CHAPTER 4

SYNTHESIS

OF 13-METHYLBERBINES
SYNTHESIS OF 13-METHYLBERBINES

1. Introduction

Though there are not many 8-methylberbine alkaloids known, so far, several 13-methylberbine alkaloids are known to be isolated from natural sources. In fact 13-methylberbine alkaloids constitute a small group of metabolites which occur in various species of Corydalis\(^1\). The first alkaloid of this series, corydaline (\(1\)) was first isolated\(^2\) in 1826, from Corydalis tuberosa.

13-Methylberbines contain two asymmetric carbons and therefore exist in two diastereomeric forms (1 and 2). Although both cis and trans diastereomers, as represented by 1 and 2 respectively have been isolated from natural sources, these alkaloids mainly occur\(^{1-3}\) in cis conformation (1). Thus, several alkaloids of type 1 (viz. 1a-i) have been isolated from natural sources. Thalictrifoline (2) is the only alkaloid known so far which has trans conformation\(^1\). It is interesting to note that all of these alkaloids have 2,3,9,10-tetra-oxygenated pattern.
Some quaternary alkaloids like dehydrocavidine\(^4\) (\(2\)) and worenine\(^1,5\) (\(4\)) have also been isolated from natural sources\(^1\).
To date not even a single 13-methylberbine alkaloid having un oxygenated ring D, as represented by structure 5, has been isolated from natural sources. As discussed in Chapter 2, (+) bharatamine (6), a berbine alkaloid, having un oxygenated ring D has been isolated recently from natural source. Similarly one cannot rule out the possibility of the natural occurrence of 13-methylberbin es like 5, which have un oxygenated ring D.
2. Pharmacology

Several 13-alkylberbines have been tested for their biological activities. Some of them are found to be potential antitumor agents. Dehydrocavidine showed antimicrobial activity. The effect of dehydrocorydaline, on the cardiovascular system, has been studied. A number of compounds like dehydrocorydalines, 13-substituted berberines and O-demethylated dehydrocorydalines have been synthesised for evaluation as antigastric ulcer agents. Dehydrocorydaline chloride is known as a promising antipeptic ulcer agent and dehydrocorydaline iodide as an antiulcer agent.

3. Biosynthesis

Though there are not many 13-methylberbine alkaloids, known from natural sources, a good amount of work has been done on the biosynthesis of these alkaloids.

It has been widely presumed that the alkaloids corydaline (1a) and ochotensimine (a spirobenzylisoquinoline alkaloid) are structural variants of the benzylisoquinoline skeleton. It was suggested that C-methyl group of corydaline (1a) arises from a one carbon unit which is introduced into C-13 of a preformed protoberberine system (Chart I).
Bhakuni and coworkers have reported the biosynthesis of (+) cavidine, which was studied by feeding labelled tyrosine, reticuline, norreticuline, (+) protosinomenine, nororientaline and norlaudanidine. Only tyrosine, reticuline and norreticuline were found to be incorporated.
(R) (-) Reticuline was incorporated more efficiently than its (S) (+) enantiomer. The same authors have further reported\textsuperscript{16} that corlumbine (a phthalide isoquinoline alkaloid), yenhusomine (a spirobenzylisoquinoline alkaloid) and (+) cavidine (1e) are stereospecifically biosynthesised from (R) (-) reticuline.

4. Stereochemistry of 13-methylberbines

As discussed in Chapter 3, the dibenzo[a,g] quinolizidine structure, forms the skeleton of the tetrahydroprotoberberine alkaloids. Although it is possible to write one trans-quinolizidine and two cis-quinolizidine conformations for any berbine, the actual conformation of a compound is decided by the nature of substitution at position 1, 8 or 13.

Good amount of work\textsuperscript{17} has been carried out for assignment of conformations to 13-methylprotoberberines. A valuable conclusion can be derived on the basis of work done on 13-methylberbines. These compounds, which have the \( C_{13} \) hydrogen and \( C_{13a} \) hydrogen cis, exist almost exclusively in the trans-quinolizidine form and the compounds in which these two hydrogens have a trans-relationship exist almost entirely in cis-quinolizidine form irrespective of their oxygenation pattern. This is explained\textsuperscript{18} as follows.

The isomer \( 2 \) with a cis relationship of the hydrogens at \( C_{13} \) and \( C_{13a} \) may be represented by three conformations
7a-c (Chart II). The conformation 7a possessing the trans-quinolizidine structure is anticipated to be the most stable one and hence 7 would be expected to exhibit Bohlmann bands$^{18}$ in its IR spectrum (in CHCl$_3$). The diastereomer 8 in which the C$_{13}$ and C$_{13a}$ hydrogens are trans, can similarly exist in three possible conformations 8a-c. However in this case the trans-quinolizidine conformation 8a is destabilised by an energetically unfavourable nonbonded interactions of the C$_{13}$ methyl hydrogens with the aromatic C$_1$ hydrogen. The most stable conformation is likely to be one of the two cis-quinolizidine structures 8b or 8c in which this steric compression is relieved. Thus, 8 would not be expected to show Bohlmann bands$^{18}$ in its IR spectrum, and this is in fact observed.
The stereochemistry of 13-methylberbines has also been established by a study of their PMR spectra\textsuperscript{17}. There are three noticeable differences between the two diastereomers 7 and 8, viz. the chemical shift of C\textsubscript{13}-Me group, the coupling constant between the protons at C\textsubscript{13} and C\textsubscript{13a} and the chemical shift of the two C\textsubscript{8} protons. The chemical shift of the C\textsubscript{13}-Me group in compounds with trans fused B/C rings and cis orientation of C\textsubscript{13} and C\textsubscript{13a} hydrogens (like in 7) is about 1.00 $\delta$ while it is about 1.50 $\delta$ in the system with cis fused B/C rings and trans hydrogens at these centres (like in 8).

In the systems in which the hydrogens are trans, the C\textsubscript{13}-Me group lies nearly in the plane of the ring D and is therefore deshielded. The C\textsubscript{13a} proton of the trans-quinolizidine (7) appears at lower field than in the corresponding cis-quinolizidine (8). The coupling constants between C\textsubscript{13} and C\textsubscript{13a} hydrogens are about 3 Hz in the systems with cis hydrogens (like in 7) and about 7.5 Hz in the system with trans-hydrogens (like in 8). In the PMR spectrum of 10,11-oxygenated-13-methylberbines the C\textsubscript{8} protons appear as an AB quartet, independent of whether the B/C ring fusion is cis or trans. The centre of AB quartet appears relatively downfield in all cases of cis quinolizidines (like 8) as compared to the trans-quinolizidines (like 7) by about 0.15-0.20 ppm. In the 10,11-oxygenated compounds the signals
of the C₈-protons are separated from each other by about 0.45-0.48 ppm in the cis (like 8) and 0.40-0.48 ppm in the trans-quinolizidines (like 7) while the corresponding values in 9,10-oxygenated compounds are 0.13-0.18 and 0.55-0.72 ppm.

Based on the above observations it could be concluded that the assignment of stereochemistry of the B/C ring fusion in 10,11-oxygenated-13-methylberbines could be made on the basis of the chemical shifts of the C₁₃-methyl doublets only, which could be further strengthened by an inspection of the chemical shifts for the C₈-protons.

5. Synthesis of 13-methylberbines

As discussed in Chapter 1 several methods have been reported for the synthesis of 2,3,10,11-tetraoxygenated berbines, in which the oxygenation pattern is easy to synthesise. The difficultly accessible 2,3,9,10-tetra-oxygenated berbines have been obtained by modification of the well known methods or by totally new approaches. Among the well known methods for the synthesis of berbines are the approaches involving Bischler-Napieralski cyclisation and Mannich cyclisation of the corresponding 1-benzyl-1,2,3,₄-tetrahydroisoquinolines. Some of the methods developed for the synthesis of simple berbines have been used for the synthesis of 13-methylberbines. While developing newer methods
for 13-methylberbines the investigators had always aimed to synthesise 2,3,9,10-oxygenated pattern, as it is present in 13-methylberbine alkaloids. Some of the methods reported for the synthesis of 13-methylberbines are presented in Charts III-XV.

Bischler-Napieralski cyclisation of 1-benzyl-1,2,3,4-tetrahydroisoquinolines is one of the oldest approaches for the synthesis of berbines. As it provides mainly the 2,3,10,11-oxygenated berbines, in modified procedures, to achieve the synthesis of 2,3,9,10-oxygenated berbines, the reactive position is usually blocked by using bromine as a blocking group. Pai and coworkers have attempted the synthesis of cavidine (1e) and thalictrifoline (2) and their bis-methylenedioxy analogues. They used 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (9) and its bismethylenedioxy analogue 10 for Bischler-Napieralski cyclisation as shown in Chart III. The compound 9 was refluxed with freshly distilled phosphorus oxychloride and the quaternary salt thus obtained was reduced with sodium borohydride to get the product. In this reaction the expected product 13 was not obtained, instead a mixture of bromine ejected compounds 11a and 12a and ring A brominated compounds 11b and 12b were obtained. The compounds 11b and 12b on catalytic hydrogenolysis gave 11a and 12a respectively.
Method due to Pai et al.\textsuperscript{20}

\[ R = \text{Me}, \quad X = \text{H} \]  
\[ R = \text{Me}, \quad X = \text{Br} \]  
\[ R + R = -\text{CH}_2-, \quad X = \text{H} \]  
\[ R + R = -\text{CH}_2-, \quad X = \text{Br} \]

\[ \text{Freshly distilled POCl}_3 \]

\[ Chart \text{ III} \]
Similar reaction of 10 gave 11c and 12c. Thus, this method provided only 2,3,10,11-oxygenated-13-methylberbines 11 and 12 and not the expected products 1e, 2 and their bis-methylene-dioxy analogues.

