The Alkaloids

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PREFACE

Recent progress on three quite different alkaloid groups are discussed in this volume of *The Alkaloids: Chemistry and Biology.*

The first chapter, by Barbosa-Filho, da-Cunha, and Gray, describes in great detail the tremendous volume of research that has been conducted in recent years on the alkaloids of the Menispermaceae, a family which produces a wide structural range of benzylisoquinoline alkaloids. The second chapter is a very special collaborative effort by three Japanese chemistry groups led by Somei, Murakami, and Ninomiya discussing the recent developments on the synthesis of the ergot alkaloids. Finally, Skaltsounis, Mitaku, and Tillequin discuss the diverse acridone alkaloids from the perspectives of their isolation, distribution, synthesis, and biological properties.

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CHAPTER 1

ALKALOIDS OF THE MENISPERMACEAE

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I. Introduction

The plant family Menispermaceae is widely known for the production of a great variety of alkaloids. This was first noticed even before the family was created, when, after the first visits of European colonists, they came back talking about soldiers being wounded by arrows tipped with poison. Further details of this poison came later when it was observed that it was composed of extracts from poisonous herbs. There were many different herbs used to produce the poison, including one known by the natives as "ourari". It is believed that the term curare, which describes

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South American arrow poisons that kill by paralysis, is derived from this Indian name (*1*). Curare is used principally for hunting and fishing purposes by the Indian tribes of the Amazon region. In 1935 it was discovered that the alkaloid tubocurarine was the main active ingredient of curare. At that time, the structure given to this alkaloid was incorrect, and only in 1970 was the correct structure elucidated, showing that only one of the isoquinoline nitrogens was quaternary. The neuromuscular blocking activity of tubocurarine, very useful in anesthesia, led scientists all over the world to try to synthesise compounds with stronger activity and less toxicity. One of the compounds discovered in this way was the anaesthetic "atracurium" developed by researchers at the University of Strathclyde and the Wellcome Laboratories.

A. Historical Aspects of the Family Menispermaceae

The Menispermaceae (Moonseed family) was named by A. L. de Jussieu in 1789 and he included the genera *Menispermum* L., *Cissampelos* L., *Leaeba* Forsk., *Epibaterium* Forsk. and *Abuta* Aubl. (*2*). It was renamed later as Ménispermoidées by Ventenant and Ménispermées by Jeaume. In 1824, it was finally designated Menispermaceae by A.P. de Candolle, who divided the family into three tribes: Menispermeae, Lardizabaleae and Schizandreae. The tribes Lardizabaleae and Schizandreae were later included in the families Berberidaceae and Magnoliaceae, respectively.

In 1851, Miers (*3*) described six tribes based on embryo structure: Heterocinaceae, Anomospermeae, Tiliacoreae, Leptogoneae, Platygoneae and Pachygoneae.

In 1867, Bentham and Hooker (*4*) subdivided the family into four tribes, containing a total of 31 genera according to the morphology of the carpels, fruits and seeds: Tinosporeae, Cocculeae, Cissampelideae and Pachygoneae.

In 1872, Baillon kept the same divisons as Bentham and Hooker, and substituted the tribe Tinosporeae with Chasmanthereae (*2*).

Finally, Diels (*5*) in 1910, based on Mier's work, published a new division of the family with 8 tribes: Anamirteae, Anomospermeae, Cocculeae, Fibraureae, Hyperbaeneae, Peniantheae, Tinosporeae and Tricliseae; three sub-tribes of the Cocculeae were delineated: Cocculineae, Stephaniineae and Cissampelineae containing a total of 72 genera.

Diel's idea, based on the morphological aspects of the albumen and cotyledons was kept by Troupin when in 1962 he published a botanical study of the African Menispermaceae (*6*). This is the division that is still used today (see Table I).

B. BOTANICAL STUDIES

The family Menispermaceae is part of the order Ranunculales and is divided into eight tribes and three sub-tribes. It is composed of some 72 genera and approximately 400 species (*5*). Its species are distributed in all continents, with predominance in the tropical regions. The largest genus in the family is *Stephania* with 43 species, followed by *Tinospora* with 35, *Abuta* with 30, *Tiliacora* with 22, and *Cissampelos* and *Cyclea*, both with 19 species.

The name Menispermaceae is derived from the half-moon shape of the seeds (*2*). According to Dahlgren's classification (*7*), the position of the family is:

KINGDOM:	Plantae
CLASS:	Magnoliopsidae (= Angiospermae)
SUB-CLASS:	Magnoliidae (= Dicotyledoneae)
SUPER ORDER:	Ranunculiflorae
ORDER:	Ranunculales
FAMILY:	Menispermaceae

The plants are perennial. They are woody, being predominantly climbing shrubs with anomalous stem structure. The leaves are alternate, the flowers are unisex and the seeds may or may not have an endosperm.

Table I shows all of the 72 genera of the family in their respective tribes and sub tribes, the approximate number of species, and their geographical distribution.

C. BRIEF DESCRIPTION OF THE ALKALOIDS

The family is well known for the production of alkaloids of various kinds, among which those derived from a 1-benzyltetrahydroisoquinoline (cf. Scheme 2) precursor are the most common. It is also notable that alkaloids of the bisbenzylisoquinoline type are the most commonly found in plants of this family. This group of compounds is an integral part in the preparation of many of the dart poisons known as "curare", used by the South American Indians to immobilise (anesthetise?) animals and birds, and that served as models for the potent drugs used in anesthesia such as "atracurium". In reviewing the alkaloids from the family Menispermaceae, covering the period from 1970 to 1997, it was found that 22 different classes of alkaloids have been isolated from this family. Among these, the bisbenzylisoquinoline types were the most abundant, with 604 citations from many different plant species. In second place came the aporphine type with 303 citations, and third, protoberberines with 275 citations. In contrast, it is interesting to note the paucity of the citations for the other 19 types of compounds isolated from plants of this family.

TABLE I
Subdivisions of the family Menispermaceae after Brummitt, 1992 (*5*, *8*).

Number of species	TRIBES *Genera* *Sub-tribe*	GEOGRAPHICAL DISTRIBUTION			
		AFRICA	AMER.	ASIA	OCEAN
	TRICLISIEAE				
17	*Albertisia* Becc			√	√
6	*Anisocycla* Baill.	√			
1	*Beinaertia* Louis ex Troupin *	√			
3	*Carronia* F. Muell. *				√
5	*Chondodendron* Ruiz et Pavon		√		
4	*Curarea* Barneby & Krukoff		√		
12	*Epinetrum* Hiern	√			
2	*Haematocarpus* Miers *			√	
1	*Macrococculus* Becc. *				√
1	*Pleogyne* Miers *				√
17	*Pycnarrhena* Miers			√	√
18	*Sciadotenia* Miers		√		
1	*Synclisia* Benth.	√			
3	*Syrrheonema* Miers *	√			
22	*Tiliacora* Colebr.	√		√	
10	*Triclisia* Benth.	√			
	PENIANTHEAE				
2	*Penianthus* Miers	√			
1	*Sphenocentrum* Pierre	√			
	ANAMIRTEAE				
1	*Anamirta* Colebr.			√	√
3	*Arcangelisia* Becc.			√	√
6	*Coscinium* Colebr.			√	
	FIBRAUREAE				
5	*Burasaia* Thouars	√			
4	*Fibraurea* Lour.			√	
7	*Tinomiscium* Miers			√	

(*continues*)

TABLE I (*Continued*)

Number of species	TRIBES *Genera* *Sub-tribe*	GEOGRAPHICAL DISTRIBUTION			
		AFRICA	AMER.	ASIA	OCEAN
	TINOSPOREAE				
1	*Aspidocarya* Hook. F. & Thomson *			√	
1	*Calycocarpum* Nutt. ex Spach *		√		
2	*Chasmanthera* Hochst.	√			
1	*Chlaenandra* Miq. *				√
1	*Dialytheca* Exell. & Mendonça *	√			
3	*Dioscoreophyllum* Engl.	√			
8	*Disciphania* Eichl. *		√		
1	*Fawcettia* F. Muell. *				√
2	*Jateorhiza* Miers	√			
4	*Kolobopetalum* Engl.	√			
1	*Leptotherantha* Louis ex Troupin *	√			
4	*Odontocarya* Miers *		√		
1	*Orthogynium* Baill. *	√			
10	*Parabaena* Miers			√	√
1	*Platytinospora* (Engl.) Diels *	√		√	
2	*Pridania* Gagnep. *			√	
2	*Rhigiocarya* Miers	√			
1	*Sarcolophium* Troupin *	√			
1	*Somphoxylum* Eichl. *		√		
1	*Synandropus* A. C. Smith *		√		
1	*Syntriandrium* Engl. *	√			
35	*Tinospora* Miers	√		√	
	ANOMOSPERMEAE				
30	*Abuta* Aubl.		√		
5	*Anomospermum* Miers *		√		
4	*Caryomene* Barneby & Krukoff		√		
1	*Elissarrhena* Miers *		√		
6	*Telitoxicum* Moldenke		√		

(*continues*)

TABLE I (*Continued*)

Number of species	TRIBES *Genera* *Sub-tribe*	GEOGRAPHICAL DISTRIBUTION. AFRICA	AMER.	ASIA	OCEAN
	HYPERBAENEAE				
1	*Hyperbaena*		√		
	COCCULEAE				
	Cocculinae				
11	*Cocculus* DC.	√	√	√	
3	*Diploclisia* Miers			√	
17	*Hypserpa* Miers *			√	√
2	*Legnephora* Miers				√
5	*Limacia* Lour.			√	
1	*Limaciopsis* Engl.	√			
8	*Menispermum* L.		√	√	
12	*Pachygone* Miers	√	√	√	√
6	*Pericampylus* Miers *			√	
6	*Rhaptonema* Miers *	√			
1	*Sarcopetalum* F. Muell.				√
2	*Sinomenium* Diels			√	
1	*Spirospermum* Thouars	√			
1	*Strychnopsis* Baill.	√			
1	*Ungulipetalum* Moldenke *	√			
	Stephaniinae				
43	*Stephania* Lour.	√		√	√
	Cissampelinae				
4	*Antizoma* Miers	√			
19	*Cissampelos* L.	√	√	√	√
19	*Cyclea* Arn. ex Wight			√	
2	*Paracyclea* Kudo & Yamamoto *			√	

* Genera with no phytochemical citation for any of their species.

II. Survey of the Alkaloids of the Menispermaceae

A. ALKALOIDS OF THE MENISPERMACEAE

As stated above, the family Menispermaceae is very rich in diverse types of alkaloids. Emphasis is given to the significant majority of alkaloids derived from the benzyltetrahydroisoquinoline nucleus. One of the most important members of this group of alkaloids is tubocurarine, which is part of curare, described for the first time in 1805 by Humboldt, who observed its utilization by South American Indians as a dart poison for hunting and fishing purposes. Its structure was elucidated by King in 1935 (*9*), although he incorrectly assigned it as being a bisquaternary salt of the bisbenzyltetrahydroisoquinoline nucleus. Only in 1970 was it discovered that it was a monoquaternary salt. The synthesis of tubocurarine in 1958 by Veronin, opened the way for the use of other quaternary ammonium salts as neuromuscular blocking agents which are more active and less toxic.

There are two previous reviews of the literature on alkaloids from the Menispermaceae. The first was published by Tomita in 1952 (*10*) and the second was by Thornber in 1970 (*11*). The fact that the last review was published some 27 years ago presented an obvious challenge, given the large volume of publications on alkaloids of the Menispermaceae that have appeared in the ensuing years. The number of papers discussed by each of the previous reviews and the number of papers reviewed in this work are seen in Table II. A limited review of alkaloids from the South American Menispermaceae was published in 1996 (*12*).

As seen in Table II, in the 18 years between Tomita's review and Thornber's review, the number of plant studies almost doubled and the number of alkaloids isolated almost trebled. However, only one new class of alkaloid appeared. If we compare Thornber's review with the present review, we can see a huge and significant increase in the number of plants studied (from 52 to 159) and in the number of alkaloids isolated (from 241 to 1525).

TABLE II. Plants of the family Menispermaceae studied, number of alkaloids described and number of bibliographic citations.

DATA OBATAINED FROM	PLANTS STUDIED	ALKALOIDS DESCRIBED	NUMBER OF CITATIONS
TOMITA'S REVIEW 1952	33	92	158
THORNBER'S REVIEW 1970	52	241	124
THIS WORK (UP TO NOVEMBER 1996)	159	1525	531

In the work shown in this chapter, the 72 genera shown in Table I, were surveyed. Among those genera, only 45 had bibliographic citations. The search was carried out in *Chemical Abstracts* (vols. 56-1950 to 123-1995), on online search in NAPRALERT, the *Dictionary of Natural Products* on CDROM (version 5:1, July 1996), and in the reviews of alkaloids derived from the benzyltetrahydroisoquinoline nucleus published in *Natural Product Reports*.

B. The Possible Common Origin of the Alkaloids Isolated from Plants of the Menispermaceae

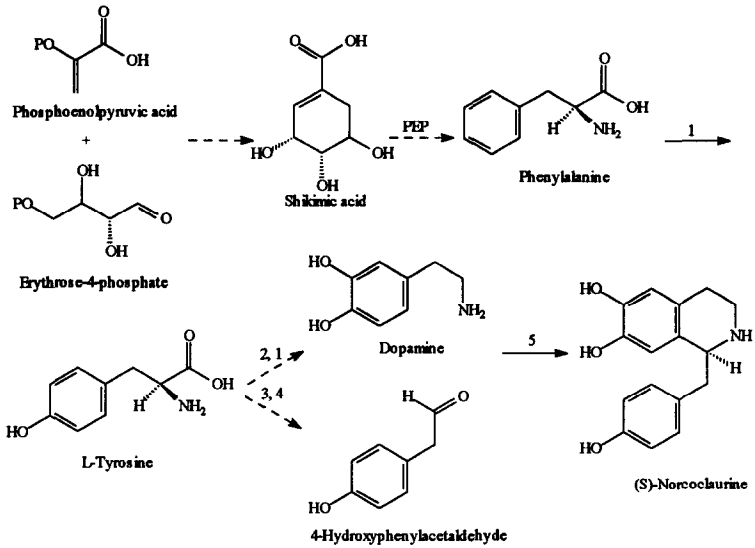
Subsequent to the discovery by Davis of the metabolic pathway to the formation of aromatic amino acids *via* shikimic acid, great advances were achieved in the understanding of the biosynthesis in living organisms. The formation of shikimic acid occurs through the reaction between phosphoenolpyruvic acid and erythrose-4-phosphate (Scheme 1). Shikimic acid reacts with phosphoenolpyruvic acid, followed by a series of steps to form phenylpyruvic acid, which, after reductive amination, is transformed into phenylalanine. This amino acid may then undergo decarboxylation to form phenylethylamine or deamination to form phenylacetaldehyde. These two compounds may react together to form the benzyltetrahydroisoquinoline nucleus (*13-16*) (Scheme 1), which is a very important intermediate in the formation of almost all of the alkaloids present in plants of the family Menispermaceae.

C. Biosynthetic Map of the Menispermaceae

To be considered as a good chemotaxonomic marker, a group of compounds must occur in dissimilar form in different groups of organisms. The benzyltetrahydroisoquinoline alkaloids can be considered as good markers because they occur mostly in the super-orders Magnoliiflorae and Ranunculiflorae. These two super-orders are very close to each other in the classification of the Angiospermae developed by Dahlgren. In this work, a biosynthetic map is defined as a group of chemical skeleta biogenetically alike, from which a series of compounds is derived.

The first step in creating a biosynthetic map is to list all of the structural types of a certain group of compounds (in this case alkaloids). This work should be preceded by a bibliographic review in specialised literature, of the occurrence of all of the chemical constituents chosen as markers.

Inspection of the compounds described in Table III and according to the origin of the alkaloids derived from the benzyltetrahydroisoquinoline nucleus, led us to propose a biosynthetic map of the family Menispermaceae. The map was constructed in accordance with the suggested biosynthetic relationships that exist between the different types of alkaloids (*17-22*) as outlined in Figure 1.



SCHEME 1 - Biosynthetic pathway for the formation of (*S*)-Norcoclaurine. The enzymes involved in the process are: 1-Phenolase; 2- L-Tyrosine decarboxylase; 3 – L-Tyrosine transaminase; 4 – *p*-Hydroxyphenylpyruvate decarboxylase; 5 – (*S*)-Norcoclaurine synthase.

When discussed individually, a biosynthetic pathway to each type of alkaloid will be suggested. This individual approach is based on a bibliographic review according to transformations observed in live organisms and also in a purely theoretical, biogenetic mechanistic approach. It should be stated that most of the biosynthetic pathways are merely speculative. And thus much experimental work remains to be conducted.

D. CLASSIFICATION OF THE ALKALOIDS OF THE MENISPERMACEAE

In this review, 22 different types of alkaloids could be identified in plants of the family Menispermaceae over the past 27 years. To be considered as a separate type, there must be at least 2 different alkaloids with the same basic skeleton. In the case where only one alkaloid has been identified, these were classified as "Others". Another problem encountered was the bibliographic citation of some alkaloids with no chemical structure elucidated. Those alkaloids were classified as CSND (chemical structure not defined). The other types of alkaloids were classified as indicated in Table III.

TABLE III
Locator codes, abbreviations used and types of alkaloids studied in this work.

LOCATOR CODE	ABREVIATION	TYPE OF ALKALOID
I	BIQ	Benzylisoquinoline alkaloids
II	Bis-BIQ	Bisbenzylisoquinoline alkaloids
III	PROAPO	Proaporphine alkaloids
IV	APORPHIN	Aporphine alkaloids
V	TROPOL	Tropoloneisoquinoline alkaloids
VI	AZAFLU	Azafluoranthene alkaloids
VII	PHENANT	Phenanthrene alkaloids
VIII	ARISTO	Aristolochic acid derived alkaloids
IX	ISOOXOA	Isooxoaporphine alkaloids
X	PROTOB	Protoberberine alkaloids
XI	HIRSUTI	Hirsutine alkaloids
XII	COHIRSI	Cohirsine alkaloids
XIII	BENZAZE	Benzazepine alkaloids
XIV	MORPHIN	Morphinan alkaloids
XV	HASUBA	Hasubanane alkaloids
XVI	ACUTUMI	Acutumine alkaloids
XVII	ERIBIDI	Eribidine alkaloids
XVIII	ERYTHRIN	Erythrina alkaloids
XIX	PAVINE	Pavine alkaloids
XX	ISOQUIN	Isoquinoline alkaloids
XXI	PHENETHYL	Phenethylcinnamide alkaloids
XXII	OXOCAN	Stephaoxocane alkaloids
XXIII	OTHERS	Miscellaneous structure alkaloids

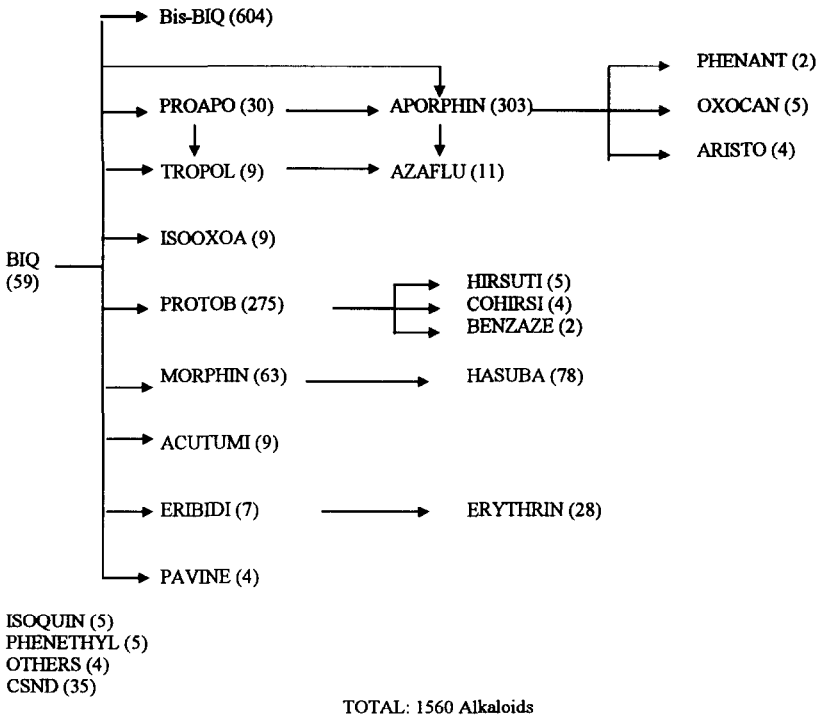
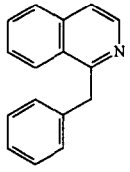
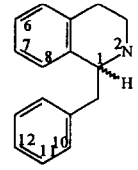


FIGURE 1. Probable biosynthetic relationships between the different classes of alkaloids isolated from plants of the family Menispermaceae. The numbers in brackets are the numbers of alkaloids isolated in each class.

1. Benzylisoquinoline alkaloids (BIQ)

1-Benzylisoquinoline alkaloids	1-Benzyltetrahydroisoquinoline alkaloids
	
Stephania	*Abuta, Burasaia, Caryomene, Cissampelos, Cocculus, Cyclea, Pachygone, Parabaena, Sarcopetalum, Sciadotenia, Stephania, Tiliacora, Tinospora*

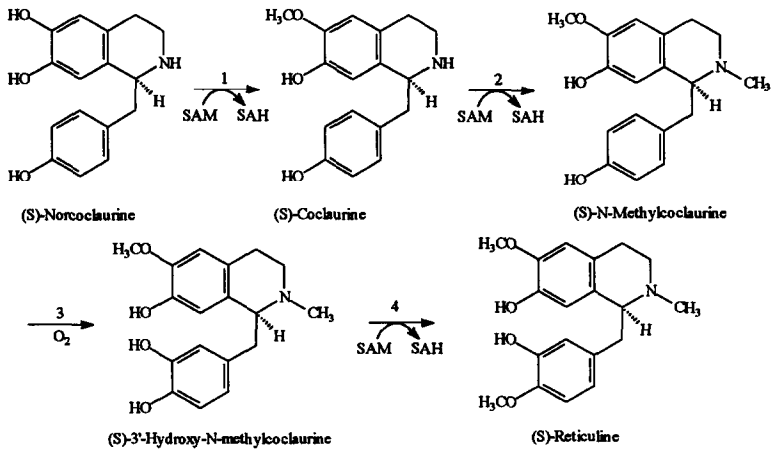
The sub type 1-benzyltetrahydroisoquinoline has a special place in the family Menispermaceae. All of the alkaloids with a tetracyclic nucleus present in the family have this tricyclic nucleus as their biogenetic origin.

More than 100 alkaloids of this sub-type are distributed throughout the families Annonaceae, Berberidaceae, Hernandiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Papaveraceae, Ranunculaceae and Rhamnaceae.

In the family Menispermaceae there are 60 bibliographic citations, representing 20 different alkaloids. This represents 3.9% of the total number of alkaloids isolated from the family. This sub-type occurs in 13 of the 45 genera studied so far. The genera in which they are most commonly found are *Stephania* (18) and *Tiliacora* (8). From the genus *Tinospora* there are seven citations of the same alkaloid - tembetarine. Of the 60 citations in the family, only one is of the sub type I.a and this alkaloid is papaverine, isolated from *Stephania gracilenta* (*402*). It is interesting to note that outside the family Papaveraceae, the only other family where we can find this type of alkaloid is the Menispermaceae.

In the Menispermaceae, the most frequently cited alkaloid of this type is coclaurine, responsible for 13 citations in plants of the genera *Abuta* (1), *Caryomene* (1), *Cocculus* (4), *Cyclea* (2), *Pachygone* (1), *Sarcopetalum* (1), *Sciadotenia* (1) and *Stephania* (2). Other important alkaloids are: reticuline (5 citations), and oblongine (4 citations).

The biosynthesis of reticuline is shown in Scheme 2, which describes the general biosynthetic pathway to this type of alkaloid (*23*).

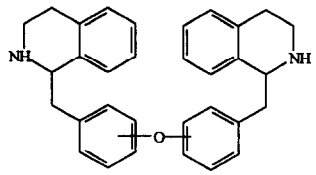
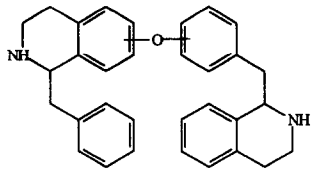


SCHEME 2. Biosynthetic pathway for reticuline. The enzymes involved in the process are: 1 – Norcoclaurine-6-*O*-methyltransferase; 2 – Coclaurine-*N*-methyltransferase; 3 – Phenolase; 4 – (*S*)-3'-Hydroxy-*N*-methylcoclaurine-4'-*O*-methyltransferase.

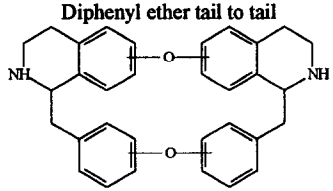
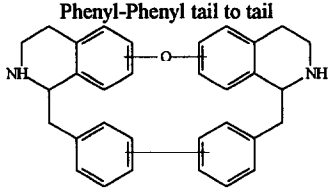
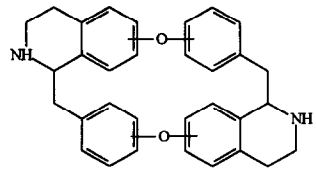
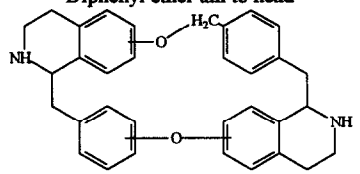
2. Bisbenzylisoquinoline alkaloids (Bis-BIQ)

This class of alkaloid is divided into several sub-types according to the number of bonds between the two monomers, the type of bond(s) and their relative position to each other:

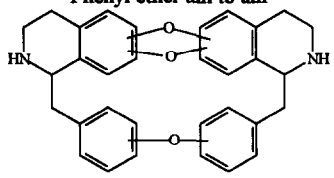
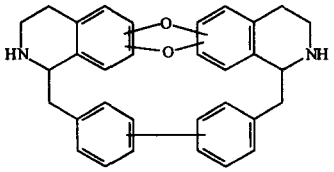
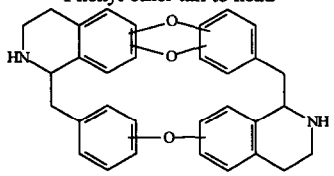
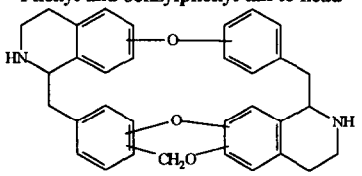
a. One bond

Diphenyl ether tail to tail	Diphenyl ether head to tail
	
Abuta, Albertisia, Caryomene, Menispermum, Sciadotenia	*Cyclea*

b. Two bonds

Diphenyl ether head to head Diphenyl ether tail to tail	Diphenyl ether head to head Phenyl-Phenyl tail to tail
	
Abuta, Albertisia, Anisocycla, Arcangelisia, Caryomene, Cissampelos, Cocculus, Curarea, Cyclea, Limacia, Limaciopsis, Pycnarrhena, Sciadotenia, Sinomenium, Spirospermum, Stephania, Strychnopsis, Tiliacora	*Tiliacora*
Diphenyl ether head to tail Diphenyl ether tail to head	Phenylbenzyl ether head to tail Diphenyl ether tail to head
	
Chondodendron, Cissampelos, Curarea, Cyclea, Epinetrum, Limaciopsis, Sciadotenia, Sinomenium, Stephania, Synclisia	*Cissampelos, Cyclea*

c. Three bonds

Diphenyl ether head to head Phenyl ether tail to tail 	Diphenyl ether head to head Phenyl-phenyl tail to tail 
Albertisia, Anisocycla, Cocculus, Pachygone, Stephania, Synclisia, Triclisia	*Pachygone, Tiliacora*
Diphenyl ether head to tail Phenyl ether tail to head 	Phenyl ether head to tail Phenyl and benzylphenyl tail to head 
Cyclea	*Cissampelos, Cyclea*

This type of alkaloid, together with the aporphines and protoberberines, are considered good chemical markers of the family Menispermaceae. They are present in the great majority of the species so far studied.

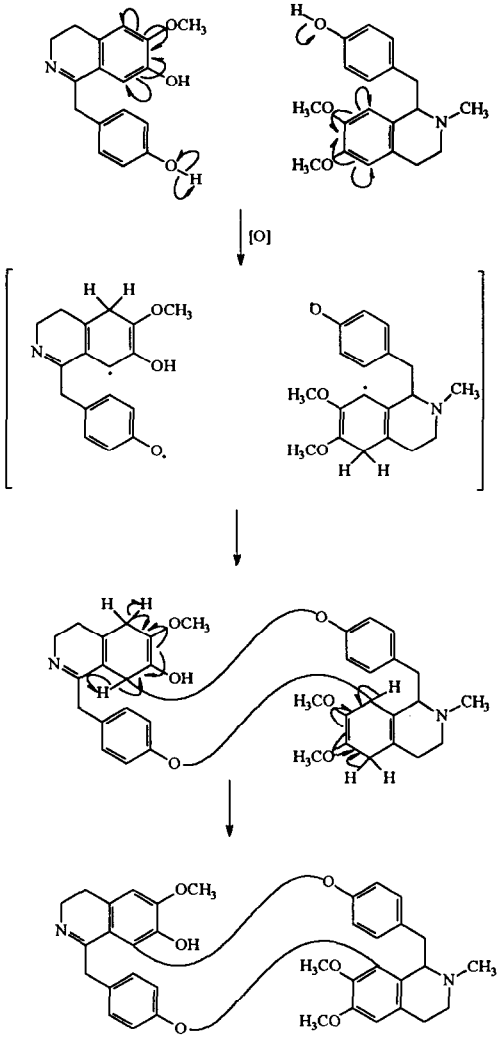
These alkaloids are present in several different plant families, with special emphasis in the family Menispermaceae. 604 citations of bisbenzylisoquinoline alkaloids were discovered during this review. This represents 39.6% of the total number of alkaloids isolated from plants of the family. They have been found in 23 of the 45 genera studied, being more frequently found in *Stephania* (171), *Cyclea* (87), and *Cocculus* (63). Other plant families rich in Bis-BIQ are Ranunculaceae (*Thalictrum*), Berberidaceae (*Berberis, Mahonia*), Monimiaceae (*Daphnandra*), Annonaceae (*Phaeanthus, Popowia, Pseudoxandra, Rollinia*, etc.) and Lauraceae.

They are called Bis-BIQ because they are made of two BIQ residues connected to each other by one, two or three ether bridges or by direct carbon-carbon bonds. Other differences between them may be the nature of the oxygenated substituents (OH, OMe, OCH_2O), or the nature of the substitution in the two nitrogen atoms (NH, NMe, $^{+}NMe_2$, NO), the degree of unsaturation in the B ring and the stereochemistry of the two asymmetric centers. The chemistry of these alkaloids has been extensively reviewed (*24-28*).

Examples of alkaloids of the sub types of Bis-BIQ are: lindoldhamine isolated from *Abuta pahni* and *Albertisia papuana*, sutchuenine isolated from *Cyclea sutchuenensis*, tetrandrine from *Stephania* spp, tiliageine from *Tiliacora dinklagei* and *T. triandra*, warifteine from *Cissampelos ovalifolia*, cissampetine from *Cissampelos fasciculata*, kohatamine from *Cocculus pendulus*, pachygonine

from *Pachygone ovata*, insulanoline from *Cyclea hipoglauca* and *Cyclea sutchuenensis*, and insularine-2-β-*N*-oxide also isolated from *Cyclea sutchuenensis*.

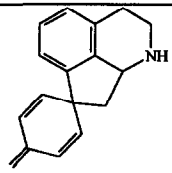
The biosynthesis of sciadoferine, isolated from *Sciadotenia toxifera* is described in Scheme 3.



Sciadoferine

SCHEME 3. Biogenesis of sciadoferine based on mechanistic considerations (*29*).

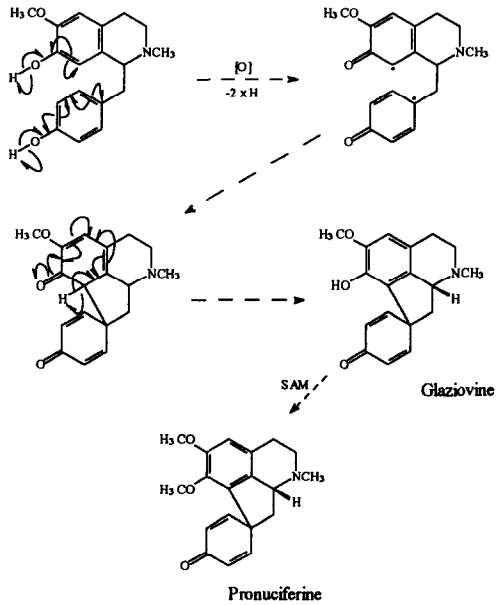
3. Proaporphine alkaloids (PROAPO)

	*Abuta, Anamirta, Caryomene, Cocculus, Diploclisia, Legnephora, Limacia, Menispermum, Pachygone, Sarcopetalum, Sciadotenia, Stephania*

The first proaporphine described in the literature was pronuciferine isolated from *Nelumbo nucifera* (Nymphaceae) and its chemical was structure elucidated by Bernauer in 1963 (*30*). This alkaloid was isolated again in 1968 from *Stephania glabra* (*31*). At that time it was the only known precursor to the aporphines. However, it is known today that the aporphines can also be formed directly from benzyltetrahydroisoquinolines.

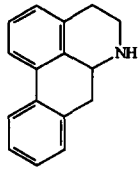
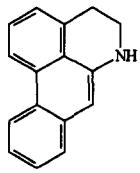
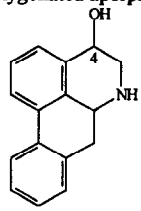
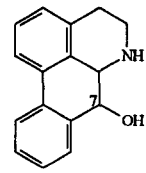
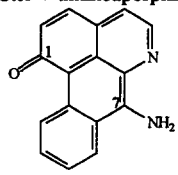
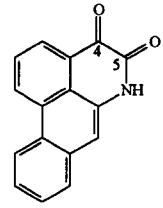
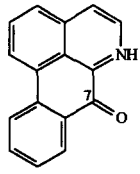
There have been 30 proaporphines (2%) isolated from the family Menispermaceae. They occur in 12 of the 45 genera, predominantly in *Stephania* (14), *Caryomene* (4), *Cocculus* (2) and *Legnephora* (2).

The biogenesis of pronuciferine and glaziovine is described in Scheme 4. A review of this group of alkaloids has been published (*32*).



SCHEME 4. Biosynthetic pathway of glaziovine and pronuciferine based on mechanistic considerations (*78*).

4. Aporphine alkaloids (APORPHIN)

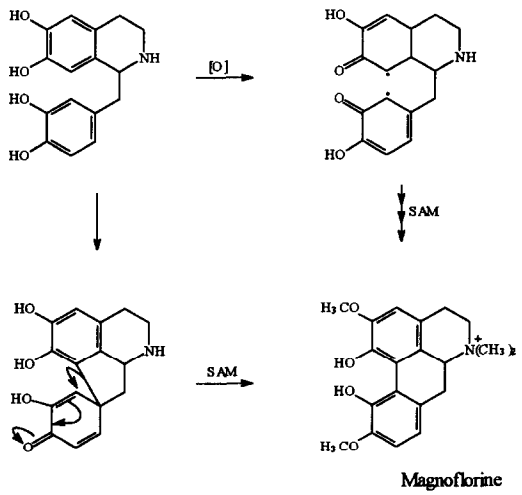
<table>
<tr><td>Aporphine
(sensu strictu)
  </td><td colspan="3">Anamirta, Anisocycla, Chasmanthera, Cissampelos, Cocculus, Coscinium, Cyclea, Dioscoreophyllum, Diploclisia, Fibraurea, Heptacyclum, Kolobopetalum, Legnephora, Menispermum, Pachygone, Penianthus, Pycnarrhena, Rhigiocarya, Sinomenium, Stephania, Strychnopsis, Tiliacora, Tinomiscium, Tinospora, Triclisia</td></tr>
<tr><td>6a,7-Didehydroaporphines
  </td><td>4-Oxygenated aporphines
  </td><td>7-Oxygenated aporphines
  </td></tr>
<tr><td>Cissampelos, Sinomenium, Stephania</td><td>Stephania</td><td>Sinomenium, Stephania</td></tr>
<tr><td colspan="2">1-Oxo-7-aminoaporphines
  </td><td colspan="2">4,5-Dioxoaporphines
  </td></tr>
<tr><td colspan="2">Telitoxicum</td><td colspan="2">Stephania</td></tr>
<tr><td>7-Oxoaporphine
  </td><td colspan="3">Abuta, Anisocycla, Chasmanthera, Cissampelos, Limacia, Limaciopsis, Pachygone, Pycnarrhena, Rhigiocarya, Sinomenium, Stephania, Telitoxicum, Triclisia</td></tr>
</table>

Aporphine alkaloids constitute a group with more than 500 different compounds, distributed between the families Annonaceae, Hernandiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Monimiaceae, Ranunculaceae and others. It is the second most abundant type of alkaloid in the family

Menispermaceae, with 303 compounds (20%) distributed in 29 genera (64%). Like most of the other alkaloid types found in the family Menispermaceae, the genus *Stephania* is the richest one, with a total of 188 isolated alkaloids. The second richest is the genus *Cocculus* with only 12 alkaloids.

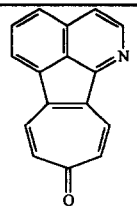
Aporphinoid is a general designation to define a series of compounds like: a) aporphines *sensu strictu*, the most common sub-type of aporphine in the family Menispermaceae, some others with small structural alterations such as: b) 6a,7-didehydroaporphines (dehydrodicentrine isolated from *Cissampelos pareira*); c) 4-oxygenated aporphines (epiglaufidine isolated from *Stephania zippeliana*); d) 7-oxygenated aporphines (ayuthianine isolated from *Stephania bancrofti*); e) 1-oxo-7-aminoaporphines (telazoline isolated from *Telitoxicum glaziovii*); f) 4,5-dioxoaporphines (cepharadione A isolated from *Stephania cepharantha*); g) 7-oxoaporphines (homomoschatoline isolated from *Abuta imene*), the second most common sub-type in the family with 51 compounds.

As a general example of the biogenesis of aporphines, Scheme 5 shows the biogenesis of magnoflorine based on mechanistic considerations. The chemistry of the aporphines has been extensively reviewed (*33-37*).



SCHEME 5. Biogenesis of magnoflorine based on mechanistic considerations.

5. Tropoloneisoquinoline alkaloids (TROPOL)

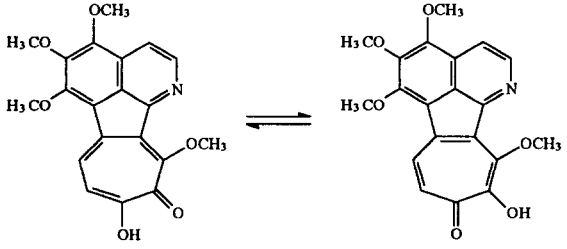
	*Abuta, Cissampelos*

This type of alkaloid has so far been found only in the family Menispermaceae. It is a good chemical marker for the family, but so far, alkaloids of this type have been isolated only from the genera *Abuta* and *Cissampelos*.

The first TROPOL was imerubrine, isolated by Cava *et al.* from *Abuta imene* (*38*). In that paper, the chemical structure was erroneously assigned as an oxoaporphine. Later when the same authors isolated a second TROPOL (grandirubrine) from *Abuta grandiflora* (*39*), this new type of alkaloid was established.

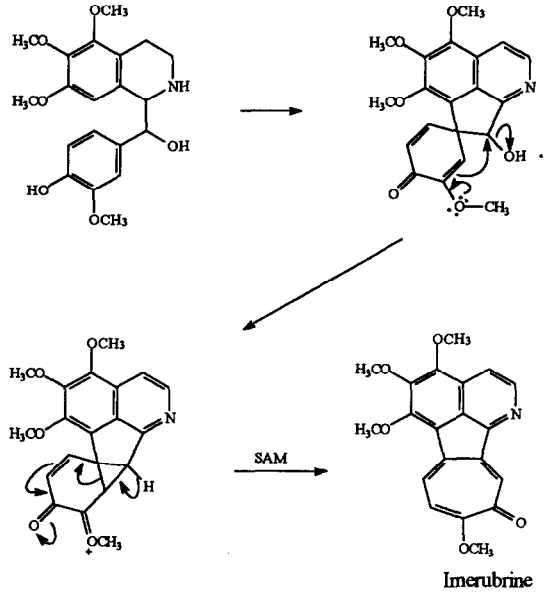
An interesting case is that of pareirubrine A, isolated from *Cissampelos pareira* (*40*). This alkaloid may exist as tautomers, in the solid state it assumes the form **1a** and in solution it assumes the form **1b**. This compound exhibits anti-leukaemic activity (IC_{50} 0.33 μg/ml) (*40*).

The biogenesis of imerubrine is described in Scheme 6.



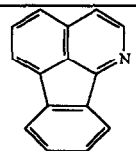
1a Pareirubrine A **1b**

solid state solution



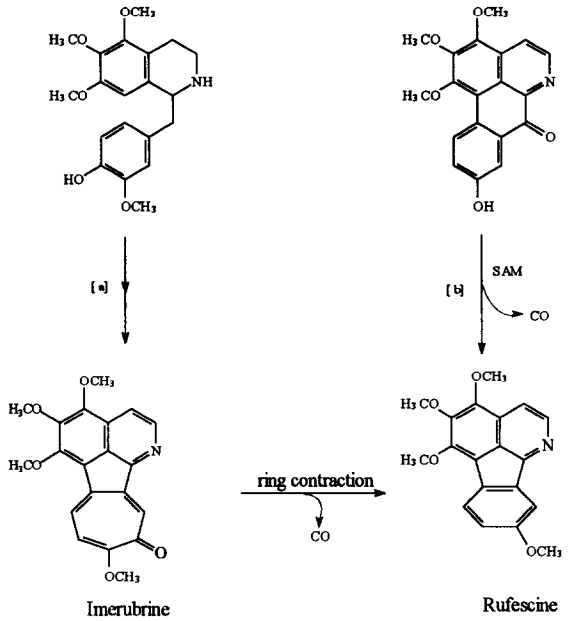
SCHEME 6. Possible biosynthesis of imerubrine based on mechanistic considerations (*78*).

6. Azafluoranthene alkaloids (AZAFLU)

	*Abuta, Cissampelos, Telitoxicum, Triclisia*

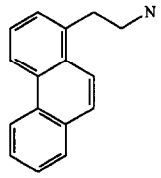
The azafluoranthene is another type of alkaloid exclusive to the family Menispermaceae. Among the 11 bibliographic citations, only 6 show different chemical structures.

There have been no pharmacological studies on this type of compound, although their chemistry was reviewed (*41*). The biogenesis of rufescine is given as a general example of the possible biosynthetic pathway for the AZAFLU in Scheme 7.



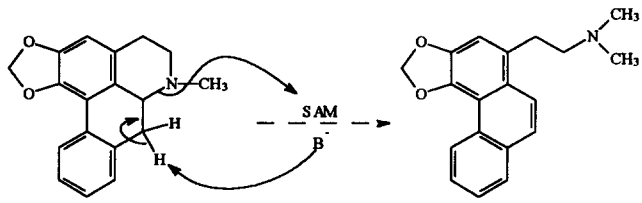
SCHEME 7. Biosynthesis of rufescine based on mechanistic considerations. Two proposals: a (*42*) and b (*43*).

7. Phenanthrene alkaloids (PHENANT)

	*Anisocycla, Stephania*

Also known as "seco-aporphines", the PHENANT is a very rare type of alkaloid. The total number of compounds isolated in this class is less than 20. They are distributed in the families, Annonaceae, Aristolochiaceae, Lauraceae, Menispermaceae, Monimiaceae and Ranunculaceae. Of this type of alkaloid, only stephenanthrine was isolated from the family Menispermaceae, being present in *Stephania tetrandra* and *Anisocycla cymosa*. The PHENANT type are probably

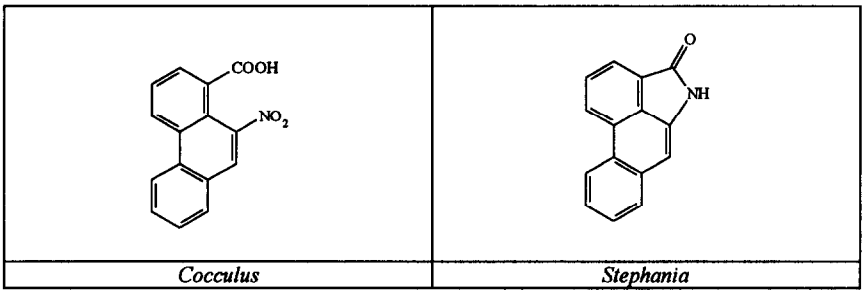
derived biogenetically from an aporphine precursor through the opening of ring B, (Scheme 8).The chemistry of these alkaloids has been reviewed (*44*).



stephenanthrine

SCHEME 8. Biogenesis of stephenanthrine based on mechanistic considerations.

8. Aristolochic acid derivative alkaloid (ARISTO)



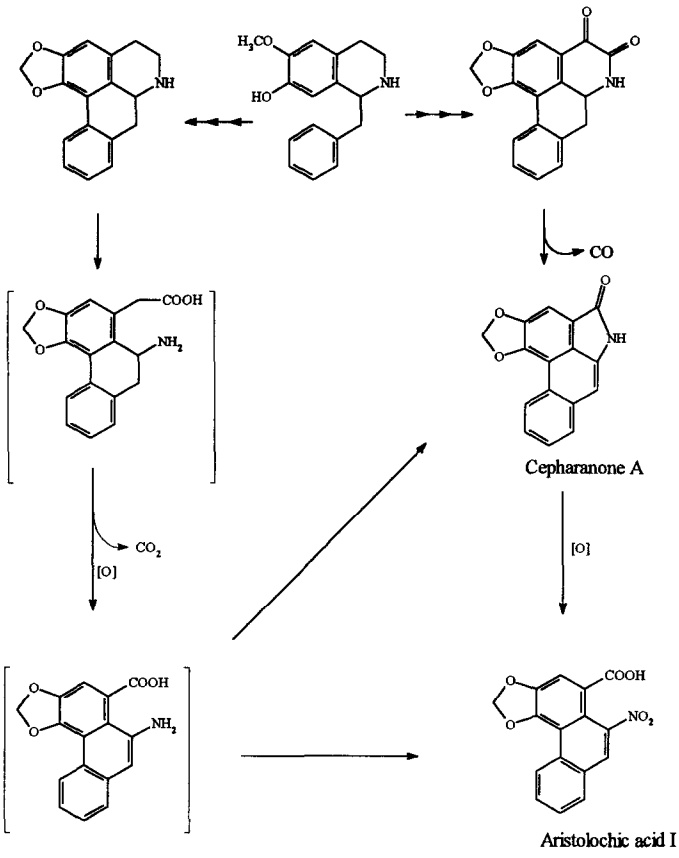
Cocculus	*Stephania*

Despite occurring in other families like the Annonaceae, Menispermaceae, Monimiaceae, Lauraceae, and Ranunculaceae, this type of alkaloid is known as a chemical marker of the family Aristolochiaceae, from which about 70 different compounds have been isolated.

In the family Menispermaceae there are 4 bibliographic citations for 3 different compounds. Aristolochic acid I was isolated from *Cocculus trilobus* and the aristolactams cepharanone A and cepharanone B (= Aristolactam BII) were isolated from *Stephania cepharantha*.

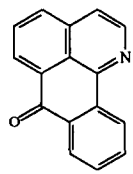
In Brazilian folk medicine, some plants of the family Aristolochiaceae are used as abortive agents. It is believed that this type of compound may be responsible for this activity. These compounds are also known to have cytotoxic activity.

The biogenesis of aristolochic acid I and cepharanone A are shown in Scheme 9. The chemistry of this class of compounds has been reviewed (*45*).

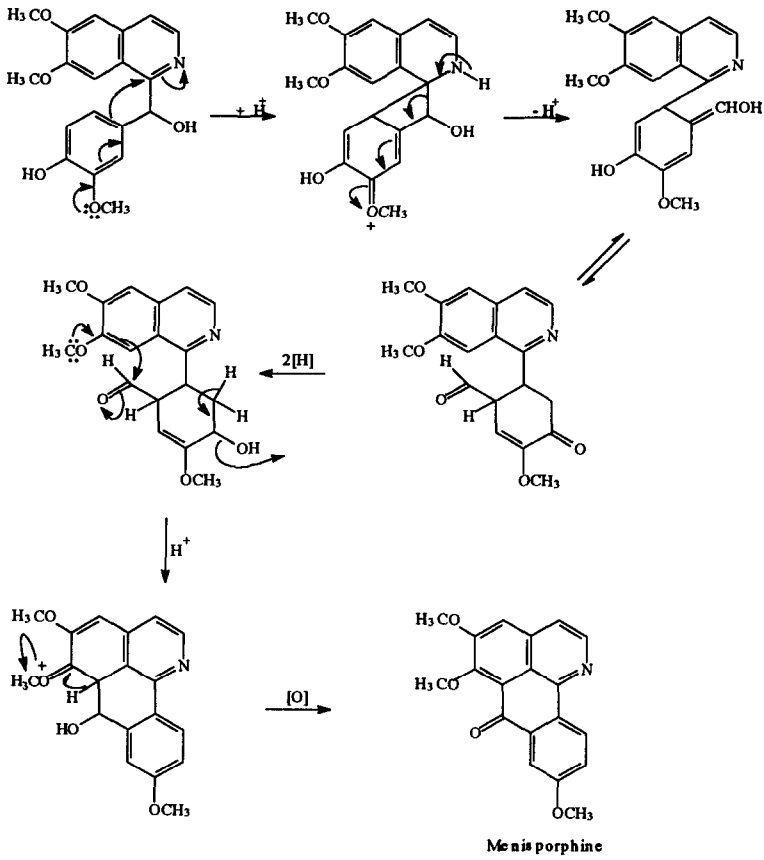


SCHEME 9. Biogenesis of aristolochic acid and cepharanone A based on mechanistic considerations (*43*).

9. Isooxoaporphine alkaloids (ISOOXOA)

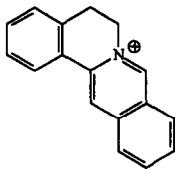
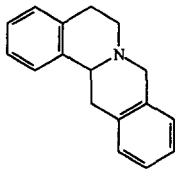
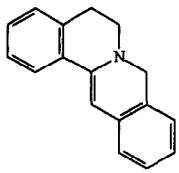
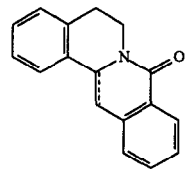
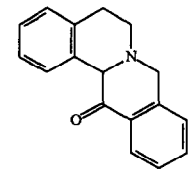
	*Menispermum, Sinomenium*

The first example of this type of alkaloid was isolated in 1982 from *Menispermum dauricum* and was named menisporphine (*46*). Later, other alkaloids with the same nucleus were isolated, all from plants of the family Menispermaceae. The biogenesis of menisporphine is shown in Scheme 10.



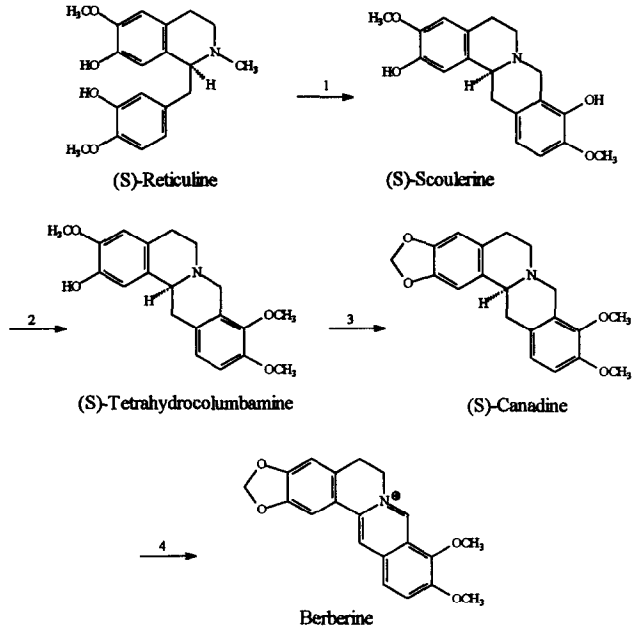
SCHEME 10. Biogenesis of menisporphine based on mechanistic considerations (*47*).

10. Protoberberine alkaloids (PROTOB)

<table>
<tr><td>Protoberberine
  </td><td colspan="2">Abuta, Anamirta, Anisocycla, Arcangelisia, Burasaia, Chasmanthera, Cocculus, Coscinium, Dioscoreophyllum, Fibraurea, Heptacyclum, Jateorhiza, Legnephora, Menispermum, Parabaena, Penianthus, Rhigiocarya, Sinomenium, Sphenocentrum, Stephania, Tinospora, Triclisia</td></tr>
<tr><td>Tetrahydroprotoberberine
  </td><td colspan="2">Anisocycla, Arcangelisia, Caryomene, Chasmanthera, Cissampelos, Cocculus, Coscinium, Cyclea, Fibraurea, Hyperbaena, Menispermum, Pachygone, Parabaena, Sinomenium, Stephania, Tinomiscium</td></tr>
<tr><td>Dehydroprotoberberine
  </td><td>8-Oxoderivative
  </td><td>13-Oxoderivative
  </td></tr>
<tr><td>Caryomene, Stephania</td><td>Anamirta, Arcangelisia, Coscinium, Limaciopsis, Stephania</td><td>Cocculus</td></tr>
</table>

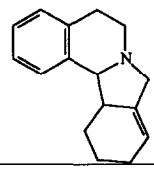
The PROTOB alkaloid group has 275 (19%) bibliographic citations among the alkaloids of the family Menispermaceae. They are distributed in 29 of the 45 genera studied. The genera richest in this type of alkaloid are *Stephania* (112), *Tinospora* (26) and *Fibraurea* (21).

Although some alkaloids of this type show pharmacological activity, very few of them have been used therapeutically. Berberine, isolated from *Berberis vulgaris*, has antimicrobial and protozoocide activity. The biogenesis of scoulerine, a tetrahydroprotoberberine alkaloid, is shown in Scheme 11. This type of alkaloid has been reviewed (*48-50*).



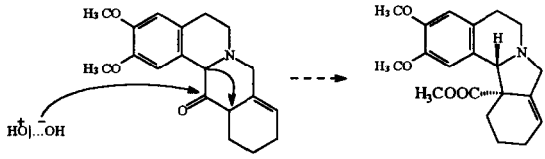
SCHEME 11. Biosynthesis of berberine based on *in vivo* experiments with *Coptis japonica* (*51*). The enzymes involved in the process are: 1- Berberine bridge enzyme; 2 – (*S*)-Scoulerine-9-*O*-methyl-transferase; 3 – Canadine synthase; 4 – (*S*)-tetrahydroberberine oxidase.

11. Hirsutine alkaloids (HIRSUTI)

	*Cocculus*

Only five alkloids of this type have been described in the literature, all isolated from *Cocculus hirsutus*.

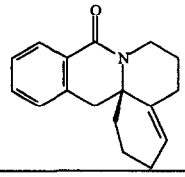
Probably these alkaloids are derived biogenetically from a precursor of the type of an 13-oxoprotoberberine alkaloid, which suffers attack from a peroxide anion to the carbonyl resulting in a contraction of ring C. Scheme 12 shows a possible pathway.



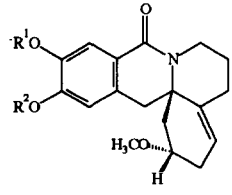
Jamtine

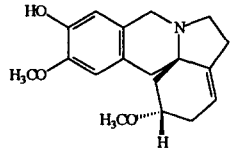
SCHEME 12. Biogenesis of Jamtine based on mechanistic considerations.

12- Cohirsine alkaloids (COHIRSI)

	*Cocculus*

In the same way as the hirsutine alkaloids, these alkaloids have only been isolated five times and all of them from *Cocculus hirsutus*. The five alkaloids were called cohirsine, cohirsitine, cohirsinine, cohirsitinine and shaheenine. The first to be isolated was cohirsine in 1987 (*52-53*).

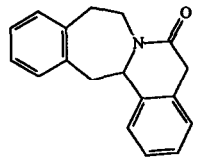




Cohirsine (R^1=R^2= CH_3)
Cohirsinine (R^1= H, R^2= CH_3)
Shaheenine (R^1=R^2= H)

Cohirsitinine

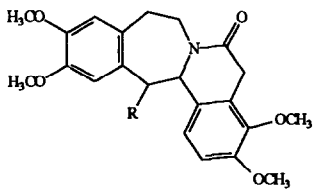
13. Benzazepine alkaloids (BENZAZE)

	*Abuta*

The alkaloids of this type have a similar carbon skeleton to the benzodiazepine drugs, known as minor tranquillisers. The first alkaloid of this type obtained from a natural source was puntarenine, isolated from *Berberis empetrifolia* (Berberidaceae). The other two alkaloids also obtained from a natural source were saulatine and dihydrosaulatine, both isolated from *Abuta bullata*.

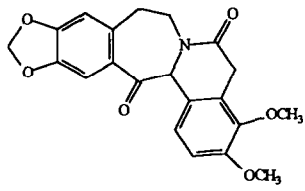
According to Hocquemiller *et al.* (*54*) "Saulatine should be considered a natural biogenetic derivative of palmatine, result of an expansion of ring B through a homologation mechanism which would be interesting to investigate". However, we should not overlook the possibility that this compound could be an artefact formed during the isolation process. It is known that berberine when isolated in $CHCl_3$ in NH_4OH medium and after passing through a silica gel column is partly transformed in berberrubine and oxyberberine (*55*).

Scheme 13 shows a proposition for the formation of saulatine as a degradation process during the isolation procedure.

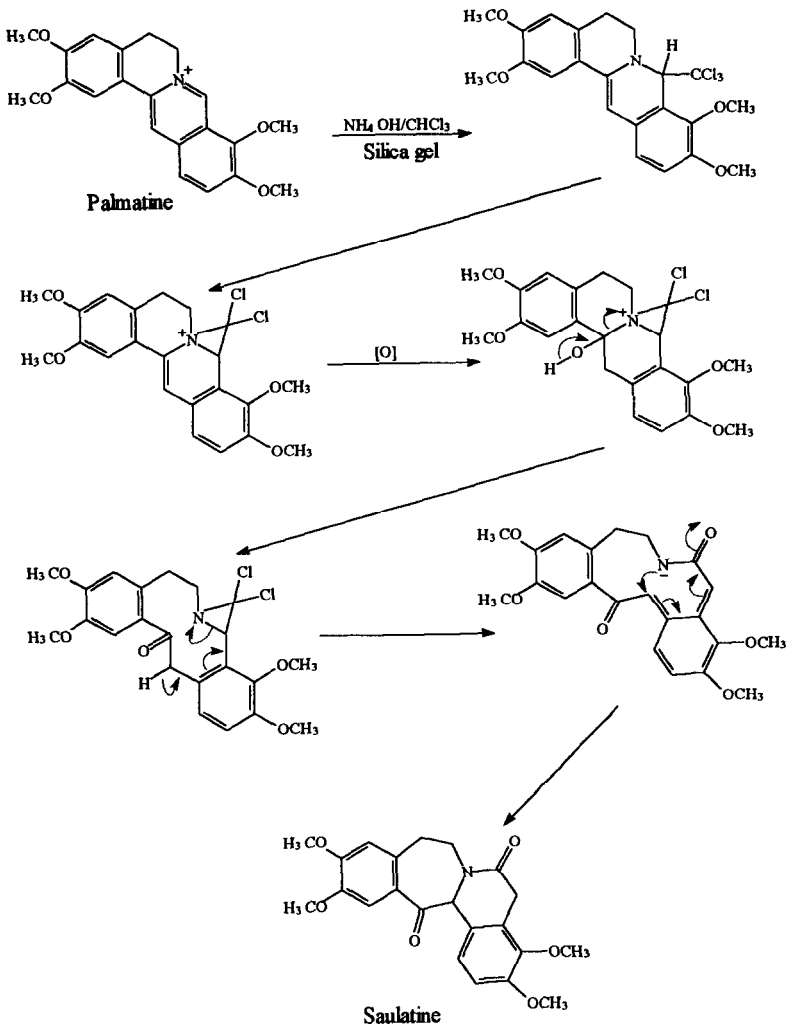


Saulatine (R= O)

Dihydrosaulatine (R= OH)

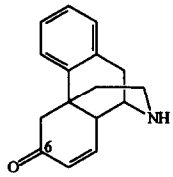
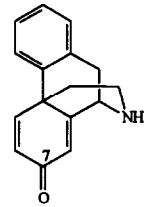
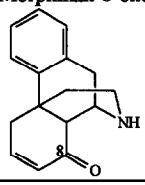
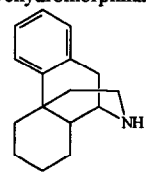


Puntarenine



SCHEME 13. Formation of saulatine as a probable degradation product during the isolation process (*55*).

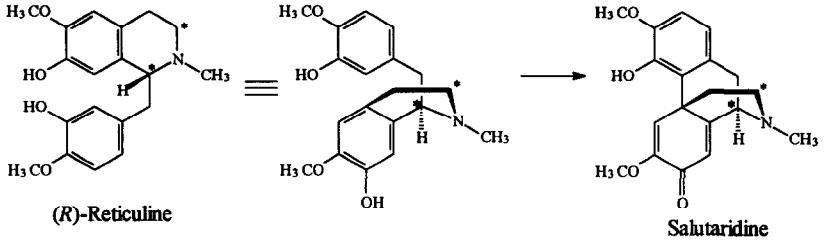
14. Morphinane alkaloids (MORPHIN)

Morphinan-6-one	Morphinan-7-one
	
Cocculus, Menispermum, Sinomenium, Stephania	*Antizoma, Chasmanthera, Cocculus, Kolobopetalum, Rhigiocarya, Sinomenium, Stephania*
Morphinan-8-one	**Dehydromorphinane**
	
Stephania, Triclisia	*Cocculus, Sinomenium, Stephania*

The morphinan alkaloids, also known as promorphine alkaloids, are present in the family Menispermaceae in 63 (4.1%) examples. They differ from those present in the family Papaveraceae in not having the ether bridge between the carbons C-4 and C-5. With the exception of cephasamine (*571*), the only alkaloid having the above bridge.

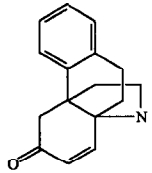
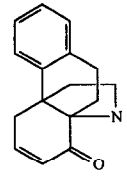
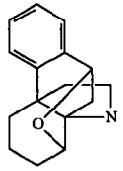
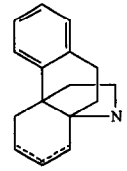
In this group, 4 different sub-groups can be assigned: a) morphinan-6-one, like sinomenine isolated from *Menispermum dauricum*, *Sinomenium acutum*, *Stephania brachyandra*, *Stephania cepharantha*, *Stephania epigaea* and *Stephania micrantha*; b) morphinan-7-one, like salutaridine obtained from *Stephania pierrei*; c) morphinan-8-one, like stephaphilline (=isostephodeline) present in *Stephania delavayi*, *Stephania suberosa* and *Stephania zippeliana*; d) dehydromorphinane, like sinococculine found in *Stephania cepharantha*, *Stephania excentrica* and *Stephania sutchuenensis*.

Sinomenine can be considered as the most important representative of this group. It has been clinically used in Japan against rheumatoid arthritis. Recent studies have shown some inhibitory effects of this alkaloid on immunologic functions (*56*). The chemistry of sinomenine has been reviewed (*57*). Scheme 14 shows the biosynthetic pathway for the formation of salutaridine.



SCHEME 14. Biosynthesis of salutaridine based on *in vivo* experiments with *Papaver somniferum* (*58*).

15. Hasubanane alkaloids (HASUBA)

Hasubanan-6-one	Hasubanan-8-one
	
Stephania	*Stephania*
8,10-Epoxyhasubanane	Dehydrohasubanane
	
Stephania	*Stephania*

There are 78 alkaloids of this type described in the literature since 1970. They were isolated only from the genus *Stephania*.

With the exception of stephadiamine, the only *nor*-C-hasubanane alkaloid isolated from *S. japonica*, the other alkaloids of this group can be subdivided into four different sub-groups: a) Hasubanan-6-one, like hasubanonine obtained from *S. japonica*; b) hasubanan-8-one, like prometaphanine, present in *S. japonica* in two equilibrium forms (see Figure 2); c) 8,10-epoxyhasubanane, like the other equilibrium form of prometaphanine; and d) dehydrohasubanane, like longetherrine from *S. longa*.

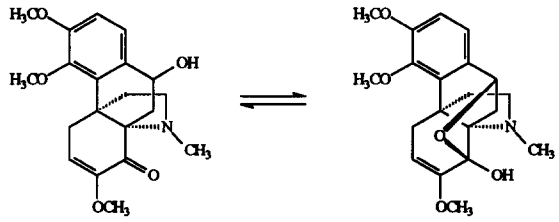
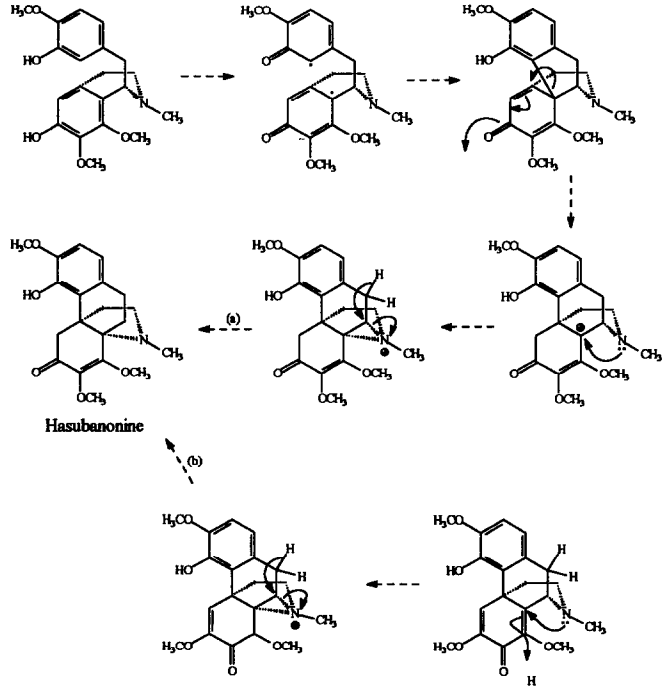


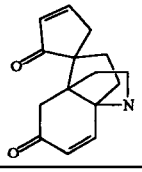
FIGURE 2. Equilibrium forms of prometaphanine.

This type of compound seems to derive biogenetically from the morphinan alkaloids, as can be demonstrated with *in vivo* experiments with *S. japonica* (*59*) or by laboratory chemical transformations (*11*) (Scheme 15). The chemistry of the hasubanane alkaloids was reviewed in 1988 by Matsui (*60*).

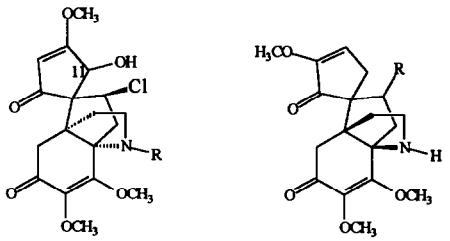


SCHEME 15. Biosynthesis of hasubanonine by *in vivo* experiments with *S. japonica* (a) (*59*) and mechanistic considerations (b) (*61*).

16. Acutumine alkaloids (ACUTUMI)

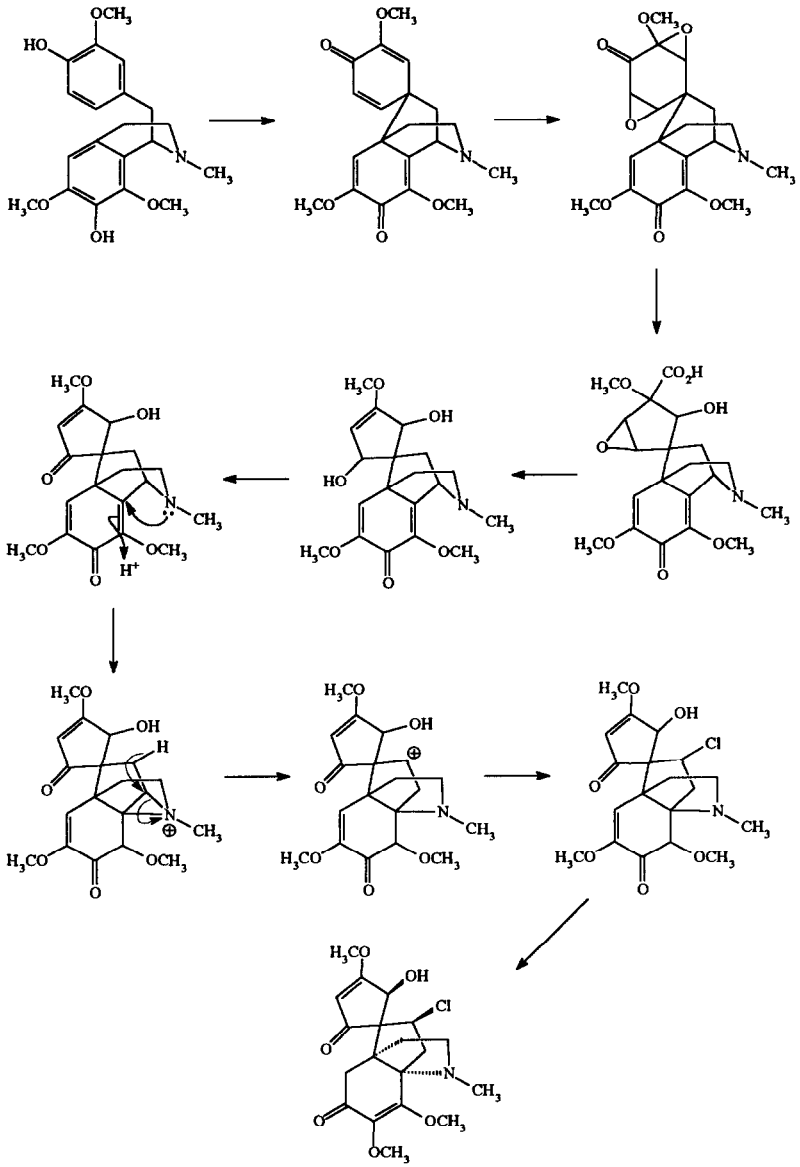
	*Limacia, Menispermum, Sinomenium*

The acutumine alkaloids are another class of alkaloids present only in the family Menispermaceae. Of the nine citations on the literature, only five are for different alkaloids. In these alkaloids rings C and D are like those in the hasubanane alkaloids, but they also derive from the benzyltetrahydroisoquinoline nucleus, as the great majority of alkaloids present in plants of this family. Figure 3 shows the five different acutumine alkaloids described in the literature and Scheme 16 presents a possible biogenetic pathway.



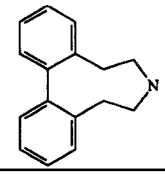
Acutumine (R= CH_3) Clolimalongine (R= Cl)
Acutumidine (R = H) Limalongine (R= H)
Acutuminine (R= CH_3, 11-deoxy)

FIGURE 3. Acutumine alkaloids.

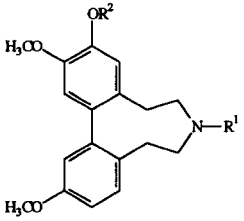


SCHEME 16. Biosynthesis of acutumine based on mechanistic considerations (*78*).

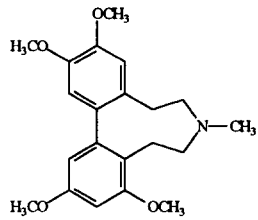
17. Eribidine alkaloids (ERIBIDI)

	*Cocculus, Hyperbaena, Stephania*

The eribidine alkaloids are a rare class of secondary metabolites. There are only 12 examples distributed in nature. Since Thornber's review (*11*), seven new citations appeared from plants of the family Menispermaceae, but only four of them show different chemical structures. From *Cocculus* were isolated laurifine, laurifinine and laurifonine; and from *Hyperbaena* and *Stephania*, protostephanine. The biogenesis of this class of alkaloids can be seen in Scheme 17.

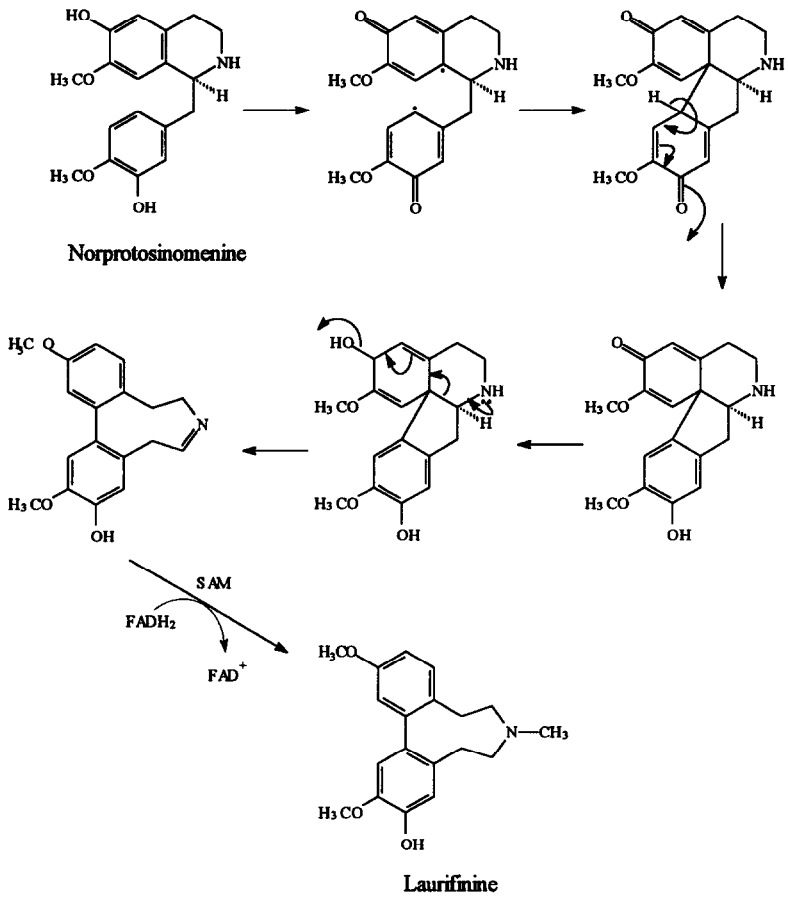


Laurifine - R^1= H, R^2= Me
Laurifinine - R^1= Me, R^2= H
Laurifonine - R^1= R^2= Me



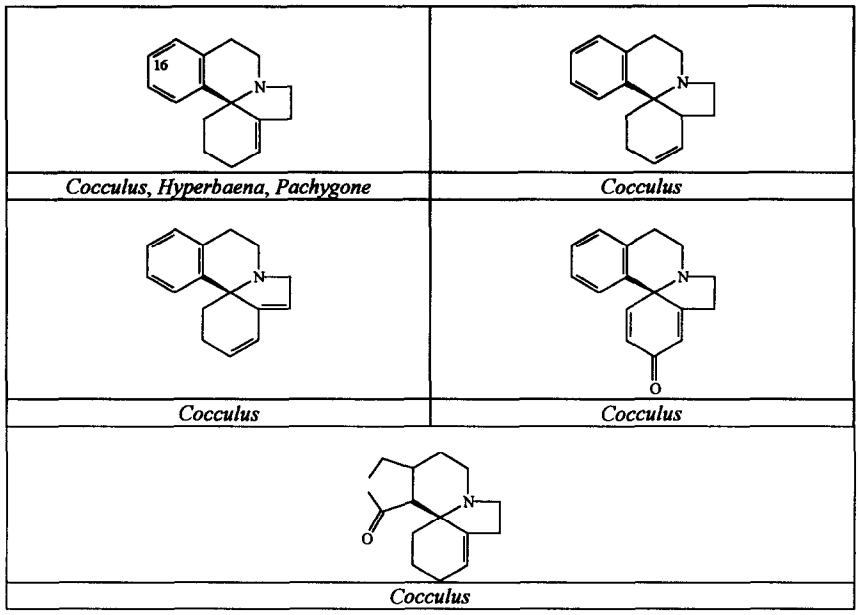
Protostephanine

FIGURE 4. Eribidine alkaloids from the Menispermaceae.



SCHEME 17. Biogenesis of laurifinine based on *in vivo* experiments with *Cocculus laurifolius* (*62, 63*).

18. Erythrine alkaloids (ERYTHRIN)

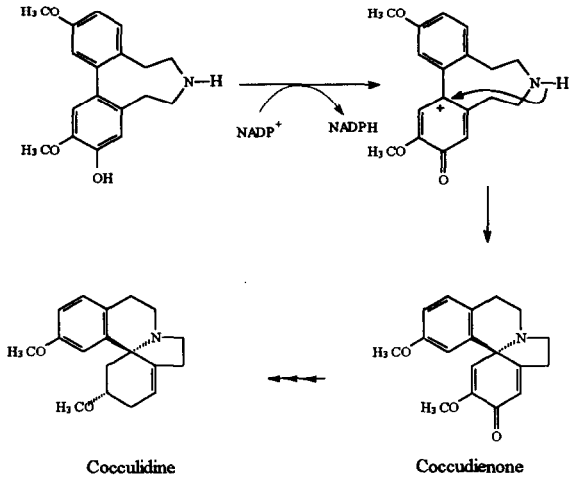


There are 28 bibliographic citations on these new alkaloids from plants of the family Menispermaceae. They are distributed between the genera *Cocculus* (25), *Hyperbaena* (2) and *Pachygone* (1). The name derives from *Erythrina*, one of the genera of the family Fabaceae, from which many alkaloids, and the first of this type, were isolated.

Changes in the position of the double bond, constitute the main differences between the five sub-types. Other important differences appear in ring A in the fifth sub type, seen above, which has a lactone ring.

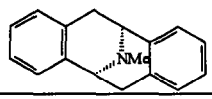
Some authors call these alkaloids "abnormal *Erythrina* alkaloids", because they do not have an oxygenated function in the carbon C-16, which is regularly encountered in the genus *Erythrina*.

These compounds derive biogenetically from the eribidine nucleus, as can be seen in Scheme 18. The chemistry of this type of alkaloid has been reviewed (*64*).



SCHEME 18. Biogenesis of coccudienone and cocculidine based on *in vivo* experiments with *Cocculus laurifolius* (*65*).

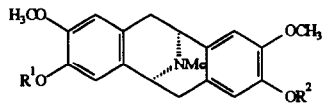
19. Pavine alkaloids (PAVINE)

	*Chasmanthera, Cyclea*

The pavine alkaloids are well distributed in the families Berberidaceae, Lauraceae, Papaveraceae, and Ranunculaceae, with about 50 different alkaloids. However, until now, only three alkaloids of this type were isolated from plants of the family Menispermaceae. They are: bisnorargemonine from *Chasmanthera dependens*, and argemonine and norargemonine from *Cyclea atjehensis* (Figure 5).

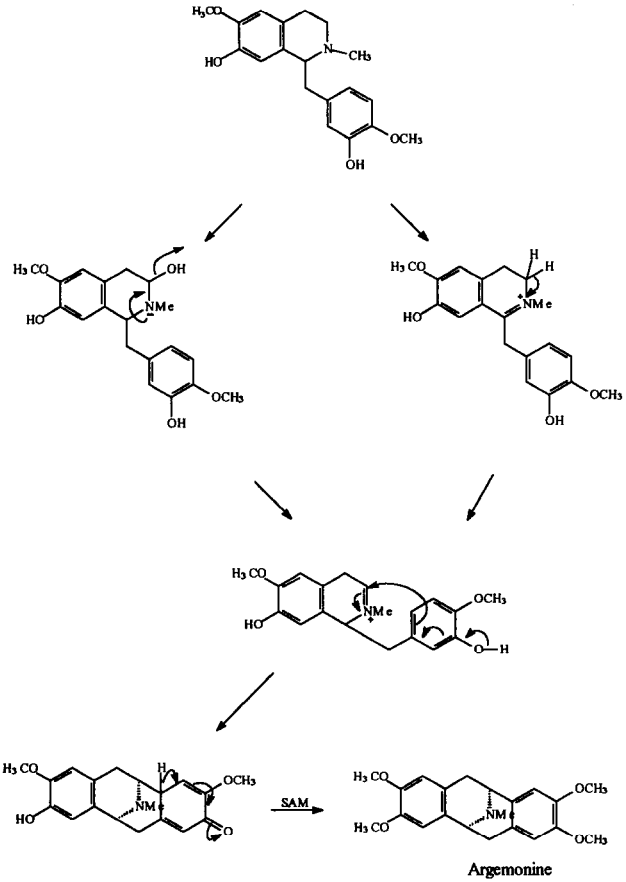
Based on *in vivo* experiments and mechanistic considerations, it can be demonstrated that these compounds derive biogenetically from reticuline, as can be seen in Scheme 19.

The chemistry of this group has been reviewed (*66*).



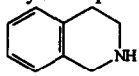
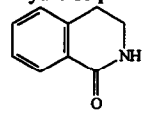
Argemonine (R^1=R^2=CH_3)
Norargemonine (R^1=H, R^2=CH_3)
Bisnorargemonine (R^1=R^2=H)

FIGURE 5. Pavine alkaloids from the Menispermaceae.



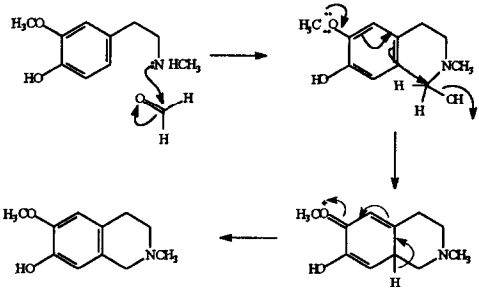
SCHEME 19. Biogenesis of argemonine based on *in vivo* experiments with *Argemone hispida* and *A. mexicana* and on mechanistic considerations (*18*).

20. Isoquinoline alkaloids (ISOQUIN)

Tetrahydroisoquinoline	Tetrahydroisoquinolone
	
Menispermum	*Abuta, Menispermum, Stephania*

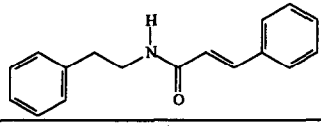
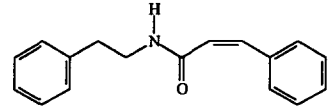
Some families like the Cactaceae, Chenopodiaceae and Fabaceae are known to produce simple isoquinoline alkaloids. In the Menispermaceae they are very rare. Up to the moment, the only compounds of this type isolated from plants of this family were: corypalline and thalflavine from *Menispermum dauricum*, thalifoline from *Abuta pahni* and 6,7-dimethoxy-2-methylisoquinolone from *Stephania sasakii*.

These alkaloids are formed through the reaction of phenylethylamine and formaldehyde, followed by cyclisation (see Scheme 20). The occurrence and properties of these alkaloids were reviewed by Menachery (*67*).



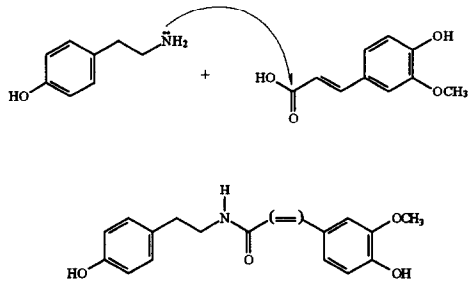
SCHEME 20. Biogenesis of corypalline based on mechanistic considerations (*78*).

21. Phenethylcinnamide alkaloids (PHENETHYL)

	
Penianthus, Sinomenium, Tinospora	*Tinospora*

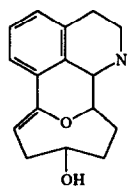
According to the biogenetic classification of the alkaloids, this group of alkaloids is sometimes called "Protoalkaloids" because they are derived from an aminoacid, but have the nitrogen out of a ring (*68*). The four citations from the family Menispermaceae are based on only two different compounds: *N-trans*-feruloyltyramine from the genera *Penianthus*, *Sinomenium* and *Tinospora* and *N-cis*-feruloyltyramine from the genus *Tinospora*.

This type of alkaloid can be also found in the families Fumariaceae, Lauraceae, Magnoliaceae, Papaveraceae, and Rutaceae. More than a hundred different compounds of this group have been presented in two literature reviews (*69*, *70*). Their biogenesis is straightforward (Scheme 21).

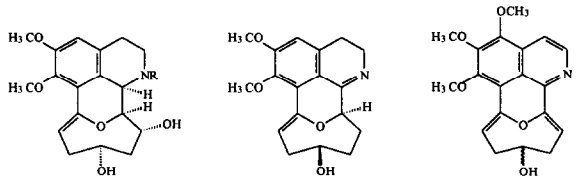


SCHEME 21. Biogenesis of *N-trans*-feruloyltyramine and *N-cis*-feruloyltyramine based on mechanistic considerations.

22. Stephaoxocane alkaloids (OXOCAN)

	*Cissampelos*, *Stephania*

A new class of alkaloids, the OXOCAN were recently discovered in *Stephania excentrica*, and so far only five examples are described in the literature, all of them from the Menispermaceae. The first alkaloid of this kind, excentricine, was isolated in 1993 from *Stephania excentrica* (*71*). The second, stephaoxocanine, was isolated in 1996 from *Stephania cepharantha* (*72*). The third was preliminarily published as a poster in the 20th Annual Meeting of the Brazilian Society of Chemistry (*578*,*579*). It was named eletefine and was isolated from *Cissampelos glaberrima* (Figure 6). There has been no presentation, as yet, of their biogenesis.



Excentricine (R = H) Stephaoxocanine Eletefine
N-Methylexcentricine (R = Me)

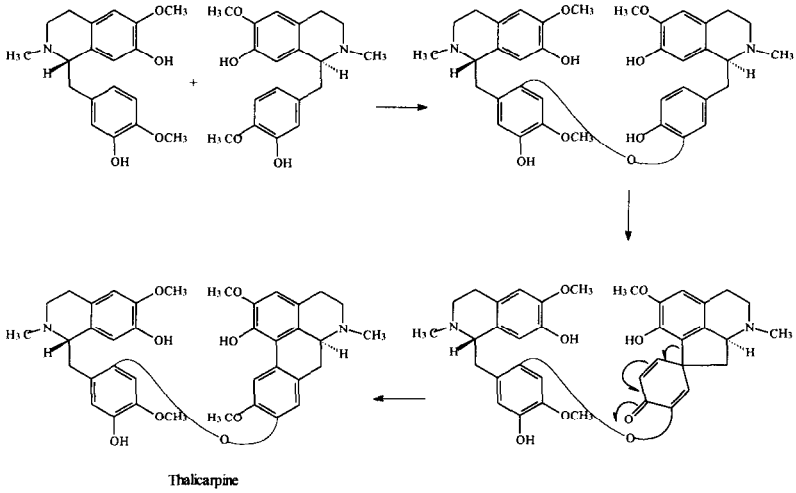
FIGURE 6. Stephaoxocane alkaloids.

23. Alkaloids with miscellaneous structures (OTHERS)

In the present work, it was observed that five types of alkaloid were isolated only once from plants of the family Menispermaceae. These alkaloids, thalicarpine, cohrisitine, gusalung C, kokusaginine and neotrilobine, are classified as "others".

a. Thalicarpine

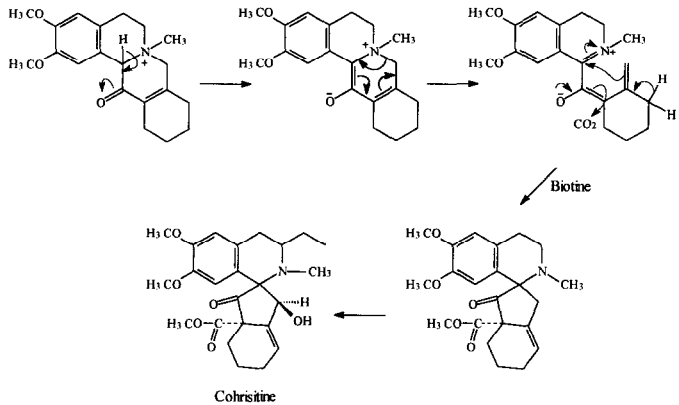
Thalicarpine was isolated from *Cocculus laurifolius* (*73*) in 1982. It is one of the rare examples of a tetrahydrobenzylisoquinoline-aporphine dimer. Thalicarpine seems to originate biogenetically from the oxidative coupling of two molecules of reticuline forming initially a Bis-BIQ. A second oxidative coupling, this one intramolecular, leads to the final product (Scheme 22). This alkaloid was also isolated from *Thalictrum* spp. (Ranunculaceae) and *Hernandia ovigera* (Hernandiaceae).



SCHEME 22. Biogenesis of thalicarpine based on *in vivo* experiments with *Cocculus laurifolius* (*73*).

b. Cohirsitine (=cohrisitine)

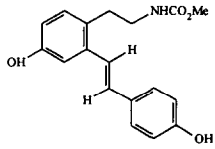
Isolated from *Cocculus hirsutus* (*52, 74*), this spirobenzyltetrahydroisoquinolone seems to directly originate, as were the HIRSUTI, COHIRSI and BENZAZE types (see *11*, *12* and *13* respectively), from a protoberberine precursor, as can be seen in Scheme 23.



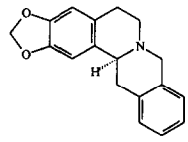
SCHEME 23. Biogenesis of cohirsitine based on mechanistic considerations.

c. Gusalung C

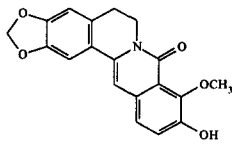
This alkaloid was isolated from *Arcangelisia gusalung* (*75*). From the same plant were also isolated gusalung D, 8-oxoberberine and 8-oxoberberrubine.



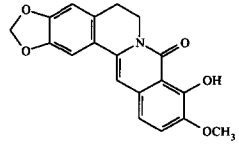
Gusalung C



Gusalung D



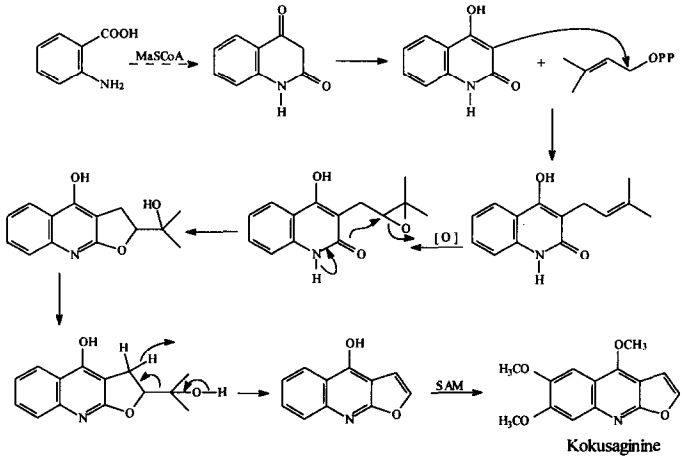
8-Oxothalifendine



8-Oxoberberrubine

d. Kokusaginine

The only furoquinoline alkaloid ever isolated from a Menispermacea was obtained from *Tinospora malabarica* when Bowen *et al.* were studying the antimalarial properties of this plant (*76*). It was isolated before from *Evodia* spp. and *Orixa* spp. (Rutaceae) and *Flindersia* spp. (Rutaceae) (*77*). Scheme 24 shows the biogenetic pathway of kokusaginine.

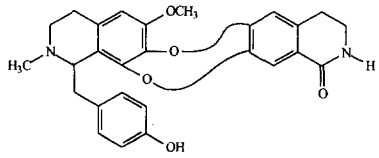


Kokusaginine

SCHEME 24. Biogenetic pathway to kokusaginine.

e. Neotrilobine

This is a very different type of BIQ compared with all the other BIQ found in the Menispermaceae. It was isolated from the roots of *Cocculus trilobus* (*569*). Possible origins for this compound may be: a) a seco Bis-BIQ of the sub type II.c.1.5 is naturally hydrolysed in the plant; b) an artefact created during the isolation procedure.



Neotrilobine

E. CHEMICAL PROFILE OF THE MENISPERMACEAE

In the second century, Dioscorides classified some plants as medicinal, toxic, edible and aromatic, as these properties depend on the presence of certain compounds, maybe this was the beginning of chemotaxonomy. In 1804, Augusto de Candolle listed the relations between the medicinal properties of the vegetables and their external morphology and emphasised the advantages of using this aspect for classification. In 1889, Eykman showed the presence of alkaloids in some plant families, and, in 1891, Greshoff indicated that the alkaloid laurotetanine was an usual chemical constituent of some plants of the family Lauraceae. He also said that the genus *Platanus* was rich in cyanogenic compounds (*78*).

We can define chemotaxonomy, also known as chemical taxonomy, systematic biochemistry, and chemosystematics, as the field of science that uses the chemical characters, especially the secondary metabolites (alkaloids, terpenoids, flavonoids, lignoids, etc.), of a group of organisms to determine its hierarchic classification among living beings (*15*). Another way to define it would be the classification of a group of organisms through their chemical constituents.

This thorough analysis showed that there is a close structural relationship among the chemical components of each genus, making it possible to "draw" a chemical profile of the family Menispermaceae. This profile is set out by tribe and genus and will now be discussed.

1. Tribe Triclisiae

This tribe has sixteen genera, among them, only ten have been chemically investigated. They are: *Albertisia*, *Anisocycla*, *Chondodendron*, *Curarea*, *Epinetrum*, *Pycnarrhena*, *Sciadotenia*, *Synclisia*, *Tiliacora* and *Triclisia*. Their chemical profiles will be discussed below.

a. Genera Albertisia, Chondodendron, Curarea, Epinetrum *and* Synclisia

The genus *Albertisia* Becc., was created by Beccari in 1872 (*79*). After being reviewed by Forman (*80*), there are seventeen species, twelve found in Africa and the remaining five in Asia and Southwestern New Guinea. Of these seventeen species, only two were phytochemically studied: *A. laurifolia* (*81*) and *A. papuana* (*82-84*). From them, twenty-six Bis-BIQ alkaloids were isolated. Table IV shows the chemical profile of the genera *Albertisia*, *Chondodendron*, *Curarea*, *Epinetrum* and *Synclisia*. They are the most homogeneous group inside the family Menispermaceae, producing only alkaloids of the type Bis-BIQ.

TABLE IV. Number of BisBIQ alkaloids isolated from the genera *Albertisia*, *Chondodendron*, *Curarea*, *Epinetrum* and *Synclisia*.

Genus	Number of alkaloids
Albertisia	26
Chondodendron	11
Curarea	13
Epinetrum	3
Synclisia	5

2. Genera Anisocycla, Triclisia, Pycnarrhena, Tiliacora *and* Sciadotenia

The only three species of *Anisocycla* cited in the literature are *A. cymosa*, *A. jolyana* and *A. grandidieri*. From these plants were isolated alkaloids of the types Bis-BIQ (16), APORPHIN (2), PHENANT (1) and PROTOB (5). It is interesting to note the presence of stephenanthrine, the only PHENANT in the family, also present in *Stephania tetrandra*. Also interesting are the three PROTOB alkaloids, anisocycline, *N*-methylthaicanine and *N,O*-dimethylthaicanine, which together with the other eight from *Stephania*, two from *Parabaena*, and one from *Coscinium* constitute a restricted group of pentamethoxylated PROTOB, while the other 272 possess the normal oxygenation pattern. The Bis-BIQ is the most common group of alkaloids in this genus, and reflects the situation in the family as a whole.

The genus *Triclisia* produces the greatest diversity of structural types. The richest group is the Bis-BIQ with 18 alkaloids, while the others show a maximum of two alkaloids such as: APORPHIN (2), MORPHIN (2), AZAFLU (1) and PROTOB (1).

Pycnarrhena presents a rich variety of Bis-BIQ alkaloids. Between the 34 alkaloids of this type isolated, 25 are of distinct structure. One interesting characteristic of this group among plants of this genus is that the majority of them show at least one secondary amine function. The only other group of alkaloids in the genus is the APORPHIN with three examples.

With only four studied out of twenty-two known species, the genus *Tiliacora* is the one that contains the largest number (38) of alkaloids of the Bis-BIQ type inside the tribe Triclisiae. The other two types are BIQ (8) and APORPHIN (2).

Sciadotenia is an American genus that is very common in the Amazon region. Among the 18 known species, only two have been phytochemically studied. The alkaloids encountered are of the types BIQ (1), Bis-BIQ (6) and PROAPO (1).

2. Tribe Peniantheae

This is the smallest tribe in the family Menispermaceae, with only two genera: *Penianthus* and *Sphenocentrum*.

a. Genera Penianthus *and* Sphenocentrum.

Both genera, *Sphenocentrum* with only one species and *Penianthus* with only two, are exclusive to the African Continent. Only one species from each genus has been studied. *Sphenocentrum* was shown to produce only PROTOB (3) alkaloids while *Penianthus* produces PROTOB (4), APORPHIN (1) and PHENETHYL (1) alkaloids.

3. Tribe Anamirteae

The main chemical characteristic of this tribe is the presence of protoberberine alkaloids. Interestingly, of the fourteen 8-oxoprotoberberine alkaloids found in the Menispermaceae, twelve are found in this tribe, while the other two have been found in *Stephania* and *Limaciopsis*, both in the tribe Cocculeae.

a. Genera Anamirta, Arcangelisia *and* Coscinium

The tribe Anamirteae contains three genera: *Anamirta*, *Arcangelisia* and *Coscinium*.

4. Tribe Fibraureae

The tribe Fibraureae consists of three genera: *Burasaia*, *Fibraurea* and *Tinomiscium*.

a. Genus Burasaia

The genus *Burasaia* revised by Engler (*86*), has five species. Only three have been subjected to chemical study: *B. australis*, *B. congesta* and *B. gracilis*; they are rich in protoberberine alkaloids.

b. Genera Fibraurea *and* Tinomiscium

Fibraurea and *Tinomiscium* both native to Asia contain the same types of protoberberine and aporphine alkaloids.

5. Tribe Tinosporeae

The tribe Tinosporeae is comprised of twenty-two genera, of which only seven were chemically studied. They are: *Chasmanthera*, *Dioscoreophyllum*, *Jateorhiza*, *Kolobopetalum*, *Parabaena*, *Rhigiocarya* and *Tinospora*. The predominant alkaloid types present in all of them are the protoberberines, followed by aporphines.

a. *Genera* Chasmanthera, Rhigiocarya *and* Kolobopetalum

Chasmanthera dependens, a climbing plant from Nigeria, is the only representative of this genus chemically studied. From it, nineteen alkaloids of four different classes were isolated: APORPHIN (10), PROTOB (7), MORPHIN (1) and PAVINE (1).

In *Rhigiocarya*, as in *Chasmanthera*, it is possible to find aporphines, protoberberines and morphinan alkaloids. *Kolobopetalum* is the third genus in this tribe and, morphinan alkaloids were also isolated.

b. *Genera* Tinospora *and* Parabaena

The species of *Tinospora* are well known to be much used in traditional medicine in Asia and Africa (*87*). From plants of this genus were isolated BIQ, aporphine, protoberberine and phenethylcinnamide alkaloids and kokusagenine,

which is the only furoquinoline alkaloid isolated from the family Menispermaceae, and is classified in this work as "OTHERS".

From *Parabaena* only BIQ and PROTOB alkaloids were isolated.

c. *Genera* Jateorhiza *and* Dioscoreophyllum

The chemical constituents of the roots of "Columba" (*Jateorhiza palmata* Miers, = *J. columba* Miers) have been known for more then a century. Berberine was the first compound to be isolated, by Boedecker in 1849 (*88*). After that came columbamine, jatrorrhizine, and palmatine. It is very common to find this combination of alkaloids distributed in the various genera of the Menispermaceae. Also isolated from the genus was the dimer bisjatrorrhizine. In *Dioscoreophyllum* were found columbamine, jatrorrhizine and palmatine.

6. Tribe Anomospermeae

The tribe Anomospermeae has five genera, of which only three have been chemically studied; *Abuta*, *Caryomene* and *Telitoxicum*. The chemical profiles of these genera are individually discussed below.

a. *Genus* Abuta

With only nine species studied among the thirty known, the genus *Abuta* is third in terms of structural diversity in the family Menispermaceae. Forty-one alkaloids of nine different types were isolated of the types BIQ (1), Bis-BIQ (18), PROAPO (1), APORPHIN (7), TROPOL (3), AZAFLU (6), PROTOB (2), BENZAZE (2) and ISOQUIN (1). This is the only genus in the family from which were isolated BENZAZE alkaloids. *A. grisebachii* (*90-91*) and *A. pahni* (*92*) are two plants native of the Amazon region used by the indigenous people for the preparation of curare. Their high yield of Bis-BIQ alkaloids (similar to curare) may justify this use.

b. *Genus* Caryomene

C. linearis and *C. olivascens* are two of the four species of a new genus created in 1971 by Barneby and Krukoff (*89*).

The seventeen alkaloids found in the genus are of the types: BIQ (1), Bis-BIQ (5), PROAPO (4) and PROTOB (7). It is interesting to note the common biogenetic origins of the above types of alkaloids.

c. *Genus* Telitoxicum

Telitoxicum, like many other genera in this family, are climbing plants found in the Amazon region. The two species investigated, *T. glaziovii* and *T. peruvianum*, have yielded aporphine and azafluoranthene alkaloids. Of the eight aporphines isolated, five are 7-oxoaporphines and three are the rare 1-oxo-7-aminoaporphines, only found in this genus. The two AZAFLU isolated are also rare, among the ten alkaloids of this type described in the family, six were found in *Abuta* and two in *Telitoxicum*, both from this tribe.

7. *Tribe Cocculeae*

The tribe Cocculeae comprises twenty genera and more than half of them have been chemically studied. It is the only tribe in the family that was divided into three sub-tribes (*5*), as follows.

a. *Sub-tribe* Cocculinae

This sub-tribe has the largest number of genera (fifteen), eleven of those genera were studied, they are *Cocculus*, *Diploclisia*, *Legnephora*, *Limacia*, *Limaciopsis*, *Menispermum*, *Pachygone*, *Sarcopetalum*, *Sinomenium*, *Spirospermum* and *Strychnopsis*. The chemical profiles of the above genera are individually discussed below.

a.1. *Genus* Cocculus

The genus *Cocculus* shows one of the greatest diversities in alkaloid types among the genera in the family Menispermaceae. Some one hundred and thirty-five alkaloids of thirteen different classes were isolated, with the following distribution: BIQ, Bis-BIQ, PROAPO, APORPHIN, ARISTO, PROTOB, HIRSUTI, COHIRSI, MORPHIN, ERIBIDI, ERYTHRIN, PAVIN and OTHERS.

Between 1970 and 1997, sixty-three Bis-BIQ alkaloids were isolated from plants of this genus, making it the main class in terms of number. It is interesting to note the homogeneity of the sub-types of Bis-BIQ isolated, among the sixty-two registered in the literature, ten were biphenyl ether bonded head-head, tail-tail and fifty-two were triphenyl ether bonded head-head, tail-tail. Forty-six of these alkaloids were present in one species encountered in the mountains of Pakistan, *Cocculus pendulus*.

The second type in terms of number is ERYTHRIN. Twenty-five alkaloids of this type were isolated. Of these alkaloids, nineteen were isolated from one

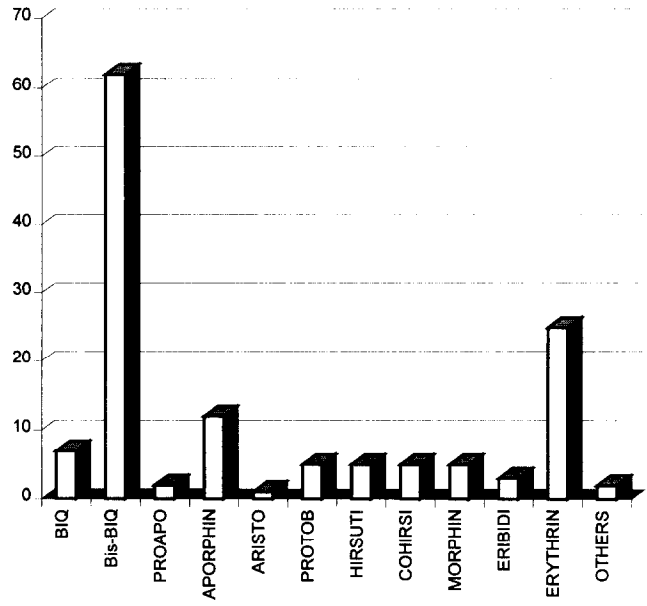
species *C. laurifolius* from India. Also isolated from this species were three of the four eribidine alkaloids found in the family Menispermaceae.

Another very important aspect to mention about this genus is the presence of the very rare hirsutine and cohirsitine types. Only five examples of the hirsutine and four of the cohirsitine types are found in nature, all of them from *C. hirsutus*, a small shrub native to the sub-tropical areas of India, Sri Lanka and Saudi Arabia.

The morphinan alkaloids also have five examples present in this genus. They are distributed in three different species: *C. laurifolius* (cuccoline, *O*-methylflavinantine and sebiferine), *C. trilobus* (sinococculine) and *C. carolinus* (carococculine).

The chemical profile of the genus *Cocculus* is shown in Chart 1.

Chart 1. - Chemical profile of the genus *Cocculus*.



a.2. *Genus* Spirospermum

This mono-specific genus, *S. penduliflorum*, native to the African continent has yielded only one alkaloid, limacine, a Bis-BIQ.

a.3. *Genera* Limacia, Menispermum *and* Sinomenium

Alkaloids of the types Bis-BIQ, PROAPO, APORPHIN, PROTOB and MORPHIN are present in the sub-tribe Cocculineae, and also in almost all of the genera of the family Menispermaceae so far investigated. However, there are two types of alkaloids which seem to differentiate chemically the sub-tribe *Cocculineae* from the others. They are the acutumine type present in *Menispermum*, *Sinomenium* and *Limacia*, and the isooxoaporphines present in *Menispermum* and *Sinomenium*.

a.4. *Genera* Diploclisia *and* Legnephora

Diploclisia glaucescens (BI) Diels (ex *Cocculus macrocarpus* W. & A.) is a climbing plant native of Sri Lanka where it is used in folk medicine against venereal diseases. Only two alkaloids were isolated from this species (the only studied in the genus). They were magnoflorine (APORPHIN) and stepharine (PROAPO) (*78*).

Legnephora moorei was the only plant studied in this genus. It is a climbing plant found in the dry areas of Australia and New Guinea. From this plant the following alkaloids were isolated: stepharine (PROAPO), laurifoline and magnoflorine (APORPHIN) and dehydrocorydalmine (PROTOB) (*93,94*).

a.5. *Genera* Limaciopsis *and* Pachygone

Limaciopsis is a mono-specific genus, and its only species is *L. loangensis*. This species is native to the central areas of Africa. From this plant were isolated eleven alkaloids of the types Bis-BIQ, APORPHIN, and PROTOB (*95*).

The genus *Pachygone* was created in 1851 by Miers (*96*), and currently comprises twelve species widely distributed throughout the world. From three species with phytochemical studies described in the literature, were isolated alkaloids of the types BIQ, Bis-BIQ, PROAPO, APORPHIN, PROTOB and ERYTHRIN.

a.6. *Genera* Sarcopetalum *and* Strychnopsis

These two genera are also comprised of one species each. From *Sarcopetalum harveyanum*, found in Australia, coclaurine (BIQ) and stepharine (PROAPO) were isolated. From *Strychnopsis thouarsii*, native to Africa, were isolated one Bis-BIQ (7-*O*-demethyltetrandrine) and four APORPHIN (isocorydine, liriotulipiferine, *N*-methyllindcarpine and predicentrine) alkaloids.

b. *Sub tribe* Stephaniinae

This sub-tribe is monogeneric being represented only by the genus *Stephania*.

b.1. *Genus* Stephania

From the previous reviews carried out by Tomita (*10*) in 1952 and by Thornber (*11*) in 1970 and this work, it is possible to conclude that the genus *Stephania* is the most chemically studied in the family. This can be easily shown by the Charts 2, 3 and 4, respectively.

CHART 2. Chemical profile of the genus *Stephania* until 1952 (*10*).

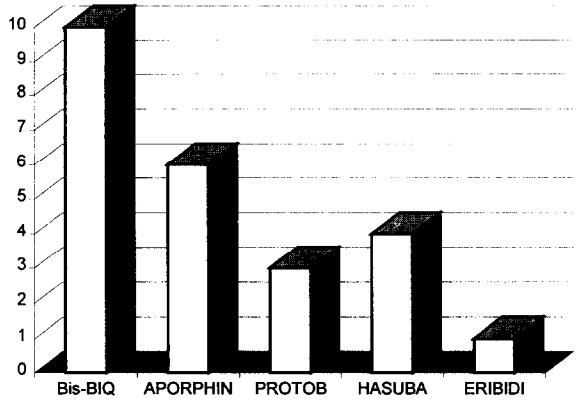


CHART 3. Chemical profile of the genus *Stephania* until 1970 (*11*).

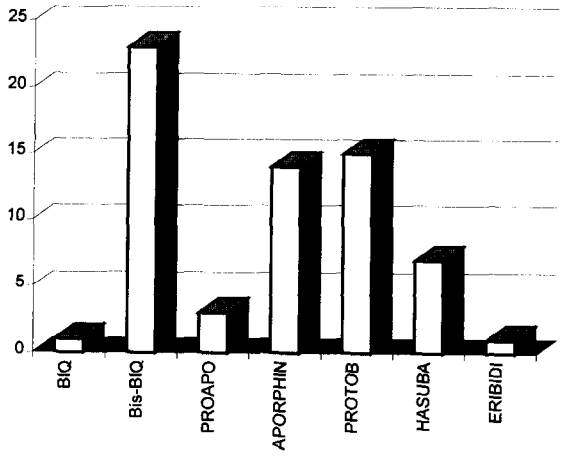


CHART 4. Chemical profile of the genus *Stephania* until 1997 (*78*).

