TETRAHYDROISOQUINOLINES BEARING A QUATERNARY CENTRE AT C-1

ENANTIOSELECTIVE SYNTHESIS OF TETRAHYDROISOQUINOLINES WHICH HAVE A QUATERNARY CENTRE AT C-1

BY

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A Thesis

Submitted to the School of Graduate Studies

in Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (1992) McMASTER UNIVERSITY

(Chemistry) Hamilton, Ontario

TITLE: Enantioselective Synthesis of Tetrahydroisoquinolines which have a Quaternary centre at C-1

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NUMBER OF PAGES: vii, 60

ABSTRACT

The reactions of methyllithium and phenyllithium with the iminium chloride, [(*2R,3S*)-2,3-dihydroxy-3-(6′,7′-dimethoxy-3′,4′-dihydroisoquinolin-1′-yl)]propionate hydrochloride, **34** as a means of preparing enantiomerically pure compounds are described. These reactions afford a single product in high yield. The nmr spectra of the products, 1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline **54** and 1-(1′,2′,3′-trihydroxy-3′,3′-diphenylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-phenylisoquinoline **62**, are discussed and an explanation is given to account for the diastereoselectivity of the reaction. By this method, enantiomerically pure compounds bearing a quaternary centre at C-1 of the tetrahydroisoquinoline system may be prepared. Oxidative degradation of the hydroxylated side chain of compound **62** has led to the preparation of several other new compounds.

The usefulness of the t-butoxycarbonyl group as a selective protecting group for nitrogen in the preparation of 2-t-butyloxycarbonyl-1,2,3,4-tetrahydro-1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropyl)-6,7-dimethoxy-1-methylisoquinoline **59** is described. It has advantages over the ethoxycarbonyl group in that it not only selectively protects the amino group but also is easy to remove by short treatment with trifluoroacetic acid and water at room temperature. Treatment of **59** with sodium periodate afforded the aldehyde, 1-formyl-2-t-butyloxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline, **60**. An attempted oxidation of the aldehyde **60** to the acid is also described.

A review of recent methods of inducing chirality at C-1 of the tetrahydroisoquinoline system is given in the Introduction.

ACKNOWLEDGEMENTS

I would like to thank Professor David B. MacLean for his boundless patience, guidance and encouragement throughout this project. My special thanks are extended to Dr. Zbigniew Czarnocki for providing his knowledge of enantioselective synthesis of tetrahydroisoquinolines.

I am very thankful to Dr. R. W. Smith and Mr. F. Ramelan for recording the mass spectra. I am also very grateful to Dr. D. W. Hughes, Mr. B. Sayer and Mr. I. Thompson for recording nmr spectra.

I would like to thank my lab group and fellow graduate students for their support. Finally, I would like to thank my family for their encouragement and for providing financial support.

Financial assistance from the Department of Chemistry, McMaster University, and the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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CHAPTER 1

INTRODUCTION

This thesis is concerned with the enantioselective synthesis of tetrahydroisoquinolines which have a quaternary centre at C-1. This structural feature is found in a number of cactus alkaloids (1a), several mammalian alkaloids (1b), and the spirobenzylisoquinoline alkaloids (1c). Examples of alkaloids bearing a quaternary centre at C-1 are shown in Figure 1.

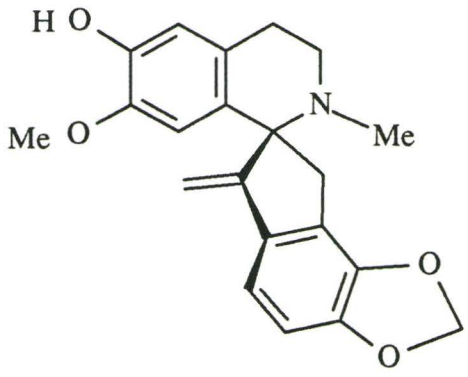
Many different methods have been reported for inducing chirality at C-1 of the tetrahydroisoquinoline system. In general, they can be classified into five categories:

1. The chirality at C-1 of the tetrahydroisoquinoline system can be induced by hydrogenation of an imine or an iminium salt using a homogeneous catalyst which has one or more enantiomerically pure ligands.

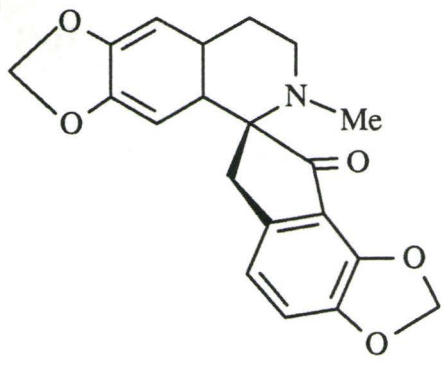
2. A tetrahydroisoquinoline which contains a chiral substituent on nitrogen can induce chirality at C-1 by lithiation followed by alkylation.

3. The Pictet-Spengler condensation or a related condensation can be used to induce chirality at C-1 of the tetrahydroisoquinoline system using an imine which contains a chiral centre either in the portion of the molecule derived from the amine or in the portion derived from the aldehyde. For example, Yamada and co-workers (2) used (*S*)-(-)-(3,4-dihydroxyphenyl)alanine (L-dopa) as starting material in the synthesis of (*S*)-(+)- and (*R*)-(-)-laudanosine and of (*S*)-(+)-reticuline.

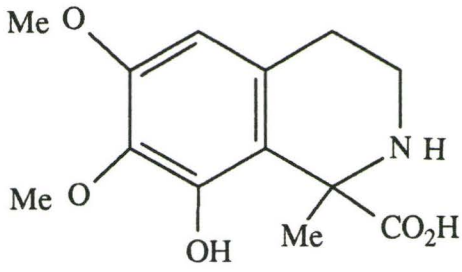
4. Reduction or alkylation of an iminium salt which carries a chiral substituent at nitrogen can also induce chirality at C-1 of the tetrahydroisoquinoline system. For example, Polniaszek and Kaufman (3) have reported that iminium ions which carry a



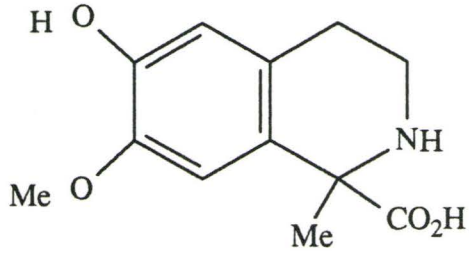
(+)-Ochotensine



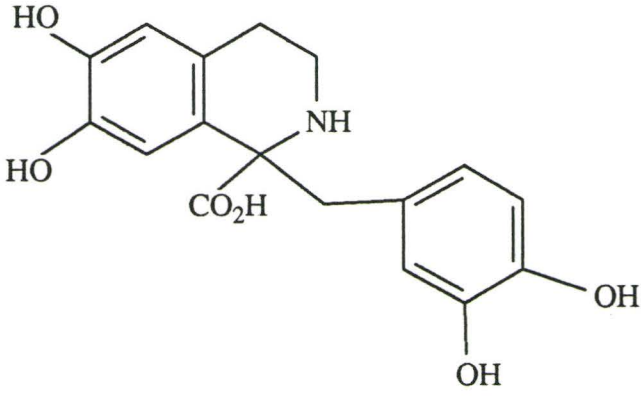
(+)-Fumariline



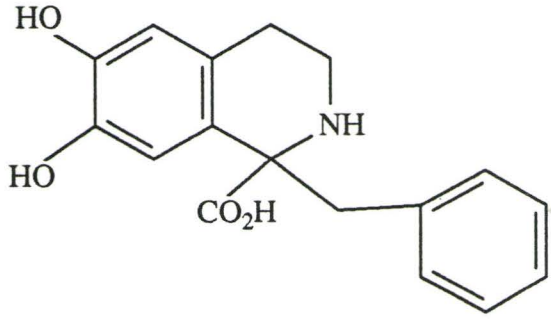
Peyoruvic acid



(±)-Salsoline-1-carboxylic acid



Norlaudanosoline carboxylic acid



3′,4′-Dideoxy-norlaudanosoline carboxylic acid

Figure 1. Examples of alkaloids bearing a quarternary centre at C-1

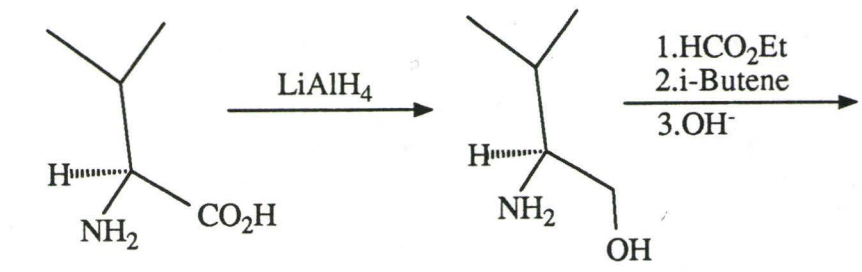
chiral centre on a group attached to nitrogen can undergo highly diastereoselective hydride reduction to afford chiral 1-sutstituted tetrahydroisoquinlines.

5. An imine or an iminium salt which bears a chiral substituent at C-1 can also induce chirality at C-1 on reduction or on alkylation.

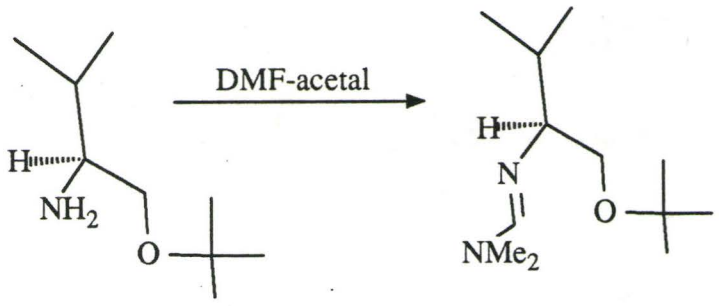
In methods 2-5, it has been possible to remove or modify the chiral substituent after induction at C-1 and in this way specific alkaloids are synthesized. Examples of the application of methods 2-5 in alkaloid synthesis are given in this introduction.

Meyers and his co-workers (4) have developed a general method for the preparation of 1-alkyl substituted tetrahydroisoquinolines in greater than 90% enantiomeric excess(e.e.) by using a chiral auxiliary which would influence the diastereoselectivity during the alkylation of the lithio carbanion. The chiral auxiliary, namely the tert-butyl ether of valinol, was prepared as shown in Scheme 1. Reaction of amidine **1** with the tetrahydroisoquinoline **2** by simple heating afforded the formamidine **3**. Metalation with LDA at -78°C followed by alkylation of **3** with various alkyl halides at -100°C gave the alkylated products **4**. The free amines **5** were regenerated in good yields with greater than 90% e.e. by heating compounds **4** in hydrazine (see Scheme 2). The chiral auxiliary is recoverable from the reaction mixture.

In another approach, Czarnocki *et al.* (5) have synthesized (*R*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7- dimethoxyisoquinoline **12** by using optically pure (*R*)-(+)-glyceraldehyde **6** and dopamine hydrochloride **7** as starting materials on their way to the preparation of (*S*)-(-)-carnegine, (*R*)-(-)-calycotomine, and (*S*)-(+)-laudanosine. Their procedure for the preparation of **12** is outlined in Scheme 3. A mixture of diastereomers, **8a** and **8b**, was obtained in 93% yield when the Picter-Spengler condensation of (*R*)-(+)-glyceraldehyde **6** and dopamine hydrochloride **7** was carried out

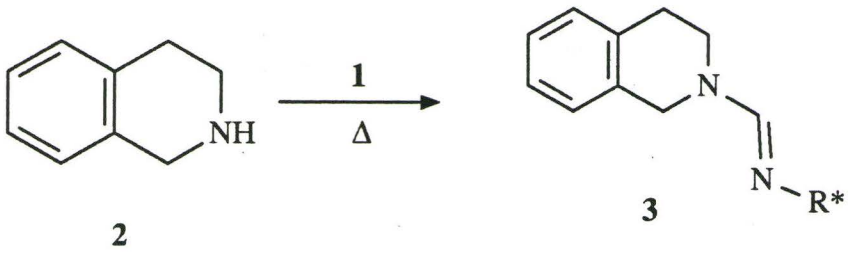


valine **valinol**

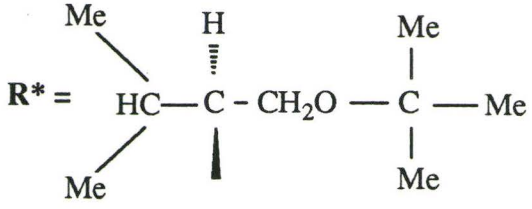


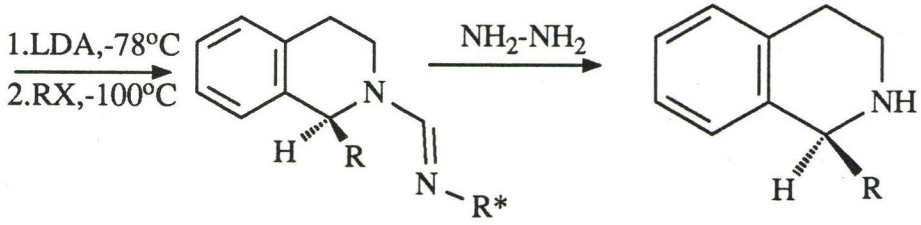
***O*-t-butylvalinol** **1**

Scheme 1



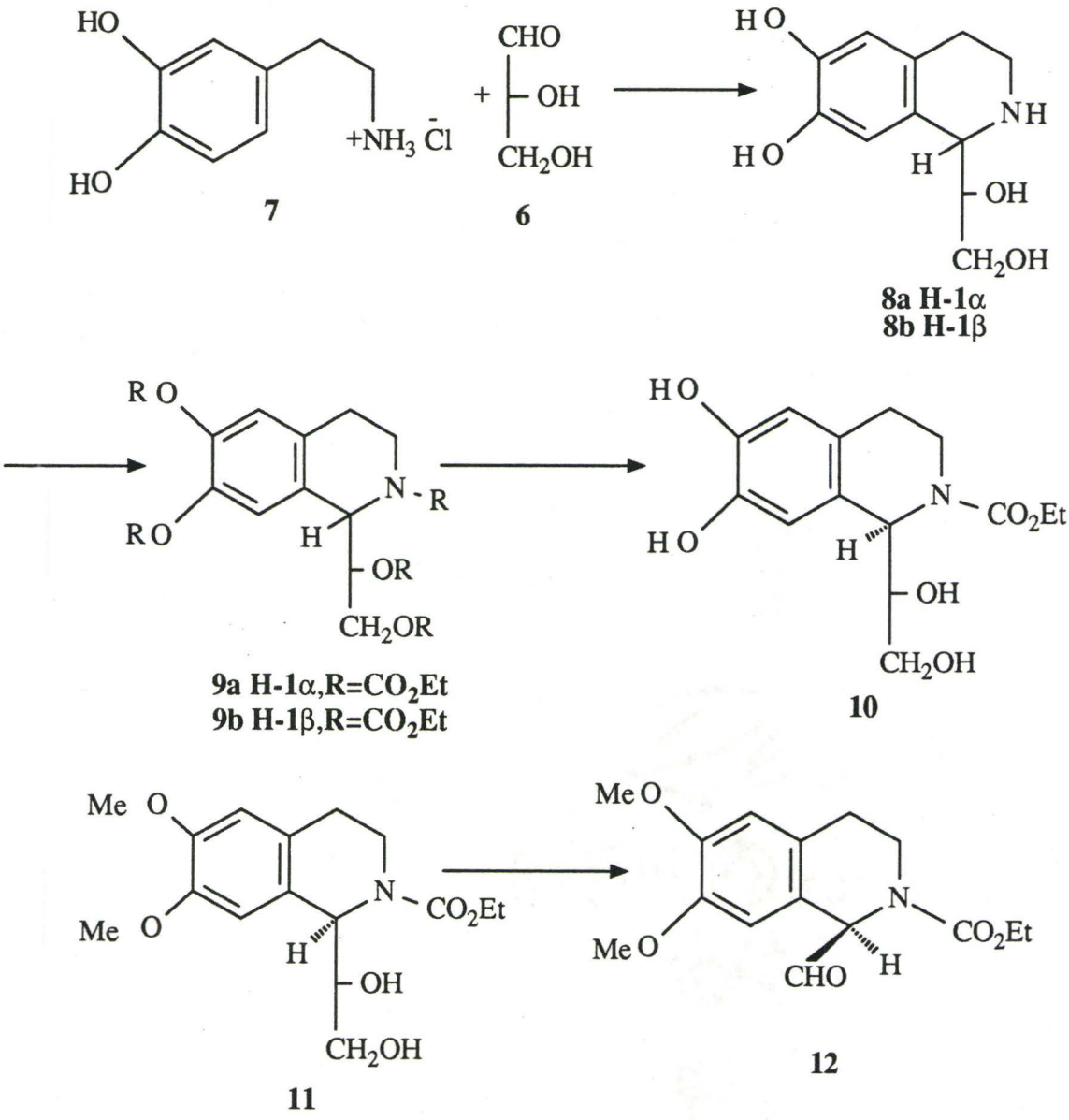
2 3





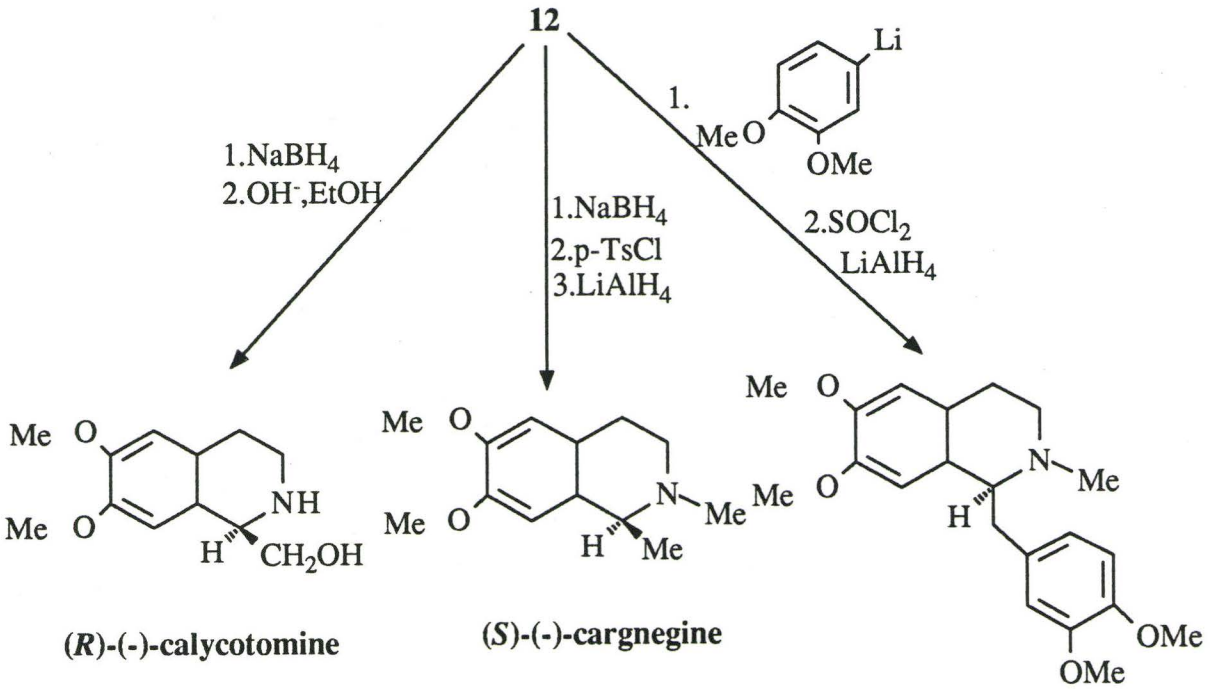
4 5

Scheme 2


HO
HO
+NH3 Cl
7
CHO
+ OH
CH2OH
6
HO
HO
NH
H
OH
CH2OH
8a H-1α
8b H-1β
RO
RO
N-R
H
OR
CH2OR
9a H-1α,R=CO2Et
9b H-1β,R=CO2Et
HO
HO
N-CO2Et
H
OH
CH2OH
10
Me O
Me O
N-CO2Et
H
OH
CH2OH
11
Me O
Me O
N-CO2Et
CHO
H
12

