STUDIES TOWARD THE SYNTHESIS OF HYDROXYLATED INDOLIZIDINE ALKALOIDS

by

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APPROCHES À LA SYNTHÈSE D'INDOLIZIDINES HYDROXYLÉS

par YVES ST-DENIS

RÉSUMÉ

La formation du système bicyclique indolizidine fut étudiée. Premièrement, la cyclisation électrophilique intramoléculaire de silanes allyliques, silanes vinyliques et d'éthers d'énole substitués fut examinée. Les réactions avec les silanes allyliques ont en effet produit le système cyclique désiré, alors que les silanes vinyliques n'ont donné aucun produit de cyclisation. Afin de pouvoir introduire facilement des fonctions oxygénées dans les cycles, des cyclisations d'éthers d'énole furent aussi essayées mais ne produisirent pas les systèmes bicycliques désirés.

Deuxièmement, la cyclisation intramoléculaire nucléophilique d'amines libres substituées avec des groupes partants appropriés fut tentée. Une méthode facile pour la formation du système indolizidine fut mise au point, permettant ainsi de développer une approche à la synthèse d'alkaloïdes polyhydroxylés biologiquement actifs tels que la Swaïnsonine et la Castanospermine. La synthèse de ces deux produits naturels, ainsi que de quelques analogues, fut tentée en utilisant la nouvelle méthodologie nucléophiliques.

Finalement, l'introduction régiosélective et stéréosélective de groupes hydroxyles dans le système cyclique pyrrolidine fut étudiée afin de préparer des pyrrolidines mono- et di-hydroxylées pour la synthèse des produits naturels mentionnés plus haut.

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ABSTRACT

The formation of the indolizidine ring system was studied. First, the intramolecular electrophilic cyclisation of substituted allylsilanes, vinylsilanes and enol ethers was attempted. Reactions with the allylsilane moiety indeed gave the desired ring system, whereas the vinylsilanes failed to give any cyclisation product. In order to easily introduce oxygen functionnalities in the rings, enol ether cyclisations were also attempted but did not produce the expected bicyclic systems.

Secondly, the intramolecular nucleophilic cyclisation of free amines bearing suitable leaving groups was attempted, providing an easy method for the formation of the indolizidine system, with an interesting entry into the synthesis of biologically active polyhydroxylated alkaloids *Swainsonine* and *Castanospermine*. The synthesis of these two natural compounds, as well as some of their analogues, using the successful nucleophilic methodology was attempted.

Finally, the regioselective and stereoselective introduction of hydroxyl groups into the pyrrolidine ring system was studied in order to prepare mono- and di-hydroxylated pyrrolidines for the synthesis of the aforementioned natural products.

REMERCIEMENTS

J'aimerais tout d'abord remercier M. Michel Savary du C.E.G.E.P. de Bois-de-Boulogne pour avoir inoculé en moi (et avec grand succès) le virus de la chimie organique. Son grand enthousiasme et son intarissable patience m'ont fait prendre la décision d'étudier la chimie, moi qui voulais devenir biologiste.

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·A tous

ceux qui ont su

conserver leurs yeux d'enfants :

ils sont les vrais chercheurs;

et specialement a mon pere et ma mere qui,

malgre les annees et les epreuves,

ont su conserver

les leurs·

TABLE OF CONTENTS

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

New methodologies for the stereoselective formation of substituted indolizidines were developed. First, it was found that the electrophilic allylsilane substitution reaction could be used in an intramolecular fashion to form nitrogen containing heterocycles. The cyclisation step produced, in the best conditions, only one of the two possible diastereomers when a dimethyl acetal was used as the electrophile.

Secondly, a very easy method for the formation of polyhydroxylated indolizidines was developed. It utilises derivatives of proline as starting materials. 6,7,8-Trihydroxyindolizidines as well as 1,6,7,8-tetrahydroxyindolizidines (castanospermine analogues) were synthesised using this methodology.

Finally, derivatives of 3,4-dihydroxyproline were prepared from *trans*-4-hydroxy-L-proline. The all *cis* compound was synthesised in modest yield utilising the oxidiative opening of an epoxide as the key step. This epoxide was prepared by the stereospecific formation of an iodohydrin followed by ring closure.

CHAPTER 1

INTRODUCTION

1.0 From *al-kîmiyâ* and *al-iksîr* to *organic chemistry*[1] :

Organic Chemistry became a science of its own only during the ninteenth century. Even if the ancients were indeed manipulating organic compounds such as acetic acid, oil of turpentine, soaps and the like, and even if they used chemical processes such as fermentation, chemistry as a science was unknown to them, the facts being not sufficient to afford a generalisation.

It is in Julius Maternus Firmicus' book on astrology (fourth century) that chemistry is first mentionned as being a science (*scientia chemiæ*). It is later explained by Zosimus of Panoplis (ninth century) that this science was "the art of making gold and silver". The precepts of such a science were found cut into the stones of the temples of the Egyptian god Pthah. These hieroglyphs were transferred on papyrus later on and were translated by modern historians. They dealt mainly with the working of metals, and more specifically of the purification of gold and silver, their imitation and falsification, the latter being quite openly acknowledged.

Since the imitation of these metals was first practised in Egypt, and since this country was formerly called Chemi, it seems probable that *scientia chemiæ* was used for *the science of Egypt*. But Chemi does not only mean *Egypt*. It also means *black* or the *black of the eye*. It is interesting to note that the first process used by the alchemists for the transmutation of metals was called *the blackening* or *melanosis*. So the name of a country slowly became the name of a process, and later on, as the Arabians took possession of the inheritance of the Egyptian alchemists, and translated *Chemi* into

Al-kîmiyâ, the name of the process became the name of a substance.

Indeed, the ancient alchemists were using a preparation in their operations, which they called *divine water*. This was prepared by boiling a mixture of sulfur and lime in water, producing a solution containing polysulfides of calcium. Such a liquid, when mixed with metals and their compounds, yielded all possible colorations. In the old arabic texts, this medium was named *al-kîmiyâ* and had a synonym : *al-iksir*. Those two words were interchanged quite freely and had the same meaning. The later arabic writers kept the word *alkîmiyâ* for the science, as in "books of *kîmiyâ*", whereas *aliksir* was used for the transmuting medium.

As long as that science existed as alchemy, the advances in the study of inorganic substances were by far more important than those of organic bodies. Up to the sixteenth century, the sole object of chemical research had been to find the philosopher's stone. At that time, though, the field began to develop itself into two new and different branches, opened by two distinguished men : Agricola, the father of metallurgy, and Paracelsus, the founder of Iatrochemistry, or medical chemistry. It could have been expected that by the development of Iatrochemistry, the knowledge of organic chemistry would have made great progresses. But this was not the case, Paracelsus and his followers mainly employing metallic preparations for their medicines. Only a few of them were interested in the extraction of organic bodies for their active medical properties. Compounds such as *pyroligneous* acid, or *acetum lignorum* (distillation of wood), *spiritus tartari* (impure pyruvic acid, from tartar), *spiritus ardens e saturno* (impure acetone), *sal succini* or *flos* (from amber) and *flores benzoïn* (benzoic acid, from gum benzoin) were extracted.

It is with Robert Boyle that chemistry became a science in itself. He was the first who clearly pointed out that *chemistry should be studied for its own sake as a natural science* and that *it should not be regarded any longer as the handmaid of any art*

or profession, but as forming an essential part of the great study of nature. Boyle was also the first one to clearly grasp the concept of the distinction between elements and compounds, and it was only when that difference had been clearly recognised that it became possible to ascertain the composition of bodies by analysis and synthesis, but only for inorganic compounds. It is also at this period that an effort to make a distinction (and classify) between inorganic and organic bodies was made, even though this classification was rather inacurate (texture, appearance, taste, were the criteria of classification).

From this early attemtps of classification to the late nineteenth century where organic chemistry was finally defined as the *Chemistry of the Hydrocarbons and their Derivatives*, many different hypotheses and theories were brought to light and were forgotten. From Lemery's *mineral, vegetable and animal* classification (1675) to the more consistant (but yet incomplete) definition of Gmelin (he defined organic compounds as the compounds of carbon : 1848), chemists have tried to define their science and have tried to find the boundaries of its different subdivisions, *for the sake of clearness* (Kekule, 1851). With Kolbe's synthesis of acetic acid in 1845, which was the first synthesis of an organic compound *directly from its elements*, the progress of organic chemistry and organic synthesis was rapid. Being quite a young science, the enthusiastic scientists who studied it brought it rapidly to the high level we know today, where their spectacular achievements seem to be limitless.

1.1 The alkaloids[2] :

It is not easy to give an exact definition of what is meant by an alkaloid. The word itself was introduced by the pharmacist W. Meisner in 1819 and simply meant *alkalilike* (Middle English *alcaly*, derived from Medieval Latin *alcali*, from Arabic

alqaliy = ashes). No other class of natural products possesses such an enormous variety of structures. Steroids, for example, are all modeled on a few skeletal types. The same holds true for triterpenes, flavonoids, or polysaccharides. But alkaloids exhibit dozens of different skeletal types. This situation causes extraordinary difficulty in defining alkaloids so they may be readily recognised and differentiated from other classes of organic nitrogen-containing compounds[2b].

An early definition of these substances described them as being basic, nitrogen containing compounds of either plant of animal origin. 'True alkaloids' were defined as compounds meeting four additional qualifications : 1- the nitrogen atom is part of a heterocyclic system, 2- the compound has a complex molecular structure, 3- the compound manifests significant pharmacological activity and 4- the compound is restricted to the plant kingdom.

That the classical definition of a true alkaloid is no longer serviceable should be clear from the recent literature. There are many examples of compounds that are universally accepted as alkaloids and that violate one or more of the requirements of the above definition. Even though alkaloid originally meant *alkalilike*, there are many compounds that are non-basic and that are considered alkaloids. Amine-oxides and some important quaternary salts are examples that prove that basicity should no longer be included in the definition. Although most early classified alkaloids contained nitrogen as part of a heterocyclic system, there are now too many exceptions for this condition to be mandatory. What exactly is a complex molecular structure and what kind of minimum dosage should be required in order to observe some pharmacological activity are concepts which are too vague to be included as requirements. As far as the restriction to the plant kingdom is concerned, a large number of compounds which have been called alkaloids were isolated from animal, fungal and bacterial sources. *'One cannot on any rational basis exclude such compounds because they happen to occur in*

living tissue other than plants.'[2b]

An appropriate definition must be workable in the sense of accomodating most, if not all, of the compounds regarded as alkaloids by most chemists. The following simple definition was suggested by Pelletier in 1983[2b] :

An alkaloid is a cyclic organic compound containing nitrogen in a negative oxidation state which is of limited distribution among living organisms.

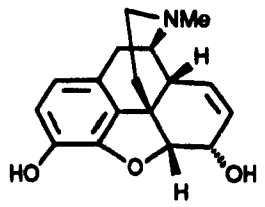
The requirement for a negative oxidation state will include amines (oxidation state : -3), amine oxides (-1), amides (-3) and quaternary ammonium salts (-3), but excludes nitro (+3) and nitroso compounds (+1). By imposing the requirement of restricted occurence among the various classes of plants, animals and other living organisms, one excludes compounds such as amino acids, proteins, nucleic acids, nucleotides, porphyrins and vitamins.

It is not possible, of course, to describe here all of the history of the alkaloids. Thousands and thousands of them have been isolated from natural sources, and a good number of synthetic compounds have been prepared. But even before Humans knew what alkaloids were, they used these compounds on an almost daily basis. As long as five thousand years ago, the Chinese "doctors" were using extracts of a plant called *Ma Huang*, or *Ephedra Gnetaceae*, to cure allergic conditions not knowing that the active ingredients of their medicinal preparation were (-)-ephedrine and (+)-pseudoephedrine. The early Egyptians knew of the soporific properties of opium[3], and the 'pre-conquest' Mexicans were using plants such as *piçietl*, *peyotl*, *teonanacatl* and *ololiuhqui* as great divinatory plants, that is, for their hallucinogenic and psychotomimetic properties[4]. In the 17th century, the Jesuits in Peru used the bark of several species of *Cinchona* and

Remijia against malaria[5]. The alkaloids were not only used for their therapeutic activities. Their toxic properties were also known, and Socrates was thus executed around 400 B.C. using an extract of the common hemlock (*Conium maculatum*). These properties were due to the presence of a group of alkaloids, the most important of which was coniine, a piperidine alkaloid.

The definition given at the beginning of this section states that the alkaloids are mainly produced in plants (with the exceptions we know today). But why do plants build up such an incredible number of structurally different nitrogen containing organic compounds is a question that remains without a definite answer. Alkaloids have not been proven to have any definite function in plant metabolism and it seems that a large number of these plants can do quite well without ever forming alkaloids. There is now considerable evidence, though, that the strange chemical 'cocktails' which accumulate in plants have arisen in evolution in response to predator pressure. Some essential nutrients needed by the plant are stored or transported in a form which renders them collectively toxic, repellent or simply indigestible to predators or pathogens.

In 1805 Sertürner isolated the first vegetable base or alkaloid. Morphine (**1.1**), isolated from opium, itself derived from *Papaver somniferum* L., is known to have hypnotic and narcotic properties. The early Egyptians knew of the soporific properties

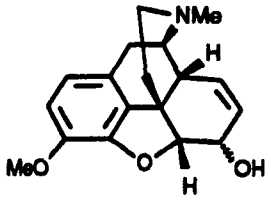


Morphine : 1.1

of opium and the habit of opium eating was established in eastern Europe in the 17th

century.

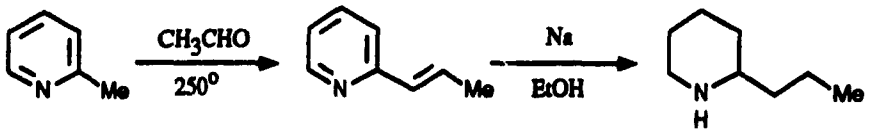
The determination of the structure of morphine was rendered considerably difficult by the many puzzling migrations that occurred during its degradation. Robinson, around 1925, suggested that the structure of codeine (the methyl ether of morphine) should be as in **1.2**. This structure was proved to be correct by X-ray diffraction in 1955[6], and the absolute stereochemistry was determined by Jeger and his collaborators in the same year[7].



Codeine : 1.2

The heterocyclic ring system present in morphine was first synthesised by Grewe and his collaborators in 1949[8], whereas the synthesis of the alkaloid itself was published by Gates and Tschudi in 1952[9].

The first alkaloid ever synthesised was coniine (**1.3**). Its synthesis was accomplished by Ladenburg in 1886[10]. **Scheme 1.1** illustrates this short synthesis.



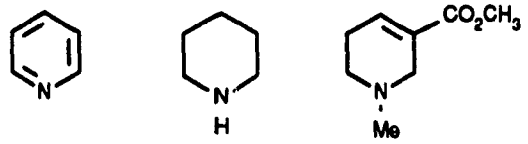
Coniine : 1.3

Scheme 1.1

2-Methylpyridine was condensed with acetaldehyde at 250°, and the resulting

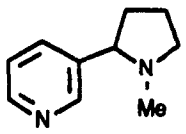
2-propenylpyridine was reduced with sodium in ethanol to give a low yield of (±)-coniine, which was resolved *via* the hydrogen (+)-tartrate derivatives.

Coniine is part of a larger class of alkaloids : the pyridine alkaloids. Included here are the alkaloids bearing the pyridine nucleus **1.4** as well as its reduced form **1.5** (piperidine). An intermediate stage of hydrogenation is found in arecoline (**1.6**) and similar compounds.



1.4 **1.5** **1.6**

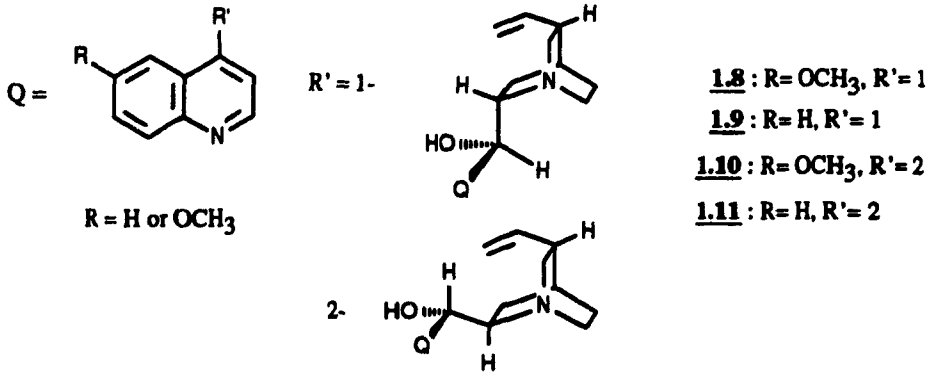
One of the most famous of the pyridine alkaloids is without a doubt nicotine (**1.7**). It was first extracted and isolated pure from *Nicotiana tabacum* L. in 1828, and its formula was established in 1843. Nicotine is rapidly fatal to all animal life. Small doses act as a respiratory stimulant, and larger doses give the same effect, but the respiratory center is soon depressed until death occurs. Thus, for human consumption, tobacco leaves of low alkaloid content is desirable (the fatal dose in man is approximately 40 mg). That smoking can be practised at all is to be explained by the ability of the human body to degrade nicotine rather quickly, therefore preventing its accumulation.



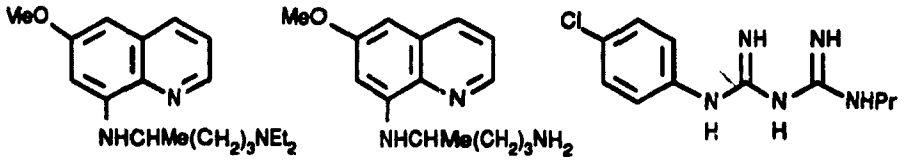
Nicotine : 1.7

Two other important groups of alkaloids are the cinchona alkaloids and the

quinoline alkaloids. Quinine (1.8), cinchonine (1.9), quinidine (1.10) and cinchonidine (1.11) are all members of the former group. They are present in the bark of several species of *Cinchona* and *Remijia*, trees native to the eastern slopes of the Andes at an altitude of 5000-8000 feet. Cinchona bark extracts were used as antimalarial agents as



early as the 17th century. As the world supply of *Cinchona* became very low due to the very high popularity of this medication, synthetic substitutes had to be devised. Compounds such as Pamaquine (1.12), Primaquine (1.13) and Proguanil (1.14) were among the first synthetic antimalarial agents.

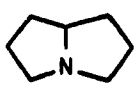


1.12 1.13 1.14

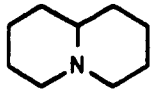
More recently, cinchonine (and its derivatives) has been used extensively as a catalyst for asymmetric synthesis[11].

The pyrrolizidine and quinolizidine alkaloids are two structurally interesting

classes of alkaloids. Their basic skeletons are bicyclic ([3.3.0] for **1.15** and [4.4.0] for **1.16** respectively) and have the nitrogen atom at the bridgehead position.

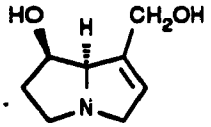


Pyrrolizidine
1.15

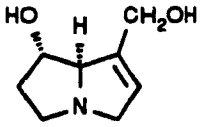


Quinolizidine
1.16

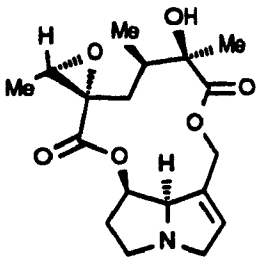
The necines are structurally related to the pyrrolizidines and have received much attention. A considerable amount of synthetic work has been devoted to compounds such as retronecine **1.17** and heliotridine **1.18**. Those two alkaloids are building blocks in the synthesis of biologically interesting jacobine[12] (**1.19**) and similar compounds.



Retronecine
1.17

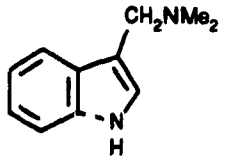


Heliotridine
1.18

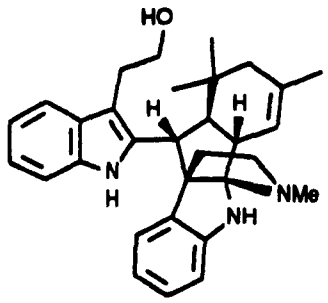


Jacobine
1.19

The last class to be discussed here are the indole alkaloids. This class comprises a very large number of structurally related compounds, ranging from the very simple gramine (1.20) to the newly isolated and more complex spermacoceine[13] (1.21).

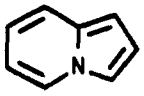


Gramine
1.20

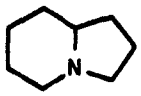


Spermacoceine
1.21

Among these structurally related compounds are the indolizine alkaloids where the nitrogen atom is now at the bridgehead position (1.22). These alkaloids, and



Indolizine
1.22



Indolizidine
1.23

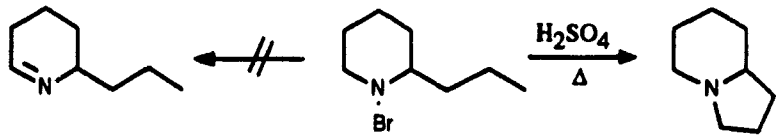
especially their reduced forms, the indolizidine alkaloids (1.23), are of great interest and will be the main topic of this thesis. They should therefore be thoroughly discussed.

1.2 The indolizidine ring system[14-16] :

It was suggested in a 1955 conference on "Tentative Rules for Organic

Nomenclature" that the name *Indolizidine* should be given to the 1-azabicyclo[4.3.0]nonane system. This name was first suggested by Tschitschibabin in a 1927 paper[17]. It had already been used by German and Japanese workers but it took a while before names such as *perhydropyrrocoline* or *piperolidine* disappeared from the literature.

Historically, indolizidines were prepared before the aromatic indolizine, and this by many years. The first compound ever synthesised having the indolizidine ring system was prepared in 1885 by Hofmann[18] (he was, however, ignorant of the nature of his product). By heating N-bromoconiine **1.24** with sulfuric acid (**Scheme 1.2**), he obtained a product (thought to be α-coniceine **1.25**) which was demonstrated to be δ-coniceine **1.26** by Lellmann a few years later[19].



1.25 **1.24** **1.26**

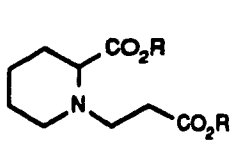
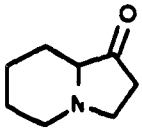
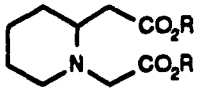
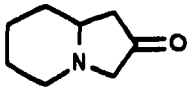
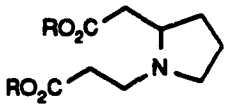
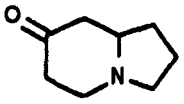
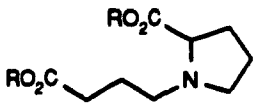
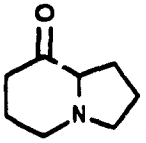
Scheme 1.2

Since then, numerous methods have been developed in order to produce the indolizidine system itself, as well as many of the di-, tetra- and hexahydroindolizidines.

The Dieckmann technique has been utilised to prepare most of the possible oxoindolizidines, starting with various piperidyl and pyrrolidinyl diesters. **Table 1.1** shows a few examples of such reactions. Decarboxylation occurs to give the amino-ketone derivatives. Reduction of the carbonyl was accomplished using the Wolff-Kischner method to give the fully saturated indolizidine, or using milder reducing agents ($LiAlH_4$, hydrogenation) to give the secondary alcohols. The ketones were also

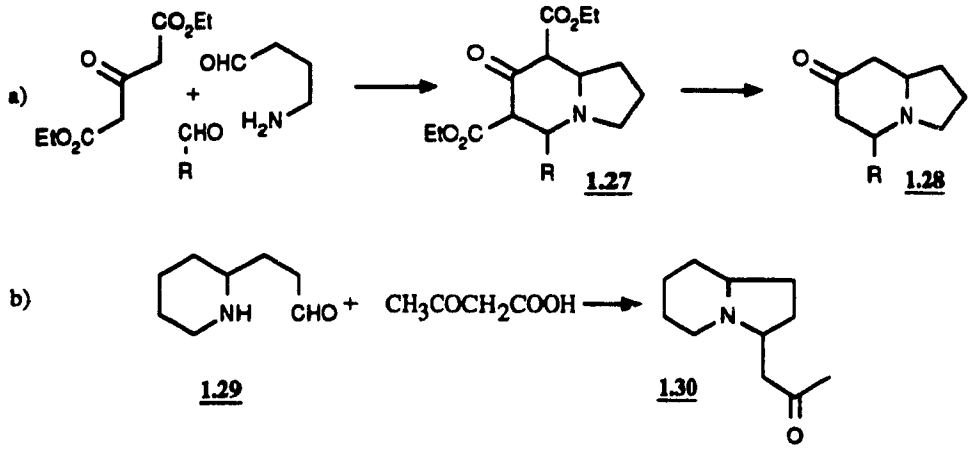
subjected to reaction with Grignard reagents, followed by dehydration and hydrogenation, to give the alkyl substituted indolizidines.

Table 1.1

Starting material	Indolizidine	Ref.
		20
		21-24
		25
		26

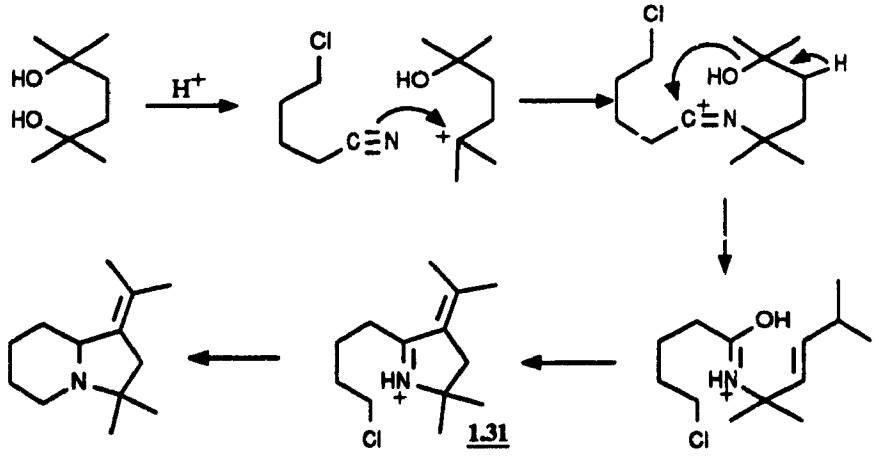
An ingenious synthesis of 5-substituted indolizidine-7-ones was devised by Lions and Willison[27] in 1940. The construction of the system was done entirely from acyclic precursors. It features the condensation of various aldehydes with γ-aminobutyraldehyde and acetonedicarboxylic esters. The intermediate dicarboethoxy compouds **1.27** were found to be rather unstable, but upon hydrolysis, readily afforded keto-indolizidine **1.28** in reasonable yields (see **Scheme 1.3a**). A somewhat similar synthesis was reported by Galinovsky and collaborators[28]. The reaction of pelletierine **1.29** with acetonedicarboxylic acid in a buffered solution yielded **1.30** (**Scheme 1.3b**).

Another synthesis entirely based on acyclic starting materials was published



Scheme 1.3

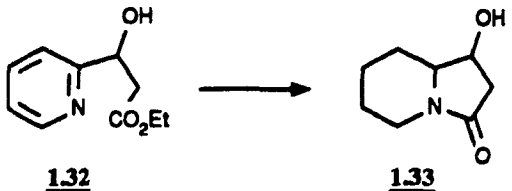
by Meyers and Libano[29] (**Scheme 1.4**). Here, an acid-catalysed condensation of a ditertiary glycol with an ω-chloronitrile was carried out to give an ω-chloroalkylpyrroline **1.31**, which was reduced with aqueous sodium borohydride and cyclised by steam distillation under basic conditions.



Scheme 1.4

Reductive cyclisations have also been used for compounds where the nitrogen

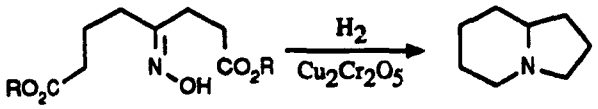
atom was at a higher oxidation state (such as pyridines or oximines). Carelli and coworkers[30], for instance, cyclised pyridine derivative **1.32** to the indolizidine system **1.33** using reductive conditions (**Scheme 1.5**).



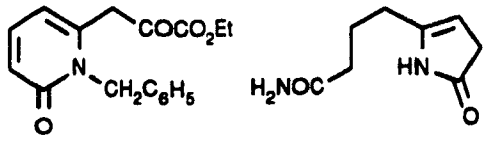
1.32 **1.33**

Scheme 1.5

In another example, Leonard and his collaborators[31] reductively cyclised oximinodiester **1.34** using a copper-chromite catalyst, affording a medium yield of δ-coniceine **1.26** (**Scheme 1.6**). Reductive cyclisation of lactams **1.35** and **1.36** also afforded **1.26**.



1.34 **1.26**

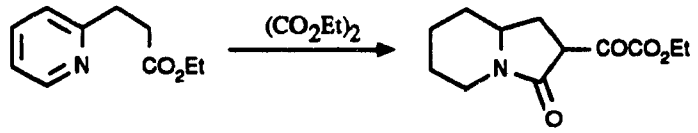


1.35 **1.36**

Scheme 1.6

Winterfeldt and Erning[32] also achieved a one pot conversion of pyridine **1.37**

into indolizidine 1.38 by a dissolving-metal reduction in the presence of diethyl oxalate (**Scheme 1.7**).



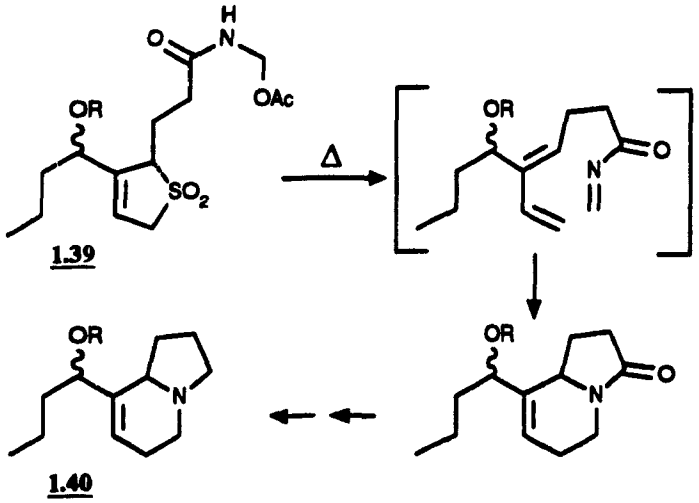
1.37 1.38

Scheme 1.7

When the characterisation of organic compounds from natural sources became easier (especially with the sophistication of NMR and X-ray experiments which led to more rapid and facile characterisation), a large number of new natural alkaloids were available for organic chemists to synthesise. Since the 'old methods' were often quite drastic (strong acids, strong bases, etc.), new mild reactions were needed for the construction of the indolizidine system. Also needed were reactions that would be stereoselective or stereospecific.

With the discovery and development of the Diels-Alder reaction, and especially with the introduction of hetero-Diels-Alder (an heteroatom is part of the diene or the dienophile), the chemistry of alkaloids saw a good number of syntheses utilizing this powerful method. Two examples are presented below. In the first example[33], the nitrogen atom is part of the dienophile (**Scheme 1.8a**). Thus, the 'masked iminedienophile' 1.39 was prepared and was converted to elaeokanine 1.40. One can see here the formation of a new carbon-carbon bond as well as a new carbon-nitrogen bond. The bicyclic system is thus constructed in one step. In the second example[34a,b], the nitrogen atom is part of the diene. Here again, it is a 'masked iminediene' and amide 1.41 is converted into the diene during the reaction (**Scheme 1.8b**). This particular

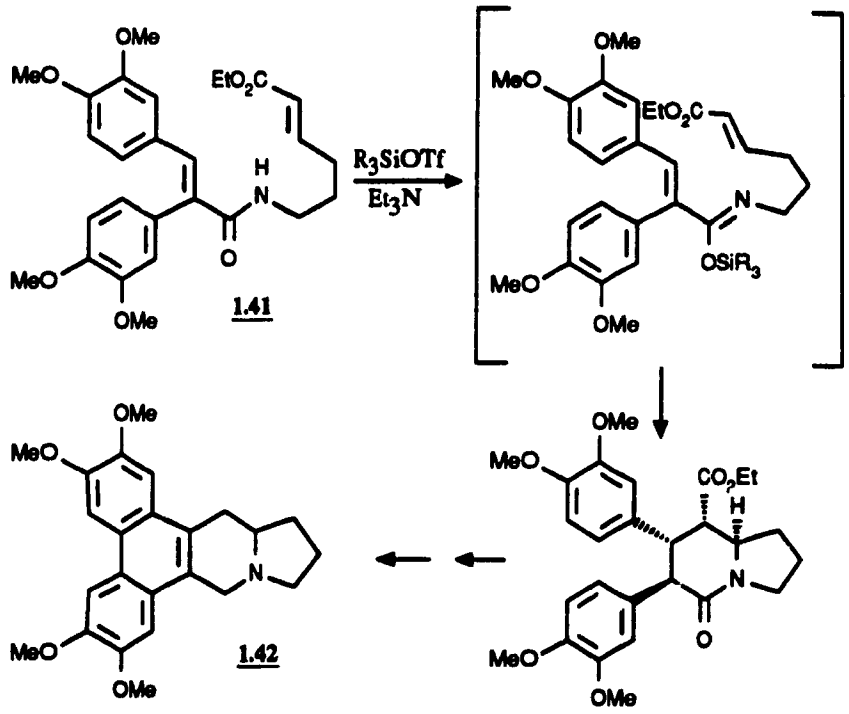
method was used in the synthesis of tylophorine[34c] (1.42).



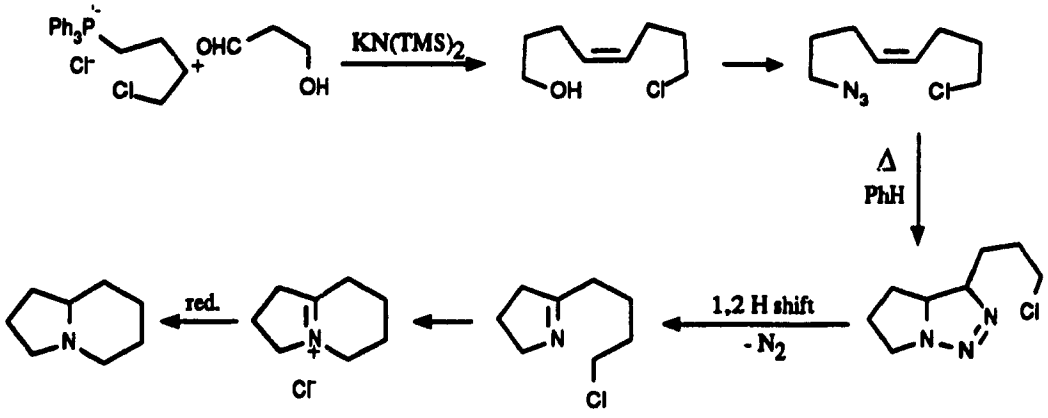
Scheme 1.8a

Another cycloaddition method for the preparation of both pyrrolizidines and indolizidines was recently reported by Pearson[35] and coworkers who developed an intramolecular 1,3-dipolar cycloaddition of aliphatic azides with certain types of electron rich 1,3-butadienes or with ω-chloroalkenes. **Scheme 1.9** describes an example where (±)-δ-coniceine is very easily synthesised in four steps.

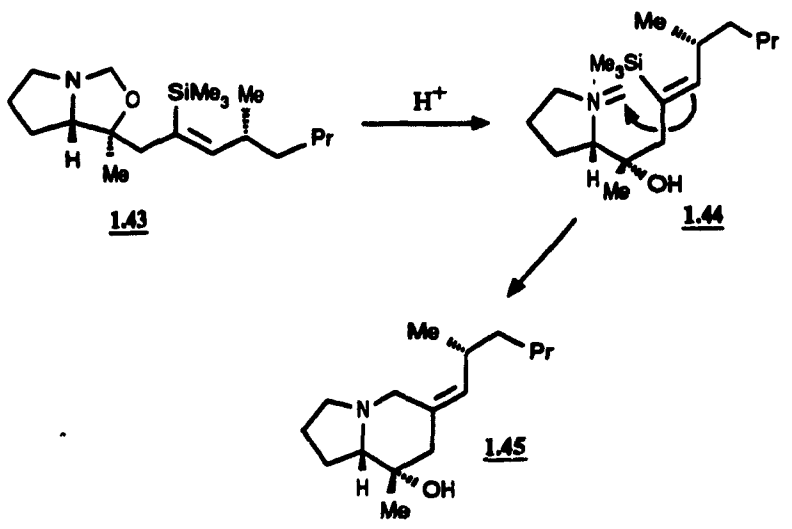
As seen in the first example of **Scheme 1.8**, an imine can act as a good dienophile. But it can also serve as a good electrophile. An even better electrophile would be one where the nitrogen atom would be positively charged, that is, an iminium ion. These have been used as electrophiles with success in the synthesis of some natural compounds. Overman[36], for instance, used an iminium ion-vinylsilane cyclisation in a highly convergent and concise synthesis of the pumiliotoxins (**Scheme 1.10**). Compound 1.43 was treated with camphorsulfonic acid in refluxing ethanol to give the intermediate unisolable iminium ion 1.44 which was trapped by the vinylsilane moiety to form pumiliotoxin 251 D (1.45).



Scheme 1.8b



Scheme 1.9



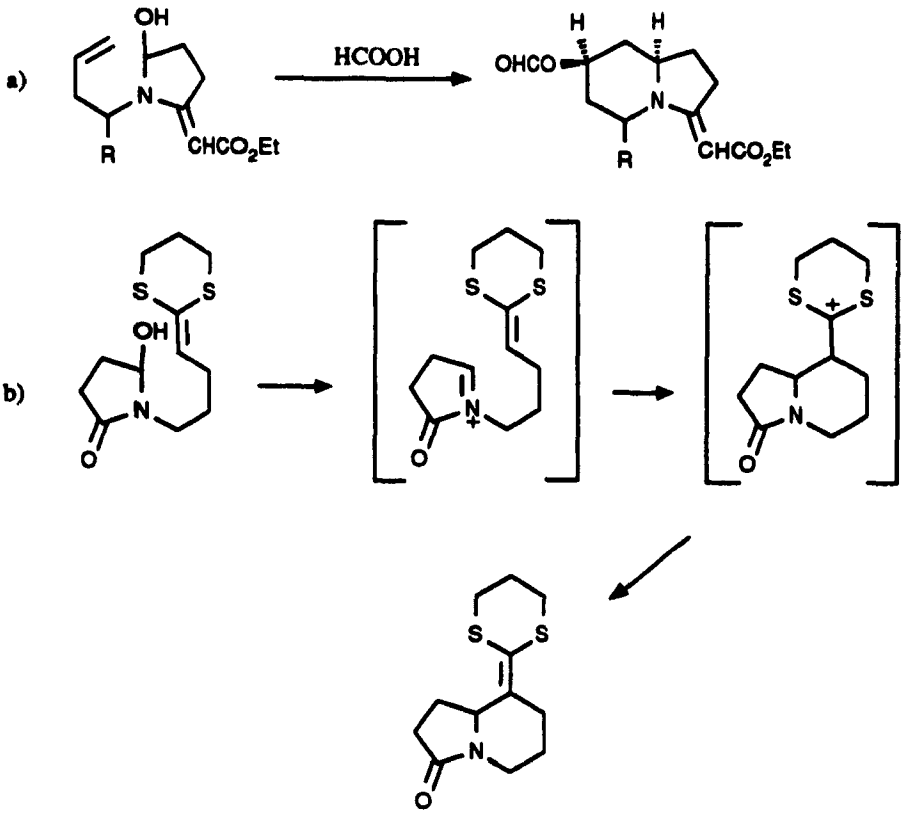
Scheme 1.10

Other examples of iminium ion induced cyclisations have appeared in the literature. One method which is commonly used is the N-acyliminium cyclisation (**Scheme 1.11**) where the nucleophile, instead of a vinylsilane, can be an ordinary vinyl group[37] (a) or a ketenedithioacetal[38] (b).

Although iminium ion-induced cyclisation has been used with much success in the synthesis of indolizidine alkaloids, other more common electrophiles (such as aldehydes and their dimethyl acetals) have also served to promote such cyclisations. An example was published recently by Dike and collaborators[39]. In their study toward the formation of pyrrolizidine and indolizidine ring systems, they found that such a reaction could be utilised. **Scheme 1.12** illustrates the cyclisation step.

Chapter 2 of this thesis will present our work in the area of indolizidine ring system formation through electrophilic cyclisations.

With the development and greater understanding of radicalar reactions, it is

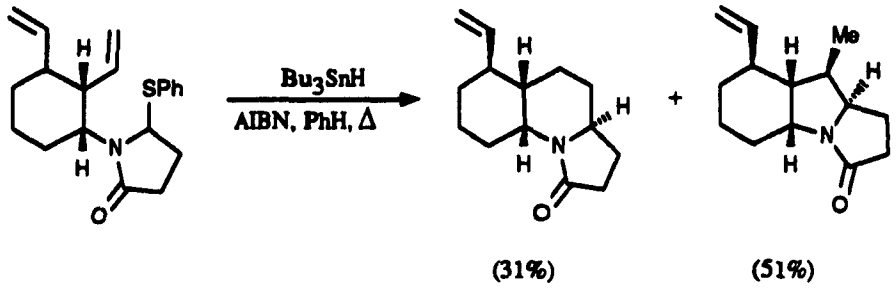


Scheme 1.11

Scheme 1.12

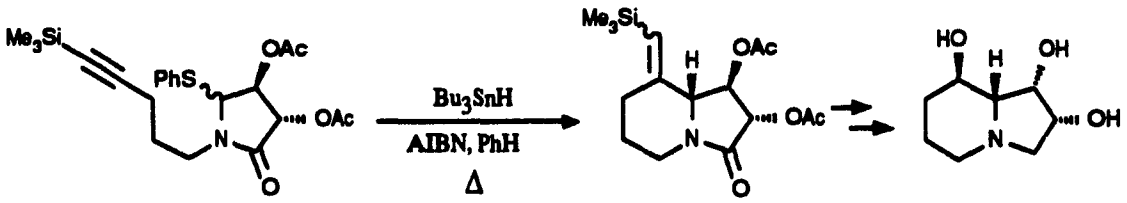
not surprising to see more and more examples of intramolecular radical based cyclisations. Hart and collaborators[40], in their synthesis of gephyrotoxin, used an

α-acylimino radicalar cyclisation in order to form the indolizidine system (**Scheme 1.13**).



Scheme 1.13

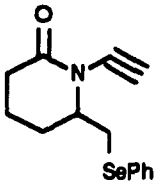
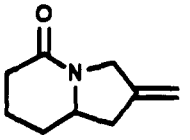
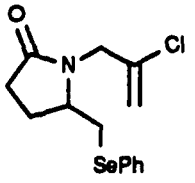
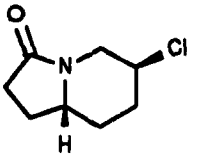
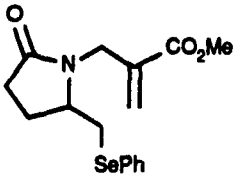
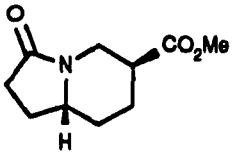
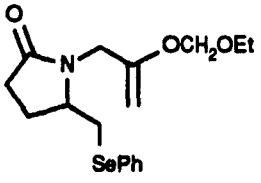
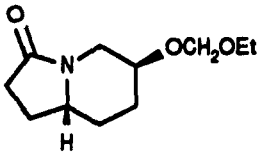
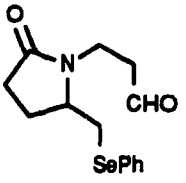
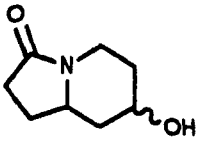
Hart used the same technology recently in the synthesis of the polyhydroxylated indolizidine alkaloid swainsonine[41] (for additional discussion, see **Part 1.3**). Using a slightly different radical acceptor, the six membered ring of the alkaloid was formed (**Scheme 1.14**).



Scheme 1.14

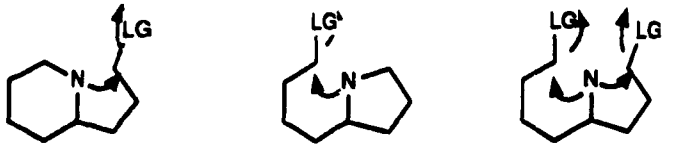
In another recent publication, Knapp and co-workers[42] introduced a radical based annulation of selenide-lactams for the synthesis of the indolizidine skeleton. **Table 1.2** shows the types of substrates that were used to form the indolizidines, substituted with useful functionalities.

Table 1.2

Stating materials	Products
	
	
	
	
	

Finally, probably the most widely used method for the formation of the indolizidine alkaloids is the nucleophilic cyclisation where the nitrogen atom itself attacks a carbon bearing a suitable leaving group. **Scheme 1.15** illustrates the two possible monocyclisations, forming either a five (**1.46**) of a six membered ring (**1.47**),

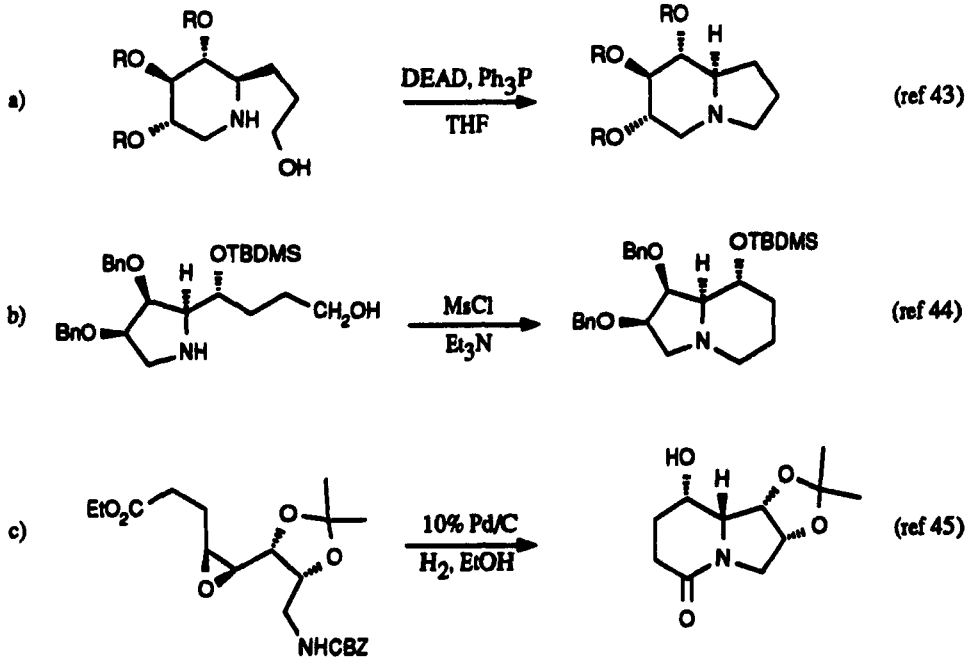
and the double cyclisation in which both rings are formed at the same time (**1.48**).



1.46 **1.47** **1.48**

Scheme 1.15

There is a large number of examples in the literature which report the use of nucleophilic cyclisation. The following scheme illustrates a few of these (**Scheme 1.16**).



Scheme 1.16

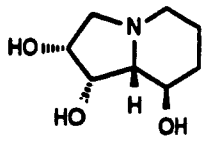
The first example (a) shows the formation of the five membered ring, the second one (b),

the six membered ring, and the last one (c) illustrates the double cyclisation.

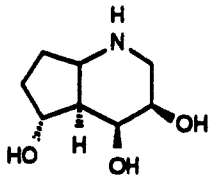
In **Chapter 4** of this thesis, the nucleophilic cyclisation method will be discussed further, and our results in this area will be presented.

1.3 The sugar mimics : swainsonine and castanospermine :

The polyhydroxylated alkaloid (1*S*,2*R*,8*R*,8a*R*)-trihydroxyindolizidine (**1.49**) was first isolated from the fungus *Rhizictonia leguminicola*[46] in 1973 by Broquist and coworkers who assigned to the new compound structure **1.50** on the basis of NMR, IR and mass spectroscopy degradation patterns. They revised their assignment in 1983[47] and corrected the structure, which was found to be identical with the alkaloid *swainsonine*, extracted from *Swainsona canescens* by Australian chemists in 1979[48]. It had also been found in the spotted locoweed *Astragalus lentiginosus* in the western regions of the United States.



1.49

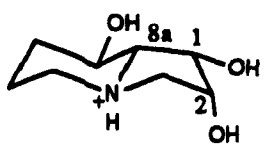


1.50

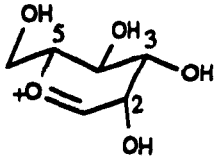
Swainsonine has been found to be the active ingredient that causes the toxicity of *Swainsona canescens*. Ingestion of this plant by livestock induces a disease which is biochemically, morphologically and clinically similar to mannosidosis[49]. The inhibition of α-mannosidase in *Swainsona* toxicosis and the genetic deficiency of α-mannosidase in mannosidosis both result in the accumulation of mannose-rich oligosaccharides in the lysosomal system of cells. Such lysosomal storage leads to organ dysfunction and

clinical disease.

Dorling and coworkers have speculated that the inhibitory action of swainsonine results from the stuctural similarity of its protonated form to the mannosyl cation, a proposed intermediate in the enzymatic mannosyl transfer reaction[50]. The absolute configuration of swainsonine and mannose supports this hypothesis. As shown in **Scheme 1.17**, C2, C1 and C8a of protonated swainsonine are equivalent to C2, C3 and C5, respectively, of the mannosyl cation.



Swainsonine cation



Mannosyl cation

Scheme 1.17

Mannosidosis is characterized by the loss of a glycosidase enzyme. But other diseases are associated with changes in the level of these enzymes. For example, glycosidases are present in a higher concentration in the serum of some cancer patients and in the interstitial fluid of the tumour itself. The β-N-acetylglucosaminidase and β-glucoronidase have also been found to be excreted into the extracellular medium by many tumours *in vitro*. These enzymes may accelerate the rate of tumour cell shedding from the primary site and/or modify the cell surface in ways which could assist local invasion or migration to secondary sites. Inhibitors of glucosidases might have value in limiting the tumour's advance and metastasis (the migration of tumour cells from their site of origin to form tumours in other tissues).

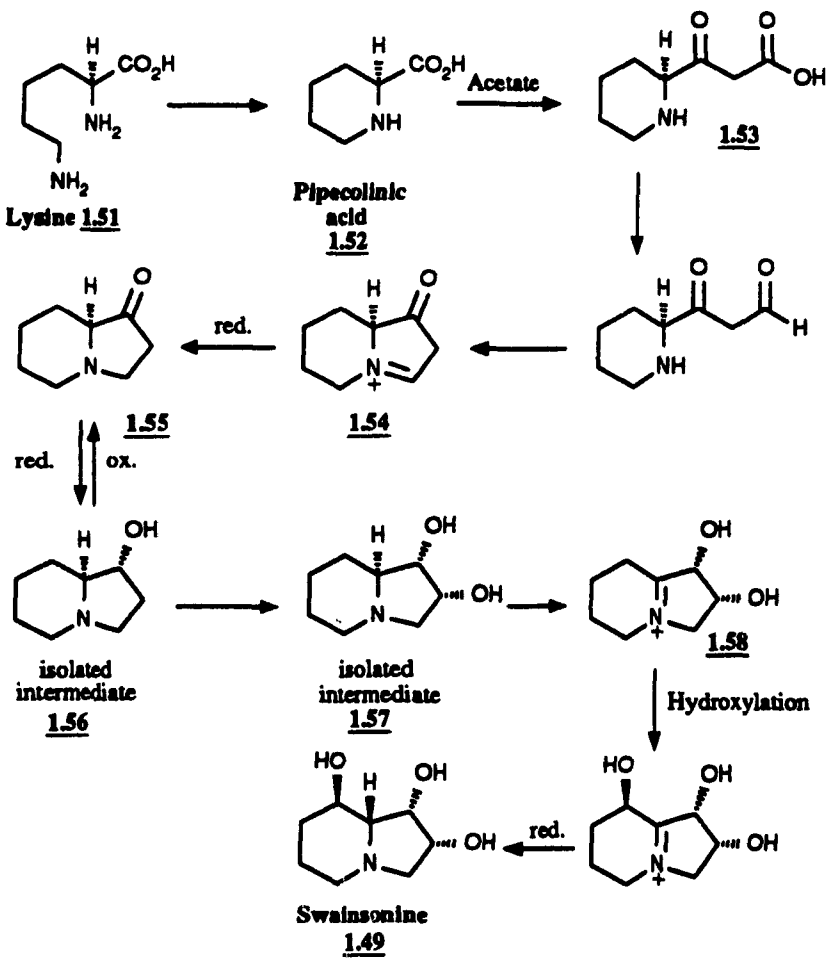
Many alkaloidal glycosidase inhibitors are now being used to investigate the

structure-function relationship of glycoproteins. Glycoproteins are proteins to which oligosaccharides are attached. They are known to play a role in many important but poorly understood biochemical processes, including cancer metastasis, viral infectivity and the immune response[51].

Swainsonine is known to reduce the invasion of lung tissue by tumour cells in mice. The tumour cells were not killed by the alkaloid, and the cells still had the ability to adhere to other tissues : what they could not do was to establish new tumour colonies at the site of invasion. It is possible that modifications by the alkaloid to the structure of the glycoproteins of the tumour cells are responsible for these effects. Swainsonine has also been shown to overcome the suppression of lymphocyte (white cells) proliferation, and thus of antibody production, normally observed when serum from tumor bearing mice is injected into normal animals. It can also improve the antibody response to foreign cells in mice treated with antitumour drugs. Because of these interesting properties, a substential amount of work has been devoted to swainsonine, as will be seen below.

Biosynthetically, swainsonine seems to be produced with very similar pathways in both the fungus (*Rhizoctonia leguminicola*)[52] and the plant (Locoweed)[53]. It has been found that this trihydroxy indolizidine is formed from lysine **1.51**, via pipecolinic acid **1.52**. **Scheme 1.18** illustrates the biosynthetic pathway that is believed to occur in living organisms.

Lysine first undergoes cyclisation into pipecolinic acid **1.52**. It is interesting to note that all six of the pipecolinate carbon atoms are incorporated in the final structure, even the carboxylic carbon, an unusual occurence in alkaloid biosynthesis. The normal course of events in the biosynthesis of such compouds involves the loss of the carboxyl group. The remaining two carbon atoms in the indolizidine nucleus, i.e., C2 and C3, are provided by a malonate unit, presumably via a Claisen-type condensation, to



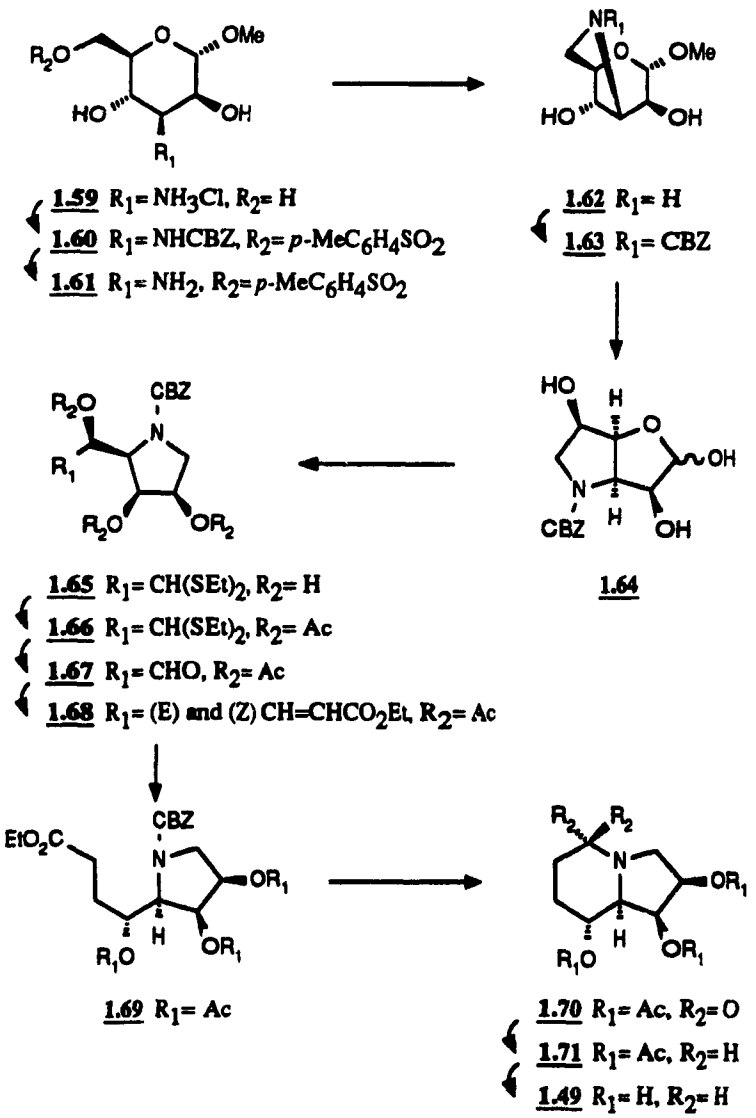
Scheme 1.18

form the pipecolyl acetate **1.53.** Reduction of the acid moiety to the aldehyde and cyclisation affords iminium ion **1.54**, which is reduced to ketoindolizidine **1.55** (there is no strong evidence for the last three steps : they are only suppositions). Reduction of the ketone gives 1-hydroxyindolizidine **1.56**, which is hydroxylated at the C2 position to diol **1.57**. This last intermediate and its precursor **1.56** are isolated in small quantities during the extraction of swainsonine from plants. When fed to cell preparations as starting materials (instead of pipecolinic acid), they produce swainsonine. Diol **1.57**, after being

transformed to iminium ion **1.58**, is selectively hydroxylated at the C8 position and reduced to give swainsonine **1.49**.

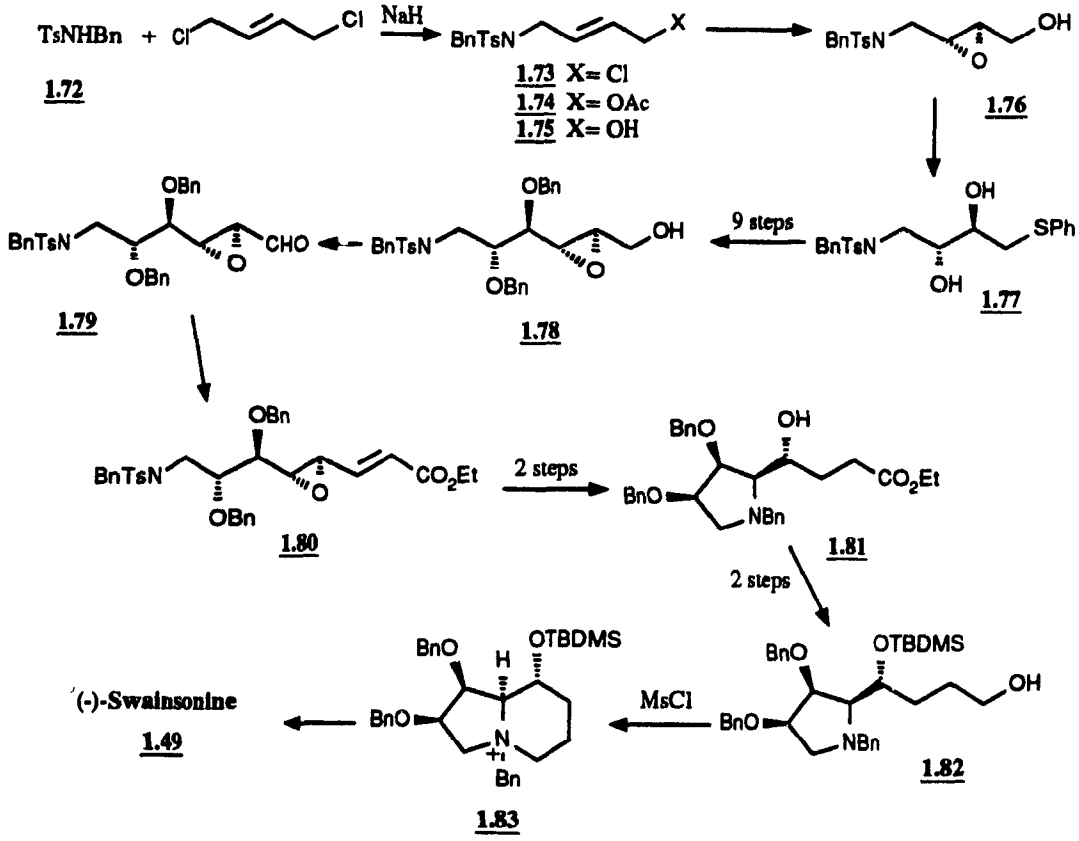
The first chemical synthesis of swainsonine was accomplished by Richardson and collaborators in 1984[54]. They have used 3-amino-3-deoxy-α-D-mannopyrroside **1.59**, readily available from glucose, as the starting material (most subsequent syntheses of swainsonine also use sugars as starting materials). **Scheme 1.19** illustrates the synthesis. Sequential N-benzyloxycarbonylation and selective tosylation of **1.59** gave the crystalline 6-*O*-toluene-*p*-sulfonate **1.60**. The N-CBZ group was removed and the free amine **1.61** was boiled in ethanol containing sodium acetate, affording bicyclic secondary amine **1.62**, which was isolated as its N-CBZ derivative **1.63**. Acid hydrolysis of **1.63** yielded the free crystalline 3,6-dideoxy-3,6-iminohexofuranose **1.64**, which was condensed with ethanethiol in the presence of hydrochloric acid to give the diethyl dithioacetal **1.65**. Protection of **1.65** as a triacetate (**1.66**) and dethioacetalation with mercury (II) chloride-cadmium carbonate proceeded smoothly to give the desired fully protected aldehydo-hexose **1.67**, which was reacted with ethoxycarbonyl methylenetriphenylphosphorane, affording α,β-unsaturated esters **1.68a** and **b**. Saturation of the double bond with palladium on charcoal simultaneously removed the CBZ protecting group to give, initially, free amine **1.69**, which then reacted further to give a 1:1 mixture of the desired bicyclic lactam **1.70** and a product of *O*→*N* acetyl migration. Reduction of the lactam with borane-dimethylsulfide complex afforded tertiary bicyclic amine **1.71** along with some minor unidentified products. Conventional *O*-deacetylation of triacetate **1.71** afforded a quantitative yield of swainsonine. The synthesis was thus completed with an overall yield of 2.7%.

As mentionned previously, most subsequent syntheses of swainsonine also use carbohydrates as starting materials. D-glucose and D-mannose are the two main sugars used in most of these syntheses. The first non-carbohydrate route to swainsonine was



Scheme 1.19

accomplished by Sharpless and coworkers[44] in 6% overall yield from N-benzyltoluene-*p*-sulfonamide 1.72 (**Scheme 1.20**). The introduction of the chirality in the molecule was achieved through the asymmetric epoxidation reaction. Thus, the anion of 1.72 was quenched with (*E*)-1,4-dichloro-2-butene to give allylic chloride 1.73. Displacement of the chloride with sodium acetate followed by hydrolysis afforded



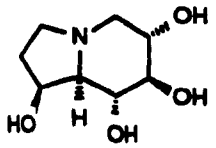
Scheme 1.20

alcohol **1.75**, which was subjected to the asymmetric epoxidation conditions ((-)-DIPT). Epoxy alcohol **1.76** was thus obtained in 95% ee. Epoxide migration to the primary position was followed by its nucleophilic opening by the thiophenoxide anion to produce dihydroxy sulfide **1.77**. Elongation of the chain to form a new allylic alcohol was performed through a series of functional group manipulations. Nine steps were required to form epoxy alcohol **1.78**, which was then oxidised to the aldehyde **1.79**. Reaction with (carbethoxymethylene)triphenylphosphorane provided the final two carbons required for the swainsonine backbone. The double bond of α,β-unsaturated ester **1.80** was reduced with diimide and the N-tosyl protecting group was removed to give cyclic

amine **1.81**. Protection of the secondary alcohol produced by the opening of the epoxide in the cyclisation step was followed by reduction of the terminal ester group to alcohol **1.82**. This alcohol was mesylated to lead directly to the bicyclic quaternary ammonium salt **1.83**. Removal of the various protecting groups afforded (-)-swainsonine **1.49**.

Since the appearance of these two publications[44,54] there has been a large number of syntheses of swainsonine as well as many of its analogues. More and more, enantioselective non-carbohydrate routes are being published which allow for the formation of lerger quantities of isomers. Studying the interaction of these isomers with biological systems might provide new tools for the understanding of biochemical processes.

Another polyhydroxylated alkaloid has attracted substantial attention in the last ten years. (+)-Castanospermine, or (1*S*,6*S*,7*R*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (**1.84**), isolated from the large Australian chesnut-like seeds of the fruit tree *Castanospermum australe*[55] and from the dried pod of *Alexa leiopatala*[56], has also been found to be a glycosidase inhibitor. Its structure and relative stereochemistry were determined by X-ray crystallography in 1981[55], and its absolute stereochemistry was unambiguously established in 1984 by Ganem and coworkers[57], who also accomplished the first total synthesis.