Mannich cyclisation of 1-(α-methyl benzyl)tetrahydroisoquinolines provide 10,11-oxygenated-13-methylberbines. Shamma and Jones have used this method for the synthesis of 2,3,10,11-tetraoxygenated-13-methylberbines as shown in Chart IV.

To achieve the synthesis of 2,3,9,10-oxygenated-13-methylberbines by this approach, the more reactive para-position in the benzyl part is protected by bromine. However, this method is also not found suitable for the synthesis of the more commonly encountered 9,10-oxygenated-13-methylberbines owing to an unexpected rearrangement during the course of the Mannich reaction. Thus, Pai and coworkers attempted the Mannich cyclisation of 1-(2-bromo-α-methyl-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (14). They obtained compound 15, instead of the expected product 13 (Chart V). Recently Mannich cyclisation approach has been used for the synthesis of both diastereomers of 2,3,9,10,11-pentaoxygenated-13-methylberbines.
Method due to Shamma and Jones

\[
\begin{align*}
\text{MeO-} & \quad \text{MeO-} \\
\text{MeO-} & \quad \text{MeO-} \\
\text{COOMe} & \quad \text{COOMe} \\
\text{NaNH}_2 & \quad \text{aq HBr} \\
\text{MeI} & \quad \text{Ac}_2\text{O}, \Delta \\
\text{MeOH} / & \quad \text{HCl}, \Delta \\
\text{HCOOMe} & \quad \text{H}_{2}\text{O} \\
\text{K}_2\text{CO}_3, \text{EtOH}, \Delta & \quad \text{K}_2\text{CO}_3, \text{EtOH}, \Delta \\
\text{KOH/MeOH, } \Delta & \quad \text{SOCl}_2, \text{ether pyridine} \\
\text{HO-} & \quad \text{HO-} \\
\text{HO-} & \quad \text{HO-} \\
\text{COOH} & \quad \text{COOMe} \\
\text{1. PhCH}_2\text{Cl} & \quad \text{2. KOH/MeOH, } \Delta \\
\text{K}_2\text{CO}_3, \text{EtOH, } \Delta & \quad \text{3. SOCl}_2, \text{ether pyridine} \\
\text{CHCl}_3, \text{aq Na}_2\text{CO}_3 & \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\text{2. KOH/MeOH, } \Delta & \\
\text{SOCl}_2, \text{ether pyridine} & \\
\text{HCHO} & \quad \text{HCHO} \\
\text{MeOH} & \quad \text{MeOH} \\
\text{Chart IV}
\end{align*}
\]
Method due to Pai et al.\textsuperscript{22}

\[ \text{MeO} + \text{MeO} \rightarrow \text{aq. Na}_2\text{CO}_3 \rightarrow \text{CHCl}_3, 0^\circ \]

\[ \text{NaBH}_4 \rightarrow \text{MeOH, CHCl}_3 \]

\[ \text{MeO} \rightarrow \text{POCl}_3 \rightarrow \text{toluene} \rightarrow \text{MeO} \]

\[ \text{HCHO, HCOOH} \rightarrow \text{H}_2\text{O, } \Delta \]

\[ \text{HCHO, HCOOH} \rightarrow \text{H}_2\text{O, } \Delta \]

\[ \text{Chart V} \]
8-Acetonyldihydroprotoberberines have also been used for the synthesis of 13-methylberbines. The alkaloids synthesised by this method are thalictricavine\(^2\) (1f), corydaline\(^2\) (1a), corysamine\(^2\) (bismethyleneedioxy analogue of 3) and corydalidzine\(^2\) (1g). The steps involved in the synthesis of dl-corydaline\(^2\) (1a) are presented in Chart VI.

Photocyclisation of Z-1-ethyldene-2-benzoyl-1,2,3,4-tetrahydroisoquinolines (16) gave\(^2\) stereospecifically only the cis isomer 17 which on reduction with sodium-bis-(methoxyethoxy) aluminium hydride provided cis-2,3,10,11-tetraoxegenated-13-methylberbine 11 as depicted in Chart VII. However this method has also not been used for the synthesis of 2,3,9,10-tetraoxegenated-13-methylberbines.

Acid catalysed cyclisations of 1-acetyl-6,7-dimethoxy-N-(2',3'-dimethoxybenzyl)isoquinolinium bromide is reported to give 2,3,9,10-tetramethoxy-13-methylbenz[a]acridizinium chloride in low yield which on reduction with platinum oxide provided\(^1\)9 corydaline (1a). The steps involved are shown in Chart VIII.

Cushman and Dekow have reported\(^3\) a convergent method for the synthesis of 13-methylberbines which involves the condensation of imines with homophthalic anhydrides. This approach is novel because it provides both cis and trans diastereomers of 13-methylberbines and both 2,3,10,11- and
Method due to Bruchhausen\textsuperscript{25}

\[
\begin{align*}
\text{MeO} & \quad \text{CH}_3\text{COCH}_3 \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\text{CH}_2\text{COMe} & \quad \text{MeO} \\
\text{OMe} & \quad \text{OMe} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OMe} & \quad \text{OMe} \\
\text{OMe} & \quad \text{OMe} \\
\end{align*}
\]

\text{CHCl}_3 \quad \text{MeI} \quad \text{CH}_3\text{COCH}_3 \quad 50\% \quad \text{NaOH} \quad 1. \text{Ag}_2\text{SO}_4 \quad 2. \text{Pt-Zn} \quad \text{H}_2\text{SO}_4

\text{Chart VI}

Method due to Lenz\textsuperscript{28}

\[
\begin{align*}
\text{MeO} & \quad \text{Cl} \quad \text{CO} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe} \\
\end{align*}
\]

\text{Pyridine} \quad \Delta \quad \text{Pyridine} \quad \Delta \quad \text{Pyridine} \quad \Delta

\text{h} \gamma \text{dioxane}

\text{Chart VII}
2,3,9,10-oxygenation patterns. The key intermediate herein is the homophthalic anhydride \( \text{18} \). Initially, Cushman and coworkers have used\(^\text{30}\) this method for the synthesis of both diastereomers of 2,3,10,11-tetraoxygenated-13-methylberbines (19 and 20) as shown in Chart IXa. Cushman and Dekow subsequently\(^\text{31,32}\) utilised this approach for the synthesis of 2,3,9,10-tetraoxygenated-13-methylberbines. The key intermediate, 7,8-dimethoxyhomophthalic anhydride (21) has been prepared from 3-hydroxy-4-methoxyphenylacetic acid as shown in Chart IXb. This was then converted into berbine \( \text{1f} \) by using the approach described in Chart IXa. Cushman et al. and Pai et al. have used\(^\text{33,34}\) this method for the synthesis of 13-methyl-9,10-methylenedioxyberbines from homophthalic anhydride \( \text{22} \). They have synthesised compound \( \text{22} \) by two different methods (Chart IXc).

Dean and Rapoport have developed\(^\text{35}\) a method for the synthesis of 13-methylberbines. This method involves a stereospecific cyclisation of iminium salts, generated by decarboxylation of \( \alpha \)-amino acids. The steps involved are presented in Chart X.

Hydroxymethyl derivative of papaverine (23) has also been used\(^\text{36}\) for the synthesis of 2,3,10,11-tetramethoxy-13-methylberbine. The steps involved in this conversion are presented in Chart XI.
Method due to Bindra et al.\(^{29}\)

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{NH}_2\text{OH} - \text{HCl}} \text{CH} = \text{NOH} \\
\text{CN} & \xrightarrow{\text{MeMgI}} \text{COMe} \\
\text{Br} & \xrightarrow{\text{HCl}} \\
\text{O} & \xrightarrow{\text{PtO}_2 - \text{H}_2} \text{MeOH}
\end{align*}
\]

(Chart VIII)

Method due to Cushman and Dekow\(^{30}\)

\[
\begin{align*}
\text{O} & + \xrightarrow{\text{CHCl}_3} \\
\text{O} & \xrightarrow{(\text{Chart IX a contd.)}}
\end{align*}
\]
Chart IX

b. Method due to Cushman and Dekow

(Chart IX contd.)
c. Synthesis of homophthalic anhydride\textsuperscript{22}

(i) Method due to Cushman et al\textsuperscript{33}

\[
\begin{align*}
\text{MeO} & \rightleftharpoons \text{OH} \quad \text{DMS, acetone, K}_2\text{CO}_3, \Delta \\
\text{MeO} & \quad \text{MeO} \quad \text{1. KMnO}_4, \text{aq KOH} \\
& \quad \text{MeO} \quad \text{2. AcCl, } \Delta \\
\end{align*}
\]

21

(ii) Method due to Pai et al\textsuperscript{34}

\[
\begin{align*}
\text{NMe}_2 & \quad \text{Me} \quad \text{1. n-BuLi, THF, } -78^\circ \\
& \quad \text{Me} \quad \text{2. ClCOOEt} \\
\text{KCN} & \quad \text{DMSO} \\
\text{CN} & \quad \text{COOEt} \quad \text{1. aq-KOH, } \Delta \\
& \quad \text{COOEt} \quad \text{2. AcCl, } \Delta \\
\end{align*}
\]

