ALKALOIDS FROM *ALSTONIA MACROPHYLLA*

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FACULTY OF SCIENCE
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KUALA LUMPUR

2013

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A THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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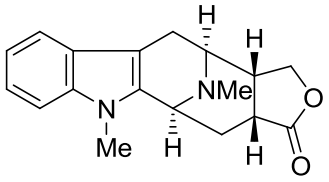
Abstract

The Malaysian plant, *Alstonia macrophylla* Wall, was investigated for its alkaloidal content and the results are summarized in the Table below. A total of 90 alkaloids were isolated and characterized from the leaf and stem-bark of *A. macrophylla*. Of these, 30 are new alkaloids. The leaf extract of *A. macrophylla* yielded a total of 13 new alkaloids, including a macroline indole **1**, a macroline oxindole **16**, eight akuammiline alkaloids (compounds **24**, **25**, **26**, **27**, **28**, **29**, **30**, and **31**), a sarpagine alkaloid **32**, and two ajmaline alkaloids (compounds **33** and **34**). The stem-bark extract of *A. macrophylla* gave a total of 19 new alkaloids. These include, in addition to the akuammiline and sarpagine alkaloids found in the leaf extract (**24** and **32**, respectively), compound **2**, **3**, **4**, **17**, the linearly fused bisindole alkaloids, lumutinines A–E (**71**–**75**), the macroline-macroline bisindoles, lumusidines A–D (**77**–**80**) and perhentidines A–B (**81** and **82**), and the macroline–pleiocarpamine bisindole alkaloids, villalstonidines B (**86**) and F (**87**). Perhentidines A–B (**81** and **82**), perhentinine (**83**), villalstonine (**88**) and macrocarpamine (**90**), showed pronounced cytotoxicity toward KB cells (IC_{50} 2.64–4.06 μg/mL), while lumutinines A–E (**71**–**75**), macralstonidine (**76**), lumusidines A-C (**77**–**79**), anhydromacralstonine (**85**), and villalstonidine B (**86**) showed moderate cytotoxicity toward KB cells (IC_{50} 4.30–18.14 μg/mL). Compounds **24**, **25**, **26**, **29**, **31**, **32**, lumusidine D (**80**), and macralstonine (**84**) showed strong activity in circumventing MDR in vincristine-resistant KB cells (IC_{50} 0.05–5.03 μg/mL).

Abstrak (Versi Bahasa Malaysia)

Satu jenis tumbuhan dari Malaysia, *Alstonia macrophylla* telah dikaji dari segi kandungan alkaloidnya, keputusan yang diperoleh telah dirumuskan di dalam jadual seperti di bawah. Sebanyak 90 alkaloid telah diasingkan dan dicirikan dari daun dan kulit-batang *A. macrophylla*. Dari jumlah tersebut, 30 alkaloid merupakan alkaloid baru. Sebanyak 13 alkaloid baru telah diasingkan dari ekstrak daun, iaitu sebatian-sebatian **1**, **16**, **24**, **25**, **26**, **27**, **28**, **29**, **30**, **31**, **32**, **33**, dan **34**. Sebanyak 19 alkaloid baru telah dipisahkan dari ekstrak kulit-batang. Selain daripada dua alkaloid yang juga didapati dari ekstrak daun (**24** dan **32**), alkaloid-alkaloid baru ini termasuklah sebatian-sebatian **2**, **3**, **4**, **17**, lumutinines A–E (**71**–**75**), lumusidines A–D (**77**–**80**), perhentidines A–B (**81** dan **82**), villalstonidines B (**86**), dan F (**87**). Perhentidines A–B (**81** dan **82**), perhentinine (**83**), villalstonine (**88**) dan macrocarpamine (**90**), menunjukkan kesan sitotoksik yang kuat terhadap sel-sel KB (IC_{50} 2.64–4.06 μg/mL), manakala lumutinines A–E (**71**–**75**), macralstonidine (**76**), lumusidines A–C (**77**–**79**), anhydromacralstonine (**85**), dan villalstonidine B (**86**) menunjukkan kesan sitotoksik yang sederhana terhadap sel-sel KB (IC_{50} 4.30–18.14 μg/mL). Sebatian-sebatian **24**, **25**, **26**, **29**, **31**, **32**, lumusidine D (**80**), dan macralstonine (**84**) menunjukkan aktiviti yang kuat dalam memintasi ketahanan *multidrug* dalam sel-sel KB *vincristine-resistant* (IC_{50} 0.05–5.03 μg/mL).



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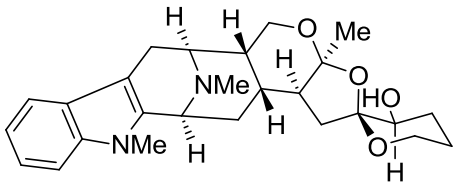

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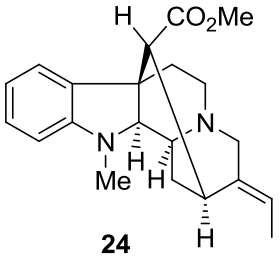

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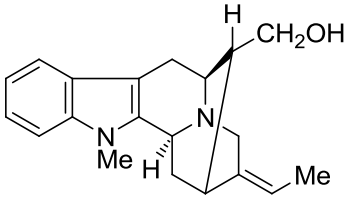

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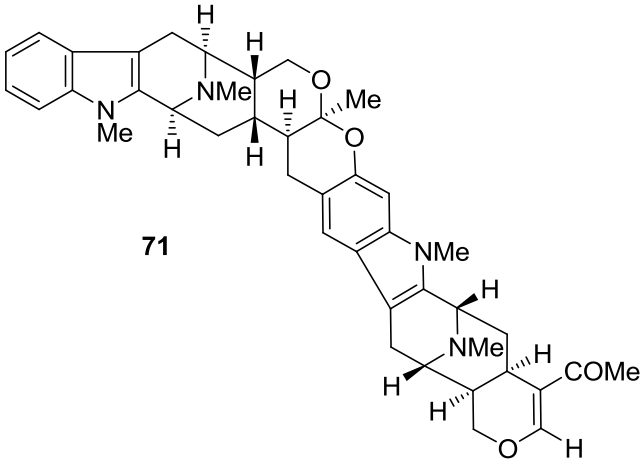

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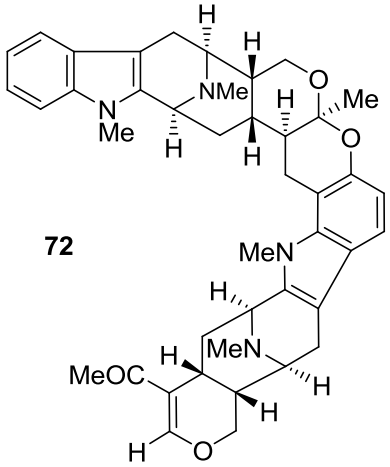

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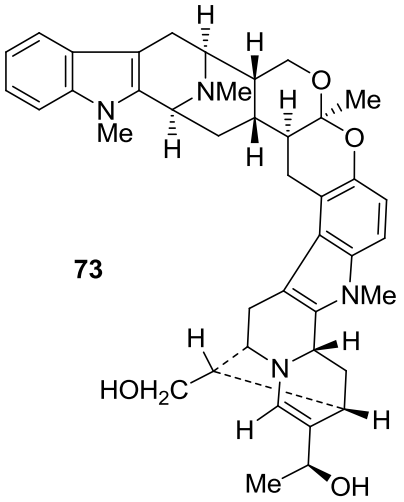

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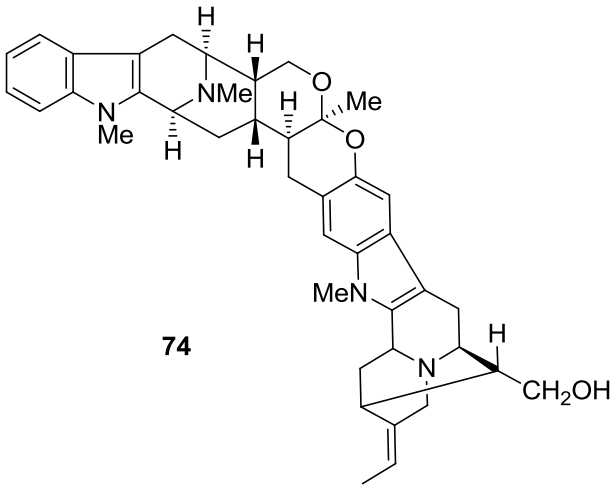

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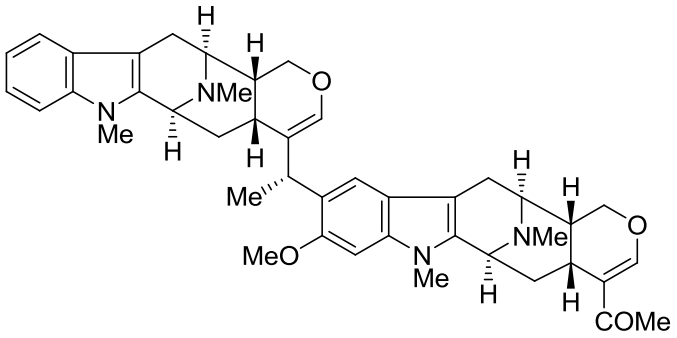

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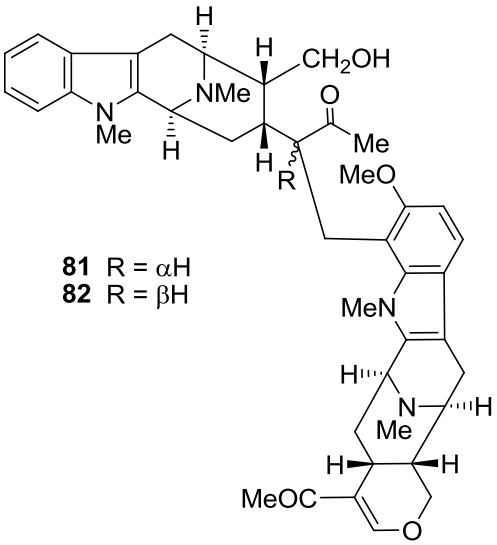
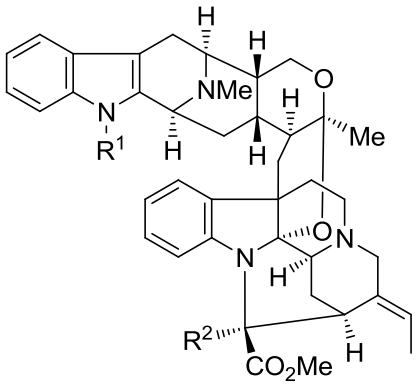


81 R = αH
82 R = βH



86 R^1 = Me, R^2 = CH_2OH
87 R^1 = H, R^2 = H

Table: Alkaloid Composition of *Alstonia macrophylla*

Plant	Plant Part	Alkaloid
A. macrophylla	Leaves	Alstofolinine (**1**) [New]
		Alstonerine (**5**)
		Alstonerinal (**6**)
		Alstophylline (**7**)
		Alstophyllal (**8**)
		Macrocarpine B (**10**)
		Talcarpine (**12**)
		N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)
		Compound **16** (11-Methoxyalstonoxine A) [New]
		Alstonoxine A (**18**)
		Alstonoxine B (**19**)
		Alstonisine (**20**)
		Alstonal (**21**)
		N(4)-Demethylalstophylline oxindole (**22**)
		N(4)-Demethylalstophyllal oxindole (**23**)
		Compound **24** (2(*S*)-Cathafoline) [New]
		Compound **25** (2(*S*)-10-Methoxycathafoline) [New]
		Compound **26** (2(*R*)-3-Hydroxycathafoline) [New]
		Compound **27** (10-Demethoxyvincorine) [New]
		Compound **28** (10-Demethoxyvincorine *N*(4)-oxide) [New]
		Compound **29 (**11-Methoxyvincorine) [New]
		Compound **30** (Vincorine *N*(4)-oxide) [New]
		Compound **31** (11-Demethoxyquaternine) [New]
		Compound **32** (19,20-*Z*-Affinisine) [New]
		Compound **33** (Vincamajine *N*(4)-oxide) [New]
		Compound **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide) [New]
		Cathafoline (**35**)
		Cathafoline *N*(4)-oxide (**36**)
		10-Methoxycathafoline (**37**)
		Strictamine (**38**)
		11-Methoxystrictamine (**39**)
		11-Hydroxystrictamine (**40**)
		Vincorine (**41**)
		Norvincorine (**42**)

Table, continued

Plant	Plant Part	Alkaloid
		Alstonamide (**43**)
		Demethoxyalstonamide (**44**)
		Alstomaline (**45**)
		Quaternine (**46**)
		Picrinine (**47**)
		12-Demethoxytabernulosine (**48**)
		Normacusine B (**51**)
		Alstoumerine (**52**)
		Quebrachidine (**53**)
		Vincamajine (**54**)
		Vincamajine 17-*O*-veratrate (**55**)
		Sitsirikine (**56**)
		16*R*,19*E*-Isositsirikine (**57**)
		18,19-Dihydroisositsirikine (**58**)
		Pleiocarpamine (**59**)
		Fluorocarpamine (**63**)
		Yohimbine (**64**)
		Talpinine (**65**)
		10,11-Dimethoxynareline (**66**)
		11-Methoxyakuammicine (**67**)
		11-Methoxyakuammicine *N*(4)-oxide (**68**)
A. macrophylla	Bark	Compound **2** (20,21-Dihydroalstonerine) [New]
		Compound **3** (*N*(1)-Demethylmacrocarpine B) [New]
		Macrodasine H (**4**) [New]
		Alstonerine (**5**)
		Alstonerinal (**6**)
		Alstophylline (**7**)
		Alstophyllal (**8**)
		Macrocarpine A (**9**)
		Macrocarpine B (**10**)
		Macrocarpine C (**11**)
		Talcarpine (**12**)
		N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)
		Macrodasine A (**14**)
		Macrodasine G (**15**)

Table, continued

Plant	Plant Part	Alkaloid
		Compound **17** (11-Methoxyalstonoxine B) [New]
		Alstonoxine B (**19**)
		Compound **24** (2(*S*)-Cathafoline) [New]
		Cathafoline (**35**)
		Cathafoline *N*(4)-oxide (**36**)
		Vincorine (**41**)
		19,20-*Z*-Affinisine (**32**) [New]
		Affinisine (**49**)
		Affinisine oxindole (**50**)
		Normacusine B (**51**)
		Alstoumerine (**52**)
		Vincamajine (**54**)
		16*R*,19*E*-Isositsirikine (**57**)
		Pleiocarpamine (**59**)
		16-Hydroxypleiocarpamine (**60**)
		Pleiomaltinine (**61**)
		Picramicine (**62**)
		Fluorocarpamine (**63**)
		11-Methoxyakuammicine (**67**)
		Antirhine (**69**)
		Talpinine (**65**)
		1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)
		Lumutinine A (**71**) [New]
		Lumutinine B (**72**) [New]
		Lumutinine C (**73**) [New]
		Lumutinine D (**74**) [New]
		Lumutinine E (**75**) [New]
		Macralstonidine (**76**)
		Lumisidine A (**77**) [New]
		Lumisidine B (**78**) [New]
		Lumisidine C (**79**) [New]
		Lumisidine D (**80**) [New]
		Perhentidine A (**81**) [New]
		Perhentidine B (**82**) [New]
		Perhentinine (**83**)

Table, continued

Plant	Plant Part	Alkaloid
		Macralstonine (**84**)
		Anhydromacralstonine (**85**)
		Villalstonidine B (**86**) [New]
		Villalstonidine F (**87**) [New]
		Villalstonine (**88**)
		Villalstonine *N*(4)-oxide (**89**)
		Macrocarpamine (**90**)

Dedication

I dedicate this dissertation…

to my late father, Lim Kim Gee and my mother, Tong Kim Sen, for instilling the importance of hard work and higher education;

to my husband, Lam Chee Kuan for his patience and understanding;

to my sister, Lim Shiow Jen, my brother-in-law, Matthew Wong Huai Chih, my brother, Lim Boon Yee, and my friend, Phyllis Barnabas, for their encouragement and support.

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This study would not have been possible without the support of many people.

First and foremost, I wish to express my deepest gratitude to my supervisor, Professor Kam Toh Seok, who was abundantly helpful and offered invaluable assistance, support, and guidance, throughout my study in the University of Malaya. I would also like to thank my co-supervisor, Professor Zanariah Abdullah, for her encouragement and help.

I wish to thank Low Yun Yee for performing the X-ray diffraction analyses. I owe my deepest gratitude to my best friend, Gan Chew Yan who was always there to encourage and support me. I would also like to thank my former colleagues, Dr. G. Subramaniam, Pang Huey Shen, and Dr Lim Kuan Hon, for their invaluable guidance and support at the beginning of my graduate study. Not forgetting my friends and colleagues in Lab C100 who gave me support, especially Dr. Tan Shin Jowl, Yap Wai Sum, Ku Wai Foong, Hong Fong Jiao, and Nge Choy Eng.

The staff of the Chemistry Department, University of Malaya are also greatly appreciated for their assistance.

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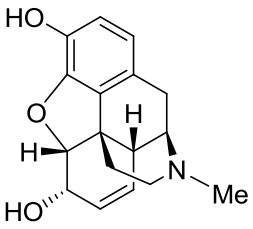
Chapter One

1 Introduction

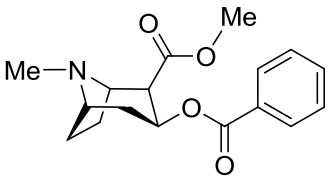
1.1 General

The exploration of natural products from plants, animals, insects, marine invertebrates, and microorganisms represents an active area of research in chemistry.[1-3] Since the mid 19th century, serious efforts were made to isolate and purify the active compounds of herbs.[4] A large variety of biologically active compounds have been obtained and their structures were determined, for example, morphine from opium, cocaine from coca leaves, and quinine from cinchona bark.[4] Today, this field continues to grow as the pharmaceutical industry is constantly searching for new lead compounds for development into new drugs.[5-27] The discovery of many therapeutic agents for cancer and infectious diseases (*e.g.*, taxol,[28-32] epothilones A and B,[33-36] doxorubicin,[37-39] platensimycin,[40-43] amoxicillin,[44-46]) has provided an added impetus for natural product-based drug discovery. Furthermore, natural products continue to provide subjects of investigation for the organic chemists in the areas of structure elucidation, biosynthesis, and biochemistry.[47-60] They also present challenging targets for total synthesis leading to the remarkable progress seen in synthetic organic chemistry.[61-63] The rich natural resources available in Malaysia provides opportunities for discovery of new bioactive compounds.[64] In addition, from an organic chemistry viewpoint, there is also great potential for discovering novel molecular structures and for investigating novel stereochemical and reactivity aspects associated with these new natural compounds.

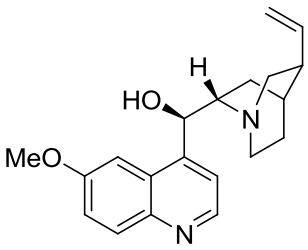
The Malayan *Alstonia macrophylla* (Apocynaceae) was chosen for investigation in the present study with emphasis on the discovery and structure elucidation of new natural products, and evaluation of biological activity.



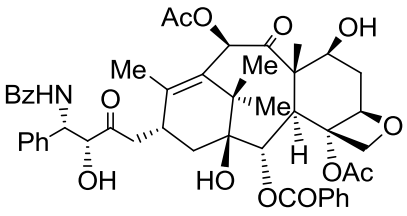
Morphine



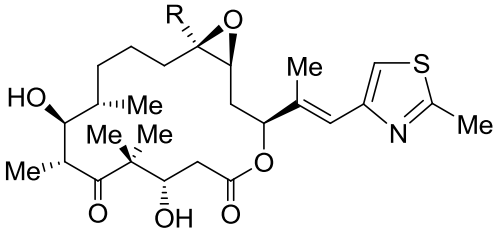
Cocaine



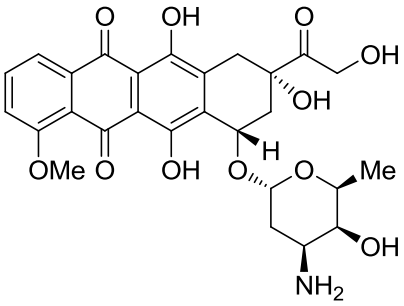
Quinine



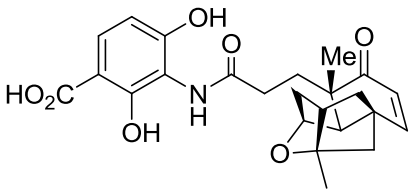
Taxol



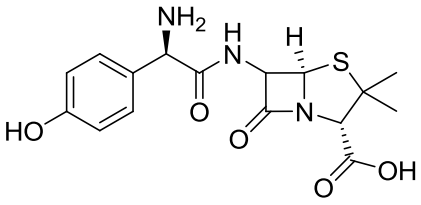
Epothilone A, R = H
Epothilone B, R = Me



Doxorubicin



Platensimycin

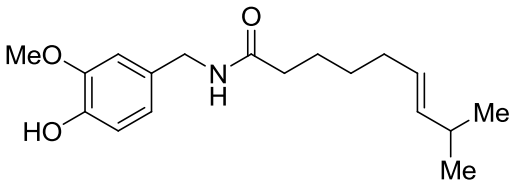


Amoxicillin

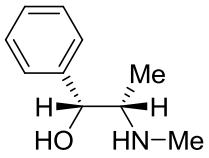
1.2 The Alkaloids

Alkaloids are natural products which humankind has used in potions, medicines, teas, poultices and poisons for 4000 years.[65] The term alkaloid was originally coined by Meissener in 1819 to cover plant derived substances that react like alkalis, in other words, basic compounds.[66] This description was put forward at a time, when only very few plant bases were known, and those only in impure form. A new definition for alkaloids was presented by Hesse: alkaloids are nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character.[67] As of 2001, a total of 26,900 known alkaloids has been isolated from various sources (plants, fungi, marine organisms, mammals, *etc.*).[68] These can be subdivided into five main alkaloid classes, according to the position of the *N*-atom in the main structural element.[67]

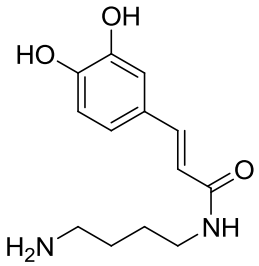
i. Heterocyclic alkaloids
ii. Alkaloids with exocyclic *N*-atoms including aliphatic amines (*e.g.* capsaicine, ephedrine)
iii. Putrescine, spermidine, and spermine alkaloids (*e.g.* paucine, lunarine, verbascenine)
iv. Peptide alkaloids (*e.g.* integerrine, mucronine A)
v. Terpene and steroid alkaloids (*e.g.* heteratisine, funtumine)



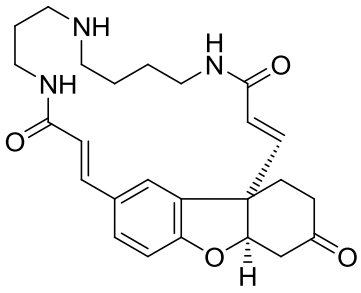
Capsaicine



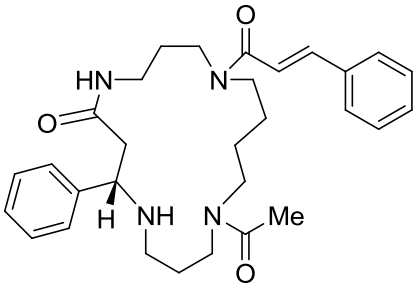
(-)-Ephedrine



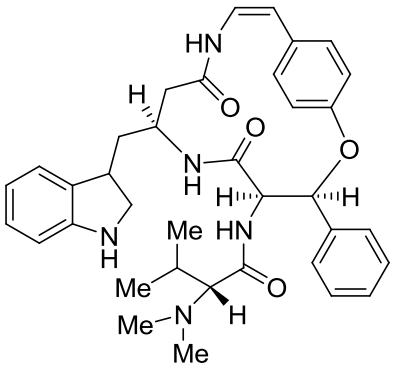
Paucine



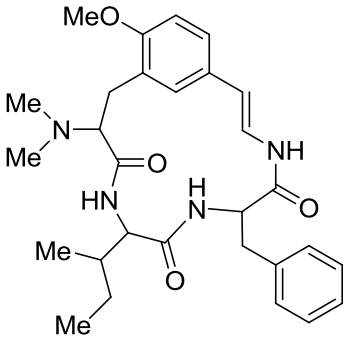
(+)-Lunarine



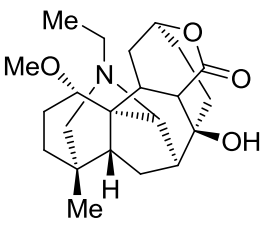
(-)-Verbascenine



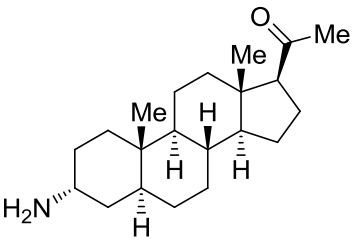
Integerrine



Mucronine A

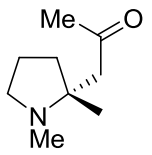
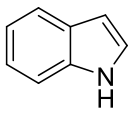
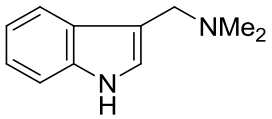
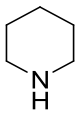
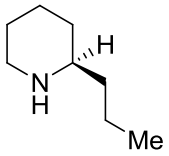
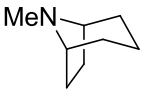
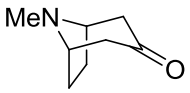
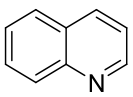
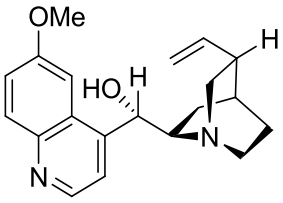


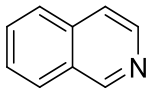
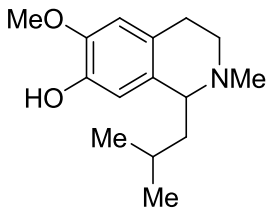
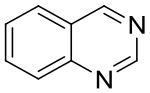
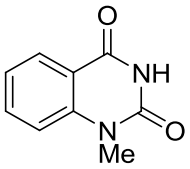
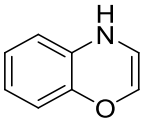
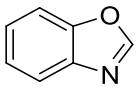
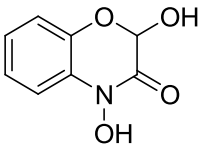
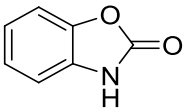
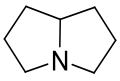
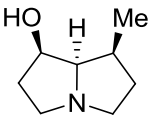
(+)-Heteratisine

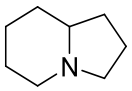
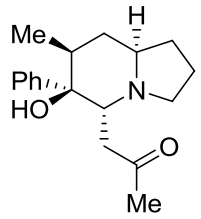
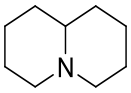
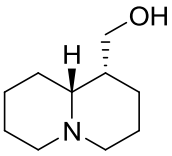
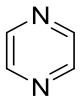
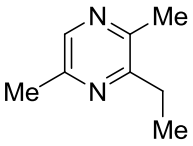
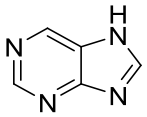
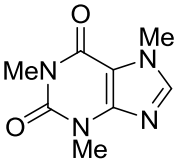
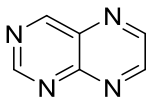
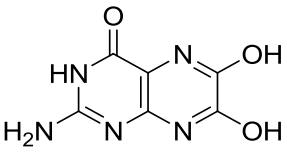


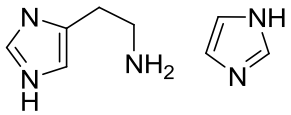
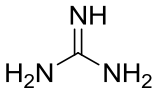
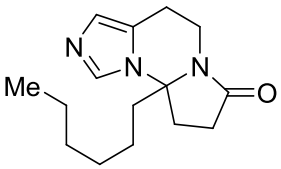
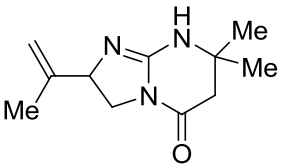
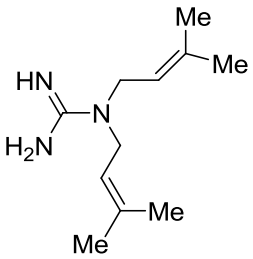
Funtumine

Among the five classes, the heterocyclic alkaloids constitute the largest group and in common usage the term ‘alkaloids’ usually refers to the heterocyclic alkaloids. These can be further divided into 15 subclasses based on the carbon-nitrogen skeleton as shown below.[65-67]

Alkaloid class	Basic ring system	Example
Pyrrolidine		 (+)-(*R*)-Hygrine
Indole		 Gramine
Piperidine		 (+)-Coniine
Tropane		 Tropinone
Quinoline		 (-)-Quinine

Alkaloid class	Basic ring system	Example
Isoquinoline		 Lophocerine
Quinazoline		 Glycosmicine
Benzoxazines and benzoxazoles	 	 3,4-Dihydro-2,4-dihydroxy-1,4-benzoxazin-3(2*H*)-one  2(3*H*)-Benzoxazoline
Pyrrolizidine		 (–)-Retronecanol

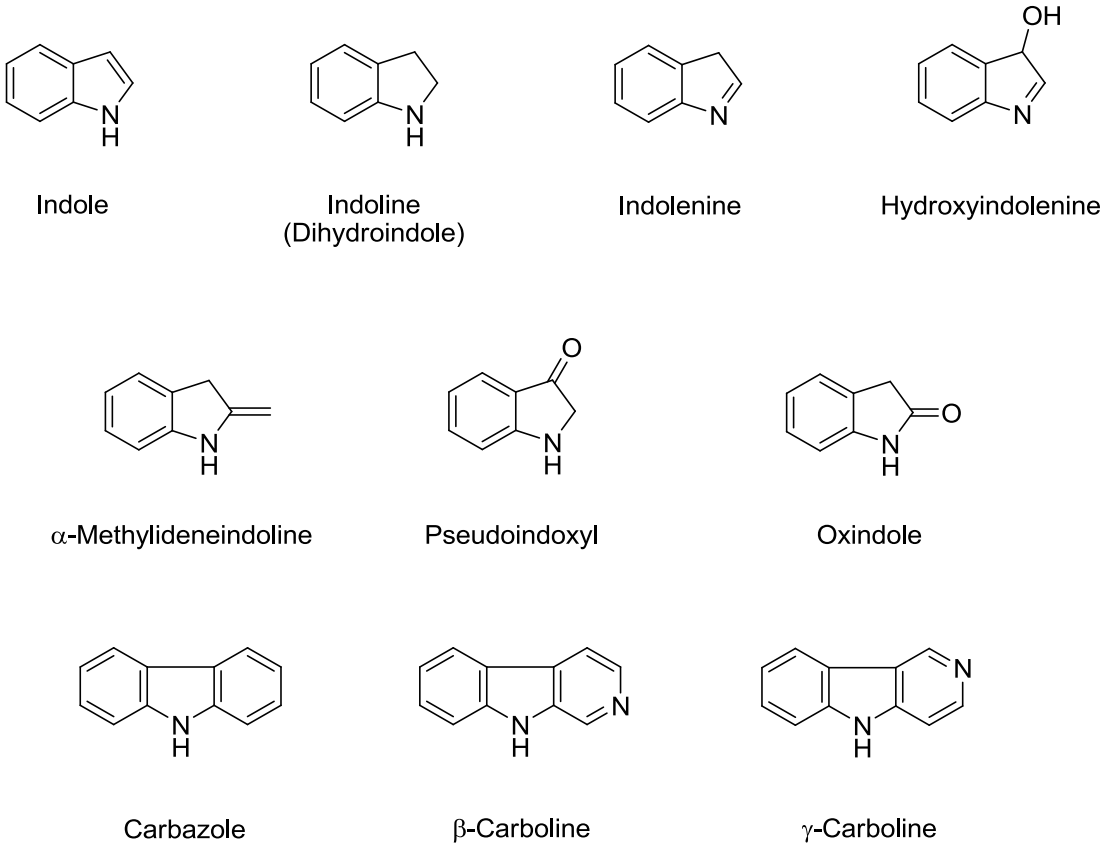
Alkaloid class	Basic ring system	Example
Indolizidine		 Crepidamine
Quinolizidine		 (–)-Lupinine
Pyrazine		 3-Ethyl-2,5-dimethyl-pyrazine
Purine		 Caffeine
Pteridine		 Leucopterin

Alkaloid class	Basic ring system	Example
Histamine, Imidazole, and guanidine	 	 Glochidine  Alchornine  N',N'-Diisopentenylguanidine

1.3 Indole Alkaloids of the Apocynaceae

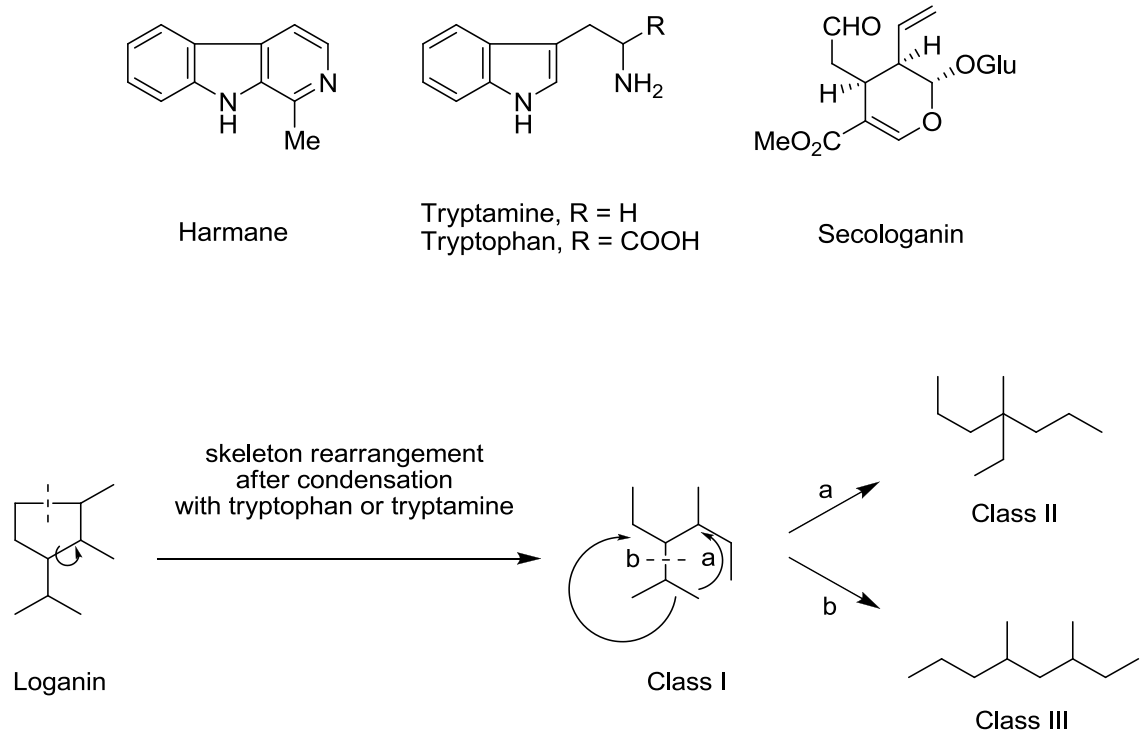
1.3.1 General

Indole alkaloids constitute one of the largest group of alkaloids and the total number of known indole alkaloids is *ca.* 1,500.[67] This figure includes both those compounds that incorporate the actual indole chromophore and those containing its derivatives: namely indoline (dihydroindole), indolenine, hydroxyindolenine, α-methylideneindoline, pseudoindoxyl, and oxindole as well as carbazole or β- and γ-carbolines and their derivatives.[67] Therefore, indole alkaloids are defined as natural products containing an indole nucleus or an oxidized, reduced or substituted equivalent of it.



1.3.2 Classification of the Indole Alkaloids

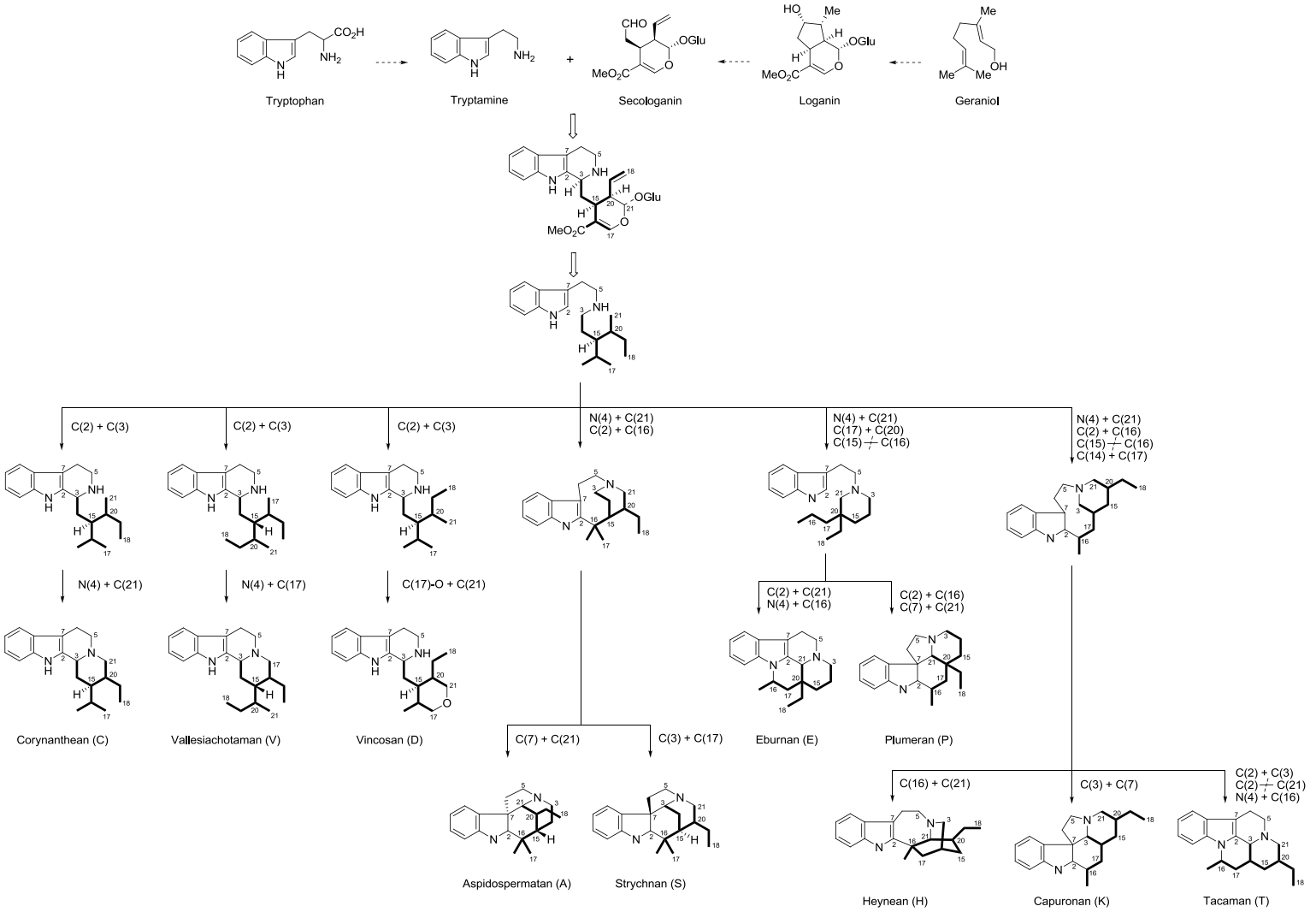
For further subclassification of indole alkaloids, structural and biogenetic criteria are applied. The indole alkaloids can be divided into two main categories. The first constitutes the simple indole alkaloids, which do not present a structural uniformity, possessing only the indole nucleus or direct derivatives of it as common features (*e.g.* harmane).



Scheme 1.1: The three major skeletal classes from loganin

The second category of indole bases, which are known as the monoterpene indole alkaloids, contains two structural units, *viz.*, tryptamine (or tryptophan) with the indole nucleus and a C_9- or C_{10}-monoterpene moiety derived from secologanin. The majority of the indole alkaloids from the plants belong to this category and can be further divided into three main classes (class I, II and III) based on the skeletal arrangement of

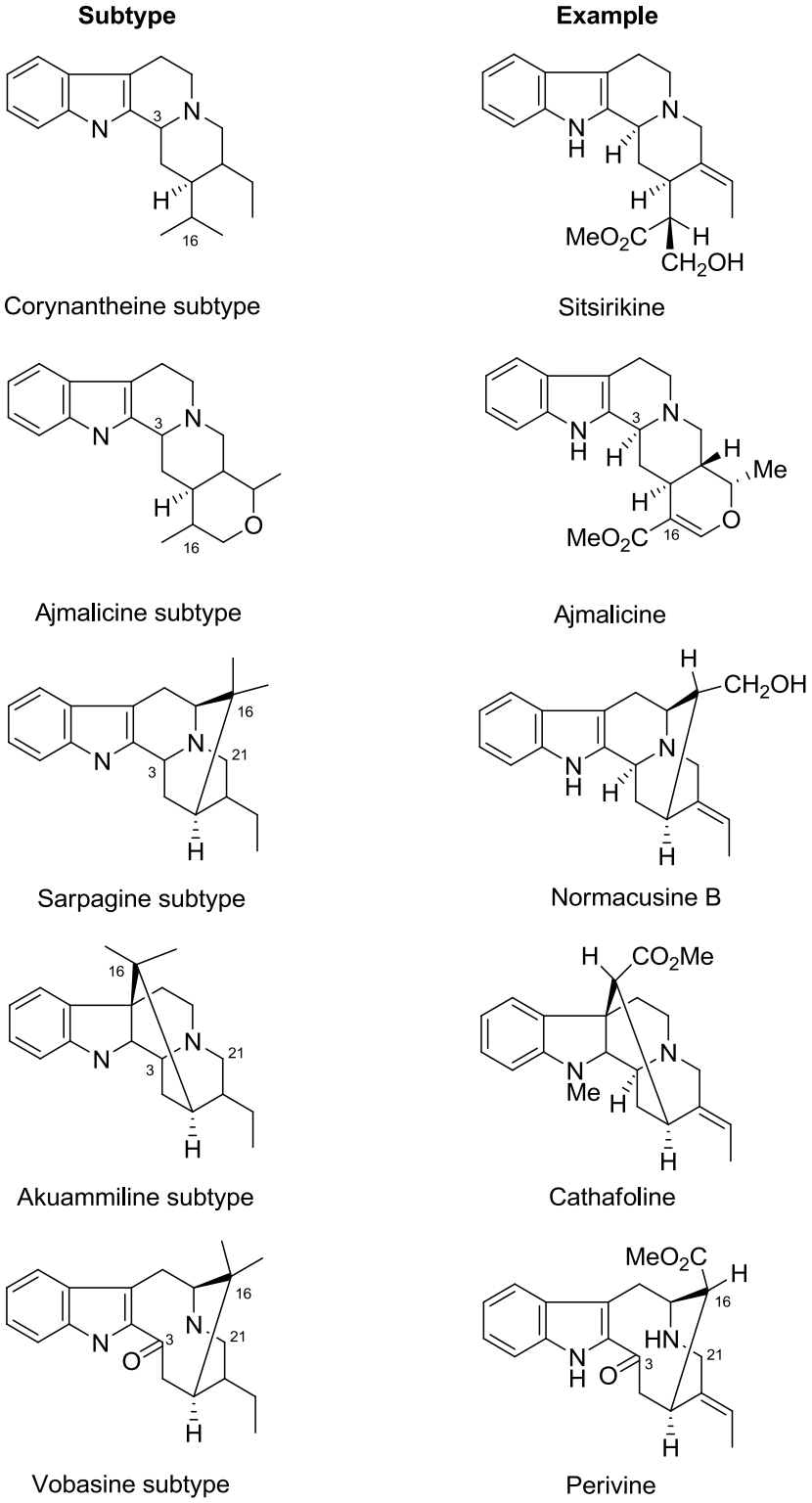
the secologanin unit (Scheme 1.1). The common precursor of all indole alkaloids is strictosidine, the condensation product of tryptamine and secologanin.[69-71] Indole alkaloids can be grouped into ten main skeletal types based on their biogenesis, *viz.*, corynanthean (C), vincosan (D), vallesiachotaman (V), strychnan (S), aspidospermatan (A), eburnan (E), plumeran (P), heynean (H), capuronan (K) and tacaman (T).[72-102] The biogenetic relationship of the indole alkaloids is presented in Scheme 1.2.[66,67,77,78,82,83,103]



Scheme 1.2: Biogenetic inter-relationship of the ten main skeletal types of indoles with C_9- or C_{-10} monoterpene moiety

1.3.3 The Corynanthean (C) Type Alkaloids

The corynanthean alkaloids are the most extensive class of the indole alkaloids. [1,2,72,77,78,83,104,105] The ten main subtypes and their respective examples are given in Figure 1.1.



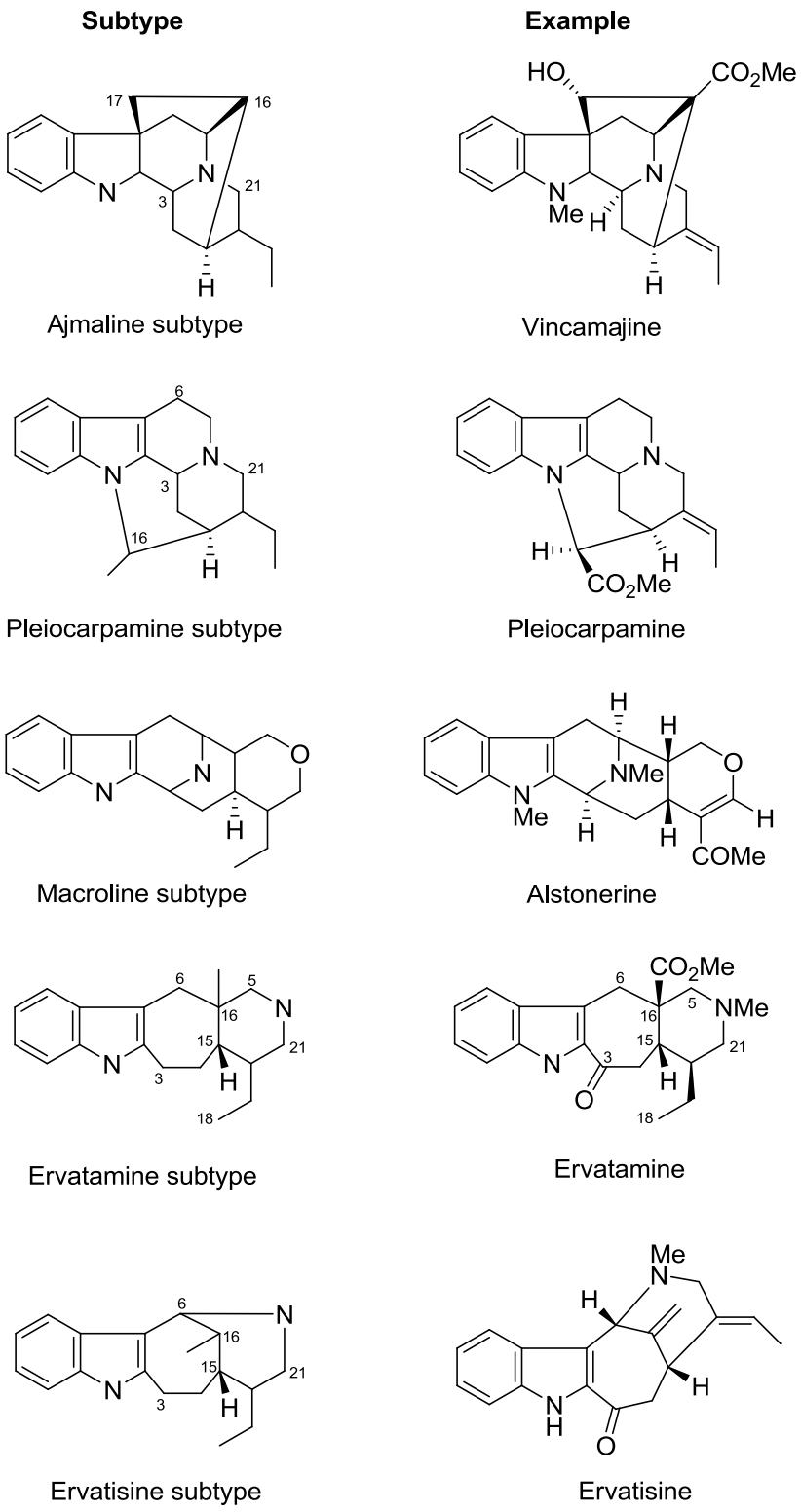


Figure 1.1: Main skeletal subtypes of the corynanthean alkaloids found in Apocynaceae

1.3.4 The Vallesiachotaman (V) Type Alkaloids

The vallesiachotaman alkaloids are a small group of indole alkaloids and share a common precursor with the corynanthean alkaloids.[1,2,72,77,78,83,104,105] Alkaloids of this group can be classified into two main subtypes, namely, antirhine, and angustine as shown in Figure 1.2.

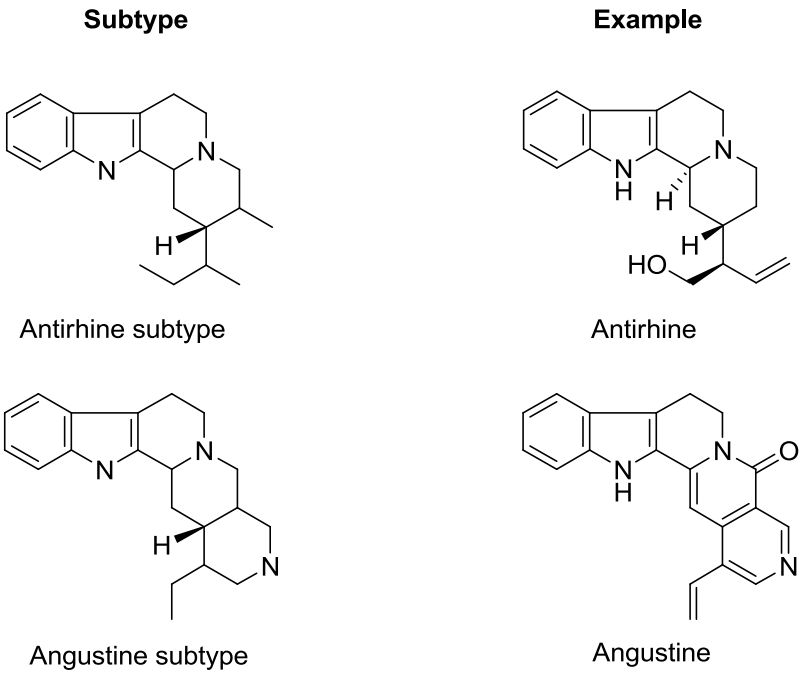
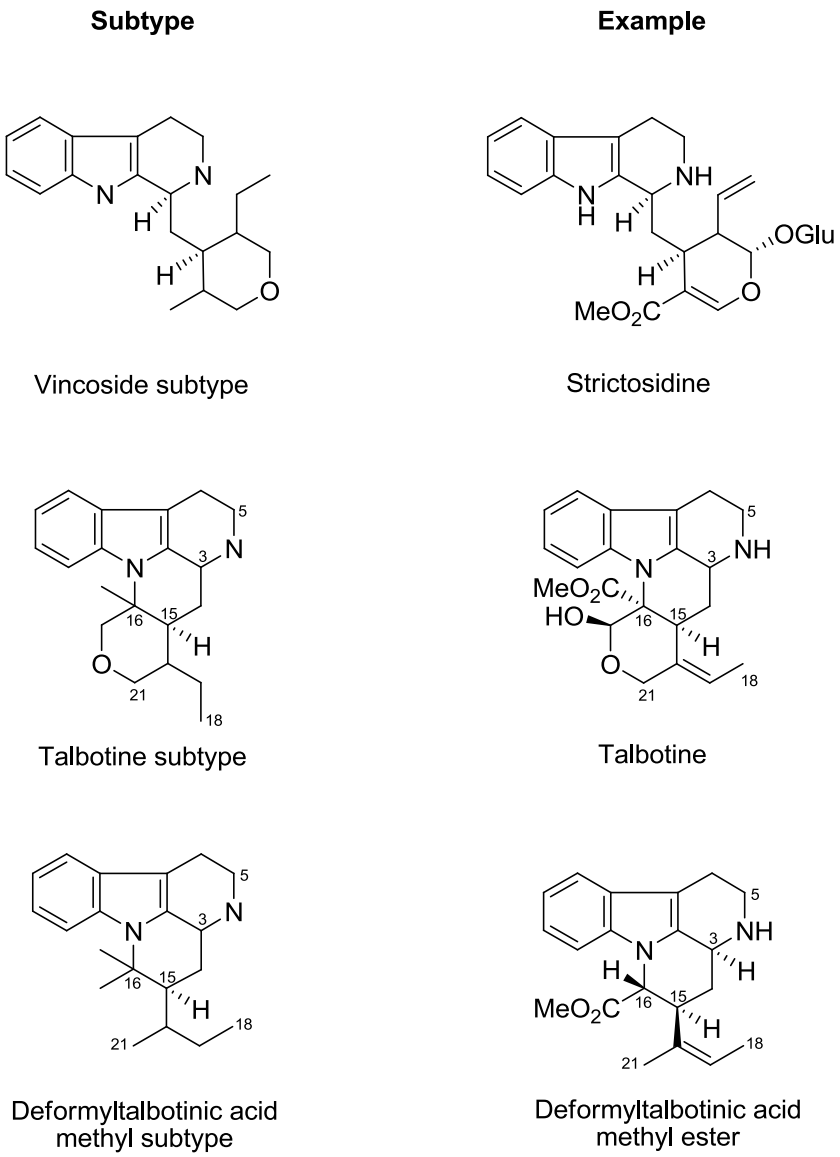


Figure 1.2: Two main skeletal subtypes of the vallesiachotaman alkaloids

1.3.5 The Vincosan (D) Type Alkaloids

The vincosan alkaloids[1,2,72,77,78,83,104,105] are a relatively small group of indole alkaloids. Although they are fairly rich in skeletal variations, the occurrence in the Apocynaceae is quite limited and can be grouped into five subtypes, namely, vincoside, talbotine, deformyltalbotinic acid methyl, perakine, and peraksine (Figure 1.3).



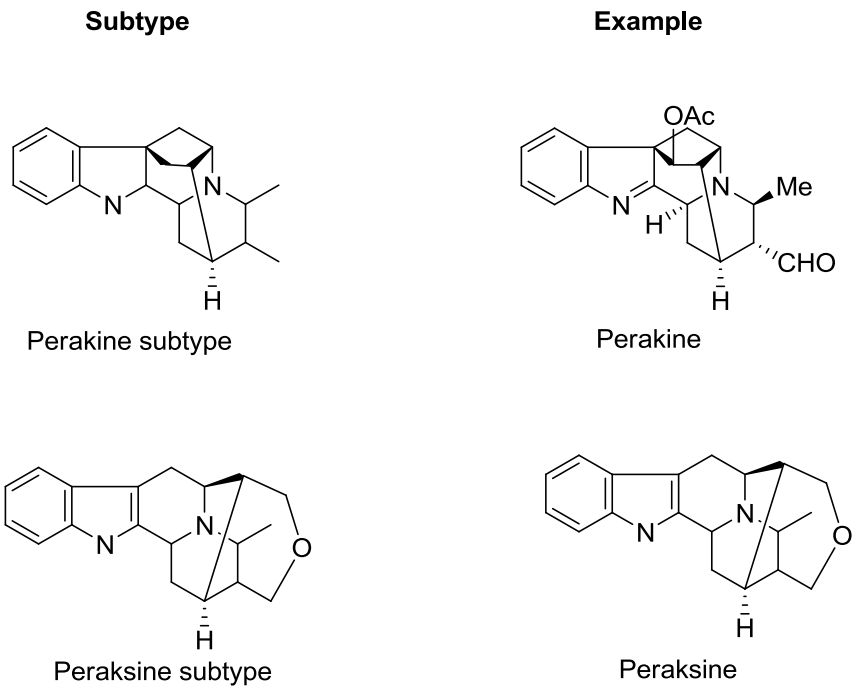


Figure 1.3: Five skeletal subtypes of the vincosan alkaloids

1.3.6 The Strychnan Type Alkaloids

The strychnan alkaloids occur predominantly in the *Strychnos* species of the Loganiaceae family and show considerable variations in the skeletal framework. However, the majority of the alkaloids isolated from the Apocynaceae are of the akuammicine subtype, which is also the simplest skeletal subtype of this group (Figure 1.4). The isostrychnine subtype is also found in the Apocynaceae, having only one representative to date. Although the structure variations of the strychnan alkaloids in the Apocynaceae are limited, the number of alkaloids in this group (mainly of the akuammicine subtype) is large.[1,2,72,77,78,83,104,105]

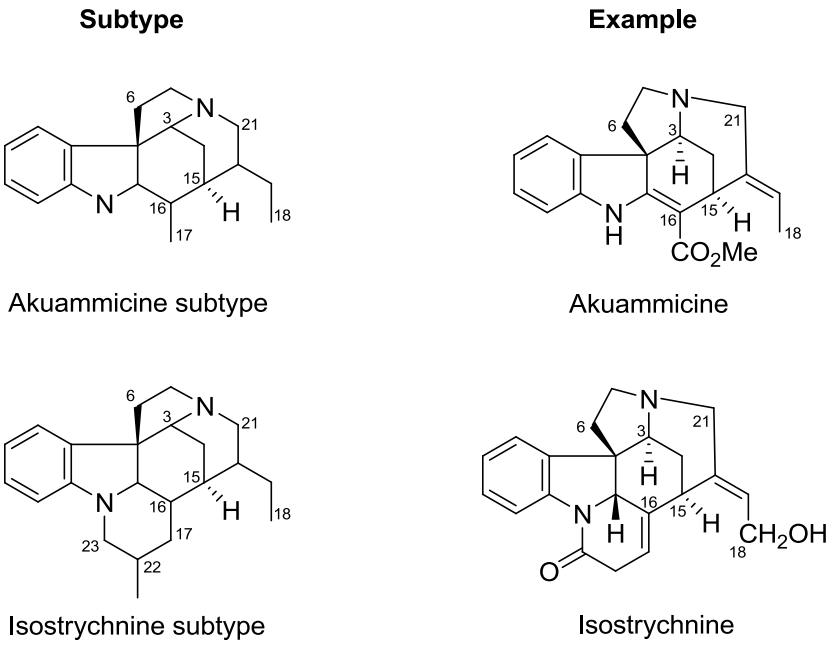
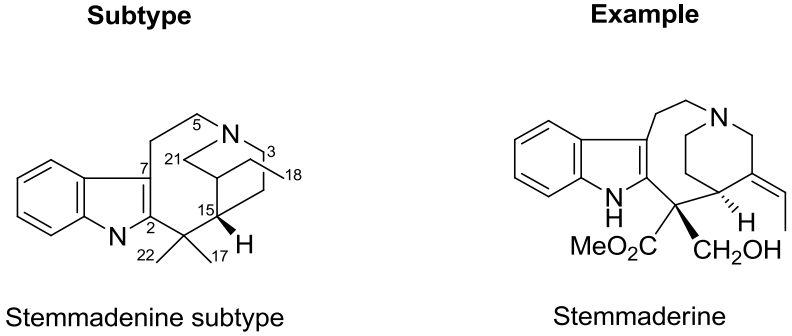


Figure 1.4: Main skeletal subtypes of the strychnan alkaloids found in the Apocynaceae

1.3.7 The Aspidospermatan (A) Type Alkaloids

Alkaloids of this group are distributed into six main subtypes based on the variations in the carbon skeleton as shown in Figure 1.5. The six main subtypes are stemmadenine, aspidospermatine, precondylocarpine, geissovelline, andraginine, and dichotine, with the largest number of alkaloids grouped in the aspidospermatine subtype.[1,2,72,77,78,83,104,105]



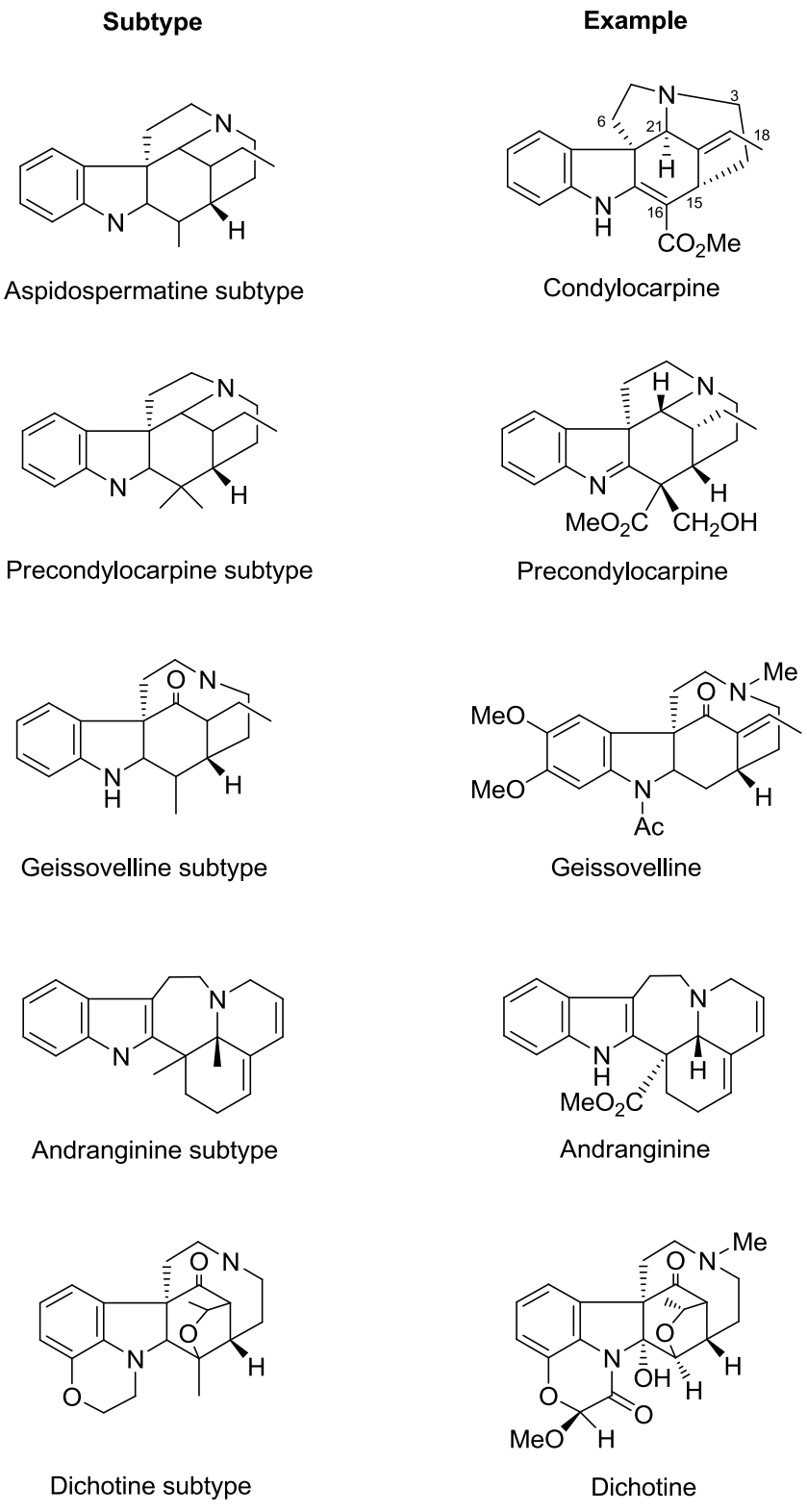
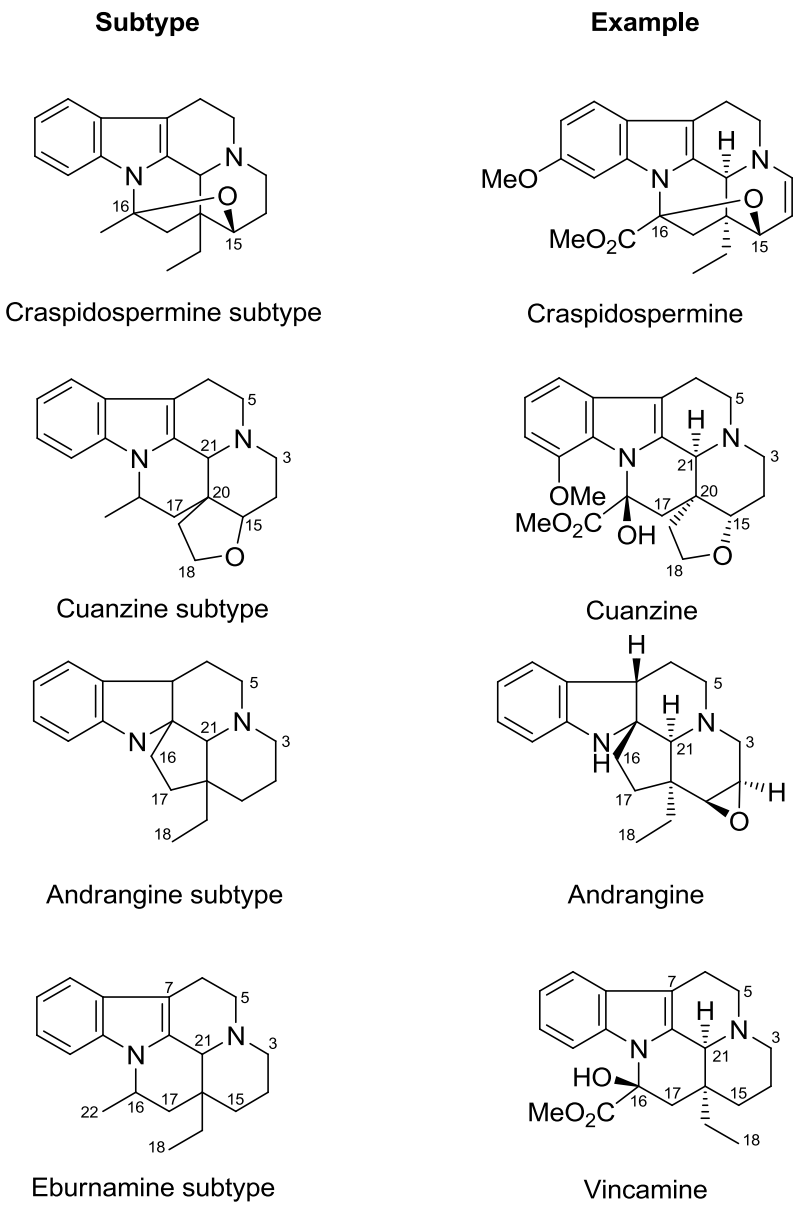


Figure 1.5: Main skeletal subtypes of the aspidospermatan alkaloids

1.3.8 The Eburnan (E) Type Alkaloids

The eburnan alkaloids can be divided into five groups, *viz*., eburnamine, schizogamine, craspidospermine, cuanzine, and andrangine. Of these, the most populated is the eburnamine subtype. The structures of these five subtypes and the corresponding examples are given in Figure 1.6.[1,2,72,77,78,83,104,105]



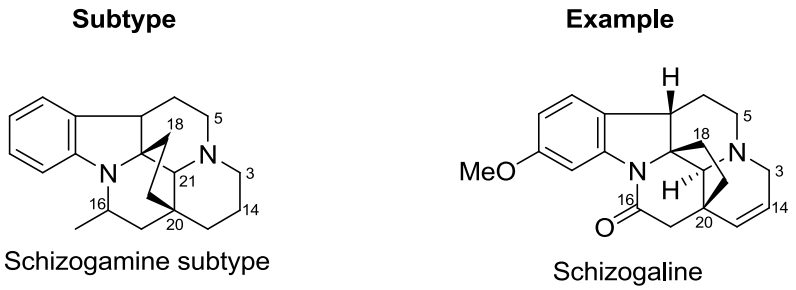
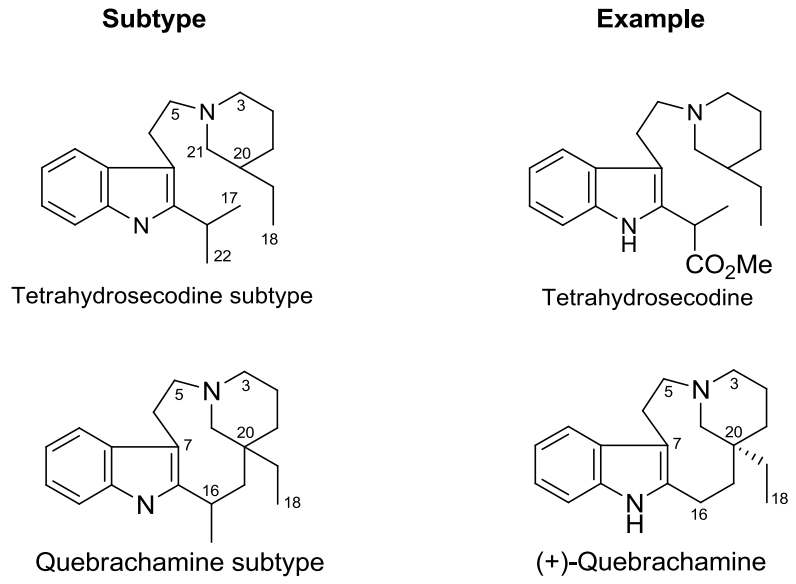
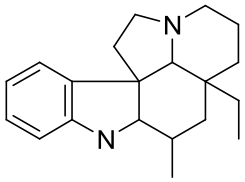
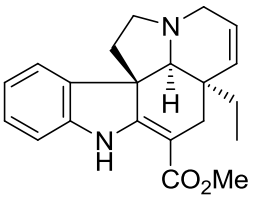
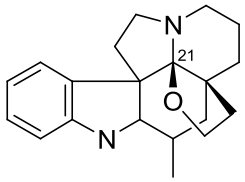
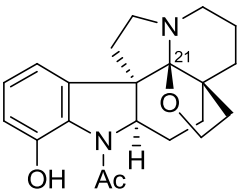
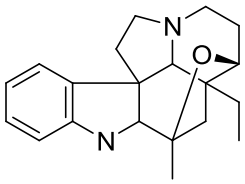
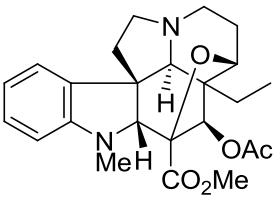
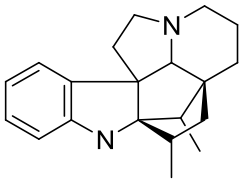
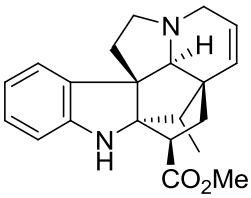
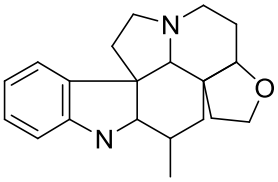
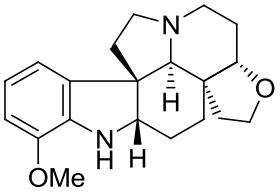
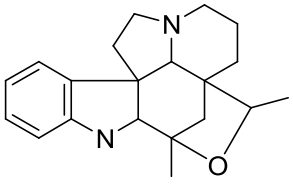
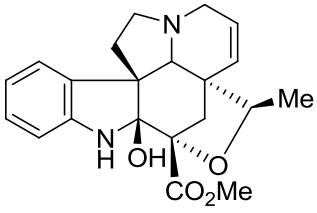
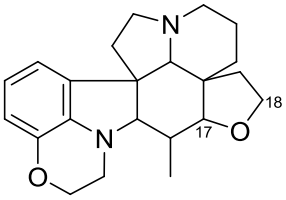
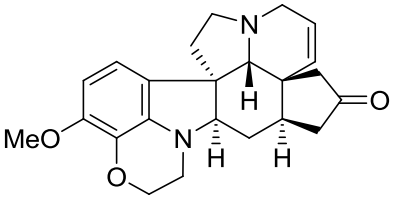


Figure 1.6: Main skeletal subtypes of the eburnan alkaloids

1.3.9 The Plumeran (P) Type Alkaloids

The plumeran alkaloids constitute the second largest group of the indole alkaloids after the corynanthean group and are characterized by a rich variation of the carbon skeleton. The alkaloids of the plumeran type are found exclusively from the subfamily Plumerioideae of the Apocynaceae which accounts for the name given to this group. Plumeran alkaloids can be further grouped into 13 subtypes (Figure 1.7).[1,2,72,77,78,83,104,105]



Subtype	Example
 Aspidospermine subtype	 Tabersonine
 Cimicidine subtype	 (+)-Haplocidine
 Cathovaline subtype	 Cathanneine
 Vindolinine subtype	 Vindolinine
 Beninine subtype	 Beninine
 Vincoline subtype	 Melobaline
 Neblinine subtype	 Neblinine

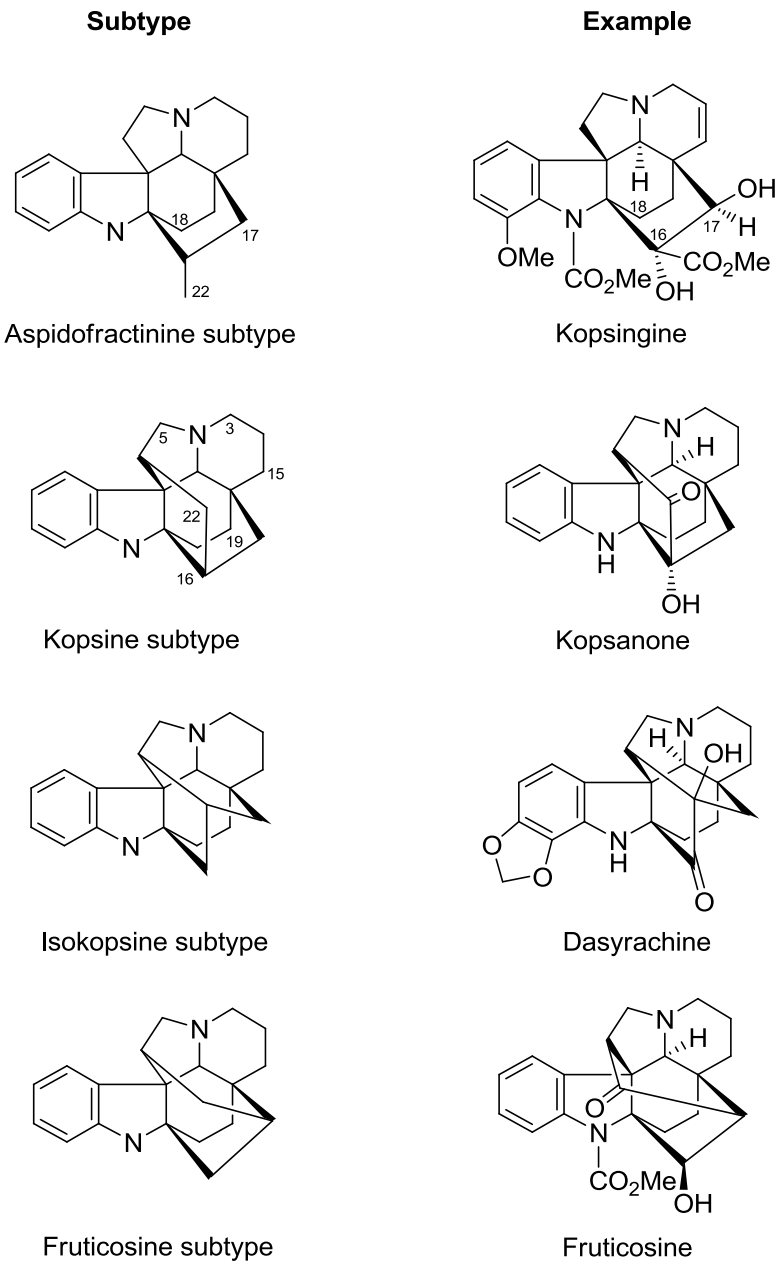


Figure 1.7: Main subtype skeletal subtypes of the plumeran alkaloids

1.3.10 The Heynean (H) Type Alkaloids

Based on new structure types found as well as from biogenetic considerations, Hesse has further divided the ibogan (J) group into two new main groups, namely, heynean (H) and capuronan (K). The heynean alkaloids can be further subdivided into four main structure subtype groups. The main subtypes of the heynean alkaloids and the corresponding examples are given in Figure 1.8.[1,2,72,77,78,83,104,105]

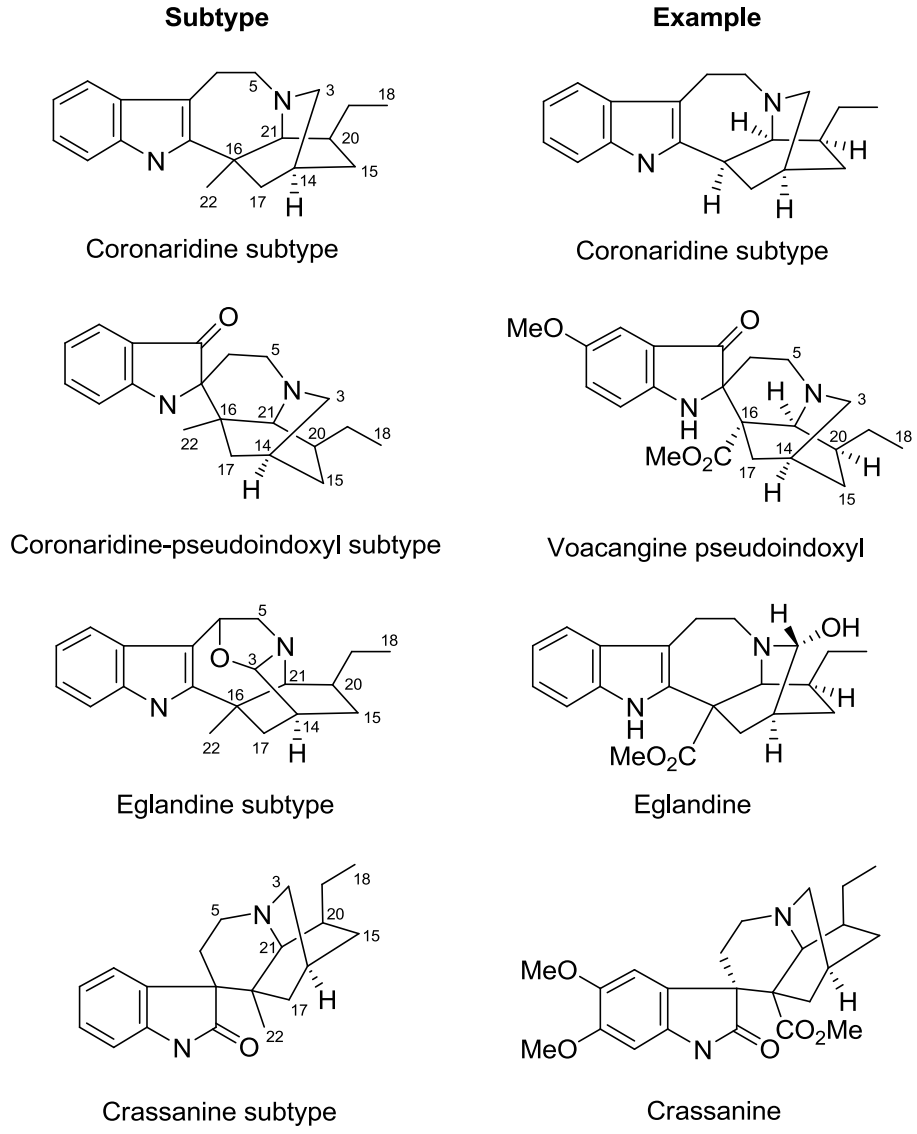


Figure 1.8: Main skeletal subtypes of the heynean alkaloids

1.3.11 The Capuranon (K) Type Alkaloids

The capuranon alkaloids possess the class III rearranged secologanine skeleton. This group of alkaloids was subdivided from the ibogan group by Hesse. The main subtype of capuranon alkaloids are shown in the Figure 1.9.[1,2,72,77,78,83,104,105]

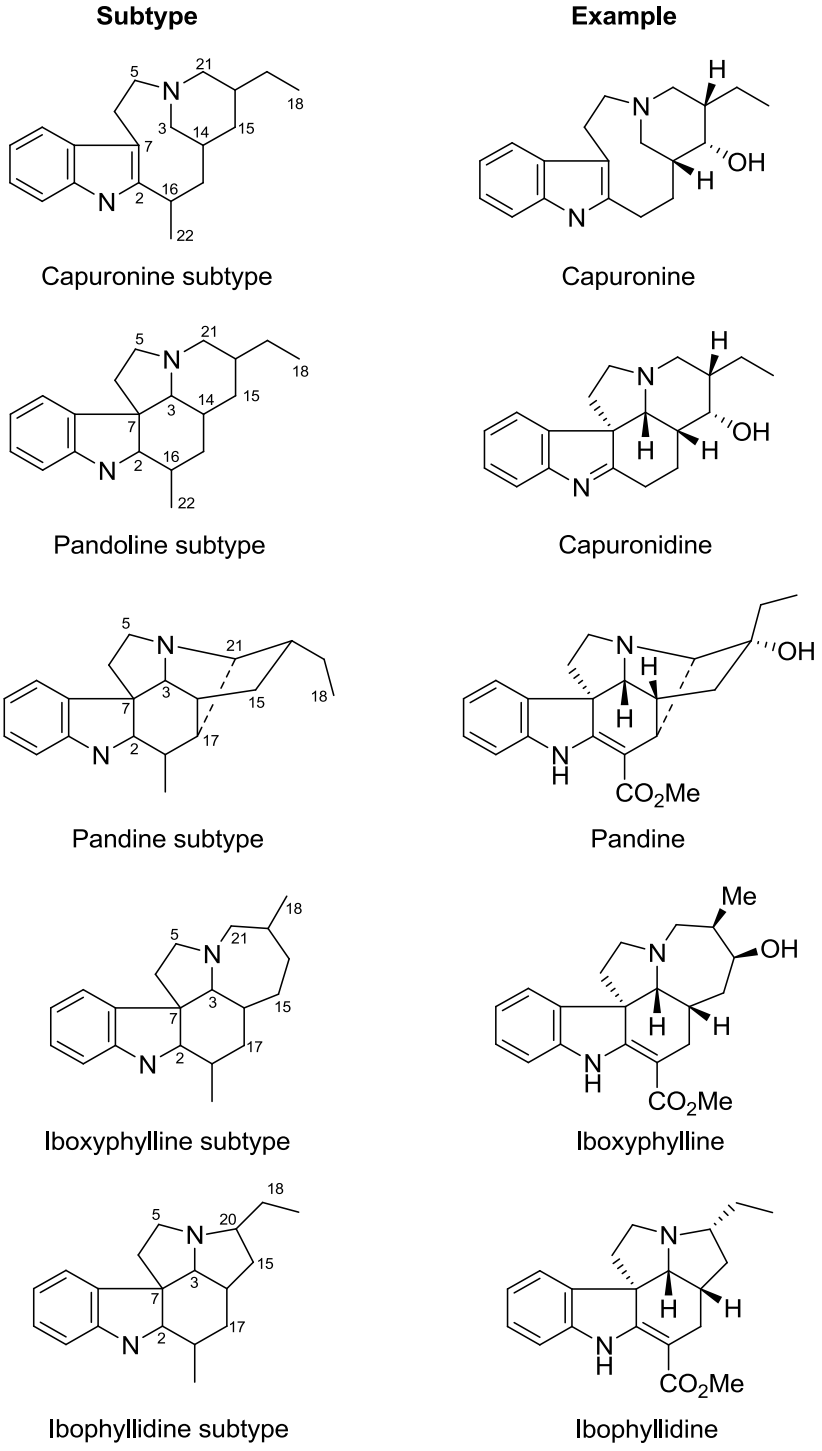


Figure 1.9: Main skeletal subtypes of the capuranon alkaloids

1.3.12 The Tacaman Type Alkaloids

The tacaman alkaloids possess the class III rearranged secologanine skeleton. This group of alkaloids was added by Verpoorte and Van Beek to account for the isolation of a few tacamines from *Tecoma* species. To date the tacaman type alkaloids are limited to only one skeletal type as shown in Figure 1.10.[1,2,72,77,78,83,104,105]

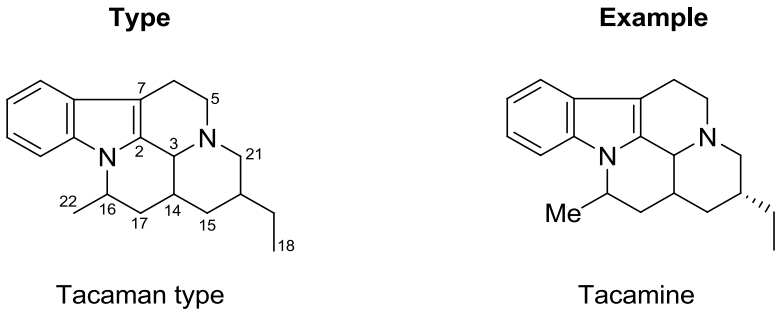


Figure 1.10: Main skeletal type of the tacaman alkaloids.

1.4 The Genus *Alstonia*

1.4.1 General

The genus *Alstonia* belongs to the tribe Plumerieae, subfamily Plumerioideae of the family Apocynaceae. This genus consists of about 40 species distributed over the tropical parts of Central America, Africa and Asia, with the center of diversity in the Malesia region.[106-108] Plants of this genus are usually found in wet ground, with some preferring peat swamp forests and others tolerating even open water. They are common in lowland and mountain rain forests. A total of 19 species of *Alstonia* are found in

Malesia, which includes Malaysia, Singapore, Indonesia, Brunei, Phllipines, and Papa New Guinea.[108] They are listed as follows:

i. *A. actiophylla* K. Schum
ii. *A. angustifolia* Wall. ex A. DC.
iii. *A. angustiloba* Miq.
iv. *A. beatricis* Sidiyasa
v. *A. boonei* De Wild.
vi. *A. breviloba* Sidiyasa
vii. *A. iwahigensis* Elmer
viii. *A. macrophylla* Wall. ex G. Don
ix. *A. muelleriana* Domin
x. *A. neriifolia* D. Don
xi. *A. parvifolia* Merr.
xii. *A. penangiana* Sidiyasa
xiii. *A. pneumatophora* Backer ex Den Berger
xiv. *A. rostrata* C. E. C. Fisch
xv. *A. rubiginosa* Sidiyasa
xvi. *A. scholaris* R. Br.
xvii. *A. spatulata* Blume
xviii. *A. spectabilis* Sidiyasa
xix. *A. venenata* R. Br.

However, only eight of the 19 species of *Alstonia* are found in Peninsular Malaysia, five species from the sect. *Alstonia*, and three from the sect. Monuraspermum (Table 1.1).[108] The morphological and physiological traits that reflect broadly the distinction between the two sect. within the genus *Alstonia* of the Peninsular Malaysia are given in Table 1.2.[106,108]

Table 1.1: The *Alstonia* species of the Peninsular Malaysia

Sect. *Alstonia*	**Sect. *Monuraspermum***
A. angustiloba	*A. angustifolia*
A. pneumatophora	*A. macrophylla*
A. rostrata	*A. penangiana*
A.scholaris	
A. spatulata	

Table 1.2: A comparison of the characteristic of the sect. *Alstonia* and the sect. *Monuraspermum*

	Sect. *Alstonia*	**Sect. *Monuraspermum***
1	Trees up to 60–70 m high, and up to 200 cm diameter	Small or big trees, up to 40–50 m high, and up to 100 cm in diameter
2	With copious white latex from the trunk bark	Without latex from the inner bark
3	Leaves in whorls of 4–8	Leaves in whorls of 3–4 or decussate
4	Lateral nerves numerous (40–100 pairs), straight, 1–5 mm apart	Lateral nerves numerous (10–20 pairs), 4–15 mm apart
5	Leaves papillose below	Leaves not papillose below
6	Flowers mostly yellow	Flowers white or cream
7	Corolla lobes overlapping to left	Corolla lobes overlapping to right
8	Seeds obtuse at both ends	Seeds acuminate at the upper end
9	Seeds glabrous or very short-haired on margin	Seeds long-haired on margin

Several species of *Alstonia* have been reported to be used in the treatment of malaria and dysentery throughout Southeast Asia.[109,110] The use of plants of the genus *Alstonia* in traditional local medicine has been well documented.[111,112] The traditional uses of *Alstonia* species are listed in Table 1.3.

Table 1.3: Traditional Medicinal Uses of *Alstonia* Species[109-112]

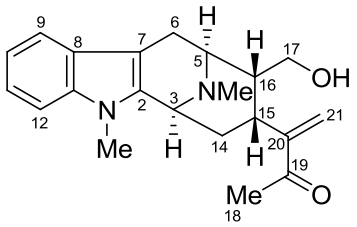
Species	**Common names**	**Country**	**Traditional uses**
A. angustifolia Wall. ex A. DC.	*Pulai penipu paya* (Malaysia)	Malaysia	• The leaves are heated and oiled, then applied to the spleen area to break malarial fever.
A. angustiloba Miq.	*Pulai* (Malaysia)	Malaysia	• The leaves and the bark extract are used to treat fevers. • The latex is used for boils and abscesses.
A. macrophylla Wall. ex G. Don.	*Pulai penipu bukit* (Malaysia); *chuharoi* (Nicobar Islands)	India	• The leaves and stem bark are made into a drink to assuage stomachache and to counteract putrefaction of urine. • Externally it is used as a treatment for the skin. • The leaves are heated and oiled and applied to sprains and dislocated joints.
		The Philippines	• The bark is used to treat fever, fatigue, irregular menses, liver disease, dysentery, malaria, diabetes, and to expel worms from the intestines. • The leaves are heated, piled, and applied to sprains, bruises, and dislocated joints.
A.scholaris Linn. R. Br.	*lettok, lettop, taungmek, toungmayobeng* (Burma)	Burma	• The latex is used to heal ulcers.
	popeal khe (Cambodia)	Cambodia	• The bark is used to promote menses and to treat chronic paludism with the enlargement of the spleen and liver discomfort.
		India	• The bark is used to promote milk secretion and to treat cancer.

Table 1.3, continued

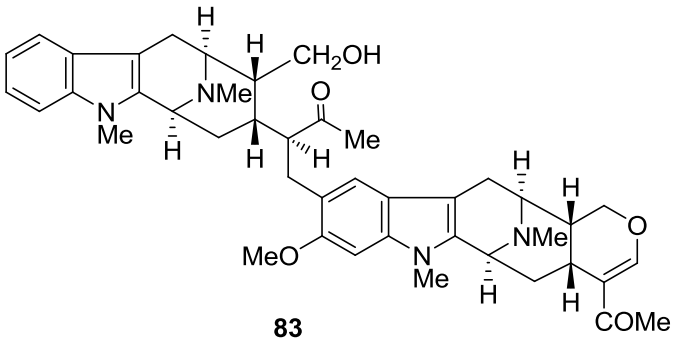
Species	Common names	Country	Traditional uses
		Indonesia	• The plant is used to stop diarrhea, treat diabetes and heal hemorrhoids. • An infusion of the young leaves is drunk to treat beriberi. • The leaf tips roasted with coconut are used to treat stomatitis.
	pulai (Malaysia)	Malaysia	• The plant is used to treat malaria. • The latex is used to assuage toothache. • A decoction of the bark is drunk to combat fever, invigorate the body, stimulate appetite, and treat yaws.
	ditaa (Philipine)	The Philippines Vietnam	• The plant is used internally to combat fever, stop dysentry, heal wounds, and treat epilepsy. • The bark is used to treat chronic malaria with enlarged spleen, while the leaves are used to promote milk secretion.
A.spatulata Bl.	*Pulai basong* (Malaysia)	Cambodia, Laos, Vietnam, Malaysia	• The latex is applied externally to sores and diseased skin. • The bark is used to lower fever and to expel worms from the intestines.
A.spectabilis R. Br. (*A. villosa* Bl.)		The Moluccas	• The bark is used to treat stomach and intestinal discomfort.

1.4.2 Alkaloids of the Genus *Alstonia*

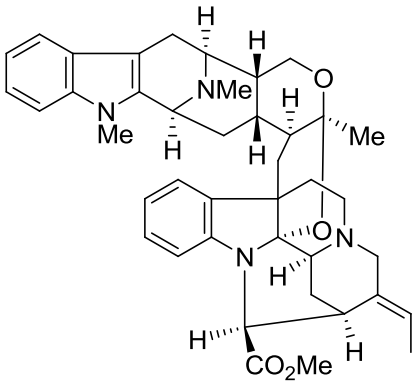
Plants of the genus *Alstonia* are rich sources of alkaloids and are characterized by a preponderance of the macroline skeleton. In addition to indole alkaloids, bisindoles related to two macroline-related units (*e.g.* perhentinine (**83**) and macralstonine (**84**)), as well as the bisindoles composed of a unit of macroline and other skeletal type of indole alkaloid (*e.g.* macralstonidine (**76**) and villalstonine (**88**)) have been isolated from the *Alstonia* species.[64,113-115] Macroline was proposed as the biomimetic precursor of many *Alstonia* alkaloids, however, it has not been isolated as a natural product to date.[116]



macroline



83



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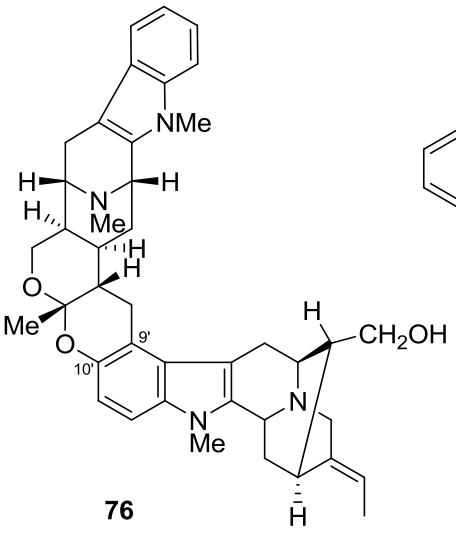

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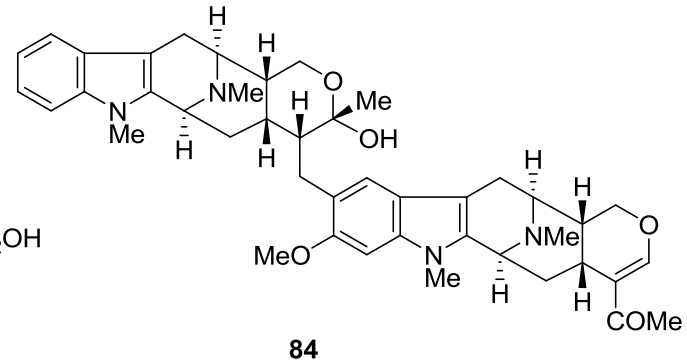


84

1.4.3 Occurrence and Distribution of Alkaloids in the Genus *Alstonia*

The occurrence of alkaloids in *Alstonia* as reported in the literature (up to 2012) is summarized in Table 1.4.

Table 1.4: Alkaloids reported from *Alstonia* species.

Species	**Plant part**	**Alkaloids**	**Ref.**
A. actinophylla (Australia)	Leaves	Actinophyllic acid (**363**)	117
A .angustifolia Wall. (Peninsular Malaya)	Leaves	10-Methoxymacrocarpamine (**422**)	64,118
		10-Methoxymacrocarpamine *N*-oxide (**423**)	64,118
		10-Methoxyvillalstonine (**424**)	64,118
		10-Methoxyvillalstonine *N*-oxide (**425**)	64,118
		11-Methoxyakuammicine (**67**)	64,118
		19,20-Dehydro-10-methoxytalcarpine (**111**)	64,118
		19,20-Dehydro-O-acetylyohimbine (**337**)	64,118
		Affinisine (**49**)	64,118
		Akuammicine (**262**)	64,118
		Alstocraline (**420**)	64,118
		Alstonerine (**5**)	64,118
		Alstonisine (**20**)	64,118
		Angusticraline (**418**)	64,118
		Antirhine (**69**)	64,118
		Cabucraline (**137**)	64,118
		Cathafoline (**35**)	64,118
		Fluorocarpamine (**63**)	64,118
		Foliacraline (**421**)	64,118
		16-Hydroxystrictamine (**150**)	64,118
		Lochnerine (**199**)	64,118
		N-desmethylquaternine (10,11-dimethoxy-picinine, volkensine, *nor*quaternine) (**170**)	64,118
		Normacusine B (**51**)	64,118
		Vincamajine (**54**)	64,118
		Pleiocarpamine (**59**)	64,118
		Tetrahydrocantleyine (**93**)	64,118
		Yohimbine (**64**)	64,118
		O-Acetylyohimbine (**335**)	64,118

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
	Stem-bark	11-Methoxyakuammicine (**67**)	64,118
		Affinisine (**49**)	64,118
		Alstonerine (**5**)	64,118
		Alstonisine (**20**)	64,118
		Alstopirocine (**124**)	119
		Alstophylline (**7**)	64,118
		Angustimaline (**98**)	64,120,121
		Angustimaline A (**99**)	121
		Angustimaline B (**100**)	121
		Angustimaline C (**101**)	121
		Angustimaline D (**102**)	121
		Angustimaline E (**103**)	121
		Fluorocarpamine (**63**)	64,118
		Macralstonine (**84**)	64,118
		Macrodasine A (**14**)	122-124
		Macrodasine B (**119**)	123,124
		Macrodasine C (**120**)	124
		Macrodasine D (**121**)	124
		Macrodasine E (**122**)	124
		Macrodasine F (**123**)	124
		Macrodasine G (**15**)	124
		Bipleiophylline (**441**)	125
		Perhentidine A (**81**)	126
		Perhentidine C (**414**)	126
		Perhentinine (**83**)	123,126
		Anhydromacralstonine (**85**)	127
		Lumutinine E (**75**)	127
		Macrocarpamine (**90**)	127
		Perhentisine A (**415**)	127
		Perhentisine B (**416**)	127
		Perhentisine C (**417**)	127
		Villalstonidine A (**426**)	127
		Villalstonidine B (**86**)	127
		Villalstonidine C (**428**)	127
		Villalstonidine D (**429**)	127
		Villalstonidine E (**430**)	127
		Pleiomalicine (**254**)	119
		Pleiomaltinine (**61**)	119

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Villalstonine (**88**)	64,118
		Villalstonine *N*-oxide (**89**)	64,118
	Root	11-Methoxyakuammicine (**67**)	64,128
		4'-Hydroxy-3',5'-dimethoxybenzoyl-vincamajine (**219**)	64,128
		Alstonerine (**5**)	64,128
		Alstophylline (**7**)	64,128
		Macralstonine (**84**)	64,128
		Macrocarpamine (**90**)	64,128
		Nor-C-fluorocurarine (**292**)	64,128
		Pleiocarpamine (**59**)	64,128
		Villalstonine (**88**)	64,128
		Vincamajine (**54**)	64,128
A. angustifolia Miq. (Indonesia)	Stem-bark	19-*Epi*alstogustine (**271**)	129
		Akuammicine (**262**)	130
		Akuammicine *N*-oxide (**267**)	130
		Alstogustine (**274**)	129
		Echitamine (**161**)	130
		N(4)-Demethylalstogustine (**276**)	130
		N(4)-Demethylalstogustine *N*-oxide (**277**)	130
		N(4)-Demethylechitamine (**158**)	130
		N(4)-Methylakuammidine (**202**)	130
		N(4)-β-Methylantirhine (**347**)	130
		Pseudoakuammigine (**215**)	130
		Pseudoakuammigine *N*-oxide (**216**)	130
		Tubotaiwine (**304**)	130
A. angustifolia var. latifolia K. and G. (Peninsular Malaysia)	Leaves	10-Methoxyaffinisine (**198**)	131
		10-Methoxycathafoline (**37**)	131
		10-Methoxycathafoline *N*-oxide (**135**)	131
		10-Methoxyvincamajine (**218**)	131
		11-Hydroxystrictamine (**40**)	131
		11-Methoxyakuammicine (**67**)	131
		11-Methoxystrictamine (**39**)	131
		16*R*,19*E*-Isositsirikine (**57**)	131
		Affinisine (**49**)	131
		Affinisine oxindole (**50**)	131

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Alstofoline (**126**)	131,132
		Alstolactone (**118**)	131
		Alstolagumine (**288**)	131
		Alstonal (**21**)	131,132
		Alstonerinal (**6**)	131
		Alstonerine (**5**)	131
		Alstonisine (**20**)	131,132
		Alstonoxine A (**18**)	131,132
		Alstonoxine B (**19**)	131,132
		Alstophylline (**7**)	131
		Alstoumerine (**52**)	131
		Alstovine (**284**)	131
		Cathafoline (**35**)	131
		Cathafoline *N*-oxide (**36**)	131
		Isoalstonisine (**125**)	131,132
		Lagumicine (**290**)	131
		Lagumidine (**291**)	131
		Lochnerine (**199**)	131
		Macrogentine (**133**)	131,132
		N(1)-Demethylalstonal (**128**)	131,132
		N(1)-Demethylalstonisine (**127**)	131,132
		N(4)-Demethylalstonerinal (**113**)	131
		N(4)-Demethylalstonerine (**112**)	131
		N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	131
		Nor-C-flourocurarine (**292**)	131
		Normacusine B (**51**)	131
		Quebrachidine (**53**)	131
		Sitsirikine (**56**)	131
		Strictamine (**38**)	131
		Talcarpine (**12**)	131
		Vincamajine (**54**)	131
		Vincorine (**41**)	131
	Stem-bark	10-Methoxyaffinisine (**198**)	133
		10-Methoxycathafoline (**37**)	133
		Alstonal (**21**)	133
		Alstonerinal (**66**)	133
		Alstonerine (**5**)	133
		Alstonisine (**20**)	133

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Alstophylline (**7**)	133
		Cathafoline (**35**)	133
		Lochnerine (**199**)	133
		Vincamajine (**54**)	133
A. angustiloba (Indonesia)	Whole plant	15-Hydroxy-angustilobine A (**381**)	134
		4,6-*Seco*angustilobinal A (**379**)	134
		6,7-*Seco*-19,20α-epoxyangustilobine B (**373**)	134
		6,7-*Seco*-6-cynostemmadenine (**375**)	134
		6,7-*Seco*angustilobine B (**370**)	134
		Angustilobine A (**382**)	134
		Angustilobine B (**387**)	134
		Cantleyine (**92**)	135
		Echitamidine (**270**)	136
		Nor-6,7-*seco*angustilobine A (**378**)	134
		O-Acetylvallesamine (**384**)	134
		19,20-*E*-Vallesamine (**383**)	134
		Venoterpine (**91**)	135
A. angustiloba Miq. (Peninsular Malaysia)	Leaves	16*R*,19*E*-Isositsirikine (**57**)	137
		19,20-*E*-Vallesamine (**383**)	137,138
		20(*S*)-Tubotaiwine (**304**)	137
		6,7-*Seco*-19,20α-epoxyangustilobine B (**373**)	138
		6,7-*Seco*angustilobine B (**370**)	137,138
		Alstolucine B (**256**)	137
		Andransinine (**327**)	137
		Angustilobine A (**382**)	137
		Angustilobine B (**387**)	137,138
		Angustilobine C (**392**)	137
		Angustilocine (**372**)	138
		Angustilodine (**397**)	138
		Condylocarpine (**308**)	137
		Echitamidine (**270**)	138
		Leuconoxine (**365**)	138
		Losbanine (**369**)	138
		O-Acetylvallesamine (**384**)	137
		Picraline (**178**)	138

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Picrinine (**47**)	138
		Scholaricine (**269**)	138
		Vincamine (**350**)	137
	Bark	17-*O*-Acetyl-*N*(4)-demethylechitamine (**159**)	137
		20(*S*)-Tubotaiwine (**304**)	137
		Ajmalicine (**328**)	138
		Akuammicine (**262**)	138
		Angustilobine B (**387**)	137,138
		Cantleyine (**92**)	137,138
		N(4)-Demethylechitamine (**158**)	137,138
		Undulifoline (**393**)	137
		Venoterpine (**91**)	137,138
		Yunnannnesine (**376**)	137
		Angustiphylline (**432**)	137
		6,7-*Seco*-19,20α-epoxyangustilobine B (**373**)	138
		6,7-*Seco*angustilobine B (**370**)	137
		19,20-*E*-Vallesamine (**383**)	137,138
A. angustiloba (Peninsular Malaysia)	Leaves	6,7-*Seco*angustilobine B (**370**)	139
		Alstilobanine A (**399**)	139
		Alstilobanine B (**395**)	139
		Alstilobanine C (**394**)	139
		Alstilobanine D (**371**)	139
		Alstilobanine E (**398**)	139
		Alstonamic acid (**389**)	139
		Undulifoline (**393**)	139
A. boonei (Africa)	Stem bark	Echitamidine (**270**)	140
		N(1)-Formylechitamidine (**275**)	140
A. congensis (Africa)	Leaves	12-Methoxytubotaiwine (**306**)	141
		17-*O*-Acetyl-*nor*-echitamine (**159**)	141
		6,7-*Seco*angustilobine A (**380**)	141
		6,7-*Seco*angustilobine B (**370**)	141
		Angustilobine A (**382**)	141
	Stem bark	12-Methoxyakuammicine (**264**)	141
		Akuammidine (**200**)	141

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Angustilobine A (**382**)	141
		Angustilobine B (**387**)	141
		Angustilobine B *N*-oxide (**390**)	141
		Echitamidine (**270**)	141
		Echitamine (**161**)	141
	Root bark	12-Methoxyakuammicine (**264**)	141
		12-Methoxy-*N*(4)-methylakuammicine (**265**)	141
		17-*O*-Acetyl-*nor*-echitamine (**159**)	141
		6,7-*Seco*angustilobine B (**370**)	141
		Akuammicine (**262**)	141
		Echitamidine (**270**)	141
		Echitamine (**161**)	141
		Nor-echitamine (**158**)	141
		Tubotaiwine (**304**)	141
A. constricta	Stem bark	14-Ketoalstonidine (**105**)	142
(Australia)		1-Carbomethoxycarboline (**104**)	142
		Alstonidine (**106**)	142
		Alstonilidine (**107**)	142
		O-3',4',5'-Trimethoxybenzoylquebrachidine (**220**)	142
		Quebrachidine (**53**)	142
		Vincamedine (**234**)	142
	Root bark	Alstonidine (**106**)	143
		Alstonilidine (**107**)	143
		O-3,4,5-Trimethoxybenzoylquebrachidine (**220**)	143
		O-3',4',5'-Trimethoxycinnamoylvincamajine (**221**)	143
		Reserpine (**330**)	143
		Vincamajine (**54**)	143
A. coriacea	Stem bark	10-Methoxy-3-*epi*-α-yohimbine (**332**)	144
(New Caledonia)		10-Methoxydeplancheine (**211**)	144
		Cabucraline (**137**)	144
		Corialstonine (**401**)	144
		Desmethylquaternine (10,11-dimethoxy-picrinine, volkensine, *nor*quaternine) (**170**)	144
		Gentianine (**94**)	144

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Vincamajine (**54**)	144
A. deplanchei	Leaves	Pleiocorine (**434**)	145
(New Caledonia)		Pleiocraline (**437**)	146
		Vincorine (**41**)	145
	Stem bark	Deplancheine (**212**)	147
A. glabriflora	Bark	Alstophylline (**7**)	148
(New Guinea)		Macralstonine (**84**)	148
		Pleiocarpamine (**59**)	148
		Villalstonine (**88**)	148
A. glaucescens	Stem bark	17-*O*-Acetyl-*N*(4)-demethylechitamine (**159**)	149
(Thailand)		20-*Epi*-19ξ-echitamidine (**273**)	149
		Echitamidine (**270**)	149
		Echitamidine *N*-oxide (**281**)	149
		Echitamine (**161**)	149
		Echitaminic acid (**162**)	149
		N(4)-Demethylechitamine (**158**)	149
		N(4)-Demethylechitamine *N*-oxide (**163**)	149
A. lanceolata	Stem bark	ψ-Akuammigine (**215**)	150
(New Caledonia)		10,11-Dimethoxy-1-methyldeacetylpicraline (**179**)	150
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**177**)	150
		10,11-Dimethoxy-1-methylpicraline (**181**)	150
		10-Methoxycompactinervine (**285**)	150
		Akuammicine (**262**)	150
		Compactinervine (**287**)	150
		Cathafoline (**35**)	150
		Gentianine (**94**)	150
		Lanceomigine (**361**)	150
		Lanceomigine *N*-oxide (**362**)	150
		Lochnericine (**318**)	150
		Picraline (**178**)	150

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
A. lanceolifera	Leaves	10-Methoxydeplancheine (**24**)	151
(New Caledonia)		10,11-Dimethoxy-1-methyldeacetylpicraline benzoate (**180**)	151
		10,11-Dimethoxy-1-methyldeacetylpicraline (**179**)	151
		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**177**)	151
	Stem bark	10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**177**)	152
		10,11-Dimethoxy-1-methylpicraline (**181**)	152
		10-Methoxycompactinervine (**285**)	152
		10-Methoxy-*nor*-C-fluorocurarine (**293**)	152
		10-Methoxyvincamajine (**218**)	152
		11-Methoxyakuammicine (**67**)	152
		11-Methoxycompactinervine (alstovine) (**284**)	152
		Akuammiline (**154**)	152
		Lochnericine (**318**)	152
		N(1)-Methyl-10-methoxyakuammidine (**210**)	153
		O-Trimethoxybenzoylhydroxyvincamajine (**223**)	153
		O-Trimethoxycinnamoyl-10-hydroxy-vincamajine (**224**)	153
		O-Trimethoxycinnamoyl-10-methoxy-vincamajine (**225**)	153
		O-3',4',5'-Trimethoxycinnamoylvincamajine (**221**)	153
		Picraline (**178**)	152
A. lenormandii var.	Leaves	10,11-Dimethoxy-1-methyldeacetylpicraline benzoate (**180**)	154
lenormandii		10,11-Dimethoxy-1-methyldeacetylpicraline-3',4',5'-trimethoxybenzoate (**177**)	154
(New Caledonia)		12-Methoxy-19,20-α-epoxyakuammicine (**289**)	154
		12-Methoxycompactinervine (**286**)	154
	Bark	10,11-Dimethoxy-1-methyldeacetylpicraline (**179**)	154
		10,11-Dimethoxy-1-methylpicraline (**181**)	154
		11-Methoxyakuammicine (**67**)	154
		11-Methoxycompactinervine (alstovine) (**284**)	154
		12-Methoxycompactinervine (**286**)	154
		Akuammiline (**154**)	154

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Lochnericine (**318**)	154
		Picraline (**178**)	154
A. lenormandii var. *minutifolia* (New Caledonia)	Leaves	10,11-Dimethoxy-1-methyldeacetyl-picraline-3',4',5'-trimethoxybenzoate (**177**)	154
		12-Methoxycompactinervine (**286**)	154
		Gentianine (**94**)	154
A. macrophylla (Sabah, Malaysia Borneo)	Bark	Alstonal (**21**)	64,155
		Alstonisine (**20**)	64,155
		N(4)-Demethylalstophyllal oxindole (**23**)	64,155
		N(4)-Demethylalstophylline oxindole (**22**)	64,155
		Talcarpine (**12**)	64,155
A. marcophylla (Sri Lanka)	Leaves	10-Hydroxystrictamine (**147**)	156
		16-Hydroxy-*N*(4)-demethylalstophylline oxindole (**132**)	157
		19-Hydroxyvincamajine (**231**)	158
		Alstomacrocine (**108**)	156
		Alstonamide (**43**)	159
		Alstophylline (**7**)	158
		Alstopicralamine (**188**)	160
		Alstoumerine (**52**)	159
		Cabucraline (**137**)	158
		Demethoxyalstonamide (**44**)	159
		Macroxine (**134**)	161
		N(1)-Methyl-1,2-dihydrostrictamine (**139**)	157
		N(4)-Demethylalstophylline oxindole (**22**)	162
		Strictaminolamine (**142**)	163
		Vincamajine (**54**)	158,160
		Vincorine (**41**)	158
	Bark	Alstonerine (**5**)	158
		Anhydromacralstonine (**85**)	158
		Macralstonine (**84**)	158
		Talcarpine (**12**)	158
A. macrophylla (Thailand)	Leaves	11-Methoxyakuammicine (**67**)	164
		11-Methoxyakuammicine *N*-oxide (**68**)	164

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Alstophylline (**7**)	164
		Cathafoline (**35**)	164
		Cathafoline *N*-oxide (**36**)	164
		N(4)-Demethylalstophylline oxindole (**22**)	164
		Vincamajine (**54**)	164
		Vincamajine-17-*O*-veratrate (**55**)	164
		Vincamajine-*N*(1)-tri-*O*-methylgallate (**228**)	164
		Vincorine (**41**)	164
	Stem	Macralstonine (**84**)	165
		Thungfaine (**80**)	165
	Root	20-*Epi*antirhine (**346**)	166
	bark	Alstomacroline (**431**)	166
		Alstomacrophylline (**413**)	166
		Alstonerine (**5**)	166
		Alstophylline (**7**)	166
		Alstoumerine (**52**)	166
		Macralstonine (**84**)	167
		Macrocarpamine (**90**)	166
		O-Methylmacralstonine (**411**)	167
		Pleiocarpamine (**59**)	167
		Talcarpine (**12**)	167
		Villalstonine (**88**)	167
		Villalstonine *N*-oxide (**89**)	166
A. macrophylla	Leaves	10,11-Dimethoxy-*N*(1)-methylpicrinine (quaternine) (**46**)	168
(The Phillipines)		10,11-Dimethoxypicrinine (Volkensine, *Nor*quaternine) (**170**)	168
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-benzoate (**172**)	168
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**173**)	168
		11-Methoxy-19,20α-epoxyakuammicine (alstolagumine) (**288**)	168
		11-Methoxy-19-oxo-20α-hydroxyakuammicine (lagumidine) (**291**)	168
		5α,10,11-Trimethoxystrictamine (**148**)	168
		Cathafoline (**35**)	168

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		N(1)-Methylburnamine-17-*O*-benzoate (**175**)	168
		Strictamine (**38**)	168
	Root	Affinisine (**49**)	169
		Alstophylline (**7**)	169,170
		Macralstonidine (**76**)	169,171
		Macralstonine (**84**)	169,172
		Macrocarpamine (**90**)	169
		Macrosalhine (**208**)	169,173
		N(1)-Methyl-2,16-dihydroakuammicine (**299**)	169
		O-Benzoylvincamajine (**222**)	169
		Picralstonine (**190**)	169
		Picrinine (**47**)	169
		Pleiocarpamine (**59**)	169
		Villalstonine (**88**)	169,174,175
A. macrophylla (India)		Affinisine (**49**)	176
		Picralstonine (**190**)	176
		Picrinine (**47**)	176
A. macrophylla (Terengganu, Peninsular Malaysia)	Leaves	10,11-Dimethoxy-1-methyldeacetyl-picraline-3',4',5'-trimethoxybenzoate (**177**)	177
		10,11-Dimethoxynareline (**66**)	177
		16-Hydroxyalstonal (**130**)	177
		16-Hydroxyalstonisine (**129**)	177
		16-Hydroxy-*N*(4)-demethylalstophyllal oxindole (**131**)	177
		16-Hydroxy-*N*(4)-demethylalstophylline oxindole (**132**)	177
		6-Methoxy-4-methylquinoline (**95**)	177
		6-Methoxy-α-methyl-4-quindine methanol (**96**)	177
		6-Oxoalstophyllal (**115**)	177
		6-Oxoalstophylline (**114**)	177
		Alstohentine (**110**)	177
		Alstomaline (**45**)	177
		Alstomicine (**109**)	177
		Alstonal (**21**)	177
		Alstonerinal (**6**)	177
		Alstonerine (**5**)	177
		Alstonisine (**20**)	177

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Alstonoxine B (**19**)	177
		Alstophyllal (**8**)	177
		Alstophylline (**7**)	177
		Demethoxyalstonamide (**44**)	177
		Macrocarpine A (**9**)	177
		Macrocarpine B (**10**)	177
		N(4)-Demethylalstophyllal oxindole (**23**)	177
		N(4)-Demethylalstophylline oxindole (**22**)	177
		N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	177
		Quaternine (**46**)	177
		Talcarpine (**12**)	177
		Vincoridine (**157**)	177
		Vincorine (**41**)	177
		Volkensine (**170**)	177
	Stem bark	11-Methoxyakuammicine (**67**)	123
		16*R*,19*E*-Isositsirikine (**57**)	123
		Alstonal (**21**)	123
		Alstonisine (**20**)	123
		Alstophyllal (**8**)	123
		Alstophylline (**7**)	123
		Angustimalal (**97**)	123
		Fluorocarpamine (**63**)	123
		Macrocarpine A (**9**)	123
		Macrocarpine B (**10**)	123
		Macrocarpine C (**11**)	123
		Macrodasine A (**14**)	122,123
		Macrodasine B (**119**)	123
		N(1)-Demethylalstophyllal (**117**)	123
		N(1)-Demethylalstophylline (**116**)	123
		N(4)-Demethylalstophyllal oxindole (**23**)	123
		N(4)-Demethylalstophylline oxindole (**22**)	123
		N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	123
		Perhentinine (**83**)	123
		Pleiocarpamine (**59**)	123
		Talcarpine (**12**)	123
		Villalstonine (**88**)	123

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
A. macrophylla	Leaves	Alstiphyllanine A (**229**)	178
Wall. Ex G. Don		Alstiphyllanine B (**182**)	178
(Indonesia)		Alstiphyllanine C (**183**)	178
		Alstiphyllanine D (**184**)	178
		Vincamedine (**234**)	178
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**173**)	178
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxy-benzoate (**192**)	178
A. macrophylla	Leaves	10,11-Dimethoxy-*N*(1)-methyl-picrinine (quaternine) (**46**)	179
(Indonesia)		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**173**)	179
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxy-benzoate (**192**)	179
		Alstiphyllanine A (**229**)	179,180
		Alstiphyllanine B (**182**)	179
		Alstiphyllanine C (**183**)	179
		Alstiphyllanine D (**184**)	179
		Alstiphyllanine E (**185**)	179
		Alstiphyllanine F (**186**)	179
		Alstiphyllanine G (**176**)	179
		Alstiphyllanine H (**230**)	179,180
		Alstiphyllanine I (**245**)	180
		Alstiphyllanine J (**246**)	180
		Alstiphyllanine K (**247**)	180
		Alstiphyllanine L (**248**)	180
		Alstiphyllanine M (**249**)	180
		Alstiphyllanine N (**250**)	180
		Alstiphyllanine O (**251**)	180
		Alstonal (**21**)	179
		Alstonerine (**5**)	179
		Burnamine (*O*-deacetylpicraline) (**194**)	179
		Picralinal (**189**)	179
		Picrinine (**47**)	179
		Vincamajine (**54**)	179,180
		Vincamajine-17-*O*-3',4',5'-trimethoxy-benzoate (**226**)	179,180
		Vincamajine-17-*O*-veratrate (**55**)	179,180
		Vincamedine (**234**)	179,180

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
A. muelleriana	Bark	11-Methoxyakuammicine (**67**)	181
(Australia)		2,7-Dihydropleiocarpamine (**253**)	182
		Alstonerine (**5**)	183,184
		Alstonisidine (**442**)	184
		Alstonisine (**20**)	184
		Des-*N*'(1)-methylanhydromacralstonine (**412**)	182
		Macralstonine (**84**)	185
		Pleiocarpamine (**59**)	182
		Quebrachidine (**53**)	182
		Villalstonine (**88**)	184
		Vinervinine (12-methoxyakuammicine) (**264**)	182
A. odontophora	Leaves	11-Methoxyakuammicine (**67**)	186
(New Caledonia)	and	Antirhine (**69**)	186
	stem	*N*(1)-Demethylpleiocorine (**433**)	186
		Pleiocarpamine (**59**)	186
		Pleiocorine (**434**)	186
		Pleiocraline (**437**)	186
		Quebrachidine (**53**)	186
		Vincamajine (**54**)	186
A. plumosa	Stem	10-Carboaldehydecabucraline (**136**)	187
(New Caledonia)	bark	11-Methoxycompactinervine (alstovine) (**284**)	187
		2,7-Dihydroxypleiocarpamine (**252**)	187
		Caberine (**140**)	187
		Caberoline (**213**)	187
		Cabucraline (**137**)	187
		Cabucraline *N*-oxide (**138**)	187
		Cathafoline (**35**)	187
		Desoxycabufiline (**435**)	187
		Fluorocarpamine (**63**)	187
		*Nor*desoxycarbufiline (**436**)	187
		Pleiocarpamine (**59**)	187
		Pleiocorine (**434**)	187
		Pleiocraline (**437**)	187
		Quaternoline (raucubaine) (**214**)	187
		Quaternoxine (**141**)	187
		Strictamine (deacetyldesformo akuammiline) (**38**)	187

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
	Root	11-Methoxycompactinervine (alstovine) (**284**)	187
		3,4-*Seco*-3,14-dehydrocabucraline (**368**)	187
		Cabucraline (**137**)	187
		Cabucraline *N*-oxide (**138**)	187
		Fluorocarpamine (**63**)	187
		Pleiocarpamine (**59**)	187
		Plumocraline (**438**)	187
A. pneumatophora (Peninsular Malaysia)	Leaves	Actinophyllic acid (**363**)	188
		Akuammidine (**200**)	188
		Alpneumine A (**294**)	188
		Alpneumine B (**295**)	188
		Alpneumine C (**296**)	188
		Alpneumine D (**297**)	188
		Alpneumine E (**298**)	188
		Alpneumine F (**364**)	188
		Alpneumine G (**352**)	188
		Alpneumine H (**396**)	188
		Alsmaphorazine A (**301**)	189
		Alsmaphorazine B (**302**)	189
		Alsmaphorazine C (**402**)	190
		Alsmaphorazine D (**403**)	190
		Alsmaphorazine E (**404**)	190
		Alstilobanine B (**395**)	188
		Apovincamine (**353**)	188
		Echitamidine (**270**)	188
		Scholarine (**279**)	188
		Vincamine (**350**)	188
A. quaternata (New Caledonia)	Whole plant	10,11-Dimethoxy-*N*(1)-methylpicrinine (quaternine) (**46**)	191
		Cathafoline (**35**)	191
		Pseudoyohimbine (**333**)	191
		Quaternatine (**334**)	191
		Quaternidine (**187**)	191
		Quaternoline (**214**)	191
		Quaternoxine (**141**)	191
		20(*R*)-Tubotaiwine (**303**)	191
		Vincamajine (**54**)	191
		Yohimbine (**64**)	191

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
A. rostrata	Leaves	Akuammidine (**200**)	192
(China)		Alstrostine A (**405**)	193
		Alstrostine B (**406**)	193
		Alstrostine C (**407**)	192
		Alstrostine D (**408**)	192
		Alstrostine E (**409**)	192
		Alstrostine F (**410**)	192
		Deacetylakuammiline (**156**)	192
		19,20-Dihydroakuammicine (**283**)	192
		Echitamidine (**270**)	192
		Isovallesiachotamine (**345**)	192
		12-Methoxyechitamidine (Scholarine) (**279**)	192
		N(4)-Demethylechitamine (**115**)	192
		17-*O*-Acetyl-*N*(4)-demethylechitamine (**159**)	192
		19-Oxo-12-methoxyechitamidine (**259**)	192
		Tabersonine (**203**)	192
		Undulifoline (**109**)	192
		Vallesiachotamine (**344**)	192
(= *A. undulifolia*)	Stem	Akuammicine (**262**)	64,194
(Peninsular	bark	Cantleyine (**92**)	64,194
Malaysia)		Echitamidine (**270**)	64,194
		Echitamine (**161**)	64,194
		20-*Epi*-19ξ-echitamidine (**273**)	64,194
		*Nor*echitamine (*N*(4)-Demethylechitamine) (**158**)	64,194
		Pleiocarpamine (**59**)	64,194
		Tetrahydrocantleyine (**93**)	64,194
		Undulifoline (**393**)	64,194
A. scholaris	Leaves	Alschomine (**168**)	195
(Thailand)		Isoalschomine (**169**)	195
		Nareline (**355**)	195
		Picrinine (**47**)	195
		Scholaricine (**269**)	195
		Tubotaiwine (**304**)	195
		Vallesamine (**383**)	195
	Stem-bark	Echitamine (**161**)	196
		Hydroxy-19,20-dihydroakuammicine (**273**)	196

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		N(4)-Demethylechitamine (*Nor*echitamine) (**158**)	196
		Picrinine (**47**)	196
		Tubotaiwine (**304**)	196
	Root	Akuammicine (**262**)	196,197
	bark	Akuammicine *N*(4)-methiodide (**266**)	196,197
		Akuammicine *N*(4)-Oxide (**267**)	196,197
		Echitamidine (**270**)	196,197
		Echitamine (**161**)	196,197
		Hydroxy-19,20-dihydroakuammicine (**273**)	196,197
		N(4)-Demethylechitamine (**158**)	196,197
		Tubotaiwine (**304**)	196,197
		ψ-Akuammigine (**215**)	196,197
A. scholaris	Leaves	5-*Epi*nareline ethyl ether (**354**)	64,198
(Peninsular		Nareline ethyl ether (**356**)	64,198
Malaysia)		Nareline methyl ether (**357**)	64,198
		Picrinine (**47**)	64,198
		Scholaricine (**269**)	64,198
		Scholarine *N*-oxide (**280**)	64,198
A. scholaris	Leave	Akuammidine (**200**)	199
(India)		Echitamidine (**270**)	200
		Echitamine (**161**)	200
		Nareline (**355**)	199
		Picralinal (**189**)	199
		Picrinine (**47**)	199,200
		Pseudoakuammigine (**215**)	199
		Scholarine (**279**)	201
	Fruit	Nareline (**355**)	202
	pods	*N*-Formylscholarine (**300**)	202
		Picrinine (**47**)	202
		Strictamine (deacetyldesformo akuammiline) (**38**)	202
A. scholaris	Leaves	19,20-*E*-Vallesamine (**383**)	203
(The Phillipines)		20(*S*)-Tubotaiwine (**304**)	195,203,204
		20(*S*)-Tubotaiwine *N*-oxide (**305**)	195,204
		6,7-*Seco*angustilobine B (**370**)	195,203,204

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Angustilobine B acid (**389**)	195,204
		Angustilobine B *N*-oxide (**390**)	203
		Lagunamine (19-hydroxytubotaiwine) (**305**)	195,204
		Losbanine (6,7-*seco*-6-*nor*-angustilobine B) (**369**)	195,204
		Manilamine (**374**)	203
		N(4)-Methylangustilobine B (**391**)	203
	Bark	6,7-*Seco*angustilobine B (**370**)	204
		Acetylechitamine (**160**)	204
		Echitamine (**161**)	204
		Losbanine (6,7-*seco*-6-*nor*-angustilobine B) (**369**)	204
		N(4)-Demethylechitamine (*Nor*echitamine) (**158**)	204
		20(*S*)-Tubotaiwine (**304**)	204
		Tubotaiwine *N*-oxide (**305**)	204
A. scholaris (Taiwan)	Leaves	19,20-*E*-Vallesamine (Vallesamine) (**383**)	195
		19-*Epi*scholaricine (**272**)	195
		6,7-*Seco*angustilobine B (**370**)	195
		Alschomine (**168**)	195,205
		Isoalschomine (**169**)	195,205
		Nareline (**355**)	195,205
		Picralinal (**189**)	195,205
		Picrinine (**47**)	195,205
A. scholaris (Indonesia)	Leaves	19,20-*E*-Vallesamine (Vallesamine) (**383**)	195
		19,20-*E*-Vallesamine *N*-oxide (**385**)	195
		6,7-*Seco*-19,20α-epoxyangustilobine B (**373**)	195
		6,7-*Seco*angustilobine B (**370**)	195
		Akuammidine (**200**)	195,206
		Akuammidine-*N*-oxide (**203**)	206
		Leuconolam (**367**)	195
		N(1)-Methylburnamine (**174**)	195
		N(4)-Methylscholaricine (**278**)	195
		Picraline (**178**)	195
		Scholaricine (**269**)	195
		ψ-Akuammigine (Pseudoakuammigine) (**215**)	195
		ψ-Akuammigine *N*-oxide (**216**)	195

Table 1. continued…

Species	Plant part	Alkaloids	Ref.
	Bark	Akuammicine *N*-oxide (**267**)	207
		Akuammiginone (**217**)	207
		Echitamidine *N*-oxide (**281**)	207
		Echitamidine-*N*-oxide 19-*O*-*β*-D-glucopyranoside (**282**)	207
		Echitaminic acid (**162**)	207
		N(4)-Demethylalstogustine (**276**)	207
		N(4)-Demethylalstogustine *N*-oxide (**277**)	207
A. scholaris (Pakistan)	Leaves	19,20-*E*-Vallesamine (Vallesamine) (**383**)	208
		19,20-*Z*-Vallesamine (**386**)	208
		Alstonamine (**388**)	209
		Rhazimanine (**348**)	209
A. scholaris (China)	Leaves	19,20-*E*-Alstoscholarine (**358**)	210
		19,20-*E*-Vallesamine (Vallesamine) (**383**)	211,212
		19,20-*Z*-Alstoscholarine (**359**)	210
		19-*Epi*scholaricine (**272**)	212
		5-Methoxystrictamine (**151**)	211,212
		5-Oxo-17-deacetyl-1,2-dihydroakuammiline (**143**)	212
		Akuammidine (**200**)	212
		Leuconolam (**367**)	
		Methyl (2*β*,16*R*,19*E*)-4,5-didehydro-1,2-dihydro-2-hydroxy-16-(hydroxymethyl)-akuammilan-4-ium-17-oate chloride (**144**)	212
		N(1)-Methoxymethylpicrinine (**171**)	211
		N(1)-Methylburnamine (**174**)	212
		N(4)-Demethylechitamine (*Nor*echitamine) (**158**)	212
		Picralinal (**189**)	211,212
		Picrinine (**47**)	211,212
		Rhazimanine (**348**)	212
		Scholaricine (**269**)	211,212
		Scholarisine A (**360**)	213
	Bark	19,20-*E*-Vallesamine (Vallesamine) (**383**)	214
		19-*Epi*-ajmalicine (**329**)	214
		19-*Epi*scholaricine (**272**)	214
		19*Z*-16-Formyl-5α-methoxystrictamine (**146**)	214
		20-*Epi*-19-oxodihydroakuammicine (Alstolucine F) (**261**)	214

