25), 407.1 (M^+, 100), 395 (65), 380.1 (45), 363.1 (45), 257.0 (35).



A solution of **38** (5.1 g, 13 mmol) in 95% ethanol (40 ml) and aqueous 4.0 M NaOH (7.0 ml) was heated at reflux for 20 h. The reaction mixture was then cooled to rt and acidified with aqueous concentrated HCl to pH=1 to give a precipitate which was filtered, and washed with water to give **41** as a yellow solid (4.7 g, 88%), m.p. 139-141 °C. ^{1}H NMR: δ 7.44-7.32 (m, 10H, Ar-H), 6.60 (s, 2H, H-2, H-6), 5.14 (s, 4H, H-α), 3.92 (s, 3H, OCH_3), 3.51 (s, 2H, CH_2); ^{13}C NMR: δ 205.45, 153.11, 137.92, 128.75, 127.83, 109.40, 71.09, 60.23, 40.82; MS(*m/z*): 379.1 (M^++1, 5), 379.1 (M^+, 25), 379.1 (M^+-1, 100), 365 (20), 350 (25), 333.1 (85), 318 (15).

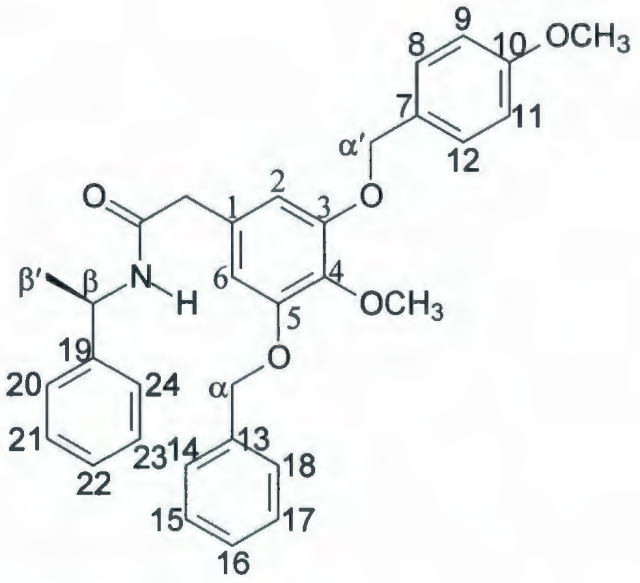
3-Benzyloxy-4, 5-dimethoxyphenylacetic acid (12).



A solution of **39** (5.9 g, 21 mmol) in 95 % ethanol (40 ml) and aqueous 4.0 M NaOH (7.0 ml) was heated at reflux for 20 h. The reaction mixture was then cooled to rt and then acidified to pH=1 to form a residue which was filtered and washed with water to give **12** (6.2 g, 88%) as a colourless solid, m.p. 104-105 °C.

^{1}H NMR: δ 7.44-7.30 (m, 5H, Ar-H), 6.57 (d, *J*= 1.5 Hz, 1H, H-6), 6.52 (d, *J*= 1.5 Hz, 1H, H-2), 5.12 (s, 2H, H-α), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2); ^{13}C NMR: δ 177.61, 153.59, 152.53, 138.23, 137.18, 128.70, 128.08, 127.52, 108.90, 107.08, 104.38, 71.36, 61.07, 56.33, 41.42; MS(*m/z*): 301 (M^+, 6), 196 (16), 151 (32), 91 (22), 84 (100), 47 (24).

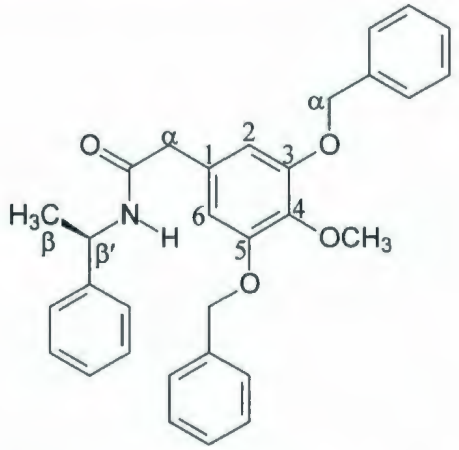
***N*-((*R*)-α-Methylbenzyl)-(3-benzyloxy-4-methoxy-5-(4-methoxybenzyloxy)-phenylacetamide (42).**



To a stirred solution of oxalyl chloride (1.3 ml, 15 mmol) in anhydrous benzene (60 ml) were added **40** (4.1 g, 9.8 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **40**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of (*R*)-α-methylbenzylamine (1.4 ml, 11 mmol) and

CH_2Cl_2/aqueous 5% NaOH (1:1.5, 14.7 ml). After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered. The solvent was evaporated and the residue was purified by flash column chromatography (30% EtOAc/hexane) to afford amide **42** (4.1 g, 79%) as a colourless solid; m.p 73-74 °C. ^{1}H NMR: δ 7.42-7.15 (m, 12H, Ar-H), 6.90 (d, *J*= 5 Hz, 2H, H-9, H-11), 6.48 (d, *J*=5 Hz, 2H, H-6, H-2), 5.54 (d, *J*=10 Hz, 1H, N-H), 5.08 (q, *J*=10 Hz, 1H, H- β), 5.08 (s, 2H, H-α), 5.01 (s, 2H, H- α'), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.43 (s, 2H, CH_2), 1.34 (d, *J*=10 Hz, 3H, H-β'); ^{13}C NMR: δ 170.00, 159.55, 153.96, 152.96, 143.28, 137.11, 129.15, 127.48, 126.12, 114.14, 109.29, 109.07, 71.22, 71.15, 61.06, 55.40, 48.80, 44.13, 21.86; APCI-MS; 512.2 (M^+ + 1, 100).

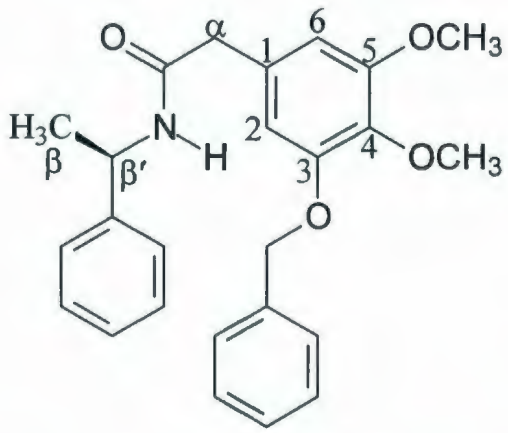
***N*-((*R*)-α-Methylbenzyl)-(3,5-dibenzyloxy-4-methoxy)phenylacetamide (43).**



To a stirred solution of oxalyl chloride (1.1 ml, 12 mmol) in anhydrous benzene (60 ml) were added **41** (3.2 g, 7.9 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The

benzene was evaporated using a rotary evaporator to give the acid chloride of **41**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of (*R*)-α-methylbenzylamine (1.2 ml, 9.5 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 12.6 ml). After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was then evaporated. The residue was purified by flash column chromatography (30% EtOAc/hexane) to afford amide **43** (3.2 g, 79%) as a yellow solid m.p. 89-90 °C; ^{1}H NMR: δ 7.41-7.16 (m, 15H, Ar-H), 6.50 (s, 2H, H-2, H-6), 5.54 (d, *J*= 5 Hz, N-H), 5.09 (q, *J*=5 Hz, H-β), 5.08 (s, 4H, H-α), 3.87 (s, 3H, OCH_3), 1.32 (d, *J*= 5Hz, H-β'); ^{13}C NMR: δ 170.11, 153.09, 137.14, 129.02, 127.73, 127.60, 126.35, 109.29, 71.39, 61.52, 49.10, 44.16, 21.85; APCI-MS; 482.1 (M^+ + 1), 100).

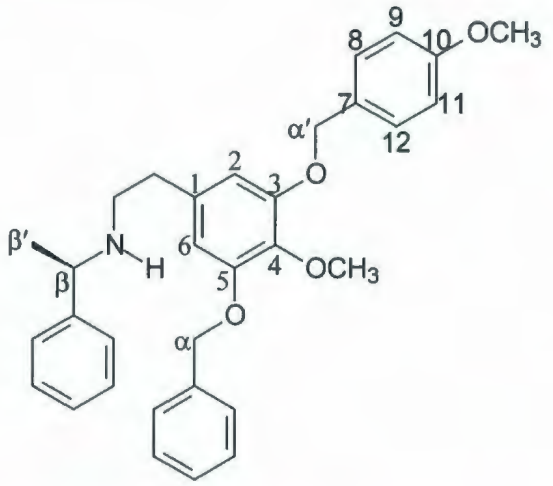
***N*-((*R*)-α-Methylbenzyl)-(3-benzyloxy-4,5-dimethoxy)phenylacetamide (44).**



To a stirred solution of oxalyl chloride (1.7 ml, 20 mmol) in anhydrous benzene (60 ml) were added **12** (3.9 g, 13 mmol) in one batch and DMF (10

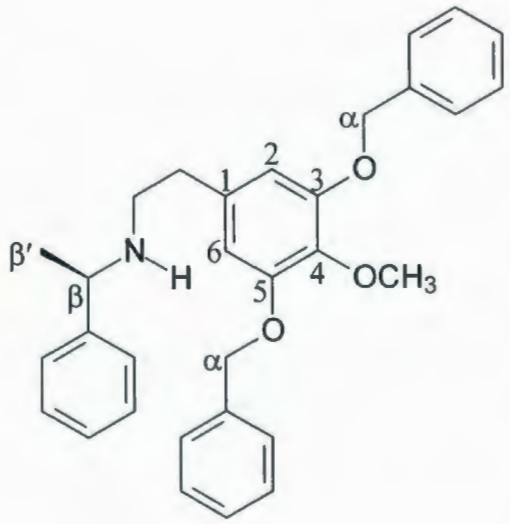
drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the acid chloride, which was used directly in the next step. The crude acyl chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of (*R*)-α-methylbenzylamine (2.1 ml, 16 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 21.5 ml). After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated to afford **44** as a viscous oil (4.1 g, 79 %); ^{1}H NMR: δ 7.44-7.21 (m, 10H, Ar-H), 6.53 (d, *J*=5 Hz, 1H, H-6), 6.48 (d, J=5 Hz, 1H, H-2), 6.12 (d, *J*=5 Hz, 1H, N-H), 5.13 (q, *J*=10Hz, 1H, H-β), 5.07 (s, 2H, H-α), 3.88 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.46 (s, 2H, CH_2), 1.40 (d, *J*=10 Hz, 3H, H-β'); ^{13}C NMR: δ 167.89, 153.68, 152.60, 143.25, 136.96, 128.53, 127.94, 127.37, 126.03, 108.43, 106.68, 71.04, 60.91, 56.07, 48.70, 43.99, 21.77; MS (*m/z*): 405 (M^+, 46), 300 (7), 257 (8), 105 (98), 91 (100).

_N_-((*R*)-α-Methylbenzyl)-2-[(3-benzyloxy-4-methoxy-5-(4-methoxy benzyloxy)] phenylethanamine (24).



To a solution of chiral amide **42** (2 g, 4 mmol) in anhydrous THF (60 ml) under argon was added $BF_3{\cdot}Et_2O$ (0.22 ml, 1.7 mmol). The mixture was heated to gentle reflux and $BH_3{\cdot}THF$ (9.7 ml, 9.7 mmol) was then added dropwise. The reaction mixture was heated at reflux for 2 h, and then cooled to 0 °C and aqueous 20% HCl (100 ml) was added to the mixture. The reaction mixture which was stirred at 0 °C for 1 h and then overnight at rt, was made basic to pH=13 with aqueous 50 % KOH solution. The mixture was then extracted with CH_2Cl_2 (30 ml × 3). The combined organic layers were washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **24** (0.29 g, 10 %) as a yellow oil. ^1H NMR: δ 7.42-7.15 (m, 12H, Ar-H), 6.90 (d, *J*= 5 Hz, 2H, H-9, H-11), 6.48 (d, *J*=5 Hz, 2H, H-6, H-2), 5.08 (s, 2H, H-α), 5.01 (s, 2H, H-α'), 3.87 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.74 (q, *J*=5Hz, 1H, H-β), 2.71-2.62 (m, 4H, CH_2CH_2), 1.32 (d, *J*= 5Hz, H-β'); ^{13}C NMR: δ 170.00, 159.55, 153.96, 152.96, 143.28, 137.11, 129.15, 127.48, 126.12, 114.14, 109.29, 109.07, 71.22, 71.15, 61.06, 55.40, 48.80, 44.13, 21.86; APCI-MS; 497.6 (M^+ + 1), 100).

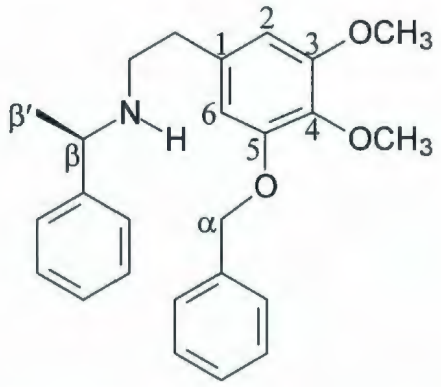
***N*-((*R*)-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (25).**



To a solution of chiral amide **43** (2.1 g, 4.2 mmol) in anhydrous THF (60 ml) under argon was added $BF_3{\cdot}Et_2O$ (0.23 ml, 1.8 mmol). The mixture was heated to gentle reflux and $BH_3{\cdot}THF$ (10 ml, 10 mmol) was then added dropwise. The reaction mixture was heated at reflux for 2 h, and then cooled to 0 °C and aqueous 20% HCl (100 ml) was added to the mixture. The reaction which was stirred at 0 °C for 1 h and then at rt overnight, was basified to pH=13 with aqueous 50% KOH solution. The mixture was then extracted with CH_2Cl_2 (30 ml × 3). The combined organic layers were washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent evaporated to afford **25** (1.7 g, 85 %) as a yellow oil, which was pure enough to be used directly in the next step. ^{1}H NMR: δ 7.46-7.24 (m, 15H, Ar-H), 6.46 (s, 2H, H-2, H-6), 5.12 (s, 4H, H-α), 3.91 (s, 3H, OCH_3), 3.74 (q, *J*=5Hz, 1H, H-β), 2.71-2.62 (m, 4H, CH_2CH_2,), 1.58

(s, 1H, NH), 1.32 (d, *J*= 5Hz, H-β'); ^{13}C NMR: δ 152.66, 145.72, 137.50, 135.71, 128.71, 128.61, 128.01, 127.47, 127.10, 126.75, 71.19, 61.06, 54.41, 48.55, 36.38, 24.22; APCI-MS; 467.2 (M^+ + 1), 100).

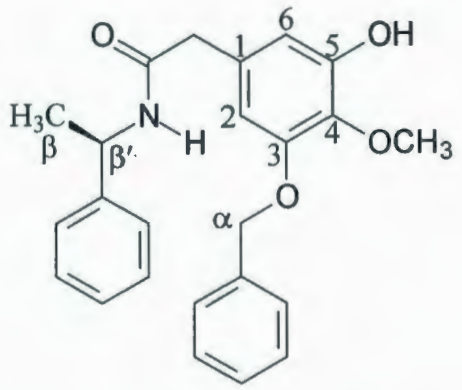
***N*-((*R*)-α-Methylbenzyl)-2-(5-benzyloxy-3,4-dimethoxy)phenylethanamine (13).**



To a solution of chiral amide **44** (2.1 g, 4.9 mmol) in anhydrous THF (60 ml) under argon, was added $BF_3{\cdot}Et_2O$ (0.33 ml, 2.2 mmol). The mixture was heated to gentle reflux and $BH_3{\cdot}THF$ (12 ml, 12 mmol) was then added dropwise. The reaction mixture was heated at reflux for 2 h, and then cooled to 0°C and aqueous 20 % HCl (100 ml) was added to the mixture. The reaction mixture which was stirred at 0°C for 1 h and then at rt overnight, was basified to pH=13 with aqueous 50% KOH solution. The mixture was then extracted with CH_2Cl_2 (30 ml × 3). The combined organic layers were washed with water (20 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **13** (1.7 g, 85%) as a yellow oil, which was pure enough to be used directly in the next step. ^{1}H NMR: δ 7.47-7.25 (m, 10H, Ar-H), 6.45 (d, *J*=5 Hz, 1H, H-6), 6.41

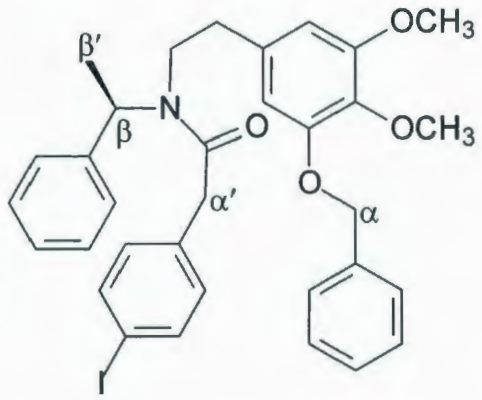
(d, *J*=5 Hz, 1H, H-2), 5.12 (s, 2H, H-α), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.78 (q, *J*=10 Hz, 1H, H-β'), 2.80-2.66 (m, 4H, CH_2CH_2), 1.35 (d, J=10 Hz, 3H, H-β'); ^{13}C NMR: 153.48, 152.38, 144.88, 137.37, 135.68, 128.66, 127.39, 127.08, 126.72, 108.01, 106.21, 71.14, 61.00, 58.35, 56.07, 48.85, 36.68, 24.16; APCI-MS 392.20 (M^+ + 1, 100).

***N*-((*R*)-α-Methylbenzyl)-5-benzyloxy-3-hydroxy-5-methoxy-benzylacetamide (45) .**



Compound **45** was prepared as outlined above as a by-product during the preparation of compound **24** to afford **45** as a by-product. ^1H NMR: δ 7.44-7.21 (m, 10H, H-Ar), 6.50 (s, 1H, H-6), 6.42 (s, 1H, H-2), 5.92 (s, 1H, OH), 5.68 (d, *J*=5 Hz, 1H, NH), 5.13-5.06 (q, 1H, H-β'), 5.03 (s, 2H, H- α), 3.92 (s, 3H, OCH_3), 3.44 (s, 2H, CH_2), 1.39 (d, *J*=10 Hz, H-β); ^{13}C NMR: δ 170.01, 151.90, 149.87, 149.87, 143.22, 135.31, 128.88, 128.21, 127.48, 126.19, 109.61, 106.86, 70.98, 61.23, 48.87, 44.06, 21.96.

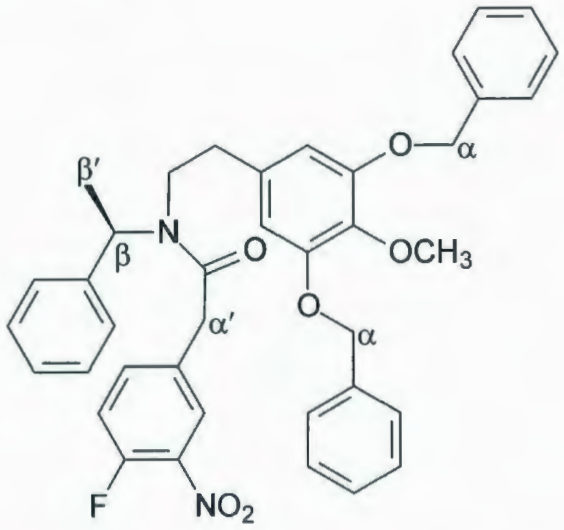
***N*-((*R*)-α-Methylbenzyl)-N-((5-benzyloxy-3,4-dimethoxy)phenylethyl)-4-iodophenylacetamide (23a).**



To a stirred solution of oxalyl chloride (2.1 ml, 24 mmol) in anhydrous benzene (60 ml) were added **14b** (4.2 g, 16 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14b**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of **13** (6.8 g, 18 mmol) and CH_2Cl_2:aqueous 5% NaOH (1:1.5, 24 ml). After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), 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 **23a** (7.8 g, 71%) as a viscous oil: ^{1}H NMR: δ 7.41-6.02 (m,16H, Ar-H), 5.99 and 5.14 (q, 1H, H-β), 5.05 and 5.00 (two s, 2H, H-α), 3.88-3.76 (four s, 6H, OCH_3), 3.62-3.57 (two s, 2H, H-α'), 3.21-2.04 (5m, 4H, CH_2CH_2), 1.49-1.37 (two d, 3H, H-β'); ^{13}C

NMR: 170.71, 153.66, 153.40, 152.58, 152.36, 139.36, 132.05, 130.81, 128.68, 128.04, 127.22, 121.11, 121.00, 108.05, 106.07, 99.73, 61.05, 60.99, 55.91, 52.01, 45.75, 41.03, 40.03, 37.47, 35.29, 18.17, 16.77. APCI-MS(*m/z*): 635.05 (M^++1, 100).

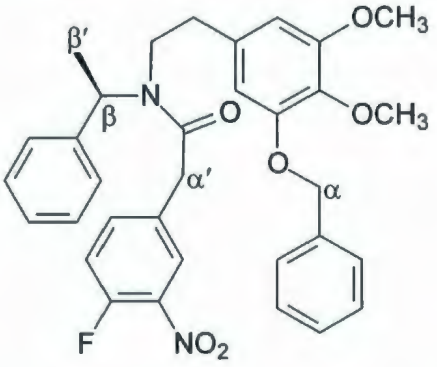
***N-((R)*-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-4-fluoro -3-nitrophenylacetamide (22b).**



To a stirred solution of oxalyl chloride (2.5 ml, 30 mmol) in anhydrous benzene (60 ml) were added **14c** (3.9 g, 20 mmol) in one batch and DMF (10 drops).The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14c**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of **33** (10 g, 22 mmol) and CH_2Cl_2/aqueous 5% NaOH (1:1.5, 29.5 ml). After stirring at rt for 1h, the reaction mixture was

extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), 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 **22b** (10 g, 70.0 %) as a viscous oil. ^1H NMR: δ 7.99-6.26 (m, 20H, Ar-H), 6.11 and 5.29 (two q, 1H, H-β), 5.17 and 5.11 (two s, 4H, H-α), 3.79-3.65 (two s, 3H, OCH_3), 3.59 (s, 2H, H-ά), 3.34-2.22 (m, 4H, CH_2CH_2), 1.63-1.51 (two d, 3H, H-β'). APCI-MS(*m/z*): 648.05 (M^++1, 100).

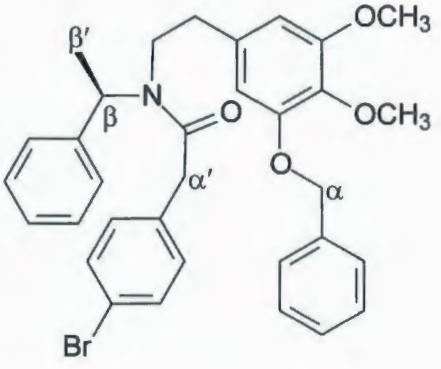
***N-((R)*-α-Methylbenzyl)-N-((5-benzyloxy-3,4-dimethoxy)phenylethyl)-4-fluoro -3-nitrophenylacetamide (23b).**



To a stirred solution of oxalyl chloride (2.5 ml, 30 mmol) in anhydrous benzene (60 ml) were added **14c** (4.1 g, 20 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14c**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of **13** (8.6 g, 22 mmol) and CH_2Cl_2:aqueous 5% NaOH (1:1.5, 29.5 ml). After stirring at rt for 1 h, the reaction mixture was

extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), 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 **23b** (9.1g, 70 %) as a viscous oil. ^{1}H NMR: δ 7.98-6.29 (m,15H, Ar-H), 6.11 and 5.29 (two q, 1H, H-β), 5.17 and 5.11 (two s, 2H, H-α), 3.79-3.65 (four s, 6H, OCH_3), 3.63 (s, 2H, H-α'), 3.34-2.22 (m, 4H, CH_2CH_2), 1.63-1.51 (two d, 3H, H-β'); ^{13}C NMR: δ 169.98, 153.73, 137.60, 137.12, 135.18, 129.31, 127.21, 118.75, 108.36, 106.51, 71.46, 61.31, 61.24, 56.52, 56.38, 46.54, 39.60, 35.72, 29.68, 19.00; APCI-MS(*m/z*): 572.04 (M^++1, 100).

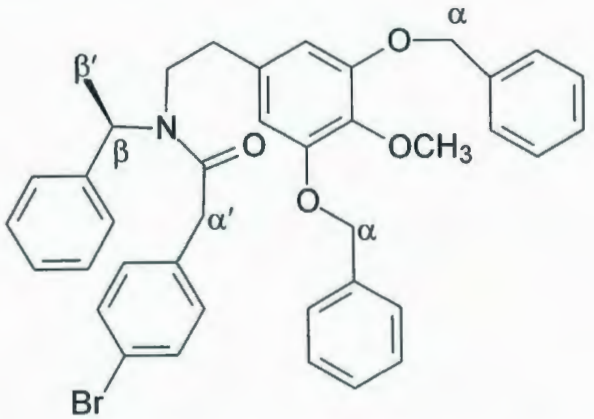
***N-((R)*-α-Methylbenzyl)-N-((5-benzyloxy-3,4-dimethoxy)phenylethyl)-4-bromophenylacetamide (23c).**



To a stirred solution of oxalyl chloride (1.8 ml, 21 mmol) in anhydrous benzene (60 ml) were added **14d** (3.1 g, 14 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14d**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added

dropwise to a stirred mixture of **13** (6.1 g, 15 mmol) and CH_2Cl_2:aqueous 5% NaOH (1:1.5, 20 ml). After stirring at rt for 1 h , the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), 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 **23c** (6.5 g, 71%) as a viscous oil: ^{1}H NMR: δ 7.57-6.18 (m,16H, Ar-H), 5.34 (q, 1H, H-β), 5.01 and 5.03 (two s, 2H, H-α), 3.79-3.65 (four s, 6H, OCH_3), 3.62-3.61 (two s, 2H, H-α'), 3.29-2.19 (m, 4H, CH_2CH_2), 1.49-1.37 (two d, 3H, H-β'); ^{13}C NMR: δ 169.15, 155.21, 153.21, 151.96, 139.65, 136.43, 136.36, 134.48, 128.61, 128.18, 127.82, 127.75, 127.63, 127.50, 126.96, 126.84, 126.51, 118.21, 118.04, 107.64, 105.82, 70.76, 60.61, 60.54, 55.68, 51.81, 45.58, 39.20, 35.02, 28.29, 18.29, APCI-MS(*m/z*): 587.03 (M^++1, 100), 585.02 (M^+-1, 96).

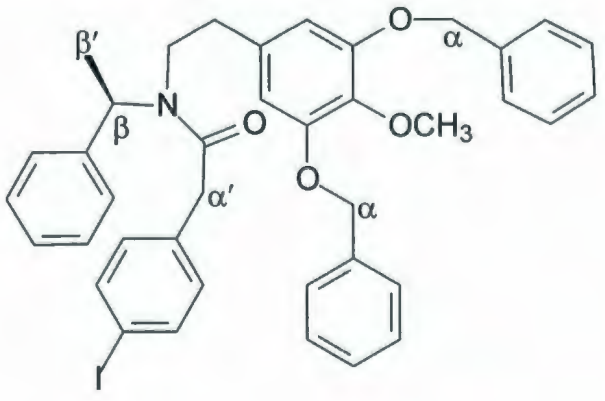
***N-((R)*-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-4-bromophenylacetamide (22c).**



To a stirred solution of oxalyl chloride (1.8 ml, 21 mmol) in anhydrous benzene (60 ml) were added **14d** (2.9 g, 14 mmol) in one batch and DMF (10

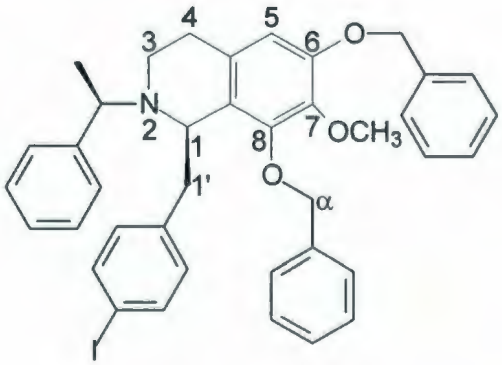
drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14d**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of **33** (7.6 g, 15 mmol) and CH_2Cl_2:aqueous 5% NaOH (1:1.5, 20 ml). After stirring at rt for 1 h , the reaction mixture was extracted with chloroform (30 ml x 3), washed with water (20 ml x 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated. The residue was purified by flash column chromatography (30% EtOAc:hexane) to afford amid **22c** (7.7 g, 71%) as a viscous oil. ^{1}H NMR: δ 7.75-6.18 (m,21H, Ar-H), 6.11 and 5.34 (two q, 1H, H-β), 5.01 and 5.03 (two s, 4H, H-α), 3.79-3.65 (four s, 3H, OCH_3), 3.60 (s, 2H, H-ά), 3.29-2.19 (m, 4H, CH_2CH_2), 1.49-1.37 (two d, 3H, H-β'). APCI-MS(*m/z*): 663.03 (M^++1, 100), 661.02 (M^+-1, 96).

***N-((R)*-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-4-iodophenylacetamide (22a).**



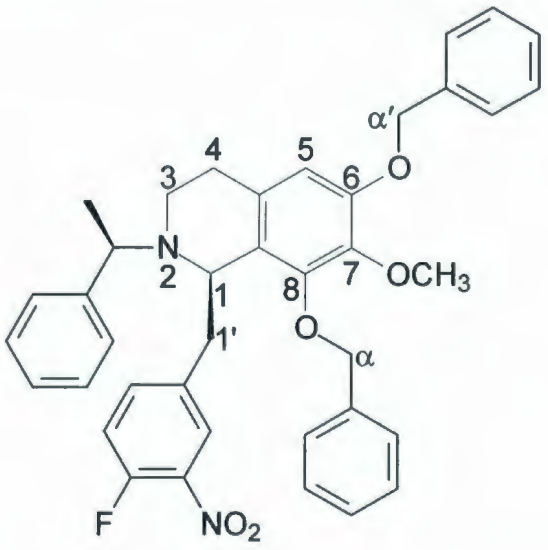
To a stirred solution of oxalyl chloride (1.5 ml, 17 mmol) in anhydrous benzene (60 ml) were added **14b** (2.9 g, 11 mmol) in one batch and DMF (10 drops). The reaction mixture was stirred until the evolution of gas ceased. The benzene was evaporated using a rotary evaporator to give the crude acid chloride of **14b**, which was used directly in the next step. The crude acid chloride was re-dissolved in CH_2Cl_2 (30 ml) at 0 °C and the resulting solution was added dropwise to a stirred mixture of **33** (6.0 g, 13 mmol) and CH_2Cl_2:aqueous 5% NaOH (1:1.5, 17.5 ml). After stirring at rt for 1 h, the reaction mixture was extracted with chloroform (30 ml × 3), washed with water (20 ml × 3), 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 **22a** (6.7 g, 70%) as a viscous oil. ^{1}H NMR: δ 7.65-6.19 (m, 21H, Ar-H), 6.01 and 5.32 (two q, 1H, H-β), 5.01 and 5.03 (two s, 4H, H-α), 3.89-3.75 (four s, 3H, OCH_3), 3.59 (s, 2H, H-α'), 3.25-2.19 (m, 4H, CH_2CH_2), 1.49-1.37 (two d, 3H, H-β'). APCI-MS(*m/z*): 711.05 (M^++1, 100).

(*R*)-6,8-Dibenzyloxy-1-(4-iodobenzyl)-7-methoxy-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (19a).



Compound **22a** (1.1 g, 1.5 mmol), $POCl_3$ (2.6 ml, 28 mmol) and benzene (50 ml) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (20 ml) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.34 g, 9.1 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (30 ml), and the mixture was stirred at rt for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (25 ml) and transferred to a separatory funnel containing H_2O (15 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (15 ml x 3). The combined organic layers were washed with brine (5 ml × 3), dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by PLC (30% EtOAc:hexane) to give compound **19a** (0.56 g, 58%) as a yellow oil. ^{1}H NMR: δ 7.54-6.50 (m, 20H, Ar-H), 5.25 (d, J_{AX}=10 Hz, 1H, Hα), 5.15 (d, J_{AB}=10 Hz, 1H, H-α'), 5.14 (d, J_{BA}=10 Hz, 1H, H-α'), 4.26 (d, J_{XA}=10 Hz, 1H, H-α), 3.96 (s, 3H, OCH_3), 3.75 (t, 1H, H-1), 3.63 (q, 1H, H-β), 3.51 (m, 1H, H-3), 3.43 (m, 1H, H-4), 2.94 (m, 1H, H-3), 2.68 (d, *J*=5, 2H, H-1'), 2.43 (dd, *J*=5, 10, 1H, H-4), 1.28 (d, *J*=5 Hz, H-β'); ^{13}C NMR: δ 154.96, 152.88, 151.61, 150.55, 145.96, 141.16, 138.00, 137.98, 137.32, 136.78, 136.72, 130.77, 129.31, 128.77, 128.31, 127.48, 127.34, 126.96, 126.77, 123.72, 117.04, 116.88, 109.68, 75.78, 71.10, 61.12, 58.79, 56.73, 39.84, 38.54, 22.48, 22.27. APCI-MS(*m/z*): 696.04 (M^++1, 100);

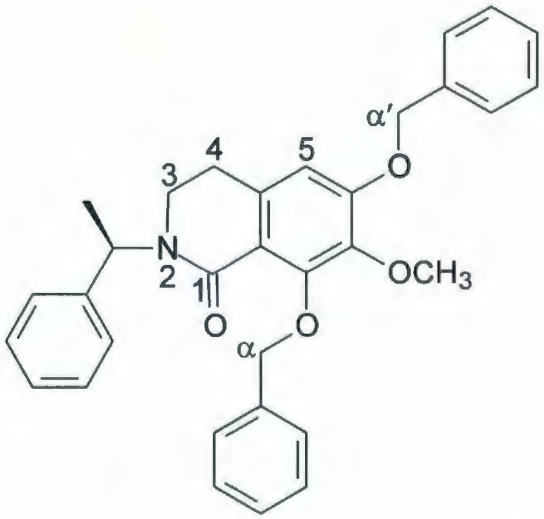
(*R*)-6,8-Dibenzyloxy-1-(4-fluoro-3-nitrobenzyl)-7-methoxy-2-((*R*)-1-*N*-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (19b).



Compound **22b** (1.1 g, 1.5 mmol), $POCl_3$ (4.7 ml, 30 mmol) and benzene (50 ml) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (20 ml) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.33 g, 8.5 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (30 ml), and the mixture was stirred at rt for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (25 ml) and transferred to a separatory funnel containing H_2O (15 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (15 ml × 3). The combined organic layers were washed with brine (5 ml × 3), dried over $MgSO_4$, filtered, and the

solvent was evaporated in *vacuo*. The residue was purified by PLC (30 % EtOAc:hexane) to give compound **19b** (0.58 g, 60%) as a yellow oil. ^{1}H NMR: ^{1}H NMR: δ 7.51-6.69 (m, 18H, Ar-H), 6.59 (s, 1H, H-5), 5.25 (d, J_{AX}=10 Hz, 1H, Hα), 5.15 (d, J_{AB}=10 Hz, 1H, H-ά), 5.11 (d, J_{BA}=10 Hz, 1H, H-α'), 4.31 (d, J_{XA}=10 Hz, 1H, H-α), 3.94 (s, 3H, OCH_3), 3.74 (m, 1H, H-1), 3.60 (q, 1H, H-β), 3.41 (m, 2H, H-3), 2.94 (m, 1H, H-4), 2.73 (m, 2H, H-1'), 2.43 (d, *J*=15, 1H, H-4), 1.28 (d, *J*=5 Hz, H-β'); ^{13}C NMR: δ 154.96, 152.88, 151.61, 150.55, 145.96, 141.16, 138.00, 137.98, 137.32, 136.78, 136.72, 130.77, 129.31, 128.77, 128.31, 128.12,127.48, 127.34, 126.96, 126.77, 123.72, 117.04, 116.88, 109.68, 75.78, 71.10, 61.12, 58.79, 56.73, 39.84, 38.54, 22.48, 22.27. APCI-MS(*m/z*): 634.2 (M^++1, 100). Small amounts of **55** and **56** were obtained

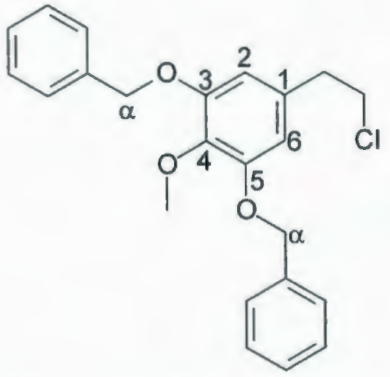
6,8-Dibenzyloxy-7-methoxy-2-((*R*)-1-*N*-phenylethyl)-3,4-isoquinoline-1-one (55).



H NMR: δ 7.76-7.31 (m, 15H, H-Ar), 6.51 (s, 1H, H-5), 6.25 (q, 1H, H-β), 5.25 (d, J_{AB}=5 Hz, 1H, H-α), 5.22 (d, J_{BA}=5 Hz, 1H, H-α), 5.18 (s, 2H, H-ά), 3.82 (s, 3H,

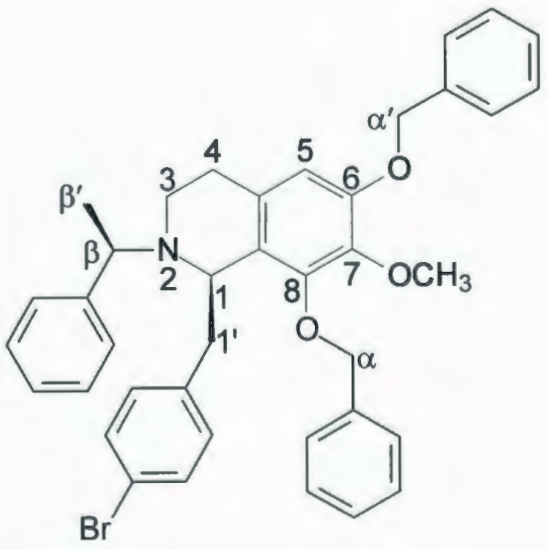
OCH_3), 3.23 (m, 1H, H-3), 2.92 (m, 1H, H-3), 2.59 (m, 2H, H-4), 1.52 (d, 3H, H-β').

1,3-Dibenzyloxy-5-(2-chloroethyl)-2-methoxybenzene (56).



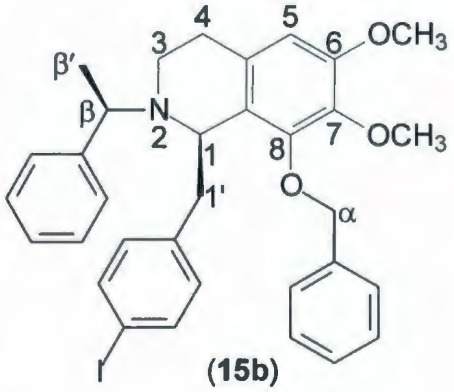
^{1}H NMR: δ 7.45-7.32 (m, 10H, H-Ar), 6.48 (s, 2H, H-6, H-2), 5.13 s, 2H, H- α), 3.89 (s, 3H, OCH_3), 3.61 (t, J= 10 Hz, 2H, H-1'), 2.93 (t, J= 10 Hz, 2H, H-2'); ^{13}C NMR: δ 152.75, 138.64, 137.35, 133.71, 128.72, 128.10, 127.47, 108.92, 71.48, 61.07, 44.51, 39.30.

(*R*)-1-(4-Bromobenzyl)-6,8-dibenzyloxy-7-methoxy-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (19c).

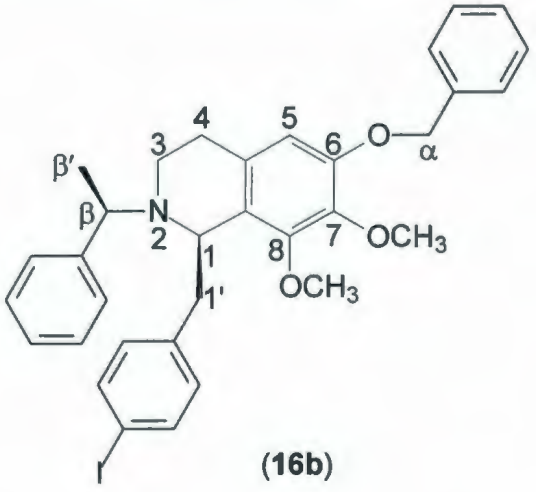


Compound **22c** (1.1 g, 1.5 mmol), $POCl_3$ (4.7 ml, 30 mmol) and benzene (50 ml) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (20 ml) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.33 g, 8.5 mmol) in five portions over 3 h. The residue was re-dissolved in CH_2Cl_2 (25 ml) and transferred to a separatory funnel containing H_2O (15 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (15 ml × 3). The combined organic layers were washed with brine (5 ml × 3) , dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by PLC (30% EtOAc/hexane) to give compound **19a** (0.58 g, 60 %) as a yellow oil. ^{1}H NMR: δ 7.54-6.49 (m, 20H, Ar-H), 5.20 (d, J_{AX}=10 Hz, 1H, Hα), 5.12 (d, J_{AB}=10 Hz, 1H, H-α'), 5.09 (d, J_{BA}=10 Hz, 1H, H-α'), 4.21 (d, J_{XA}=10 Hz, 1H, H-α), 3.91 (s, 3H, OCH_3), 3.73 (t, 1H, H-1), 3.45 (q, 1H, H-β), 3.37 (m, 1H, H-3), 2.92 (m, 1H, H-4), 2.65 (d, *J*=5, 2H, H-α'), 2.37 (dd, *J*=5, 10, 1H, H-4), 1.22 (d, *J*=5 Hz, H-β'); ^{13}C NMR: δ 150.85, 145.97, 140.17, 137.49, 132.10, 128.38, 124.96, 119.53, 107.90, 71.32, 61.44, 59.10, 57.34, 40.69, 38.66, 23.17, 22.51. APCI-MS(*m/z*): 648.2 (M^++1, 100), 546.2 (M^+−1, 96).

(*R*)-8-Benzyloxy-6,7-dimethoxy-1-(4-iodobenzyl)-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (15b) and (*R*)-6-benzyloxy-7,8-dimethoxy-1-(4-iodobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (16b).



(15b)



(16b)

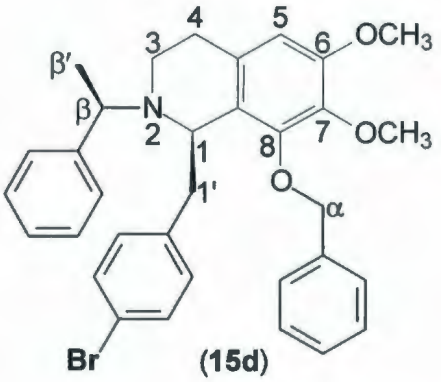
Compound **22a** (1.1 g, 1.6 mmol), $POCl_3$ (2.9 ml, 32 mmol) and benzene (50 ml) were combined under an atmosphere of argon and brought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (20 ml) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.29 g, 7.8 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (30 ml), and the mixture was stirred at rt for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (25 ml) and transferred to a separatory funnel containing H_2O (15 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (15 ml × 3). The combined organic

layers were washed with brine (5 ml × 3) , dried over $MgSO_4$, filtered, and the solvent was evaporated in *vacuo*. The residue was purified by PLC (30% EtOAc/hexane) to give two diastereoisomers **15b** (0.22 g 23%) and **16b** (0.31 g, 31%) as yellow oils. **15b**:

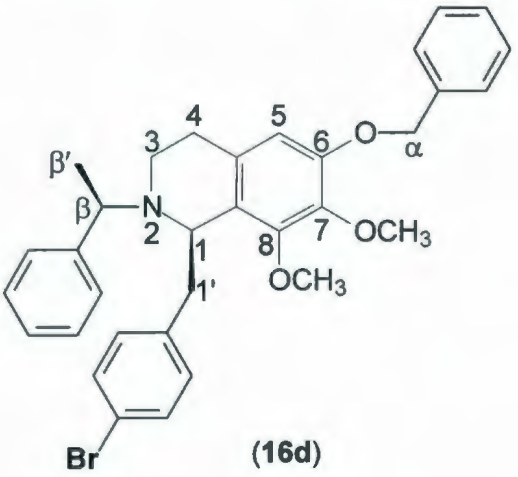
^{1}H NMR: δ 7.39-6.61 (m, 14H, Ar-H), 6.47 (s, 1H, H-5), 5.20 (d, J_{AX}=9.7 Hz, 1H, Hα), 4.20 (d, J_{XA}=9.7 Hz, 1H, H-α), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.73 (t, 1H, H-1), 3.60 (q, *J*=7.3 Hz, 1H, H-β), 3.50 (m, 1H, H-3), 3.39 (m, 1H, H-4), 2.96 (m, 1H, H-3), 2.73 (d, *J*=4.5, 2H, H-α'), 2.49 (dd, *J*=5, 10, 1H, H-4), 1.31 (d, *J*=7.3 Hz, H-β'); ^{13}C NMR: δ 152.05, 150.53, 146.31, 143. 54, 140.54, 137.21, 133.21, 132.98, 132.88, 130.01, 129.19, 127.34, 126.98, 124.95, 119.99, 107.77, 75.87, 62.67, 58.77, 57.32, 56.33, 40.01, 38.21, 24.34, 22.89; ^{13}C NMR: δ 152.12, 150.61, 146.42, 140.82, 137.31, 136.63, 132.41, 130.82, 129.53, 128.65, 128.51, 127.42, 126.63, 124.21, 107.81, 90.66, 75.72, 61.22, 58.93, 57.22, 56.22, 40.71, 38.51, 31.11, 23.01, 22.43; APCI-MS(*m/z*): 620.05 (M^++1, 100);

(16b): ^{1}H NMR: δ 7.53-6.66 (m,14H, Ar-H), 6.52 (s, 1H, H-5), 5.09 (d, J_{AB}=10 Hz, 1H, H-α), 5.06 (d, J_{BA}=10 Hz, 1H, H-α), 3.87 (s, 3H, OCH_3), 3.68 (m, 1H, H-1), 3.65 (s, 3H, OCH_3), 3.52 (q, *J*=6.4 Hz, 1H, H-β), 3.45 (m, 1H, H-3), 3.33 (m, 1H, H-4), 2.88 (m, 1H, H-3), 2.69 (m, 2H, H-ά), 2.36 (dd, *J*=5, 10, 1H, H-4), 1.23 (d, *J*=5 Hz, H-β'). APCI-MS(*m/z*): 620.05 (M^++1, 100);

(*R*)-8-Benzyloxy-1-(4-bromobenzyl)-6,7-dimethoxy-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (15d) and *R*)-6-benzyloxy-1-(4-bromobenzyl)-7,8-dimethoxy-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (16d).



(15d)



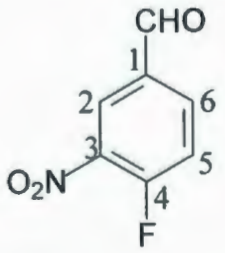
(16d)

Compound **22b** (1.2 g, 1.7 mmol), $POCl_3$ (3.3 ml, 33 mmol) and benzene (50 ml) were combined under an atmosphere of argon and bought to a gentle reflux. After approximately 5 h, the solvent and excess $POCl_3$ were evaporated on a rotary evaporator and finally on a vacuum pump for 1 h. The resultant residue was re-dissolved in MeOH (20 ml) and the solution was cooled to -78 °C in a dry ice bath. To this solution was added $NaBH_4$ (0.38 g, 10 mmol) in five portions over 3 h. The reaction was quenched through the addition of aqueous 10% HCl (30 ml), and the mixture was stirred at rt for 30 min. The MeOH was evaporated on a rotary evaporator. The residue was re-dissolved in CH_2Cl_2 (25 ml) and transferred to a separatory funnel containing H_2O (15 ml). The combined aqueous layers were re-extracted with CH_2Cl_2 (15 ml × 3). The combined organic layers were washed with brine (5 ml × 3), dried over $MgSO_4$, filtered, and the

solvent was evaporated in *vacuo*. The residue was purified by PLC (30 % EtOAc/hexane) to give compound **15d** and **16d** as a yellow oils in 23% and 30% respectively. **15d:** ^{1}H NMR: δ 7.41-6.57 (m,15H, Ar-H), 5.28 (d, J_{AX}=10 Hz, 1H, Hα), 4.29 (d, J_{XA}=10 Hz, 1H, H-α), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.66 (t, 1H, H-1), 3.57 (q, 1H, H-β), 3.54 (m, 1H, H-3), 3.43 (m, 1H, H-4), 3.00 (m, 1H, H-3), 2.73 (d, *J*=5, 2H, H-1'), 2.49 (dd, *J*=5, 10, 1H, H-4), 1.31 (d, *J*=5 Hz, H-β'); ^{13}C NMR: δ 152.05, 150.53, 146.31, 143. 54, 140.54, 137.21, 133.21, 132.98, 132.88, 130.01, 129.19, 127.34, 126.98, 124.95, 119.99, 107.77, 75.87, 62.67, 58.77, 57.32, 56.33, 40.01, 38.21, 24.34, 22.89; APCI-MS(*m/z*): 574.2 (M^++1, 100), 572.2 (M^+-1, 96).

(16d): ^{1}H NMR: δ 7.46-6.51 (m, 15H, Ar-H), 5.09 (d, J_{AB}=10 Hz, 1H, H-α), 5.06 (d, J_{BA}=10 Hz, 1H, H-α), 3.86 (s, 3H, OCH_3), 3.69 (m, 1H, H-1), 3.65 (s, 3H, OCH_3), 3.52 (q, 1H, H-β), 3.39 (m, 1H, H-3), 3.32 (m, 1H, H-4), 2.88 (m, 1H, H-3), 2.73 (m, 2H, H-1'), 2.34 (dd, *J*=5, 10, 1H, H-4), 1.23 (d, *J*=5 Hz, H-β'). APCI-MS(*m/z*): 574.2 (M^++1, 100), 572.2 (M^+-1, 96).

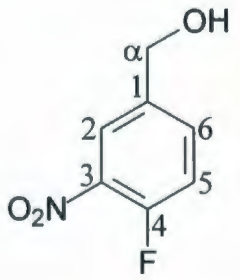
4-Fluoro-3-nitrobenzaldehyde (47).



To a solution of 4-fluorobenzaldehyde (5.1 g, 50 mmol) in concentrated sulfuric acid (25 ml) at 0 °C was added 70% nitric acid (3 ml) slowly. The

resulting reaction mixture was stirred under argon for 2 h and then was poured into ice water (100 ml), and extracted with benzene (30 ml × 3). The combined benzene extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The residue was purified by flash column chromatography (EtOAc/hexane= 5:95) to afford **47** (5.1 g, 85%) as a yellow solid m.p 44-45 °C. ^{1}H NMR: δ 10.04 (s, 1H, CHO), 8.61 (dd, *J*=2, 5 Hz, 1H, H-2), 8.21 (m, 1H, H-6), 7.51 (m, 1H, H-5); ^{13}C NMR: 188.35, 160.08, 157.90, 135.71, 133.06, 128.01, 119.89; MS(*m/z*): 169 (M^+. 97), 168 (100), 122 (55), 94 (56), 75 (97).

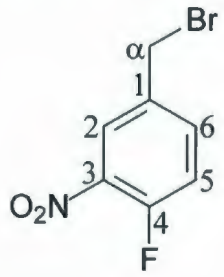
4-Fluoro-3-nitrobenzyl alcohol (48).



To a solution of **47** (4.9 g, 29 mmol) in THF (25 ml) and methanol (25 ml) was added sodium borohydride (0.65 g, 17 mmol) in portions. The reaction mixture was stirred for 2 h, and then concentrated to give a residue which then was dissolved in CH_2Cl_2 (25 ml) and water (25 ml) containing aqueous 1M HCl solution (15.6 ml). The organic phase was washed with water, and dried over anhydrous $MgSO_4$. The solvent was then removed to yield a yellowish oil which was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to afford **48** as a yellow oil (4.7 g, 95%). ^{1}H NMR: δ 8.07 (dd, *J*=2, 5 Hz, 1H, H-2), 7.63 (m, 1H, H-6), 7.29 (m, 1H, H-5), 4.77 (s, 2H, -CH_2-), 2.18 (bs, 1H, OH);

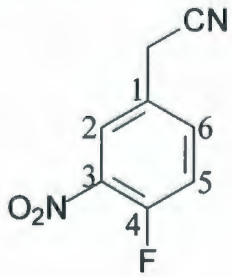
^{13}C NMR: 156.08, 153.69, 137.83, 133.77, 124.17, 118.35, 63.36; MS (*m/z*): 171 (M^+. 78), 154 (30), 125 (99), 107 (86), 95 (100), 75 (73).

4-Fluoro-3-nitrobenzyl bromide (49).



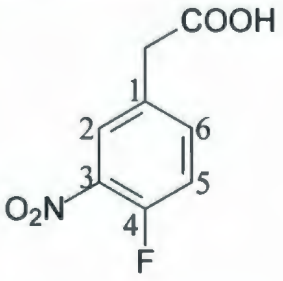
To a solution of **48** (10 g, 58 mmol) in CH_2Cl_2 (300 ml), PBr_3 (4.5 ml, 58 mmol) was added dropwise at 0 °C. After 3 h of stirring at 0 °C, the reaction mixture was quenched by addition of water, the organic phase was washed with aqueous $NaHCO_3$, water, dried over anhydrous $MgSO_4$, and concentrated in *vacuo*. The crude product was further purified by flash chromatography (EtOAc:hexane=2:8) to afford **49** as a colourless solid (11 g, 80%). m.p 56-57 °C; ^1H NMR: δ 8.10 (dd, *J*=2, 5 Hz, 1H, H-2), 7.67 (m, 1H, H-6), 7.29 (m, 1H, H-5), 4.48 (s, 2H, $-CH_2-$); MS (*m/z*): 235 (M^++2, 3), 233 (M^+-1, 3), 154 (99), 108 (100), 96 (23), 81 (28).

4-Fluoro-3-nitrophenylacetonitrile (50).



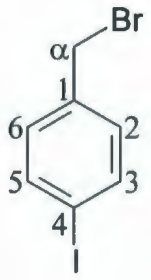
To a solution of **49** (6.1 g, 26 mmol) in DMSO (20 ml) and benzene (15 ml) was added NaCN (1.3 g, 26 mmol) powder in 3 portions. After stirring for 2 h at rt, the reaction mixture was poured into water (40 ml) and extracted with benzene (40 ml × 3). The combined organic layers were washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, filtered, and the solvent was evaporated to afford **50** (3.4 g, 75%) as a colourless oil. ^{1}H NMR: δ 8.06 (dd, *J*=2, 5 Hz, 1H, H-2), 7.78 (m, 1H, H-6), 7.36 (m, 1H, H-5), 3.91 (s, 2H, -CH_2-); ^{13}C NMR: 156.32, 154.03, 135.16, 127.06, 125.90, 119.56, 116.30; MS (*m/z*): 180 (M^+, 100), 134 (80), 122 (77), 107 (99), 95 (74), 81 (50).

4-Fluoro-3-nitrophenylacetic acid (14c).



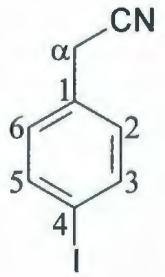
A solution of **59** (5.1 g, 27 mmol) in 95% ethanol (40 ml) and aqueous 4.0 M NaOH (7 ml) was heated at reflux for 20 h. The reaction mixture was then cooled to rt and then acidified to pH=1 to form a residue which was filtered and washed with water to give crude **14c** (5.1 g, 92%) as a colourless solid. m.p 95-96 °C. ^{1}H NMR: δ 8.01 (dd, *J*=2, 5 Hz, 1H, H-2), 7.56 (m, 1H, H-6), 7.29 (m, 1H, H-5), 3.74 (s, 2H, CH_2); ^{13}C NMR: δ: 176.75, 156.32, 154.21, 137.02, 130.51, 127.37, 119.16, 39.94; MS (*m/z*): 199 (M^+, 100), 154 (99), 122 (77), 108 (99), 97 (48), 77 (50).

4-Iodobenzyl bromide (52).



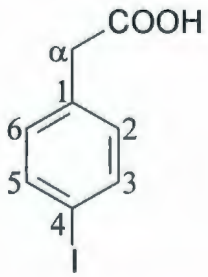
To a solution of **51** (1.1 g, 4.6 mmol) and a few crystal of dibenzoyl peroxide in CH_2Cl_2 was added NBS (0.9 g, 5 mmol). The mixture was stirred under the light of a 100-watt lamp at a gentle reflux. After 1 h, the reaction was stopped, brine (8 ml) with KI (0.26 g) was added to the reaction mixture. Then aqueous $Na_2S_2O_3$ solution (20 ml) was added to remove the produced I_2. After this, the organic layer was separated and the aqueous layer was extracted by CH_2Cl_2 (4 ml × 3). The combined organic layers was washed by brine(8 ml), dried by $MgSO_4$, filtered and the solvent was evaporated to give crude **52** which was further purified by crystallization by using EtOH to afford **52** as a colourless solid (1.50 g, 100%); m.p. 77-78 °C; ^{1}H NMR: δ 7.68 (d, *J*=5 Hz, 2H, H-3, H-5), 7.13, (d, *J*=10 Hz, 2H, H-2, H-6), 4.42 (s, 2H, CH_2); ^{13}C NMR: 137.92, 137.37, 130.72, 94.07, 32.45; MS (*m/z*): 298 (M^++1, 10), 296 (M^+-1, 9), 217 (100), 127 (41), 90 (74), 63 (43).