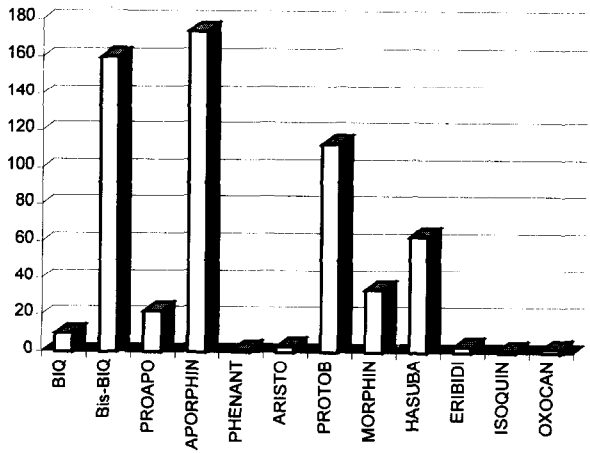


Table V shows the distribution of the alkaloids isolated from plants of the genus *Stephania* by species. Analysis of the data contained in the table led to some observations about the genus:

a) Of the twenty-two types of alkaloid found in the family Menispermaceae, thirteen are present in the genus *Stephania*.

b) The alkaloids of the APORPHIN (188), Bis-BIQ (171) and PROTOB (112) types are the most common, accounting for a total of 471 alkaloids.

c) All of the seventy-eight hasubanane alkaloids described in the literature were isolated from fifteen species of this genus.

d) The forty-three morphinan alkaloids were isolated from seventeen species and the fourteen proaporphines were isolated from eleven species.

e) The ten BIQ alkaloids in the genus were isolated from five species.

f) In Hutchinson's work (*97*) it was suggested that the families Menispermaceae and Aristolochiaceae have a lot in common in terms of the morphological aspects of the stem. The isolation of three aristolochic acid-type alkaloids from *Stephania* and one from *Cocculus* species, alkaloids that were considered exclusive to the Aristolochiaceae, has established some chemotaxonomic relations between the two families.

g) On the basis of the chemical data available, there is almost no difference between *Stephania japonica* and *S. japonica* var. *australis*.

h) Four species of *Stephania* occur in Thailand: *S. erecta*, *S. pierrei*, *S. suberosa* and *S. venosa*. Some controversy exists in relation to the morphological aspects of *S. erecta* and *S. pierrei* (*98-100*). However, analysing the data from the literature (*100-102*) related to the chemical studies of the two plants it is possible to see that the compounds isolated from *S. erecta* were fourteen Bis-BIQ. On the other hand, from *S. pierrei* forty-nine alkaloids were isolated distributed as: BIQ (5), Bis-BIQ (22), PROTOB (7), APORPHIN (12), MORPHIN (2) and HASUBA (1). These chemical differences seem to be sufficient to conclude that the two plants should be considered distinct species.

The complete list of alkaloids isolated from this genus is given in Table V.

c. Sub-tribe Cissampelinae

This sub-tribe contains four genera, they are: *Antizoma*, *Cissampelos*, *Cyclea* and *Paracyclea*. Phytochemical studies have been carried out for the first three genera.

c.1. Genus Antizoma

A bibliographic search on this genus yielded only one phytochemical study. *A. angustifolia* is a plant native to South Africa, and yielded sinoacutine, a MORPHIN alkaloid (*104*).

TABLE V
Occurrence of alkaloids in the *genus Stephania* by species.

SPECIES (Geographical distribution)	ERIBIDI	ISOQUIN	PHENETHYL	ARISTO	PHENANT	BIQ	BIS-BIQ	PROTOB	APORPHIN	PROAPO	MORPHIN	OXOCAN	HASUBA	TOTAL
S. abyssinica (Ethiopia)									10				7	**17**
S. aculeata (Australia)						1					1			**2**
S. brachyandra (China)							4	1	8		3			**16**
S. bancroftii (Australia)								1	3	1	1			**6**
S. cepharantha (China, Japan)			1	3		7	22	1	19	2	13	2	15	**85**
S. corymbosa (Indonesia)	1													**1**
S. delavayi (China, Russia)							6	1	2		1		2	**12**
S. dielsiana (China)							4	1	4		1			**10**
S. dinklagei (Gana)									5					**5**
S. discentrinifera (China)							4	1	2					**7**
S. disciflora (China)								2	4					**6**
S. dolichopoda (China)								1						**1**
S. elegans (India)							3	2	1		2		3	**11**
S. epigaea (China)							6	1	8		3			**18**
S. erecta (Thailand)							14							**14**
S. excentrica (China)						1	4		4		1	2	1	**13**
S. glabra (India, Russia)							2	13	1	3				**19**
S. gracilenta (China)						1			1		2			**4**
S. hainanensis (China)							4	3	3	1				**11**
S. hernandifolia (India)							11		1				9	**21**
S. intermedia (China)								9		1				**10**
S. japonica (Japan)	1						4		3				17	**25**

(*Continues*)

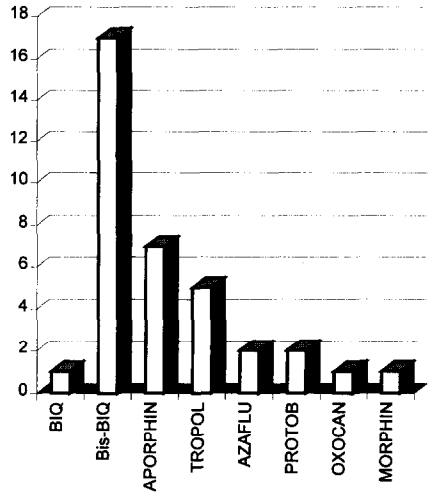
Table V (*Continued*)

SPECIES (Geographical distribution)	ERIBIDI	ISOQUIN	PHENETHYL	ARISTO	PHENANT	BIQ	BIS-BIQ	PROTOB	APORPHIN	PROAPO	MORPHIN	OXOCAN	HASUBA	TOTAL
S. japonica var. *australis* (Japan)	1						1	1	1				4	8
S. kuinanensis (China)								1	1					2
S. kwangsiensis (China)							3	4	6					13
S. lincangensis (China)								5	3					8
S. longa (China)							3						7	10
S. longipes (China)								1						1
S. longana (China)													1	1
S. mashanica (China)							2	3	3		1			9
S. micrantha (China)						1	2	8	9		2			22
S. officinarum (China)								2	4		1			7
S. pierrei (Thailand)						5	22	7	12		2		1	49
S. rotunda (Japan)							1	1					1	3
S. sasakii (Japan, Taiwan)		1					6	1	15	1			4	28
S. sinica (China)							3	1					1	5
S. suberosa (Thailand)							6	15			1		3	25
S. succinifera (China)							1	7	6					14
S. sutchunenensis (China)							2		1	1	1		2	7
S. tetandra (China, Japan)					1	1	24	3	9					38
S. venosa (Thailand, Japan)						1	1	2	26	3				33
S. viridiflavans (China)							2	5						7
S. yunnanensis (China)							1	6	2	1	1			11
S. zippeliana (Vannatu)									8		6			14
Stephania sp (China)							3	2	3					8
TOTAL	**3**	**1**	**1**	**3**		**18**	**171**	**112**	**188**	**14**	**43**	**4**	**78**	**637**

c.2. *Genus* Cissampelos

The genus *Cissampelos* was revised by Rhodes in 1975 (*105*) and consists of 19 species. Since Thornber's review (*11*), five new species were phytochemically studied: *C. fasciculata*, from which were isolated an APORPHIN (corydine) and a Bis-BIQ (cissampetine); *C. ovalifolia* from which was isolated four Bis-BIQ (warifteine, dihydrowarifteine, methylwarifteine and dimethylwarifteine); *C. sympodialis* from which were isolated a MORPHIN (milonine) and a Bis-BIQ (warifteine); *C. glaberrima* from which were isolated an OXOCAN (eletefine), three APORPHIN (cissaglaberrimine, oxobuxifolin and magnoflorine), and *C. pareira*, the most studied species, from which was obtained APORPHIN (6), Bis-BIQ (10), TROPOL (5), AZAFLU (2), PROTOB (2) and BIQ (1). The chemical profile of the genus can be seen in Chart 4.

CHART 4. Chemical profile of the genus *Cissampelos*.



c.3. *Genus* Cyclea

The genus *Cyclea* was created in 1840 by Arnotti (*78*). In 1910 it was classified as a member of the tribe Cocculeae, sub-tribe *Cissampelinae* by Diels (*78*). Of the nineteen known species, only eleven have phytochemical studies described in the literature, from which were isolated alkaloids of the types BIQ (4), Bis-BIQ (87), APORPHIN (6), PROTOB (5) and PAVINE (2).

8. Tribe Hyperbaeneae

The tribe Hyperbaeneae is monogeneric, the only genus being *Hyperbaena*.

a. Genus Hyperbaena

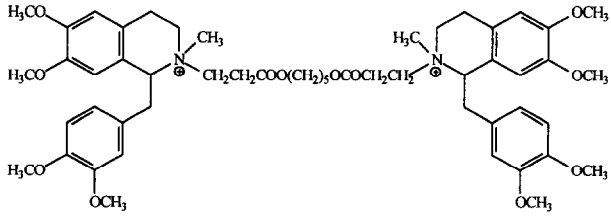
This genus *Hyperbaena* is mono-specific, the only species described is *H. columbica*, a shrub native to Cuba. From this species only four alkaloids were isolated, two ERYTHRIN (erythroculine and 3-demethoxy-2α,3α-methylenedioxyerythroculine), one PROTOB (tetrahydropalmatine) and one ERIBIDI (protostephanine).

Chart 5 shows the complete chemical profile of the family Menispermaceae.

III. Summary

The alkaloid profile of the familly (Chart 5) shows twenty-three different chemical types of alkalods. A total of 1525 alkaloids have been isolated from Menispermaceae in the period 1970 to 1997. The abundance of bisbenzyltetrahydroisoquinoline alkaloids (604 citations) isolated during that period is striking followed by aporphines (303 citations) and the protoberberines (275 citations). One hundred and sixty different species were studied for their alkaloid content during that period. The genus *Stephania* was the most popular target with 43 species examined followed by *Tinospora* with 15 species and *Cyclea* with 11 species investigated. In line with its popularity, the genus *Stephania* yielded the greatest number of alkaloids (637 isolated) followed by *Cocculus* (135 alkaloids) and *Cyclea* (104 alkaloids). In terms of diversity of alkaloid types *Stephania* was again at the top, but tied with *Cocculus* producing thirteen different types followed by the genus *Abuta* with nine different types. Some of the alkaloids have so far only been encountered in Menispermaceae, several confined to a particular genus. For example, *Cocculus* sp. producing hirsutine and cohirsine types and *Stephania* sp. producing hasubanane type alkaloids. A few alkaloid types, although so far restricted to the Menispermaceae, are encountered in several genera. For example the acutumine type alkaloids from *Limacia*, *Menispermum* and *Sinomenium*, azafluoranthenes from *Abuta*, *Cissampelos*, *Telitoxicum* and *Triclisia*, Isooxoaporphines from *Menispermum* and *Sinomenium*. Other alkaloid types have been found in the Menispermaceae and several other plant families. For example, the 1-benzyltetrahydroisoquinolines in nine plant families *viz.* Annonaceae, Berberidaceae, Hernandiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Papaveraceae, Ranunculaceae and Rhamnaceae. Whether the biosynthetic

provenance of the alkaloids in these families follow common routes is not known and must wait individual biosynthetic studies. A few of the biosynthetic secrets of these families of alkaloids have been firmly laid by the elegant work of Meinhart Zenk (*16*). The Menispermaceous alkaloids include many important discoveries in the field of medicines and pharmaceuticals (*27*), such as the bisbenzylisoquinoline tubocurarine. Many of the alkaloids have served directly as medicines or as lead compounds for the synthesis of improved derivatives. For example, alkaloids like tubocurarine have served as the stimulus to medicinal chemists and others to synthesise safer and/or more potent/selective derivatives/analogues such as atracurium, based on a bistetrahydropapaverine dimer (*580*).



Atracurium

IV. Conclusions

The family Menispermaceae continues to be a rich source of 1-benzylisoquinoline-derived alkaloids. The plants of this family are used world-wide in traditional or folk medicine for the treatment of numerous diseases and for other purposes. The rate of discovery of new and exciting alkaloid templates from Menispermaceae continues to rise and this, linked to investigation of the metabolic pathways that control their biosynthesis coupled with the future isolation of the enzymes/genes that control specific steps, should provide us with new pharmacological tools, medicinal and agricultural products for the foreseeable future.

Acknowledgments

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Chart 5. Chemical profile of the family Menispermaceae.

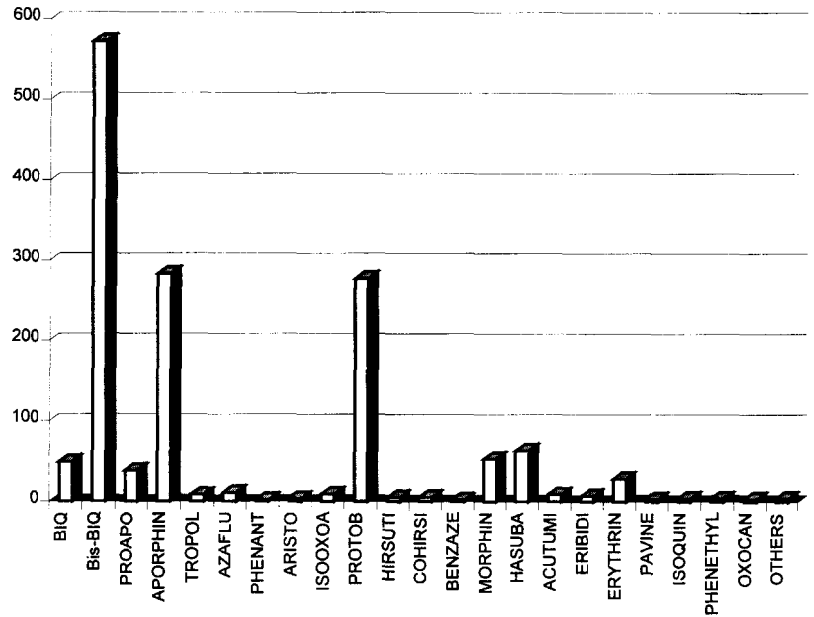


TABLE VI

ALKALOIDS ISOLATED FROM PLANTS OF THE FAMILY MENISPERMACEAE BETWEEN JULY, 1969 AND APRIL, 1997.

Plant Species	Alkaloids	Locator code	References
Abuta species	*O*-Methylmoschatoline	IV.c.3	*106*
Abuta bulata Moldenke	Dihydrosaulatine	XIII.2	*54*
	Palmatine	X.a.3	*54*
	Saulatine	XIII.1	*54*
Abuta grandifolia (Mart.) Sandw. Kew.	Grandirubrine	V.a.2	*39*
	Palmatine	X.a.3	*107*
Abuta grisebachii Triana & Planch.	7-*O*-Demethylpeinamine	II.b.1.2.53	*91*
	Grisabine	II.a.1.1.14	*90*
	Grisabutine	II.a.1.1.13	*90*
	Macoline	II.b.1.1.18	*91*
	Macolidine	II.b.1.1.17	*91*
	N-Methyl-7-*O*-demethylpeinamine	II.b.1.2.55	*91*
	Peinamine	II.b.1.2.54	*91*
Abuta imene Eichl.	Homomoschatoline	IV.c.3	*38*
	Imeluteine	VI.5	*38*
	Imenine	IV.c.4	*38*
	Imerubrine	V.b.2	*38*
	Norrufescine	VI.4	*38,108*
	Rufescine	VI.3	*38*
Abuta pahni (Martius) Krukoff & Barneby	(+)-Coclaurine	I.b.1	*92*
	(-)-Daurisoline	II.a.1.1.4	*92*
	N,N'-Dimethyllindoldhamine	II.a.1.1.11	*92*
	(-)-Lindoldhamine	II.a.1.1.8	*92*
	2'-*N*-Methyllindoldhamine	II.a.1.1.10	*92*
	2-*N*-Methyllindoldhamine	II.a.1.1.9	*92*
	2'-*N*-Nordaurisoline	II.a.1.1.5	*92*
	Stepharine	III.a.1	*92*
	Thalifoline	XX.b.1	*92*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Abuta panurensis Eichl.	Norpanurensine	II.b.1.3.2	*109*
	Panurensine	II.b.1.3.1	*109*
Abuta rufescens Aubl. (= *A. splendida* Krukoff & Moldenke)	Homomoschatoline	IV.c.3	*38,110*
	Imeluteine	VI.5	*38*
	Imenine	IV.c.4	*38,110*
	Imerubrine	V.b.2	*38*
	Lysicamine	IV.c.2	*110*
	Norrufescine	VI.4	*38,110*
	Rufescine	VI.3	*38*
	Splendidine	IV.c.5	*110*
Abuta splendida Krukoff & Moldenke	Aromoline	II.b.1.1.14	*111*
	Homoaromoline	II.b.1.1.16	*111*
	Krukovine	II.b.1.2.29	*111*
Albertisia laurifolia Yamamoto	Apateline	II.c.1.1.18	*81*
	Aromoline	II.b.1.1.14	*81*
	Cocsoline	II.c.1.1.5	*81*
	Cocsuline	II.c.1.1.7	*81*
	Daphnoline	II.b.1.1.13	*81*
	N-Methylapateline	II.c.1.1.19	*81*
Albertisia papuana Becc.	Apateline	II.c.1.1.18	*82*
	Aromoline	II.b.1.1.14	*82*
	(-)-2,2'-Bisnorphaeanthine	II.b.1.2.22	*84*
	Cocsoline	II.c.1.1.5	*82*
	Cocsuline	II.c.1.1.7	*82*
	(+)-Daphnoline	II.b.1.1.13	*84*
	1,2-Dehydrotelobine	II.c.1.1.22	*82*
	N,O-Dimethylcocsoline	II.c.1.1.4	*83*
	Daphnandrine	II.b.1.1.12	*82*
	Daphnoline	II.b.1.1.13	*82*
	Homoaromoline	II.b.1.1.16	*82*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Isotrilobine	II.c.1.1.4	*82*
	Lindoldhamine	II.a.1.1.8	*82*
	O-Methylcocsoline	II.c.1.1.6	*82*
	(+)-2'-Norcocsuline	II.c.1.1.9	*82*
	2,2'-Noraromoline	II.b.1.1.15	*82*
	Obaberine	II.b.1.1.8	*82*
	Oxyacanthine	II.b.1.1.19	*82*
	(+)-Pangkoramine	II.b.1.1.26	*84*
	(+)-Pangkorimine	II.b.1.1.27	*84*
Anamirta cocculus (L.) Wight & Arn.	Berberine	X.a.4	*112*
	Columbamine	X.a.2	*112*
	Magnoflorine	IV.a.54	*112*
	(-)-8-Oxo-tetrahydropalmatine	X.b.25	*112,113*
	Oxypalmatine	X.c.4	*113*
	Palmatine	X.a.3	*112*
	Stepharine	III.a.1	*113*
Anisocycla cymosa Troupin	Anisocycline	X.a.14	*114-116*
	(+)-Cocsoline, 2'β-*N*-oxide	II.c.1.1.10	*117*
	Coclobine	II.b.1.1.31	*116*
	Cocsoline	II.c.1.1.5	*114*
	(-)-*N,O*-Dimethylthaicanine	X.b.41	*115*
	1,2-Dehydroapateline	II.c.1.1.20	*114*
	1,2-Dehydrotelobine	II.c.1.1.22	*114*
	Daphnandrine	II.b.1.1.12	*116*
	Liriodenine	IV.c.1	*114*
	(-)-*N*-Methyltetrahydropalmatine	X.b.42	*115*
	(-)-*N*-Methylthaicanine	X.b.40	*115*
	(+)-12-*O*-Methylcocsoline, 2'β-*N*-oxide	II.c.1.1.11	*117*
	(+)-2'-Norcocsoline	II.c.1.1.12	*117*
	(+)-2-Norobaberine, 2'β-*N*-oxide	II.b.1.1.11	*116*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	2-Norobaberine	II.b.1.1.10	*116*
	Palmatine	X.a.3	*114-116*
	Remrefidine	IV.a.7	*114,116*
	Stephenanthrine	VII	*115*
	Trilobine	II.c.1.1.1	*114*
Anisocycla grandidieri H. Bn.	12-*O*-Demethyltrilobine	II.c.1.1.2	*118*
	N,O-Dimethylcocsoline	II.c.1.1.4	*83*
	(-)-Epistephanine	II.b.1.1.32	*118*
	Stebisimine	II.b.1.1.34	*118*
	Trilobine	II.c.1.1.1	*118*
Anisocycla jollyana (Pierre) Diels	1,2-Dehydrotelobine	II.c.1.1.22	*565*
	Homoaromoline	II.b.1.1.16	*565*
	Isotrilobine	II.c.1.1.4	*565*
	Limacine	II.b.1.2.6	*565*
	Limacine, 2'-β-*N*-oxide	II.b.1.2.9	*565*
	Limacusine, 2'-β-*N*-oxide	II.b.1.1.42	*565*
	O-Methylpunjabine	II.c.1.5.2	*566*
	2'-Norlimacine	II.b.1.2.60	*565*
	2-Norlimacine	II.b.1.2.10	*565*
	Remrefidine	IV.a.7	*565*
	(-)-Secohomoaromoline	II.b.1.4.3	*566*
	(-)-Secojollyanine	II.c.1.5.5	*566*
	Trilobine	II.c.1.1.1	*565*
Antizoma angustifolia Miers	Sinoacutine	XIV.b.1.2	*104*
Arcangelisia flava (L.) Merr.	Berberine	X.a.4	*119,120*
	Dehydrocorydalmine	X.a.6	*120*
	8-Hydroxyberberine	X.c.2	*120*
	Homoaromoline	II.b.1.1.16	*121*
	Jatrorrhizine	X.a.1	*120*
	Limacine	II.b.1.2.6	*120*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Palmatine	X.a.3	*120*
	Pycnarrhine	XX.a.1	*120*
	Thalifendine	X.a.7	*120*
Arcangelisia gusanlung H.S.Lo	Berberine	X.a.4	*122*
	12,13-Dihydro-8-oxoberberine	X.b.21	*75*
	Gusanlung A	X.b.23	*122*
	Gusanlung B	X.b.24	*122*
	Gusanlung C	XXIII.3	*75*
	Gusanlung D	X.b.26	*75*
	Jatrorrhizine	X.a.1	*122*
	8-Oxoberberrubine	X.c.3	*75*
	8-Oxotetrahydrothalifendine	X.b.22	*75*
Burasaia australis Scott Elliot	Columbamine	X.a.2	*123*
	Palmatine	X.a.3	*123*
Burasaia congesta Decne	Alkaloid 6	I.b.13	*123*
	Columbamine	X.a.2	*123*
	Palmatine	X.a.3	*123*
Burasaia gracilis Decne	Jatrorrhizine	X.a.1	*123*
	Palmatine	X.a.3	*123*
Caryomene linearis	Homolinearisine	III.a.5	*124*
Caryomene olivascens Barneby & Krukoff	(-)-Caryolivine	II.b.1.2.50	*125*
	(+)-Coclaurine	I.b.1	*125,126*
	(-)-Coreximine	X.b.9	*126*
	1,2-Dehydro-2-norlimacusine	II.b.1.1.22	*125*
	(-)-10-Demethyldiscretine	X.b.6	*126*
	(-)-Discretine	X.b.12	*126*
	(-)-*N*,*N*'-Dimethyllindoldhamine	II.a.1.1.11	*125*
	(-)-*N*-Formylstepharine	III.a.3	*125*
	(-)-Govadine	X.b.10	*126*
	(-)-2-Norlimacine	II.b.1.2.10	*125*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(-)-2-Norlimacusine	II.b.1.1.21	*125*
	Pronuciferine	III.a.2	*125*
	(+)-Pseudopalmatine	X.c.6	*125*
	Pseudopalmatine	X.c.6	*126*
	(-)-Stepharine	III.a.1	*125,126*
	(-)-Xylopinine	X.b.31	*126*
Chasmanthera dependens Hochst	(-)-Anonaine	IV.a.1	*127*
	Bisnorargemonine	XIX.3	*128*
	(-)-Coreximine	X.b.9	*128*
	Columbamine	X.a.2	*127*
	(+)-*O,O*-Dimethylcorituberine	IV.a.68	*127*
	(+)-Glaucine	IV.a.31	*127*
	(-)-Govanine	X.b.11	*128*
	Jatrorrhizine	X.a.1	*127,129*
	Liriodenine	IV.c.1	*127*
	Lysicamine	IV.c.2	*127*
	Magnoflorine	IV.a.54	*127*
	(+)-Norglaucine	IV.a.13	*127*
	(+)-*N*-Nornuciferine	IV.a.16	*127*
	(+)-Oxoglaucine	IV.c.9	*127*
	Pallidine	XIV.b.1.3	*128*
	Palmatine	X.a.3	*127,129*
	Pseudocolumbamine	X.a.13	*127*
	(-)-Tetrahydropalmatine	X.b.32	*127*
	Xylopine	IV.a.10	*128*
Chondodendron platyphyllum (A.St.Hil) Miers	Chondrofoline	II.b.2.2.12	*130*
	(-)-Curine	II.b.2.2.11	*130*
Chondodendron tomentosum Ruiz & Pavon	Chondrocurine	II.b.2.2.7	*131*
	(-)-Curine	II.b.2.2.11	*131*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-Tubocurarine	II.b.2.2.5	*131*
Chondodendron toxicoferum (Wedd.) Krukoff & Moldenke	Isochondodendrine	II.b.2.1.1	*132*
	Curine	II.b.2.2.11	*133*
	(-)-Curine	II.b.2.2.11	*132*
	Isochondodendrine	II.b.2.1.1	*132*
	N^b-Norchondocurine	II.b.2.2.8	*133*
	(-)-Tubocurine	II.b.2.2.6	*132*
Cissampelos fasciculata Benth.	Cissampetine	II.b.2.3.1	*134*
	Corydine	IV.a.28	*134*
Cissampelos glaberrima St. Hill	Cissaglaberrimine	IV.a.8	*135*
	Eletefine	XXII.5	*578, 579*
	Magnoflorine	IV.a.54	*135*
	Oxobuxifoline	IV.c.20	*135*
Cissampelos ovalifolia DC.	Dihydrowarifteine	II.b.2.4.2	*136*
	Dimethyldihydrowarifteine	II.b.2.4.6	*136*
	Dimethywarifteine	II.b.2.4.5	*136*
	Methyldihydrowarifteine	II.b.2.4.3	*136*
	Methylwarifteine	II.b.2.4.4	*136*
	Warifteine	II.b.2.4.1	*136*
Cissampelos pareira L.	Bulbocapnine	IV.a.24	*137*
	Cissamine	X.b.43	*138*
	Corytuberine	IV.a.30	*137*
	(±)-Curine	II.b.2.2.11	*139*
	(-)-Curine	II.b.2.2.11	*138,140-142*
	β-Cyclanoline	X.b.44	*143*
	Cycleanine	II.b.2.1.4	*141,144,145*
	Daijisong	II.b2.2.15	*146*
	Dehydrodicentrine	IV.b.8	*144*
	Dicentrine	IV.a.44	*144*
	Grandirubrine	V.a.2	*40*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Hayatine	II.b.2.2.14	*138,140,141,147*
	Hayatinine	II.b.2.2.10	*141,147*
	Insularine	II.c.2.2.2	*144*
	Isochondodendrine	II.b.2.1.1	*140,144*
	Isoimerubrine	V.a.4	*40*
	Laudanosine	I.b.8	*137*
	Magnoflorine	IV.a.54	*137*
	Menismine	CSND	*138*
	Monomethyltetrandrinium	II.b.1.2.17	*148*
	Norimeluteine	VI.6	*149*
	Norrufescine	VI.4	*149*
	Nuciferine	IV.a.15	*137*
	Pareirine	CSND	*138*
	Pareirubrine	V.a.3 + V.b.3	*150*
	Pareirubrine A	V.a.3 + V.b.3	*40*
	Pareirubrine B	V.a.1 + V.b.1	*40*
	Pareitropone	V.a.5	*567*
	(+)-Tetrandrine	II.b.1.2.14	*148,151*
Cissampelos sympodialis Eichl.	Milonine	XIV.b.3.2	*152*
	Warifteine	II.b.2.4.1	*153,154*
Cocculus carolinus DC.	Carococculine	XIV.a.2.1	*155,156*
	Cocculine	XVIII.a.1	*156*
	Cocculolidine	XVIII.e	*156*
	Magnoflorine	IV.a.54	*156*
	Palmatine	X.a.3	*156*
Cocculus hirsutus (L.) Diels (= *C. villosus* DC.)	Coclaurine	I.b.1	*52,157*
	(±)-Coclaurine	I.b.1	*158*
	Cocsoline	II.c.1.1.5	*157,159*
	Cocsuline *N*-2-oxide	II.c.1.1.8	*157,159,160*
	Cohirsine	XII.a.3	*52,53*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Cohirsinine	XII.a.2	*52,161*
	Cohirsitine = cohrisitine	XXIII.2	*52,74*
	Cohirsitinine	XII.b	*52,162*
	Daphnoline	II.b.1.1.13	*158*
	12-*O*-Demethyltrilobine	II.c.1.1.2	*157*
	N,*O*-Dimethylcocsoline	II.c.1.1.4	*163*
	Haiderine	XI.1	*52*
	Hirsutine	XI.2	*164*
	Isotrilobine	II.c.1.1.4	*52,157,158,165*
	Jamtine	XI.3	*52,166*
	Jamtine *N*-oxide	XI.5	*52,166*
	Jamtinine	XI.4	*52*
	Magnoflorine	IV.a.54	*157,158*
	Shaheenine	XII.a.1	*52,167*
	Trilobine	II.c.1.1.1	*52,157,165*
Cocculus laurifolius DC.	Boldine	IV.a.25	*168*
	Coccoline	XVIII.c.4	*169,170*
	Coccolinine	XVIII.c.5	*169,171,172*
	Coccudienone	XVIII.d	*169*
	Cocculidine	XVIII.a.7	*65,169,170,172-174*
	Cocculidinone	XVIII.a.6	*169,172*
	Cocculimine	XVIII.b.1	*169*
	Cocculine	XVIII.a.1	*65,169,170,173,175*
	Cocculitine	XVIII.a.4	*169,173,175*
	Cocculitinine	XVIII.a.5	*169*
	Coccuvine	XVIII.c.2	*169,172,176*
	Coccuvinine	XVIII.c.3	*169,172,174*
	Coclafine	XVIII.a.2	*167*
	Coclaurine	I.b.1	*169,177*
	Cocsuline	II.c.1.1.7	*178*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Cucoline	XIV.a.1.1	*172*
	Dihydroerysodine	XVIII.a.9	*169*
	N,O-Dimethylisocorydine	IV.a.48	*179*
	Erysotrine	XVIII.c.1	*172*
	Erythlaurine	XVIII.a.3	*180,181*
	Erythramide	XVIII.a.12	*180,181*
	Erythroculine	XVIII.a.11	*181*
	Isoboldine	IV.a.23	*182*
	Isococculidine	XVIII.b.2	*62,169-171,183,184*
	Isococculine	XVIII.b.3	*169,174,185*
	Isocorydine	IV.a.47	*168,169*
	Isotetrandrine	II.b.1.2.30	*186*
	Laudanidine	I.b.5	*169*
	Laurifine	XVII.1	*63,169,187*
	Laurifinine	XVII.2	*63,169,172*
	Laurifoline	IV.a.55	*168,169*
	Laurifonine	XVII.3	*63,169,172,187*
	Magnoflorine	IV.a.54	*168,169*
	N-Methylboldine	IV.a.26	*188*
	N-Methylstepharine	III.a.2	*169*
	O-Methylflavinantine	XIV.b.2.2	*181*
	O-Methylisocorydine methocloride	IV.a.49	*168,169*
	N-Methylcoclaurine	I.b.2	*169,172*
	Norisoboldine	IV.a.69	*182*
	Reticuline	I.b.9	*169*
	Sebiferine	XIV.b.2.2	*169,172,188*
	(+)-Sinactine	X.b.3	*189*
	Stepharine	III.a.1	*169*
	Stepholidine	X.b.5	*181*
	Thalicarpine	XXIII.1	*73*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Cocculus macrocarpus W. & A.	Trilobine	II.c.1.1.1	*190*
Cocculus pendulus (Forsk.) Diels	(+)-Cheratamine	II.b.1.2.49	*191*
(= *C. leaeba* DC.)	Coclaurine	I.b.1	*192*
	Cocsiline	II.c.1.4.1	*193*
	Cocsilinine	II.c.1.4.2	*193*
	(+)-Cocsoline	II.c.1.1.5	*191*
	Cocsoline	II.c.1.1.5	*193-195*
	(+)-Cocsuline	II.c.1.17	*191*
	Cocsuline	II.c.1.1.7	*193-198*
	Cocsulinine	II.c.1.3.1	*193,195,199*
	(+)-Cocsupendine	II.c.1.3.2	*200*
	(+)-Daphnoline	II.b.1.1.13	*191*
	(+)-1,2-Dehydroapateline	II.c.1.1.20	*191*
	(+)-1,2-Dehydro-2'-nortelobine	II.c.1.1.23	*200,201*
	(+)-1,2-Dehydrokohatamine	II.c.1.1.13	*201*
	(+)-1,2-Dehydrokohatine	II.c.1.2.3	*200,201*
	(+)-1,2-Dehydro-*O,O*-dimethylkohatine	II.c.1.2.5	*200*
	1,2-Dehydrokohatine 2β-*N*-oxide	II.c.1.2.6	*200*
	(+)-*O,O*-Dimethylcocsulinine	II.c.1.4.5	*193*
	N,O-Dimethylcocsoline	II.c.1.1.4	*163*
	Hernandezine	II.b.1.2.58	*198*
	(+)-Kohatine	II.c.1.2.1	*191*
	5'-Hydroxyapateline	II.c.1.1.21	*191,201*
	(+)-5'-Hydroxytelobine	II.c.1.1.24	*200,201*
	(+)-Isotrilobine	II.c.1.1.4	*191*
	Isotrilobine	II.c.1.1.4	*193*
	(+)-Kohatamine	II.c.1.1.25	*201*
	(+)-Kurramine	II.c.1.1.16	*191*
	Menisarine	II.c.1.3.6	*192*
	(+)-*N*-Methylapateline	II.c.1.1.19	*191*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	12'-*O*-Methyldehydrokohatine	II.c.1.2.4	*200*
	12'-*O*-Methylkohatine	II.c.1.2.2	*200*
	O-Methylcocsulinine	II.c.1.4.3	*193*
	(+)-2*N*-Norberbamine	II.b.1.2.57	*191*
	N-Norcocsulinine	II.c.1.4.4	*193*
	(+)-Norpenduline	II.b.1.2.38	*191*
	Nortrilobine	II.c.1.1.3	*193*
	(+)-Ophiocarpinone	X.b.29	*202*
	(+)-Pendilinine	II.c.1.3.5	*193*
	Pendilinine	II.c.1.3.5	*193,195*
	Pendine	II.c.1.3.7	*193*
	(+)-Penduline	II.b.1.2.37	*191*
	Penduline	II.b.1.2.37	*193-196,198,199,203*
	Punjabine	II.c.1.5.1	*198*
	(+)-Siddiquamine	II.c.1.2.8	*200,201*
	(+)-Siddiquine	II.c.1.2.7	*200,201*
	Sinactine	X.b.3	*192*
	(+)-Tetrandrine	II.b.1.2.14	*191,193,198*
	(+)-Tricordatine	II.c.1.1.15	*191*
	Trilobine	II.c.1.1.1	*193*
Cocculus sarmentosus Diels	*N,O*-Dimethylcocsoline	II.c.1.1.4	*163*
Cocculus trilobus DC.	Aristolochic acid	VIII.a	*204*
	Cocculine	XVIII.a.1	*205,206*
	Cocculolidine	XVIII.e	*206,207*
	Coccutrine	XVIII.a.8	*205,206*
	Coclobine	II.b.1.1.31	*208*
	1,2-Dehydroapateline	II.c.1.1.20	*569*
	Dihydroerysovine	XVIII.a.10	*206,209*
	Isoboldine	IV.a.23	*207*
	Isosinococuline	XIX.d.6	*568*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Isotrilobine	II.c.1.1.4	*210,211*
	Isotrilobine 2-*N*-oxide	II.c.1.2.9	*210*
	Neotrilobine	XXIII.5	*569*
	Nortrilobine	II.c.1.1.3	*210*
	Sinococuline	XIV.d.1	*212*
	Trilobine	II.c.1.1.1	*210,211*
Coscinium fenestratum (Gaertn.) Colebr. (= *C. wallichianum* Miers = *C. usitatum* Pierre)	Berberine	X.a.4	*213-217*
	Berberrubine	X.a.10	*213*
	Berlambine	X.c.1	*218*
	Canadine	X.b.20	*216*
	12,13-Dihydro-8-oxoberberine	X.b.21	*216*
	N,N-Dimethyllindcarpine	IV.a.51	*213*
	Jatrorrhizine	X.a.1	*213*
	(-)-8-Oxocanadine	X.b.27	*217*
	(-)-8-Oxoisocorypalmine	X.b.28	*217*
	(-)-8-Oxotetrahydrothalifendine	X.b.22	*217*
	(-)-8-Oxothaicanine	X.b.35	*217*
	Oxyberberine	X.c.1	*217*
	Oxypalmatine	X.c.4	*217*
	Palmatine	X.a.3	*213*
	Thalifendine	X.a.7	*213*
Coscinium usitatum Pierre	Berberine	X.a.4	*219*
Curarea candicans (LC. Richard) Barneby & Kurkoff	(+)-Candicusine	II.b.1.1.23	*220*
	(+)-Curine	II.b.2.2.11	*221*
	(+)-Isochondodendrine	II.b.2.1.1	*221*
	(-)-Krukovine	II.b.1.2.29	*220*
	(-)-Limacine	II.b.1.2.6	*220*
	(-)-Limacine, 2'-α-*N*-oxide	II.b.1.2.7	*220*
	(-)-Limacine, 2'-β-*N*-oxide	II.b.1.2.9	*220*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(-)-Limacine, 2-β-*N*-oxide	II.b.1.2.8	*220*
	(+)-Limacusine	II.b.1.1.20	*220*
Curarea tecunarum Barneby & Krukoff	(+)-Isochondodendrine	II.b.2.1.1	*221*
Curarea toxicoferum (Weddell) Barneby & Krukoff	(-)-Chondrocurine	II.b.2.2.7	*221*
	(-)-Curine	II.b.2.2.11	*221*
	(+)-Isochondodendrine	II.b.2.1.1	*221*
Cyclea atjehensis Forman	(-)-Argemonine	XIX.1	*222*
	(-)-Curicycleatjina	II.b.2.2.1	*223*
	(-)-Curicycleatjenine	II.b.2.2.2	*223*
	(+)-Cycleatjehenine	II.b.2.5.2	*224*
	(+)-Cycleatjehine	II.b.2.5.1	*224*
	Cycleatjehenine	II.b.2.5.2	*225*
	(+)-*N*-Formylnornantenine	IV.a.35	*222*
	(-)-Isocuricycleatjine	II.b.2.2.3	*223*
	(-)-Isocuricycleatjenine	II.b.2.2.4	*223*
	(+)-Laurotetanine	IV.a.20	*222*
	(-)-Norargemonine	XIX.2	*222*
	(+)-Nornantenine	IV.a.34	*222*
Cyclea barbata Miers	Berbamine	II.b.1.2.47	*226,227*
	Chondocurine	II.b.2.2.7	*226*
	(+)-Coclaurine	I.b.1	*226*
	(-)-Curine	II.b.2.2.11	*226,228*
	(+)-Cycleabarbatine	II.b.1.2.35	*226*
	Cycleadrine	II.b.1.2.11	*229*
	(+)-Cycleanorine	II.b.1.2.42	*226*
	(-)-Cycleapeltine	II.b.1.1.24	*226*
	(+)-Daphnandrine	II.b.1.1.12	*226*
	Homoaromoline	II.b.1.1.16	*226,227*
	Isochondodendrine	II.b.2.1.1	*226,230*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Isotetrandrine	II.b.1.2.30	*226,227*
	Limacine	II.b.1.2.6	*226,227*
	Magnoflorine	IV.a.54	*226*
	(-)-*N*-Methylcoclaurine	I.b.2	*226*
	Monomethyltetrandrinium	II.b.1.2.17	*231*
	(-)-2-Norlimacine	II.b.1.2.10	*226*
	(-)-Repandine	II.b.1.1.30	*226*
	(±)-Tetrandrine	II.b.1.2.14	*226,227*
	(+)-Tetrandrine	II.b.1.2.14	*226,227,230*
	Tetrandrine 2'β-*N*-oxide	II.b.1.2.15	*226*
	Tetrandrine mono-*N*-2'-oxide	II.b.1.2.16	*231*
	(+)-Thalrugosine	II.b.1.2.39	*226*
Cyclea burmani (DC.) Miers ex. Hook & Thoms	Phaeanthine	II.b.1.2.20	*232*
	Tetrandrine	II.b.1.2.14	*232*
Cyclea hainanensis Merr.	(-)-Curine	II.b.2.2.11	*233*
	(-,-)-Curine	II.b.2.2.11	*234*
	α-Cyclanoline	X.b.43	*234*
	Haiatine	II.b.2.2.14	*234*
	(+)-Isochondodendrine	II.b.2.1.1	*234*
Cyclea hypoglauca Diels	(-)-Curine	II.b.2.2.11	*235,236*
	Cyclanoline	X.b.43	*236*
	Cycleanine	II.b.2.1.4	*235,236*
	Insulanoline	II.c.2.2.1	*237*
	Insularine	II.c.2.2.2	*237*
	Isochondodendrine	II.b.2.1.1	*235*
Cyclea laxiflora Miers	Dicentrine	IV.a.44	*238*
	α-Cyclanoline	X.b.43	*239*
	β-Cyclanoline	X.b.44	*239*
Cyclea peltata Diels	Alkaloid 16	II.b.1.2.51	*240*
	Alkaloid 26	II.b.1.7.2	*240*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Alkaloid 31	II.b.1.7.3	*240*
	(+)-Berbamine	II.b.1.2.47	*226*
	N^2-Chloromethyltetrandrinium	II.b.1.2.18	*231*
	(+)-Chondodendrine	II.b.2.2.11	*241*
	Chondocurine	II.b.2.2.7	*242*
	(+)-Coclaurine	I.b.1	*223*
	(-)-Curine	II.b.2.2.11	*233,241*
	(+)-Cycleabarbatine	II.b.1.2.35	*226*
	Cycleacurine	II.b.2.2.13	*240*
	Cycleadrine	II.b.1.2.11	*240*
	Cycleahomine	II.b.1.2.43	*240*
	(+)-Cycleanorine	II.b.1.2.42	*226*
	Cycleanorine	II.b.1.2.42	*240*
	(-)-Cycleapeltine	II.b.1.1.24	*243*
	Cycleapeltine	II.b.1.1.24	*240*
	(+)-Daphnandrine	II.b.1.1.12	*226*
	Fangchinoline	II.b.1.2.1	*140,240,244*
	(+)-Homoaromoline	II.b.1.1.16	*243*
	Homoaromoline	II.b.1.1.16	*241*
	(+)-Isochondodendrine	II.b.2.1.1	*244*
	Isochondodendrine	II.b.2.1.1	*242,244*
	(-)-Limacine	II.b.1.2.6	*243*
	Magnoflorine	IV.a.54	*245,246*
	12-*O*-Methylatherospermoline	II.b.1.2.1	*229*
	(-)-*N*-Methylcoclaurine	I.b.2	*226*
	(-)-2'-Norlimacine	II.b.1.2.10	*226*
	(-)-Repandine	II.b.1.1.30	*226*
	(±)-Tetrandrine	II.b.1.2.14	*244*
	(+)-Tetrandrine	II.b.1.2.14	*140,240,241,243,244*
	(+)-Tetrandrine 2'β-*N*-oxide	II.b.1.2.15	*226*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Tetrandrine mono-*N*-2'-oxide	II.b.1.2.16	*242*
	(+)-Thalrugosine	II.b.1.2.39	*243*
Cyclea racemosa Oliv.	Cycleaneonine	II.b.2.4.7	*247*
	(+)-Cycleaneonine	II.b.2.4.7	*248*
	Isocycleaneonine	II.b.2.4.8	*248*
Cyclea sutchuenensis Gagnep.	(-)-Cycleaneonine	II.b.2.4.7	*248*
	Cycleanine	II.b.2.1.4	*249*
	Insulanoline	II.c.2.2.1	*250,251*
	Insularine	II.c.2.2.2	*251*
	Insularine 2'β-*N*-oxide	II.c.2.1.2	*251*
	Insularine 2β-*N*-oxide	II.c.2.1.1	*251*
	Isochondodendrine	II.b.2.1.1	*249*
	Isocycleanine	II.b.2.1.10	*249*
	Neosutchuenine	II.a.2.1.3	*250*
	Sutchueneneonine	II.a.2.1.2	*250*
	Sutchuenensine	II.b.2.1.11	*249*
	Sutchuenine	II.a.2.1.1	*250*
Cyclea tonkinensis Gagnep.	(-)-Curine	II.b.2.2.11	*252*
	Cyclanoline	X.b.43	*252*
	Cycleanine	II.b.2.1.4	*252*
Cyclea toxicoferum	Chondocurine	II.b.2.2.7	*253*
Dioscoreophyllum cumminsii (Stapf.) Diels	Columbamine	X.a.2	*254,255*
	Jatrorrhizine	X.a.1	*255*
	Magnoflorine	IV.a.54	*254,255*
	Palmatine	X.a.3	*255*
Diploclisia glaucescens Diels	Magnoflorine	IV.a.54	*255*
	Stepharine	III.a.1	*113*
Epinetrum delagoense Diels	Alkaloid E-1	CSND	*256,257*
	Alkaloid E-2	CSND	*256,257*
	Alkaloid E-3	CSND	*256,257*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Epinetrum villosum (Exell.) Troupin	Cycleanine	II.b.2.1.4	*258*
	Isochondodendrine	II.b.2.1.1	*258*
	Norcycleanine	II.b.2.1.7	*258*
Fibraurea chloroleuca Miers	Berberine	X.a.4	*259-261*
	Berberrubine	X.a.10	*260,261*
	Columbamine	X.a.2	*262*
	Dehydrocorydalmine	X.a.6	*261*
	Jatrorrhizine	X.a.1	*262*
	Magnoflorine	IV.a.54	*261*
	Palmatine	X.a.3	*262*
	Palmatrubine	X.a.9	*261*
	Pseudocolumbamine	X.a.13	*261,262*
	Pseudojatrorrhizine	X.a.12	*262*
	Tetrahydrojatrorrhizine	X.b.4	*262*
	Tetrahydropalmatine	X.b.32	*262*
	Thalifendine	X.a.7	*260*
Fibraurea recisa Pierre	Jatrorrhizine	X.a.1	*263*
	Palmatine	X.a.3	*263,264*
	Pseudocolumbamine	X.a.13	*263*
Fibraurea species	Columbamine	X.a.2	*262*
	Jatrorrhizine	X.a.1	*262*
	Palmatine	X.a.3	*262*
Fibraurea tinctoria Lour.	Jatrorrhizine	X.a.1	*265*
	Palmatine	X.a.3	*265,266*
	Tetrahydropalmatine	X.b.32	*267*
Heptacyclum zenkeri Engl. (= *Penianthus zenkeri* Diels)	Dehydrodiscretine	X.a.12	*268*
	Jatrorrhizine	X.a.1	*269*
	Magnoflorine	IV.a.54	*269*
	Palmatine	X.a.3	*269*
Hyperbaena columbica (Eichl.) Miers	3-Demethoxy-2α-3α-methylenedioxyerythroculine	XVIII.a.14	*270*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Erythroculine	XVIII.a.11	*270*
	Protostephanine	XVII.4	*270*
	Tetrahydropalmatine	X.b.32	*271*
Jateorhiza palmata Miers (= *J. columba* Miers)	Berberine	X.a.4	*272*
	Columbamine	X.a.2	*129,272*
	Bisjatrorrhizine	X.a.17	*273*
	Jatrorrhizine	X.a.1	*129,272*
	Palmatine	X.a.3	*129,272*
Kolobopetalum auriculatum Engl.	Corydine	IV.a.28	*274*
	Corytuberine	IV.a.30	*274*
	Magnoflorine	IV.a.54	*274,275*
	N-Methylcorydine	IV.a.29	*275*
	O-Methylflavinantine	XIV.b.2.2	*275,276*
Legnephora moorei Miers	Dehydrocorydalmine	X.a.6	*93,94*
	(+)-Laurifoline	IV.a.55	*93*
	Laurifoline	IV.a.55	*94*
	Magnoflorine	IV.a.54	*93,94*
	(+)-Stepharine	III.a.1	*93*
	Stepharine	III.a.1	*94*
Limacia oblonga (Miers) Hook. & Thoms.	(+)-Clolimalongine	XVI.b.1	*277*
	Homomoschatoline	IV.c.3	*277*
	Imenine	IV.c.4	*277*
	(+)-Limalongine	XVI.b.2	*277*
	Lysicamine	IV.c.2	*277*
	Splendidine	IV.c.5	*277*
	(+)-Stepharine	III.a.1	*277*
Limaciopsis loangensis Engl.	Alkaloid K	CSND	*95*
	Berbamine	II.b.1.2.47	*95*
	2'-*N*-Chloromethylisotetrandrine	II.b.1.2.26	*95*
	Cycleanine	II.b.2.1.4	*95*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Homoaromoline	II.b.1.1.16	*121*
	Isotetrandrine	II.b.1.2.30	*95*
	Liriodenine	IV.c.1	*95*
	2'-Nortetrandrine	II.b.1.2.32	*95*
	2'-*N*-Oxyisotetrandrine	II.b.1.2.24	*95*
	8-Oxypalmatine	X.c.4	*95*
	Thalrugosamine	II.b.1.1.41	*95*
	Thalrugosine	II.b.1.2.39	*95*
Menispermum canadense L.	Acutumidine	XVI.a.2	*278*
	Acutumine	XVI.a.1	*278*
	Alkaloid A	CSND	*278*
	Dauricine	II.a.1.1.1	*278*
	Daurinoline	II.a.1.1.3	*278*
	Dehydrocheilanthifoline	X.a.11	*278*
	N'-Demethyldauricine	II.a.1.1.2	*278*
	Magnoflorine	IV.a.54	*278*
	N-Methyllindcarpine	IV.a.50	*278*
	N,N-Dimethyllindcarpine	IV.a.51	*279*
Menispermum dauricum DC.	Acutumidine	XVI.a.2	*280*
	Acutumine	XVI.a.1	*280*
	Acutuminine	XVI.a.3	*281*
	Bianfugecine	IX.5	*280,282,283*
	Bianfugedine	IX.6	*280,282*
	Bianfugenine	IX.4	*280,282*
	Cheilanthifoline	X.b.2	*284*
	Corypalline	XX.a	*285,569*
	Dauriciline	II.a.1.1.11	*286*
	Dauricine	II.a.1.1.1	*287-295*
	Dauricinoline	II.a.1.1.7	*287,289,294*
	Dauricoline	II.a.1.1.6	*294*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Dauricoside	X.b.17	*295*
	Daurinoline	II.a.1.1.3	*294*
	Dauriporphine	IX.4	*295-297*
	Dauriporphinoline	IX.7	*298*
	Daurisoline	II.a.1.1.4	*299*
	N-Demethyldauricine	II.a.1.1.2	*293*
	6-*O*-Demethylmenisporphine	IX.7	*295*
	2,3-Dihydromenisporphine	IX.2	*297*
	Guattegaumerine	II.a.1.1.11	*300*
	Menisporphine	IX.1	*46,47,295*
	(+)-Stepharine	III.a.1	*284*
	Sinomenine	XIV.a.1.1	*301*
	Stepholidine	X.b.5	*284*
	Thalflavine	XX.b.3	*285*
Pachygone dasycarpa Kurz	(+)-Angchibangkine	II.d.1	*573*
	(+)-Atherospermoline	II.b.1.2.61	*573*
	(+)-Cocsuline	II.c.1.1.7	*573*
	(+)-Daphnoline	II.b.1.1.13	*573*
	(+)-Fangchinoline	II.b.1.2.1	*573*
	(+)-Isotrilobine	II.c.1.1.4	*573*
	(+)-*O*-Methylangchibangkine	II.d.2	*573*
	(+)-12-*O*-Methyltricordatine	II.c.1.1.26	*573*
	(+)-*N*-Methyl-7-*O*-demethylpeinamine	II.b.1.2.55	*573*
	(+)-2'-Norcocsuline	II.c.1.1.9	*573*
	(+)-Penduline	II.b.1.2.37	*573*
	(+)-Tetrandrine	II.b.1.2.14	*573*
	(+)-Tricordatine	II.c.1.1.15	*573*
Pachygone loyaltiensis Diels	(+)-Apateline	II.c.1.1.18	*302*
	(+)-*N,N*-Bisnoraromoline	II.b.1.1.15	*302*
	(+)-Daphnandrine	II.b.1.1.12	*302*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-Daphnoline	II.b.1.1.13	*302*
	(+)-1,2-Dehydroapateline	II.c.1.1.20	*302*
	(+)-1,2-Dehydrotelobine	II.c.1.1.22	*302*
	(+)-Isotrilobine	II.c.1.1.4	*302*
	(+)-*O*-Methylcocsoline	II.c.1.1.6	*302*
Pachygone ovata Miers	*N,N'*-Bisdemethyltiliacorinine	II.c.1.6.14	*303*
	Coclaurine	I.b.1	*303-306*
	Coreximine	X.b.9	*303-305*
	N-Demethyltiliacorinine	II.c.1.6.12	*303*
	N,O-Dimethylisocorydine	IV.a.48	*179*
	O,O'-Dimethylmagnoflorine	IV.a.48	*307*
	Isoboldine	IV.a.23	*303,304*
	Liriodenine	IV.c.1	*303-306*
	Magnoflorine	IV.a.54	*303-305,307*
	N-Methylcrotsparine	III.a.7	*306*
	N-Methylpachygonamine	II.c.1.6.3	*303,308-310*
	Norjuziphine	I.b.4	*303,304*
	Nortrilobine	II.c.1.1.3	*303,304*
	Pachygonamine	II.c.1.6.2	*304,308,309*
	Pachygonine	XVIII.a.13	*307*
	Pachyovatamine	II.c.1.6.7	*309*
	Reticuline	I.b.9	*306*
	Reticuline *N*-oxide	I.b.10	*306*
	Stepholidine	X.b.5	*303-305*
	Tiliamosine	II.c.1.6.4	*303,308-310*
	Trilobine	II.c.1.1.1	*303-306*
Pachygone somniferum Miq.	Codamine	I.b.11	*311*
	Reticuline	I.b.9	*311*
Parabaena megalocarpa Miers	Palmatine	X.a.3	*312*
	Tembetarine	I.b.12	*312*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Parabaena sagittata Miers	Berberine	X.a.4	*313*
	(-)-*O*-Methylthaicanine	X.b.34	*313*
	Palmatine	X.a.3	*312*
	Tembetarine	I.b.12	*312*
	(-)-Tetrahydropalmatine	X.b.32	*313*
	(-)-Thaicanine	X.b.33	*313*
Parabaena tuberculata Miers	Palmatine	X.a.3	*312*
	Tembetarine	I.b.12	*312*
Penianthus zenkeri Engl & Diels	Berberine	X.a.4	*314*
	Dehydrodiscretine	X.a.12	*268*
	Jatrorrhizine	X.a.1	*314*
	Menisperine	IV.a.53	*314*
	Palmatine	X.a.3	*268,269*
	N-trans-Feruloyltyramine	XXI.1	*314*
Pycnarrhena australiana Muell.	Alkaloid $C_{19}H_{19}NO_5$	CSND	*315*
	Berbamine	II.b.1.2.47	*315*
	Liriodenine	IV.c.1	*315*
	2-*N*-Norberbamine	II.b.1.2.57	*315*
	2-*N*-Norobamegine	II.b.1.2.56	*315*
	Isotetrandrine	II.b.1.2.30	*315*
Pycnarrhena longifolia (Decne ex. Miq.) Becc.	Aromoline	II.b.1.1.14	*316*
	Berbacolorflammine	II.b.1.2.48	*317,318*
	Colorflammine	II.b.1.1.38	*317,318*
	Daphnoline	II.b.1.1.13	*316*
	Homoaromoline	II.b.1.1.16	*316*
	Krukovine	II.b.1.2.29	*316*
	Limacine	II.b.1.2.6	*316*
	Limacusine	II.b.1.1.20	*318*
	Magnoflorine	IV.a.54	*316*
	Obaberine	II.b.1.1.8	*316*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Pycnarrhine	XX.a.1	*316*
	1',2',3',4'-Tetrahydrolimacusine	II.b.1.1.25	*319*
Pycnarrhena manillensis Vidal	Berbamine	II.b.1.2.47	*320*
	Isotetrandrine	II.b.1.2.30	*320*
	Phaeantine	II.b.1.2.20	*320*
	Phaeantine 2'α-*N*-oxide	II.b.1.2.21	*320*
	Pycmanilline	II.b.1.5.1	*320*
	Pycnamine	II.b.1.2.36	*320*
	Pycnanthina	II.b.1.5.2	*320*
	Pycnarrhenamine	CSND	*321*
	Pycnarrhenine	CSND	*322*
Pycnarrhena novoguineensis	Limacine	II.b.1.2.6	*229*
	Magnoflorine	IV.a.54	*245*
	Phaeantine	II.b.1.2.20	*231*
	Pycnamine	II.b.1.2.36	*323*
	Thalrugosine	II.b.1.2.39	*324*
Pycnarrhena ozantha Diels	*N*,*N*'-Bisnoraromoline	II.b.1.1.15	*325*
	(+)-Bisnorobamegine	II.b.1.2.45	*85*
	(+)-Bisnorthalrugosine	II.b.1.2.41	*85*
	(+)-Daphnoline	II.b.1.1.13	*85*
	(+)-2-Norberbamine	II.b.1.2.57	*85*
	(+)-Norobamegine	II.b.1.2.56	*85*
	2-*N*-Norobamegine	II.b.1.2.56	*325*
	(+)-Pycnazanthine	II.b.1.2.28	*85*
	(+)-2-Northalrugosine	II.b.1.2.40	*85*
Rhigiocarya racemifora Miers	Alkaloid RRQ	CSND	*326*
	Liriodenine	IV.c.1	*326*
	Magnoflorine	IV.a.54	*326*
	Menisperine	IV.a.53	*326*
	(±)-*O*-Methylflavinantine	XIV.b.2.2	*327*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	O-Methylflavinatine	XIV.b.2.2	*326*
	Palmatine	X.a.3	*326*
Sarcopetalum harveyanum F. Muell.	Coclaurine	I.b.1	*328*
	(+)-Stepharine	III.a.1	*328*
Sciadotenia eichleriana Miers	(+)-Coclaurine	I.b.1	*329*
	(-)-Grisabine	II.a.1.1.14	*329*
	(+)-2-Norlimacusine	II.b.1.1.21	*329*
	(+)-Stepharine	III.a.1	*329*
Sciadotenia toxifera Krukoff	Isochondodendrine	II.b.2.1.1	*330*
	Sciadenine	II.b.2.1.12	*330,331*
	Sciadoferine	II.b.2.1.9	*331*
	Sciadoline	II.b.2.1.8	*330*
Sinomenium acutum Rehder & Wilson	Alkaloid FK-2000	XIV.d.4	*332*
	Alkaloid FK-3000	XIV.d.2	*332*
	Acutumidine	XVI.a.2	*333*
	Acutumine	XVI.a.1	*334-336*
	Bianfugenine	IX.4	*337*
	Dehydrodiscretine	X.a.12	*336*
	N-Demethyl-*N*-formyldehydronuciferine	IV.b.7	*338,339*
	8,14-Dihydrosalutaridine	XIV.b.3.1	*337*
	Disinomenine	XIV.a.1.2	*334*
	Epiberberine	X.a.18	*336*
	N-Feruloyltyramine	XXI.1	*335*
	(+)-Laurifoline	IV.a.55	*336*
	Liriodenine	IV.c.1	*334,338*
	Magnoflorine	IV.a.54	*340*
	(+)-Menispermine	IV.a.53	*336*
	Palmatine	X.a.3	*336*
	(±)-Sinactine	X.b.3	*333*
	Sinoacutine	XIV.b.1.2	*333,341*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Sinomendine	IV.e.1	*337*
	Sinomenine	XIV.a.1.1	*56,333-335,338,340,341*
	(-)-Stepholidine	X.b.5	*334*
	Stepharanine	X.a.5	*337*
Sinomenium diversifolium Diels	Aromoline	II.b.1.1.14	*296,297*
	Berbamine	II.b.1.2.47	*342*
	Cepharanthine	II.b.1.1.1	*342,343*
	Cepharanoline	II.b.1.1.3	*342,343*
	Cycleanine	II.b.2.1.4	*342,343*
	Homoaromoline	II.b.1.1.16	*342*
	Isotetrandrine	II.b.1.2.30	*342*
Sphenocentrum jollyanum Pierre	Jateorrhizine	X.a.1	*344*
	Jatrorrhizine	X.a.1	*345-347*
	Palmatine	X.a.3	*344-347*
Spirospermum penduliflorum Thou.	Limacine	II.b.1.2.6	*348*
Stephania abyssinica Walp.	Corydine	IV.a.28	*349*
	Crebanine	IV.a.59	*349*
	Dicentrine	IV.a.44	*349*
	Dicentrinone	IV.c.16	*349*
	6-Dihydroepistephamiersine	XV.e.1.14	*350*
	N-Methyllaurotetanine	IV.a.21	*349*
	4'-*O*-Methylstephavanine	XV.e.2.3	*351*
	Oxoxylopine	IV.c.14	*352,353*
	Prostephabyssine	XV.e.1.18	*354*
	Roemerine	IV.a.6	*349*
	Stephaboline	XV.e.1.8	*355*
	Stephabyssine	XV.e.1.9	*355*
	Stephalagine	IV.a.9	*349*
	Stephanine	IV.a.66	*349*
	Stephavanine	XV.e.2.4	*351,352*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	N,O,O-Trimethylstephavanine	XV.e.2.5	*356*
	Xylopine	IV.a.10	*353*
Stephania aculeata Bailey	(-)-Amurine	XIV.b.1.4	*570*
	(+)-Laudanidine	I.b.18	*570*
Stephania bancroftii Bailey	Ayuthianine	IV.a.43	*357*
	(-)-Crebanine	IV.a.59	*357*
	(+)-Sebiferine	XIV.b.2.2	*357*
	(-)-Stephanine	IV.a.66	*357*
	(+)-Stepharine	III.a.1	*357*
	Tetrahydropalmatine	X.b.32	*357*
Stephania brachyandra Diels	(+)-Cepharanthine	II.b.1.1.1	*358*
	Corytuberine	IV.a.30	*359*
	Crebanine	IV.a.59	*360*
	(-)-Curine	II.b.2.2.11	*358*
	Cycleanine	II.b.2.1.4	*358*
	Dehydrodicentrine	IV.b.8	*359*
	Dicentrine	IV.a.44	*359,360*
	8,14-Dihydrosalutaridine	XIV.b.3.1	*359*
	Homoaromoline	II.b.1.1.16	*358*
	Isoboldine	IV.a.23	*359*
	Isocorydine	IV.a.47	*358,359,361*
	N-Methyllaurotetanine	IV.a.21	*359*
	Sinoacutine	XIV.b.1.2	*359,360*
	Sinomenine	XIV.a.1.1	*359*
	Stephanine	IV.a.66	*360*
	Tetrahydropalmatine	X.b.32	*358,359,361*
Stephania cepharantha Hayata	Aknadicine	XV.a.11	*571,575*
	Aknadilactam	XV.a.12	*571,575,576*
	Aknadinine	XV.a.10	*571,575,576*
	Alkaloid FK-3000	XIV.d.2	*362, 571*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Homoaromoline	II.b.1.1.16	*358,365,366,367,370*
	(+)-Isoboldine	IV.a.23	*575*
	Isocorydine	IV.a.47	*358,362*
	Isocorytuberine	IV.a.71	*575*
	Isotetrandrine	II.b.1.2.30	*358,365,366,367,370,371*
	Juziphine	I.b.3	*575,576*
	(+)-Laudanidine	I.b.18	*575*
	Liriodenine	IV.c.1	*374*
	Litseferine	IV.a.72	*576*
	Lysicamine	IV.c.2	*374*
	(+)-*N*-Methylcoclaurine	I.b.2	*575*
	N-Methylcrotsparine	III.a.7	*575*
	N-Methyllaurotetanine	IV.a.21	*575*
	2-Norberbamine	II.b.1.2.57	*575*
	Norcepharadione	IV.b.12	*374*
	Norcepharadione B	IV.b.12	*375*
	2-Norcepharanoline	II.b.1.1.6	*575*
	2-Norcepharanthine	II.b.1.1.4	*575*
	(-)-Norcycleanine	II.b.2.1.7	*367*
	2-Norisotetrandrine	II.b.1.2.34	*575*
	Norjuziphine	I.b.4	*576*
	O-Nornuciferine	IV.a.70	*371*
	Obaberine	II.b.1.1.8	*575*
	Obamegine	II.b.1.2.44	*367*
	Oxyacanthine	II.b.1.1.19	*575*
	Palmatine	X.a.3	*376*
	Protosinomenine	I.b.19	*575*
	(+)-Reticuline	I.b.9	*575,576*
	(-)-Scoulerine	X.b.45	*575*
	Secocepharanthine	II.b.1.4.2	*575*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(-)-Anonaine	IV.a.1	*575*
	Aromoline	II.b.1.1.14	*363-368,575*
	Arystolactam B-II	VIII.b.2	*369*
	Berbamine	II.b.1.2.47	*358,362,363,365-368,371*
	Cephakicine	XIV.d.5	*571*
	Cephamonine	XIV.a.1.3	*367,576*
	Cephamorphinanine	XIV.d.3	*362*
	Cephamuline	XIV.a.1.4	*367,576*
	Cepharadione A	IV.b.10	*372*
	Cepharadione B	IV.b.11	*372*
	Cepharamine	XV.a.5	*571,576*
	Cepharanoline	II.b.1.1.3	*365,367,371,576*
	Cepharanone A	VIII.b.1	*369,372*
	Cepharanone B	VIII.b.2	*372*
	(+)-Cepharantine	II.b.1.1.1	*358,361,365,367,370,371,373*
	Cepharantine	II.b.1.1.1	*362*
	Cephasamine	XIV.e	*571*
	Cephasugine	XIV.d.7	*576*
	Cephatonine	XV.a.13	*571,576*
	(+)-Coclaurine	I.b.1	*575*
	Corydine	IV.a.28	*575*
	Crebanine	IV.a.59	*371*
	(-)-Cycleanine	II.b.2.1.4	*367*
	Cycleanine	II.b.2.1.4	*358,365,366,370,371,575*
	Dehydrocrebanine	IV.b.1	*371*
	3,4-Dehydrocycleanine	II.b.2.1.13	*575*
	Dehydrostephanine	IV.b.4	*371*
	3',4'-Dihydrostephasubine	II.b.1.1.39	*575*
	14-Episinomenine	XIV.a.1.4	*571*
	N-trans-Feruloyltryramine	XXI.1	*575*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Sinoacutine	XIV.b.1.2	*571*
	Sinococculine	XIV.d.1	*362*
	Sinomenine	XIV.a.1.1	*362,367,576*
	Stephanine	IV.a.66	*371*
	Stephaoxocanine	XXII.3	*72*
	Stephaoxocanidine	XXII.4	*575*
	Stepharine	III.a.1	*367,576*
	Stephibaberine	II.b.1.1.29	*575*
	Stephodeline	XIV.a.2.3	*576*
	Stesakine	IV.a.65	*371*
	Tannagine	XIV.a.2.2	*571*
	Thalrugosine	II.b.1.2.39	*575*
Stephania corymbosa BL.	Protostephanine	XVII.4	*377*
Stephania delavayi Diels	Berbamine	II.b.1.2.47	*358*
	(+)-Cepharantine	II.b.1.1.1	*358*
	Cycleanine	II.b.2.1.4	*358*
	Delavaine	XV.a.1	*378*
	(-)-Dicentrine	IV.a.44	*358*
	Homoaromoline	II.b.1.1.16	*358*
	Isocorydine	IV.a.47	*358*
	Isostephodeline	XIV.c.2	*379*
	Isotetrandrine	II.b.1.2.30	*358*
	16-Oxodelavaine	XV.a.3	*378*
	Tetrahydropalmatine	X.b.32	*358*
	(+)-Tetrandrine	II.b.1.2.14	*358*
Stephania dicentrinifera H.S.Lo & M. Yang	Berbamine	II.b.1.2.47	*358*
	(+)-Cepharanthine	II.b.1.1.1	*358*
	Cycleanine	II.b.2.1.4	*358*
	(-)-Dicentrine	IV.a.44	*358,362*
	8-Hydroxydehydroroemerine	IV.b.9	*380*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Isotetrandrine	II.b.1.2.30	*358*
	Tetrahydropalmatine	X.b.32	*358,380*
Stephania dielsiana Wu	Berbamine	II.b.1.2.47	*358*
	(+)-Cepharanthine	II.b.1.1.1	*358*
	Crebanine	IV.a.59	*381*
	Dehydrostephanine	IV.b.4	*382*
	Homoaromoline	II.b.1.1.16	*358*
	Isotetrandrine	II.b.1.2.30	*358*
	Sinoacutine	XIV.b.1.2	*361,381,382*
	Stephanine	IV.a.66	*381,382*
	Tetrahydropalmatine	X.b.32	*358,382*
	Xylopine	IV.a.10	*382*
Stephania dinklagei (Engl.) Diels	Alkaloid SDQ-3	CSND	*383*
	(+)-*N*-Methylcorydine	IV.a.29	*383*
	(+)-*N*-Methylglaucine	IV.a.52	*383*
	Norcorydine	IV.a.14	*384*
	Stephalagine	IV.a.9	*385*
	Steporphine	IV.a.38	*386*
Stephania disciflora Hand.-Mazz.	Capaurine	X.b.16	*387*
	Dehydroroemerine	IV.b.6	*387*
	Dicentrine	IV.a.44	*387*
	Isocorydine	IV.a.47	*387*
	Roemerine	IV.a.6	*387*
	Tetrahydropalmatine	X.b.32	*387*
Stephania dolichopoda Diels	Tetrahydropalmatine	X.b.32	*361*
Stephania elegans Hook. & Thoms.	Aknadinine	XV.a.10	*388*
	Cyclanoline	X.b.43	*388*
	(-)-Cycleanine	II.b.2.1.4	*388*
	Epihernandolinol	XV.c.2	*388*
	Hasubanonine	XV.a.3	*388*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Isochondodendrine	II.b.2.1.1	*388*
	Isosinoacutine	XIV.b.1.1	*389*
	(+)-Isotetrandrine	II.b.1.2.30	*388*
	Magnoflorine	IV.a.54	*388*
	N-Methylcorydalmine	X.b.39	*388*
	Sinoacutine	XIV.b.1.2	*389*
Stephania epigaea H.S. Lo	Berbamine	II.b.1.2.47	*358*
	(-)-Cassithicine	IV.a.27	*390*
	(+)-Cepharanthine	II.b.1.1.1	*358,361,390,391*
	Cepharanthine	II.b.1.1.1	*392*
	(-)-Curine	II.b.2.2.11	*358,391,392*
	Cycleanine	II.b.2.1.4	*361,390,391*
	Dehydrodicentrine	IV.b.8	*390*
	Dehydrostephanine	IV.b.4	*390*
	(-)-Dicentrine	IV.a.44	*390*
	Isochondodendrine	II.b.2.1.1	*392*
	Isocorydine	IV.a.47	*391*
	Isostephodeline	XIV.c.2	*390*
	Oliveroline	IV.a.40	*393,572*
	Sinoacutine	XIV.b.1.2	*390*
	Sinomenine	XIV.a.1.1	*390*
	Stephanine	IV.a.66	*390*
	Tetrahydropalmatine	X.b.32	*390*
	Ushinsunine	IV.a.41	*392*
Stephania erecta Craib.	(+)-Cepharanthine	II.b.1.1.1	*101-103*
	(+)-Daphnandrine	II.b.1.1.12	*103*
	(+)-1,2-Dehydrotelobine	II.c.1.1.22	*103*
	(+)-Homoaromoline	II.b.1.1.16	*103*
	Homoaromoline	II.b.1.1.16	*101,102*
	(+)-Isotetrandrine	II.b.1.2.30	*103*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-2-*N*-Methyltelobine	II.c.1.1.14	*103*
	(+)-Norcepharanthine	II.b.1.2.34	*103*
	(+)-2-Norisotetrandrine	II.b.1.1.4	*103*
	2-Norobaberine	II.b.1.1.10	*103*
	(+)-2-Northalrugosine	II.b.1.2.40	*103*
	(+)-Obaberine	II.b.1.1.8	*103*
	(+)-Stephibaberine	II.b.1.1.29	*103*
	(+)-Thalrugosine	II.b.1.2.39	*103*
Stephania excentrica H.S. Lo	Berbamine	II.b.1.2.47	*358*
	(+)-Cepharanthine	II.b.1.1.1	*358,361*
	(+)-Coclaurine	I.b.1	*71*
	Curine	II.b.2.2.11	*358*
	4-Demethylhasubanonine	XV.a.10	*71*
	Excentricine	XXII.1	*71*
	Homoaromoline	II.b.1.1.16	*71*
	Isoboldine	IV.a.23	*71*
	2-*N*-Methylexcentricine	XXII.2	*574*
	Oxoanolobine	IV.c.15	*71*
	Oxoputerine	IV.c.11	*71*
	Roemerine	IV.a.6	*71*
	Sinococculine	XIV.d.1	*71*
Stephania glabra Miers	Capaurine	X.b.16	*394*
	Corydalmine	X.b.30	*394,395*
	Corynoxidine	X.b.36	*394*
	Cycleanine	II.b.2.1.4	*394*
	Dehydrocorydalmine	X.a.6	*394,395*
	N-Desmethylcycleanine	II.b.2.1.6	*394*
	Gindarine	X.b.32	*396-398*
	Jatrorrhizine	X.a.1	*394*
	Palmatine	X.a.3	*394,395*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Palmatrubine	X.a.9	*395*
	Pronuciferine	III.a.2	*394*
	(+)-Stepharine	III.a.1	*399*
	Stephanine	IV.a.66	*400*
	Stepharanine	X.a.5	*394*
	Stepharanine	X.a.5	*395*
	Stepharine	III.a.1	*394*
	Stepholidine	X.b.5	*394,395*
	(-)-Tetrahydropalmatine	X.b.32	*399,401*
	Tetrahydropalmatine	X.b.32	*394,395*
Stephania gracilenta Miers	Isosinoacutine	XIV.b.1.1	*402*
	Magnoflorine	IV.a.54	*402*
	Papaverine	I.a	*402*
	Sinoacutine	XIV.b.1.2	*402*
Stephania hainanensis H.S. Lo & Y.	(-)-Corydalmine	X.b.30	*403*
	Crebanine	IV.a.59	*403*
	Cycleanine	II.b.2.1.4	*358,403*
	Dehydrocrebanine	IV.b.1	*403*
	Homoaromoline	II.b.1.1.16	*358*
	Isotetrandrine	II.b.1.2.30	*358*
	Oxocrebanine	IV.c.8	*403*
	Palmatine	X.a.3	*403*
	Stepharine	III.a.1	*358,403*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,403*
	(+)-Tetrandrine	II.b.1.2.14	*358*
Stephania hernandifolia (Willd.) Walp.	Aknadicine	XV.a.11	*404*
	Aknadinine	XV.a.10	*405*
	Cycleanine	II.b.2.1.4	*406*
	4-Demethylhasubanonine	XV.a.11	*352*
	O-Demethylhernandifoline	XV.e.1.7	*407*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-3',4'-Dihydrostephasubine	II.b.1.1.39	*408*
	N,O-Dimethylcocsoline	II.c.1.1.4	*83*
	(+)-Epistephanine	II.b.1.1.32	*408*
	Epistephanine	II.b.1.1.32	*405,409*
	(+)-Fangchinoline	II.b.1.2.1	*409*
	Hernandifoline	XV.e.1.6	*405*
	Hernandine	XV.e.1.10	*410*
	Hernandolinol	XV.c.1	*411*
	Isochondodendrine	II.b.2.1.1	*406,409*
	Magnoflorine	IV.a.54	*405*
	O-Methylhernandine	XV.e.1.11	*410*
	12-*O*-Methylatherospermoline	II.b.1.2.1	*229*
	Oxoepistephanine	II.b.1.1.35	*352*
	(+)-Stephasubine	II.b.1.1.36	*408*
	Stephisoferuline	XV.e.1.6	*352*
	(+)-Tetrandrine	II.b.1.2.14	*409*
Stephania intermedia	(-)-Corydalmine	X.b.30	*412*
	Dehydrocorydalmine	X.a.6	*412*
	Dehydrodiscretamine	X.a.8	*412*
	(-)-Discretamine	X.b.1	*412*
	Jatrorrhizine	X.a.1	*412*
	Palmatine	X.a.3	*412*
	(+)-Stepharine	III.a.1	*412*
	(-)-Stepholidine	X.b.5	*412*
	Stepharanine	X.a.5	*412*
	(-)-Tetrahydropalmatine	X.b.32	*412*
Stephania japonica Miers	Alkaloid S	CSND	*413*
	Alkaloid X	CSND	*413*
	N,O-Dimethyloxostephine	XV.e.1.5	*413*
	Epistephamiersine	XV.e.1.2	*413*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Epistephanine	II.b.1.1.32	*413*
	Hasubanonine	XV.a.8	*59,414-416*
	Hipoepistephanine	II.b.1.1.33	*413*
	Lanuginosine	IV.c.14	*417,418*
	Metaphanine	XV.e.1.17	*413,419*
	Oxoepistephamiersine	XV.e.1.4	*418*
	16-Oxohasubanonine	XV.a.9	*416*
	16-Oxoprometaphanine	XV.f.3.2	*416,420*
	Oxostephabenine	XV.e.2.2	*421*
	Oxostephamiersine	XV.e.1.3	*413,418,420*
	Oxostephanine	IV.c.12	*417*
	Oxostephasunoline	XV.e.1.16	*422*
	Prometaphanine	XV.f.3.1	*420*
	Prostephanaberrine	XV.b.1	*423*
	Protostephanine	XVII.4	*59,413,415,416*
	Stebisimine	II.b.1.1.34	*413,420*
	Stephabenine	XV.e.2.1	*424*
	Stephadiamine	XV.f.1	*419*
	Stephamiersine	XV.e.1.1	*413*
	Stephanaberrine	XV.e.1.19	*423*
	Stephani base A	CSND	*425*
	Stephanine	IV.a.66	*413*
	Stephasunoline	XV.e.1.13	*413*
	Stepinonine	II.b.1.7.1	*413*
Stephania japonica (Thunb.) Miers var. *australis*	Cyclanoline	X.b.43	*426*
	Hasubanonine	XV.a.8	*426*
	Magnoflorine	IV.a.54	*426*
	Metaphanine	XV.e.1.17	*426*
	Stephabyssine	XV.e.1.9	*426*
	Oxostephamiersine	XV.e.1.3	*426*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Protostephanine	XVII.4	*426*
	Thalrugosine	II.b.1.2.39	*426*
Stephania kuinanensis H.S. Lo & M. Yang	(-)-Dicentrine	IV.a.44	*361*
	Tetrahydropalmatine	X.b.32	*361*
Stephania kwangsiensis H.S. Lo	Berbamine	II.b.1.2.47	*358*
	(-)-Capaurine	X.b.16	*427*
	(+)-Cepharanthine	II.b.1.1.1	*358*
	Cycleanine	II.b.2.1.4	*358*
	Dehydroroemerine	IV.b.6	*427*
	Dehydrostephanine	IV.b.4	*427*
	(+)-Isocorydine	IV.a.47	*427*
	Isocorydine	IV.a.47	*358*
	Palmatine	X.a.3	*376,428,429*
	(-)-Roemerine	IV.a.6	*427*
	Stephanine	IV.a.66	*428,429*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,427,428*
	Tetrahydropalmatine	X.b.32	*429*
Stephania lincangensis	Capaurine	X.b.16	*430*
	Corydine	IV.a.28	*430*
	Isocorydine	IV.a.47	*430*
	Lincangenine	X.a.15	*430*
	Palmatine	X.a.3	*430*
	(-)-1,2,3,9,10-Pentamethoxy-Tetrahydroprotoberberine	X.b.14	*430*
	Roemerine	IV.a.6	*430*
	Tetrahydropalmatine	X.b.32	*430*
Stephania longa L.	Homoaromoline	II.b.1.1.16	*358*
	Berbamine	II.b.1.2.47	*358*
	Cycleanine	II.b.2.1.4	*358*
	Longanine	XV.e.1.12	*431*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Longaninine	XV.e.1.12	*432*
	Longanone	XV.e.1.15	*432*
	Longetherine	XV.d	*433*
	Stephaboline	XV.e.1.8	*431-433*
	Stephabyssine	XV.e.1.9	*432,433*
	Prostephabyssine	XV.e.1.18	*432*
Stephania longana	Longanone	XV.e.1.15	*434*
Stephania longipes H.S. Lo	(-)-Stepholidine	X.b.5	*435*
Stephania mashanica H.S. Lo & B.N.	(+)-Cepharanthine	II.b.1.1.1	*358*
	(-)-Curine	II.b.2.2.11	*358*
	(-)-Dicentrine	IV.a.44	*358,361,436*
	Dicentrinone	IV.c.16	*436*
	Isocorydine	IV.a.47	*358*
	Sinoacutine	XIV.b.1.2	*361,436*
	(-)-Tetrahydrocolumbamine	X.b.13	*436*
	(-)-Tetrahydrojatrorrhizine	X.b.4	*436*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,436*
Stephania micrantha H.S. Lo	(-)-Capaurine	X.b.16	*437*
	Corydalmine	X.b.30	*438*
	Corydine	IV.a.28	*438*
	Corypalmine	X.b.4	*437*
	Corytuberine	IV.a.30	*438*
	(-)-Curine	II.b.2.2.11	*358*
	Cycleanine	II.b.2.1.4	*358*
	Dehydroisolaureline	IV.b.5	*439*
	Dehydroroemerine	IV.b.6	*437,459*
	Dehydrostephanine	IV.b.4	*437,459*
	(-)-Dicentrine	IV.a.44	*358*
	(+)-Isocorydine	IV.a.47	*437*
	Isocorydine	IV.a.47	*358,438*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Laudanidine	I.b.5	*438*
	Palmatine	X.a.3	*376,438*
	Sinoacutine	XIV.b.1.2	*437*
	Sinomenine	XIV.a.1.1	*437*
	Stephanine	IV.a.66	*437*
	Stepholidine	X.b.5	*438*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,437,438*
	Tetrahydrocolumbamine	X.b.13	*437*
	Xylopinine	X.b.31	*437*
Stephania officinarum	Corytuberine	IV.a.30	*440*
	Crebanine	IV.a.59	*440*
	Isoboldine	IV.a.23	*440*
	Isocorydine	IV.a.47	*440*
	Palmatine	X.a.3	*440*
	Sinoacutine	XIV.b.1.2	*440*
	Tetrahydropalmatine	X.b.32	*440*
Stephania pierrei Diels (= *S. erecta* Craib.)	(-)-Anonaine	IV.a.1	*441*
	(+)-Aromoline	II.b.1.1.14	*442*
	Asimilobine 2-*O*-β-D-glicoside	IV.a.4	*441*
	(-)-Asimilobine	IV.a.3	*441*
	(+)-Berbamunine	II.a.1.1.12	*442*
	(-)-Capaurine	X.b.16	*441*
	(-)-Cassithicine	IV.a.27	*441*
	(+)-Cepharanthine	II.b.1.1.1	*442*
	Coclaurine	I.b.1	*442*
	(+)-Codamine	I.b.11	*442*
	(-)-Corydalmine	X.b.30	*441*
	(-)-Cycleanine	II.b.2.1.4	*442*
	(-)-Daphnandrine	II.b.1.1.12	*442*
	Dehatridine	II.b.1.2.46	*443*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-1,2-Dehydroapateline	II.c.1.1.20	*442*
	(-)-Delavaine	XV.a.1	*441*
	(-)-*N*-Demethylcycleanine	II.b.2.1.6	*442*
	(-)-Dicentrine	IV.a.44	*441*
	(+)-Homoaromoline	II.b.1.1.16	*442*
	(+)-Isocorydine	IV.a.47	*442*
	(-)-Isolaureline	IV.a.67	*441*
	(+)-Isotetrandrine	II.b.1.2.30	*442*
	Magnoflorine	IV.a.54	*441*
	(+)-*N*-Methylcoclaurine	I.b.2	*442*
	N-Methyltetrahydropalmatine	X.b.42	*441*
	(+)-2-*N*-Norberbamine	II.b.1.2.57	*442*
	(+)-2'-Norcepharanthine	II.b.1.1.5	*442*
	(+)-2-Norcepharanoline	II.b.1.1.6	*442*
	(-)-Nordicentrine	IV.a.45	*441*
	(-)-2-Norisocepharanthine	II.b.1.1.7	*442*
	(+)-2-Norisotetrandrine	II.b.1.2.34	*442*
	(+)-2'-Norisotetrandrine	II.b.1.2.32	*442*
	(+)-2-Norobaberine	II.b.1.1.10	*442*
	(+)-2'-Norobaberine	*II.b.1.1.9*	*442*
	(+)-Obaberine	II.b.1.1.8	*442*
	(±)-Oblongine	I.b.14	*441*
	(-)-Phanostenine	IV.a.64	*441*
	(+)-Reticuline	I.b.9	*442*
	(-)-Roemeroline	IV.a.11	*441*
	(-)-Salutaridine	XIV.b.2.1	*441*
	Sinoacutine	XIV.b.1.2	*441*
	(+)-Stephibaberine	II.b.1.1.29	*442*
	(+)-Stepierrine	II.b.1.2.46	*442*
	(-)-Tetrahydropalmatine	X.b.32	*441*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(-)-Tetrahydrostephabine	X.b.19	*441*
	(-)-Thaicanine	X.b.33	*441*
	(+)-Thalrugosamine	II.b.1.1.41	*442*
	(-)-Xylopinine	X.b.31	*441*
	Xylopine	IV.a.10	*442*
Stephania rotunda Lour.	Cepharamine	XV.a.5	*443*
	Cycleanine	II.b.2.1.4	*444*
	Stepharotine	X.b.15	*445*
Stephania sasakii Hayata	*N*-Acetylstepharine	III.a.6	*446*
	Aknadilactam	XV.a.12	*404*
	Aknadinine	XV.a.10	*404*
	Alkaloid A	CSND	*447*
	Alkaloid B	CSND	*447*
	Alkaloid C	CSND	*447*
	Alkaloid D	CSND	*447*
	Alkaloid E	CSND	*446*
	Alkaloid F	CSND	*446*
	Alkaloid G	CSND	*446*
	Alkaloid H	CSND	*446*
	Alkaloid I	CSND	*446*
	Bisaknadinine	XV.f.2	*447*
	Cepharadione A	IV.b.10	*446*
	Cepharamine	XV.a.5	*446*
	Dehydrocrebanine	IV.b.1	*447*
	Dehydrophanostenine	IV.b.2	*446*
	Dehydroroemerine	IV.b.6	*446*
	Dehydrostesakine	IV.b.3	*447*
	Dihydrosecocepharanthine	II.b.1.4.1	*448*
	6,7-Dimethoxy-2-methylisoquinoline	XX.b.2	*446,449*
	4,5-Dioxodehydrocrebanine	IV.b.14	*447*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	4-Hydroxycrebanine	IV.a.60	*447,450*
	(+)-Isocorydine	IV.a.47	*447*
	Lanuginosine	IV.c.14	*447*
	Liriodenine	IV.c.1	*447*
	Lysicamine	IV.c.2	*446*
	O-Methyldeoxopunjabine	II.c.1.5.3	*448*
	O-Methylpunjabine	II.c.1.5.2	*448*
	Obaberine	II.b.1.1.8	*448*
	7-Oxocrebanine	IV.c.8	*446*
	(R)-Roemeroline	IV.a.11	*447,450*
	Secocepharanthine	II.b.1.4.2	*448*
	Steporphine	IV.a.38	*386*
	Stesakine	IV.a.65	*447*
	(-)-Tetrahydropalmatine	X.b.32	*447*
	Thalrugosine	II.b.1.2.39	*448*
Stephania sinica Diels	Berbamine	II.b.1.2.47	*358*
	(+)-Cepharanthine	II.b.1.1.1	*358,361,451*
	Cycleanine	II.b.2.1.4	*358,361*
	Runanine	XV.a.6	*451*
	(-)-Tetrahydropalmatine	X.b.32	*358*
Stephania specie	(+)-Cepharanthine	II.b.1.1.1	*458,453*
	Crebanine	IV.a.59	*453*
	Cycleanine	II.b.2.1.4	*453*
	Dicentrine	IV.a.44	*453*
	Gindarine	X.b.32	*454*
	Isocorydine	IV.a.47	*453*
	Stepholidine	X.b.5	*453*
	(+)-Tetrandrine	II.b.1.2.14	*453*
Stephania suberosa Forman	(-)-Capaurimine	X.b.17	*455*
	(+)-Cepharanthine	II.b.1.1.1	*456*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(+)-Cepharanthine 2'-β-*N*-oxide	II.b.1.1.2	*456*
	(-)-Coreximine	X.b.9	*455*
	(-)-Corytenchine	X.b.8	*455*
	Delavaine	XV.a.1	*457*
	(-)-Discretine	X.b.12	*455*
	Isostephodeline	XIV.c.2	*458*
	(-)-Kikemanine	X.b.30	*455*
	(+)-2-Norcepharanthine	II.b.1.1.4	*456*
	Nordelavaine	XV.a.2	*457*
	(+)-Norstephasubine	II.b.1.1.37	*456*
	8-0xypseudopalmatine	X.c.5	*455*
	Pseudopalmatine	X.c.6	*455*
	(-)-Stephabinamine	X.b.18	*455*
	Stephabine	X.a.16	*455*
	Stephanubine	XV.a.7	*457*
	Stephaphylline	XIV.c.2	*457*
	(+)-Stephasubine	II.b.1.1.36	*456*
	Stephasubimine	II.b.1.1.39	*456*
	(-)-Stepholidine	X.b.5	*455*
	(-)-Tetrahydropalmatine	X.b.32	*455*
	Tetrahydrostephabine	X.b.19	*455*
	(-)-Xylopinine	X.b.31	*455*
	(-)-*cis*-Xylopinine *N*-oxide	X.b.37	*455*
	(-)-*trans*-Xylopinine *N*-oxide	X.b.38	*455*
Stephania succinifera H.S. Lo	Asimilobine	IV.a.3	*459*
	Corydalmine	X.b.30	*383,440*
	Corypalmine	X.b.4	*383,440*
	Crebanine	IV.a.59	*459*
	Crebanine *N*-oxide	IV.a.57	*459*
	Cycleanine	II.b.2.1.4	*358*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Dehydrocorydalmine	X.a.6	*383,440*
	Dehydrocrebanine	IV.b.1	*459*
	Discretamine	X.b.1	*383,440*
	Oxocrebanine	IV.c.8	*383,440*
	Palmatine	X.a.3	*383,440*
	Phanostenine	IV.a.64	*383,440*
	Schefferine	X.b.30	*459*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,459*
Stephania sutchuenensis H.S. Lo	Aknadinine	XV.a.10	*460*
	Liriodenine	IV.c.1	*460,461*
	1-Nitroaknadinine	XV.a.4	*460*
	Pronuciferine	III.a.2	*462*
	Sinococculine	XIV.d.1	*462*
	(+)-Tetrandrine	II.b.1.2.14	*461*
	Thalrugosine	II.b.1.2.39	*462*
Stephania tetrandra S. Moore	Alkaloid AA-1	IV.a.56	*463*
	Berbamine	II.b.1.2.47	*358,464*
	β-Cyclanoline	X.b.44	*143*
	N^2,$N^{2'}$-Bis(chloromethyl)tetrandrinium	II.b.1.2.19	*463,465*
	Cassameridine	IV.c.17	*466*
	Cassithicine	IV.a.27	*466*
	(+)-Cepharanthine	II.b.1.1.1	*358*
	Corydione	IV.b.15	*466*
	Curine	II.b.2.2.11	*358*
	Cyclanoline	X.b.43	*463,464,467-469,470*
	Cycleanine	II.b.2.1.4	*358,463*
	Demethyltetrandrine	II.b.1.2.25	*471*
	Fangchinoline	II.b.1.2.1	*463,464,467-470,472-474*
	(+)-Fangchinoline	II.b.1.2.1	*475*
	Fenfangjine A	II.b.1.2.15	*463*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Fenfangjine B	II.b.1.2.3	*462*
	Fenfangjine C	II.b.1.2.4	*463*
	Fenfangjine D	II.b.1.2.5	*463*
	Homoaromoline	II.b.1.1.16	*358*
	Isocorydine	IV.a.47	*476*
	Magnoflorine	IV.a.54	*463*
	12-*O*-Methylatherospermoline	II.b.1.2.1	*229*
	(+)-2-*N*-Methylfangchinoline	II.b.1.2.17	*475*
	(+)-2-*N*-Methyltetrandrine	II.b.1.2.59	*463,475*
	2'-*N*-Methyltetrandrine	II.b.1.2.27	*463*
	Nantenine	IV.a.33	*466*
	2'-Norfangchinoline	II.b.1.2.13	*477*
	Oblongine	I.b.14	*463*
	Oxofangchirine	II.b.1.2.12	*467*
	Oxonantenine	IV.c.10	*466*
	Stephadione	IV.b.13	*466*
	Stephenanthrine	VII	*463,467*
	(-)-Tetrahydropalmatine	X.b.32	*476*
	(+)-Tetrandrine	II.b.1.2.14	*463,464,466-471,474,475,478-483*
	Tetrandrine 2'-*N*-α-oxide	II.b.1.2.16	*463*
	Tetrandrine 2'-*N*-β-oxide	II.b.1.2.15	*463*
	Tetrandrine 2-*N*-β-oxide	II.b.1.2.15	*484*
	1,3,4-Tridehydrofangchinolinium	II.b.1.2.5	*485*
Stephania venosa Spreng (= *S. rotunda* Lour.)	(-)-Anonaine	IV.a.1	*486*
	(-)-Asimilobine	IV.a.3	*486*
	(-)-*O*-Acetylsukhodianine	IV.a.62	*487*
	(-)-Apoglaziovine	IV.a.22	*486*
	Ayuthianine	IV.a.43	*488,489*
	(-)-*N*-Carboxamidostepharine	III.a.4	*486*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	(-)-Crebanine	IV.a.59	*486,490,491,487*
	Dehydrocrebanine	IV.b.1	*486,487*
	(-)-4-α-Hydroxycrebanine	IV.a.60	*486*
	Kalamine	IV.a.5	*492*
	(-)-Kikemanine	X.b.30	*486,487*
	Liriodenine	IV.c.1	*487*
	(-)-Mecambroline	IV.a.32	*486*
	(-)-*O*-Methylstepharinosine	III.b.2	*486*
	(-)-Nuciferoline	IV.a.19	*486*
	7-Oxocrebanine	IV.c.8	*493*
	Oxocrebanine	IV.c.8	*487*
	Oxostephanine	IV.c.12	*487,93*
	Oxostephanosine	IV.c.13	*487*
	(+)-Reticuline	I.b.9	*486*
	(+)-Stepharine	III.a.1	*486,494*
	Stephadiolamine β-*N*-oxide	IV.a.58	*486*
	(-)-Stepharinosine	III.b.1	*486*
	(-)-Stesakine	IV.a.65	*486*
	(-)-Sukhodianine	IV.a.61	*486,487*
	(-)-Sukhodianine β-*N*-oxide	IV.a.63	*486*
	Sukhodianine	IV.a.61	*488,489*
	(-)-Tetrahydropalmatine	X.b.32	*486,487*
	Thailandine	IV.c.18	*493,495*
	(+)-Thalrugosamine	II.b.1.1.41	*486*
	(-)-Tudoranine	IV.a.12	*486*
	(-)-Ushinsunine	IV.a.41	*486,489*
	(-)-Ushinsunine β-*N*-oxide	IV.a.42	*486*
	Uthongine	IV.c.19	*493,495*
Stephania viridiflavens H.S. Lo & M. Yang	Berbamine	II.b.1.2.47	*358*
	Cycleanine	II.b.2.1.4	*358*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Jatrorrhizine	X.a.1	*496*
	Palmatine	X.a.3	*496*
	Pseudopalmatine methylnitrate	CSND	*497*
	(-)-Tetrahydropalmatine	X.b.32	*358,361,496*
	(-)-Xylopinine	X.b.31	*496*
Stephania yunnanensis H.S Lo	(+)-Cepharanthine	II.b.1.1.1	*358*
	(-)-Corydalmine	X.b.30	*498*
	Dehydrocorydalmine	X.a.6	*498*
	Palmatine	X.a.3	*498*
	Roemerine	IV.a.6	*498*
	Sinoacutine	XIV.b.1.2	*361,498*
	(+)-Stepharine	III.a.1	*498*
	Stephanine	IV.a.66	*498*
	Stepharanine	X.a.5	*498*
	(-)-Stepholidine	X.b.5	*498*
	(-)-Tetrahydropalmatine	X.b.32	*358,498*
Stephania zippeliana Miq.	(+)-Corydine	IV.a.28	*499*
	(+)-Crebanine	IV.a.59	*499*
	(+)-Dicentrine	IV.a.44	*499*
	Dicentrinone	IV.c.16	*499*
	(+)-Epiglaufidine	IV.a.39	*499*
	(+)-Erromangine	XIV.c.1	*499*
	(+)-4-Hydroxydicentrine	IV.a.46	*499*
	(+)-Isostephodeline	XIV.c.2	*499*
	Oxocrebanine	IV.c.8	*499*
	(+)-Stephodeline	XIV.a.2.3	*499*
	(+)-Stesakine	IV.a.65	*499*
	(+)-Tannagine	XIV.a.2.2	*499*
	(+)-Zippelianine	XIV.a.2.4	*499*
	(+)-Zippeline	XIV.a.2.5	*499*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Strychnopsis thouarsii Baill.	7-*O*-Demethyltetrandrine	II.b.1.2.23	*348*
	Isocorydine	IV.a.47	*348*
	Liriotulipiferine	IV.a.37	*348*
	N-Methyllindcarpine	IV.a.50	*348*
	Predicentrine	IV.a.36	*348*
Synclisia scabrida Miers	Cocsoline	II.c.1.1.5	*500,501*
	Cocsuline	II.c.1.1.7	*500,501*
	Cycleanine	II.b.2.1.4	*500-502*
	Cycleanine N^2-oxide	II.b.2.1.5	*501*
	Norcycleanine	II.b.2.1.7	*501*
Telitoxicum glaziovii Moldenke	Lysicamine	IV.c.2	*503*
	O-Methylmoschatoline	IV.c.3	*503*
	Teladiazoline	IV.d.2	*503*
	Telazoline	IV.d.1	*503*
Telitoxicum krukovii Moldenke	7-Chloro-6-demethylcepharadione B	IV.b.17	*577*
	N-Demethyl-*N*-formyldehydronuciferine	IV.b.7	*577*
	N-Formyldehydroanonaine	IV.b.16	*577*
	N-Formylnuciferine	IV.a.73	*577*
	Telikovinone	IV.e.2	*577*
Telitoxicum peruvianum Moldenke	Lysicamine	IV.c.2	*504*
	Norrufescine	VI.4	*504*
	Peruvianine	IV.c.7	*504*
	Subsessiline	IV.c.6	*504*
	Telazoline	IV.d.1	*504*
	Telitoxine	VI.2	*504*
Tiliacora dinklagei Engl.	Alkaloid TD-2	CSND	*505*
	Dinklacorine	II.c.1.6.1	*506*
	Funiferine	II.c.1.6.3	*505*
	Juziphine	I.b.3	*507*
	Nortiliacorinine A	II.c.1.6.12	*505*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Oblongine	I.b.4	*507*
	1,2,3,4-Tetrahydro-7,8-dimethoxy-2-methyl-1-(4-hydroxybenzyl)-isoquinoline	I.b.15	*507*
	1,2,3,4-Tetrahydro-7-hydroxy-8-methoxy-2methyl-1-(4-methoxybenzyl)-isoquinoline	I.b.17	*507*
	1,2,3,4-Tetrahydro-7-hydroxy-8-methoxy-2-methyl-1-(4-hydroxybenzyl)-isoquinoline	I.b.16	*507*
	Tiliacorinine	II.c.1.6.10	*505*
	Tiliageine	II.b.1.6.2	*505*
Tiliacora funifera Engl. ex Diels	Funiferine	II.b.1.6.3	*508,509*
(= *T. warneckei)*	Funiferine dimethyliodide	II.b.1.6.5	*509-511*
	Funiferine *N*-oxide	II.b.1.6.4	*509*
	Isotetrandrine	II.b.1.2.30	*512*
	(+)-Isotetrandrine	II.b.1.2.30	*274,512*
	Nortiliacorinine A	II.c.1.6.12	*513*
	Oblongine	I.b.14	*274*
	Thalrugosine	II.b.1.2.39	*274,512*
	Tiliacorine	II.c.1.6.8	*513*
	Tiliafunimine	II.b.1.2.52	*274,512*
Tiliacora racemosa Colebr.	*N*-Acetylnortiliacorinine	II.c.1.6.15	*514*
	N-Acetyltiliamosine	II.c.1.6.6	*514*
	Corine	CSND	*515*
	Lotusine	I.b.7	*516*
	Magnocurarine	I.b.6	*516*
	Magnoflorine	IV.a.54	*516*
	N-Methyltiliamosine	II.c.1.6.5	*517-519*
	(+)-*N*-Methyltiliamosine	II.c.1.6.5	*520*
	Mohinine	CSND	*515*
	Mosine	CSND	*515*
	Nortiliacorinine A	II.c.1.6.12	*514,517,521*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Nortiliacorinine B	II.c.1.6.13	*522*
	Tiliacine	CSND	*515*
	Tiliacoridine	CSND	*523*
	Tiliacorine	II.c.1.6.8	*524*
	Tiliacorinine	II.c.1.6.10	*521,524*
	Tiliamosine	II.c.1.6.4	*514,517-519*
	Tiliaresine	II.c.1.6.17	*518,519*
	Tiliarine	II.c.1.6.16	*525*
Tiliacora triandra Diels	Alkaloid G	CSND	*526*
	Alkaloid H	CSND	*526*
	Dinklacorine	II.c.1.6.1	*527,528*
	Magnoflorine	IV.a.54	*529*
	Norisoyanangine	II.c.1.6.22	*529*
	Nortiliacorine A	II.c.1.6.9	*529*
	Nortiliacorinine A	II.c.1.6.12	*526,528,530-534*
	Noryanangine	II.c.1.6.21	*529*
	Tiliacorine	II.c.1.6.8	*526,528,530-534*
	Tiliacorinine	II.c.1.6.10	*526,528,530-534*
	Tiliacorinine 2'-*N*-oxide	II.c.1.6.11	*533*
	Tiliageine	II.b.1.6.2	*535*
	Tilianangine	II.c.1.6.20	*528*
	Tiliandrine	CSND	*536*
	Tilitriandrine	II.b.1.6.1	*535*
	Yanangcorinine	II.c.1.6.18	*532*
	Yanangine	II.c.1.6.19	*527*
Tinomiscium tonkinense Gagnep.	(-)-Isocorypalmine	X.b.13	*537*
	Magnoflorine	IV.a.54	*538*
Tinospora baenzigeri Forman	Berberine	X.a.4	*87*
	Jatrorrhizine	X.a.1	*87*
	Palmatine	X.a.3	*87*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Tembetarine	I.b.12	*87*
Tinospora capillipes Gagnep.	Columbamine	X.a.2	*539,540*
	Dehydrodiscretamine	X.a.8	*539,540*
	Jatrorrhizine	X.a.1	*539,540*
	Magnoflorine	IV.a.54	*539,540*
	Menisperine	IV.a.53	*539,540*
	Palmatine	X.a.3	*539,540*
	Stepharanine	X.a.5	*539,540*
Tinospora cordifolia Miers	Jatrorrhizine	X.a.1	*541*
	Magnoflorine	IV.a.54	*542*
	Tembetarine	I.b.12	*542*
Tinospora cordifolia (Willd.)	Palmatine	X.a.3	*87*
Hook. & Thoms.	Tembetarine	I.b.12	*87*
Tinospora crispa Miers	*N*-Acetylnornuciferine	IV.a.18	*543*
	N-Formylanonaine	IV.a.2	*543*
	N-Formylnornuciferine	IV.a.17	*543*
Tinospora crispa (L.) Hook. & Thoms.	Berberine	X.a.4	*87*
(= *T. masteri* Diels = *T. tuberculata* (Lam.)	Jatrorrhizine	X.a.1	*87*
Beaumée ex K. Heyne; = *T. rumphii* Boerl.)	Palmatine	X.a.3	*87*
	Tembetarine	I.b.12	*87*
Tinospora dentata Diels	Jatrorrhizine	X.a.1	*544*
	Palmatine	X.a.3	*544*
Tinospora glabra (Burm. F.) Merr.	Berberine	X.a.4	*87*
	Jatrorrhizine	X.a.1	*87*
	Palmatine	X.a.3	*87*
	Tembetarine	I.b.12	*87*
Tinospora malabarica Miers	*N*-Formylanonaine	IV.a.2	*545*
	Kokusaginine	XXIII.4	*76,546*
	Magnoflorine	IV.a.54	*547*
	Palmatine	X.a.3	*548*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
Tinospora merriliana Diels	Berberine	X.a.4	*87*
	Jatrorrhizine	X.a.1	*87*
	Palmatine	X.a.3	*87*
	Tembetarine	I.b.12	*87*
Tinospora sagittata Gagnep.	Palmatine	X.a.3	*87*
Tinospora sinensis (Lour.) Merr. (= *T. tomentosa* (Colebr.) Hook. & Thoms. = *T. malabarica* (Lam.) Hook. & Thoms.	Palmatine	X.a.3	*87*
Tinospora smilacina	Berberine	X.a.4	*87*
	Palmatine	X.a.3	*87*
	Tembetarine	I.b.12	*87*
Tinospora tuberculata Beaumée (= *T. crispa* Diels)	*N-cis*-Feruloyltyramine	XXI.2	*549,550*
	N-trans-Feruloyltyramine	XXI.1	*549,550*
Triclisia dictyophylla Diels	Cocsuline	II.c.1.1.7	*551*
	Tridictiophylline	XIV.c.3	*551,552*
	Trigilletimine	II.c.1.1.17	*551*
Triclisia gilletii (De Wild.) Staner	Cocsuline	II.c.1.1.7	*553*
	Gilletine	II.c.1.3.3	*554-556*
	Isogilletine *N*-oxide	II.c.1.3.4	*555*
	Isotetrandrine	II.b.1.2.30	*557*
	Obamegine	II.b.1.2.44	*555*
	Stebyssimine	II.b.1.1.34	*555*
	Triclisine	VI.1	*558*
	Tridictiophylline	XIV.c.3	*559*
	Trigilletimine	II.c.1.1.17	*560*
Triclisia patens Oliv.	Aromoline	II.b.1.1.14	*561,562*
	Cocsuline	II.c.1.1.7	*561*
	Homomoschatoline	IV.c.3	*562*
	Phaeanthine	II.b.1.2.20	*561,563*
	Pycnamine	II.b.1.2.36	*561*

(*Continues*)

Table VI (*Continued*)

Plant Species	Alkaloids	Locator code	References
	Thalicrine	II.b.1.1.14	*565*
	Trigilletimine	II.c.1.1.17	*561*
Triclisia subcordata Oliv.	Alkaloid A	CSND	*347*
	Alkaloid B	CSND	*347*
	Magnoflorine	IV.a.54	*344,347*
	12-*O*-Methylatherospermoline	II.b.1.2.1	*229*
	Palmatine	X.a.3	*344,347*
	Tetrandrine	II.b.1.2.14	*562*
	Tricordatine	II.c.1.1.15	*508*

CSND = Chemical structure not defined.

TABLE VII

Number of occurrences of each type of alkaloids by genus (according to Table VI).

	GENUS (Number of species)	TYPE																						TOTAL
		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII	
		BIQ	BIS-BIQ	PROAPO	APORPHIN	TROPOL	AZAFLU	PHENANT	ARISTO	ISOXOA	PROTOB	HIRSUTI	COHIRSI	BENZAZE	MORPHIN	HASUBA	ACUTUMI	ERIBIDI	ERYTHRIN	PAVINE	ISOQUIN	PHENETHYL	OXOCAN	OTHERS	
01	*Abuta (9)*	01	18	01	07	03	06				02			02							01				41
02	*Albertisia (2)*		26																						26
03	*Anamirta (1)*			01	01						05														07
04	*Anisocycla (2)*		28		03			01			05														39
05	*Antizoma (1)*														01										01
06	*Arcangelisia (2)*		02								14										01			01	18
07	*Burasaia (3)*	01									06														07
08	*Caryomene (2)*	01	05	04							07														17
09	*Chasmanthera (1)*				10						07				01					01					19
10	*Chondodendron (3)*		11																						11
11	*Cissampelos (5)*	01	18		08	06	02				02				01								01		37
12	*Cocculus (7)*	07	63	02	12				01		05	05	04		05			03	25	01				02	135
13	*Coscinium (2)*				01						15														16
14	*Curarea (1)*		13																						13
15	*Cyclea (11)*	04	87		06						05									02					104
16	*Dioscoreophyllum (1)*				01						03														04
17	*Diploclisia (1)*			01	01																				02
18	*Epinetrum (2)*		03																						03
19	*Fibraurea (4)*				01						21														22
20	*Heptacyclum (1)*				01						03														04
21	*Hyperbaena (1)*										01							01	02						04
22	*Jateorrhiza (1)*										05														05
23	*Kolobopetalum (1)*				04										01										05
24	*Legnephora (1)*			02	03						01														06
25	*Limacia (1)*			01	04												02								07
26	*Limaciopsis (1)*		09		01						01														11

(Continues)

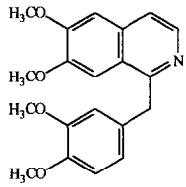
Table VII (*Continued*)

	GENUS (Number of species)	TYPE I BIQ	II BIS-BIQ	III PROAPO	IV APORPHIN	V TROPOL	VI AZAFLU	VII PHENANT	VIII ARISTO	IX ISOOXOA	X PROTOB	XI HIRSUTI	XII COHIRSI	XIII BENZAZE	XIV MORPHIN	XV HASUBA	XVI ACUTUMI	XVII ERIBIDI	XVIII ERYTHRIN	XIX PAVINE	XX ISOQUIN	XXI PHENETHYL	XXII OXOCAN	XXIII OTHERS	TOTAL
27	*Menispermum (2)*		11	01	03					08	04				01		05				02				35
28	*Pachygone (3)*	06	29	01	05						02								01						44
29	*Parabaena (3)*	03									07														10
30	*Penianthus (1)*				01						04											01			06
31	*Pycnarrhena (5)*		34		03																				37
32	*Rhigiocarya (1)*				03						01				02										06
33	*Sarcopetalum (1)*	01		01																					02
34	*Sciadotenia (2)*	01	06	01																					08
35	*Sinomenium (2)*		07		06					01	06				06		02					01			29
36	*Sphenocentrum (1)*										03														03
37	*Spirospermum (1)*		01																						01
38	*Stephania (43)*	18	171	14	188			01	03		112				43	78		03			01	01	04		637
39	*Strychnopsis (1)*		01		04																				05
40	*Synclisia (1)*		05																						05
41	*Telitoxicum (2)*				13		02																		15
42	*Tiliacora (4)*	08	38		02																				48
43	*Tinomiscium (1)*				01						01														02
44	*Tinospora (15)*	07			08						26											02		01	44
45	*Triclisia (4)*		18		02		01				01				02										24
	TOTAL (160)	59	604	30	303	09	11	02	04	09	275	05	04	02	63	78	09	07	28	04	05	05	05	04	1.525

This table does not show the CSND alkaloids.