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		3-*Epi*-dihydrocorymine (**164**)	214
		5-Methoxystrictamine (**151**)	214
		Akuammidine (**200**)	214
		Echitamidine (**270**)	214
		Echitamine (**161**)	214
		Leuconoxine (**365**)	214
		N(4)-Demethylechitamine (*Nor*echitamine) (**158**)	214
		Nareline (**355**)	214
		Picralinal (**189**)	214
		Picrinine (**47**)	214
		Scholarisine B (**195**)	214
		Scholarisine C (**165**)	214
		Scholarisine D (**166**)	214
		Scholarisine E (**167**)	214
		Scholarisine F (**191**)	214
		Scholarisine G (**366**)	214
A. spatulata Bl. (Peninsular Malaysia)	Leaves	(**–**)-Alstolucine A (**255**)	215
		(**–**)-Alstolucine B (**256**)	215
		(**–**)-Alstolucine C (**257**)	215
		(**–**)-Alstolucine D (**258**)	215
		(**–**)-Alstolucine E (**260**)	215
		(**–**)-Alstolucine F (**261**)	215
		16-*Epi*vincamine (**351**)	215
		16*R*, 19*E*-Isositsirikine (**57**)	215
		20(*R*)-Tubotaiwine (**303**)	215
		4,6-*Seco*angustilobinal A (**379**)	215
		Akuammicine (**262**)	215
		Alstolobine A (**377**)	215
		N(4)-Demethyl-12-methoxyalstogustine (**268**)	215
		Nor-6,7-*seco*angustilobine A (**378**)	215
		Picrinine (**47**)	215
		Undulifoline (**393**)	215
		Vincaddiformine (**309**)	215
		Vincamine (**350**)	215
		Vinervine/12-Hydroxyakuammicine (**263**)	215
	Stem	(±)-Angustilobine B (**387**)	215
	Bark	15-Hydroxy-angustilobine A (**381**)	215

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		19,20-*E*-Vallesamine (Vallesamine) (**383**)	215
		20(*R*)-Tubotaiwine (**303**)	215
		20(*S*)-Tubotaiwine (**304**)	215
		Akuammicine (**262**)	215
		Leuconoxine (**365**)	215
		N(4)-Demethyl-12-methoxyalstogustine (**268**)	215
		N(4)-Demethylechitamine (*Nor*echitamine) (**158**)	215
		Undulifoline (**393**)	215
		Vinervine/12-Hydroxyakuammicine (**263**)	215
A. spectabilis	Bark	Macralstonine (**84**)	148
(New Guinea)		*N*(1)-Methylsarpagine (**197**)	148
		Pleiocarpamine (**59**)	148
		Quebrachidine (**53**)	148
		Villalstonine (**88**)	148
		Vincamajine (**54**)	148
A. sphaerocapitata	Leaves	10-Methoxyvincamedine (**232**)	216
(New Caledonia)		10-Methoxyvincamedine *N*-oxide (**233**)	216
		11-Methoxyakuammicine (**67**)	216
		Akuammicine (**262**)	216
		Caberoline (**213**)	216
		Cabucraline (**137**)	216
		Cathafoline (**35**)	216
		Desoxycabufiline (**435**)	216
		Quaternoline (**214**)	216
		20(*S*)-Tubotaiwine (**304**)	216
		Vincamedine (**234**)	216
		Z-Isositsirikine (**349**)	216
	Stem bark	10-Methoxyvincamedine (**232**)	216
		10-Methoxyvincamedine *N*-oxide (**233**)	216
		11-Methoxyakuammicine (**67**)	216
		Akuammicine (**262**)	216
		Cabucraline (**137**)	216
		Cathafoline (**35**)	216
		Desoxycabufiline (**435**)	216
		Nor-C-fluorocurarine (**292**)	216
		*Nor*desoxycabufiline (**436**)	216

Table 1.4, continued…

Species	Plant part	Alkaloids	Ref.
		Undulatine (**439**)	217
		Vincamedine (**234**)	216
	Fruit	10-Methoxyvincamedine (**232**)	216
		10-Methoxyvincamedine *N*-oxide (**233**)	216
		11-Methoxyakuammicine (**67**)	216
		Akuammicine (**262**)	216
		Cabucraline (**137**)	216
		Cathafoline (**35**)	216
		Desoxycabufiline (**435**)	216
		Quaternoxine (**141**)	216
		Quebrachidine (**53**)	216
		Vincamedine (**234**)	216
		Vincoridine (**157**)	216
A. undulata (New Caledonia)	Leaves	Cabucraline (**137**)	218
		Cathafoline (**35**)	218
		Deformylundulatine (**440**)	218
		Pericyclivine (**196**)	218
		Tetrahydroalstonine (**331**)	218
		Vincorine (**41**)	218
	Root bark	11-Methoxyakuammicine (**67**)	218
		11-Methoxyakuammicine *N*-oxide (**68**)	218
		Alstonisidine (**442**)	218
		Cabucraline (**137**)	218
		Cabucraline *N*-oxide (**138**)	218
		Deplancheine (**212**)	218
		Desoxycabufiline (**435**)	218
		Fluorocarpamine (**63**)	218
		Gentiacraline (**145**)	218
		Pleiocarpamine (**59**)	218
		Plumocraline (**438**)	218
		Tetrahydroalstonine (**331**)	218
		Vincamedine (**234**)	218
A. venenata (India)	Leaves	11-Methoxyechitovenedine (**320**)	219
		11-Methoxyechitoveniline (**324**)	219
		19,20-Dihydropolyneuridine (**207**)	220

Table 1.4, continued…

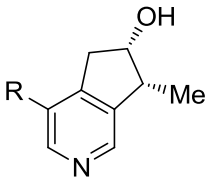
Species	Plant part	Alkaloids	Ref.
		Alstolenine (**155**)	220
		Deacetylakuammiline (**156**)	220
		Echitoveniline (**325**)	219
		Polyneuridine (**206**)	220
		Raucaffrinoline (**239**)	220
	Fruit	(+)-Minovincinine (**319**)	221
		11-Methoxyechitovenedine (**320**)	219
		11-Methoxyechitoveniline (**324**)	219
		Echitoserpine (**322**)	222
		Echitoserpidine (**323**)	223
		Echitovenedine (**321**)	221
		Echitoveniline (**325**)	219
		Venoterpine (**91**)	224
	Root bark	16-*Epi*alstovenine (**339**)	225
		16-*Epi*venenatine (**340**)	225
		5,22-Dioxokopsane (**326**)	225
		Alstovenine (**341**)	225
		Isovenenatine (**338**)	225
		Venenatine (**342**)	225,226
		Venoxidine (**343**)	225
A. villosa (Indonesia)	Leaves	10-Methoxy-*N*(1)-methylburnamine-17-*O*-benzoate (**172**)	227
		10-Methoxy-*N*(1)-methylburnamine-17-*O*-veratrate (**173**)	227
		11-Methoxy-19,20α-epoxyakuammicine (alstolagumine) (**288**)	227
		17-Deacetyl-5α,10-dimethoxyakuammiline-17-*O*-3',4',5'-trimethoxybenzoate (**152**)	227
		17-Deacetyl-5α,10-dimethoxyakuammiline-17-*O*-benzoate (**153**)	227
		19*Z*-16-Formyl-5α-methoxystrictamine (**146**)	227
		19*Z*-5α-Methoxyrhazimine (**400**)	227
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxy-benzoate (**192**)	227
		19*Z*-Picralinal (**193**)	227
		5α,10,11-Trimethoxystrictamine (**148**)	227
		5α,10-Dimethoxystrictamine (**149**)	227
		*Nor*quaternine (10,11-dimethoxypicrinine, volkensine) (**170**)	227

Table 1.4, continued…

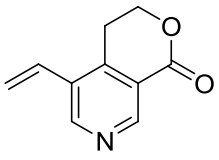
Species	Plant part	Alkaloids	Ref.
		Quaternine (10,11-dimethoxy-*N*(1)-methyl-picrinine) (**46**)	227
		Vincamajine (**54**)	227
		Vincamajine-17-*O*-3',4',5'-trimethoxy-benzoate (**226**)	227
		Vincamajine-17-*O*-3',4',5'-trimethoxy-benzoate *N*-oxide (**227**)	227
		Yohimbine-17-*O*-acetate (*O*-Acetyl-yohimbine) (**335**)	227
A. vitiensis var. *novo ebudica monachino* (New Caledonia)	Stem	11-Methoxycompactinervine (alstovine) (**284**)	228
		Cabucraline (**137**)	228
		Pleiocarpamine (**59**)	228
		Quaternoxine (**141**)	228
		Vincorine (**41**)	228
A. yunnanensis (Kunming, Yunnan Province, People's Republic of China)	Whole plant	(–)-Echitoveniline (**325**)	229
		11-Methoxytabersonine (**310**)	229
		19-Acetoxy-11-methoxytabersonine (**311**)	229
		19-*Epi*-ajmalicine (**329**)	229
		19*Z*-Burnamine-17-*O*-3',4',5'-trimethoxy-benzoate (**192**)	229
		Alloyohimbine (**336**)	229
		Alstoyunines A (**209**)	229
		Alstoyunines B (**210**)	229
		Alstoyunines C (**241**)	229
		Alstoyunines D (**242**)	229
		Alstoyunines E (**236**)	229
		Alstoyunines F (**235**)	229
		Alstoyunines G (**312**)	229
		Alstoyunines H (**315**)	229
		Compactinervine (**287**)	229
		Echitoserpidine (**323**)	229
		Lochnerinine (**314**)	229
		Perakine (**243**)	229
		Picraline (**178**)	229
		Picrinine (**47**)	229
		Raucaffrinoline (**239**)	229
		Tabersonine (**317**)	229
		Vellosimine (**204**)	229
		Vellosiminol (**205**)	229
		Vinorine (**237**)	229

Table 1.4, continued…

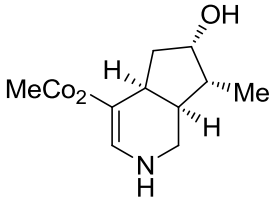
Species	Plant part	Alkaloids	Ref.
A. yunnanensis	Whole plant	11-Hydroxy-6,7-epoxy-8-oxo-vincadifformine (**313**)	230
Chuxiong, Yunnan		14-chloro-15-hydroxyvincadifformine (**316**)	230
Province, China		Perakine *N*(4)-oxide (**244**)	230
		Raucaffrinoline *N*(4)-oxide (**240**)	230
		Vinorine *N*(1), *N*(4)-dioxide (**238**)	230
		11-Methoxy-6,7-epoxy-8-oxo-vincadifformine (Alstoyunine G) (**312**)	230
		Vinorine *N*(4)-oxide (Alstoyunine E) (**236**)	230



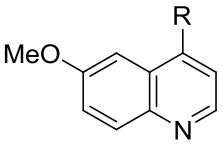
91 R = H
92 R = CO_2Me



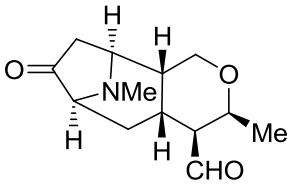
93



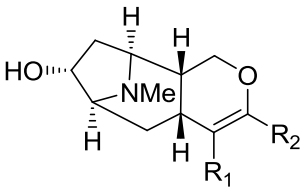
94



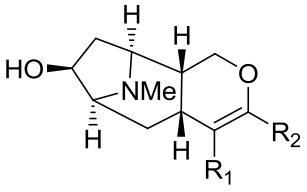
95 R = Me
96 R = CH(Me)OH



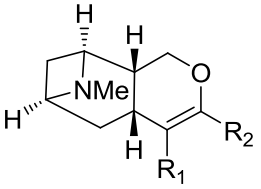
97



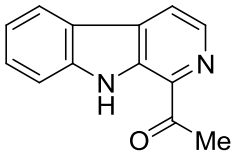
98 R_1 = COMe, R_2 = H
99 R_1 = CHO, R_2 = Me



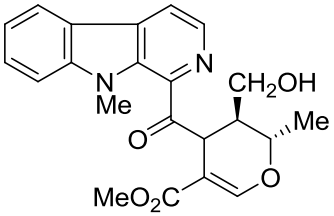
100 R_1 = CHO, R_2 = Me
101 R_1 = COMe, R_2 = H



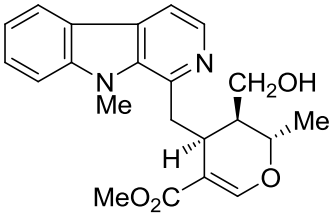
102 R_1 = CHO, R_2 = Me
103 R_1 = COMe, R_2 = H



104



105



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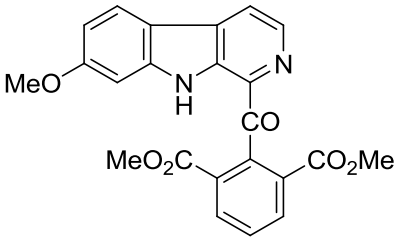
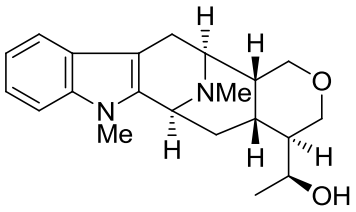


107



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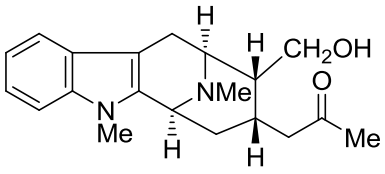

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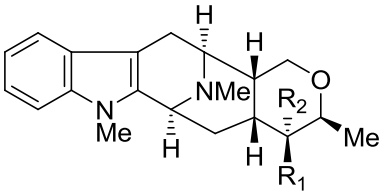
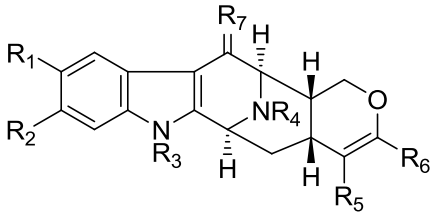
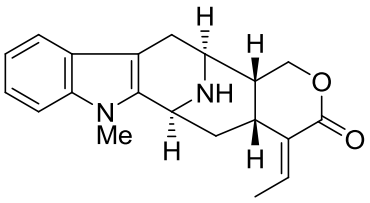


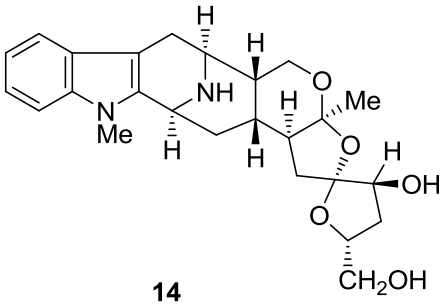
9 R_1 = CH_2OH, R_2 = H
10 R_1 = H, R_2 = CH_2OH
11 R_1 = H, R_2 = CH_2OAc
12 R_1 = CHO, R_2 = H
13 R_1 = H, R_2 = CHO
110 R_1 = CH_2OH, R_2 = OH



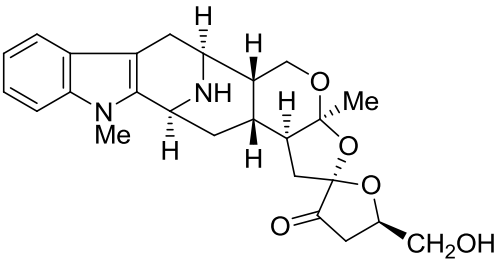


118

5 R_1 = H, R_2 = H, R_3 = Me, R_4 = Me, R_5 = COMe, R_6 = H, R_7 = H,H
6 R_1 = H, R_2 = H, R_3 = Me, R_4 = Me, R_5 = CHO, R_6 = Me, R_7 = H,H
7 R_1 = H, R_2 = OMe, R_3 = Me, R_4 = Me, R_5 = COMe, R_6 = H, R_7 = H,H
8 R_1 = H, R_2 = OMe, R_3 = Me, R_4 = Me, R_5 = CHO, R_6 = Me, R_7 = H,H
111 R_1 = OMe, R_2 = H, R_3 = Me, R_4 = Me, R_5 = CHO, R_6 = Me, R_7 = H,H
112 R_1 = H, R_2 = H, R_3 = Me, R_4 = H, R_5 = COMe, R_6 = H, R_7 = H,H
113 R_1 = H, R_2 = H, R_3 = Me, R_4 = H, R_5 = CHO, R_6 = Me, R_7 = H,H
114 R_1 = H, R_2 = OMe, R_3 = Me, R_4 = Me, R_5 = COMe, R_6 = H, R_7 = O
115 R_1 = H, R_2 = OMe, R_3 = Me, R_4 = Me, R_5 = CHO, R_6 = Me, R_7 = O
116 R_1 = H, R_2 = OMe, R_3 = H, R_4 = Me, R_5 = COMe, R_6 = H, R_7 = H,H
117 R_1 = H, R_2 = OMe, R_3 = H, R_4 = Me, R_5 = CHO, R_6 = Me, R_7 = H,H



14



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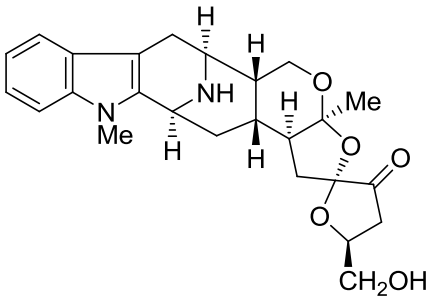
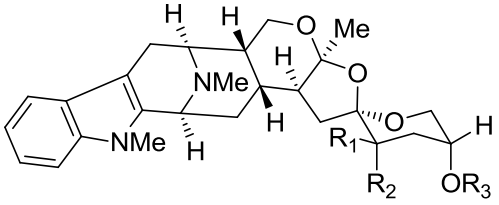
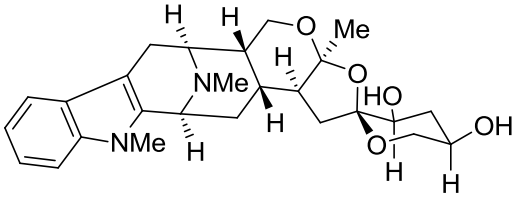


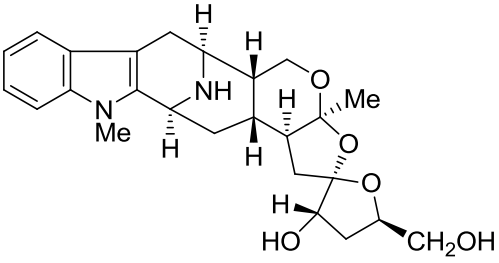
120



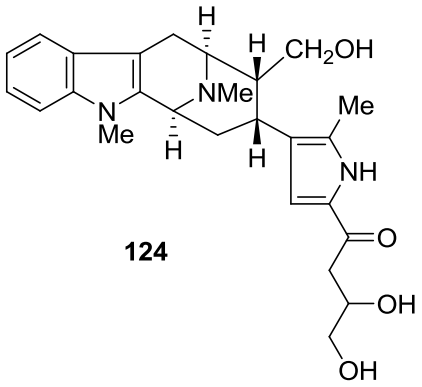
121 R_1 = OH, R_2 = H, R_3 = H
122 R_1 = H, R_2 = OH, R_3 = H



123



15



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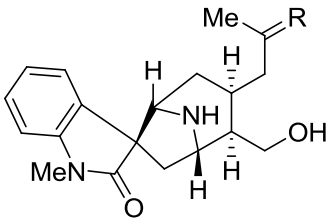
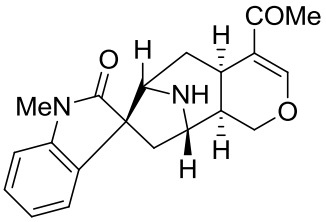
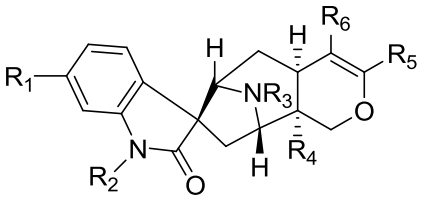


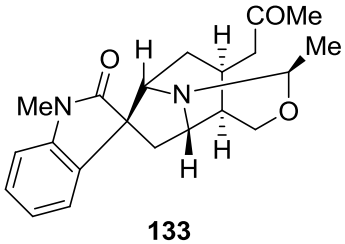
18 R = O
19 R = H, OH



125



20 R_1 = H, R_2 = Me, R_3 = H, R_4 = H, R_5 = H, R_6 = COMe
21 R_1 = H, R_2 = Me, R_3 = H, R_4 = H, R_5 = Me, R_6 = CHO
22 R_1 = OMe, R_2 = Me, R_3 = H, R_4 = H, R_5 = H, R_6 = COMe
23 R_1 = OMe, R_2 = Me, R_3 = H, R_4 = H, R_5 = Me, R_6 = CHO
126 R_1 = H, R_2 = Me, R_3 = CHO, R_4 = H, R_5 = H, R_6 =COMe
127 R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = COMe
128 R_1 = H, R_2 = H, R_3 = H, R_4 = H, R_5 = Me, R_6 = CHO
129 R_1 = H, R_2 = Me, R_3 = H, R_4 = OH, R_5 = H, R_6 = COMe
130 R_1 = H, R_2 = Me, R_3 = H, R_4 = OH, R_5 = Me, R_6 = CHO
131 R_1 = OMe, R_2 = Me, R_3 = H, R_4 = OH, R_5 = Me, R_6 = CHO
132 R_1 = OMe, R_2 = Me, R_3 = H, R_4 = OH, R_5 = H, R_6 = COMe



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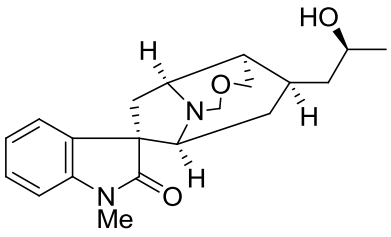

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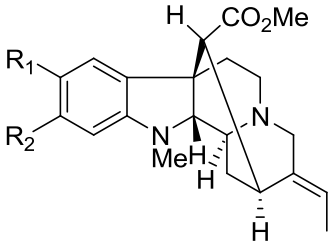
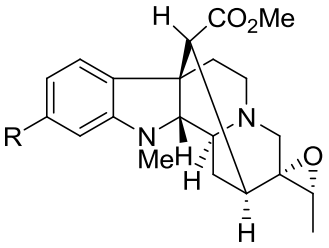
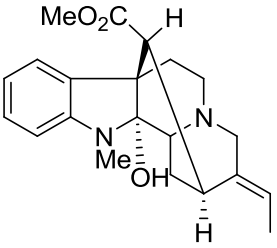


35 R_1 = H, R_2 = H
36 R_1 = H, R_2 = H, N(4)→O
37 R_1 = OMe, R_2 = H
135 R_1 = OMe, R_2 = H, N(4)→O
136 R_1 = CHO, R_2 = OMe
137 R_1 = H, R_2 = OMe
138 R_1 = H, R_2 = OMe, N(4)→O
139 R_1 = H, R_2 = H



140 R = OMe
141 R = H



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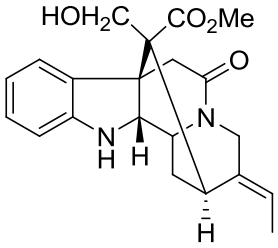

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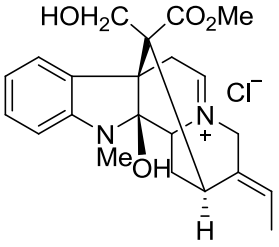

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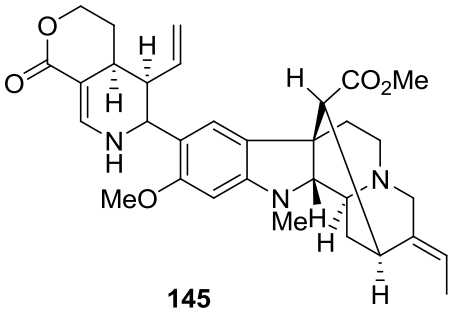

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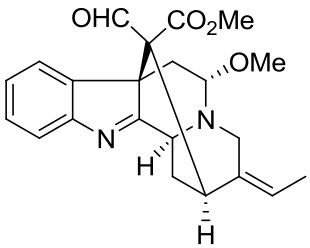
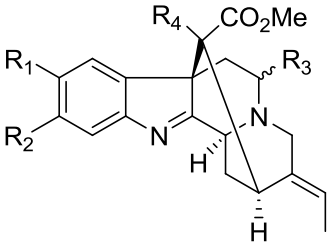
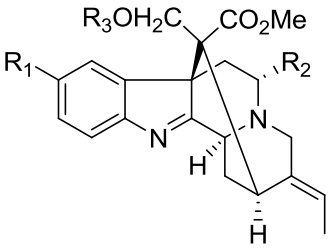


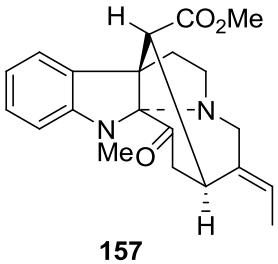
146



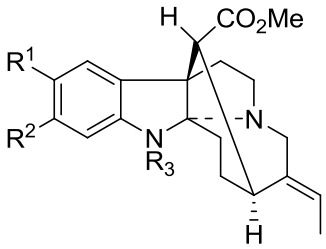
38 R_1 = H, R_2 = H, R_3 = H, R_4 = H
39 R_1 = H, R_2 = OMe, R_3 = H, R_4 = H
40 R_1 = H, R_2 = OH, R_3 = H, R_4 = H
147 R_1 = OH, R_2 = H, R_3 = H, R_4 = H
148 R_1 = OMe, R_2 = OMe, R_3 = α-OMe, R_4 = H
149 R_1 = OMe, R_2 = H, R_3 = α-OMe, R_4 = H
150 R_1 = H, R_2 = H, R_3 = H, R_4 = OH
151 R_1 = H, R_2 = H, R_3 = β-OMe, R_4 = H



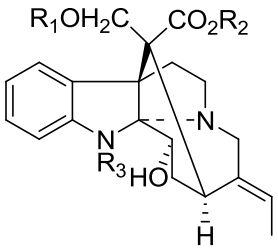
152 R_1 = OMe, R_2 = OMe, R_3 = 3',4',5'-trimethoxybenzoate
153 R_1 = OMe, R_2 = OMe, R_3 = benzoate
154 R_1 = H, R_2 = H, R_3 = acetyl
155 R_1 = H, R_2 = H, R_3 = 3',4',5'-trimethoxybenzoate
156 R_1 = H, R_2 = H, R_3 = H



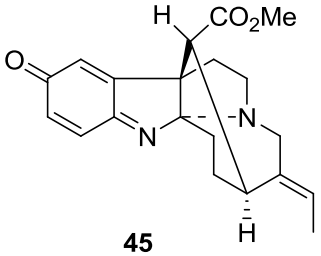
157



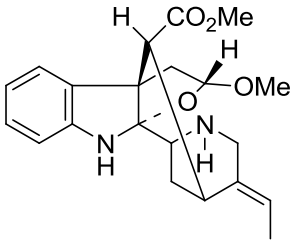
41 R_1 = OMe, R_2 = H, R_3 = Me
43 R_1 = OMe, R_2 = OMe, R_3 = CHO
44 R_1 = OMe, R_2 = H, R_3 = CHO



158 R_1 = H, R_2 = Me, R_3 = H
159 R_1 = Ac, R_2 = Me, R_3 = H
160 R_1 = Ac, R_2 = Me, R_3 = H, N(4)-Me
161 R_1 = H, R_2 = Me, R_3 = H, N(4)-Me
162 R_1 = H, R_2 = H, R_3 = H, N(4)-Me
163 R_1 = H, R_2 = Me, R_3 = H, N(4)→O
164 R_1 = Ac, R_2 = Me, R_3 = Me



45



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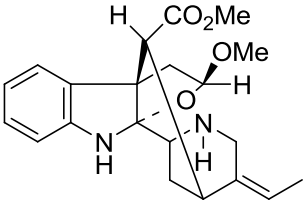
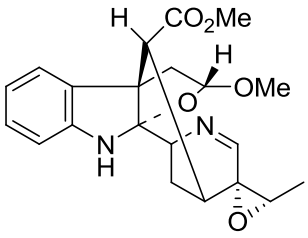
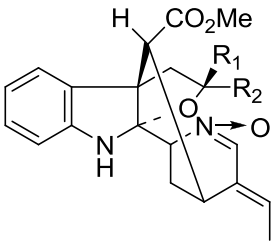


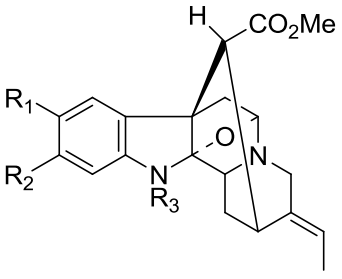
166



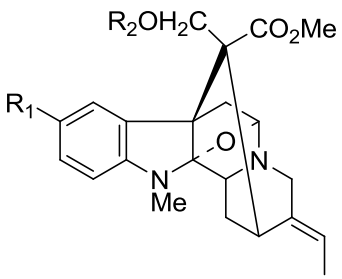
167



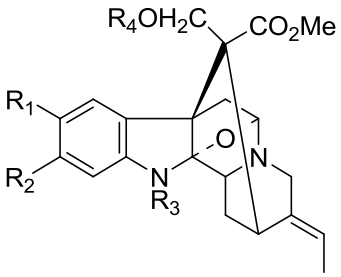
168 R_1 = H, R_2 = OMe
169 R_1 = OMe, R_2 = H



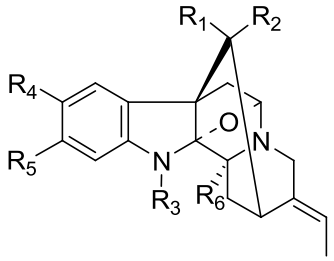
46 R_1 = OMe, R_2 = OMe, R_3 = Me
47 R_1 = H, R_2 = H, R_3 = H
170 R_1 = OMe, R_2 = OMe, R_3 = H
171 R_1 = H, R_2 = H, R_3 = CH_2OMe



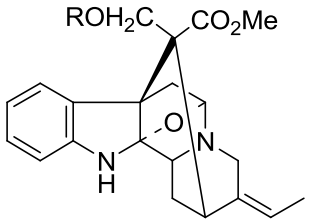
172 R_1 = OMe, R_2 = Benzoate
173 R_1 = OMe, R_2 = Veratrate
174 R_1 = H, R_2 = H
175 R_1 = H, R_2 = Benzoate
176 R_1 = OMe, R_2 = H



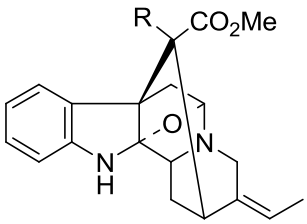
177 R_1 = OMe, R_2 = OMe, R_3 = Me, R_4 = 3',4',5'-trimethoxybenzoate
178 R_1 = H, R_2 = H, R_3 = H, R_4 = acetyl
179 R_1 = OMe, R_2 = OMe, R_3 = Me, R_4 = H
180 R_1 = OMe, R_2 = OMe, R_3 = Me, R_4 = benzoate
181 R_1 = OMe, R_2 = OMe, R_3 = Me, R_4 = acetyl
182 R_1 = OMe, R_2 = H, R_3 = Me, R_4 = 3',4'-dimethoxybenzoate, N(4)-Me
183 R_1 = OMe, R_2 = H, R_3 = Me, R_4 = 3',4',5'-trimethoxybenzoate, N(4)-Me
184 R_1 = OMe, R_2 = H, R_3 = Me, R_4 = 3',4',5'-trimethoxybenzoate
185 R_1 = H, R_2 = H, R_3 = H, R_4 = 3',4'-dimethoxybenzoate
186 R_1 = OMe, R_2 = H, R_3 = H, R_4 = 3',4',5'-trimethoxybenzoate



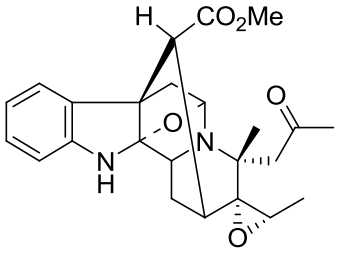
188 R_1 = H, R_2 = CO_2Me, R_3 = Me, R_4 = OMe, R_5 = OMe, R_6 = H
189 R_1 = CHO, R_2 = CO_2Me, R_3 = H, R_4 = H, R_5 = H, R_6 = H
190 R_1 = CO_2Me, R_2 = H, R_3 = H, R_4 = H, R_5 = H, R_6 = H
191 R_1 = H, R_2 = CO_2Me, R_3 = H, R_4 = H, R_5 = H, R_6 = OMe



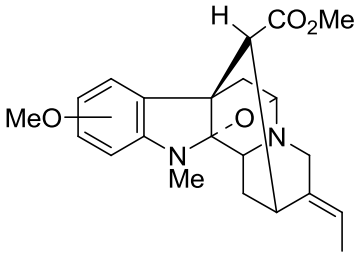
192
R = 3',4',5'-trimethoxybenzoate



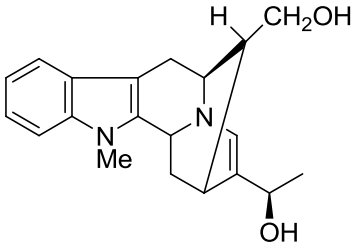
193 R = CHO
194 R = CH_2OH



195



187



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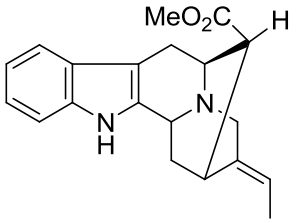

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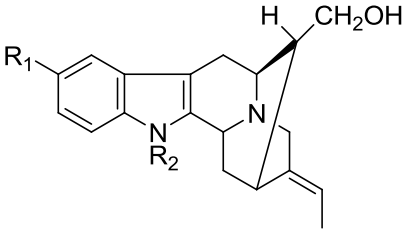
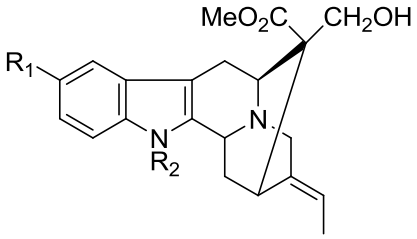
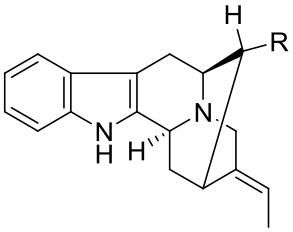


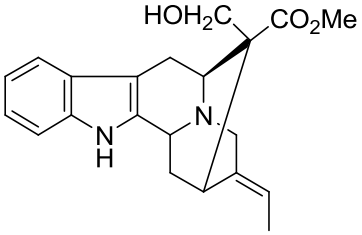
49 R_1 = H, R_2 = Me
51 R_1 = H, R_2 = H
197 R_1 = OH, R_2 = H
198 R_1 = OMe, R_2 = Me
199 R_1 = OMe, R_2 = H



200 R_1 = H, R_2 = H
201 R_1 = OMe, R_2 = Me
202 R_1 = H, R_2 = H, N(4)→Me
203 R_1 = H, R_2 = H, N(4)→O



204 R = CHO
205 R = CH_2OH



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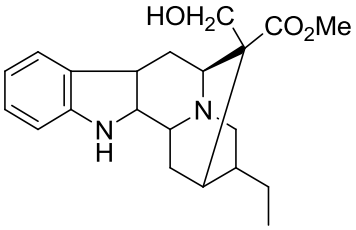

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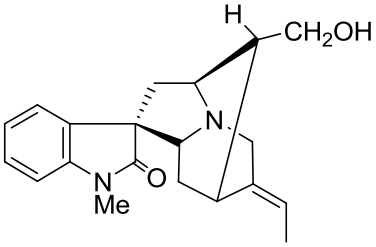
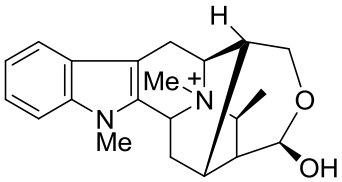


50



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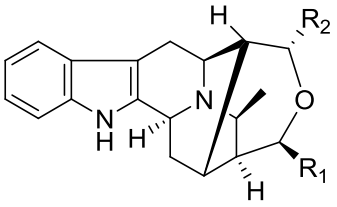
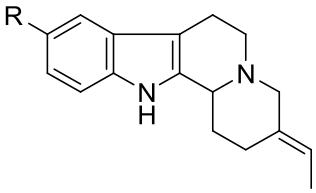
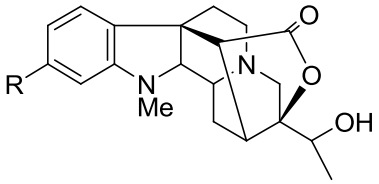


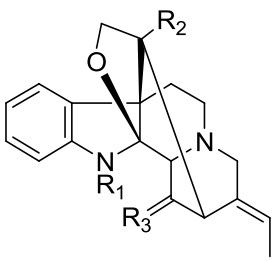
209 R_1 = OMe, R_2 = OH
210 R_1 = OH, R_2 = OMe



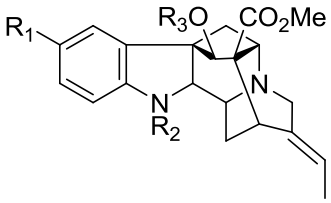
211 R = OMe
212 R = H

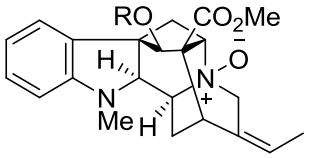


213 R = OMe
214 R = H



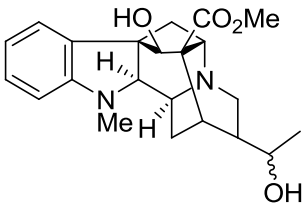
215 R_1 = Me, R_2 = CO_2Me, R_3 = H,H
216 R_1 = Me, R_2 = CO_2Me, R_3 = H,H, N(4→O
217 R_1 = H, R_2 = COO^-, R_3 = O





229 R = Ac
230 R = H

53 R_1 = H, R_2 = H, R_3 = H
54 R_1 = H, R_2 = Me, R_3 = H
55 R_1 = H, R_2 = Me, R_3 = Veratrate
218 R_1 = OMe, R_2 = Me, R_3 = H
219 R_1 = H, R_2 = Me, R_3 = 4'-OH-3',5'-trimethoxybenzoyl
220 R_1 = H, R_2 = H, R_3 = 3',4',5'-trimethoxybenzoyl
221 R_1 = H, R_2 = Me, R_3 = 3',4',5'-trimethoxycinnamoyl
222 R_1 = H, R_2 = Me, R_3 = Benzoyl
223 R_1 = OH, R_2 = Me, R_3 = Trimethoxybenzoyl
224 R_1 = OH, R_2 = Me, R_3 = Trimethoxycinnamoyl
225 R_1 = OMe, R_2 = Me, R_3 = Trimethoxycinnamoyl
226 R_1 = H, R_2 = Me, R_3 = 3',4',5'-trimethoxybenzoate
227 R_1 = H, R_2 = Me, R_3 = 3',4',5'-trimethoxybenzoate, N(4)→O
228 R_1 = H, R_2 = Tri-O-methylgallate, R_3 = H



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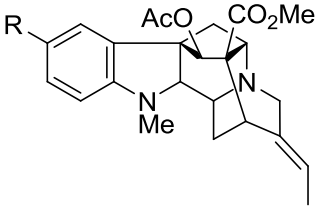
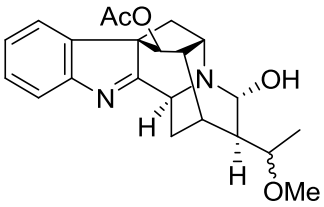


232 R = OMe
233 R = OMe, N(4)→O
234 R = H



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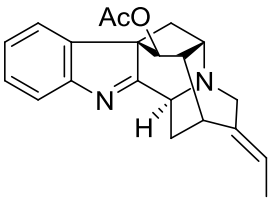
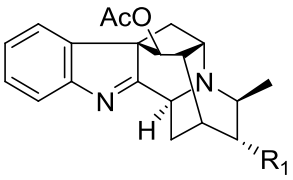
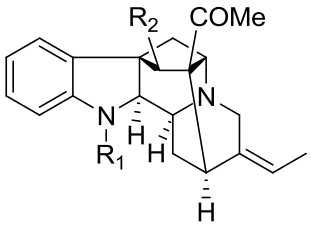
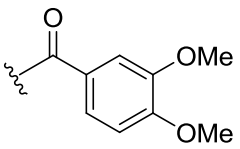


236 N(4)→O
237
238 N(1)→O, N(4)→O

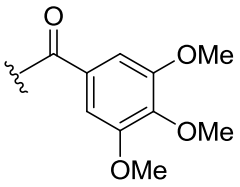


239 R = CH_2OH
240 R = CH_2OH, N(4)→O
241 R = COOH, N(4)→O
242 R = COOH, N(1)→O, N(4)→O
243 R = CHO
244 R = CHO, N(4)→O



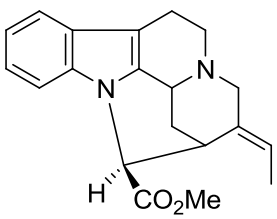


veratroyl



eudesmoyl

245 R_1 = veratroyl, R_2 = OAc
246 R_1 = eudesmoyl, R_2 = OAc
247 R_1 = Bz, R_2 = OAc
248 R_1 = veratroyl, R_2 = OH
249 R_1 = eudesmoyl, R_2 = OH
250 R_1 = Bz, R_2 = OH
251 R_1 = eudesmoyl, R_2 = OH



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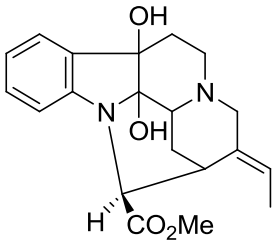

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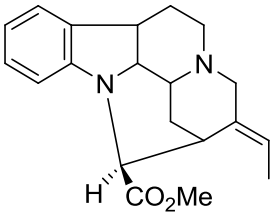

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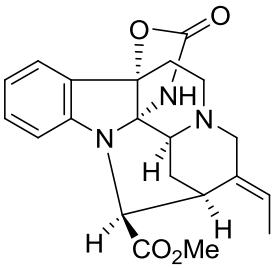
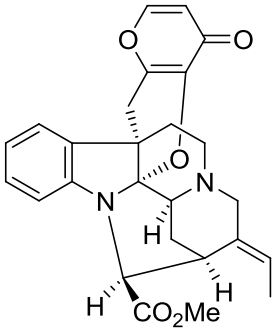


254



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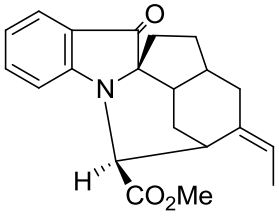

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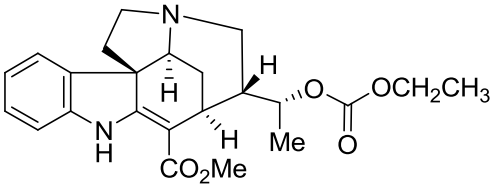

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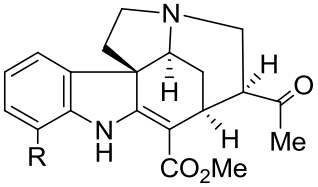
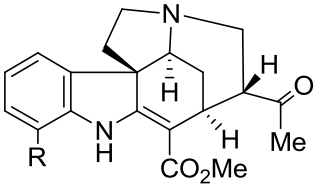
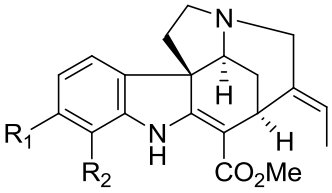


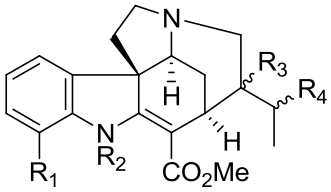
256 R = H
257 R = H, N(4)→O
258 R = OH
259 R = OMe



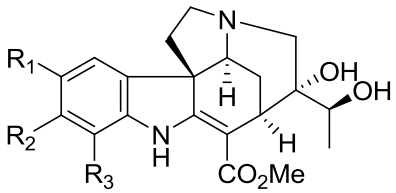
260 R = OH
261 R = H



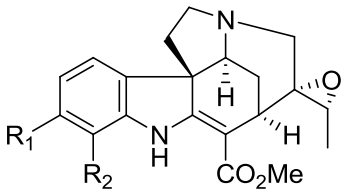
67 R_1 = OMe, R_2 = H
68 R_1 = OMe, R_2 = H, N(4)→O
262 R_1 = H, R_2 = H
263 R_1 = H, R_2 = OH
264 R_1 = H, R_2 = OMe
265 R_1 = H, R_2 = OMe, N(4)-Me
266 R_1 = H, R_2 = H, N(4)→MeI
267 R_1 = H, R_2 = H, N(4)→O



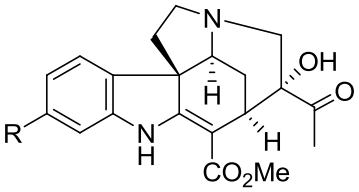
268 R_1 = OMe, R_2 = H, R_3 = β-H, R_4 = α-OH
269 R_1 = OH, R_2 = H, R_3 = α-H, R_4 = β-OH
270 R_1 = H, R_2 = H, R_3 = α-H, R_4 = β-OH
271 R_1 = H, R_2 = H, R_3 = β-H, R_4 = β-OH, N(4)-Me
272 R_1 = OH, R_2 = H, R_3 = β-H, R_4 = α-OH
273 R_1 = H, R_2 = H, R_3 = β-H, R_4 = β-OH
274 R_1 = H, R_2 = H, R_3 = β-H, R_4 = α-OH, N(4)-Me
275 R_1 = H, R_2 = CHO, R_3 = α-H, R_4 = β-OH
276 R_1 = H, R_2 = H, R_3 = β-H, R_4 = α-OH
277 R_1 = H, R_2 = H, R_3 = β-H, R_4 = α-OH, N(4)→O
278 R_1 = OH, R_2 = H, R_3 = α-H, R_4 = β-OH, N(4)-Me
279 R_1 = OMe, R_2 = H, R_3 = α-H, R_4 = β-OH
280 R_1 = OMe, R_2 = H, R_3 = α-H, R_4 = β-OH, N(4)→O
281 R_1 = H, R_2 = H, R_3 = α-H, R_4 = β-OH, N(4)→O
282 R_1 = H, R_2 = H, R_3 = α-H, R_4 = β-O-D-glucopyranoside, N(4)→O
283 R_1 = H, R_2 = H, R_3 = H, R_4 = H



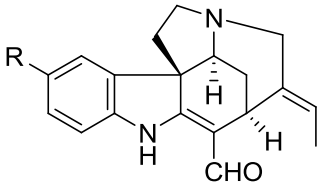
284 R_1 = H, R_2 = OMe, R_3 = H
285 R_1 = OMe, R_2 = H, R_3 = H
286 R_1 = H, R_2 = H, R_3 = OMe
287 R_1 = H, R_2 = H, R_3 = H



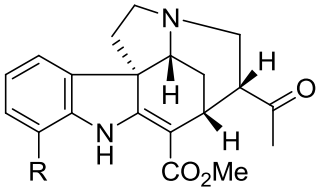
288 R_1 = OMe, R_2 = H
289 R_1 = H, R_2 = OMe



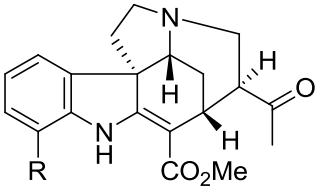
290 R = H
291 R = OMe



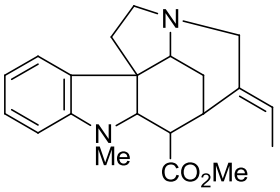
292 R = H
293 R = OMe



294 R = OH, N(4)→O
295 R = OH
296 R = H, N(4)→O



297 R = OH
298 R = H



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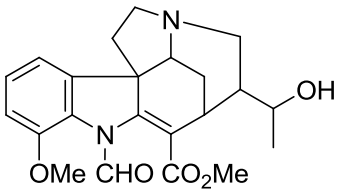

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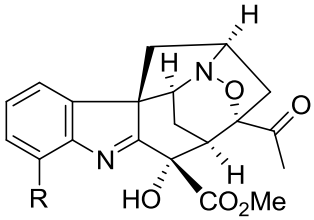
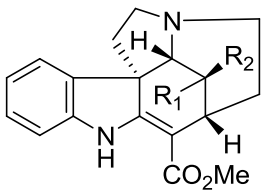
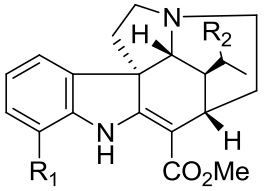


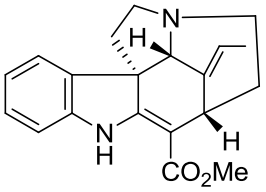
301 R = OH
302 R = H



303 R_1 = Et, R_2 = H
304 R_1 = H,R_2 = Et
305 R_1 = H, R_2 = Et, N(4)→O



306 R_1 = OMe, R_2 = H
307 R_1 = H, R_2 = OH



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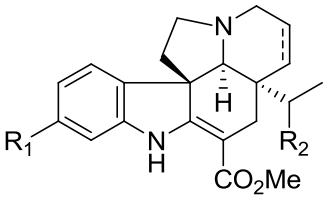
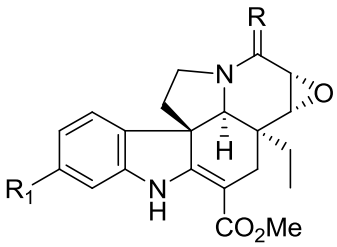
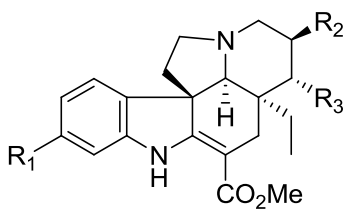


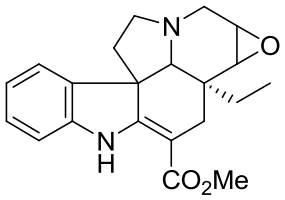
309 R_1 = H, R_2 = H
310 R_1 = OMe, R_2 = H, $\Delta^{14,15}$
311 R_1 = OMe, R_2 = OAc, $\Delta^{14,15}$



312 R_1 = OMe, R_2 = O
313 R_1 = OH, R_2 = O
314 R_1 = OMe, R_2 = H,H



315 R_1 = OMe, R_2 = Cl, R_3 = OH
316 R_1 = H, R_2 = Cl, R_3 = OH
317 R_1 = H, R_2 = H, R_3 = H, $\Delta^{19,20}$



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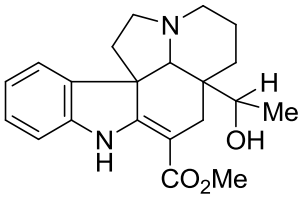

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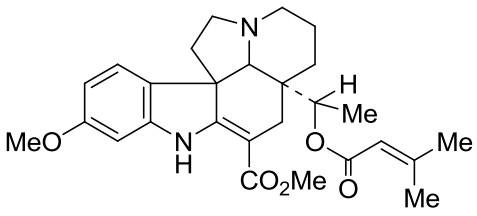

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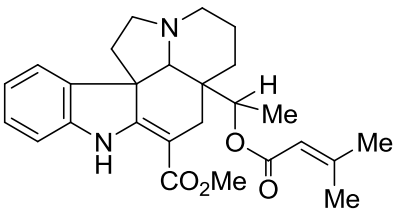

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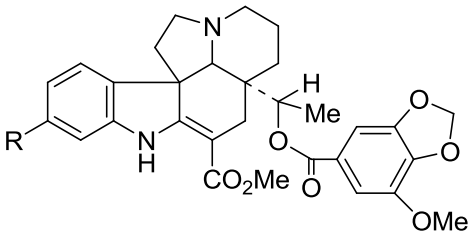
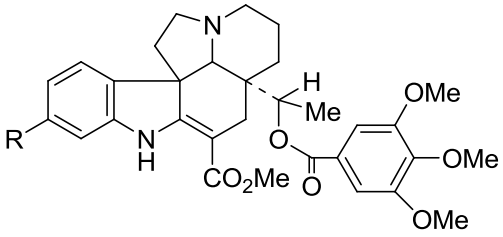
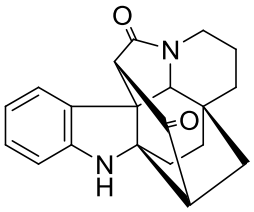


322 R = OMe
323 R = H



324 R = OMe
325 R = H



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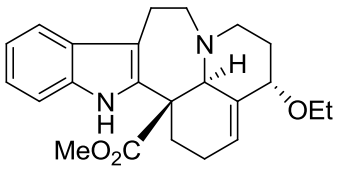

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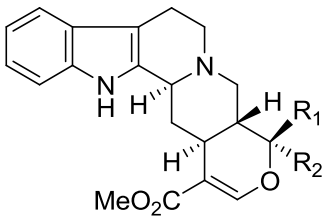
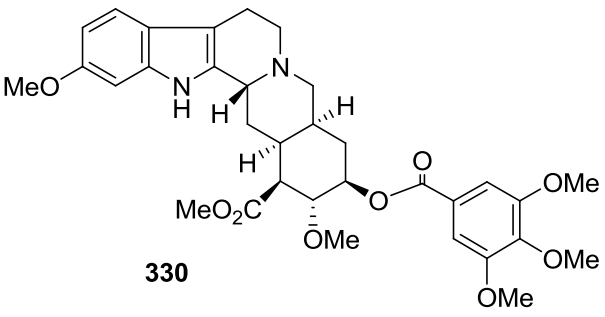


328 R_1 = H, R_2 = Me
329 R_1 = Me, R_2 = H



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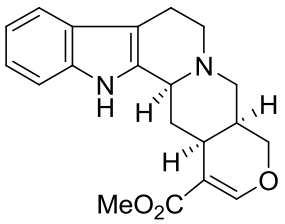

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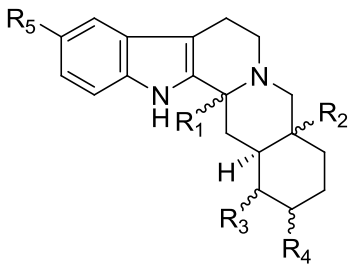
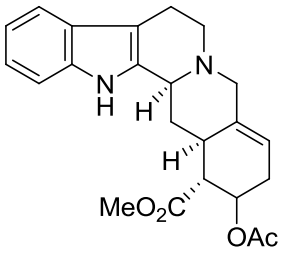


64 R_1 = α-H, R_2 = β-H, R_3 = α-CO_2Me, R_4 = α-OH, R_5 = H
332 R_1 = β-H, R_2 = α-H, R_3 = β-CO_2Me, R_4 = α-OH, R_5 = OMe
333 R_1 = β-H, R_2 = β-H, R_3 = α-CO_2Me, R_4 = α-OH, R_5 = H
334 R_1 = α-H, R_2 = α-H, R_3 = β-CO_2Me, R_4 = β-OH, R_5 = H
335 R_1 = α-H, R_2 = β-H, R_3 = α-CO_2Me, R_4 = α-OAc, R_5 = H
336 R_1 = α-H, R_2 = α-H, R_3 = α-CO_2Me, R_4 = α-OH, R_5 = H



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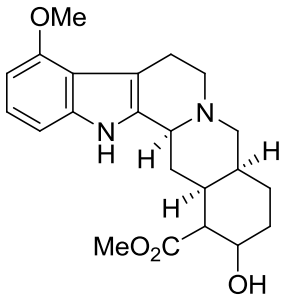

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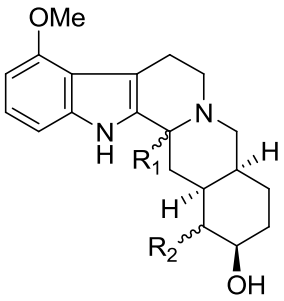
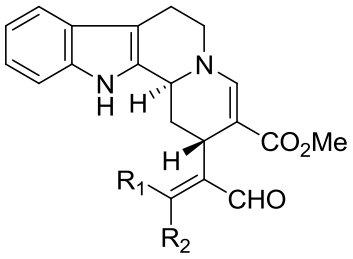
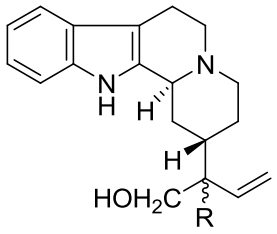


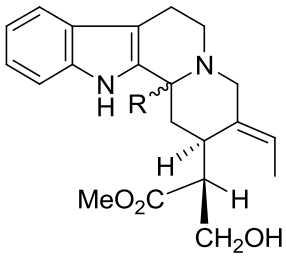
339 R_1 = α-H, R_2 = α-CO_2Me
340 R_1 = β-H, R_2 = α-CO_2Me
341 R_1 = α-H, R_2 = β-CO_2Me
342 R_1 = β-H, R_2 = β-CO_2Me
343 R_1 = β-H, R_2 = β-CO_2Me, N(4)→O



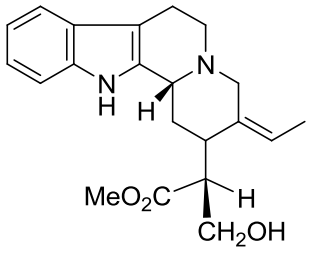
344 R_1 = H, R_2 = Me
345 R_1 = Me, R_2 = H



69 R = α-H
346 R = β-H
347 R = α-H, N(4)-Me



57 R = α-H
348 R = β-H



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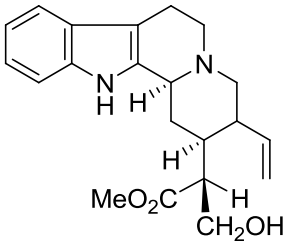
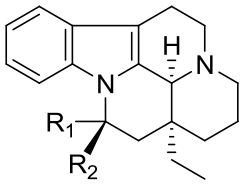
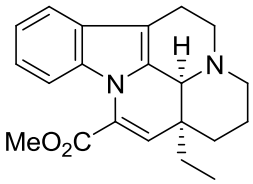


56



350 R_1 = CO_2Me, R_2 = OH
351 R_1 = OH, R_2 = CO_2Me
352 R_1 = CO_2Me, R_2 = OH, N(4)→O



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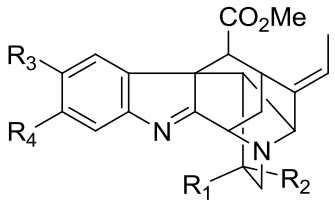
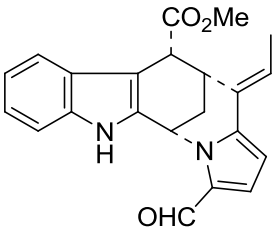


66 R_1 = OH, R_2 = H, R_3 = OMe, R_4 = OMe
354 R_1 = H, R_2 = OEt, R_3 = H, R_4 = H
355 R_1 = OH, R_2 = H, R_3 = H, R_4 = H
356 R_1 = OEt, R_2 = H, R_3 = H, R_4 = H
357 R_1 = OMe, R_2 = H, R_3 = H, R_4 = H



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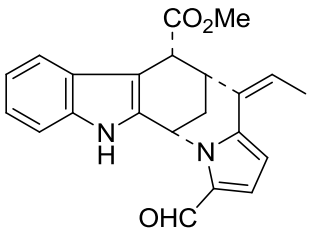

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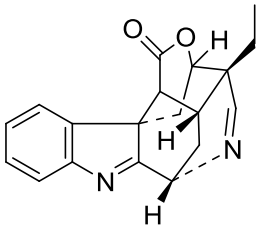

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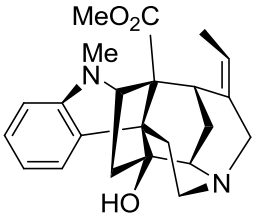
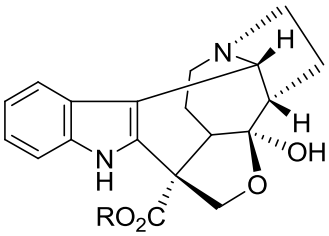
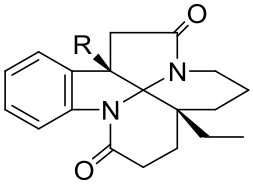


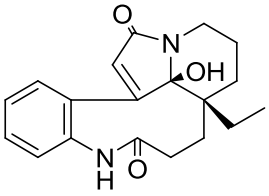
361
362 N(4)→O



363 R = H
364 R = Me



365 R = H
366 R = OH



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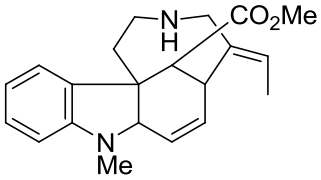
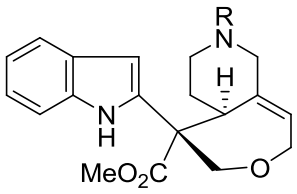
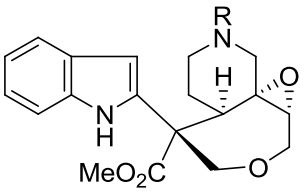


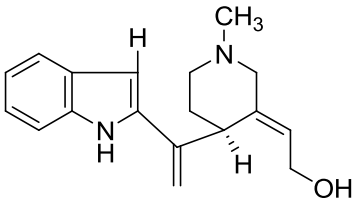
368



369 R = H
370 R = Me
371 R = Me, N(4)→O



372 R = H
373 R = Me



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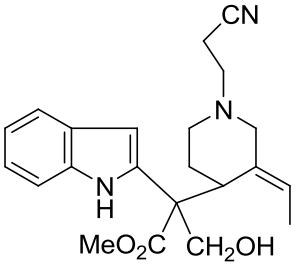

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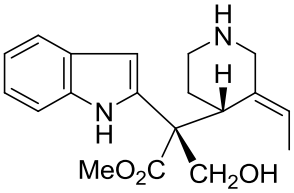

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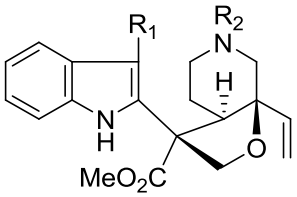
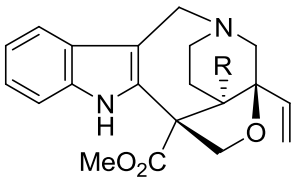
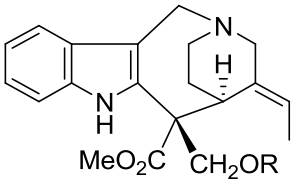


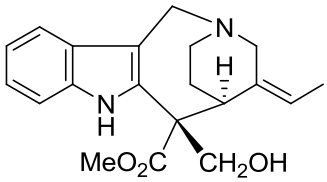
377 R_1 = H, R_2 = CO_2Et
378 R_1 = H, R_2 = H
379 R_1 = CHO, R_2 = H
380 R_1 = H, R_2 = Me



381 R = OH
382 R = H



383 R = H
384 R = Ac
385 R = H, N(4)→O



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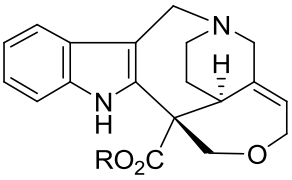
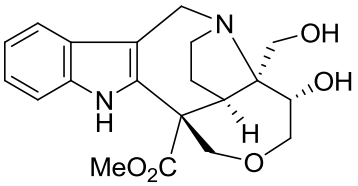


387 (–), R = Me
388 (+), R = Me
389 R = H
390 R = Me, N(4)→O
391 R = Me, N(4)→Me



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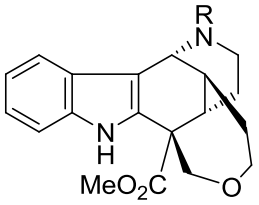
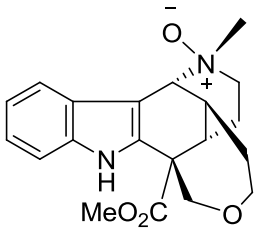


393 R = Me
394 R = H



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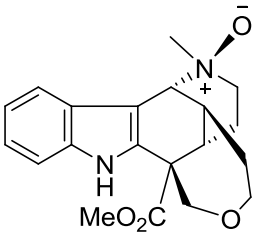

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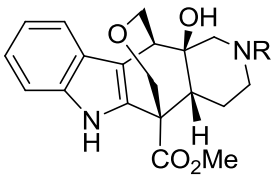
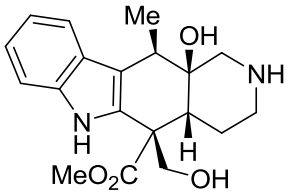


397 R = Me
398 R = H



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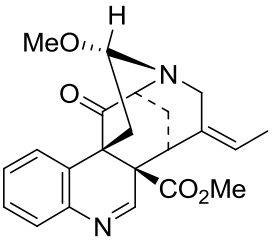

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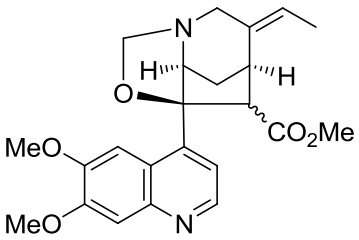

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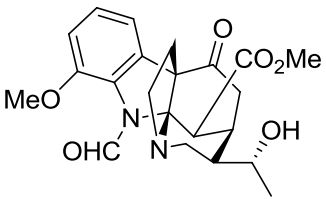

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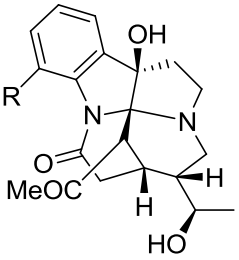
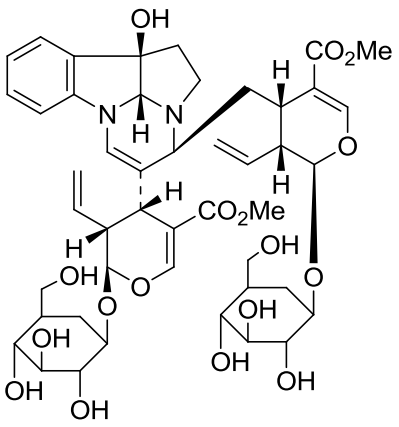


403 R = H
404 R = OMe



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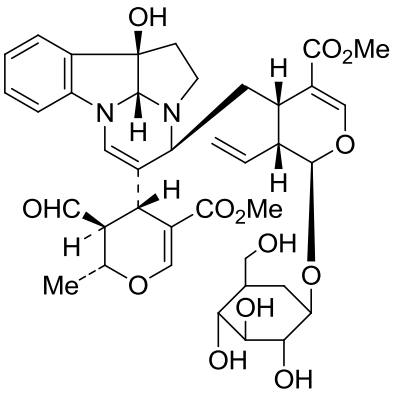

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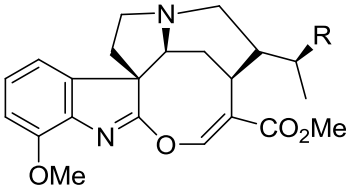
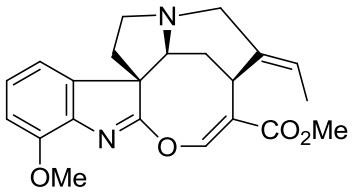


407 R = OH
408 R = O



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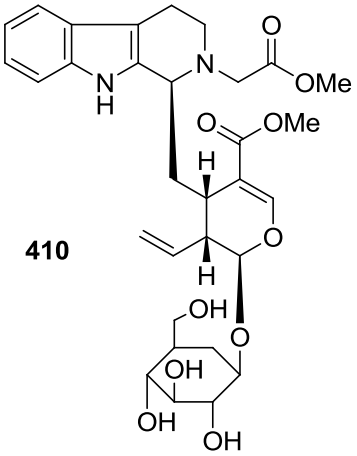

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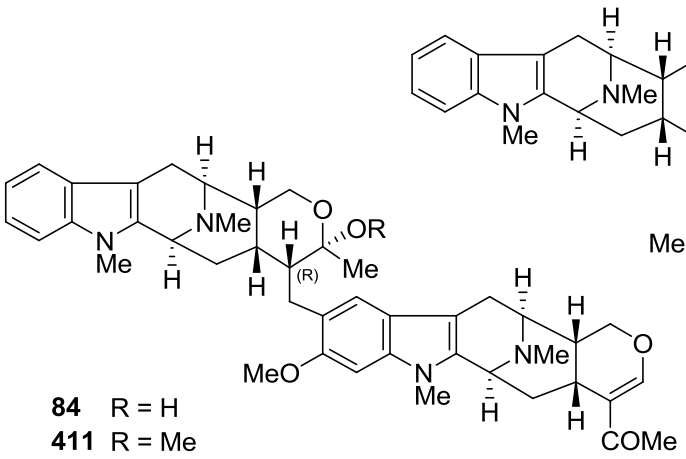
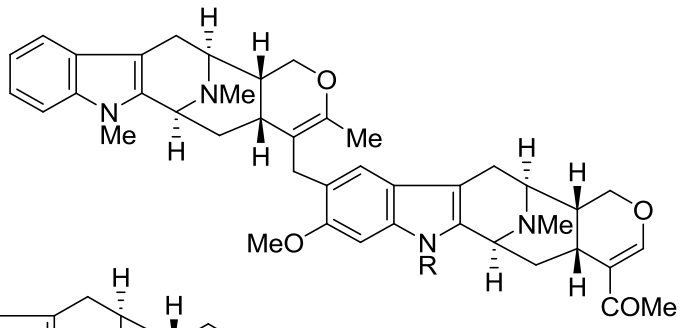
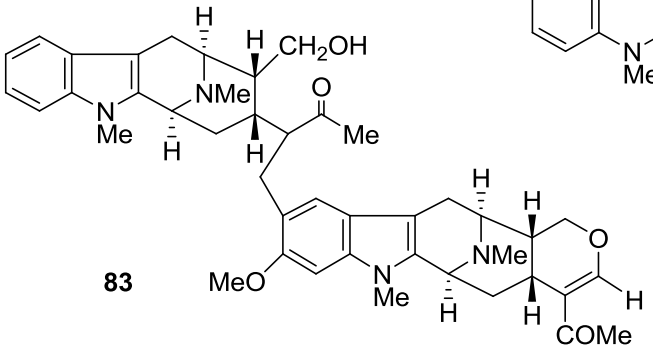


84 R = H
411 R = Me



85 R = Me
412 R = H



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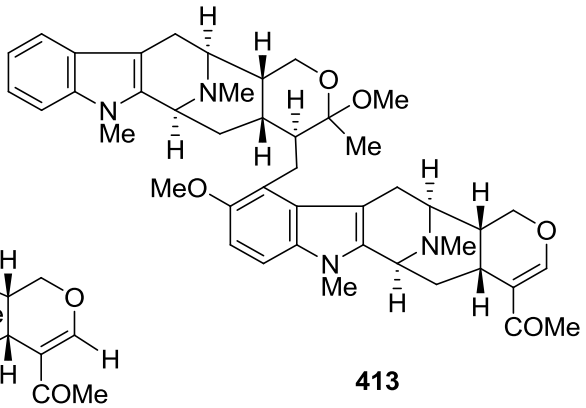

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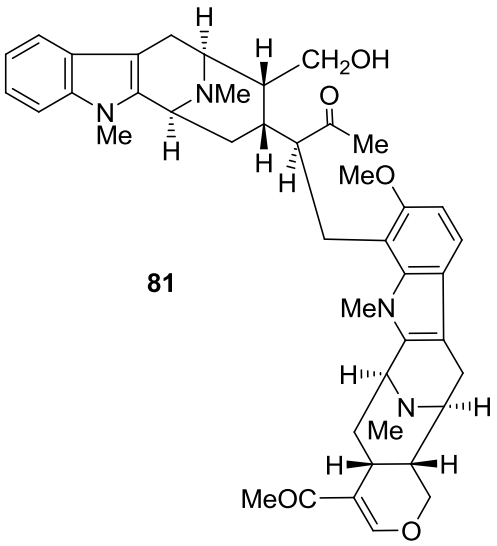

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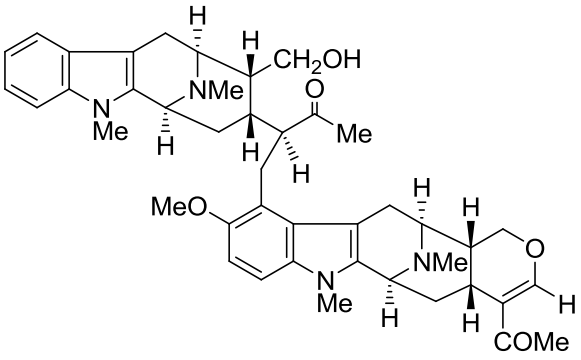

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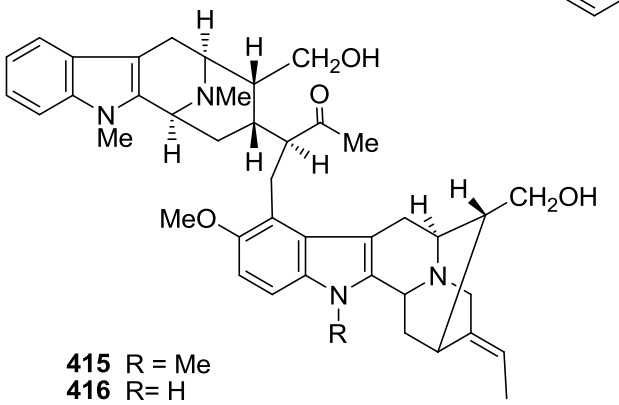
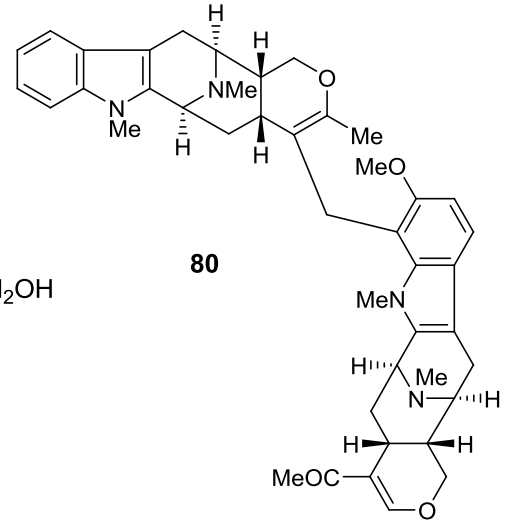


415 R = Me
416 R= H



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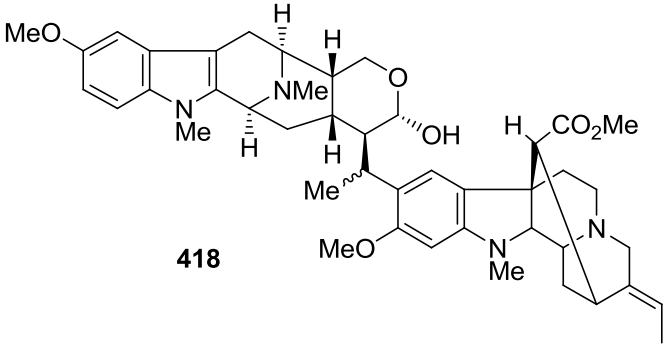

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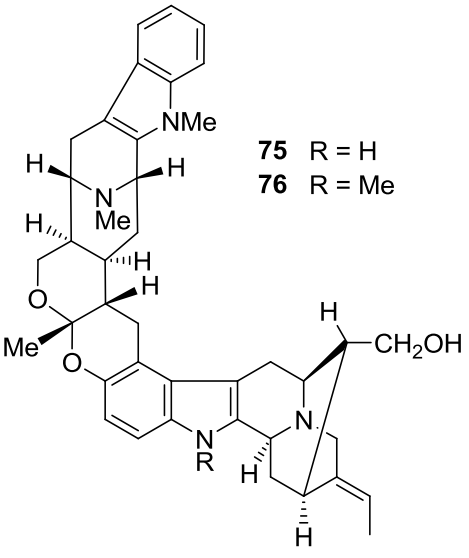
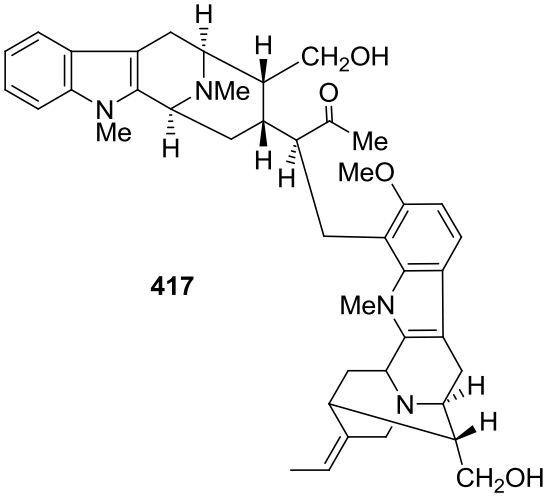


75 R = H
76 R = Me



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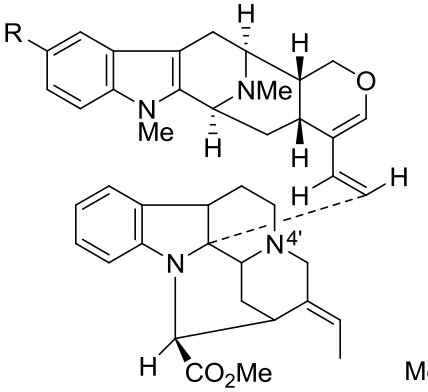
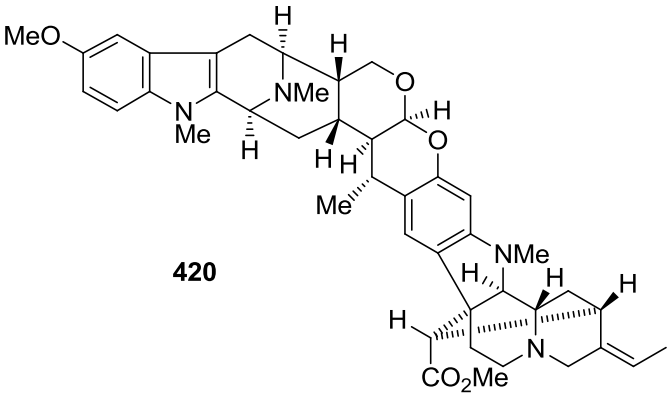


90 R = H
422 R = OMe
423 R = OMe, N(4')→O



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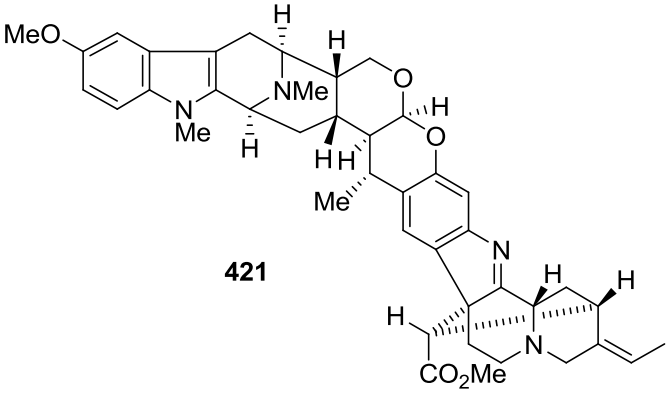

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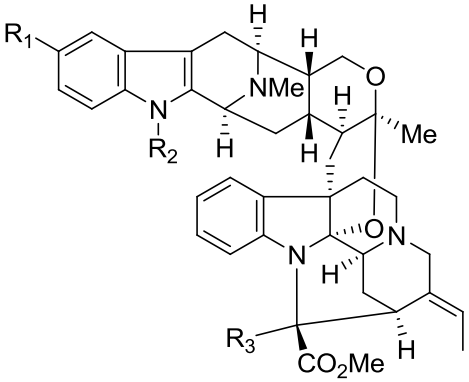
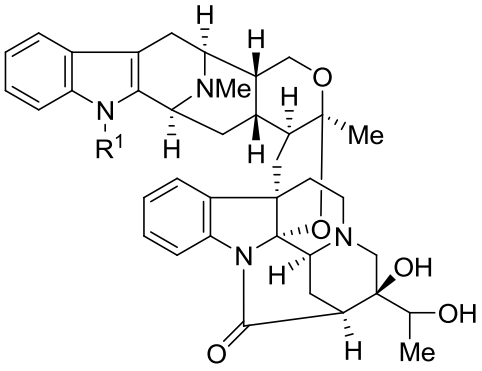


86 R_1 = H, R_2 = Me, R_3 = CH_2OH
88 R_1 = H, R_2 = Me, R_3 = H
89 R_1 = H, R_2 = Me, R_3 = H, N(4)→ O
424 R_1 = OMe, R_2 =Me, R_3 = H
425 R_1 = OMe, R_2 =Me, R_3 = H, N(4)→ O



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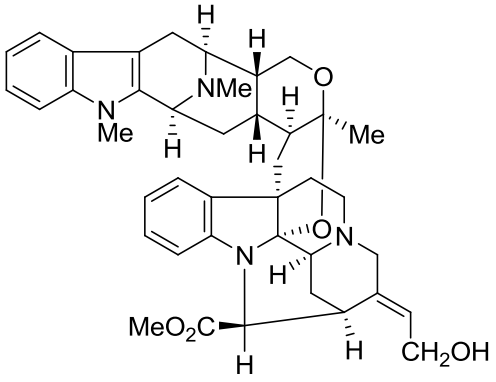

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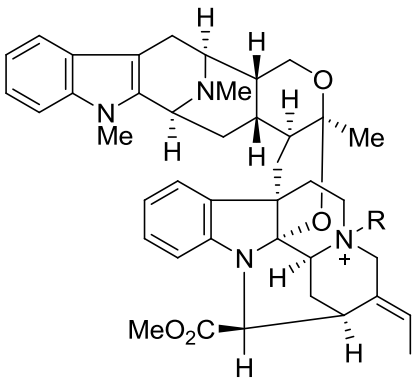
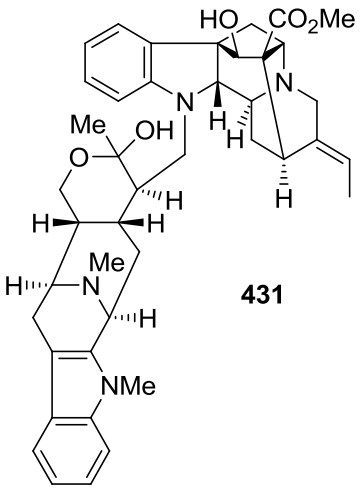


429 R = Me
430 R = CH_2Cl; Cl^-



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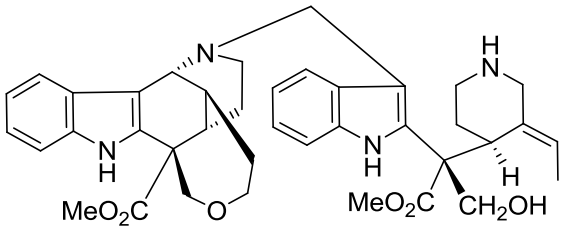

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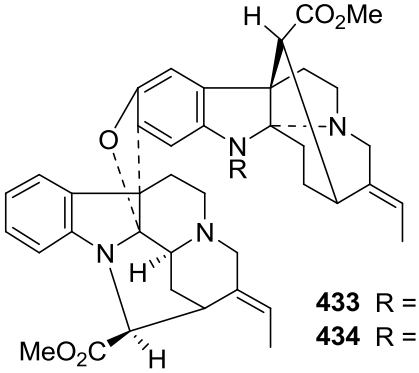
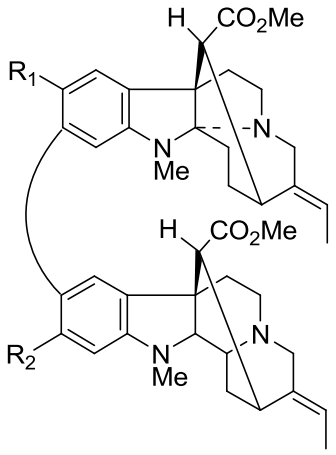
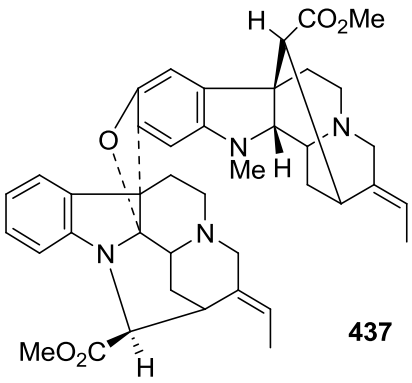


433 R = H
434 R = Me



435 R_1 = OMe, R_2 = OMe
436 R_1 = OMe, R_2 = H, or
R_1 = H, R_2 = OMe



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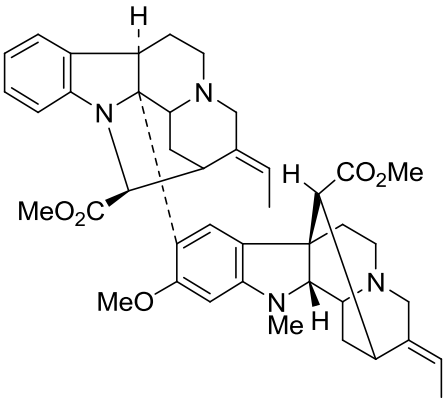

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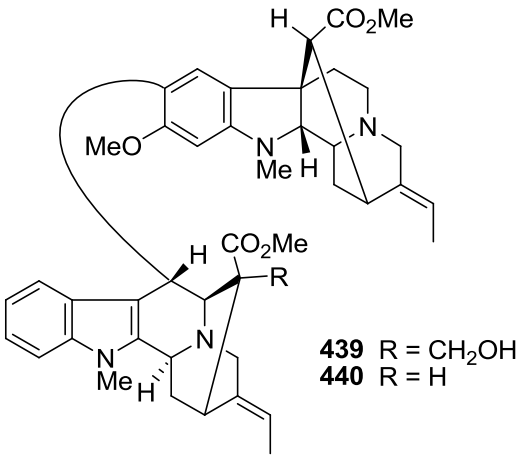
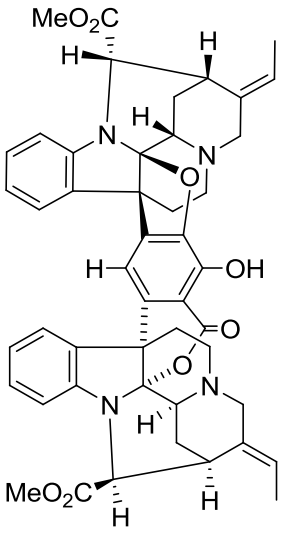


439 R = CH_2OH
440 R = H



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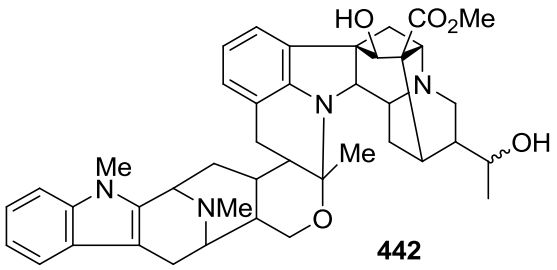


442

1.5 Objective of the Present Research

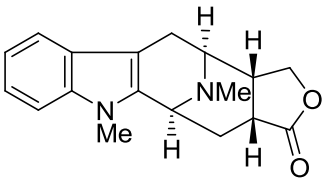
The aim of the present research is to carry out a detailed investigation of the alkaloid composition of *Alstonia macrophylla*, collected near Lumut, Perak, on the western coast of Peninsular Malaysia. This study involes several aspects, such as characterization of the isolated alkaloids, the discovery of new alkaloids, and the screening and evaluation of biological activity.

Chapter Two

2 Results and Discussion

2.1 Alkaloids from *Alstonia macrophylla*

The Malaysian plant, *Alstonia macrophylla* Wall, was investigated for its alkaloidal content and the results are summarized in the Table below. A total of 90 alkaloids were isolated and characterized from the leaf and stem-bark of *A. macrophylla*. Of these, 30 are new alkaloids. The leaf extract of *A. macrophylla* yielded a total of 13 new alkaloids, including a macroline indole **1**, a macroline oxindole **16**, eight akuammiline alkaloids (compounds **24**, **25**, **26**, **27**, **28**, **29**, **30**, and **31**), a sarpagine alkaloid **32**, and two ajmaline alkaloids (**33** and **34**). The stem-bark extract of *A. macrophylla* gave a total of 19 new alkaloids. These include, in addition to the akuammiline and sarpagine alkaloids found in the leaf extract (**24** and **32**, respectively), compound **2**, **3**, **4**, **17**, the linearly fused bisindole alkaloids, lumutinines A–E (**71**–**75**), the macroline-macroline bisindoles, lumusidines A–D (**77**–**80**) and perhentidines A–B (**81** and **82**), and the macroline–pleiocarpamine bisindole alkaloids, villalstonidines B (**86**) and F (**87**).



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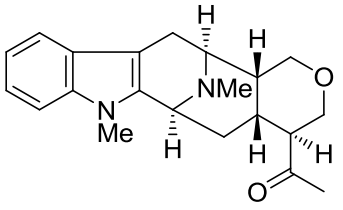

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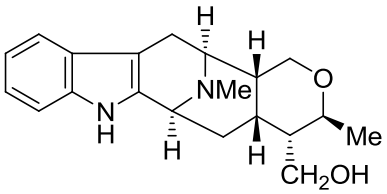

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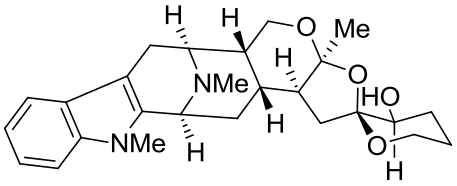

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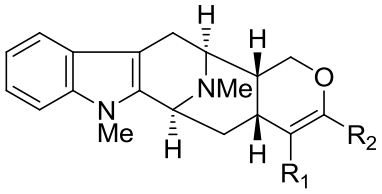
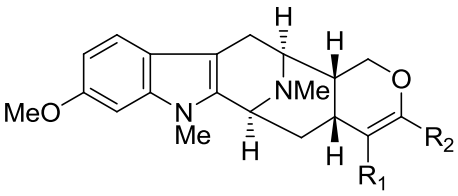
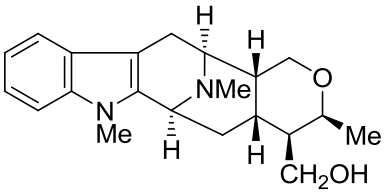


5 R_1 = COMe, R_2 = H
6 R_1 = CHO, R_2 = Me



7 R_1 = COMe, R_2 = H
8 R_1 = CHO, R_2 = Me



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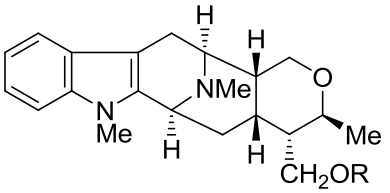
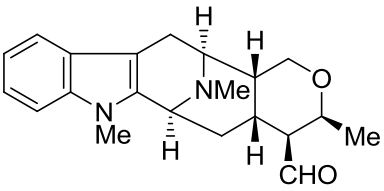


10 R = H
11 R = Ac



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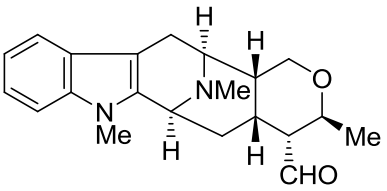

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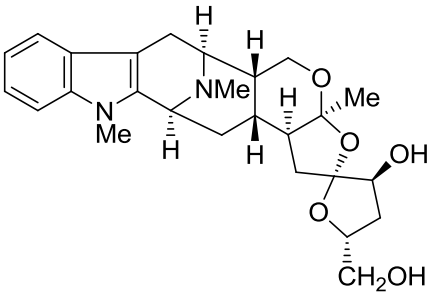

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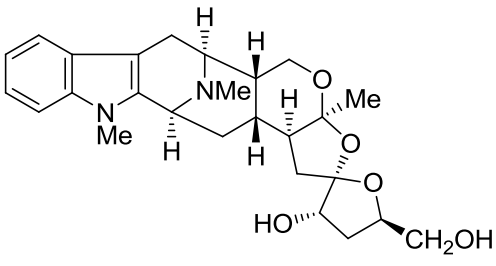

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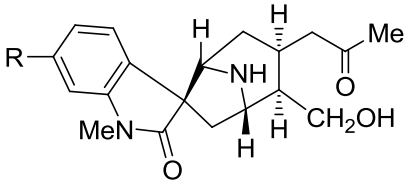
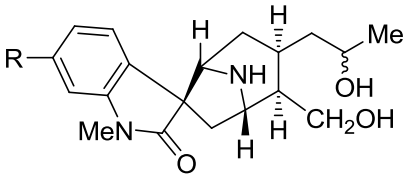
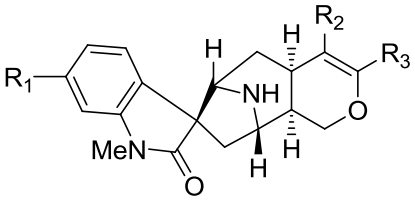


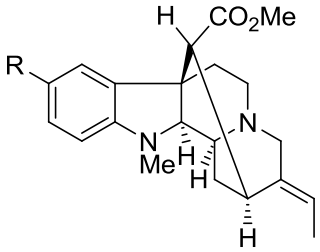
16 R = OMe
18 R = H



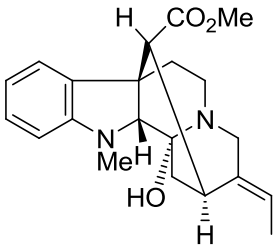
17 R = OMe
19 R = H



20 R_1 = H, R_2 = COMe, R_3 = H
21 R_1 = H, R_2 = CHO, R_3 = Me
22 R_1 = OMe, R_2 = COMe, R_3 = H
23 R_1 = OMe, R_2 = CHO, R_3 = Me



24 R = H
25 R = OMe



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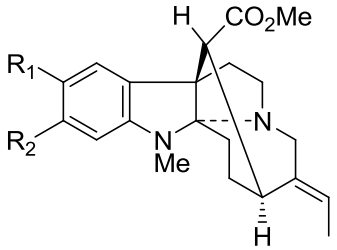
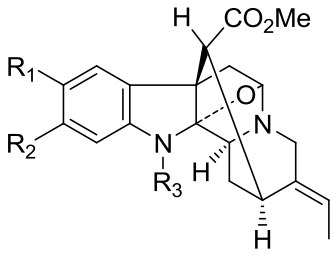
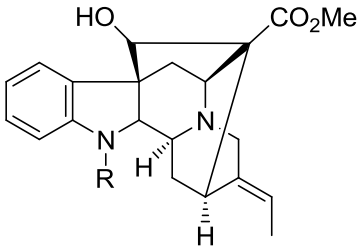


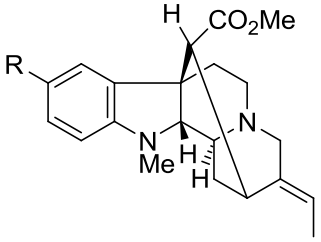
27 R_1 = H, R_2 = H
28 R_1 = H, R_2 = H, N(4)→O
29 R_1 = OMe, R_2 = OMe
30 R_1 = OMe, R_2 = H, N(4)→O



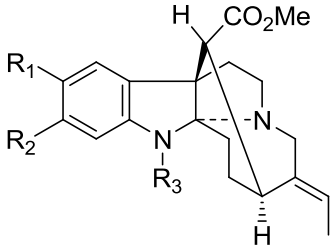
31 R_1 = OMe, R_2 = H, R_3 = H
46 R_1 = R_2 = OMe, R_3 = Me
47 R_1 = H, R_2 = H, R_3 = H
48 R_1 = OMe, R_2 = H, R_3 = Me



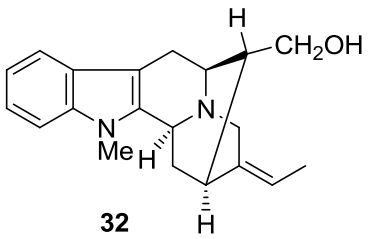
33 R = Me, N(4)→O
53 R = H
54 R = Me



35 R = H
36 R = H, N(4)→O
37 R = OMe



41 R_1 = OMe, R_2 = H, R_3 = Me
42 R_1 = OMe, R_2 = H, R_3 = H
43 R_1 = OMe, R_2 = OMe, R_3 = CHO
44 R_1 = OMe, R_2 = H, R_3 = CHO



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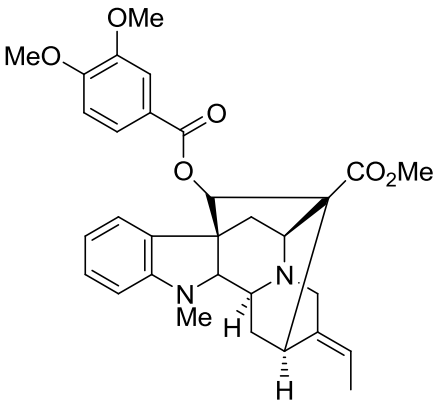
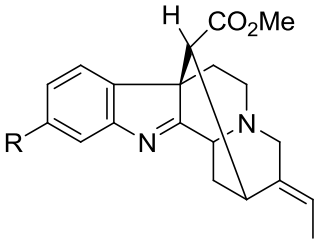
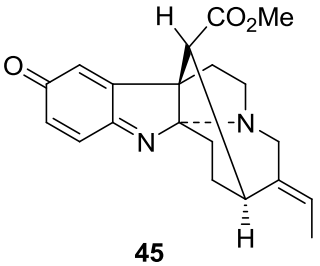


34 N(4)→O
55



38 R = H
39 R = OMe
40 R = OH



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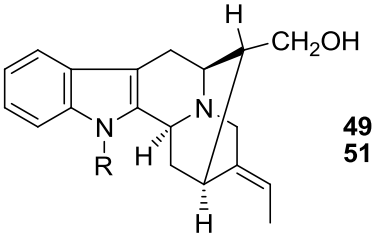
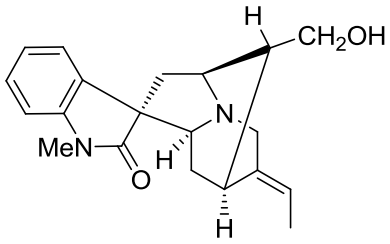


49 R = Me
51 R = H



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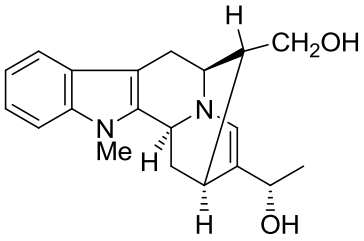

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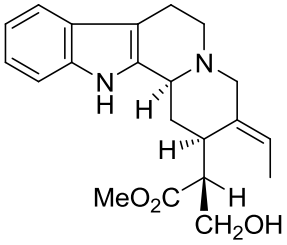

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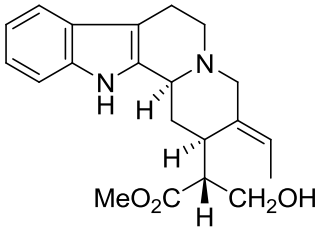

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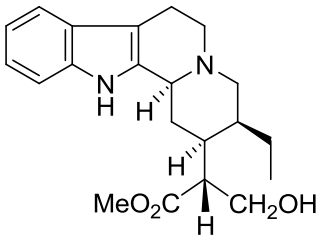

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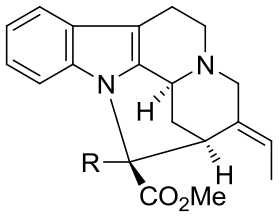
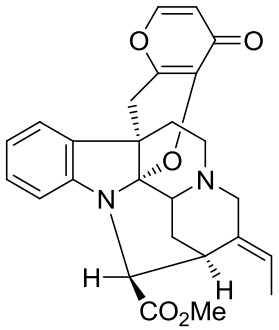


59 R = H
60 R = CH_2OH



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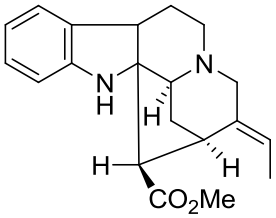

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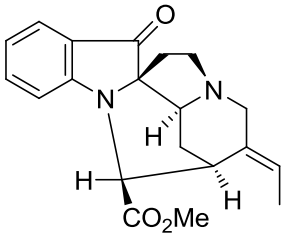

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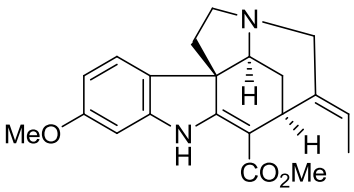
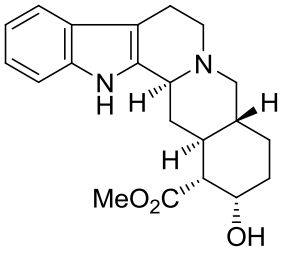


67
68 N(4)→O



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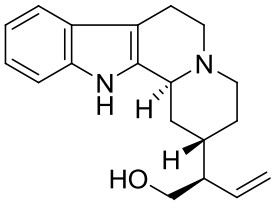

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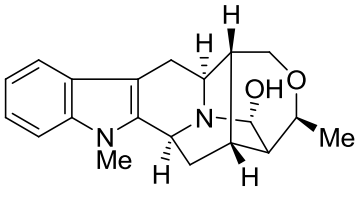

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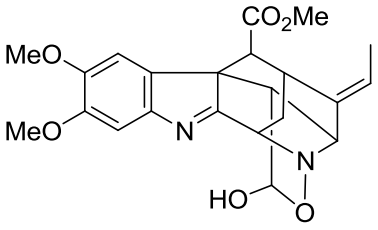

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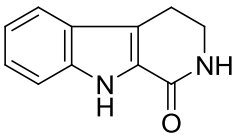

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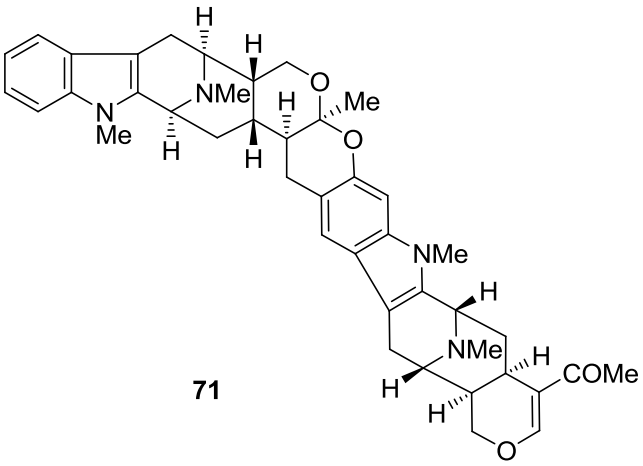

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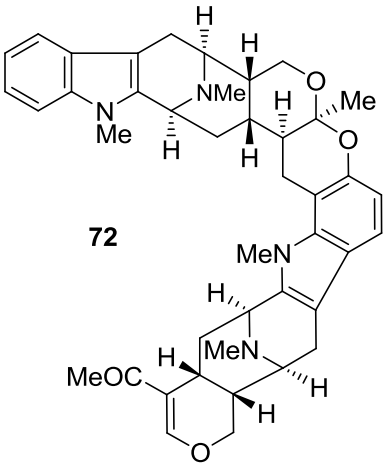

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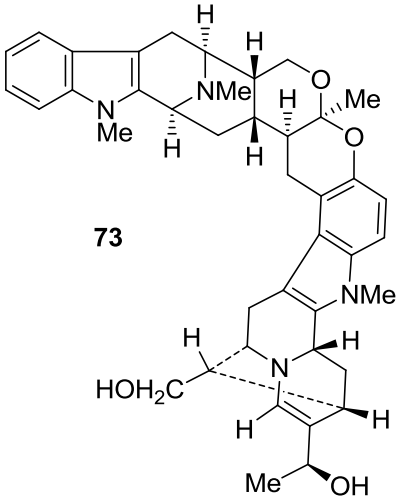

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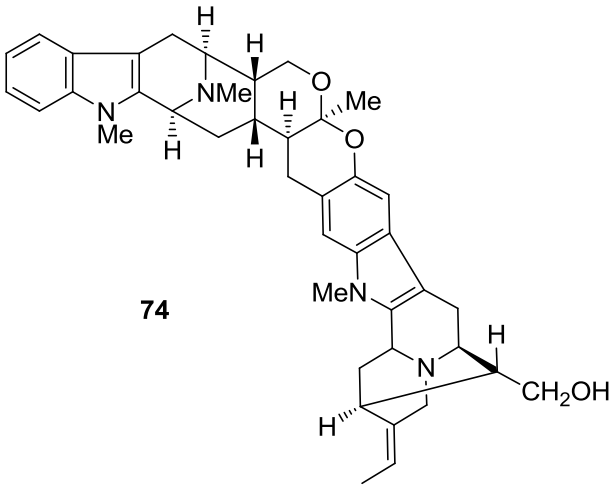

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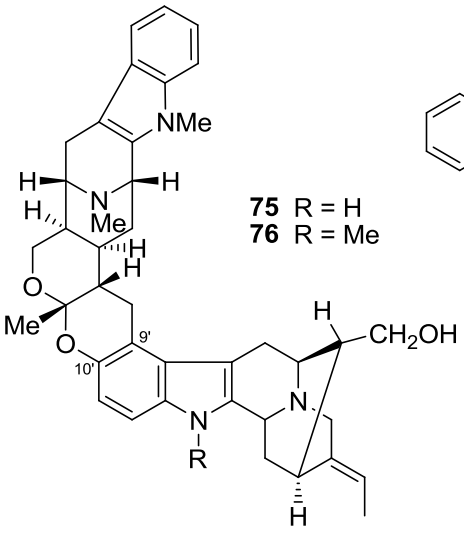
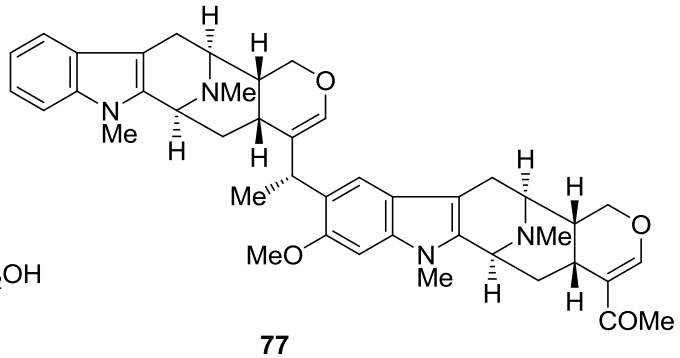


75 R = H
76 R = Me



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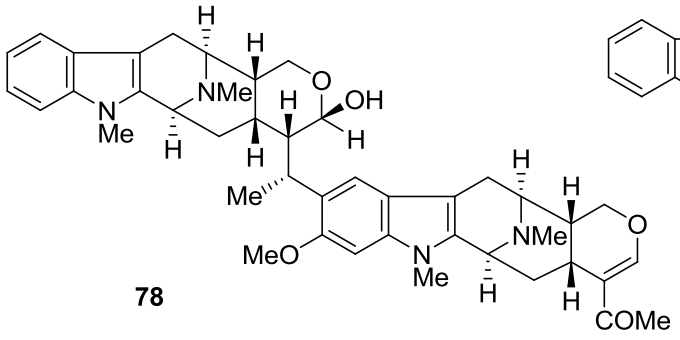

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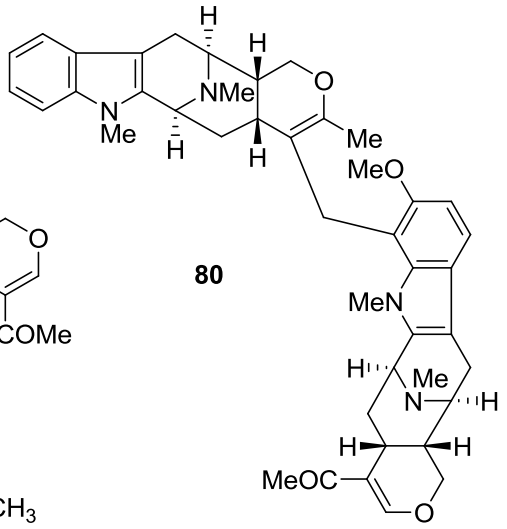

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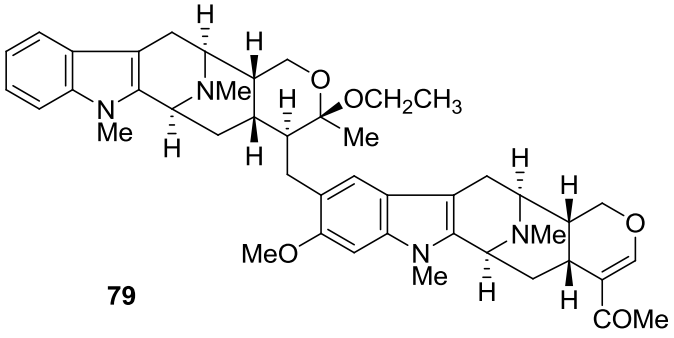

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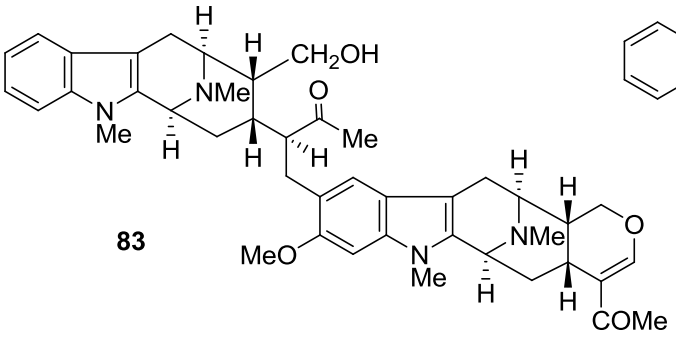

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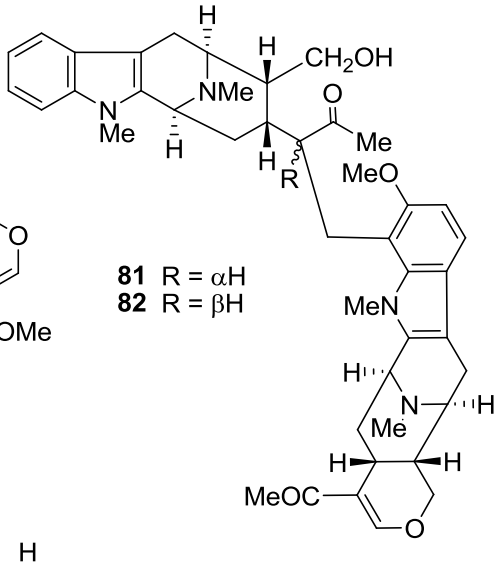
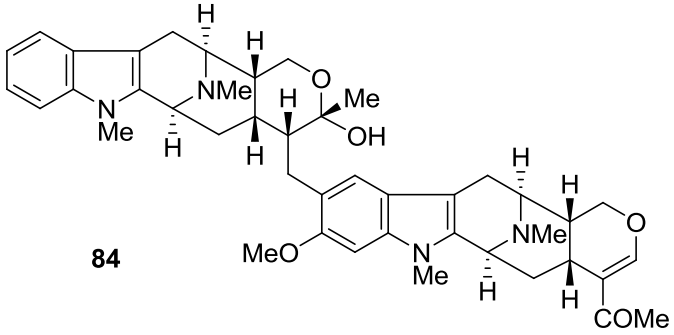


81 R = αH
82 R = βH



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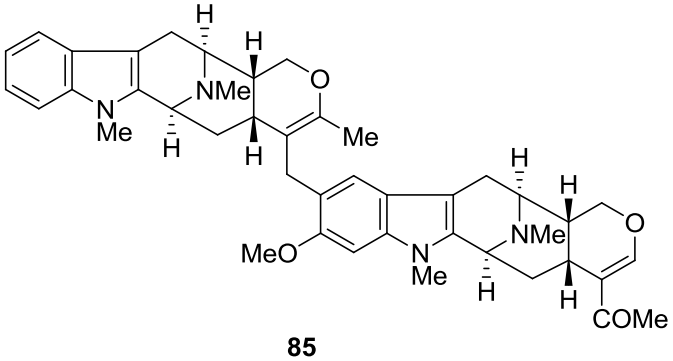

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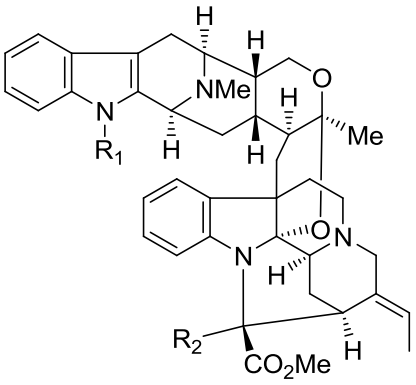
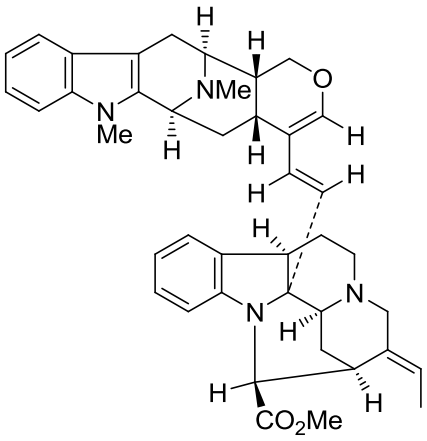


86 R_1 = Me, R_2 = CH_2OH
87 R_1 = H, R_2 = H
88 R_1 = Me, R_2 = H
89 R_1 = Me, R_2 = H, N(4)→O



90

Table 2.1: Alkaloid Composition of *A. macrophylla*

Plant part	**Alkaloid**	**Yield (g Kg^{-1})**
Leaves	Alstofolinine (**1**) [New]	0.0009
	Alstonerine (**5**)	0.2220
	Alstonerinal (**6**)	0.2220
	Alstophylline (**7**)	0.1746
	Alstophyllal (**8**)	0.1746
	Macrocarpine B (**10**)	0.0009
	Talcarpine (**12**)	0.0607
	N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	0.0977
	Compound **16** (11-Methoxyalstonoxine A) [New]	0.0079
	Alstonoxine A (**18**)	0.0110
	Alstonoxine B (**19**)	0.0024
	Alstonisine (**20**)	0.0817
	Alstonal (**21**)	0.0817
	N(4)-Demethylalstophylline oxindole (**22**)	0.0575
	N(4)-Demethylalstophyllal oxindole (**23**)	0.0674
	Compound **24** (2(*S*)-Cathafoline) [New]	0.0047
	Compound **25** (2(*S*)-10-Methoxycathafoline) [New]	0.0069
	Compound **26** (2(*R)*-3-Hydroxycathafoline) [New]	0.0050
	Compound **27** (10-Demethoxyvincorine) [New]	0.0010
	Compound **28** (10-Demethoxyvincorine *N*(4)-oxide) [New]	0.0018
	Compound **29** (11-Methoxyvincorine) [New]	0.0007
	Compound **30** (Vincorine *N*(4)-oxide) [New]	0.0206
	Compound **31** (11-Demethoxyquaternine) [New]	0.0132
	Compound **32** (19,20-*Z*-Affinisine) [New]	0.0040
	Compound **33** (Vincamajine *N*(4)-oxide) [New]	0.0002
	Compound **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide) [New]	0.0019
	Cathafoline (**35**)	0.0556
	Cathafoline *N*(4)-oxide (**36**)	0.0625
	10-Methoxycathafoline (**37**)	0.0048
	Strictamine (**38**)	0.0149
	11-Methoxystrictamine (**39**)	0.0404
	11-Hydroxystrictamine (**40**)	0.0152
	Vincorine (**41**)	0.0949
	Norvincorine (**42**)	0.0186
	Alstonamide (**43**)	0.0020

Table 2.1, continued

Plant part	Alkaloid	Yield (g Kg^{-1})
	Demethoxyalstonamide (**44**)	0.0139
	Alstomaline (**45**)	0.0042
	Quaternine (**46**)	0.3689
	Picrinine (**47**)	0.0054
	12-Demethoxytabernulosine (**48**)	0.0066
	Normacusine B (**51**)	0.0027
	Alstoumerine (**52**)	0.0243
	Quebrachidine (**53**)	0.0503
	Vincamajine (**54**)	0.1403
	Vincamajine 17-*O*-veratrate (**55**)	0.0178
	Sitsirikine (**56**)	0.0076
	16*R*,19*E*-Isositsirikine (**57**)	0.0053
	18,19-Dihydroisositsirikine (**58**)	0.0005
	Pleiocarpamine (**59**)	0.0146
	Fluorocarpamine (**63**)	0.0010
	11-Methoxyakuammicine (**67**)	0.0777
	11-Methoxyakuammicine *N*(4)-oxide (**68**)	0.0109
	Yohimbine (**64**)	0.0007
	Talpinine (**65**)	0.0010
	10,11-Dimethoxynareline (**66**)	0.0013
Stem-bark	Compound **2** (20,21-Dihydroalstonerine) [New]	0.0002
	Compound **3** (*N*(1)-Demethylmacrocarpine B) [New]	0.0035
	Macrodasine H (**4**) [New]	0.0003
	Alstonerine (**5**)	0.1278
	Alstonerinal (**6**)	0.1278
	Alstophylline (**7**)	0.2322
	Alstophyllal (**8**)	0.2322
	Macrocarpine A (**9**)	0.0042
	Macrocarpine B (**10**)	0.0571
	Macrocarpine C (**11**)	0.0037
	Talcarpine (**12**)	0.0205
	N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	0.0163
	Macrodasine A (**14**)	0.0064
	Macrodasine G (**15**)	0.0006

Table 2.1, continued

Plant part	Alkaloid	Yield (g Kg^{-1})
	Compound **17** (11-Methoxyalstonoxine B) [New]	0.0022
	Alstonoxine B (**19**)	0.0006
	Compound **24** (2(*S*)-Cathafoline) [New]	0.0001
	Compound **32** (19,20-*Z*-Affinisine) [New]	0.0043
	Cathafoline (**35**)	0.0013
	Cathafoline *N*(4)-oxide (**36**)	0.0006
	Vincorine (**41**)	0.0003
	Affinisine (**49**)	0.0003
	Affinisine oxindole (**50**)	0.0005
	Normacusine B (**51**)	0.0040
	Alstoumerine (**52**)	0.0027
	Vincamajine (**54**)	0.0003
	16*R*, 19*E*-Isositsirikine (**57**)	0.0202
	Pleiocarpamine (**59**)	0.0283
	16-Hydroxymethylpleiocarpamine (**60**)	0.0015
	Pleiomaltinine (**61**)	0.0006
	Picramicine (**62**)	0.0076
	Fluorocarpamine (**63**)	0.0011
	Talpinine (**65**)	0.0002
	11-Methoxyakuammicine (**67**)	0.0014
	Antirhine (**69**)	0.0009
	1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)	0.0001
	Lumutinine A (**71**) [New]	0.0046
	Lumutinine B (**72**) [New]	0.0025
	Lumutinine C (**73**) [New]	0.0010
	Lumutinine D (**74**) [New]	0.0047
	Lumutinine E (**75**) [New]	0.0011
	Macralstonidine (**76**)	0.0959
	Lumusidine A (**77**) [New]	0.0073
	Lumusidine B (**78**) [New]	0.0065
	Lumusidine C (**79**) [New]	0.0007
	Lumusidine D (**80**) [New]	0.0061
	Perhentidine A (**81**) [New]	0.0126
	Perhentidine B (**82**) [New]	0.0207
	Perhentinine (**83**)	0.0270

Table 2.1, continued

Plant part	Alkaloid	Yield (g Kg^{-1})
	Macralstonine (**84**)	0.0336
	Anhydromacralstonine (**85**)	0.0020
	Villalstonidine B (**86**) [New]	0.0079
	Villalstonidine F (**87**) [New]	0.0005
	Villalstonine (**88**)	0.7126
	Villalstonine *N*(4)-oxide (**89**)	0.0109
	Macrocarpamine (**90**)	0.0651

2.1.1 Macroline Alkaloids

2.1.1.1 Alstofolinine (1)

Alstofolinine (**1**) was one of the minor alkaloids isolated from the leaf extract of *A. macropylla*. It was obtained as a light yellowish oil, with $[\alpha]_D$ −104 (*c* 0.36, $CHCl_3$). The UV spectrum showed two absorption bands (227 and 285 nm) characteristic of an indole chromophore. The IR spectrum showed a sharp band at 1769 cm^{-1} due to a lactone function. The EIMS of **1** showed a molecular ion at *m/z* 296, and high resolution measurements yielded the molecular formula $C_{18}H_{20}N_2O_2$ (DBE 10). Other notable fragment peaks observed at *m/z* 197, 182, 181, 170, and 144, are typical of macroline derivatives,[169,231] while the mass fragment at *m/z* 281 can be attributed to loss of a CH_3.

The ^{13}C NMR spectrum (Table 2.2) displayed a total of 18 carbon resonances, corresponding to two methyl, three methylene, eight methine and five quaternary carbons, in agreement with the molecular formula. The presence of the lactone functionality and an oxymethylene carbon, was supported by the observed carbon signals at δ 181.0 and δ 70.7, respectively. The ^1H NMR spectrum (Figure 2.2; Table 2.2) showed the presence of an unsubstituted indole moiety (δ 7.11–7.49), two methyl groups corresponding to N1-Me at δ 3.64 and N4-Me at δ 2.42, and two downfield signals at δ 4.42 (H-17β, t, *J* = 8 Hz) and 4.52 (H-17α, dd, *J* = 11, 8 Hz) due to the geminal hydrogens of an oxymethylene corresponding to C-17.

The COSY and HSQC data disclosed partial structures that are characteristic of a macroline-type skeleton, such as $NCHCH_2$ and $NCHCH_2CHCHCH_2O$, corresponding to the N-4–C-5–C-6 and N-4–C-3–C-14–C-15–C-16–C-17-O fragments, respectively. The NMR data were suggestive of a macroline derivative, such as alstonerine (**5**),[133] except for the absence of the typical α,β unsaturated ketone group and the vinyl-H, in the ring

E of **1**. In addition, both the H-17 signals in **1** were shifted downfield to δ_H 4.42 and 4.52, when compared to those in alstonerine (**5**) (δ_H 4.16 and 4.40) as well as other typical macroline-type compounds.[123,177] Furthermore, the observed coupling constants for the H-17 resonances in the case of **1** differed significantly when compared to those in **5** (**1**: H-17β, t, *J* = 8 Hz; H-17α, dd, *J* = 11 and 8 Hz; **5**: H-17β, ddd, *J* = 11, 4, 2 Hz; H-17α, t, *J* = 11 Hz) indicating changes in ring E of **1** compared to the ring E of normal macrolines as exemplified by alstonerine (**5**). The presence of a lactone functionality as a part of ring E is deduced from the observed three-bond correlations from H-14α, H-14β, and H-17α, to the lactone carbonyl C-18 in the HMBC spectrum (Figure 2.1). The NMR data at this point allowed the proposed structure **1** to be assembled. The relative configurations at the various stereogenic centers of **1** were established by 2D-NOESY which were similar to those in other macroline alkaloids. Alstofolinine (**1**) represents the first example of a macroline type alkaloid incorporating a γ-butyrolactone in ring E.

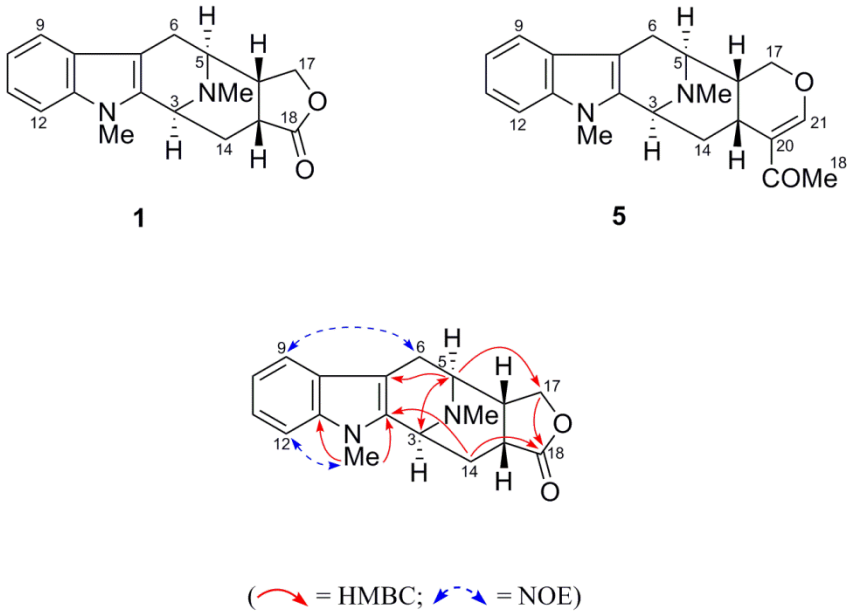


Figure 2.1: Selected HMBCs and NOEs of **1**

Table 2.2: ^{1}H and ^{13}C NMR Spectroscopic Data for Alstofolinine (**1**)[a]

Position	δ_H	δ_C
2	–	132.4
3	3.91 br s	52.0
5	3.06 d (6)	52.4
6β	2.47 br d (16)	23.6
6α	3.27 dd (16, 6)	–
7	–	106.8
8	–	127.3
9	7.49 d (8)	119.0
10	7.11 td (8, 1)	120.0
11	7.22 td (8, 1)	122.3
12	7.31 d (8)	109.8
13	–	138.1
14β	2.10 m	29.5
14α	2.13 m	–
15	2.17 m	34.1
16	2.54 m	43.2
17β	4.42 t (8)	70.7
17α	4.52 dd (11, 8)	–
18	–	181.0
N(1)-Me	3.64 s	30.1
N(4)-Me	2.42 s	42.2

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY/NOE.

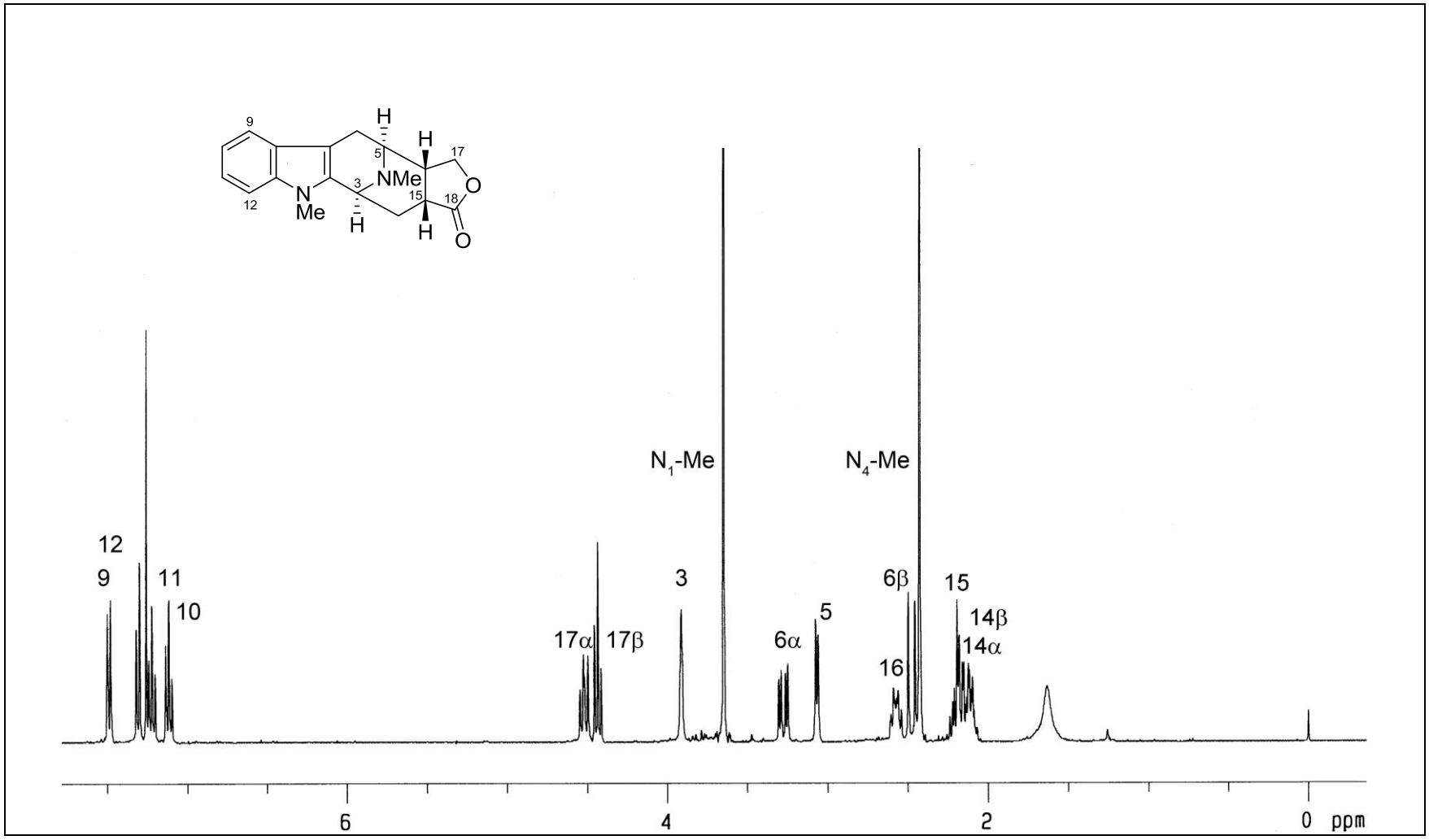


Figure 2.2: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstofolinine (**1**)

2.1.1.2 Compound 2 (20,21-Dihydroalstonerine)

Compound **2** was isolated in small amount as a light yellowish oil, with $[\alpha]_D$ –31 (*c* 0.11, $CHCl_3$). The IR spectrum showed a band at 1710 cm^{-1} due to a ketone function. The presence of a ketone function was confirmed by the observed resonance at δ 208.6 in the ^{13}C NMR spectrum. The ESIMS of **2** showed a $[M + H]^+$ ion at *m/z* 339, which analyzed for $C_{21}H_{26}N_2O_2$ + H. The UV spectrum showed absorption maxima at 228 and 286 nm which are characteristic of an indole chromophore.