4-Iodophenylacetonitrile (53).



To a solution of **52** (9.9 g, 33 mmol) in DMSO (40 ml) and benzene (60 ml) was added NaCN (4.25 g, 87.7 mmol) powder in 3 portions. After stirring for 2 h at rt, the reaction mixture was poured into water (40 ml) and extracted with benzene (40 ml × 3).The combined organic layers were washed with brine (30 ml × 3), dried over anhydrous $MgSO_4$, filtered , and the solvent was evaporated to afford **53** (6.1 g, 75%) as a colourless solid, m.p 52-53 °C. ^{1}H NMR: δ 7.65 (d, *J*=10 Hz, 2H, H-3, H-5), 7.08 (d, *J*=10 Hz, 2H, H-2, H-6), 3.69 (s, 2H, H-α); ^{13}C NMR: δ 138.37, 130.26, 117.57, 93.77, 23.70; MS(*m/z*): 243 (M^+ + 1, 100), 116 (88), 89 (42).

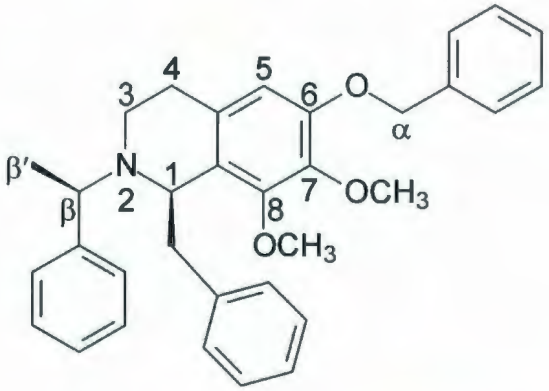
4-Iodophenylacetic acid (14b).



A solution of **53** (7.5 g, 31 mmol) in 95 % ethanol (150 ml) and aqueous 4.0 M NaOH (30 ml) was heated at reflux for 20 h. The reaction mixture was then

cooled to rt and then acidified to pH=1 to form a residue which was filtered and washed with water to to give **14b** (7.6 g, 95 %) as a yellow solid, m.p.126-127 °C. ^{1}H NMR: δ 7.67 (d, *J*=5 Hz, 2H, H-3, H-5), 7.03 (d, *J*=5 Hz, 2H, H-2, H-6), 3.57 (s, 2H, Hα); ^{13}C NMR: δ 177.19, 137.79, 132.85, 131.36, 93.19, 40.73; MS(*m/z*): 261 (M^{+}, 93), 217 (100), 91 (21).

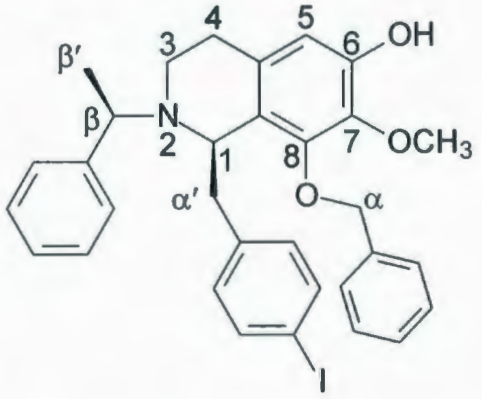
(*R*)-1-Benzyl-6-benzyloxy-7,8-dimethoxy-2-((*R*)-1-*N*-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (64).



A solution of compound **16d** (75 mg, 0.13 mmol) in CH_2Cl_2 (5 ml) and 10% Pd/C was hydrogenated for 14 h. The solution was then Filtered through Celite followed by evaporation of solvent which afforded a residue, which was dissolved in water (5 ml) and CH_2Cl_2 and basified to pH 8 with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afforded a colourless oil which was purified by preparative TLC (silica gel, 10% EtOAc in hexane) to afford compound **64** as a yellow oil (45 mg, 70%). ^{1}H NMR: δ 7.48-6.66 (m, 15H, Ar-H), 6.51 (s, 1H, H-5), 5.10 (d, J_{AB}=5 Hz, 1H, H-α), (d, J_{BA}=5 Hz, 1H, H-α), 3.87 (s, 3H, OCH_3), 3.56 (t, J=10 Hz, 1H, H-β), 3.66 (s, 3H, OCH_3), 3.56 (q, J=6.4 Hz, 1H, H-β), 3.48 (m, 1H, H-3), 3.31 (m, 1H, H-4), 2.90 (m, 1H, H-3), 2.80 (m, 2H, H-ά), 2.37 (dd, J=5, 15 Hz, 1H, H-4), 1.22 (d, J=6.4 Hz, 3H, H-β'); ^{13}C NMR: δ 151.38, 151.15, 145.77, 140.77, 140.71, 137.24, 136.62, 131.88, 130.49, 128.56, 127.89, 127.33, 127.23,

126.37, 124.42, 109.24, 90.51, 70.89, 60.89, 60.53, 58.67, 56.50, 40.76, 38.40, 22.39, 22.09. APCI-MS: 494.2 (M^++1, 100).

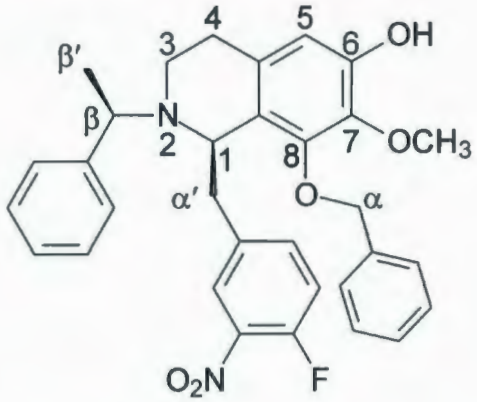
(*R*)-8-Benzyloxy-6-hydroxy-7-methoxy-1-(4-Iodobenzyl)-2-(*R*)-1-phenyl ethyl)-1,2,3,4-tetrahydroisoquinoline (58a).



To a solution of **19b** (63 mg, 0.090 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.18 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 30:7) to give **58a** as yellow oil (15 mg, 29%); ^{1}H NMR: δ 7.46-6.69 (m, 14H, Ar-H), 6.59 (s, 1H, H-5), 5.11 (d, J_{AX}=10 Hz, 1H, H-α), 4.20 (d, J_{XA}=10 Hz, 1H, H-α), 3.95 (s, 3H, OCH_3), 3.74 (dd, J=5, 5 Hz, 1H, H-1), 3.62 (q, J=5 Hz, 1H, H-β), 3.43 (m, 2H, H-

3), 2.96-2.90 (m, 1H, H-4), 2.76-2.72 (m, 2H, H-α'), 2.44 (d, *J*=15 Hz, 1H, H- 4), 1.28 (d, *J*=5 Hz, 3H, H-β'); APCI-MS(*m/z*): 605.5 (M^++1, 100).

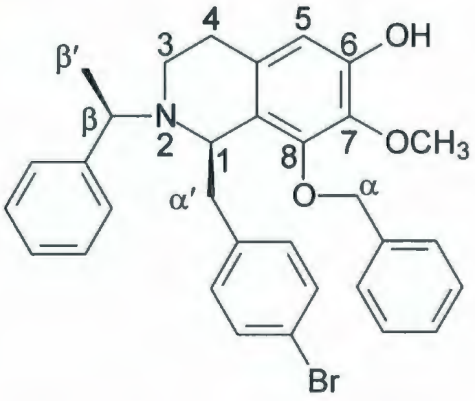
(*R*)-8-Benzyloxy-7-Hydroxy-6-methoxy-1-(4-fluoro-3-nitrobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (58b).



To a solution of **19b** (51 mg, 0.080 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.16 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 30:7) to give **58b** as yellow oil (13 mg, 29%); ^{1}H NMR: δ 7.46-6.69 (m, 13H, Ar-H), 6.59 (s, 1H, H-5), 5.75 (s, 1H, OH), 5.11 (d, J_{AX}=10 Hz, 1H, H-α), 4.22 (d, J_{XA}=10 Hz, 1H, H-α), 3.95 (s, 3H, OCH_3), 3.74 (dd, *J*=5, 5 Hz, 1H, H-1), 3.61 (q, *J*=5 Hz, 1H, H-β), 3.44 (m, 2H, H-3), 2.96-2.90 (m, 1H, H-4), 2.76-2.72 (m, 2H, H-α'), 2.44 (d,

J=15 Hz, 1H, H- 4), 1.28 (d, *J*=5 Hz, 3H, H-β'); ^{13}C NMR: δ 150.53, 146.42, 140.65, 139.92, 137.19, 131.96, 130.47, 129.46, 128.27, 127.24, 126.55, 124.17, 119.28, 107.78, 61.08, 58.85, 57.02, 56.05, 40.48, 38.44, 22.96, 22.29; APCI-MS(*m/z*): 543.1 (M^++1, 100).

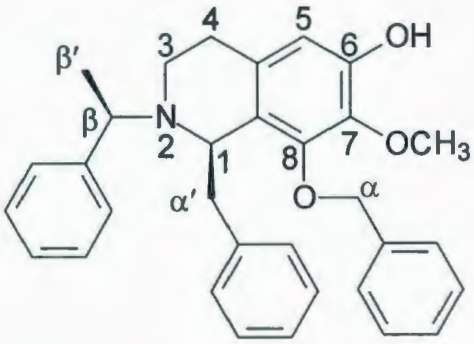
(*R*)-8-Benzyloxy-6-hydroxy-7-methoxy-1-(4-bromobenzyl)-2-(*R*)-1-phenyl ethyl)-1,2,3,4-tetrahydroisoquinoline (58c).



A solution of compound **19c** (71 mg, 0.11mmol) in MeOH (5 ml) at 0 °C was treated with Raney Nickel and the reaction mixture was stirred under an atmosphere of H_2 at 0 °C for 15 h. The mixture was then filtered over Celite followed by evaporation of solvent afforded a residue, which was dissolved in water (5 ml) and EtOAc and basified to pH 8 with saturated $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afforded a brown oil which was purified by preparative TLC (silica gel, 20% EtOAc in hexane) to afford compound **58** as a yellow oil (20 mg, 33%). ^{1}H NMR: δ 7.29-.6.0 (m, 15H, Ar-H), 5.65 (s, 1H, OH),

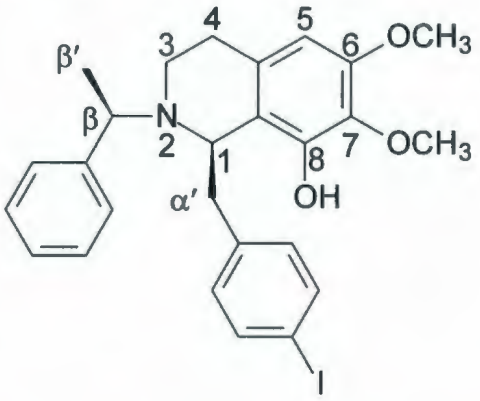
5.11 (d, J_{AB}=5 Hz, 1H, H-α), 4.16 (d, J_{BA}=5 Hz, 1H, H-α), 3.98 (s, 3H, OCH_3), 3.56 (dd, *J*=5, 10 Hz, 1H, H-1), 3.60 (q, *J=5* Hz, 1H, H-β), 3.51 (m, 1H, H-3), 3.41 (m, 1H, H-4), 2.95 (m, 1H, H-3), 2.68 (m, 2H, H-ά), 2.45 (dd, *J*=5, 15 Hz, 1H, H-4), 1.28 (d, *J*=5 Hz, 3H, H-β'); APCI-MS(*m/z*): 558.1 (M^++1, 96), 560.1 (M^+-1, 100). (16 mg, 30%) of **59** and (10 mg, 19%) of **57** were obtained.

(*R*)-1-Benzyl-8-Benzyloxy-6-hydroxy-7-methoxy-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (59).



^{1}H NMR: δ 7.29-.6.0 (m, 16H, Ar-H), 5.65 (s, 1H, OH), 5.11 (d, J_{AB}=5 Hz, 1H, H-α), 4.16 (d, J_{BA}=5 Hz, 1H, H-α), 3.98 (s, 3H, OCH_3), 3.56 (dd, *J*=5, 10 Hz, 1H, H-1), 3.60 (q, *J=5* Hz, 1H, H-β), 3.51 (m, 1H, H-3), 3.41 (m, 1H, H-4), 2.95 (m, 1H, H-3), 2.68 (m, 2H, H-ά), 2.45 (dd, *J*=5, 15 Hz, 1H, H-4), 1.28 (d, *J*=5 Hz, 3H, H-β'); APCI-MS(*m/z*): 480.2 (M^++1, 100).

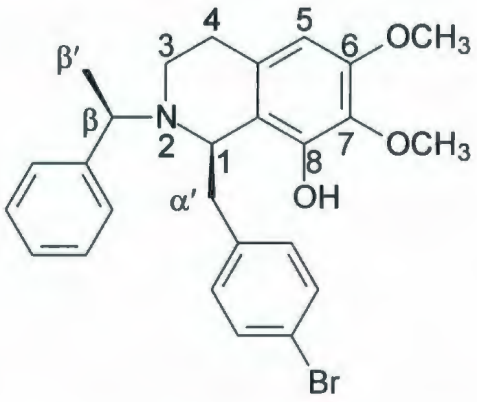
(*R*)-8-Hydroxy-6,7-dimethoxy-1-(4-iodoenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (65a).



To a solution of **15b** (55 mg, 0.088 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.18 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 30:7) to give **65a** as a yellow oil (13 mg, 29%); ^{1}H NMR: δ 7.50-6.71 (m, 9H, Ar-H), 6.25 (s, 1H, H-5), 5.75 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.80 (m, 1H, H-1), 3.56 (q, 1H, H- β), 3.31 (m, 1H, H-3), 2.86-2.67 (m, 2H, H-4), 2.76 (m, 1H, H-3), 2.36 (d, *J*=16 Hz, 2H, H- ά), 1.26 (d, *J*=5 Hz, 3H, H-β'); ^{13}C NMR: δ 150.35, 146.79, 146.00, 140.21, 133.51, 132.61, 131.82, 131.28, 130.82, 128.11,

127.44, 126.42, 119.42, 117.91, 103.72, 61.21, 58.91, 56.44, 55.91, 39.63, 38.91, 23.11, 22.11; APCI-MS(*m/z*): 530.1 (M^++1, 100).

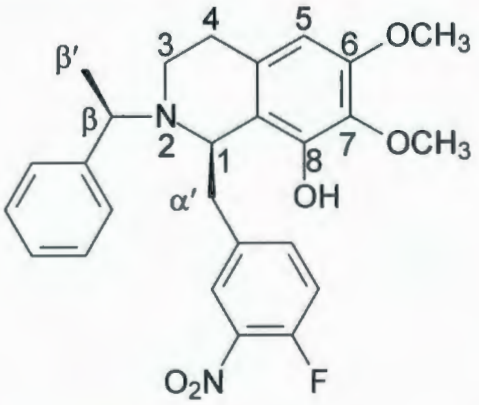
(*R*)-8-Hydroxy-1-(4-bromobenzyl)-6,7-dimethoxy-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (65c).



To a solution of **15d** (74 mg, 0.13 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.2 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 30:7) to give **65c** as a yellow oil (20 mg, 34%); ^{1}H NMR: δ 7.33-6.76 (m, 9H, Ar-H), 6.28 (s, 1H, H-5), 5.80 (p, 1H, OH), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.85 (m, 1H, H-β), 3.61 (t, 1H, H-1), 3.40 (m, 1H, H-3), 3.34 (m, 1H, H-4), 2.91 (m, 1H, H-3), 2.73 (m, 2H, H- ά), 2.40 (m, 1H, H-4), 1.28 (d, 3H, H-β'); ^{13}C NMR: δ 150.34,

146.81, 145.79, 140.11, 133.51, 132.61, 130.94, 130.89, 128.11, 127.82, 126.18, 119.16, 117.75, 103.46, 61.22, 58.90, 56.44, 55.91, 39.61, 38.90, 23.11, 22.11; APCI-MS(*m/z*): 484.1 (M^++1, 100), 482.2 (M^+−1, 96).

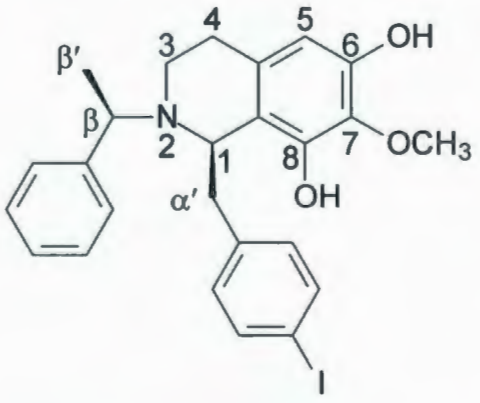
(*R*)-8-Hydroxy-6,7-dimethoxy-1-(4-fluoro-3-nitrobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (65b).



To a solution of **15c** (99 mg, 0.18 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.2 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 30:7) to give **65b** as a yellow oil (27 mg, 33%); ^{1}H NMR: δ 7.67-6.96 (m, 8H, Ar-H), 6.27 (s, 1H, H-5), 5.83 (s, 1H, OH), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.80 (dd, *J*=5, 10 Hz, 1H, H-1), 3.57 (q, 1H, H- β), 3.73 (m, 1H, H-3), 2.94-2.85 (m, 2H, H-

4), 2.76 (m, 1H, H-3), 2.73 (d, *J*=16 Hz, 2H, H- ά), 1.28 (d, *J*=5 Hz, 3H, H-β'); ^{13}C NMR: δ 150.54, 146.48, 145.32, 143.21, 138.31, 136.77, 136.62, 133.33, 130.92, 127.67, 127.21, 126.59, 126.51, 116.96, 116.81, 103.54, 61.03, 58.52, 56.02, 55.69, 38.83, 38.78, 22.80, 21.31; APCI-MS(*m/z*): 467.3 (M^++1, 100).

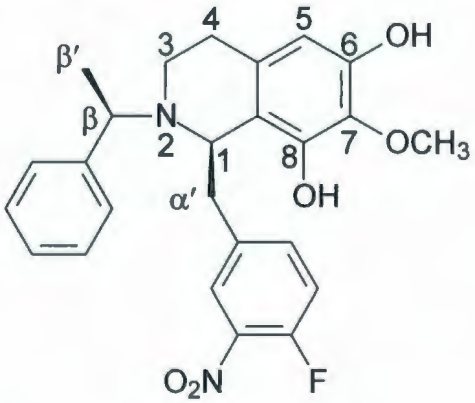
(*R*)-6,8-Dihydroxy-7-methoxy-1-(4-iodobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (68a).



To a solution of **19a** (63 mg, 0.091 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.36 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 50:50) to give **68b** as a yellow oil (22 mg, 48%); ^1H NMR: δ 7.54-6.75 (m, 8H, Ar-H), 6.33 (s, 1H, H-5), 5.40 (s, 1H, OH), 5.21 (s, 1H, OH), 3.86 (s, 3H, OCH_3), 3.77

(m, 1H, H-1), 3.59 (q, *J*=5 Hz, 1H, H-β), 3.38 (m, 1H, H-3), 3.32 (m, 1H, H-3), 2.86 (m, 2H, H-α'), 2.75 (m, 1H, H-4), 2.39 (dd, *J*=5, 15 Hz, 1H, H-4), 1.27 (d, *J*=5 Hz, 1H, H-β'); ^{13}C NMR: δ 146.92, 146.60, 146.21, 141.11, 137.00, 132,88, 132.47, 132.39, 128.29, 127.63, 126.63, 116.91, 107.72, 99.99, 61.69, 59.17, 56.51, 40.10, 39.09, 23.10, 22.35; APCI-MS(*m/z*): 516.0 (M^++1, 100).

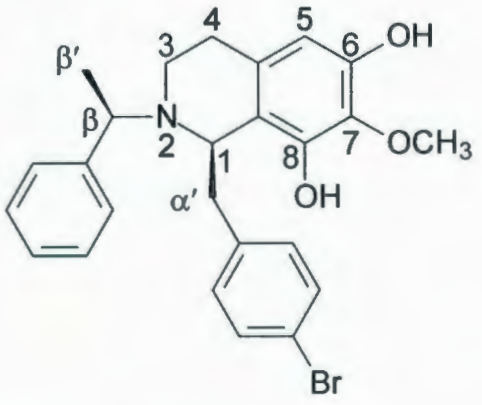
(*R*)-6,8-Dihydroxy-7-methoxy-1-(4-fluoro-3-nitrobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (68b).



To a solution of **19b** (51 mg, 0.086 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.34 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 50:50) to give **68b** as a yellow oil (18 mg, 52%); ^{1}H NMR: δ 7.65-6.72 (m, 8H, Ar-H),

6.32 (s, 1H, H-5), 5.63 (s, 1H, OH), 3.84 (s, 3H, OCH_3), 3.79 (m, 1H, H-1), 3.57 (q, *J*=5 Hz, 1H, H-β), 3.36 (d, *J*=10 Hz, H-α'), 2.92-2.74 (m, 3H, H-3, H-4), 2.37 (d, *J*=20 Hz, 1H, H- 4); APCI-MS(*m/z*): 454.1 (M^++1, 100).

(*R*)-6,8-Dihydroxy-7-methoxy-1-(4-bromobenzyl)-2-(*R*)-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (68b).



To a solution of **19c** (54 mg, 0.083 mmol) in dry CH_2Cl_2 was added dropwise $TiCl_4$ (0.33 ml) at °C. The solution was warmed to rt and stirred for 5 h. The reaction solution was poured into cooled aqueous saturated $NaHCO_3$. The combined mixture was filtered through a Celite pad, and the organic layer was isolated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 3). The combined organic layers were washed with brain (5 ml × 3), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on a rotary evaporator. The residue obtained was further purified by using PLC (EtOAc/hexane= 50:50) to give **68c** as a yellow oil (19 mg, 50%); ^1H NMR: δ 7.53-6.75 (m, 8H, Ar-H), 6.33 (s, 1H, H-5), 5.40 (s, 1H, OH), 3.86 (s, 3H, OCH_3), 3.77 (m, 1H, H-1), 3.59 (q, *J*=5 Hz, 1H, H-β), 3.38 (m, 1H, H-3), 3.32 (m, 1H, H-3), 2.86 (m, 2H, H-α'),

2.75 (m, 1H, H-4), 2.39 (dd, *J*=5, 15 Hz, 1H, H-4), 1.27 (d, *J*=5 Hz, 1H, H-β'); ^{13}C NMR: δ 146.92, 146.60, 146.21, 141.11, 137.00, 132,88, 132.47, 132.39, 128.29, 127.63, 126.63, 116.91, 107.72, 99.99, 61.69, 59.17, 56.51, 40.10, 39.09, 23.10, 22.35; APCI-MS(*m/z*): 468.3 (M^++1, 100), 467.2 (M^+-1, 94).

Chapter 3

3.1 Introduction.

Anthrax is an acute infectious disease caused by *Bacillus anthracis (B.anthracis),* a Gram-positive, spore-forming, aerobic, and rod-shaped bacterium.[1] Humans usually contract the disease either by contact with infected livestock, or ingestion of contaminated animal products. Anthrax recently gained public attention as a result of a preceded bioterrorism.[2]

3.1.1 Classification of Anthrax.

Anthrax has been divided into three types, depending on the way in which the spore enters the body[3]: (1) *Cutaneous anthrax*, in which spores infect the host through skin cuts or abrasions. This type of anthrax is not as dangerous and it can be treated effectively or the organism's immune system eliminates the spore. (2) *Gastrointestinal anthrax disease* which results from the consumption of spore-contaminated meat by the host. Even though it is a very rare form of anthrax infection it is extremely violent and has a high mortality rate; and (3) *Inhalational anthrax* which is the most dangerous form. The bacterium enters the host by aerosols which carry it into the lungs and ultimately to the alveoli which is facilitated by the small ≈ 5 μm aerosol size. Once the bacteria crosses the membrane and enters the blood stream the mortality rate is ≈ 100%, if untreated.

3.1.2 The lethality of *B. anthracis.*

The lethality of *B. anthracis* can be attributed to two factors: (1) The capsule, which consists of poly-α-D-glutamic acid, is a necessary virulence factor that reduces the natural host defense through its antiphagocytic action. Poly-α-D-glutamic acid (Figure 3.1) itself is a weak immunogenic, but when covalently bound to a carrier protein, it stimulates the production of serum antibodies.[4, 5] (2) The anthrax toxin, consists of three proteins, namely Lethal Factor (LF), Edema Factor (EF) and Protective Antigen (PA). Experiments have shown that each protein individually, is nontoxic. However, a mixture of PA and LF can cause lethal shock in experimental animals, and a mixture of PA and EF leads to edema at the position of injection in test animals.[6] Among these three proteins, LF has been shown to act as the key virulence factor for *B. anthracis*.

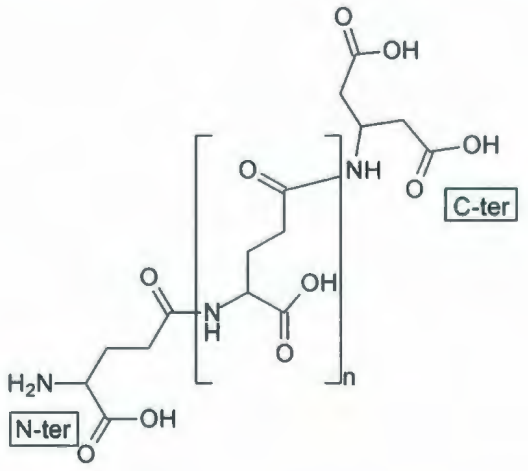


Figure 3.1. Poly-α-D-glutamic acid.

(According to Forino. *et. al.*[7] *"Anthrax lethal toxin must enter inside the cell compartment to exert its lethal effect. PA binds to the ubiquitously expressed cellular receptors and, after its proteolytic activation by the furin-like proprotein convertases and the release of the N-terminal 20-kDa fragment, generates the mature PA protein. PA heptamerizes and binds both of LF and EF. After endocytosis of the resulting complexes, the engulfed molecules of LF and EF are liberated and exert their toxic action. Inside the cell compartment, LF cleaves mitogen-activated protein kinase kinases (MAPKK), disrupts signal transduction, and finally leads to macrophage lysis through a mechanism that is not completely understood to date. Accordingly, inhibition of LF is the most promising means for treating postexposure anthrax".*

3.1.3 Lethal factor (LF).

Anthrax Lethal Factor is a zinc-dependent protease that cleaves mitogen-activated protein kinase kinase and causes lysis of macrophages.[8,9] The mature spore exhibits high resistance to: harsh chemicals, desiccation, extreme temperatures, radiation, and physical damage.[10] This allows the spore to survive in soil for many years. It is therefore, highly desirable to develop an effective and inexpensive vaccine as well as a method to detect this dangerous bacterium. The preparation of effective inhibitors against LF and an understanding of its manner of action has become the focus of several studies.[11-17]

3.1.4 Detection and inhibition of anthrax lethal factor.

In 2004 Turnbough[11] isolated anthrax tetrasaccharide from the surface of the exosporium glycoprotein BC1A of *B. anthracis* (Figure 3.2). He also explained that the anthrax tetrasaccharide consists of three L-rhamnose sugars and a D-anthrose sugar. The structure of anthrax tetrasaccharide is unique to *B.anthracis* and is not found in other spores of the *Bacillus species*. Thus, anthrax tetrasaccharide has become a target for anthrax detection.

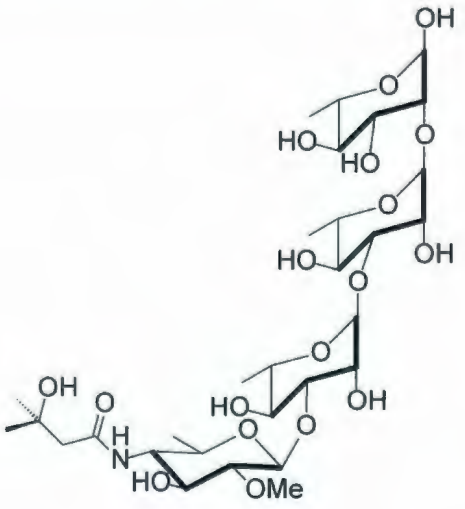
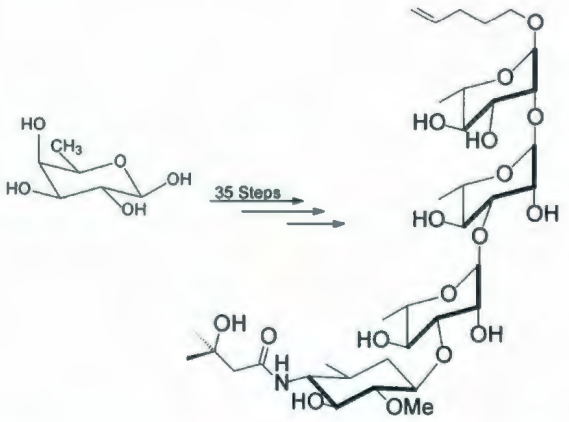


Figure 3.2. Structure of the surface tetrasaccharide of *B. anthracis*.

The tetrasaccharide was first chemically synthesized in the form of an *n*-pentenyl glycoside by Seeberger[12] in 2005 (Scheme 3.1). Starting with D-fucose the desired target was prepared in 35 steps. The reason for using a terminal pentenyl group is to enable its conjugation with the protein in vaccine development.



Scheme 3.1. Synthetic approach for Anthrax tetrasaccharide analogues.

O'Doherty[13] used the *de novo* asymmetric approach to synthesize the anthrax tetrasaccharide and its analogue, with an anomeric hexyl azide group (Figure 3.3). The total synthesis of anthrax tetrasaccharide has been the major goal of many recent reports.[14]

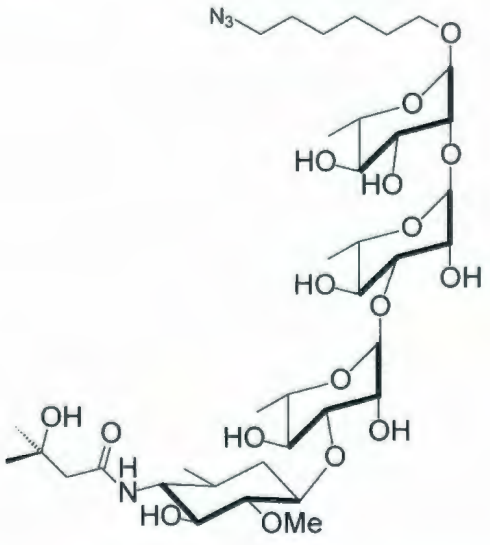


Figure 3.3. The anomeric hexyl azide analogue of tetrasaccharide.

In 2005 Forino *et al.*[7] prepared a series of phenylfuran-2-ylmethylene-rhodanineacetic acid derivatives of LF inhibitors with low-micromolar and

submicromolar activity. For example, derivatives of compound **1** illustrated in Figure 3.4 showed good reactivity as LF inhibitors.

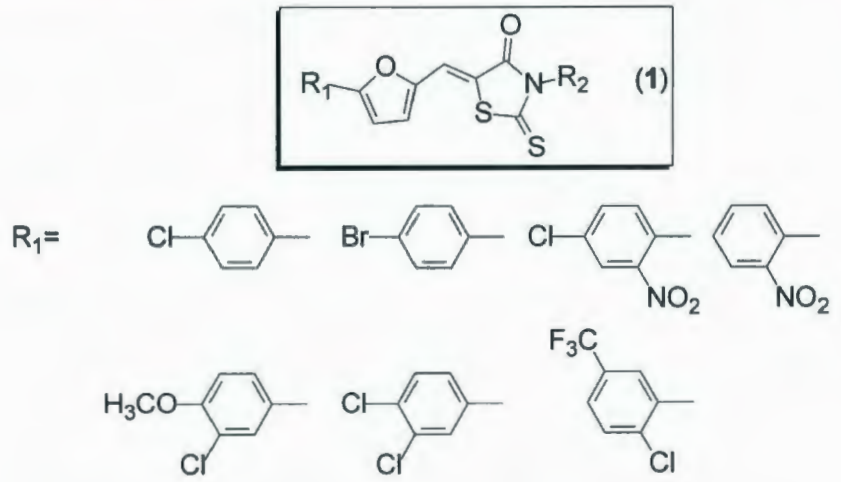
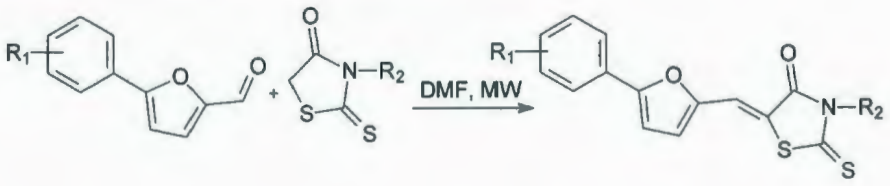


Figure 3.4. Derivatives of compound 1.

This study revealed that the presence of a phenyl moiety with a small electronegative group in the R_1 position, and a carboxylic group in the R_2 position increased the reactivity of these compounds. All positions on the phenyl moiety gave similar results, however an acetyl group in position R_2 however, gave the best results. It was also concluded from this study that, the presence of multiple substituents increases the reactivity. The strategy which was applied to prepare those compounds is illustrated in Scheme 3.2.



Scheme 3.2. Synthetic approach to prepare derivatives of compound 1

Cohen *et al.*[15] described the preparation of several nitrogen ligands (Figure 4.5) which were identified as being useful for the inhibition of Zn^{2+} metallo-proteinases. Their study showed that these compounds exhibited selectivity for Zn^{2+}-metalloproteins over other metalloproteins.

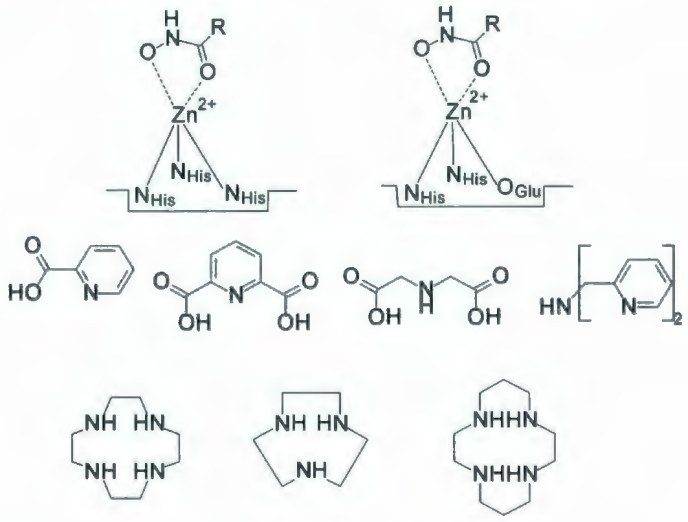


Figure 3.5. Some nitrogen ligands as LF inhibitors.

Two recent reports[16,17] showed that galloyl derivatives (Figure 3.6) which were extracted from green tea can be utilized as LF inhibitors. Wong[17] tested more than ten commercial compounds, for example, alizarin (**5**), purpurin (**6**), and purpurogallin (**7**). 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose (**2**) is one of four compounds which were identified as inhibitors against the anthrax lethal factor.

It was found that the presence of the gallate architecture is important for the inhibition of LF. In order to test other gallate-like derivatives, the commercially-available 5-hydroxydopamine hydrochloride (**3**) was reacted with fifty-nine

structurally-diverse aldehydes and seven dialdehydes, respectively, using the Pictet–Spengler reaction (Scheme 3.3).

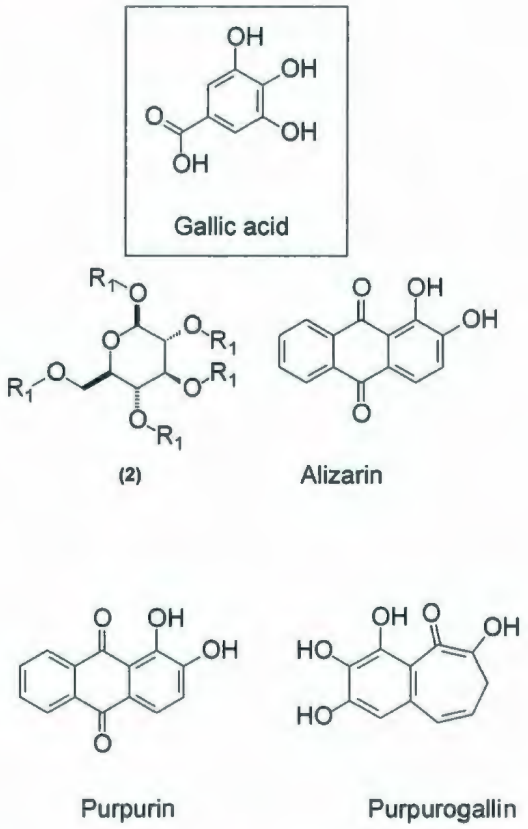
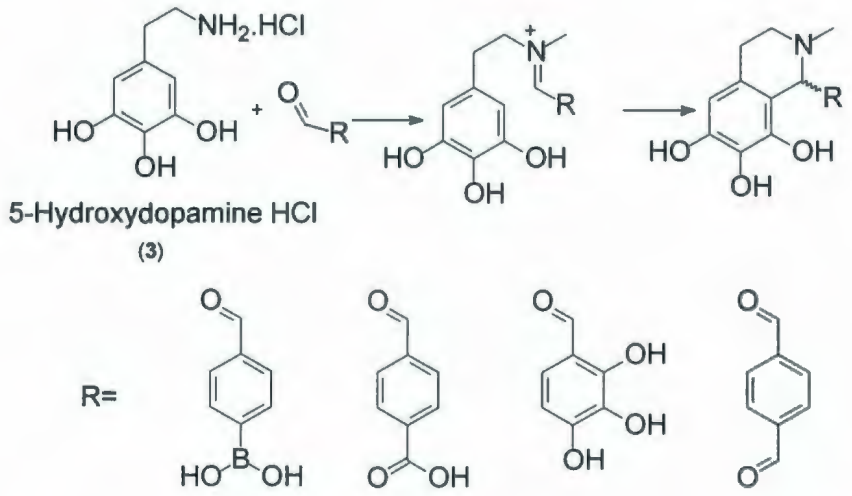


Figure 3.6. Examples of galloyl derivatives which are extracted from green tea.

Better lethal factor inhibition was found for compounds derived from dialdehyde moieties. Based upon these results, Wong *et al.*[17] prepared a group of three paired gallate-like tetrahydroisoquinoline polyphenols, compounds **4a-6b**, starting from 5-hydroxydopamine hydrochloride (Figure 3.7). All of these compounds were found to be "noncompetitive" inhibitors of anthrax LF. The report is scant on details of the characterization of these compounds, however the authors state that "chiral derivatization led to the identification of **4a** and **4b**".



Scheme 3.3. Using 5-hydroxydopamine HCl to prepare some LF inhibitors.

It should be noted that **4b**, for example, was stated to be "(+/-)". It was also represented however, in the paper as being the "*S,R*" isomer, and therefore it is clearly a *meso* structure as written. As reported therefore, **4b** could either be a racemic mixture of enantiomers which are respectively, *R,R* and *S,S,* and thus are "(+/-)"; or, that it is a *meso* compound. The paper is ambiguous as written. Similar observations can be made for the other compounds **5a**-**6b**.

Nevertheless, the data presented show that under physiological salt concentration conditions (150 mM) the most potent inhibitor of LF was **4a** having K_i = 4.3 ± 1.8 μM compared to a value of K_i = 51.8 ± 1.2 μM for the "racemic" mixture, **4b**. The authors did state, however that "the chiral resolution of each racemic mixture is one of our future objectives".

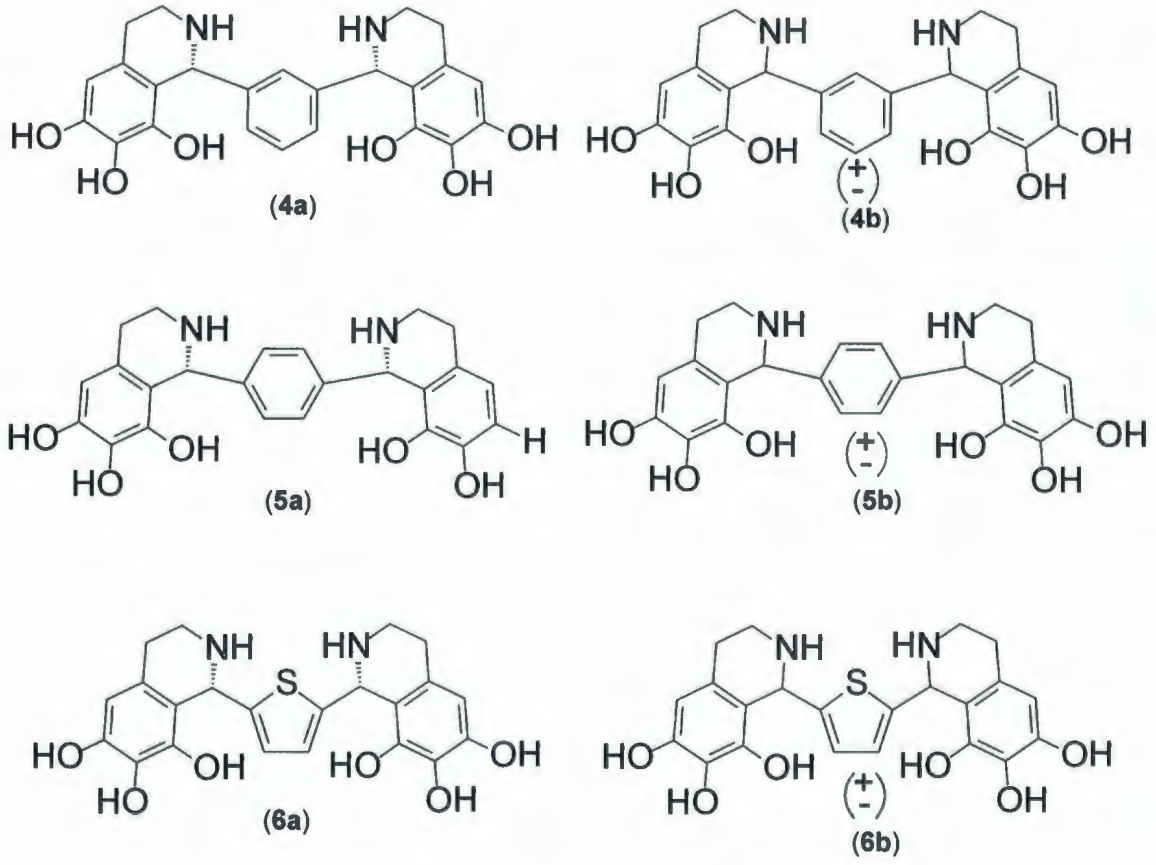
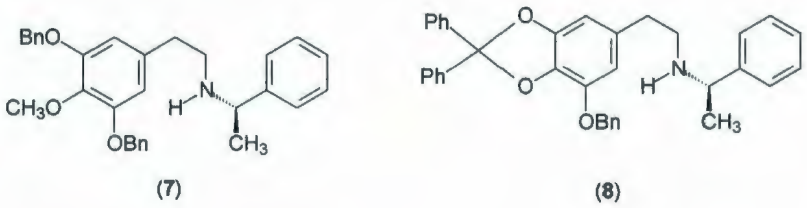


Figure 3.7. Structures of bis(tetrahydroisoquinoline) compounds 4a-6b.

They also concluded from their screening studies of these and other compounds, that "derivatives of tetrahydroisoquinolines, such as dihydroisoquinolines and isoquinolines, are also interesting targets for the identification of new potent LF inhibitors", and that "the actual potencies of the enantiomers are still unknown".[16, 17]

These studies[16,17] led us to consider the use of some of the intermediates obtained in the course of our on-going studies towards the enantioselective synthesis of (-)-cycleanine and of other BBIQs of interest, for the enantioselective

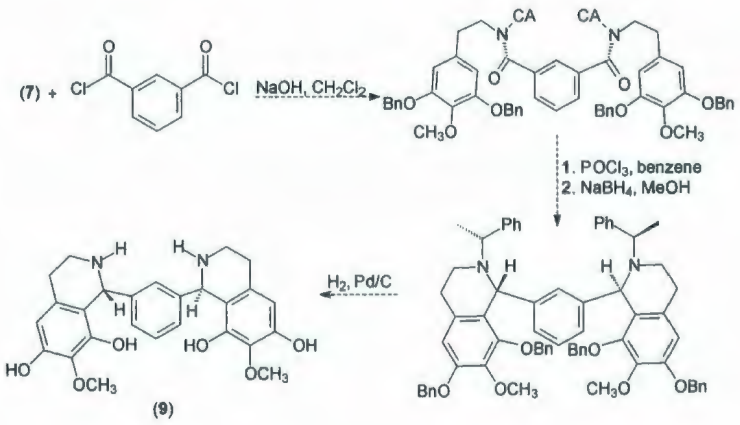
synthesis of some analogues of those which have been reported. In particular, *N*-[2-(3,5-dibenzyloxy-4-methoxyphenyl)-ethyl]-*N*-[1-phenylethylamine (**7**) and *N*-[(*R*)-methylbenzyl]-(5-benzyloxy-3,4-diphenylmethylenedioxy)phenylacetamine (**8**) were considered Figure 3.8.



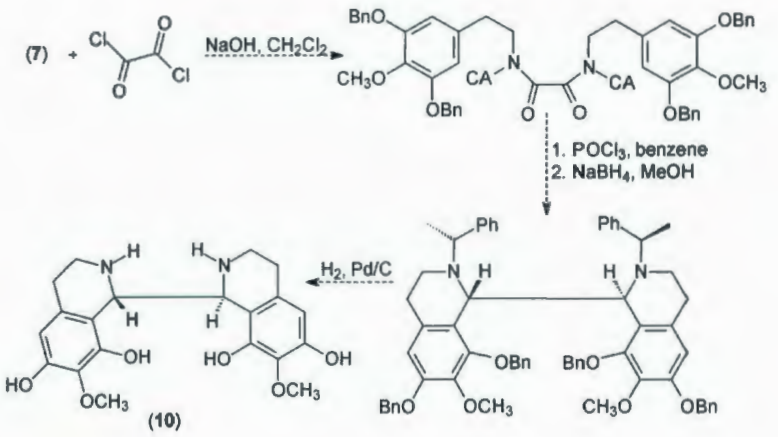
(7) (8)

Figure 3.8. The structure of 7 and 8.

Thus, **9**, the dismethoxy analogue of **5a** was targeted, as were compounds **10-12** via the Schotten-Baumann and subsequent Bischler-Napieralski cyclization methodologies employed in our BBIQ synthetic approach. The synthesis of **9** is outlined in Scheme 3.4 using 1,3-benzenedicarbonyl chloride (isophthaloyl chloride).

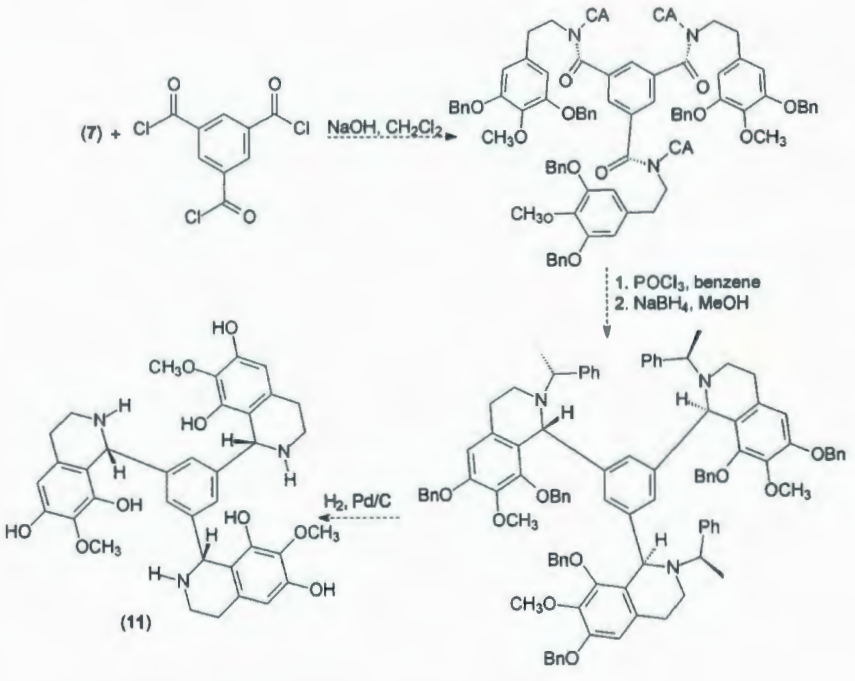


Scheme 3.4. Synthesis of compound **9** starting from **7.**



Scheme 3.5. Synthesis of compound **10** starting from **7**

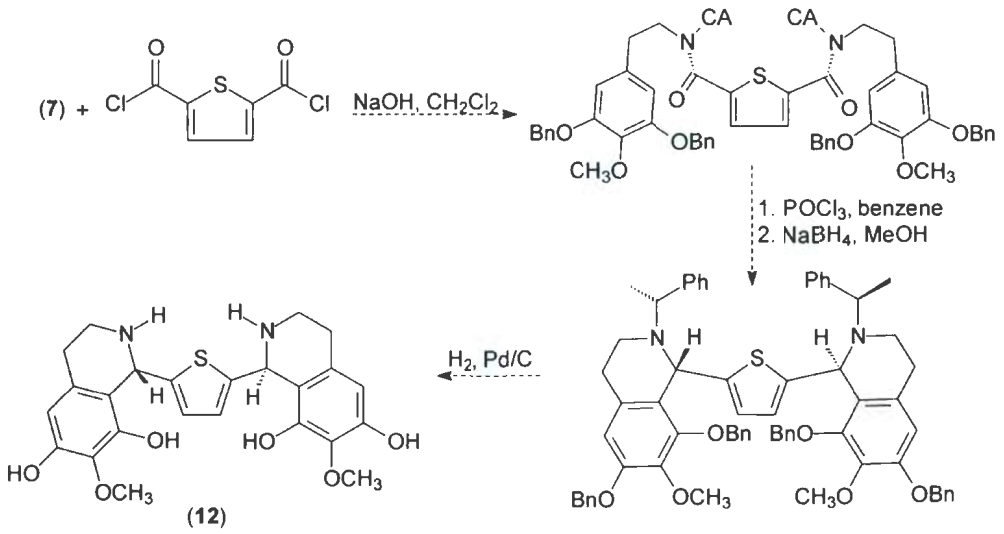
Compound **10** was envisioned to be synthesized using oxalylchloride in the key bis-coupling step (Scheme 3.5) while, **11** will be obtained by 1,3,5-Benzenetri-carbonylchloride (Scheme 3.6).



Scheme 3.6. Synthesis of compound **11** starting from **7**

The syntheses of compounds **9-11** containing methoxy group could help in determining whether they would be less reactive in the presence of O_2, a factor noted by Numa *et al* for their non-methoxy group-containing compounds **4a-6b**.

Finally, the enantioselective synthesis of the bismethoxythiophene analogue, **12**, was also envisioned (scheme 3.7).



Scheme 3.7. Synthesis of compound **10** starting from **7**

Chapter 4

4.1 A retrosynthetic analysis for the synthesis of tetrahydroisoquinolines 1 - 4.

Since the strategies which were applied to prepare 2,5-bis[(*R*)-6,8-dihydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline]-thiophene (**1**), 1,3-bis[(*R*)-6,8-dihydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline]-benzene (**2**), 1,3,5-tris[(*R*)-6,8-dihydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline]-benzene (**3**) and 1,1'-bi[(*R*)-6,8,6',8'-tetrahydroxy-7,7'-dimethoxy]-1,2,3,4,1',2',3',4'-octahydroisoquinoline (**4**) were similar, compound **3** can be chosen as an example to describe the retrosynthetic analysis for the synthesis of compounds **1** - **4** (Figure **4**.1).

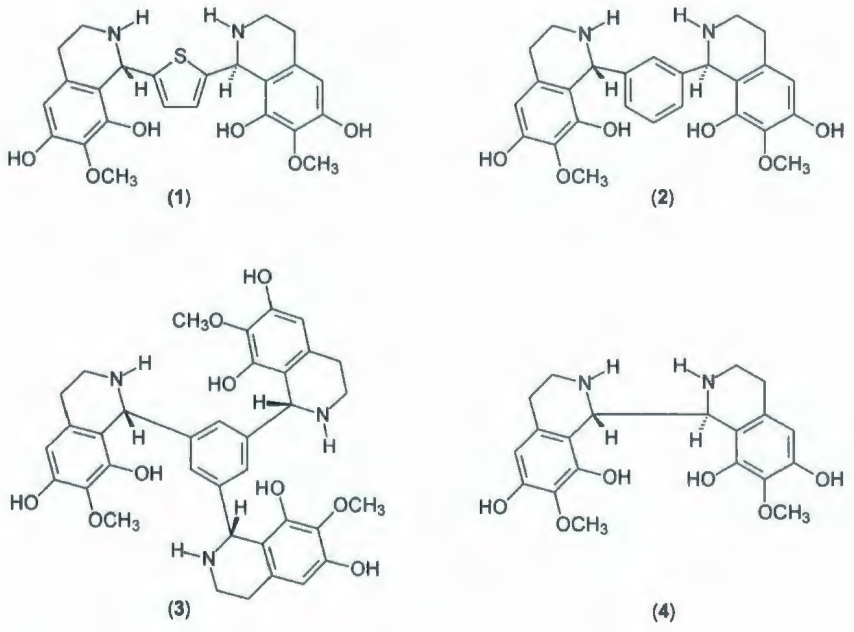
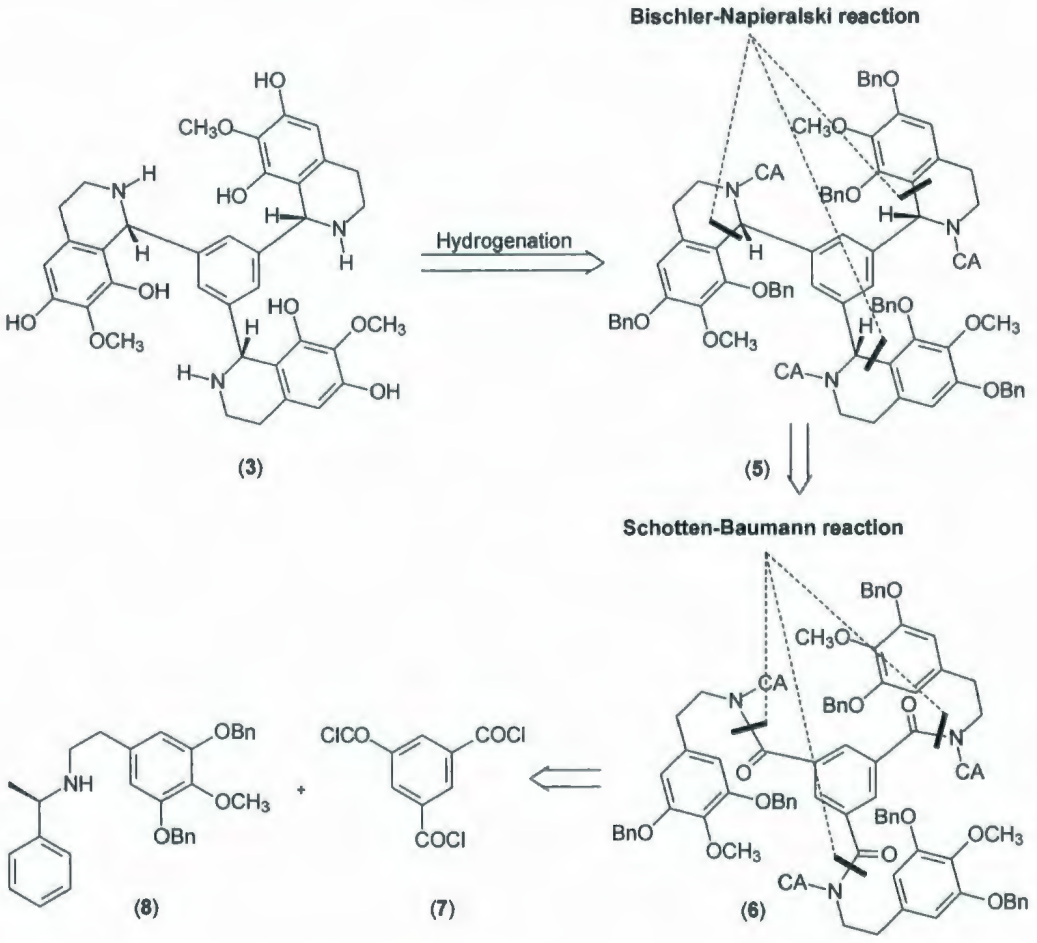


Figure 4.1. Structures of compounds **1** - **4**.