Scheme 3

cont'd



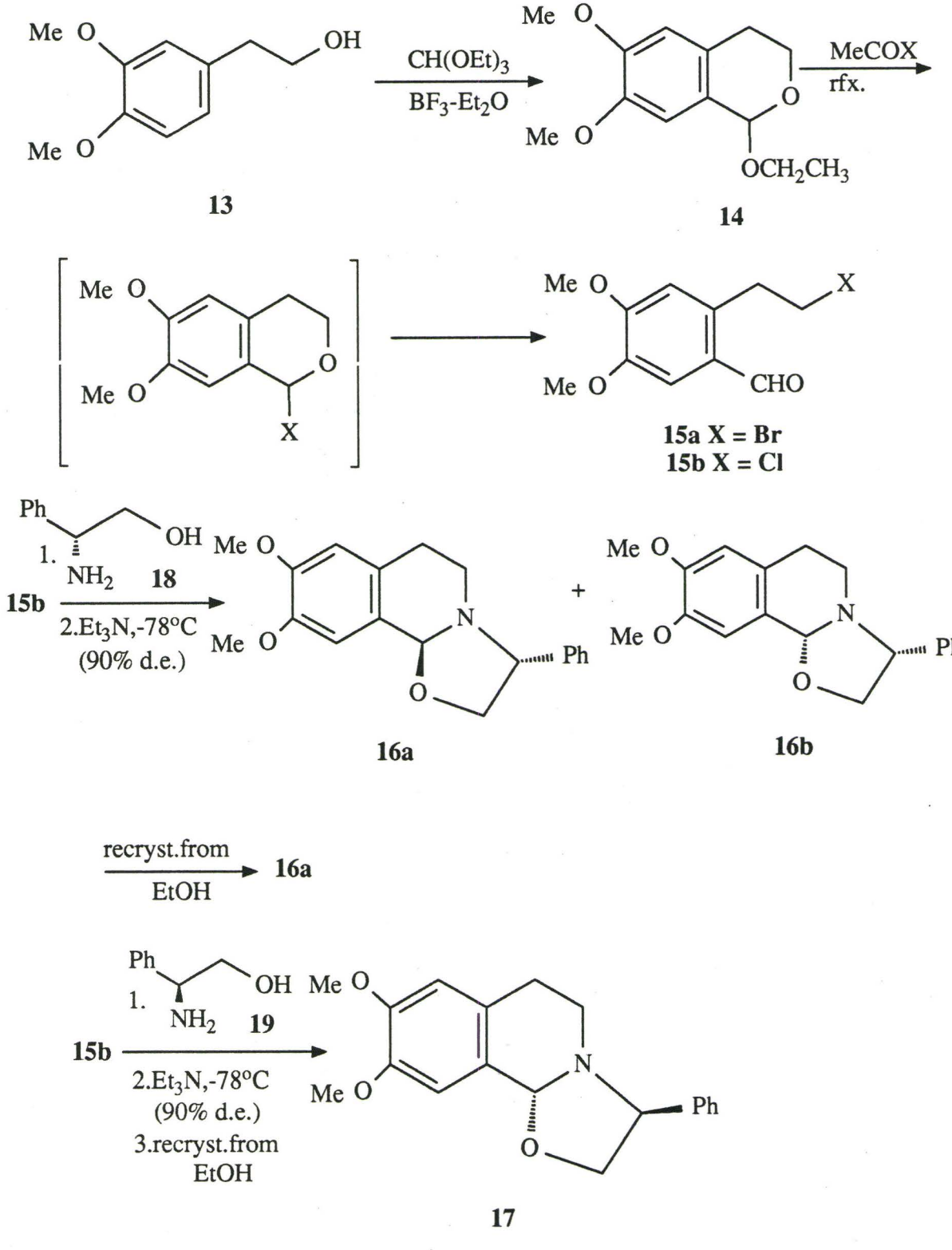
(*R*)-(-)-calycotomine **(*S*)-(-)-cargnegine** **(*S*)-(+)-laudanosine**

Scheme 3

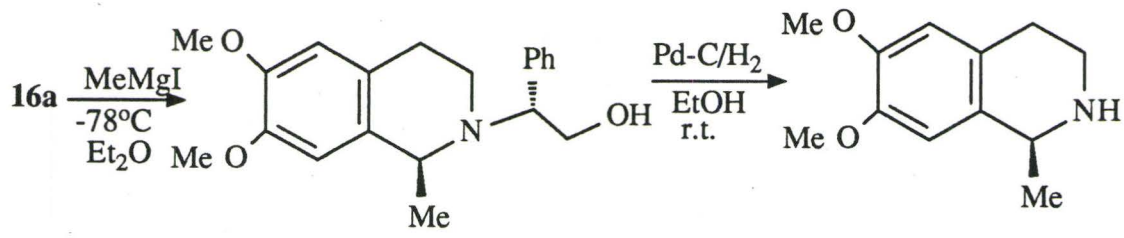
in boiling methanol. Treatment of the mixture, **8a** and **8b**, with an excess of ethyl chloroformate afforded the compounds **9a** and **9b**, in which the NH group is converted into carbamate and the OH groups into carbonates. The mixture of diastereomers, **9a** and **9b**, was separated by chromatography yielding the major isomer, **9a**, in 56% yield. Treatment of compound **9a** with methanolic ammonia removed all of the carbonic ester functions to afford compound **10**. Methylation at the phenolic hydroxyls was carried out with methyl iodide in the presence of potassium carbonate to afford compound **11** in 44% yield from **6**. Treatment of compound **11** with sodium periodate afforded compound **12** in 93% yield.

In a recently reported method,Yamato *et al.* (6) have used cyclic chiral 1-alkoxyisoquinolines, namely, oxazolo[2,3-a]-tetrahydroisoquinolines **17**, as intermediates for the synthesis of enantiomerically pure (*R*)- and (*S*)-1-alkyl- and 1-aryltetrahydroisoquinolines. Their synthetic scheme is outlined in Scheme 4. Compound **14** was obtained by treating **13** with ethyl orthoformate in BF_3-Et_2O at 0°C in 47% yield. 1-Ethoxy-6,7-dimethoxyisochroman **14** was refluxed with an acetyl halide to give 2-(2-haloethyl)-4,5-dimethoxybenzaldehyde **15**. Treatment of compound **15b** with (*R*)-phenylglycinol **18** and then with triethylamine in methylene chloride at -78°C gave a crystalline product as a 19:1(90% d.e.) mixture of **16a** and **16b**. Recrystallization of the mixture from ethanol gave pure **16a** in 93% yield. The enantiomer of **16a**, *(3S,10bR)*-oxazoloisoquinoline **17**, was also obtained from **15b** by using (*S*)-phenylglycinol **19**.

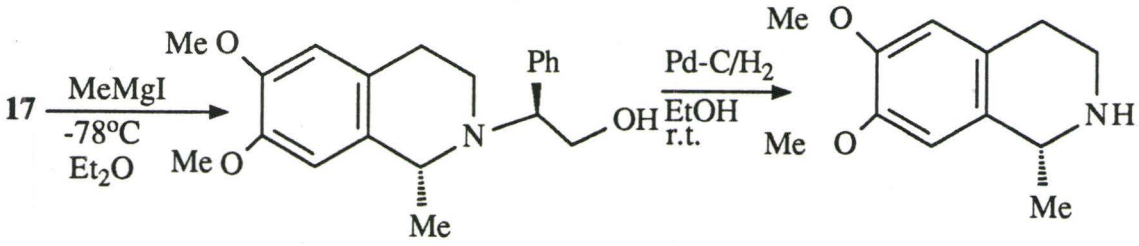
The procedure for the synthesis of 1-alkyl- and 1-aryltetrahydroisoquinolines is outlined in Scheme 5. Alkylation of compound **16a** was achieved by using methylmagnesium iodide in ether at -78°C to give compound **20**. Hydrogenolysis of


Me O
OH
Me O
13
CH(OEt)3
BF3-Et2O
Me O
O
Me O
OCH2CH3
14
MeCOX
rfx.
Me O
O
Me O
X
Me O
X
Me O
CHO
15a X = Br
15b X = Cl
Ph
OH
1.
NH2
18
15b
2.Et3N,-78°C
(90% d.e.)
Me O
N
Me O
Ph
O
16a
+
16b
recryst.from
EtOH
16a
19
17

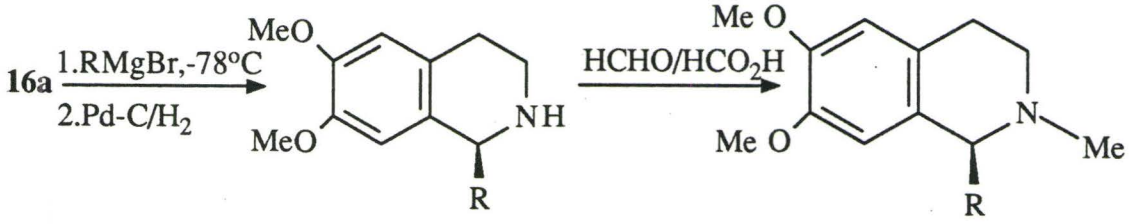
Scheme 4

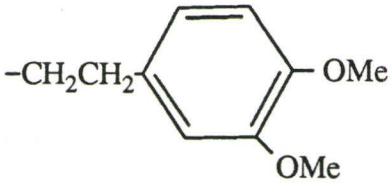


20 **21. (*S*)-(-)-salsolidine**

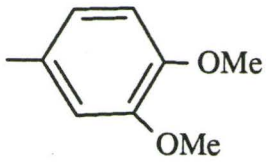


22 **23. (*R*)-(+)-salsolidine**



24. R = 

26.(*S*)-(-)-homolaudanosine

25. R = 

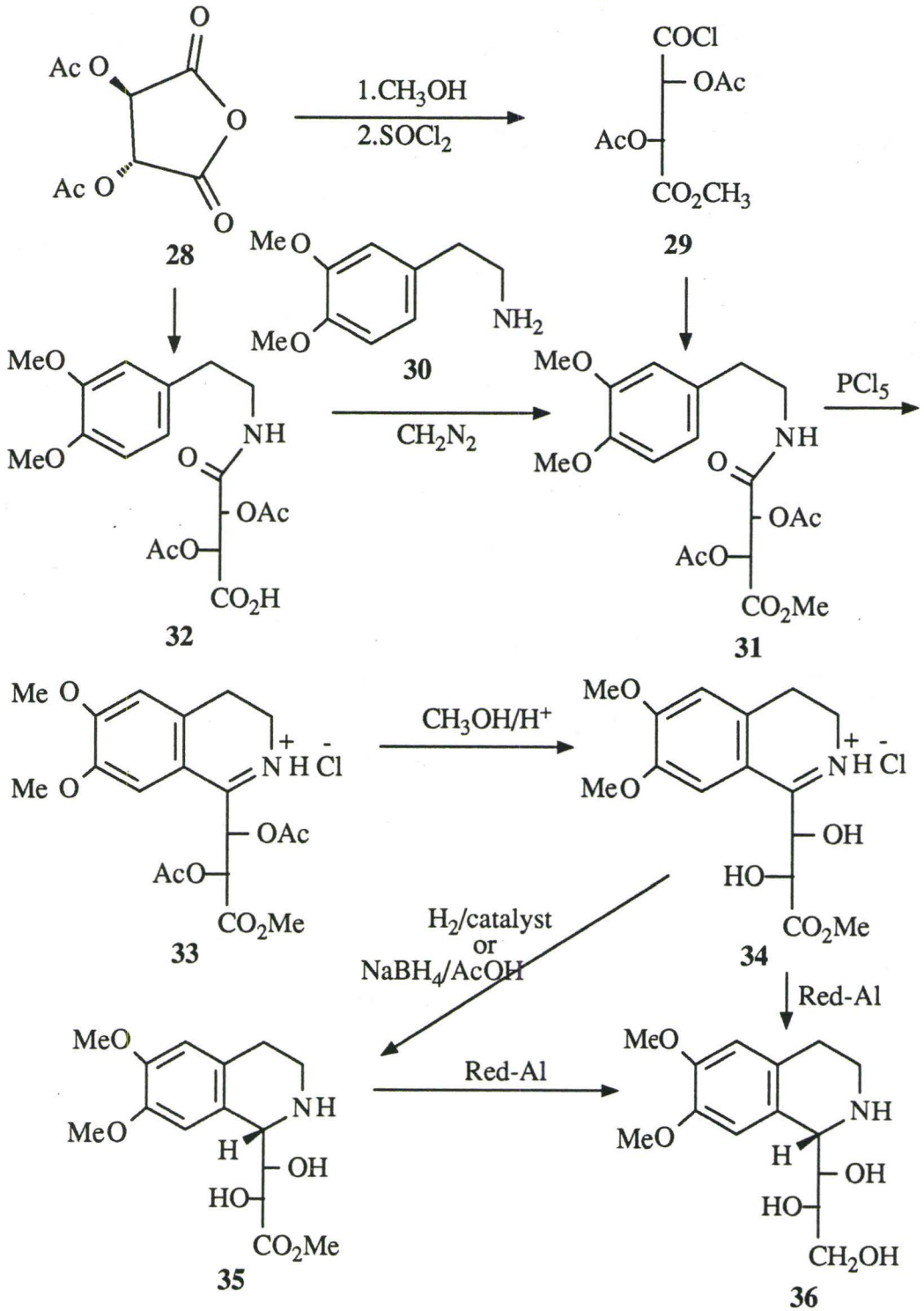
27.(*S*)-(+)-cryptostyline II

Scheme 5

compound **20** on Pd-C in acidic ethanol gave the natural (*S*)-(-)-salsolidine **21** in 92% yield(100% e.e.). In a similar way, (*R*)-(+)-salsolidine **23** was obtained from **17** in 100% e.e. Also, 1-phenyl- **25** and 1-phenylethyl- **24** isoquinoline alkaloids were synthesized from **16a** in 73% and 75%yields, respectively. N-Methylation of **24** and **25** was carried out by the reaction with formaldehyde and formic acid to give (*S*)-(-)-homolaudanosine **26** and (*S*)-(+)-cryptostyline II **27** in 41% and 80% yields, respectively.

Some years ago, Dörnyei and Szántay (7) established a method for obtaining enantioselectively 1-substituted-1,2,3,4-tetrahydroisoquinolines with a chiral centre at C-1 using optically pure L-(+)-tartaric acid as starting material. Their procedure for the synthesis of 1-trihydroxypropyl-1,2,3,4-tetrahydroisoquinoline **36** is outlined in Scheme 6. The optically pure L-(+)-tartaric acid was acylated by using acetic anhydride to afford L-*O*,*O*-diacetyl tartaric anhydride **28**. The half-ester chloride **29** was obtained by methanolysis of **28** followed by treatment with thionyl chloride. Treatment of **29** with 3,4-dimethoxyphenylethylamine **30** afforded the ester-amide **31** in 65% yield. The ester-amide **31** was also prepared in almost quantitative yield when L-*O*,*O*-diacetyltartaric anhydride **28** was treated directly with **30** to afford the amide-carboxylic acid **32** followed by methylation with diazomethane. The ester-amide **31** underwent Bischler-Napieralski ring closure to give compound **33** using PCl_5 as a condensing agent. Deacetylation of **33** was carried out under refluxing methanol to give the iminium salt **34**. The tetrahydroisoquinoline hydrochloride **35** was obtained diastereoselectively from **34** by either catalytic hydrogenation or sodium borohydride reduction in acetic acid. Treatment of compounds **34** or **35** with bis-(2-methoxyethoxy)alumininum hydride(Red-Al) afforded the 1-substituted- 1,2,3,4-tetrahydroisoquinoline **36**.

Czarnocki *et al.* (5) have prepared the (*R*)-aldehyde **12** by inducing a chiral centre

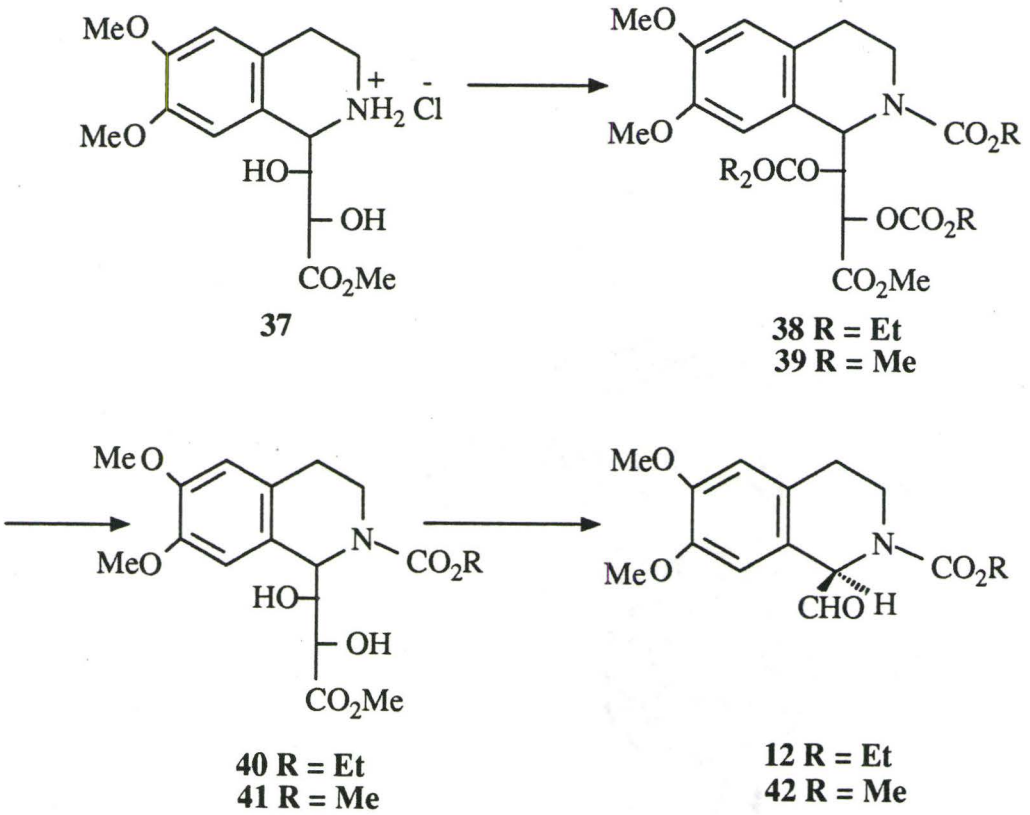

Ac O
Ac O
O
O
O
1.CH3OH
2.SOCl2
COCl
OAc
AcO
CO2CH3
28
29
Me O
Me O
NH2
30
MeO
MeO
NH
O
OAc
AcO
CO2H
32
CH2N2
MeO
MeO
NH
O
OAc
AcO
CO2Me
31
PCl5
Me O
Me O
+ -
N H Cl
OAc
AcO
CO2Me
33
CH3OH/H+
MeO
MeO
+ -
N H Cl
OH
HO
CO2Me
34
H2/catalyst
or
NaBH4/AcOH
Red-Al
MeO
MeO
NH
H
OH
HO
CO2Me
35
Red-Al
MeO
MeO
NH
H
OH
HO
CH2OH
36

Scheme 6

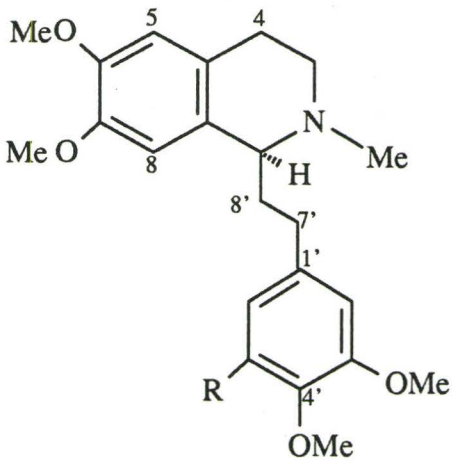
at C-1 of the tetrahydroisoquinoline system through a Picter-Spengler reaction of dopamine hydrochloride **7** with (*R*)-glyceraldehyde **6** followed by subsequent transformation of the condensation product (see Scheme 3). They have reported also an improved method for the synthesis of (*R*)-aldehyde **12** and the 2-methoxycarbonyl analogue (*R*)-**42** (8) by using D-(-)-tartaric acid as a means of inducing asymmetry at C-1 of the tetrahydroisoquinoline system. Their procedure for the preparation of compounds **12** and **42** is partially outlined in Scheme 7.