The ^1H and ^{13}C NMR data (Table 2.3; Figure 2.4) showed the presence of an unsubstituted indole moiety (δ_H 7.09–7.50, δ_C 108.7–120.9), two N-methyl signals (N4-Me, δ_C 41.8, δ_H 2.29; N1-Me, δ_C 29.1, δ_H 3.61), a methyl ketone function (δ_C 208.6; δ_C 28.4, δ_H 2.12), an oxymethylene, characteristic of C-17 in macroline type alkaloids (δ_C 68.6, δ_H 3.72, and 3.95), and another oxymethylene signal at δ_C 64.3. The NMR signals, assigned with the aid of COSY and HSQC, indicated that **2** was a macroline-type alkaloid. The NMR data resembled that of alstonerine (**5**),[133] which was also isolated from the extract of this plant, except for the absence of signals associated with the trisubstituted C-20–C-21 double bond, such as the olefinic carbon signals at C-20 (δ 126.5) and C-21 (δ 157.4), and the signal due to the vinylic H-21 in the ^1H NMR spectrum (δ 7.52). These signals have in **2** been replaced by a methine at C-20 (δ_C 51.9, δ_H 1.97, m) and a methylene at C-21 (δ_C 64.3; δ_H 3.86, dd, *J* = 12.5, 3 Hz, δ_H 4.18, d, *J* = 12.5 Hz), consistent with saturation of the C20–C21 double bond in **2**. Less substantial changes were observed for the signals of carbons β to both of these carbons (C-20, C-21) in the ^{13}C NMR spectrum. The configuration at C-20 can be deduced from the observed NOEs, viz., H-20/H-14β, H-18, H-21α; H-21α/H-14α, H-20, H-21β (Figure 2.3), which indicated that the orientation of H-20 is α. Compound **2** is

therefore, the 20,21-dihydro derivative of alstonerine (**5**), which, while previously encountered as an intermediate compound in synthesis,[232] is here encountered as an optically active natural product for the first time. Compound **2** was also independently isolated from the stem-bark extract of *A. angustifolia*.[233]

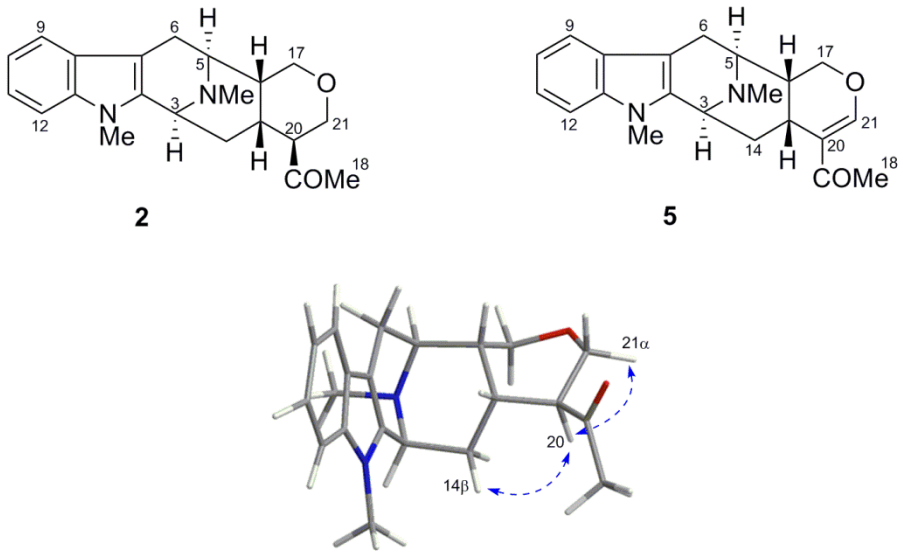


Figure 2.3: Selected NOEs of **2**

Table 2.3: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **2** (20,21-Dihydroalstonerine)[a]

Position	δ_H	δ_C
2	–	133.0
3	3.97 m	53.6
5	2.83 d (7)	54.8
6β	2.52 dd (16)	22.4
6α	3.24 dd (16, 7)	
7	–	107.0
8	–	126.6
9	7.50 d (8)	118.4
10	7.09 td (8, 1)	118.9
11	7.18 td (8, 1)	120.9
12	7.27 d (8)	108.7
13	–	137.1
14β	1.42 dt (12, 3)	30.3
14'α	2.44 dd (12, 4)	
15	2.35 m	24.6
16	2.12 m	39.3
17β	3.72 dd (11.5, 5)	68.6
17α	3.95 t (11.5)	
18	2.12 s	28.4
19	–	208.6
20	1.97 m	51.9
21α	3.86 dd (12.5, 3)	64.3
21β	4.18 d (12.5)	
N(1)-Me	3.61 s	29.1
N(4)-Me	2.29 s	41.8

[a]$CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOE.

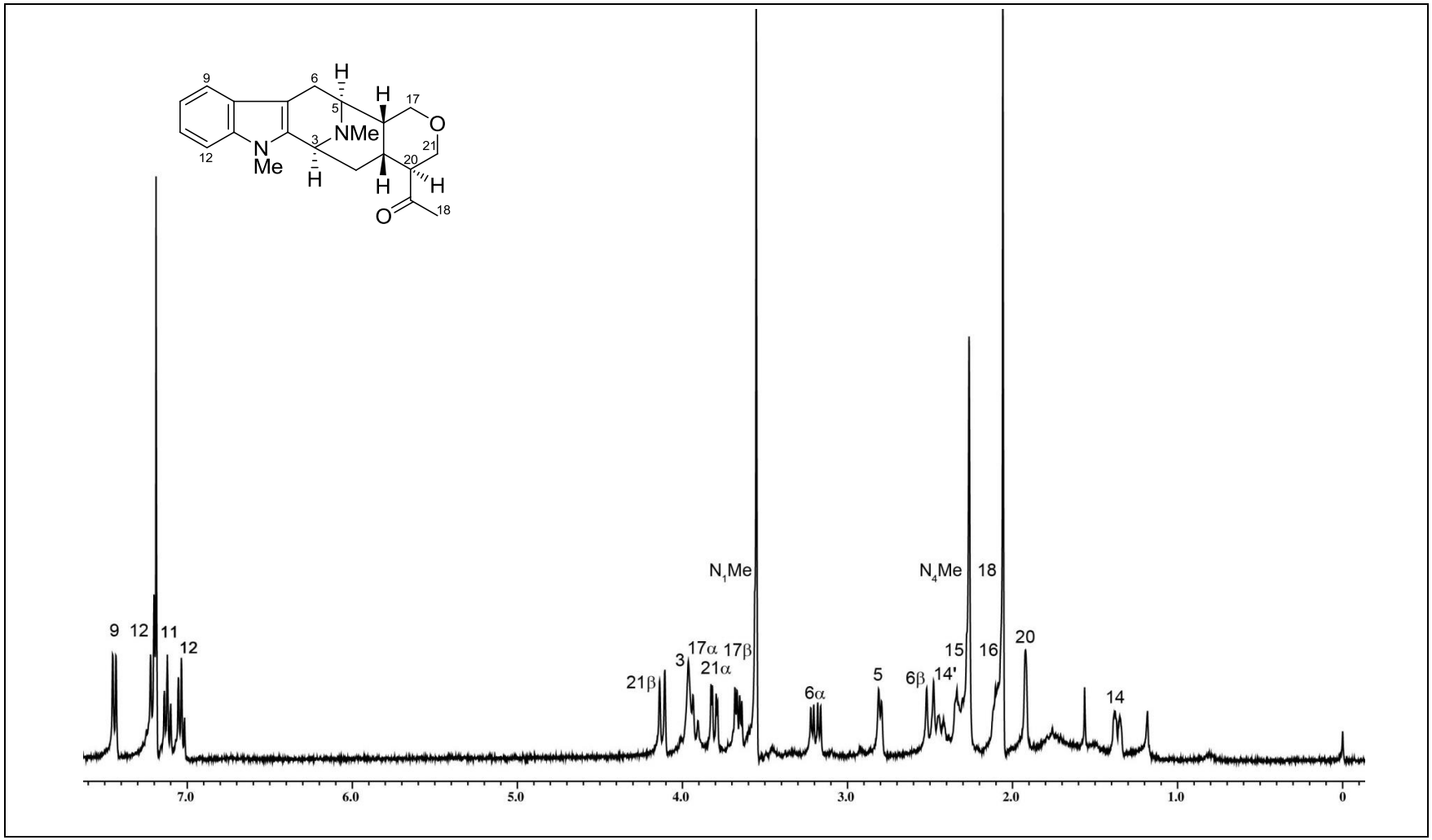
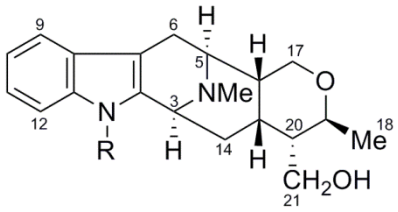


Figure 2.4: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **2** (20,21-Dihydroalstonerine)

2.1.1.3 Compound 3 [Macrocarpine D (*N*(1)-Demethylmacrocarpine B)]

Compound **3** was obtained as a light yellowish oil, with $[\alpha]_D$ –43 (*c* 0.89, $CHCl_3$). It was isolated from the stem-bark extract of *A. macrophylla* as well as *A. angustifolia*.[233] The IR spectrum indicated the presence of hydroxyl and primary amine functions at 3395 and 3292 cm^{-1}, respectively, while the UV spectrum indicated an indole chromophore (λ_{max} 231 and 286 nm). The ESIMS of **3** showed a $[M + H]^+$ peak at *m*/*z* 327, and HRESIMS measurements established the molecular formula as $C_{20}H_{26}N_2O_2$ + H, 15 mass units less than that of macrocarpine B (**10**).[123] The ^1H NMR spectrum (Table 2.4; Figure 2.6) of **3** showed the presence of four aromatic hydrogens due to an unsubstituted indole chromophore (δ 7.11–7.49), a singlet at δ 2.34 due to N4-Me, a methyl doublet at δ 1.16 corresponding to 18-Me, an oxymethine at δ 3.50 (δ 70.5), a pair of doublet-doublets at δ 3.34 and 3.50 (δ_C 61.7) due to a hydroxymethyl group, two signals at δ 3.74 and 4.08 (δ_C 67.7) due to an oxymethylene, and a low-field broad singlet at δ 7.89 due to an NH function. The ^{13}C NMR spectrum (Table 2.4) gave a total of 20 carbon signals, comprising two methyl, four methylene, 10 methine, and four quaternary carbons. The spectrum was somewhat similar to that of macrocarpine B (**10**). Comparison of the NMR data of **3** with those of **10** revealed that these two compounds were similar in all respects, except for the replacement of the N1-Me group by an NH function. The relative configurations at the various stereogenic centers of **3**, follow those in the macroline-type alkaloids. In common with compound **10**, the orientation of H-19 and H-20 in **3**, were deduced to be α and β, respectively from the observed NOEs for H-19/H-14α and H-20/H-15, H-16 (Figure 2.5).



3 R = H
10 R = Me

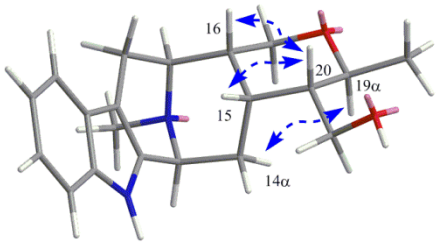


Figure 2.5: Selected NOEs of **3**

Table 2.4: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **3** (*N*(1)-Demethylmacrocarpine B)[a]

Position	δ_H	δ_C
2	–	132.2
3	3.95 m	55.0
5	2.94 d (7)	55.1
6β	2.46 d (16)	22.5
6α	3.27 dd (16, 7)	–
7	–	107.7
8	–	127.1
9	7.49 d (7.5)	118.0
10	7.11 t (7.5)	119.4
11	7.15 t (7.5)	121.3
12	7.32 d (7.5)	110.9
13	–	135.5
14β	1.62 dt (13, 4)	26.1
14α	2.28 td (13, 4)	–
15	2.01 m	27.1
16	1.89 dt (12, 4)	43.6
17β	3.74 dd (12, 5)	67.7
17α	4.08 t (12)	–
18	1.16 d (6)	20.3
19	3.50 m	70.5
20β	1.50 m	46.9
21a	3.34 dd (11, 8)	61.7
21b	3.50 dd (11, 5)	
N(1)-H	7.89 br s	–
N(4)-Me	2.34 s	41.6

[a] $CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOESY

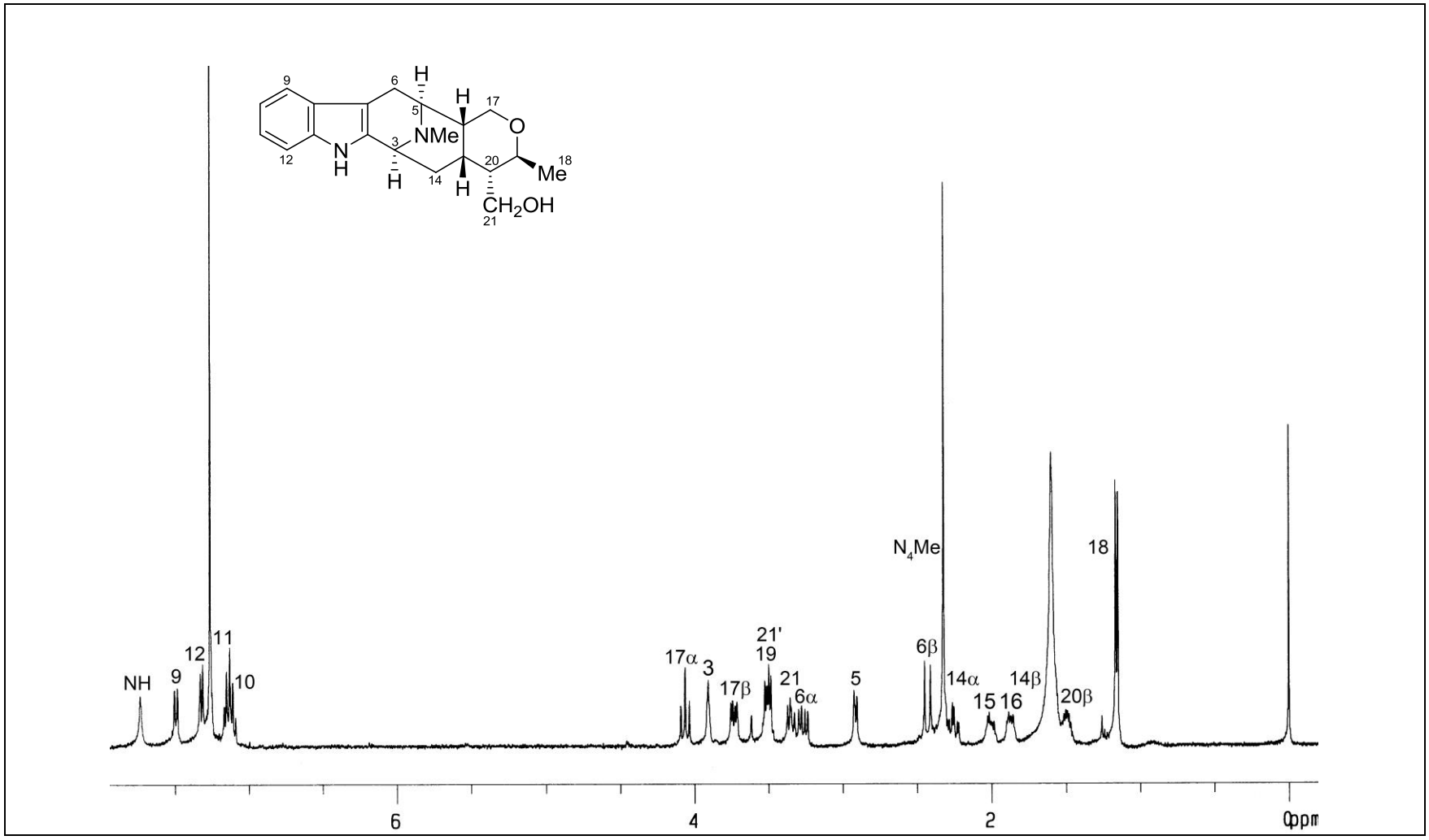


Figure 2.6: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **3** [Macrocarpine D (*N*(1)-Demethylmacrocarpaine B)]

2.1.1.4 Macrodasine H (4)

Compound **4** was obtained as a light yellowish oil, with $[\alpha]_D$ −11 (*c* 0.14, $CHCl_3$). The UV spectrum showed two absorption maxima at 233 and 288 nm, indicating the presence of an indole chromophore. The IR spectrum showed a broad band at 3423 cm^{-1} due to a hydroxyl function. The ESIMS of **4** showed a $[M + H]^+$ peak at *m*/*z* 439, and high-resolution measurements yielded the molecular formula $C_{26}H_{34}N_2O_2$ + H (DBE 11). The ^{13}C NMR spectrum (Table 2.5) showed a total of 26 carbon signals comprising three methyl, seven methylene, ten methine and six quaternary carbons, in agreement with the molecular formula. The observed carbon resonance at δ 70.1 was due to an oxymethine carbon, while the carbon resonances at δ 64.6 (C-17) and 64.0 (C-26) were due to two oxymethylene carbon atoms. In addition, two low-field quaternary carbon signals were observed at δ 108.6 and 105.1, each of which was attached to two oxygen atoms. The ^1H NMR spectrum (Table 2.5; Figure 2.9) showed the presence of an unsubstituted indole moiety (δ 7.11–7.50), three methyl groups corresponding to N1-Me, N4-Me, and 18-Me at δ 3.62, 2.33, and 1.62, respectively, and two sets of signals due to two oxymethylenes at δ 3.75, 4.05; and at δ 3.39, 3.84.

The COSY spectrum disclosed some partial structures, which are characteristic of a macroline-type skeleton, such as $NCHCH_2$, $CHCH_2$, and $NCHCH_2CHCHCH_2O$, corresponding to the N-4–C-5–C-6, C-20–C-21, and N-4–C-3–C-14–C-15–C-16–C-17-O fragments, respectively. An additional fragment, viz., $OCHCH_2CH_2CH_2O$, was also indicated from the COSY spectrum which, taken with the other NMR data, indicated affinity to the macrodasine group of alkaloids reported recently.[124] These macroline alkaloids incorporate additional fused spirocyclic tetrahydrofuran-tetrahydrofuran (macrodasines A, B, C, G (**14**, **119**, **120**, **15**)) and tetrahydrofuran-tetrahydropyran (macrodasines D, E, F (**121**–**123**)) rings. The $OCHCH_2CH_2CH_2O$ partial structure noted

from the COSY spectrum suggested that compound **4** belong to the latter group of macrodasine alkaloids (macrodasines D, E, and F (**121**–**123**)) characterized by incorporation of fused 5/6 (F/G) spirocyclic rings.[124] This was further supported by the observed HMBC data viz., H-26b, H-24 to C-22, H-24 to C-26, H-25 to C-23, H-21 to C-15, C-23, etc. (Figure 2.7). The proposed structure is consistent with the full HMBC data. The structure of compound **4** is similar to that of macrodasine F (**123**), except for the absence of the OH substituent at C-25.

The ring junction stereochemistries between rings C, D, E, and F were deduced to be similar to those of the macroline alkaloids as well as the macrodasines (A–G (**14**, **119**–**123**, **15**)) from the NOE data. The reciprocal NOEs observed for H-23/H-21β, H-25a and H-24a/H-26a suggested a chair conformation adopted by the tetrahydropyran ring G as shown in Figure 2.8, in which H-24a, H-25a, and H-26a are axially oriented. As in the case of macrodasine F, NOE was not observed between the C-26 hydrogens and 18-Me, suggesting that the configuration of the spirocyclic C-22 is *S* (the C-26 hydrogens and 18-Me are directed away from each other; if C-22 is *R*, NOE would have been observed between H-26 and 18-Me[124]).

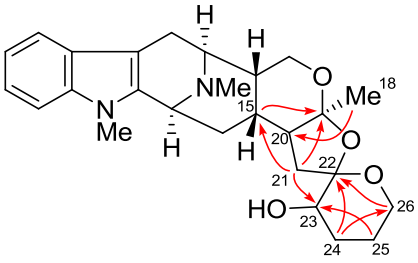


Figure 2.7: Selected HMBCs of **4**

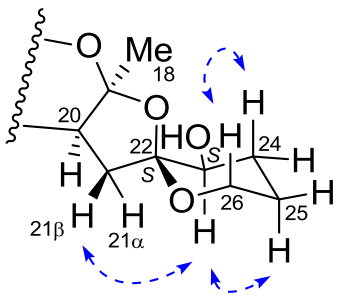
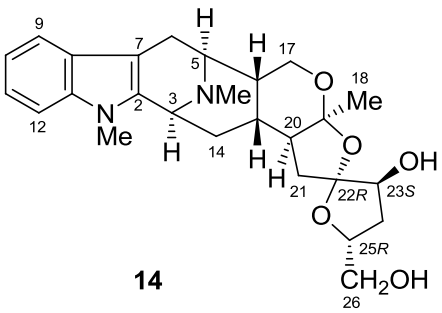


Figure 2.8: Selected NOEs of **4**



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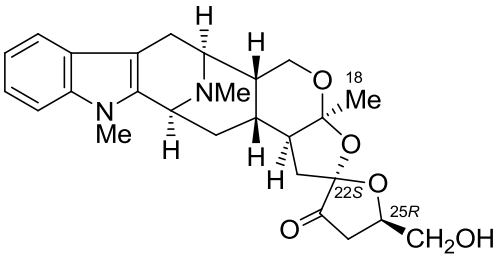

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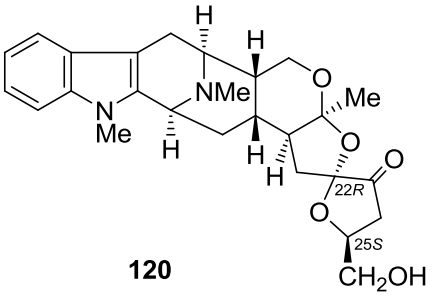

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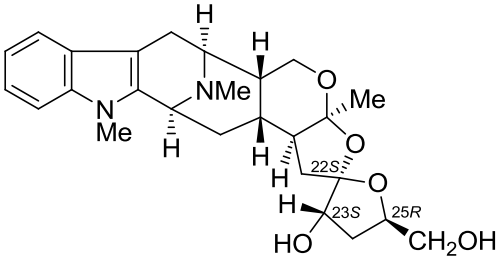
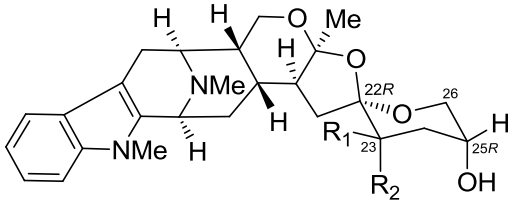
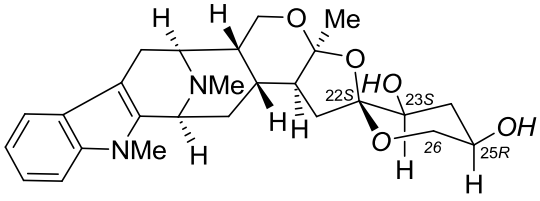


15



121 R_1 = OH, R_2 = H (23*R*)
122 R_1 = H, R_2 = OH (23*S*)



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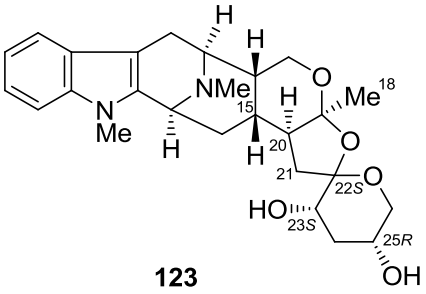

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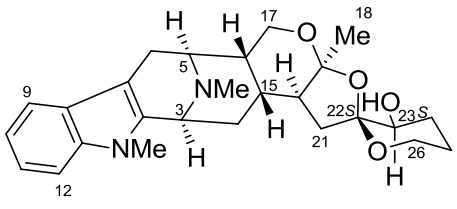

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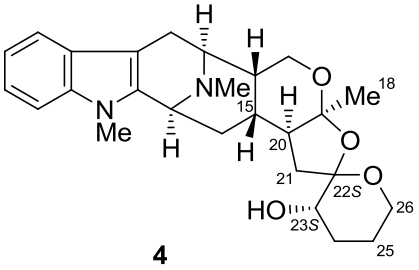


4

Table 2.5: ^{1}H and ^{13}C NMR Spectroscopic Data for Macrodasine H (**4**)[a]

Position	δ_H	δ_C
2	–	132.7
3	3.93 m	53.5
5	2.96 d (7)	54.9
6β	2.41 d (16)	22.6
6α	3.26 dd (16, 7)	–
7	–	106.7
8	–	126.4
9	7.50 d (8)	118.2
10	7.11 t (8)	119
11	7.20 t (8)	121.1
12	7.30 d (8)	108.9
13	–	137.0
14β	1.50 m	32.0
14α	2.41 m	–
15	1.84 m	26.7
16	2.09 m	37.0
17β	3.75 dd (12, 5)	64.6
17α	4.05 t (12)	–
18	1.62 s	23.8
19	–	105.1
20	1.96 dd (12.5, 8)	44.1
21α	1.81 dd (12.5, 8)	32.2
21β	2.16 t (12.5)	
22	–	108.6
23 (ax)	3.51 dd (10, 5)	70.1
24 (ax)	1.37 m	27.9
24' (eq)	2.05 m	
25	1.56 m	23.0
25'	1.56 m	
26 (ax)	3.39 td (10, 4.5)	64.0
26' (eq)	3.84 m	
N(1)-Me	3.62 s	30.1
N(4)-Me	2.33 s	42.2

[a] $CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

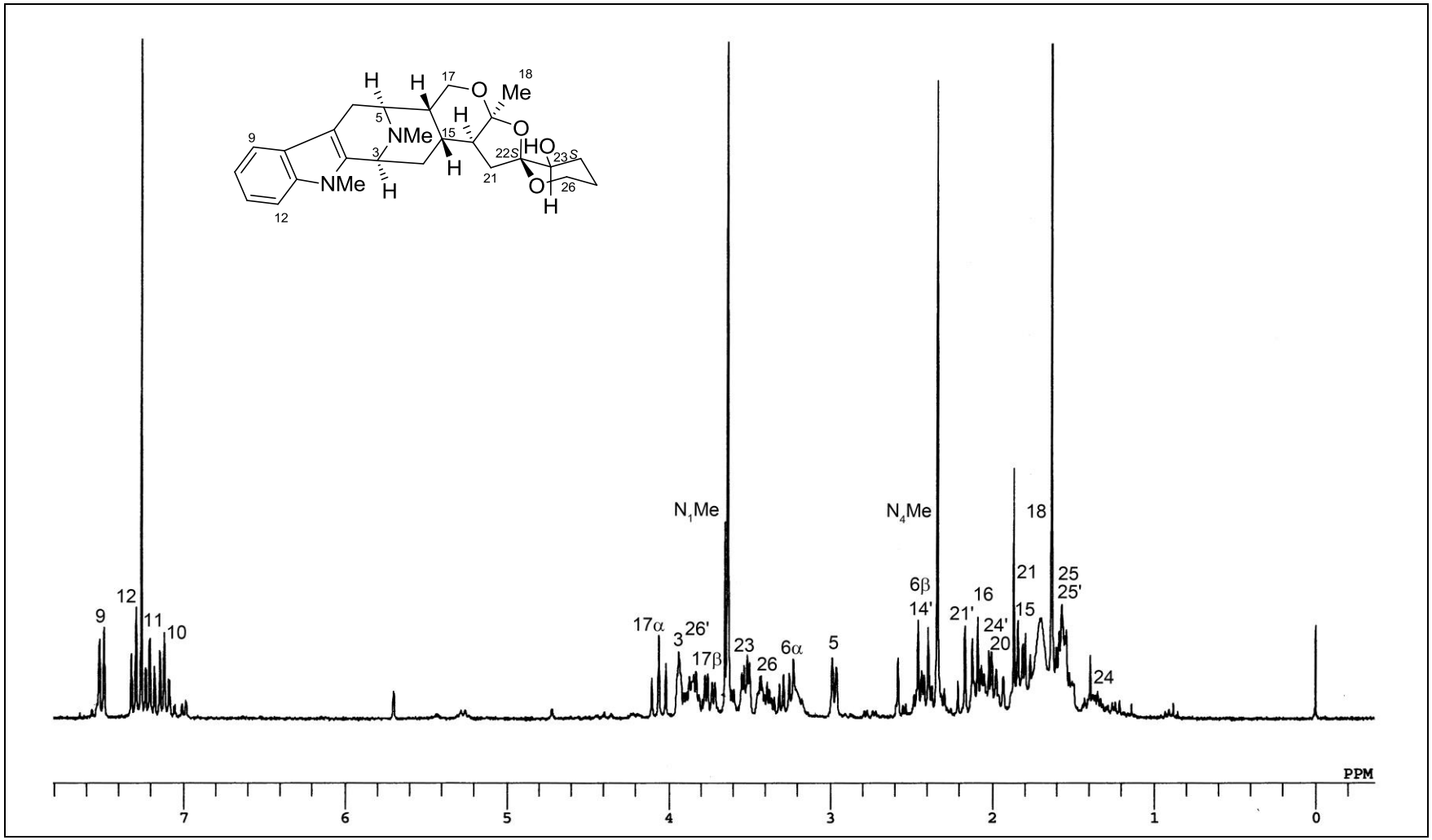


Figure 2.9: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrodasine H (**4**)

2.1.1.5 Alstonerine (5), Alstonerinal (6), Alstophylline (7), Alstophyllal (8), Macrocarpine A (9), Macrocarpine B (10), Macrocarpine C (11), Talcarpine (12), *N*(4)-Methyl-*N*(4),21-*seco*talpinine (13), Macrodasine A (14), and Macrodasine G (15)

Eleven known alkaloids belonging to this group, viz., alstonerine (**5**),[118,133,158,184] alstonerinal (**6**),[133,234] alstophylline (**7**),[118,164,166] alstophyllal (**8**),[177] macrocarpine A (**9**),[123] macrocarpine B (**10**),[123] macrocarpine C (**11**),[123] talcarpine (**12**),[234-236] *N*(4)-methyl-*N*(4),21-*seco*talpinine (**13**),[123,234] macrodasine A (**16**),[122-124] and macrodasine G (**15**)[124] were also isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.10–2.18 and the NMR spectroscopic data are summarized in Tables 2.6–2.11. Other data are given in the Experimental Section.

Table 2.6: ^{1}H NMR Spectroscopic Data for Alstonerine (**5**), Alstonerinal (**6**), Alstophylline (**7**) and Alstophyllal (**8**)[a]

H	**5**	**6**	**7**	**8**
3	3.87 m	3.86 m	3.86 m	3.84 m
5	3.07 br d (7)	3.07 br d (7)	3.09 d (7)	3.06 d (7)
6a	2.49 d (16)	2.48 d (16)	2.48 d (16)	2.45 d (16)
6b	3.32 dd (16, 7)	3.31 dd (16, 7)	3.30 dd (16, 7)	3.29 dd (16, 7)
9	7.49 br d (8)	7.44 br d (8)	7.34 d (8)	7.34 d (8)
10	7.08 td (8, 1)	7.08 td (8, 1)	6.76 dd (8, 1)	6.76 dd (8, 2)
11	7.19 td (8, 1)	7.19 td (8, 1)	–	–
12	7.31 br d (8)	7.31 br d (8)	6.81 d (1)	6.81 d (2)
14a	1.81 td (12, 3)	1.79 td (12, 3)	1.80 td (12, 3)	1.77 td (12, 4)
14b	2.12 ddd	2.12 ddd	2.11 m	2.14 m
	(12, 5, 3)	(12, 5, 3)		
15	2.61 dt (12, 5)	2.61 dt (12, 5)	2.62 m	2.61 m
16	1.89 m	1.89 m	1.90 m	1.89 m
17a	4.16 ddd	4.18 ddd	4.18 ddd	4.19 ddd
	(11, 4, 2)	(11, 4, 2)	(11, 4, 2)	(11, 4, 2)
17b	4.40 t (11)	4.46 t (11)	4.42 t (11)	4.46 t (11)
18	2.07 s	2.15 s	2.09 s	2.17 s
21	7.52 s	9.65 s	7.53 s	9.66 s
N(1)-Me	3.64 s	3.63 s	3.60 s	3.60 s
N(4)-Me	2.31 s	2.31 s	2.34 s	2.32 s
11-OMe	–	–	3.89 s	3.89 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.7: ^{13}C NMR Spectroscopic Data for Alstonerine (**5**), Alstonerinal (**6**), Alstophylline (**7**), and Alstophyllal (**8**)[a]

C	5	6	7	8
2	137.1	137.1	131.8	132.6
3	54.6	54.6	53.6	53.9
5	53.7	53.6	54.6	54.8
6	22.8	22.3	22.3	25.0
7	105.8	105.8	105.8	105.7
8	126.5	126.5	121.0	121.0
9	117.7	117.3	118.2	118.3
10	120.7	121.0	108.1	108.3
11	118.6	118.6	155.9	155.8
12	108.6	108.6	93.2	93.4
13	137.1	137.1	137.9	137.9
14	38.5	38.5	31.8	32.3
15	32.3	31.8	24.9	25.0
16	41.7	41.7	38.4	38.5
17	67.7	68.0	67.7	67.7
18	22.7	16.5	16.5	22.9
19	195.7	170.6	170.0	195.5
20	126.5	126.5	121.0	121.0
21	157.4	188.6	188.8	157.0
N(1)-Me	29.0	29.0	29.0	29.1
N(4)-Me	24.9	24.9	41.6	41.7
11-OMe	–	–	55.8	56.1

[a] $CDCl_3$, 100 MHz, assignments based on HMQC, and HMBC.

Table 2.8: ^{1}H NMR Spectroscopic Data for Macrocarpine A (**9**), Macrocarpine B (**10**), and Macrocarpine C (**11**)[a]

H	9	10	11
3	3.96 m	3.98 t (3)	3.97 t (4)
5	2.87 d (7)	2.91 d (7)	2.91 d (7)
6a	2.47 d (17)	2.43 d (17)	2.45 d (17)
6b	3.25 dd (17, 7)	3.26 dd (17, 7)	3.27 dd (17, 7)
9	7.49 br d (8)	7.49 br d (8)	7.49 dd (8, 1)
10	7.10 td (8, 1)	7.10 td (8, 1)	7.09 td (8, 1)
11	7.19 td (8, 1)	7.18 td (8, 1)	7.17 td (8, 1)
12	7.29 br d (8)	7.29 br d (8)	7.27 dd (8, 1)
14a	1.42 ddd (13, 5, 2)	1.54 ddd (12, 4, 3)	1.39 dt (13, 4)
14b	2.50 td (13, 4)	2.29 m	2.26 td (13, 4)
15	2.06 dt (13, 5)	1.97 dt (13, 4)	1.86 m
16	2.15 dt (11, 5)	1.86 dt (11, 4)	1.86 m
17a	3.79 dd (11, 5)	3.73 dd (11, 4)	3.74 dd (11, 4)
17b	4.07 t (11)	4.06 t (11)	4.07 t (11)
18	1.24 d (7)	1.15 d (6)	1.13 d (6)
19	3.96 m	3.49 m	3.51 dq (10, 6)
20	1.07 m	1.46 m	1.69 m
21a	3.69 dd (11, 4)	3.31 dd (11, 8)	3.83 d (7)
21b	3.81 dd (11, 6)	3.49 m	3.83 d (7)
23	–	–	1.68 s
N(1)-Me	3.62 s	3.62 s	3.60 s
N(4)-Me	2.31 s	2.30 s	2.34 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.9: ^{13}C NMR Spectroscopic Data for Macrocarpine A (**9**), Macrocarpine B (**10**), and Macrocarpine C (**11**)[a]

C	9	10	11
2	133.2	133.2	133.0
3	53.7	53.6	53.5
5	54.6	55.1	54.9
6	22.6	22.5	22.4
7	106.6	106.7	106.7
8	126.4	126.4	126.3
9	118.1	117.9	117.9
10	118.8	118.8	118.8
11	120.8	120.7	120.8
12	108.7	108.8	108.5
13	136.9	137.0	136.9
14	30.7	25.3	25.0
15	28.6	26.7	27.1
16	39.3	43.5	43.4
17	68.9	67.6	67.5
18	18.8	20.2	20.1
19	71.2	70.5	70.3
20	43.6	46.8	43.2
21	63.1	61.6	62.9
22	–	–	170.8
23	–	–	20.3
N(1)-Me	29.0	29.0	28.9
N(4)-Me	41.7	41.7	41.6

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.10: ^{1}H and ^{13}C NMR Spectroscopic Data for Talcarpine (**12**), and *N*(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)[a]

Position	**12**		**13**	
	δ_H	δ_C	δ_H	δ_C
2	–	132.8	–	132.8
3	3.98 m	53.5	3.93 m	53.1
5	2.90 d (7)	54.5	2.96 d (7)	54.9
6β	2.45 d (16)	22.5	2.49 d (16)	22.4
6α	3.27 dd (16, 7)		3.30 dd (16, 7)	
7	–	106.6	–	106.6
8	–	126.2	–	126.2
9	7.49 br d (8)	118.1	7.52 br d (8)	117.9
10	7.10 td (8, 1)	118.9	7.13 td (8, 1)	118.9
11	7.19 td (8, 1)	121.0	7.21 td (8, 1)	121.0
12	7.29 br d (8)	108.7	7.31 br d (8)	108.9
13	–	137.2	–	137.0
14β	1.45 ddd (12, 4, 3)	30.1	1.28 m	26.7
14α	2.50 td (12, 4)		2.37 m	
15	2.20 m	27.0	2.37 m	26.1
16	2.06 dt (11, 5)	39.4	1.93 m	42.5
17	3.89 dd (12, 5)	68.8	3.75 dd (12, 5)	67.1
17'	4.14 t (12)		4.06 t (12)	
18	1.30 d (7)	19.2	1.20 d (7)	20.2
19	3.98 m	69.4	3.93 m	67.8
20	1.79 br s	54.6	2.37 m	57.7
21	9.95 d (3)	204.7	9.41 br s	203.0
N(1)-Me	3.62 s	29.1	3.58 s	29.0
N(4)-Me	2.32 s	41.8	2.31 s	41.6

[a] $CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, and HMQC.

Table 2.11: ^{1}H and ^{13}C NMR Spectroscopic Data for Macrodasine A (**14**), and Macrodasine G (**15**)[a]

Position	**14**		**15**	
	δ_H	δ_C	δ_H	δ_C
2	–	132.8	–	132.5
3	3.95 t (3)	53.3	3.95 m	53.3
5	2.98 d (7)	54.8	3.50 d (7)	54.7
6β	2.39 m	22.5	2.42 d (17)	22.5
6α	3.27 dd (17, 7)		3.27 δδ (17, 7)	
7	–	106.4	–	106.5
8	–	126.4	–	126.2
9	7.50 d (8)	118.0	7.50 d (8)	118.0
10	7.12 t (8)	118.9	7.12 t (8)	118.9
11	7.21 td (8, 1)	121.0	7.21 t (8)	121.0
12	7.31 d (8)	108.0	7.30 d (8)	108.8
13	–	136.9	–	136.9
14β	1.55 ddd (13, 5, 3)	31.9	1.52 ddd (13, 5, 3)	31.9
14α	2.39 m		2.42 m	
15	1.85 m	26.5	1.81 m	27.0
16	2.03 dt (12, 5)	36.9	2.16 dt (12, 5)	36.5
17β	3.70 dd (12, 5)	64.3	3.87 dd (12, 5)	64.7
17α	4.04 t (12)		4.09 t (12)	
18	1.59 s	24.2	1.59 s	23.6
19	–	105.5	–	105.3
20	2.01 dd (12, 8)	44.3	1.85 m	45.6
21α	1.85 m	34.7	2.00 dd (13, 8)	38.2
21β	2.39 m		2.32 t (13)	
22	–	114.8	–	112.0
23α	4.13 d (5)	77.7	3.95 m	75.7
24a	1.85 m	33.0	1.87 m	34.2
24b	2.39 m		2.08 ddd (13, 8, 5)	
25	4.42 m	79.2	4.32 m	77.0
26a	3.43 dd (12, 3)	63.9	3.43 dd (12, 4)	64.6
26b	3.77 dd (12, 2)		3.69 dd (12, 3)	
N(1)-Me	3.63 s	29.0	3.62 s	29.0
N(4)-Me	2.33 s	41.6	2.35 s	41.6

[a] $CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

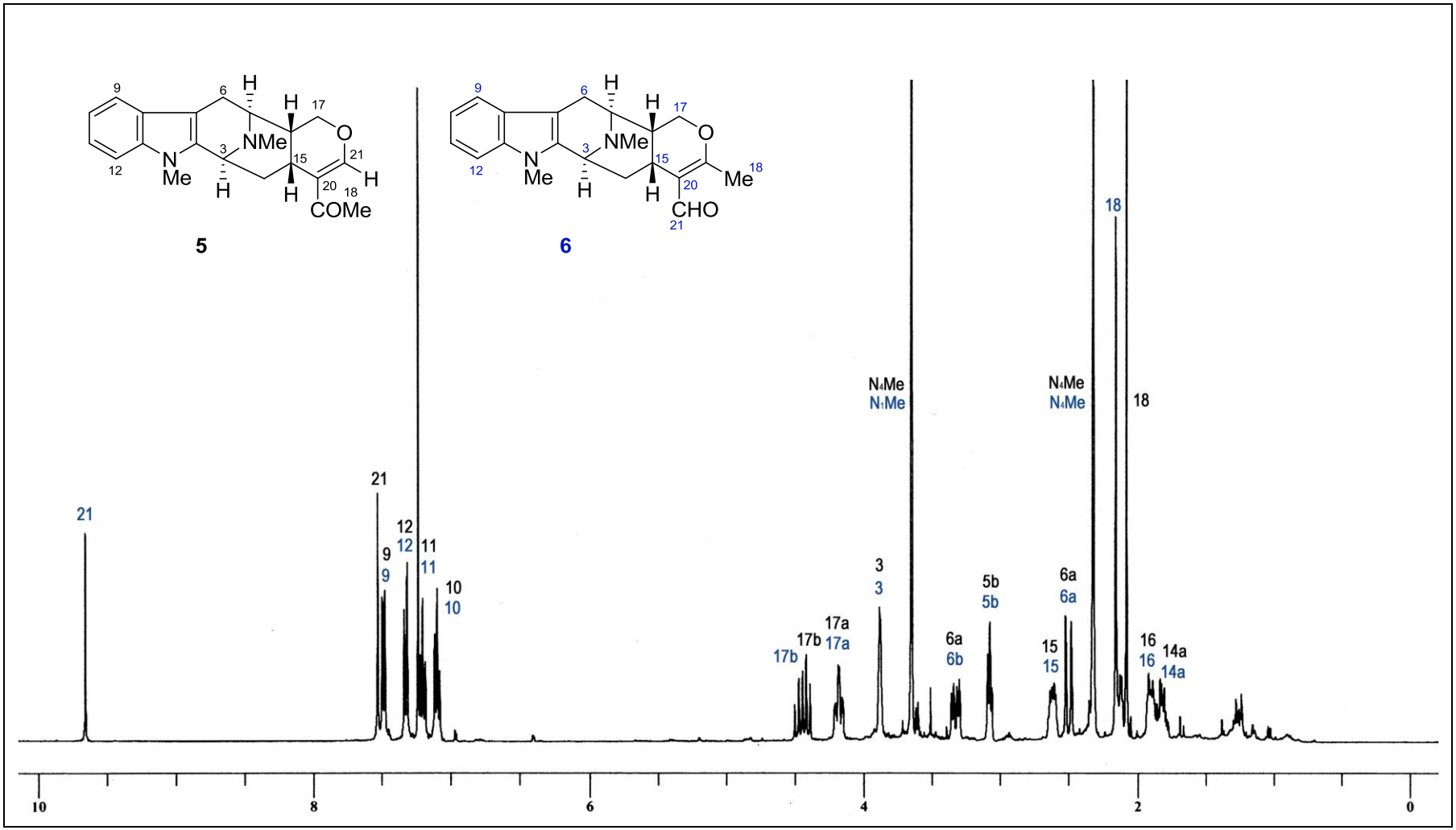


Figure 2.10: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstonerine (**5**) and Alstonerinal (**6**)

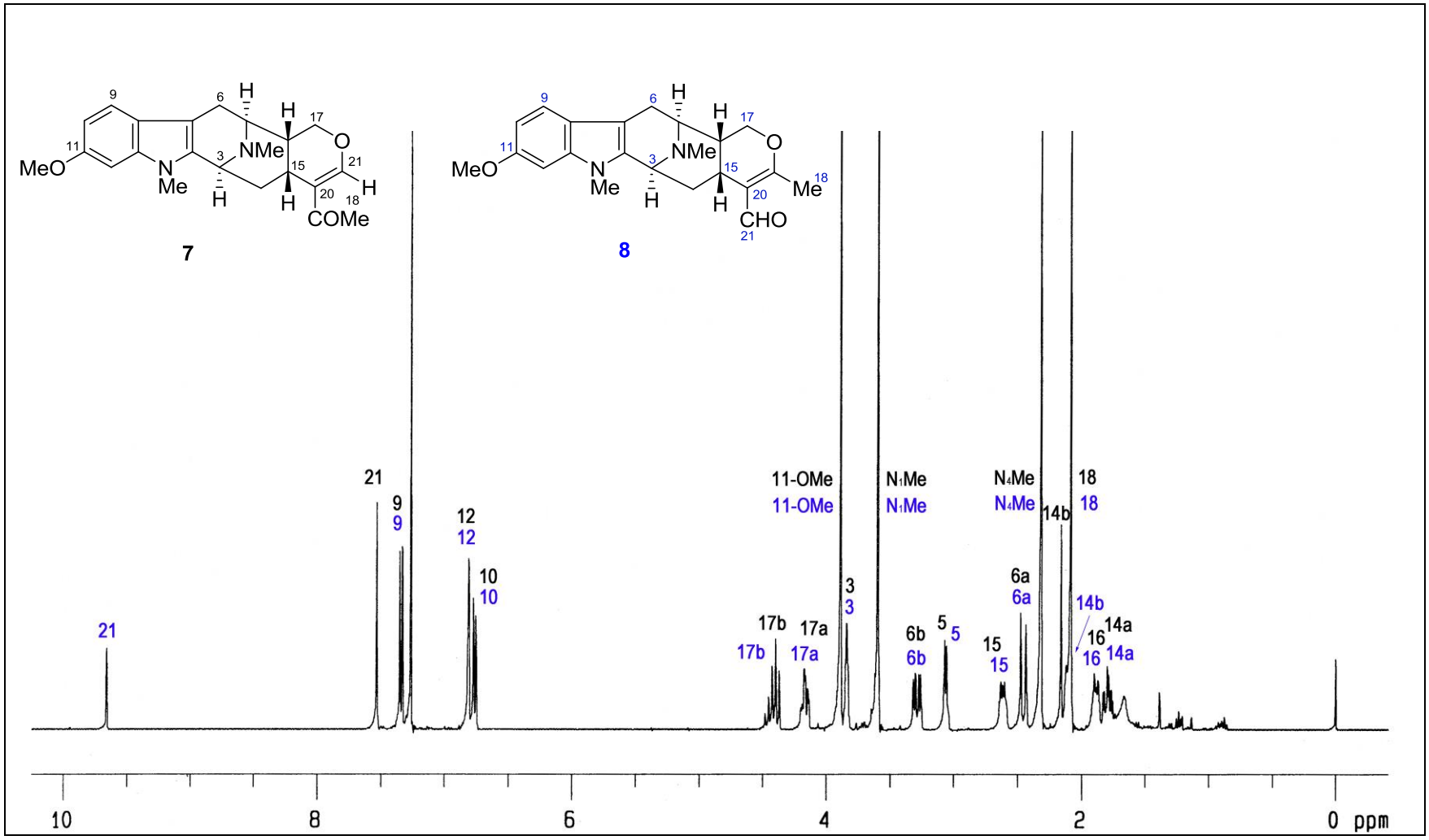


Figure 2.11: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstophylline (**7**) and Alstophyllal (**8**)

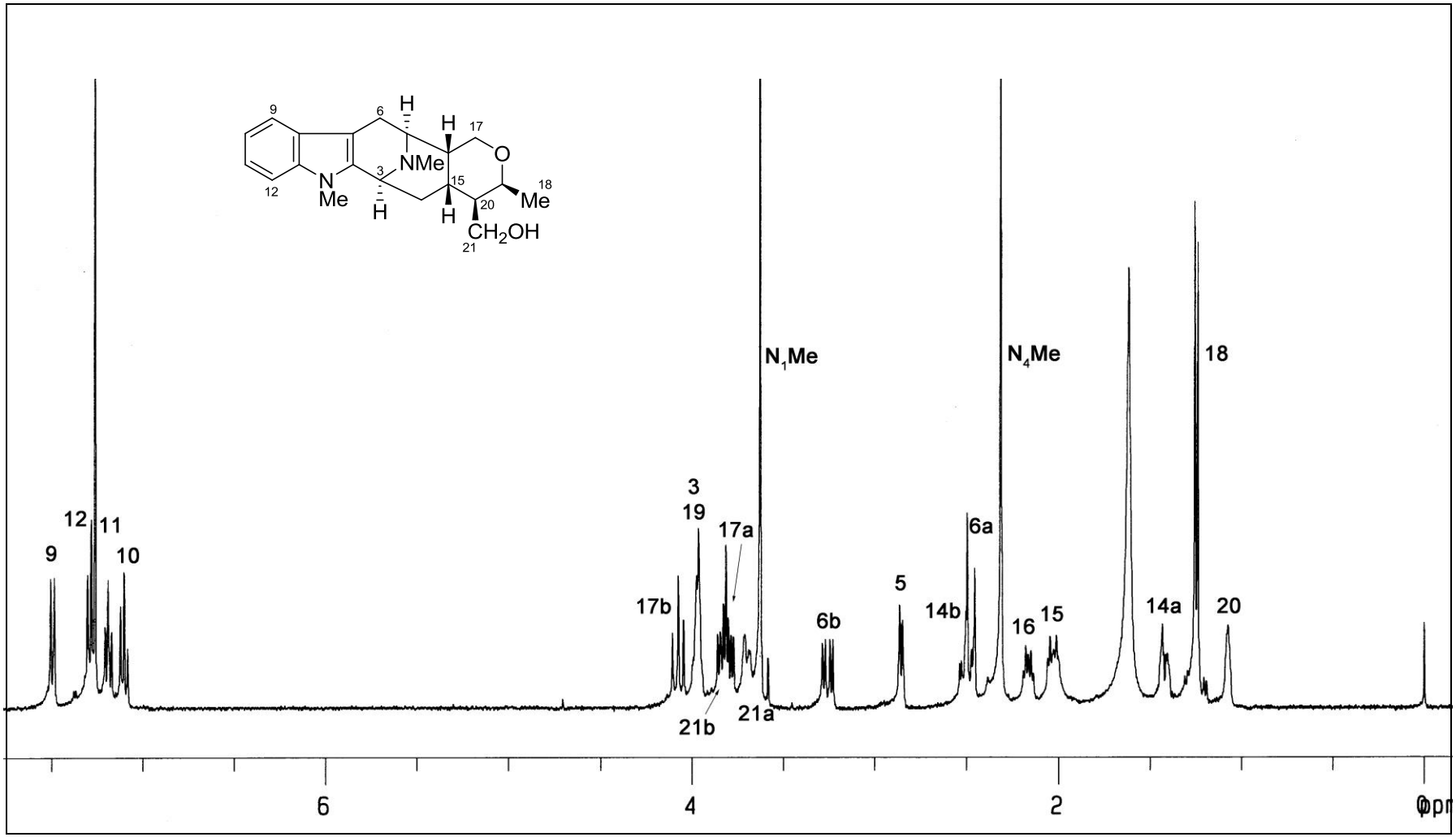


Figure 2.12: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrocarpine A (**9**)

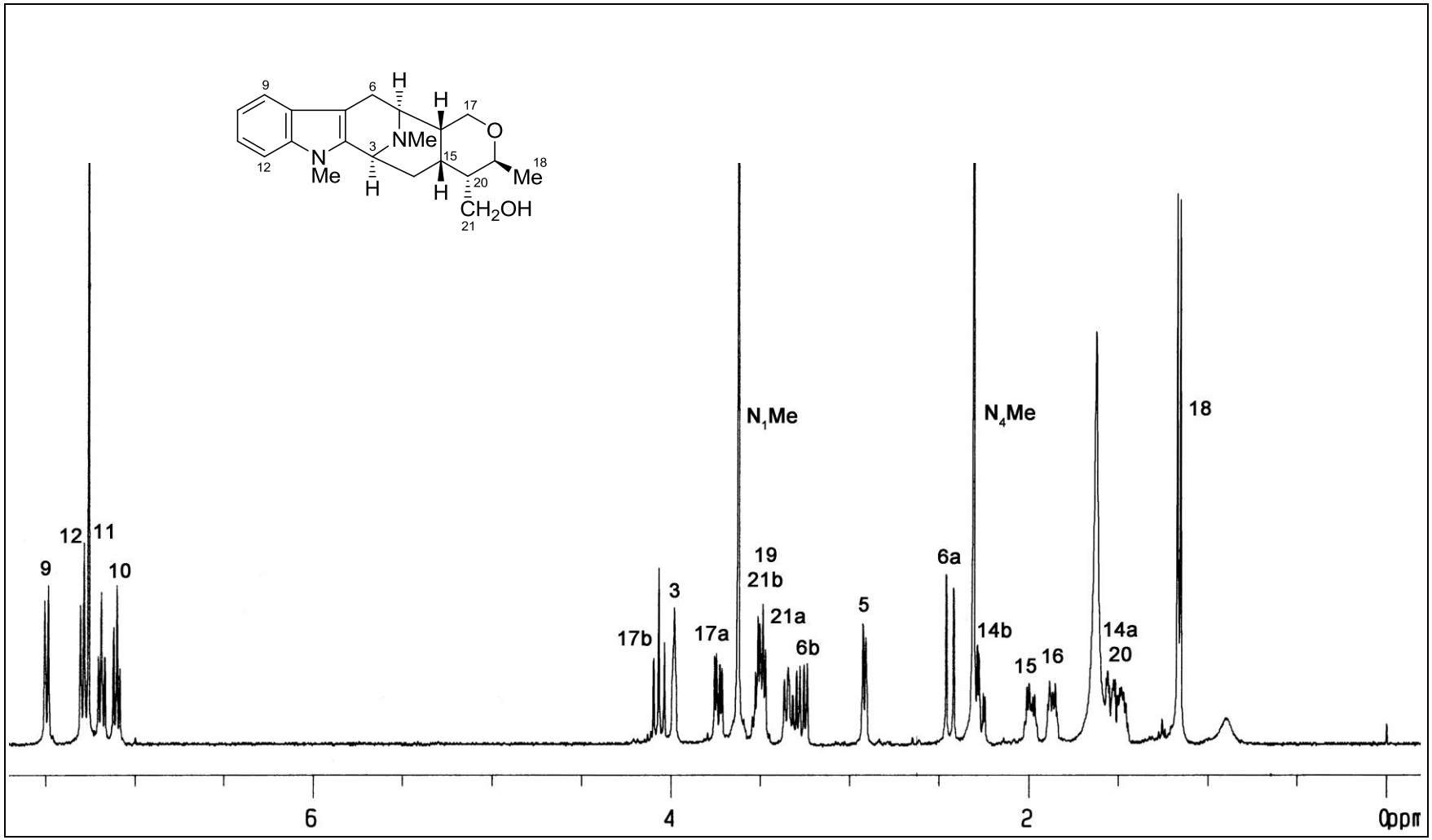


Figure 2.13: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrocarpine B (**10**)

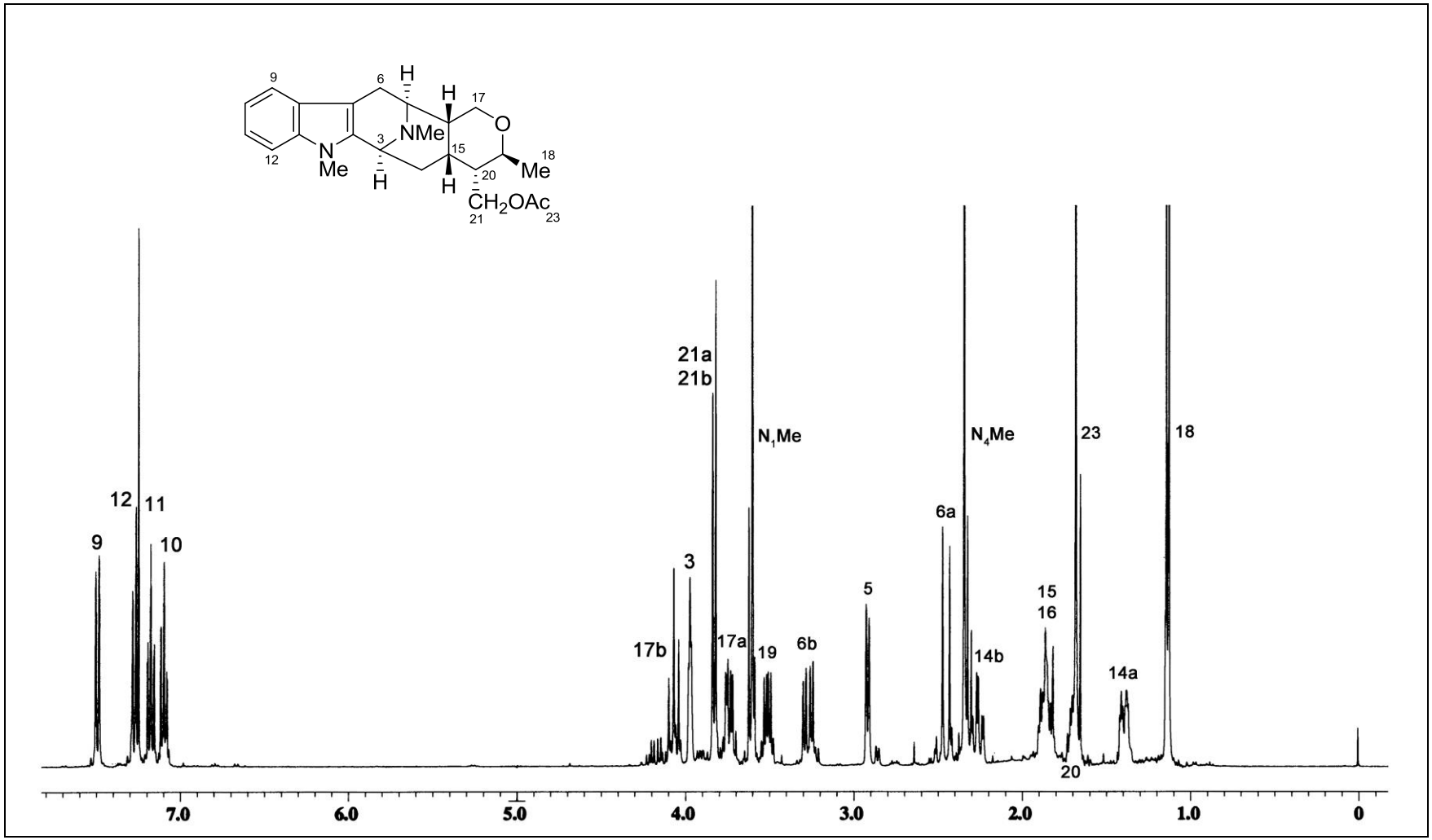


Figure 2.14: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrocarpine C (**11**)

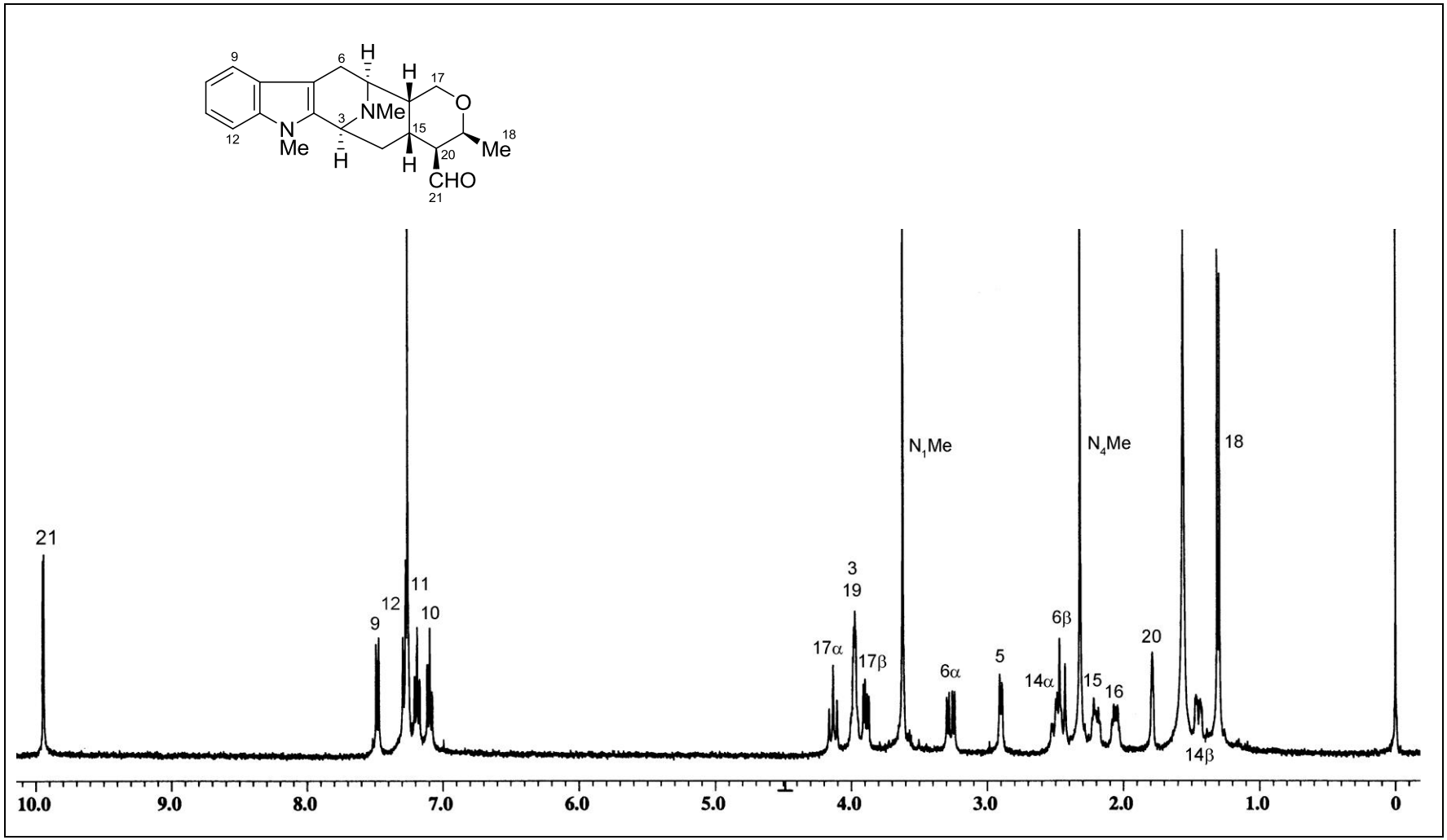


Figure 2.15: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Talcarpine (**12**)

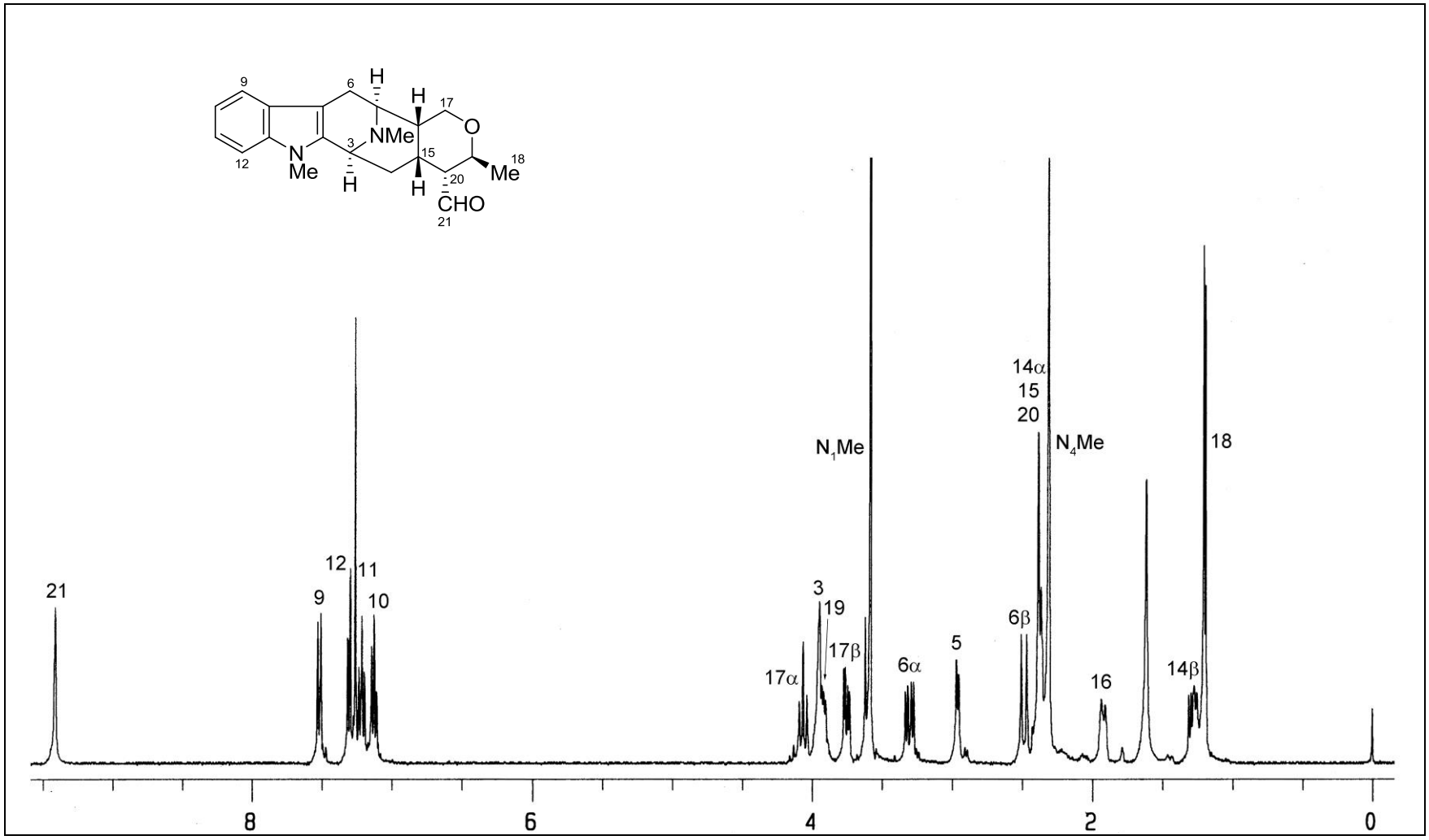


Figure 2.16: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *N*(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)

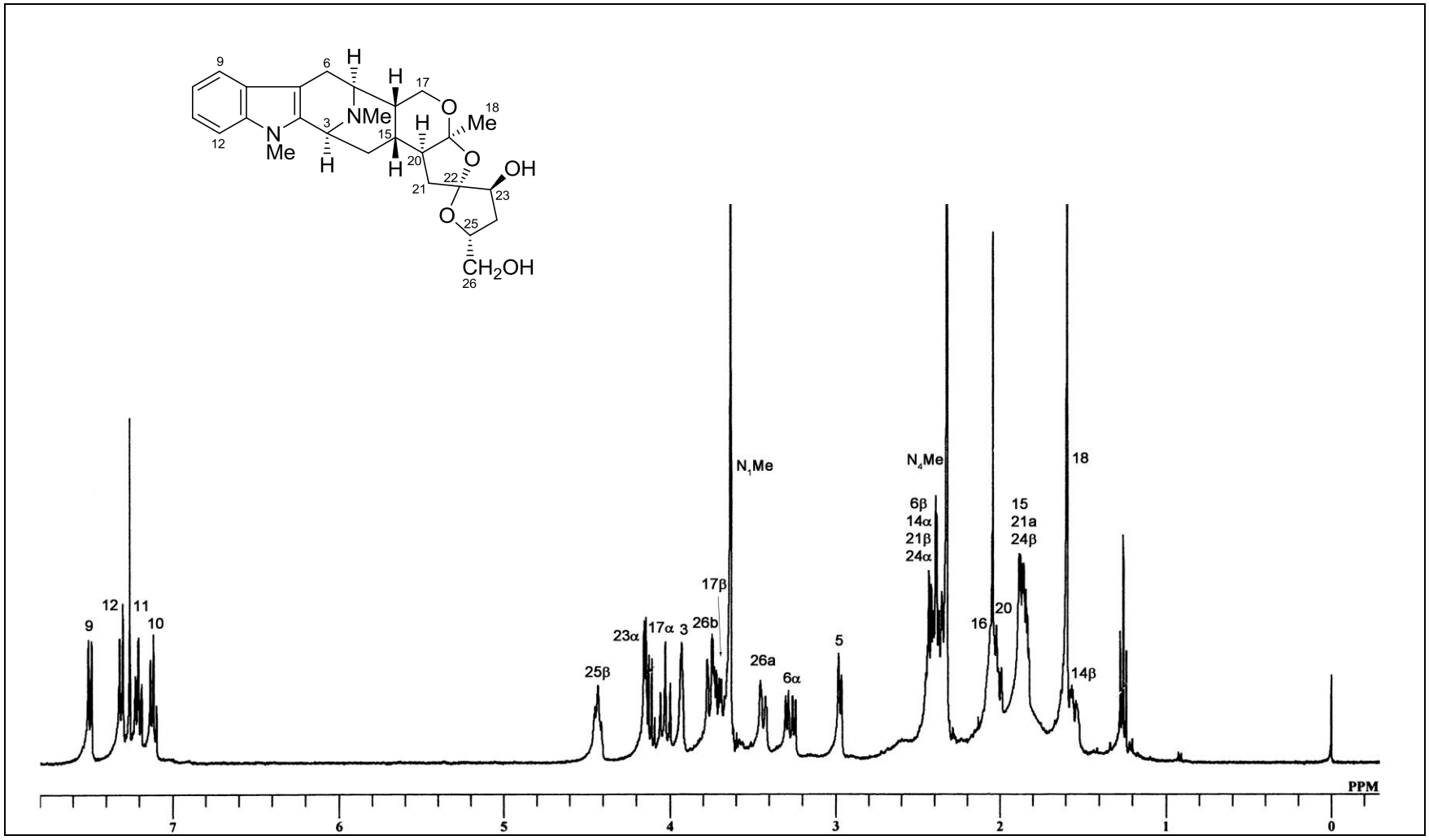


Figure 2.17: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrodasine A (**14**)

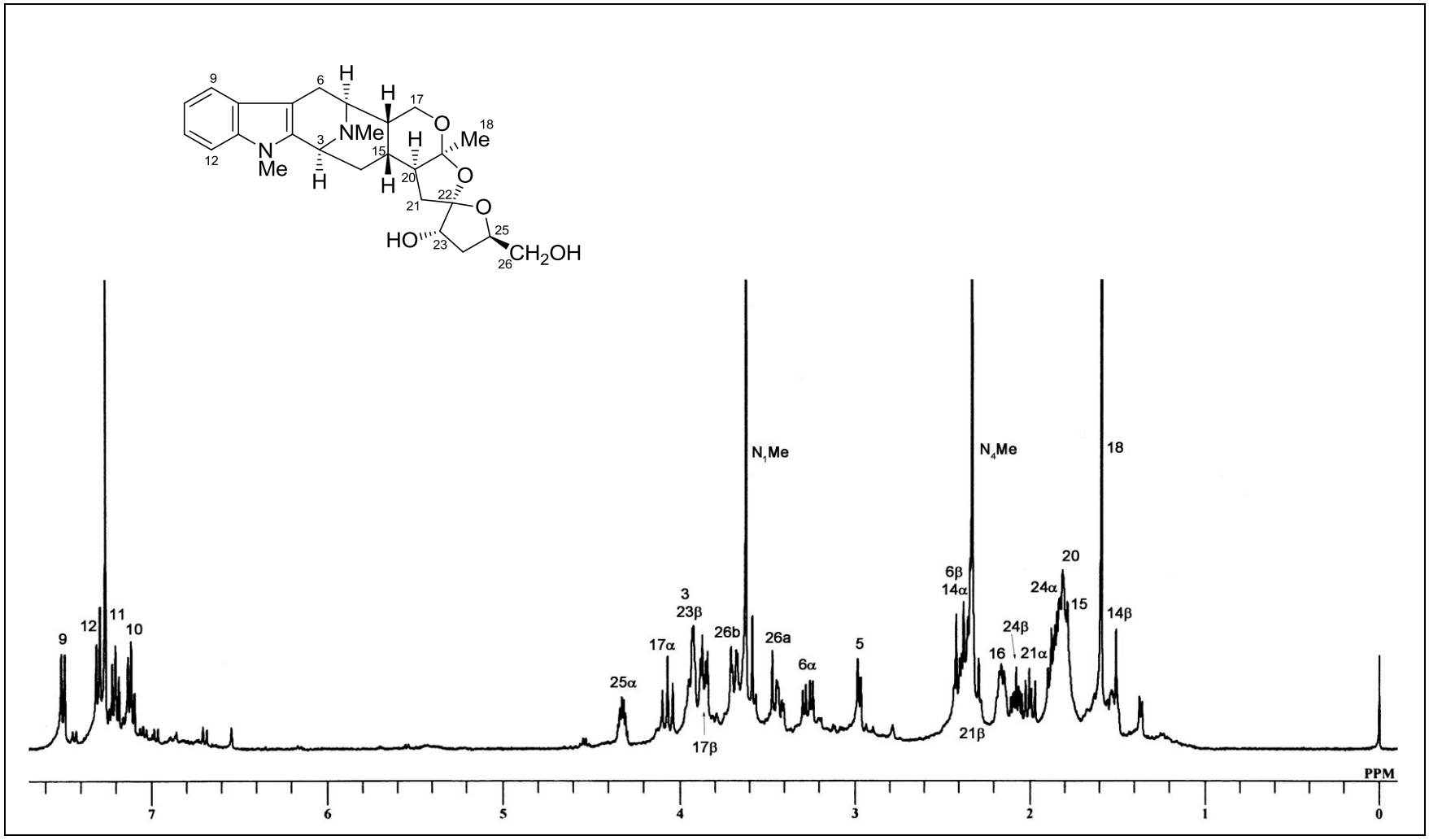


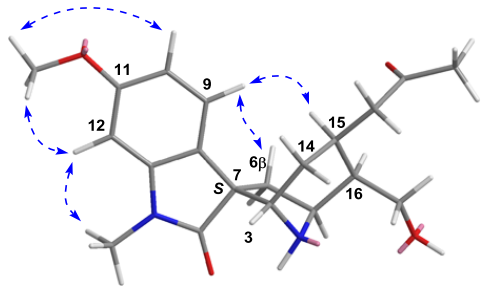
Figure 2.18: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrodasine G (**15**)

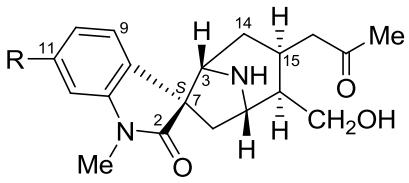
2.1.2 Macroline Oxindole Alkaloids

2.1.2.1 Compound 16 [Alstonoxine C (11-Methoxyalstonoxine A)]

Compound **16** was isolated as a light yellowish oil, with $[\alpha]_D$ –30 (*c* 0.39, $CHCl_3$), and subsequently crystallized from CH_2Cl_2-hexane as colorless block crystals. The UV spectrum showed absorption maxima at 216, 255, and 285 nm indicative of an oxindole chromophore. The IR spectrum showed the presence of lactam (1694 cm^{-1}), ketone carbonyl (1694 cm^{-1}), NH (3295 cm^{-1}) and hydroxyl (3395 cm^{-1}) functions, while the carbon resonances at δ 183.0, 208.7, 65.9 confirm the presence of lactam, ketone, and oxymethylene groups, respectively. The ESIMS showed a $[M + H]^+$ peak at *m/z* 359, analyzing for $C_{20}H_{26}N_2O_4$ + H.

The ^1H and ^{13}C NMR spectroscopic data (Table 2.12; Figure 2.23) of **16** showed a close rememblance to those of 7(*S*)-alstonoxine A (**18**),[132,233] except for the absence of an aromatic hydrogen signal at C-11, which was replaced in **16** by a 3H singlet at δ 3.84 of an aromatic methoxy substituent. The placement of the methoxy substituent at C-11 was further confirmed by the observed NOEs between OMe and H-10 as well as H-12. The configuration of the spirocyclic C-7 was assigned as *S* from the observed NOEs between H-9 and H-15 (Figure 2.19). In view of the availability of suitable crystals, an X-ray diffraction analysis was carried out which provided confirmation of the structure and relative configuration of **16** deduced from the spectroscopic data (Figure 2.20). The X-ray structure of **16** also provided additional support for the original assignment of the structure and relative configuration of alstonoxine A (**18**).





16 R = OMe
18 R = H

Figure 2.19: Selected NOEs of **16**

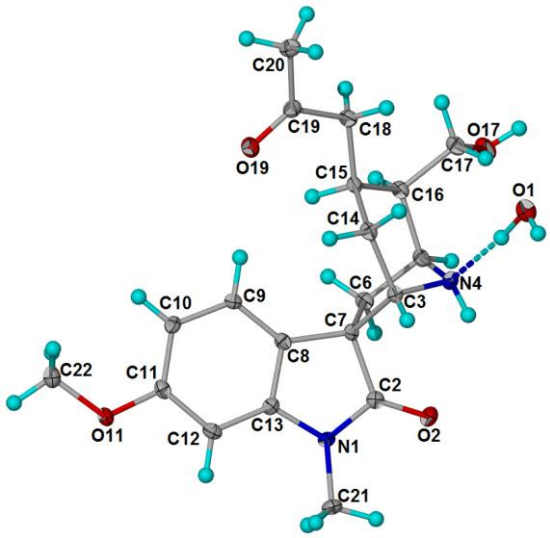


Figure 2.20: X-ray Strcuture of **16**

2.1.2.2 Compound 17 [Alstonoxine D (11-Methoxyalstonoxine B)]

Compound **17** was isolated as a light yellowish oil, with $[\alpha]_D$ –16 (*c* 0.23, $CHCl_3$). The UV and IR spectrum of **17** were similar to those of alstonoxine B (**19**),[132,233] while the ESIMS showed a $[M + H]^+$ peak at *m/z* 361 ($C_{20}H_{28}N_2O_4$ + H).

The ^1H and ^{13}C NMR data (Table 2.12; Figure 2.24) of **17** were generally similar to those of alstonoxine B (**19**),[132,233] except for the presence of an additional aromatic methoxy singlet at δ 3.83, and the absence of one aromatic-H signal. The placement of the methoxy substituent at C-11 was supported by the observed coupling behaviour of the aromatic hydrogens as well as from the observed three-bond correlations from H-9 to C-11 and C-13, in the HMBC spectrum (Figure 2.21). This assignment was further supported by the observed NOEs between 11-OMe and H-10, H-12 (Figure 2.21). The configuration of the spirocenter C-7 was assigned as *S* from the observed NOEs between H-9 and H-15. The NMR data of **17** were however insufficient to establish the stereochemistry of C-19. Towards this end, alstonoxine C (**16**) was treated with $NaBH_4$/MeOH, which gave a mixture of the epimeric alcohol products in approximately equal amounts, which were separated by preparative centrifugal TLC (SiO_2, 1% MeOH/$CHCl_3$, NH_3-saturated). The NMR data revealed that the slower eluting compound corresponded to compound **17**. With sufficient amounts of **17** obtained in this manner, the configuration at C-19 could be determined by Horeau's procedure (see Experimental Section),[237,238] which showed that the C-19 configuration in **17** is *S* (the faster eluting compound **6a** therefore corresponded to the 19*R* epimer). The structure and relative configuration of alstonoxine B (**19**) was previously reported from *Alstonia angustifolia* var. *latifolia*, based on analysis of the NMR and MS data which at the time were insufficient to assign the configuration at C-19. Alstonoxine B (**19**) was also isolated in the present study, and since suitable crystals were obtained from CH_2Cl_2-

hexane solution in this instance, X-ray diffraction analysis was carried which established the relative configuration of C-19 in alstonoxine B (**19**) as *S* (Figure 2.22). The X-ray structure of **19** also provided additional support for the determination of the C-19 configuration of **17** as 19*S*, using Horeau's procedure (*vide supra*), since the NMR data of **17** and **19** indicated that the non-aromatic portion of **6** was virtually identical to the non-aromatic portion of **19**, and therefore the configuration of C-19 in **17** can be assumed to be similar to that of alstonoxine B (**19**).

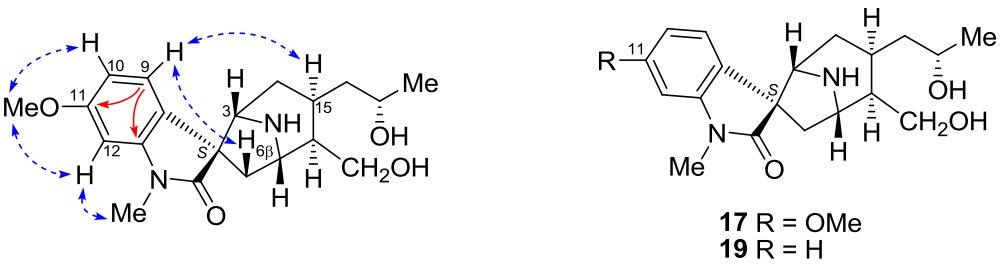


Figure 2.21: Selected HMBCs and NOEs of **17**

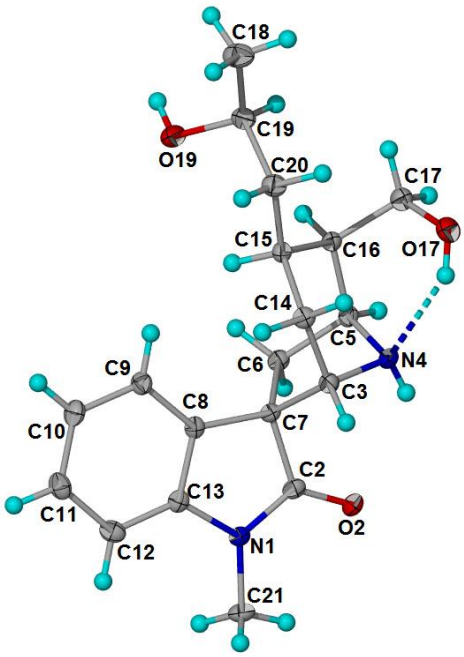


Figure 2.22: X-ray structure of **19**

Table 2.12: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **16** (11-Methoxyalstonoxine A) and Compound **17** (11-Methoxyalstonoxine B)[a]

Position	**16**		**17**	
	δ_H	δ_C	δ_H	δ_C
2	–	183.0	–	183.1
3	3.19 m	62.9	3.20 m	63.4
5	3.86 m	61.7	3.90 m	61.8
6β	2.08 d (14)	41.0	2.06 d (14)	40.8
6α	2.39 dd (14, 8)		2.38 dd (14, 8)	
7	-	56.8	-	57.0
8	-	120.8	-	121.1
9	7.76 d (9)	125.8	7.39 d (8)	125.1
10	6.70 dd (9, 2)	106.4	6.60 dd (8, 2)	106.6
11	-	160.2	-	160.2
12	6.45 d (2)	96.6	6.45 d (2)	96.5
13	-	145.5	-	145.6
14β	1.69 m	33.1	1.72 m	34.2
14α	1.86 dd (13, 5)		1.82 m	
15	2.97 m	26.2	2.69 m	26.9
16	1.69 m	41.6	1.72 m	40.7
17	3.81 m	65.9	3.90 m	65.3
17'	4.01 d (12)		4.00 dd (11, 1)	
18	2.20 s	31.0	1.29 d (6)	24.9
19	-	208.7	3.90 m	65.5
20	2.69 dd (18, 5)	47.1	1.53 m	42.5
20'	2.80 dd (18, 8)		1.86 m	
N(1)-Me	3.16 s	26.4	3.17 s	26.4
11-OMe	3.84 s	55.7	3.83 s	55.6

[a] $CDCl_3$, 400 MHz and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

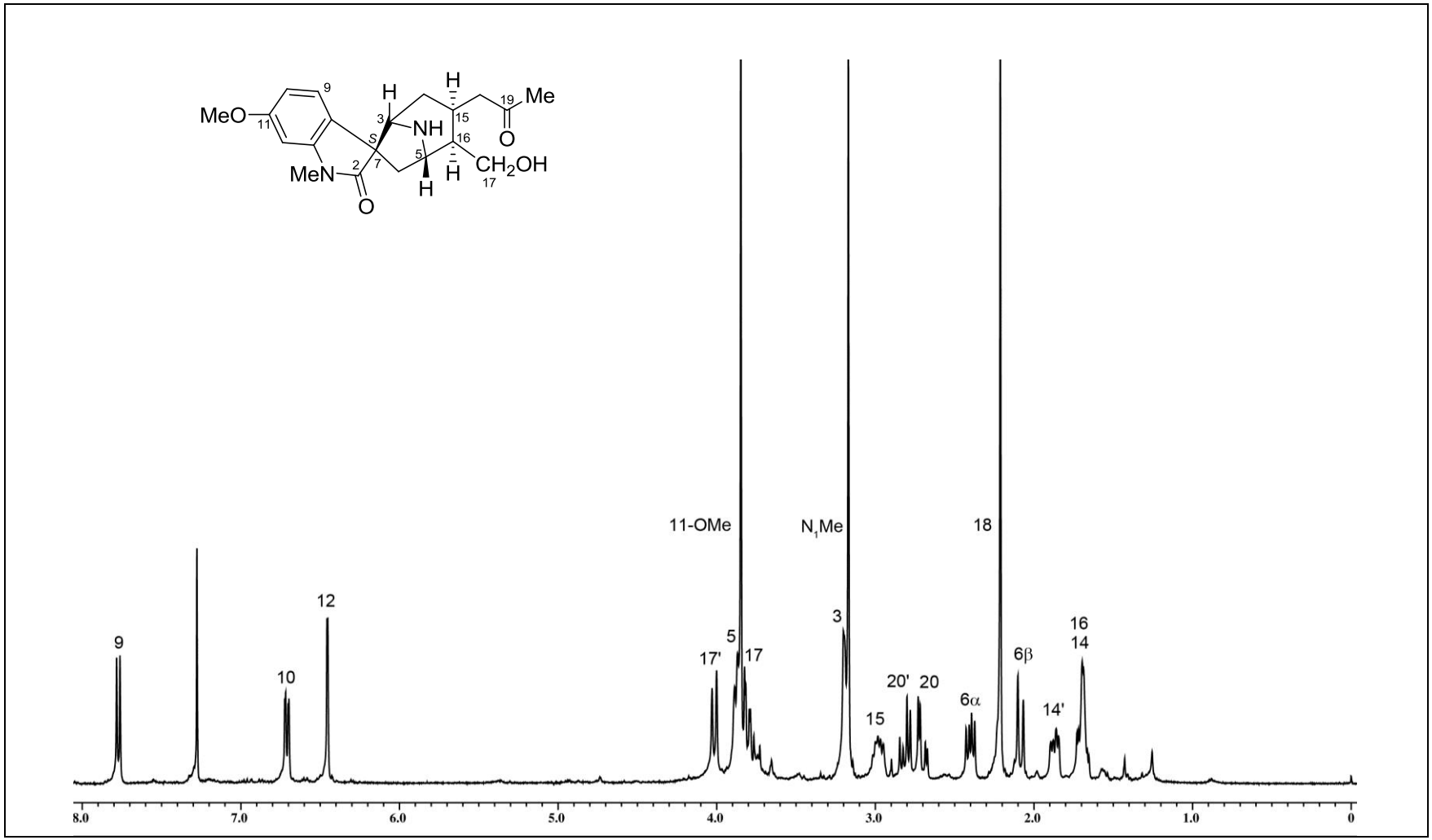


Figure 2.23: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **16** (11-Methoxyalstonoxine A)

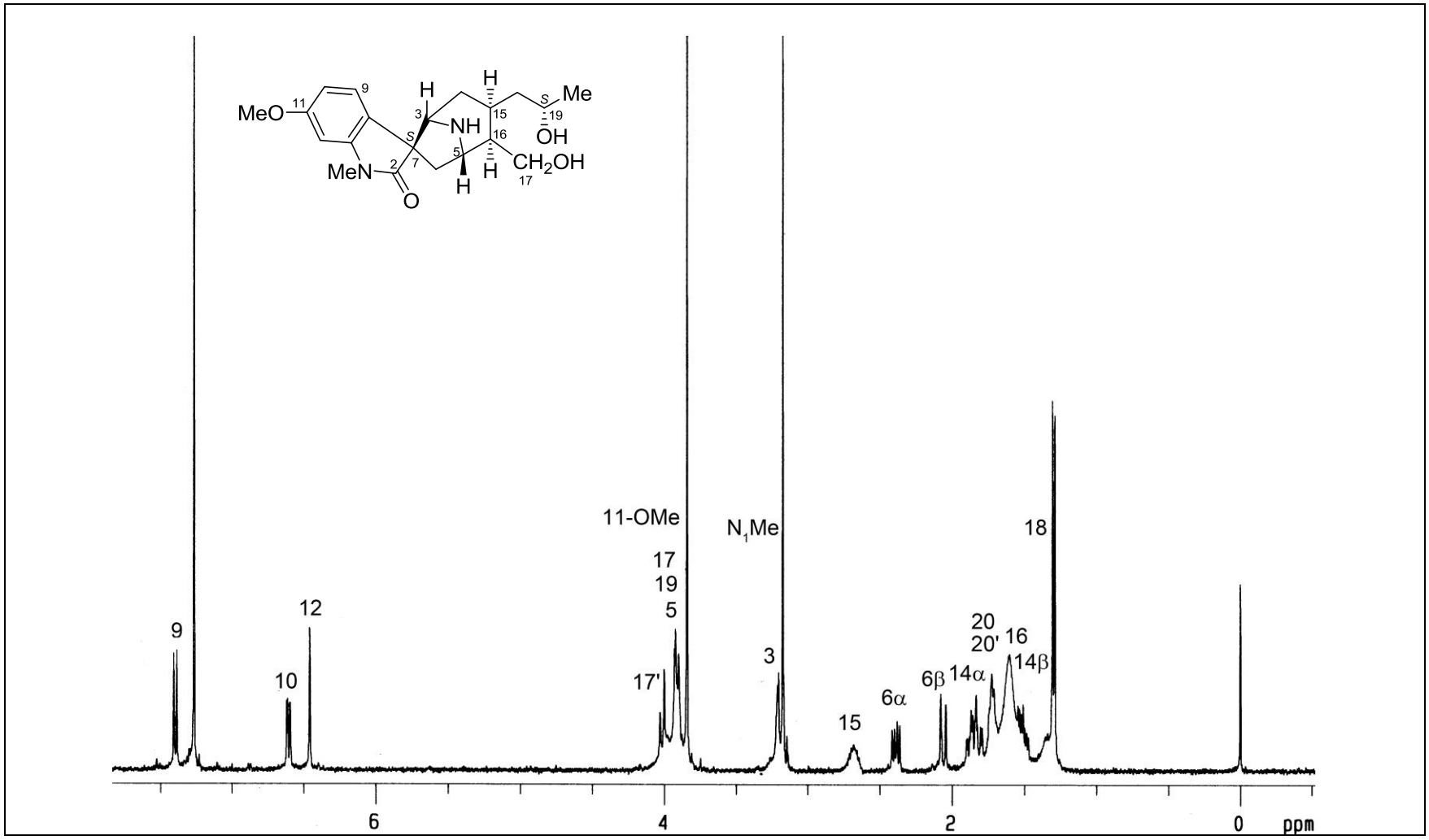


Figure 2.24: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **17** (11-Methoxyalstonoxine B)

2.1.2.3 Alstonoxine A (18), Alstonoxine B (19), Alstonisine (20), Alstonal (21), *N*(4)-Demethylalstophylline oxindole (22) and *N*(4)-Demethylalstophyllal oxindole (23)

Six known alkaloids belonging to this group, viz., alstonoxine A (**18**),[132,239] alstonoxine B (**19**),[132,239] alstonisine (**20**),[64,116,118,184,235,240] alstonal (**21**),[131,132] *N*(4)-demethylalstophylline oxindole (**22**),[162,164,235] and *N*(4)-demethylalstophyllal oxindole (**23**)[235] were isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.25–2.28, and the NMR spectroscopic data are summarized in Tables 2.13–2.15. Other data are given in the Experimental Section.

Table 2.13: ^{1}H and ^{13}C NMR Spectroscopic Data for Alstonoxine A (**18**), and Alstonoxine B (**19**)[a]

Position	**18**		**19**	
	δ_H	δ_C	δ_H	δ_C
2	-	182.3	-	182.4
3	3.25 m	63.1	3.25 m	63.5
5	3.90 br d (8)	61.7	3.91 m	61.7
6β	2.15 dd (13, 2)	40.7	2.13 dd (14, 1)	40.5
6α	2.43 dd (13, 8)		2.41 dd (14, 8)	
7	-	57.2	-	57.4
8	-	129.0	-	129.2
9	7.84 br d (8)	125.0	7.52 br d (8)	124.3
10	7.20 td (8, 1)	123.1	7.10 td (8, 1)	122.8
11	7.32 td (8, 1)	128.1	7.31 td (8, 1)	128.1
12	6.87 br d (8)	108.1	6.88 br d (8)	108.2
13	-	144.1	-	144.2
14β	1.71 m	33.0	1.53 ddd (14, 9, 5)	42.3
14α	1.87 (14, 6, 2)		1.85 ddd (14, 9, 3)	
15	3.05 m	26.1	2.72 m	26.8
16	1.71 m	41.4	1.77 m	40.7
17	3.80 dd (12, 2)	65.8	3.91 m	65.2
17'	4.02 dd (12, 1)		4.01 dd (11, 1)	
18	2.21 s	30.8	1.30 d (6)	24.7
19	-	208.4	3.91 m	65.1
20	2.72 dd (18, 6)	47.0	1.77 m	34.0
20'	2.79 dd (18, 7)		1.77 m	
N(1)-Me	3.20 s	26.2	3.20 s	26.5

[a] $CDCl_3$, 400 and 100 MHz, respectively, assignments based on COSY, HMQC, and HMBC.

Table 2.14: ^{1}H NMR Spectroscopic Data for Alstonisine (**20**), Alstonal (**21**), *N*(4)-Demethylalstophylline oxindole (**22**), and *N*(4)-Demethylalstophyllal oxindole (**23**)[a]

H	**20**	**21**	**22**	**23**
3	3.18 br s	3.18 br s	3.16 br s	3.16 br s
5	3.68 br d (7)	3.67 dd (7, 2)	3.68 m	3.68 m
6	2.19 br d (13)	2.18 br d (13)	2.14 dd (13, 1)	2.13 dd (13, 1)
	2.52 dd (13, 7)	2.51 dd (13, 2)	2.51 dd (13, 8)	2.50 dd (13, 8)
9	8.25 br d (8)	8.24 br d (8)	8.17 d (8)	8.16 d (8)
10	7.30 td (8, 1)	7.30 td (8, 1)	6.81 dd (8, 2)	6.80 dd (8, 2)
11	7.33 td (8, 1)	7.34 td (8, 1)	–	–
12	6.88 br d (8)	6.87 br d (8)	6.46 d (2)	6.46 d (2)
14	1.55 ddd (14, 12, 3)	1.54 ddd (14, 12, 3)	1.57 m	1.57 m
	2.25 ddd (14, 6, 3)	2.29 ddd (14, 6, 3)	2.26 m	2.26 m
15	3.40 dt (12, 6)	3.36 dt (12, 6)	3.35 m	3.35 m
16	1.96 m	1.97 m	1.96 m	1.96 m
17	4.26 ddd (11, 4, 2)	4.28 ddd (11, 4, 2)	4.26 ddd (11, 4, 2)	4.28 ddd (11, 4, 2)
	4.45 t (11)	4.51 t (11)	4.47 t (11)	4.53 t (11)
18	2.24 s	2.24 s	2.25 s	2.25 s
21	7.62 s	9.86 s	7.63 s	9.85 s
N(1)-Me	3.20 s	3.20 s	3.17 s	3.17 s
11-OMe	–	–	3.85 s	3.86 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.15: ^{13}C NMR Spectroscopic Data for Alstonisine (**20**), Alstonal (21), *N*(4)-Demethylalstophylline oxindole (**22**), and *N*(4)-Demethylalstophyllal oxindole (**23**)[a]

C	**20**	**21**	**22**	**23**
2	181.9	181.9	183.1	183.1
3	63.4	63.4	63.8	63.8
5	55.9	55.9	56.2	56.2
6	41.5	41.5	42.1	42.1
7	56.5	56.5	56.3	56.3
8	128.7	128.7	121.2	121.2
9	125.1	125.1	126.2	126.2
10	122.8	122.8	106.3	106.4
11	127.5	127.5	160.0	160.0
12	107.5	107.5	96.9	96.9
13	143.6	143.6	145.3	145.3
14	30.6	30.3	31.2	31.2
15	23.8	23.5	24.2	24.1
16	36.5	36.5	37.0	37.0
17	68.2	67.9	68.5	68.6
18	24.5	16.2	25.0	16.6
19	196.0	170.5	196.6	171.0
20	121.3	117.7	122.0	118.4
21	157.2	189.0	158.0	189.4
N(1)-Me	25.8	25.8	26.3	26.3
11-OMe	–	–	55.5	55.5

[a] $CDCl_3$, 100 MHz, assignments based on HMQC, and HMBC.

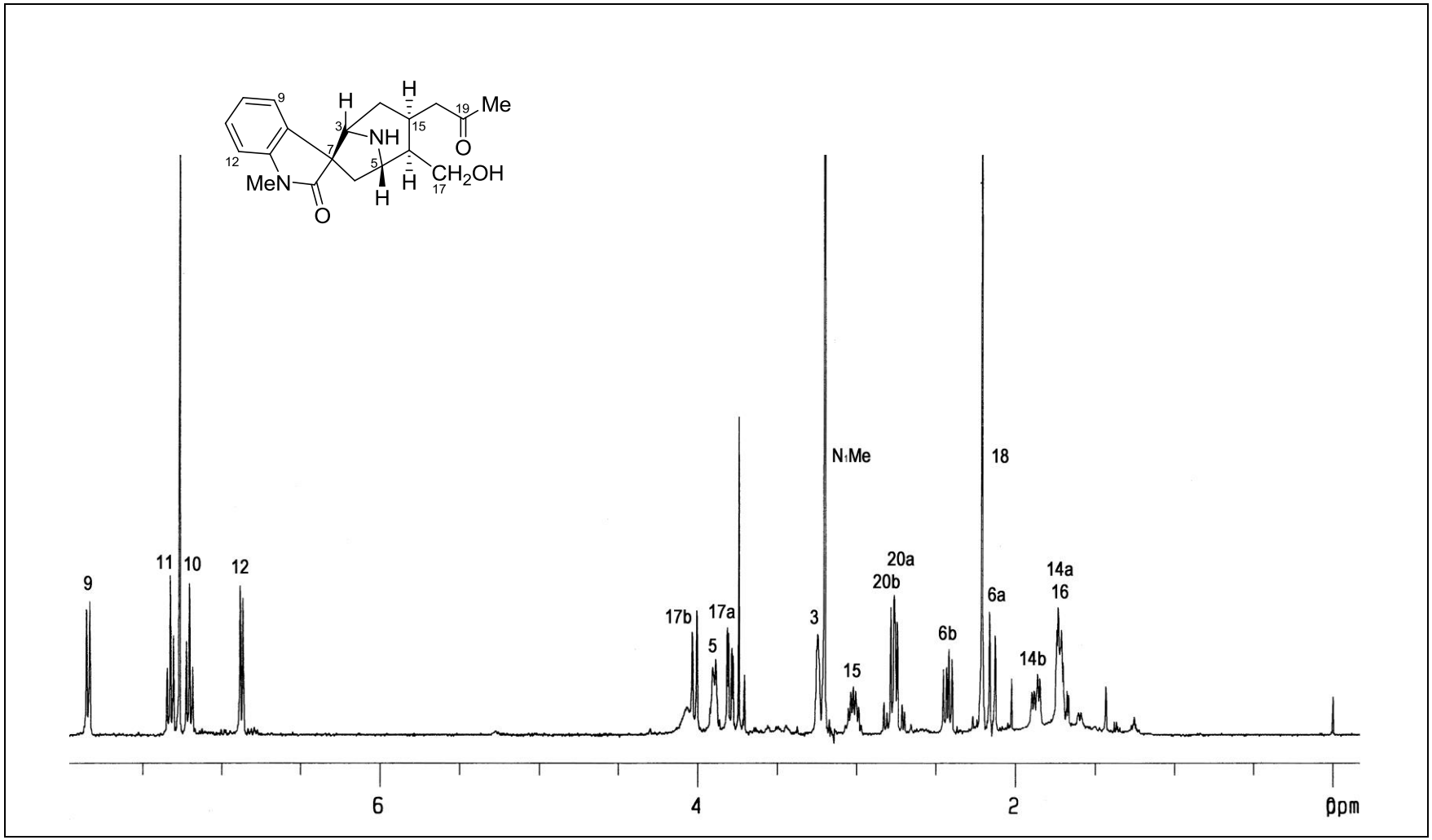


Figure 2.25: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstonoxine A (**18**)

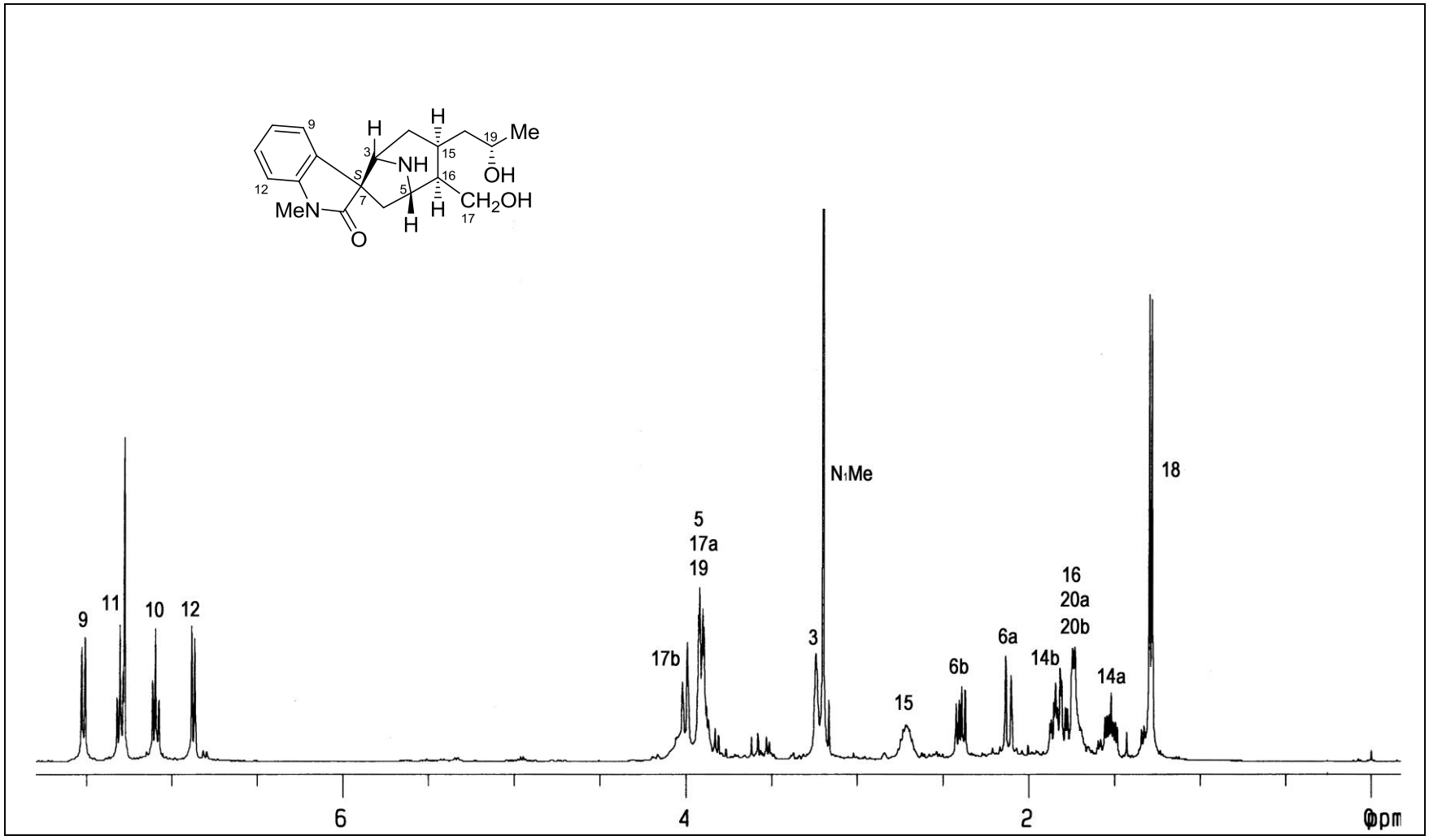


Figure 2.26: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstonoxine B (**19**)

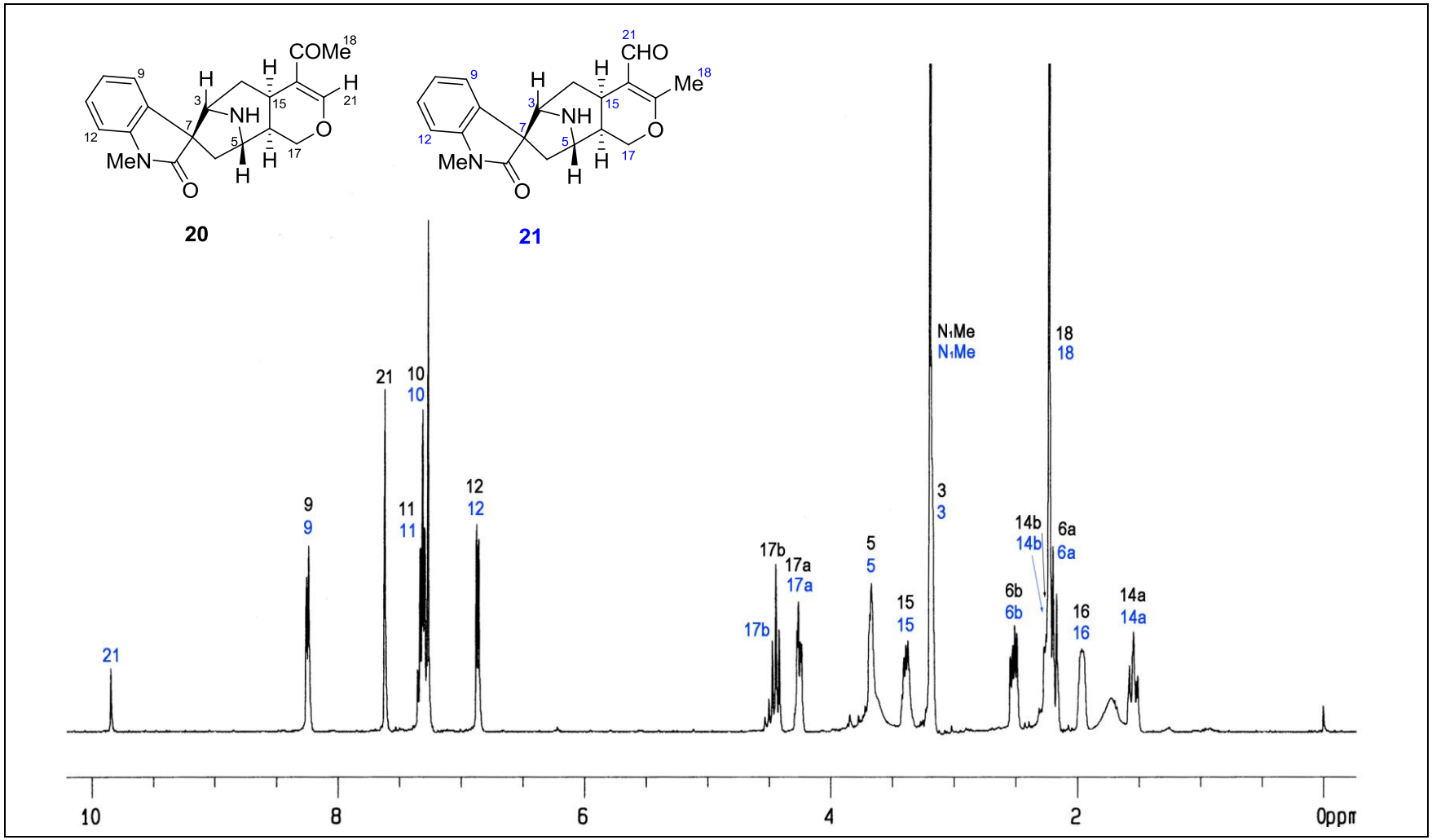


Figure 2.27: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstonisine (**20**) and Alstonal (**21**)

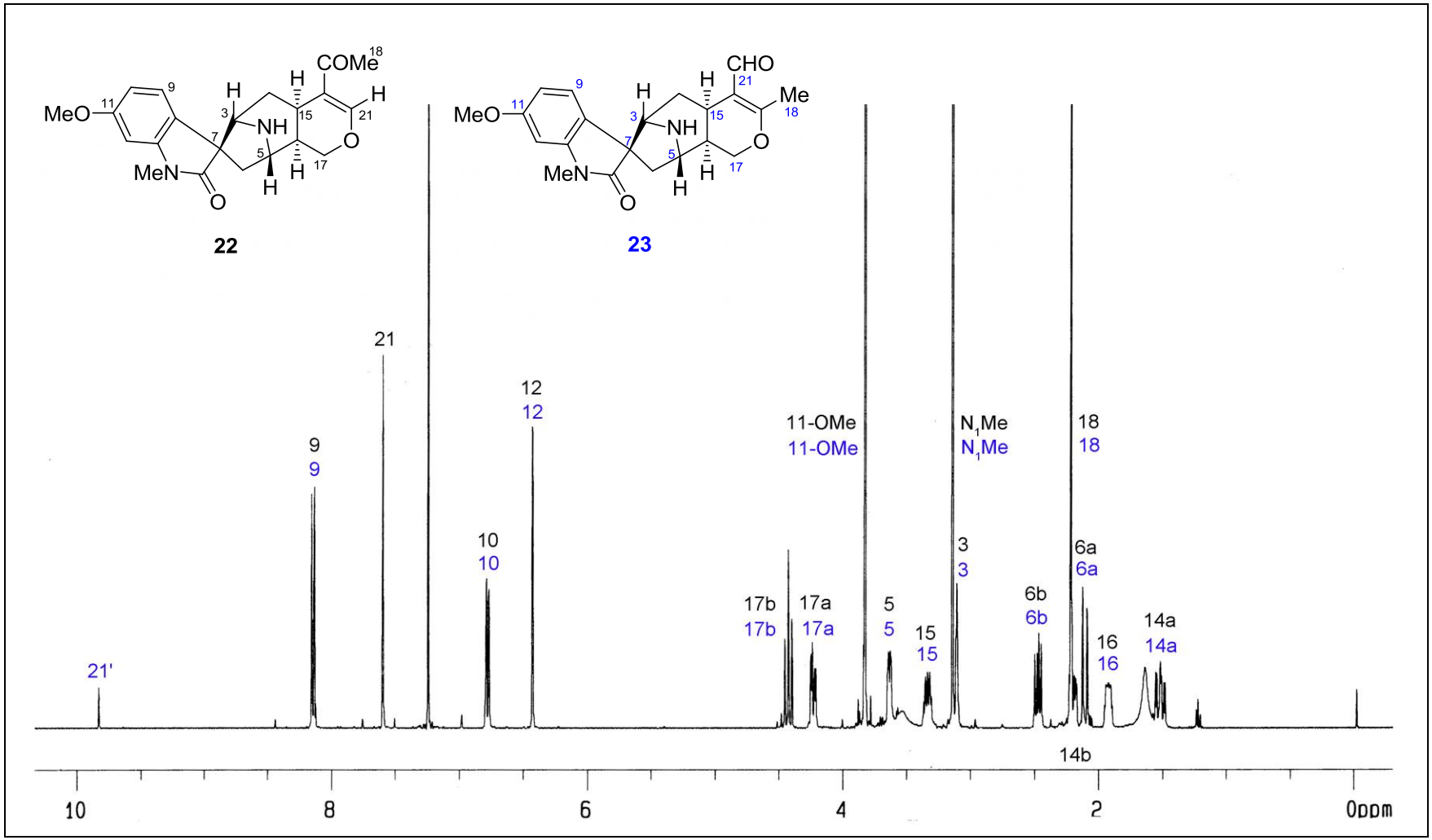


Figure 2.28: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *N*(4)-Demethylalstophylline oxindole (**22**) and *N*(4)-Demethylalstophyllal oxindole (**23**)

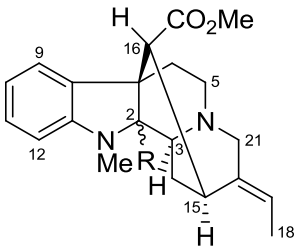
2.1.3 Akuammiline, Sarpagine and Ajmaline Alkaloids

2.1.3.1 Compound 24 (2(*S*)-Cathafoline)

Compound **24** was isolated as a light yellowish oil, with $[\alpha]_D$ –175 (*c* 0.22, $CHCl_3$), and was subsequently crystallized from CH_2Cl_2-hexane as colorless block crystals. The UV spectrum showed absorption maxima at 208, 246, 308 nm, consistent with a dihydroindole chromophore. The IR spectrum showed a sharp band at 1737 cm^{-1} due to an ester function, which was confirmed by the observed carbon shift of the carbonyl function at δ 172.8 in the ^{13}C NMR spectrum. The ESIMS showed a $[M + H]^+$ peak at *m/z* 339, which analyzed for $C_{21}H_{26}N_2O_2$ + H.

The ^1H and ^{13}C NMR data (Table 2.16; Figure 2.33) were generally similar to those of cathafoline (**35**),[146,241] except for differences in the chemical shift of C-2, C-6, C-8, C-14, and C-16, in the ^{13}C NMR spectrum, and H-2, H-5b, H-6a, H-14, and H-16, in the ^1H NMR spectrum.

The relative configurations at the various stereogenic centers of **24** were similar to those of cathafoline (**35**), except for the configuration at C-2. The reciprocal NOEs observed for H-2/H-3, H-6α, N1-Me, and H-6α/H-2, H-5α, H-6β, H-9, allowed the relative configuration at C-2 to be assigned as *S* (H-2α) (Figure 2.29). Since suitable crystals of **3** were obtained from CH_2Cl_2–hexane, an X-ray diffraction analysis was carried out which confirmed the assignment of configuration of C-2 as *S* based on the NMR data (Figure 2.30). Compound **24** is therefore the C-2 epimer of cathafoline (**35**).



24 R = α-H, 20*S*
35 R = β-H, 20*R*

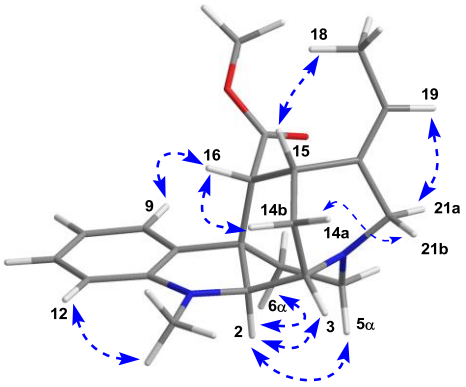


Figure 2.29: Selected NOEs of **24**

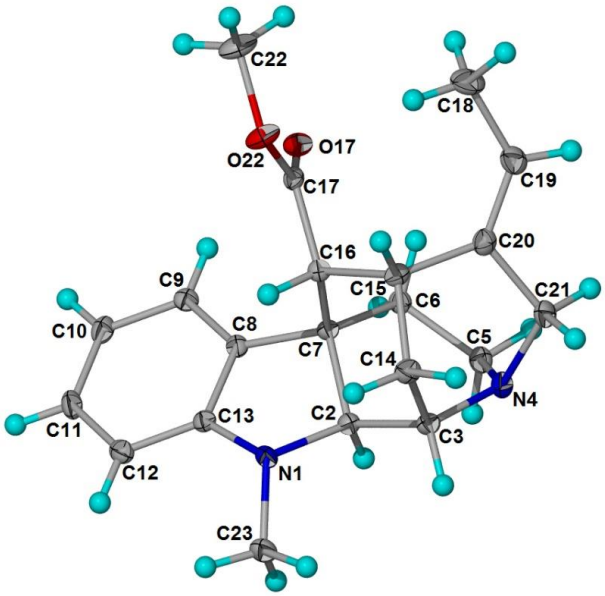


Figure 2.30: X-ray structure of **24**

2.1.3.2 Compound 25 (2(*S*)-10-Methoxycathafoline)

Compound **25** was obtained as a light yellowish oil, with $[\alpha]_D$ −138 (*c* 0.47, $CHCl_3$). The UV and IR spectrum were similar to those of compound **24**. The ESIMS showed a $[M + H]^+$ peak at *m/z* 369, which is 30 mass-units more than **24**. The NMR data of **24** and **25** (Table 2.16; Figure 2.34) were generally similar except for the presence of a methoxy group in **25**. The substitution of the methoxy group at C-10 was deduced from the coupling behaviour of the aromatic hydrogens as well as from the observed three-bond correlations (Figure 2.31) from H-12 and 10-OMe to C-10 in the HMBC spectrum. The placement of the methoxy substituent at C-10 was further confirmed by the reciprocal NOEs observed for H-9/10-OMe; H-11/10-OMe, H-12; and H-12/H-11, N1-Me (Figure 2.31). Compound **25** is therefore, 2(*S*)-10-methoxycathafoline.

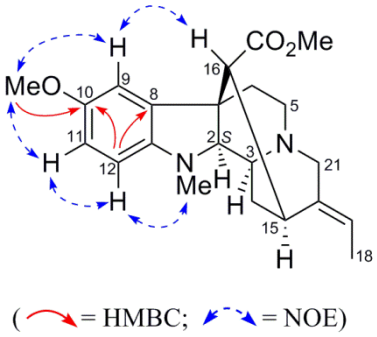
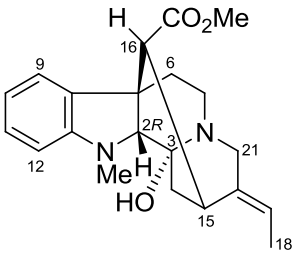


Figure 2.31: Selected HMBCs and NOEs of **25**

2.1.3.3 Compound 26 (2(*R*)-3-Hydroxycathafoline)

Compound **26** was isolated as a light yellowish oil, with $[\alpha]_D$ –48 (c 0.24, CHCl3). The IR spectrum showed bands at 3395 and 1739 cm^{-1} due to OH and ester functionalities, respectively. The UV spectrum showed typical dihydroindole absorptions at 202, 252, and 295 nm. The ESIMS of **26** showed a $[M + H]^+$ peak at *m/z* 355, which analyzed for $C_{21}H_{26}N_2O_3$ + H, differing from cathafoline (**35)** by addition of 16 mass units (consistent with replacement of a hydrogen by an OH group). This was further supported by ^1H and ^{13}C NMR spectroscopic data (Table 2.17; Figure 2.35), which showed a close correspondence with those of **35** except for some notable differences. In ^{13}C NMR spectrum, the chemical shif for C-3 signal was shifted down-field (from δ 47.2 to 85.3) due to the attachement of an OH group. The various stereogenic centers were same to those of cathafoline (**35**) (the observed NOEs, viz. H-2/H-14a; and H-9/H-16 (Figure 2.32)). The rigid architecture of the molecule restricts the configuration at C-3 to *R* only. Compound **26** was previously encountered as an intermediate compound in synthesis,[242] is here encountered as an optically active natural product for the first time.



26

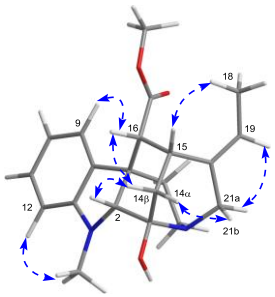


Figure 2.32: Selected NOEs of **26**

Table 2.16: ^{1}H and ^{13}C NMR Spectroscopic Data for 2(*S*)-Cathafoline (**24**) and 2(*S*)-10-Methoxycathafoline (**25**)[a]

Position	**24**		**25**	
	δ_H	δ_C	δ_H	δ_C
2	3.20 d (4)	70.1	3.21 d (4)	70.7
3	3.86 d (4)	48.7	3.92 d (4)	48.9
5β	2.46 dd (14, 7)	46.5	2.55 dd (14, 7)	46.6
5α	3.33 td (14, 6)		3.43 td (14, 6)	
6α	1.95 dd (14, 6)	28.7	2.02 dd (14, 6)	28.7
6β	3.23 m		3.28 td (14, 7)	
7	–	42.9	–	43.2
8	–	137.8	–	139.4
9	6.98 d (7)	123.3	6.72 d (2)	110.6
10	6.64 t (7)	119.5	–	153.8
11	7.01 t (7)	127.5	6.66 dd (9, 2)	112.3
12	6.51 d (7)	109.1	6.52 br d (9)	109.7
13	–	152.6	–	146.8
14a	1.98 dt (15, 4)	25.2	1.97 m	25.2
14b	2.01 dd (15, 3)		2.13 dd (14, 3)	
15	3.27 br s	32.5	3.36 br s	32.6
16	2.60 d (3)	49.6	2.71 d (4)	49.6
18	1.34 dd (7, 2)	12.9	1.43 dd (7, 2)	13.0
19	5.29 q (7)	119.5	5.38 br q (7)	119.9
20	–	138.1	–	138.0
21a	2.86 d (16)	56.2	2.96 br d (16)	56.3
21b	3.84 d (16)		3.94 br d (16)	
N(1)-Me	2.56 s	34.0	2.61 s	34.9
10-OMe	–	–	3.70 s	56.0
CO_2*Me*	3.41 s	51.0	3.52 s	51.1
CO_2Me	–	172.8	–	172.9

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.17: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **26** (2(*R*)-3-Hydroxycathafoline) [a]

Position	δ_H	δ_C
2β	2.89 s	80.7
3	–	85.3
5β	2.77 dd (13, 6.5)	51.5
5α	4.02 td (13, 5)	
6α	1.32 dd (15, 5)	30.8
6β	2.87 m	
7	–	46.3
8	–	140.0
9	6.91 dd (8, 1)	120.9
10	6.68 td (8, 1)	119.4
11	7.09 td (8, 1)	127.3
12	6.61 br d (8)	109.8
13	–	153.8
14a	1.90 dd (14, 3)	42.3
14b	2.20 dd (14, 3)	
15	3.61 m	36.5
16	2.90 d (4)	52.0
18	1.49 dd (7, 2)	13.6
19	5.41 br q (7)	119.1
20	–	137.5
21a	2.98 m	55.0
21b	4.10 br d (17)	
N(1)-Me	2.95 s	51.7
CO_2*Me*	–	173.0
CO_2Me	3.78 s	37.6

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

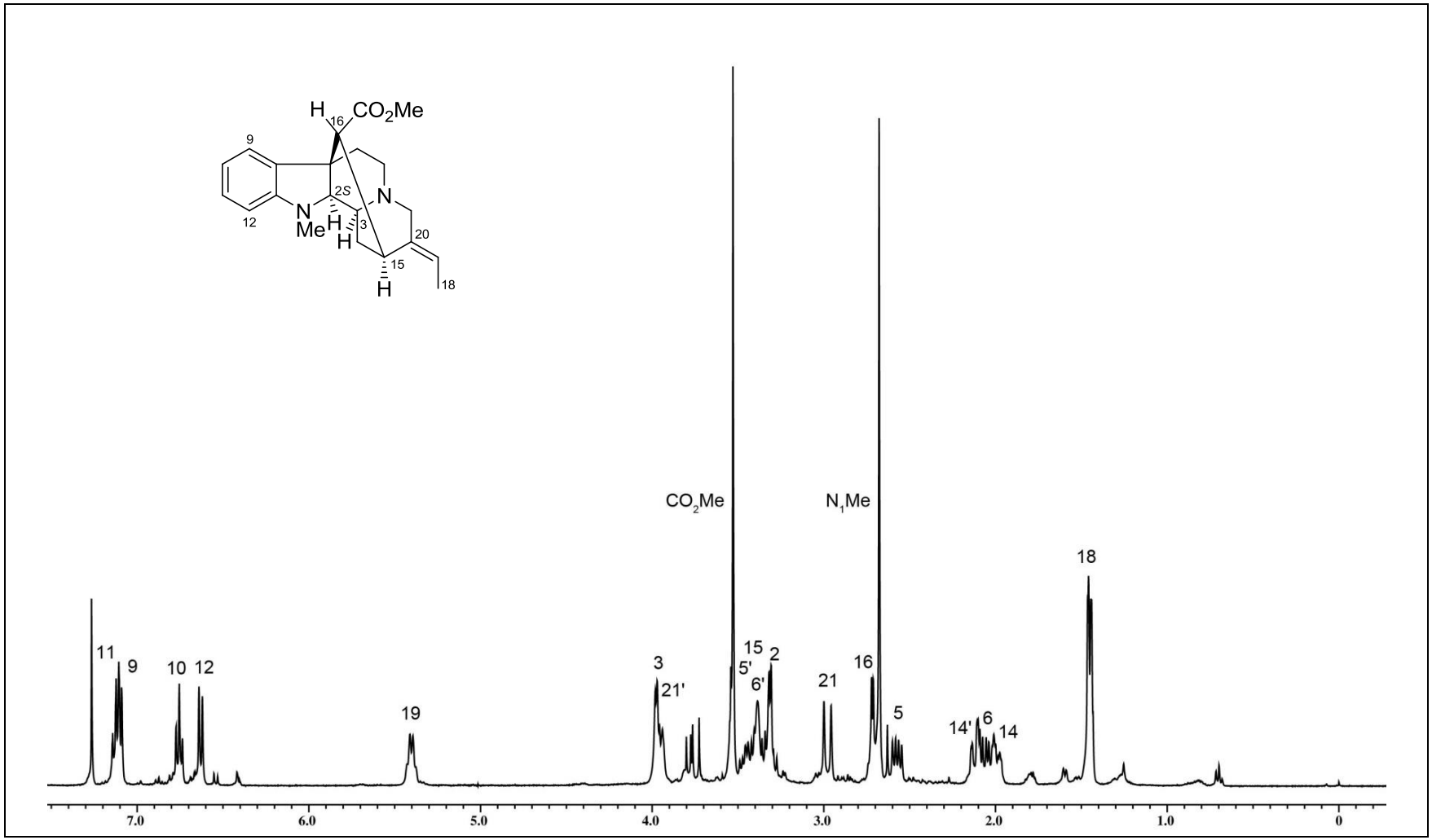


Figure 2.33: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **24** (2(*S*)-Cathafoline)

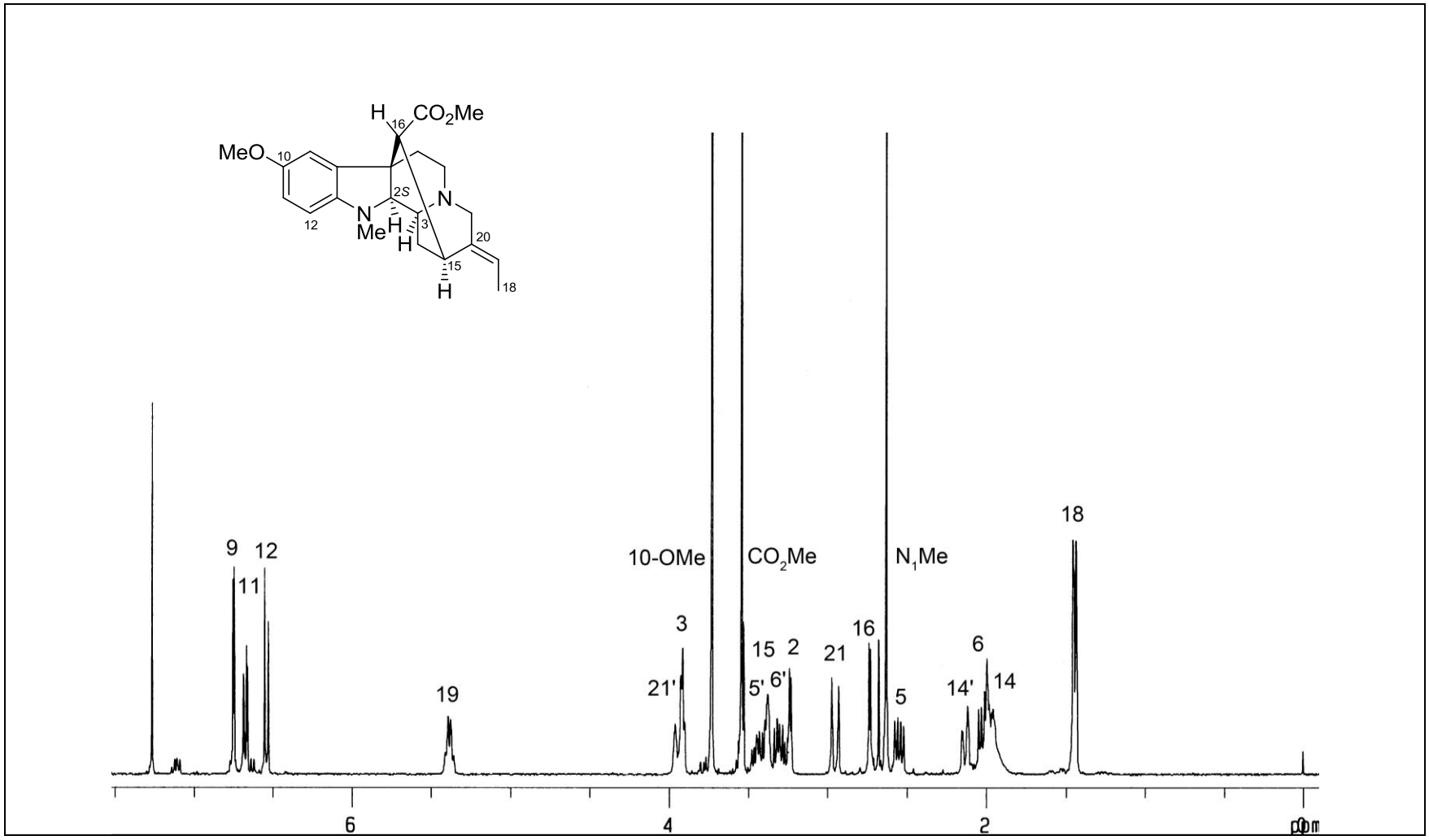


Figure 2.34: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **25** (2(*S*)-10-Methoxycathafoline)

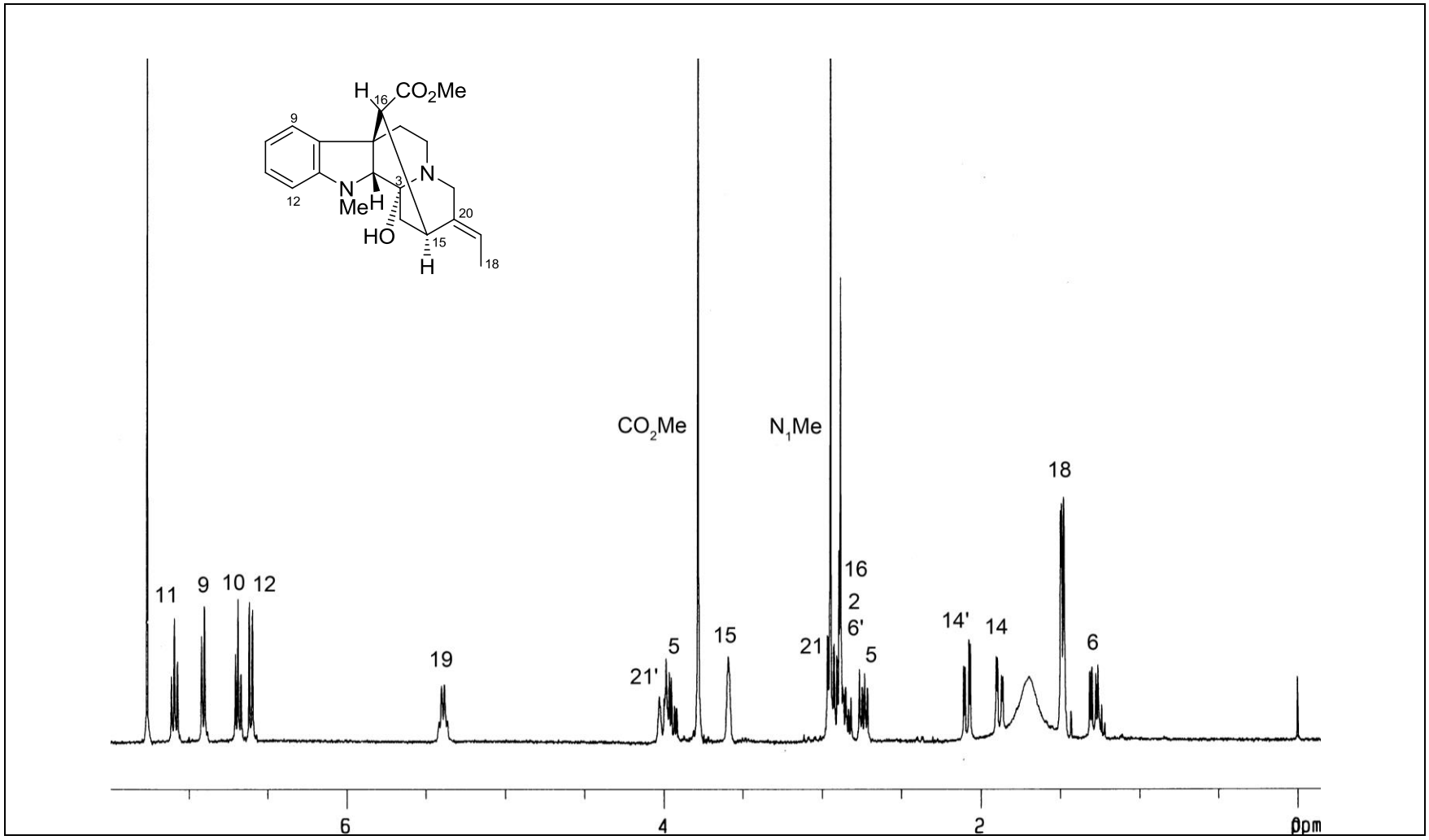
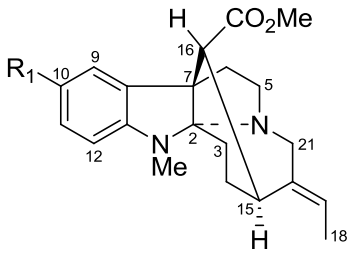


Figure 2.35: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **26** (2(*R*)-3-Hydroxycathafoline)

2.1.3.4 Compound 27 (10-Demethoxyvincorine)

Compound **27** was isolated as a light yellowish oil, with $[\alpha]_D$ –127 (*c* 0.48, $CHCl_3$). The UV spectrum showed absorption bands (205, 256, and 308 nm) characteristic of a dihydroindole chromophore. The IR spectrum showed a band at 1736 cm^{-1} due to an ester carbonyl function. It was supported by the observed chemical shift of the carbonyl function at δ 173.8 in the ^{13}C NMR spectrum. The ESIMS of **27** showed a pseudomolecular ion $[M + H]^+$ at *m/z* 339, and high resolution measurements gave the formula $C_{21}H_{26}N_2O_2$ + H (HRESIMS found *m/z* 339.2072, calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073). The ^1H and ^{13}C NMR spectroscopic data (Table 2.18, and Figure 2.38) showed the close resemblance to those of vincorine (**41**),[145,243-245] except for the absence of the methoxy group (C-10) and the presence of an unsubstituted indole moeity. The relative configuration of C-16, and the geometry of the 19,20-double bond, were similar to those of vincorine (**41**) as shown by the NOE data (Figure 2.36).