Castanospermine
1.84

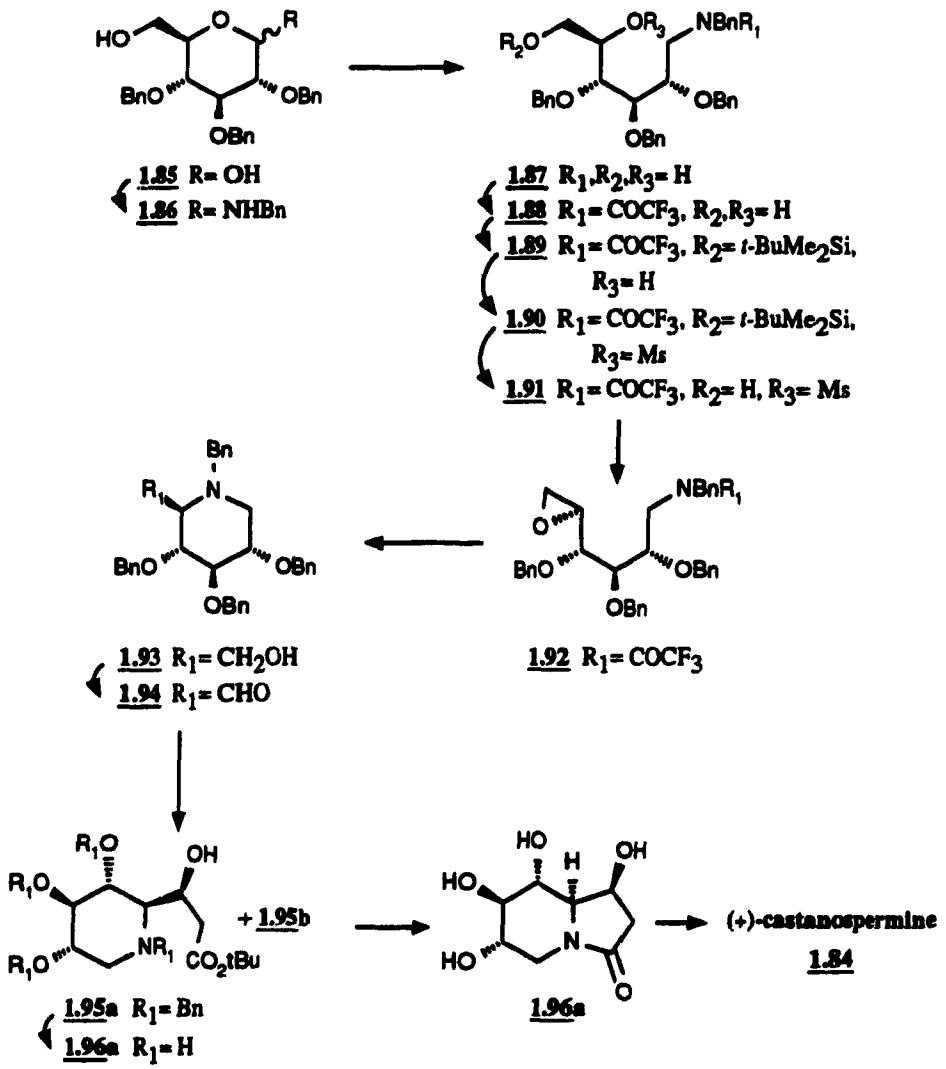
Because castanospermine is an inhibitor of various glucosidases, it has been

found to inhibit the replication of the AIDS virus in cultured cells. It has been shown that castanospermine causes changes to the structure of a glycoprotein on the surface of the AIDS virus, thus preventing it from escaping from cells and/or colonizing new cells[51].

Castanospermine shares many interesting properties with swainsonine, which will therefore not be discussed again. It has been the center of attention, though, since the recent finding of its inhibition properties of the AIDS virus. This has led to a flurry of subsequent activity on its potential uses. A recent review article[58] summerizes its ability to function as a plant growth regulator; as an insect antifeedant; as an inhibitor of allergic encephalomyelitis; as a disaccharidase inhibitor, with implications for the treatment of diabetes mellitus; as an antiretroviral agent and as a possible therapeutic agent against human cytomegalovirus, a virus not harmful to healthy adults but which frequently attacks patients suffering from AIDS. Moreover, and of particular interest, is the finding that 3'-azido-3'-deoxythymidine (AZT) and castanospermine can operate synergistically in the inhibition of HIV (human immunodeficiency virus) replication *in vitro*.

Interestingly, there are, by far, fewer syntheses of castanospermine (and analogues) when compared to swainsonine, even though its absolute stereochemistry was established only two years after that of swainsonine. Here again, most early syntheses were based on carbohydrate starting materials.

The very first synthesis by Ganem and coworkers[57] involved the use of D-glucose as a starting material. **Scheme 1.21** illustrates the synthesis. Condensation of 2,3,4-tri-*O*-benzyl-glucopyranose **1.85** with benzylamine afforded glucosamine **1.86** (anomeric mixture) which was reduced to amino alcohol **1.87**. Protection of the amine (trifluoroacetate) provided **1.88**, and the primary alcohol was protected with a *t*-butyldimethylsilyl group (**1.89**). Mesylation of the C5 hydroxy group was followed by

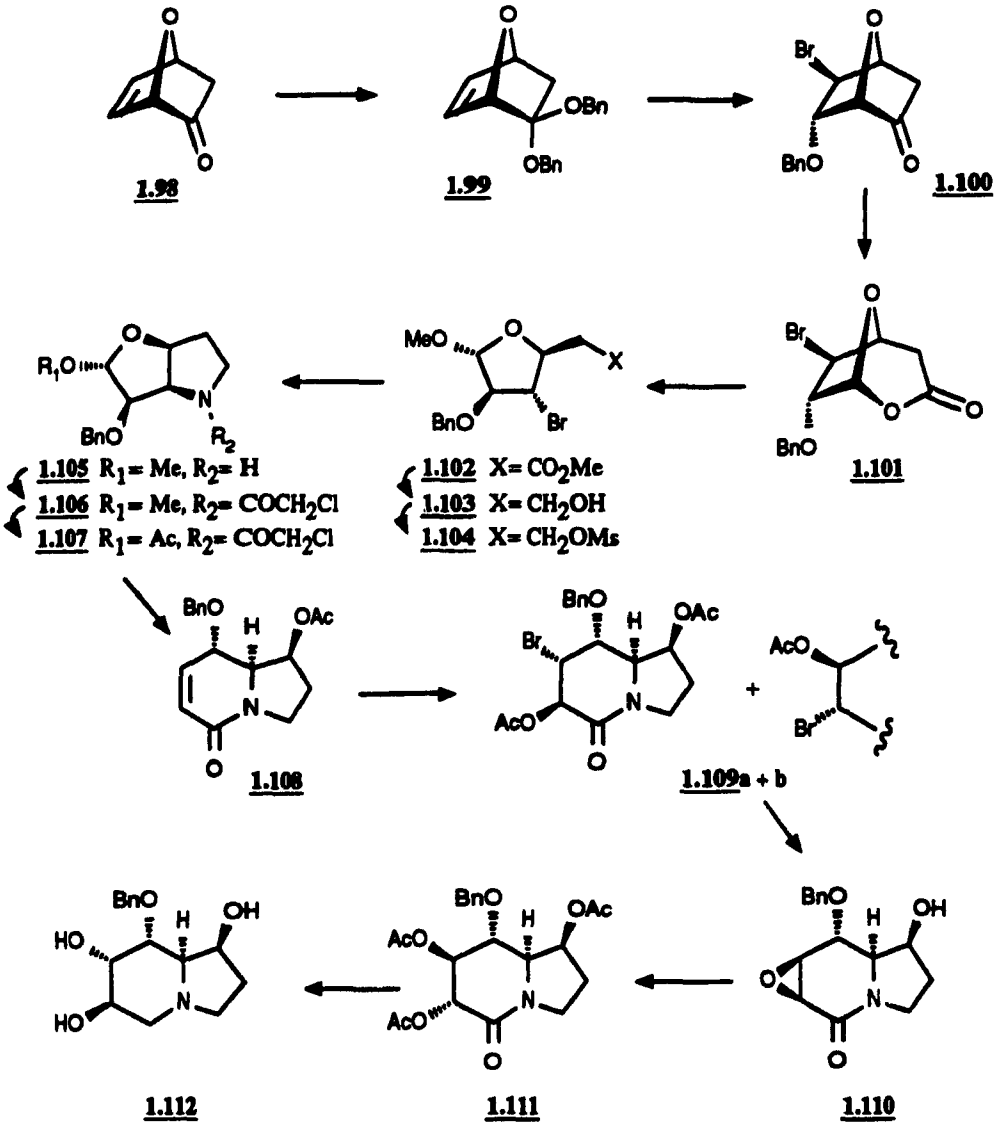


Scheme 1.21

cleavage of the silyl protecting group and cyclisation to epoxide 1.92. Removal of the N-trifluoroacetate ($NaBH_4$) produced an amino epoxide which underwent cyclisation spontaneously to a mixture of piperidine 1.93 and an azepane (seven membered ring) side product. Oxidation of 1.93 led to sensitive aldehyde 1.94, which was condensed immediately with lithio-t-butyl acetate to produce a 1:1 mixture of two separable

diastereomers **1.95a** and **b**. The less polar diastereomer was transformed by hydrogenolysis into tetrahydroxy amine **1.96a**, which underwent cyclisation to bicyclic lactam **1.97a**. Reduction with diisobutylaluminium hydride afforded (+)-castanospermine **1.84**. The more polar diastereomer **1.95b** was transformed into 1-epicastanospermine.

The first racemic non-carbohydrate synthesis of castanospermine was reported in 1989 by Vogel and Reymond[59]. It is a highly stereoselective synthesis with possibilities of forming stereoisomers and analogues. 7-Oxanorbonenone (±)-**1.98**, or a "naked sugar", is used as the starting material. In a subsequent publication[60], the authors describe how to prepare optically pure (-)- and (+)-**1.98**, thus lengthening the synthesis but making it enantioselective. **Scheme 1.22** shows how the dibenzyl acetal **1.99** of enone **1.98** will be transformed into castanospermine. Bromination of the acetal gave the protected bromohydrin **1.100** stereoselctively. Oxidation of **1.100** with *m*-CPBA furnished lactone **1.101**, which was treated with thionyl chloride in methanol to produce the methylfuranoside **1.102** along with a small amount of its anomer. Reduction of **1.102** with diisobutylaluminium hydride afforded alcohol **1.103** which was mesylated (MsCl, Et_3N). Heating mesylate **1.104** with ammonia in an ethanol/water mixture gave bicyclic amine **1.105** which was protected as chloroacetate **1.106** (this chloroacetate will serve later on as the two carbon unit introduced during the Wittig-Horner reaction : see **1.107**→**1.108**). Treatment of **1.106** with acetic anhydride and concentrated sulfuruc acid provided acetate **1.107** (+ anomer) which was converted to lactam **1.108** by means of a Wittig-Horner condensation, followed by treatment with potassium carbonate in ethanol and acetylation. Bromination of **1.108** gave a 1.5:1 mixture of **1.109a** and **b**, which were converted to epoxide **1.110** (hydrolysis of acetates and then ring closure). The epoxide was hydrolysed with water and the triol was triacetylated (**1.111**). Reduction of **1.111** with borane-dimethyl sulfide complex led to aminotriol **1.112** which was debenzylated



Scheme 1.22

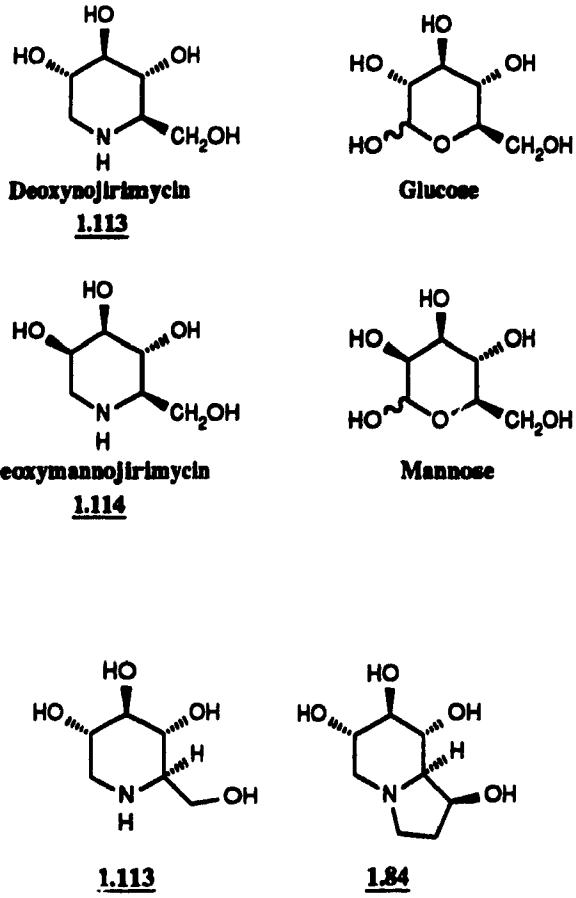
(H_2, Pd/C) to give (±)-castanospermine.

The potential usefulness of castanospermine in the clinic is limited, primarily due to its low potency *in vitro* and *in vivo*. Indeed, the concentration of the alkaloid necessary to achieve the interesting effects observed is quite high, in the millimolar

range, and eventhough the human lymphocytes are surprisingly not affected by these high concentrations[51], smaller amounts of compound would prevent undesirable side effects. It has been shown recently, on the other hand, that the activity of castanospermine can be improved significantly by increasing the lipophilicity of the compound[61,62]. Several mono- and poly esters of castanospermine have been prepared and have been shown to be more efficacious than the parent compound. Any chemist preparing a synthetic plan for the synthesis of castanospermine should consider the possibility of regioselectively introducing aliphatic esters at various positions, since regioselective synthesis of castanospermine's monoesters from the natural compound itself represents a laborious task, requiring several protection and deprotection steps. Some enzyme catalysed regioselective acylations of castanospermine have been published[61,62].

Swainsonine and castanospermine were discussed first here because their basic skeleton is related to the indolizidine ring system. Other more simple 'sugar mimics' which have interesting inhibition properties are known and being studied. Among the first of these compounds to be isolated were deoxynojirimycin (DNJ) **1.113** and deoxymannojirimycin (DMJ) **1.114**. Both of these compounds bear a striking resemblance to glucose and mannose respectively. It is not surprising, thus, to find that these compounds are powerful inhibitors of glucosidases[63] and mannosidases[64].

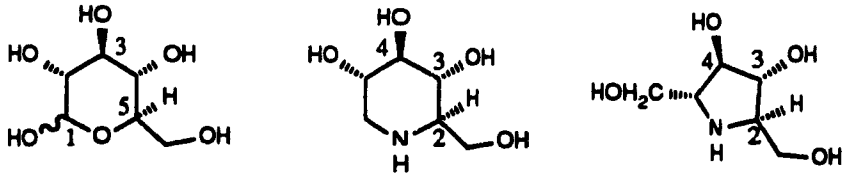
Interestingly, the structure of DNJ **1.113** also bears resemblance to castanospermine **1.84** (see **Scheme 1.23**), the latter being regarded as a conformationally restrained analogue of DNJ. Their six membered rings are indeed substituted exactly the same way, and the hydroxymethyl group at C5 of DNJ is the equivalent of the OH group at C1 of castanospermine. Both compounds have been shown to be glusocidases inhibitors. Here again, the protonated form of these compounds are very similar to the glucosyl cation.



Scheme 1.23

The five membered ring (pyrrolidine) analogues of these sugars have also shown interesting properties, even though they have been studied less than the parent piperidines. 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine (DMDP) **1.115**, isolated in 1976[65], has been shown to inhibit a glycoprotein processing glucosidase I, a yeast α-glucosidase and invertase, an almond α-glucosidase and a fungal β-xylosidase[66]. Because it is a glucosidase inhibitor, **1.115** may be considered to be structurally related to glucose, or to DNJ **1.113**. **Scheme 1.24** shows that C2, C3 and C4 of **1.115** indeed have a structural resemblance with the C2, C3 and C4 sequence of **1.113**. The fact that

DNJ **1.113** is a good inhibitor of glucosidase even with no hydroxyl substituent at C6 (C1 of the sugar) might mean that this portion of the molecule is not important in the recognition and binding process with the enzyme. That would also explain why **1.115** is still a good inhibitor even with its structural difference at C5.

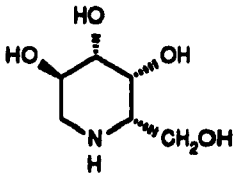


Glucose **DNJ 1.113** **DMDP 1.115**

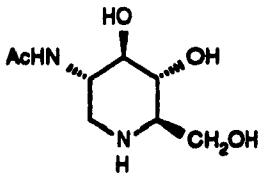
Scheme 1.24

Synthetic analogues of these natural compounds, both of the piperidine and pyrrolidine class, have started to appear in the literature. Fleet and collaborators have synthesised many of these[67] and **Scheme 1.25** illustrates a few of them. It is interesting to see that compound **1.118** is structurally very similar to swainsonine **1.49** (**Scheme 1.26**) and is indeed a very potent inhibitor of mannosidases both *in vitro* and *in vivo*. Ganem and coworkers[68], in an effort to simplify both the structure and the synthesis of **1.118** synthesised pyrrolidine compound **1.122**, which proved to be as good an inhibitor of the jack bean α-mannosidase as **1.118**.

It is very unfortunate that there seems to be no reliable way, at present, to predict how a particular sugar analogue will affect a particular glycosidase. This can only be determined by trial and error, which is why so many groups are devoting great effort into the synthesis of so many analogues. But by doing so, one will eventually (hopefully) understand the interactions that take place in the active site of the studied enzymes and will be able to extract from this information structural patterns that have to



1.116



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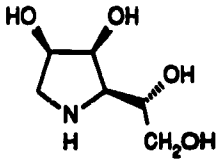
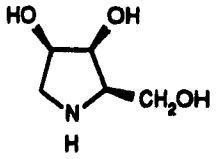


1.118



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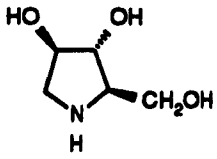

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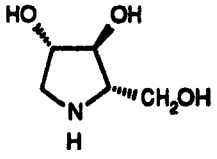
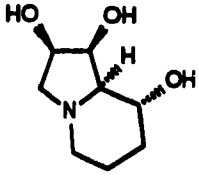


1.121

Scheme 1.25

1.118



1.49

Swainsonine

1.122

Scheme 1.26

be followed in the design of more potent inhibitors and drugs. **Chapter 4** of this thesis describes our work in the area of castanospermine analogues synthesis. But before the synthesis itself is attempted, various paths leading to the indolizidine ring system will be explored (**Chapter 2** and **4**). Also, the problem of stereoselective hydroxyl groups introduction into the pyrrolidine ring system will be studied (**Chapter 3**). It is the hope of the author that this small contribution in the field of polyhydroxylated alkaloids synthesis will help for a better understanding of biological processes, including those

characteristic of cancer and the AIDS virus, which have been the curse of many people around the world.

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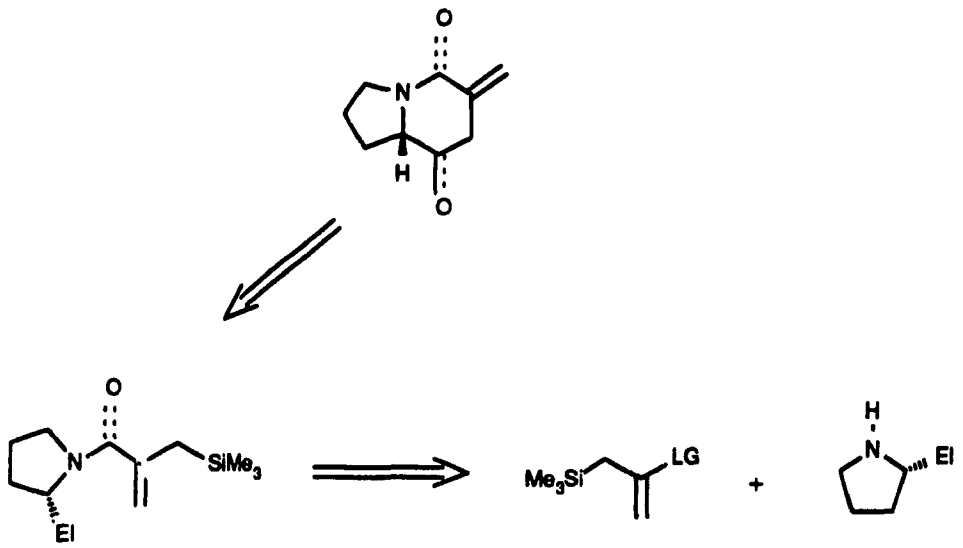
CHAPTER 2

THE INDOLIZIDINE SYSTEM I : ELECTROPHILIC CYCLISATION.

2.0 Introduction :

The first approach envisaged for the formation of the indolizidine ring system is delineated in **Scheme 2.1.** It features the Lewis acid-catalysed intramolecular electrophilic cyclisation of an allylsilane substituted at the β position with either an electron withdrawing N,N-disubstituted amide group or a N,N-disubstituted amino-methyl group. This amide (or amine) group bears the electrophilic center with



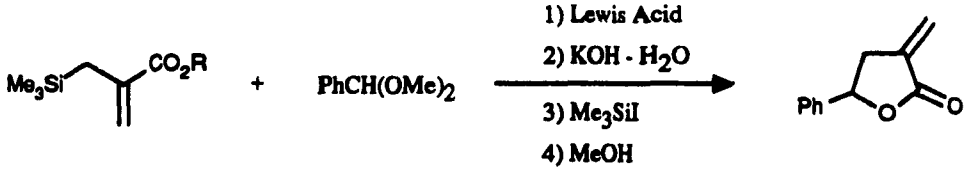
Scheme 2.1

which the allylsilane will react.

To our knowledge, the use of electrophilic allylsilane cyclisations has not been used much for the construction of nitrogen heterocycles. On the other hand, this reaction has been used extensively in the synthesis of carbocyclic systems[1]. More recently, oxygen heterocycles such as tetrahydropyrans have been constructed by allylsilane cyclisation[2]. Overman, in his ingenious synthesis of the pumiliotoxins, used vinylsilane cyclisations[3].

2.1 Cyclisation of an α,β-Unsaturated Amidoacid Imidazolide :

The electrophilic substitution of allylsilanes bearing an electron withdrawing group at the β position is known in the literature[4a,b]. In the example reported here[4a] (**Scheme 2.2**), Sakurai and co-workers have used this reaction in order to construct

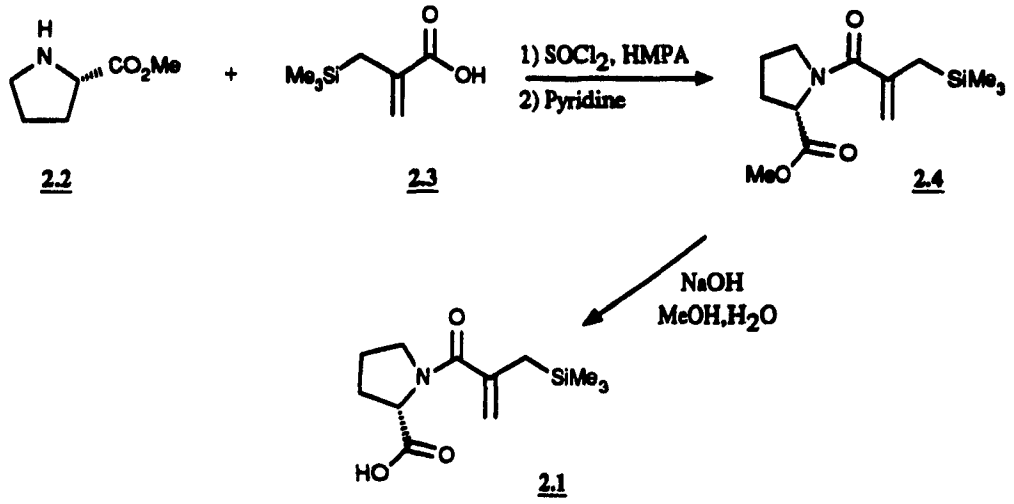


Scheme 2.2

simple α-methylene-γ-butyrolactones which are key structures of a number of naturally occurring sesquiterpenes with potential cytotoxic activity[5]. It seems that even if the nucleophilic properties of the double bond are reduced because of the presence of the electron withdrawing group (here, an ester), the allylsilane moiety is still able to react with an activated acetal. It is reasonable to think that the replacement of this electron

withdrawing ester with an amide group should not change dramatically the course of the reaction.

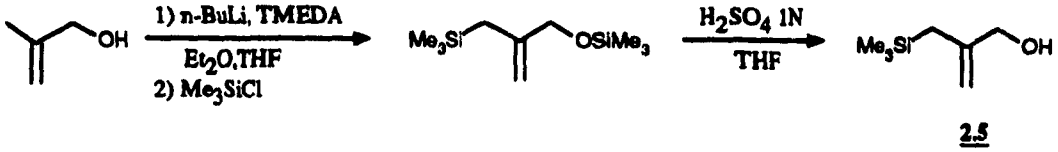
Amidoacid 2.1, the key molecule for the first attempted cyclisations, was thus prepared. Its synthesis was considered to be very simple : condensation of a suitably protected proline derivative 2.2 with an activated α,β-unsaturated acid 2.3 should yield the amido ester 2.4 which can then be deprotected and activated for the cyclisation step (Scheme 2.3). Protection of the acid group of proline was easily performed



2.2 2.3 2.4 2.1

Scheme 2.3

($SOCl_2$/MeOH) and gave a high yield of the ester 2.2, either as the hydrochloride or as the free amine. Both compounds could be stored for a very long period of time at 0°C. On the other hand, the acid 2.3 was not as easy to synthesise as expected. The plan was to first prepare alcohol 2.5 according to the method of Trost and Renaut[6] (Scheme 2.4), and then to oxidize it to the corresponding acid in a one step or two step oxidation. The oxidation proved to be difficult as illustrated in Table 2.1. Among conditions attempted were neutral, basic and acidic conditions and, in each case, no trace of the acid was



2.5

Scheme 2.4

detected. While these conditions were under study, the two step oxidation was also

Table 2.1 : One step oxidation

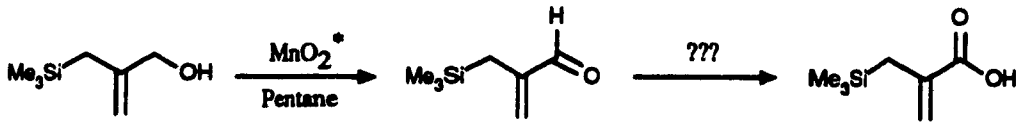
Conditions :	Results :
1- CrO_3-H_2SO_4, Acetone/H_2O	Decomposed
2- $KMnO_4$, 18-Crown-6, Benzene	Starting material
3- $KMnO_4$, $PhEt_3NCl$, H_2O-Benzene	Starting material
4- $KMnO_4$, NaOH, H_2O	Starting material
5- $KMnO_4$, Acetone/H_2O	Starting material

investigated. It was found that alcohol 2.5 could be rapidly oxidized with actived manganese dioxide (MnO_2/pentane or hexane)[7] to the volatile aldehyde 2.6. At this point, the yield of the aldehyde was not satisfactory (only 65% for a reaction which was very clean by t.l.c.). This was attributed to the fact that 2.6 was almost as volatile as the

pentane (or hexane) solvent used. This problem was solved later during the study of the second oxidation step.

There are many methods for the oxidation of aldehydes to acids and **Table 2.2** gives a list of those studied. Included are methods developed by Corey et al.[8] with some

Table 2.2 : Two steps oxidation, second step



2.5 2.6 2.3

Conditons :	Results :
1- AgO, NaCN, MeOH	Decomposed
2- MnO_2, NaCN, NH_3, $(CH_3)_2CHOH$	7.5% of Amide
3- MnO_2, NaCN, $PhNH_2$, $(CH_3)_2CHOH$	Starting material
4- MnO_2, NaCN, MeOH	Starting material
5- (Bipy)H_2CrOCl_5, CH_2Cl_2	Decomposed
6- H_2O_2, SeO_2, $CH_3CH_2C(CH_3)_2OH$	Up to 50% of 2.3
7- $NaClO_2$, NaH_2PO_4, t-BuOH/H_2O	85% (Choice of solvent)

of their modifications[9,10], as well as a chromium complex[11]. All of them failed to give the desired acid. The first reaction that indicated that the oxidation was feasable was the hydrogen peroxide oxidation catalysed by selenium dioxide in *tert*-amyl alcohol[12]. Indeed, this method gave a 50% yield of the acid which seemed to be constantly contaminated with unknown products (peroxides perhaps) of the solvent. Even though

the acid was now available to continue the project, the three step sequence for its synthesis was not a high yielding one. There were two problems that had to be solved : first, find a way in which the aldehyde would not be lost during the evaporation of the large quantity of solvent required for the MnO_2 oxidation; second, find an alternative for the second step oxidation. A careful inspection of the literature was found to be very fruitful. Indeed, it seemed that there were not very many methods for the oxidation of α,β-unsaturated aldehydes *with no substituent at the* β *position*. These molecules polymerize very easily under a variety of conditions (especially basic and acidic) and a carefully buffered reaction seemed to be the "trick" for success. A method was finally found: oxidation with sodium chlorite ($NaClO_2$) in a *tert*-butanol/water mixture with sodium dihydrogen phosphate as buffer and 2-methyl-2-butene as a chlorine scavenger was used to oxidize a very similar molecule[13]. With aldehyde 2.6, the yield was excellent (85%) and the acid so obtained was very pure. After many attemps, it was found that the solvent of the reaction could be exchanged with a variety of common organic solvents such as acetone, tetrahydrofuran or methylene chloride. It was also found that the pentane or hexane in which the first step was performed, but which couldn't be used for the second step due to a lack of polarity, could also be exchanged with different solvents. **Table 2.3** shows these various solvents. As one can see, methylene chloride seemed to be the solvent of choice for this reaction. The reaction time was reasonably short and the yield was excellent.

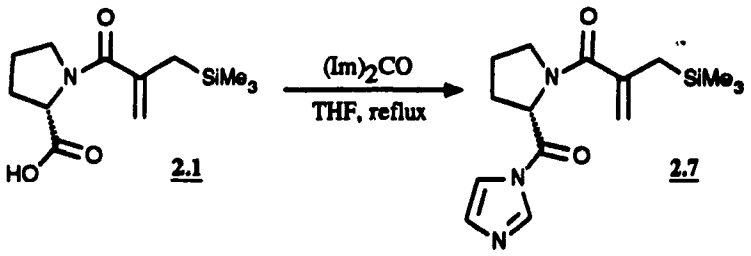
With a good method for the synthesis of acid 2.3 in hand, it was now possible to try the coupling reaction. However, the acid had to be activated first. Attempts to make the acyl chloride (see **Scheme 2.3**) with conventional methods ($SOCl_2$/benzene-reflux or $(COCl)_2$/benzene-reflux) failed to give the chloride. Milder conditions and lower temperatures were required. Since 2.3 polymerizes easily, a base was used to neutralise the hydrochloric acid formed during the reaction. Thus, thionyl

Table 2.3

Solvent Choice

Solvent	Step #1	Step #2	Comments
$(CH_3)_3OH$	4 hrs	4 hrs	Low yield
Acetone	2 hrs	0.5 hr	Low yield
THF	1 hr	2 hrs	Medium yield (50-60%)
CH_2Cl_2	0.5 hr	6 hrs	Good yield (80-85%)
Pentane	15 min	--	Aldehyde only

chloride was added to a solution of 2.3 in HMPA at 0°C[14]. After the appropriate amount of time, this mixture was transferred to a pyridine solution of the methyl prolinate hydrochloride. Using this method, a good yield of amidoester 2.4 was obtained. Hydrolysis of the methyl ester was easily achieved under basic aqueous conditions (**Scheme 2.3**) and acid 2.1 was activated as the imidazolide 2.7 (**Scheme 2.5**). This

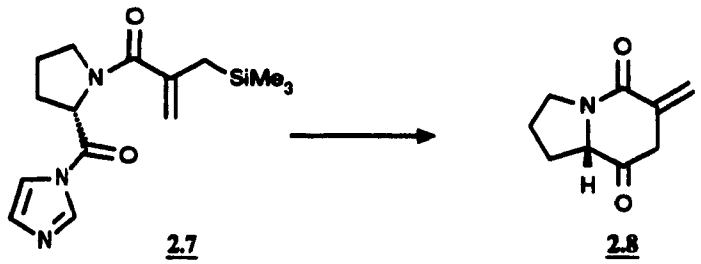


Scheme 2.5

particular activating group was chosen because of its ease of formation and its greater stability[15]. Here, again, the acyl chloride was very difficult to produce and was very unstable.

Next, the cyclisation reaction was studied. The imidazolide 2.7 was exposed to a variety of conditions, as seen in **Table 2.4**. All of them failed to give the expected

Table 2.4



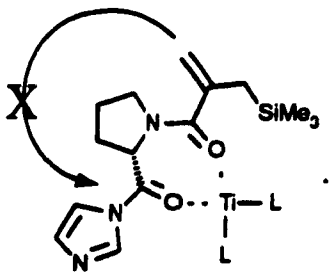
2.7 2.8

Cyclisation

Conditions :	Results :
$TiCl_4$, CH_2Cl_2	Acid
BF_3-OEt_2, CH_2Cl_2	Acid
CsF, CH_3CN	Decomposed
CsF, CH_3CN, reflux	Decomposed
CsF, CH_3CN, ultrasound	Decomposed
CsF, 18-Crown-6, DMF	Decomposed
$(n\text{-}Bu)_4NF$, THF	Protodesilylation

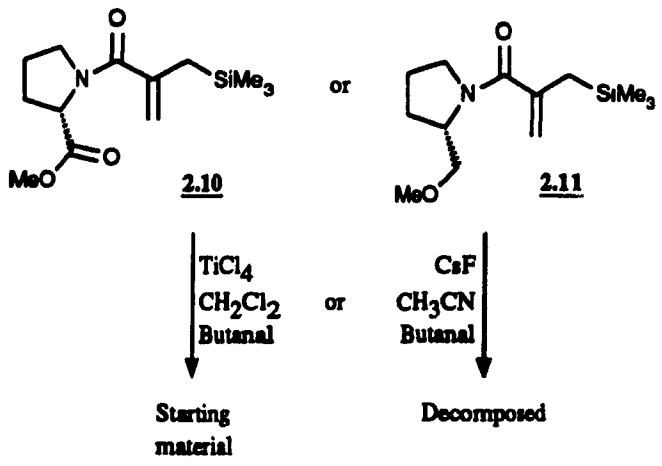
cyclised product 2.8. When electrophilic conditions were tried ($TiCl_4$, BF_3-OEt_2), no reaction was observed until the work-up, where the imidazolide underwent hydrolysis to

the acid. On the other hand, when nucleophilic conditions were used (different sources of F^-), either decomposition or protodesilylation was observed. It was thought that the lack of reactivity in the electrophilic reaction (with Lewis acids) could be due to the complexation of this acid with the two carbonyls of 2.7, as in 2.9. The allylsilane would



2.9

then be too far away and would not be able to "reach" the activated imidazolide. To test this hypothesis, an intermolecular reaction was attempted in which this cyclic complexation would not stop the reaction. **Scheme 2.6** suggests that this hypothesis is

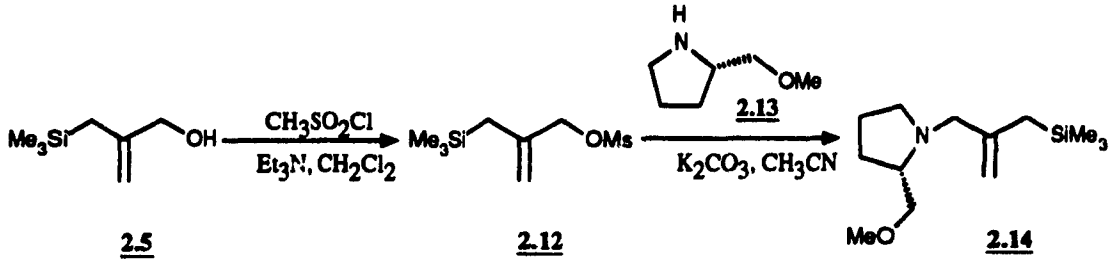


Scheme 2.6

not true. Indeed, when the reaction was carried out with compounds 2.10 and/or 2.11 (prepared in a similar way), the same lack of condensation was obtained : starting material in the case of the electrophilic reaction, and decomposition in the case of the nucleophilic one. Clearly, the cyclisation reaction with the amidoacid derivative was more difficult than expected, and it was decided at this point to turn to the second approach.

2.2 Cyclisation of an Allylsilane Aminoacetal :

One of the problems with the cyclisation of the amidoacid derivative 2.7 could have been the electron withdrawing ability of the amide. Indeed, this carbonyl group next to the double bond of the allylsilane made the latter electron poorer, hence less prone to attack the activated carbonyl. One way to avoid this particular problem is to eliminate the carbonyl of the amide and work with the amine. This route was followed with much success, as will be seen. But in order to see if such a system was indeed reactive, it was decided that the intermolecular case would first be tried. If that system proved to be reactive enough, then there was greater likelihood that the intramolecular



Scheme 2.7

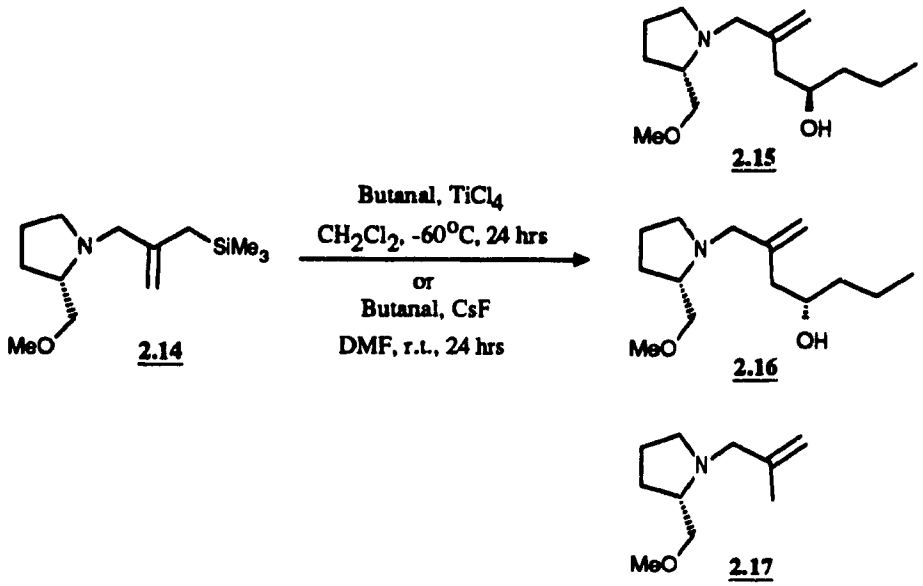
reaction would proceed as well (or better). **Scheme 2.7** illustrates the synthesis of

allylsilane aminoether **2.14**, where the activated carbonyl has been replaced by a non reactive ether group. The sequence was initiated as in the first section (**Scheme 2.3**), but instead of being oxidised, alcohol **2.5** was activated with methanesulfonyl chloride (81%) and the mesylate group of **2.12** was displaced by the commercially available chiral amine **2.13** to give **2.14** in excellent yield. The high overall yield of this route gave high hopes that the intramolecular case (see below) would behave similarly.

Intermolecular electrophilic addition of the allylsilane moiety of **2.14** did work with a simple aldehyde (butanaldehyde) under Lewis acid conditions as seen in **Scheme 2.8**, to give a diastereomeric mixture of homoallylic alcohols **2.15** and **2.16** along with some protodesilylated product **2.17**. The ratios and yields are listed in **Table 2.5**. When the reaction was tried under nucleophilic conditions, no reaction took place until ultrasound (or heat : not included in the table) was used. In the latter case, no starting material was detected after work-up, but a considerable amout of **2.17** was found. These results were encouraging enough to continue and try the intramolecular case.

Before any attempt of intramolecular cyclisation, the ether group of **2.14** had to be replaced by a suitable electrophile like an aldehyde or its dimethyl acetal. Since the acetal group is more easily handled, a plan for the synthesis of amine **2.22** was devised. **Scheme 2.9** illustrates this synthesis : the amino group of the commercially available chiral aminoalcohol **2.18** was selectively protected with a CBZ group in 90% yield (no protected alcohol was detected under these conditions)[16] and the free hydroxyl group of **2.19** was oxidised to the aldehyde **2.20** using Swern's methodology[17](85%). Protection of **2.20** as the dimethyl acetal **2.21** was easily accomplished under acid catalysed conditions (PTSA, $HC(OMe)_3$, MeOH : 95%) and the carbamate of the latter was removed by hydrogenolysis using cyclohexene as a hydrogen source[18] to yield amine **2.22** in 85% as a yellow oil which could be distilled.

This amine was then treated with mesylate **2.12** (from **Scheme 2.7**) and the

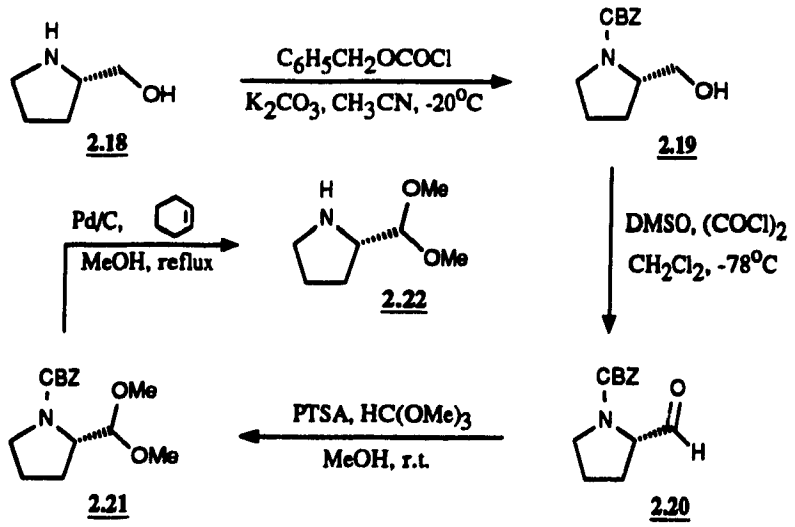


Scheme 2.8

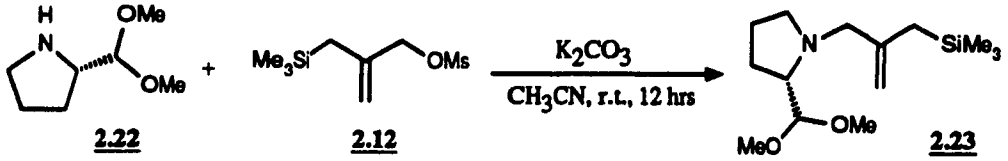
Table 2.5

Conditions :	14 : 15 +16 : 17 (GC determination)	Yield (of alcohols)
$TiCl_4$	10 : 80 : 10	50%
CsF	No reaction	
CsF with ultrasound	0 : 60 : 40	--

allylsilane aminoacetal 2.23 was obtained in 78% yield (**Scheme 2.10**). At this point, everything was set for the intramolecular cyclisation reaction. Different conditions were used (see **Scheme 2.11** and **Table 2.6**) and after several attempts, bicyclic amine 2.24 was obtained in 70% yield, after distillation, along with protodesilylated compound 2.26 and another unknown compound (2.25). Compounds 2.24 and 2.26 were isolated and characterised, but it was impossible, in our hands, to isolate the unknown. This



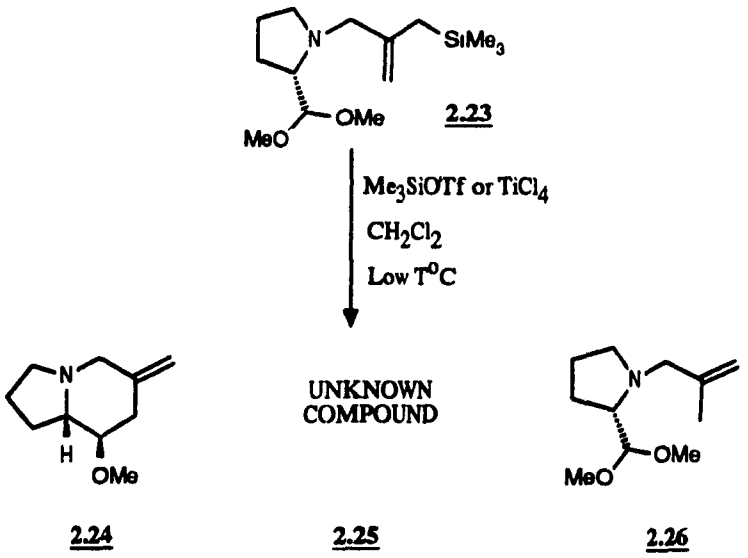
Scheme 2.9



Scheme 2.10

compound may be the diastereomer of **2.24** (8*S*,8a*S* instead of 8*R*,8a*S*), even though there were no spectroscopic proof, **2.25** being observed only by GC-MS. On the other hand, when the reaction was repeated on a larger scale (100 mg or more), only compound **2.24** was detected and isolated.

The stereochemistry of **2.24** was established on the basis of ^{1}H NMR studies. It was quite simple to assign each proton of the structure to its corresponding peak (most of them multiplets) with homocorrelated and heterocorrelated two dimensional



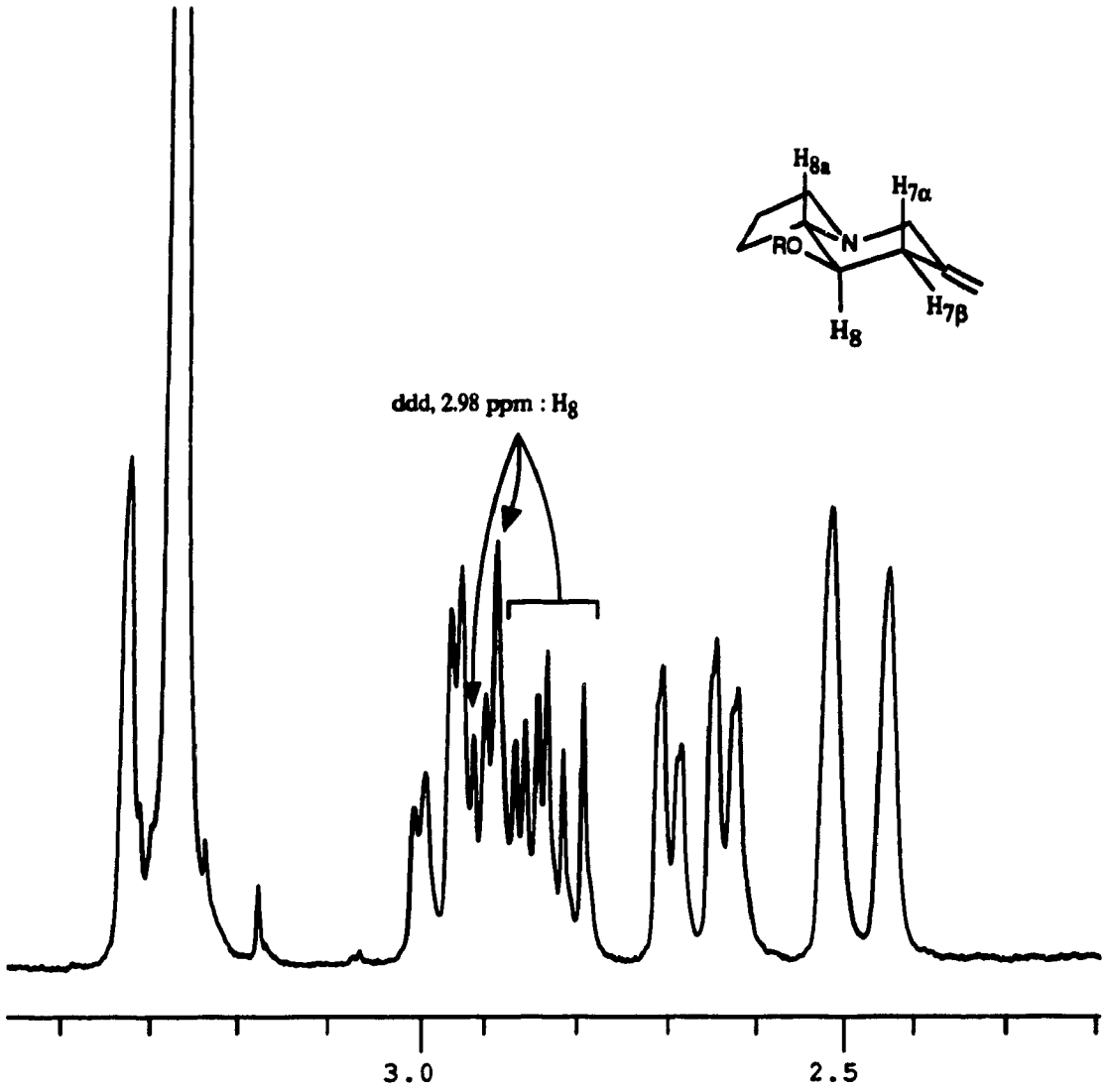
2.24 2.25 2.26

Scheme 2.11

Table 2.6

Conditions	24 : 25 : 26 (GC determination)	24 : 25 (GC determination)
$TiCl_4$, -78°C, 20 hrs	59 :38 :3	1.5 : 1
Me_3SiOTf, -78°C, 20 hrs	83 : 11 : 6	7.5 : 1
Me_3SiOTf, -20°C, 4 hrs	90 : 9 : 1	10 : 1

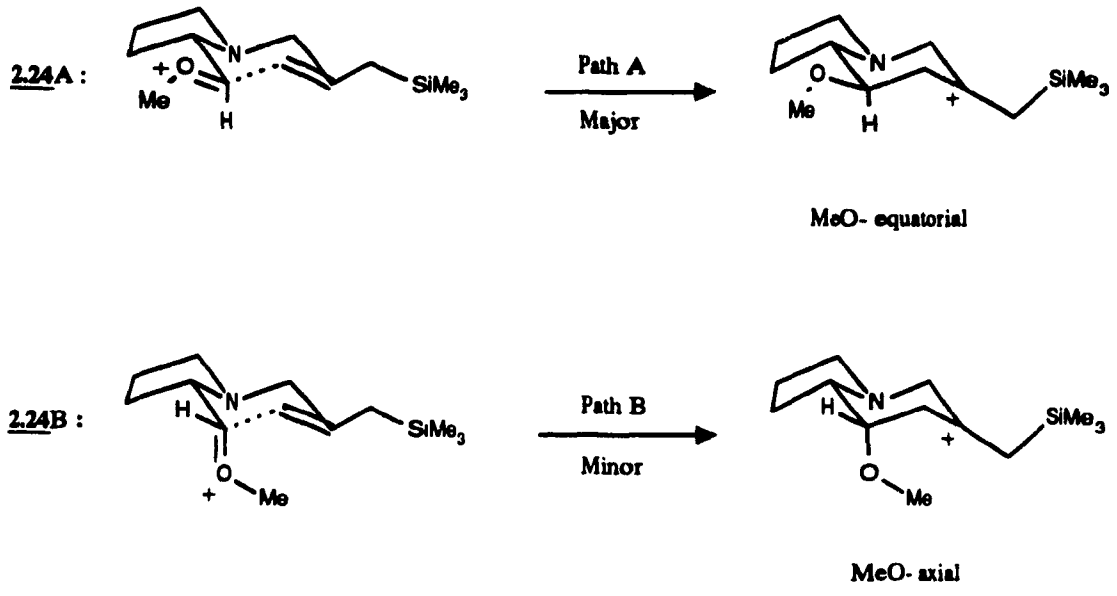
spectroscopy (COSY and HETCOR). A careful look at the peak representing H_8 (**Scheme 2.12**) revealed the presence of three coupling constants, one small (4.8 Hz) and two large (8.6 and 10.8 Hz). The only possibility for such a pattern was that H_8 had two *trans* neighbors (*trans* diaxial couplings, 180°, large coupling constants) and one *cis* neighbor (*cis* axial-equatorial coupling, 60°, small coupling constant). *All other possibilities would have given a pattern with two small coupling constants and one large.* This is also supported by the fact that the transition state for the formation of



Scheme 2.12

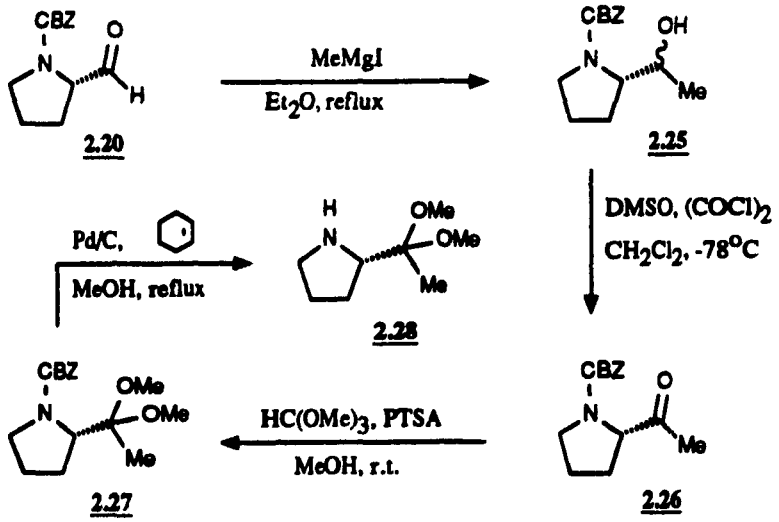
2.24A is the most stable one in terms of steric hinderance. **Scheme 2.13** shows the two possible pathways for the cyclisation reaction. Path A leads to compound 2.24A which has an equatorial methoxy group, whereas path B leads to 2.24B which has a more sterically hindered axial methoxy group.

Now that it was possible to synthesise the indolizidine ring system 2.24, it was

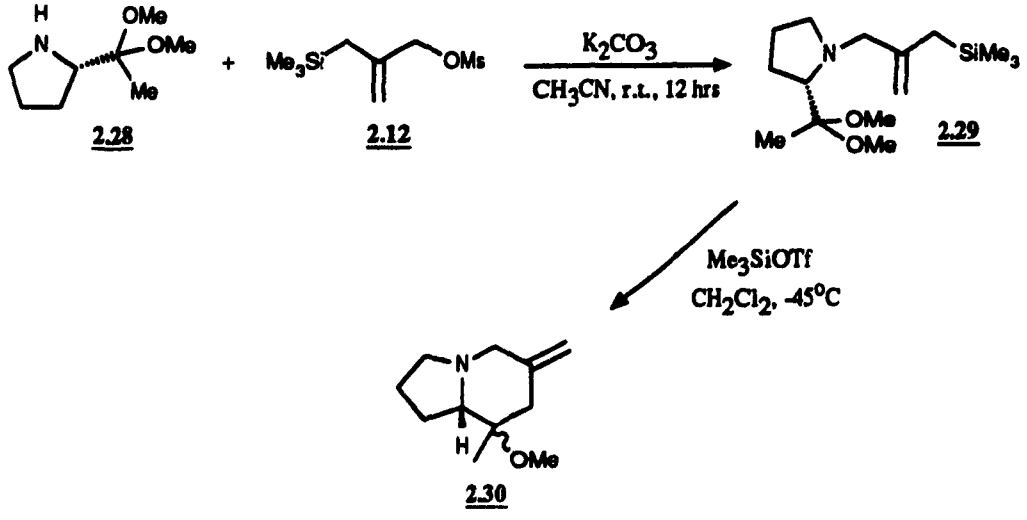


Scheme 2.13

thought that a similar system, the 8-methyl substituted one, could be synthesised in a similar way. The introduction of a methyl group at that position would give an interesting entry into the pumiliotoxin family[3]. The only difference would be in the synthesis of the amine precursor. Indeed, instead of going directly from prolinol **2.18** to the free amine **2.22**, a small number of steps was added to the sequence. Thus, aldehyde **2.20** was treated with methyl magnesium bromide in ether to give a mixture of diastereomeric alcohols **2.25** (**Scheme 2.14**) in 68%. This mixture was oxidized to the parent ketone **2.26** again using Swern's methodology. The rest of the sequence was similar to **Scheme 2.9**, and amine **2.28** was obtained in 72% yield after removal of the CBZ protecting group.



Scheme 2.14



Scheme 2.15

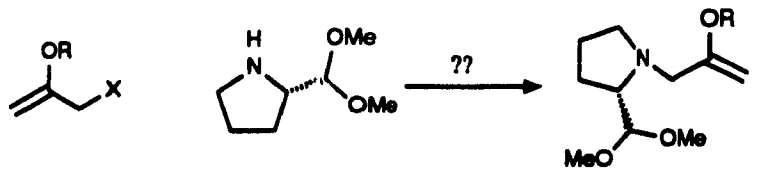
Coupling of **2.28** with mesylate **2.12** proceeded smoothly and compound **2.29**

was obtained in good yield. Treatment of **2.29** with one equivalent of trimethylsilyl trifluoromethanesulfonate at -78°C afforded methyl-cyclic compound **2.30** (**Scheme 2.15** : at higher temperatures, the reaction was extremely fast and extensive decomposition of both the starting material and the formed bicyclic product was observed.). Both the NMR spectrum and chromatogram indicated the presence of only one of the two possible diastereomers. Compound **2.30**, on the other hand, was quite unstable and its purification/isolation proved to be very difficult.

2.3 Cyclisation of an Enol Ether Aminoacetal :

Bicyclic compound **2.24** has two interesting features : the ether group is *cis* with respect to the proton of the ring junction (see **Scheme 2.11**), which is the same stereochemistry found in the two molecules of interest (swainsonine and castanospermine), and it features an exocyclic methylene group at the right position if one is interested in the pumiliotoxins series. Since this project was directed towards the synthesis of the two aforementionned polyhydroxylated alkaloids, and since these two molecules have no exocyclic methylene group, a similar synthesis that would lead to the oxygenated analog of **2.23** was an interesting challenge. The most obvious analog would be one bearing an oxygen α to the silicon in **2.23**. This particular case would lead to an enol silyl ether, but other enol ethers could also be envisaged. Since the condensation of enol ethers (both alkyl and silyl) with electrophiles such as aldehydes and their parent acetals is a well known reaction[19,20], there was reasonable hope that the cyclisation step would be an easy one.

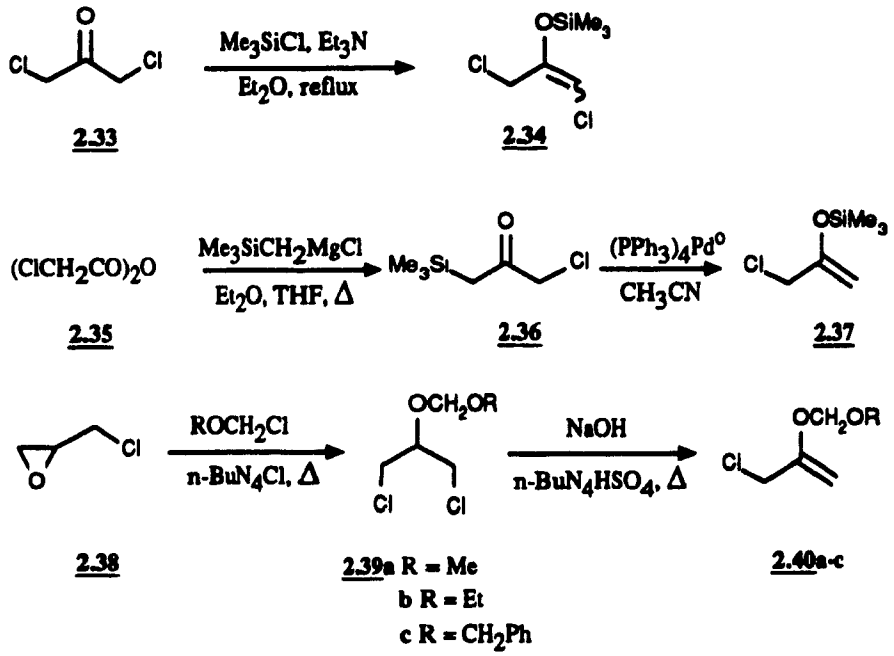
Synthesis of an enol ether directly from an α-amino ketone has been reported[21,22]. Unfortunately, there seems to be a tendancy for the products to enolise toward the nitrogen[22], which is not what was required in our work. Thus, it was decided



2.31 2.22 2.32

Scheme 2.16

to follow another plan, outlined in **Scheme 2.16**. The first attempt was to try to synthesise α-halogeno-enol ether 2.31 and to condense it with chiral aminoacetal 2.22 to give enol ether aminoacetal 2.32. The former could be synthesised in various ways, and

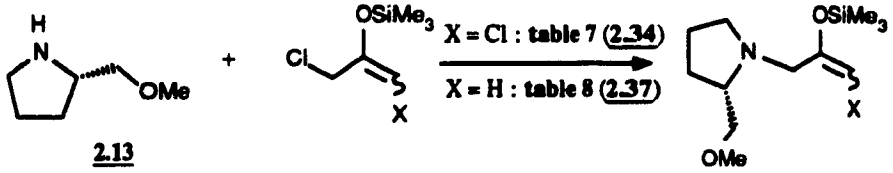


2.38 2.39a R = Me
b R = Et
c R = CH_2Ph 2.40a-c

Scheme 2.17

the R group of the enol ether could vary from silicon substituents to alkyl ones. **Scheme**

2.17 illustrates the different enol ethers that were synthesised. All of them were easily prepared in reasonable yields and were founf to be stable at room temperature. Compound 2.34 was first synthesised because of its reported ease of preparation[23]. 1,3-Dichloroacetone was chosen as the starting material because of its symmetry. Shimizu and co-workers reported reactions of compounds similar to 2.34 with alcohols in the presence of silver perchlorate to form alkoxy substituted enol silyl ether. It was thought that the alcohols could be replaced by an amine. Compound 2.37 also proved to be very easy to make[24,25]. Unfortunately, neither 2.34 nor 2.37 could be condensed with amines such as 2.13 (as a test) or 2.22. Table 2.7 and 2.8 list the different reaction conditions attempted for both compounds.



2.13

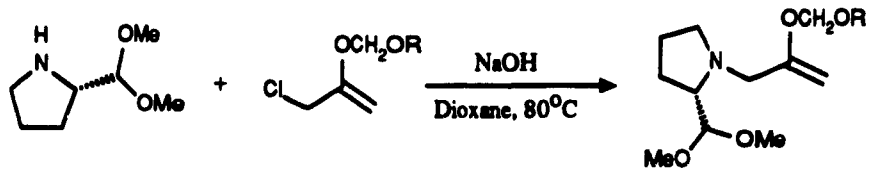
Table 2.7 : Condensation of 2.34

Conditions	Comments
K_2CO_3, CH_3CN	Deprotection of enol ether
Neat, Δ	"
CH_2Cl_2, 0°C	"
CH_2Cl_2, Amberlist A-21, 0°C-r.t.	"
$AgClO_4$, $CaCO_3$, CH_3CN, 0°C	"
$AgClO_4$, Et_3N, CH_3CN	"

On the other hand, enol ethers 2.40a-c[26,27] reacted with amine 2.22 (Scheme 2.18) to give moderate to good yields of α-amino enol ethers 2.41a-c. Reactions of these

Table 2.8 : Condensation of 2.37

Conditions	Comments
K_2CO_3, CH_2Cl_2	Deprotection of enol ether
CH_2Cl_2, r.t.	"
Et_3N, CH_3CN, Δ	"
DMAP, CH_3CN	"
$isoPr_2EtN$, CH_3CN	"



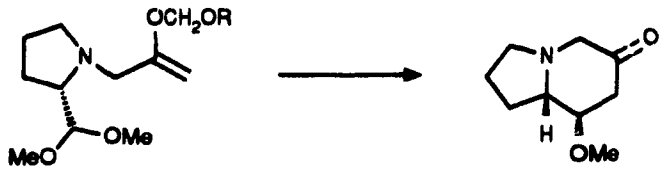
2.22 2.40a R = Me; b R = Et; c R = CH_2Ph 2.41a-c

Scheme 2.18

enol ethers with numerous Lewis acids under a large variety of conditions (**Table 2.9**) failed to give cyclic product 2.42. The main product detected for almost all of these reactions was the deprotected enol ether (ketone) 2.43. It was first thought that the presence of water was responsible for the hydrolysis of the enol ether and/or the acetal group, but decreasing the temperature to -100°C and adding molecular sieves to prevent this deprotection proved to be unsuccessful.

