The Alkaloids

Volume 67

THE ALKALOIDS

Chemistry and Biology

VOLUME **67**

Edited by

Geoffrey A. Cordell

Evanston, Illinois

Amsterdam • Boston • Heidelberg • London • New York
Oxford Paris • San Diego • San Francisco • Sydney • Tokyo
Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
84 Theobald's Road, London WC1X 8RR, UK
Radarweg 29, PO Box 211, 1000 AE Amsterdam, The Netherlands
Linacre House, Jordan Hill, Oxford OX2 8DP, UK
30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, CA 92101-4495, USA

First edition 2009

ISBN: 978-0-12-374785-3
ISSN: 1099-4831

Printed and bound in USA

09 10 11 12 13 10 9 8 7 6 5 4 3 2 1

THE ALKALOIDS

Chemistry and Biology

VOLUME **67**

CONTRIBUTORS

Numbers in parentheses indicate the pages on which the authors' contributions begin.

Malgorzata Baranska (217), Department of Chemistry, Jagiellonian University, Krakow, Poland

Qiao-Hong Chen (1), Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, Sichuan University, Chengdu, People's Republic of China

Vinicius Ilha (79), Departamento de Química, NPPN, Universidade Federal de Santa Maria, Rio Grande do Sul, Brazil

Xiao-Tian Liang (1), Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

Graciela Maldaner (79), Departamento de Química, NPPN, Universidade Federal de Santa Maria, Rio Grande do Sul, Brazil

Russell J. Molyneux (143), Western Regional Research Center, Agricultural Research Service, USDA, Albany, California, USA

Ademir Farias Morel (79), Departamento de Química, NPPN, Universidade Federal de Santa Maria, Rio Grande do Sul, Brazil

Kip E. Panter (143), Poisonous Plant Research Laboratory, Agricultural Research Service, USDA, Logan, Utah, USA

Hartwig Schulz (217), Federal Research Centre for Cultivated Plants, Institute for Ecological Chemistry, Plant Analysis and Stored Product Protection, Quedlinburg, Germany

Feng-Peng Wang (1), Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, Sichuan University, Chengdu, People's Republic of China

PREFACE

As each volume of *The Alkaloids* series unfolds, much as one might have a vision to accumulate certain chapters, the reality of life intervenes. When this happens, one recalls the fourth "rule" of life's events: "Don't anticipate the outcome." The chapters here actually were planned originally to appear in two quite distinct volumes. Now they are gathered here; and actually they fit together quite well.

The diterpenoid alkaloids have been studied by several major research groups over the years in a number of countries. One of the leading sites for structure elucidation has been Professor Feng-Peng Wang's group at Sichuan University in Chengdu, People's Republic of China. This is the first review, with Qiao-Hong Chen and the venerable Xiao-Tian Liang as co-authors, summarizing the chemistry and biology of what has developed to be a quite distinct group within the diterpenoid alkaloids, the C_{18}-diterpenoid alkaloids.

The cyclopeptide alkaloids were previously reviewed in Volume 49 of this series in 1997, and were thus due for an update. This has been provided by Professor Ademir Farias Morel, Graciela Maldaner, and Vinicius Ilha from the Universidade Federal de Santa Maria, Brazil. The review examines the isolation, chemistry, synthesis, and several of the important biological aspects of the cyclopeptide alkaloids obtained in the past 13 years.

We frequently think of natural products research as being focused on the health beneficent effects for humans. The final two new chapters serve to remind us that there are nondesirable animal and human effects that also need to be studied. The chapter by Russell J. Molyneux and Kip E. Panter from laboratories of the United States Department of Agriculture focuses on the tremendous research efforts that have been undertaken on the toxic effects of several major alkaloid groups to the livestock that graze the fields in several major areas of the world. Aspects of these studies have been discussed in other chapters previously, but this is the first collection in this series.

A new topic to *The Alkaloids* series recognizes that the detection of alkaloids, particularly those with significant social implications, such as the opioids and cocaine, is of great interest. Rather than isolate and characterize compounds through liquid or solid spectroscopic or spectrometric methods, the remote detection and characterization of alkaloids, as discussed by Malgorzata Baranska and Hartwig Schulz, has become an area witnessing significant developments in the past few years.