27 R = H
28 R = H, N(4)→O
42 R = OMe

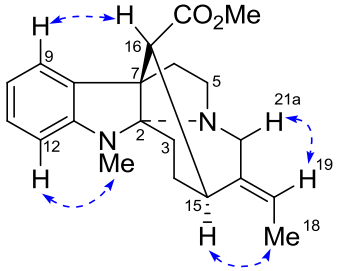


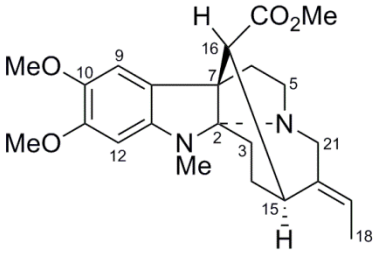
Figure 2.36: Selected NOEs of **27**

2.1.3.5 Compound 28 (10-Demethoxyvincorine *N*(4)-oxide)

Compound **28** was obtained as a yellowish oil, with $[\alpha]_D$ –62 (c 0.5, $CHCl_3$). The UV spectrum (208, 247, and 299 nm) showed absorption maxima characteristic of an dihydroindole chromophore, while the IR spectrum showed the presence of an ester carbonyl (1734 cm^{-1}) function. The ESIMS of **28** showed a $[M + H]^+$ peak at *m/z* 355, which analyzed for $C_{21}H_{26}N_2O_3$ + H (16 mass units higher than that of 10-demethoxyvincorine (**27**)). Compound **28** was readily identified as the N(4)-oxide of 10-demthoxyvincorine from its NMR spectroscopic data (Table 2.18; Figure 2.39), in particular, the characteristic downfield shifts of the carbon resonances for C-2, C-5, and C-21, when compared with those of 10-demethoxyvincorine (**27**).

2.1.3.6 Compound 29 (11-Methoxyvincorine)

Compound **29** was obtained as a light yellowish oil, $[\alpha]_D$ –86 (*c* 0.27, $CHCl_3$). The UV spectrum showed absorption maxima at 208, 256 and 317 nm, characteristic of a dihydroxyindole chromophore, while the IR spectrum indicated the presence of ester carbonyl (1733 cm^{-1}) function. The ESIMS of **29** showed a $[M + H]^+$ peak at *m/z* 399, corresponding to the molecular formula $C_{23}H_{30}N_2O_4$ + H, differing from vincorine (**41**)[145,243-245] by addition of 30 mass units. The ^1H and ^{13}C NMR spectral data (Table 2.19; Figure 2.40) are similar in all respects to those of **41**, except for the aromatic region, which indicated the presence of a methoxy substituent at C-11 (which was also supported by the NOE data, Figure 2.37).



29

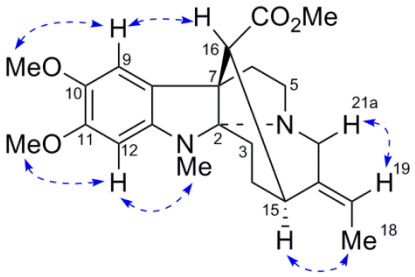


Figure 2.37: Selected NOEs of **29**

2.1.3.7 Compound 30 (Vincorine *N*(4)-oxide)

Compound **30** was obtained as yellowish oil, with $[\alpha]_D$ –84 (*c* 0.40, $CHCl_3$). The UV spectrum (211, 250 and 323 nm) was characteristic of a dihydroindole chromophore, while the IR spectrum showed the presence of an ester (1734 cm^{-1}) function. The ESIMS of **30** showed an MH^+ at *m/z* 385, which analyzed for $C_{22}H_{28}N_2O_3$ + H (16 mass units higher than that of vincorine (**41**)).[145,243-245] Compound **30** was readily identified as the N(4)-oxide of vincorine from its NMR spectroscopic data (Table 2.19; Figure 2.41), in particular the characteristic downfield shifts of the carbon resonances for C-2, C-5, and C-21, when compared with those of vincorine (**41**).

Table 2.18: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **27** (10-Demethoxyvincorine) and **28** (10-Demethoxyvincorine *N*(4)-oxide)[a]

Position	**27**		**28**	
	δ_H	**δ_C**	**δ_H**	**δ_C**
2	–	97.4	–	102.5
3	1.68 m (β)	20.8	1.73 m	17.5
	2.32 m (α)		2.90 m	
5	2.73 br t (11) (β)	55.0	3.42 dd (11, 9)	66.3
	3.33 td (11, 9) (α)		3.91 m	
6	1.97 ddd (14, 9, 1) (α)	41.0	2.06 dd (15, 9)	35.1
	2.50 ddd (14, 11, 9) (β)		2.81 m	
7	–	57.0	–	54.1
8	–	137.0	–	135.5
9	7.22 dd (7.5, 1)	123.5	7.11 d (8)	122.6
10	6.58 td (7.5, 1)	116.9	6.69 td (8, 1)	119.4
11	7.06 td (7.5, 1)	127.8	7.13 td (8, 1)	129.0
12	6.27 br d (7.5)	105.3	6.47 d (8)	107.8
13	–	149.0	–	149.7
14	1.76 m	26.2	1.85 m	25.3
	1.76 m		1.92 m	
15	3.61 m	34.8	3.65 m	33.8
16	2.83 br s	50.6	2.80 br s	49.3
18	1.59 dd (7, 2)	13.5	1.60 dd (7, 2)	13.7
19	5.40 q (7)	122.4	5.73 q (7)	128.3
20	–	138.9	–	132.0
21a	3.00 br d (15)	58.3	3.91 br d (15)	74.0
21b	3.81 m		4.20 m	
N(1)-Me	2.63 s	27.3	3.07 s	32.9
CO_2*Me*	3.79 s	51.5	3.79 s	52.1
CO_2Me	–	173.8	–	172.6

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.19: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **29** (11-Methoxyvincorine) and **30** (Vincorine *N*(4)-oxide)[a]

Position	**29**		**30**	
	δ_H	**δ_C**	**δ_H**	**δ_C**
2	–	98.2	–	102.7
3	1.68 m (β)	20.8	1.71 m	17.1
	2.32 m (α)		2.85 m	
5	2.75 br t (10.5) (β)	55.2	3.35 br t (10)	66.1
	3.38 m (α)		3.94 m	
6	1.97 dd (14, 8) (α)	41.4	2.06 dd (15, 9)	34.9
	2.41 m (β)		2.74 m	
7	–	57.4	–	54.3
8	–	128.0	–	136.6
9	7.02 s	111.9	6.76 d (2.5)	110.6
10	–	140.9	–	153.6
11	–	150.1	6.67 dd (8.5, 2.5)	112.8
12	5.96 s	92.3	6.37 br d (8.5)	107.9
13	–	144.5	–	143.9
14	1.77 m	26.6	1.83 m	25.2
	1.77 m		1.91 m	
15	3.62 m	34.9	3.64 d (4)	33.8
16	2.79 br s	51.5	2.77 br s	49.3
18	1.60 dd (7, 2)	13.9	1.58 d (7)	13.6
19	5.41 q (7)	123.1	5.69 q (7)	128.4
20	–	139.0	–	131.9
21a	3.02 br d (15)	58.6	3.85 br d (15)	73.7
21b	3.84 m		4.18 br d (15)	
N(1)-Me	2.63 s	28.4	3.02 s	33.3
CO_2*Me*	3.80 s	51.9	3.77 s	52.1
CO_2Me	–	174.0	–	172.5
10-OMe	3.78 s	58.2	3.69 s	56.1
11-OMe	3.86 s	56.4	–	–

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

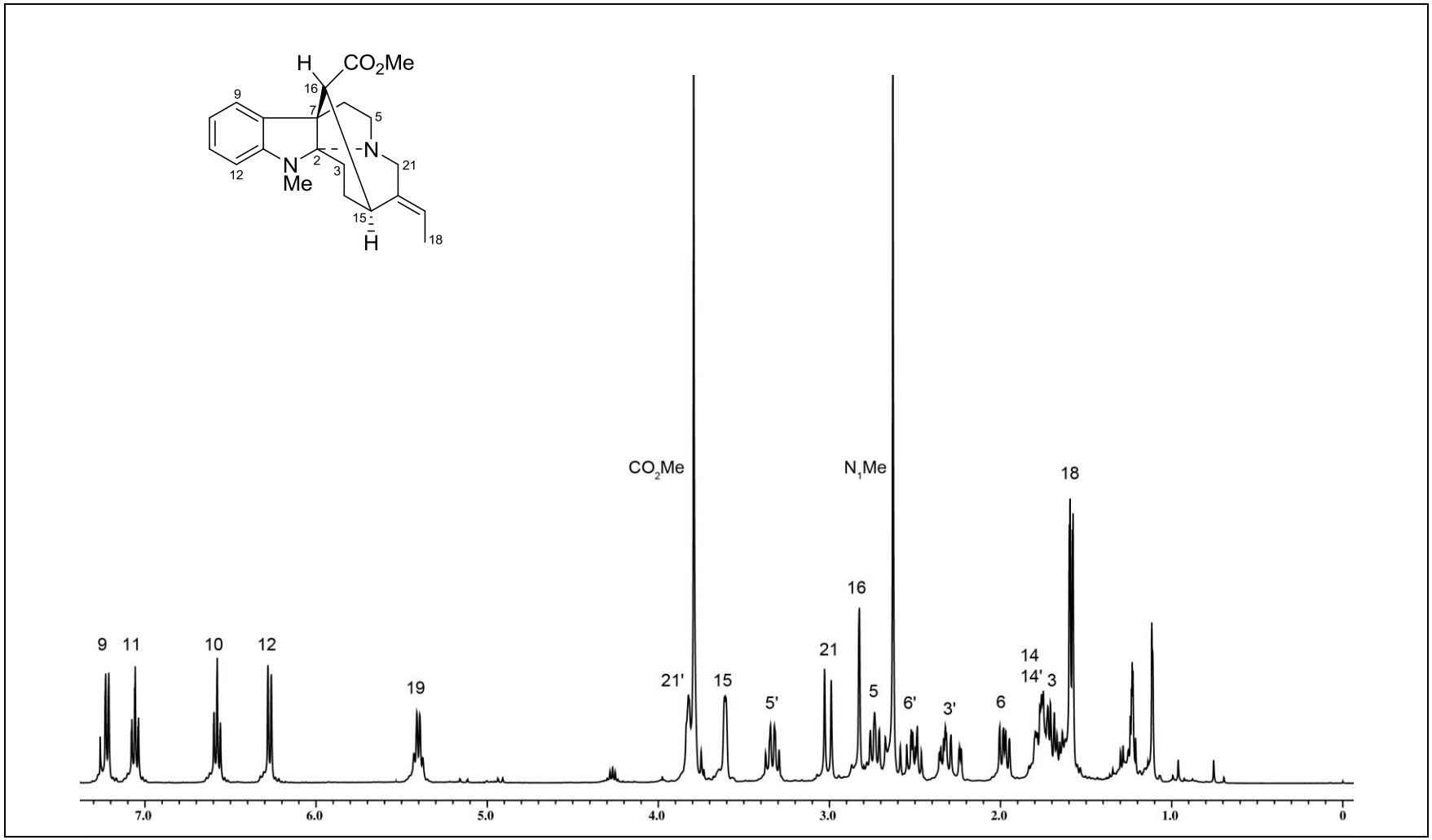


Figure 2.38: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **27** (10-Demethoxyvincorine)

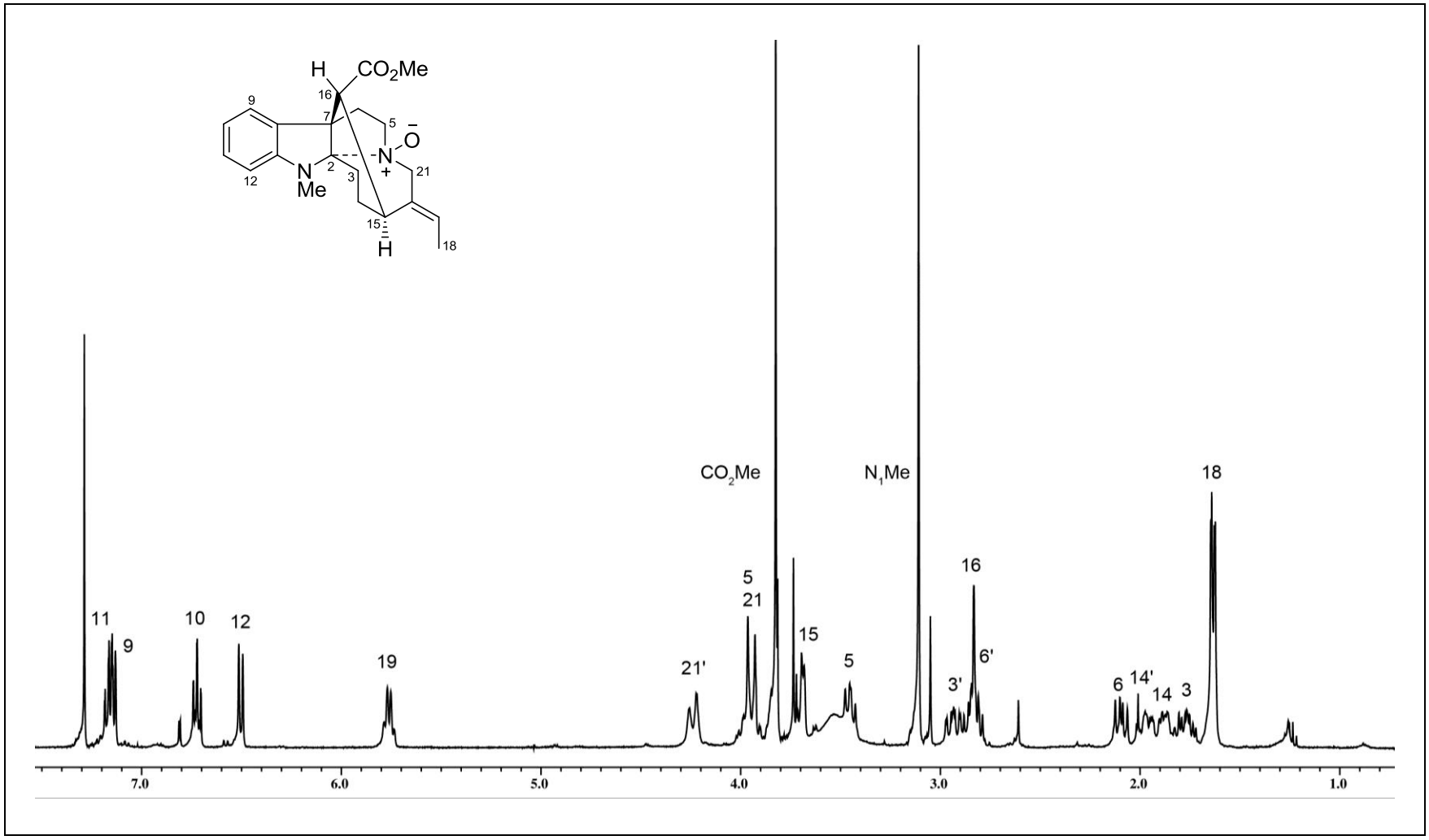


Figure 2.39: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **28** (10-Demethoxyvincorine *N*(4)-oxide)

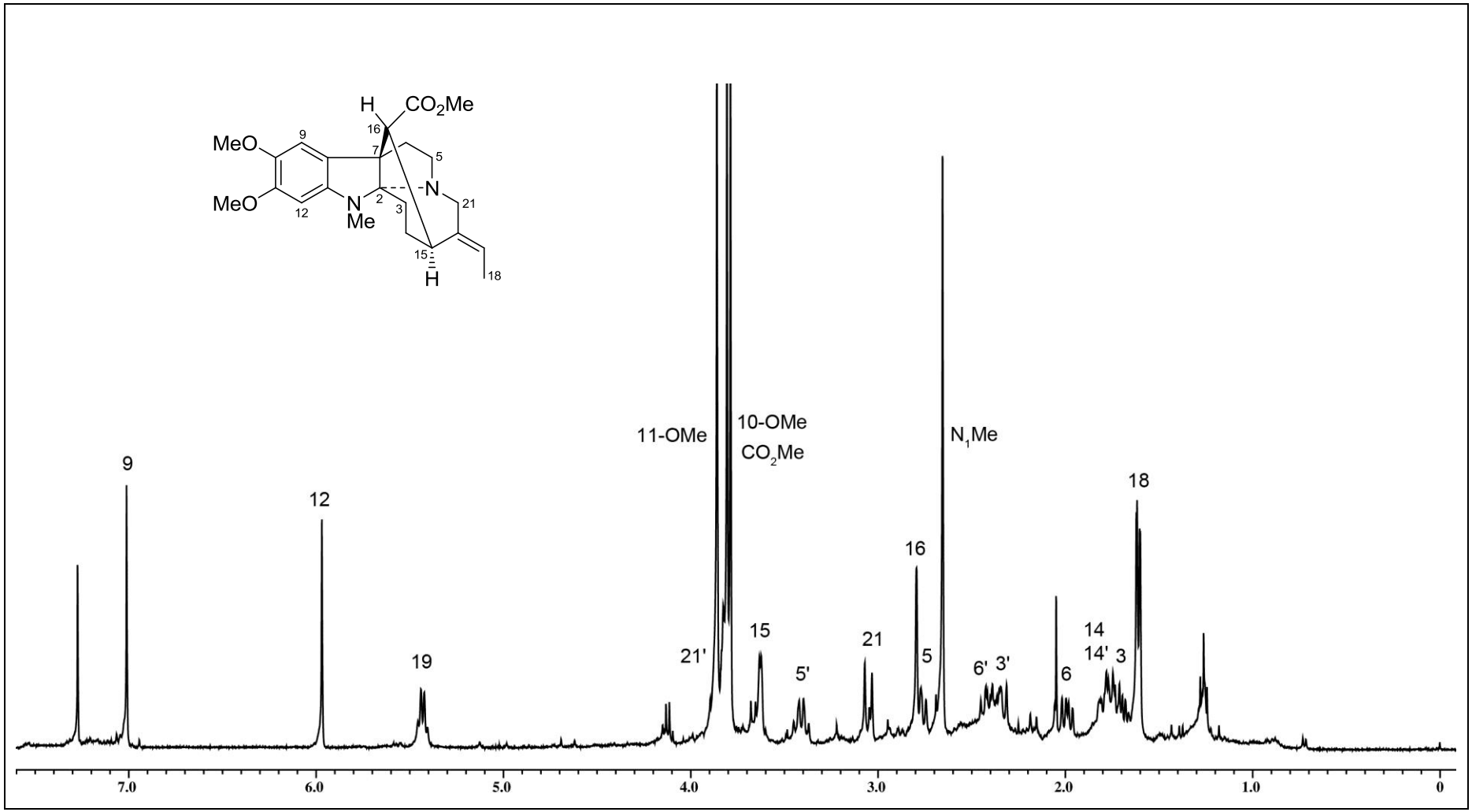


Figure 2.40: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **29** (11-Methoxyvincorine)

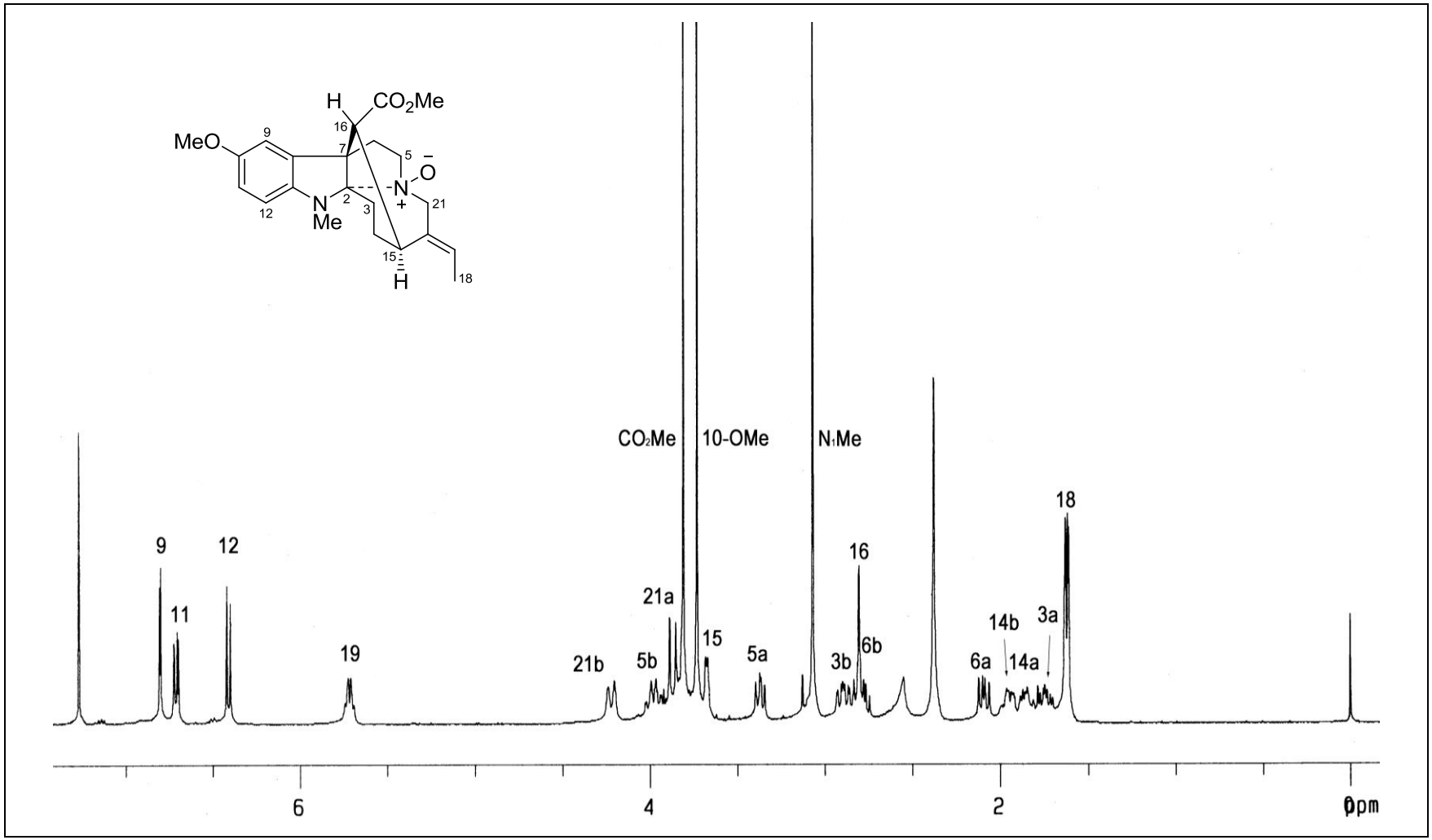


Figure 2.41: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **30** (Vincorine *N*(4)-oxide)

2.1.3.8 Compound 31 (11-Demethoxyquaternine)

Compound **31** was obtained from the leaf extract of *A. macrophylla* as a light yellowish oil, $[\alpha]_D$ –10 (*c* 0.21, $CHCl_3$). The UV spectrum showed absorption maxima at 208, 241, 307 nm, suggesting the presence of a dihydroindole chromophore. The IR spectrum showed a sharp band due to an ester function at 1736 cm^{-1}. The presence of an ester function was supported by the signal observed at δ 172.5 in the ^{13}C NMR spectrum. The ESIMS showed a $[M + H]^+$ peak at *m/z* 383, which analyzed for $C_{22}H_{26}N_2O_4$ + H, differing from quaternine (**46**) by loss of a methoxy group (OMe). The ^1H and ^{13}C NMR spectroscopic data (Table 2.20; Figure 2.43) showed the presence of a substituted indole ring (δ 6.54, br d (*J* = 9 Hz); 6.76, d (*J* = 2.5 Hz); 6.69, dd (*J* = 9, 2.5 Hz)), three 3H singlets at δ_H 3.70, 3.64, and 2.90, due to an aromatic methoxy (δ_C 56.0), a methyl ester (δ_C 172.5, and 51.7), and an N1-Me (δ_C 30.0) group, respectively, an isolated methine characteristic of H-5 (where the C-5 is adjacent to a nitrogen and an oxygen atom) as a doublet at δ_H 4.70 (d, *J* = 3 Hz, δ_C 87.2), and an ethylidene side chain at δ_H 5.39 (q, *J* = 7 Hz; δ_C 120.6, C-19) and 1.48 (dd, *J* = 7, 2 Hz; δ_C 12.8, C-18). The NMR spectroscopic data revealed a similarity of quaternine (**46**)[168,246] which also present in the same plant. The main departure noted from the NMR data was the absence of one of the aromatic methoxy group (two aromatic methoxy groups were presence in quaternine). The aromatic doublet at δ 6.54 was assigned to H-9 from its NOE with H-6α (Figure 2.42), while the placement of the remaining aromatic methoxy substituent at C-10 was confirmed by the observed NOEs for 10-OMe (δ 3.70)/H-9 and H-11 (δ 6.69). Another aromatic doublet at δ 6.76 was assigned to H-12 from the observed NOE between H-12 and N1-Me. These assignments were further supported by the observed three-bond correlations from H-9 to C-7, C-11, and C-13, H-11 to C-9 and C-13, and, H-12 to C-10 and C-8, in the HMBC spectrum (Figure 2.42). The relative configuration

of C-16 was same as in quaternine. It was assigned as *R* from the observed NOEs between H-16 and H-14a, H-15 (Figure 2.42).

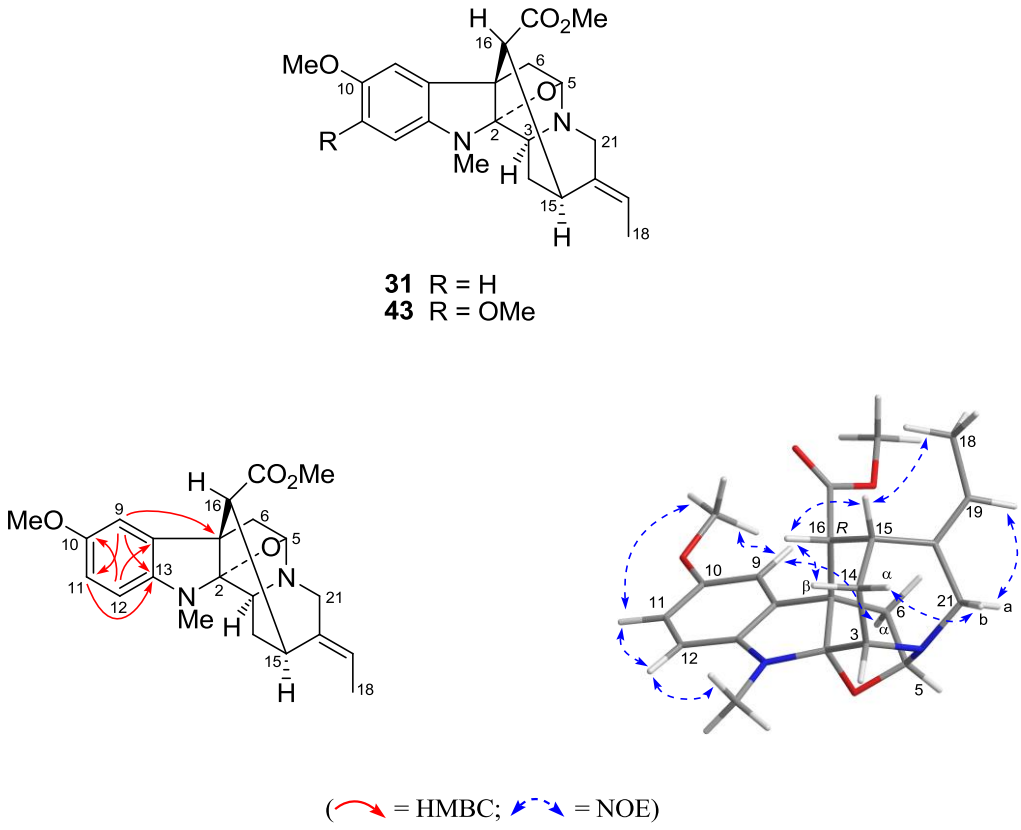


Figure 2.42: Selected HMBCs and NOEs of **31**

Table 2.20: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **31**(11-Demethoxyquaternine)[a]

Position	δ_H	δ_C
2	–	109.3
3	3.72 m	49.7
5	4.70 d (3)	87.2
6	2.17 dd (14, 3)	40.5
	3.37 br d (14)	
7	–	50.8
8	–	136.5
9	6.76 d (2.5)	112.1
10	–	154.3
11	6.69 dd (9, 2.5)	112.6
12	6.54 br d (9)	108.8
13	–	144.2
14	1.79 br d (14)	25.9
	2.11 dt (14, 4)	
15	3.27 br s	31.3
16	2.41 d (4)	51.6
18	1.48 dd (7, 2)	12.8
19	5.39 q (7)	120.6
20	–	136.0
21	3.06 br d (18)	46.4
	3.75 m	
CO_2*Me*	3.64 s	51.7
CO_2Me	–	172.5
N(1)-Me	2.90 s	30.0
10-OMe	3.70 s	56.0

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

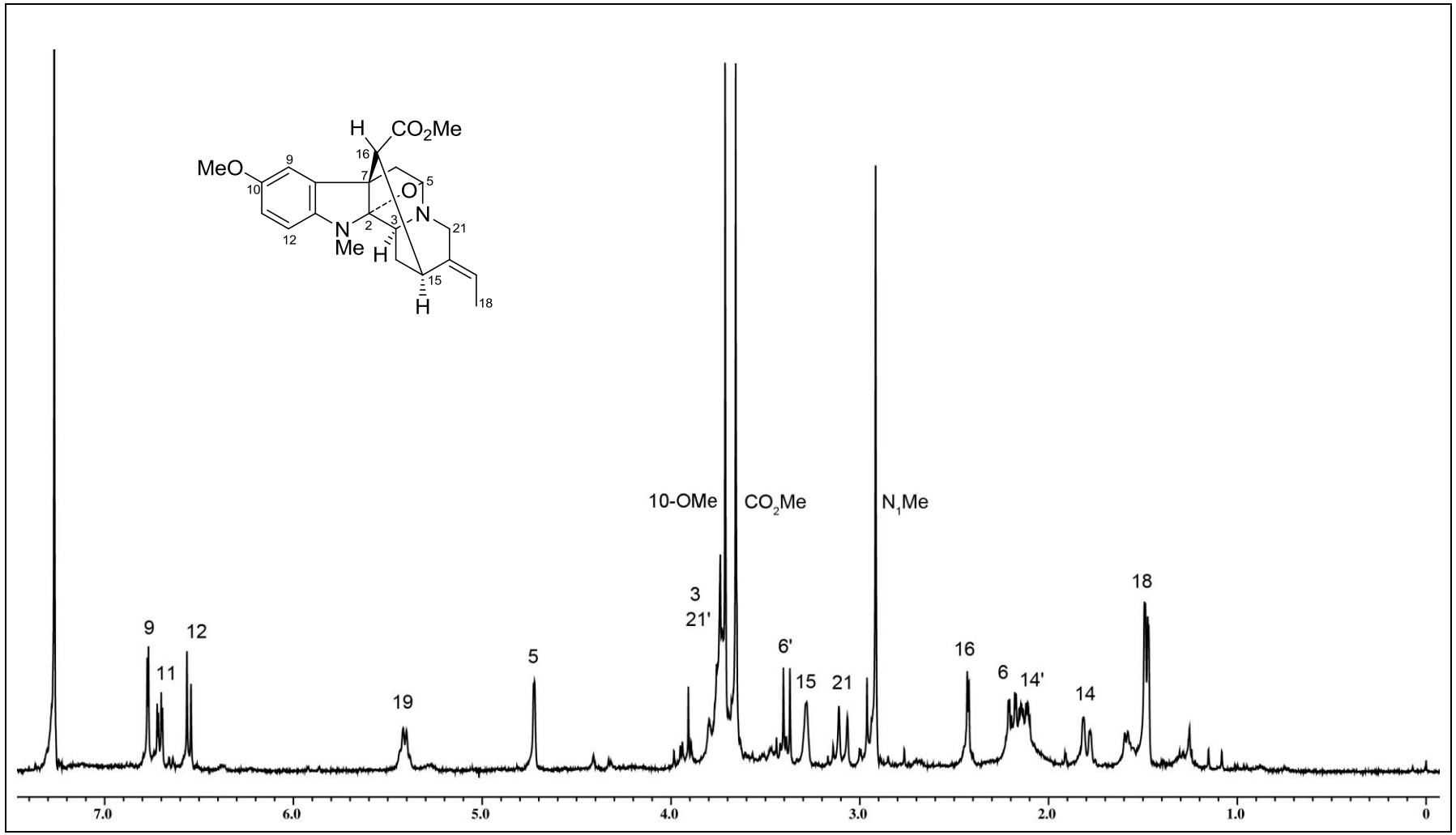
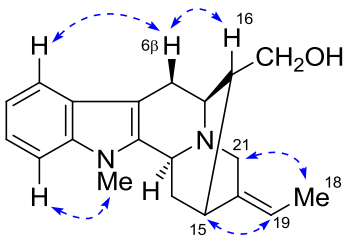


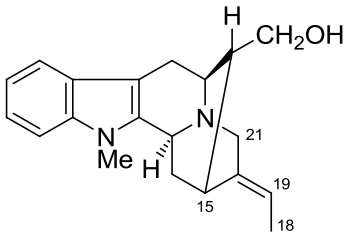
Figure 2.43: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **31** (11-Demethoxyquaternine)

2.1.3.9 Compound 32 (19,20-*Z*-Affinisine)

Compound **32** was obtained as a light yellowish oil, $[\alpha]_D$ +8 (*c* 0.45, $CHCl_3$) from the leaf extract of *A. macrophylla*. The UV spectrum showed absorption maxima at 229, 254, and 284, nm indicative of an indole chromophore. The IR spectrum showed a broad band at 3400 cm^{-1} due to an OH function. The ESIMS of **32** showed a $[M + H]^+$ peak at *m/z* 309, which analyzed for $C_{20}H_{24}N_2O$ + H. The ^{13}C NMR spectrum (Table 2.21) showed a total of 20 resonances, comprising two methyl, four methylene, nine methine, and five quaternary carbon atoms, in agreement with the molecular formula. The ^1H NMR (Table 2.21, Figure 2.45) showed the presence of an unsubstituted indole moiety, an N1-Me, and an ethylidene side chain. The COSY spectrum yielded fragments consistent with a sarpagine-type compound, viz. $NCHCH_2$, NCH_2, $NCHCH_2CH$, $CHCH_2O$, and $C{=}CHCH_3$. With the help of HMBC data, the structure of **32** was assembled, which revealed that it possesses the same structure as affinisine (**49**), which was also isolated from this plant. The ^1H and ^{13}C NMR data (Table 2.21) of **32** are generally similar to those of **49** except for differences in the chemical shifts of C-15, C-17, C-19, C-20, and C-21 in the ^{13}C NMR spectrum, and H-5, H-15, H-16, H-19 and H-21, in the ^1H NMR spectrum. The configuration at C-16 can be deduced from the NOESY spectrum (Figure 2.44). The observed H-16/H-6β, H-15, H-17 NOEs indicated that the configuration of C-16 is *R*. In addition, the reciprocal NOEs observed for H-19/H-15 and H-21/H-18, established the geometry of the 19,20-double bond as *Z*. Compound **32** is therefore the *Z* isomer of affinisine.



32



49

Figure 2.44: Selected NOEs of **32**

Table 2.21: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **32** (19,20-*Z*-Affinisine)[a]

Position	**32**	
	δ_H	**δ_C**
2	–	139.8
3	4.14 dd (10, 2)	49.2
5α	2.73 t (6)	54.9
6β	2.60 br d (15)	27.3
6α	3.03 dd (15, 5)	
7	–	103.4
8	–	127.4
9	7.41 d (8)	118.2
10	7.08 td (8, 1)	118.9
11	7.19 td (8, 1)	120.9
12	7.29 d (8)	108.8
13	–	137.4
14a	1.53 m	34.5
14b	2.04 td (12, 2)	
15	2.23 br s	34.9
16	1.62 m	44.1
17	3.47 m	65.4
	3.47 m	
18	1.57 d (7)	12.6
19	5.28 q (7)	117.0
20	–	136.9
21	3.63 m	53.9
	3.63 m	
N(1)-Me	3.61 s	29.4

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

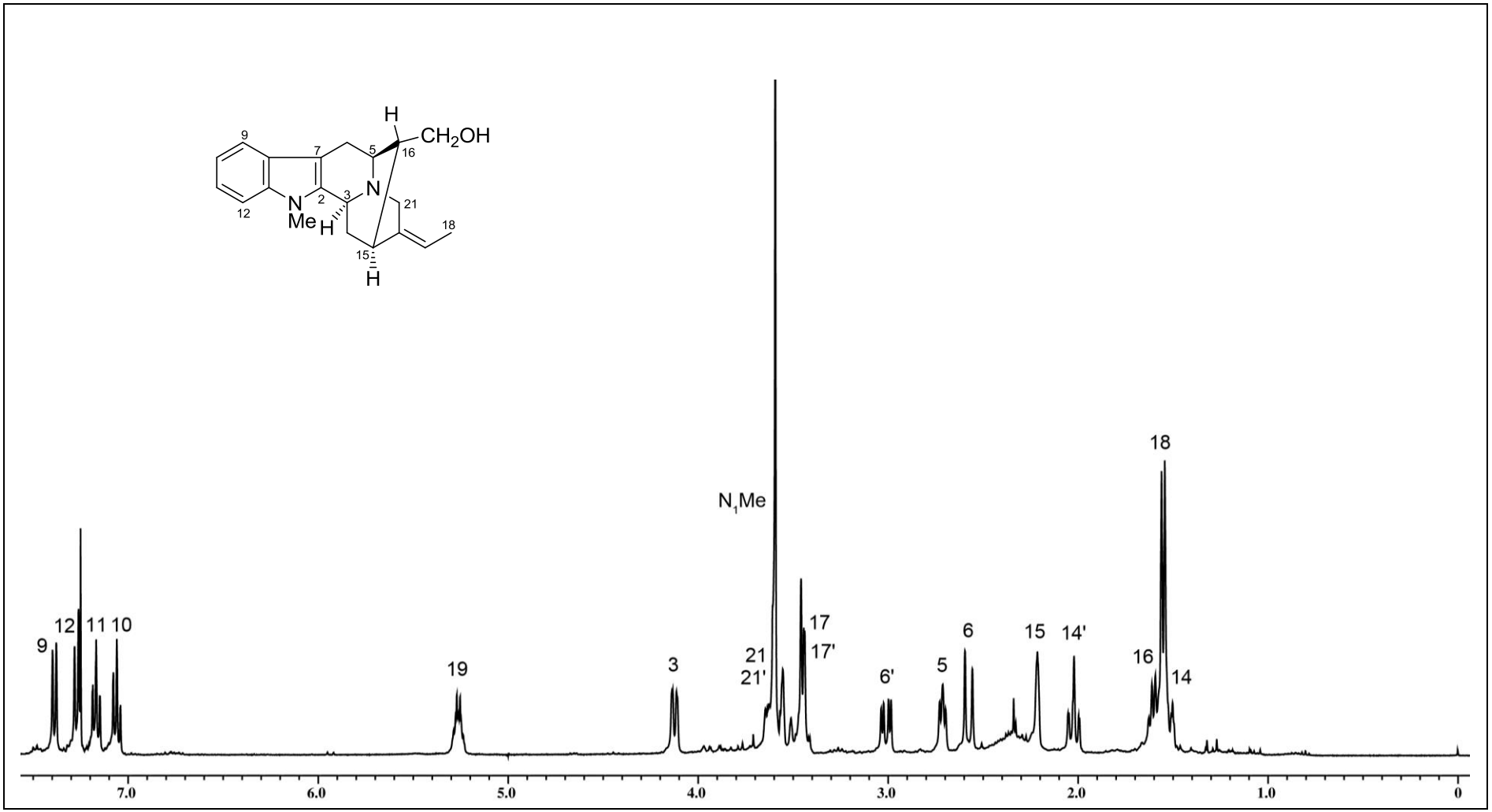


Figure 2.45: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **32** (19,20-*Z*-Affinisine)

2.1.3.10 Compound 33 (Vincamajine *N*(4)-oxide)

Compound **33** was obtained as yellowish oil, with $[\alpha]_D$ –29 (*c* 0.04, $CHCl_3$). The UV spectrum (210, 231 and 282 nm) was characteristic of a dihydroindole chromophore, while the IR spectrum showed the presence of an ester and an OH (3400 and 1736 cm^{-1}) functions. The ESIMS of **33** showed an $[M + H]^+$ at *m/z* 383, which analyzed for $C_{22}H_{26}N_2O_4$ + H (16 mass units higher than that of vincamajine (**54**)).[143,144,164,247-249] Compound **33** was readily identified as the N4-oxide of vincamajine from its NMR spectroscopic data (Table 2.22; Figure 2.46), in particular the characteristic downfield shifts of the carbon resonances for C-3, C-5, and C-21, when compared with those of vincamajine (**54**).

2.1.3.11 Compound 34 (Vincamajine 17-*O*-veratrate *N*(4)-oxide)

Compound **34** was obtained as yellowish oil, with $[\alpha]_D$ –75 (*c* 0.94, $CHCl_3$). The UV spectrum (209, 254 and 292 nm) was characteristic of a dihydroindole chromophore, while the IR spectrum showed the presence of an ester (1737 cm^{-1}) function. The ESIMS of **34** showed an $[M + H]^+$ at *m/z* 547, which analyzed for $C_{31}H_{34}N_2O_7$ + H (16 mass units higher than that of vincamajine 17-*O*-veratrate (**55**)).[164] Compound **34** was readily identified as the N4-oxide of vincamajine 17-*O*-veratrate from its NMR spectroscopic data (Table 2.22; Figure 2.47), in particular the characteristic downfield shifts of the carbon resonances for C-3, C-5, and C-21, when compared with those of vincamajine 17-*O*-veratrate (**55**).

Table 2.22: ^{1}H and ^{13}C NMR Spectroscopic Data for Compound **33** (Vincamajine *N*(4)-oxide) and **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide)[a]

Position	**33**		**34**	
	δ_H	δ_C	δ_H	δ_C
2	3.86 d (5)	69.8	3.93 m	70.0
3	3.76 m	69.8	3.93 m	69.7
5	3.96 m	76.0	4.13 d (4)	75.9
6a	2.53 m	30.3	2.62 m	31.6
6b	2.78 br d (13)		3.00 br d (13)	
7	–	56.1	–	55.5
8	–	128.9	–	127.1
9	7.18 m	128.8	6.82 m	123.6
10	6.80 t (8)	109.7	6.51 m	119.7
11	7.16 m	124.6	7.07 m	129.0
12	6.66 d (8)	119.6	6.63 br d (8)	109.8
13	–	154.3	–	153.9
14a	1.82 td (10, 3)	22.2	1.96 m	22.1
14b	2.55 m		2.81 dd (14, 5)	
15	3.56 m	29.5	3.61m	29.7
16	–	60.6	–	59.8
17	4.13 s	74.0	5.76 br s	74.9
18	1.60 dd (7, 1)	12.6	1.53 d (7)	12.6
19	5.29 br q (7)	119.6	5.35 q (7)	120.4
20	–	130.1	–	129.5
21a	3.72 m	70.8	3.87 m	71.0
21b	3.96 m		4.25 br d (16)	
N(1)-Me	2.61 s	34.8	2.62 s	34.6
CO_2*Me*	3.70 s	52.3	3.38 s	52.5
CO_2Me	–	170.8	–	169.9
1'	–	–	–	121.5
2'	–	–	7.30 d (2)	111.9
3'	–	–	–	148.8
4'	–	–	–	153.4
5'	–	–	6.84 m	110.4
6'	–	–	7.49 dd (9, 2)	123.4
3'-OMe	–	–	3.84[b] s	56.1
4'-OMe	–	–	3.89[b] s	56.1
–C=O	–	–	–	163.7

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and HMBC. [b] Assignments are interchangeable.

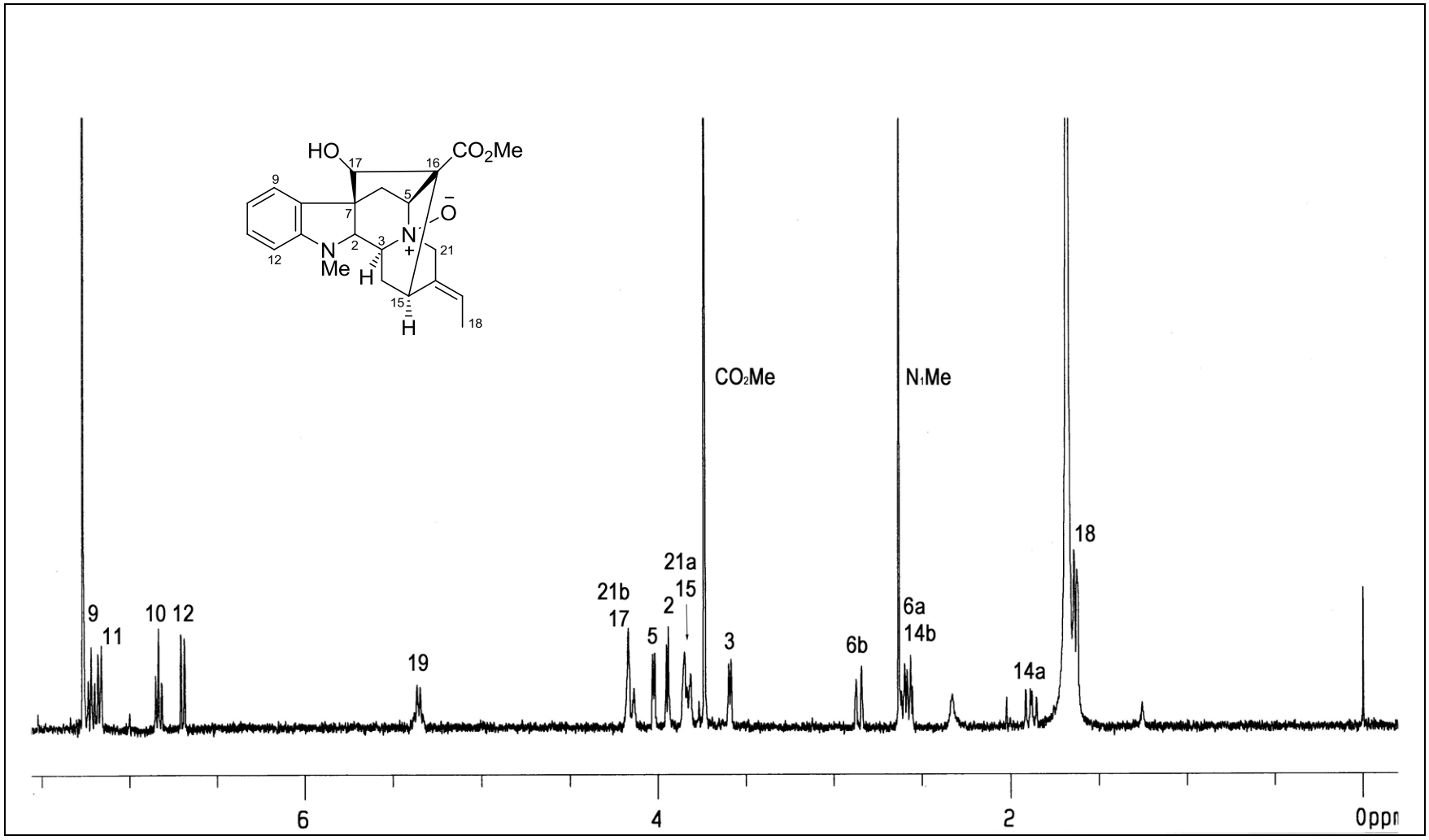


Figure 2.46: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **33** (Vincamajine *N*(4)-oxide)

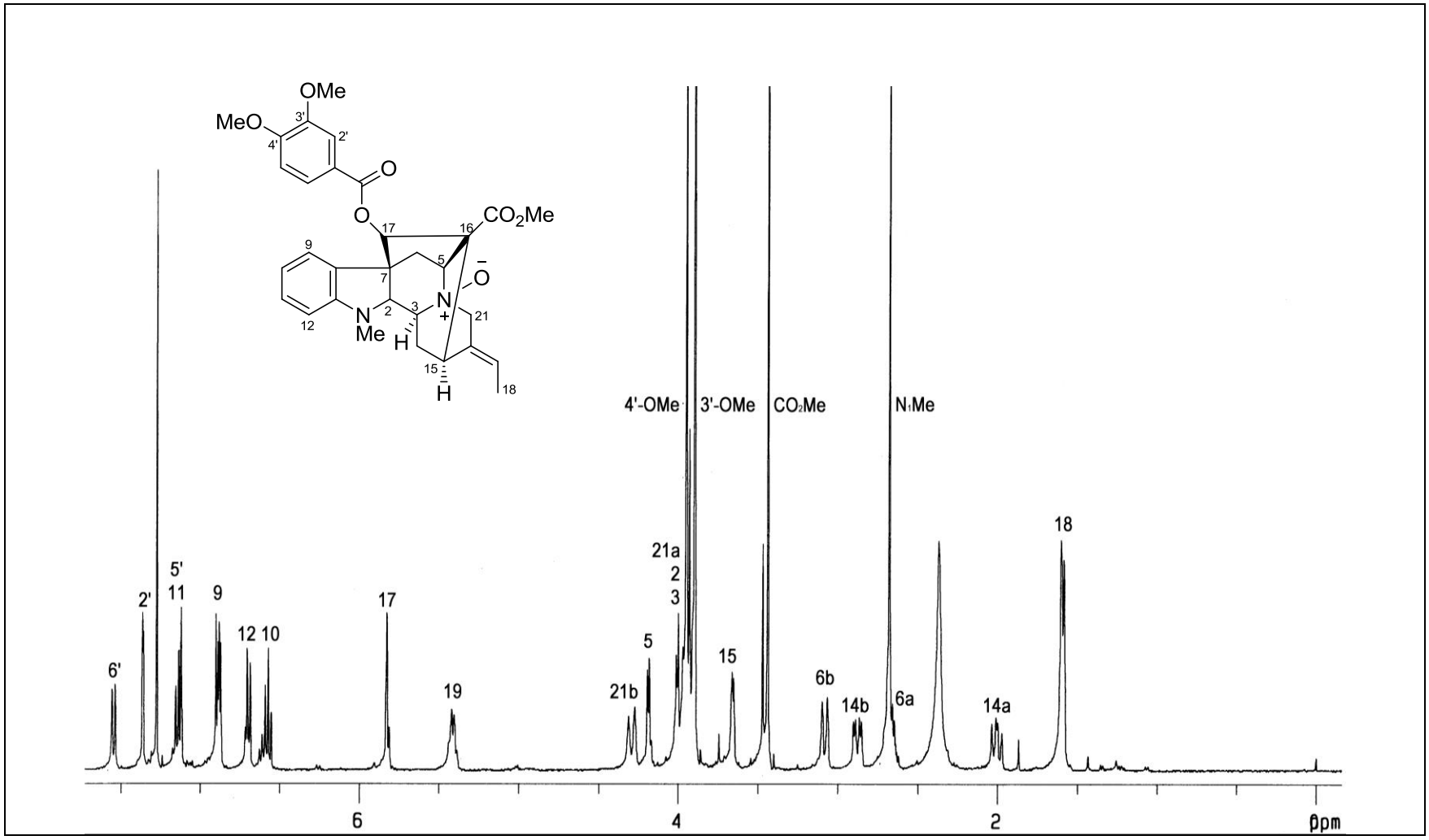


Figure 2.47: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Compound **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide)

2.1.3.12 Cathafoline (35), Cathafoline *N*(4)-oxide (36), 10-Methoxycathafoline (37), Strictamine (38), 11-Methoxystrictamine (39), 11-Hydroxystrictamine (40), Vincorine (41), Norvincorine (42), Alstonamide (43), Demethoxyalstonamide (44), Alstomaline (45), Quaternine (46), Picrinine (47), and 12-Demethoxytabernulosine (48)

The known akuammiline alkaloids which were isolated from *A. macrophylla* are cathafoline (**35**),[133,250] cathafoline *N*(4)-oxide (**36**),[164,250] 10-methoxycathafoline (**37**),[133] strictamine (**38**),[251,252] 11-methoxystrictamine (**39**),[253] 11-hydroxystrictamine (**40**),[252] vincorine (**41**),[145,243-245] norvincorine (**42**),[243] alstonamide (**43**),[159] demethoxyalstonamide (**44**),[159] alstomaline (**45**),[177] quaternine (**46**),[168,246] picrinine (**47**),[176,205] and 12-demethoxytabernulosine (**48**). The ^{1}H NMR spectra of compounds **35**–**48** are shown in Figures 2.48–2.61. The ^{1}H and ^{13}C NMR spectroscopic data of compounds **35**–**37**, **38**–**40**, **41**–**42**, **43**–**45**, and **46**–**48** are summarized in Tables 2.23–2.24, 2.25–2.26, 2.27, 2.28–2.29, and 2.30–2.31, respectively, while other data are given in the Experimental Section.

Table 2.23: ^{1}H NMR Spectroscopic Data for Cathafoline (**35**), Cathafoline *N*(4)-oxide (**36**), and 10-Methoxycathafoline (**37**)[a]

H	**35**	**36**	**37**
2	2.50 s	2.88 s	2.44 s
3	4.10 d (5)	4.64 d (5)	4.12 d (5)
5	2.62 dd (14, 5)	3.36 dd (14, 6)	2.64 m
	3.82 td (14, 5)	4.47 m	3.88 td (14, 5)
6	1.41 dd (15, 5)	1.73 dd (16, 6)	1.45 dd (15, 5)
	3.07 ddd (15, 14, 5)	3.21 ddd (16, 14, 6)	3.07 ddd (15, 14, 5)
9	6.94 dd (8, 1)	6.69 br d (8)	6.61 d (1)
10	6.69 td (8, 1)	6.75 td (8, 1)	–
11	7.09 td (8, 1)	7.15 td (8, 1)	6.63 dd (8, 1)
12	6.60 dd (8, 1)	6.66 br d (8)	6.53 d (8)
14	1.59 dd (14, 3)	1.87 dd (14, 2)	1.61 dd (14, 3)
	2.37 ddd (14, 5, 3)	2.82 m	2.37 ddd (14, 5, 3)
15	3.59 br s	3.65 br s	3.60 br s
16	2.96 d (3)	3.03 d (3)	2.94 d (3)
18	1.50 dd (7, 3)	1.57 dd (7, 2)	1.50 dd (7, 3)
19	5.38 br q (7)	5.62 br q (7)	5.41 br q (7)
21a	2.90 d (16)	3.82 m	2.94 d (16)
21b	3.91 br d (16)	4.45 br d (13)	3.95 br d (16)
N(1)-Me	2.63 s	2.82 s	2.65 s
CO_2*Me*	3.79 s	3.82 s	3.77 s
10-OMe	–	–	3.73 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.24: ^{13}C NMR Spectroscopic Data for Cathafoline (**35**), Cathafoline *N*(4)-oxide (**36**), and 10-Methoxycathafoline (**37**)[a]

C	35	36	37
2	79.3	78.6	79.3
3	47.4	69.8	47.5
5	50.8	66.8	50.3
6	31.2	29.3	30.1
7	43.1	41.2	43.0
8	140.5	138.3	141.5
9	121.0	121.2	109.3
10	119.4	120.1	153.7
11	127.2	128.0	110.9
12	109.4	110.2	109.8
13	153.2	151.3	147.2
14	33.9	31.5	36.6
15	34.4	32.3	34.9
16	52.9	51.5	52.7
18	13.0	13.3	13.0
19	119.2	124.1	120.0
20	139.3	129.8	138.0
21	54.9	72.4	54.7
N(1)-Me	34.0	34.3	34.2
CO_2*Me*	51.5	51.8	51.5
CO_2Me	172.9	171.9	172.6
10-OMe	–	–	55.8

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.25: ^{1}H NMR Spectroscopic Data for Strictamine (**38**), 11-Methoxystrictamine (**39**), and 11-Hydroxystrictamine (**40**)[a]

H	38	39	40
3	4.77 d (5)	4.71 d (5)	4.68 d (5)
5	2.63 td (14, 5)	2.60 td (14, 5)	2.58 td (14, 5)
	2.78 dd (14, 6)	2.75 dd (14, 6)	2.72 dd (14, 6)
6	2.02 dd (14, 5)	1.99 dd (14, 5)	1.98 dd (14, 5)
	3.73 td (14, 6)	3.67 td (14, 6)	3.67 td (14, 6)
9	7.43 br d (8)	7.31 d (8)	7.23 d (8)
10	7.18 td (8, 1)	6.72 dd (8, 2)	6.64 dd (8, 2)
11	7.35 td (8, 1)	–	–
12	7.64 br d (8)	7.20 d (2)	7.14 d (2)
14	1.78 dd (14, 3)	1.75 dd (14, 3)	1.74 dd (14, 3)
	2.70 ddd (14, 5, 3)	2.69 ddd (14, 5, 3)	2.67 ddd (14, 5, 3)
15	3.53 br s	3.52 br s	3.50 br s
16	2.09 d (3)	2.07 d (3)	2.09 d (3)
18	1.57 dd (7, 3)	1.55 dd (7, 2)	1.54 dd (7, 2)
19	5.55 br q (7)	5.53 br q (7)	5.50 br q (7)
21a	3.18 d (17)	3.17 d (17)	3.12 d (17)
21b	4.11 br d (17)	4.07 br d (17)	4.04 br d (17)
CO_2Me	3.73 s	3.72 s	3.72 s
11-OMe	–	3.79 s	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.26: ^{13}C NMR Spectroscopic Data for Strictamine (**38**), 11-Methoxystrictamine (**39**), and 11-Hydroxystrictamine (**40**)[a]

C	38	39	40
2	189.4	189.5	191.9
3	55.0	55.1	54.6
5	51.8	51.6	51.7
6	32.5	32.0	33.4
7	55.9	55.3	55.4
8	145.9	138.0	137.0
9	123.4	123.6	123.8
10	125.7	111.7	113.0
11	128.2	160.3	157.6
12	121.0	107.0	108.4
13	155.3	156.8	156.0
14	35.6	35.5	35.9
15	32.2	32.0	32.2
16	55.1	55.5	55.7
18	12.9	13.0	12.9
19	120.8	121.5	120.2
20	136.5	135.5	137.3
21	53.4	53.4	53.3
CO_2*Me*	51.6	51.7	51.5
CO_2Me	171.4	171.4	171.5
11-OMe	–	55.6	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.27: ^{1}H and ^{13}C NMR Spectroscopic Data for Vincorine (**41**) and Norvincorine (**42**)[a]

Position	**41**		**42**	
	δ_H	**δ_C**	**δ_H**	**δ_C**
2	–	97.7	–	94.8
3	1.66 m	20.4	1.77 m	26.2
	2.29 m		2.45 ddd (15, 11, 2)	
5	2.73 ddd (11, 9, 2)	55.0	2.80 ddd (12, 9, 1)	54.3
	3.38 td (11, 9)		3.62 m	
6	1.99 ddd (14, 9, 2)	40.9	2.07 m	40.5
	2.47 ddd (14, 11, 9)		2.56 ddd (14, 11, 9)	
7	–	57.2	–	57.5
8	–	138.5	–	137.4
9	6.95 d (2)	112.2	6.93 d (2)	112.4
10	–	152.0	–	153.4
11	6.63 dd (8, 2)	111.3	6.60 dd (8, 2)	111.8
12	6.19 d (8)	105.0	6.48 d (8)	109.6
13	–	143.7	–	141.4
14	1.77 m	26.3	1.86 m	26.3
	1.77 m		1.86 m	
15	3.60 d (4)	34.7	3.67 d (5)	35.2
16	2.80 d (2)	50.7	2.85 br s	50.3
18	1.59 dd (7, 2)	13.5	1.60 dd (7, 2)	13.6
19	5.40 br q (7)	122.3	5.46 br q (7)	124.0
20	–	139.0	–	137.9
21a	3.00 br d (15)	58.3	3.04 br d (15)	57.6
21b	3.80 br d (15)		3.93 br d (15)	
N(1)-Me	2.58 s	27.9		
CO_2*Me*	3.79 s	51.6	3.80 s	51.7
CO_2Me	–	173.6	3.73 s	173.3
10-OMe	3.73 s	56.0		55.9

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and HMBC.

Table 2.28: ^{1}H NMR Spectroscopic Data for Alstonamide (**43**), Demethoxyalstonamide (**44**), and Alstomaline (**45**)[a]

H	**43**	**44**	**45**
3	1.86 m	1.83 m	1.28 ddd (16, 10, 8)
	2.37 ddd (15, 11, 3)	2.37 ddd (16, 11, 2)	2.75 m
5	2.78 t (11)	2.79 dd (12, 9)	2.75 m
	3.19 td (11, 9)	3.21 ddd (12, 11, 8)	2.75 m
6	2.07 m	2.02 m	1.87 m
	2.44 ddd (14, 11, 9)	2.56 ddd (14, 11, 9)	2.52 ddd (14, 11, 8)
9	7.07 s	7.01 d (3)	6.54 d (2)
10	–	–	-
11	–	6.74 dd (9, 3)	6.60 dd (10, 2)
12	7.80 s	8.01 d (9)	7.38 d (10)
14	1.86 m	1.83 m	1.87 m
	1.98 m	2.02 m	1.87 m
15	3.74 br s	3.71 br d (5)	3.79 m
16	2.83 br s	2.83 br s	2.75 m
18	1.61 dd (7, 2)	1.60 dd (7, 2)	1.64 dd (7, 2)
19	5.44 br q (7)	5.44 br q (7)	5.44 q (7)
21a	3.01 br d (15)	3.01 d (16)	3.02 d (16)
21b	3.91 br d (15)	3.91 br d (16)	4.02 d (16)
N(1)-CHO	8.48 s	8.50 s	–
CO_2*Me*	3.89 s	3.82 s	3.79 s
10-OMe	3.83 s	3.78 s	–
11-OMe	3.84 s	–	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.29: ^{13}C NMR Spectroscopic Data for Alstonamide (**43**), Demethoxyalstonamide (**44**), and Alstomaline (**45**)[a]

C	43	44	45
2	94.8	94.7	104.3
3	26.3	26.3	27.6
5	54.3	54.3	53.6
6	41.6	41.3	40.8
7	58.4	58.4	56.9
8	132.5	139.8	159.0
9	108.2	112.0	123.0
10	148.6	157.0	188.9
11	146.1	110.0	135.6
12	100.8	117.0	133.8
13	129.3	132.3	164.1
14	27.8	27.7	26.5
15	35.2	35.4	35.6
16	51.8	49.9	50.2
18	13.5	13.5	13.8
19	123.1	123.2	123.7
20	138.5	138.9	138.7
21	58.0	58.0	59.0
N(1)-CHO	160.0	160.0	–
CO_2*Me*	50.4	51.8	51.9
CO_2Me	173.3	173.0	172.5
10-OMe	56.1	55.6	–
11-OMe	56.3	–	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.30: ^{1}H NMR Spectroscopic Data for Quaternine (**46**), Picrinine (**47**), and 12-Demethoxytabernulosine (**48**)[a]

H	46	47	48
3	3.75 m	3.75 m	3.55 d (5)
5	4.82 d (2)	4.82 d (2)	4.82 d (3)
6	2.20 dd (14, 2)	2.20 dd (14, 2)	2.25 dd (14, 3)
	3.37 d (14)	3.37 d (14)	3.40 br d (14)
9	6.78 s	7.14 br d (8)	6.75 br s
10	–	6.79 td (8, 1)	–
11	–	7.09 td (8, 1)	6.63 m
12	6.31 s	6.76 br d (8)	6.63 m
14	1.79 dd (14, 3)	1.86 dd (14, 3)	1.84 dd (14, 2)
	2.14 ddd (14, 5, 3)	2.15 ddd (14, 5, 3)	2.12 dt (14, 5)
15	3.28 br s	3.28 br d (3)	3.27 br s
16	2.39 d (3)	2.44 d (3)	2.45 d (3)
18	1.48 dd (7, 2)	1.49 dd (7, 3)	1.44 dd (7, 2)
19	5.41 br q (7)	5.40 qt (7, 2)	5.39 q (7)
21	3.10 d (18)	3.09 d (18)	3.08 br d (18)
	3.79 m	3.76 m	3.75 m
N(1)-Me	2.94 s	–	–
N(1)-H	–	4.77 s	4.87 br s
CO_2*Me*	3.65 s	3.66 s	3.66 s
10-OMe	3.87 s	–	3.70 s
11-OMe	3.76 s	–	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.31: ^{13}C NMR Spectroscopic Data for Quaternine (**46**), Picrinine (**47**), and 12-Demethoxytabernulosine (**48**)[a]

C	46	47	48
2	109.2	109.2	107.2
3	49.7	49.7	52.1
5	87.2	87.2	87.4
6	40.3	40.3	40.6
7	50.6	51.4	51.6
8	125.9	135.1	136.6
9	110.3	125.1	112.0
10	144.2	120.8	154.5
11	149.6	127.9	113.0
12	94.6	110.6	111.0
13	143.2	147.6	141.5
14	25.8	26.0	26.1
15	31.1	31.0	31.2
16	52.0	52.0	51.8
18	12.7	12.7	12.8
19	120.5	120.4	120.4
20	135.9	136.1	136.4
21	46.3	46.3	46.4
N(1)-Me	29.8	–	–
CO_2*Me*	51.4	51.8	51.6
CO_2Me	172.5	172.4	172.6
10-OMe	56.2	–	55.9
11-OMe	57.0	–	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

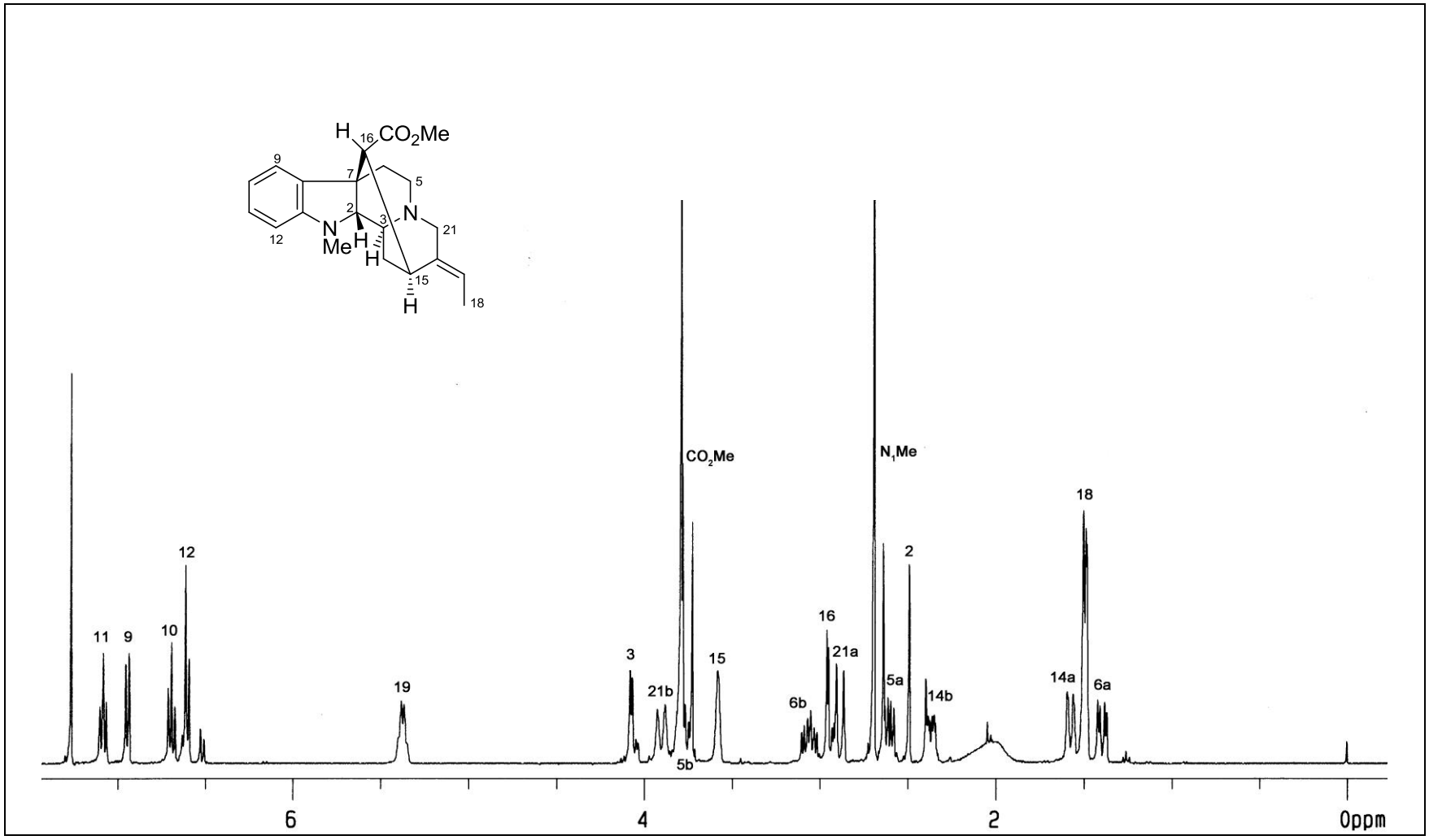


Figure 2.48: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Cathafoline (**35**)

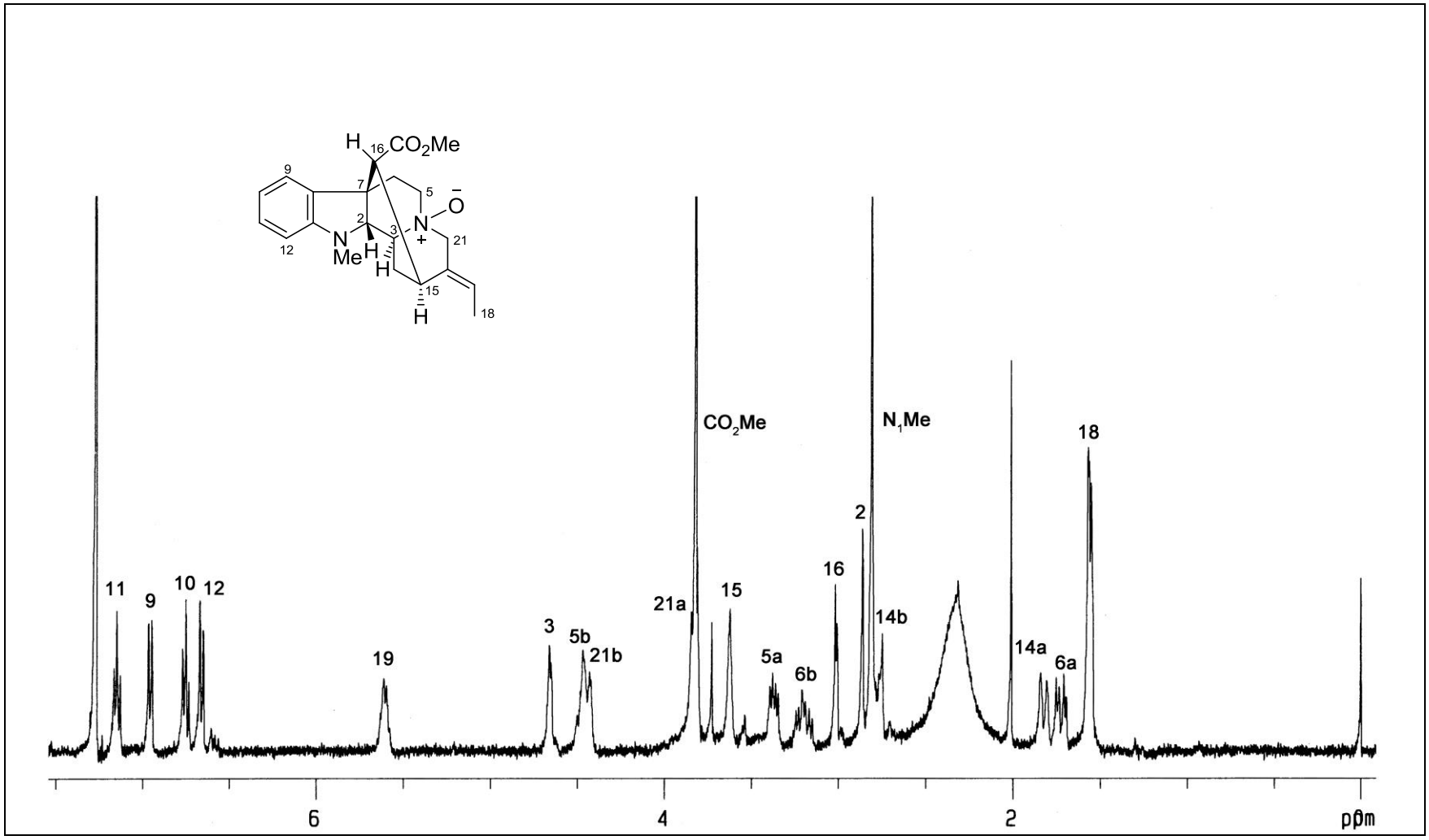


Figure 2.49: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Cathafoline *N*(4)-oxide (**36**)

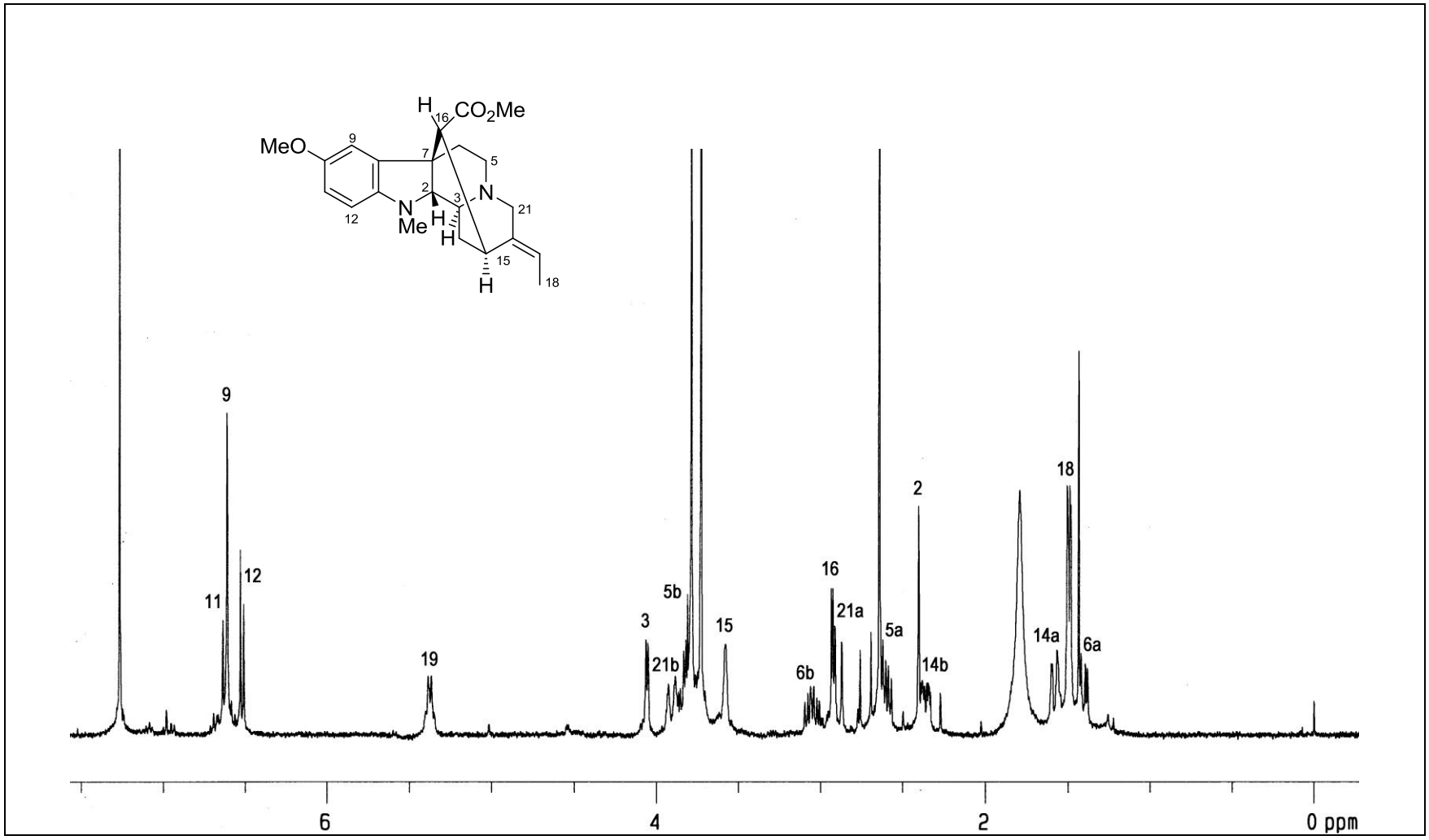


Figure 2.50: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 10-Methoxycathafoline (**37**)

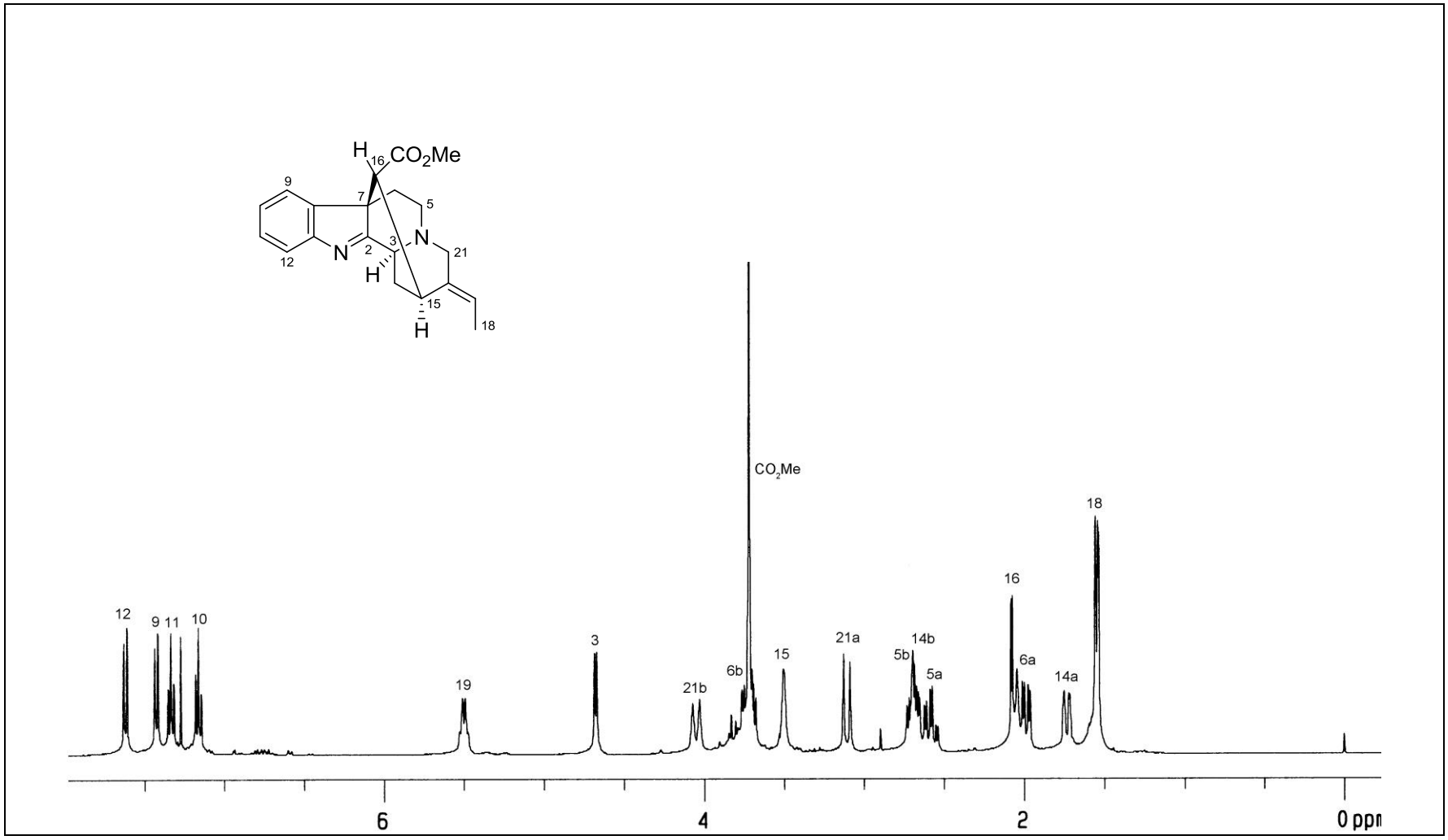


Figure 2.51: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Strictamine (**38**)

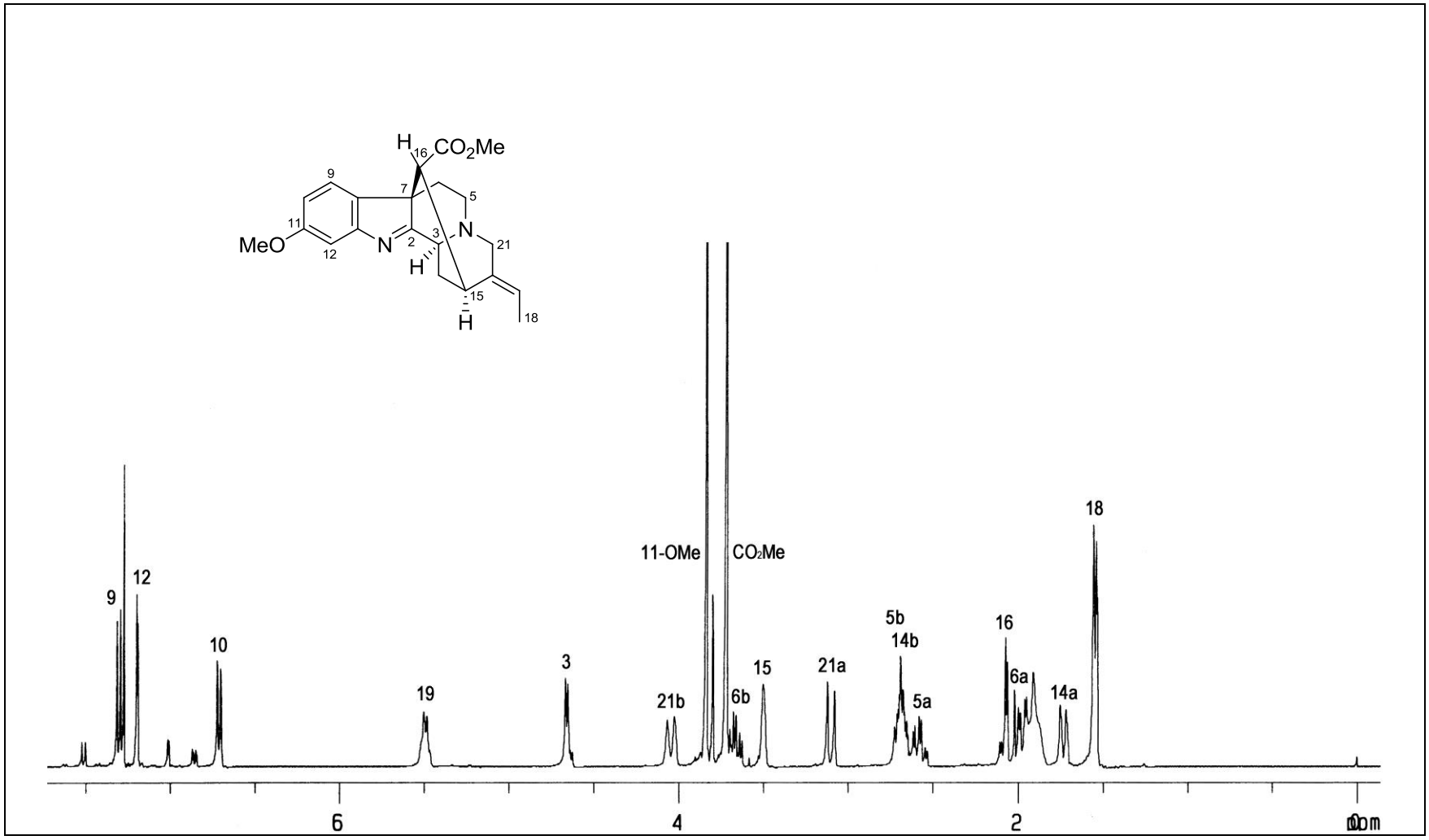


Figure 2.52: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 11-Methoxystrictamine (**39**)

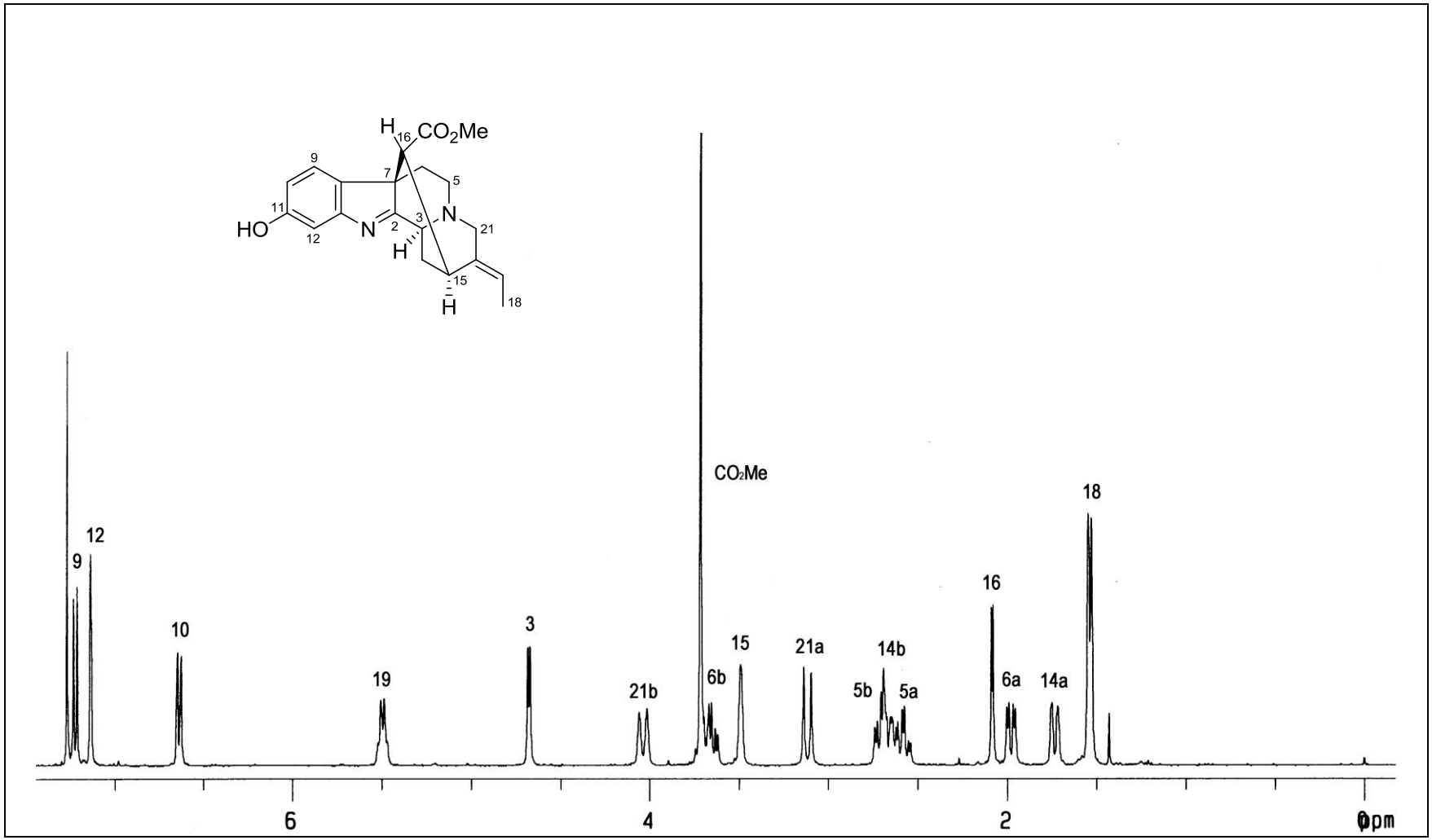


Figure 2.53: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 11-Hydroxystrictamine (**40**)

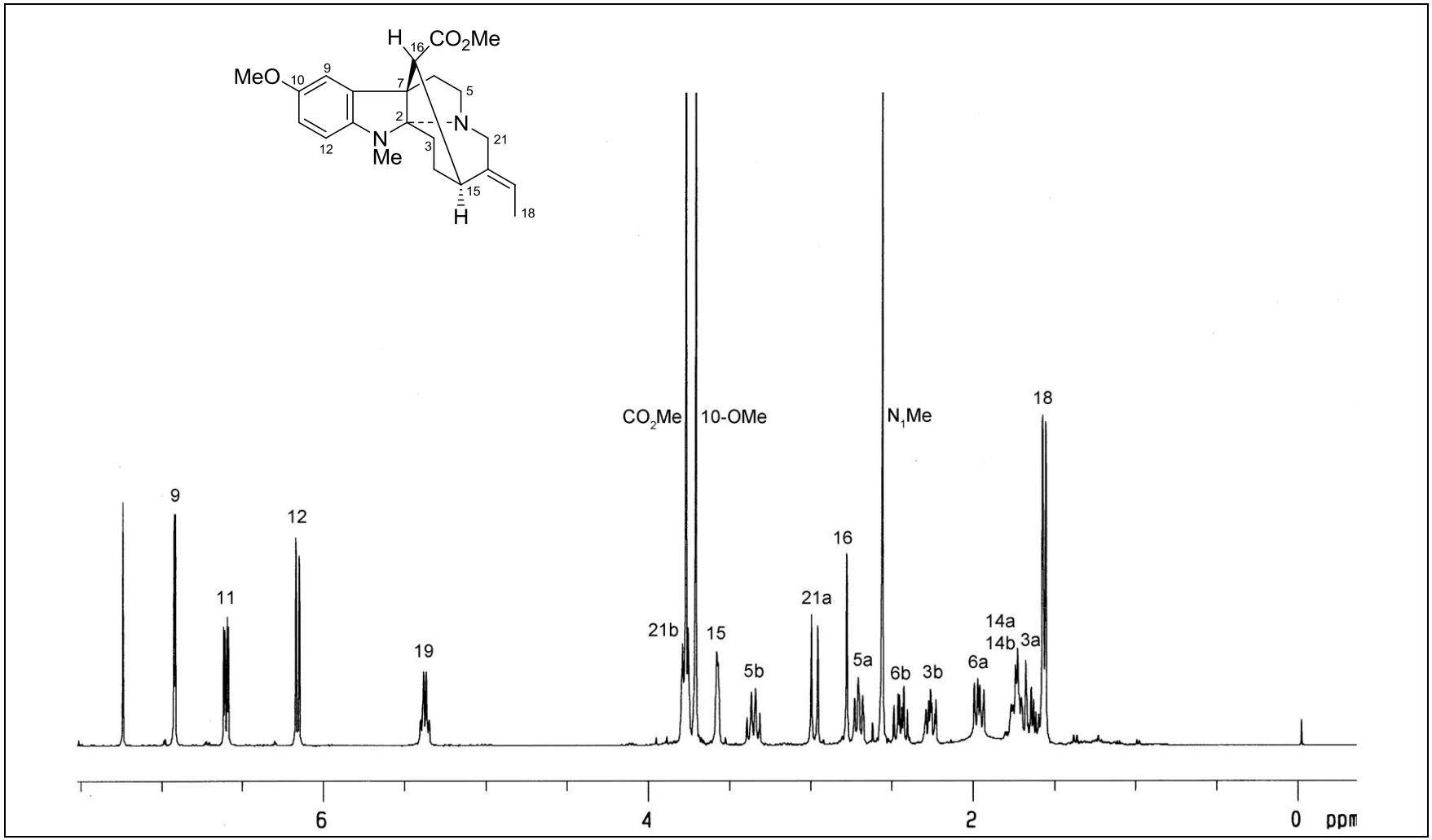


Figure 2.54: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Vincorine (**41**)

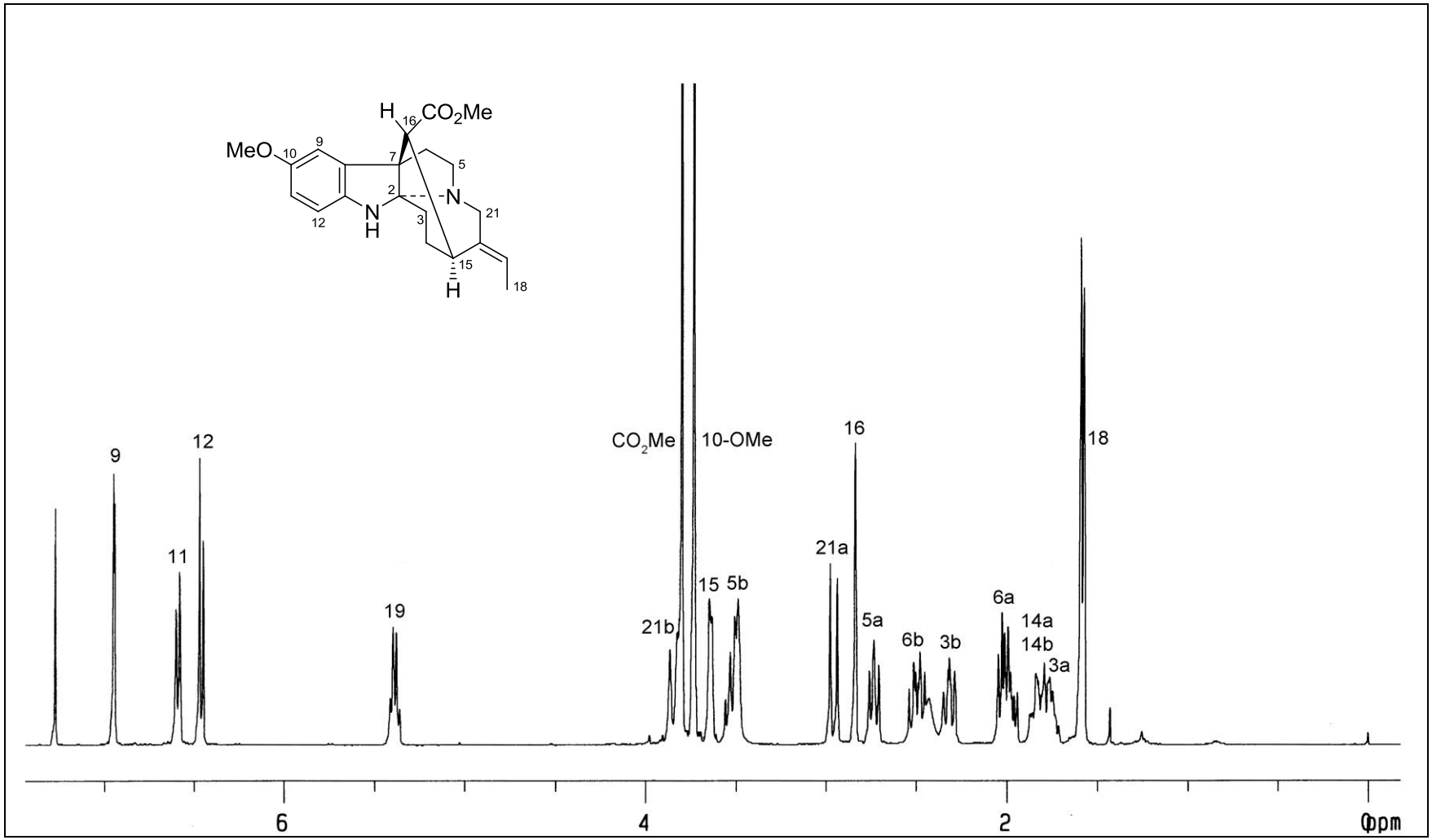


Figure 2.55: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Norvincorine (**42**)

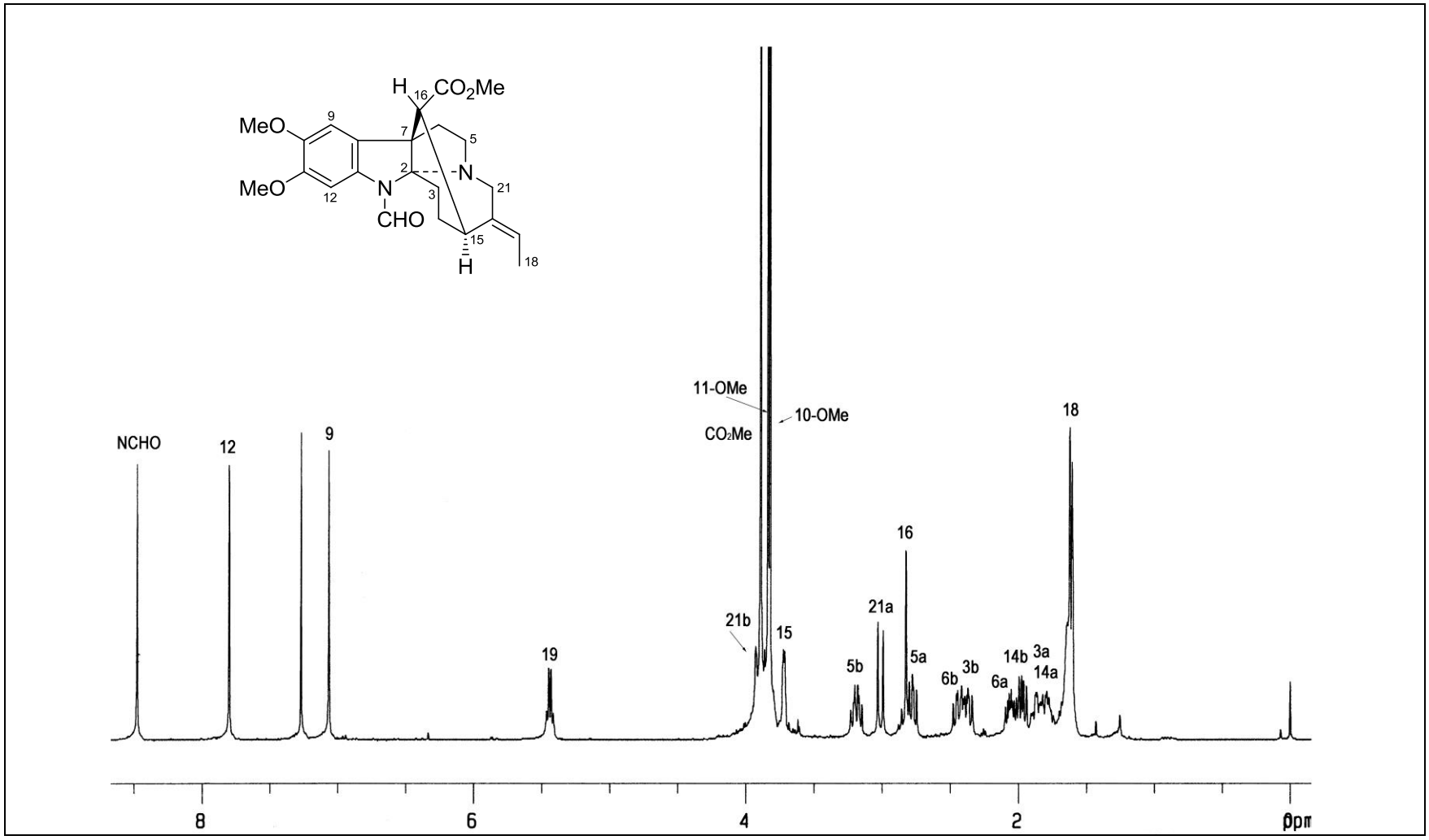


Figure 2.56: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstonamide (**43**)

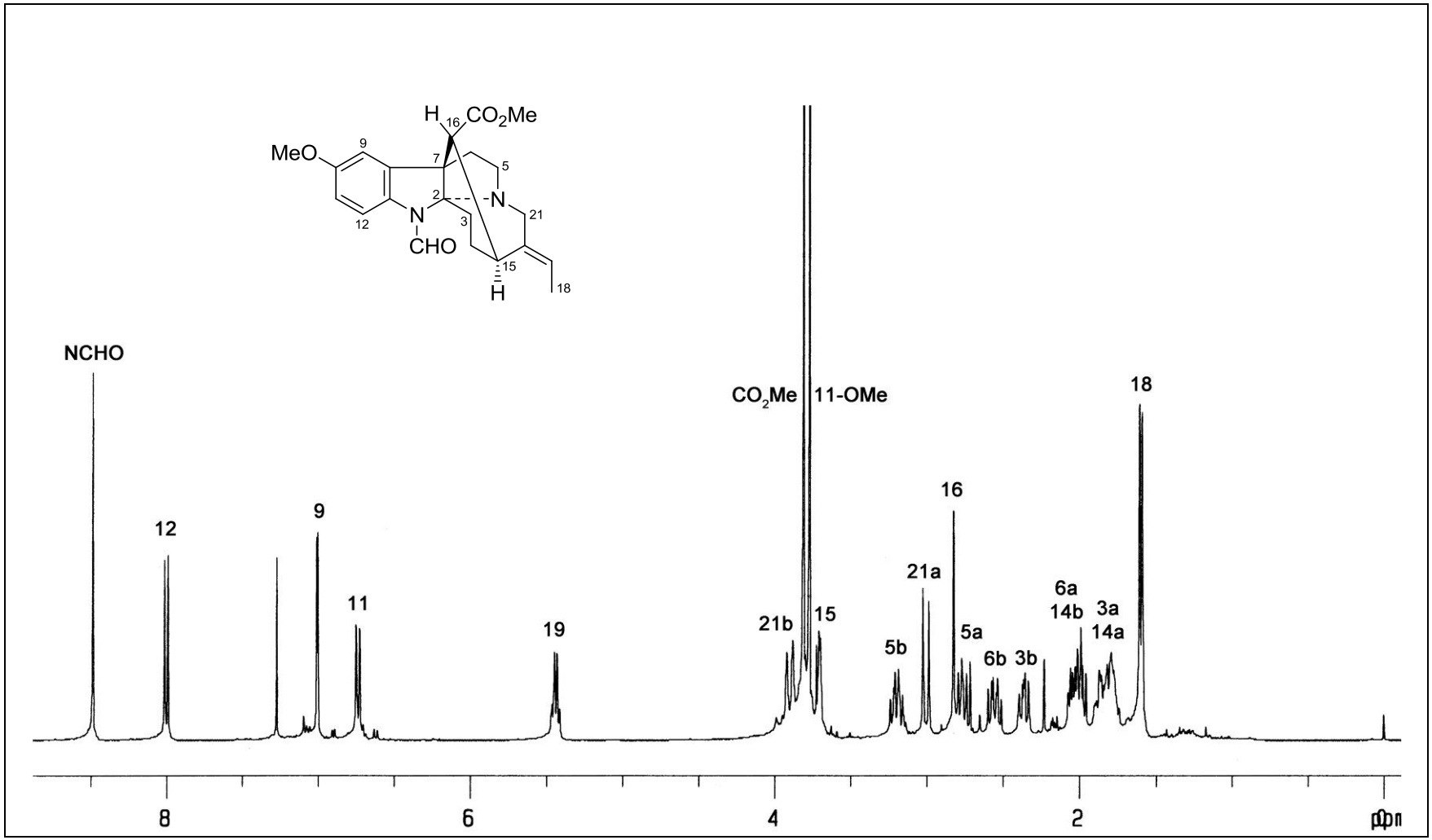


Figure 2.57: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Demethoxyalstonamide (**44**)

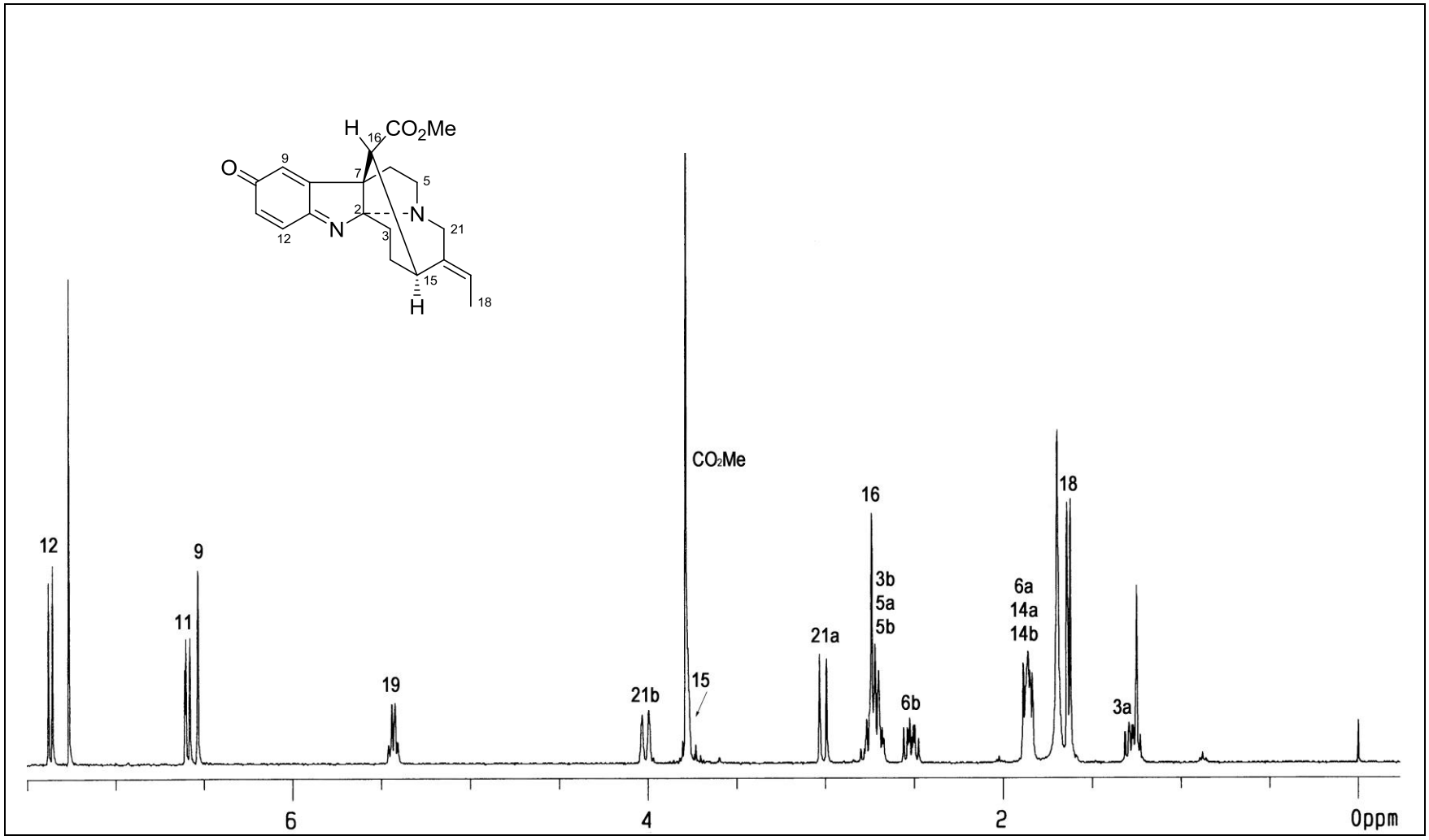


Figure 2.58: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstomaline (**45**)

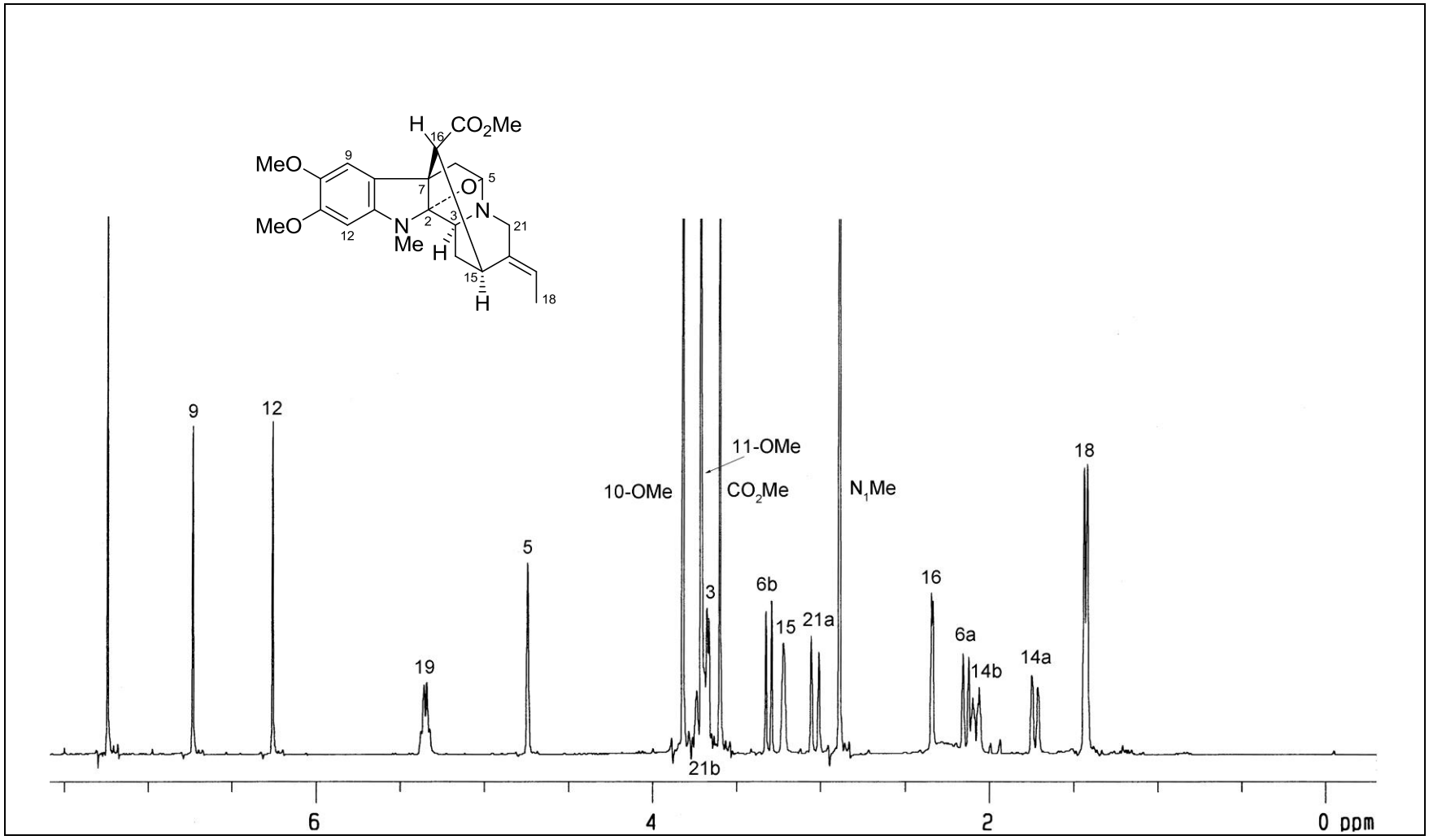


Figure 2.59: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Quaternine (**46**)

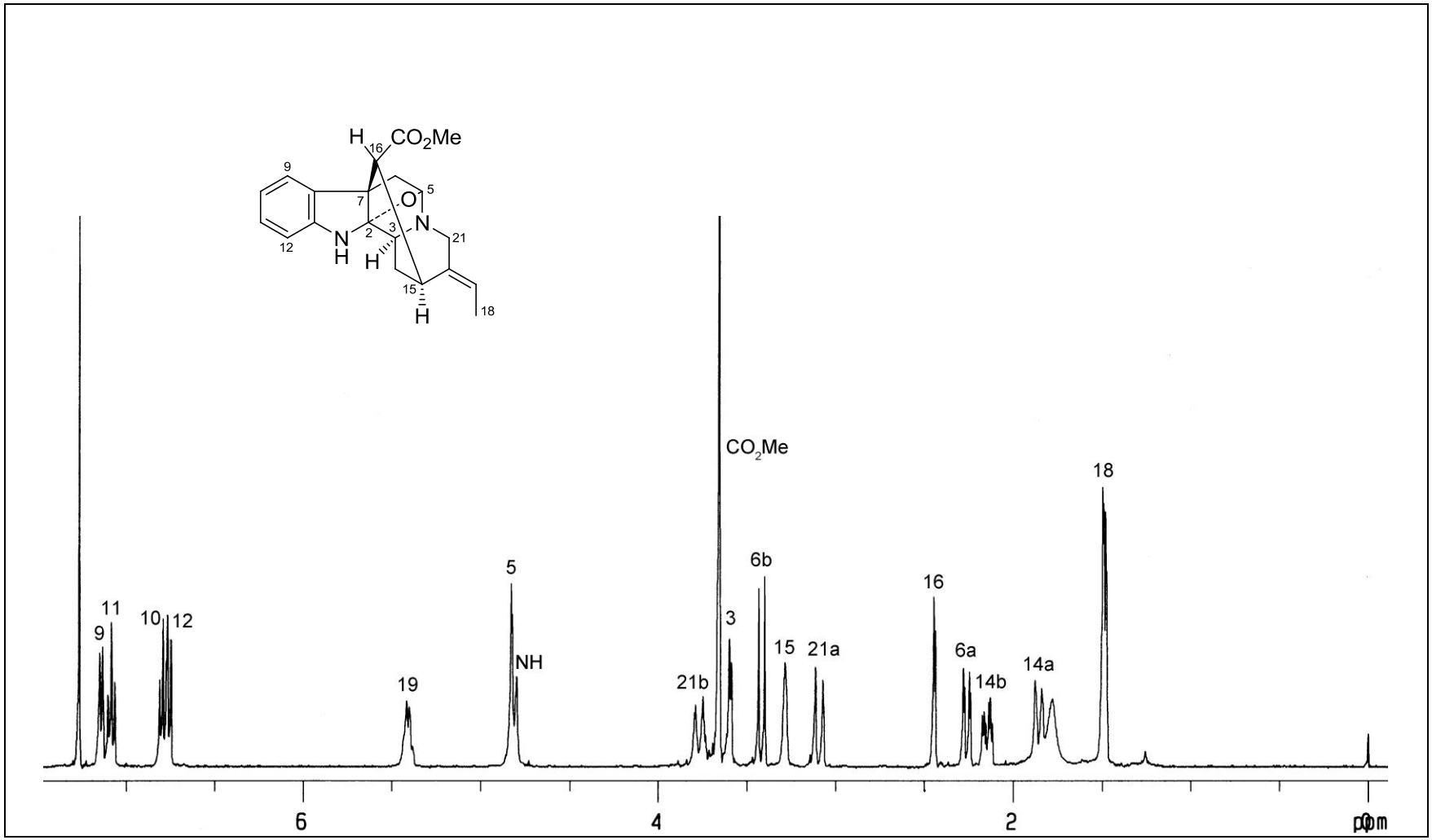


Figure 2.60: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Picrinine (**47**)

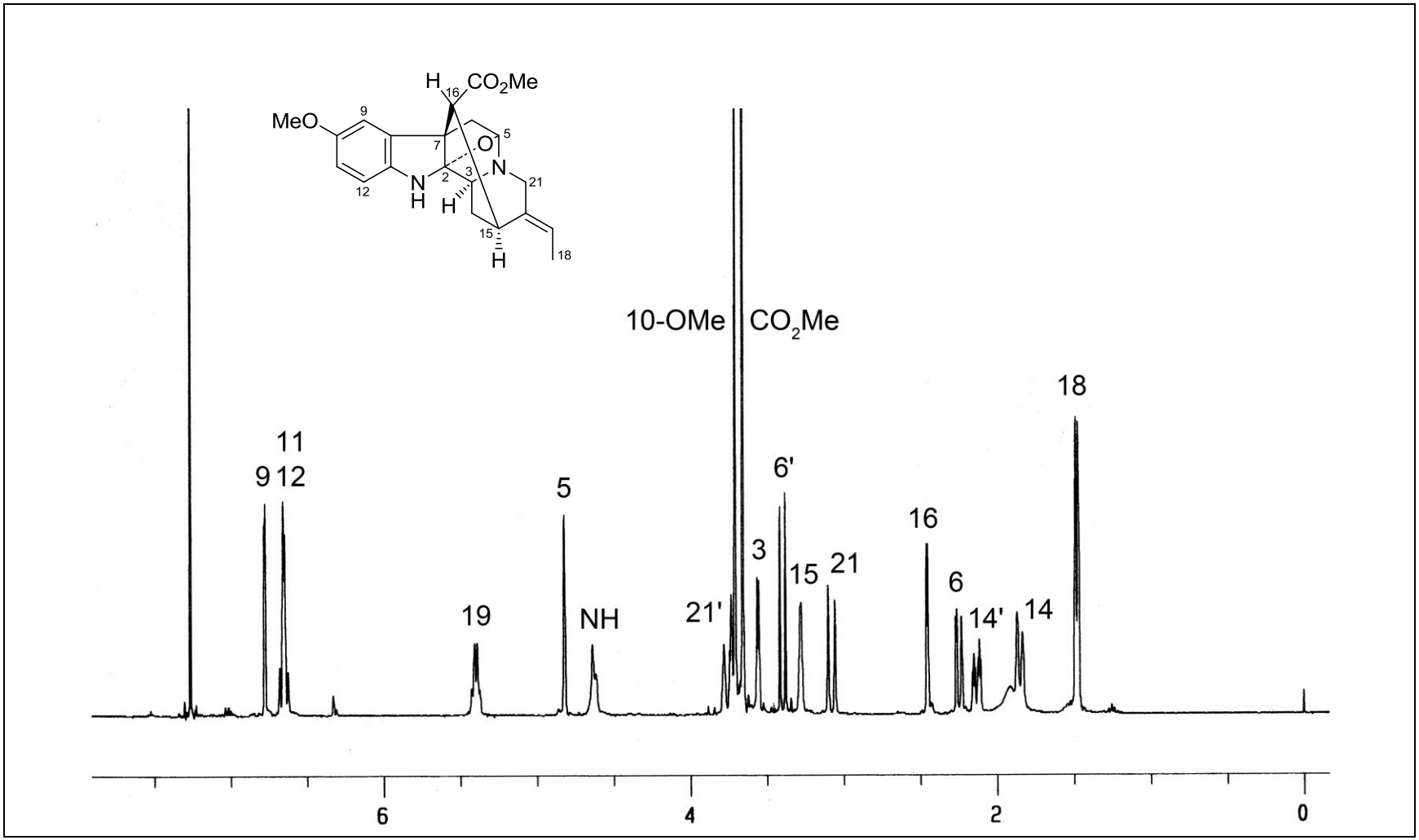


Figure 2.61: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 12-Demethoxytabernulosine (**48**)

2.1.3.13 Affinisine (49), Affinisine oxindole (50), Normacusine B (51), Alstoumerine (52), Quebrachidine (53), Vincamajine (54), and Vincamajine 17-*O*-veratrate (55)

Four known sarpagine alkaloids were isolated, viz., affinisine (**49**),[254-256] affinisine oxindole (**50**),[132] normacusine B (**51**),[254,257] and alstoumerine (**52**),[159,166,258] while three ajmaline alkaloids were also obtained from this study, namely, quebrachidine (**53**),[247] vincamajine (**54**),[143,144,168,247-249] and vincamajine 17-*O*-veratrate (**55**).[164] The ^{1}H NMR spectra of these compounds are shown in Figures 2.62–2.68, the NMR spectroscopic data are summarized in Tables 2.32–2.35. Other data are given in the Experimental Section.

Table 2.32: ^{1}H and ^{13}C NMR Spectroscopic Data for Affinisine (**49**) and Affinisine oxindole (**50**)

Position	**49**		**50**	
	δ_H	δ_C	δ_H	δ_C
2	–	139.5		181.4
3	4.17 dd (10, 2)	49.5	3.36 dd (10, 2)	63.0
5	2.73 m (α)	54.5	3.31 dd (6, 3)	59.3
6	2.59 br d (15) (β)	27.1	1.81 d (13)	44.4
	3.02 dd (15, 5) (α)		2.79 dd (13, 6)	
7	–	103.7	–	56.4
8	–	127.4	–	129.9
9	7.40 d (7.5)	118.2	7.37 br d (8)	126.7
10	7.07 t (7.5)	118.9	7.10 td (8, 1)	121.8
11	7.18 t (7.5)	121.0	7.32 td (8, 1)	128.4
12	7.28 d (7.5)	108.8	6.84 br d (8)	108.0
13	–	137.4	–	144.5
14a	1.57 m	32.9	1.57 ddd (14, 10, 2)	28.7
14b	2.10 td (11, 1.4)		2.18 ddd (14, 4, 2)	
15	2.73 m	27.5	2.89 br s	26.3
16	1.73 m	44.3	2.05 m	48.0
17	3.42 m	65.0	3.63 m	65.5
	3.45 m		3.63 m	
18	1.59 d (6.5)	12.9	1.61 dt (7, 2)	12.5
19	5.34 q (6.5)	116.8	5.32 br q (7)	115.2
20	–	135.7	–	135.9
21	3.49 m	56.3	3.78 m	48.9
	3.58 m		3.78 m	
N(1)-Me	3.60 s	29.4	3.21 s	26.6

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC and NOESY.

Table 2.33: ^{1}H and ^{13}C NMR Spectroscopic Data for Normacusine B (**51**) and Alstoumerine (**52**)

Position	**51**		**52**	
	δ_H	δ_C	δ_H	δ_C
2	–	138.2	–	139.4
3	4.08 dd (10, 2)	50.4	3.88 dd (10, 2)	48.6
5	2.75 m	54.3	3.03 t (6)	56.4
6	2.61 dd (15, 1)	27.0	2.69 d (15)	29.6
	3.03 dd (15, 5)		3.12 dd (15, 6)	
7	–	104.8	–	102.5
8	–	127.7	–	127.2
9	7.44 br d (8)	118.1	7.48 br d (8)	118.1
10	7.08 td (8, 1)	119.3	7.10 td (8, 1)	118.9
11	7.13 td (8, 1)	121.4	7.19 td (8, 1)	121.0
12	7.29 br d (8)	110.9	7.28 br d (8)	108.7
13	–	136.3	–	137.4
14a	1.68 m	33.5	1.61 m	38.7
14b	1.97 ddd (12, 10, 2)		1.88 ddd (12, 10, 2)	
15	2.75 m	27.7	2.78 br s	29.2
16	1.79 tdd (8, 6, 2)	44.3	1.61 m	44.4
17	3.51 m	65.0	3.46 dd (12, 5)	64.6
	3.51 m		3.62 dd (12, 4)	
18	1.60 dt (7, 2)	12.7	1.36 d (7)	22.3
19	5.33 br q (7)	116.6	4.52 d (7)	67.3
20	–	136.0	–	136.4
21	3.51 m	56.0	6.54 d (1)	149.3
	3.51 m		–	
N(1)-H	8.07 br s	–	–	–
N(1)-Me	–	–	3.58 s	25.4

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and HMBC.