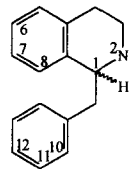
Type I
Benzylisoquinoline Alkaloids

Sub-type I.a - 1-benzylisoquinoline Alkaloids.



I.a = Papaverine

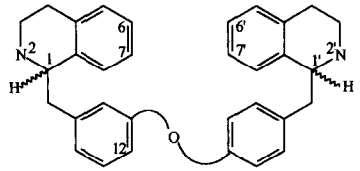
Table VIII. Sub-type I.b - 1-benzyltetrahydroisoquinoline Alkaloids.



I.b	1	2	6	7	8	10	11	12
I.b.1	β	H	OMe	OH	H	H	H	OH
I.b.2	β	Me	OMe	OH	H	H	H	OH
I.b.3	β	Me	H	OMe	OH	H	H	OH
I.b.4	β	H	H	OMe	OH	H	H	OH
I.b.5	β	Me	OMe	OMe	H	H	OH	OMe
I.b.6	β	$(CH_3)_2$	OMe	OH	H	H	H	OH
I.b.7	β	$(CH_3)_2$	OH	OMe	H	H	H	OH
I.b.8	α	Me	OMe	OMe	H	H	OMe	OMe
I.b.9	α	Me	OMe	OH	H	H	OH	OMe
I.b.10	α	Me, oxide	OMe	OH	H	H	OH	OMe
I.b.11	α	Me	OMe	OH	H	H	OMe	OMe
I.b.12	α	$(CH_3)_2$	OMe	OH	H	H	OH	OMe
I.b.13	α	$(CH_3)_2$	OMe	OMe	H	OMe	H	OH
I.b.14	α	$(CH_3)_2$	H	OMe	OH	H	H	OH
I.b.15	-	Me	H	OMe	OMe	H	H	OH
I.b.16	-	Me	H	OH	OMe	H	H	OH
I.b.17	-	Me	H	OH	OMe	H	H	OMe
I.b.18	α	Me	OMe	OMe	H	H	OH	OMe
I.b.19	β	Me	OH	OMe	H	H	OH	OMe

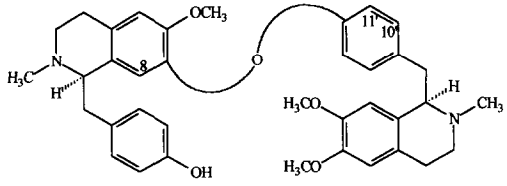
Type II
Bisbenzylisoquinoline Alkaloids

Table IX. Sub-type II.a.1.1 - Bisbenzylisoquinolinine Alkaloids Bonded Tail to Tail and Bearing One Joint.



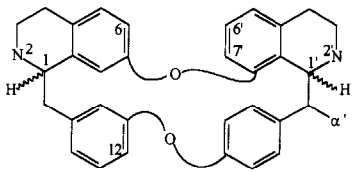
II.a.1.1	Note	1	2	6	7	12	1'	2'	6'	7'
II.a.1.1.1	-	R	Me	OMe	OMe	OH	R	Me	OMe	OMe
II.a.1.1.2	-	R	Me	OMe	OMe	OH	R	H	OMe	OMe
II.a.1.1.3	-	R	Me	OMe	OMe	OH	R	Me	OH	OMe
II.a.1.1.4	-	R	Me	OMe	OH	OH	R	Me	OMe	OMe
II.a.1.1.5	-	R	Me	OMe	OH	OH	R	H	OMe	OMe
II.a.1.1.6	-	R	Me	OH	OMe	OH	R	Me	OH	OMe
II.a.1.1.7	-	R	Me	H	OMe	OH	R	Me	OMe	OMe
II.a.1.1.8	-	R	H	OMe	OH	OH	R	H	OMe	OH
II.a.1.1.9	-	R	Me	OMe	OH	OH	R	H	OMe	OH
II.a.1.1.10	-	R	H	OMe	OH	OH	R	Me	OMe	OH
II.a.1.1.11	-	R	Me	OMe	OH	OH	R	Me	OMe	OH
II.a.1.1.12	(+)-form	R	Me	OMe	OH	OH	S	Me	OMe	OH
II.a.1.1.13	(-)-form	S	Me	OMe	OH	OH	R	Me	OMe	OH
II.a.1.1.14	(-)-form	S	Me	OMe	OH	OMe	R	Me	OMe	OH

Table X. Sub type II.a.2.1 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail and Bearing One Joint.



II.a.2.1	8	10'	11'
II.a.2.1.1	OH	H	H
II.a.2.1.2	H	OH	H
II.a.2.1.3	H	H	OH

Table XI. Sub-type II.b.1.1 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Two Joints (7-8' and 11-12').



II.b.1.1	Note	1	2	6	12	1'	2'	6'	7'	α'
II.b.1.1.1	-	R	Me	OMe	OMe	S	Me	OCH_2O		H
II.b.1.1.2	*N* '-oxide (β-)	R	Me	OMe	OMe	S	Me, oxide	OCH_2O		H
II.b.1.1.3	O^{12}-de-Me	R	Me	OMe	OH	S	Me	OCH_2O		H
II.b.1.1.4	*N*-de-Me	R	H	OMe	OMe	S	Me	OCH_2O		H
II.b.1.1.5	*N* '-de-Me	R	Me	OMe	OMe	S	H	OCH_2O		H
II.b.1.1.6	O^{12}, *N*-di- de-Me	R	H	OMe	OH	S	Me	OCH_2O		H
II.b.1.1.7	*N*-de-Me, 1-epimer	S	H	OMe	OMe	S	Me	OCH_2O		H
II.b.1.1.8	-	R	Me	OMe	OMe	S	Me	OMe	OMe	H
II.b.1.1.9	*N* ' de-Me	R	Me	OMe	OMe	S	H	OMe	OMe	H
II.b.1.1.10	*N*-de-Me	R	H	OMe	OMe	S	Me	OMe	OMe	H
II.b.1.1.11	*N*-de-Me, *N* ' β oxide	R	H	OMe	OMe	S	Me oxide	OMe	OMe	H

(*Continues*)

Table XI (*Continued*)

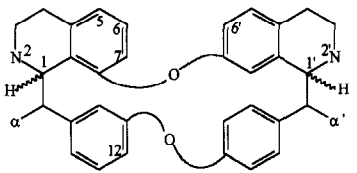
II.b.1.1	Note	1	2	6	12	1'	2'	6'	7'	α'
II.b.1.1.12	-	R	H	OMe	OMe	S	Me	OMe	OH	H
II.b.1.1.13	-	R	H	OMe	OH	S	Me	OMe	OH	H
II.b.1.1.14	-	R	Me	OMe	OH	S	Me	OMe	OH	H
II.b.1.1.15	*N*,*N*'-di-de-Me	R	H	OMe	OH	S	H	OMe	OH	H
II.b.1.1.16	-	R	Me	OMe	OMe	S	Me	OMe	OH	H
II.b.1.1.17	(-)form	S	Me	OMe	OH	R	Me	OMe	OH	H
II.b.1.1.18	*N*'-de-Me	S	Me	OMe	OH	R	$(Me)_2$	OMe	OH	H
II.b.1.1.19	-	R	Me	OMe	OH	S	Me	OMe	OMe	H
II.b.1.1.20	(+)form	R	Me	OMe	OMe	R	Me	OMe	OH	H
II.b.1.1.21	*N*-de-Me	R	H	OMe	OMe	R	Me	OMe	OH	H
II.b.1.1.22	1,2-didehydro	-	-	OMe	OMe	R	Me	OMe	OH	H
II.b.1.1.23	O^{12}-de-Me	R	Me	OMe	OH	R	Me	OMe	OH	H
II.b.1.1.24	(-)form	S	Me	OMe	OMe	S	Me	OMe	OH	H
II.b.1.1.25	1',2',3',4'-tetradehydro	R	Me	OMe	OMe	-	Me	OMe	OH	H
II.b.1.1.26	-	R	H	OMe	OH	R	H	OMe	OH	H
II.b.1.1.27	1',2'-didehydro	R	H	OMe	OH	-	-	OMe	OH	H
II.b.1.1.28	1',2',3',4'-tetradehydro	R	H	OMe	OH	-	-	OMe	OH	H
II.b.1.1.29	-	S	Me	OMe	OMe	R	Me	OH	OMe	H
II.b.1.1.30	-	S	Me	OMe	OH	S	Me	OMe	OMe	H
II.b.1.1.31	1,2-didehydro	-	-	OMe	OMe	S	Me	OMe	OMe	H
II.b.1.1.32	1',2'-didehydro	R	Me	OMe	OMe	-	-	OMe	OMe	H

(*Continues*)

Table XI (*Continued*)

II.b.1.1	**Note**	**1**	**2**	**6**	**12**	**1'**	**2'**	**6'**	**7'**	**α'**
II.b.1.1.33	1',2'-didehydro O^{12}-de-Me	R	Me	OMe	OH	-	-	OMe	OMe	H
II.b.1.1.34	1,1',2,2'-tetradehydro	-	-	OMe	OMe	-	-	OMe	OMe	H
II.b.1.1.35	1',2'-didehydro	undef.	Me	OMe	OMe	-	-	OMe	OMe	=O
II.b.1.1.36	1',2',3',4'-tetradehydro	R	Me	OMe	OMe	-	-	OMe	OH	H
II.b.1.1.37	1',2',3',4'-tetradehydro, *N*-de-Me	R	H	OMe	OMe	-	-	OMe	OH	H
II.b.1.1.38	1',2',3',4'-tetradehydro, *N'*-Me	R	Me	OMe	OMe	-	Me	OMe	OH	H
II.b.1.1.39	1',2',3',4'-tetradehydro, 1,2-didehydro, *N*-de-Me	-	-	OMe	OMe	-	-	OMe	OH	H
II.b.1.1.40	-	R	Me	OMe	OMe	-	-	OMe	OH	H
II.b.1.1.41	-	S	Me	OMe	OMe	R	Me	OMe	OH	H
II.b.1.1.42	2'-β-*N*-oxide	R	Me	OMe	OMe	R	Me oxide	OMe	OH	H

Table XII – Sub-type II.b.1.2 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Two Joints (8-7' and 11-12').



II.b.1.2	Note	1	2	5	6	7	12	1'	2'	6'	α	α'
II.b.1.2.1	(+)form	S	Me	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.2	*N*-Me	S	$(Me)_2$	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.3	*N'*-α-oxide	S	Me	H	OMe	OH	OMe	S	Me α-oxide	OMe	H	H
II.b.1.2.4	*N'*-β-oxide	S	Me	H	OMe	OH	OMe	S	Me β-oxide	OMe	H	H
II.b.1.2.5	1,3,4-tridehydro	-	Me	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.6	(-)form	R	Me	H	OMe	OH	OMe	R	Me	OMe	H	H
II.b.1.2.7	*N'*-α-oxide	R	Me	H	OMe	OH	OMe	R	Me α-oxide	OMe	H	H
II.b.1.2.8	*N*-β-oxide	R	Me β-oxide	H	OMe	OH	OMe	R	Me	OMe	H	H
II.b.1.2.9	*N'*-β-oxide	R	Me	H	OMe	OH	OMe	R	Me β-oxide	OMe	H	H
II.b.1.2.10	*N*-de-Me	R	H	H	OMe	OH	OMe	R	Me	OMe	H	H
II.b.1.2.11	(±)form	undef.	Me	H	OMe	OH	OMe	undef.	Me	OMe	H	H
II.b.1.2.12	1',3',4'-tridehydro	undef.	Me	H	OMe	OMe	OMe	-	-	OMe	H	=O
II.b.1.2.13	*N'*-de-Me	S	Me	H	OMe	OH	OMe	S	H	OMe	H	H
II.b.1.2.14	(+)form	S	Me	H	OMe	OMe	OMe	S	Me	OMe	H	H

(*Continues*)

Table XII (*Continued*)

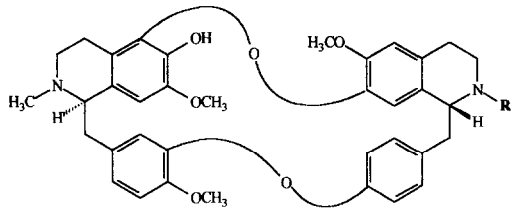
II.b.1.2	Note	1	2	5	6	7	12	1'	2'	6'	α	α'
II.b.1.2.15	*N*-β-oxide	S	Me β-oxide	H	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.16	*N'*-oxide	S	Me	H	OMe	OMe	OMe	S	Me oxide	OMe	H	H
II.b.1.2.17	*N*-Me	S	$(Me)_2$	H	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.18	*N*-Chloro-methyl	S	Me CH_2Cl	H	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.19	*N*, *N'* bis (chlo-romethyl)	S	Me CH_2Cl	H	OMe	OMe	OMe	S	Me CH_2Cl	OMe	H	H
II.b.1.2.20	(-)form	R	Me	H	OMe	OMe	OMe	R	Me	OMe	H	H
II.b.1.2.21	*N'*-α-oxide	R	Me	H	OMe	OMe	OMe	R	Me α-oxide	OMe	H	H
II.b.1.2.22	*N*, *N'*-di-de-Me	R	H	H	OMe	OMe	OMe	R	H	OMe	H	H
II.b.1.2.23	-	S	Me	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.24	*N'*-oxide	R	Me	H	OMe	OMe	OMe	S	Me oxide	OMe	H	H
II.b.1.2.25	*N*, *N'*-di-de-Me	S	H	H	OMe	OMe	OMe	S	H	OMe	H	H
II.b.1.2.26	*N'*-chloromethyl	R	Me	H	OMe	OMe	OMe	undef.	Me CH_2Cl	OMe	H	H
II.b.1.2.27	*N'*-Me	S	Me	H	OMe	OMe	OMe	undef.	$(Me)_2$	OMe	H	H
II.b.1.2.28	*N*, *N'*-di-di-Me Iodide	S	$(Me)_2$	H	OMe	OH	OH	S	$(Me)_2$	OMe	H	H
II.b.1.2.29	(-)form	R	Me	H	OMe	OH	OH	R	Me	OMe	H	H
II.b.1.2.30	-	R	Me	H	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.31	*N'*-oxide	R	Me	H	OMe	OMe	OMe	S	Me oxide	OMe	H	H
II.b.1.2.32	*N'*-de-Me	R	Me	H	OMe	OMe	OMe	S	H	OMe	H	H
II.b.1.2.33	*N'*-Me	R	Me	H	OMe	OMe	OMe	S	$(Me)_2$	OMe	H	H
II.b.1.2.34	*N*-de-Me	R	H	H	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.35	O^6-de-Me	R	Me	H	OH	OMe	OMe	S	Me	OMe	H	H

(*Continues*)

Table XII (*Continued*)

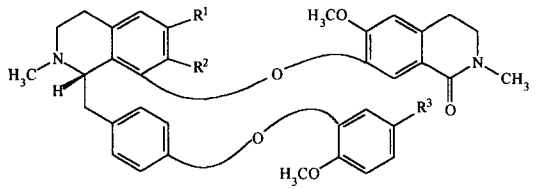
II.b.1.2	Note	1	2	5	6	7	12	1'	2'	6'	α	α'
II.b.1.2.36	(-)form	R	Me	H	OMe	OMe	OH	R	Me	OMe	H	H
II.b.1.2.37	(+)form	S	Me	H	OMe	OMe	OH	S	Me	OMe	H	H
II.b.1.2.38	*N*-de-Me	S	H	H	OMe	OMe	OH	S	Me	OMe	H	H
II.b.1.2.39	-	R	Me	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.40	*N*-de-Me	R	H	H	OMe	OH	OMe	S	Me	OMe	H	H
II.b.1.2.41	*N*, *N'* di-de-Me	R	H	H	OMe	OH	OMe	S	H	OMe	H	H
II.b.1.2.42	-	S	Me	H	OMe	OMe	OMe	S	H	OMe	H	H
II.b.1.2.43	*N*, *N'* di-di-Me	S	$(Me)_2$	H	OMe	OMe	OMe	S	H	OMe	H	H
									Me			
II.b.1.2.44	-	R	Me	H	OMe	OH	OH	S	Me	OMe	H	H
II.b.1.2.45	*N*, *N'* di-de-Me	R	H	H	OMe	OH	OH	S	H	OMe	H	H
II.b.1.2.46	1,3,4-tridehydro	-	-	H	OMe	OH	OH	S	Me	OMe	H	H
II.b.1.2.47	-	R	Me	H	OMe	OMe	OH	S	Me	OMe	H	H
II.b.1.2.48	1,3,4-tridehydro	-	Me	H	OMe	OH	OMe	R	Me	OMe	H	H
II.b.1.2.49	1-dehydro	-	-	H	OMe	OMe	OH	S	Me	OMe	=O	H
II.b.1.2.50	1,3,4-tridehydro	-	-	H	OMe	OH	OMe	R	Me	OMe	H	H
II.b.1.2.51	*N'*-chloromethyl	S	Me	H	OMe	OMe	OMe	S	Me	OMe	H	H
									CH_2Cl			
II.b.1.2.52	1-dehydro	-	-	H	OMe	OH	OMe	undef.	Me	OMe	H	H
II.b.1.2.53	(-)form	S	H	H	OMe	OH	OH	R	Me	OMe	H	H
II.b.1.2.54	O^7-Me	S	H	H	OMe	OMe	OH	R	Me	OMe	H	H
II.b.1.2.55	*N*-Me	S	Me	H	OMe	OH	OH	R	Me	OMe	H	H
II.b.1.2.56	(+)form	R	H	H	OMe	OH	OH	S	Me	OMe	H	H
II.b.1.2.57	O^7-Me	R	H	H	OMe	OMe	OH	S	Me	OMe	H	H
II.b.1.2.58	-	S	Me	OMe	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.59	-	S	$(Me)_2$	OMe	OMe	OMe	OMe	S	Me	OMe	H	H
II.b.1.2.60	*N'*-de-Me	R	Me	H	OMe	OH	OMe	R	H	OMe	H	H
II.b.1.2.61	(+)form	S	Me	H	OMe	OH	OH	S	Me	OMe	H	H

Sub-type II.b.1.3 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Two Joints (5-7' and 11-12').



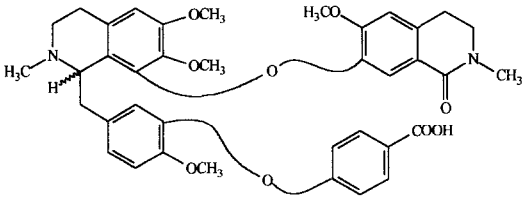
II.b.1.3.1 R = Me
II.b.1.3.2 R = H

Table XIII. Sub-type II.b.1.4 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail, Bearing TwoJoints and With the Bond α'-1' Broken (seco).



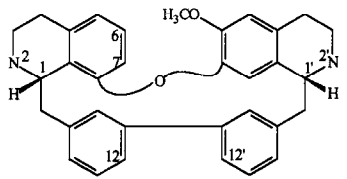
II.b.1.4	R^1	R^2	R^3
II.b.1.4.1	OCH_2O		CH_2OH
II.b.1.4.2	OCH_2O		CHO
II.b.1.4.3	OMe	OH	CHO

Sub type II.b.1.5 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail, Bearing Two Joints and Having the Bond α'-1' Broken (seco).



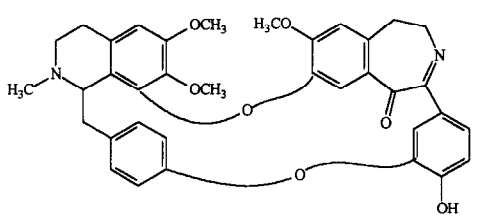
II.b.1.5.1 Stereochemistry of H1 = R
II.b.1.5.2 Stereochemistry of H1 is undefined

Table XIV. Sub-type II.b.1.6 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail, Bearing Two Bonds (8-7' and 11-11') and Having no Oxygen in the Bridge 11-11'.

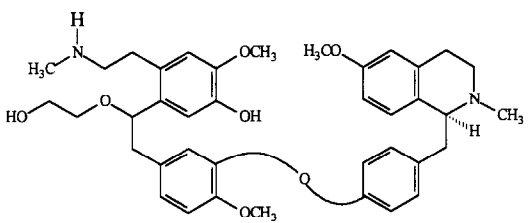


II.b.1.6	Note	2	6	7	12	2'	12'
II.b.1.6.1	*N* de-Me	H	OMe	OH	OMe	Me	OH
II.b.1.6.2	-	Me	OMe	OH	OH	Me	OMe
II.b.1.6.3	O^7 Me	Me	OMe	OMe	OH	Me	OMe
II.b.1.6.4	O^7 Me, *N* oxide	Me, oxide	OMe	OMe	OH	Me	OMe
II.b.1.6.5	-	$(Me)_2$ I	OMe	OMe	OH	$(Me)_2$ I	OMe

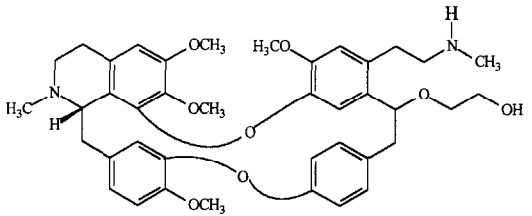
Sub type II.b.1.7 - Miscellaneous Bisbenzylisoquinoline Alkaloids.



II.b.1.7.1

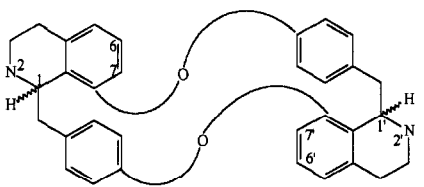


II.b.1.7.2



II.b.1.7.3

Table XV. Sub-type II.b.2.1 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail and Bearing Two Joints (8-12' and 12-8').



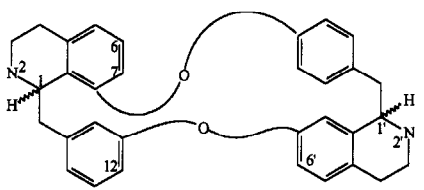
II.b.2.1	Note	1	2	6	7	1'	2'	6'	7'
II.b.2.1.1	-	R	Me	OMe	OH	R	Me	OMe	OH
II.b.2.1.2	-	undef.	Me	OH	OMe	undef.	Me	OMe	OH
II.b.2.1.3	* 6,7 or 6',7' positional isomer of protocuridine	undef	Me	*OH	*OMe	undef	Me	*OMe	*OH

(*Continues*)

Table XV (*Continued*)

II.b.2.1	Note	1	2	6	7	1'	2'	6'	7'
II.b.2.1.4	-	R	Me	OMe	OMe	R	Me	OMe	OMe
II.b.2.1.5	*N* oxide	R	Me oxide	OMe	OMe	R	Me	OMe	OMe
II.b.2.1.6	*N'* de-Me	R	Me	OMe	OMe	R	H	OMe	OMe
II.b.2.1.7	O^7 de-Me	R	Me	OMe	OH	R	Me	OMe	OMe
II.b.2.1.8	1,3,4-Tridehydro	-	-	OMe	OH	R	Me	OMe	OMe
II.b.2.1.9	3,4-Dihydro	-	-	OMe	OH	R	Me	OMe	OMe
II.b.2.1.10	-	R	Me	OMe	OMe	S	Me	H	H
II.b.2.1.11	-	R	Me	OMe	OMe	S	Me	OMe	H
II.b.2.1.12	-	S	Me	OMe	OH	R	Me	OMe	OMe
II.b.2.1.13	3,4-Dehydro	R	Me	OMe	OMe	R	Me	OMe	OMe

Table XVI. Sub-type II.b.2.2 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail and Bearing Two Joints (8-12' and 11-7').



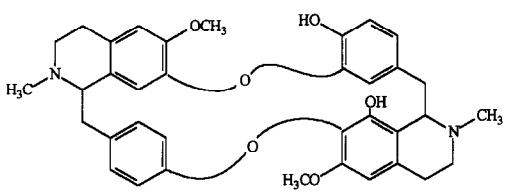
II.b.2.2	Note	1	2	6	7	12	1'	2'	6'
II.b.2.2.1	-	S	Me	OCH_2O		OH	R	Ac	OMe
II.b.2.2.2	12-Me-ether	S	Me	OCH_2O		OMe	R	Ac	OMe
II.b.2.2.3	1-epimer	R	Me	OCH_2O		OH	R	Ac	OMe
II.b.2.2.4	1-epimer, 12-Me-ether	R	Me	OCH_2O		OMe	R	Ac	OMe

(*Continues*)

Table XVI (*Continued*)

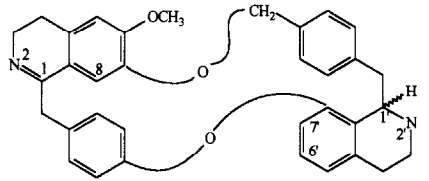
II.b.2.2	Note	1	2	6	7	12	1'	2'	6'
II.b.2.2.4	1-epimer, 12-Me-ether	R	Me	OCH_2O		OMe	R	Ac	OMe
II.b.2.2.5	(+)form	R	$(Me)_2$	OMe	OH	OH	S	H, Me	OMe
II.b.2.2.6	Dichloride	R	$(Me)_2$	OMe	OH	OH	S	H, Me	OMe
II.b.2.2.7	(+)form	R	Me	OMe	OH	OH	S	Me	OMe
II.b.2.2.8	*N'* de-Me	R	Me	OMe	OH	OH	S	H	OMe
II.b.2.2.9	O^{12} Me	R	Me	OMe	OH	OMe	S	Me	OMe
II.b.2.2.10	(±)form of 12-*O*-Methylcurine	S	Me	OMe	OH	OMe	S	Me	OMe
II.b.2.2.11	(+)form	S	Me	OMe	OH	OH	S	Me	OMe
II.b.2.2.12	O^7 Me	S	Me	OMe	OMe	OH	S	Me	OMe
II.b.2.2.13	$O^{6'}$ de-Me, (-)form	R	Me	OMe	OMe	OH	R	Me	OH
II.b.2.2.14	(±)form of curine	S	Me	OMe	OH	OH	S	Me	OMe
II.b.2.2.15	*N,N'* di-Me, (±)-form of curine	S	$(Me)_2$	OMe	OH	OH	S	$(Me)_2$	OMe

Sub-type II.b.2.3 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail and Bearing Two Joints (7-11' and 12-7').



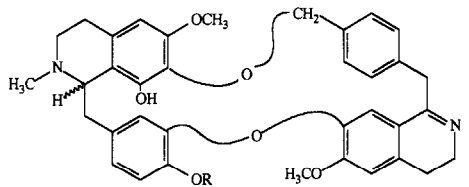
II.b.2.3.1

Table XVII. Sub-type II.b.2.4 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail, Bearing Two Joints (7-12' and 12-8') and Having a CH_2 in One of the Joints.



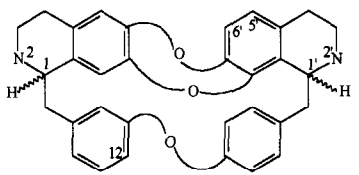
II.b.2.4	Note	1	2	8	1'	2'	6'	7'
II.b.2.4.1	-	-	-	OH	R	Me	OMe	OH
II.b.2.4.2	1,2 dihydro	undef.	H	OH	R	Me	OMe	OH
II.b.2.4.3	1,2 dihydro, Me ether	undef.	Me	OH	R	Me	OMe	OH
II.b.2.4.4	7' Me-ether	-	-	OH	R	Me	OMe	OMe
II.b.2.4.5	di-Me-ether	-	-	OMe	R	Me	OMe	OMe
II.b.2.4.6	di-hydro, di-Me-ether	undef.	H	OMe	R	Me	OMe	OMe
II.b.2.4.7	1-hydro, 2-Me	R	Me	OH	R	Me	OMe	OMe
II.b.2.4.8	(1R, 1'S) form	R	Me	OH	S	Me	OMe	OMe

Sub type II.b.2.5 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail, Bearing Two Joints (7-12' and 11-7') and Having a CH_2 in One of the Joints.



II.b.2.5.1 R = H
II.b.2.5.2 R = Me

Table XVIII. Sub-type II.c.1.1 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (6-7', 7-8' and 11-12').



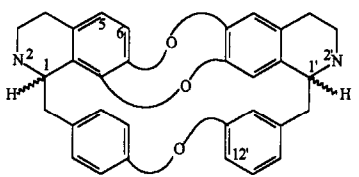
II.c.1.1	Note	1	2	12	1'	2'	5'	6'
II.c.1.1.1	-	S	Me	OMe	S	H	H	OMe
II.c.1.1.2	O^{12} de-Me	S	Me	OH	S	H	H	OMe
II.c.1.1.3	*N* de Me	S	H	OMe	S	H	H	OMe
II.c.1.1.4	*N'* Me	S	Me	OMe	S	Me	H	OMe
II.c.1.1.5	-	S	H	OH	S	Me	H	OMe
II.c.1.1.6	Me ether	S	H	OMe	S	Me	H	OMe
II.c.1.1.7	*N* Me	S	Me	OH	S	Me	H	OMe
II.c.1.1.8	*N* Me, *N* oxide	S	Me, oxide	OH	S	Me	H	OMe
II.c.1.1.9	*N* Me, *N'* de-Me	S	Me	OH	S	H	H	OMe
II.c.1.1.10	*N'* β-oxide	S	H	OH	S	Me, β-oxide	H	OMe
II.c.1.1.11	*N'* β-oxide, Me-ether	S	H	OMe	S	Me, β-oxide	H	OMe
II.c.1.1.12	-	S	H	OH	S	H	H	OMe
II.c.1.1.13	1,2 di-dehydro, 5' hydroxy	-	-	OMe	S	Me	OH	OMe
II.c.1.1.14	-	R	Me	OMe	S	Me	H	OMe
II.c.1.1.15	-	S	Me	OH	S	Me	H	OH
II.c.1.1.16	*N* de-Me, 1,2-dehydro	-	-	OH	S	Me	H	OH

(*Continues*)

Table XVIII (*Continued*)

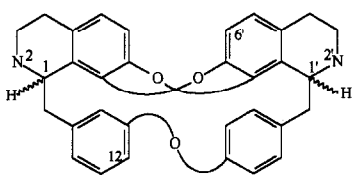
II.c.1.1	Note	1	2	12	1'	2'	5'	6'
II.c.1.1.17	1',3',4'-tridehydro	S	Me	OMe	-	-	H	OMe
II.c.1.1.18	-	R	H	OH	S	Me	H	OMe
II.c.1.1.19	*N* Me	R	Me	OH	S	Me	H	OMe
II.c.1.1.20	1,2-dehydro	-	-	OH	S	Me	H	OMe
II.c.1.1.21	5' hydroxy	R	H	OH	S	Me	OH	OMe
II.c.1.1.22	1,2-di-dedhydro, Me-ether	-	-	OMe	S	Me	H	OMe
II.c.1.1.23	Me-ether, 1,2-di-dehydro, *N'* de-Me	-	-	OMe	S	H	H	OMe
II.c.1.1.24	Me-ether, 5' hydroxy	R	H	OMe	S	Me	OH	OMe
II.c.1.1.25	-	S	H	OMe	S	Me	OH	OMe
II.c.1.1.26	-	S	H	OMe	S	Me	H	OMe

Table XIX. Sub-type II.c.1.2 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (7-6', 8-7' and 12-11').



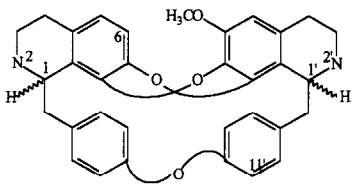
II.c.1.2	Note	1	2	5	6	1'	2'	12'
II.c.1.2.1	-	S	Me	OH	OMe	S	H	OH
II.c.1.2.2	$O^{12'}$ Me	S	Me	OH	OMe	S	H	OMe
II.c.1.2.3	1',2'-di-dehydro	S	Me	OH	OMe	-	-	OH
II.c.1.2.4	1',2'-di-dehydro, $O^{12'}$ Me	S	Me	OH	OMe	-	-	OMe
II.c.1.2.5	1',2'-di-dehydro, di-Me-ether, *N* de-Me	S	H	OMe	OMe	-	-	OMe
II.c.1.2.6	1', 2'-di-dehydro, *N*'-β-oxide	S	Me, oxide	OH	OMe	-	-	OH
II.c.1.2.7	1',2',3',4'-tetradehydro	S	Me	OH	OMe	-	-	OH
II.c.1.2.8	1',2',3',4'-tetradehydro $O^{12'}$ Me	S	Me	OH	OMe	-	-	OMe
II.c.1.2.9	*N* oxide	S	Me, oxide	H	OMe	S	Me	OMe

Table XX. Sub-type II.c.1.3 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (7-8', 8-7' and 11-12').



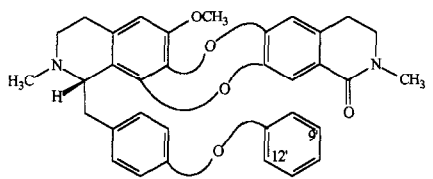
II.c.1.3	Note	1	2	12	1'	2'	6'
II.c.1.3.1	-	S	Me	OH	S	Me	OH
II.c.1.3.2	1,2-di-dehydro	-	-	OH	S	H	OMe
II.c.1.3.3	-	S	Me	OMe	S	H	OH
II.c.1.3.4	*N*-oxide	S	Me, oxide	OMe	S	H	OH
II.c.1.3.5	-	S	Me	OMe	S	H	OMe
II.c.1.3.6	1,2-di-dehydro	S	Me	OMe	-	-	OMe
II.c.1.3.7	-	S	Me	OH	S	H	OMe

Table XXI. Sub-type II.c.1.4 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (7-8', 8-7' and 12-12').



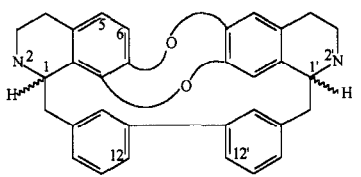
II.c.1.4	2	6	2'	11'
II.c.1.4.1	Me	OMe	H	OH
II.c.1.4.2	H	OH	H	OH
II.c.1.4.3	Me	OMe	Me	OH
II.c.1.4.4	Me	OH	H	OH
II.c.1.4.5	Me	OMe	Me	OMe

Table XXII. Sub-type II.c.1.5 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail, Bearing Three Joints (7-6', 8-7' and 12-11') and Having the Bond α'-1' Broken (seco).



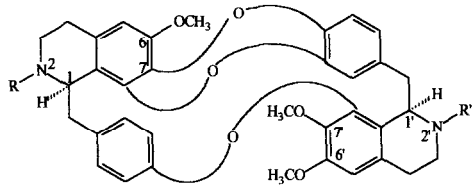
II.c.1.5	9'	12'
II.c.1.5.1	CHO	OH
II.c.1.5.2	CHO	OMe
II.c.1.5.3	Me	OMe
II.c.1.5.4	CH_2OH	OMe

Table XXIII. Sub-type II.c.1.6 - Bisbenzylisoquinoline Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (7-6', 8-7' and 11-11') and having no oxygen in the bridge 11-11'.



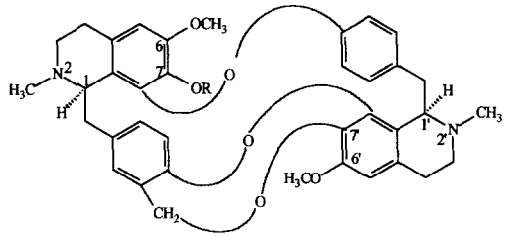
II.c.1.6	Note	1	2	5	6	12	1'	2'	12'
II.c.1.6.1	-	R	Me	H	OMe	OH	S	Me	OMe
II.c.1.6.2	-	S	H	OMe	OH	OMe	S	H	OH
II.c.1.6.3	*N* Me	S	Me	OMe	OH	OMe	S	H	OH
II.c.1.6.4	*N*, O^6 di-Me	S	Me	OMe	OMe	OMe	S	H	OH
II.c.1.6.5	*N*, *N'*, O^6 tri-Me	S	Me	OMe	OMe	OMe	S	Me	OH
II.c.1.6.6	*N*, O^6 di-Me, *N'* Ac	S	Me	OMe	OMe	OMe	S	Ac	OH
II.c.1.6.7	-	S	H	H	OMe	OMe	S	H	OH
II.c.1.6.8	-	R	Me	H	OMe	OMe	S	Me	OH
II.c.1.6.9	*N* de-Me	R	Me	H	OMe	OMe	S	Me	OH
II.c.1.6.10	-	S	Me	H	OMe	OMe	S	Me	OH
II.c.1.6.11	*N'* oxide	S	Me	H	OMe	OMe	S	Me, oxide	OH
II.c.1.6.12	*N* de-Me	S	H	H	OMe	OMe	S	Me	OH
II.c.1.6.13	*N'* de-Me	S	Me	H	OMe	OMe	S	H	OH
II.c.1.6.14	*N*, *N'* di-de-Me	S	H	H	OMe	OMe	S	H	OH
II.c.1.6.15	*N*, de-Me, *N* Acetyl	S	Ac	H	OMe	OMe	S	Me	OH
II.c.1.6.16	-	S	Me	H	OMe	OH	S	H	OMe
II.c.1.6.17	-	S	Me	OMe	H	OMe	S	Me	OH
II.c.1.6.18	-	S	Me	H	OMe	OH	S	Me	OMe
II.c.1.6.19	-	S	Me	OH	OMe	OMe	S	Me	OH
II.c.1.6.20	-	S	Me	OH	OMe	OH	S	Me	OMe
II.c.1.6.21	*N'* de-Me	S	Me	OH	OMe	OMe	S	H	OH
II.c.1.6.22	*N'* de-Me, 1-epimer	R	Me	OH	OMe	OMe	S	H	OH

Sub-type II.c.2.1 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail, and Bearing Three Joints (7-12', 8-11' and 12-8').



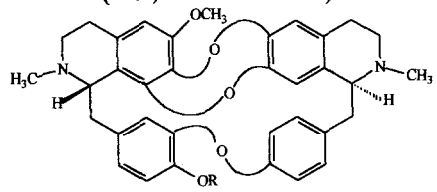
II.c.2.1.1 R = Me, β-oxide; R' = Me
II.c.2.1.2 R = Me; R' = Me, β-oxide

Sub-type II.c.2.2 - Bisbenzylisoquinoline Alkaloids Bonded Head to Tail, and Bearing Three Joints (8-12', 12-8' and 11-7') and having a CH_2 in one of the joints.



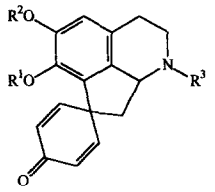
II.c.2.2.1 R = H
II.c.2.2.2 R = Me

Sub-type II.d - Bisbenzylisoquinolinine Alkaloids Bonded Head to Head, Tail to Tail and Bearing Three Joints (7-6', 8-7' and 11-12').



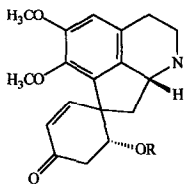
II.d.1 R = H
II.d.2 R = CH_3

Type III
Proaporphine Alkaloids
Table XXIV. Sub-type III.a - Proaporphine Alkaloids.



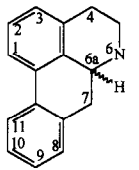
IIIa	R^1	R^2	R^3
III.a.1	Me	Me	H
III.a.2	Me	Me	Me
III.a.3	Me	Me	COOH
III.a.4	Me	Me	$CONH_2$
III.a.5	Me	H	Me
III.a.6	Me	Me	Ac
III.a.7	H	Me	Me

Sub type III.b - 10, 11 Di-dehydro Proaporphine Alkaloids.



III.b.1 R = H
III.b.2 R = Me

Type IV
Aporphine Alkaloids
Table XXV. Sub-type IV.a - Aporphine Alkaloids (*Strictu sensu*).



IV.a	1	2	3	4	6	6a	7	8	9	10	11
IV.a.1	OCH_2O		H	H	H	R	H	H	H	H	H
IV.a.2	OCH_2O		H	H	Formyl	R	H	H	H	H	H
IV.a.3	OMe	OH	H	H	H	R	H	H	H	H	H
IV.a.4	OMe	*O*-β-D-glucoside	H	H	H	R	H	H	H	H	H
IV.a.5	OMe	*O*-β-D-glucoside	H	H	COOEt	R	H	H	H	H	H
IV.a.6	OCH_2O		H	H	Me	R	H	H	H	H	H
IV.a.7	OCH_2O		H	H	$(CH_3)_2$	R	H	H	H	H	H
IV.a.8	OCH_2O		OH	H	H	-	H	H	H	H	H
IV.a.9	OCH_2O		OMe	H	Me	R	H	H	H	H	H
IV.a.10	OCH_2O		H	H	H	R	H	H	OMe	H	H
IV.a.11	OCH_2O		H	H	Me	R	H	H	OH	H	H
IV.a.12	OMe	OMe	H	H	H	R	H	H	H	OH	H
IV.a.13	OMe	OMe	H	H	H	S	H	H	OMe	OMe	H
IV.a.14	OH	OMe	H	H	H	S	H	H	H	OMe	OMe
IV.a.15	OMe	OMe	H	H	Me	R	H	H	H	H	H
IV.a.16	OMe	OMe	H	H	H	R	H	H	H	H	H

(*Continues*)

Table XXV (*Continued*)

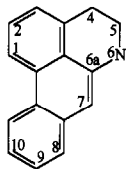
IV.a	1	2	3	4	6	6a	7	8	9	10	11
IV.a.17	OMe	OMe	H	H	Formyl	R	H	H	H	H	H
IV.a.18	OMe	OMe	H	H	Ac	R	H	H	H	H	H
IV.a.19	OMe	OMe	H	H	Me	S	H	H	H	OH	H
IV.a.20	OMe	OMe	H	H	H	S	H	H	OH	OMe	H
IV.a.21	OMe	OMe	H	H	Me	S	H	H	OH	OMe	H
IV.a.22	OH	OMe	H	H	Me	R	H	H	H	OH	H
IV.a.23	OH	OMe	H	H	Me	S	H	H	OH	OMe	H
IV.a.24	OCH_2O		H	H	Me	S	H	H	H	OMe	OH
IV.a.25	OMe	OH	H	H	Me	S	H	H	OH	OMe	H
IV.a.26	OMe	OH	H	H	$(CH_3)_2$	S	H	H	OH	OMe	H
IV.a.27	OCH_2O		H	H	Me	S	H	H	OH	OMe	H
IV.a.28	OH	OMe	H	H	Me	S	H	H	H	OMe	OMe
IV.a.29	OH	OMe	H	H	$(CH_3)_2$	S	H	H	H	OMe	OMe
IV.a.30	OH	OMe	H	H	Me	S	H	H	H	OMe	OH
IV.a.31	OMe	OMe	H	H	Me	S	H	H	OMe	OMe	H
IV.a.32	OCH_2O		H	H	Me	R	H	H	H	OH	H
IV.a.33	OMe	OMe	H	H	Me	S	H	H	OCH_2O		H
IV.a.34	OMe	OMe	H	H	H	S	H	H	OCH_2O		H
IV.a.35	OMe	OMe	H	H	Formyl	S	H	H	OCH_2O		H
IV.a.36	OMe	OH	H	H	Me	S	H	H	OMe	OMe	H
IV.a.37	OMe	OH	H	H	Me	S	H	H	OMe	OH	H
IV.a.38	OCH_2O		H	α-OH	Me	R	H	H	H	H	H
IV.a.39	OH	OMe	H	α-OH	Me	S	H	H	H	OMe	OMe
IV.a.40	OCH_2O		H	H	Me	R	β-OH	H	H	H	H
IV.a.41	OCH_2O		H	H	Me	R	α-OH	H	H	H	H
IV.a.42	OCH_2O		H	H	Me β-oxide	R	α-OH	H	H	H	H
IV.a.43	OCH_2O		H	H	Me	R	α-OH	OMe	H	H	H
IV.a.44	OCH_2O		H	H	Me	R	H	H	OMe	OMe	H
IV.a.45	OCH_2O		H	H	H	R	H	H	OMe	OMe	H

(*Continues*)

Table XXV (*Continued*)

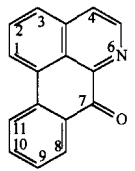
IV.a	1	2	3	4	6	6a	7	8	9	10	11
IV.a.46	OCH_2O		H	α-OH	Me	R	H	H	OMe	OMe	H
IV.a.47	OH	OMe	H	H	Me	S	H	H	H	OH	OMe
IV.a.48	OMe	OMe	H	H	$(CH_3)_2$	S	H	H	H	OMe	OMe
IV.a.49	OMe	OMe	H	H	$(CH_3)_2$, Cl^-	S	H	H	H	OMe	OMe
IV.a.50	OMe	OH	H	H	Me	S	H	H	H	OMe	OH
IV.a.51	OMe	OH	H	H	$(CH_3)_2$	S	H	H	H	OMe	OH
IV.a.52	OME	OMe	H	H	$(CH_3)_2$	S	H	H	OMe	OMe	H
IV.a.53	OMe	OMe	H	H	$(CH_3)_2$	S	H	H	H	OMe	OH
IV.a.54	OH	OMe	H	H	$(CH_3)_2$	S	H	H	H	OMe	OH
IV.a.55	OH	OMe	H	H	$(CH_3)_2$	S	H	H	OH	OMe	H
IV.a.56	OH	OMe	H	H	$(CH_3)_2$	-	H	H	H	OMe	OH
IV.a.57	OCH_2O		H	H	Me, Oxide	R	H	OMe	OMe	H	H
IV.a.58	OCH_2O		H	α-OH	Me	R	α-OH	H	H	H	H
IV.a.59	OCH_2O		H	H	Me	R	H	OMe	OMe	H	H
IV.a.60	OCH_2O		H	α-OH	Me	R	H	OMe	OMe	H	H
IV.a.61	OCH_2O		H	H	Me	R	β-OH	OMe	OMe	H	H
IV.a.62	OCH_2O		H	H	Me	R	β-Acetoxy	OMe	OMe	H	H
IV.a.63	OCH_2O		H	H	Me, oxide	R	β-OH	OMe	OMe	H	H
IV.a.64	OCH_2O		H	H	Me	R	H	H	OMe	OH	H
IV.a.65	OCH_2O		H	H	Me	R	H	OMe	OH	H	H
IV.a.66	OCH_2O		H	H	Me	R	H	OMe	H	H	H
IV.a.67	OCH_2O		H	H	Me	R	H	H	OMe	H	H
IV.a.68	OMe	OMe	H	H	Me	S	H	H	H	OMe	OH
IV.a.69	OH	OMe	H	H	H	S	H	H	OH	OMe	H
IV.a.70	OMe	OH	H	H	Me	-	H	H	H	H	H
IV.a.71	OMe	OH	H	H	Me	S	H	H	H	OH	H
IV.a.72	OCH_2O		H	H	H	S	H	H	OMe	OH	H
IV.a.73	OMe	OMe	H	H	Formyl	R	H	H	H	H	H

Table XXVI. Sub-type IV.b - 6a,7-Di-dehydroaporphines Alkaloids.



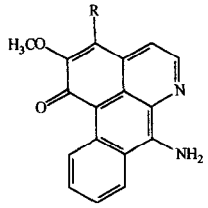
IV.b	1	2	4	5	6	7	8	9	10
IV.b.1	OCH_2O		H	H	Me	H	OMe	OMe	H
IV.b.2	OCH_2O		H	H	Me	H	H	OMe	OH
IV.b.3	OCH_2O		H	H	Me	H	OMe	OH	H
IV.b.4	OCH_2O		H	H	Me	H	OMe	H	H
IV.b.5	OCH_2O		H	H	Me	H	H	OMe	H
IV.b.6	OCH_2O		H	H	Me	H	H	H	H
IV.b.7	OMe	OMe	H	H	Formyl	H	H	H	H
IV.b.8	OCH_2O		H	H	Me	H	H	OMe	OMe
IV.b.9	OCH_2O		H	H	Me	H	OH	H	H
IV.b.10	OCH_2O		=O	=O	Me	H	H	H	H
IV.b.11	OMe	OMe	=O	=O	Me	H	H	H	H
IV.b.12	OMe	OMe	=O	=O	H	H	H	H	H
IV.b.13	OCH_2O		=O	=O	Me	H	H	OCH_2O	
IV.b.14	OCH_2O		=O	=O	Me	H	OMe	OMe	H
IV.b.15	OMe	OMe	=O	=O	Me	H	H	OCH_2O	
IV.b.16	OCH_2O		H	H	Formyl	H	H	H	H
IV.b.17	OMe	OMe	=O	=O	H	Cl	H	H	H

Table XXVII. Sub-type IV.c - 7-Oxoaporphine Alkaloids.



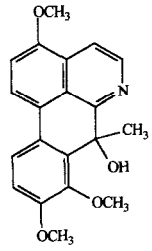
IV.c	1	2	3	4	6	8	9	10	11
IV.c.1	OCH_2O		H	H	-	H	H	H	H
IV.c.2	OMe	OMe	H	H	-	H	H	H	H
IV.c.3	OMe	OMe	OMe	H	-	H	H	H	H
IV.c.4	OMe	OMe	OMe	OMe	-	H	H	H	H
IV.c.5	OMe	OMe	H	OMe	-	H	H	H	H
IV.c.6	OMe	OMe	OMe	H	-	H	OH	H	H
IV.c.7	OMe	OMe	H	H	-	H	OH	H	H
IV.c.8	OCH_2O		H	H	-	OMe	OMe	H	H
IV.c.9	OMe	OMe	H	H	-	H	OMe	OMe	H
IV.c.10	OMe	OMe	H	H	-	H	OCH_2O		H
IV.c.11	OCH_2O		H	H	-	H	H	H	OMe
IV.c.12	OCH_2O		H	H	-	OMe	H	H	H
IV.c.13	OCH_2O		H	H	-	OH	H	H	H
IV.c.14	OCH_2O		H	H	-	H	OMe	H	H
IV.c.15	OCH_2O		H	H	-	H	OH	H	H
IV.c.16	OCH_2O		H	H	-	H	OMe	OMe	H
IV.c.17	OCH_2O		H	H	-	H	OCH_2O		H
IV.c.18	OCH_2O		H	H	Me	OMe	H	H	H
IV.c.19	OCH_2O		H	H	Me	OMe	OMe	H	H
IV.c.20	OCH_2O		OMe	H	-	H	OMe	H	H

Sub-type IV.d - 1-Oxo, 7-aminoaporphine Alkaloids.

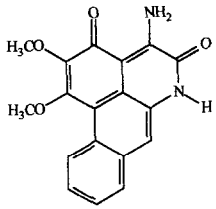


IV.d.1 R = H
IV.d.2 R = OMe

Sub-type IV.e - Miscellaneous Aporphine Alkaloids.



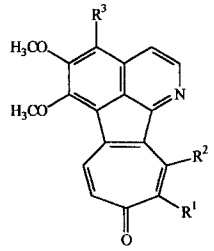
IV.e.1



IV.e.2

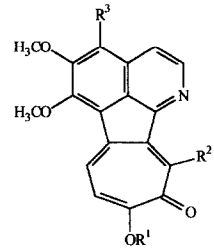
Type V
Tropoloneisoquinoline Alkaloids

Table XXVIII. Sub-type V.a - 10-Oxo-tropoloneisoquinoline Alkaloids.



V.a	R^1	R^2	R^3	
V.a.1	OH	OMe	H	*
V.a.2	OH	H	OMe	
V.a.3	OH	OMe	OMe	**
V.a.4	OMe	H	OMe	
V.a.5	H	H	H	

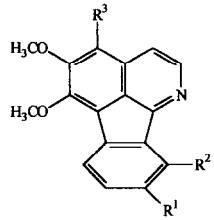
Table XXIX. Sub-type V.b - 11-oxo-tropoloneisoquinoline Alkaloids.



V.b	R^1	R^2	R^3	
V.b.1	H	OMe	H	*
V.b.2	Me	H	OMe	
V.b.3	H	OMe	OMe	**

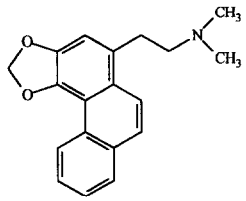
* Exist in equilibrium.
** Exist in equilibrium.

Type VI
Table XXX. Azafluorantene Alkaloids



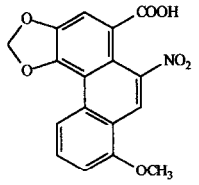
VI	R^1	R^2	R^3
VI.1	H	H	H
VI.2	OH	H	H
VI.3	OMe	H	OMe
VI.4	OH	H	OMe
VI.5	OMe	OMe	OMe
VI.6	OH	OMe	OMe

Type VII
Phenantrene Alkaloids



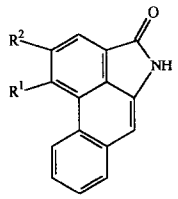
VII

Type VIII
Aristolochic Acid Derivative Alkaloids



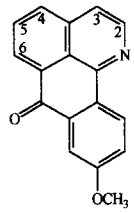
VIII.a

Sub-type VIII.b - Aristolactams.



VIII.b.1 $R^1 = R^2 = OCH_2O$
VIII.b.2 $R^1 = R^2 = OCH_3$

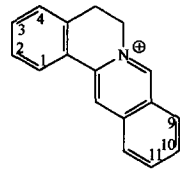
Type IX
Table XXXI. Isooxoaporphine Alkaloids.



IX	2-3	4	5	6
IX.1	-	H	OMe	OMe
IX.2	di-dehydro	H	OMe	OMe
IX.3	-	H	OMe	OH
IX.4	-	OMe	OMe	OMe
IX.5	-	H	OMe	H
IX.6	-	H	OCH_2O	
IX.7	-	OMe	OMe	OH

Type X
Protoberberine Alkaloids

Table XXXII. Sub-type X.a - Protoberbeine Alkaloids (*Strictu sensu*).



X.a	1	2	3	4	9	10	11
X.a.1	H	OMe	OH	H	OMe	OMe	H
X.a.2	H	OH	OMe	H	OMe	OMe	H
X.a.3	H	OMe	OMe	H	OMe	OMe	H
X.a.4	H	OCH_2O		H	OMe	OMe	H
X.a.5	H	OH	OMe	H	OMe	OH	H
X.a.6	H	OMe	OMe	H	OMe	OH	H
X.a.7	H	OCH_2O		H	OMe	OH	H
X.a.8	H	OMe	OH	H	OMe	OH	H
X.a.9	H	OMe	OMe	H	OH	OMe	H
X.a.10	H	OCH_2O		H	OH	OMe	H
X.a.11	H	OH	OMe	H	OCH_2O		H
X.a.12	H	OMe	OH	H	H	OMe	OMe
X.a.13	H	OH	OMe	H	H	OMe	OMe
X.a.14	H	OMe	OMe	OMe	OMe	OMe	H
X.a.15	H	OMe	OMe	OH	OMe	OMe	H
X.a.16	OH	OMe	OMe	H	H	OMe	OMe
X.a.17	H	OMe	OH	Dimer *	OMe	OMe	H
X.a.18	H	OMe	OMe	H	OMe	OMe	H

* Structure of X.a.17:

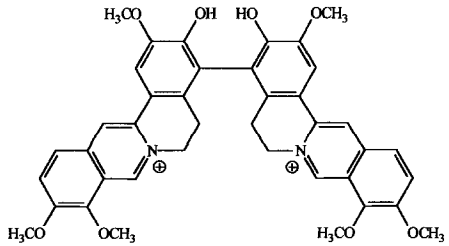
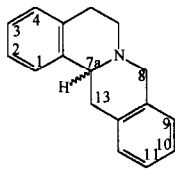


Table XXXIII. Sub-type X.b - Tetrahydroprotoberberine Alkaloids.



X.b	1	2	3	4	7a	8	9	10	11	13	N
X.b.1	H	OMe	OH	H	α	H	OMe	OH	H	H	-
X.b.2	H	OH	OMe	H	α	H	OCH_2O		H	H	-
X.b.3	H	OMe	OMe	H	β	H	OCH_2O		H	H	-
X.b.4	H	OMe	OH	H	α	H	OMe	OMe	H	H	-
X.b.5	H	OH	OMe	H	α	H	OMe	OH	H	H	-
X.b.6	H	OMe	OH	H	undef.	H	H	OH	OMe	H	-
X.b.7	H	OMe	OH	H	α	H	H	OH	*	H	-
X.b.8	H	OMe	OMe	H	α	H	H	OMe	OH	H	-
X.b.9	H	OH	OMe	H	α	H	H	OMe	OH	H	-
X.b.10	H	OH	OMe	H	α	H	H	OH	OMe	H	-
X.b.11	H	OH	OMe	H	α	H	H	OMe	OMe	H	-
X.b.12	H	OMe	OH	H	α	H	H	OMe	OMe	H	-
X.b.13	H	OH	OMe	H	β	H	OMe	OMe	H	H	-
X.b.14	OMe	OMe	OMe	H	undef.	H	OMe	OMe	H	H	-
X.b.15	H	OMe	OMe	H	α	H	OMe	OMe	OH	H	-
X.b.16	OH	OMe	OMe	H	α	H	OMe	OMe	H	H	-
X.b.17	OH	OMe	OMe	H	α	H	OMe	OH	H	H	-
X.b.18	OH	OMe	OMe	H	α	H	H	OMe	OH	H	-

(*Continues*)

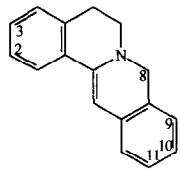
Table XXXIII (*Continued*)

X.b	1	2	3	4	7a	8	9	10	11	13	N
X.b.19	OH†	OMe	OMe	H	α	H	H	OMe	OMe†	H	-
X.b.20	H	OCH_2O		H	β	H	OMe	OMe	H	H	-
X.b.21	H	OCH_2O		H	β	=O	OMe	OMe	H	H	-
X.b.22	H	OCH_2O		H	α	=O	OMe	OH	H	H	-
X.b.23	H	OCH_2O		H	α	=O	OH	OMe	H	H	-
X.b.24	H	OCH_2O		H	α	=O	OMe	OMe	H	H	-
X.b.25	H	OMe	OMe	H	α	=O	OMe	OMe	H	H	-
X.b.26	H	OCH_2O		H	α	=O	H	H	H	H	-
X.b.27	H	OCH_2O		H	α	=O	OMe	OMe	H	H	-
X.b.28	H	OH	OMe	H	β	=O	OMe	OMe	H	H	-
X.b.29	H	OCH_2O		H	α	H	OMe	OMe	H	=O	-
X.b.30	H	OMe	OMe	H	α	H	OMe	OH	H	H	-
X.b.31	H	OMe	OMe	H	α	H	H	OMe	OMe	H	-
X.b.32	H	OMe	OMe	H	β	H	OMe	OMe	H	H	-
X.b.33	H	OMe	OMe	OH	α	H	OMe	OMe	H	H	-
X.b.34	H	OMe	OMe	OMe	α	H	OMe	OMe	H	H	-
X.b.35	H	OMe	OMe	OH	α	=O	OMe	OMe	H	H	-
X.b.36	H	OMe	OMe	H	β	H	OMe	OMe	H	H	oxide
X.b.37	H	OMe	OMe	H	α	H	H	OMe	OMe	H	α-oxide
X.b.38	H	OMe	OMe	H	α	H	H	OMe	OMe	H	β-oxide
X.b.39	H	OMe	OMe	H	α	H	OMe	OH	H	H	Me
X.b.40	H	OMe	OMe	OH	α	H	OMe	OMe	H	H	Me
X.b.41	H	OMe	OMe	OMe	α	H	OMe	OMe	H	H	Me
X.b.42	H	OMe	OMe	H	undef.	H	OMe	OMe	H	H	Me
X.b.43	H	OH	OMe	H	α	H	OH	OMe	H	H	α-Me
X.b.44	H	OH	OMe	H	β	H	OH	OMe	H	H	α-Me
X.b.45	H	OH	OMe	H	α	H	OH	OMe	H	H	-

* *O*-β-D-glucopyranoside

† Interchangeable

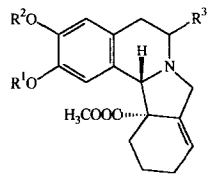
Table XXXIV. Sub-type X.c - Dihydroprotoberberine Alkaloids.



X.c	2	3	8	9	10	11
X.c.1	OCH_2O		=O	OMe	OMe	H
X.c.2	OCH_2O		OH	OMe	OMe	H
X.c.3	OCH_2O		=O	OH	OMe	H
X.c.4	OMe	OMe	=O	OMe	OMe	H
X.c.5	OMe	OMe	=O	H	OMe	OMe
X.c.6	OMe	OMe	H	H	OMe	OMe

Type XI
Hirsutine Alkaloids

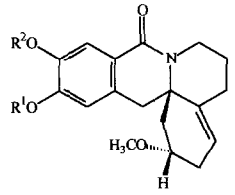
Table XXXV. Hirsutine Alkaloids.



XI	R^1	R^2	R^3	N
XI.1	H	H	H	-
XI.2	Me	H	H	-
XI.3	Me	Me	H	-
XI.4	Me	Me	=O	-
XI.5	Me	Me	H	*N-oxide*

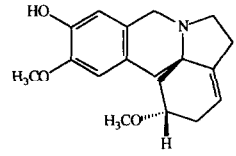
Type XII
Cohirsine Alkaloids

Table XXXVI. Sub-type XII.a - Cohirsine Alkaloids Bearing Six Carbons in Ring C.



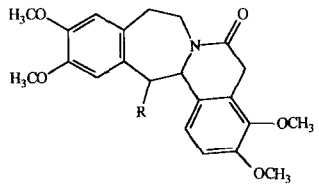
XII.a	R^1	R^2
XII.a.1	H	H
XII.a.2	Me	H
XII.a.3	Me	Me

Sub-type XII.b - Cohirsine Alkaloids Bearing Five Carbons in Ring C.



XII.b

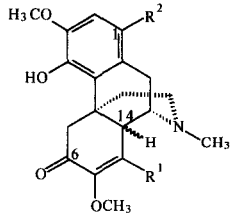
Type XIII
Benzazepine Alkaloids



XIII.1 R = O
XIII.2 R = OH

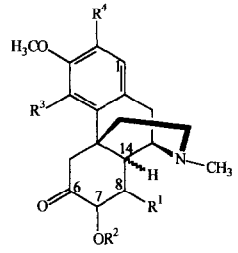
Type XIV
Morphinan Alkaloids

Table XXXVII. Sub-type XIV.a.1 - 9,13-α-Morphinan-6-one Alkaloids.



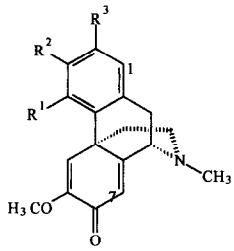
XIV.a.1	R^1	R^2	H-14
XIV.a.1.1	H	H	α
XIV.a.1.2	H	1,1'-dimer	α
XIV.a.1.3	OMe	H	α
XIV.a.1.4	OMe	H	β

Table XXXVIII. Sub-type XIV.a.2 - 9,13-β-Morphinan-6-one Alkaloids.



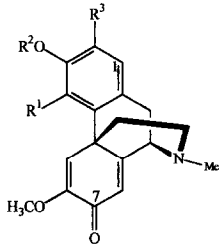
XIV.a.2	R^1	R^2	R^3	R^4	H-14	C7-C8
XIV.a.2.1	OMe	H	OH	H	β	unsat.
XIV.a.2.2	OMe	Me	H	OMe	β	unsat.
XIV.a.2.3	OMe	Me	H	OMe	α	unsat
XIV.a.2.4	OMe	Me	H	OH	α	unsat.
XIV.a.2.5	H	Me	H	OMe	α	sat.

Table XXXIX. Sub-type XIV.b.1 - 9,13-α-Morphinan-7-one Alkaloids.



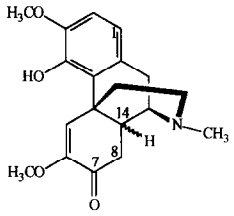
XIV.b.1	R^1	R^2	R^3
XIV.b.1.1	OMe	OH	H
XIV.b.1.2	OH	OMe	H
XIV.b.1.3	H	OMe	OH
XIV.b.1.4	H	OCH_2O	

Table XL. Sub-type XIV.b.2 - 9,13-β-Morphinan-7-one Alkaloids.



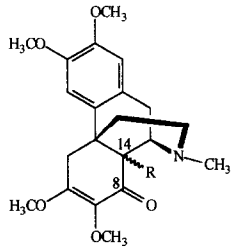
XIV.b.2	R^1	R^2	R^3
XIV.b.2.1	OH	Me	H
XIV.b.2.2	H	Me	OMe

Sub-type XIV.b.3 - 9,13-β-8,14-Dihydro-morphinan-7-one Alkaloids.



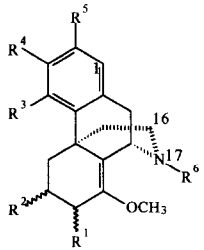
XIV.b.3.1 - Stereochemistry of H-14 = β
XIV.b.3.2 - Stereochemistry of H-14 = α

Sub type XIV.c - 9,13-β-Morphinan-8-one Alkaloids.



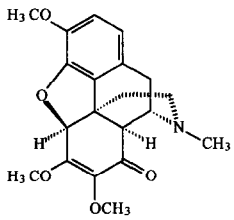
XIV.c.1 - R = Hα
XIV.c.2 - R = Hβ
XIV.c.3 - R = OHβ

Table XLI. Sub-type XIV.d - 9,13-α-Morphinane Alkaloids.



XIV.d	R^1	R^2	R^3	R^4	R^5	R^6	16-17
XIV.d.1	β-OH	β-OH	OH	OMe	H	H	sat.
XIV.d.2	β-OAc	β-OAc	OH	OMe	H	H	sat.
XIV.d.3	β-OH	β-OH	OH	OMe	H	H	unsat.
XIV.d.4	OMe	OH	H	OH	OMe	H	sat.
XIV.d.5	β-OAc	β-OAc	OH	OMe	H	Me	sat
XIV.d.6	β-OH	β-OH	H	OH	OMe	H	sat
XIV.d.7	β-OH	β-OH	OH	OMe	H	Me	sat.

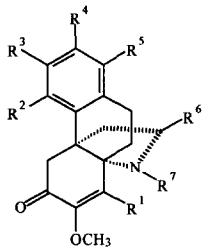
Sub-type XIV.e - Morphinane Alkaloid With an Ether Bridge Between C-4 and C-5.



XIV.e

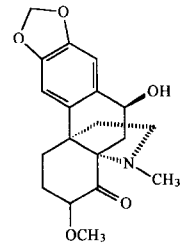
Type XV
Hasubanane Alkaloids

Table XLII. Sub-type XV.a - Hasubanan-6-one Alkaloids.



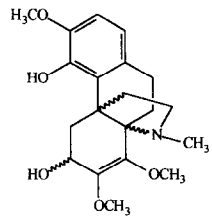
XV.a	R^1	R^2	R^3	R^4	R^5	R^6	R^7
XV.a.1	OMe	H	OCH_2O		H	H	Me
XV.a.2	OMe	H	OCH_2O		H	H	H
XV.a.3	OMe	H	OCH_2O		H	=O	Me
XV.a.4	OMe	OH	OMe	H	NO_2	H	Me
XV.a.5	H	OH	OMe	H	H	H	Me
XV.a.6	OMe	H	OMe	OMe	H	H	Me
XV.a.7	OMe	H	OMe	OMe	H	H	H
XV.a.8	OMe	OMe	OMe	H	H	H	Me
XV.a.9	OMe	OMe	OMe	H	H	=O	Me
XV.a.10	OMe	OH	OMe	H	H	H	Me
XV.a.11	OMe	OH	OMe	H	H	H	H
XV.a.12	OMe	OH	OMe	H	H	=O	Me
XV.a.13	OMe	H	OMe	OH	H	H	Me

Sub-type XV.b - Hasubanan-8-one Alkaloids.



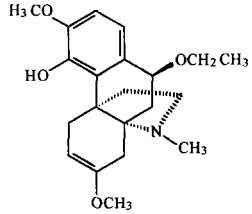
XV.b

Sub-type XV.c - 7,8-Dehydro-hasubanan Alkaloids.



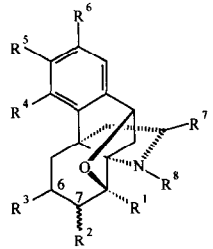
XV.c.1 = Hernandolinol
XV.c.2 = Epihernandolinol (epimer)

Sub-type XV.d - 6,7-Dehydro-hasubanan Alkaloids.



XV.d

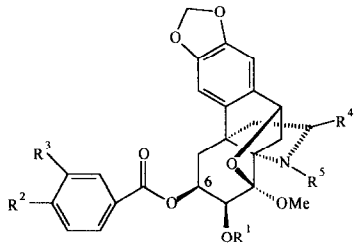
Table XLIII. Sub-type XV.e.1 - 8,10-Epoxihasubanan Alkaloids.



XV.e.1	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	C6-C7
XV.e.1.1	OMe	α-OMe	=O	OMe	OMe	H	H	Me	sat.
XV.e.1.2	OMe	β-OMe	=O	OMe	OMe	H	H	Me	sat.
XV.e.1.3	OMe	α-OMe	=O	OMe	OMe	H	=O	Me	sat.
XV.e.1.4	OMe	β-OMe	=O	OMe	OMe	H	=O	Me	sat.
XV.e.1.5	OMe	β-OMe	β-OH	H	OCH_2O		=O	Me	sat.
XV.e.1.6	OMe	β-OMe	β-OH	OH	OMe	H	H	H	sat.
XV.e.1.7	OMe	β-OMe	β-OH	OH	OH	H	H	H	sat.
XV.e.1.8	OH	β-OH	H	OH	OMe	H	H	Me	sat.
XV.e.1.9	OH	β-OH	H	OH	OH	H	H	Me	sat.
XV.e.1.10	OMe*	β-OH*	β-OH	OH	OMe	H	H	Me	sat.
XV.e.1.11	OMe	β-OMe	β-OH	OH	OMe	H	H	Me	sat.
XV.e.1.12	OH	β-OMe	β-OH	OH	OMe	H	H	Me	sat.
XV.e.1.13	OH	β-OMe	β-OH	OMe	OMe	H	H	Me	sat.
XV.e.1.14	OMe	β-OMe	β-OAc	OMe	OMe	H	H	Me	sat.
XV.e.1.15	OMe	β-OH	=O	OH	OMe	H	H	Me	sat.
XV.e.1.16	OH	β-OMe	β-OH	OMe	OMe	H	=O	Me	sat.
XV.e.1.17	OH	=O	H	OMe	OMe	H	H	Me	sat.
XV.e.1.18	OH	OMe	H	OH	OMe	H	H	Me	unsat.
XV.e.1.19	OH	=O	H	H	OCH_2O		H	Me	sat.

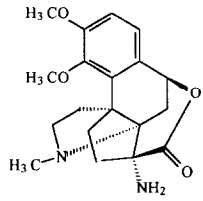
* Could be interchangeable.

Table XLIV. Sub-type XV.e.2 - 8,10-Epoxihasubanan Alkaloids Bearing a Disubstituted Benzoate in C6.

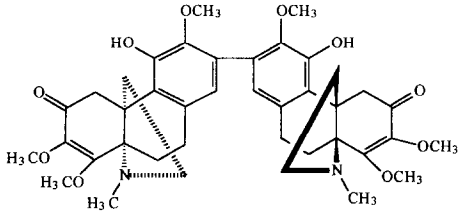


XV.e.2	R^1	R^2	R^3	R^4	R^5
XV.e.2.1	Me	H	H	H	Me
XV.e.2.2	Me	H	H	=O	Me
XV.e.2.3	H	OMe	OMe	H	H
XV.e.2.4	H	OH	OMe	H	H
XV.e.2.5	Me	OMe	OMe	H	Me

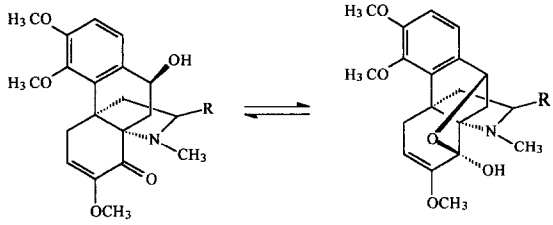
Sub-type XV.f - Miscellaneous Hasubanan Alkaloids.



XV.f.1



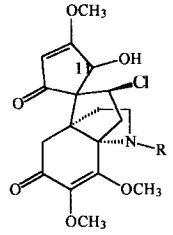
XV.f.2



XV.f.3.1 R = H
XV.f.3.2 R = O

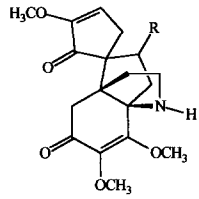
Type XVI
Acutumine Alkaloids

Sub-type XVI.a - α-Acutumine Alkaloids.



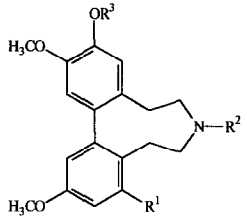
XVI.a.1 R = Me
XVI.a.2 R = H
XVI.a.3 R = Me, 11-deoxi

Sub-type XVI.b - β-Acutumine Alkaloids.



XVI.b.1 R = Cl
XVI.b.2 R = H

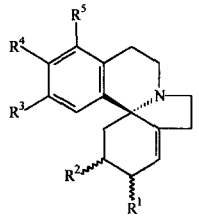
Type XVII
Table XLV. Eribidine Alkaloids.



XVII	R^1	R^2	R^3
XVII.1	H	H	Me
XVII.2	H	Me	H
XVII.3	H	Me	Me
XVII.4	OMe	Me	Me

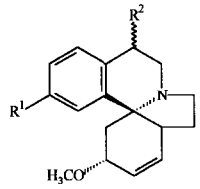
Type XVIII
Erythrine Alkaloids

Table XLVI. Sub-type XVIII.a - 1,6-Didehydro Erythrine Alkaloids.



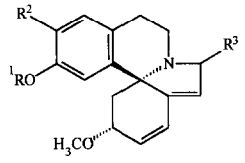
XVIII.a	R^1	R^2	R^3	R^4	R^5	N
XVIII.a.1	H	α-OMe	OH	H	H	-
XVIII.a.2	H	α-OH	OH	H	H	-
XVIII.a.3	H	α-OMe	COOMe	OMe	H	-
XVIII.a.4	β-OH	α-OMe	OMe	H	H	-
XVIII.a.5	β-OH	αOMe	OH	H	H	-
XVIII.a.6	=O	α-OMe	OMe	H	H	-
XVIII.a.7	H	α-OMe	OMe	H	H	-
XVIII.a.8	H	α-OMe	OH	H	OMe	-
XVIII.a.9	H	α-OMe	OMe	OH	H	-
XVIII.a.10	H	α-OMe	OH	OMe	H	-
XVIII.a.11	H	α-OMe	COOH	OMe	H	-
XVIII.a.12	H	α-OMe	$CONH_2$	OMe	H	-
XVIII.a.13	H	α-OMe	OH	H	H	Me
XVIII.a.14	OCH_2O		COOMe	OMe	H	-

Table XLVII. Sub-type XVIII.b - 1,2-Didehydro Erythrine Alkaloids.



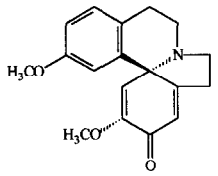
XVIII.b	R^1	R^2
XVIII.b.1	H	OMe
XVIII.b.2	OMe	H
XVIII.b.3	H	H

Table XLVIII. Sub-type XVIII.c - 1,2,6,7-Tetradehydro Erythrine Alkaloids.



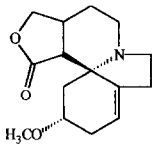
XVIII.c	R^1	R^2	R^3
XVIII.c.1	Me	OH	H
XVIII.c.2	H	H	H
XVIII.c.3	Me	H	H
XVIII.c.4	H	H	=O
XVIII.c.5	Me	H	=O

Sub-type XVIII.d



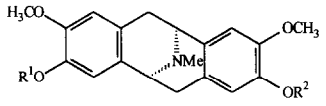
XVIII.d

Sub-type XVIII.e



XVIII.e

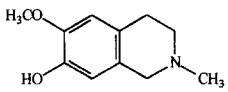
Type XIX
Table XLXIX. Pavine Alkaloids.



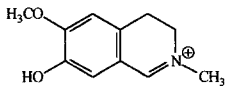
XIX	R^1	R^2
XIX.1	Me	Me
XIX.2	H	Me
XIX.3	H	H

Type XX
Isoquinoline Alkaloids

Sub-type XX.a - Tetrahydro Isoquinoline Alkaloids.

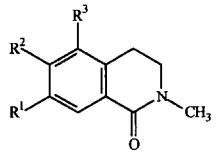


XX.a



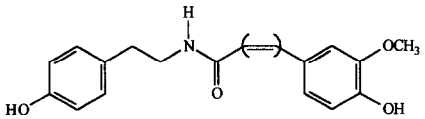
XX.a.1

Table L. Sub-type XX.b - Isoquinolinone Alkaloids.



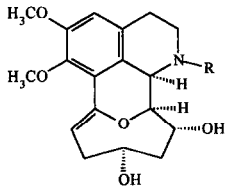
XX.b	R^1	R^2	R^3	C3-C4
XX.b.1	OH	OMe	H	sat.
XX.b.2	OMe	OMe	H	unsat.
XX.b.3	OMe	OCH_2O		sat.

Type XXI
Phenethylcinamide Alkaloids

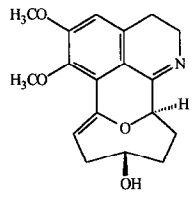


XXI.1 (E-form)
XXI.2 (Z-form)

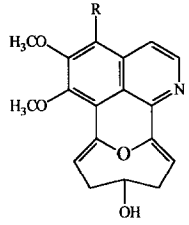
Type XXII
Stephaoxocane Alkaloids



XXII.1 R = H
XXII.2 R = CH_3

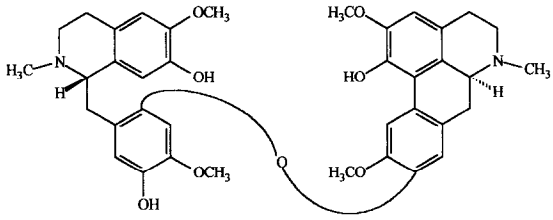


XXII.3

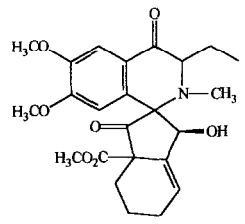


XXII.4 R = H
XXII.5 R = OCH_3

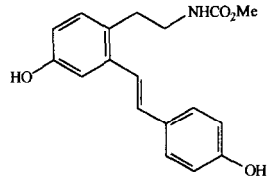
Type XXIII
Miscellaneous Structure Alkaloids



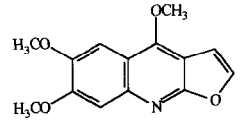
XXIII.1 - Thalicarpine



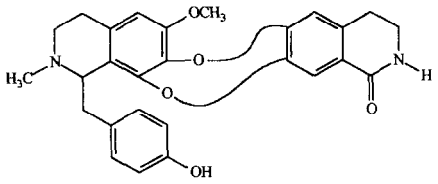
XXIII.2 - Cohirsitine



XXIII.3 - Gusalung C



XXIII.4 - Kokusaginine



XXIII.5 - Neotrilobine

References

1. W. Sneader, *Drug News Persp.* **9**, 627 (1996).
2. A.L. De-Jussieu, *Genera Plantarum Secundarum Ordines Naturales Disposita.* 284, Paris, 1789.
3. J. Miers, A few remarks on the Menispermaceae. *Ann. Mag. Nat. Hist.* **7**, 33 (1851).
4. G. Bentham and J.D. Hooker, Genera Plantarum. *Londini I* 31-34 (1862-1867).
5. L. Diels, Menispermaceae. in *Das Pflazenreich-Leipzig* **46**, 4 (1910).
6. G. Troupin, Monographie des Menispermaceae Africaines. *Acad. Roy. Soc. Outre-Mer cl. Sc. Nat. et Méd.* **13**, 2 (1962).
7. R.M.T. Dahlgren, *Bot. J. Linn. Soc.* **80**, 91 (1980).
8. R.K. Brummitt, *Vascular Plant Families and Genera.* p. 754, Royal Botanic Gardens, Kew, England, 1992.
9. H. King, *J. Chem. Soc*, 1381 (1935).
10. M. Tomita, *Fortschr. Chem. Org. Naturs.* **9**, 175 (1952).
11. C.W. Thornber, *Phytochemistry* **9**, 157 (1970).
12. M.D. Menachery, *in* "Alkaloids: Chemical and Biological Perspectives" (S.W. Pelletier, ed.), Volume 11, p. 269, Pergamon Press, Oxford, England,1996.
13. G.A. Cordell, *Introduction to Alkaloids - A Biogenetic Approach.* Wiley Intercience, New York, 1981.
14. J. Staunton, *Planta Med.* **36**, 1 (1979).
15. X.A. Dominguez, *Métodos de Investigacion Fitoquímica.* p. 58, Editorial Limusa, Mexico, 1973.
16. M.H. Zenk, *in* "Organic Reactivity: Physical and Biological Aspects" (B.T. Golding, R.J. Griffin, and H. Maskill, eds.), p. 89, The Royal Society of Chemistry, Special Publication No. 148, Cambridge, England, 1995.
17. C.M.A.M. Rezende, *Sistemática Bioquímica - Princípios e Métodos.* PhD Thesis - USP, São Paulo, Brasil, 1975.
18. M.C.M. Young, *Métodos Quimiotaxonômicos e sua Aplicação em Sistemática Vegetal.* PhD Thesis - USP, São Paulo, Brasil, 1979.
19. E.L. Barreiros, *Evolução de Alcalóides Benzilisoquinolínicos em Angiospermae.* MSc. Dissertation, UFRRJ - Rio de Janeiro, Brasil, 1983.
20. C.M.A.M. Rezende, O.R. Gottlieb, and M.C. Marx, *Biochem. Syst. Ecol.* **3**, 63 (1975).
21. P.G. Waterman and A.I Gray, *Nat. Prod. Rep.* **4**, 175 (1987).
22. E. Haslam, *Nat. Prod. Rep* **3**. 217 (1986).
23. T. Frenzel and M.H. Zenk, *Phytochemistry* **29**, 2505 (1990).
24. K.P. Guha, B. Mukherjee, and R. Mukherjee, *J. Nat. Prod.* **42**, 1 (1979).
25. P.L. Schiff, *J. Nat. Prod.* **46**, 1 (1983).
26. P.L. Schiff, *J. Nat. Prod.* **54**, 645 (1991).

27. K.T. Buck, *in* "The Alkaloids" (A. Brossi, ed.), Volume 30, p. 1. Academic Pree, San Diego, 1987.
28. P. Pachaly, *Planta Med.* **56**, 135 (1990).
29. I.R.C. Bick, *Heterocycles* **16**, 2105 (1981).
30. J. Buckingham, *Dictionary of Natural Products*, P-01871. Chapman & Hall, London, 1996.
31. M.P. Cava, K. Nomura, S.K. Talapatra, M.J. Mitchell, R.H. Schlessinger, K.T. Buck, J.L. Beal, B. Douglas, R.F. Raffauf, and J.A. Weisbach, *J. Org. Chem.* **33**, 2785 (1968).
32. K.L. Stuart, and M.P. Cava, *Chem. Rev.* **68**, 321 (1968).
33. H. Guinaudeau, M. Leboueuf, and A. Cavé, *Lloydia* **38**, 275 (1975).
34. H. Guinaudeau, M. Leboueuf, and A. Cavé, *J. Nat. Prod.* **42**, 325 (1979).
35. H. Guinaudeau, *J. Nat. Prod.* **46**, 761 (1983).
36. H. Guinaudeau, *J. Nat. Prod.* **51**, 389 (1988).
37. H. Guinaudeau, *J. Nat. Prod.* **57**, 1033 (1994).
38. M.P. Cava, K.T. Buck, I. Noguchi, M. Srinivasan, M.G. Rao, and A.I. da-Rocha, *Tetrahedron* **31**, 1667 (1975).
39. M.D. Menachery and M.P. Cava, *Heterocycles* **14**, 943 (1980).
40. H. Morita, K. Matsumoto, K. Takeya, H. Itokawa, and Y. Iitaka, *Chem. Pharm. Bull.* **41**, 1418 (1993).
41. K.T. Buck, *in* "The Alkaloids" (A. Brossi, ed.), Volume 23, p. 301. Academic Press, New York, 1984.
42. J.V. Silverton, C. Kabuto, K.T. Buck, and M.P. Cava, *J. Am. Chem. Soc.* **99**, 6708 (1977).
43. M. Shamma, *in* "The Alkaloids, Specialist Periodical Reports" (M.F. Grundon ed.), Volume 6, p. 170. The Chemical Society, London, 1976.
44. L. Castedo and G. Tojo, *in* "The Alkaloids" (A. Brossi, ed.), Volume 39, p. 99. Academic Press, San Diego, 1992.
45. Z.-L. Chen and D.-Y Zhu,. *in* "The Alkaloids" (A. Brossi, ed.), Volume 31, p. 29. Academic Press, San Diego, 1987.
46. J.I. K.unimoto and M. Satoh, *Chem. Pharm. Bull.* **30**, 2659 (1982).
47. J.I. Kunimoto, M. Satoh and T. Shingu, *Tetrahedron* **39**, 3261 (1983).
48. R.H.F. Manske and W.R. Ashford, *in* " The Alkaloids" (R.H.F. Manske and H.L. Holmes, eds.) Volume 4, p. 77. Academic Press, New York, 1954.
49. P.W. Jeffs, *in* "The Alkaloids" (R.H.F. Manske and H.L. Holmes, eds.), Volume 9, p. 41. Academic Press, New York, 1967.
50. D.S. Bhakuni and S. Jain, *in* "The Alkaloids" (A. Brossi, ed.), Volume 28, p. 95. Academic Press, New York, 1986.
51. M.J. Müller and M.H. Zenk, *Planta Med.* **58**, 524 (1992).
52. V.U. Ahmad and S. Iqbal, *Nat. Prod. Lett.* **22**, 105 (1993).
53. V.U. Ahmad, Atta-ur-Rahman, T. Rasheed, Habib-ur-Rahman, and A.Q. Khan, *Tetrahedron* **43**, 5865 (1987).
54. R. Hocquemiller and A. Cavé, *J. Nat. Prod.* **47**, 539 (1984).

55. K.W. Bentley, *Nat. Prod. Rep.* **5**, 265 (1988).
56. J. Wang, P.G. Xiao, S.Y. Li, P. Gao, and R.H. Wang, *Phytother. Res.* **6**, 117 (1992).
57. S.L. Holmes, *in* "The Alkaloids" (R.H.F. Manske and H.L. Holmes, eds.), Volume 2, p. 219. Academic Press, New York, 1952.
58. J.E. Robbers, M.K. Speedie, and V.E. Tyler, *Pharmacognosy and Pharmacobiotechnology*, p. 159. Williams & Wilkins, Baltimore, 1996.
59. S. Ruchirawat, J. Staunton, A.R. Battersby, R.C.F. Jones, R. Kazlauskas, C. Poupat and C.W. Thornber, *Chem. Commun.* 773 (1974).
60. M. Matsui, *in* "The Alkaloids" (A. Brossi, ed.), Volume 33, p. 307. Academic Press, San Diego, 1988.
61. S. McLean and J. Whelan, in "Alkaloids IX". MTP International Review of Science, Butterworths, London, 1973.
62. D.S. Bhakuni, A.N. Singh, and R.S. Kapil, *Chem. Commun.* 211 (1977).
63. H. Pande and D.S. Bhakuni, *J. Chem. Soc., Perkin Trans. I*, 2197 (1976).
64. F.S. Dyke and S.N. Quessy, *in* "The Alkaloids" (R.H.F. Manske and R.G.A. Rodrigo, eds.), Volume 18, p. 1. Academic Press, New York, 1981.
65. D.S. Bhakuni and A.N. Singh, *J. Chem. Soc., Perkin Trans. I*, 618 (1978).
66. B. Gözler, *in* "The Alkaloids" (A. Brossi, ed.), Volume **2**, p. 317. Academic Press, San Diego,1988.
67. M.D. Menachery, G.L. Lavanier, M.L. Wetherley, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.* **49**, 745 (1986).
68. R. Hegnauer, *in* "Chemical Plant Taxonomy" (T. Swain, ed.), 389, 1963.
69. T.A. Smith, *Phytochemistry* **16**, 9 (1977).
70. J. Lundstrom, *in* "The Alkaloids" (A. Brossi, ed.) Volume 35, p. 77. Academic Press, San Diego, 1989.
71. J.-Z. Deng, S.-X. Zhao, and Z.-C. Miao, *Nat. Prod. Lett.* **2**, 283 (1993).
72. J. Toda, H. Suzuki, and T. Sano, *J. Nat. Prod.* **59**, 803 (1996).
73. D.S. Bhakuni and S. Jain, *Tetrahedron* **38**, 729 (1982).
74. V.U. Ahmad and S. Iqbal, *Fitoterapia* **63**, 308 (1992).
75. J.S. Zhang, L.L. Men-Olivier, and G. Massiot, *Phytochemistry* **39**, 457 (1995).
76. I.H. Bowen and H.M. Motawe, *Planta Med.* **6**, 529 (1985).
77. J. Buckingham, *Dictionary of Natural Products*, T-02756. Chapman & Hall, London, 1993.
78. J.M. Barbosa-Filho, *Contribuição à Farmacognosia de Menispermaceae Jussieu.*, Professorship Thesis, Universidade Federal da Paraiba – Brazil, 1996.
79. Reference 1 cited in: Lebouef, P. M. *et al.* (1982) *Plant. Med. Phytother.* **16**, 280.
80. Reference 4 cited in: Lebouef, P. M. *et al.* (1982) *Plant. Med. Phytother.* **16**, 280.
81. Z. Xue, Y. Wu, P.L. Zhang, J.M. Ma, and J.P. He, *Chih Wu Hsueh Pao* **27**, 630 (1985).

82. P.M. Lebouef, M.L. Abouchacra, T. Sévenet, and A. Cavé, *Plant. Med. Phytother.* **16**, 280 (1982).
83. J. Buckingham, *Dictionary of Natural Products*, I-00890. Chapman & Hall, London, 1993.
84. M. Lavault, J. Bruneton, A. Cavé, A. Chan, J.R. Deverre, T. Sévenet, and H. Guinaudeau, *Can. J. Chem.* **65**, 343 (1987).
85. M.-L. Abouchacra, M. Lebouef, H. Guinaudeau, A. Cavé, and P. Cabalion, *J. Nat. Prod.* **50**, 375 (1987).
86. A. Engler, *Syllabus der Planzen-Familien* **II**, Gerbruder Borntrager, Berlin-Kiloklasse, 1994.
87. N.G. Bisset and J. Nwaiwu, *Planta Med.* **48**, 275 (1983).
88. C. Boedecker, *Ann.* **69**, 40 (1849).
89. J.M.Z. Gladych, R. Hornby, J.H. Hunt, D. Jack, J.J. Boyle, R.F. Ferlauto, C.G. Haff, F.J. Kormendy, and R.C. Stewart, *J. Med. Chem.* **15**, 277 (1972).
90. R. Ahmad and M.P. Cava, *J. Org. Chem.* **42**, 2271 (1977).
91. C. Galeffi, P. Scarpetti, and G.B. Marini-Bettolo, *Farmaco Ed. Sci.* **32**, 853 (1977).
92. P. Dute, J.F. Weber, A. Fournet, A. Cavé, and J. Bruneton, *Phytochemistry* **26**, 2136 (1987).
93. S. Campos-Flor, N.J. Doorenbos, G.H. Svoboda, J.E. Knapp, and P.L. Schiff, *J. Pharm. Sci.* **63**, 618 (1974).
94. S. Campos-Flor, N.J. Doorenbos, and L.J. Robertson, *Diss. Abstr. Int.* B **35**, 5511 (1975).
95. A. Cavé, M. Lebouef, R. Hocquemiller, A. Bouquet, and A. Fournet, *Planta Med.* **35**, 31 (1979).
96. J. Miers, *Ann. Mag. Nat. Hist.* 7, 43 (1851).
97. J. Hutchinson, *The Families of Flowering Plants*, 3rd Edition, p. 510. Oxford at Clarendon Press, 1973.
98. L. Diels, *Das Pflazenreich: Regnis Vegetabilis Conspectus*, p. 1. Weinheim, Germany, 1910.
99. L.L. Forman, *Studies of the Flora of Thailand*, p. 190. Odense, Andelsbogtrykkeriet, 1962.
100. S. Pongboorod, *Mat. Ted Muang Thai*, p. 348. Kasen Bannakich Press, Bangkok, Thailand, 1979.
101. U. Prawat, P. Wiriyachitra, V. Lojanapiwatna, and S. Nimgirawath, *Abstr. 10th Conference of Science and Technology*, p. 381. Chiangmai University, Chiangmai, Thailand, 1984.
102. U. Prawat, P. Wiriyachitra, V. Lojanapiwatna, and S. Nimgirawath, *J. Sci. Soc. Thailand* **8**, 65 (1982).
103. K. Likhitwitayawuid, C.K. Angerhofer, G.A. Cordell, and J.M. Pezzuto, *J. Nat. Prod.* **56**, 30 (1993).
104. T.G. Dekker, T.G. Fourie, E. Mattee, and F.O. Snyckers, *J. Nat. Prod.* **51**, 584 (1988).

105. D.G. Rhodes, *Phytologia* **30**, 415 .
106. J. Buckingham, *Dictionary of Natural Products*, M-01706. Chapman & Hall, London, 1993.
107. A.I. Da-Rocha, K. Bessho, and M.P. Cava, *Instituto Nacional de Pesquisas da Amazônia*, Química, Publicação No. 11, 1 (1967).
108. M.D. Klein, K.T. Buck, M.P. Cava, and D. Voet, *J. Am. Chem. Soc.* **100**, 662 (1978).
109. M.P. Cava, J.M. Saa, M.V. Lakshimikantham, and M.J. Mitchell, *J. Org. Chem.* **40**, 2647 (1975).
110. J.W. Skiles, J.M. Saa, and M.P. Cava, *Can. J. Chem.* **57**, 1642 (1979).
111. J.M. Saa, M.V. Lakshimikantham, M.J. Mitchell, and M.P. Cava, *J. Org. Chem.* **41**, 317 (1976).
112. R. Verpoorte, J. Siwon, M.E.M. Tieken, and A. Baerheim-Svendsen, *J. Nat. Prod.* **44**, 221 (1981).
113. U.L.B. Jayasinghe, G.P. Wannigama, S. Balasubramanian, H. Nasir, and Atta-ur-Rahman *J. Natl. Sci. Counc. Sri Lanka* **20**, 187 (1992).
114. B. Kanyinda, R. Vanhaelen-Fastre, and M. Vanhaelen, *Planta Med.* **55**, 394 (1989).
115. B. Kanyinda, R.Vanhaelen-Fastre, M. Vanhaelen, and R. Ottinger, *J. Nat. Prod.* **55**, 607 (1992).
116. B. Kanyinda, R. Vanhaelen-Fastre, and M. Vanhaelen, *J. Nat. Prod.* **56**, 618 (1993).
117. B. Kanyinda, R. Vanhaelen-Fastre, M. Vanhaelen, and R. Ottinger, *J. Nat. Prod.* **56**, 957 (1993).
118. E. Schlittler and N. Weber, *Helv. Chim. Acta* **55**, 2061 (1972).
119. T. Tojirakarn and P. Chumsri, *Asian J. Pharm.* (Suppl. 6), 122 (1986).
120. R., Verpoorte, J. Siwon, G.F.A. Van-Essen, M. Tieken, and A. Baerheim-Svendsen, *J. Nat. Prod.* **45**, 582 (1982).
121. J. Buckingham, *Dictionary of Natural Products*, H-00968. Chapman & Hall, London, 1993.
122. J.S. Zhang and Z.L. Chen, *Planta Med.* **57**, 457 (1991).
123. P.H. Rasoanaivo, S. Ratsimamanga-Urverg, A. Rakoto-Ratsimamanga, and A. Raharisololalao, *Biochem. Syst. Ecol.* **19**, 433 (1991).
124. J. Buckingham, *Dictionary of Natural Products*, C-02044. Chapman & Hall, London, 1993.
125. M. Lavault, A. Fournet, H. Guinaudeau, and J. Bruneton, *Chem. Pharm. Bull.* **34**, 1148 (1986).
126. A. Fournet, M. Lavault, and J. Bruneton, *Acta Farm. Bonaerense* **6**, 163 (1987).
127. F.C. Ohiri, R. Verpoorte, and A. Baerheim-Svendsen, *Planta Med.* **46**, 228 (1982).
128. F.C. Ohiri, R. Verpoorte, and A. Baerheim-Svendsen, *Planta Med.* **49**, 17 (1983).

129. A. Baerheim-Svendsen, A.M. Van-Kempen-Verleun, and R. Verpoorte, *J. Chromatogr.* **291**, 389 (1984).
130. J. Baldas, I.R.C. Bick, Q.N. Porter, and M.J. Vernengo, *Chem. Commun.*, 132 (1971).
131. K.F. Taha and F.M. Soliman, *J. Drug. Res. (Egypt)* **15**, 235 (1984).
132. M.P. Cava, J. Kunitomo, and A.I. da-Rocha, *Phytochemistry* **8**, 2341 (1969).
133. J. Lemli, C. Galeffi, I. Messana, M. Nicoletti, and G.B. Marini-Bettolo, *Planta Med.* **1**, 68 (1985).
134. D.L. Galinis, D.F. Wiemer, and J. Cazin, *Tetrahedron* **49**, 1337 (1993).
135. J.M. Barbosa-Filho, E.V.L. da-Cunha, M.L. Cornélio, C.S. Dias, and A.I. Gray, *Phytochemistry* **44**, 959 (1997).
136. W. Snedden, R.B. Parker, and C. Gorinsky, *Org. Mass Spec.* **4**, 607 (1970).
137. M.R. Ahmad, M.A. Malik, and H. Zia-Ul, *Fitoterapia* **63**, 282 (1992).
138. R.M. Srivastava and M.P. Khare, *Chem. Ber.* **97**, 2732 (1964).
139. Z.L. Chen, *Hua Hsueh Hsueh Pao* **38**, 567 (1980).
140. K.S. Brown and S.M. Kupchan, *J. Chromatogr.* **9**, 71 (1962).
141. A.R. Chowdhury, *Sci. Cult.* **38**, 358 (1972).
142. J.R. Boissier, G. Combes, R. Pernet, and C. Dumont, *Lloydia* **28**, 191 (1965).
143. J. Buckingham, *Dictionary of Natural Products*, C-02214. Chapman & Hall, London, 1993.
144. D. Dwuma-Badu, J.S.K. Ayim, C.A. Mingle, A.N. Tackie, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *Phytochemistry* **14**, 2520 (1975).
145. A.K. Bhatnagar, S. Bhattacharji and S.P. Popli, *Indian J. Chem.* **6**, 125 (1968).
146. J. Buckingham, *Dictionary of Natural Products*, C-02174. Chapman & Hall, London, 1993.
147. B. Mukherji and P.R. Bhandari, *Planta Med.* **7**, 250 (1959).
148. B. Hoffstadt, D. Moecke, P. Pachaly, and P. Zymalkowsky, *Tetrahedron* **30**, 307 (1974).
149. H. Morita, K. Matsumoto, K. Takeya, and H. Itokawa, *Chem. Pharm. Bull.* **41**, 1307 (1993).
150. H. Morita, K. Matsumoto, K. Takeya, H. Itokawa, and Y. Iitaka, *Chem. Lett.* **2**, 339 (1993).
151. C. Goepel, S.V. Kurten, T. Yupraphat P. Pachaly, and P. Zymalkowsky, *Planta Med.* **22**, 402 (1972).
152. M.R. Freitas, J.L. Alencar, E.V.L. da-Cunha, J.M. Barbosa-Filho, and A.I. Gray, *Phytochemistry* **40**, 1553 (1995).
153. S.F. Cortes, J.L. Alencar, G. Thomas, and J.M. Barbosa-Filho, *Phytother. Res.* **9**, 579 (1995).
154. M.R. Freitas, S.F. Cortes, G. Thomas, and J.M. Barbosa-Filho, *J. Pharm. Pharmacol.* **48**, 335 (1996).
155. D.J. Slatkin, N.J. Doorenbos, J.E. Knapp, and P.L. Schiff, *Lloydia* **37**, 488 (1974).

156. M.A. El-Sohly, J.E. Knapp, P.L. Schiff, and D.J. Slatkin, *J. Pharm. Sci.* **65**, 132 (1976).
157. E. Shabrawy, *Diss. Abstr. Int.* **B 45**, 3514 (1985).
158. V.J. Tripathi, A.B. Ray and B. Dasgupta, *Indian J. Chem. Ser.* **B 14**, 62 (1976).
159. A.O. El-Shabrawy, P.L. Schiff, D.J. Slatkin, V.J. Tripathi, A.B. Ray, and B. Dasgupta, *Abstr. 23rd Annual Meeting American Society of Pharmacognosy.* p. 23, Pittsburgh, U.S.A, 1982.
160. A.O. El-Shabrawy, P.L. Schiff, D.J. Slatkin, B. Dasgupta, A.B. Ray, and V.J. Tripathi, *Heterocycles* **22**, 993 (1984).
161. V.U. Ahmad, T. Rasheed and S. Iqbal, *Phytochemistry* **30**, 1350 (1991).
162. V.U. Ahmad and S. Iqbal, *J. Nat. Prod.* **55**, 237 (1992).
163. J. Buckingham, *Dictionary of Natural Products*, I-00890. Chapman & Hall, London, 1993.
164. T. Rasheed, N.I. Khan, S.S.A. Zhadi, and S. Durrani, *J. Nat. Prod.* **54**, 582 (1991).
165. V.U. Ahmad and T. Rasheed, *J. Chem. Soc. Pak.* **8**, 537 (1986).
166. V.U. Ahmad, Atta-ur-Rahman, T. Rasheed, and Habib-ur-Rahman. *Heterocycles* **26**, 1251 (1987).
167. T. Rasheed, N.I. Khan, S.S.A. Zhadi, and S. Durrani, *Fitoterapia* **62**, 157 (1991).
168. N.K. Saxena and D.S. Bhakuni, *J. Indian Chem. Soc.* **56**, 1020 (1979).
169. D.S. Bhakuni and S. Jain, *Tetrahedron* **36**, 3107 (1980).
170. D.S. Bhakuni, H. Uprety, and D.A. Widdowson, *Phytochemistry* **15**, 739 (1976).
171. H. Pande, N.K. Saxena, and D.S. Bhakuni, *Indian J. Chem. Ser. B* **14**, 366 (1976).
172. S. Jain, K.P. Madhusudanan, and D.S. Bhakuni, *Indian J. Chem. Ser. B* **26**, 308 (1987).
173. U.B. Zakirov, K.U. Aliev, and N.V. Abdumalikova, *Farmakol. Alkaloidov Glikozidov*, 197 (1971).
174. A.N. Singh and D.S. Bhakuni, *Indian J. Chem. Ser.* **B 15**, 388 (1977).
175. A.N. Singh and H. Pande, *Lloydia* **40**, 322 (1977).
176. A.N. Singh, H. Pande, and D.S. Bhakuni, *Experientia* **32**, 1368 (1976).
177. X. Zhang, M. Ke and Z. Huang, *Chung Tsao Yao* **13**, 489 (1982).
178. D.S. Bhakuni, V.M. Labroo, A.N. Singh, and R.S. Kapil, *J. Chem. Soc., Perkin Trans. I*, 121 (1978).
179. J. Buckingham, *Dictionary of Natural Products*, I-00368, Chapman & Hall, London, 1993.
180. M. Ju-ichi, Y. Fujitani, T. Shingu, and H. Furukawa, *Heterocycles* **16**, 555 (1981).
181. M. Ju-ichi, Y. Fujitani, and H. Furukawa, *Yakugaku Zasshi* **104** (9), 946 (1984).

182. R. Ziyaev, A. Abdusamatov, M.S. Yunusov, and S.Yu Yunusov, *Chem. Nat. Prod.* **27**, 73 (1991).
183. K. Kar, K.C. Mukherjee, and B.N. Dhawan, *Indian J. Exp. Biol.* **15**, 547 (1977).
184. O. Prakash, R. Roy, S. Jain, and D.S. Bhakuni, *J. Nat. Prod.* **51**, 603 (1988).
185. R.S. Singh, S. Jain, and D.S. Bhakuni, *Nas. Lett. (India)* **1**, 93 (1978).
186. D.S. Bhakuni, A.N. Singh, and S. Jain, *Tetrahedron* **36**, 2149 (1980).
187. H. Uprety and D.S. Bhakuni, *Tetrahedron Lett.* 1201 (1975).
188. J. Buckingham, *Dictionary of Natural Products*, B-00669. Chapman & Hall, London, 1993.
189. D.S. Bhakuni, S. Jain and S. Gupta, *Tetrahedron* **39**, 455 (1983).
190. V. Joshi, J.R. Merchant, V.V. Nadkarny, K. Namboori, and D.D. Vaghani, *Indian J. Chem.* **12**, 226 (1974).
191. S.F. Hussain, L. Khan, H. Guinaudeau, J.E. Leet, A.J. Freyer, and M. Shamma, *Tetrahedron* **40**, 2513 (1984).
192. A. Sinha, *J. Proc. Inst. Chem. (India)* **32**, 250 (1960).
193. S. Jain, K. Shukla, and D.S. Bhakuni, *Fitoterapia* **62**, 391 (1991).
194. M. Ikram, N. Shafi, and M. Abu-Zarga, *Planta Med.* **45**, 253 (1982).
195. D.S. Bhakuni and P.P. Joshi, *Tetrahedron* **31**, 2575 (1975).
196. N.C. Gupta, *Curr. Sci.* **47**, 768 (1978).
197. D.S. Bhakuni, N.C. Gupta, and M.M. Dhar, *Experientia* **26**, 241 (1970).
198. A.K. Suleiman, A.E. Dawud, A.E., Maged S., and P.L. Schiff, *Planta Med.* **59**, 276 (1993).
199. D.S. Bhakuni, *Proc. 5th. Asian Symposium on Medicinal Plants and Spices.*, p. 509, Seoul, Korea, 1984.
200. Atta-ur-Rahman, *Pure & Appl. Chem.* **58**, 663 (1986).
201. H. Guinaudeau, M. Bashir, M.D.Colton, A.J. Freyer, M. Shamma, K. Jehan, A. Nilofar, and Atta-ur-Rahman *Phytochemistry* **26**, 829 (1987).
202. D.S. Bhakuni, P.K. Gupta, P.P. Joshi, and S. Gupta, *Indian J. Chem. Ser. B* **21**, 389 (1982).
203. N.C. Gupta, D.S. Bhakuni, and M.M. Dhar, *Experientia* **26**, 12 (1970).
204. K. Watanabe, M. Miyakado, T. Iwai, K. Izumi, and K. Yanagi, *Agr. Biol. Chem.* **52**, 1079 (1988).
205. A.T. McPhail, K.D. Onan, H. Furukawa, and M. Ju-ichi, *Tetrahedron Lett.*, 485 (1976).
206. M. Ju-ichi, Y. Ando, Y. Yoshida, J.I. Kunitomo, T. Shingu and H. Furukawa, *Yakugaku Zasshi* **98**, 886 (1978).
207. K. Munakata and K. Wada, *in* "Advances in Natural Product Chemistry-Extraction & Isolation of Biologically Active Compounds" (S. Natori, N. Ikekawa and M. Susuki, eds.), p. 240, Wiley, New York, 1981.
208. J. Buckingham, *Dictionary of Natural Products*, C-01600. Chapman & Hall, London, 1993.

209. M. Ju-ichi, Y. Ando, Y. Yoshida, J.I. Kunitomo, T. Shingu, and H. Furukawa, *Chem. Pharm. Bull.* **25**, 533 (1977).
210. H.S. Chen, H.Q. Liang, and S.X. Liao, *Yao Hsueh Hsueh Pao* **26**, 755 (1991).
211. C.T. Fu, *Shan-His Hsin I Yao* **10**, 55 (1981).
212. H. Itokawa, S. Tsuruoka, K. Takeya, N. Mori, T. Sonobe, S. Kosemura, and T. Hamanaka, *Chem. Pharm. Bull.* **35**, 1660 (1987).
213. J. Siwon, R. Verpoorte, G.F.A. Van-Essen, and A. Baerheim-Svendsen, *Planta Med.* **38**, 24 (1980).
214. C. Palasuntheam, K.S. Iyer, L.B. Silva, and T. Silva, *Indian J. Med. Res.* **76**, 71 (1982).
215. N.S. Varier and P.P. Pillai, *Curr. Sci.* **12**, 228 (1943).
216. S. Malhotra, S.C. Taneja, and K.L. Dhar, *Phytochemistry* **28**, 1988 (1989).
217. P.M.M. Pinho, M.M.M. Pinto, A. Kijoa, K. Pharadai, J.G. Diaz, and W. Herz, *Phytochemistry* **31**, 1403 (1992).
218. S.C. Datta, R.K. Mathur, and J.N. Baruah, *Indian Drugs* **25**, 350 (1988).
219. H.D. Trinh, *Tap. Chi. Duoc Hoc* **3**, 19 (1983).
220. M. Lavault, A. Fournet, H. Guinaudeau, and J. Bruneton, *J. Chem. Res. S* **8**, 248 (1985).
221. N.G. Bisset, *Acta Amazônica* **18**, 255 (1988).
222. B. Tantisewie, T. Pharadai, M. Pandughanont, H. Guinaudeau, A.J. Freyer, and M. Shamma, *J. Nat. Prod.* **52**, 652 (1989).
223. B. Tantisewie, T. Pharadai, A.J. Freyer, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.* **53**, 553 (1990).
224. B. Tantisewie, T. Pharadai, S. Amnaauypol, A.J. Freyer, H. Guinaudeau, and M. Shamma, *Tetrahedron* **46**, 325 (1990).
225. M. Parvez, H. Guinaudeau, and M. Shamma, *Acta Cryst. Sect. C* **47**, 448 (1991).
226. H. Guinaudeau, L.Z. Lin, N. Ruangrungsi, and G.A. Cordell, *J. Nat. Prod.* **56**, 1989 (1993).
227. V.T. Yupraphat, P. Pachaly, and F. Zymalkowsky, *Planta Med.* **25**, 315 (1974).
228. Q.Z. Yan and L.Z. Lin, *Chung-Kuo Yao Li Hsueh Pao* **2**, 19 (1981).
229. J. Buckingham, *Dictionary of Natural Products*, F-00025. Chapman & Hall, London, 1993.
230. R.R. Paris and S.K. Sasorith, *Ann. Pharm. Fr.* **25**, 627 (1967).
231. J. Buckingham, *Dictionary of Natural Products*, T01149. Chapman & Hall, London, 1993.
232. B.M.R. Bandara, N.K. Illangasekara, U.L.B. Jayasinghe, V. Karunarante, G.P. Wannigama, M. Bokel, W. Kraus, and S. Sotheeswaran, *Planta Med.* **56**, 245 (1990).
233. Anonymous, *K'o Hsueh T'ung Pao* **24**, 574 (1979).
234. X.X. Zhang, Z.J. Tang, Y.L. Gao, R. Chen, A.N. Lao, and C.G. Wang, *Chih Wu Hsueh Pao* **23**, 216 (1981).