Geoffrey A. Cordell
Evanston, Illinois

CONTENTS

CHAPTER 1

The C_{18}-Diterpenoid Alkaloids

Feng-Peng Wang[1,*], Qiao-Hong Chen[1] and Xiao-Tian Liang[2]

Contents

I. INTRODUCTION

The C_{18}-diterpenoid alkaloids constitute a small group within the diterpenoid alkaloids. The first C_{18}-diterpenoid alkaloid, lappaconitine, was isolated from the plants *Aconitum septentrionale* (1–3), *A. orientale* (4), and *A. excelsum* (5) by German and Russian scientists during the period 1922–1958. The structure of lappaconitine was confirmed by extensive chemical studies (6) and single-crystal X-ray analysis of its hydrolyzed

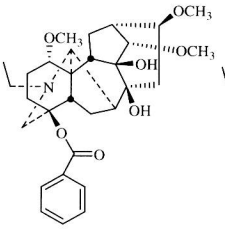
[1] Department of Chemistry of Medicinal Natural Products, West China School of Pharmacy, Sichuan University, Chengdu, People's Republic of China

[2] Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, People's Republic of China

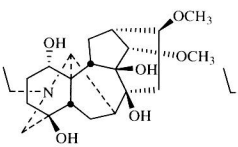
* Corresponding author.
E-mail address: wfp@scu.edu.cn (F.P. Wang)

The Alkaloids, Volume 67
ISSN: 1099-4831, DOI 10.1016/S1099-4831(09)06701-7

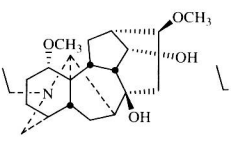
product, lappaconine hydrobromide (7,8). Following lappaconitine, three important C_{18}-diterpenoid alkaloids, lappaconidine (9,10), aconosine (11), and excelsine (12,13), were isolated and identified. These alkaloids have served as the cornerstones for subsequent advancements in C_{18}-diterpenoid alkaloids over the past 40 years.



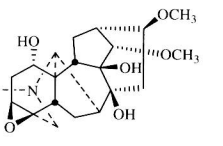
lappaconitine



lappaconidine



aconosine



excelsine

Lapaconitine, together with other C_{18}-diterpenoid alkaloids, was structurally classified as belonging to the broad C_{19}-diterpenoid alkaloids for a long time (4). However, Wang and Fang in 1985 (14) suggested the use of the term "C_{18}-diterpenoid alkaloids" for these alkaloids, which were subsequently also named as "norditerpenoid alkaloids" (15) or "bisnorditerpenoid alkaloids" (16), distinguishing them from the C_{19}-diterpenoid alkaloids. In order to clarify this confusing situation, Wang and Liang suggested the restoration of the original terms "C_{18}-," "C_{19}-," and "C_{20}-diterpenoid alkaloids" (17).

There were only 19 C_{18}-diterpenoid alkaloids discussed in the review by Pelletier *et al.* in 1984 (18). However, by the end of July 2008 the number of naturally occurring C_{18}-diterpenoid alkaloids isolated from 40 plant species had risen to a count of 78 delineated structures.

A careful analysis of the chemical structures and distribution of known C_{18}-diterpenoid alkaloids led to the conclusion that they possess the following distinctive features relative to C_{19}-diterpenoid alkaloids:

1. Structurally, C-4 is a methine unit or an oxygenated quaternary carbon; the former is similar to the C_{19}-diterpenoid alkaloids, but with fewer substitutions when compared with C_{19}-diterpenoid alkaloids; while the latter often possesses 4-OH, 4-OAc, or 4-*N*-acetyl anthranoyl groups and their derivatives. In very few instances, it contains a 3,4-epoxy structural unit.
2. From the distribution perspective, all of the C_{18}-diterpenoid alkaloids isolated from Chinese *Aconitum* plants are thus far distributed exclusively in plants of the subgenus *Lycoctonum* of the genus *Aconitum*, which is of chemotaxonomic significance (19).

Based on these aforementioned features, we strongly believe in the separation of this type of alkaloids from the C_{19}-diterpenoid alkaloids, and naming them as an independent group, the "C_{18}-diterpenoid alkaloids."

There are relatively few studies on the biological activities of the C_{18}-diterpenoid alkaloids. However, it is of interest to note that lappaconitine, obtained from various *Aconitum* plants, has been clinically developed as an antiarrhythmic drug in Uzbekistan (20,21), and as a non-narcotic analgesic drug in China (22–24).