22

(Chart IX contd.)
Chart IX
Method due to Dean and Rapoport

\[
\begin{align*}
\text{MeO} & \quad \text{Me} & \quad \text{COOH} \\
\text{MeO} & \quad \text{Me} & \quad \text{NH}_2
\end{align*}
\]

\[
\text{HCHO} \quad \rightarrow \quad \begin{align*}
\text{MeO} & \quad \text{Me} & \quad \text{COOH} \\
\text{MeO} & \quad \text{Me} & \quad \text{NH}
\end{align*}
\]

\[\text{p-TsOH} \cdot \text{H}_2\text{O} \rightarrow \begin{align*}
\text{MeO} & \quad \text{Me} & \quad \text{COOEt} \\
\text{MeO} & \quad \text{Me} & \quad \text{Br}
\end{align*}\]

\[\text{K}_2\text{CO}_3, \text{DMF} \quad \text{benzene}\]

\[\Delta\]

Chart - X

Method due to Mathieu and Gardent

\[
\begin{align*}
\text{MeO} & \quad \text{Me} & \quad \text{CO}_2\text{Et} \\
\text{MeO} & \quad \text{Me} & \quad \text{OMe}
\end{align*}
\]

\[1. \text{KOH-} \quad \text{EtOH}\]

\[2. \text{POC}_3\]

\[3. \text{HCl}\]

Chart XI
Recently\textsuperscript{37} a novel method has been developed for the synthesis of 13-alkyl and 13-aryl-8-oxoprotoberberines, which involves intramolecular benzyne cycloaddition of isoquinolino-pyrrolediones with arynes. This convergent and highly regioselective method has been used for the synthesis of (\(\pm\)) corydaline (1\textsubscript{a}). The key intermediate in this approach is 13-methyl-8-oxoprotoberberine 2\textsubscript{4}. The steps involved are depicted in Chart XII.

A novel and efficient method has been developed by Hanaoka and coworkers\textsuperscript{38}, for the synthesis of 13-methylprotoberberine alkaloids, which on sodium borohydride reduction provided 13-methylberbines having oxygen functions at 2,3,9,10-positions (Chart XIII).

MacLean and coworkers have developed\textsuperscript{39} a route for the synthesis of 2,3,9,10-tetramethoxy-13-methylberbine (1\textsubscript{a}). The first step in this approach is N-benzylation of 3,4-dihydroisoquinoline. The steps involved are shown in Chart XIV.

Even though there are several methods known for the synthesis of 13-methylberbines having oxygen functions in both rings A and D, until 1978 there was not even a single method reported for the total synthesis of 13-methylberbines having unoxygenated ring D. Iida and coworkers have developed\textsuperscript{40}
Method due to Saa et al.\textsuperscript{37}

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

+ COCl \quad \text{Pyridine} \quad \rightarrow

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

Method due to Hanaoka et al.\textsuperscript{38}

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]

\(1 \text{ LiAlH}_4\) \quad \(2 \text{ NaBH}_4\) \quad \rightarrow

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO}
\end{align*}
\]


\(\pm \) 1a

\text{Chart XII}

(Chart XIII contd.)
Chart XIII

Method due to MacLean et al. 39

CHART XIV contd
Method due to Iida et al.\textsuperscript{40}

\[ \text{NaBH}_4 \quad 95\% \text{EtOH} \]

(\pm) 1\text{a}

\textbf{Chart XIV}

\[ \text{NaH} \quad \text{MeI} \]

1. Triton B

2. NaH, MeI

\[ \text{HOCH}_2\text{CH}_2\text{OH} \quad \text{H}^+ \]

NaBH\textsubscript{4}

p-TsOH

benzene

(Chart XV contd.)
Chart - XV

1. LiAlH₄
2. HCl, Δ
a method for the synthesis of 2,3-dimethoxy-13-methylberbine. This method, utilising homophthalic anhydride, involves several steps as depicted in Chart XV.

6. Present work

There are three different types of 13-methylberbines like 2,3,9,10-oxygenated-, 2,3,10,11-oxygenated-and 2,3-oxygenated-13-methylberbines. Various methods are known for the synthesis of these berbines as already shown in Charts III-XV. It is clear from these charts, that there are methods which can provide both 2,3,9,10- and 2,3,10-11-tetraoxygenated-13-methylberbines (e.g. Chart IX) but these methods have not been used for the synthesis of 2,3-oxygenated-13-methylberbines. However, Haimova and coworkers have used the method involving the use of homophthalic anhydride for the synthesis of 2,3-dioxygenated-13-hydroxymethylberbine, which could be converted into 13-methylberbine. The steps involved are similar to the method presented in Chart IXa. Similarly the methods developed for 2,3-oxygenated-13-methylberbines (e.g. Chart XV) have not been extended for the synthesis of 2,3,9,10- and 2,3,10,11-oxygenated-13-methylberbines. A general method is thus needed for the synthesis of 13-methylberbines which could provide all the three types of 13-methylberbines. For this purpose, a retrosynthetic analysis of
13-methylberbines 25 was visualised as shown in Chart XVI.

Thus, 13-methylberbines could be synthesised from hydroxyamide 26 which in turn could be obtained by condensation of β-arylethylamines (27) and 4-methylisochromanones (28). This route could be a general one for 13-methylberbines. Thus, by making use of properly substituted 27 and 28, all the three possible 13-methylberbines like 2,3-dioxygenated-, 2,3,10,11- and 2,3,9,10-tetraoxygenated-13-methylberbines could be synthesised. It was then planned to synthesise 2,3-dimethoxy-13-methylberbines and 2,3,10,11-tetramethoxy-13-methylberbines. The amino compound 27 required for this purpose is the easily accessible 3,4-dimethoxy-β-phenylethylamine (homoveratrylamine). The other synthons in the projected synthesis are the 4-methylisochroman-3-ones 28 (R₂=H and R₂=6,7-dimethoxy).
Literature survey revealed that 4-methyl- and 6,7-dimethoxy-4-methyl-isochromanones have not been reported so far. When the general methods were searched for 4-substituted isochromanones it was found that some of these are used in the synthesis of some natural products like sclerin\textsuperscript{4,2} (a metabolite showing growth promoting effect on plants) and (±) physovenine\textsuperscript{4,3}, as shown below.

Three general methods are found in the literature for the synthesis of 4-substituted isochromanones which are presented in Chart XVII. The methods\textsuperscript{4,2,4,4} described in Chart XVIIa and b make use of methyl esters of α-alkyl or α-aryl-phenylacetic acids while the second approach (Chart XVIIc-f) makes use of preformed isochromanones. The method\textsuperscript{4,5} presented in Chart XVIIc
a. Method due to Tokoroyama et al. 42

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{COOMe} & \quad \xrightarrow{\text{HCHO, HCl, } \Delta} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} & \quad \text{O} & & & & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} \\
\end{align*}
\]

b. Method due to Arcoleo et al. 44

\[
\begin{align*}
\text{Me} & \quad \text{MeO} & \quad \text{OMe} & \quad \xrightarrow{\text{H}_2\text{SO}_4, \text{Cl}_3\text{CCH(OH)}_2, \text{AcOH}} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{CCl}_3 \\
\text{Me} & \quad \text{MeO} & \quad \text{OMe} & \quad \xrightarrow{\text{AcOH}} & \quad \text{MeO} & \quad \text{MeO} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{CCl}_3 \\
\end{align*}
\]

c. Method due to Sainsbury and Wyatt 45

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{O} & \quad \xrightarrow{\text{Pyrrolidine, veratraldehyde, } \Delta} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{Me} & \quad \text{O} & \quad \xrightarrow{\text{Adams catalyst, H}_2, \text{AcOH}} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} & \quad \text{Me} & \quad \text{Me} & \quad \text{O} \\
\end{align*}
\]

(Chart XVII contd.)
gives 4-benzylisochromanone via 4-benzylideneisochromanone. The approach, described in Chart XVId, involves alkylation of isochromanones using sodium hydride and higher alkyl halide (e.g. 6-bromo-1-hexene) as an alkylation agent. By this method, the monoalkylated product was formed in 51% yield. When Khanapure used this procedure for the alkylation (NaH, 6-bromo-1-hexene) of 7-methoxyisochroman-3-one, the alkylation product was obtained in poor yield. In the modified procedure, NaNH₂ was used as a base and allyl bromide as the alkylation agent. The isochromanone was reacted with NaNH₂ at room temperature and the anion thus formed was treated with allyl bromide. The monoalkylated product was obtained in 20% yield and the dialkylated product was obtained in 40% yield. When tetrahydropyranyl ether of ethylene bromohydrin was used as an alkylation agent, the monoalkylated product was obtained in 60% yield (Chart XVIIe). It was suggested that the monoalkylation occurred because of the steric bulk of the tetrahydropyranyl ring.