235. S.L. Huang, C.S. Zhao, H.Y. Wei, X.X. Bong, Y.D. Li, W.L. Yang, D.Z. Chen, and Y.Q. Wu, *Yao Hsueh T'ung Pao* **18**, 669 (1983).
236. F.X. Zhou and X.J. Xu, *Chih Wu Hsueh Pao* **21**, 41 (1979).
237. X.D. Fang, L.J. Qian, P.Z. Shen, and Z.Y. Shi, *Zhongcaoyao* **16**, 536 (1985).
238. N.H. Lajis, Z. Samadi, and N. Ismail, *Pertanika* **14**, 353 (1991).
239. J.M. Heinz, P. Peter, and Z. Felix, *Arch. Pharm. (Weinheim)* **310**, 314 (1977).
240. S.M. Kupchan, A.J. Liepa, R.L. Baxter, and H.P.J. Hintz, *J. Org. Chem.* **38**, 1846 (1973).
241. X.C. Tang, G.Z. Jin, J. Feng, Z.D. Zhang, and Y.F. Han, *Yao Hsueh Hsueh Pao* **15**, 513 (1980).
242. K. Dahmen, P. Pachaly, and F. Zymalkowsky, *Arch. Pharm (Weinheim)* **310**, 95 (1977).
243. L.Z. Lin, H.L. Shieh, C.K. Angerhofer, J.M. Pezzuto, G.A. Cordell, L. Xue, M.E. Johnson, and N. Ruangrungsi, *J. Nat. Prod.* **56**, 22 (1993).
244. N. Yokoyama and S.M. Kupchan, *Diss. Abstr. Int. B* **24**, 1412 (1963).
245. R. Verpoorte, T.A. Van Beek, H. Siwon, and A. Baerheim-Svendsen, *Pharm. Weekbl. (Sci. Ed.)* **4**, 87 (1982).
246. G. Klughardt and F. Zymalkowsky, *Arch. Pharm. (Weinheim)* **315**, 7 (1982).
247. S. Lai, T.F. Zhao, and X.K. Wang, *Yao Hsueh Hsueh Pao* **23**, 356 (1988).
248. X.K. Wang, T.F. Zhao, S. Lai, Y. Shizuri, and S. Yamamura, *Phytochemistry* **33**, 1249 (1993).
249. S. Lai, T.F. Zhao, X.K. Wang, Y. Shizuri, and S. Yamamura, *Yao Hsueh Hsueh Pao* **28**, 599 (1993).
250. X.K. Wang, T.F. Zhao, S. Lai, Y. Shizuri, and S. Yamamura, *Phytochemistry* **33**, 1253 (1993).
251. S. Lai, T.F. Zhao, X.K. Wang, Y. Shizuri, and S. Yamamura, *Hua Hsueh Hsueh Pao* **51**, 1133 (1993).
252. F.X. Zhou, Z.Q. Chen, P.Y. Liang, and J. Wen, *Chung Ts'ao Yao* **12**, 7 (1981).
253. J. Buckingham, *Dictionary of Natural Products*, C-01221. Chapman & Hall, London, 1993.
254. S.K. Adesina, J.B. Harborne, and J.D. Phillipson, *Planta Med.* **33**, 217 (1978).
255. T. Furuya, T. Yoshikawa, and H. Kiyohara, *Phytochemistry* **22**, 1671 (1983).
256. R. Rondanelli, R. Guaglio, E. Sartirana, E. Zizzi, and P. Olliaro, *Il Farmaco Ed. Sci.* **41**, 185 (1986).
257. R. Rondanelli, R. Guaglio, E. Guarnone, E. Bre, P. Olliaro, and R. Cipelli, *Il Farmaco Ed. Pr.* **41**, 190 (1986).
258. A. Bouquet and A. Cavé, *Plant. Med. Phytoter.* **5**, 131 (1971).
259. I.H. Burkill, *Dictionary of the Economic Products of the Malay Peninsula*, Vol. I, p. 1. Ministry of Agriculture and Cooperatives, Kuala Lumpur, Malyasia, 1966.
260. J.R. Dai, H.B. Chai, J.M., Pezzuto, A.D. Kinghorn, S. Tsauri, and K. Padmawinata, *Phytother. Res.* **7**, 290 (1993).

261. J. Siwon, R. Verpoorte, and A. Baerheim-Svendesen, *Planta Med.* **41**, 65 (1981).
262. J. Siwon, C. Thijs, R. Verpoorte, and A. Baerheim-Svendsen. *Pharm. Weekbl.* **113**, 1153 (1978).
263. R.M. Liu, S.X. Zhao, Z.D. Min, M.S. Wang, and C.J. Liu, *Nan-Ching Yao Hsueh Yuan Hsueh Pao* **2**, 77 (1982).
264. Y. Xu, *Chih Wu Fen Lei Hsueh Pao* **18**, 389 (1980).
265. K.W. Bentley, *Nat. Prod. Rep.* **3**, 153 (1986).
266. J.H. Chu, R.Q. Chen, and S.D. Fang, *Hua Hsueh Hsueh Pao* **28**, 89 (1962).
267. B.Q. Pan, M.S. Lan, and S.J. Sun, *Yiyao Gongye* **7**, 319 (1988).
268. F.K. Duah, P.D. Owusu, D.J. Slatkin, and Schiff, P.L. *Phytochemistry* **22**, 321 (1983).
269. F.K. Duah, P.D. Owusu, J.E. Knapp, D.J. Slatkin, and P.L. Schiff, *Planta Med.* **42**, 275 (1981).
270. H. Ripperger, A. Preiss, and M. Diaz, *Phytochemistry* **22**, 2603 (1983).
271. A. Cuellar-Cuellar and S. Diaz-Azcuy, *Rev. Cubana Farm.* **13**, 109 (1979).
272. M.P. Cava, T.A. Reed, and J.L. Beal, *Lloydia* **28**, 73 (1986).
273. M.L. Carvalhas, *J. Chem. Soc., Perkin Trans. I*, 327 (1972).
274. A.M.M. Ateya and P.L. Schiff, *Diss. Abstr. Int. B* **40**, 2143 (1979).
275. D. Dwuma-Badu, J.S.K. Ayim, O. Rexford, A.M. Ateya, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *Phytochemistry* **19**, 1564 (1980).
276. D. Dwuma-Badu, *Fitoterapia* **58**, 348 (1987).
277. S. Berthou, M. Lebouef, A. Cavé, J. Mahuteau, B. David, and H. Guinaudeau, *J. Org. Chem.* **54**, 3491 (1989).
278. R.W. Doskotch and J.E. Knapp, *Lloydia* **34**, 292 (1971).
279. J. Buckingham, *Dictionary of Natural Products*, I-00597. Chapman & Hall, London, 1993.
280. C.Y. Hou and H. Xue, *Yao Hsueh Hsueh Pao* **20**, 112 (1985).
281. Y. Okamoto, *Tetrahedron Lett.*,1933 (1969).
282. C.Y. Hou and H. Xue, *Yao Hsueh Hsueh Pao* **19**, 471 (1985).
283. J.I. Kunitomo and Y. Miyata, *Heterocycles* **24**, 437 (1986).
284. Y. Okamoto, S. Tanaka, K. Kitayama, M. Isomoto, M. Massaiachi, H. Yanagawa, and J. Kunitomo, *Yakugaku Zasshi* **91**, 684 (1971).
285. K.W. Bentley, *Nat. Prod. Rep.*, 419 (1995).
286. X.P. Pang, Y.W. Chen, X.J. Li, and J.G. Long, *Yao Hsueh Hsueh Pao* **26**, 387 (1991).
287. Y.Q. Sun, F. Li, L.Wang, H. Cai, C.Y. Gao, A. Zhang, and L. Zhang, *Sepu* **2**, 169 (1985).
288. Y. Sugimoto, A. Yoshida, S. Uchida, S. Inanaga, and Y. Yamada, *Phytochemistry* **36**, 679 (1994).
289. Y. Sun, C. Gao, L. Zhang, A. Zhang, F. Li, L. Wang, and H. Cai, *Shenyang Yaoxueyuan Xuebao* **1**, 223 (1984).
290. J.C. He, *Chung Ts'ao Yao* **14**, 564 (1983).

291. X.P. Pan, Process for extracting therapeutic dauricine from *Menispermum dauricum* roots and stems. *Faming Zhuanli Shenqing Gongkai Shuomingshu* 1,047,861 (1990).
292. X.T. Guan, W.J. Wang, X.P. Sun, C.H. Zhao, and J.F. Hu, *Wu-Han I Hsueh Yuan Hsueh Pao* **12**, 156 (1983).
293. X.P. Pan, *Yao Hsueh Hsueh Pao* **27**, 788 (1993).
294. X.W. Zheng, Z.D. Min, and S.X. Zhao, *K'o Hsueh T'ung Pao* **24**, 285 (1979).
295. S.M. Hu, S.X. Xu, X.S. Yao, C.B. Cui, Y. Tezuka, and T. Kikuchi, *Chem. Pharm. Bull.* **41**, 1866 (1993).
296. M. Takani, Y. Takasu, and K. Takahashi, *Chem. Pharm. Bull.* **31**, 3091 (1983).
297. J.I. Kuniitomo, S. Kaede, and M. Satoh, *Chem. Pharm. Bull.* **33**, 2778 (1985).
298. K. Bentley, *Nat. Prod. Rep.* **9**, 365 (1992).
299. T. Gong and Z.Y. Wu, *Yao Hsueh Hsueh Pao* **14**, 439 (1979).
300. J. Buckingham, *Dictionary of Natural Products*, L-00610. Chapman & Hall, London, 1993.
301. V.V. Berezhiskaya and B.S. Nilkolskaya, *Farmakol Toksikol (Moscow)* **19S**, 13 (1956).
302. M. Lebouef, M.L. Abouchacra, A. Cavé, and M. Debray, *Plant. Med. Phytoter.* **21**, 106 (1987).
303. A.K. Moustafa-Aly, *Diss. Abstr. Int. B* **45**, 567 (1984).
304. M.A. El-Kawi, D.J. Slatkin, P.L. Schiff, S. Dasgupta, S.K. Chattopadhyay, and A.B. Ray, *J. Nat. Prod.* **47**, 459 (1984).
305. A.B. Ray, M. Abd-El-Kawi, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *Abstr. Joint Meeting American Society of Pharmacognosy and Society for Economic Botany*, p. 77, Boston, MA, U.S.A, 1981.
306. S. Dasgupta, A.B. Ray, S.K. Bhattacharya, and R. Bose, *J. Nat. Prod.* **42**, 399 (1979).
307. S.V. Bhat, H. Dornauer, and N.J. De-Souza, *J. Nat. Prod.* **43**, 588 (1980).
308. M.U.S. Sultanbawa, S. Sotheeswaran, S. Balasubramanian, M.A. El-Kawi, D.J. Slatkin, and P.L. Schiff, *Heterocycles* **20**, 1927 (1983).
309. M.U.S. Sultanbawa, S. Sotheeswaran, S. Balasubramanian, M.A. El-Kawi, D.J. Slatkin, and P.L. Schiff, *Phytochemistry* **24**, 589 (1985).
310. M.U.S. Sultanbawa, S. Sotheeswaran, S. Balasubramanian, D.J. Slatkin, and P.L. Schiff, *Abstr. 24th Annual Meeting of the American Society of Pharmacognosy*, p. 28. Oxford, MS, U.S.A, 1983.
311. J. Buckingham, *Dictionary of Natural Products*, R-00142. Chapman & Hall, London, 1993.
312. N.G. Bisset and J. Nwaiwu, *Planta Med.* **48**, 275 (1983).
313. N. Ruangrungsi, G.L. Lange, and M. Lee, *J. Nat. Prod.* **49**, 253 (1986).
314. H. Achenbach and H. Hemrich, *Phytochemistry* **30**, 1957 (1991).
315. A.A. Sioumis and V.N. Vashit, *Aust. J. Chem.* **25**, 2251 (1972).

316. J. Siwon, R. Verpoorte, T. Van Beek, H. Meerburg, and A. Baerheim-Svendsen, *Phytochemistry* **20**, 323 (1981).
317. T. Van Beek, R. Verpoorte, and A. Baerheim-Svendsen, *Abstr. Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany*, p. 44, Boston, MA, U.S.A, 1981.
318. T. Van Beek, R. Verpoorte, and A. Baerheim-Svendsen, *J. Org. Chem.* **47**, 898 (1982).
319. T. Van Beek, R. Verpoorte, and A. Baerheim-Svendsen, *Planta Med.* **42**, 141 (1981).
320. J.C. Regalado, C.Y. Gao, E. Fu, F.T. Lin, M.C. Lin, L.K. Wong, and P.L. Schiff, *Heterocycles* **26**, 2573 (1987).
321. J. Buckingham, *Dictionary of Natural Products*, P-02226. Chapman & Hall, London, 1993.
322. J. Buckingham, *Dictionary of Natural Products*, P-02227. Chapman & Hall, London, 1993.
323. J. Buckingham, *Dictionary of Natural Products*, P-02223. Chapman & Hall, London, 1993.
324. J. Buckingham, *Dictionary of Natural Products*, T-01295. Chapman & Hall, London, 1993.
325. J.W. Loder and R.H. Nearn, *Aust. J. Chem.* **25**, 2197 (1972).
326. D. Dwuma-Badu, J.S.K. Ayim, S.F. Withers, N.O. Agyemang, A.M. Ateya, M.M. El-Azizi, J.E. Knapp, D.J. Slatkin, and Schiff, P.L. *J. Nat. Prod.* **43**, 123 (1980).
327. A.N. Tackie, D. Dwuma-Badu, J.E. Knapp, D.J. Slatkin, and P.L. Schiff, *Phytochemistry* **13**, 2884 (1974).
328. B.O. Sowemimo, J.L. Beal, R.W. Doskotch, and G.H. Svoboda, *Lloydia* **35**, 90 (1972).
329. P. Damas, J. Bruneton, A. Fournet, and H. Guinaudeau, *J. Nat. Prod.* **48**, 69 (1985).
330. C. Galeffi, R. La-Bua, I. Messana, R. Zapata-Alcazar, and G.B. Marini-Bettolo, *Gazz. Chim. Ital.* **108**, 97 (1978).
331. K. Takahashi, M.J. Mitchell, and M.P. Cava *Heterocycles* **4**, 471 (1976).
332. H. Itokawa, K. Takeya, N. Mori, T. Sonobe, S., Kosemura, N. Okamura, T. Ogawa, M. Ogoshi, K. Yamakawa, and T. Hamanaka, Isolation and antitumor activity of FK-2000 and FK-3000, two new alkaloids from *Sinomenium acutum*. *Japan Kokai Tokkyo Koho* 62 289,565 (1988).
333. J.J. Willaman and H.L. Li, *Lloydia* **33**, 1 (1970).
334. K. Ichikawa, T. Kinoshita, A. Ital, Y. Litaka, and U. Sankawa, *Heterocycles* **22**, 2071 (1984).
335. H. Otsuka, A. Ito, N. Fujikowa, K.I. Kawamata, R. Kasai, K. Yamasaki, and T. Satoh, *Phytochemistry* **33**, 389 (1993).
336. M. Moriyasu, M. Ichimaru, Y. Nishiyama, and A. Kato, *Nat. Med.* **48**, 287 (1994).

337. Y.Y. Chen, C.C. Qiu, L. Shen, C.Y. Gao, L. Qiao, and D. Wang, *Beijing Yike Daxue Xuebao* **23**, 235 (1991).
338. T. Nozaka, I. Morimoto, M. Ishino, and S. Natori, *Chem. Pharm. Bull.* **36**, 2259 (1988).
339. T. Nozaka, I. Moromoto, M. Ishino, T. Okitsu, H., Kondoh, K. Kyogoku, Y. Sugawara, and H. Iwasaki, *Chem. Pharm. Bull.* **35**, 2844 (1987).
340. S. Nunome, M. Okada, and H. Mitsuhashi, *Shoyakugagku Zasshi* **45**, 40 (1991).
341. J.H. Chu, S.Y. Li, and Y.L. Chou, *Hua Hsueh Hsueh Pao* **30**, 265 (1964).
342. Y. Sugimoto and Y. Sugimura, Extraction of therapeutic aromoline from *Sinomenium diversifolium* roots and bulbs. *Japan Kokai Tokkyo Koho* 04 05,238. (1992).
343. Y. Yamada, Y. Sugimoto, and K. Okamoto, Bisbenzylisoquinoline alkaloid and its manufacture with *Sinomenium diversifolium*. *Japan Kokai Tokkyo Koho* JP02 138984. (1990).
344. D. Dwuma-Badu and T.U. Okarter, *Phytochemistry* **15**, 2025 (1976).
345. R.A. Hussain, J.W. Kim, C.W.W. Beecher, and A.D. Kinghorn, *Abstr. International Congress on Natural Products Research* p. 22, Park City, UT, U.S.A, 1988.
346. R.A. Hussain, J.W. Kim, C.W.W. Beecher, and A.D. Kinghorn, *Heterocycles* **29**, 2257 (1989).
347. T.U. Okarter, *Diss. Abstr. Int. B* **37**, 2169 (1976).
348. S. Ratsimamanqa-Urverg, P. Rasoanaivo, L. Ramiaramanana, R. Milijaoana, H. Rafatro, F. Verdier, A. Rakoto-Ratismananga, and J. Le-Bras, *Planta Med.* **58**, 540 (1992).
349. K.M. Kande, S. Philipov, and H. Dutschewska, *Fitoterapia* **65**, 90 (1994).
350. A.J. Van Wyk, *J. S. Afr. Chem. Inst.* **28**, 284 (1975).
351. E. Dagne, A.A.L. Gunatilaka, D.G.I. Kingston, and M. Alemu, *J. Nat. Prod.* **56**, 2022 (1993).
352. M.I. Suffness, *Diss. Abstr. Int. B* **31**, 1854 (1970).
353. S.M. Kupchan, M.I. Suffness, and E.M. Gordon, *J. Org. Chem.* **35**, 1682 (1967).
354. J. Buckingham, *Dictionary of Natural Products*, P-01939. Chapman & Hall, London, 1993.
355. J. Buckingham, *Dictionary of Natural Products*, S-01268. Chapman & Hall, London, 1993.
356. J. Buckingham, *Dictionary of Natural Products*, S-01280. Chapman & Hall, London, 1993.
357. J.P. Bartley, L.T. Baker, and C.F. Carvalho, *Phytochemistry* **36**, 1327 (1994).
358. Z.Y. Zhu, Y.X. Feng, L.Y. Ho, and Y.C. Wang, *Yao Hsueh Hsueh Pao* **18**, 460 (1983).
359. Y. Chen, Q.S. Kang, G.Q. Song, Z.P. Hu, and J.X. Huang, *Chung Ts'ao Yao* **13**, 1 (1982).

360. S.L. Peng, L. Chen, G.L. Zhang, W.I. Pan, and W.X. Chen, *Tianran Chanwu Yanjiu Yu Kaifa* **4**, 11 (1992).
361. H.M. Yang and X.R. Luo, *Yao Hsueh Hsueh Pao* **15**, 674 (1980).
362. J.Z. Deng, S.X. Zhao, and Z.C. Miao, *Phytochemistry* **31**, 1448 (1992).
363. Y. Sugimoto, Y. Sugimura, and Y. Yamada, *Agr. Biol. Chem.* **52**, 1495 (1988).
364. Y. Sugimoto, Y. Yamada and Y. Sugimura, Preparation of aromolline from *Stephania cepharantha* roots. *Japan Kokai Tokkyo Koho* 03,34,980 (1991).
365. Y. Sugimoto and Y. Yamada, *J. Nat. Prod.* **52**, 199 (1989).
366. Y. Sugimoto, Y. Sugimura, and Y. Yamada, *Phytochemistry* **27**, 1379 (1988).
367. N. Kashiwaba, S. Morroka, M. Kimura, Y. Murakoshi, J. Toda, and T. Sano, *Chem. Pharm. Bull.* **42**, 2452 (1994).
368. M. Akasu, H. Itokawa, and H. Fujita, M. *Phytochemistry* **15**, 471 (1976).
369. D.B. Mix, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.* **45**, 657 (1982).
370. K. Kinoshita, K. Morikawa, M. Fujita, and S. Natori, *Planta Med.* **58**, 137 (1992).
371. J.I. Kunimoto, M. Oshikata, and M. Akasu, *Yakugaku Zasshi* **101**, 951 (1981).
372. M. Akasu, H. Itokawa, and M. Fujita, *Tetrahedron Lett.* 3609 (1974).
373. K. Utsumi, E. Okimasu, and M. Miyahara, *Abstr. 3rd. Congress of the Federation of Asian and Oceanian Biochemists*, p. 87. Bangkok, Thailand
374. M. Akasu, H. Itokawa, and M. Fujita, *Phytochemistry* **14**, 1673 (1975).
375. J.Buckingham, *Dictionary of Natural Products*, C-00739. Chapman & Hall, London, 1993.
376. G. Xia, Y. Qin, Q. Yang, Y. Zhang, and X. Liu, *Chung Ts'ao Yao* **16**, 266 (1985).
377. S.Y. Gustini, Alkaloid of *Stephania corymbosa* Bl. Thesis of Post Graduate Student, Inst. Techn. Bandung, Indonesia, 1989.
378. J. Buckingham, *Dictionary of Natural Products*, D-00352. Chapman & Hall, London, 1993.
379. M.E. Perel'son, I.I. Fadeeva, and T.N. Il'inskaya, *Chem. Nat. Comp.* **11**, 197 (1975).
380. T.B. Wu, G.Q. Liu, Z. Min, Z.Q. Ma, and X.J. Liu, *Zhongguo Yaoke Daxue Xuebao* **20**, 235 (1989).
381. P.S. Xie, D.Y. Xu, and Z.X. Yang, *Chung Ts'ao Yao* **11**, 433 (1980).
382. Z.D. Min, *Chung Ts'ao Yao* **14**, 57 (1983).
383. Y. Chen, *Zhiwu Xuebau* **31**, 544 (1989).
384. J. Buckingham, *Dictionary of Natural Products*, N-00688. Chapman & Hall, London, 1993.
385. J. Buckingham, *Dictionary of Natural Products*, S-01271. Chapman & Hall, London, 1993.
386. J. Buckingham, *Dictionary of Natural Products*, S-01286. Chapman & Hall, London, 1993.
387. C. Tian and J. Wu, *Zhogcaoyao* **19**, 392 (1988).

388. R.S. Singh, P. Kumar, and D.S. Bhakuni, *J. Nat. Prod.* **44**, 664 (1981).
389. R.L. Khosa, V.K. Lal, A.K. Wahi, and A.B. Ray, *Chem. Ind. (London)*, 662 (1980).
390. Z.Q. Chen, S.L. Yang, and X.L. Ding, *Nanjing Yixueyuan Xuebao* **5**, 203 (1985).
391. J.X. Huang and Y. Chen, *Yao Hsueh Hsueh Pao* **14**, 612 (1979).
392. S.L. Peng, L. Chen, G.L. Zhang, W. Pan, and W.X. Chen, *Tianran Chanwu Yanjiu Yu Kaifa* **2**, 37 (1990).
393. K.W. Bentley, *Nat. Prod. Rep.* **6**, 405 (1989).
394. D.S. Bhakuni and S. Gupta, *J. Nat. Prod.* **45**, 407 (1982).
395. A. Patra, A. Ghosh, and A.K. Mitra, *Planta Med.* **40**, 333 (1980).
396. T.N. Il'inskaya, P.N. Kibal'Chich, I.M. Rabinovich and I.I. Fadeeva, Extraction of gindarine from the tubers of *Stephania glabra*. *Fr. Patent* 1,598,036 (1970).
397. V.K. Pendse, R.K. Soni, V. Madan, and V.S. Acharya, *J. Res. Indian Med. Yoga Homeopathy* **14**, 44 (1979).
398. E.V. Arzamastev, M.I. Mironova, L.V. Krepkova, V.V. Bortnikova, and Y.B. Kuzneitsov, *Farmakol Toksikol (Moscow)* **46**, 107 (1983).
399. P.D. Desai, A.K. Ganguly, T.R. Govindachari, B.S. Joshi, V.N. Kamat, A.H. Manmade, P.A. Mohamed, S.K. Nagle, , R.H. Nayak, A.K. Saksena, S.S. Sathe, and N. Viswanathan, *Indian J. Chem.* **4**, 457 (1966).
400. T.F. Gurova, Y.G. Popov, I.I. Fadeyeva, S.S. Shain, and O.N. Tolkachov, *Rast. Resur.* **16**, 421 (1980).
401. A.K. Wahi, S.P. Wahi, and S. Ghosal, *Indian J. Pharm.* **39**, 36 (1977).
402. R.L. Khosa, Y. Mohan, and A.K. Wahi, *Indian J. Nat. Prod.* **3**, 8 (1987).
403. S.D. Fang, X.J. Xu, Y. Chen, and Y. Zhong, *Chung Ts'ao Yao* **18**, 146 (1987).
404. J. Buckingham, *Dictionary of Natural Products*, A-00626. Chapman & Hall, London, 1993.
405. A.B. Ray, S. Chattopadhyay, R.M. Tripathi, S.S. Gambhir, and P.K. Das, *Planta Med.* **35**, 167 (1979).
406. P.D. Desai, M.D. Dutia, A.K. Ganculy, T.R. Govindachari, B.S. Joshi, V.N. Kamat, D. Prakash, D.F. Rane, S.S. Sathe, and N. Viswanathan, *Indian J. Chem.* **5**, 523 (1967).
407. J. Buckingham, *Dictionary of Natural Products*, S-01283. Chapman & Hall, London, 1993.
408. A. Patra, T.K. Mandal, P.K. Mukhopadhyay, and B.C. Ranu, *Phytochemistry* **27**, 653 (1988).
409. T.R. Govindachari, S.J. Jadhav, B.S. Joshi, V.N. Kamat, P.A. Mohamed, P.C. Parthasarathy, S.J. Patankar, D. Prakash, D.F. Rane, and N. Viswanathan, *Indian J. Chem.* **7**, 308 (1969).
410. J. Buckingham, *Dictionary of Natural Products*, H-00492. Chapman & Hall, London, 1993.

411. I.I. Fadeeva, T.N. Il'inskaya, M.E. Perel'son, and A.D. Kuzovkov, *Khim. Prir. Soedin.* **6**, 492 (1970).
412. Y. Chen, Y.Y. Chen, G.Q. Song, and H.N. Wang, *Yao Hsueh T'ung Pao* **16**, 1 (1985).
413. M. Matsui, Y. Watanabe, T. Ibuka, and K. Tanaka, *Chem. Pharm. Bull.* **23**, 1323 (1975).
414. A.R. Battersby, R.C.F. Jones, R. Kazlauskas, C.W. Thornber, S. Ruchirawat, and J. Staunton, *J. Chem. Soc., Perkin Trans. I*, 2016 (1981).
415. A.R. Battersby, R.C.F. Jones, A. Minta, A.P. Ottridge, and J. Staunton, *J. Chem. Soc., Perkin Trans. I*, 2030 (1981).
416. Y. Watanabe, M. Matsui, and M. Uchida, *Phytochemistry* **14**, 2695 (1975).
417. Y. Watanabe, M. Matsui, M. Iibuchi, and S. Hiroe, *Phytochemistry* **14**, 2522 (1975).
418. M. Matsui, Y. Yamamura, T. Takebayashi, K. Iwaki, Y. Takami, K. Kunitake, F. Koga, S. Urasaki, and Y. Watanabe, *J. Nat. Prod.* **47**, 858 (1984).
419. T. Taga, N. Akimoto, and T. Ibuka, *Chem. Pharm. Bull.* **32**, 4223 (1984).
420. M. Matsui, T. Kabashima, K. Ishida, T. Takebayashi, and Y. Watanabe, *J. Nat. Prod.* **45**, 497 (1982).
421. Y. Yamamura and M. Matsui, *J. Nat. Prod.* **48**, 746 (1985).
422. M. Matsui and Y. Watanabe, *J. Nat. Prod.* **47**, 465 (1984).
423. M. Matsui and Y. Yamamura, *J. Nat. Prod.* **49**, 588 (1986).
424. S. Kondo, M. Matsui, and Y. Watanabe, *Chem. Pharm. Bull.* **31**, 2574 (1983).
425. J. Buckingham, *Dictionary of Natural Products*, B-00118. Chapman & Hall, London, 1993.
426. M. Matsui, M. Uchida, I. Usuki, Y. Saionji, H. Murata, and Y. Watanabe, *Phytochemistry* **18**, 1087 (1979).
427. Z.D. Min and S.M. Zhong, *Yao Hsueh Hsueh Pao* **15**, 532 (1980).
428. G.R. Cheng, K.C.Wang, and Y.S. Wen, *Chung Ts'ao Yao* **12**, 6 (1981).
429. K.J. Cheng, K.C. Wang, and Y.H. Wang, *Yao Hsueh Hsueh Pao* **16**, 49 (1981).
430. Y. Chen, S.D. Fang, H.W. Li, Y.H. Li, and H.M. Yang, *Chih. Wu Hsueh Pao* **33**, 552 (1991).
431. A. Lao, Y. Gao, Z. Tang, and R. Xu, *Yao Hsueh Hsueh Pao* **15**, 696 (1980).
432. A.N. Lao, Y.L. Gao, Z.G. Tang, Y.H. Wang, X.X. Zhang, C.G.Wang, and R.S. Xu, *Hua Hsueh Hsueh Pao* **40**, 1038 (1982).
433. J.Z. Deng and S.X. Zhao, *Phytochemistry* **33**, 941 (1993).
434. A.N. Lao, Z.J. Zong, and R.S. Xu, *Yao Hsueh Hsueh Pao* **16**, 940 (1981).
435. L.F. Chen, J.Z. Gao, F.C. Wang, and C.R. Fang, *Chung-Kuo Yao Li Hsueh Pao* **6**, 156 (1985).
436. X.F. Wang and R.F. Wei, *Chung Ts'ao Yao* **14**, 249 (1983).
437. Z.D. Min, X.S. Liu, and W.J. Sun, *Yao Hsueh Hsueh Pao* **16**, 557 (1981).
438. Y. Chen, T. Yuan, Y. Xu, and G.M. Liu, *Chih Wu Hsueh Pao* **36**, 486 (1994).

439. Z.Q. Chen, X.L. Ding, Z.D. Min, M.Y. Wu, and Z.G. Yong, *Nanjing Yisueyuan Xuebao* 7, 13 (1987).
440. K.W. Bentley, *Nat. Prod. Rep.* **9**, 365 (1992).
441. K. Likhitwitayawuid, C.K. Angerhofer, H. Chai, J.M. Pezzuto, G.A. Cordell, and N. Ruangrungsi, *J. Nat. Prod.* **56**, 1468 (1993).
442. B. Tantisewie, S. Amurrio, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.* **52**, 846 (1989).
443. M. Kozuka, K. Miyaji, S.T. Awada, and M. Tomita, *J. Nat. Prod.* **48**, 341 (1985).
444. J. Buckingham, *Dictionary of Natural Products*, C-02216. Chapman & Hall, London, 1993.
445. J. Buckingham, *Dictionary of Natural Products*, S-01278. Chapman & Hall, London, 1993.
446. J.I. Kunitomo, Y. Murakami, M. Oshikata, T. Shingu, S.T. Lu, I.S. Chen, and M. Akasu, *Yakugaku Zasshi* **101**, 431 (1981).
447. J.I. Kunitomo, Y. Murakami, M. Oshikata, T. Shingu, M. Akasu, and I.S. Chen, *Phytochemistry* **19**, 2735 (1980).
448. J.I. Kunitomo, Y. Murakami, M. Oshikata, M. Akasu, K. Kodama, N. Takeda, K.I. Harada, M. Suzuki, A. Tatematsu, E. Kawanabe, and H. Ishii, *Chem. Pharm. Bull.* **33**, 135 (1985).
449. B.D. Krane and M. Shamma, *J. Nat. Prod.* **45**, 377 (1982).
450. J.I. Kunitomo M. Oshikata, and Y. Murakami, *Chem. Pharm. Bull.* **29**, 2251 (1981).
451. Z.D. Min, G. Lin, G.X. Xu, M. Iinuma, T. Tanaka, and M. Mizuno, *Phytochemistry* **24**, 3084 (1985).
452. Anonymous *Chih Wu Hsueh Pao* **19**, 257 (1977).
453. D.C. Ruan, X.M. Zhang, C.J. Zhao, F.C. Wang, L.X. Tian, and C.G. Yang, *Yun-Nan Chih Wu Yen Chiu* **13**, 225 (1991).
454. I.I. Fadeeva, T.N. Il'inskaya and O.N. Tolkachev, Gindarine. *Patent USSR* 721,101. (1980).
455. A. Patra, C.T. Montgomery, A.J. Freyer, H. Guinaudeau, and M. Shamma, *Phytochemistry* **26**, 547 (1987).
456. A. Patra, C.T. Montgomery, A.J. Freyer, H. Guinaudeau, M. Shamma, B. Tantisewie, and K. Pharadai, *J. Nat. Prod.* **49**, 424 (1986).
457. A. Patra, *Phytochemistry* **26**, 2391 (1987).
458. J. Buckingham, *Dictionary of Natural Products*, I-00817. Chapman & Hall, London, 1993.
459. Z. Xue, P.L. Zhang and J.M. Ma, *Yao Hsueh Hsueh Pao* **21**, 223 (1986).
460. X.K. Wang, Y.R. Zhao, T.F. Zhao, S. Lai, and C.T. Che, *Phytochemistry* **35**, 263 (1994).
461. C. Deng, T.F. Zhao, and X.K. Wang, *West China J. Pharm. Sci.* **3**, 65 (1988).
462. X.K. Wang, Y.R. Zhao, T.F. Zhao, and C.T. Che, *Planta Med.* **61**, 99 (1995).

463 T. Ogino, T. Sato, H. Sasaki, M. Chin, and H. Mitsuhashi, *Heterocycles* **27**, 1149 (1988).
464. Y. Feng and H. Chen, *Yaowu, Fenxi Zazhi* **5**, 28 (1985).
465. J.Z. Deng, S.X. Zhao, T. Lu, and F.C. Lou, *Chin. Chem. Lett.* **2**, 231 (1991).
466. D.Y. Si, S.X. Zhao, and J.Z. Deng, *J. Nat. Prod.* **55**, 828 (1992).
467. T.M. Hu and S.X. Zhao, *Yao Hsueh Hsueh Pao* **21**, 29 (1986).
468. D.G. Cai, M.J. Gu, X.S. Chen, and J. Zhang, *Cheung Ts'ao Yao* **24**, 339 (1993).
469. T.Y. Zhang, L.K., Pannell, D.G. Cai, and Y. Ito, *J. Liq. Chromatogr.* **11**, 1661 (1988).
470. Y.F. Yang, S.X. Zhao, and C. Liu, *Chung Yao T'ung Pao* **13**, 740 (1988).
471. P. Zehn, P.R. Chen, and H.Q. Wang, *Chung Ts'ao Yao* **25**, 575 (1994).
472. T. Ogino, S. Sato, M. Chin, and K. Kawashima, Isolation of a fangchinoline derivative as an antihypertensive. *Japan Kokai Tokkyo Koho* 63,179,878 (1988).
473. T.Ogino, M. Chin, K. Fukuyama, and M. Kawashima, Antihypertensive fangchinolines from Menispermaceae and pharmaceutical compositions containing them. *Japan Kokai Tokkyo Koho* 01,113,392 (1989).
474. R.H. Yang and X.M. Wang, *Chung Ts'ao Yao* **13**, 452 (1982).
475. J.Z. Deng, S.X. Zhao, and F.C. Lou, *J. Nat. Prod.* **53**, 993 (1990).
476. Y.F. Xue, S.X. Zhao, and C. Liu, Extraction of rotundine and isocorydine from *Stephania tetrandra* with nontoxic solvents. *Faming Zhuanli Shenqing Gongkai Shuomingshu* 1,030,416 (1989).
477. T. Ogino, T. Yamaguchi, S. Sato, and M. Chin, Isolation of berbamine alkaloids from *Stephania tetrandra* as acetylcholine esterase inhibitors. *Japan Kokai Tokkyo Koho* 04,159,278 (1992).
478. Anonymous, *Natl. Med. J. China* **54**, 539 (1974).
479. Z.R. Wu and W.P. Jin, *Chung Ts'ao Yao* **19**, 349 (1988).
480. Anonymous, *Chung-Hua I Hsueh Tsa Chih (Engl. Ed.)* **92**, 193 (1979).
481. F.H. Lu, *Acta Acad. Med. Wuhan*, 89 (1979).
482. Y. Yang, *Chung Ts'ao Yao* **16**, 281 (1985).
483. Anonymous, *Chung-Hua I Hsueh Tsa Chih* **54**, 539 (1974).
484. T. Ogino, S. Sato, H. Sasaki and M. Chin, Isolation of new alkaloids from *Stephania tetrandra* as antihypertensives. *Japan Kokai Tokkyo Koho* 62,205,084 (1987).
485. T. Ogino, S. Sato, H. Sasaki, and M. Chin, Isolation and structure determination of 1,3,4-tridehydrofangchinolinium hydroxyde. *Japan Kokai Tokkyo Koho* 62,294,684 (1986).
486. B. Charles, J. Bruneton, K. Pharadai, B. Tantisewie, H. Guinaudeau, and M. Shamma, *J. Nat. Prod.* **50**, 1113 (1987).
487. B. Tantisewie, H. Guinaudeau, A.J. Freyer, and M. Shamma, *J. Nat. Prod.* **48**, 658 (1985).

488. H. Guinaudeau and M. Shamma, *Abstr. Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany*. p. 8, Boston, MA, U.S.A, 1981.
489. H. Guinaudeau, M. Shamma, B. Tantisewie, and K. Pharadai, *J. Nat. Prod.* **45**, 355 (1982).
490. K. Pharadai, B. Tantisewie, S. Ruchirawat, S.F. Hussain, and M. Shamma, *Heterocycles* **15**, 1067 (1981).
491. J. Buckingham, *Dictionary of Natural Products*, C-01976. Chapman & Hall, London, 1993.
492. J. Banerji, A. Chaterjee, A. Patra, P. Bose, R. Das, M. Shamma, and B. Tantisewie, *Phytochemistry* **36**, 1053 (1994).
493. H. Guinaudeau, M. Shamma, B. Tantisewie, and K. Pharadai, *Chem. Commun.*, 1118 (1981).
494. H. Guinaudeau, A.J. Freyer, and M. Shamma, *Tetrahedron* **43**, 1759 (1987).
495. H. Guinaudeau and M. Shamma, *Abstr. Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany*, p. 79. Boston, MA, U.S.A, 1981.
496. S.D. Fang, W.L. Wang, Y. Chen, and J.B. Hu, *Chung Ts'ao Yao* **12**, 1 (1981).
497. S.D. Fang, Y. Chen, H.N. Wang, Y.C. Li, and C.H. Xu. *Chung Ts'ao Yao* **24**, 457 (1993).
498. Y. Chen, S.D. Fang, D. Liang, and F.Y. Jiang, *Chih Wu Hsueh Pao* **31**, 296 (1989).
499. B. Charles, H. Guinaudeau, J. Bruneton, and P. Cabalion, *Can. J. Chem.* **67**, 1257 (1989).
500. F.C. Ohiri, R. Verpoorte, and A. Baerheim-Svendsen, *Planta Med.* **42**, 142 (1981).
501. F.C. Ohiri, R. Verpoorte, and A. Baerheim-Svendsen, *Planta Med.* **47**, 87 (1983).
502. F., Scheinmann, E.F.V. Scriven, and O.N. Ogbeibe, *Phytochemistry* **19**, 1837 (1980).
503. M.D. Menachery and D.L. Edgren, *J. Nat. Prod.* **51**, 1283 (1988).
504. M.D. Menachery and M.P. Cava, *J. Nat. Prod.* **44**, 320 (1981).
505. A.N. Tackie, D. Dwuma-Badu, J.S.K. Ayim, T.T. Dabra, J.E. Knapp, D.J. Slatkin, and P.L. Schiff, *Lloydia* **38**, 210 (1975).
506. D. Dwuma-Badu, J.S.K. Ayim, N.Y. Fiagbe, A.N. Tackie, J.E. Knapp. D.J. Slatkin, and P.L. Schiff, *Lloydia* **39**, 213 (1976).
507. D. Dwuma-Badu, J.S.K. Ayim, T.T. Dabra, M.M. El-Azizi, P.L. Schiff, D.J. Slatkin, and J.E. Knapp, *J. Nat. Prod.* **46**, 342 (1983).
508. A.N. Tackie, Summary of the work on some Menispermaceae plants of Ghana. *African Medicinal Plants Proc. Conf. Univ. Ife, Ife, Nigeria.*, p. 112.
509. J.E. Knapp, A.N. Tackie, J.B. Reighard, M.M. Al-Azizi, D.J. Slatkin, and P.L. Schiff, *Phytochemistry* **19**, 1882 (1980).

510. D. Dwuma-Badu, T.U. Okarter, A.N. Tackie, J.A. Lopez, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *J. Pharm. Sci.* **66**, 1242 (1977).
511. J.A. Lopez, *Diss. Abstr. Int. B* **37**, 2168 (1976).
512. J.S.K. Ayim, D. Dwuma-Badu, N.Y. Fiagbe, A.M. Ateya, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *Lloydia* **40**, 561 (1977).
513. J. Buckingham, *Dictionary of Natural Products*, T-01472. Chapman & Hall, London, 1993.
514. K.P. Guha, P.C. Das, B. Mukherjee, R. Mukherjee, G.P. Juneau, and N. Bhaca, *Tetrahedron Lett.*, 4241 (1976).
515. T.K. Palit and M.P. Khare, *Phytochemistry* **8**, 1559 (1969).
516. N.K. Saxena and D.S. Bhakuni, *J. Indian Chem. Soc.* **57**, 773 (1980).
517. K.P. Guha and B. Mukherjee, *Abstr. 4th Asian Symposium on Medicinal Plants and Spices*, p. 56. Bangkok, Thailand (1980).
518. A.K. Ray, G. Mukhopadhyay, S.K. Mitra, K.P. Guha, B. Mukherjee, Atta-ur-Rahman, and A. Nelofar, *Phytochemistry* **29**, 1020 (1990).
519. A.K. Ray, G. Mukhopadhyay, S.K. Mitra, B. Mukherjee, A. Nelofar, and Atta-ur-Rahman, *Phytochemistry* **29**, 1023 (1990).
520. A.K. Ray, G. Mukhopadhyay, S.K. Mitra, K.P. Guha, B. Mukherjee, Atta-ur-Rahman and A. Nelofar, *Phytochemistry* **28**, 675 (1989).
521. K.P. Singh, V.B. Pandey, Y.C. Tripathi, and U.P. Singh, *Z. Pflanzen. Pflanzen.* **98**, 213 (1991).
522. J. Buckingham, *Dictionary of Natural Products*, T-01473. Chapman & Hall, London, 1993.
523. J. Buckingham, *Dictionary of Natural Products*, T-01471. Chapman & Hall, London, 1993.
524. D.S. Bhakuni and S. Jain, *J. Chem. Soc., Perkin Trans. I*, 2598 (1981).
525. J. Buckingham, *Dictionary of Natural Products*, T-01478. Chapman & Hall, London, 1993.
526. K. Pavanand, H.K. Webster, K. Yongvanitchit, and T. Dechatiwongse, *Phytother. Res.* **3**, 215 (1989).
527. P. Pachaly and T.J. Tan, *Arch. Pharm. (Weinheim)* **319**, 841 (1986).
528. P. Pachaly and T.J. Tan, *Arch. Pharm. (Weinheim)* **319**, 872 (1986).
529. P. Pachaly and H. Khosravian, *Planta Med.* **54**, 433 (1988).
530. P. Wiriyachitra and B. Phuriyacorn, *Abstr. 4th Asian Symposium on Medicinal Plants and Spices*, p. 55. Bangkok, Thailand, 1980.
531. T.D. Ayudhaya, W. Nutakul, U. Khunanek, J. Bhunsith, P. Chawaritthumrong, Y. Jewawechdumrongkul, K. Pawanunth, K. Yongwaichjit, and H.K. Webster, *Bull. Dept. Med. Sci.* **29**, 22 (1987).
532. T. Pachaly, T.J. Tan, H. Khosravian, and M. Klein, *Arch. Pharm. (Weinheim)* **319**, 126 (1986).
533. P. Wiriyachitra and B. Phuriyakorn, *Aust. J. Chem.* **34**, 2001 (1981).

534. D. Pornsiriprasert, W. Rittitid, C. Janaakul, and P. Wiriyachitra, *Abstr. 10th Conference of Science and Technology*, p. 371. Chiangmai University, Thailand, 1984.
535. P. Pachaly and H. Khosravian, *Planta Med.* **54**, 516 (1988).
536. J. Buckingham, *Dictionary of Natural Products*, T-01476. Chapman & Hall, London, 1993.
537. F. Zhou, L. Fu, and J. Wen, *Zhongyaocao Keji* **16**, 239 (1985).
538. Y.Q. Qin, W.P. Zhang, and G.Q. Zhang, *Chung Ts'ao Pao* **16**, 426 (1985).
539. H.M. Chang, A.M. El-Fishawy, D.J. Slatkin, and P.L. Schiff, *Abstr. 24th Annual Meeting of the American Society of Pharmacognosy*, p. 48. Oxford, MS, U.S.A, 1983.
540. H.M. Chang, A.M. El-Fishawy, D.J. Slatkin, and P.L. Schiff, *Planta Med.* **1**, 88 (1984).
541. D.N.K. Sarma, R.L. Khosa, and M. Sahai, *Planta Med.* **61**, 98 (1995).
542. P. Pachaly and C. Schneider, *Arch. Pharm (Weinheim)* **314**, 251 (1981).
543. P. Pachaly, A.Z. Adnan, and G. Will, *Planta Med.* **58**, 184 (1992).
544. Y.P. Chen, *Proceedings of the International Symposium on Recent Advances in Natural Products Research*, p. 18. Seoul, Korea, 1979.
545. Atta-ur-Rahman and S. Ahmad, *Fitoterapia* **58**, 266 (1987).
546. S.K. Bhattacharya, P.C. Maity, P. Mediratta, and P. Sen, *Indian J. Exp. Biol.* **29**, 971 (1991).
547. A.M. El-Fishawy, M.A. Abd-El-Kawy, M. Motawe, and I.H. Bowen, *Herba Hung.* **28**, 63 (1989).
548. Atta-ur-Rahman, S.S. Ali, S. Ahmad, and M.I. Choudhary *Phytochemistry* **31**, 3155 (1992).
549. N. Fukuda, M. Yonemitsu, and T. Kimura, *Abstr. International Congress on Natural Products*, p. 34. Chapel Hill. NC, U.S.A, 1985.
550. N. Fukuda, M. Yonemitsu, and T. Kimura, *Chem. Pharm. Bull.* **31**, 156 (1983).
551. A.I. Spiff, V. Zabel, W.H. Watson, M.A. Zemaitis, A.M. Ateya, D.J. Slatkin, J.E. Knapp and P.L. Schiff, *J. Nat. Prod.* **44**, 160 (1981).
552. A.I. Spiff, V. Zabel, W.H. Watson, D.J. Slatkin, J.E. Knapp, and P.L. Schiff, *Abstr. Academy of Pharmaceutical Sciences Meeting*, p. 109. San Antonio, TX, U.S.A, 1981.
553. J. Buckingham, *Dictionary of Natural Products*, C-01602. Chapman & Hall, London, 1993.
554. D. Dwuma-Badu, J.S.K. Ayim, A.N. Tackie, P.D. Owusu, J.E. Knapp, D.J. Slatkin and P.L. Schiff, *Heterocycles* **9**, 995 (1978).
555. P.D. Owusu, J.E. Knapp, D.J. Slatkin, and P.L. Schiff, *J. Nat. Prod.* **44**, 61 (1981).
556. D. Dwuma-Badu, J.S.K. Ayim, A.N. Tackie, P.D. Owusu, J.E. Knapp, D.J. Slatkin and P.L. Schiff, *Lloydia* **41**, 658 (1978).

557. J. Buckingham, *Dictionary of Natural Products*, I-00832. Chapman & Hall, London, 1993.
558. J. Buckingham, *Dictionary of Natural Products*, T-01748. Chapman & Hall, London, 1993.
559. J. Buckingham, *Dictionary of Natural Products*, T-01865. Chapman & Hall, London, 1993.
560. D. Dwuma-Badu, J.S.K. Ayim, A.N. Tackie, M.A. El-Sohly, J.E. Knapp, D.J. Slatkin, and P.L. Schiff, *Experientia* **31**, 1251 (1978).
561. S.J. Partridge, P.F. Russel, G.C. Kirby, D.H. Bray, D.C. Warhurst, J.D. Phillipson, M.J. O'Neill, and P.L. Schiff, *J. Pharm. Pharmacol. (Suppl. 40)*, 53 (1988).
562. D. Dwuma-Badu, J.S.K. Ayim, and A.N. Tackie, *Phytochemistry* **14**, 2524 (1975).
563. R. Ekong, S.J. Partridge, M.M. Anderson, G.C. Kirby, D.C. Warhurst, P.F. Russel, and J.D. Phillipson, *Ann. Trop. Med. Parasitol.* **85**, 205 (1991).
564. J. Buckingham, *Dictionary of Natural Products*, A-02804. Chapman & Hall, London, 1993.
565. B. Kanyinda, R. Vanhaelen-Fastre, and M. Vanhaelen, *J. Nat. Prod.* **58**, 1587 (1995).
566. B. Kanyinda, R. Vanhaelen-Fastre, and M. Vanhaelen, *J. Nat. Prod.* **59**, 498 (1996).
567. H. Morita, K. Takeya, and H. Itokawa, *Bioorg. Med. Chem. Lett.* **5**, 597 (1995).
568. H. Itokawa, K. Nishimura, Y. Hototsuyanagi, and K. Takeya, *Bioorg. Med. Chem. Lett.* **5**, 821 (1995).
569. H.S. Chen, H.Q. Liang, S.X. Liao, and Q.M. Wang, *Chin. Chem. Lett.* **5**, 385 (1994).
570. J.T. Blachfield, W. Kitching, D.P.A. Sands, Y.A. Thong, C.H.L.Kennard, and K.A. Byriel, *Nat. Prod. Lett.* **3**, 305 (1993).
571. N. Kashiwaba, S. Morooka, M. Ono, J. Toda, H. Suzuki, and T. Sano, *J. Nat. Prod.* **59**, 476 (1996).
572. Y. Chen, Y.P. Pan, and S.D. Fang, *Chung Ts'ao Yao* **18**, 438 (1987).
573. H. Guinaudeau, M. Böhlke, L-Z. Lin, C.K. Angerhofer, G.A. Cordell, and N. Ruangrungsi, *J. Nat. Prod.* **60**, 258 (1997).
574. J-Z. Deng and S-X. Zhao, *J. Nat. Prod.* **60**, 294 (1997).
575. N. Kashibawa, S. Morooka, M. Kimura, M. Ono, J. Toda, H. Suzuki, and T. Sano, *J. Nat. Prod.* **59**, 803 (1996).
576. N. Kashiwaba, S. Morooka, M. Ono, J. Toda, H. Suzuki, and T. Sano, *Chem. Pharm. Bull.* **45**, 545 (1997).
577. M.D. Menachery, G.W. Blake, C. Beiswenger, and A. Freyer, *Heterocycles* **41**, 1425 (1995).

578. E.V.L. da-Cunha, J.M. Barbosa-Filho, C.S. Dias, and A.I. Gray, *Abstr. XX Annual Meeting of the Brazilian Chemistry Society.* Poços de Caldas, MG, Brazil, 1997.
579. E.V.L. da-Cunha, M.L. Cornélio, J.M. Barbosa-Filho, R. Braz-Filho, and A.I. Gray, *J. Nat. Prod.* **61**, 1140 (1998).
580. I.G. Marshal and R.D. Waigh, *in* "Applied Neuromuscular Pharmacology" (B.J. Pollard, ed.), p. 44, Oxford University Press, Oxford, England, 1994.

CHAPTER 2

RECENT SYNTHETIC STUDIES ON THE ERGOT ALKALOIDS AND RELATED COMPOUNDS

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I. Introduction
II. Total Synthesis of Lysergic Acid
  A. The First Total Synthesis by Kornfeld and Woodward
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I. Introduction

Ergot alkaloids are one of the most prolific groups of alkaloids derived from *Claviceps* species with respect to their structures and biological activity. Their structures are typically designated as an ergoline alkaloid having the characteristic structure of a tetracyclic indole ring system. The potential of this group of alkaloids as medicinal agents is very high based on their broad pharmacological activity, responding to such physiologically important biosubstances as noradrenaline, serotonin and/or dopamine and their receptors. Therefore, there have been a number of reviews written concerning their chemistry and synthesis and also their biological and metabolic aspects. The first review was written by two of the pioneers of ergot alkaloid chemistry, A. Stoll and A. Hoffmann in 1965, who originated the research and gave the first introduction to this group of natural products regrding their occurrence and distribution and opened the door to this group of alkaloids by shedding the light of modern chemistry *(1)*. Then a decade later in 1975, most of the ergot alkaloids presently known were summarized by two specialists in Basel, P.A. Stadler and P. Stutz, who triggered various aspects of the research which followed, including synthetic research on these alkaloids and the biological and pharmacological studies of ergot alkaloids *(2)*. By 1975, virtually all of the structures of the ergot alkaloids had been proposed, thereby making them attractive targets for synthesis and biological research on their development as medicinals. The decade from 1980 was that of synthesis, thus we enjoyed the very prolific results of the total syntheses of most of the ergoline alkaloids, as witnessed by the review articles written in the later years of the eighties. Then there came a time ripe for summarizing the synthetic works conducted in the decade of 1990.

We have reviewed all of the synthetic studies achieved since 1990, at the request of the editor of this series *(3)*. Then in 1998, this series presented an excellent review on the biochemistry of ergot alkaloids by Gröger and Floss, who assisted us to widen our sights further *(4)*.

For the synthetic achievement of ergot alkaloids, we were asked to review the addition of new results at the end of the 20th century. Here we will review the synthetic achievements of the last decade. The particular focus is on the studies of three Japanese groups including the groups led by Profs. Somei and Yokoyama, who have respectively poured their extensive efforts towards the exploitation of synthetic methodology on indole compounds, aiming at the establishment of the synthesis of ergot alkaloids.

II. Total Syntheses of Lysergic Acid

Lysergic acid (**1**) has stood out as the central figure in ergot alkaloid research throughout the twentieth century from the beginning of research on the ergot alkaloids.

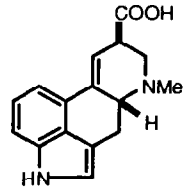
During this period, its structure was established by its total syntheses and its biological activity was well-studied. The total synthesis of lysergic acid (**1**) has attracted the significant attention of synthetic organic chemists, as witnessed by the number of total syntheses so far achieved, which now count to nine. All of these appeared in a short span of time in the nineties, except for the first one by Woodward and Kornfeld. Only one new addition to the list appeared since the previous review written in 1990 (*3*), where all the syntheses were well-documented, showing that the research in this decade has been focused in other directions. Here the authors want to mention briefly the total syntheses previously carried out simply for the basic strategies involved.

A. The First Total Synthesis by Kornfeld and Woodward (1956) (*5*)

This synthesis was achieved by the successful approach to the tricyclic ketone, what we have now called Kornfeld's ketone, which has been continuously playing a key role in the subsequent syntheses of many ergot alkaloid researchers, thus providing a number of improved syntheses. This synthesis was first reviewed by Stadler and Stutz in 1975 in Volume 15 of this series (*2*).

B. The Julia Synthesis (1969) (*6*)

Aiming at the formation of the C/D ring junction by the intramolecular attack of a stabilized allylic anion on an aryne generated from the A ring, the oxindole obtained from 5-bromoisatin was transformed to a mixture of stereoisomers which were further converted to the target molecule.



1 Lysergic acid

C. THE RAMAGE SYNTHESIS (1981) (*7*)

The suggestion by Woodward on the epimerization of lysergic acid (**1**) through an achiral tricyclic amine gave a hint to the authors for the synthesis of lysergic acid (**1**) via a route which involved a tricyclic amine as a key intermediate in their lengthy total synthesis. Similar routes were also followed by two other syntheses.

D. THE OPPOLZER SYNTHESIS (1981) (*8*)

By inventing an intramolecular imino-Diels-Alder cycloaddition of a diene formed by the thermolysis of an oxime-ether, the construction of the alkaloid skeleton, and the usefulness of this methodology, was successfully exemplified, first by the total synthesis of the benzo[*c*]phenanthridine alkaloid, chelidonine, and then in a beautiful total synthesis of lysergic acid (**1**).

E. THE NINOMIYA SYNTHESIS (1982) (*9,10*)

Irradiation of an enamide, which was readily prepared from the imine of the tricyclic Kornfeld's ketone by acylation with 3-furoyl chloride, in the presence of sodium borohydride, yielded the skeletal structure of the ergoline alkaloids, which was readily converted by conventional procedures to lysergic acid (**1**). This photochemical route offered a wide potential for application to variously substituted analogs of lysergic acid (**1**) having high synthetic interest.

F. THE REBEK SYNTHESIS (1983) (*11*)

By using *dl*-tryptophan as the starting unit, highly stereoselective steps via the tricyclic ketone completed the total synthesis of lysergic acid (**1**), thereby also paving a route for an enantioselective synthesis.

G. THE KURIHARA SYNTHESIS (1988) (*12*)

Modifying the synthesis of a key tricyclic aldehyde in the Ramage synthesis, subsequent Wittig-Horner reaction successfully linked their synthesis to the target lysergic acid (**1**).

H. The Cacchi Synthesis (1988) (*13*)

Also using the key intermediates in the Ramage synthesis, the newly developed oxidative addition of vinyl triflates to palladium(II) and the Heck reaction paved a way to lysergic acid (**1**).

I. The Vollhardt Synthesis (1994) (*14*)

Cocyclization of 4-ethynyl-3-indoleacetonitrile with an alkyne in the presence of a cupric complex gave rise to the ergoline skeleton, which was converted into lysergic acid diethylamide as discussed in Section III, C.

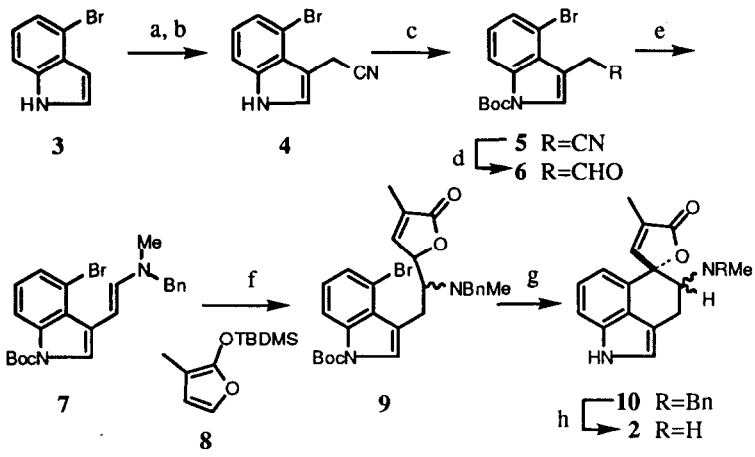
III. Total Synthesis of Ergot Alkaloids Other Than Lysergic Acid

Efforts toward the total synthesis of other members of the ergot alkaloid group have been carried out mostly by applying newly developed synthetic methodologies. Therefore, there are a number of new synthetic methodologies in the total synthesis and the syntheses aimed at the target alkaloids. The synthetic routes were often decorated by the author's own instinct. Although lysergic acid (**1**) has occupied a position at the center of interest for synthetic study, focus has also been directed toward other members of the ergot alkaloid group having non-ergoline structures.

A. Total Synthesis of Rugulovasines A and B

The alkaloids, rugulovasines A and B (**2**), were isolated in racemic form and were found to very easily interconvert upon warming. Rebek's group had succeeded in the enantioselective synthesis of (–)-rugulovasine early in 1980 and noticed its facile equilibration to form a mixture of the two alkaloids (*15–17*). A proposal for the intermediacy of an achiral structure in the facile interconversion of the two isomers in rugulovasines A and B (**2**) was confirmed by Rebek himself in the first enantioselective total synthesis (*15,16*). Martin's group have extensively studied its conversion aiming at the development of a new general synthetic methodology (*18*).

As a result, they have succeeded in using a vinylogous Mannich reaction as a method for the transformation applicable to the construction of a structural subunit common to different alkaloidal natural products. Starting from 4-bromoindole (**3**), a functionalized side chain was introduced into the 3-position



SCHEME 1. Reagents: a, aq. Me_2NH, aq. HCHO, AcOH; b, KCN, DMF-H_2O; c, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; d, DIBALH, CH_2Cl_2; e, BnNHMe, CH_2Cl_2; f, CSA, then **8**; g, *t*-BuOK, NH_3, *hv*; h, HCl, MeOH, H_2, $Pd(OH)_2$.

of the indole nucleus. This side chain was then converted into the corresponding 3-acetaldehyde. The reaction of the acetaldehyde **6** with benzylmethylamine furnished the enamine **7**, which was then treated *in situ* with the siloxyfuran **8** to give the adducts **9** as a diastereomeric mixture. Irradiation of the adducts in refluxing ammonia in the presence of potassium *t*-butoxide brought about smooth cyclization to give an inseparable mixture of the protected rugulovasines **10**. Though removal of the *N*-benzyl protecting group from the photocyclized product **10** was far more difficult than anticipated, after many attempts, it was found that hydrogenolysis of the hydrochloride over the Pearlman's catalyst furnished smooth debenzylation to complete the total synthesis of the two alkaloids **2** (Scheme 1).

B. SYNTHESIS OF CLAVICIPITIC ACID

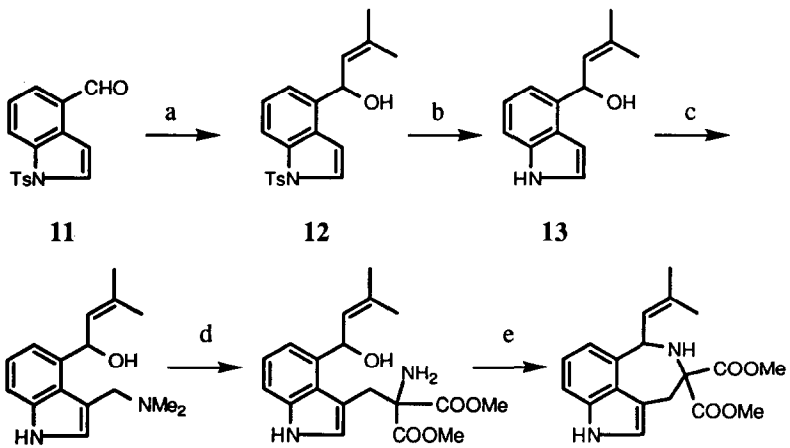
Clavicipitic acid and aurantioclavine are alkaloids having a fused seven-membered azepinoindole skeleton. As mentioned in the previous review (*3*), by 1988 clavicipitic acid had been synthesized by five groups, and aurantioclavine by two groups of chemists.

Clavicipitic acid is currently regarded as a derailment product of normal ergot metabolism (*4*). From its structural features of a seven-membered ring system, and also from biomimetic interest, this alkaloid has attracted the attention of many synthetic organic chemists. Therefore, a number of syntheses have been

reported of this particular alkaloid. As mentioned previously, there were already five by 1988, including Kozikowski and Greco (1982) (*19*), Munakata and Natsume (1983) (*20*), Kozikowski and Ohta again in 1985 (*21*), Matsumoto and Watanabe (1987) (*22*), Harrington (1987) (*23*), and Goto (1989), along with the synthesis of aurantioclavine by Somei (1985) (*24*), which were successively reported. Among, them, Kozikowski's biomimetic synthesis was entirely based on Floss' proposed sequence for the biosynthesis of the ergot alkaloid chanoclavine, as described in the previous review.

1. Formal Total Synthesis by Nichols group.

Nichols' group (*25*) successfully applied an acid-catalyzed intramolecular aminoalkylation reaction between an amine and alcohol to form the azepino ring system, the characteristic structure of this indolic amino acid in the route, via a functional equivalent of 10-hydroxylated DMAT **15**. This hypothetical biochemical precursor of the alkaloid, which was not prepared previously, was the key intermediate for their efficient synthesis to clavicipitic acid. Nichols' group first prepared the requisite alcohol **12** by the Grignard reaction of *N*-tosylated indole-4-carboxaldehyde **11** with 2-methyl-1-propenylmagnesium



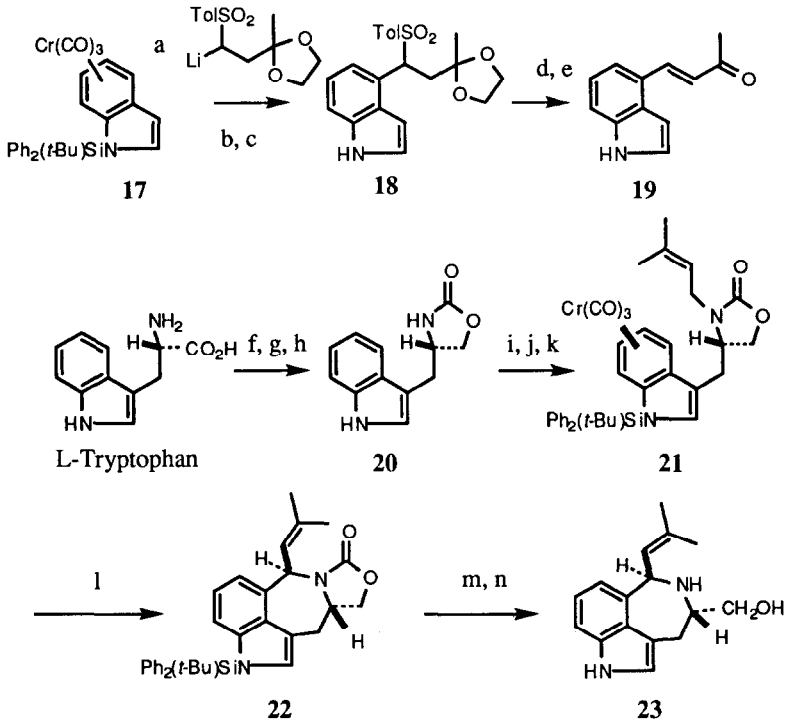
SCHEME 2. Reagents: a, $BrCH{=}C(Me)_2$, Mg, THF; b, Na-Hg, MeOH; c, HCHO, $HN(Me)_2$, AcOH; d, $H_2NCH(COOMe)_2$, $(n\text{-}Bu)_3P$, MeCN; e, TsOH, MeCN.

bromide. Deprotection of the indole nitrogen was smoothly achieved in nearly quantitative yield by the application of Trost's buffered amalgam method (*26*). Under classic Mannich conditions, the new indole **13** was converted to its gramine derivative **14**, which was then subjected to Somei's procedure (*27*) for conversion to the amino alcohol **15** in 80% yield. Cyclization of **15** was smoothly carried out by acid treatment giving the azepine **16** (Scheme 2).

The diester **16** has been shown to undergo decarbonylation to a *cis-trans* mixture of clavicipitic acids, thus furnishing a formal total synthesis of this alkaloid.

2. *Syntheses of Clavicipitic Acid by Somei's Group and Yokoyama's Groups*

Total syntheses of clavicipitic acid were achieved by two Japanese groups using their respective methodologies, as reviewed in Section IV.



SCHEME 3. Reagents: b, I_2; c, $(n\text{-Bu})_4NF$; d, cat. TsOH; e, Et_3N, f, $LiAlH_4$; g, NaOH; h, $COCl_2$; i, $Cr(CO)_3(MeCN)_3$; j, NaH, $Ph_2(t\text{-Bu})SiCl$; k, MeLi, $BrCH_2CH{=}C(Me)_2$; l, LDA, then I_2; m, $(n\text{-Bu})_4NF$; n, 3M KOH.

3. Attempted Synthesis by Semmelhack

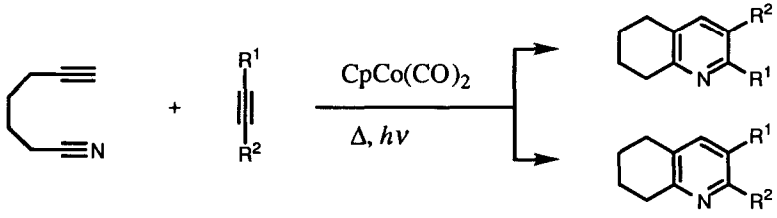
The activating effect of π-complexation of a $Cr(CO)_3$ complex allows for selective nucleophilic substitution in indoles, such as tryptophan, providing intermediates for the synthesis of clavicipitic acid. Indole was readily transformed into the corresponding tricarbonylchromium complex and silylated to the orange-colored complex **17**. The addition of **17** to a solution of the lithiated sulfone followed by oxidative quenching with iodine and desilylation furnished the C-4 substituted indole **18** in 90% yield. The conversion of **18** to the enone **19** was achieved in 78% yield by sequential acid and base treatment.

Reduction of L-tryptophan and the conversion of the resulting amino alcohol afforded the oxazolidinone **20** in good yield. By applying the activating effect of the π-complex **21**, formed with a tricarbonylchromium complex, an alkenyl side chain was introduced into the 4-position of the tryptophan ring to give the intermediate **22** for the synthesis of clavicipitic alcohol (**23**) (Scheme 3) (*28*).

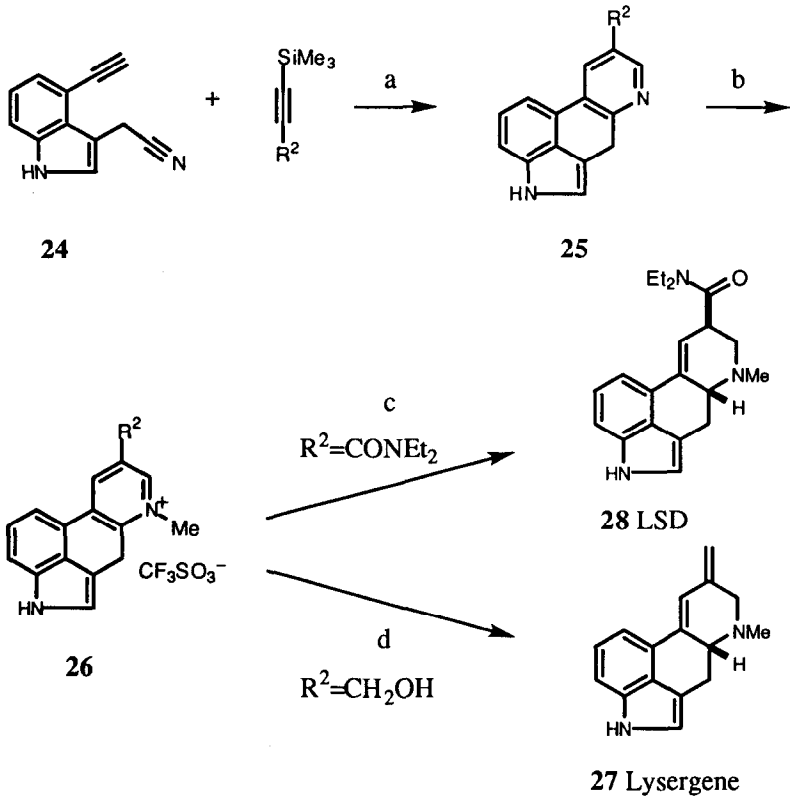
C. Total Synthesis of Lysergene and Lysergic Acid Diethylamide (LSD)

Vollhardt and coworkers (*14*) have developed the cocyclization reaction using a cobalt-catalyst, successfully applied the reaction to the construction of the ergoline skeleton, and then extended its application to the synthesis of ergoline alkaloids. They found that the η^5-cyclopentadienylcobalt-catalyzed cocyclization of α,ω-alkynenitriles with alkynes yielded the [2+2+2] cycloaddition products as shown in Scheme 4, thus showing the possibility for its application to the synthesis of nitrogen-containing polycyclic ring systems.

The utility of this cocyclization was shown in the synthesis of the ergoline framework when an ethynylic indole was employed, as in Scheme 5. The requisite 4-ethynyl-3-indoleacetonitrile (**24**) was prepared readily from the 4-bromoindole precursor followed by palladium-catalyzed trimethylsilyl-ethynylation-deprotonation.



Scheme 4

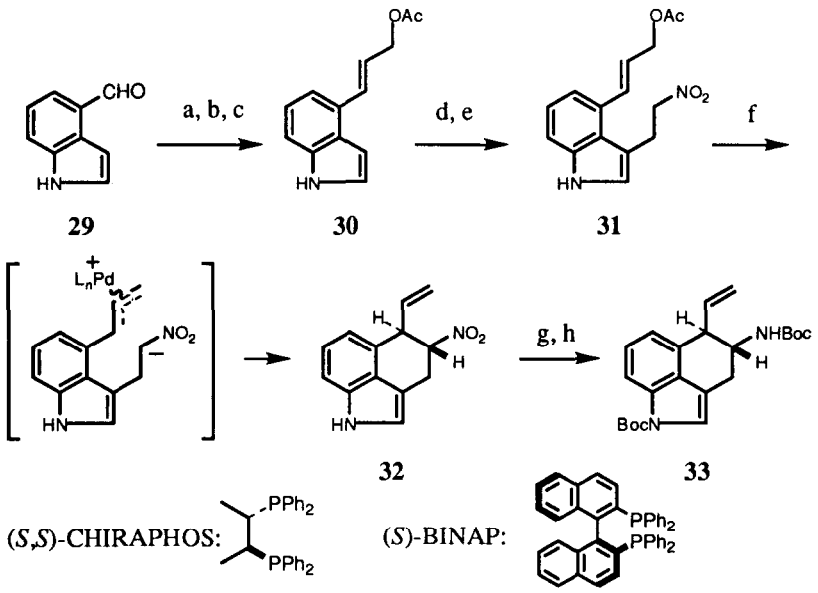


SCHEME 5. Reagents: a, $CpCo(CO)_2$, Δ, *hν*; b, CF_3SO_2Me, THF; c, 3-4 eq. $NaBH_4$, MeOH; d, excess $NaBH_4$, CD_3CN.

The compound **25**; R^2=CH_2OH in these products, which carries a pyridine ring, was quaternized with methyl iodide and then reduced to give the tetrahydropyridine moiety, thereby completing a short total synthesis of lysergene (**27**) (Scheme 5). Similarly, LSD (**28**) was conveniently synthesized from the cycloaddition product **25** with a carboxamide group on the ring.

D. SYNTHESIS OF (–)-CHANOCLAVINE I

As mentioned in the previous review, chanoclavine I was synthesized previously in the last decade by several groups. The first total synthesis was achieved by Plieninger's group (*29*) which was followed by the syntheses of

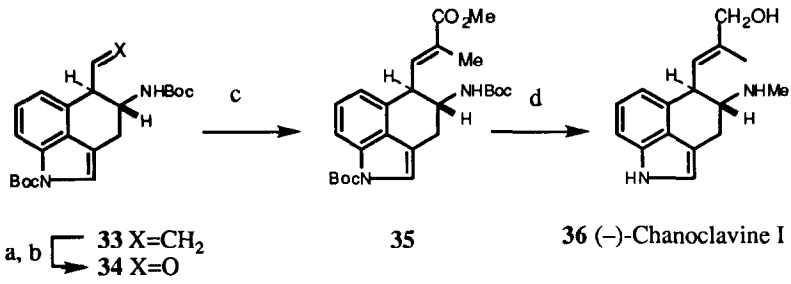


SCHEME 6. Reagents: a, $(MeO)_2P(O)CH_2CO_2Me$; b, DIBALH; c, Ac_2O; d, $Me_2NCH{=}CHNO_2$; e, $NaBH_4$; f, $Pd(dba)_2$, K_2CO_3, (*S*,*S*)-CHIRAPHOS, or $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP; g, Zn-Hg, HCl; h, $(Boc)_2O$.

Natsume (*30*), Kozikowski (*31*), Oppolzer (*32*), and Ninomiya (*33*), in addition to the synthesis of secoergolines by Somei's group (*34*).

The first enantioselective total synthesis of (–)-chanoclavine I (**36**) was reported by French chemists (*35,36*), who invented an unique method of constructing the ring system, including the C ring, together with the enantioselective introduction of two side chains into the D ring, by the application of an intramolecular palladium-catalyzed allylation of a nitroacetate. Genet *et al.* selected 4-formylindole (**29**) as the bifunctional starting compound. The Horner-Emmons reaction of the aldehyde **29** with trimethyl phosphonoacetate in the presence of potassium carbonate in refluxing tetrahydrofuran yielded the unsaturated ester **30** in 95% yield, which was reduced with DIBALH to the allylic alcohol, and then converted into the allylic acetate **30**.

The C-3 functionalization of **30** was achieved in two steps, that is, first, treatment with 1-dimethylamino-2-nitroethylene to the unsaturated nitroacetate **31** and then reduction of the double bond with sodium borohydride in tetrahydrofuran-methanol to furnish the desired nitroacetate **31** in 50% overall yield from the aldehyde **29**. Asymmetric formation of the C-5, C-10 bond of the nitroacetate **31** was achieved by using the palladium (0) complex catalyst. The best results of this key cyclization were obtained using $Pd(dba)_2$ and (*S*,*S*)-



SCHEME 7. Reagents: a, OsO_4, NMO; b, $NaIO_4$; c, $Ph_3P{=}C(Me)CO_2Me$; d, $LiAlH_4$.

CHIROPHOS, or $Pd(OAc)_2$ and (*S*)-BINAP as the chiral diphosphine, at room temperature. The desired enantiomer 5*R*-**32** was obtained under mild conditions in 60% yield, and with diastereo- and enantioselectivity of up to 95% (Scheme 6).

For the synthesis of (–)-chanoclavine I (**36**), they applied the same methodology devised by Kozikowski (*31*) and Oppolzer (*32*). The nitro group in **32** was reduced to the primary amine with amalgamated zinc, and then the two nitrogens were converted to the corresponding dicarbamate **33** with $(Boc)_2O$ in acetonitrile at room temperature. The carbamate **33** was then treated with a catalytic amount of osmium tetroxide in the presence of NMO in aqueous acetone to furnish the crude diol, which was cleaved with sodium periodate to yield the unstable key aldehyde **34**. The Wittig reaction of the aldehyde **34** afforded the unsaturated ester **35**, which was then reduced with lithium aluminum hydride under reflux to give (–)-chanoclavine I (**36**) in 13% yield upon chromatography, thereby completing the first total asymmetric synthesis of (–)-chanoclavine I (**36**) from the optically active nitro compound **32** (Scheme 7). This methodology could be applied to the synthesis of analogous ergot alkaloids, including 6,7-secoagroclavine, (+)-paliclavine, or the rugulovasines.

IV. Research on the Synthesis of Ergot Alkaloids by Three Japanese Groups

In the past decade, two Japanese groups, led by Somei and Yokoyama, respectively, have concentrated their synthetic interests and efforts on the ergot alkaloids by exploiting respective methodologies and achieving the total synthesis of clavicipitic acid and many related alkaloids. Originally, they had

directed their interests to the chemistry and reactions with the intention to apply their methods to the synthesis of natural indole alkaloids, particularly ergot alkaloids. During the course of their extensive research on indole alkaloids, reactions were developed and knowledge on the chemistry and reactions of indole derivatives was generated. Therefore, here we summarize our results and offer a perspective on the research outcomes.

Iwao's group has independently established an efficient methodology for the synthesis of 3,4-differentially substituted indoles. Their contributions in the total synthesis of ergot alkaloids are also reviewed.

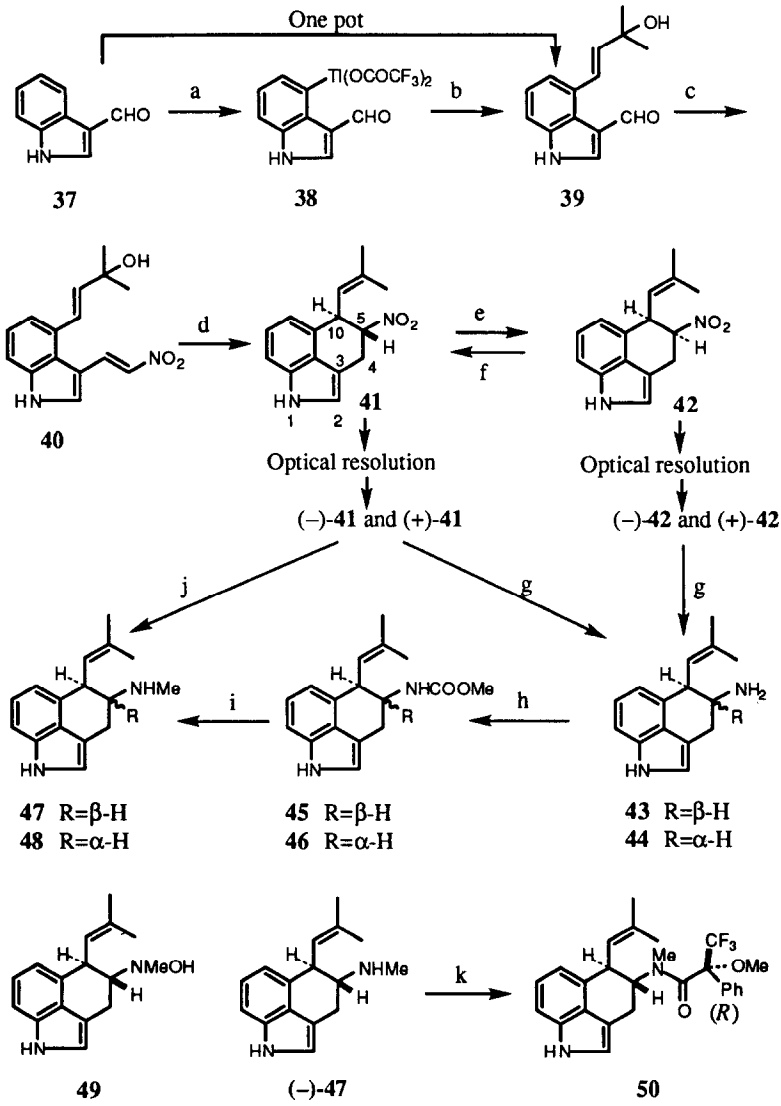
A. Synthetic Studies by Somei's Group

As already mentioned in the previous review (*3*), Somei *et al.* began their involvement in the synthesis of ergot alkaloids with the intention of applying two new reactions, a palladium-catalyzed tin-thall reaction and the intramolecular cyclization by nitronate anions for the construction of the ergoline skeleton. In the past decade, Somei *et al.* further extended their reactions and chemistry into the ergot alkaloids in order to carry out the synthesis with the least number of steps in the common synthetic route (*37*).

1. Synthesis of 6,7-Secoagroclavines, Chanoclavine I, Isochanoclavine I, Norchanoclavine I, Chanoclavine II, Norchanoclavine II, and Their Enantiomers

The synthetic methodologies, consisting of the routes shown in Schemes 8, 9, and 10 (*37*), were demonstrated to be effective for the total syntheses of a number of (–)-ergot alkaloids and their (+)-enantiomers (*38*). The alkaloids synthesized in this manner were (–)-6,7-secoagroclavine, (–)-chanoclavine I, (–)-isochanoclavine I, (–)-norchanoclavine I, (–)-chanoclavine II, (–)-norchanoclavine II, (–)-agroclavine, (–)-agroclavine I, and their (+)-enantiomers. All of the syntheses started from 3-formylindole (**37**). They first prepared the 4-substituted indole **39** by the procedure of a one-pot tin-thall reaction (*39*) which proceeded via the formation of (3-formylindol-4-yl)thallium bis(trifluoroacetate) (**38**), followed by palladium-catalyzed reaction with tri-*n*-butyl (3-hydroxy-3-methyl-1-butenyl)stannane (*40*).

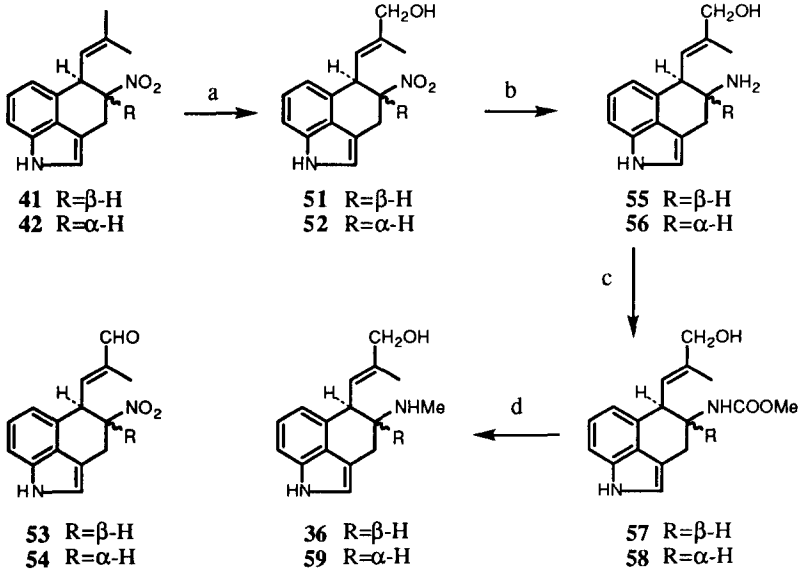
Aldol condensation of **39** with nitromethane afforded the nitrovinylindole **40**, which was then reduced with sodium borohydride in methanol followed by acid treatment (*41*) in a one-pot procedure to bring about the stereospecific cyclization to the tricyclic *trans* isomer **41**. This *trans* isomer **41** was readily isomerized to the *cis* isomer **42** by treatment with sodium methoxide in methanol, while the reverse isomerization of *cis* **42** to *trans* **41** was achieved by treatment with triethylamine in benzene (*37*).



SCHEME 8. Reagents: a, $Tl(OCOCF_3)_3$, CF_3COOH; b, $(n\text{-}Bu)_3SnCH{=}CHC(OH)Me_2$, $Pd(OAc)_2$, DMF; c, $MeNO_2$, NH_4OAc; d, $NaBH_4$, MeOH, then $HCl\text{-}H_2O$; e, NaOMe, MeOH; f, Et_3N, benzene; g, Zn-Hg, HCl, H_2O, MeOH; h, ClCOOMe, Et_3N, CH_2Cl_2; i, $LiAlH_4$, THF; j, MeMgI, THF, then Zn-HCl, MeOH; k, $ClCOCPh(CF_3)(OMe)$.

Optical resolution of the key intermediates, *trans* **41** and *cis* **42**, was achieved, with base-line resolution, by chiral column chromatography on a chiralpak AS column, to afford (–)-*trans* **41**, (+)-*trans* **41**, (–)-*cis* **42**, and (+)-*cis* **42** on a semi-preparative scale. The first total syntheses of (–)-6,7-secoagroclavine [(–)-*trans* **47**] and its (+)-enantiomer [(+)-*trans* **47**] were completed in a one-pot operation by the reaction of (–)- and (+)-*trans* **41** with an excess of methylmagnesium iodide, respectively, followed by reduction of the resulting methylhydroxylamines [(–)- and (+)-*trans* **49**], with zinc in methanolic hydrochloric acid.

Alternatively, three-step syntheses of (–)-6,7-secoagroclavine [(–)-**47**] and its (+)-enantiomer [(+)-**47**] were also achieved (*38*). Reduction of both (–)- and (+)-*trans* **41** with amalgamated zinc in methanolic hydrochloric acid afforded the respective (–)- and (+)-*trans* isomers **43**, which were then treated with methyl chloroformate to afford the corresponding carbamates [(–)- and (+)-*trans* **45**], respectively. These respective carbamates were then reduced with lithium aluminum hydride to give the enantiomeric *N*-methyl amines **47**. This series of conversions was also applied to the corresponding optically active *cis*-compounds **44**, **46**, and **48**, as shown in Scheme 8 (*38*). The structures of these products were unambiguously determined from the X-ray crystallographic



41 R=β-H
42 R=α-H

51 R=β-H
52 R=α-H

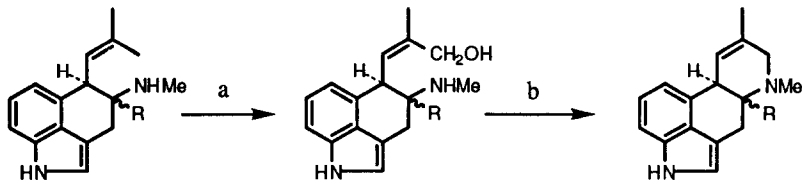
55 R=β-H
56 R=α-H

53 R=β-H
54 R=α-H

36 R=β-H
59 R=α-H

57 R=β-H
58 R=α-H

SCHEME 9. Reagents: a, SeO_2, dioxane, H_2O; b, Zn-Hg, HCl, H_2O, MeOH; c, ClCOOMe, Et_3N, CH_2Cl_2; d, $LiAlH_4$, THF.



47 R=β-H
48 R=α-H

60 R=β-H
61 R=α-H

62 R=β-H
63 R=α-H

SCHEME 10. Reagents: a, SeO_2, dioxane, H_2O; b, $POCl_3$, K_2CO_3.

analysis of the compound **50**, which was prepared by the *N*-acylation of (–)-**47** with (*R*)-(+)-2-methoxy-2-trifluoromethylphenyl-acetyl chloride (*40*).

Oxidation of (–)-*trans* **41** with *t*-butyl hydroperoxide in the presence of 5% selenium dioxide on silica gel (*42*) in dioxane, followed by reduction of the resulting mixture of (–)-*trans* **51** and the overoxidized aldehyde [(–)-*trans* **53**] with sodium borohydride, afforded the (–)-(*E*)-hydroxymethyl compound [(–)-*trans* **51**]. Similarly, (+)-*trans* **41** was converted to the (+)-(*E*)-hydroxymethyl compound [(+)-*trans* **51**]. The subsequent reduction of (–)- and (+)-*trans* **51** with amalgamated zinc in methanolic hydrochloric acid afforded (–)- and (+)-norchanoclavine I (**55**), respectively, which were then converted to the (–)- and (+)-*trans* methyl carbamates (**57**) by reaction with methyl chloroformate.

Total syntheses of the *N*-methyl derivatives, (–)-chanoclavine I [(–)-**36**] and its enantiomer [(+)-**36**] were achieved, respectively, by the reduction of these carbamates with lithium aluminum hydride, which completed the total synthesis of (–)-chanoclavine I [(–)-**58**] and its enantiomer [(+)-**58**], respectively. Application of this series of conversions to the corresponding optically active *cis*-compounds [(–)- and (+)-*cis* **52**] completed the total syntheses of norchanoclavine II [(–)-**56**] and chanoclavine II [(–)-**59**] (*43*), and their enantiomers, through **58**, as shown in Scheme 9.

Oxidation of the *Z*-methyl of the isobutenyl group of (–)-**47** with selenium dioxide in dioxane produced (–)-isochanoclavine I [(–)-**60**], as shown in Scheme 10. This regioselective functionalization can be explained by the coordination of the methylamino group at the 5-position to selenium, bringing the selenium dioxide molecule close to the *Z*-methyl group (*44*).

2. *Synthesis of* (–)- *and* (+)-*Agroclavines, and of* (–)- *and* (+)-*Agroclavine I*

Syntheses of the enantiomeric agroclavines [(–)- and (+)-**62**] were achieved, respectively, as shown in Scheme 10, starting from enantiomeric **47**. Oxidation of the *Z*-methyl of the isobutenyl group of (–)- and (+)-**47** with selenium

dioxide in dioxane afforded (–)-isochanoclavine I [(–)-**60**] and (+)-**60**, respectively. Subsequent cyclization of both enantiomers [(–)- and (+)-**60**] proceeded smoothly with phosphorus oxychloride in the presence of potassium carbonate to give (–)-agroclavine [(–)-**62**] and (+)-agroclavine [(+)-**62**], respectively. Since (–)-agroclavine **62** was previously converted to festuclavine, costaclavine, isosetoclavine, and setoclavine (*45*), the formal total syntheses of these ergoline alkaloids were completed.

Somei *et al.* also succeeded in the first total synthesis of (–)-agroclavine I [(–)-**63**] and the determination of the absolute configuration of this alkaloid (*46*). They prepared (–)-*cis* **61** and its enantiomer [(+)-*cis* **61**] by applying their regioselective allylic oxidation with 30% selenium dioxide on celite. It was found that the sign of the optical rotation changed upon the ring closure of (–)-*cis* **61** with phosphorus oxychloride in the presence of potassium carbonate, giving rise to (+)-agroclavine I [(+)-**63**]. Similarly, (+)-*cis* **61** yielded (–)-agroclavine I [(–)-**63**]. As a result, the compound [(+)-*cis* **42**] was determined to have the [5*R*,10*S*] absolute configuration, and consequently (–)-agroclavine I [(–)-**63**] has the [5*R*,10*S*] configuration (*40*).

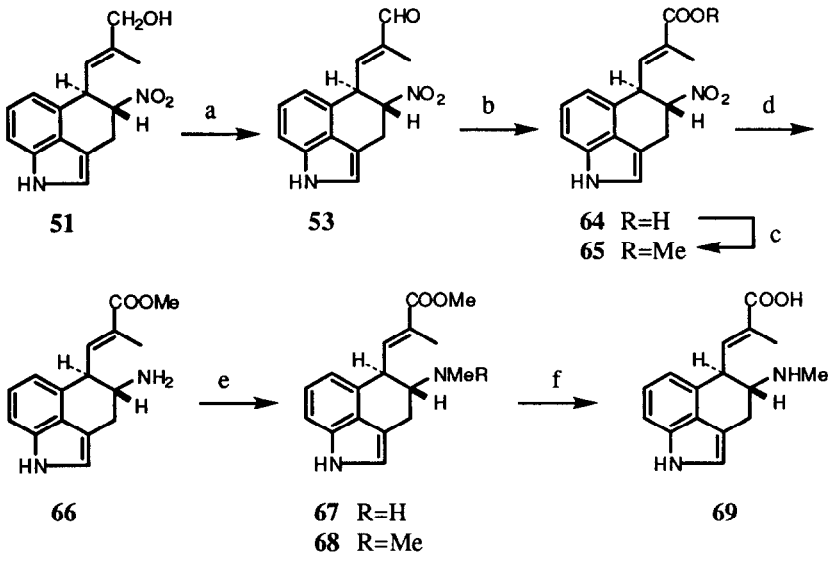
3. Synthesis of (±)-*Chanoclavine I Acid*

The first total synthesis of chanoclavine I acid (*47*), a major alkaloid in the seeds of *Ipomea violacea* (*48*), was completed by Somei *et al.* who employed the key intermediate **51** for the formation of chanoclavine I (**36**), and also for the synthesis of chanoclavine I acid (**69**). Compound **51** was oxidized with pyridinium chlorochromate in dichloromethane to give the aldehyde **53**, which was further oxidized to the carboxylic acid **64** by employing sodium hypochlorite in the presence of 2-methyl-2-butene (*49*), as shown in Scheme 11.

Methylation of **64** with ethereal diazomethane afforded the methyl ester **65**, which was then reduced with amalgamated zinc and hydrochloric acid to give the amine **66**. Methylation of the primary amine with dimethyl sulfate in the presence of potassium carbonate afforded a mixture of the monomethylamine **67** and the dimethylamine **68**, which were separated. Alkaline hydrolysis of **67** in methanol and subsequent column chromatography on Amberlite IRA-120 completed the total synthesis of (±)-chanoclavine I acid (**69**).

4. Synthesis of (±)-*Chanoclavine I and of* (–)- *and* (+)-*KSU 1415*

Application of the primary amine **66**, obtained as shown in Scheme 11, to an alternative synthesis of (±)-chanoclavine I (**36**) was carried out as an example to demonstrate the potential of employing a common intermediate for the synthesis of a wide variety of ergoline alkaloids (*47*). The route for applying the key intermediate **66** to this synthesis consisted of a series of conventional reactions:



SCHEME 11. Reagents: a, pyridinium chlorochromate, CH_2Cl_2; b, NaOCl, NaH_2PO_4, $(Me)_2C{=}CHMe$; c, CH_2N_2, MeOH; d, Zn-Hg, HCl, H_2O, MeOH; e, Me_2SO_4, K_2CO_3; f, NaOH, MeOH.

treatment of the primary amine **66** with methyl chloroformate in the presence of triethylamine produced the carbamate **70**, which was then reduced with lithium aluminum hydride in tetrahydrofuran to give (±)-chanoclavine I (**36**) (Scheme 12).

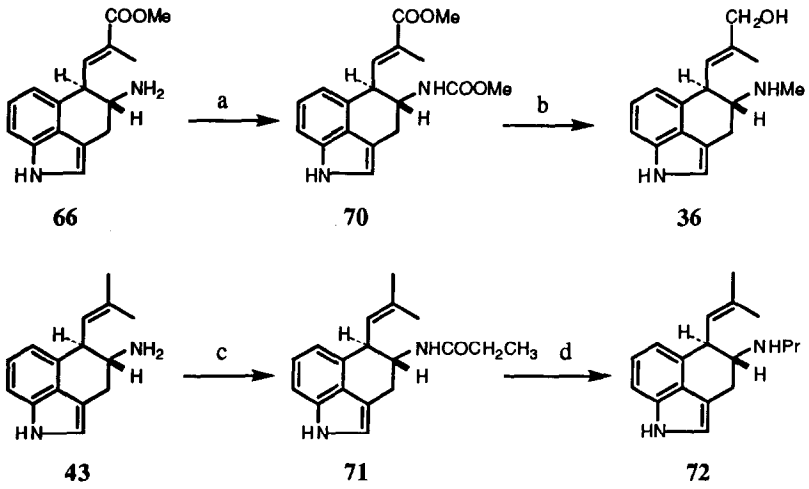
Somei *et al.* also disclosed that (±)-6-nor-6-propyl-6,7-secoagroclavine [(±)-**72**, KSU 1415] showed potent dopamine agonistic activity (*50*).

In continuing research, (–)- and (+)-KSU 1415 [(–)- and (+)-**72**] were similarly prepared by the reaction of the respective enantiomers [(–)- and (+)-**43**] with propionyl chloride followed by reduction of the resulting enantiomeric **71** with lithium aluminum hydride in tetrahydrofuran (*40*) (Scheme 12). The biological evaluations of these compounds have not been reported.

5. Total Synthesis of (±)-*Clavicipitic Acid*

Somei *et al.* developed two further synthetic methodologies by manipulating the substituents at the 3-position of indoles, as shown in Scheme 13.

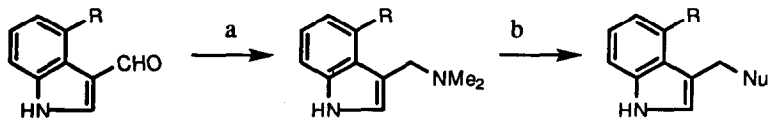
The first was a route for the formation of the gramine **74**, which was obtained directly from the 3-formylindoles **37** and **73**, by reaction with sodium borohydride in 50% dimethylamine and methanol (*51*). The other was a route including selective monoalkylation of the gramine **74** with active methylene



SCHEME 12. Reagents: a, ClCOOMe, Et_3N; b, $LiAlH_4$, THF; c, propionyl chloride, Et_3N, CH_2Cl_2; d, $LiAlH_4$, THF.

compounds, using tri-*n*-butylphosphine as a catalyst, to give the compounds **75** (*27*). They applied the gramine synthesis to the compound **39** and succeeded in synthesizing **76** in two steps from 3-formylindole (**37**), as shown in Scheme 14. The compound **77** was then prepared by selective monoalkylation of the gramine **76** with methyl nitroacetate as an active methylene compound.

Application of the amino-cyclization method (*52*) to the compound **77** was also developed by Somei *et al.* Reduction of the nitroester **77** with amalgamated zinc in hydrochloric acid yielded the seven-membered ring system as a mixture



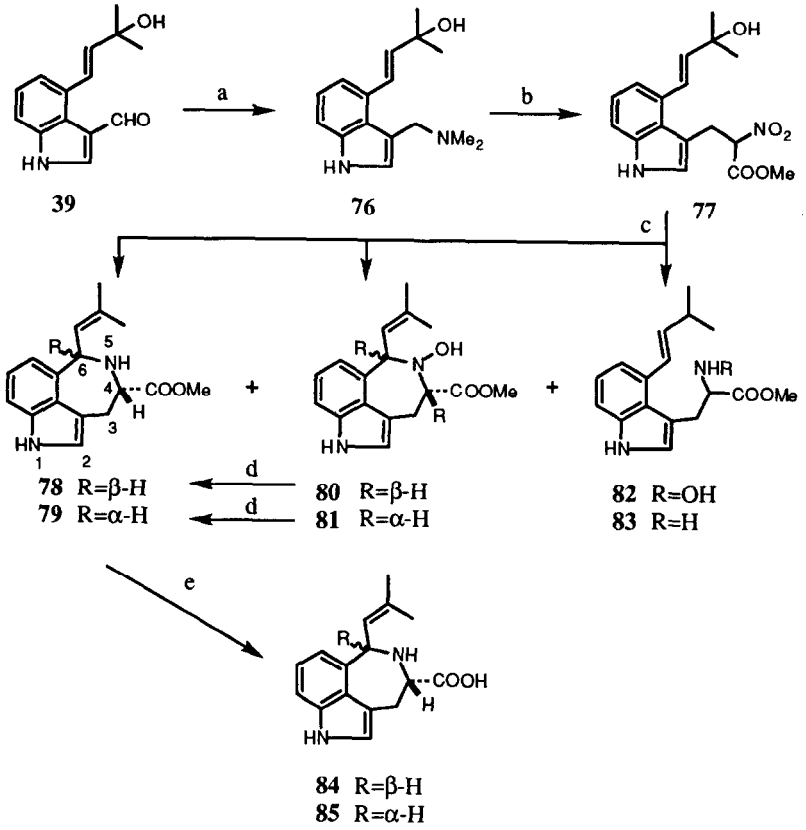
37 R=H
73 R=NO_2, CN, I, OMe

74 **75**

SCHEME 13. Reagents: a, $NaBH_4$, Me_2NH, MeOH ; b, nucleophiles (Nu=$CHNO_2$, $C(COOEt)_2NHAc$, $CH(COOMe)_2$, etc.), (*n*-Bu)$_3$P, MeCN.

of stereoisomeric isomers of (±)-*cis* **78** and *trans* **79** (*53*). *trans*-Clavicipitic acid methyl ester (**79**) was obtained as the major product, together with other products, *N*-hydroxy compounds as the racemates *cis* **80** and *trans* **81**, and the

noncyclized products (**82** and **83**) (Scheme 14). Treatment of (±)-*cis* **80** and *trans* **81** with aqueous titanium(III) chloride brought about dehydroxylation on nitrogen to afford (±)-*cis* **78** and *trans* **79**, respectively, which were known previously from the synthesis of *cis*- and *trans*-clavicipitic acid (**84**,**85**) by Natsume *et al.* (*54*).

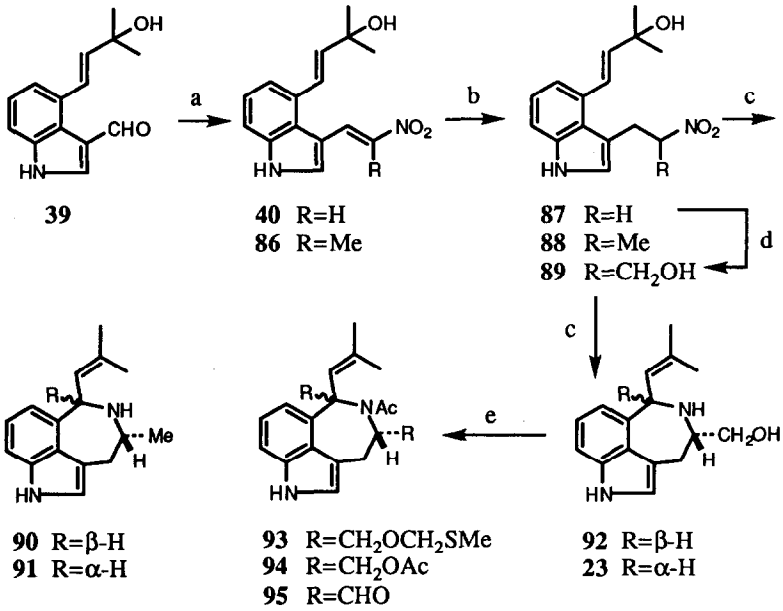


SCHEME 14. Reagents: a, $NaBH_4$, Me_2NH, MeOH; b, O_2NCH_2COOMe, $(n\text{-}Bu)_3P$, MeCN; c, Zn-Hg, HCl, MeOH; d, $TiCl_3$, H_2O, MeOH; e, NaOH, MeOH, H_2O.

6. Syntheses of Clavicipitic Acid Analogs

Somei *et al.* further applied the above synthetic route for clavicipitic acid, to the preparation of analogs of (±)-clavicipitic acid (*53*). Aldol condensation of **39** with nitromethane and nitroethane afforded the nitroalkenes **40** and **86**, respectively, which were reduced with sodium borohydride to give the nitroalkanes **87** and **88** in high yields, ready for the amino-cyclization method, as shown in Scheme 15. Amino-cyclization of **87** and **88** was similarly carried out employing amalgamated zinc in hydrochloric acid to afford *cis* **90** and *trans* **91**, the 4-methyl analogs of clavicipitic acid. Application of this cyclization to the compound **89**, obtained by reacting **87** with formaldehyde in the presence of potassium *t*-butoxide, gave *cis* **92** and *trans* **23**, the 4-hydroxymethyl analogs.

Contrary to the expectation that the hydroxymethyl group at the 4-position of **23** would be readily oxidized to a carboxyl group, and thereby was expected to provide another route to *trans*-clavicipitic acid, it resisted various oxidative conditions. On the other hand, oxidation of **23** with acetic anhydride and



39

40 R=H
86 R=Me

87 R=H
88 R=Me
89 R=CH_2OH

90 R=β-H
91 R=α-H

93 R=CH_2OCH_2SMe
94 R=CH_2OAc
95 R=CHO

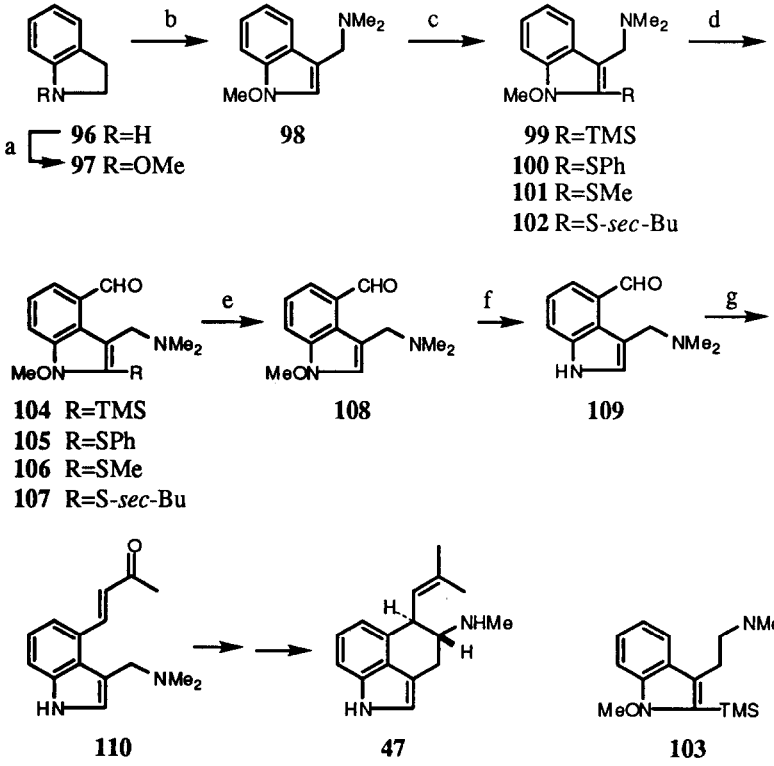
92 R=β-H
23 R=α-H

SCHEME 15. Reagents: a, RCH_2NO_2, NH_4OAc; b, $NaBH_4$, MeOH; c, Zn-Hg, HCl, MeOH; d, CH_2O, *t*-BuOK; e, Ac_2O, DMSO.

dimethyl sulfoxide yielded the analogous *N*-acetates, (±)-*trans* **93**, **94**, and **95** (*53*).

7. *Synthesis of (±)-6,7-Secoagroclavine, (±)-Aurantioclavine, and (±)-Clavicipitic Acid*

Somei *et al.* investigated the lithiation of 2-substituted 1-methoxy-3-dimethylaminomethylindoles at the 4-position, expecting that the introduction of a bulky 2-substituent would force the dimethylamino group in the desired direction (*55*). Suitable substrates **99–102** with a bulky substituent at the 2-position were prepared from indoline **96** in a series of reactions: 1) oxidation of



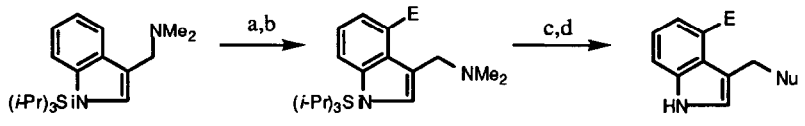
SCHEME 16. Reagents: a, Na_2WO_4, 30% H_2O_2, then CH_2N_2; b, CH_2O, Me_2NH, AcOH; c, *n*-BuLi, THF, then TMSCl, Ph_2S_2, Me_2S_2, or $(sec\text{-}Bu)_2S_2$; d, *n*-BuLi, ether, then DMF; e, $(n\text{-}Bu)_4NF$; f, $h\nu$, EtOH; g, acetone, NaOH, H_2O.