II. CLASSIFICATION, DISTRIBUTION, AND OCCURRENCE

As indicated previously, the C_{18}-diterpenoid alkaloids have also been classified as C_{19}-diterpenoid alkaloids (6), norditerpenoid alkaloids (15), or bisnorditerpenoid alkaloids (16). Perhaps due to the limited number of characterized C_{18}-diterpenoid alkaloids, no extensive investigation on their classification was conducted prior to the report by Ichinohe et al. (25). In 2004, Ichinohe *et al.* (25) classified the C_{18}-diterpenoid alkaloids into two broad categories: the lappaconitine type (A) and the ranaconitine type (B, see Figure 1), based on whether an oxygen-containing functionality is attached at C-7. The lappaconitine-type C_{18}-diterpenoid alkaloids are similar to the aconitine-type C_{19}-diterpenoid alkaloids, while the ranaconitine-type C_{18}-diterpenoid alkaloids are similar to the lycoctonine-type C_{19}-diterpenoid alkaloids. We absolutely concur with this classification criterion, and recognize it as an appropriate structural classification of the C_{18}-diterpenoid alkaloids. In addition, according to whether an oxygen-containing functionality is attached at C-4, we have further subdivided the lappaconitine and ranaconitine types, respectively, into two subtypes: the aconosine (AI) and lappaconine (AII) subtypes, and the leuconine (BI) and ranaconitine (BII) subtypes (Figure 1).

The aconosine (AI) and leuconine (BI) subtypes are characterized by a C-4 methine moiety, while the lappaconitine (AII) and ranaconitine (BII) subtypes feature a C-4 oxygenated quaternary carbon. It is worth pointing out that the names of the subtypes were designated by the name of the first alkaloid discovered within the corresponding subtype.

1. Aconosine subtype (AI): few substituents; lacks a hydroxyl group at C-4; similar to the aconitine-type C_{19}-diterpenoid alkaloids, an acetoxyl group or aromatic ester group (such as OBz, OAs) attached to C-8 or C-14 in most cases. Only a few alkaloids possess the imine (e.g., liconosine A) or the amide (e.g., piepunendine A) structural unit.

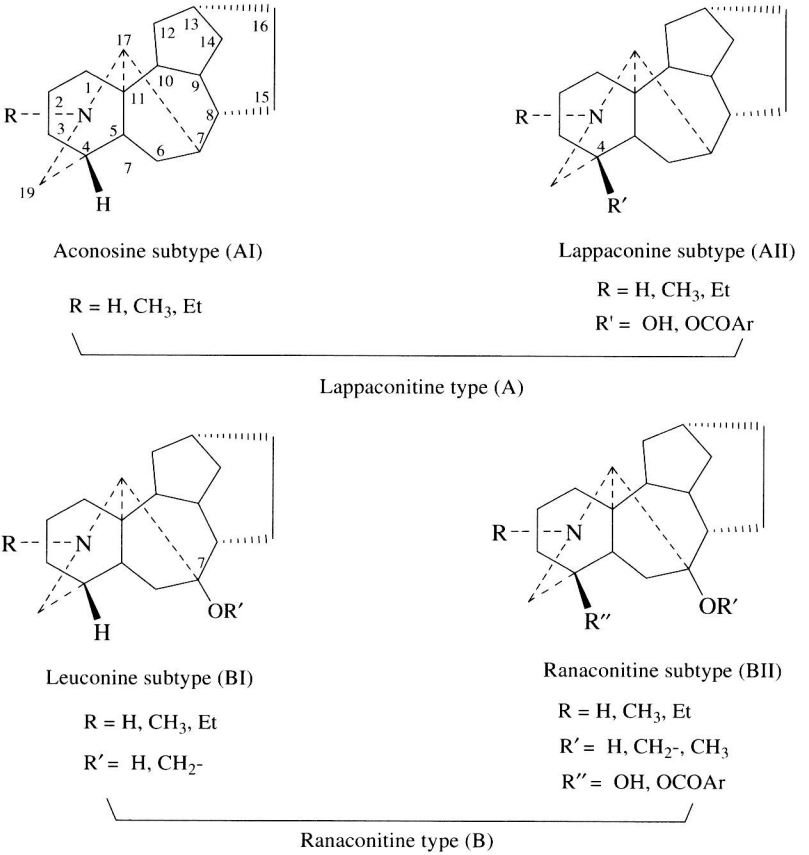


Figure 1 Classification of the C_{18}-diterpenoid alkaloids.