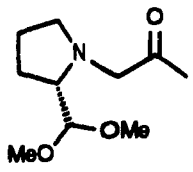
2.4 Cyclisation of a Vinylsilane Aminoacetal :

Table 2.9



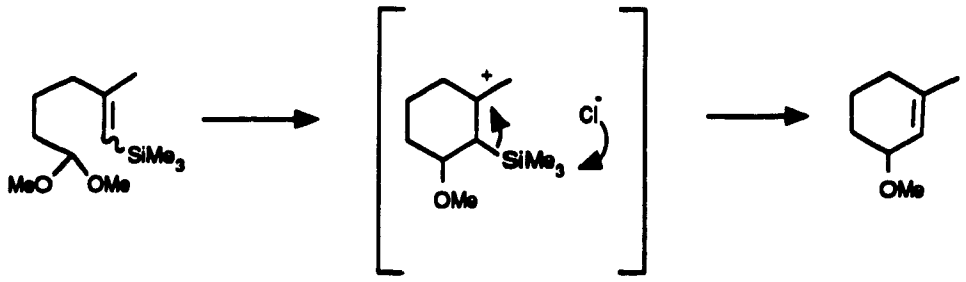
2.41a-c 2.42

R	Conditions	Comments
Me	BBr_3, CH_2Cl_2, -78°c	2.43
Me	TMSOTf, CH_2Cl_2, -78°C	"
Me	$TiCl_4$, CH_2Cl_2, -78°c	"
Me	$AlBr_3$, CH_2Cl_2, -78°C	"
Me	BF_3-OEt_2, CH_2Cl_2, -78°C	"
Et	TMSOTf, CH_2Cl_2, -78°C	"
Et	TMSOTf, CH_2Cl_2, -100°C	"
CH_2Ph	TMSOTf, CH_2Cl_2, -78°C	Unidentified product
CH_2Ph	TMSOTf, CH_2Cl_2, -78°C K_2CO_3, 4A M.S.	"



2.43

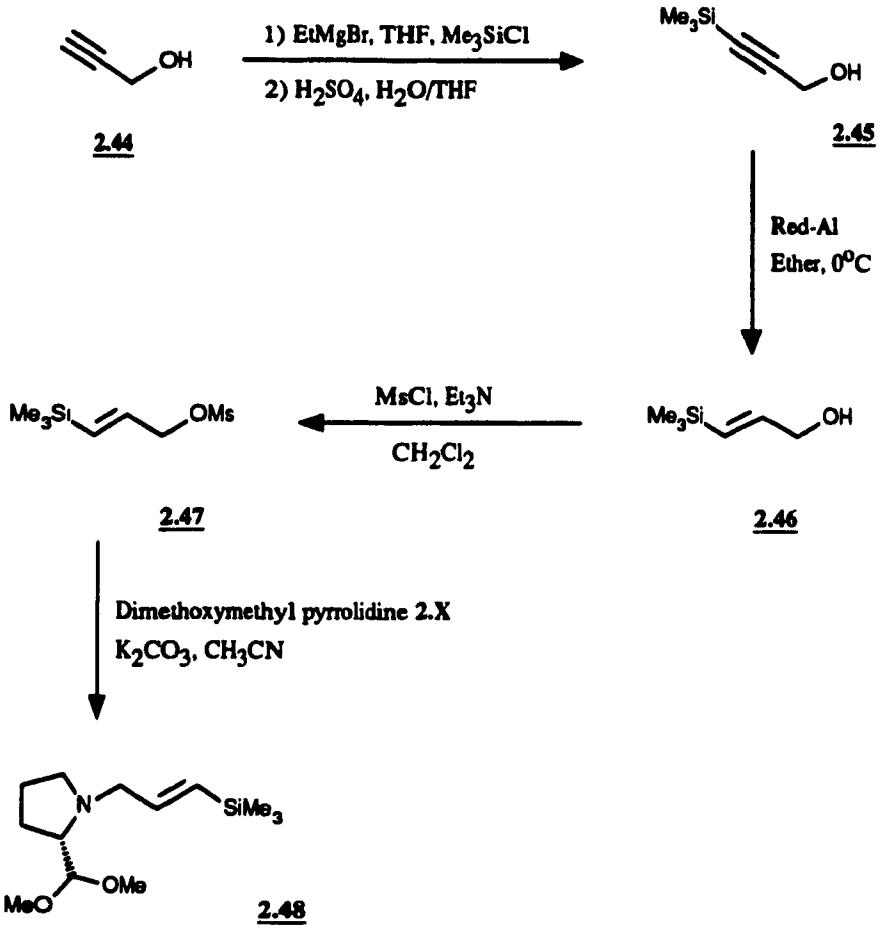
Another reaction known in the literature that was of interest is the cyclisation of vinylsilane acetals[28a,b]. **Scheme 2.19** shows that such a molecule can indeed be cyclised using Lewis acids as catalysts. In this example[28b], a six membered ring is formed having an endocyclic double bond. Such a result would suit our purposes since there would be no need to eliminate (or oxidise) an exocyclic double bond, as in **Part 2.2** (compound **2.24**). The only difference in our case would be the presence of the tertiary



Scheme 2.19

amine, and the absence of a methyl group at the β position (with respect to the silicon atom). The absence of this methyl group, on the other hand, would probably destabilise the carbocation formed during the reaction (**scheme 2.19**), a secondary carbocation being less stable than a teriary one. Nevertheless, we decided to test this type of reaction.

The synthesis of the precursor **2.48** is described in **Scheme 2.20**. The dianion of propargylic alcohol **2.44**, formed using an excess of ethyl magnesium bromide, was quenched with trimethylsilyl chloride[29], to give, after deprotection of the alcohol (H_2SO_4, THF) and distillation, a good yield of 3-trimethylsilyl-2-propyn-1-ol **2.45**. Reduction of **2.45** with Red-Al[29] (sodium bis(2-methoxyethoxy)aluminium hydride) in



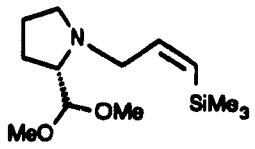
Scheme 2.20

ether afforded the propenol derivative **2.46**, which was mesylated (MsCl, Et_3N, CH_2Cl_2) to give mesylate **2.47** in excellent yield. Coupling of mesylate **2.47** with aminoacetal **2.22** was performed in acetonitrile using potassium carbonate as a base to give tertiary amine **2.48** in good yield. Here again, cyclisation of compound **2.48** using a variety of Lewis acids failed to give bicyclic aminoether **2.49** (**Scheme 2.21**). Unfortunately, it was impossible, in our hands, to synthesise the cis-isomer **2.50**, this geometry of the

2.48 2.49

Scheme 2.21

double bond being known to cyclise more readily (vinylsilanes react with carbon electrophiles with retention of configuration[30]).



2.50

In this chapter, we have shown that the indolizidine ring system can indeed be prepared by Lewis acid catalysed intramolecular electrophilic cyclisation of an allylsilane. In order to form compounds that were more easily transformed into the desired polyhydroxylated indolizidines, enol ethers (both silyl and alkyl enol ethers) were prepared but their intramolecular cyclisations were not successful.

In **Chapter 4**, intramolecular nucleophilic cyclisation attemps will be

described. Such a reation will hopefully permit us to form easily functionalisable systems.

2.5 Experimental :

General Methods. Materials were obtained from commercial suppliers unless noted otherwise. Methylene chloride and acetonitrile were dried over calcium hydride, methanol was dried over magnesium and tetrahydrofuran was dried over sodium-benzophenone ketyl. All solvents were distilled immediately prior to use. Hexamethylphosphoramide (HMPA) and N,N,N',N'-tetramethylethylenediamine (TMEDA) were distilled over calcium hydride and stored over 3Å molecular sieves. Melting points (mp), determined on a Gallenkamp block, and boiling points (bp) are uncorrected. Analytical thin layer chromatography (tlc) was done on Merck silica del 60 F_{254}. Ceric acid mist or iodine vapor were used for compound visualisation, unless noted otherwise. Flash chromatography[31] was done on Merck silica gel 60 (230-400 mesh ASTM). Capillary gas chromatography analysis was performed on a Hewlett Packard 5890 A instrument fitted with a 25 m x 0.2 mm high performance column (crosslinked methylsilicone, film thickness of 0.33 μm). Infrared spectra were obtained on an Analect Instruments AQS-20 FTIR spectrometer and are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded on Varian FT XL-200 or XL-300, Varian Gemini-200 and Varian CW T-60 instruments. ^{13}C NMR spectra were recorded on Varian FT XL-300 and Varian Gemini-200. All NMR spectra were done with deuterated chloroform ($CDCl_3$)as the solvent, unless noted otherwise. Chemical shifts (δ) are expressed in part per million (ppm). Significant ^1H NMR data are tabulated as the multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; b, broad), number of portons (H) and coupling constants (*J*, in Hertz). Decoupling experiments as well as two dimentional homo and heterocorrolated experiments were performed to umambiguously assign selected spectra. Low and high resolution mass spectra (MS) were obtained with the HP 5980A GC/MS fitted with a packed column (6% OV-101, 2

m x 6 mm) and the ZAB 2F HS mass spectrometers respectively (CI, NH_3) and are reported as *m/z* (relative intensity in percent). Other mass spectra were obtained on a Finnigan Mat series 700 ion trap detector coupled to a Varian series 3500 capillary gas chromatograph (30 m x 0.25 mm, methylsilicon with 5% phenylsilicon, 0.25 μm).

Preparation of 2-((trimethylsilyl)methyl)-2-propen-1-ol[6] (2.5): In a 500 mL three-neck flask equipped with a mechanical stirrer and a dropping funnel and containing 154 mL of dry ether, at 0°C, was added 10.5 M *n*-butyllithium (30.4 mL, 2.3 eq) and freshly distilled TMEDA (48.1 mL, 2.3 eq). The solution was stirred at 0°C for 10 min and the dropping funnel was charged with 2-methyl-2-propene-1-ol (0.14 mol, 11.6 mL) which was added dropwise. After the addition was completed, 68 mL of dry THF were added to the cloudy solution, which turned clear again. The reaction was then allowed to warm very slowly to room temperature over 13 hrs with mechanical stirring and then was stirred for an additional 9 hrs. The mixture was then quenched with chlorotrimethylsilane (70.4 mL, 4 eq) at 0°C. The dark reaction mixture was allowed to stir for 10 min before being diluted with 1 L of ether. The ether solution was then washed with sat. aq. $NaHCO_3$ (1 x 250 mL), water (1 x 250 mL), sat. aq. $CuSO_4$ (2 x 250 mL), water (1 x 250 mL) and brine (1 x 250 ml), dried over magnesium sulfate and distilled (70°C under 10 mmHg) to give the protected alcohol as a colourless oil (14.9 g, 50%). ^1H NMR ($CDCl_3$) : δ 4.92 (m, 1H), 4.63 (m, 1H), 3.95 (bs, 2H), 1.49 (bs, 2H), 0.13 (s, 9H), 0.03 (s, 9H).

To the solution of this oil (14.9 g) in 140 mL of THF was added 2.7 mL of 1 N H_2SO_4 (0.01 eq) and the solution was stirred at r.t. for 30 min. The bulk of THF was then removed under vacuum, the residue taken up in ether, washed with sat. aq. $NaHCO_3$ (1 x 100 mL) and brine (1 x 100 mL), and dried with magnesium sulfate. The solvent was removed under vacuum to give 9.47 g (95%) of the pure alcohol 2.5. ^1H NMR

($CDCl_3$) : δ 4.91 (m, 1H), 4.67 (m, 1H), 3.98 (bs, 2H), 1.55 (bs, 1H), 1.54 (s, 2H), 0.03 (s, 9H).

Preparation of 2-((trimethylsilyl)methyl)-2-propenoic acid (2.3): To a solution of alcohol 2.5 (2.06 g, 13.86 mmol) in 280 mL of dry methylene chloride, under argon, at room temperature, was rapidly added activated manganese dioxide (24.10 g, 20 eq). After 6 hrs of vigorous stirring, the suspension was filtered through celite and the solids were copiously rinsed with acetone. To the filtrate was added slowly a solution of sodium chlorite (11.28 g, 9 eq) and sodium dihydrogen phosphate (13.39 g, 7 eq) in 125 mL of water and the two phase solution was stirred for an additional 30 min after which the organic solvents were evaporated. The aqueous phase was then diluted with 200 mL of water, brought to a basic pH by the addition of solid NaOH, extracted with ether (2x) and acidified with conc. HCl. It was extracted again with ether (3x) and the combined organic layers were washed with cold water, brine, and dried over magnesium sulfate. Evaporation of the solvent under vacuum and purification by flash chromatography (silica gel, 8:2 hexane/ethyl acetate) gave 2.3 as a pale yellow oil (1.81 g, 82%). IR (neat) : 2955 (broad), 1704 and 1618 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.14 (d, 1H, J=1.2), 5.43 (d, 1H, J=1.2), 1.82 (s, 2H), 0.01 (s, 9H). This compound was reported previously in the literature[4a] (5 steps from commercialy available diethyl malonate : 56% overall yield) but no physical data were provided.

Preparation of methyl (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenoyl)-pyrrolidine-2-carboxylate (2.4): To a solution of acid 2.3 (0.78 g, 4.92 mmol) in dry HMPA (0.86 mL, 1 eq), under argon, at -10°C, was added thionyl chloride dropwise (0.36 mL, 1 eq). The solution was stirred at -10°C for 2 hrs after which it was transferred, via a double tipped needle, to a solution of methyl prolinate hydrochloride 2

(0.81 gm, 1 eq) in 12.3 mL of dry pyridine also at -10°C. After 3 hrs, the pyridine was evaporated under vacuum and the residue was dissolved in ethyl acetate, washed with 1 M HCl (1x), 0.5 M Na_2CO_3 (1x), brine and dried over magnesium sulfate. Filtration and evaporation of the solvent under vacuum followed by flash chromatography purification (silica gel, 7:3 hexane/ethyl acetate) gave **2.4** as a colourless oil (0.98 g, 74%). IR (neat) : 2955, 1751, 1645 and 1613 cm^{-1}. ^1H NMR ($CDCl_3$) : 5.14 (d, 2H, *J*=5.4), 4.47 (dd, 1H, *J*=5.8, 8.8), 3.72 (s, 3H), 3.65 (t, 2H, *J*=5.4), 2.35-1.72 (m, 6H). GC-MS : 256 (9, $M^{\cdot+}$ + H^+), 196 (93), 182 (10), 109 (7), 83 (7), 70 (100).

Preparation of (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenoyl)-pyrrolidine-2-carboxylic acid (2.1): To a solution of **2.4** (0.25 g, 0.91 mmol) in 6.1 mL of methanol was added an aqueous solution of sodium hydroxide (43.7 mg, 1.2 eq, in 1.8 mL of water). The mixture was heated to reflux for 10 h, cooled to room temperature, and treated with 10% NaOH. The aqueous phase was extracted with ether (2x), acidified with 1 M HCl (pH 3) and reextracted with ether (3x). The combined organic layers were washed with brine, dried over magnesium sulfate and filtered. Evaporation of the solvents gave pure acid **2.1** as a clear oil (0.20 g, 85%). IR (neat) : 2955 (broad), 1743, 1640 and 1608 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 9.91 (bs, 1H), 5.15 (d, 2H, *J*=5.0), 4.55(dd, 1H, *J*=5.6, 8.0), 3.78-3.56 (m, 2H), 2.93-1.75 (m, 6H).

Preparation of (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenoyl)-pyrrolidine-2-carboxylic acid imidazolide (2.7): To a solution of **2.1** (0.44 g, 1.73 mmol) in 11.5 mL of dry tetrahydrofuran was added 1,1'-carbonyldiimidazole (0.36 g, 1.3 eq) and the solution was heated to reflux for 2 hrs. The THF was then evaporated under vacuum and the residue dissolved in carbon tetrachloride, washed with cold brine and dried over magnesium sulfate. Evaporation of the solvent under vacuum gave pure

imidazolide 2.7 as a colourless oil (0.44g, 83%). IR (neat) : 3080, 2955, 2250, 1745, 1635 and 1608 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 8.25 (m, 1H), 7.51 (m, 1H), 7.07 (m, 1H), 5.18 (m, 3H), 3.92-3.63 (m, 2H), 2.58-1.65 (m, 6H).

Preparation of 2-((trimethylsilyl)methyl)-2-propenyl mesylate (2.12): To a solution of alcohol 2.5 (4.03 g, 27.91 mmol) in 56.0 mL of dry methylene chloride was added dry triethylamine (6.61 mL, 1.7 eq). The solution was cooled to -20°C and methanesulfonyl chloride (3.24 mL, 1.5 eq) was added slowly. A white precipitate formed immediately and the solution was stirred 1 hr at -20°C, and 1 hr at room temperature. It was then diluted in 50 mL of distilled water and extracted with ether (4x). The combined organic layers were washed successively with 1 M HCl (1x), water (1x), brine (1x) and dried over magnesium sulfate. Filtration followed by evaporation of the solvents gave mesylate 2.12 as a clear yellow oil (5.51 g, 89%). This oil could be further purified by distillation (71°C, 0.025 mmHg). ^1H NMR ($CDCl_3$) : δ 5.02 (d, 1H, J=1.2), 4.83 (d, 1H, J=1.2), 4.55 (s, 2H), 3.00 (s, 3H), 1.58 (s, 2H), 0.03 (s, 9H).

Preparation of (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenyl)-2-methoxymethylpyrrolidine (2.14): To a solution of methoxymethyl pyrrolidine 2.13 (3.15 g, 21.70 mmol, Aldrich) in 98 mL of dry acetonitrile, under argon, at room temperature, was added finely powdered potassium carbonate (15.0 g, 5eq), followed by a solution of mesylate 2.12 (4.83 g, 1 eq) in acetonitrile (10 mL). The suspension was stirred at room temperature for 16 h, after which it was poured in 50 ml of water. Methylene chloride (150 mL) was added, the phases were separated and the aqueous phase was further extracted with methylene chloride (3x). The combined organic extracts were then washed with brine and dried with magnesium sulfate. Evaporation of the solvent and purification by flash chromatography (silica gel, 8:2 hexanes/ethyl acetate) gave 2.14 as

a colourless oil (4.84 g, 82%) : ^{1}H NMR ($CDCl_3$) : δ 4.79 (m, 1H), 4.55 (m, 1H), 3.43-3.21 (m, 6H), 3.33 (s, 3H), 3.03 (m, 1H), 2.67 (d, 1H, *J*=13.4), 2.58 (m, 1H), 2.17-1.51 (m, 7H).

Preparation of (2*S*)-1-(2'-(2-hydroxypentyl)-2-propenyl)-2-methoxymethylpyrrolidines (2.15 and 2.16): To a solution of butyraldehyde (57 μL, 1.5 eq) in 1 M $TiCl_4$/methylene chloride (1.71 mL, 4 eq), at -60°C, under argon, was added slowly a solution of silane **2.14** (0.10 g, 0.43 mmol) in dichloromethane (1.14 mL). The solution was stirred for 24 hrs at -60°C and was then poured in sat. aq. $NaHCO_3$. The aqueous phase was rendered basic by the addition of a few drops of 10% NaOH and the phases were separated. The aqueous phase was extracted with ether (3x) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvents followed by flash chromatography (silica gel, 7:3 hexane/ethyl acetate) gave two compounds in a 50% total yield (50.0 mg). The NMR spectra did not help in determining the absolute stereochemistry of each compound. **Compound #1** (less polar by chromatography and by GC) : 38.8 mg (major). ^{1}H NMR ($CDCl_3$) : δ 4.92 (m, 2H), 3.60-3.42 (m, 3H), 3.35 (s, 3H), 3.35 (m, 1H), 3.06 (m, 1H), 2.80 (d, 1H), 2.67 (m, 1H), 2.45 (m, 1H), 2.17 (m, 1H), 2.04-1.87 (m, 2H), 1.81-1.22 (m, 8H), 0.95 (m, 3H). **Compound #2** (more polar by chromatography and by GC) : 11.2 mg (minor). ^{1}H NMR ($CDCl_3$) : δ 5.00 (m, 1H), 4.91 (m, 1H), 3.69 (m, 1H), 3.60-3.47 (m, 2H), 3.35 (s, 3H), 3.30 (m, 1H), 3.08 (m, 1H), 2.89 (d, 2H), 2.73 (m, 1H), 2.48-2.18 (m, 3H), 1.95 (m, 1H), 1.80-1.25 (m, 7H), 0.90 (m, 3H).

Preparation of (2*S*)-N-benzyloxycarbonyl-2-hydroxymethylpyrrolidine (2.19): To a solution of L-prolinol **2.18** (2.05 g, 20.23 mmol, Aldrich) and finely powdered potassium carbonate (6.71 g, 2.4 eq) in 20 mL of dry acetonitrile, at -20°C,

under argon, was added slowly a solution of benzyl chloroformate (3.17 mL, 1.1 eq) in 5 mL of acetonitrile. After the addition was completed, the solution was stirred at -20°C for 2 hrs. Water was then added (50 mL) and the aqueous phase was extracted with chloroform (4x). The combined organic extracts were washed successively with water (1x), 5% HCl (1x), water (1x)and brine. After drying with magnesium sulfate, the solvent was removed under vacuum and the crude product was purified by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) to give 4.14 g (87 %) of **2.19** as a colourless oil : $[\alpha]^{20}_D$= -41.4° (*c* : 2.2 in $CHCl_3$). IR (neat) : 3413 (broad), 2958, 2880 and 1688 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.42-7.28 (m, 5H), 5.13 (s, 2H), 4.47-4.38 (m, 1H), 4.09-3.91 (m, 1H), 3.70-3.32 (m, 4H), 2.10-1.51 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 157.63, 137.04, 129.04, 128.59, 128.43, 67.56, 66.86, 60.90, 47.58, 28.72, 24.20. Exact mass calcd for $C_{13}H_{17}NO_3$ ($M^{\cdot+} + H^+$) 236.1287, found 236.1287.

Preparation of (2*S*)-N-benzyloxycarbonylpyrrolidine-2-carboxaldehyde (2.20): A solution of dimethyl sulfoxide (1.77 mL, 2.84 eq) in 5 mL of dry methylene chloride was slowly added, via a double tipped needle, to a stirring solution of oxalyl chloride (1.08 mL, 1.41 eq) in 15 mL of methylene chloride, under argon, at -45°C. The colourless solution was stirred for 15 min after which a solution of alcohol **2.19** (2.06 g, 8.76 mmol) in 5 mL of methylene chloride was added dropwise over a period of 15 min. A white precipitate was then formed, and the suspension was stirred for 1 hr. Triethylamine (6.02 mL, 5 eq) in methylene chloride was added and the solution was allowed to slowly warm to room temperature. The reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 5% HCl, water (1x), brine, and was dried over magnesium sulfate. Evaporation of the solvent under vacuum gave a pale brown oil which was purified by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate : 1.77 g, 87%) : $[\alpha]^{20}_D$= -63.7° (*c* : 1.3 in MeOH). IR (neat) : 2978, 2881, 1736

and 1693 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 9.62 + 9.50 (2d, 1H), 7.46-7.27 (m, 5H), 5.18 + 5.14 (2s, 2H), 4.39-4.18 (2m, 1H), 3.67-3.40 (m, 2H), 1.70-2.28 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 155.96 + 155.09 (1C), 137.02, 136.80, 129.04, 128.64, 128.49, 67.59, 65.62 + 65.22 (1C), 47.59 + 47.01 (1C), 28.02 + 26.83 (1C), 24.72 + 23.94 (1C). Exact mass calcd for $C_{13}H_{15}NO_3$ ($M^{\cdot+}$ + H^+) 234.1131, found 234.1130.

Preparation of (2*S*)-N-benzyloxycarbonyl-2-dimethoxymethylpyrrolidine (2.21): To a solution of aldehyde **2.20** (1.04g, 4.47 mmol) in 4.5 mL of dry methanol, under argon, at room temperature, was added trimethylorthoformate (3.9 mL, 8 eq) and p-toluenesulfonic acid (40 mg, .05 eq) and the reaction mixture was stirred for 1 hr. The solution was then diluted with 30 mL of ether and washed with a 1:1 solution of brine and 5% NaOH, water, brine and was dried over magnesium sulfate. Evaporation of the solvent under vacuum and purification by flash chromatography gave **2.21** as a colourless oil (0.98 g, 80%) : $[\alpha]^{20}_D$= -64.7° (*c* : 1.1 in $CHCl_3$). IR (neat) : 2952, 1691 and 1093 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.43-7.30 (m, 5H), 5.30-5.11 (m, 2H), 4.72-4.34 (m, 1H), 4.06-3.88 (m, 1H), 3.59-3.38 (m, 8H), 2.18-1.70 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 155.14, 136.95, 128.45, 127.91, 127.73, 106.36 + 105.34 (1C), 66.82 + 66.63 (1C), 59.57 + 59.03 (1C), 57.67, 56.18 + 56.13 (1C), 47.21 + 47.14 (1C), 25.39 + 24.55 + 23.83 (2C). MS : 280 (5, $M^{\cdot+}$ + H^+), 264 (4), 248 (100), 204 (94), 172 (10), 158 (58), 114 (23).

Preparation of (2*S*)-2-dimethoxymethylpyrrolidine (2.22): To a solution of **2.21** (0.21 g, 0.75 mmol) in 3.5 mL of dry methanol was added cyclohexene (0.38 mL, 5 eq) and 10% palladium on activated carbon (2:1 substrate/catalyst, 0.11 g). The solution was refluxed for 30 min and allowed to cool to room temperature. The black suspension was then filtered on a short pad of celite and the solid was rinsed with several small

portions of methanol. The solvent was evaporated and the resulting oil was distilled under vacuum (61°C, 5 mmHg) to give 90 mg (83%) of amine 2.22 as a clear liquid : $[\alpha]^{20}_D$= -7.4° (*c* : 1.1 in $CHCl_3$). IR (neat) : 3343, 2952 and 1126 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.11 (d, 1H, *J*=7.0), 3.38 (s, 3H), 3.36 (s, 3H), 3.19 (q, 1H, *J*=7.2), 2.95-2.80 (m, 2H), 2.76 (bs, 1H), 1.90-1.51 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 107.40, 59.24, 54.17, 53.90, 46.42, 26.93, 25.21. MS : 145 (2, $M^{\cdot+}$ + H^+), 114 (21), 83 (4), 70 (100), 43 (6).

Preparation of (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenyl)-2-dimethoxymethylpyrrolidine (2.23): To a solution of 2.22 (3.15 g, 21.70 mmol) in 98 mL of dry acetonitrile, under argon, at room temperature, was added finely powdered potassium carbonate (15.0 g, 5 eq), followed by a solution of mesylate 2.12 (4.83 g, 1 eq) in acetonitrile (10 mL). The suspension was stirred at room temperature for 16 h, after which it was poured in 50 ml of water. Methylene chloride (150 mL) was added, the phases were separated and the aqueous phase was further extracted with methylene chloride (4x). The combined organic extracts were then washed with brine and dried with magnesium sulfate. Evaporation of the solvent and purification by flash chromatography (silica gel, 9:1 hexanes/ethyl acetate) gave 2.23 as a colourless oil (4.84 g, 82%) : $[\alpha]^{20}_D$= -5.2° (*c* : 1.8 in $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 4.83 (m, 1H), 4.59 (m, 1H), 4.17 (d, 1H, *J*=5.4), 3.46 (d, 1H, *J*=13.2), 3.39 (s, 6H), 3.04 (m, 1H), 2.73 (d, 1H, *J*=13.2), 2.63 (m, 1H), 2.16 (m, 1H), 1.90-1.50 (m, 6H). MS : 272 (1, $M^{\cdot+}$ + H^+), 271 (1, $M^{\cdot+}$), 256 (1), 240 (3), 198 (3), 196 (46), 122 (44), 73 (100).

Preparation of (8*R*,8a*S*)-6-exomethylene-8-methoxyindolizidine (2.24): To a solution of 2.23 (0.33 g, 1.20 mmol) in 12 mL of dry methylene chloride, under argon, at -20°C, was added dropwise 0.23 mL of trimethylsilyl trifluoromethanesulfonate. The solution was stirred for 4 hrs and was then poured in 10 mL of water. 10% NaOH was

added until the aqueous phase was basic to litmus paper. The phases were then separated and the aqueous phase was further extracted with chloroform (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate, and the solvent was removed under vacuum. Distillation (31°C, 0.1 mmHg) gave **2.24** (0.14 g, 71%) as a clear yellow oil : $[\alpha]^{20}_D$= -20° (*c* : 2.9 in $CHCl_3$). IR (neat) : 2941, 2821, 1655 and 1189 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.88 (m, 2H), 3.40 (dd, 1H, *J*=1.2, 11.8), 3.38 (s, 3H), 3.06 (dt, 1H, *J*=2.6, 8.6), 2.98 (ddd, 1H, *J*=4.8, 8.6, 10.6), 2.79 (ddd, 1H, *J*=1.2, 4.8, 13.0), 2.62 (d, 1H, *J*=11.8), 2.23-1.51 (m, 7H). ^{13}C NMR ($CDCl_3$) : δ 142.68, 111.73, 82.51, 68.54, 58.75, 57.23, 54.09, 39.17, 28.94, 21.80. MS : 168 (8, $M^{\cdot+}$ + H^+), 167 (88, $M^{\cdot+}$), 152 (74), 136 (58), 83 (64), 70 (100). Exact mass calcd for $C_{10}H_{17}NO$ ($M^{\cdot+}$ + H^+) 168.1389, found 168.1388.

Preparation of (2*S*)-N-benzyloxycarbonyl-2-(1'-hydroxyethyl)-pyrrolidine (2.25): To a solution of aldehyde **2.20** (4.41 g, 18.88 mmol) in 33.5 mL of dry ether, at room temperature, under argon, was added a 3.0 M solution of methyl magnesium iodide in ether (1.5 eq, 9.44 mL) dropwise in order to maintain a gentle reflux. When the solution ceased to reflux by itself, it was heated to reflux for 1 hr. The reaction mixture was then cooled to 0°C and approximately 5 mL of sat. aq. NH_4Cl were added slowly. The phases were separated, the aqueous layer was extracted with ether (4x) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (1x), brine, and dried over magnesium sulfate. Evaporation of the solvent followed by flash chromatography (silica gel, 1:1 hexane/ethyl acetate) gave a mixture of alcohols **2.25** as a thick clear oil (3.09 g, 68%). IR (neat) : 3412 (broad), 2975, 2883), 1674 and 1191 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.35 (m, 5H), 5.15 (s, 2H), 4.93 (bs, 1H), 4.01 (m, 1H), 3.70 (m, 2H), 3.35 (m, 1H), 2.10-1.55 (m, 4H), 1.43-1.07 (m, 3H). ^{13}C NMR ($CDCl_3$) : major isomer : δ 158.54, 136.97, 129.03, 128.60, 128.44, 72.12, 67.71, 65.18, 47.57, 28.87, 24.30, 20.83; minor

isomer : δ 157.31, 137.16, 128.75, 128.54, 128.37, 69.51, 67.43, 64.32, 48.16, 27.61, 24.30, 18.02. MS : 250 (100, $M^{\cdot+}$ + H^+), 232 (5), 206 (72), 204 (26), 142 (82), 114 (19).

Preparation of (2*S*)-N-benzyloxycarbonyl-2-(1'-ketoethyl)-pyrrolidine (2.26): A solution of dimethyl sulfoxide (2.50 mL, 2.84 eq) in 5 mL of dry methylene chloride was slowly added, via a double tipped needle, to a stirring solution of oxalyl chloride (1.53 mL, 1.41 eq) in 25.5 mL of methylene chloride, under argon, at -45°C. The colourless solution was stirred for 15 min after which a solution of alcohols 2.25 (3.09 g, 12.41 mmol) in 5 mL of methylene chloride was added dropwise over a period of 15 min. A white precipitate was then formed, and the suspension was stirred for 1 hr. Triethylamine (8.65 mL, 5 eq) in methylene chloride was added and the solution was allowed to slowly warm to room temperature. The reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 5% HCl, water (1x), brine, and was dried over magnesium sulfate. Evaporation of the solvent under vacuum and flash chromatography purification (silica gel, 1:1 hexanes/ethyl acetate) gave a colourless oil (2.38 g, 78%) : $[\alpha]^{20}_D$= -43.7° (*c* : 1.1 in $CHCl_3$). IR (neat) : 2978, 2880, 1728 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.19 (m, 5H), 5.10 + 5.05 (2 AB systems, 2H, $J_{5.10ppm}$= 12.5, $J_{5.05ppm}$= 12.3), 4.37 + 4.28 (2dd, 1H, $J_{4.37ppm}$= 4.2, 8.4, $J_{4.28ppm}$= 4.8, 8.6), 3.59-3.46 (m, 2H), 2.15 + 1.99 (2s, 3H), 2.10 (m, 1H), 1.85 (m, 3H). ^{13}C NMR ($CDCl_3$) :δ 208.27 + 207.94 (1C), 155.49 + 154.83 (1C), 137.14 + 136.83 (1C), 128.93, 128.53, 128.43 + 128.32 (1C), 67.59 + 67.48 (1C), 66.01 + 65.87 (1C), 47.69 + 47.14 (1C), 30.24 + 29.12 (1C), 27.16 + 26.36 (1C), 24.80 + 24.08 (1C).

Preparation of (2*S*)-N-benzyloxycarbonyl-2-(1',1'-dimethoxyethyl)-pyrrolidine (2.27): To a solution of ketone 2.26 (2.38 g, 9.60 eq) in 9.6 mL of dry methanol, under argon, at room temperature, was added trimethylorthoformate (8.4 mL,

8 eq) and p-toluenesulfonic acid (90 mg, .05 eq) and the reaction mixture was stirred for 1 hr. The solution was then diluted with 60 mL of ether and washed with a 1:1 solution of brine and 5% NaOH, water, brine and was dried over magnesium sulfate. Evaporation of the solvent under vacuum and purification with flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) gave **2.27** as a colourless oil (2.60 g, 92%) : $[\alpha]^{20}_D$= -43.9° (*c* : 1.2 in $CHCl_3$). IR (neat) : 2944 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.35 (m, 5H), 5.13 (AB system, 2H, *J*=13.2), 4.26 (m, 1H), 3.70 (m, 1H). 3.32 (s, 3H), 3.28 (m, 1H), 3.22 (s, 3H), 2.05-1.70 (m, 4H), 1.23 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 156.52, 137.40, 128.86, 128.31, 104.01, 67.37, 60.87, 49.48, 48.18, 27.01, 24.34, 18.15.

Preparation of 2(*S*)-2-(1',1'-dimethoxyethyl)-pyrrolidine (2.28): To a solution of dimethyl ketal **2.27** (2.60 g, 8.87 mmol) in 44.4 mL of dry methanol was added cyclohexene (4.49 mL, 5 eq) and 10% palladium on activated carbon (2:1 substrate/catalyst, 1.30 g). The solution was refluxed for 30 min and allowed to cool to room temperature. The black suspension was then filtered on a short pad of celite and the solid was rinsed with several small portions of methanol. The solvent was evaporated to give 1.01 g (72%) of amine **2.28** as a clear liquid : $[\alpha]^{20}_D$= -6.1 (*c* : 1.2 in $CHCl_3$). IR (neat) : 2952 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.36 (m, 1H), 3.21 (s, 6H), 3.05-2.83 (m, 2H), 1.89-1.50 (m, 4H), 1.21 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 104.06, 61.57, 48.79, 47.45, 27.12, 26.18, 17.22.

Preparation of (2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenyl)-2-(1',1'-dimethoxyethyl)-pyrrolidine (2.29): To a solution of amine **2.28** (0.14 g, 0.87 mmol) in 4.4 mL of dry methylene chloride, under argon, at room temperature, was added dry triethyl amine (0.13 ml, 1.1 eq), followed by a solution of mesylate **2.12** (0.19 g, 1 eq) in methylene chloride (1 mL). The solution was stirred at room temperature for 48 hrs,

after which it was poured in 5 ml of water. Methylene chloride (10 mL) was added and the aqueous phase was rendered basic by the addition of a few drops of 10% NaOH. The phases were separated and the aqueous phase was further extracted with methylene chloride (3x). The combined organic extracts were then washed with brine and dried with magnesium sulfate. Evaporation of the solvent and purification by flash chromatography (silica gel, 98:2 hexanes/ethyl acetate) gave **2.29** as an unstable colourless oil (0.13 g, 51%) : $[\alpha]^{20}_D$= +1.1 (*c* : 1.2 in $CHCl_3$). IR (neat) : 2952 and 1635 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.77 (s, 1H), 4.51 (s, 1H), 3.70 (d, 1H, *J*=13.0), 3.18 (s, 6H), 3.02 (m, 1H), 2.74 (m, 1H), 2.53 (d, 1H, *J*=13.0), 2.14-1.37 (m, 7H), 1.27 (s, 3H), 0.01 (s, 9H). ^{13}C NMR ($CDCl_3$) : δ 147.05, 108.35, 105.41, 66.32, 63.64, 55.38, 48.51, 48.39, 27.56, 24.09, 23.95, 17.87, -0.92.

Preparation of (8a*S*)-6-exomethylene-8-methoxy-8-methylindolizidine (2.30): To a solution of **2.29** (98.4 mg, 0.34 mmol) in 3.45 mL of dry methylene chloride, under argon, at -45°C, was added 66 μL of trimethylsilyl trifluoromethanesulfonate dropwise. The solution was stirred for 15 min and was then poured in 5 mL of water. 10% NaOH was added until the aqueous phase was basic to litmus paper. The phases were then separated and the aqueous phase was further extracted with chloroform (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate, and the solvent was removed under vacuum. Chromatography (silica gel, 8:2 hexane ethyl acetate) gave **2.30** as a clear yellow oil. Alternatively, the crude oil could be distilled using a Kugelrohr apparatus. Unfortunately, compound **2.30** was very unstable and its isolation-characterisation prouved to be very difficult. ^1H NMR ($CDCl_3$) : δ 4.84 (m, 1H), 4.78 (d, 1H, J=1.0), 3.45 (d, 1H, J=11.6), 3.25 (s, 3H), 3.06 (m, 1H), 2.62-2.45 (m, 2H), 2.18-2.01 (m, 3H), 1.88-1.52 (m, 4H), 1.10, (s, 3H). GC-MS : 182 (5, $M^{\cdot+} + H^+$), 181 (5, M^+), 166 (26), 151

(31), 134 (8), 122 (19), 97 (29), 84 (20), 70 (100).

Preparation of E- and Z-1,3-dichloro-2-trimethylsiloxy-1-propene[23] (**2.34**): To a solution of trimethylsilyl chloride (4.50 mL, 1.1 eq) and triethylamine (5.39 mL, 1.2 eq) in 12.4 mL of dry ether, under argon, at room temperature, was added a solution of 1,3-dichloroacetone (2.21 g, 17.42 mmol) in 5.0 mL of ether. The mixture was heated to reflux for 7 hrs, after which it was washed with cold water and dried with magnesium sulfate. Evaporation of the solvent followed by distillation under reduced pressure of the residual oil (57°C, 5 mmHg) gave **2.34** as a pale yellow oil (5.09 g, 80%). ^{1}H NMR ($CDCl_3$) : δ 5.64 (s, 1H), 3.95 (s, 2H), 0.30 (s, 1H).

Preparation of 3-chloro-1-trimethylsilylpropan-2-one[24,25] (**2.36**): To a solution of chloroacetic acid anhydride (4.20 g, 24.57 mmol) in 24.5 ml of a 1:1 mixture of dry tetrahydrofuran and ether, under argon, at -78°C, was added slowly, via a dropping funnel, trimethylsilylmethylmagnesium chloride (24.6 mL of a 1.0 M solution in ether, 1 eq) over a period of 30 min. The solution was stirred for 3 additional hours at -78°C and then allowed to warm up to 0°C. 50 mL of 10% NH_4Cl were added and the biphasic mixture was stirred for 15 min, after which the phases were separated. The aqueous phase was further extracted with ether (2x) and the combined organic extracts were washed with sat. aq. $NaHCO_3$, brine and dried over magnesium sulfate. Evaporation of the solvent followed by distillation under reduced pressure (29°C, 5 mmHg) of the residual oil gave **2.36** in 33% (1.31 g). ^{1}H NMR ($CDCl_3$) : δ 4.00 (s, 2H), 2.42 (s, 2H), 0.14 (s, 9H).

Preparation of 1-chloro-2-trimethylsiloxy-2-propene[24,25] (**2.37**): To a solution of ketone **2.36** (0.12 g, 0.71 mmol) in benzene, under argon, at room

temperature, was added tetrakis(triphenylphosphine)palladium(0) (41.2 mg, 0.05 eq) and the solution was stirred for 1 hr after which the solvent was evaporated under vacuum. 2.37 was used as such for all subsequent reactions. ^{1}H NMR ($CDCl_3$) : δ 4.44 (d, 1H, *J*=1.5), 4.26 (s, 1H, *J*=1.5), 3.89 (s, 2H), 0.24 (s, 9H).

Preparation of 1,3-dichloro-2-propyl alkoxymethyl ethers[26,27] (2.39a-c): In a 25 mL flask equipped with a Vigreux column which is itself mounted with a small distillation apparatus, were mixed epichlorohydrine (**2.38**) (8.45 mL, 0.108 mol), chloromethyl alkyl ether (**2.39a** methyl : 6.84 ml, **2.39b** ethyl : 8.36 ml, **2.39c** benzyl : 12.50 ml; 1 eq) and tetrabutylammonium chloride (1.20 g, 0.04 eq). The heterogeneous mixture was heated at 30°C for 20 hrs and then distilled under reduced pressure to give clear yellow oils. **2.39a** : 85°C under 15 mmHg (15.14 g, 81%). ^{1}H NMR ($CDCl_3$) : δ 4.74 (s, 2H), 3.98 (quintet, 1H, *J*=5.1), 3.72 (d, 4H, *J*=5.1), 3.42 (s, 3H). **2.39b** : 95°C under 15 mmHg (14.33 g, 71%). ^{1}H NMR ($CDCl_3$) : δ 4.79 (s, 2H), 4.00 (quintet, 1H, *J*=5.2), 3.72 (d, 4H, *J*=5.2), 3.66 (q, 2H, *J*=7.2), 1.22 (t, 3H, *J*=7.2). **2.39c** : 122°C under 0.015 mmHg (15.99 g, 71%). ^{1}H NMR ($CDCl_3$) : δ 7.35 (m, 5H), 4.89 (s, 2H), 4.68 (s, 2H), 4.06 (quintet, 1H, *J*=5.0), 3.73 (d, 4H, *J*=5.0).

Preparation of 1-chloro-2-alkoxymethoxy-2-propenes[26,27] (2.40a-c): 2.40a : To **2.39a** (15.14 g, 0.088 mole) was added finely powdered sodium hydroxide (5.25 g, 1.5 eq) and tetrabutylammonium hydrogen sulfate (0.75 g, 0.05 eq). The flask was equipped with a Vigreux column mounted with a small distillation apparatus. The heterogeneous mixture was heated until **2.40a** distilled : 60°C under 15 mmHg (9.56 g, 80%). ^{1}H NMR ($CDCl_3$) : δ 5.01 (s, 2H), 4.40 (s, 2H), 3.99 (s, 2H), 3.44 (s, 3H). **2.40b** and **c** were prepared exactly the same way. **2.40b** : 58°C under 10 mmHg (82%). ^{1}H NMR ($CDCl_3$) : δ 5.05 (s, 2H), 4.40 (m, 2H), 3.97 (s, 2H), 3.68 (q, 2H, *J*=7.0), 1.22 (t,

3H,*J*=7.0). **2.40c** : 102°C under 0.03 mmHg (70%). ^{1}H NMR ($CDCl_3$) : δ 7.34 (m, 5H), 5.13 (s, 2H), 4.68 (s, 2H), 4.49 (d, 1H, *J*=2.2), 4.44 (d, 1H, *J*=2.2), 4.00 (s, 2H).

Preparation of (2*S*)-1-(2'-alkoxymethyloxy-2'-propenyl)-2-dimethoxymethylpyrrolidines (2.41a-c): 2.41a : To a solution of allyl chloride **2.40a** (0.39 g, 2.83 mmol) in 5.67 mL of 1,4-dioxane were added successivly dimethoxymethylpyrrolidine (**2.22**) (0.35 ml, 1 eq) and powdered sodium hydroxide (0.26 g, 2.3 eq). The heterogeneous mixture was heated to 80°C for 6 hrs after which it was taken up in methylene chloride. Water was added and the phases separated. The aqueous phase was extracted with methylene chloride (2x) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvents and purification by flash chromatography (silica gel, 3% methanol/methylene chloride) gave **2.41a** as a colourless oil (0.32g, 53%). ^{1}H NMR $CDCl_3$: δ 4.97 (s, 2H), 4.24 (d, 1H, *J*=1.8), 4.19 (d,1H, *J*=1.8), 4.17 (d, 1H, *J*=6.0), 3.60 (d, 1H, *J*=13.8), 3.43 (s, 3H), 3.41 (s, 3H), 3.39 (s, 3H), 3.09 (m, 1H), 3.00 (d, 1H, *J*=13.8), 2.78 (m, 1H), 2.39 (m, 1H), 1.90-1.63 (m, 4H). **2.41b** and **c** were prepared exactly the same way. **2.41b** : 73% after chromatography. ^{1}H NMR ($CDCl_3$) : δ 5.01 (s, 2H), 4.24 (s, 1H), 4.18 (s, 1H), 4.16 (d, 1H, *J*=5.8), 3.64 (q, 2H, *J*=7.2), 3.59 (d, 1H, *J*=13.9), 3.42 (s, 3H), 3.39 (s, 3H), 3.10 (m, 1H), 3.00 (d, 1H, *J*=13.9), 2.78 (m, 1H), 2.38 (m, 1H), 1.90-1.60 (m, 4H). **2.41c** : 77% after chromatography. ^{1}H NMR ($CDCl_3$) : δ 7.32 (m, 5H), 5.10 (s, 2H), 4.64 (s, 2H), 4.34 (s, 1H), 4.23 (s, 1H), 4.18 (d, 1H, *J*=5.8), 3.62 (d, 1H, *J*=14.0), 3.43 (s, 3H), 3.39 (s, 3H), 3.12 (m, 1H), 3.02 (d, 1H, *J*=14.0), 2.79 (m, 1H), 2.40 (m, 1H), 1.90-1.65 (m, 4H).

Attempted preparation of (8a*S*)-6-keto-8-methoxyindolizidine (2.42): The following experimental procedure is typical of the conditions tried : to a solution of methoxymethyloxy enol ether **2.41a** (0.11g, 0.43 mmol) in dry methylene chloride (4.3

mL), at -78°C, under argon, was added the Lewis acid (1, 2, 5 and 10 eq were tried with different acids : see **Table 2.9**). The solution was stirred at -78°C (or higher) during variable amounts of time. The reaction was followed both by t.l.c. and gas chromatography (small aliquots were taken out of the reaction mixture and the Lewis acid was neutralised with either sat. aq. $NaHCO_3$, sat. aq. Na_2CO_3 or 10% NaOH : there seemed to be no difference depending on which quenching method was used in the reaction of **2.41a** and **b**; there was a difference in the ratio of ketone **2.43** and unidentified product in the reaction of **2.41c**). After workup (neutralisation with one of the aqueous bases mentionned previously and extraction with methylene chloride), only ketone **2.43** could be isolated : ^1H NMR ($CDCl_3$) : δ 4.19 (d, 1H, J= 5.7), 3.85 (d, 1H, J= 12.8), 3.40 (s, 3H), 3.37 (s, 3H), 3.37 (m, 1H), 3.16 (m, 1H), 2.80 (m, 1H), 2.42 (m, 1H), 2.13 (s, 3H), 2.03-1.69 (m, 4H). GC-MS : 202 (12, $M^{\cdot+} + H^+$), 170 (26), 158 (23), 126 (100), 113 (5), 69 (6). The unidentified product from the reaction of **2.41c** could never be isolated.

Preparation of 3-trimethylsilylpropynol[29] (**2.45**): Powdered magnesium (8.10 g, 2.8 eq) was suspended in 171 mL of dry tetrahydrofuran in a 500 mL three-necked flask equiped with a mechanical stirrer, a condenser and a thermometer. To this suspension, at r.t., under argon, was added slowly bromoethane (25.1 mL, 2.8 eq) over a 1 hr period ($T°_{sol.}$= 50°C or less). When the addition was completed, the solution was heated at 50°C for 1 hr and cooled down to 5°C. 2-propynol (6.73 g, 0.12 mmol) in 7 mL of THF was then added slowly (45 min, T°= 10°C). The solution was stirred at r.t. overnight and once again cooled down to 5°C. Chlorotrimethylsilane (42.6 mL, 2.8 eq) was then added (T°= 25°C or less) and the solution was refluxed for 2 hr. It was cooled to r.t. and 133 mL of 1.4 M H_2SO_4 were added. After 15 min, the reaction mixture was poured in 200 mL of ether and the phases were separated. The aqueous phase was

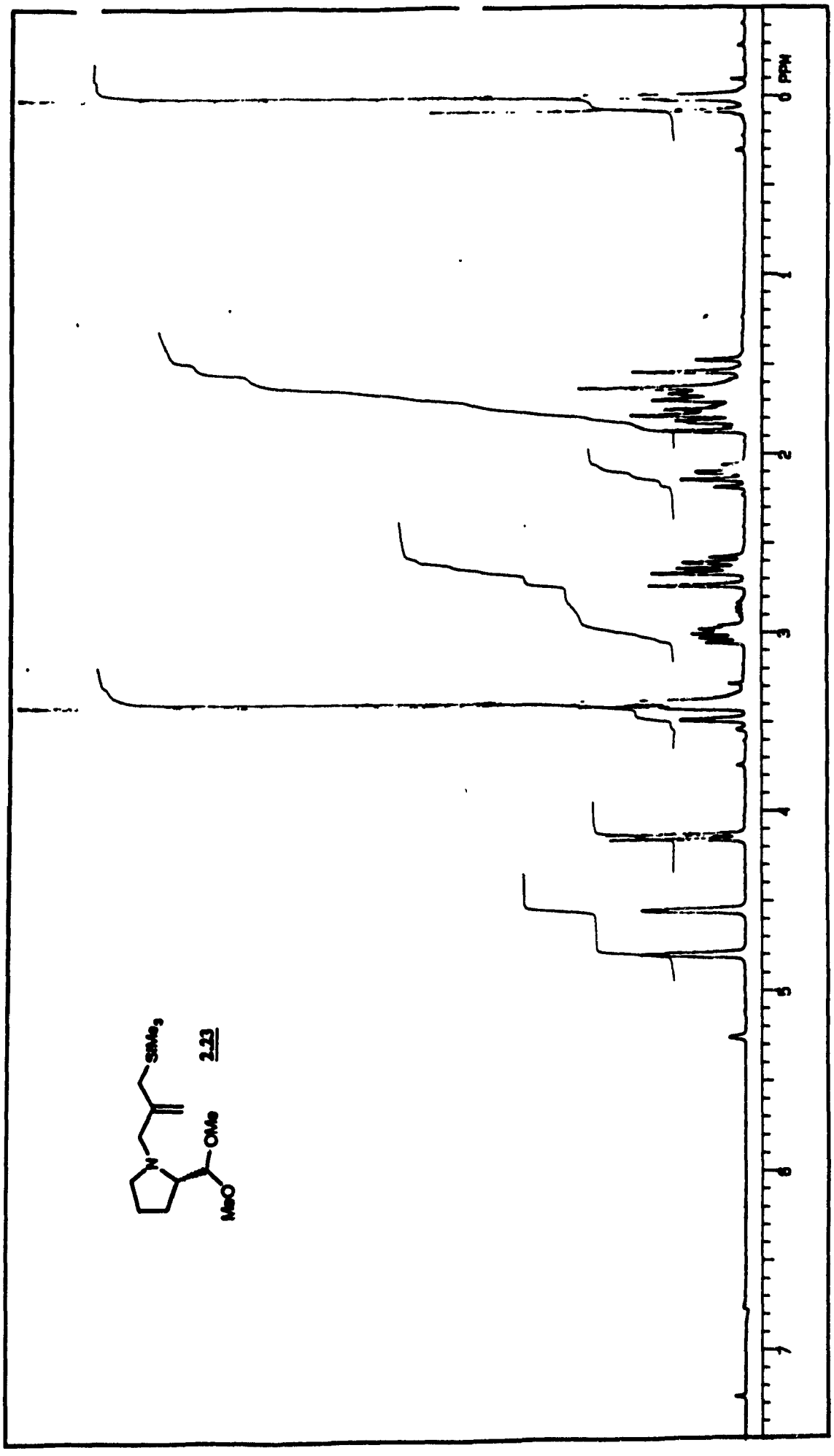
extracted with ether (2x) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents was followed by distillation of the crude oil (66-68°C, 15 mmg) to give 11.75 g (76%) of **2.45** as a colorless oil. IR (neat) : 3304 (broad), 2960, 2178 and 1042 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.26 (s, 2H), 0.17 (s, 9H).

Preparation of (E)-3-trimethylsilylpropenol[29] (2.46): To a solution of sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al : 3.71 mL, 1.6 eq, 3.4 M in toluene) in 5 mL of dry ether, at 0°C, under argon, was added alcohol **2.45** (1.01 g, 7.82 mmol : in 5 mL of ether). The solution was stirred at 0°C for 10 min, warmed up at r.t. for 1 hr and cooled down to 0°C. 3.6 M H_2SO_4 (25 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2x) and the combined organic extracts were washed with water (1x), brine and dried over magnesium sulfate. Filtration and evaporation of the solvents gave 2.46 as a colourless oil (0.68 g, 67%) which was not further purified. ^1H NMR ($CDCl_3$) : δ 6.18 (dt, 1H, *J*= 4.3, 18.8), 5.91 (dt, 1H, *J*= 1.6, 18.8), 4.17 (dd, 1H, *J*= 1.6, 4.3), 1.47 (bs, 1H), 0.07 (s, 9H).

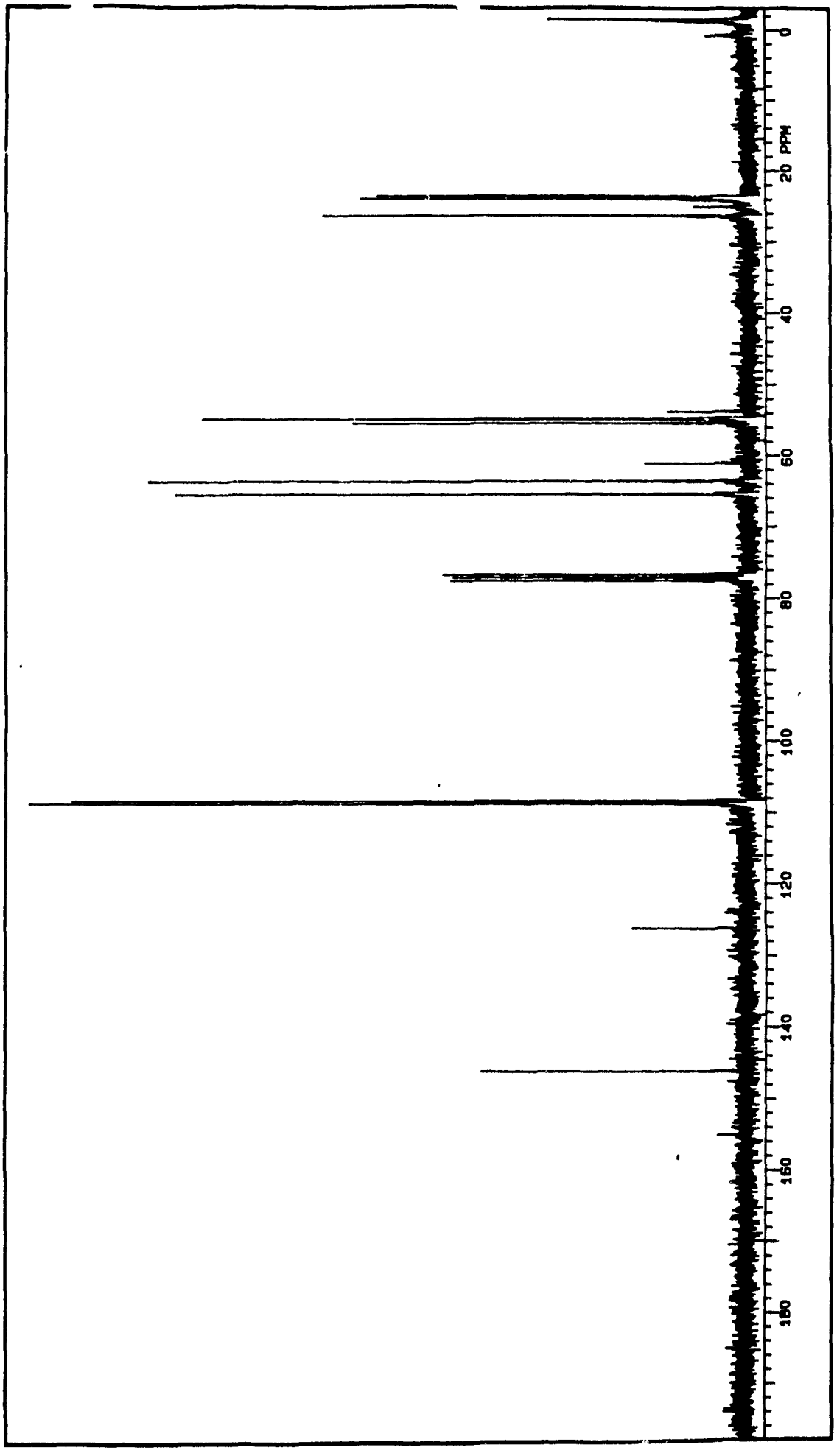
Preparation of (E)-3-trimethylsilylpropeny mesylate (2.47): To a solution of alcohol **2.46** (0.22 g, 1.72 mmol) in 3.4 mL of dry methylene chloride, under argon, at 0°C, were added successively triethylamine (0.41 mL, 1.7 eq) and methylsulfonyl chloride (0.20 mL, 1.5 eq). The solution was stirred at 0°C for 45 min after which it was poored in ether. It was then washed with 5% HCl (1x), water (1x), brine and dried over magnesium sulfate. Filtration and evaporation of the solvents gave mesylate **2.47** as a pale yellow oil (0.33 g, 92%). ^1H NMR ($CDCl_3$) : δ 6.10 (m, 2H), 4.71 (dd, 2H, *J*= 1.2, 2.6), 3.01 (s, 3H), 0.09 (s, 9H).

Preparation of (E)-(2*S*)-1-(3'-trimethylsilyl-2'-propenyl)-2-dimethoxymethylpyrrolidine (2.48): To a solution of mesylate **2.47** (0.23 g, 1.12 mmol) in 4.6 mL of dry acetonitrile, under argon, at r.t., were added successively finely powdered potassium carbonate (0.15 g, 1 eq) and chiral aminoacetal **2.22** (0.18 g, 1.1 eq) and the solution was stirred overnight. It was then poured in water and the phases were separated. The aqueous phase was extracted with methylene chloride (3x) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents was followed by flash chromatography purification (silica gel, 8:2 hexanes/ethyl acetate) to give amine **2.48** as a colourless oil (0.21 g, 73%). ^{1}H NMR ($CDCl_3$) : δ 6.13 (ddd, 1H, *J*= 5.1, 6.8, 18.5), 5.78 (dt, 1H, *J*= 1.5, 18.5), 4.18 (d, 1H, *J*= 5.6), 3.65 (ddd, 1H, *J*= 1.5, 5.1, 6.8), 3.41 (s, 3H), 3.39 (s, 3H), 3.13-2.94 (m, 2H), 2.65 (m, 1H), 2.26 (m, 1H), 1.90-1.61 (m, 4H), 0.05 (s, 9H).

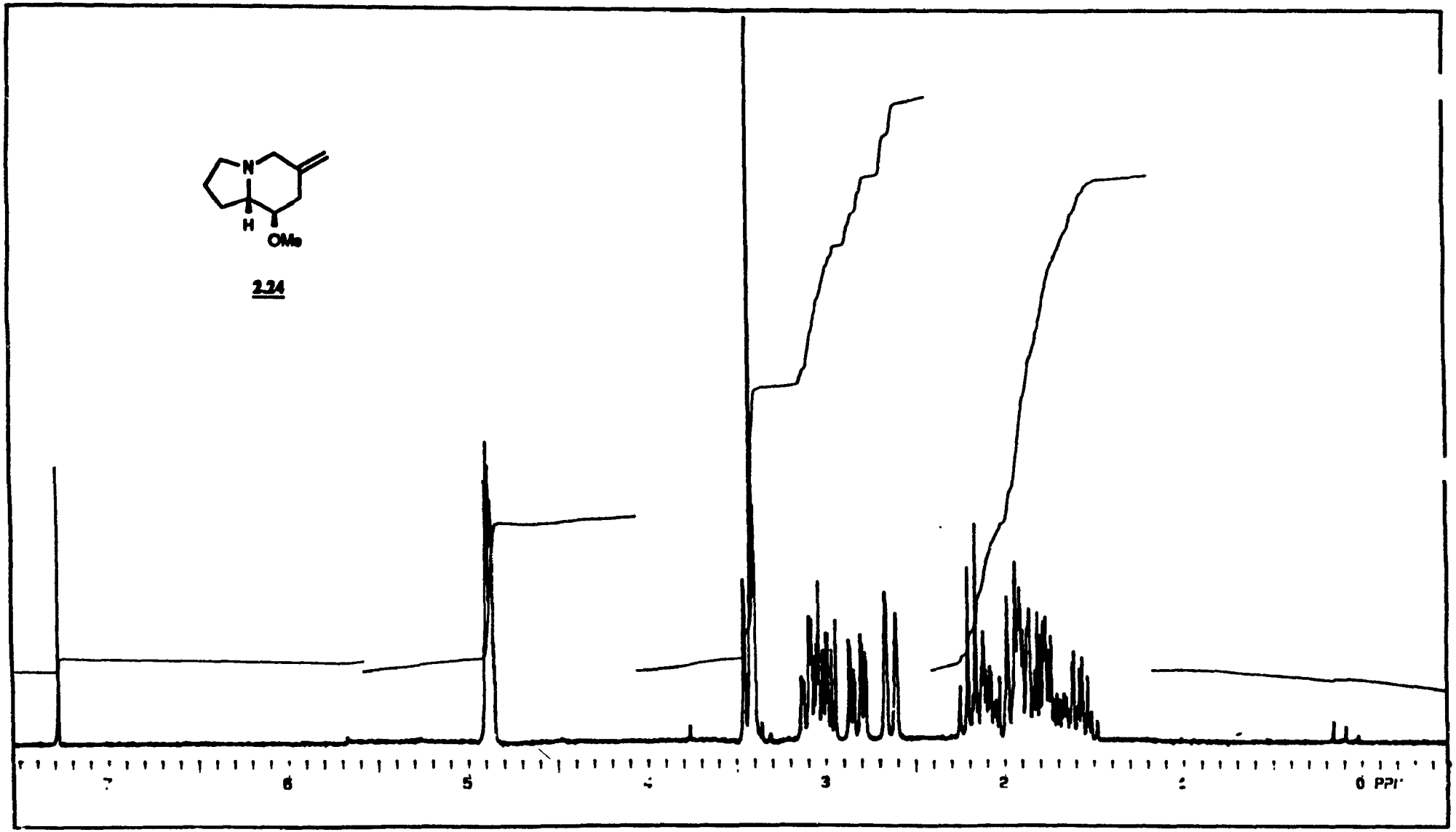
(2S)-1-(2'-((trimethylsilyl)methyl)-2'-propenyl)-2-dimethoxymethylpyrrolidine (2.23)



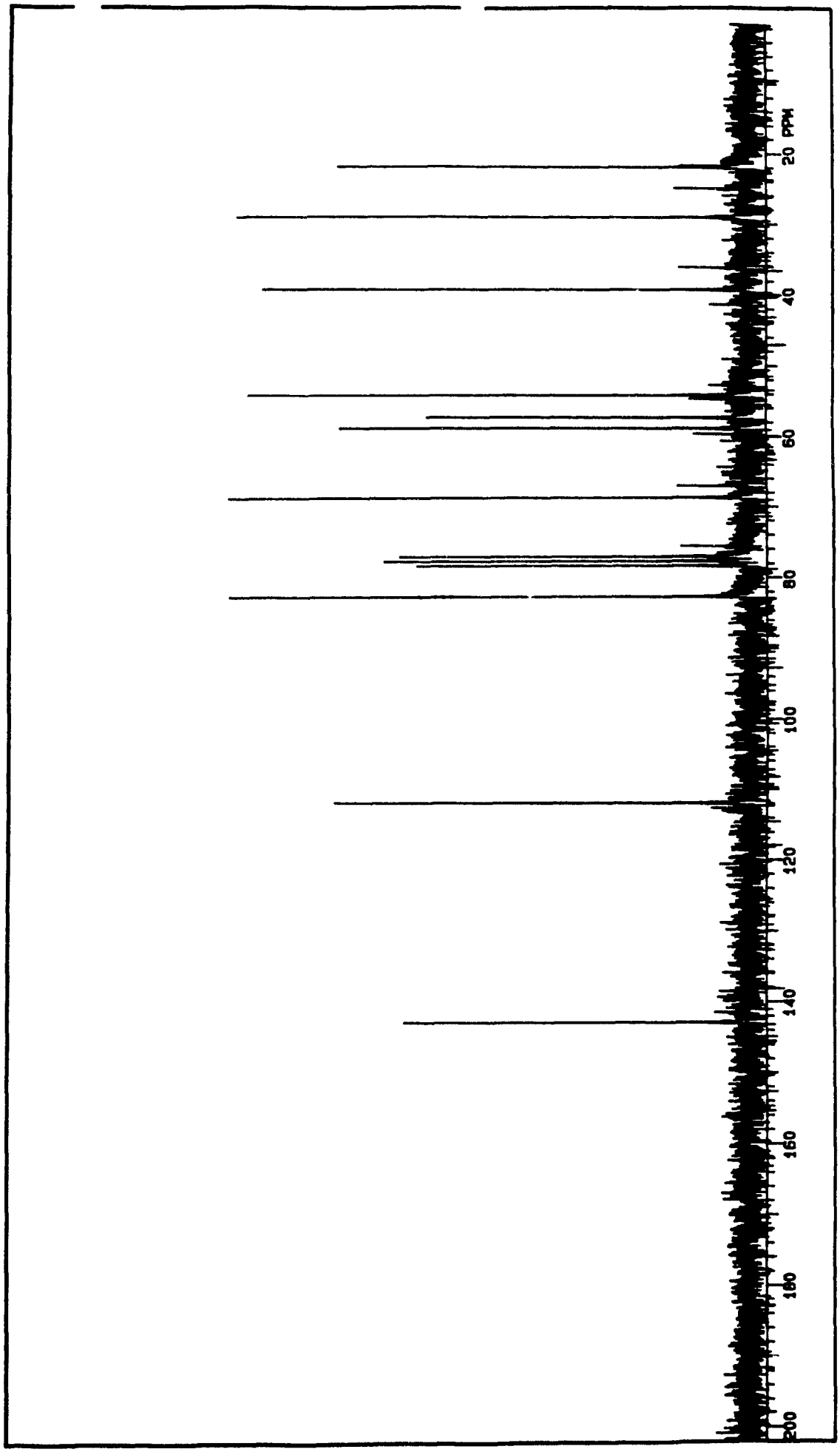
(2*S*)-1-(2'-((trimethylsilyl)methyl)-2'-propenyl)-2-dimethoxymethylpyrrolidine (2.23)



(8*R*,8a*S*)-6-exomethylene-8-methoxyindolizidine (2.24)



(8*R*,8a*S*)-6-exomethylene-8-methoxyindolizidine (2.24)



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CHAPTER 3

HYDROXYLATED PROLINE DERIVATIVES.