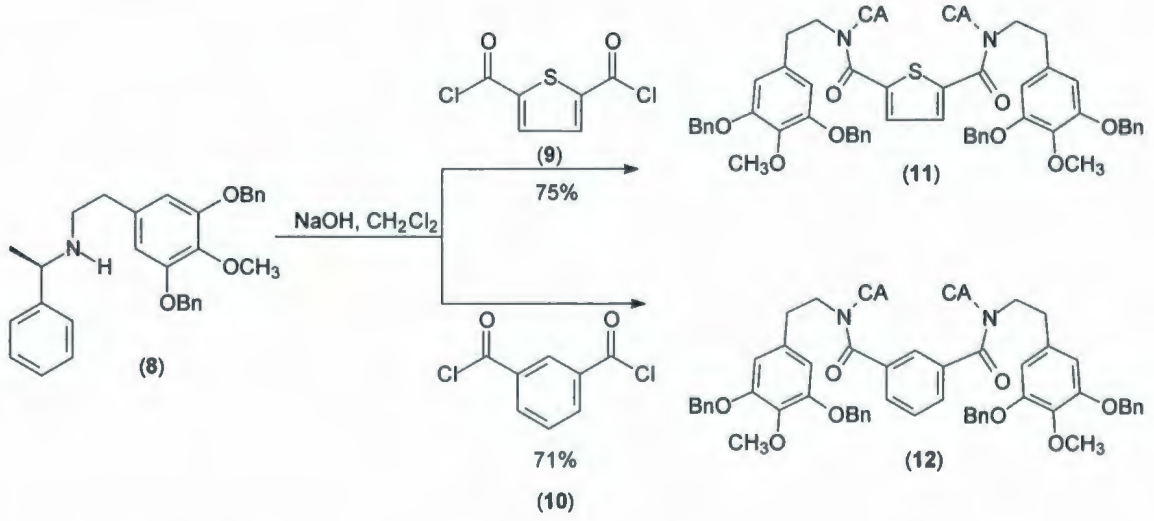
As shown in Scheme 4.1, compound **3** was formed by hydrogenation of 1,3,5-tris[(*R*)-6,8-dibenzyloxy-7-methoxy-2-((*R*)-1-phenylethyl)-1,2,3,4-tetrahydro isoquinoline]-benzene (**5**). Application of the BNC conditions on 1,3,5-tricarbonyltris[*N*-((*R*)-α-methylbenzyl)-*N*-((3,5-dibenzyloxy-4-methoxy)phenyl-ethyl]-benzene (**6**) led to the formation of (**5**) by triple cyclization. Compound **6** was prepared by reaction of 1,3,5-benzenetricarbonyl trichloride (**7**) with *N*-((*R*)-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (**8**).



Scheme 4.1. Retrosynthetic analysis of **3**.

4.2. Synthetic analysis for the synthesis of tetrahydroisoquinolines 1-4.

Scheme 4.2 shows the reaction of 1 mole equivalent of (**8**) with 0.5 mole equivalent of the commercially-available 2,5-thiophene-dicarbonyl dichloride (**9**) and 0.5 mole equivalent of the commercially-available isophthaloyl chloride (**10**).

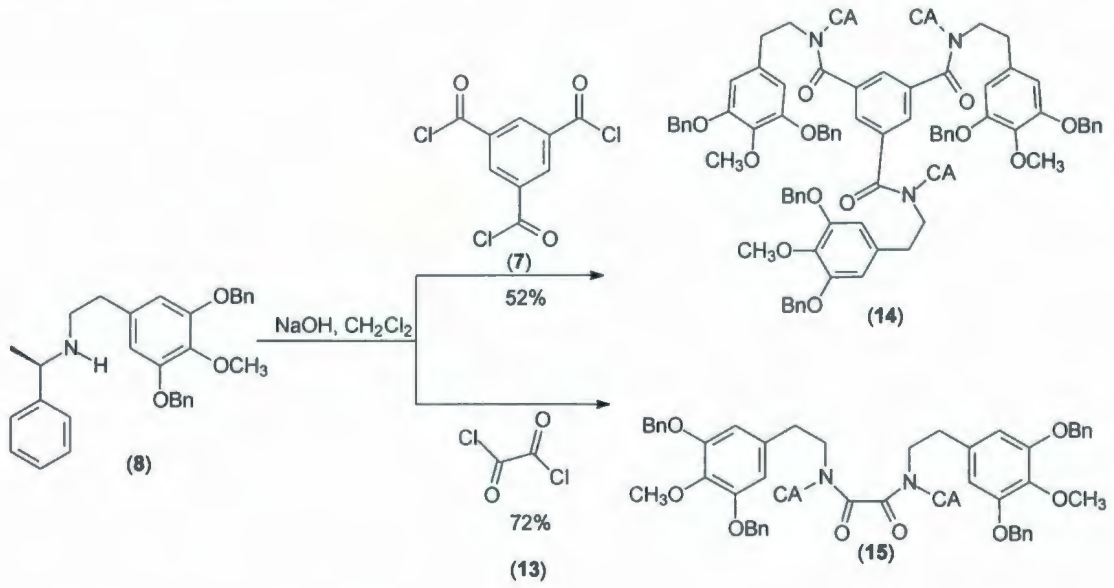


Scheme 4.2. Preparation of the chiral amides **11** and **12**.

Applying of Schotten-Baumann reaction conditions, the two chiral amides 2,5-dicarbonyl-bis[*N*-((*R*)-α-methylbenzyl)-*N*-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-thiophene (**11**) and 1,3-dicarbonyl-bis[*N*-((*R*)-α-methylbenzyl)-*N*-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-benzene (**12**) were produced by double amidation in 65% and 61% yields repectively.

The same conditions were applied using 1 mole equivalent of **8** with 0.33 mole equivalents of the commercially-available 1,3,5-benzene tricarbonyl

trichloride (**7**) and 0.5 mole equivalent of the commercially-available oxalyl chloride (**13**) respectively.



Scheme 4.3. Preparation of the chiral amides **14** and **15**.

As shown in Scheme 4.3, the chiral intermediate 1,3,5-tricarbonyl-tri[*N*-((*R*)-α-methylbenzyl)-*N*-((3,5-dibenzyloxy-4-methoxy)phenylethyl)-benzene (**14**) was prepared in 52% yield, while 1,2-bis[*N*-((*R*)-α-methylbenzyl)-*N*-((3,5-dibenzyloxy-4-methoxy)phenylethyl]-oxalamide (**15**) was prepared in 72% yield. As mentioned in Chapter 2, rotation about the amide bond of some tetrahydroisoquinolines leads to interconversion of two rotamers and as a result, the ^{1}H- and ^{13}C-NMR signals are duplicated. The ^{1}H- and ^{13}C-NMR spectra of **11**, **12**, **14** and **15** showed interconversions of more than two rotamers in each compound. As a result, most of the ^{1}H-NMR signals were broader than usual.

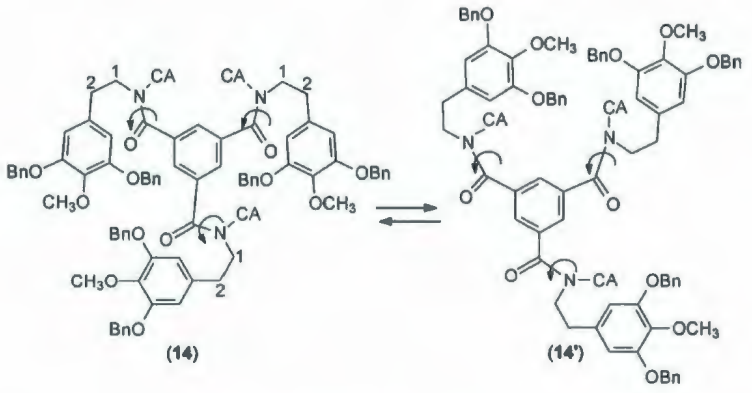


Figure 4.2. The rotation about three amide bonds in **14**.

As example, the rotation about three amide bonds in compound **14** presumably led to the formation of more than four rotamers. The ^{1}H-NMR spectrum of **14** in $CDCl_3$ (Figure 4.3) as an example, showed the CH_2-CH_2 signals as a broad signal at δ 3.39-2.52 ppm, while the methoxy groups appeared as a broad signal at δ 3.84-3.74 ppm. Furthermore, the breadth of the ^{1}H-NMR peaks made the calculation of the rotational conformer ratio extremely difficult.

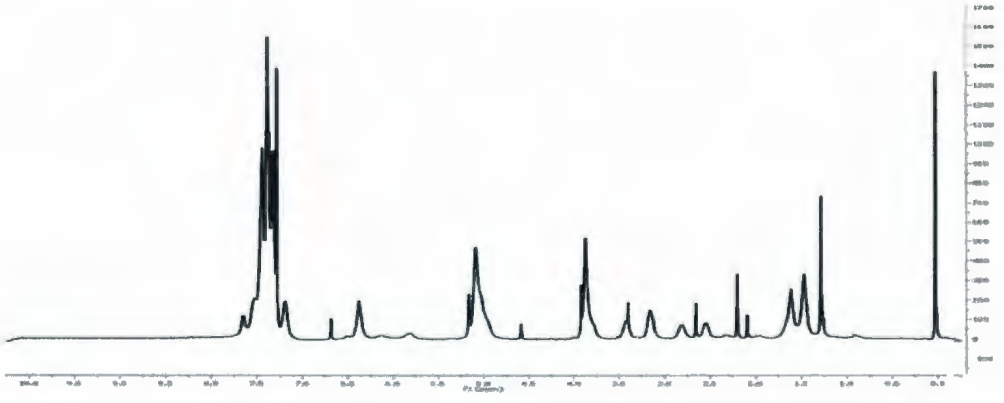
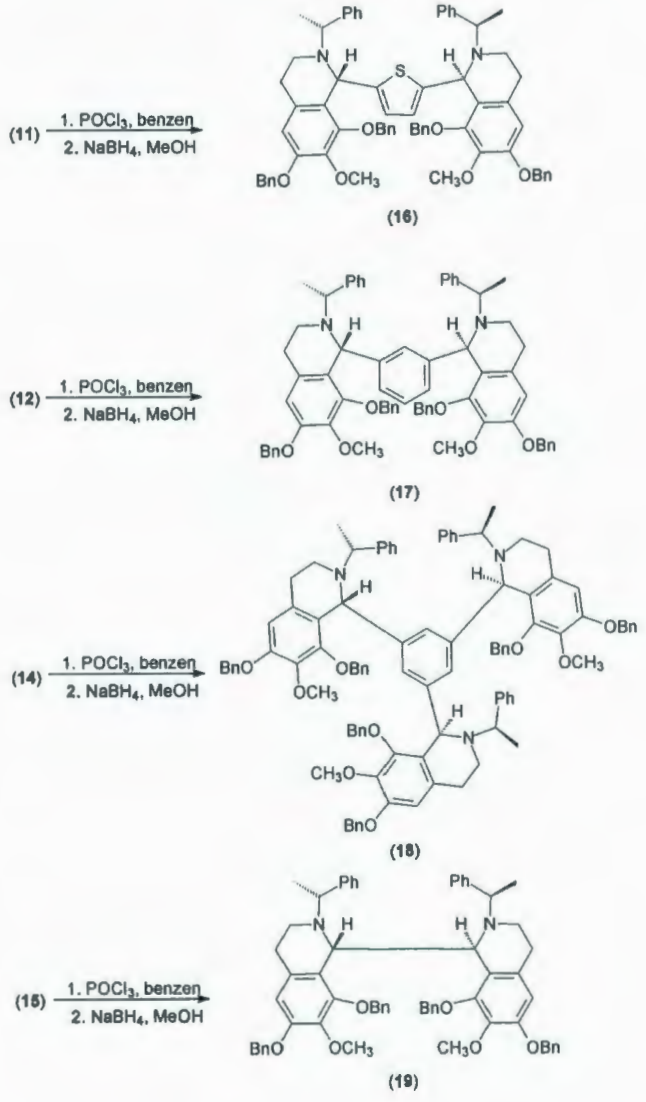


Figure 4.3. The ^{1}H-NMR spectrum of **14**.

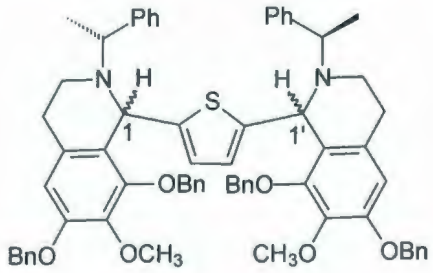
Compounds **11**, **12**, **14** and **15** were then each subjected to the BNC conditions, at reflux in benzene with $POCl_3$ for 12 h, followed by reduction with $NaBH_4$. The corresponding products **16** - **19**, respectively were obtained as mixtures (Schemes **4.4**).



Scheme 4.4. The structures of compounds **16** - **19**.

Since there were two new stereogenic centers generated in compounds **16**, **17** and **19**, and there were three stereogenic centers generated in compound **18**, the crude products of these compounds appeared as complex mixtures. For example, compound (**16**) could conceivably afford four different distereoisomers (Figure 4.4).

However, even though the corresponding masses of compounds **16** - **19** were detected by HPLC-MS, the desired diastereoisomers could not be easily separated. No further investigations were conducted on this project by this author.



(16)

(1,1') = (*R*, *S*), (1,1') = (*R*, *R*), (1,1') = (*S*, *S*) and (1,1') = (*S*, *R*)

Figure 4.4. The distereoisomers of compound **16.**

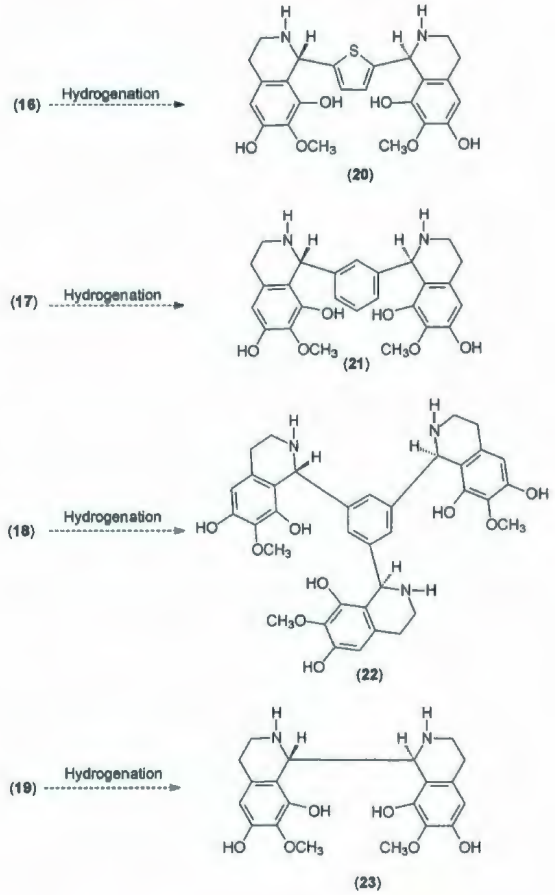
4.3. Summary.

The chiral amine (**8**) was successfully reacted with the acyl chlorides **7**, **9**, **10** and **13** to prepare the secondary amides **11**, **12**, **14** and **15**, respectively. These intermediates were subjected to the BNC conditions to produce after reduction the tetrahydroisoquinolines **16** - **19**, respectively. Due to the formation

of many products pure distereoisomers of those intermediates could not be isolated due to this author's time constraints.

4.4. Proposal for future work.

Reduction of compounds **16** - **19** may lead to the formation of the respective final target products **20** - **23** by debenzylation, and the removal of the chiral auxiliaries (Schemes 5.5). If obtained, the final products need then to be tested to see if they would be effective inhibitors for anthrax lethal factor.



Scheme 4.5. The structures of **20**, **21**, **22** and **23**.

References

1. Smith, H.; Keppie, J. *Nature.* **1954**, *173,* 869.

2. Puhar, A.; Montecucco, C. *Trends Microbiol.* **2007**, *15*, 477.

3. Collier, R. J.; Young, J. A. T. *Annu. Rev. Cell Dev. Biol.* **2003**, *19*, 45.

4. Kubler-Kielb, J.; Liu, T.-Y.; Mocca, C.; Majadly, F.; Robbins, J. B.; Schneerson, R. *Infect. Immun.* **2006**, *74*, 4744.

5. Candela, T.; Fouet, A. *Mol. Microbiol.* **2006**, *60*, 1091.

6. Gujraty, K.; Sadacharan, S.; Frost, M.; Poon, V.; Kane, S. R.; Mogridge, J. *Mol. Pharmaceutics.* **2005**, *2* , 367.

7. Forino, M.; Johnson, S.; Wong, T. Y.; Rozanov, D. V.; Savinov, A. Y.; Li, W.; Fattorusso, R.; Becattini, B.; Orry A. J.; Jung, D.; Abagyan, R. A.; Smith, J. W.; Alibek, K.; Liddington, R. C.; Strongin, A. Y.; Pellecchia, M. *Proc. Natl. Acad. Sci. U.S.A.* **2005,** *102*, 499.

8. O'Brien, J. *Infect. Immun.* **1985,** *47*, 306.

9. Duesbery, N. S. *Science.* **1998**, *280*, 734.

10. Nicholson, W. L.; Munakata, N.; Horneck, G.; Melosh, H. J.; Setlow, P. *Microbiol. Mol. Biol. Rev.* **2000,** *64,* 548.

11. Daubenspeck, J. M.; Zeng, H.; Chen, P.; Dong, S.; Steichen, C. T.; Krishna, N. R.; Pritchard, D. G.; Turnbough, C. L., Jr *J. Biol. Chem.* **2004,** *279,* 30945.

12. Werz, D. B.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2005**, *44*, 6315 – 6318.

13. Guo, H.; O'Doherty, A. G. *J. Org. Chem.* **2008**, *73*, 5211.

14. (a) Adamo, R.; Saksena, R.; Kovac., P. *Carbohydr. Res.* **2005**, *340*, 2579.
(b) Saksena, R.; Adamo, R.; Kovac, P. *Bioorg. Med. Chem. Lett.* **2006**,

16, 615. (c) Adamo, R.; Saksena, R.; Kovac, P. *Helv. Chim. Acta* **2006**, *89*, 1075. (d) Mehta, A. S.; Saile, E.; Zhong, W.; Buskas, T.; Carlson, R.; Kannenberg, E.; Reed, Y.; Quinn, C. P.; Boons, G.-J. *Chem. Eur. J.* **2006**, *12*, 9136. (e) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 6513. (f) Werz, D. B.; Adibekian, A.; Seeberger, P. H. *Eur. J. Org. Chem.* **2007**, 1976.

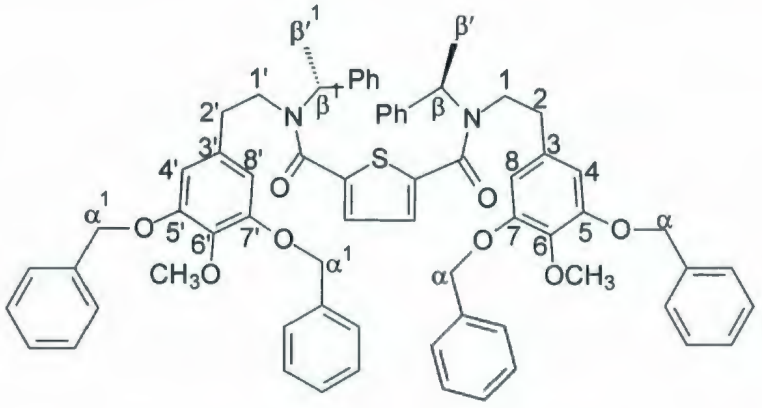
15. Jacobsen, F. E.; Lewis, J. A.; Cohen, S. M. *J. Am. Chem. Soc.* **2006**, *128*, 3156.

16. Dell'Aica, I .; Don, M.; Tonello, F.; Piris, A.; Mock, M.; Montecucco, C.; Garbisa, S. *EMBO Rep.* **2004,** *5,* 418.

17. Numa, M. M. D.; Lee, L. V.; Hsu, C.; Bower, K. E.; Wong, C. *Chem. Bio. Chem.* **2005,** *6,*1002.

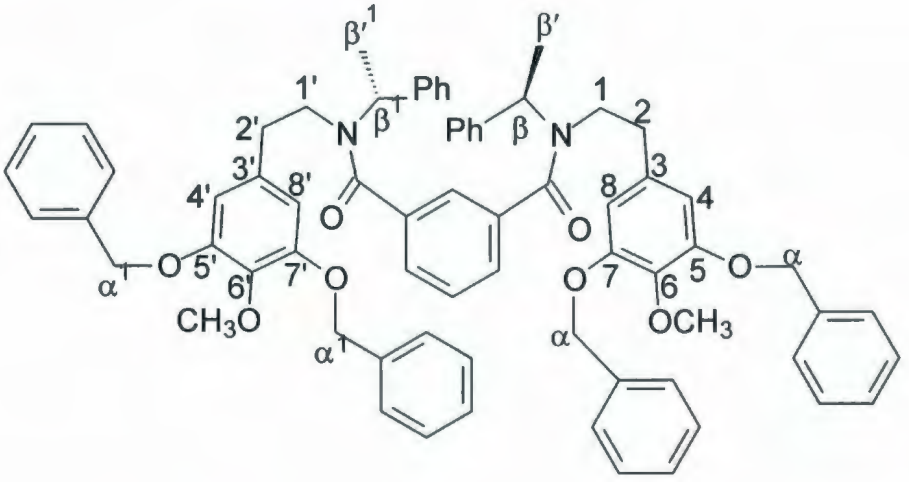
Experimental

2,5-Dicarbonyl bis[*N*-((*R*)-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy) phenylethyl) thiophene (11)



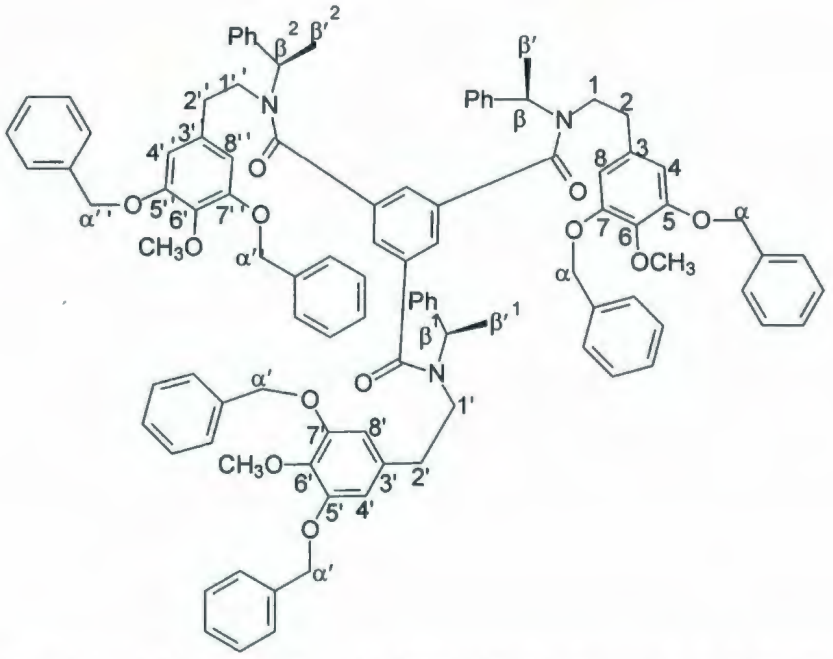
To a stirred mixture of *N*-((*R*)-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (**8**) (3.1 g, 6.4 mmol) in CH_2Cl_2:aqueous 5% NaOH (1:1.5, 8.5 ml) at 0 °C was added dropwise a solution of 2,5-thiophene dicrabonyl dichloride (**9**) (694 mg 3.32 mmol) in CH_2Cl_2. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (30 ml x 3), washed with water (20 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by PLC (30% EtOAc:hexane) to afford the amide **11** as a green oil (5.4 g, 75%): ^{1}H NMR: δ 7.45-7.23 (m, 32H, Ar-H), 6.30-6.26 (br, 4H, H-2, 2', 6, 6'), 5.58-5.55 (br, 2H, H-β, β^1), 5.08-5.03 (br, 8H, H-α, α^1), 3.86-3.82 (s, 6H, OCH_3), 3.40-2.43 (4br, 8H, CH_2CH_2, $CH'_2CH'_2$), 1.59-1.51 (m, 6H, H-β', β'^1); ^{13}C NMR: 163.98, 152.44, 140.31, 139.74, 138.10, 137.19, 128.69, 128.50, 128.45, 127.87, 127.82, 127.64, 127.25, 127.23, 108.49, 106.49, 71.06, 65.24, 60.88, 46.19, 29.67, 29.22, 17.60, 14.02; APCI-MS(*m/z*): 1072.0 (M^++1, 100).

1,3-Dicarbonybis[*N*-((*R*)-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy)phenyl ethyl) benzene (12)



To a stirred mixture of *N*-((*R*)-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (**8**) (3.0 g, 6.4 mmol) in CH_2Cl_2:aqueous 5% NaOH (1:1.5, 8.5 ml) at 0 °C was added dropwise a solution of isophthaloyl chloride (**10**) (652 mg 3.32 mmol) in CH_2Cl_2. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (30 ml x 3), washed with water (20 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by PLC (30% EtOAc:hexane) to afford the amide **12** as a yellow oil (4.8 g, 71%): ^{1}H NMR: δ 7.85-7.16 (m, 34H, Ar-H), 6.29-6.25 (br, 4H, H-4, 4', 8, 8'), 5.80-5.77 (br, 2H, H-β, β^1), 5.09-5.04 (br, 8H, H-α, α^1), 4.03-3.74 (br, 6H, OCH_3), 3.39-2.20 (4br, 8H, CH_2CH_2, $CH'_2CH'_2$), 1.60-1.25 (2br, 6H, H-β', β'^1); ^{13}C NMR: 172.11, 152.60, 138.30, 137.37, 128.75, 127.92, 127.41, 127.13, 124.64, 108.62, 71.19, 60.80, 56.99, 53.74, 44.77, 34.89, 31.40, 29.49, 17.69; APCI-MS(*m/z*): 1066.2 (M^++1, 100).

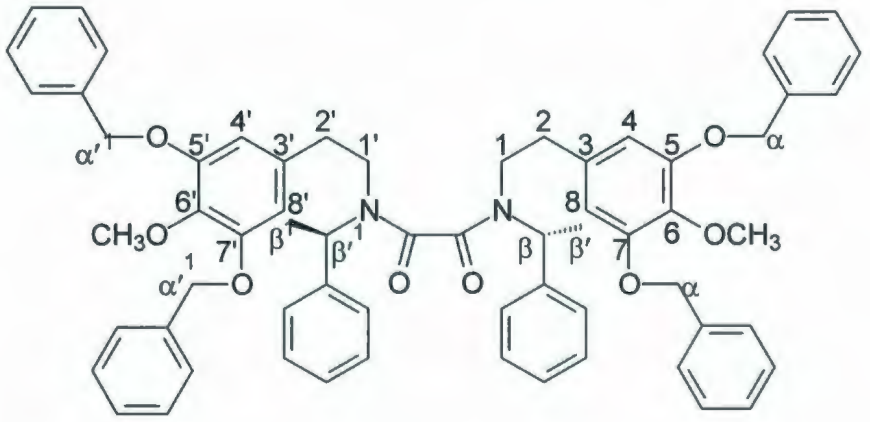
1,3,5-tricarbony tri[*N-((R)*-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-methoxy) (phenylethyl) benzene (14).



To a stirred mixture of *N-((R)*-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (**8**) (3.0 g, 6.4 mmol) in CH_2Cl_2:aqueous 5% NaOH (1:1.5, 8.5 ml) at 0 °C was added dropwise a solution of 1,3,5-benzene tricarbony trichloride (**7**) (560 mg 2.12 mmol) in CH_2Cl_2. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (30 ml x 3), washed with water (20 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by PLC (30% EtOAc:hexane) to afford the amide **14** as a yellow oil (5.2 g, 52%): ^{1}H NMR: δ 7.65-7.19 (m, 48H, Ar-H), 6.40-6.36 (br, 6H, H-4, 4', 8, 8', 4", 8"), 6.13-5.82 (2br, 3H, H-β, β^1, β^2), 5.17-5.04 (brs, 12H, H-α, α^1, α^2), 4.01-3.88 (br, 9H, OCH_3), 3.46-2.55 (4br, 12H, CH_2CH_2, $CH'_2CH'_2$, $CH''_2CH''_2$), 1.60-1.47 (2br s, 9H, H-β', β'^1, β'^2); ^{13}C NMR: 172.11, 152.60, 138.30, 137.37, 128.75, 127.92, 127.41, 127.13,

124.64, 108.62, 71.19, 60.80, 56.99, 53.74, 44.77, 34.89, 31.40, 29.49, 17.69; APCI-MS(*m/z*): 1559.4 (M^++1, 100).

1,2-bis[*N*-((*R*)-α-Methylbenzyl)-N-((3,5-dibenzyloxy-4-ethoxy)phenylethyl] oxalamide (15).



To a stirred mixture of *N*-((*R*)-α-Methylbenzyl)-2-(3,5-dibenzyloxy-4-methoxy)phenylethanamine (**8**) (3.0 g, 6.4 mmol) in CH_2Cl_2:aqueous 5% NaOH (1:1.5, 8.5 ml) at 0 °C was added dropwise a solution of oxalyl chloride (**13**) (0.28 ml 3.2 mmol) in CH_2Cl_2. After stirring at room temperature for 1 h, the reaction mixture was extracted with chloroform (30 ml x 3), washed with water (20 ml x 3), dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated. The residue was purified by PLC (30% EtOAc:hexane) to afford the amide **15** as a yellow oil (4.5 g, 72%): ^{1}H NMR: δ 7.60-7.26 (m, 30H, Ar-H), 6.25-6.21 (4s, 4H, H-4, 4', 8, 8'), 5.94 and 5.16 (2 m, 2H, H-β, β^1), 4.95-4.91 (4s, 8H, H-α, α^1), 3.83-3.74 (br, 6H, OCH_3), 3.30-2.28 (4br, 8H, CH_2CH_2, $CH'_2CH'_2$), 1.72-1.25 (5 d, 6H, H-β', β'^{1}); ^{13}C NMR: 167.11, 152.60, 152.33,

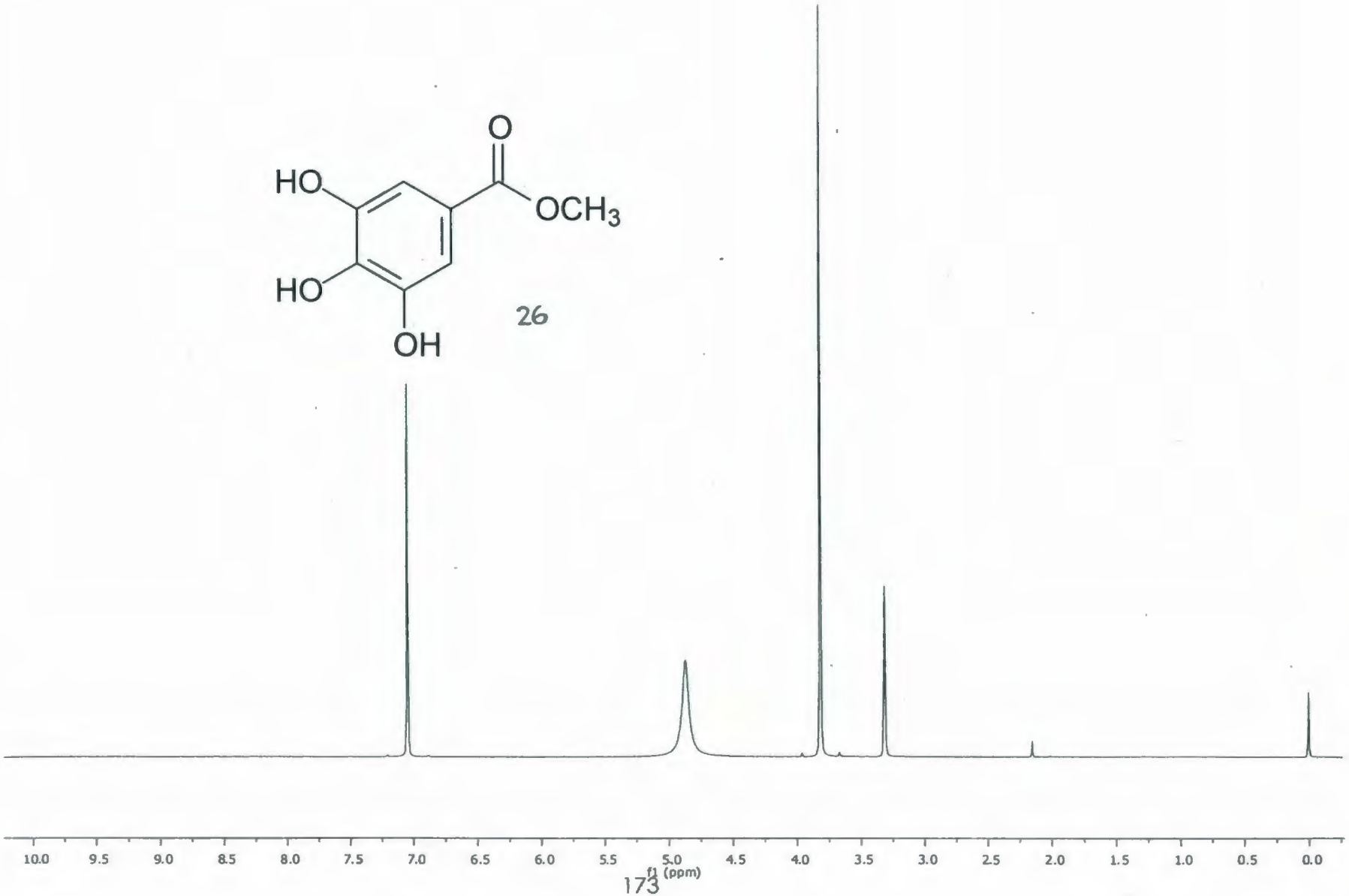
138.30, 137.37, 128.75, 127.92, 127.41, 127.13, 124.64, 108.62, 71.19, 60.80, 56.99, 53.74, 44.77, 34.89, 31.40, 29.49, 17.69; APCI-MS(*m/z*): 1066.2 (M^++1, 100).

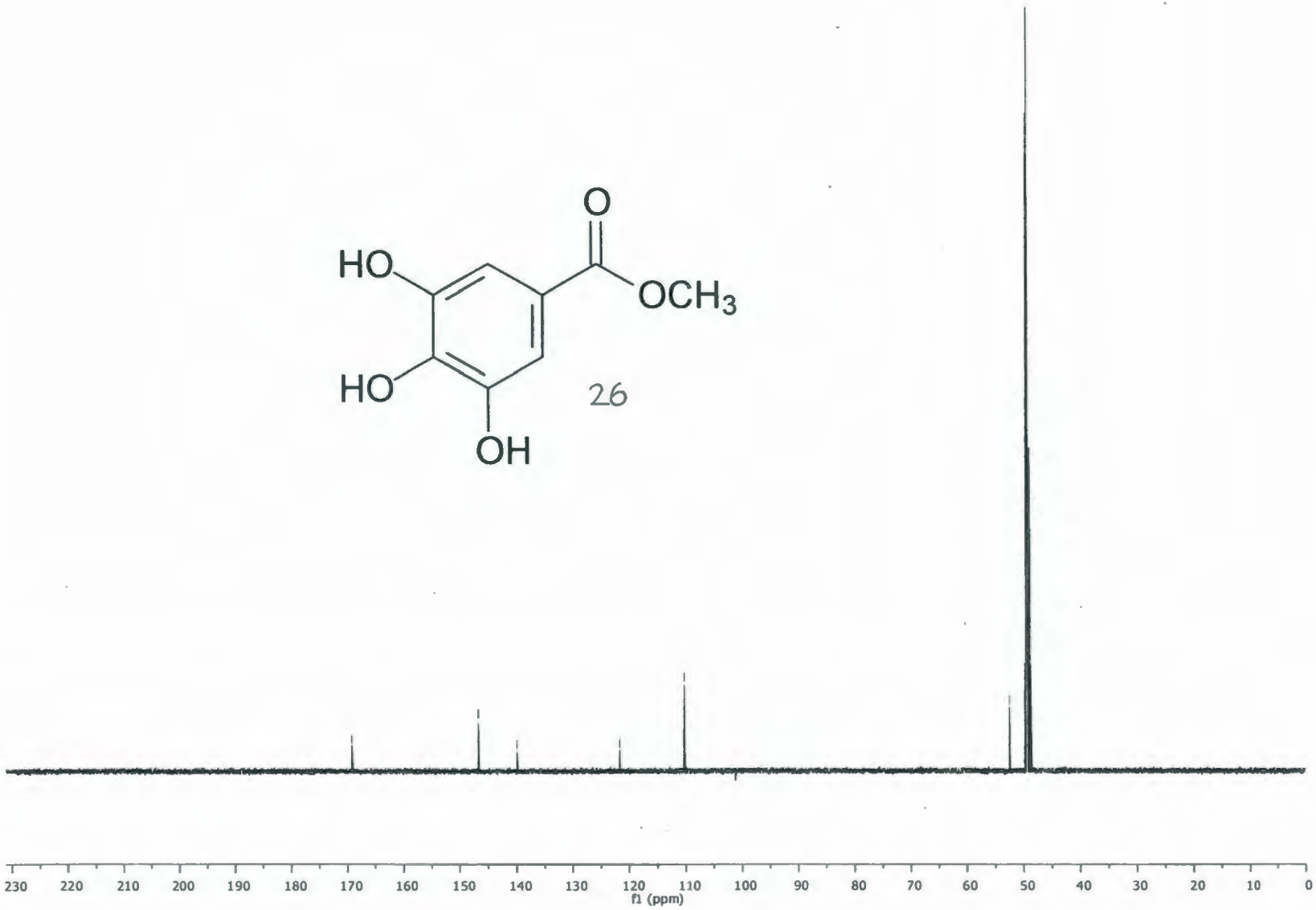
Appendix A:

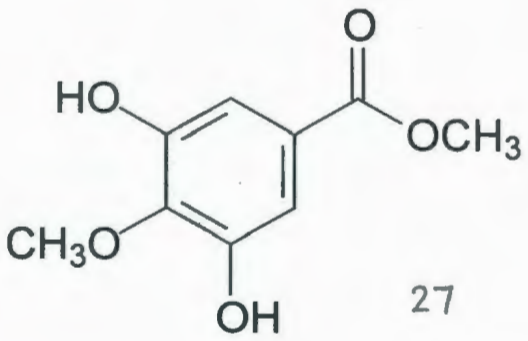
Selected ^{1}H NMR and ^{13}C NMR spectra of compounds of Chapter 2

Index of NMR spectra : page numbers and compound numbers

Compound*	Page # ^{1}H-NMR	Page # ^{13}C-NMR	Compound*	Page # ^{1}H-NMR	Page # ^{13}C-NMR
12	206	207	**55**	259	
13	216	217	**56**	257	258
18	189	190	**59**	266	
25	214	215	**64**	260	261
26	173	174	**14b**	242	243
27	175	176	**14c**	238	239
28	177	178	**15b**	244	245
29	179	180	**15d**	248	249
30	181	182	**16b**	246	247
31	183	184	**16d**	250	
32	185	186	**19a**	253	254
33	187	188	**19b**	251	252
34	191	192	**19c**	255	256
35	193	194	**22a**	226	227
36	195	196	**22b**	228	
37	197	198	**22c**	229	
38	199	200	**23a**	220	221
39	201	202	**23b**	222	223
40	203	204	**23c**	224	225
41	205		**58a**	262	
42	208	209	**58b**	263	264
43	210	211	**58c**	265	
44	212	213	**65a**	267	268
45	218	219	**65b**	269	270
47	230	231	**66c**	271	272
48	232	233	**68a**	273	274
49	234	235	**68b**	275	
50	236	237	**68c**	276	
53	240	241			

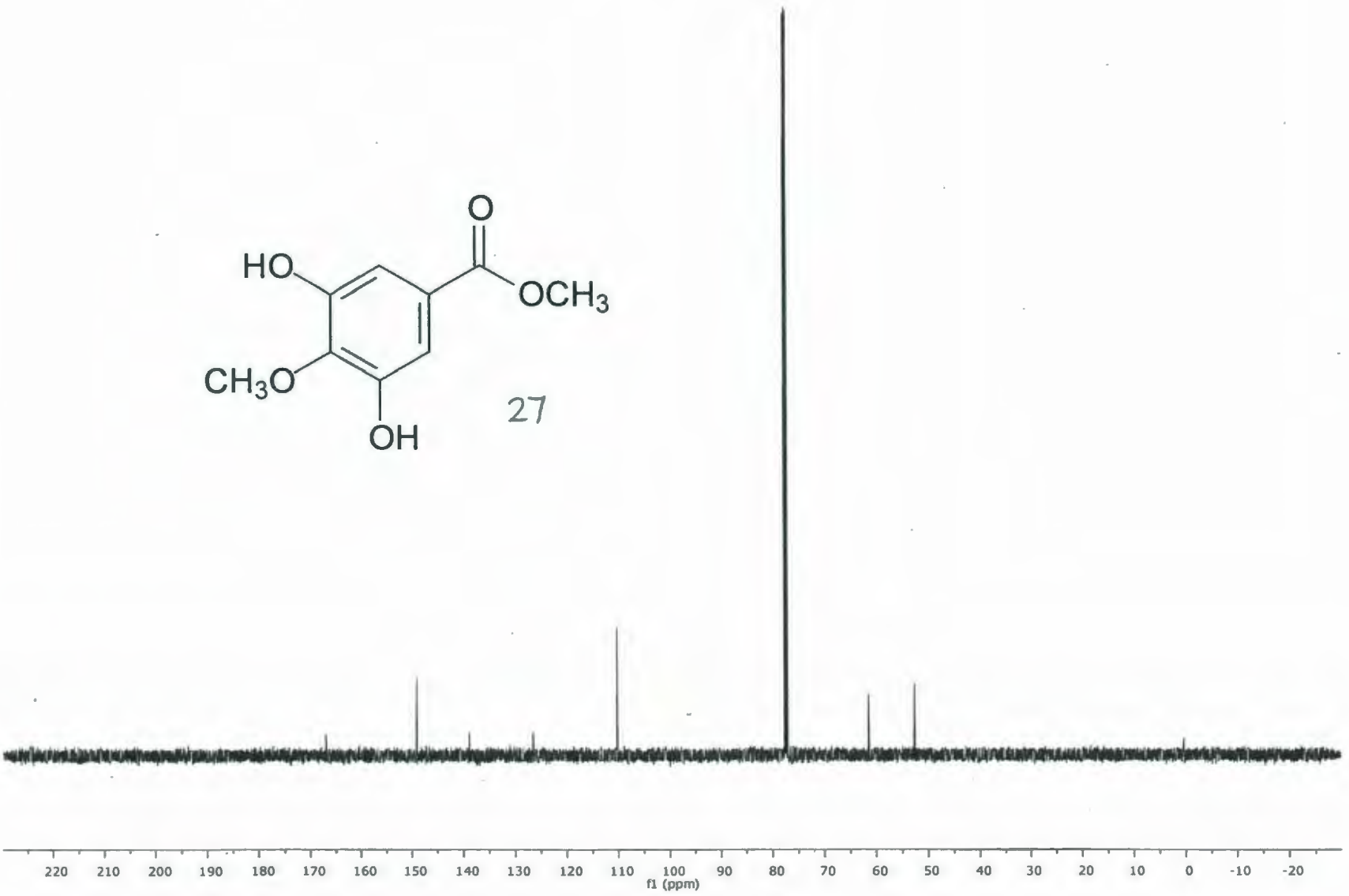

HO
HO
OH
O
OCH3
26
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

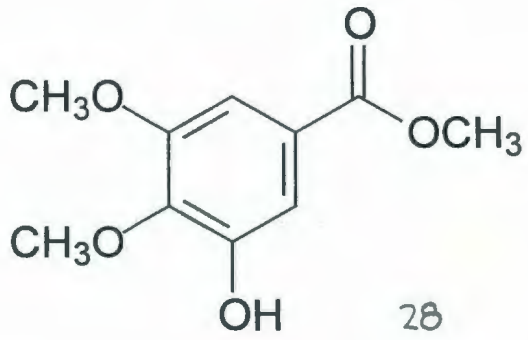

O
HO
OCH3
HO
OH
26
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
OCH3
CH3O
OH

27

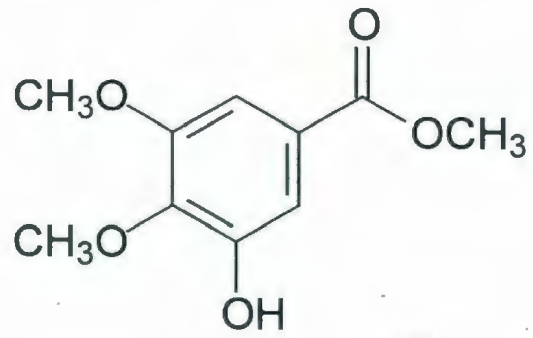
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
HO
OCH3
CH3O
OH
27
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