2. Lappaconine subtype (AII): most alkaloids of this subtype contain a hydroxyl group at the C-9 position; an anthranoyl group or its derivatives is located at C-4 in most cases, if it is present in the alkaloids; a very few alkaloids, such as monticamine, excelsine, and 8-acetylexcelsine, possess a 3β,4β-epoxy group.
3. Leuconine subtype (BI): generally contains fewer oxygenated functionalities (such as hydroxyl and ester groups); lacks a hydroxyl group at the C-9 position; almost all of the alkaloids of this subtype have an oxygenated functionality at the C-6 position; only a very few alkaloids have a C-8 methine moiety (e.g., leuconine) or an amide unit (e.g., lamarckinine).
4. Ranaconitine subtype (BII): some alkaloids have an amine-containing aromatic ester (e.g., an anthranilic acid ester or its derivatives) located at the C-4 position in most cases; some alkaloids, such as

sinomontanine D and ranaconitine, possess a hydroxyl group at C-9; individual alkaloids, such as finaconitine and *N*-deacetylfinaconitine, contain a hydroxyl group at C-10; a very few alkaloids, such as sinomontanine G and monticoline, contain a 3β,4β-epoxy group.

Almost all of the lappaconitine-type C_{18}-diterpenoid alkaloids are distributed exclusively in plants of the genus *Aconitum*, whereas only about 65% of the ranaconitine-type alkaloids have been isolated from plants of the genus *Aconitum*. Very few alkaloids (e.g., hohenackeridine and 14-*O*-demethoxydelboxine) have been obtained from plants of the genus *Cosolida*; all of the remaining alkaloids have been isolated from plants of the genus *Delphinium*.

The C_{18}-diterpenoid alkaloids are listed in Tables I and II according to the above-mentioned criteria, including their name, code, chemical structure, molecular formula, molecular weight, melting point, optical rotation, ^{1}H NMR, ^{13}C NMR, MS, and plant source. Table III lists the C_{18}-diterpenoid alkaloids occurring in the genera *Aconitum*, *Delphinium*, and *Cosolida* of the Ranunculaceae family. The C_{18}-diterpenoid alkaloids listed in this chapter and their code numbers are cross-indexed in Table IV.

III. NMR SPECTROSCOPY

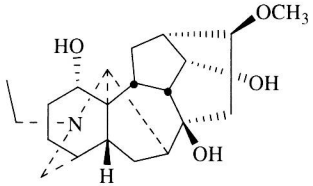
No comprehensive, systematic summary of the NMR data of the C_{18}-diterpenoid alkaloids has been provided thus far. Pelletier *et al.* (18,122) and Atta-ur-Rahman (123) have presented the NMR data for only around 20 C_{18}-diterpenoid alkaloids in their summarizing tables, in which the NMR data of the C_{18}-diterpenoid alkaloids were listed. Herein, the ^{1}H NMR data of 76 C_{18}-diterpenoid alkaloids and the ^{13}C NMR data of 64 C_{18}-diterpenoid alkaloids are presented in Tables V and VI, and VII and VIII, respectively, arranged in the order of the proposed classification criteria. In most cases, only the characteristic signals in the ^{1}H NMR spectra of the alkaloids have been reported (Tables V and VI). The major signals of most of the C_{18}-diterpenoid alkaloids were assigned based on comparison with those of similar alkaloids. Only for some of the alkaloids, such as 8-acetyldolaconine (31); piepanendine B (40); piepunendine A (40); delphicrispuline (63); kiridine (94); leucostine (97); anthriscifolcines A (102), C (102), and D (102); linearilin (106); sinomontanine D (55); tiantaishansine (118); 14-*O*-demethyldelboxine (120); and hohenackeridine (119), were all of the ^{1}H (^{13}C) NMR signals assigned according to their 2D NMR spectra. It is therefore difficult to avoid some assignment errors in the ^{13}C signals of the individual alkaloids. However, this does not affect the correctness of the structures.