Compound **37**, methyl [(*2S,3R*)-dihydroxy-3-(6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydro-isoquinolin-1′(*R*)-yl]propanoate hydrochloride, was synthesized by the method of Dörnyei and Szántay (7) for the preparation of the enantiomer. Compounds **38** and **39** were obtained upon treatment of **37** with an excess of ethyl chloroformate or an excess of methyl chloroformate, respectively. Selective deacylation on the oxygen was carried out by methanolysis to afford the N-alkoxycarbonyldihydroxy compounds **40** and **41**. Treatment of **40** and **41** with sodium periodate afforded the (*R*)-aldehydes **12** and **42**, respectively. These aldehydes were used as starting materials in the asymmetric synthesis of (*S*)-homolaudanosine **43**, (*S*)-5-methoxyhomolaudanosine **44**, (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine **45**, and (*S*)-*O*-methylkreysigine **46**. Their structural features are shown in Figure 2.

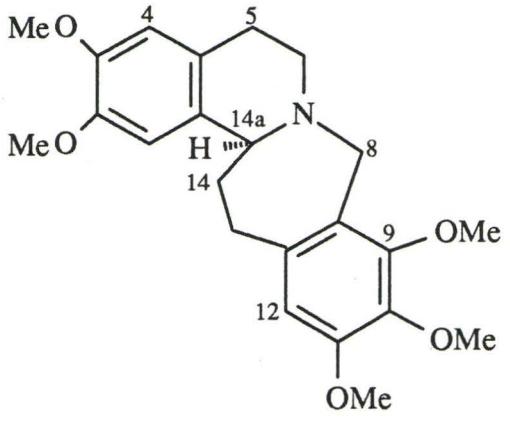
The procedure for the synthesis of **43** is outlined in Scheme 8. The ylid **47** was prepared by treating 3,4-dimethoxybenzylphosphonium chloride with n-BuLi in THF, first at -78°C and then at -20°C. The resulting mixture was then cooled to -78°C and treated with a solution of **12** in THF. The product **48** obtained was a *trans*-alkene as indicated by the coupling constant of H-7′ and H-8′ in the ^{1}H nmr spectrum. Hydrogenation of **48** over Adam's catalyst afforded the carbamate **49**, which was reduced to (*S*)-homolaudanosine


MeO
MeO
NH2 Cl
HO
OH
CO2Me
37
MeO
MeO
N
CO2R
R2OCO
OCO2R
CO2Me
38 R = Et
39 R = Me
MeO
MeO
N
CO2R
HO
OH
CO2Me
40 R = Et
41 R = Me
MeO
MeO
N
CO2R
CHO H
12 R = Et
42 R = Me

Scheme 7



43 R = H
44 R = OMe



45

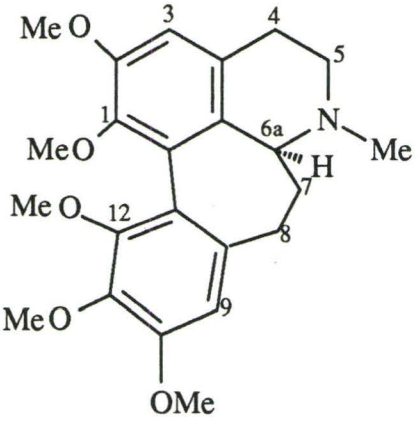


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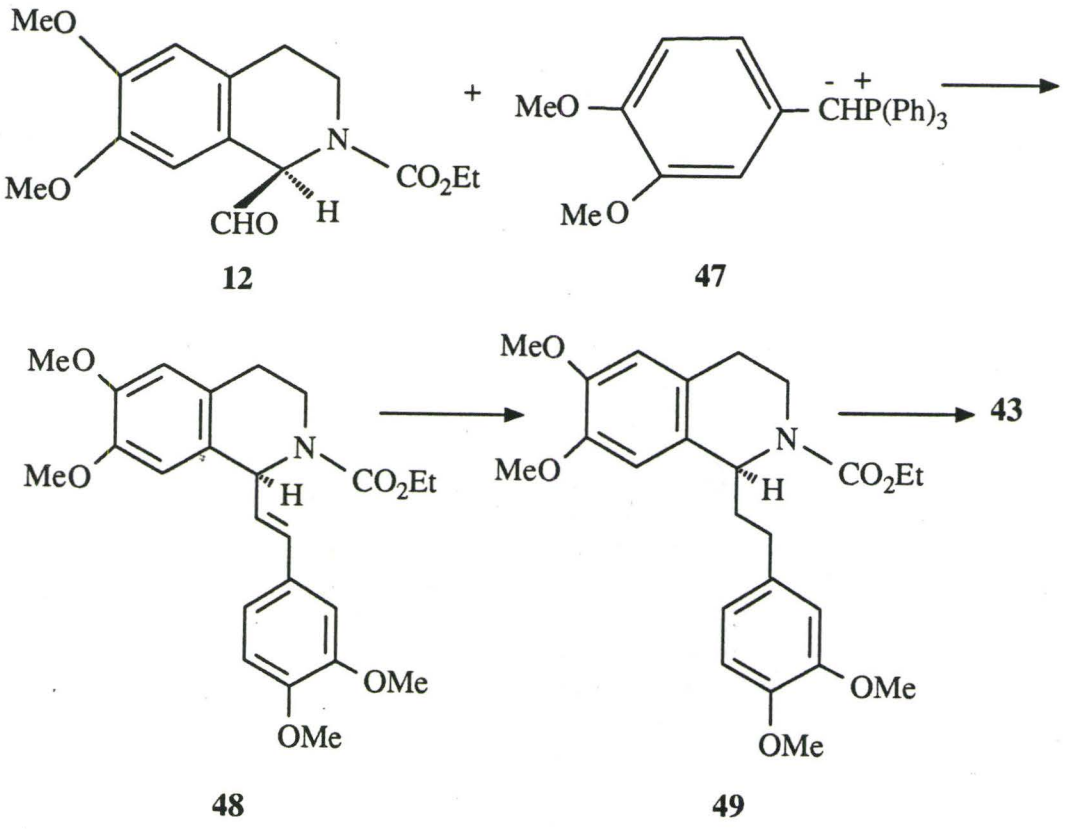
Figure 2. Structures of alkaloids of 43,44,45 and 46


MeO
MeO
CHO
H
N
CO2Et
12
+
MeO
MeO
- +
CHP(Ph)3
47
MeO
MeO
N
CO2Et
H
OMe
OMe
48
MeO
MeO
N
CO2Et
H
OMe
OMe
49
43

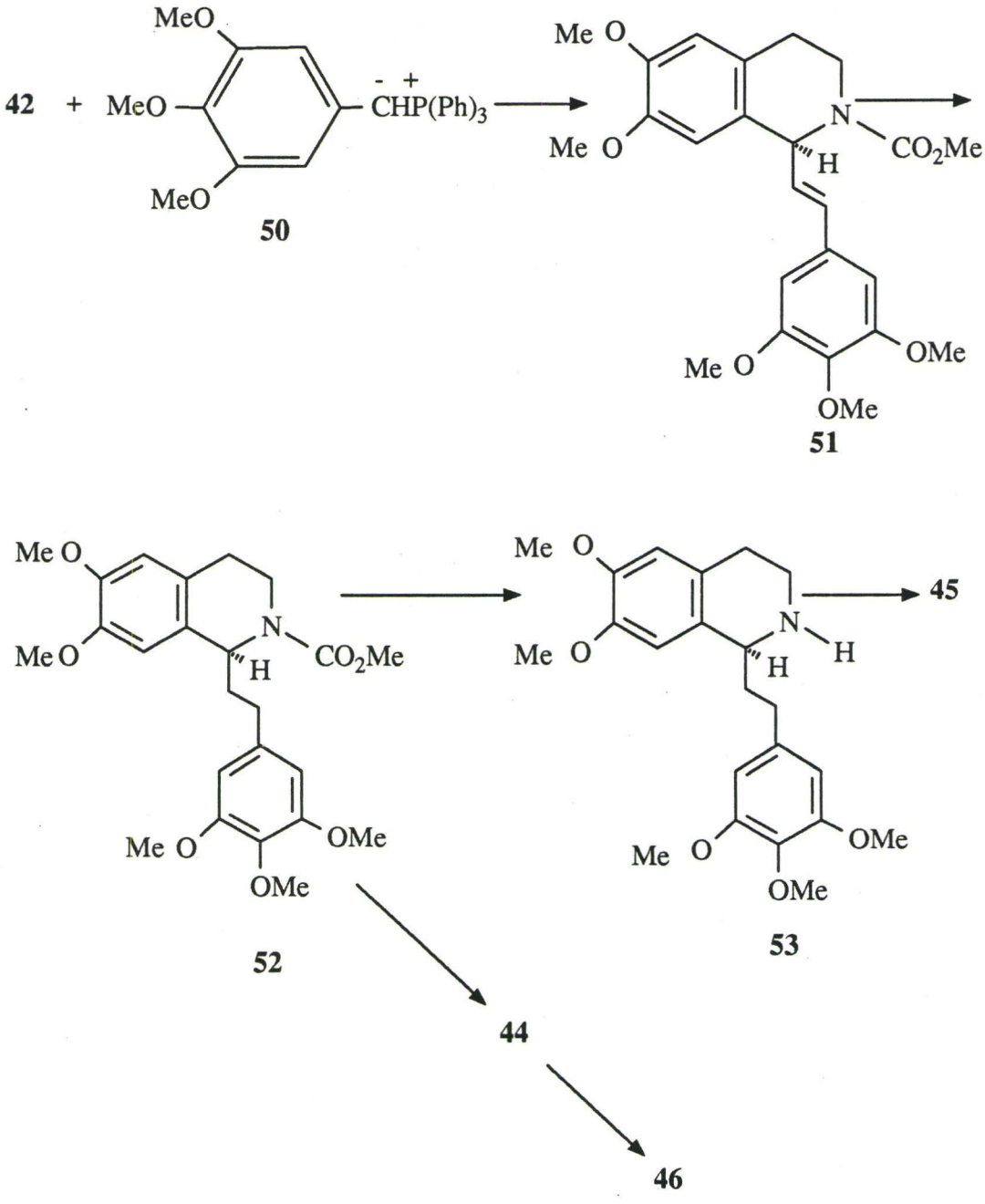
Scheme 8

43 by lithium aluminum hydride (LAH).

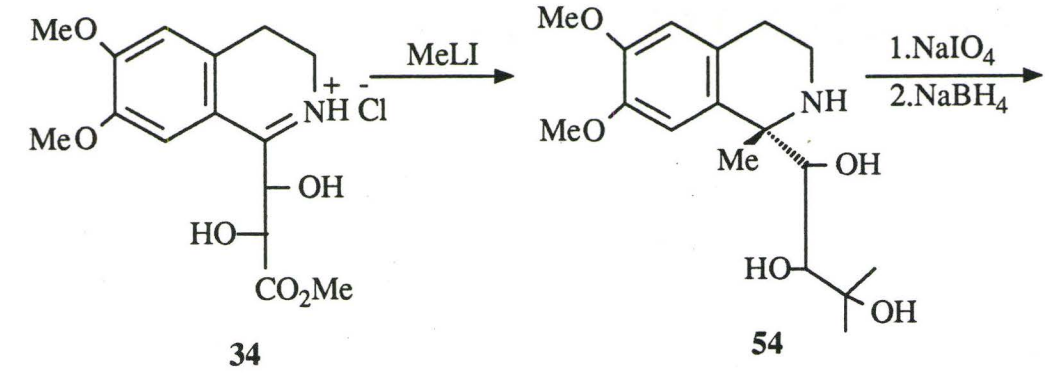
The syntheis of alkaloids, **44**,**45**, and **46** is shown in Scheme 9. The starting aldehyde, (*R*)-**42**, was treated with 3,4,5- trimethoxybenzyltriphenylphosphonium ylid **50** under conditions similar to those used for the conversion of **12** to **48** affording a *trans*-alkene **51** as evidenced by its ^{1}H nmr spectrum. The carbamate **52** was obtained by catalytic reduction of **51**. The removal of the methoxycarbonyl group was carried out by treating **52** with an excess of MeLi in THF at room temperature to afford **53**. Compound **45** was made when a solution of the hydrobromide of **53** was treated with formaldehyde. Reduction of **52** with LAH afforded compound **44**, which in turn afforded **46** upon treatment with thallium(III) trifluoro acetate.

Czarnocki *et al.* (9) have also used compounds derived from tartaric acid to synthesize (+)- and (-)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline-1-carboxylic acids **59**. Their procedure for the synthesis of **59** is partially outlined in Scheme 10. The starting material, methyl [(*2R*,*3S*)-dihydroxy-3-(6′,7′-dimethoxy-3′,4′-dihydroisoquinolin-1′-yl)]propanoate hydrochloride **34**,was prepared by the method used by Dörnyei and Szántay (7). The trihydroxy compound **54** was obtained in 80% yield when the compound **34** was treated with an excess of MeLi under an argon atmosphere. Sodium periodate oxidation followed by sodium borohydride reduction of compound **54** afforded the amino alcohol **55** in 76% yield. Compound **56** was obtained by treating **55** with an excess of ethyl chloroformate under carefully controlled conditions. Oxidation of **56** with ruthenium dioxide and sodium periodate gave compound **57**, which upon hydrolysis with aqueous ethanolic hydrochloric acid afforded the amino acid hydrochloride **58** in 98% yield.

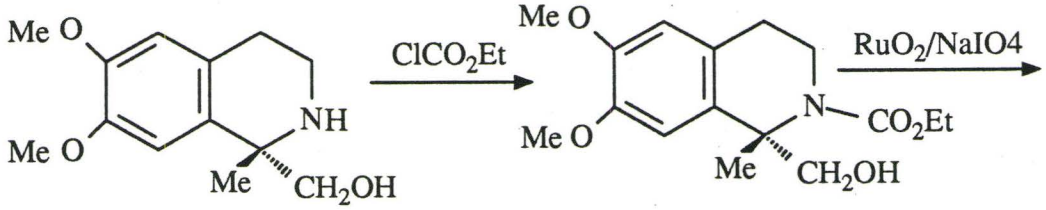
In this chapter, four different methods of inducing chirality at C-1 of the


42
MeO
MeO
MeO
CHP(Ph)3
50
Me O
Me O
N
CO2Me
H
OMe
OMe
51
Me O
Me O
N
CO2Me
H
Me O
OMe
OMe
52
Me O
Me O
N
H
H
45
Me O
OMe
OMe
53
44
46

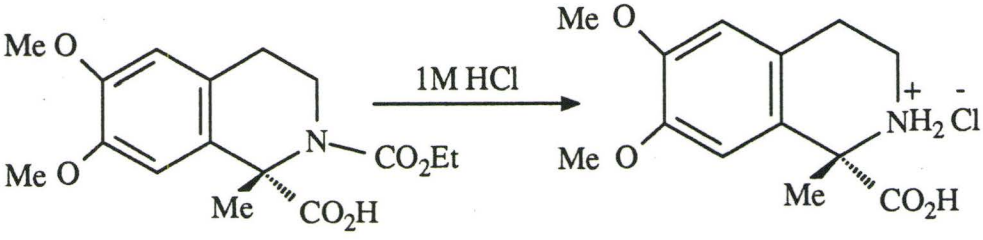
Scheme 9



34 **54**



55 **56**



57 **58**

Scheme 10

tetrahydroisoquinoline system were discussed. The method developed by Meyers and his co-workers (4) involves the preparation of 1-alkyl-substituted tetrahydroisoquinolines by using a chiral auxiliary, namely the t-butyl ether of valinol (Scheme 2). Secondly, Czarnocki *et al.*(5) have utilized the Pictet-Spengler condensation to induce chirality at C-1 of the THQ system using an imine which contains a chiral centre in the portion derived from the aldehyde (Scheme 3). Third, Yamato *et al.* (6) have used cyclic chiral 1-alkoxyisoquinolines (Scheme 4) on their way to the preparation of enantiomerically pure (*R*)- and (*S*)-1-alkyl- and 1-aryltetrahydroisoquinolines (Scheme 5). The 1-alkoxyisoquinoline may be considered to be masked iminium salts. Finally, Dörnyei and Szántay (7) have developed another way of inducing chirality at C-1 of the tetrahydroisoquinoline system. Their method involves the reduction of an iminium salt bearing a chiral centre at C-1 (see Scheme 6). Czarnocki *et al.* (9) have extended this method to a generate a quaternary centre at C-1.

In this thesis, Czarnocki's method for the preparation of compound **58** has been reexamined with the object of making it more convenient. The methodlogy has also been used to prepare ,enantioselectively, 1-phenylisoquinolines with a quaternary centre at C-1.

CHAPTER 2

RESULTS AND DISCUSSION

2.1. Introduction

Tetrahydroisoquinoline-1-carboxylic acids in which a methyl- or benzyl-group is substituted at C-1 have shown anti- inflammatory activity and other pharmacological effects (10). The 1-benzyl substituted 1-carboxylic acids, known as 'mammalian alkaloids', have been shown to have a wide range of physiological and behavioral actions (11). These alkaloids were also found in patients having a variety of enzymatic disorders (12). The 1-methyl substituted 1-carboxylic acids are known to be biosynthetic precursors of isoquinoline cactus alkaloids (13). Brossi and Schonenberger (14) have prepared optically pure (+)- and (-)-salsoline-1-carboxylic acid, a mammalian alkaloid known previously only in racemic from, by chemical resolution.

Czarnocki *et al.* (9) have shown that compound **34** would undergo diastereo-selective addition to the C=N double bond with a large excess of MeLi in the isoquinoline alkaloid framework on their way to the asymmetric synthesis of (*R*)- and (*S*)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-isoquinoline-1-carboxylic acid hydro-chloride **58**(see Scheme 10). Here, we reexamine some aspects of the enantioselective synthesis of compound **58** starting from the optically pure L-(+)-tartaric acid. Also, we demonstrate that phenyllithium adds diastereoselectively to the double bond of **34**.