O
CH3O
OCH3
CH3O
OH

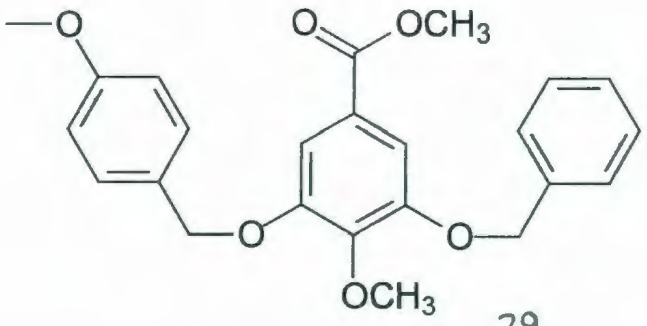
28

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

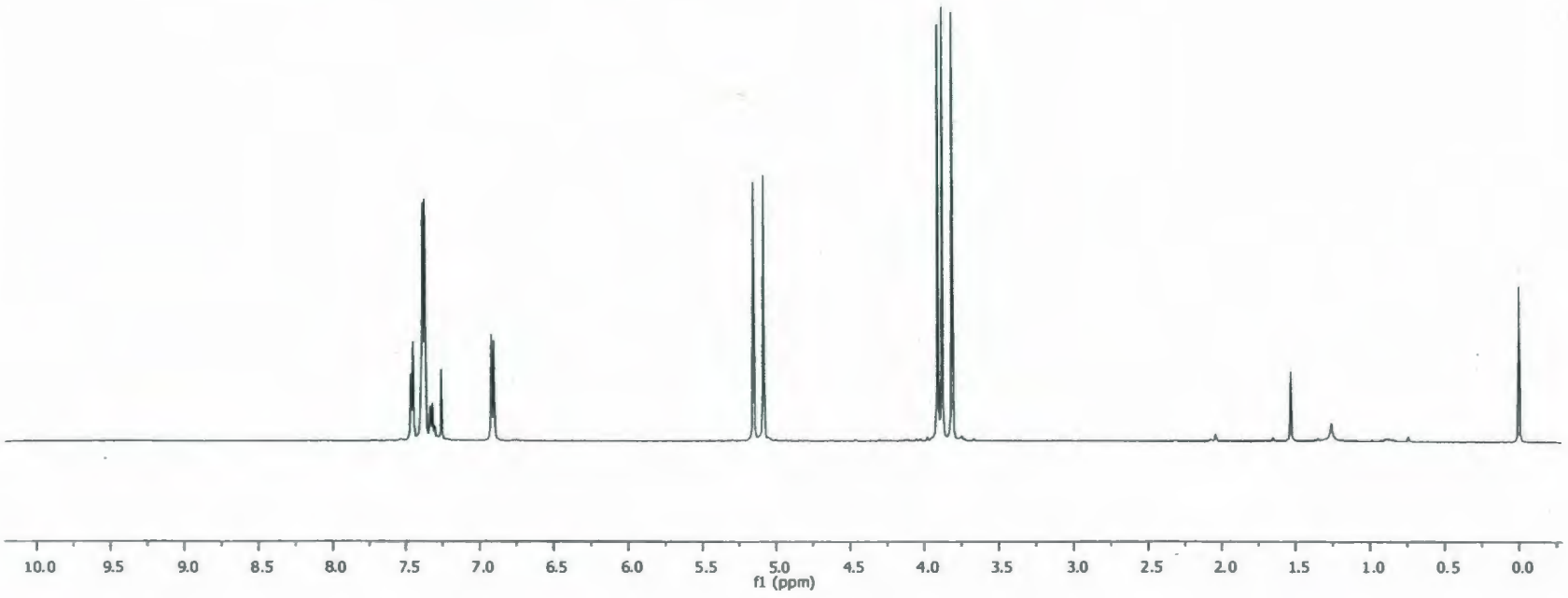

O
CH3O
OCH3
CH3O
OH

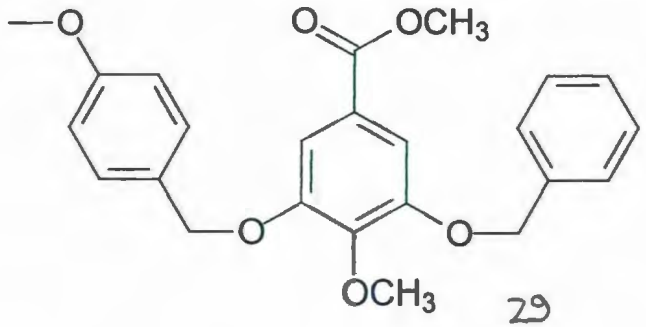
28

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

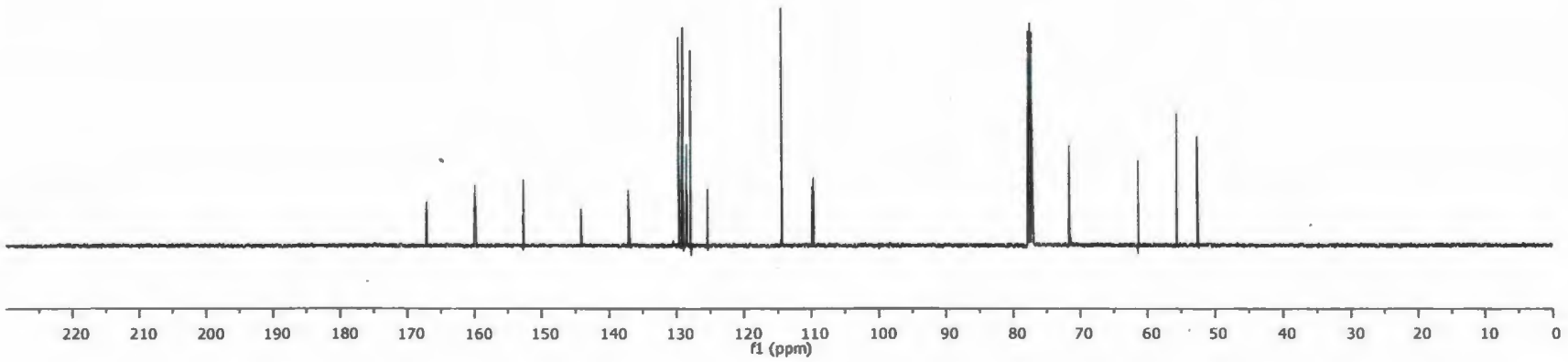

O
O
OCH3
O
O
OCH3

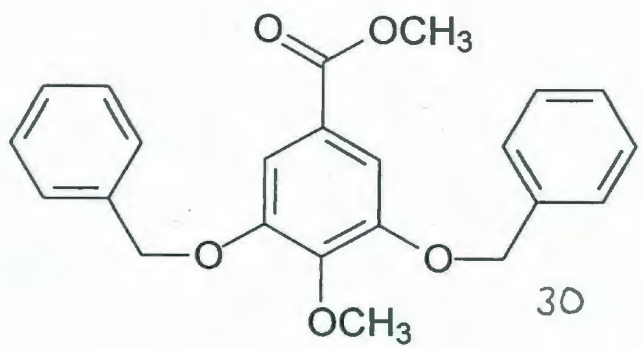
29


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
OCH3
O
O
OCH3

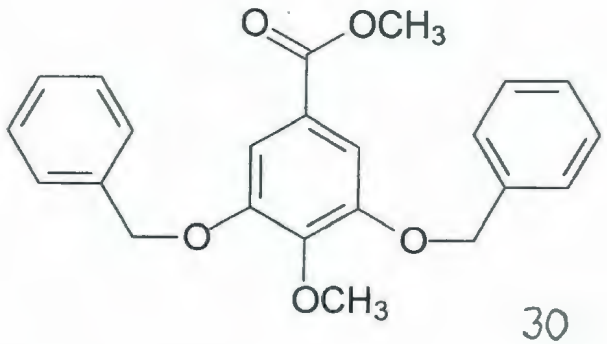
29


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
OCH3
O
O
OCH3

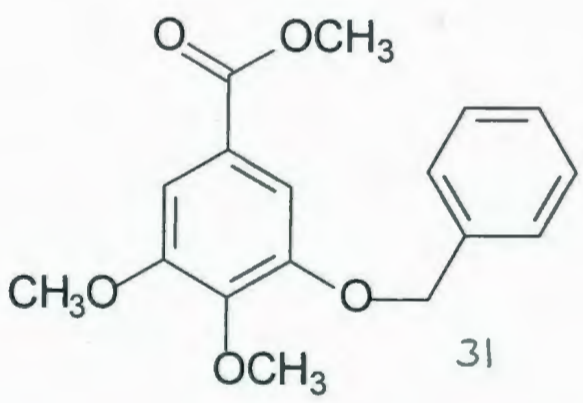
30

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
OCH3
O
O
OCH3

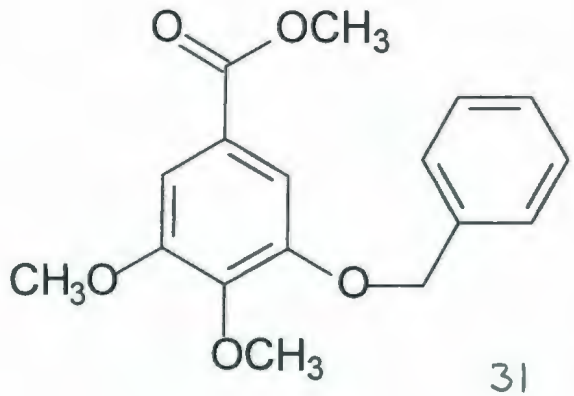
30

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

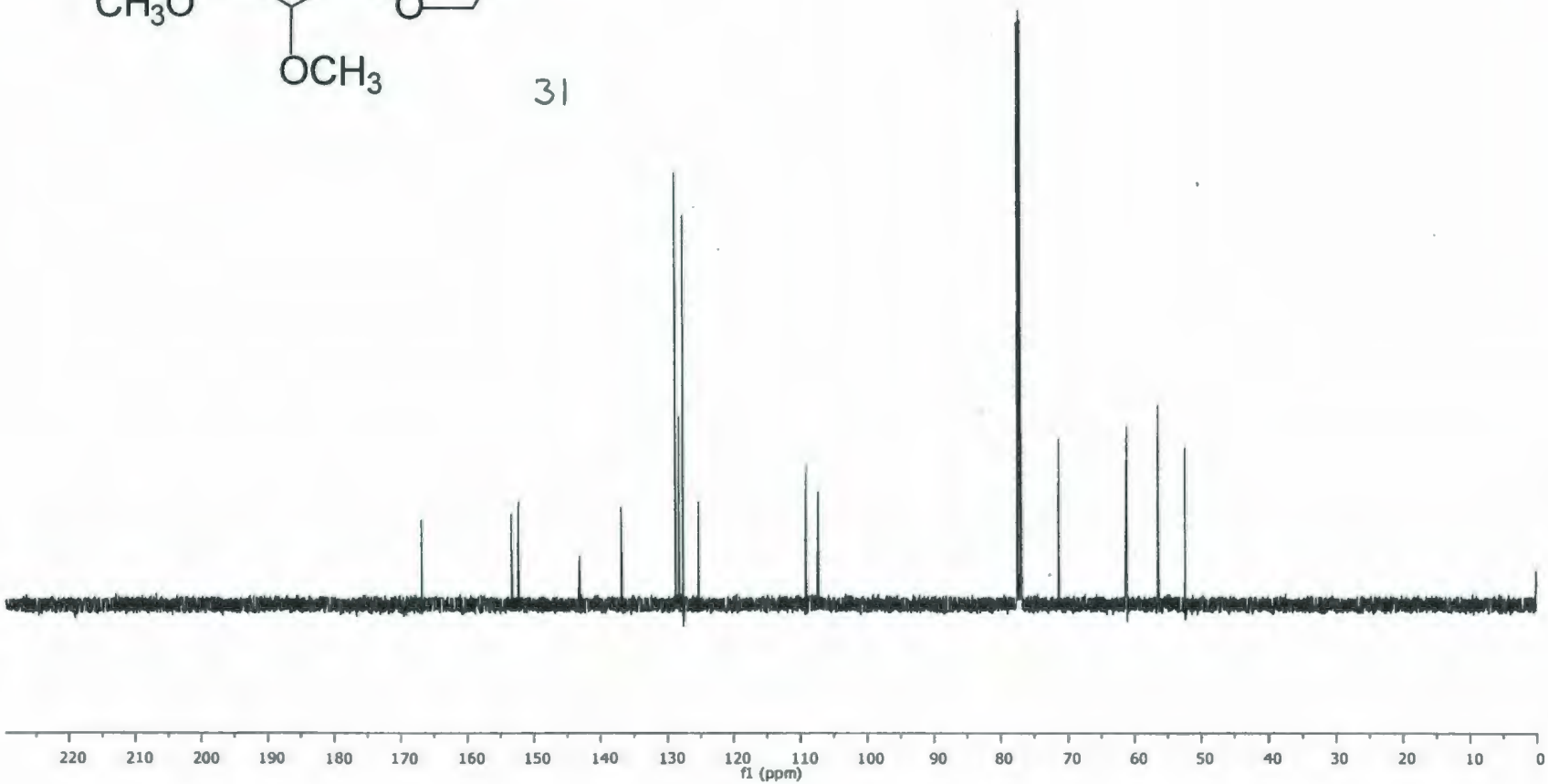

O
OCH3
CH3O
O
OCH3

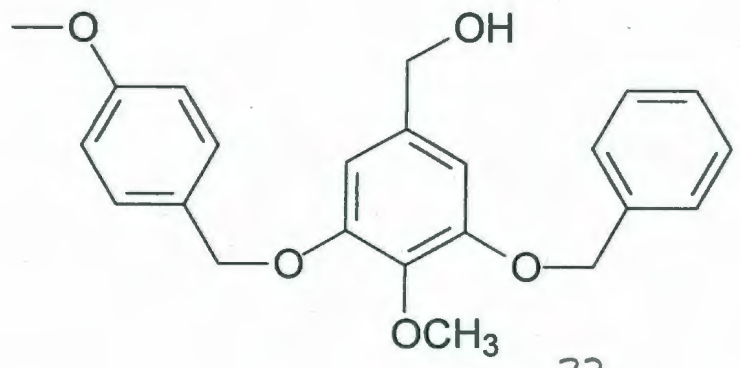
31

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

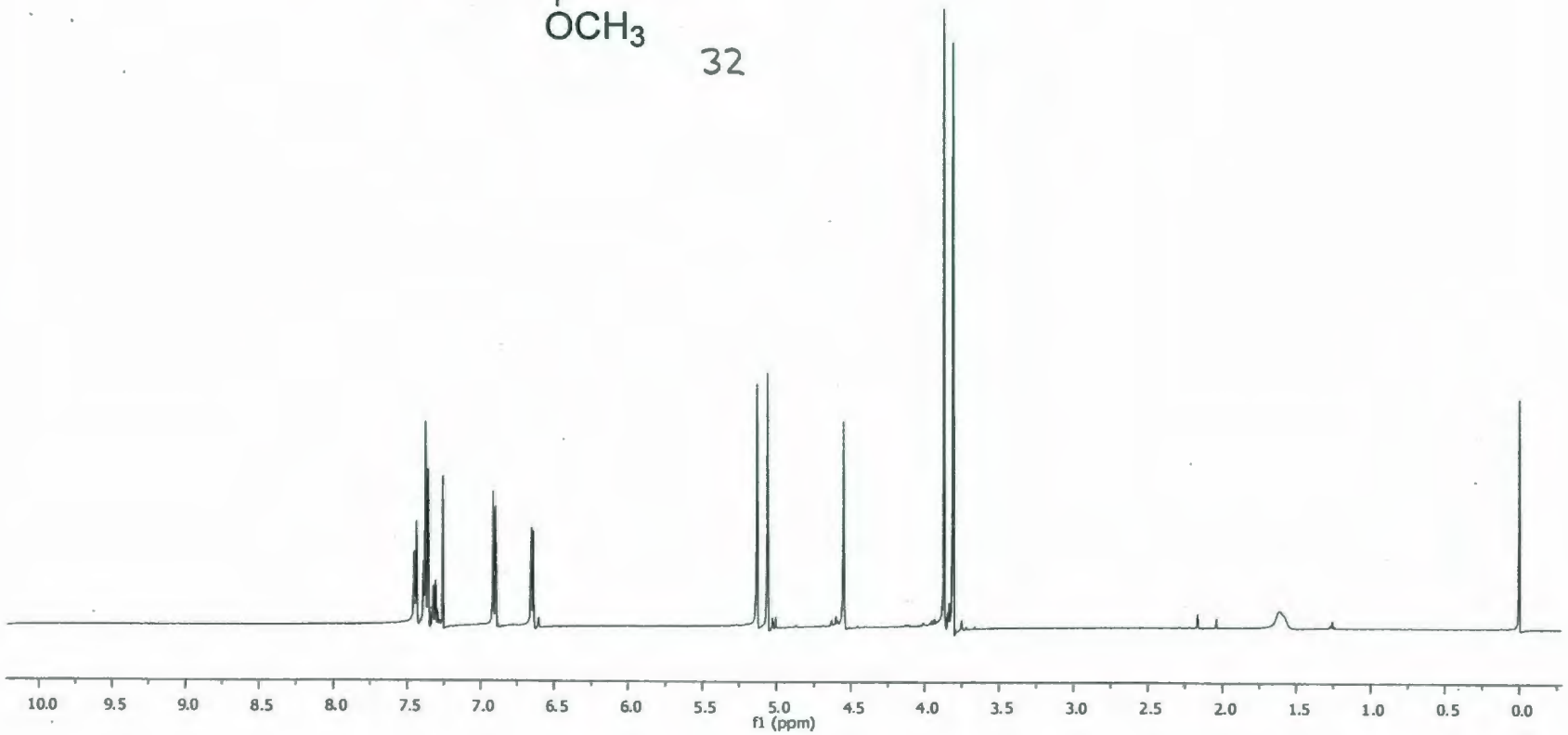

O
OCH3
CH3O
O
OCH3

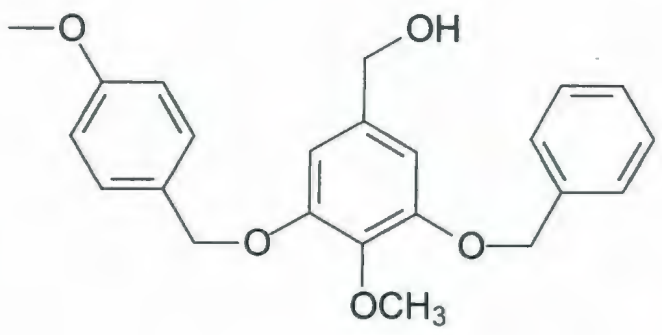
31


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


—O
OH
O
O
OCH3

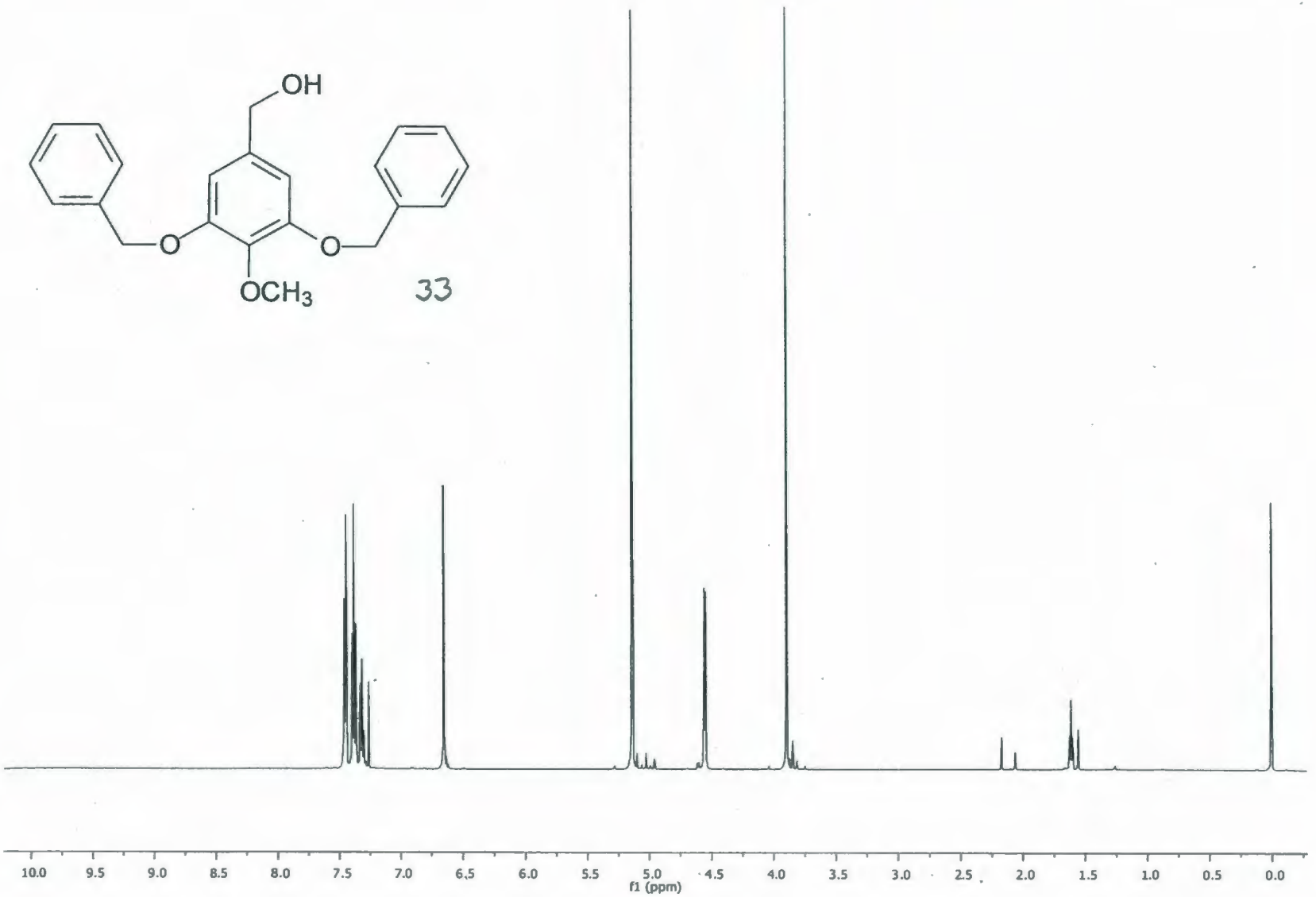
32

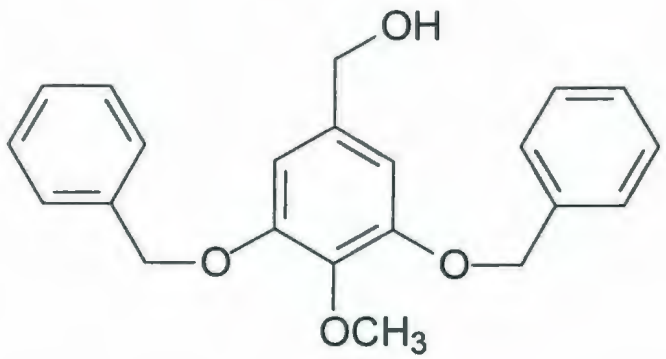

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


—O
OH
O
O
OCH3

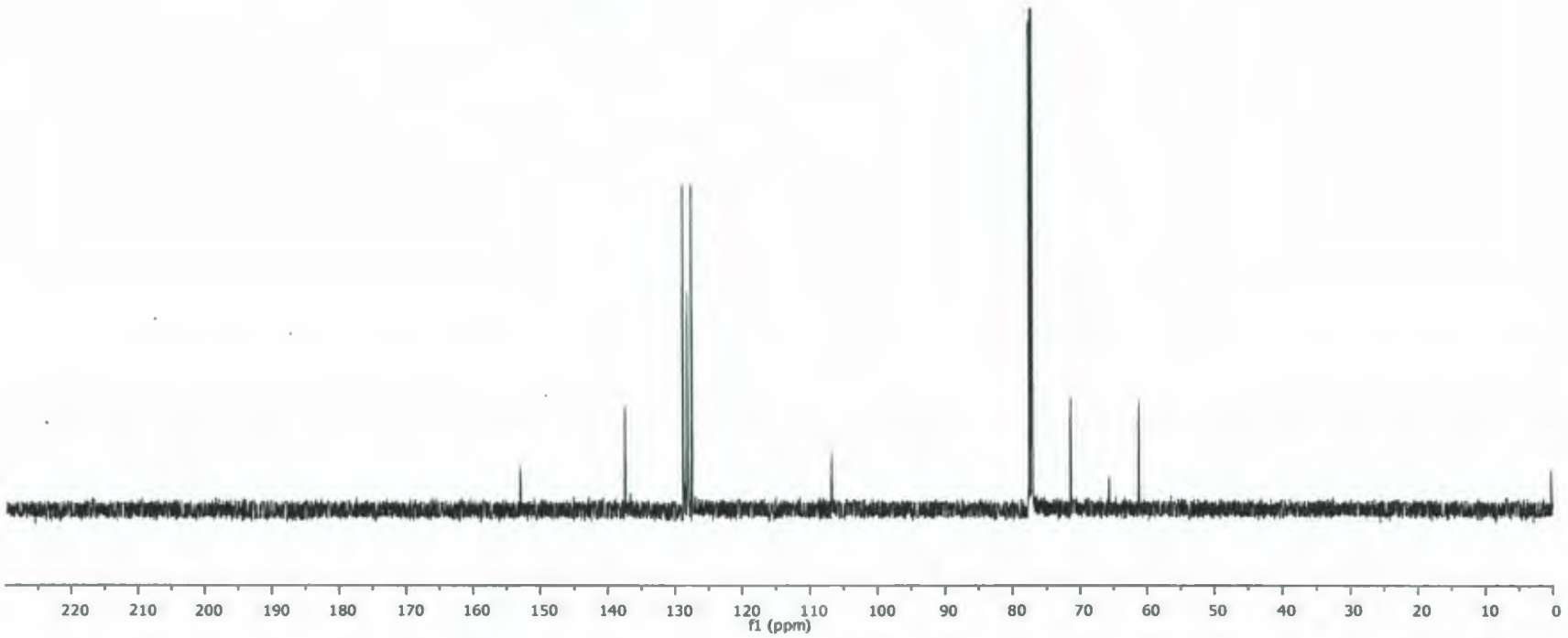
32

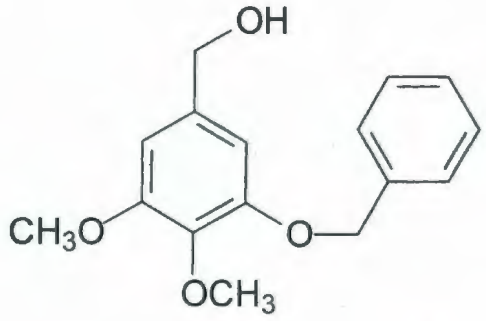
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
O
O
OCH3
33
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH
O
O
OCH3

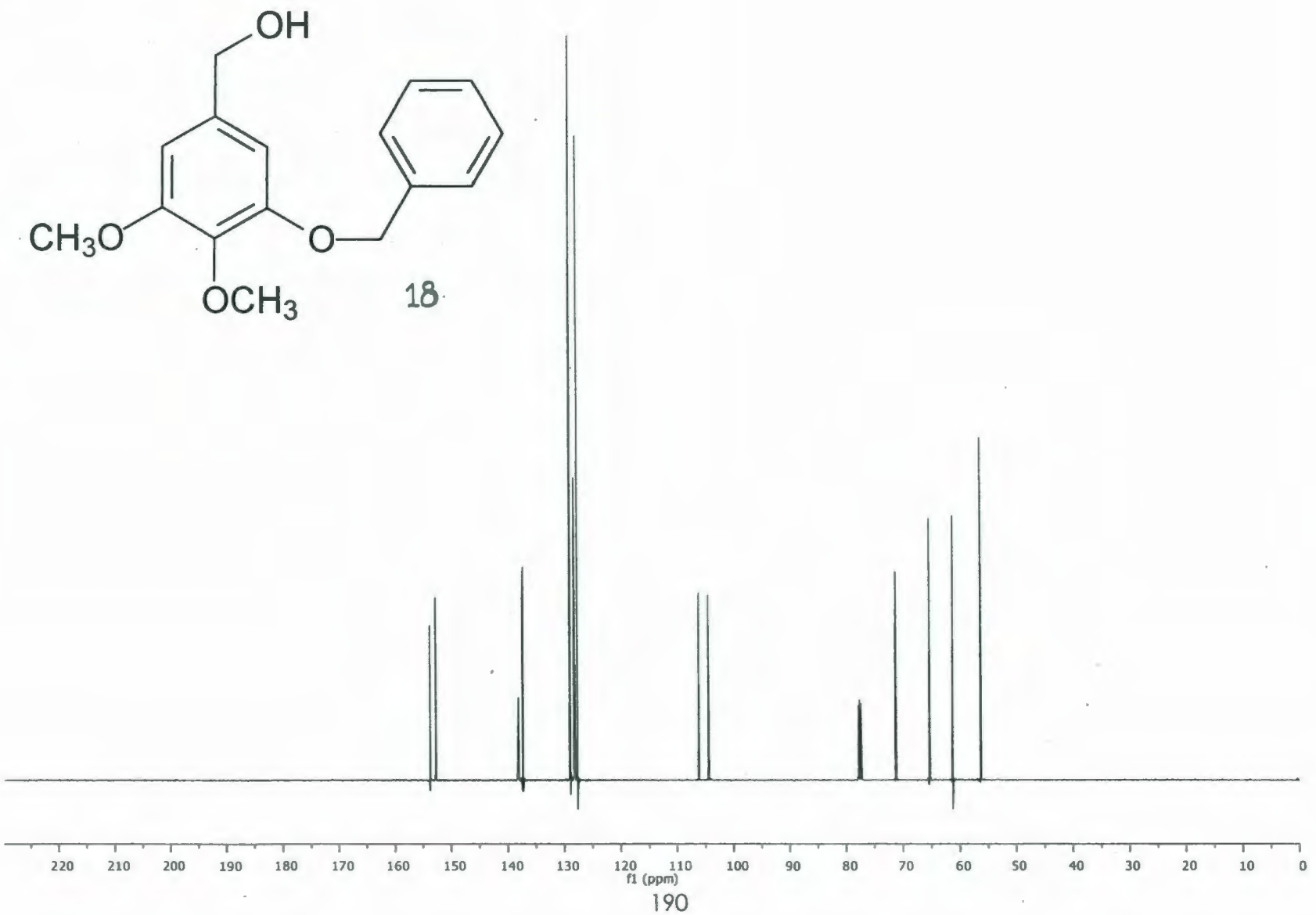
33


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

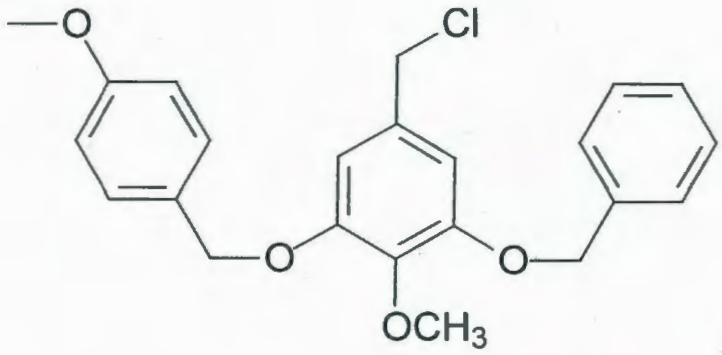

OH
CH3O
O
OCH3

18

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

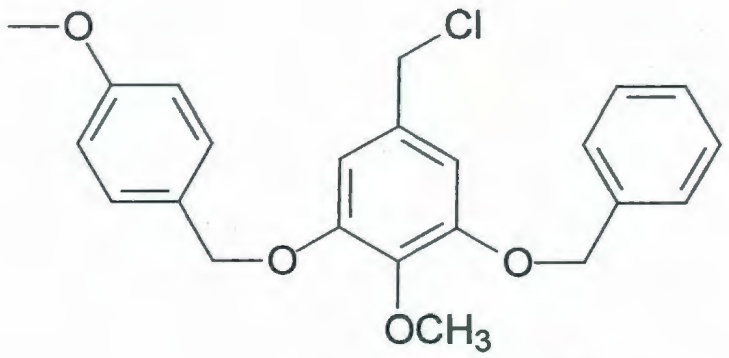

OH
CH3O
O
OCH3
18
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

190


O
Cl
O
O
OCH3

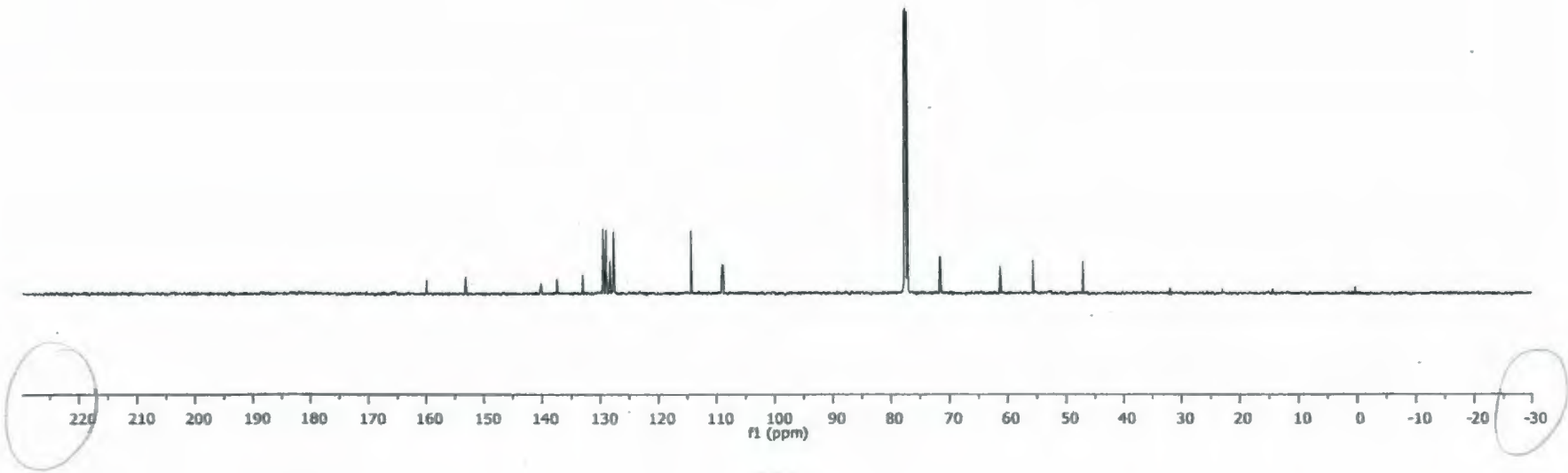
34

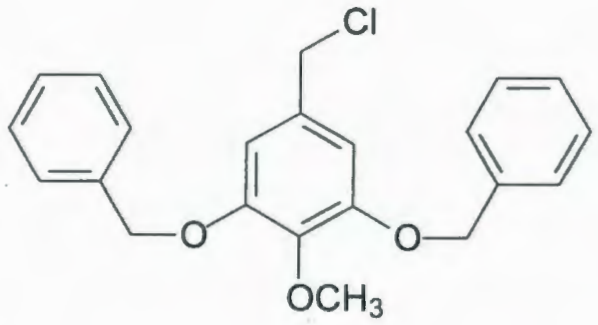
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)



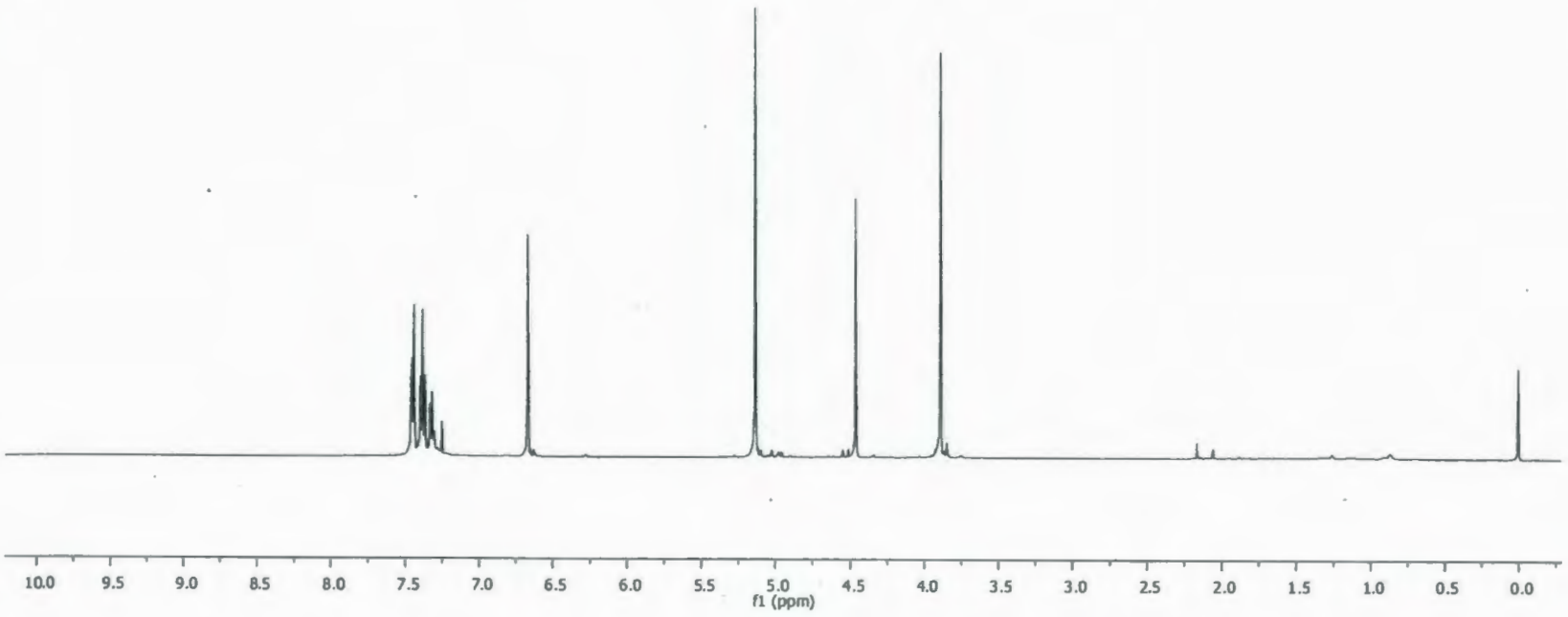
34

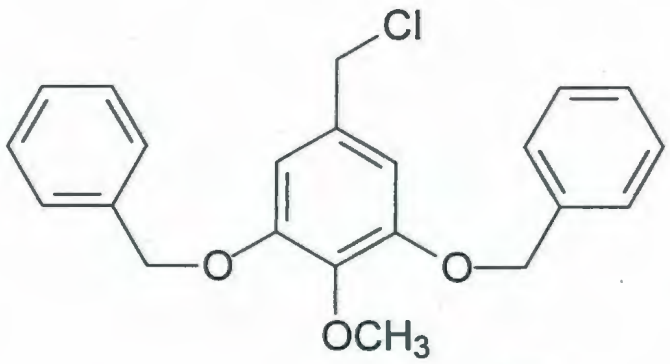
Plot -10 – 200 ppm



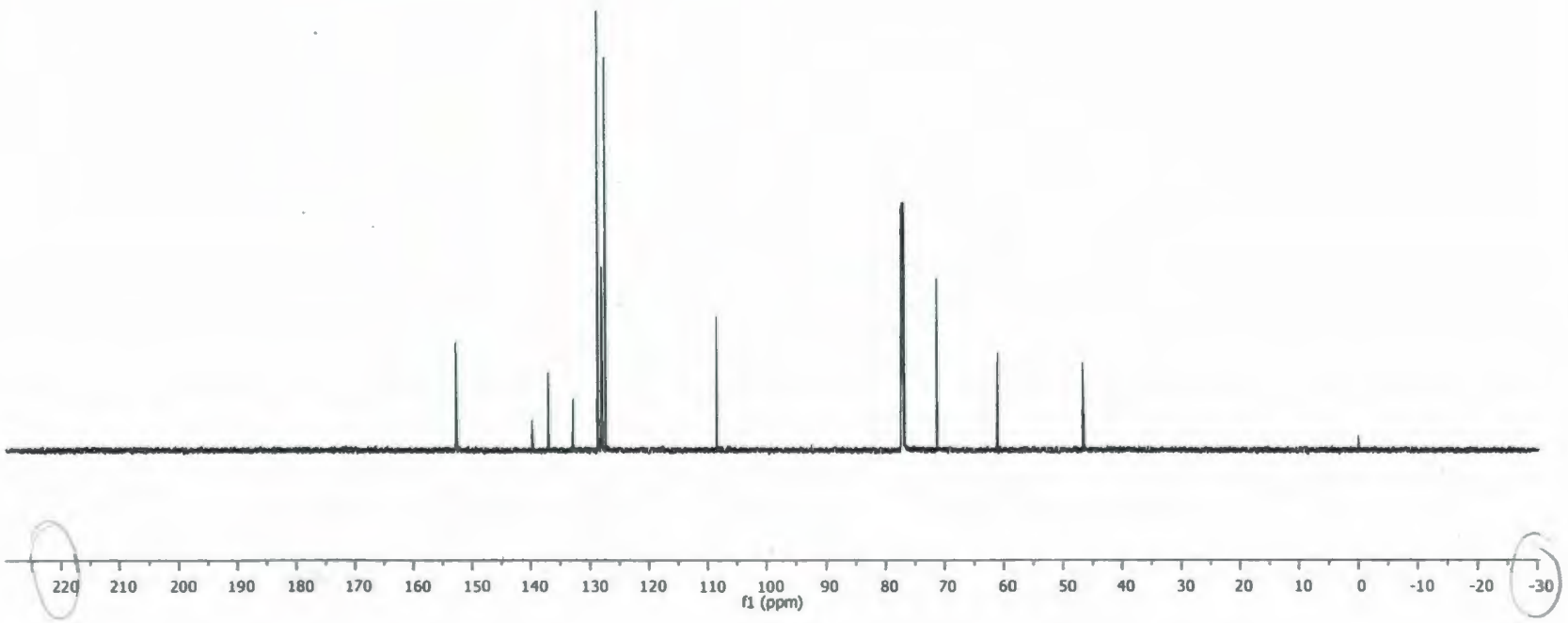

Cl
O
O
OCH3

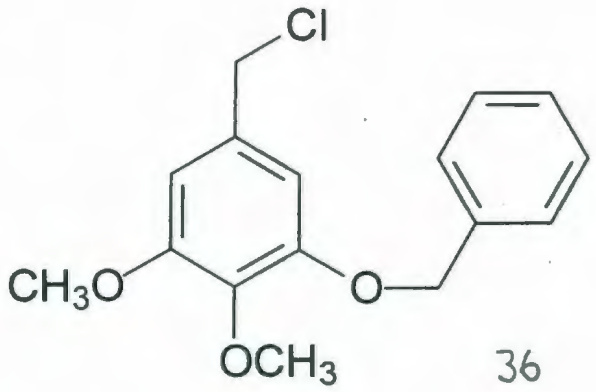
35


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Cl
O
O
OCH3

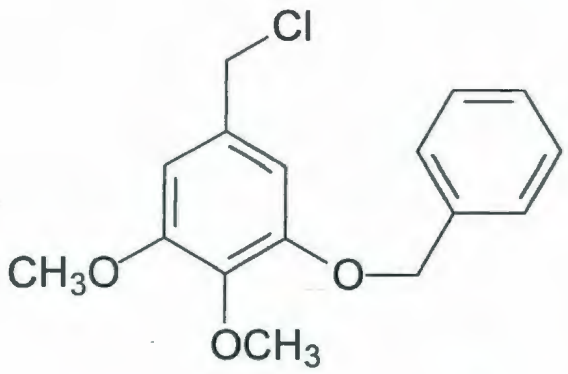
35


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)


Cl
CH3O
O
OCH3

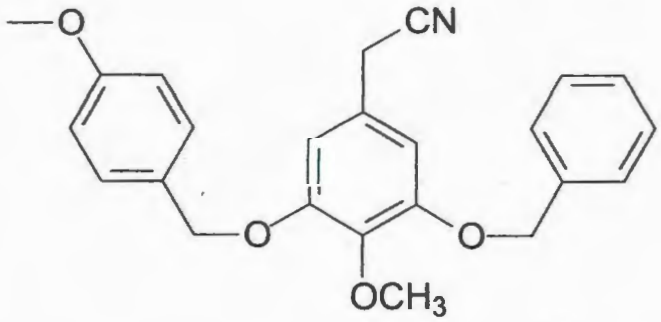
36

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Cl
CH3O
O
OCH3

36

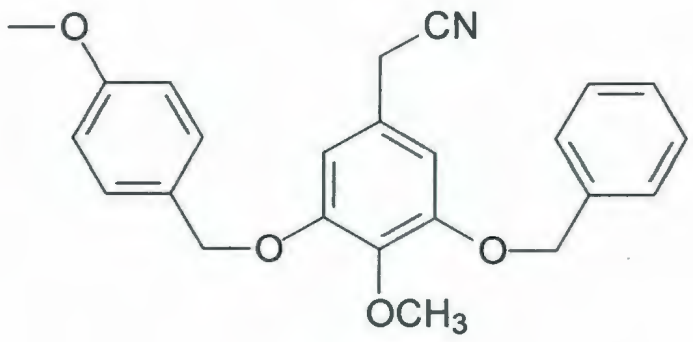
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CN
O
O
O
OCH3

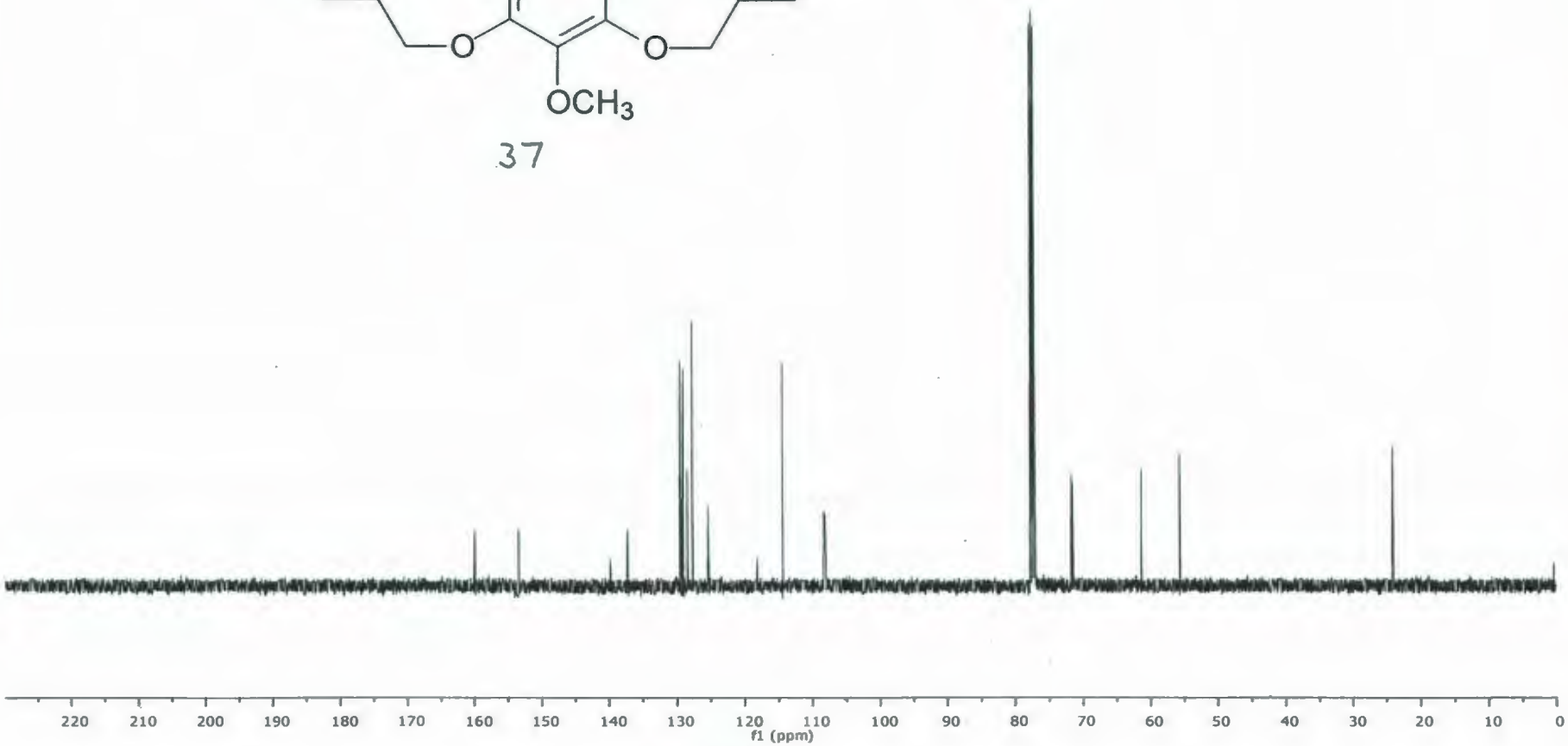
37

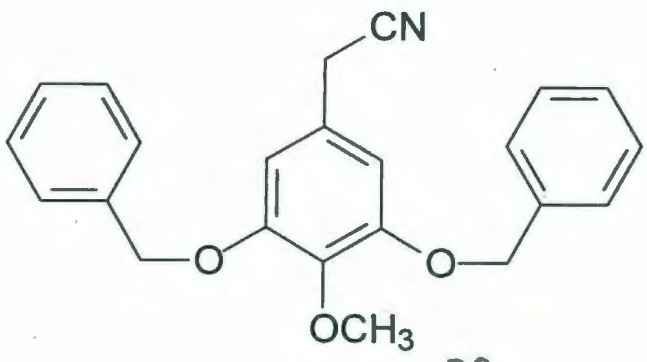
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

197


CN
O
O
O
OCH3

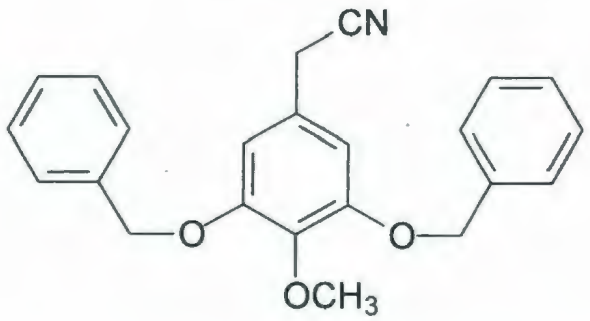
37


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CN
O
O
OCH3

38

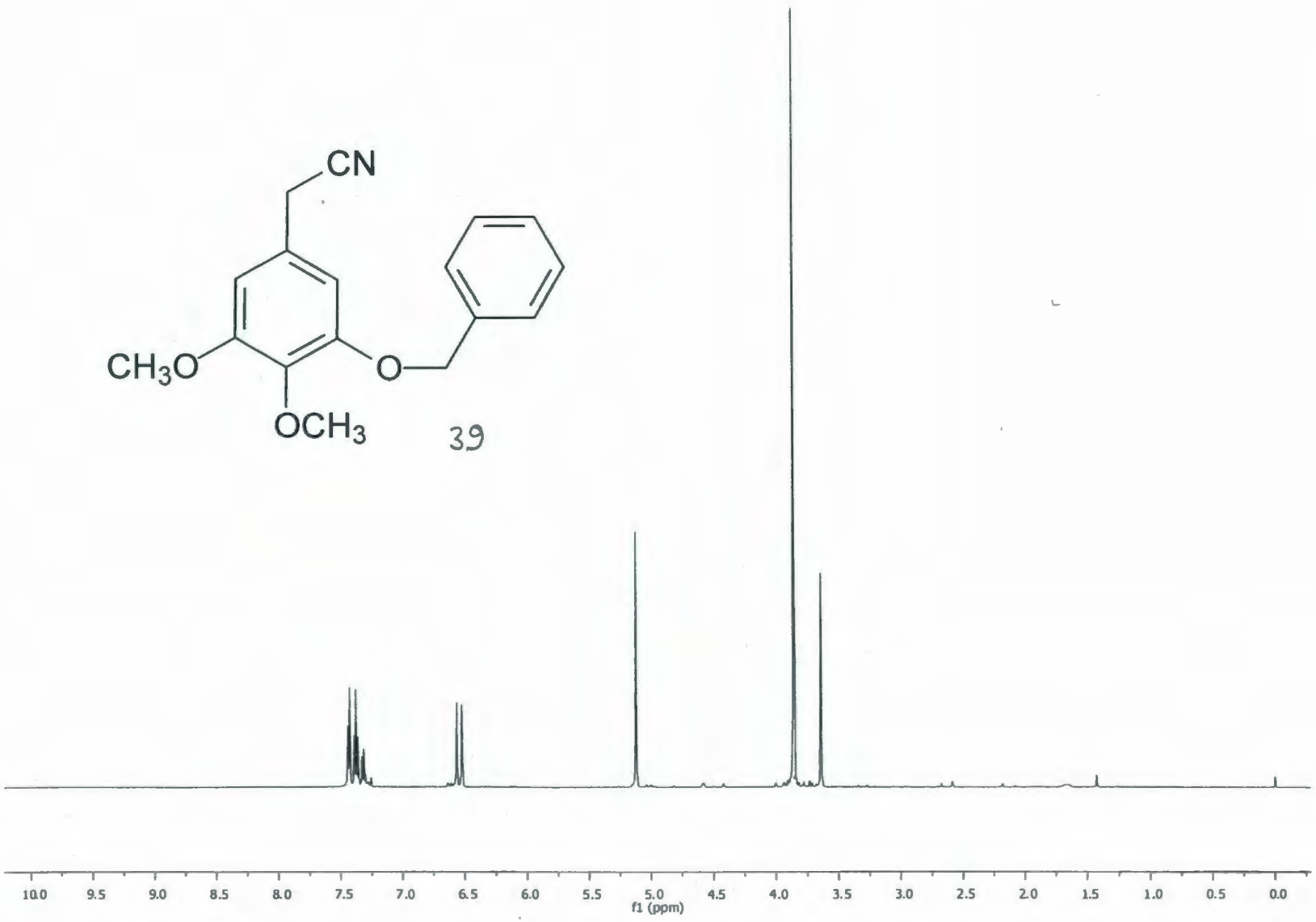
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

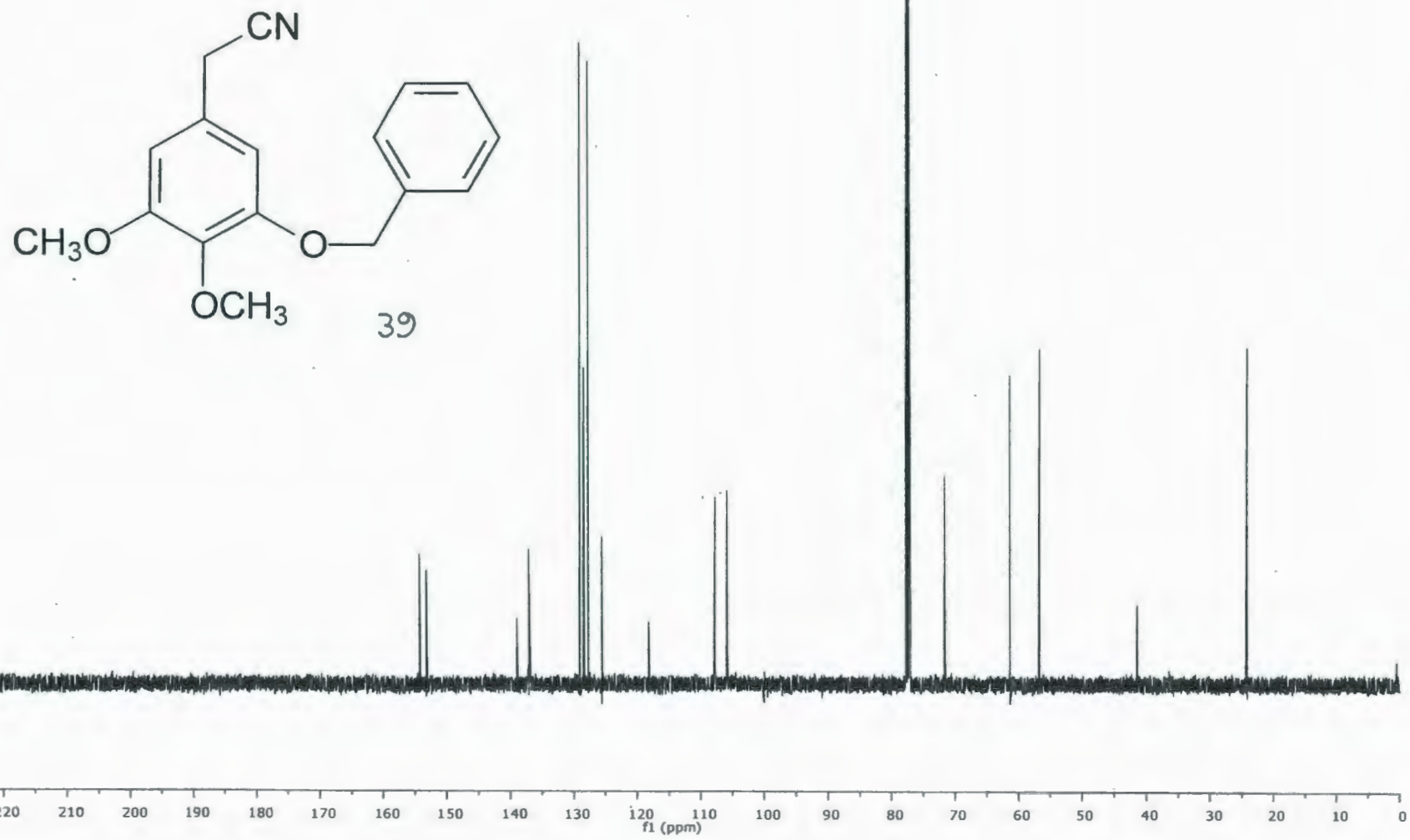

CN
O
O
OCH3

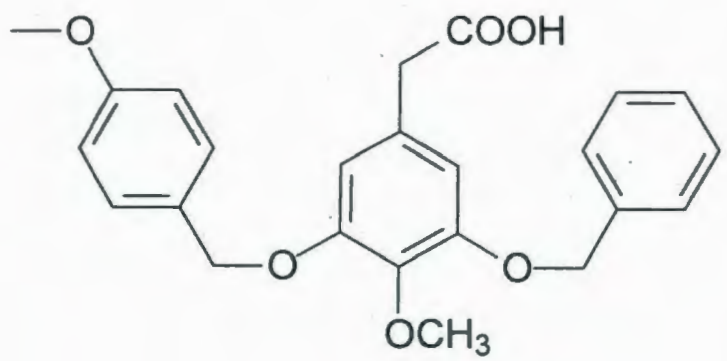
38

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

200

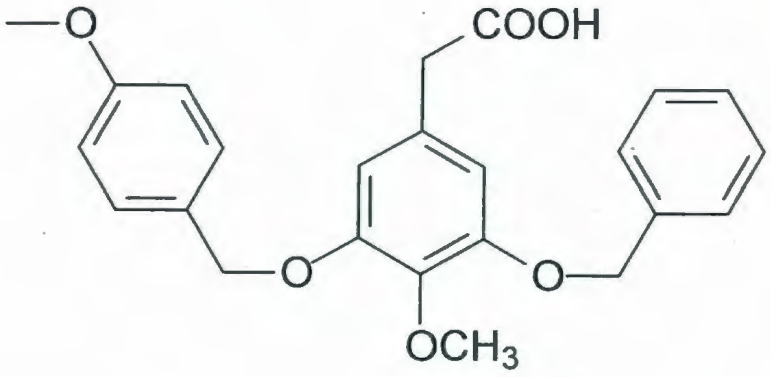

CN
CH3O
O
OCH3
39
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CN
CH3O
O
OCH3
39
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