Recently Black and Sainsbury have studied the alkylation of isochroman-3-ones (Chart XVIIf). They have reported that the anions could be formed by reacting the isochromanones with lithium diisopropyl amide, however these anions were found to be unreactive towards the simple alkyl halides (MeI, n-BuBr, etc.). To improve the reactivity of the
d. Method due to Oppolzer\textsuperscript{46}

\[
\text{MeO} \quad \begin{array}{c}
\text{1. NaH, HMPT, THF} \\
\text{2. Br} \end{array} \quad \text{MeO} \\
\]

\[\text{e. Method due to Khanapure}\textsuperscript{47}\]

\[
\text{MeO} \quad \begin{array}{c}
\text{1. NaNH}_2/\text{liq. NH}_3 \\
\text{2. Br} \end{array} \quad \begin{array}{c}
\text{MeO} \\
\text{1. NaNH}_2/\text{liq. NH}_3 \\
\text{2. BrCH}_2\text{CH}_2\text{OTHP} \end{array} \\
\]

\[
\text{f. Method due to Black and Sainsbury}\textsuperscript{48}\]

\[
\text{MeO} \quad \begin{array}{c}
\text{1. Chromium hexa-carbonyl, THF, } \Delta \\
\text{2. LDA, HMPT, THF, } -78^\circ \\
\text{3. n BuBr} \end{array} \quad \text{MeO} \\
\]

\text{Chart XVII}
anions, they prepared the tricarbonylchromium complexes of the isochromanones before generating the anions. When butyl bromide was used as the alkylating agent the monoalkylated product was formed in 60% yield. However, in case of 6-bromo-1-hexene the dialkylated product (10%) was also formed along with the monoalkylated product (60%). These reports indicated the difficulty in obtaining the monoalkylated product in alkylation of isochromanones.

Recently Kametani and coworkers have developed a new approach for 4,4-disubstituted isochroman-3-ones which involved a tandem electrocyclic-sigmatropic reaction of benzocyclobutenes (Chart XVIIg).

By looking at the reported methods (Chart XVII), initially it was planned to synthesise the required 4-methyl-6,7-dimethoxyisochroman-3-one by methylation of 6,7-dimethoxyisochroman-3-one (29), which in turn was readily available from 3,4-dimethoxyphenylacetic acid. Though the strategy appeared simple, it posed several problems in methylation reaction. Methylation was first tried using methyl iodide as an alkylating agent and various bases like $\text{K}_2\text{CO}_3$, $\text{KO}^\text{t-Bu}$, $\text{PhCH}_2\text{NET}_3\text{Cl}/\text{NaOH}$, $\text{NET}_3\text{-ClSiMe}_3$. Under various conditions the reaction was tried. Unfortunately in all cases either a complex mixture of products was formed or the unreacted
When the thesis was almost completed, we came across the synthesis of 4-substituted isochromanones reported by Khanapure and Biehl. The steps involved are presented in Chart XVII h. These authors have also commented on the difficulties in monoalkylation of isochromanones and separation of the monoalkylated product from the mixture.
starting compound was recovered.

Methylation of isochroman-3-one $29a$ using sodium hydride (tetrahydrofuran, $0^\circ$) as a base gave a thick liquid which was chromatographed over silica gel using benzene:ethylacetate (9:1) as an eluent to give a solid. It melted at $107-9^\circ$ and analysed correctly for $C_{13}H_{16}O_4$. In its IR spectrum (Nujol) it showed a band at $1750 \text{cm}^{-1}$ for $\delta$-lactone carbonyl.

In PMR (CDCl$_3$) spectrum (Fig. 1) it exhibited a singlet for six protons at $1.56 \delta$ which could be assigned to two methyl groups. Two singlets ($3\text{H}$ each) were seen at $3.89$ and $3.92 \delta$ for two-OMe groups. A singlet ($2\text{H}$) which appeared at $5.35 \delta$ could be assigned to methylene protons from $\text{Ar-CH}_2-\text{O}$-unit. Two singlets ($1\text{H}$ each) were observed in aromatic region at $6.68$ and $6.85 \delta$ for the aromatic protons. The analytical and spectral data discussed above and the mode of formation suggested the structure $31\equiv$ for this compound.

In the alkylation of $29a$, two steps are involved. The first one is formation of the anion $29a$ and the second step is the alkylation of $29a$ to obtain the desired product $30$. As the above bases failed to give the desired product, it was planned to generate the lithium enolate using LDA as a base. As sodium enolate ($29a$, M=Na) failed to give monoalkylated product, it was planned to generate the lithium enolate
The anion 29a (M=Li) was generated by reacting the isochromanone 29 (in tetrahydrofuran solution) with 1.5 equivalents of LDA at -78°C and warming the reaction mixture to room temperature during 1.5 hr. It was reacted with 7.5 equivalents of methyl iodide at -10°C and the reaction was kept between -10 to 0°C for 1 hr. On workup it gave an oily product which was chromatographed over silica gel to give a solid which melted at 107-8°C. It was found to be the dimethylated product 31 (TLC, superimposable IR).

As the dialkylated product 31 was obtained when methylation was carried out at -10 to 0°C, it was decided to methylate it at -78°C for 2 hr using 1.5 equivalents of methyl iodide. By using this procedure the starting compound (29)
remained unreacted. It was then decided to methylate it at slightly higher temperature. The anion \( \text{29a} \) was then reacted with 1.5 equivalents of methyl iodide at \(-78^\circ\) and by keeping the reaction at \(-60\) to \(-45^\circ\) for 3 hr. The oily product obtained from this reaction showed two spots on TLC. It was chromatographed over silica gel using benzene:ethylacetate (9:1) as an eluent. A white solid was obtained from the initial fractions. It melted at 114-16\(^\circ\). It analysed correctly for \( \text{C}_{12}\text{H}_{14}\text{O}_4 \). Its IR spectrum (Nujol) showed the presence of \( \delta \)-lactone carbonyl (presence of a band at 1750 cm\(^{-1}\)). In its PMR (CDCl\(_3\)) spectrum (Fig. 2) a doublet (3H, \( J=7 \) Hz) appeared at 1.59 \( \delta \) which could be assigned to a methyl group. A quartet (1H, \( J=7 \) Hz) at 3.59 \( \delta \) could be due to \( \text{Ar-CH(CH}_3\text{-CO-group} \). The two -OMe groups appeared as two singlets (3H each) at 3.87 and 3.89 \( \delta \) . The other two proton singlets which appeared at 5.23 and 6.76 \( \delta \) were assigned to \( \text{Ar-CH\text{O}\text{-CO} and two aromatic protons respectively.} \)

On the basis of the mode of formation, the analytical and spectral properties, structure \( \text{30} \) was assigned to the product.

Further elution with the same solvent gave another solid which melted at 106-7\(^\circ\) and analysed correctly for \( \text{C}_{11}\text{H}_{12}\text{O}_4 \). It was found to be the unreacted starting isochromanone \( \text{29} \) (co-TLC, mixed m.p. and superimposable IR).
This reaction was also not clean, and most of the times the dimethylated product $31$ was formed along with the desired monoalkylated product $30$. Sometimes the starting compound was also found to be present in the product mixture. Because of the close RF values of starting isochromanone (22), monoalkylated product (30) and dialkylated product (31), separation of monoalkylated product was becoming a challenging problem. Most of the times these compounds were separated by using HPLC. To improve the yield of the monoalkylated product, various modifications were tried. All these results are summarised in Table 1.

By looking at the results summarised in Table 1, it is clear that the best results of the monoalkylated product are obtained when 4 equivalents of LDA was used for enolate formation and excess (15 equivalents) of methyl iodide was used for alkylation. The alkylation was carried out by stirring the reaction mixture at $-45$ to $-40^\circ$C for 4 hr. The reaction mixture was separated using HPLC. The monoalkylated product $30$ was obtained in 65% yield, and the dialkylated product $31$ in 5% yield. The starting compound (5%) was also recovered.
Table 1:

<table>
<thead>
<tr>
<th>Reaction No.</th>
<th>Ratio of Starting:LDA:MeI</th>
<th>Reaction conditions</th>
<th>Product</th>
<th>Starting recovered (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Temperature (°C)</td>
<td>Time (hr)</td>
<td>Mono (%)</td>
</tr>
<tr>
<td>1.</td>
<td>1 : 1.5 : 7.5</td>
<td>-10 to 0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2.</td>
<td>1 : 1.25 : 1.5</td>
<td>-78</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>3.</td>
<td>1 : 1.25 : 1.5</td>
<td>-60 to -45</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>4.</td>
<td>1 : 1.25 : 3</td>
<td>-60 to -40</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>5.</td>
<td>1 : 1.5 : 1.5</td>
<td>-60 to -30</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>6.</td>
<td>1 : 1.5 : 2</td>
<td>-60 to -30</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>7.</td>
<td>1 : 1.5 : 5</td>
<td>-70 to -60</td>
<td>1</td>
<td>No reaction (TLC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-60 to -50</td>
<td>1</td>
<td>&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-50 to -45</td>
<td>1</td>
<td>Slight reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-45 to -40</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Reaction No.</td>
<td>Reaction conditions</td>
<td>Product</td>
<td>Starting DI (%)</td>
<td>Mono DI (%)</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>--------</td>
<td>----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>8.</td>
<td>1 : 4 : 7.5</td>
<td>-50</td>
<td>0.5</td>
<td>No reaction</td>
</tr>
<tr>
<td>9.</td>
<td>1 : 4 : 15</td>
<td>-50 to -45</td>
<td>1.5</td>
<td>Slight reaction</td>
</tr>
<tr>
<td>10.</td>
<td>1 : 4 : 15</td>
<td>-50 to -45</td>
<td>1</td>
<td>Slight reaction</td>
</tr>
<tr>
<td>11.</td>
<td>1 : 4 : 15</td>
<td>-50 to -45</td>
<td>1</td>
<td>Slight reaction</td>
</tr>
<tr>
<td>12.</td>
<td>1 : 4 : 15</td>
<td>-10 to 0</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>
The following conclusions can be drawn from the results summarised in Table 1.

(1) The temperature factor plays a vital role in the formation of mono- or dimethylated product.