96 with sodium tungstate and 30% hydrogen peroxide, followed by methylation with diazomethane, 2) Mannich reaction, and 3) regioselective lithiation of **98** at the 2-position, followed by reaction with electrophiles, as shown in Scheme 16. They found when the solvent was ether, lithiation of **99–102** took place smoothly at the 4-position, while as long as tetrahydrofuran was used, lithiation did not occur. Lespedamine derivative **103**, a homolog of **99**, was not lithiated at the 4-position at all.

Based on the above results, Somei *et al.* developed a novel synthetic route for multi-functionalized 4-substituted indoles starting from indoline **96**, and applied it to the synthesis of ergot alkaloids (*55*). Lithiation of 1-methoxy-3-dimethylaminomethylindoles **99–102** with *n*-butyllithium in ether, followed by trapping with *N*,*N*-dimethylformamide, afforded **104–107** in good yields. Subsequent treatment of **104** or **105–107** with tetra-*n*-butylammonium fluoride or Raney nickel, respectively, afforded **108**. Ultraviolet irradiation removed the 1-methoxy group to afford 4-formylgramine (**109**), which was then converted to **110** by aldol condensation with acetone. Compound **110** had been already converted to (–)-6,7-secoagroclavine [(–)-**47**], (±)-aurantioclavine and (±)-clavicipitic acid through **41** and **76**, respectively (*38,56*).

B. Synthetic Studies by Iwao's Group

Iwao *et al.* introduced an efficient methodology for the synthesis of 3,4-disubstituted indoles **113** (*57*). Their strategy comprises two sequential steps: 1) selective functionalization of 1-silyl-3-dimethylaminomethylindole (**111**) at the 4-position by directed lithiation, followed by quenching with electrophiles, for the preparation of 4-dimethylamino-substituted indole **112** (*58*); 2) substitution of the dimethylamino group of **112** for various nucleophiles giving **113** upon desilylation through quaternization followed by a fluoride ion-induced elimination-addition reaction (Scheme 17) (*59*).



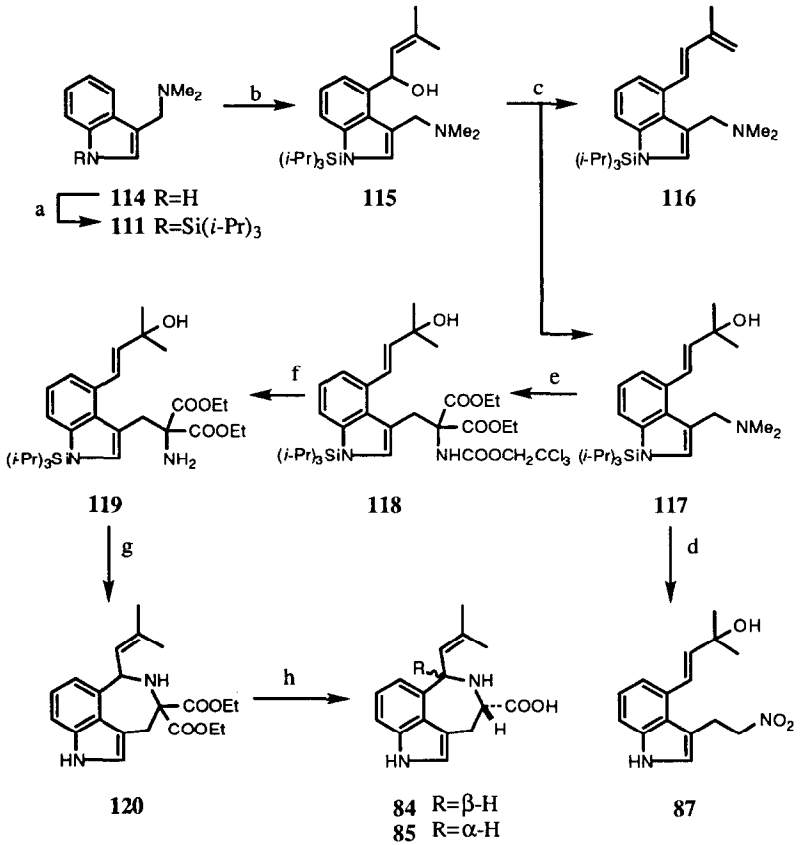
111 **112** **113**

Scheme 17. Reagents: a, *t*-BuLi, ether; b, electrophiles (E=Me_3Si, PhS, I, CHO, Me_2C=CHCHOH, etc.); c, MeI; d, nucleophiles (Nu=$CHNO_2$, $C(TrocNH)(COOEt)_2$, etc.), $(n\text{-}Bu)_4NF$.

1. Synthesis of (±)-6,7-Secoagroclavine, (±)-Aurantioclavine, and (±)-Clavicipitic Acid

Iwao *et al.* applied the above methodology to the total syntheses of ergot alkaloids (*58,59*).

3-Dimethylaminomethylindole (**114**) was silylated on nitrogen, first by metalation with *n*-butyllithium in tetrahydrofuran followed by silylation with triisopropylsilyl chloride. Lithiation of **111** with *t*-butyllithium in ether at



SCHEME 18. Reagents: a, *n*-BuLi, $(i\text{-Pr})_3SiCl$; b, *t*-BuLi, ether, then $Me_2C{=}CHCHO$; c, 85% H_3PO_4, dioxane; d, MeI, benzene, then $MeNO_2$, $(n\text{-Bu})_4NF$; e, MeI, benzene, then $Cl_3CCH_2OCONHCH(COOEt)_2$, $(n\text{-Bu})_4NF$, THF; f, Zn, THF, 1M KH_2PO_4; g, PPTS, CH_2Cl_2; h, 2M KOH, MeOH, then 2M HCl, and then aqeous EtOH, reflux.

–78°C occurred regioselectively at the 4-position due to the steric hindrance of a bulky substituent on the 1-position. The resulting 4-lithiated intermediate was reacted with 3-methyl-2-butenal to afford the alcohol **115**. Acid-catalyzed allylic rearrangement of **115**, by treatment with 85% phosphoric acid in dioxane, produced **117**, together with **116** as a minor product. Quaternization of **117** with methyl iodide in benzene, and subsequent reaction of the methiodide with nitromethane as a nucleophile in the presence of tetra-*n*-butylammonium fluoride, afforded **87** in an excellent yield, thereby establishing for Iwao's group alternative formal total syntheses of (–)-6,7-secoagroclavine [(–)-**47**] and (±)-aurantioclavine. Somei's group had already succeeded in the synthesis of the same alkaloids employing **87** as a key intermediate (*37,38*).

Similarly, the methiodide was reacted with diethyl (2,2,2-trichloroethoxycarbonyl)aminomalonate as a nucleophile to give **118**, which was then converted to the amine **119** by deprotection of the 2,2,2-trichloroethoxycarbonyl group with zinc and potassium dihydrogen phosphate. Dehydrative cyclization of **119** to the azepinoindole **120** was achieved by heating **119** in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate in dichloromethane. Hydrolysis of **120** with potassium hydroxide in methanol yielded the malonic acid derivative which was then readily decarboxylated on heating in aqueous ethanol to accomplish total syntheses of (±)-*cis*- and (±)-*trans*-clavicipitic acid (**84,85**) in a ratio 3 : 2 (Scheme 18) (*57*).

C. Synthetic Studies by Yokoyama and Murakami's Group

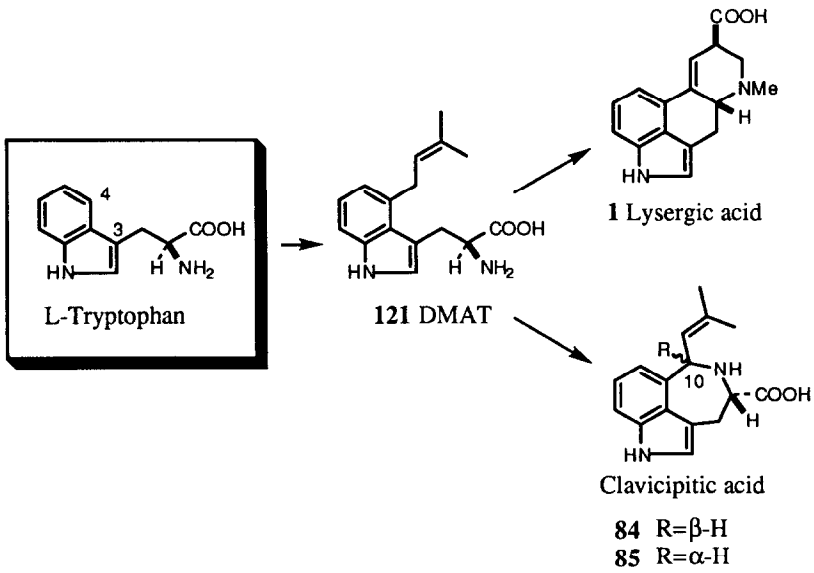
Yokoyama *et al.* have carried out extensive synthetic studies on nitrogen-containing heterocyclic compounds with a particular focus on the indole ring system. In a continuation of their work, following synthetic work on the benzo[*c*]phenanthridine alkaloids, they initiated synthetic studies by tackling the synthesis of ergoline alkaloids. Their approach to this group of alkaloids has been based on the exploitation of the chemistry and reactions of tryptophan.

Tryptophan, existing as an optically active form, and commercially available in the L-form, has been known as one of the important essential amino acids, and is also regarded as the important key intermediate in the biosynthesis of many important biological compounds. Ergot alkaloids, as represented by lysergic acid (**1**) and clavicipitic acid (**84,85**), are known to be biosynthesized from L-tryptophan through a common intermediate, 4-(γ,γ-dimethylallyl)tryptophan (DMAT) (**121**) (Scheme 19) (*4*).

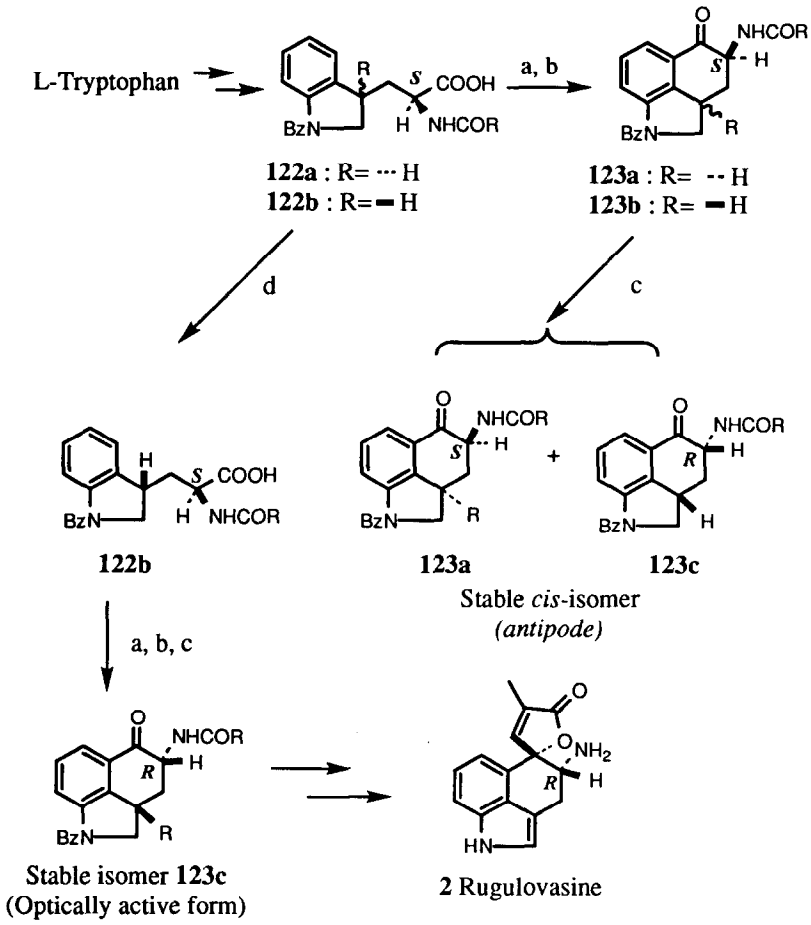
However, many ideas and then studies have been based on the effective use of tryptophan as the synthetic starting material for substitution at the 4-position of the ring system, but so far without much success in the synthesis of the optically active form of the ergot alkaloids. The reason for the failure of its application to the synthesis has been regarded as the facile racemization which

occurred during substitution at the 4-position, together with the poor reactivity of the 4-position of tryptophan.

For example, Rebek (*15–17*) and Varie (*60*) reported that intramolecular Friedel-Crafts acylation of a diastereomeric mixture of dihydrotryptophans **122a** and **122b** prepared from L-tryptophan yielded the ketone as a mixture of diastereomers **123a** and **123b**, and they also noticed that one of the isomers **123b** was readily epimerized to give the stable *cis* isomer **123c**, thus giving rise to the racemates **123a** and **123c** as the cyclization product. In order to obtain enantiomerically pure isomer **123c**, it was necessary to isolate **123b** from the diastereomeric mixture of **123a** and **123b**. Rebek *et al.* thus succeeded in synthesizing optically pure rugulovasine (**2**) from **123c** (Scheme 20). This is the only complete synthesis of an optically active ergot alkaloid from L-tryptophan thus far achieved. In order to establish a higher level of synthetic chemistry in the ergoline alkaloids, Yokoyama and Murakami's group has carried out research by making an effective use of tryptophan, to open this area to asymmetric synthesis, and to bring it closer to biochemical importance.



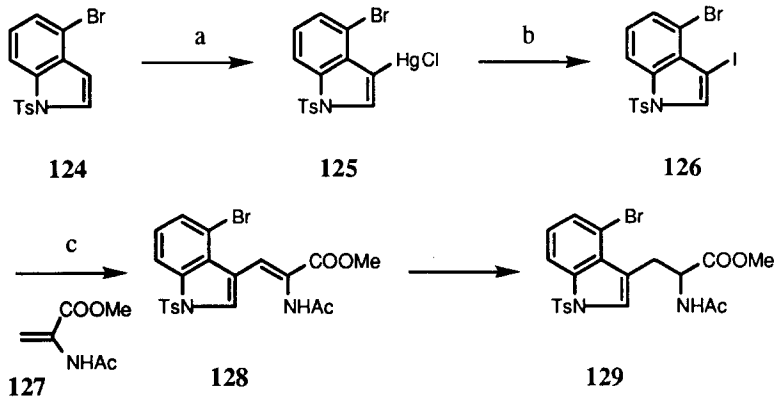
SCHEME 19. Biogenetic route for the ergot alkaloids.



SCHEME 20. Reagents: a, $(COCl)_2$; b, $AlCl_3$; c, epimerization; d, separation of diastereomers.

1. Use of Optically Active 4-Bromotryptophan as the Key Synthetic Intermediate

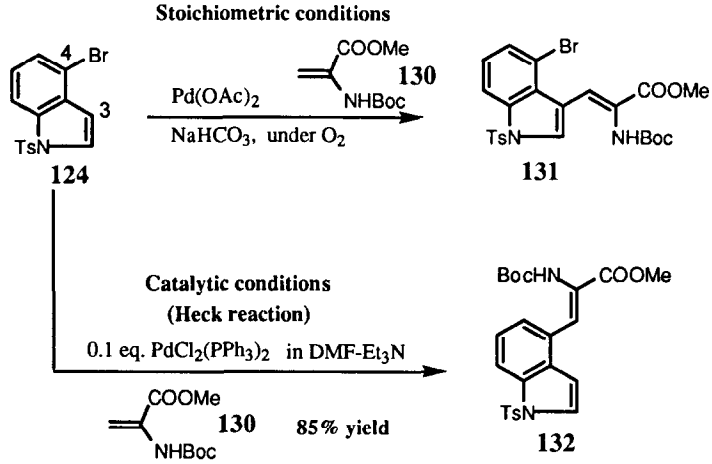
The use of 4-bromotryptophan was regarded as having a high potential for the synthesis of a variety of 4-substituted derivatives for further conversion into many biologically important compounds, though not many promising results were available until 1995.



SCHEME 21. Reagents: a, $HgCl_2$; b, I_2; c,15 mol% $Pd(OAc)_2$.

Hegedus reported the synthesis of *dl*-4-bromotryptophan **129** from *N*-tosyl-4-bromoindole **124** as a precursor for ergot alkaloid synthesis (*23*) (Scheme 21). 4-Bromodehydrotryptophan **128** was prepared from the *N*-protected 4-bromoindole **124** in a three-step synthesis, which involved a mercuration-iodination reaction followed by chemoselective palladium-catalyzed vinylation of 4-bromo-3-iodo-1-tosylindole **126** with *N*-acetyldehydroalanine methyl ester **127**. Although this route was short and applicable to the preparation of variously substituted dehydrotryptophans, the use of a hazardous mercury reagent during the synthetic process turned attention to other methods, for example, the one-step synthesis of *N*-Boc-4-bromodehydrotryptophan methyl ester (**131**) from the same starting material **124** (*61,62*).

Vinylation of **124** with *N*-Boc-dehydroalanine methyl ester (**130**) occurred only at the 3-position in the presence of a stoichiometric amount of $Pd(OAc)_2$. This reaction was interesting because vinylation occurred chemoselectively only at the 3-position, in spite of the presence of a reactive carbon-bromine bond, while the C-4 vinylated product **132** was obtained in the presence of a catalytic amount of $PdCl_2(PPh_2)_2$ according to the Heck reaction. Thereby the two reactive positions of 3 and 4 were completely distinguishable towards vinylation by changing the reaction conditions (Scheme 22). The yield of **131** was markedly improved by the addition of chloranil, as shown in Table I. On the assumption that chloranil acts as an oxidizing agent to recycle palladium(0) to palladium(II), the role of a catalytic amount of $Pd(OAc)_2$ was deduced, and thus employed, though the yield of **131** stayed only at 38% under these condition (Scheme 22). Other oxidizing reagents such as DDQ, MnO_2, Ag_2CO_3, $(Coşalen)_2$-O_2, and $Cu(OAc)_2$ were found to be not as effective as chloranil.



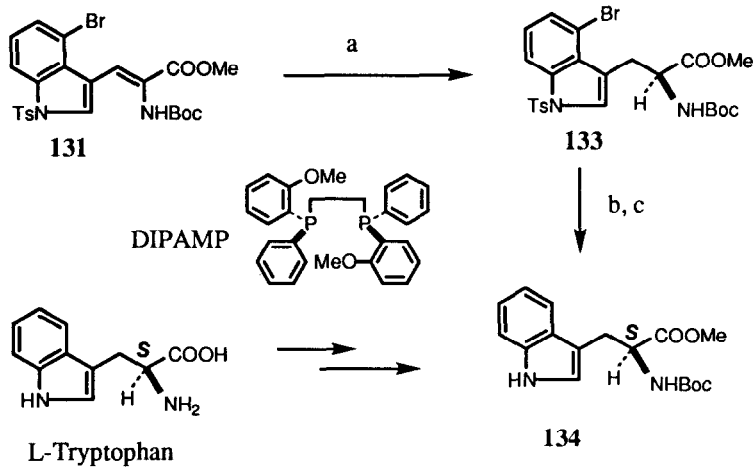
SCHEME 22

Asymmetric reduction of **131** was carried out using DIPAMP as a chiral phosphine ligand to give the 4-bromotryptophan derivative **133** with high optical purity (94% ee). The absolute configuration was determined as *S* by the conversion of **133** into *N*-Boc-tryptophan methyl ester (**134**), which was correlated with a sample synthesized from L-tryptophan. Although there have been numerous reports of the asymmetric reduction of *N*-acetyl- or *N*-benzoyl-protected dehydroamino acids with high enantiomeric excess, there are only a limited number of reports of the asymmetric reduction of a *N*-urethane-protected dehydroamino acid such as **131**. Schmidt recorded the highest optical yield (95% ee) by the asymmetric reduction of *N*-Boc-dehydrotryptophan using a rhodium-DIPAMP complex (*63*) (Scheme 23).

TABLE I. SYNTHESIS OF 4-BROMODEHYDROTRYPTOPHAN (**131**)

Expt.	$Pd(OAc)_2$ eq.	chloranil eq.	time (h)	temp.(°C)	solvent	Yield of 131 (%)
1	1.0	–	3	70	CH_2ClCH_2Cl	41[a)]
2	1.0	0.25	7.5	70	CH_2ClCH_2Cl	74
3	1.0	1.0	7	90	TCB	85
4	0.25	1.0	3	90	TCB	38

a) under Ar TCB=1,2,4-trichlorobenzene

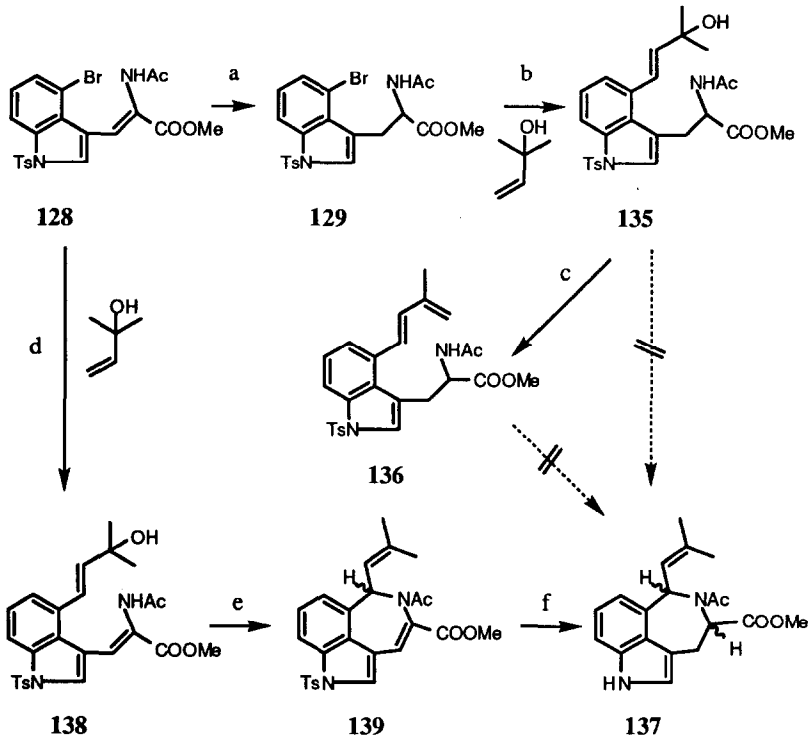


SCHEME 23. Reagents: a, H_2, $Rh(COD)_2BF_4$, DIPAMP; b, Pd-C, H_2; c, Mg, MeOH.

2. *Synthesis of Optically Active Clavicipitic Acid*

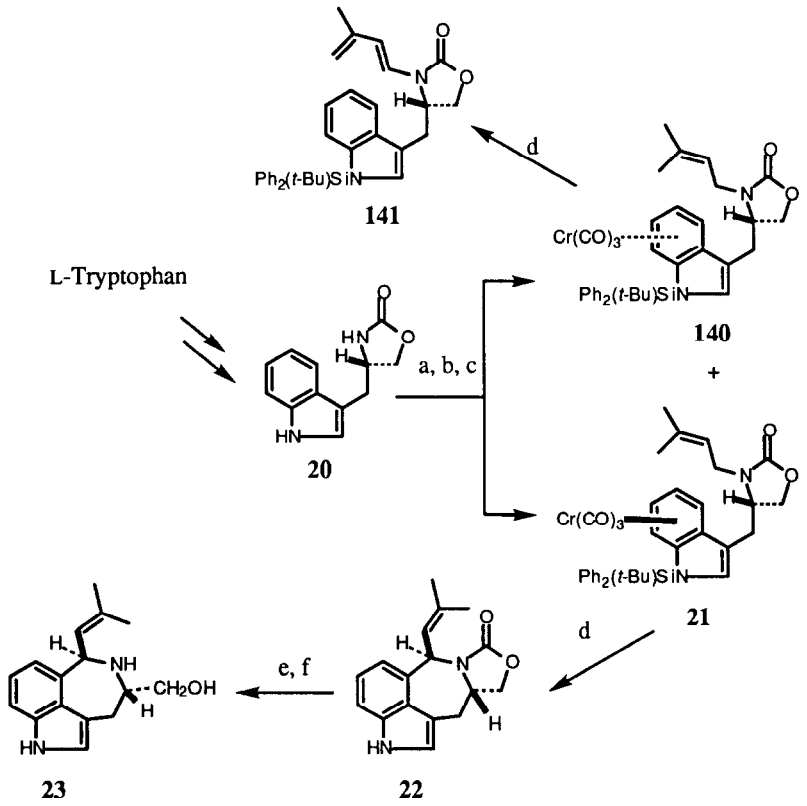
Clavicipitic acid (**84,85**) is an ergot alkaloid isolated from one of the *Claviceps* strains as a mixture of diastereomers, and has a unique ring system different from that of the ergoline alkaloids, including lysergic acid (**1**) (*64*). By the end of the last decade, a number of syntheses of this alkaloid had been reported (*19–23,28,47,53,57*) including two groups who reported the synthesis using a tryptophan derivative.

Hegedus *et al.* (*23*) reported an efficient vinylation of **129** with 1,1-dimethylallyl alcohol by the Heck reaction to give the C-4 vinylated product **135**, which was found to be unstable and readily dehydrated to give the diene **136**. The compounds **135** and **136** failed to give rise to cyclization to the tricyclic azepinoindole **137** under various conditions. However, the cyclization of the 4-vinylated dehydrotryptophan **138**, which was prepared by Heck reaction on the 4-bromodehydrotrytophan **128** with the palladium catalyst, proceeded smoothly on heating in the presence of stoichiometric or catalytic quantities of $PdCl_2(MeCN)_2$ to give the cyclized azepinoindole product **139** quantitatively. This facile cyclization of **138**, in contrast to **135** and **136**, could be attributed to the rigid conformation of the acetamidoacrylate side chain. Photochemical reduction of the cyclized compound **139** with sodium borohydride removed the tosyl group on nitrogen to give *N*-acetylclavicipitic acid methyl ester **137** as a mixture of diastereomers (Scheme 24).



SCHEME 24. Reagents: a, H_2, $Rh(PPh_3)_3$, MeOH; b, $Pd(OAc)_2$, $(o\text{-tol})_3P$; c, MeCOCl, pyridine; d, $Pd(OAc)_2$, $(o\text{-tol})_3P$; e, $PdCl_2(MeCN)$, MeCN; f, $NaBH_4$, Na_2CO_3, $h\nu$.

Semmelhack and coworkers (*28*) reported the synthesis of optically active clavicipitic alcohol (**23**) via the route involving an intramolecular cyclization of the chromium complex **21** starting from L-tryptophan. Although this cyclization proceeded smoothly to give the optically active azepinoindole **22** in good yield, the intermediary chromium complex was not isolated stereoselectively from the oxazolinone **20**. Compound **20** was reacted with $Cr(CO)_3(MeCN)_3$ followed by silylation and allylation to give a diastereomeric mixture of chromium complexes **21** and **140** in a 1:1 ratio. Each diastereomer showed contrasting behavior to cyclization, one isomer, **21**, rapidly cyclized to the pure tetracyclic product **22** in 77% yield, while the other isomer, **140**, gave only the diene **141** in 70% yield under the same conditions, as a result of dehydration of the product. The cyclized product **22** was then converted to clavicipitic alcohol (**23**) in 83% yield (Scheme 25).

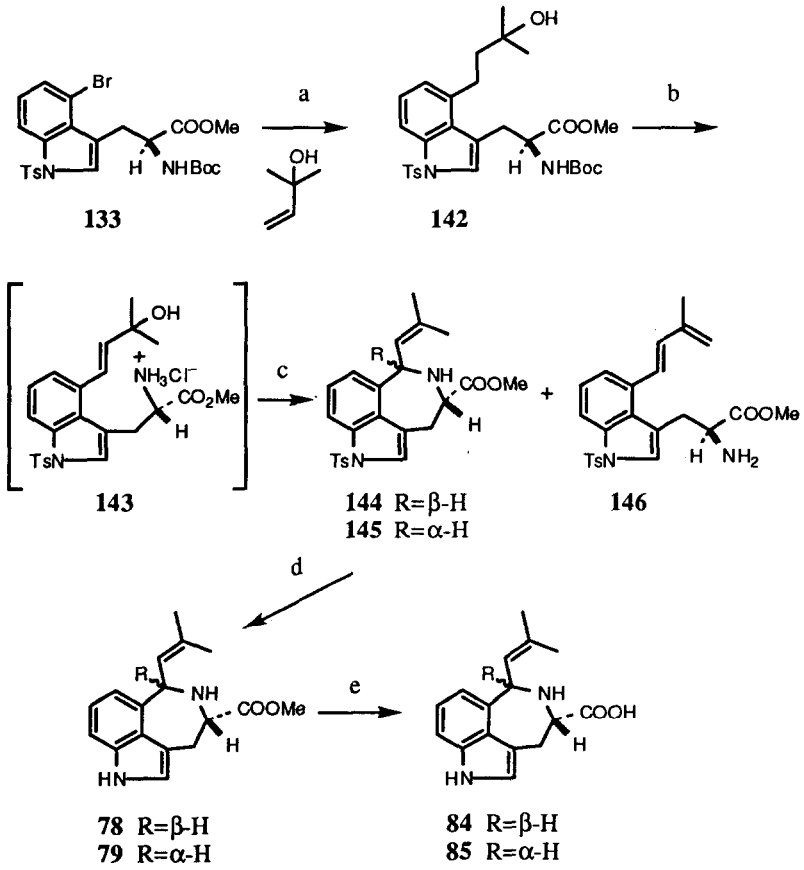


SCHEME 25. Reagents: a, $Cr(CO)_3(MeCN)_3$; b, NaH, $Ph_2(t\text{-Bu})SiCl$; c, MeLi, $(Me)_2C{=}CHCH_2Br$; d, LDA then I_2; e, $(n\text{-Bu})_4NF$; f, 3M KOH.

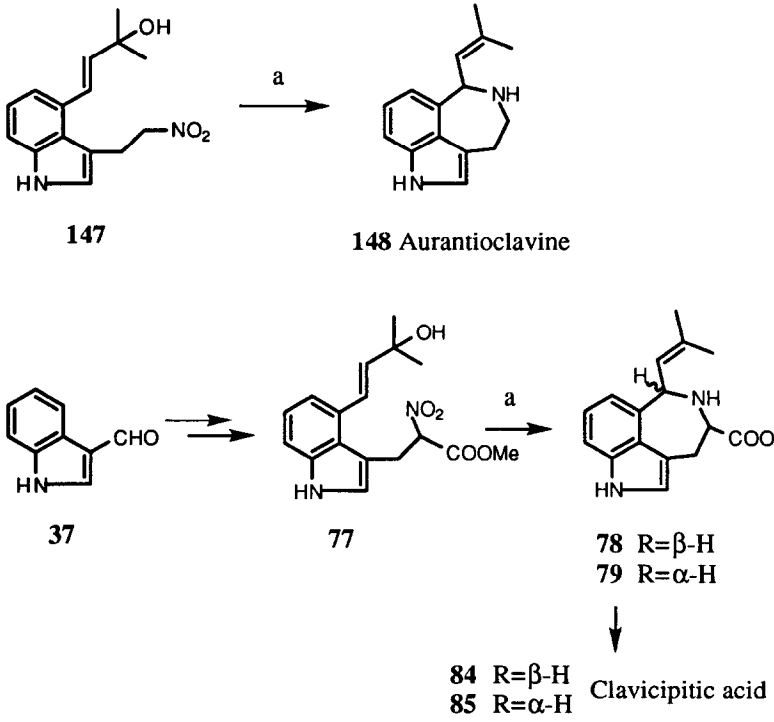
In 1995, Yokoyama and Murakami reported the first chiral synthesis of clavicipitic acid (**84**,**85**) using the optically active 4-bromotryptophan **133** as the starting compound with protection on nitrogen by a *t*-butoxycarbonyl group, which was later readily removed (*65*).

Vinylation of **133** under Heck conditions in the presence of silver carbonate proceeded smoothly to give the C-4 vinylated product **142** in 83% yield without racemization. This reaction in the absence of silver carbonate required higher temperature (120°C) and gave poor results with significant racemization (82% yield, 71% ee). When **142** was treated with acid, followed by neutralization using triethylamine, spontaneous cyclization of the resulting amine **143** took place giving a mixture of the *cis* and *trans* isomers **144** and **145** in 62% yield,

together with some of the dehydrated diene **146**, in 29% yield. This result was in sharp contrast to Hegedus's results, and could be explained by the effect of the substituent in the acetamide group which is poorly nucleophilic to attack by the double bond, thereby giving only the diene **136**. On the other hand, the free amine obtained from **142** was reactive enough to cause spontaneous cyclization under the reaction conditions. On the respective isomers *cis*-**144** and *trans*-**145**, detosylation with magnesium-methanol proceeded smoothly to give clavicipitic acid methyl esters as a mixture of *cis*-**78** and *trans*-**79**, which were purified by



SCHEME 26. Reagents: a, 0.1 eq. $PdCl_2(PPh_3)_2$, 1.0 eq. Ag_2CO_3, DMF-Et_3N, b. HCl, AcOEt; c, Et_3N; d. Mg, MeOH; e, KOH, MeOH-H_2O, Zn-Hg, HCl, MeOH-H_2O.

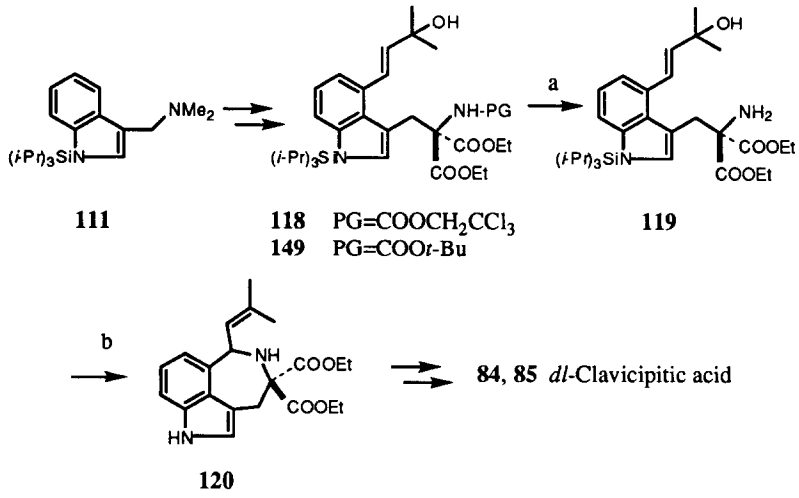


SCHEME 27. Reagents: a, Zn-Hg, HCl, MeOH-H_2O.

one recrystallization to give the pure samples, respectively. Alkaline hydrolysis of the esters **78** and **79** afforded pure clavicipitic acids (**84,85**), *cis* and *trans*, respectively. Their optical rotations were –195.3° (EtOH) for the *cis* isomer and –129.1° (EtOH) for the *trans* isomer (Scheme 26).

Somei's group (*24*) has reported a similar one-pot cyclization of the nitroolefin **147** by reductive amino-cyclization for the synthesis of *dl*-aurantioclavine (**148**). They later applied this method to the synthesis of *dl*-clavicipitic acids (**84,85**) (*47*). Nitroolefin **77**, prepared from 3-formylindole (**37**), was treated with amalgamated zinc in HCl and methanol to give the clavicipitic acid methyl esters (**78, 79**) (Scheme 27).

Recently, Iwao reported (*57*) the dehydrative cyclization of **119** in the total synthesis of *dl*-clavicipitic acid. Iwao prepared the diester **118**, having protected the amino group with a trichloroethoxycarbonyl group, which was then readily cleaved by treatment with zinc dust to recover the free amine **119** in



111 **118** PG=$COOCH_2CCl_3$ **119**
149 PG=COO*t*-Bu

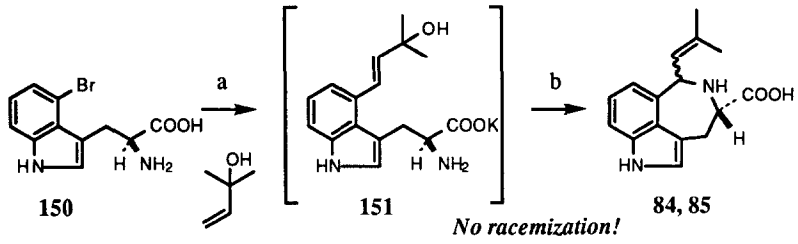
120

SCHEME 28. Reagents: a, Zn dust, KH_2PO_4; b, PPTS, CH_2Cl_2.

good yield. When the resulting amine **119** was heated in the presence of a catalytic amount of PPTS in refluxing dichloromethane, cyclization occurred smoothly to give the azepinoindole **120** in good yield (Scheme 28). In contrast to **118**, deprotection of the Boc group of **149** under acidic conditions (2M-HCl in dioxane or 98% HCOOH) gave only complex mixtures.

Although Yokoyama's synthetic route (*65*) was very efficient and practical, when compared to the other methods, it still required four steps from **133**, including three deprotecton steps. They have tried to improve further their synthetic route aiming at the one-pot synthesis of (–)-**84**, (–)-**85** from free (*S*)-4-bromotryptophan (**150**) without using any protective groups.

Heck reaction of **150** with 1,1-dimethylallyl alcohol was thoroughly investigated to find the conditions suitable for the one pot synthesis of the target alkaloid. Since the amino acid **150** is soluble only in water, the reaction of **150**, without using any protecting group on nitrogen was carried out in aqueous media using a water-soluble phosphine ligand, TPPTS, in the presence of potassium carbonate as a base. The product obtained was not the expected clavicipitic acid, but the potassium salt of the C-4 vinylated compound **151**, which had an uncyclized structure. This compound, **151**, was found to be stable under basic conditions and was isolated by ODS column chromatography. It smoothly cyclized under weakly acidic conditions to give a 1 : 1 mixture of diastereomeric clavicipitic acids (**84,85**) in 78% yield, thereby completing a two-step synthesis of **84,85**. Then, in order to establish the one-pot synthesis, after the vinylation of **150** in aqueous basic solution, the reaction mixture was



SCHEME 29. Reagents: a, 01 eq. $Pd(OAc)_2$, 0.2 eq. TPPTS, K_2CO_3, H_2O, in sealed tube; b, 50% AcOH.

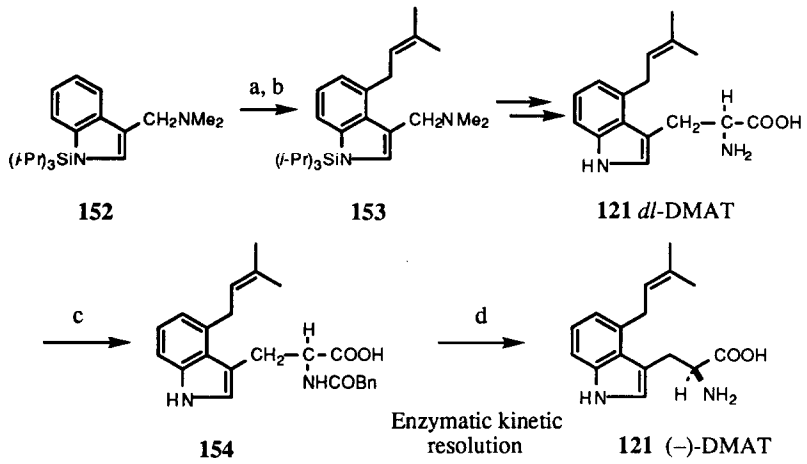
quenched with 60% aq. acetic acid and warmed to 50°C. Thus, the one-pot transformation from **150** to **84,85** was achieved smoothly to give clavicipitic acid (**84,85**) in 61% yield from **150** (Scheme 29). The optical purities of the intermediate **151** in this synthesis and clavicipitic acid (**84,85**) obtained (*cis* and *trans*) were 92% ee as determined by HPLC. During this process, no sign of racemization was detected and it was suggested that water played an important role for minimizing racemization under such strong basic conditions. Matsuo observed that facile racemization of amino acids occurs in 100% acetic acid, and that the rates of racemization were considerably lower in 50% aq. acetic acid than in 100% acetic acid (*66*).

3. Synthesis of Optically Active DMAT

DMAT (**121**) was first proposed (*1*) as an important key intermediate in the biosynthesis of ergot alkaloids, and this was confirmed later by isolation from the culture broth of *Claviceps* species (*67*). As studies have progressed, its importance became apparent from both the biosynthetic and the synthetic points of view (*4*).

The first synthesis of DMAT (**121**) was reported in 1967 by Plieninger's group (*68*) starting from 4-formylindole. This synthesis played an important role in the supply of DMAT (**121**) for biosynthetic research. In 1995, Nettekoven's group developed a method for the synthesis of optically active DMAT (*69*). They prepared 4-dimethylallylgramine (**153**) by selective C-4 lithiation of the *N*-silyl protected gramine **152** followed by treatment with dimethylallyl bromide. Then *dl*-DMAT (**121**) was synthesized from the above gramine **153** according to Plieninger's method (*68*). On conversion of *dl*-**121** to the phenacyl amide **154**, enzymatic kinetic resolution of **154** afforded enantiomerically pure (–)-DMAT (**121**) with 98% ee (Scheme 30).

Recently, Yokoyama and Murakami reported another synthesis of optically active DMAT (**121**) (*70*). Dehydration of **142** gave the unstable diene **155**



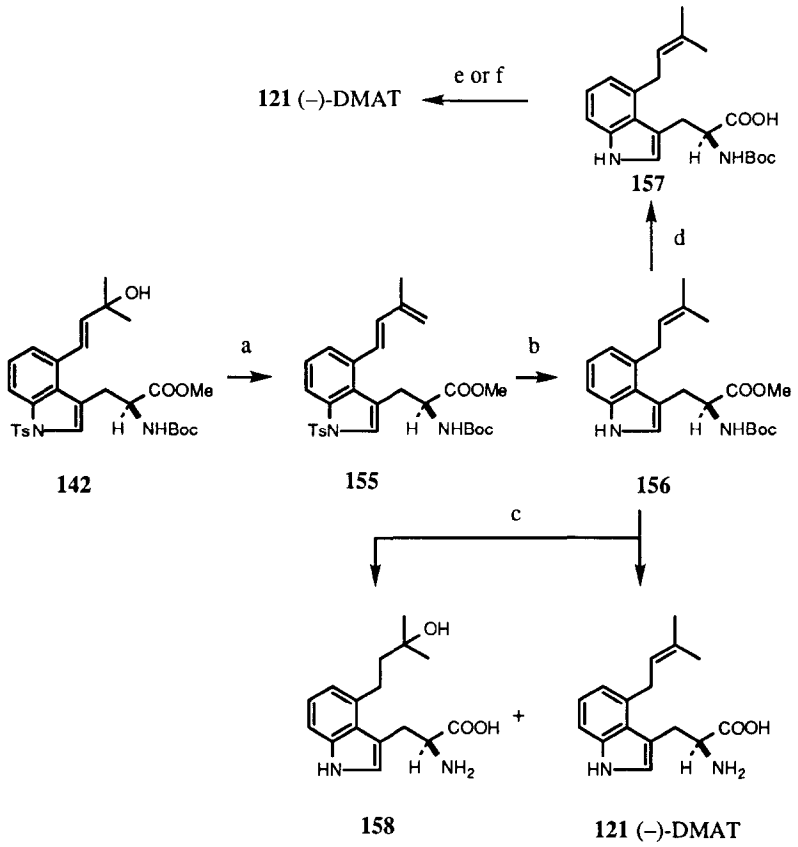
SCHEME 30. Reagents: a, *t*-BuLi; b, $BrCH_2CH{=}C(Me)_2$; c, BnCOCl; d, Penicillin G Acylase.

which was then treated with magnesium-methanol for reduction of the diene moiety in a 1,4 manner. Concomitant detosylation gave *N*-Boc-DMAT methyl ester (**156**). Since the optical purities of **142** and **156** were 93% and 91%, respectively, racemization was negligible. Alkaline hydrolysis of the ester **156** gave the acid **157** in 92% yield, and the Boc group was removed by heating in acetic acid at 120°C (Scheme 31).

Although (–)-**121** was obtained as the sole product in 57% yield, serious racemization occurred (25% ee). On investigation it was found that hydrolysis of the ester **156** in 50% aq. acetic acid proceeded smoothly at lower temperature (80°C) to give (–)-DMAT (**121**) without racemization (94% ee) and in good yield (90%) (Scheme 31). Low temperature treatment thus might minimize both the racemization and the addition of water to the double bond **158**.

4. Synthesis of Optically Active Chanoclavine I

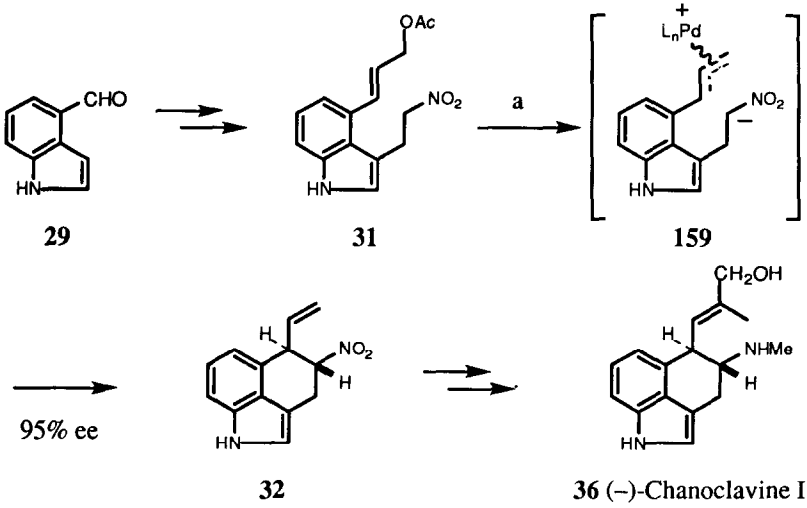
Chanoclavine I belongs to a class of 6,7-secoagroclavines having a tricyclic ring system. Its occurrence has a special significance since it is an important intermediate in the biosynthesis of tetracyclic ergolines, including lysergic acid (**1**) (*4*). Although *dl*-chanoclavine I (**36**) was synthesized previously by several groups (*29–33*), there were only a few reports on the synthesis in optically active form. In 1994, French chemists (*35,36*) reported the first asymmetric total synthesis of chanoclavine I (**36**) in 12 steps involving a process of the formation of C ring by asymmetric palladium-catalyzed cyclization as the key



SCHEME 31. Reagents: a, TsOH, benzene; b, Mg, MeOH; c, 50% aq. AcOH, sealed tube; d, 4% KOH-dioxane; e, 120°C, AcOH; f, 80°C, 50% aq. AcOH.

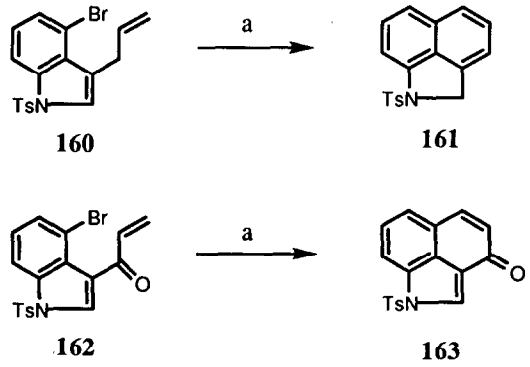
step via the π-allyl complex **159** with a chiral phosphine ligand (Scheme 32).

In order to use tryptophan as the starting material for the construction of an ergoline skeleton, it was necessary to develop an intramolecular cyclization for the formation of cyclohexa[*cd*]indole. For this purpose, there were several methods reported, particularly through the formation of a cyclohexa[*cd*]indole. Hegedus's group (*71*) developed a route by applying the Heck reacton to the cyclization of 3-allyl-4-bromo-*N*-tosylindole (**160**). Although they succeeded in synthesizing a tricyclic ring system, rearrangement of the double bond in the product occurred to form the more stable naphthalene derivative **161**. Further, Hegedus (*72*) attempted a similar cyclization of the α,β-unsaturated ketone **162**

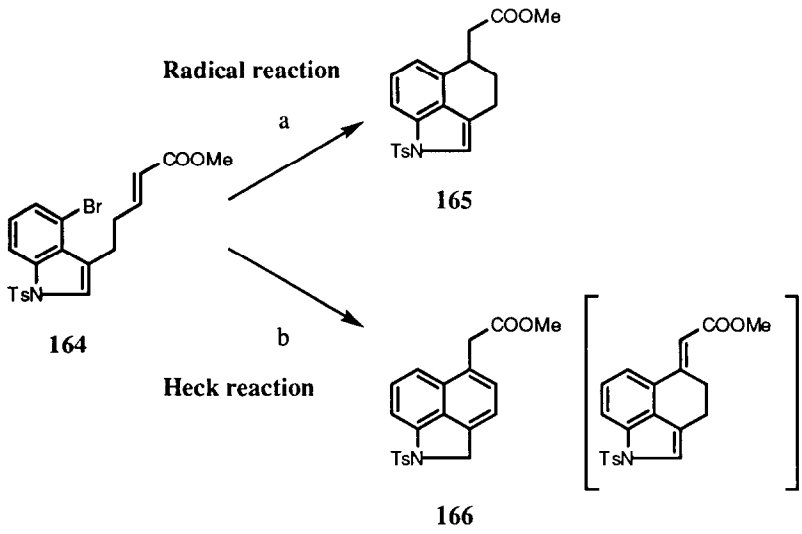


SCHEME 32. Reagents: a, $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP, THF.

to synthesize the tricyclic ketone **163** (Scheme 33). The presence of a keto group blocked rearrangement to the benz[*cd*]indoline system.



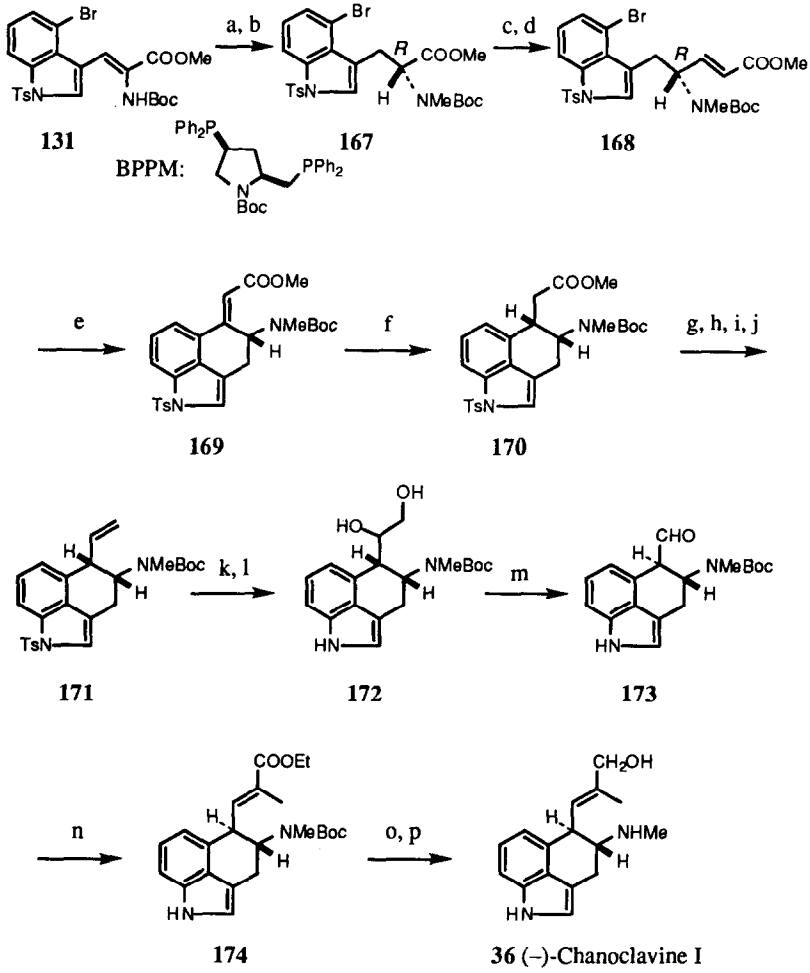
SCHEME 33. Reagents: a, $Pd(OAc)_2$, (*o*-tol)$_3$P, Et_3N in CH_3CN.



SCHEME 34. Reagents: a, $(n\text{-Bu})_3SnH$, AIBN, toluene; b, 0.1 eq. $PdCl_2(PPh_3)_2$, DMF-Et_3N.

Yokoyama *et al.* (*73,74*) also attempted an intramolecular palladium-catalyzed vinylation (Heck reaction) or radical reaction of the 4-bromoindole derivative **164** carrying an α,β-unsaturated ester group in the 3-substituent. Though the Heck reaction on this compound **164** was unsuccessful to give **166**, radical cyclization of **164** resulted in the desired tricyclic ring system **165** in moderate yield (Scheme 34). Accumulating the information on the reactions and results of these reactions, including the Heck reaction, aimed at the synthesis of chanoclavine I (**36**), the strategy for the synthesis of this alkaloid by the cyclization of tryptophan derivatives finally allowed completion of the total synthesis.

Optically active, doubly-protected 4-bromo-*N*-methyltryptophan **167** was prepared by asymmetric reduction of the corresponding dehydrotryptophan derivative **131**. The optical yield, however, was 55% ee, when BBPM was used as a chiral phosphine ligand. The absolute configuration of **167** was *R*, opposite to that of the natural amino acid, but this configuration was required for the synthesis of the natural ergoline alkaloids. Palladium-catalyzed intramolecular cyclization of the optically active conjugated ester **168**, which was prepared from **167**, proceeded smoothly in the presence of 1,3-bisdiphenylphosphino-propane (BPPP) and tribasic silver phosphonate-calcium carbonate to give the expected tricyclic ester **169** in good yield.



SCHEME 35. Reagents: a, MeI, Ag_2CO_3; b, $[Rh(COD)_2]BF_4$, BPPM, H_2, 5 atm; c, DIBALH; d, $Ph_3P{=}CHCO_2Me$; e, 0.1 eq. $PdCl_2$-BPPP, Ag_3PO_4, $CaCO_3$, DMF; f, H_2, 10% Pd-C; g, Li[Bu(*iso*-Bu)$_2$AlH], THF; h, $NaBH_4$, EtOH; i, *o*-NO_2PhSeCN, (*n*-Bu)$_3$P, pyridine-THF; j, $NaIO_4$, THF-H_2O; k, OsO_4 (cat.), NMO, Acetone-H_2O; l, Mg, MeOH; m, $NaIO_4$, MeOH-H_2O; n, $Ph_3P{=}C(Me)COOEt$, CH_2Cl_2; o, TFA, $CHCl_3$; p, DIBALH, THF.

On the other hand, radical cyclization of **168** by heating with tri-*n*-butyltin hydride and AIBN did not occur, only recovering the starting material. These

confusing results compared to the above preliminary experiment might be explained by a rigid conformation of the C ring due to the presence of a bulky protective group on the amino group in **168**. Catalytic reduction of the tricyclic compound **169** gave the homogeneous product **170** with an undesired *cis* configuration. Conversion of the ester **170** to the olefin **171** was accomplished smoothly by a straightforward four-step sequence of reactions including one-pot reduction, selenylation and *syn*-elimination. The optical purities of the products **168** and **171** were both 55% ee determined by HPLC, thus proving that no racemization was involved in the processes of the conversion [**167** to **168**] and cyclization steps [**168** to **169**] (Scheme 35).

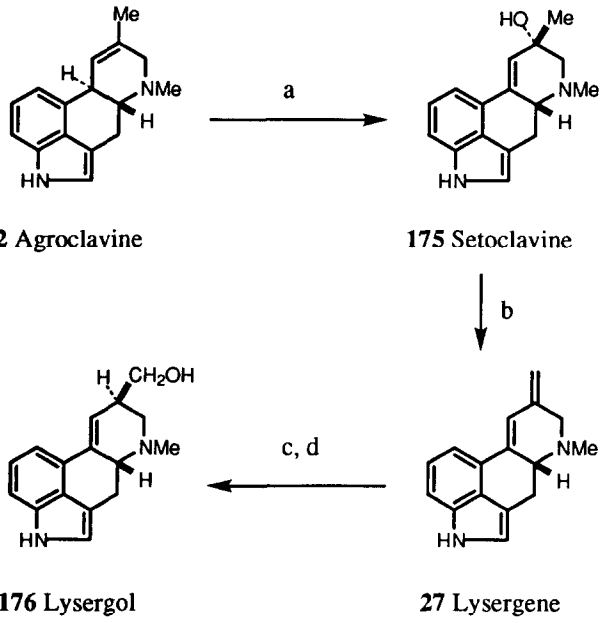
Oxidation of the olefin **171** with osmium tetroxide-NMO, followed by deprotection of the tosyl group with magnesium-methanol and cleavage of the diol with sodium periodate, gave the unstable aldehyde **173** which was immediately converted to the ester **174** by the Wittig reaction. Ready isomerization to the stable *trans* isomer **173** brought about the sole formation of the product with a *trans* configuration. Finally, the conversion of **174** to chanoclavine I (**36**) was carried out according to Oppolzer's procedure (*32*). The synthetic compound, which showed 75% ee after one recrystallization, had the same optical rotation as the natural alkaloid.

V. Interconversion of Ergoline Alkaloids

Most of the important conversions and interconversions of ergoline alkaloids were reported in the previous review (*3*). However, some further conversions were described in the literature based on a need for supply of the alkaloids.

A. Conversion of Agroclavine to Lysergol

Based on the previous results of the oxidative conversion of setoclavine (**175**) to lysergene (**27**), agroclavine (**62**), now readily available by the fermentation of *Claviceps purpurea* AA218, was successfully converted into lysergol (**176**) by functionalizing the 8-methyl group of agroclavine (**62**) (*75*). Regioselective dehydration of setoclavine (**175**) to lysergene (**27**) was achieved by heating **175** under reflux with predried Woelm alumina N-super 1 (type W200) in 1,2-dichloroethane to give lysergene (**27**). Then the exocyclic double bond was selectively hydroborated with 9-BBN at 60°C in tetrahydrofuran. Treatment of the adduct with aqueous sodium hydroxide and 30% hydrogen peroxide gave lysergol (**176**) (Scheme 36).



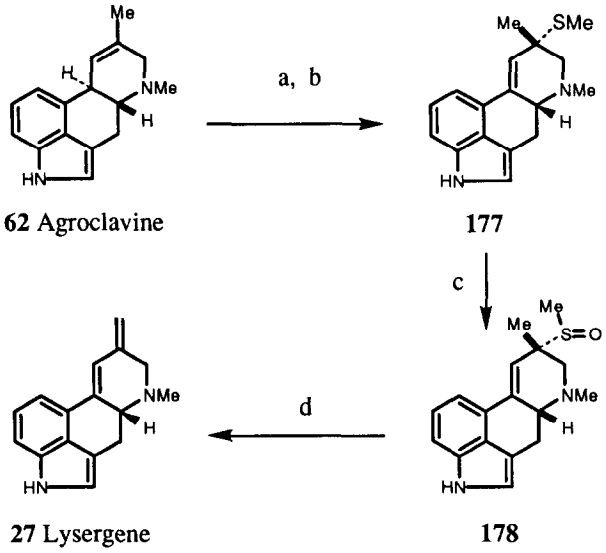
62 Agroclavine **175** Setoclavine

176 Lysergol **27** Lysergene

SCHEME 36. Reagents: a, $K_2Cr_2O_7$, c H_2SO_4, aq. acetone; b, Woelm alumina, $ClCH_2CH_2Cl$; c, 9-BBN, THF; d, NaOH, H_2O_2.

B. CONVERSION OF AGROCLAVINE TO LYSERGENE AND LYSERGINE

Ready availability of one of the most useful ergoline alkaloids agroclavine (**62**) has continuously drawn attention for its conversion to other ergot alkaloids (*76*). The hydrogen at C-10 of agroclavine (**62**) was readily removed by *n*-butyllithium to form an ambident carbanion which was then treated with a range of electrophiles to yield 10-substituted agroclavines, 8-substituted lysergines and isolysergic acid derivatives, one of which, 8-methylthio-lysergine (**177**), was prepared by the addition of dimethyl sulfide to agroclavine (**62**). The 8-methylthiolysergine (**177**) was then oxidized with sodium periodate to the sulfoxide **178**, and the methylthio group was eliminated in 40% yield to give the lysergene (**27**) (Scheme 37).



62 Agroclavine **177**

27 Lysergene **178**

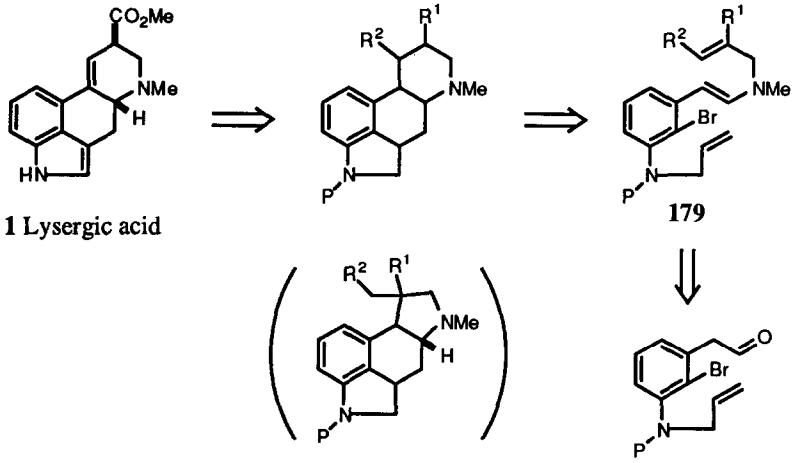
SCHEME 37. Reagents: a, *n*-BuLi, THF; b, MeSSMe; c, $NaIO_4$, aq, MeOH; d, heat.

VI. Reactions Developed for the Synthesis of Ergoline Alkaloids

Development of reactions designed or intended for the synthesis of ergot alkaloids and their analogs are summarized in this section, though successful invention and application of new synthetic methodologies were described in the section of new syntheses of ergoline alkaloids (Sections III and IV). There have been many reports describing the accumulated efforts and ideas aimed at the synthesis of natural products by new methods. In this section we have tried to collect these ideas in order to give chemists some concepts of the routes that have been investigated.

A. TANDEM RADICAL CYCLIZATION FOR THE CONSTRUCTION OF THE ERGOLINE SKELETON

Parsons *et al.* have developed a new free radical cyclization with the potential for application to the construction of the lysergic acid framework by a reaction



1 Lysergic acid

179

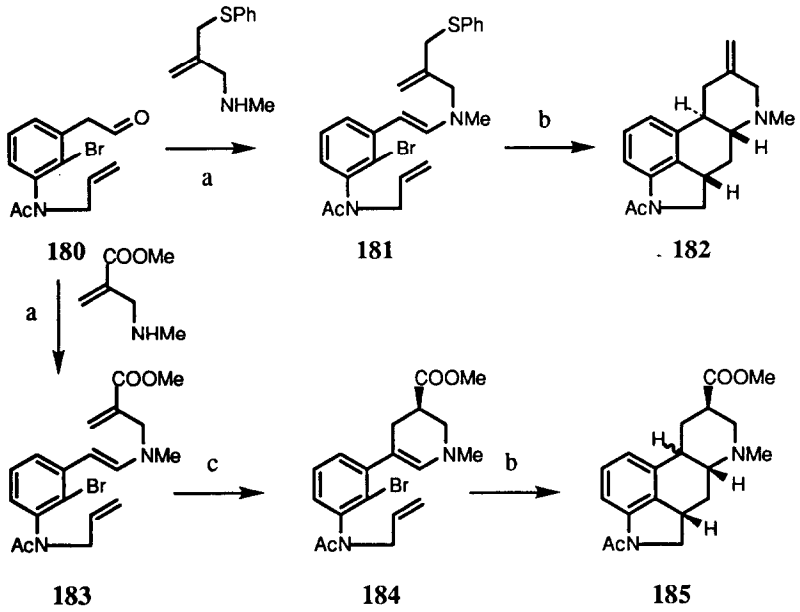
SCHEME 38. Retrosynthetic analysis.

involving the homolytic cleavage of a carbon-bromine bond, mediated by tri-*n*-butyltin hydride (*77*). This led to the development of a method for the construction of 3,4-disubstituted dihydroindoles via a single cyclization; hexahydrobenz[*cd*]indoles via double tandem cyclizations, and both octahydroindolo[6,5,4-*cd*]indoles and decahydroindolo[4,3-*fg*]quinolines via triple radical cyclizations of **179**. These synthetic ideas can be appreciated readily from the retrosynthetic scheme shown (Scheme 38).

Allyl sulfides have been used in radical cyclization to control the regiochemistry in 6-endo ring closures. This, indeed was found to be the case when the enamine **181** was subjected to radical cyclization under high dilution conditions. The ergoline **182** was isolated after successful 5-*exo*-trig, 6-*endo*-trig, 6-*endo*-trig cyclization.

The uncyclized enamine **183** was treated in boiling toluene for 5 h. prior to radical cyclization, and then further treated with tri-*n*-butyltin hydride in boiling toluene. A successful tandem double 5-*exo*-trig, 6-*endo*-trig cyclization of the aryl radical generated from **184** afforded the tetrahydrolysergate **185** which was obtained as the only isolable product in 75% yield as a 3:1 mixture of two epimers at the 10-position (Scheme 39).

Although introduction of a 9,10-double bond in the lysergic acid framework remains unaccomplished, this tandem radical cyclization approach can be used for the synthesis of tetrahydrolysergic acid derivatives. With the appropriate choice of starting materials, the synthesis of other ergot alkaloids and their synthetic derivatives could be achieved using this novel approach.

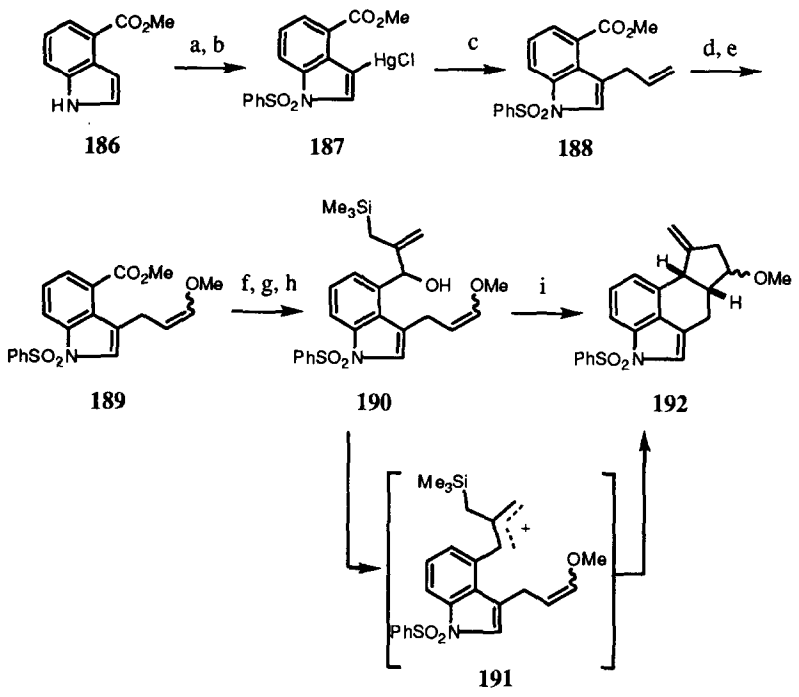


SCHEME 39. Reagents: a, molecular sieves, toluene; b, $(n\text{-Bu})_3SnH$; c, toluene [thermal cyclization].

B. INTRAMOLECULAR CYCLIZATION OF AN ALLYL CATION FOR THE SYNTHESIS OF THE ERGOLINE SKELETON

The intramolecular cyclization reaction involving the allyl cation **191** derived from the 3,4-disubstituted indole **190** was applied to the construction of the ergoline skeleton *(78)*.

4-Carbomethoxyindole (**186**) was reacted with benzenesulfonyl chloride in the presence of tetrabutylammonium hydroxide to yield the *N*-benzenesulfonamide in 95% yield. Treatment with mercuric acetate in acetic acid followed by aqueous sodium chloride yielded the indole-mercurichloride **187** quantitatively. Palladium-catalyzed coupling of the mercury salt with allyl bromide in the presence of Li_2PdCl_4 provided a fair yield of the 3-allylindole **188**. Cleavage of the alkene was achieved using catalytic osmium tetroxide and excess sodium periodate to form the desired aldehyde in 81% yield. This aldehyde was converted into the enol ether **189** in 95% yield, with a 1 : 1 ratio



SCHEME 40. Reagents: a, $PhSO_2Cl$, KOH, $(n\text{-}Bu)_4NOH$; b, $Hg(OAc)_2$, AcOH, cat. perchloric acid; c, allyl bromide, Li_2PdCl_4, MeOH; d, OsO_4, NMO then $NaIO_4$; e, $Ph_3PCHOMe{\cdot}HCl$, *t*-BuLi; f, DIBALH; g, MnO_2; h, Mg, 2-bromo-3-trimethylsilylpropene; i, $TiCl_4$, *N*-methylaniline.

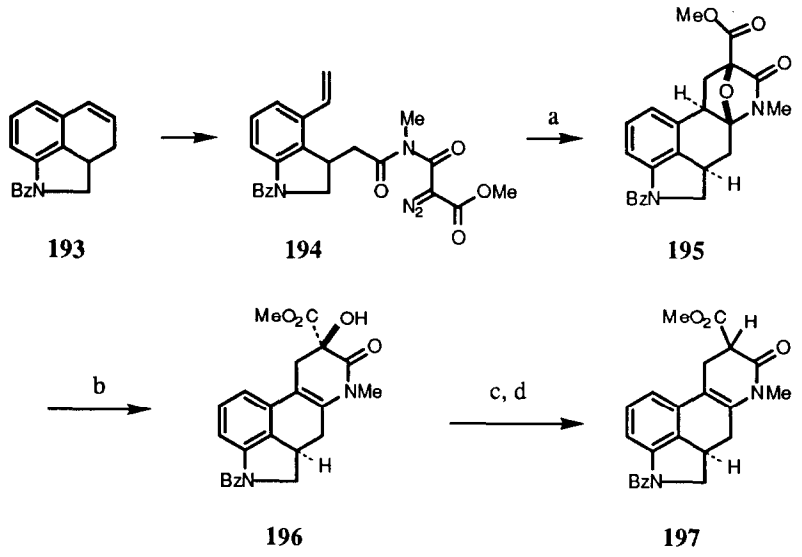
of the *cis* and *trans* mixed products, using methoxymethyltriphenylphosphonium chloride in conjunction with 2.2 equivalents of *t*-butyllithium. Finally, reduction of the ester **189** with DIBALH and reoxidation with manganese(IV) oxide provided the aldehyde in 84% yield. which was then reacted with the Grignard reagent formed from 2-bromo-3-trimethylsilylpropene to produce the key intermediate **190** in 62% yield. The intramolecular cycloaddition was achieved through reaction of **190** in the presence of $TiCl_4$ and *N*-methylaniline to yield a 1:1 mixture of two cycloadducts **192** (Scheme 40). This compound, **192**, was to serve as the synthetic precursor for the ergoline alkaloids.

C. Intramolecular Isomunchnone Cycloaddition Pathway to Lysergic Acid

As a viable approach to the synthesis of lysergic acid, intramolecular cycloaddition of alkenyl- and alkynyl-substituted diazoimides **194** across a transient isomunchnone dipole was investigated, aiming at the construction of the ring system of the quinoline ring system (C and D rings) of the ergot alkaloids (*79*).

Although the inability to carry out a double bond isomerization to the position required for lysergic acid is a drawback, this unique route of constructing the skeleton of the target alkaloid has the potential to become a new synthetic methodology for lysergic acid.

The known tricyclic olefin **193** was oxidatively ring opened at the olefinic ring to give an indoline derivative which was transformed to the starting prerequisite diazo imide **194**. The rhodium-catalyzed reaction of **194** proceeded smoothly, using rhodium(II) perfluorobutyrate as the catalyst, to give the cycloadduct **195** as the exclusive product in 93% yield. The conversion of the cycloadduct **195** to methyl paspalate was undertaken by treating **195** with



193 **194** **195**

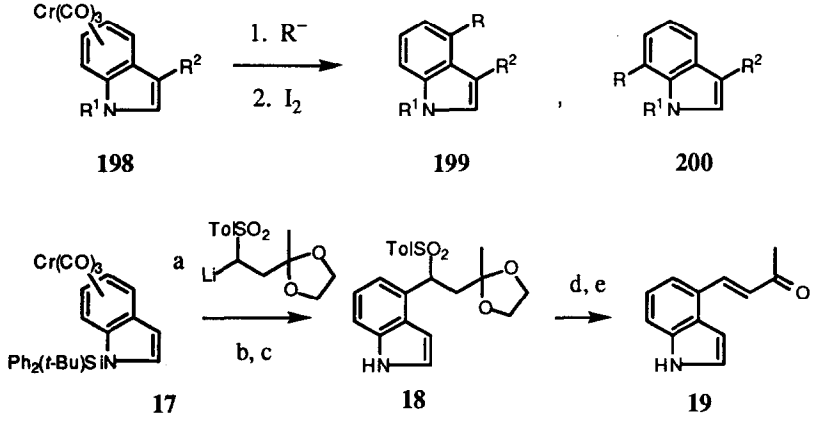
196 **197**

Scheme 41. Reagents: a, $[(CF_3CF_2CF_2CO_2)_2Rh]_2$, CH_2Cl_2; b, $BF_3{\cdot}OEt_2$, CH_2Cl_2; c, phenyl chloroformate; d, $(n\text{-}Bu)_3SnH$, AIBN, Δ.

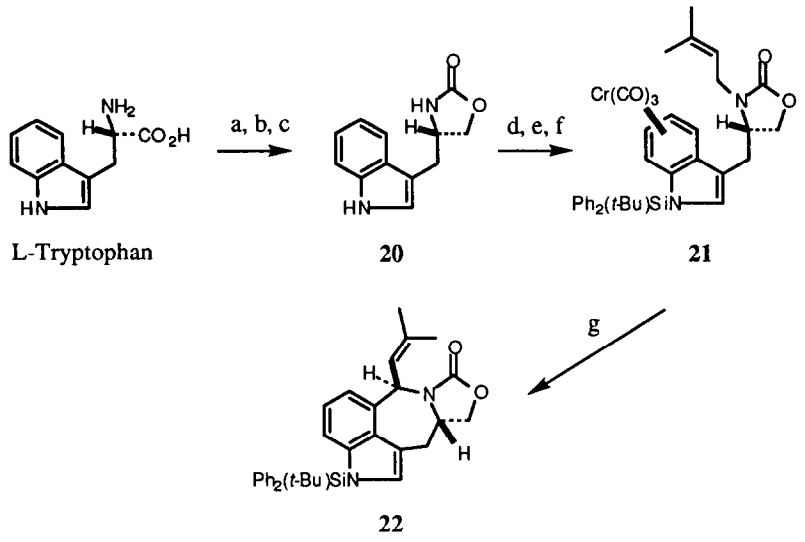
boron trifluoride etherate in dichloromethane to furnish the expected tetrasubstituted enamide **196** in quantitative yield. The Barton- McCombie reaction, using the phenyl thiocarbonate derivative with tri-*n*-butyltin hydride, afforded the expected deoxygenated amido ester **197** as a 2:1 mixture of diastereomers, which, however, resisted all attempts, using a variety of bases, to isomerize the double bond (Scheme 41).

D. Use of an Indole Chromium Complex for the Synthesis of Ergot Alkaloids

The activating effect of π-complexation of a $Cr(CO)_3$ unit allows selective nucleophilic substitution in indoles, including tryptophan derivatives, and thus provides intermediates for the synthesis of clavicipitic acid and related indole alkaloids. The addition of a nucleophile to an *N*-protected indole-$Cr(CO)_3$ complex **198** provided **199** and/or **200** for the regioselective introduction of a substituent at C-4 or C-7 on the indole ring, depending on the substituents at C-3 and N-1, as well as the nature of the nucleophile (*80*). This methodology was successfully applied to indole itself (*28*). Indole is readily transformed into the corresponding tricarbonylchromium complex and silylated with *t*-butylchloro-diphenylsilane to produce the crystalline complex **17**. The addition of **17** to a solution of the lithiated sulfone, followed by oxidative quenching with iodine and desilylation, furnished the C-4 substituted indole **18** in 90% yield. The indole **18** was converted to the enone **19** with the alkenyl side chain at the 4-position in 78% yield by sequential acid and base treatment (Scheme 42).



Scheme 42. Reagents: b, I_2; c, TBAF; d, cat. TsOH; e, Et_3N.



L-Tryptophan **20** **21**

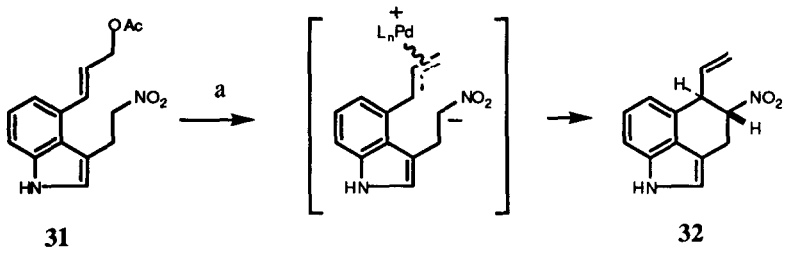
22

SCHEME 43. Reagents: a, $LiAlH_4$; b, NaOH; c, $COCl_2$; d, $Cr(CO)_3(MeCN)_3$; e NaH, $Ph_2(t\text{-Bu})SiCl$; f, MeLi, $(Me)_2C{=}C(H)CH_2Br$; g, LDA, then I_2.

A similar sequence of reactions was applied to L-tryptophan, and the subcequent conversion of the resulting amino alcohol into the oxazolidinone **20** proceeded in 82% yield (*28*). Following formation of the tricarbonylchromium complex **21**, treatment with LDA and iodine yielded the synthetic precursor **22** of clavicipitic acid (**84**,**85**) (Scheme 43).

E. ENANTIOSELECTIVE PALLADIUM-CATALYZED CARBOCYCLIZATION OF NITROACETATE FOR THE ERGOLINE SKELETON

Genet *et al.* (*35*) have developed an intermolecular, palladium-catalyzed alkylation of a nitroacetate, and applied the reaction to its intramolecular version using chiral ligands on the metal for the synthesis of the C ring of ergoline synthons in an optically active fashion. The preparation of these chiral synthons **32** was achieved by palladium-catalyzed enantioselective carbocyclization of the bifunctional nitroacetate **31**, synthesized from 4-formylindole. On exposing **31** to $Pd(dba)_2$ and (*S*)-CHIRAPHOS with potassium carbonate as the base, the chiral derivative **32** was obtained on a practical scale with an acceptable level of optical purity (69% ee). Genet *et al.* optimized these results by employing



31 **32**

SCHEME 44. Reagents: a, $Pd(OAc)_2$, K_2CO_3, (*S*)-BINAP.

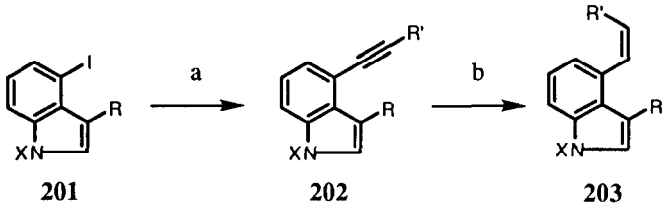
$Pd(OAc)_2$ and (*S*)-BINAP. The desired enantiomer **32** was obtained enantioselectively with a 95% ee (*36*) (Scheme 44).

This catalytic, enantioselective, palladium(0)-promoted C-5, C-10 ring closure provides a simple, direct and versatile synthesis of chiral ergoline compounds.

F. PALLADIUM-CATALYZED REACTIONS OF 3-ALKENYL-4-IODOINDOLES FOR THE SYNTHESIS OF 3,4-DISUBSTITUTED INDOLES

Palladium-catalyzed coupling of 4-iodoindoles with acetylenes established the smooth synthesis of 3,4-disubstituted indole derivatives suitable for the synthesis of ergoline alkaloids. Szántay *et al.* (*81*) thoroughly investigated the conditions of the relatively harsh conditions of the Heck reaction and succeeded in establishing satisfactory conditions for the substitution of 4-iodoindoles **201**. They examined four different 4-iodoindoles **201** with various electron densities in the aromatic ring, and three different palladium catalyst systems of $[Ph_3P]_4P$, $[Ph_3P]_2PdCl_2$, as well as $[Ph_3P]_4Pd$, generated *in situ* from Pd-C and triphenyl phosphine, for the addition of various acetylenes. As a result, they found that the reaction proceeded well on a scale of 1 mmol in DMF (ca. 20-30 mg/ml indole concentration) under argon atmosphere in the presence of 2 equivalents of triethylamine as base, in addition to the use of 2-5 equivalents of acetylene, 0.2 equivalents of cuprous iodide, and 0.02 equivalents of the palladium catalyst. The reactions were run at room temperature, giving mostly fair to good yields of chromatographically pure products (Scheme 45).

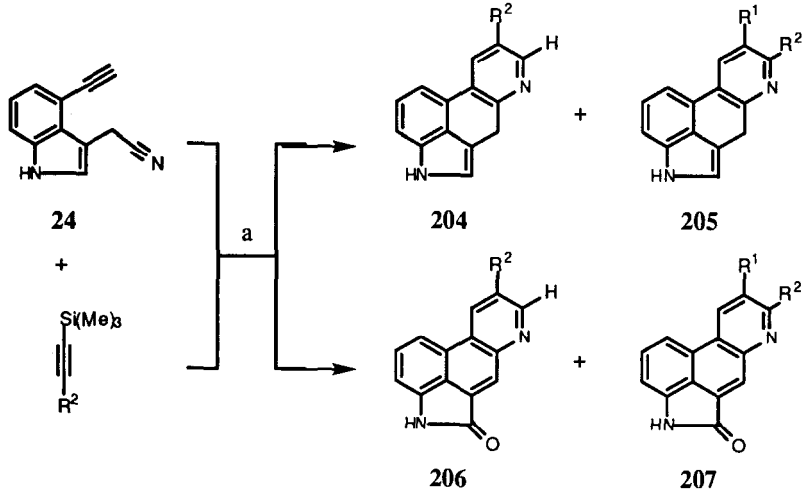
The acetylenic indoles **202** were partially saturated over the Lindlar catalyst to **203**, which was transformed previously to secoagroclavine by Somei *et al.* (*82*). Thus, these reaction conditions could provide a promising opportunity for the synthesis of many ergoline alkaloids.



SCHEME 45. Reagents: a, [Pd], CuI, Et_3N, DMF, H—≡—R' ; b, Lindlar catalyst.

G. COBALT-CATALYZED COCYCLIZATION OF 4-ETHYNYL-3-INDOLEACETONITRILES WITH ACETYLENES

4-Ethynyl-3-indoleacetonitriles (**24**), which were readily prepared from the corresponding 4-bromo precursors followed by palladium-catalyzed trimethylsilylethynylation-deprotection, were reacted with acetylenes in the presence of $CpCo(CO)_2$ catalyst to give rise to a mixture of the compounds **204–207** having the structure of the annelated tetracyclic ergot framework in one step (*14*) (Scheme 46). Although the formation of several products was not desired, this cocyclization reaction has several advantages for forming the ergoline skeleton in one step.



SCHEME 46. Reagents: a, $CpCo(CO)_2$, Δ, *hν*.

VII. Further Developments on the Synthetic Supply of Key Intermediates Useful in the Synthesis of Ergot Alkaloids

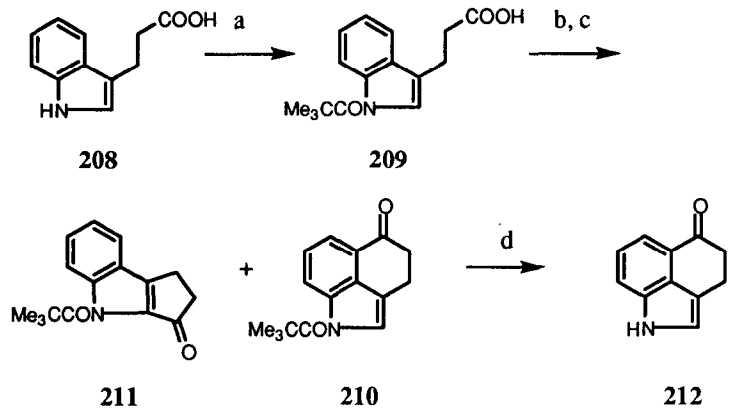
Due to the complexity of the structure of the ergot alkaloids and their remarkable biological potency, many synthetic approaches have accumulated. In addition, the establishment of convenient and facile synthetic procedures for the key synthetic intermediates have been sought as exemplified by the key intermediate tricyclic ketone in the synthesis by Woodward and Kornfeld. Actually, in many of the total syntheses of the ergot alkaloids, success has depended on the development of the convenient and efficient supply of the key intermediates.

Therefore, for synthetic studies aimed at the development of new medicinals, some of the most important and useful synthetic methods for key synthetic intermediates are selected as follows.

A. Facile Synthesis of Uhle's Ketone

A facile synthesis of Uhle's ketone (**212**) starting from indolepropionic acid **208** was reported (*83*).

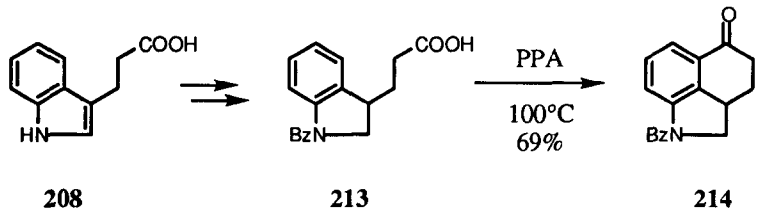
Uhle's ketone (**212**) was first synthesized from 6-chloro-2-nitrotoluene in eight steps by Uhle in 1949 (*84*), and has played an important key role in the synthesis of lysergic acid and many other indole derivatives. The increased importance of this ketone prompted the establishment of a facile synthetic supply of this ketone as one of the important starting compounds for the study of ergoline derivatives. Recently, Nakatsuka *et al.* (*83*) described a highly regioselective cyclization for the synthesis of Uhle's ketone from indolepropionic acid (**208**) using a novel Friedel-Crafts cyclization system. 3-(1-Trimethylacetylindol-3-yl)propionic acid (**209**) was prepared by trimethylacetylation of the starting indolepropionic acid **208** with *n*-butyllithium and trimethylacetyl chloride in tetrahydrofuran at –78°C in 91% yield. Compound **209** was treated with thionyl chloride to give the acid chloride which was then stirred with aluminum chloride in 1,2-dichloroethane at –10°C for 3 h. or at 10°C for 0.3 h. to give the cyclized products as a mixture of the two ketones **210** and **211**. Yields and relative ratios depended on the reaction temperature. The best result was obtained at 15°C for 1 h. in 83% combined yield and a 94:6 ratio. This cyclization was catalyzed by the reagent formed *in situ* from chloroacetyl chloride and aluminum chloride, which would generate a donor-acceptor complex species as an electron acceptor *in situ*. Removal of the trimethylacetyl moiety was achieved with catalytic sodium methoxide in methanol at 15°C for 10 min. giving Uhle's ketone (**212**) in 95% yield (Scheme 47).



SCHEME 47. Reagents: a, *n*-BuLi, Me_3CCOCl; b, $SOCl_2$; c, $AlCl_3$, additive ($ClCH_2COCl$), $ClCH_2CH_2Cl$; d, $NaHCO_3$, MeOH.

B. IMPROVED SYNTHESIS OF KORNFELD'S TRICYCLIC KETONE

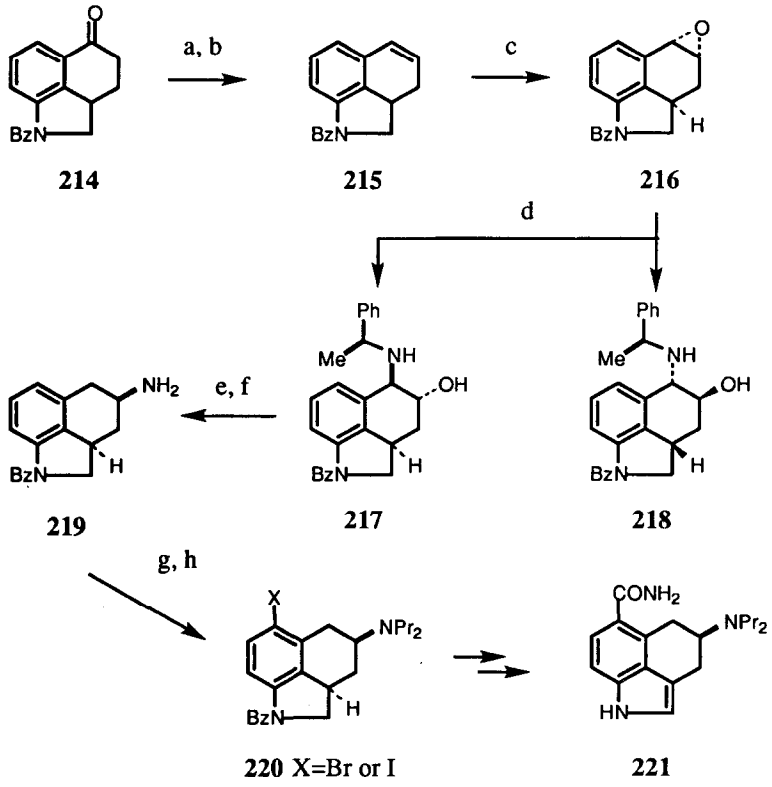
The tricyclic ketone (Kornfeld's ketone) **214** is well-known as the starting ketone in the first total synthesis of lysergic acid. Since then, a number of synthetic studies have employed this tricyclic ketone for the synthesis of lysergic acid and other ergoline alkaloids. This ketone **214** is now readily prepared from indolepropionic acid (**208**) according to the original route, but under improved reaction conditions (*85*) to give a good yield of this tricyclic ketone **214**. In practice the cyclization by polyphosphoric acid proceeded very smoothly at 100°C for 2 h. After cooling, the reaction mixture was simply poured into ice-water and extracted with dichloromethane, washed with water and dried. This simple and convenient procedure yields the ketone **214** in 69% (Scheme 48).



SCHEME 48

C. SYNTHESIS OF A TRICYCLIC AMINE DERIVED FROM KORNFELD'S KETONE

The utilities of Kornfeld's ketone **214** continues to attract interest, particularly for the synthesis of potential analogs related to the serotonin receptors. Martinelli and coworkers (*86*) have succeeded in synthesizing the aminotetralin derivatives which possess a tricyclic amine structure, and which are target drug candidates for clinical evaluation. They started their synthetic route from Kornfeld's ketone **214**, which was reduced with sodium borohydride. Subsequent dehydration afforded the crystalline olefin **215** in excellent yield. Epoxidation of this olefin with peracids proceeded highly



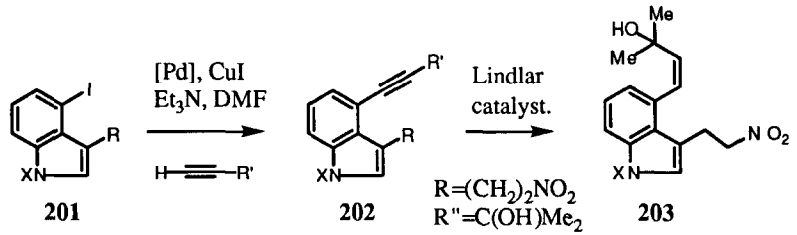
SCHEME 49. Reagents: a, $NaBH_4$; b, Amberlist 15; c, monomagnesium-peroxyphthalate, H_2O, *n*-BuOH; d, (*S*)-phenethylamine, *n*-BuOH; e, MsCl, Et_3N; f, Pd-C, H_2, H_3PO_4; g, Br_2, NaOAc or H_3IO_4; h, PrI, K_2CO_3.

stereoselectively affording primarily the *anti*-epoxides **216** with >96% de. Epoxide ring opening of **216** was best conducted in *n*-butanol at 110°C, thus fitting very well with the epoxide forming step above in the same solvent. Consequently, a solution of the racemic epoxide when reacted with an optically pure amine, such as (*S*)-α-phenethylamine, produced a 1:1 mixture of the diastereomers **217** and **218**, which, on cooling, provided the single isomer **217** in 43% yield. Mesylation of **217** was successfully carried out using methanesulfonyl chloride and triethylamine, giving rise to an aziridine which was then subjected to tandem benzylic hydrogenolysis in the presence of a palladium catalyst to give the optically active aminotetralin **219**. The usefulness of the tricyclic amine **219** was clear from its facile conversions, including regioselective, aromatic electrophilic *para*-substitution on the indoline moiety to afford the carbamoyl group substituted derivatives, and simple *N,N*-dialkylation to a variety of analogs. By utilizing the tricyclic amine **219**, a number of lysergic acid diethylamide analogs were synthesized (*86,87*) (Scheme 49).

D. Synthesis of 3,4-Disubstituted Indoles

Since the structural features of 3,4-disubstituted indoles are abundantly seen in the structures of various alkaloids, a number of synthetic approaches have appeared in the literature for the preparation of indole derivatives with the 3,4-disubstitution pattern. One of the recent methods was disclosed by Somei *et al.* (*37,88*) who took advantage of the reaction of thallium/iodination of a 3-carbonyl substituted indole, followed by the Heck reaction, for the preparation of a number of derivatives.

Szántay *et al.* (*81*) modified the original method by Somei by applying the



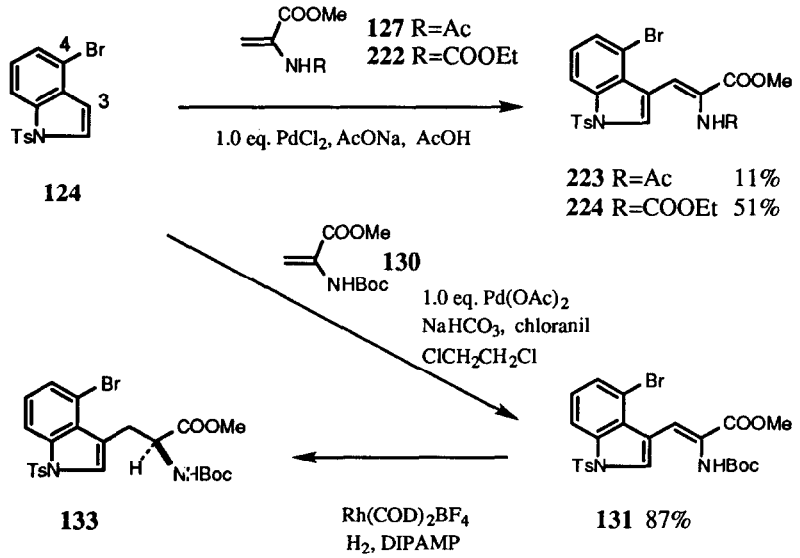
R=$(CH_2)_2NO_2$, $CH{=}CHNO_2$ (*E*)
R'=TMS, *n*-Bu, $C(OH)Me_2$

Scheme 50

Cu(I)-Pd(0) coupling of terminal acetylenes with the indole systems **201** at the 4-position, thereby improving the yield (Scheme 50). The ethynyl group in **202** was partially saturated over the Lindlar catalyst to afford the alkenes **203**, one of which was transformed previously to secoagroclavine (*82*).

E. Synthesis of 4-Bromotryptophan from 4-Bromoindole

In the course of studies aimed at the development of a method for introducing substituents into the indole ring, Yokoyama *et al.* (*61,62,65*) succeeded in a simple synthesis of 4-bromodehydrotryptophan **131** by the vinylation of *N*-tosyl 4-bromoindole (**124**) in the presence of a stoichiometric amount of palladium salt. Vinylation of *N*-acetyldehydroalanine methyl ester **127** and *N*-(ethoxycarbonyl)dehydroalanine methyl ester **222** with **124** occurred in the presence of a stoichiometric amount of $PdCl_2$ to give the corresponding 4-bromodehydrotryptophan **223** and **224**, respectively. This result opened the route for a simple synthesis of tryptophan derivatives. Actual preparation of the 4-bromotryptophan **133** was achieved by the vinylation of 4-bromoindole **124** with the *N*-Boc-dehydroalanine methyl ester **130** in the presence of a stoichiometric amount of $Pd(OAc)_2$. The literature conditions [1.0 equiv. of



Scheme 51

$Pd(OAc)_2$ in AcOH at 120°C for 2 h] (*62*) were not suited for this preparation. However, the compound **131** was obtained in 74-85% yield when the reaction was carried out in the presence of sodium hydrogen carbonate and chloranil as an oxidizing agent in an aprotic solvent, such as 1,2-dichloroethane or 1,2,4-trichlorobenzene. Asymmetric reduction in the presence of a rhodium-complex as catalyst afforded the 4-bromotryptophan **133** (Scheme 51).

VIII. MEDICINALS STRUCTURALLY RELATED TO ERGOLINES

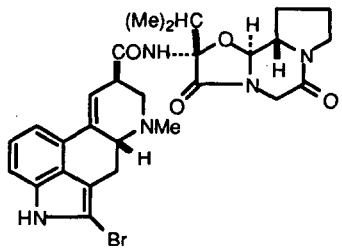
Originating from research on the development of medicinals structurally related to the natural ergoline-type of alkaloids, the ergoline-related major medicinals are summarized below.

The ergot alkaloids and their derivatives display such a diversified range of biological activities that they cannot be regarded within a single pharmacological or therapeutical entity. In spite of a great number of investigations on many derivatives and analogs of ergot alkaloids, aimed establishing the structure-activity relationships, much is yet to be done to reach appropriate conclusions. However, most of the ergoline derivatives, including the natural products and their synthetic analogs, generally exhibit both marked central and peripheral pharmacological activities. The generally non-selective interaction with the adrenalin, dopamine and serotonin receptors accounts for their wide spectra of pharmacological behaviors. The dopamine agonist components D_1 and D_2, which have many important clinical applications in the treatment of Parkinsonism, and the agonist/antagonist serotonergic components 5-HT_{1A}, 5-HT_{1C}, and 5-HT_{2C} with their documented connection with psychiatric disorders, such as depression and anxiety, have fostered interest in this class of compounds by a group of chemists led by Mantegani (*89–94*).

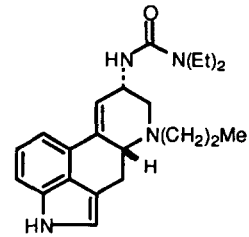
In this section, some of the medicinals with clinical applications are presented.

A. Bromocriptine

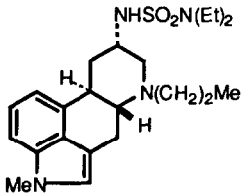
Bromocriptine (**225**) was first introduced in 1969 as a dopamine receptor agonist, produced from derivatives of the ergotoxine group of ergot alkaloids, prepared by the Sandoz group (Fluckiger *et al.*). Following research by many groups, its potentiality as a useful medicinal in the market was established (*95–*



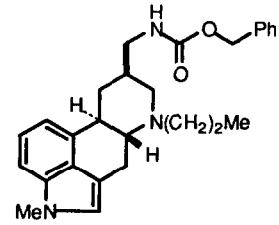
225 Bromocriptine



226 Lisuride



227 Mesulergine



228 Metergoline

97). The relationship between its stereochemistry and biological activity was established in 1980. Many aspects of its biological activity, including its endocrine profile, its usefulness as an immuno-modulator, in obstetrics and in gynecology, and in the treatment of pituitary tumors, have been described, along with clinical studies in the treatment Parkinson's disease.

Bromocriptine (**225**) is available as its methanesulfonate, known as Parlodel, Pravidel, or Serono-Bagren, and now is used as an enzymatic inhibitor for its prolactin and also for antiparkinsonian activity.

The chemisry and biology of bromocriptine (**225**) have been reviewed frequently, e.g. Ho and Thorner (*95*).

B. Lisuride

Structurally closely related to LSD, Lisuride (**226**) is a compound having a 3,3-dimethylureido substituent at the 9-position of the ergoline skeleton, and was first prepared in 1960 as a dopamine D_2-receptor agonist (*98*). Lisuride, as its acid maleate, is commercially available under the names of Cuvalit, Dopergin, Eunal, or Lysenyl, and is used clinically as an antimigraine and also as a prolactin inhibitor. The pharmacological activity and toxicity of lisuride were

reviewed previously in 1963 by L. Votava.

C. MESULERGINE

This compound, **227**, was first introduced by the Sandoz chemist Stutz, who not only had led research on the ergot alkaloids, but also contributed by writing the first review in "Manske's Alkaloids" series in 1982 (*2,99*). The principal structural feature is the *N*,*N*-dimethylsulfamide substituent on the 9-position of the ergoline skeleton, in addition to a methyl group on the indolic nitrogen. Mesulergine (**227**) has a variety of clinical activities, including central dopamine agonistic activity, hypotensive activity comparable to bromocriptine, inhibition of prolactin release, and antiparkinsonism.

D. METERGOLINE

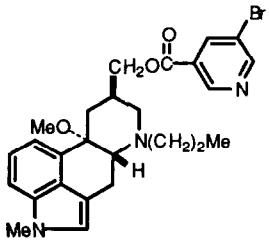
Developed by an Italian group in 1964, this compound, **228**, also known as Liserdol, has the structural features of an aminomethyl group protected by a benzyloxycarbonyl group at the 8-position, along with two methyl groups on both ring nitrogens, which provide a different pharmacological profile for this compound from most of the ergoline derivatives. It is used as an analgesic and antipyretic (*101*).

E. NICERGOLINE

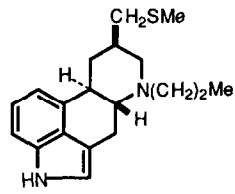
Also known as Nicotergoline and Nimergoline, this compound, **229**, has a characteristic structure at several points, including having a *trans* methanol adduct at the double bond at the 9-position, methyl groups on both ring nitrogens and the 8-hydroxymethyl group protected by a 5-bromonicotinate group. This compound, **229**, was attractive from the aspect of its dopaminergic activity and is used as a vasodilator (*99*).

F. PERGOLIDE

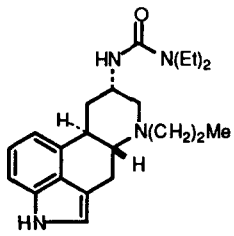
Introduced by Kornfeld and coworkers in 1979 as a dopaminergic agonist that also decreases plasma prolactin concentration, this compound, **230**, shows activity in the treatment of acute myocardial infarction with diastolic hypertension. It is also effective in the treatment of pituitary tumors secreting prolactin or growth hormone (*102*). Its clinical study revealed its effectiveness in Parkinson's disease, and it is now used clinically. This compound, **230**,



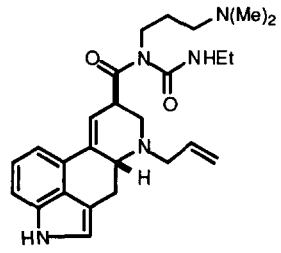
229 Nicergoline



230 Pergolide



231 Terguride



232 Cabergoline

induces the structural feature of a 8β-methylmercaptomethyl substituent, together with an ethyl group on the 6-nitrogen instead of a methyl group.

G. TERGURIDE

This is the dihydrogenated analog of lisuride (**226**) having the structure of 9,10-*trans*-dihydrolisuride, thereby exhibiting dopamine agonistic and antagonistic activities. Synthesized by Czechoslovakian chemists in 1972, this compound, **231**, is also called Dieonyl, Mysalfon, etc., and used in the form of the hydrogen maleate salt for its antiparkinsonian and antihyperprolactinemic activities (*103*).

H. CABERGOLINE

Selected from a group of dihydolysergylurea derivatives for its outstanding pharmacological and pharmacodynamic activity, carbergoline (**232**) has been used for its significant prolactin secretion inhibitory activity. This compound

was obtained by treatment of dihydrolysergic acid with an appropriate carbodiimide, or by the reaction of dihydrolysergamide with a large excess of an alkyl isocyanate (*104,105*). Carbergoline (**232**) is also recognized as a potent and selective D_2 receptor agonist, and is at least two-hundred fold more potent than bromocriptine in the prevention of the fertilized egg implantation in rats (ED_{50} 0.025 mg/Kg). It is devoid of the hypotensive activity and emesis present in almost all of the compounds in this therapeutic class.

IX. ADDENDUM

In nature, many types of natural products exist also in the form of glycosides, which, more importantly, are known to have potent and useful pharmacological activities. However, in the area of the ergot alkaloids, few ergot alkaloid glycosides are known, and their study remains in the future; a recent review mentioned the existence of elymoclavine fructoside and a few others (*106*).

Acknowledgments

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References

1. A. Stoll and A. Hofmann, *in* "The Alkaloids" (R.H.F. Manske and H.L. Holmes, eds.), Vol. 8, p. 725. Academic Press, New York, 1965.
2. P.A. Stadler and P. Stutz, *in* "The Alkaloids" (R.H.F. Manske and H.L. Holmes, eds.), Vol. 15, p. 1. Academic Press, New York, 1975.
3. I. Ninomiya and T. Kiguchi, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 38, p. 1. Academic Press, New York, 1990.
4. D. Gröger and H.G. Floss, *in* "The Alkaloids" (G.A. Cordell, ed.), Vol. 50, p. 171. Academic Press, New York, 1990.
5. E.C. Kornfeld, E.J. Fornefeld, G.B. Kline, M.J. Mann, R.G. Jones, and R.B. Woodward, *J. Am. Chem. Soc.* **76**, 5256 (1956).
6. M. Julia, F. Le Goffic, J. Igolen, and M. Baillage, *Tetrahedron Lett.* 1569 (1969).
7. V.W. Armstrong, S. Coulton, and R. Ramage, *Tetrahedron, Suppl. 1* **37**,

157 (1981).
8. W. Oppolzer, E. Francotte, and K. Battig, *Helv. Chim. Acta* **64**, 478 (1981).
9. I. Ninomiya, C. Hashimoto, T. Kiguchi, and T. Naito, *J. Chem. Soc., Perkin Trans. I* 941 (1985).
10. I. Ninomiya and T. Naito, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 22, p. 189. Academic Press, New York, 1983.
11. J. Rebek, Jr. and D.F. Tai, *Tetrahedron Lett.* **24**, 959 (1983).
12. Y. Matsubara, R. Yoneda, S. Harusawa, and T. Kurihara, *Chem. Pharm. Bull.* **36**, 1597 (1988).
13. S. Cacchi, P.G. Ciattini, E. Morera, and G. Ortar, *Tetrahedron Lett.* **39**, 3117 (1988).
14. C. Saa, D.D. Crotts, G. Hsu, and K.P.C. Vollhardt, *Synlett* 487 (1994).
15. J. Rebek, Jr. and Y.K. Shue, *J. Am. Chem, Soc.* **102**, 5426 (1980).
16. J. Rebek, D.F. Tai, and Y.K. Shue, *J. Am. Chem. Soc.* **106**, 1813 (1984).
17. J. Rebek, Y.K. Shue, and D. F. Tai, *J. Org. Chem.* **49**, 3540 (1984).
18. S.F. Martin and S. Liras, *J. Am. Chem. Soc.* **115**, 10450 (1993).
19. A.P. Kozikowski and M.N. Greco, *J. Org. Chem.* **49**, 2310 (1984).
20. H. Muratake, T. Takahashi, and M. Natsume, *Heterocycles* **20**, 1963 (1983).
21. A.P. Kozikowski and M. Ohta, *Tetrahedron Lett.* **26**, 4043 (1985).
22. M. Matsumoto, H. Kobayashi, and M. Watanabe, *Heterocycles* **26**, 1197 (1987).
23. P.J. Harrington, L.S. Hegedus, and K.F. McDaniel, *J. Am. Chem. Soc.* **109**, 4335 (1987).
24. F. Yamada, Y. Makita, T. Suzuki, and M. Somei, *Chem. Pharm. Bull.* **33**, 2162 (1985).
25. D.A. Boyles and D.E. Nichols, *J. Org. Chem.* **53**, 5128 (1988).
26. B.M. Trost, H.C. Arndt, P.E. Strete, and T.R. Verhoeven, *Tetrahedron Lett.* 3477 (1976).
27. M. Somei, Y. Hasegawa, and C. Kaneko, *Heterocycles* **16**, 941 (1981).
28. M.F. Semmelhack, P. Knochel, and T. Singleton, *Tetrahedron Lett.* **34**, 5051 (1993).
29. H. Plieninger and D. Schmalz, *Chem. Ber.* **109**, 2140 (1976).
30. M. Natsume and H. Muratake, *Heterocycles* **16**, 375 (1981).
31. A.P. Kozikowski and H. Ishida, *J. Am. Chem. Soc.* **102**, 4265 (1980).
32. W. Oppolzer, J.I. Grayson, H. Wegemann, and M. Urrea, *Tetrahedron* **39**, 3695 (1983).
33. I. Ninomiya, N. Habe, T. Kiguchi, and T. Naito, *J. Chem. Soc., Perkin*

Trans. I 3275 (1991).
34. M. Somei, Y. Makita, and F. Yamada, *Chem. Pharm. Bull.* **34**, 948 (1986).
35. J.P. Genet and S. Grisoni, *Tetrahedron Lett.* **29**, 4543 (1988).
36. N. Kardos and J.P. Genet, *Tetrahedron, Asymmetry* **5**, 1525 (1994).
37. M. Somei, *Yakugaku Zasshi* **108**, 361 (1988).
38. M. Somei and K. Nakagawa, *Heterocycles* **45**, 1263 (1997).
39. M. Somei, F. Yamada, and K. Nakagawa, *Chem. Pharm. Bull.* **35**, 1322 (1987).
40. K. Nakagawa and M. Somei, *Heterocycles* **32**, 873 (1991).
41. M. Somei and F. Yamada, *Chem. Pharm. Bull.* **32**, 5064 (1984).
42. B.R. Chhabra, K. Hayano, T. Ohtsuka, H. Shirahama, and T. Matsumoto, *Chem. Lett.* 1703 (1981).
43. M. Somei and K. Nakagawa, in preparation.
44. M. Somei, Y. Makita, and F. Yamada, *Chem. Pharm. Bull.* **34**, 948 (1986).
45. S. Yamatodani and H. Abe, *J. Agr. Chem. Soc. Japan* **34**, 366 (1960).
46. V.G. Sakharovsky and A.G. Kozlovsky, *Tetrahedron Lett.* **25**, 109 (1984).
47. M. Somei, H. Mukaiyama, Y. Nomura, and K. Nakagawa, *Heterocycles* **31**, 1919 (1990).
48. T.C. Choong and H.R. Shough, *Tetrahedron Lett.* 3137 (1977).
49. B.S. Bal, W.E. Childers, Jr., and H.W. Pinnick, *Tetrahedron* **37**, 2091 (1981).
50. H. Watanabe, M. Somei, S. Sekihara, K. Nakagawa, and F. Yamada, *Japan J. Pharmacol.* **45**, 501 (1987).
51. F. Yamada, K. Kobayashi, A. Shimizu, N. Aoki, and M. Somei, *Heterocycles* **36**, 2783 (1993).
52. F. Yamada, T. Hasegawa, M. Wakita, M. Sugiyama, and M. Somei, *Heterocycles* **24**, 1223 (1986).
53. M. Somei, S. Hamamoto, K. Nakagawa, F. Yamada, and T. Ohta, *Heterocycles* **37**, 719 (1994).
54. H. Muratake, T. Takahashi, and M. Natsume, *Heterocycles* **20**, 1963 (1983).
55. K. Nakagawa and M. Somei, *Heterocycles* **39**, 31 (1994).
56. M. Somei, F. Yamada, Y. Karasawa, and C. Kaneko, *Chemistry Lett.* 615 (1981).
57. M. Iwao and F. Ishibashi, *Tetrahedron* **53**, 51 (1997).
58. M. Iwao, *Heterocycles* **36**, 29 (1993).
59. M. Iwao and O. Motoi, *Tetrahedron Lett.* **36**, 5929 (1995).
60. D.L. Varie, *Tetrahedron Lett.* **31**. 7583 (1990).
61. Y. Yokoyama, M. Takahashi, Y. Kohno, K. Kataoka, Y. Fujikawa, and Y. Murakami, *Heterocycles* **31**, 803 (1990).