3.0 Introduction :

In **Chapter 4**, it will be demonstrated how the intramolecular nucleophilic cyclisation strategy will indeed give hydroxylated indolizidines, in good yield and short sequences. This method also will allow us to introduce oxygenated functionalities in the *six membered ring* of the system. In the present chapter, the introduction of hydroxyl groups in the *five membered ring* will be studied. Such derivatives will have to be easily transformed into the aldehyde required for the coupling with the [(arylthio)allyl]titanium reagent that will be used (see **Chapter 4, Scheme 4.2**).

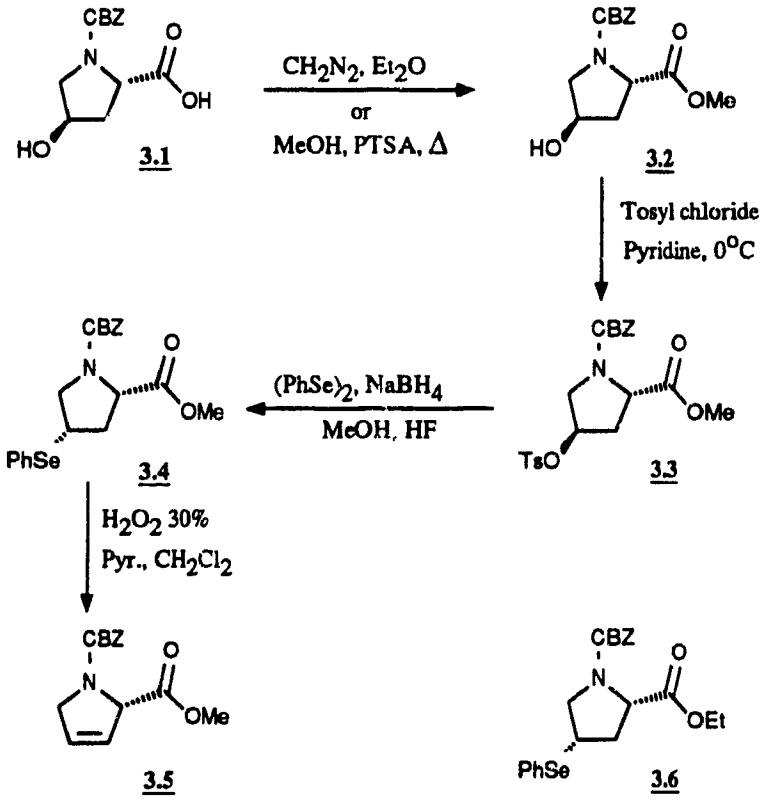
3.1 Dihydroxylated proline derivatives for the synthesis of Swainsonine :

Robertson and co-workers studied the hydroxylation and epoxidation of a variety of 3,4-dehydroproline derivatives[1,2]. As shown in these reports, 3,4-dehydroprolines could be hydroxylated and epoxidised easily and in good yield, *but the oxygen(s) were only delivered trans to the already existing ester group.* This particular stereoselectivity is not the one required for the synthesis of swainsonine, the molecule of interest. Hence, a new methodology had to be designed for the synthesis of an *all cis* dihydroxylated proline. These derivatives of the common amino acid L-proline have been synthesised in the past[3a-d], but most of the syntheses used sugars as starting materials. Other works showed very low yields and/or selectivities. Thus, a highly stereoselective preparation of these compounds, starting from protected

3,4-dehydroproline was desired.

3.11 Synthesis of a general precursor : an iodohydrin :

The first step was to synthesise this dehydroproline derivative in high yield. It was decided that the synthesis of Benn and Rüeger[4] was appropriate for the needs of the project. **Scheme 3.1** illustrates this particular synthesis which starts with N-benzyloxycarbonyl-*trans*-4-hydroxy-L-proline 3.1. The acid group of 3.1 was

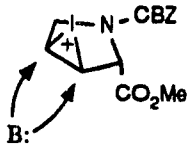


Scheme 3.1

protected as an ester either with diazomethane or by the Fisher esterification method. Both of the two methods afforded high yields of the methyl ester 3.2 (90% and 85%,

respectively). The free hydroxyl group was then transformed into a suitable leaving group by tosylation (tosyl chloride/pyridine), but unfortunately it seemed to be impossible to recrystallise tosylate **3.3**. Instead, chromatography was required, and the yield dropped from 91%[4] to a maximum of 70%. Nevertheless, the preparation was continued with the displacement of the tosylate of **3.3** by the phenylselenide anion, generated by the reduction of diphenyl diselenide with sodium borohydride in methanol. Even though the authors claimed that the major product of this reaction was phenylselenide methyl ester **3.4**, only a moderate yield of the ethyl ester **3.6** was obtained. In a footnote, they explained that the transesterification could be avoided by using a mixture of methanol and tetrahydrofuran as the solvents. When this modification was applied, methyl ester **3.4** was obtained in good yield. Oxidation of the selenium atom with hydrogen peroxide followed by elimination afforded N-benzyloxycarbonyl-3,4-dehydroproline methyl ester **3.5**.

The next step was to add substituents to the double bond in an indirect fashion so that the introduction would be *cis* to the ester group. One way to accomplish such an introduction would be to block the *trans* face with a large enough group so that any incoming nucleophile would have to approach from the opposite face, that is, the same face as the ester. The most obvious reaction was the complexation of iodine with the double bond followed by nucleophilic opening of the iodonium complex (see **Scheme 3.2**). The literature contains a vast number of methods to accomplish this type of

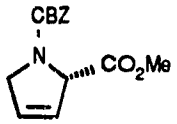


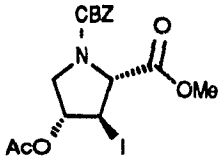
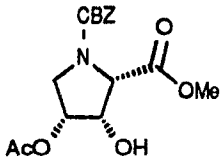
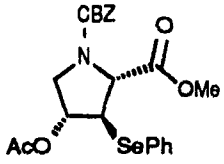
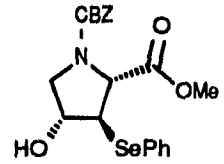
Scheme 3.2

process[5a-d]. **Tables** 3.1 and 3.2 list the different methods attempted with ester **3.5** or its parent acid **3.7** respectively (the hydrolysis was accomplished by treatment of **3.5** with

Table 3.1

Reaction of **3.5** :

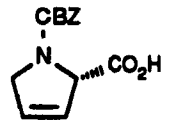


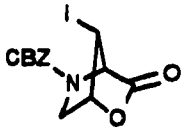
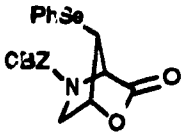
Conditions	Desired product	Result*
I_2, AgOAc, CH_3CO_2H, Δ		Pyrrole **3.8**
I_2, TlOAc, CH_3CO_2H, Δ	"	Pyrrole **3.8**
I_2, AgOAc, CH_3CO_2H, H_2O, Δ		Pyrrole **3.8**
PhSeBr, AgOAc, CH_2Cl_2,		S.M. **3.5**
PhSeBr, TlOAc, CH_3CO_2H, Δ	"	Pyrrole **3.8**
N-Phenylselenyl phtalimide, CH_2Cl_2, H_2O, PTSA		S.M. **3.5**

*S.M. = starting material

sodium hydroxide in methanol/water : 92%). Acid **3.7** was used in order to perform the

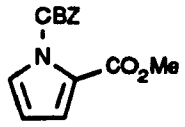
Table 3.2

Reaction of 3.7 : 

Conditions	Desired product	Result*
I_2, KI, $NaHCO_3$, H_2O		S.M. 3.7
PhSeBr, Et_3N, CH_2Cl_2		S.M. 3.7

*S.M. = starting material

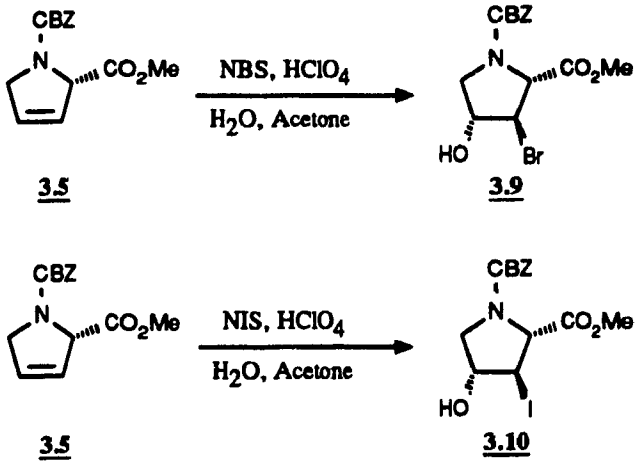
intramolecular reaction (iodolactonisation or similar reactions). Unfortunately, none of these reactions gave addition products. In some instances, the starting material was recovered, and in most cases, the aromatised compound 3.8 was isolated. This aromatic



3.8

pyrrole, though, indicated that there was indeed some addition to the double bond, but that the reaction conditions were too severe for this substrate to survive. Thus, milder conditions were required.

Addition of hypobromous acid to double bonds is a known reaction. It has been studied by Marples and Saint[6] in 1982. The main advantage of this method is the mild conditions (0°C in aqueous acetone). The hypobromous acid is generated *in situ* by the reaction of perchloric acid and N-bromoamides or imides. Since mild conditions were required for the present work, this reaction was attempted. Thus, addition of N-bromosuccinimide to a solution of alkene **3.5** in aqueous acetone and 14% perchloric acid gave, after a few minutes and in excellent yield, the bromohydrin **3.9** (**Scheme 3.3**). In order to make an even more reactive compound, the same reaction was performed, but with N-iodosuccinimide (prepared by the addition of the silver salt of succinimide to a solution of iodine in acetone[7]) instead of the bromo reagent. Here again, iodohydrin **3.10** was obtained in excellent yield and after a very short time. The ^{1}H NMR spectra of these



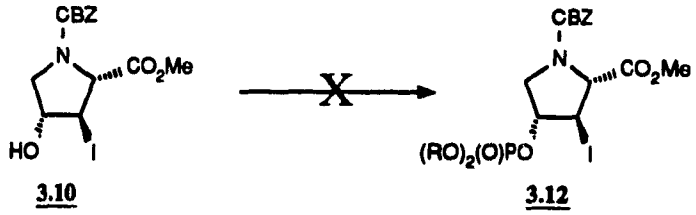
Scheme 3.3

molecules on the other hand, were quite complicated. It was first thought that the reaction was giving a mixture of isomers, even though there was only one spot by t.l.c., because of the numerous peaks observed. It is only after a very carefull inspection of the spectra that the regio and stereospecificity of the reaction was discovered. In fact, the

spectra were complicated not because of the regio and stereo outcome of the reaction, but because of the two possible rotamers of the carbamate protecting group. The different intensities were due to an unequal population distribution of these rotamers. When **3.10** was dissolved in deuterated toluene and warmed up *in the NMR probe*, the peaks on the spectrum collapsed and gave a simpler pattern.

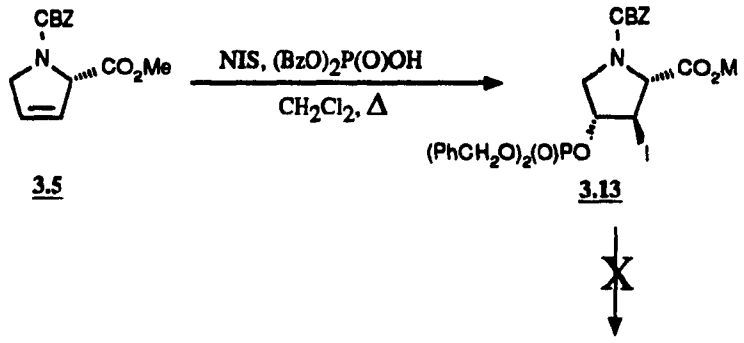
3.12 Reactions of the iodohydrin or its derivatives :

It was very quickly realised that iodohydrin **3.10** was as easily decomposed as it was formed. After the alcohol was protected as its acetate, any attempts to form the diol failed. In fact, the only isolated product from all of these reactions was the pyrrole **3.8**. It must be said here, that most of the reactions attempted employed strongly acidic or basic conditions. Under milder conditions, only starting material was recovered. In order to facilitate the displacement of the iodine atom, it was thought that an intramolecular reaction would be helpful. Indeed, if the nucleophile was to come from a group attached to the molecule, the energy required for such a displacement would be less than the one required for the intermolecular case, thus rendering the conditions milder. Replacing the acetate protecting group of **3.11** by a group having a free hydroxyl moiety was the first idea that was tried. It seemed that phosphorus would be a good choice. Its introduction could be accomplished with a reaction similar to the one used for the acetylation, that is, through the use of a chlorophosphate (phosphorochloridate). Unfortunately, such an attempt was unsuccessful (**Scheme 3.4**). Another way of introducing the phosphate group was to start with compound **3.5** and perform a reaction similar to the iodohydrin formation, but replacing the nucleophile (water in this case) by a dialkyl monohydroxy phosphate. Subsequent deprotection of one (or two) of the alkyl group(s) would lead to the desired intermediate. **Scheme 3.5** shows that this reaction



Scheme 3.4

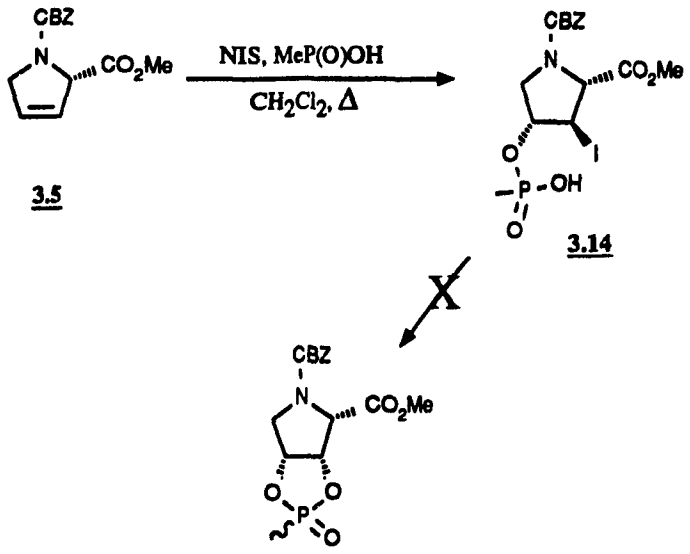
was indeed feasible and that compound **3.13** could be isolated in good yield. Unfortunately, deprotection of the phosphate failed.



Scheme 3.5

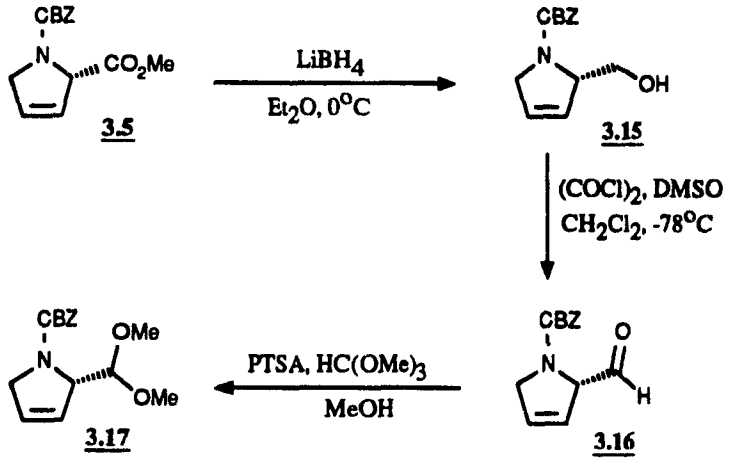
In order to introduce a phosphate derivative that already had a free hydroxyl group, the same reaction was attempted, but with alkylphosphonic acids instead of dialkyl phosphates. Indeed, these contain two free hydroxyl groups : one of them could react with the double bond (with NIS), and the second one would be ready for cyclisation. **Scheme 3.6** illustrates this particular reaction. Not surprisingly, attempts to cyclise compound **3.14** gave only the pyrrole **3.8**.

Molecules such as **3.10** and **3.13** are expected to be easily aromatised due to the fact that the proton α to the ester group is acidic and can induce dehydrohalogenation



Scheme 3.6

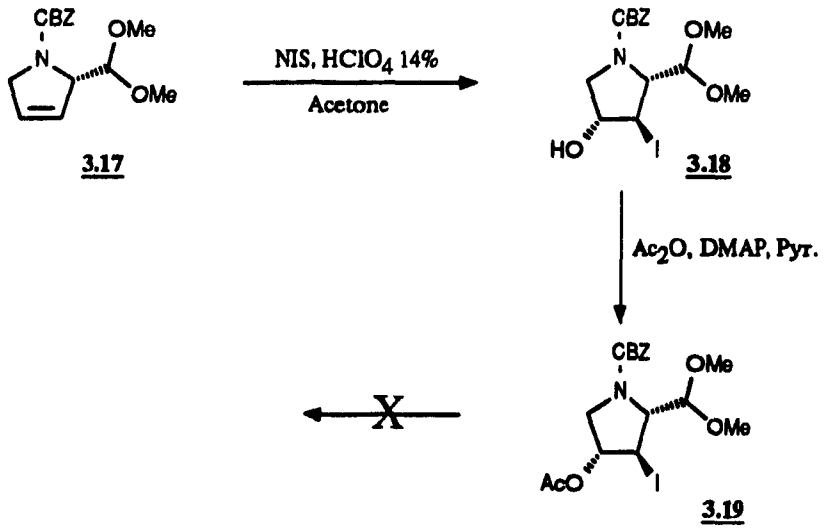
or elimination. To avoid such a potential problem, it was thought that a molecule similar to 3.5, *but having a non-acidic proton*, would behave differently and would not aromatise. Since the corresponding dimethyl acetal had to be synthesised for the cyclisation step (an aldehyde is required, see **Chapter 4**), and since such an acetal does not have an acidic α-proton, it was decided that this would be a good candidate for the indirect dihydroxylation. Thus, reduction of the ester group of 3.5 gave alcohol 3.15 in good yield (**Scheme 3.7**). Attempts to form the iodohydrin directly from protected 3.15 gave a complex mixture of products, even when the very bulky *tert*-butyldiphenylsilyl protecting group was used. It is possible that in these protected alcohols, the bulk is too far away from the ring and allows the iodine to complex on both sides of the olefin. Thus, alcohol 3.15 was oxidised to aldehyde 3.16 using Swern's methodology to give an excellent yield of the crude aldehyde. Acetalisation of 3.16, on the other hand, gave only the dimethyl acetal 3.17 in medium yield (55%). After a careful examination of these



Scheme 3.7

last two steps, it was found that the oxidation was a very unclean reaction. Attempts to modify the conditions (temperature, number of equivalents) did not improve the yield of the reaction. Other oxidising agents such as Corey's PCC[8] or Ley's perruthenate catalysed oxidation[9] were attempted without success. Apparently, the presence of the double bond in **3.15** considerably modified its reactivity and/or stability. The best that could be achieved was a reasonable 71% for both steps.

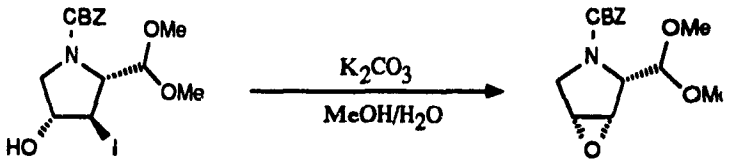
Iodohydrin formation proceeded smoothly to give a very good yield of compound **3.18**, which was protected as the acetate **3.19** (**Scheme 3.8**). It was rapidly found though, that iodoacetate **3.19** was not very stable under the conditions used previously for the formation of the *cis*-diol, since these conditions also resulted in the deprotection of the dimethyl acetal. Since a proton α to an aldehyde is even more acidic than a proton α to an ester, aromatisation proceeded rapidly. Clearly, the direct conversion of the iodoacetate (or iodohydrin) to the diol had to be abandoned. More stable intermediates had to be synthesised, or milder conditions had to be found.



Scheme 3.8

3.13 Indirect oxidative opening of an epoxide :

Oxidative opening of an epoxide is a known reaction[10a-d]. This reaction can be performed directly through the use of a reagent that opens the epoxide and is then oxidised in the reaction medium, or indirectly, through the use of a reagent that opens the epoxide and is then oxidised under another set of conditions. Both possibilities were studied. First, the indirect opening was attempted. Thus, epoxide **3.20** was easily formed by the reaction of the iodohydrin **3.18** with potassium carbonate in methanolic water (**Scheme 3.9**). The epoxide was obtained in excellent yield and purity. The fact that only one epoxide was observed (^{1}H NMR determination) confirmed the regio- and stereospecificity of the iodohydrin formation. A variety of nucleophiles were used for the opening of the epoxide. All of them were chosen because of the possibility of oxidising them later to the hydroxy ketone, which would then be reduced to the desired



3.18 3.20

Scheme 3.9

cis-diol. Among them are "PhS^-"(a, see below)[11], "$PhSe^-$"(b)[12], "N_3^-"(c)[13] and "Me_3Sn^-"(d)[14]. They all gave very good yields of the two possible alcohols (regioisomers) in an approximative ratio of 1:1 (**Scheme 3.10**).

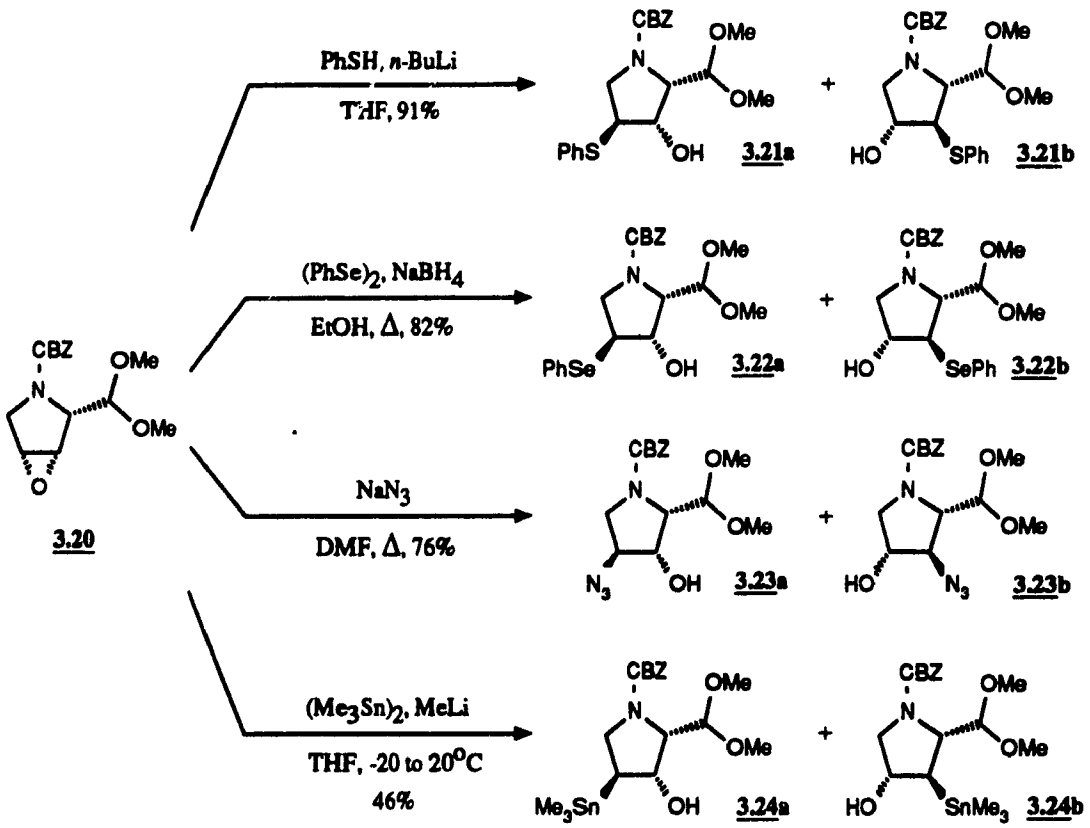
The different oxidising methods used to convert compounds 3.21-3.24 to the hydroxy ketones (or mostly acetoxy ketones) are listed below. Most of the reactions were a :empted on the corresponding acetates (acetic anhydride, DMAP/pyridine : (a) 95%, (b) 95%, (c) 99% and (d) 75% respectively) :

(a) Halogenation (NCS or NBS) of the sulfur atom of the acetates of 3.21a and b followed by mercury (II) iodide catalysed hydrolysis of the sulfonium salt (in CH_3CN/H_2O)[15], or...

(a) Sulfoxide formation (m-CPBA/CH_2Cl_2; on the acetates : 93%) followed by a Pummerer type rearrangement (trifluoroacetic anhydride, heat)[16].

(b) Selenoxide formation (m-CPBA/CH_2Cl_2; on the acetates) followed by a Pummerer type rearrangement (trifluoroacetic anhydride, heat)[17].

(c) Reduction of the azide to the amine (PPh_3, H_2O/THF). Oxidation of the



Scheme 3.10

amine to the imine followed by hydrolysis.[18]

(d) Oxidative destannylation (CrO_3.2Pyr/CH_2Cl_2)[14].

All of the oxidations failed to give the desired dihydroxylated compounds.

3.14 Direct oxidative opening of an epoxide :

Another possible route to the desired hydroxy ketones is the direct oxidative

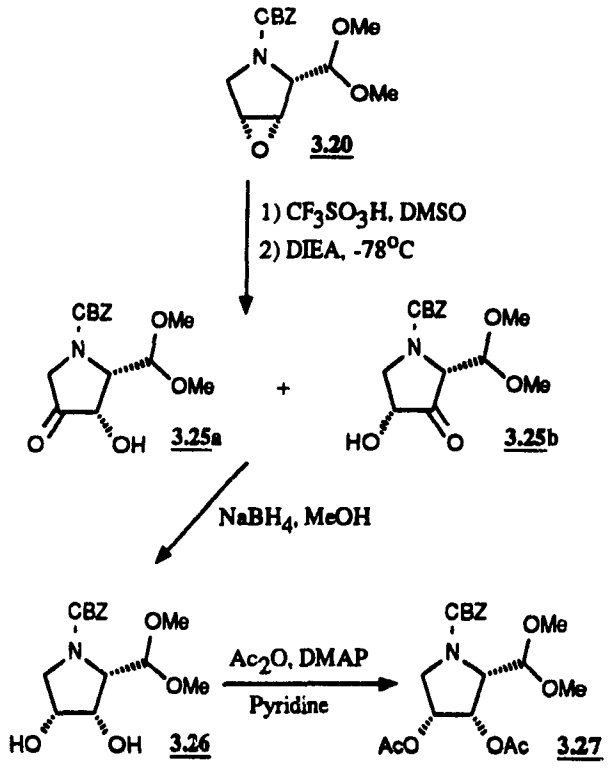
opening of epoxide 3.20. Indeed, Trost and Fray[19] described such a method which is a modification of the well-known reaction developed by Swern[10b,c]. In this report, the epoxides are dissolved in dimethyl sulfoxide and a solution of trifluoromethanesulphonic acid in DMSO is added slowly. The sulfonium salt thus formed is then treated with diisopropylethylamine to give the hydroxy ketones. The reported yields vary from poor to good.

When these conditions were applied to epoxide 3.20, the reaction time was considerably longer (24 hours compared to the 1 hour reported by Trost) and the crude product was a complex mixture of many unidentified compounds. A major spot was isolated, which was likely a mixture of more then one compound, probably the two regioisomers 3.25a and b. The ^{1}H NMR of these compounds was not very informative. Reduction of this mixture with sodium borohydride gave one compound in moderate yield (indeed, reduction of the two different ketones provided the same diol 3.26), which was protected as its diacetate 3.27 (see **Scheme 3.11**).

^{1}H NMR and decoupling, as well as two dimensional NMR experiments (COSY and HETCOR) aided in the assignment of the relative stereochemistry of diacetate 3.27. This route provided therefore an entry to the cis-dihydroxylated proline derivatives, even though the overall yield was moderate. Since it did not seem possible in our hands to improve the method (and thus accumulate large amounts of this intermediate) and since there were still many steps to perform, the total synthesis of swainsonine using this particular approach was abandoned.

3.2 Monohydroxylated proline derivatives for the synthesis of Castanospermine :

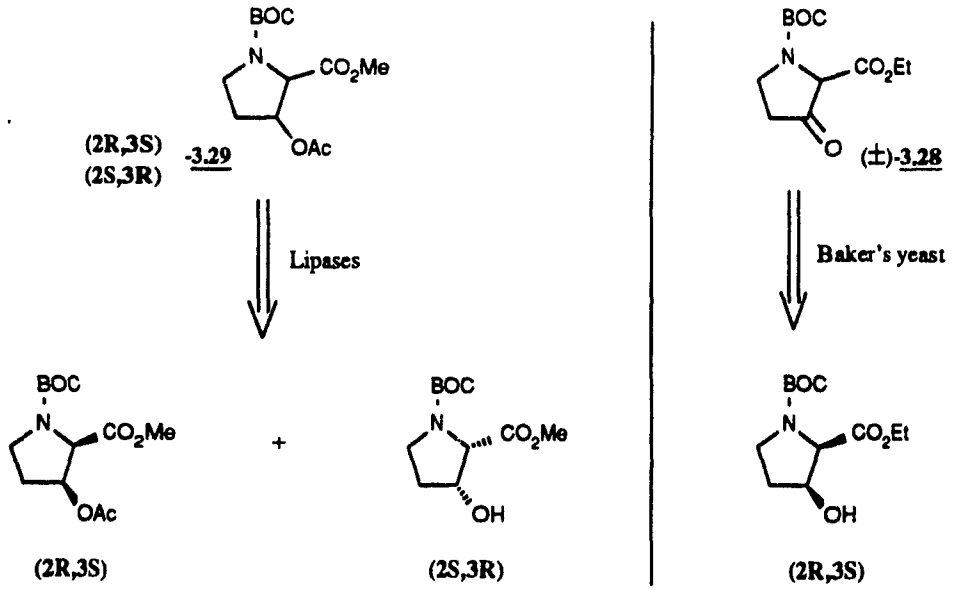
The construction of 3-hydroxylated proline derivatives is not very well documented in the literature. There are scattered reports of its syntheses, both racemic[20]



Scheme 3.11

and chiral[21,22]. It is only recently that reliable methods giving both good yields and good enantiomeric purities were published[23,24]. **Scheme 3.12** shows the two methods that have been the most successful up to now. In the first paper, Sih and co-workers studied both the microbial asymmetric reduction of racemic keto-ester **3.28** and the enantioselective hydrolysis of acetate **3.29** using microbial lipases. In both cases, the chemical yield (or percent conversion) is very good, and the enantiomeric excess is >99%. In the second paper, Sibi and Christensen improved an already known baker's yeast reduction[24] by modifying slightly the substrate and the conditions of the reduction. Here again, the chemical yield is very good and optical purity >95%.

Since the baker's yeast reduction is very easy to perform and does not require

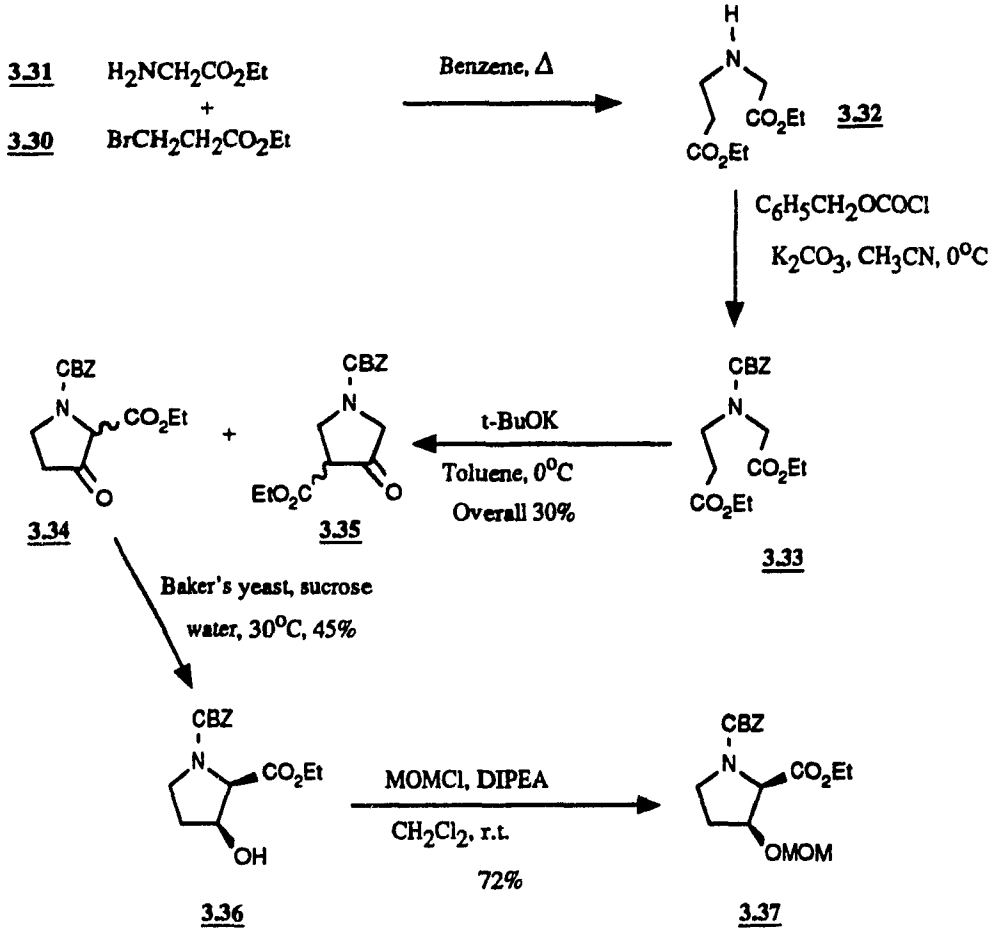


Scheme 3.12

expensive (or hardly available) microorganisms, the method of Sih was chosen. The synthesis of the keto-ester precursor is described in the literature[20,25] and was only slightly modified in order to have the CBZ and not the *t*-BOC amine protecting group.

Scheme 3.13 illustrates the synthesis of the 3-keto proline derivative. Condensation of ethyl 3-bromopropionate **3.30** with freshly prepared ethyl glycinate **3.31** was accomplished in refluxing benzene to give a good yield of the N,N-disubstituted aminodiester **3.32**. Protection of the free secondary amine with the CBZ group was carried out as in **Chapter 2** (compound **2.19**) and provided carbamate **3.33** in very good yield (80%) after distillation. The literature yield for this step was only 32%[25], which is somewhat unexpected for such an easy reaction.

Dieckmann cyclisation of **3.33** using potassium *t*-butoxide in toluene afforded



Scheme 3.13

a 1.3:1 mixture of regioisomers 3.34 and 3.35 which can be separated by distillation *and* chromatography. The results of this cyclisation step are disappointing. The minor isomer is the one required for our purposes. But since the sequence for its preparation is quite short and utilises cheap and readily available starting materials, it was nevertheless used.

Thus, baker's yeast reduction of minor isomer 3.34 (baker's yeast, sucrose,

water, 30°C, 72 hr) afforded β-hydroxy ester **3.36** in medium yield and good enantioselectivity. In order to easily prepare a sample of **3.36** (for t.l.c. comparision), **3.34** was also reduced using sodium borohydride in ethanol to give a racemic mixture of only the *cis* diastereomer in good yield. This racemic β-hydroxy ester was spectroscopically identical (^{1}H and ^{13}C NMR) with the enantiomerically pure compound. Protection of the secondary alcohol of (+)-**3.36** with the MOM protecting group gave fully protected 3-hydroxyproline derivative **3.37**. The synthesis of the required intermediate was thus completed and it was used successfully in the synthesis of castanospermine analogues, as shown in **Chapter 4**.

3.3 Experimental :

General Methods. See Chapter 2, section 2.5.

Preparation of methyl (2*S*,4*R*)-N-benzyloxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylate (3.2): To a solution of (2*S*,4*R*)-N-benzyloxycarbonyl-4-hydroxypyrrolidine-2-carboxylic acid 3.1 (10.97 g, 41.40 mmol) (Sigma) in 104 mL of dry methanol, under argon, at room temperature, was added a catalytic amount of p-toluenesulfonic acid (0.05 eq) and the solution was refluxed for 12 h. The solvent was then evaporated under vacuum and the thick oil obtained was purified by flash chromatography (silica gel, 2:8 hexane/ethyl acetate) to give 11.46 g (99%) of 3.2 : ^{1}H NMR ($CDCl_3$) : δ 7.29 (m, 5H), 5.10 (3d, 2H), 4.47 (m, 2H), 3.74 + 3.54 (2s, 3H), 3.63 (m, 2H), 2.29 (m, 2H), 2.10 (m, 1H). Compound 3.2 could also be purchased from the Sigma company.

Preparation of methyl (2*S*,4*R*)-N-benzyloxycarbonyl-4-tosyloxy-pyrrolidine-2-carboxylate[4] (3.3): To a solution of 3.2 (4.08 g, 14.59 mmol) in 40 mL of dry pyridine, under argon, at 0°C, was added p-toluenesulfonyl chloride (3.06 g, 1.1 eq) in small portions. The solution was left at 0°C for 7 days, after which the pyridine was removed under vacuum. The residue was dissolved in ether and washed successively with cold 5% HCl (3x), cold water (3x) and was dried over magnesium sulfate. The solvent was removed under vacuum, and the product was purified by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate) to give 4.24 g (67%) of pure 3.3 as a pale yellow solid : $[\alpha]^{20}_D$= -30.9° (*c* : 1.2 in $CHCl_3$). IR (neat) : 2952, 1746 and 1686 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.9-7.1 (m, 10H), 5.10 (m, 3H), 4.45 (m, 1H), 3.72 + 3.50 (2s, 3H), 3.80-3.50 (m, 2H), 2.44 + 2.42 (2s, 3H), 2.65-2.40 (m, 1H), 2.15 (m, 1H). ^{13}C

NMR ($CDCl_3$) : δ 172.33 + 172.22 (1C), 154.42 + 154.86 (1C), 145.40, 136.11 + 136.03 (1C), 133.34 + 133.28 (1C), 130.14 + 130.11 (1C), 128.52 + 128.46 (1C), 128.16, 127.92, 127.75, 77.13 + 76.70 (1C), 67.47, 57.48 + 57.21 (1C), 52.57 + 52.32 (1C), 52.46 + 52.10 (1C), 37.25 + 36.10 (1C), 21.69.

Preparation of methyl (2*S*,4*S*)-N-benzyloxycarbonyl-4-phenylselenyl-pyrrolidine-2-carboxylate[4] (3.4): To a solution of diphenyl diselenide (2.15 g, 0.7 eq) in 28 mL of dry tetrahydrofuran, under argon, at room temperature, was added sodium borohydride (0.52 g, 1.4 eq) in small portions and the solution was stirred until the evolution of hydrogen ceased. Dry methanol was then added (19 mL) and the clear yellow reaction mixture turned colourless. A solution of 3.3 (4.27 g, 9.85 mmol) in 19 mL of methanol was then added dropwise, via a double tipped needle. After the addition, the flask was equipped with a water condenser, and the solution was refluxed for 3.5 h, after which it was allowed to cool down to room temperature. The solvent was removed under vacuum, and the residue was dissolved in ether (60 mL), washed with water (2x) and dried over magnesium sulfate. Evaporation of the solvent under vacuum gave a yellow oil which was purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) to give 3.4 (2.76 g, 67%) as a colourless oil : $[\alpha]^{20}_D$= -24.3 (*c* : 1.5 in $CHCl_3$). IR (neat) : 2952, 1711 and 1690 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.70-7.13 (m, 10), 5.18 and 5.10 (#1) + 5.18 and 5.02 (#2) (2 AB systems, 2H, $J_{\#1 \text{ and } \#2}$= 8.2), 4.39 + 4.34 (2t, 1H, *J*=5.0), 4.03 (2dd, 1H, *J*= 4.0, 6.7), 3.75 + 3.57 (2s, 3H), 3.61 (m, 1H), 3.51 (2dd, 1H, *J*= 3.4, 6.7), 2.69 (ddd, 1H, *J*= 3.4, 5.0, 8.7), 2.20 (ddd, 1H, *J*= 5.0, 5.9, 8.7). ^{13}C NMR ($CDCl_3$) : δ 172.86 + 172.65 (1C), 154.83 + 154.29 (1C), 136.85 + 136.79 (1C), 135.49 + 135.41 (1C), 129.78, 128.97, 128.91, 128.73, 128.53, 128.40 + 128.30 (1C), 67.74, 59.50 + 59.28 (1C), 53.99 + 53.35 (1C), 52.90 + 52.69 (1C), 38.38 + 37.74 (1C), 37.64 + 37.02 (1C).

Preparation of methyl (2*S*)-N-benzyloxycarbonyl-3,4-dehydropyrrolidine-2-carboxylate[4] (3.5): To a solution of 3.4 (8.68 g, 20.74 mmol) in 104 mL of dry methylene chloride was added pyridine (2.51 mL, 1.5 eq). The solution was cooled to 0°C and hydrogen peroxide (30% in water : 3.31 mL, 2.5 eq) was slowly added. The solution was vigorously stirred for 4 h while the temperature was allowed to slowly warm up to 25°C. Dilution in methylene chloride (50 mL) followed by successive washing with 5% HCl, sat. aq. sodium bicarbonate, brine, drying with magnesium sulfate and evaporation of the solvent under vacuum gave crude 3.5 which was purified by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate), yielding a colourless oil (3.94 g, 73%) : $[\alpha]^{20}_{D}$= -225.3° (*c* : 1.2 in $CHCl_3$). IR (neat) : 3033, 2954, 1758, 1704 and 1621 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.32 (m, 5H), 5.97 (#1) + 5.92 (#2) (2dq, 1H, $J_{\#1 \text{ and } \#2}$= 2.1, 6.3), 5.75 (#1) + 5.70 (#2) (2dq, 1H, $J_{\#1 \text{ and } \#2}$= 2.3, 6.3), 5.28-5.05 (m, 3H), 4.32 (m, 2H), 3.78 + 3.60 (2s, 3H). ^{13}C NMR ($CDCl_3$) : δ 171.10 + 170.86 (1C), 154.83 + 154.38 (1C), 137.00 + 136.92 (1C), 129.67 + 129.60 (1C), 128.95 + 128.89 (1C), 128.68 + 128.47 (1C), 128.39 + 128.28 (1C), 125.14, 67.61 + 67.55 (1C), 67.03 + 66.72 (1C), 54.32 + 53.83 (1C), 52.89 + 52.73 (1C).

Preparation of (2*S*)-N-benzyloxycarbonyl-3,4-dehydropyrrolidine-2-carboxylic acid (3.7): To a solution of ester 3.5 (0.11 g, 0.42 mmol) in 4.2 mL of a 5:1 solution of methanol/water, at room temperature, was added sodium hydroxide (20.1 mg, 1.2 eq) and the reaction mixture was refluxed for 2 h. It was then dissolved in 5 mL of water and washed with ether (1x). The aqueous phase was acidified to pH 3 with 1 M HCl and extracted with ether (3x). The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was evaporated affording 0.10 g (91%) of the pure 3.7. ^1H NMR ($CDCl_3$) : δ 10.16 (s, 1H), 7.43-7.25 (m, 5H), 5.98 (m, 1H), 5.79

(m, 1H), 5.29-5.05 (m, 3H), 4.38-4.23 (m, 2H).

Preparation of methyl (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-bromo-4-hydroxypyrrolidine-2-carboxylate (3.9): To a solution of **3.5** (0.14 g, 0.53 mmol) in 1.88 mL of acetone, at 0°C, was added 14% perchloric acid (0.45 mL, 1.2 eq of acid), water (0.12 mL, 13 eq) and N-bromosuccinimide (0.28 g, 3 eq). The solution was stirred for 5 h at 0°C at which time sodium dithionite (1% solution, 5 mL) was added. The reaction mixture was poured into 5 mL of water, and the aqueous phase was extracted with ether (3x). The combined organic extracts were washed with 5% sodium bicarbonate, 10% sodium thiosulfate, brine, and dried over magnesium sulfate. Flash chromatography of the crude product (silica gel, 6:4 hexanes/ethyl acetate) gave **3.9** as a colourless oil (0.15g, 82%) : ^{1}H NMR ($CDCl_3$) : δ 7.43-7.25 (m, 5H), 5.26-4.98 (m, 2H), 4.72 + 4.65 (2s, 1H), 4.41 (m, 1H), 4.32 (bs, 1H), 4.04 (dd, 1H, *J*=4.4, 8.0), 3.81 + 3.63 (2s, 3H), 3.73 (m, 1H), 3.35 + 3.24 (2d, 1H, *J*=7.9).

Preparation of methyl (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-4-hydroxy-3-iodopyrrolidine-2-carboxylate (3.10): To a stirred solution of **3.5** (1.07 g, 4.13 mmol) in 14.7 mL of acetone, at 0°C, was added 14% perchloric acid (5.9 mL, 2 eq of acid), water (0.97 mL, 13 eq) and N-iodosuccinimide (2.79 g, 3 eq). The solution was stirred for 5 h at 0°C and sodium dithionite (1% solution, 30 mL) was added. The reaction mixture was poured into 40 mL of water, and the aqueous phase was extracted with ether (3x). The combined organic extracts were washed with 5% sodium bicarbonate, 10% sodium thiosulfate, brine, and dried over magnesium sulfate. Flash chromatography of the crude product (silica gel, 6:4 hexanes/ethyl acetate) gave **3.10** as a colourless oil (1.39 g, 83%) : ^{1}H NMR ($CDCl_3$) : δ 7.43-7.25 (m, 5H), 5.22 (d of AB system, *J*=12.4) + 5.18 (s) + 5.04 (d of AB system, *J*=12.4)(2H), 4.71 + 4.64 (2d, 1H, *J*=1.3), 4.49 (dd, 1H,

J=4.6, 8.0), 4.32 (bs, 1H), 4.18 + 4.11 (2t, 1H, *J*=4.6), 3.81 + 3.62 (2s, 3H), 3.75 (m, 1H), 3.42 + 3.29 (2d, 1H, *J*=8.0).

Preparation of methyl (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-4-acetoxy-3-iodopyrrolidine-2-carboxylate (3.11): To a solution of iodoalcohol **3.10** (0.11 g, 0.27 mmol) in 0.6 mL of dry pyridine, at room temperature, under argon, were added successively 4-dimethylaminopyridine (1.7 mg, 0.05 eq) and acetic anhydride (31 µL, 1.2 eq) and the mixture was stirred 15 h. It was then dissolved in ethyl acetate and washed with 5% HCl, sat. aq. sodium bicarbonate, brine, and dried over magnesium sulfate. Filtration, followed by evaporation of the solvent gave crude **3.11**, which was purified by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) affording 69 mg (56%) of a colourless oil. ^{1}H NMR ($CDCl_3$) : δ 7.45-7.26 (m, 5H), 5.32 (m, 1H), 5.25 (d of AB system, *J*=10.0) + 5.22 (s) + 5.09 (d of AB system, *J*=10.0)(2H), 4.78 + 4.68 (2s, 1H), 4.56 (s, 1H), 4.24 + 4.18 (2t, 1H, *J*=5.0), 3.78 + 3.66 (2s, 3H), 3.72 (m, 1H), 1.99 (s, 3H).

Preparation of methyl (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-iodo-4-dibenzylphosphatoxypyrrolidine-2-carboxylate (3.13): To a solution of **3.5** (0.92 g, 3.53 mmol) in 35 mL of dry methylene chloride, at 0°C, under argon, were added successively dibenzyl phosphate (2.94 g, 3 eq) and then, when all the phosphate was dissolved, very slowly, N-iodosuccinimide (2.38 g, 3 eq). The red solution was stirred at room temperature for 3 h and refluxed for 3 h. After cooling down to room temperature, 30 mL of 1% sodium thiosulfate were added and the dark suspension was stirred for 15 min. It was then poured into water and extracted with ether (3x). The combined organic extracts were washed with 5% sodium bicarbonate, 10% sodium thiosulfite , brine, and dried over magnesium sulfate. Filtration, followed by evaporation, gave an orange oil

which was purified by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) affording 3.13 as a clear yellow oil (1.58 g, 69%). ^{1}H NMR ($CDCl_3$) : δ 7.42-7.23 (m, 15H), 5.23-4.89 (m, 7H), 4.70 + 4.62 (2s, 1H), 4.52 (d, 1H, *J*=8.9), 4.06 (m, 1H), 3.72 (m, 1H), 3.63 + 3.52 (2s, 3H).

Preparation of methyl (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-iodo-4-methyl-hydroxyphosphonatoxypyrrolidine-2-carboxylate (3.14): To a stirred solution of 3.5 (96.2 mg, 0.37 mmol) in 5.0 mL of dry methylene chloride, under argon, at room temperature, was added methyl phosphonic acid (70.7 mg, 2 eq) and N-iodosuccinimide (0.17 g, 2 eq) and the solution was refluxed for 15 h. It was then dissolved in methylene chloride and washed with 10% sodium thiosulfite, sat. aq. sodium bicarbonate, brine, and dried over magnesium sulfate. Recrystallisation (ethyl acetate/hexanes) of the crude product afforded 3.14 (0.18 g, 49%) as a yellow solid : m.p. 154-157°C. ^{1}H NMR ($CDCl_3$) : δ 8.72 (s, 1H), 7.42-7.25 (m, 5H), 5.31-5.00 (m, 3H), 4.76 + 4.67 (2s, 1H), 4.72 (s, 1H), 4.18 (m, 1H), 3.81 (m, 1H), 3.74 + 3.64 (2s, 3H), 1.47 (m, 3H).

Preparation of (2*S*)-N-benzyloxycarbonyl-3,4-dehydro-2-hydroxymethyl-pyrrolidine (3.15): To a solution of 3.5 (0.13 g, 0.49 mmol) in 4.9 mL of dry ether, at 0°C, under argon, was added slowly lithium borohydride (21.2 mg, 1.1 eq). The reaction mixture was stirred at 0°C for 3 h and the excess of lithium borohydride was destroyed with acetic acid. The solution was poured into sat. aq. sodium bicarbonate and the aqueous phase was extracted with ethyl acetate (3x). The combined organic extracts were dried over magnesium sulfate, and the solvent was removed under vacuum. The crude product was purified by flash chromatography (silica gel, 4:6 hexanes/ethyl acetate) to give 3.15 as a colourless oil (79.7 mg, 70%) : $[\alpha]^{20}_D$= -87.1 (*c* : 1.1 in $CHCl_3$). IR (neat) : 3413 (broad), 2869, 1698 and 1624 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.46

(m, 5H), 5.99-5.78 (m, 1H), 5.76-5.62 (m, 1H), 5.17 (s, 2H), 4.85-4.60 (m, 1H), 4.37-4.08 (m, 2H), 3.90-3.75 (m, 1H), 3.70-3.57 (m,1H). ^{13}C NMR ($CDCl_3$) : δ 157.09, 136.80, 129.03, 128.65, 128.56, 128.43, 127.23, 68.45 + 67.85 (1C), 67.69 + 66.89 (1C), 54.47, 47.80. MS : 234 (100, $M^{\cdot+} + H^+$), 202 (20), 190 (52), 126 (13).

Preparation of (2*S*)-N-benzyloxycarbonyl-3,4-dehydropyrrolidine-2-carboxaldehyde (3.16): A solution of dimethyl sulfoxide (0.21 mL, 2.84 eq) in 0.5 mL of dry methylene chloride was slowly added, *via* a double tipped needle, to a stirring solution of oxalyl chloride (0.13 mL, 1.41 eq) in 2 mL of methylene chloride, under argon, at -45°C. The colourless solution was stirred for 15 min after which a solution of **3.15** (0.24 g, 1.04 mmol) in 0.5 mL of methylene chloride was added dropwise over a period of 15 min. A white precipitate was then formed, and the suspension was stirred for 1 h. Triethylamine (0.7 ml, 5 eq) in methylene chloride was added and the solution was allowed to slowly warm up to room temperature. The reaction mixture was diluted with 10 mL of methylene chloride and washed successively with 5% HCl, water, brine, and was dried over magnesium sulfate. Evaporation of the solvent under vacuum gave **3.16** as a pale brown oil (0.21 g, 88%) which was not further purified for synthesis purposes. A small sample was passed through silica gel (6:4 hexanes/ethyl acetate) for structure determination : ^1H NMR ($CDCl_3$) : δ 9.47 + 9.30 (2d, 1H), (m, 5H), 6.05 (m, 1H), 5.63 (m, 1H), 5.22-5.10 (m, 2H), 5.02-4.86 (m, 1H), 4.33 (m, 2H).

Preparation of (2*S*)-N-benzyloxycarbonyl-3,4-dehydro-2-dimethoxy-methylpyrrolidine (3.17): To a solution of **3.16** (24.5 mg, 0.11 mmol) in 0.2 mL of dry methanol, under argon, at room temperature, was added trimethylorthoformate (0.2 mL, 8 eq) and p-toluenesulfonic acid (0.9 mg, 0.05 eq) and the reaction mixture was stirred for 1 h. The solution was then diluted with 3 mL of ether and washed with a 1:1 solution

of brine and 5% NaOH, water, brine and was dried over magnesium sulfate. Evaporation of the solvent under vacuum and purification by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) gave **3.17** as a colourless oil (75.4 mg, 71%) : $[\alpha]^{20}_D$= -82.1° (*c* : 1.2 in $CHCl_3$). IR (neat) : 2933, 1696 and 1622 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.50-7.20 (m, 5H), 5.98-5.73 (m, 2H), 5.32-5.11 (m, 2H), 4.77 + 4.47 (2d, 1H, *J*=2.2), 4.67 (m, 1H), 4.24 (m, 1H), 4.11 (m, 1H), 3.48 + 3.42 + 3.35 + 3.33 (4s, 3H). ^{13}C NMR ($CDCl_3$) : δ 155.21 + 154.87 (1C), 137.24 + 137.05 (1C), 128.95, 128.66 + 128.47 (1C), 128.27 + 128.08 (1C), 127.79 + 127.66 (1C), 125.79 + 125.70 (1C), 106.22 + 105.14 (1C), 67.45, 67.25 + 66.88 (1C), 58.66, 57.00 + 56.72 (1C), 54.74 + 54.36 (1C). MS : 278 (12, $M^{\cdot+}$ + H^+), 246 (100), 202 (51), 186 (2), 170 (12), 156 (37).

Preparation of (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-iodo-4-hydroxy-2-dimethoxymethylpyrrolidine (3.18): To a stirring solution of **3.17** (0.11 g, 0.39 mmol) in 1.4 mL of acetone, at room temperature, was added 14% perchloric acid (0.34 mL, 1.2 eq of acid), water (92 μL, 13 eq) and N-iodosuccinimide (0.27 g, 3 eq). The solution was stirred for 30 min at which time sodium dithionite (1% solution, 3 mL) was added. The reaction mixture was poured into 5 mL of water, and the aqueous phase was extracted with ether (3x). The combined organic extract was washed with 5% sodium bicarbonate, 10% sodium thiosulfate, brine, and dried over magnesium sulfate. Flash chromatography of the crude product (silica gel, 6:4 hexanes/ethyl acetate) gave **3.18** as a colourless oil (0.34 g, 85%) : $[\alpha]^{20}_D$= -1.5° (*c* : 1.1 in $CHCl_3$). IR (neat) : 3399 (broad), 2890 and 1698 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.35 (m, 5H), (5.30 and 5.08) + (5.20 and 5.13) (4d, 2 AB systems, 2H, *J*=12.5), 4.92 + 4.77 (2d, 1H, *J*=12.06), 4.67-4.33 (m, 2H), 4.43 (s, 1H), 4.17 + 4.11 (2dd, 1H, *J*=4.6, 11.8), 3.59 (m, 1H), (3.51 + 3.48) + (3.38 + 3.37) (2 x 2s, 6H). ^{13}C NMR ($CDCl_3$) : δ 156.49, 137.66 + 136.64 (1C), 129.90, 129.74 + 129.09 (1C), 129.50, 106.39 + 105.38 (1C), 80.08 + 79.37 (1C), 73.15 + 72.72 (1C),

68.83 + 68.62 (1C), 59.56, 58.62 + 58.35 (1C), 55.48 + 55.07 (1C), 25.10 + 23.88 (1C). MS : 422 (8, $M^{\cdot+} + H^+$), 390 (100), 346 (47), 314 (4), 294 (2), 202 (6).

Preparation of (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-iodo-4-acetoxy-2-dimethoxymethylpyrrolidine (3.19): To a solution of alcohol **3.18** (56.6 mg, 0.13 mmol) in 0.30 mL of dry pyridine, at room temperature, under argon, were added a catalytic amount of 4-dimethylaminopyridine and acetic anhydride (15.2 µL, 1.2 eq). The solution was stirred for 15 h, after which it was dissolved in ethyl acetate and washed successively with 5% HCl (1x), sat. aq. sodium bicarbonate (1x), brine, and dried over magnesium sulfate. Filtration, followed by evaporation of the solvent under vacuum, gave 61.6 mg (99%) of iodoacetate **3.19**, which was pure by t.l.c. and ^{1}H NMR. ^{1}H NMR ($CDCl_3$) : δ 7.42-7.26 (m, 5H), 5.31 (m, 1H), 5.25-5.10 (m, 2H), 4.65-35 (m, 3H), 4.21 (m, 1H), 3.49-3.20 (m, 7H), 2.06 (s, 3H).

Preparation of (2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-epoxy-2-dimethoxy-methylpyrrolidine (3.20): To a solution of **3.18** (0.14 g, 0.32 mmol) in 3.2 mL of a 2:1 mixture of methanol/water, at room temperature, was added potassium carbonate (88.5 mg, 2 eq). The solution was stirred for 30 min, diluted in 5 ml of water and extracted with ether (3x). The combined organic extracts were washed with 10% sodium thiosulfate, brine, dried with magnesium sulfate and concentrated under vacuum. The crude **3.20** was pure by t.l.c. and ^{1}H NMR (85.9 mg, 92%) : $[\alpha]^{20}_D$= -38.3° (*c* : 1.7 in $CHCl_3$). IR (neat) : 2941 and 1706 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.33 (m, 5H), 5.12 + 5.04 (2d, AB system, 2H, J= 12.4), 4.90 (m, 1H; at 40°C : d, *J*= 4.6), 3.91 (dd, 1H, J= 2.2, 4.6), 3.83 (dd, 1H, J= 2.2, 3.1), 3.77 (d, 1H, J= 12.7), 3.60 (dd, 1H, J= 2.2, 3.1), 3.52 (dd, 2H, J= 2.2, 12.7), 3.41 (s, 6H). ^{13}C NMR ($CDCl_3$) : δ 156.29, 136.88, 128.95, 128.58, 128.48, 105.11, 67.53. 60.39, 58.11, 56.37, 54.31, 49.96. Exact mass calcd for

$C_{15}H_{19}NO_5$ ($M^{\cdot+} + H^+$) 294.1342, found 294.1341.

Preparation of (2*S*,3*S*,4*S*) and (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-(or 4)-hydroxy-4-(or 3)-thiophenyl-2-dimethoxymethylpyrrolidine (3.21a and b): To a solution of thiophenol (0.14 mL, 3.6 eq) in 2.8 mL of dry tetrahydrofuran, at -10°C, under argon, was added *n*-butyllithium (2.5 M in pentane : 0.46 mL, 3.0 eq). The reaction mixture was slowly warmed up to room temperature and the epoxide **3.20** (0.11 g, 0.38 mmol : dissolved in 1.0 mL of THF) was added *via* a double tipped needle. The solution was stirred for 30 min after which it was dissolved in 10 mL of water. The aqueous phase was extracted with ether (3x), the combined organic extracts washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents under vacuum, followed by flash chromatography purification (silica gel : 6:4 hexanes/ethyl acetate) afforded 0.15 g (95%) of a 1:1.2 mixture of **3.21a** and **b** . **3.21a** : 65.6 mg, 43%. ^{1}H NMR ($CDCl_3$) : δ 7.48-7.29 (m, 10H), 5.30-5.06 (m, 2H), 4.82-4.44 (m, 2H), 4.13-3.81 (m, 3H), 3.50 (m, 1H), 3.50 + 3.39 (2s, 3H), 3.23 (bs, 1H). **3.21b** : 79.6 mg, 52%. ^{1}H NMR ($CDCl_3$) : δ 7.48-7.32 (m, 10H), 5.25-4.95 (m, 2H), 4.32 (m, 1H), 4.10 (m, 1H), 3.88 (m, 1H), 3.72 (m, 1H), 3.62-3.30 (m, 8H).

Preparation of (2*S*,3*S*,4*S*) and (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-(or 4)-hydroxy-4-(or 3)-phenylseleno-2-dimethoxymethylpyrrolidine (3.22a and b): To a solution of diphenyldiselenide (0.29 g, 0.7 eq) in 5.3 mL of absolute ethanol, at room temperature, under argon, was added slowly sodium borohydride (69.6 mg, 1.4 eq) and the reaction mixture was stirred until the yellow color disappeared. To this clear solution was added a solution of the epoxide **3.20** (0.39 g, 1.31 mmol : dissolved in 2.0 mL of ethanol) and the mixture was stirred for 30 min. It was then dissolved in ether (40 mL), washed with water (3x) and dried over magnesium sulfate. Filtration, followed by

evaporation of the solvents under vacuum, gave a yellow oil which was purified by flash chromatography (7:3 hexanes/ethyl acetate) affording 0.49 g (82%) of 3.22a and b as a mixture of isomers. The first fractions of 3.22a were uncontaminated by its isomer (0.30 g, 50% : these were used in all the subsequent reactions). ^{1}H NMR ($CDCl_3$) : δ 7.52 (m, 2H), 7.40-7.16 (m, 8H), 5.25-5.03 (m, 2H), 4.79-4.36 (m, 2H), 4.20-3.77 (m, 3H), 3.47 + 3.33 (2s, 3H), 3.45 (m, 1H), 3.16 (s, 1H).

Preparation of (2*S*,3*S*,4*S*) and (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-(or 4)-hydroxy-4-(or 3)-azido-2-dimethoxymethylpyrrolidine (3.23a and b): To a solution of epoxide 3.20 (0.14 g, 0.46 mmol) in 2.3 mL of dry dimethylformamide, at room temperature, under argon, was added sodium azide (74.8 mg, 2.5 eq). The reaction mixture was heated at 75°C for 15 h, after which it was poured into sat. aq. ammonium chloride. The aqueous phase was extracted with ether (3x) and the combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvent under vacuum, followed by flash chromatography purification (silica gel, 7:3 hexanes/ethyl actate) gave 0.12 g (76%) of 3.23a and b as a mixture of isomers. The first few fractions of 3.23a (72.0 mg, 47%) were uncontaminated by its isomer and were used in all the subsequent reactions). ^{1}H NMR ($CDCl_3$) : δ 7.38 (s, 5H), 5.32-5.04 (m, 2H), 4.85 (m, 1H), 4.49 (m, 1H), 4.20 (s, 1H), 4.12-3.65 (m, 3H), 3.59-3.33 (m, 7H).

Preparation of (2*S*,3*S*,4*S*) and (2*S*,3*R*,4*R*)-N-benzyloxycarbonyl-3-(or 4)-hydroxy-4-(or 3)-trimethylstannyl-2-dimethoxymethylpyrrolidine (3.24a and b): To a solution of hexamethylditin (0.21 g, 2 eq) in 2.2 mL of dry tetrahydrofuran, at -20°C, under argon, was added methyllithium (0.45 mL of a 1.4 M solution in ether, 2 eq) and the solution was stirred for 15 min. Epoxide 3.20 (92.1 mg, 0.31 mmol, in 1 mL

of THF) was then added slowly *via* a double tipped needle and the reaction mixture was stirred at room temperature for 30 min. It was then poured in 10 mL of water and the aqueous phase was extracted with ether (3x). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents under vacuum was followed by flash chromatography purification (silica gel, 6:4 hexanes/ethyl acetate) to give an inseparable mixture of isomers **3.24a** and **b** (66.6 mg, 46 %). ^{1}H NMR ($CDCl_3$) : 7.42-7.30 (m, 5H), 5.19-5.08 (m, 2H), 4.90-3.62 (m, 6H), 3.57-3.29 (m, 6H), 1.90 (m, 1H), 0.09 + 0.07 (2t, 9H, J= 26.5).

Preparation of (2*S*,3*S*) and (2*S*,4*R*)-N-benzyloxycarbonyl-3-(or 4)-hydroxy-4-(or 3)-keto-2-dimethoxymethylpyrrolidine (3.25a and b): To a solution of epoxide **3.20** (85.9 mg, 0.29 mmol) in 0.59 mL of dry dimethyl sulfoxide, at room temperature, under argon, was added trifluoromethanesulfonic acid (31.1 µL, 1.2 eq). The solution was stirred for 24 h and was then cooled down to -70°C. Diisopropylethyl amine was added (0.20 mL, 5 eq) and the reaction mixture was slowly warmed up to room temperature. It was then poured into 2 mL of 10% sodium sulfate and extracted with methylene chloride (3x). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvent under vacuum was followed by flash chromatography purification (silica gel, 4:6 hexanes/ethyl acetate) to give 23.5 mg (26%) of an unseparable mixture of isomers. IR (neat) : 3350 (broad), 2937, 1776 and 1701 cm^{-1}. **3.25a + b** : ^{1}H NMR ($CDCl_3$) : δ 7.42-7.25 (m, 5H), 5.27-5.04 (m, 2H), 4.68-3.69 (m, 5H), 3.43 + (3.33 and 3.28) (3s, 6H). ^{13}C NMR ($CDCl_3$) : δ 208.98, 208.69, 155.36, 136.44, 129.06, 128.81, 128.72, 128.57, 106.68, 106.47, 77.89, 77.26, 77.16, 74.58, 74.36, 68.23, 68.14, 57.85, 57.71, 57.59, 57.45, 57.23, 57.12, 50.91. Exact mass calcd for $C_{15}H_{19}NO_6$ ($M^{\cdot+} + H^+$) 310.1291, found 310.1291.