(2) The molar ratio of LDA and MeI to starting compound shows effect on the yield of the products formed.

Thus, even if a large excess of LDA and MeI is used, methylation does not occur below -50°. At -45 to -40°, the monomethylation occurs in major proportion. The dimethylation starts occurring between -35 to -40°. Above -30° dimethylation is the major process. Thus, at -10 to 0° only dimethylation occurs. The yield varies according to the molar ratio of LDA and MeI and reaction time at these temperatures.

The synthesis of 4-methyl-6,7-dimethoxyisochroman-3-one (30) was thus achieved by methylation of 6,7-dimethoxyisochroman-3-one (29) which was easily available. For the synthesis of simple 4-methylisochroman-3-one (35) by methylation approach, unsubstituted isochroman-3-one was required, which has already been synthesised by lithiation approach as described in Chapter 2. Instead of preparing isochroman-3-one by lithiation approach and using it for the synthesis of 4-methylisochroman-3-one, it was planned to use heteroatom directed lithiation reaction for the synthesis of 4-methylisochroman-3-one (35), as shown in Chart XVIII.
\( \alpha \)-Methyl-\( \text{N}, \text{N} \)-dimethylbenzylamine (32) required for synthesis of 4-methylisochroman-3-one (35), was prepared from acetophenone\(^{51}\). It has already been reported\(^{52}\) that lithiation of \( \alpha \)-methyl-\( \text{N}, \text{N} \)-dimethylbenzylamine (32) occurs ortho to \( \text{CH(CH}_3)_2 \text{-NMe}_2 \) group to give the lithioderivative 33.

Thus, \( \alpha \)-methyl-\( \text{N}, \text{N} \)-dimethylbenzylamine (32) was lithiated using \( \text{n} \)-butyllithium in ether and the lithioderivative 33 thus obtained was reacted with paraformaldehyde to give a liquid product. Elemental analysis suggested \( \text{C}_{11}\text{H}_{17}\text{NO} \) as the molecular formula. In IR spectrum (Liquid film) it showed a band at 3350 cm\(^{-1}\) assignable to -OH group. In PMR spectrum (CDCl\(_3\)) it exhibited a doublet at 1.33 \( \delta \) (3H, \( J=7 \text{ Hz} \)) which could be assigned to the methyl from -\( \text{CH(CH}_3)_2 \text{-NMe}_2 \) group. A singlet (6H) which appeared at 2.14 \( \delta \)
could be attributed to -NMe₂ group. A proton from -CH(CH₃)-NMe₂ appeared as a quartet (J=7 Hz) at 3.92 δ . Other two doublets (J=12 Hz) integrating for one proton each were present at 4.42 and 4.72 δ , which are assignable to protons from ArCH₂-O group. A broad singlet which appeared at 6.48 δ (exchanged with D₂O) could be attributed to -OH proton. Aromatic protons appeared as four proton singlet at 7.20 δ . On the basis of the above discussed analytical and spectral properties, structure 3₄ was assigned to the product.

As discussed in the previous chapters, to convert the amino alcohol 3₄ into isochroman-3-one 3₅, it was necessary to replace the -NMe₂ group with -COOH group. For this purpose the amino alcohol was reacted successively with ethylchloroformate in benzene solution, potassium cyanide in dimethylformamide, alcoholic potassium hydroxide, followed by acidic workup to get a low melting solid. This solid melted at 44-45°. Elemental analysis suggested C₁₀H₁₀O₂ as the molecular formula. In IR spectrum (Nujol) it showed a peak at 1750 cm⁻¹ which could be assigned to lactone carbonyl. In PMR (CDCl₃) spectrum (Fig. 3) it showed a doublet at 1.60 δ (3H, J=7 Hz) which was assigned to C₄-methyl group. The C₄-H appeared as a quartet (1H, J=7 Hz) at 3.60 δ . The singlet (2H) which appeared at 5.22 δ was assigned to the ArCH₂-O
Fig. 3: 90 MHz PMR spectrum of the lactone 25
group. The aromatic protons appeared as a four proton multiplet at 7.10-7.41. The structure 35 was assigned to the product on the basis of its mode of formation and analytical and spectral data.

Once 4-methylisochromanones 30 and 35 were at hand the next target was to synthesise 13-methylberbines 38 and 39 as shown in Chart XIX.
The strategy visualised in Chart XIX involves two steps. The first step is the condensation of homoveratrylamine (36) with isochromanones (30 and 35) to get hydroxyamides (37a and 37b). The second step involves Bischler-Napieralski cyclisation of amides 37a and 37b using phosphorus pentachloride followed by sodium borohydride reduction of the cyclic product to get the corresponding berines 38 and 39.

**Step 1: Formation of hydroxyamides 37a and 37b**

(i) N-[2-(3,4-Dimethoxyphenyl) ethyl]- (3,4-dimethoxy-2- hydroxymethyl)-α-methyl-phenylacetamide (37a)

Condensation of 4-methyl-6,7-dimethoxyisochroman-3-one (30) with homoveratrylamine (36) in ethanolic isochromanone resulted in the formation of a thick oily product which was purified by flash chromatography over silica gel. Its IR spectrum (Liquid film) showed absence of lactone carbonyl. It exhibited a broad band at 3275-3370 cm\(^{-1}\) which could be assigned to OH/NH group. Another band which appeared at 1660 cm\(^{-1}\) could be due to the amide carbonyl. In its PMR spectrum (CDCl\(_3\)) it exhibited a doublet at 1.44 \(\delta\) (3H, J=7 Hz) which could be attributed to \(\text{ArCH(CH}_3\text{)}\)-O group. A broad singlet was seen at 2.30 \(\delta\) which disappeared on addition of \(\text{D}_2\text{O}\). It could be assigned to -OH/-NH protons. A triplet was
observed at 2.62 δ (2H, J=7 Hz) which was assigned to
ArCH₂CH₂N. A multiplet integrating for two protons appeared
at 3.60 δ could be attributed to ArCH₂CH₂N. The four
methoxyl groups appeared at 3.79, 3.83, 3.85 and 3.87 δ as
merged singlets. This region integrated for thirteen protons.
The decoupling technique revealed that the signal due to
ArCH(CH₃)⁻ was hidden in these merged singlets at 3.80 δ.
Thus, irradiation at 3.80 δ resulted in disappearance of the
doublet (1.44 δ) due to ArCH(CH₃)⁻ protons. In turn a
singlet appeared at 1.44 δ. Two doublets, integrating for
one proton each were seen at 4.42 and 4.77 δ (J=11 Hz) which
could be assigned to ArCH₂OH protons. Five aromatic protons
appeared at 6.30-6.90 δ as a multiplet. On the basis of the
mode of formation and the spectral properties discussed above,
estrucre 37a was assigned to the product.

(ii) N-[2-(3,4-Dimethoxyphenyl)ethyl]-(2-hydroxymethyl)-α-methyl-phenylacetamide (37b)

Condensation of 4-methylisochroman-3-one (35) with
homoveratrylamine (36), as discussed in case of 37a, gave a
thick liquid which was purified by flash chromatography to
gain a solid, m.p. 85-86°. Elemental analysis suggested
C₂₀H₂₅NO₄ as the molecular formula. Structure 37b was
assigned to it on the basis of its mode of formation, elemental
analysis and spectral properties which are as follows:
IR (Nujol) : \( \nu_{\text{max}} \) 3250 cm\(^{-1}\) (OH/NH), 1645 cm\(^{-1}\) (CONH).

PMR (CDCl\(_3\)) :

<table>
<thead>
<tr>
<th>Chemical Shift</th>
<th>Multiplicity</th>
<th>Proton Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.46</td>
<td>d (J=7 Hz)</td>
<td>3H</td>
<td>( \text{ArCH(CH}_3\text{)CO} )</td>
</tr>
<tr>
<td>2.11</td>
<td>bs</td>
<td>2H</td>
<td>OH/NH</td>
</tr>
<tr>
<td>2.63</td>
<td>t (J=7 Hz)</td>
<td>2H</td>
<td>( \text{ArCH}_2\text{CH}_2\text{N} )</td>
</tr>
<tr>
<td>3.29-3.60</td>
<td>m</td>
<td>2H</td>
<td>( \text{ArCH}_2\text{CH}_2\text{N} )</td>
</tr>
<tr>
<td>3.78</td>
<td>s</td>
<td>3H</td>
<td>OMe</td>
</tr>
<tr>
<td>3.84</td>
<td>s</td>
<td>3H</td>
<td>OMe</td>
</tr>
<tr>
<td>4.47</td>
<td>d (J=13 Hz)</td>
<td>1H</td>
<td>( \text{ArHCH-O} )</td>
</tr>
<tr>
<td>4.90</td>
<td>d (J=13 Hz)</td>
<td>1H</td>
<td>( \text{ArHCH-O} )</td>
</tr>
<tr>
<td>6.45</td>
<td>dd (J=2,7 Hz)</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>6.57</td>
<td>d (J=2 Hz)</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>6.71</td>
<td>d (J=7 Hz)</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>7.16-7.45</td>
<td>m</td>
<td>4H</td>
<td>4 x ArH</td>
</tr>
<tr>
<td>*3.92</td>
<td>q (J=7 Hz)</td>
<td>1H</td>
<td>( \text{ArCH(CH}_3\text{)CO} )</td>
</tr>
</tbody>
</table>

**Step 2 : Formation of berbines (38a, 39a and 38b, 39b)**

The hydroxyamides 37a and 37b were cyclised in chloroform solution using phosphorus pentachloride. The salts obtained were then reduced with sodium borohydride in methanol to get the berbines 38a, 39a and 38b, 39b respectively.
(1) Synthesis of (+) 2,3,10,11-tetramethoxy-13-methyl-berbines (38a and 39a)

The hydroxyamide 37a was cyclised with phosphorus pentachloride and the salt thus obtained was reduced with sodium borohydride to get a thick liquid which showed one major spot on TLC. When it was cooled and scratched in dry ether it gave a solid which showed almost single spot on TLC. It was then thought that the $R_f$ values of both the expected epimers might be very close. Therefore it was carefully purified on alumina column using chloroform as an eluent. It gave a pure solid, m.p. 146-48°, which analysed correctly for $C_{22}H_{27}NO_{4}$. It did not show the bands between 2700-2800 cm$^{-1}$ (Bohlman bands) in its IR spectrum (in chloroform). In its UV spectrum (MeOH) it exhibited $\lambda_{max}$ at 284.5 and 225.5 nm.