Table I Lappaconitine-type alkaloids (A)

Aconosine subtype (AI)

AI-1

Scopaline (**1**)



$C_{21}H_{33}NO_4$

MW = 363

mp 167–169 (26)

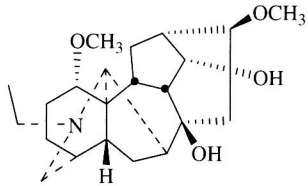
$[\alpha]_D$

^1H NMR (26), ^{13}C NMR (26), MS (26)

Aconitum episcopale (26)

AI-2

Aconosine (**2**)



$C_{22}H_{35}NO_4$

MW = 377

mp 148 (27,28), 142–143 (29), 147 (30), 149–151 (31), 149–152 (32), 150 (33,29), 147–48 (34)

$[\alpha]_D$ −21 (MeOH) (27), −25.4 (CH_3OH) (29), −24.4 (EtOH) (32)

^1H NMR (27*,28,29,31,32), ^{13}C NMR (28*,30–32,124), MS (19)

A. arcuatum (34)

A. campylorrhynchum (31)

A. contortum (32)

A. dunhuaense (37)

A. fischeri (34)

A. forrestii (29,30)

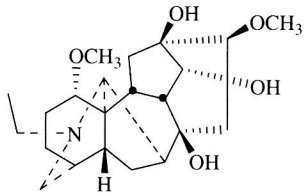
A. napellus (33)

A. nasutum (27)

A. stapfianum var. *pubiceps* (28)

AI-3

Delavaconine (Episcopalisinine) (**3**)



$C_{22}H_{35}NO_5$

MW = 393

mp 148–149 (32), 152–154 (14), 152 (35)

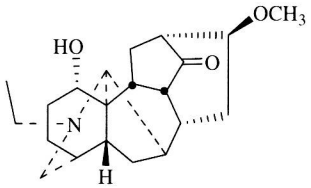
$[\alpha]_D$ −5 (EtOH) (32), −3.8 (EtOH) (14), −6.4 ($CHCl_3$) (35)

^1H NMR (14,32,35*), ^{13}C NMR (32,35), MS (14,35)

A. contortum (14,32,36)

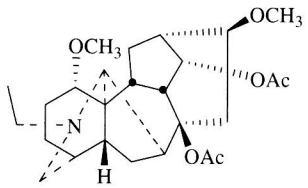
A. delavayi (35)

AI-4
8-Deoxy-14-dehydroaconosine (**4**)



$C_{21}H_{31}NO_3$
MW = 345
mp 142–145 (38)
$[\alpha]_D$
^1H NMR (38), ^{13}C NMR, MS (38)
A. stapfianum (38)

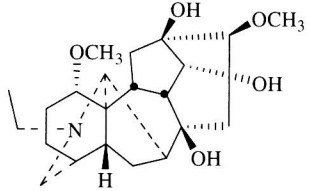
AI-5
8-Acetyldolaconine (**5**)



$C_{26}H_{39}NO_6$
MW = 461
mp 148 (31)
$[\alpha]_D$
^1H NMR (31), ^{13}C NMR (31), MS (31)

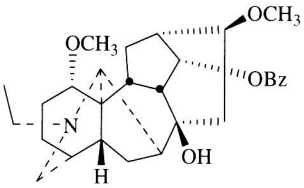
A. campylorrhynchum (31)

AI-6
Dolaconine (14-Acetyl aconosine, Episcopalitine) (**6**)



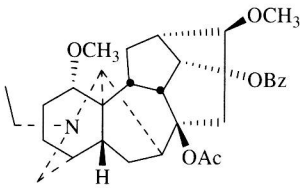
$C_{24}H_{37}NO_5$
MW = 419
mp 44–46 (28), 81–83 (31)
$[\alpha]_D$ −0.9 (EtOH) (14), −8.7 (EtOH) (32)
^1H NMR (28*,31,32,39), ^{13}C NMR (14), MS (32)
A. campylarrhynchum (31)
A. contortum (*A. episcopale*) (14,32,36)
A. nasutum (39)
A. stapfianum var. *pubiseps* (28)

AI-7
Delavaconitine C (**7**)



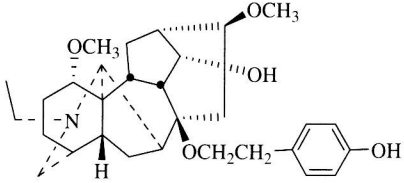
$C_{29}H_{39}NO_5$
MW = 481

AI-8
Delavaconitine D (**8**)