62. Y. Yokoyama, M. Takahashi, M. Takashima, Y. Kohno, H. Kobayashi, K. Kataoka, K. Shidori, and Y. Murakami, *Chem. Pharm. Bull.* **42**, 832 (1994).
63. U. Schmidt and J. Wild, *Liebigs Ann. Chem.* 1882 (1985).
64. J.E. Robbers, H. Ohtsuka, H.G. Floss, E.V. Arnold, and J. Clardy, *J. Org. Chem.* **45**, 1117 (1980).
65. Y. Yokoyama, T. Matsumoto, and Y. Murakami, *J. Org. Chem.* **60**, 1486 (1995).
66. H. Matsuo, Y. Kawazoe, M. Sato, M. Ohnishi, and T. Tatsuno, *Chem. Pharm. Bull.* **18**, 1788 (1970).
67. P.F. Heinstein, S.L. Lee, and H.G. Floss, *Biochem. Biophys.* **98**, 457 (1962).
68. H. Plieninger, M. Hobel, and V. Liede, *Justus Liebig's Ann. Chem.* **672**, 223 (1964).
69. M. Nettekoven, M. Psiorz, and H. Waldmann, *Tetrahedron Lett.* **36**, 1425 (1995).
70. Y. Yokoyama, H. Hikawa, and Y. Murakami, in preparation.
71. P.J. Harrington and L.S. Hegedus, *J. Org. Chem.* **49**, 2657 (1984).
72. L.S. Hegedus, M.R. Sestrick, E.T. Michaelson, and P.J. Harrington, *J. Org. Chem.* **54**, 141 (1989).
73. Y. Yokoyama, H. Matsushima, M. Takashima, T. Suzuki, and Y. Murakami, *Heterocycles* **46**, 133 (1997).
74. Y. Yokoyama, K. Kondo, M. Mitsuhashi, and Y. Murakami, *Tetrahedron Lett.* **37**, 9309 (1996).
75. J.R. Harris and D.C. Horwell, *Synth. Commun.* **22**, 995 (1992).
76. G.H. Timms, D.E. Tupper, and S.E. Morgan, *J. Chem. Soc., Perkin Trans. I* 817 (1989).
77. Y. Ozlu, D.E. Cladingoel, and P.J. Parsons, *Tetrahedron* **50**, 2183 (1994).
78. S. Barbey and J. Mann, *Synlett* 27 (1995).
79. J.P. Marino, Jr., M.H. Osterhout, and A. Padwa, *J. Org. Chem.* **60**, 2704 (1995).
80. M.F. Semmelhack, G.R. Clark, J.L. Garcia, J.J. Harrison, Y. Thebtaranonth, W. Wulff, and A. Yamashita, *Tetrahedron* **37**, 3957 (1981).
81. G. Galambos, Cs. Szántay, Jr., J. Tamás, and Cs. Szántay, *Heterocycles* **36**, 2241 (1993).
82. M. Somei, F. Yamada, and Y. Makita, *Heterocycles* **26**, 895 (1987).
83. K. Teranishi, S. Hayashi, S. Nakatsuka, and T. Goto, *Synthesis* 506 (1995).
84. F.C. Uhle, *J. Am. Chem. Soc.* **71**, 761 (1949).
85. G.B. Okide, *Tetrahedron* **49**, 9517 (1993).
86. M.A. Carr, P.E. Creviston, D.R. Hutchison, J.H. Kennedy, V.V. Khau,

T.J. Kress, M.R. Leanna, J.D. Marshall, M.J. Martinelli, B.C. Peterson, D.L. Varie, and J.P. Wepsiec, *J. Org. Chem.* **62**, 8640 (1997).
87. B.A. Anderson, L.M. Becke, R.N. Booher, M.E. Flaugh, N.K. Harn, T.J. Kress, D.L. Varie, and J.P. Wepsiec, *J. Org. Chem.* **62**, 8634 (1997).
88. S. Hamabuchi, H. Hamada, A. Hironaka, and M. Somei, *Heterocycles* **32**, 443 (1991).
89. S. Mantegani, E. Brambilla, C. Caccia, G. Damiani, M.G. Fornaretto, R.A. McArthur, and M. Varasi, *Bioorg. & Med. Chem. Lett.* **8**, 1117 (1998).
90. S. Mantegani, E. Brambilla, C. Caccia, A.D. Salle, M.A. Cervini, R.A. McArthur, G. Traquandi, and M. Varasi, *Il Farmaco* **53**, 65 (1998).
91. S. Mantegani, E. Brambilla, C. Caccia, M.G. Fornaretto, R.A, McArthur, and M. Varasi, *Eur. J. Med. Chem.* **32**, 795 (1997).
92. S, Mantegani, E, Arlandini, D, Borghi, E. Brambilla, and M. Varasi, *Heterocycles* **45**, 1493 (1997).
93. S. Mantegani, L. Baumer, E. Brambilla, C. Caccia, M.G. Fornaretto, and M. Varasi, *Eur. J. Med. Chem.* **33**, 279 (1998).
94. S. Mantegani, E. Brambilla, C. Caccia, L. Chiodini, D. Ruggieri, E. Lamberti, E. di Salle, and P. Salvati, *Il Farmaco* **53**, 293 (1998).
95. K.Y. Ho and M.O. Thorner, *Drugs* **36**, 57 (1988).
96. A. Renodon, J.-L. Boucher, M.-A. Sari, M. Delaforge, J. Ouazzani, and D. Maansuy, *FEBS Lett.* **406**, 33 (1997).
97. K. Inoue, N. Kiriike, M. Kurioka, Y. Fujisaki, S. Iwasaki, and S. Yamagamo, *Pharmcol. Biochem. Behav.* **58**, 183 (1997).
98. A. Lieberman, M. Goldstein, G. Gopinathan, A. Neophytides, and M. Leibowitz, *in* "Lisuride and other Dopamine Agonists" (D.B. Calne, R.Horowsky, R.J. McDonald, and W. Wittke, eds.), p. 419, Raven, New York, 1983.
99. I.J. Kopin, *Annu. Rev. Pharmacol. Toxicol*, **32**, 467 (1993).
100. I. Bernardi and A. Temperilli, *Experientia* **54**, 998 (1972).
101. B. Saletu, E. Paulus, and L. Linzmayer, *Psychopharmacology* **117**, 285 (1995).
102. W.C. Koller, *Neuropharmacology* **19**, 831 (1980).
103. W.C. Koller and G. Herbster, *Neurology* **37**, 723 (1987).
104. E. Bambilla, E. DiSalle, G. Briatio, S. Mantegani, and A. Temperilli, *Eur. J. Med. Chem.* **24**, 421 (1989).
105. C. Ferrari, E. di Salle, S. Persiani, G. Piscitelli, and B.M. Strolin, *Drugs of Today* **31**, 589 (1995).
106. V. Kren, *in* "Topics in Current Chemistry", Vol. 186, p. 45, Springer Verlag, Berlin, 1997.

CHAPTER 3

ACRIDONE ALKALOIDS

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I. Introduction
II. Biosynthetic Considerations
III. Structural Elucidation
IV. Occurrence
  A. Simple Acridones
  B. *C*-Prenylacridones
  C. Furanoacridones
  D. Pyranoacridones
  E. Dimeric Acridone Alkaloids and Related Compounds
V. Synthesis
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I. Introduction

The acridone alkaloids represent a series of some 190 secondary metabolites derived from the 9(10*H*)-acridinone (**1**) basic skeleton. To date, these alkaloids have only been isolated from some 35 genera of the Rutaceae and one genus of the Simaroubaceae. They appear to be unique to the order Rutales. Most acridone alkaloids bear oxygenated substituents, at the C-1 and C-3 positions. The group also comprises many representatives with furano or pyrano rings fused on the C ring.

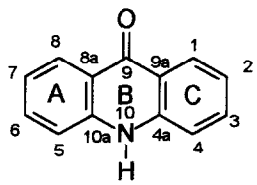
The only previous review fully devoted to this type of compounds in this series was published as early as 1952 by Price (*1*), who isolated the first naturally occurring acridones from the yellow bark of several trees growing in the Australian rain forests (*2*). Since 1969, the subject was regularly reviewed by Snieckus, Grundon, and Michael, in *The Alkaloids: Specialist Periodical Reports* (*3-15*) and subsequently in *Natural Products Reports* (*16-29*), both published by the Royal Society of Chemistry, London. Other review articles cover, at least in part, the chemistry, the biochemistry, or the biological activities of naturally occurring acridones (*30-37*). The alkaloids which include the pyrano[2,3-*c*]acridine-7-one skeleton have recently received more attention (*38-44*), due to the promising antitumor properties of acronycine (**2**).

In terms of organization, biosynthetic considerations take precedence. These are followed by a description of the various groups of naturally occurring acridone alkaloids: the simple acridones, *C*-prenylacridones, furoacridones, pyranoacridones, and finally the dimeric acridone alkaloids and related compounds.

Graebe's system of numbering of the acridine system, approved by the International Union of Pure and Applied Chemistry and adopted in *Beilstein's Handbuch der organischen Chemie* and in *Chemical Abstracts* since 1937, is used throughout this chapter. It should be noted that it differs from the numbering system used in some original papers.

II. Biosynthetic considerations

From a biogenetic point of view, Robinson (*45*) first postulated that the 9(10*H*)-acridinone skeleton should arise from the condensation of an anthranilic acid unit with three acetate units, leading, *via* a polyketoacid, to the tricyclic nucleus typically oxygenated at C-1 and C-3. Experimental support of this hypothesis was



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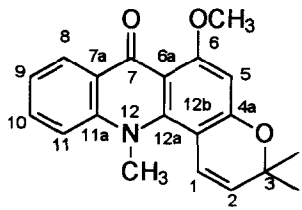

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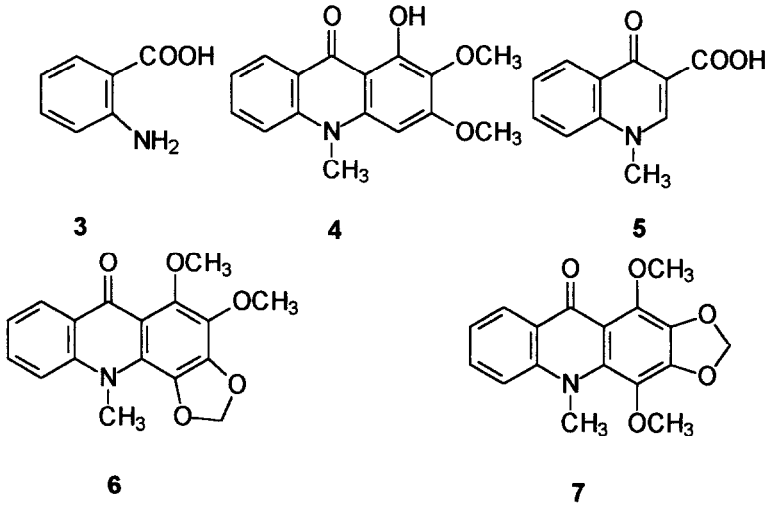
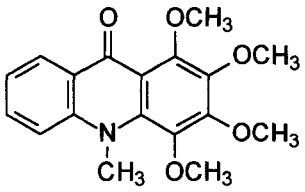
first obtained independently by two groups at the very end of the sixties. Gröger and Johne (*46, 47*) fed *Glycosmis arborea* plants with generally ^{3}H-labeled anthranilic acid (**3**) and obtained radioactive arborinine (**4**) shown to be labeled on the A ring by nitric acid oxidation to 1-methyl-4-quinolinone-3-carboxylic acid (**5**). Prager and Thredgold (*48*) used anthranilic acid specifically labeled at C-5 with ^{3}H to feed *Acronychia baueri* (= *Sarcomelicope simplicifolia* ssp. *simplicifolia*) and isolated radioactive melicopine (**6**), melicopidine (**7**), and melicopicine (**8**). Bromination of melicopicine gave an inactive bromo-derivative **9**, providing evidence that ring A, and not ring C, of the alkaloid was derived from anthranilic acid. In the same series of experiments, 4-hydroxy-2-quinolinone (**10**) and 4-hydroxy-1-methyl-2-quinolinone (**11**) were shown to be possible precursors of melicopicine (**8**), but use of the *N*-methyl derivative yielded better results, suggesting that the *N*-methylation step should precede the formation of the acridone nucleus. In agreement with this hypothesis, *N*-methylanthranilic acid (**12**) labeled at C-5 was a good precursor of evoxanthine (**13**) in *Evodia xanthoxyloides*. The acetate origin of ring C was unambiguously determined by experiments performed on *Acronychia baueri* with [1-^{14}C]acetate (*48*), and on *Glycosmis arborea* with [2-^{14}C]acetate (*49*). Established rutacridone-producing cell suspension cultures of *Ruta graveolens* (*50, 51*) permitted Gröger and co-workers to achieve important results concerning the biosynthesis of the acridones (*52-67*). The origin of the nucleus was first confirmed by use of ^{14}C labeled anthranilic acid (*52*).





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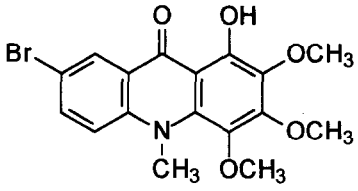

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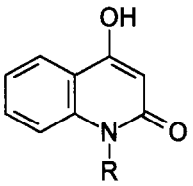
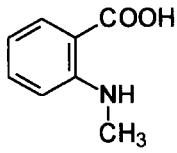


10 R=H
11 R=CH_3



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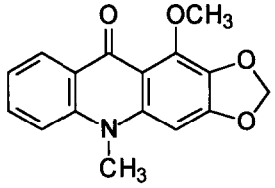

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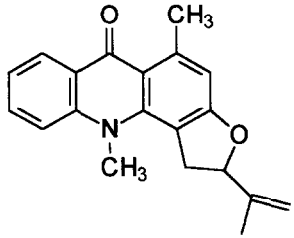
Application of acetate labeled with ^{13}C at both C-1 and C-2 gave rutacridone (**14**) showing intense satellite resonances due to ^{13}C-^{13}C spin coupling (*53*). Six bonded ^{13}C-^{13}C pairs were identified by matching coupling constants in the positions C-5-C-5a, C-11a-C-11b, and C-3a-C-4 on one hand, and C-5a-C-11a, C-11b-C-3a, and C-4-C-5, on the other hand (*53*). The intensities of the two series of doublets were approximately equal. Therefore, the six carbons of ring C were enriched from the incorporation of three intact acetate units. The enrichment distribution pattern observed implied the existence of an aminobenzophenone biogenetic intermediate, enabling free rotation between the future C-5a and C-6, such as **15**. It excluded the stepwise addition of acetate to anthranilic acid, through a quinolone intermediate, as previously suggested by Leete (*68*) and by Australian authors (*48*). This finding was in good agreement with the scheme initially proposed by Robinson (*45*), and with the isolation of the 2-methylaminobenzophenone alkaloid tecleanone (**16**) from *Teclea*, *Oricia* and *Diphasia* species which also contain acridone alkaloids (*69-73*).



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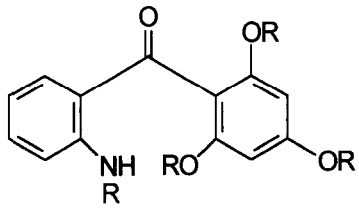
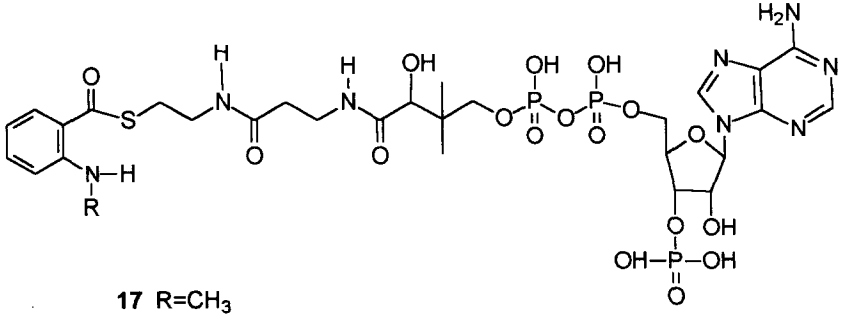


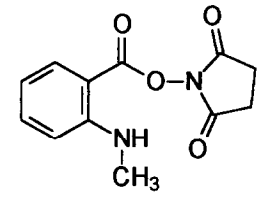
15 R=H
16 R=CH_3

It was additionally supported by the facile *in vitro* cyclization of 2-aminobenzophenones to 9(10*H*)-acridinones observed by Lewis in the course of the biomimetic synthesis of several alkaloids, including acronycine (*74-79*). Further experiments by Gröger *et al.* aimed at the characterization, and ultimately at the isolation of all the enzymes implied in the course of rutacridone biosynthesis (*54-67*). Careful study of the *N*-methylation step permitted the demonstration that *S*-adenosyl-L-methionine provided the *N*-methyl group of the acridone alkaloids and confirmed that this reaction took place at a very early stage of the biosynthetic process (*54, 55*). Indeed, *N*-methylanthranilic acid was an excellent precursor of rutacridone and could be trapped after feeding *Ruta graveolens* cell suspension cultures with anthranilic acid in short term experiments (*54*). Partial purification and characterization of the enzyme *S*-adenosyl-L-methionine-anthranilic acid-*N*-methyltransferase was recently achieved (*56*). Consequently, *N*-methylation of anthranilic acid was postulated as the first, pathway-specific, reaction in acridone alkaloid biosynthesis (*55, 56*). Activation of *N*-methylanthranilic acid (*57*) to *N*-methylanthraniloyl-CoA (**17**) was confirmed by the synthesis of this latter thioester *via* *N*-hydroxysuccinimidyl *N*-methylanthranilate (**18**) and subsequent transesterification with CoA-SH (*58*). Formation of 1,3-dihydroxy-10-methylacridone (**19**) by condensation of *N*-methylanthraniloyl-CoA (**17**) with malonyl-CoA (**20**) is catalyzed by the enzyme acridone synthase, present only in acridone producing tissue cultures (*59, 60*). The enzyme was isolated (*62*), fully characterized (*63*), cloned from elicited *Ruta graveolens* cell suspension cultures, and expressed in transfected *Escherichia coli* (*64*).

Recently, the differential distribution and regulation of acridone synthase was studied in the common rue (*65*). Expression *in planta* and the induction response of the enzyme suggest that acridone alkaloids serve as phytoantipicins or phytoalexins in the defense of *Ruta*, particularly to soil-born pathogens or as feeding deterrents (*65*). Purified acridone synthase has an apparent molecular mass of 69 kDa and its K_m-values for both *N*-methylanthraniloyl-CoA and malonyl-CoA were determined (*63*). Interestingly, the partial enzyme polypeptide sequence, elucidated from six tryptic fragments, revealed homology to heterogeneous



17 R=CH_3
21 R=H



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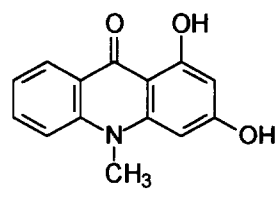

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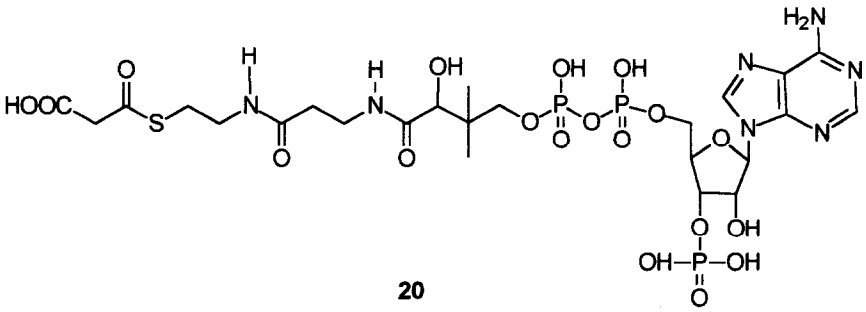

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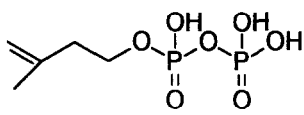
chalcone synthases, and particularly with chalcone synthase 3 from garden pea (*63*, *80*). When anthraniloyl-CoA (**21**) was synthesized and used as substrate instead of *N*-methylanthraniloyl-CoA (**17**), acridone synthase catalyzed the formation of 1,3-dihydroxyacridone (**22**) (*66*). Nevertheless, the substrate specificity of the enzyme was ten times lower towards anthraniloyl-CoA than towards *N*-methylanthraniloyl-CoA (*66*). This should account for the presence of acridones lacking a methyl group at the *N*-position in certain Rutaceae species, even if one cannot exclude *N*-demethylation of the acridone skeleton at a later step of the biosynthesis or as a catabolic process (*55*). 1,3-Dihydroxy-10-methylacridone (**19**), and perhaps to a lesser extent 1,3-dihydroxyacridone (**22**), are the key intermediates in the pathway leading to more complex acridones. Both possess nucleophilic centers at C-2 and C-4, and prenyl groups, or fused furano and pyrano rings derived from them, are found frequently at these positions in natural alkaloids. Indeed, microsomes prepared from cultured *Ruta graveolens* cells catalyzed the condensation of 1,3-dihydroxy-10-methylacridone (**19**) with either isopentenylpyrophosphate (**23**) or dimethylallylpyrophosphate (**24**) (*67*). When the experiments were conducted without NADPH, the alkaloid glycocitrine-II (**25**), previously isolated from the roots and stem bark of *Glycosmis citrifolia* (*81*), accumulated. In the presence of NADPH and oxygen, rutacridone (**14**) was obtained. Under *in vivo* conditions, glycocitrine-II (**25**) was incorporated into rutacridone (**14**), but a clear-cut cyclization of glycocitrine-II by microsomal preparations was not observed (*62*). In contrast, microsomes converted the dihydrofuroacridone alkaloid rutacridone (**14**) into the fully aromatic furoacridone furofoline-I (= furacridone) (**26**) (*62*).



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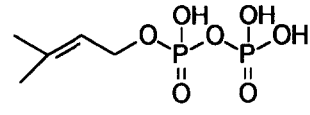

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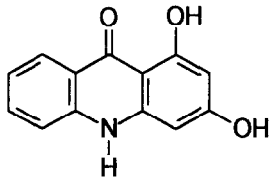

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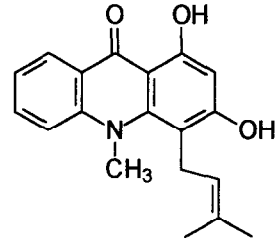

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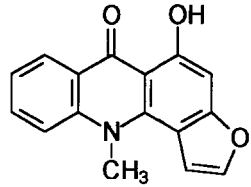

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III. Structural Elucidation

Chemical degradation methods were widely used to establish the structures of the first acridone alkaloids isolated in Australia during the period 1948-1953. This work generated much interesting chemistry which was previously extensively reviewed (*1, 82*). Some of the reactions described permit an understanding of the routes involved in the formation of quinolinone alkaloids recently isolated from *Melicope* and *Sarcomelicope* which appear as degraded products of highly oxygenated C-ring acridones. In contrast, these degradation studies are now only of historical interest as far as structural elucidation is concerned, due to the development of spectroscopic methods.

Acridone alkaloids exhibit characteristic UV spectra, which have been previously discussed in detail and interpreted on the basis of theoretical treatment (*31, 83*). The UV spectra of acridones typically show three series of bands. The first one, at shorter wavelength, appears at around 240-280 nm. It corresponds to the well-known $^1A \rightarrow {}^1B_b$ transition (^1B_b band), also present in the spectra of anthracene

and acridine derivatives, and is only weakly influenced by the substituents present on the basic skeleton. The second one, at 280-330 nm, is the weakest in intensity. It can be interpreted as the $^1A \rightarrow {}^1L_b$ transition (^1L_b band), which is forbidden in anthracene derivatives, but permitted in the case of acridines and acridones due to the symmetry perturbation induced by the nitrogen atom at the 12-position. The third one, at around 380-430 nm, corresponds to the $^1A \rightarrow {}^1L_a$ transition (^1L_a band). Both the ^1L_b and ^1L_a bands are very sensitive to the presence of substituents on the acridone ring system and are of diagnostic value to determine the oxygen substitution pattern on the basic skeleton (*31*). It should be noted that 1-hydroxyacridones bearing a 3-oxy substituent exhibit a ^1L_a band significantly shifted to longer wavelengths, when compared with their 1-alkoxy counterparts (*83*). The UV spectra of acridones are also strongly pH-dependant, due to equilibrium displacement towards the 9-hydroxyacridinium form in acidic medium, or the 9-hydroxyacridinate ion in alkaline medium (*31*).

The IR spectra of acridone alkaloids are much less informative (*84*). The carbonyl group frequency, at 1610-1640 cm^{-1}, is only little affected by hydrogen bonding. Typical C=C and C=N stretching bands appear between 1500 and 1600 cm^{-1}. The free NH and OH absorptions are observed within the same region, at 3100-3300 and 3000-3200 cm^{-1}, respectively.

The electron impact mass spectra of numerous, naturally occurring, acridones have been thoroughly examined (*85*, *86*).

As a general rule, pronounced molecular ions are observed for simple acridones. In the spectrum of 9(10*H*)-acridinone (**1**), successive loss of carbon monoxide and hydrogen cyanide give rise to moderately abundant fragment ions (*85*). In more complex compounds, the fragmentation patterns are dependent on the nature and position of the substituents. Acridones containing oxygenated substituents on the C ring behave characteristically. In the absence of C-2 or C-4 methoxy groups, the molecular ion is the base peak, and the $[M-15]^+$ ions, due to the fragmentation of $N-CH_3$ or $O-CH_3$ groups, remain of relatively weak intensity. In contrast, for simple acridones containing C-2 or C-4 methoxy groups, the $[M-15]^+$ ions become the base peaks (*85*, *86*).

In the 3,3-dimethylpyrano[2,3-*c*]acridin-7-one series, exemplified by acronycine (**2**), cleavage of one of the methyl groups at C-3 gives rise to a highly stabilized $[M-15]^+$ fragment ion which is generally the base peak (*85*, *86*).

Both proton (*87*, *88*) and carbon NMR (*88-93*) spectroscopy provide crucial information for the structural determination of natural acridones. It should be noted that some early assignments, mainly of quaternary carbon resonances, have been recently revised in the light of multi-dimensional techniques. Therefore, care should be taken when relying on comparison with older literature descriptions for the structural elucidation of new products.

IV. Occurrence

A. SIMPLE ACRIDONES

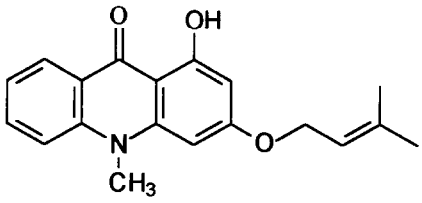
Alkaloids considered in this section derive biogenetically from 1,3-dihydroxy-10-methylacridone (**19**) and 1,3-dihydroxyacridone (**22**) by simple deoxygenation and/or oxidation of the acridone aromatic skeleton. Subsequent *O*-alkylation very often takes place, and most natural acridones bear methoxy or methylenedioxy substituents. A few, exemplified by vebilocine (**27**) (*94*), evoprenine (**28**) (*95*), and 3-geranyloxy-1-hydroxy-4-methoxy-10-methylacridone (**29**) (*96*), are also substituted by prenyloxy or geranyloxy groups.

Deoxygenated products have a restricted distribution. Acridone itself (**1**) was isolated from *Toddalia aculeata* (*97*) and *Thamnosma montana* (*98*), which also contains 10-methylacridone (**30**) (*99*, *100*). Alkaloids lacking oxygenated substitution at C-3 include 1-hydroxyacridone, 1,7-dihydroxyacridone, and 1,8-dihydroxyacridone derivatives. It should be noted that 1-methoxy-10-methylacridone (**31**) and 1,8-dihydroxyacridone (**32**) were isolated from *Samadera* aff. *bidwillii*, the only species of the Simaroubaceae which has afforded this type of secondary metabolite (*101*).

In contrast, oxidation products are frequently encountered and acridones bearing oxygenated substituents at C-2 and/or C-4, in addition to those at C-1 and C-3, are the most widely distributed within the family Rutaceae. Alkaloids substituted in ring A, at C-5 and/or C-6, have been isolated from *Glycosmis* and *Teclea*, and mainly *Citrus* species. From a chemotaxonomic point of view, their presence seems to be a characteristic feature in the latter genus. Interestingly, *Citrus* plants also afforded homoacridone alkaloids, such as citropone-A (**33**), -B (**34**), and -C (**35**), including a unique seven-membered tropolone A-ring (*102*, *103*), and to that of azaacridone-A (**36**), the only natural azaacridone alkaloid containing a pyridinic A-ring (*104*). Up till now, acridone alkaloids bearing an oxygenated substituent at C-8 in ring A have only been obtained, in the Rutaceae, from *Boronia* and *Acronychia* species.

A series of alkaloids recently isolated from *Melicope* and *Sarcomelicope* species are likely to be degraded products of highly oxygenated C-ring acridones. Fareanine (**37**), isolated from *Melicope fareana* (*105*) has close structural similarities with **38**, obtained by Prager and Thredgold by bromination of melicopine (**6**) in methanol when attempting to find a convenient degradation method for the oxygenated C-ring of various acridones (*106-109*). Similarly, 2,3-dicarbomethoxy-1-methyl-4(1*H*)-quinolinone (**39**), isolated from the leaves of *Sarcomelicope dogniensis* (*110*), is closely related to **40**, which was obtained by Crow and Price when melicopidine (**7**) was reacted with nitrous acid, and also when 1,2-dihydroxy-3,4-dimethoxy-10-methylacridone (**41**) was oxidized by air in alkaline solution (*111*).

The wide representation of natural 1-hydroxyacridones in this group of alkaloids is remarkable. This should be related to the strong intramolecular hydrogen bonding between the free hydroxy at C-1 and the keto function at C-9 which favors, for thermodynamic reasons, such compounds, when compared with



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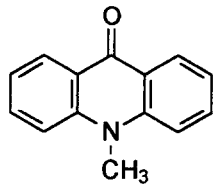

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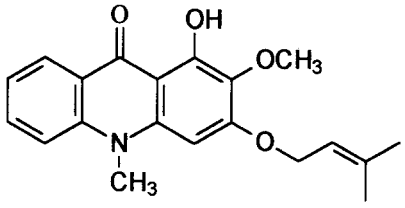

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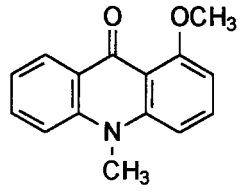

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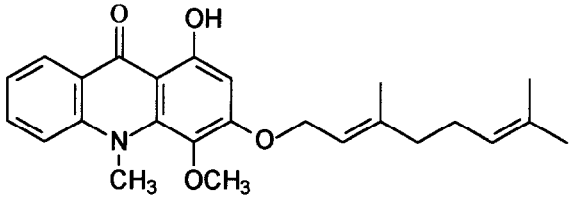
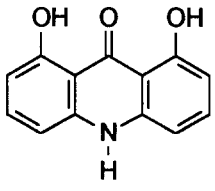
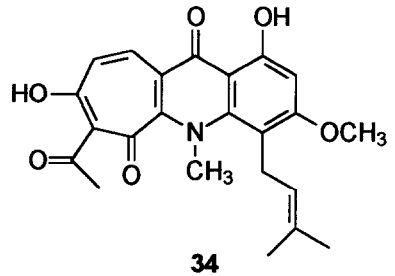


29



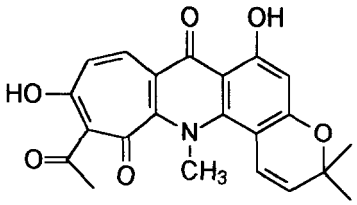
32



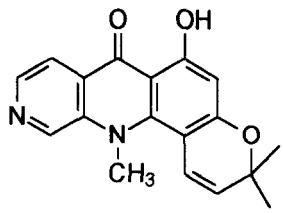
34

their 1-alkyloxy counterparts. This is also the reason why 1-methoxyacridone alkaloids can be easily converted into the corresponding 1-hydroxy derivatives under the acidic conditions, sometimes used in the course of the extraction and purification processes. Some 1-hydroxyacridones isolated from natural sources have therefore been considered as artifacts arising from genuine 1-methoxy products.

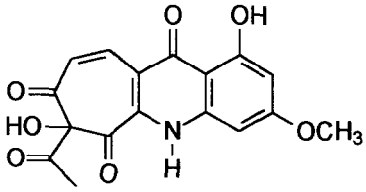
Sixty-seven simple acridone alkaloids have been isolated to date from various *Acronychia, Angostura, Araliopsis, Atalantia, Balfouroderon, Baurella, Boenninghausenia, Boronia, Bosistoa, Citrus, Diphasia, Esenbeckia, Evodia, Fagara, Glycosmis, Helietta, Lemonia, Lungusta, Medicosma, Melicope, Monnieria, Oricia, Pleiospermum, Ruta, Sarcomelicope, Teclea, Thamnosma,*



33



36



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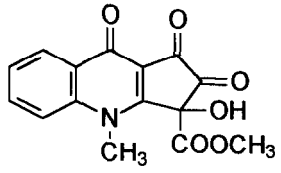
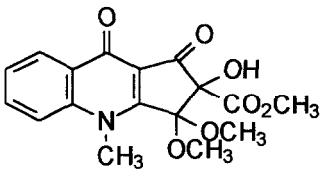
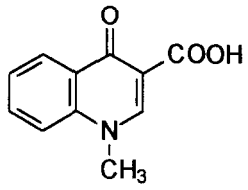


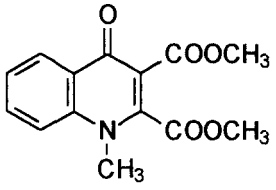
38



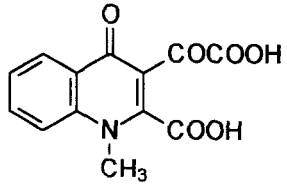
37



40



39

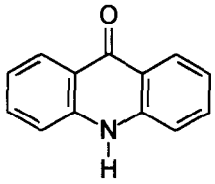


41

Toddalia, Vepris and *Zanthoxylum* species of the Rutaceae family, and *Samadera bidwillii* of the Simaroubaceae family.

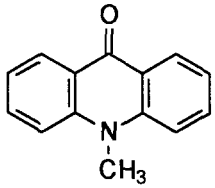
Table I surveys the structures, the properties, and the distribution of the naturally occurring simple acridone alkaloids.

TABLE 1. Simple Acridones, Occurrence and Spectral Data



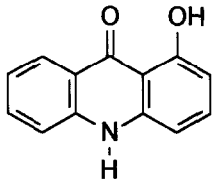
1

Acridone
$C_{13}H_9NO$ MW: 195
mp: 279-281°
spectral data: *91, 97, 98, 112*
source: *97, 98, 112*



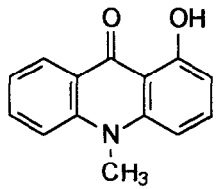
30

10-Methylacridone
$C_{14}H_{11}NO$ MW: 209
mp: 193-195°
spectral data: *91, 98, 99*
source: *98-100*



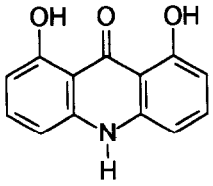
42

1-Hydroxyacridone
$C_{13}H_9NO_2$ MW: 222
mp: 252°
spectral data: *113, 115*
source: *113-116, 121,124*



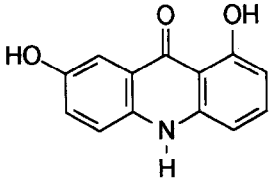
43

1-Hydroxy-10-methylacridone
$C_{14}H_{11}NO_2$ MW: 225
mp: 191-193°
spectral data: *113-115*
source: *113-115, 117-121, 124, 225*



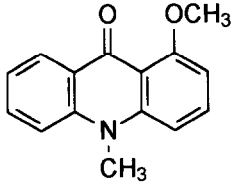
32

1,8-Dihydroxyacridone
$C_{13}H_9NO_3$ MW: 227
mp: 250°
spectral data: *115*
source: *101, 115, 116*



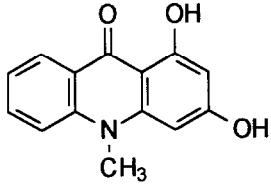
44

1,7-Dihydroxyacridone
$C_{13}H_9NO_3$ MW: 227
mp: 278°
spectral data: *115*
source: *115, 121*



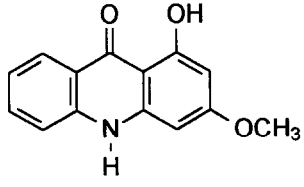
31

1-Methoxy-10-methylacridone
$C_{15}H_{13}NO_2$ MW: 239
mp: 162°
spectral data: *101*
source: *101*



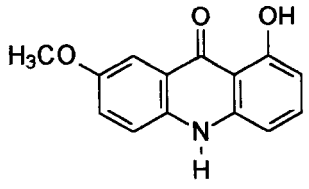
19

1,3-Dihydroxy-10-methylacridone
$C_{14}H_{11}NO_3$ MW: 241
mp: 295°
spectral data: *91, 115, 122*
source: *115, 122, 136*



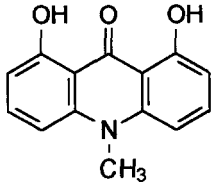
45

1-Hydroxy-3-methoxyacridone
$C_{14}H_{11}NO_3$ MW: 241
mp: 267°
spectral data: *123*
source: *123*



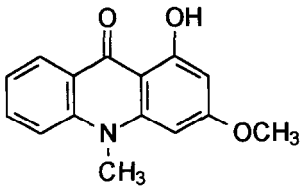
46

1-Hydroxy-7-methoxyacridone
$C_{14}H_{11}NO_3$ MW: 241
mp: 308°
spectral data: *91, 124*
source : *113, 124*
(*113 erroneous structure*)



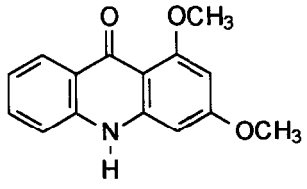
47

1,8-Dihydroxy-10- methylacridone
$C_{14}H_{11}NO_3$ MW: 241
mp: 235°
spectral data: *115*
source: *115*



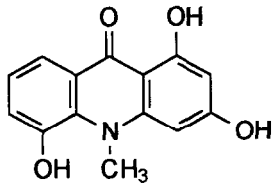
48

1-Hydroxy-3-methoxy-10-methylacridone
$C_{15}H_{13}NO_3$ MW: 255
mp: 174°
spectral data: *91, 100, 123, 125*
source: *100, 120, 123-134*



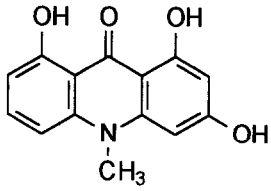
49

1,3-Dimethoxyacridone
$C_{15}H_{13}NO_3$ MW: 255
mp: 256°
spectral data: *135*
source: *135*



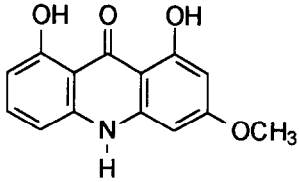
50

1,3,5-Trihydroxy-10-methylacridone
$C_{14}H_{11}NO_4$ MW: 257
mp: yellow oil
spectral data: *136*
source: *136*



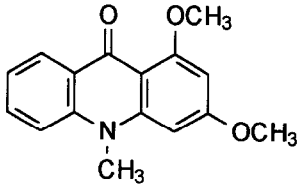
51

1,3,8-Trihydroxy-10-methylacridone
$C_{14}H_{11}NO_4$ MW: 257
mp: 285°
spectral data: *115*
source: *115*



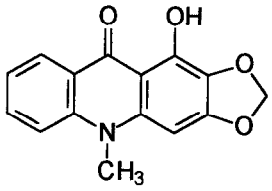
52

1,8-Dihydroxy-3-methoxyacridone
$C_{14}H_{11}NO_4$ MW: 257
mp: 275°
spectral data: *116*
source: *116*



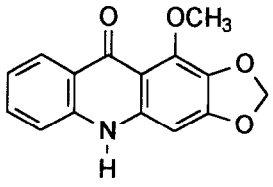
53

1,3-Dimethoxy-10-methylacridone
$C_{16}H_{16}NO_3$ MW: 269
mp: 165°
spectral data: *91, 129*
source: *71, 72, 129, 135, 137-141*



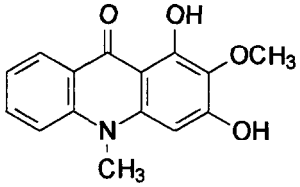
54

Norevoxanthine
$C_{15}H_{11}NO_4$ MW: 269
mp: 274°
spectral data: *156*
source: *142, 156*



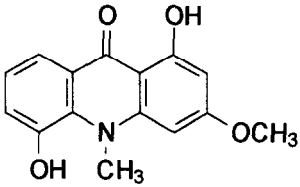
55

Evoxanthidine
$C_{15}H_{11}NO_4$ MW: 269
source: *143*



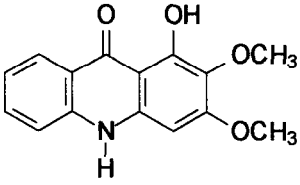
56

1,3-Dihydroxy-2-methoxy-10-methylacridone
$C_{15}H_{13}NO_4$ MW: 271
spectral data: *144*
source: *144*



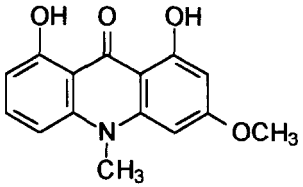
57

Citrusamine
$C_{15}H_{13}NO_4$ MW: 271
mp: 243°
spectral data: *122, 145*
source: *122, 136, 145-147*



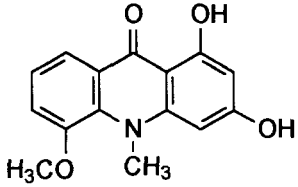
58

Xanthoxoline
$C_{15}H_{13}NO_4$ MW: 271
mp: 250°
spectral data: *123*
source: *123, 132, 143, 148, 149*



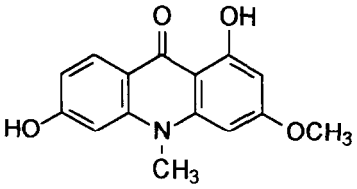
59

Oligophylidine
$C_{15}H_{13}NO_4$ MW: 271
spectral data: *150*
source: *150*



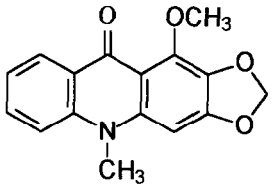
60

Yukodine
$C_{15}H_{13}NO_4$ MW: 271
mp: 246°
spectral data: *151*
source: *151*



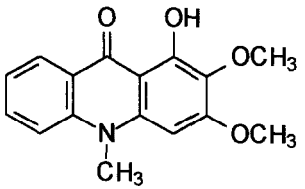
61

Pummeline
$C_{15}H_{13}NO_4$ MW: 271
mp: 235°
spectral data: *151*
source: *136, 151*



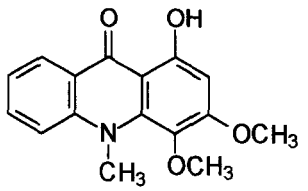
13

Evoxanthine
$C_{16}H_{13}NO_4$ MW: 283
mp: 216°
spectral data: *156, 158*
source: *2, 70, 71, 73, 95, 137, 139-143, 152-160, 200, 202*



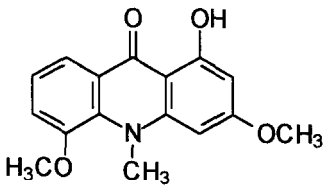
4

Arborinine
$C_{16}H_{15}NO_4$ MW: 285
mp: 175°
spectral data: *91, 123, 125, 132, 162*
source: *46, 73, 94, 95, 123, 125-127, 129, 132-134, 137, 139, 143, 149, 156, 157, 160-174, 202, 228, 275*



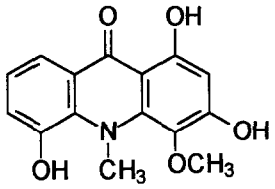
62

1-Hydroxy-3,4-dimethoxy-10-methylacridone
$C_{16}H_{15}NO_4$ MW: 285
mp: 129°
spectral data: *96*
source: *96*



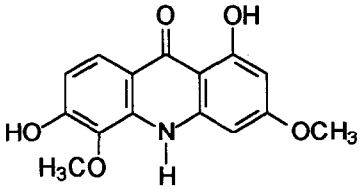
63

Yukodinine
$C_{16}H_{15}NO_4$ MW: 285
mp: yellow oil
spectral data: *151*
source: *151*



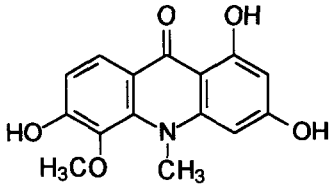
64

Citrusinine-II
$C_{15}H_{13}NO_5$ MW: 287
mp: 244°
spectral data: *175*
source: *136,175*



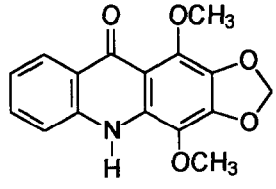
65

Natsucitrine-I
$C_{15}H_{13}NO_5$ MW: 287
mp: 292°
spectral data: *176*
source: *136, 176, 177*



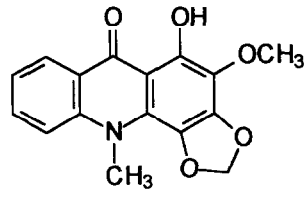
66

Grandisine-III
$C_{15}H_{13}NO_5$ MW: 287
spectral data: *151*
source: *151*



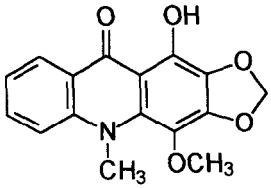
67

Xanthevodine
$C_{16}H_{13}NO_5$ MW: 299
mp: 213°
spectral data: *179*
source: *96, 135, 143, 152, 178, 179, 200*



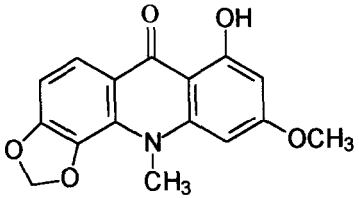
68

Normelicopine
$C_{16}H_{13}NO_5$ MW: 299
mp: 234°
spectral data: *181*
source: *180, 181, 185*



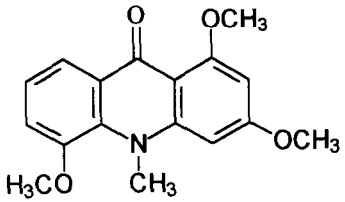
69

Normelicopidine
$C_{16}H_{13}NO_5$ MW: 299
spectral data: *180*
source: *180, 182, 183*



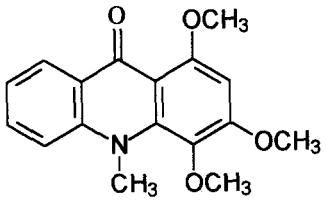
70

Marshdine
$C_{16}H_{13}NO_5$ MW: 299
mp: 210°
spectral data: *184*
source: *184*



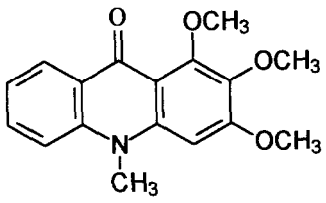
71

1,3,5-Trimethoxy-10-methylacridone
$C_{17}H_{17}NO_4$ MW: 299
mp: 141°
spectral data: 158
source: 158



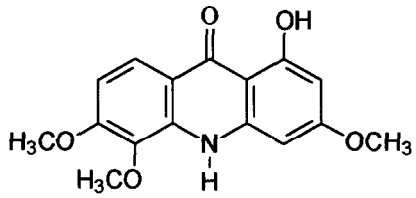
72

1,3,4-Trimethoxy-10-methylacridone
$C_{17}H_{17}NO_4$ MW: 299
mp: 134°
spectral data: *181*
source: *96, 105, 181, 202*



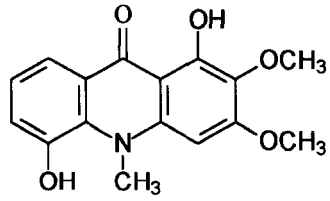
73

1,2,3-Trimethoxy-10-methylacridone
$C_{17}H_{17}NO_4$ MW: 299
mp: 157°
spectral data: *179, 181, 185*
source: *94-96, 139, 153, 179, 181, 182, 185-187*



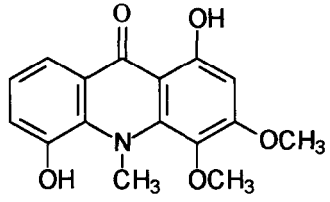
74

Natsucitrine II
$C_{16}H_{15}NO_5$ MW: 301
mp: 292°
spectral data: *176*
source: *136, 176, 216, 278*



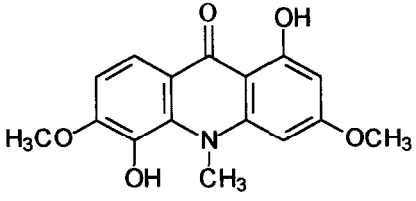
75

5-Hydroxyarborinine
$C_{16}H_{15}NO_5$ MW: 301
mp: 202°
spectral data: *189*
source: *171, 188-190, 194*



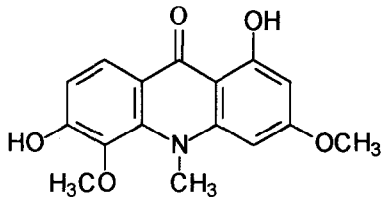
76

Citrusinine-I
$C_{16}H_{15}NO_5$ MW: 301
mp: 206°
spectral data: *175*
source: *136, 175, 191-193*



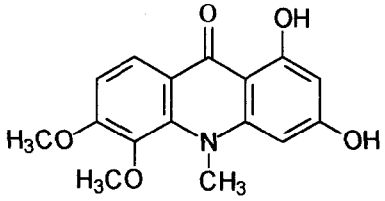
77

Grandisine-I
$C_{16}H_{15}NO_5$ MW: 301
mp: 262°
spectral data: *191*
source: *191, 216*



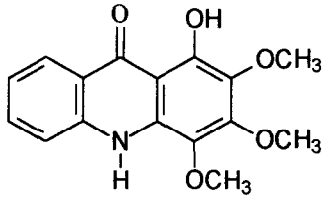
78

Citpressine-I
$C_{16}H_{15}NO_5$ MW: 301
mp: 183°
spectral data: *195-197*
source: *136, 177, 191, 195- 197, 209, 217, 278*



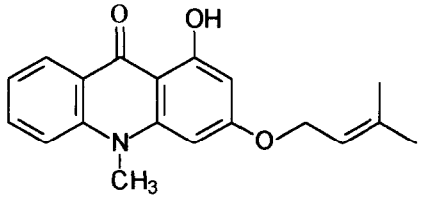
79

Grandisine-II
$C_{16}H_{15}NO_5$ MW: 301
mp: 266°
spectral data: *191*
source: *191, 198, 216*



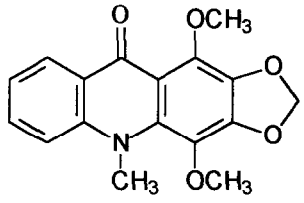
80

$C_{16}H_{15}NO_5$ MW: 301
mp: 200°
spectral data: *137*
source: *137*



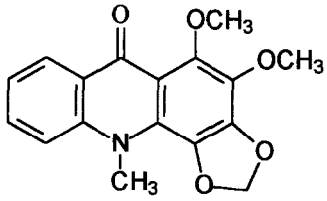
27

Vebilocine
$C_{19}H_{19}NO_3$ MW: 309
mp: 145°
spectral data: *94*
source: *94*



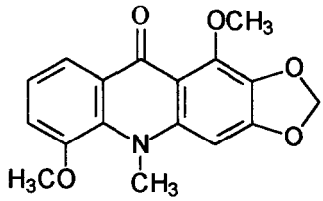
7

Melicopidine
$C_{17}H_{15}NO_5$ MW: 313
mp: 121°
spectral data: *135, 199*
source: *2, 95, 96, 105, 135,138, 153, 156, 179, 180, 182, 185-187, 199, 274*



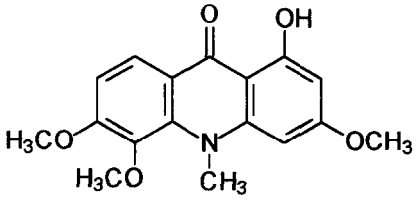
6

Melicopine
$C_{17}H_{15}NO_2$ MW: 313
mp: 175°
spectral data: *135*
source: *2, 96, 135, 180, 183, 185, 200, 201*



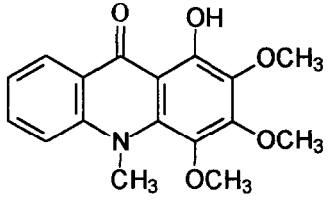
81

Tecleanthine
$C_{17}H_{15}NO_5$ MW: 313
mp: 153°
spectral data: *156, 158*
source: *72, 141, 156, 158, 202, 211*



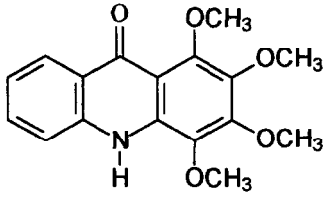
82

Citpressine-II
$C_{17}H_{17}NO_5$ MW: 315
mp: 168°
spectral data: *195, 196*
source: *136, 191, 195, 196, 209, 216, 217, 278*



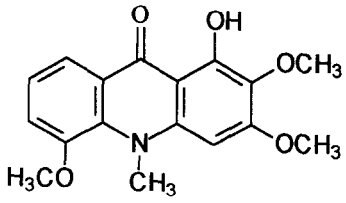
83

Normelicopicine
$C_{17}H_{17}NO_5$ MW: 315
mp: 122°
spectral data: *180*
source: *96, 100, 105, 180, 274*



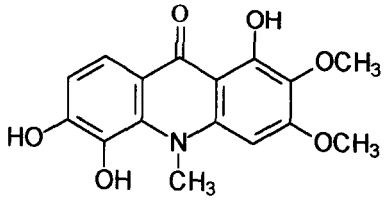
84

1,2,3,4Ttetramethoxyacridone
$C_{17}H_{17}NO_5$ MW: 315
mp: 238°
spectral data: *135*
source: *96, 135, 274*



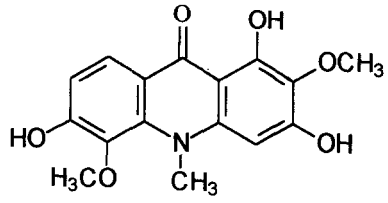
85

5-Methoxyarborinine
$C_{17}H_{17}NO_5$ MW: 315
mp: 130°
spectral data: *190*
source: *190*



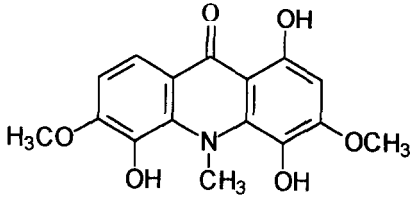
86

$C_{16}H_{15}NO_6$ MW: 317
mp: 118°
spectral data: *203*
source: *203*



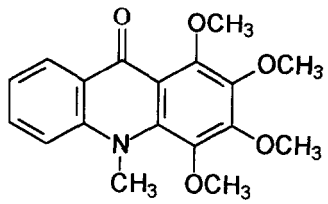
87

Citramine
$C_{16}H_{15}NO_6$ MW: 317
mp: 277°
spectral data: *204*
source: *136, 204*



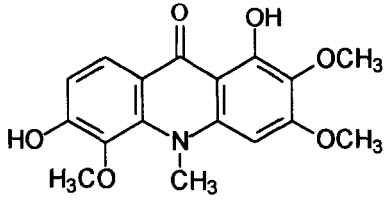
88

Atalafoline B
$C_{16}H_{15}NO_6$ MW: 317
spectral data: *205*
source: *205*



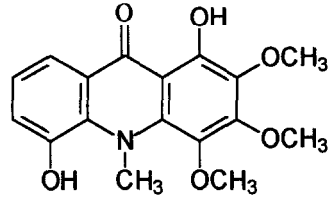
8

Melicopicine
$C_{18}H_{19}NO_5$ MW: 329
mp: 130°
spectral data: *158, 185*
source: *2, 96, 135, 138, 158, 180, 185, 186, 200, 201, 206, 207, 211, 274*



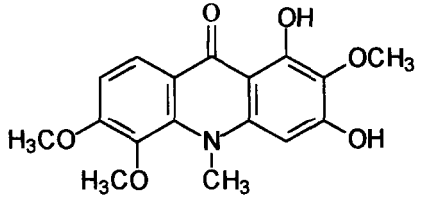
89

$C_{17}H_{17}NO_6$ MW: 331
mp: 181°
spectral data: *194*
source: *194*



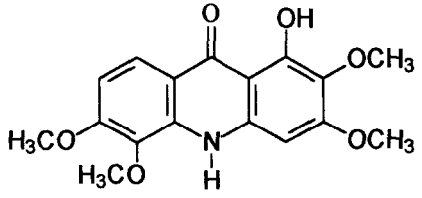
90

Citbrasine
$C_{17}H_{17}NO_6$ MW: 331
mp: 154°
spectral data: *175*
source: *175*



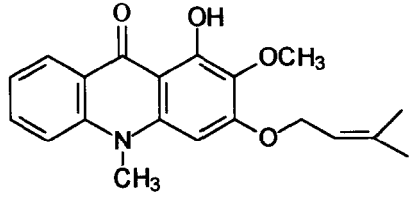
91

Atalafoline
$C_{17}H_{17}NO_6$ MW: 331
mp: 155°
spectral data: *209*
source: *205, 208, 209*



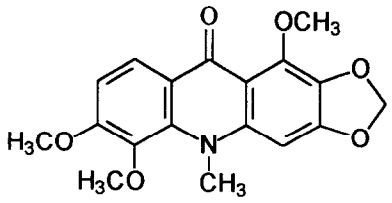
92

Cuspanine
$C_{17}H_{17}NO_6$ MW: 331
mp: 164°
spectral data: *210*
source: *210*



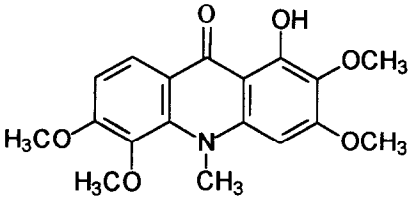
28

Evoprenine
$C_{20}H_{21}NO_4$ MW: 339
mp: 143°
spectral data: *95*
source: *95*



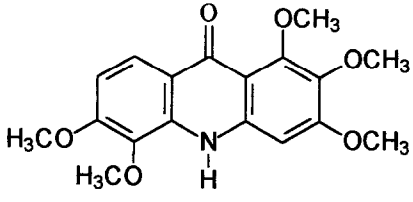
93

6-Methoxytecleanthine
$C_{18}H_{17}NO_6$ MW: 343
mp: 168°
spectral data: *158*
source: *158, 202, 211*



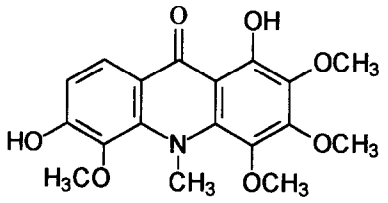
94

$C_{18}H_{19}NO_6$ MW: 345
mp: 198°
spectral data: *203*
source: *203*



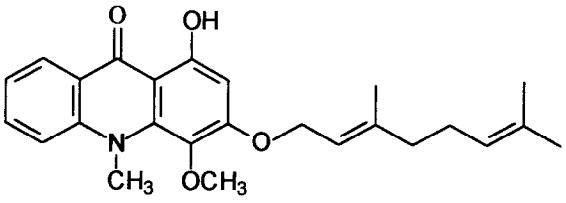
95

Cusculine
$C_{18}H_{19}NO_6$ MW: 345
mp: 223°
spectral data: *210*
source: *210*



96

Glyfoline
$C_{18}H_{19}NO_7$ MW: 361
mp: 215°
spectral data: *212*
source: *212*



29

$C_{25}H_{29}NO_4$ MW: 407
mp: 114°
spectral data: *96*
source: *96*

B. *C*-PRENYLACRIDONES

Twenty *C*-prenylacridones have been isolated from *Atalantia*, *Bosistoa*, *Glycosmis*, *Citrus* and *Severinia* species. In all of the alkaloids, with one exception, compound **108**, the site of the prenylation is the C-ring at the carbons 2 or/and 4.

C. FURANOACRIDONES

Twenty-three furanoacridones have been isolated from plants belonging to the genera *Boenninghausenia*, *Citrus*, *Glycosmis*, *Haplophyllum*, *Ruta* and *Thamnosma*. A number of furanoacridones, as well as simple acridone alkaloids, have been isolated from cell and tissue cultures of *Thamnosma montana*, *Ruta graveolens* and *R. chalepensis* (100, 120, 223, 230, 232, 236, 239, 280). The structure of hallacridone (**117**) was first attributed erroneously as a pyranoacridone (230, 232) and was revised later after its total synthesis (233). From a chemotaxonomic point of view it is interesting to point out that thehaplosine (**118**) is the unique representative of acridone alkaloids in the genus *Haplophyllum*.

D. PYRANOACRIDONES

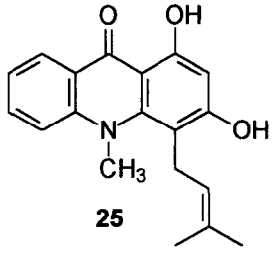
Thirty-three pyranoacridones have been isolated until now from various *Acronychia, Atalantia, Bauerella, Boenninghausenia, Bosistoa, Citrus, Glycosmis, Lungusta, Melicope, Murraya, Pleiospermum, Poncirus, Sarcomelicope, Severinia* and *Toddalia* species. This group of acridone alkaloids is probably the most studied, due to the interesting antitumor properties of acronycine (**2**) which was isolated for the first time in 1948 from the methanolic extract of *Acronychia baueri* bark (2). The botanical status of *Acronychia baueri* Schott within the Rutaceae family has been revised several times by Hartley, in the course of successive taxonomic studies of genera *Acronychia* (387), *Bauerella* (388), and *Sarcomelicope* (389, 390). Today it is considered that this taxon belongs to the genus *Sarcomelicope* and should be named *Sarcomelicope simplicifolia* (Endl) Hartley subsp. *simplicifolia* (389). Acronycine later was also isolated from other *Sarcomelicope* species. Its structure was established in 1966 by chemical degradation studies (282) and confirmed three years later by X-ray crystallographic data of 5-bromo-1,2-dihydroacronycine (281).

E. DIMERIC ACRIDONE ALKALOIDS AND RELATED COMPOUNDS

Twenty-five acridone-coumarin, eleven acridone-acridone and one acridone-lignan dimeric compounds have been isolated until now from various *Citrus*, *Clycosmis* and *Atalantia* species.

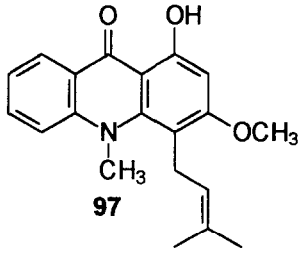
Tables II, III, IV and V survey the structures, properties and the distribution of naturally occurring *C*-prenylacridones, furanoacridones, pyranoacridones and dimeric acridone alkaloids, respectively.

TABLE 2. *C*-Prenylacridones, Occurrence and Spectral Data



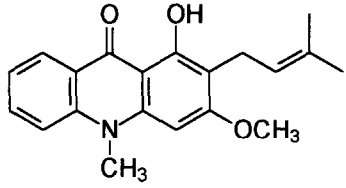
25

Glycocitrine II
$C_{19}H_{19}NO_3$ MW: 309
mp: 168°
spectral data: *212*
source: *81, 212*



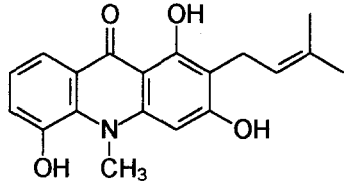
97

O-Methylglycocitrine II
$C_{20}H_{21}NO_3$ MW: 323
mp: 134°
spectral data: *212*
source: *212*



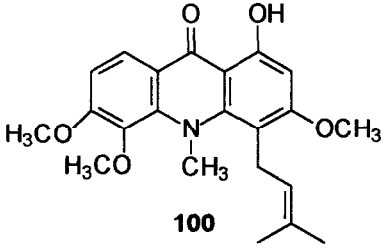
98

$C_{20}H_{21}NO_3$ MW: 323
mp: 134°
spectral data: *173*
source: *173*



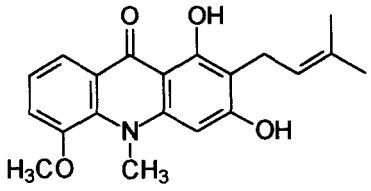
99

Junosine
$C_{19}H_{19}NO_4$ MW: 325
mp: 210°
spectral data: *213*
source: *146, 147, 213, 276*



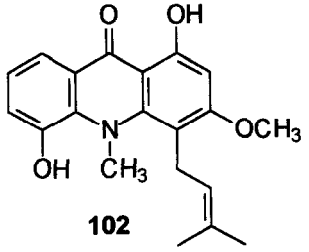
100

Baiyumine-B
$C_{25}H_{25}NO_5$ MW: 383
mp: 145°
spectral data: *214*
source: *214, 217*



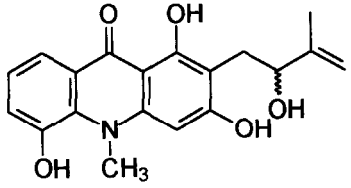
101

Yukomine
$C_{20}H_{21}NO_4$ MW: 339
mp: 214°
spectral data: *215*
source: *215*



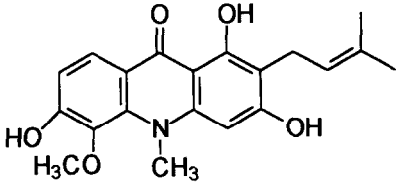
102

Glycocitrine I
$C_{20}H_{21}NO_4$ MW: 339
mp: 210°
spectral data: *81, 212*
source: *81, 136, 191, 212, 216, 217, 278*



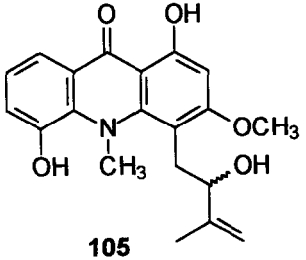
103

Bosistidine
$C_{19}H_{19}NO_5$ MW: 341
mp: yellow amorphous solid
spectral data: *147*
source: *147*



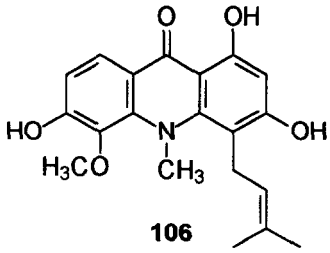
104

Buntanine
$C_{20}H_{21}NO_5$ MW: 355
mp: 247°
spectral data: *217*
source: *217*



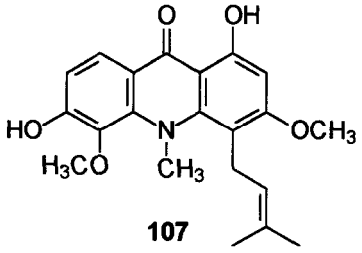
105

Marshmine
$C_{20}H_{21}NO_5$ MW: 355
mp: yellow oil
spectral data: *184*
source: *136, 184*



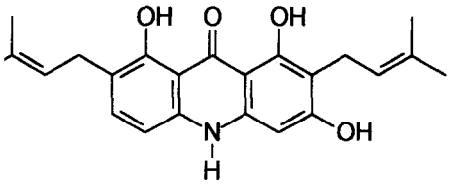
106

Prenylcitpressine
$C_{20}H_{21}NO_5$ MW: 355
mp: 160°
spectral data: *195, 196*
source: *191, 195, 196, 217, 218*



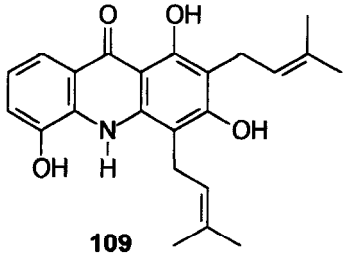
107

Grandisinine
$C_{21}H_{23}NO_5$ MW: 369
mp: 194°
spectral data: *191*
source: *136, 191, 209, 216-218, 278*



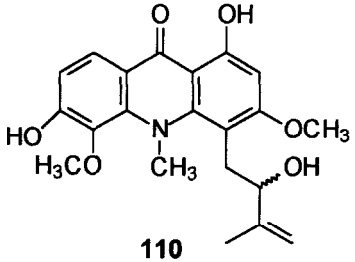
108

$C_{23}H_{25}NO_4$ MW: 379
mp: 222°
spectral data: *219*
source: *219*



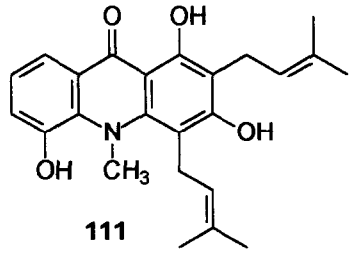
109

Atalaphylline
$C_{23}H_{25}NO_4$ MW: 379
mp: 246°
spectral data: *220*
source: *220, 221*



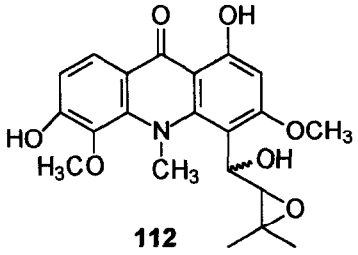
110

(-)-Buntanmine A
$C_{21}H_{23}NO_6$ MW: 385
mp: 201°
spectral data: *209*
source: *209*



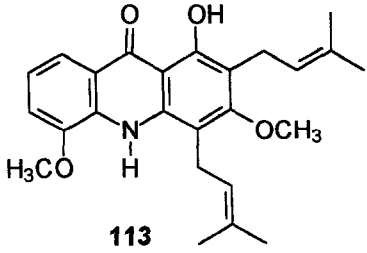
111

N-Methylatalaphylline
$C_{24}H_{27}NO_4$ MW: 393
mp: 192°
spectral data: *220*
source: *146, 147, 189, 220, 221, 276*



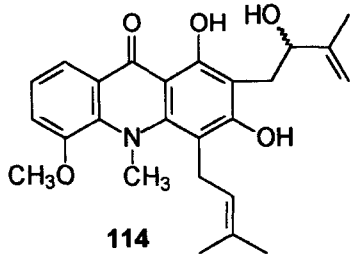
112

Margrapine-A
$C_{21}H_{23}NO_7$ MW: 401
mp: yellow oil
spectral data: *222*
source: *222*



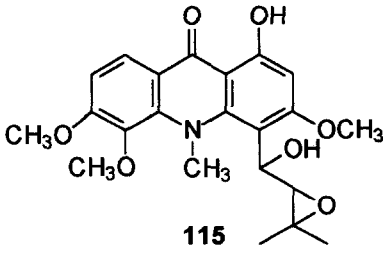
113

$C_{25}H_{29}NO_4$ MW: 407
mp: 145°
spectral data: *223*
source: *223*



114

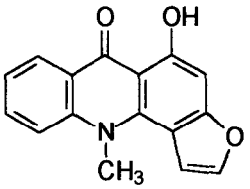
Bosistine
$C_{24}H_{27}NO_5$ MW: 409
mp: yellow amorphous solid
spectral data: *147*
source: *146, 147*



115

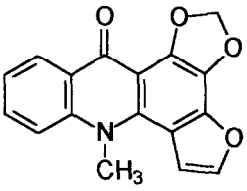
(-)-Margrapine-B
$C_{22}H_{25}NO_7$ MW: 415
mp: yellow oil
spectral data: *222*
source: *222*

TABLE 3. Furanoacridones, Occurrence and Spectral Data



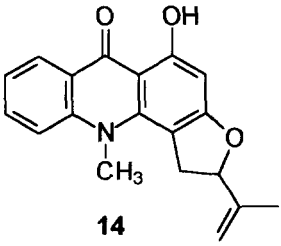
26

Furacridone = Furofoline
$C_{16}H_{11}NO_3$ MW: 265
mp: 245°
spectral data: *224*
source: *128, 224, 225*



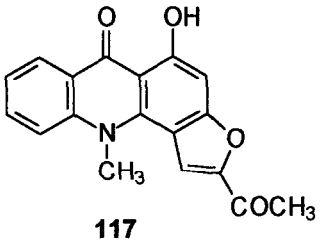
116

Chaloridone
$C_{17}H_{11}NO_4$ MW: 293
spectral data: *226*
source: *226*



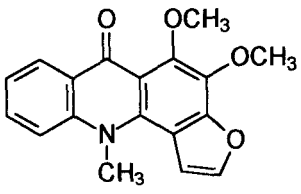
14

Rutacridone
$C_{19}H_{17}NO_3$ MW: 307
mp: 160°
spectral data: *170*
source: *100, 113, 120, 121, 124 134, 170, 227-231, 283*



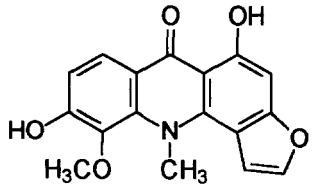
117

Hallacridone
$C_{18}H_{13}NO_4$ MW: 307
mp: 295°
spectral data: *230, 233*
source: *100, 121, 134, 230, 232, 233* (*230, 232* erroneous structure)



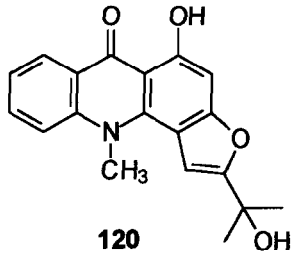
118

Theaplosine
$C_{18}H_{15}NO_4$ MW: 309
mp: amorphous crystal
spectral data: *234*
source: *234*



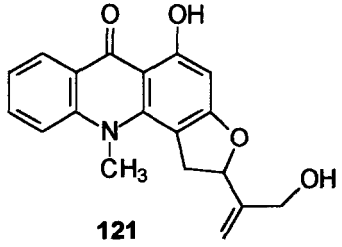
119

Furoparadine
$C_{17}H_{13}NO_5$ MW: 311
mp: yellow oil
spectral data: *235*
source: *235*



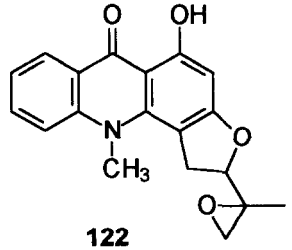
120

Furofoline-II
$C_{19}H_{17}NO_4$ MW: 323
mp: 213°
spectral data: *224*
source: *81, 224*



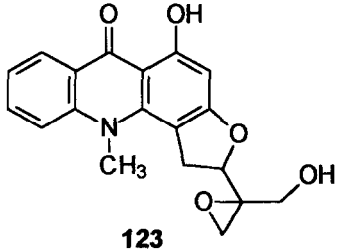
121

Gravacridonol
$C_{19}H_{17}NO_4$ MW: 323
mp: 153°
spectral data: *236, 237*
source: *100, 134, 236-238*



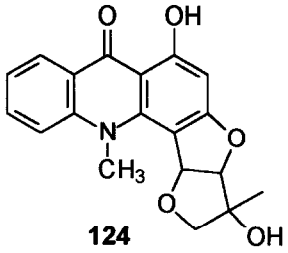
122

Rutacridone epoxide
$C_{19}H_{17}NO_4$ MW: 323
mp: 219°
spectral data: *238*
source: *100, 121, 134, 229, 230, 232, 237-240*



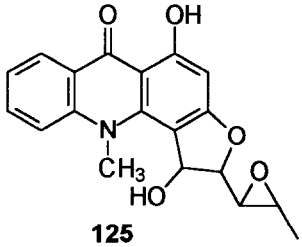
123

Hydroxyrutacridone epoxide
$C_{19}H_{17}NO_5$ MW: 339
spectral data: *240*
source: *134, 239, 240*



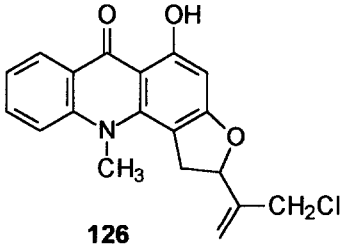
124

Rutagravine
$C_{19}H_{17}NO_5$ MW: 339
spectral data: *236*
source: *236*



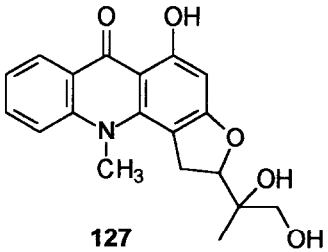
125

1-Hydroxyrutacridone epoxide
$C_{19}H_{17}NO_5$ MW: 339
spectral data: *236*
source: *236*



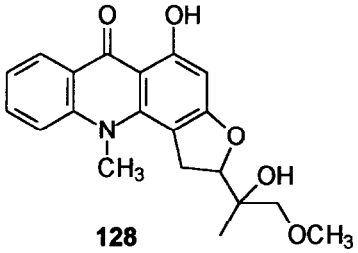
126

Alcaloid A_6
$C_{19}H_{16}NO_3Cl$ MW: 341
spectral data: *134*
source: *134*



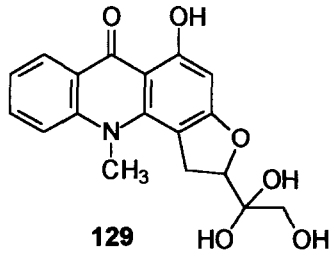
127

Gravacridondiol
$C_{19}H_{19}NO_5$ MW: 341
mp: 224°
spectral data: *229, 241, 280*
source: *100, 120, 229, 241, 280*



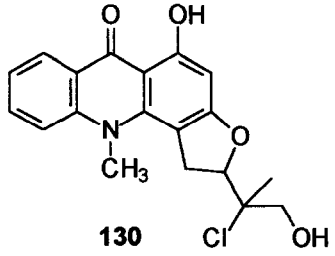
128

Gravacridondiol monomethylether
$C_{20}H_{21}NO_5$ MW: 355
mp: 219°
spectral data: *241*
source: *241*



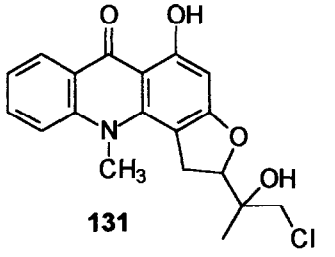
129

Gravacridontriol
$C_{19}H_{19}NO_6$ MW: 357
mp: 230°
spectral data: *100, 229, 242*
source: *100, 229, 242*



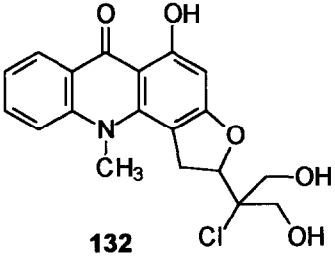
130

Gravacridonchlorine
$C_{19}H_{18}NO_4Cl$ MW: 359
mp: 254°
spectral data: *243*
source: *134, 230, 232, 243*



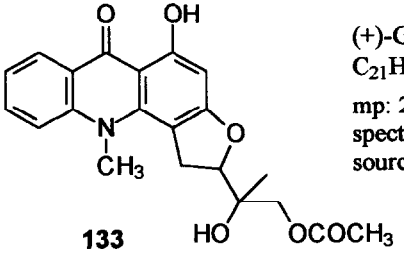
131

Isogravacridonchlorine
$C_{19}H_{18}NO_4Cl$ MW: 359
mp: 248°
spectral data: *100, 128, 244*
source: *100, 128, 244*



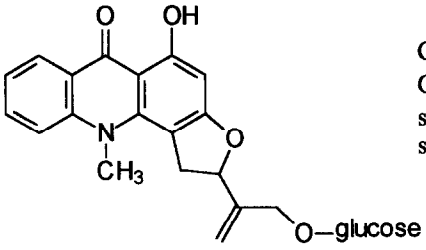
132

Gravacridonolchlorine
$C_{19}H_{18}NO_5Cl$ MW: 375
mp: 223°
spectral data: *243*
source: *243*



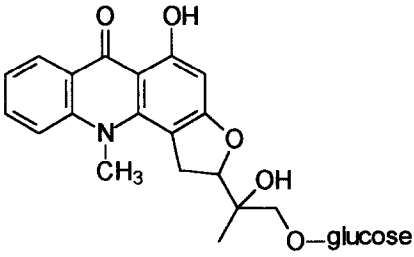
133

(+)-Gravacridondiolacetate
$C_{21}H_{21}NO_6$ MW: 383
mp: 221°
spectral data: *229*
source: *229*



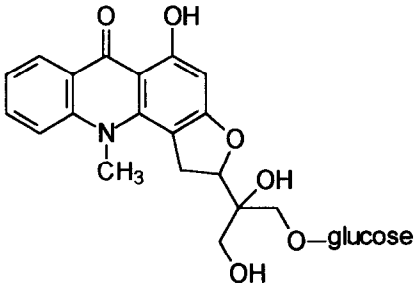
134

Gravacridonol glucoside
$C_{25}H_{27}NO_9$ MW: 485
spectral data: *100*
source: *100*



135

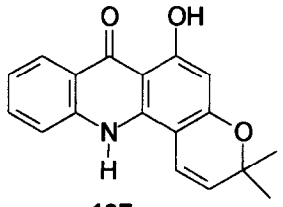
Gravacridondiol glucoside
$C_{25}H_{29}NO_{10}$ MW: 503
mp: 151°
spectral data: *242*
source: *100, 242, 280*



136

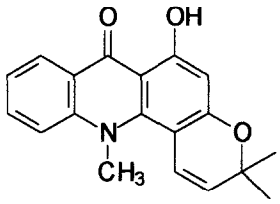
Gravacridontriol glucoside
$C_{25}H_{29}NO_{11}$ MW: 519
mp: 151°
spectral data: *242*
source: *100, 242*

TABLE 4. Pyranoacridones, Occurrence and Spectral Data



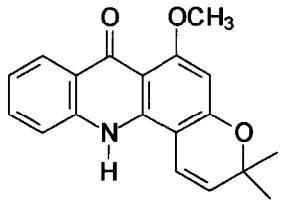
137

12-Demethylnoracronycine
$C_{18}H_{15}NO_3$ MW: 293
mp: 246°
spectral data: *245, 246*
source: *81, 245, 246*



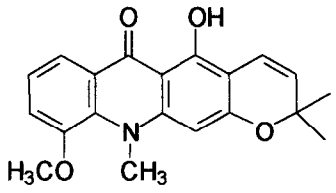
138

Noracronycine
$C_{19}H_{17}NO3$ MW: 307
mp: 200°
spectral data: *113, 245, 246*
source: *81, 113, 181, 245, 246, 248*



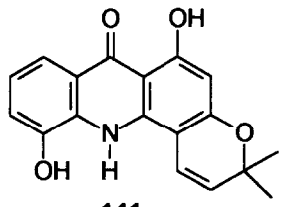
139

12-Demethylacronycine
$C_{19}H_{17}NO_3$ MW: 307
mp: 253°
spectral data: *181, 245, 246*
source: *81, 181, 245, 246, 248, 249, 276*



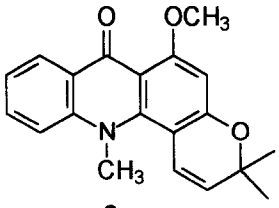
140

Junosidine
$C_{20}H_{19}NO_4$ MW: 337
mp: 188°
spectral data: *250*
source: *250*



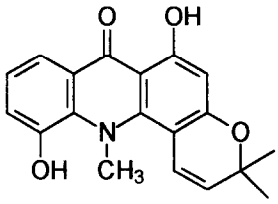
141

Atalaphyllidine
$C_{18}H_{15}NO_4$ MW: 309
mp: 275°
spectral data: *251*
source: *81, 251*



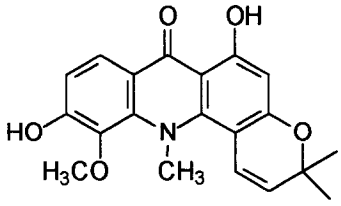
2

Acronycine
$C_{20}H_{19}NO_3$ MW: 321
mp: 174°
spectral data: *185*
source: *2, 174, 180, 182, 183, 185, 186, 199, 200, 206, 247, 249*



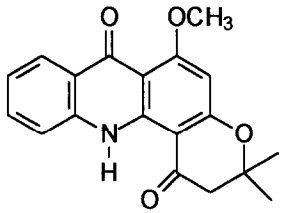
142

11-Hydroxynoracronycine
$C_{19}H_{17}NO_4$ MW: 323
mp: 252°
spectral data: *252*
source: *81, 136, 145, 177, 190-193, 195, 196, 209, 216, 217, 252, 253, 276*



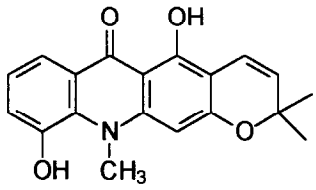
143

Acrifoline
$C_{19}H_{17}NO_5$ MW: 339
mp: amorphous powder
spectral data: *254*
source: *254*



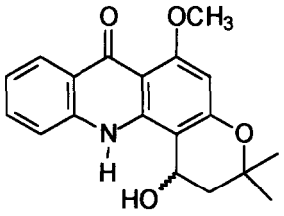
144

$C_{19}H_{17}NO_4$ MW: 323
mp: yellow amorphous solid
spectral data: *249*
source: *249*



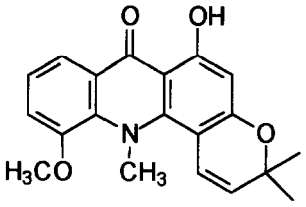
145

Yukocitrine
$C_{19}H_{17}NO_4$ MW: 323
mp: yellow oil
spectral data: *151*
source: *146, 147, 151, 276*



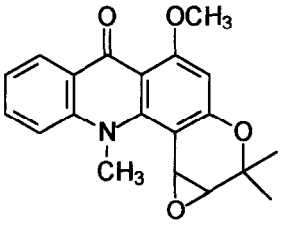
146

$C_{19}H_{19}NO_4$ MW: 325
mp: 212°
spectral data: *249*
source: *249*



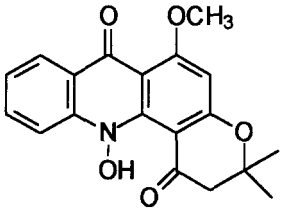
147

Baiyumine-A
$C_{20}H_{19}NO_4$ MW: 337
mp: 160°
spectral data: *214*
source: *213, 214, 217, 250*



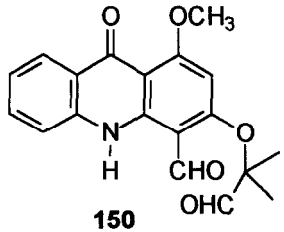
148

Acronycine epoxide
$C_{20}H_{19}NO_4$ MW: 337
mp: yellow foam
spectral data: *255*
source: *255*



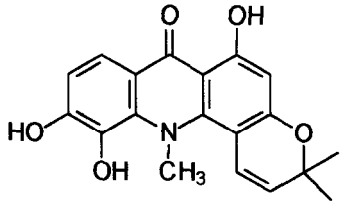
149

$C_{19}H_{17}NO_5$ MW: 339
mp: yellow amorphous solid
spectral data: *110*
source: *110*



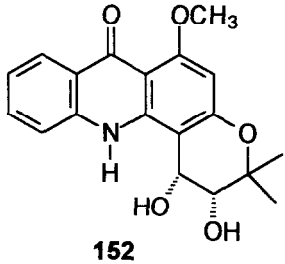
150

$C_{19}H_{17}NO_5$ MW: 339
mp: yellow amorphous solid
spectral data: *249*
source: *249*



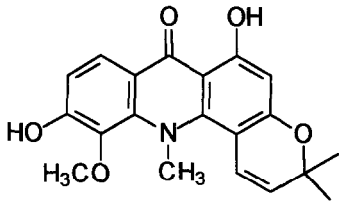
151

Citracridone-III
$C_{19}H_{17}NO_5$ MW: 339
mp: 135°
spectral data: *215*
source: *136, 215*



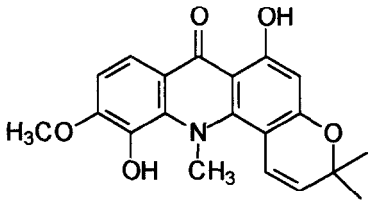
152

$C_{19}H_{19}NO_5$ MW: 341
mp: yellow amorphous solid
spectral data: *249*
source: *249*



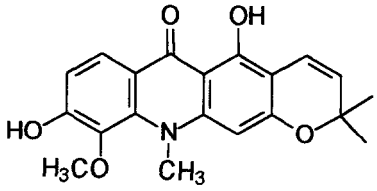
153

Citracridone-I
$C_{20}H_{19}NO_5$ MW: 353
mp: 275°
spectral data: *195*
source: *81, 136, 175, 177, 191, 192, 193, 195, 196, 209, 216, 217*



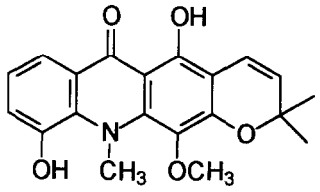
154

$C_{20}H_{19}NO_5$ MW: 353
mp: 260°
spectral data: *256*
source: *256*



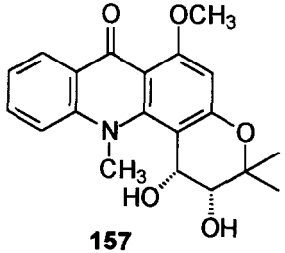
155

Honyumine
$C_{20}H_{19}NO_5$ MW: 353
mp: 175°
spectral data: *387*
source: *387*



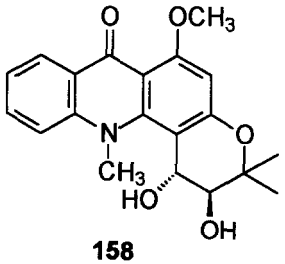
156

Pyranofoline
$C_{20}H_{19}NO_5$ MW: 353
mp: 212°
spectral data: *224*
source: *81, 224*



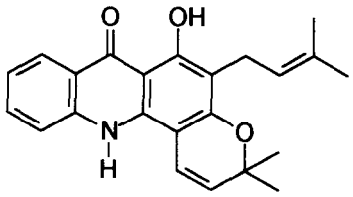
157

$C_{20}H_{21}NO_5$ MW: 355
mp: 232°
spectral data: *274*
source: *182, 274*



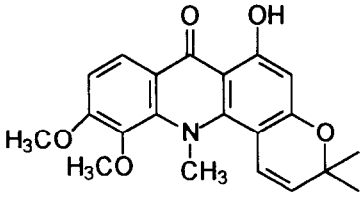
158

$C_{20}H_{21}NO_5$ MW: 355
mp: 232°
spectral data: *274*
source: *182, 274*



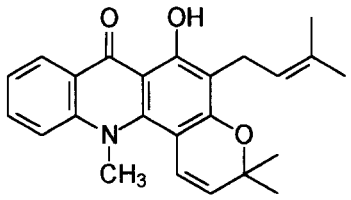
159

Severifoline
$C_{23}H_{23}NO_3$ MW: 361
mp: 253°
spectral data: *257*
source: *257*



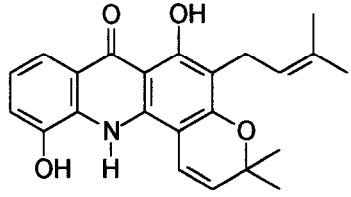
160

Citracridone-II
$C_{21}H_{21}NO_5$ MW: 365
mp: 161°
spectral data: *196*
source: *136, 191, 195, 196, 217, 256*



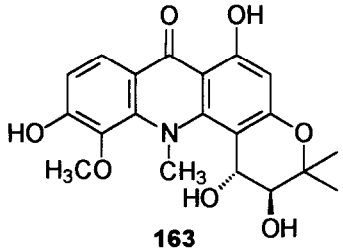
161

$C_{24}H_{25}NO_3$ MW: 375
mp: 152°
spectral data: *257*
source: *81, 257*



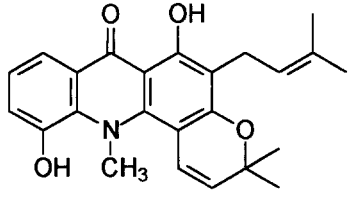
162

Atalaphyllinine
$C_{23}H_{23}NO_4$ MW: 377
mp: 205°
spectral data: *258*
source: *257, 258*



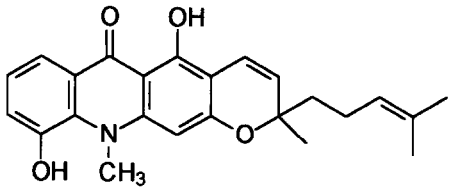
163

(+)-*trans*-Dihydroxycitracridone-I
$C_{20}H_{21}NO_7$ MW: 387
mp: 235°
spectral data: *235*
source: *235*



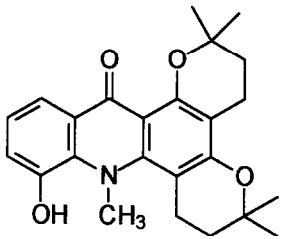
164

$C_{24}H_{25}NO_4$ MW: 391
mp: 190°
spectral data: 252
source: *81, 146, 147, 189, 221, 252, 257, 276*



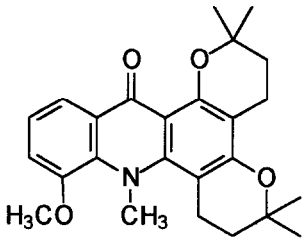
165

Glycofoline
$C_{24}H_{25}NO_4$ MW: 391
mp: 216°
spectral data: *81, 259*
source: *81, 259*



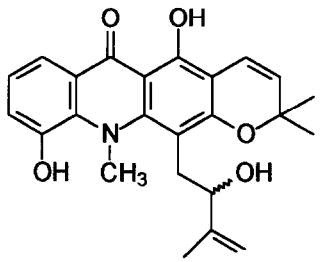
166

$C_{24}H_{27}NO_4$ MW: 393
mp: 185°
spectral data: *260*
source: *260*



167

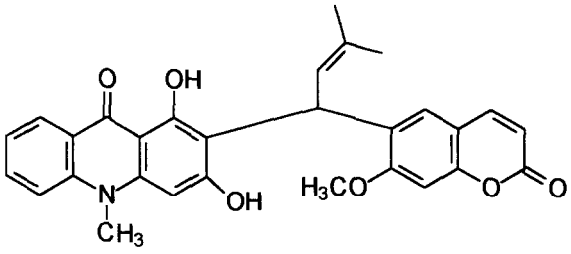
$C_{25}H_{29}NO_4$ MW: 407
mp: 205°
spectral data: *260*
source: Obtained by methylation of **166**



168

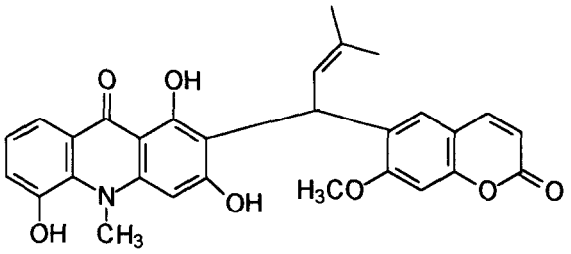
$C_{24}H_{25}NO_5$ MW: 407
mp: yellow oil
spectral data: *147*
source: (*147*)

TABLE 5. Dimeric Acridones, Occurrence and Spectral Data



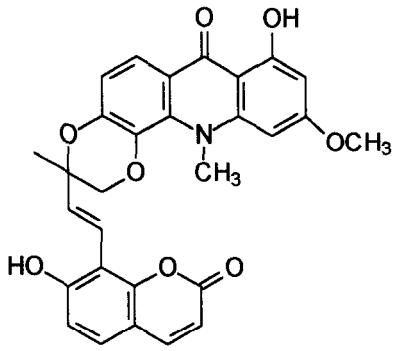
169

Acrimarine M
$C_{29}H_{25}NO_6$
MW: 483
mp: yellow oil
spectral data: *261*
source: *261*



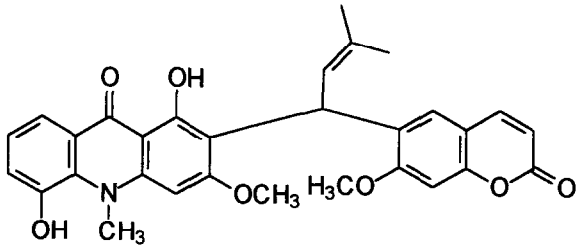
170

Acrimarine G
$C_{29}H_{25}NO_7$
MW: 499
mp: yellow oil
spectral data: *262*
source: *262*



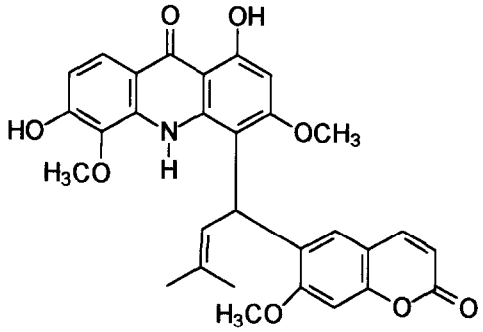
171

(+)-Dioxinoacrimarine A
$C_{29}H_{23}NO_8$ MW: 513
mp: 179°
spectral data: *263*
source: *136, 263*



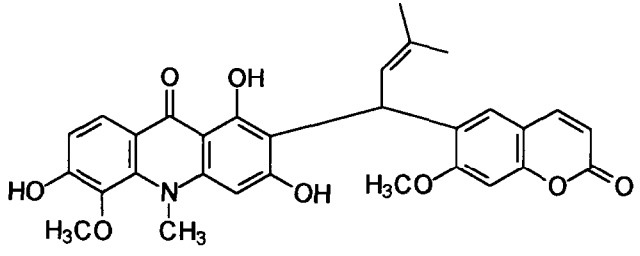
172

Acrimarine H
$C_{30}H_{27}NO_7$ MW: 513
spectral data: *136, 386*
source: *136, 386*



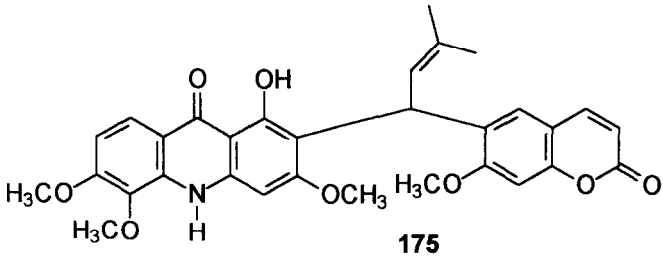
173

Acrimarine C = Acrimarine L
$C_{30}H_{27}NO_8$ MW: 529
mp: yellow oil
spectral data: *198, 261*
source: *136, 198, 261, 262*



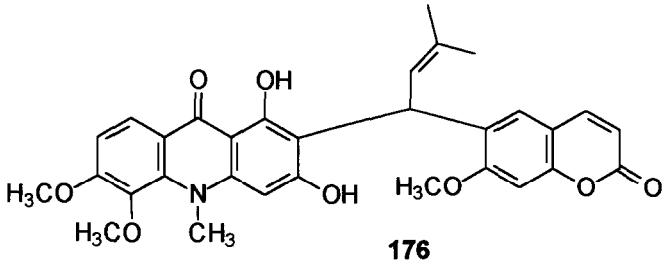
174

Acrimarine K
$C_{30}H_{27}NO_8$
MW: 529°
mp: yellow oil
spectral data: *261*
source: *261*



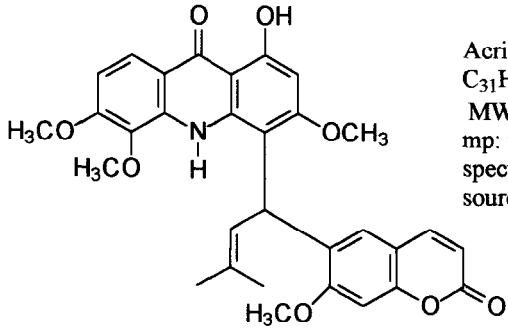
175

Acrimarine B
$C_{31}H_{29}NO_8$
MW: 543
mp: 288°
spectral data: *198*
source: *136, 198, 262*



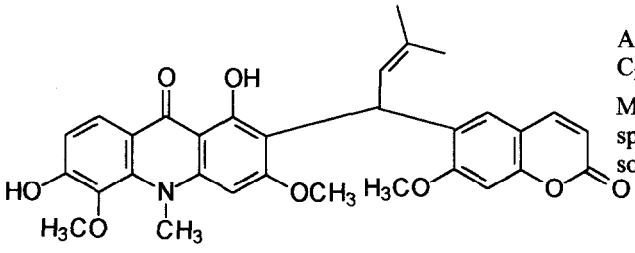
176

Acrimarine A
$C_{31}H_{29}NO_8$
MW: 543
mp: yellow oil
spectral data: *198*
source: *198, 262*



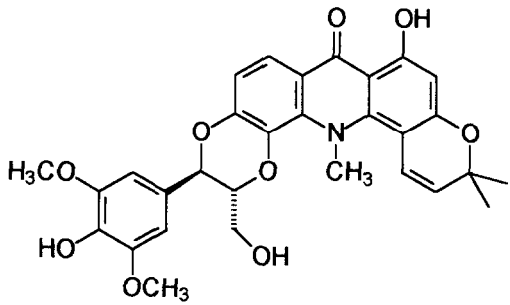
177

Acrimarine D
$C_{31}H_{29}NO_8$
MW: 543
mp: yellow oil
spectral data: *262*
source: 136, 262



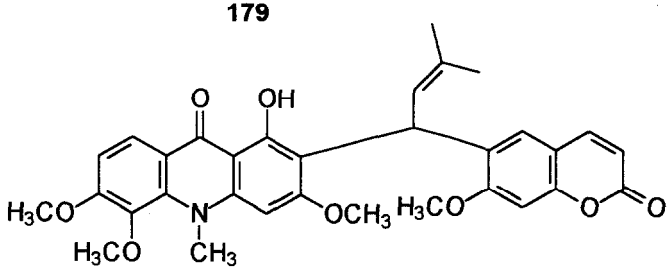
178

Acrimarine F
$C_{31}H_{29}NO_8$
MW: 543°
spectral data: *262*
source: *136,262*



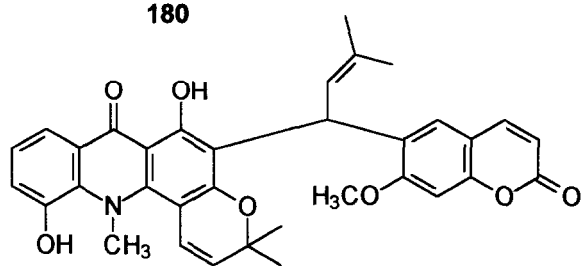
179

Acrignine A
$C_{30}H_{29}NO_9$
MW: 547
mp: 177°
spectral data: *264*
source: *264*



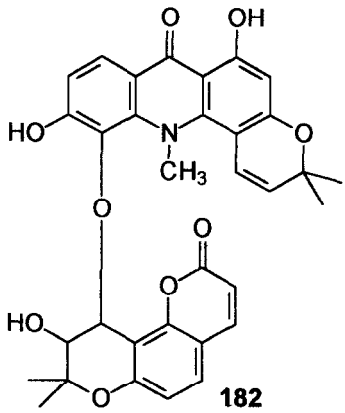
180

Acrimarine N
$C_{32}H_{31}NO_8$
MW: 557
mp: yellow oil
spectral data: *263*
source: *136, 263*



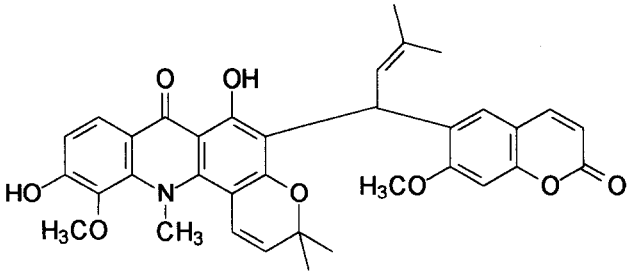
181

Acrimarine I
$C_{34}H_{31}NO_7$
MW: 565
mp: yellow oil
spectral data: *261*
source: *136, 261*



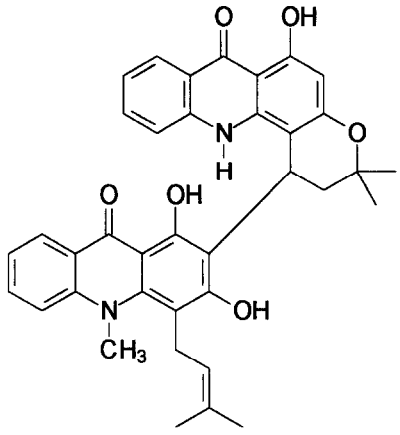
182

Neoacrimarine C
$C_{33}H_{29}NO_9$
MW: 583
mp: 111°
spectral data: *265*
source: *136, 265*



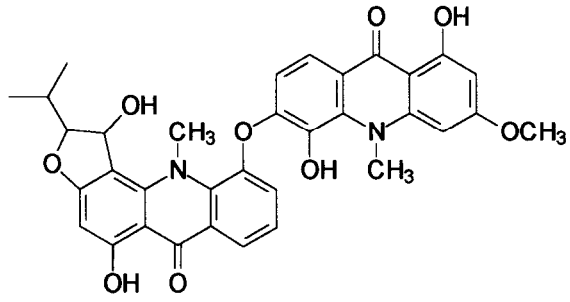
183

Acrimarine J
$C_{35}H_{33}NO_8$
MW: 595
mp: yellow oil
spectral data: *261*
source: *136, 261*



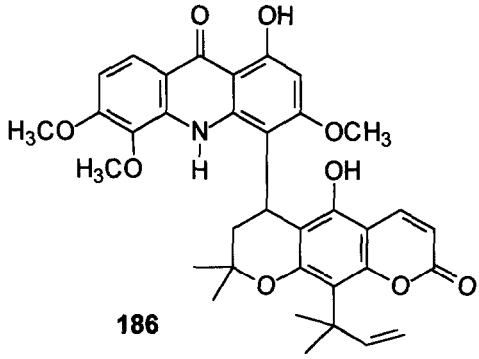
184

Glycobismine A
$C_{37}H_{34}N_2O_6$
MW: 602
mp: 256°
spectral data: *266*
source: *266, 268*



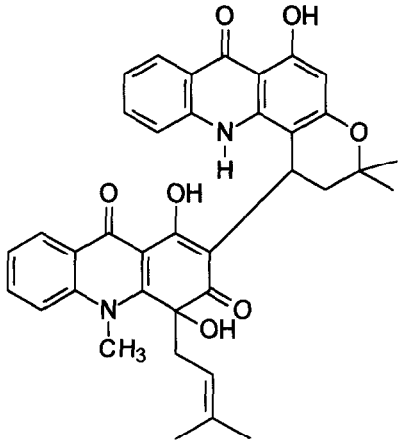
185

Atalanine
$C_{34}H_{30}N_2O_9$
MW: 610
mp: 216°
spectral data: *267*
source: *267*



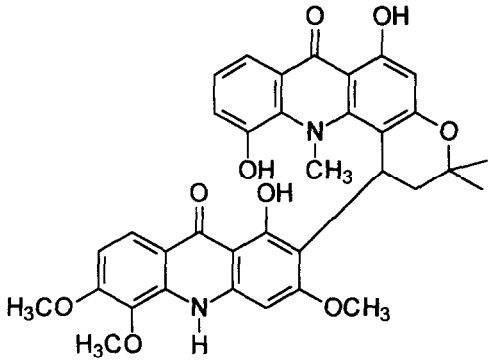
186

Neoacrimarine E
$C_{35}H_{35}NO_9$ MW: 613
mp: 212°
spectral data: *263*
source: *136, 263*



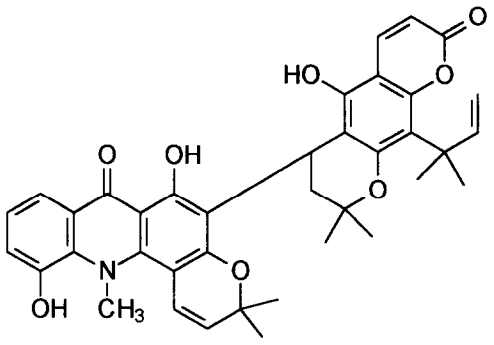
187

Glycobismine B/C
$C_{37}H_{34}N_2O_7$ MW: 618
mp: yellow oil
spectral data: *268*
source: *268*



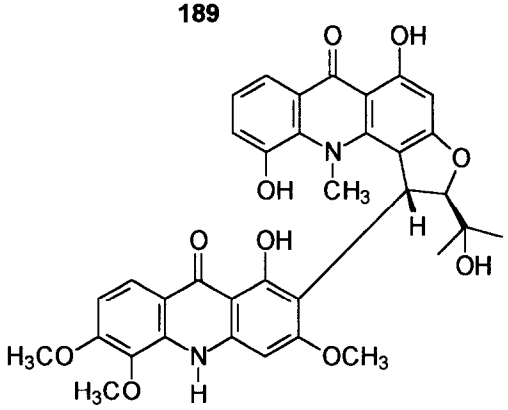
188

Buntanbismine
$C_{35}H_{32}N_2O_9$ MW: 624
mp: 300°
spectral data: *269*
source: *269*



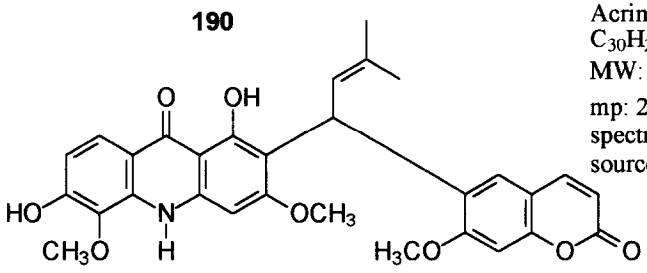
189

Neoacrimarine D
$C_{38}H_{37}NO_8$
MW: 635
mp: yellow oil
spectral data: *265*
source: *265*



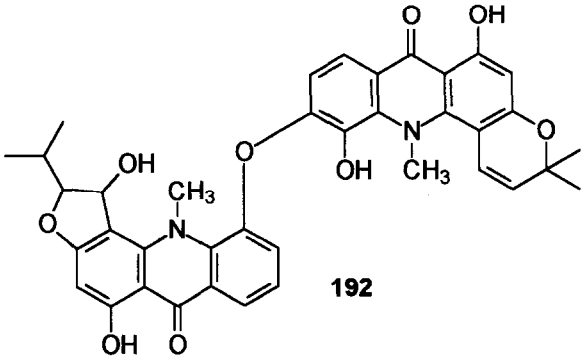
190

Citbismine A
$C_{35}H_{32}N_2O_{10}$
MW: 640
mp: 335°
spectral data: *270*
source: *270, 271*



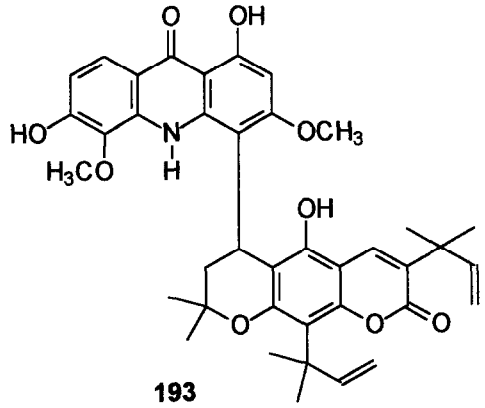
191

Acrimarine E
$C_{30}H_{27}NO_8$
MW: 529
mp: 274°
spectral data: *262*
source: *136, 262*



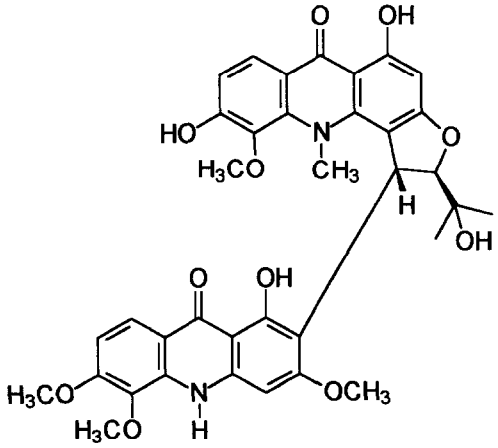
192

Ataline
$C_{38}H_{34}N_2O_9$
MW: 662
mp: 209°
spectral data: *267*
source: *267*



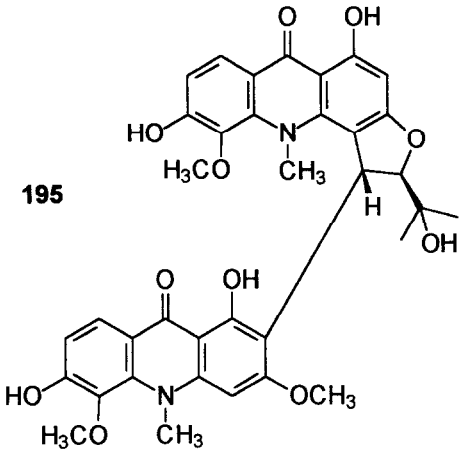
193

Neoacrimarine B
$C_{39}H_{41}NO_9$
MW: 667
mp: 240°
spectral data: *272*
source: *136, 272*



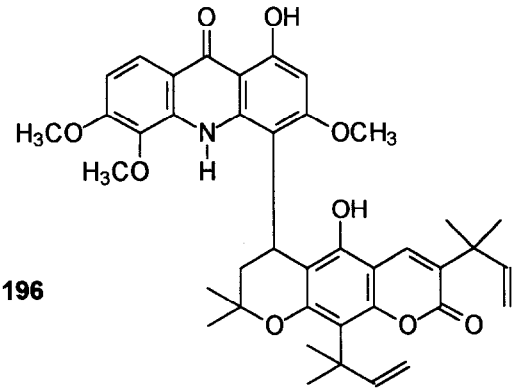
194

Citbismine B
$C_{36}H_{34}N_2O_{11}$
MW: 670
mp: 336°
spectral data: *271*
source: *271*



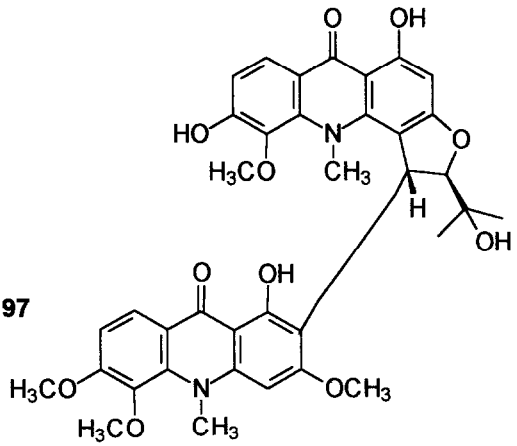
195

Citbismine E
$C_{36}H_{34}N_2O_{11}$
MW: 670
mp: yellow oil
spectral data: *273*
source: *273*



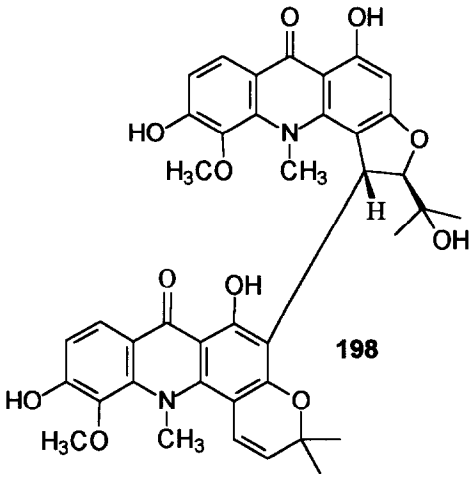
196

Neoacrimarine A
$C_{40}H_{43}NO_9$
MW: 681
mp: 225°
spectral data: *272*
source: *136, 272*



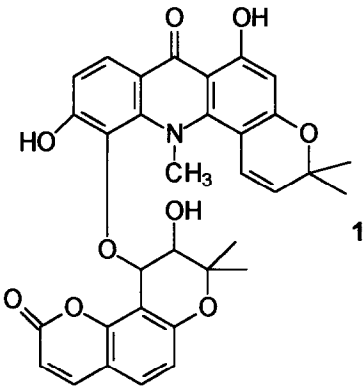
197

Citbismine C
$C_{37}H_{36}N_2O_{11}$
MW: 684
mp: 314°
spectral data: *271*
source: *271*



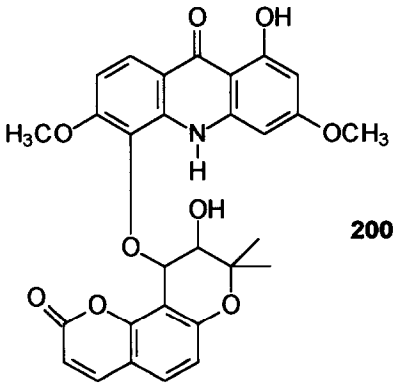
198

Citbismine D
$C_{40}H_{38}N_2O_{11}$ MW: 722
mp: yellow oil
spectral data: *273*
source: *273*



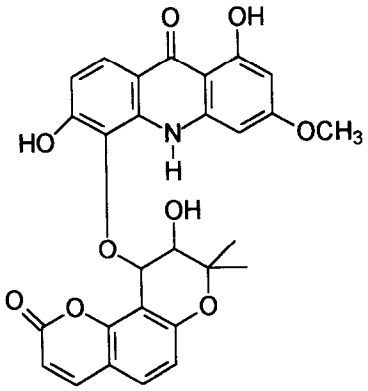
199

Neoacrimarine H
$C_{33}H_{29}NO_8$ MW: 567
mp: yellow oil
spectral data: *277*
source: *277*



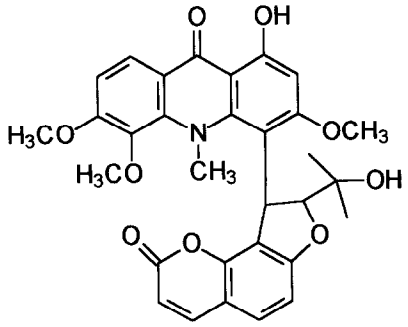
200

Neoacrimarine I
$C_{29}H_{25}NO_9$ MW: 531
mp: yellow oil
spectral data: *277*
source: *277*



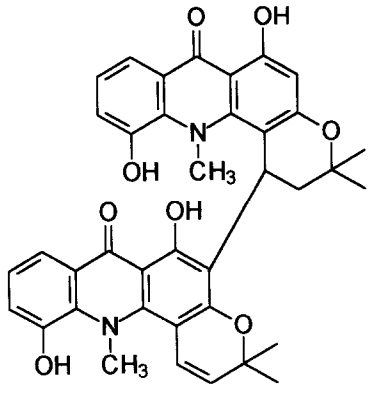
Neoacrimarine J
$C_{28}H_{23}NO_9$ MW: 517
mp: yellow oil
spectral data: *277*
source: *277*

201



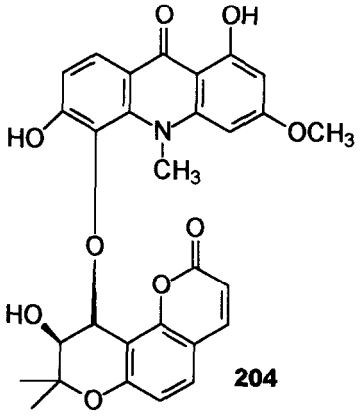
Neoacrimarine K
$C_{31}H_{29}NO_9$ MW: 559
mp: yellow oil
spectral data: *277*
source: *277*

202



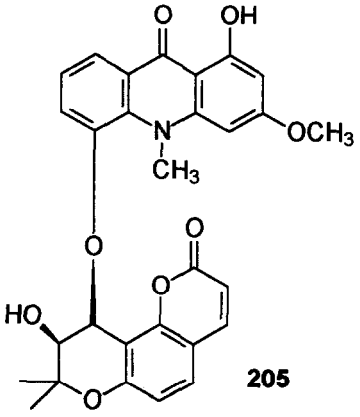
Bis-11-hydroxynoracronycine
$C_{38}H_{34}N_2O_8$ MW: 646
mp: 207°
spectral data: *278*
source: *278*

203



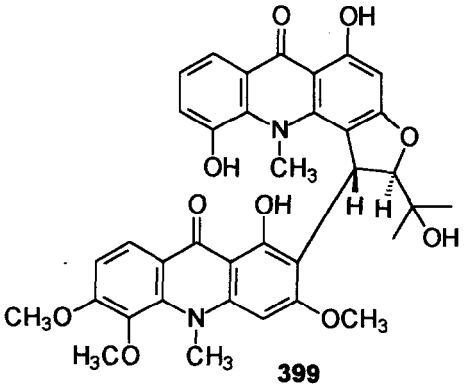
204

Neoacrimarine F
$C_{29}H_{25}NO_9$ MW: 531
mp: 218°
spectral data: *279*
source: *279*



205

Neoacrimarine G
$C_{29}H_{25}NO_8$ MW: 515
mp: yellow oil
spectral data: *279*
source: *279*



399

Citbismine F
$C_{36}H_{34}N_2O_{10}$ MW: 654
mp: 330°
spectral data: 409
source: *409*

V. Synthesis

A. SIMPLE ACRIDONES

The historical condensation of anthranilic acid (**3**) with phloroglucinol (**206**) to give 1,3-dihydroxyacridone (**22**) by Baczynski and von Niementowski should be considered as the first biomimetic synthesis of an acridone alkaloid (*284*). The yield of the reaction was initially very poor, but was increased by subsequent modifications by Beck *et al.* (*285*) and by Hlubucek *et al.* (*286*). More recently, Smolders *et al.* described an efficient condensation of methyl anthranilate (**207**) with phloroglucinol, in the presence of 4-toluenesulfonic acid in 1-heptanol, which gave **22** in 80% yield (*287*).