In PMR (CDCl$_3$) spectrum (Fig. 4) it showed a doublet at 1.48 $\delta$ (3H, $J=7$ Hz) which was assigned to C-13 methyl group. A five proton multiplet was observed at 2.73-3.19 $\delta$ which could be due to methylene and methine protons from ArCH$_2$CH$_2$N- and ArCH(Me)-groups. A doublet was seen at 3.69 $\delta$ (1H, $J=8$ Hz) which could be assigned to C-13a proton. One AB quartet appeared at 3.74 and 4.21 $\delta$ (2H, $J=15$ Hz), the centre of the quartet was at 3.98 $\delta$. It was assigned to C$_8$-protons. The four methoxy groups appeared at 3.84 $\delta$ as a singlet.
Fig. 4: 90 MHz PMR spectrum of the 13-methylberbine 38a
integrating for twelve protons. Four singlets (1H each) were seen at 6.52, 6.59, 6.67 and 6.70 δ which could be attributed to aromatic protons.

On the basis of mode of formation and analytical data, structure 38a or 39a could be assigned to the product which was supported by the mass spectral data. Thus, in its mass spectrum, in addition to the molecular ion peak (M⁺, m/z 369, 14%) it showed peaks at m/z 178 (100%) and 192 (8%) which could be assigned to fragments a and b respectively. These fragments could be obtained by way of retro Diels-Alder cleavage of ring C.
As reported in the literature and discussed in the stereochemistry section, the compound 39a having trans-quinolizidine structure, is expected to exhibit trans-quinolizidine bands (in the region 2700-2800 cm\(^{-1}\)) in its IR spectrum (CHCl\(_3\)). In its PMR spectrum it should exhibit a doublet at 0.88-0.99 \(\delta\) due to \(C_{13}\)-methyl protons. However, in its IR spectrum (CHCl\(_3\)) the product showed absence of trans-quinolizidine bands in 2700-2800 cm\(^{-1}\) region. Furthermore in its PMR spectrum it exhibited a doublet at 1.48 \(\delta\) for \(C_{13}\)-methyl protons. Thus, structure 39a was ruled out and structure 38a was assigned to the product. The observed m.p. (146-148\(^\circ\)) of 38a is similar to the reported\(^{35}\) m.p. (148\(^\circ\)). The PMR spectral properties of this compound are identical with the reported\(^{35}\) values.

\((ii)\) Synthesis of (+) 2,3-dimethoxy-13-methylberbines

\((38b and 39b)\)

The hydroxyamide 37b was similarly subjected to cyclisation (PCl\(_5\)) followed by reduction (NaBH\(_4\)) of the salt to get a thick liquid. It showed only one major spot on TLC. This liquid on purification gave a white solid, m.p. 87-89\(^\circ\). It analysed correctly for C\(_{20}\)H\(_{23}\)NO\(_2\). The structure 38b or 39b could be assigned to the product on the basis of its spectral properties which are given below.
Fig. 5: 80 MHz PMR spectrum of the 13-methylberbine 38b
UV (MeOH) : \( \lambda_{\text{max}} \): 234 (log \( \varepsilon \) 3.73), 283 (3.59) nm.

IR (CHCl\(_3\)) : No bands in 2800-2700 cm\(^{-1}\) region.

PMR (CDCl\(_3\)) : (Fig. 5)

1.49 d (J=6.5 Hz) 3H ArCH(CH\(_3\))
2.60-3.25 m 5H ArCH\(_2\)CH\(_2\)N and ArCH(CH\(_3\))
3.60 d (J=8 Hz) 1H C\(_{13}\)a-H
3.70, 4.15 q (J=15 Hz) 2H C\(_8\)-H (centred at 3.90)
3.78 s 3H -OMe
3.82 s 3H -OMe
6.54 s 1H ArH
6.70 s 1H ArH
6.95-7.25 m 4H 4 x ArH

MS : m/z : 309 (M\(^+\)), 294, 192, 190, 176, 118.

As discussed in the case of 32a, this compound also did not exhibit trans-quinolizidine bands (2700-2800 cm\(^{-1}\)) in its IR spectrum (CHCl\(_3\)). In its PMR spectrum, a doublet was seen at 1.49 s for C\(_{13}\)-methyl group. Thus, in this case also the trans-quinolizidine structure 32b was ruled out and structure 38b was assigned to the product. The spectral properties of the compound are in agreement with the reported\(^{10}\) values.
In this chapter two methods have been described for the synthesis of 4-methylisochromanones, which are useful synthons for 13-methylberbines. 4-Methylisochroman-3-one (35) was synthesised by making use of a heteroatom directed lithiation reaction. An useful procedure has been developed for monomethylation of 6,7-dimethoxyisochroman-3-one (29) to get 4-methyl-6,7-dimethoxyisochroman-3-one (30). These isochromanones (30 and 35) have been converted into 13-methylberbines (38a and 38b) in simple two steps.

A method has been developed\textsuperscript{53} in our laboratory for the synthesis of 7,8-dialkoxy isochroman-3-ones. By using our newly developed procedure these could be converted into the corresponding 4-methylisochromanones which in turn could be used for the synthesis of 9,10-dialkoxy-13-methylberbine alkaloids.

Thus, the method described in this chapter could be a general one for the synthesis of variously substituted 13-methylberbines. The present method involves less number of steps and provide 13-methylberbines in reasonably good overall yield.
EXPERIMENTAL
Expt. No. 4.1 : Synthesis of 6,7-dimethoxyisochroman-3-one (29)

Expt. No. 4.2 : Synthesis of 4,1-dimethyl-6,7-dimethoxyisochroman-3-one (31)

Expt. No. 4.3 : Synthesis of 4-methyl-6,7-dimethoxyisochroman-3-one (30)

Expt. No. 4.4 : Synthesis of α-methyl-N,N-dimethylbenzylamine (32)
Expt.No. 4.5: Synthesis of α-methyl-N,N-dimethyl-2-hydroxymethyl-benzylamine (34)

\[
\text{MeMe} \quad \text{NMe}_2 \quad 1. \text{n-} \text{BuLi} \quad 2. (\text{HCHO})_n \quad \text{Me} \quad \text{Me} \quad \text{NMe}_2
\]

Expt.No. 4.6: Synthesis of 4-methylisochroman-3-one (35)

\[
\text{MeMe} \quad \text{NMe}_2 \quad 1. \text{CICOEt} \quad 2. \text{KCN} \quad 3. \text{OH}^\ominus \quad 4. \text{H}^\ominus \quad \text{Me}
\]

Expt.No. 4.7: Synthesis of N-[2-(3,4-dimethoxyphenyl)ethyl]-[4,5-dimethoxy-2-hydroxymethyl-α-methyl phenylacetamide (37a)

\[
\text{MeO} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{Me}
\]
Expt.No. 4.8: Synthesis of N-([2-(3,4-dimethoxyphenyl)ethyl]-[2-hydroxymethyl]-α-methyl-phenylacetamide (37b)

Expt.No. 4.9: Synthesis of (+)-2,3,10,11-tetramethoxy-13-methylberbine (38a)

Expt.No. 4.10: Synthesis of (+)-2,3-dimethoxy-13-methylberbine (38b)
Expt.No. 4.1 : Synthesis of 6,7-dimethoxyisochroman-3-one (22)

A mixture of 3,4-dimethoxyphenylacetic acid (4.9 g, 0.025 mol), glacial acetic acid (12.5 ml), concentrated HCl (4.0 ml) and formalin (4.0 ml, 37%) was heated on steam bath for 1 hr. The dark brown reaction mixture was allowed to cool to room temperature. The solution was then poured into cold water containing ice, with stirring. It was extracted with chloroform (3 x 50 ml). The chloroform extract was washed with 5% sodium bicarbonate solution until neutral. It was then washed with water and dried over anhydrous sodium sulphate. The chloroform layer was evaporated to give a crude solid which on recrystallisation from ethanol gave 29 (3.0 g, 57%), m.p. 106-107° (lit.50 m.p. 106-108°).

Expt.No. 4.2 : Synthesis of 1,3-dimethyl-6,7-dimethoxyisochroman-3-one (31)

A solution of 6,7-dimethoxyisochroman-3-one (0.500 g, 0.0024 mol) in dry tetrahydrofuran (10 ml) was added to a stirred mixture of methyl iodide (1.5 ml, 0.025 mol) and sodium hydride (0.100 g) in tetrahydrofuran (5 ml) at -10°. The reaction mixture was stirred at 0° for 0.5 hr, at room temperature for 0.5 hr and then decomposed with water. Most of
the solvent was removed under reduced pressure. The residue was acidified with 1:1 HCl and extracted with ether (2 x 50 ml). The ether layer was dried (Na₂SO₄) and evaporated to give a thick liquid which was chromatographed over silica gel using benzene:ethyl acetate (9:1) as an eluent. A white solid thus obtained was recrystallised from methylene chloride-n-hexane to give \( \text{31} \) (0.150 g, 26.3%), m.p. 107-109°.