2.2. Preparation of methyl [(*2R,3S*)-dihydroxy-3-(6′,7′-dimethoxy-3′,4′-dihydroisoquinolin-1′-yl)]propionate hydrochloride (**34**)

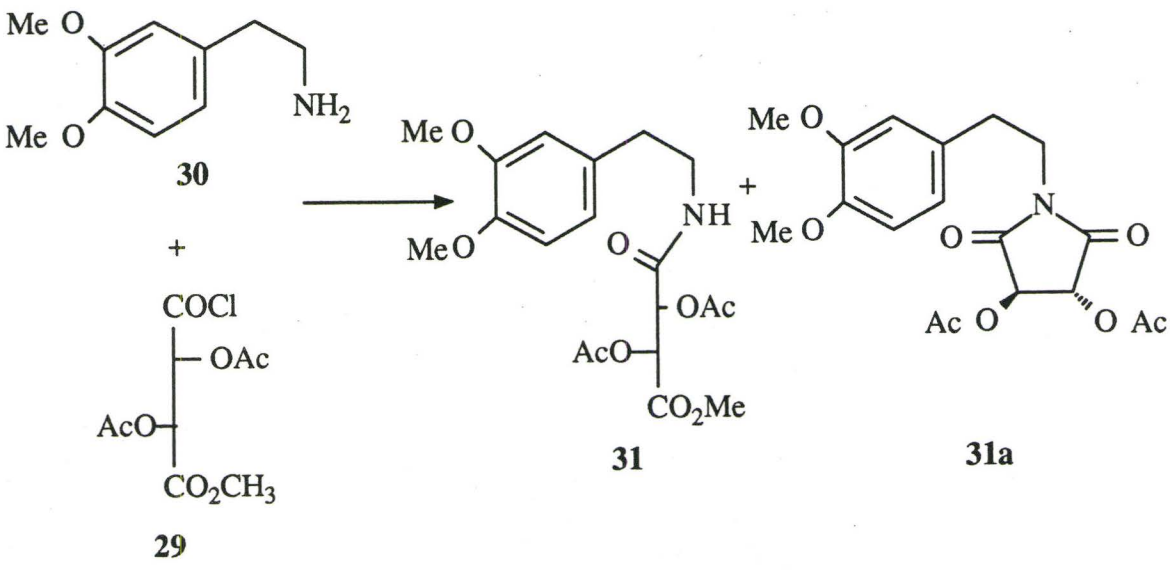
L-(+)-Tartaric acid was treated with acetic anhydride to afford the anhydride **28** (Scheme 6). The anhydride **28** was subjected to methanolysis, and the product was treated with thionyl chloride to give the half-ester chloride **29**. When

3,4-dimethoxyphenylethylamine **30** was treated with **29**, two compounds were obtained (Scheme 11). The imide **31a** was separated from **31** by using a Chromatotron eluting with benzene - methanol (5:1, v/v) on a silica plate. The R_f values of **31** and **31a** in benzene - methanol (5:1,v/v) were 0.38 and 0.57, respectively. The structure of the minor product **31a** of the reaction is shown in Scheme 11. Compound **31a** was not previvously reported to be a product of the reaction. The absence of a singlet due to a -CO_2Me group at δ3.80 ppm in the ^{1}H nmr spectrum of compound **31a** indicated that the methyl group had been lost during its formation. Two carbonyl absorbtion bands at frequencies of 1755 cm^{-1} and 1725 cm^{-1} in the I.R. spectrum of **31a** indicated the presence of an imide functional group (15) and suggested that it had structure **31a**. A molecular ion at m/z 379 shown in the EI mass spectrum lends further support to the proposed structure.

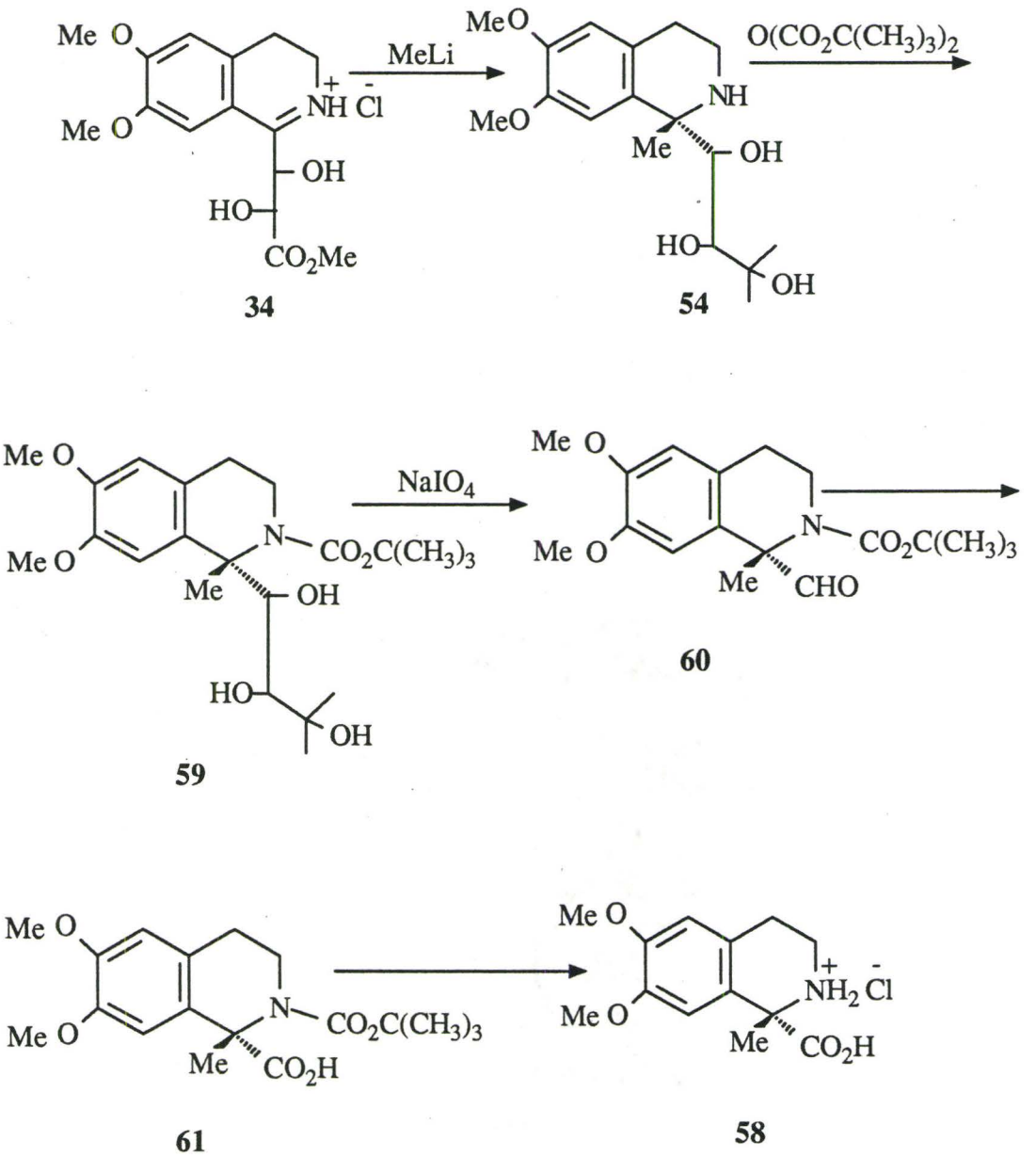
The acid-amide **32** was prepared in almost quantitative yield when the acylation was carried out directly with the anhydride **28**. The resutling amide-carboxylic acid **32** was methylated with diazomethane to afford compounds **31** and **31a**. Treatment of **31** with PCl_5 in methylene chloride followed by methanolic deacetylation afforded compound **34**.

2.3. Preparation of (+)-1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropanyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**54**)

The procedure for the synthesis of 1-methylisoquinoline-1-carboxylic acid hydrochloride **58** was partially outlined in Scheme 12. The first step, treatment of compound **34** with MeLi under an argon atmosphere, afforded a single isomer of **54** as judged by ^{1}H nmr spectroscopic and chromatographic analyses (t.l.c.). The structure of compound **54** was deduced from its ^{1}H nmr and mass spectra. Here, we report a more detailed analysis of its ^{1}H and ^{13}C nmr spectra.


Me O
Me O
NH2
30
+
COCl
OAc
AcO
CO2CH3
29
Me O
Me O
NH
O
OAc
AcO
CO2Me
31
+
Me O
Me O
N
O
O
Ac O
O Ac
31a

Scheme 11


Me O
Me O
MeLi
NH Cl
OH
HO
CO2Me
34
MeO
MeO
NH
Me
OH
HO
OH
54
O(CO2C(CH3)3)2
Me O
Me O
NaIO4
N
CO2C(CH3)3
Me
OH
HO
OH
59
Me O
Me O
N
CO2C(CH3)3
Me
CHO
60
Me O
Me O
N
CO2C(CH3)3
Me
CO2H
61
Me O
Me O
NH2 Cl
Me
CO2H
58

Scheme 12

The presence of three singlets at δ 1.08, 1.18 and 1.55 ppm in the spectrum run at 500 MHz (Appendix, Fig. 1) indicated that there were three methyl groups in the structure. The MeLi had added not only to the C=N double bond but also to the ester group to afford a tertiary alcohol. The signal of the methyl group at C-1 was assigned through the use of nuclear Overhauser enhancement (nOe) difference spectra. Irradiation of the C-Me signal at δ 1.55 ppm enchanced the signals at δ 6.45 and 4.08 ppm. On this basis the signal at δ 1.55 ppm was assigned to the methyl group at C-1 and those at δ 6.45 and 4.08 ppm to H-8 and H-1′, respectively. Thus, the C-Me signals at δ 1.08 and 1.18 were assigned to the methyl groups at C-3′. The evidence of diastereoselective addition of MeLi at the C=N double bond is further supported by the ^{13}C nmr spectrum in $CDCl_3$ (Appendix, Fig. 2). If a diastereomer of compound **54** were present, one might expect to observe satellite peaks associated with some of the signals in the ^{13}C nmr spectrum. Since none were observed, one may conclude that only a single isomer was present. The presence of an $(M+H)^+$ ion at m/z 326 and a fragment ion at m/z 206 in the NH_3-CI mass spectrum (Appendix, Fig. 3) lends further support to the structure of compound **54**.

The presence of a single diastereomer of compound **54** indicated that the MeLi had added diastereoselectively to the C=N double bond of compound **34**. It is very likely that the methyl group has been added from the top face of the C=N double bond of the isoquinoline framework rather than from the bottom face. The reason for this can easily be seen by looking at a molecular model of compound **54**. Owing to the presence of the C=N double bond in the isoquinoline framework, C-1 is sp^2 hybridized . Thus, C-1, C-1′, C-8a, N and C-3 must lie in the same plane; C-2′ and C-3′ of the side chain will be directed towards the bottom face of the C=N double bond when the C-1′ oxygen and the imine nitrogen are coordinated with Li in a cyclic five-membered ring (see Figure 3). Thus, the

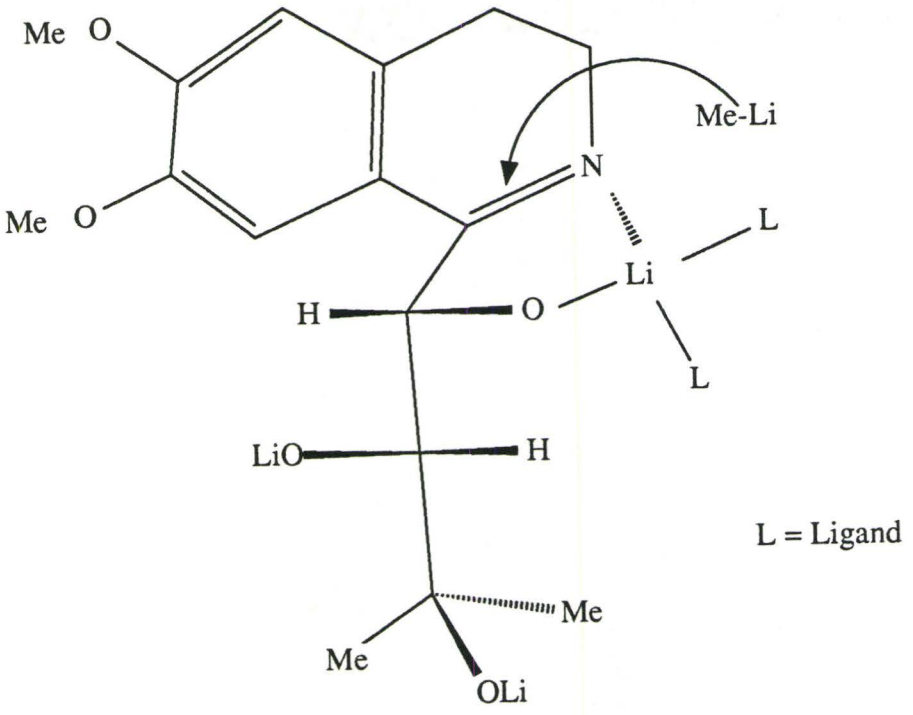


Figure 3. Rationalization of the stereoselectivity of the addition of methyllithium to 1

steric hindrance caused by the side chain at C-1 prevents the methyl group from attacking the bottom face of the C=N double bond. This conformation leads to the predominant formation of only one diastereomer, in which the methyl group has been added from the top face of the C=N double bond. Experiments carried out at Queen's University have established that this deduction is valid (16).

2.4. Preparation of 2-t-butoxycarbonyl-1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**59**)

Czarnocki's method of preparation of enantiomerically pure (+)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline -1-carboxylic acid **58** (Scheme 10) has some drawbacks in the synthetic method. Protection of the amine group in compound **55** with ethyl chloroformate in a phase transfer reaction gives a mixture of two compounds, the expected product **56** and a carbonated product **56a**. The compound **56** must be purified before going on to the next step. Also, the removal of the ethoxy carbonyl group in compound **57** with 1M HCl takes about a week for the completion. To avoid such problems, we explored the use of a reagent, namely di-t-butyl dicarbonate, which not only selectively protects the amine group but also is reported to be very easy to remove by short treatment with trifluoroacetic acid (17). The proposed synthetic scheme is outlined in Scheme 12.

The triol **54** was converted to its 2-t-butoxycarbonyl derivative **59** by treating compound **54** with di-t-butyldicarbonate. The structure of compound **59** was deduced from its ^{1}H nmr ,^{13}C nmr, and mass spectra. The ^{1}H nmr spectrum of **59** in $CDCl_3$ at 500 MHz (Appendix, Fig. 4) showed two doublets as an AB quartet at δ 7.75 and 4.03 ppm. From the homonuclear (^{1}H-^{1}H) decoupling experiment, the two protons are coupled to each other with a coupling constant of 9.1 Hz. At first glance, this would lead one to think

that the di-t-butyldicarbonate had reacted with one of the OH groups rather than with the NH group. However, the signal for H-1′ was further downfield than one would expect of a proton attached to a carbon bearing an ester group. When the spectrum was taken with the addition of D_2O, the doublet at δ 7.75 ppm disappeared and two singlets assigned to H-1′ and H-2′ were clearly shown at δ4.02 and 2.94 ppm. On this basis the two protons at C-1′ and C-2′ were not coupled to each other and the OH proton at C-1′ was strongly H-bonded. Thus, the dihedral angle(ϕ) between the two protons, H-1′ and H-2′, must approximate 90° and the OH proton at C-1′ must be H-bonded to the oxygen at C-2′ to form a cyclic five-membered ring (see Figure 4). Thus, the signal at δ 7.75 ppm may be assigned to the OH proton at C-1′ coupled to H-1′ with ^3J= 9.1 Hz. The ^{13}C nmr spectrum of compound **59** (Appendix, Fig. 5) was compatible with the proposed structure.

Additional information was obtained from nOe difference spectra. Irradiation of the C-Me signal at δ 1.84 ppm enhanced the signal at δ 6.77 ppm indicating that the signals at δ 1.84 and 6.77 ppm were due to the methyl group at C-1 and to H-8, respectively. Thus, the signal at δ 6.56 ppm could be assigned to the H-5 signal. When the signal at δ 6.77 ppm, the H-8 signal, was irradiated, enhancement of the signals at δ 4.03 and 3.83 ppm was observed indicating that these signals could be assigned to the H-1′ and the methoxy group at C-7, respectively. Thus, the singlet shown at δ 3.87 ppm could be attributed to the methoxy group at C-6.

The NH_3-CI mass spectrum of compound **59** (Appendix, Fig. 6) showed ions at m/z 426$(M+H)^+$, 370$(MH-56)^+$, 352$(MH-74)^+$ and 326$(MH-100)^+$ which are characteristic ions of the BOC protecting group(18). The ion at m/z 370 is derived from the cleavage of the BOC-protecting group through a Mclafferty rearrangement (18). A mechanism for the fragmentation of the BOC-protecting group is proposed in Scheme 13.

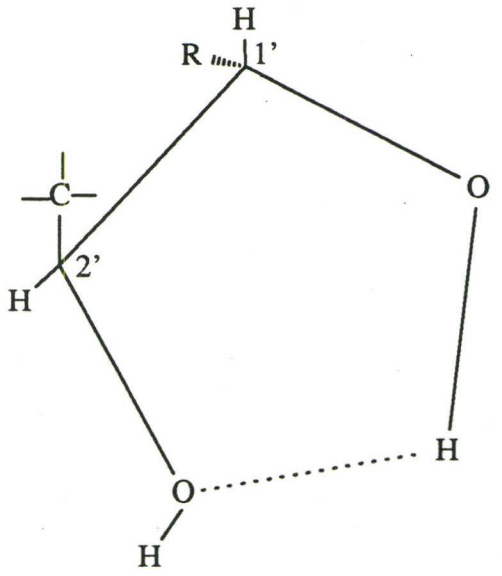
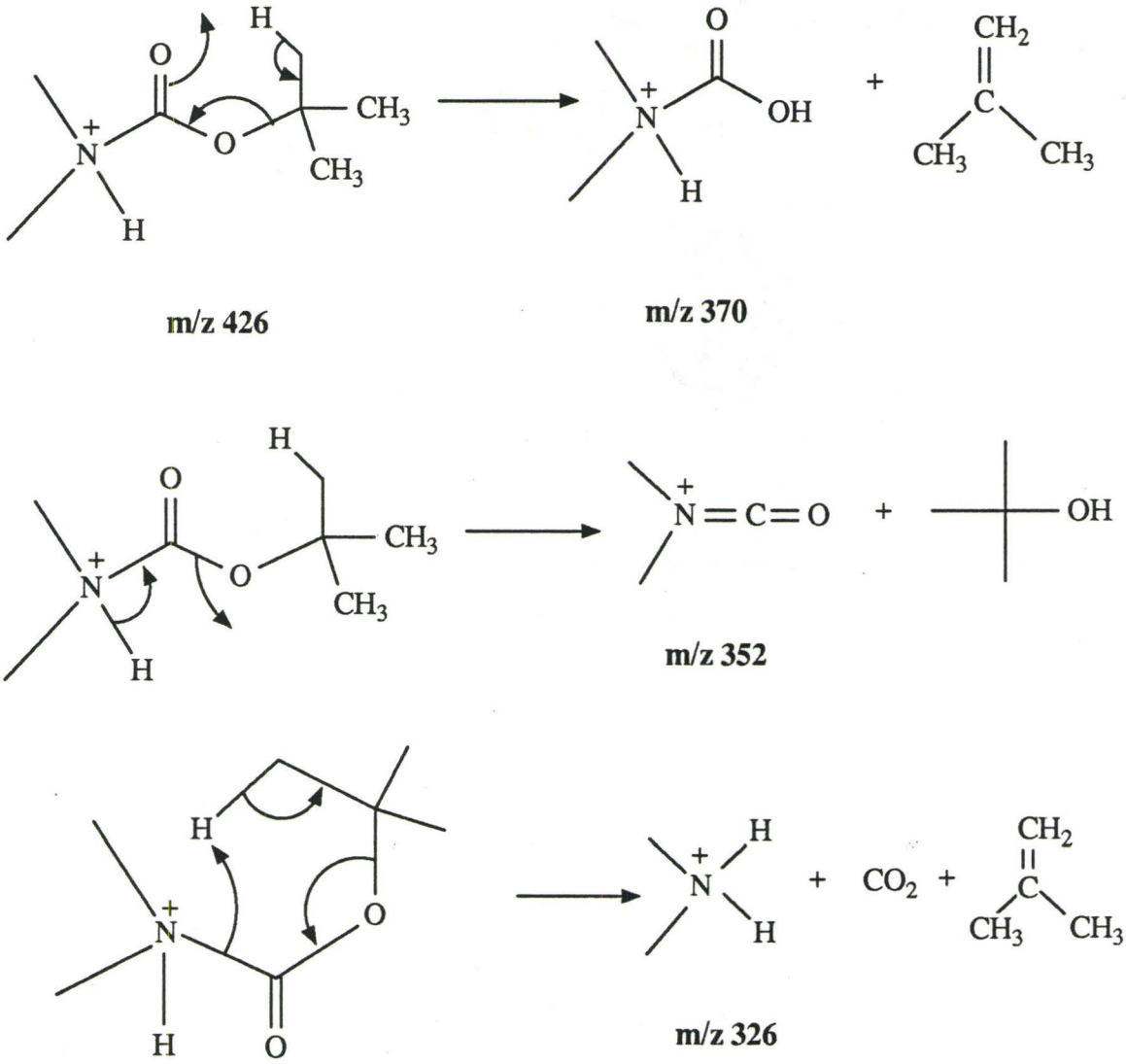


Figure 4. The staggered conformation of 54 about the C-1 - C-2 bond


H
O
CH3
+
N
O
CH3
H
O
OH
N
H
+
CH2
C
CH3
CH3
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H
O
CH3
+
N
O
CH3
H
+
N=C=O
+
OH
m/z 352
H
H
+
N
O
H
O
+
CO2
+
CH2
C
CH3
CH3
m/z 326

Scheme 13

2.5. Preparation of 1-formyl-2-t-butoxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**60**)

The oxidation of the side chain at C-1 of compound **59** was effected with sodium periodate to afford the aldehyde **60**. The structure of **60** was deduced from analysis of its ^1H nmr (Appendix, Fig. 7) and its mass spectrum (Appendix, Fig. 8) and comparison of these spectra with those of **59**. The absence of two singlets due to the methyl groups at C-3 in the ^1H nmr spectrum indicated that the side chain at C-1 had been cleaved by sodium periodate. The presence of a sharp singlet at δ 9.13 ppm indicated that the aldehyde **60** was produced. The peak shown at m/z 336 in the NH_3-CI spectrum may be assigned to the $(M+H)^+$ ion. The fragment ions shown at m/z $280(MH-56)^+$, $262(MH-74)^+$ and $236(MH-100)^+$ are the characteristic ions of the BOC-protecting group.