1,3-Dihydroxyacridone prepared in this way has been used frequently as a starting material for the synthesis of other acridone alkaloids including simple *O*- and *N*-alkylated derivatives (*288*) and more complex *C*-prenylacridones (*289*), pyranoacridones (*290*, *291*), and acridone-coumarin dimers (*292*).

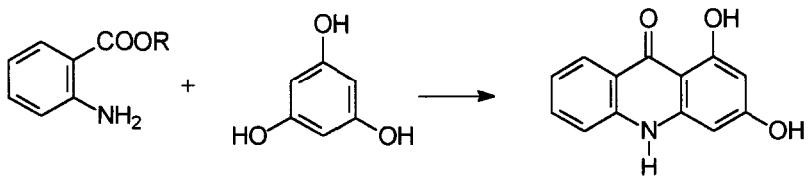
Most methods applicable for the synthesis of a greater variety of simple acridones, including alkaloids bearing numerous oxygenated substituents, also rely on the coupling of two aromatic substrates, which bring the preformed A and C rings of the future acridone skeleton. Thus, closure of the central B ring can be obtained either by cyclization of an intermediate diphenylamine or by cyclization of an intermediate benzophenone.

A different approach using a A + C ring methodology was introduced by Coppola (*293*), by condensation of an isatoic anhydride with the non-aromatic lithium enolate of a 2-cyclohexen-1-one.

Finally, a completely different strategy was recently developed by Deady (*294*), by aromatization of 1,2,3,4,9,10-hexahydroacridine-1,9-diones, prepared from suitably substituted quinolin-4-ones which bring the future A and B or B and C rings of the acridone skeleton. This methodology proved particularly efficient for the preparation of acridones with a 1,3,8-trioxygenated pattern.

1. Methods Involving the Cyclization of a Diphenylamine Intermediate

Synthesis of highly oxygenated acridone alkaloids by cyclization of a carboxylic diphenylamine was first introduced by Hughes, Neill and Ritchie for the

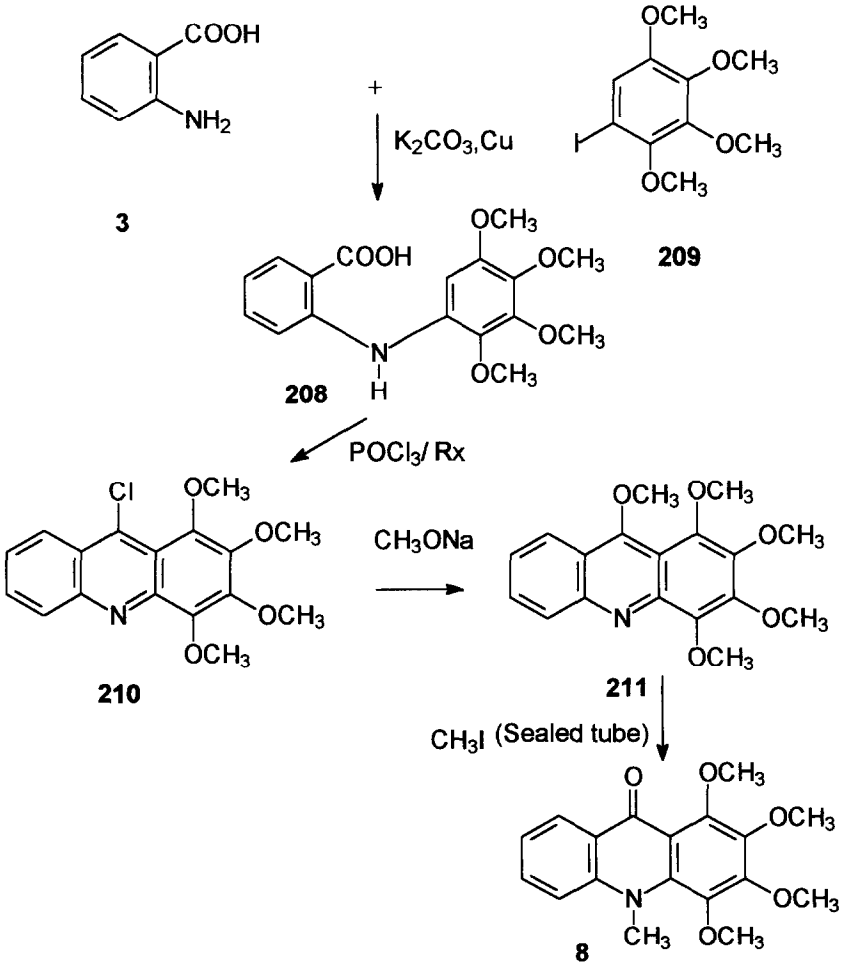


3 R=H
207 R=CH_3

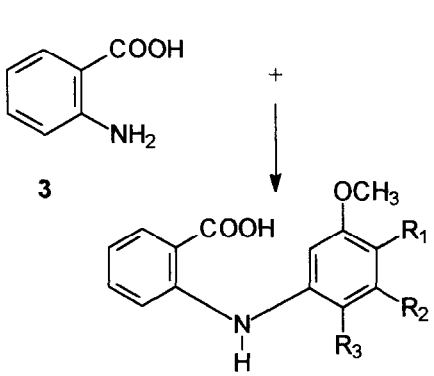
206

22

preparation of melicopicine (**8**) (*295*). Thus, 2',3',4',5'-tetramethoxydiphenylamine-2-carboxylic acid (**208**) was obtained by copper-catalyzed Ullmann condensation (*296*) between anthranilic acid (**3**) and 2,3,4,5-tetramethoxyiodobenzene (**209**). Cyclization, ensured by use of phosphoryl chloride under reflux, led to the corresponding 9-chloroacridine **210**, which was readily converted to the 9-methoxyacridine **211**, upon treatment with sodium methoxide. Final heating with methyl iodide in a sealed tube afforded melicopicine (**8**), identical with the naturally occurring compound. A similar approach was used subsequently for the synthesis of xanthevodine (**67**), melicopidine (**7**), and melicopine (**6**) (*297, 298*). Ullmann reaction of 2,5-dimethoxy-3,4-methylenedioxyiodobenzene (**212**) or 4,5-dimethoxy-2,3-methylenedioxyiodobenzene (**213**) with anthranilic acid (**3**) afforded the carboxylic diphenylamines **214** and **215**, which were cyclized to the corresponding 9-chloroacridines **216** and **217**.

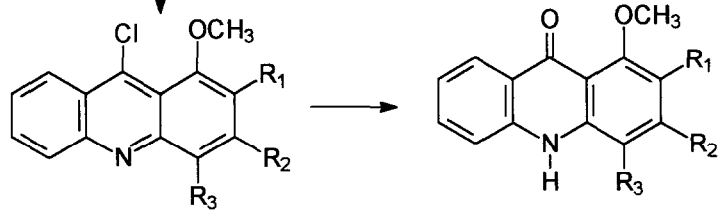


Hydrolysis by hot dilute hydrochloric acid gave the corresponding 9-acridanones, xanthevodine (**67**) and **218**. Finally, *N*-methylation with methyl iodide and potassium hydroxide in acetone gave melicopidine (**7**) and melicopine (**6**), respectively. The same reaction sequence, applied to 3'-methoxy-4',5'-methylenedioxydiphenylamine-2-carboxylic acid (**219**), prepared either from 3-methoxy-4,5-methylenedioxyiodobenzene (**220**) and anthranilic acid (**3**) (*299*) or from 3-methoxy-4,5-methylenedioxyaniline (**221**) and 2-bromobenzoic acid (**222**) (*300*), afforded evoxanthidine (**55**) and evoxanthine (**13**).



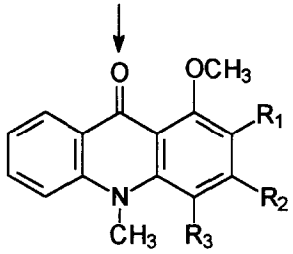
212 R_1=R_2=OCH_2O, R_3=OCH_3
213 R_1=OCH_3, R_2=R_3=OCH_2O
220 R_1=R_2=OCH_2O, R_3=H

214 R_1=R_2=OCH_2O, R_3=OCH_3
215 R_1=OCH_3, R_2=R_3=OCH_2O
219 R_1=R_2=OCH_2O, R_3=H

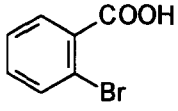


216 R_1=R_2=OCH_2O, R_3=OCH_3
217 R_1=OCH_3, R_2=R_3=OCH_2O

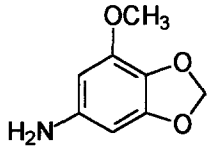
67 R_1=R_2=OCH_2O, R_3=OCH_3
218 R_1=OCH_3, R_2=R_3=OCH_2O
55 R_1=R_2=OCH_2O, R_3=H



7 R_1=R_2=OCH_2O, R_3=OCH_3
6 R_1=OCH_3, R_2=R_3=OCH_2O
13 R_1=R_2=OCH_2O, R_3=H

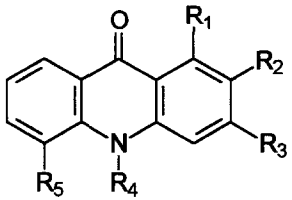


222



221

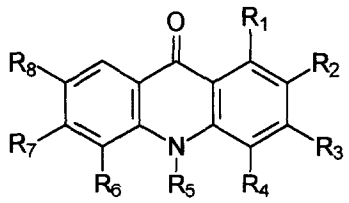
This versatile methodology was successfully applied, with slight modifications, for the synthesis of a number of other acridone alkaloids, including 1-hydroxy-3-methoxy-10-methylacridone (**48**) (*301*), 1,3-dimethoxy-10-methylacridone (**53**) (*301, 302*), 1,3-dihydroxy-10-methylacridone (**19**) (*301, 302*), 1,2,3-trimethoxy-10-methylacridone (**73**) (*303*), xanthoxoline (**58**) (*303*), and 1,5-dihydroxy-2,3-dimethoxy-10-methylacridone (5-hydroxyarborinine) (**75**) (*188*).



48 R_1=OH, R_2=H, R_3=OCH_3, R_4=CH_3, R_5=H
53 R_1=OCH_3, R_2=H, R_3=OCH_3, R_4=CH_3, R_5=H
19 R_1=OH, R_2=H, R_3=OH, R_4=CH_3, R_5=H
73 R_1=R_2=R_3=OCH_3, R_4=CH_3, R_5=H
58 R_1=OH, R_2=R_3=OCH_3, R_4=R_5=H
75 R_1=OH, R_2=R_3=OCH_3, R_4=CH_3, R_5=OH

The introduction of polyphosphoric acid, instead of phosphoryl chloride, as the reagent for the cyclization of carboxylic diphenylamines permitted the direct access to 9-acridanones, avoiding the tedious steps of acid hydrolysis or alkaline methanolysis of the intermediate 9-chloroacridines (*304*). This modified process appears as the most popular for the synthesis of simple natural acridones and has been applied to the synthesis of 1,3-dimethoxyacridone (**49**) (*305*), 1,3-dimethoxy-10-methylacridone (**53**) (*305*), 1,2,3-trimethoxyacridone (**223**) (*306*), 1,2,3-trimethoxy-10-methylacridone (**73**) (*306*), 1,2,4-trimethoxy-10-methylacridone (**72**) (*202*), 1-hydroxy-7-methoxyacridone (**46**) (*307*), 1,2,3,5,6-pentamethoxyacridone (**95**) (*210*), 1-hydroxy-2,3,5,6-tetramethoxyacridone (**92**) (*210*), glyfoline (**96**) (*308*), and several congeners of this latter alkaloid (*309*).

An improved access to carboxylic diphenylamine precursors of highly oxygenated acridones was recently described by Brassard *et al.* (*310, 311*). Regiospecific substitution of halogenoquinones by appropriate sulfonamides in the presence of fluoride ions gave *o*-methoxycarbonylanilinoquinones of definite structure. Reductive methylation and saponification of these latter compounds afforded carboxylic diphenylamines, whose cyclization efficiently provided highly substituted acridones. For instance, condensation of 2-chloro-6-methoxybenzoquinone (**224**), or 2-chloro-5,6-dimethoxybenzoquinone (**225**) with methyl *N*-mesylanthranilate (**226**) gave smoothly the corresponding *N*-mesyl-2-(2-methoxycarbonylanilino)quinones **227** and **228**, when carried out in dry dimethylformamide, in the presence of CsF on celite and 18-crown-6 ether.



49 R_1=R_3=OCH_3, R_2=R_4=R_5=R_6=R_7=R_8=H

53 R_1=R_3=OCH_3, R_5=CH_3, R_2=R_4=R_6=R_7=R_8=H

223 R_1=R_2=R_3=OCH_3, R_4=R_5=R_6=R_7=R_8=H

73 R_1=R_2=R_3=OCH_3, R_5=CH_3, R_4=R_6=R_7=R_8=H

72 R_1=R_3=R_4=OCH_3, R_5=CH_3, R_2=R_6=R_7=R_8=H

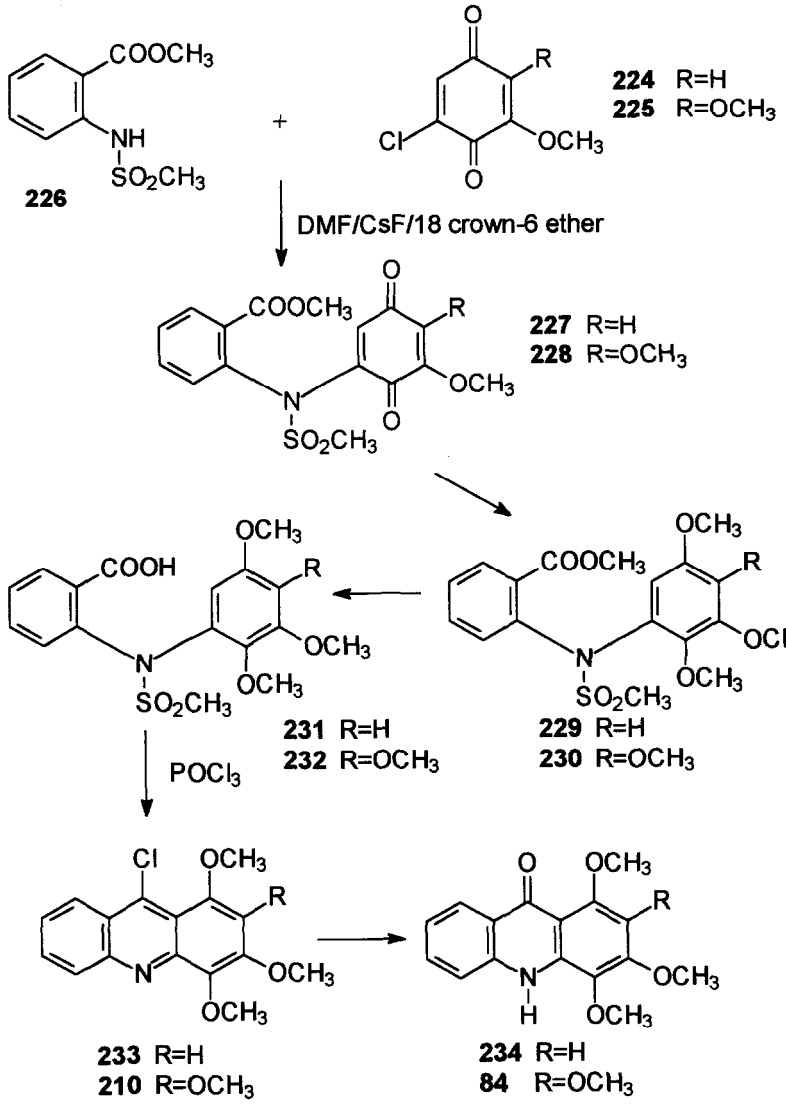
46 R_1=OH, R_8=OCH_3, R_2=R_3=R_4=R_5=R_6=R_7=H

95 R_1=R_2=R_3=R_6=R_7=OCH_3, R_4=R_5=R_8=H

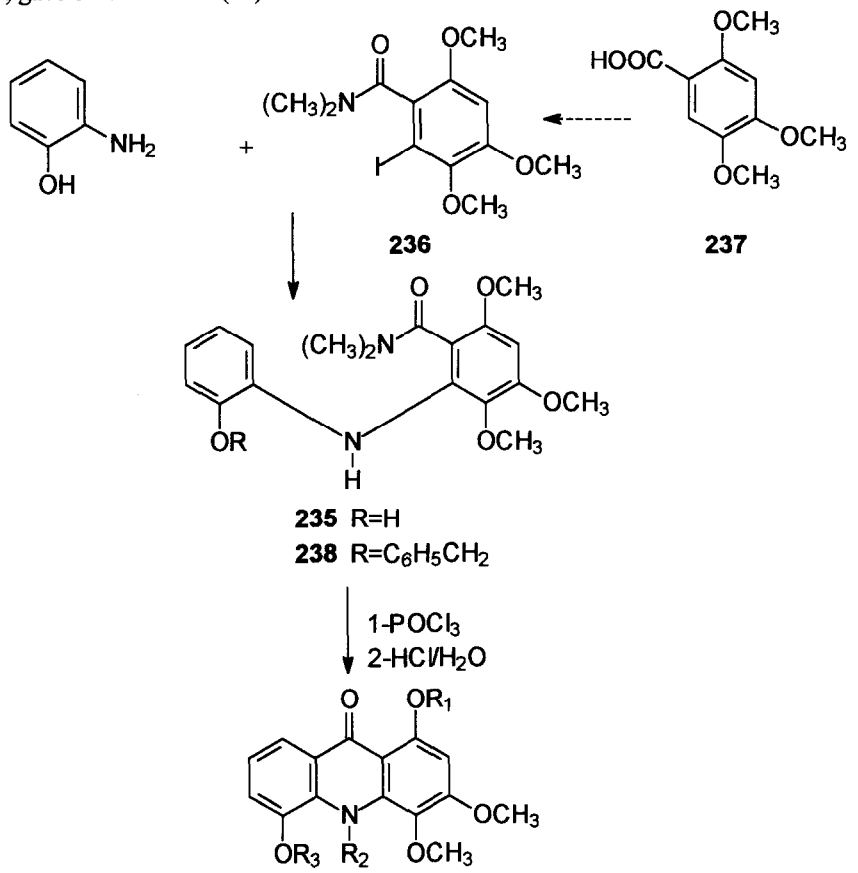
92 R_1=OH, R_2=R_3=R_6=R_7=OCH_3, R_4=R_5=R_8=H

96 R_1=R_7=OH, R_2=R_3=R_4=R_6=OCH_3, R_5=CH_3, R_8=H

Simultaneous reduction and methylation under phase-transfer conditions afforded the *N*-mesyl-carbomethoxydiphenylamines **229** and **230**, which were converted to the corresponding carboxylic *N*-mesyl-diphenylamines, **231** and **232**. Phosphoryl chloride permitted cyclization to the 9-chloroacridines **233** and **210**, with simultaneous elimination of the sulfonyl group. Final hydrolysis of these latter compounds under acidic conditions gave the desired 1,3,4-trimethoxyacridone (**234**), and 1,2,3,4-tetramethoxyacridone (**84**), respectively.

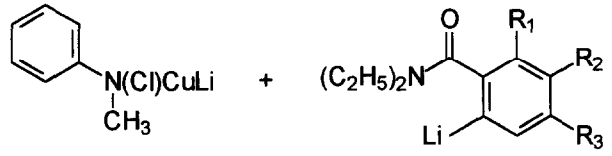


Cyclization of a substituted *N*-arylanthranilamide was the key step for the synthesis of citrusinine-I (**76**) described by Kato *et al.* (*312*). The required 2-(2-hydroxyphenylamino)-3,4,6-trimethoxy-*N,N*-dimethylbenzamide (**235**) was obtained by Ullmann reaction of 2-aminophenol with 2-iodo-3,4,6-trimethoxy-*N,N*-dimethylbenzamide (**236**), prepared in three steps from commercially available 2,4,5-trimethoxybenzoic acid (**237**) via *o*-lithiation of the corresponding amide and subsequent iodination. Benzylation of **235** to **238** was followed by phosphoryl chloride cyclization and hydrolysis of the intermediate with aqueous hydrochloric acid to give 5-benzyloxy-1,3,4-trimethoxyacridone (**239**) as the major product. Methylation to 5-benzyloxy-1,3,4-trimethoxy-10-methylacridone (**240**), followed by simultaneous hydrolysis of the benzyloxy group, and of the methoxy group at C-1, gave citrusinine-I I (**64**).



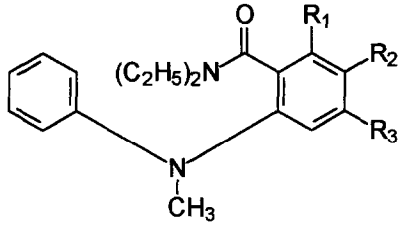
An efficient route for the preparation of *N*-arylanthranilamide precursors of acridones was described by Snieckus *et al.*, by oxidative coupling reaction of *o*-lithiated benzamides with anilido-chloro or –cyano cuprates (*313*). Thus, *o*-lithiated benzamides derived from *N,N*-diethylbenzamide (**241**), *N,N*-dimethyl-2-methoxybenzamide (**242**), *N,N*-dimethyl-2,4-dimethoxybenzamide (**243**), and *N,N*-dimethyl-2-methoxy-3,4-methylenedioxybenzamide (**244**), were treated with the anilidocuprate **245**, generated from the corresponding lithioanilide and CuCl. Oxygenation using molecular O_2 gave the *N*-arylanthranilamides **246-249**. Direct cyclization of these latter into the acridones **30**, **31**, **53** and **13** was effected by refluxing in heptafluorobutyric acid or trifluoroacetic acid.

Another approach to the acridone skeleton, developed by Watanabe *et al.* (*314*), was based on an earlier observation that small amounts of acridones were formed when benzynes were generated by diazotization of anthranilic acids (*315-317*). The acridones result in these cases from the reaction of benzynes with undiazotized anthranilic acids. Therefore, a new route was developed through tandem metallation synthesis. The lithium salt of methyl *N*-methylanthranilate (**250**) could be easily coupled with the benzynes **251**, **252**, and **253**, generated by treatment of chlorobenzene, 1-bromo-2-methoxybenzene, and 1-chloro-3,5-

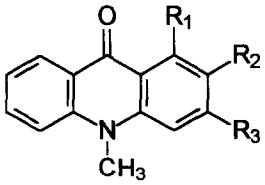


245

241 $R_1=R_2=R_3=H$
242 $R_1=OCH_3$, $R_2=R_3=H$
243 $R_1=R_3=OCH_3$, $R_2=H$
244 $R_1=OCH_3$, $R_2=R_3=OCH_2O$



246 $R_1=R_2=R_3=H$
247 $R_1=OCH_3$, $R_2=R_3=H$
248 $R_1=R_3=OCH_3$, $R_2=H$
249 $R_1=OCH_3$, $R_2=R_3=OCH_2O$

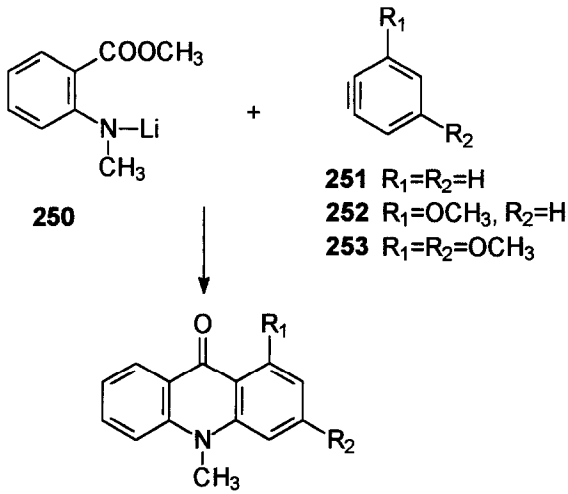


30 $R_1=R_2=R_3=H$
31 $R_1=OCH_3$, $R_2=R_3=H$
53 $R_1=R_3=OCH_3$, $R_2=H$
13 $R_1=OCH_3$, $R_2=R_3=OCH_2O$

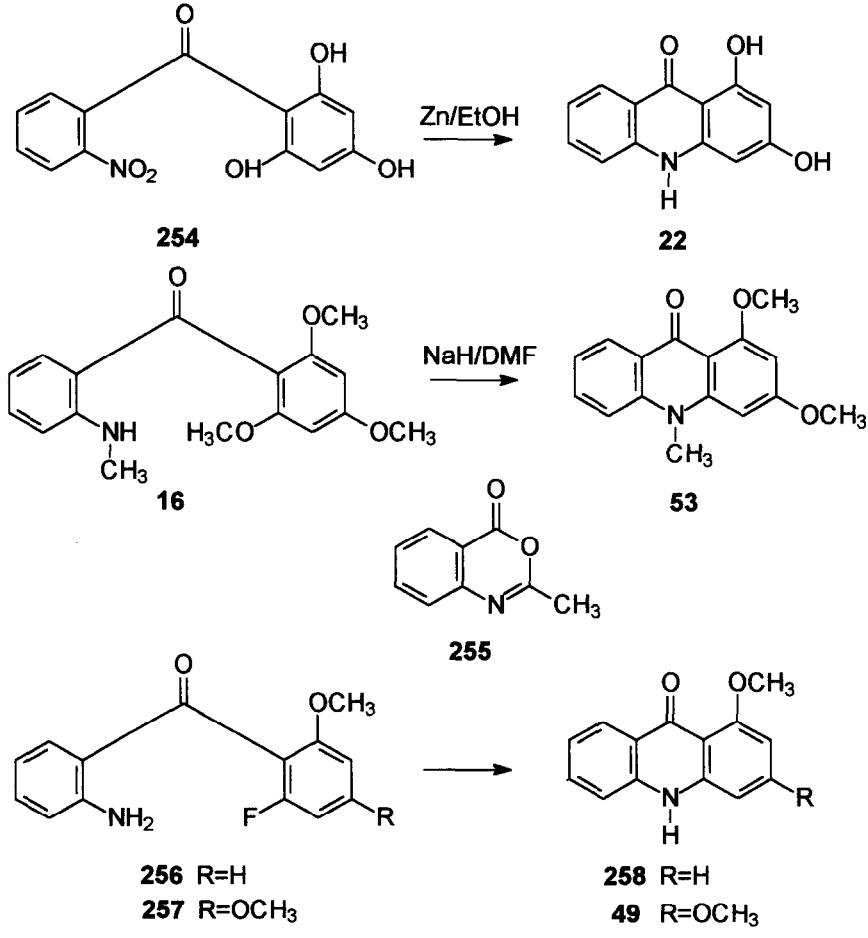
dimethoxybenzene with lithium *N*-isopropylcyclohexylamide in tetrahydrofuran, to give 10-methylacridone (**30**), 1-methoxy-10-methylacridone (**31**) and 1,3-dimethoxyacridone (**53**), respectively. The method could be successfully applied to a great variety of acridones, including the pyranoacridone alkaloid acronycine (*314*).

2. Methods Involving the Cyclization of a Benzophenone Intermediate

The isolation of the 2-methylaminobenzophenone alkaloid tecleanone (**16**) from various species of Rutaceae (*69-73*) led to the speculation that 9(10*H*)-acridinones should arise *in vivo* from the cyclization of 2-aminobenzophenones. A series of syntheses of acridone alkaloids, based on the cyclization of benzophenone intermediates, was subsequently developed by Lewis *et al.* (*74-79*). The feasibility of this approach was first demonstrated by the mild reduction of 2,4,6-trihydroxy-2'-nitrobenzophenone (**254**) with zinc dust in ethanol, which produced solely, and almost quantitatively, 1,3-dihydroxyacridone (**22**) (*74*). Methylation of one or more of the hydroxy-functions of **254** prevented cyclization concomitant with reduction (*76*). In contrast, cyclization of 2'-amino-, 2'-acetylamino-, or 2'-methylamino-2-methoxybenzophenones could be achieved at room temperature through the use of sodium hydride in dimethylformamide, whereby the corresponding acridones were obtained (*76*, *78*). The general scope of this method was exemplified by the biomimetic cyclization of tecleanone (**16**) into 1,3-dimethoxy-10-methylacridone (**53**) (*75*). Condensation of 2-methyl-3,1-benzoxazin-4-one (**255**), prepared from anthranilic acid and acetic anhydride by distillation, with the Grignard reagent of the appropriate bromomethoxybenzene, was the most convenient access to the starting aminobenzophenones (*76*).



A similar approach, using 2-amino-2'-fluorobenzophenones as key intermediates, was more recently developed by Horne and Rodrigo (*318*). The starting materials were prepared by Fries type rearrangement of *N*-tosyl-*o*-iodobenzanilides, triggered by lithium-iodine exchange at low temperature. Hydrolysis of the 2-tosylamidobenzophenones obtained gave the required 2-amino-2'-fluoro-6'-methoxybenzophenone (**256**) and 2-amino-2'-fluoro-4',6'-dimethoxybenzophenone (**257**). Cyclization, accomplished by the use of tetraethylammonium hydroxide, yielded 1-methoxyacridone (**258**) and 1,3-dimethoxyacridone (**49**), respectively, with complete regiospecificity, since only the fluorine, and not the equivalently situated methoxy, was replaced.

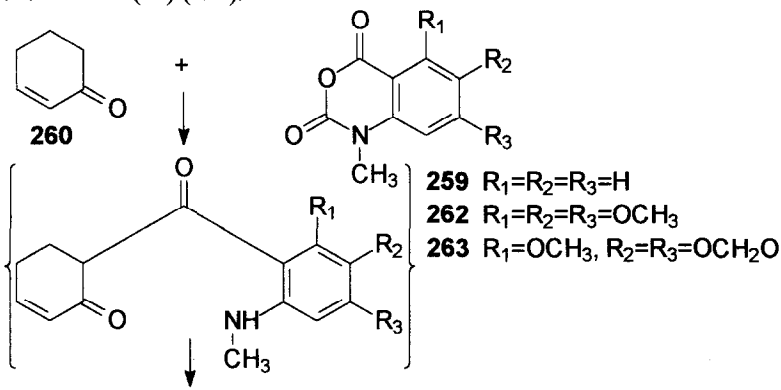


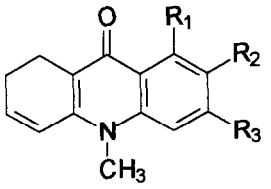
3. Condensation of an Isatoic Anhydride with the Enolate of a 2-Cyclohexen-1-one

The key step of the acridone synthesis introduced by Coppola is the condensation of a *N*-methylisatoic anhydride with the lithium enolate of a 2-cyclohexen-1-one. The formed diketo intermediate spontaneously cyclizes into a dihydroacridone, easily aromatized to the corresponding acridone. The versatility of this method, which enables carbon-carbon and carbon-nitrogen bond formation under very mild conditions, is illustrated by the efficient syntheses of the demethoxy analogues of natural furo and pyranoacridones (*319*, *320*), as well as by those of several naturally occurring alkaloids, including 10-methylacridone (**30**), 1,2,3-trimethoxy-10-methylacridone (**73**) and evoxanthine (**13**) (*293*).

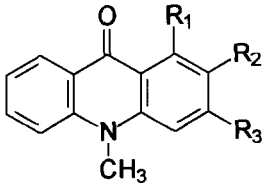
Condensation of *N*-methylisatoic anhydride (**259**) with the lithium enolate generated from 2-cyclohexen-1-one (**260**) gave a β-diketo species which spontaneously cyclized into 1,2-dihydro-10-methylacridone (**261**) during the work-up process. The dihydroacridone **261** was then quantitatively aromatized to 10-methylacridone (**30**) in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dichloromethane at room temperature (*293*).

Synthesis of 1,2,3-trimethoxy-10-methylacridone (**73**) and evoxanthine (**13**) by the same approach necessitated the preparation of 4,5,6-trimethoxy-*N*-methyl-isatoic anhydride (**262**) and 6-methoxy-4,5-methylenedioxy-*N*-methylisatoic anhydride (**263**). Nitration of 2,3,4-trimethoxybenzoic acid (**264**) afforded 6-nitro-2,3,4-trimethoxybenzoic acid (**265**) which was reduced to 6-amino-2,3,4-trimethoxybenzoic acid (**266**) by catalytic hydrogenation. Treatment of the sodium salt of this latter with phosgene provided 4,5,6-trimethoxyisatoic anhydride (**267**). Methylation on nitrogen with sodium hydride and methyl iodide furnished the desired *N*-methylisatoic anhydride **262**. Treatment of this anhydride with the lithium enolate of 2-cyclohexen-1-one (**260**) produced the expected dihydroacridone **268**, which was smoothly aromatized to 1,2,3-trimethoxy-10-methylacridone (**73**), using palladium-on-charcoal as dehydrogenating agent. The same reaction sequence applied to croweacic acid (**269**), prepared in three steps from commercially available 3-methoxycatechol (**270**) (*321*), gave an easy access to 6-methoxy-4,5-methylenedioxy-*N*-methylisatoic anhydride (**263**) and ultimately to evoxanthine (**13**) (*293*).

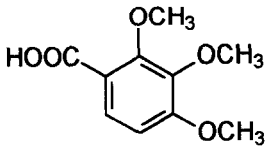




261 $R_1=R_2=R_3=H$
268 $R_1=R_2=R_3=OCH_3$



30 $R_1=R_2=R_3=H$
73 $R_1=R_2=R_3=OCH_3$
13 $R_1=OCH_3$, $R_2=R_3=OCH_2O$



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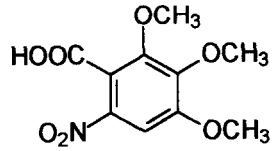

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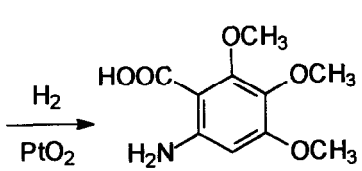

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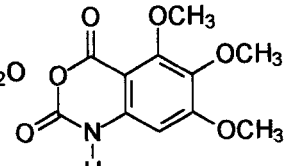

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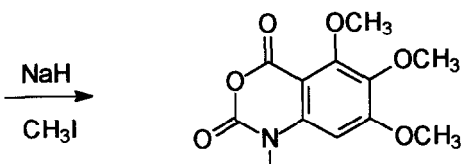

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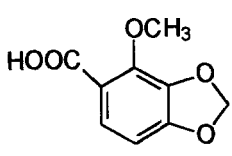

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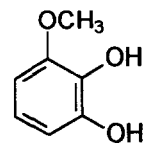

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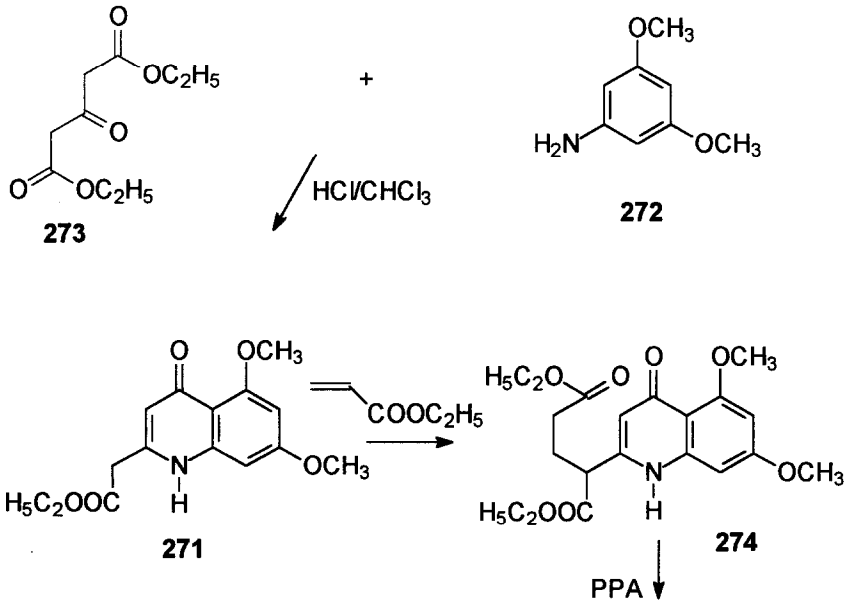
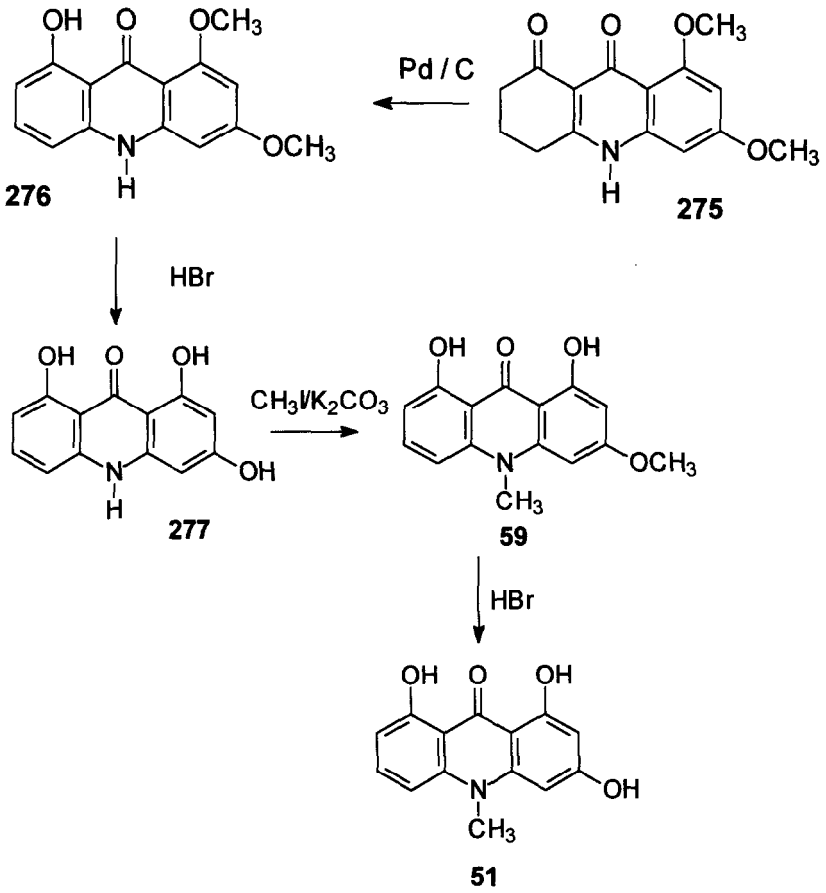
4. Aromatization of a 1,2,3,4,9,10-Hexahydroacridine-1,9-dione Prepared from a Quinolin-4-one

A stepwise approach employing successive construction of the acridone rings starting from an aniline precursor was recently reported by Deady *et al.* (*322, 294*). This versatile methodology is particularly useful to obtain acridones bearing an oxygen substituent at the 8-position, which are otherwise difficult to prepare. The final substitution pattern depends on the aniline chosen as the starting material. The synthesis of 1,3,8-trihydroxy-10-methylacridone (**51**), will illustrate this approach. Ethyl (1,4-dihydro-5,7-dimethoxy-4-oxoquinolin-2-yl)acetate (**271**) was prepared from 3,5-dimethoxyaniline (**272**) and diethyl 3-oxoglutarate (**273**) by the classical Conrad-Limpach method (*323, 294*). Michael addition of ethylacrylate, carried out in dimethylsulfoxide on the sodium salt of **271** preformed by reaction of sodium ethoxide in ethanol, afforded diethyl (1,4-dihydro-5,7-dimethoxy-4-oxoquinolin-2-yl)pentandioate (**274**). Hot polyphosphoric acid permitted cyclization to the corresponding 1,2,3,4,9,10-hexahydroacridine-1,9-dione **275**, with simultaneous loss of the ester group at the 4-position. Aromatization by refluxing in diphenyl ether containing palladium-on-charcoal gave 1,3-dimethoxy-8-hydroxyacridone (**276**). Demethylation with hydrobromic acid afforded 1,3,8-trihydroxyacridone (**277**), which was methylated with methyl iodide and potassium carbonate in acetone to 1,8-dihydroxy-3-methoxy-10-methyl-acridone (**59**). A second *O*-demethylation reaction finally gave 1,3,8-trihydroxy-10-methylacridone (**51**), identical with the natural product isolated from *Boronia lanceolata* (*115*).





B. *C*-PRENYLACRIDONES

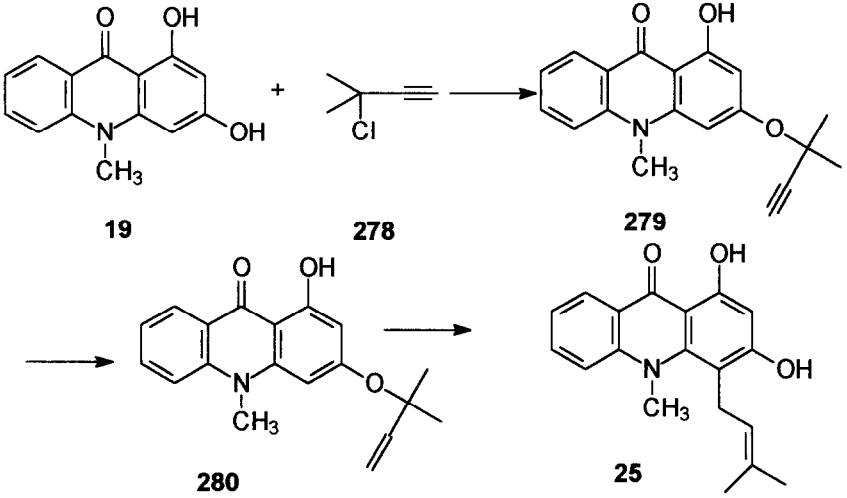
Two main strategies have been developed for the synthesis of *C*-prenylacridones. One applies *C*-alkylation to a preformed 1,3-dioxygenated acridone, taking advantage of the nucleophilicity of the two centers at C-2 and C-4. A second approach, mainly explored by Anand *et al.* envisages construction of the acridone nucleus in course of the synthesis.

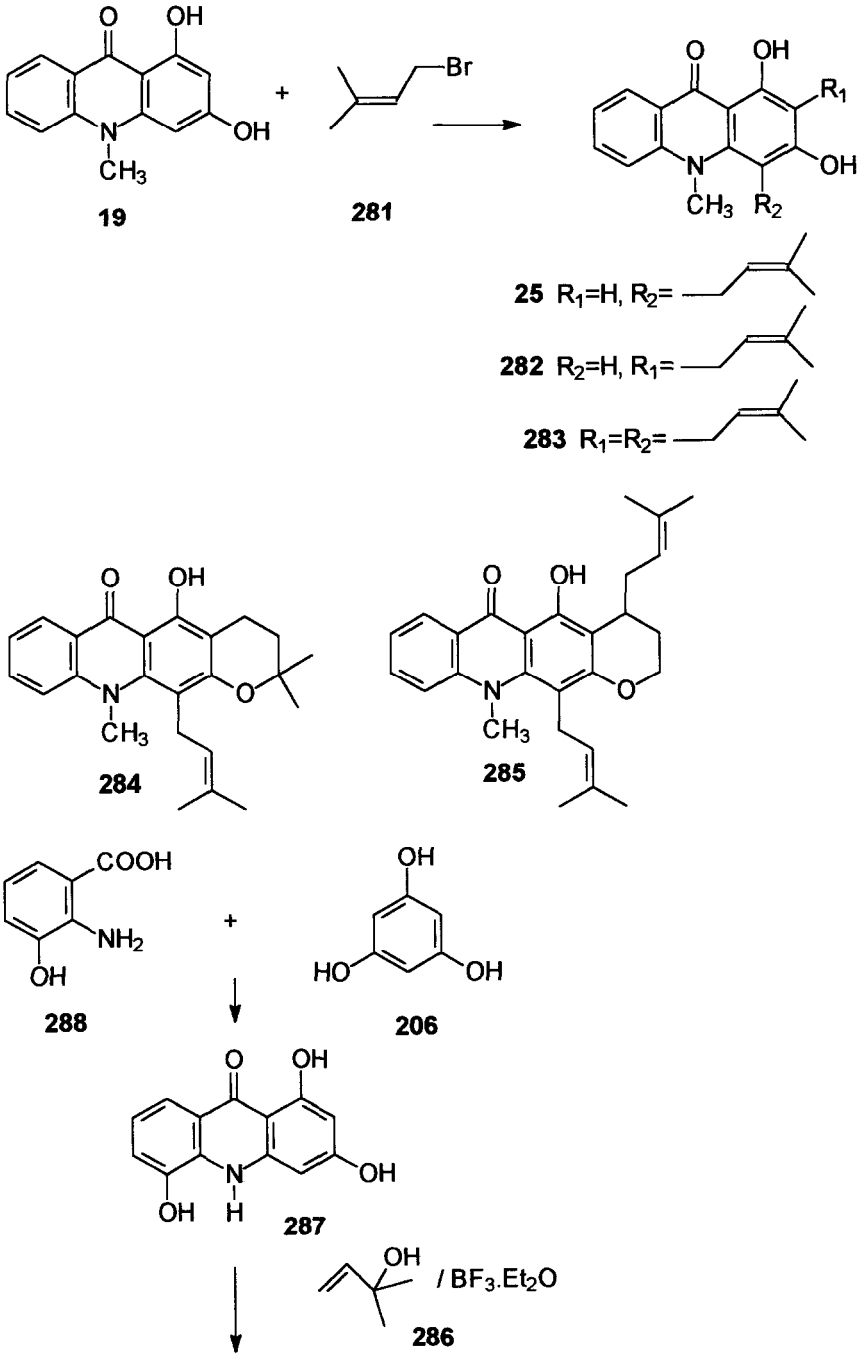
1. Syntheses by Alkylation of a Preformed Acridone Nucleus

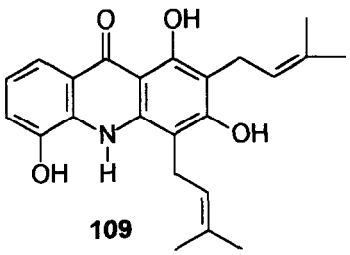
Prior to its isolation from *Glycosmis citrifolia* (*81*), glycocitrine-II (**25**), one of the simplest *C*-prenylated acridone alkaloids, was obtained synthetically by Hlubucek *et al.* in the course of their synthesis of the pyranoacridone alkaloid acronycine (*286*). Treatment of 1,3-dihydroxy-10-methylacridone (**19**) with 3-chloro-3-methyl-1-butyne (**278**) (*324, 325*), in dimethylformamide in the presence of potassium carbonate and sodium iodide gave the acetylenic ether **279**. Partial hydrogenation using the Lindlar catalyst afforded the corresponding α,α-dimethylallyl ether **280**, which underwent regioselective Claisen rearrangement in boiling diethylaniline to yield glycocitrine-II (**25**) as the single reaction product.

A more straightforward access to glycocitrine-II (**25**) was described by Grundon and Reisch, through direct *C*-alkylation of 1,3-dihydroxy-10-methylacridone (**19**) with one equivalent of the readily available 1-bromo-3-methyl-2-butene (**281**), in tetrahydrofuran at 20°C, in the presence of alumina in order to prevent *O*-alkylation (*326*). The isomeric 1,3-dihydroxy-10-methyl-2-(3-methyl-2-butenyl)-acridone (**282**) and the dialkylated 1,3-dihydroxy-10-methyl-2,4-bis(3-methyl-2-butenyl)-acridone (**283**) were also formed during the reaction. Excess of alkylating agent resulted in the formation of tetracyclic compounds **284** and **285**.

The use of 2-methyl-3-buten-2-ol (**286**) in the presence of boron trifluoride etherate permitted dialkylation of 1,3,5-trihydroxyacridone (**287**), prepared by condensing phloroglucinol (**206**) and 3-hydroxyanthranilic acid (**288**), into atalaphylline (**109**) and to confirm the structure of this latter alkaloid. Nevertheless, the reaction proceeded in poor yield and the monoalkylated product **289** was also isolated from the reaction mixture (*221*).




O
OH
N
CH3
OH
19
+
Br
281
R1
R2
25 R1=H, R2=
282 R2=H, R1=
283 R1=R2=
284
285
COOH
NH2
OH
288
HO
206
287
/ BF3.Et2O
286



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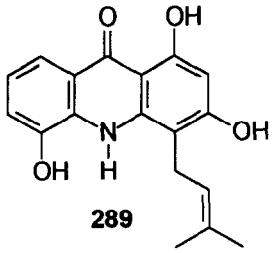

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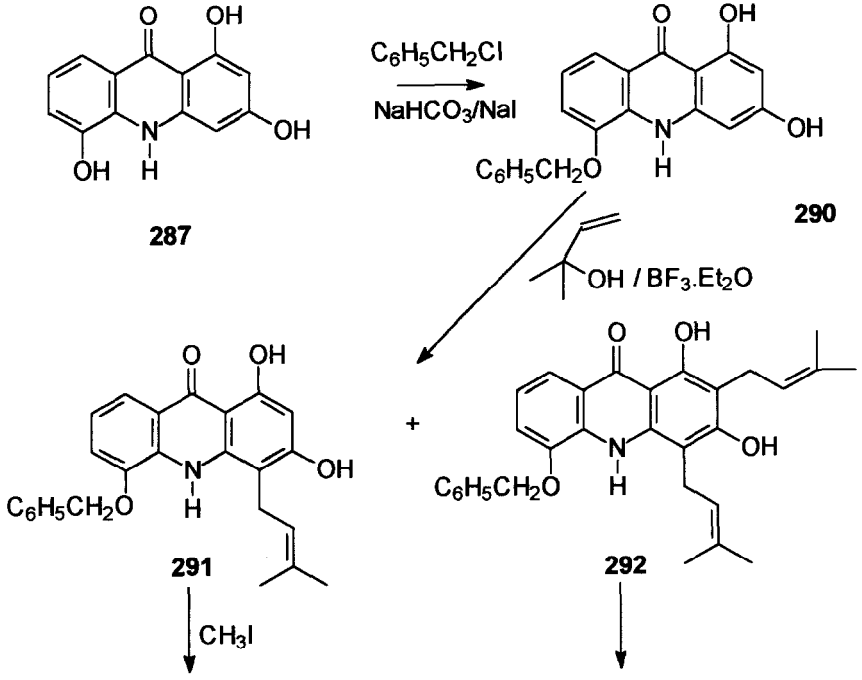
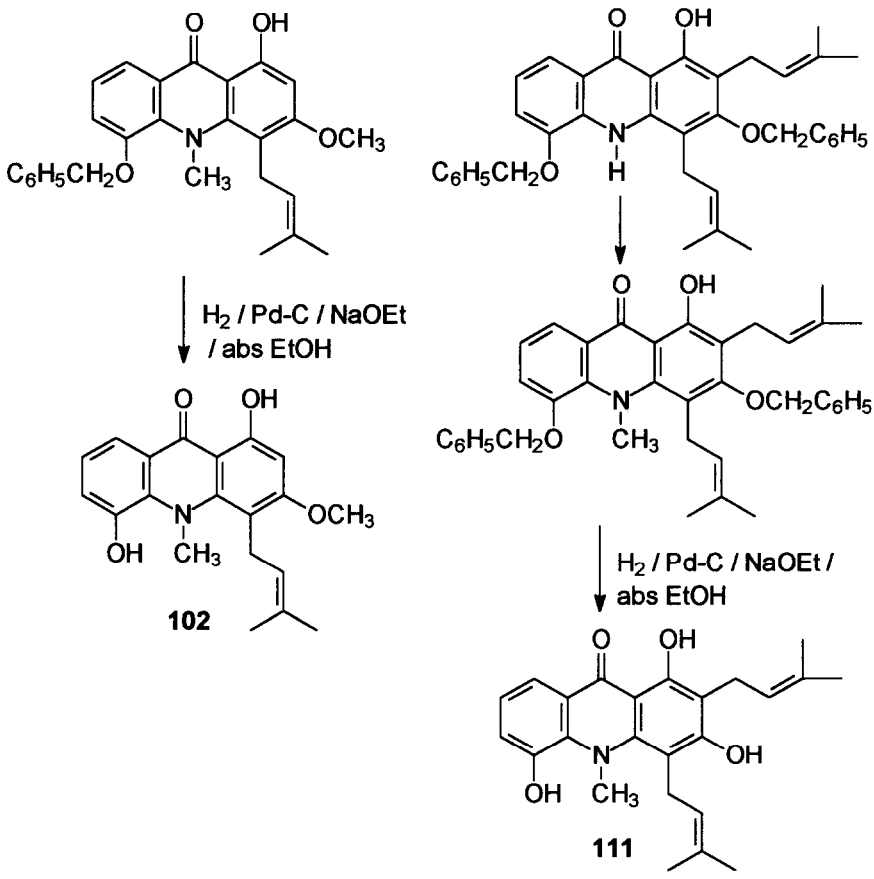
Similarly, regioselective benzylation of 1,3,5-trihydroxyacridone (**287**) gave 1,3-dihydroxy-5-benzyloxyacridone (**290**), which, on prenylation with 2-methyl-3-buten-2-ol (**286**) and boron trifluoride etherate, afforded a mixture of monoprenylated 1,3-dihydroxy-5-benzyloxy-4-(3-methyl-2-butenyl)-acridone (**291**) and diprenylated 1,3-dihydroxy-5-benzyloxy-2,4-bis(3-methyl-2-butenyl)-acridone (**292**). Treatment of **291** with methyl iodide, followed by hydrogenolysis with palladium-on-charcoal, furnished glycocitrine-I (**102**). Benzylation of **292**, followed by *N*-methylation and debenzylation yielded *N*-methyl atalaphylline (**111**) (*289*).



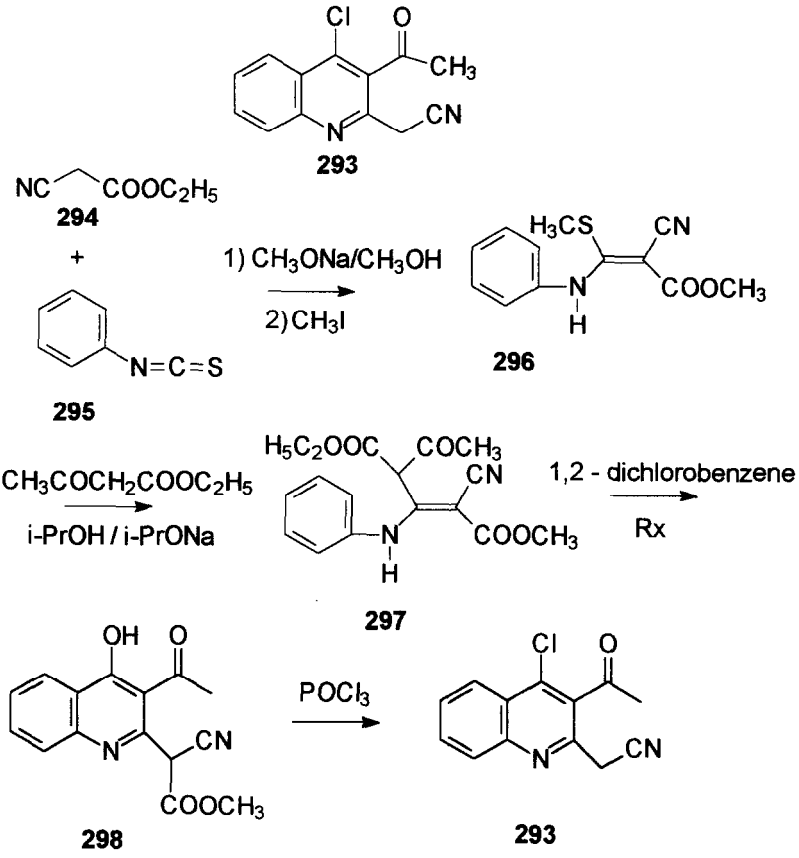
287 290 291 292



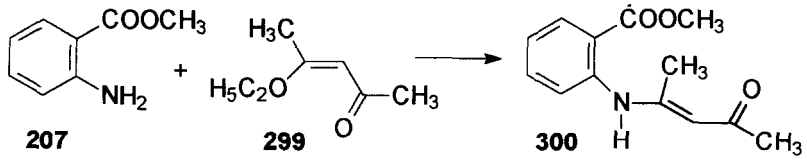
2. Syntheses Involving the Construction of the Acridone Nucleus

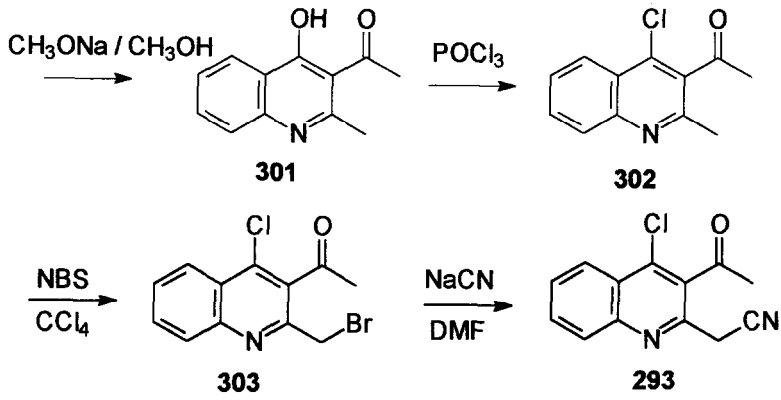
The key intermediate in the regioselective synthesis of glycocitrine-II (**25**) by Anand and Sinha was 3-acetyl-4-chloro-2-cyanomethylquinoline (**293**), which was obtained by two independent routes (*327, 328*).

The first one involved reaction of the carbanion of ethyl cyanoacetate (**294**) with phenylisothiocyanate (**295**), followed by addition of methyl iodide to afford the ketene *S, N*-ketal **296**. Substitution of the methylthio group of **296** by the carbanion of ethyl acetoacetate in refluxing isopropanol yielded the ketoester **297**. Refluxing in 1,2-dichlorobenzene permitted cyclization of the ethoxycarbonyl group onto the phenyl ring, to give the quinoline **298**. Treatment of **298** with phosphoryl chloride at 120-125°C for 5 hours transformed the 4-hydroxy group into a 4-chloro group, with simultaneous demethoxycarbonylation, affording the required 3-acetyl-4-chloro-2-cyanomethylquinoline (**293**).

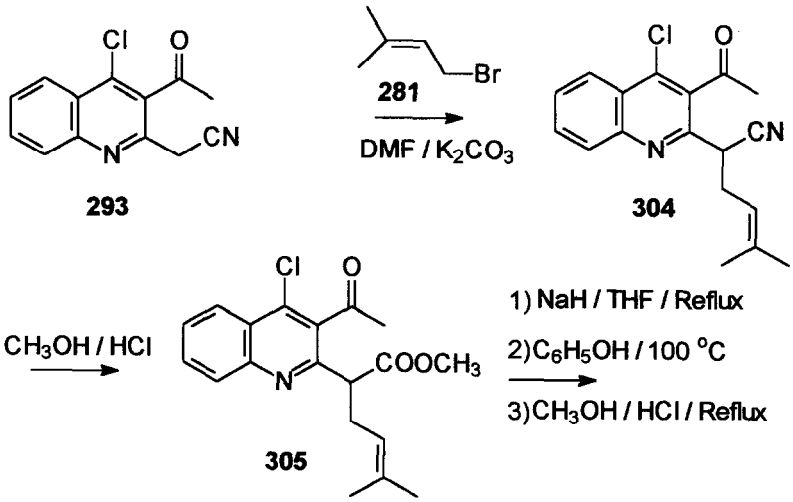


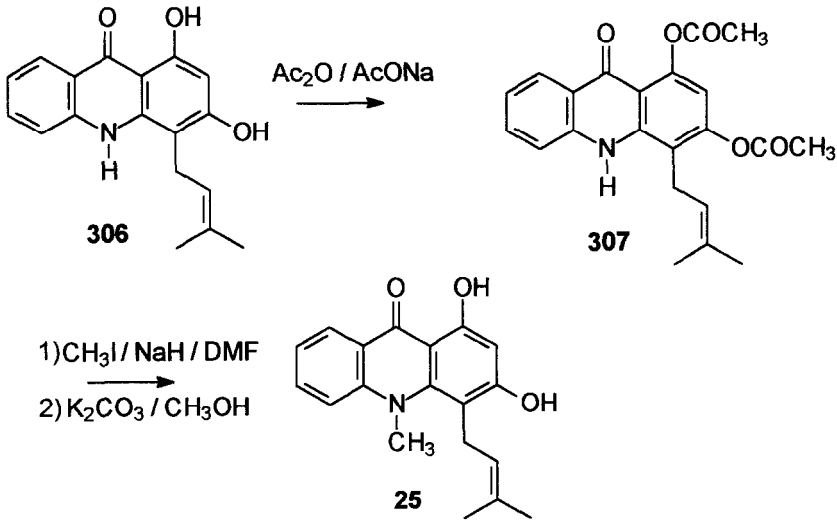
Alternatively, the ethoxy group in the ethyl enol ether of acetylacetone (**299**) was substituted by heating with methyl anthranilate (**207**) in 1,2-dichlorobenzene to give the enaminone **300.** Cyclization of **300** to 3-acetyl-4-hydroxy-2-methylquinoline (**301**) was catalyzed by sodium methoxide. The corresponding 4-chloro derivative **302** was obtained by heating **301** with phosphoryl chloride. Functionalization of **302** by bromination with *N*-bromosuccinimide gave **303**, which was converted to the desired 3-acetyl-4-chloro-2-cyanomethylquinoline (**293**) upon treatment with sodium cyanide in dimethylformamide.



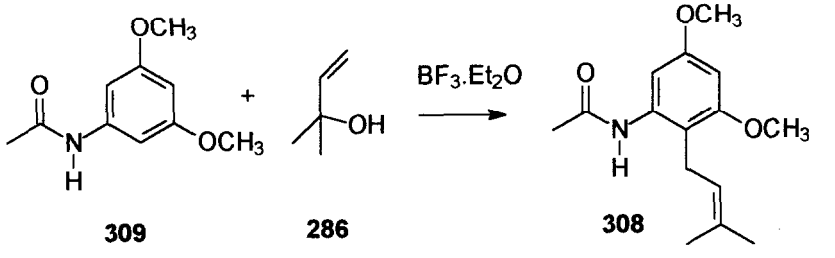


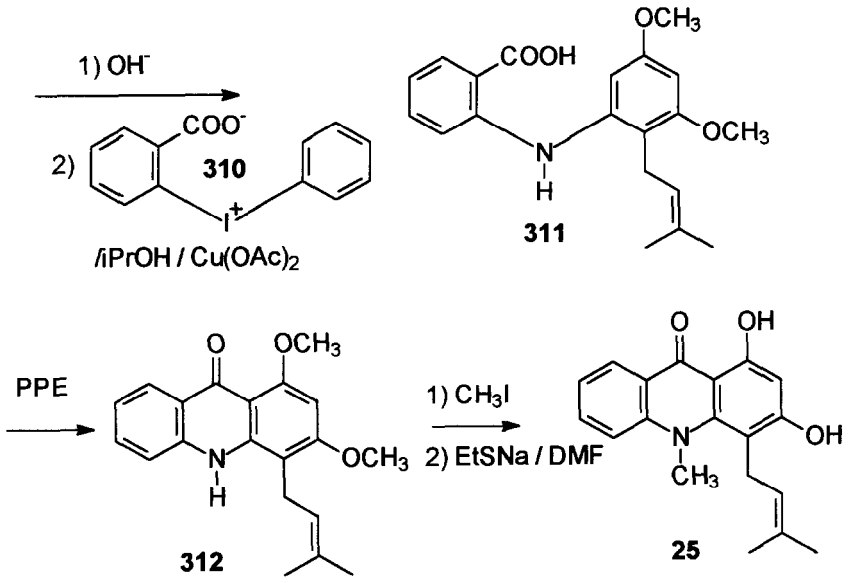
Alkylation of **293** with 1-bromo-3-methylbut-2-ene (**281**), performed in dimethylformamide in the presence of potassium carbonate, afforded **304** in good yield. Methanolysis of the nitrile group of **304** gave ketoester **305**. Cyclization of **305** was carried out by refluxing with sodium hydride in tetrahydrofuran, followed by heating with phenol at 100°C and refluxing the crude product obtained with hydrochloric acid, to provide 10-demethylglycocitrine-II (**306**). Acetylation of the phenolic hydroxy groups of **306** by acetic anhydride and sodium acetate gave the diacetate **307**. *N*-Methylation of this compound with methyl iodide and sodium hydride in dimethylformamide, followed by hydrolysis of the crude product in the presence of potassium carbonate, finally afforded glycocitrine-II (**25**).



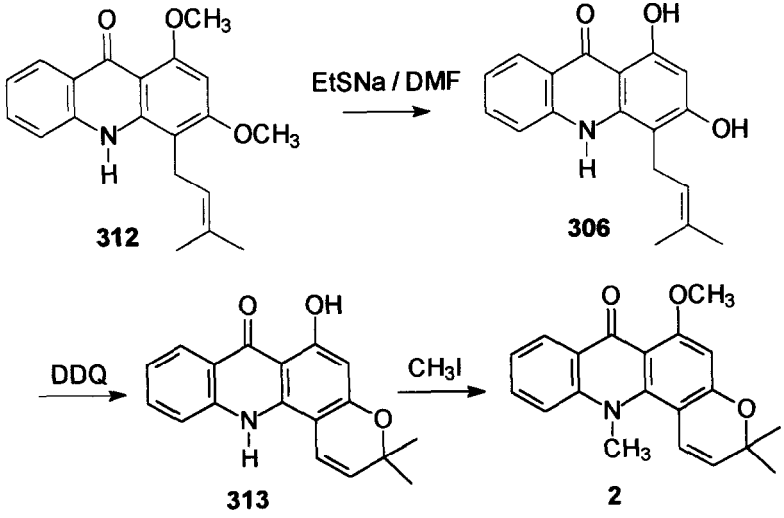


Another regioselective synthesis of glycocitrine-II, recently achieved by Anand and Selvapalam, was based on the initial observation that 3,5-dimethoxy-2-(3-methylbut-2-enyl)-acetanilide (**308**) was obtained in good yield when 3,5-dimethoxyacetanilide (**309**) and 3-methyl-1-buten-3-ol (**286**) were refluxed in dioxane in the presence of a catalytic amount of boron trifluoride etherate (*329*). Alkaline hydrolysis of **308**, followed by condensation of the corresponding crude aniline with diphenyliodonium-2-carboxylate (**310**) in isopropanol in the presence of cupric acetate, afforded the prenylated carboxylic diphenylamine **311**. Despite the fragility of the prenyl group, **311** could be efficiently cyclized to the corresponding 1,3-dimethoxy-4-(3-methylbut-2-enyl)-acridone (**312**), upon treatment with polyphosphoric ester under rigorously anhydrous conditions, followed by quenching the reaction mixture through the slow addition to cold sodium bicarbonate solution. Transformation of **312** into glycocitrine-II (**25**) was carried out by *N*-methylation with methyl iodide, followed by demethoxylation of the crude product by sodium ethanethiolate in dimethylformamide.





It should be noted that the key intermediates in the various syntheses of glycocitrine-II by Anand *et al.* also furnished an interesting access to the pyrano[2,3-*c*]acridin-7-one series. For instance, demethoxylation of intermediate **312** with sodium ethanethiolate in dimethylformamide gave **306**, which could be cyclized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to 12-demethylnoracronycine (**313**). Methylation of this latter product afforded acronycine (**2**) (*329*).

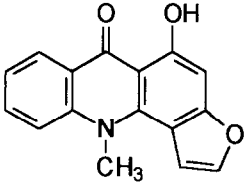


C. FURANOACRIDONES

The three, naturally occurring, angular furanoacridone alkaloids furacridone (= furofoline-I) (**26**), rutacridone (**14**), and hallacridone (**117**) were synthesized by the group of Reisch, using 1,3-dihydroxy-10-methylacridone (**19**) as a starting material. Oxidation reactions performed on rutacridone (**14**) permitted access to several other furano and difuranoacridones, including gravacridonol (**121**), gravacridondiol (**127**), and rutagravine (**124**).

1. Synthesis of Furacridone

Selective etherification of the 3-hydroxy group of 1,3-dihydroxy-10-methylacridone (**19**) with excess bromoacetaldehyde diethylacetal in dry dimethylformamide, either by use of sodium hydride at 120°C in a bomb, or in the presence of potassium carbonate at 100°C under nitrogen, afforded 3-(2,2-diethoxyethoxy)-1-hydroxy-10-methylacridone (**314**). Cyclodehydration of **314** by refluxing in a mixture of dioxane and dilute aqueous sulfuric acid, followed by alkalization by addition of sodium hydroxide and heating, gave the desired furacridone (**26**), accompanied by smaller amounts of the linear isomer, isofuracridone (**315**) (*330*).



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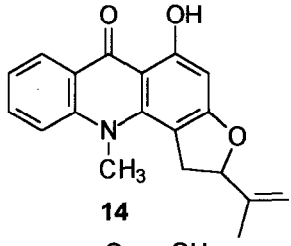

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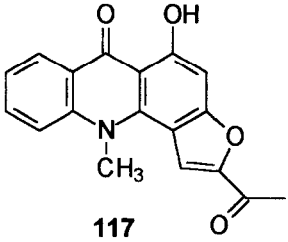

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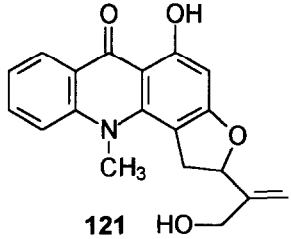

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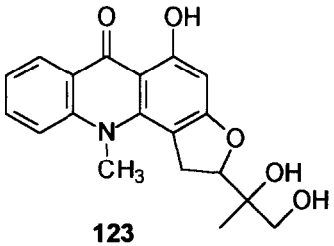

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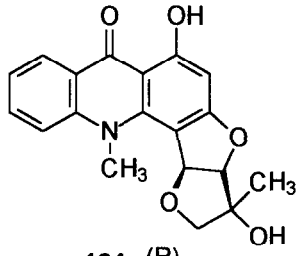

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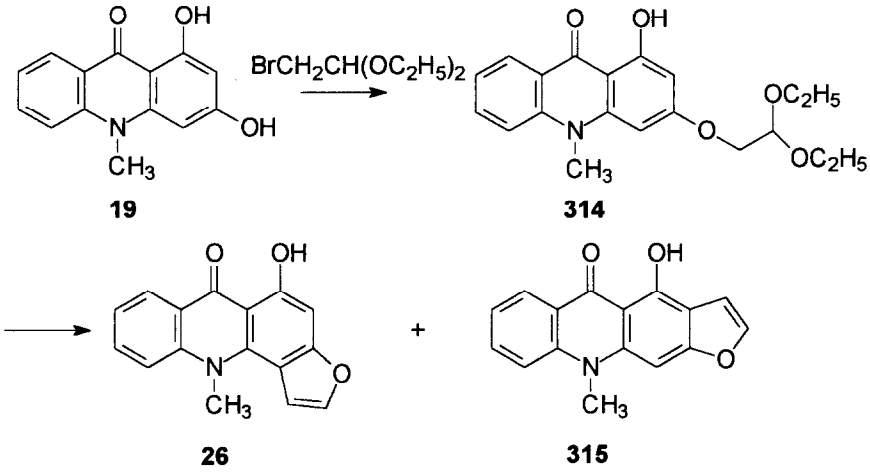
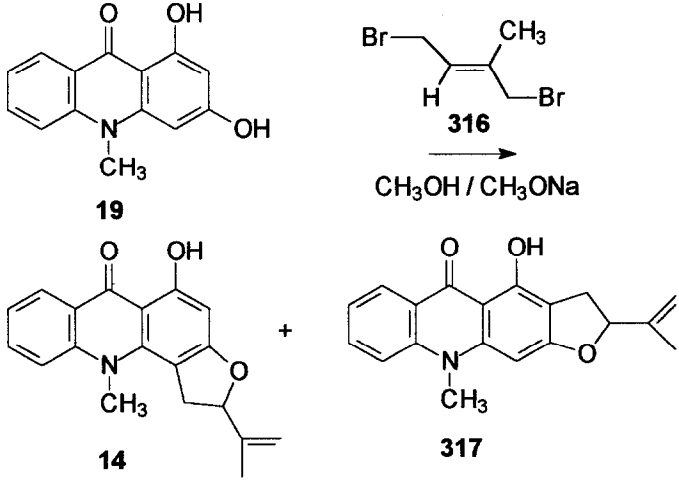


2. Synthesis of Rutacridone and Related Alkaloids

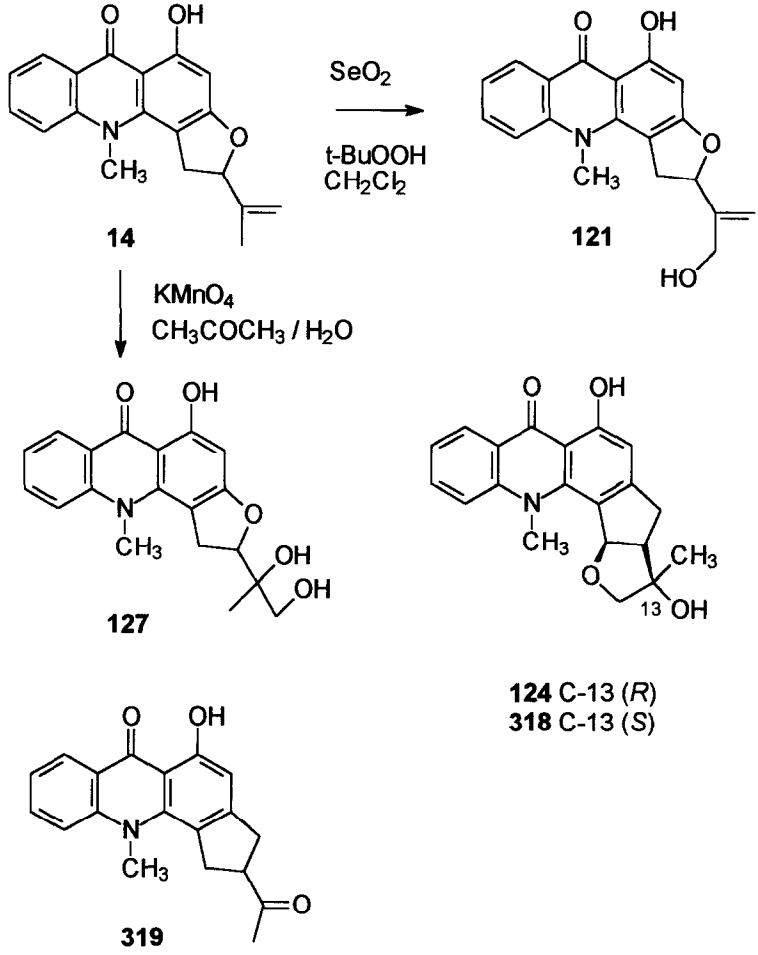
Alkylation of 1,3-dihydroxy-10-methylacridone (**19**) with 1,4-dibromo-2-methyl-2-butene (**316**) in methanol containing sodium methoxide, using the procedure of Nickl for the synthesis of isopropenylbenzofuran derivatives (*331*), produced rutacridone (**14**), together with smaller amounts of its linear isomer isorutacridone (**317**) (*332*). The overall yield of the reaction and the percentage of isomers obtained greatly depended on the base used to catalyze the reaction (*333*). Rutacridone (**14**) and isorutacridone (**317**) were obtained in 77% combined yield under optimized conditions, when the reaction was carried out in tetrahydrofuran at room temperature, using Amberlite® IRA 68 anion exchange resin as the alkaline agent (*334*).



Allylic oxidation of rutacridone (**14**) with selenium dioxide and *t*-butylhydroperoxide in dichloromethane at room temperature afforded gravacridonol (**121**) in 23% yield (*335*). In contrast, oxidation of rutacridone (**14**) with aqueous potassium permanganate in acetone gave a mixture of gravacridondiol (**127**), rutagravine (**124**), its isomer **318**, and dihydrohallacridone (**319**). This latter compound could be further oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone into the fully aromatic hallacridone (**117**) (*336*).

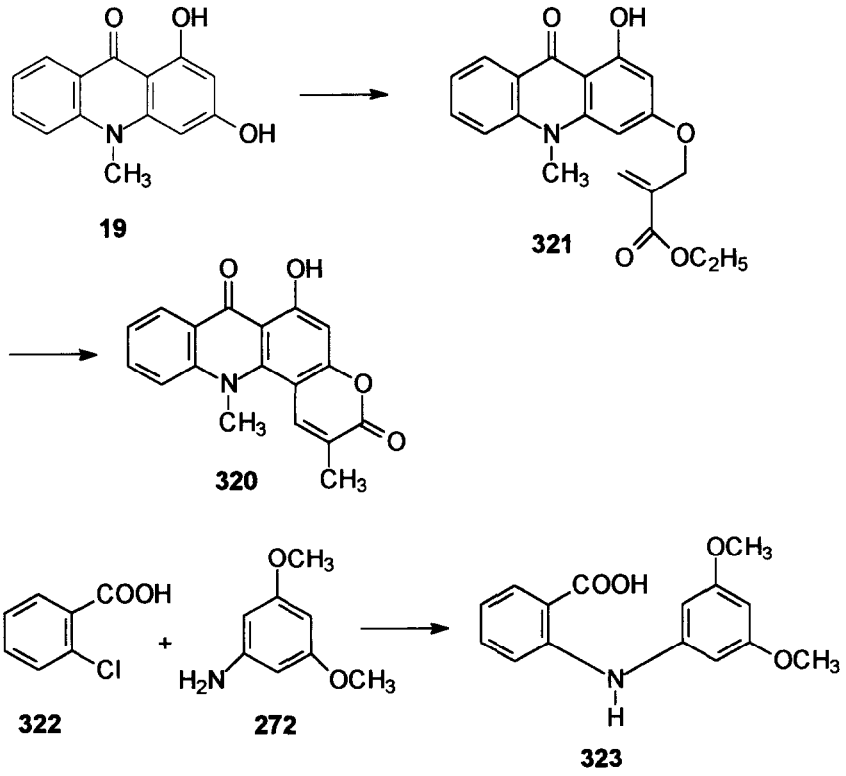
3. Synthesis of Hallacridone

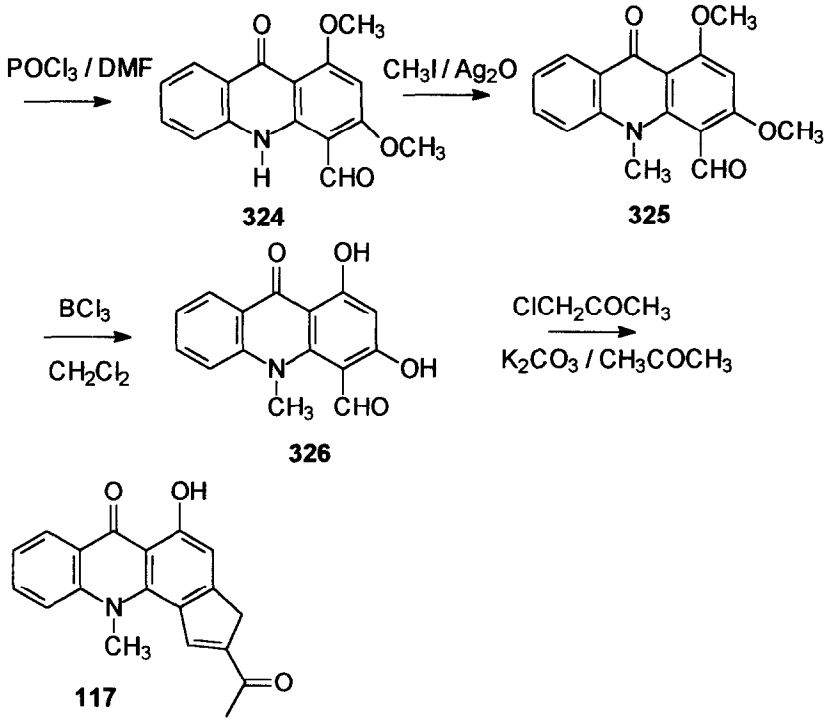
Hallacridone is a minor alkaloid obtained from the tissue cultures of *Ruta graveolens*, whose structure was first tentatively assigned as 6-hydroxy-2,12-dimethyl-3*H*-pyrano[2,3-*c*]acridine-3,7(12*H*)-dione (**320**) on the basis of spectroscopic evidence (*232*, *230*). Reisch and Gunaherath synthesized **320** in two steps, starting from 1,3-dihydroxy-10-methylacridone (**19**) (*233*).



Condensation of **19** with ethyl bromomethacrylate gave the corresponding ether **321**. Heating **321** in polyoxyethyleneglycol afforded the desired **320**, by regioselective *o*-Claisen rearrangement and ring closure, followed by double-bond isomerization. The compound obtained was different from natural hallacridone, whose structure was consequently revised to 2-acetyl-5-hydroxy-11-methylfuro[2,3-*c*]acridin-6(11*H*)-one (**117**) (*233*).

This result was unambiguously confirmed by the total synthesis of **117**. Ullmann condensation between 2-chlorobenzoic acid (**322**) and 3,5-dimethoxyaniline (**272**) gave 3',5'-dimethoxydiphenylamine-2-carboxylic acid (**323**), which underwent simultaneous formylation and cyclization, upon treatment with dimethylformamide and phosphoryl chloride, to yield 4-formyl-1,3-dimethoxydroxyacridone (**324**). *N*-Methylation to 4-formyl-1,3-dimethoxy-10-methylacridone (**325**) on treatment with methyl iodide and silver oxide was followed by complete *O*-demethylation with excess boron trichloride in dichloromethane. Darzens condensation between 4-formyl-1,3-dihydroxy-10-methylacridone (**326**) and monochloroacetone in the presence of potassium carbonate in anhydrous acetone gave 2-acetyl-5-hydroxy-11-methylfuro[2,3-*c*]acridin-6(11*H*)-one (**117**), identical with natural hallacridone (*233*).





324 325 326 117

D. PYRANOACRIDONES

The synthesis of natural pyranoacridone alkaloids and analogues has received more attention than that of their furano counterparts, due to the interesting antitumor properties exhibited by acronycine and some of its derivatives. Two main strategies have been developed for the synthesis of pyrano[2,3-*c*]acridin-7-one and pyrano[3,2-*b*]acridin-7-one alkaloids.

The first one envisages alkylation of a preformed 1,3-dioxygenated acridone comprising the ABC tricyclic portion of the alkaloid by a C_5 unit, and elaboration of the pyran D ring from this unit, by simultaneous or subsequent cyclization.

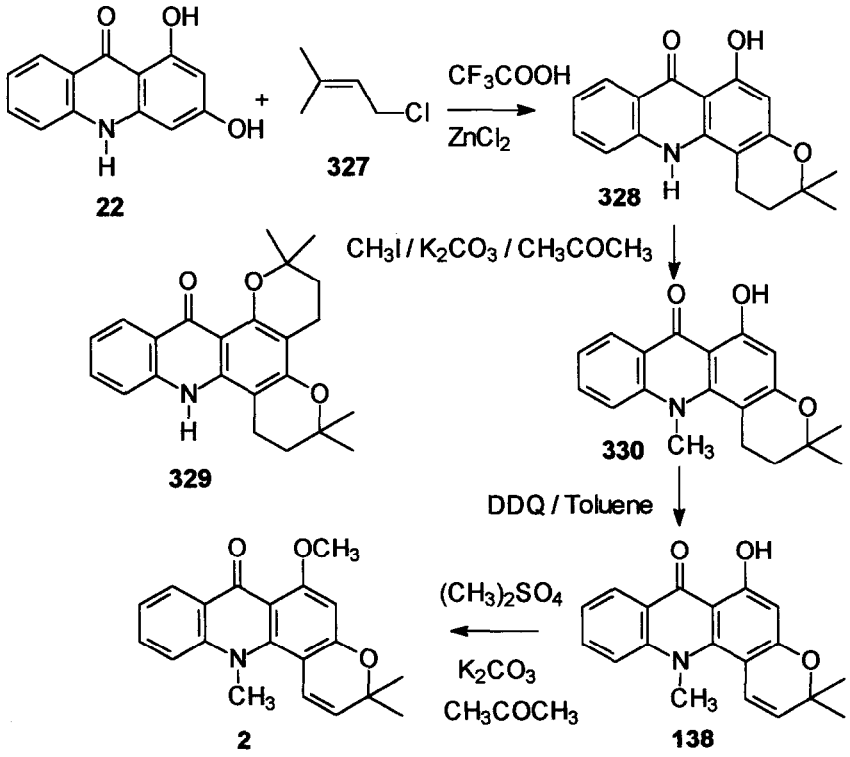
The second involves construction of the acridone nucleus in the course of the synthesis. The main approaches used in this latter case are very similar to those which permitted access to the simple acridone alkaloids, e.g. (i) cyclization of a diarylamine intermediate, (ii) cyclization of a benzophenone intermediate, or (iii) construction of the acridone system starting from a quinoline or a quinolinone which bring together the A and B or B and C rings of the acridone skeleton.

In addition, oxidation reactions performed on pyranoacridones led to several alkaloids modified on the C and D rings, and to acronycine analogues with improved antitumor activity.

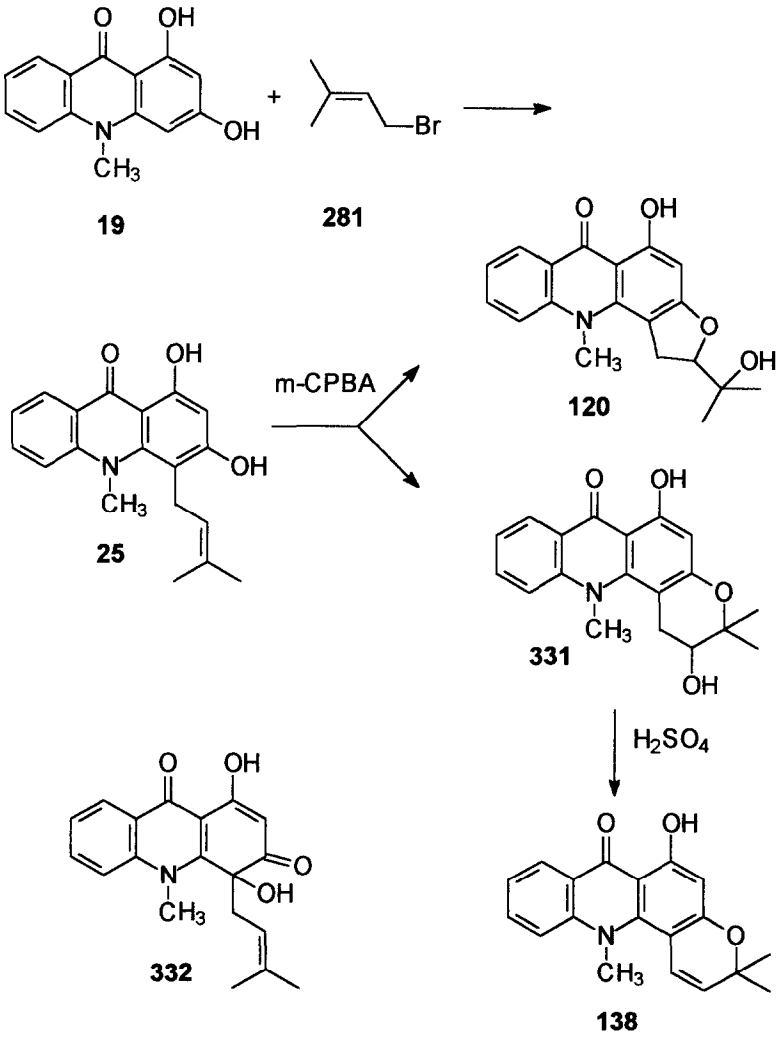
1. Syntheses Starting from a Preformed Acridone Nucleus

Three different types of reagents have been used for the alkylation of 1,3-dioxyacridones and subsequent construction of the fused dimethylpyran D ring of pyranoacridone alkaloids. 1-Halo-3-methyl-2-butenes enable cyclization to a dihydrodimethylpyran ring, and dehydrogenation or oxidation has to take place in the course of the synthesis, in order to obtain the desired pyranoacridone. In contrast, the use of the tertiary alcoholic 3-hydroxyisovaleraldehyde dimethylacetal and of the acetylenic 3-chloro-3-methyl-1-butyne permit direct cyclization to the required dimethylpyran.

a. 1-Halo-3-methyl-2-butenes. In one of the first syntheses of acronycine, Beck *et al.*, at the Eli Lilly Research Laboratories, condensed 1,3-dihydroxyacridone (**22**) with 1-chloro-3-methyl-2-butene (**327**) in trifluoroacetic acid, in the presence of zinc chloride as catalytst (*285*, *290*). Under such conditions, 1,2-dihydro-12-demethylnoracronycine (**328**) was obtained in moderate yield, together with the bischromane **329**. Methylation of **328** with methyl iodide and potassium carbonate in acetone afforded 1,2-dihydronoracronycine (**330**), which was subsequently dehydrogenated into noracronycine (**138**) by refluxing in toluene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Finally, methylation of **138** by methyl sulfate and potassium carbonate in acetone gave acronycine (**2**).

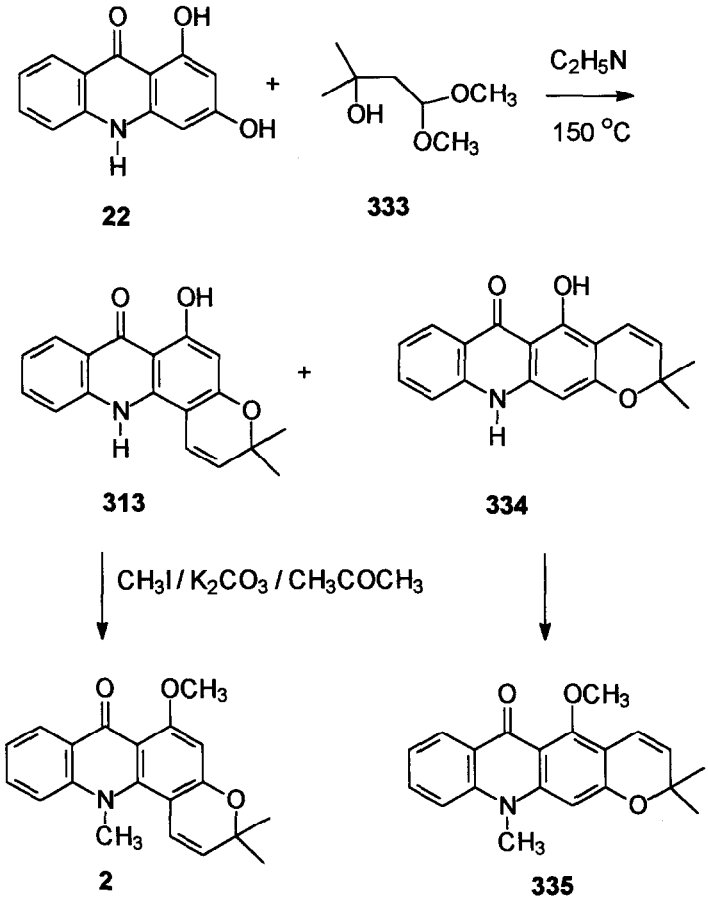


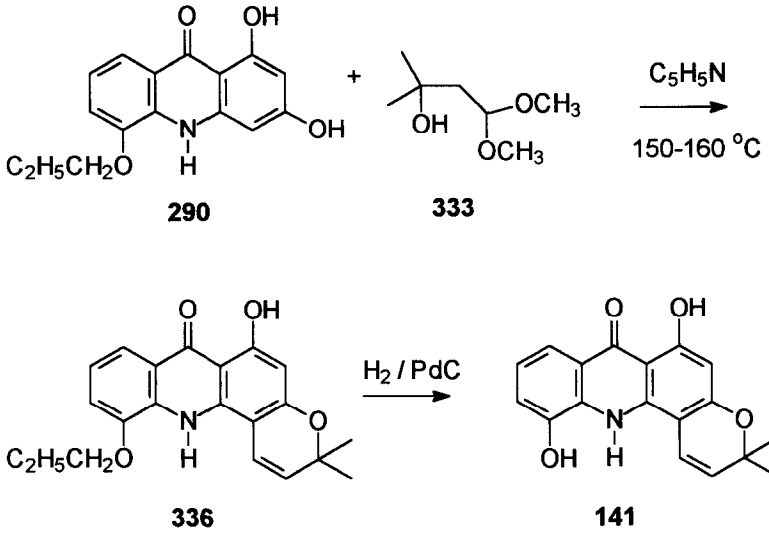
More recently, when studying the biomimetic condensation of 1,3-dihydroxy-10-methylacridone (**19**) with one equivalent of 1-bromo-3-methyl-2-butene (**281**) in the presence of alumina, Grundon and Reisch obtained glycocitrine-II (**25**). Oxidative cyclization of **25** with 3-chloroperbenzoic acid gave 2-hydroxy-1,2-dihydronoracronycine (**331**), accompanied by its dihydrofuran isomer **120**. Dehydration of **331**, by concentrated sulfuric acid afforded noracronycine (**138**) (*326*). Moreover compound **332** was obtained during the oxidative cyclization of **25** (*337*)



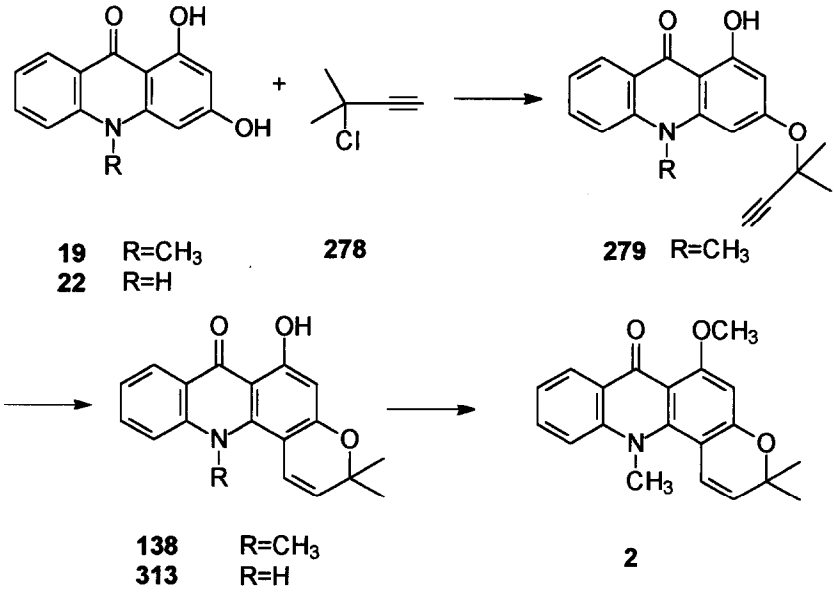
b. 3-Hydroxyisovaleraldehyde dimethylacetal. In 1969, Crombie *et al.* introduced the use of 3-hydroxyisovaleraldehyde dimethylacetal (**333**) for the dimethylchromenylation of phenols (*338*). The method was applied to the synthesis of acronycine (**2**) (*339*). Thus, condensation of 1,3-dihydroxyacridone (**22**) with the hydroxy-acetal **333** in pyridine at 150°C afforded 12-demethylnoracronycine (**313**), accompanied by its linear isomer **334**. Usual methylation with excess methyl iodide and potassium carbonate in acetone gave acronycine (**2**) from **313** and isoacronycine (**335**) from **334** (*340*).

The same approach was used later by Kapil *et al.* for the synthesis of atalaphyllidine (**141**) (*289*). Condensation of 1,3-dihydroxy-5-benzyloxyacridone (**290**) with 3-hydroxyisovaleraldehyde dimethylacetal (**333**) gave **336** which was readily debenzylated into atalaphyllidine (**141**) by palladium-on-charcoal and sodium acetate in refluxing ethanol.





c. 3-Chloro-3-methyl-1-butyne. Hlubucek, Ritchie, and Taylor introduced in 1969 the employment of 3-chloro-3-methyl-1-butyne (**278**) (*324, 325*) for the synthesis of 2,2-dimethylchromenes by the *O*-alkylation of phenols, followed by Claisen rearrangement (*341*). The method was applied by the same authors to several interrelated syntheses of acronycine (**2**) (*286, 342*). When 1,3-dihydroxy-10-methylacridone (**19**) was used as a starting material, the propargyl ether **279** was obtained in 70% yield upon treatment with 3-chloro-3-methyl-1-butyne (**278**) in dimethylformamide in the presence of potassium carbonate and potassium iodide at 52°C. Etherification of the 1-hydroxyl group was precluded, due to hydrogen bonding with the carbonyl at the 9-position. Claisen rearrangement performed on **279**, by refluxing in *N,N*-diethylaniline, provided noracronycine (**138**) in almost 90% yield. When the same reaction sequence was applied to 1,3-dihydroxyacridone (**22**), the Claisen rearrangement occurred during the etherification. The corresponding pure ether was not isolated. Heating the crude reaction mixture in dimethylformamide at 130°C gave 12-demethylnoracronycine (**313**) in 85% yield from **22**. In crude products obtained from these cyclization reactions, no traces of corresponding linear isomers could be detected by tlc, but Fryer *et al.*, when repeating these experiments, could isolate minute amounts of isomeric products belonging to the pyrano[3,2-*b*]acridin-7-one series (*343*). Finally, classical methylation reactions performed on **138** and **313** afforded acronycine (**2**). As far as overall yields are concerned, this approach towards pyrano[2,3-*c*]acridin-7-one alkaloids is certainly one of the most successful. This is probably the reason why several modifications (*344*), improvements (*345*), and applications to the preparation of related natural alkaloids (*346*) or synthetic congeners (*340, 347-353*) were published subsequently.