Table 2.34: ^{1}H NMR Spectroscopic Data for Quebrachidine (**53**), Vincamajine (**54**) and Vincamajine 17-*O*-veratrate (**55**)[a]

H	**53**	**54**	**55**
2	3.82 br s	3.23 d (5)	3.27 d (5)
3	3.45 m	3.55 dd (10, 5)	3.60 dd (9, 5)
5	3.54 d (5)	3.57 d (5)	3.69 d (5)
6	1.73 d (12)	1.76 d (12)	1.88 d (11)
	2.63 dd (12, 5)	2.58 dd (12, 5)	2.72 d (11)
9	7.18 br d (8)	7.12 dd (8, 1)	6.87 br d (7)
10	6.81 td (8, 1)	6.77 td (8, 1)	6.53 t (7)
11	7.12 td (8, 1)	7.14 td (8, 1)	7.11 t (7)
12	6.78 br d (8)	6.63 dd (8, 1)	6.67 br d (7)
14	1.44 dd (14, 10)	1.49 dd (14, 10)	1.59 td (12, 4)
	2.56 dd (14, 5)	2.42 dd (14, 5)	2.72 br d (12)
15	3.45 m	3.46 d (5)	3.55 d (4)
17	4.29 s	4.02 s	5.91 br s
18	1.59 dt (7, 2)	1.57 br d (7)	1.55 d (7)
19	5.26 br q (7)	5.26 br q (7)	5.29 br q (7)
21	3.45 m	3.44 m	3.50 br s
	3.45 m	3.44 m	3.50 br s
N(1)-Me	–	2.61 s	2.68 s
CO_2*Me*	3.70 s	3.67 s	3.39 s
2'	–	–	7.39 d (2)
5'	–	–	6.88 br d (8)
6'	–	–	7.55 dd (8, 2)
3'-OMe	–	–	3.90 s
4'-OMe	–	–	3.94 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.35: ^{13}C NMR Spectroscopic Data for Quebrachidine (**53**), Vincamajine (**54**) and Vincamajine 17-*O*-veratrate (**55**)[a]

C	53	54	55
2	68.5	74.4	74.9
3	54.6	53.1	53.2
5	61.6	61.6	61.6
6	35.6	35.2	36.7
7	57.8	57.0	56.3
8	129.6	130.1	128.7
9	124.8	128.2	123.5
10	119.6	119.1	119.0
11	128.2	124.4	128.5
12	110.9	109.0	109.1
13	151.7	154.4	154.2
14	22.3	21.8	21.8
15	30.3	30.0	30.2
16	59.6	59.4	59.1
17	74.3	74.5	75.9
18	12.8	12.8	12.6
19	116.4	116.5	116.8
20	136.8	136.5	136.5
21	55.3	55.2	55.5
N(1)-Me	–	34.2	34.2
CO_2*Me*	51.6	51.5	51.6
CO_2Me	173.3	173.0	172.2
1'	–	–	122.1
2'	–	–	111.9
3'	–	–	148.6
4'	–	–	153.0
5'	–	–	110.3
6'	–	–	123.2
3'-OMe	–	–	55.9
4'-OMe	–	–	55.9
–C=O	–	–	163.8

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

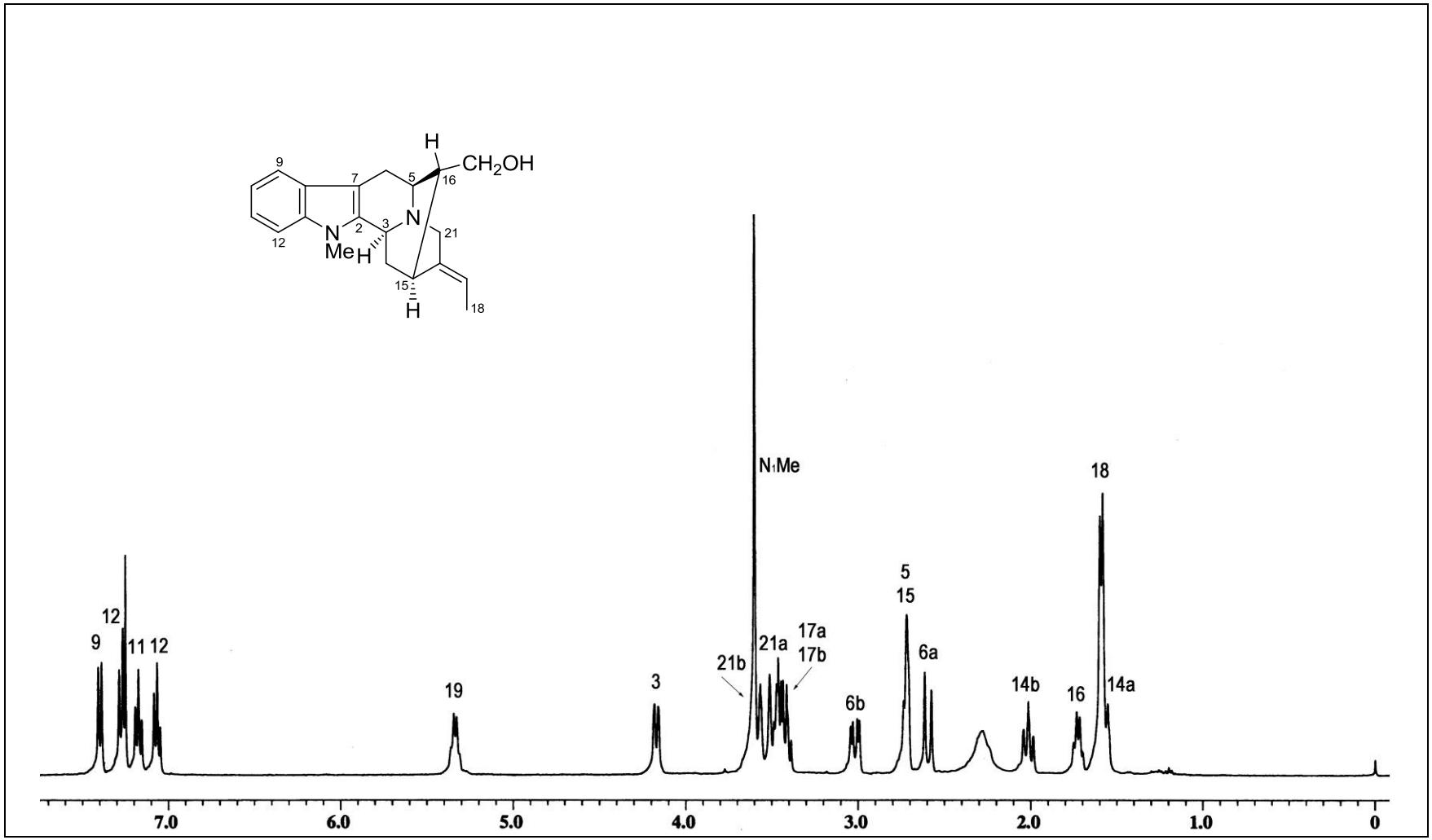


Figure 2.62: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Affinisine (**49**)

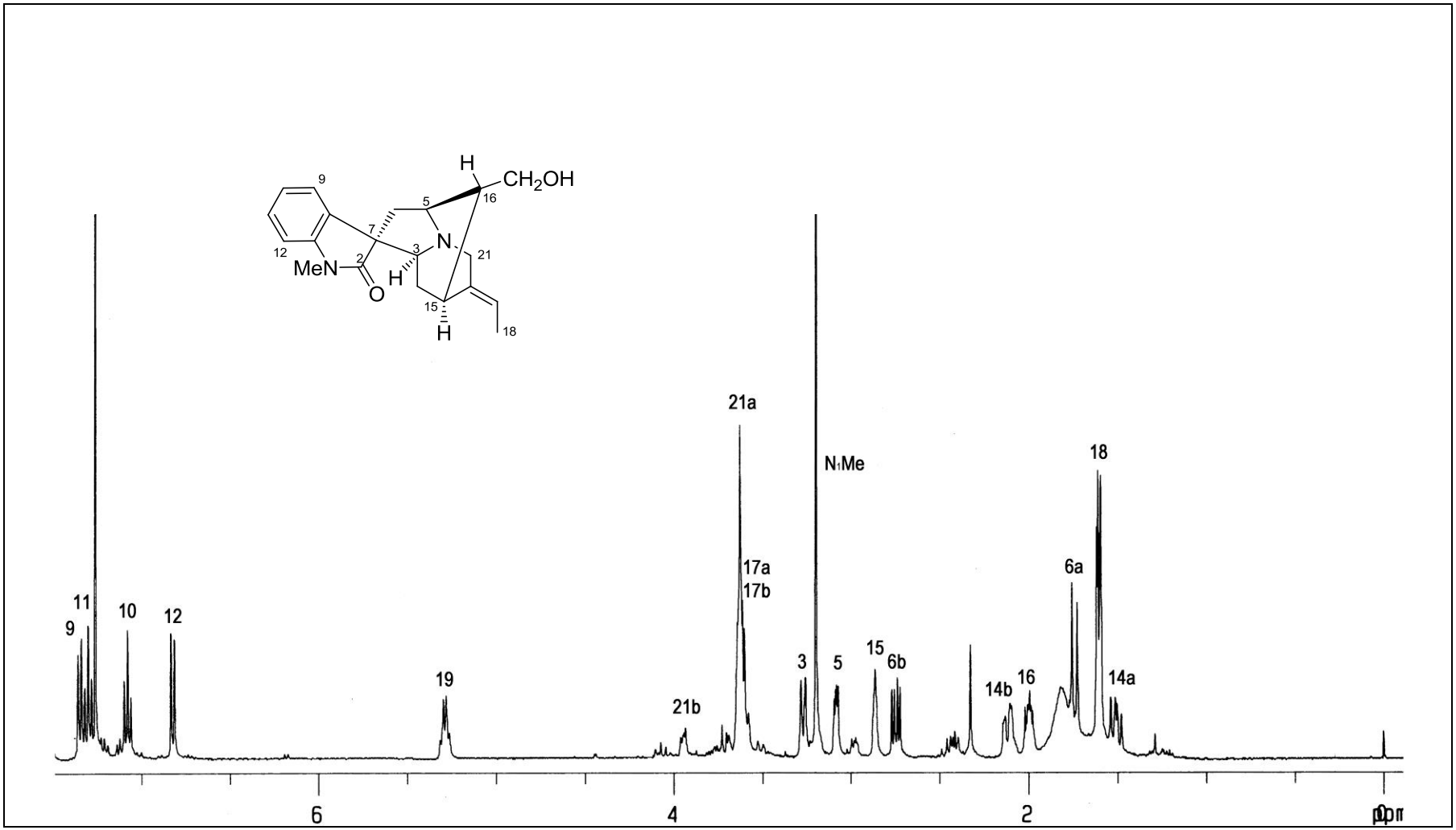


Figure 2.63: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Affinisine oxindole (**50**)

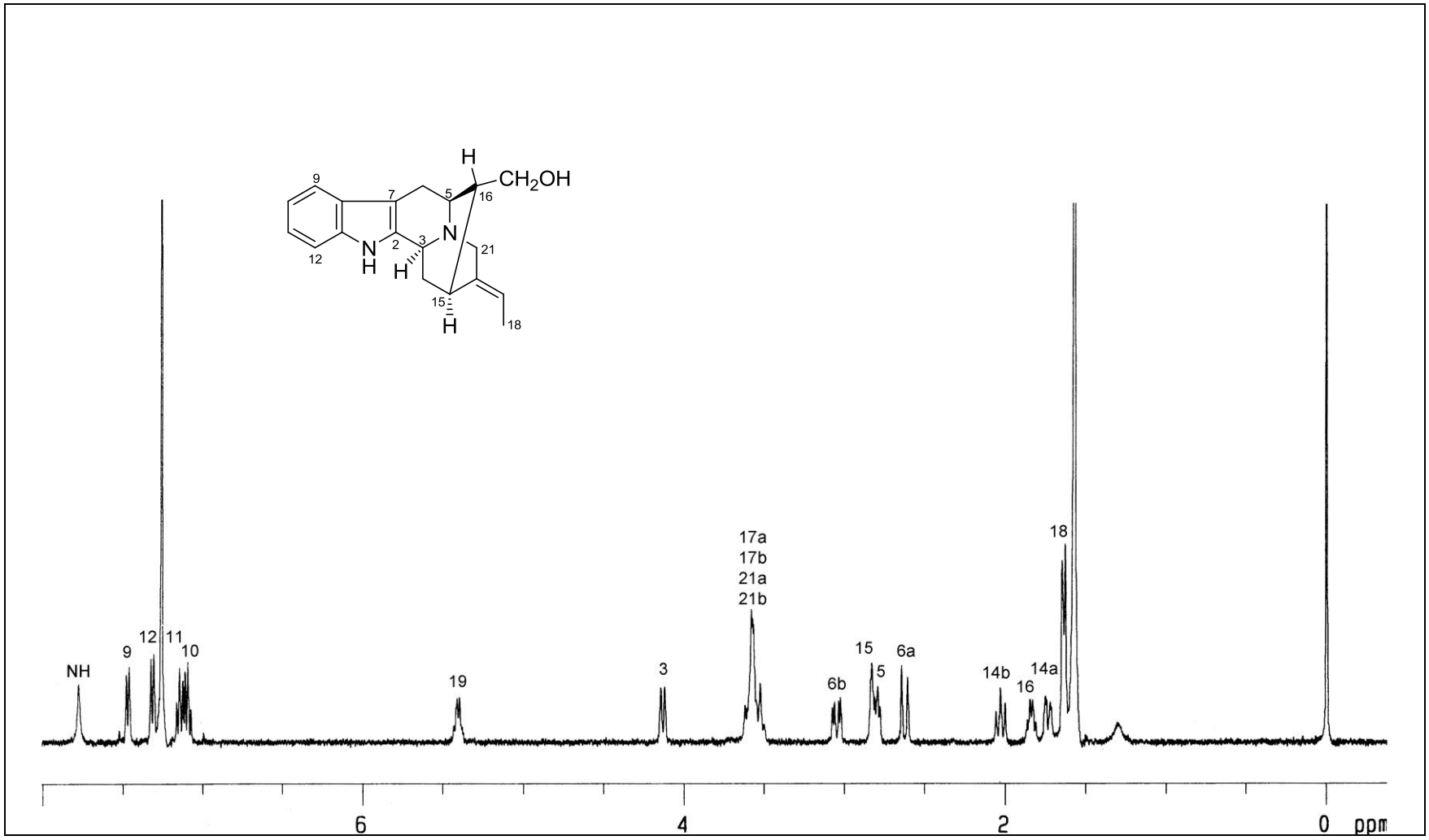


Figure 2.64: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Normacusine B (**51**)

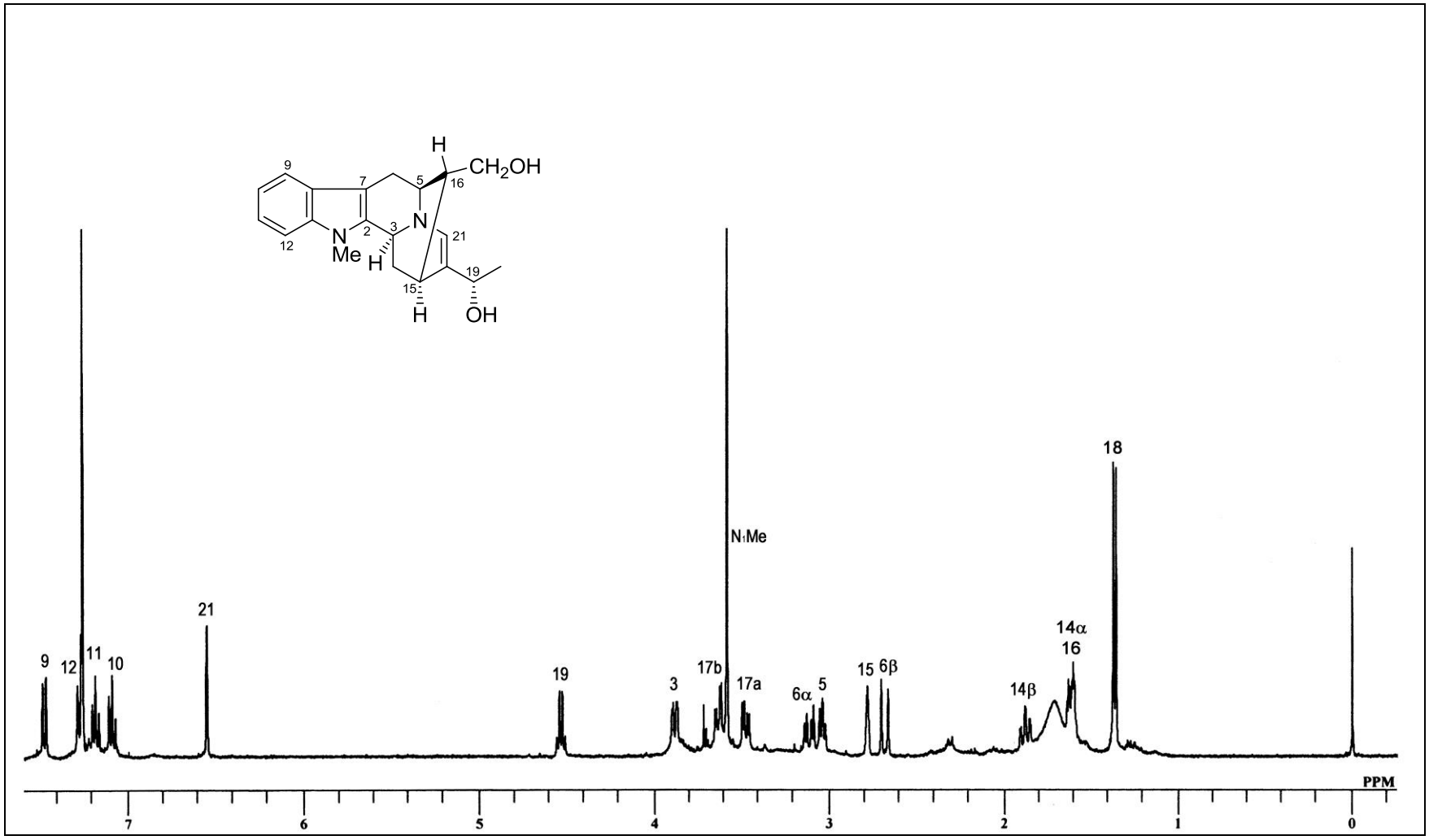


Figure 2.65: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Alstoumerine (**52**)

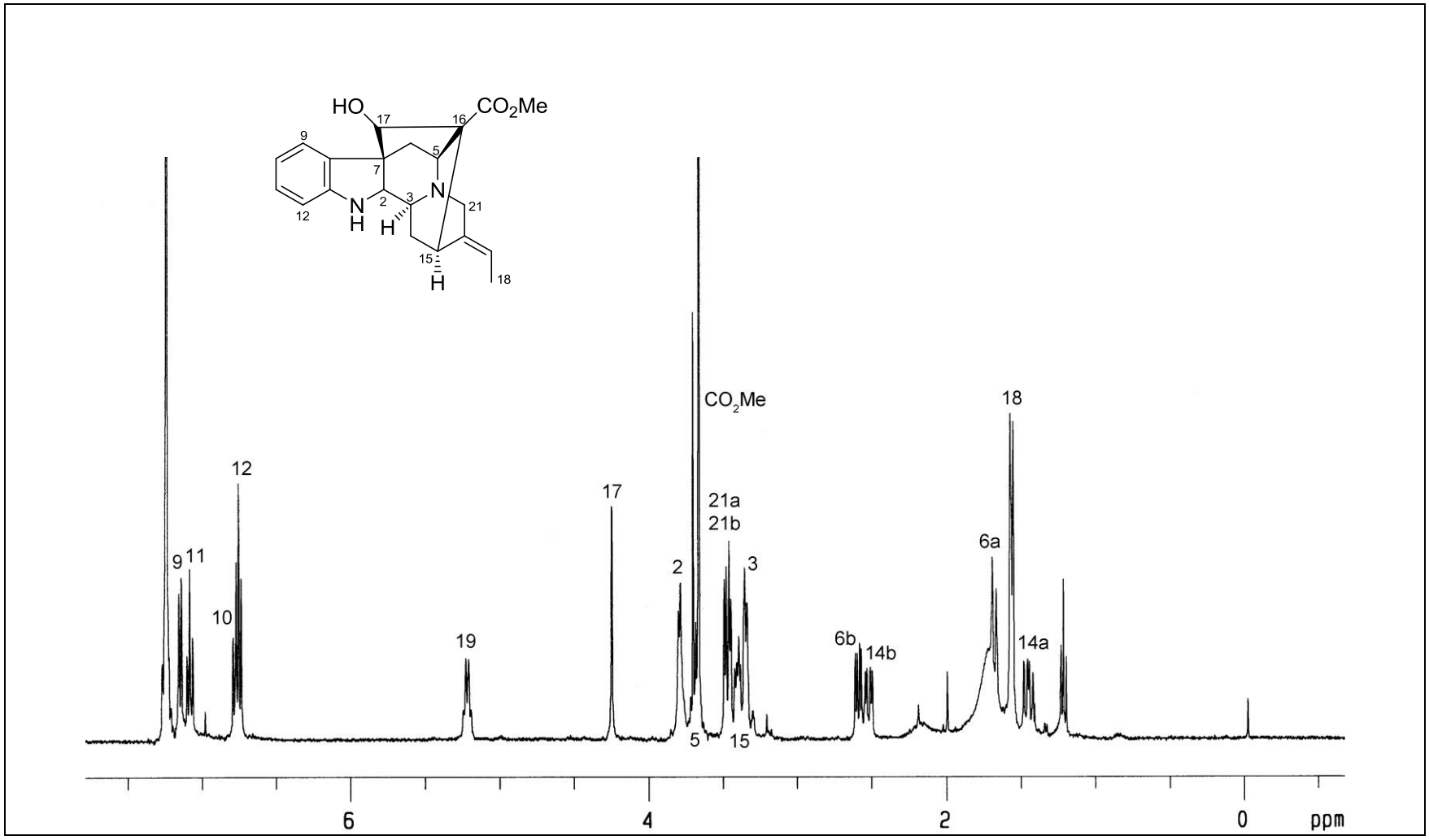


Figure 2.66: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Quebrachidine (**53**)

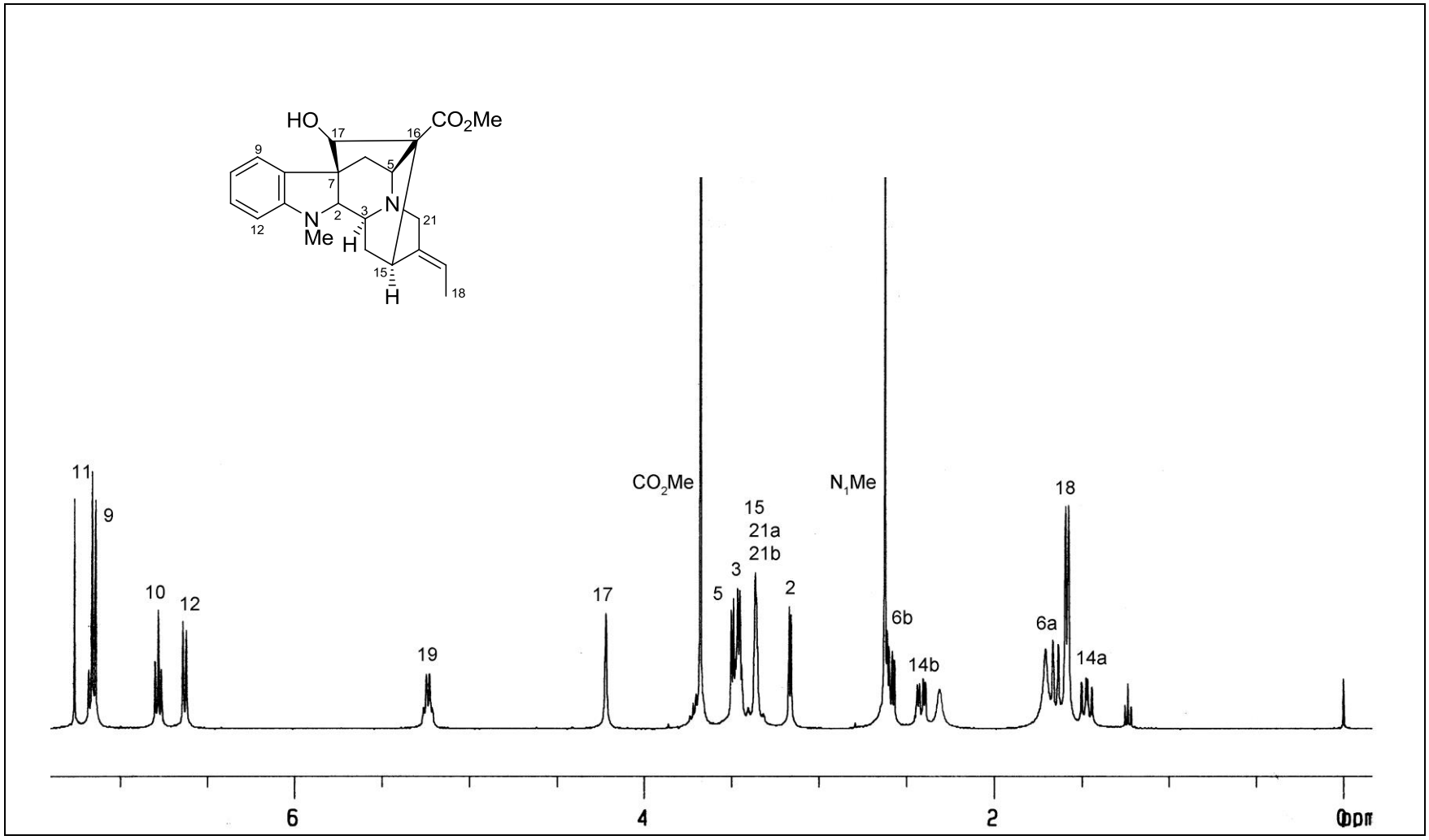


Figure 2.67: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Vincamajine (**54**)

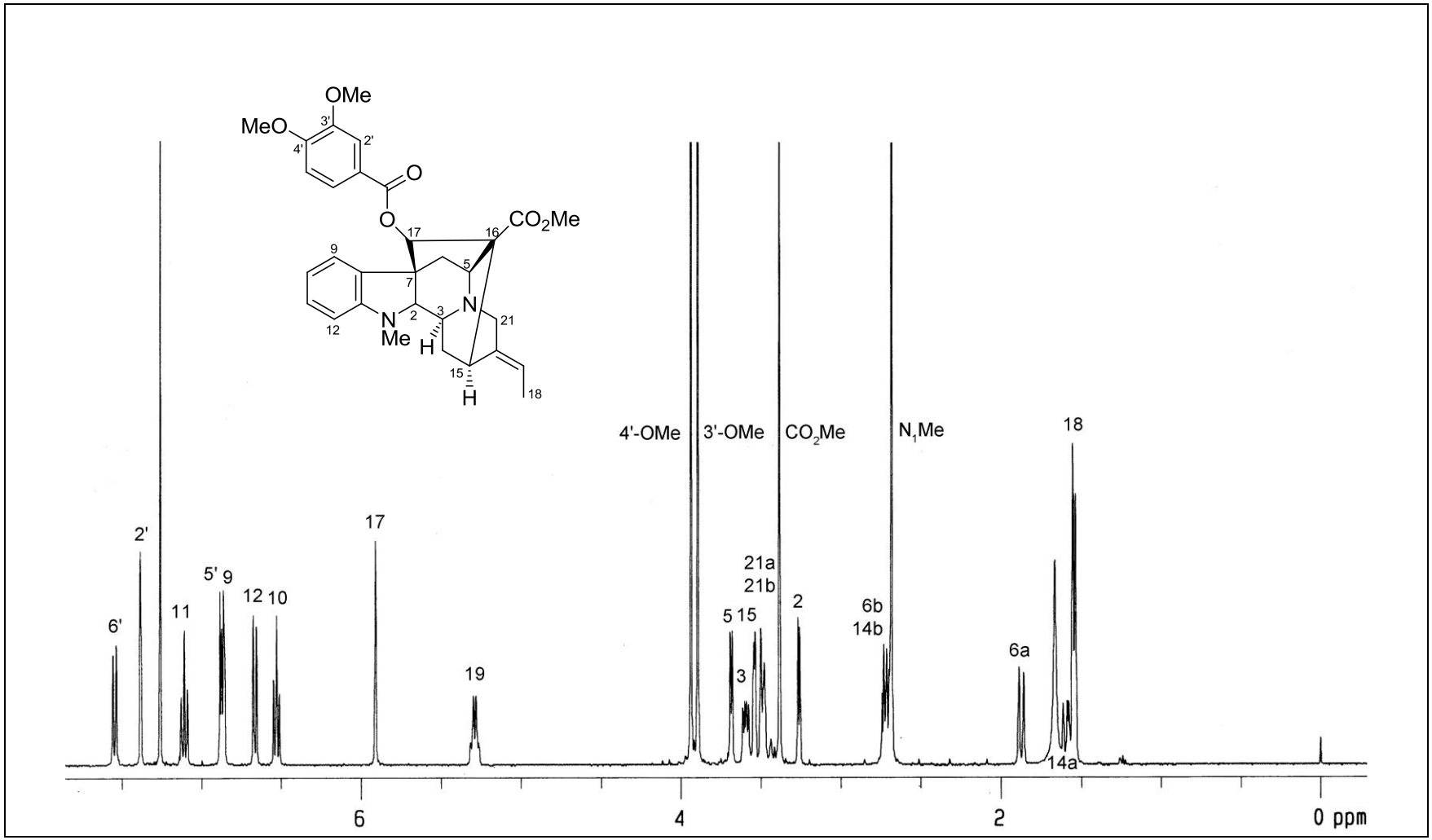


Figure 2.68: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Vincamajine 17-*O*-veratrate (**55**)

2.1.4 Corynantheine alkaloids

2.1.4.1 Sitsirikine (56), 16(*R*),19(*E*)-Isositsirikine (57), 18,19-Dihydroisositsirikine (58), Pleiocarpamine (59), 16-Hydroxymethylpleiocarpamine (60), Pleiomaltinine (61), Picramicine (62), Fluorocarpamine (63), Yohimbine (64), Talpinine (65), and 10,11-Dimethoxynareline (66)

Eleven known corynantheine alkaloids are obtained in this study, *viz*., sitsirikine (**56**),[259] 16(*R*),19(*E*)-isositsirikine (**57**),[260,261] 18,19-dihydroisositsirikine (**58**),[261] pleiocarpamine (**59**),[246] 16-hydroxymethylpleiocarpamine (**60**),[262] pleiomaltinine (**61**),[119] picramicine (**62**),[263] fluorocarpamine (**63**),[187] yohimbine (**64**),[64,118,191,264] talpinine (**65**),[234,236] and 10,11-dimethoxynareline (**66**).[265] The ^{1}H NMR spectra of these compounds are shown in Figures 2.69–2.79. The ^{1}H and ^{13}C NMR data are summarized in Tables 2.36–2.42, while other data are given in the Experimental Section.

Table 2.36: ^{1}H NMR Spectroscopic Data for Sitsirikine (**56**), 16(*R*),19(*E*)-Isositsirikine (**57**) and 18,19-Dihydroisositsirikine (**58**)[a]

H	**56**	**57**	**58**
3	3.04 br d (12)	4.33 br s	2.98 m
5	2.50 m	3.15 m	2.44 m
	2.95 m	3.27 ddd (13, 6, 2)	2.98 m
6	2.70 dd (14, 5)	2.67 dd (16, 6)	2.69 dd (14, 5)
	2.95 m	2.99 m	2.98 m
9	7.46 br d (8)	7.47 br d (8)	7.45 br d (8)
10	7.08 td (8, 1)	7.10 td (8, 1)	7.07 td (8, 1)
11	7.13 td (8, 1)	7.16 td (8, 1)	7.12 br t (8)
12	7.28 br d (8)	7.39 br d (8)	7.27 br d (8)
14	1.35 q (12)	2.24 m	1.36 m
	2.19 dt (12, 3)	2.24 m	2.13 br d (12.5)
15	1.66 br t (12)	3.15 m	1.56 m
16	2.50 m	2.52 ddd (11, 8, 5)	2.98 m
17	1.99 t (11)	3.54 m	3.69 dd (11, 6)
	2.88 dd (11, 4)	3.54 m	3.96 dd (11, 7)
18	5.17 dd (10, 2)	1.66 dd (7, 2)	0.90 t (8)
	5.21 dd (17, 2)		
19	5.52 dt (17, 10)	5.65 br q (7)	1.15 m
	–	–	1.68 m
20	2.95 m	–	1.68 m
21	3.71 dd (11, 6)	2.98 d (13)	1.78 t (11)
	3.91 dd (11, 7)	3.54 m	2.98 m
N(1)-H	8.36 br s	8.81 br s	8.42 br s
CO_2*Me*	3.62 s	3.81 s	3.61 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.37: ^{13}C NMR Spectroscopic Data for Sitsirikine (**56**), 16(*R*),19(*E*)-Isositsirikine (**57**), and 18,19-Dihydroisositsirikine (**58**)[a]

C	56	57	58
2	134.3	133.8	134.5
3	59.5	52.8	59.9
5	52.6	51.3	53.1
6	21.5	17.7	21.6
7	107.8	107.7	108.0
8	127.2	127.6	127.4
9	118.1	118.0	118.2
10	119.4	119.5	119.4
11	121.4	121.6	121.4
12	111.1	111.3	111.0
13	136.1	136.2	136.2
14	31.6	30.2	32.2
15	40.1	32.6	40.5
16	44.5	49.6	47.6
17	60.7	62.1	62.1
18	118.2	13.3	10.8
19	138.3	123.7	23.2
20	48.1	133.7	39.6
21	61.6	52.5	60.2
CO_2*Me*	51.7	52.2	51.9
CO_2Me	174.7	175.4	174.4

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.38: ^{1}H NMR Spectroscopic Data for Pleiocarpamine (**59**), 16-Hydroxymethylpleiocarpamine (**60**) and Pleiomaltinine (**61**)[a]

H	**59**	**60**	**61**
3	3.84 m	3.77 m	3.19 m
5	2.28 m	2.26 ddd (13, 9, 7)	2.86 m (a)
	3.35 ddd (13, 10, 3)	3.37 ddd (13, 10, 3)	3.15 m (b)
6	2.66 ddd (16, 10, 6)	2.65 m	1.45 dt (14.4, 2) (α)
	3.14 ddd (16, 9, 3)	3.16 ddd (16, 9, 3)	2.32 td (14.4, 4) (β)
9	7.53 m	7.55 m	7.08 br d (7.8)
10	7.09 m	7.10 m	6.82 td (7.8, 1)
11	7.09 m	7.10 m	7.06 td (7.8, 1)
12	6.94 m	7.10 m	6.30 br d (7.8)
14	2.19 ddd (13, 3, 2)	2.05 ddd (14, 4, 2)	1.74 dt (13, 3.6) (α)
	2.49 ddd (13, 3, 2)	2.65 m	2.83 m (β)
15	3.51 br s	3.77 m	3.37 q (3.6)
16	5.21 d (4)	–	4.79 d (3.6)
17	–	4.24 d (12)	–
	–	4.54 d (12)	–
18	1.47 dd (7, 2)	1.52 dd (7, 2)	1.59 dd (6.8, 2)
19	5.30 qd (7, 2)	5.30 qd (7, 2)	5.42 qd (6.8, 2)
21	1.73 br d (13)	1.87 dt (13, 2)	3.04 d (12.4) (α)
	2.59 d (13)	2.65 m	4.27 dt (12.4, 2) (β)
CO_2*Me*	3.56 s	3.32 s	3.73 s
5'	–	–	6.20 d (5.6)
6'	–	–	7.53 d (5.6)
7'	–	–	3.20 m
	–	–	3.20 m

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.39: ^{13}C NMR Spectroscopic Data for Pleiocarpamine (**59**), 16-Hydroxymethylpleiocarpamine (**60**) and Pleiomaltinine (**61**)[a]

C	59	60	61
2	136.8	137.2	95.7
3	50.5	50.5	50.3
5	49.8	49.5	47.4
6	20.6	20.6	31.6
7	107.9	108.7	44.9
8	128.5	128.8	134.1
9	118.2	118.3	120.5
10	119.8	120.2	119.8
11	120.5	121.0	127.6
12	112.2	112.1	110.6
13	137.4	139.0	146.7
14	28.4	25.4	27.2
15	33.6	33.4	31.6
16	61.1	68.5	57.3
17	–	66.0	–
18	12.4	12.6	12.2
19	122.7	122.2	119.1
20	133.1	134.6	134.9
21	56.4	56.6	52.9
CO_2*Me*	51.8	51.5	51.8
CO_2Me	169.0	173.1	170.0
2'	–	–	146.3
3'	–	–	142.5
4'	–	–	171.6
5'	–	–	115.8
6'	–	–	152.6
7'	–	–	26.6

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.40: ^{1}H and ^{13}C NMR Spectroscopic Data for Picramicine (**62**) and Fluorocarpamine (**63**)[a]

Position	**62**		**63**	
	δ_H	δ_C	δ_H	δ_C
2	–	n.d	–	76.0
3	3.15 m	63.6	3.51 br s	61.8
5	2.95 m	50.2	2.99 m	55.0
	3.15 m		2.99 m	
6	1.41 ddt (14, 7, 2)	19.7	2.21 dd (12, 6)	39.0
	1.88 m		2.99 m	
7	2.95 m	38.7	–	205.2
8	–	134.9	–	120.4
9	7.14 br d (8)	123.3	7.62 d (8)	124.1
10	6.71 td (8, 1)	118.6	6.90 t (8)	119.5
11	7.01 td (8, 1)	126.9	7.51 t (8)	137.2
12	6.16 br d (8)	108.3	6.70 d (8)	111.1
13	–	148.4	–	163.6
14	1.88 m	32.7	1.37 dt (13, 3)	24.9
	2.05 dt (13, 3)		1.91 dt (13, 3)	
15	3.28 q (3)	32.1	3.64 br d (9)	30.5
16	4.05 d (3)	60.9	4.56 d (9)	63.0
18	1.57 dd (7, 2)	12.3	1.63 d (6)	12.3
19	5.44 qd (7, 2)	120.1	5.50 br q (6)	121.0
20	–	134.9	–	133.9
21	3.03 d (12)	53.6	3.31 d (14)	53.4
	4.37 dt (12, 2)		3.38 br d (14)	
CO_2Me	3.71 s	51.8	3.72 s	51.8
CO_2Me	–	170.6	–	172.5

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

Table 2.41: ^{1}H NMR Spectroscopic Data for Yohimbine (**64**), Talpinine (**65**) and 10,11-Dimethoxynareline (**66**)[a]

H	**64**	**65**	**66**
3α	3.27 br d (11) (α)	4.22 dd (10, 2.5)	4.59 t (3)
5α	2.58 td (11, 4) (α)	3.52 br t (5)	4.28 br s
5β	3.06 dd (11, 5) (β)		
6α	2.70 dd (15, 4) (α)	2.64 d (15.6) (β)	3.72 m
6β	2.98 m (β)	3.22 dd (15.6, 5) (α)	
9	7.45 br d (7.6)	7.46 br d (7.5)	7.33 s
10	7.06 br t (7.6)	7.08 td (7.5, 1)	–
11	7.11 br t (7.6)	7.19 td (7.5, 1)	–
12	7.29 br d (7.6)	7.28 br d (7.5)	7.27 s
14β	1.33 m (β)	1.33 ddd (12, 4, 2.5) (β)	2.07 dt (14, 3)
14α	2.04 m (α)	1.85 br t (12) (α)	2.33 dt (14, 3)
15	2.01 m	1.89 br d (2)	3.35 q (3)
16	2.31 br d (12)	1.24 m	2.26 d (3)
17β	4.22 br s (β)	3.45 dd (11, 1) (β)	–
		3.68 d (11) (α)	–
18	1.55 m	1.29 d (7)	1.70 d (7)
	1.97 m		
19	1.40 m	4.05 q (7)	5.80 q (7)
	1.55 m		
20	1.55 m	1.30 m	–
21	2.19 t (11)	4.72 br d (2)	4.10 d (3)
	2.91 br d (11)		
N(1)-H	8.17 br s	–	–
N(1)-Me	–	3.57 s	–
CO_2*Me*	3.79 s	–	3.72 s
10-OMe	–	–	3.90 s
11-OMe	–	–	3.94 s

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

Table 2.42: ^{13}C NMR Spectroscopic Data for Yohimbine (**64**), Talpinine (**65**), and 10,11-Dimethoxynareline (**66**)[a]

C	64	65	66
2	134.6	138.9	183.1
3	60.0	40.1	62.4
5	52.9	49.8	100.2
6	21.7	26.2	55.9
7	108.1	103.3	55.5
8	127.4	127.2	131.2
9	118.2	118.3	108.7
10	119.4	118.9	147.4
11	121.4	120.9	149.7
12	110.9	108.7	104.3
13	136.1	137.5	150.7
14	34.2	31.9	35.1
15	36.7	23.2	31.3
16	52.1	35.2	53.9
17	67.1	63.9	–
18	31.6	15.7	12.6
19	23.4	72.5	122.7
20	40.2	43.7	130.6
21	61.3	87.9	65.5
N(1)-Me	–	29.2	–
CO_2*Me*	52.3	–	–
CO_2Me	175.7	–	–

[a] $CDCl_3$, 400 MHz, assignments based on COSY, and HMQC.

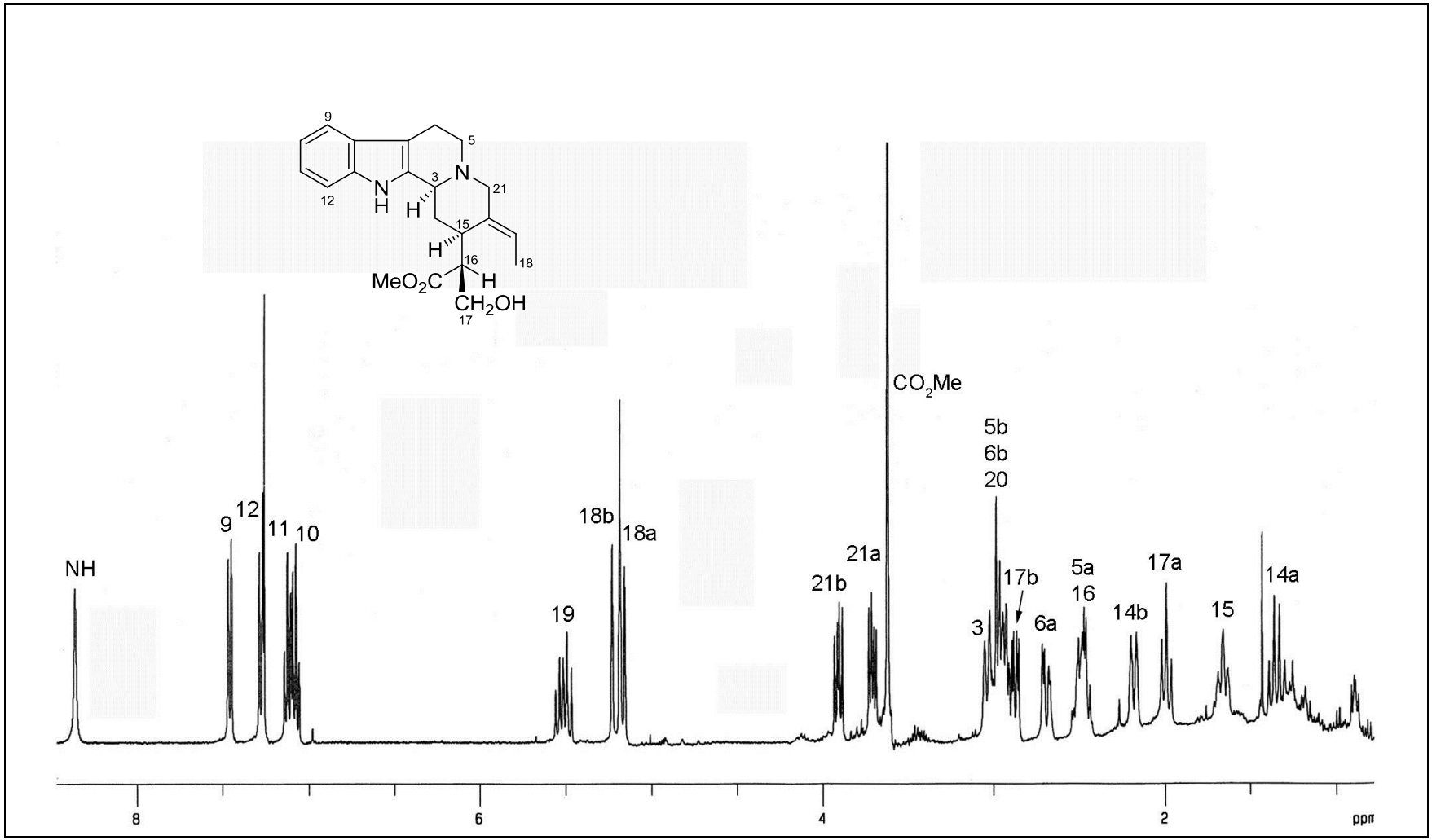


Figure 2.69: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Sitsirikine (**56**)

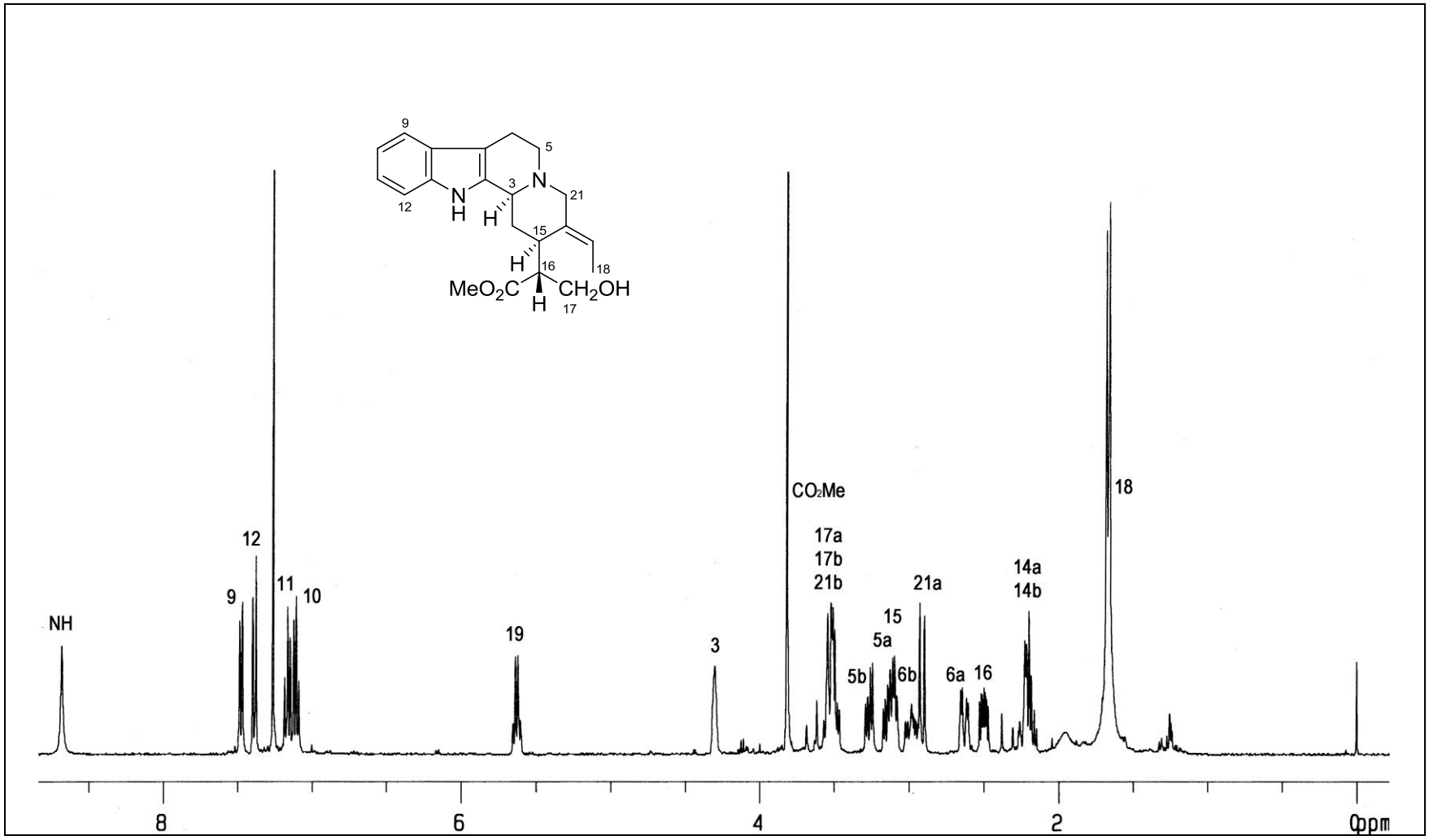


Figure 2.70: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 16(*R*),19(*E*)-Isositsirikine (**57**)

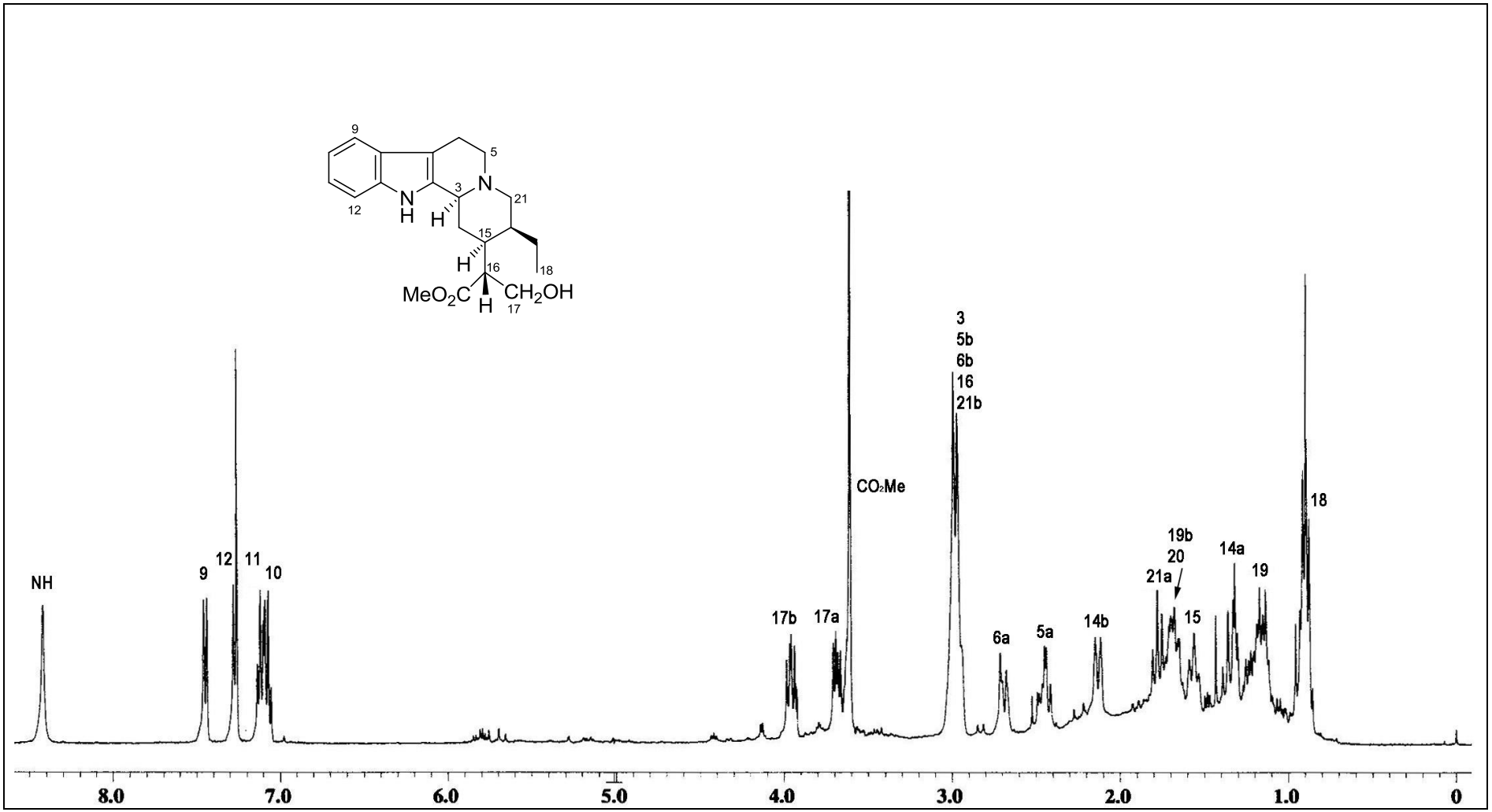


Figure 2.71: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 18,19-Dihydroisositsirikine (**58**)

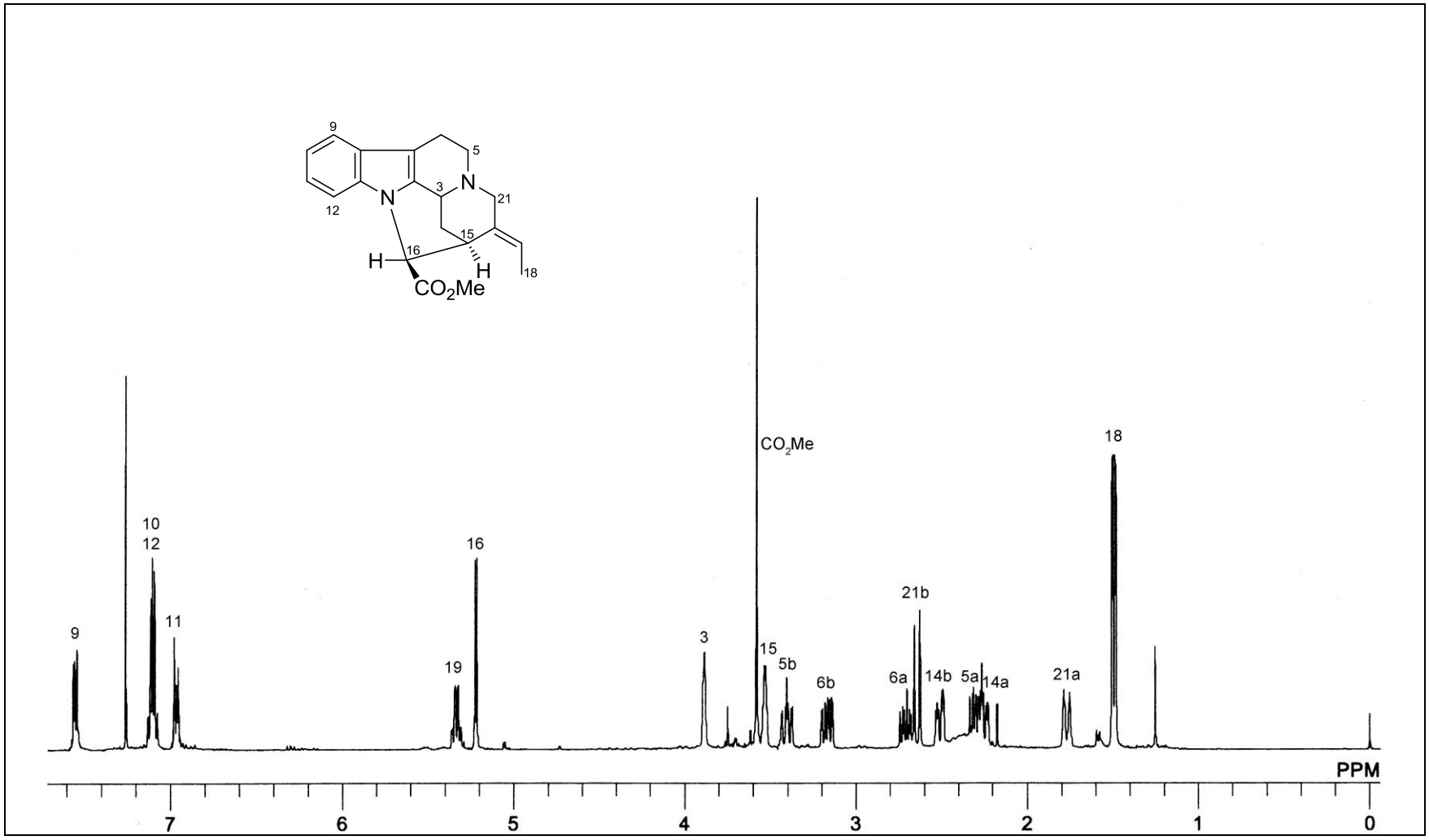


Figure 2.72: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Pleiocarpamine (**59**)

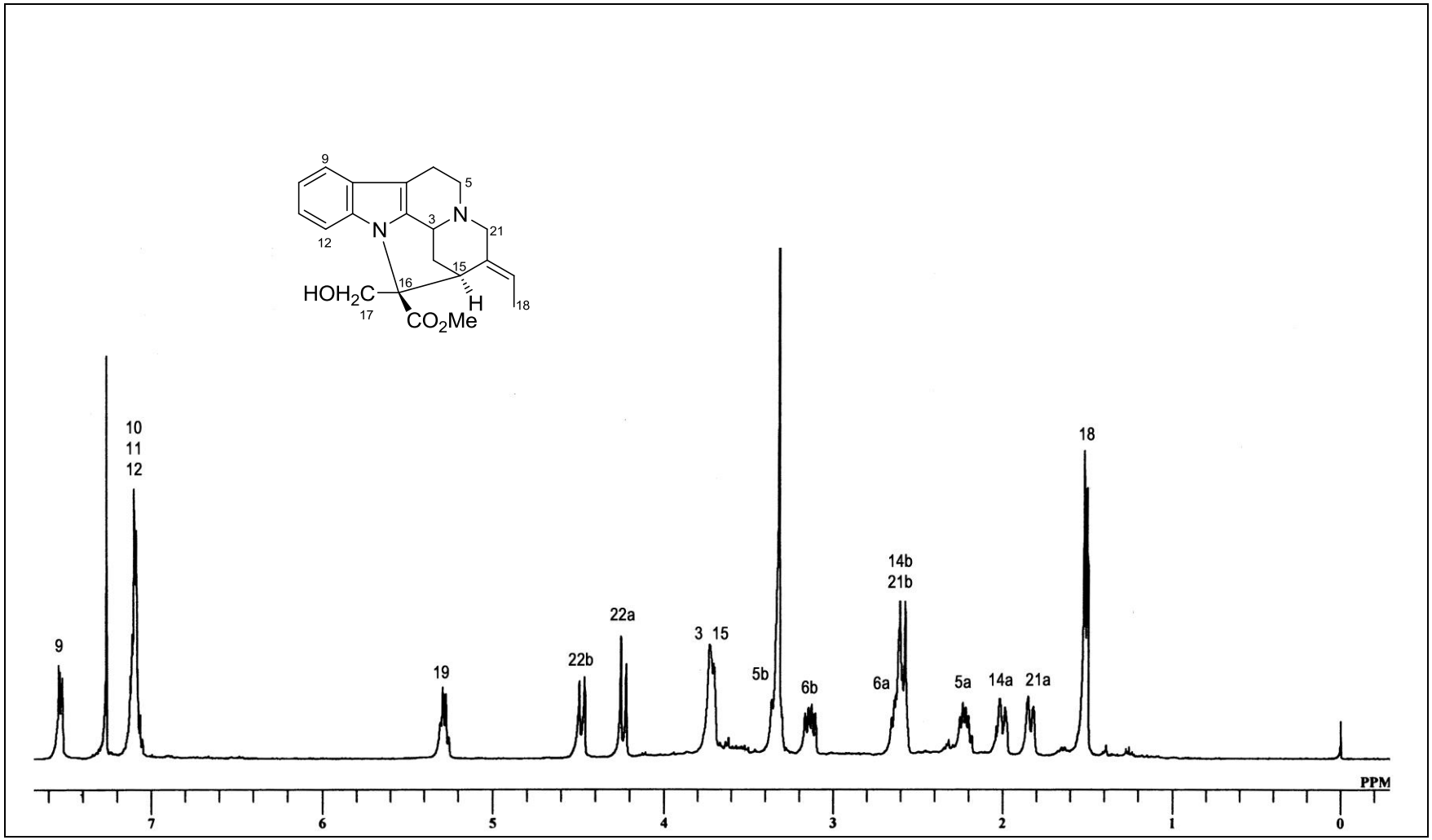


Figure 2.73: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 16-Hydroxymethylpleiocarpamine (**60**)

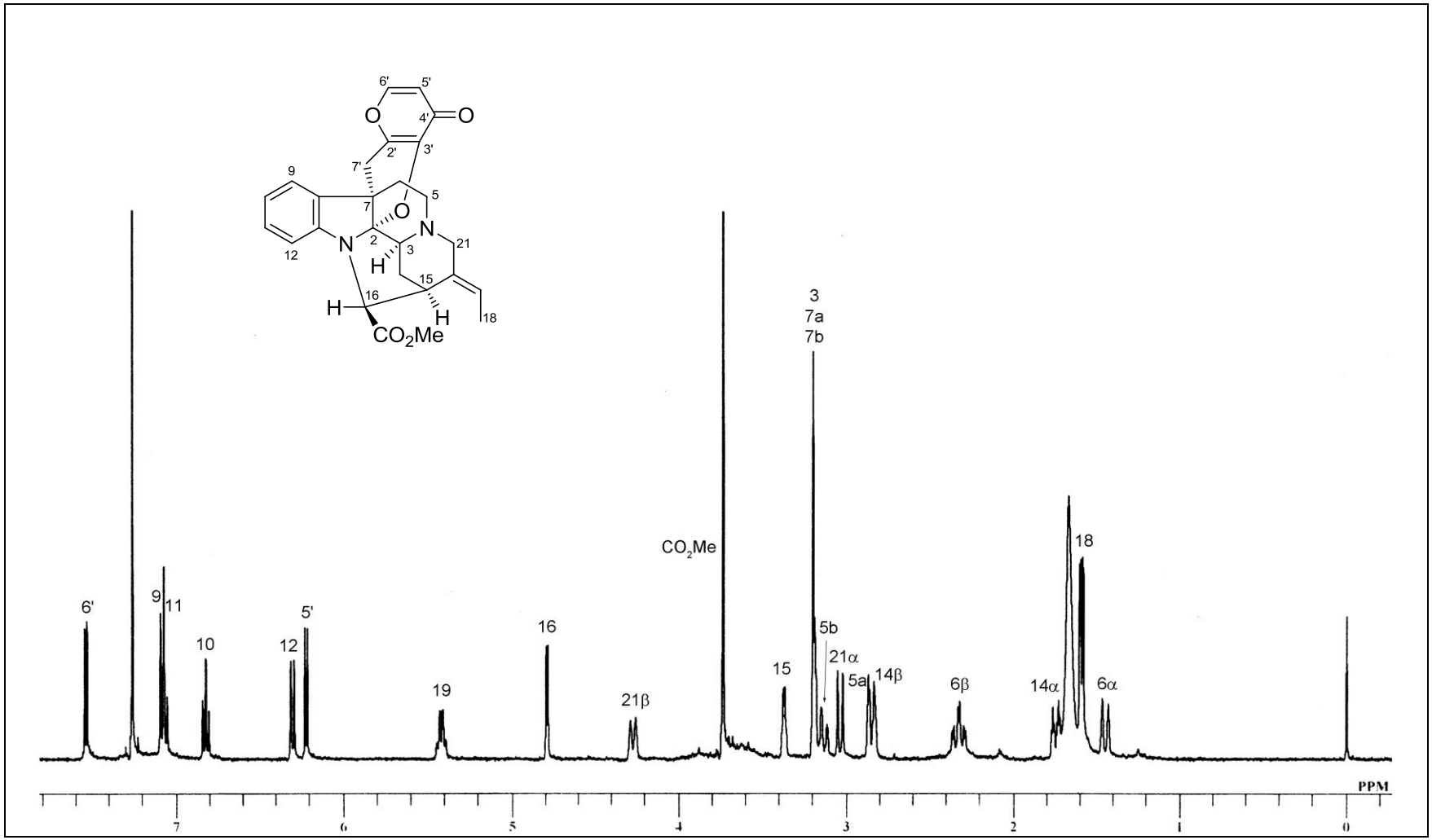


Figure 2.74: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Pleiomaltinine (**61**)

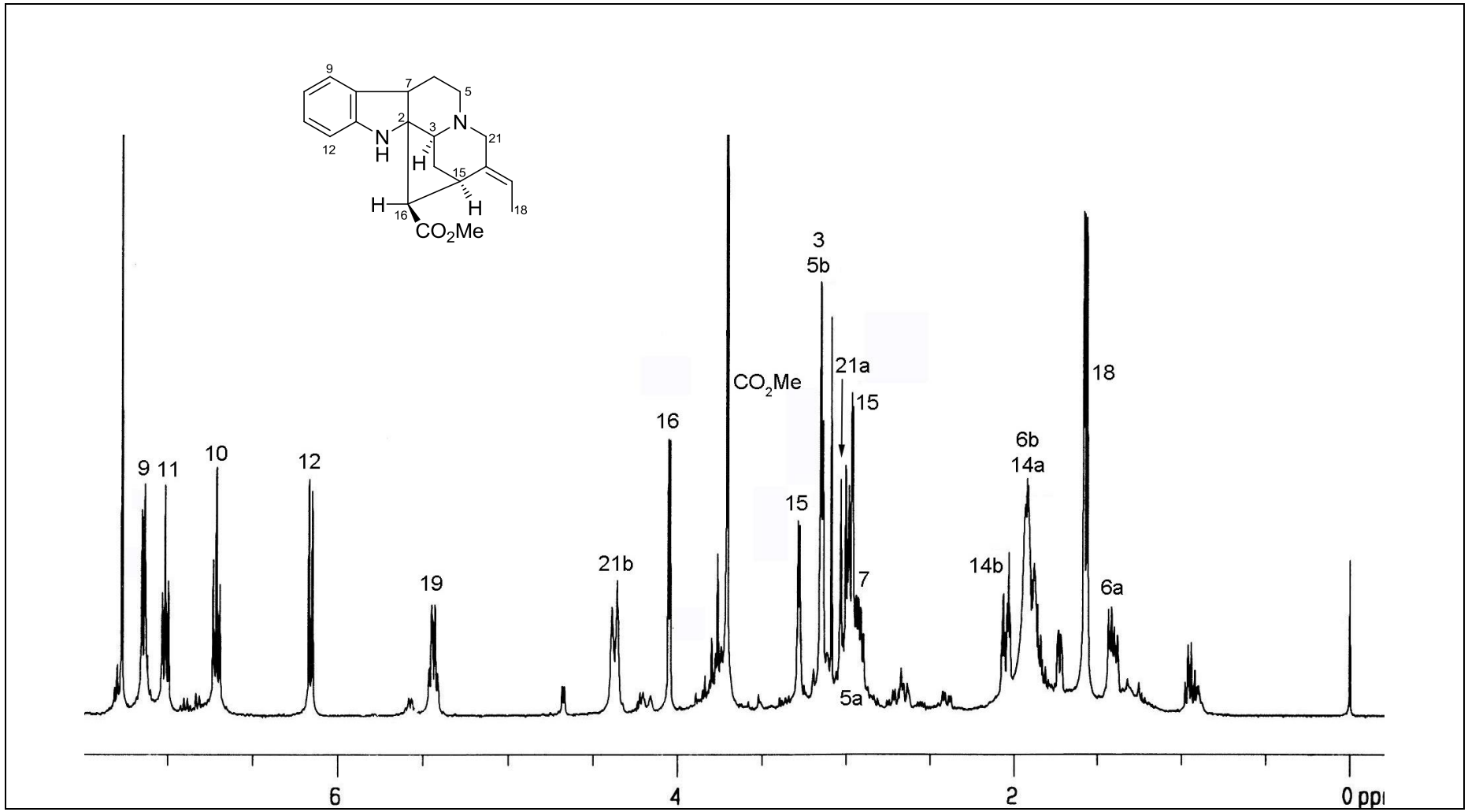


Figure 2.75: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Picramicine (**62**)

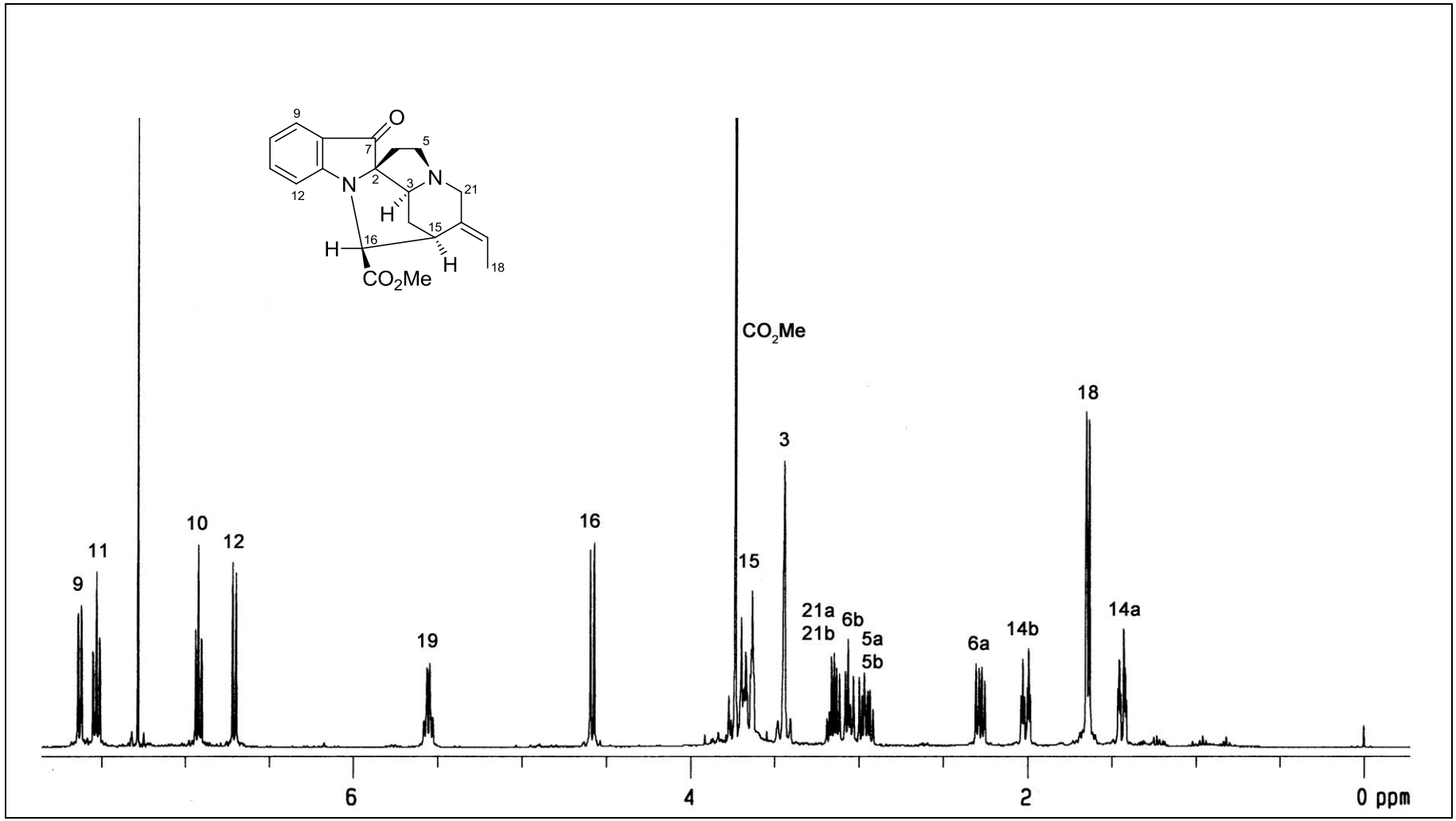


Figure 2.76: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Fluorocarpamine (**63**)

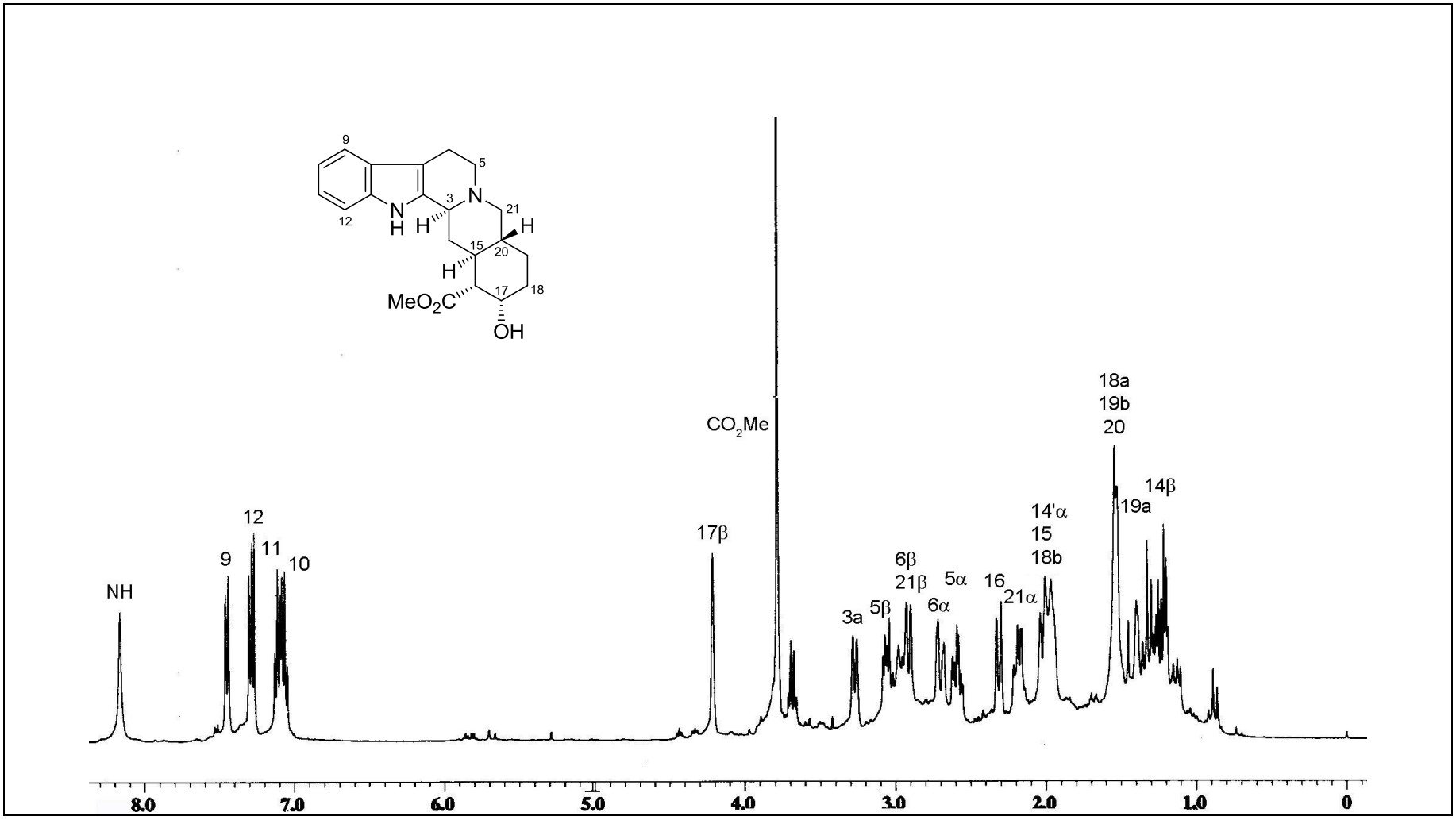


Figure 2.77: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Yohimbine (**64**)

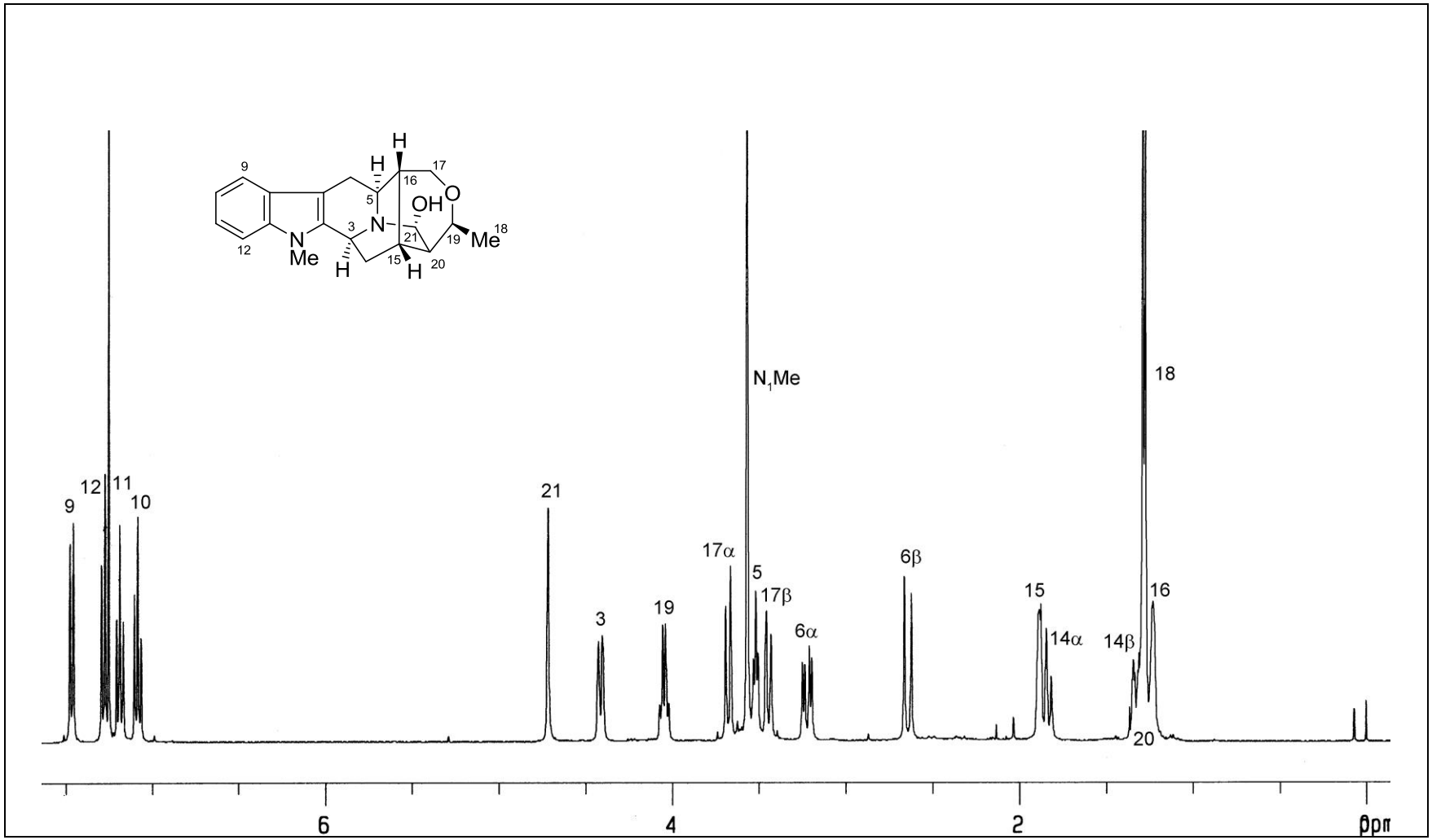


Figure 2.78: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Talpinine (**65**)

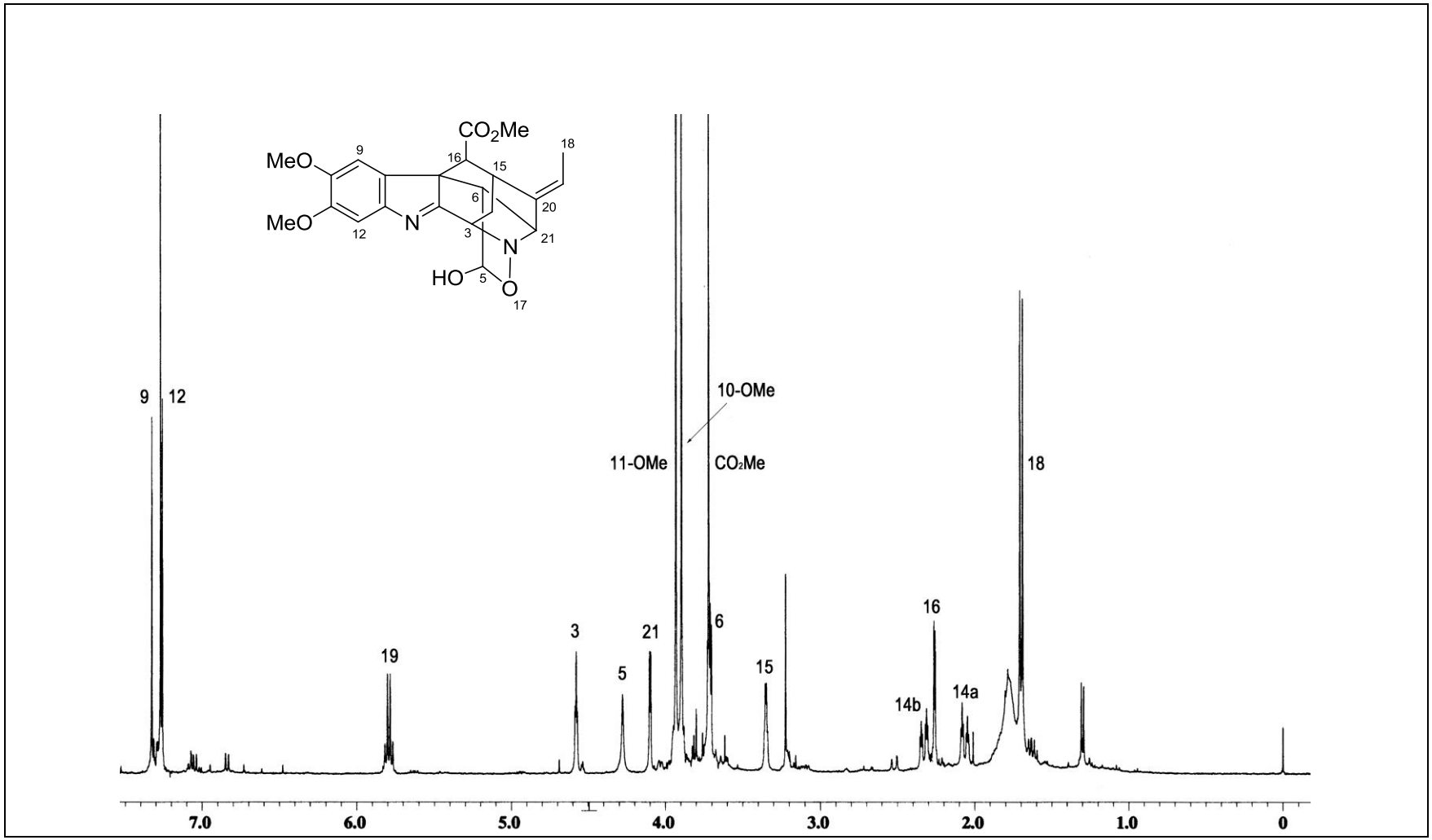


Figure 2.79: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 10,11-Dimethoxynareline (**66**)

2.1.5 Strychnan Alkaloids

2.1.5.1 11-Methoxyakuammicine (67) and 11-Methoxyakuammicine *N*(4)-oxide (68)

Two known strychnan alkaloids belonging to this group, viz., 11-methoxyakuammicine (**67**)[181,266] and 11-methoxyakuammicine *N*(4)-oxide (**68**)[164] were isolated in this study. The ^{1}H NMR spectra of these compounds are shown in Figures 2.80 and 2.81, and the NMR spectroscopic data are summarized in Table 2.43. Other data are given in the Experimental Section.

Table 2.43: ^{1}H and ^{13}C NMR Data for 11-Methoxyakuammicine (**67**) and 11-Methoxyakuammicine *N*(4)-oxide (**68**)[a]

Position	67		68	
	δ_H	δ_C	δ_H	δ_C
2	–	167.5	–	164.7
3	4.12 br s	61.8	4.29 br s	78.3
5	3.06 dd (12, 6) 3.37 td (12, 6)	55.7	3.71 m 3.99 m	69.9
6	1.87 dd (12, 6) 2.53 td (12, 6)	45.6	1.93 dd (14, 7) 2.47 td (14, 7)	41.7
7	–	56.5	–	54.1
8	–	128.8	–	126.8
9	7.14 d (8)	121.2	7.41 d (8.5)	121.9
10	6.43 dd (8, 2)	105.5	6.40 dd (8.5, 2)	106.0
11	–	160.3	–	160.9
12	6.43 d (2)	97.0	6.37 d (2)	97.5
13	–	144.5	–	144.1
14	1.34 dt (14, 3) 2.44 ddd (14, 3, 2)	29.4	1.37 br d (14) 2.75 br d (14)	27.9
15	3.96 br s	30.5	3.97 br s	28.5
16	–	101.6	–	102.0
18	1.67 dt (7, 1)	13.0	1.58 d (6.8)	13.6
19	5.42 br q (7)	122.4	5.55 br q (6.9)	127.1
20	–	137.4	–	133.3
21	3.03 d (14) 3.98 br d (14)	56.4	3.99 d (14.5) 4.19 d (14.5)	74.0
N(1)-H	8.95 s	–	8.85 s	–
CO_2*Me*	3.81 s	51.1	3.75 s	51.4
CO_2Me	–	167.7	–	167.2
11-OMe	3.78 s	55.5	3.70 s	55.6

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

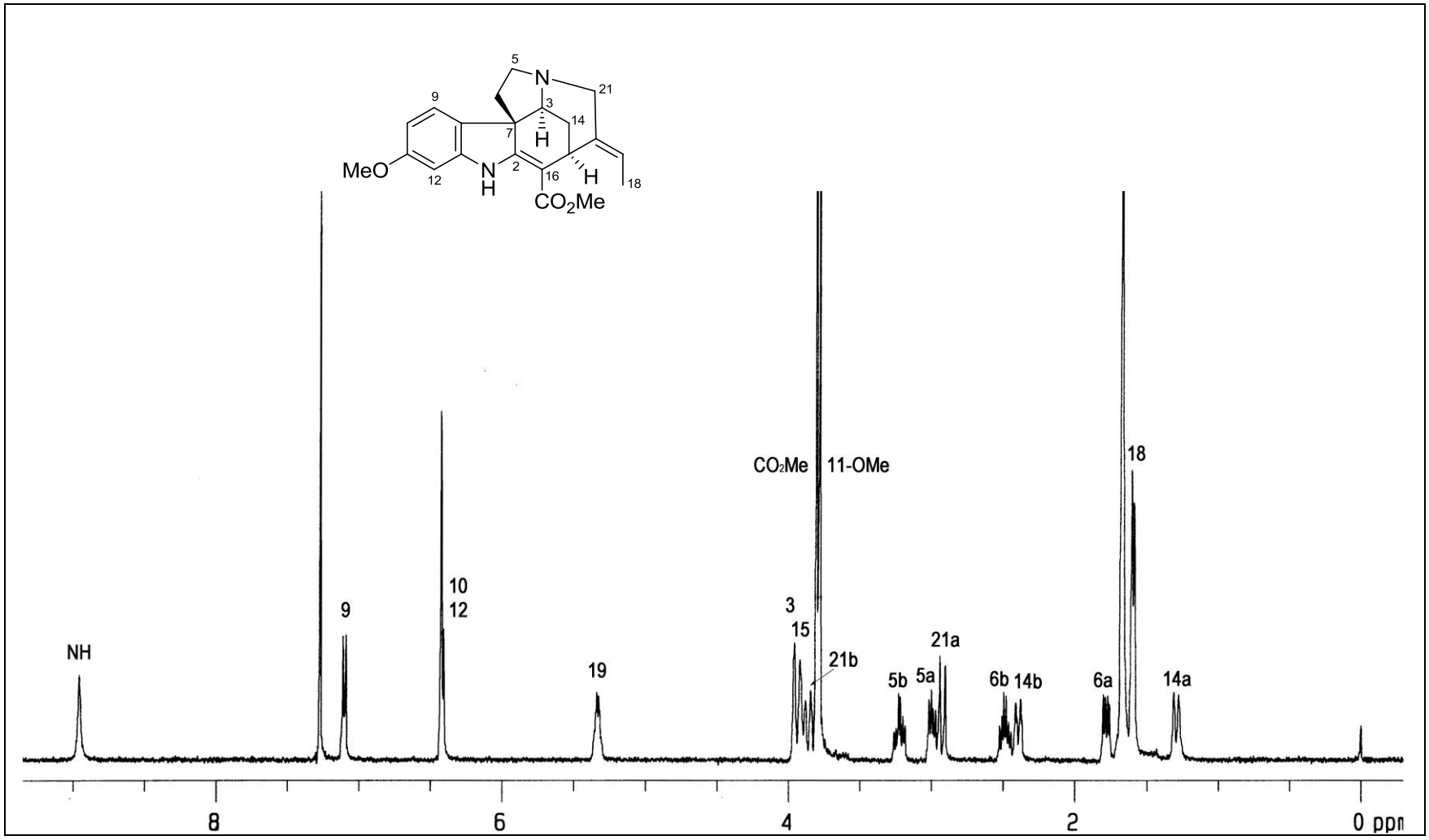


Figure 2.80: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 11-Methoxyakuammicine (**67**)

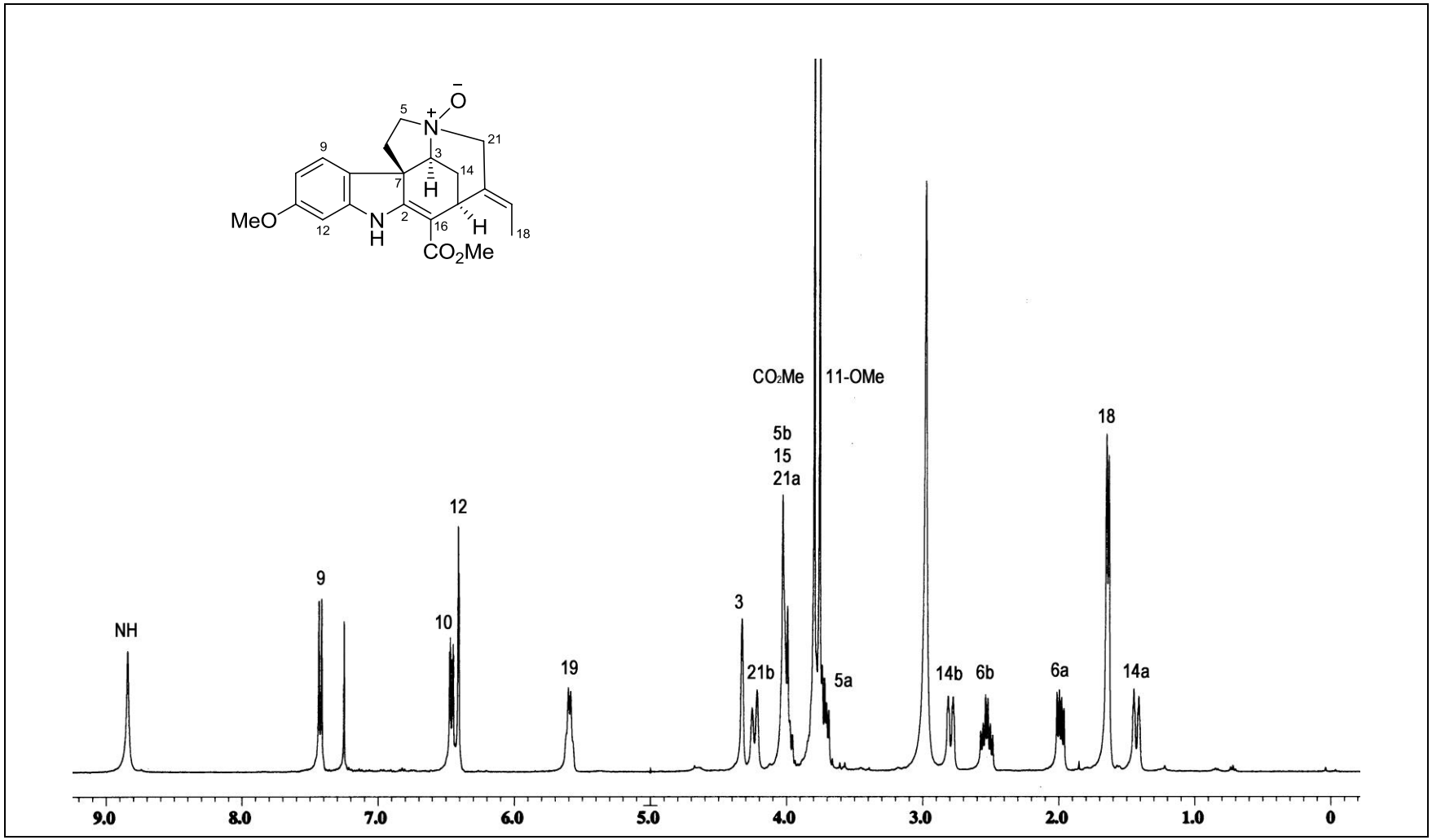


Figure 2.81: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 11-Methoxyakuammicine *N*(4)-oxide (**68**)

2.1.6 Miscellaneous Monoterpene Indole Alkaloids

2.1.6.1 Antirhine (69) and 1,2,3,4-Tetrahydro-1-oxo-β-carboline (70)

Two known monoterpene indole alkaloids isolated in this study are antirhine (**69**)[267] and 1,2,3,4-tetrahydro-1-oxo-β-carboline (**70**).[268,269] The ^{1}H NMR spectra of these compounds are shown in Figures 2.82 and 2.83, while the ^{1}H and ^{13}C NMR spectroscopic data are summarized in Table 2.44. Other data are given in the Experimental Section.

Table 2.44: ^{1}H and ^{13}C NMR Data for Antirhine (**69**) and 1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)[a]

Position	**69**		**70**	
	δ_H	δ_C	δ_H	δ_C
2	–	133.2	–	126.3
3	4.15 br s	54.2	–	163.6
5	3.03 m	51.5	3.71 td (7, 2.5)	42.2
	3.21 m			
6	2.64 m	18.0	3.06 t (7)	20.9
	3.03 m			
7	–	107.0	–	120.1
8	–	127.2	–	125.3
9	7.47 br d (7.5)	117.7	7.58 br d (8)	120.4
10	7.09 td (7.5, 1)	119.0	7.13 td (8, 1.5)	120.3
11	7.14 td (7.5, 1)	121.0	7.29 td (8, 1.5)	125.3
12	7.33 br d (7.5)	110.9	7.48 br d (8)	112.8
13	–	135.8	–	137.6
14	1.90 m	31.2	–	–
	2.05 m			
15	1.54 m	31.1	–	–
16	1.47 m	28.6	–	–
	1.72 m			
17	2.62 m	46.6	–	–
	2.76 ddd (12, 9, 4)			
18	5.16 dd (17, 1.5)	117.7	–	–
	–			
19	5.22 dd (10, 1.5)	138.3	–	–
	5.60 ddd (17, 10, 9)			
20	2.24 m	49.6	–	–
21	3.59 dd (10.5, 7)	63.3	–	–
	3.74 dd (10.5, 4.5)			
N(1)H	8.03 br s	–	10.12 s	–
N(4)H	–	–	6.37 s	–

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

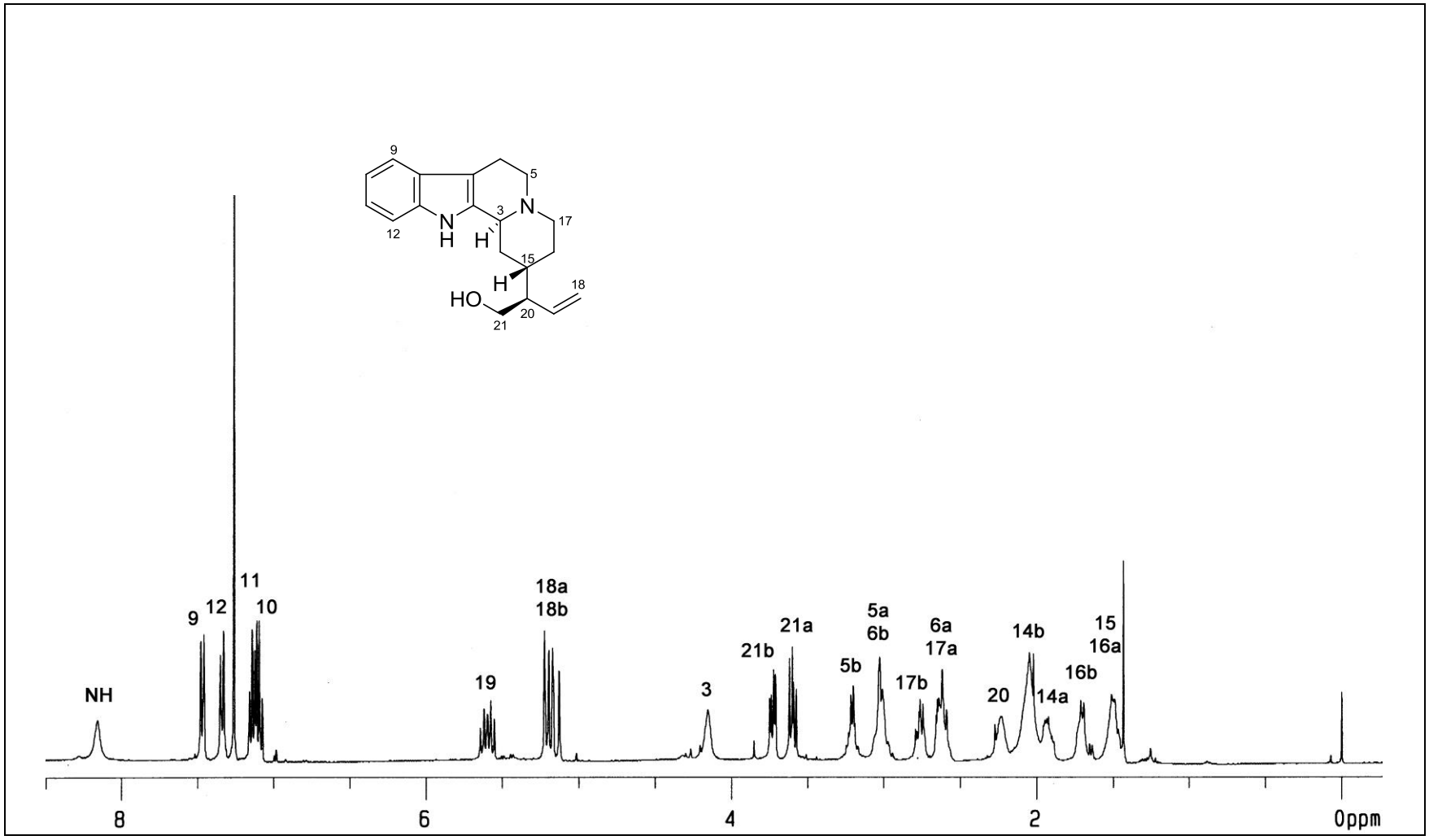


Figure 2.82: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Antirhine (**69**)

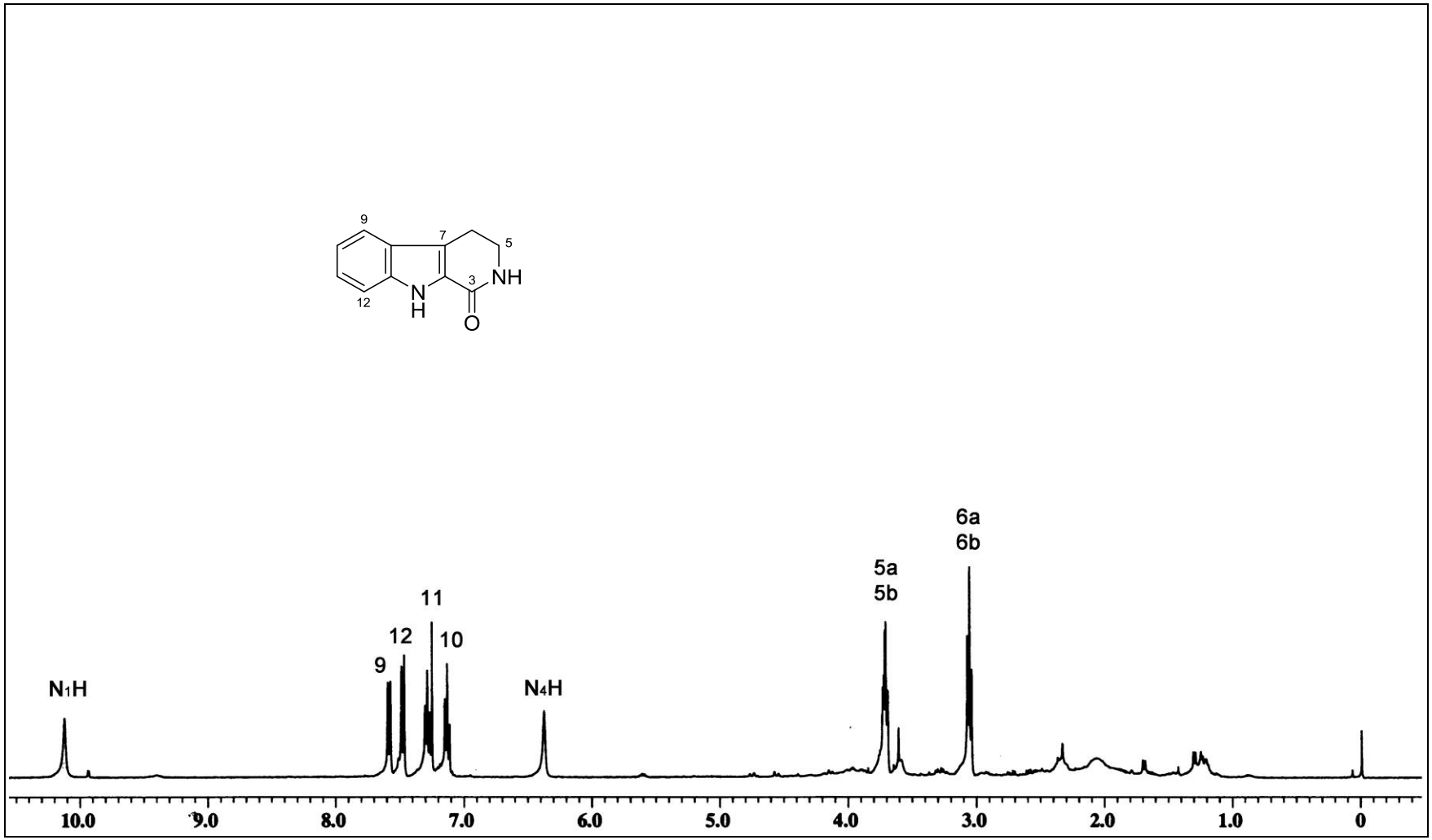


Figure 2.83: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of 1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)

2.1.7 Bisindole Alkaloids

2.1.7.1 Linearly Fused Bisindole Alkaloids

Four new linearly-fused bisindole alkaloids, lumutinines A–E (**71**–**75**),[127,258] were isolated from the stem-bark extract of *Alstonia macrophylla*. Lumutinines A and B (**71** and **72**) represent the first examples of linear, ring A/F-fused macroline-macroline type bisindoles, while lumutinines C–E (**73**–**75**) were constituted from the union of macroline and sarpagine moieties.

2.1.7.1.1 Lumutinine A (71)

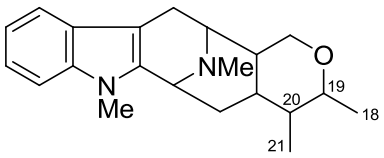
Lumutinine A (**71**)[258] was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ +160 (*c* 0.4, $CHCl_3$). The IR spectrum showed bands at 1617 and 1651 cm^{-1} due to the presence of an α,β-unsaturated carbonyl group, while the UV spectrum showed absorption maxima at 210, 233, 254 (sh), and 283 nm, showing the presence of indole chromophores and an α,β-unsaturated carbonyl moiety. The ESIMS of **71** showed a $[M + H]^+$ peak at *m/z* 673, which analyzed for $C_{42}H_{48}N_4O_4$ + H. The ^{13}C NMR spectrum (Table 2.45) showed a total of 42 resonances, comprising six methyl, seven methylene, 16 methine, and 13 quaternary carbon atoms, in agreement with the molecular formula. The observed quaternary carbon resonance at δ 196.4, and the olefinic carbon signals at δ 121.4 and 158.1, are consistent with the presence of the α,β-unsaturated carbonyl group, while the unusually low field resonance of the β-carbon at δ 158.1 indicated oxygen substitution. The ^1H NMR spectrum (Table 2.45; Figure 2.89) showed the presence of four aromatic hydrogens (δ 7.11–7.50) associated with an unsubstituted indole moiety, two aromatic

singlets (δ 6.76, 6.98) associated with another indole moiety substituted at C-10' and C-11', a vinylic singlet at δ 7.58 associated with a trisubstituted double bond, a total of six methyl singlets, corresponding to two N1-Me (δ 3.54, 3.55), two N4-Me (δ 2.27, 2.29), one acetyl methyl (δ 2.15, 18'-Me), and a methyl attached to a quaternary carbon (δ 1.38, 18-Me). Since only six aromatic hydrogens were observed and both indolic nitrogens are substituted, it can be inferred from the observation of the two H-9' and H-12' aromatic singlets, that the bisindole is branched from C-10' and C-11' of one monomeric unit. Furthermore, the observed NOE between the aromatic singlet at δ 6.76 and the N1-Me' singlet at δ 3.54 allowed this aromatic singlet and the one at δ 6.98 and to be assigned to H-12' and H-9', respectively. The observation of the low field vinylic singlet at δ 7.58 (H-21') with the associated acetyl methyl singlet at δ 2.15, indicated this 10',11'-branched monomer to be a type-B macroline.[118] Examination of the ^{1}H and ^{13}C NMR data with the help of 2-D COSY and HSQC experiments indicated that this type-B macroline corresponded to a 10,11-substituted alstonerine,[133,158,164] with C-11' carrying some form of oxygenation as deduced from the observed ^{13}C NMR shift of this carbon at δ 150.3 and the observed correlation from H-9' to this carbon (C-11') in the HMBC spectrum.

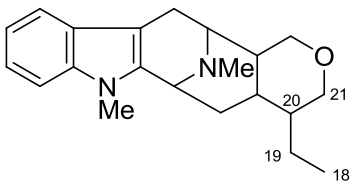
The other unit of the bisindole, after discounting the signals due to the substituted alstonerine half, corresponded to that of another macroline derivative with an unsubstituted indole moiety. The C-17 oxymethylene hydrogens were observed as a doublet of doublets at δ 3.69 and a triplet at δ 4.67, while the 18-methyl singlet was observed at δ 1.38. The C-19 resonance at δ 99.5 indicated attachment to two oxygen atoms while the methine H-20 was seen as a multiplet at δ 1.93. These features corresponded to a pentacyclic macroline alkaloid with a saturated ring E (for example, macrocarpines A–C and talcarpine[123]), which was also supported by the observed three-

bond correlation from the 18-methyl hydrogens to C-20. The observed NOE between 18-Me and H-20 requires a *cis*-orientation (Figure 2.84). In addition, an NOE was also observed between 18-Me and H-21α, which in turn facilitated the assignment of the orientation of both 18-Me and H-20 as α. Examination of models showed that had the orientation of 18-Me and H-20 been β, NOE would have been impossible between 18-Me and both the C-21 hydrogens. This mode of ring E/F fusion is also seen in the spirocyclic macrodasines[124] and macralstonidine (**76**, *vide infra*).

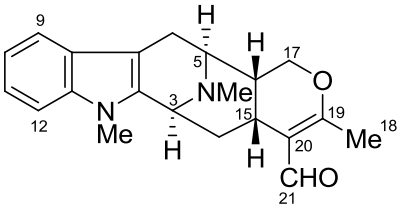
Of the two oxygens linked to C-19, one was also attached to C-17 (C-19–O–C-17 connection) from the observed three-bond correlation from H-17 to C-19 in the HMBC spectrum, while the other was attached to the aromatic C-11', from its observed downfield shift at δ 150.3, which had been previously noted (*vide supra*). Connection from the ring E C-20 of the upper macroline unit to C-10' of the lower half was mediated via a methylene bridge (C-21), as shown by the observed H-21 to C-9' and C-11' three-bond correlations in the HMBC spectrum, while that from C-19 to C-11' was via an oxygen atom. These observations revealed the mode of union of the two macroline halves, which from a biogenetic viewpoint (*vide infra*) can be considered as comprising a macroline (**443**) and an 11'-hydroxy- or 11'-methoxyalstonerine (alstophylline) (**7**). The structure is entirely consistent with the full HMBC as well as the NOE data, in particular the observed NOE between H-9' and H-21 (Figure 2.84).



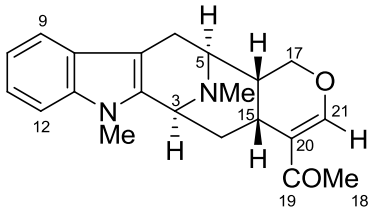
Type A macroline



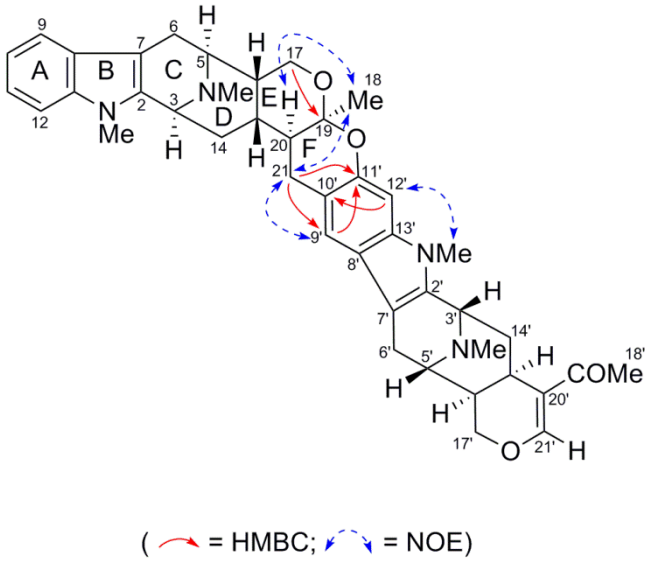
Type B macroline



6 Alstonerinal

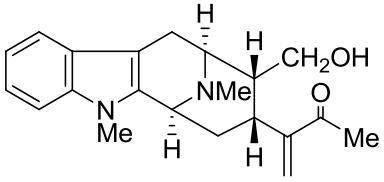


5 Alstonerine

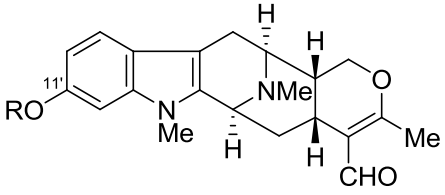


(= HMBC; = NOE)

Figure 2.84: Selected HMBCs and NOEs of **71**.



443



7 R = H or Me

2.1.7.1.2 Lumutinine B (72)

The second bisindole, lumutinine B (7**2**),[258] was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ −11 (*c* 0.5, $CHCl_3$). As in the case of **71** the IR spectrum showed similar bands at 1616 and 1651 cm^{-1}, while the UV spectrum (210, 232, 255, and 285 nm) was also similar to that of **71**. The ESIMS of **72** showed a $[M + H]^+$ peak at *m/z* 673, which analyzed for $C_{42}H_{48}N_4O_4$ + H, indicating that **71** and **72** are isomers. Examination of the ^1H and ^{13}C NMR data (Table 2.46; Figure 2.90) showed the presence of similar functionalities as in **72**, such as an unsubstituted indole moiety (δ 7.09–7.49), another indole moiety substituted at C-11' and C-12' from the presence of a pair of AB doublets at δ 6.66 and 7.16, a vinylic singlet at δ 7.55 associated with a trisubstituted double bond, an *α,β*-unsaturated carbonyl moiety (δ_C 195.9, 121.3, and 157.9; δ_H 2.12), and six methyl singlets, corresponding to two N1-Me, two N4-Me, one acetyl methyl, and a methyl attached to a quaternary carbon (18-Me). Thus, except for the aromatic AB doublets in place of the two aromatic singlets, and overall, small differences in the chemical shifts of the other signals, the NMR data bear a close resemblance to those of **71**, indicating the presence of the same two constituent units.

The HMBC and NOE data, however, showed significant differences, indicating a different mode of union of the two halves (Figure 2.85). In the case of **72**, a three-bond correlation from H-10' to the quaternary C-12' was observed in the HMBC spectrum. The observed NOE from the aromatic doublet at δ 7.16 to both the H-6' signals allowed this doublet to be assigned to H-9' and the other doublet at δ 6.66 to H-10'. This was in contrast to compound **71** where a three-bond correlation was observed from H-12' to the quaternary C-10'. In addition, in **72**, three-bond correlations were observed from H-21 and H-9' to C-11' (δ 149.6, oxygenated) and C-13', indicating C-12' to be a branching point and C-11' to be the site of oxygen substitution, whereas in **71**, three-bond

correlations were observed from H-21 to C-11' (oxygenated) and C-9', indicating C-10' to be the branching point. These observations, therefore, indicated that in **72**, the bisindole is branched at C-11' and C-12'. The branching from C-11' is mediated by a ketalic oxygen atom, while that from C-12' is mediated by a methylene (C-21). This difference in the mode of attachment of the two monomeric units was further supported by the NOE's observed for N1-Me'/H-21 and N1-Me'/H-14 (Figure 2.85). Bisindoles **71** and **72** are, therefore, regioisomers constituted from the union of similar macroline moieties, but differing in the mode of union of these moieties.

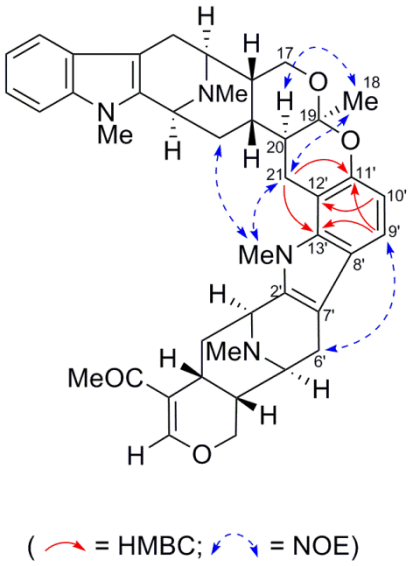


Figure 2.85: Selected HMBCs and NOEs of **72**.

2.1.7.1.3 Lumutinine C (73)

Lumutinine C (**73**)[258] was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ +84 (*c* 0.32, $CHCl_3$). The IR spectrum showed an absorption band at 3360 cm^{-1} due to the presence of an OH group, while the UV spectrum showed absorption maxima at 208, 228, and 284 nm, consistent with an indole chromophore. The ESIMS of **73** showed a $[M + H]^+$ peak at *m/z* 661, which analyzed for $C_{41}H_{48}N_4O_4$ + H. The ^{13}C NMR spectrum (Table 2.47) showed a total of 41 resonances, comprising five methyl, seven methylene, 17 methine, and 12 quaternary carbon atoms, in agreement with the molecular formula. Of these, two were oxymethylenes (δ 62.3, C-17; 64.5, C-17'), one an oxymethine (δ 67.3, C-19'), and another, a quaternary carbon linked to two oxygen atoms (δ 99.0, C-19). The olefinic carbon signals at δ 136.1 and 149.3 are consistent with the presence of trisubstituted double bond and the resonance at δ 136.1 is consistent with the presence of an *N*-substituted sp^2 methine (C-21') with the corresponding hydrogen shift observed as a downfield singlet at δ 6.44.

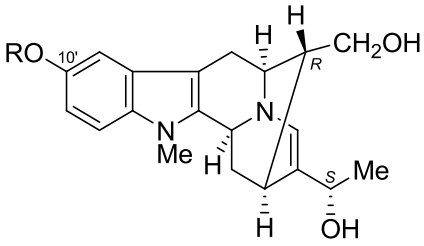
The ^1H NMR spectrum (Table 2.47; Figure 2.91) showed the presence of four aromatic hydrogens (δ 7.10–7.50) associated with an unsubstituted indole moiety, a pair of aromatic doublets (δ 6.71, 7.01) associated with another indole moiety substituted at C-9' and C-10', a vinylic singlet at δ 6.44 associated with a trisubstituted double bond, four methyl singlets, corresponding to two N1-Me, one N4-Me, and a methyl attached to a quaternary carbon (18-Me). In addition, a hydroxyethyl side chain was present from the characteristic signals at δ 1.34 (d, 3H) and 4.46 (q, 1H). The observed NOE (Figure 2.86) between the aromatic doublet at δ 7.01 and the N1-Me' signal at δ 3.48 permitted the assignment of this signal to H-12' and the other aromatic doublet at δ 6.71 to H-11'. This pattern of aromatic substitution, although similar to that in compound **72**, in that

the aromatic ring is vicinally substituted, differs from **72** from the viewpoint of the actual site of aromatic substitution. In **72**, the bisindole is branched at C-11' and C-12' with C-11' (δ 149.6) being the site of oxygenation, whereas in **73**, the bisindole is branched at C-9' and C-10' with C-10' (δ 147.7) being the site of oxygenation. Examination of the NMR data showed that the monomeric unit corresponding to the upper half and incorporating the unsubstituted indole moiety, corresponded to the same macroline-derived moiety present in the previous two compounds. In the case of **73**, therefore, the bisindole is branched at C-9' and C-10' of the lower monomeric unit, with C-9' connected to the upper ring E via a methylene bridge (C-21), and C-10' connected via an oxygen atom to C-19. This conclusion was supported by the HMBC data (Figure 2.86), in particular, the observed three-bond correlations from H-21 to C-8' and to the oxygenated C-10', from H-11' to C-9', and from H-12' to C-10'.

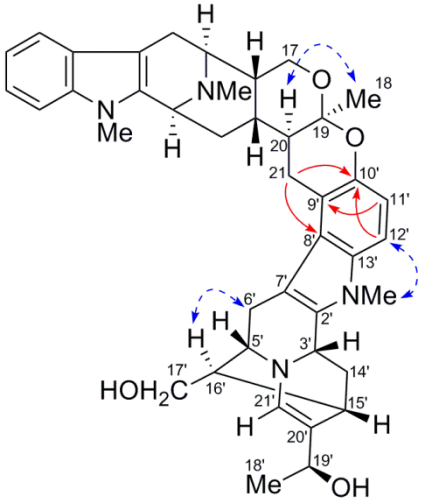
After discounting the upper macroline-derived half, the monomeric unit corresponding to the lower half was deduced from the NMR data to comprise an alkaloid of the sarpagine type, specifically, a 10-hydroxy- or 10-methoxyalstoumerine (**444**). Comparison of the NMR data with that reported for alstoumerine (**52**)[159,233] showed a general agreement for the non-indole portion of the molecule, providing support for such a conclusion.

In lumutinine C (**73**), the resonance due to H-16' was observed at δ 1.55, while the resonance due to the C-17' oxymethylene hydrogens were seen at δ 3.42 and 3.61. These values were similar to those in alstoumerine (**52**) and require H-16' to be directed towards the indole moiety (16*R*). In addition to the chemical shift considerations mentioned above, the 16*R* configuration of **73** was further confirmed by NOE experiments, which showed strong NOE between H-16 and H-6*β*, requiring H-16 to be directed towards the indole moiety and hence proximate to H-6*β*. The assignment of the

configuration C-19 as *S* followed those in alstoumerine (**52**), which was confirmed by X-ray diffraction analysis in another study of *A. angustifolia* from our group.[233]



52 R = H
444 R = H or Me



(= HMBC; = NOE)

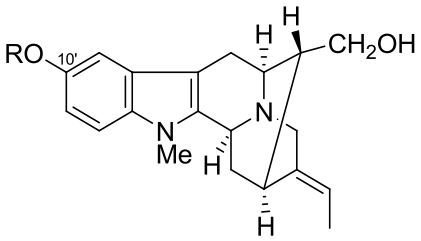
Figure 2.86: Selected HMBCs and NOEs of **73**

2.1.7.1.4 Lumutinine D (74)

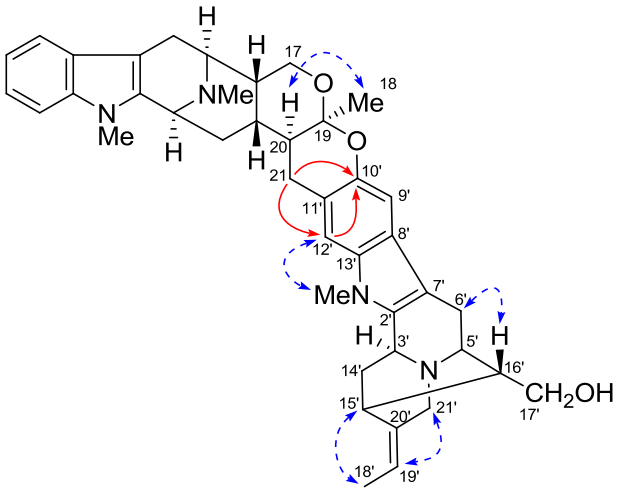
Lumutinine D (**74**)[258] was isolated as a light yellowish oil with $[\alpha]^{25}_{D}$ +209 (*c* 0.4, $CHCl_3$). The IR spectrum showed an OH absorption band at 3370 cm^{-1} and the UV spectrum indicated the presence of an indole chromophore (209, 231, 290 nm). The ESIMS of **74** showed a $[M + H]^+$ peak at *m/z* 645, which analyzed for $C_{41}H_{48}N_4O_3$ + H. The ^{13}C NMR spectrum (Table 2.48) showed a total of 41 resonances (five methyl, eight methylene, 16 methine, and 12 quaternary carbon atoms). The ^1H NMR spectrum (Table 2.48; Figure 2.92) showed signals associated with the same macroline-derived upper monomeric unit common to bisindoles **71**–**73**, such as those due to the four aromatic hydrogens of an unsubstituted indole moiety (δ 7.10–7.49), three methyl singlets corresponding to N1-Me, N4-Me, and 18-Me (attached to a quaternary carbon), an oxymethylene due to the C-17 hydrogens, and another methylene due to the hydrogens of the C-21 methylene bridge. The remaining discernable signals included the two aromatic singlets (δ 6.85, 6.91) associated with another indole moiety substituted at C-10' and C-11', a methyl singlet corresponding to N1-Me', a methyl doublet (δ 1.63) and the associated vinylic quartet (δ 5.40) due to an ethylidene side-chain (H-19'/H-21' and H-18'/H-15' NOEs (Figure 2.87) indicated that the geometry of the 19', 20'-double bond is *E*), and an oxymethylene (δ_C 64.8, δ_H 3.48, 3.53) associated with a hydroxymethyl group. These features suggested the presence of another sarpagine unit. Examination of the NMR data and comparison with the literature, revealed this lower unit to be a 10-hydroxy(or 10-methoxy)affinisine (**445**).[131,133] The observed shift of H-16' at δ 1.82 and the observed H-16'/H-6' NOE, are consistent with the assigned 16*R* configuration.

The mode of union of the two units can be inferred from the NOE and HMBC data (Figure 2.87). As in the previous compounds, the observed NOE between the aromatic

singlet at δ 6.85 and the N1-Me' singlet at δ 3.56 allowed this aromatic singlet to be assigned to H-12' and the other at δ 6.91 to be assigned to H-9'. The three-bond correlation from H-12' to the oxygenated carbon at δ 148.3 in the HMBC spectrum (Figure 2.87) facilitated the assignment of this quaternary aromatic signal to C-10'. The three-bond correlation from the C-21 methylene bridge hydrogens to C-10' and C-12' indicated direct attachment of C-21 to C-11'. These observations revealed the bridging of the affinisine moiety at C-11' to C-21 and at C-10', via an oxygen atom, to C-19. It transpires that the structure of lumutinine D (**74**) deduced from the NMR data corresponded to a regioisomer of the known bisindole, macralstonidine (**76**),[145,171] differing from **7** in the mode of union of the same constituent monomeric moieties, *i.e.*, C-11' to C-21, C-10' to C-19–O in lumutinine D (**74**), *c.f.*, C-9' to C-21, C-10' to C-19–O in macralstonidine (**76**).



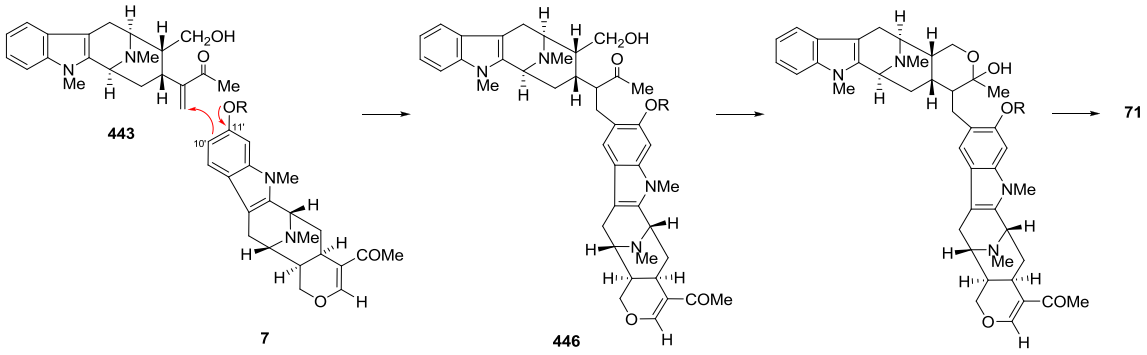
445 R = H or Me



(= HMBC; = NOE)

Figure 2.87: Selected HMBCs and NOEs of **74**

A plausible origin of these linearly-fused bisindoles (illustrated for lumutinine A (**71**), Scheme 2.1)[118] derives from Michael addition of the electron-rich C-10' of 11'-hydroxyalstonerine or alstophylline (**7**) onto macroline (**443**) to give the hydroxyketone **446**, which on subsequent ring closure via hemiketal formation, followed by ketalization, yields lumutinine A (**71**). The formation of lumutinine B (**72**) from attack of C-12' of **7**, lumutinine C (**73**) from attack of C-9' of **444**, and lumutinine D (**74**) from attack of C-11' of **445**, follows a similar pathway. While the linear, ring A/F-fused macroline-sarpagine type bisindoles similar to **73** and **74** are known, this is the first report of linear, ring A/F-fused macroline-macroline type bisindoles (**71** and **72**).[103,115]



Scheme 2.1: Possible Biogenetic Pathway to **71**

2.1.7.1.5 Lumutinine E (75)

Lumutinine E (**75**)[127] was isolated as a light yellowish oil, $[\alpha]_D$ +74 (*c* 0.14, $CHCl_3$). The UV spectrum showed absorption maxima at 229 and 284 nm, indicating the presence of an indole chromophore, while the IR spectrum showed a broad band at 3380 cm^{-1} due to NH and OH groups. The EI-mass spectrum showed a molecular ion at *m/z* 630, which was also the base peak, with a peak due to loss of CH_2OH observed at *m/z* 599. HREIMS measurements gave the molecular formula $C_{40}H_{46}N_4O_3$ (DBE 20).

The ^{13}C NMR spectrum (Table 2.49) showed a total of 40 carbon signals, comprising four methyl, eight methylene, 16 methine, and 12 quaternary carbon atoms. Examination of the ^{1}H and ^{13}C NMR spectroscopic data with the aid of COSY, HMQC, and HMBC data confirmed the presence of macroline and sarpagine units. Thus the ^{1}H NMR spectrum (Table 2.49; Figure 2.93) of **75** showed the presence of an indolic NH (δ 7.95, sarpagine), an unsubstituted indole ring (δ 7.11–7.51, macroline), another indole ring substituted at C-9' and C-10' (δ 6.65, δ 6.97, sarpagine), a hydroxymethyl (δ 3.43, sarpagine), and three methyl singlets, corresponding to N1-Me, N4-Me, and Me-18, associated with a macroline moiety (δ 3.41, 2.27, and 1.37, respectively).

The aromatic-H resonances of the sarpagine unit were observed as a pair of AB doublets at δ 6.65 and 6.97 (*J* = 8.6 Hz), due to a pair of *ortho*-coupled aromatic hydrogens, suggesting branching of the bisindole from C-9' and C-10' of the sarpagine half. The observed interaction between the indolic NH and the aromatic doublet at δ 6.97 in the NOESY spectrum (Figure 2.88) allowed assignment of this resonance to H-12' and the other doublet at δ 6.65 to H-11'. The oxygenated aromatic carbon resonance at δ 147.6 was assigned to C-10' of the sarpagine unit, based on comparison of the aromatic carbon resonances with those of N1-methylsarpagine and 10-methoxyaffinisine.[131,133] The downfield shift of C-19 of the macroline unit at δ 98.8 indicated that it was linked to

two oxygen atoms. One of the oxygen atoms was also linked to C-17 of the macroline unit (C-19–O–C-17 connection), which was supported by the observed three-bond correlation from H-17 to C-19 in the HMBC spectrum (Figure 2.88), whereas the other was linked to C-10' of the sarpagine unit, which was consistent with the molecular formula as well as the carbon chemical shift of C-10' (δ 147.6). Further proof of the C-19–O–C-10' connection was provided by the observed interaction between H-11' and 18-Me in the NOESY spectrum. The connection from C-9' of the sarpagine unit to C-21 of the macroline unit, was inferred from the observed three-bond correlation from H-21 to C-10' in the HMBC spectrum. This was further confirmed by the observed interaction between H-21 and H-6'α in the NOESY spectrum (Figure 2.88). Examination of the NMR spectroscopic data (Table 2.49) of **75** revealed similarity of this compound with macralstonidine (**76**)[145,171] (which has a similar mode of branching of the monomeric units), except for the signal of the N1'-Me group of the sarpagine unit which was absent in the NMR spectra of **75**. Instead, an indolic NH was observed at δ 7.95 in the ^{1}H NMR spectrum of **75**.

The relative configurations at the various stereogenic centers in the macroline and sarpagine moieties were established from the NOESY spectrum (Figure 2.88), which showed that these were similar to those in **76**. The E/F ring junction stereochemistry was deduced to be *cis* from the observed interaction between H-20 and 18-Me (both β-oriented) in the NOESY spectrum. The signal due to H-16' of the sarpagine unit was unusually shielded (δ 1.79), which is in agreement with the configuration at C-16', which places H-16' in the shielding zone of the indole moiety of the sarpagine unit (i.e., 16'*R*).[133,254,270-272] This was further confirmed by the observed NOE between H-16' and H-6'β (Figure 2.88). Lumutinine E (**75**) therefore represents a new member of the linearly-fused macroline-sarpagine bisindoles, is assigned as the N1'-demethyl derivative of macralstonidine.

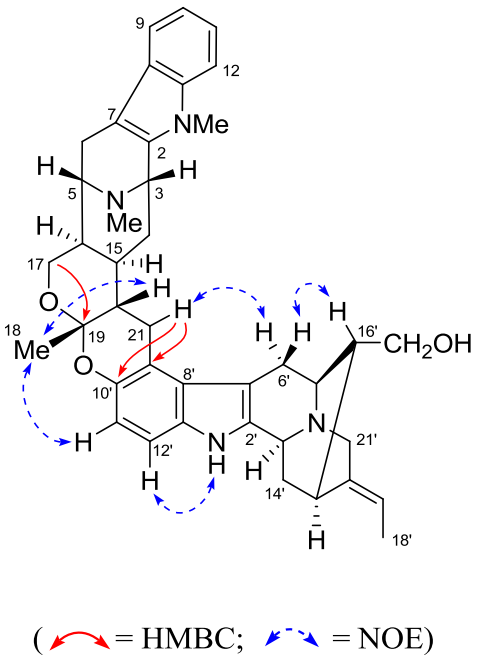


Figure 2.88: Selected HMBCs and NOEs of **75**

Table 2.45: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumutinine A (**71**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.7	2'	–	132.3
3	3.90 m	53.8	3'	3.83 m	53.9
5	3.00 d (7)	55.2	5'	3.07 d (6)	54.8
6	2.48 m	22.8	6'	2.33 m	23.1
	3.28 m			3.20 m	
7	–	106.8	7'	–	104.9
8	–	126.5	8'	–	112.6
9	7.50 d (7.5)	117.9	9'	6.98 s	116.5
10	7.11 t (7.5)	118.8	10'	–	121.9
11	7.18 t (7.5)	120.7	11'	–	150.3
12	7.28 d (7.5)	108.9	12'	6.76 s	96.9
13	–	137.0	13'	–	137.2
14β	1.25 m	27.1	14'α	1.84 m	32.5
14α	2.34 m		14β	2.15 m	
15	1.87 m	30.3	15'	2.76 m	23.0
16	2.00 m	43.5	16'	1.93 m	38.7
17α	4.67 t (12)	62.5	17'α	4.19 dd (11.5, 3)	68.0
17β	3.69 dd (12, 4)		17β	4.44 t (11.5)	
18	1.38 s	25.7	18'	2.15 s	25.2
19	–	99.5	19'	–	196.4
20	1.93 m	37.5	20'	–	121.4
21β	2.43 m	28.9	21'	7.58 s	158.1
21α	3.24 m			–	
N(1)-Me	3.55 s	29.2[b]	N(1)-Me'	3.54 s	29.6[b]
N(4)-Me	2.29 s	41.8	N(4)-Me'	2.27 s	41.8

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b] Assignments are interchangeable.

Table 2.46: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumutinine B (**72**)[a]

Position	δ_H	δ_C	**Position**	δ_H	δ_C
2	–	136.8[b]	2'	–	132.1
3	3.93 d (8)	51.3	3'	3.81 m	53.9
5	3.37 m	54.1	5'	3.06 d (7)	54.7
6	2.35 m	21.6	6'	2.41 m	22.8
	3.12 dd (16, 5)			3.22 dd (16.5, 7)	
7	–	104.7	7'	–	106.3
8	–	127.5	8'	–	121.8
9	7.49 br d (7.5)	118.1	9'	7.16 d (8)	116.7
10	7.09 td (7.5, 1)	118.9	10'	6.66 d (8)	110.6
11	7.17 m	120.8	11'	–	149.6
12	7.28 br d (7.5)	108.9	12'	–	103.2
13	–	137.1[b]	13'	–	135.7
14α	2.52 m	31.0	14'α	2.15 m	32.5
14β	1.78 m		14'β	1.79 m	
15	1.78 m	28.3	15'	2.66 m	23.0
16	1.75 m	37.3	16'	1.88 m	38.6
17α	4.22 dd (11, 3)	65.0	17'α	4.41 t (11)	68.0
17β	3.75 m		17'β	4.16 dd (11, 3)	
18	1.54 s	25.6	18'	2.12 s	25.3
19	–	99.4	19'	–	195.9
20	2.68 m	38.0	20'	–	121.3
21α	3.33 m	24.2	21'	7.55 s	157.9
21β	3.54 m				
N(1)-Me	3.65 s	29.6	N(1)-Me'	3.86 s	32.5
N(4)-Me	2.39 s	40.2	N(4)-Me'	2.29 s	41.9

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b] Assignments are interchangeable.