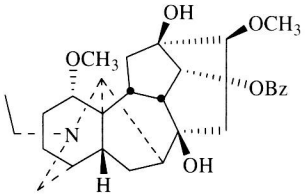
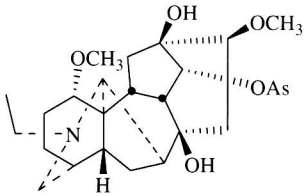
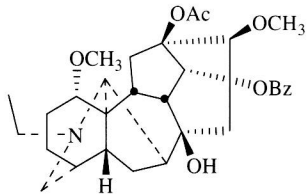
$C_{31}H_{41}NO_6$
MW = 523

AI-9
Piepunendine B (**9**)

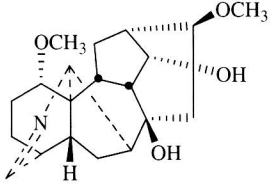


$C_{30}H_{43}NO_5$
MW = 497

Table I (*Continued*)

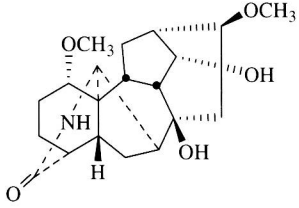
mp $[\alpha]_D$ −0.03 (CH_3OH) (41), +10.4 (EtOH) (32) ^1H NMR (32,41), ^{13}C NMR (32,41), MS (41) *A. contortum* (32) *A. delavayi* (41)	mp 185–186 (35) $[\alpha]_D$ −45.6 (CH_3OH) (35) ^1H NMR (35), ^{13}C NMR (35), MS (35) *A. delavayi* (35)	mp 85–87 (40) $[\alpha]_D$ −10.6 ($CHCl_3$) (40) ^1H NMR (40), ^{13}C NMR (40), MS (40) *A. piepunense* (40)
AI-10 Delavaconitine (Episcopalisine) (**10**)  $C_{29}H_{39}NO_6$ MW = 497 mp 59–64 (42) $[\alpha]_D$−9.56 (EtOH) (35,42), −11.7 (EtOH) (14), −14.4 (EtOH) (32) ^1H NMR (32*,35), ^{13}C NMR (32,35), MS (32,35) *A. contortum* (14,32) *A. delavayi* (35,42–44)	AI-11 Contortumine (**11**)  $C_{30}H_{41}NO_7$ MW = 527 mp $[\alpha]_D$ −4.8 (EtOH) (32) ^1H NMR (32), ^{13}C NMR (32), MS (32) *A. contortum* (32)	AI-12 Delavaconitine E (**12**)  $C_{31}H_{41}NO_7$ MW = 539 mp 118–119 (41) $[\alpha]_D$ −30.0 (CH_3OH) (41) ^1H NMR (41), ^{13}C NMR, MS (41) *A. delavayi* (41)

AI-13
Liconosine A (**13**)



$C_{20}H_{29}NO_4$
MW = 347
mp 240–242 (30)
$[\alpha]_D$
^1H NMR (30), ^{13}C NMR (30), MS (30)
A. forrest (30)

AI-14
Piepunendine A (**14**)

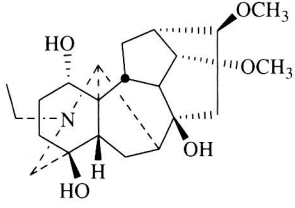


$C_{20}H_{29}NO_5$
MW = 385
mp 107–109 (40)
$[\alpha]_D$ −14.3 ($CHCl_3$) (40)
^1H NMR (40), ^{13}C NMR (40), MS

A. piepunense (40)

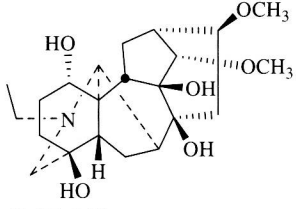
Lappaconine subtype (AII)

AII-1
Dihydromonticamine (**15**)



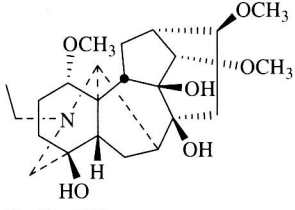
$C_{22}H_{35}NO_5$
MW = 393

AII-2
Lappaconidine (**16**)



$C_{22}H_{35}NO_6$
MW = 409

AII-3
Lappaconine (**17**)



$C_{23}H_{37}NO_6$
MW = 423