COOH
O
O
O
OCH3

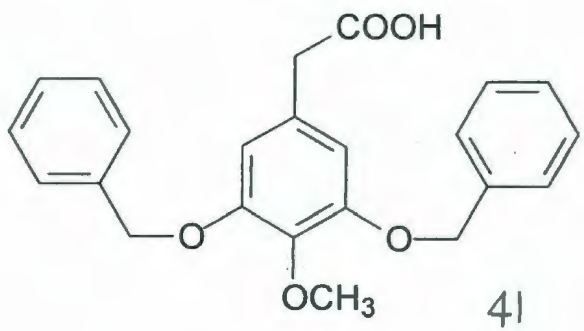
40

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


—O
COOH
O
O
OCH3

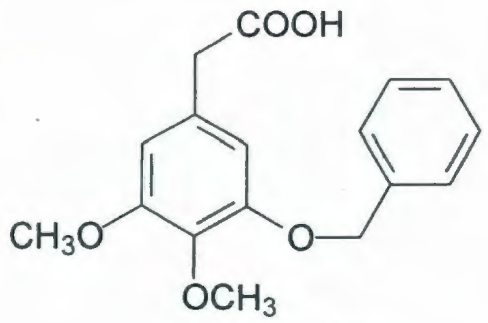
40

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

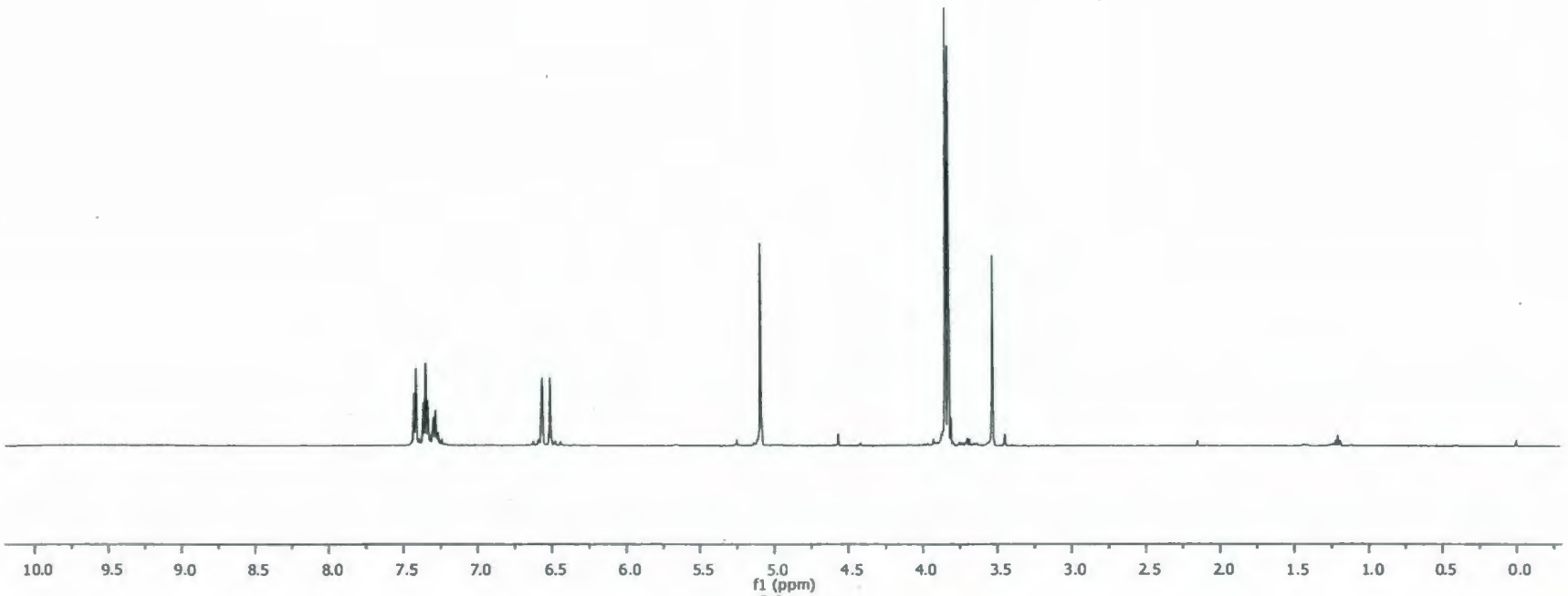

COOH
O
O
OCH3

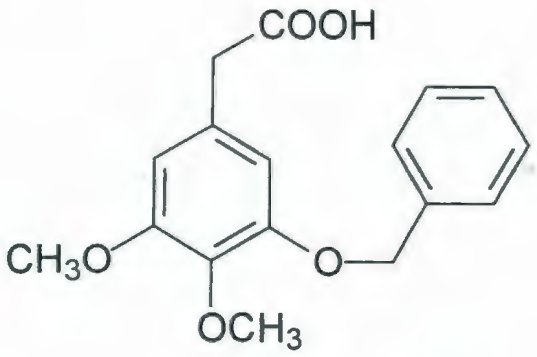
41

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


COOH
CH3O
O
OCH3

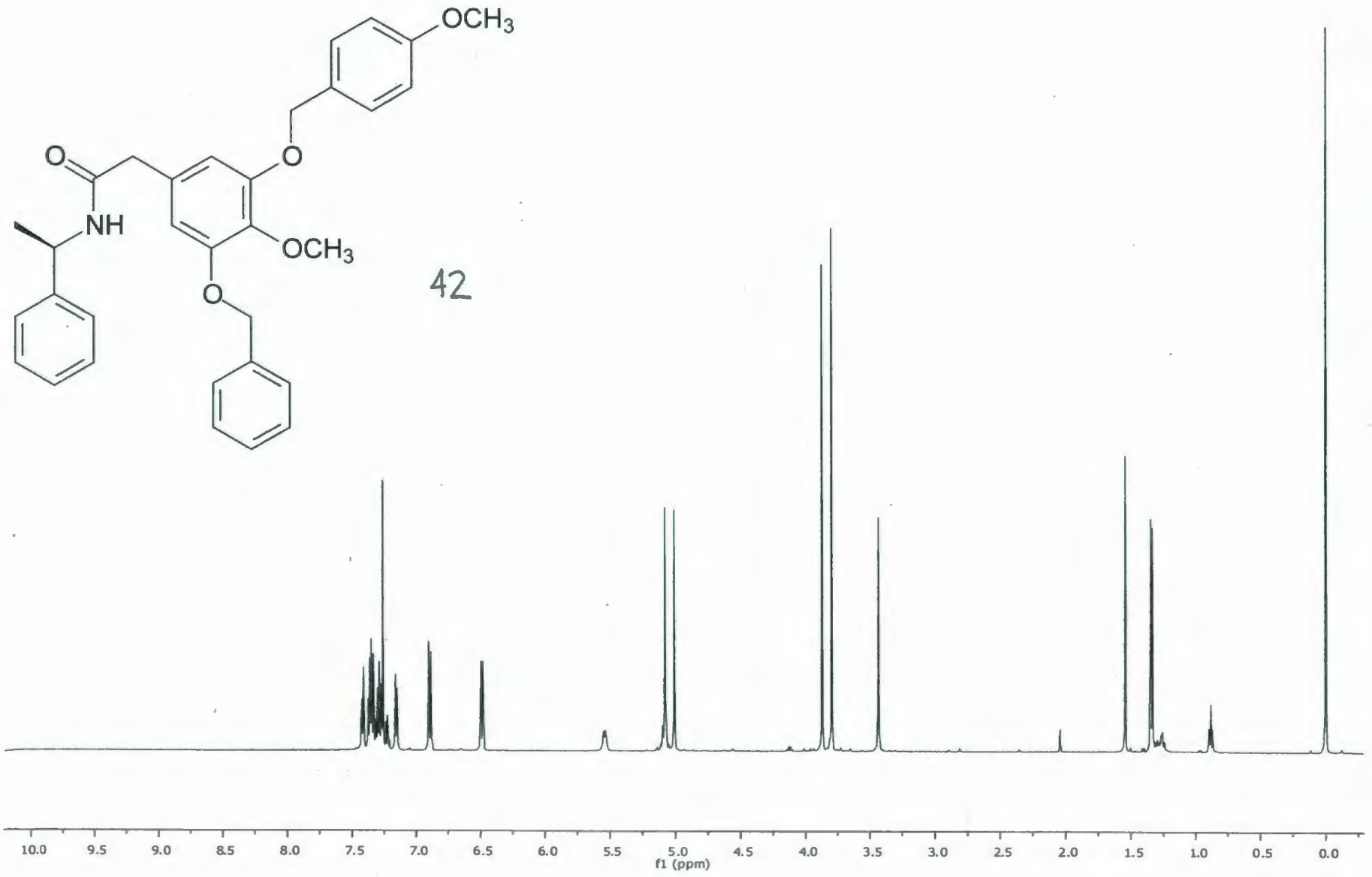
12

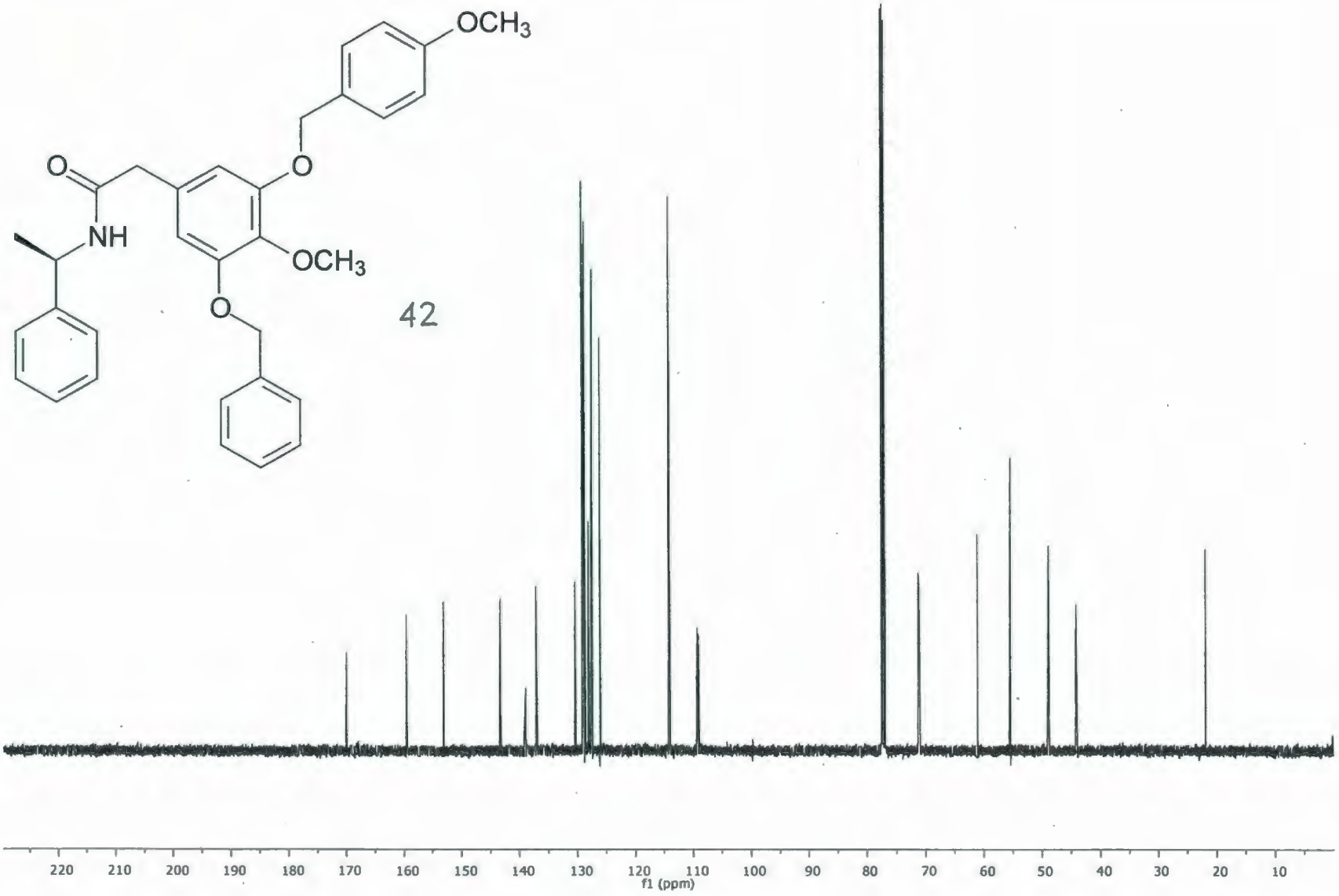

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

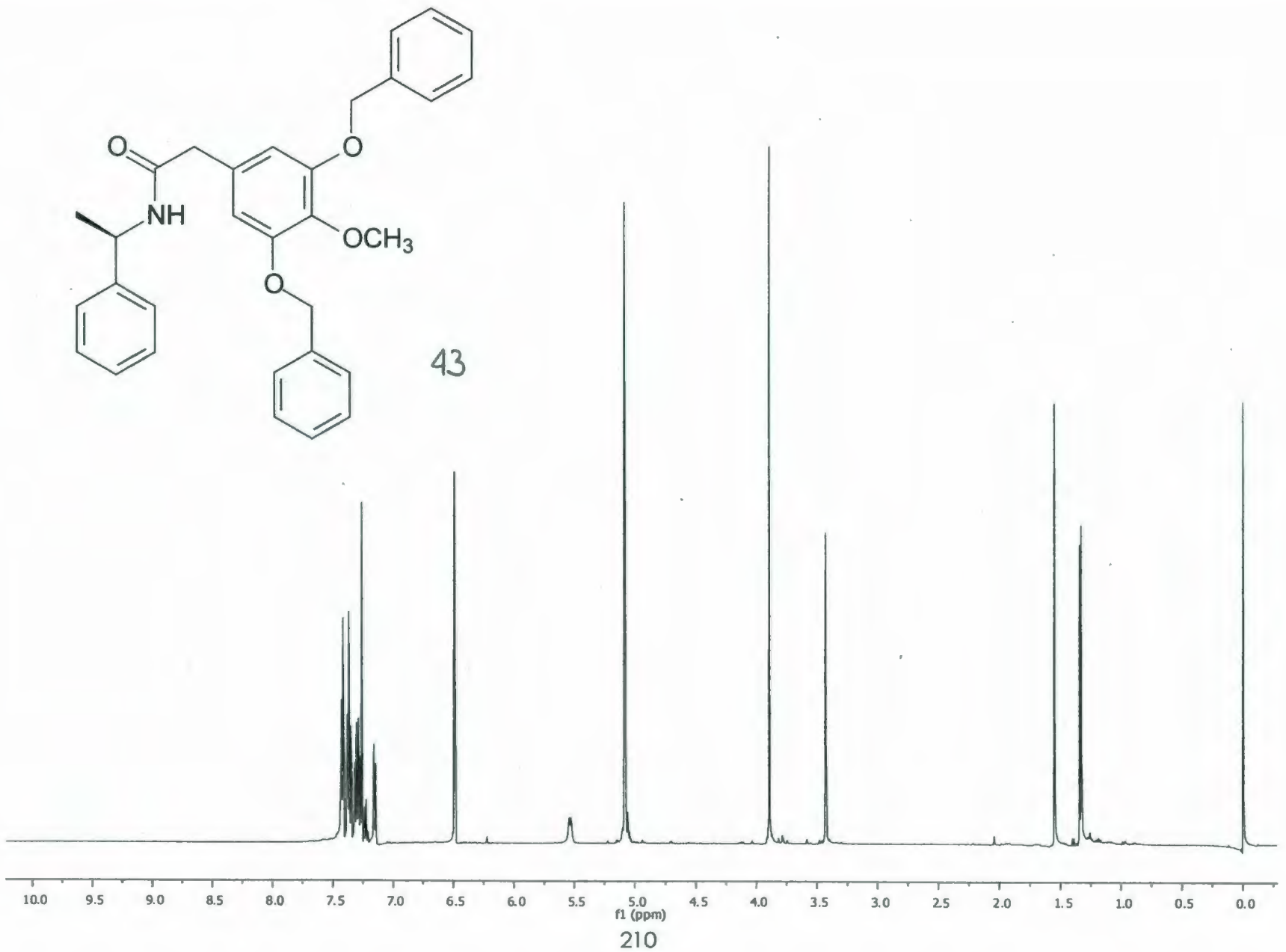

COOH
CH3O
O
OCH3

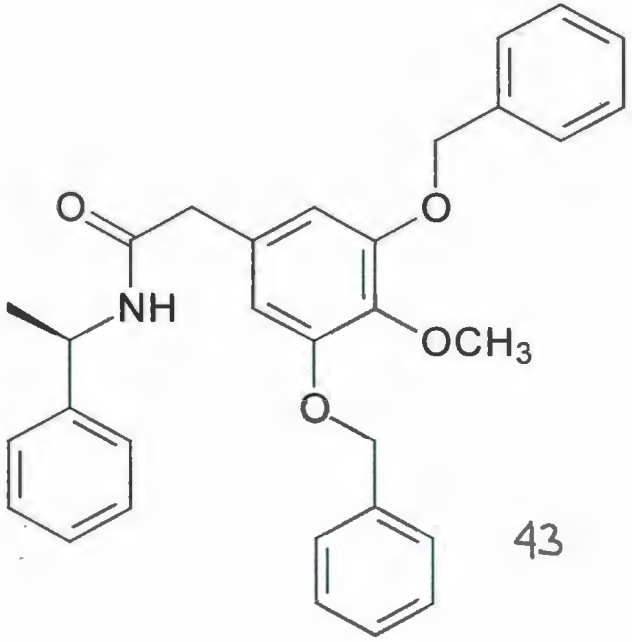
12

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
O
O
NH
OCH3
O
42
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

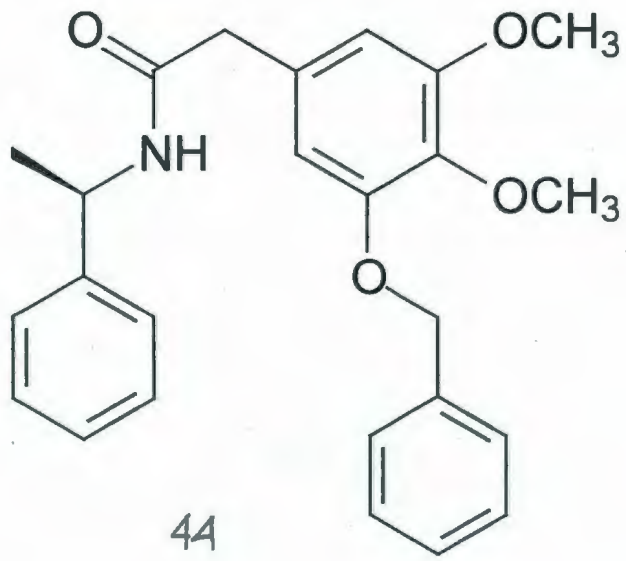

OCH3
O
O
NH
OCH3
O
42
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


O
NH
O
OCH3
O
43
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
NH
O
OCH3
O

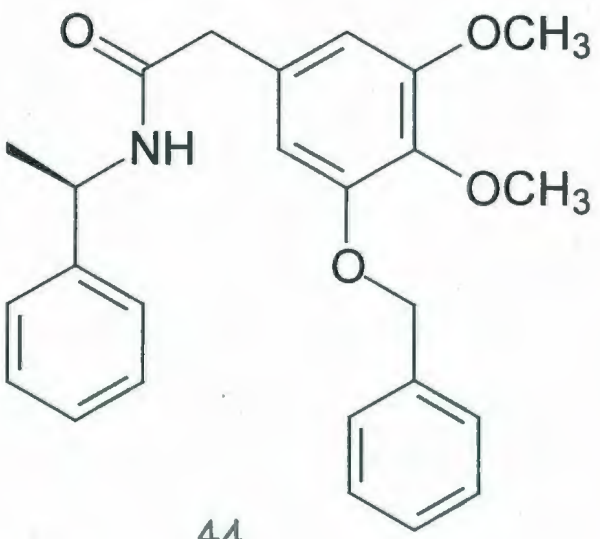
43

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH
OCH3
OCH3
O

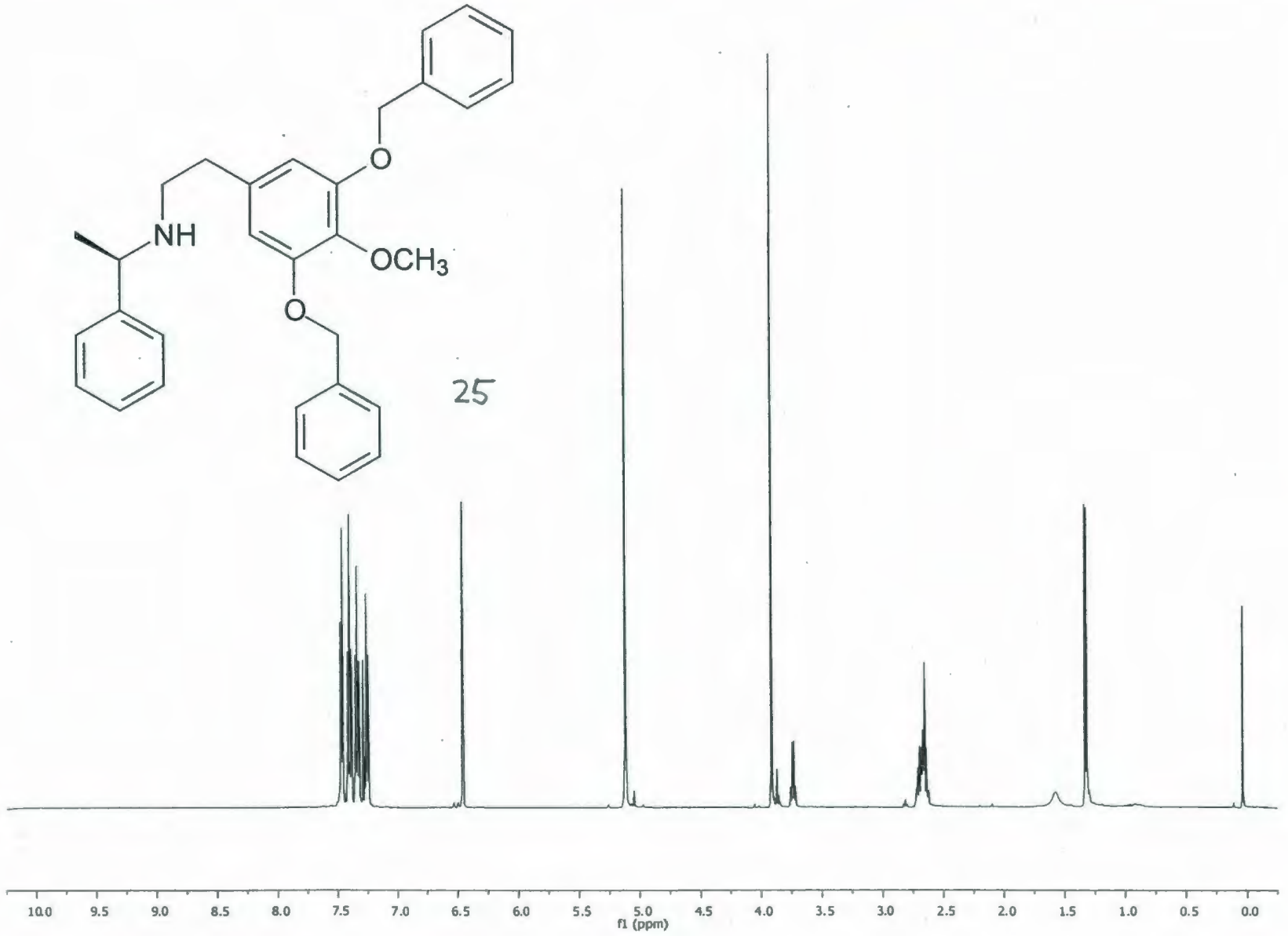
44

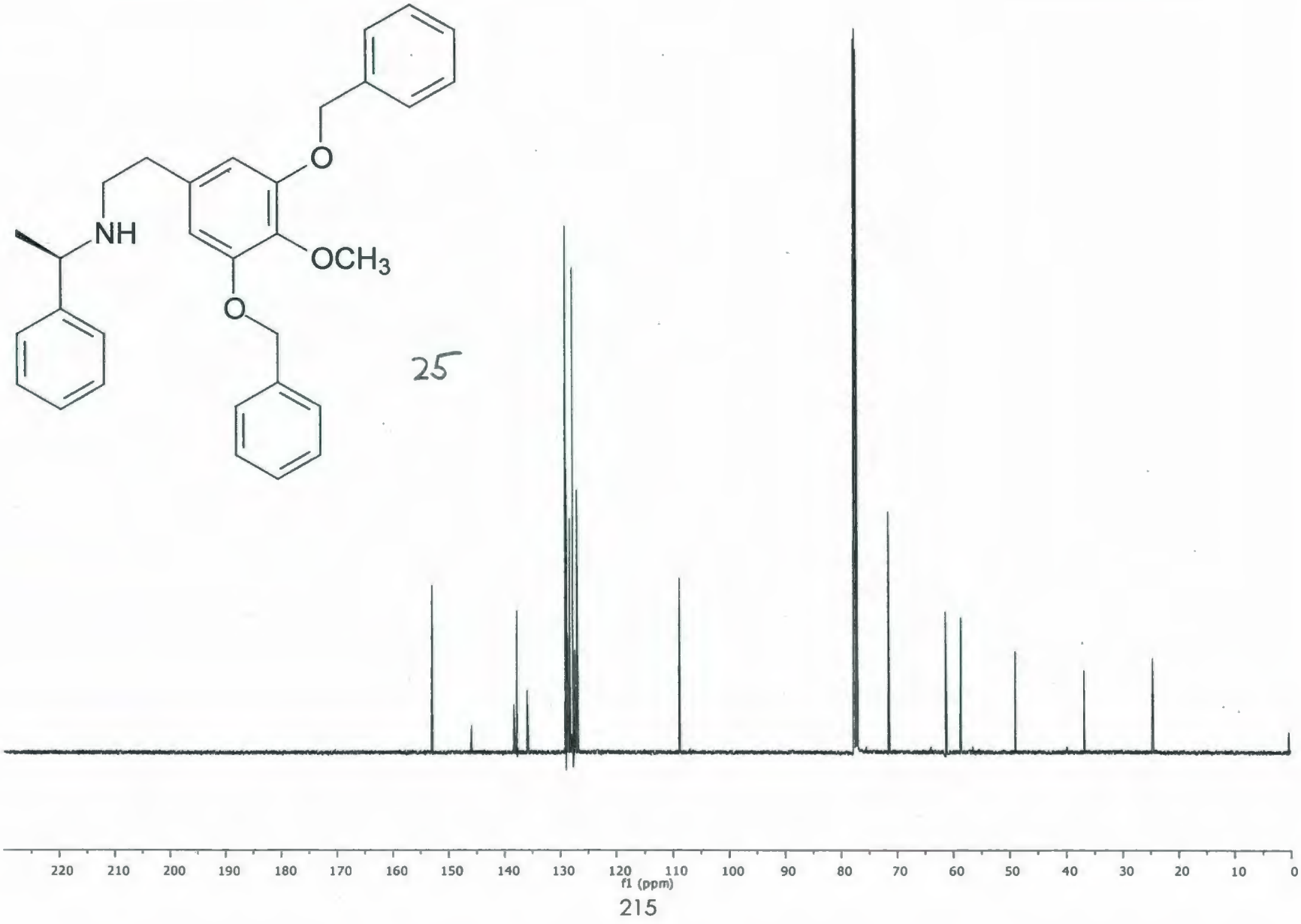
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

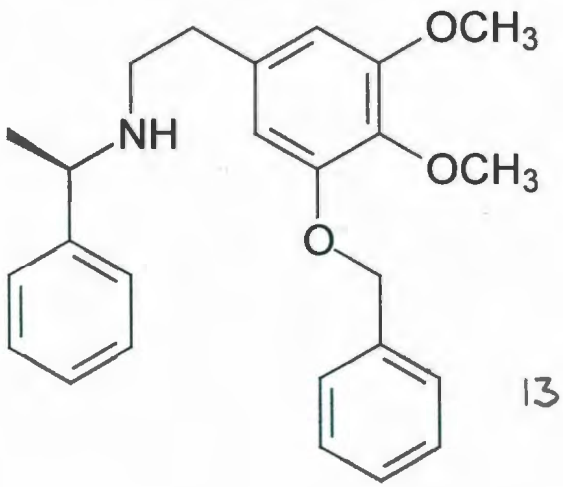

O
NH
OCH3
OCH3
O

44

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

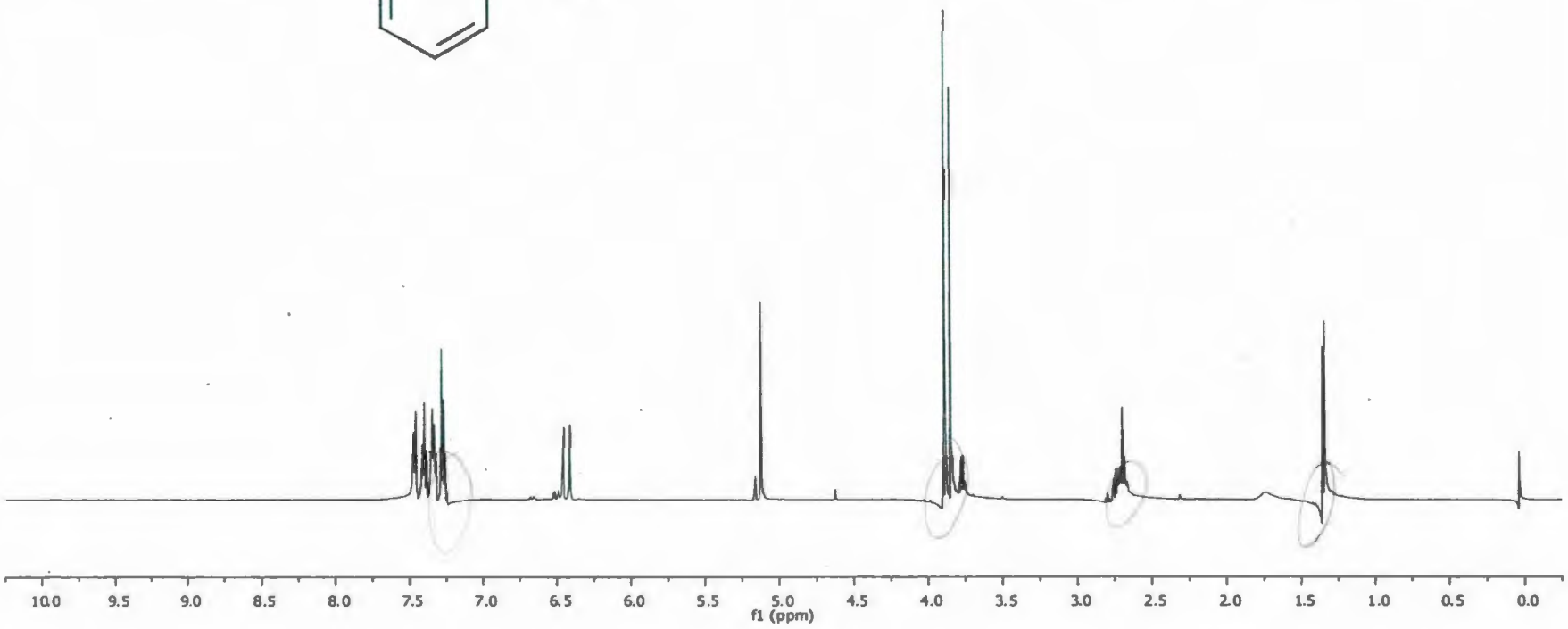

NH
O
OCH3
O
25
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

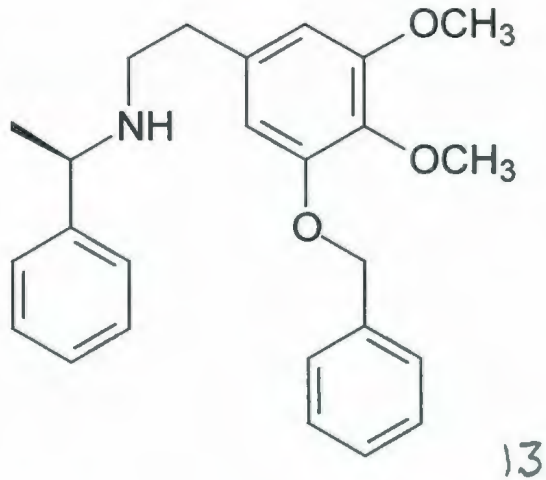

NH
O
OCH3
O
25
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
NH
OCH3
O

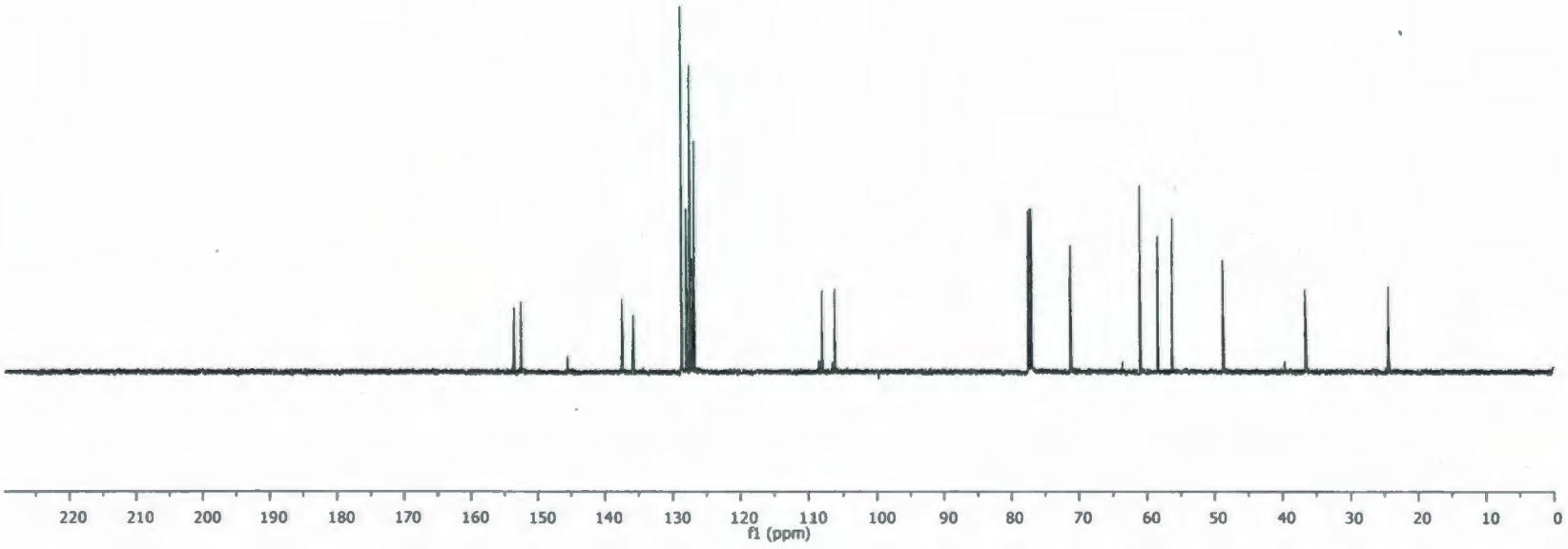
13

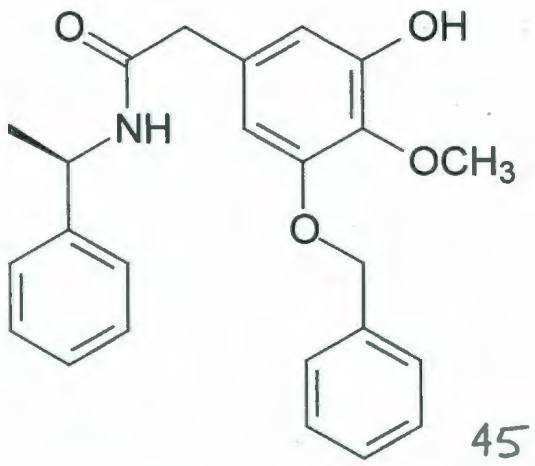
Phase!


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
NH
OCH3
O

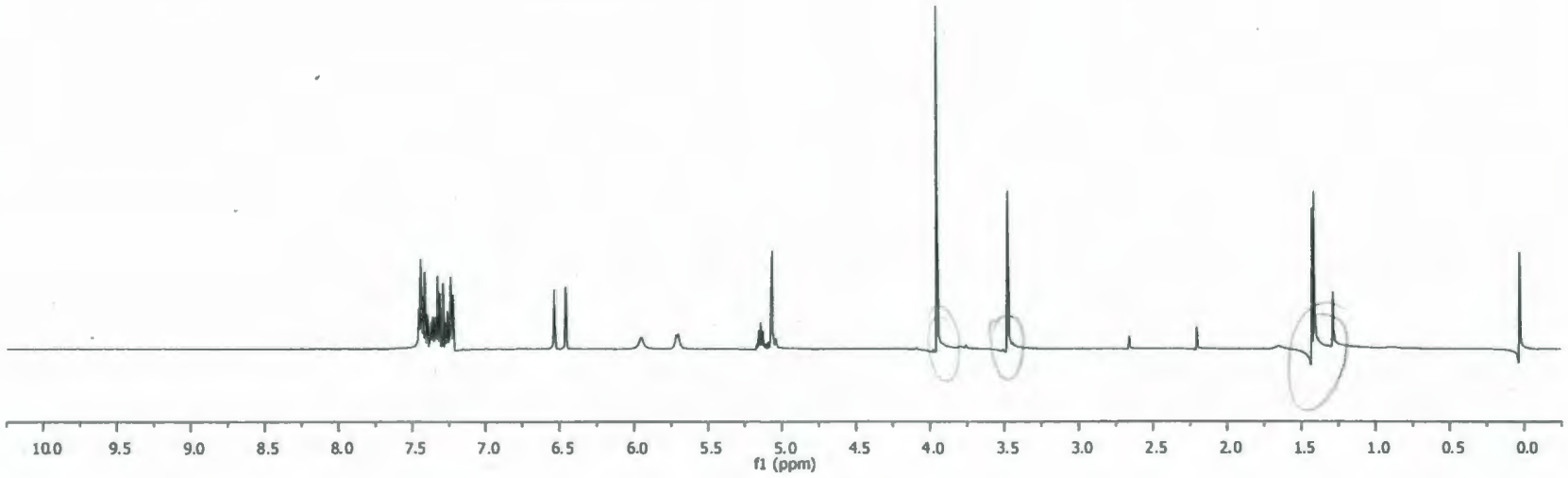
13

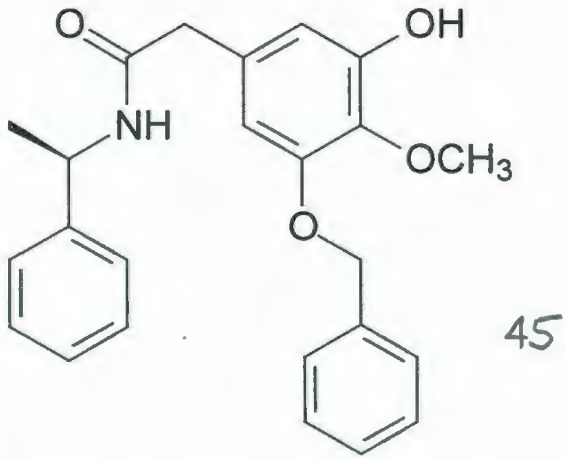

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
NH
OH
OCH3
O

45

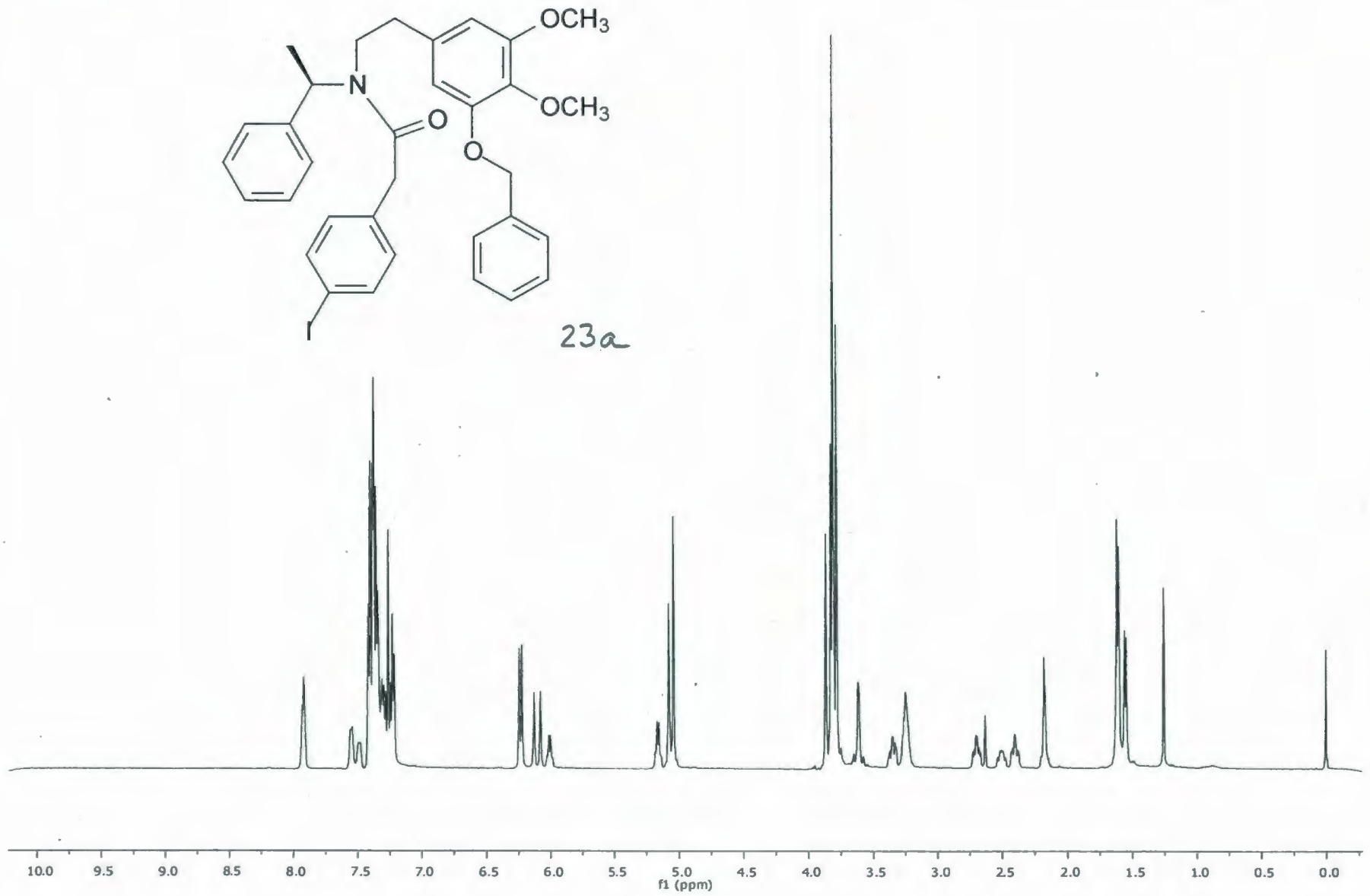
phase

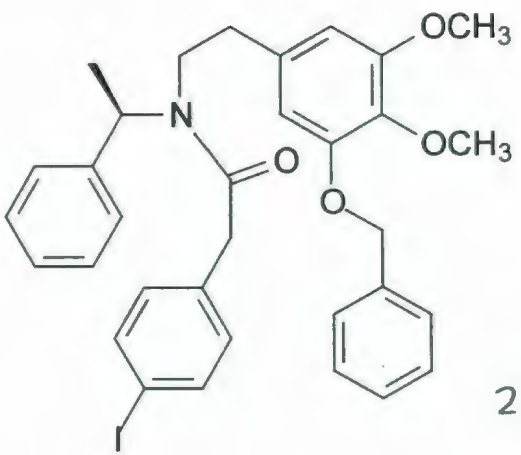

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
NH
OH
OCH3
O

45

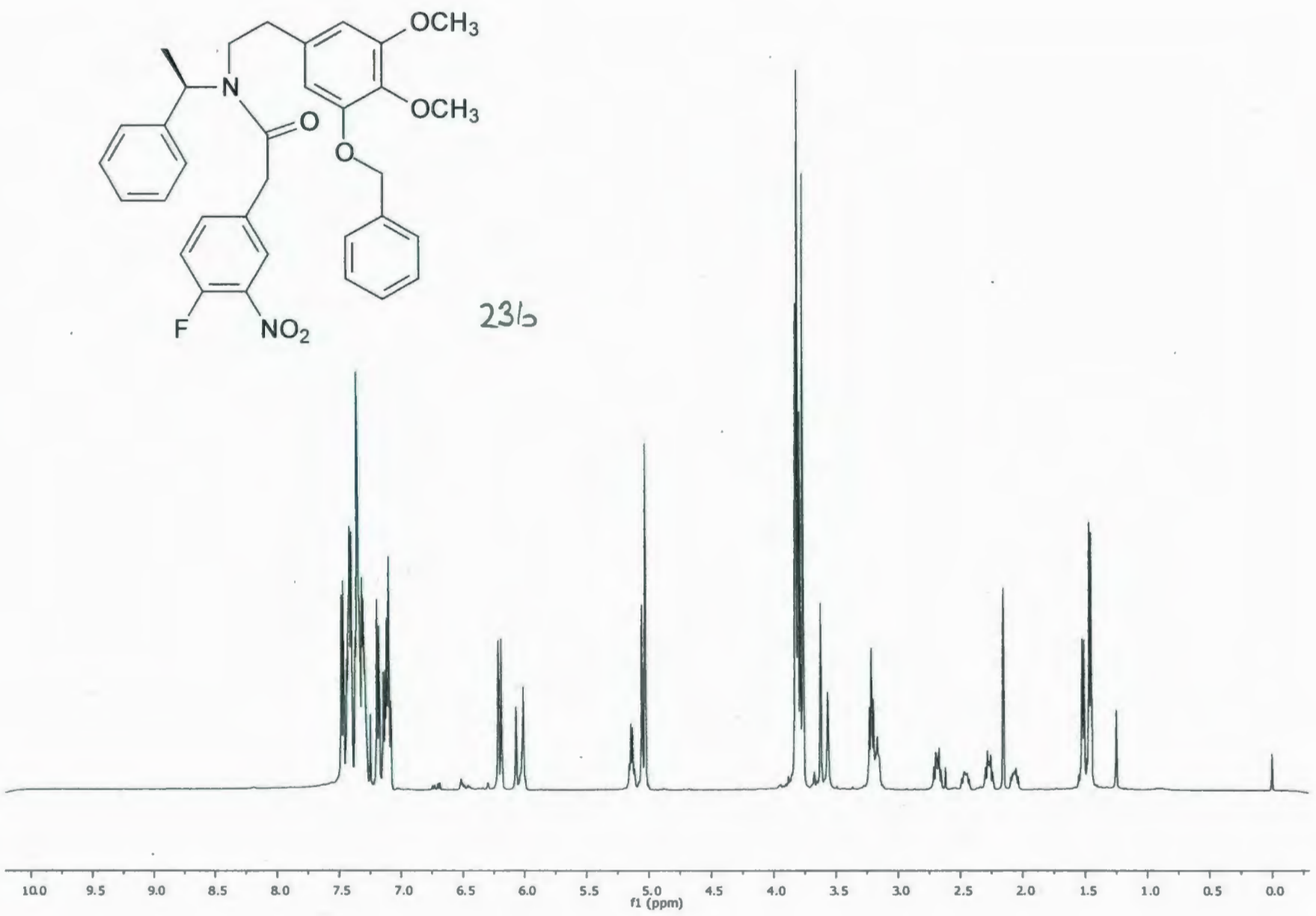
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

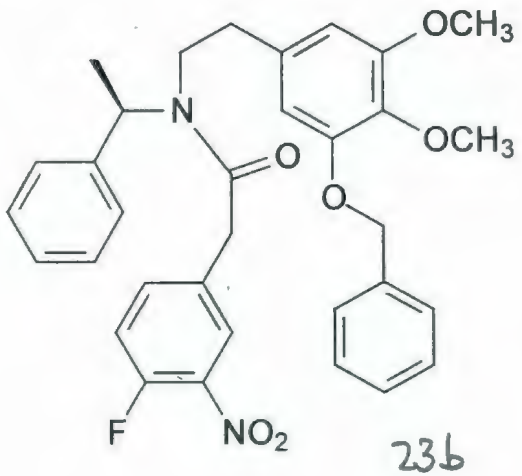

OCH3
OCH3
N
O
O
I
23a
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
OCH3
N
O
O

23a

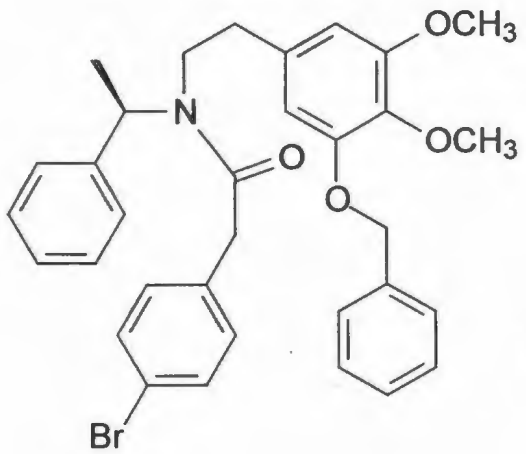
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
OCH3
N
O
O
F
NO2
23b
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

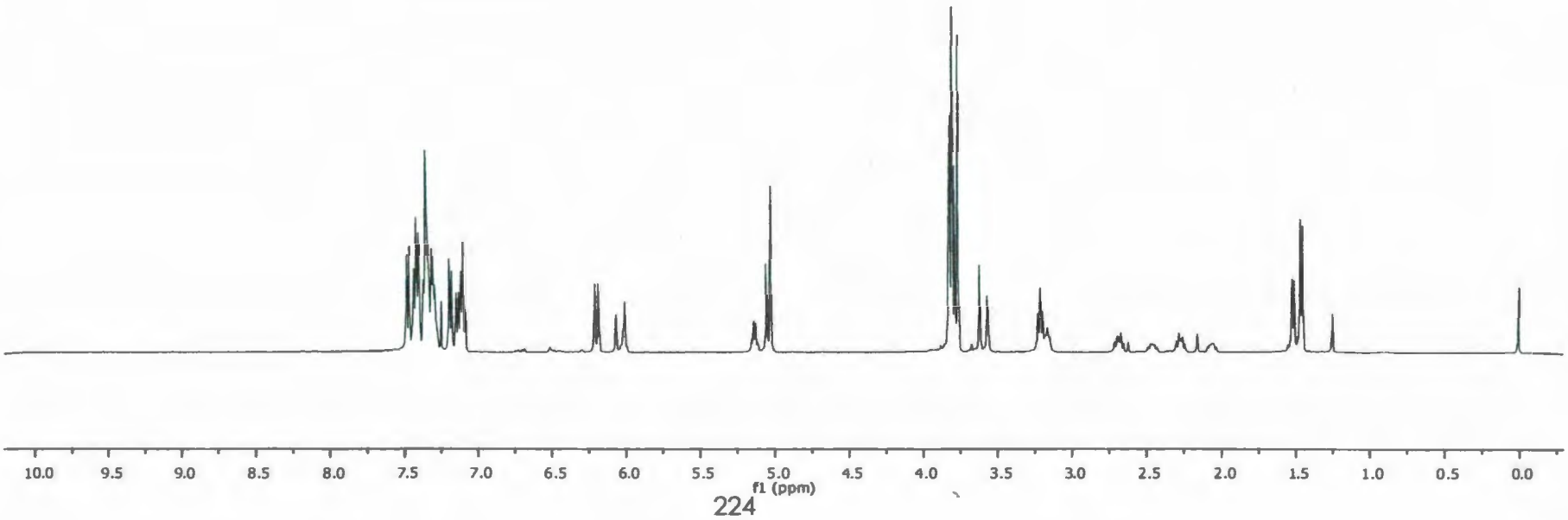

OCH3
OCH3
N
O
O
F
NO2

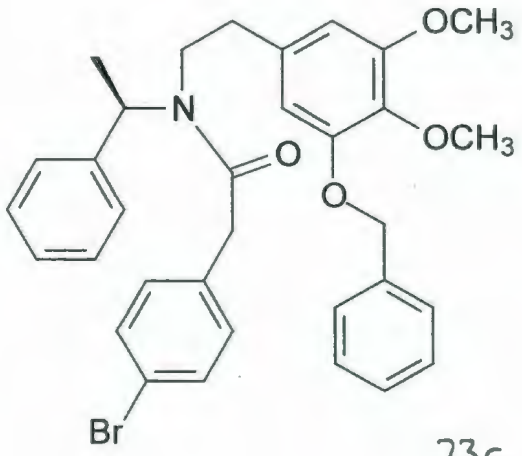
23b

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

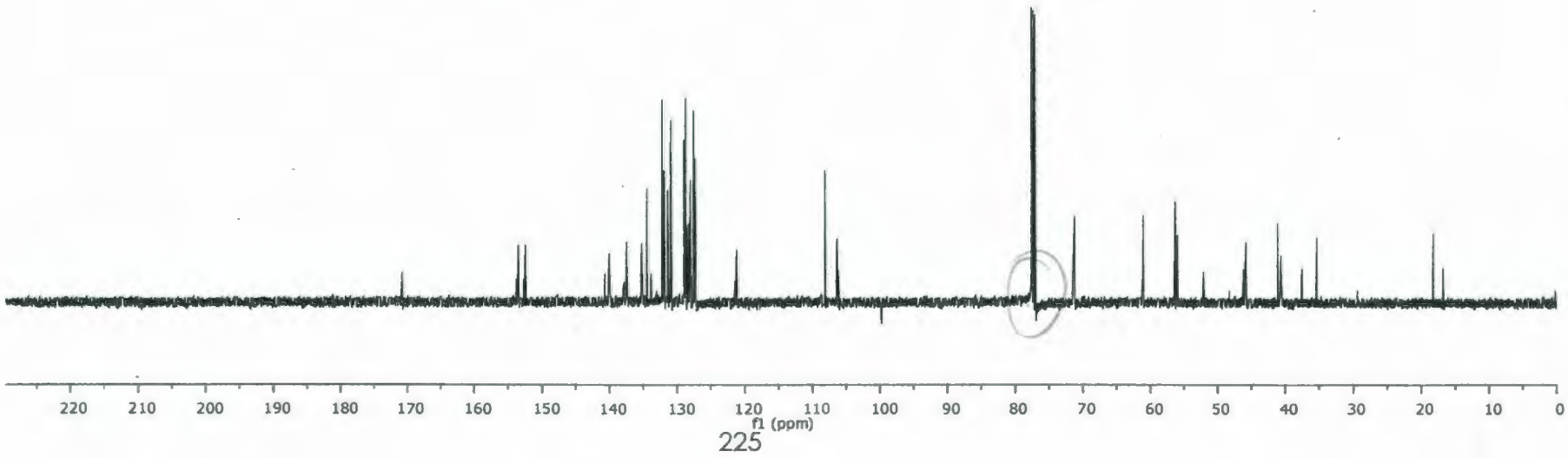

OCH3
OCH3
N
O
O
Br

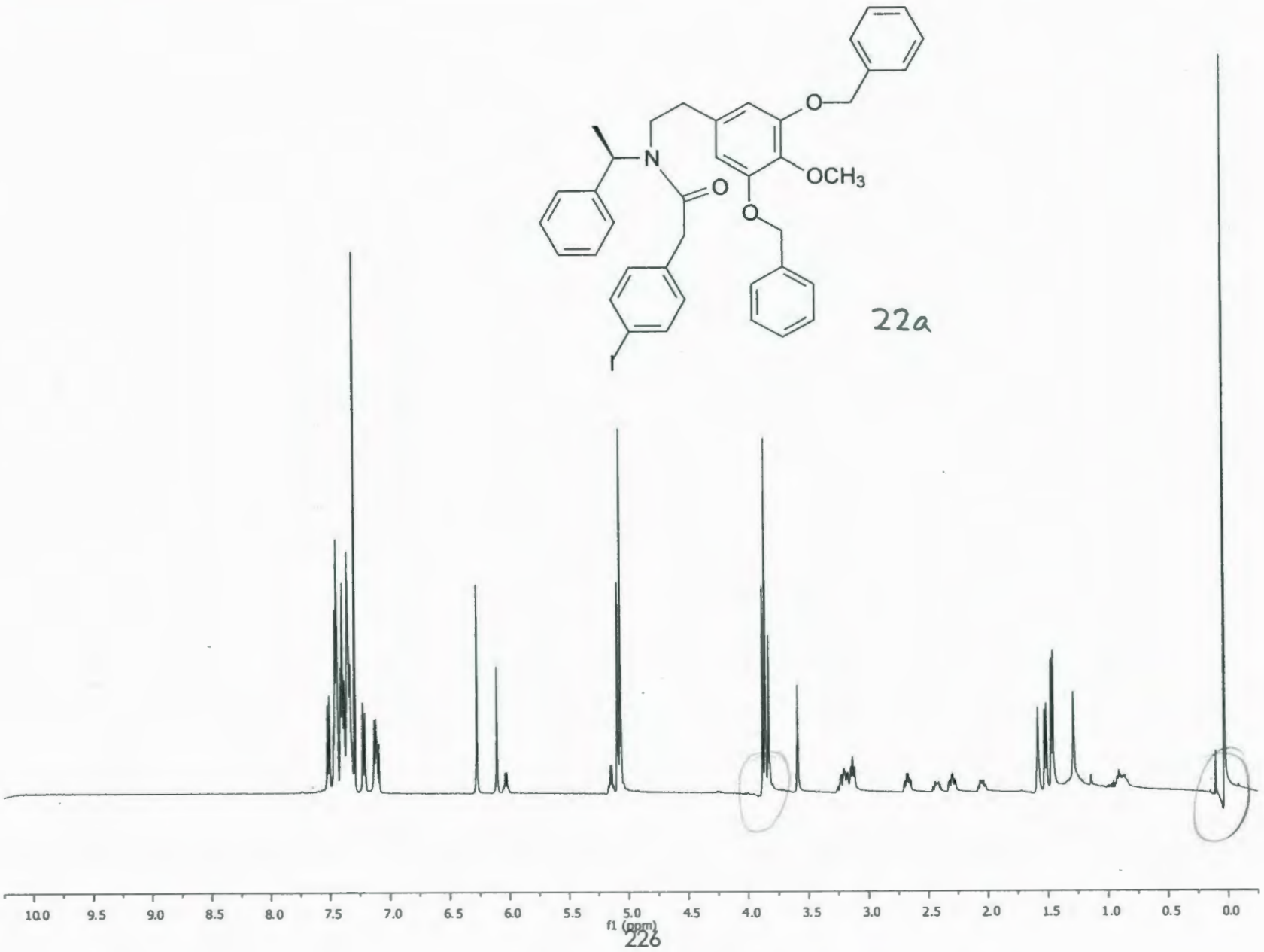
23c

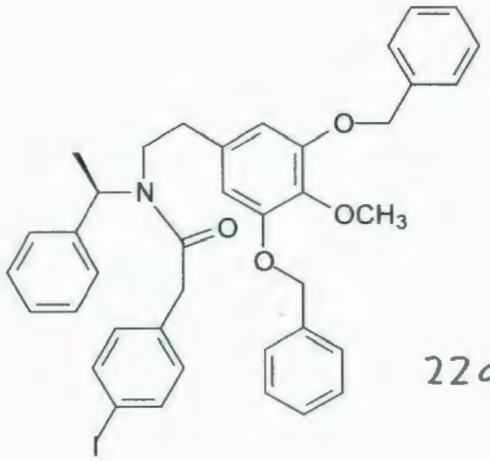

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
OCH3
N
O
O
Br

23c

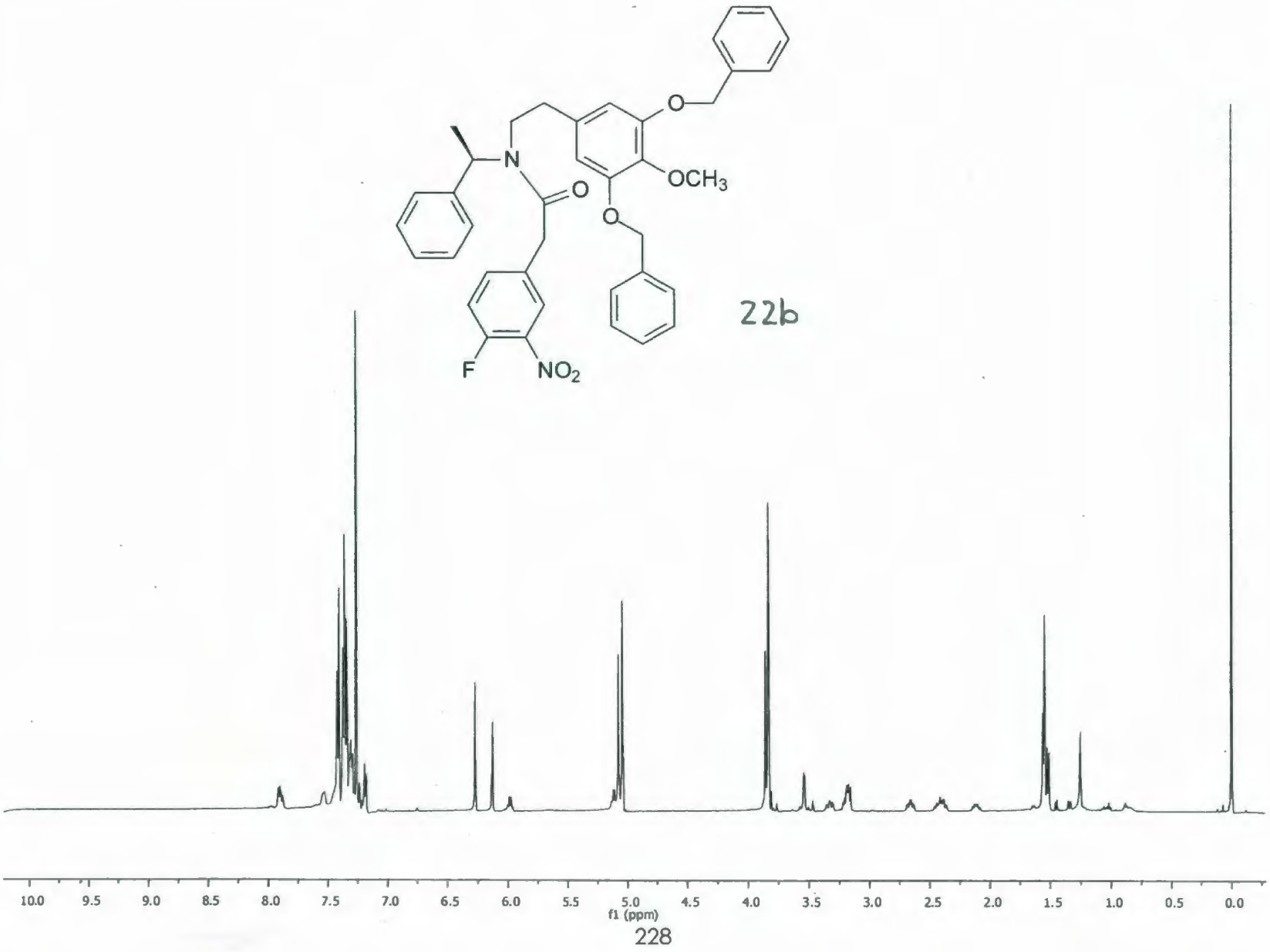

48.21
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

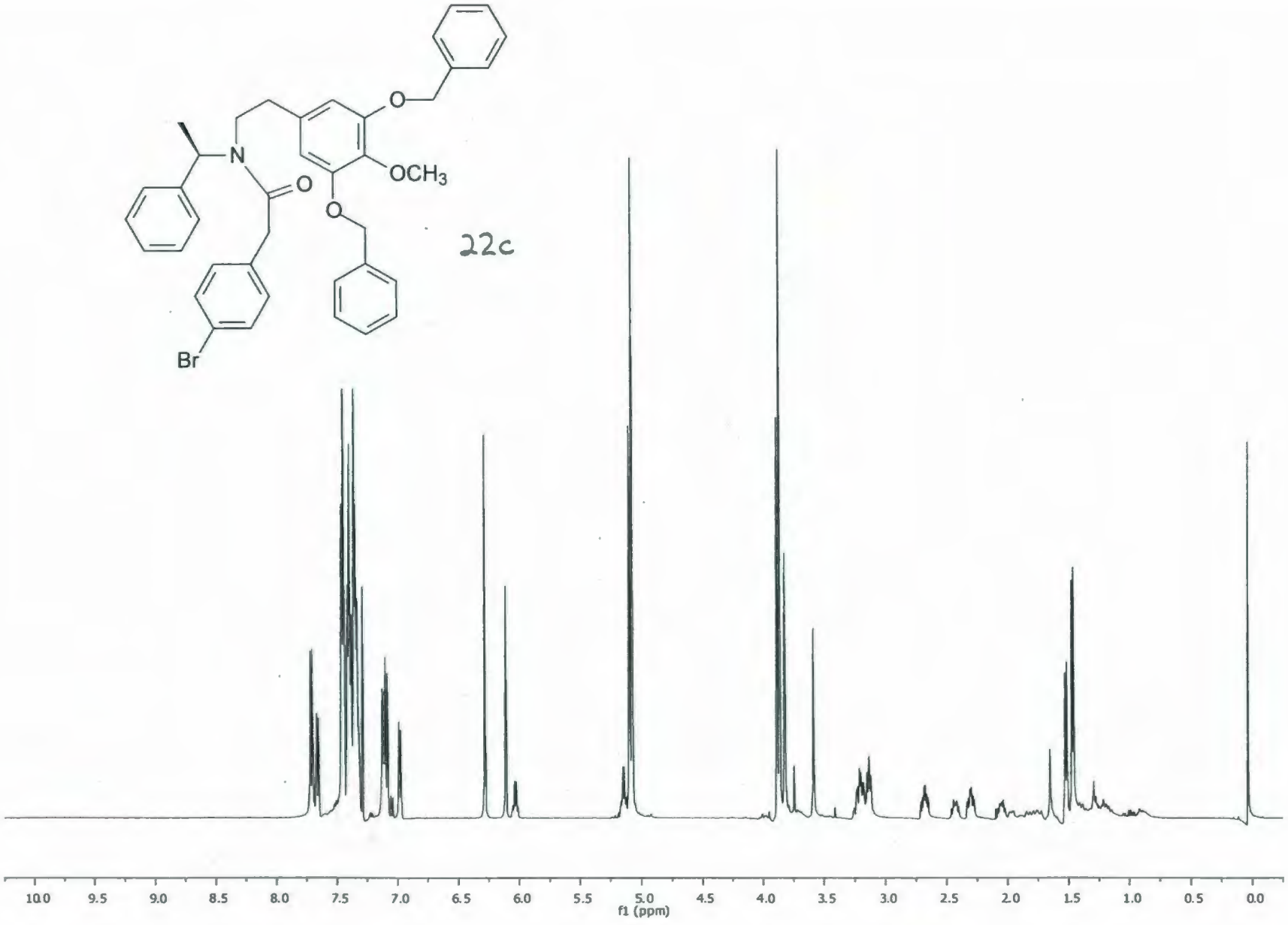

N
O
O
O
OCH3
I
22a
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

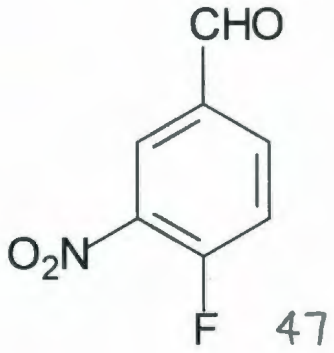

O
N
O
OCH3
O

22a

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

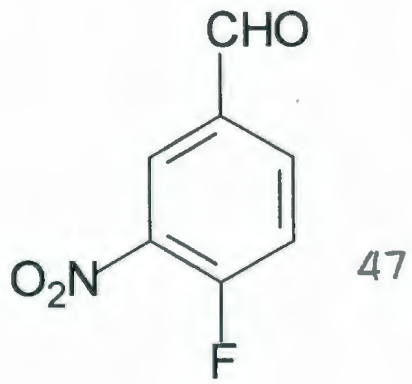

O
N
O
OCH3
O
F
NO2
22b
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
O
OCH3
O
Br
22c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CHO
O_2N
F