Table 2.47: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumutinine C (**73**)[a]

Position	δ_H	δ_C	**Position**	δ_H	δ_C
2	–	133.4	2'	–	139.3
3	3.74 m	54.0	3'	3.82 m	48.7
5	2.99 m	55.2	5'	2.87 m	56.4
6	2.45 d (16)	22.8	6'β	3.22 m	27.9
	3.28 m		6α	2.71 m	
7	–	107.0	7'	–	102.1
8	–	126.4	8'	–	125.0
9	7.50 d (7.5)	118.1	9'	–	111.4
10	7.10 t (7.5)	119.0	10'	–	147.7
11	7.17 t (7.5)	120.9	11'	6.71 d (9)	112.6
12	7.25 d (7.5)	108.9	12'	7.01 d (9)	107.7
13	–	136.9	13'	–	132.4
14α	2.35 td (13, 3)	26.7	14'α	1.89 m	38.6
14β	1.18 m		14'β	1.66 m	
15	1.87 m	30.4	15'	2.82 m	29.2
16	2.00 m	43.5	16'	1.55 m	45.0
17α	4.62 t (11.5)	62.3	17'	3.42 m	64.5
17β	3.67 dd (11.5, 4)			3.61 dd (12, 3)	
18	1.35 s	25.4	18'	1.34 d (6)	22.5
19	–	99.0	19'	4.46 q (6)	67.3
20	1.97 m	37.2	20'	–	149.3
21α	3.25 m	26.8	21'	6.44 s	136.1
21β	2.75 m				
N(1)-Me	3.40 s	29.3	N(1)-Me'	3.48 s	29.4
N(4)-Me	2.26 s	41.8			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.48: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumutinine D (**74**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.5[b]	2'	–	140.0
3	3.70 m	53.8	3'	4.16 br d (9)	49.7
5	2.97 m	55.2	5'	2.76 m	54.4
6β	2.43 d (17)	22.7	6'β	2.57 d (15)	27.1
6α	3.25 m		6'α	3.01 m	
7	–	106.8	7'	–	102.8
8	–	126.5	8'	–	126.8
9	7.49 d (7.5)	117.9	9'	6.91 s	105.1
10	7.10 t (7.5)	118.9	10'	–	148.3
11	7.18 t (7.5)	120.8	11'	–	114.9
12	7.27 d (7.5)	108.9	12'	6.85 s	107.5
13	–	137.0	13'	–	133.5[b]
14β	1.10 d (13)	26.9	14'a	1.65 m	32.9
14α	2.28 m		14'b	2.05 m	
15	1.84 m	30.2	15'	2.82 m	27.5
16	1.99 m	43.5	16'	1.82 m	44.4
17β	3.66 m	62.4	17'a	3.48 m	64.8
17α	4.63 t (11.5)		17'b	3.53 m	
18	1.39 s	25.6	18'	1.63 d (6.5)	12.9
19	–	99.3	19'	5.40 q (6.5)	117.0
20	1.93 m	37.4	20'	–	135.7
21β	2.48 d (19)	29.5	21'a	3.59 m	56.3
21α	3.25 m		21'b	3.59 m	
N(1)-Me	3.47 s	29.3	N(1)-Me'	3.56 s	29.6
N(4)-Me	2.24 s	41.8			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b] Assignments are interchangeable.

Table 2.49: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumutinine E (**75**)[a]

Position	δ_H	δ_C	**Position**	δ_H	δ_C
2	–	133.3	2'	–	138.5
3	3.71 m	53.9	3'	4.01 br d (9.5)	50.4
5	2.99 d (6.8)	55.1	5'	2.60 br t (5)	54.2
6α	2.45 d (16)	22.7	6'β	2.64 d (15)	29.4
6β	3.27 dd (16, 6.8)		6'α	3.13 dd (15, 5)	
7	–	106.8	7'	–	104.4
8	–	126.3	8'	–	125.4
9	7.51 d (7.5)	117.9	9'	–	111.1
10	7.11 t (7.5)	118.8	10'	–	147.6
11	7.17 t (7.5)	120.7	11'	6.65 d (8.6)	112.8
12	7.26 d (7.5)	108.8	12'	6.97 d (8.6)	109.7
13	–	136.9	13'	–	131.1
14α	1.17 m	26.7	14'a	1.76 m	33.5
14β	2.34 td (13, 4)		14'b	1.96 m	
15	1.83 m	30.3	15'	2.82 m	27.7
16	2.00 m	43.4	16'	1.79 m	44.2
17α	3.67 dd (11.5, 4)	62.2	17'a	3.43 m	64.8
17β	4.61 t (11.5)		17'b	3.43 m	
18	1.37 s	25.5	18'	1.63 br d (6.8)	12.8
19	–	98.8	19'	5.34 br q (6.8)	116.8
20	1.94 m	36.9	20'	–	135.8
21	2.73 d (18)	26.5	21'a	3.50 m	55.8
21	3.20 dd (18, 8)		21'b	3.50 m	
N(1)-Me	3.41 s	29.0	N(1)-H'	7.95 s	
N(4)-Me	2.27 s	41.6			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

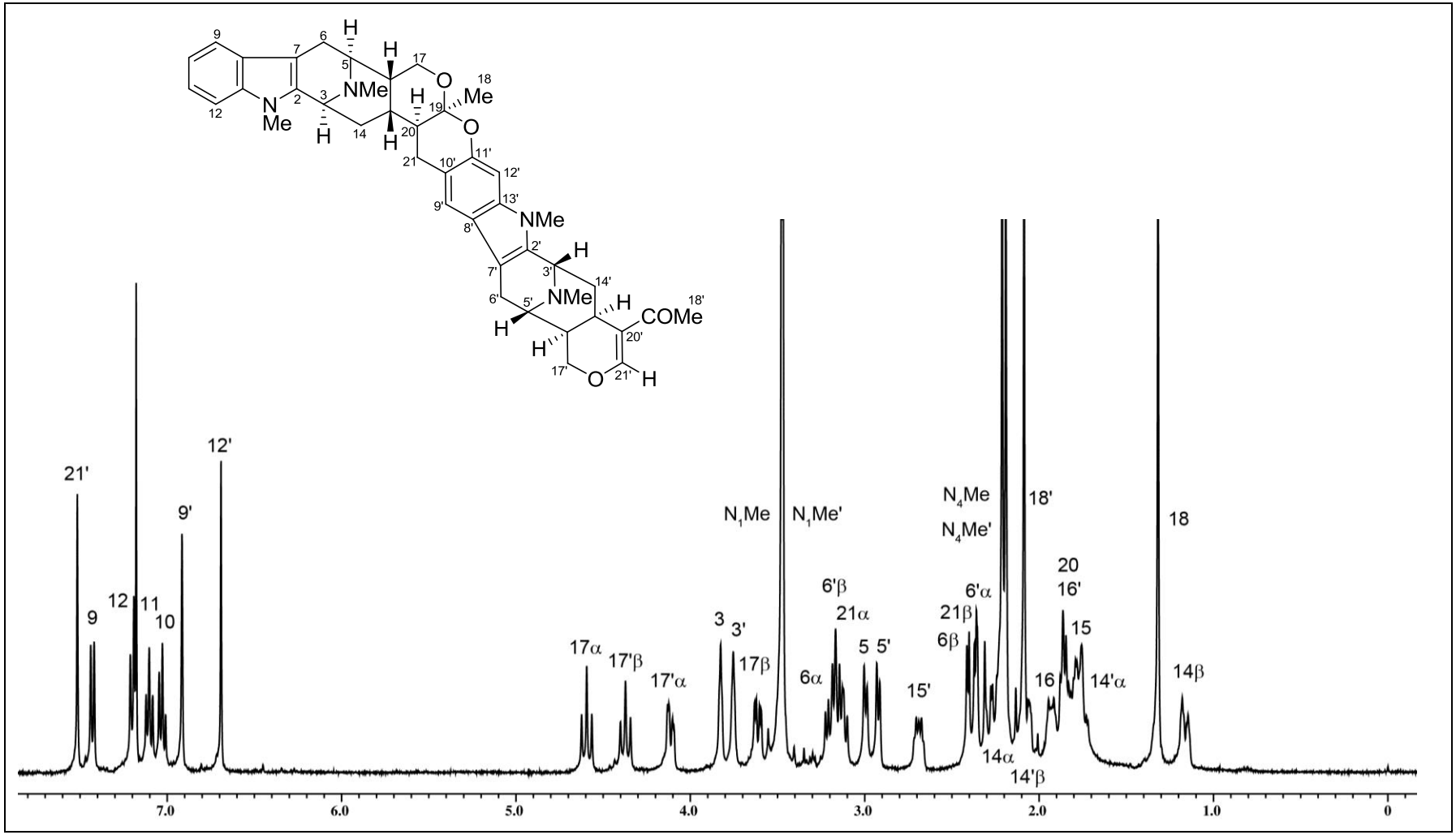


Figure 2.89: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumutinine A (**71**)

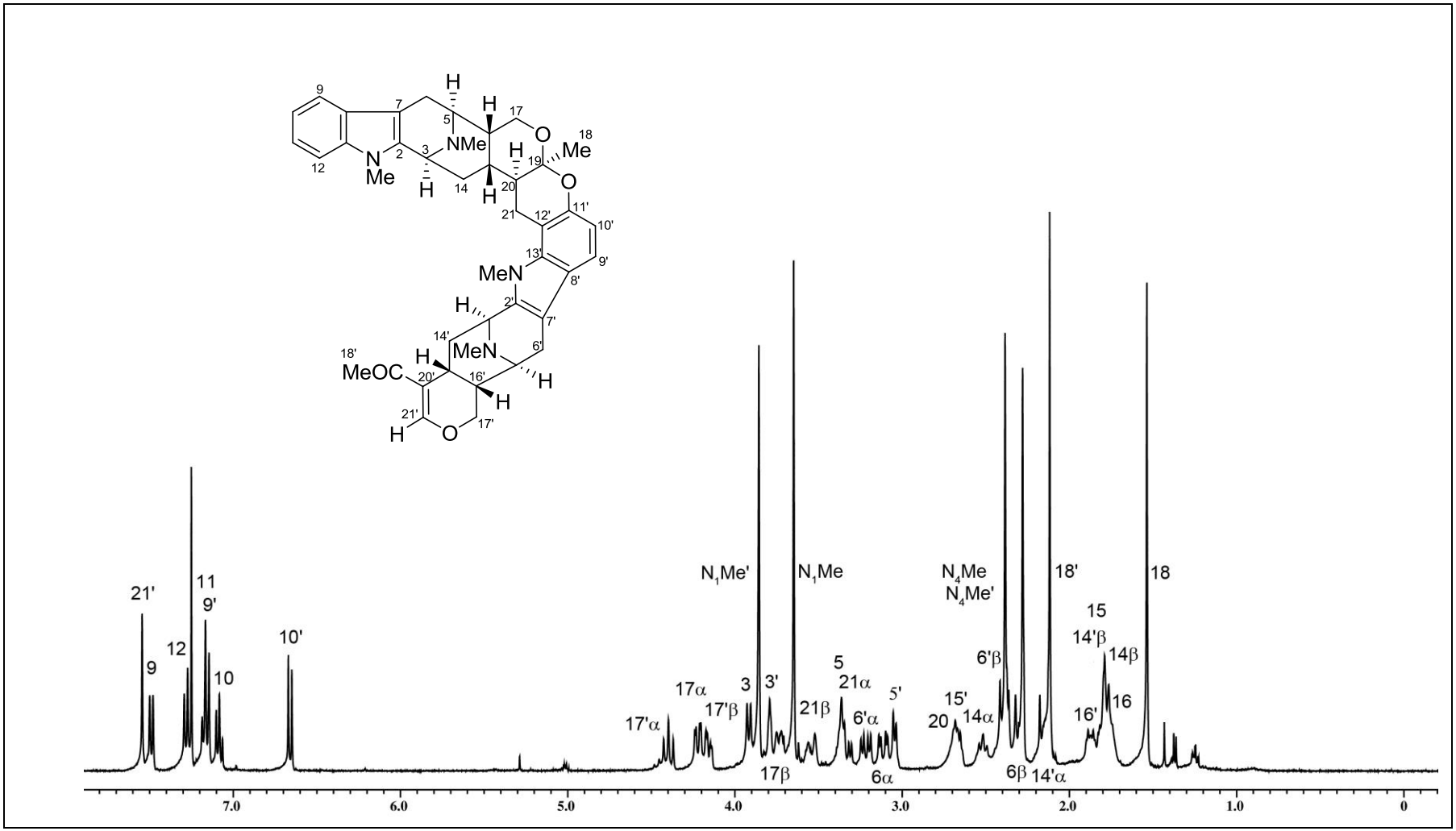


Figure 2.90: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumutinine B (**72**)

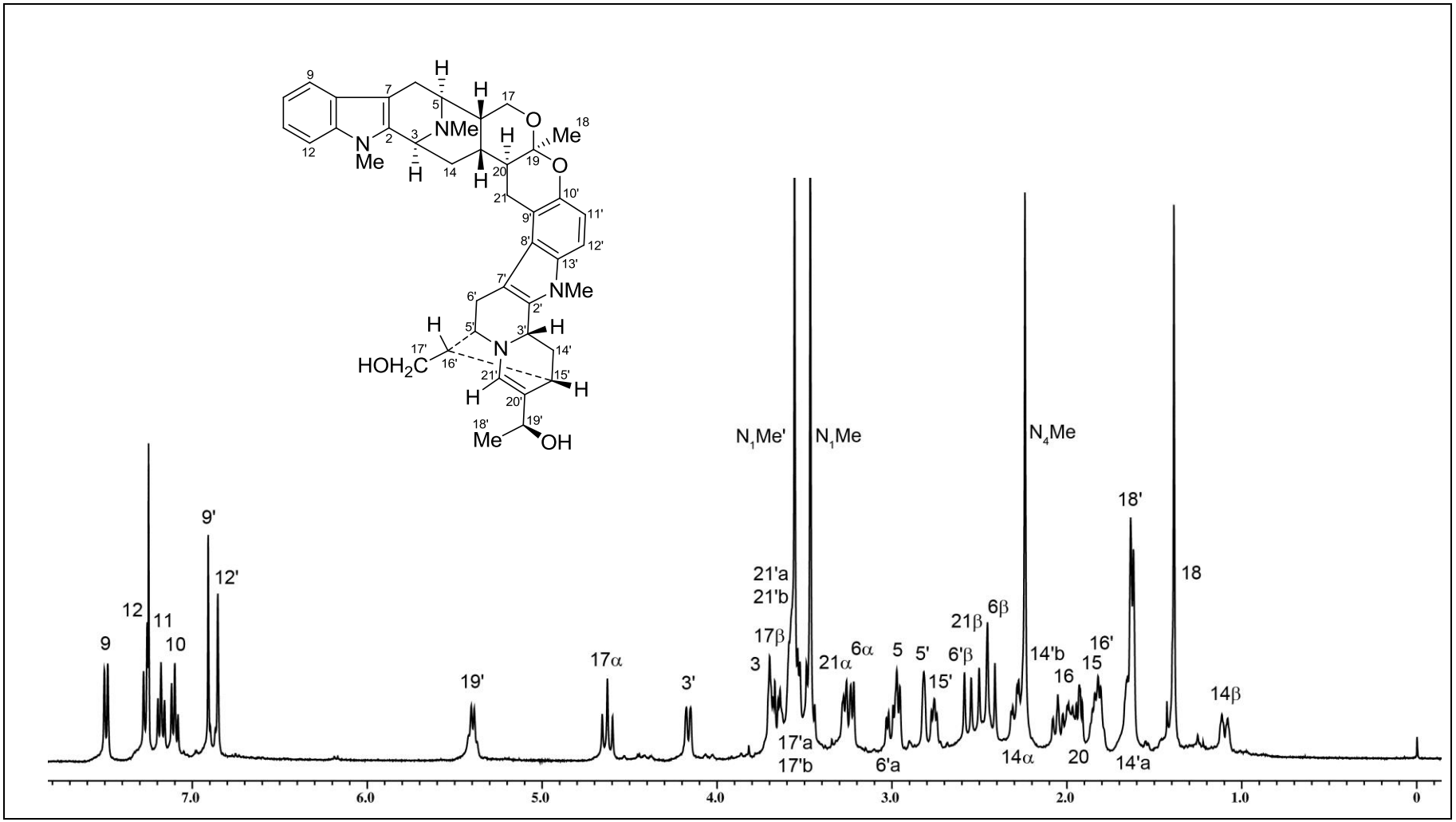


Figure 2.91: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumutinine C (**73**)

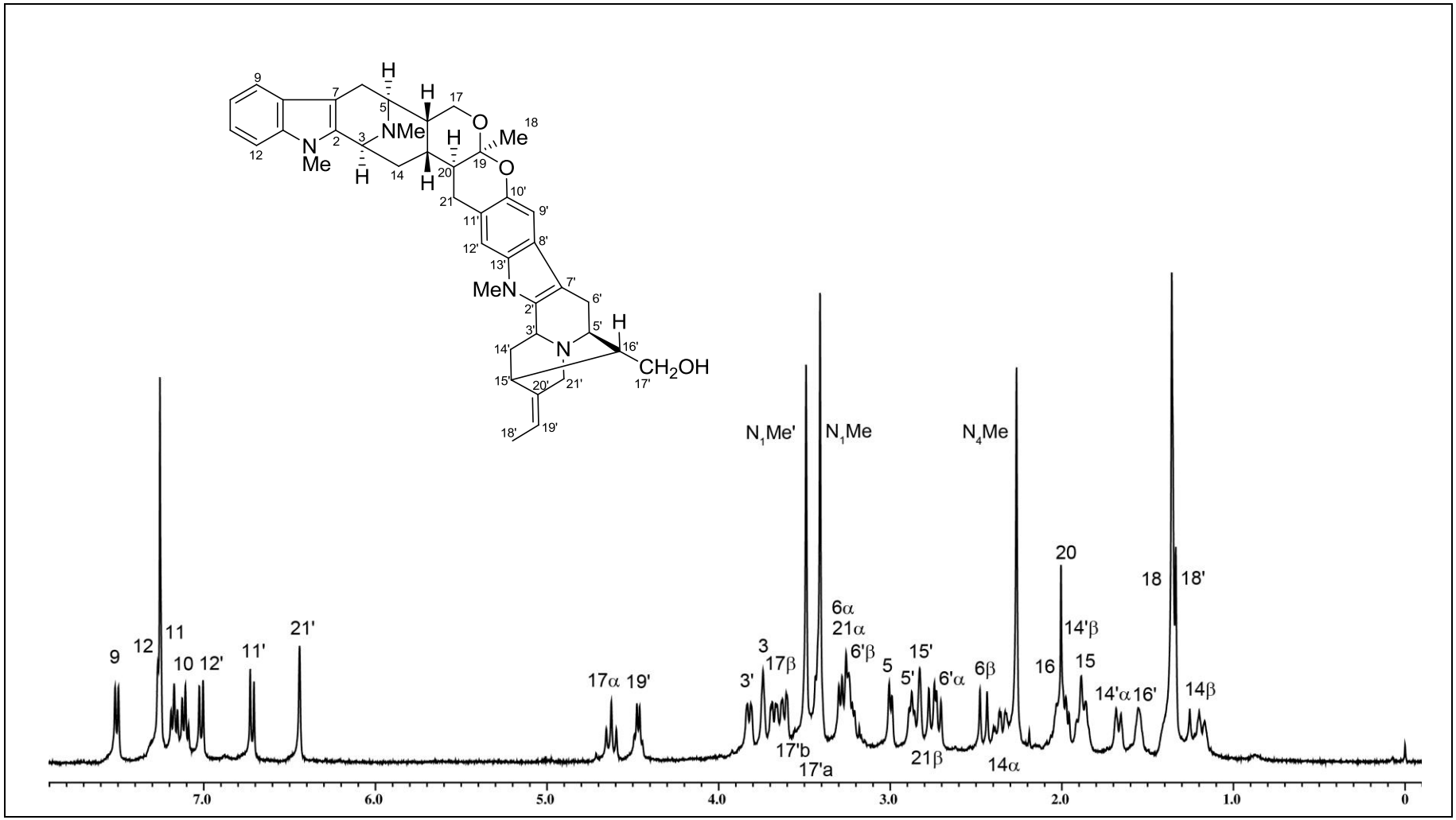


Figure 2.92: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumutinine D (**74**)

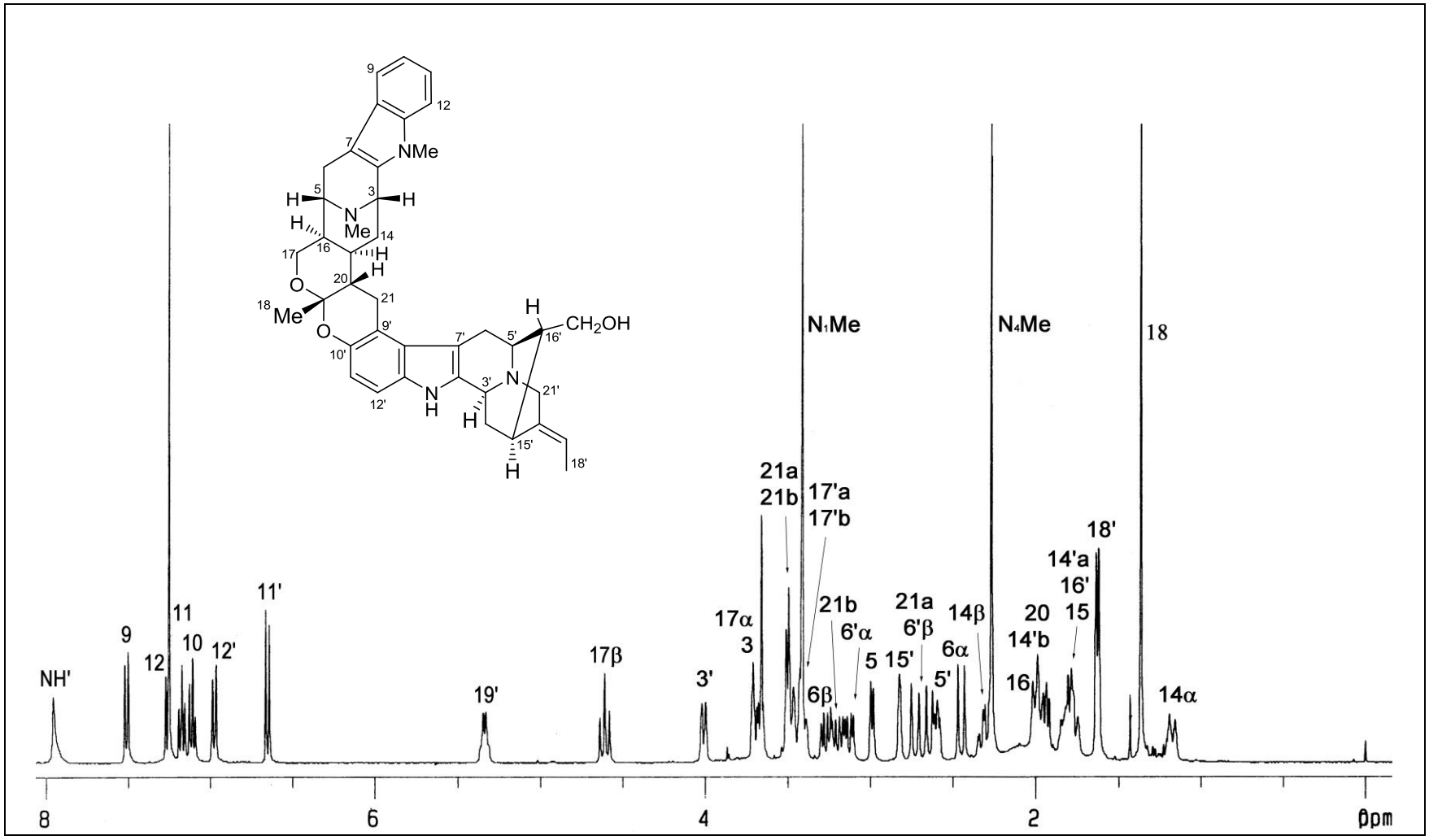


Figure 2.93: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumutinine E (**75**)

2.1.7.1.6 Macralstonidine (76)

Another known linearly fused bisindole was also isolated from the stem-bark extract of *A. macrophylla*, viz. macralstonidine (**76**).[146,171,258] The ^{1}H NMR spectrum of compound **76** is shown in Figure 2.94, while the ^{1}H and ^{13}C NMR data of compound **76** is summarized in Table 2.50, respectively. Other data are given in the Experimental Section.

Table 2.50: ^{1}H and ^{13}C NMR Spectroscopic Data for Macralstonidine (**76**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.3	2'	–	139.4
3	3.75 m	53.9	3'	4.16 br d (10)	49.4
5	3.00 d (7)	55.0	5'	2.64 d (5)	54.2
6	2.45 br d (16)	22.6	6'	2.67 br d (15)	29.3
	3.27 dd (16, 7)			3.17 dd (15, 5)	
7	–	106.8	7'	–	103.1
8	–	126.3	8'	–	124.9
9	7.51 br d (7.5)	117.8	9'	–	111.2
10	7.11 td (7.5, 1)	118.7	10'	–	147.4
11	7.18 td (7.5, 1)	120.6	11'	6.72 d (9)	112.3
12	7.27 br d (7.5)	108.8	12'	7.04 d (9)	107.5
13	–	136.8	13'	–	132.3
14	1.21 m	26.7	14'	1.74 m	32.8
	2.33 td (13, 4)			2.10 m	
15	1.86 m	30.3	15'	2.87 m	27.4
16	2.01 m	43.3	16'	1.79 m	44.1
17	3.68 dd (11.5, 4)	62.2	17'	3.53 m	64.7
	4.62 t (11.5)			3.53 m	
18	1.37 s	25.4	18'	1.65 d (6.8)	12.8
19	–	98.8	19'	5.41 q (6.8)	116.8
20	1.96 m	36.9	20'	–	135.5
21	2.77 br d (17.5)	26.5	21'	3.53 m	55.9
	3.23 m			3.60 m	
N(1)-Me	3.45 s	29.3[b]	N(1)-Me'	3.57 s	29.0[b]
N(4)-Me	2.28 s	41.6			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, and HMBC.

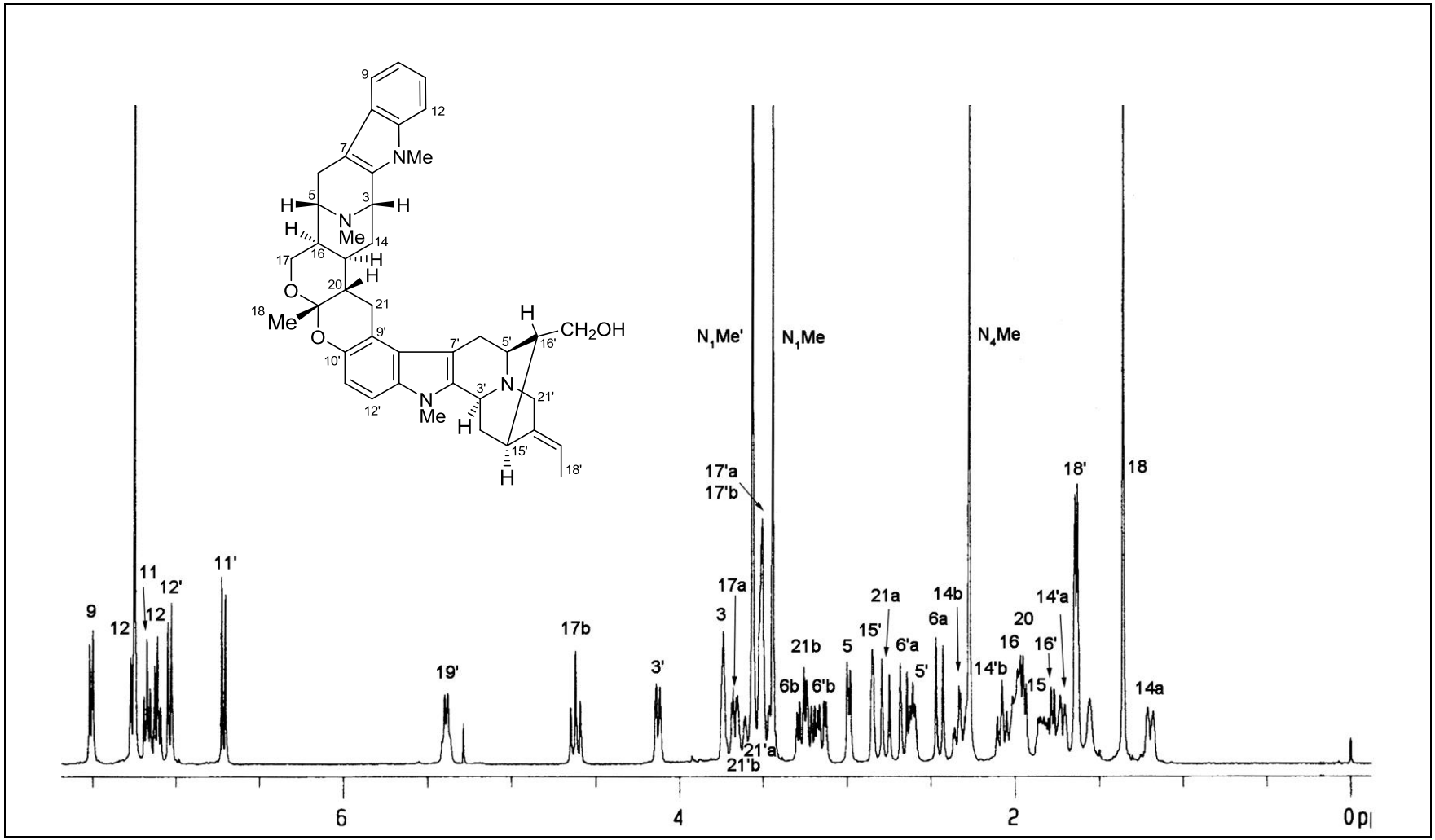


Figure 2.94: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macralstonidine (**76**)

2.1.7.2 Macroline–Macroline Bisindole Alkaloids

2.1.7.2.1 Lumusidine A (77)

Lumusidine A (**77**)[273] was isolated as a light yellowish oil, $[\alpha]_D$–138 (*c* 0.24, $CHCl_3$). The IR spectrum showed bands at 1618 and 1655 cm^{-1} due to the presence of an α,β-unsaturated carbonyl group, while the UV spectrum showed absorption maxima at 231 and 285 nm, indicating the presence of an indole chromophore. The ESIMS of **77** showed a $[M + H]^+$ peak at *m/z* 687, which analyzed for $C_{43}H_{50}N_4O_4$ + H. The ^{13}C NMR spectrum (Table 2.51) showed a total of 43 resonances, comprising seven methyl, six methylene, 17 methine, and 13 quaternary carbon atoms. The observed quaternary carbon resonance at δ 195.2, and the olefinic carbon signals at δ 120.8 (quaternary carbon) and 157.3 (methine), are consistent with the presence of the α,β-unsaturated carbonyl group, while the unusually low field resonance of the *β*-carbon at δ 157.3 indicated oxygen substitution. Another pair of olefinic signals associated with another trisubstituted double bond was observed at δ 120.5 (quaternary carbon) and 138.2 (oxymethine), in addition to two oxymethylenes at δ 65.6 and 67.5.

The ^1H NMR spectrum (Table 2.51; Figure 2.102) showed the presence of four aromatic hydrogens (δ 7.07–7.47) corresponding to an unsubstituted indole moiety, two aromatic singlets at δ 6.38 and 7.00, corresponding to another aromatic moiety substituted at C-10' and C-11', two vinylic singlets associated with the two trisubstituted double bonds at δ 6.42 and 7.59, six methyl singlets, corresponding to two N1-Me (δ 3.48, 3.32), two N4-Me (δ 2.26, 2.26), one acetyl (δ 2.12), and one aromatic methoxy group (δ 3.39). In addition, a methyl doublet was observed at *δ* 1.26 which was coupled (*J* = 7.5 Hz) with a methine quartet at *δ* 3.68. In view of the presence of only six aromatic hydrogens and

the substitution of both indolic nitrogens, it can be inferred from the observation of the two H-9' and H-12' aromatic singlets, that the bisindole is branched from C-10' or C-11' of one of the monomeric units (lower unit). The observed reciprocal NOEs between the aromatic singlet at δ 7.00 and H-6', and between the aromatic singlet at δ 6.38 and the N1'-Me signal at δ 3.48, allowed the assignment of thesearomatic resonances to H-9' and H-12', respectively (Figure 2.95). The observed NOE between H-12' and the aromatic methoxy group at δ 3.39, allowed placement of the OMe substituent at the adjacent C-11', which in turn indicated C-10' as the branching point of the bisindole from this lower monomeric unit. These conclusions were also supported by the observed three-bond correlations from H-9' to C-7', C-11', and C-13', from 11'-OMe to C-11', and from H-12' to C-10' and C-8' (Figure 2.95).

Examination of the NMR chemical shifts (Table 2.51) as well as the 2-D NMR data (COSY, HSQC, and HMBC), revealed that one unit of the bisindole (the lower half) corresponds to a 10-substituted alstophylline (**7**). Thus the COSY spectrum revealed the presence of $NCHCH_2$ and $NCHCH_2CHCHCH_2O$ partial structures, corresponding to the N-4'–C-5'–C-6' and N-4'–C-3'–C-14'–C-15'–C-16'–C-17'–O units,respectively,of the lower macroline (or alstophylline) half. The observed three-bond correlations from the vinylic H-21' (δ 7.59) to C-15', C-17', and C-19' (δ 195.2, acetyl carbonyl) accounted for the ring E of a typical type-B macroline moiety. The same alstophylline unit has been previously encountered as a constituent half in the *Alstonia* bisindoles, perhentinine (**83**)[123] and perhentidines A–C (**81, 82**, and **414**).[126]

The other unit (upper half) of the bisindole, after discounting the signals due to the alstophylline half, corresponded to another macroline derivative with an unsubstituted indole ring and a modified ring E. In addition to the signals due to the four contiguous aromatic hydrogens, and the typical macroline fragments corresponding to the N-4–C-5–C-6 and N-4–C-3–C-14–C-15–C-16–C-17–O units, as well as the presence of an

oxygenated trisubstituted double bond, the NMR data indicated a residual fragment corresponding to a CH_3CH (C-18–C-19) unit. This two-carbon fragment is linked, via the methine C-19, to the quaternary carbon of the trisubstituted double bond (C-20, δ 120.5) of the upper half moiety, as well as to the aromatic C-10' (δ 126.2) of the lower half unit, as shown by the following three-bond correlations in the HMBC spectrum: H-19 to C-21, C-15; H-21, H-15 to C-19; H-19 to C-9', C-11'; H-9' to C-19; Me-18 to C-20, C-10' (Figure 2.95). The lower alstophylline half is therefore linked to the upper macroline half via the C-19 methine of the CH_3CH group. The origin of the upper macroline moiety is likely a hypothetical ring E-opened talcarpine derivative (*vide infra*).

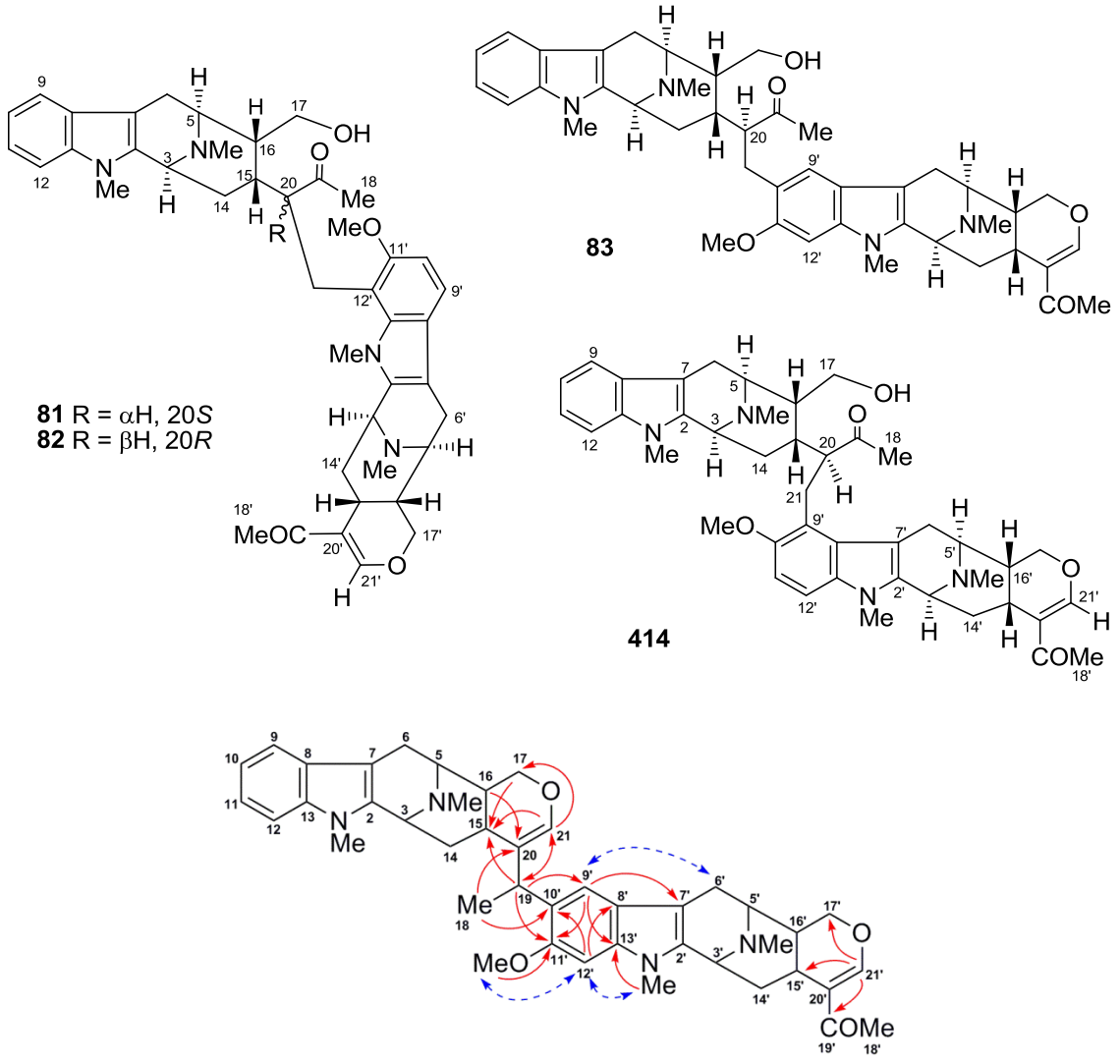


Figure 2.95: Selected HMBCs and NOEs of **77**

The remaining issue concerns the configuration at C-19, and as the NMR data in this instance did not prove helpful, a solution of this problem by X-ray crystallographic analysis was indicated. Attempts to obtain suitable crystals however, were singularly unsuccessful and eventually conversion of lumusidine A (**77**) to its dimethyl diiodide salt **77a** furnished suitable crystals, which on X-ray diffraction analysis yielded the absolute configuration of lumusidine A (19*R*, Figure 2.96).

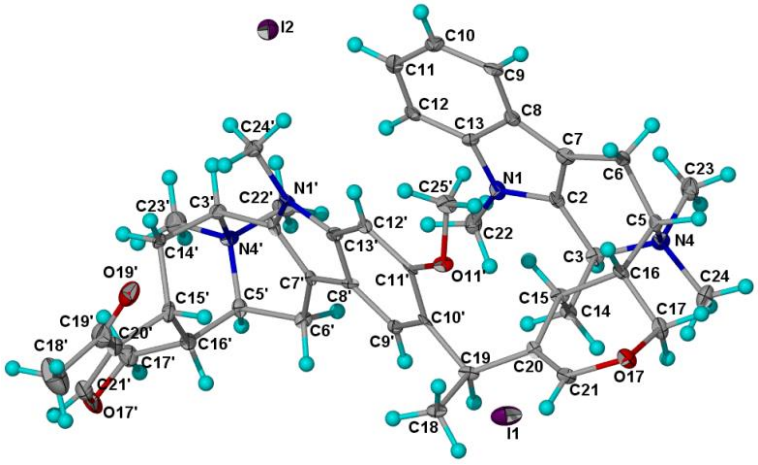
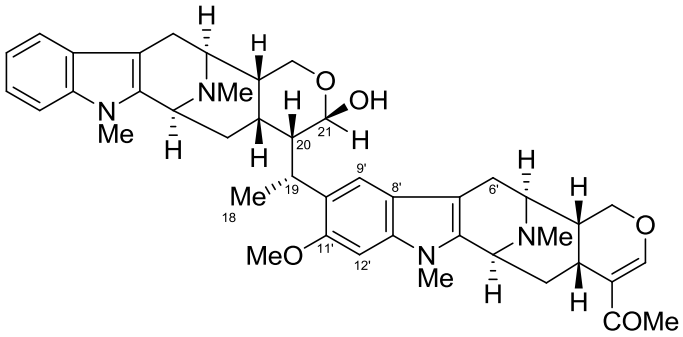


Figure 2.96: X-ray crystal structure of **77a**. [Flack parameter: x = 0.01(0.03)]

2.1.7.2.2 Lumusidine B (78)

Lumusidine B (**78**)[273] was isolated as a light yellowish oil, $[\alpha]_D$–59 (*c* 0.73, $CHCl_3$). The IR spectrum showed bands at 3366, 1652 and 1615 cm^{-1} due to the presence of OH and α,β-unsaturated carbonyl groups, respectively, while the UV spectrum showed typical indole chromophore absorption maxima at 229 and 285 nm. The ESIMS of **78** showed a $[M + H]^+$ peak at *m/z* 705, which analyzed for $C_{43}H_{52}N_4O_5$ + H, differing from that of **77** by the addition of H_2O. The presence of an OH function was supported by acetylation (Ac_2O, pyridine), which yielded an *O*-acetyl derivative (**78a**) (Figure 2.113). The ^{13}C NMR spectrum (Table 2.53) showed a total of 43 resonances, comprising seven methyl, six methylene, 18 methine, and 12 quaternary carbon atoms. Examination of the ^1H and ^{13}C NMR data and comparison with those of **77** (Table 2.51; Figure 2.103) showed that while the signals corresponding to the lower alstophylline half remained essentially unchanged, including the presence of the CH_3CH fragment, noticeable changes have occurred in the signals corresponding to the upper macroline half, in particular with respect to the ring E signals. Thus comparison of the ^{13}C NMR data showed that the resonances due to the olefinic carbons (δ 120.5, C-20 and δ 138.2, C-21) in **77**, were absent in the ^{13}C NMR spectrum of **78**. These signals have been replaced by signals at δ 44.9 (C-20) and 93.4 (C-21), the noticeable downfield shift of the C-21 methine carbon at δ 93.4, indicating substitution by two oxygen atoms (hemiacetal). Less substantial changes are observed for the signals of carbons β to both these carbons (C-20, C-21). These observations are consistent with the structure of lumusidine B as shown in **78**, where H and OH have added across the C-20–C-21 double bond. The configuration at C-20 can be deduced from the NOESY spectrum. The observed H-20/H-15, H-16 NOEs indicated that the orientation of H-20 is β. The H-21 signal was observed as a doublet at δ 5.39 with $J_{20\text{-}21}$ of 3.2 Hz, which is

consistent with an equatorial disposition of H-21 (H-21α). As in the case of **77**, it remained to establish the configuration at C-19. The NMR data in this case was also not helpful as the signals of both H-19 and H-20 were multiplets in lumusidine B (**78**) as well as in the *O*-acetyl derivative, **78a**. As with **77**, repeated attempts at crystallization proved fruitless, but eventually, suitable crystals were obtained upon conversion to the dimethyl diiodide salt **78b**. X-ray diffraction analysis of this salt confirmed the structural assignments discussed above and established the absolute configuration of lumusidine B (**78**) (19*R*, Figure 2.97).



78

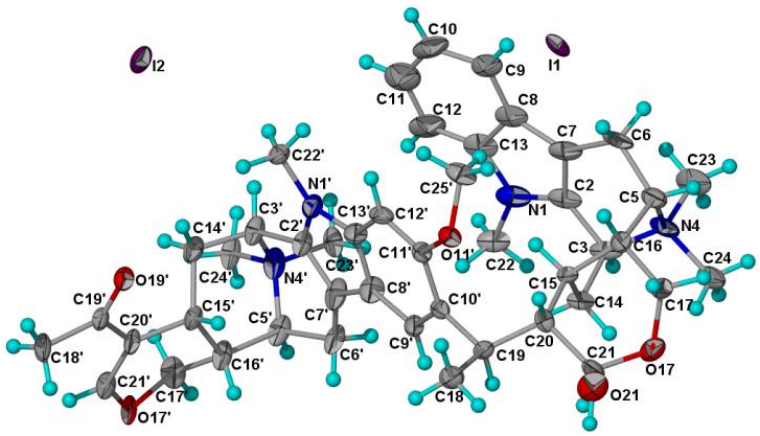
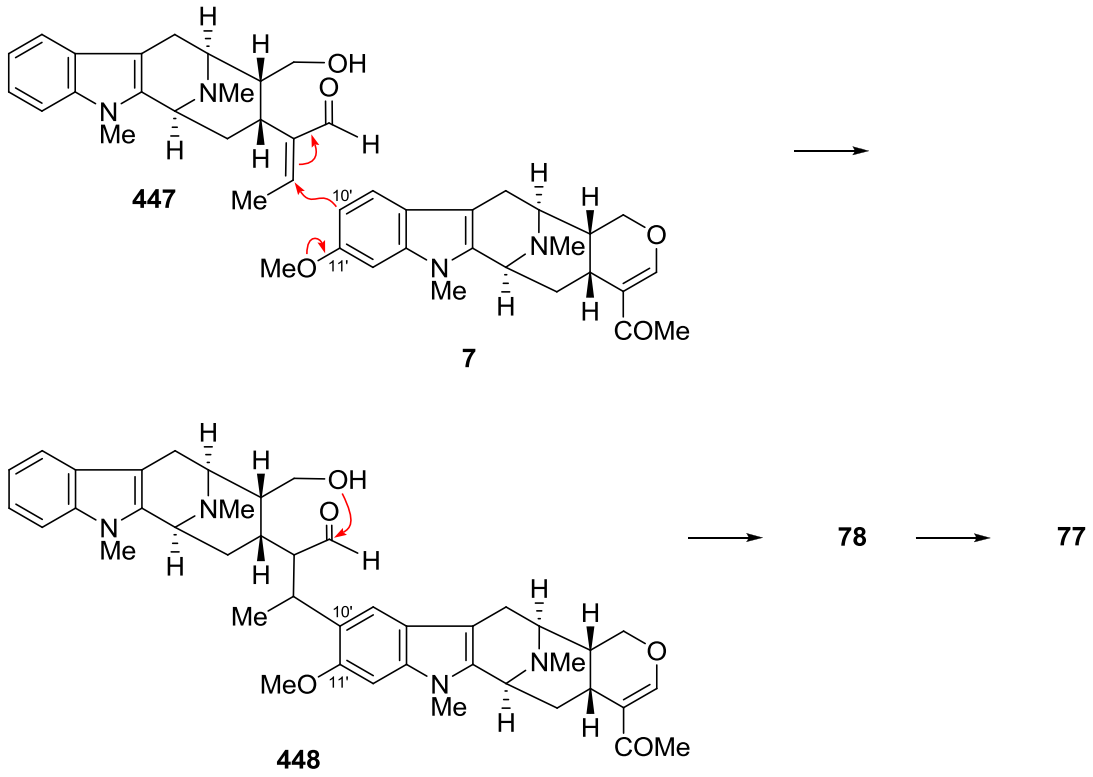


Figure 2.97: X-ray crystal structure of **78b**. [Flack parameter: x = 0.05(0.03)]

Lumusidine A (**77**) is likely derived by dehydration of the hemiacetal, lumusidine B (**78**), which in turn can be considered as having originated from conjugate addition of alstophylline (**7**) via its nucleophilic C-10' onto a hypothetical ring E-opened talcarpine derivative **447**, to give the hydroxy-aldehyde **448**, which on subsequent ring closure gives the hemiacetal **78** (Scheme 2.2).



Scheme 2.2: Possible biogenetic pathway to **77** and **78**

2.1.7.2.3 Lumusidine C (79)

Lumusidine C (**79**)[273] was isolated as a light yellowish oil, $[\alpha]_D$–16 (*c* 0.21, $CHCl_3$). The IR spectrum showed bands at 1619 and 1653 cm^{-1} due to the presence of an α,β-unsaturated carbonyl group, while the UV spectrum showed typical indole chromophore absorption maxima at 231 and 283 nm. The ESIMS of **79** showed a $[M + H]^+$ peak at *m/z* 733, which analyzed for $C_{45}H_{56}N_4O_5$ + H. The ^{13}C NMR spectrum (Table 2.54) showed a total of 45 resonances, comprising eight methyl, eight methylene, 16 methine, and 13 quaternary carbon atoms. Examination of the ^1H and ^{13}C NMR data and comparison with those of **77** and **78**, showed the presence of signals corresponding to the same lower alstophylline half present in **77** and **78**. These include, the two isolated aromatic singlets due to H-9' (δ 6.86) and H-12' (δ 6.06), four singlets due to N1'-Me (δ 3.32), N4'-Me (δ 2.28), 11'-OMe (δ 3.61), and COMe (δ 2.08, C-18'), and signals due to a trisubstituted, oxygenated double bond corresponding to C-20'–C-21' (δ_C 121.5, 157.5). The remaining signals corresponded to those of another macroline unit constituting the upper half such as, the four aromatic resonances corresponding to those of an unsubstituted indole moiety (δ 6.95-7.34), three methyl singlets corresponding to N1-Me (δ 3.34), N4-Me (δ 2.25), and a methyl (δ 1.36, C-18) attached to a quaternary carbon. In addition, signals due to an ethoxy group were observed at δ 1.30 and 3.58. This ethoxy group must be attached to the ring E quaternary C-19, as part of aketal functionality, consistent the observed downfield shift of this carbon at δ 101.6, indicating its attachment to two oxygen atoms. The COSY spectrum also showed the presence of another set of macroline fragments corresponding to the N-4–C-5–C-6 and N-4–C-3–C-14–C-15–C-16–C-17–O units. In addition, a $CHCH_2$ fragment was observed corresponding to C-20–C-21, which was linked via the methine C-20 to C-15

and C-19, as indicated by the three-bond correlations from H-21 to C-15 and C-19 in the HMBC spectrum (Figure 2.98). The observed three-bond correlations from the methylene H-21 to the aromatic C-9' and C-11' of the lower half macroline moiety, indicated that the two macroline halves are connected via the C-21 methylene bridge. These observations allowed the structure of lumusidine C to be assembled as shown in **79**. Finally, the observed H-20/H-14β and H-20/H-18 NOEs (Figure 2.99) allowed the assignment of α-orientation for H-20 and Me-18, which were also consistent with the other NOEs observed (Figure 2.99). In view of the use of ethanol during extraction, lumusidine C (**79**) is most likely an artifact derived from the precursor hemiketal alkaloid **449** (closed form of perhentinine) (which to date has not been encountered and which in turn is the closed form of perhentinine (**83)**).

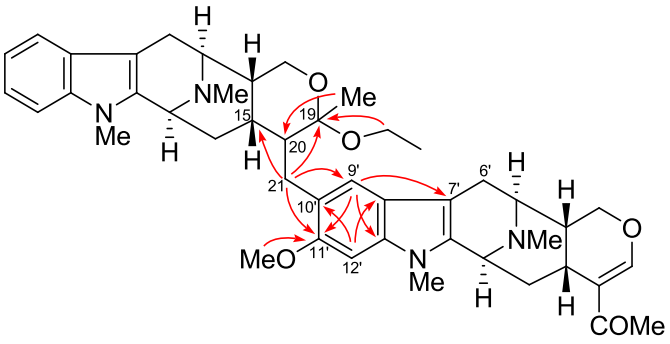


Figure 2.98: Selected HMBCs of **79**

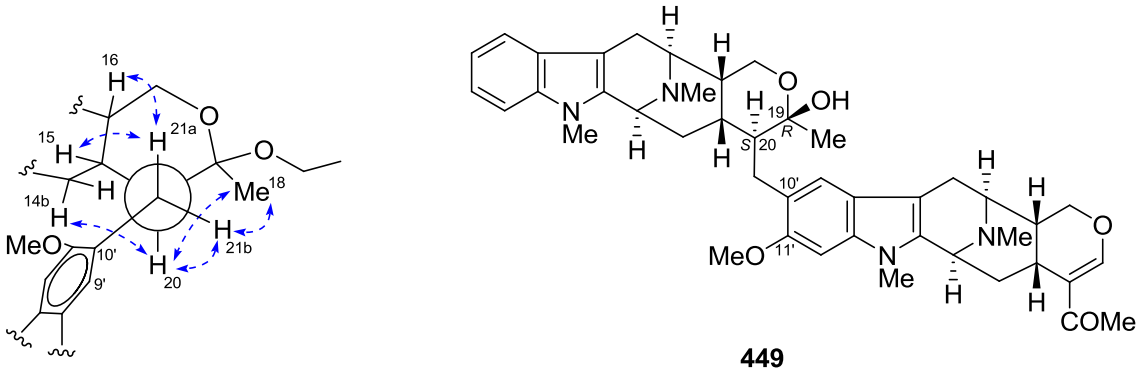


Figure 2.99: Selected NOEs of **79**

2.1.7.2.4 Lumusidine D (80)

Lumutisine D (**80**)[273] was isolated as a light yellowish oil, $[\alpha]_D$ −161 (*c* 0.38, $CHCl_3$). The IR spectrum showed bands at 1618 and 1654 cm^{-1} due to the presence of an *α,β*-unsaturated carbonyl group, while the UV spectrum showed typical indole chromophore absorption maxima at 233 and 283 nm. The ESIMS of **80** showed a $[M + H]^+$ peak at *m/z* 687, which analyzed for $C_{43}H_{50}N_4O_4$ + H. The ^{13}C NMR spectrum (Table 2.55) showed a total of 43 resonances, comprising seven methyl, seven methylene, 15 methine, and 14 quaternary carbon atoms. Examination of the ^1H and ^{13}C NMR data of **80** (Table 2.55; Figure 2.106), indicated a number of similarities with those of lumusidine A (**77**). For instance most of the signals corresponding to the upper half macroline unit were observed with the exception of a vinyl-H at C-21 in place of a methyl group. Another difference is in the bridging of the two macroline halves, which in the case of **80** was similar to that in **79**, i.e., via a C-21 methylene bridge. The NMR signals corresponding to the lower macroline unit were essentially similar to those in the previous bisindoles, **77**–**79**, indicating the presence of a similar alstophylline unit, but with one notable difference. In **80**, the signals of the aromatic hydrogens of the lower alstophylline unit were seen as a pair of AB doublets, indicating that the aromatic ring is vicinally substituted. The observed reciprocal NOEs (Figure 2.100) between the aromatic doublet at δ 7.01 and the signal due to H-6' permitted the assignment of this signal to H-9' and the signal at δ 6.08 to H-10'. The observed reciprocal NOEs between the H-10' signal (δ 6.08) and the aromatic methoxy signal at δ 2.92 confirmed its placement at C-11', which in turn indicated C-12' as the branching point of the bisindole from the lower alstophylline unit. In bisindole **80** therefore, branching is from C-12' of the lower alstophylline unit to the olefinic C-20 of the upper unit, the connection being mediated by the C-21 methylene bridge. These conclusions are consistent with the

observed three bond correlations in the HMBC spectrum (Figure 2.100), viz., from H-21 to C-15, C-19, C-11', and C-13'. It transpired that lumusidine D corresponds to thungfaine, recently independently isolated from a Thai *Alstonia*.[165] It's likely origin is probably from conjugate addition of the electron-rich C-12' of alstophylline (**7**) onto macroline **443**, followed by cyclization of the product hydroxyketone to the hemiketal **450**, and its subsequent dehydration (Scheme 2.3). It is also noteworthy that the hemiketal **450** is also the immediate precursor of one of the linearly fused macroline-macroline bisindole, lumutinine B (**72**), via a subsequent ketalization.[258] Since we were able to obtain suitable crystals of **80**, X-ray diffraction was also carried out, which confirmed the assignment of the structure based on spectroscopic data (Figure 2.101).

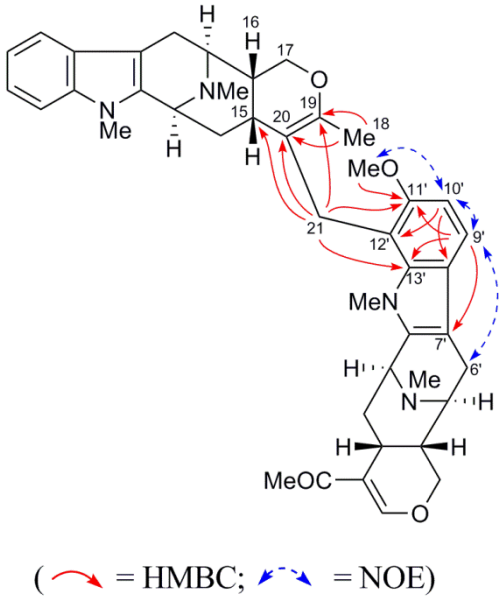


Figure 2.100: Selected HMBCs and NOEs of **80**

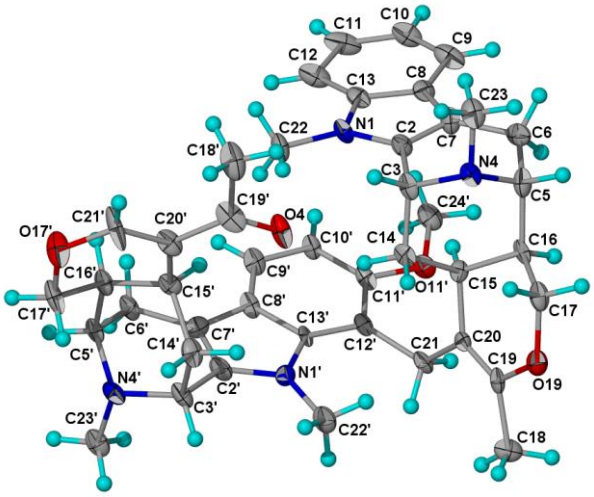
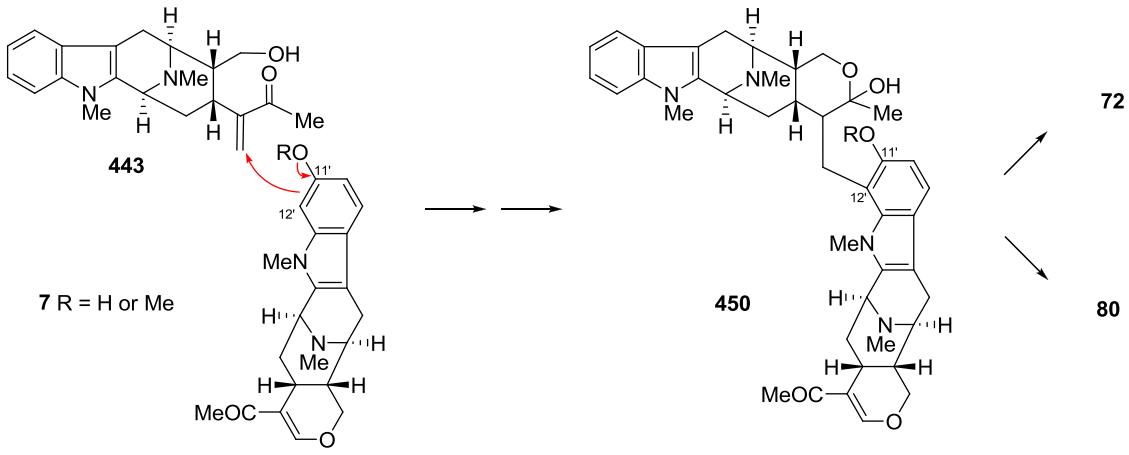


Figure 2.101: X-ray crystal structure of **80**.



Scheme 2.3: Possible biogenetic pathway to **72** and **80**.

Table 2.51: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumusidine A (**77**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.0	2'	–	131.0
3	3.76 m	53.5	3'	3.81 m	53.5
5	3.01 d (7)	54.9	5'	3.06 d (7)	54.4
6β	2.43 br d (16)	22.3	6'β	2.34 br d (17)	22.7
6α	3.19 m		6'α	3.16 m	
7	–	105.8	7'	–	105.0
8	–	126.2[b]	8'	–	119.9
9	7.47 d (7.7)	118.1[c]	9'	7.00 s	115.5
10	7.07 m	117.9[c]	10'	–	126.2[b]
11	7.09 m	120.0	11'	–	153.5
12	7.14 m	107.8	12'	6.38 s	91.1
13	–	136.5	13'	–	135.8
14β	1.57 m	35.6	14'β	1.80 m	32.1
14α	1.86 m		14'α	2.08 m	
15	1.86 m	25.0	15'	2.71 m	22.7
16	1.86 m	39.8	16'	1.96 m	38.4
17β	3.92 br d (11)	65.6	17'β	4.21 br d (11)	67.5
17α	4.29 t (11)		17'α	4.44 t (11)	
18	1.26 d (7.5)	20.2	18'	2.12 s	24.7
19	3.68 q (7.5)	33.1	19'	–	195.2
20	–	120.5	20'	–	120.8
21	6.42 s	138.2	21'	7.59 s	157.3
N(1)-Me	3.32 s	28.3	N(1)-Me'	3.48 s	28.7
N(4)-Me	2.26 s	41.4	N(4)-Me'	2.26 s	41.4
			11'-OMe	3.39 s	55.2

[a] $CDCl_3$, 400 and 100 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b–c] Assignment are interchangeable.

Table 2.52: ^{1}H NMR Spectroscopic Data for Lumusidine B (**78**) and *O*-Acetyllumusidine B (**78a**)[a]

H	**80**	**80a**	**H**	**80**	**80a**
3	3.63 m	3.61 m	3'	3.98 m	3.97 m
5	2.90 d (7)	2.86 d (7)	5'	3.11 m	3.17 m
6β	2.31 m	2.44 d (16)	6'β	2.51 m	2.31 d (16)
6α	3.17 m	3.26 dd (16, 7)	6'α	3.13 m	3.13 m
9	7.33 d (7)	7.38 d (7)	9'	7.01 s	6.91 s
10	7.03 m	7.05 td (7, 1)	12'	5.63 s	5.61 s
11	7.05 m	7.11 td (7, 1)	14'β	1.79 m	1.82 td (13, 4)
12	6.51 d (7)	6.58 d (7)	14'α	2.11 m	2.15 m
14β	1.38 m	1.30 m	15'	2.48 m	2.53 m
14α	2.57 m	2.59 m	16'	1.87 m	1.90 m
15	1.30 m	1.30 m	17'β	4.17 dd (11.5, 3)	4.18 dd (11.5, 3)
16	1.84 m	1.90 m	17'α	4.41 t (11.5)	4.42 t (11.5)
17β	3.48 dd (12, 4)	3.88 dd (11.5, 4)	18'	2.06 s	2.08 s
17α	4.47 t (12)	4.31 t (11.5)	21'	7.51 s	7.53 s
18	1.18 d (6.8)	1.24 d (6.9)	N(1)-Me'	3.44 s	3.45 s
19	2.87 m	2.60 m	N(4)-Me'	2.51 s	2.48 s
20	2.46 m	2.29 m	11'-OMe	3.21 s	3.22 s
21	5.39 d (3.2)	5.96 d (9)			
N(1)-Me	2.57 s	3.45 s			
N(4)-Me	2.29 s	2.23 s			
OCOMe	–	2.14 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.53: ^{13}C NMR Spectroscopic Data for Lumusidine B (**78**) and *O*-Acetyllumusidine B (**78a**)[a]

C	80	80a	C	80	80a
2	132.4	132.5	2'	131.1	131.2
3	54.3	53.7	3'	54.1	54.1
5	55.5	54.9	5'	54.9	54.8
6	22.9	22.9	6'	22.8	22.8
7	106.0	106.3	7'	105.1	105.2
8	125.9	126.0	8'	120.2	120.1
9	117.3	117.4	9'	119.6	120.0
10	118.3	118.3	10'	124.8	126.0
11	119.8	120.0	11'	154.4	153.6
12	108.1	108.1	12'	91.8	91.5
13	136.4	136.4	13'	136.5	136.4
14	26.9	25.0	14'	32.4	32.3
15	26.2	28.5	15'	23.0	27.4
16	44.5	43.8	16'	38.6	38.5
17	59.8	66.6	17'	67.9	67.8
18	19.5	21.6	18'	25.1	25.0
19	40.3	40.1	19'	195.6	195.5
20	44.9	45.9	20'	121.2	121.1
21	93.4	96.2	21'	157.6	157.5
N(1)-Me	27.6	29.3	N(1)-Me'	29.4	29.3
N(4)-Me	41.9	41.7	N(4)-Me'	41.8	41.7
OCO*Me*	–	21.6	11'-OMe	54.7	54.3
O*C*OMe	–	170.1			

[a] $CDCl_3$, 100 MHz; assignments based on COSY, HMQC, and HMBC.

Table 2.54: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumusidine C (**79**)[a]

Position	δ_H	δ_C	**Position**	δ_H	δ_C
2	–	133.0	2'	–	131.0
3	3.77 m	54.3	3'	3.75 m	53.9
5	2.92 d (7)	55.3	5'	2.98 d (7)	54.8
6β	2.26 m	22.6	6'β	2.10 m	22.6
6α	3.14 dd (16, 7)		6'α	3.14 dd (16, 7)	
7	–	106.6	7'	–	104.9
8	–	126.6	8'	–	119.9
9	7.34 d (7)	117.9	9'	6.86 s	118.1
10	7.06 t (7)	118.4	10'	–	121.4
11	7.02 t (7)	120.1	11'	–	154.0
12	6.95 d (7)	108.2	12'	6.06 s	90.8
13	–	136.8	13'	–	136.1
14β	1.24 m	32.4	14'β	1.75 td (13, 4)	32.6
14α	3.05 m		14'α	2.05 m	
15	1.61 m	27.2	15'	2.50 m	22.9
16	2.12 m	37.5	16'	1.84 m	38.3
17β	3.49 dd (11, 4)	62.0	17'β	4.15 m	68.0
17α	4.18 m		17'α	4.38 t (11)	
18	1.36 s	22.1	18'	2.08 s	25.2
19	–	101.6	19'	–	195.6
20	1.67 dd (10.4, 4.5)	45.8	20'	–	121.5
21a	2.60 dd (13.6, 10.4)	30.4	21'	7.55 s	157.5
21b	2.83 dd (13.6, 4.5)				
N(1)-Me	3.34 s	29.1	N(1)-Me'	3.32 s	28.8
N(4)-Me	2.25[b] s	41.8[c]	N(4)-Me'	2.28[b] s	42.0[c]
O*CH*$_2$CH$_3$	3.58 m	55.3	11'-OMe	3.61 s	55.3
	3.58 m				
OCH$_2$*CH*$_3$	1.30 t (7)	15.9			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b–c] Assignments are interchangeable

Table 2.55: ^{1}H and ^{13}C NMR Spectroscopic Data for Lumusidine D (**80**)[a]

Position	δ_H	δ_C	**Position**	δ_H	δ_C
2	–	133.5	2'	–	132.6
3	3.72 m	53.5	3'	3.80 m	53.9
5	3.00 d (7)	55.3	5'	3.06 d (7)	54.6
6β	2.34 m	22.8	6'β	2.34 m	22.9
6α	3.17 d (16)		6'α	3.15 d (16)	
7	–	105.3[b]	7'	–	105.4[b]
8	–	126.3	8'	–	121.8
9	7.34 d (8)	117.6	9'	7.01 d (8.5)	115.7
10	7.02 t (8)	118.3	10'	6.08 d (8.5)	104.9
11	7.15 m	120.1	11'	–	153.7
12	7.17 m	108.9	12'	–	110.3
13	–	136.8	13'	–	137.2
14β	0.85 d (13)	32.5	14'α	1.76 m	32.3
14α	1.86 m		14'β	1.99 d (13)	
15	1.61 m	25.9	15'	2.53 m	22.6
16	1.89 m	40.8	16'	1.86 m	38.7
17β	3.95 dd (11, 3)	66.1	17'β	4.17 dd (11, 3)	67.8
17α	4.42 t (11)		17'α	4.42 t (11)	
18	1.82 s	16.8	18'	2.11 s	25.1
19	–	144.1	19'	–	195.4
20	–	108.3	20'	–	121.1
21	3.65 m	25.5	21'	7.52 s	157.4
	3.65 m		N(1)-Me'	3.72 s	31.4
N(1)-Me	2.83 s	28.2	N(4)-Me'	2.33 s	42.0[c]
N(4)-Me	2.24 s	41.6[c]	11'-OMe	2.92 s	55.7

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b–c] Assignments are interchangeable.

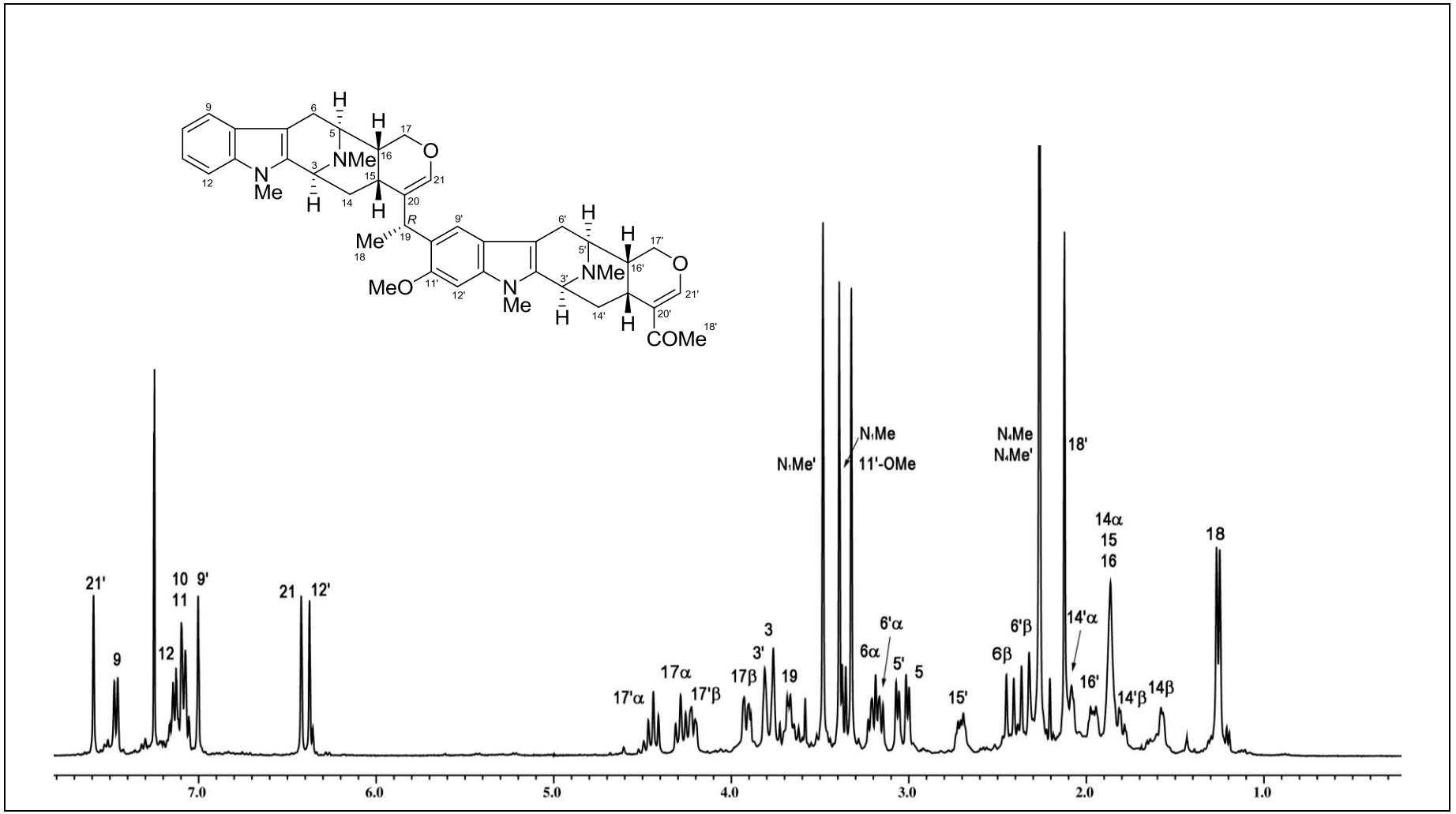


Figure 2.102: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumusidine A (**77**)

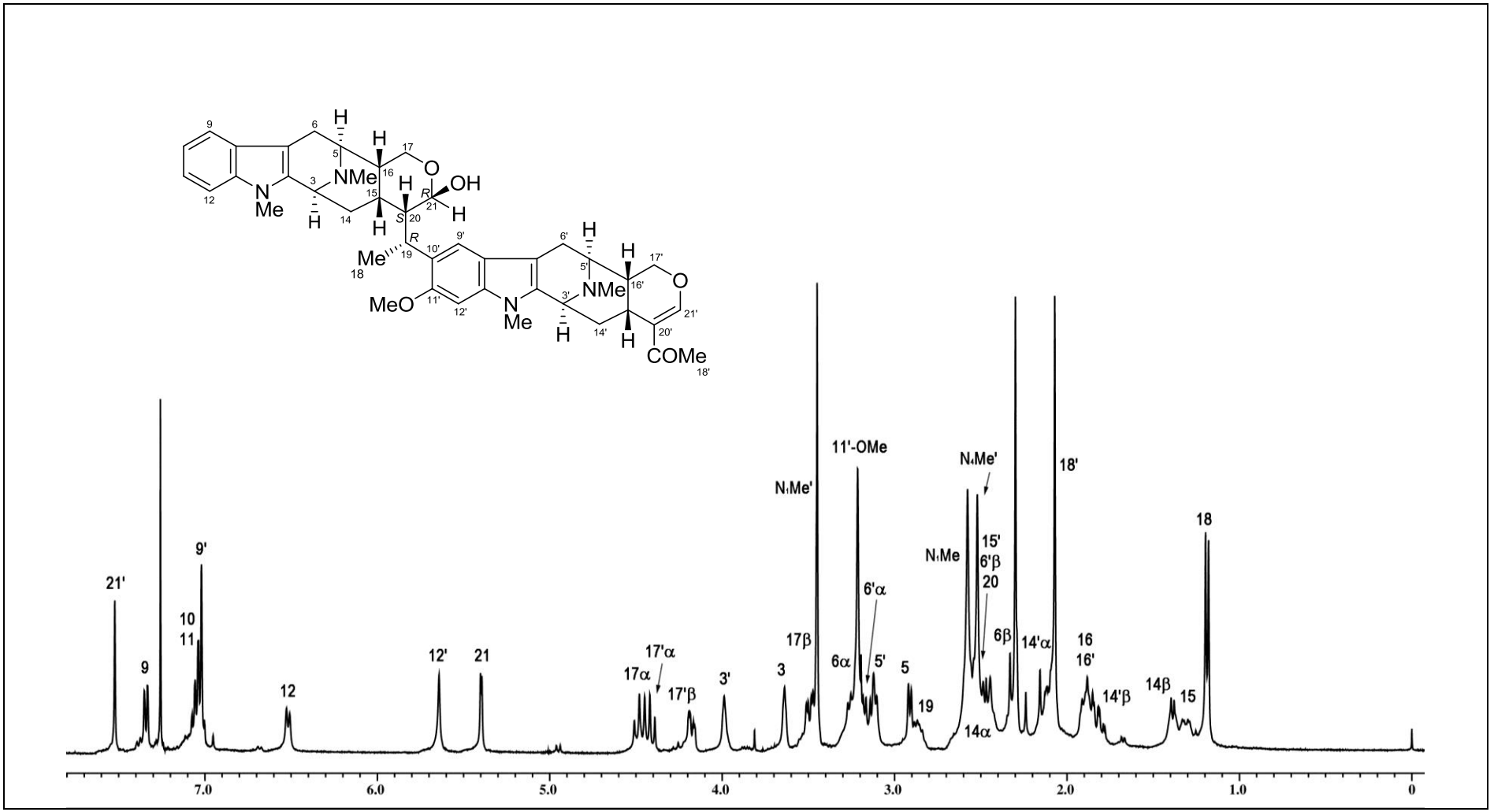


Figure 2.103: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumusidine B (**78**)

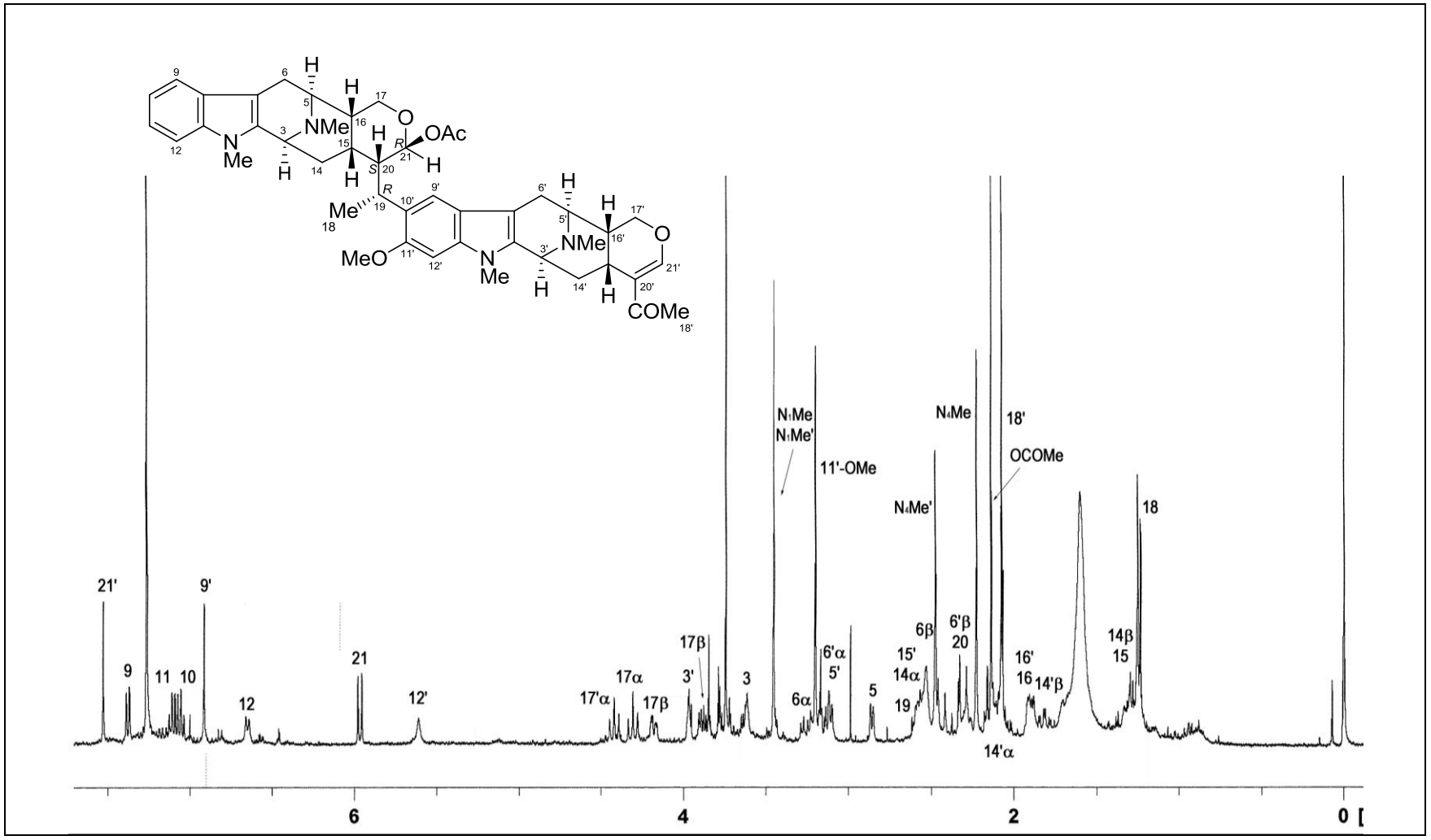


Figure 2.104: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *O*-Acetyllumusidine B (**78a**)

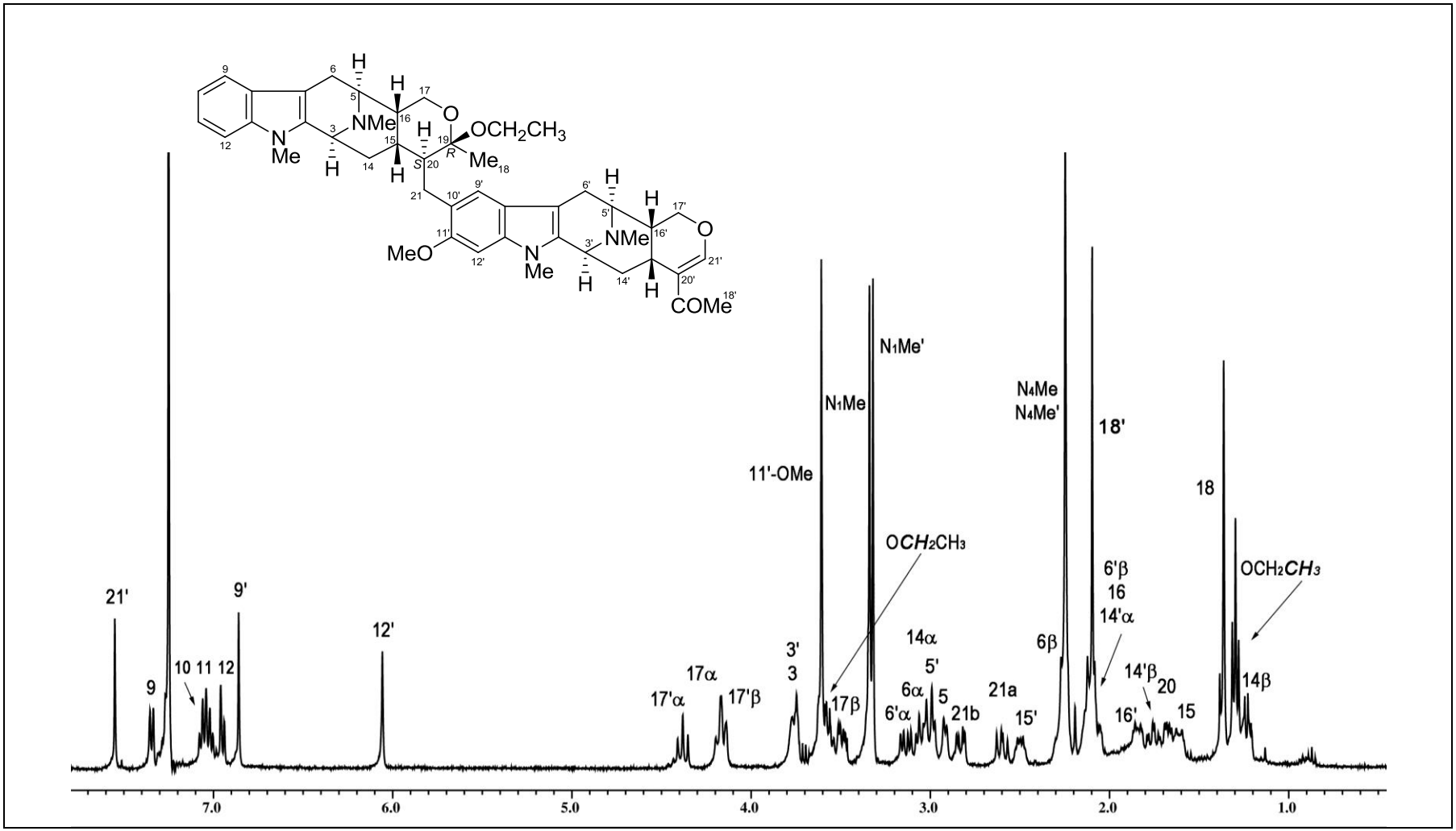


Figure 2.105: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumusidine C (**79**)

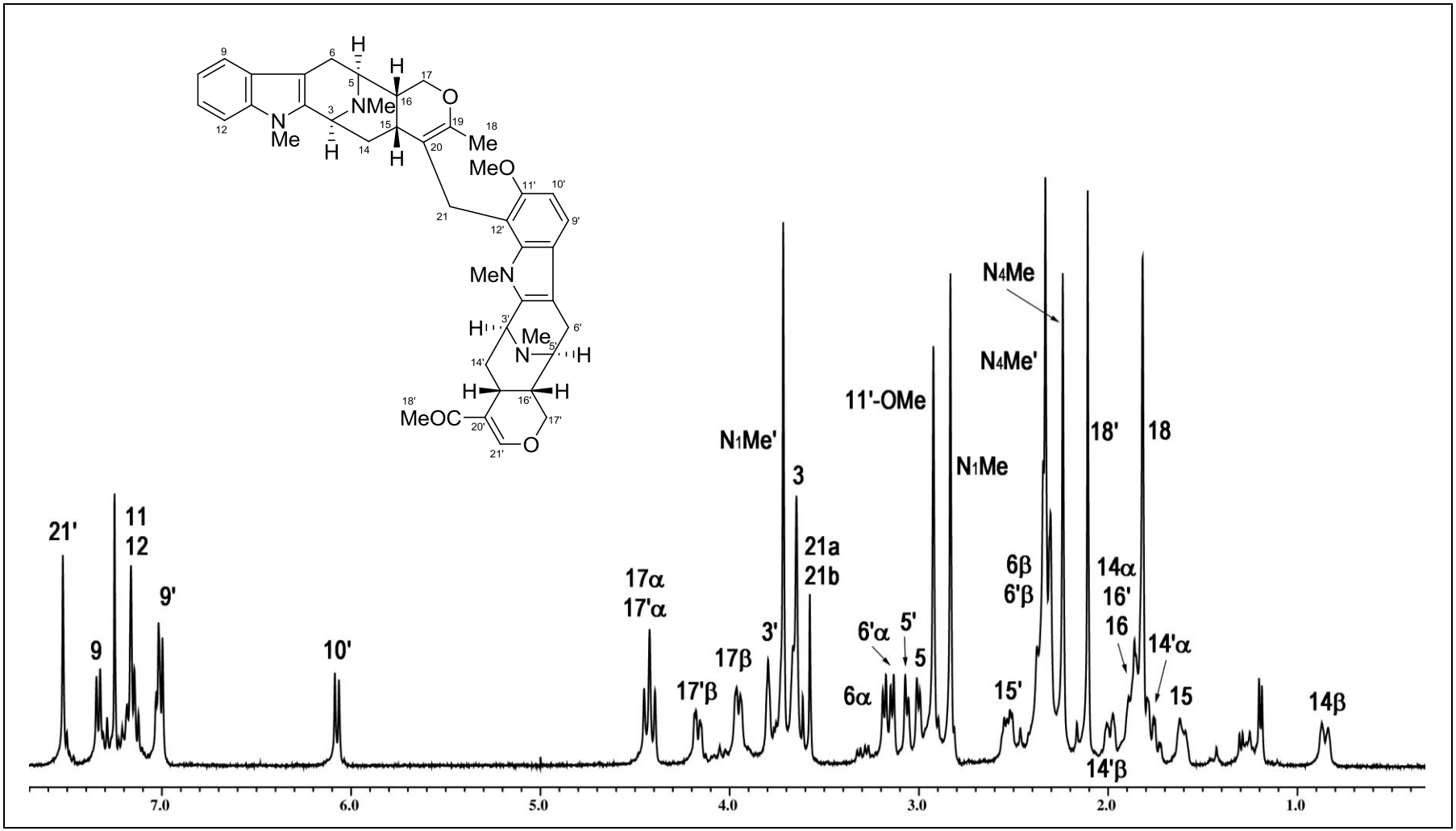


Figure 2.106: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Lumusidine D (**80**)

2.1.7.2.5 Perhentidine A (81)

Perhentidine A (**81**)[126] was obtained as a light yellowish oil with $[\alpha]^{25}_{D}$ –77 (*c* 0.40, $CHCl_3$). The IR spectrum showed bands at 3400, 1702, 1648 and 1617 cm^{-1}, due to the presence of OH, ketone carbonyl, and an α,β-unsaturated carbonyl group, respectively, while the UV spectrum showed absorption maxima at 231 and 286 nm, consistent with the presence of indole chromophores. The ESIMS of **81** showed a $[M + H]^+$ peak at *m/z* 705, which analyzed for $C_{43}H_{52}N_4O_5$ + H. The ^{13}C NMR spectrum (Table 2.57) showed a total of 43 resonances, comprising seven methyl, seven methylene, 16 methine, and 13 quaternary carbon atoms, in agreement with the molecular formula. The quaternary carbon resonance at δ_C 212.9 is consistent with the presence of a ketone carbonyl, while the other quaternary carbon resonance at δ_C 195.2 and the associated olefinic carbon signals at δ_C 121.0 and 157.2, are consistent with the presence of an α,β-unsaturated carbonyl group. The unusually low field resonance of the β-carbon at δ_C 157.2 indicated oxygen substitution. In addition, two oxymethylene carbons were observed at δ_C 66.8 and 67.6, the former due to a hydroxymethyl group as shown by acetylation, which yielded an acetate derivative (**81a**).

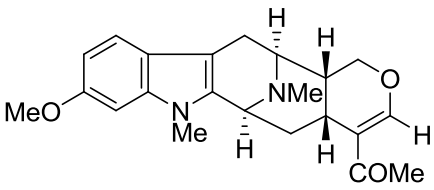
The ^1H NMR spectrum (Table 2.56; Figure 2.110) showed the presence of four aromatic hydrogens (δ_H 7.16–7.56) associated with an unsubstituted indole moiety, a pair of AB doublets at δ_H 6.75 and 7.22 associated with another indole moiety substituted at positions 11' and 12', a vinylic singlet at δ_H 7.49 associated with a trisubstituted double bond, a total of seven methyl singlets, corresponding to two N1-Me (δ_H 3.58, 3.69), two N4-Me (δ_H 2.36, 2.37), two acetyl methyls (δ_H 1.55, 2.06), and an aromatic methoxy substituent (δ_H 3.83, 11'-OMe). Since only six aromatic hydrogens were observed and both indolic nitrogens are substituted, it is reasonable to conclude that the bisindole is

branched from one of the aromatic carbon atoms of one monomer, with the adjacent position occupied by the methoxy substituent. The aromatic doublet at δ_H 7.22 was assigned to H-9' from its NOE with H-6', while the placement of the methoxy substituent at C-11' was confirmed by the observed NOE between H-10' (δ_H 6.75) and 11'-OMe (δ_H 3.83). These assignments were further supported by the observed three-bond correlations from H-9' to C-7' and C-13', and from H-9' and 11'-OMe to C-11' in the HMBC spectrum (Figure 2.107). These observations indicated position 12' as the site of branching of the bisindole from this monomeric unit.

The remaining part of this macroline half can be assembled with the help of the 2-D NMR data. The COSY spectrum revealed a $NCHCH_2CHCHCH_2O$ fragment, which corresponds to the N-4'–C-3'–C-14'–C-15'–C-16'–C-17'–O unit of the lower macroline half. The observed three-bond correlations from the vinylic H-21' (which is associated with the acetyl group forming the α,β-unsaturated carbonyl chromophore) to C-17' and C-15' in the HMBC spectrum indicated that the lower macroline half corresponds to a type-B macroline[118] (a 12'-substituted alstophylline (**7**))[118,158,164] which was in agreement with the NMR data.

The other unit of the bisindole, after discounting the signals due to the substituted alstophylline (**7**) half, corresponded to that of another macroline derivative with an unsubstituted indole moiety. The oxymethylene C-17 hydrogens were observed as two doublet of doublets at δ_H 3.88 and 3.91 (δ_C 66.8). This oxymethylene constitutes part of a primary alcohol function as shown by acetylation (δ_H 4.15 and 4.53; δ_C 63.7). The 18-methyl (acetyl) singlet was observed at δ_H 1.55 with the C-19 ketone carbonyl observed at δ_C 212.9. An additional methine corresponding to C-20 was observed at δ_C 55.5 (δ_H 3.26), which was linked to C-19 from the observed three-bond correlations from 18-Me to C-20. These features are suggestive of a *seco*-macroline (with an opened ring E) such as alstomicine (**109**),[177] which was also in agreement with the COSY spectrum which

showed the presence of an $NCHCH_2CH(CHCH_2)CHCH_2O$ partial structure. The branching of the bisindole from this upper *seco*-macroline unit must be from this methine C-20. Connection from C-20 of the upper macroline unit to C-12' of the lower half was mediated via a methylene bridge (C-21), as shown by the observed H-21 to C-11', C-13', and C-19 three-bond correlations in the HMBC spectrum (Figure 2.107). The structure of perhentidine A (**81**) indicated that it is a regioisomer of the previously encountered *Alstonia* bisindole, perhentinine (**83**).[123]



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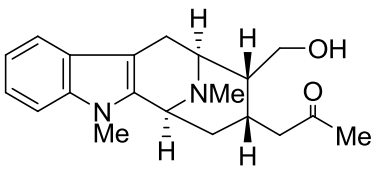
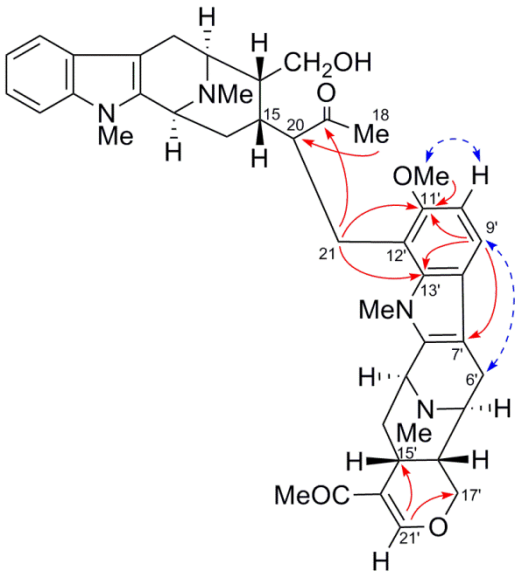


109



(= HMBC; = NOE)

Figure 2.107: Selected HMBCs and NOEs of **81**

2.1.7.2.6 Perhentidine B (82)

Perhentidine B (**82**)[126] was isolated as a light yellowish oil with $[\alpha]^{25}_{D}$ –38 (*c* 0.52, $CHCl_3$). The UV (234 and 286 nm) and IR (3392, 1707, 1653 and 1618 cm^{-1}) spectra were similar to those of **81**, suggesting the presence of similar functionalities. The ESIMS of **82** showed a $[M + H]^+$ peak at *m/z* 705, which also analyzed for $C_{43}H_{52}N_4O_5$ + H, indicating that **82** and **81** are isomers.

Inspection of the ^1H and ^{13}C NMR data (Tables 2.58 and 2.59; Figure 2.112) of **82** indicated a general similarity with those of **81**, showing the presence of an unsubstituted indole moiety (δ_H 7.14-7.56), another indole moiety substituted at C-11' and C-12' (a pair of AB doublets at δ 6.76 and 7.20; NOE: H-9'/H-6', H-10'/11'-OMe), a vinylic singlet at δ_H 7.48 associated with a trisubstituted double bond, an α,β-unsaturated ketone moiety (δ_C 195.6, 121.2, and 157.9; δ_H 2.05), a ketone carbonyl (δ_C 214.7), a hydroxylmethyl group (δ_C 66.1; δ_H 4.09 and 4.49; acetylation yielded an acetate derivative **82a**), and seven methyl singlets, corresponding to two N1-Me, two N4-Me, two acetyl methyls, and an aromatic methoxy group. The ^1H and ^{13}C NMR data of **82** are generally similar to those of **81** except for differences in the chemical shifts of C-15, C-18, C-19 and C-20 in the ^{13}C NMR spectrum, and H-14β, H-17, and H-20, in the ^1H NMR spectrum. The NMR data therefore indicated that **82** was also a bisindole of the macroline-macroline type incorporating the same two constituent halves as in **81**.

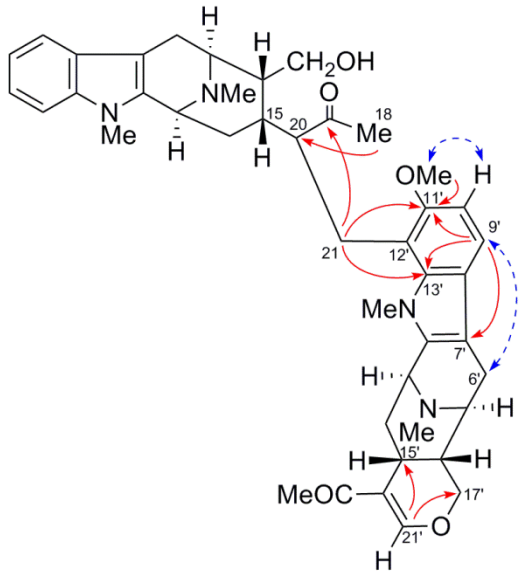
The COSY and HSQC data of **82** disclosed the same partial fragments as in those of **81**. In addition, the HMBC data of **82** (Figure 2.108), showed the same key three-bond correlations (H-21 to C-11', C-13' and C-19) as those of **81**, indicating similar branching of the bisindole from C-12' of the lower macroline half to C-20 of the upper half, the C-20 connection being mediated by the C-21 methylene bridge. Based on the above

observations, it can be concluded that perhentidine B (**82**) is the C-20 epimer of perhentidine A (**81**).

The remaining issue concerns the assignment of relative configuration of C-20 in **81** and **82**. Examination of the ^{1}H NMR data of perhentidines A (**81**) and B (**82**) showed that the signals of H-20 in both compounds were observed as multiplets (Tables 2.56 and 2.58; Figures 2.110 and 2.112). Furthermore the signal of one of the C-21 hydrogens in perhentidine A (**81**) and of both the C-21 hydrogens in perhentidine B (**82**), were also observed as multiplets. In the case of the acetate derivatives of both compounds (**81a** and **82a**) however, the signals for H-20 and H-21 were clearly resolved (Tables 2.56 and 2.58; Figures 2.111 and 2.113). The signal due to H-20 in perhentidine A acetate (**81a**) was seen as a triplet of doublets at δ_H 2.99 with J = 10.7 and 3.8 Hz (i.e., $J_{20\text{-}21a} = J_{15\text{-}20}$ = 10.7, $J_{20\text{-}21b}$ = 3.8 Hz). The signal of one of the hydrogens on C-21 was observed as a doublet of doublets at δ_H 2.83 ($J_{21a\text{-}21b}$ = 14 Hz, $J_{20\text{-}21a}$ = 10.7 Hz). The large coupling constant of 10.7 Hz due to the coupling between H-20 and H-21a, suggested that the conformation adopted about the C-21–C-20 bond was one that places the two vicinal hydrogens at C-21 and C-20 *anti* (*trans*-diaxial) to one another. The preferred *anti* conformation was likely due to the presence of three bulky groups, two on C-20, and one on C-21, which resulted in steric hindrance to free rotation about the C-20–C-21 bond. The observation that H-20 is *trans*-diaxial to H-21a, coupled with the observed NOE interactions between H-21a and H-15; H-20 and H-14, H-21b; H-21b and H-14; 18-Me and H-17, H-20 (Figure 2.109) allowed the configuration at C-20 in the acetate derivative **81a**, and therefore in perhentidine A (**81**) as well, to be assigned as 20*S*.

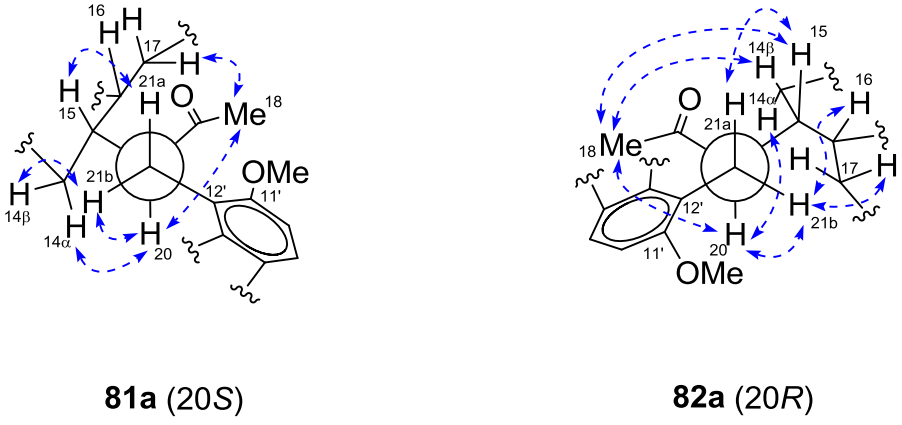
In the case of perhentidine B acetate (**82a**), the signal due to H-20 was also seen as a triplet of doublets at δ_H 3.23 with J = 11 and 5 Hz. The observed H-20–H-21a coupling of 11 Hz, indicated a *trans*-diaxial disposition of the two hydrogens as before in the case of perhentidine A acetate (**81a**). In this instance however, the definitive NOEs,

which allowed the assignment of the configuration at C-20, were different from those observed in **81a**. Thus, in the case of perhentidine B acetate (**82a**), NOEs were observed between H-20 and H-14, H-21b; H-21a and H-15; H-21b and H-16, H-17; H-18 and H-14, H-15, H-20 (Figure 2.109). These NOEs are consistent with the assignment of the C-20 configuration in **82a** (and **82**) as 20*R*.



(↷ = HMBC; ⇢ = NOE)

Figure 2.108: Selected HMBCs and NOEs of **82**



81a (20*S*) **82a** (20*R*)

Figure 2.109: Selected NOEs of **81a** and **82a**

Table 2.56: ^{1}H NMR Spectroscopic Data for Perhentidine A (**81**) and *O*-Acetylperhentidine A (**81a**)[a]

H	81	81a	H	81	81a
3	4.14 m	4.03 m	3'	3.80 m	3.79 m
5	3.48 d (7.6)	3.25 m	5'	3.05 d (7)	3.05 m
6β	2.57 d (17)	2.50 m	6'α	2.40 m	2.40 d (16)
6α	3.29 m	3.25 m	6'β	3.23 dd (17, 7)	3.23 m
9	7.56 d (7.5)	7.57 d (8)	9'	7.22 d (8.6)	7.23 d (8.5)
10	7.16 t (7.5)	7.15 t (8)	10'	6.75 d (8.6)	6.76 d (8.5)
11	7.26 m	7.23 t (8)	14'α	1.75 td (12, 4)	1.74 m
12	7.36 d (7.5)	7.34 d (8)	14'β	2.01 m	1.98 m
14β	2.01 m	1.94 m	15'	2.50 m	2.48 m
14α	2.46 m	1.94 m	16'	1.84 m	1.84 m
15	2.27 m	2.25 m	17'β	4.14 m	4.13 dd (11.5, 3.5)
16	1.66 m	1.94 m	17'α	4.39 t (11)	4.39 t (11.5)
17β	3.88 dd (11, 2)	4.15 dd (11, 3.5)	18'	2.06 s	2.06 s
17α	3.91 dd (11, 2)	4.53 dd (11, 9)	21'	7.49 s	7.49 s
18	1.55 s	1.59 s	N(1')-Me	3.58 s	3.48 s
20	3.26 m	2.99 td (10.7, 3.8)	N(4')-Me	2.37[b] s	2.27 s
21a	2.92 dd (13, 10.5)	2.83 dd (14, 10.7)	11'-OMe	3.83 s	3.85
21b	3.26 m	3.17 dd (14, 3.8)			
N(1)-Me	3.69 s	3.66 s			
N(4)-Me	2.36[b] s	2.35 s			
OCOMe		2.03 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b] Assignments are interchangeable

Table 2.57: ^{13}C NMR Spectroscopic Data for Perhentidine A (**81**) and *O*-Acetylperhentidine A (**81a**)[a]

C	81	81a	C	81	81a
2	132.8	133.6	2'	133.5	133.8
3	53.2	53.5	3'	53.9	53.9
5	59.5	54.6	5'	54.6	54.6
6	22.1	21.7	6'	22.5	22.5
7	106.1	107.0	7'	105.8	105.8
8	126.4	126.7	8'	122.9	122.9
9	118.4	118.4	9'	116.0	116.1
10	118.9	118.8	10'	104.8	104.7
11	121.0	120.7	11'	153.6	153.5
12	108.8	108.8	12'	110.9	110.9
13	137.1	137.0	13'	136.3	136.3
14	32.2	30.3	14'	32.2	32.2[c]
15	31.5	30.8	15'	22.7	22.7
16	42.6	43.0	16'	38.4	38.4
17	66.8	63.7	17'	67.6	67.7
18	31.8	32.2[c]	18'	24.9	25.0
19	212.9	212.8	19'	195.2	195.3
20	55.5	54.8	20'	121.0	121.0
21	26.0	26.2	21'	157.2	157.2
N(1)-Me	29.1	29.1	N(1)-Me'	32.3	32.2[c]
N(4)-Me	41.3[b]	41.9	N(4)-Me'	41.9[b]	42.1
OCO*Me*	–	21.2	11'-OMe	56.7	56.6
O*C*OMe	–	171.3			

[a] $CDCl_3$, 100 MHz; assignments based on COSY, HMQC, and HMBC. [b–c] Assignments are interchangeable.

Table 2.58: ^{1}H NMR Spectroscopic Data for Perhentidine B (**82**) and *O*-Acetylperhentidine B (**82a**)[a]

H	82	82a	H	82	82a
3	3.98 m	3.88 m	3'	3.72 m	3.72 m
5	3.63 m	3.44 m	5'	3.01 m	3.01 m
6β	2.58 d (17)	2.52 m	6'α	2.34 m	2.35 d (16)
6α	3.37 dd (17, 7)	3.35 dd (17, 8)	6'β	3.20 m	3.18 dd (16, 7)
9	7.56 d (8)	7.58 d (7.5)	9'	7.20 d (8.6)	7.19 d (8.5)
10	7.14 m	7.14 t (7.5)	10'	6.76 d (8.6)	6.77 d (8.5)
11	7.22 m	7.22 t (7.5)	14'α	1.70 td (12.5, 3.5)	1.71 td (12, 3.5)
12	7.32 d (8)	7.31 d (7.5)	14'β	1.99 m	1.99 m
14β	1.48 m	1.32 m	15'	2.51 m	2.50 m
14α	2.26 m	1.81 m	16'	1.82 m	1.82 m
15	2.11 m	2.14 m	17'β	4.12 m	4.12 dd (11, 3)
16	1.88 m	2.21 m	17'α	4.37 t (11)	4.37 t (11)
17β	4.09 m	4.63 m	18'	2.05 s	2.06 s
17α	4.49 d (12)	4.63 m	21'	7.48 s	7.50 s
18	1.40 s	1.30 s	N(1)-Me'	3.53 s	3.52 s
20	3.55 m	3.23 td (11, 5)	N(4)-Me'	2.24 s	2.24 s
21a	3.05 m	3.04 m	11'-OMe	3.94 s	3.92 s
21b	3.17 m	3.32 dd (14, 5)			
N(1)-Me	3.57 s	3.55 s			
N(4)-Me	2.36 s	2.28 s			
OCOMe	–	2.16 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.59: ^{13}C NMR Spectroscopic Data for Perhentidine B (**82**) and *O*-Acetylperhentidine B (**82a**)[a]

C	82	82a	C	82	82a
2	132.9	133.6	2'	133.7	133.6
3	53.2	53.2	3'	53.9	53.8
5	59.6	53.3	5'	54.7	54.6
6	22.5	22.1	6'	22.77	22.7
7	106.1	106.7	7'	105.3	105.2
8	126.5	126.7	8'	123.3	123.2
9	118.2	118.0	9'	115.9	115.8
10	118.9	118.6	10'	104.3	104.5
11	121.1	120.7	11'	153.9	153.8
12	109.2	109.1	12'	110.2	110.0
13	137.4	137.2	13'	136.2	136.1
14	32.7	31.3	14'	32.1	32.0
15	32.4	31.6	15'	22.85	22.8
16	42.2	42.0	16'	38.6	38.5
17	66.1	62.6	17'	67.8	67.7
18	34.4	34.1	18'	25.1	25.0
19	214.7	214.1	19'	195.6	195.5
20	52.7	52.4	20'	121.2	121.1
21	26.3	25.6	21'	157.5	157.4
N(1)-Me	29.1	28.9	N(1)-Me'	32.5	32.4
N(4)-Me	41.4	41.9	N(4)-Me'	41.8	41.7
OCO*Me*	–	21.3	11'-OMe	56.7	56.6
O*C*OMe	–	171.6			

[a] $CDCl_3$, 100 MHz; assignments based on COSY, HMQC, and HMBC.

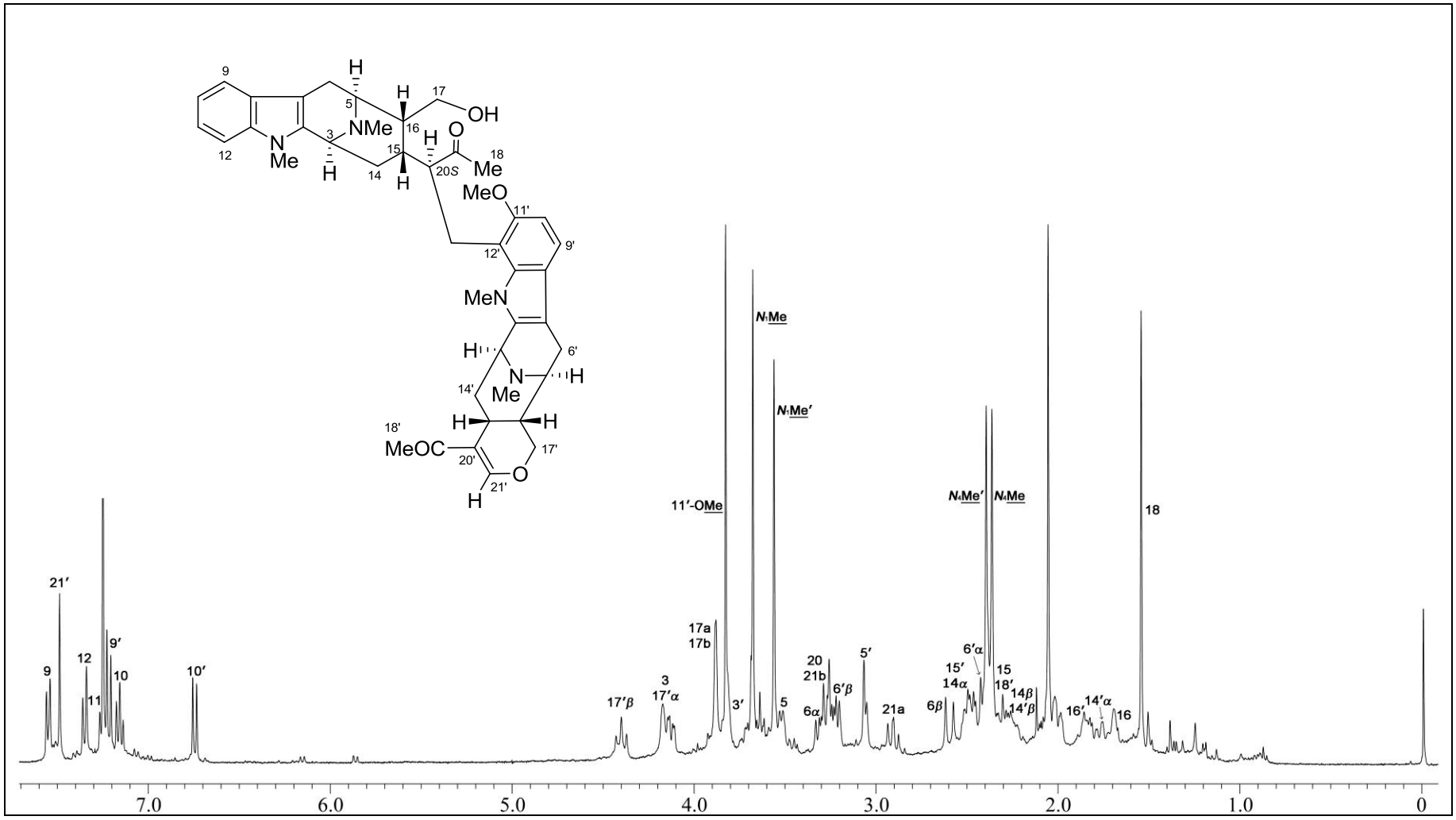


Figure 2.110: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Perhentidine A (**81**)

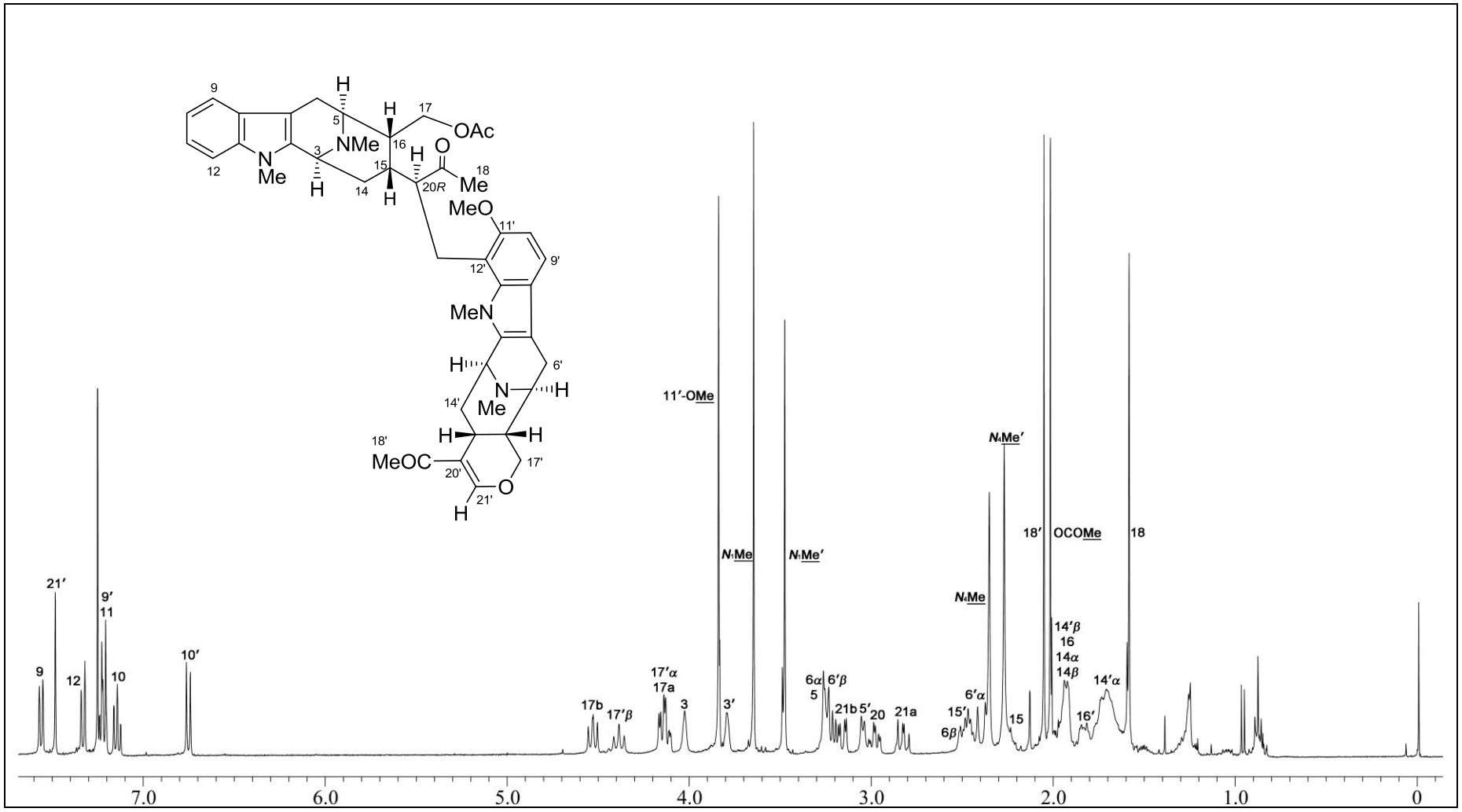


Figure 2.111: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *O*-Acetylperhentidine A (**81a**)

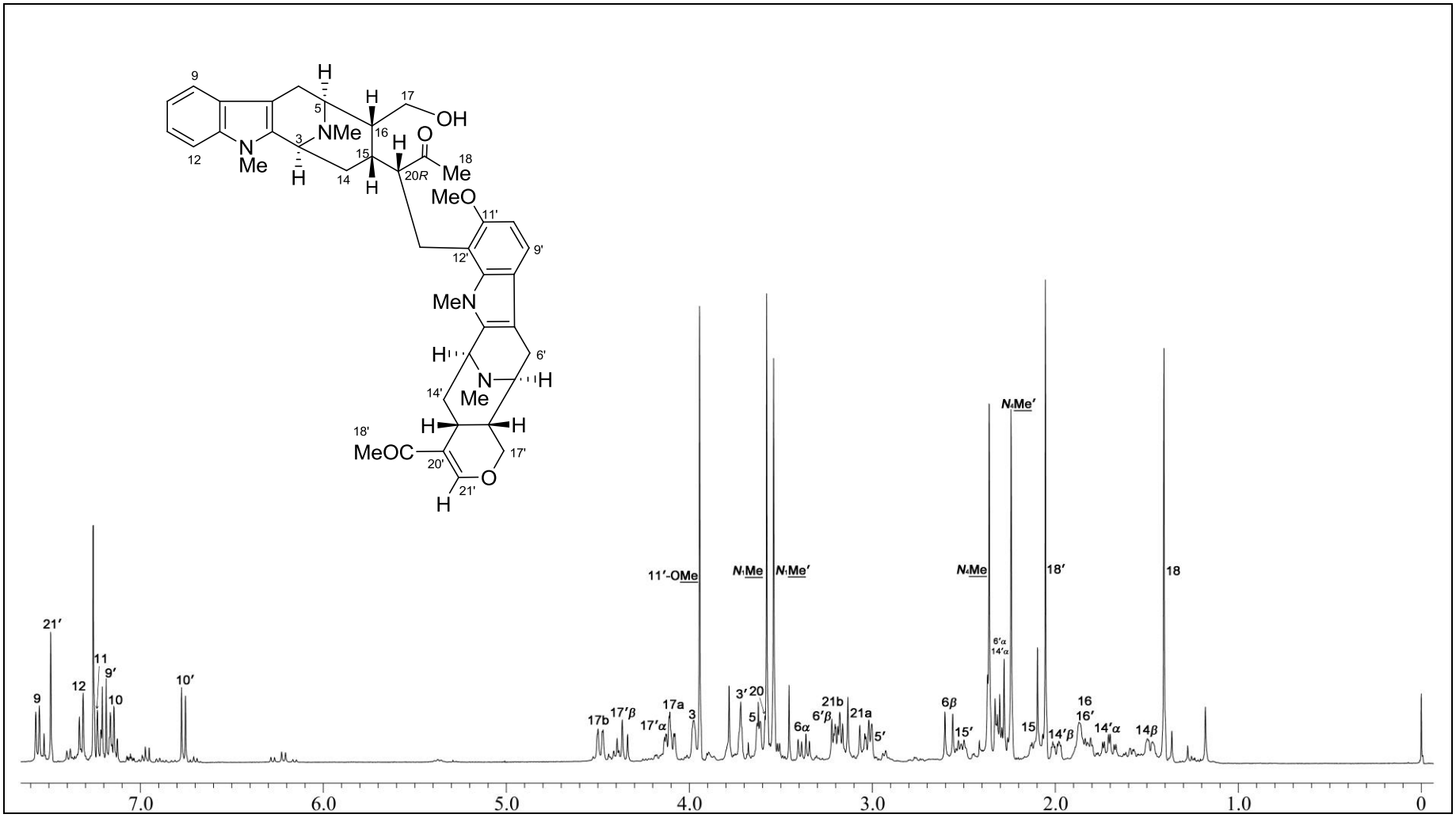


Figure 2.112: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Perhentidine B (**82**)

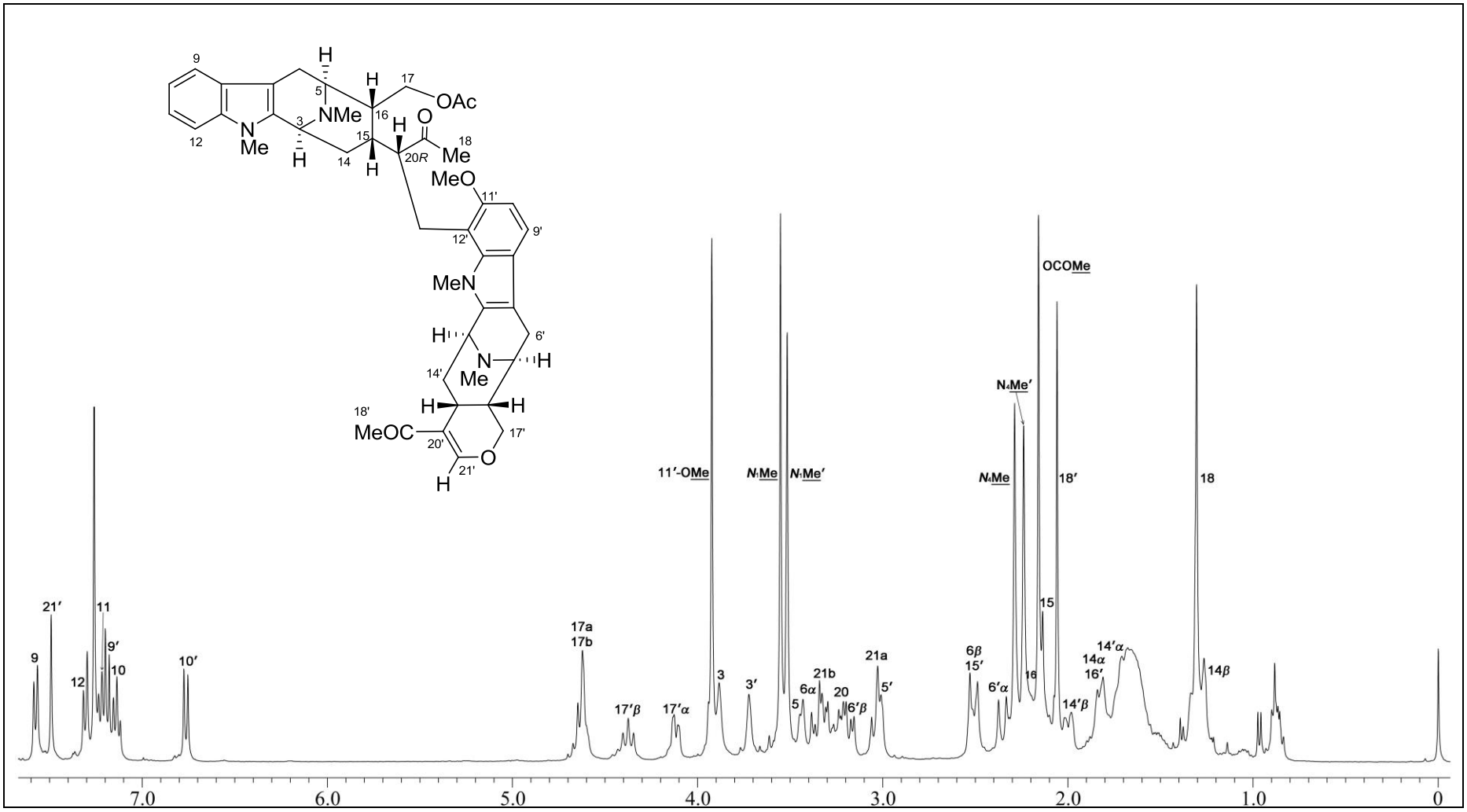


Figure 2.113: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of *O*-Acetylperhentidine B (**82a**)

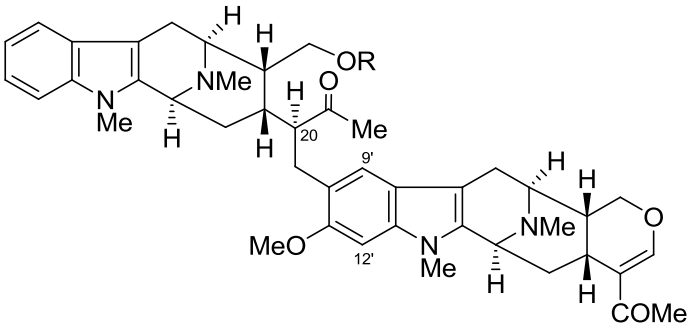
2.1.7.2.7 Perhentinine (83) and macralstonine (84)

Perhentinine (**83**)[123,126] was previously isolated by our group from the stem-bark of *A. macrophylla* which was collected from Terengganu. The structure of perhentinine (**83**) was established based on interpretation of the NMR (Tables 2.60 and 2.61; Figure 2.116) and MS data, which revealed a macroline-macroline type bisindole alkaloid, which was incorporating by a ring *E*-opened macroline (alstomicine) and a type-B macroline as the upper and lower units, respectively. The relative configurations at the various stereogenic centers were established by 2D NOESY experiments, except for the configuration of C-20, which was unable to obtained meaningful NOEs due to the overlapped of the key signals.

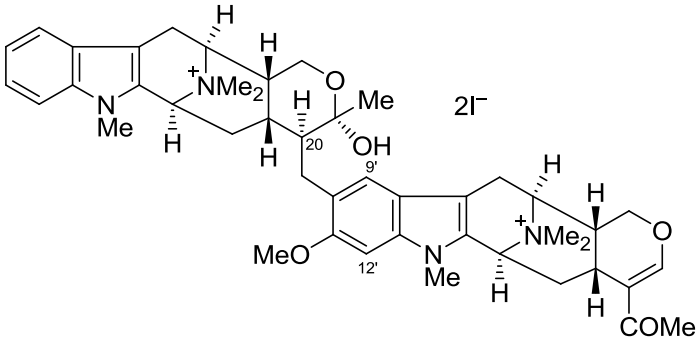
Repeated attempts to obtain crystals of perhentinine were singularly unsuccessful. Eventually it was found that in the case of perhentinine (**83**), treatment with excess MeI gave suitable crystals for X-ray diffraction analysis (X-ray analysis by Y. Y. Low), which revealed formation of the dimethyl diiodide salt of the ring-*E* cyclized (hemiketal) product (**83b**) (Figure 2.114), from which the absolute configuration at C-20 of the precursor *E*-*seco*-compound, perhentinine, could be established as *S*. This was also in agreement with the results of analysis of the coupling constants ($J_{20\text{-}21a}$ = 11.0, $J_{20\text{-}21b}$ = 3.5 Hz) and NOEs (H-21a/H-15; H-21b/H-14, H-20; 18-Me/H-17, H-20) of *O*-acetylperhentinine (**83a**), carried out in a similar manner as described for perhentidines A and B (**81** and **82**) (*vide supra*).

Since we have secured firm confirmation of the C-20 configuration of perhentinine by X-ray diffraction analysis of its cyclized or hemiketal derivative (in the form of its dimethyl diiodide salt, **83b**), it would be advantageous if the X-ray structure of a corresponding 20*R* bisindole alkaloid was also available to serve as a model compound for comparison. In the present series, perhentidine B (**82**) would constitute such a

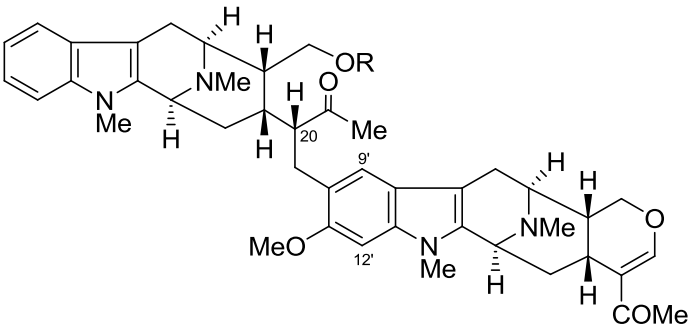
candidate. However, repeated attempts at crystallization (including treatment with MeI) proved fruitless. Another relevant bisindole candidate available from *A. macrophylla*, is macralstonine (**84**),[118,165,167] which has been previously investigated by Hesse and Schmid.[172] It has been observed that macralstonine exists as an equilibrium mixture of acyclic (ketone, **84a**) and cyclized (hemiketal, **84**) forms in $CHCl_3$ solution.[172] We have confirmed this by analysis of high-field NMR data (600 MHz) of macralstonine. Thus, in $CDCl_3$ solution, the ratio of acyclic to cyclized form was 2.32:1, while in CD_2Cl_2, it was 1.14:1, and in THF-d_8, it was virtually detected as the cyclized hemiketal form (**84**), albeit with poor solubility in this solvent. With the help of 2-D methods, the NMR data of the two forms could be distinguished (Tables 2.62 and 2.63; Figure 2.118). The *E*-*seco*-macralstonine (**84a**) could be trapped by conversion to its *O*-acetyl derivative **84b**,[172] in which case the NMR data of the pure *O*-acetyl-*E*-*seco*-macralstonine could be determined (Table 2.64). The relative configuration at C-20 in the *O*-methyl congener of macralstonine isolated from the Thai *A. macrophylla* was established as *R* based on its NOESY spectrum.[165,167] In the case of macralstonine, however, NOE was not feasible due to the observation of H-20 and H-21 as multiplets. In the case of the *O*-acetyl-*E*-*seco*-macralstonine derivative **84b**, H-20 was clearly seen as a triplet of doublets ($J_{20\text{-}21a}$ = 11.0, $J_{20\text{-}21b}$ = 4.0 Hz) and this, coupled with the observed NOEs (H-21a/H-15, H-9'; H-21b/H-16, H-17, H-9'), allowed assignment of the C-20 configuration as *R*. In the event, macralstonine crystallized wholly as the cyclized hemiketal form (**84**) from CH_2Cl_2-MeOH solution. X-ray analysis (X-ray analysis by Y. Y. Low) was therefore carried out and confirmed the 20*R* absolute configuration (Figure 2.115).