Preparation of (2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-dihydroxy-2-dimethoxymethylpyrrolidine (3.26): To a solution of hydroxy ketones **3.25a** and **b** (23.5 mg, 0.076 mmol) in 0.8 mL of dry ether, at room temperature, under argon, was added sodium borohydride (2.9 mg, 1 eq) and the reaction mixture was stirred for 4 h. It was then poured into 1 mL of water and extracted with ethyl acetate (4x). The combined organic extracts were dried over magnesium sulfate, filtered and the solvent was evaporated under vacuum. Flash chromatography purification (silica gel, 1:9 hexanes/ethyl acetate) gave 9.5 mg (40%) of diol **3.26** as a colourless oil : $[\alpha]^{20}_{D}$: -25.7° (*c* : 1.3 in $CHCl_3$). IR (neat) : 3407 (broad), 2958 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.28 (m, 5H), 5.25-4.98 (m, 2H), 4.93 + 4.65 (2m, 1H), 4.32 (m, 1H), 4.12 (m, 1H), 3.75 (m, 2H), 3.60-3.31 (m, 7H). ^{13}C NMR ($CDCl_3$) : δ 156.75, 137.69, 129.90, 129.53, 135.92, 106.76, 73.68, 71.73, 68.52, 60.30, 58.67, 54.11, 53.16. Exact mass calcd for $C_{15}H_{21}NO_6$ ($M^{\cdot+} + H^+$) 312.1447, found 312.1446.

Preparation of (2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-diacetoxy-2-dimethoxymethylpyrrolidine (3.27): To a solution of diol **3.26** (9.5 mg, 0.031 mmol) in 0.31 mL of dry pyridine, at room temperature, under argon, were added successively 4-dimethylaminopyridine (1 small crystal) and acetic anhydride (6.9 µL, 2.4 eq). The reaction mixture was stirred for 16 h and was then dissolved in ethyl acetate, washed with 5% HCl, sat. aq. sodium bicarbonate, brine and dried over magnesium sulfate. Filtration and evaporation of the solvent under vacuum was followed by flash chromatography purification (silica gel, 1:1 hexanes/ethyl acetate) affording 6.2 mg (52%) of the diacetate **3.27** as a colourless oil : $[\alpha]^{20}_{D}$= +8.0 (*c* : 1.1 in $CHCl_3$). IR (solution in $CHCl_3$) : 2978, 1750 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.43-7.28 (m, 5H), 5.38 (ddd, 1H, *J*= 3.2, 6.4, 6.8), 5.27 (t, 1H, *J*= 6.8), 4.67 (d, 1H, *J*=6.8), 4.35 (t, 1H, *J*=6.8), 3.95 (dd, 1H, *J*=6.4, 12.7), 3.43 (dd, 1H, *J*=3.2, 12.7), 3.34 (s, 6H), 2.09 (s, 3H),

2.07 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 171.04, 170.98, 156.65, 137.69, 129.80, 129.42, 129.37, 103.88, 71.61, 71.46, 68.73, 58.03, 55.70, 51.11, 31.04, 22.16, 21.90. Exact mass calcd for $C_{19}H_{25}NO_8$ ($M^{\cdot+} + H^+ - CH_3OH$) 364.1396, found 364.1397.

Preparation of ethyl N-(2-ethoxycarbonylethyl)-glycinate (3.32): To a solution of freshly prepared ethyl glycinate **3.31** (10.15 g, 98.43 mmol : from ethyl glycinate hydrochloride neutralised with 10 M NaOH : pH 9.5, and extracted with chloroform) in 10 mL of dry benzene was added ethyl 3-bromopropionate **3.30** (6.3 mL, 0.5 eq : in 5 mL of benzene). A white solid formed immediately upon addition. The suspension was heated at 60°C for 5 h and poured in sat. aq. sodium carbonate. The aqueous phase was extracted with chloroform (3x) and the combined organic extracts were dried over magnesium sulfate. Evaporation of the solvents followed by distillation of the crude product (95°C, 0.25 mmHg) yielded amine **3.32** as a colourless oil (6.30 g, 63%). IR (neat) : 3348, 2985, 1721 and 1121 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.05 (q, 2H, *J*=7.2), 4.01 (q, 2H, *J*=7.2), 3.27 (s, 2H), 2.76 (t, 2H, *J*=6.6), 2.36 (t, 2H, *J*=6.6), 1.72 (s, 1H), 1.14 (t, 3H, *J*=7.2), 1.12 (t, 3H, *J*=7.2). ^{13}C NMR ($CDCl_3$) : δ 172.75, 172.58, 61.05, 60.77, 51.21, 45.12, 35.22, 14.55. MS : 204 (5, $M^{\cdot+} + H^+$), 203 (7, $M^{\cdot+}$), 174 (2), 158 (4), 130 (100), 116 (49), 84 (76), 56 (14), 42 (38).

Preparation of ethyl N-benzoxycarbonyl-N-(2-ethoxycarbonylethyl)-glycinate (3.33): To a solution of amine **3.32** (3.88 g, 20.17 mmol) in 40 mL of dry acetonitrile, at 0°C, under argon, was added slowly benzyl chloroformate (3.17 mL, 1.1 eq). The solution was stirred at 0°C for 1 h after which it was poured in 50 mL of water. The phases were separated and the aqueous layer was extracted with methylene chloride (3x). The combined organic extracts were washed with 5% HCl, water, brine and dried over magnesium sulfate. Filtration and evaporation of the solvents was followed by

distillation (198°C, 0.25 mmHg) to afford 3.33 as a colourless oil (5.41 g, 80%). IR (neat) : 2978, 1722 and 1693 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.18 (m, 5H), 5.13 + 5.07 (2s, 2H), 4.14 + 4.11 (2q, 2H, *J*=7.1), 4.064 + 4.061 (2q, 2H, *J*=7.1), 3.59 + 3.58 (2t, 2H, *J*=6.4), 2.64 + 2.58 (2t, 2H, *J*=6.4), 1.22 + 1.15 (2t, 3H, *J*=7.1), 1.21 + 1.20 (2t, 3H, *J*=7.1). ^{13}C NMR ($CDCl_3$) : δ 172.74 + 172.38 (1C), 170.37 + 170.28 (1C), 156.72 + 156.20 (1C), 136.83, 128.98 + 128.87 (1C), 128.53 + 128.45 (1C), 128.27 + 128.21 (1C), 68.03 + 67.80 (1C), 61.59, 61.11 + 61.04 (1C), 50.94, 45.83 + 44.96 (1C), 34.55 + 33.99 (1C), 14.61. MS : 337 (4, $M^{\cdot+}$), 292 (2), 264 (2), 220 (12), 202 (28), 91 (100).

Preparation of ethyl N-benzyloxycarbonyl-3-oxopyrrolidine-2-carboxylate (3.34): To a suspension of potassium *t*-butoxide (2.52 g, 1.4 eq) in 54 mL of dry toluene, at 0°C, under argon, was added 3.33 (5.41 g, 16.03 mmol, in 10 mL of toluene) over a period of 10 min. The suspension was stirred at 0°C for 30 min after which 2 mL of glacial acetic acid were added, immediately followed by 9.1 g of sodium dihydrogenephosphate hydrate in 91 mL of water. The heterogeneous mixture was extracted with chloroform (3x), the combined organic extracts were dried over magnesium sulfate and the solvents were evaporated. The residue obtained after evaporation was dissolved in 100 mL of cold toluene and was washed with cold, pH 9.5 carbonate buffer (3x). The toluene solution was washed with water (1x), dried over magnesium sulfate, and the solvent was evaporated to a clear colorless oil. Distillation (Kugelrohr : oven temperature 160°C, 0.03 mmHg) was followed by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) affording 3.34 (1.63 g, 35%) as a colourless oil still contaminated with a small amount of ethyl N-benzyloxycarbonyl-4-oxopyrrolidine-3-carboxylate 3.35. Compound 3.34 : IR (neat) : 2978, 1741, 1712 and 1695 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.41-7.23 (m, 5H), (5.22 and 5.15 (#1)) + (5.20 and 5.07 (#2)) (2 AB systems, 2H, $J_{\#1}$= 8.2, $J_{\#2}$= 8.2), 4.58 + 4.54 (2s,

1H), 4.24 (q, 2H, *J*=4.7), 4.08 (m, 1H), 3.96 (m, 1H), 3.85 (m, 1H), 2.67 (t, 2H, *J*=4.9), 1.28 + 1.14 (2t, 3H, *J*=4.7). ^{13}C NMR ($CDCl_3$) : δ 204.58, 166.39, 154.95, 136.55 + 136.38 (1C), 128.95, 128.70, 128.53 + 128.42 (1C), 68.03, 65.97 + 65.83 (1C), 62.81, 42.62, 37.34 + 36.65 (1C), 14.51 + 14.43 (1C). MS : 292 (100, $M^{\cdot} + H^{+}$), 248 (80), 176 (32), 158 (23).

Preparation of ethyl (2*R*,3*S*)-N-benzyloxycarbonyl-3-hydroxypyrrolidine-2-carboxylate (3.36): To a solution of sucrose (300 mg) in 4.1 mL of distilled water was added 200 mg of baker's yeast. The flask was equipped with a bubble counter and the suspension was heated at 32°C for 1 hr. The content of the flask was then poured into a 15 mL flask containing keto ester 3.34 (0.12 g, 0.42 mmol). Stirring was continued for 24 h after which 300 mg of sucrose in 1 mL of warm (40°C) distilled water were added. After 48 h, celite (500 mg) was added and the suspension was filtered through a sintered glass funnel (medium porosity). After the filtrate was washed with water, the aqueous layer was extracted with ether (3x) and the combined organic extracts were dried over magnesium sulfate. Filtration and evaporation of the solvent was followed by flash chromatography purification (silica gel, 3:7 hexanes/ethyl acetate) to give 54.8 mg (45%) of β-hydroxy ester 3.36. Alternatively, 3.34 (0.29 g, 0.72 mmol) was dissolved in absolute ethanol (3.6 mL), at 0°C, under argon, and sodium borohydride (29.8 mg, 1.1 eq) was added. The solution was stirred at 0°C for 60 min after which a few drops of acetic acid were added. The solution was poured in sat. aq. sodium bicarbonate and the aqueous layer was extracted with ether (3x). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents was followed by flash chromatography purification (same solvent system) to give racemic 3.36 (0.14 g, 66%). (+)-3.36 : $[\alpha]^{20}_{D}$= +22.8° (*c* : 2.7 in CH_2Cl_2; lit.[24] $[\alpha]^{20}_{D}$= +21.9, *c* : 2.0 in CH_2Cl_2). IR (neat) : 3378 (broad), 2978, 1741

distillation (198°C, 0.25 mmHg) to afford 3.33 as a colourless oil (5.41 g, 80%). IR (neat) : 2978, 1722 and 1693 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.18 (m, 5H), 5.13 + 5.07 (2s, 2H), 4.14 + 4.11 (2q, 2H, *J*=7.1), 4.064 + 4.061 (2q, 2H, *J*=7.1), 3.59 + 3.58 (2t, 2H, *J*=6.4), 2.64 + 2.58 (2t, 2H, *J*=6.4), 1.22 + 1.15 (2t, 3H, *J*=7.1), 1.21 + 1.20 (2t, 3H, *J*=7.1). ^{13}C NMR ($CDCl_3$) : δ 172.74 + 172.38 (1C), 170.37 + 170.28 (1C), 156.72 + 156.20 (1C), 136.83, 128.98 + 128.87 (1C), 128.53 + 128.45 (1C), 128.27 + 128.21 (1C), 68.03 + 67.80 (1C), 61.59, 61.11 + 61.04 (1C), 50.94, 45.83 + 44.96 (1C), 34.55 + 33.99 (1C), 14.61. MS : 337 (4, $M^{\cdot+}$), 292 (2), 264 (2), 220 (12), 202 (28), 91 (100).

Preparation of ethyl N-benzyloxycarbonyl-3-oxopyrrolidine-2-carboxylate (3.34): To a suspension of potassium *t*-butoxide (2.52 g, 1.4 eq) in 54 mL of dry toluene, at 0°C, under argon, was added 3.33 (5.41 g, 16.03 mmol, in 10 mL of toluene) over a period of 10 min. The suspension was stirred at 0°C for 30 min after which 2 mL of glacial acetic acid were added, immediately followed by 9.1 g of sodium dihydrogenephosphate hydrate in 91 mL of water. The heterogeneous mixture was extracted with chloroform (3x), the combined organic extracts were dried over magnesium sulfate and the solvents were evaporated. The residue obtained after evaporation was dissolved in 100 mL of cold toluene and was washed with cold, pH 9.5 carbonate buffer (3x). The toluene solution was washed with water (1x), dried over magnesium sulfate, and the solvent was evaporated to a clear colorless oil. Distillation (Kugelrohr : oven temperature 160°C, 0.03 mmHg) was followed by flash chromatography (silica gel, 2:1 hexanes/ethyl acetate) affording 3.34 (1.63 g, 35%) as a colourless oil still contaminated with a small amount of ethyl N-benzyloxycarbonyl-4-oxopyrrolidine-3-carboxylate 3.35. Compound 3.34 : IR (neat) : 2978, 1741, 1712 and 1695 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.41-7.23 (m, 5H), (5.22 and 5.15 (#1)) + (5.20 and 5.07 (#2)) (2 AB systems, 2H, $J_{\#1}$= 8.2, $J_{\#2}$= 8.2), 4.58 + 4.54 (2s,

1H), 4.24 (q, 2H, *J*=4.7), 4.08 (m, 1H), 3.96 (m, 1H), 3.85 (m, 1H), 2.67 (t, 2H, *J*=4.9), 1.28 + 1.14 (2t, 3H, *J*=4.7). ^{13}C NMR ($CDCl_3$) : δ 204.58, 166.39, 154.95, 136.55 + 136.38 (1C), 128.95, 128.70, 128.53 + 128.42 (1C), 68.03, 65.97 + 65.83 (1C), 62.81, 42.62, 37.34 + 36.65 (1C), 14.51 + 14.43 (1C). MS : 292 (100, $M^{\cdot} + H^{+}$), 248 (80), 176 (32), 158 (23).

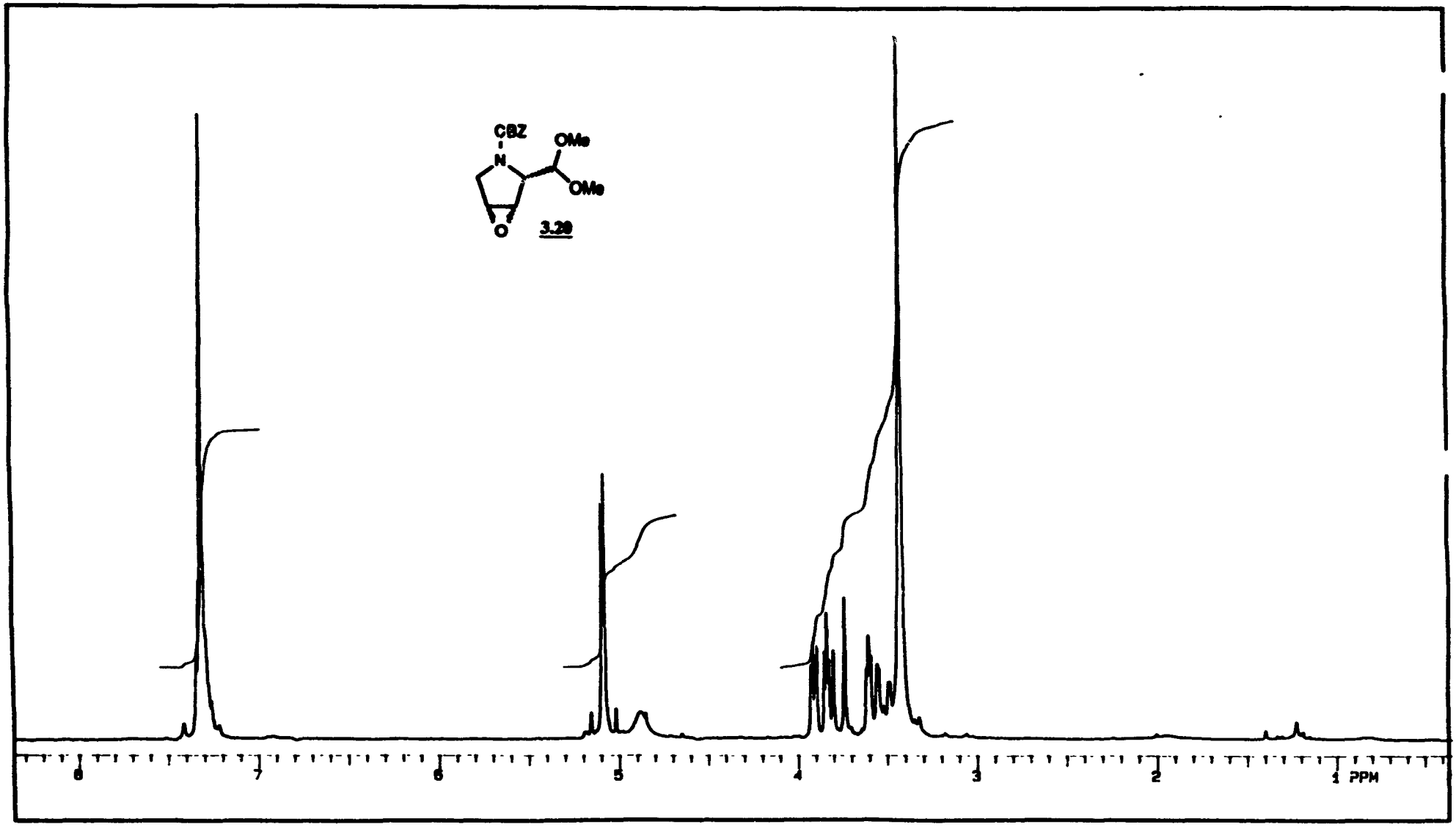
Preparation of ethyl (2*R*,3*S*)-N-benzyloxycarbonyl-3-hydroxypyrrolidine-2-carboxylate (3.36): To a solution of sucrose (300 mg) in 4.1 mL of distilled water was added 200 mg of baker's yeast. The flask was equipped with a bubble counter and the suspension was heated at 32°C for 1 hr. The content of the flask was then poured into a 15 mL flask containing keto ester 3.34 (0.12 g, 0.42 mmol). Stirring was continued for 24 h after which 300 mg of sucrose in 1 mL of warm (40°C) distilled water were added. After 48 h, celite (500 mg) was added and the suspension was filtered through a sintered glass funnel (medium porosity). After the filtrate was washed with water, the aqueous layer was extracted with ether (3x) and the combined organic extracts were dried over magnesium sulfate. Filtration and evaporation of the solvent was followed by flash chromatography purification (silica gel, 3:7 hexanes/ethyl acetate) to give 54.8 mg (45%) of β-hydroxy ester 3.36. Alternatively, 3.34 (0.29 g, 0.72 mmol) was dissolved in absolute ethanol (3.6 mL), at 0°C, under argon, and sodium borohydride (29.8 mg, 1.1 eq) was added. The solution was stirred at 0°C for 60 min after which a few drops of acetic acid were added. The solution was poured in sat. aq. sodium bicarbonate and the aqueous layer was extracted with ether (3x). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvents was followed by flash chromatography purification (same solvent system) to give racemic 3.36 (0.14 g, 66%). (+)-3.36 : $[\alpha]^{20}_{D}$= +22.8° (*c* : 2.7 in CH_2Cl_2; lit.[24] $[\alpha]^{20}_{D}$= +21.9, *c* : 2.0 in CH_2Cl_2). IR (neat) : 3378 (broad), 2978, 1741

and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.22 (m, 5H), (5.13 and 5.00) + 5.11 (1 AB system + 1s, 2H, *J*=12.5), 4.56 (q, 1H, *J*=6.4), 4.39 (t, 1H, *J*=6.4), 4.19 (q, *J*=7.1) and 4.06 (2q, AB system, *J*=7.1) (2H), 3.66 (m, 1H), 3.49 (m, 1H), 2.02 (m, 1H), 1.23 + 1.11 (2t, 3H, *J*=7.1). ^{13}C NMR ($CDCl_3$) : δ 170.69 + 170.50 (1C), 155.38 + 154.94 (1C), 136.95 + 136.79 (1C), 128.94 + 128.87 (1C), 128.47, 128.35 + 128.21 (1C), 72.65 + 71.80 (1C), 67.61, 64.35 + 64.09 (1C), 61.82 + 61.72 (1C), 44.93 + 44.70 (1C), 33.18 + 32.41 (1C), 14.64 + 14.57 (1C). Exact mass calcd for $C_{15}H_{19}NO_5$ ($M^{\cdot+}$ + H^+) 294.1342, found 294.1341.

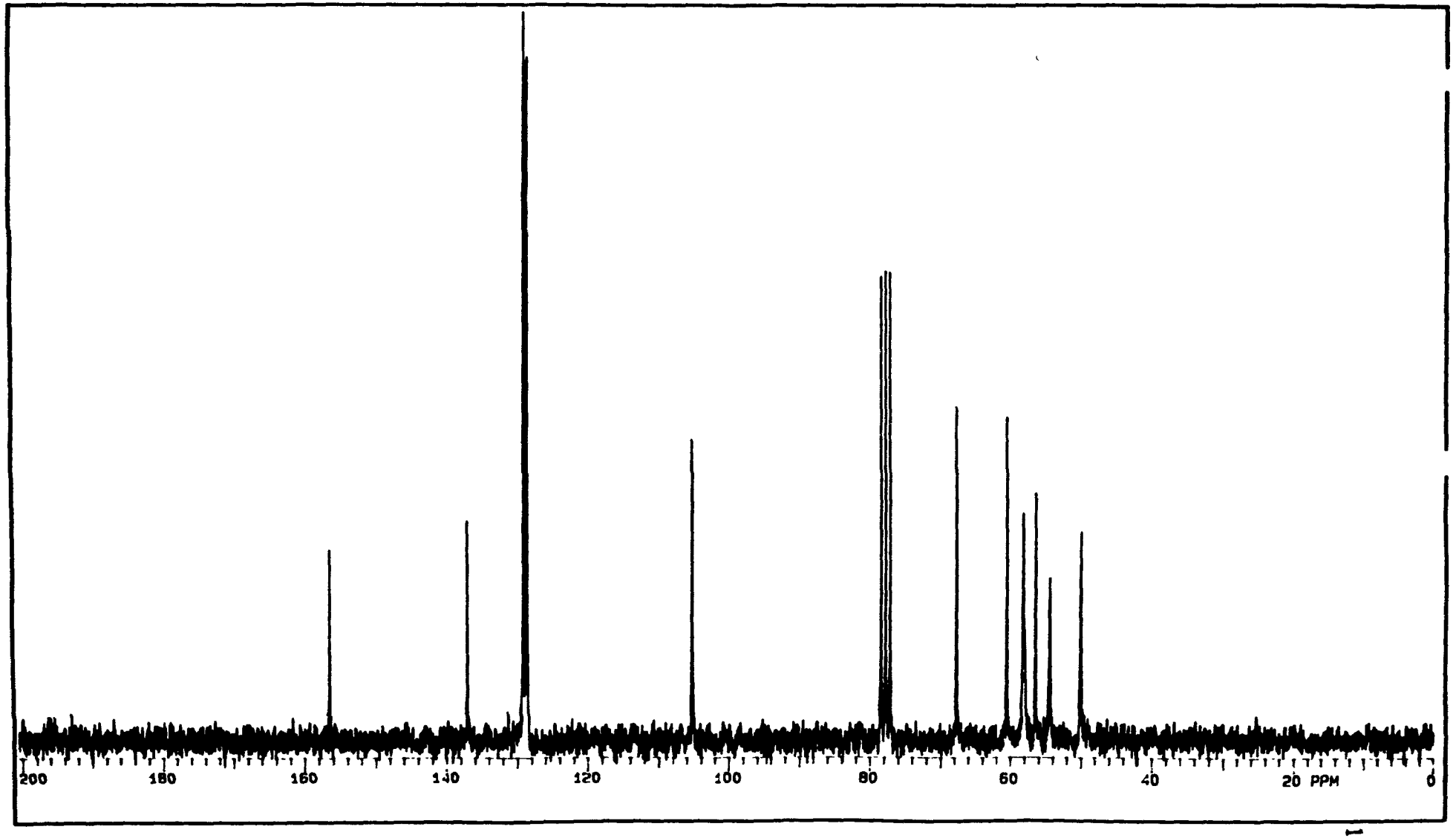
Preparation of ethyl (2*R*,3*S*)-N-benzyloxycarbonyl-3-methoxymethyloxy-pyrrolidine-2-carboxylate (3.37): To a solution of alcohol 3.36 (0.14 g, 0.48 mmol) in 4.8 mL of dry methylene chloride, at 0°C, under argon, were added successively diisopropyethylamine (0.25 mL, 3 eq) and chloromethyl methyl ether (0.11 mL, 3 eq). The solution was stirred at room temperature for 24 hr after which it was poured into 5% HCl. The aqueous phase was extracted with methylene chloride (3x) and the combined organic extracts were washed with sat. aq. sodium bicarbonate and dried over magnesium sulfate. Filtration and evaporation of the solvent was followed by flash chromatography purification (silica gel, 1:1 hexanes/ethyl acetate) to give 3.37 as a colourless oil (0.15 g, 92%) : $[\alpha]^{20}_D$= -18.4° (*c* : 1.1 in $CHCl_3$). IR (neat) : 2957, 1746 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.42-7.20 (m, 5H), (5.14 and 5.02) + 5.11 (1 AB system + 1s, 2H, *J*=12.2), (4.68 and 4.60) + (4.66 and 4.58) (2 AB systems, 2H, *J*=6.9), 4.21 (q) + (4.09 and 4.07) (2q) (2H, *J*=7.1), 3.70 (m, 1H), 3.49 (m, 1H), 3.34 + 3.33 (2s, 3H), 2.10 (m, 2H), 1.25 + 1.14 (2t, 3H, *J*=7.1). ^{13}C NMR ($CDCl_3$) : δ 170.04 + 169.86 (1C), 155.24 + 154.77 (1C), 136.87, 128.93 + 128.85 (1C), 128.48 + 128.40 (1C), 128.19, 96.13, 76.74 + 75.98 (1C), 67.59, 62.62 + 62.32 (1C), 61.53 + 61.45 (1C), 56.15, 44.77 + 44.60 (1C), 30.96 + 30.17 (1C), 14.67 + 14.61 (1C). Exact mass calcd for

$C_{17}H_{23}NO_6$ ($M^{\cdot+} + H^+$) 338.1605, found 338.1604.

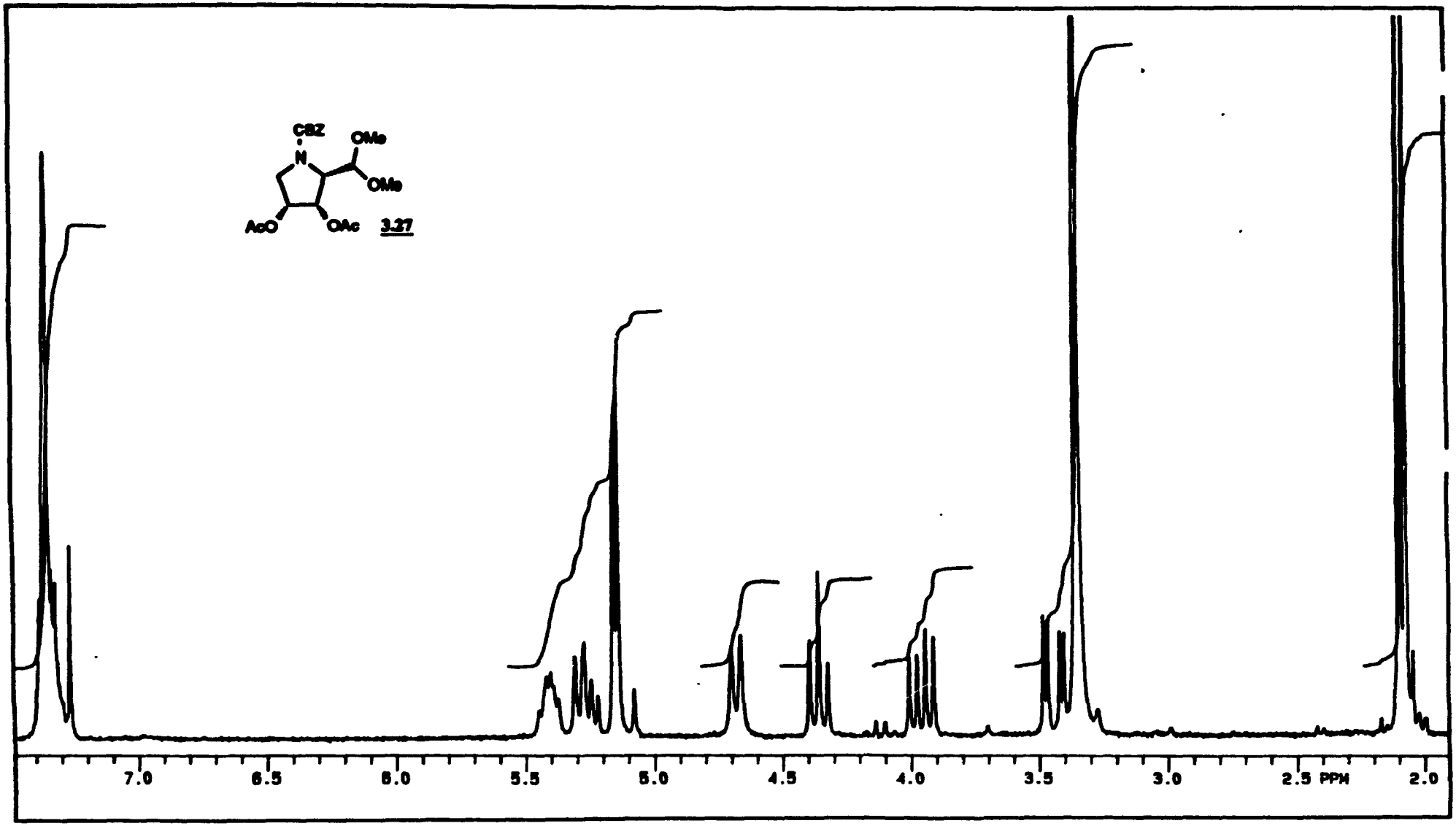
(2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-epoxy-2-dimethoxymethylpyrrolidine (3.20)



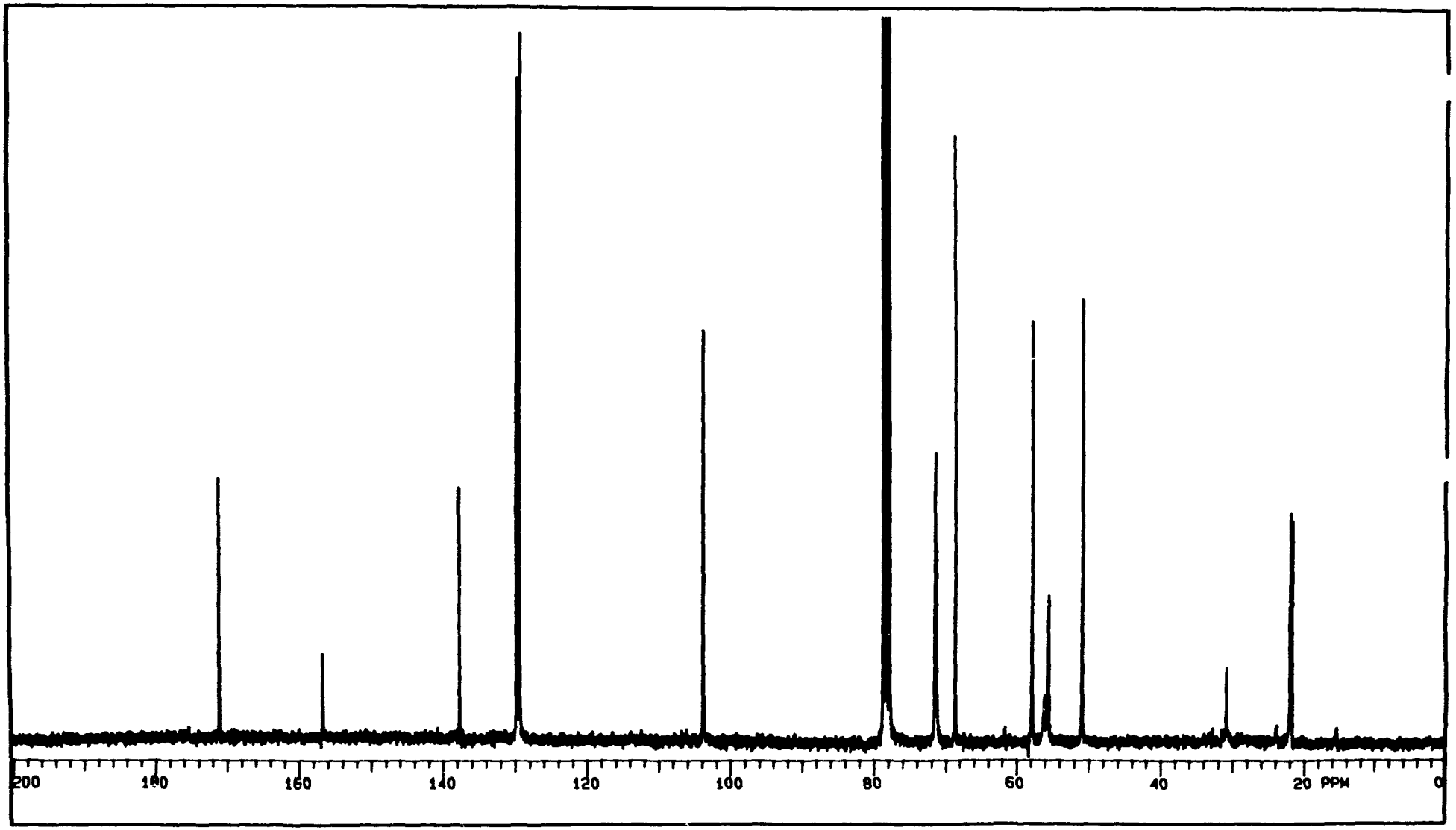
(2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-epoxy-2-dimethoxymethylpyrrolidine (3.20)



(2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-diacetoxy-2-dimethoxymethylpyrrolidine (3.27)



(2*S*,3*S*,4*R*)-N-benzyloxycarbonyl-3,4-diacetoxy-2-dimethoxymethylpyrrolidine (3.27)



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CHAPTER 4

THE INDOLIZIDINE SYSTEM II : NUCLEOPHILIC CYCLISATION.

4.0 A new approach to the cyclisation :

It is clear from the work descrideb in **Chapter 2** that another methodology had to be devised for the construction of the indolizidine ring system. Up to now, all the different approaches had a similar strategy : to the nitrogen atom was appended the chain that would ultimately cyclise onto the modified carboxylic group of the proline derivative (**Scheme 4.1**). An alternative would be to add a chain to this carboxylic derivative that would eventually bear a leaving group. This leaving group could then be displaced by the free nitrogen atom to form the bicyclic system. Such a chain should bear some reactive moieties that would later form the substituents of the molecules of interest.

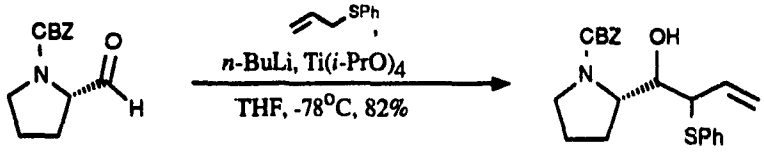
First strategy Second strategy

Scheme 4.1

4.1 A model for castanospermine :

There are numerous methods for the addition of substituted carbon chains to

an aldehyde (or one of its many derivatives)[1]. After searching the literature for such methods, it was found that the addition of an [(arylthio)allyl]titanium reagent[2] suited our purposes very well. The addition of this reagent to the protected prolinaldehyde (see **Chapter 2**) would introduce an alcohol next to the already existing chiral center of the proline derivative and an allylsulfide. The latter could then be modified to the desired substituted chain.

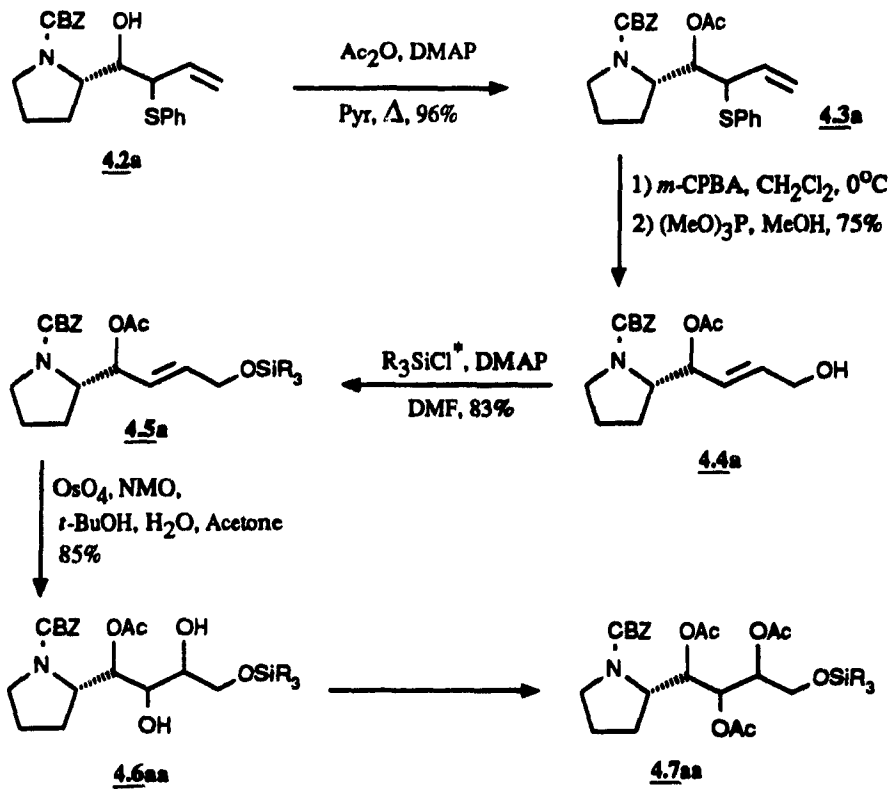


2.20 4.2a and b

Scheme 4.2

Thus, addition of the titanium reagent to aldehyde **2.20** was carried out according to the literature methodology[2,3] and gave a mixture of only two out of the four possible isomers in a ratio of 2:1 (**Scheme 4.2**). At this point, the NMR analysis was inconclusive in the assignment of the relative (and/or absolute) stereochemistry of alcohols **4.2a** and **4.2b**. As will be seen later, the structure of these alcohols was determined only at the bicyclic stage.

The next few steps were envisaged to introduce both the reactive functionalities and the leaving group. An allylic sulfoxide rearrangement appeared to be the perfect reaction for such a modification. It would form an allylic alcohol, which, after suitable protection, could be oxidized to the diol. **Scheme 4.3** illustrates this sequence, which was performed only on compound **4.2a**. The other isomer **4.2b** was studied later. Thus, alcohol **4.2a** was protected as acetate **4.3a** in excellent yield. The sulfide was then oxidized with *meta*-chloroperoxybenzoic acid to the sulfoxide, which

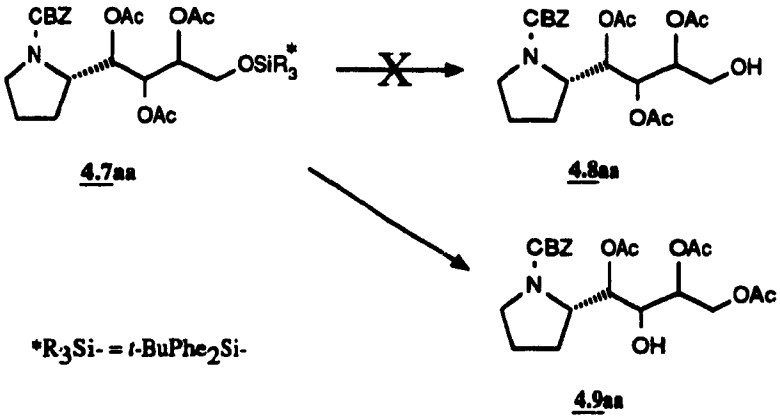


* R_3SiCl = *t*-BuPhe$_2$SiCl

Scheme 4.3

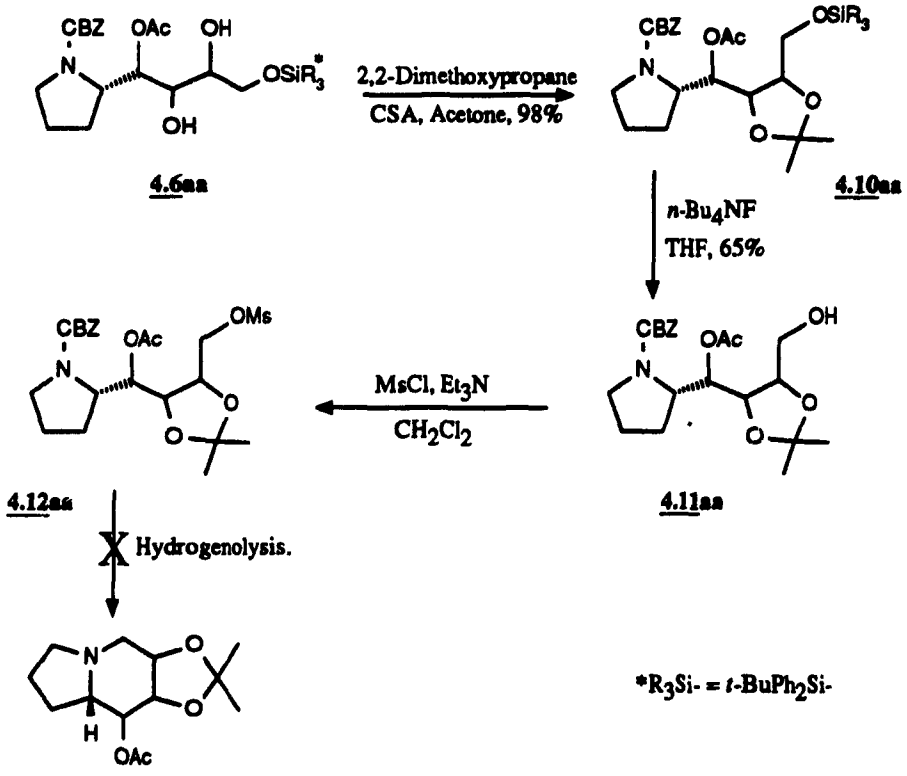
was treated with trimethyl phosphite[4] to give allylic alcohol **4.4a** in 75% overall yield. Protection of the alcohol with *t*-butylchlorodiphenylsilane[5] (**4.5a**) was followed by dihydroxylation of the double bond with osmium tetroxide using N-methylmorpholine-N-oxide[6] as a cooxidant, to give a mixture of two isomers **4.6aa** and **ab** in a 3:1 ratio. These isomers were easily separated by flash chromatography. Here again, the stereochemistry was not determined and the sequence was continued with the major isomer. Protection of the diol **4.6aa** afforded triacetate **4.7aa** in 88% yield.

Conversion of the primary alcohol into a good leaving group and deprotection of the amine were the next steps. The silicon protecting group of **4.7aa** was removed with tetra-*n*-butylammonium fluoride[7] (**Scheme 4.4**). Unfortunately, the major



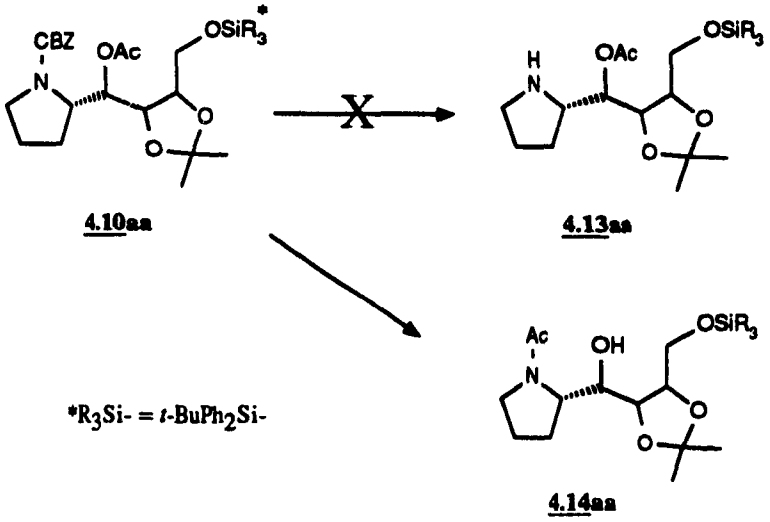
Scheme 4.4

compound of the reaction was not the free primary alcohol **4.8aa**, but the free secondary alcohol **4.9aa**. Modifying the conditions did not change the outcome of the reaction. So, instead of using actetate groups for the protection of **4.6aa**, an isopropylidene (**4.10aa**) was prepared (**Scheme 4.5**). This time, the removal of the silicon moiety was not accompanied by the migration of the other protecting groups. Mesylation of alcohol **4.11aa** afforded the mesylate **4.12aa** which was subjected to hydrogenolysis[8,9] conditions in the hopes that the benzoxycarbonyl protecting group would be removed and that the free amine would displace the mesylate leaving group *in situ* to form the bicyclic tertiary amine. Such a reaction did not take place, and even under forcing conditions, the CBZ protecting group was not removed. Other reagents such as trimethylsilyl iodide (TMSI) are known to cleave the CBZ group[10]. Since it was not sure at this point if the mesylate group would survive the conditions required for such a reaction, it was first attempted on the protected alcohol **4.10aa** (**Scheme 4.6**). The



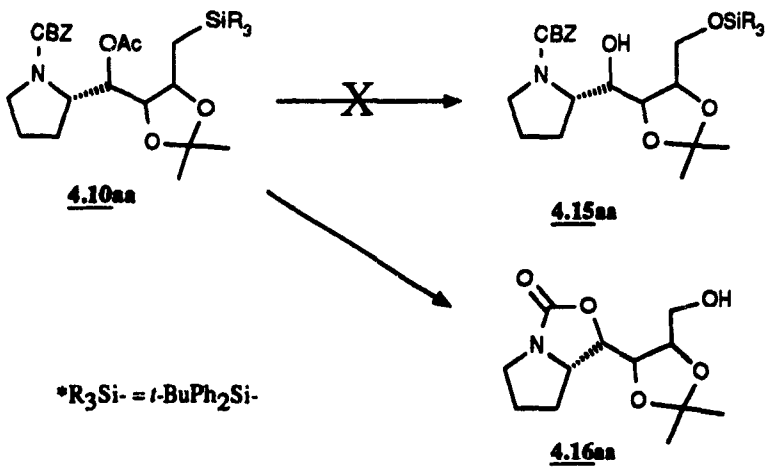
Scheme 4.5

primary alcohol could then be deprotected and activated (not with a mesylate, since mesyl chloride would react first with the free amine) using Mitsunobu's conditions[11,12]. So, **4.10aa** was treated with TMSI in acetonitrile to give a modest yield of a compound (**4.14**) which had no more benzylic protons by ^{1}H NMR. On the other hand, the infra-red spectrum of the compound showed a strong absorbtion in the carbonyl region, *but not at the expected 1750-1730 cm^{-1}* (acetate). The peak was at 1636 cm^{-1}, which is characteristic of an amide. Thus, the carbamate was indeed cleaved by the TMSI reagent, but the acetate rapidly migrated to the nitrogen atom. This facile migration might have occured as a result of the steric hindrance around the acetate due to the presence of the large *t*-butyldiphenylsilyl protecting group and the dimethyl acetonide.



Scheme 4.6

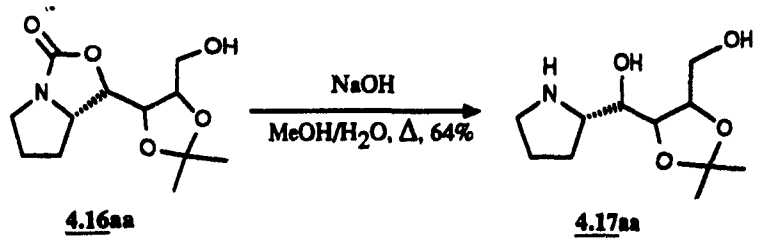
Since it did not seem possible to deprotect the nitrogen atom without deprotecting its neighbouring alcohol, a sequence involving the deprotection of both the amine and the alcohol was envisaged. The deprotection of the primary alcohol could be carried out right after this step and a cyclisation could be attempted, hoping that the free secondary alcohol would not interfere with this reaction. The cleavage of the acetate was first attempted so that there would be no subsequent migration problems. Thus, **4.10aa** was subjected to basic conditons (potassium carbonate in a methanol/water mixture : **Scheme 4.7**) to give a good yield of only one compound (**4.16aa**). This compound, though, proved not to be the expected free alcohol **4.15**. Indeed, the ^{1}H NMR showed the disappearance of the acetate protons, *as well as the t-butyl, phenyl and benzylic protons*. The only protecting group left was the acetonide. It was first thought that these conditions were hydrolysing the acetate as well as the carbamate and silicon protecting groups. But the analysis of the infra-red spectrum of **4.16aa** showed the presence of a strong carbonyl absorption at 1757 cm^{-1}. The only part of the molecule which could possibly feature a carbonyl would be the carbamate, so this carbonyl was



Scheme 4.7

still bonded to **4.16aa**, but had somehow lost its benzylic moiety. Because of the proximity of the secondary alcohol (its acetate protecting group being probably hydrolysed before the carbamate) and because of the ease of formation of five membered rings, it is plausible to assume that the free alcohol could displace the benzyl alcohol of the carbamate and form bicyclic carbamate **4.16aa**.

In order to confirm this hypothesis, **4.16aa** was treated with sodium hydroxide in a methanol/water mixture (**Scheme 4.8**). The cyclic carbamate was easily hydrolysed

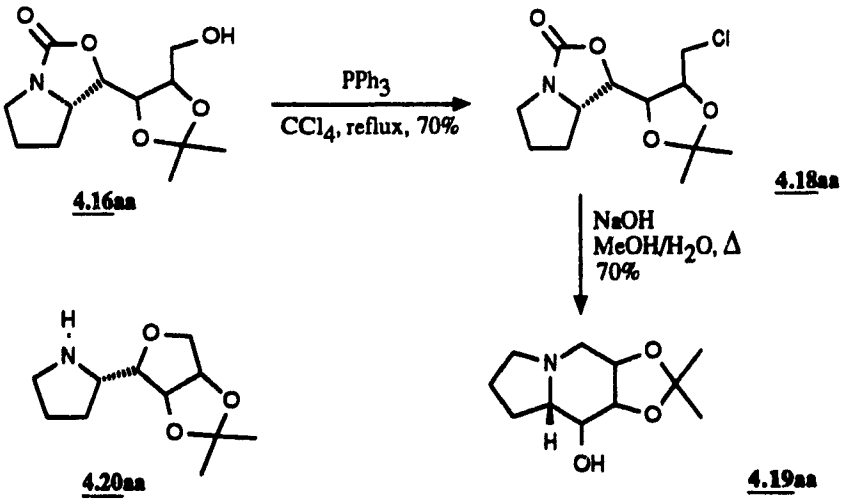


Scheme 4.8

to give the very polar amino-diol **4.17aa**. There was no carbonyl absorption in the infra-red spectrum of this compound.

It appeared at that moment that the cyclic carbamate of **4.16aa** was a very good protecting group since it was protecting both the secondary alcohol and the amine at the same time. It could be introduced at the very beginning of the synthesis, preventing the use of an acetate group and all its following problems. But before going back to the beginning, the synthesis of the cyclic compound was completed using **4.16aa**.

Since the hydrolysis of the carbamate required basic conditions, it was not sure at this point if a mesylate was the leaving group of choice. It could very well be displaced by the hydroxide ion. In order to have a leaving group that would not be displaced that easily by an intermolecular S_N2 displacement but that would still be displaced by an intramolecular one, the primary alcohol of **4.16aa** was transformed into a chloride by the action of triphenylphosphine in carbon tetrachloride[13] (**Scheme 4.9**).



4.16aa **4.18aa** **4.20aa** **4.19aa**

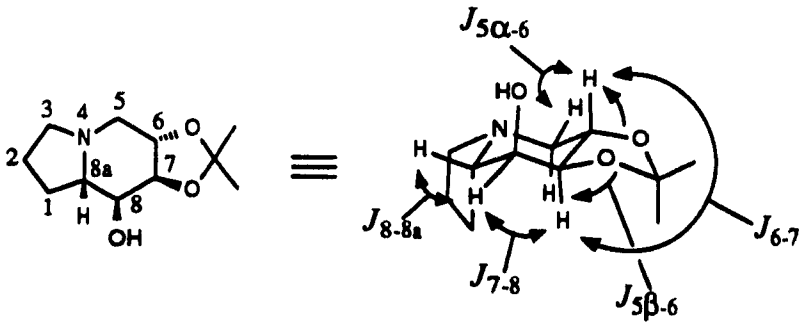
Scheme 4.9

This reaction gave chloride **4.18aa** in excellent yield, which was subjected to the hydrolysis conditions previously mentioned. Bicyclic [4.3.0] amino-alcohol **4.19aa**, produced by the nucleophilic displacement of the chloride by the free secondary amine, was the only expected product; bicyclic amino-ether **4.20aa**, produced by the nucleophilic displacement of the chloride by the free secondary alcohol also deprotected during the hydrolysis being too strained to be formed.

After 48 hours at 70°C, all of the starting chloride had disappeared to give, after work-up, a waxy solid that proved to be bicylcic amino-alcohol **4.19aa**.

The next task was to determine the stereochemistry of **4.19aa**. With the help of COSY, HETCOR and decoupling experiments, all the protons were assigned. Using the coupling constants of each peak, the stereochemistry was determined as shown in **Scheme 4.10**. The coupling constants between H7 and H8, and H8 and H8a, are important in the determination of the absolute stereochemistry of **4.19aa**. Indeed, the coupling constant between H6 and H7 will always be large, whatever the conformation of the product, since these hydrogens will always have a *trans* diaxial relationship (because the hydroxylation reaction always gives a *cis* diol : after rotation, the diol is always *trans* and the two oxygens cannot be diaxial due to the presence of the acetonide). The relation between H6, H5α and H5β will also be similar regardless of the conformation : there will always be one proton with a *trans* diaxial relationship (large constant) with H6 and one with a *cis* axial-equatorial relationship (small constant) with H6. Since the absolute stereochemistry at C8a is known, it is easy, with the help of the observed $J_{7\text{-}8}$ and $J_{8\text{-}8a}$, to determine the stereochemistry at C8, and thus, the conformation of the whole molecule. Since H8 displays two small coupling constants, the only possibility is the one shown in **Scheme 4.10**

The stereochemistry of carbon 8 of **4.19aa** is generated by the very first step of the sequence, that is the additon of the titanium reagent to aldehyde **2.20**. The



4.19aa

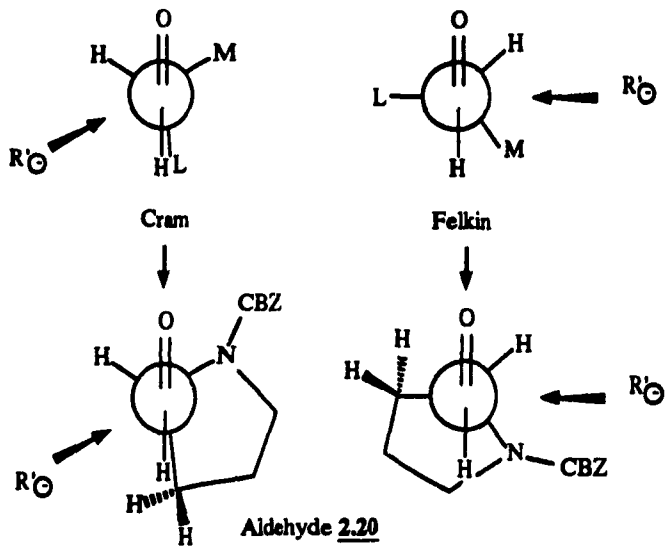
Scheme 4.10

Table 4.1

Coupling constants (Hz)	
$J_{5\alpha\text{-}5\beta}$	9.7
$J_{5\alpha\text{-}6}$	4.1
$J_{5\beta\text{-}6}$	9.7
$J_{6\text{-}7}$	9.7
$J_{7\text{-}8}$	2.2
$J_{8\text{-}8a}$	2.2

stereochemical outcome of this reaction should be governed by the Cram[14] or Felkin[15] rules. Using one or the other set of rules, one discovers that the predicted major isomer is indeed the one that was obtained (see **Scheme 4.11**). The relative stereochemistry between carbons 8 and 8a in **4.19aa** is the same as in both swainsonine and castanospermine, the absolute stereochemistry being the opposite (8*R*,8a*R* instead of 8*S*,8a*S*) in the case of the latter.

The stereochemistry of carbons 7 and 6 is generated by the hydroxylation reaction (**4.5a** → **4.6aa**). The stereochemical outcome of the hydroxylation of a double bond that has a chiral center (one of the substituents of that chiral center being a protected alcohol) at the allylic position has been studied extensively by Kishi *et al*[16].

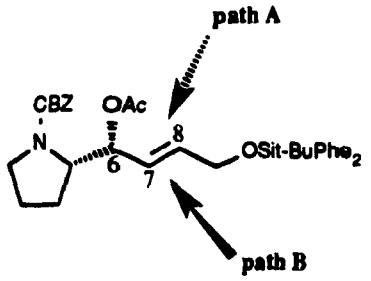


M = Medium sized group.
L = Large sized group.

Scheme 4.11

They have concluded that "*the relative stereochemistry between the preexisting hydroxyl or alkoxyl group and the adjacent newly introduced hydroxyl group of the major product in all cases is erythro*". The result for the hydroxylation of **4.5a** is in complete agreement with that conclusion (see **Scheme 4.12**). Unfortunately, the relative stereochemistry of carbons 8,7 and 6 in **4.19aa** is wrong as far as castanospermine is concerned, the stereochemistry of both carbons 7 and 6 being the opposite one. Thus, the minor compound in the hydroxylation of **4.5a** (compound **4.6ab**) would have those three centers with the right stereochemistry. As for swainsonine, it does not have hydroxyl groups at positions 7 and 6.

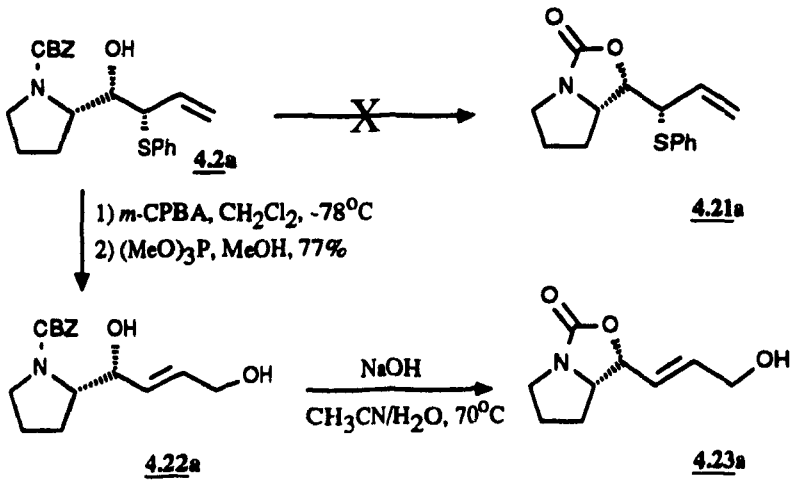
Scheme 4.9 has demonstrated that it was possible to use the cyclic carbamate in order to produce the bicyclic amine **4.19aa**. In order to shorten the synthesis by one step, it was thought that such a cyclic carbamate could be introduced at the very beginning of the sequence, instead of using an acetate group (refer to **Scheme 4.3**).



Path B is favored : OsO_4 attacks the double bond opposite to the existing acetoxy group (position 6) leading to the erythro compound.

Scheme 4.12

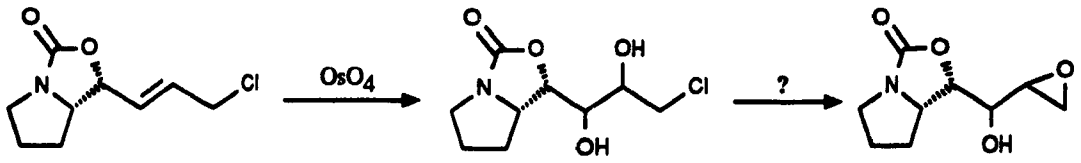
Attempts to cyclise 4.2a using the hydrolytic conditions failed to give the desired carbamate 4.21a (**Scheme 4.13**). On the other hand, when the sulfoxide



Scheme 4.13

rearrangement was first carried out directly on 4.2a, the allylic diol obtained (4.22a) easily cyclised to form the cyclic carbamate 4.23a. At this point, the sequence shown

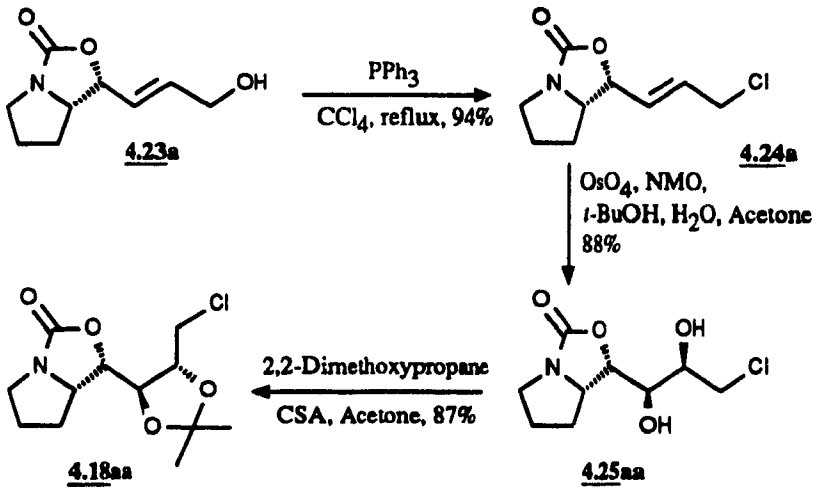
previously could have been used in order to finish the synthesis, that is, protection of the primary allylic alcohol with *tert*-butyldiphenylsilyl chloride, hydroxyxlation of the double bond and protection of the diol thus formed as an acetonide, deprotection of the primary alcohol and conversion to the chloride. This sequence should lead to **4.18aa** (**Scheme 4.9**). But converting the allylic alcohol directly to the chloride and then performing the hydroxylation reaction would shorten the sequence by two further steps. One possible problem could be the cylisation of the hydroxy-chloride to form the epoxide, as in **Scheme 4.14**. But since the protection step would be done right after the



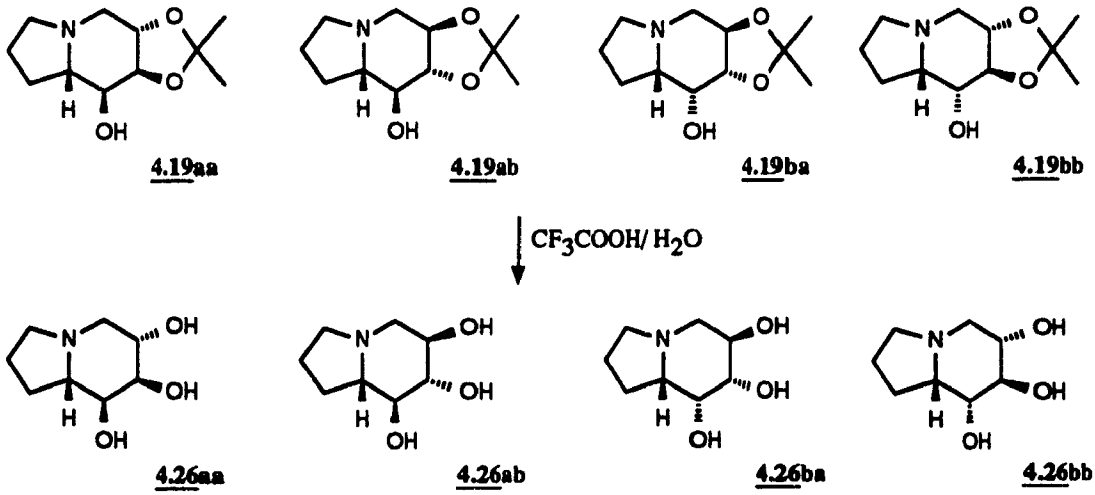
Scheme 4.14

hydroxylation, and since only mild acidic conditions would be used for that protection, the new sequence was worth trying. **Scheme 4.15** shows that such worries were unnecessary. Primary allylic alcohol **4.23a** was easily tranformed into chloride **4.24a** using the triphenylphosphine-carbon tetrachloride method, which was then hydroxylated to the diols **4.25aa** and **4.25ab** (3:1 mixture). Here again, only the major isomer **4.25aa** was used to continue the sequence. Protection of the diol with 2,2-dimethoxypropane in acetone gave a protected chloride which was identical to **4.18aa**. Of course, the cyclisation proceeded in an identical fashion.