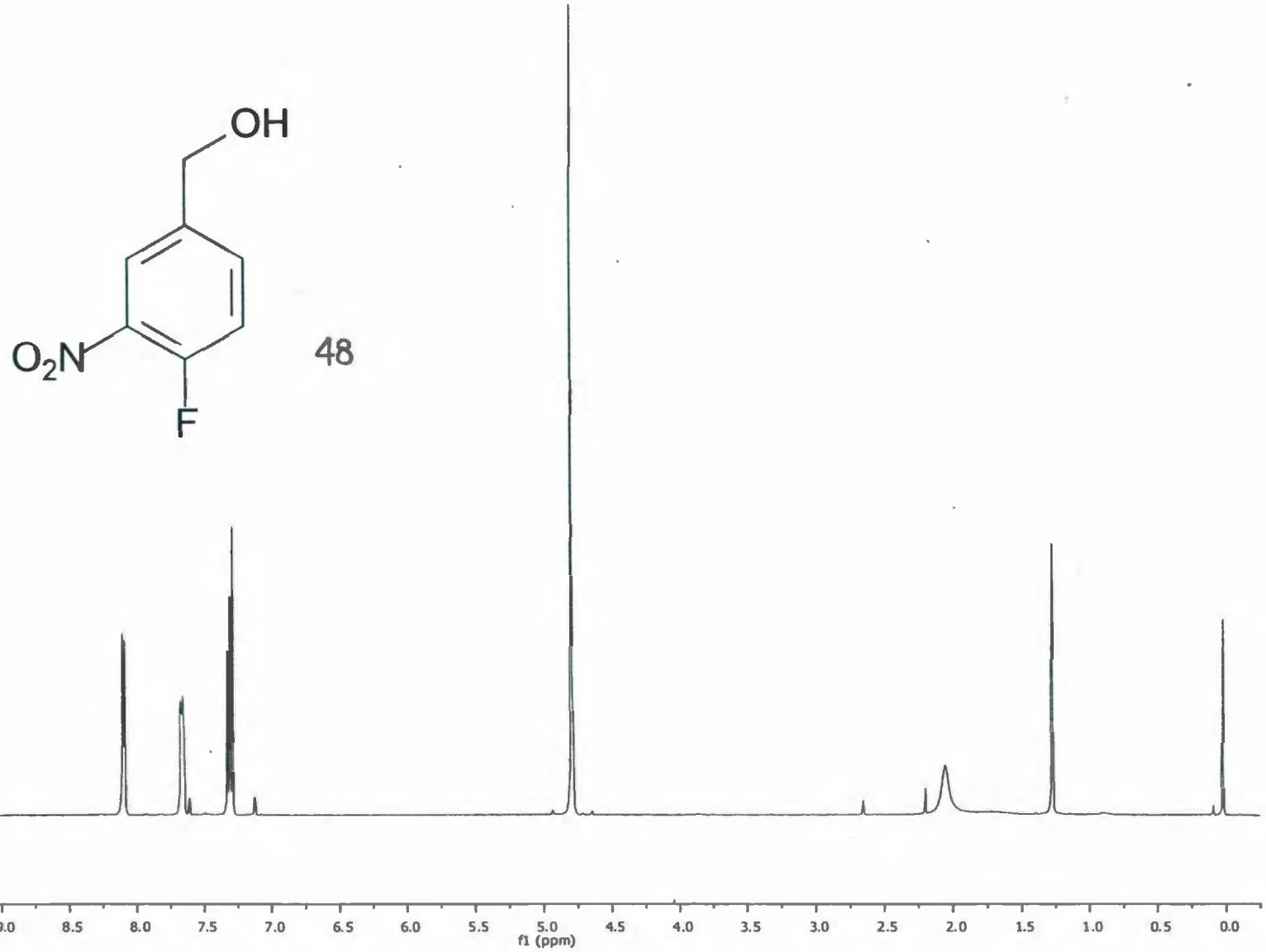
47

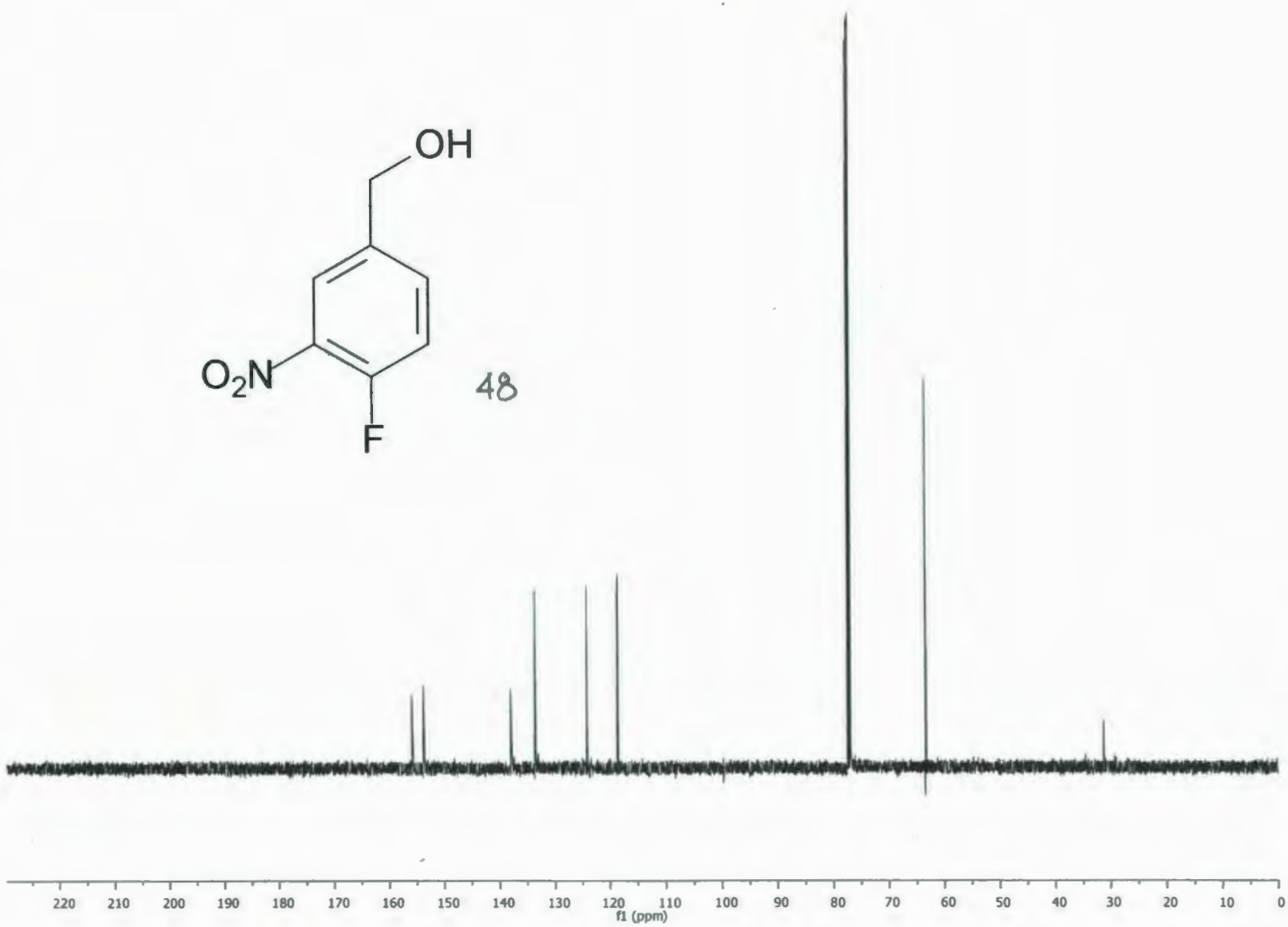
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

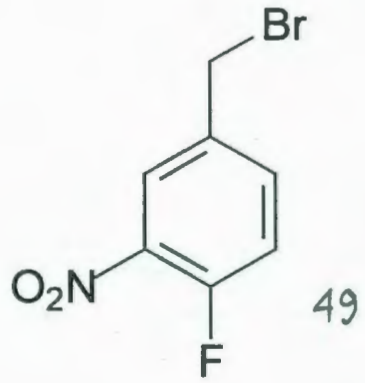

CHO
O_2N
F

47

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

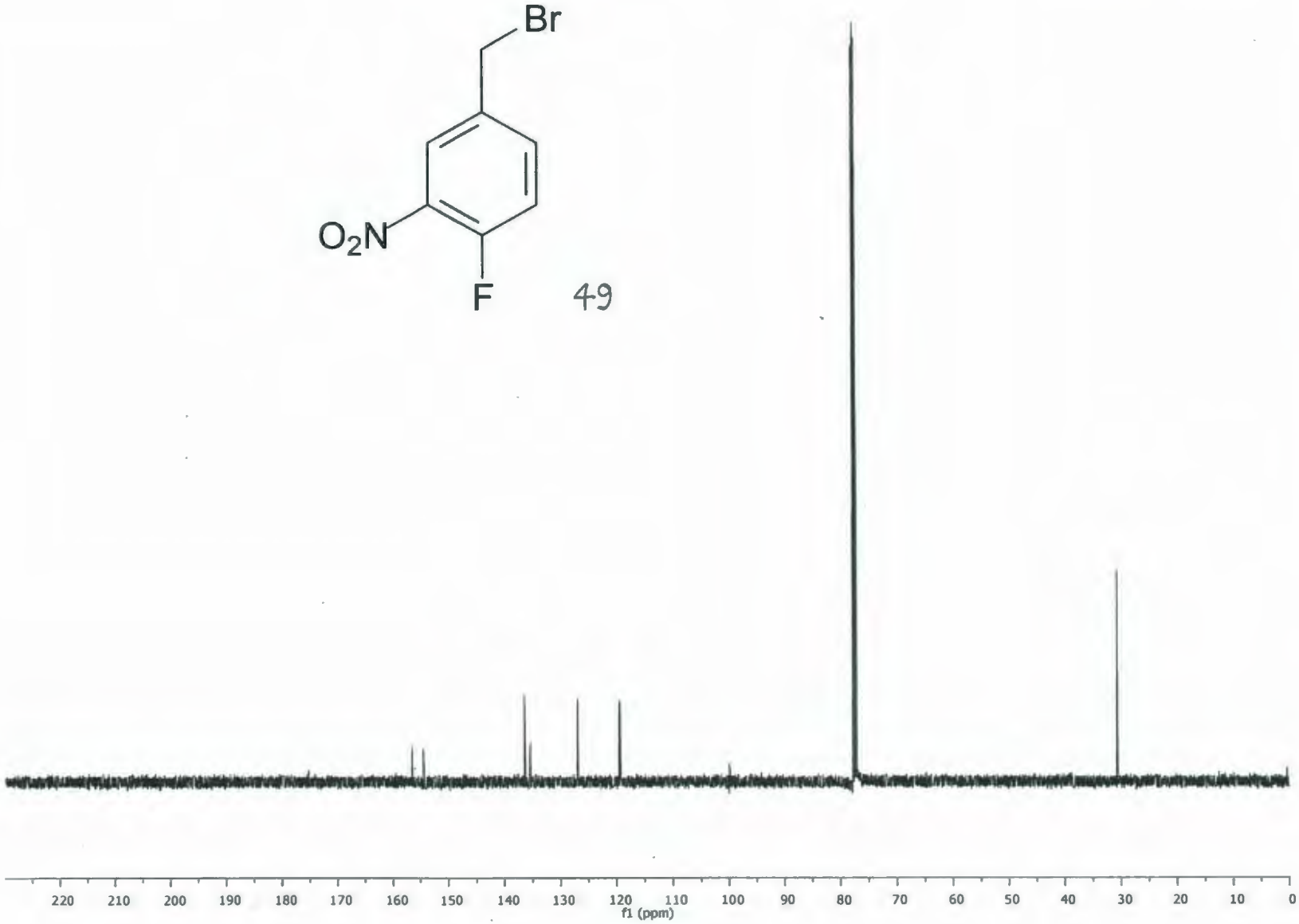

OH
O_2N
F
48
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

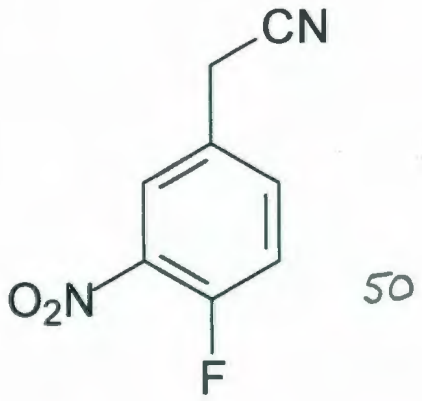

OH
O_2N
F
48
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Br
O2N
F

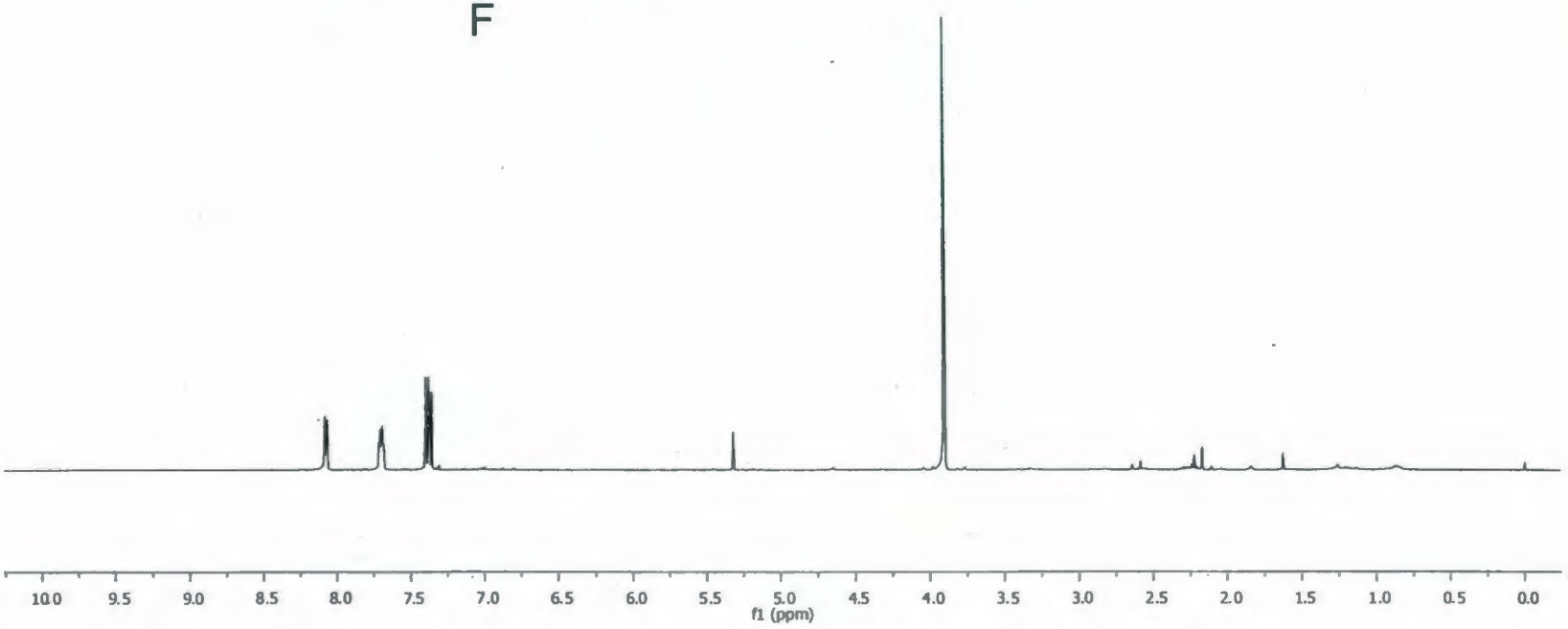
49

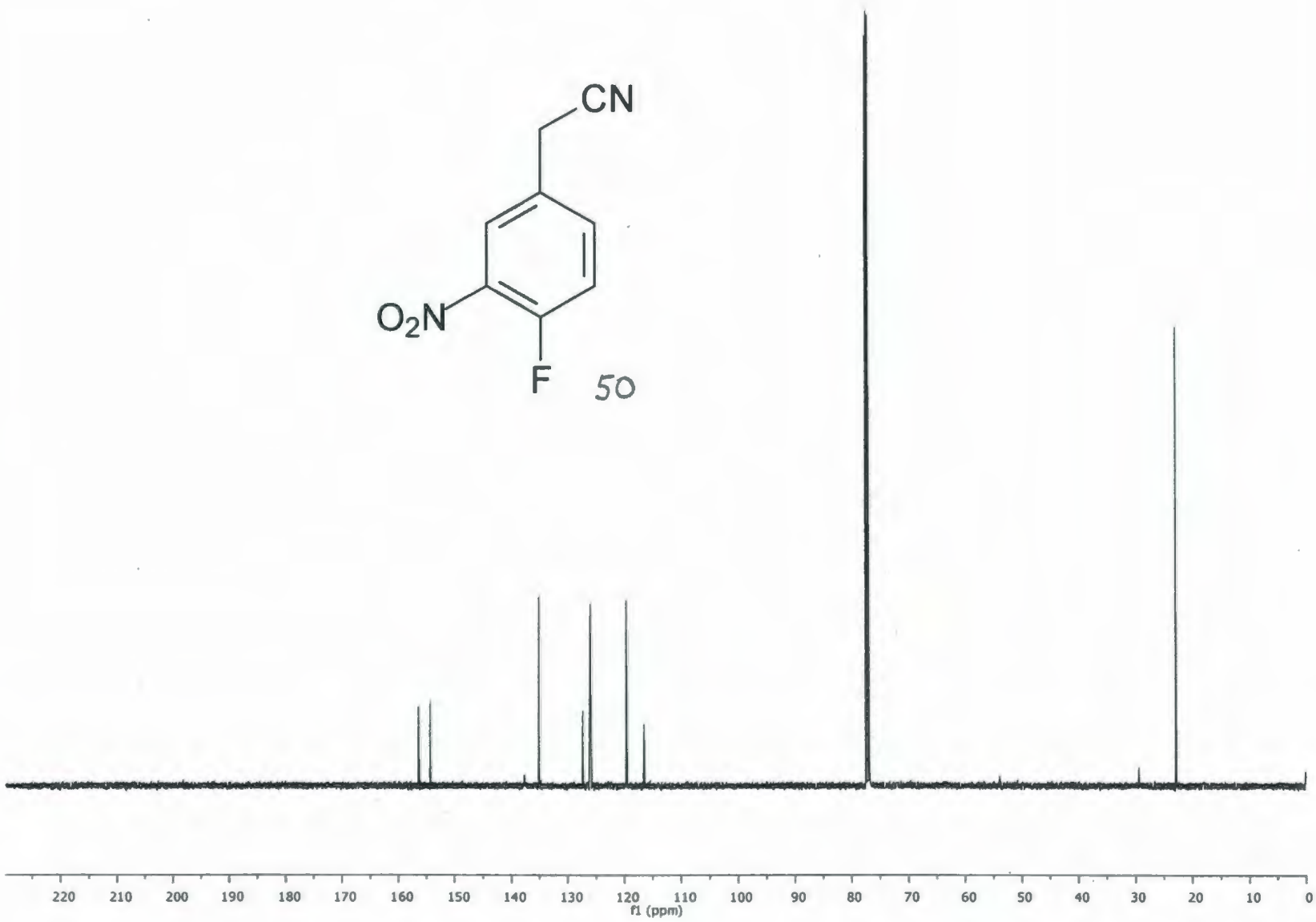
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