**Analysis**: Found: C, 66.16%; H, 6.93%
calculated for C_{13}H_{16}O_4: C, 66.08%; H, 6.83%

**IR** (Nujol): \( \nu_{\text{max}} = 1750 \text{ cm}^{-1} \)

**PMR** (CDCl₃): (Fig.1)

<table>
<thead>
<tr>
<th>( \delta ) (ppm)</th>
<th>Multiplicity</th>
<th>Protons</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.56</td>
<td>s</td>
<td>6H</td>
<td>2 x -CH₃</td>
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<tr>
<td>3.89</td>
<td>s</td>
<td>3H</td>
<td>OMe</td>
</tr>
<tr>
<td>3.92</td>
<td>s</td>
<td>3H</td>
<td>OMe</td>
</tr>
<tr>
<td>5.35</td>
<td>s</td>
<td>2H</td>
<td>ArCH₂O</td>
</tr>
<tr>
<td>6.68</td>
<td>s</td>
<td>1H</td>
<td>ArH</td>
</tr>
<tr>
<td>6.85</td>
<td>s</td>
<td>1H</td>
<td>ArH</td>
</tr>
</tbody>
</table>

**Expt.No. 4.3**: Synthesis of 4-methyl-6,7-dimethoxyisochroman-3-one (30)

Diisopropylamine (1.1 ml, 0.008 mol) in dry tetrahydrofuran (5 ml) was stirred at -10°. n-Butyllithium (0.008 mol, prepared from 1.7 ml n-butylbromide and 0.21 g lithium in 25 ml ether) was added to it and the reaction mixture was stirred at -10 to 0° for 10 min. The reaction
mixture was cooled to -60° and a solution of 6,7-dimethoxy-
isochroman-3-one (22, 0.416 g, 0.002 mol) in tetrahydrofuran
(25 ml) was added to it. The reaction mixture was allowed to
warm to room temperature during 1.5 hr. The initial grey
colour of the reaction mixture changed to violet grey indicating
the formation of anion. It was again cooled to -50° and
methyl iodide (2 ml, 0.03 mol) was added to it in one lot. The
reaction mixture was stirred at -50 to -45° for 4 hr and then
decomposed with water. Organic solvent was removed under
reduced pressure. The aqueous layer was acidified with 1:1
HCl and allowed to stand for few hours. It was extracted with
methylene chloride (3 x 50 ml). The methylene chloride layer
was first washed with sodium thiosulphate solution (2 x 30 ml)
and then with water (2 x 30 ml). It was dried over anhydrous
sodium sulphate and evaporated to give a thick liquid. HPLC
analysis of the crude product indicated three major peaks.
It was chromatographed over HPLC, using ethyl acetate:benzene
(1:9) as an eluent. A white solid was obtained in the initial
fractions which corresponded to the first peak. It was
recrystallised from methylene chloride-n-hexane to give 32
(0.023 g, 5%), m.p. 107-109°, mixed m.p. with authentic sample
remained undepressed.
Evaporation of the fractions corresponding to the second peak gave another white solid which was also recrystallised from methylene chloride-n-hexane to give 30 (0.280 g, 64.5%), m.p. 11°-16°.

**Analysis**: Found: C, 65.14%; H, 6.43%
calculated for C₁₂H₁₄O₄: C, 64.85%; H, 6.35%

**IR (Nujol)**: \( \nu_{\text{max}} \) 1750 cm⁻¹

**PMR (CDCl₃)**: (Fig. 2)

1.59 d (J=7 Hz) 3H -CH₃
3.59 q (J=7 Hz) 1H ArCH(CH₃)CO
3.87-3.89 s s 3H each 2xOMe₂
5.23 s 2H ArH
6.76 s 2H ArH

The fractions corresponding to the third peak gave the unreacted starting isochromanone 29 (0.020 g, 5%), m.p. 105-106°, mixed m.p. with authentic sample remained undepressed.

When methyl iodide was added to the anion (29a) at -10° and the reaction mixture stirred at 0 to -10° for 1 hr, only the dimethylated product 31 was obtained in 73% yield.

**Expt.No. 4.1**: Synthesis of α-methyl-\( N, N \)-dimethyl-benzylamine (32)

A mixture of acetophenone (6.0 g, 0.05 mol), dimethyl-formamide (14.6 g, 0.2 mol) and formic acid (2 ml, 85%) was
refluxed on an oil bath at 180-90° for 20 hr. The reaction mixture was then cooled to room temperature and made acidic with concentrated hydrochloric acid. It was extracted with ether (2 x 50 ml) and the ether layer was discarded. On basification of the aqueous acidic layer, with 10 N sodium hydroxide, an oily product was separated out. It was extracted with ether (3 x 50 ml). The ether extract was dried over anhydrous sodium sulphate and evaporated to give an oily product which was distilled under reduced pressure to furnish \( \text{Expt. No. 4.5 : Synthesis of } \alpha\text{-methyl-N,N-dimethyl-2-}
\text{-hydroxymethylbenzylamine} (32') \)

To a solution of \( \alpha\text{-methyl-N,N-trimethylbenzylamine} \)
(32, 5.96 g, 0.04 mol) in ether (30 ml) was added \( n\text{-butyllithium} \)
(0.08 mol, prepared from 11.4 ml \( n\text{-butylbromide} \) and 1.5 g lithium in 100 ml ether) at room temperature. The metallation mixture was stirred at room temperature for 24 hr and paraformaldehyde (10 g) was added to it in lots. Initially a vigorous reaction was observed. The reaction mixture was stirred at room temperature for 2 hr and then decomposed with water (100 ml). The organic phase separated and the aqueous layer was extracted with ether (3 x 50 mol). The combined ether layer was extracted with 1:1 HCl (2 x 30 ml) and the ether layer discarded. The aqueous layer was cooled and
basified with 10 N sodium hydroxide and extracted with ether (3 x 50 ml). The ether layer was dried over anhydrous sodium sulphate and evaporated to give an oily product. It was distilled under reduced pressure to give $\frac{3}{2}$ (3.6 g, 50%), b.p. 108°/2 mm.

**Analysis:** Found: C, 73.60%; H, 9.51%
calculated for C$_{11}$H$_{17}$NO: C, 73.70%; H, 9.56%.

**IR (Liquid film):** $\nu_{\text{max}}$ 3350 cm$^{-1}$.

**PMR (CDCl$_3$):**

- 1.33 d (J=7 Hz) 3H $-\text{CH(CH$_3$)}$NMe$_2$
- 2.14 s 6H $-\text{NMe$_2$}$
- 3.92 q (J=7 Hz) 1H $-\text{CH(CH$_3$)}$NMe$_2$
- 4.42 d (J=12 Hz) 1H $-\text{HCH-OH}$
- 4.72 d (J=12 Hz) 1H $-\text{HCH-OH}$
- 6.48 brs 1H $-\text{OH}$ (exchangeable with D$_2$O)
- 7.20 s 4H 4 x ArH

**Expt. No. 4.6:** *Synthesis of 4-methylisochroman-3-one (35)*

To a vigorously stirred solution of the amino alcohol 3/4 (2 g, 0.011 mol) in benzene (30 ml) containing sodium bicarbonate (5 g), ethyl chloroformate (8 ml) was added. The reaction mixture was stirred for 2 hr and filtered. The filtrate was concentrated in vacuo to give a thick liquid
which showed one major spot on TLC along with some minor impurities. The compound corresponding to major spot was isolated by using flash chromatography over silica gel. Ethyl acetate:n-hexane (2:8) was used as an eluent. The chloroester thus obtained was dissolved in dry dimethylformamide (10 ml). Potassium iodide (0.100 g) and potassium cyanide (2 g) was added to it and the reaction mixture was stirred at 80° for 4 hr. The reaction mixture was decomposed with water (100 ml) and extracted with ether (2 x 100 ml). The ether layer was washed with water, dried over anhydrous sodium sulphate and evaporated to give the crude nitrile as a thick liquid which was subjected to a flash chromatography over silica gel using ethyl acetate:n-hexane (2:8) as an eluent to furnish a thick liquid. It was dissolved in methanol (30 ml), alcoholic potassium hydroxide (1.5 g of potassium hydroxide in 20 ml water and 20 ml methanol) was added to it and the reaction mixture was refluxed for 6 hr. Methanol was removed under reduced pressure. Water (50 ml) was added to the residue and extracted with ether (2 x 30 ml). The ether layer discarded and the aqueous layer was acidified with 1:1 HCl. After allowing it to stand for few hr, it was extracted with ether (2 x 100 ml). The ether layer was dried (Na₂SO₄) and evaporated to give a thick liquid which was purified by flash chromatography over silica gel using ethyl acetate:n-hexane (2:8) as an eluent to furnish 35 (0.640 g, 35.4%), m.p. 44-45°.
Analysis: Found: C, 74.14%; H, 6.21%
calculated for C\textsubscript{10}H\textsubscript{10}O\textsubscript{2}: C, 74.05%; H, 6.22%
IR (Nujol): \( \nu_{\text{max}} \) 1750 cm\(^{-1}\).
PMR (CDCl\textsubscript{3}): (Fig. 3)