Having thus completed the sequence for the major isomer of the bicylic amino-alcohol, the last task was to synthesise the three other possible isomers (**Scheme 4.16**) : **4.19ab** (major alkylation, minor hydroxylation), **4.19ba** (minor alkylation, major



Scheme 4.15



Scheme 4.16

hydroxylation) and **4.19bb** (minor alkylation, minor hydroxylation). Derprotection of the four isomers was accomplished using trifluoroacetic acid[17] in water to give the four

different amino-triols **4.26aa-bb**. The ^{1}H and ^{13}C NMR chemical shifts of the four different isomers (protected as the acetonide since the patterns of the ^{1}H NMR are clearer) are shown in **Table 4.2** and **Table 4.3** respectively. The coupling constants and the conformations of the four isomers are also reported (**Table 4.4**).

Table 4.2

(chemical shifts in p.p.m.)

Isomer	H#1 + H#2(4H)	H#3 (2H)	H#5α	H#5β	H#6	H#7	H#8	H#8a
4.19aa	1.95-1.63	3.02 + 2.28	2.21	3.37	4.01	3.39	4.12	2.28
4.19ab	1.98-1.55	2.94 2.75	2.93	2.63	3.62	3.64	4.13	2.76
4.19ba	2.01-1.50	2.92 + 2.58	2.96	2.72	4.11	3.70	4.19	2.92
4.19bb	2.15-1.55	2.99 + 2.35	2.24	3.26	3.64	3.33	3.54	2.05

Table 4.3

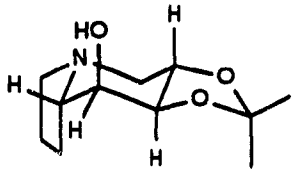
(chemical shifts in p.p.m.)

Isomer	C#1 + C#2	C#3	C#5	C#6	C#7	C#8	C#8a
4.19aa	23.8 + 22.4	52.6	52.8	65.5	71.2	83.1	65.2
4.19ab	22.5 + 21.4	51.1	54.4	69.1	74.5	81.4	65.0
4.19ba	26.7 + 21.9	52.2	54.2	67.2	71.0	78.5	67.2
4.19bb	26.7 + 22.3	52.0	52.4	72.8	75.0	85.0	67.7

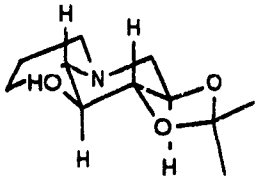
Table 4.4

(coupling constants in Hz)

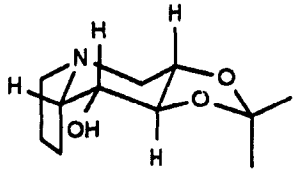
Isomer	$J_{5\alpha\text{-}5\beta}$	$J_{5\alpha\text{-}6}$	$J_{5\beta\text{-}6}$	$J_{6\text{-}7}$	$J_{7\text{-}8}$	$J_{8\text{-}8a}$
4.19aa	9.7	9.7	4.1	9.7	2.2	2.2
4.19ab	9.7	4.6	9.7	9.4	8.6	6.2
4.19ba	9.6	5.6	9.6	9.6	3.6	3.6
4.19bb	9.7	9.7	3.8	9.3	9.3	8.6



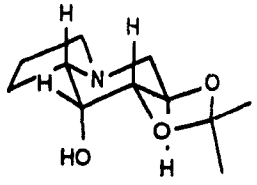
4.19aa



4.19ab

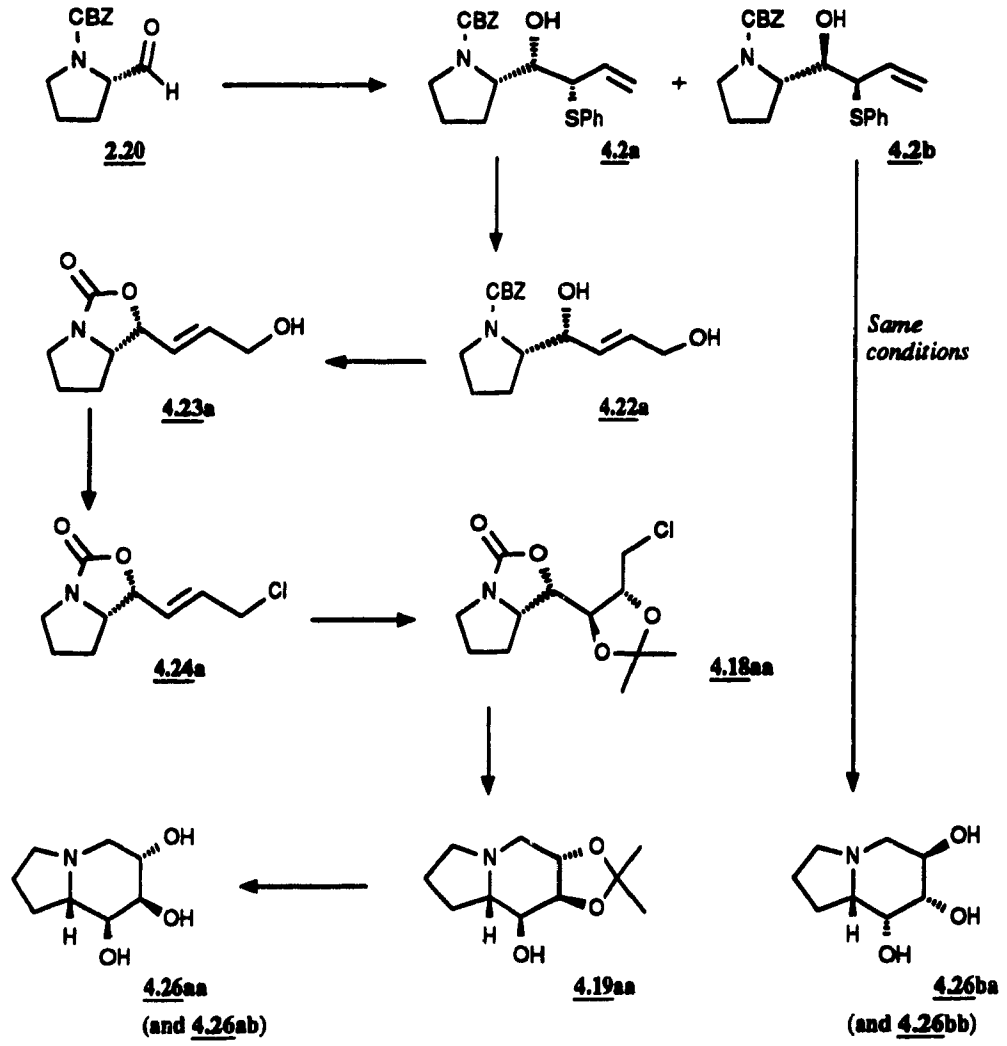


4.19bb



4.19ba

Scheme 4.17 summarises the overall sequence, starting from aldehyde **2.20**.



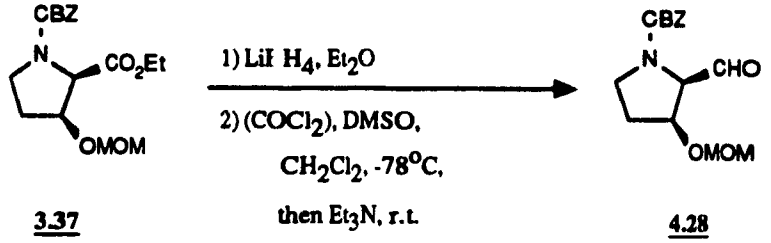
Scheme 4.17

4.2 Attempted synthesis of castanospermine :

Utilising the strategy developed in **Section 4.1** and starting with the 3-hydroxyproline derivative prepared in **Chapter 3** (see **Section 3.2**), the total synthesis of the natural (+)-castanospermine could now be attemped. The first step was to

transform the ethyl ester of compoud **3.37** into an aldehyde to which the [(arylthio)allyl]titanium reagent (similar to **Scheme 4.2**) could be added. The allyl sulfide thus produced would then be modified as described previously.

Thus, reduction of **3.37** with lithium borohydride in ether gave a good yield of primary alcohol **4.27** (**Scheme 4.18**), which was oxidized to the aldehyde **4.28** (DMSO,

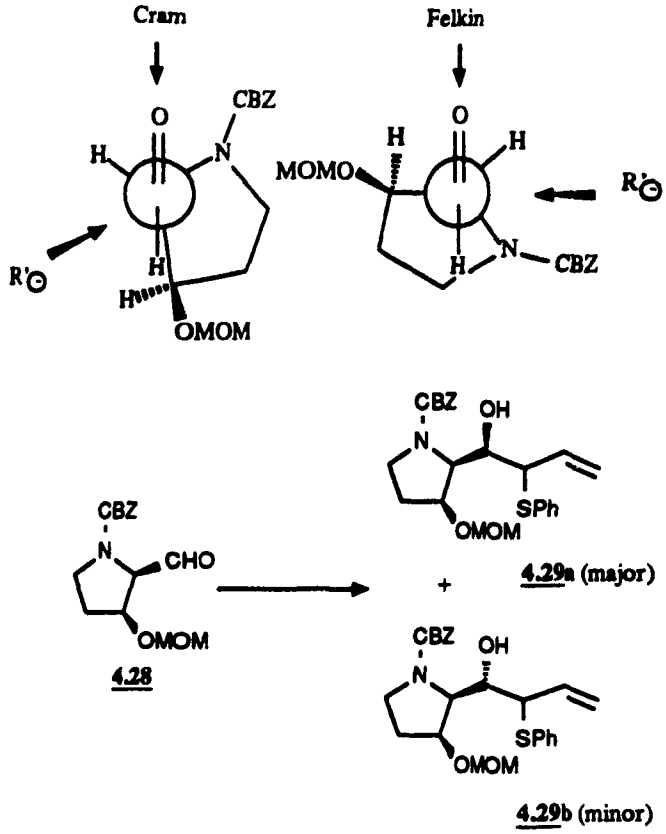


3.37 **4.28**

Scheme 4.18

$(COCl)_2$) in quantitative yield. The presence of an additional group at the 3 position of the pyrrolidine ring should now improve the stereoselectivity of the titanium reagent addition. Since this protected hydroxyl group is at the position of the "large" substituent of both Cram's and Felkin's models (see **Scheme 4.11**) and since the incoming nucleophile prefers to attack the aldehyde from the opposite side (2:1 mixture in the case of aldehyde **2.20**), it is reasonable to think that the facial stereoselectivity should be improved. Experimentally, when the titanium reagent was added to aldehyde **4.28**, only one isomer was obtained, tentatively assigned as **4.29a** (**Scheme 4.19**).

The rest of the sequence was staightforward and similar to the one described in **Scheme 4.17**. The presence of the newly introduced protected hydroxyl group didn't seem to change dramatically the reactivity of the molecule when compared with the



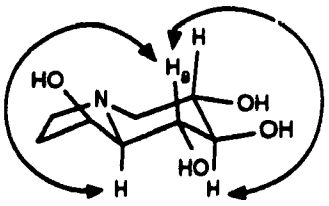
Scheme 4.19

models. A few reaction times were longer, or some reactions had to be conducted at slightly higher temperatures. The osmium tetroxide catalised hydroxylation of **4.33a** gave a slightly poorer ratio (2:1) if compared to the hydroxylation of **4.25aa-bb (Scheme 4.15)**. Interestingly, the cyclisation of compound **4.34ab (Scheme 4.21)** also promoted the cleavage of both the isopropylidene and MOM protecting groups. This was highly unexpected since those two protecting groups are expected to be stable to basic conditions[20]. The final deprotection of **4.35aa** was not as described in **Scheme 4.17** : a method that would hydrolyse both the acetonide and MOM ether protecting groups was used here. Thus, 6 M HCl in tetrahydrofuran[21] was used instead of the trifluoroacetic

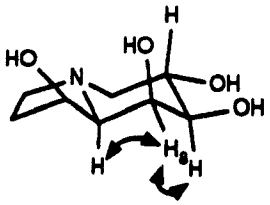
acid/water method, affording, to our great surprise, not (+)-castanospermine and its (+)-6,7-epi-isomer but (+)-8-epicastanospermine (**4.36aa**) and (-)-6,7,8-triepicastanospermine (**4.36ab**). The fact that the stereochemistry of carbon 8 is not the one predicted means that the models proposed in **Scheme 4.19** are wrong. It is possible that the determining factor here is not the increase of the steric hinderance due to the newly introduced MOM group but the complexing ability of this very group. The two oxygens of the MOM group could very well complex the titanium atom of the organometallic reagent and help deliver the allylic sulfide from the other face of the aldehyde.

Scheme 4.20 compares the coupling constants of H_8 in compound **4.36aa** with (+)-castanospermine itself[22], whereas compound **4.36ab** is compared with the structurally similar **4.26bb**. The H_8 proton of (+)-castanospermine is axial, has two *trans* diaxial couplings and displays two equally large coupling constants (180°, large coupling constants : 9.6 Hz[22]). The H_8 proton of **4.36aa** is equatorial, has two *cis* axial-equatorial couplings and therefore should display two small coupling constants. This is actually confirmed by the ^{1}H NMR (see experimental : 60°, two small coupling constants : 1.2 and 3.0 Hz). As for compound **4.36ab**, its six membered ring has exactly the same arrangement as in compound **4.26bb**. On the other hand, it has an extra hydroxyl group pointing directly inside the concave face of the molecule. Because of this, the six membered ring cannot adopt a chair conformation and probably has a tendency to push this OH group away from the concave face, thus adopting a semi-boat conformation. The result of this is that the protons do not have the same conformation as in **4.26bb** (these protons are almost all axial and display large coupling constants : see experimental **4.26bb**) but have an eclipsed arrangement with dihedral angles smaller than 120° (this will give rise to small coupling constants, as observed in the ^{1}H NMR of **4.36ab**). This sterically demanding conformation could also explain why **4.36ab** is more

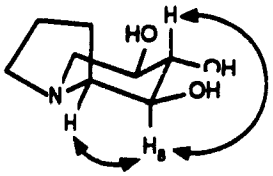
difficult to form than its isomer **4.36aa** (a longer time is necessary for the complete consumption of the starting material). It could also explain why the MOM group is eliminated from the molecule, therefore reducing the steric constraints.



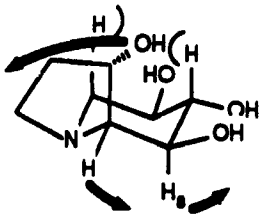
(+)-castanospermine
Two *trans* diaxial couplings :
large constants.



4.36aa
Two *cis* axial-equarorial couplin
Small constants.



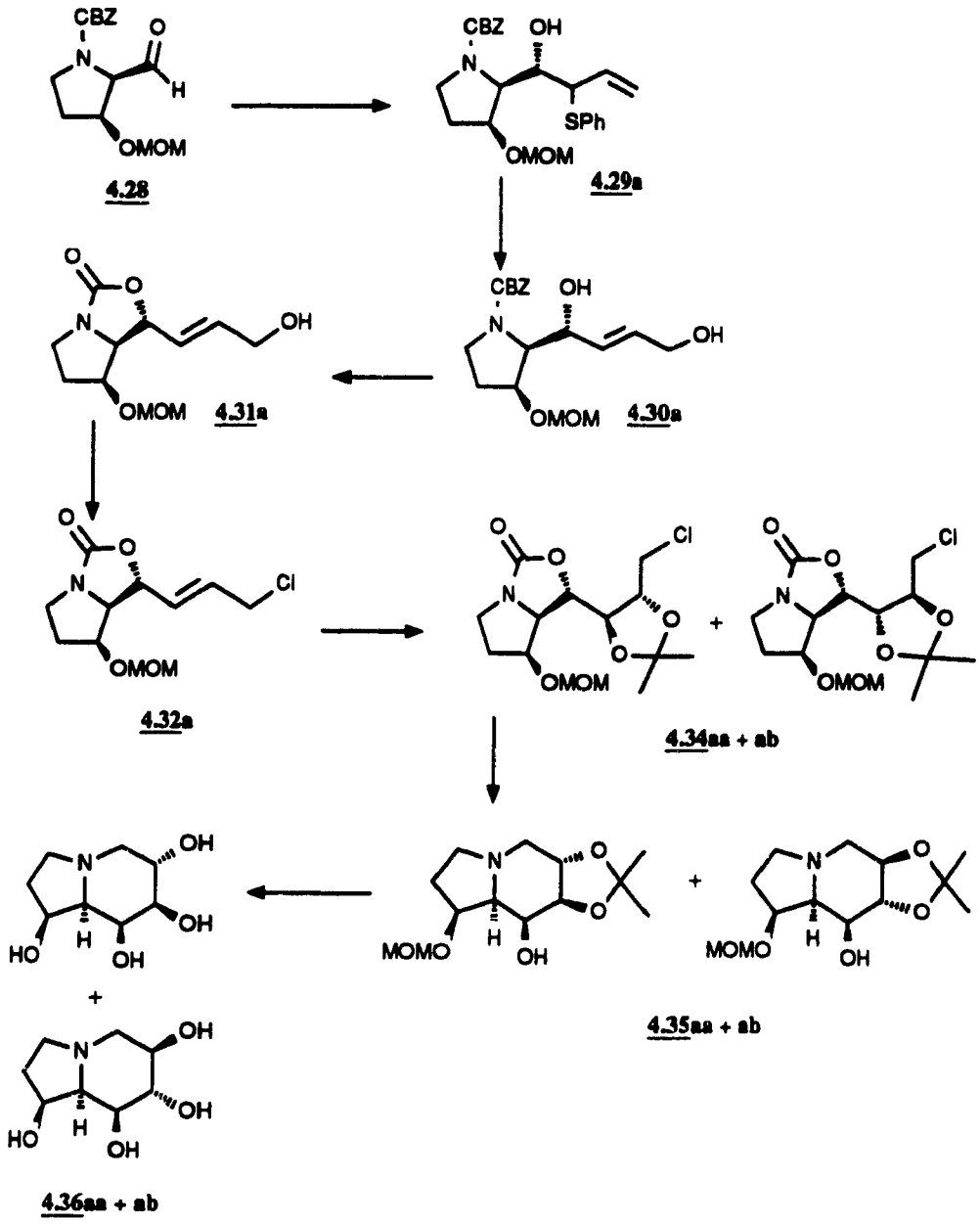
4.26bb : mirror image
Two large constnts



4.36ab
Steric repulsion
Small constants

Scheme 4.20

Finally, **Scheme 4.21** illustrates the whole sequence.



Scheme 4.21

4.3 Experimental :

General methods. See Chapter 2, section 2.5.

Preparation of Allylphenyl sulfide (4.1): To a freshly prepared solution of sodium ethoxide in ethanol (1.25 g of Na, 1 eq, in 18.0 mL of absolute ethanol) at 0°C, under argon, were added successively thiophenol (5.59 mL, 54.4 mmol) and then slowly allyl bromide (5.18 mL, 1.1 eq). The solution was stirred at room temperature for 15 hr and the ethanol and excess allyl bromide were evaporated. The residual slurry was dissolved in water, the aqueous phase extracted with ether (2x) and the combined organic extracts were dried over magnesium sulfate. Filtration followed by evaporation of the solvent gave a yellow oil that was distilled (48°C, 0.025 mmHg) to yield 7.30 g (90%) of the sulfide as a colourless oil. ^{1}H NMR ($CDCl_3$)[18] : δ 7.38-7.15 (m, 5H), 5.83 (ddt, 1H, *J*=6.5, 10, 18), 5.02 (dd, 1H, J=1,18), 4.98 (dd, 1H, *J*=1,10), 3.43 (d, 2H, *J*=6.5).; exact mass calcd for $C_9H_{10}S$ ($M^{\cdot+} + H^+$) 151.0582, found 151.0582.

Preparation of (2*S*,1'*S*,2'*S*) and (2*S*,1'R,2'*R*)-N-benzoxycarbonyl-2-(1'-hydroxy-2'-thiophenyl-3'-butenyl)-pyrrolidine (4.2a and 4.2b): To a solution of allylphenyl sulfide **4.1** (0.23 g, 1.5 eq) in 3.46 mL of dry THF, at -78°C, under argon, was added *n*-butyllithium (2.0 M in pentane, 0.74 mL, 1.5 eq) and the solution was stirred at 0°C for 30 min. It was then cooled down to -78°C and titanium (IV) isopropoxide (0.44 mL, 1.5 eq) was added slowly. After 10 min, the aldehyde **2.20** (0.23 g, 0.99 mmol, in 0.5 mL of THF) was added over a period of 10 min. The solution was stirred for 10 min and warmed up at 0°C for 30 min. It was then poured into sat. aq. NH_4Cl and extracted with ether (3x). The combined organic extracts were washed with brine, dried over magnesium sulfate and filtered. Evaporation of the solvents followed

by flash chromatography (silica gel, 8:2 hexanes/ethyl acetate; for prevention of thioallylic rearrangements of the produced phenyl sulfides, small amounts of 2,6-di-*tert*-butyl-4-methylphenol were added to the solvents during the work-up and chromatographic operations[19]) gave two different isomers **4.2a** and **b** in a total combined yield of 82% (**a**:**b** = 1.7:1.0). **4.2a** (2*S*,1'*S*,2'*S*): 0.20 g, 52% : $[\alpha]^{20}_D$= -107.7° (*c* : 1.54 in $CDCl_3$). IR (neat) : 3328 (broad), 2976, 2883 and 1666 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.62-7.20 (m, 10H), 6.12 (m, 1H), 5.32 (bs, 1H), 5.14 (s, 2H), 5.08 (dd, 1H, *J*=0.7, 6.8), 4.88 (dd, 1H, *J*=0.7, 11.4), 3.99 (m, 1H), 3.84 (m, 1H), 3.66-3.54 (m, 2H), 3.34 (dt, 1H, *J*=4.4, 7.2), 2.06-1.60 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 159.14, 136.75, 134.15, 133.66, 129.30, 129.08, 128.72, 128.56, 127.88, 118.46, 77.80, 68.04, 61.92, 57.71, 47.45, 28.60, 24.28. Exact mass calcd for $C_{22}H_{25}NO_3S$ ($M^{\cdot+}$ + H^+) 384.1635, found 384.1633. **4.2b** (contaminated with a small amount of **4.2a**)(2*S*,1'*R*,2'*R*): 0.12 g, 30% : $[\alpha]^{20}_D$= -55.7° (*c* : 1.86 in $CHCl_3$). IR (neat) : 3380 (broad), 2976, 2880 and 1666 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.62-7.20 (m, 10H), 5.82 (m, 1H), 5.20-4.75 (m, 4H), 4.31-3.90 (m, 2H), 3.72-3.20 (m, 4H), 2.15-1.60 (m, 4H). ^{13}C NMR : δ 156.57, 137.25, 135.33, 133.62, 129.36, 129.03, 128.56, 128.47, 127.96, 117.75, 77.82, 67.34, 61.59, 55.97, 47.76, 26.61, 24.61. Exact mass calcd for $C_{22}H_{25}NO_3S$ ($M^{\cdot+}$ + H^+) 384.1635, found 384.1633.

Preparation of (2*S*,1'S,2'S)-N-benzoxycarbonyl-2-(1'-acetoxy-2'-thiophenyl-3'-butenyl)-pyrrolidine (4.3a): To a solution of alcohol **4.2a** (0.14 g, 0.36 mmol) in 3.6 mL of dry pyridine, at rt, under argon, were added successively 4-dimethylaminopyridine (4.4 mg, 0.1 eq) and acetic anhydride (0.14 mL, 4 eq) and the solution was warmed to 70°C and maintained at this temperature for 15 hr. The pyridine was then evaporated *in vacuo* and the residue taken up in ethyl acetate, washed with 5% HCl (1x), sat. aq. $NaHCO_3$, brine and dried over magnesium sulfate. Filtration followed by evaporation of the solvent and flash chromatography (silica gel, 8:2 hexanes/ethyl

acetate) gave 0.15 g (96%) of acetate **4.3a** as a pale yellow oil : $[\alpha]^{20}_D$= -32.9° (*c* : 1.91 in $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 7.62-7.20 (m, 10H), 5.89 (m, 1H), 5.22-4.86 (m, 5H), 4.27 (m, 1H), 3.70 (m, 1H), 3.48 (m, 1H), 3.32 (m, 1H), 1.90 (s, 3H), 1.98-1.60 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 155.86, 134.29, 134.04, 129.41, 128.95, 128.42, 119.11, 77.68, 75.17, 74.67, 67.07, 58.45, 58.35, 54.84, 46.60, 29.29, 28.36, 23.83, 22.96, 20.79. Exact mass calcd for $C_{24}H_{27}NO_4S$ ($M^{\cdot+}$ + H^+) 426.1740, found 426.1737.

Preparation of (2*S*,1'*R*)-N-benzoxycarbonyl-2-(1'-acetoxy-2'-buten-4'-ol)-pyrrolidine (4.4a): To a solution of acetoxysulfide **4.3a** (0.14 g, 0.32 mmol) in 3.2 mL of dry methylene chloride, at 0°C, under argon, was added *m*-chloroperoxybenzoic acid (69.4 mg. 1.3 eq) and the solution was stirred for 2 hr. Ether was then added, and the solution was washed with sat. aq. $NaHCO_3$ (2x), dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was dissolved in 3.2 mL of dry methanol and trimethyl phosphite (0.38 mL, 10 eq) was added slowly. After 3 hr of stirring, the methanol was evaporated and the thick oil was purified by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate) to give 80.2 mg (75%) of the pure allylic alcohol **4.4a** : $[\alpha]^{20}_D$= -55.2° (*c* : 1.50 in $CHCl_3$). IR (neat) : 3345 (broad), 2978, 1733 and 1693 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.50-7.22 (m, 5H), 5.93-5.50 (m, 2H), 5.51 (dd, 1H, *J*=6.0), 5.15 (m, 2H), 4.10 (m, 3H), 3.51 (m, 1H), 3.34 (m, 1H), 1.90 (s, 3H), 2.05-1.75 (m, 5H).; exact mass calcd for $C_{18}H_{23}NO_5$ ($M^{\cdot+}$ + H^+) 334.1655, found 334.1656.

Preparation of (2*S*,1'*R*)-N-benzoxycarbonyl-2-(1'-acetoxy-2'-buten-4'-*t*-butyldiphenyl-silyloxy)-pyrrolidine (4.5a): To a solution of allylic alcohol **4.4a** (0.32 g, 0.95 mmol) in 1.90 mL of dry dimethylformamide, at room temperature, under argon, were added successively imidazole (0.26 g, 4 eq) and *t*-butylchlorodiphenylsilane (0.50 mL, 2 eq). The solution was heated at 70°C for 5 hr. Ether was then added and the

solution was washed with water (2x), brine, and was dried over magnesium sulfate. Evaporation of the solvent was followed by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) to give the protected allylic alcohol **4.5a** as a colourless oil (0.45 g, 83%) : $[\alpha]^{20}_D$= -26.5° (*c* : 1.46 in $CHCl_3$). IR (neat) : 3070, 2930, 1741 and 1711 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.65 (m, 4H), 7.50-7.22 (m, 11H), 5.77 (m, 2H), 5.58 (m, 1H), 5.18 (m, 2H), 4.15 (m, 3H), 3.52 (m, 1H), 3.33 (m, 1H), 1.99 (s, 3H), 2.05-1.75 (m, 4H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) : δ 170.51, 155.69, 136.01, 134.25, 133.98, 130.26, 128.97, 128.45, 128.24, 124.55, 124.11, 74.13, 67.12, 63.71, 59.90, 59.23, 47.29, 46.85, 27.02, 23.50, 23.46, 21.31, 19.45. Exact mass calcd for $C_{34}H_{41}NO_5Si$ ($M^{\cdot+}$ + H^+ - CH_3COOH) 512.2623, found 512.2623.

Preparation of (2*S*,1'*S*,2'*S*,3'*S*) and (2*S*,1'*S*,2'*R*,3'*R*)-N-benzoxycarbonyl-2-(1'-acetoxy-2',3'-dihydroxy-4'-*t*-butyl-diphenylsilyloxybutanyl)-pyrrolidine (4.6aa and ab): To a solution of N-methylmorpholineN-oxide (0.10 g, 1.1 eq) and osmium tetroxide (10.0 mg, 0.05 eq) in a mixture of water/*t*-BuOH (6/1, 0.7 mL), at room temperature was added the protected allylic alcohol **4.5a** (0.45 g, 0.78 mmol) dissolved in 0.25 mL of acetone. The solution was stirred for 15 hr, after which 2 mL of a solution-suspension of magnesium silicate and sodium hydrosulfite (1.2 g and 0.1 g respectively in 8 mL of water) was added. The slurry was filtered through celite and the cake rinsed with acetone. The solvents were evaporated and the residue was acidified to pH 2 with 10 M sulfuric acid, saturated with solid NaCl and extracted with ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave a dark brown oil, which was purified by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) affording two diols **4.6aa** and **4.6ab** (3:1 mixture) in a total yield of 85%. **4.6aa** (2*S*,1'*S*,2'*S*,3'*S*): 0.30 g, 64%; $[\alpha]^{20}_D$= -42.1° (*c* : 1.53 in $CHCl_3$). IR (neat) : 3383 (broad), 2957, 1746 and 1674 cm^{-1}. ^1H

NMR ($CDCl_3$) : δ 7.65 (m, 4H), 7.50-7.22 (m, 11H), 5.37-5.00 (m, 4H), 4.53 (m, 1H), 3.90-3.39 (m, 6H), 2.51 (m, 1H), 2.12 (s, 3H), 2.05-1.77 (m, 4H), 1.07 (s, 9H). ^{13}C NMR ($CDCl_3$) : δ 171.27, 158.06, 136.78, 136.14, 134.08, 130.28, 129.11, 128.78, 128.51, 128.29, 77.82, 75.98, 70.31, 68.04, 67.83, 64.81, 57.41, 47.81, 28.69, 27.12, 24.34, 21.41, 19.48. Exact mass calcd for $C_{34}H_{43}NO_7Si$ ($M^{\cdot+} + H^+$) 606.2889, found 606.2887. **4.6ab** (2*S*,1'*S*,2'*R*,3'*R*): 0.10 g, 21%. ^1H NMR ($CDCl_3$) : δ 7.65 (m, 4H), 7.50-7.22 (m, 11H), 5.37-5.01 (m, 4H), 4.25-3.29 (m, 7H), 2.82 (m, 1H), 2.08 (s, 3H), 2.20-1.70 (m, 4H), 1.07 (s, 9H).

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)-N-benzoxycarbonyl-2-(1',2',3'-triacetoxy-4'-*t*-butyldiphenylsilyloxybutanyl)-pyrrolidine (4.7aa): To a solution of diol **4.6aa** (0.19 g, 0.31 eq) in 3.1 mL of dry pyridine were added successively 4-dimethylaminopyridine (3.8 mg, 0.1 eq) and acetic anhydride (88.0 μL, 3 eq). The solution was stirred for 3 h, after which the pyridine was evaporated. The residue was dissolved in ethyl acetate and the resulting solution was washed with 5% HCl, sat. aq. $NaHCO_3$, brine and was dried over magnesium sulfate. Filtration and evaporation of the solvent was followed by flash chromatography purification (silica gel, 7:3 hexanes/ethyl acetate) to give 0.19 g (88%) of triacetate **4.7aa** as a colourless oil. IR (neat) : 2960, 2891, 1741 and 1709 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.64 (m, 4H), 7.50-7.22 (m, 11H), 5.43 (m, 1H), 5.32 (m, 1H), 5.11 (m, 2H), 5.00 (m, 1H), 4.29 (m, 1H), 3.82 (m, 1H), 3.65 (m, 1H), 3.43 (m, 1H), 3.26 (m, 1H), 1.90 (s, 9H), 1.95-1.73 (m, 4H), 1.05 (s, 9H).

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)-N-benzoxycarbonyl-2-(1',3',4'-triacetoxy-2'-hydroxybutanyl)-pyrrolidine (4.9aa): To a solution of triacetate **4.7aa** (0.19 g, 0.27 mmol) in 2.7 mL of dry tetrahydrofuran, at room temperature, under argon, was added tetra-*n*-butylammonium fluoride (1.0 M in THF : 0.33 mL, 1.2 eq) and the solution was

stirred for 1.5 hr. Evaporation of the solvent followed by flash chromatography purification (silica gel, 6:4 hexanes/ethyl acetate) afforded alcohol **4.9aa** (80.8 mg, 66%) as a colourless oil. ^{1}H NMR ($CDCl_3$) : δ 7.35 (m, 5H), 5.40 (d, 1H, J=5.3), 5.14 (s, 2H), 5.11 (m, 1H), 5.04 (dd, 1H, J=1.7, 10.1), 4.45 (d, 1H, J=10.1), 4.40 (dd, 1H, 4.1, 11.8), 4.16 (dd, 1H, J=8.3, 11.8), 3.72 (ddd, 1H, J=1.7, 5.3, 9.8), 3.47 (m, 2H), 2.05 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 2.00 (m, 1H), 1.92-1.65 (m, 3H). ^{13}C NMR ($CDCl_3$) : δ 171.55, 171.50, 170.98, 158.40, 136.61, 129.12, 128.84, 128.49, 74.54, 69.14,

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)-N-benzoxycarbonyl-2-(1'-acetoxy-2',3'-*O*-isopropylidene-4'-*t*-butyldiphenylsilyloxybutanyl)-pyrrolidine (4.10aa): To a solution of diol **4.6aa** (0.30 g, 0.50 mmol) in 1.99 mL of dry acetone, at room temperature, under argon, were added 2,2-dimethoxypropane (0.27 mL, 4.4 eq) and camphorsulfonic acid (6.0 mg, 0.05 eq). The solution was stirred for 15 hr after which a few drops of conc. ammonium hydroxide were added. The solvent was evaporated and the residue taken up in ether. The etheral solution was washed with water, brine and dried over magnesium sulfate. Evaporation of the solvent followed by purification (flash chromatography : silica gel, 8:2 hexanes/ethyl acetate) yielded 0.32 g (98%) of **4.10aa** as a colourless oil : $[\alpha]^{20}_D$= -2.9° (*c* : 0.8 in $CHCl_3$). IR (neat) : 3070, 2930, 1753 and 1704 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 7.65 (m, 4H), 7.50-7.22 (m, 11H), 5.18-4.90 (m, 3H), 4.40-3.27 (m, 7H), 2.11-1.78 (m, 4H), 1.73 (s, 3H), 1.40 (m, 6H), 1.07 (s, 9H).; exact mass calcd for $C_{37}H_{47}NO_7Si$ ($M^{\cdot+}$ + H^+) 646.3202, found 646.3202.

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)- N-benzoxycarbonyl-2-(1'-acetoxy-2',3'-*O*-isopropylidene-4'-hydroxybutanyl)-pyrrolidine (4.11aa): To a solution of protected alcohol **4.10aa** (0.32 g, 0.49 mmol) in 4.90 mL of dry tetrahydrofuran, at room temperature, under argon, was added tetra-*n*-butylammonium fluoride (1.0 M in THF :

0.59 mL, 1.2 eq) and the solution was stirred for 1.5 hr. Evaporation of the solvent followed by flash chromatography purification (silica gel, 6:4 hexanes/ethyl acetate) afforded alcohol **4.11aa** (0.13 g, 65%) as a colourless oil : $[\alpha]^{D}_{20}$= -3.0° (*c* : 0.84 in $CHCl_3$). ^1H NMR ($CDCl_3$) : δ 7.23 (s, 5H), 5.13 (s, 2H), 4.88 (bs, 1H), 4.50 (d, 1H, *J*=11.5), 4.28 (t, 1H, *J*=6.4), 4.08 (dd, 1H, *J*=6.4, 11.5), 4.97 (m, 1H), 3.69 (t, 1H, *J*=8.0), 3.55-3.40 (m, 3H), 2.12 (m, 1H), 2.08 (s, 3H), 1.99-1.75 (m, 3H), 1.38 (s, 6H).

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)- N-benzoxycarbonyl-2-(1'-acetoxy-2',3'-*O*-isopropylidene-4'-mesyloxybutanyl)-pyrrolidine (4.12aa): To a solution of alcohol **4.11aa** (0.13 g, 0.32 mmol) in 1.0 mL of dry methylene chloride, under argon, at room temperature, were added successively triethylamine (88.8 µL, 2.0 eq) and methanesulfonyl chloride (41.9 µL, 1.7 eq) and the solution was stirred for 3 hr. It was then dissolved in ether and washed with 5% HCl, sat. aq. $NaHCO_3$, brine and was dried over magnesium sulfate. Filtration and evaporation of the solvents yielded 0.14 g (88%) of mesylate **4.12aa** as a yellow oil. ^1H NMR ($CDCl_3$) : δ 7.35 (m, 5H), 5.11 (m, 2H), 4.78 (m, 1H), 4.40 (m, 1H), 4.23 (m, 1H), 4.00 (m, 2H), 3.65 (s, 3H), 2.98-2.73 (m, 2H), 2.10 (s, 3H), 2.10-1.82 (m, 4H), 1.38 (s, 3H), 1.32 (s, 3H).

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)-1,1'-*N*,*O*-carbonyl-2-(1',4'-dihydroxy-2',3'-*O*-isopropylidenebutanyl)-pyrrolidine (4.16aa): To a solution of protected triol **4.10aa** (0.30 g, 0.47 mmol) in 4.7 mL of a 2:1 mixture of MeOH/H_2O was added potassium carbonate (0.20 g, 3 eq) and the solution was heated at 70°C for 4 hr. The solvents were evaporated and the residue purified by flash chromatography (silica gel, 2:8 hexanes/ethyl acetate) to give 76.0 mg (63%) of alcohol **4.16aa** as a colourless oil. IR (neat) : 3455 (broad), 2938 and 1757 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.25 (dd, 1H, *J*=3.6, 7.6), 4.10-3.97 (m, 2H), 3.94-3.80 (m, 2H), 3.70 (dd, 1H, *J*=3.6, 12.1), 3.59 (ddd, 1H,

J=7.6, 7.6, 11.3), 3.16 (ddd, 1H, *J*=4.3, 9.1, 11.3), 2.20-1.81 (m, 4H), 1.49 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H).

Preparation of (2*S*,1'*S*,2'*S*,3'*S*)-2-(1',4'-dihydroxy-2',3'-*O*-isopropylidene-butanyl)-pyrrolidine (4.17aa): To a solution of cyclic carbamate **4.16aa** (70.1 mg, 0.27 mmol) in 2.73 mL of a 2:1 mixture of methanol/water was added sodium hydroxide (21.8 mg, 2 eq) and the solution was heated at 70°C for 18 hr. The solvents were evaporated and the residue was dissolved in methylene chloride and filtered through a plug of cotton wool. The solution was dried over magnesium sulfate, filtered and the solvent evaporated to give 40.0 mg (64%) of amino-diol **4.17aa** as a waxy solid. IR (neat) : 3370 (broad) and 2972 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.03 (ddd, 1H, J=4.0, 6.5, 7.5), 3.79 (dd, 1H, J=4.0, 11.1), 3.68 (dd, 1H, J=6.4, 11.1), 3.59 (dd, 1H, J=7.7), 3.49 (bs, 3H), 3.43-3.30 (m, 3H), 2.91 (bt, 2H, J=6.7), 1.90 (m, 1H), 1.81-1.63 (m, 3H), 1.38 (s, 6H).

Preparation of (2*S*,1'*S*,2'*S*,3'*R*)-1,1'-*N*,*O*-carbonyl-2-(1'-hydroxy-2',3'-*O*-isopropylidene-4'-chlorobutanyl)-pyrrolidine (4.18aa): From alcohol **4.16aa** : to a solution of alcohol **4.16aa** (76.0 mg, 0.30 mmol) in 2.9 mL of dry carbon tetrachloride was added triphenylphosphine (0.12 g, 1.5 eq) and the solution was stirred at 60°C for 3 hr. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 4:6 hexanes/ethyl acetate) affording 57.3 mg (70%) of chloride **4.18aa** as a colorless oil. From diol **4.25aa** : to a solution of diol **4.25aa** (0.19 g, 0.82 mmol) in 4.1 mL of dry acetone, at room temperature, under argon, were added 2,2-dimethoxypropane (0.4 mL, 4 eq) and camphorsulfonic acid (9.5 mg, 0.05 eq). The solution was stirred for 15 hr after which a few drops of conc. ammonium hydroxide were added. The solvent was evaporated and the residue taken up in ethyl acetate. It was washed with brine and dried over magnesium sulfate. Evaporation of the solvent followed by flash

chromatography purification (silica gel, 1:1 hexanes/ethyl acetate) yielded **4.18aa** as a colourless oil : $[\alpha]^{20}_D$= -23.1° (*c* : 0.93 in $CHCl_3$). IR (neat) : 2986, 1751 and 751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.26 (dd, 1H, *J*=3.5, 8.1), 4.18 (ddd, 1H, *J*=3.8, 5.2, 6.9), 4.02 (dd, 1H, *J*=6.9, 8.1), 3.85 (ddd, 1H, *J*=3.5, 5.6, 9.4), 3.79 (dd, 1H, *J*=3.8, 11.9), 3.64 (dd, 1H, *J*=5.2, 11.9), 3.59 (m, 1H), 3.16 (ddd, 1H, *J*=4.3, 9.0, 11.4), 2.18-1.80 (m, 3H), 1.45 (m, 1H), 1.41 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 161.37, 112.08, 81.37, 80.55, 79.59, 63.68, 46.86, 45.68, 31.95, 28.54, 28.36, 26.97. Exact mass calcd for $C_{12}H_{18}NO_4$ ($M^{\cdot+}$ + H^+) 276.1003, found 276.1003.

Preparation of (6*S*,7*R*,8*S*,8a*S*)-6,7-*O*-isopropylidene-8hydroxyindolizidine (4.19aa): To a solution of chloride **4.18aa** (0.56 g, 0.2.03 mmol) in 20 mL of a 2:1 mixture of MeOH/H_2O was added sodium hydroxide (0.24 g, 3.0 eq) and the soution was heated at 80°C for 15 hr. The solvents were evaporated and the residue dissolved in methylene chloride and filtered. Flash chromatography purification (silica gel, 7% MeOH/CH_2Cl_2; spray reagent : cobalt (II) isocyanate) gave 0.34 g (79%) of the bicyclic aminoalcohol **4.19aa** : $[\alpha]^{20}_D$= -23.3° (*c* : 1.64 in MeOH). IR (neat) : 3341 and 2957 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.12 (t, 1H, *J*=2.2), 4.01 (ddd, 1H, *J*=4.1, 9.7, 9.7), 3.39 (dd, 1H, *J*=2.2, 9.7), 3.37 (dd, 1H, *J*=4.1, 9.7), 3.02 (t, 1H, *J*=8.1), 2.36-2.20 (m, 2H), 2.21 (dd, 1H, *J*=9.7, 9.7), 1.95-1.63 (m, 4H), 1.44 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 110.81, 83.11, 71.21, 65.45,.65.19, 52.78, 52.55, 26.81, 26.52, 23.67, 22.40. Exact mass calcd for $C_{11}H_{19}NO_3$ ($M^{\cdot+}$ + H^+) 214.1444, found 214.1443.

Preparation of (2*S*,1'*R*)-N-benzyloxycarbonyl-2-(1',4'-dihydroxy-2'-butenyl)-pyrrolidine (4.22a): To a solution of hydroxysulfide **4.2a** (2.79 g, 7.27 mmol) in 73 mL of dry methylene chloride, at -78°C, under argon, was added *m*-chloroperoxybenzoic acid (1.88 g, 1.4 eq) and the solution was stirred for 2 hr. It was

then dissolved in ether, washed with sat. aq. $NaHCO_3$ (2x), dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was dissolved in 73 mL of dry methanol and trimethyl phosphite (9.0 mL, 10 eq) was added slowly. After 3 hr of stirring, the methanol was evaporated and the thick oil was purified by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate, under the fumehood) to give 1.63 g (77%) of pure allylic diol **4.22a** : $[\alpha]^{20}_D$= -46.1° (*c* : 1.36 in $CHCl_3$). IR (neat) : 3383 (broad), 3085, 2865 and 1685 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.31 (m, 5H), 5.88 (m, 1H), 5.63 (m, 1H), 5.11 (s, 2H), 4.09, (m, 2H), 3.89 (m, 1H), 3.50 (m, 1H), 3.36 (m, 1H), 1.95-1.63 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 157.73, 136.35, 132.45, 130.23, 128.50, 128.08, 127.89, 75.98, 67.43, 63.01, 54.38, 54.31, 47.29, 28.05, 23.95. Exact mass calcd for $C_{16}H_{21}NO_4$ ($M^{\cdot+}$ + H^+) 292.1550, found 292.1549.

Preparation of (2*S*,1'*R*)-1,1'-*N*,*O*-carbonyl-2-(1',4'-dihydroxy-2'-butenyl)-pyrrolidine (4.23a): To a solution of allylic diol **4.22a** (1.63 g, 5.60 mmol) in 56 mL of a 1:1 mixture of 2-propanol/water was added finely powdered potassium carbonate (2.32 g, 3 eq) and the solution was heated at 70°C for 15 hr. The solvent was evaporated and the residue purified by flash chromatography (silica gel, ethyl acetate) to give 1.14 g (70%) of allylic alcohol **4.23a** as a colourless oil : $[\alpha]^{20}_D$= -78.6° (*c* : 1.32 in $CHCl_3$). IR (neat) : 3359 (broad), 2978, 2880 and 1736 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 5.94 (dt, 1H, *J*=4.2, 15.5), 5.80 (dd, 1H, *J*=6.6, 15.5), 4.69 (dd, 1H, *J*=4.2, 6.6), 4.12 (d, 2H, *J*=4.2), 3.56 (m, 2H), 3.08 (ddd, 1H, *J*=4.7, 8.8, 11.3), 2.96 (bs, 1H), 2.15-2.77 (m, 3H), 1.49 (m, 1H). ^{13}C NMR ($CDCl_3$) : δ 162.47, 135.72, 128.11, 82.03, 66.32, 63.21, 46.96, 31.64, 27.04. Exact mass calcd for $C_9H_{13}NO_3$ ($M^{\cdot+}$ + H^+) 184.0974, found 184.0974.

Preparation of (2*S*,1'*R*)-1,1'-*N*,*O*-carbonyl-2-(1'-hydroxy-2'-buten-4'-chloro)-pyrrolidine (4.24a): To a solution of allylic alcohol **4.23a** (0.33 g, 1.80 mmol)

in 18.0 mL of a 4:1 mixture of dry carbon tetrachloride/methylene chloride were added successively finely powdered potassium carbonate (0.50 g, 2 eq) and triphenylphosphine (1.18 g, 2.5 eq) and the solution was stirred at 60°C for 8 hr. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 3:7 hexanes/ethyl acetate) affording 0.34 g (94%) of allylic chloride **4.24a** as a white solid (mp : 55-57°C) : $[\alpha]^{20}_D$= -49.1° (*c* : 1.37 in $CHCl_3$). IR (neat) : 3004, 2975 and 1751cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 6.03-5.80 (m, 2H), 4.69 (dd, 1H, *J*=4.0, 5.2), 4.03 (d, 2H, *J*=4.8), 3.56 (m, 2H), 3.09 (ddd, 1H, *J*=4.6, 8.9, 11.3), 2.15-1.76 (m, 3H), 1.48 (m, 1H). ^{13}C NMR ($CDCl_3$) : δ 161.29, 131.42, 130.19, 79.66, 65.07, 45.97, 43.73, 30.54, 25.81. Exact mass calcd for $C_9H_{12}NO_2Cl$ ($M^{\cdot+} + H^+$) 202.0635, found 202.0635.

Preparation of (2*S*,1'*S*,2'*S*,3'*R*) and (2*S*,1'*S*,2'*R*,3'*S*)-1,1'-*N*,*O*-carbonyl-2-(1',2',3'-trihydroxy-4'-chlorobutanyl)-pyrrolidine (4.25aa and 4.25ab): To a solution of allylic chloride **4.24a** (0.34 g, 1.70 mmol) in 3.4 mL of a 6:3:1 mixture of acetone/water/*t*-butanol were added successively N-methylmorpholine-N-oxide (0.24 g, 1.2 eq) and osmium tetroxide (21.6 mg, 0.05 eq). The orange solution was stirred at room temperature for 3 hr, after which 2 mL of a solution-suspension of magnesium silicate and sodium hydrosulfite (1.2 g and 0.1 g respectively in 8 mL of water) was added. The slurry was filtered through celite and the cake rinsed with acetone. The solvents were evaporated and the dark oil was purified by flash chromatography (silica gel, 2:8 hexanes/ethyl acetate) providing 0.35 g (88%) of a 2:1 mixture (by NMR) of diols **4.25aa** and **4.25ab** respectively. Only **4.25aa** was isolated as a pure compound at this stage : $[\alpha]^{20}_D$= -56.7° (*c* : 1.93 in MeOH). IR (neat) : 3357 (broad), 2938, 1751 and 766 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 4.33 (dd, 1H, J=4.0, 7.8), 4.05-3.93 (m, 2H), 3.80 (bt, 1H, J=7.0), 3.64-3.42 (m, 3H), 3.16 (ddd, 1H, J=4.1, 8.9, 11.4), 2.19-1.80 (m, 3H), 1.50 (m, 1H). ^{13}C NMR ($CDCl_3$) : δ 162.43, 81.13, 72.36, 71.30, 63.44, 46.67. 46.58, 32.26,

27.25. Exact mass calcd for $C_9H_{14}NO_4Cl$ ($M^{\cdot+} + H^+$) 236.0690, found 236.0690.

Preparation of (2*S*,1'*S*)-N-benzyloxycarbonyl-2-(1',4'-dihydroxy-2'-butenyl)-pyrrolidine (4.22b): This compound was prepared according to the method descrideb for **4.22a** : 80%, $[\alpha]^{20}_D$= -47.0° (*c* : 1.06 in $CHCl_3$). IR (neat) : 3363 (broad), 3080, 2990 and 1685 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.32 (m, 5H), 5.84 (dt, 1H, *J*=4.6, 15.5), 5.61 (dd, 1H, *J*=6.3, 15.6), 5.09 (s, 2H), 4.30 (m, 1H), 4.04 (d, 2H, *J*=4.6), 3.55 (m, 1H), 3.31 (m, 1H), 2.03-1.61 (m, 4H). ^{13}C NMR ($CDCl_3$) : δ 156.91, 134.39, 132.09, 129.19, 128.52, 128.09, 127.87, 74.30, 67.27, 63.13, 54.43, 54.35, 27.67, 24.07. Exact mass calcd for $C_{16}H_{21}NO_4$ ($M^{\cdot+} + H^+$) 292.1550, found 292.15488.

Preparation of (2*S*,1'*S*)-1,1'-*N*,*O*-carbonyl-2-(1',4'-dihydroxy-butenyl)-pyrrolidine (4.23b): This compound was prepared according to the method descrideb for **4.23a** : 71%, $[\alpha]^{20}_D$= -42.4° (*c* : 0.77 in $CHCl_3$). IR (neat) : 3423 (broad), 2967, 2904, 1741 and 1676 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.02 (dt, 1H, J=4.2, 15.5), 5.72 (dd, 1H, J=6.7, 15.5), 5.13 (dd, 1H, J=5.7, 6.7), 4.16 (d, 2H, J=4.2), 3.86 (ddd, 1H, J=5.7, 7.6, 10.5), 3.59 (m, 1H), 3.14 (ddd, 1H, J=3.7, 9.25, 11.6), 2.11-1.62 (m, 3H), 1.48 (m, 1H). ^{13}C NMR ($CDCl_3$) : δ 162.08, 135.51, 123.68, 76.43, 63.77, 62.49, 46.27, 26.13, 25.43. Exact mass calcd for $C_9H_{13}NO_3$ ($M^{\cdot+} + H^+$) 184.0974, found 184.0974.

Preparation of (2*S*,1'*S*)-1,1'-*N*,*O*-carbonyl-2-(1'hydroxy-4'-chloro-butenyl)-pyrrolidine (4.24b): This compound was prepared according to the method descrideb for **4.24a** : 78%, $[\alpha]^{20}_D$= -57.7° (*c* : 1.30 in $CHCl_3$). IR (neat) : 2978, 2952 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.04 (dtd, 1H, *J*=1.1, 6.4, 15.2), 5.77 (ddt, 1H, *J*=1.1, 5.9, 15.2), 5.13 (dd, 1H, *J*=6.8), 4.05 (dt, 2H, *J*=1.1, 6.4), 3.88 (ddd, 1H, *J*=5.6, 7.7, 10.3), 3.60 (m, 1H), 3.15 (ddd, 1H, *J*=3.8, 9.0, 11.3), 2.15-1.63 (m, 3H), 1.45 (m, 1H).

^{13}C NMR ($CDCl_3$) : δ 162.33, 131.65, 128.72, 76.39, 64.52, 47.35, 44.82, 27.29, 26.56. Exact mass calcd for $C_9H_{12}NO_2Cl$ ($M^{\cdot+} + H^+$) 202.0635, found 202.0635.

Preparation of (2*S*,1'*R*,2'*R*,3'*S*) and (2*S*,1'*R*,2'*S*,3'*R*)-1,1'-*N*,*O*-carbonyl-2-(1',2',3'-trihydroxy-4'-chlorobutanyl)-pyrrolidine (4.25ba and 4.25bb): This compound was prepared according to the method descrideb for **4.25aa** and **ab**. The mixture of isomers was unseparable by flash chromatography. IR (neat) : 3333 (broad), 2967, 1736 and 771 cm^{-1}. ^1H NMR ($CDCl_3$) : **4.25ba + bb** : δ 4.70 (m, 1H), 4.35-3.41 (m, 7H), 3.28-3.07 (m, 2H), 2 21-1.78 (m, 3H), 1.70-1.45 (m, 1H).. ^{13}C NMR ($CDCl_3$) : **4.25ba** : δ 161.48, 73.88, 69.90, 69.20, 62.62, 45.44, 45.21, 25.52, 25.16. **4.25bb** : 161.09, 71.61, 69.02, 61.65, 45.28, 44.39, 30.97, 25.78, 25.30. Exact mass calcd for $C_9H_{14}NO_4Cl$ ($M^{\cdot+} + H^+$) 236.0690, found 236.0690.

Preparation of (2*S*,1'*S*,2'*R*,3'*S*)-1,1'-*N*,*O*-carbonyl-2-(1'-hydroxy-2',3'-*O*-isopropylidene-4'-chlorobutanyl)-pyrrolidine (4.18ab): This compound was prepared according to the method descrideb for **4.18aa**. The reaction was performed on a mixture of **4.25aa** and **4.25ab** from the hydroxylation reaction. Compounds **4.18aa** and **4.18ab** were separated by flash chromatography (silica gel, 7:3 hexanes/ethyl acetate) to give a total yield of 87% (0.23 g of **4.18aa** and 0.12 g of **4.18ab**). **4.18ab** : white solid, mp = 92-94°C. $[\alpha]^{20}_D$= -54.9° (*c* : 1.23 in $CHCl_3$). IR (solution in $CHCl_3$) : 2988 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.40 (dd, 1H, *J*=2.0, 3.7), 4.34 (ddd, 1H, *J*=4.6, 6.4, 7.5), 4.06 (dd, 1H, *J*=2.0, 7.5), 3.84 (ddd, 1H, *J*=3.7, 5.5, 9.4), 3.69 (dd, 1H, *J*=4.6, 11.4), 3.60 (dd, 1H, *J*=6.4, 11.4), 3.57 (m, 1H), 3.19 (ddd, 1H, *J*=4.0, 8.6, 10.8), 2.20-1.75 (m, 3H), 1.45 (m, 1H), 1.41 (s, 6H). ^{13}C NMR ($CDCl_3$) : δ 162.05, 112.12, 81.39, 79.11, 76.85, 62.93, 47.10, 45.32, 32.43, 28.57, 27.93, 26.90. Exact mass calcd for $C_{12}H_{18}NO_4Cl$ ($M^{\cdot+} + H^+$) 276.1003, found 276.1003.

Preparation of (2*S*,1'*R*,2'*R*,3'*S*) and (2*S*,1'*R*,2'*S*,3'*R*)-1,1'-*N*,*O*-carbonyl-2-(1'-hydroxy-2',3'-*O*-isopropylidene-4'-chlorobutanyl)pyrrolidine (4.18ba and 4.18bb): This compound was prepared according to the method descrideb for **4.18aa**. The two isomers were separated by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate). **4.18ba** : $[\alpha]^{20}_D$= -37.5° (*c* : 0.81 in CH_3OH). IR (solution in $CHCl_3$) : 2978 and 1750 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.54 (dd, 1H, *J*=7.3, 9.5), 4.24 (ddd, 1H, *J*=3.1, 5.3, 7.1), 3.93 (dd, 1H, *J*=7.1, 9.5), 3.91 (m, 1H), 3.83 (dd, 1H, *J*=3.1, 12.0), 3.63 (dd, 1H, *J*=5.3, 12.0), 3.57 (ddd, 1H, *J*=7.7, 7.7, 11.3), 3.17 (ddd, 1H, *J*=3.1, 8.9, 11.3), 2.18-1.79 (m, 3H), 1.55 (m, 1H), 1.42 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 160.98, 111.33, 80.75, 76.32, 75.65, 62.73, 45.85, 44.41, 27.50, 27.32, 25.76, 25.45. Exact mass calcd for $C_{12}H_{18}NO_4Cl$ ($M^{\cdot+}$ + H^+) 276.1003, found 276.1003. **4.18bb** : $[\alpha]^{20}_D$= +23.3° (*c* : 0.84 in CH_3OH). IR (solution in $CHCl_3$) : 2969 and 1747 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.68 (dd, 1H, *J*=1.1, 8.4), 4.34 (ddd, 1H, *J*=4.2, 6.5, 7.7), 4.15 (m, 1H), 4.02 (dd, 1H, *J*=1.1, 7.7), 3.72 (dd, 1H, *J*=4.2, 11.5), 3.62 (dd, 1H, *J*=6.5, 11.5), 3.53 (m, 1H), 3.13 (ddd, 1H, *J*=4.6, 8.2, 10.9), 2.21-1.73 (m, 4H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 160.16, 111.58, 78.45, 76.44, 75.04, 61.81, 45.46, 43.94, 27.58, 27.13, 26.76, 26.56. Exact mass calcd for $C_{12}H_{18}NO_4Cl$ ($M^{\cdot+}$ + H^+) 276.1003, found 276.1003.

Preparation of (6*R*,7*S*,8*S*,8a*S*)-6,7-*O*-isopropylidene-8hydroxyindolizidine (4.19ab): This compound was prepared according to the method descrideb for **4.19aa** : 78% (silica gel, 10% MeOH/CH_2Cl_2), $[\alpha]^{20}_D$= -9.9° (*c* : 0.81 in MeOH). IR (solution in $CHCl_3$) : 3ɔó0 (broad) and 2965 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.13 (dd, 1H, *J*=6.2, 8.6), 3.64 (dd, 1H, *J*= 8.6, 9.4), 3.60 (ddd, 1H, *J*= 4.6, 9.4, 9.7), 3.19 (ddd, 1H, *J*= 6.2, 6.2, 9.0), 2.95 (m, 1H), 2.93 (dd, 1H, *J*= 4.6, 9.7), 2.76 (ddd, 1H, *J*= 8.5, 8.5, 11.5), 2.63 (t, 1H, *J*= 9.7), 1.98-1.55 (m, 4H), 1.40 (s, 6H). ^{13}C NMR ($CDCl_3$) : δ 111.44, 81.38, 74.52,

69.08, 64.96, 54.40, 51.05, 26.92, 26.81, 22.46, 21.39. Exact mass calcd for $C_{11}H_{19}NO_3$ ($M^{\cdot+} + H^+$) 214.1444, found 214.1443.

Preparation of (6*R*,7*S*,8*R*,8a*S*)-6,7-*O*-isopropylidene-8hydroxyindolizidine (4.19ba): This compound was prepared according to the method descrideb for **4.19aa** : 68% (silica gel, 10% MeOH/CH_2Cl_2), $[\alpha]^{20}_D$= +65.0° (*c* : 1.05 in $CHCl_3$). IR (neat) : 3350 (broad) and 2954 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.19 (t, 1H, *J*=3.6), 4.11 (ddd, 1H, *J*=5.6, 9.6, 9.6), 3.70 (dd, 1H, *J*=3.6, 9.6), 2.96 (dd, 1H, *J*=5.6, 9.6), 2.95-2.88 (m, 2H), 2.72 (dd, 1H, *J*=9.6, 9.6), 2.58 (ddd, 1H, *J*=9.0, 11.0), 2.01-1.79 (m, 2H), 1.68 (m, 1H), 1.50 (m, 1H), 1.41 (s, 6H). ^{13}C NMR ($CDCl_3$) : δ 111.27, 78.51, 70.96, 67.27, 67.23, 54.16, 52.15, 27.08, 26.67, 21.87. Exact mass calcd for $C_{11}H_{19}NO_3$ ($M^{\cdot+}$ + H^+) 214.1444, found 214.1443.

Preparation of (6*S*,7*R*,8*R*,8a*S*)-6,7-*O*-isopropylidene-8hydroxyindolizidine (4.19bb): This compound was prepared according to the method descrideb for **4.19aa** : 77% (silica gel, 7% MeOH/CH_2Cl_2), $[\alpha]^{20}_D$= -59.4° (*c* : 1.58 in $CHCl_3$). IR (neat) : 3399 (broad) and 2985 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 3.64 (ddd, 1H, *J*=3.8, 9.3, 9.7), 3.54 (dd, 1H, *J*=8.6, 9.3), 3.44 (bs, 1H), 3.33 (dd, 1H, *J*=9.3, 9.3), 3.26 (dd, 1H, *J*=3.8, 9.7), 2.99 (ddd, 1H, *J*=2.8, 8.6, 8.6), 2.35 (dd, 1H, *J*=8.6, 8.6), 2.24 (dd, 1H, *J*=9.7, 9.7) 2.15-1.95 (m, 2H), 1.91-1.71 (m, 2H), 1.55 (m, 1H), 1.40 (s, 6H). ^{13}C ($CDCl_3$) : δ 111.52, 85.01, 75.03, 72.75, 67.72, 52.40, 51.69, 27.24, 26.80, 26.72, 22.32. Exact mass calcd for $C_{11}H_{19}NO_3$ ($M^{\cdot+}$ + H^+) 214.1444, found 214.1443.

Preparation of (6*S*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine (4.26aa): Amino-alcohol **4.19aa** (0.34 g, 1.60 mmol) was dissolved in 8.0 mL of a 4:1 mixture of trifluoroacetic acid/water. The solution was stirred at room temperature for 50 hr after

which the solvents were evaporated. The thick dark oil was dissolved in methanol and was stirred with amberlyst A-26 (OH^- form) resin for 2 hr. The solution was filtered and the solvent was evaporated. Flash chromatography purification (silica gel, 1:1 chloroform/ethanol, then ethanol; spray reagent : $KMnO_4$/NaOH in water) gave **4.26aa** (0.28 g, quantitative) as a waxy solid : $[\alpha]^{20}_D$= -36.5°(*c* : 1.11 in MeOH). IR (KBr) : 3450 cm^{-1}. ^1H NMR (CD_3OD) : δ 4.59 (dd, 1H, J=1.1, 3.0), 4.50 (ddd, 1H, J=5.3, 9.2, 11.1), 4.10-3.96 (m, 3H), 3.87 (bt, 1H, J=8.5), 3.54 (m, 1H), 3.28 (dd, 1H, J=11.1, 11.1), 2.72-2.43 (m, 4H). ^{13}C NMR (CD_3OD) : δ 77.25, 70.83, 69.52, 68.62, 55.90, 55.55, 25.80, 23.60. Exact mass calcd for $C_8H_{15}NO_3$ ($M^{\cdot+}$ + H^+) 174.1131, found 174.1130.

Preparation of (6*R*,7*S*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine (4.26ab): This compound was prepared according to the method descrideb for **4.26aa** : $[\alpha]^{20}_D$= +22.5° (*c* : 1.13 in MeOH). IR (KBr) : 3487 cm^{-1}. ^1H NMR (CD_3OD) : δ 4.49-4.32 (m, 3H), 4.85 (m, 1H), 3.78 (dd, 1H, *J*= 2.6, 12.4), 3.62 (t, 1H, *J*= 6.2), 3.49 (dd, 1H, *J*= 2.0, 12.4), 3.24 (q, 1H, *J*= 9.4), 2.50-2.33 (m, 4H). ^{13}C NMR (CD_3OD) : δ 71.93, 71.81, 71.62, 66.56, 56.83, 56.40, 25,93, 22.44. Exact mass calcd for $C_8H_{15}NO_3$ ($M^{\cdot+}$ + H^+) 174.1131, found 174.1130.

Preparation of (6*R*,7*S*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (4.26ba): This compound was prepared according to the method descrideb for **4.26aa** : $[\alpha]^{20}_D$= -17.3 (*c* : 0.85 in MeOH). IR (KBr) : 3500 cm^{-1}. ^1H NMR (CD_3OD) : δ 4.52-4.20 (m, 3H), 3.90-3.55 (m, 2H), 3.48-3.10 (m, 3H), 2.65 (m, 1H), 2.55-2.10 (m, 3H). ^{13}C NMR (CD_3OD) : δ 73.36, 72.68, 71.92, 66.02, 56.30, 55.11, 29.60, 22.67. Exact mass calcd for $C_8H_{15}NO_3$ ($M^{\cdot+}$ + H^+) 174.1131, found 174.1130.

Preparation of (6*S*,7*R*,8*R*,8a*S*)-6,7,8-trihydroxyindolizidine (4.26bb): This

compound was prepared according to the method descrideb for **4.26aa** : $[\alpha]^{20}_D$= -40.8° (*c* : 1.28 in MeOH). IR (KBr) : 3470 cm^{-1}. ^1H NMR (CD_3OD) : δ 4.15 (m, 2H), 3.90-3.58 (m, 4H), 2.85-2.52 (m, 4H), 2.40 (m, 2H), 2.15 (m, 1H). ^{13}C NMR (CD_3OD) : δ 81.88, 77.08, 72.98, 70.66, 58.05, 55.89, 30.31, 24.08. Exact mass calcd for $C_8H_{15}NO_3$ ($M^{\cdot+}$ + H^+) 174.1131, found 174.1130.