2.6. Attempted oxidation of aldehyde **60** to carboxylic acid **61**

The oxidation of the aldehyde **60** into the acid **61** by using $RuO_2/NaIO_4$ was attempted but the starting aldehyde **60** was recovered from the reaction mixture. The reason might be due to the steric hindrance caused by the presence of the t-butoxycarbonyl group on the nitrogen. Therefore, a different approach was investigated.

Sam and Simmons (19) have reported that potassium permanganate can be solubilized in benzene by complexing with dicyclohexyl-18-crown-6 not only to provide a convenient and efficient oxidant but to increase the anion reactivity in organic solvents. Also, the insolubility of the potassium salts of the acids in benzene is advantageous not only for product isolation but also because the salts are not subject to further oxidation. Here, we used a reagent prepared by stirring equimolar amounts of dicyclohexyl-18-crown-6 and potassium permanganate in benzene at 25°C to attempt to oxidize the aldehyde **60** into the acid **61**. Unfortunately, the expected product **61** could

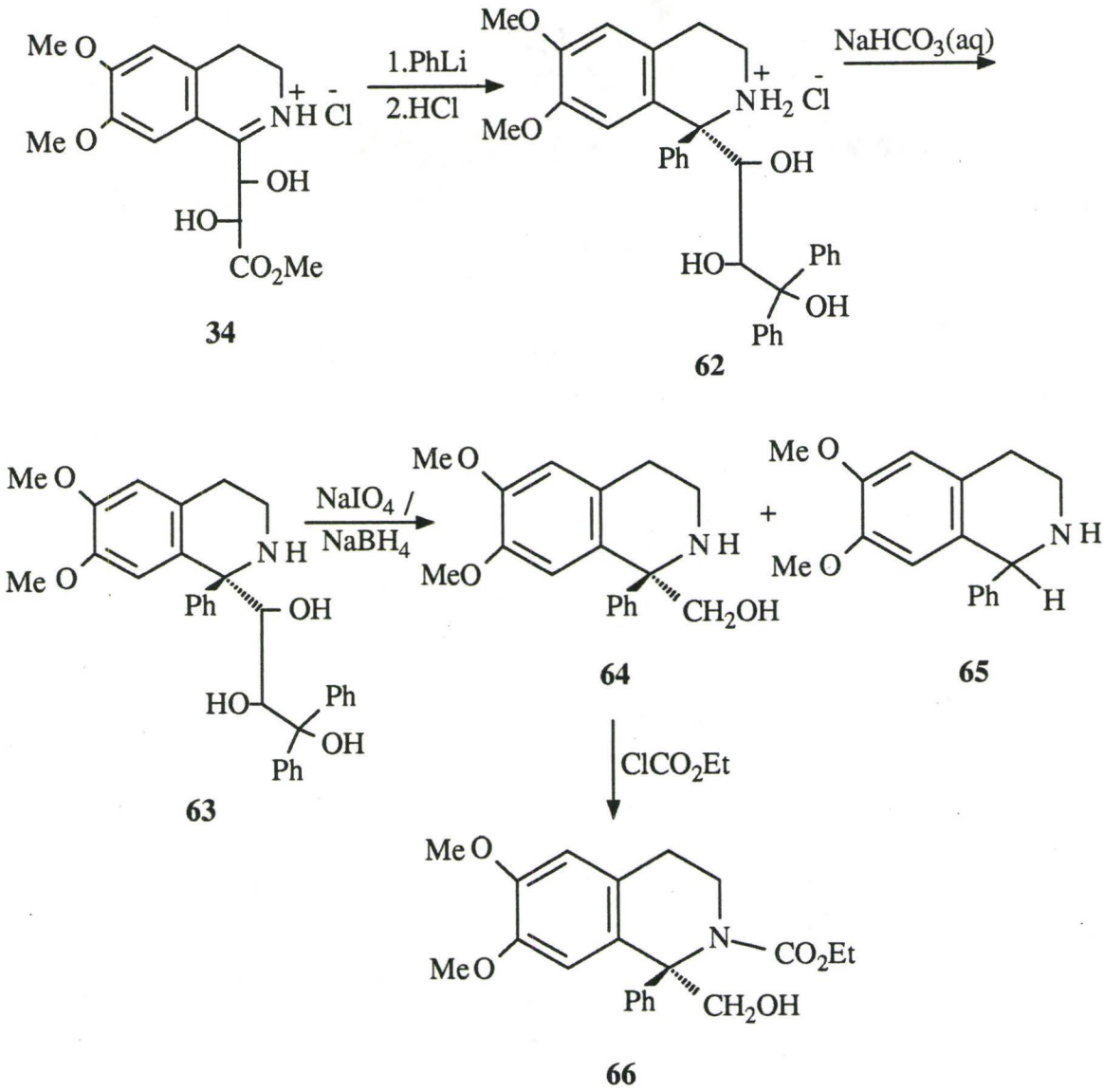
not be isolated from the reaction mixture because the oxidation reaction resulted in a complicated mixture of products. However, there is evidence that compound **61** might be formed from the reaction. The fragment ions shown at m/z 295, 266, 252, 220, 206, 192 in the NH_3-CI mass spectrum of the crude reaction mixture were indicative of the presence of the oxidation product **61**.

The crude reaction product obtained above was treated with trifluoroacetic acid and water in the hope that removal of the t-BOC protecting group might facilitate purification of the mixture. However, the crude hydrolysis product proved resistant to purification. To demonstrate that removal of the t-BOC group could be accomplished in this system, compound **60** was treated with trifluoroacetic acid and water for 15 min. at room temperature. The $(M+H)^+$ ion at m/z 236 and the $(M-29)^+$ ion at m/z 206 shown in the NH_3-CI mass spectrum of the crude reaction mixture strongly suggested that the t-BOC protecting group had been removed.

2.7. Preparation of 1-phenyl-1-(1′,2′,3′-trihydroxy-3′,3′-diphenylpropanyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**63**)

The title compound **63** was prepared as shown in Scheme 14. The methodology used for the synthesis of 1-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid hydrochloride **58** shown in Scheme 11 was applied here to prepare compound **63**, in which a phenyl group is introduced at C-1. This experiment was carried out because it was of interest to determine whether other lithiated compounds would react in a manner similar to MeLi.

Compound **62** was obtained in a crystalline form when **34** was first treated with PhLi and then with 5% HCl(aq). The hydrochloride **62**, which was isolated from the chloroform extract and obtained as a crystalline product, was converted to the free base **63**



34 **62** **63** **64** **65** **66**

Scheme 14

upon treatment of **62** with 8% $NaHCO_3$(aq); compound **63** was isolated also in a crystalline from. The structure of **63** was deduced from its ^1H nmr, ^{13}C nmr and mass spectra. The presence of 15H assigned to three phenyl groups at δ 7.11-7.46 ppm in the ^1H nmr spectrum (Appendix, Fig. 9) indicated that phenyl groups had been added to the C=N double bond and to the ester group at C-3 of **34**. The signals of the ^1H nmr spectrum were assigned through the use of nOe difference spectra in a similar manner to that used for **54**. A signal shown at δ 7.46 ppm was assigned to the ortho protons of the phenyl group at C-1 because it appeared as a doublet due to the orthho coupling. Irradiation of the signal at δ 7.46 ppm, enchanced the signals at δ 6.11 and 4.08 ppm. On this basis, the signals at δ 6.11 and 4.08 ppm could be assigned to a H-8 and H-1, respectively. Thus, the signal at δ 6.74 ppm was assigned to H-5. When the signal at δ 6.11 ppm, the H-8 signal, was irradiated, enhancement of the signals at δ 4.08 and 3.67 ppm was observed. From this information, the signal at δ 3.67 ppm was assigned to the methoxy group at C-7. Thus, the singlet shown at δ 3.95 ppm was assigned to the methoxy group at C-6. The absence of satellite peaks in the ^{13}C nmr spectrum of **63** (Appendix, Fig. 10) which might be expected if a diastereomer were present lends further support to the presence of a single isomer. The isolation of a single diastereomer of **63** indicated that the PhLi has added diastereoselectively to the C=N double bond of compound **34**. The absolute stereochemistry at C-1 was not determined but it is likely to be the same as that established for compound **54**.

The oxidation of the side chain at C-1 of compound **63** was carried out by using sodium periodate and the crude oxidation product was reduced by sodium borohydride to afford compound **64**. The structure of **64** was deduced from analysis of its ^1H nmr spectrum (Appendix, Fig. 11). The presence of only 5 H's in the aromatic region, δ

7.23-7.56 ppm, indicated that the side chain at C-1 of **63** had cleaved on treatment with sodium periodate. The AB quartet shown at δ 3.91 and 4.06 ppm with J=7.0 Hz suggested that the initial oxidation product (the aldehyde) had been reduced to the alcohol **64**. Compound **65** was isolated as a minor product of the reaction. The structure of compound **65** was deduced from analysis of its ^{1}H nmr and mass spectra. A singlet shown at δ 5.72 ppm in the ^{1}H nmr spectrum run at 500 MHz was unexpected. However, this could be explained if compound **63** was overoxidized by sodium periodate. An α-aminoalcohol or an α-aminoaldehyde can be cleaved by sodium periodate to affford in this case an imine. Reduction with borohydride would afford **65**. Thus, the signal at δ 5.72 ppm was assigned to the proton attached at C-1. The peak at m/z 270, which may be assigned to an $(M+H)^+$ ion, in the NH_3-CI mass spectrum, lends further support to the structure of **65**.

The amino group in compound **64** was treated with ethyl chloroformate to afford compound **66**. The structure of **66** was deduced from analysis of its ^{1}H nmr (Appendix, Fig. 12) and its mass spectrum. The presence of a triplet at δ 1.29 and a quartet at δ 4.20 ppm with J=7.5 Hz indicated that an ethoxycarbonyl group had been incorporated into compound **64**. Also, the AB quartet due to the 1-hydroxymethyl group had shifted further downfield because of the presence of the ethoxycarbonyl group on the nitrogen. The peak shown at m/z 372 in the NH_3-CI mass spectrum of **66** may be assigned to the $(M+H)^+$ ion and the fragmentation pattern shown in the spectrum is compatible with the proposed structure of **66**.

2.8. Summary and Conclusion

Czarnocki's procedure for the preparation of compound **58** was reexamined because of some drawbacks in the synthetic method. To begin with, the protection of the amino group of compound **55** prior to oxidation to acid by using ethyl chloroformate

resulted in a mixture of products which must be purified before going on to the next step. Secondly, the removal of the protecting group after oxidation to acid took about a week for completion. Finally, the oxidation itself of the aminoalcohol **56** to acid **57** by using ruthenium dioxide and sodium periodate was also very slow.

Here, we used di-t-butyldicarbonate rather than ethyl chloroformate not only because it selectively protects the amino group but also because it is very easy to remove by short treatment with trifluoroacetic acid and water. The oxidation of the aldehyde **60** to the acid **61** was attempted using a reagent prepared by stirring equimolar amounts of dicyclohexyl-18-crown-6 and potassium permanganate in benzene at 25°C. This is one of the synthetic applications of crown polyethers which makes use of their ability to complex metal salts and hence to increase anion reactivity in organic solvents. It is also easy to monitor the oxidation reaction by decolourization of the reagent. Unfortunately, the oxidation reaction resulted in a complicated mixture of products in which some of the expected product **61** may have formed as indicated by analysis of the NH_3-CI mass spectrum of the crude reaction product. Further investigation to find reaction conditions which lead to the formation of the desired acid should be investigated.

Czarnocki's method of preparation of compound **58** was extended to prepare, enantioselectively, 1-phenylisoquinolines with a quaternary centre at C-1 using PhLi as a reagent. Although the absolute stereochemistry of these compounds at C-1 was not established, it seems likely that the PhLi would add diastereoselectively to the C=N double bond of the isoquinoline framework as MeLi did. It should be possible to extend this methodology to prepare other 1-alkyl- and 1-aryl-substituted isoquinolines by using different lithiating reagents, like benzyllithium, n-butyllithium, and sec-butyllithium.

CHAPTER 3

EXPERIMENTAL

3.1. Apparatus and Methods

The ^{1}H nmr spectra were recorded on a Varian EM390 spectrometer at 90 MHz or a Bruker AM500 spectromer at 500 MHz. Tetramethylsilane (TMS) was used as internal standard. Chemical shifts were measured in relation to TMS and were reported in ppm(δ). The symbols, s(singlet), d(doublet), t(triplet), q(quartet), m(multiplet), br(broad), were used in reporting spectra. The ^{13}C nmr spectra were recorded at 125.76 MHz on a Bruker AM500 FT spectrometer at ambient temperature.

Proton-proton nOe difference spectra were acquired by substraction of a control FID from an on-resonance FID. The decoupler in the control FID irradiated a position in the spectrum where there were no proton signals. The on-resonance FID was obtained with the proton of interest being selectively saturated. In both cases the same decoupler power and duration of saturation (5.0 s) were used. This saturation period also served as the relaxation delay for both the control and on-resonance FID's. The decoupler was gated off during acquisiton.

The ^{13}C - ^{1}H 2-D chemical shift correlation spectra were acquired using the standard pulse sequence incorporating the BIRD pulse during the evolution period for ^{1}H - ^{1}H decoupling in F1. The spectra in F2 were recorded over a spectral width of 12.821 KHz in 4K data points. The 256 FIDs in F1 were obtained over the ^{1}H spectral width stated above. Each FID was acquired in 320 scans.

^{13}C NMR spectra were recorded at 125.759 MHz using 5 mm dual frequency ^{1}H - ^{13}C probe. The spectra were acquired over a 30.0 KHz spectral width in 32K data points (0.557 s acquisition time) using the standard J-modulated spin sort pulse sequence for

editing. The ^{13}C 90° pulse width was 6.4 μs. A 1.0 s relaxation delay was used. The FIDs were processed using exponential multiplication (line broadening: 4.0 Hz).

EI and CI mass spectra were recorded on a VG analytical ZAB-E mass spectrometer and CI mass spectra were recorded using NH_3 as reagent gas. Exact masses were determined under DEI conditions. Infrared spectra were recorded on a Perkin-Elmer Infrared Spectrometer 283. Melting points were recorded using a Gallenkamp melting point apparatus and were uncorrected. Silica gel 60 PF_{254} containing gypsum ($CaSO_4$) (from BDH) was used to prepare 4 mm, 2 mm, and 1 mm plates for the Chromatotron.Thin layer chromatography (t.l.c.) was performed on Polygram Sil G/UV_{254} and was used to determine the homogeneity of the products

All reactions involving lithiating reagents were carried out under an argon atmosphere in a flame dried glassware using septa and syringes for transfer of reagents. 1,2-Dimethoxy ethane was dried by distillation from Na/benzophenone under a nitrogen atmosphere just prior to use.

The starting materials, L-(+)-tartaric acid, MeLi (1.4 M solution in diethyl ether), PhLi [2.0 M solution in cyclohexane/diethyl ether (70:30)], and 3,4-dimethoxyphenylethyl amine were obtained from Aldrich Chemical Company, Inc.; 1001 West Saint Paul Avenue; Milwaukee, Wisconsin 53233 USA.

3.2. Preparation of (*2R,3R*)-*O,O*-diacetyltartaric anhydride (**28**)

The title compound was synthesized by the method described in the literature (20). Yield: 70%; mp 133-134°C [lit. 133-134° (20)]; IR($CHCl_3$ film), ν_{max}: 1905, 1830 (C=O anhydride), 1765 (C=O ester).

3.3. Preparation of monomethyl (*2R,3R*)-*O,O*-diacetyltartrate

The title compound was prepared by the method described in the literature (21).

Yield: Quantitative; mp 117-118°C [lit. 124.7° (21)].

3.4. Preparation of the acid chloride of monomethyl (*2R,3R*)-*O,O*-diacetyltartrate (**29**)

The title compound was prepared by the method described in the literature (21). Yield: 83%; mp 103-105°C [lit. 108.5° (21)]; IR($CHCl_3$film), ν_{max}: 1815 (-ClC=O), 1780, 1770, 1760 (3 ester groups).

3.5. Preparation of methyl [(*2R,3R*)-diacetoxy-3-(*N*-3,4-dimethoxyphenylethyl-carbamoyl)] propionate (**31**)

The title compound was isolated as a major product upon treatment of the acid chloride **29** with 3,4-dimethoxyphenylethylamine **30**. Separation of the reaction mixture on a Chromatotron afforded compound **31**. Yield: 75%; mp 81-83°C [lit. 81-83°(7)]; IR($CHCl_3$ film), ν_{max}: 1755(C=O ester), 1680(amide I), 1515(amide II); ^{1}H nmr(90 MHz, $CDCl_3$) δ: 2.12 and 2.16(3H each, 2 s, 2 MeC=O), 2.83(2H, m, Ph-CH_2-), 3.56(2H, m, -CH_2-NHCO), 3.80(3H, s, CO_2Me), 3.98 and 4.0(3H each, 2 s, 2 OMe), 5.65 and 5.80(1H each, AB system, J=2.5 Hz, -CH-OAc), 6.28(1H, br, -NH), 6.84 and 6.90(3H, aromatic H's).