1.60 d (J=7 Hz) 3H CH(CH\textsubscript{3})\textsubscript{2}Co
3.60 q (J=7 Hz) 1H CH(CH\textsubscript{3})\textsubscript{2}Co
5.22 s 2H ArCH\textsubscript{2}O
7.10-7.41 m 4H ArH

Expt. No. 4, 7: Synthesis of N-[\( \alpha-(3,4\)-dimethoxyphenyl\]-
edethyl]-[\( \alpha,5\)-dimethoxy-\( \alpha\)-hydroxymethyl]-
\( \alpha\)-methyl phenylacetamide (37a)

A solution of isochromanone 30 (0.300 g, 0.0013 mol) and homoveratrylamine (0.6 g) in absolute ethanol (10 ml) was refluxed for 8 hr. Ethanol was removed under reduced pressure to give an oily product. It showed two major spots on TLC. The spot having the lower \( R_F \) value was corresponding to the starting amine. The other spot having higher \( R_F \) value might due to the product amide. It was purified by flash chromatography (or HPLC) over silica gel using ethyl acetate as an eluent. All the fractions corresponding to less polar product were concentrated under reduced pressure to give the hydroxyamide as a thick liquid (37a, 0.530 g, 97.3%).
IR (Liquid film): \( \nu_{\text{max}} \) 1660, 3275-3370 (br) cm\(^{-1}\).
**PMR (CDCl₃) :**

1.44  d (J=7 Hz)  3H  ArCH(CH₃)CO
2.30  brs           1H  OH/NH (exchangeable with D₂O)
2.62  t (J=7 Hz)  2H  ArCH₂CH₂N
3.22-3.60  m  2H  ArCH₂CH₂N
3.79  s           13H  4 x OMe and
3.83  s
3.85  s
3.87  s
4.42  d (J=11 Hz)  1H  ArHCH-0
4.77  d (J=11 Hz)  1H  ArHCH-0
6.30-6.90  m  5H  5 x ArH

**Expt. No. 4.8 : Synthesis of N-[2-(3,4-dimethoxyphenyl)-ethyl]-[2-hydroxymethyl]-α-methyl-phenyl-acetamide (27b)**

The isochromanone 35 (0.500 g, 0.003 mol) was dissolved in absolute ethanol. Homoveratrylamine (36, 1 g) was added to it and the reaction mixture was refluxed for 8 hr. Ethanol was removed under reduced pressure and the residual thick liquid was subjected to flash chromatography over silica gel using ethyl acetate as an eluent to give a thick, pale yellow liquid which solidified on cooling. It was recrystallised from n-hexane to furnish 27b (1.0 g, 94.5%), m.p. 85-86°.

**Analysis :** Found : C, 70.08%; H, 7.28%
calculated for C₂₀H₂₅NO₄ : C, 69.95%; H, 7.33%
IR (Nujol): $\nu_{max} 1630, 3250 \text{ cm}^{-1}$.

PMR (CDCl$_3$):

1.46  d ($J=7$ Hz)  3H  ArCH(CH$_3$)CO
2.11  bs                        2H  OH/NE (exchangeable with D$_2$O)
2.63  t ($J=7$ Hz)  2H  ArCH$_2$CH$_2$N
3.92  q ($J=7$ Hz)  1H  ArCH(CH$_3$)CO (partly hidden in methoxy signal)

3.84  s                        3H  OMe
3.78  s                        3H  OMe
4.47  d ($J=13$ Hz)  1H  ArCH$_2$OH
4.80  d ($J=13$ Hz)  1H  ArCH$_2$OH
6.45  dd ($J=2,7$ Hz)  1H  ArH
6.57  d ($J=2$ Hz)  1H  ArH
6.71  d ($J=7$ Hz)  1H  ArH
7.16-7.45  m  4H  4 x ArH
7.29-3.60  m  2H  ArCH$_2$CH$_2$N

Expt.No. 4,9: Synthesis of (+)-2,3,10,11-tetramethoxy-13-methylberbine (38a)

A solution of hydroxyamide $37a$ (0.4 g, 0.0009 mol) in dry chloroform (30 ml) was cooled in ice bath. To this ice cooled and well stirred solution, phosphorus pentachloride (1.2 g) was added and the reaction mixture was stirred at room temperature for 3 hr under the atmosphere of dry nitrogen. The solvent was removed under reduced pressure and the residue was
decomposed with crushed ice. It was washed with ether (2 x 25 ml) and the aqueous layer was extracted with chloroform. The chloroform layer was dried (Na₂SO₄) and evaporated in vacuo to give a foamy solid which was dissolved in methanol (30 ml). The solution was cooled in ice bath and sodium borohydride (0.8 g) was added to it in lots at 0°C during 0.5 hr. It was then stirred at room temperature for 20 hr. Methanol was removed in vacuo. Water (50 ml) was added to the residue and it was extracted with ether (2 x 100 ml). The ether extract was dried (Na₂SO₄) and evaporated at low temperature (40-50°C) to give a thick pale yellowish brown liquid (0.250 g) which was scratched in dry ether to give a yellow solid (0.240 g). It was purified by filtration through alumina column using chloroform as an eluent to give a pale yellow solid which was recrystallised from methylene chloride-n-hexane to furnish 38a (0.2 g, 54.6%), m.p. 146-48°C (lit. 140 m.p. 148°C).

**Analysis**
- Found: C, 71.28%; H, 7.43%
- Calculated for C₂₂H₂₇NO₄: C, 71.52%; H, 7.37%

**UV (MeOH):**
- λ_max: 284.5 (log ε 3.9), 225.5 (3.13) nm.

**IR (CHCl₃):**
- No bands in 2800-2700 cm⁻¹ region.

**PMR (CDCl₃):** (Fig. 4)

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>J (Hz)</th>
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<tbody>
<tr>
<td>1.49</td>
<td></td>
<td>3H ArCHCH₃</td>
</tr>
<tr>
<td>2.73-3.19</td>
<td></td>
<td>5H ArCH₂CH₂H and ArCH(CH₃)</td>
</tr>
</tbody>
</table>
3.69 d (J=8 Hz) 1H C\textsubscript{13a}-H
3.74 and 4.21 AB quartet 2H C\textsubscript{8}-H (centre at 3.95)
3.84 s 12H 4-x OMe
6.52 s 1H Ar\textsubscript{H}
6.59 s 1H Ar\textsubscript{H}
6.67 s 1H Ar\textsubscript{H}
6.70 s 1H Ar\textsubscript{H}

\textbf{MS:} m/z 369 (M\textsuperscript{+}), 178, 192, 163.

\textbf{Expt. No. 4.10:} \textit{Synthesis of (+)-2,3-dimethoxy-13-methyl-berbine (38b)}

Phosphorus pentachloride (1 g) was added to a well stirred and ice cooled solution of the hydroxyamide \textsuperscript{38b} (0.450 g, 0.0013 mol) in chloroform (30 ml) and the reaction mixture was stirred at room temperature for 3 hr under the atmosphere of dry nitrogen. The solvent was removed under reduced pressure. Crushed ice was added to the residue and it was washed with ether (2 x 30 ml). The aqueous layer was extracted with methylene chloride. Drying (\textit{Na}_2\text{SO}_4) and evaporation of methylene chloride layer gave a thick liquid which was dissolved in methanol (25 ml). Sodium borohydride (0.9 g) was added to this precooled solution (0\textdegree), during 0.5 hr. The reaction mixture was stirred at room temperature for 20 hr. Methanol was removed under reduced pressure and
and water (50 ml) was added to the residue. It was then extracted with ether (2 x 100 ml). The ether layer was dried over anhydrous sodium sulphate and evaporated on water bath (40°) to give a thick liquid. Scratching in dry ether gave a yellow solid. It was subjected to filtration through alumina column using chloroform as an eluent to give a solid. It was recrystallised from n-hexane to furnish 38b (0.300 g, 74%), m.p. 87-89°.

**Analysis**

<table>
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<tr>
<th>Found</th>
<th>Calculated for C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;23&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
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<tbody>
<tr>
<td>C, 77.47%; H, 7.63%</td>
<td>C, 77.64%; H, 7.49%</td>
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</table>

**UV (MeOH)**: λ<sub>max</sub>: 234 (log ε 3.73), 283 (3.59) nm.

**IR (CHCl<sub>3</sub>)**: No bands in 2800-2700 cm<sup>-1</sup> region.

**PMA** (CDCl<sub>3</sub>): (Fig. 5)

- 1.49 d (J=6.5 Hz) 3H ArCH(CH<sub>3</sub>)
- 2.60-3.25 m 5H ArCH<sub>2</sub>CH<sub>2</sub>N and ArCH(CH<sub>3</sub>)
- 3.60 d (J=8 Hz) 1H C<sub>13a</sub>-H
- 3.70, 4.15 AB quartet (centre at 3.90) 2H C<sub>8</sub>-H
- 3.78 s 3H OMe
- 3.82 s 3H OMe
- 6.54 s 1H ArH
- 6.70 s 1H ArH
- 6.95-7.25 m 4H 4 x ArH

**MS**: m/z 309 (M<sup>+</sup>), 294, 192, 190, 176, 118.
REFERENCES
References


24. (a) M. Freund and K. Fleischer, Ann., 409, 188 (1915); (b) T. Takemoto and Y. Kondo, J.Pharm.Soc. Japan, 82, 1408 (1962).