Preparation of (2*S*,3*S*)-N-benzyloxycarbonyl-2-hydroxymethyl-3-methoxymethyloxypyrrolidine (4.27): To a solution of ester **3.37** (0.84 g, 2.48 mmol) in 25 mL of dry ether, at 0°C, under argon, was added lithium borohydride (0.12 g, 2.2 eq) and the suspension was stirred at 0°C for 4 hr. Acetic acid (1 mL) was then added to destroy the excess hydride and the solution was poured in sat. aq. sodium bicarbonate. The phases were separated and the aqueous layer was extracted with ether (2x). The combined organic extracts were washed with brine and dried over magnesium sulfate. Filtration and evaporation of the solvent was followed by flash chromatography purification (silica gel, 4:6 hexanes/ethyl acetate) to give alcohol **4.27** as a colourless oil (0.53 g, 72%) : $[\alpha]^{20}_D$= +44.7° (*c* : 1.1 in $CHCl_3$). IR (neat) : 3450 (broad), 2948, 2888 and 1704 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.40-7.22 (m, 5H), 5.12 (s, 2H), 4.71-4.58 (m, 2H), 4.32 (q, 1H, *J*= 5.3), 3.96 (m, 1H), 3.89-3.75 (m, 2H), 3.51 (t, 2H, *J*= 6.8), 3.36 (s, 3H), 3.27 (bs, 1H), 1.98 (t, 2H, *J*= 6.8). ^{13}C NMR ($CDCl_3$) : δ 156.87, 136.91, 128.99, 128.57, 128.42, 96.24, 77.81, 67.66, 63.41, 63.18, 56.29, 45.14, 30.57. Exact mass calcd for $C_{15}H_{21}NO_5$ ($M^{\cdot+}$ + H^+) 296.1499, found 296.1498.

Preparation of (2*R*,3*S*)-N-benzyloxycarbonyl-3-methoxymethyloxy-pyrrolidine-2-carboxaldehyde (4.28): Dimethyl sulfoxide (49.3 μL, 2.84 eq) was slowly added to a solution of oxalyl chloride (30.1 μL, 1.41 eq) in 2 mL of methylene chloride, under argon, at -78°C. The colourless solution was stirred for 15 min after

which a solution of alcohol **4.27** (72.2 mg, 0.24 mmol) in 1 mL of methylene chloride was added dropwise over a period of 5 min. A white precipitate was then formed, and the suspension was stirred for 1 hr. Triethylamine (0.17 mL, 5 eq) in methylene chloride was added and the solution was allowed to slowly warm to room temperature. The reaction mixture was diluted with 10 mL of methylene chloride and washed successively with 5% HCl (1x), water (1x), brine, and was dried over magnesium sulfate. Evaporation of the solvent under vacuum gave a pale brown oil which was purified by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate) yielding aldehyde **4.28** as a pale yellow oil (70.0 mg, 98%) : $[\alpha]^{20}_{D}$= +70.4° (*c* : 1.1 in $CHCl_3$). IR (neat) : 2958, 2888, 1736 and 1701 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 9.53 + 9.44 (2d, 1H, *J*= 2.5), 7.42-7.21 (m, 5H), 5.14 and 5.09 (2s, 2H), 4.72-4.51 (m, 3H), 4.27 + 4.21 (2dd, 1H, *J*= 2.5, 5.7), 3.75-3.60 (m, 2H), 3.29 (s, 3H), 2.16-1.80 (m, 2H). ^{13}C NMR ($CDCl_3$) : δ 200.18 + 200.08 (1C), 155.73 + 154.85 (1C), 136.82 + 136.56 (1C), 128.98, 128.61, 128.51 + 128.45 (1C), 95.81, 79.42 + 78.28 (1C), 68.36 + 68.00 (1C), 67.80, 56.30, 45.67 + 45.14 (1C), 31.54 + 30.92 (1C). Exact mass calcd for $C_{15}H_{19}NO_5$ ($M^{\cdot+}$ + H^+) 294.1342, found 294.1341.

Preparation of (2*R*,3*S*,1'*S*,2'*S*)-N-benzoxycarbonyl-2-(1'-hydroxy-2'-thiophenyl-3'-butenyl)-3-methoxymethyloxypyrrolidine (4.29a): To a solution of allyl.phenyl sulfide (0.35 g, 1.5 eq) in 10.5 mL of dry THF, at -78°C, under argon, was added *n*-butyllithium (2.0 M in pentane, 1.16 mL, 1.5 eq) and the solution was stirred at 0°C for 30 min. It was then brought back to -78°C and titanium (IV) isopropoxide (0.69 mL, 1.5 eq) was added slowly. After 10 min, aldehyde **4.28** (0.45 g, 1.55 mmol, in 5 mL of THF) was added over a period of 10 min. The solution was stirred for 10 min and warmed up at 0°C for 30 min. It was then poored in 5% HCl and extracted with ether (3x). The combined organic extracts were washed with brine, dried over magnesium

sulfate and filtered. Evaporation of the solvents followed by flash chromatography (silica gel, 1:1 hexanes/ethyl acetate) gave **4.29a** (>90%) as a colourless oil (0.49 g, 72%) : $[\alpha]^{20}_D$= +50.2° (*c* : 1.1 in $CHCl_3$). IR (neat) : 3425 (broad), 2948, 2893 and 1693 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.54-7.09 (m, 10H), 6.06 (m, 1H), 5.12 (s, 2H), 5.06 (d, 1H, *J*= 10.7), 4.90 (d, 1H, *J*= 17.2), 4.63 (s, 2H), 4.60 (m, 1H), 4.26 (q, 1H, *J*= 6.0), 4.14 (bs, 1H), 3.95 (d, 1H, *J*= 9.6), 3.66-3.42 (m, 2H), 3.33 (s, 3H), 2.15-1.84 (m, 2H). ^{13}C NMR ($CDCl_3$) : δ 158.16, 136.74, 134.93, 133.40, 129.12, 129.01, 128.66, 128.55, 127.60, 126.00, 118.53, 96.44, 77.08, 72.79, 68.04, 63.10, 56.81, 56.48, 45.32, 30.80. Exact mass calcd for $C_{24}H_{29}NO_5S$ ($M^{\cdot+}$ + H^+) 444.1846, found 444.1845.

Preparation of (2*R*,3*S*,1'*R*)-N-benzyloxycarbonyl-2-(1',4'-dihydroxy-2'-butenyl)-3-methoxymethyloxypyrrolidine (4.30a): To a solution of hydroxysulfide **4.29a** (0.49 g, 1.11 mmol) in 11.1 mL of dry methylene chloride, at 0°C, under argon, was added *m*-chloroperoxybenzoic acid (0.27 g, 1.4 eq) and the solution was stirred for 60 min. It was then dissolved in ether, washed with sat. aq. sodium bicarbonate (2x), dried over magnesium sulfate, filtered and the solvent was evaporated. The residue was dissolved in 11.1 mL of dry methanol and trimethyl phosphite (0.65 mL, 5 eq) was added slowly. After 2 hr of stirring at 60°C, the methanol was evaporated and the thick oil was purified by flash chromatography (silica gel, 2:8 hexanes/ethyl acetate, then ethyl acetate, under the fumehood) to give 0.28 g (71%) of pure allylic diol **4.30a** : $[\alpha]^{20}_D$= +31.2° (*c* : 1.5 in $CHCl_3$). IR (neat) : 3450 (broad), 2948, 2888, 1704 and 1671 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 7.42-7.21 (m, 5H), 5.96-5.70 (m, 2H), 5.12 (s, 2H), 4.67 (s, 2H), 4.51 (m, 1H), 4.29 (m, 1H), 4.21-3.88 (m, 3H), 3.62-3.43 (m, 2H), 3.37 (s, 3H), 3.29 (m, 1H), 3.16 (bs, 1H), 2.20-1.91 (m, 2H). ^{13}C NMR ($CDCl_3$) : δ 157.34, 136.85, 131.83, 131.00, 129.00, 128.61, 128.39, 96.99, 78.22, 72.13, 67.79, 63.23, 56.39, 45.52, 30.88. Exact mass calcd for $C_{18}H_{25}NO_6$ ($M^{\cdot+}$ + H^+) 352.1761, found 352.1760.

Preparation of (2*R*,3*S*,1'*R*)-1,1'-N,O-carbonyl-2-(1',4'-dihydroxy-2'-butenyl)-3-methoxymethyloxypyrrolidine (4.31a): To a solution of allylic diol **4.30a** (0.21 g, 0.61 mmol) in 6.1 mL of a 2:1 mixture of 2-propanol/water was added finely powdered potassium carbonate (0.17 g, 2 eq) and the solution was heated at 65°C for 15 hr. The solvent was evaporated and the residue purified by flash chromatography (silica gel, ethyl acetate) to give g (0.11 g, 77%) of allylic alcohol **4.31a** as a colourless oil : $[\alpha]^{20}_{D}$= +99.6° (*c* : 1.1 in $CHCl_3$). IR (neat) : 3436 (broad), 2946, 2895, 1751 and 1674 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 5.96 (dt, 1H, *J*= 4.0, 15.5), 5.83 (dd, 1H, *J*= 6.5, 15.5), 5.04 (dd, 1H, *J*= 3.6, 6.5), 4.67 + 4.59 (2d, AB system, 2H, *J*= 7.0), 4.13 (d, 2H, *J*= 4.0), 4.08 (td, 1H, *J*= 0.9, 3.6), 3.62 (t, 1H, *J*= 3.6), 3.54 (ddd, 1H, *J*= 7.8, 9.5, 10.8), 3.32 (s, 3H), 3.19 (ddd, 1H, *J*= 2.1, 9.6, 10.8), 2.83 (bs, 1H), 2.25 (dddd, 1H, *J*= 0.9, 2.1, 7.8, 14.1), 1.92 (dddd, 1H, *J*= 3.6, 9.5, 9.6, 14.1). ^{13}C NMR ($CDCl_3$) : δ 162.17, 134.54, 127.60, 95.48, 75.50, 75.44, 69.35, 62.34, 56.32, 44.17, 32.56. Exact mass calcd for $C_{11}H_{17}NO_5$ ($M^{\cdot+}$ + H^+) 244.1186, found 244.1185.

Preparation of (2*R*,3*S*,1'*R*)-1,1'-N,O-carbonyl-2-(1'-hydroxy-4'-chloro-2'butenyl)-3-methoxymethyloxypyrrolidine (4.32a): To a solution of allylic alcohol **4.31a** (0.11 g, 0.47 mmol) in 6.0 mL of a 4:1 mixture of dry carbon tetrachloride/methylene chloride were added successively finely powdered potassium carbonate (0.13 g, 2 eq) and triphenylphosphine (0.31 g, 2.5 eq) and the solution was stirred at 60°C for 8 hr. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 2:8 hexanes/ethyl acetate) affording 83.9 mg (70%) of allylic chloride **4.32a** as a pale yellow oil : $[\alpha]^{20}_{D}$= +87.7° (*c* : 1.5 in $CHCl_3$). IR (neat) : 2965, 2895 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 6.06-5.84 (m, 2H), 5.06 (dd, 1H, *J*= 3.6, 5.1), 4.68 + 4.61 (2d, AB system, 2H, *J*= 7.0), 4.11 (td, 1H, *J*= 1.1, 3.6), 4.05 (d, 2H,

J= 6.2), 3.62, (t, 1H, *J*= 3.6), 3.58 (ddd, 1H, *J*= 7.9, 9.5. 11.0), 3.33 (s, 3H), 3.22 (ddd, 1H, *J*= 2.2, 9.7, 11.0), 2.28 (dddd, 1H, *J*= 1.1, 2.2, 7.9, 14.1), 1.93 (dddd, 1H, *J*= 3.6, 9.5, 9.7, 14.1). ^{13}C NMR ($CDCl_3$) : δ 161.75, 131.67, 129.92, 95.53, 75.58, 74.37, 69.10, 56.38, 44.27, 43.93, 32.52. Exact mass calcd for $C_{11}H_{16}NO_4Cl$ ($M^{\cdot+}$ + H^+) 262.0847, found 262.0846

Preparation of (2*R*,3*S*,1'*S*,2'*S*,3'*R*) and (2*R*,3*S*,1'*S*,2'*R*,3'*S*)-1,1'-*N*,*O*-carbonyl-2-(1',2',3'-trihydroxy-4'-chlorobutanyl)-3-methoxymethyloxypyrrolidine (4.33aa and 4.33ab): To a solution of allylic chloride **4.32a** (83.9 mg, 0.32 mmol) in 2.0 mL of a 6:3:1 mixture of acetone/water/*t*-butanol were added successively N-methylmorpholine-N-oxide (45.1 mg, 1.2 eq) and osmium tetroxide (15.0 mg, 0.05 eq). The orange solution was stirred at room temperature for 3 hr, after which 2 mL of a solution-suspension of magnesium silicate and sodium hydrosulfite (1.2 g and 0.1 g respectively in 8 mL of water) was added. The slurry was filtered through celite and the cake rinced with acetone. The solvents were evaporated and the dark oil was purified by flash chromatography (silica gel, ethyl acetate) providing 94.8 mg (99%) of an unseparable 2:1 mixture (by NMR) of diols **4.33aa** and **4.33ab** respectively. IR (neat) : 3335 (broad), 2952 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.83-4.59 (m, 3H), 4.09 (m, 2H), 3.95 (m, 1H), 3.86 (m, 1H), 3.77-3.46 (m, 5H), 3.32 (s, 3H), 3.27 (m, 1H), 2.29 (m, 1H), 2.01 (m, 1H). ^{13}C NMR ($CDCl_3$) : **4.33aa** : δ 162.11, 95.73, 76.13, 75.49, 71.13, 70.84, 66.11, 56.34, 45.83, 44.03, 32.99. **4.33ab** : δ 162.05, 95.45, 76.39, 75.30, 72.14, 71.61, 65.96, 56.34, 45.83, 44.03, 32.80. Exact mass calcd for $C_{11}H_{18}NO_6Cl$ ($M^{\cdot+}$ + H^+) 296.0902, found 296.0901

**Preparation of (2*R*,3*S*,1'*S*,2'*S*,3'*R*) and (2*R*,3*S*,1'*S*,2'*R*,3'*S*)-1,1'-*N*,*O*-carbonyl-2-(1'-hydroxy-2',3'-*O*-isopropylidene-4'-chlorobutanyl)-3-methoxy-

methyloxypyrrolidine (4.34aa and 4.34ab): To a solution of diols **4.33aa** and **ab** (94.8 mg, 0.32 mmol) in 3.2 mL of dry acetone, at room temperature, under argon, were added 2,2-dimethoxypropane (0.20 mL, 5 eq) and camphorsulfonic acid (5.2 mg, 0.05 eq). The solution was stirred for 15 hr at room temperature and heated at 40°C for 1 hr after which a few drops of conc. ammonium hydroxide were added. The solvent was evaporated and the residue taken up in ethyl acetate. It was washed with brine and dried over magnesium sulfate. Evaporation of the solvent followed by flash chromatography purification (silica gel, 6:4 hexanes/ethyl acetate) yielded **4.34aa** (51.0 mg, 48 %) and **4.34ab** (31.7 mg, 29%), both of them as white solids, in a total yield of 77%. **4.34aa** : mp : 74-76°C. $[\alpha]^{20}_D$= +50.8° (*c* : 1.0 in $CHCl_3$). IR (solution in $CHCl_3$) : 2980 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.70 + 4.62 (2d, AB system, 2H, *J*= 7.04), 4.60 (dd, 1H, *J*= 3.2, 8.3), 4.21 (ddd, 1H, *J*= 3.8, 5.2, 7.0), 4.13 (td, 1H, *J*= 0.9, 3.2), 4.05 (dd, 1H, *J*= 7.0, 8.3), 3.88 (t, 1H, *J*= 3.2), 3.80 (dd, 1H, *J*= 3.8, 11.8), 3.65 (dd, 1H, *J*= 5.2, 11.8), 3.59 (ddd, 1H, *J*= 7.8, 9.5, 10.8), 3.34 (s, 3H), 3.26 (ddd, 1H, *J*= 2.1, 9.8, 10.8), 2.32 (dddd, 1H, *J* - 0.9, 2.1, 7.8, 14.1), 1.98 (dddd, 1H, *J*= 3.2, 9.5, 9.8, 14.1), 1.44 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 162.00, 112.13, 96.26, 80.78, 79.44, 76.51, 76.40, 67.65, 57.19, 45.70, 45.07, 33.45, 28.56, 28.41. Exact mass calcd for $C_{14}H_{22}NO_6Cl$ ($M^{\cdot+}$ + H^+) 336.1215, found 336.1214. **4.34ab** : mp : 153-155°C. $[\alpha]^{20}_D$= +66.1° (*c* : 1.6 in $CHCl_3$). IR (solution) : 2997 and 1751 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.77 (dd, 1H, *J*= 1.8, 3.4), 4.71 + 4.63 (2d, AB system, 2H, *J*= 7.0), 4.40 (ddd, 1H, *J*= 4.4, 6.6, 7.5), 4.11 (td, 1H, *J*= 0.9, 3.4), 4.08 (dd, 1H, *J*= 1.8, 7.5), 3.91 (t, 1H, *J*= 3.4), 3.73 (dd, 1H, *J*= 4.4, 11.4), 3.62 (dd, 1H, *J*= 6.6, 11.4), 3.40 (ddd, 1H, *J*= 8.0, 9.5, 10.9), 3.34 (s, 3H), 3.31 (ddd, 1H, *J*= 2.1, 9.8, 10.9), 2.32 (dddd, 1H, *J*= 0.9, 2.1, 8.0, 14.3), 1.97 (dddd, 1H, *J*= 3.4, 9.5, 9.8, 14.3), 1.43 (s, 6H). ^{13}C NMR ($CDCl_3$) : δ 171.14, 112.15, 96.35, 81.80, 76.70, 76.53, 74.07, 67.09, 57.28, 45.36, 45.30, 33.48, 28.58, 27.92. Exact mass calcd for $C_{14}H_{22}NO_6Cl$ ($M^{\cdot+}$ + H^+) 336.1215, found 336.1214.

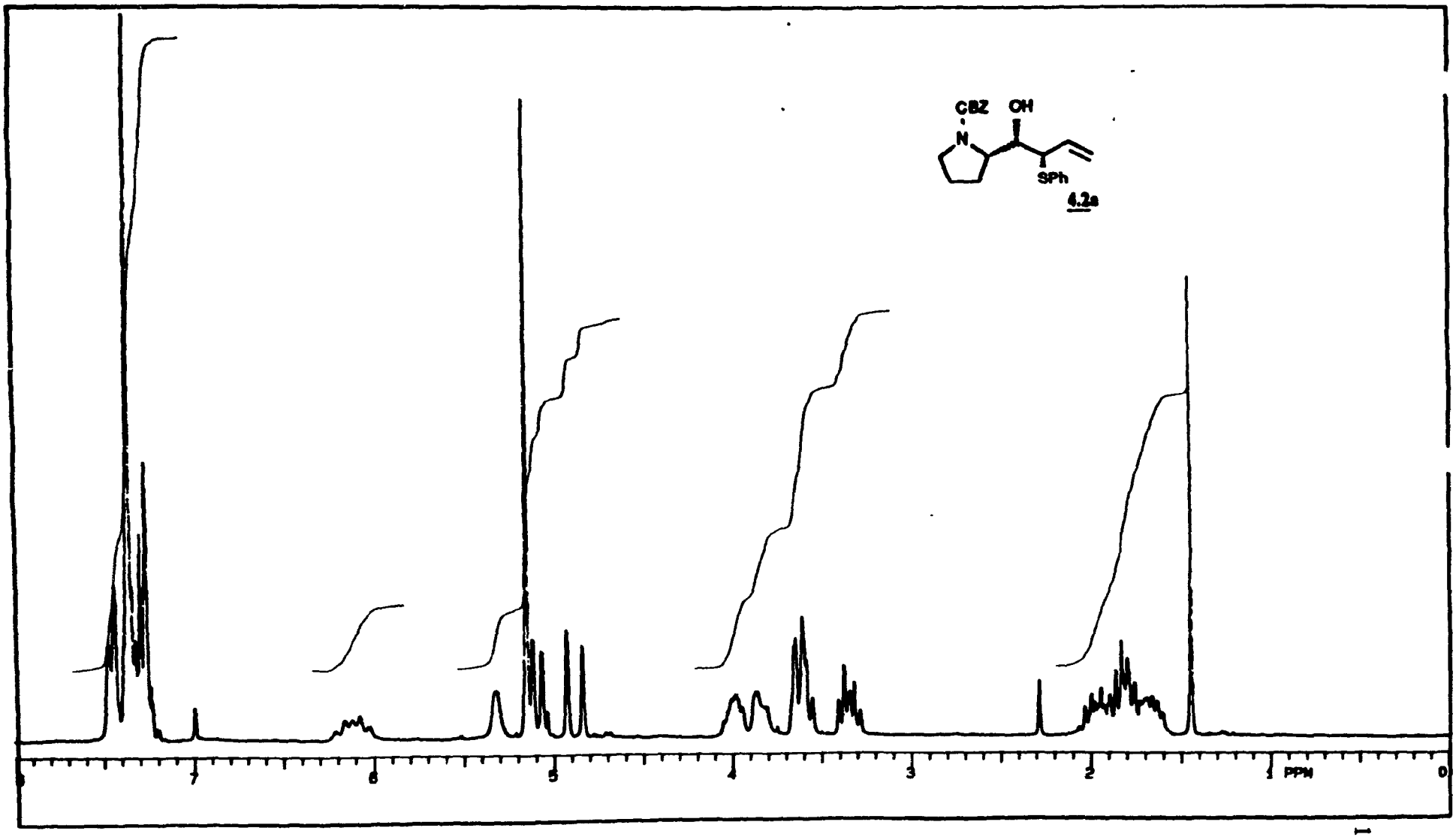
Preparation of (1*S*,6*S*,7*R*,8*S*,8a*R*)-1-methoxymethyloxy-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.35aa): To a solution of chloride **4.34aa** (51.0 mg, 0.15 mmol) in 2 mL of a 1:1 mixture of methanol/water was added sodium hydroxide (18.3 mg, 3 eq) and the solution was stirred at 85°C for 18 hr. The solvents were evaporated and the solid residue was extracted with chloroform. The chloroform was evaporated to give aminoalcohol **4.35aa** as a waxy solid (41.0 mg, 98%) : $[\alpha]^{20}_D$= +50.6° (*c* : 0.83 in $CHCl_3$). IR (solution in $CHCl_3$) : 3450 (broad) and 2986 cm^{-1}. ^1H NMR ($CDCl_3$) : δ 4.67 + 4.59 (2d, AB system, 2H, *J*= 7.1), 4.54 (bs, 1H), 4.46 (m, 1H), 4.35 (td, 1H, *J*= 4.2, 10.2), 3.49 (dd, 1H, *J*= 4.2, 9.3), 3.36 (s, 3H), 3.33 (m, 1H), 3.19 (t, 1H, *J*= 8.4), 2.25-2.12 (m, 4H), 1.95 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$) : δ 111.52, 95.11, 83.22, 77.94, 77.73, 71.27, 68.35, 66.41, 54.04, 51.71, 32.53, 27.38, 27.05. Exact mass calcd for $C_{13}H_{23}NO_5$ ($M^{\cdot+}$ + H^+) 274.1655, found 274.1654.

Preparation of (1*S*,6*S*,7*R*,8*S*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36aa): A solution of aminoalcohol **4.35aa** (41.0 mg, 0.15 mmol) in a 4:4:2 mixture of 6 M HCl/water/tetrahydrofuran was stirred for 15 hr after which the solvents were evaporated. The residue was dissolved in methanol and stirred for 1 hr with Amberlyst A-26 ion exchange resin (OH^- form). Filtration followed by evaporation of the methanol gave a brownish solid which was purified by flash chromatography (silica gel, 70:20:5:5 chloroform/methanol/water/NH_4OH; spray reagent : $KMnO_4$/NaOH in water) affording tetraol **4.36aa** as a off white solid in quantitative yield (28.4 mg) : mp 190-192 °C dec. $[\alpha]^{20}_D$= +44.4° (*c* : 1.3 in H_2O). IR (KBr) : 3450 (broad) cm^{-1}. ^1H NMR (D_2O) : δ 4.07 (ddd, 1H, *J*= 2.1, 4.5, 6.5), 3.89 (dd, 1H, *J*= 1.2, 3.0), 3.43 (ddd, 1H, *J*= 5.5, 9.5, 11.2), 3.09 (ddd, 1H, *J*= 4.4, 9.0, 10.0), 3.07 (dd, 1H, *J*= 5.5, 11.2), 2.96 (dd, 1H, *J*= 3.0, 9.5), 2.70 (d, 1H, *J*= 4.5), 2.45 (ddd, 1H, *J*= 7.9, 10.0, 10.1), 2.23 (t, 1H, *J*= 11.2), 1.87 (dddd,

1H, *J*= 4.4, 6.5, 10.1, 14.3), 1.31 (dddd, 1H, *J*= 2.1, 7.9, 9.0, 14.3). ^{13}C NMR (D_2O) : δ 76.19, 73.06, 71.79, 69.83, 67.91, 55.96, 53.82, 35.44. Exact mass calcd for $C_8H_{15}NO_4$ ($M^{\cdot+} + H^+$) 190.1080, found 190.1079.

Preparation of (1*S*,6*R*,7*S*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36ab): See experimental for compound 4.35aa. The deprotection of the MOM ether group as well as the isopropylidene occurred during the cyclisation. Time : 36 hr. Chromatography : silica gel, 70:24:3:3 chloroform/methanol/water/NH_4OH : 65% yield. $[\alpha]^{20}_D$= -7.3° (*c* : 1.0 in H_2O). IR (KBr) : 3500 (broad) cm^{-1}. ^1H NMR (D_2O) : δ 4.00 (ddd, 1H, *J*= 2.4, 4.8, 7.1), 3.55 (t, 1H, *J*= 4.3), 3.27 (t, 1H, *J*=4.8), 3.14 (q, 1H, *J*= 4.2), 2.79-2.59 (m, 2H), 2.46-2.31 (m, 2H), 2.17 (m, 1H), 1.71 (dddd, 1H, *J*= 3.8, 7.1, 9.5, 14.0), 1.21 (dddd, 1H, *J*= 2.4, 8.8, 8.8, 14.0). ^{13}C NMR (D_2O) : δ 74.45, 72.70, 72.57, 71.24, 68.07, 56.92, 55.03, 34.65. Exact mass calcd for $C_8H_{15}NO_4$ ($M^{\cdot+} + H^+$) 190.1080, found 190.1079.

(2*S*,1'*S*,2'*S*)-N-benzyloxycarbonyl-2-(1'-hydroxy-2'-thiophenyl-3'-butenyl)-pyrrolidine (4.2a)



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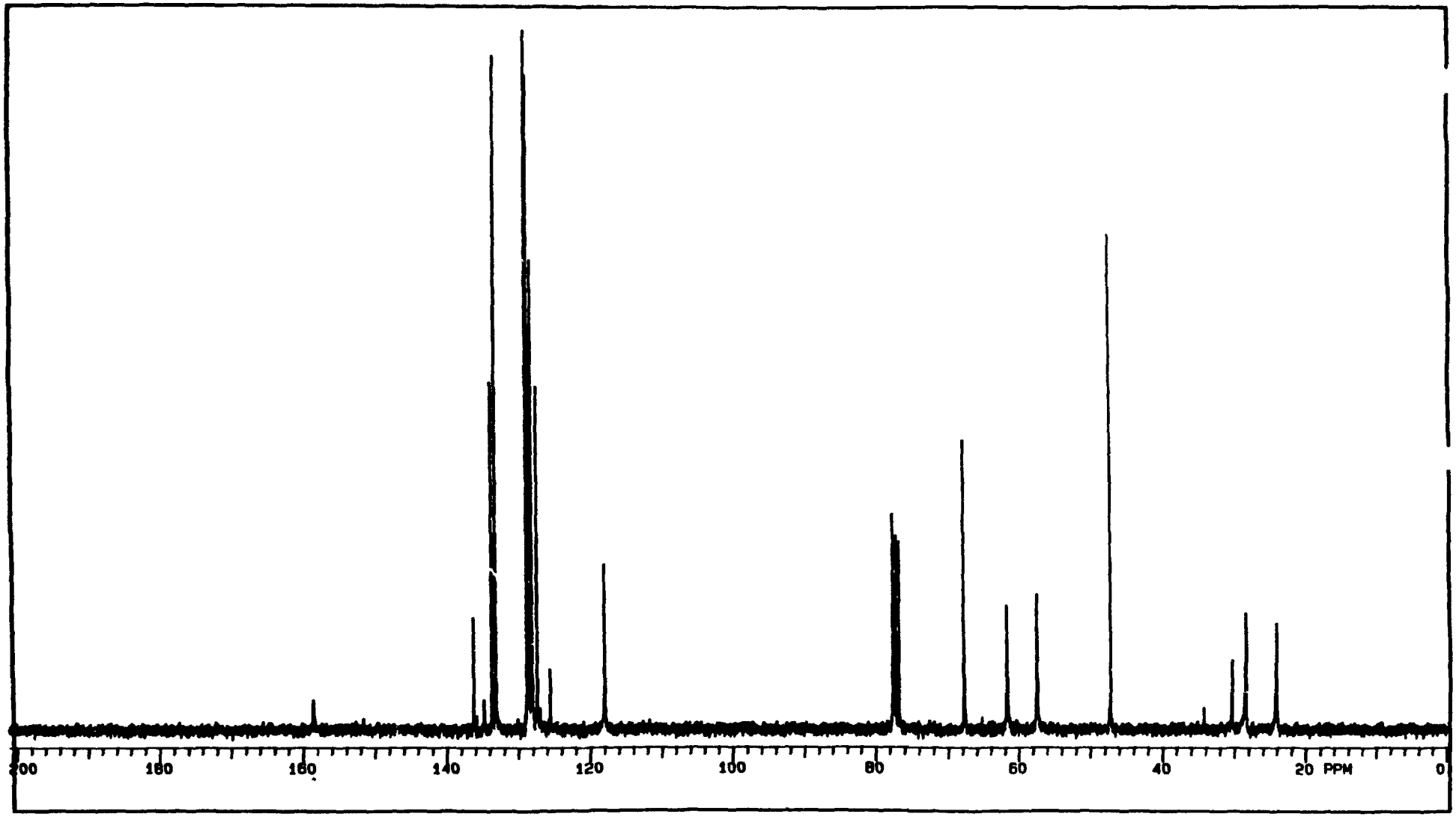

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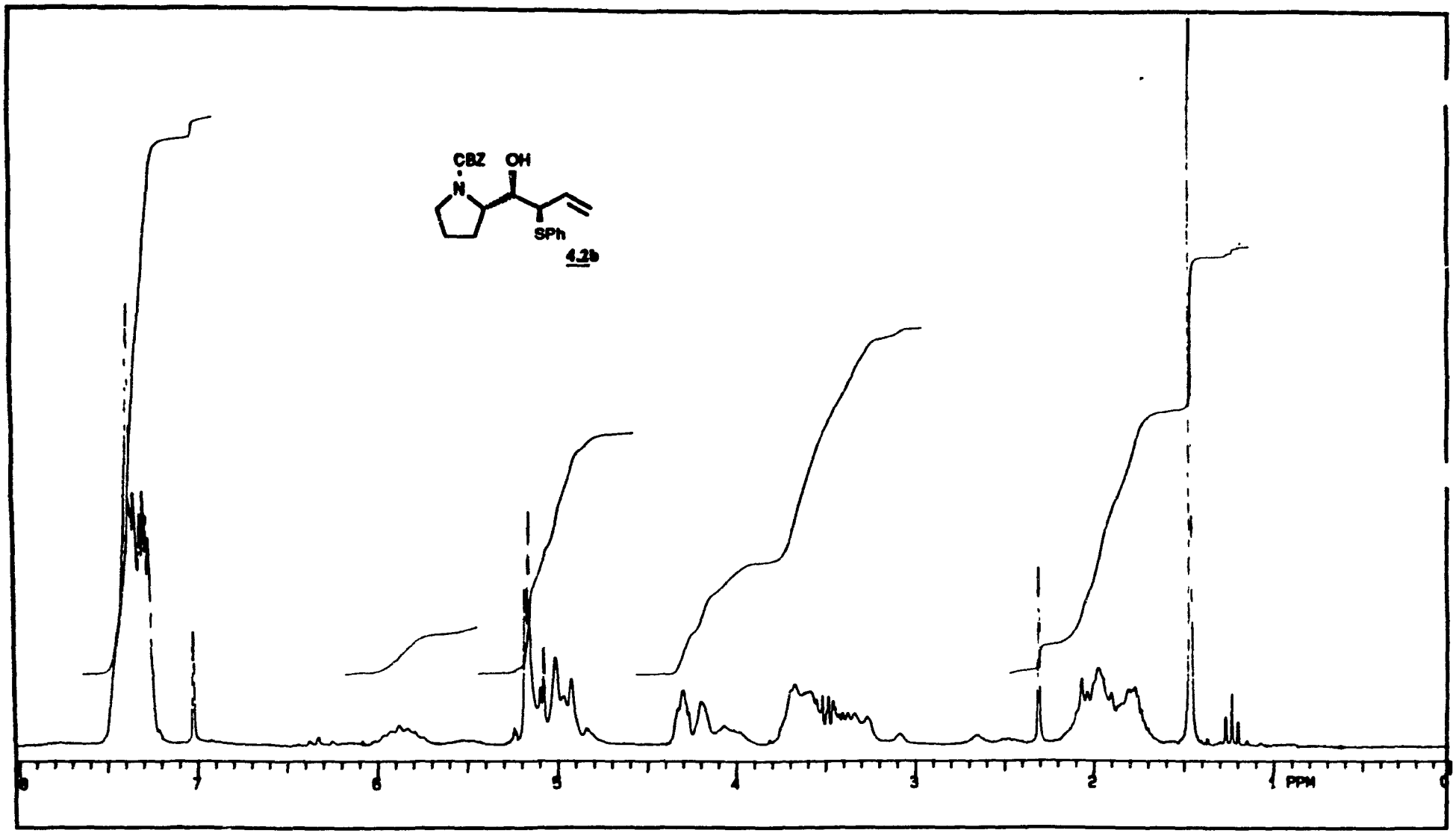

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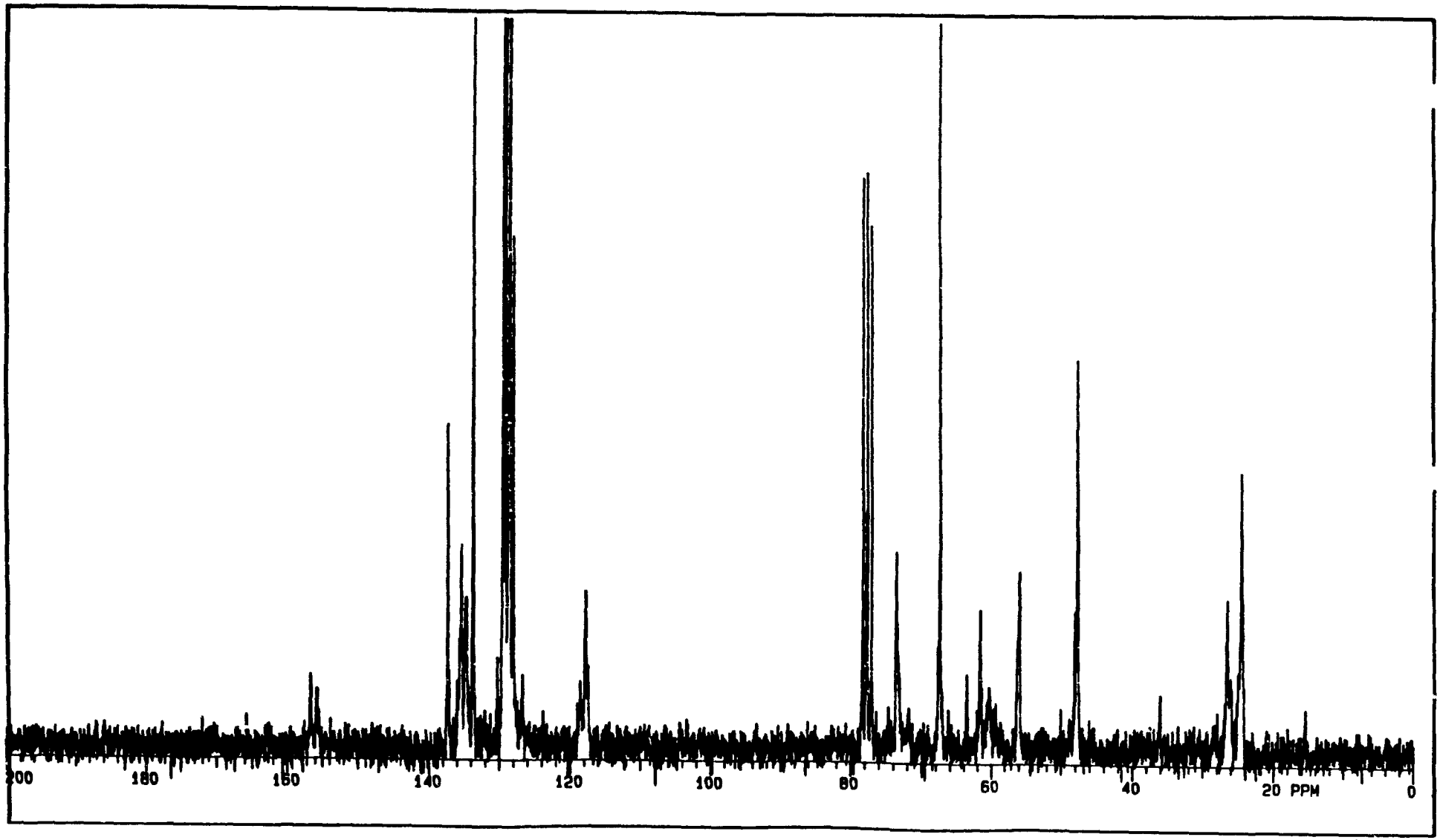
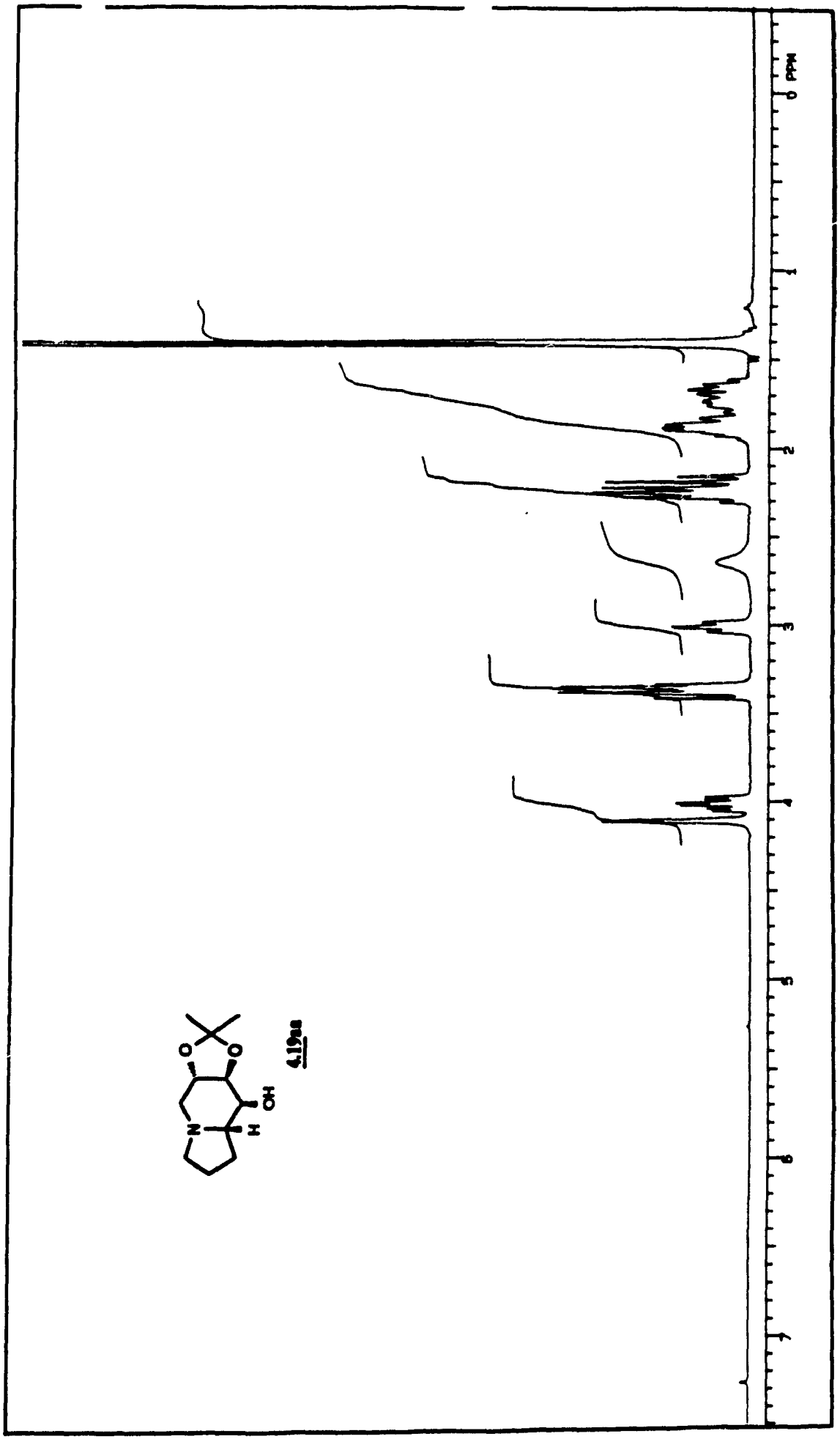
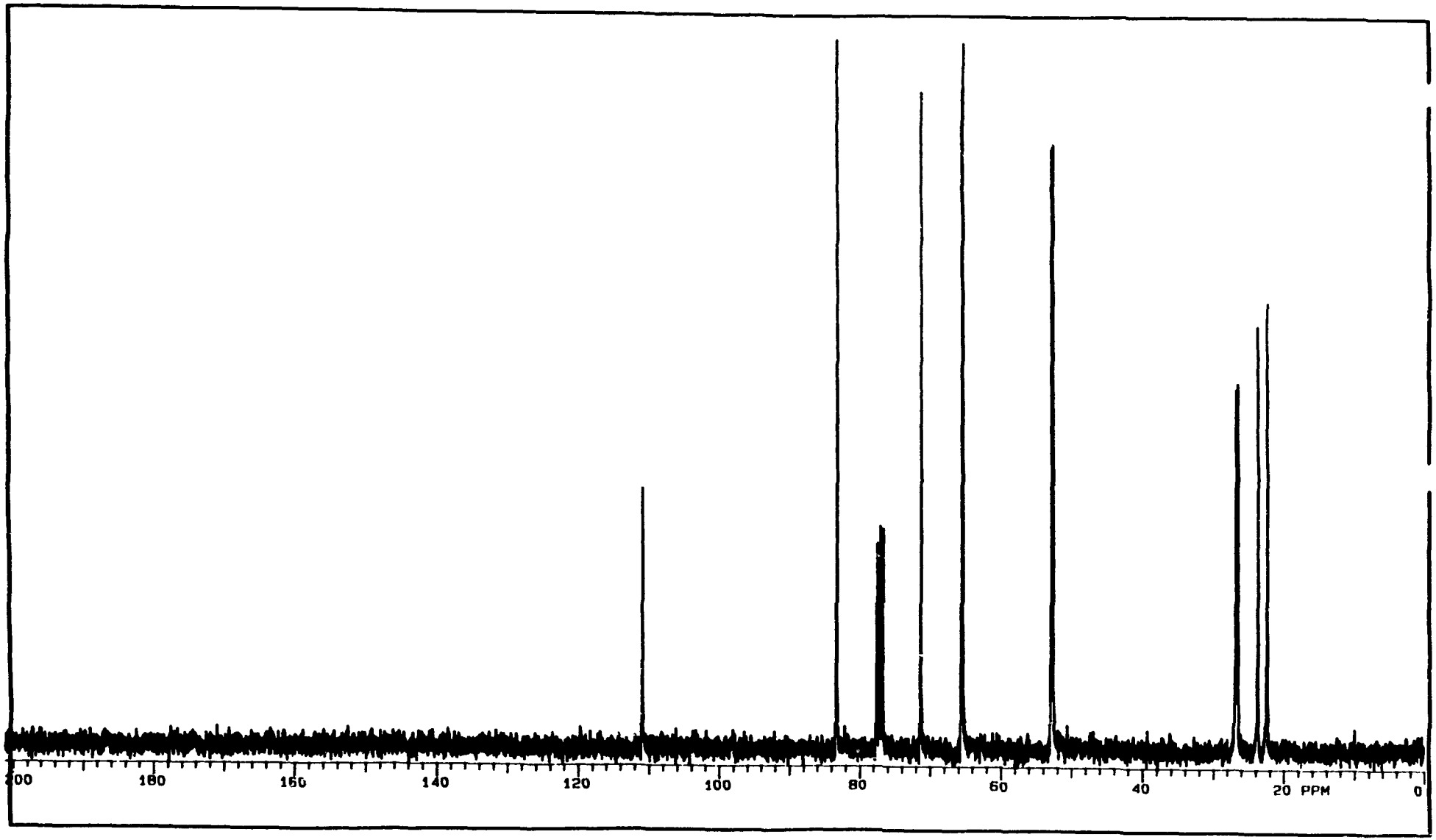


(6*S*,7*R*,8*S*,8a*S*)-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.19aa)



4.19aa

(6*S*,7*R*,8*S*,8a*S*)-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.19aa)



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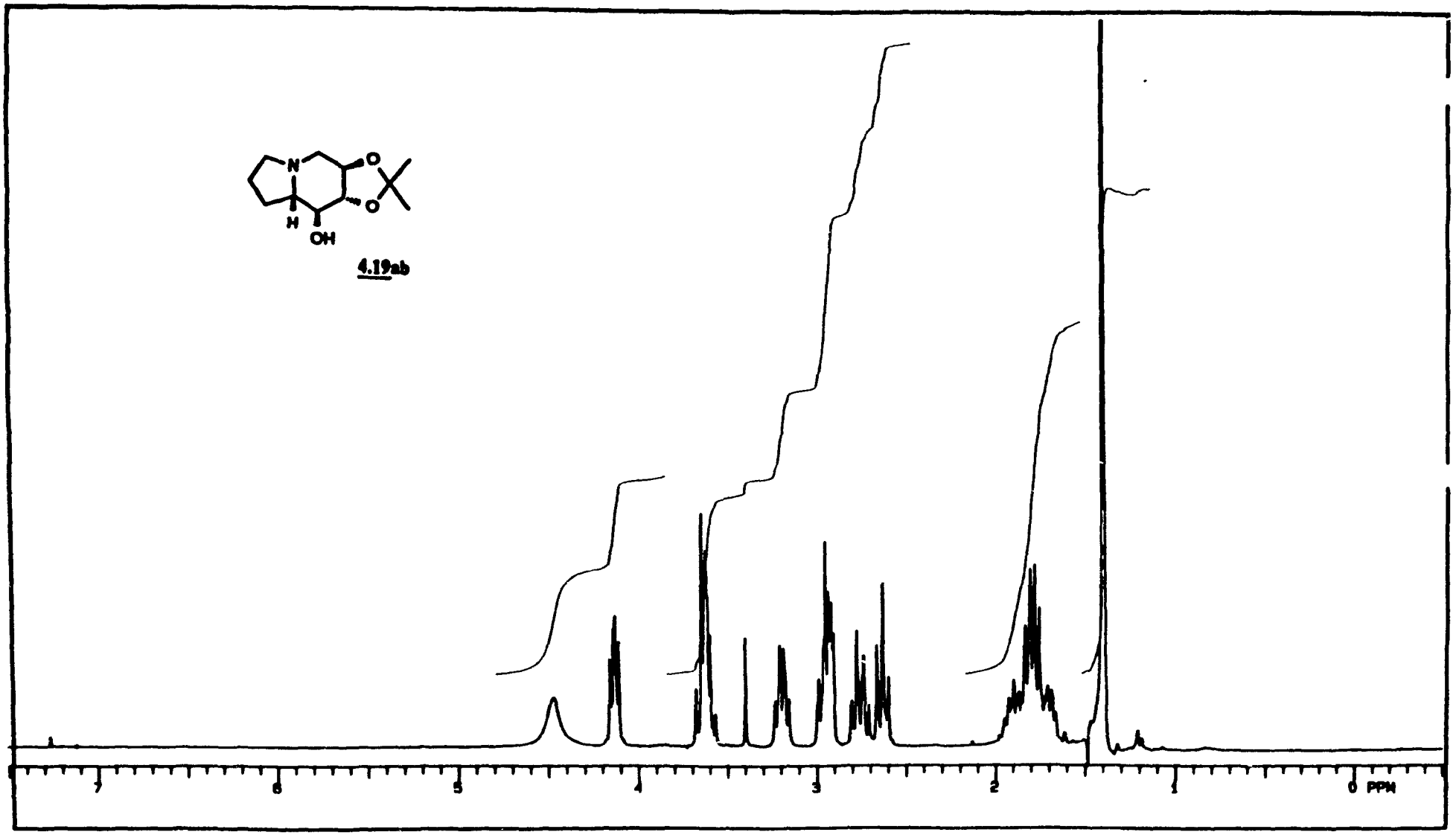

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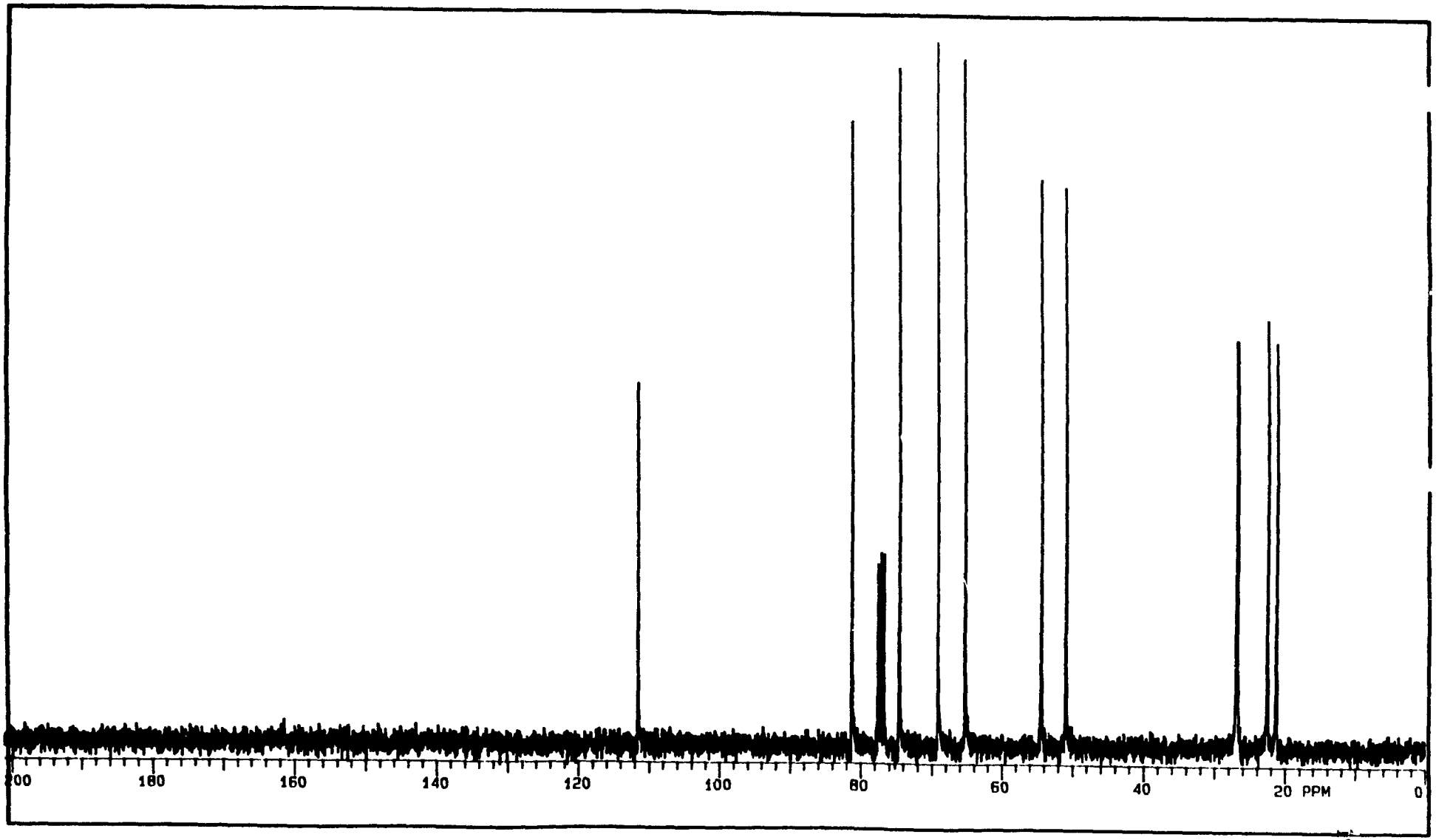

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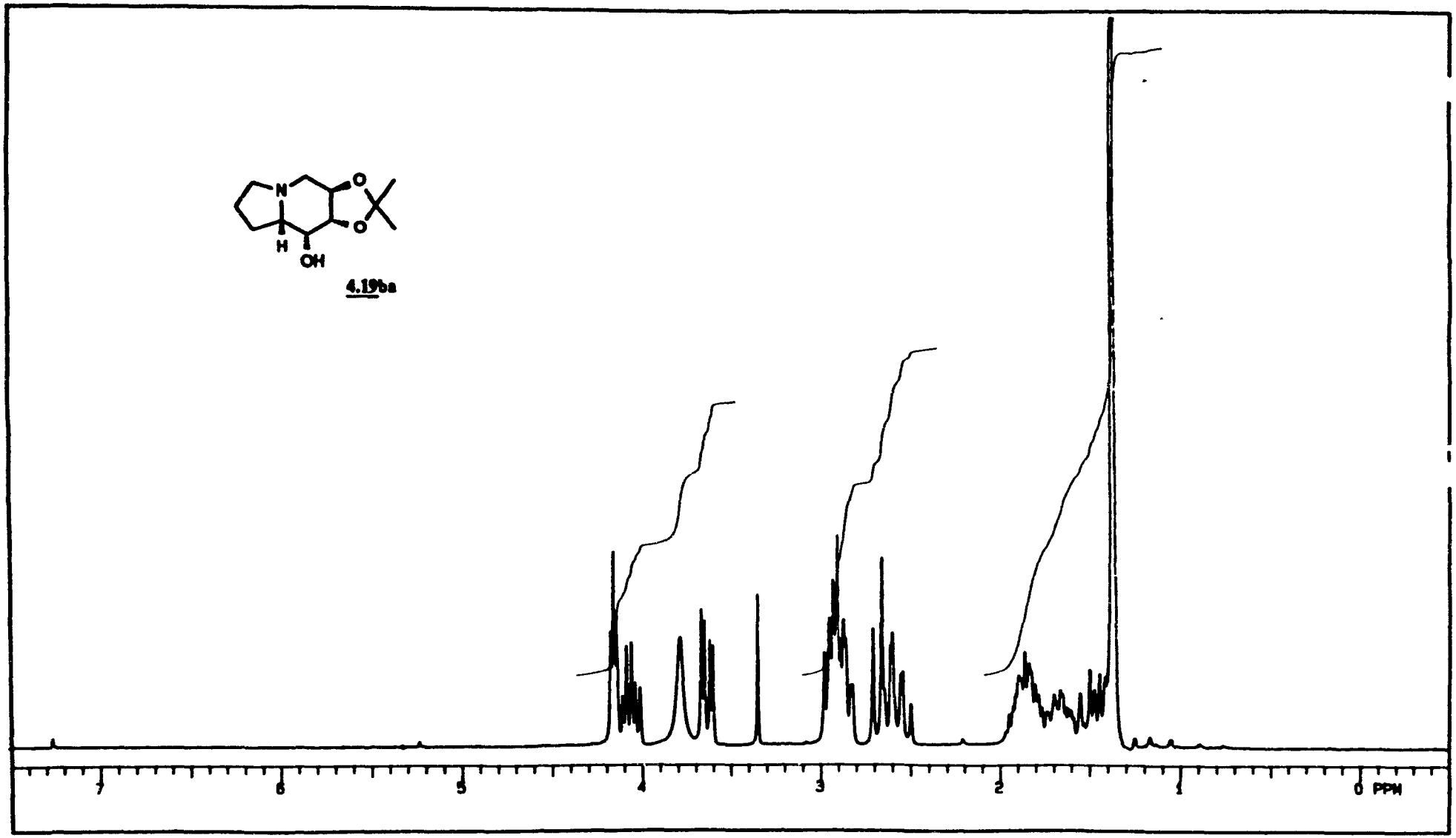

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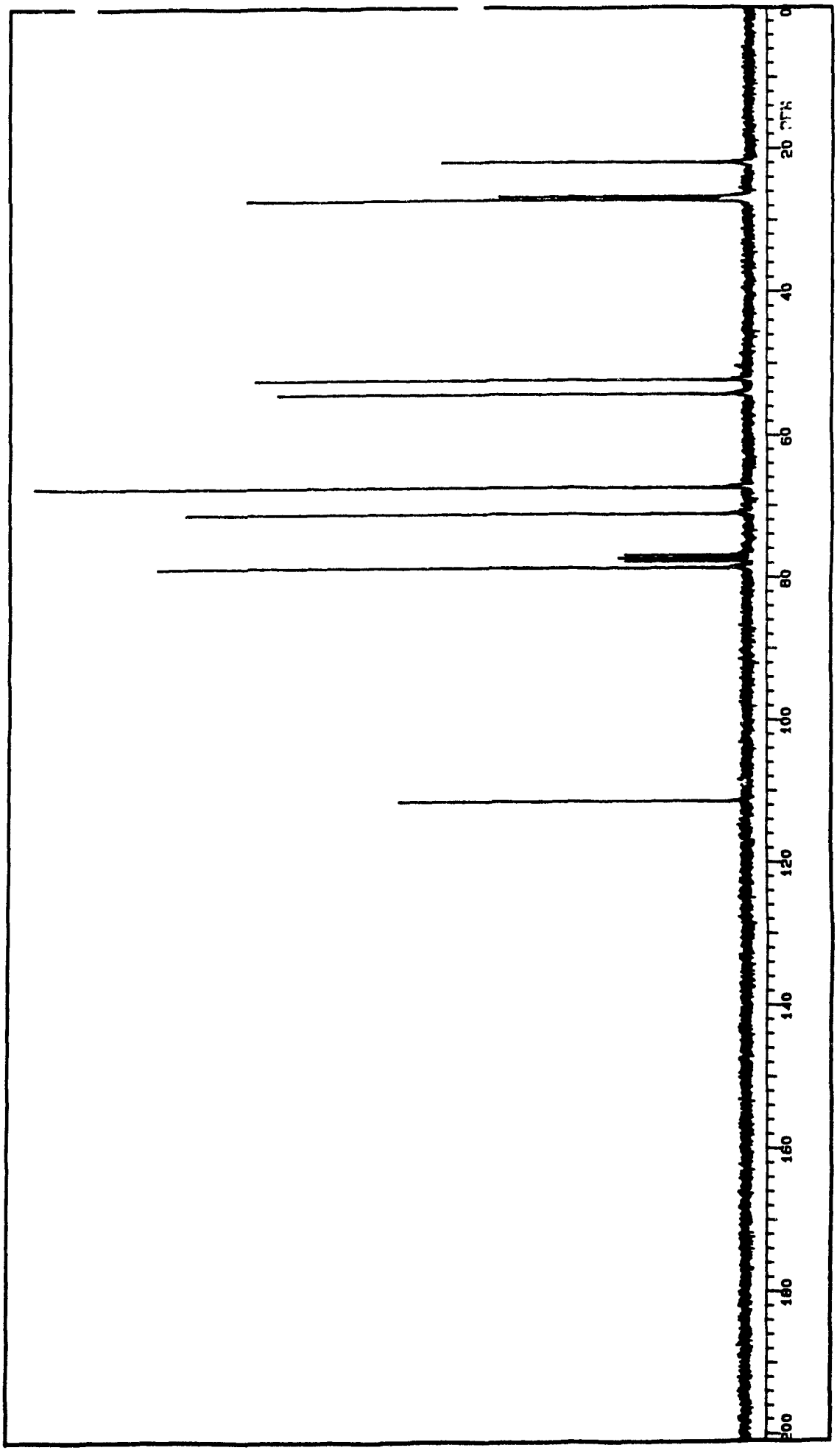
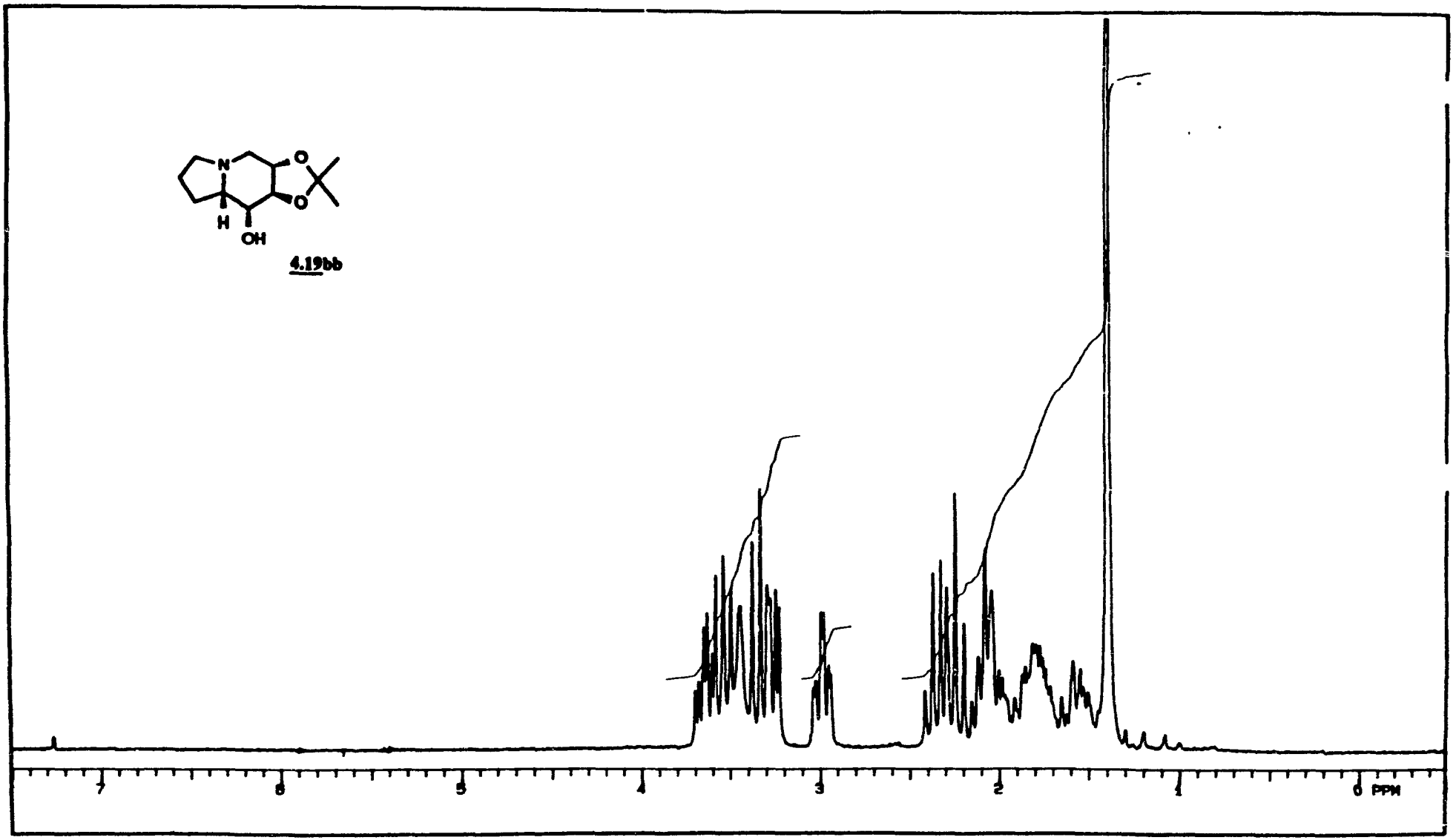


(6*S*,7*R*,8*R*,8a*S*)-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.19bb)