3.6. Preparation of [(*3R,4R*)-diacetoxy-(*N*-3,4-dimethoxyphenylethyl)]succinimide (**31a**)

The title compound was isolated as a minor product (by using a Chromatotron), an oil, upon treatment of the acid chloride with 3,4-dimethoxyphenylethylamine. Yield: 15%; IR($CHCl_3$ film), ν_{max}: 1750(imide), 1725(C=O ester); ^{1}H nmr(90 MHz, $CDCl_3$) δ: 2.30 and 2.33(3H each, 2s, 2MeC=O), 2.90-3.13(2H, m, Ph-CH_2), 3.87-3.97(2H, m, -CH_2-N-), 4.03 and 4.04(3H each, 2s, 2OMe), 5.73 and 5.87(1H each, AB quartet, J=1.5 Hz, -CH-OAc), 6.93, 6.94, and 6.97(3H, 3s, aromatic H's); ms(EI),m/z(%): 379(24)$M^{+\cdot}$, 164(100), 151(57), 83(28).

3.7. Preparation of (*2R,3R*)-diacetoxy-3-(*N*-3′,4′-dimethoxyphenylethylcarbamoyl)-propionic acid (**32**)

The title compound was obtained upon treatment of (*2R,3R*)-*O,O*-diacetyltartaric anhydride with 3,4-dimethoxyphenylethylamine. Yield: 85-90%; mp 219-220°C [lit. 220° (7)]; IR(KBr), ν_{max}: 1760(C=O ester), 1735(C=O acid), 1640(C=O amide).

3.8. Preparation of methyl [(*2R,3S*)-dihydroxy-3-(6′,7′-dimethoxy-3′,4′-dihydroisoquinolin-1′-yl)]propionate hydrochloride (**34**)

The title compound was prepared by the method described in the literature (7). Yield: 85%; mp 156-157°C [lit. 162-163°(7)]; IR(KBr), ν_{max}: 1719(C=O ester), 1655(-C=N^+); ^{1}H nmr(90 MHz, $CDCl_3$) δ: 3.12(2H, m, Ph-$\underline{CH_2}$), 3.50(2H, m, -$\underline{CH_2}$-NH-), 3.88, 3.98, and 4.02(3H each, 3s, 3O$\underline{Me}$), 4.52(1H, d, J=2.2 Hz, H-2), 5.88(1H, m, H-1), 7.22 and 7.46(1H each, H-5′ and H-8′).

3.9. Preparation of 1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**54**)

A suspension of the iminium chloride **34**(0.60g, 0.0017 mol) in dry 1,2-dimethoxyethane (DME,20 mL) at -10°C to -5°C was treated with MeLi (20 mL, 1.4M in diethyl ether) under an argon atmosphere. The mixture was stirred at the same temperature range for 3h and then treated with MeOH (5 mL) to destroy the excess reagent. The volatile solvents were removed *in vacuo* and water (6 mL) was added to the residue. The resulting mixture was thoroughly extracted with chloroform, washed with brine, and dried over Na_2SO_4(anhyd.). The solvent was evaporated *in vacuo* and the residue was chromatographed on silica using $CHCl_3$ - MeOH (20:1, v/v) to remove non-polar impurities. Further elution with $CHCl_3$ - MeOH (3:1,v/v) gave **54** as a

brownish oil (0.40g, 71%); $[\alpha]_D$ +80.5° (c 2.30, $CHCl_3$). ^1H nmr(500 MHz, $CDCl_3$) δ: 1.08 and 1.18 (3H each, 2s, C-Me's at C-3′), 1.55(3H, s, C-Me at C-1), 2.55(1H, m, H-4_{ax}), 2.98(1H, s, H-2′), 2.99(1H, m, H-4_{eq}), 3.01-3.10(2H, m, H-3′s), 3.77 and 3.82(3H each, 2s, 2OMe's), 4.07(1H, s, H-1′), 6.45(1H, s, H-8), 6.57(1H, s, H-5); ^{13}C nmr (125.76 MHz, $CDCl_3$) δ: 24.1 and 27.6(C-Me's at C-3′), 25.7(C-Me at C-1), 29.8(C-4), 37.9(C-3), 59.7(C-1), 74.0(C-3′), 74.6(C-2′), 75.5(C-1′), 108.5(C-8), 112.1(C-5), 127.7(C-8a), 130.5(C-4a), 147.5(C-6 and C-7); ms (CI, NH_3), m/z(%): 326$(M+H)^+$(100), 206(14).

3.10. Preparation of 2-t-butyloxycarbonyl-1,2,3,4-tetrahydro-1-(1′,2′,3′-trihydroxy-3′,3′-dimethylpropyl)-6,7-dimethoxy-1-methylisoquinoline (**59**)

Compound **54**(0.2g, 0.00062 mol) was dissolved in $CHCl_3$(3 mL), and 0.13g of $NaHCO_3$ in 2.3 mL H_2O was added. To this solution, 0.31g of NaCl and 0.27g(0.0012 mol) of di-t-butyldicarbonate dissolved in 1 mL of $CHCl_3$ were added. The resulting reaction mixture was refluxed for 8 h. After the solution cooled, the organic layer was separated, dried with Na_2SO_4(anhyd.) and evaporated *in vacuo*. The residue was purified by using a Chromatotron with a silica plate eluting with hexane - EtOAc (2:1,v/v) to remove excess di-t-butyldicarbonate, and then with EtOAc to elute first some unreacted **54** and then the product **59**. The compound **59** was isolated as a yellowish oil(0.12g, 55%). ^1H nmr(500 MHz, $CDCl_3$) δ: 0.78 and 0.97(3H each, 2s, Me's at C-3′), 1.51(9H, s, $OC(Me)_3$), 1.84(3H, s, Me at C-1), 2.58-2.65(1H, m, H-4_{ax}), 2.86-2.96(2H, m, H-4_{eq} and H-2′), 3.13-3.19(1H, m, H-3_{ax}), 3.83(3H, s, OMe at C-7), 3.87(3H, s, OMe at C-6), 4.03(1H, d, J=9.1 Hz, H-1', it becomes a singlet at δ 4.01 on addition of D_2O), 4.14-4.18(1H, m, H-3_{eq}), 6.56(1H, s, H-5), 6.77(1H, s, H-8), 7.75(1H, d, J=9.1 Hz, OH at C-1′, disappeared on addition of D_2O); ^{13}C nmr(125.76 MHz, $CDCl_3$) δ: 22.8(Me at C-1), 25.2 and 25.4(Me's at C-3′), 28.4($OC(Me)_3$, 3 Me's), 29.9(C-4), 42.8(C-3), 55.8 and 56.1(2

OMe), 66.0(O<u>C</u>(Me)$_3$), 73.2(C-1), 74.2(C-1′), 78.9(C-2′), 81.6(C-3′), 110.5(C-5 and C-8), 129.0 and 132.0(C-4a and C-8a), 147.7 and 147.9(C-6 and C-7), 158.2(-N<u>C</u>O$_2$-); ms(EI), m/z(%): 306(11), 250(100), 236(8), 206(37), 190(6); ms(CI, NH_3), m/z(%): 426(M+1, 48), 369(7), 352(48), 326(68), 250(10), 206(100).

3.11. Preparation of 1-formyl-2-t-butyloxycarbonyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**60**)

Compound **59**(0.10g, 0.00024 mol) in methanol(12.5 mL) was treated at -5°C all at once with a solution of $NaIO_4$(0.13g) in water(0.6 mL). The reaction mixture was stirred at -5°C until the reaction was complete as judged by t.l.c. analysis using $CHCl_3$. After the reaction was complete, the volatile solvent was evaporated to dryness. The residue was quenched with water(10 mL) and extracted with chloroform. The chloroform extract was dried with Na_2SO_4(anhyd.) and then evaporated *in vacuo* to afford compound **60**. The crude product was purified by using a Chromatotron with a silica plate eluting with $CHCl_3$. Evaporation of the chloroform afforded an oily residue(0.067g, 85%). ^{1}H nmr(90 MHz, $CDCl_3$) δ: 1.50(9H, s, -OC(Me)$_3$), 1.70(3H, s, Me at C-1), 2.67-3.13(4H, m, C-3 and C-4 H's), 3.80(3H, s, OMe at C-7), 3.87(3H, s, OMe at C-6), 6.60(1H, s, H-5), 6.61(1H, s, H-8), 9.13(1H, s, CHO); ms(CI, NH_3), m/z(%): 336(M+H, 2), 280(100), 236(26), 220(8), 206(95).

3.12. Preparation of 1-phenyl-1-(1′,2′,3′-trihydroxy-3′,3′-diphenylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (**62**)

A suspension of the iminium chloride **34** (2.0g, 0.0058 mol) in dry DME (90 mL) at -10°C to -5°C was treated dropwise with PhLi (2.0M, 45 mL) under an argon atmosphere. The mixture was stirred at the same temperature range for 3h and then the excess PhLi was destroyed with methanol (25 mL). The solvents were evaporated *in*

vacuo. The residue was quenched with water (40 mL) and the mixture was extracted with chloroform. The chloroform extract was treated with 5% HCl. The aqueous layer was extracted three times with chloroform. The extract was washed with brine, dried with Na_2SO_4(anhyd.) and evaporated *in vacuo* to afford a residue which was crystalized from ethyl acetate to give **62** in 70% yield. mp 189-191°C; $[\alpha]_D$ +77.1° (c 1.0, $CHCl_3$); ^1H nmr (500 MHz, $CDCl_3$) δ: 2.71-2.77(2H, m, H-4), 3.40-3.46(2H, m, H-3), 3.60(3H, s, OMe at C-7), 3.98(3H, s, OMe at C-6), 4.36(1H, s, H-1′), 4.51(1H, s, H-2′), 5.86(1H, s, H-8), 6.81(1H, s, H-5), 7.08-7.68 (aromatic H's); ^{13}C nmr (125.76 MHz, $CDCl_3$), δ: 26.0(C-4), 37.1(C-3), 68.7(C-1), 73.3(C-1′), 74.3(C-2′), 82.4(C-3′), 110.2(C-5), 111.5(C-8), 124.0(C-8a), 148.0(C-7), 149.1(C-6), 138.7, 143.8, 143.9 (quaternary aromatic C's), 125.2, 126.2, 126.9, 127.0, 128.1, 128.4, 129.2, 130.1 (aromatic CH's); ms(CI, NH_3), m/z(%): 512$(M+H)^+$(88), 268(100).

3.13. Preparation of 1-phenyl-1-(1′,2′,3′-trihydroxy-3′,3′-diphenylpropyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**63**)

The hydrochloride **62** was dissolved in chloroform and the mixture was treated with 8% $NaHCO_3$(aq.). The aqueous layer was extracted with chloroform. The extract was washed with brine, dried with Na_2SO_4(anhyd.), and evaporated *in vacuo* to afford a residue which was recrystallized with ethyl acetate to give **63** quantitatively. mp 184-185 °C; ^1H nmr (500 MHz, $CDCl_3$) δ: 2.63(1H, m, H-4_{eq}), 2.75(1H, m, H-3_{ax}), 2.96(1H, m, H-3_{eq}), 3.19(1H, m, H-4_{ax}), 3.67(3H, s, OMe at C-7), 3.95(3H, s, OMe at C-6), 4.08(1H, s, H-1′), 4.53(1H, s, H-2′), 6.11(1H, s, H-8), 6.74(1H, s, H-5), 7.11-7.46(3 aromatic H's); ^{13}C nmr (125.76 MHz, $CDCl_3$), δ: 29.2(C-4), 37.5(C-3), 65.0(C-1), 72.9(C-1′), 74.9(C-2′), 81.7(C-3′), 110.3(C-5), 111.7(C-8), 128.1(C-8a), 128.5(C-4a), 147.0(C-7), 147.8(C-6), 142.9, 145.1, 145.6 (quaternary aromatic C's), 124.9,126.4, 126.9, 127.7, 128.1, 128.2,

128.5 (aromatic CH's); ms (CI, NH_3), m/z(%): 512$(M+H)^+$(100), 268(82).

3.14. Treatment of **63** with sodium periodate

(a) Isolation of 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-hydroxymethylisoquinoline (**64**)

The amine **63** (1.2g, 0.0023 mol) in methanol (150 mL) at -5°C was treated all at once with a solution of sodium periodate (1.5g) in water (8 mL). When the starting material was consumed as indicated by t.l.c. analysis, sodium borohydride (2.3g) was added over a period of 15 min. The mixture was allowed to warm to room temperature, filtered to remove inorganic matter, and the filtrate evaporated to dryness. The residue was extracted with chloroform. The extract was washed with brine, dried with Na_2SO_4(anhyd.) and evaporated *in vacuo* to dryness. The residue was separated into two componets on a Chromatotron. Elution with $CHCl_3$ - MeOH (19:1, v/v) afforded compound **65** (see 3.14b). The title compound was isolated as a major product by eluting with $CHCl_3$ - MeOH (4:1, v/v). Evaporation of the solvent *in vacuo* afforded a residue which was recrystallized from ethyl acetate to give **64** in 75% yield. mp 192-194°C; ^1H nmr (90 MHz, $CDCl_3$) δ: 2.60-2.97(4H, m, H-3 and H-4), 3.70(3H, s, OMe at C-7), 3.85(3H, s, OMe at C-6), 3.91 and 4.06 (2H, ABq, J=7.0 Hz, $\underline{CH_2}OH$), 6.50(1H, s, H-8), 6.67(1H, s, H-5), 7.23-7.56(aromatic H's); ms(DEI), m/z(%): 268$(M-31)^+$(100), 192(31); Exact mass calcd. for $C_{17}H_{18}NO_2(M-31)^+$: 268.1338; found (hrms): 268.1350.

(b) Isolation of 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**65**)

The title compound was isolated as a minor product as described in 3.14(a) as an oil in 15% yield. ^1H nmr(500 MHz, $CDCl_3$) δ: 3.11-3.15(1H, m, $H\text{-}4_{ax}$), 3.23-3.30(1H, m, $H\text{-}4_{eq}$), 3.42-3.51(2H, m, H-3), 3.58(3H, s, OMe at C-7), 3.85(3H, s, OMe at C-6), 5.72(1H, s, H-1), 6.34(1H, s, H-8), 6.89(1H, s, H-5), 7.39-7.47(5H, aromatic H's); ms(CI,

NH_3), m/z(%): 270$(M+H)^+$(100), 192(33); ms(DEI), m/z(%): 269$(M)^{+\cdot}$(34), 268(M-H)(30), 192(100); Exact mass calcd. for $C_{17}H_{19}NO_2(M)^{+\cdot}$: 269.1417; found (hrms): 269.1411.

3.15. Preparation of 2-ethoxycarbonyl-1,2,3,4-tetrahydro-1-hydroxymethyl-6,7-dimethoxy-1-phenylisoquinoline (**66**)

A solution of **64** (0.87g, 0.0029 mol) in chloroform (50 mL) and an aqueous solution (50 mL) comprised of sodium hydroxide (5g) and acetic acid (0.5g) were mixed and vigorously stirred. To this two phase system, ethyl chloroformate (4 mL) was added in two protions at 5-min. intervals and the stirring was continued for 15 min. The temperature was kept below 20°C. After stirring the mixture for 15 min., the chloroform layer was separated, washed with a brine and dried on Na_2SO_4(anhyd.). The volatile solvent was evaporated *in vacuo* to give **66** as yellowish oil (0.81g, 75%). ^{1}H nmr (90 MHz, $CDCl_3$) δ: 1.29(3H, t, J=7.5 Hz, $OCH_2\underline{CH_3}$), 2.73-3.13(4H, m, H-3 and H-4), 3.81(3H, s, OMe at C-7), 3.93(3H, s, OMe at C-6), 4.20(2H, q, J=7.5 Hz, $O\underline{CH_2}CH_3$), 4.66 and 4.87(2H, ABq, J=10.5 Hz, -$\underline{CH_2}$OH), 6.67(1H, s, H-8), 6.73(1H, s, H-5), 7.33-7.60(aromatic H's); ms (CI, NH_3), m/z(%): 372$(M+H)^+$(18), 343(59), 326(100), 282(53), 248(12), 208(28); ms(DEI), m/z(%): 340$(M-31)^+$(4), 325(16), 268(19), 248$(M-123)^+$(100); Exact mass calcd. for $C_{20}H_{22}NO_4(M-31)^+$: 340.1556; found (hrms): 340.1556 and for $C_{13}H_{14}NO_4(M-123)^+$: 248.0923; found (hrms): 248.0944.