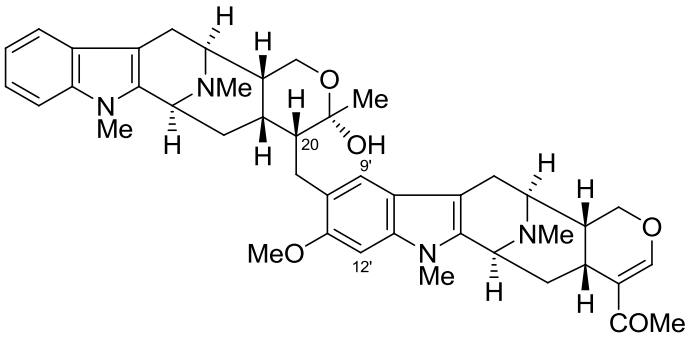
83 R = H, 20*S*
83a R = Ac, 20*S*



83b 20*S*



84a R = H, 20*R*
84b R = Ac, 20*R*



84 20*R*

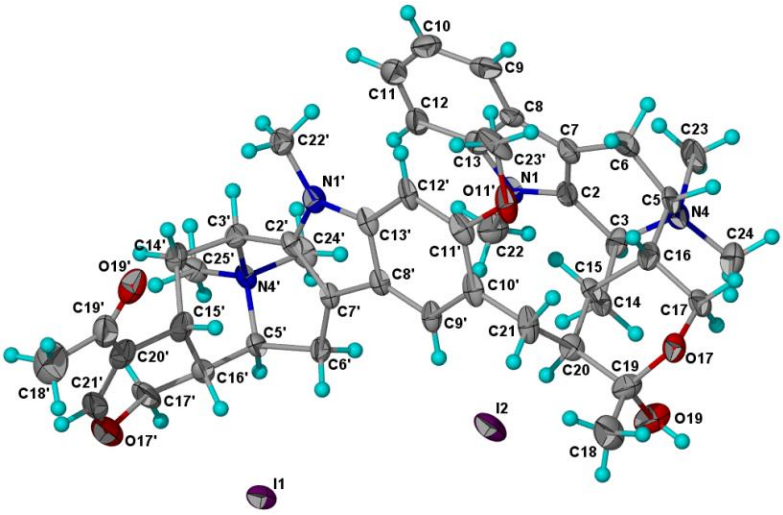


Figure 2.114**:** X-ray crystal structure of **83b.** [Flack parameter: *x* = –0.04(0.03)]

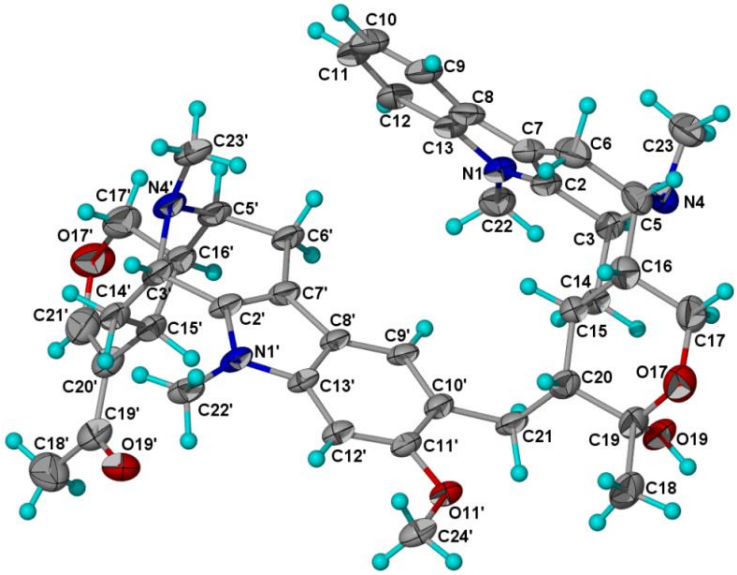


Figure 2.115: X-ray crystal structure of **84**. [Flack parameter: *x* = –0.1(0.4);

Hooft parameter: *y* = –0.30(0.14)]

Table 2.60: ^{1}H NMR Spectroscopic Data for Perhentinine (**83**) and *O*-Acetylperhentinine (**83a**)[a]

H	83	83a	H	83	83a
3	4.09 dd (4, 2)	4.00 m	3'	3.79 t (3)	3.80 br s
5	3.46 d (7)	3.26 m	5'	2.99 d (7)	3.02 d (7)
6β	2.54 m	2.44 d (17)	6'α	2.28 m	2.54 m
6α	3.32 m	3.14 dd (17, 7)	6'β	3.08 m	3.14 dd (16.5, 7)
9	7.52 d (8)	7.54 br d (7.5)	9'	6.90 s	6.87 s
10	7.13 td (8, 1)	7.13 td (7.5, 1)	12′	6.69 s	6.69 s
11	7.22 td (8, 1)	7.22 td (7.5, 1)	14'α	1.75 td (12, 3)	1.75 m
12	7.32 d (8)	7.32 br d (7.5)	14'β	2.04 m	2.06 m
14β	1.98 m	1.86 m	15'	2.54 m	2.53 dt (11.5, 6)
14α	2.41 m	1.86 m	16'	1.84 dt (11, 4)	1.88 m
15	2.14 m	2.14 m	17'β	4.13 ddd (11, 4, 1)	4.14 dd (11, 2)
16	1.57 m	1.88 m	17'α	4.37 t (11)	4.41 t (11)
17a	3.95 dd (11, 3)	4.28 dd (11, 3.5)	18'	2.05 s	2.07 s
17b	4.01 dd (11, 2)	4.58 t (11)	21'	7.51 s	7.51 s
18	1.72 s	1.71 s	N(1)-Me'	3.55 s	3.57 s
20	3.32 m	3.08 td (11, 3.5)	N(4)-Me'	2.25 s	2.30 s
21a	2.41 m	2.31 m	11'-OMe	3.87 s	3.88 s
21b	3.08 m	2.97 dd (13.5, 3.5)			
N(1)-Me	3.65 s	3.64 s			
N(4)-Me	2.34 s	2.28 s			
OCO*Me*	-	2.06 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.61: ^{13}C NMR Spectroscopic data for Perhentinine (**83**) and *O*-Acetylperhentinine (**83a**)[a]

C	**83**[b]	**83a**[c]	C	**83**[b]	**83a**[c]
2	132.9	133.8	2'	131.1	131.5
3	53.1	53.5	3'	53.7	53.8
5	59.2	54.2	5'	54.7	54.7
6	22.6	21.8	6'	22.0	22.8
7	105.9	106.8	7'	105.4	105.6
8	126.3	126.6	8'	120.1	119.2
9	118.2	118.3	9'	118.7	119.4
10	119.0	118.7	10'	119.1	118.7
11	120.9	120.7	11'	153.6	153.7
12	108.7	108.8	12'	91.3	91.4
13	137.0	137.0	13'	136.5	136.7
14	32.3	30.3	14'	32.4	32.4
15	31.5	31.3	15'	22.8	22.9
16	43.1	43.6	16'	38.3	38.4
17	66.5	63.5	17'	67.7	67.8
18	31.1	31.7	18'	24.9	25.4
19	213.2	213.1	19'	195.4	195.6
20	54.5	54.1	20'	120.8	121.1
21	32.0	33.2	21'	157.4	157.7
N(1)-Me	29.0	29.2	N(1)-Me'	28.9	29.0
N(4)-Me	41.7	42.1	N(4)-Me'	41.2	41.9
OCO*Me*	–	21.1	11'-OMe	55.5	55.6
O*C*OMe	–	171.4			

[a] $CDCl_3$; [b] 100 MHz; [c] 150 MHz; assignments are based on COSY, HSQC, and HMBC.

Table 2.62: ^{1}H NMR Spectroscopic Data for Macralstonine (**84**) and *E-Seco*-macralstonine (**84a**)[a,b]

H	84	84a	H	84	84a
3	3.95 m	4.00 m	3'	3.75 m	3.79 m
5	2.93 d (d)	3.59 m	5'	3.00 m	3.00 m
6	2.13 m	2.56 br d (17)	6'	2.33 m	2.35 m
	2.63 dd	3.35 dd		3.00 m	3.17 dd
	(17, 10)	(17, 7.5)			(16.5, 7)
9	7.33 (7.5)	7.51 d (7.5)	9'	6.74 s	6.90 s
10	7.00 m	7.12 t (7.5)	10'	–	–
11	7.09 m	7.21 t (7.5)	11'	–	–
12	7.09 m	7.30 d (7.5)	12'	6.40 s	6.69 s
14	1.87 m	1.44 br d (12)	14'	1.76 m	1.77 m
	2.86 td (13, 3.5)	2.35 m		2.01 m	2.01 m
15	1.77 m	2.01 m	15'	2.60 m	2.60 m
16	1.77 m	1.90 m	16'	1.87 m	1.87 m
17	3.49 m	4.12 dd (12, 3)	17'	4.19 dd (11, 3)	4.14 dd (12, 3)
	4.52 t (11.5)	4.43 d (12)		4.38 m	4.38 t (12)
18	1.51 s	1.68 s	18'	2.07 s	2.09 s
20	1.91 m	3.39 td (11, 4)	20'	–	–
21	2.43 m	2.39 m	21'	7.52 s	7.53 s
	3.06 dd (14, 3.5)	3.00 m		–	–
N(1)-Me	3.47 s	3.56 s	N(1)-Me'	3.50 s	3.59 s
N(4)-Me	2.28 s	2.38 s	N(4)-Me'	2.13 s	2.24 s
			11'-OMe	3.92 s	3.65 s

[a] $CDCl_3$, 600 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b] Since only partial low-field ^{1}H NMR data of macralstonine (**84**) were previously available (ref. 172) and the high-field NMR data (refs 118, 165, 167) require revision for some of the original assignments, the full ^{13}C and ^{1}H NMR data for **84** were included in Tables 2.61 and 2.62.

Table 2.63: ^{13}C NMR Spectroscopic Data for Macralstonine (**84**) and *E-Seco*-macralstonine (**84a**)[a]

C	84	84a	C	84	84a
2	133.3	132.6	2'	131.2	131.5
3	54.0	53.1	3'	53.76	53.8[b]
5	55.5	59.6	5'	54.7[d]	54.7[d]
6	22.7	22.4	6'	22.5	22.8
7	106.5	105.9	7'	105.1	105.6
8	126.45	126.36	8'	119.7	119.1
9	117.9	118.0	9'	118.8	119.5
10	118.4	118.9	10'	120.1	120.2[e]
11	120.2[e]	121.0	11'	153.9	153.8
12	108.5	109.0	12'	91.4	91.2
13	136.8	137.2	13'	136.1	136.6
14	26.9	33.0	14'	32.4	32.47[c]
15	25.9	32.3	15'	22.9[f]	22.9[f]
16	44.0	42.1	16'	38.5	38.4
17	61.4	66.2	17'	67.87	67.85
18	29.5	33.9	18'	25.0	25.1
19	99.0	214.5	19'	195.5	195.8
20	45.6	53.8[b]	20'	121.2[g]	121.2[g]
21	28.8	32.49[c]	21'	157.4	157.7
N(1)-Me	29.07	29.14	N(1)-Me'	28.7	29.04
N(4)-Me	41.69	41.4	N(4)-Me'	41.77	41.74
			11'-OMe	55.3	55.6

[a] $CDCl_3$, 150 MHz; assignments based on COSY, HMQC, HMBC, and NOESY. [b,d –g] Peaks are overlapped. [c]Assignments are interchangeable.

Table 2.64: ^{1}H and ^{13}C NMR Spectroscopic Data for *O*-Acetyl-*E*-*seco*-macralstonine (**85**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.4	2'	–	131.3
3	3.90 m	53.2	3'	3.81 m	53.9
5	3.43 d (6)	53.6	5'	3.03 m	54.7
6β	2.49 d (17)	22.1	6'β	2.39 m	22.9
6α	3.33 dd (17, 7)		6'α	3.17 m	
7	–	106.6	7'	–	105.5
8	–	126.5	8'	–	120.1
9	7.53 d (7.5)	118.0	9'	6.90 s	119.4
10	7.12 td (7.5, 1)	118.7	10'	–	119.0
11	7.19 td (7.5, 1)	120.8	11'	–	153.9
12	7.29 d (7.5)	109.0	12'	6.69 s	91.3
13	–	137.2	13'	–	136.7
14a	1.28 d (12)	31.5	14'a	1.78 m	32.4
14b	1.89 m		14'b	2.07 m	
15	2.03 m	31.5	15'	2.59 m	22.8
16	2.23 m	41.9	16'	1.89 m	38.4
17β	4.59 m	62.6	17'β	4.14 d (11)	67.8
17α	4.59 m		17'α	4.39 t (11)	
18	1.59 s	32.7	18'	2.09 s	25.1
19	–	213.9	19'	–	195.7
20	3.06 td (11, 4)	53.9	20'	–	121.1
21a	2.37 m	31.8	21'	7.54 s	157.6
21b	3.15 m		N(1)-Me'	3.57 s	29.0
N(1)-Me	3.55 s	29.1	N(4)-Me'	2.26 s	41.9
N(4)-Me	2.31 s	42.1	11-OMe'	3.91 s	55.5
OCO*Me*	2.15 s	21.3			
O*C*OMe	–	171.4			

[a] $CDCl_3$, 400 and 100 MHz, respectively; assignments based on COSY, HMQC, and HMBC.
[b-c] Assignments are interchangeable.

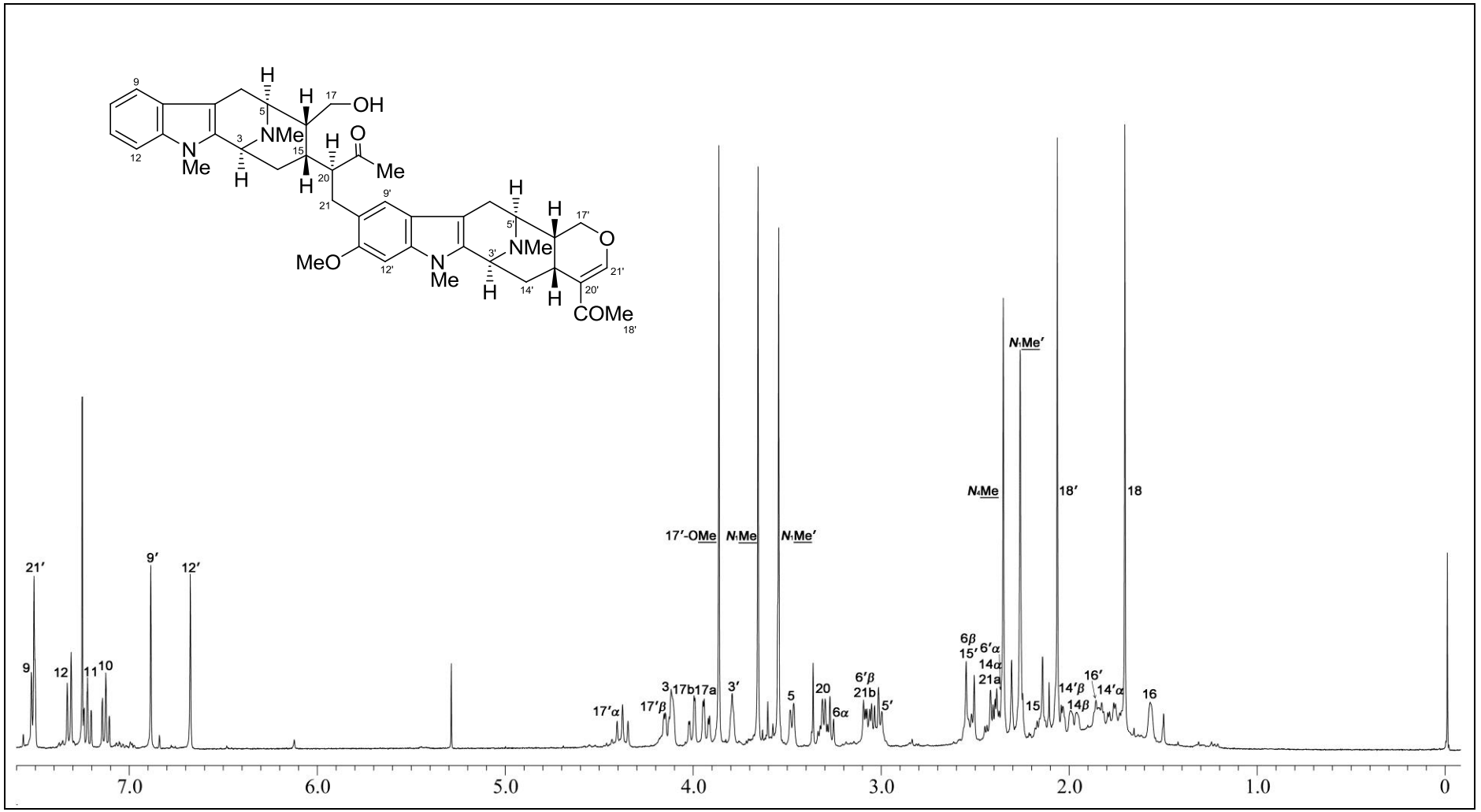


Figure 2.116: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Perhentinine (**83**)

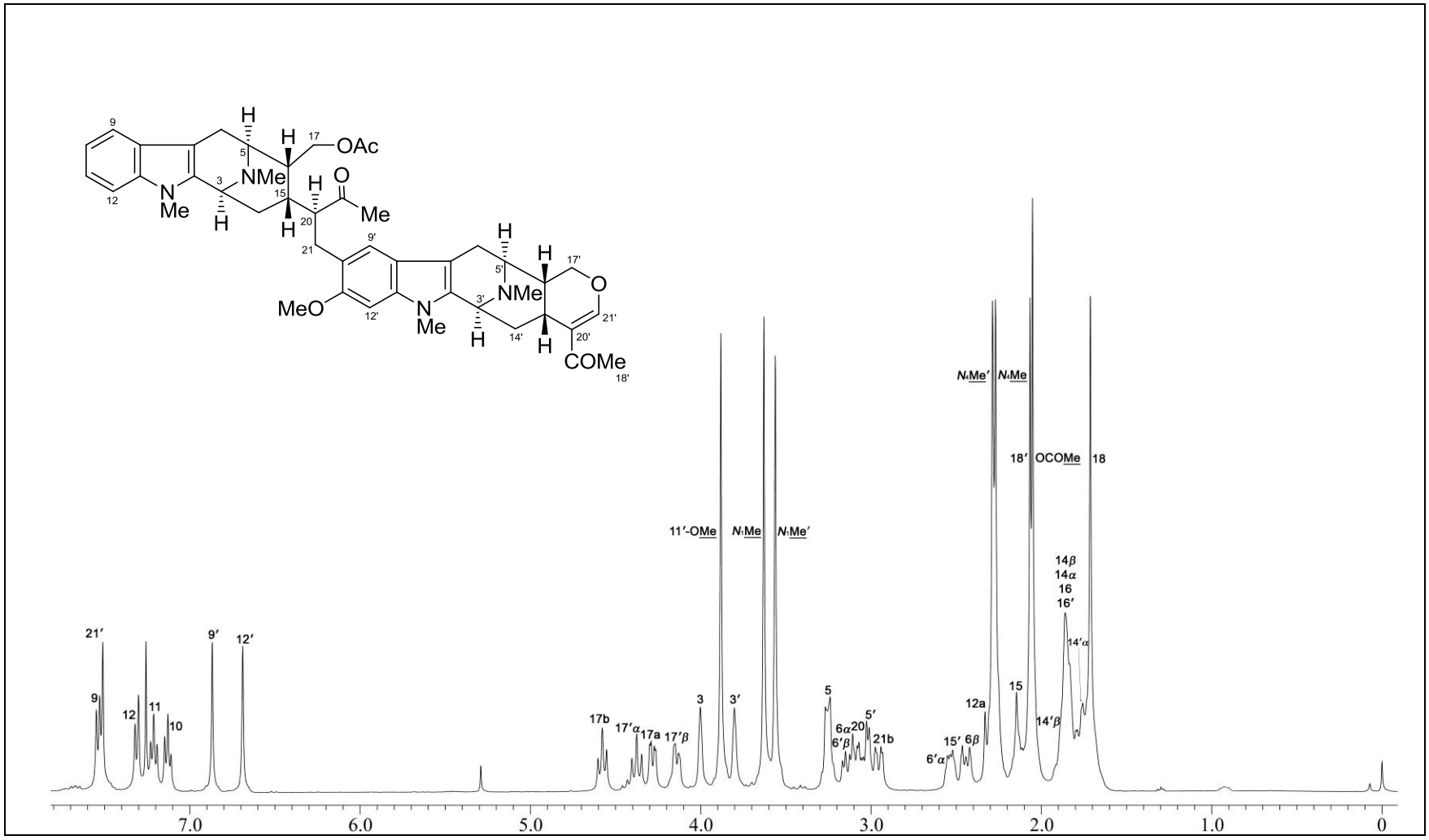


Figure 2.117: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of *O*-Acetylperhentinine (**83a**)

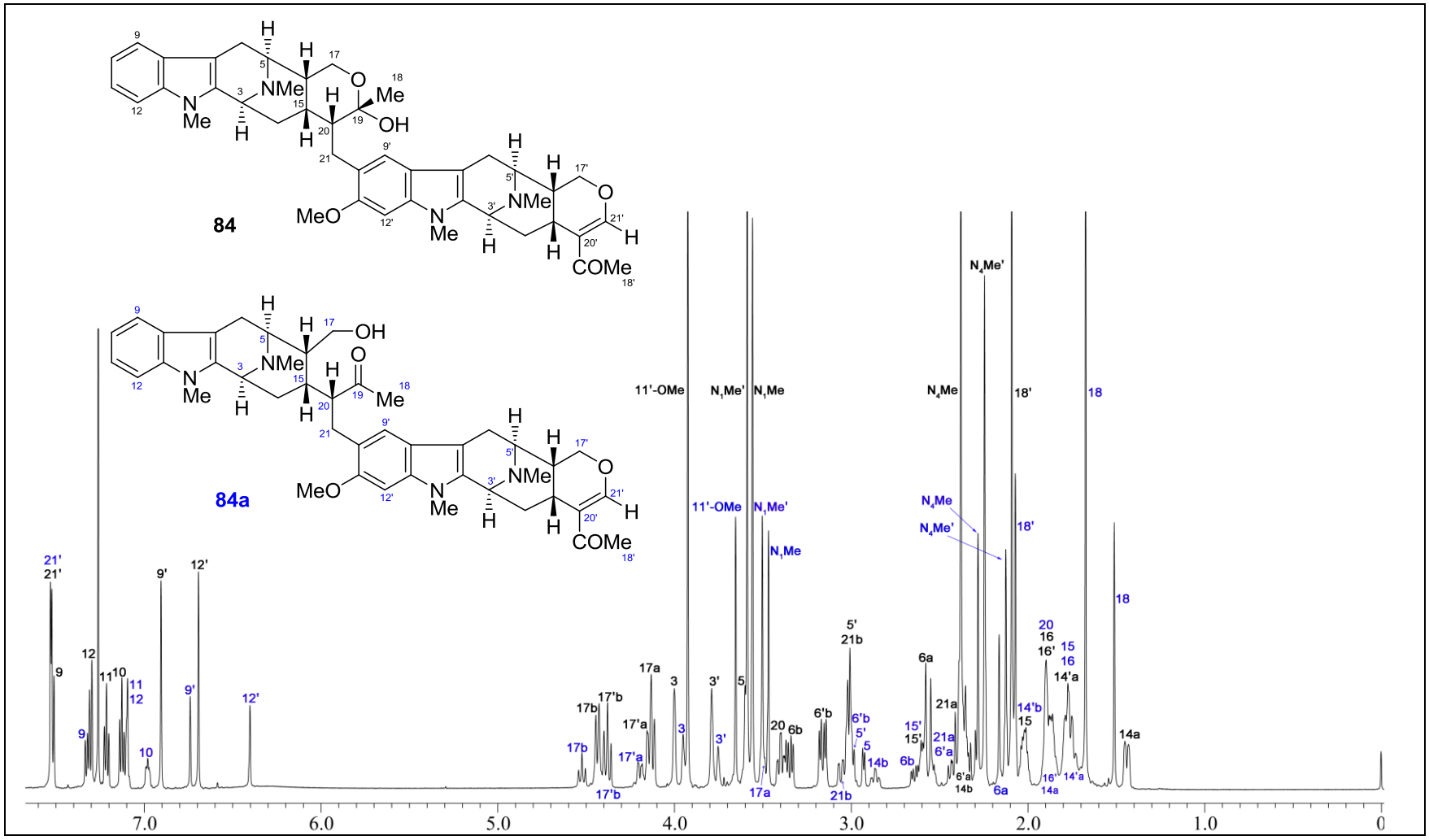


Figure 2.118: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of Macralstonine (**84**) and *E-Seco*macralstonine (**84a**)

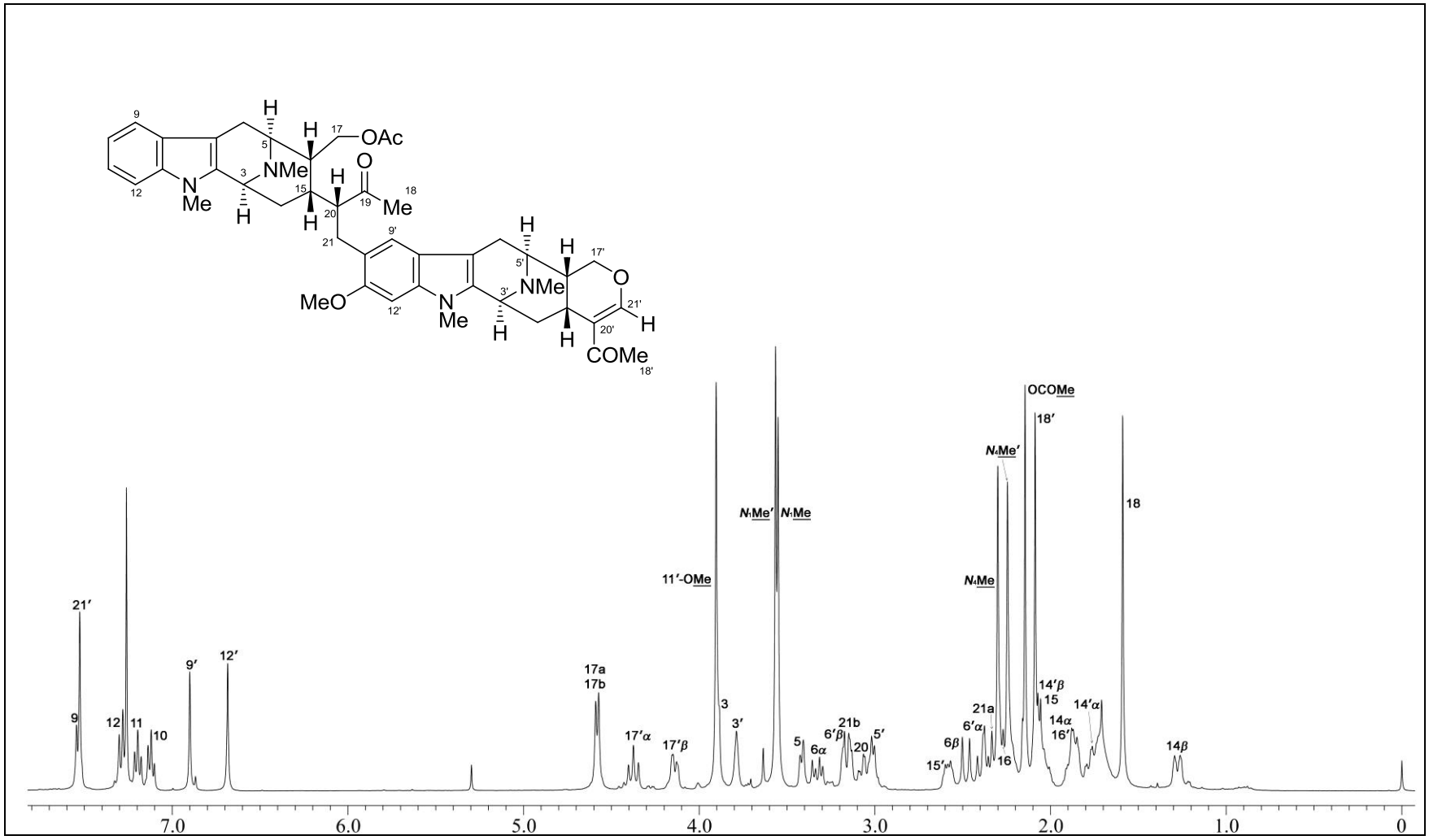


Figure 2.119: ^{1}H NMR Spectrum ($CDCl_3$, 600 MHz) of *O*-Acetyl-*E*-*seco*macralstonine (**84b**)

2.1.7.2.8 Anhydromacralstonine (85)

Another known macroline-macroline bisindole was also isolated from the stem-bark extract of *A. macrophylla*, viz. anhydromacralstonine (**85**).[158] The ^{1}H NMR spectrum of compound **85** is shown in Figure 2.120, while the ^{1}H and ^{13}C NMR data of compound **85** is summarized in Table 2.65, respectively. Other data are given in the Experimental Section.

Table 2.65: ^{1}H and ^{13}C NMR Spectroscopic Data for Anhydromacralstonine (**85**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	133.4	2'	–	131.0
3	3.85 m	53.9[b]	3'	3.85 m	54.0[b]
5	3.10 d (6.7)	55.5	5'	3.04 d (7)	54.8
6β	2.49 d (17)	23.0	6'β	2.19 d (17)	22.8
6α	3.24 dd (17, 6.7)		6'α	2.88 dd (17, 7)	
7	–	106.2	7'	–	105.5
8	–	126.7	8'	–	119.9
9	7.43 br d (7.7)	118.1	9'	6.87 s	117.4
10	7. 05 br t (7.7)	118.7	10'	–	121.5
11	7.16 br t (7.7)	120.6	11'	–	154.1
12	7.20 br d (7.7)	108.7	12'	6.52 s	91.3
13	–	137.0	13'		136.2
14a	1.77 m	33.0	14'a	1.77 m	32.5
14b	1.94 m		14'b	2.05 m	
15	2.01 m	27.7	15'	2.58 dt (12, 6)	23.0
16	2.05 m	40.9	16'	1.90 m	38.6
17β	3.97 dd (11, 2)	66.4	17'β	4.19 dd (11, 3)	67.9
17α	4.45 t (11)		17'α	4.37 t (11)	
18	1.82 s	17.0	18'	2.08 s	25.2
19	–	146.1	19'	–	195.6
20	–	107.9	20'	7.55 s	121.2
21a	3.19 m	30.9	21'	–	157.6
21b	3.19 m	29.0	N(1)-Me'	3.53 s	29.2
N(1)-Me	3.43 s	41.8[c]	N(4)-Me'	2.32 s	41.9[c]
N(4)-Me	2.27 s		11'-OMe	3.63 s	55.5

[a] $CDCl_3$, 400 and 100 MHz, respectively; assignments based on COSY, HMQC, and HMBC.
[b-c] Assignments are interchangeable.

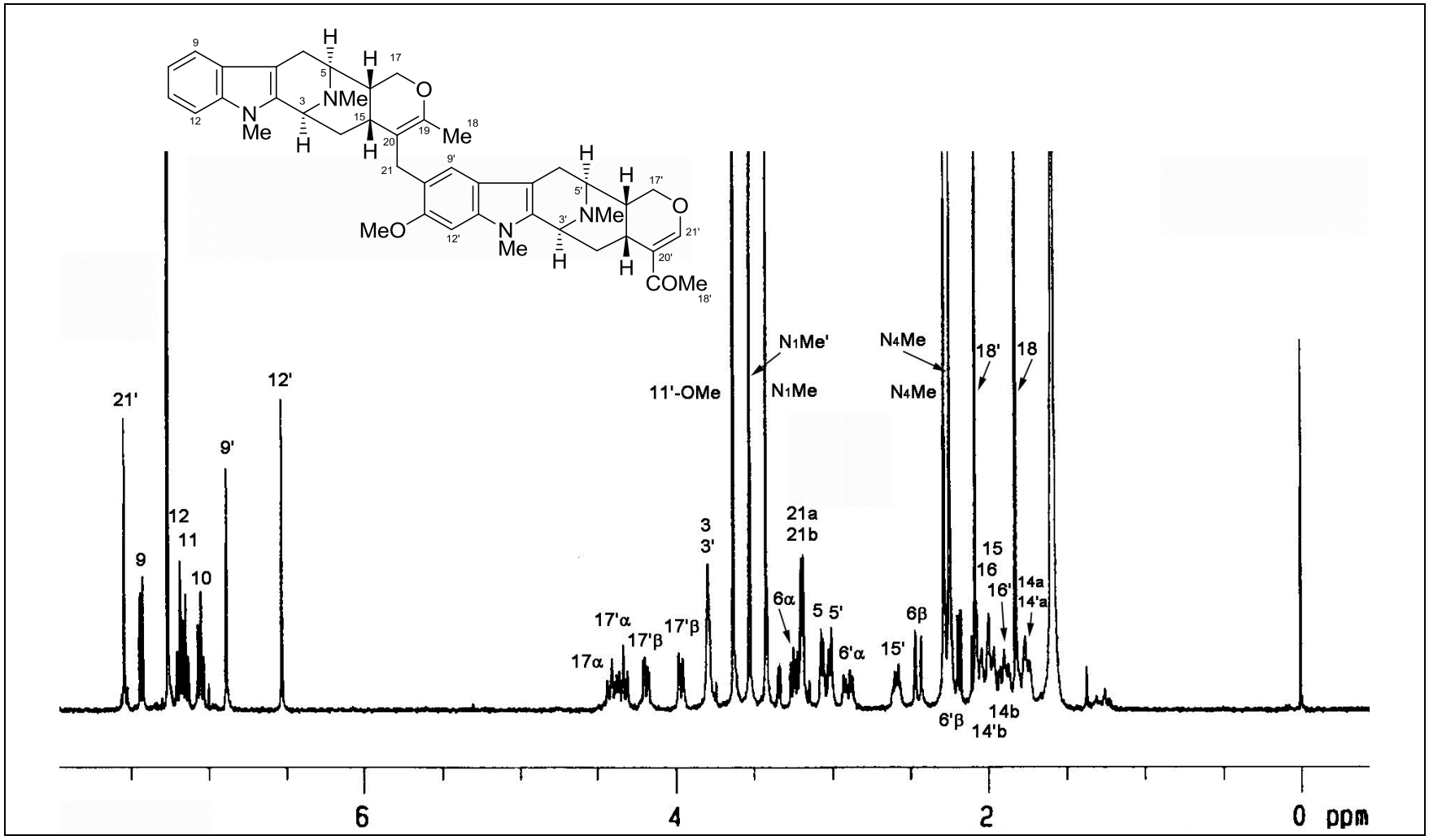


Figure 2.120: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Anhydromacralstonine (**85**)

2.1.7.3 Macroline-pleiocarpamine Bisindole Alkaloids

2.1.7.3.1 Villalstonidine B (86)

Villalstonidine B (**86**) was isolated as a colorless oil, $[\alpha]_D$ + 98 (*c* 0.45, $CHCl_3$). The UV spectrum showed absorption maxima at 230, 246 (shoulder), and 287 nm, showing the presence of superimposition of indole and indolic chromophores, while The IR spectrum showed the presence of OH (3388 cm^{-1}) and ester carbonyl (1747 cm^{-1}) functions. The ESIMS of **86** showed a $[M + H]^+$ peak at *m/z* 691, which analysed for $C_{42}H_{50}N_4O_5$ + H.

The ^{13}C NMR spectrum (Table 2.67) showed a total of 42 carbon signals, comprising five methyl, nine methylene, 16 methine, and 12 quaternary carbon atoms. The observed quaternary carbon resonances at δ 172.5 and 51.8, are due to the presence of an ester carbonyl group, while two downfield carbon signals at δ 136.0 (quaternary carbon) and 119.0 (methine) indicating the presence of the trisubstituted olefinic carbons. In addition, other two carbon signals were observed at δ 99.2 and 92.1, which are due to two quaternary carbons. The former is linked to two oxygen atoms, while the latter is linked to a nitrogen (N1') and an oxygen atom. Other signals observed include a quaternary carbon resonance at (δ_C 67.1) due to the attachment of a nitrogen atom (N1'), and two oxymethylene carbon signals at δ_C 65.8 (δ_H 3.94, and 3.70), and 64.5 (δ_H 4.34, and 4.16), where the latter one was associated with a primary alcohol function. The ^1H NMR spectrum (Table 2.66; Figure 2.125) of **86** showed signals due to eight aromatic hydrogens, corresponding to two unsubstituted indole moieties (δ 7.47–6.20), four methyl singlets corresponding to N1-Me (δ 3.55), N4-Me (δ 2.24), Me-18 (δ 1.29), and CO_2Me' (δ 3.51), an ethylidene (a methine quartet at δ 5.28 and a methyl doublets of doublets at δ 1.51), and a hydroxymethyl group (δ 4.34 and 4.16).

The COSY spectrum also disclosed partial structures, which are characteristic of a macroline skeleton, such as $NCHCH_2$, $NCHCH_2CHCHCH_2O$, and $CHCH_2$, corresponding to the C-5–C-6, C-3–C-14–C-15–C-16–C-17, and C-20–C-21 fragments, respectively. The second moiety constituting the bisindole was deduced to be a 2,7-substituted pleiocarpamine derivative, similar to the pleiocarpamine half of villalstonine (**88**),[118,175] from initial inspection of the NMR spectroscopic data. However, the ^{1}H and ^{13}C NMR data of **86** showed that the signals due to the H-16' signal in **88** were absent in **86** and have been replaced by a hydroxymethyl function (δ_C 67.1; δ_H 4.34 and 4.16). The presence of the hydroxymethyl function at C-16' was confirmed by the observed three-bond correlations from H-17'a, H-17'b to C-15' and CO_2Me, in the HMBC spectrum (Figure 2.121). Examination of the NMR spectroscopic data indicated that in common with villalstonine (**88**), branching from the pleiocarpamine moiety in **86** was from C-2' and C-7'. The connection from C-2' to C-19 of the macroline unit is mediated by an oxygen atom. This was consistent with the resonances of C-2' and C-19 which were observed at δ 99.2 and 92.1, respectively. The branching from C-7' of the pleiocarpamine moiety to the macroline unit via a methylene (C-21), was shown by the three-bond correlations from H-21 to C-15, C-19, C-2' and C-8'; and from H-6' to C-21, C-2'; in the HMBC spectrum (Figure 2.121). This was also consistent with the NOEs seen for H-21a/H-20, H-9', H-6'a (Figure 2.122). The observed reciprocal NOEs H-17'/H-15'; H-12'/CO_2Me' established the relative configuration of C-16' as *R*. The NMR data from 2D-NOESY also confirmed the various stereogenic centers in **86** which were same as those in villalstonine (**88**). Thus, villalstonidine B (**86**) is the 16'-hydroxymethyl derivative of villalstonine (**88**).

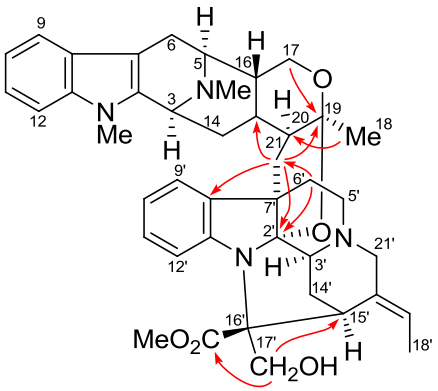


Figure 2.121: Selected HMBCs of **86**

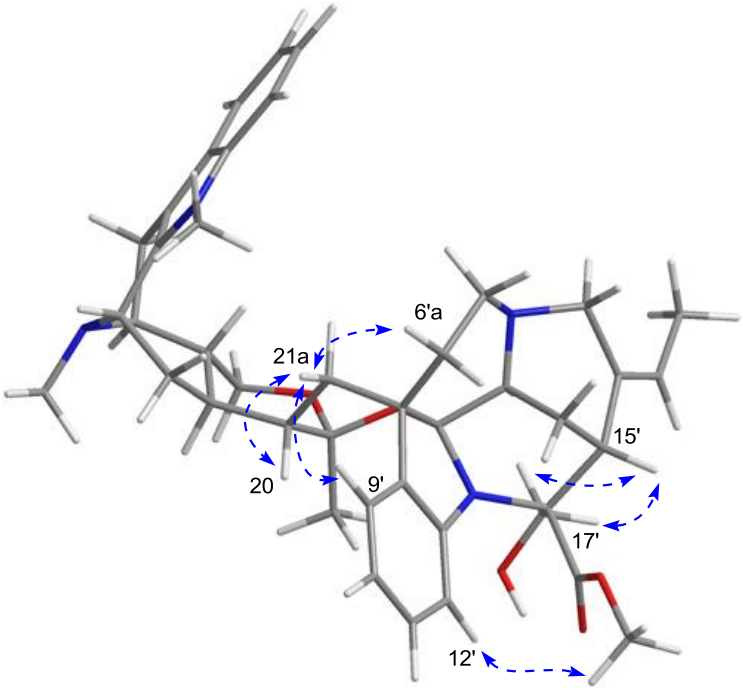


Figure 2.122: Selected NOEs of **86**

2.1.7.3.2 Villalstonidine F (87)

Villalstonidine F (**87**) was obtained as a light yellowish oil, $[\alpha]_D$ +40 (*c* 0.10, $CHCl_3$). The IR spectrum showed the presence of NH (3400 cm^{-1}) and ester carbonyl (1753 cm^{-1}) functions, while the UV spectrum (230, 251, 288, and 294 nm) can be considered as the result of superimposition of indole and indoline chromophores. The ESIMS of **87** showed a $[M + H]^+$ peak at *m/z* 647, which analyzed for $C_{40}H_{46}N_4O_4$ + H. The ^{13}C NMR spectrum (Table 2.67) showed a total of 40 resonances, comprising four methyl, eight methylene, 17 methine, and 11 quaternary carbon atoms. The ^1H and ^{13}C NMR data of **87** (Tables 2.66 and 2.67; Figure 2.126), indicated the presence of a pentacyclic macroline moiety (upper unit) with a saturated E ring incorporating a methyl-substituted ketalic carbon (C-19) and an adjacent methine. The usual fragments corresponding to a macroline indole were present, such as those corresponding to the N–C-5–C-6, N–C-3–C-14–C-15–C-16–C-17–O, and C-15–C-20–C-21 partial structures, in addition to the presence of four aromatic hydrogens (δ 7.15-7.55) of an unsubstituted indole moiety. Other groups present include an indolic NH (δ 7.84), an N4-Me (δ 2.31), an oxymethylene corresponding to C-17 (δ_C 65.7), and an isolated methyl (δ 1.23, C-18) attached to a quaternary carbon, which is linked to two oxygen atoms (δ_C 98.7, C-19).

The signals due to the other (lower) monomeric unit indicated the presence of another unsubstituted indole moiety (δ 6.14-6.98), a methyl ester group (δ 3.67; δ_C 171.2, 51.9), and an ethylidene side chain (δ 1.55, 5.38). In addition, a downfield resonance due to a quaternary carbon was observed at δ_C 92.0, indicating a quaternary carbon linked to a nitrogen (N-1') and an oxygen atom (C-2'). The ^1H NMR spectrum also showed a characteristic methine doublet at δ 4.43 (*J* 3.6 Hz, δ_C 57.8), reminiscent of the H-16 signal of pleiocarpamine (δ 5.21, *J* = 4 Hz; δ_C 61.6)[167] and of bisindoles incorporating

pleiocarpamine units, such as, for example, villalstonine (δ 4.42, *J* = 4 Hz; δ_C 57.7)[118,175] and bipleiophylline[125]. As with other bisindoles, incorporating a pleiocarpamine unit, branching of the bisindole is from C-7' and C-2' of the pleiocarpamine half to C-20 and C-19 respectively, of the upper macroline half. The connection between C-7' and C-20 is mediated by a methylene bridge (C-21), while that between C-2' and C-19 is via an oxygen. These conclusions are supported by the NMR, HMBC (Figure 2.123) and NOE (Figure 2.124) data. Villalstonidine F (**87**) is therefore the N1-demethyl derivative of villalstonine (**88**), which also occurs in the stem-bark extract.

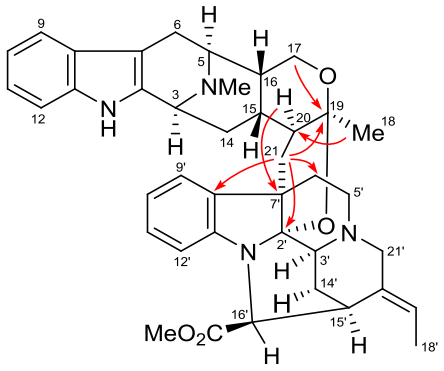


Figure 2.123: Selected HMBCs of **87**

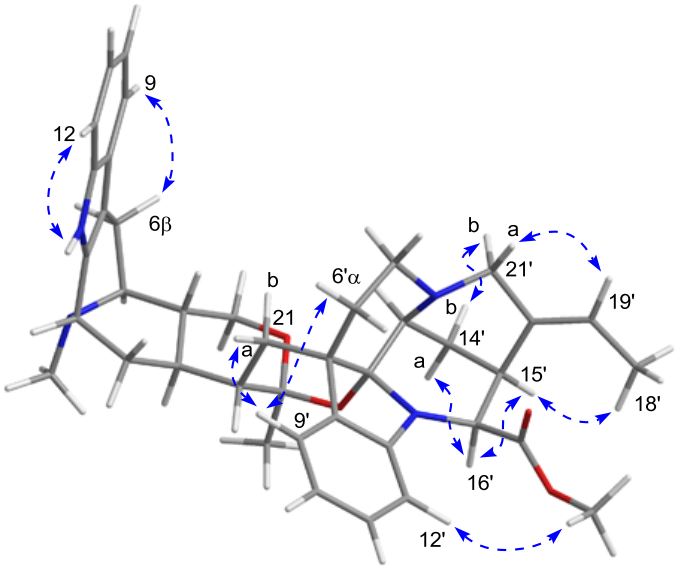


Figure 2.124: Selected NOEs of **87**

Table 2.66: ^{1}H NMR Spectroscopic Data for Villalstonidine B (**86**) and Villalstonidine F (**87**)[a]

Position	86	87	Position	86	87
3	3.80 m	3.77 m	3'	3.70 m	3.77 m
5	2.85 d (7)	2.90 m	5'β	2.58 dd (14, 4)	2.69 m
6β	2.40 d (16)	2.44 d (17)	5'α	3.06 td (14, 2)	3.14 m
6α	3.23 dd (16, 7)	3.28 dd (17, 6.5)	6'a	1.06 br d (14)	1.16 m
9	7.47 br d (8)	7.53 d (8)	6'b	1.83 td (14, 4)	2.00 m
10	7.07 td (8, 1)	7.16 t (8)	9'	6.82 br d (7.5)	6.85 d (7.5)
11	7.16 td (8, 1)	7.18 t (8)	10'	6.63 br t (7.5)	6.69 t (7.5)
12	7.26 br d (8)	7.35 d (8)	11'	6.91 td (7.5, 1)	6.98 t (7.5)
14β	1.38 ddd (13, 5, 2)	1.47 m	12'	6.20 br d (7.5)	6.14 d (7.5)
14α	2.36 m	2.35 m	14'a	1.55 m	1.73 m
15	1.58 m	1.60 m	14'b	2.81 m	2.69 br d (13)
16	2.04 dt (12, 5)	2.06 m	15'	3.22 m	3.21 m
17β	3.70 m	3.71 m	16'	–	4.43 d (3.6)
17α	3.94 t (12)	3.97 t (11)	17'a	4.16 dd (12, 6)	–
18	1.29 s	1.23 s	17'b	4.34 dd (12, 7)	–
19	–	1.16 m	18'	1.51 dd (7, 2)	1.55 d (7)
20	1.19 m	1.55 m	19'	5.28 br q (7)	5.38 q (6.6)
21a	1.55 m	2.35 m	21'a	2.80 d (13)	2.97 br d (12)
21b	2.38 m	2.35 m	21'b	4.00 br d (13)	4.22 br d (12)
N(1)-Me	3.55 s	–	17'-OH	3.70 m	–
N(4)-Me	2.24 s	2.31 s	CO_2Me'	3.51 s	3.67 s
N(1)-H	–	7.84 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

Table 2.67: ^{13}C NMR Spectroscopic Data for Villalstonidine B (**86**) and Villalstonidine F (**87**)[a]

Position	86	87	Position	86	87
2	132.8	131.8	2'	92.1	92.0
3	53.3	54.8	3'	51.4	51.9
5	54.3	54.5	5'	47.1	47.4
6	22.8	23.0	6'	32.0	31.3
7	106.6	107.7	7'	44.6	44.1
8	126.4	127.1	8'	134.8	135.7
9	118.1	118.2	9'	120.7	120.9
10	118.8	119.5	10'	118.4	118.7
11	120.9	121.5	11'	126.3	126.7
12	108.7	110.9	12'	111.1	109.5
13	137.0	135.7	13'	145.6	146.9
14	32.5	33.2	14'	25.5	27.3
15	31.8	32.1	15'	33.8	32.3
16	37.7	38.0	16'	67.1	57.8
17	65.8	65.7	17′	64.5	–
18	26.6	26.6	18'	12.4	12.4
19	99.2	98.7	19'	119.0	119.5
20	36.5	36.8	20'	136.0	135.7
21	28.6	28.6	21'	51.9	53.0
N(1)-Me	29.0	–	CO_2Me'	51.8	51.9
N(4)-Me	41.8	41.7	CO_2Me'	172.5	171.2

[a] $CDCl_3$, 400 MHz; assignments based on COSY, HMQC, HMBC, and NOESY.

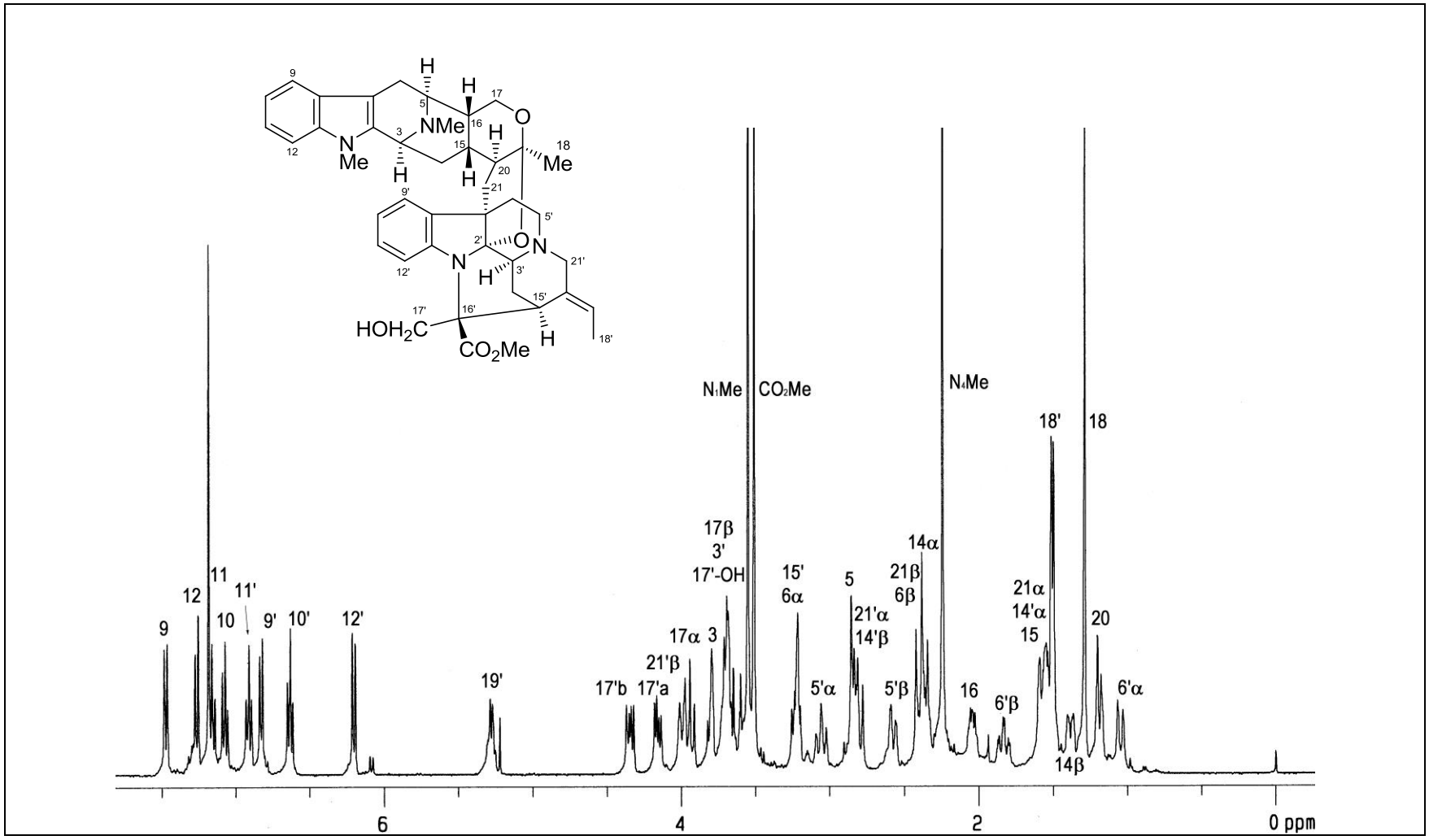


Figure 2.125: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Villalstonidine B (**86**)

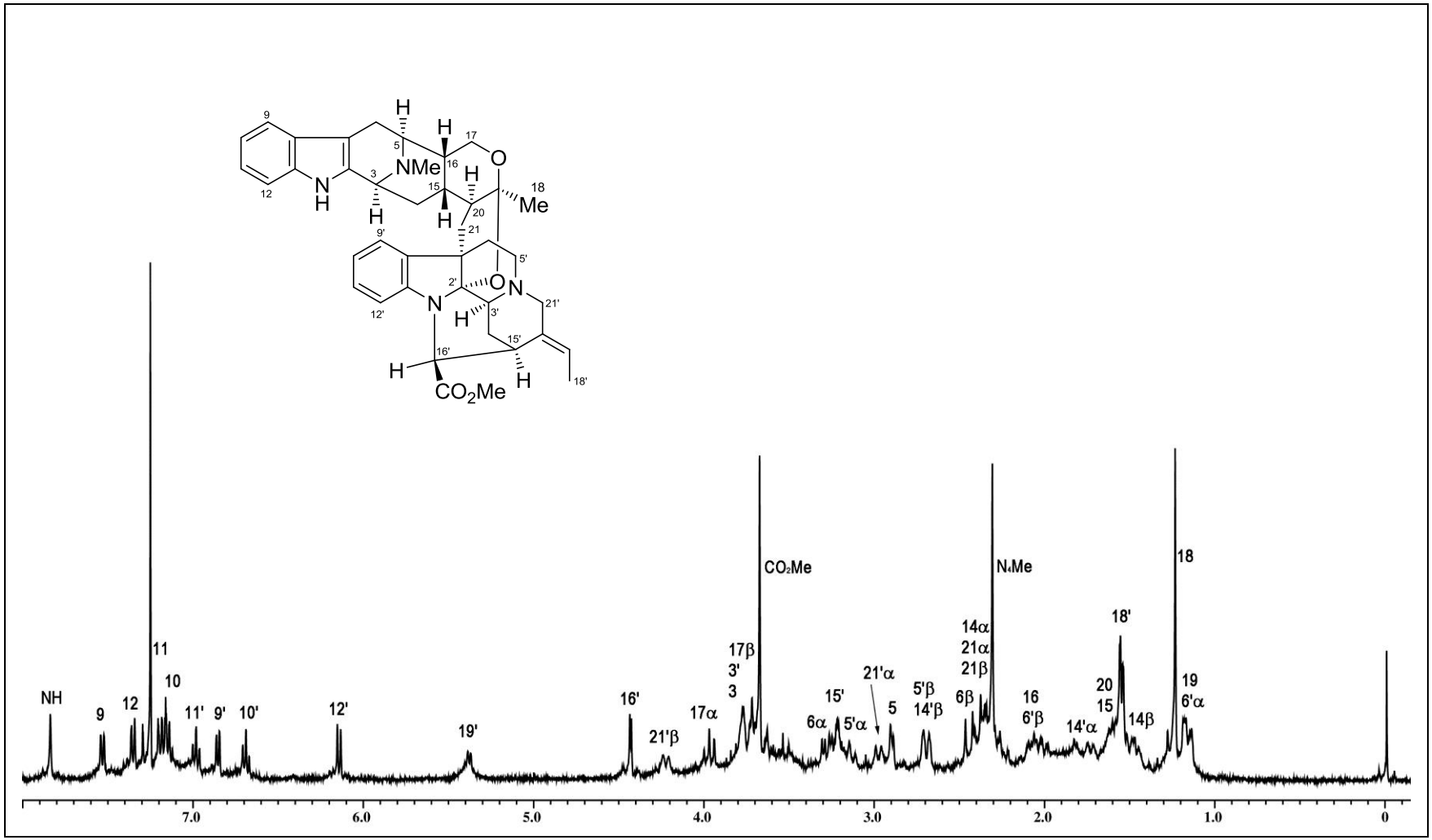


Figure 2.126: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Villalstonidine F (**87**)

2.1.7.3.3 Villalstonine (88), Villalstonine *N*(4)-oxide (89), and Macrocarpamine (90)

Other known macroline-pleiocarpamine bisindole alkaloids, which were isolated in the present study are villalstonine (**88**),[118,123,128,148,169,174,175,184] villalstonine *N*(4)-oxide (**89**),[118,166] and macrocarpamine (**90**).[128,166,169] The ^{1}H NMR spectra of these three compounds are shown in Figures 2.127–2.129, while the ^{1}H and ^{13}C NMR data of compounds **88**–**89** and **90** are summarized in Tables 2.68–2.70, respectively. Other data are given in the Experimental Section.

Table 2.68: ^{1}H NMR Spectroscopic Data for Villalstonine (**88**) and Villalstonine *N*(4)-oxide (**89**)[a]

Position	88	89	Position	88	89
3	3.86 t (3)	3.86 m	3'	3.73 m	4.26 m
5	2.91 br d (7)	2.91 d (7)	5'	2.69 m	3.35 m
6	2.47 d (16)	2.41 m	5'	3.12 td (14, 2)	3.62 m
6	3.29 dd (16, 7)	3.30 m	6'	1.11 br d (14)	1.64 m
9	7.55 br d (8)	7.55 br d (8)	6'	2.03 td (14, 4)	1.88 td (16, 5)
10	7.15 br t (8)	7.15 br t (8)	9'	6.88 br d (8)	6.92 d (8)
11	7.23 br t (8)	7.23 td (8, 1)	10'	6.99 br t (8)	6.77 t (8)
12	7.34 br d (8)	7.33 br d (8)	11'	6.70 br t (8)	7.04 dt (8, 1)
14	1.44 dt (13, 3)	1.43 m	12'	6.15 br d (8)	6.17 d (8)
14	2.42 m	2.41 m	14'	1.68 dt (12, 3)	2.57 br d (14)
15	1.60 m	1.60 m	14'	2.69 m	2.82 dt (14, 3)
16	2.09 m	2.08 dt (12, 5)	15'	3.22 br d (3)	3.27 br d (3)
17	3.73 m	3.75 dd (12, 5)	16'	4.42 d (4)	4.44 d (3.7)
17	4.00 t (11)	3.96 t (12)	18'	1.55 d (7)	1.62 dd (7, 2)
18	1.25 s	1.27 s	19'	5.36 q (7)	5.49 q (7)
20	1.16 dd (12, 3)	1.20 dd (14, 5)	21'	2.92 d (12)	3.30 m
21	1.60 m	1.64 m	21'	4.19 br d (12)	5.01 br d (13)
21	2.42 m	2.37 m	CO_2Me'	3.68 s	3.70 s
N(1)-Me	3.62 s	3.61 s			
N(4)-Me	2.31 s	2.31 s			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

Table 2.69: ^{13}C NMR Spectroscopic Data for Villalstonine (**88**) and Villalstonine *N*(4)-oxide (**89**)[a]

C	88	89	C	88	89
2	135.8	132.7	2'	92.1	93.1
3	53.4	53.4	3'	51.7	67.1
5	54.4	54.3	5'	47.4	64.2
6	22.8	23.1	6'	31.2	34.5
7	106.6	106.8	7'	44.1	42.9
8	126.4	126.5	8'	132.8	133.6
9	118.3	118.4	9'	120.7	121.5
10	120.8	119.0	10'	118.1	119.8
11	118.3	121.1	11'	126.4	127.5
12	108.7	108.8	12'	109.2	110.2
13	136.9	137.0	13'	146.9	146.0
14	32.4	32.6	14'	27.4	21.7
15	32.3	31.8	15'	31.7	31.4
16	37.8	37.6	16'	57.7	57.7
17	65.6	65.6	18'	12.4	12.8
18	26.5	26.4	19'	118.2	125.0
19	98.5	99.1	20'	136.1	130.1
20	36.7	36.5	21'	52.9	67.8
21	28.4	28.0	CO_2Me'	51.6	52.1
N(1)-Me	29.0	29.1	CO_2Me'	171.3	170.3
N(4)-Me	41.7	41.9			

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

Table 2.70: ^{1}H and ^{13}C NMR Spectroscopic Data for Macrocarpamine (**90**)[a]

Position	δ_H	δ_C	Position	δ_H	δ_C
2	–	132.9	2'	–	66.7
3	3.79 br t (3.4)	53.8	3'	2.86 m	54.3
5	2.97 d (7)	54.9	5'	2.86 m	49.9
6β	2.39 d (16)	22.6	5'	2.86 m	
6α	3.20 dd (16, 7)		6'	1.39 m	21.4
7	–	106.6	6'	1.71 m	
8	–	126.4	7'	2.53 dd (11, 8)	45.6
9	7.37 br d (7.5)	117.9	8'	–	133.6
10	7. 03 td (7.5, 1)	118.9	9'	6.83 br d (7.5)	123.2
11	7.15 td (7.5, 1)	120.9	10'	6.44 td (7.5, 1)	117.6
12	7.29 br d (7.5)	108.8	11'	6.72 td (7.5, 1)	126.6
13	–	137.1	12'	5.77 br d (7.5)	107.8
14	1.79 m	32.3	13'	–	147.2
14	1.79 m		14'	1.62 dt (14, 4)	29.3
15	1.98 m	23.7	14'	2.02 dt (14, 4)	
16	1.84 dt (12, 4)	38.9	15'	3.07 m	32.0
17β	3.88 dd (11, 3)	66.8	16'	4.10 br d (4)	58.1
17α	4.19 t (11)		18'	1.48 dd (7, 2)	12.2
18	4.50 d (16)	125.5	19'	5.29 qd (7, 2)	118.5
19	5.37 d (16)	127.3	20'	–	135.7
20	–	115.6	21'	4.25 dt (13, 2)	52.8
21	6.19 s	144.5	21'	2.86 m	
N(1)-Me	3.61 s	29.1	CO_2*Me*'	3.63 s	51.7
N(4)-Me	2.25 s	41.8	*C*O_2Me'	–	170.5

[a] $CDCl_3$, 400 MHz; assignments based on COSY, and HMQC.

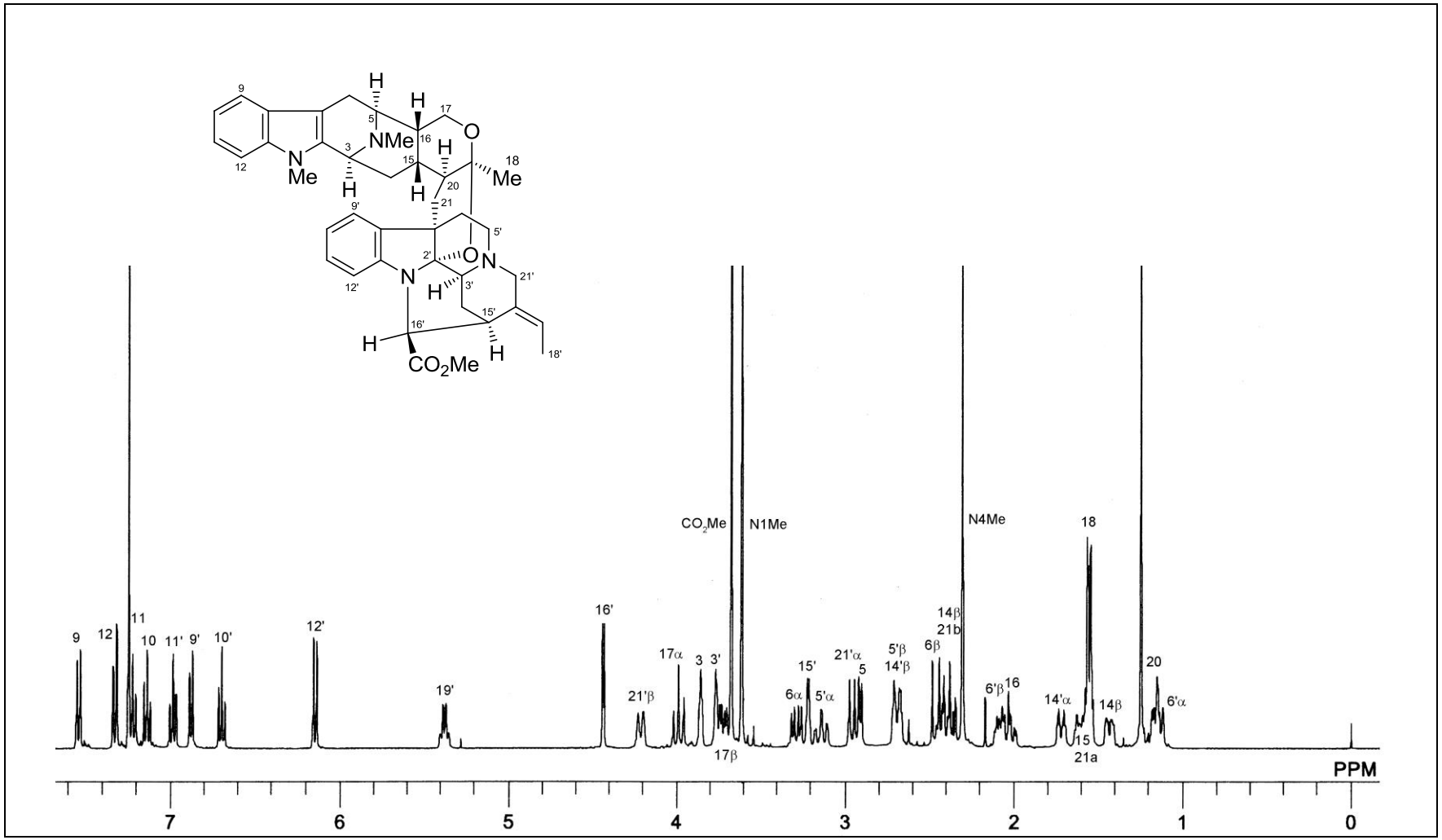


Figure 2.127: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Villalstonine (**88**)

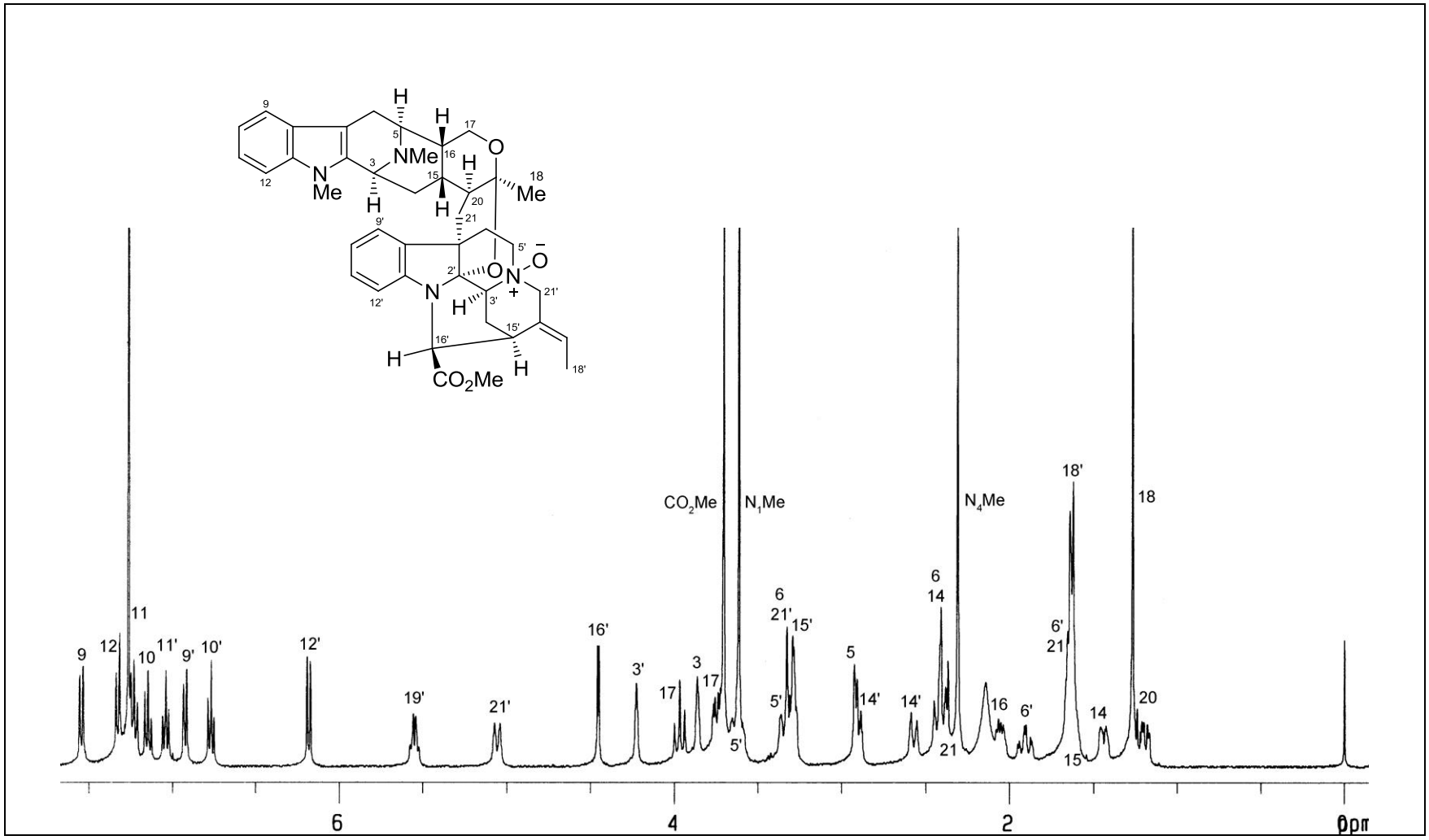


Figure 2.128: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Villalstonine *N*(4')-oxide (**89**)

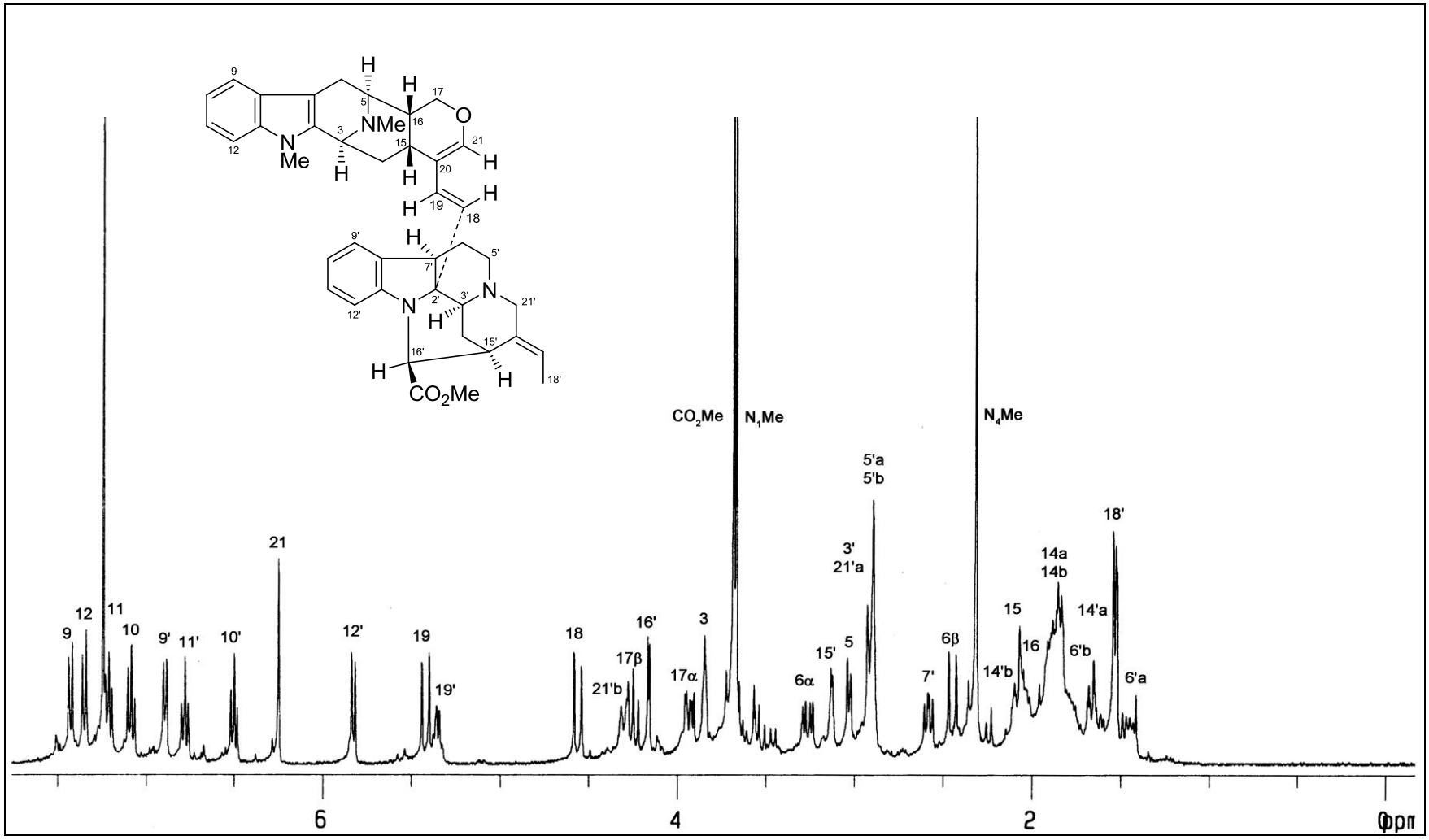


Figure 2.129: ^{1}H NMR Spectrum ($CDCl_3$, 400 MHz) of Macrocarpamine (**90**)

2.2 Alkaloid Variation in *A. macrophylla*

The present investigation of the stem-bark and leaf of *A. macrophylla* yielded a total of 90 alkaloids, which 17 indole (**1**–**4**, **16**–**17**, **24**–**34**) and 13 bisindole (**71**–**75**, **77**–**82**, **86**, **87**) alkaloids are new. A total of 20 alkaloids were common in both the stem-bark and leaf extracts, comprising seven macroline-type (**5**–**8**, **10**, **12**–**13**), four akuammiline-type (**24**, **35, 36**, **41**), three sarpagine-type (**32**, **51, 52**), one ajmaline-type (**54**), four corynantheine alkaloids (**57**, **59**, **63**, **65**), and one strychnan alkaloid (**67**).

A comparison of the present results with that of an earlier study of the alkaloids collected from the different location, showed a significant variation in the alkaloid composition between the two samples. The samples of the earlier study were collected from the East Coast (Terengganu) while those of the present study were collected from the West Coast (Perak) of Penisular Malaysia (Malaya), respectively.

Firtsly, indole alkaloids which were common to both studies included 10 macroline-type alkaloids (**5**–**14**), five macroline oxindole alkaloids (**19**–**23**), four akuammiline-type alkaloids (**41**, **44**–**46**), four corynantheine alkaloids (**57**, **59**, **63**, **66**), and one strychnan alkaloid (**67**). In the case of bisindole alkaloids, a total of 20 (**71–90**) were found in the present study, of which only two were found in the previous study, viz. perhentinine (**83**) and villalstonine (**88**).

Several of the alkaloids obtained in the earlier study, but which were not found in the present study were alstohentine (**110**), alstomicine (**109**), 6-oxoalstophylline (**114**), 6-oxoalstophyllal (**115**), Macrodasine B (**119**), *N*(1)-demethylalstophylline (**116**), *N*(1)-demethylalstophyllal (**117**), angustimalal (**97**), 16-hydroxyalstonisine (**129**), 16-hydroxyalstonal (**130**), 16-hydroxy-*N*(4)-demethylalstophylline oxindole (**132**), 16-hydroxy-*N*(4)-demethylalstophyllal oxindole (**131**), vincoridine (**157**), and volkenisne (**170**).

Conversely, a total of 64 alkaloids (46 indoles and 18 bisindoles) such as the five macroline alkaloids (**1**–**4**, **15**), three macroline oxindole alkaloids (**16**–**18**), 18 akuammiline alkaloids (**24**–**31**, **35**–**40**, **42**, **43**, **47**, **48**), 10 sarpagine and ajmaline-type alkaloids (**32**–**34**, **49**–**55**), seven corynantheine alkaloids (**56**, **58**, **60**–**62**, **66**, **68**), one strychnan alkaloid (**65**), one vallesiachotaman alkaloid (**69**), one carboline alkaloid (**70**), and 18 bisindole alkaloids (**71**–**82**, **84**–**87**, **89**–**90**) were obtained in the present study but were not detected in the previous study (see Table 2.71). It is therefore apparent from the above comparison that the alkaloidal composition varies with the different locality, a feature which has been previously noted in our ongoing investigation of the phytochemistry of the Malaysian Apocynaceae.

Table 2.71: Comparison of the Alkaloids Obtained from *A. macrophylla* in the Present Investigation (Perak, Malaya) Versus those from an Earlier Study (Terengganu, Malaya)

Alkaloids	**Previous Study 2004**[274]		**Present Study 2012**	
	Stem-bark	**Leaves**	**Stem-bark**	**Leaves**
Macroline Alkaloids				
Alstofolinine (**1**) (New)				+
Compound **2** (20,21-Dihydroalstonerine) (New)			+	
Compound **3** (*N*(1)-Demethylmacrocarpine B) (New)			+	
Macrodasine H (**4**) (New)			+	
Alstonerine (**5**)		+	+	+
Alstonerinal (**6**)		+	+	+
Alstophylline (**7**)	+	+	+	+
Alstophyllal (**8**)	+	+	+	+
Macrocarpine A (**9**)	+	+	+	
Macrocarpine B (**10**)	+	+	+	+
Macrocarpine C (**11**)	+		+	
Talcarpine (**12**)	+	+	+	+
N(4)-Methyl-*N*(4),21-*seco*alpinine (**13**)	+	+	+	+
Macrodasine A (**14**)	+		+	
Macrodasine G (**15**)			+	
Angustimalal (**97**)	+			
Alstomicine (**109**)		+		
Alstohentine (**110**)		+		
6-Oxoalstophylline (**114**)		+		
6-Oxoalstophyllal (**115**)		+		
N(1)-Demethylalstophylline (**116**)	+			
N(1)-Demethylalstophyllal (**117**)	+			
Macrodasine B (**119**)	+			
Macroline Oxindole Alkaloids				
Compound **16** (11-Methoxyalstonoxine A) (New)				+
Compound **17** (11-Methoxyalstonoxine B) (New)			+	
Alstonoxine A (**18**)				+
Alstonoxine B (**19**)		+		+

Table 2.71, continued

Alkaloids	**Previous Study 2004**[274]		**Present Study 2012**	
	Stem-bark	**Leaves**	**Stem-bark**	**Leaves**
Alstonisine (**20**)	+	+		+
Alstonal (**21**)	+	+		+
N(4)-Demethylalstophylline oxindole (**22**)	+	+		+
N(4)-Demethylalstophyllal oxindole (**23**)	+	+		+
16-Hydroxyalstonisine (**129**)		+		
16-Hydroxyalstonal (**130**)		+		
16-Hydroxy-*N*(4)-demethylalstophyllal oxindole (**131**)		+		
16-Hydroxy-*N*(4)-demethylalstophylline oxindole (**132**)		+		
Akuammiline alkaloids				
Compound **24** (2(*S*)-Cathafoline) (New)			+	+
Compound **25** (2(*S*)-10-Methoxycathafoline) (New)				+
Compound **26** (2(*R*)-3-Hydroxycathafoline) (New)				+
Compound **27** (10-Demethoxyvincorine) (New)				+
Compound **28** (10-Demethoxyvincorine *N*(4)-oxide) (New)				+
Compound **29** (11-Methoxyvincorine) (New)				+
Compound **30** (Vincorine *N*(4)-oxide) (New)				+
Compound **31** (11-Demethoxyquaternine) (New)				+
Cathafoline (**35**)			+	+
Cathafoline *N*(4)-oxide (**36**)			+	+
10-Methoxycathafoline (**37**)				+
Strictamine (**38**)				+
11-Methoxystrictamine (**39**)				+
11-Hydroxystrictamine (**40**)				+
Vincorine (**41**)		+	+	+
Norvincorine (**42**)				+
Alstonamide (**43**)				+
Demethoxyalstonamide (**44**)		+		+
Alstomaline (**45**)		+		+
Quaternine (**46**)		+		+
Picrinine (**47**)				+
12-Demethoxytabernulosine (**48**)				+

Table 2.71, continued

Alkaloids	**Previous Study 2004**[274]		**Present Study 2012**	
	Stem-Bark	**Leaves**	**Stem-Bark**	**Leaves**
Vincoridine (**157**)		+		
Volkensine (**170**)		+		
Sarpagine and Ajmaline Alkaloids				
Compound **32** (19,20-*Z*-Affinisine) (New)			+	+
Compound **33** (Vincamajine *N*(4)-oxide) (New)				+
Compound **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide) (New)				+
Affinisine (**49**)			+	
Affinisine oxindole (**50**)			+	
Normacusine B (**51**)			+	+
Alstoumerine (**52**)			+	+
Quebrachidine (**53**)				+
Vincamajine (**54**)			+	+
Vincamajine 17-*O*-veratrate (**55**)				+
Corynantheine Alkaloids				
Sitsirikine (**56**)				+
16(*R*),19(*E*)-Isositsirikine (**57**)	+		+	+
18,19-Dihydroisositsirikine (**58**)				+
Pleiocarpamine (**59**)	+		+	+
16-Hydroxymethylpleiocarpamine (**60**)			+	
Pleiomaltinine (**61**)			+	
Picramicine (**62**)			+	
Fluorocarpamine (**63**)	+		+	+
Yohimbine (**64**)				+
Talpinine (**65**)			+	+
10,11-Dimethoxynareline (**66**)		+		+
Strychnan Alkaloids				
11-Methoxyakuammicine (**67**)	+		+	+
11-Methoxyakuammicine *N*(4)-oxide (**68**)				+

Table 2.71, continued

Alkaloids	**Previous Study 2004[274]**		**Present Study 2012**	
	Stem-Bark	**Leaves**	**Stem-Bark**	**Leaves**
Miscellaneous Monoterpene Indole Alkaloids				
Antirhine (**69**)			+	
1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)			+	
Linearly Fused Bisindoles				
Lumutinine A (**71**) (New)			+	
Lumutinine B (**72**) (New)			+	
Lumutinine C (**73**) (New)			+	
Lumutinine D (**74**) (New)			+	
Lumutinine E (**75**) (New)			+	
Macralstonidine (**76**)			+	
Macroline-Macroline Bisindoles				
Lumusidine A (**77**) (New)			+	
Lumusidine B (**78**) (New)			+	
Lumusidine C (**79**) (New)			+	
Lumusidine D (**80**) (New)			+	
Perhentidine A (**81**) (New)			+	
Perhentidine B (**82**) (New)			+	
Perhentinine (**83**)	+		+	
Macralstonine (**84**)			+	
Anhydromacralstonine (**85**)			+	
Macroline-Pleiocarpamine Bisindoles				
Villalstonidine B (**86**) (New)			+	
Villalstonidine F (**87**) (New)			+	
Villalstonine (**88**)	+		+	
Villalstonine *N*(4)-oxide (**89**)			+	
Macrocarpamine (**90**)			+	

2.3 Biological Activity

2.3.1 General

Alkaloids are particularly interesting substances because of their multiple pharmacological activities. In addition to our systematic chemical investigations, alkaloids isolated from the present study were screened for their biological activity, in particular for their cytotoxic effects, including their potential in reversing multidrug resistance (MDR) in drug-resistant tumor cells. This part of the work was carried out by Dr. K. Komiyama of the Kitasato University, Japan, and his associates at Iwaki Meisei University, Japan.

2.3.2 Cytotoxicity and Reversal Multidrug Resistance (MDR)

Cancer represents one of the leading causes of death worldwide. The development of new anticancer drugs as well as more effective treatment strategies are crucial in drug discovery and clinical therapy. Multidrug resistance (MDR) is one of the significant obstacles in cancer chemotherapy. MDR is defined as the ability of cells exposed to a single drug to develop resistance to a broad range of structurally and functionally unrelated drugs due to enhanced outward transport of drugs mediated by a membrane glycoprotein "drug transport pump".[275-277] The cytotoxic drugs that are most frequently associated with MDR are hydrophobic, amphipathic natural products, such as *Vinca* alkaloids (vinblastine and vincristine), taxanes (docetaxel and paclitaxel), anthracyclines

(daunorubicin and epirubicin), podophyllotoxins (etoposide), topotecan, dactinomycin, and mitomycin C.[278]

The mechanism of MDR is attributed to the over-expression of P-glycoprotein (P-gp) or multidrug resistance-associated protein (MRP), which act as transmembrance drug efflux pumps, reducing intracellular accumulation of anticancer drugs in the cell.[278,279] By introducing a modulator of MDR (also known as a chemosensitizer) together with the anticancer drug, this effect can be reversed, which is termed reversal of multidrug resistance. When a modulator is present in the growth medium, the sensitivity of the resistant cells to the oncolytic can be enhanced by inhibiting the efflux mechanism so that cells accumulate a higher intracellular concentration of drug thereby becoming more drug-sensitive. Many agents that modulate the function of P-gp have been identified, such as calcium channel blockers (*e.g.* verapamil[280] and azidopine[281]), calmodulin antagonists (*e.g.* trifluoperazine and chlorpromazine), steroidal agents (*e.g.* cortisol and tamoxifen), protein kinase C inhibitors, immunosuppressive drugs (*e.g.* tacrolimus and andsirolimus), antibiotics (*e.g.* clarithromycin and erythromycin), and surfactants.[278,282,283]

While the first generation agents (*e.g.* verapamil and cyclosporin) suffered from limitations due to unacceptable toxicity, the second generation agents (*e.g.* valspodar and biricodar) were found to possess better tolerability but were limited by displaying unpredictable pharmacokinetic interactions, including interactions with other transporter proteins.[278] Third generation agents (*e.g.* tariquidar and zosuquidar) possess both higher potency as well as specificity and their evaluation are still ongoing.[278]

The alkaloids obtained from the present study were screened for cytotoxic effects against KB cells as well as their potential in reversing multidrug resistance (MDR) in drug-resistant KB cells. KB refers to the human oral epidermoid carcinoma cell line. The alkaloids were tested at an initial concentration of 25 μg/mL and the IC_{50} values were then determined for the more active compounds and the results are presented in Table 2.72.

Compounds **24**, **25**, **29**, **33**, **48** and **80** displayed strong activity in reversing MDR in vincristine-resistant KB cells, while compounds **16**, **26**, **31**, **38**, **80**, and **87** displayed only moderate activity.

Villalstonine (**88**) and macrocarpamine (**90**) showed appreciable cytotoxicity towards drug-sensitive and drug-resistant KB cells, while lumutinines A–E (**71–75**), macralstonidine (**76**), lumusidines A–C (**77**–**79**), anhydromacralstonine (**85**), and villalstonidine B (**86**) displayed only moderate activity.

Perhentidines A and B (**81** and **82**) and perhentinine (**83**) showed strong cytotoxicity toward drug-sensitive and drug-resistant KB cells, while the *O*-acetyl derivatives of these bisindoles (**81a**–**83a**) revealed that acetylation resulted in a reduction of the biological activity. Macralstonine (**84**) was found to be effective in reversing MDR in vincristine-resistant KB cells, while the *O*-acetyl-*E*-*seco*-macralstonine (**84b**) showed strong cytotoxicity toward drug-sensitive as well as vincristine-resistant KB cells.

Table 2.72: Cytotoxic effects of compounds from *A. macrophylla* against KB cells

Compound Name	**IC_{50}, μg/mL (μM)**		
	KB/S	**KB/VJ300 VCR (–)**	**KB/VJ300 VCR (+)**
Macroline alkaloids			
Alstofolinine (**1**)	>25	>25	>25
N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	>25	>25	2.87 (8.48)
Macroline Oxindoles			
Compound **16** (11-Methoxyalstonoxine A)	>25	>25	9.25 (25.81)
Alstonoxine A (**18**)	>25	>25	>25
Alstonoxine B (**19**)	>25	>25	>25
Akuammiline, sarpagine and ajmaline alkaloids			
Compound **24** (2(*S*)-Cathafoline)	>25	>25	0.62 (1.83)
Compound **25** (2(*S*)-10-Methoxycathafoline)	>25	>25	0.31 (0.88)
Compound **26** (2(*R*)-3-Hydroxycathafoline)	>25	>25	3.74 (10.55)
Compound **29** (11-Methoxyvincorine)	>25	>25	1.32 (3.31)
Compound **31** (11-Demethoxyquaternine)	>25	>25	3.54 (9.26)
Compound **32** (19,20-*Z*-Affinisine)	>25	>25	0.05 (0.16)
10-Methoxycathafoline (**37**)	>25	>25	3.11 (8.44)
Strictamine (**38**)	>25	>25	14.4 (44.67)
11-Methoxystrictamine (**39**)	>25	>25	0.51 (1.45)
11-Hydroxystrictamine (**40**)	>25	>25	>25
Norvincorine (**42**)	>25	>25	>25
Alstonamide (**43**)	>25	>25	1.06 (2.57)
Demethoxyalstonamide (**44**)	>25	>25	1.38 (3.61)
Picrinine (**47**)	>25	>25	1.87 (5.53)
12-Demethoxytabernulosine (**48**)	>25	>25	1.55 (4.21)
Normacusine B (**51**)	>25	>25	>25
Alstoumerine (**52**)	>25	>25	>25
Quebrachidine (**53**)	>25	>25	6.76 (19.18)
Vincamajine (**54**)	>25	>25	3.33 (9.09)
Corynantheine alkaloids			
Fluorocarpamine (**63**)	>25	>25	13.87 (40.99)
10,11-Dimethoxynareline (**69**)	>25	>25	>25
Strychnan alkaloid			
11-Methoxyakuammicine (**64**)	>25	>25	19.44 (55.16)

Table 2.72, continued

Compound Name	IC_{50}, μg/mL (μM)		
	KB/S	KB/VJ300 VCR (–)	KB/VJ300 VCR (+)
Linearly fused bisindoles			
Lumutinine A (**71**)	10.52 (15.63)	10.62 (15.78)	0.21 (0.31)
Lumutinine B (**72**)	4.63 (6.88)	5.51 (8.19)	0.10 (0.15)
Lumutinine C (**73**)	12.01 (18.17)	13.30 (20.31)	4.61 (6.98)
Lumutinine D (**74**)	12.78 (19.82)	18.14 (28.13)	3.93 (6.09)
Lumutinine E (**75**)	11.4 (18.07)	11.53 (18.28)	2.74 (4.34)
Macralstonidine (**76**)	6.62 (10.27)	4.52 (7.01)	0.13 (0.20)
Macroline-macroline bisindoles			
Lumusidine A (**77**)	9.59 (13.96)	10.62 (15.46)	0.16 (0.23)
Lumusidine B (**78**)	5.51 (7.82)	7.71 (10.94)	0.70 (0.99)
Lumusidine C (**79**)	12.63 (17.23)	16.63 (22.69)	1.19 (1.62)
Lumusidine D (**80**)	>25	>25	5.03 (7.32)
Perhentidine A (**81**)	2.91 (4.13)	3.91 (5.55)	2.29 (3.25)
O-Acetylperhentidine A (**81a**)	8.57 (11.47)	12.84 (17.19)	0.36 (0.48)
Perhentidine B (**82**)	3.35 (4.75)	4.06 (5.76)	0.84 (1.19)
O-Acetylperhentidine B (**82a**)	12.83 (17.18)	11.94 (15.99)	0.28 (0.37)
Perhentinine (**83**)	3.17 (4.50)	3.94 (5.59)	0.52 (0.74)
O-Acetylperhentinine (**83a**)	10.59 (14.18)	11.56 (15.48)	0.30 (0.40)
Macralstonine (**84**)	>25	>25	1.71 (2.43)
O-Acetyl-*E*-*seco*-macralstonine (**84b**)	3.02 (4.04)	3.75 (5.02)	0.27 (0.36)
Anhydromacralstonine (**85**)	5.65 (8.18)	9.06 (13.11)	0.44 (0.64)
Macroline-pleiocarpamine bisindoles			
Villalstonidine B (**86**)	4.30 (6.22)	5.01 (7.25)	0.35 (0.51)
Villalstonidine F (**87**)	>25	>25	5.64 (8.72)
Villalstonine (**88**)	2.95 (4.46)	2.64 (3.99)	0.42 (0.64)
Macrocarpamine (**90**)	3.32 (5.16)	3.47 (5.40)	0.53 (0.82)
Control			
Vincristine	1.4 ng/mL (1.70 nM)	0.8 μg/mL (0.97 μM)	
Verapamil	>1.0 (> 2.20)	>1.0 (> 2.2)	

KB/S – vincristine-sensitive human oral epidermoid carcinoma cell line.

KB/VJ300 – vincristine-resistant human oral epidermoid carcinoma cell line.

VCR (+) – with added vincristine, 0.1 μg/mL (0.12 μM), which did not affect the growth of the KB/VJ300 cells.

VCR (-) – without added vincristine.

Chapter Three

3 Experimental

3.1 Source and authentication of plant materials

The plant materials (leaf and bark of *Alstonia macropylla*, K671) were collected from Lumut, Perak in Malaysia on September 2004 and were identified by Dr. Richard C. K. Chung (Forest Research Institute, Malaysia). The plant materials were screened for their alkaloidal constituents before any chemical analysis was carried out. Voucher specimens are deposited at the Herbarium, University of Malaya (UM).

3.2 General

Melting points were determined on Mel-Temp melting point apparatus and were uncorrected. Optical rotations were determined on a Jasco P-1020 digital polarimeter. UV spectra were obtained on a Shimadzu UV-3101PC spectrophotometer. IR spectra were recorded on a Perkin-Elmer 1600 Series or a Perkin-Elmer RX1 FT-IR spectrophotometer. ESIMS and HRESIMS were obtained on an Agilent 6530 Q-TOF mass spectrometer. HREIMS, and HRLSIMS were obtained at Organic Mass Spectrometry, Central Science Laboratory, University of Tasmania, Tasmania, Australia. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on a JEOL JNM-LA 400, or JNM-ECA 400 or Bruker Avance III 400 spectrometers, at 400 and 100 Hz, respectively, or on a Bruker Avance III 600 spectrometers at 600 and 150 MHz, respectively. Coupling constants (*J*) are reported in Hz and δ in ppm. X-ray

diffraction analysis was carried out on a Bruker SMART APEX II CCD area detector system equipped with a graphite monochromator and using Mo Kα radiation (λ=0.71073 Å), or on an Agilent Technologies SuperNova Dual CCD area detector system equipped with mirror monochromator and using Cu Kα radiation (λ=1.54184 Å), at 100 K. The structure was solved by direct methods (SHELXS-97) and refined with full-matrix least-squares on F^2 (SHELXL-97). (I thank Mr Low Yun Yee for carrying out X-ray diffraction analysis). All solvents were distilled prior to use with the exception of diethyl ether, which was passed through activated neutral alumina before use. All reactions were carried out under N_2 in oven-dried glasswares. CH_2Cl_2 and pyridine were distilled from CaH_2 under N_2.

3.3 Chromatographic methods

3.3.1 Column Chromatography

Flash chromatography was performed using Merck silica gel 9385 (230–400 Mesh ASTM). The ratio of silica gel to the sample was approximately 30:1 for crude samples and 100:1 for semi-pure fractions. The gel was made into a slurry with chloroform before it was packed onto the column and was allowed to equilibrate for at least an hour before use. When diethyl ether was used as an eluting solvent, the column was packed by the dry packing method. The solvent systems normally used as eluents were chloroform with increasing methanol gradient or diethyl ether with increasing ethyl acetate gradient. Fractions were monitored by thin layer chromatography (TLC) and appropriate fractions were combined and where necessary subjected to further separation by re-chromatography or preparative centrifugal TLC.

3.3.2 Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) was routinely used to detect and separate the various alkaloids. The crude alkaloidal extracts, fractions from chromatography, and isolated pure alkaloids were examined by TLC using pre-coated 5 x 10 cm aluminium plates, 0.25 mm thickness, silica gel 60 F_{254} (Merck, Darmstadt, G.F.R.). The TLC plates were spotted with a piece of fine glass capillary tube and then developed in saturated chromatographic tanks with various solvent systems at room temperature. The alkaloidal spots were visualized by examination of the TLC plates under UV light (254 nm), followed by spraying with Dragendorff's reagent, which formed orange spots. The hR_f values of the alkaloids are tabulated in Table 3.1.

Table 3.1: The hR_f Values of Alkaloids Isolated from *Alstonia macrophylla*

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
Alstofolinine (**1**)	12	44	21	72	52
Compound **2** (20,21-Dihydroalstonerine)	4	10	5	62	21
Compound **3** (*N*(1)-Demethylmacrocarpine B)	0	10	3	28	16
Macrodasine H (**4**)	4	13	5	64	30
Alstonerine (**5**)	12	38	24	72	48
Alstonerinal (**6**)	12	38	24	72	48
Alstophylline (**7**)	11	35	20	70	44
Alstophyllal (**8**)	11	35	20	70	44
Macrocarpine A (**9**)	4	15	9	55	27
Macrocarpine B (**10**)	0	10	4	48	21
Macrocarpine C (**11**)	7	23	15	71	37
Talcarpine (**12**)	11	25	15	68	40
N(4)-Methyl-*N*(4),21-*seco*talpinine (**13**)	3	10	11	49	26
Macrodasine A (**14**)	0	5	0	51	13
Macrodasine G (**15**)	0	1	0	45	9
Compound **16** (11-Methoxyalstonoxine A)	2	5	2	58	15
Compound **17** (11-Methoxyalstonoxine B)	0	4	1	34	9
Alstonoxine A (**18**)	2	5	2	57	15
Alstonoxine B (**19**)	0	6	1	41	11
Alstonisine (**20**)	8	40	25	68	50
Alstonal (**21**)	8	40	25	68	50

Table 3.1: continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
N(4)-Demethylalstophylline oxindole (**22**)	8	39	20	70	48
N(4)-Demethylalstophyllal oxindole (**23**)	8	39	20	70	48
Compound **24** (2(*S*)-Cathafoline)	2	2	1	42	4
Compound **25** (2(*S*)-10-Methoxycathafoline)	0	0	0	34	2
Compound **26** (2(*R*)-3-Hydroxycathafoline)	9	39	32	65	55
Compound **27** (10-Demethoxyvincorine)	11	48	45	72	55
Compound **28** (10-Demethoxyvincorine *N*(4)-oxide)	0	0	0	30	0
Compound **29** (11-Methoxyvincorine)	9	33	26	69	41
Compound **30** (Vincorine *N*(4)-oxide)	0	0	0	35	0
Compound **31** (11-Demethoxyquaternine)	1	7	2	43	13
Compound **32** (19,20-*Z*-Affinisine)	2	12	6	48	25
Compound **33** (Vincamajine *N*(4)-oxide)	0	0	0	30	0
Compound **34** (Vincamajine 17-*O*-veratrate *N*(4)-oxide)	0	0	0	41	0
Cathafoline (**35**)	1	2	1	32	4
Cathafoline *N*(4)-oxide (**36**)	0	1	0	20	1
10-Methoxycathafoline (**37**)	3	3	2	37	4
Strictamine (**38**)	3	4	2	50	9
11-Methoxystrictamine (**39**)	1	3	2	49	8
11-Hydroxystrictamine (**40**)	2	5	2	36	9
Vincorine (**41**)	18	44	40	70	51
Norvincorine (**42**)	1	6	2	44	12
Alstonamide (**43**)	17	52	29	76	59
Demethoxyalstonamide (**44**)	1	6	2	44	12
Alstomaline (**45**)	3	7	2	61	16
Quaternine (**46**)	4	9	3	61	15
Picrinine (**47**)	1	8	4	42	16
12-Demethoxytabernulosine (**48**)	3	11	5	62	20
Affinisine (**49**)	1	12	5	40	20
Affinisine oxindole (**50**)	0	5	1	37	11
Normacusine B (**51**)	0	7	2	23	13
Alstoumerine (**52**)	0	4	0	38	9
Quebrachidine (**53**)	2	11	5	49	21
Vincamajine (**54**)	6	26	13	61	35
Vincamajine 17-*O*-veratrate (**55**)	9	30	12	71	38
Sitsirikine (**56**)	0	4	1	21	7
16(*R*),19(*E*)-Isositsirikine (**57**)	0	8	4	41	22
18,19-Dihydroisositsirikine (**58**)	2	41	22	49	50
Pleiocarpamine (**59**)	2	3	2	43	7
16-Hydroxymethylpleiocarpamine (**60**)	0	1	0	28	4
Pleiomaltinine (**61**)	0	0	0	52	2
Picramicine (**62**)	1	1	1	33	4

Table 3.1: continued

Alkaloid	$CHCl_3$	EtOAc	Et_2O	$CHCl_3$/MeOH (10:1)	EtOAc/MeOH (20:1)
Fluorocarpamine (**63**)	1	9	5	57	18
Yohimbine (**64**)	2	20	9	51	33
Talpinine (**65**)	1	9	4	55	23
10,11-Dimethoxynareline (**66**)	1	17	3	53	29
11-Methoxyakuammicine (**67**)	1	2	1	38	4
11-Methoxyakuammicine *N*(4)-oxide (**68**)	0	0	0	29	0
Antirhine (**69**)	0	4	1	21	7
1,2,3,4-Tetrahydro-1-oxo-β-carboline (**70**)	4	13	5	64	30
Lumutinine A (**71**)	2	22	6	74	38
Lumutinine B (**72**)	2	9	3	69	21
Lumutinine C (**73**)	0	1	0	55	8
Lumutinine D (**74**)	0	1	0	45	4
Lumutinine E (**75**)	0	6	0	44	16
Macralstonidine (**76**)	0	10	2	62	20
Lumusidine A (**77**)	7	22	7	68	38
Lumusidine B (**78**)	0	4	1	32	8
Lumusidine C (**79**)	1	10	4	62	24
Lumusidine D (**80**)	1	18	7	61	34
Perhentidine A (**81**)	0	1	0	41	4
Perhentidine B (**82**)	0	1	0	41	5
Perhentinine (**83**)	1	4	0	52	10
Macralstonine (**84**)	0	5	1	48	11
Anhydromacralstonine (**85**)	2	15	4	68	33
Villalstonidine B (**86**)	1	3	0	43	6
Villalstonidine F (**87**)	0	1	0	34	5
Villalstonine (**88**)	0	2	0	56	7
Villalstonine *N*(4')-oxide (**89**)	0	1	0	35	0
Macrocarpamine (**90**)	0	2	1	46	5

3.3.3 Preparative Centrifugal TLC

Preparative centrifugal TLC was carried out using a round chromatographic plate measuring 24 cm in diameter. To prepare the chromatographic plate, the edge of the plate is secured with cellophane tape to form a mould. Silica gel (Merck 7749, 50 g) is added to about 110 ml of cold distilled water to give a slurry. The slurry is shaken and is

then quickly poured on to the circular glass plate before setting commences. The circular glass plate is rotated while the gel is being poured to obtain an even setting. The plate is then left to air-dry for about an hour before being dried in an oven at 80 ℃ for about 12 hours. The sample was dissolved in a minimum volume of a suitable solvent and loaded at the centre of the plate while the plate is spinning to form a thin band. Elution is then carried with the appropriate solvent system. The fractions are collected, concentrated by rotary-evaporation, examined by TLC, and combined where appropriate. Some of the solvent systems used as eluents were:

1. Chloroform
2. Chloroform: Hexanes
3. Chloroform with added 1% of liquid ammonia
4. Chloroform: Methanol
5. Diethyl ether
6. Diethyl ether: Hexanes
7. Diethyl ether: Methanol
8. Diethyl ether with added 1% of liquid ammonia
9. Ethyl acetate
10. Ethyl acetate: Hexanes
11. Ethyl acetate: Methanol
12. Ethyl acetate with added 1% of liquid ammonia

3.4 Spray Reagent (Dragendorff's Reagent)

Solution A: 0.85 g of bismuth nitrate was dissolved in a mixture of 10 mL glacial acetic acid and 40 mL of distilled water.

Solution B: 8 g of potassium iodide was dissolved in 20 mL of distilled water.

A stock solution was prepared by mixing equal volumes of solutions A and B. Dragendorff's reagent was prepared by mixing 1 mL of stock solution with 2 mL of glacial acetic acid and 10 mL of distilled water. Orange spots on the developed TLC plates indicate the presence of alkaloids.

3.5 Extraction of Alkaloids

The plant materials were dried and ground before extracting with 95% ethanol for 2–3 days at room temperature. The ethanol extract was filtered and the residue was then re-extracted with a fresh portion of distilled ethanol. This procedure was repeated 5 or 6 times. The combined extract was then concentrated by distillation under reduced pressure using a rotary-evaporator to about a tenth of the original volume. The concentrated extract was then added slowly into 3 % tartaric acid with constant stirring. The acidic solution was then filtered through kieselguhr to remove the non-alkaloidal substances. The filtrate was then basified with concentrated ammonia solution to about pH 10 with cooling and the liberated alkaloids were extracted exhaustively with chloroform. The chloroform extract was then washed with distilled water and dried over anhydrous sodium sulfate. Finally, the solvent was removed by evaporation under reduced pressure to furnish the crude alkaloidal mixture.

3.6 Isolation of Alkaloids

3.6.1 General Procedure

The crude mixture obtained from the extraction procedure described above was initially fractionated by vacuum chromatography over silica gel. The column was eluted with chloroform, followed by a stepwise increase of methanol gradient. Based on TLC, the many fractions collected were pooled into several major fractions, which were then subjected to further fractionation by flash chromatography, vacuum chromatography, HPLC, or preparative centrifugal TLC until pure compounds are obtained.

3.6.2 Isolation of Alkaloids from the Stem-bark of *Alstonia macrophylla*

Extraction of 9.0 kg of stem-bark material yielded *ca.* 57.6 g of crude alkaloidal mixture. This mixture was then subjected to chromatography as summarized in the flow diagram shown in Figure 3.1 to yield 56 pure alkaloids.

3.6.3 Isolation of Alkaloids from the Leaf of *Alstonia macrophylla*

Extraction of 7 kg of leaf material yielded *ca.* 45.1 g of crude alkaloidal mixture. This mixture was then subjected to chromatography as summarized in the flow diagram shown in Figure 3.2 to yield 55 pure alkaloids.

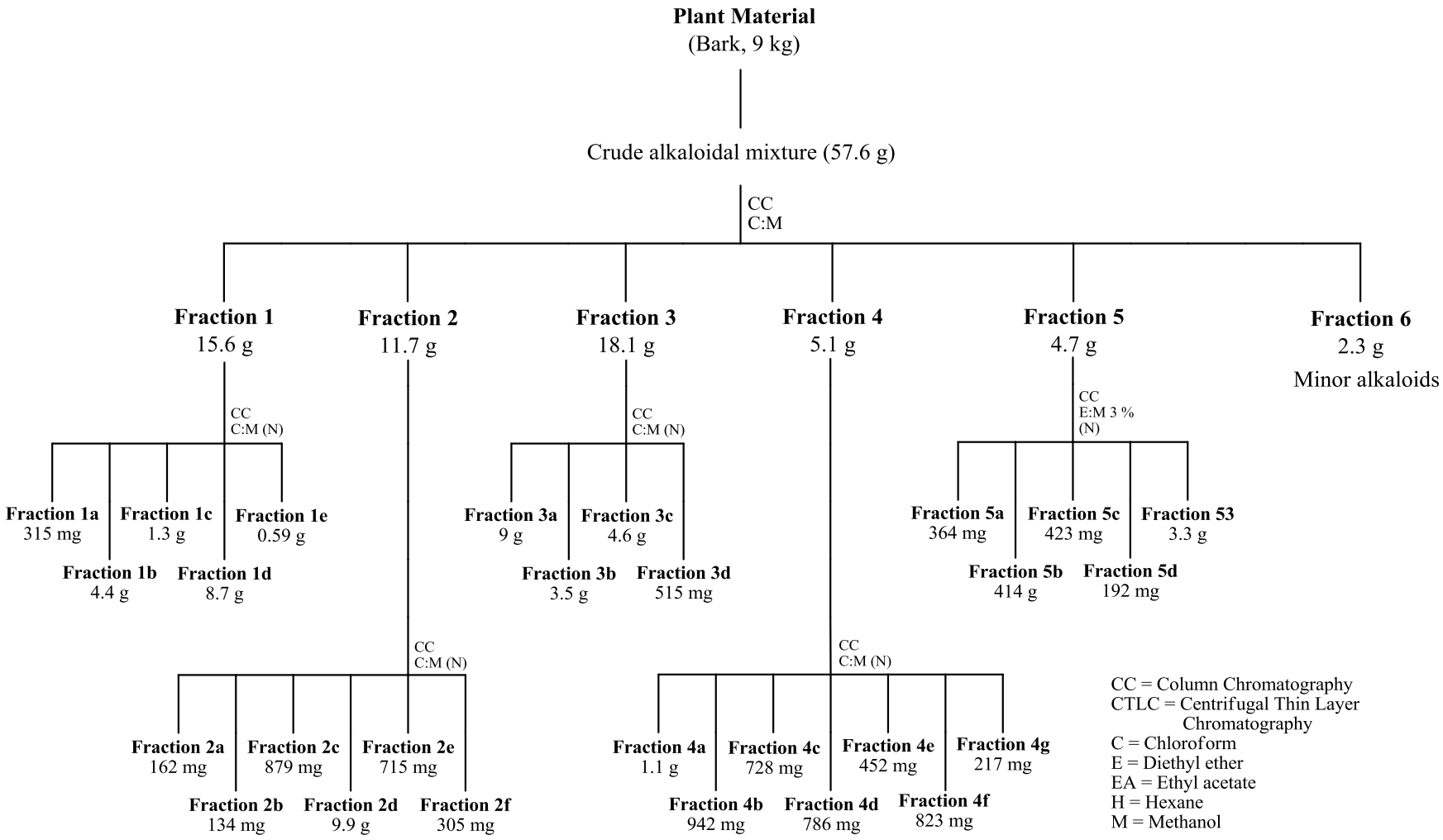


Figure 3.1: Isolation of alkaloids from the stem-bark extract of *Alstonia macrophylla*

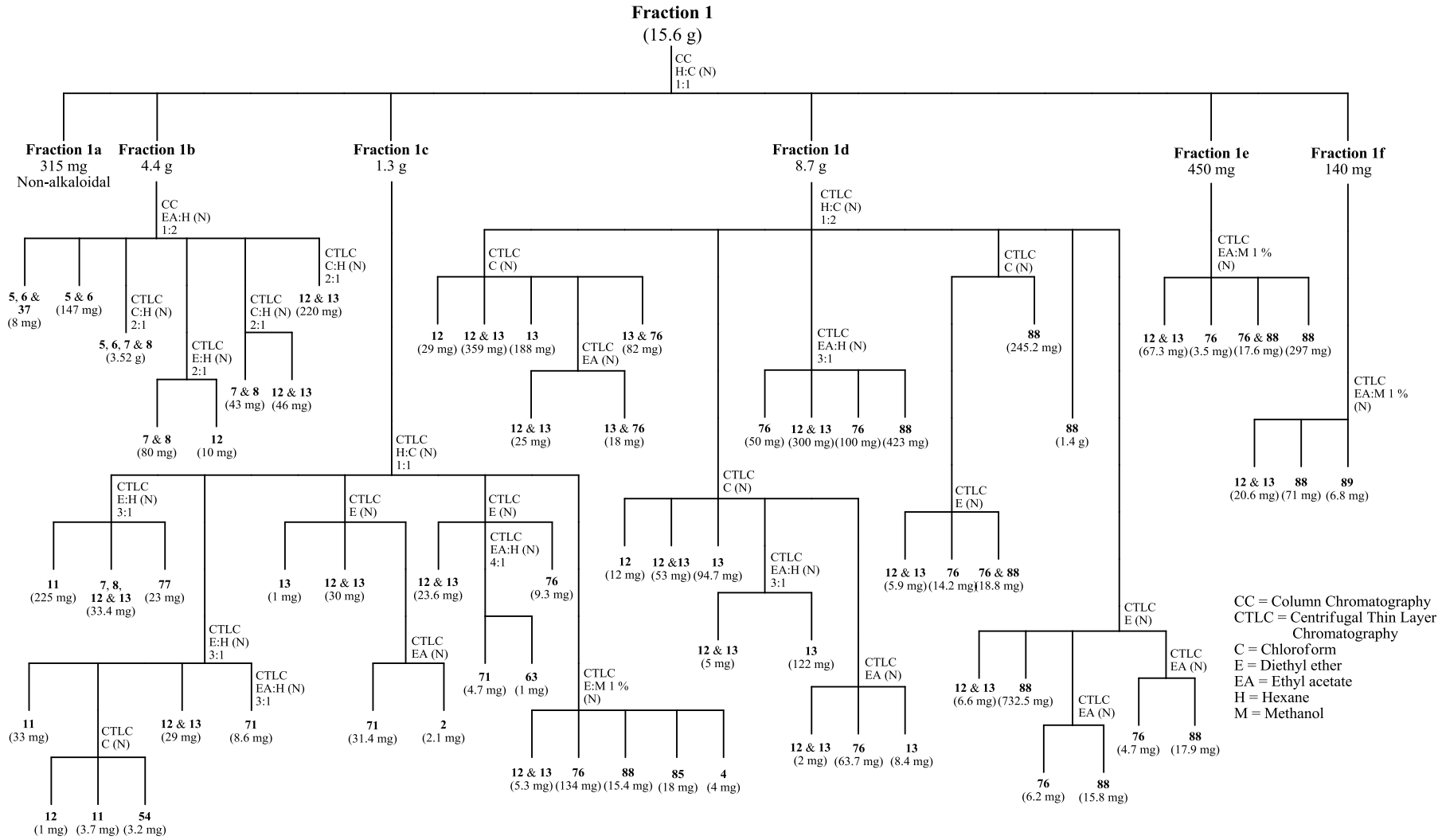


Figure 3.1, continued

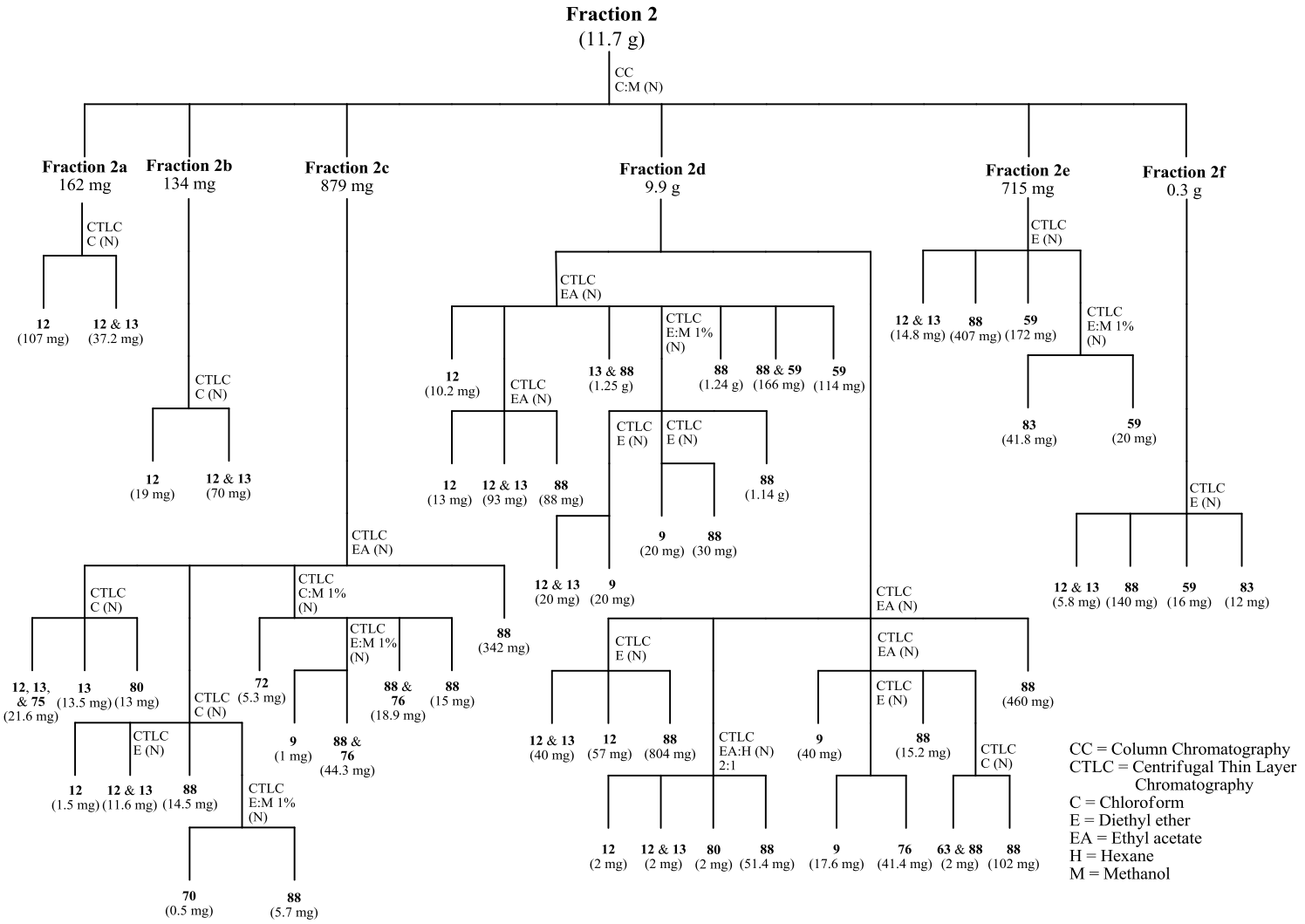


Figure 3.1, continued

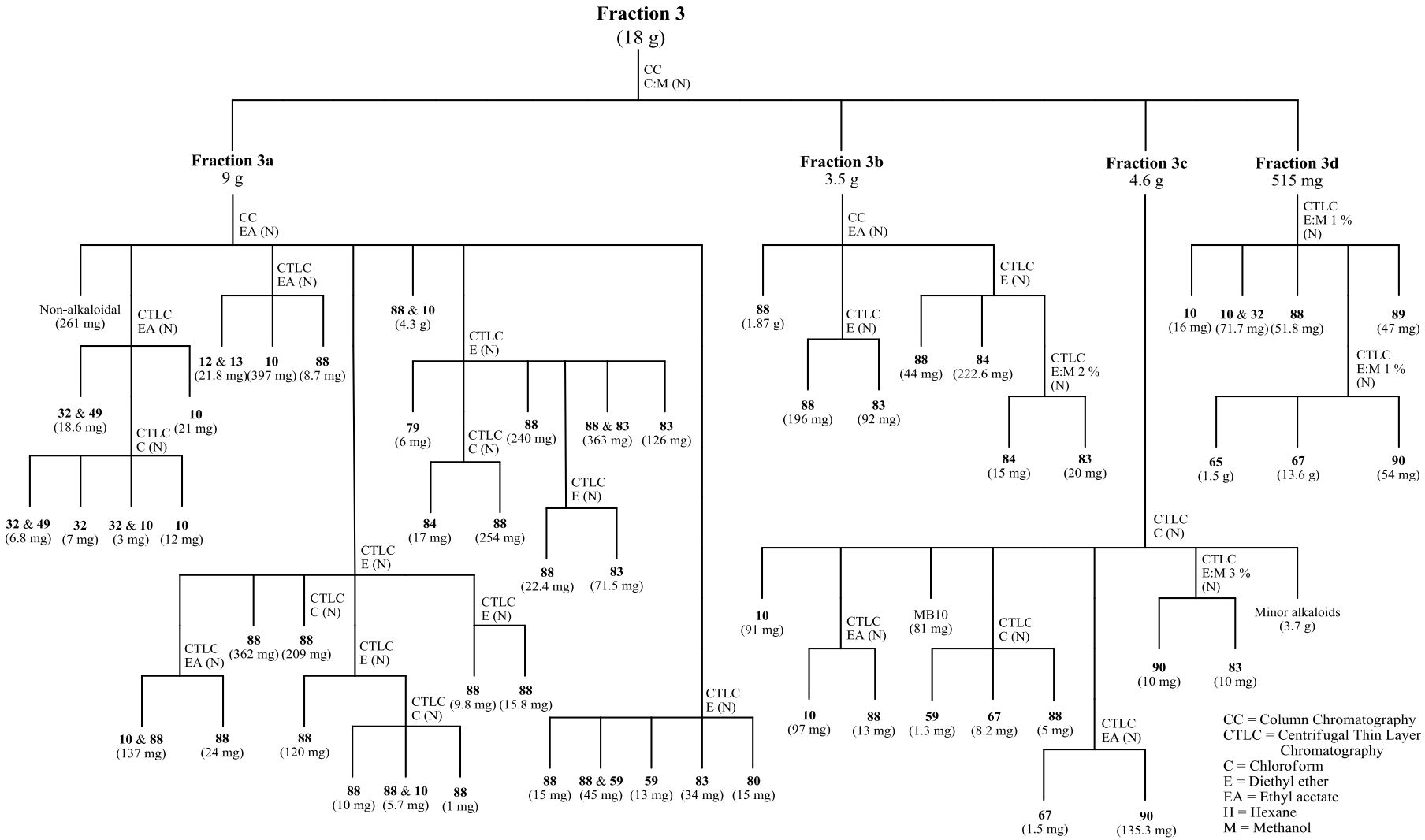


Figure 3.1, continued

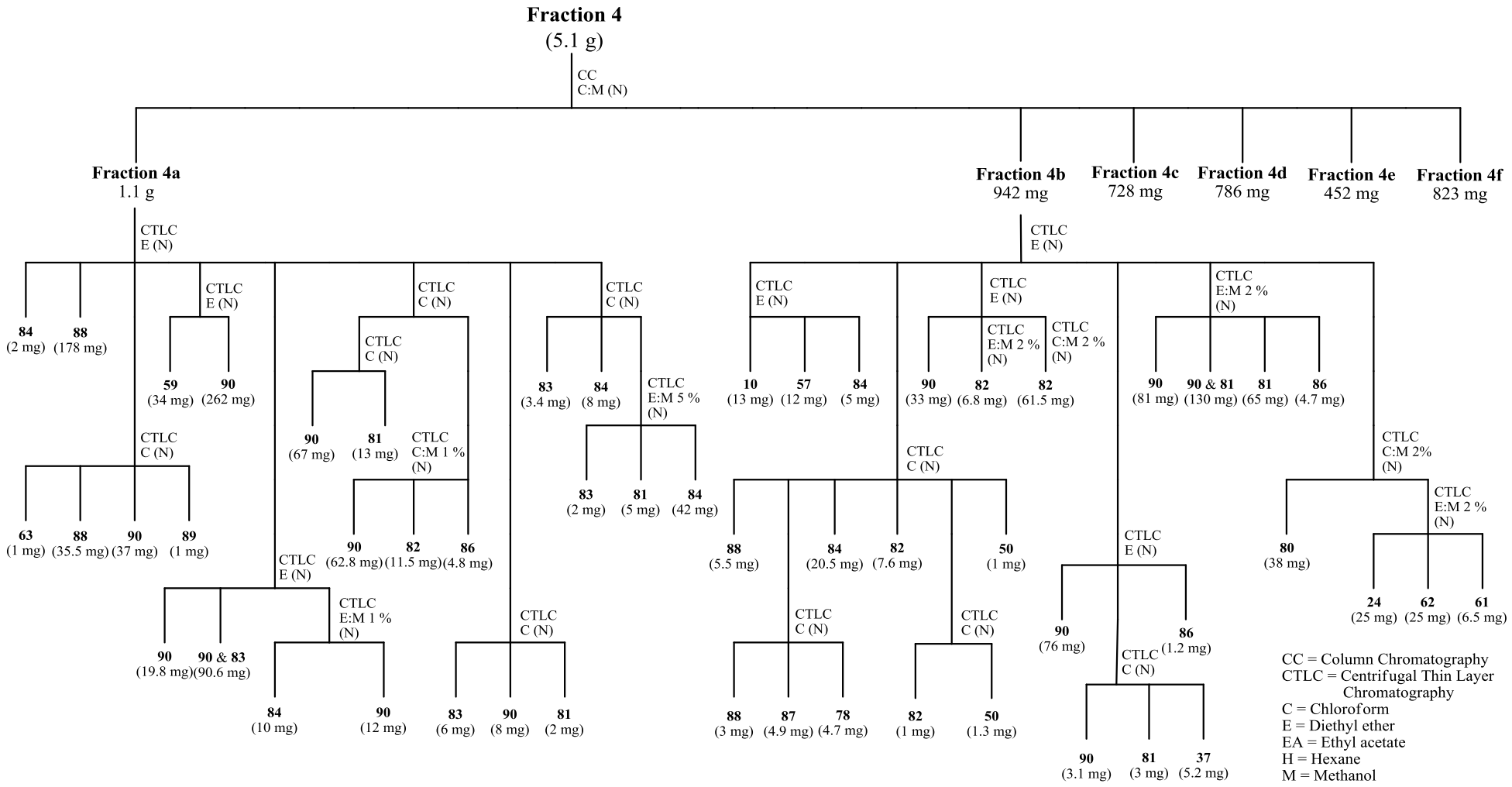


Figure 3.1, continued

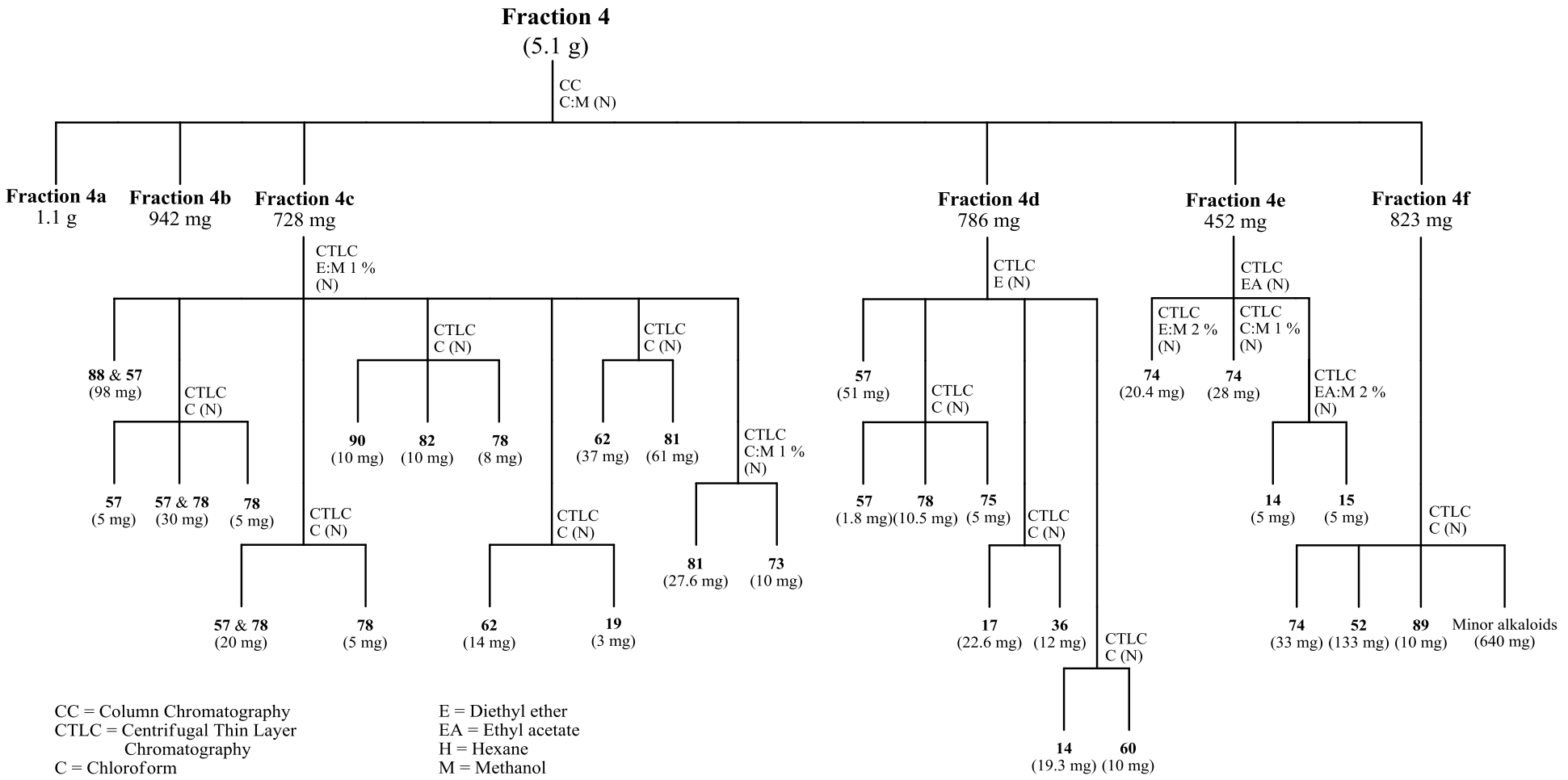


Figure 3.1, continued

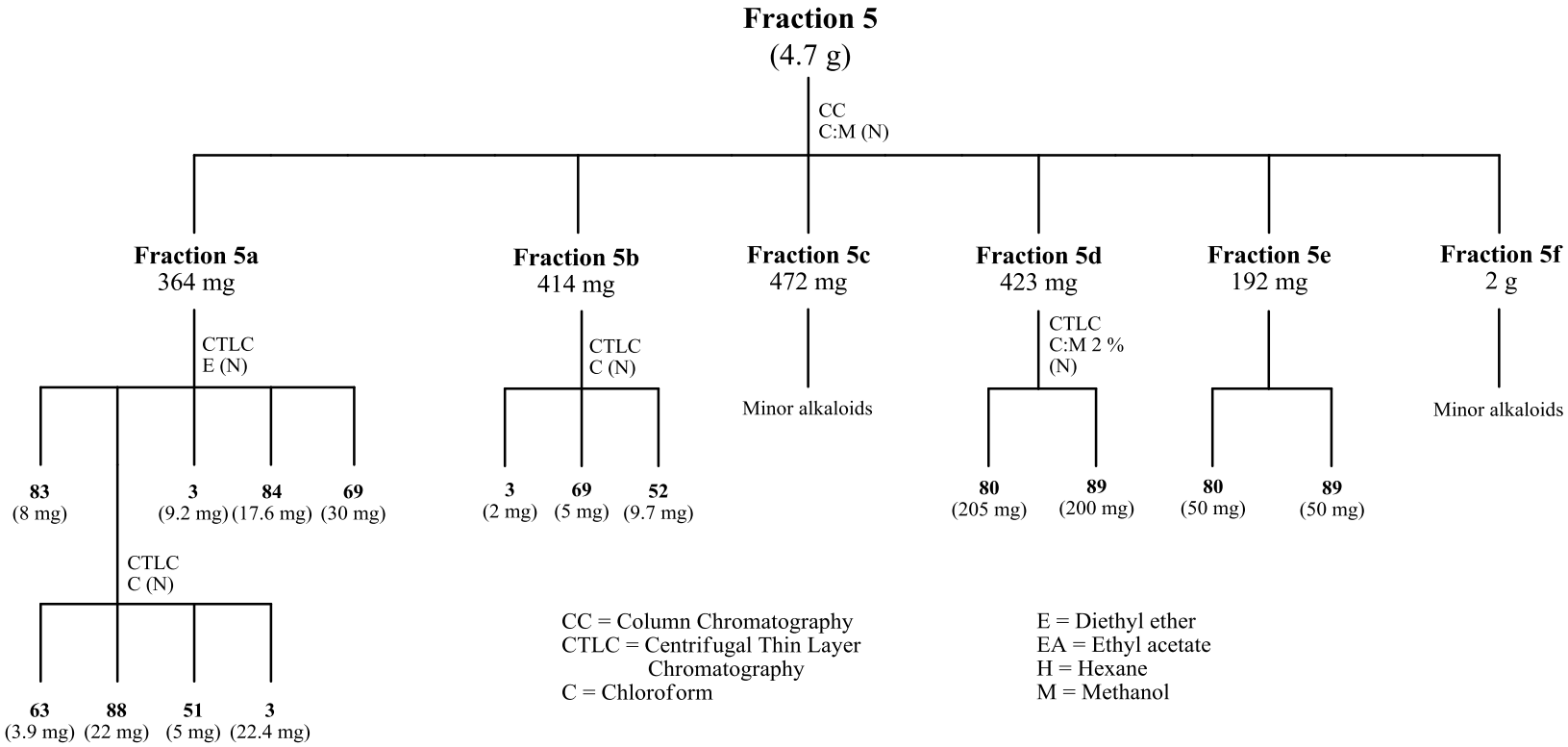


Figure 3.1, continued

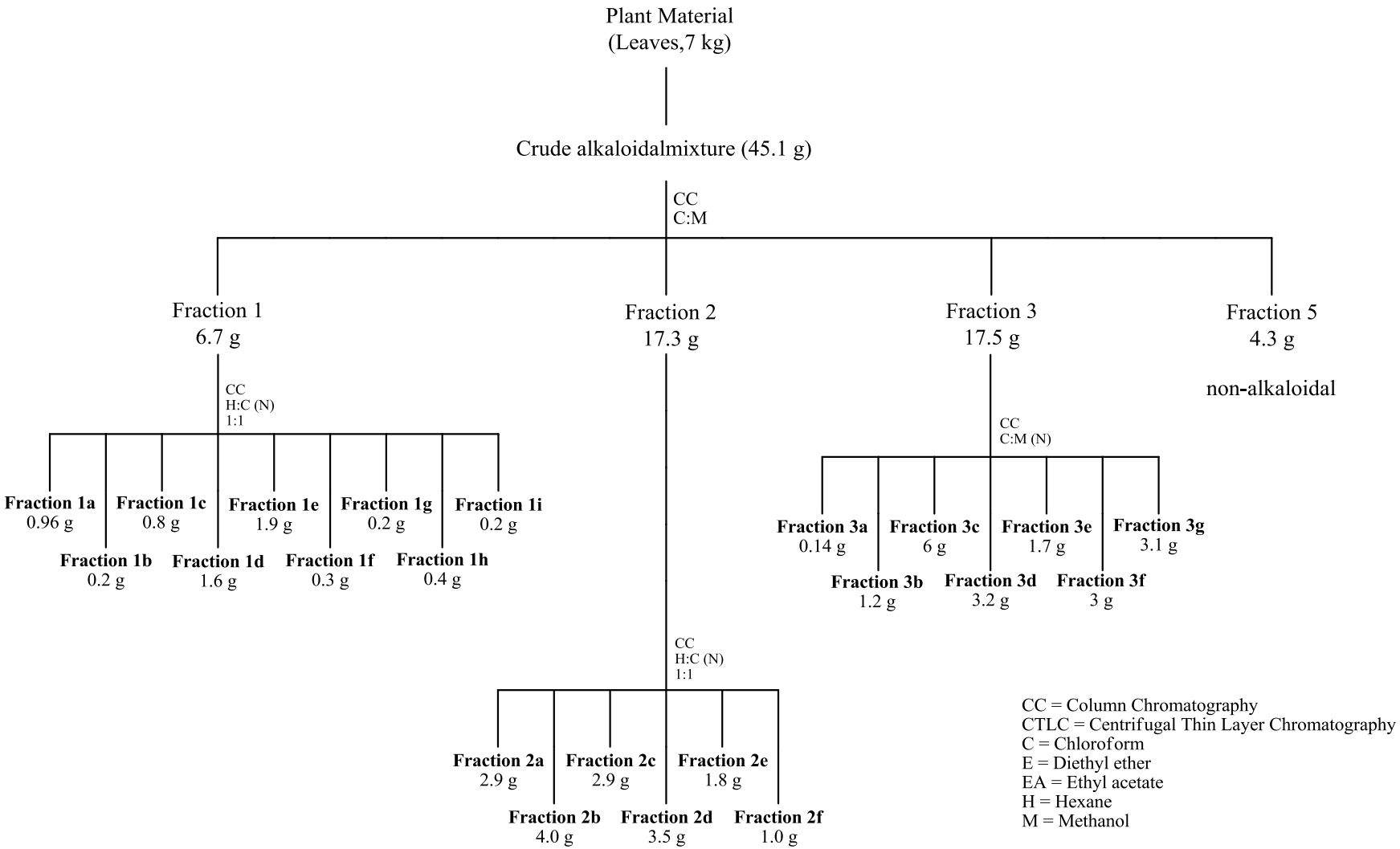


Figure 3.2: Isolation of alkaloids from the leaf extract of *Alstonia macrophylla*

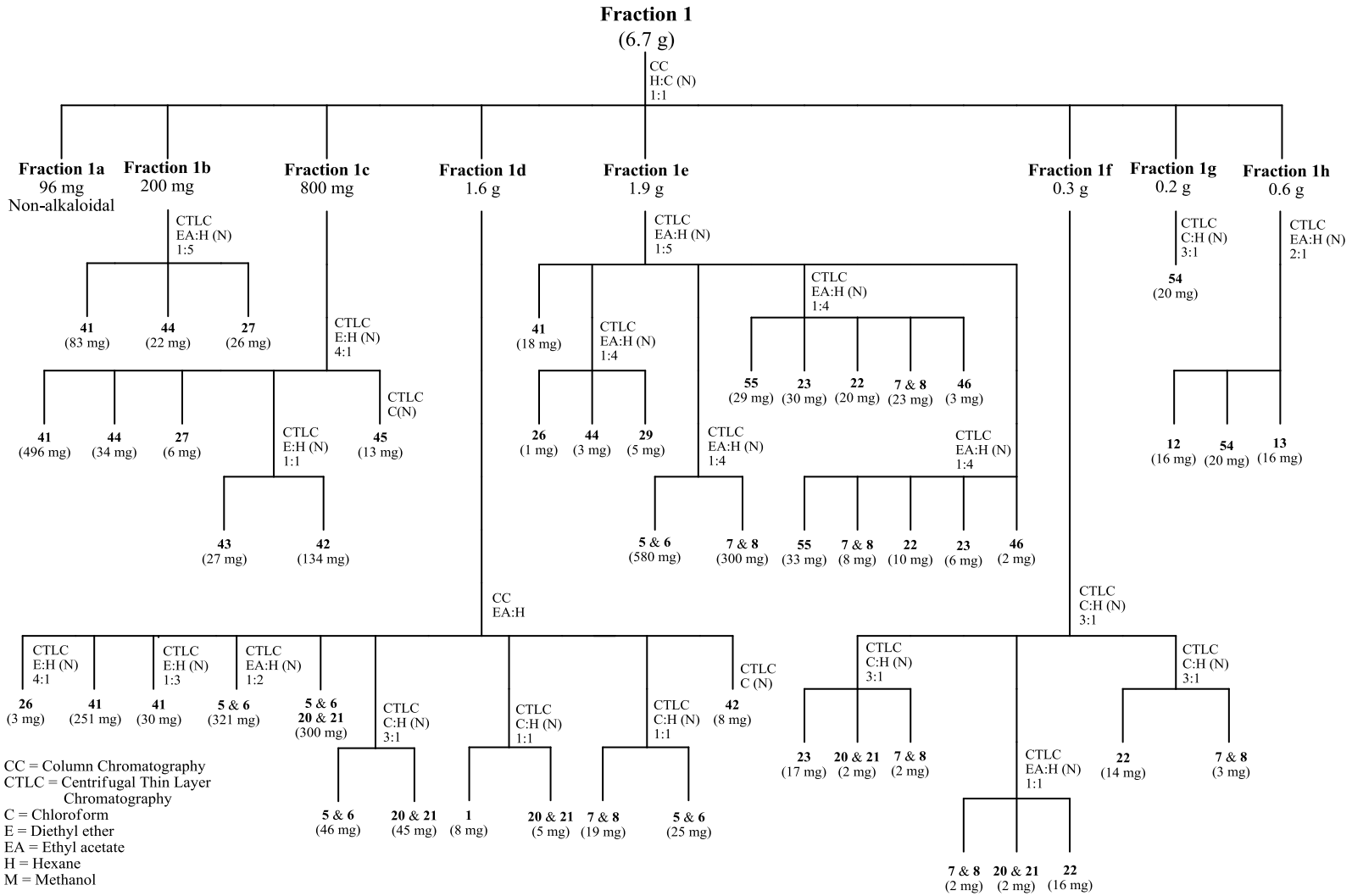


Figure 3.2, continued

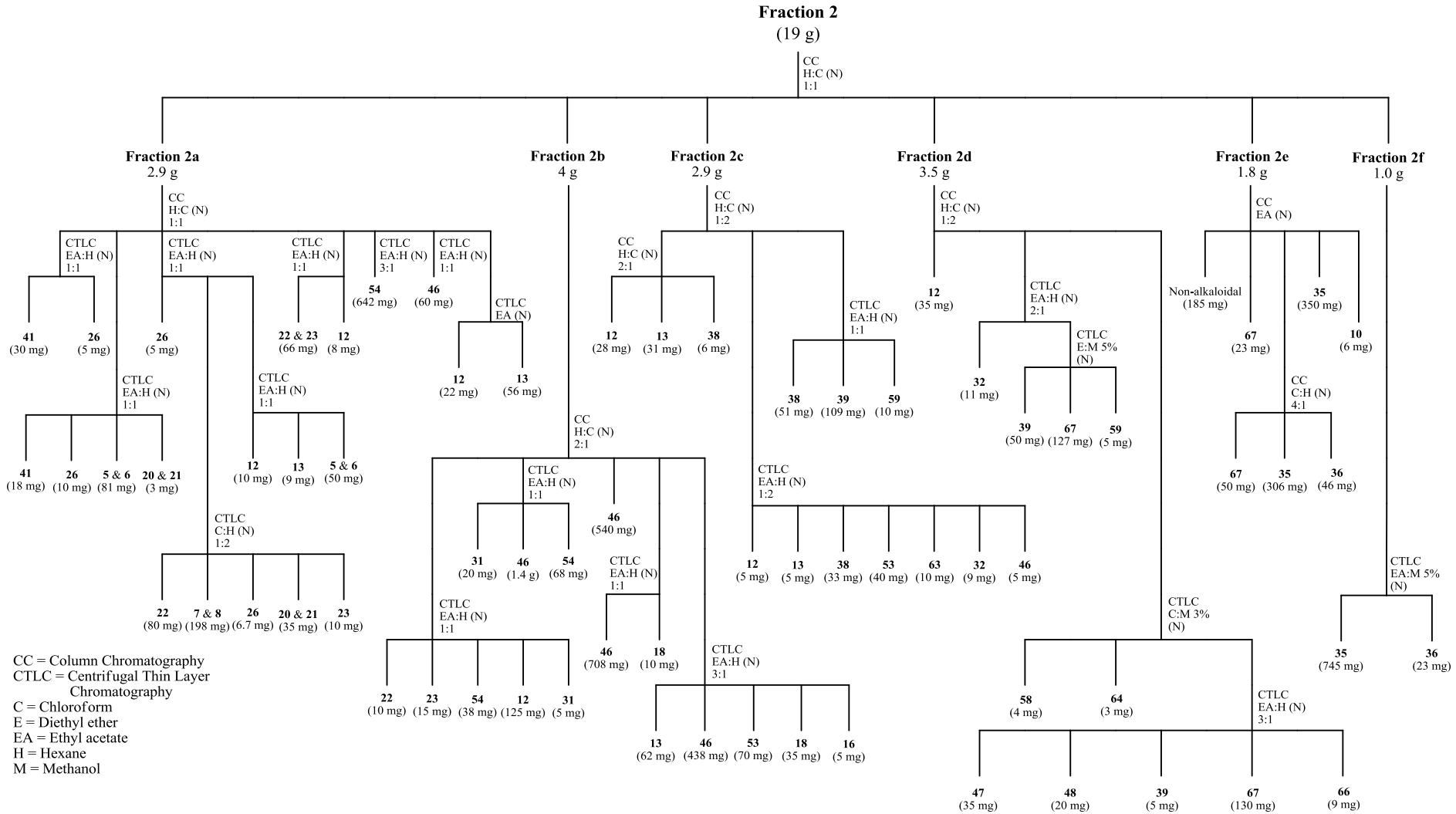


Figure 3.2, continued

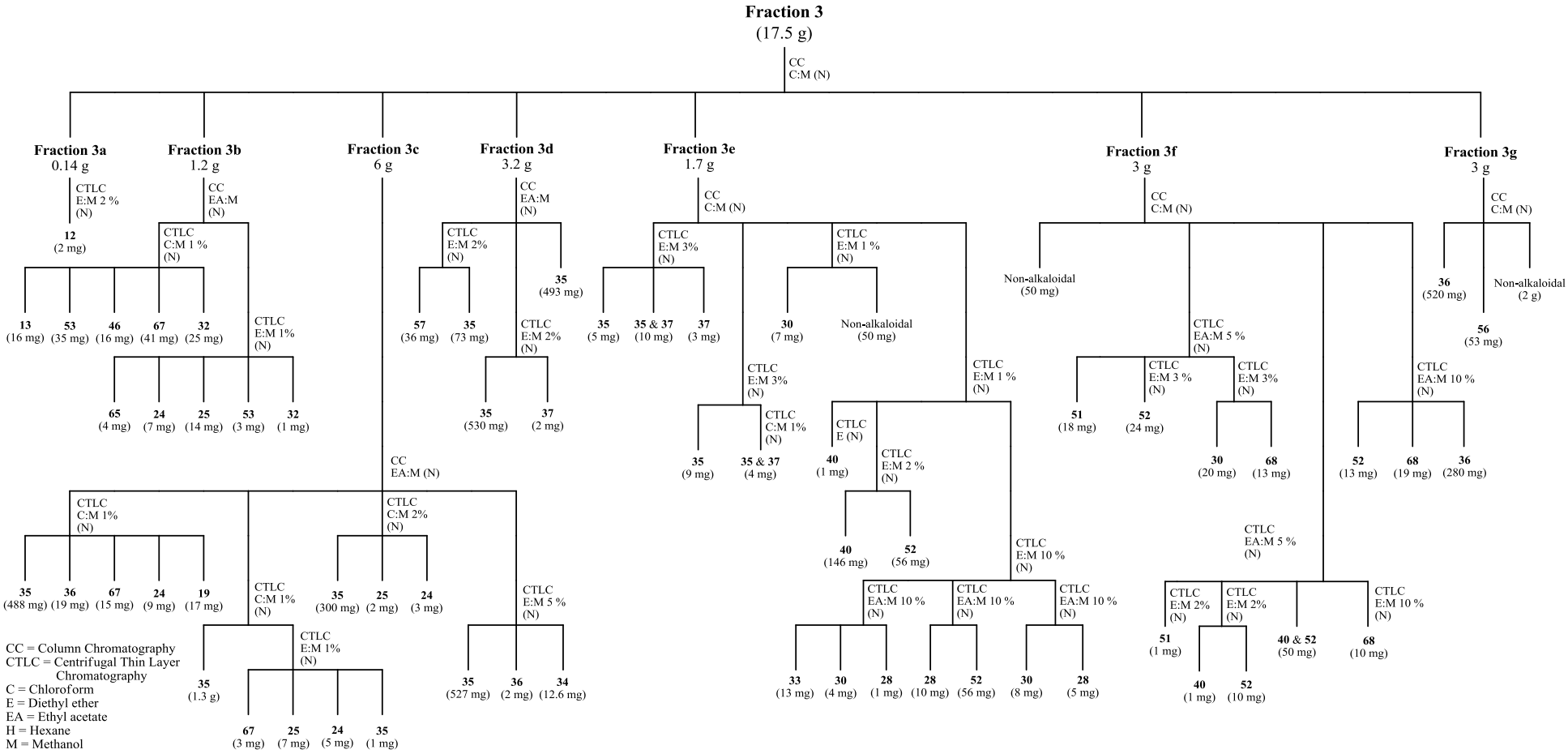


Figure 3.2, continued

3.7 Compound data

The following alkaloids were isolated from the stem-bark and leaf of *A. macrophylla*:

Alstofolinine (1): light yellowish oil; $[\alpha]_D$ –104 (*c* 0.36, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 227 (4.10), 285 (3.43) nm; IR (dry film) ν_{max} 1769 (lactone) cm^{-1}; EIMS *m/z* 296 $[M]^+$ (91), 281 (7), 265 (4), 240 (5), 227 (40), 212 (5), 197 (78), 182 (23), 181 (98), 170 (24), 167 (36), 154 (12), 144 (7), 119 (11); HREIMS *m/z* 296.1528 (calcd for $C_{18}H_{20}N_2O_2$, 296.1525); ESIMS *m/z* 297 $[M + H]^+$; HRESIMS *m/z* 297.1606 (calcd for $C_{18}H_{20}N_2O_2$ + H, 297.1603); for ^{1}H NMR and ^{13}C NMR data**,** see Table 2.2. HMBC: ^2J H-3 to C-2; H-6α, H-6β to C-5; H-6α, H-6β to C-7; H-15 to C-14; H-14α, H-14β, H-16 to C-15; H-5, H-17α, H-17β to C-16; H-16 to C-17. ^3J H-6α, H-6β, H-14β, N-1-Me to C-2; H-5, H-15, N-4-Me to C-3; H-3, H-15, H-17α, N-4-Me to C-5; H-3, H-5, H-9 to C-7; H-6β, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N-1-Me to C-13; H-16 to C-14; H-3, H-5, H-17β to C-15; H-6α, H-6β, H-14α, H-14β to C-16; H-5, H-15 to C-17; H-14α, H-14β, H-17β to C-18. NOESY: H-3/H-14α, H-14β, N-1-Me, N-4-Me; H-5/H-6α, H-6β, H-17α, H-17β, N-4-Me; H-6α/H-5, H-6β; H-6β/H-5, H-6α, H-9; H-9/H-6β, H-10; H-10/H-9; H-12/N-1-Me; H-14α/H-3; H-14β/H-3, N-1-Me; H-15/H-16; H-16/H-15, H-17α, H-17β; H-17α/H-5, H-16; H-17β/H-5, H-16; N-1-Me/H-3, H-12, H-14β; N-4-Me/H-3, H-5. 1D-NOE: H-3/H-14α, H-14β, N-1-Me, N-4-Me; H-5/H-6α, H-6β, H-16, H-17α, H-17β, N-4-Me; H-6α/H-5, H-6β, N-4-Me; H-9/H-6β, H-10; H-16/H-5, H-6β, H-15, H-17β; H-17α/H-5, H-17β; H-17β/H-5, H-16, H-17α; N-1-Me/H-3, H-12, H-14β.