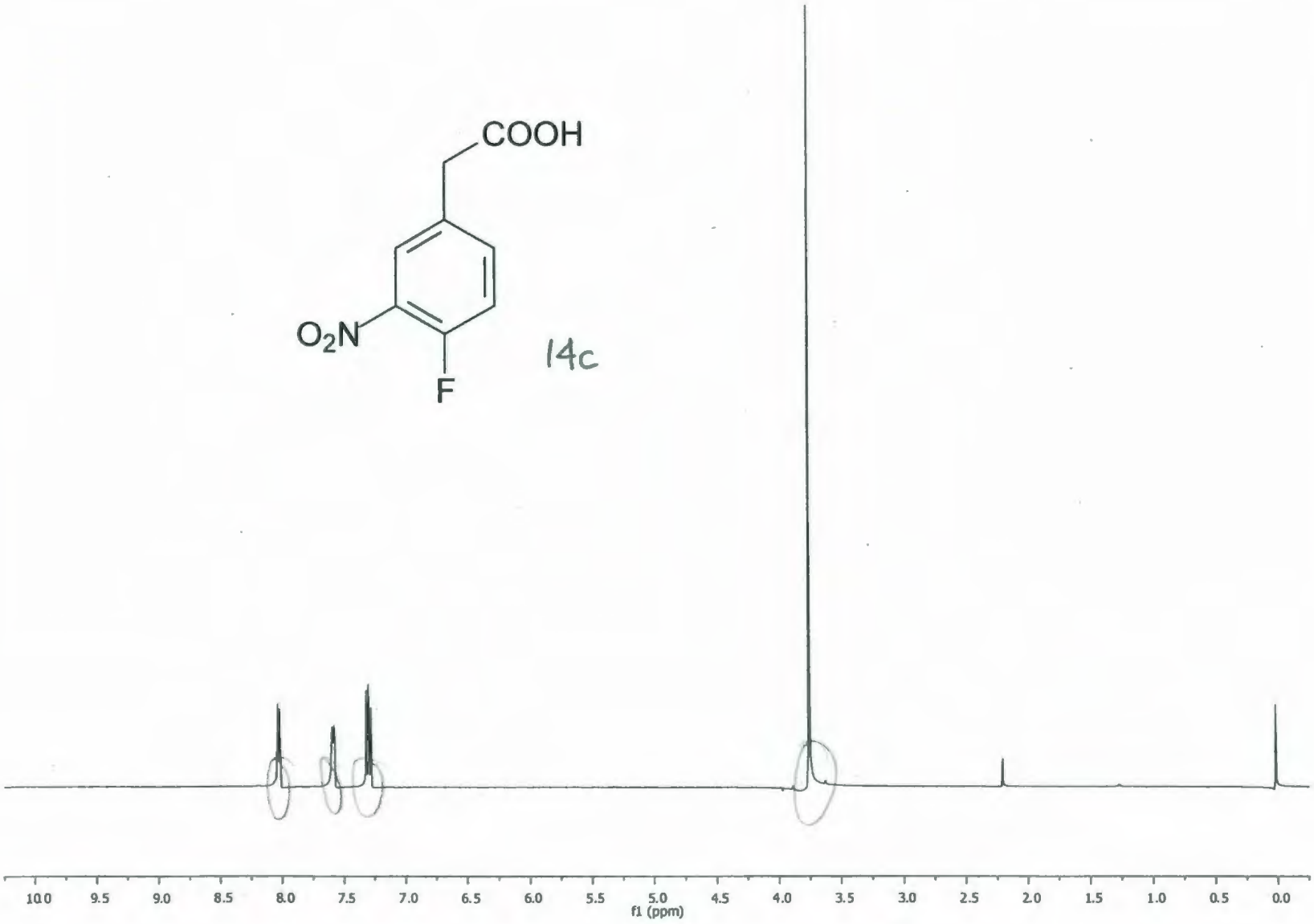

Br
O_2N
F
49
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

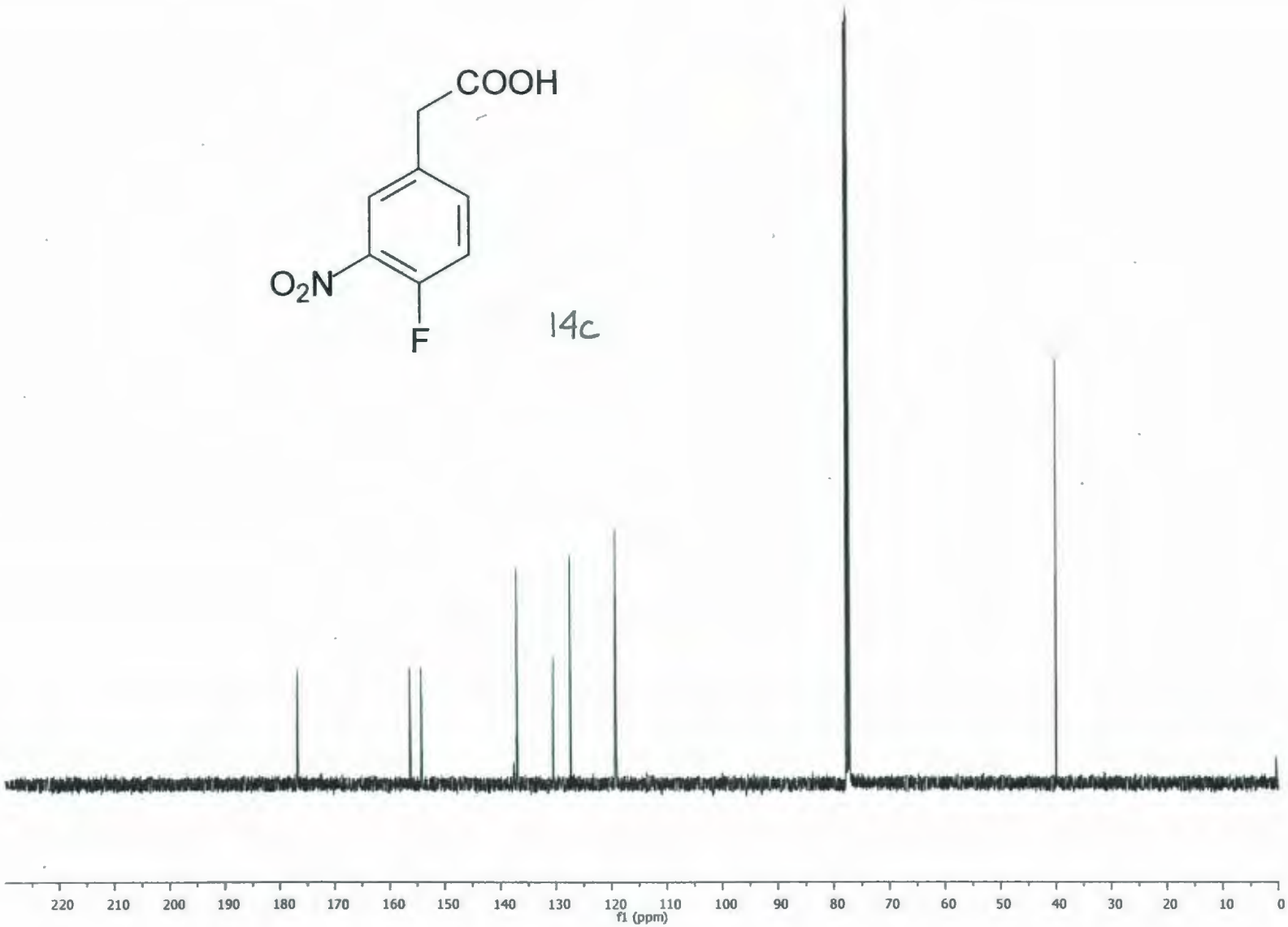

CN
O_2N
F

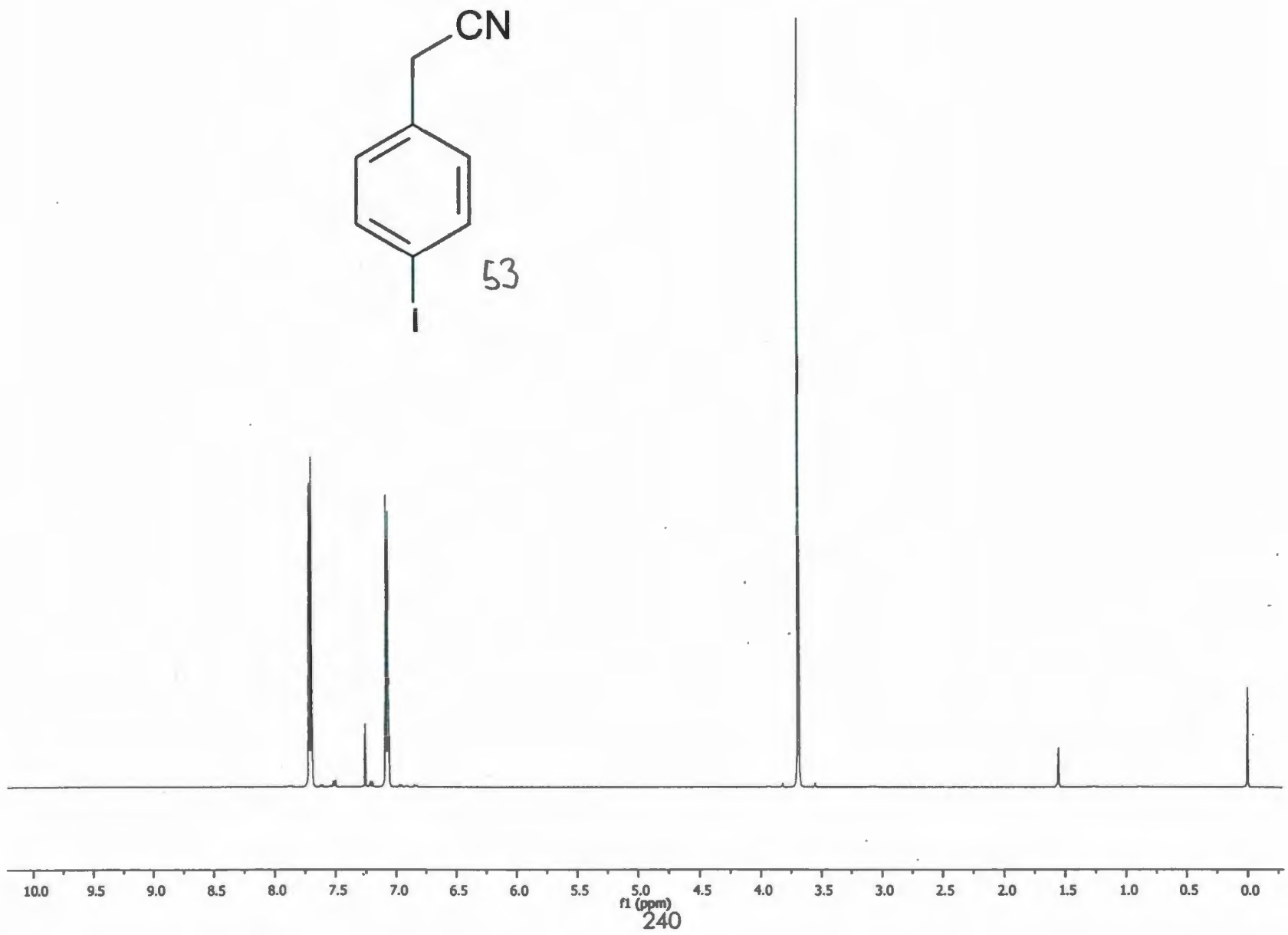
50

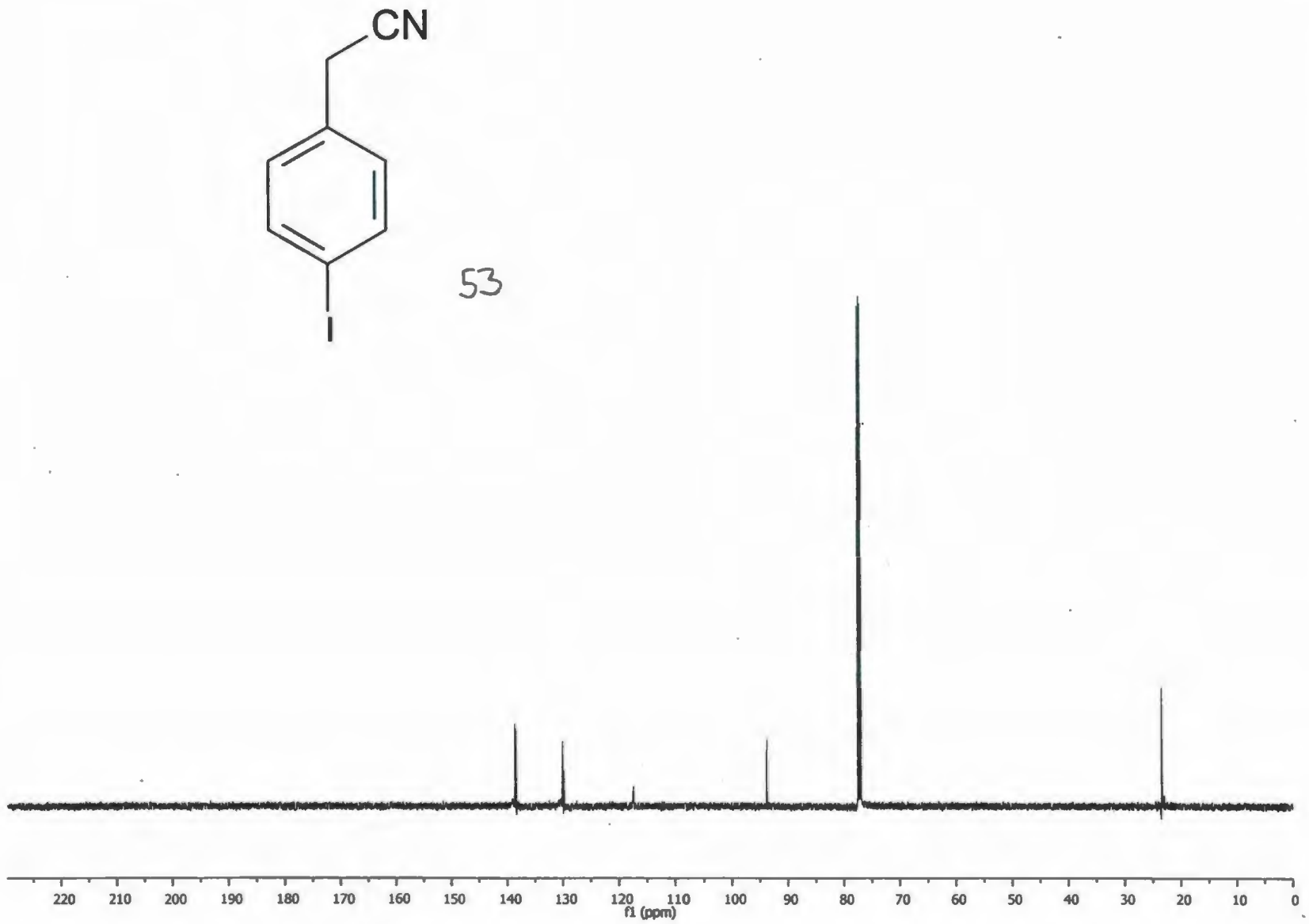

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

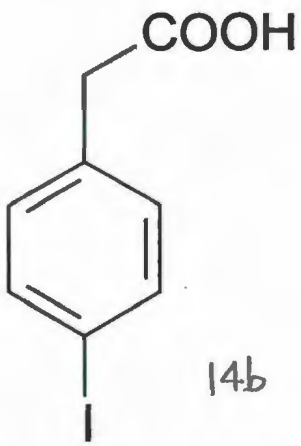

CN
O2N
F
50
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


COOH
O_2N
F
14c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

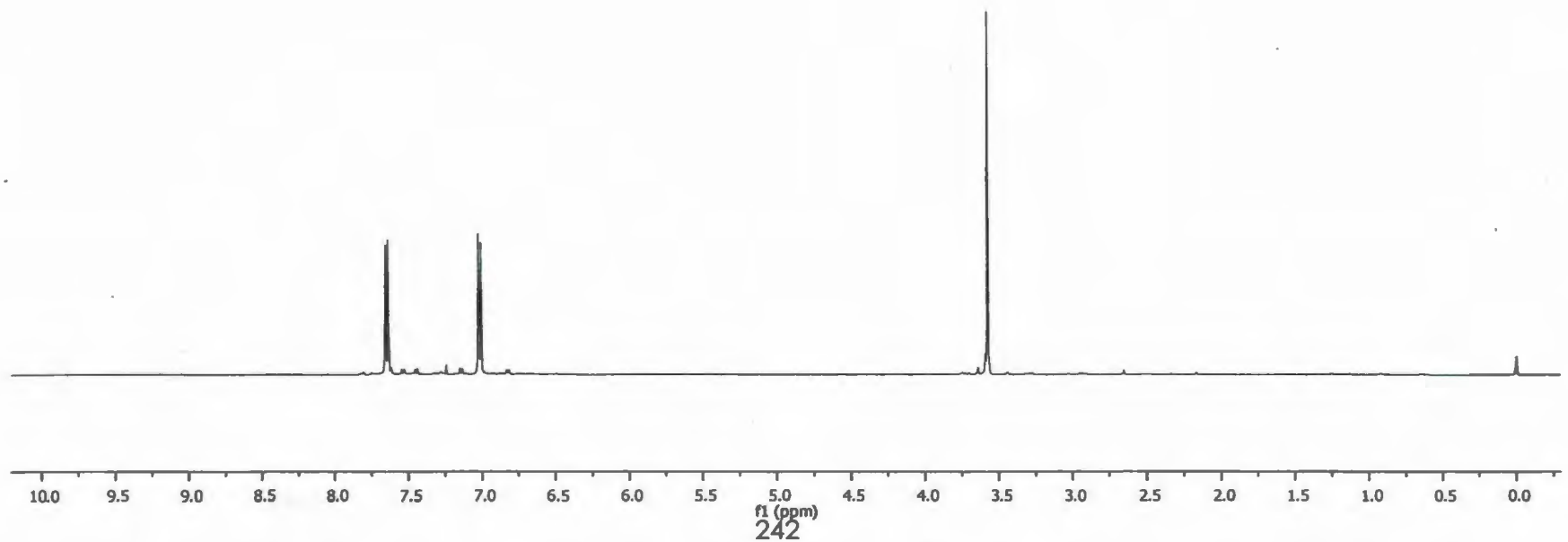

COOH
O_2N
F
14c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

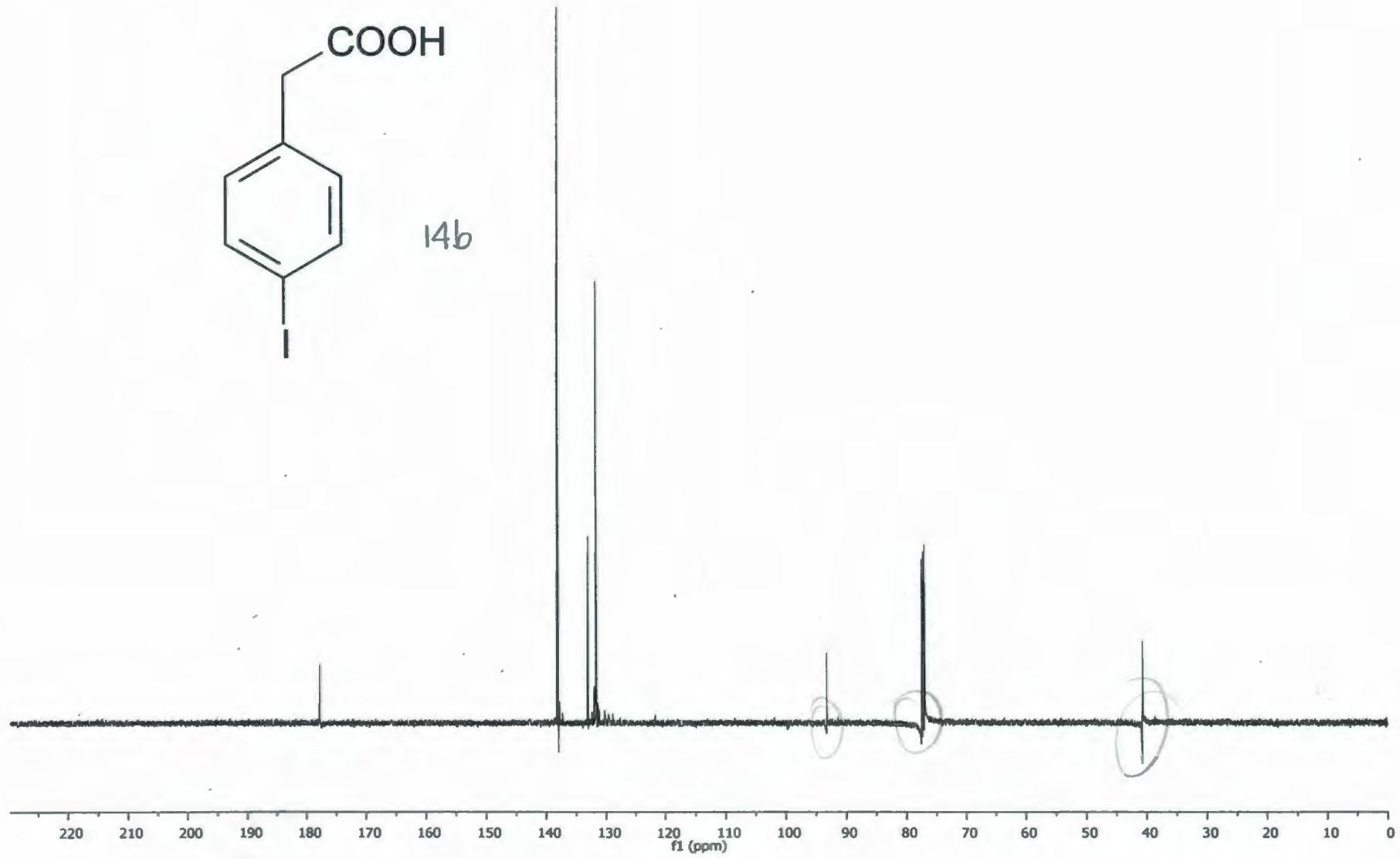

CN
53
I
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

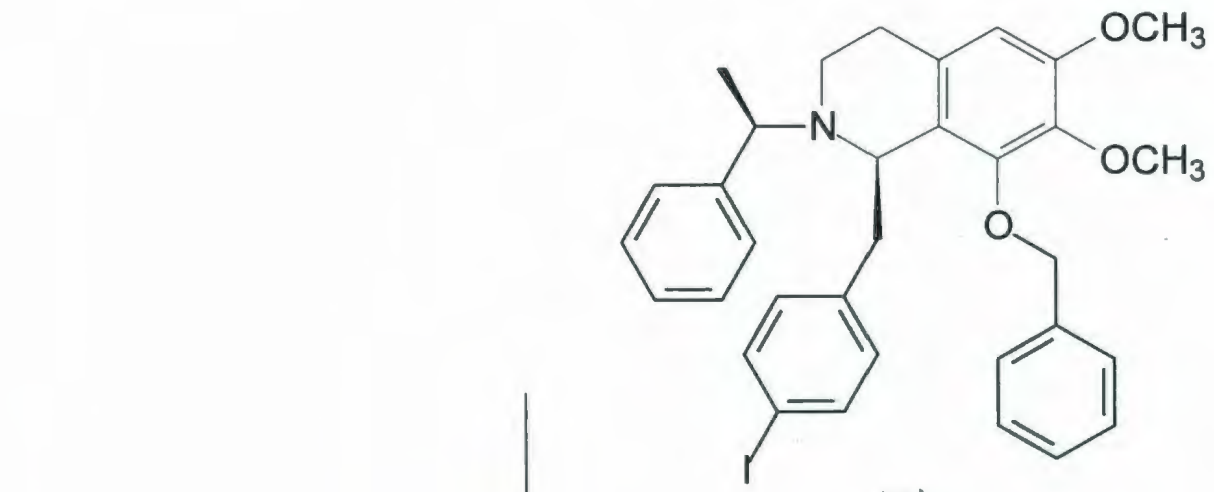

CN
I
53
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


COOH

14b

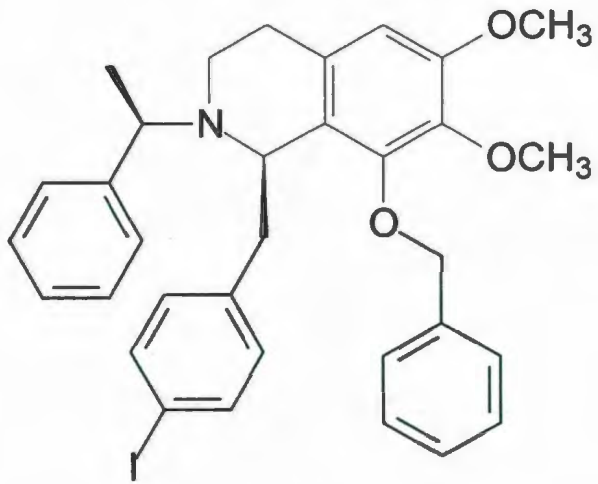

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


COOH
14b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

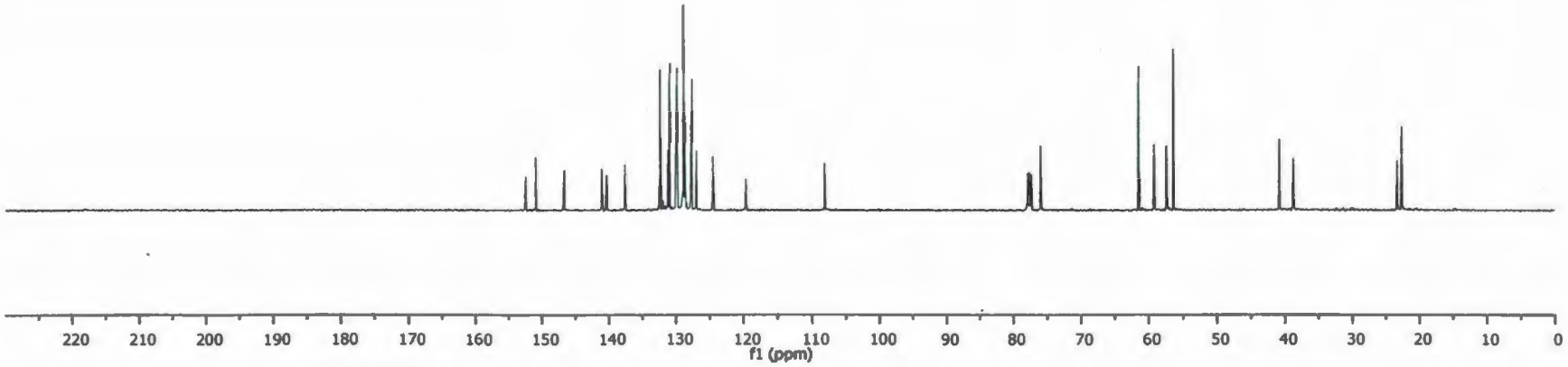

OCH3
OCH3
N
O
I

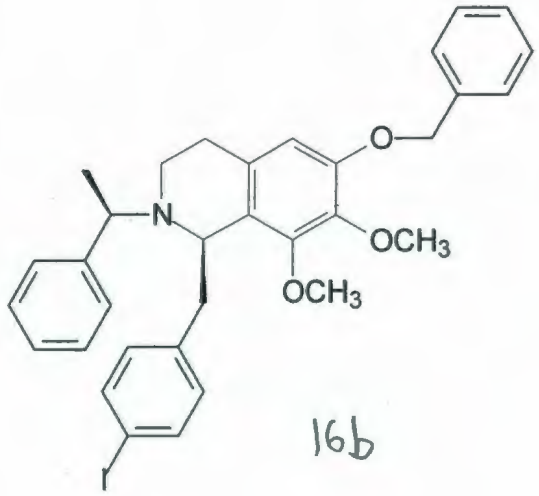
15b

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

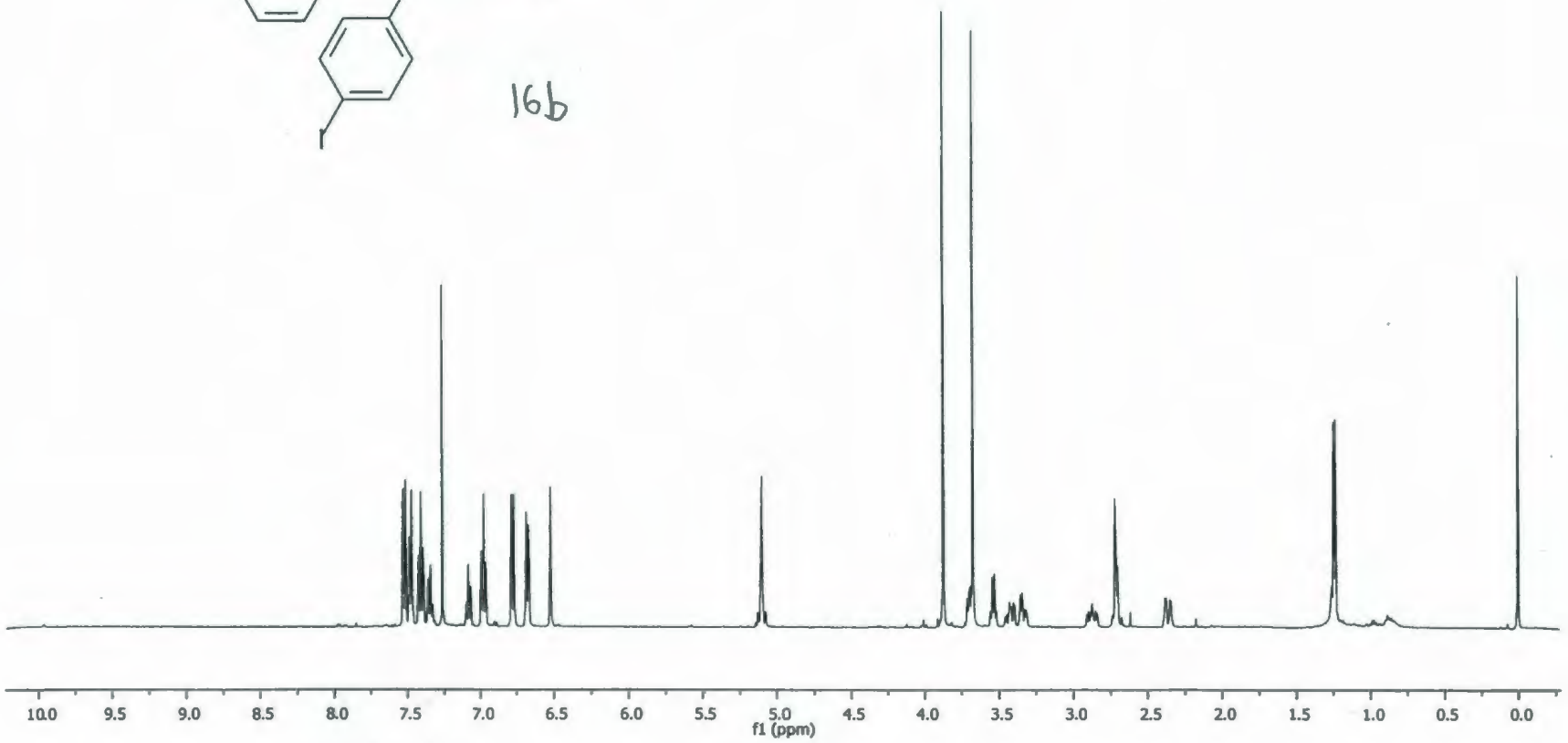

OCH3
OCH3
N
O
I

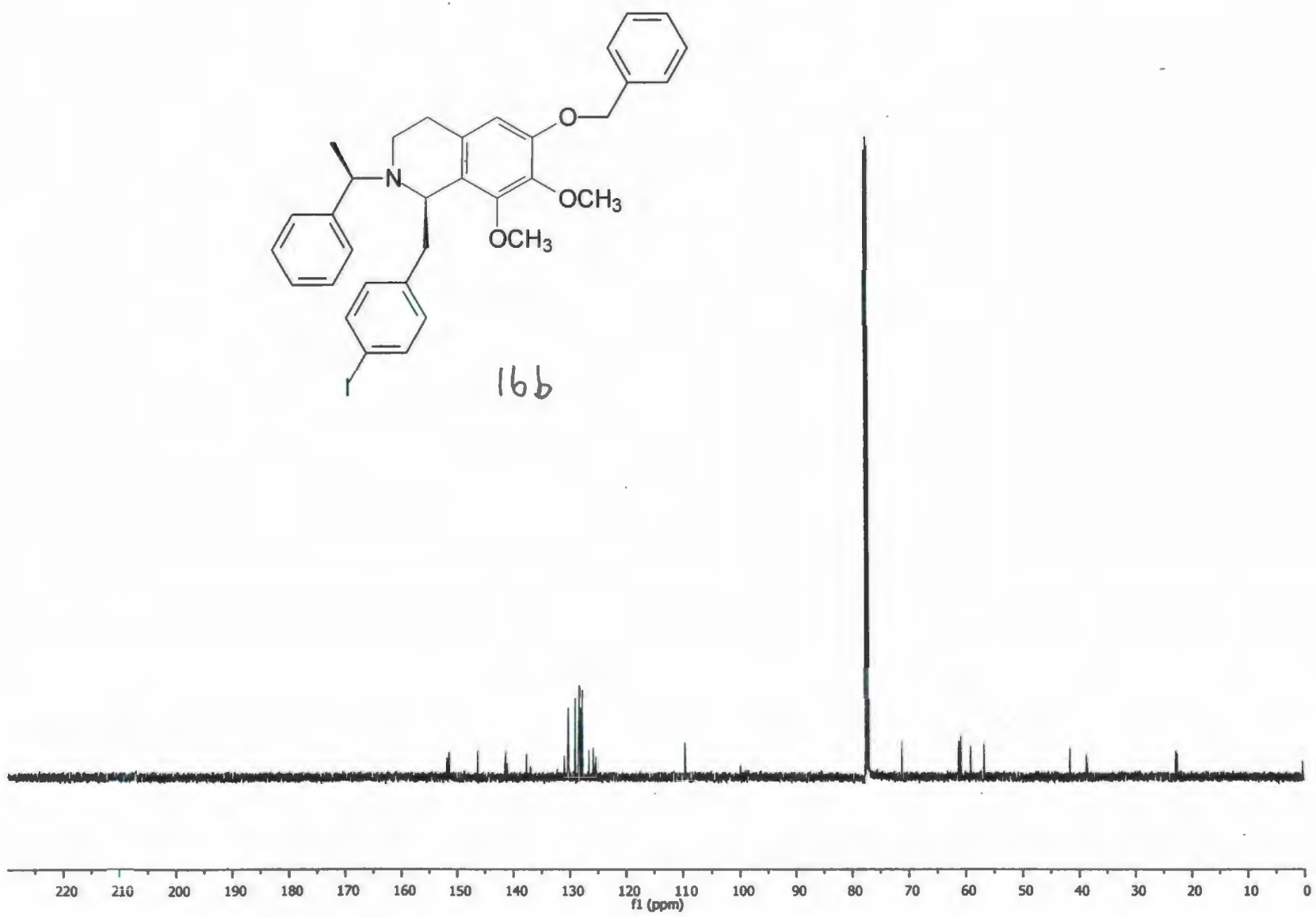
15b

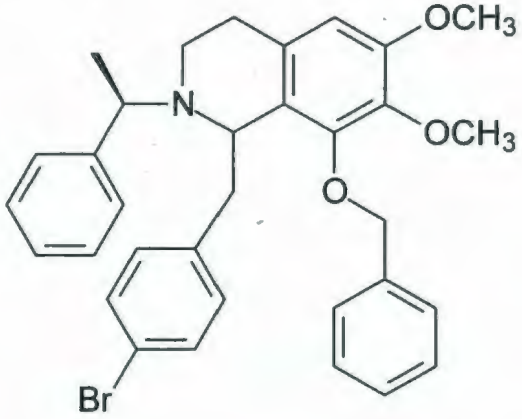

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
OCH3
OCH3
I

16b

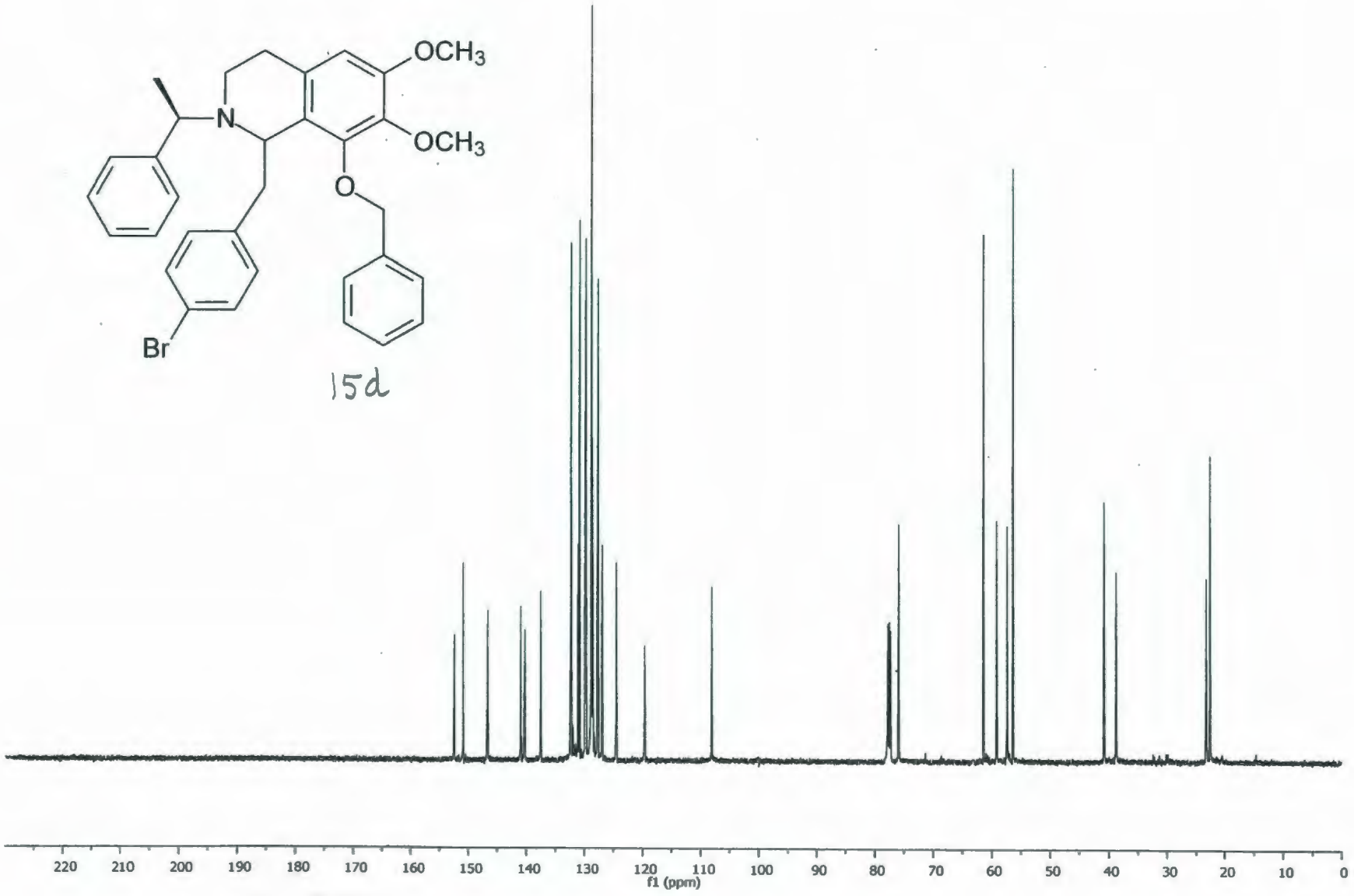

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

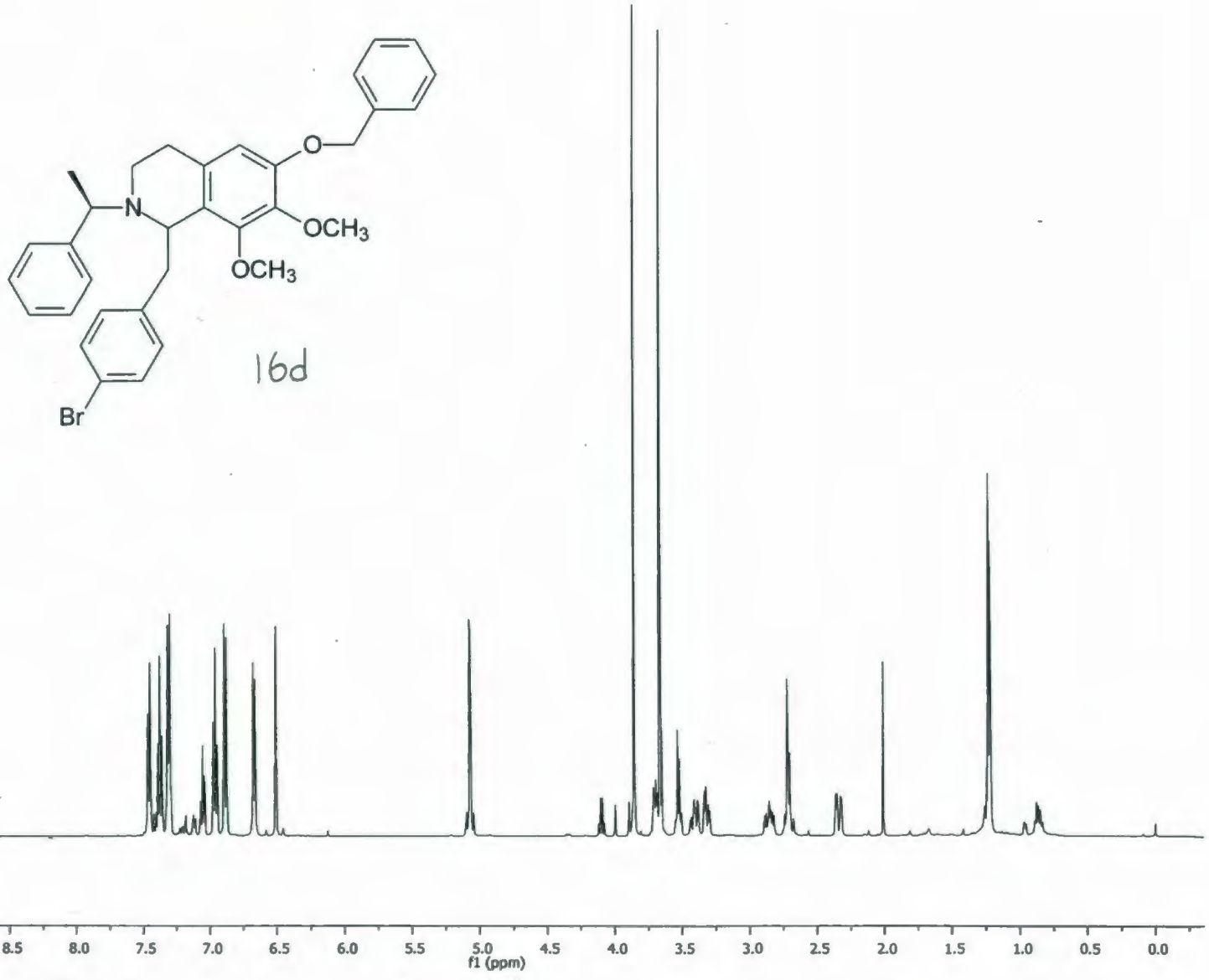

O
N
OCH3
OCH3
I
16b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

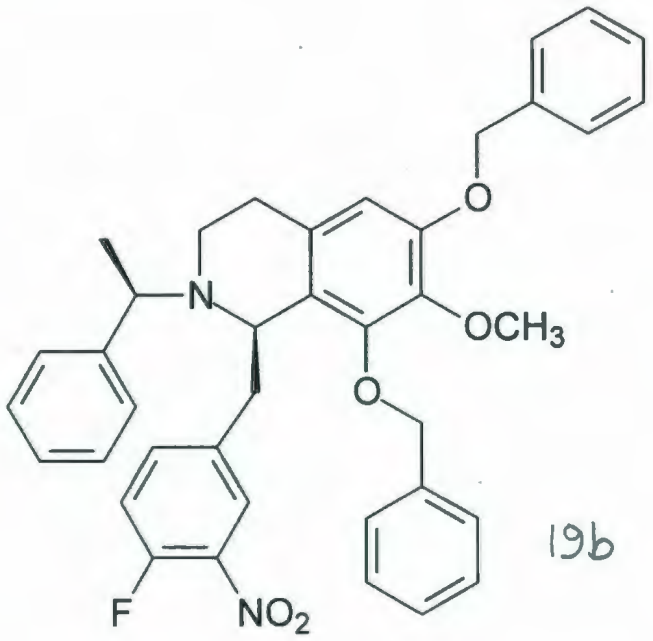

OCH3
OCH3
N
O
Br

15d

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

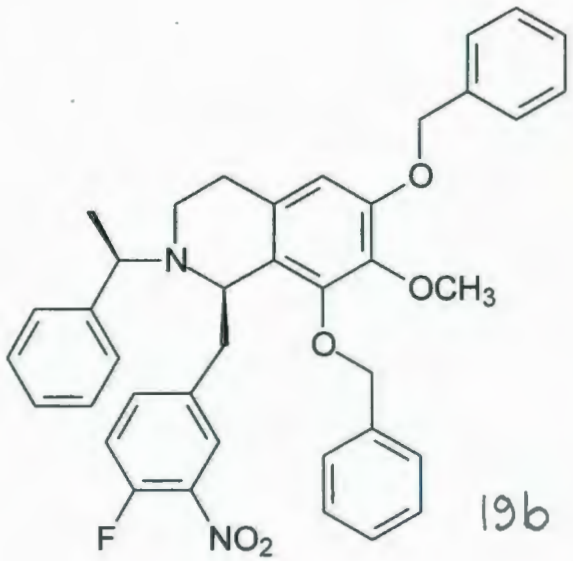

OCH3
OCH3
N
O
Br
15d
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
OCH3
OCH3
Br
16d
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
OCH3
O
F
NO2

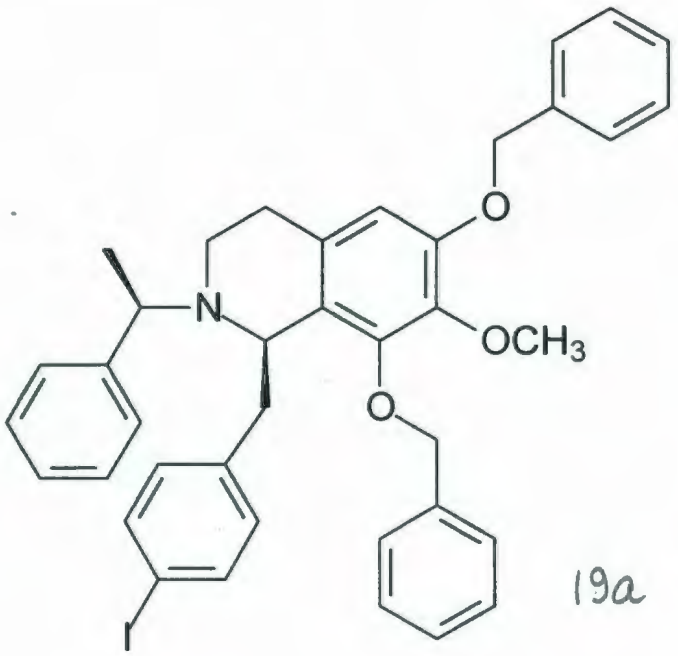
19b

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

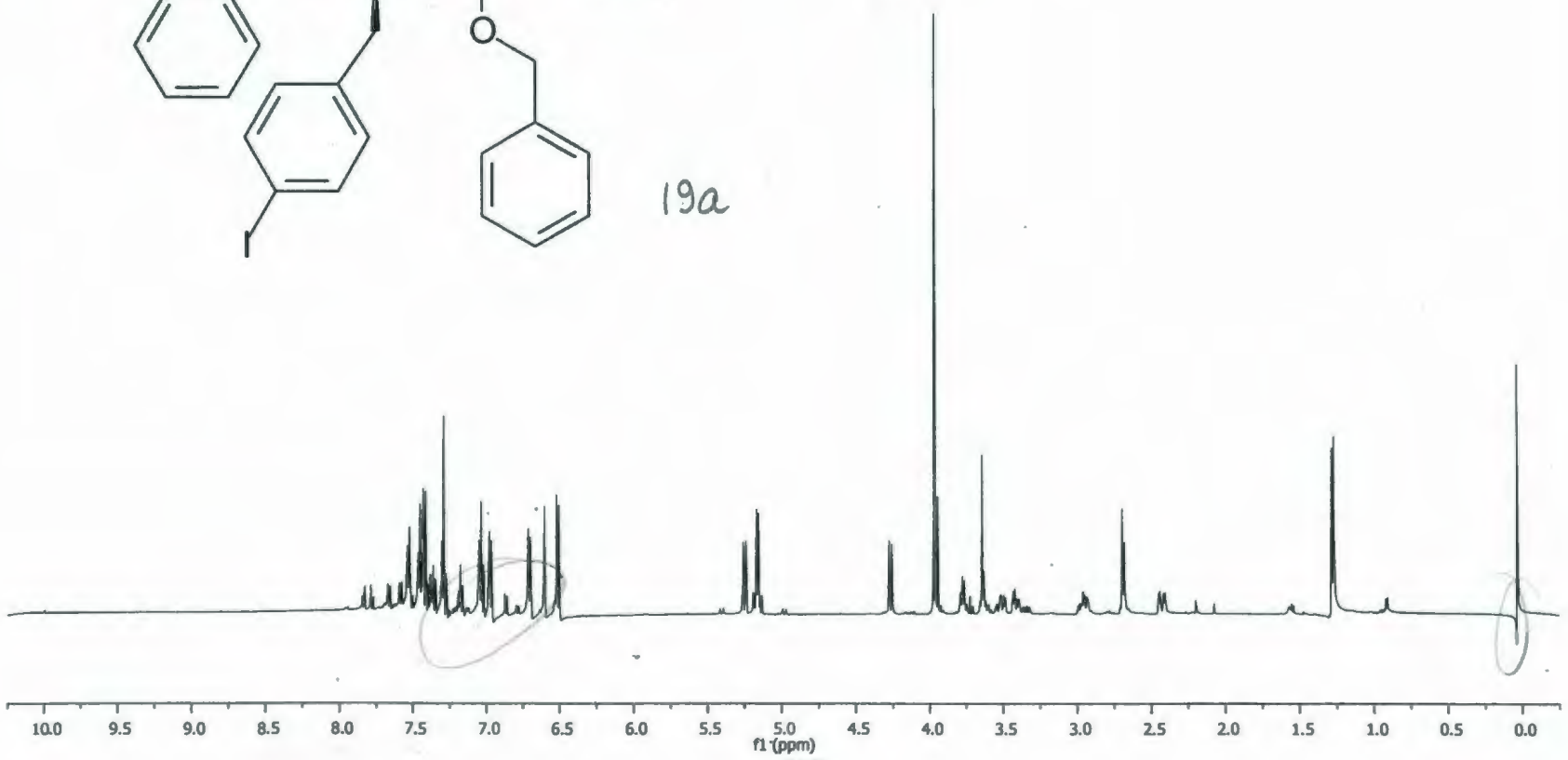

O
N
OCH3
O
F
NO2

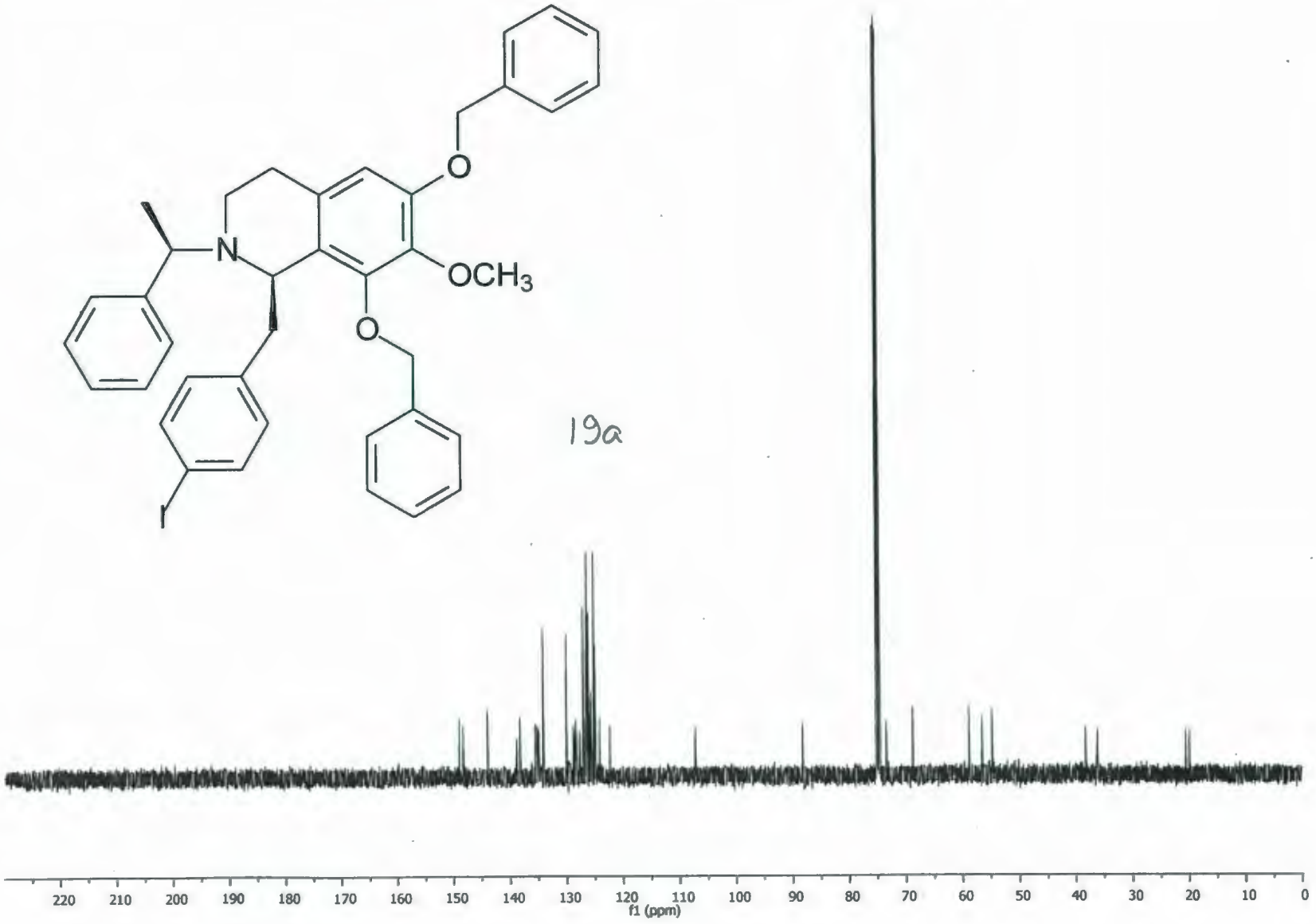
19b

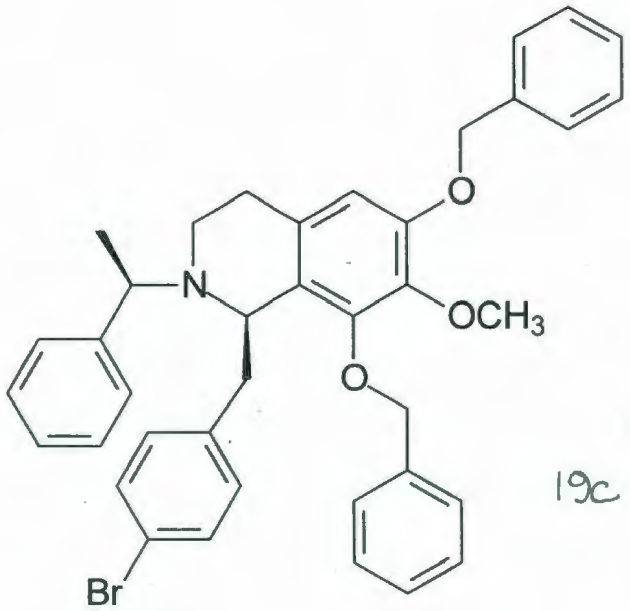
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
OCH3
O
I

19a

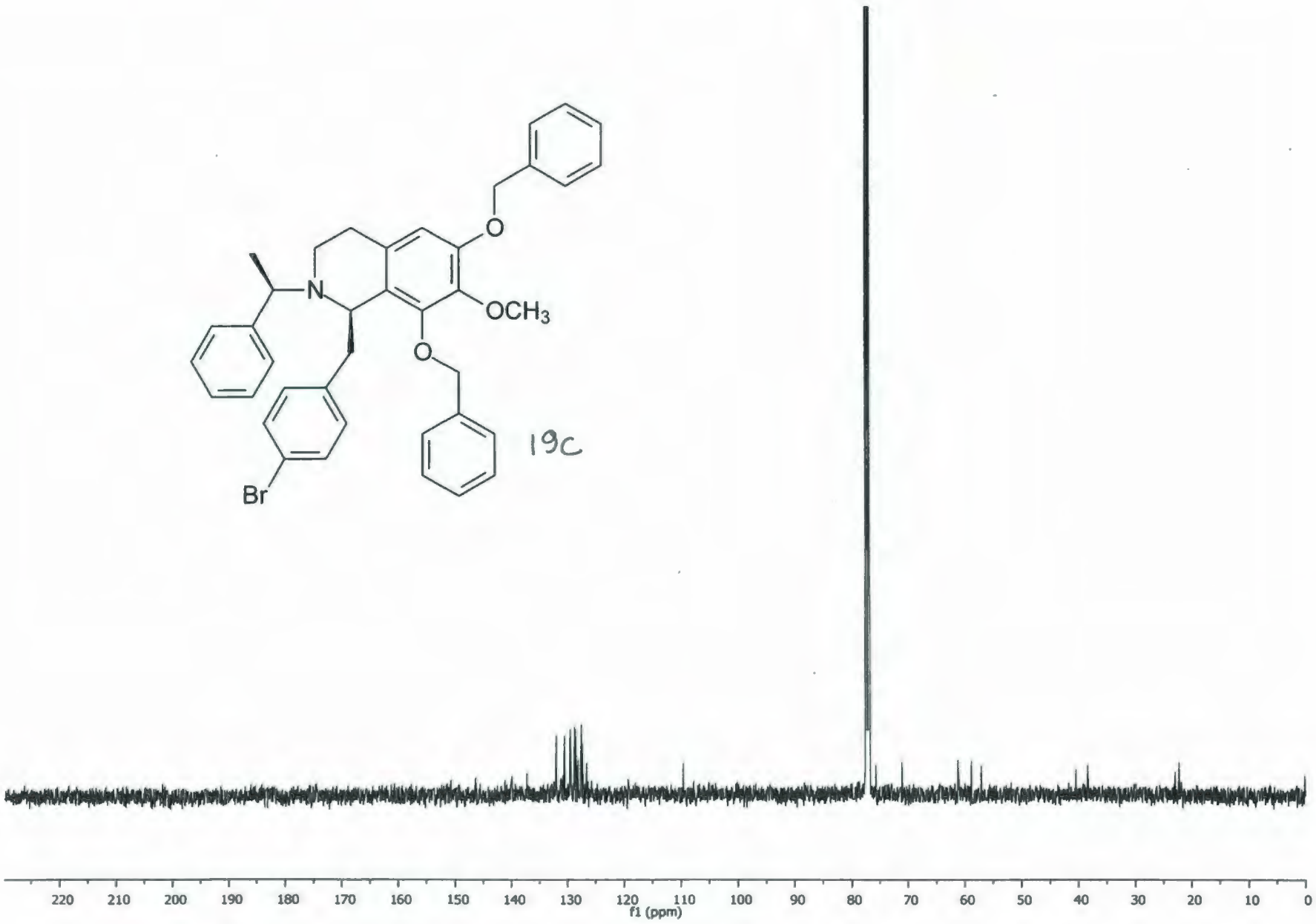

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

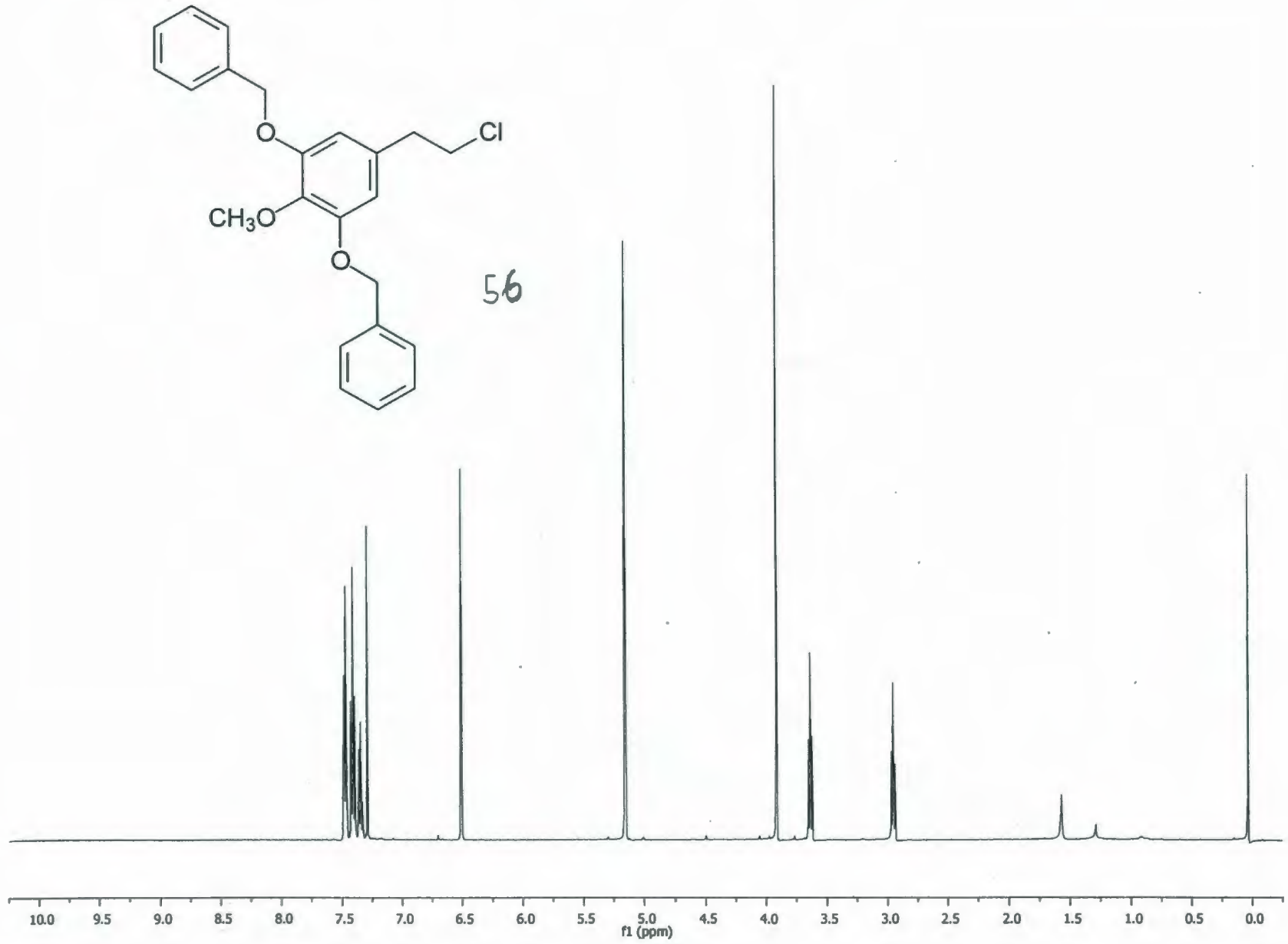

O
N
OCH3
O
I
19a
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

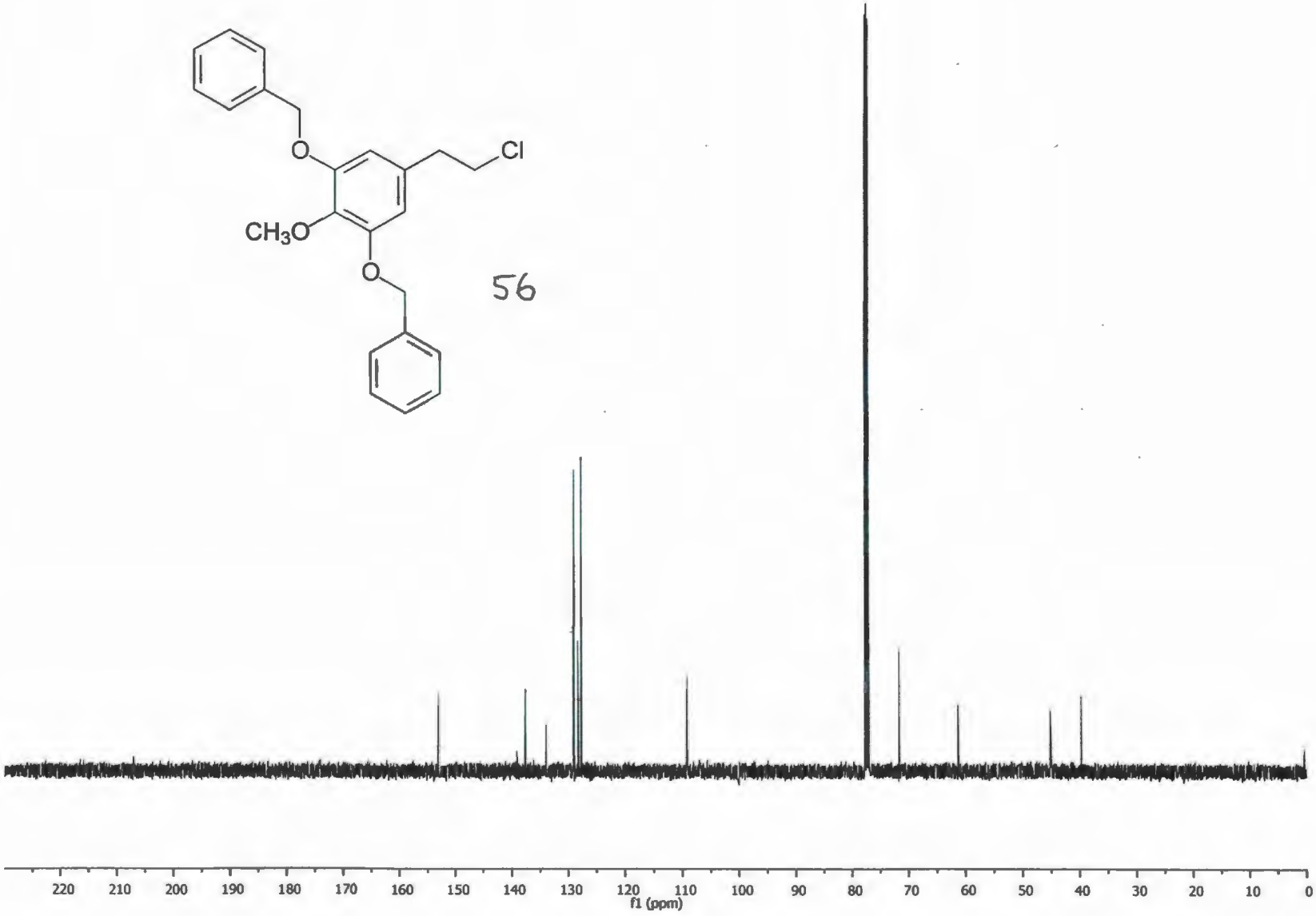

O
N
OCH3
O
Br

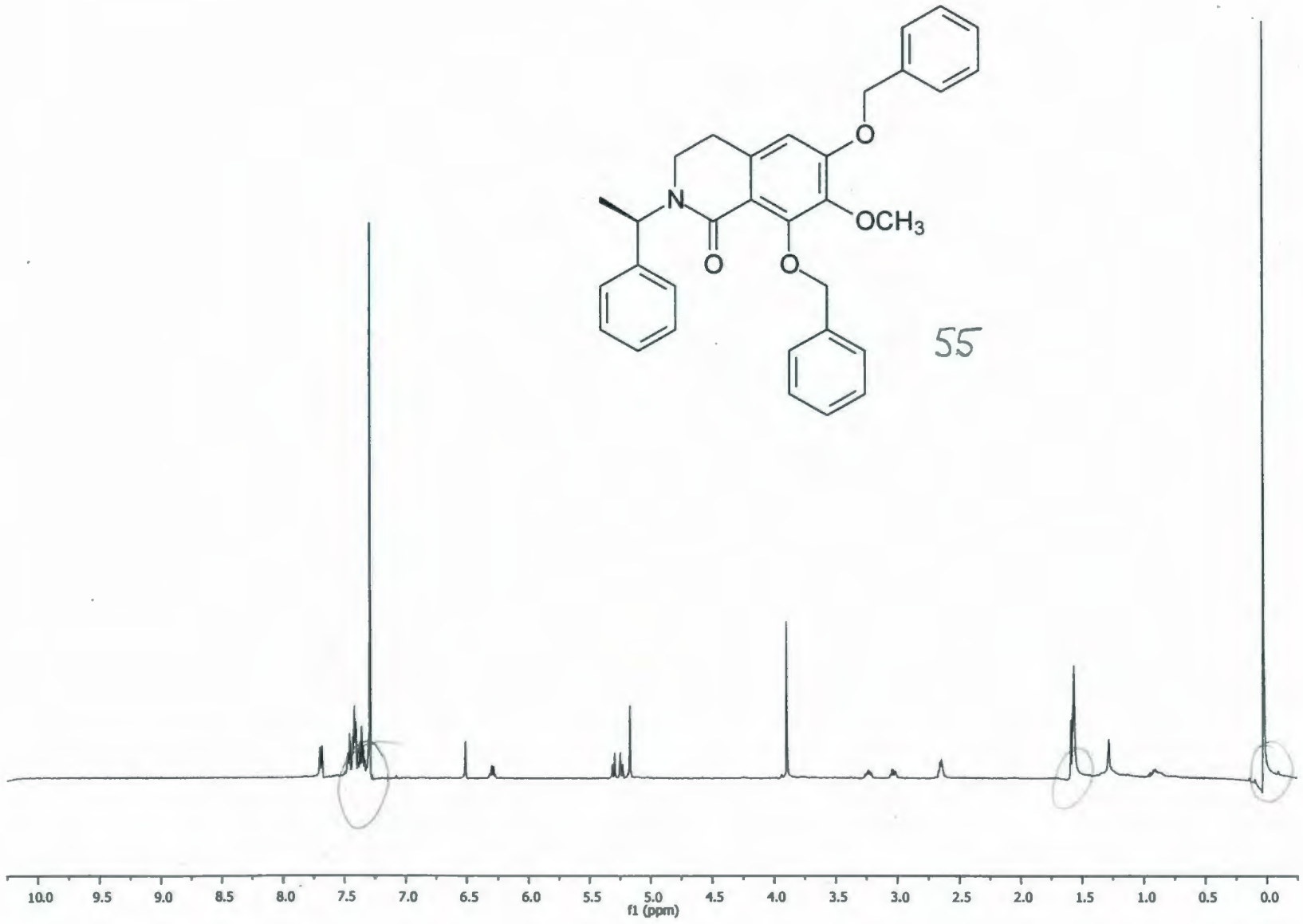
19c

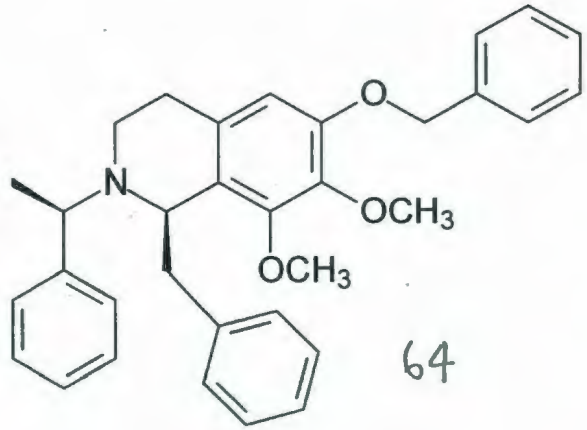
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
OCH3
O
Br
19c
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

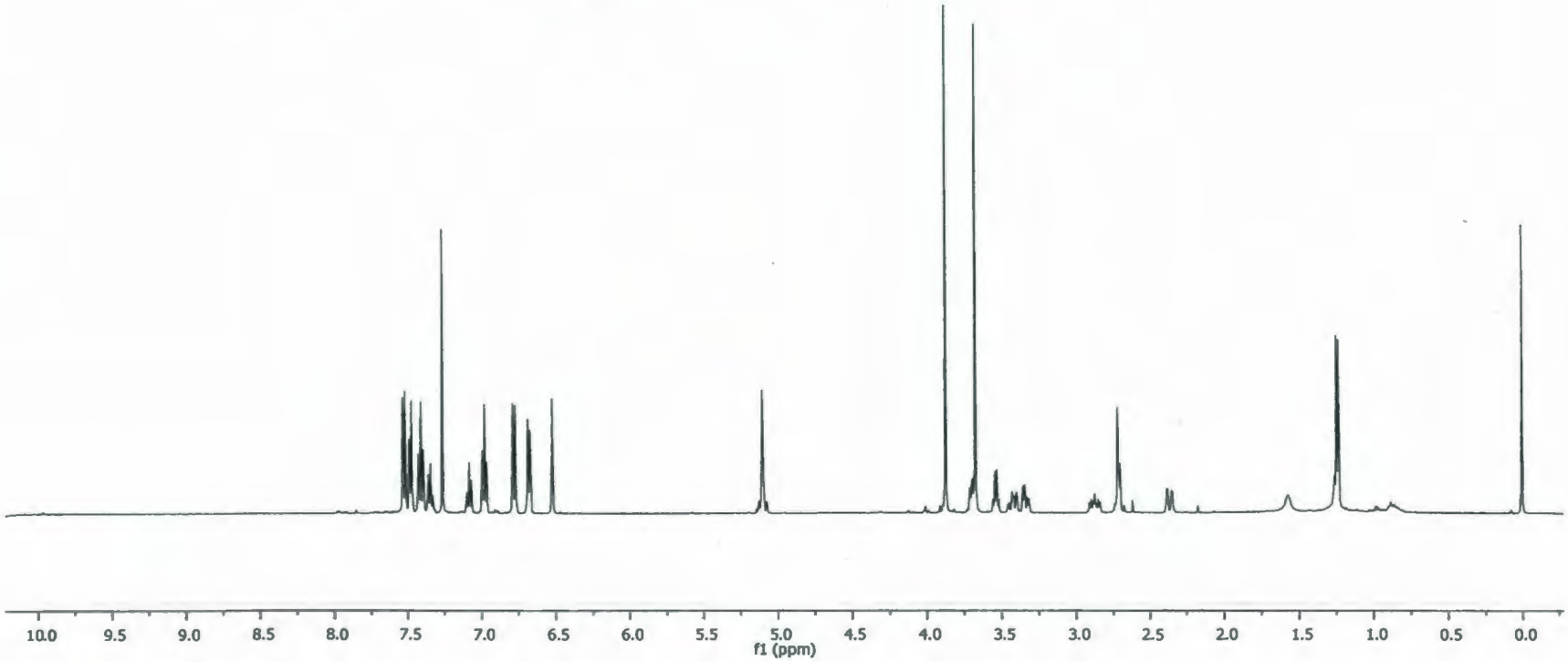

Cl
O
CH3O
O
56
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

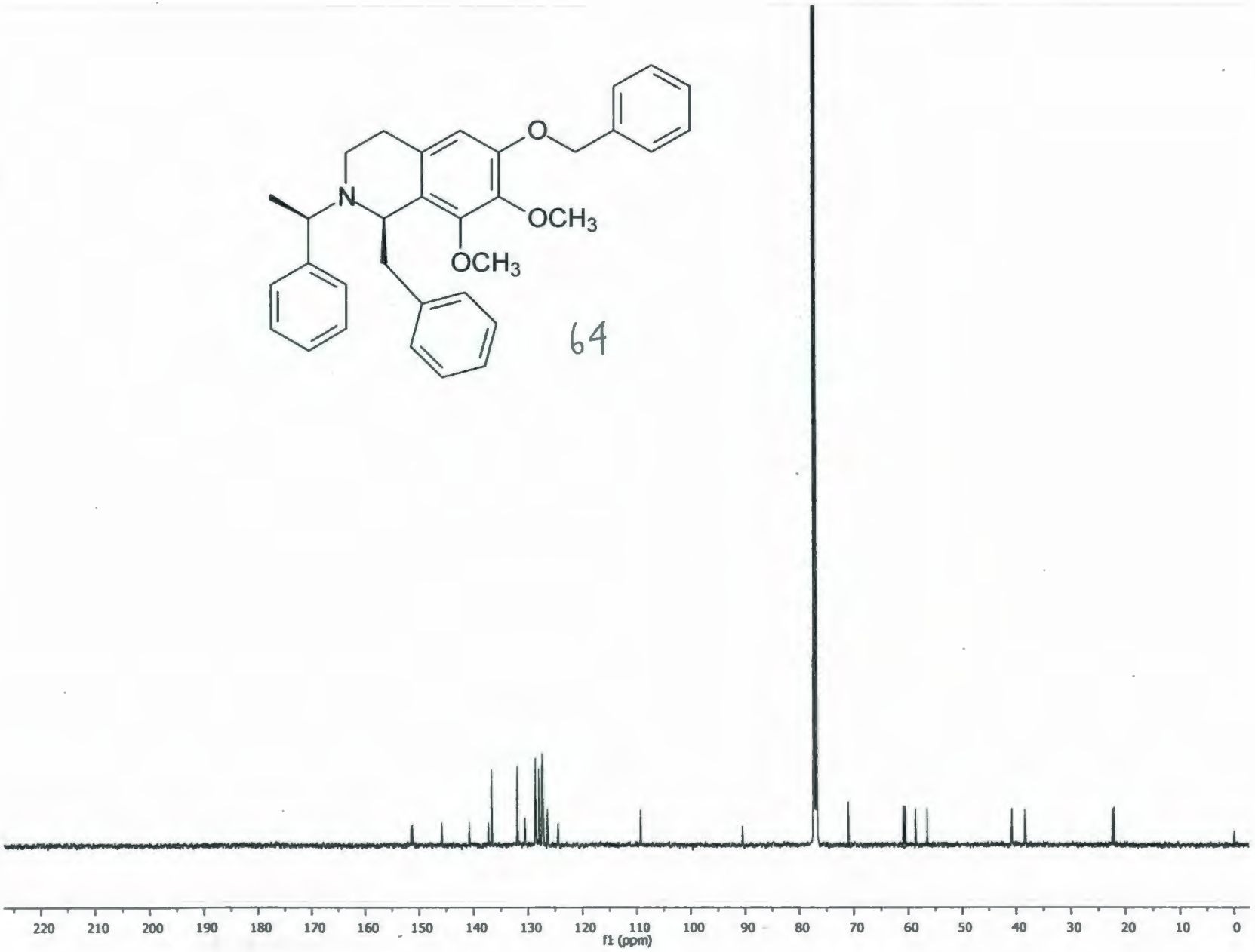

Cl
O
CH3O
O
56
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

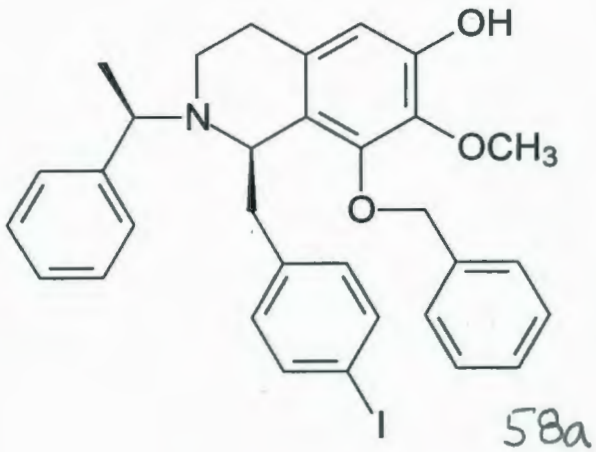

N
O
O
O
OCH3
55
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
OCH3
OCH3

64

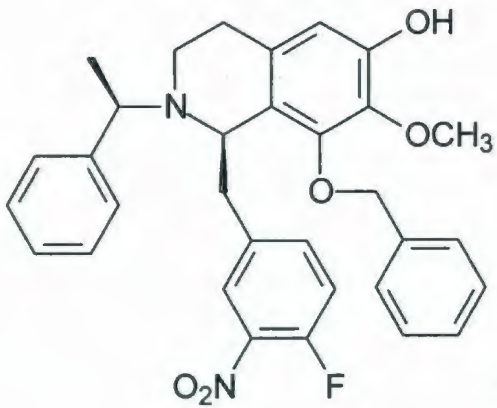

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
OCH3
OCH3
64
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

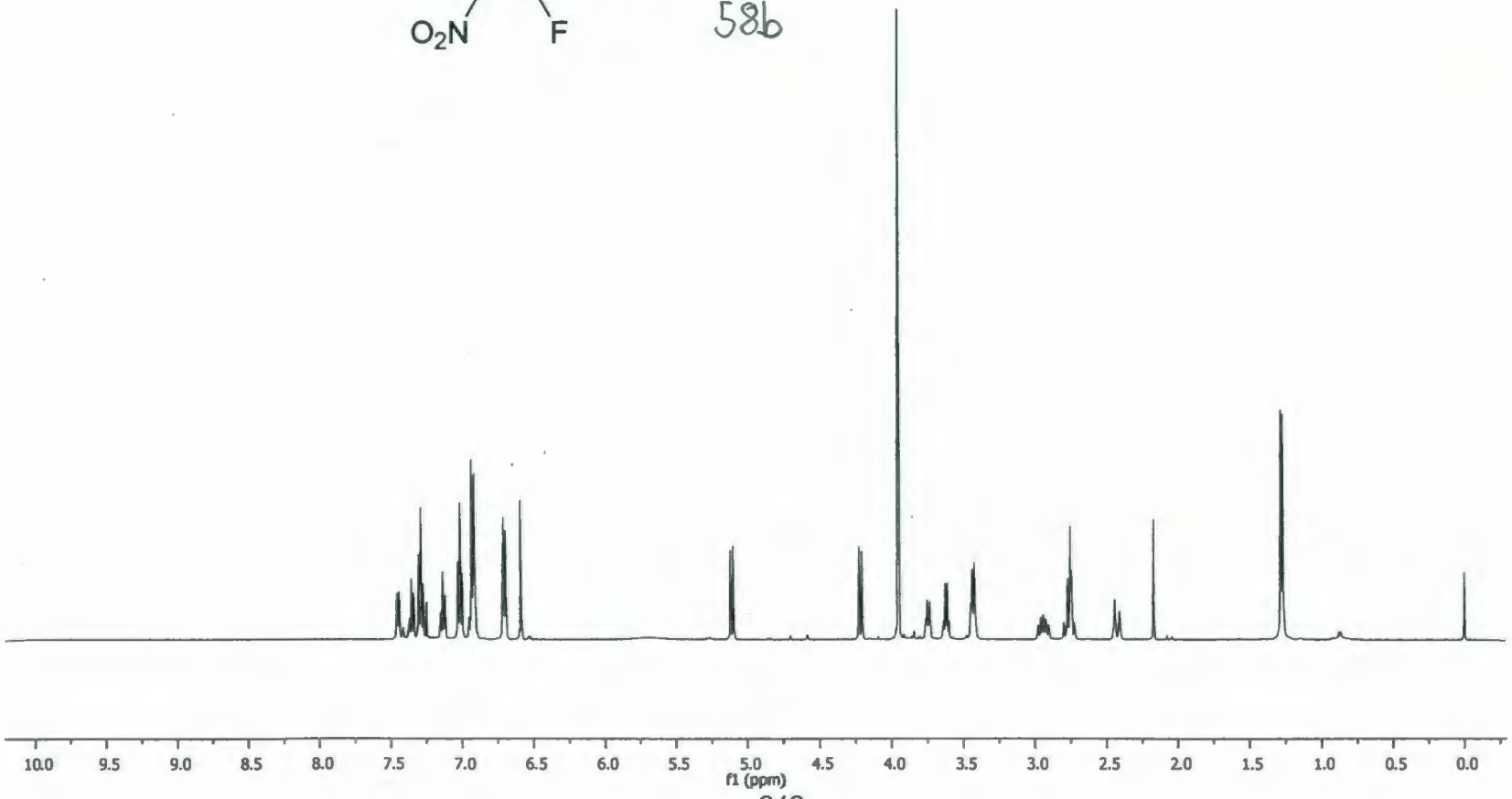

OH
N
OCH3
O
I

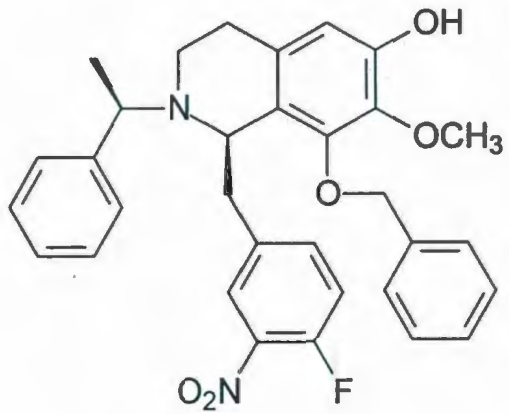
58a

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
f1 (ppm)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

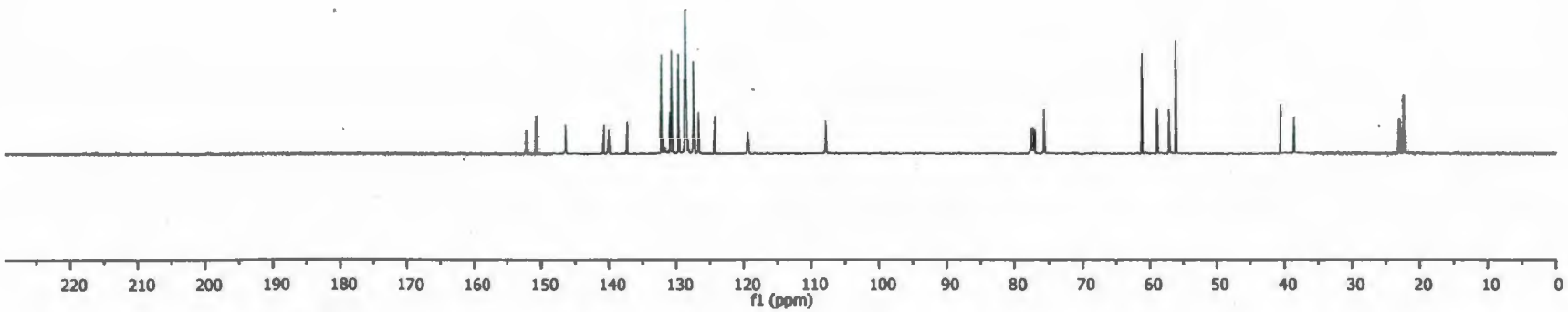

OH
N
OCH3
O
O2N
F

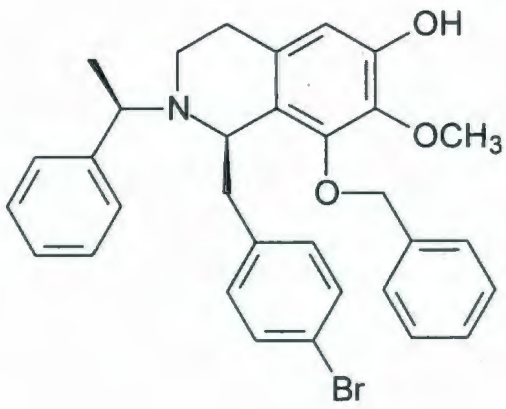
58b


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

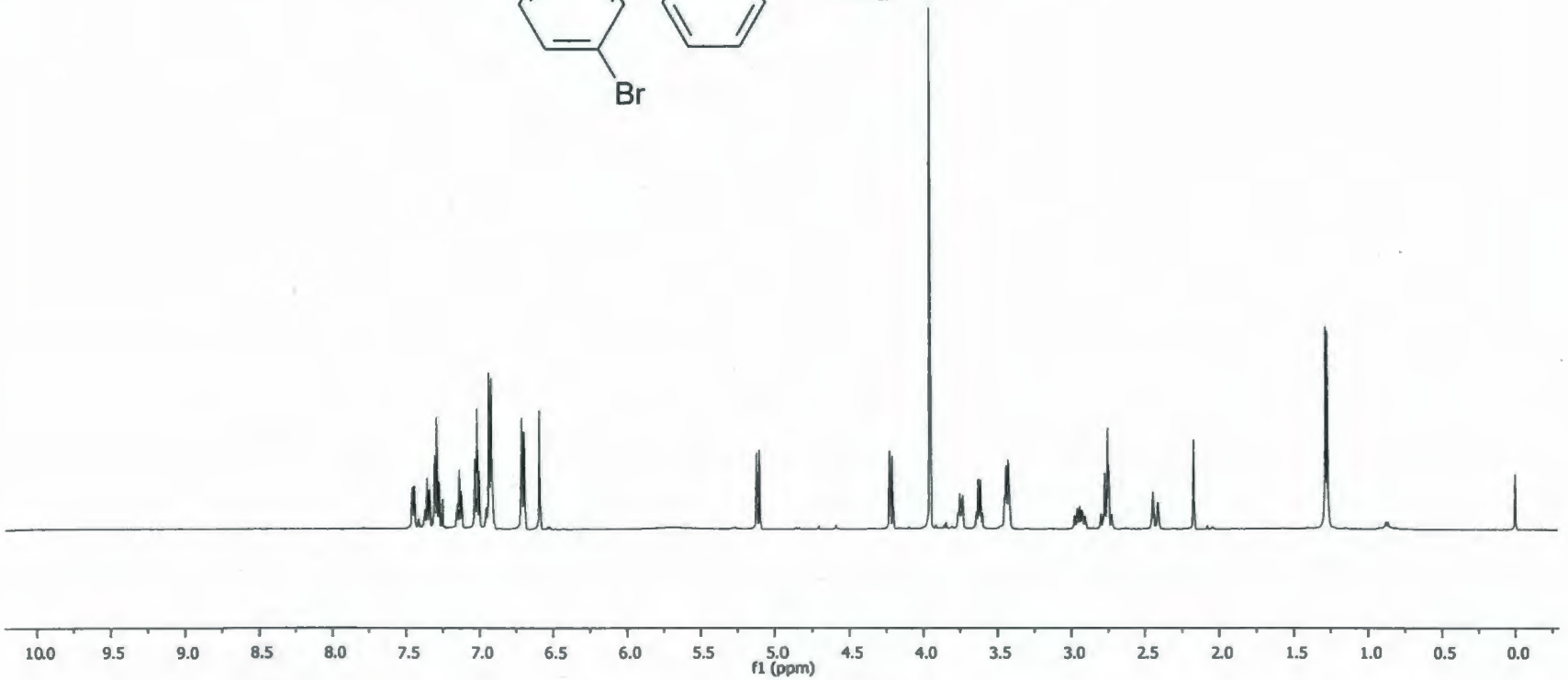

OH
N
OCH3
O
O2N
F

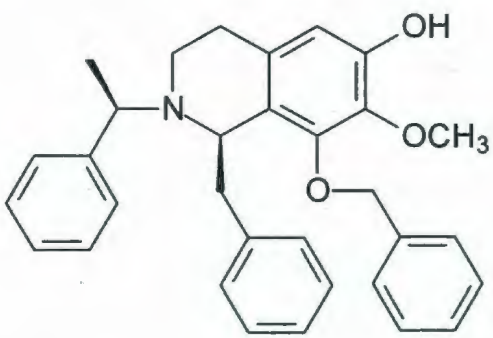
586


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
N
OCH3
O
Br

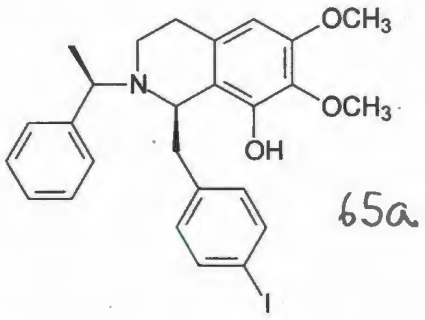
58C


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

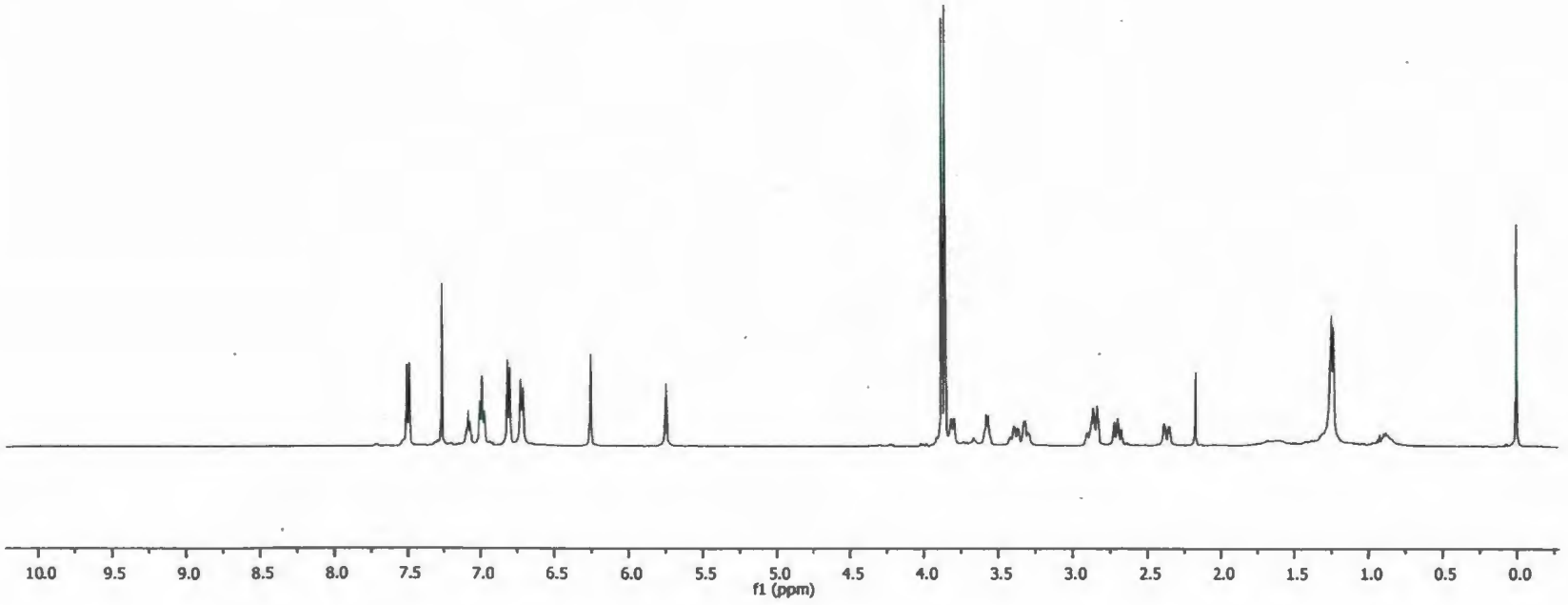

OH
N
OCH3
O

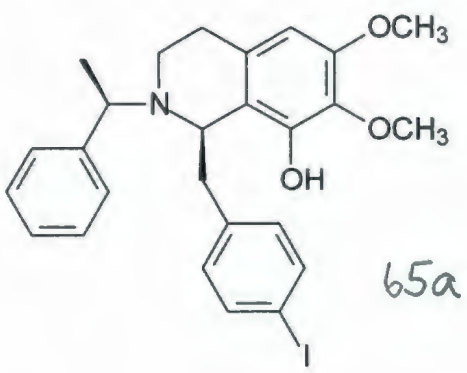
59

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
OCH3
N
OH
I

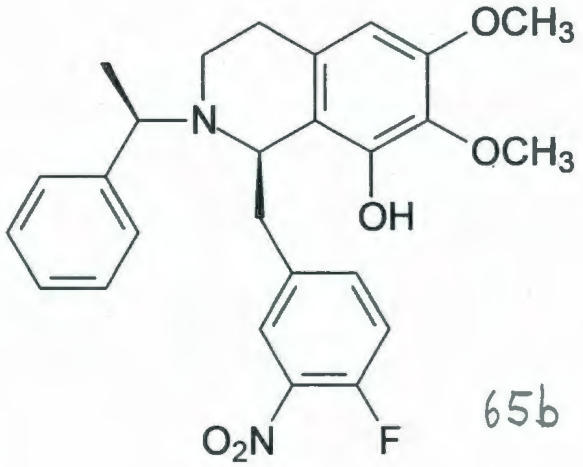
65a.