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APPENDIX

LIST OF SPECTRA PAGE

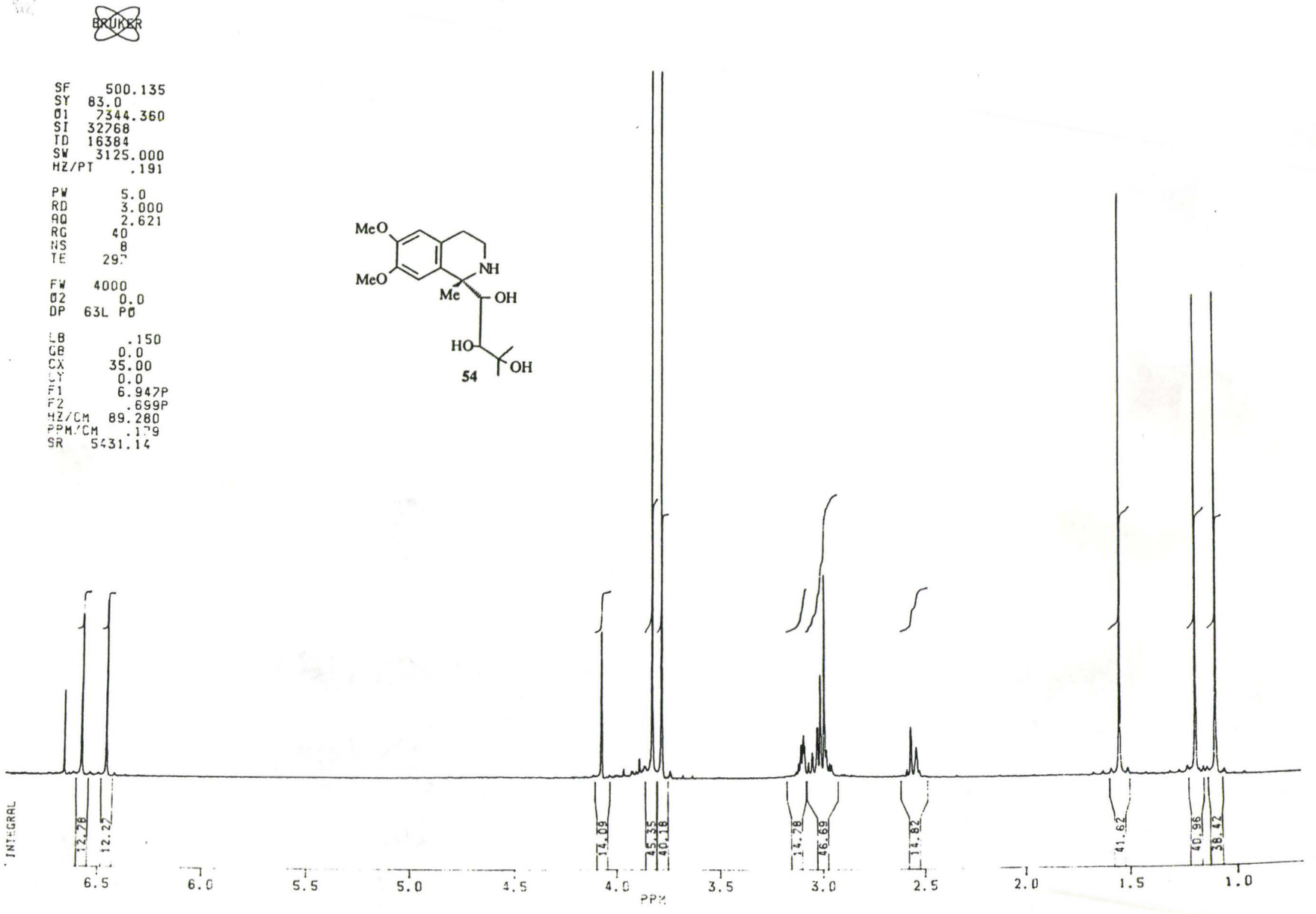

Fig. 1. ^{1}H nmr of compound 54

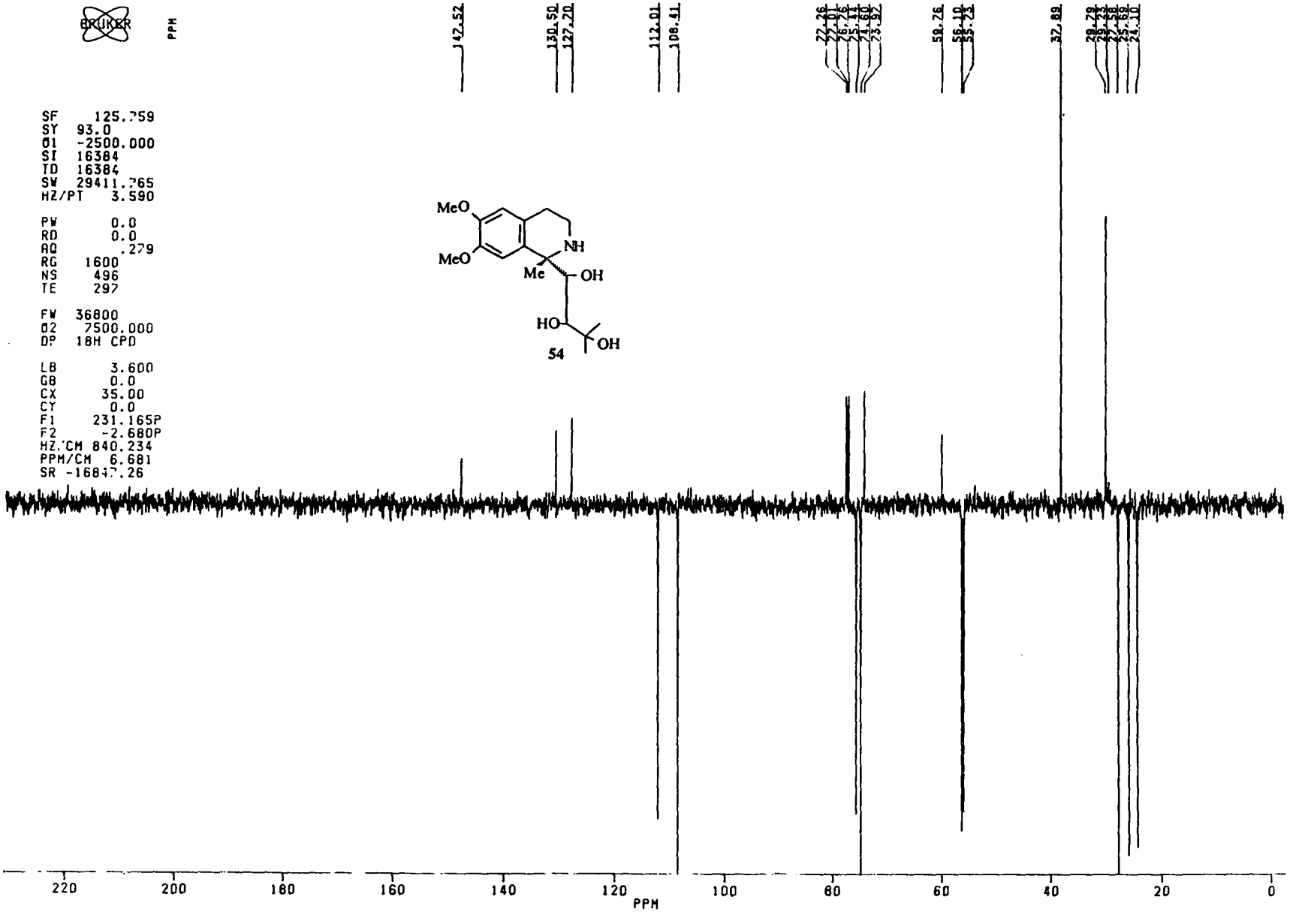

Fig. 2. ^{13}C nmr of compound 54

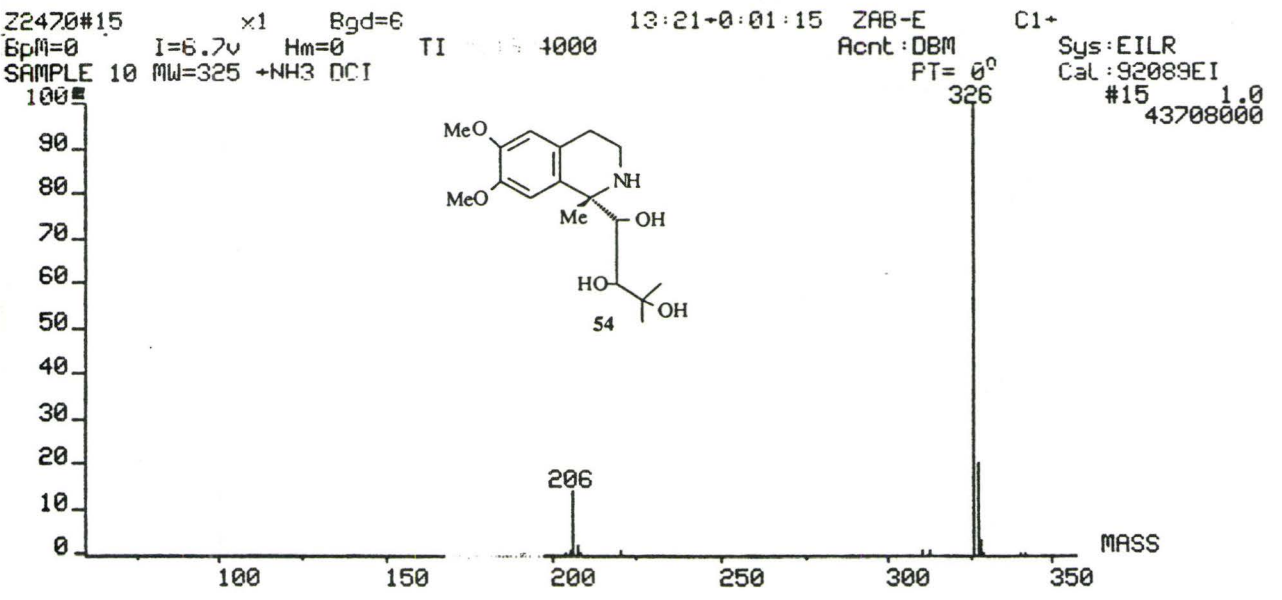

Fig. 3. NH_3-CI mass spectrum of compound 54

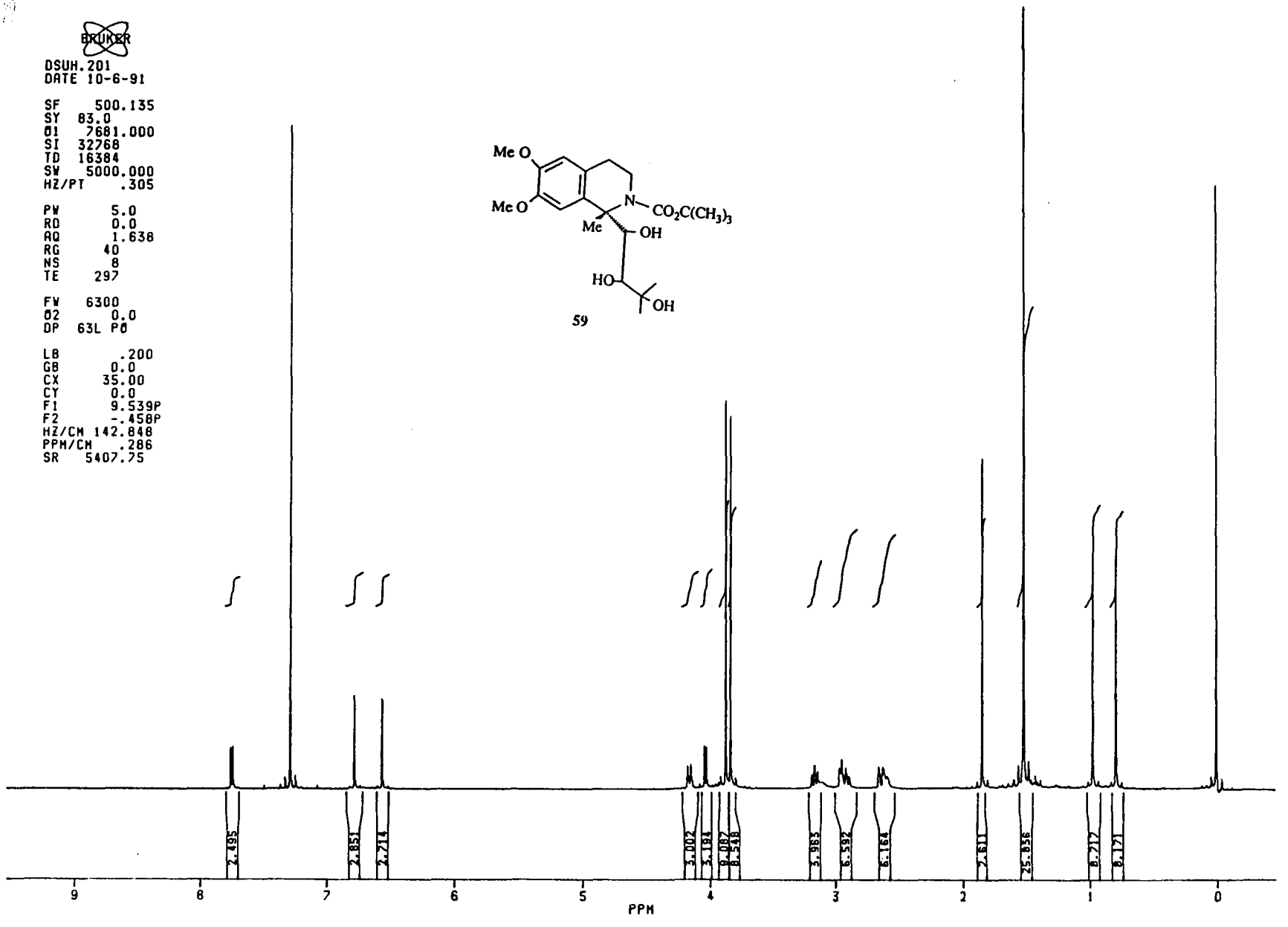

Fig. 4. ^{1}H nmr of compound 59

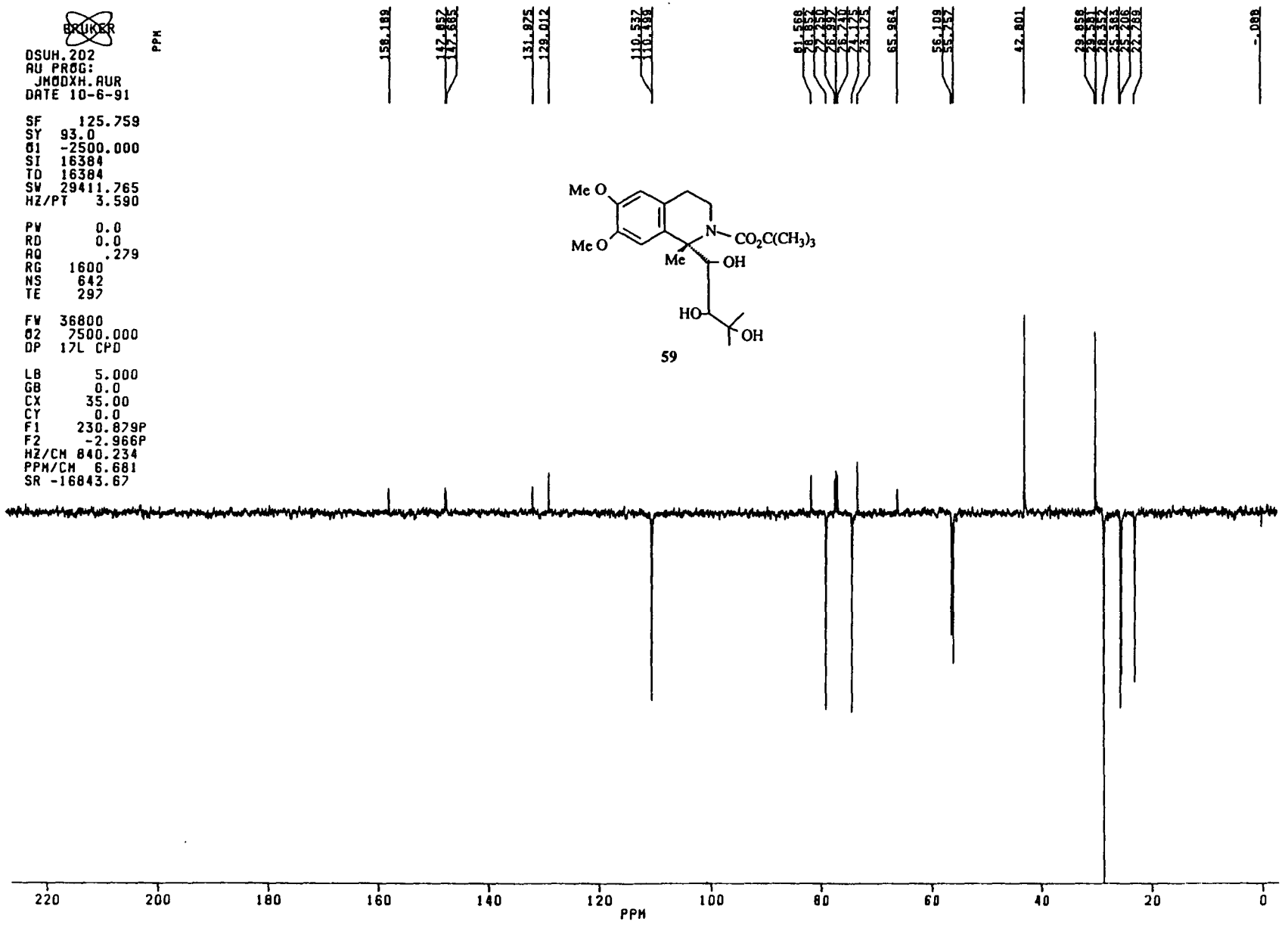

Fig. 5. ^{13}C nmr of compound 59

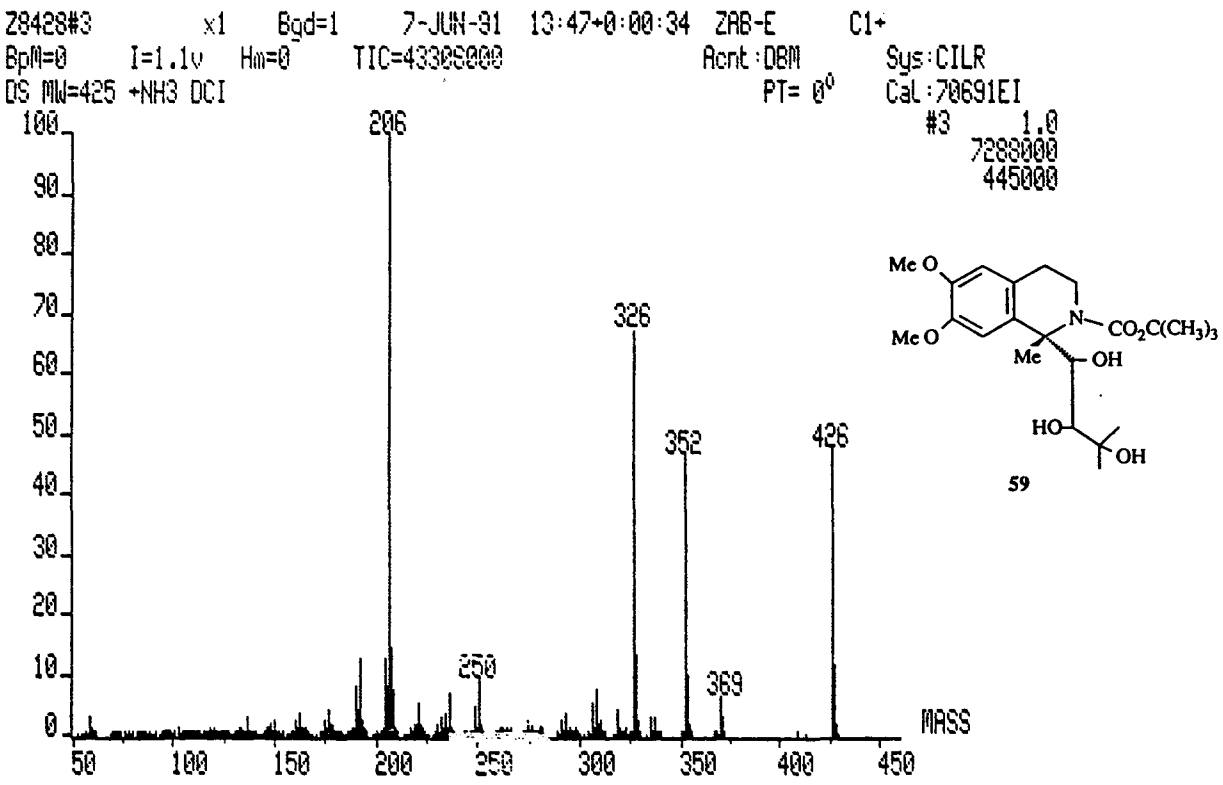