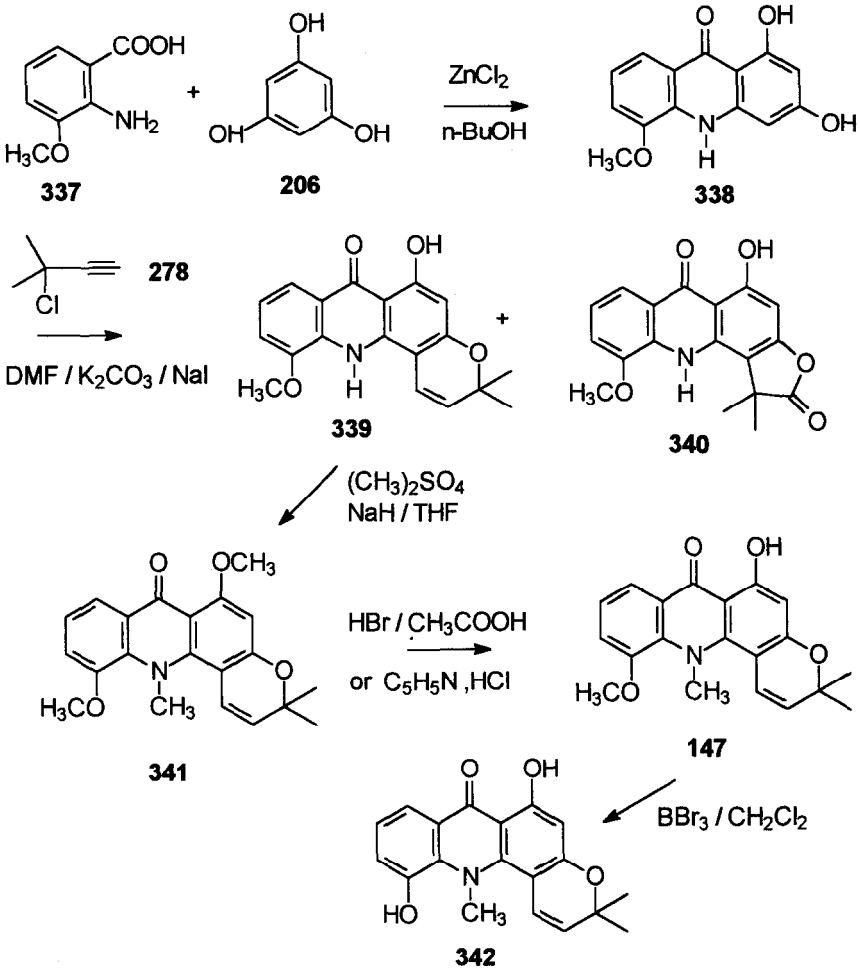


For instance, Lewis *et al.* used the same strategy for the synthesis of 11-hydroxynoracronycine (**142**) (*346*). Condensation of phloroglucinol (**206**) with 3-methoxyanthranilic acid (**337**) in 1-butanol in the presence of zinc chloride gave 1,3-dihydroxy-5-methoxy-9-acridone (**338**). Treatment of **338** with 3-chloro-3-methyl-1-butyne (**278**) in dimethylformamide containing potassium carbonate and sodium iodide, followed by *in situ* cyclization of the intermediate propargyl ether, gave the expected 11-methoxy-12-demethylnoracronycine (**339**), accompanied by a secondary product whose structure was established later as **340** (*354*). This latter compound should be considered to arise from cyclization in alkaline medium of a product of *C*-alkylation of **338** by 3-chloro-3-methyl-1-butyne (*355*). Alkylation of **339** with dimethylsulfate afforded 11-methoxyacronycine (**341**). Demethylation on treatment with hydrogen bromide or pyridine chloride gave baiyumine-A (**147**), which was further demethylated by boron tribromide in methylene chloride into 11-hydroxynoracronycine (**342**), identical with the alkaloid isolated from *Atalantia ceylanica* (*346*).

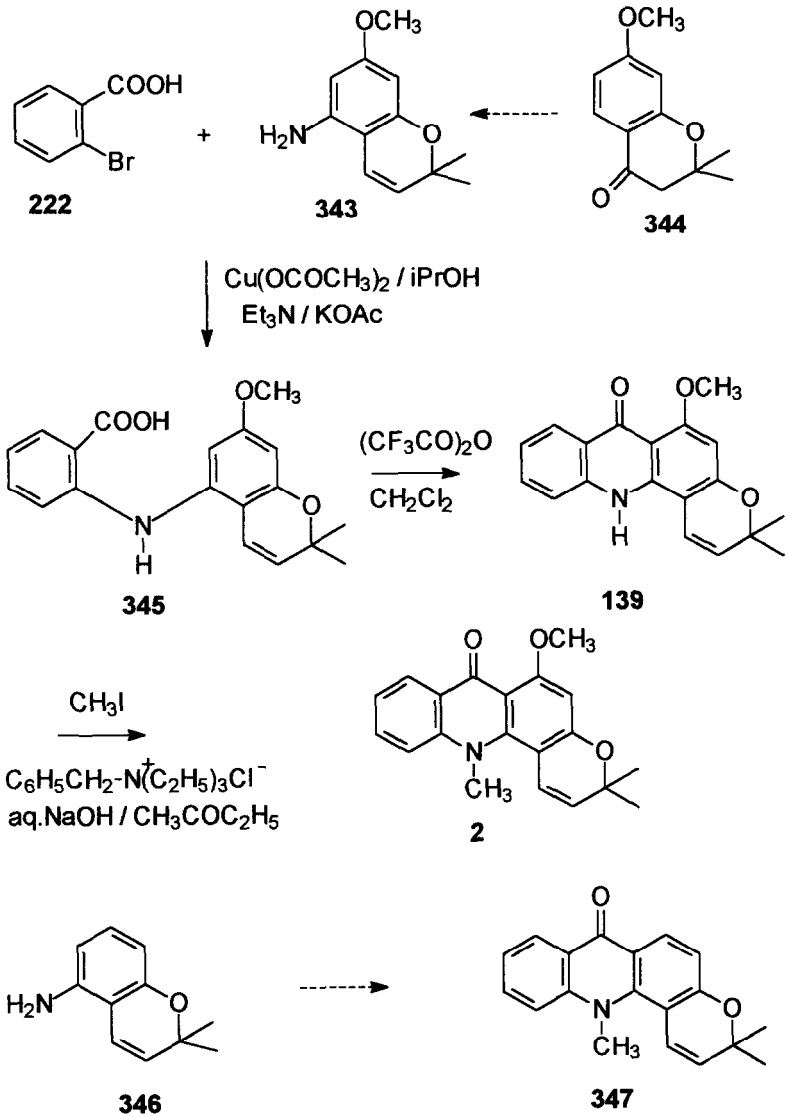
2. Syntheses Involving Construction of the Acridone Nucleus

a. Cyclization of a diarylamine intermediate. Several of the first acronycine syntheses described by Beck *et al.* were based on this strategy (*285*, 290). These approaches, which have been previously reviewed (*43*, *82*), are now mainly of historical interest, since they proceed in numerous steps and poor overall yields.

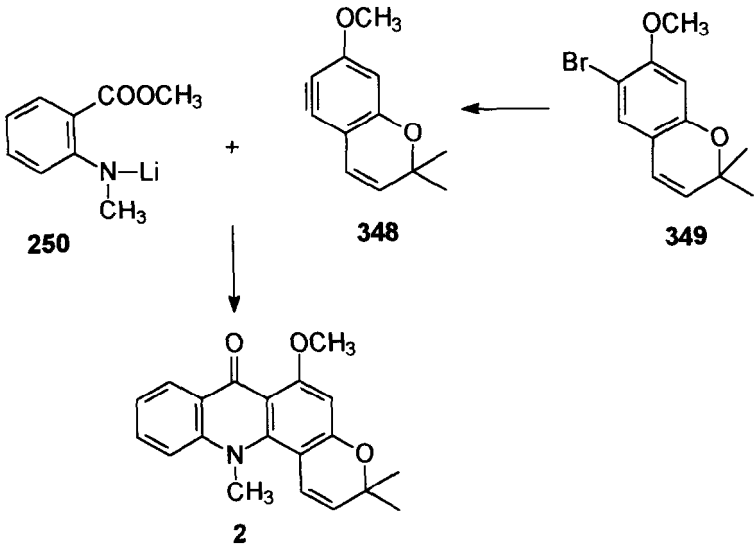
Loughhead published more recently an expeditious synthesis of acronycine based on the cyclization of a diarylamine key intermediate (*356*). Condensation of



methoxy-2,2-dimethyl-4-chromanone (**344**) by the method of Winterfeldt (*357*), with 2-bromobenzoic acid (**222**) under Ullmann conditions gave the corresponding carboxylic chromenylphenylamine **345**. Cyclization of **345** to 12-demethylacronycine (**139**) was efficiently induced by treatment with 5 equivalents of trifluoroacetic anhydride in dichloromethane for three days at room temperature. Final conversion to acronycine (**2**) was achieved by alkylation with methyl iodide under phase transfer conditions. This efficient preparation permitted the formation of 12-demethylacronycine (**139**) and acronycine (**2**) in approximately 40% yield from the aminochromene **343**. An essentially similar methodology, starting from 5-amino-2,2-dimethylchromene (**346**), gave a versatile access to the 6-demethoxyacronycine (**347**) series (*358, 359*).

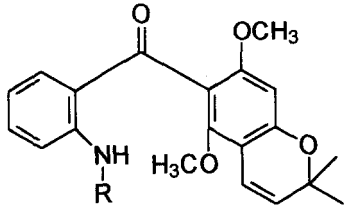


Tandem metallation synthesis of acridones was also successfully applied by Watanabe to the synthesis of acronycine (**2**) (*314*). Thus, the lithium salt of methyl *N*-methylanthranilate (**250**) easily reacted with the benzyne **348** generated from 6-bromo-9-methoxy-2,2-dimethylchromene (**349**) (*357*) to afford directly acronycine (**2**) in 41% yield.

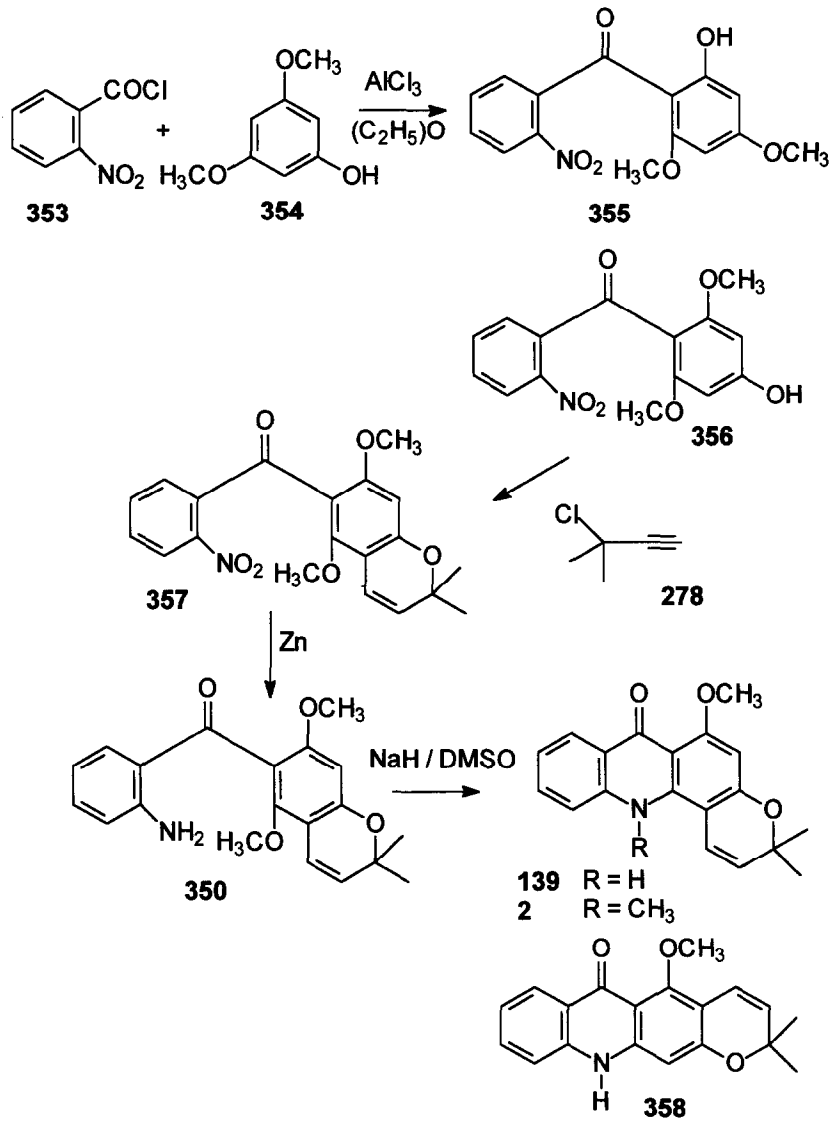


b. Cyclization of a benzophenone intermediate. The biomimetic cyclization of aminobenzophenones to acridones developed by Lewis *et al.* was applied by these authors to the synthesis of acronycine (**2**) and 12-demethylacronycine (**139**) (*77*, *79*). The key-intermediates were benzophenones **350**, **351**, and **352**.

In a first route, through **350**, Friedel Crafts reaction between 2-nitrobenzoyl chloride (**353**) and 3,5-dimethoxyphenol (**354**) gave 4,6-dimethoxy-2-hydroxy-2'-nitrobenzophenone (**355**) in 15% yield, together with the required 2,6-dimethoxy-4-hydroxy-2'-nitrobenzophenone (**356**), produced in only 5% yield. Alkylation of **356** with 3-chloro-3-methyl-1-butyne (**278**), followed by Claisen rearrangement, afforded 6-(2-nitrobenzoyl)-5,7-dimethoxy-2,2-dimethylchromene (**357**), whose nitro group was reduced by zinc dust to give the aminobenzophenone **350**. Cyclization with sodium hydride in dimethylsulfoxide furnished 12-demethoxyacronycine (**139**) in 27% yield, accompanied by its pyrano[3,2-*b*]acridin-7-one isomer, 12- demethylisoacronycine (**358**) in 39% yield.



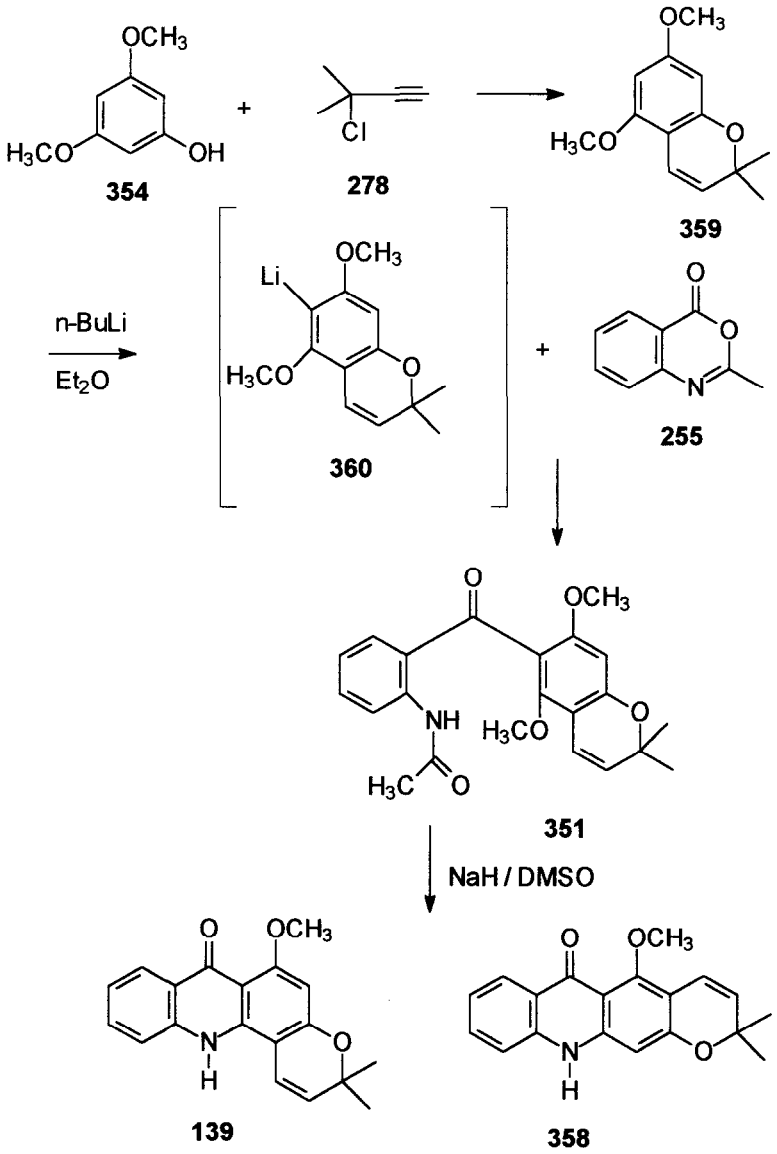
350 R=H
351 R=COCH3
352 R=CH3

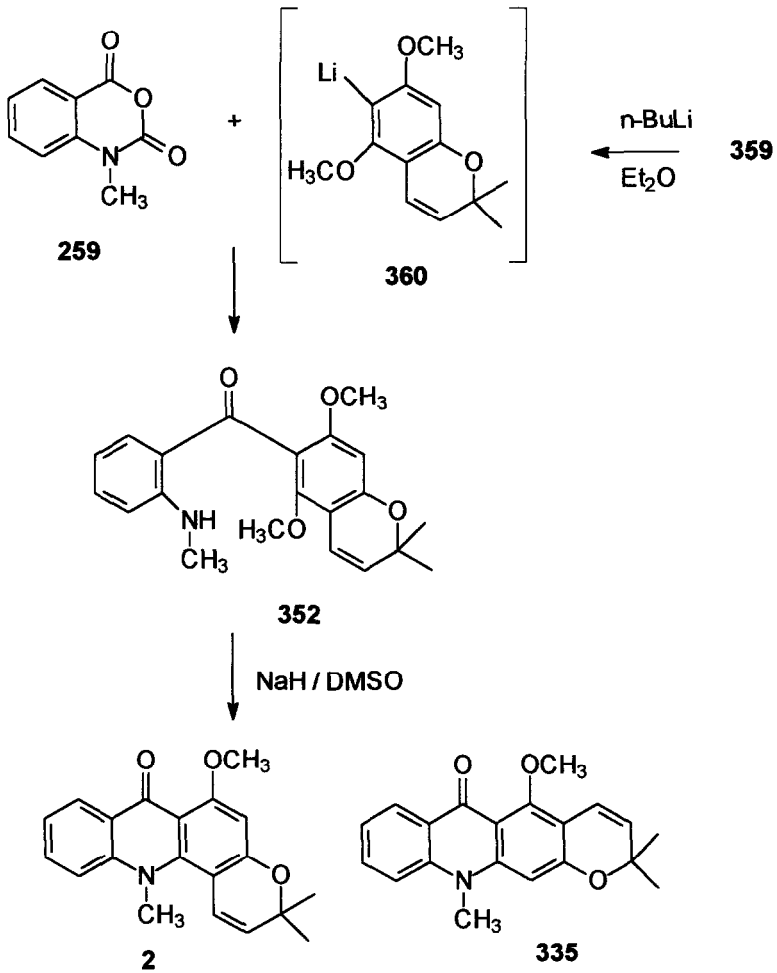


A second route involved the intermediacy of benzophenone **351**. Treatment of 3,5-dimethoxyphenol (**354**) with 3-chloro-3-methyl-1-butyne (**278**) gave 5,7-dimethoxy-2,2-dimethylchromene (**359**), which could be regioselectively lithiated at the 6-position by use of butyllithium in ether. Reaction of the lithio derivative **360** with 2-methyl-3,1-benzoxazin-4-one (**255**) smoothly afforded the required aminobenzophenone **351**. Cyclization with sodium hydride in dimethylsulfoxide occurred with simultaneous loss of the acetyl group, to give 12-

demethoxyacronycine (**139**) in 43% yield, and 12-demethylisoacronycine (**358**) in 46% yield.

The third route permitted a direct access to acronycine (**2**), by cyclization of the aminobenzophenone **352**, efficiently prepared by condensing *N*-methylisatoic anhydride (**259**) with the lithiated chromene **360**. Treatment of **352** with sodium hydride in dimethylsulfoxide gave acronycine (**2**) and isoacronycine (**335**), both obtained in 38% yield.

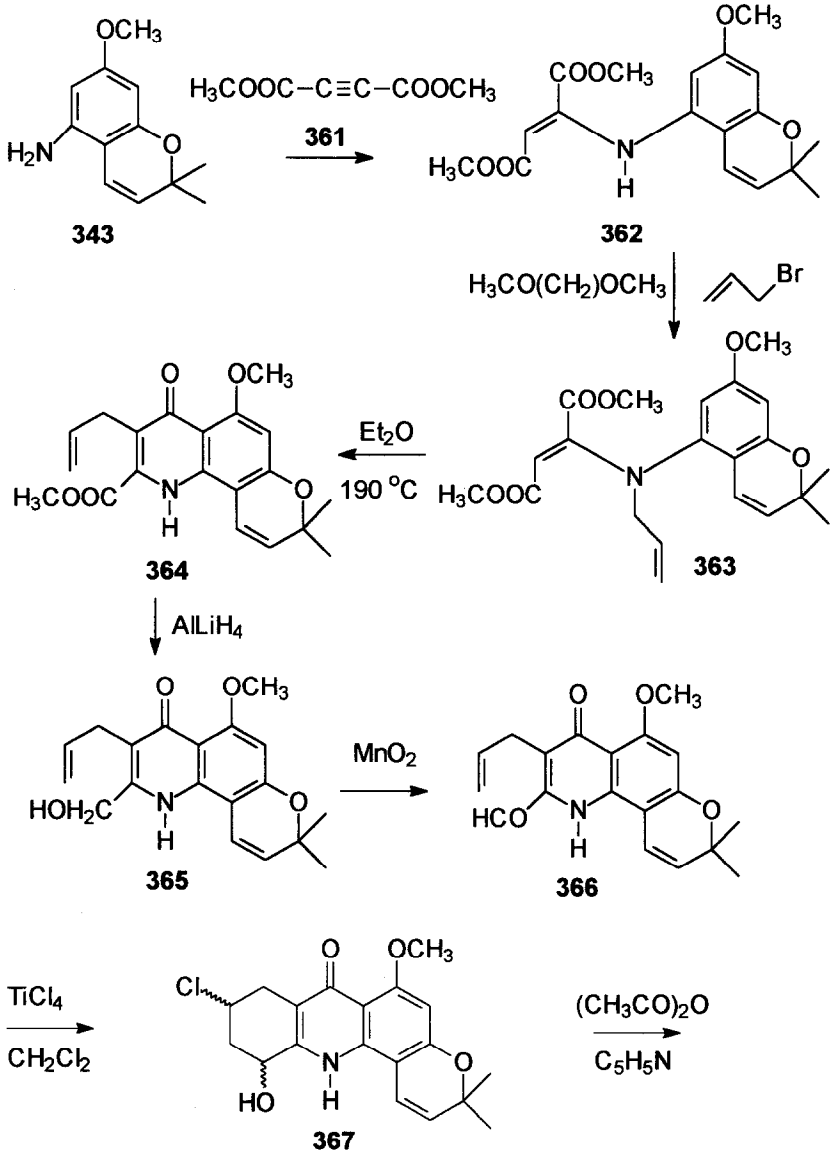


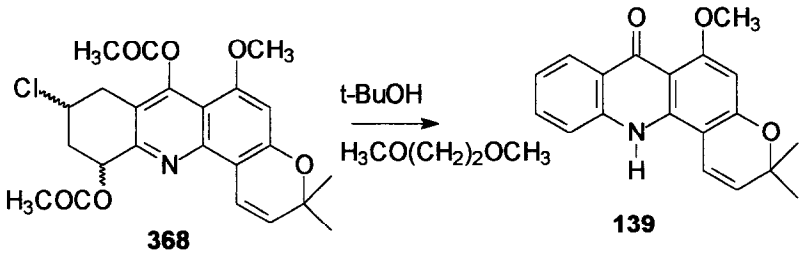


c. Construction of the acridone from a quinoline or a quinolinone. The strategy described by Winterfeldt *et al.* for the preparation of acronycine involves construction of the aromatic A ring of the of pyrano[2,3-*c*]acridin-7-one tetracyclic core at the final steps of the synthesis (*357*). Consequently, it provides an elegant entry towards derivatives substituted on the A ring (*360*), and was developed subsequently, with slight modifications, for the synthesis of various analogues, including the phenolic metabolites of acronycine in mammals (*361*).

Condensation of 5-amino-7-methoxy-2,2-dimethylchromene (**343**) with dimethylacetylenedicarboxylate (**361**) gave **362**, which was converted to **363** by reaction with allyl bromide in alkaline medium. Cope rearrangement of **363** into **364**, ensued by heating in ether, permitted creation of ring B of the target compound. Reduction of the carbomethoxy group of **364** by lithium aluminum

hydride gave alcohol **365**, which was oxidized to aldehyde **366** on treatment with manganese dioxide. Olefin aldehyde cyclization of **366** catalyzed by titanium tetrachloride afforded the chlorocarbinol **367** as a diastereoisomeric mixture, which was acetylated to the diacetate **368**. Finally, treatment of **368** with potassium *tert*-butoxide gave 12-demethylacronycine (**139**), which could be methylated to acronycine (**2**).

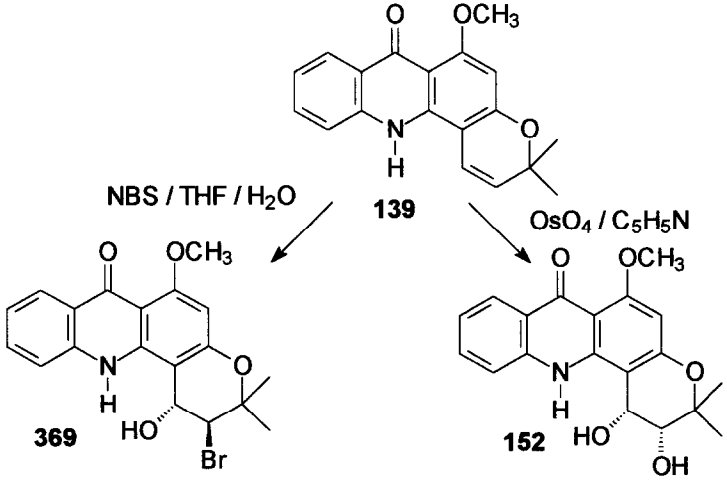


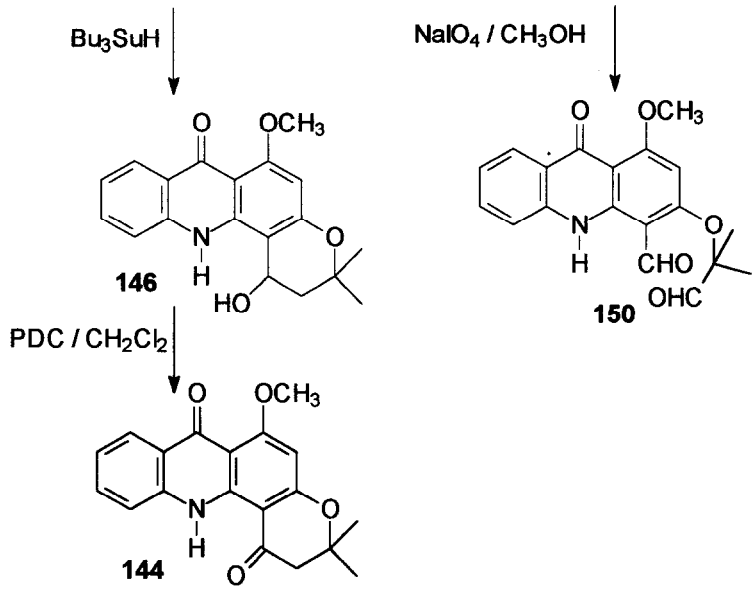


3. Oxidation Reactions of Pyranoacridones

Oxidation reactions performed on the pyran D ring of pyrano[2,3-*c*]acridin-7-one alkaloids provided an entry to several related natural products.

a. Oxidation reactions of 12-demethoxyacronycine. The structures of four alkaloids isolated from the leaves of *Sarcomelicope dogniensis*, 1,2-dihydro-1-hydroxy-12-demethylacronycine (**146**), 1,2-dihydro-1-oxo-12-demethoxy-acronycine (**144**), *cis*-1,2-dihydro-1,2-dihydroxy-12-demethylacronycine (**152**), and the *seco*-alkaloid **150** were confirmed by oxidation reactions performed on 12-demethoxyacronycine (**139**) (*249*). Thus, hydroxybromination of **139** by *N*-bromosuccinimide in aqueous tetrahydrofuran yielded racemic *trans*-2-bromo-1,2-dihydro-1-hydroxy-12-demethylacronycine (**369**) which was smoothly debrominated into racemic 1,2-dihydro-1-hydroxy-12-demethylacronycine (**146**) by treatment with tributyltin hydride. Chromic oxidation of the benzylic alcohol **146** gave 1,2-dihydro-1-oxo-12-demethoxyacronycine (**144**). Osmium tetroxide oxidation of 12-demethylacronycine (**139**) carried out in pyridine readily afforded racemic *cis*-1,2-dihydro-1,2-dihydroxy-12-demethylacronycine (**152**). Finally, further oxidation of the *cis*-diol **152** with sodium periodate led to the D ring opened dialdehyde **150**.



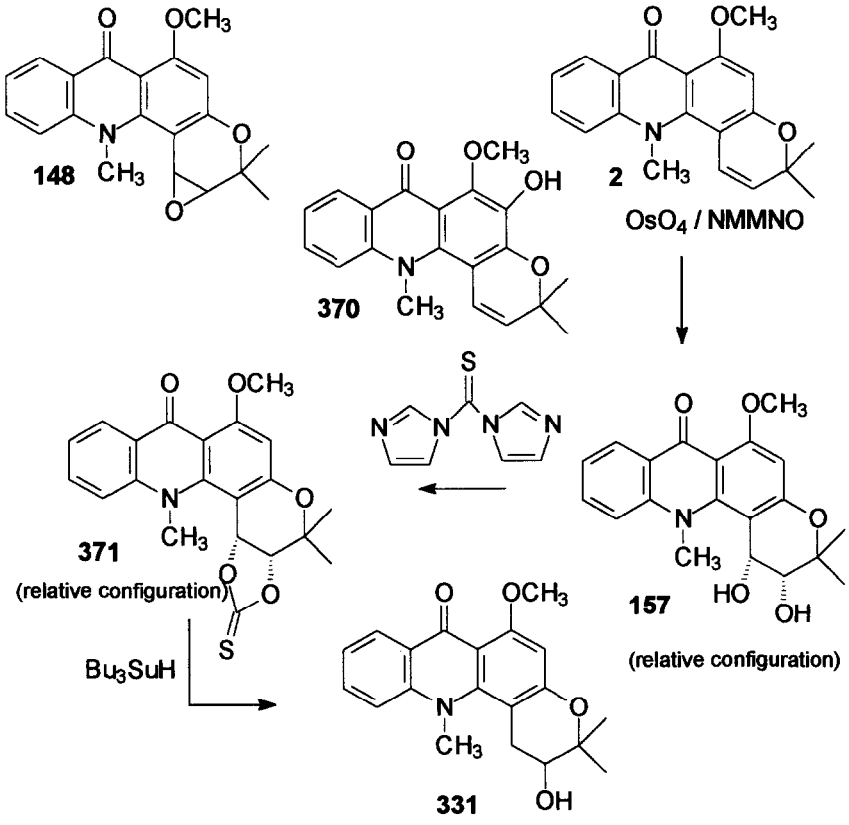


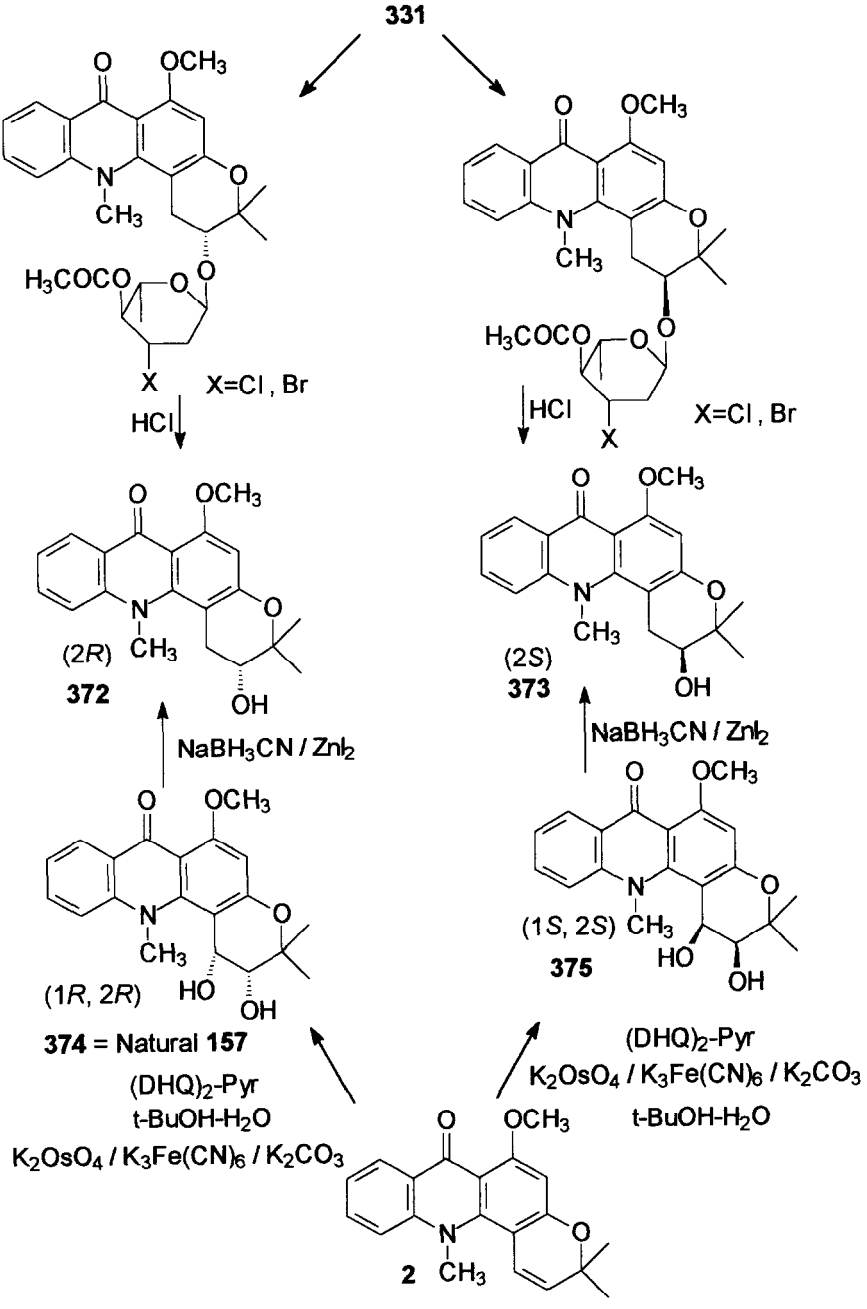
b. Oxidation reactions of acronycine. Acronycine epoxide (**148**), an unstable alkaloid isolated in minute amounts from various *Sarcomelicope* species (*255*), was the final target of several oxidation reactions studied in the group of Reisch (*362*, *363*, *364*). The first attempts towards the synthesis of **148**, by treatment of acronycine (**2**) with 3-chloroperbenzoic acid only resulted in hydroxylation on the aromatic C ring, leading to 5-hydroxyacronycine (**370**) (*362*). When acronycine (**2**) was oxidized with dimethyldioxirane, acronycine epoxide (**148**) and the diols, resulting from opening of the epoxide, were obtained as an unseparable mixture (*363*). Finally, when dimethyldioxirane oxidation was carried out in the presence of potassium carbonate, acronycine epoxide was isolated in 14% yield, together with 5-hydroxyacronycine (**370**) obtained in 13% yield (*364*).

The optically active alkaloid (-)-*cis*-1,2-dihydro-1,2-dihydroxyacronycine (**157**), isolated from *Sarcomelicope glauca* and *Sarcomelicope dogniensis*, was first synthesized as a racemate by oxidation of acronycine (**2**) with osmium tetroxide (*274*, *365*). Better results were obtained when a catalytic amount of osmium tetroxide was used in pyridine, with *N*-methylmorpholine *N*-oxide as the re-oxidizing agent (*359*). Racemic diol **157** could be easily converted into the corresponding cyclic thiocarbonate by treatment with *N,N*-thiocarbonyldiimidazole. Benzylic reduction of **371** with tributyltin hydride afforded racemic 2-hydroxy-1,2-dihydroacronycine (**331**) (*365*). Alcohol **331** was used to prepare several glycosides (*366*, *367*). Of particular interest were the 1,4-di-*O*-acetyl-3-chloro and 3-bromo-2,3,6-trideoxy-L-arabino-hexopyranosides, since the two diastereoisomers obtained in each series were easily separated by column chromatography. The absolute configuration at C-2 on the aglycone part of each glycoside was deduced from ^{1}H and ^{13}C NMR data, compared with those of related angular

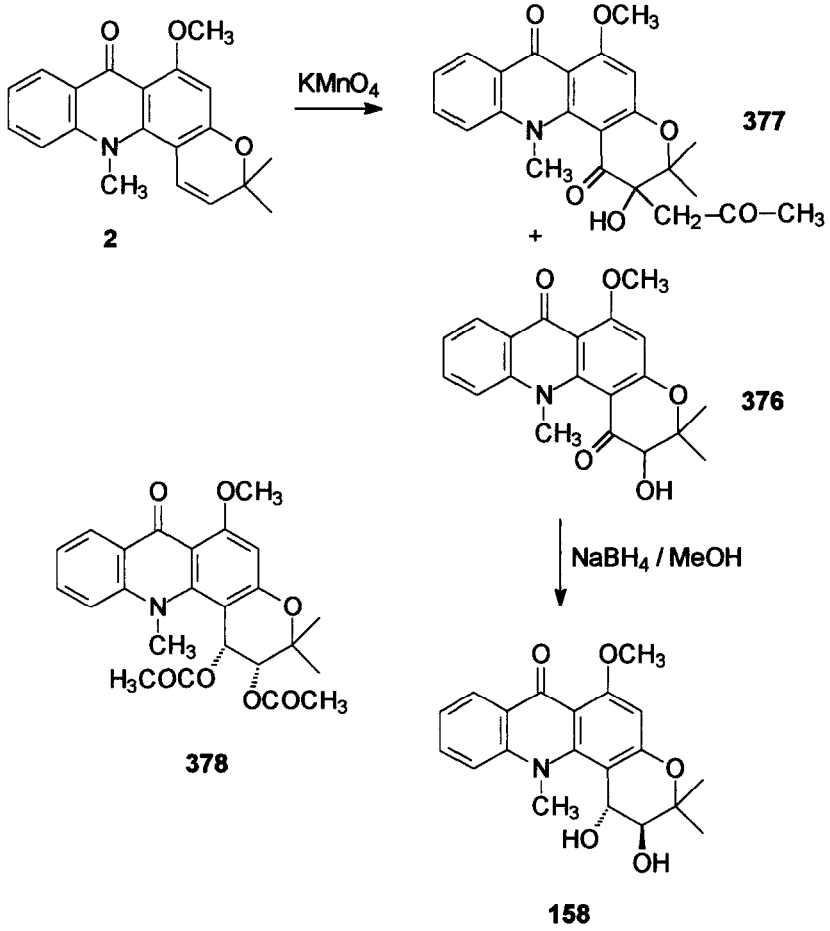
hydroxydihydropyranocoumarin hexopyranosides of known absolute configuration (*368*). Acidic hydrolysis of the glycosides finally gave access to (2*R*)-2-hydroxy-1,2-dihydroacronycine (**372**) and (2*S*)-2-hydroxy-1,2-dihydroacronycine (**373**) (*367*).

More recently, application of the Sharpless asymmetric dihydroxylation methodology (*369*) to acronycine (**2**) permitted the enantioselective preparation of (1*R*, 2*R*)-*cis*-1,2-dihydro-1,2-dihydroxyacronycine (**374**) and (1*S*, 2*S*)-*cis*-1,2-dihydro-1,2-dihydroxyacronycine (**375**), by use of diphenylpyrimidine ligands involving dihydroquinine and dihydroquinidine, repectively. Each enantiomer was purified using chiral high performance liquid chromatography and its absolute configuration was confirmed by benzylic reduction into the corresponding 2-hydroxy-1,2-dihydroacronycine, on treatment with sodium cyanoborohydride in the presence of zinc iodide. In this way, the absolute configuration of natural *cis*-1,2-dihydro-1,2-dihydroxyacronycine was determined as (1*R*, 2*R*) (*274*, *370*).




331
X=Cl, Br
HCl
(2R)
372
NaBH3CN / ZnI2
(1R, 2R)
374 = Natural 157
(DHQ)2-Pyr
t-BuOH-H2O
K2OsO4 / K3Fe(CN)6 / K2CO3
X=Cl, Br
HCl
(2S)
373
NaBH3CN / ZnI2
(1S, 2S)
375
(DHQ)2-Pyr
K2OsO4 / K3Fe(CN)6 / K2CO3
t-BuOH-H2O
2

Racemic *trans*-1,2-dihydro-1,2-dihydroxyacronycine (**158**) was first obtained in very low yield by oxidation of acronycine (**2**) with chromium trioxide in acetic acid followed by alkaline hydrolysis of the intermediate *trans*-diol monoacetate (*274*). A more convenient access was recently described (*371*), based on a previous study of the oxidation of acronycine by potassium permanganate (*372*). Thus, treatment of acronycine (**2**) with potassium permanganate in aqueous acetone gave 1-oxo-2-hydroxy-1,2-dihydroacronycine (**376**) in 31% yield, accompanied by smaller amounts of *cis*-1,2-dihydro-1,2-dihydroxyacronycine (**157**) and of the acetone adduct **377**. Sodium borohydride reduction of 1-oxo-2-hydroxy-1,2-dihydroacronycine (**376**) in methanol afforded the desired *trans*-1,2-dihydro-1,2-dihydroxyacronycine (**158**) as a racemate in 50% yield (*371*).



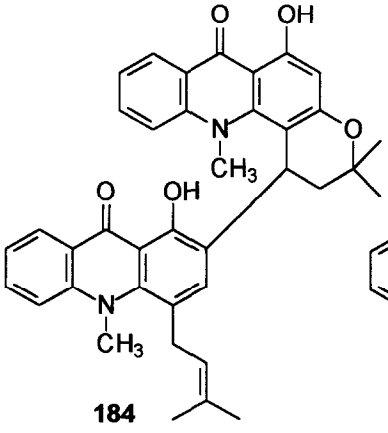
The high chemical unstability of acronycine epoxide led to the speculation that it may be the biologically active metabolite of acronycine *in vivo*, able to alkylate nucleophilic targets within the cell (*255*). Nevertheless, its fast reaction with water, to give the corresponding *cis* and *trans* diols, precludes its possible use in therapeutics (*359*). Therefore, in a search for candidates possessing the same type of benzylic reactivity as acronycine epoxide towards nucleophilic targets, but a better chemical stability, a series of *cis*- and *trans*-1,2-dihydroxy-1,2-dihydroacronycine esters was prepared (*359, 371*). These compounds, exemplified by *cis*-1,2-diacetoxy-1,2-dihydroacronycine (**378**) exhibit promising antitumor properties, with a broadened spectrum of activity and an increased potency when compared to acronycine itself both *in vivo* and *in vitro* (*359*).

E. DIMERIC ACRIDONE ALKALOIDS AND RELATED COMPOUNDS

1. *Polymerization Reactions of Pyranoacridones and Oxidation of C-Prenylacridones*

None of the naturally occurring dimeric acridone alkaloids containing a carbon-carbon linkage have been synthesized to date. Nevertheless, glycobismine-A (**184**), and the diastereoisomeric glycobismines-B and C, both represented by structure **187**, should be considered to arise most probably by acid-catalyzed condensation between the two corresponding monomeric acridone units.

In good agreement with this hypothesis, an interesting series of polymerization and rearrangement reactions was performed in acidic medium on acronycine (**2**) and noracronycine (**138**) by Cordell *et al.* (*373-383*). Thus, by heating noracronycine with methanolic hydrochloric acid, eight major oligomers, named AB-1, AB-2, AB-3, AB-4, AB-5A, AB-5B, AB-6A, and AB-6B were obtained. The structures were established as dimeric for AB-1 (**379**) and AB-2 (**380**), trimeric for AB-3 (**381**), tetrameric for AB-4 (**382**) and AB-5B (**383**), and pentameric for AB-5A (**384**), AB-6A (**385**), and AB-6B (**386**). It should be emphasized that the mode of linkage between the benzylic pyran position of a unit and the C-5 position of the following one is exactly the same as that encountered in natural glycobismines.



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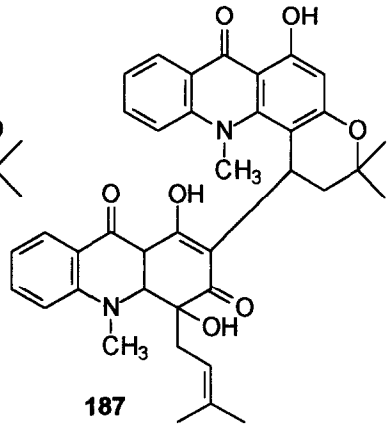

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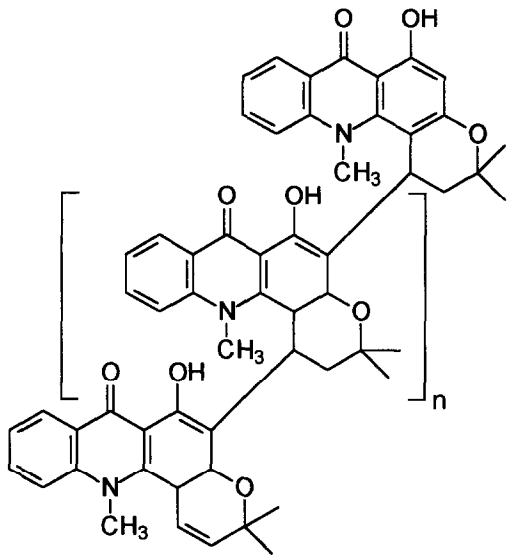
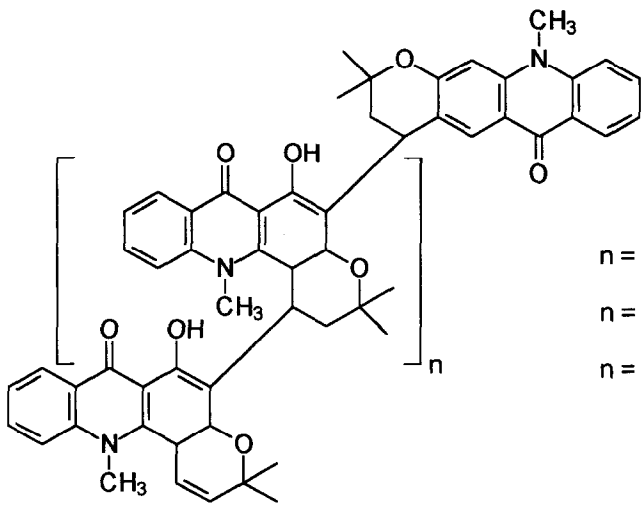


n = 0 **379**

n = 1 **381**

n = 2 **382**

n = 3 **384**

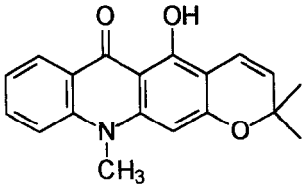


n = 0 **380**

n = 2 **383**

n = 3 **385**

Subsequently, some of these oligomers (e.g. **379**, **380**, and **381**) were also isolated as thermal rearrangement products when noracronycine was heated at 180°C. At 210°C however, a completely different array of products was obtained. Indeed, the two diastereoisomeric Diels-Alder adducts **387** and **388**, formed from norisoacronycine (**397**) and the putative diene **389** were isolated from the reaction mixture (*384*). Moreover, some new acronycine derivatives, **390**, **391**, **392** and **397** were recently obtained by heating the HCl salt of acronycine at 250^0 C for 2.5 hours (385).



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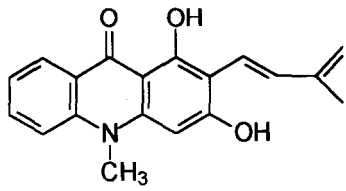

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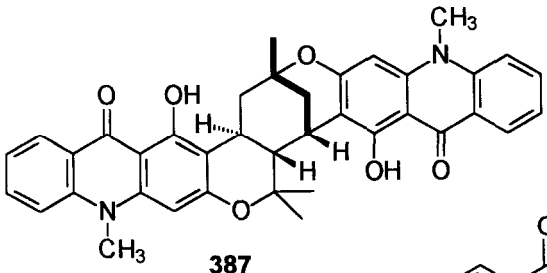

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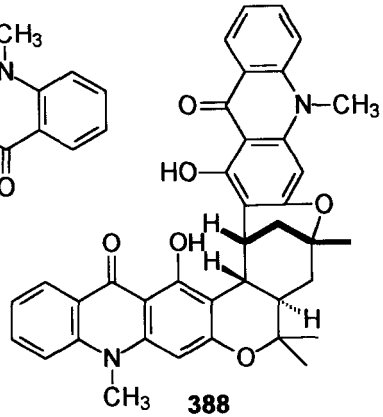

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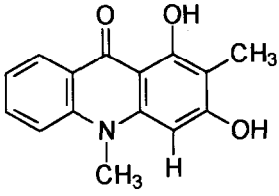

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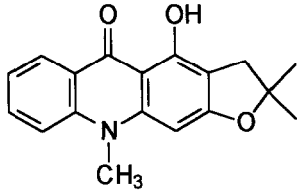

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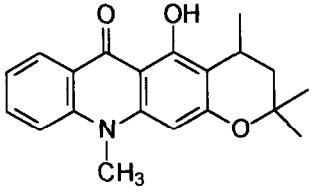

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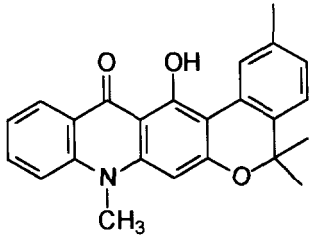
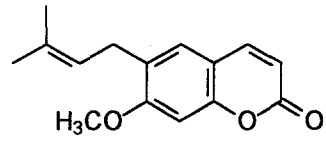


392

1. Synthesis of Acridone-Coumarin Dimers

The acridone-coumarin dimers acrimarine-A (**176**) and –F (**178**) were synthesized by Furukawa *et al.* from the corresponding monomeric units, the acridones grandisine-II (**79**) and citpressin-I (**78**) on one hand, and the prenylcoumarin suberenol (**393**) on the other hand (*262*). Suberenol (**393**) was first synthesized from the readily available prenylcoumarin suberosin (**394**), through haematoporphyrin-sensitized photo-oxidation, followed by treatment with triphenylphosphine. Condensation of suberenol (**393**) and grandisine-II (**79**) to acrimarine-A (**176**) was successfully achieved in ethanolic solution, in the presence of perfluorinated resin Naflon® H, acting as a superacid catalyst (*262*). The same reaction applied to suberenol (**393**) and citpressin-I (**78**) gave acrimarine–F (**178**) (*262*). Application of this method to simple acridones, including 1,3-dihydroxy-10-methylacridone (**19**), 1-hydroxy-3-methoxy-10-methylacridone (**48**), and 1,3-dihydroxyacridone (**22**) permitted Reisch *et al.* to obtain synthetic acrimarins **169**, **395** and **396** (*292*). It is interesting to note that one of them, **169**, was subsequently isolated from *Citrus funadoko* and named acrimarine M (*261*).



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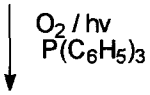

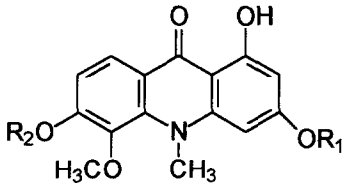

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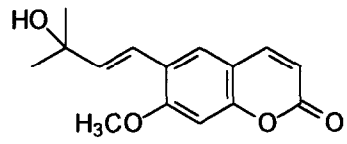
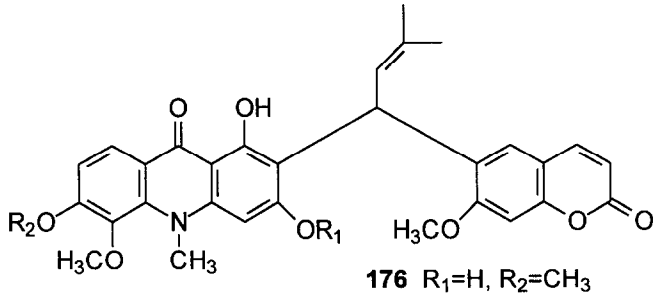
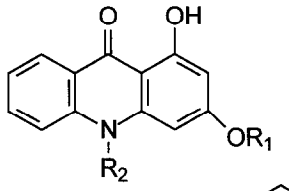


393

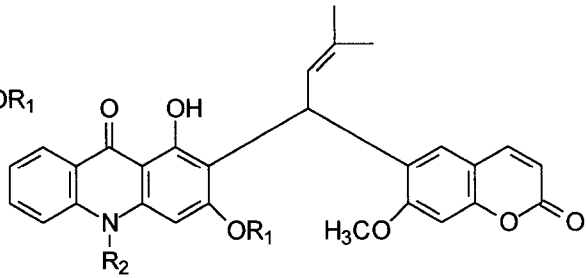
79 R_1=H, R_2=CH_3
78 R_1=CH_3, R_2=H



176 R_1=H, R_2=CH_3
178 R_1=CH_3, R_2=H



19 R_1=H, R_2=CH_3
48 R_1=R_2=CH_3
22 R_1=R_2=H



169 R_1=H, R_2=CH_3
395 R_1=R_2=CH_3
396 R_1=R_2=H

VI. Biological Properties of Natural Acridone Alkaloids

Acridone alkaloids are known to have various interesting biological activities. Renowned is the antitumor activity of acronycine (**2**), which has been covered by Svoboda *et al.* and Cordell *et al.* in two reviews included in this series *(38, 40),* and by Tillequin *et al.* in two recent review articles *(43, 44).* The latter also cover the chemistry, cytotoxicity and antitumor activity of some new, recently synthesized acronycine derivatives. Most interesting are the *cis-* and *trans*-1,2-dihydroxy-1,2-dihydroacronycine diesters, which exhibit promising antitumor properties, with a broad spectrum and increased potency when compared with acronycine on several tumor strains *in vitro* and *in vivo (359, 371). Cis*-1,2-diacetoxy-1,2-dihydroacronycine (**378**) appears to present particular interest in this respect, due to its high *in vivo* activity against P388 leukemia, the highly resistant solid tumor C-38, and the human HT-29 adenocarcinoma *(392).*

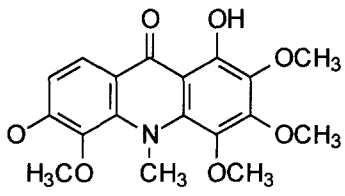
It is noteworthy that acronycine induced a partial accumulation of cells in the G2+M phase *(393),* whereas the new hemisynthetic derivatives, modified in ring D, induced a marked accumulation of cells in the S phase. This fact could suggest several differences in their mechanism of action at molecular level.

The cytotoxic activity of various natural and hemisynthetic acridones has been the subject of many studies, which have well determined their antiproliferative

activity on i) several leukemia cell lines such as HL-60, L-1210, T-cell leukemia, and the human promyelotic leukemia cell line *(359-396)* ii) cell lines derived from solid tumors, such as human lung carcinoma, melanoma, gastric cancer, breast cancer and lymph-node metastasis *(396, 397)*. As far as structure activity relationships are concerned, it is clear that in the pyranoacridone series the presence of a hydroxyl group at C-6 results in a decrease of cytotoxic activity; opposingly, the presence of a methoxy group at C-6, an hydroxy or methoxy group at C-11 and the replacement of NCH_3 by an NH group are followed by an increase of cytotoxicity. In the simple acridone series, the presence of hydroxy or methoxy groups in positions C-1,2,3,4,5,6 seem to produce an increased antiproliferative effect. These compounds, exemplified by glyfoline (**96**), showed a 2- to 25-fold increase of their *in vitro* potency, as compared to acronycine *(309, 395)*. The chemistry and pharmacology of these substituted simple acridone alkaloids have been recently covered by Su *et al. (41)*. However, it is worth pointing out that all the natural and synthetic acridone derivatives, even the highly antitumor 1,2-dihydroxy-1,2-dihydroacronycine diesters, showed weak *in vitro* potency, not exceeding an IC_{50} of 0.5 M, when compared with other antitumor agents. The only exception is 2-nitroacronycine (**398**) obtained by treatment of acronycine with nitric acid. This compound was strongly cytotoxic with an IC_{50} of 0.09 M (300-fold more potent than acronycine) in inhibiting the proliferation of L1210 cells *(398)* and other solid tumors *(399)*, but it was completely devoid of antitumor activity against P388 leukemia and C38 colon adenocarcinoma *(398)*.

Recent investigations have documented that several 1,3-dihydroxyacridone derivatives present a moderate *in vitro* cytotoxic activity on the multidrug resistant KB cell line, through a topoisomerase II - mediated mechanism *(400)*.

Apart from their anticancer activity, acridone alkaloids have been shown to possess interesting pharmacological activities against protozoa, such as *Plasmodia* and *Pneumocystis carinii*. In regard to anti-malarial activity, 150 natural and synthetic acridone alkaloids have been tested for their activity *in vitro* and *in vivo*



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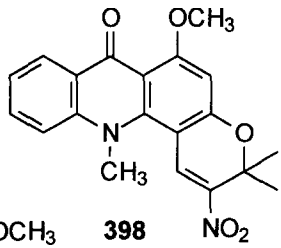

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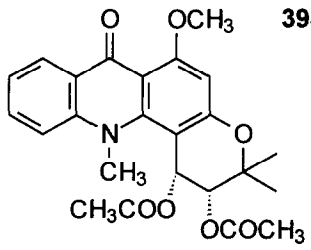

378

(401-403). Acronycine and some analogs such as 2-nitroacronycine showed interesting activity against chloroquine resistant W2 clones of *Plasmodium falciparum (402).* Among the other natural acridones the more interesting was atallaphyllinine (**162**) which was evaluated *in vivo* in mice infected with 107 erythrocytes parasitized with *Plasmodium berdhei* or *P. vinckei* (IP administration in a daily dose of 50 mg/Kg for 3 days). Following this treatment, the development of malaria parasites was completely suppressed without observation of acute toxic effects *(403).* Moreover atalaphyllinine and glycobismine (**184**) showed significant activity against *Pneumocystis carinii in vitro (404).*

Natural acridone alkaloids have also attracted attention for their antimolluscicidal *(210),* antiviral (405), inhibition of Epstein-Barr virus activation *(406),* antispasmodic *(407),* and antiplatelet aggregation *(408)* activities.

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References

1. J. R. Price, *in* "The Alkaloids" (R. H. F. Manske and H. L. Holmes, eds.), Vol. 2, p. 353. Academic Press, New York, 1952.
2. G. K. Hughes, F. N. Lahey, J. R. Price, and L. J. Webb, *Nature* **162**, 223 (1948).
3. V. A. Snieckus, *in* "The Alkaloids: Specialist Periodical Reports" (J. E. Saxton, ed.), Vol. 1, p. 96. The Chemical Society, London, 1971.
4. V. A. Snieckus, *in* "The Alkaloids: Specialist Periodical Reports" (J. E. Saxton, ed.), Vol. 2, p. 86. The Chemical Society, London, 1972.
5. V. A. Snieckus, *in* "The Alkaloids: Specialist Periodical Reports" (J. E. Saxton, ed.), Vol. 3, p. 104. The Chemical Society, London, 1973.
6. V. A. Snieckus, *in* "The Alkaloids: Specialist Periodical Reports" (J. E. Saxton, ed.), Vol. 4, p. 117. The Chemical Society, London, 1974.
7. V. A. Snieckus, *in* "The Alkaloids: Specialist Periodical Reports" (J. E. Saxton, ed.), Vol. 5, p. 103. The Chemical Society, London, 1975.
8. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 6, p. 103. The Chemical Society, London, 1976.
9. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 7, p. 81. The Chemical Society, London, 1977.
10. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 8, p. 77. The Chemical Society, London, 1978.
11. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 9, p. 78. The Chemical Society, London, 1979.

12. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 10, p. 74. Royal Society of Chemistry, London, 1981.
13. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 11, p. 71. Royal Society of Chemistry, London, 1981.
14. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 12, p. 84. Royal Society of Chemistry, London, 1982.
15. M. F. Grundon, *in* "The Alkaloids: Specialist Periodical Reports" (M. F. Grundon, ed.), Vol. 13, p. 87. Royal Society of Chemistry, London, 1983.
16. M. F. Grundon, *Nat. Prod. Rep.* **1**, 195 (1984).
17. M. F. Grundon, *Nat. Prod. Rep.* **2**, 393 (1985).
18. M. F. Grundon, *Nat. Prod. Rep.* **4**, 225 (1987).
19. M. F. Grundon, *Nat. Prod. Rep.* **5**, 293 (1988).
20. M. F. Grundon, *Nat. Prod. Rep.* **7**, 131 (1990).
21. J. P. Michael, *Nat. Prod. Rep.* **8**, 53 (1991).
22. J. P. Michael, *Nat. Prod. Rep.* **9**, 25 (1992).
23. J. P. Michael, *Nat. Prod. Rep.* **10**, 99 (1993).
24. J. P. Michael, *Nat. Prod. Rep.* **11**, 163 (1994).
25. J. P. Michael, *Nat. Prod. Rep.* **12**, 77 (1995).
26. J. P. Michael, *Nat. Prod. Rep.* **12**, 465 (1995).
27. J. P. Michael, *Nat. Prod. Rep.* **14**, 11 (1997).
28. J. P. Michael, *Nat. Prod. Rep.* **14**, 605 (1997).
29. J. P. Michael, *Nat. Prod. Rep.* **15**, 595 (1998).
30. S. Johne and D. Gröger, *Pharmazie* **27**, 195 (1972).
31. J. Reisch, K. Szendrei, E. Minker, and I. Novak, *Pharmazie* **27**, 208 (1972).
32. J. E. Saxton, *in* "Acridines" (R.M. Acheson, ed.), p. 379. John Wiley, New York, 1973.
33. I. Mester, *Fitoterapia* (Milano) **44**, 123 (1973).
34. I. Mester, *Fitoterapia* (Milano) **48**, 268 (1977).
35. I. Mester, *in* "Chemistry and Chemical Taxonomy of the Rutales" (P. G. Waterman and M. F. Grundon, eds.), p. 31. Academic Press, London, 1983.
36. D. Gröger, *Pharmazie* **43**, 815 (1988).
37. M. F. Grundon, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 6, p. 339.Wiley-Interscience, New York, 1988.
38. K. Gerzon and G. H. Svoboda, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 21, p.1. Academic Press, New York, 1983.
39. J. R. Lewis, *in* "Chemistry and Chemical Taxonomy of the Rutales" (P. G. Waterman and M. F. Grundon, eds.), p. 301. Academic Press, London, 1983.
40. M. Suffness and G. A. Cordell, *in* "The Alkaloids" (A. Brossi, ed.), Vol. 25, p. 38. Academic Press, New York, 1985.
41. T.-L. Su and K. A. Watanabe, *in* "Studies in Natural Products Chemistry" (Atta-ur-Rahman, ed.), Vol. 13, p. 347. Elsevier, Amsterdam, 1993.
42. F. Tillequin, *Act. Chim. Ther.* **23**, 247 (1997).
43. F. Tillequin, S. Michel, and A.-L. Skaltsounis, *in* "Alkaloids: Chemical and Biological Perspectives" (S. W. Pelletier, ed.), Vol. 12, p. 1. Pergamon, Oxford, 1998.

44. F. Tillequin and S. Michel, *in* "Studies in Natural Products Chemistry"(Atta-ur-Rahman, ed.), Vol. 20, p. 789. Elsevier, Amsterdam, 1998.
45. R. Robinson, *The Structural Relations of Natural Products*. Clarendon Press, Oxford, 1955.
46. D. Gröger and S. Johne, *Z. Naturforsch.* **23b**, 1072 (1968).
47. D. Gröger, *Lloydia* **32**, 221 (1969).
48. R. H. Prager and H. M. Thredgold, *Aust. J. Chem.* **22**, 2627 (1969).
49. S. Johne, H. Bernasch, and D. Gröger, *Pharmazie* **25**, 777 (1970).
50. I. N. Kuzovkina, T. P. Chernysheva, and I. E. Alterman, *Fiziol. Rast.* 26, 492 (1979).
51. I. N. Kuzovkina, L. D. Kislov, M. N. Zhivopistseva, Zs. Rózsa, and K. Szendrei, *Khim. Prir. Soedin.* 758 (1984).
52. A. Baumert, I. N. Kuzovkina, G. Krauss, M. Hieke, and D. Gröger, *Plant Cell. Rep.* **1**, 168 (1982).
53. A. Zschunke, A. Baumert, and D. Gröger, *J. Chem. Soc., Chem. Commun.* 1263 (1982).
54. A. Baumert, I. N. Kuzovkina, M. Hieke, and D. Gröger, *Planta Med.* **48**, 142 (1983).
55. A. Baumert, M. Hieke, and D. Gröger, *Planta Med.* **48**, 258 (1983).
56. W. Maier, A. Baumert, and D. Gröger, *J. Plant Physiol.* **145**, 1 (1995).
57. A. Baumert, I. N. Kuzovkina, and D. Gröger, *Planta Med.* **51**, 125 (1985).
58. A. Baumert, A. Porzel, J. Schmidt, and D. Gröger, *Z. Naturforsch.* **47c**, 365 (1992).
59. A. Baumert and D. Gröger, *FEBS Lett.* **187**, 311 (1985).
60. A. Baumert, G. Schneider, and D. Gröger, *Z. Naturforsch.* **41c**, 187 (1986).
61. A. Baumert, W. Maier, B. Schumann, and D. Gröger, *J. Plant Physiol.* **139**, 224 (1991).
62. W. Maier, A. Baumert, B. Schumann, H. Furukawa, and D. Gröger, *Phytochemistry* **32**, 691 (1993).
63. A. Baumert, W. Maier, D. Gröger, and R. Deutzmann, *Z. Naturforsch.* **49c**, 26 (1994).
64. K. T. Junghanns, R. E. Kneusel, A. Baumert, W. Maier, D. Gröger, and U. Matern, *Plant Molecular Biol.* **27**, 681 (1995).
65. K. T. Junghanns, R. E. Kneusel, D. Gröger, and U. Matern, *Phytochemistry* **49**, 403 (1998).
66. A. Baumert, J. Schmidt, and D. Gröger, *Phytochem. Anal.* **4**, 165 (1993).
67. W. Maier, G. Schneider, and D. Gröger, *FEBS Lett.* **263**, 289 (1990).
68. E. Leete, *in* "Biogenesis of Natural Compounds" (P. Bernfeld, ed.), p. 780. Pergamon Press, London, 1963.
69. A. C. Casey and A. Malhotra, *Tetrahedron Lett.*, 401 (1975).
70. P. G. Waterman, *Phytochemistry* **14**, 2092 (1975).
71. F. Fish, I. A. Meshal, and P. G. Waterman, *Planta Med.* **33**, 228 (1978).
72. P. G. Waterman, I. A. Meshal, J. B. Hall, and M. D. Swaine, *Biochem. Syst. Ecol.* **6**, 239 (1978).
73. S. A. Khalid and P. G. Waterman, *Phytochemistry* **20**, 2761 (1981).
74. I. H. Bowen, P. Gupta, and J. R. Lewis, *Chem. Commun.* 1625 (1970).

75. M. S. Khan, J. R. Lewis, and R. A. Watt, *Chem. Ind. (London)* 744 (1975).
76. J. H. Adams, P. Gupta, M. S. Khan, J. R. Lewis, and R. A. Watt, *J. Chem. Soc., Perkin Trans. I* 2089 (1976).
77. J. H. Adams, P. Gupta, and J. R. Lewis, *Chem. Ind. (London)* 109 (1976).
78. J. H. Adams, P. Gupta, M. S. Khan, and J. R. Lewis, *J. Chem. Soc., Perkin Trans. I* 2173 (1977).
79. J. H. Adams, P. M. Brown, P. Gupta, M. S. Khan, and J. R. Lewis, *Tetrahedron* **37**, 209 (1981).
80. J. Schröder, *Trends Plant Sci.* **2**, 373 (1997).
81. T.-S. Wu, H. Furukawa, C.-S. Kuoh, and K.-S. Hsu, *J. Chem. Soc., Perkin Trans. I* 1681 (1983).
82. J. E. Saxton, *in* "Acridines" (R. M. Acheson, ed.), p. 379. John Wiley, New York, 1973.
83. R. D. Brown and F. N. Lahey, *Aust. J. Sci. Res.* **A3**, 593 (1950).
84. R. M. Acheson, *in* "Acridines" (R. M. Acheson, ed.), p. 665. John Wiley, New York, 1973.
85. J. H. Bowie, R. G. Cooks, R. H. Prager, and H. M. Thredgold, *Aust. J. Chem.* **20**, 1179 (1967).
86. S.-T. Lin, T.-S. Wu, and H. Furukawa, *Org. Mass Spectrom.* **27**, 116 (1992).
87. S. Funayama and G. A. Cordell, *Planta Med.* **50**, 121 (1984).
88. E. Mikros, S. Mitaku, A. L. Skaltsounis, F. Libot, F. Tillequin, and M. Koch, *Magn. Reson. Chem.* **37**, in press (1999).
89. A. Ahond, C. Poupat, and P. Potier, *Tetrahedron* **14**, 2385 (1978).
90. I. Mester, D. Bergenthal, Zs. Rózsa, and J. Reisch, *Z. Naturforsch.* **34b**, 516 (1979).
91. D. Bergenthal, I. Mester, Zs. Rózsa, and J. Reisch, *Phytochemistry* **18**, 161 (1979).
92. H. Furukawa, M. Yogo, and T.-S. Wu, *Chem. Pharm. Bull.* **31**, 3084 (1983).
93. S. Funayama, R. P. Borris, and G. A. Cordell, *J. Nat. Prod.* **46**, 391 (1983).
94. G. Brader, M. Bacher, H. Greger, and O. Hofer, *Phytochemistry* **42**, 881 (1996).
95. J. A. Diment, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.* **20**, 1719 (1967).
96. G. Baudouin, F. Tillequin, M. Koch, M. E. Tran Huu Dau, J. Guilhem, J. Pusset, and G. Chauvière, *J. Nat. Prod.* **48**, 260 (1985).
97. J. Reisch and H. Strobel, *Pharmazie* **37**, 862 (1982).
98. P. T. O. Chang, G. A. Cordell, G. H. Aynilian, H. H. S. Fong, and N. R. Farnsworth, *Lloydia* **39**, 134 (1976).
99. D. L. Dreyer, *Tetrahedron* **22**, 2923 (1966).
100. A. Baumert, W. Maier, U. Matern, J. Schmidt, B. Schumann, and D. Gröger, *Planta Med.* **60**, 143 (1994).
101. S. Gibbons, L. Craven, C. Dunlop, A. I. Gray, T. G. Hartley, and P. G. Waterman, *Phytochemistry* **44**, 1109 (1997).
102. A. T. McPhail, M. Ju-ichi, Y. Fujitani, M. Inoue, T.-S. Wu, and H. Furukawa, *Tetrahedron Lett.* **26**, 3271 (1985).

103. C. Ito, S. Tanahashi, K. Fujiwara, M. Nakagawa, M. Ju-ichi, Y. Fujitani, M. Inoue, A. T. McPhail, T.-S. Wu, I. Kajiura, M. Omura, and H. Furukawa, *Chem. Pharm. Bull.* **38**, 1881 (1990).
104. Y. Takemura, Y. Isono, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **41**, 789 (1993).
105. S. Habtemariam, P. G. Waterman, and T. G. Hartley, *Phytochemistry* **43**, 291 (1996).
106. R. H. Prager and H. M. Thredgold, *Aust. J. Chem.* **21**, 229 (1968).
107. R. H. Prager and H. M. Thredgold, *Aust. J. Chem.* **22**, 1477 (1969).
108. R. H. Prager and H. M. Thredgold, *Aust. J. Chem.* **22**, 1493 (1969).
109. R. H. Prager and H. M. Thredgold, *Aust. J. Chem.* **22**, 1503 (1969).
110. S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and T. Sévenet, *Nat. Prod. Lett.* 7, 219 (1995).
111. W. D. Crow and J. R. Price, *Aust. J. Sci. Res.* **A2**, 282 (1949).
112. J. P. Koko and J. H. Goldstein, *Spectrochim. Acta* **19**, 1119 (1963).
113. Zs. Rózsa, K. Szendrei, Z. Kovacs, I. Novák, E. Minker and J. Reisch, *Phytochemistry* **17**, 169 (1978).
114. Zs. Rózsa, K. Szendrei, Z. Kovacs, I. Novák, J. Reisch, and E. Minker, *Pharmazie* **30**, 753 (1975).
115. M. Ahsan, A. I. Gray, G. Leach and P. G. Waterman, *Phytochemistry* **33,** 1507 (1993).
116. M. Ahsan, A. I. Gray, P. G. Waterman, and J. A. Armstrong, *J. Nat. Prod.* **57**, 670 (1994).
117. J. Reisch, K. Szendrei, I. Novák, E. Minker, and Zs. Rózsa, *Experientia* **27,** 1005 (1971).
118. A. Ulubelen and N. Tan, *Phytochemistry* **29**, 3991 (1990).
119. A. Ulubelen, H. Güner, and M. Cetindag, *Planta Med.* **54,** 551 (1988).
120. W. Scharlemann, *Z. Naturforsch.* **27b,** 806 (1972).
121. J. Reisch, W. Probst, and D. Gröger, *Pharmazie* **45,** 500 (1990).
122. M. Ju-ichi, M. Inoue, C. Ito, M. Matsuoka, H. Furukawa, and I. Kajiura, *Heterocycles* **26,** 1873 (1987).
123. C. Spatafora and C. Tringali, *Phytochem. Anal.* **8,** 139 (1997).
124. Zs. Rózsa, J. Reisch, I. Mester, and K. Szendrei, *Fitoterapia* **52,** 37 (1981).
125. F. Fish and P. G. Waterman, *Phytochemistry* **10,** 3322 (1971).
126. F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.* **23, suppl.** 132S (1971).
127. P. G. Waterman, A. I. Gray, and E. G. Crichton, *Biochem. Syst. Ecol.* **4,** 259 (1976).
128. J. Reisch, Zs. Rózsa, K. Szendrei, I. Novak, and E. Minker, *Phytochemistry* **16,** 151 (1977).
129. R. Hänsel and E.-M. Cybulski, *Arch. Pharm. (Weinheim)* **311,** 135 (1978).
130. D. L. Dreyer, *Phytochemistry* **19,** 941 (1980).
131. F. Bevalot, A. Fournier, C. Moretti, and J. Vaquette, *Planta Med.* **50**, 522 (1984)
132. J. Reisch, S. K. Adesina, and D. Bergenthal, *Pharmazie* **40,** 811 (1985).
133. X. A. Dominquez, R. Franco, S, Garcia, A. Merijian, G. Espinoza, S. Tamez, and A. B. Zilli, *Latinoamer. Chim.* **17**, 60 (1986).

134. A. Baumert, D. Gröger, I. N. Kuzovkina, and J. Reisch, *Plant Cell Tiss. Org. Chem.* **28**, 159, (1992).
135. F. Tillequin, G. Baudouin, M. Koch, and T. Sévenet, *J. Nat. Prod.* **43,** 498 (1980).
136. Y. Takemura, H. Kawaguchi, S. Maki, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **44,** 804 (1996).
137. Y. Kofi, J. Gleye, C. Moulis, and E. Stanislas, *Planta Med.* **53,** 570 (1987).
138. J. A. Lamberton and J. R. Price, *Aust. J. Chem.* **6**, 66 (1953).
139. A. Ganguly, T. R. Govindachari, A. Manmade, and P. A. Mohamed, *Indian J. Chem.* **4**, 334 (1966).
140. C. Kan-Fan, B. C. Das, P. Boiteau, and P. Potier, *Phytochemistry* **9**, 1283 (1970).
141. F. Fish, A. I. Gray, and P. G. Waterman, *J. Pharm. Pharmacol.* **28,** suppl. 72p (1976).
142. F. D. Popp and D. P. Chakraborty, *J. Pharm. Sci.* **53,** 968 (1964).
143. G.K. Hughes, K.G. Neill, E. Ritchie, *Aust. J. Sci. Res.* **A5,** 401 (1952).
144. Zs. Rózsa, Dissertation, Szeged (1977).
145. I. H. Bowen and Y. N. Patel, *Planta Med.* **53,** 73 (1987).
146. A. A. Auzi, R. D. Waigh, and P. G. Waterman, *J. Pharm. Pharmacol.* **42,** 1087 (1994).
147. A. A. Auzi, T. G. Hartley, R. D. Waigh, and P. G. Waterman, *Phytochemistry* **42,** 235 (1996).
148. S. K. Adesina, *Fitoterapia* **58,** 123 (1987).
149. E. Dagne, A. Yenesew, P. G. Waterman, and A. I. Gray, *Biochem. Syst. Ecol.* **16,** 179 (1988).
150. W.- H. Xu and Z. Xue, *Acta Chim. Sinica* **42,** 899 (1984).
151. Y. Takemura, H. Uchida, M. Ju-ichi, M. Omura, C. Ito, K. Nakagawa, T. Ono, and H. Furukawa, *Heterocycles* **34,** 2123 (1992).
152. G. K. Hughes and K. G. Neill, *Aust. J. Sci. Res.* **A2**, 429 (1949).
153. J. Gell, G. K. Hughes and E. Ritchie, *Aust. J. Chem.* **8,** 114 (1955).
154. R. R. Paris and A. Stambouli, *Compt. Rend.*, C **247,** 2421 (1958).
155. H. Rapoport and K. G. Holden, *J. Am. Chem. Soc.* **82,** 4395 (1960).
156. K. H. Pegel and W. G. Wright, *J. Chem Soc. C* 2327 (1969).
157. P. G. Waterman, *Biochem. Syst.* **1,** 153 (1973).
158. J. Vaquette, M. O. Clériot, M. R. Paris, J. L. Pousset, A. Cavé, and R. R. Paris, *Plant. Med. Phytother.* **8,** 57 (1974)
159. J. Vaquette, M. O. Cleriot, M. R. Paris, J. L. Pousset, A. Cavé, and R. R. Paris, *Plant. Med. Phytother.* **9,** 304 (1975).
160. S. R. Johns and J. A. Lamberton, *Aust. J. Chem.* **19,** 895 (1966).
161. R. N. Chakravarti, D. Chakravarti, and S. C. Chakravarti, *J. Chem. Soc.* 3337 (1953).
162. S. C. Pakrashi, S. K. Roy, L. F. Johnson, T. George, and C. Djerassi, *Chem. Ind. (London),* 464 (1961).
163. T. N. Vasudevan and M. Luckner, *Pharmazie* **23,** 520 (1968).
164. I. Novák, G. Buzás, E. Minker, M. Koltai, and K. Szendrei, *Pharmazie* **20,** 655 (1965).

165. L. Fonzes and F. Winternitz, *Compt. Rend. C* **266,** 930 (1968).
166. F. N. Lahey, M. Mc Camish, and T. Mc Ewan, *Aust. J. Chem.* **22,** 447 (1969).
167. S. K. Talapatra, B. C. Maiti, and B. Talapatra, *Tetrahedron Lett.* 2683 (1971).
168. F. Fish and P. G. Waterman, *J. Pharm. Pharmacol.* **23,** 67 (1971).
169. A. Cavé, J. I. Ramos de Souza, and R. R. Paris, *Plant. Med. Phytother.* **5,** 327 (1971)
170. A. G. Gonzalez, E. C. Diaz, H. D. Lopez, J. R. Luis, and F. L. Rodriquez, *An. Quim.* **73,** 430 (1977).
171. I. H. Bowen, K. P. Perera, and J. R. Lewis, *Phytochemistry* **17,** 2125 (1978).
172. B. T. Ngadjui, J. F. Ayafor, and B. L. Sondengam, *Bull. Chem. Soc. Ethiop.* 2, 21 (1988).
173. K. Rastogi, R. S. Kapil, and S. P. Popli, *Phytochemistry* **19,** 945 (1980).
174. S. K. Talapatra, B. Karmacharya, S. C. De, and B. Talapatra, *Ind. J. Chem. Sect. B* **28,** 356 (1989).
175. T.- S. Wu and H. Furukawa, *Chem. Pharm. Bull.* **31,** 901 (1983).
176. M. Ju-ichi, M. Inoue, Y. Fujitani, and H. Furukawa, *Heterocycles* **23,** 1131 (1985).
177. C. Ito, K. Fujiwara, M. Kajita, M. Ju-ichi, Y. Takemura, Y. Suzuki, K. Tanaka, M.Omura, and H. Furukawa, *Chem. Pharm. Bull.* **39,** 2509 (1991).
178. J. A. Lamberton, *Aust. J. Chem.* **19,** 1995 (1966).
179. A. Ahond, F. Picot, P. Potier, C. Poupat, and T. Sévenet, *Phytochemistry* **17,** 166 (1978).
180. G. H. Svoboda, *Lloydia* **29,** 206 (1966).
181. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **47, 285** (1984).
182. S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, and J. Pusset, *Ann. Pharm. Fr.* **47,** 149 (1989).
183. G. H. Svoboda, G. A. Poore, P. J. Simpson, and G. B. Boder, *J. Pharm. Sci.* **55,** 758 (1966).
184. Y. Takemura, J. Kuwahara, N. Nagareya, M. Ju-ichi, M. Omura, I. Kajiura, C. Ito, and H. Furukawa, *Heterocycles* **39,** 315 (1994).
185. B. Cougé, F. Tillequin, M. Koch, and T. Sévenet, *Pl. Med. Phytother.* **14,** 208 (1980).
186. M. Brum-Bousquet, F. Tillequin, M. Koch, and T. Sévenet, *Planta Med.* **51,** 536 (1985).
187. A. L. Skaltsounis, L. Sedrati, F. Tillequin, M. Koch, and J. Pusset, *Nat. Prod. Lett.* **5,** 281 (1995).
188. I. H. Bowen, K. P. Perera, and J. R. Lewis, *Phytochemistry* **19,** 1566 (1980).
189. J. S. Shah and B. K. Sabata, *Ind. J. Chem., Sect. B* **21,** 16 (1982).
190. E. M. K. Wijeratne, B. M. R. Bandara, A. A. L. Gunatilaka, Y. Tezuka, and T. Kikuchi, *J. Nat. Prod.* **55,** 1261 (1992).
191. T.-S. Wu, C.-S. Kuoh, and H. Furukawa, *Phytochemistry* **22,** 1493 (1983).
192. T.-S. Wu, *Phytochemistry* **26,** 3094 (1987).
193. S.-H. Chang, *Phytochemistry* **29,** 351 (1990).
194. I. H. Bowen, and Y. N. Patel, *Phytochemistry* **25,** 429 (1986).

195. T.-S. Wu, H. Furukawa, and C.-S. Kuoh, *Heterocycles* **19,** 273 (1982).
196. T.-S. Wu, C.-S. Kuoh, and H. Furukawa, *Chem. Pharm. Bull.* **31,** 895 (1983).
197. A. M. El Shafae and A. S. Soliman, *Pharmazie* **53,** 640 (1998).
198. M. Ju-ichi, M. Inoue, I. Kajiura, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **36,** 3202 (1987).
199. M. Bert, M. Koch, and M.Plat, *Phytochemistry* **13,** 301 (1974).
200. F. N. Lahey and W. C. Thomas, *Aust. J. Sci. Res.* **A2,** 423 (1949).
201. J. R. Price, *Aust. J. Sci. Res.* **A2,** 249 (1949).
202. J. Vaquette, R. Hocquemiller, J. L. Pousset, and A. Cavé, *Planta Med.* **33,** 78 (1978).
203. B. M. R. Bandara, A. A. L. Gunatilaka, E. M. K. Wijeratne, and J. K. MacLeod, *Phytochemistry* **29,** 297 (1990).
204. M. Ju-ichi, H. Kaga, M. Muraguchi, M. Inoue, I. Kajiura, M. Omura, and H. Furukawa, *Heterocycles* **27,** 2197 (1988).
205. G. Gu, *Xaoxue Xuebao* **22,** 886 (1987). *CA* **109,** 183612 (1988).
206. S. Mitaku and J. Pusset, *Plant. Med. Phytother.* **22,** 83 (1988).
207. A. L. Skaltsounis, F. Tillequin, M. Koch, and T. Sévenet, *J. Nat. Prod.* **46,** 732 (1983).
208. D.-K. Qin, *Xaoxue Xuebao* **21,** 683 (1986). *CA* **106,** 135228 (1987).
209. S.-C. Huang, M.-T. Chen, and T.-S. Wu, *Phytochemistry* **28,** 3574 (1989).
210. P. C. Vieira, I. Kubo, H. Kujime, Y. Yamagiwa, and T. Kamikawa, *J. Nat. Prod.* **55,** 1112 (1992).
211. W. Lwande, T. Gebreyesus, A. Chapya, C. MacFoy, A. Hassana, and M. Okecch, *Insect Sci. Appl.* **4,** 393 (1983).
212. T. -S. Wu, H. Furukawa, and C.-S. Kuoh, *Heterocycles* **19,** 1047 (1982).
213. M. Ju-ichi, M. Inoue, K. Aoki, and H. Furukawa, *Heterocycles* **24,** 1595 (1986).
214. T.-S. Wu, *Phytochemistry* **26,** 871 (1987).
215. M. Ju-ichi, Y. Takemura, C. Ito, and H. Furukawa, *Heterocycles* **32,** 1781 (1991).
216. T.-S. Wu, S.-C. Huang, T.-T. Jong, J.-S. Lai, and C.-S. Kuoh, *Phytochemistry* **27,** 585 (1988).
217. T.-S. Wu, *Phytochemistry* **27,** 3717 (1988).
218. S. C. Basa, *Indian J. Nat. Prod.* **8,** 18 (1992). *CA* **119,** 91186 (1993).
219. A. Chatterjee and D. Ganguly, *Phytochemistry* **15,** 1303 (1976).
220. T. R. Govindachari, N. Viswanathan, B. R. Pai, V. N. Ramachandran, and P. S. Subramanian, *Tetrahedron* **26,** 2905 (1970).
221. J. Banerji, N. Ghoshal, S. Sarkar, A. Patra, K. Abraham, and J. N. Shoolery, *Indian J. Chem., Sect. B* **20,** 835 (1981).
222. Y. Takemura, J. Takaya, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **43,** 2483 (1996).
223. G. H. Kulkarni and B. K. Sabata, *Phytochemistry* **20,** 867 (1981).
224. T.-S. Wu, H. Furukawa, and K.-S. Hsu, *Heterocycles* **19,** 1227 (1982).
225. A. Ulubelen and H. Güner *J. Nat. Prod.* **51,** 1012 (1988).
226. A. Ulubelen and B. Terem, *Phytochemistry* **27,** 650 (1988).

227. G. A. Gonzales, C. A. Diaz, D. H. Lopez, J. R. Luis, and L. F. Rodriguez, *Ann. Quim.* **72,** 94 (1976).
228. J. Reisch, K. Szendrei, E. Minker, and I. Novak, *Acta Pharm. Suec.* **4,** 265 (1967).
229. H. Paulini, R. Waibel, J. Kiefer, and O. Schimmer, *Planta Med.* **57,** 82 (1991).
230. A. Baumer, D. Gröger, J. Schmidt, I. N. Kuzovkina, and C. Mügge, *Fitoterapia* **59,** 83 (1988).
231. J. Reisch, Zs. Rózsa, and I. Mester *Z. Naturforsch.* **33b,** 957 (1978).
232. A. Baumer, D. Gröger, J. Schmidt, and C. Mügge, *Pharmazie* **42,** 67 (1987).
233. J. Reisch and G. M. K. Gunaherath, *J. Chem. Soc., Perkin Trans. 1,* 1047 (1989).
234. A. Ulubelen, A. H. Mericli, F. Mericli, U. Sonmez, and R. Ilarslan, *Nat. Prod. Lett.* **1,** 269 (1993).
235. Y. Takemura, Y. Matsushita, S. Onishi, T. Atarashi, K. Kunito, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **41,** 187 (1995).
236. A. Nahrstedt, V. Wray, B. Engel, and E. Reinhard, *Planta Med.* **51,** 517 (1985).
237. Zs. Rózsa, J. Reisch, K. Szendrei, and E. Minker, *Fitoterapia* **52,** 93 (1981).
238. A. Nahrstedt, V. Eilert, B. Wolters, and V. Wray, *Z. Naturforsch.* **36c,** 200 (1981).
239. B. Wolters and U. Eilert, *Planta Med.* **43,** 166 (1981).
240. U. Eilert, B. Wolters, A. Nohrsted, and V. Wray, *Z. Naturforsch.* **37c,** 132 (1982).
241. J. Reisch, Zs. Rózsa, K. Szendrei, I. Novák, and E. Minker, *Phytochemistry* **11,** 2121 (1972).
242. J. Reisch, Zs. Rózsa, K. Szendrei, I. Novák, and E. Minker, *Phytochemistry* **15,** 240 (1976).
243. J. Reisch, K. Szendrei, Zs. Rózsa, I. Novák, and E. Minker, *Phytochemistry* **11,** 2359 (1972).
244. A. Baumert, W. Maier, U. Matern, J. Schmidt, B. Schumann, and D. Gröger, *Planta Med.* **60,** 143 (1994).
245. M. T. Fauvel. J. Gleye, C. Moulis, and I. Fouraste, *Plant. Med. Phytother.* **12,** 207 (1978).
246. T. R. Govindachari, B. R. Pai, and P. S. Subramaniam, *Tetrahedron* **22,** 3245 (1966).
247. S. Funayama, R. P. Borris, and G. A. Cordell, *J. Nat. Prod.* **46,** 391 (1983).
248. V. Kumar, J. Reisch and A. Wickramasinghe, *Aust. J. Chem.* **42,** 1375 (1989).
249. S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and G. Chauviere, *Heterocycles* **26,** 2057 (1987).
250. T.-S. Wu, S.-C. Huang, T. T. Jong, J.-S. Lai, and C.-S. Kuoh, *Heterocycles* **26,** 2077 (1987).
251. S. C. Basa, *Experientia* **31,** 1387 (1975).
252. A. W. Fraser and J. R. Lewis, *J. Chem. Soc., Perkin Trans I* 1173 (1973).

253. T.-S. Wu, R. J. Cheng, S. C. Huang, and H. Furukawa, *J. Nat. Prod.* **49,** 1154 (1986).
254. T. Ono, C. Ito, H. Furukawa, T.-S. Wu, C.-S. Kuoh, and K.-S. Hsu, *J. Nat. Prod.* **58,** 1629 (1995).
255. M. Brum-Bousquet, S. Mitaku, A. L. Skaltsounis, F. Tillequin and M. Koch, *Planta Med.* **54,** 470 (1988).
256. S. C. Basa and R. N. Tripathy, *J. Nat. Prod.* **47,** 325 (1984).
257. T.-S. Wu, C.-S. Kuoh, and H. Furukawa, *Phytochemistry* **21,** 1771 (1982).
258. S. C. Basa, *Phytochemistry* **14,** 835 (1975).
259. T.-S. Wu and H. Furukawa, *Heterocycles* **19,** 825 (1982).
260. D. Basu and S. C. Basa, *J. Org. Chem.* **37,** 3035 (1972).
261. Y. Takemura, M. Inoue, H. Kawaguchi, M. Ju-ichi, C. Ito, H. Furukawa, and M. Omura, *Heterocycles* **34,** 2363 (1992).
262. H. Furukawa, C. Ito, T. Mizuno, M. Ju-ichi, M. Inoue, I. Kajiura, and M. Omura, *J. Chem. Soc., Perkin Trans. 1* 1593 (1990).
263. Y. Takemura, M. Ju-ichi, M. Omura, M. Haruna, C. Ito, and H. Furukawa, *Heterocycles* **38,** 1937 (1994).
264. Y. Takemura, M. Abe, M. Ju-ichi, C. Ito, K. Hatano, M. Omura, and H. Furukawa, *Chem. Pharm. Bull.* **41,** 406 (1993).
265. Y. Takemura, T. Kurozumi, M. Ju-ichi, M. Okano, N. Fukamiya, C. Ito, T. Ono, and H. Furukawa, *Chem. Pharm. Bull.* **41,** 1757 (1993).
266. H. Furukawa, T.-S. Wu, C.-S. Kuoh, T. Sato, Y. Nagai, and K. Kagei, *Chem. Pharm. Bull.* **32,** 1647 (1984).
267. A. W. Fraser and J. R. Lewis, *J. Chem. Soc. Chem. Commun.* 615 (1973).
268. H. Furukawa, C. Ito, T. Ono, T.-S. Wu, and C.-S. Kuoh, *J. Chem. Soc., Perkin Trans. 1* 471 (1993).
269. T.-S. Wu, S.-C. Huang and P.-L. Wu, *Phytochemistry* **42,** 221 (1996).
270. Y. Takemura, Y. Matsushita, N. Nagareya, M. Abe, J. Takaya, M. Ju-ichi, T. Hashimoto, Y. Kan, S. Takaoka, Y. Asakawa, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **42,** 1548 (1994).
271. Y. Takemura, M. Ju-ichi, T. Hashimoto, Y. Kan, S. Takaoka, Y. Asakawa, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **43,** 1340 (1995).
272. Y. Takemura, S. Maki, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **36,** 675 (1993).
273. M. Ju-ichi, Y. Takemura, N. Nagareya, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **42,** 237 (1996).
274. S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, J. Pusset, and G. Chauviere, *J. Nat. Prod.* **49,** 1091 (1986).
275. A. Ulubelen, B. Terem, E. Tuzlaci, K. F. Cheng, and Y. C. Kong, *Phytochemistry* **25,** 2692 (1986).
276. S. Vajrodaya, M. Bacher, H. Greger, and O. Hofer, *Phytochemistry* **48,** 897 (1998).
277. Y. Takemura, J. Takaya, Y. Okamura, Y. Arima, T. Atarashi, N. Nagareya, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **46,** 1518 (1998).

278. Y. Takemura, M. Wada, M. Ju-ichi, C. Ito, and H. Furukawa, *Chem. Pharm. Bull.* **46,** 693 (1998).
279. Y. Takemura, J. Kuwahara, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **45,** 1411 (1997).
280. Z. Rózsa, I. N. Kusovkina, J. Reisch, I. Novák, K. Szendrei, and E. Minker, *Fitoterapia* **47**, 147 (1976).
281. J. Zanos Gougoutas and B. A. Kaski, *Acta Cryst.* **B26**, 853 (1970).
282. P. L. Macdonald, A. V. Robertson, *Aust. J. Chem.* **19**, 275 (1966).
283. H. Fischer, A. Römer, B. Ulbrich, and H. Arens, *Planta Med.* **52**, 398 (1988).
284. W. Baczynski and S. von Niementowski, *Ber. Dtsch. Chem. Ges.* **38**, 3009 (1905).
285. J. R. Beck, R. Kwok, R. N. Booher, A. C. Brown, L. E. Patterson, P. Pranc, B. Rockey, and A. Pohland, *J. Am. Chem. Soc.* **90**, 4706 (1968).
286. J. Hlubucek, E. Ritchie, and W. C. Taylor, *Aust. J. Chem.* **23**, 1881 (1970).
287. R. R. Smolders, J. Hanuise, and N. Voglet, *Bull. Soc. Chim. Belg.* **93**, 239 (1984).
288. M. H. Bahar and B. K. Sabata, *Ind. J. Chem.* **26b**, 782 (1987).
289. K. Ramesh and R. S. Kapil, *Ind. J. Chem.* **25b**, 684 (1986).
290. J. R. Beck, Hlubucek, J. R. Beck, R. N. Booher, A. C. Brown, R. Kwok, and A. Pohland, *J. Am. Chem. Soc.* **89**, 3934 (1967).
291. W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. I* 998 (1974).
292. J. Reisch, H. M. T. A. Herath, and N. S. Kumar, *Liebigs Ann. Chem.* 839 (1991).
293. G. M. Coppola and H. F. Schuster, *J. Het. Chem.* **26**, 957 (1989).
294. J.-J. Chen, L. W. Deady, and M. F. Mackay, *Tetrahedron* **53**, 12717 (1997).
295. G. K. Hughes, K. G. Neill, and E. Ritchie, *Aust. J. Sci. Res.* **A3**, 497 (1950).
296. F. Ullmann, *Ber. Dtsch. Chem. Ges.* **36**, 2382 (1903).
297. F. Dallacker and G. Adolphen, *Tetrahedron Lett.*, 2023 (1965).
298. F. Dallacker and G. Adolphen, *Liebigs Ann. Chem.* **691**, 138 (1966).
299. F. Dallacker and G. Adolphen, *Liebigs Ann. Chem.* **691**, 134 (1966).
300. T. R. Govindachari, B. R. Pai, P. S. Subramanian, and V. Subramanyam, *Tetrahedron* **23**, 1827 (1967).
301. L. J. Drummond and F. N. Lahey, *Aust. J. Sci. Res.* **A2**, 630 (1949).
302. C. S. Oh and C. V. Greco, *J. Het. Chem.* **7**, 261 (1970).
303. J. R. Cannon, G. K. Hughes, K. G. Neill, and E. Ritchie, *Aust. J. Sci. Res.* **A5**, 406 (1952).
304. I. Tănăsescu, M. Ionescu, I. Goia, and H. Mantsch, *Bull. Soc. Chim. Fr.* 698 (1960).
305. M. Ionescu and I. Mester, *Rev. Roum. Chim.* **14**, 789 (1969).
306. M. Ionescu and M. Vlassa, *Rev. Roum. Chim.* **16**, 743 (1971).
307. J. Reisch, *Arch. Pharm. (Weinheim)* **320**, 1065 (1987).
308. T.-S. Su, K. Dziewiszek, and T.-S. Wu, *Tetrahedron Lett.* **32**, 1541 (1991).
309. T.-S. Su, B. Köhler, T.-C. Chou, M. W. Chun, and K. A. Watanabe, *J. Med. Chem.* **35**, 2703 (1992).

310. C. Mongrain, L. Lee, and P. Brassard, *Synthesis* 678 (1993).
311. C. Mongrain and P. Brassard, *Heterocycles* **36**, 2109 (1993).
312. N. Kato, M. Fujita, K. Fujimura, Y. Kawashima, and Y. Nishiyama, *Chem. Pharm. Bull.* **41**, 445 (1993).
313. M. Iwao, J. N. Reed, and V. Snieckus, *J. Am. Chem. Soc.* **104**, 5531 (1982).
314. M. Watanabe, A. Kurosaki, and S. Furukawa, *Chem. Pharm. Bull.* **32**, 1264 (1984).
315. S. K. Dyke, A. R. Marshall, and J. P. Watson, *Tetrahedron* **22**, 2515 (1966).
316. H.Heaney and J. M. Jablonski, *J. Chem. Soc. (C)* 1895 (1968).
317. H.Heaney and K. G. Mason, and J. M. Stetchley, *J. Chem. Soc. (C)* 567 (1971).
318. S. Horne and R. Rodrigo, *J. Chem. Soc., Chem. Commun.* 1046 (1991).
319. G. M. Coppola, *J. Het. Chem.* **21**, 1569 (1984).
320. G. M. Coppola, *J. Het. Chem.* **21**, 913 (1984).
321. F. Benington and R. D. Morin, *J. Org. Chem.*, **27**, 142 (1962).
322. J.-J. Chen and L. W. Deady, *Synth. Commun.* **27**, 95 (1997).
323. L. W. Deady and D. M. Werden, *J. Org. Chem.* **52**, 3930 (1987).
324. J. Favorskaya, *J. Gen. Chem. USSR* **9**, 386 (1939).
325. G. F. Hennion and A. P. Boisselle, *J. Org. Chem.* **26**, 725 (1961).
326. M. F. Grundon, W. Probst, and J. Reisch, *Monatsh. Chem.* **121**, 157 (1990).
327. R. C. Anand and A. K. Sinha, *Heterocycles* **31**, 1733 (1990).
328. R. C. Anand and A. K. Sinha, *J. Chem. Soc., Perkin Trans. I* 2339 (1991).
329. R. C. Anand and N. Selvapalam, *J. Chem. Soc., Chem. Commun.* 199 (1996).
330. J. Reisch, I. Mester, S. K. Kapoor, Zs. Rózsa, and K.Szendrei, *Liebigs Ann. Chem.*, 85 (1981).
331. J. Nickl, *Chem. Ber.* **91**, 553 (1958).
332. I. Mester, J. Reisch, Zs. Rózsa, and K.Szendrei, *Heterocycles* **16**, 77 (1981).
333. A. Wickramasinghe and J. Reisch, *Planta Med.* **55**, 586 (1989).
334. J. Reisch, A. Wickramasinghe, and W. Probst, *Monatsh. Chem.* **121**, 829 (1990).
335. J. Reisch and A. A. Voerste, *Liebigs Ann. Chem.*, 299 (1991).
336. J. Reisch, H. R. W. Dharmaratne, K. Schiwek, and G. Henkel, *J. Chem. Res. (S)* 157; *J. Chem. Res. (M)* 910 (1994).
337. C. Ito, T. Ono, K. Hatano, and H. Furukawa, *Chem. Pharm. Bull.* **41**, 383 (1993).
338. W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *J. Chem. Soc. (C)* 811 (1971).
339. W. M. Bandaranayake, L. Crombie, and D. A. Whiting, *Chem. Commun.* 970 (1969).
340. W. M. Bandaranayake, M. J. Begley, B. O. Brown, D. G. Clarke, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. I* 998 (1974).
341. J. Hlubucek, E. Ritchie, and W. C. Taylor, *Tetrahedron Lett.* 1369 (1969).
342. J. Hlubucek, E. Ritchie, and W. C. Taylor, *Chem. Ind. (London)* 1809 (1969).

343. J. Schneider, E. L. Evans, E. Grunberg, and R. I. Fryer, *J. Med. Chem.* **15**, 266 (1972).
344. J. Reisch, I. Mester, and S. M. El-Moghazy Aly, *Liebigs Ann. Chem.* 31 (1984).
345. J. Reisch, A. A. W. Voerste, M. Top, and P. Dziemba, *Monatsh. Chem.* **123**, 473 (1992).
346. J. H. Adams, P. J. Bruce, and J. R. Lewis, *Lloydia* **39**, 399 (1976).
347. R. R. Smolders, A. Waefelaer, R. Coomans, D. Francart, J. Hanuise, and N. Voglet, *Bull. Soc. Chim. Belg.* **91**, 33 (1982).
348. R. R. Smolders, J. Hanuise, T. Lepoint, N. Voglet, B. Tinant, J. P. Declercq, and N. van Meerssche, *Tetrahedron* **40**, 5181 (1984).
349. J. Reisch and S. M. El-Moghazy Aly, *Arch. Pharm. (Weinheim)* **319**, 25 (1986).
350. J. Reisch and V. Probst, *Arch. Pharm. (Weinheim)* **322**, 31 (1989).
351. J. Reisch and P. Dziemba, *Arch. Pharm. (Weinheim)* **324**, 67 (1991).
352. J. Reisch and P. Dziemba, *J. Het. Chem.* **29**, 1293 (1992).
353. J. Reisch, P. Dziemba, and T. Adam, *J. Het. Chem.* **30**, 1469 (1993).
354. J. K. Kirtany, *Ind. J. Chem.* **20b**, 614 (1981).
355. C. M. Evans and A. J. Kirby, *J. Chem. Soc., Perkin Trans. II* 1269 (1984).
356. D. G. Loughhead, *J. Org. Chem.* **55**, 2245 (1990).
357. S. Blechert, K.-E. Fischer, and E. Winterfeldt, *Chem. Ber.* **111**, 439 (1978).
358. A. Elomri, S. Michel, F. Tillequin, and M. Koch, *Heterocycles* **34**, 799 (1992).
359. A. Elomri, S. Mitaku, S. Michel, A. L. Skaltsounis, F. Tillequin, M. Koch, A. Pierré, N. Guilbaud, S. Léonce, L. Kraus-Berthier, Y. Rolland, and Gh. Atassi, *J. Med. Chem.* **39**, 4762 (1996).
360. S. Blechert, K.-E. Fischer, J. Lindner, and E. Winterfeldt, *Liebigs Ann. Chem.*, 503 (1980).
361. H. Sullivan, R. Billings, J. Occolowitz, H. Boaz, F. Marshall, and R. McMahon, *J. Med. Chem.* **13**, 904 (1970).
362. J. Reisch and A. Wickramasinghe, *Monatsh. Chem.* **121**, 709 (1990).
363. J. Reisch and M. Top, *Pharmazie* **46**, 745 (1991).
364. J. Reisch and K. Schiwek, *Liebigs Ann. Chem.* 317 (1994).
365. S. Mitaku, A. L. Skaltsounis, F. Tillequin, and M. Koch, *Planta Med.* **54**, 24 (1988).
366. S. Mitaku, A. L. Skaltsounis, F. Tillequin, and M. Koch, *Synthesis* 1068 (1992).
367. S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, Y. Rolland, A. Pierré, and Gh. Atassi, *Pharm. Res.* **13**, 939 (1996).
368. A. L. Skaltsounis, S. Mitaku, G. Gaudel, F. Tillequin, and M. Koch, *Heterocycles* **34**, 121 (1992).
369. Z.-M. Wang, K. Kakiuchi, and K. B. Sharpless, *J. Org. Chem.* **59**, 6895 (1994).
370. N. Costes, S. Michel, F. Tillequin, M. Koch, A. Pierré, and Gh. Atassi, *J. Nat. Prod.* **62**, 490 (1999).

371. P. Magiatis, S. Mitaku, A. L. Skaltsounis, F. Tillequin, M. Koch, A. Pierré, and Gh. Atassi, *J. Nat. Prod.* **61**, 198 (1998).
372. J. Reisch and K. Schiwek, *Monatsh. Chem.* **125**, 731 (1994).
373. S. Funayama, G. A. Cordell, H. Wagner, and H. L. Lotter, *J. Nat. Prod.* **47**, 183 (1984).
374. S. Funayama and G. A. Cordell, *Planta Med.* **48**, 263 (1983).
375. S. Funayama and G. A. Cordell, *Heterocycles* **20**, 2379 (1983).
376. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **48**, 114 (1985).
377. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **48**, 536 (1985).
378. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **48**, 547 (1985).
379. S. Funayama, G. A. Cordell, R. D. Macfarlane, and C. J. McNeal, *J. Org. Chem.* **50**, 1737 (1985).
380. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **48**, 938 (1985).
381. S. Funayama and G. A. Cordell, *J. Nat. Prod.* **49**, 210 (1986).
382. S. Funayama, T. Aoyagi, K. Tadauchi, T.-Y. Pan, S. Nozoe, and G. A. Cordell, *Heterocycles* **41**, 1381 (1995).
383. S. Funayama and G. A. Cordell, *Heterocycles* **29**, 815 (1989).
384. G. Baudouin, S. Mitaku, E. Mikros, A. L. Skaltsounis, and F. Tillequin, *Heterocycles* **34**, 1691 (1992).
385. S. Funayama, T.-Y. Pan, S. Nozoe, and G. A. Cordell, *Heterocycles* **43**, 1251 (1996).
386. C. Ito, S. Tanahashi, Y. Tani, M. Ju-ichi, M. Omura, and H. Furukawa, *Chem. Pharm. Bull* **38**, 2586 (1990).
387. T. S. Wu, S. C. Huang, T. T. Jong, and J. S. Lai, *Heterocycles* **24**, 41 (1986).
388. T. G. Hartley, *J. Arnold. Arbor.* **55**, 469 (1974).
389. T. G. Hartley, *J. Arnold. Arbor.* **56**, 164 (1975).
390. T. G. Hartley, *Aust. J. Bot.* **30**, 359 (1982).
391. T. G. Hartley, *Adansonia* **8**, 183 (1986).
392. M. Koch, F. Tillequin, A. L. Skaltsounis, Y. Rolland, A. Pierré, and Gh. Atassi, *European Patent* N^0 95400314 (1995).
393. S. B. Reddy, W. A. Linden, F. Zywietz, H. Baisch, and U. Struck, *Arzneim.-Forsch./ Drug Res.* **27**, 1549 (1977).
394. B. P. Dunn, P. W. Gout, and C. T. Beer, *Cancer Res.* **33**, 2310 (1973).
395. T. C. Chou, C. C. Tzeng, T. S. Wu, K. A. Watanable, and T. L. Su, Phytother. Res. **3**, 237 (1989).
396. S. Kawaii, Y. Tomono, E. Katase, K. Ogawa, M. Yano, Y. Takemura, M. Ju-ichi, C. Ito, and H. Furukawa, *J. Nat. Prod.* **62**, 587 (1999).
397. R. T. Dorr, J. D. Liddil, D. D. Von Hoff, M. Soble, and C. K. Osborne, *Cancer Res.* **49**, 340 (1989).
398. A. Elomri, A. L. Skaltsounis, S. Michel, F. Tillequin, M. Koch, Y. Rolland, A. Pierré, and Gh. Atassi, *Chem. Pharm. Bull.* **44**, 2165 (1996).
399. H. L. Shieh, J. M. Pezzuto, and G. A. Cordell, *Chem. Biol. Interact.* **81**, 35 (1992).
400. K. F. Bastow, M. Itoigawa, H. Furukawa, Y. Kashiwada, I. D. Bori, L. M. Ballas, and K.-H. Lee, *Bioorg. Med. Chem.* **2**, 1403 (1994).

401. H. Fujioka, N. Kato, M. Fujita, K. Fujimura, and Y. Nishiyama, *Arzneim.-Forsch./ Drug Res.* **40**, 1026 (1990).
402. L. K. Basko, S. Mitaku, A. L. Skaltsounis, N. Ravelomanantsoa, F. Tillequin, M. Koch, and J. Le Bras, *Antimicrob. Agents Chemother.* **38**, 1169 (1994).
403. H. Fujioka, Y. Nishiyama, H. Furukawa, and N. Kumada, *Antimicrob. Agents Chemother.* **33**, 6 (1989).
404. S. F. Queener, H. Fujioka, Y. Nishiyama, H. Furukawa, M. S. Bartlett, and J. W. Smith, *Antimicrob. Agents Chemother.* **35**, 377 (1991).
405. N. Yamamoto, H. Furukawa, Y. Ito, S. Yoshida, K. Maeno, and Y. Nishiyama, *Antiviral Res.* **12**, 21 (1989).
406. Y. Takemura, M. Ju-ichi, C. Ito, H. Furukawa, and H. Tokuda, *Planta Med.* **61**, 366 (1995).
407. M. S. Yang, T. S. Wu, and C. H. Wang, *Planta Med.* **53**, 143 (1987).
408. Y. L. Leu, Y. Y. Chan, T. S. Wu, C. M. Teng, and K. T. Chen, *Phytother. Res.* **12**, S77 (1998).
409. Y. Takemura, M. Ju-ichi, M. Omura, C. Ito, and H. Furukawa, *Heterocycles* **51**, 854 (1999).

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