Compound 2 (20,21-Dihydroalstonerine): light yellowish oil; $[\alpha]_D$ –31 (*c* 0.11, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.50), 286 (3.79) nm; IR (dry film) ν_{max} 1710 cm^{-1}; EIMS *m/z* 338 $[M]^+$ (100), 307 (8), 295 (11), 264 (10), 251 (6), 238 (8), 223 (5), 210 (14), 197 (78), 182 (19), 170 (13), 158 (10), 119 (4), 84 (12), 70 (25), 57 (6), 49 (10); HREIMS *m/z* 338.1993 (calcd for $C_{21}H_{26}N_2O_2$, 338.1994); for ^1H NMR and ^{13}C NMR data, see Table 2.3. NOE: H-14β/H-3, H-14'α, H-15, H-20; H-17β/H-5, H-17'α; H-18/H-20, H-21'β; H-21α/H-20, H-21'β; H-21'β/H-18, H-21α; N-1-Me/H-3, H-12; N-4-Me/H-3, H-5, H-6'α, H-14β.

Compound 3 [Macrocarpine D (*N*(1)-Demethylmacrocarpine B)]: light yellowish oil; $[\alpha]_D$ –43 (*c* 0.89, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (5.16), 286 (4.48) nm; IR (dry film) ν_{max} 3395, 3292 cm^{-1}; ESIMS *m/z* 327 $[M + H]^+$; HRESIMS *m/z* 327.2079 (calcd for $C_{20}H_{26}N_2O_2$ + H, 327.2073); for ^1H NMR and ^{13}C NMR data, see Table 2.4, respectively. HMBC: ^2J H-3 to C-2; H-6β, H-6'α to C-5; H-6β, H-6'α to C-7; H-10 to C-11; H-11 to C-12; H-5 to C-16; H-18 to C-19. ^3J H-6β, H-6'α, H-14'α to C-2; H-3, N-4-Me to C-3; H-3, N-4-Me to C-5; H-5, H-9 to C-7; H-6β, H-10, H-12, NH to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11 to C-13; H-3, H-5, H-17β, H-21, H-21' to C-15; H-6β, H-6'α to C-16; H-5 to C-17; H-17β, H-17'α, H-21 to C-19; H-18 to C-20. NOE: H-3/N-4-Me; H-5/H-6'α, H-16, H-17β, N-4-Me; H-6β/H-6'α; H-6'α/H-5, H-6β, N-4-Me; H-9/H-10; H-14β/H-3, H-14'α, H-15; H-14'α/H-3, H-14β, H-19; H-15/H-14β, H-20; H-16/H-5, H-6β, H-17β, H-20; H-17β/H-5, H-16, H-17'α; H-17'α/H-14'α, H-17β, H-19; H-18/H-19, H-20, H-21'; H-19/H-14'α, H-17'α, H-18, H-20; H-20/H-15, H-16, H-18, H-19, H-21, H-21'; H-21/H-21'; H-21'/H-18, H-20, H-21; N-4-Me/H-3, H-5, H-6'α.

Macrodasine H (4): light yellowish oil; $[\alpha]_D$ −11 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 233 (4.22), 288 (3.55) nm; IR (dry film) ν_{max} 3423 cm^{-1}; ESIMS *m/z* 439 $[M + H]^+$; HRESIMS *m/z* 439.2598 (calcd for $C_{26}H_{34}N_2O_4$ + H, 439.2591); for ^1H NMR and ^{13}C NMR data, see Table 2.5, respectively; HMBC: ^2J H-6α, H-6β to C-5; H-18 to C-19; H-15, H-21α, H-21β to C-20; H-21, H-23 to C-22; H-24 to C-23. ^3J H-6α, H-6β, N-1-Me to C-2; H-5, N-4-Me to C-3; N-4-Me to C-5; H-9 to C-7; H-6β, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N-1-Me to C-13; H-20 to C-14; H-5, H-21β to C-15; H-5, H-6α, H-6β, H-14β to C-16; H-5, H-15 to C-17; H-17β to C-19; H-18 to C-20. NOESY: H-3/H-14α, H-14β, N-1-Me, N-4-Me; H-5/H-6α, H-16, H-17β, N-4-Me; H-6α/H-5, H-6β, H-9; H-6β/H-6α, H-9, H-16; H-9/H-6α, H-6β, H-10; H-10/H-9, H-11; H-11/H-10, H-12; H-12/H-11, N-1-Me; H-14α/H-3, H-14β, H-17α; H-14β/H-3, H-14α, H-15, H-20; H-15/H-14β, H-16; H-16/H-5, H-6β, H-15, H-17β, H-21β; H-17α/H-14α, H-17β, H-18; H-17β/H-5, H-16, H-17α; H-18/H-17α, H-23; H-20/H-14β, H-21α; H-21α/H-20, H-21β; H-21β/H-16, H-21α, H-23; H-23/H-21β, H-25a; H-24a/H-24b, H-26a; H-24b/H-24a; H-25a/H-23, H-26b; H-26a/H-25, H-26b; H-26b/H-25, H-26a; N-1-Me/H-3, H-12; N-4-Me/H-3, H-5.

Alstonerine (**5**)**:** light yellowish oil; $[\alpha]_D$ −127 (*c* 0.59, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 230 (4.48), 264 (4.01) and 293 (3.77) nm; ESIMS *m/z* 337 (MH^+, $C_{21}H_{24}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data: see Table 2.6 and Table 2.7.

Alstonerinal (**6**)**:** light yellowish oil; $[\alpha]_D$ −32 (*c* 0.03, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 228 (4.30), 267 (4.00) and 291 (3.80) nm; ESIMS *m/z* 337 (MH^+, $C_{21}H_{24}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.6 and Table 2.7.

Alstophylline (**7**)**:** light yellowish oil; $[\alpha]_D$ –101 (*c* 0.04, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 203 (4.54), 232 (4.49), 255 (4.10) and 310 (3.73) nm; ESIMS *m/z* 367 (MH^+, $C_{22}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.6 and Table 2.7.

Alstophyllal (**8**)**:** light yellowish oil; ESIMS *m/z* 367 (MH^+, $C_{22}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.6 and Table 2.7.

Macrocarpine A (**9**)**:** light yellowish oil; $[\alpha]_D$ +117 ($CHCl_3$, *c* 0.11); UV (EtOH), λ_{max} nm (log ε): 230 (4.15) and 286 (3.46); IR (dry film) ν_{max} 3400 (OH) cm^{-1}; ESIMS *m/z* 341 (MH^+, $C_{21}H_{28}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR, see Table 2.8 and Table 2.9.

Macrocarpine B (**10**)**:** light yellowish oil; $[\alpha]_D$ –51 (*c* 0.34, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 230 (4.34) and 288 (3.64) nm; IR (dry film) ν_{max} 3400 (OH) cm^{-1}; ESIMS *m/z* 341 (MH^+, $C_{21}H_{28}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.8 and Table 2.9.

Macrocarpine C (**11**)**:** light yellowish oil; $[\alpha]_D$ –35 ($CHCl_3$, *c* 1.55); UV (EtOH), λ_{max} nm (log ε): 230 (4.30) and 287 (3.62); IR(dry film) ν_{max} 1737 (C=O, ester) cm^{-1}; ESIMS *m/z* 383 (MH^+, $C_{23}H_{30}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.8 and Table 2.9.

(-)-Talcarpine (**12**)**:** light yellowish oil; $[\alpha]_D$ –26 (*c* 0.12, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 209 (3.86), 226 (4.01), 277 (2.65), 285 (2.91) and 294 (2.65) nm; ESIMS *m/z* 339 (MH^+, $C_{21}H_{26}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.10.

***N*(4)-Methyl-*N*(4),21-*seco*talpinine (13):** light yellowish oil; $[\alpha]_D$ +19 (*c* 0.45, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 205 (3.95), 228 (4.21), 280 (3.00), 285 (3.42) and 300 (3.12) nm; ESIMS *m/z* 339 (MH^+, $C_{21}H_{26}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.10.

Macrodasine A (14): colorless plates from ethanol; mp 149–154 ℃; $[\alpha]_D$ +36 (*c* 0.36, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (3.88), 287 (3.17) nm; IR (dry film) ν_{max} 3411 cm^{-1}; ESIMS *m/z* 455 (MH^+, $C_{26}H_{34}N_2O_5$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.11.

Macrodasine G (15): colorless oil; $[\alpha]_D$ –59 (*c* 0.27, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 206 (4.50), 229 (4.50), 286 (3.79) nm; IR (dry film) ν_{max} 3424 cm^{-1}; EIMS *m/z* 454 $[M]^+$ (40), 436 (5), 423 (12), 394 (6), 367 (3), 321 (7), 277 (3), 237 (6), 197 (100), 170 (44), 144 (10), 128 (7), 98 (5), 70 (13), 55 (5), 44 (20); HREIMS *m/z* 454.2469 (calcd for $C_{26}H_{34}N_2O_5$, 454.2468); for ^{1}H NMR and ^{13}C NMR data, see Table 2.11.

Compound 16 [Alstonoxine C (11-Methoxyalstonoxine A)]: light yellowish oil; $[\alpha]_D$ –30 (*c* 0.39, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 219 (5.17), 266 (4.33) and 291 (4.24) nm; IR (dry film) ν_{max} 3390, 3295, and 1694 cm^{-1}; ESIMS *m/z* 359 $[M + H]^+$; HRESIMS *m/z* 359.1979 (calcd for $C_{20}H_{26}N_2O_4$ + H, 359.1971); for ^{1}H NMR and ^{13}C NMR data, see Table 2.12. HMBC: ^2J H(14), H(14') to C(3); H(6) to C(5); H(6), H(6') to C(7); H(12) to C(11); H(12) to C(13); H(14'), H(20), H(20') to C(15); H(18), H(20), H(20') to C(19); H(15) to C(20). ^3J H(6), H(6'), N(1)-Me to C(2); H(5) to C(3); H(3), H(17), H(17') to C(5); H(5), H(9), H(14) to C(7); H(6), H(10), H(12) to C(8); H(12) to C(10); H(9), 11-OMe to C(11); H(10) to C(12); H(9), N(1)-Me to C(13); H(20), H(20') to C(14); H(3), H(5), H(17') to C(15); H(6), H(6'), H(14'), H(20), H(20') to C(16); H(15)

to C(17); H(18) to C(20). NOESY: H(3)/H(14), H(14'); H(5)/H(6'), H(16); H(6)/H(6'), H(9), H(15), H(16); H(6')/H(5), H(6), H(9); H(9)/H(6), H(6'), H(10), H(15); H(10)/H(9); H(14)/H(3), H(14'), H(15), H(20), H(20'); H(14')/H(3), H(14); H(15)/H(6), H(14), H(16); H(16)/H(5), H(6), H(15), H(17), H(17'); H(17)/H(16), H(17'), H(20); H(17')/H(16), H(17); H(18)/H(20), H(20'); H(20)/H(14), H(17), H(18), H(20'); H(20')/H(14), H(18), H(20).

Crystallographic data of Alstonoxine C (16): Colorless block crystals, $C_{20}H_{26}N_2O_4.H_2O$, *M*r = 376.44, orthorhombic, space group $P2_12_12_1$, a = 7.3753(2) Å, b = 12.6375(3) Å, c = 19.5260(4) Å, $\alpha = \beta = \gamma = 90^{o}$, V = 1819.93(8) Å^3, T = 100 K, Z = 4, D_{calcd} = 1.374 gcm^{-3}, crystal size 0.16 x 0.18 x 0.24 mm^3, F(000) = 704. The final R_1 value is 0.0383 (wR_2 = 0.0898) for 3750 reflections [$I>2\sigma(I)$]. CCDC number: 935820

$NaBH_4$ reduction of alstonoxine C (16). To a mixture of compound **16** (12.4 mg, 0.035 mmol) in 5 ml of MeOH at 0 ^{o}C was added $NaBH_4$ (6.5 mg, 0.17 mmol). The solution was stirred at 0 ^{o}C for 1 h. Saturated Na_2CO_3 (5 ml) solution was added, and the product was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo, and the residue was purified by centrifugal preparative TLC (SiO_2, 1% MeOH:$CHCl_3$, NH_3-saturated) to afford **17** (5.1 mg, 41%) and **17a** (4.8 mg, 39%). **Compound 17a**: colorless oil; $[\alpha]^{25}_{D}$ –33 (*c* 0.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (1H, d, J = 8.3 Hz), 6.58 (1H, dd, J = 8.3, 2.2 Hz), 6.45 (1H, d, J = 2.2 Hz), 4.02 (1H, m), 3.99 (1H, m), 3.96 (1H, m), 3.92 (1H, m), 3.83 (3H, s), 3.24 (1H, m), 3.17 (3H, s), 2.76 (1H, m), 2.38 (1H, dd, J = 8.4, 2.3 Hz), 2.06 (1H, d, J = 8.4 Hz), 1.94 (1H, m), 1.77 (1H, m), 1.72 (1H, m), 1.58 (1H, m), 1.53 (1H, m), 1.29 (1H, d, J = 6 Hz); HRESIMS *m/z* 327.1718 (calcd for $C_{19}H_{22}N_2O_3$ + H, 327.1703).

Compound 17 [Alstonoxine D (11-Methoxyalstonoxine B)]: light yellowish oil; $[\alpha]_D$ –16.1 (*c* 0.23, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 224 (4.62), 274 (3.80) and 286 (3.80) nm; IR (dry film) ν_{max} 3391, 3298, and 1695 cm^{-1}; ESIMS *m/z* 361 $[M + H]^+$; HRESIMS *m/z* 361.2125 (calcd for $C_{20}H_{28}N_2O_4$ + H, 361.2127); for ^1H NMR and ^{13}C NMR data, see Table 2.12. HMBC: ^2J H(14), H(14') to C(3); H(6), H(6'), H(16) to C(5); H(6), H(6') to C(7); H(10), H(12) to C(11); H(12) to C(13); H(14), H(14'), H(20') to C(15); H(5), H(17) to C(16); H(18), H(20) to C(19). ^3J H(6), H(6'), N(1)-Me to C(2); H(6'), H(15) to C(3); H(3), H(17), H(17') to C(5); H(14') to C(7); H(6), H(10), H(12) to C(8); H(12) to C(10); H(9), 11-OMe to C(11); H(10) to C(12); H(9), H(12), N(1)-Me to C(13); H(16), H(20) to C(14); H(3), H(17), H(17'), H(19) to C(15); H(6), H(6'), H(14), H(14'), H(20) to C(16); H(18) to C(20). NOESY: H(3)/H(14), H(14'); H(5)/H(6'), H(16); H(6)/H(6'), H(9), H(14), H(15), H(16); H(6')/H(5), H(6); H(9)/H(6), H(10), H(15), H(14) or H(16); H(10)/H(9), 11-OMe; H(12)/N(1)-Me, 11-OMe; H(14)/H(3), H(6), H(9) or H(16), H(14'), H(15), H(20); H(14')/H(3), H(14); H(15)/H(6), H(9), H(14), H(16), H(20); H(16)/H(5), H(6), H(9), H(14), H(15), H(17), H(20); H(17)/H(16), H(17'), H(20); H(17')/H(14), H(16), H(17); H(18)/H(19), H(20'); H(19)/H(18), H(20); H(20)/H(14), H(15), H(16), H(17), H(19), H(20'); H(20')/H(18), H(20); N(1)-Me/H(12); 11-OMe/H(10), H(12).

Determination of the C-19 configuration of compound 17 by Horeau's method.[237,238] To a solution of compound **17** (5 mg, 0.038 mmol) and anhydrous pyridine (1 ml), was added, racemic 2-phenylbutyric anhydride (0.1 ml). The resulting mixture was stirred for 24 h at rt. Water (3 ml) was then added and the mixture was allowed to stand for 30 min. The pH of the solution was adjusted to pH 9 by drop-wise addition of NaOH (0.1 M), after which the solution was extracted with CH_2Cl_2 (3 x 20 ml). The aqueous layer was acidified to pH 3 using 1.0 M HCl and extracted with

CH_2Cl_2 (3 x 10 ml). Evaporation of the solvent from the organic phase gave the unreacted 2-phenylbutyric acid. The optical rotation of the unreacted 2-phenylbutyric acid was found to be negative (*R*), indicating the *S* configuration at C-19 in compound **17**.

Alstonoxine A (**18**)**:** light yellowish oil; $[\alpha]_D$ –34 (*c* 0.19, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 216 (3.89), 255 (3.70) and 285 (3.18) nm; IR (dry film) ν_{max} 3390 (OH), 3288 (NH) and 1694 (broad, multiplet C=O) cm^{-1}; ESIMS *m*/*z* 329 (MH^+, $C_{19}H_{24}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.13.

Alstonoxine B (**19**)**:** light yellowish oil; $[\alpha]_D$ –12 (*c* 0.41, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 213 (4.15), 255 (3.65) and 286 (3.04) nm; IR (dry film) ν_{max} 3370 (OH), 3288 (NH) and 1693 (C=O) cm^{-1}; ESIMS *m*/*z* 331 (MH^+, $C_{19}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.13.

Crystallographic data of Alstonoxine B (19): colorless block crystals, $C_{19}H_{26}N_2O_3$, *M*r = 330.42, monoclinic, space group $P2_1$, *a* = 10.7388(4) Å, *b* = 10.5321(3) Å, *c* = 15.2354(5) Å, $\alpha = \gamma = 90^{\circ}$, β = 92.851(2), *V* = 1721.02(10) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.275 gcm^{-3}, crystal size 0.21 x 0.41 x 0.49 mm^3, *F*(000) = 712. The final R_1 value is 0.0382 (wR_2 = 0.1076) for 7729 reflections [$I>2\sigma(I)$]. CCDC number: 935819

Alstonisine (**20**)**:** colorless oil; $[\alpha]_D$ +191 (*c* 0.08, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 212 (4.02) and 255 (3.88) nm; ESIMS *m*/*z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.14 and Table 2.15.

Alstonal (**21**)**:** colorless oil; $[\alpha]_D$ +256 (*c* 0.05, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 205 (4.27), 212 (4.27) and 262 (3.92) nm; ESIMS *m*/*z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.14 and Table 2.15.

***N*(4)-Demethylalstophylline oxindole** (**22**)**:** light yellowish oil; $[\alpha]_D$ +119 (*c* 0.32, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 213 (4.72), 248 (4.39), and 296 (3.97) nm; ESIMS *m*/*z* 369 (MH^+, $C_{21}H_{24}N_2O_4$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.14 and Table 2.15.

***N*(4)-Demethylalstophyllal oxindole** (**23**)**:** light yellowish oil; ESIMS *m*/*z* 369 (MH^+, $C_{21}H_{24}N_2O_4$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.14 and Table 2.15.

Compound 24 (2(*S*)-Cathafoline): light yellowish oil; $[\alpha]_D$ –175 (*c* 0.22, $CHCl_3$) and subsequently colorless needles from CH_2Cl_2-hexane; mp 121–123 ℃; UV (EtOH) λ_{max} (log ε) 208 (4.68), 246 (4.38), 308 (4.06) nm; IR (dry film) ν_{max} 1737 cm^{-1}; ESIMS *m/z* 339 $[M + H]^+$; HRESIMS *m/z* 339.2071 (calcd for $C_{21}H_{26}N_2O_2$ + H, 339.2073); for ^{1}H NMR and ^{13}C NMR data, see Table 2.16. HMBC: ^2J H(3) to C(2); H(6α), H(6β) to C(5); H(5α), H(5β) to C(6); H(2), H(6α), H(16) to C(7); H(10) to C(9); H(11) to C(10); H(10) to C(11); H(11) to C(12); H(14a), H(14b), H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a), H(21b) to C(20); H(16) to *C*O_2Me. ^3J H(6β), H(14a), H(16), N_1Me to C(2); H(5β), H(15), H(21a) to C(3); H(3), H(21a), H(21b) to C(5); H(2), H(16) to C(6); H(3), H(9), H(5β) to C(7); H(2), H(6α), H(10), H(12), H(16) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N_1Me to C(13); H(2), H(16) to C(14); H(3), H(19), H(21a), H(21b) to C(15); H(2), H(6α), H(6β) to C(16); H(21a), H(21b) to C(19); H(18) to C(20); H(5α), H(5β), H(19) to C(21); H(2) to N_1Me; CO_2*Me*

to *C*O_2Me. NOESY: H(2)/H(3), H(6α), N_1Me; H(3)/H(2), H(14a), H(14b), N_1Me; H(5α)/H(5β), H(6α); H(5β)/H(5α), H(6β), H(21a); H(6α)/H(2), H(5α), H(6β), H(9); H(6β)/H(5β), H(6α); H(9)/H(6α), H(10); H(11)/H(10), H(12); H(12)/H(11), N_1Me; H(14a)/H(3), H(14b), H(15), H(21b); H(14b)/H(3), H(14a), H(15), H(16); H(15)/H(14a), H(14b), H(16), H(18); H(16)/H(14b), H(15); H(18)/H(15), H(19), CO_2*Me*; H(19)/H(18), H(21a); H(21a)/H(5β), H(19), H(21b); H(21b)/H(14a), H(21a); CO_2*Me*/H(18); N_1Me/H(2), H(3), H(12).

Compound 25 (2(*S*)-10-Methoxycathafoline): light yellowish oil; $[\alpha]_D$ −138 (*c* 0.47, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.85), 245 (4.60), 307 (4.17) nm; IR (dry film) ν_{max} 1737 cm^{-1}; ESIMS *m/z* 369 $[M + H]^+$; HRESIMS *m/z* 369.2172 (calcd for $C_{22}H_{28}N_2O_2$ + H, 369.2178); for ^{1}H NMR and ^{13}C NMR data, see Table 2.16. HMBC: ^2J H(3) to C(2); H(6α), H(6β) to C(5); H(5α), H(5β) to C(6); H(2), H(6α), H(6β), H(16) to C(7); H(9), H(11) to C(10); H(14b), H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a), H(21b) to C(20); H(16) to CO_2Me. ^3J H(6β), H(14a), N_1Me to C(2); H(5β), H(21a) to C(3); H(3), H(21a), H(21b) to C(5); H(2), H(16) to C(6); H(3), H(9), H(5β) to C(7); H(6α), H(12) to C(8); H(11) to C(9); H(12), 10-OMe to C(10); H(9) to C(11); H(9), H(11), N_1Me to C(13); H(2), H(16) to C(14); H(3), H(19), H(21a), H(21b) to C(15); H(2), H(6α), H(6β) to C(16); H(21a) to C(19); H(14b), H(16), H(18) to C(20); H(5α), H(5β), H(19) to C(21); H(2) to N_1Me; CO_2Me to CO_2Me. ^4J H(18) to C(21). NOESY: H(2)/H(3), H(5α), H(6α), N_1Me; H(3)/H(2), H(14a), H(14b), N_1Me; H(5α)/H(2), H(5β), H(6α); H(5β)/H(5α), H(6β), H(21a); H(6α)/H(2), H(5α), H(6β), H(9); H(6β)/H(5β), H(6α), H(9); H(9)/H(6α), H(6β), H(16), 10-OMe, CO_2Me; H(11)/H(12), 10-OMe; H(12)/H(11), N_1Me; H(14a)/H(3), H(14b), H(15), H(21b); H(14b)/H(3), H(14a), H(15), H(16); H(15)/H(14a), H(14b), H(16), H(18); H(16)/H(9),

H(14b), H(15); H(18)/H(15), H(19), CO_2Me; H(19)/H(18), H(21a); H(21a)/H(5β), H(19), H(21b); H(21b)/H(14a), H(21a); CO_2Me/H(9), H(18); N_1Me/H(2), H(3), H(12); 10-OMe/H(9), H(11).

Compound 26 (2(*R*)-3-Hydroxycathafoline): light yellowish oil; $[\alpha]_D$ −48 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 202 (4.64), 252 (4.11), 295 (3.69) nm; IR (dry film) ν_{max} 1737 cm^{-1}; ESIMS *m/z* 355 $[M + H]^+$; HRESIMS *m/z* 355.2028 (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); for ^{1}H NMR and ^{13}C NMR data, see Table 2.17. HMBC: ^2J H(14a), H(14b) to C(3); H(6β) to C(5); H(5β) to C(6); H(2), H(6α), H(6β), H(16) to C(7); H(10) to C(9); H(9) to C(10); H(10) to C(11); H(11) to C(12); H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a) to C(20); H(16) to *C*O_2Me. ^3J H(14a), H(14b), *N*(1)-Me to C(2); H(5α), H(21a) to C(3); H(21a) to C(5); H(2) to C(6); H(5α), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to H(12); H(9), H(11), *N*(1)-Me to C(13); H(16) to C(14); H(19), H(21a) to C(15); H(2), H(6α), H(6β), H(14b) to C(16); H(21a) to C(19); H(14a), H(18) to C(20); H(5α), H(19) to C(21); CO_2*Me* to *C*O_2Me. NOESY: H(2)/H(14a); H(5β)/H(5α), H(21a); H(5α)/H(5β), H(6α); H(6α)/H(5α), H(6β); H(6β)/H(6α), H(9); H(9)/H(6β), H(10), CO_2*Me*; H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), *N*(1)-Me; H(14a)/H(2), H(14b), H(15), H(16); H(14b)/H(14a), H(15), H(21b); H(15)/H(14a), H(14b), H(16), H(18); H(16)/H(14a), H(15); H(18)/H(15), H(19); H(19)/H(18), H(21a); H(21a)/H(19), H(21b); H(21b)/H(14b), H(21a); CO_2*Me*/H(9); *N*(1)-Me/H(12).

Compound 27 (10-Demethoxyvincorine): light yellowish oil; $[\alpha]_D$ −127 (*c* 0.48, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (5.21), 256 (4.78), 308 (4.29) nm; IR (dry film) ν_{max} 1736 cm^{-1}; ESIMS *m/z* 339 $[M + H]^+$; HRESIMS *m/z* 339.2072 (calcd for

$C_{21}H_{26}N_2O_2$ + H, 339.2073); for ^{1}H NMR and ^{13}C NMR data, see Table 2.18. HMBC: ^2J H(3α), H(3β) to C(2); H(14a/b) to C(3); H(6β) to C(5); H(5α) to C(6); H(6α), H(6β), H(16) to C(7); H(10) to C(9); H(11) to C(10); H(11) to C(12); H(3α), H(3β) to C(14); H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a), H(21b) to C(20); H(16) to *C*O_2Me. ^3J H(5β), H(14a/b), H(21a), N(1)-Me to C(2); H(15) to C(3); H(21a), H(21b) to C(5); H(16) to C(6); H(3α), H(5β), H(9), H(15), H(21a), H(21b) to C(7); H(6α), H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(16) to C(14); H(19), H(21a) to C(15); H(6α), H(6β), H(14a/b) to C(16); H(21a), H(21b) to C(19); H(14a/b), H(16), H(18) to C(20); H(5α), H(5β), H(19) to C(21); CO_2*Me* to *C*O_2Me. NOESY: H(3β)/H(3α); H(3α)/H(3β), 21b; H(5β)/H(5α), H(6β), H(21a); H(5α)/H(5β), H(6α), H(6β); H(6α)/H(5α), H(6β); H(6β)/H(5α), H(5β), H(6α); H(9)/H(10), H(16); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N(1)-Me; H(14a/b)/H(15), H(16), H(21b); H(15)/H(14a/b), H(16), H(18); H(16)/H(9), H(14a/b), H(15); H(18)/H(15), H(19); H(19)/H(18), H(21a); H(21a)/H(5β), H(19), H(21b); H(21b)/H(3α), H(14a/b), H(21a); N(1)Me/H(12).

Compound 28 (10-Demethoxyvincorine *N*(4)-oxide): light yellowish oil; $[\alpha]_D$ −62 (*c* 0.5, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (5.43), 247 (5.19), 299 (4.70) nm; IR (dry film) ν_{max} 1734 cm^{-1}; ESIMS *m/z* 355 $[M + H]^+$; HRESIMS *m/z* 355.2019 (calcd for $C_{21}H_{26}N_2O_3$ + H, 355.2022); for ^{1}H NMR and ^{13}C NMR data, see Table 2.18. HMBC ^2J: H(3α) to C(2); H(6β) to C(5); H(6α), H(16) to C(7); H(10) to C(9); H(10) to C(11); H(3α), H(3β) to C(14); H(16) to C(15); H(15) to C(16); H(19) to C(18); H(18) to H(19); H(15), H(21a), H(21b) to C(20); H(16) to *C*O_2Me. ^3J: H(5a), H(5b), H(6α), H(21a), N(1)-Me to C(2); H(15) to C(3); H(21a) to C(5); H(16) to C(6); H(3α), H(5a), H(9), H(15) to C(7); H(6α), H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9)

to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(16) to C(14); H(19), H(21a) to C(15); H(6β), H(14α) to C(16); H(15), H(21a) to C(19); H(16), H(18) to C(20); H(5b), H(15), H(19) to C(21); CO_2*Me* to *C*O_2Me. NOESY: H(3β)/H(3α), H(14β), H(16), N(1)-Me; H(3α)/H(3β), H(21b), N(1)-Me; H(5a)/H(5b), H(6α), H(6β); H(5b)/H(5a), H(6α); H(6α)/H(6β), H(5a), H(5b); H(6β)/H(5a), H(6α), H(19); H(9)/H(6α), H(10), H(16), CO_2*Me*; H(9), H(11) to C(10); H(10), H(12) to C(11); H(11), N(1)-Me to C(12); H(14α)/H(14β), H(15), H(21b); H(14β)/H(3β), H(14α), H(15), H(16); H(15)/H(14α), H(14β), H(16), H(18); H(16)/H(3β), H(9), H(14β), H(15); H(18)/H(15), H(19), CO_2*Me*; H(19)/H(6β), H(18), H(21a); H(21a)/H(19), H(21b); H(21b)/H(3α), H(14α), H(21a); N(1)-Me/H(3α), H(3β), H(12); CO_2*Me*/H(9), H(18).

Compound 29 (11-Methoxyvincorine): light yellowish oil; $[\alpha]_D$ –86 (*c* 0.27, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.16), 256 (3.75), 317 (3.54) nm; IR (dry film) ν_{max} 1733 cm^{-1}; ESIMS *m/z* 399 $[M + H]^+$; HRESIMS *m/z* 399.2078 (calcd for $C_{23}H_{30}N_2O_4$ + H, 339.2084); for ^{1}H NMR and ^{13}C NMR data, see Table 2.19. HMBC ^2J: H(3β), H(16) to C(2); H(6β) to C(5); H(6α), H(16) to C(7); H(9) to C(10); H(12) to C(11); H(12) to C(13); H(3β) to C(14); H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a), H(21b) to C(20); H(16) to *C*O_2Me. ^3J: H(21a), N(1)-Me to C(2); H(21a), H(21b) to C(5); H(16) to C(6); H(5α), H(5β), H(9) to C(7); H(6α), H(12), H(16) to C(8); H(12), 10-OMe to C(10); H(9), 11-OMe to C(11); H(9), N(1)-Me to C(13); H(16) to C(14); H(21a) to C(15); H(6β), H(14) to C(16); H(15), H(21a), H(21b) to C(19); H(16), H(18) to C(20); H(5α), H(5β), H(19) to C(21); CO_2*Me* to *C*O_2Me. NOESY: H(3β)/H(3α), H(16), N(1)-Me; H(3α)/H(3β), N(1)-Me; H(5β)/H(5α), H(21a); H(5α)/H(5β), H(6α); H(6α)/H(5α), H(6β); H(6β)/H(6α); H(9)/H(16), 10-OMe; H(12)/N(1)-Me, 11-OMe; H(14)/H(15), H(16); H(15)/H(14), H(16), H(18); H(16)/H(3β), H(9), H(14), H(15); H(18)/H(15),

H(19), CO_2Me; H(19)/H(18), H(21a); H(21a)/H(5β), H(19), H(21b); H(21b)/H(21a); CO_2Me/H(18); N(1)-Me/H(3α), H(3β), H(12); 10-OMe/H(9); 11-OMe/H(12).

Compound 30 (Vincorine *N*(4)-oxide): light yellowish oil; $[\alpha]_D$ –84 (*c* 0.4, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.16), 256 (3.75), 317 (3.54)nm; IR (dry film) ν_{max} 1734 cm^{-1}; ESIMS *m/z* 385 $[M + H]^+$; HRESIMS *m/z* 385.2130 (calcd for $C_{22}H_{28}N_2O_4$ + H, 385.2127); for ^{1}H NMR and ^{13}C NMR data, see Table 2.19.

Compound 31 (11-Demethoxyquaternine): light yellowish oil; $[\alpha]_D$ –10 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (4.64), 241 (4.35), 307 (3.96) nm; IR (dry film) ν_{max} 1736 cm^{-1}; ESIMS *m/z* 383 $[M + H]^+$; HRESIMS *m/z* 383.1978 (calcd for $C_{22}H_{26}N_2O_4$ + H, 383.1971); for ^{1}H NMR and ^{13}C NMR data, see Table 2.20. HMBC ^2J: H(3) to C(2); H(6α) to C(5); H(5) to C(6); H(6α), H(6β) to C(7); H(9), H(11) to C(10); H(16) to C(15); H(19) to C(18); H(18) to C(19); H(21a) to C(20); H(16) to CO_2Me. ^3J: H(5), H(6β), N(1)-Me to C(2); H(5), H(21a) to C(3); H(3), H(21a), H(21b) to C(5); H(16) to C(6); H(3), H(5), H(9) to C(7); H(6α), H(12), H(16) to C(8); H(11) to C(9); H(12), 10-OMe to C(10); H(9) to C(11); H(9), H(11), N(1)-Me to C(13); H(3), H(21a), H(21b), H(19) to C(15); H(6β) to C(16); H(21a) to C(19); H(14a), H(14b), H(16), H(18) to C(20); H(19) to C(21); CO_2Me to CO_2Me. NOESY: H(3)/H(14a), H(14b), N(1)-Me; H(5)/H(6α), H(6β), H(21a); H(6α)/H(5), H(6β), H(9); H(6β)/H(5), H(6α); H(9)/H(6α), CO_2Me, 10-OMe; H(11)/H(12), 10-OMe; H(12)/H(11), N(1)-Me; H(14a)/H(3), H(14b), H(15), H(16); H(14b)/H(3), H(14a), H(15), H(21b); H(15)/H(14a), H(14b), H(16), H(18); H(16)/H(14a), H(15); H(18)/H(15), H(19), CO_2Me; H(19)/H(18), H(21a); H(21a)/H(5), H(19), H(21b); H(21b)/H(14b), H(21a); N(1)-Me/H(3), H(12); CO_2Me/H(9), H(18); 10-OMe/H(9), H(11).

Compound 32 (19,20-*Z*-Affinisine): light yellowish oil; $[\alpha]_D$ +8 (*c* 0.45, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (5.44), 229 (5.37), 254 (4.92), 284 (4.73) nm; IR (dry film) ν_{max} 3395 cm^{-1}; ESIMS *m/z* 309 $[M + H]^+$; HRESIMS *m/z* 309.1973 (calcd for $C_{20}H_{24}N_2O$ + H, 309.1967); for ^1H NMR and ^{13}C NMR data, see Table 2.21. HMBC ^2J: H(3) to C(2); H(6α), H(6β), H(16) to C(5); H(5) to C(6); H(6α), H(6β) to C(7); H(9) to C(8); H(3) to C(14); H(14b), H(16) to C(15); H(5), H(17) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19). ^3J: H(6α), H(6β), H(14a), H(14b), N(1)-Me to C(2); H(5), H(15), H(21) to C(3); H(3), H(17), H(21) to C(5); H(16) to C(6); H(3), H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(16) to C(14); H(3), H(17), H(19) to C(15); H(6α), H(6β), H(14a), H(14b) to C(16); H(5) to C(17); H(21) to C(19); H(14a), H(14b), H(18) to C(20); H(3), H(5), H(19) to C(21). NOESY: H(3)/H(14b), N(1)-Me; H(5)/H(6α), H(17), H(21); H(6β)/H(6α), H(9), H(16); H(6α)/H(5), H(6β); H(9)/H(6β), H(10); H(10)/H(9); H(12)/N(1)-Me; H(14a)/H(14b), H(15); H(14b)/H(3), H(14a); H(15)/H(14a), H(16), H(17), H(19); H(16)/H(6β), H(15), H(17); H(17)/H(5), H(15), H(16); H(18)/H(19), H(21); H(19)/H(15), H(18); H(21)/H(5), H(18); N(1)-Me/H(3), H(12).

Compound 33 (Vincamajine *N*(4)-oxide): light yellowish oil; $[\alpha]_D$ −29 (*c* 0.04, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 210 (4.94), 231 (4.70) and 282 (4.30) nm; IR (dry film) ν_{max} 3400 and 1737 cm^{-1}; ESIMS *m/z* 383 $[M + H]^+$; HRESIMS m/z 383.1980 (calcd for $C_{22}H_{26}N_2O_4$ + H, 383.1971); for ^1H NMR and ^{13}C NMR data, see Table 2.22.

Compound 34 (Vincamajine 17-*O*-veratrate *N*(4)-oxide): light yellowish oil; $[\alpha]_D$ −75 (*c* 0.94, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 209 (5.75), 254 (5.40) and 292 (5.07)

nm; IR (dry film) ν_{max} 1737 cm^{-1}; ESIMS *m/z* 547 $[M + H]^+$; HRESIMS *m/z* 547.2443 (calcd for $C_{31}H_{34}N_2O_7$ + H, 547.2444), for ^1H NMR and ^{13}C NMR data, see Table 2.22.

Cathafoline (**35**)**:** light yellowish oil; $[\alpha]_D$ –35 (*c* 0.24, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 208 (3.22), 250 (3.62) and 306 (4.18) nm; ESIMS *m/z* 399 (MH^+, $C_{21}H_{26}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.23 and Table 2.24.

Cathafoline *N*(4)-oxide (**36**)**:** light yellowish oil; $[\alpha]_D$ –36 (*c* 0.22, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 212 (3.98), 250 (3.81) and 294 (3.31) nm; IR (dry film) ν_{max} 3392 (N-O), 1736 (C=O) cm^{-1}; ESIMS *m/z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.23 and Table 2.24.

10-Methoxycathafoline (**37**)**:** light yellowish oil; $[\alpha]_D$ –57 (*c* 0.09, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 204 (4.23), 249 (3.74) and 315 (3.88) nm; IR (dry film) ν_{max} 1736 (C=O) cm^{-1}; ESIMS *m/z* 369 (MH^+, $C_{22}H_{28}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.23 and Table 2.24.

Strictamine (**38**)**:** light yellowish oil; $[\alpha]_D$ +61 (*c* 0.32, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 219 (4.07), 264 (3.59), 284 (3.47) and 296 (3.35) nm; ESIMS *m/z* 323 (MH^+, $C_{20}H_{22}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.25 and Table 2.26.

11-Methoxystrictamine (**39**)**:** light yellowish oil; $[\alpha]_D$ +72 (*c* 0.09, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 214 (4.15), 250 (3.72), 282 (3.50) and 299 (3.04) nm; ESIMS *m/z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.25 and Table 2.26.

11-Hydroxystrictamine (**40**)**:** light yellowish oil; $[\alpha]_D$ +83 (*c* 0.68, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 215 (3.99), 265 (3.48), 280 (3.55) and 296 (3.00) nm; ESIMS *m/z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.25 and Table 2.26.

Vincorine (**41**)**:** $[\alpha]_D$ −47 (*c* 0.20, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 255 (4.00) and 326 (3.58) nm; ESIMS *m/z* 369 (MH^+, $C_{22}H_{28}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.27.

Norvincorine (**42**): light yellowish oil; $[\alpha]_D$ −162 (*c* 0.29, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 201 (4.46), 241 (3.94), 316 (3.52) nm; IR (dry film) ν_{max} 1734 cm^{-1}; ESIMS *m/z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.27.

Alstonamide (**43**): light yellowish oil; $[\alpha]_D$ −82 (*c* 0.63, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 205 (5.53), 212 (5.51), 266 (5.20), 303 (5.06) nm; IR (dry film) ν_{max} 1732, 1665 cm^{-1}; ESIMS *m/z* 413 (MH^+, $C_{23}H_{28}N_2O_5$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.28 and Table 2.29.

Demethoxyalstonamide (**44**)**:** light yellowish oil; $[\alpha]_D$ −64 (*c* 0.12, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 205 (4.33), 264 (4.01), 291 (3.62) and 361 (3.50) nm; IR (dry film) ν_{max} 1733 (C=O, ester) and 1665 (C=O, amide) cm^{-1}; ESIMS *m/z* 383 (MH^+, $C_{22}H_{26}N_2O_4$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.28 and Table 2.29.

Alstomaline (**45**)**:** light yellowish oil; $[\alpha]_D$ −244 (*c* 0.04, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 202 (3.77), 273 (3.85) and 317 (3.12) nm; IR (dry film) ν_{max} 1737, 1634 and

1646 cm^{-1}; ESIMS *m/z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.28 and Table 2.29.

Quaternine (**46**)**:** light yellowish oil; $[\alpha]_D$ +51 (*c* 0.20, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 205 (4.62), 245 (3.91) and 303 (3.71) nm; IR (dry film) ν_{max} 1734 (C=O) cm^{-1}; ESIMS *m/z* 413 (MH^+, $C_{23}H_{28}N_2O_5$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.30.

Picrinine (**47**)**:** colorless oil; $[\alpha]_D$ −110 (*c* 0.05, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 220 (3.81), 235 (3.67) and 287 (3.32) nm; ESIMS *m/z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.30.

12-Demethoxytabernulosine (**48**)**:** light yellowish oil; $[\alpha]_D$ −12 (*c* 0.76, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (5.46), 241 (5.14), 305 (4.69) nm; IR (dry film) ν_{max} 3353, 1738 cm^{-1}; ESIMS *m/z* 369 $[M + H]^+$; HRESIMS *m/z* 369.1819 (calcd for $C_{21}H_{24}N_2O_4$ + H, 369.1814); for ^1H NMR and ^{13}C NMR data, see Table 2.20. HMBC ^2J: H(3) to C(2); H(14a), H(14b) to C(3); H(6α), H(6β) to C(5); H(5) to C(6); H(6α), H(6β), H(16) to C(7); H(9), H(11) to C(10); H(14a), H(16) to C(15); H(15) to C(16); H(18) to C(19); H(21a), H(21b) to C(20); H(16) to *C*O_2Me. ^3J: H(5), H(6β), H(14b) to C(2); H(15), H(21a), H(21b), NH to C(3); H(21a), H(21b) to C(5); H(16) to C(6); H(3), H(5), H(9), H(15), NH to C(7); H(6α), H(6β), H(12), H(16), NH to C(8); H(11) to C(9); H(12), 10-OMe to C(10); H(9) to C(11); H(9), H(11) to C(13); H(16) to C(14); H(3), H(19), H(21a) to C(15); H(6α), H(6β), H(14a), H(14b) to C(16); H(19) to C(18); H(21a), H(21b) to C(19); H(14a), H(16), H(18) to C(20); H(19) to C(21); CO_2*Me* to *C*O_2Me. NOESY: H(3)/H(14a), H(14b), NH; H(5)/H(6α), H(6β), H(21a); H(6α)/H(5), H(6β),

H(9); H(6β)/H(5), H(6α); H(9)/H(6α), 10-OMe; H(11)/10-OMe; H(12)/NH; H(14a)/H(3), H(14b), H(15), H(16); H(14b)/H(3), H(14a), H(15); H(15)/H(14a), H(14b), H(16), H(18); H(16)/H(14a), H(15); H(18)/H(15), H(19), CO_2Me; H(19)/H(18), H(21a); H(21a)/H(5), H(19), H(21b); H(21b)/H(21a); NH/H(3), H(12); CO_2Me/H(18); 10-OMe/H(9), H(11).

Affinisine (**49**): light yellowish oil; $[\alpha]_D$ +18 (*c* 3.75, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.15), 288 (3.98), 302 (3.82) nm; ESIMS *m/z* 309 (MH^+, $C_{20}H_{24}N_2O$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.32.

Affinisine oxindole (50): light yellowish oil; $[\alpha]_D$ −70 (*c* 0.063, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 211 (4.31), 233 (3.82), 255 (3.87), 290 (3.35) nm; IR (dry film) ν_{max} 3384, 1712 cm^{-1}; ESIMS *m/z* 325 (MH^+, $C_{20}H_{24}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.32.

Normacusine B (51): light yellowish oil; $[\alpha]_D$ +16 (*c* 0.26, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 225 (4.01), 265 (3.48) and 281 (3.41) nm; ESIMS *m/z* 295 (MH^+, $C_{19}H_{22}N_2O$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.33.

Alstoumerine (**52**): colorless needles from $CHCl_3$; mp 174–176 ^oC; $[\alpha]_D$ −30 (*c* 0.09, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 219 (3.89), 234 (3.93), 274 (3.73), 284 (3.77) and 293 (3.71) nm; ESIMS *m/z* 325 (MH^+, $C_{20}H_{24}N_2O_2$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.33.

Quebrachidine (**53**)**:** light yellowish oil; $[\alpha]_D$ +41 (*c* 0.63, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 202 (3.82), 245 (4.19) and 288 (3.92) nm; ESIMS *m/z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.34 and Table 2.35.

Vincamajine (**54**)**:** light yellowish oil; $[\alpha]_D$ −13 (*c* 0.03, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 204 (2.88), 249 (3.29) and 292 (2.90) nm; ESIMS *m/z* 367 (MH^+, $C_{22}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.34 and Table 2.35.

Vincamajine 17-*O*-veratrate (**55**): light yellowish oil; $[\alpha]_D$ −89 (*c* 1.11, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 204 (5.50), 213 sh (5.33), 255 (5.04) and 294 (4.81) nm; ESIMS *m/z* 531 (MH^+, $C_{31}H_{34}N_2O_6$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.34 and Table 2.35.

Sitsirikine (**56**)**:** yellowish oil; $[\alpha]_D$ +40 ($CHCl_3$, *c* 0.14). UV (EtOH), λ_{max} nm (log ε): 233 (3.91), 272 (3.76), 282 (3.78) and 290 (3.72); IR (dry film) ν_{max} 3370 (OH) and 1708 (C=O) cm^{-1}; ESIMS *m/z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.36 and Table 2.37.

16*R*, 19*E*-Isositsirikine (**57**)**:** yellowish oil; $[\alpha]_D$ −21 (*c* 0.05, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 225 (4.27), 286 (3.96) and 295 (3.65) nm; ESIMS *m/z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.36 and Table 2.37.

18,19-Dihydroisositsirikine (58): light yellowish oil; $[\alpha]_D$ −86 (*c* 0.06, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.13), 280 (3.46) nm; IR (dry film) ν_{max} 3373, 2877, 1710 cm^{-1}; ESIMS *m/z* 357 $[M + H]^+$; HRESIMS *m/z* 357.2179 (calcd for $C_{21}H_{28}N_2O_3$ + H, 357.2173); for ^{1}H NMR and ^{13}C NMR data, see Table 2.36 and Table 2.37.

Pleiocarpamine (**59**)**:** light yellowish oil; $[\alpha]_D$ +87 (*c* 0.08, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 230 (4.32) and 284 (3.85) nm; IR (dry film) ν_{max} 1758 cm^{-1}; ESIMS *m/z* 323 (MH^+, $C_{20}H_{22}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.38 and Table 2.39.

16-Hydroxymethylpleiocarpamine (60): light yellowish oil; $[\alpha]_D$ +102 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 227 (4.20), 284 (3.71) nm; IR (dry film) ν_{max} 3352, 1745 cm^{-1}; ESIMS *m/z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.38 and Table 2.39.

Pleiomaltinine (61): yellowish oil; $[\alpha]_D$ +94 (*c* 0.48, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 214 (4.15), 240 (3.86), 284 (3.81) nm; IR (dry film) ν_{max} 1752, 1650, 1614, 1576 cm^{-1}; EIMS *m/z* 446 $[M]^+$ (28), 387 $[M - CO_2Me]^+$ (12), 339 (6), 322 (81), 263 (100), 248 (23), 232 (35), 218 (19), 180 (72), 135 (34), 108 (19), 96 (8), 71 (8), 43 (8); HREIMS *m/z* 446.1842 (calcd for $C_{26}H_{26}N_2O_5$, 446.1842); LSIMS *m/z* 447 (MH^+, $C_{26}H_{26}N_2O_5$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.38 and Table 2.39.

Picramicine (62): light yellowish oil; $[\alpha]_D$ +109 (*c* 0.16, $CHcCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.33), 253 (3.78), 292 (3.38) nm; ESIMS *m/z* 325 (MH^+, $C_{20}H_{24}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.40.

Fluorocarpamine (**63**)**:** light yellowish oil; $[\alpha]_D$ +243 (*c* 1.64, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 232 (4.15), 260 (3.59) and 289 (3.20) nm; IR (dry film) νmax 1748 and 1696 (C=O); ESIMS *m/z* 339 (MH^+, $C_{20}H_{22}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.40.

Yohimbine (64): light yellowish oil; $[\alpha]_D$ +37 (*c* 1.24, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 224 (4.44), 281 (3.83) nm; IR (dry film) ν_{max} 3362, 2864, 2811, 2760, 1715 cm^{-1}; ESIMS *m/z* 355 (MH^+, $C_{21}H_{26}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.41 and Table 2.42.

Talpinine (**65**)**:** light yellowish oil; $[\alpha]_D$ –4 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 228 (4.25), 284 (3.60) nm; IR (dry film) ν_{max} 3345 cm^{-1}; ESIMS *m/z* 325 (MH^+, $C_{20}H_{24}N_2O_2$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.41 and Table 2.42.

10,11-Dimethoxynareline (**66**)**:** light yellowish oil; $[\alpha]_D$ –56 (*c* 1.57, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 232 (4.38) and 294 (3.81) nm; IR (dry film) ν_{max} 3201 (OH) and 1737 (C=O) cm^{-1}; ESIMS *m/z* 413 (MH^+, $C_{22}H_{24}N_2O_6$ + H); for ^1H NMR and ^{13}C NMR, see Table 2.41 and Table 2.42.

11-Methoxyakuammicine (**67**)**:** light yellowish oil; $[\alpha]_D$ –398 (*c* 0.11, $CHCl_3$); UV (EtOH), λ_{max} nm (log ε): 209 (4.05), 223 (4.06), 242 (3.94), 307 (3.88) and 327 (4.01) nm; ESIMS *m/z* 353 (MH^+, $C_{21}H_{24}N_2O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.43.

11-Methoxyakuammicine *N*(4)-oxide (**68**): light yellowish oil; $[\alpha]_D$ –295 (*c* 0.2, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 209 (4.49), 232 (4.27), 253 (4.16), 296 (3.98), and 308 (4.04) nm; IR (dry film) ν_{max} 3201 (OH) and 1737 (C=O) cm^{-1}; ESIMS *m/z* 661 (MH^+, $C_{21}H_{24}N_2O_4$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.43.

Antirhine (69): colorless oil; $[\alpha]_D$ –40 (*c* 0.01, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 225 (4.41), 282 (3.80), 289 (3.68) nm; ESIMS *m/z* 297 (MH^+, $C_{19}H_{24}N_2O$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.44.

1,2,3,4-Tetrahydro-1-oxo-*β*-carboline (**70**): yellowish oil; $[\alpha]_D$ +56 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 210 (4.98), 231 (5.05), 296 (4.72), 307 (4.74) nm; ESIMS *m/z* 187 (MH^+, $C_{11}H_{10}N_2O$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.44

Lumutinine A (**71**): light yellowish oil; $[\alpha]_D$ +160 (*c* 0.40, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 210 (5.61), 233 (5.61), 254 (5.26) shoulder, 283 (4.94) nm; IR (dry film) ν_{max} 1617, 1651 cm^{-1}; ESIMS *m/z* 673 $[M + H]^+$; HRESIMS *m/z* 673.3755 (calcd for $C_{42}H_{48}N_4O_4$ + H, 673.3748); for ^{1}H NMR and ^{13}C NMR data, see Table 2.45. HMBC: ^2J H-3 to C-2; H-6 to C-5; H-5 to C-6; H-6 to C-7; H-9 to C-8; H-20 to C-15; H-5 to C-16; H-18, H-20 to C-19; H-21 to C-20; H-3' to C-2'; H-6' to C-5'; H-5' to C-6'; H-6' to C-7'; H-21 to C-10'; H-12' to C-11', H-12' to C-13'; H-5', H-17' to C-16'; H-18' to C-19'; H-15', H-21' to C-20'. ^3J H-6, H-14, N_1Me to C-2; H-5, N_4Me to C-3; H-3, N_4Me to C-5; H-5, H-9 to C-7; H-6, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N_1Me to C-13; H-20 to C-14; H-3, H-5, H-21 to C-15; H-6, H-14 to C-16; H-5 to C-17; H-17, H-21 to C-19; H-18 to C-20; H-9' to C-21; H-6', N_1Me' to C-2'; H-5', N_4Me' to C-3'; H-3', H-15', N_4Me' to C-5'; H-5', H-9' to C-7'; H-6', H-12' to C-8'; H-21 to C-9'; H-12' to C-10', H-9', H-21 to C-11'; H-9', N_1Me' to C-13'; H-3', H-5', H-17', H-21' to C-15'; H-6', H-14' to C-16'; H-5', H-15', H-21' to C-17'; H-21' to C-19'; H-14' to C-20'; H-17' to C-21'. 1D-NOE: H-5/H-6α, H-6β, H-16, H-17β; H-17α/ H-5, H-17β; H-17β/ H-5, H-16, H-17α; H-18/ H-20, H-21α; H-5'/ H-6'α, H-6'β, H-17'α, N_4Me'; H-9'/ H-6'α, H-6'β, H-21α, H-21β; H-12'/ H-18, N_1Me'. NOESY: H-3/ H-14α,

H-14β, N_1Me, N_4Me; H-5/ H-16, N_4Me; H-6/ H-5; H-9/ H-10; H-12/ H-11, N_1Me; H-15/ H-14; H-17α/ H-17β, H-14α; H-17β/ H-5, H-16; H-20/ H-18; H-21α/ H-18, H-20; H-21β/ H-14β; N_1Me/ H-14β; H-3'/ H-14'a, H-14'b, N_1Me', N_4Me'; H-5'/ H-16', N_4Me'; H-6'/ H-16', N_4Me'; H-9'/ H-6', H-21α; H-12'/ N_1Me'; H-15'/ H-14', H-16'; H-17'α/ H-5', H-16'; H-17'β/ H-5', H-14', H-16', H-17'α; H-21'/ H-18'; N_1Me'/ H-14'β.

Lumutinine B (**72**): Yellowish oil; $[\alpha]_D$ –11.0 (*c* 0.48, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 210 (5.71), 232 (5.64), 255 (5.35), 285 (4.95) nm; IR (dry film) ν_{max} 1616, 1651 cm^{-1}; ESIMS *m/z* 673 $[M + H]^+$; HRESIMS *m/z* 673.3751 (calcd for $C_{42}H_{48}N_4O_4$ + H, 673.3748); for ^{1}H NMR and ^{13}C NMR data, see Table 2.46. HMBC: ^2J H-3 to C-2; H-14 to C-3; H-6 to C-7; H-9 to C-8; H-3 to C-14; H-14 to C-15; H-18 to C-19; H-15, H-21 to C-20; H-3' to C-2'; H-5' to C-3'; H-6' to C-5'; H-6' to H-7'; H-10' to C-11'; H-21 to C-12'; H-21' to C-20'. ^3J H-6, H-14, N_1Me to C-2; N_4Me to C-3; H-3, H-17, N_4Me to C-5; H-3, H-5, H-9 to C-7; H-6, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N_1Me to C-13; H-3, H-16, H-21 to C-15; H-6, H-14 to C-16; H-17, H-21 to C-19; H-14, H-18 to C-20; H-3 to N_4Me; H-6', H-14', N_1Me to C-2'; N_4Me to C-3'; H-3', N_4Me to C-5'; H-5', H-9' to C-7'; H-6', H-10' to C-8'; H-9', H-21' to C-11', H-10' to C-12'; H-9', N_1Me' to C-13'; H-3', H-5', H-15', H-17' to C-15'; H-5', H-6', H-17' to C-16'; H-5', H-21' to C-17'; H-18', H-21' to C-19'; H-17' to C-21'; H-5' to N_4Me. NOE: NOE: H-3/ H-14α, H-14β, N_1Me, N_4Me; H-14α/ H-14β, H-21β, H-3; H-17α/ H-17β, H-16; H-18/ H-20, H-21α; H-21α/ H-18, H-20, H-21β, N_1Me'; H-5'/ H-6'β, H-16', H-17'α, N_4Me'; H-6'α/ H-5', H-6'β, N_4Me'; H-9'/ H-6'α, H-6'β, H-10'; H-10'/ H-9'; H-16'/ H-5', H-6'α, H-15', H-17'β; H-17'α/ H-17'β; H-17'β/ H-17'α, H-5', H-16'; H-21'/ H-18'; N_1Me'/ H-3', H-14'α, H-21α, H-21β. NOESY: H-3/ H-14α, H-14β, N_1Me, N_4Me; H-5/ H-6, H-16, N_4Me; H-6α/ H-6β; H-9/ H-10; H-11/ H-10; H-12/ H-11, N_1Me; H-

17α/ H-16, H-17β; H-17β/ H-5; H-20/ H-14α, H-14β, H-18; H-21α/ H-18, H-20; H-21β/ H-14α, H-21α; H-3'/ H-14α, H-14β, N_4Me'; H-5'/ H-16', N_4Me'; H-6'α/ H-6'β, H-16'; H-9'/ H-10'; H-14'α/ H-14'β; H-15'/ H-14'α, H-14'β, 16'; H-17'α/ H-17β; H-17'β/ H-5', H-16'; H-21'/ H-18'; N_1Me'/ H-14'α, H-21α, H-21β.

Lumutinine C (**73**): light yellowish oil; $[\alpha]_D$ +84 (*c* 0.32, $CHCl_3$); UV (EtOH) λ_{max} (log ε): 208 (5.31), 228 (5.33), 284 (4.78) nm; IR (dry film) ν_{max} 3360 cm^{-1}; ESIMS *m/z* 661 $[M + H]^+$; HRESIMS *m/z* 661.3749 (calcd for $C_{41}H_{48}N_4O_4$ + H, 661.3748); for ^{1}H NMR and ^{13}C NMR data, see Table 2.47. HMBC: ^2J H-3 to C-2; H-6 to C-5; H-5 to C-6; H-6 to C-7; H-9 to C-8; H-20 to C-15; H-5, H-17 to C-16; H-18, H-20 to C-19; H-21 to C-20; H-20 to C-21; H-3' to C-2'; H-14' to C-3'; H-6' to C-5'; H-5' to C-6'; H-6' to C-7'; H-21 to C-9'; H-11' to C-10'; H-3' to C-14', H-14' to C-15'; H-5' to C-16'; H-19' to C-18'; H-18' to C-19'; H-15', H-19', H-21' to C-20'. ^3J H-6, H-14, N_1Me to C-2; H-5, N_4Me to C-3; H-3, N_4Me to C-5; H-3, H-5, H-9 to C-7; H-6, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N_1Me to C-13; H-20 to C-14; H-3, H-5, H-21 to C-15; H-6 to C-16; H-5 to C-17; H-17, H-21 to C-19; H-18 to C-20; H-20 to C-21; H-6', H-14', N_1Me' to C-2'; H-15', H-21' to C-3'; H-3', H-15', H-17', H-21' to C-5'; H-3', H-5' to C-7'; H-21, H-12' to C-8'; H-20, H-11' to C-9'; H-21, H-12' to C-10', H-11', N_1Me' to C-13'; H-17', H-19', H-21' to C-15'; H-6', H-14' to C-16'; H-5' to C-17'; H-15', H-21' to C-19'; H-14', H-18' to C-20'; H-15', H-19' to C-21'. NOESY: H-3/ N_1Me, N_4Me; H-5/ H-6β, N_4Me; H-6α/ H-5, H-6β, N_4Me; H-6β/ H-16; H-9/H-10; H-12/ H-11, N_1Me; H-14α/ H-14β, H-15; H-15/ H-14β; H-17α/ H-17β; H-17β/ H-5, H-16; H-20/ H-18; H-21α/ H-18, H-20, H-21β; H-3'/ H-14'α, N_1Me'; H-5'/ H-16'; H-6'α/ H-16'; H-12'/ H-11', N_1Me'; H-14'α/ H-14'β; H-15'/ H-14'α, H-14'β, H-16', H-18'; H-17'/ H-16'; H-19'/ H-18', H-21'; H-21'/ H-18', H-19'

Lumutinine D (**74**): light yellowish oil; $[\alpha]_D$ +209 (*c* 0.40, $CHCl_3$); UV (EtOH) λ_{max} (log ε): 209 (5.40), 231 (5.49), 290 (4.89) nm; IR (dry film) ν_{max} 3370 cm^{-1}; ESIMS *m/z* 645 $[M + H]^+$; HRESIMS *m/z* 645.3809 (calcd for $C_{41}H_{48}N_4O_3$ + H, 645.3799); for ^1H NMR and ^{13}C NMR data, see Table 2.48. HMBC: ^2J H-3 to C-2; H-6 to C-5; H-5 to C-6; H-6 to C-7; H-9 to C-8; H-3 to C-14; H-5, H-17 to C-16; H-18, H-20 to C-19; H-21 to C-20; H-3' to C-2'; H-6', H-16' to C-5'; H-5' to C-6'; H-6' to C-7'; H-9' to C-10'; H-21 to C-11', H-3' to C-14'; H-15', H-17' to C-16'; H-16' to C-17'; H-19' to C-18'; H-18' to C-19'. ^3J H-6, H-14, N_1Me to C-2; H-5, N_4Me to C-3; H-3, N_4Me to C-5; H-3, H-5, H-9 to C-7; H-6, H-10, H-12 to C-8; H-11 to C-9; H-12 to C-10; H-9 to C-11; H-10 to C-12; H-9, H-11, N_1Me to C-13; H-20 to C-14; H-3, H-5, H-17, H-21 to C-15; H-6, H-14 to C-16; H-5 to C-17; H-17, H-21 to C-19; H-18 to C-20; H-21' to C-21; H-6', H-14', N_1Me' to C-2'; H-5', H-15' to C-3'; H-3', H-17' to C-5'; H-16' to C-6'; H-3', H-5', H-9' to C-7'; H-6', H-12' to C-8'; H-21, H-12' to C-10'; H-20, H-9' to C-11'; H-21 to C-12'; H-9', N_1Me' to C-13'; H-16' to C-14'; H-17', H-19' to C-15'; H-6', H-14' to C-16'; H-5' to C-17'; H-15', H-21' to C-19'; H-14', H-16' to C-20'; H-5', H-19' to C-21'. NOESY: H-3/ H-14α, H-14β, N_4Me; H-5/ H-16, N_4Me; H-6α/ H-6β; H-6β/ H-5; H-9/ H-6α, H-6β, H-10; H-10/ H-11; H-12/ H-11, N_1Me; H-14α/ H-14β, H-15; H-14β/ H-3, N_1Me; H-15/ H-14β; H-16/ H-5; H-17α/ H-14α, H-17β; H-17β/ H-5, H-16; H-20/ H-18; H-21α/ H-14α, H-18, H-20, H-21β; H-21β/ H-14β; N_1Me/ H-14β; H-3'/ H-14'α, H-21'α, N_1Me'; H-6'α/ H-6'β; H-12'/ H-21α, H-21β, N_1Me'; H-15'/ H-14α, H-14β; H-17'/ H-5', H-15'; H-19'/ H-17', H-18'; H-21'/ H-18'.

Lumutinine E (75): light yellowish oil; $[\alpha]_D$ +74 (*c* 0.14, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (3.66), 284 (3.06) nm; IR (dry film) ν_{max} 3380 cm^{-1}; EIMS *m/z* 630 $[M]^+$ (100), 599 $[M - CH_2OH]^+$ (9), 560 (3), 505 (8), 430 (11), 403 (2), 361 (19), 308 (47),

238 (12), 197 (76), 170 (18), 108 (2), 70 (7); HREIMS *m/z* 630.3572 (calcd for $C_{40}H_{46}N_4O_3$, 630.3570); for ^{1}H NMR and ^{13}C NMR data, see Table 2.49, respectively. HMBC: ^{2}J H(6β), H(6α) to C(5); H(6β), H(6α) to C(7); H(20) to C(15); H(18), H(20) to C(19); H(21a), H(21b) to C(20); H(3'), N(1')H to C(2'); H(6'β), H(16') to C(5'); H(6'β), H(6'α) to C(7'); H(21a), H(21b) to C(9'); H(11') to C(10'); N(1')H to C(13'); H(16') to C(17'); H(19') to C(18'); H(18') to C(19'). ^{3}J H(6β), H(6α), N(1)-Me to C(2); H(5), N(4)-Me to C(3); H(17α), H(17β), N(4)-Me to C(5); H(5), H(9) to C(7); H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(20) to C(14); H(5), H(21a), H(21b) to C(15); H(6β), H(6α) to C(16); H(5) to C(17); H(17α), H(21b) to C(19); H(18) to C(20); H(6'β) to C(2'); H(5'), H(21'a,b) to C(3'); H(3'), H(17'a,b) to C(5'); H(3'), H(5'), N(1')H to C(7'); H(12'), N(1')H to C(8'); H(11') to C(9'); H(21a), H(21b), H(12') to C(10'); H(11') to C(13'); H(17'a,b), H(19'), H(21'a,b) to C(15'); H(6'α) to C(16'); H(5') to C(17'); H(16'), H(18') to C(20'); H(19') to C(21'). 1D-ROESY: H(3)/N(1)-Me, N(4)-Me; H(5)/H(16), H(17α), N(4)-Me; H(6α)/H(6β), H(9), H(16); H(6β)/H(5), H(6α); H(9)/H(10); H(10)/H(9), H(11); H(12)/H(11), N(1)-Me; H(14α)/H(3), H(14β), H(15), N(1)-Me; H(14β)/H(14α), H(17β); H(15)/H(16), H(20); H(17α)/H(5), H(17β); H(17β)/H(14β), H(17α); 18-Me/H(20), H(11'); H(21a)/H(21b), H(6'α); H(21b)/H(21a); N(1)-Me/H(3), H(12); N(4)-Me/H(3), H(5); H(3')/H(14'a), H(14'b); H(5')/H(21'a,b), H(17'a,b); H(6'β)/H(6'α), H(16'); H(6'α)/H(6'β), H(21a); H(11')/H(12'), 18-Me; H(12')/H(11'), N(1')H; H(14'a)/H(14'b), H(15'); H(14'b)/H(3'), H(14'a); H(15')/H(14'a), H(16'), 18'-Me; H(16')/H(15'), H(17'a,b); 18'-Me/H(15'), H(19'); H(19')/H(18'), H(21'a,b); H(21'a,b)/H(18'); N(1')H/H(12').

Macralstonidine (**76**): light yellowish oil; $[\alpha]_D$ +96 (*c* 0.72, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 229 (4.20), 285 (3.67) nm; ESIMS *m/z* 645 (MH^+, $C_{41}H_{48}N_4O_3$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.50.

Lumusidine A (77): light yellowish oil; $[\alpha]^{25}_D$ −138 (*c* 0.24, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 231 (5.56), 285 (4.90) nm; IR (dry film) ν_{max} 1618, 1655 cm^{-1}; ESIMS *m/z* 687 $[M + H]^+$; HRESIMS *m/z* 687.3897 (calcd for $C_{43}H_{50}N_4O_4$ + H, 687.3907); for ^1H NMR and ^{13}C NMR data, see Table 2.51. HMBC: ^2J H(3) to C(2); H(14α) to C(3); H(6α), H(6β) to C(5); H(6α), H(6β) to C(7); H(9) to C(8); H(11) to C(10); H(5), H(17α) to C(16); H(16) to C(17); H(19) to C(18); H(18) to C(19); H(15), H(19), H(21) to C(20); H(3') to C(2'); H(14'β) to C(3'); H(6') to C(5'); H(5') to C(6'); H(6'α), H(6'β) to C(7'); H(9') to C(8'); H(19) to C(10'); H(12') to C(11'); H(12') to C(13'); H(5'), H(17'α) to C(16'); H(15'), H(21') to C(20'). ^3J H(6α), H(6β), H(14α), H(14β), N_1Me to C(2); H(5), H(15), N_4Me to C(3); H(3) to C(5); H(3), H(5), H(9) to C(7); H(6β), H(10) to C(8); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N_1Me to C(13); H(3), H(5), H(17α), H(17β), H(19), H(21) to C(15); H(6α), H(6β), H(14β) to C(16); H(5), H(15), H(21) to C(17); H(15), H(21), H(9') to C(19); H(14α), H(14β), H(16), H(18) to C(20); H(15), H(17β), H(19) to C(21); H(3) to N_4Me; H(6'α), H(6'β), H(14'β), N_1Me' to C(2'); H(5'), N_4Me' to C(3'); H(3') to C(5'); H(5'), H(9') to C(7'); H(6'β), H(12') to C(8'); H(19) to C(9'); H(18), H(12') to C(10'); H(19), H(9'), 11'-OMe to C(11'); H(9'), N_1Me' to C(13'); H(3'), H(5'), H(17'α), H(17'β), H(21') to C(15'); H(6'α), H(6'β), H(14'α) to C(16'); H(5'), H(15'), H(21') to C(17'); H(18'), H(21') to C(19'); H(17'β) to C(21'); H(5') to N_4Me'. NOESY: H(3)/H(14α), H(14β), N_1Me, N_4Me; H(5)/H(16), H(17β), N_4Me; H(6α)/H(6β), H(9); H(6β)/H(6α), H(9), H(16); H(9)/H(6α), H(6β), H(10);

H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N_1Me; H(14α)/H(3), H(14β); H(14β)/H(3), H(14α), H(19), N_1Me; H(15)/H(14β), H(19); H(16)/H(5), H(6β), H(17α), H(17β); H(17α)/H(16), H(17β); H(17β)/H(5), H(16), H(17α); H(18)/H(19), H(21), H(9'); H(19)/H(14β), H(18), H(21), H(9'); H(21)/H(18), H(19), H(9'); N_1Me/H(3), H(12), H(14β); N_4Me/H(3), H(5); H(3')/H(14'α), H(14'β), N_1Me', N_4Me'; H(5')/H(16'), H(17'β), N_4Me'; H(6'α)/H(6'β), H(9'); H(6'β)/H(6'α), H(9'), H(16'); H(9')/H(18), H(19), H(21), H(6'α), H(6'β); H(12')/11'-OMe, N_1Me'; H(14'α)/H(14'β), H(18'); H(14'β)/H(3'), H(14'α), H(15'), N_1Me'; H(15')/H(14'α), H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'β); H(17'α)/H(17'β); H(17'β)/H(5'), H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N_1Me'/H(3'), H(12'), H(14'β); N_4Me'/H(3'), H(5'); 11'-OMe/H(12').

Conversion of Lumusidine A (77) to Its Dimethyl Diiodide Salt 77a: Iodomethane (0.5 ml) was added to lumusidine A (**77**) (6.1 mg, 0.009 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to furnish a yellowish residue, which on recrystallization from hot MeOH gave the corresponding dimethyl diiodide salt **77a** (3.8 mg, 43%): light yellowish block crystals; >198 ℃ dec.; ESIMS m/z 358 $[M]^{2+}$; HRESIMS m/z 358.2157 $[M]^{2+}$ (calcd for $C_{45}H_{56}N_4O_4$, 716.4302).

Crystallographic data of lumusidine A dimethyl diiodide salt (77a): light yellowish block crystals, $C_{45}H_{56}N_4O_4{}^2$ 2I , *M*r = 970.76, monoclinic, space group $P2_1$, a = 15.8916(2) Å, b = 8.92620(10) Å, c = 17.1572(3) Å, $\alpha = \gamma = 90$, β = 112.2430 (10), V = 2252.67(5) $Å^3$, T = 100 K, Z = 2, D_{calcd} = 1.511 gcm ^{3}, crystal size 0.10 x 0.12 x 0.18 mm^3, $F(000)$ = 1044. The final R_1 value is 0.0505 (wR_2 = 0.1373) for

7729 reflections [$I>2\ (I)$]. The absolute configuration of compound **77a** was determined on the basis of Flack parameter[284,285] [x = 0.01(0.03)] and corroborated by the Hooft parameter[286,287] [y = 0.010(0.015)]. CCDC number: 893347

Lumusidine B (78): light yellowish oil; $[\alpha]^{25}_{D}$ –59 (*c* 0.73, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 229 (5.48), 285 (4.84) nm; IR (dry film) ν_{max} 1615, 1652 cm^{-1}; ESIMS *m/z* 705 $[M + H]^+$; HRESIMS *m/z* 705.4008 (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4013); for ^1H NMR and ^{13}C NMR data, see Table 2.52 and Table 2.53. HMBC: ^2J H(3) to C(2); H(6α) to C(5); H(5) to C(6); H(6α), H(6β) to C(7); H(9) to C(8); H(5) to C(16); H(18) to C(19); H(19) to C(20); H(3') to C(2'); H(14'α) to C(3'); H(6'α) to C(5'); H(6'α), H(6'β) to C(7'); H(19), H(9') to C(10'); H(12') to C(11'); H(12') to C(13'); H(5'), H(15'), H(17'α) to C(16'); H(21') to C(20'). ^3J H(6α), H(6β), N_1Me to C(2); H(5), N_4Me to C(3); H(3), N_4Me to C(5); H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N_1Me to C(13); H(3), H(5), H(17β), H(21) to C(15); H(6α), H(6β) to C(16); H(5), H(21) to C(17); H(18) to C(20); H(17β) to C(21); H(5) to N_4Me; H(6'α), H(6'β), H(14'α), N_1Me' to C(2'); H(5'), H(15'), N_4Me' to C(3'); H(3'), N_4Me' to C(5'); H(5'), H(9') to C(7'); H(12') to C(8'); H(19) to C(9'); H(18), H(20), H(12') to C(10'); H(19), H(9'), 11'-OMe to C(11'); H(9'), N_1Me' to C(13'); H(3'), H(5'), H(17'α), H(17'β), H(21') to C(15'); H(6'α), H(6'β), H(14'α) to C(16'); H(5') to C(17'); H(14'α), H(14'β) to C(20'); H(17'β) to C(21'); H(5') to N_4Me'. NOESY: H(3)/H(14α), H(14β), N_1Me, N_4Me; H(5)/H(16), H(17β); H(6α)/H(6β), H(9); H(6β)/H(6α), H(9), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N_1Me; H(14α)/H(3), H(14β); H(14β)/H(3), H(14α), H(19), H(9'); H(15)/H(16), H(20), 11'-OMe; H(16)/H(5), H(6β), H(15), H(17β), H(20); H(17α)/H(17β); H(17β)/H(5), H(16), H(17α); H(18)/H(19), H(20), H(21), H(9'), 11'-

OMe; H(19)/H(14β), H(18), H(21), H(9'); H(20)/H(15), H(16), H(18), H(21), 11'-OMe; H(21)/H(18), H(19), H(20); N_1Me/H(3), H(12); N_4Me/H(3); H(3')/H(14'α), H(14'β), N_1Me', N_4Me'; H(5')/H(16'), N_4Me'; H(6'α)/H(6'β), H(9'), H(16'), H(17'β); H(6'β)/H(6'α), H(9'); H(9')/H(6'α), H(6'β), H(14'β), H(18), H(19); H(12')/11'-OMe, N_1Me'; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15'), N_1Me'; H(15')/H(14'β), H(16'); H(16')/H(6'α), H(15'), H(17'β); H(17'α)/H(14'α), H(17'β); H(17'β)/H(6'α), H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N_1Me'/H(3'), H(12'), H(14'β); N_4Me'/H(3'), H(5'); 11'-OMe/H(15), H(18), H(20), H(12').

Acetylation of lumusidine B (78): To a solution of lumusidine B (**78**) (4.2 mg, 0.006 mmol), pyridine (1.45 μl, 0.018 mmol), and CH_2Cl_2 (2 ml) was added Ac_2O (0.9 μl, 0.009 mmol), and the mixture was stirred at rt. The progress of the reaction was monitored with TLC and stopped at ca. 95% completion by addition of 5% Na_2CO_3 solution (2 ml). The organic layer was washed with water, dried with Na_2SO_4, concentrated in vacuo, and the residue was purified via centrifugal preparative TLC (SiO_2, 100:5 $CHCl_3$ /MeOH, NH_3-saturated) to give 2.5 mg (56%) of *O*-acetyl derivative **78a**: light yellowish oil; $[\alpha]^{25}_D$ –56 (*c* 0.09, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 208 (6.50), 226 (6.55), 264 (6.01), 296 (5.89) nm; IR (dry film) ν_{max} 1739, 1698, 1650, 1618 cm^{-1}; for ^{1}H NMR and ^{13}C NMR data, see Table 2.52 and Table 2.53, respectively; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4123 (calcd for $C_{45}H_{54}N_4O_4$ + H, 747.4122).

Conversion of Lumusidine B (78) to Its Dimethyl Diiodode Salt 78b: Iodomethane (0.5 ml) was added to lumusidine B (**78**) (5.4 mg, 0.008 mmol), and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced

pressure to furnish a yellowish residue, which on recrystallization from hot MeOH gave the corresponding dimethyl diiodide salt **78b** (4.2 mg, 53%): light yellowish block crystals; mp 230−234 °C; ESIMS *m/z* 367 $[M]^{2+}$; HRESIMS *m/z* 367.2207 $[M]^{2+}$ (calcd for $C_{45}H_{58}N_4O_5$, 734.4407).

Crystallographic data of lumusidine B dimethyl diiodide salt (**78b**): light yellowish block crystals, $C_{45}H_{58}N_4O_5^{2+}2I^-$, *M*r = 988.77, monoclinic, space group *C*2, *a* = 28.5993(5) Å, *b* = 11.4265(2) Å, *c* = 18.3052(4) Å, $\alpha = \gamma = 90^o$, $\beta = 127.1400^o$ (10), *V* = 4768.59(16) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.404 gcm^{-3}, crystal size 0.07 x 0.21 x 0.42 mm^3, *F*(000) = 540. The final R_1 value is 0.0703 (wR_2 = 0.1874) for 8792 reflections [$I>2\sigma(I)$]. The absolute configuration of compound 78b was determined on the basis of Flack parameter[284,285] [*x* = 0.01(0.03)] and corroborated by the Hooft parameter[286,287] [*y* = 0.052(0.011)]. CCDC number: 893348

Lumusidine C (**79**)**:** light yellowish oil; $[\alpha]^{25}_D$ −16 (*c* 0.21, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 231 (5.66), 283 (5.01) nm; IR (dry film) ν_{max} 1619, 1653 cm^{-1}; ESIMS *m/z* 733 $[M + H]^+$; HRESIMS *m/z* 733.4323 (calcd for $C_{45}H_{56}N_4O_5$ + H, 733.4326); for ^{1}H NMR and ^{13}C NMR data, see Table 2.54; HMBC: ^2J H(6α) to C(5); H(6α), H(6β) to C(7); H(9) to C(8); H(5) to C(16); H(18) to C(19); H(21a), H(21b) to C(20); OCH_2CH_3 to OCH_2CH_3; H(3') to C(2'); H(6'α), H(6'β) to C(5'); H(6'α), H(6'β) to C(7'); H(9') to C(8'); H(21a), H(21b) to C(10'); H(12') to C(11'); H(12') to C(13'); H(17'α) to C(16'); H(18') to C(19'); H(21') to C(20'). ^3J H(6α), H(6β), N_1Me to C(2); H(5), N_4Me to C(3); H(3), N_4Me to C(5); H(5), H(9) to C(7); H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N_1Me to C(13); H(5), H(21a), H(21b) to C(15); H(6α), H(6β), H(14α), H(14β) to C(16); H(5) to C(17); H(17β),

H(21a), O*CH*$_2$CH$_3$ to C(19); H(18) to C(20); H(6'α), H(6'β), H(14'β), N$_1$Me' to C(2'); H(5'), N$_4$Me' to C(3'); H(3'), N$_4$Me' to C(5'); H(5'), H(9') to C(7'); H(12') to C(8'); H(21a), H(21b) to C(9'); H(12') to C(10'); H(21a), H(21b), H(9'), 11'-OMe to C(11'); H(9'), N$_1$Me' to C(13'); H(3'), H(5'), H(17'α), H(17'β), H(21') to C(15'); H(6'α), H(6'β) to C(16'); H(5'), H(21') to C(17'); H(21') to C(19'); H(15'), H(17'β) to C(21'); H(5') to N$_4$Me'. NOESY: H(3)/H(14α), H(14β), N$_1$Me, N$_4$Me; H(5)/H(6β), H(16), H(17β), N$_4$Me; H(6α)/ H(6β), H(9); H(6β)/H(5), H(6α), H(9), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N$_1$Me; H(14α)/H(3), H(14β); H(14β)/H(3), H(14α), H(15), H(18), H(20), N$_1$Me; H(15)/H(14β), H(16), H(21a), H(9'); H(16)/H(15), H(17β), H(21a); H(17α)/H(17β); H(17β)/H(5), H(16), H(17α); H(18)/H(14β), H(20), H(21b), O*CH*$_2$CH$_3$; H(20)/H(14β), H(18), H(21b), H(9'); H(21a)/H(15), H(16), H(21b), H(9'); H(21b)/H(18), H(20), H(21a), H(9'); N$_1$Me/H(3), H(14β), H(12); N$_4$Me/H(3), H(5); O*CH*$_2$CH$_3$/H(18), OCH$_2$*CH*$_3$; H(3')/H(14'α), H(14'β), N$_1$Me', N$_4$Me'; H(5')/H(6'β), H(16'), H(17'α), N$_4$Me'; H(6'α)/H(6'β), H(9'); H(6'β)/H(5'), H(6'α), H(16'), H(9'); H(9')/H(6'α), H(6'β), H(20), H(21a), H(21b); H(12')/11'-OMe, N$_1$Me'; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15'), N$_1$Me'; H(15')/H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'β); H(17'α)/H(5'), H(14'α), H(17'β); H(17'β)/ H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N$_1$Me'/H(3'), H(12'), H(14'β); N$_4$Me'/H(3'), H(5'); 11'-OMe/H(12').

Lumusidine D (**80**)**:** light yellowish oil; $[\alpha]^{25}_{D}$ –161 (*c* 0.38, CHCl$_3$); UV (EtOH) λ_{max} nm (log ε) 233 (5.86), 283 (5.17) nm; IR (dry film) ν_{max} 1618, 1654 cm^{-1}; ESIMS *m/z* 687 [M + H]$^+$; HRESIMS *m/z* 687.3914 (calcd for C$_{43}$H$_{50}$N$_4$O$_4$ + H, 687.3907); for ^{1}H NMR and ^{13}C NMR data, see Table 2.55; HMBC: ^2J H(6α) to C(5); H(6α), H(6β) to C(7); H(11) to C(12); H(12) to C(13); H(5) to C(16); H(18) to C(19); H(21) to C(20);

H(3') to C(2'); H(6'α) to C(5'); H(6'α), H(6'β) to C(7'); H(9') to C(8'); H(11') to C(10'); H(21)/H(12'); H(5'), H(17'α) to C(16'); H(15'), H(21') to C(20'). ^{3}J H(6α), H(6β), H(14α), H(14β), N_1Me to C(2); H(5) to C(3); N_4Me to C(5); H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N_1Me to C(13); H(5), H(17α), H(17β), H(21) to C(15); H(6α) to C(16); H(5) to C(17); H(17β), H(21) to C(19); H(18) to C(20); H(3), H(5) to N_4Me; H(6'α), H(6'β), H(14'α), H(14'β), N_1Me' to C(2'); H(5') to C(3'); H(3'), N_4Me' to C(5'); H(5'), H(9') to C(7'); H(6'β), H(10') to C(8'); H(21), H(9'), 11'-OMe to C(11'); H(10') to C(12'); H(21), H(9'), N_1Me' to C(13'); H(16') to C(14'); H(3'), H(5'), H(17'α), H(17'β), H(21') to C(15'); H(6'β), H(14'α) to C(16'); H(5'), H(21') to C(17'); H(17'β) to C(21'); H(3'), H(5') to N_4Me'. NOESY: H(3)/H(14α), H(14β), N_1Me, N_4Me; H(5)/H(6β), H(16), H(17β), N_4Me; H(6α)/ H(6β), H(9); H(6β)/H(5), H(6α), H(9), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10); H(12)/N_1Me; H(14α)/H(3), H(14β), H(17α); H(14β)/H(3), H(14α), H(15), N_1Me; H(15)/H(14β); H(16)/H(5), H(6β), H(17α); H(17α)/H(14α), H(16), H(17β); H(17β)/H(5), H(17α); H(18)/H(21); H(21)/H(18); N_1Me/H(3), H(14β), H(12); N_4Me/H(3); H(3')/H(14'α), H(14'β), N_4Me'; H(5')/H(6'β), H(16'), H(17'β), N_4Me'; H(6'α)/H(6'β), H(9'); H(6'β)/H(5'), H(6'α), H(16'), H(9'); H(9')/H(6'α), H(6'β), H(10); H(10')/H(9'), 11'-OMe; H(14'α)/H(3'), H(14'β); H(14'β)/H(3'), H(14'α), H(15'); H(15')/H(14'α), H(16'); H(16')/H(5'), H(6'β), H(15'); H(17'α)/H(17'β); H(17'β)/H(5'), H(17'α); H(18')/H(21'); H(21')/H(18'); N_4Me'/H(3'); 11'-OMe/H(10').

Crystallographic data of lumusidine D (**80**): colorless needles, $C_{43}H_{50}N_4O_4$, *M*r = 686.87, orthorhombic, space group $P2_12_12_1$, a = 9.8437(14) Å, b = 14.164(2) Å, c = 25.802(4) Å, $\alpha = \beta = \gamma = 90^{o}$, T = 100 K, Z = 4, D_{calcd} = 1.268 gcm^{-3}, crystal size

0.07 x 0.21 x 0.32 mm^3, $F(000)$ = 1472.0. The final R_1 value is 0.0694 (wR_2 = 0.1483) for 4209 reflections [$I>2\sigma(I)$]. CCDC number: 893349

Perhentidine A (**81**): light yellowish oil; $[\alpha]_D$ −78 (*c* 0.34, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.69), 285 (4.87) nm; IR (dry film) ν_{max} 3380, 1702, 1652, 1618 cm^{-1}; EIMS *m*/*z* 686 $[M - H_2O]^+$ (100), 617 (4), 547 (10), 486 (33), 454 (5), 379 (12), 343 (9), 307 (13), 250 (13), 197 (67), 170 (17), 149 (8), 43 (9); HRLSIMS *m*/*z* 705.4020 $[M + H]^+$ (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4016); for ^{1}H NMR and ^{13}C NMR data, see Table 2.56 and Table 2.57, respectively. HMBC: ^2J H(3) to C(2); H(6β), H(6α) to C(5); H(6β), H(6α) to C(7); H(5) to C(16); H(18), H(20) to C(19); H(15), H(21a) to C(20); H(3') to C(2'); H(6'α) to C(5'); H(6'β), H(6'α) to C(7'); H(9') to C(8'); H(10') to C(11'); H(21a), H(21b) to C(12'); H(5'), H(17'β), H(17'α) to C(16'); H(18') to C(19'); H(21') to C(20'). ^3J H(6β), H(6α), H(14α), N(1)-Me to C(2); H(5), N(4)-Me to C(3); H(17a), N(4)-Me to C(5); H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), N(1)-Me to C(13); H(20) to C(14); H(3), H(5), H(17a) to C(15); H(6β), H(6α) to C(16); H(5) to C(17); H(21b) to C(19); H(18) to C(20); H(3'), N(4)-Me' to C(5'); H(5'), H(17'β), H(21') to C(15'); H(6'β), H(6'α), H(14'α), N(1)-Me' to C(2'); H(5'), N(4)-Me' to C(3'); H(5'), H(9') to C(7'); H(10') to C(8'); H(9'), H(21a), H(21b), 11-OMe' to C(11'); H(10') to C(12'); H(21a), H(9'), N(1)-Me' to C(13'); H(3') to C(15'); H(6'β), H(6'α) to C(16'); H(5'), H(21') to C(17'); H(17'β) to C(21'). ^4J H(18') to C(21'). NOESY: H(3)/H(14α), H(14β), N(1)-Me, N(4)-Me; H(5)/H(6α), H(6β), H(16), H(17), N(4)-Me; H(6α)/H(5), H(6β), H(9), N(4)-Me; H(6β)/H(5), H(6α), H(9), H(15), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N(1)-Me; H(14β)/H(3), H(20) [or H(21b)], H(14α), H(15), N(1)-Me; H(14α)/H(3), H(14β); H(15)/H(6β), H(14α), H(14β), H(16), H(21a);

H(16)/H(5), H(6β), H(15), H(17); H(17)/H(5), H(16), H(20) [or H(21b)]; H(18)/H(14α), H(17), H(20) [or H(21b)], 11'-OMe, N(1')-Me; H(20)/H(14α), H(17), H(18), H(21b); H(21a)/H(15), H(20) [or H(21b)], N(1')-Me; H(21b)/H(14α), H(14β), H(15), H(21a), N(1')-Me; N(1)-Me/H(3), H(12), H(14β); N(4)-Me/H(3), H(5), H(6α); H(3')/H(14'α), H(14'β), N(1')-Me, N(4')-Me ; H(5')/H(6'α), H(6'β), H(16'), H(17'α), H(17'β), N(4')-Me; H(6'α)/H(5'), H(6'β), H(9'), N(4')-Me; H(6'β)/H(5'), H(6'α), H(9'), H(16'), H(17'β); H(9')/H(6'α), H(6'β), H(10'); H(10')/H(9'), 11'-OMe; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15'), N(1')-Me; H(15')/H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'β), H(17α); H(17'α)/H(5'), H(16'), H(17'β), H(14'α); H(17'β)/H(5'), H(6'β), H(16'), H(17'α), H(18'); H(18')/H(17'β), H(21'); H(21')/H(18'); N1'-Me/H(3'), H(14'β), H(21a), H(18), H(20) [or H(21b)]; N(4')-Me/H(3'), H(5'), H(6'α); 11'-OMe/H(10'), H(18).

Acetylation of perhentidine A (81): To a stirred solution of **81** (18.3 mg, 0.026 mmol), in CH_2Cl_2 (2 mL) and pyridine (6.3 μl, 0.079 mmol) was added dropwise acetic anhydride (3.7 μl, 0.039 mmol), and the mixture was stirred at room temperature for 2 h. The mixture was quenched with 10% Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated in vacuo, and the residue purified by preparative centrifugal TLC (SiO_2, C(N)) to give 9.1 mg (47%) of the diacetate derivative **81a** as a light yellowish oil; $[\alpha]^{25}_D$ –111 (*c* 0.45, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.99), 285 (4.30) nm; IR (dry film) ν_{max} 1732, 1703, 1652, 1620 cm^{-1}; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4122 (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119); for ^1H NMR and ^{13}C NMR data, see Table 2.56 and Table 2.57, respectively. NOESY: H(3)/H(14), N(1)-Me, N(4)-Me; H(5)/H(6β), H(16), H(17b), N(4)-Me; H(6α)/H(6β), H(9), N(4)-Me; H(6β)/H(5), H(6α), H(9), H(15),

H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N(1)-Me; H(14)/H(3), H(20), H(21b), N(1)-Me, H(17); H(15)/H(6β), H(16), H(21a); H(16)/H(5), H(6β), H(15), H(17); H(17a)/H(16) [or H(14)], H(17b), H(18), H(20); H(17b)/H(5), H(14) [or H(16)], H(17a); H(18)/H(17a), H(20); H(20α)/H(14), H(17a), H(18), H(21b); H(21a)/H(15), H(21b), N(1')-Me; H(21b)/H(14), H(20), H(21a); N(1)-Me/H(3), H(12), H(14); N(4)-Me/H(3), H(5), H(6α); H(3')/H(14'α), H(14'β), N(1')-Me, N(4')-Me; H(5')/H(6'α), H(6'β), H(16'), H(17'α), H(17'β), N(4')-Me; H(6'α)/H(5'), H(6'β), H(9'); H(6'β)/H(5'), H(6'α), H(9'), H(16'); H(9')/H(6'α), H(6'β), H(10'); H(10')/ H(9'), 11'-OMe; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15'), N(1')-Me; H(15')/H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'β); H(17'α)/H(5'), H(17'β), H(14'α); H(17'β)/H(5'), H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N(1')-Me/H(3'), H(14'β), H(21a); N(4')-Me/H(3'), H(5'); 11'-OMe/H(10').

Perhentidine B (82): light yellowish oil; $[\alpha]^{25}_{D}$ −38 (*c* 0.52, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 234 (4.49), 286 (3.81) nm; IR (dry film) ν_{max} 3392 (OH), 1707, 1653, 1618 cm^{-1}; ESIMS *m/z* 705 $[M + H]^+$; HRESIMS *m/z* 705.3993 (calcd for $C_{43}H_{52}N_4O_5$ + H, 705.4013); for ^{1}H NMR and ^{13}C NMR data, see Table 2.58 and Table 2.59. HMBC: ^2J H(6α), H(6β) to C(5); H(6α), H(6β) to C(7); H(17b) to C(16); H(5) to C(17); H(18) to C(19); H(21b) to C(20); H(3') to C(2'); H(6'α), H(6'β) to C(7'); H(10') to C(11'); H(21a), H(21b) to C(12'); H(17'α) to C(16'); H(18') to C(19'); H(21') to C(20'); ^3J: H(6α), H(6β), N(1)-Me to C(2); H(5), N(4)-Me to C(3); H(17b), N(4)-Me to C(5); H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(3), H(5), H(17a) to C(15); H(5), H(6α), H(6β) to C(16); H(21b) to

C(19); H(18) to C(20); H(6'α), H(6'β), H(14'β), N(1')-Me to C(2'); H(5'), N(4')-Me to C(3'); H(3'), N(4')-Me to C(5'); H(5'), H(9') to C(7'); H(6'α), H(10') to C(8'); H(9'), H(21a), H(21b), 11'-OMe to C(11'); H(10') to C(12'); H(9'), H(21a), H(21b), N(1')-Me to C(13'); H(3'), H(5'), H(17'α),H(17'β), H(21') to (15'); H(5'), H(6'α), H(6'β) to C(16'); H(5'), H(21') to C(17'). NOESY: H(3)/H(14α), H(14β), N(1)-Me, N(4)-Me; H(5)/H(6β), H(16), H(17a), N(4)-Me; H(6α)/H(5), H(6β), H(9), N(4)-Me; H(6β)/H(5), H(6α), H(9), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N(1)-Me; H(14α)/H(3), H(14β), H(20); H(14β)/H(3), H(14α), H(15), N(1)-Me; H(15)/H(6β), H(14β), H(21a); H(16)/H(5), H(6β), H(17a), H(17b), H(21b); H(17a)/H(5), H(16), H(17b), H(20), H(21b); H(17b)/H(16), H(17a), H(20), H(21b), 11'-OMe; H(18)/H(20), 11'-OMe; H(20)/ H(14α), H(17a), H(17b), H(18), H(21b); H(21a)/H(15), H(21b), N(1')-Me (signals overlapped with H(20)); H(21b)/H(16), H(17b), H(20), H(21a); N(1)-Me/H(3), H(12), H(14β); N(4)-Me/H(3), H(5), H(6α); H(3')/H(14'α), H(14'β), N(1')-Me, N(4')-Me; H(5')/H(6'α), H(6'β), H(16), H(17'α), H(17'β), N(4')-Me; H(6'α)/H(5'), H(6'β), H(9'), N(1')-Me; H(6'β)/H(5'), H(6'α), H(9'), H(15'), H(16'); H(9')/H(6'α), H(6'β), H(10'); H(10')/H(9'), 11'-OMe; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15), N(1')-Me; H(15')/H(6'β), H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'β); H(17'α)/H(5'), H(14'α), H(17'β); H(17'β)/H(5'), H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N(1')-Me/H(3'), H(14'β), H(21a); N(4')-Me/H(3'), H(5'), H(6α); 11'-OMe/H(10'), H(17b).

Acetylation of perhentidine B (82): To a stirred solution of 82 (18.8 mg, 0.027 mmol), in CH_2Cl_2 (2 mL) and pyridine (6.4 μl, 0.081 mmol) was added dropwise acetic anhydride (3.9 μl, 0.04 mmol), and the mixture was stirred at room

temperature for 2 h. The mixture was quenched with 10% Na_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated in vacuo, and the residue purified by preparative centrifugal TLC (SiO_2, C(N)) to give 8.5 mg (43%) of the diacetate derivative 82a as a light yellowish oil; $[\alpha]^{25}_D$ −42 (*c* 0.43, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.01), 288 (4.32) nm; IR (dry film) ν_{max} 1734, 1709, 1654, 1619 cm^{-1}; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4109 (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119); for ^1H NMR and ^{13}C NMR data, see Table 2.58 and Table 2.59, respectively. NOESY: H(3)/H(14α), H(14β), N(1)-Me, N(4)-Me; H(5)/H(6β), H(16), H(17), N(4)-Me; H(6α)/H(9), H(6β), N(4)-Me; H(6β)/H(5), H(6α), H(9), H(15), H(16); H(9)/H(6α), H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), N(1)-Me; H(14α)/H(3), H(14β), H(17), H(20); H(14β)/H(3), H(14α), H(15), N(1)-Me; H(15)/H(6β), H(14β), H(21a); H(16)/H(5), H(6β),H(17), H(21b); H(17)/H(5), H(16), H(20), H(21b), 11'-OMe; H(18)/H(5), H(16), H(20), H(21b), 11'-OMe; H(20)/H(14α), H(17), H(18) [or H(14β)]; H(21a)/H(15), H(21b), N(1')-Me; H(21b)/ H(16), H(17), H(21a); N(1)-Me/H(3), H(12), H(14β); N(4)-Me/H(3), H(5), H(6α); H(3')/H(14'α), H(14'β), N(1')-Me, N(4')-Me; H(5')/H(6'α), H(6'β), H(16), H(17'α), H(17'β), N(4')-Me; H(6'α)/H(5'), H(6'β), H(9'), N(1')-Me; H(6'β)/H(5'), H(6'α), H(9'), H(15'), H(16'); H(9')/H(6'α), H(6'β), H(10'); H(10')/H(9'), 11'-OMe; H(14'α)/H(3'), H(14'β), H(17'α); H(14'β)/H(3'), H(14'α), H(15), N(1')-Me; H(15')/H(6'β), H(14'β), H(16'); H(16')/H(5'), H(6'β), H(15'), H(17'α), H(17'β); H(17'α)/H(5'), H(14'α), H(17'β); H(17'β)/H(5'), H(16'), H(17'α); H(18')/H(21'); H(21')/H(18'); N(1')-Me/H(3'), H(14'β), H(21a); N(4')-Me/H(3'), H(5'), H(6α); 11'-OMe/H(10'), H(17), H(18).

Perhentinine (**83**): light yellowish oil; $[\alpha]_D$ –61 (*c* 1.19, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 231 (4.25), 298 (3.45) nm; IR (dry film) ν_{max} 3400, 1701, 1651, 1616 cm^{-1}; ESIMS *m/z* 705 (MH^+, $C_{43}H_{52}N_4O_5$ + H); for ^1H NMR and ^{13}C NMR data, see Table 2.60 and Table 2.61.

Acetylation of perhentinine (83): Reaction of **83** (15.1 mg, 0.021 mmol) with acetic anhydride (3 μl, 0.032 mmol) in pyridine (5 μl, 0.063 mmol) and CH_2Cl_2 (2 ml) gave **83a** (8.2 mg, 52%): light yellowish oil; $[\alpha]^{25}_D$ –103 (*c* 0.35, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.15), 295 (4.41) nm; IR (dry film) ν_{max} 1736, 1706, 1651, 1618 cm^{-1}; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4123 (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119); for ^1H NMR and ^{13}C NMR data, see Table 2.60 and Table 2.61, respectively.

Conversion of Perhentinine (83) to its Dimethyl Diiodide Salt 83b. Iodomethane (0.5 ml, 8 mmol) was added to perhentinine (**83**) (16 mg, 0.02 mmol) and the mixture allowed to stand for 24 h at rt. Excess iodomethane was then removed under reduced pressure to furnish a yellowish residue which on recrystallization from hot MeOH gave the corresponding dimethyl diiodide salt **83b** (14 mg, 62%): light yellowish block crystals; mp 228-230 ^oC; $[\alpha]^{25}_D$ –55 (*c* 0.05, MeOH); UV (EtOH) λ_{max} (log ε) 221 (5.83), 295 (4.97) nm; ESIMS *m/z* 367 $[M]^{2+}$; HRESIMS *m/z* 367.2207 $[M]^{2+}$ (calcd for $C_{45}H_{58}N_4O_5$, 734.4396).

Crystallographic data of perhentinine dimethyl diiodide salt (**83b**): $C_{45}H_{58}N_4O_5^{2+}2I^-$, *M*r = 988.77, orthorhombic, space group $P2_12_12_1$, *a* = 14.5059(2) Å, *b* = 14.8002(2) Å, *c* = 22.4594(3) Å, *V* = 4821.81(11) $Å^3$, *T* = 100 K, *Z* = 4, D_{calcd} = 1.307 gcm^{-3}, crystal size 0.16 x 0.19 x 0.21 mm^3, *F*(000) = 1920. The final R_1 value is 0.0634 (wR_2 = 0.1921) for 8480 reflections [$I>2\sigma(I)$]. The absolute configuration of **83b** was determined on the

basis of Flack parameter [x = 0.04(0.03)] and corroborated by the Hooft parameter [y = 0.022(0.07)]. CCDC number: 865674

Macralstonine (**84**)**:** colorless rectangular rod crystals from CH_2Cl_2/MeOH; mp 260-263 ^oC (lit.[172] mp 279-282 ^oC); $[\alpha]^{25}_D$ +22 (*c* 0.5, $CHCl_3$){lit.[172] $[\alpha]^{25}_D$ +22 (*c* 2.0, $CHCl_3$)}; UV (EtOH) λ_{max} (log ε) 233 (5.44), 288 (4.81) nm; for ^1H NMR and ^{13}C NMR data, see Table 2.62 and Table 2.63, respectively.

***O*-Acetyl-*E*-*seco*-macralstonine (84a):** Reaction of **84** (16.8 mg, 0.024 mmol) with acetic anhydride (3.4 μl, 0.036 mmol) in pyridine (5.8 μl, 0.071 mmol) and CH_2Cl_2 (2 ml) gave **84a** (11 mg, 62%): light yellowish oil; $[\alpha]^{25}_D$ +34 (*c* 1.1, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.00), 297 (4.21) nm; IR (dry film) ν_{max} 1732, 1715, 1651, 1614 cm^{-1}; ESIMS *m/z* 747 $[M + H]^+$; HRESIMS *m/z* 747.4119 (calcd for $C_{45}H_{54}N_4O_6$ + H, 747.4119); for ^1H NMR and ^{13}C NMR data, see Table 2.64.

Crystallographic data of macralstonine (**84**): $C_{43}H_{52}N_4O_5$, *M*r = 704.89, monoclinic, space group *C*2, a = 11.73280(10) Å, b = 13.07670(10) Å, c = 19.2454(2) Å, $\alpha = \gamma$ = 90°, β = 108.475°(3), V = 3632.9(7) $Å^3$, T = 100 K, Z = 4, D_{calcd} = 1.289 gcm^{-3}, crystal size 0.02 x 0.10 x 0.20 mm^3, F(000) = 1512. The final R_1 value is 0.0720 (wR_2 = 0.1869) for 6280 reflections [$I>2\sigma(I)$]. The absolute configuration of compound **84** was determined based on the Flack parameter [x = –0.1(0.4)] in conjunction with the Hooft parameter [y = –0.30(0.14)] obtained from a statistical analysis of the Bijvoet pairs. CCDC number: 865675

Anhydromacralstonine (85): light yellowish oil; $[\alpha]_D$ –86 (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.66), 294 (3.94) nm; IR (dry film) ν_{max} 1651 cm^{-1}; HREIMS *m*/*z* 686.3816 $[M]^+$ (calcd for $C_{43}H_{50}N_4O_4$, 686.3832); for ^1H NMR and ^{13}C NMR data, see Table 2.65.

Villalstonidine B (86): light yellowish oil; $[\alpha]_D$ +101 (*c* 0.58, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (4.58), 246 (4.17) (shoulder), 287 (3.98) nm; IR (dry film) ν_{max} 3388, 1747 cm^{-1}; EIMS *m*/*z* 690 $[M]^+$ (16), 659 $[M - CH_2OH]^+$ (27), 583 (8), 368 (38), 321 (36), 248 (23), 197 (63), 170 (29), 135 (100), 70 (17); HREIMS *m*/*z* 690.3781 (calcd for $C_{42}H_{50}N_4O_5$, 690.3781); for ^1H NMR and ^{13}C NMR data, see Table 2.66 and Table 2.67. HMBC: ^2J H(3) to C(2); H(6β), H(6α) to C(5); H(5) to C(6); H(6β), H(6α) to C(7); H(14β), H(14α), H(20) to C(15); H(5) to C(16); H(18) to C(19); H(21α) to C(20); H(20) to C(21); H(14'b) to C(3'); H(6'a), H(21α), H(21β) to C(7'); H(10') to C(9'); H(9') to C(10'); H(14'b) to C(15'); H(19') to C(18'); H(18') to C(19'); H(21'a), H(21'b) to C(20'). ^3J H(6β), H(6α), H(14α), N(1)-Me to C(2); H(5), N(4)-Me to C(3); N(4)-Me to C(5); H(5), H(9) to C(7); H(6β), H(10), H(12) to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11), N(1)-Me to C(13); H(20) to C(14); H(3), H(5), H(17β), H(21β) to C(15); H(5), H(6β), H(6α) to C(16); H(5), H(15) to C(17); H(15), H(17β), H(21α) to C(19); H(18) to C(20); H(6'a), H(6'b) to C(21); H(6'a), H(14'a) to C(2'); H(5'β), H(15'), H(21'a) to C(3'); H(5'β), H(9') to C(7'); H(21β), H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(10') to C(12'); H(9'), H(11') to C(13'); H(3'), H(22'a), H(22'b), H(19') to C(15'); H(21'a), H(15') to C(19'); H(18') to C(20'); H(3'), H(5'β), H(5'α), H(19') to C(21'). NOESY: H(3)/N(1)-Me, N(4)-Me; H(5)/N(4)-Me; H(6β)/H(6α); (6α)/H(6β), N(4)-Me; H(12)/N(1)-Me; H(14β)/H(3), H(14α), N(1)-Me; H(14α)/H(14β), H(18α); H(15)/H(14α), H(21β); H(16)/H(6β);

H(17β)/H(17α); H(17α)/H(17β), H(18α); H(18α)/H(17α); H(20α)/H(18α); H(21α)/H(21β), H(9'); H(21β)/H(21α); N(1)-Me/H(3), H(12); N(4)-Me/H(3), H(5); H(3')/H(14'b); H(5'β)/H(5'α); H(5'α)/H(3'α), H(5'β); H(6'a)/H(6'b); H(6'b)/H(6'a); H(12')/H(11'); H(14'a)/H(3'), H(14'b); H(14'b)/H(3'), H(14'a), H(15'); H(15')/H(18'); H(22'a)/H(15'), H(22'b); H(22'b)/H(12'), H(22'a); H(18')/H(15'), H(19'); H(19')/H(18'), H(21'a); H(21'a)/H(19'), H(21'b); H(21'b)/H(21'a). NOE: H(12')/H(11'), H(22'b); H(15')/H(14'a), H(14'b), H(22'a), H(22'b), H(18'); H(22'a)/H(12'), H(15'), H(22'b); H(22'b)/H(12'), H(22'a); CO_2*Me*'/H(12'), H(18').

Villalstonidine F (**87**)**:** light yellowish oil; $[\alpha]^{25}_{D}$ +40 (*c* 0.10, $CHCl_3$); UV (EtOH) λ_{max} nm (log ε) 230 (5.80), 251 (5.83), 288 (5.90), 294 (5.91) nm; IR (dry film) ν_{max} 3400, 1753 cm^{-1}; ESIMS *m/z* 647 $[M + H]^+$; HRESIMS *m/z* 647.3603 (calcd for $C_{40}H_{46}N_4O_4$ + H, 647.3594); for ^{1}H NMR and ^{13}C NMR data, see Table 2.66 and Table 2.67. HMBC: ^{2}*J* NH to C(2); H(6α), H(6β) to C(5); H(6α), H(6β) to C(7); NH to C(13); H(5) to C(16); H(18) to C(19); H(19') to C(18'); H(18') to C(19'); H(19') to C(20'). ^{3}*J* H(6α), H(6β) to C(2); H(5), N_4Me to C(3); N_4Me to C(5); H(5), NH to C(7); H(10), H(12), NH to C(8); H(11) to C(9); H(12) to C(10); H(9) to C(11); H(10) to C(12); H(9), H(11) to C(13); H(5) to C(15); H(6α), H(6β) to C(16); H(5) to C(17); H(21) to C(19); H(18) to C(20); H(3), H(5) to N_4Me; H(21a), H(6'β) to C(2'); H(9') to C(7'); H(21b), H(10'), H(12') to C(8'); H(11') to C(9'); H(12') to C(10'); H(9') to C(11'); H(11') to C(12'); H(9'), H(11') to C(13'); H(18') to C(20'); H(19') to C(21'); CO_2*Me*' to *C*O_2Me. NOESY: H(3)/H(14α), H(14β), NH, N_4Me; H(5)/H(6α), H(16), H(17β), N_4Me; H(6α)/H(5), H(6β); H(6β)/H(6α), H(9), H(16); H(9)/H(6β), H(10); H(10)/H(9), H(11); H(11)/H(10), H(12); H(12)/H(11), NH; H(14α)/H(3), H(14β), H(17α); H(14β)/H(3), H(14α), H(20), H(21b), NH; H(16)/H(5), H(6β); H(17α)/H(14α), H(17β), H(18); H(17β)/H(5), H(17α);

H(18)/H(17α); H(20)/H(14β); H(21a)/H(9'); NH/H(3), H(14β), H(12); N_4Me/H(3), H(5); H(5'α)/H(5'β), H(6'α); H(5'β)/H(5'α); H(6'α)/H(5'α), H(6'β), H(9'); H(6'β)/H(6'α); H(9')/H(21a), H(6'α), H(10'); H(10')/H(9'), H(11'); H(11')/H(10'), H(12'); H(12')/H(11'), H(16'), CO_2*Me*'; H(14'α)/H(14'β), H(15'), H(16'); H(14'β)/H(14'α), H(15'); H(15')/H(14'α), H(14'β), H(16'), H(18'); H(16')/H(12'), H(14'α), H(15'); H(18')/H(15'), H(19'); H(19')/H(18'), H(21'α); H(21'α)/H(19'), H(21'β); H(21'β)/H(21'α); CO_2*Me*'/H(12').

Villalstonine (88): light yellowish oil; $[\alpha]_D$ +56 (*c* 0.25, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 230 (5.80), 251 (5.83), 286 (5.90), 294 (5.91) nm; ESIMS *m/z* 661 (MH^+, $C_{41}H_{48}N_4O_4$ + H); for ^{1}H NMR and ^{13}C NMR data, see Table 2.68 and Table 2.69, respectively.

Villalstonine *N*(4')-oxide (89): light yellowish oil; $[\alpha]_D$ +43 (*c* 0.40, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 203 (4.25), 229 (4.13), 286 (3.54) nm; EIMS *m/z* 660 ($M–O^+$, $C_{41}H_{48}N_4O_5 – O$); for ^{1}H NMR and ^{13}C NMR data, see Table 2.68 and Table 2.69.

Macrocarpamine (90): light yellowish oil; $[\alpha]_D$ −10 (*c* 0.44, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 207 (4.14), 231 (4.25), 255 (4.10), 290 (3.55) nm; IR (dry film) ν_{max} 1757 cm^{-1}; EIMS *m/z* 642 (M^+, $C_{41}H_{46}N_4O_3$); for ^{1}H NMR and ^{13}C NMR data, see Table 2.70.

3.8 Cytotoxicity Assays

Cytotoxicity assays were carried out on KB (human oral epidermoid carcinoma cell line), or Jurkat (human T-cell-leukemia cell line) cells. The cells were maintained in culture flasks in Eagle's MEM, supplemented with 10% fetal calf serum and kanamycin (60 μg/mL). The KB or Jurkat cells (1.5×10^5/mL) were seeded in 0.2 mL of culture medium/well in 96-well plates (Corning Glass Works). The cells were treated in triplicate with graded concentrations of 5 μL test samples and were then incubated in a 5% carbon dioxide atmosphere at 37 ℃ for 72 h. The MTT assay was used to measure the cytotoxicity effect.[288] The activity was shown as the IC_{50} value, which was the concentration (μg/mL) of test compound to give 50% inhibition of cell growth.

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