Fig. 6. NH_3-CI mass spectrum of compound 59

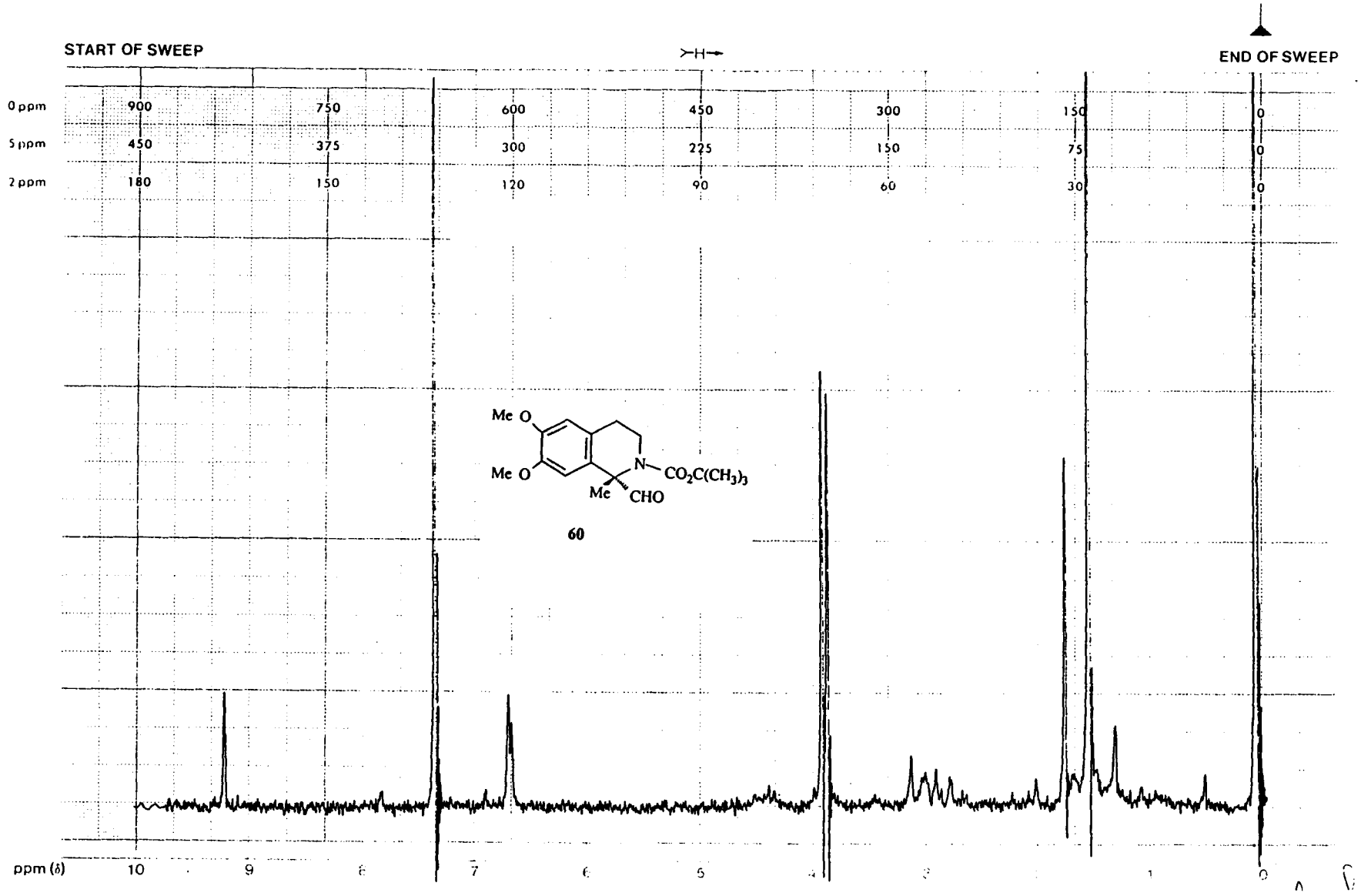

Fig. 7. ^{1}H nmr of compound 60

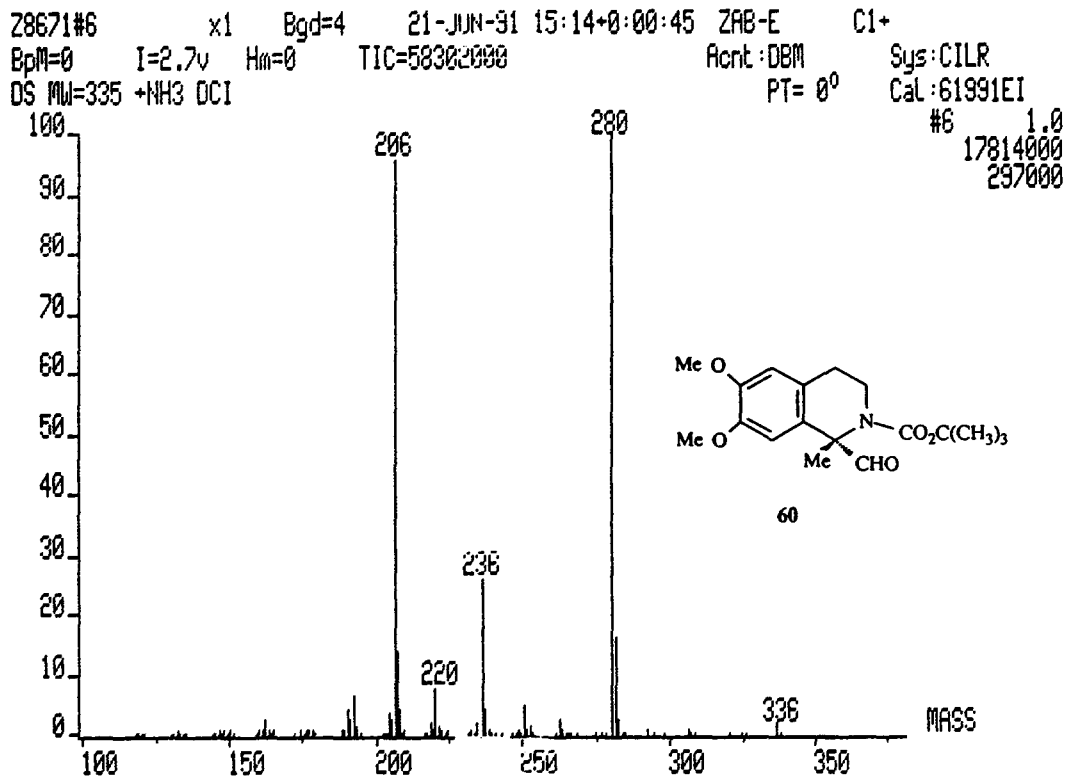

Fig. 8. NH_3-CI mass spectrum of compound 60

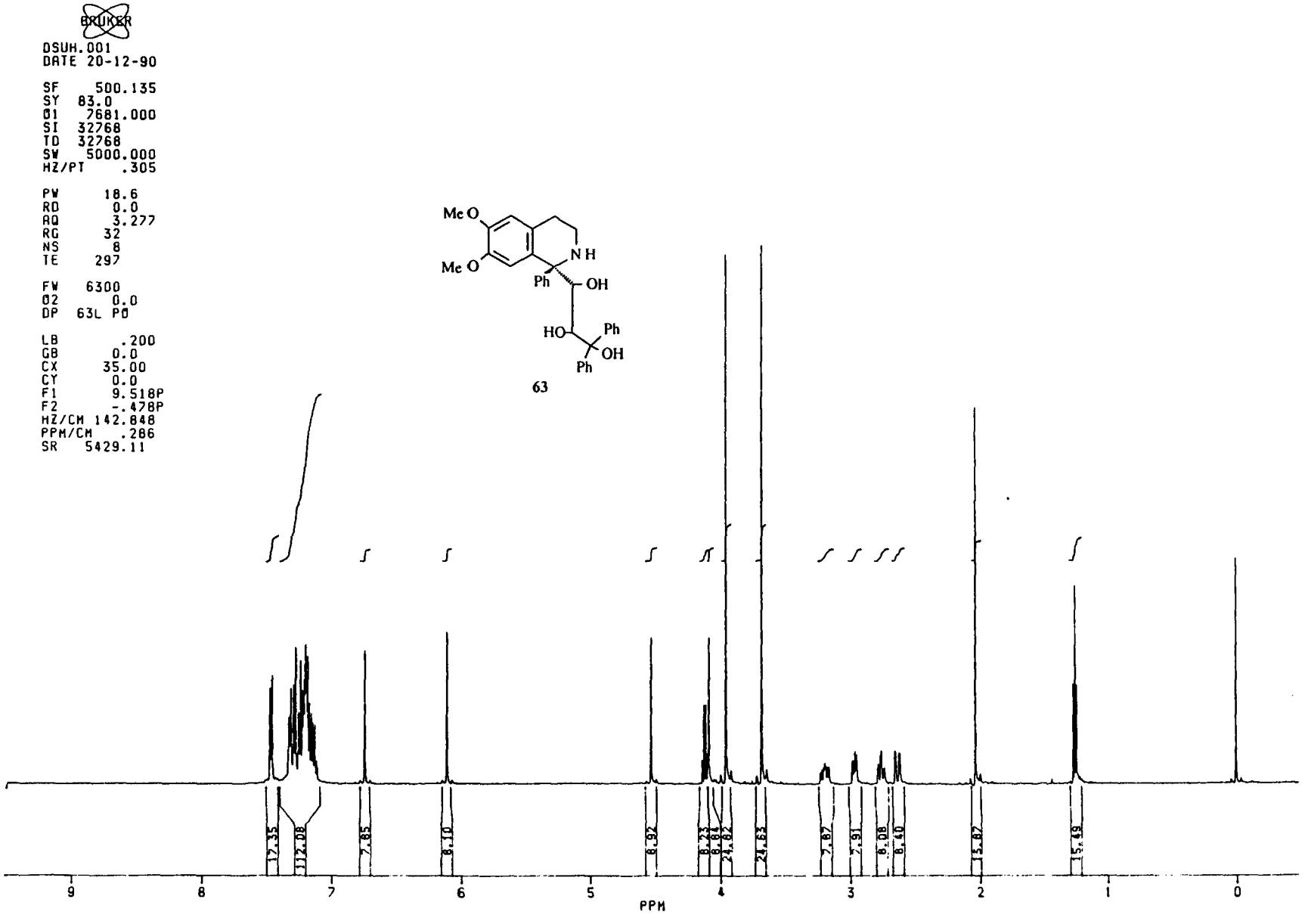

Fig. 9. ^{1}H nmr of compound 63

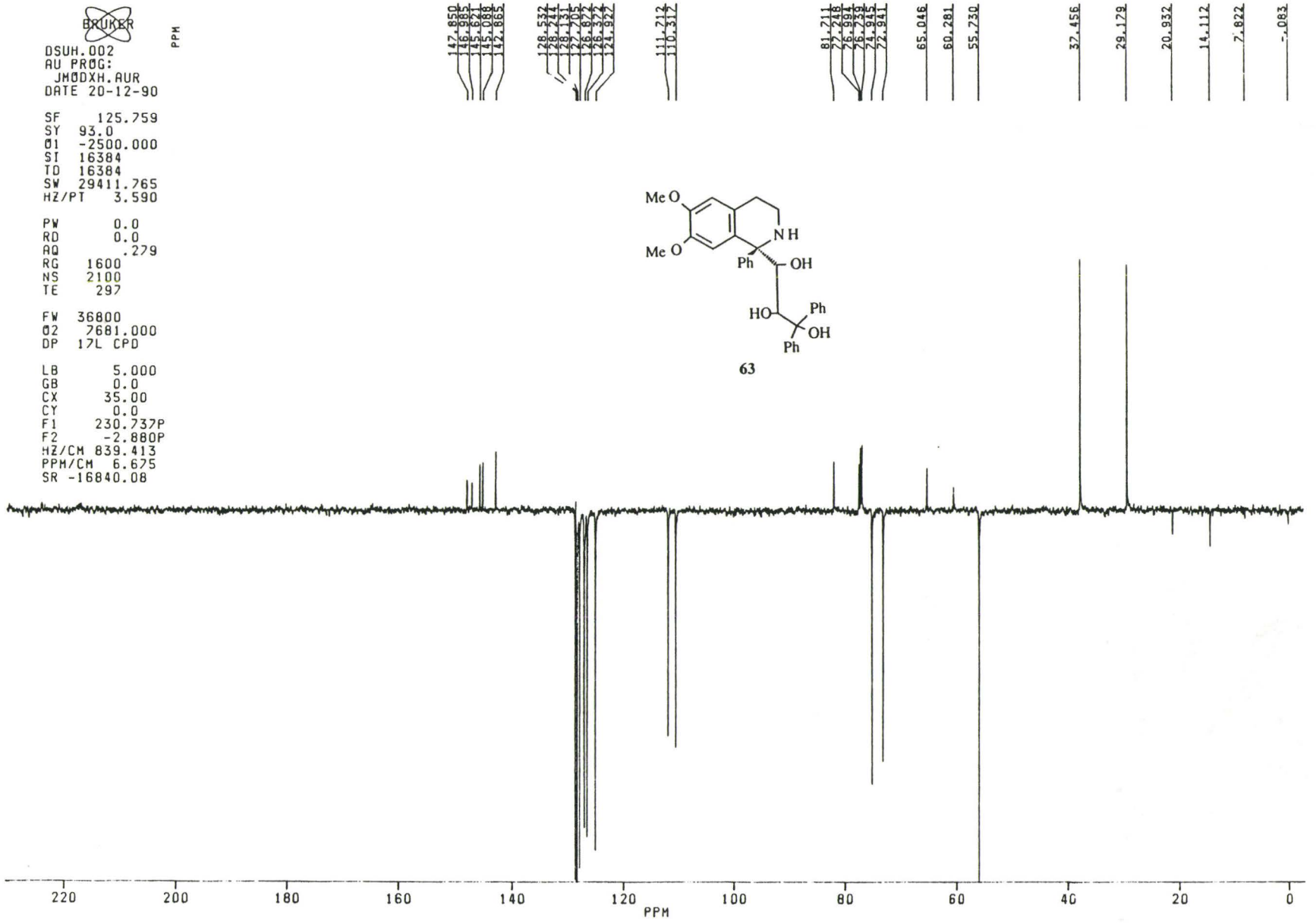

Fig. 10. ^{13}C nmr of compound 63

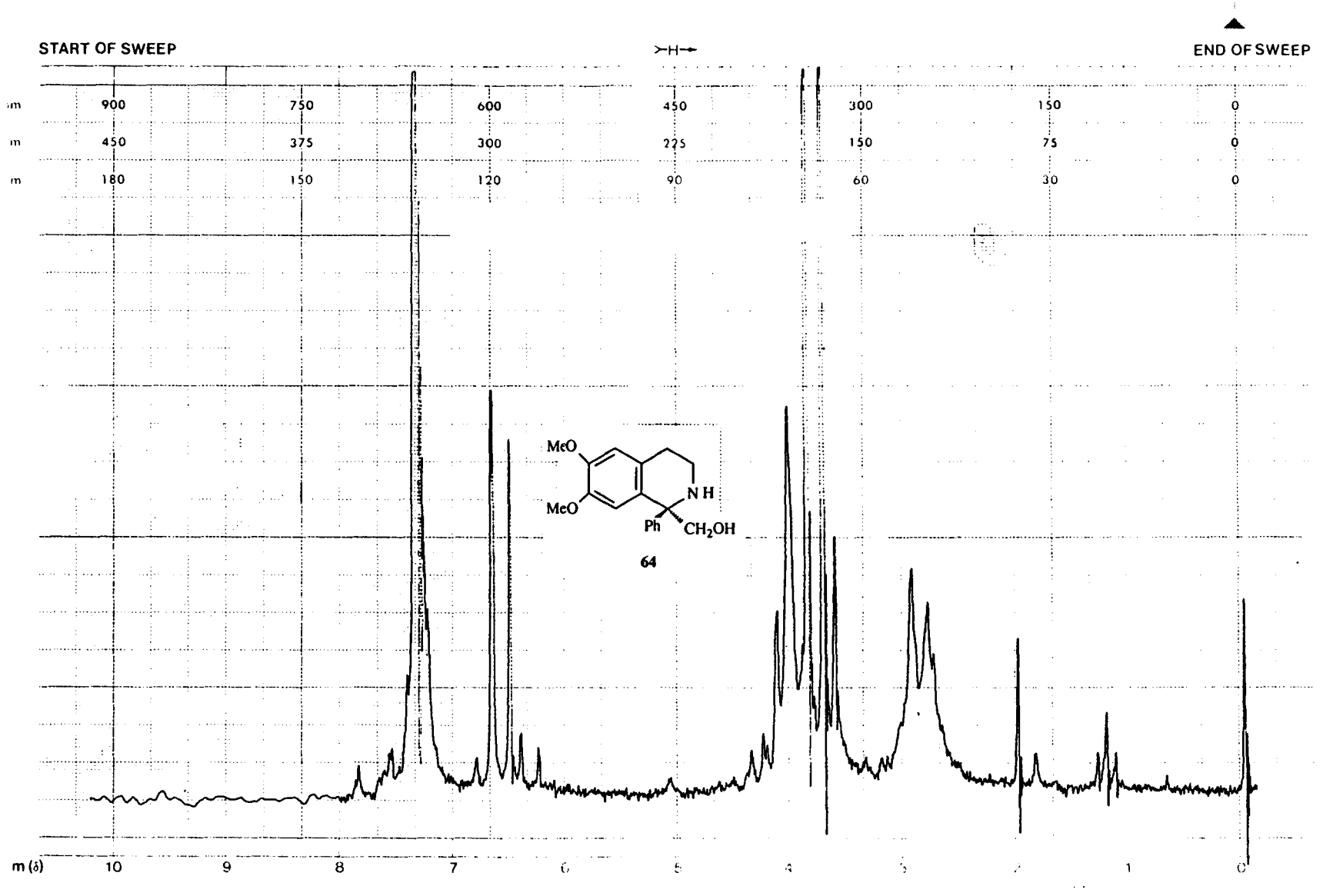

Fig. 11. ^{1}H nmr of compound 64

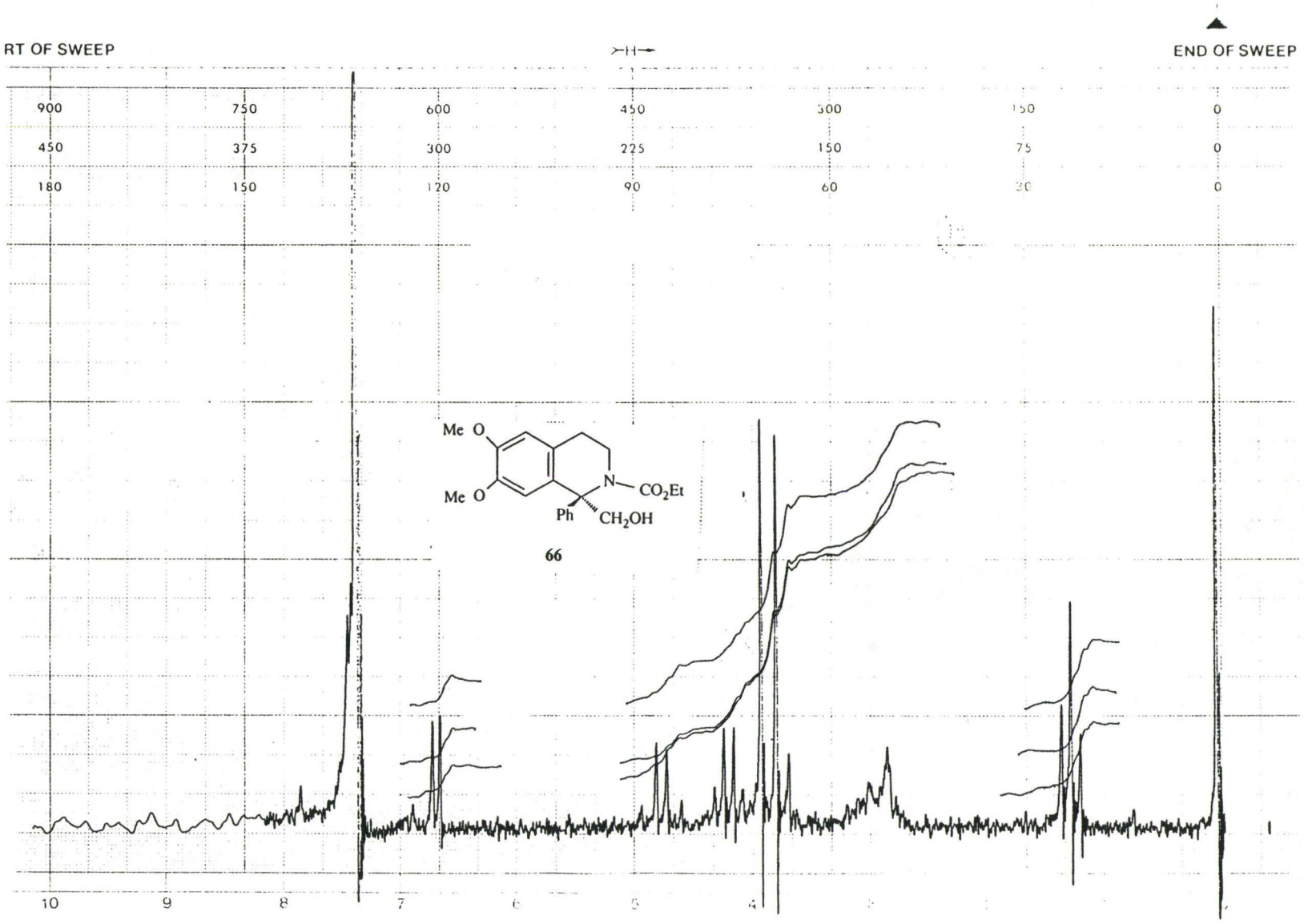

Fig. 12. ^{1}H nmr of compound 66