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

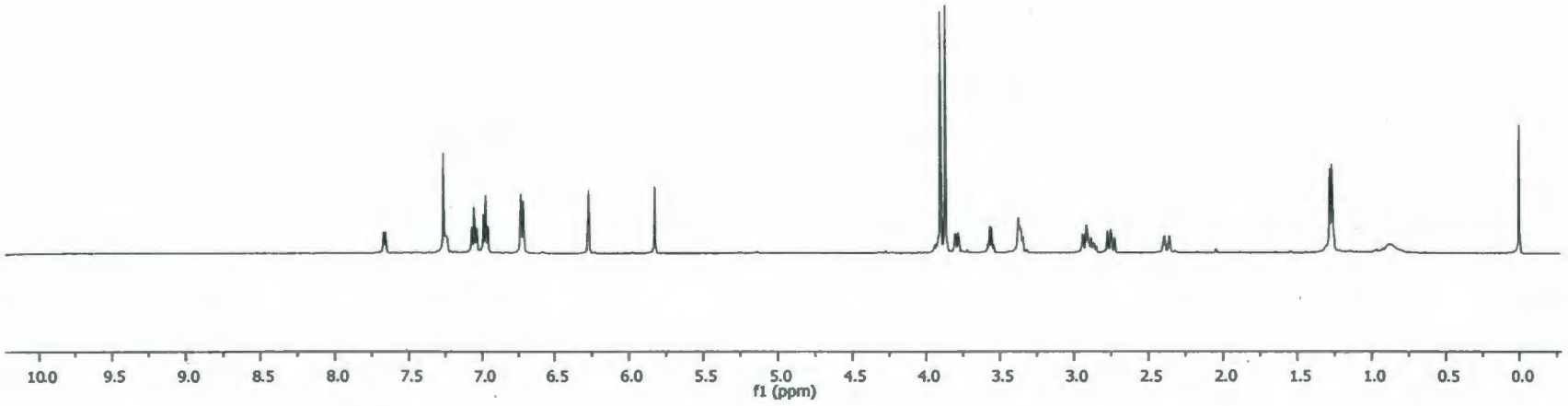

OCH3
OCH3
N
OH
I

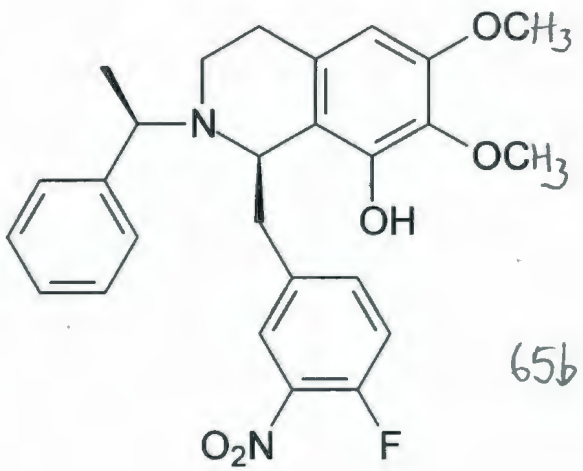
65a

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OCH3
OCH3
N
OH
O2N
F

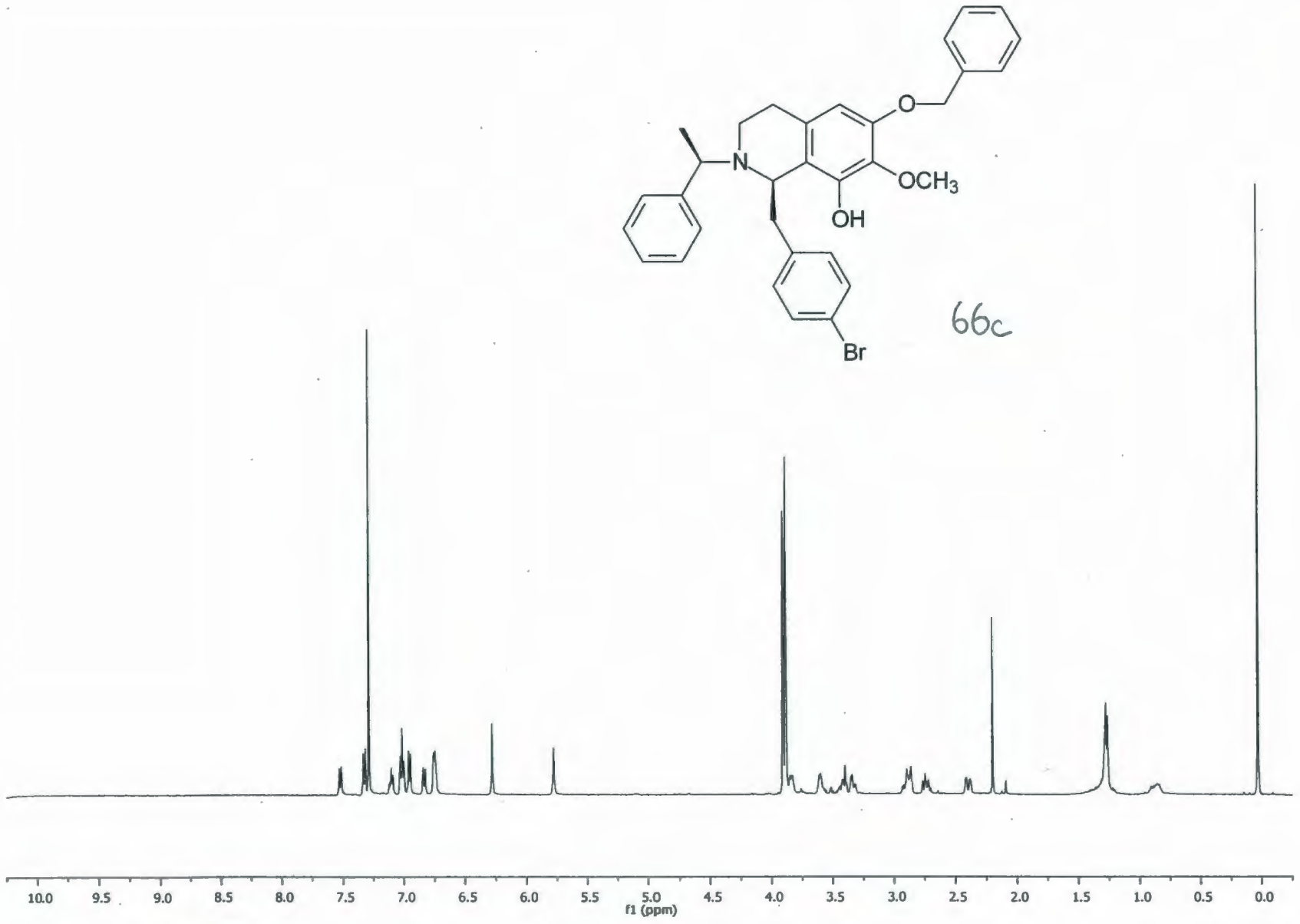
65b

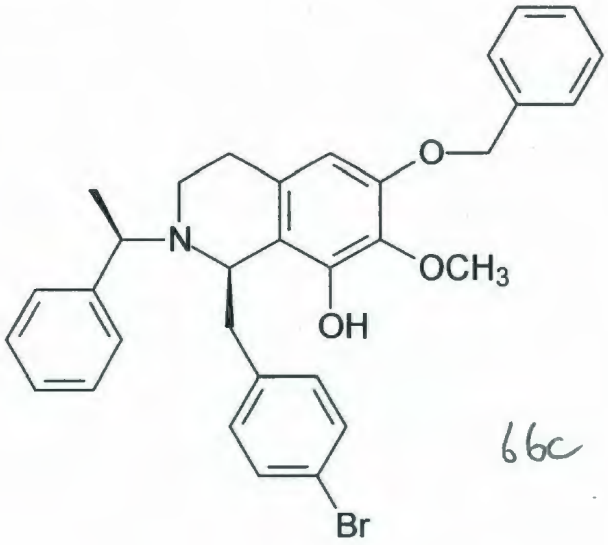

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OCH3
OCH3
N
OH
O2N
F

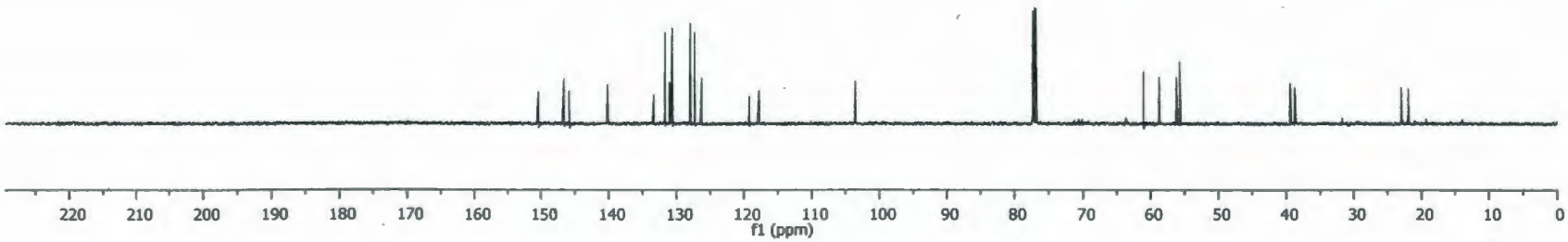
65b

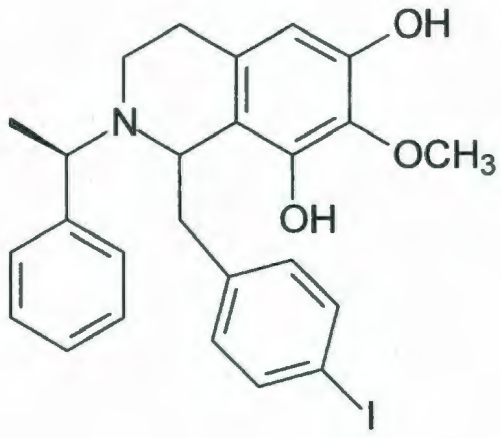
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
N
OCH3
OH
Br
66c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

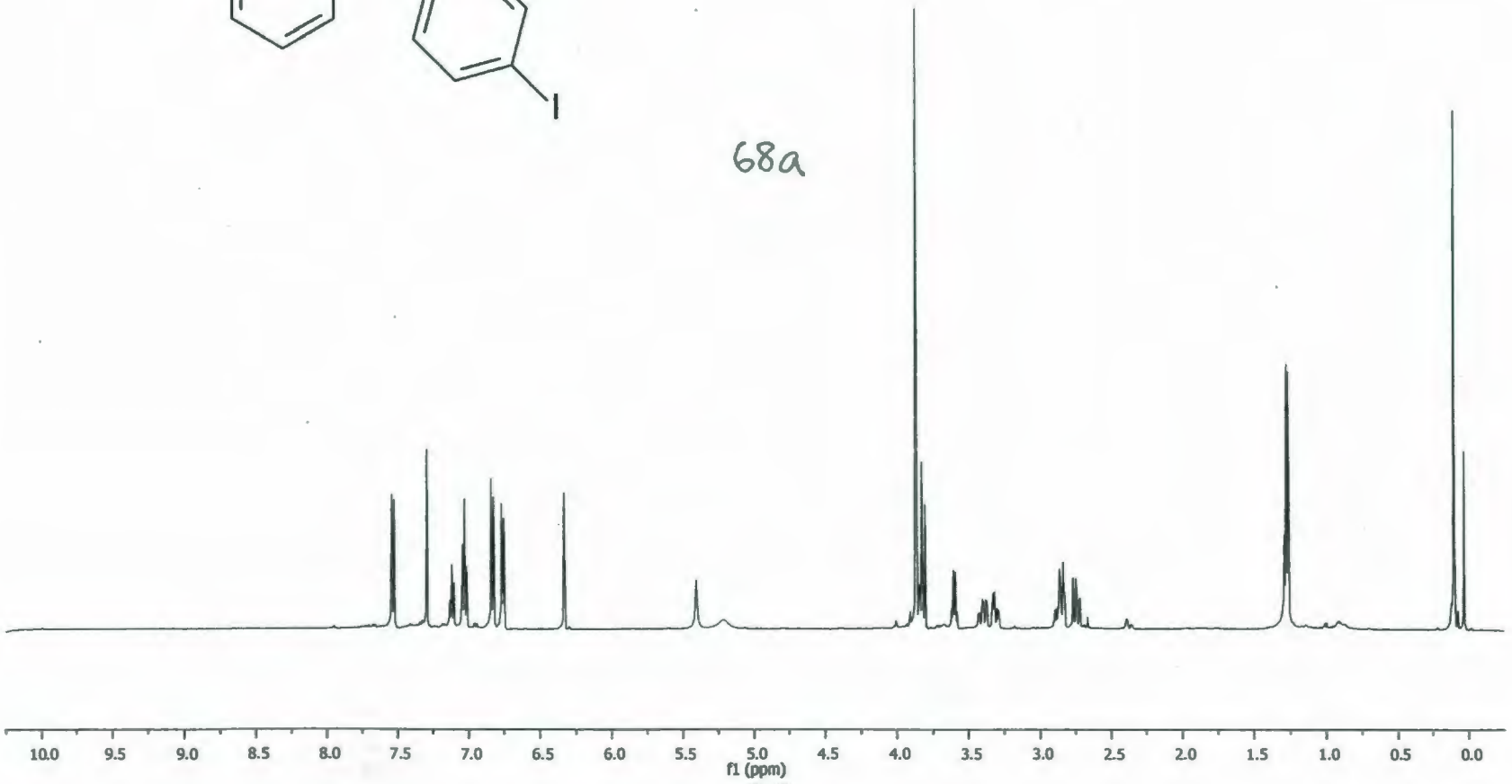

O
N
OCH3
OH
Br

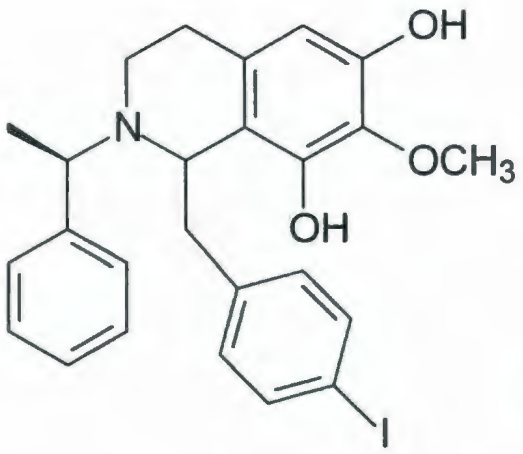
66c


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
N
OCH3
OH
I

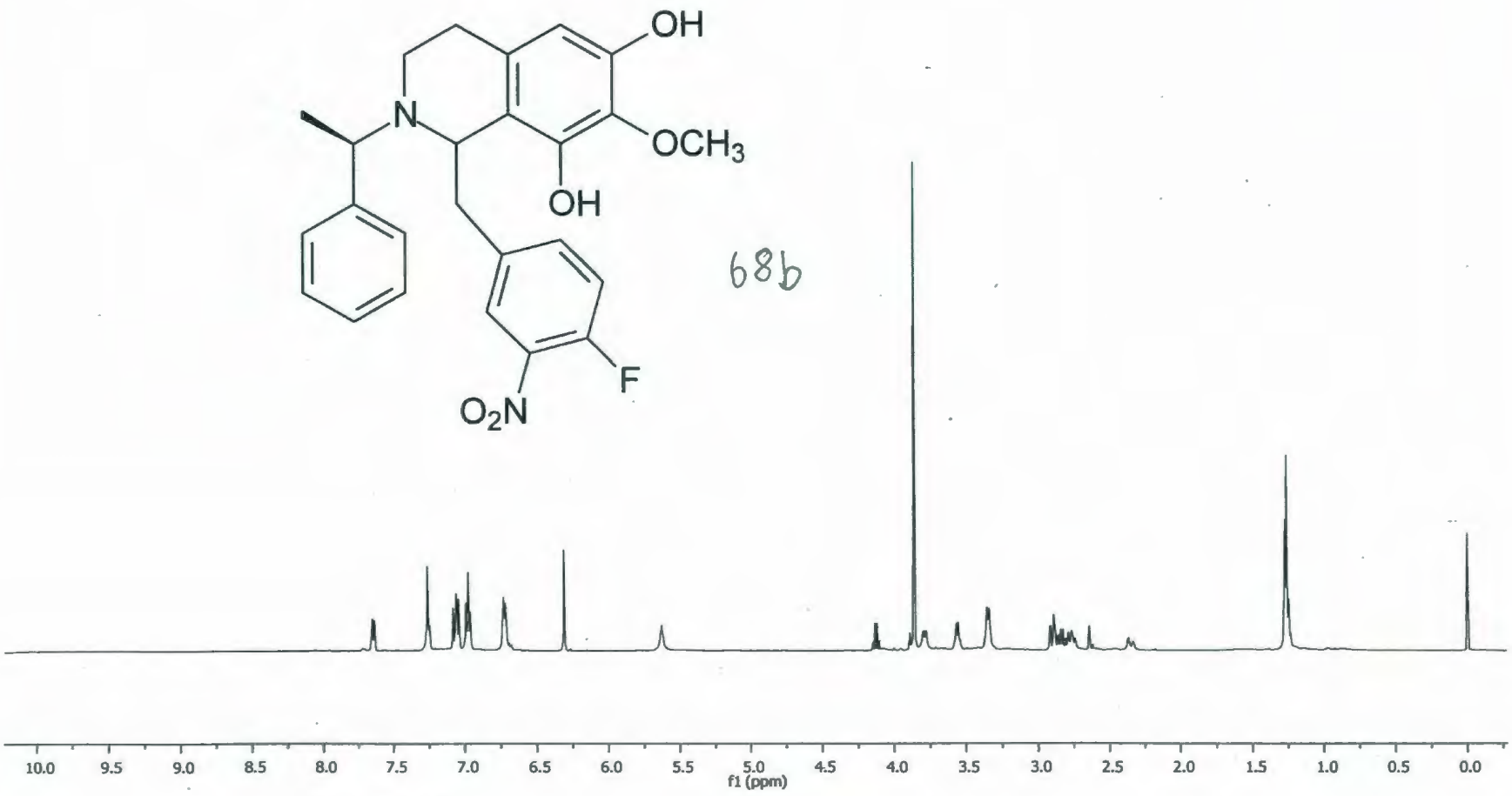
68a

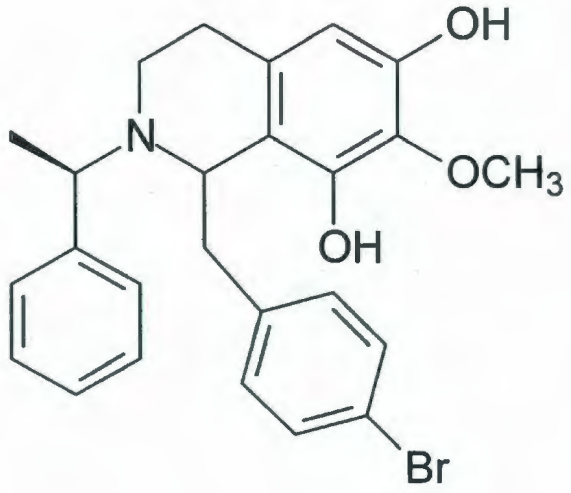

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

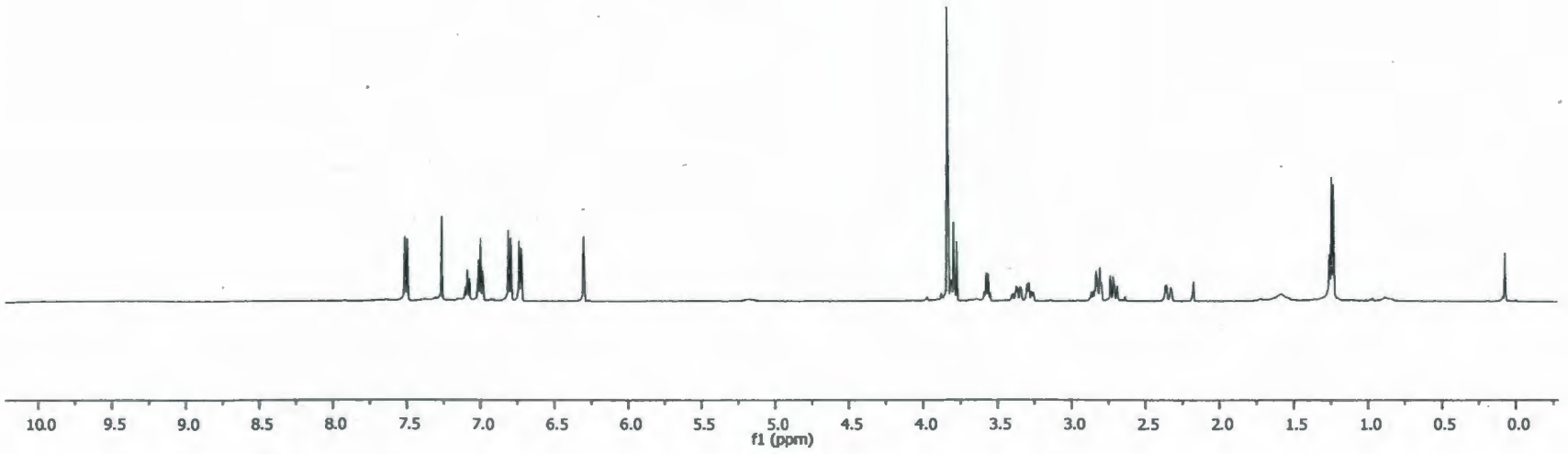

OH
N
OCH3
OH
I

68a

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

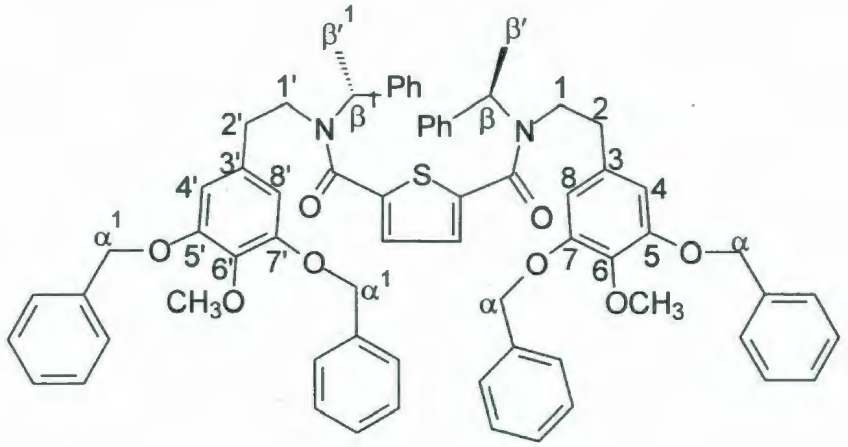

OH
N
OCH3
OH
F
O2N
68b
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OH
N
OCH3
OH
Br

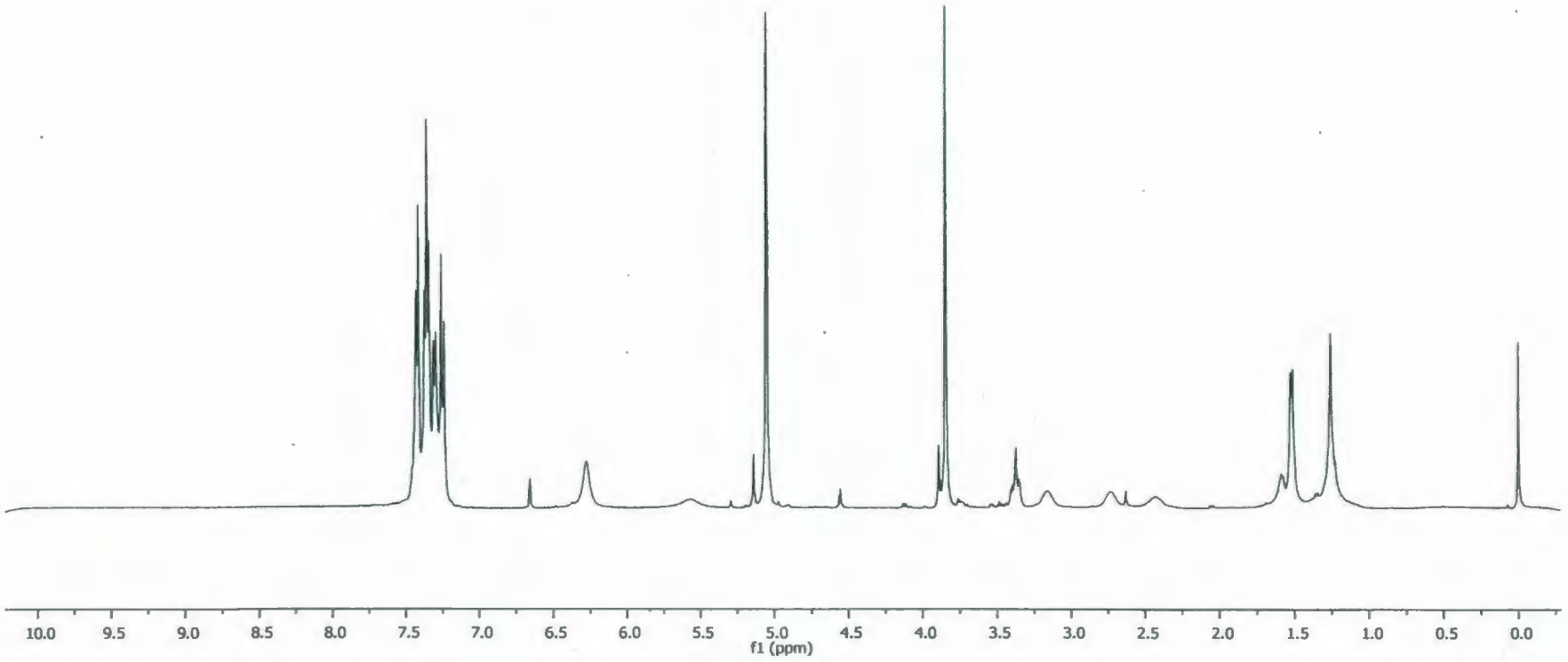

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

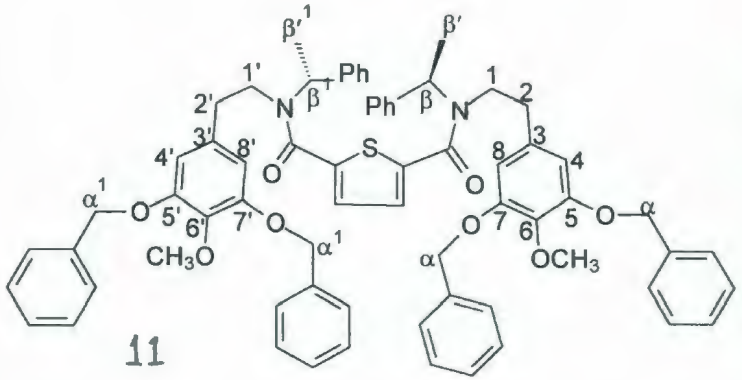
Appendix B:

Selected ^{1}H NMR and ^{13}C NMR spectra of compounds in of Chapter 4


β′ 1
β′
1′
Ph
β
Ph
β
N
1
2
2′
N
3′
8′
3
4′
S
8
4
O
O
α 1
O
5′
6′
7′
O
α 1
O
7
6
5
O
α
CH3O
α
OCH3

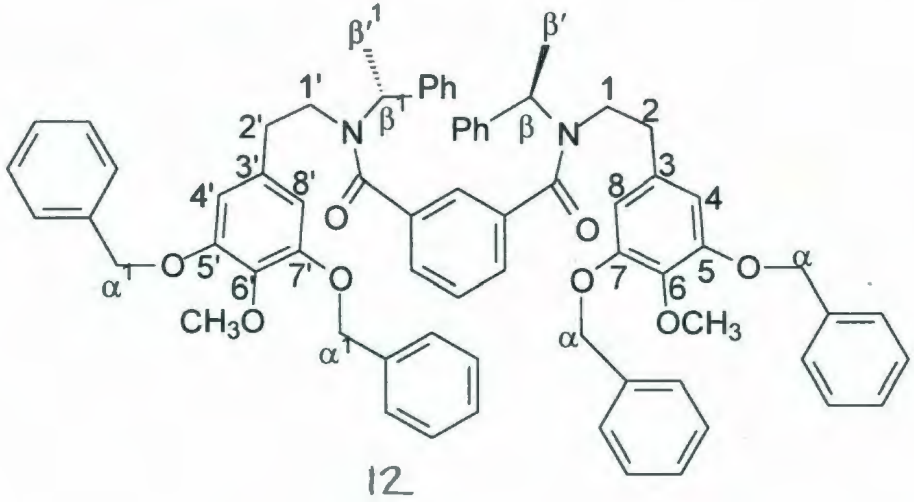
11


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

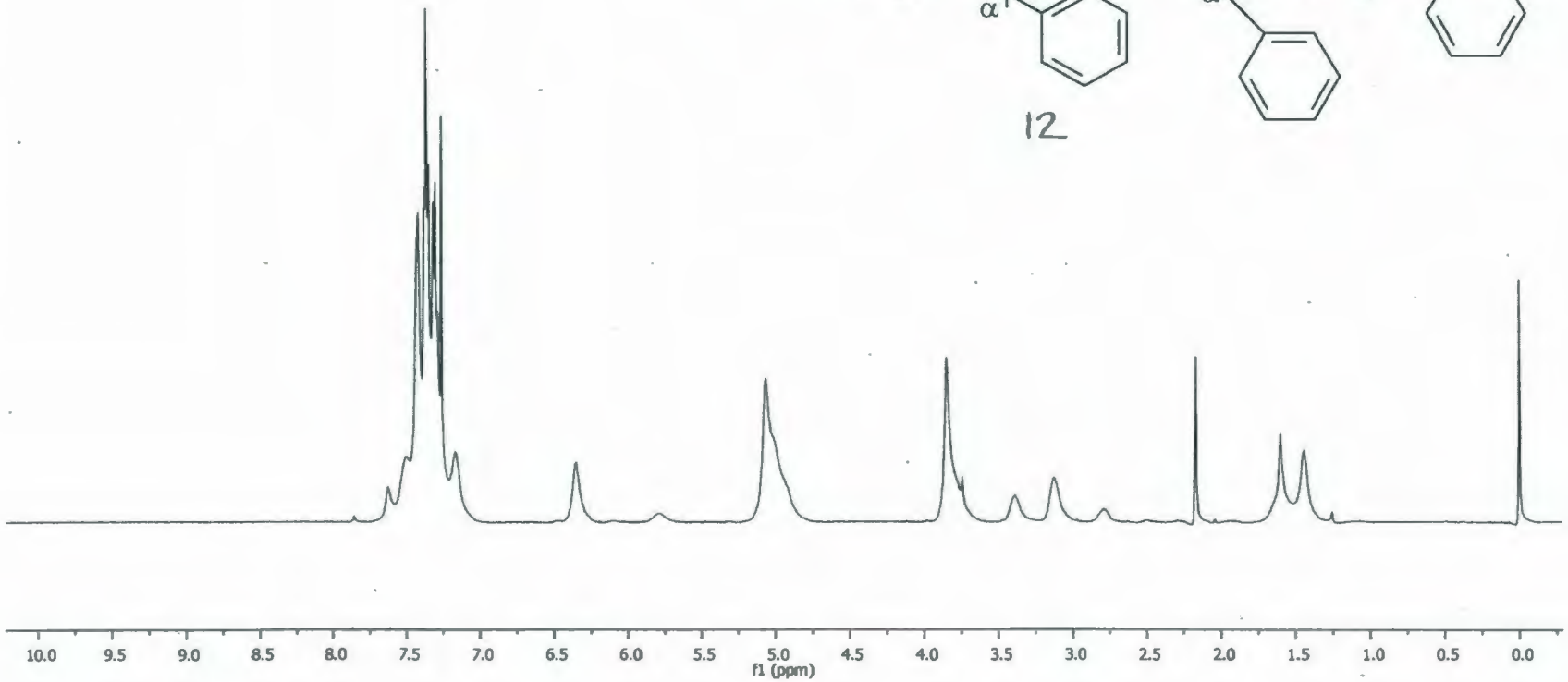

β'1
β'
1'
Ph
2'
N
β
Ph
β
N
1
2
3'
8'
S
8
3
4'
4
O
O
α1
O
5'
6'
7'
O
α1
O
7
6
5
O
α
CH3O
α
OCH3

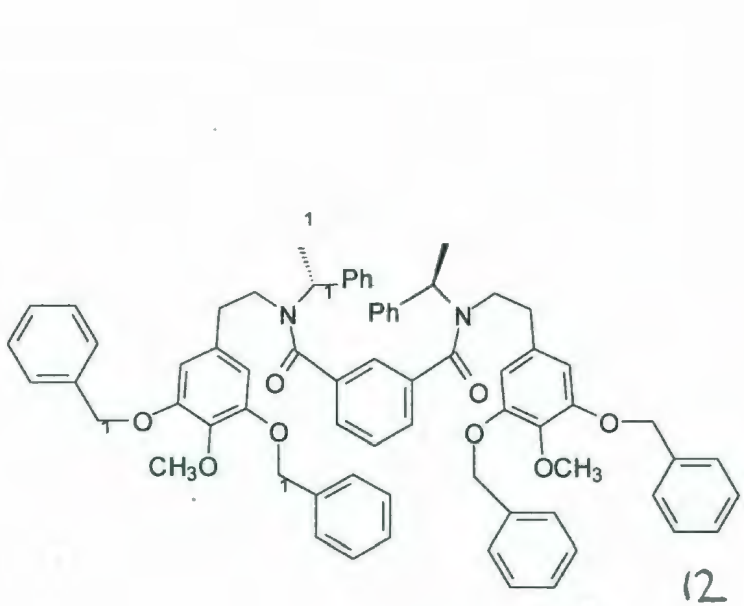
11

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)


β'1
β'
1'
Ph
2'
N
β'1
Ph
β
N
1
2
3'
8'
3
4'
8
4
O
O
α1
O
5'
6'
7'
O
O
7
6
5
O
α
CH3O
α1
α
OCH3

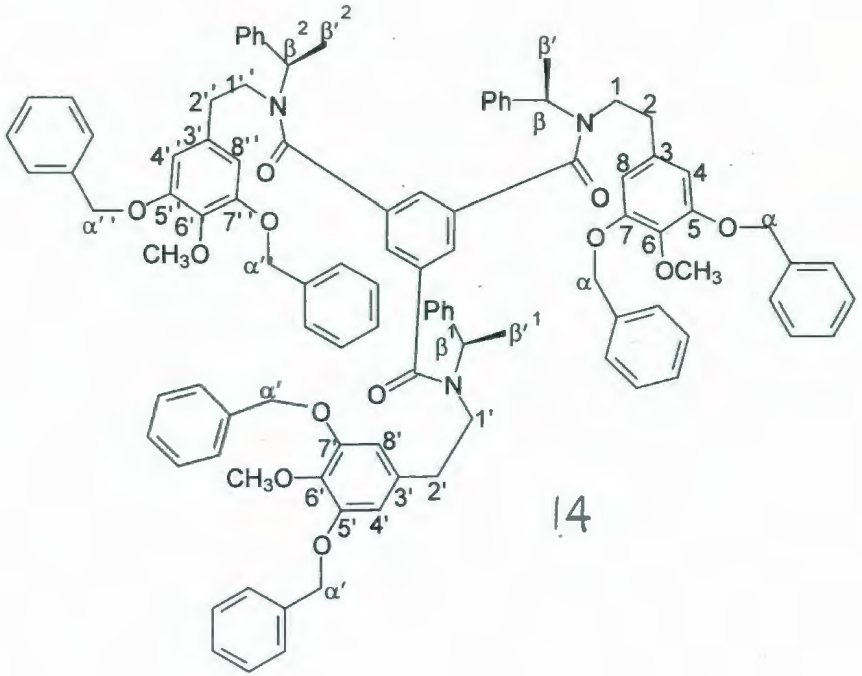
12


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

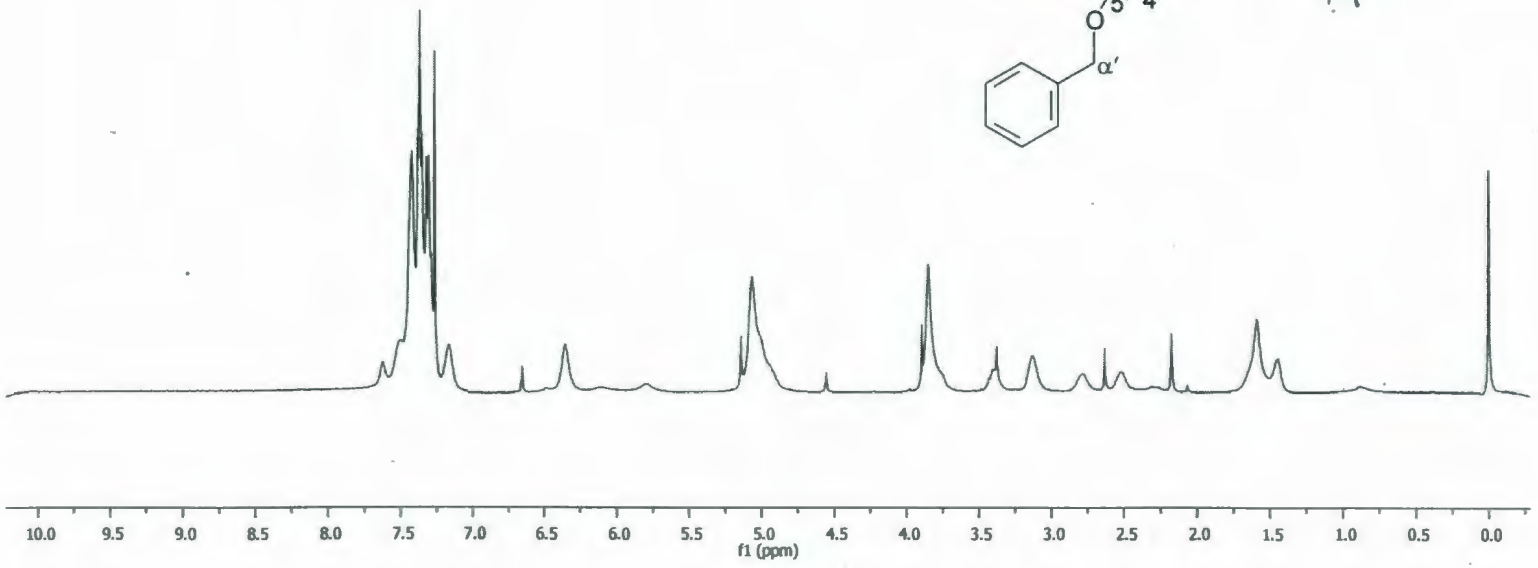

1
Ph
Ph
N
N
O
O
O
O
O
O
O
CH3O
OCH3
1

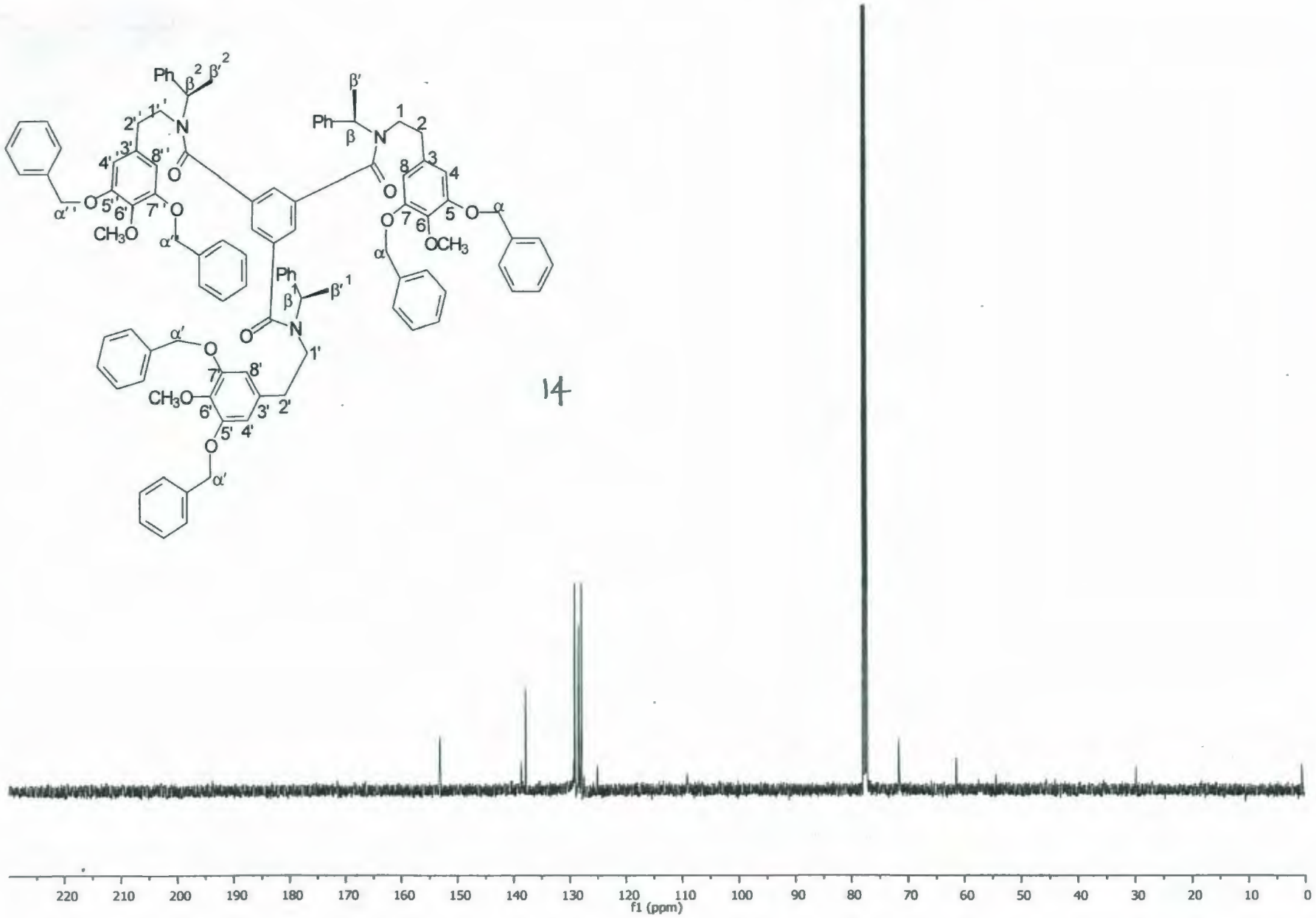
12

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

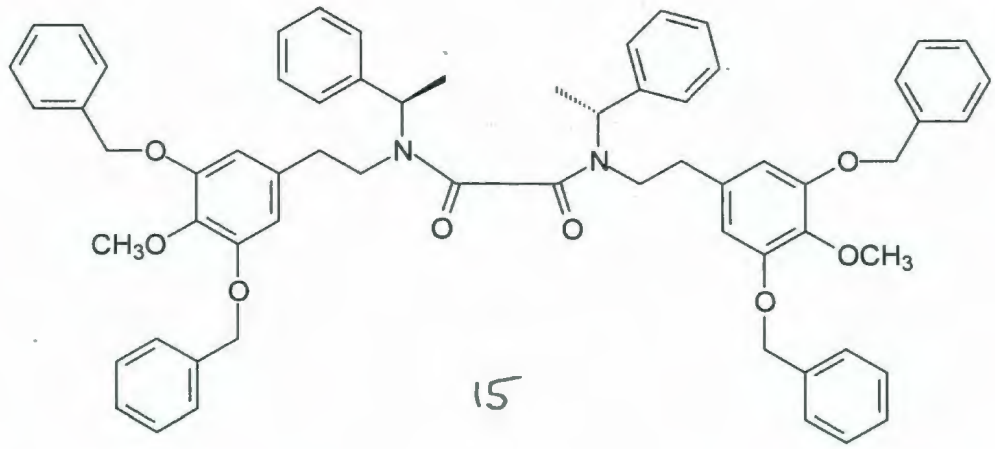

Ph
β
β′
2
1′′
2′′
3′
4′′
8′′
N
O
α′′
5′′
6′
7′′
CH3O
α′
1
2
3
4
8
5
6
7
OCH3
α
1′
7′
8′
2′
3′
4′
5′

14

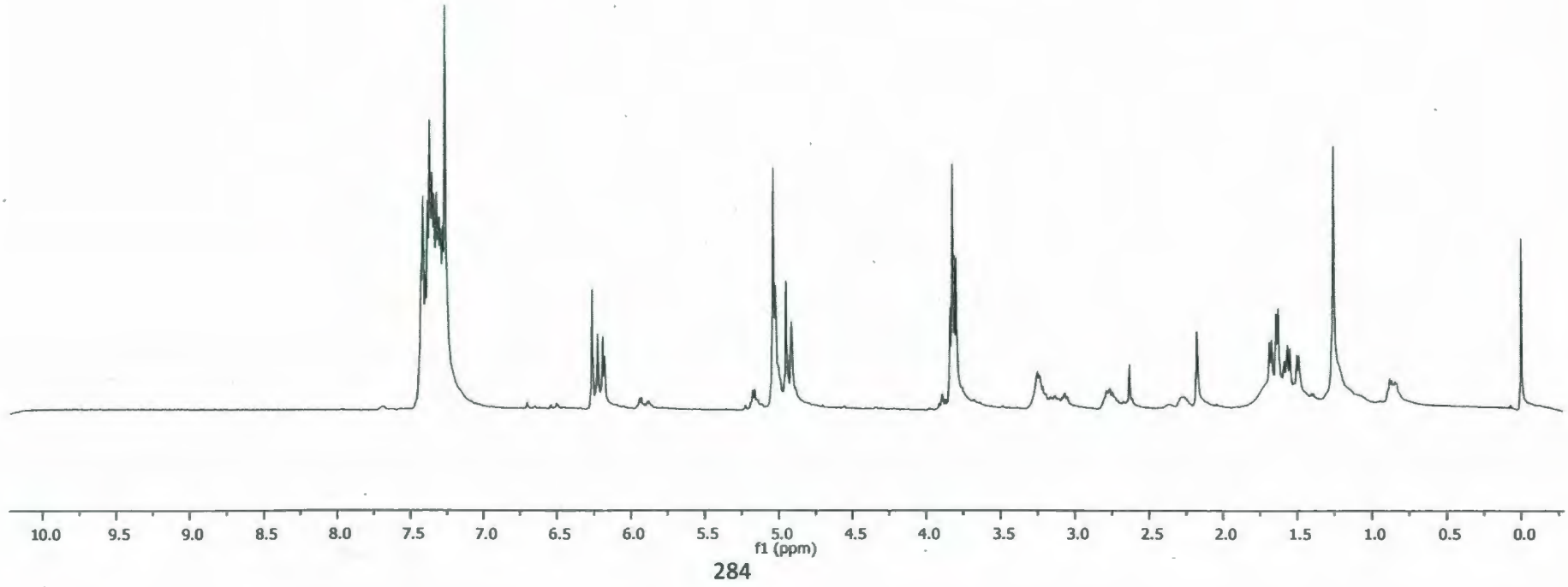

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

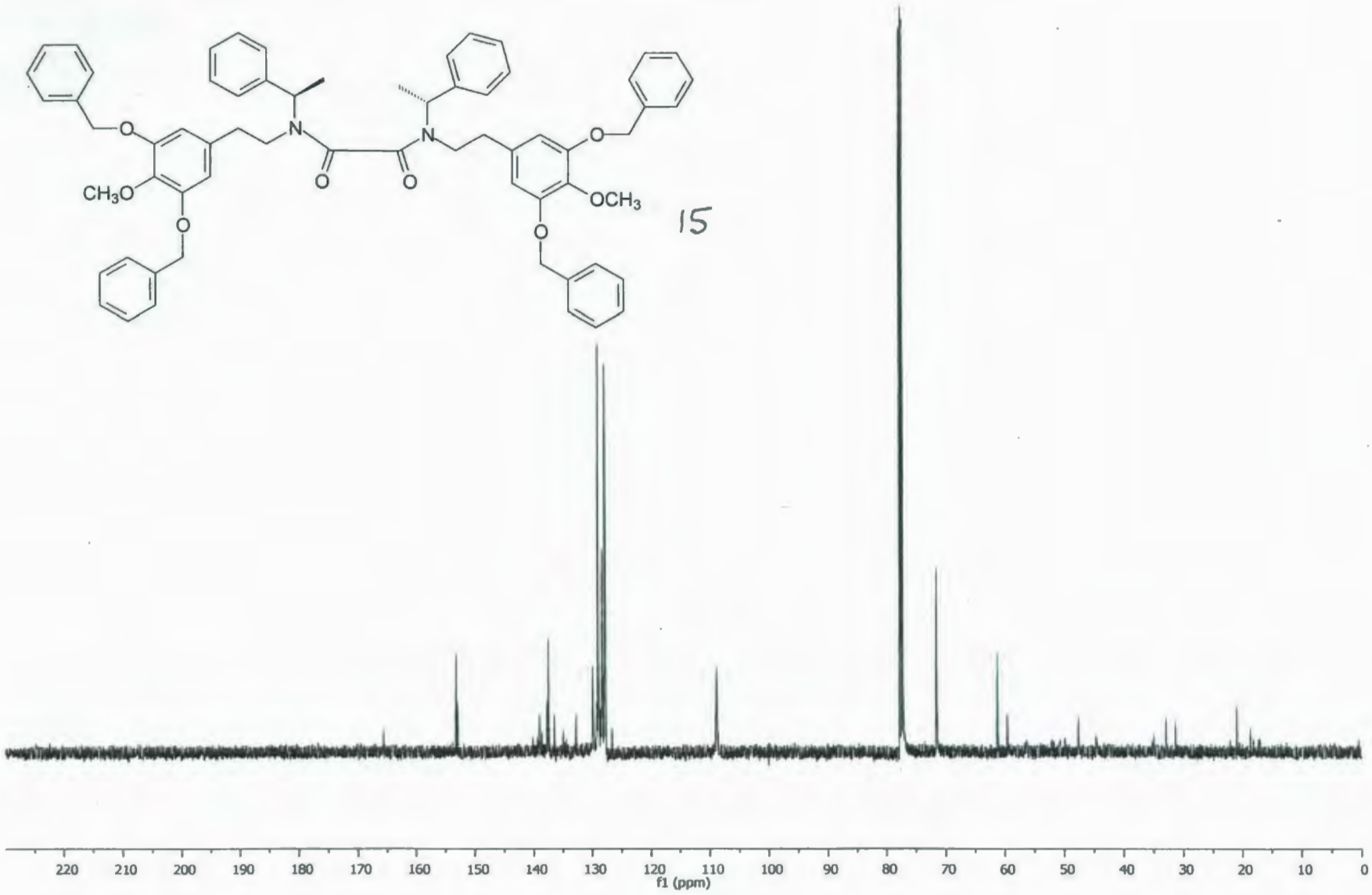

Ph
β
β′
2
1′
2′
N
3′
4′
8′
O
α′
5′
6′
7′
CH3O
1
2
3
4
8
5
6
7
OCH3
α
1′
β′1
CH3O
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

14


O
N
O
O
N
O
CH_3O
OCH_3
O
O

15


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


CH3O
OCH3
O
N
O
15
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)