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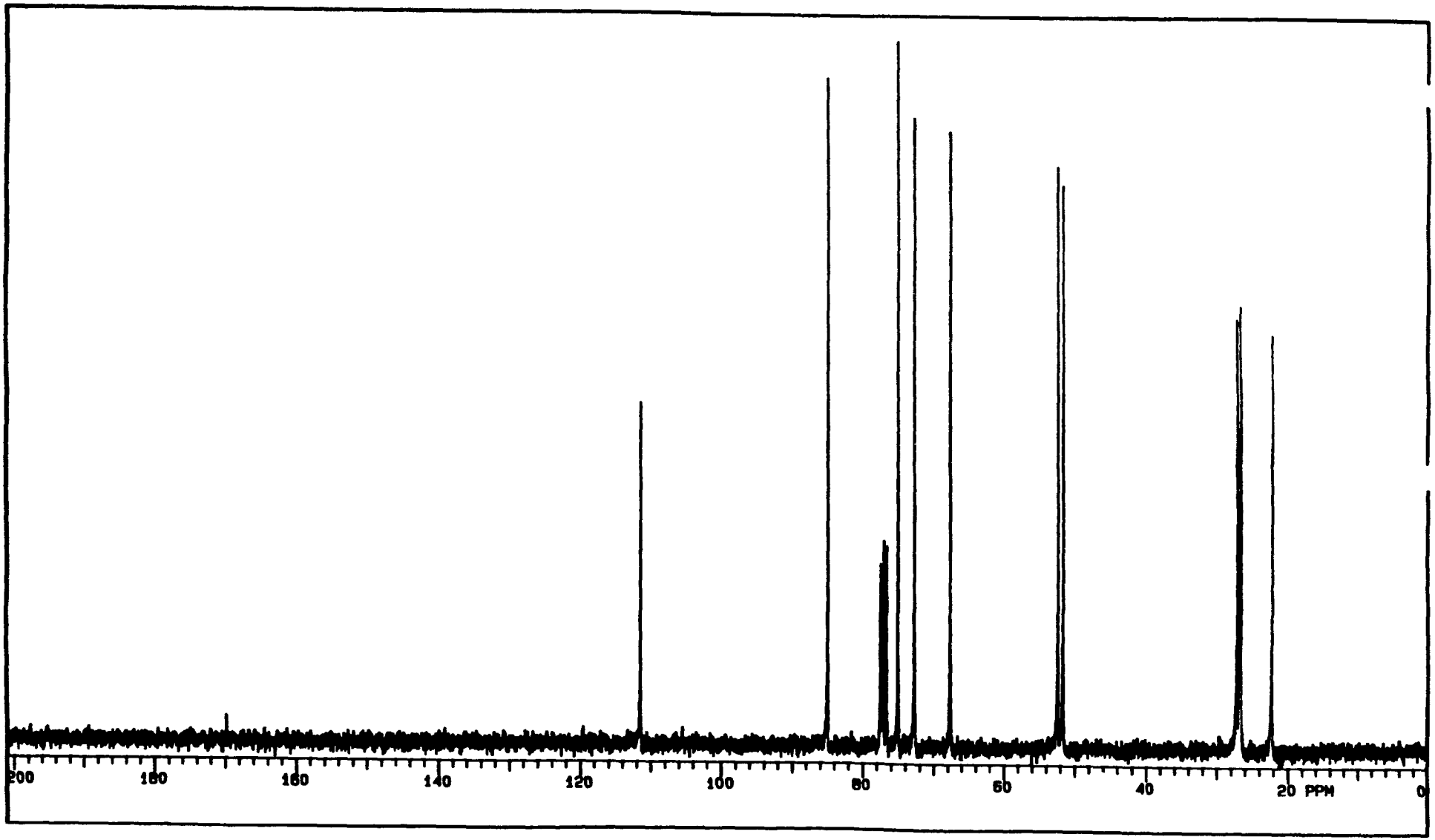
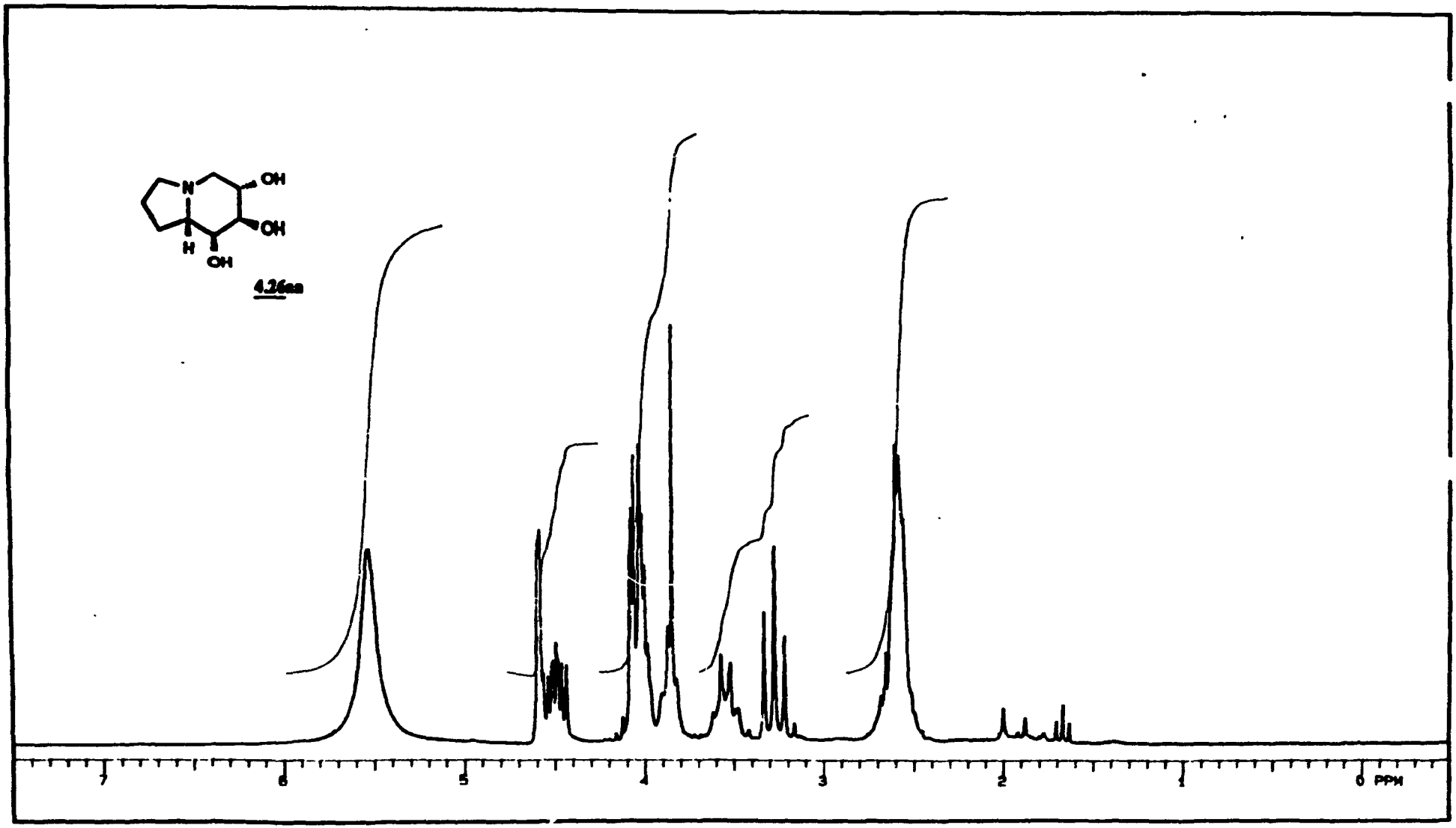


(6*S*,7*R*,8*S*,8a*S*)-6,7,8-trihydroxyindolizidine (4.26aa)



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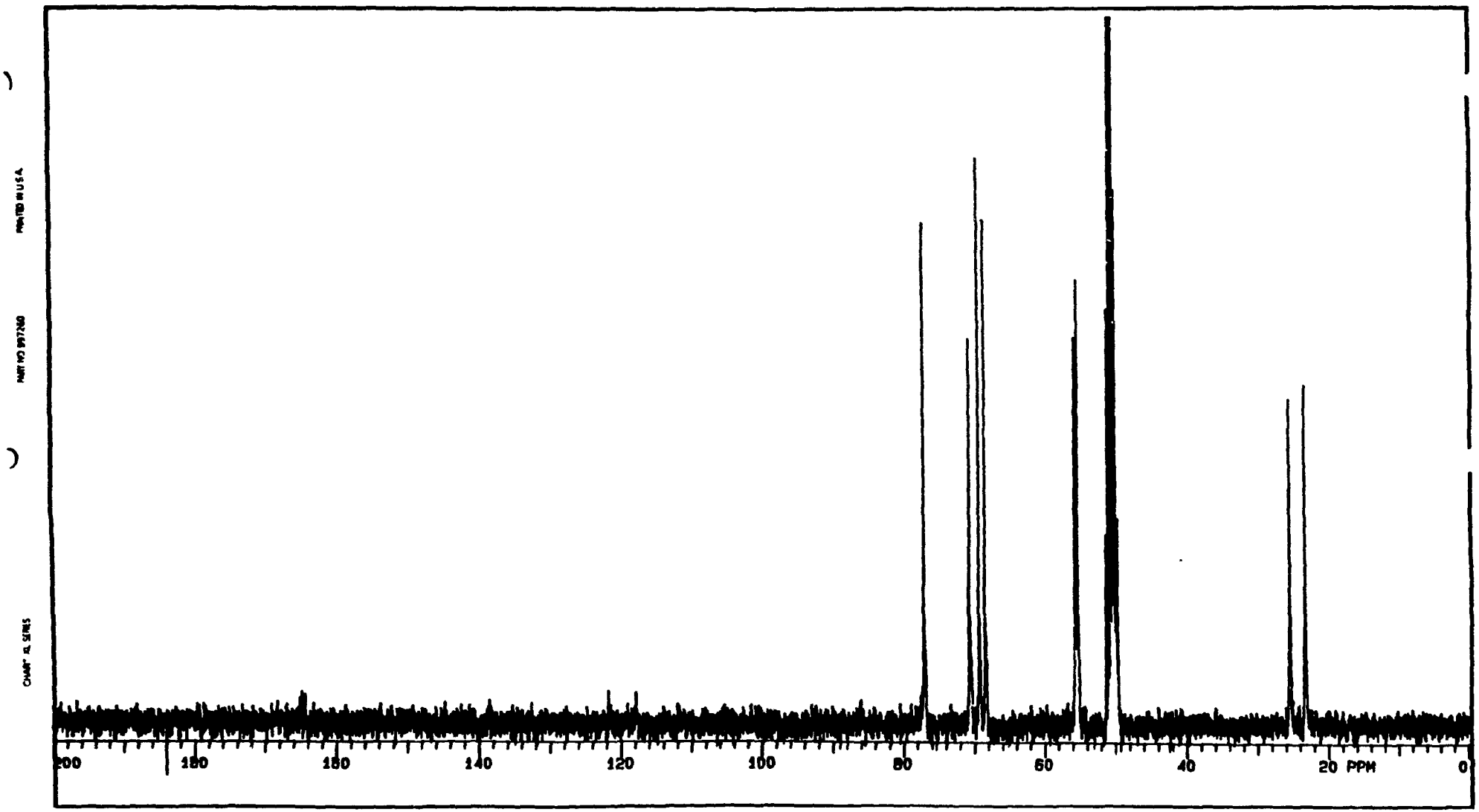

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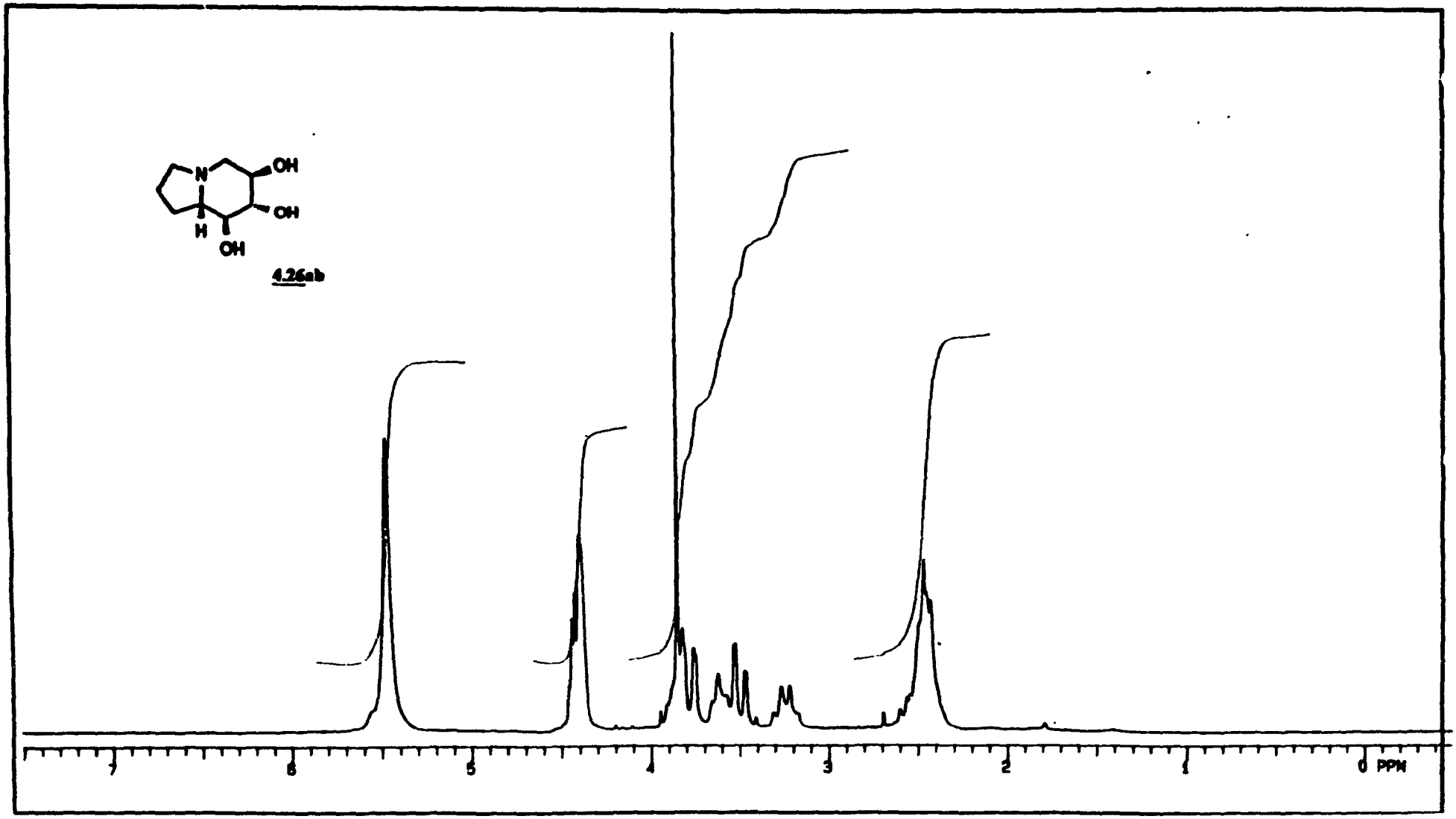

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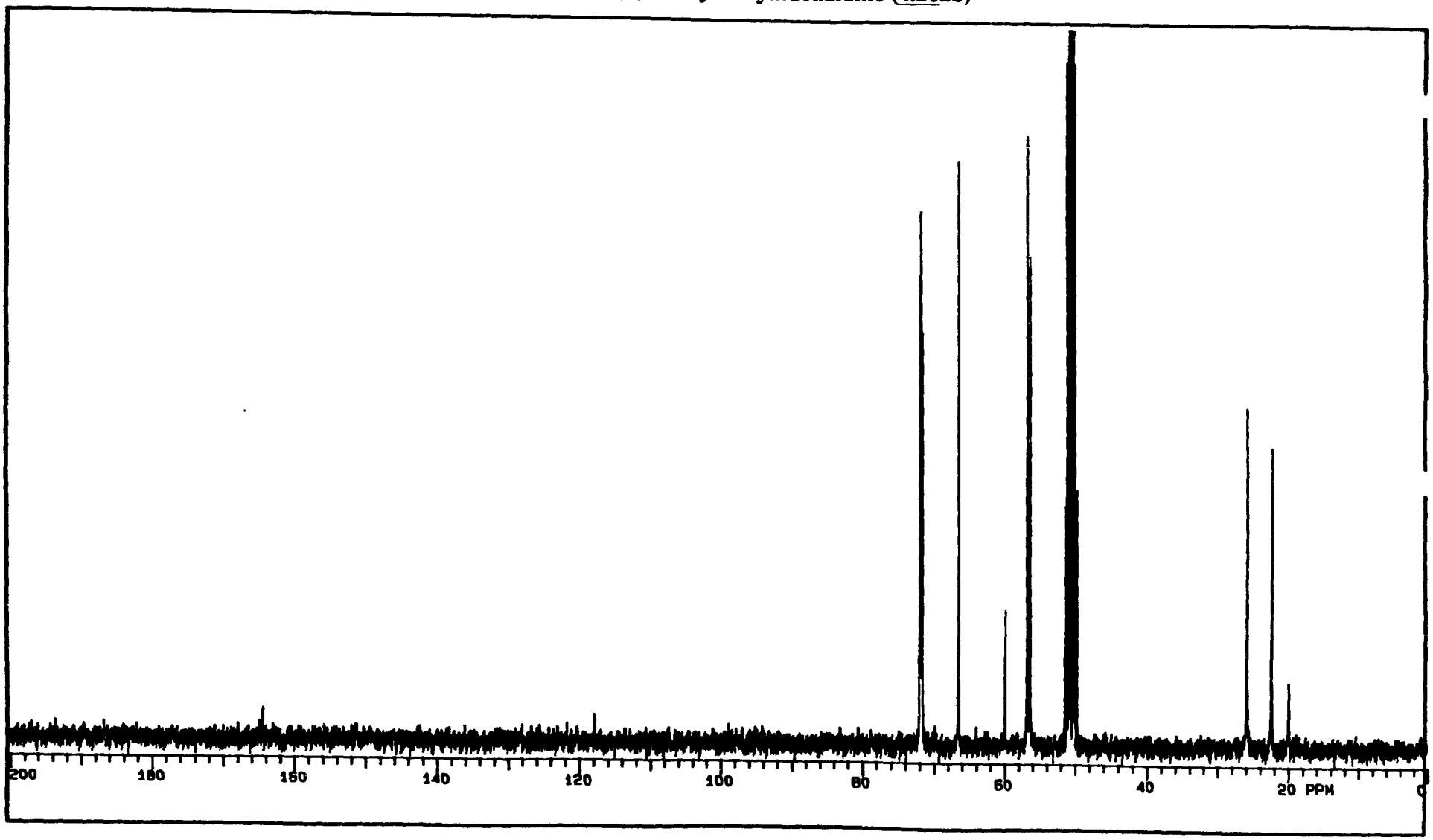

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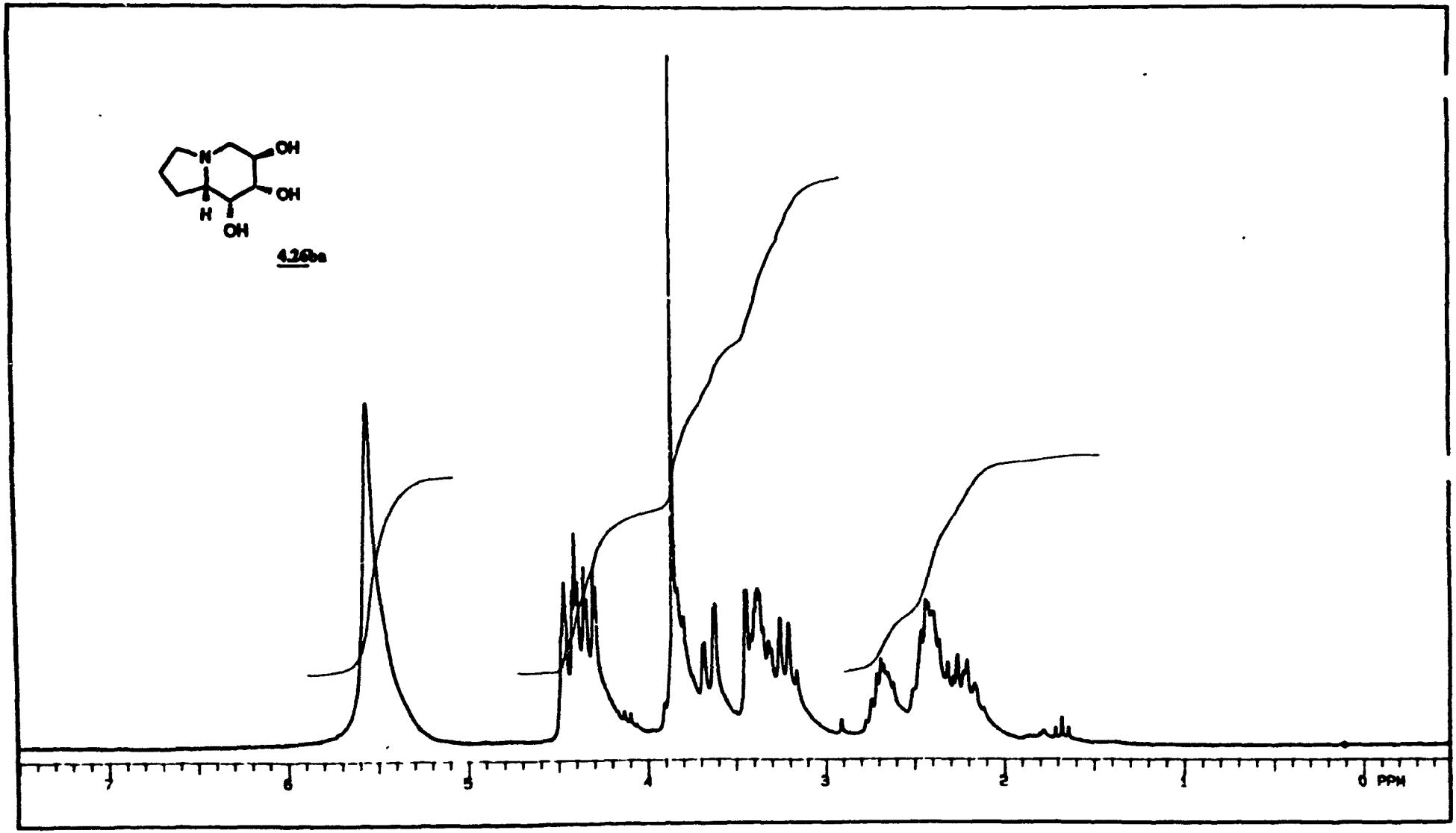

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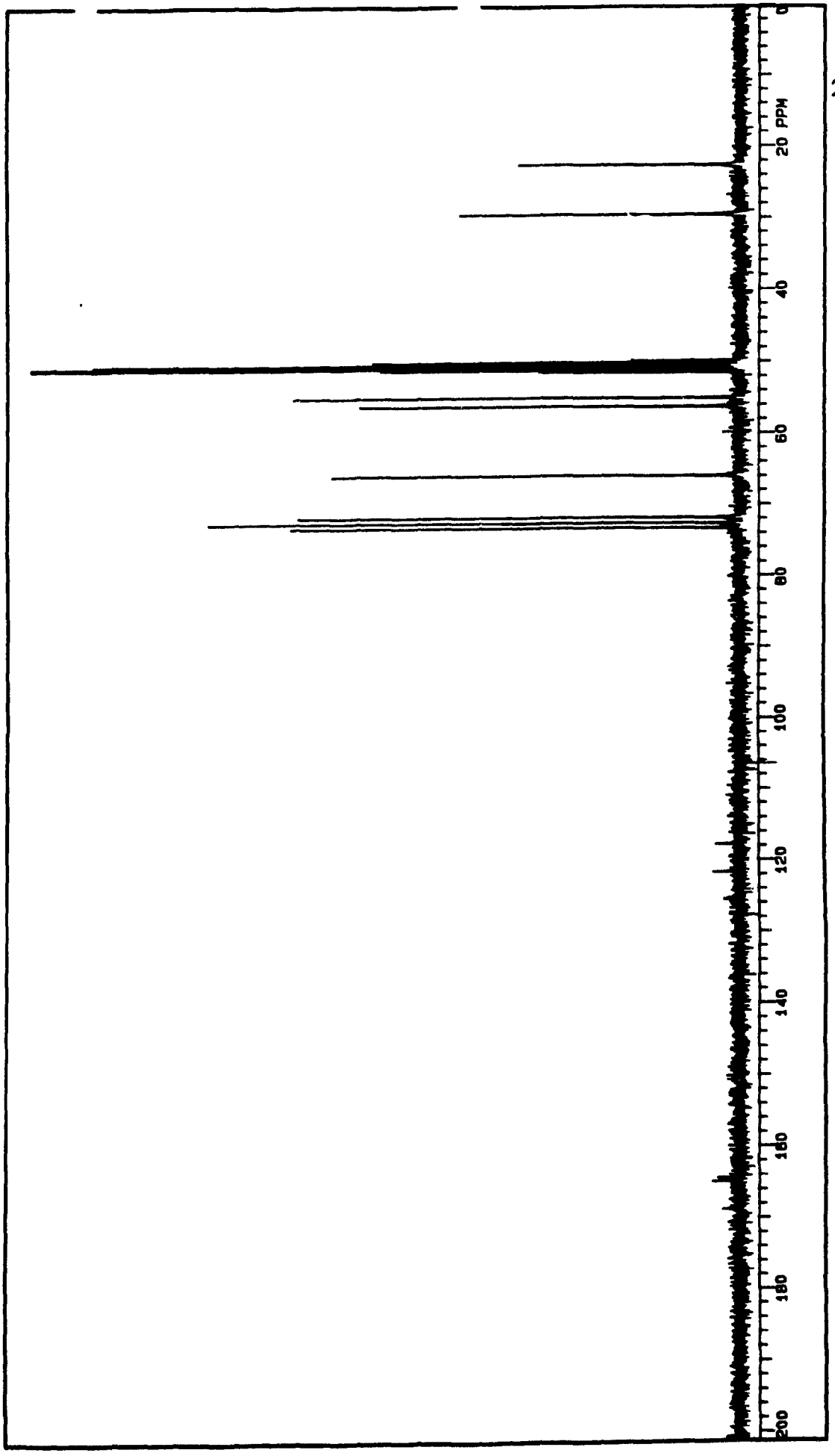

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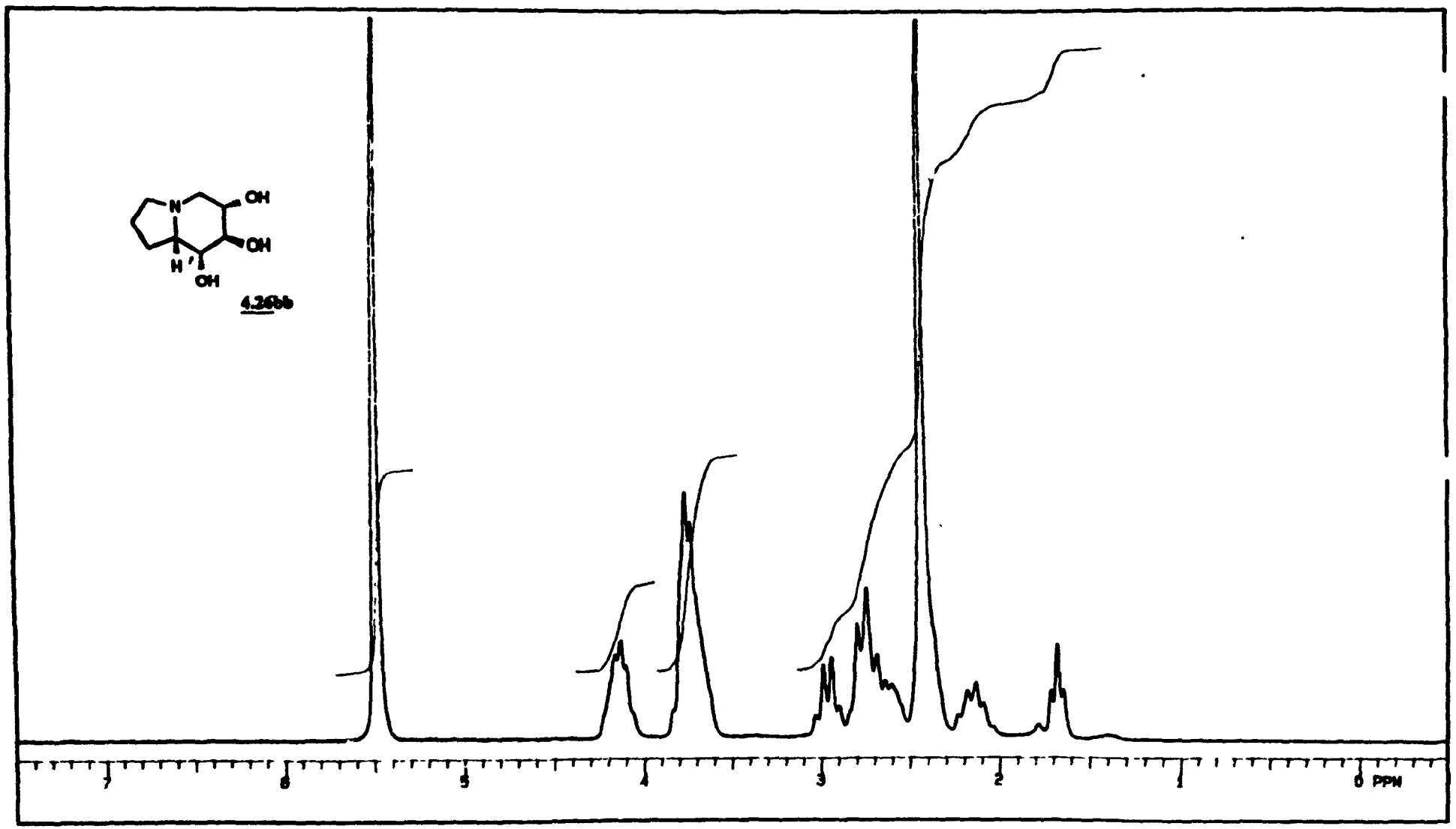

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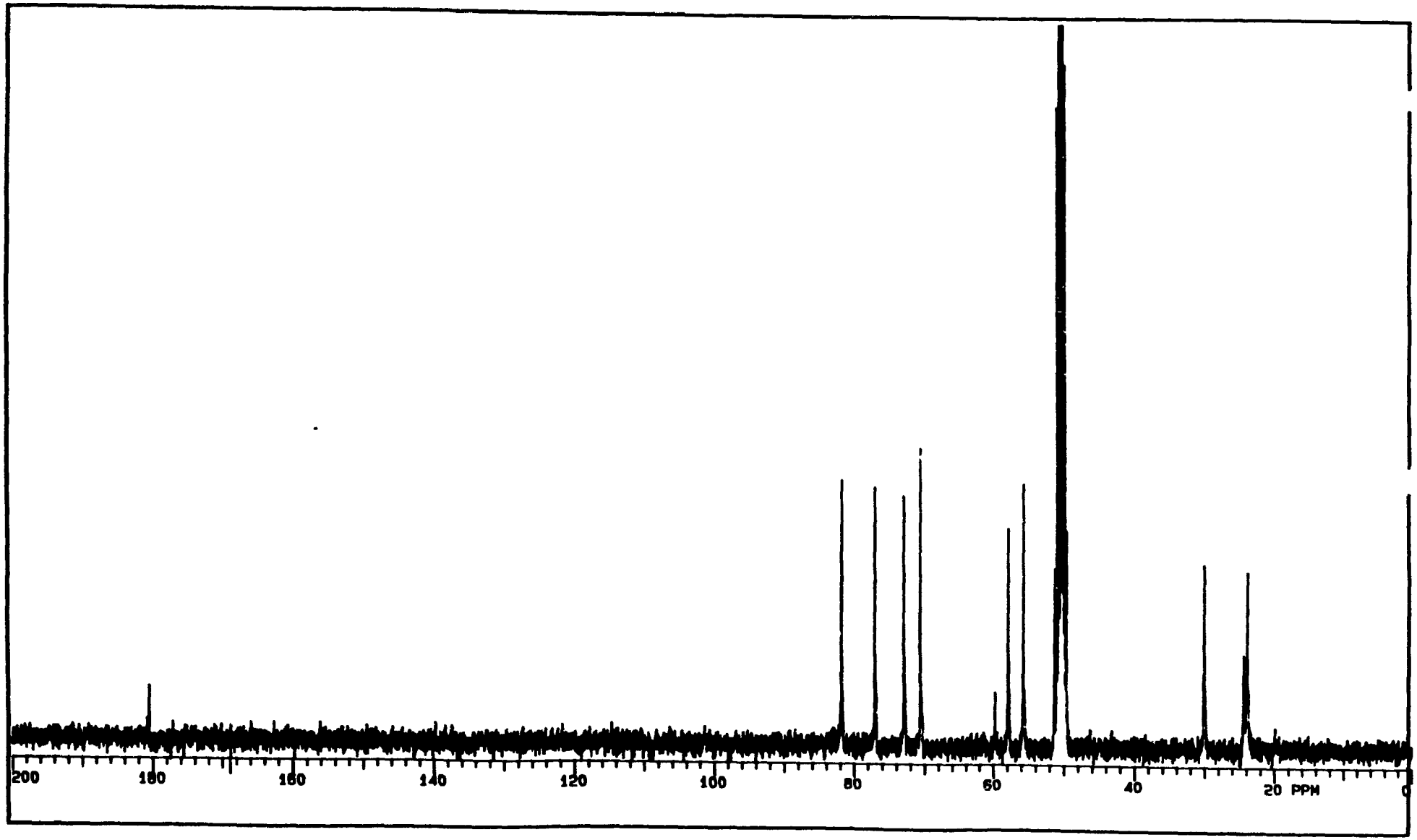
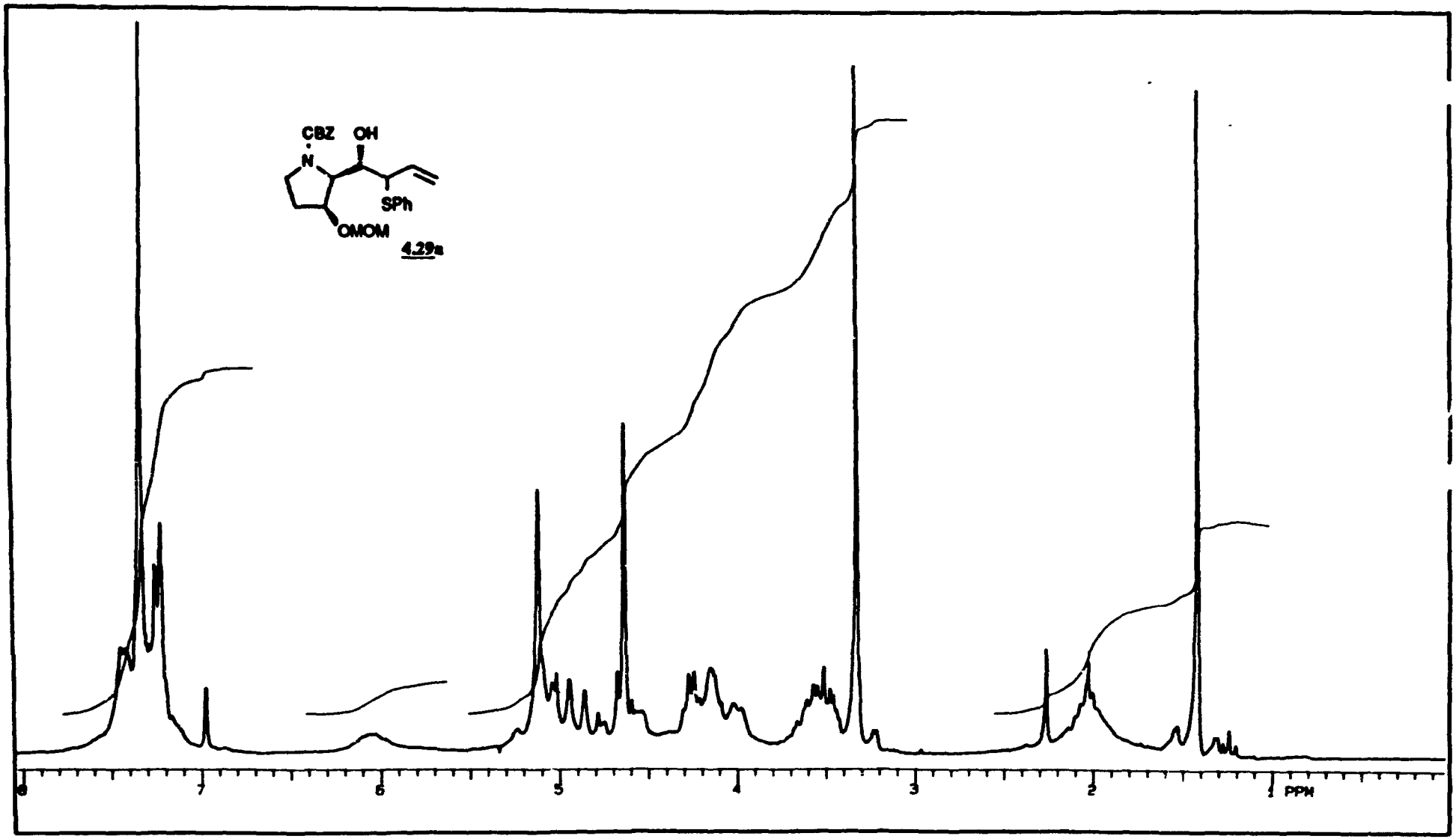
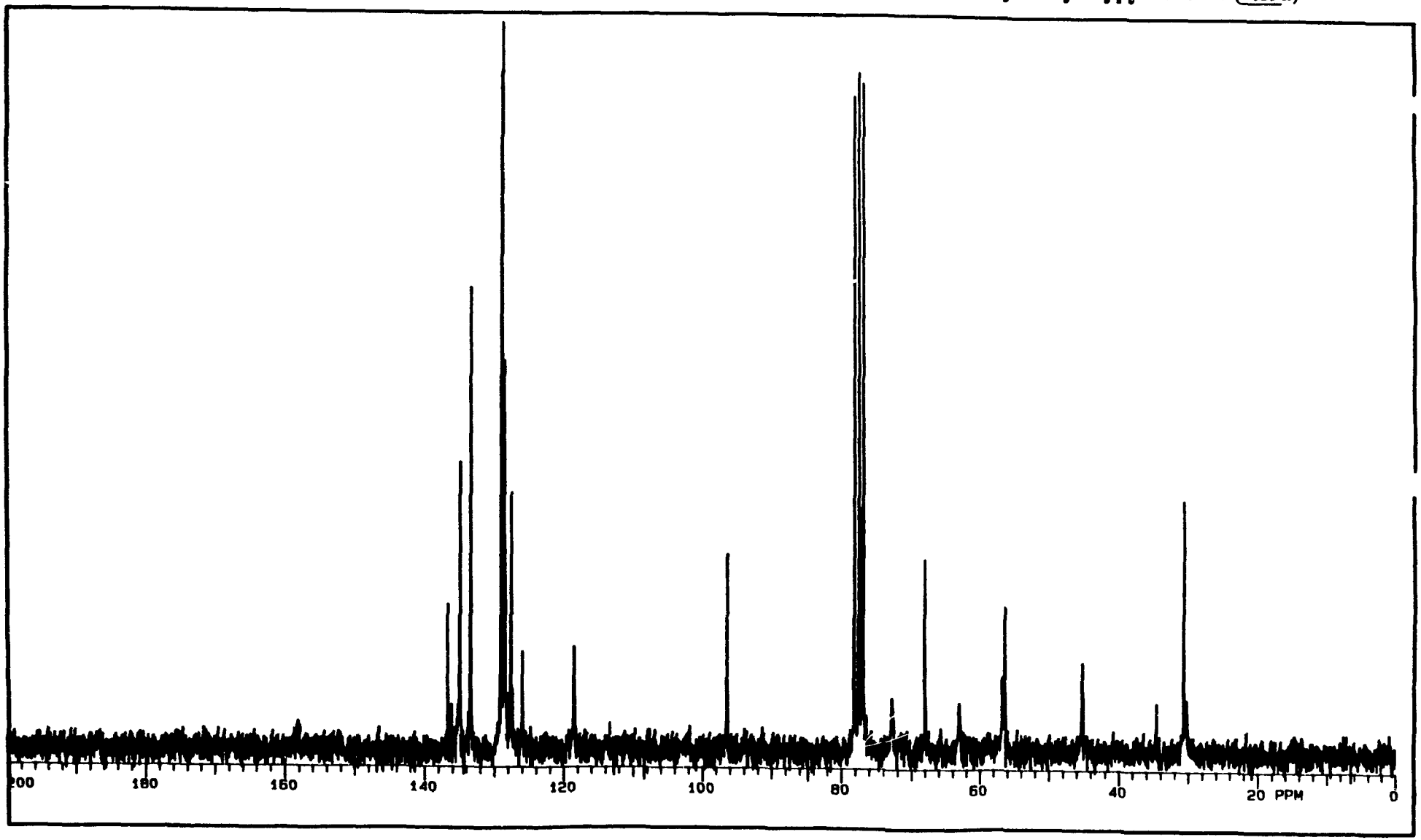


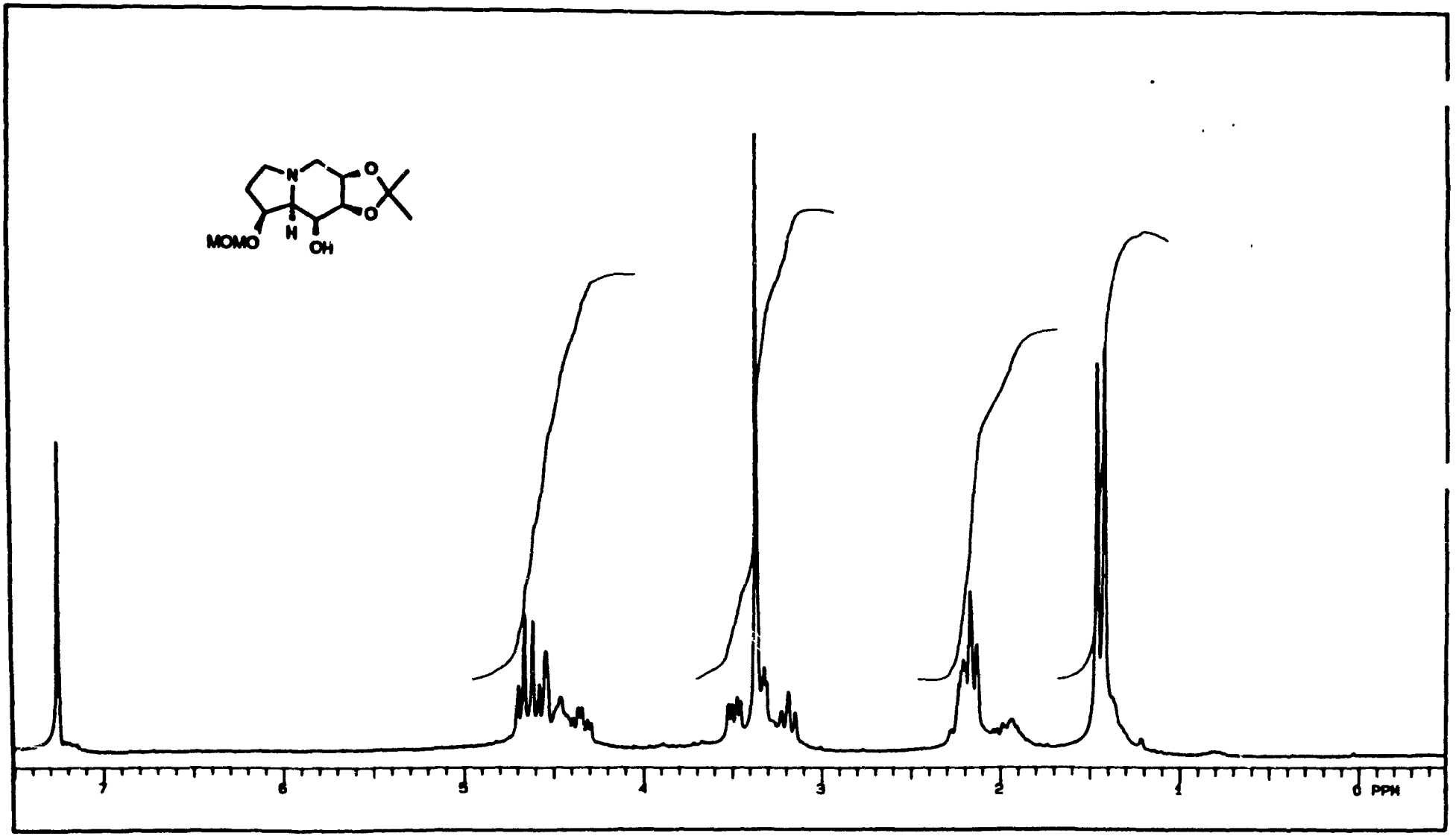
(2*R*,3*S*,1'*S*,2'*S*)-N-benzyloxycarbonyl-2-(1'-hydroxy-2'-thiophenyl-3'-butenyl)-3-methoxymethyloxypyrrolidine (4.29a)



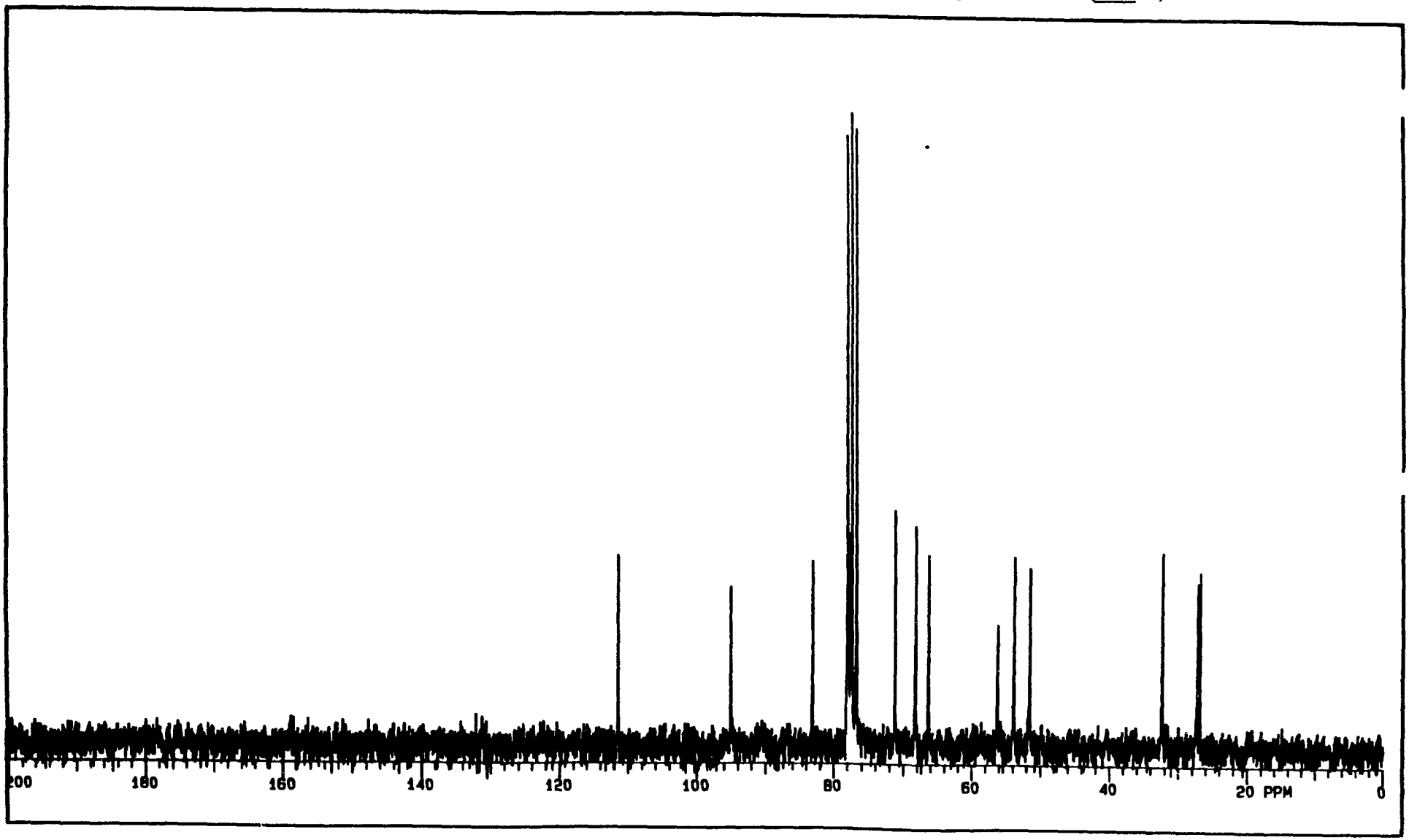
(2*R*,3*S*,1'*S*,2'*S*)-N-benzyloxycarbonyl-2-(1'-hydroxy-2'-thiophenyl-3'-butenyl)-3-methoxymethyloxypyrrolidine (4.29a)



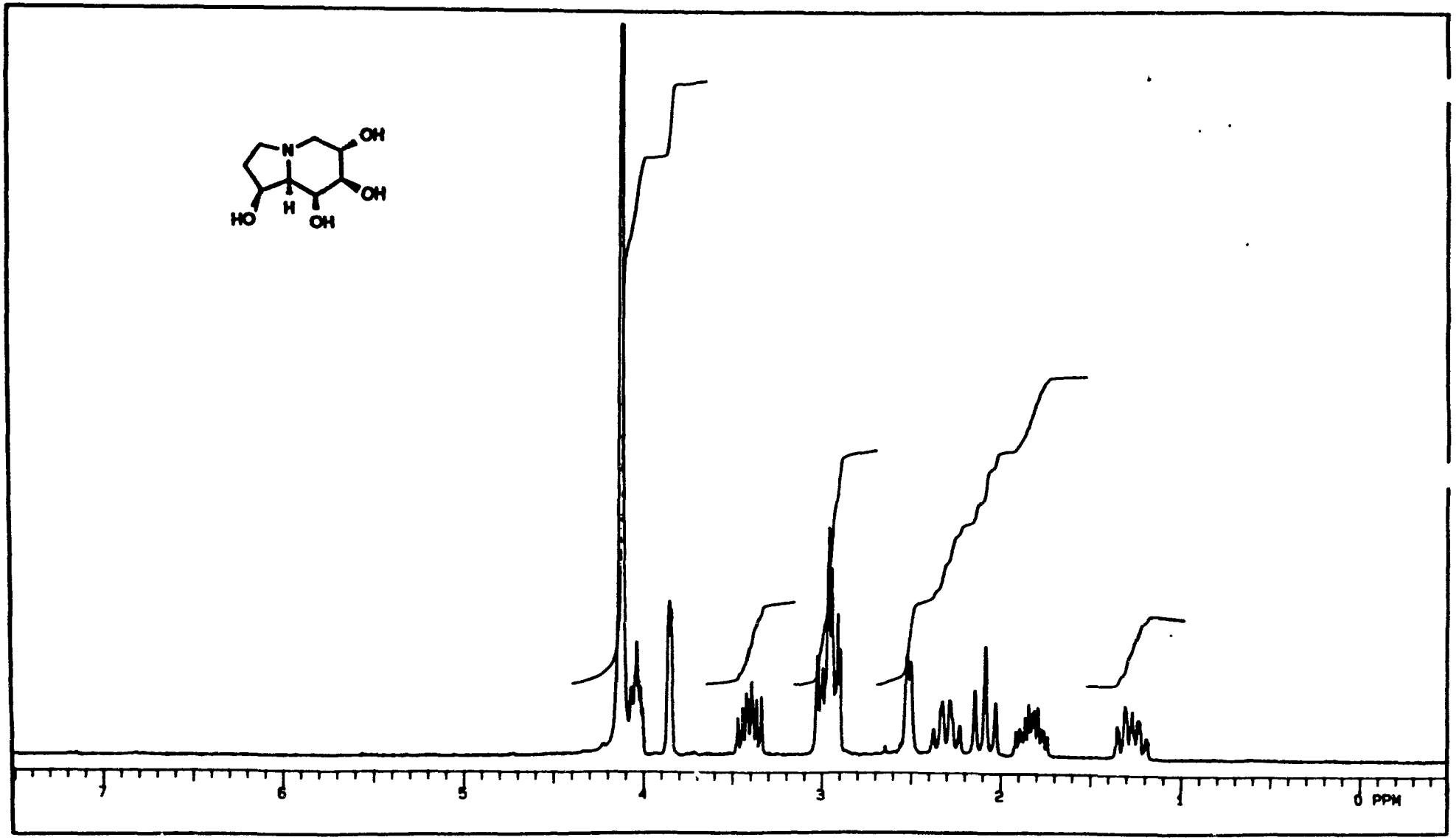
(1*S*,6*S*,7*R*,8*S*,8a*R*)-1-methoxymethyloxy-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.35aa)



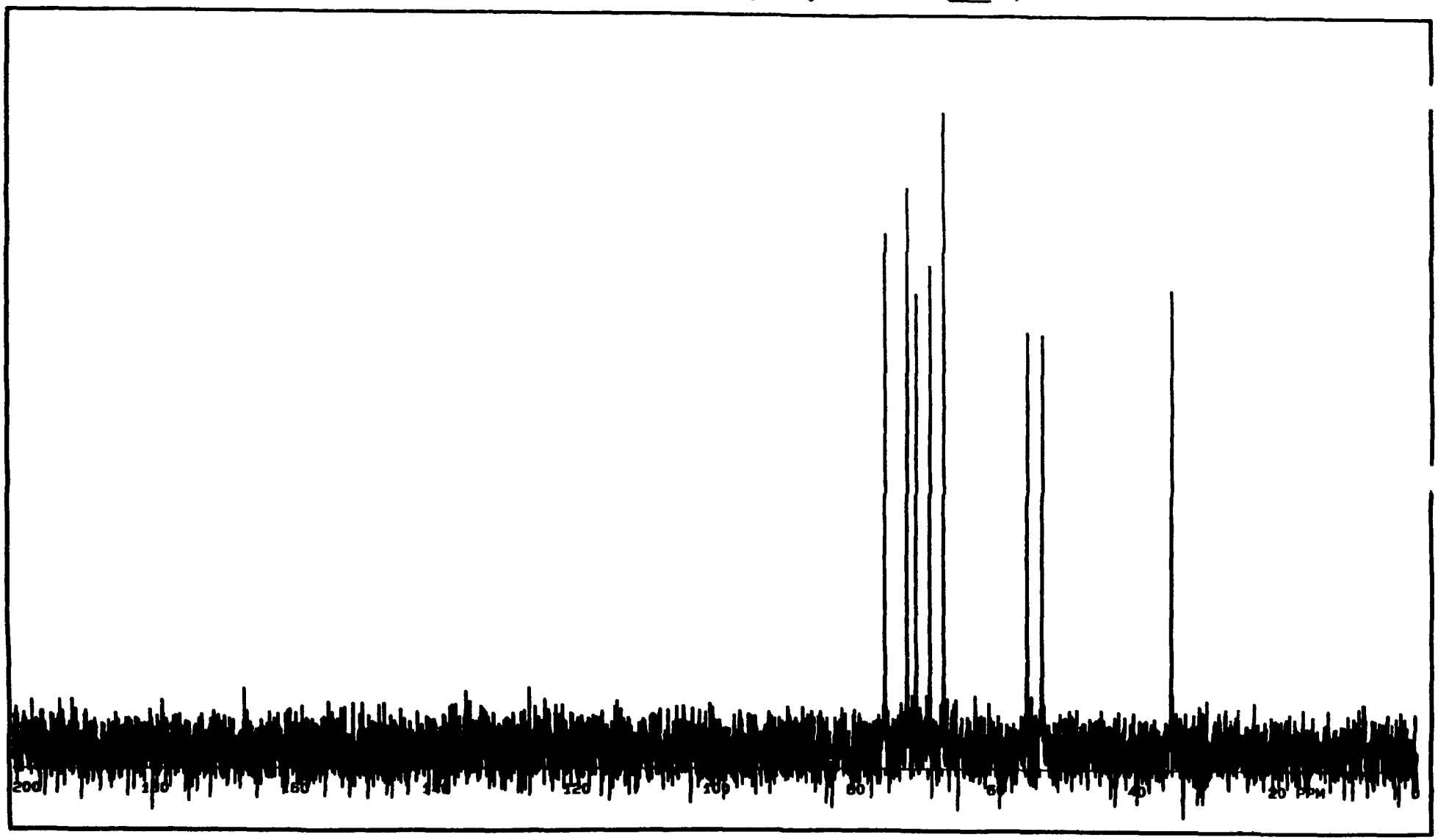
(1*S*,6*S*,7*R*,8*S*,8a*R*)-1-methoxymethyloxy-6,7-*O*-isopropylidene-8-hydroxyindolizidine (4.35aa)



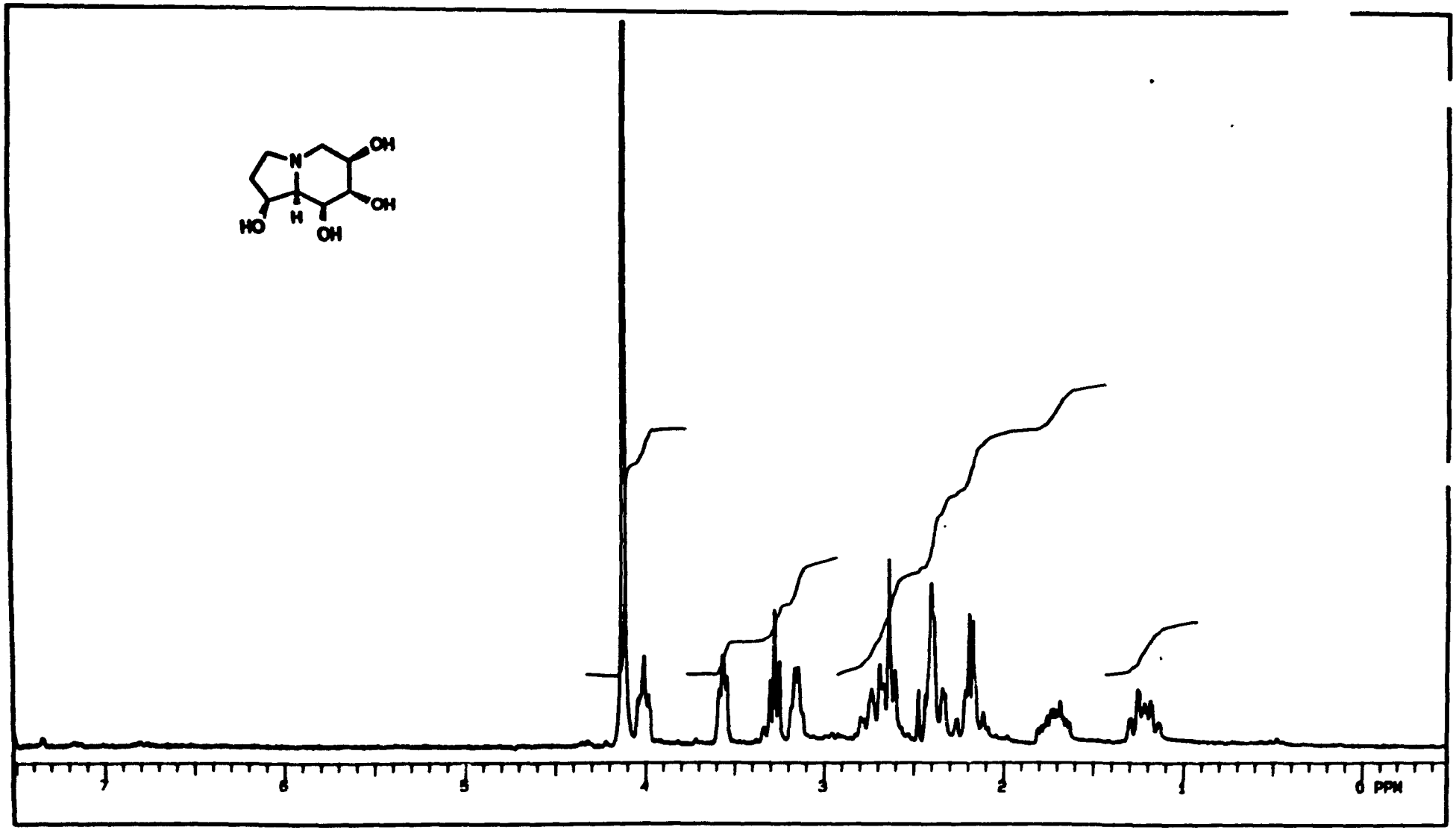
(1*S*,6*S*,7*R*,8*S*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36aa)



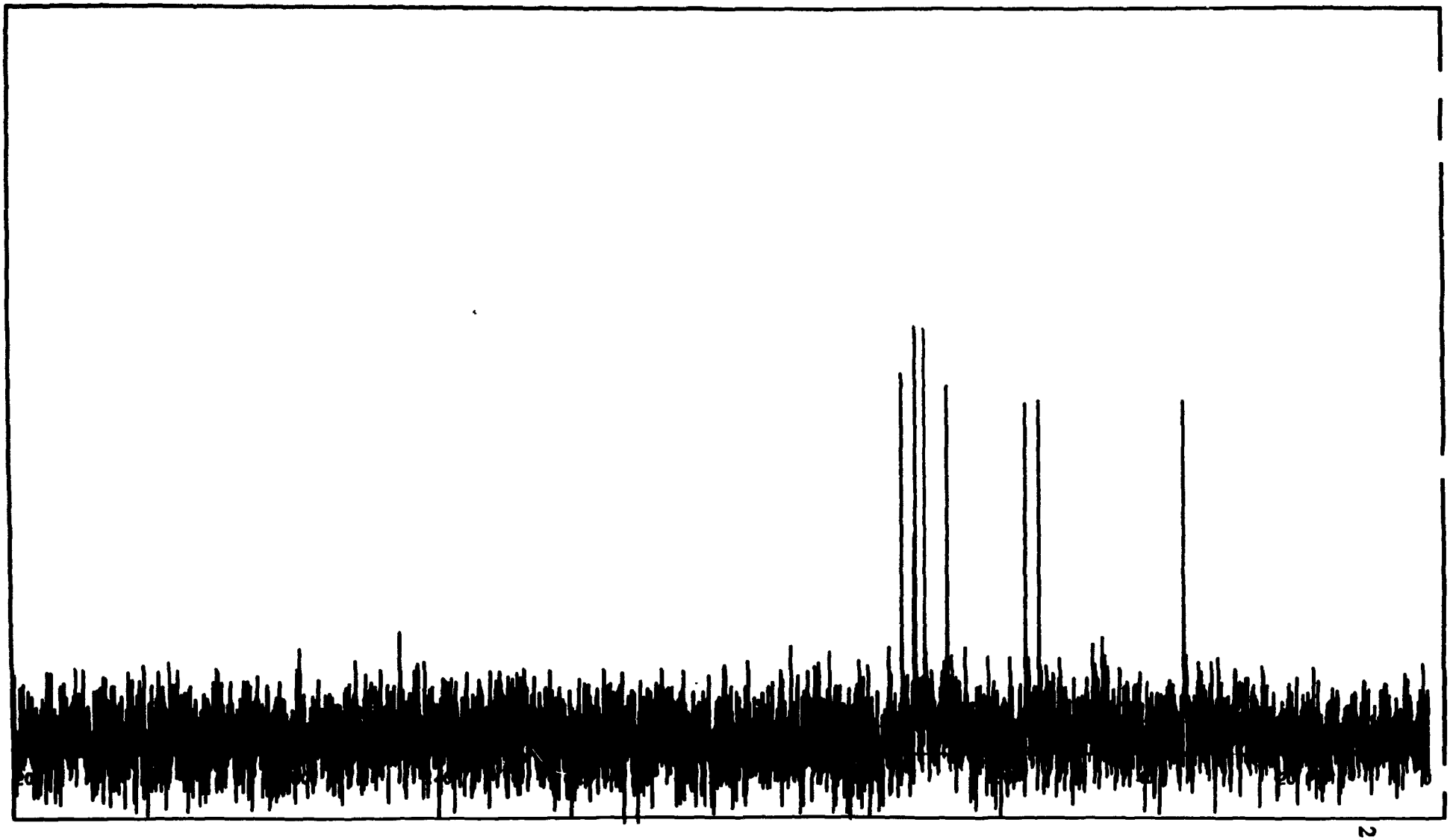
(1*S*,6*S*,7*R*,8*S*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36aa)



(1*S*,6*R*,7*S*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36ab)



(1*S*,6*R*,7*S*,8*R*,8a*R*)-1,6,7,8-tetrahydroxyindolizidine (4.36ab)



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CONCLUSION

This work has demonstrated that both the electrophilic and nucleophilic intramolecular cyclisation methodologies can be used to prepare the indolizidine ring system easily and with reasonably short sequences. The electrophilic cyclisation of allylsilanes had never been used, to the best of our knowledge, for the preparation of nitrogen containing heterocycles. On the other hand, the nucleophilic cyclisation has been used extensively (see **Chapter 1 : Introduction**) but it was demonstrated that the precursors to the cyclic molecules can be prepared easily.

It was found in the course of this study that other interesting avenues could be explored utilising similar strategies. A number of different analogues of polyhydroxylated indolizidines could be prepared by modifying slightly the sequences presented in **Chapter 4**. For instance, the introduction of the two last hydroxyl groups was done by means of an osmium tetroxide catalysed hydroxylation of a *trans* double bond. By preparing the *cis* analogue, a new series of isomers could be synthesised. Also, in order to prepare the 8a*R* series (which would have the same stereochemistry as in castanospermine at that position), the unnatural (and less available) D-proline could be used as starting material.

It was found in our attempted synthesis of castanospermine that the introduction of a MOM ether protecting group completely changed the selectivity of the stereofacial attack of the organometallic reagent onto the aldehyde, possibly by complexing the metal of the reagent. One could envisage changing this protecting group to a non-complexing group, or one could add 'ligand competitors' such as TMEDA in the reaction mixture.

Because of the simplicity of the method, one can easily prepare a variety of new analogues which can than be tested for glycosidase inhibition (and other biological

activity). The better understanding of the structure-activity relationship will help in the understanding of how proteins (and enzymes) work in living sytems. This knowledge can only lead to an amelioration of the already existing methods, or to the discovery of new methods for the treatment of diseases which have been, up to now, cured with only moderate success, and thus to the improvement of the living standards of the human race and their animal friends.