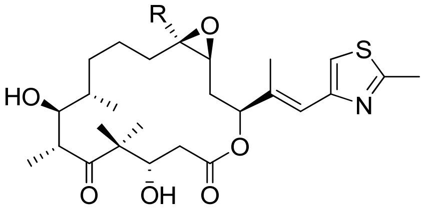
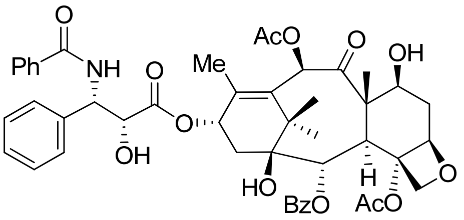
CHAPTER ONE

GENERAL INTRODUCTION

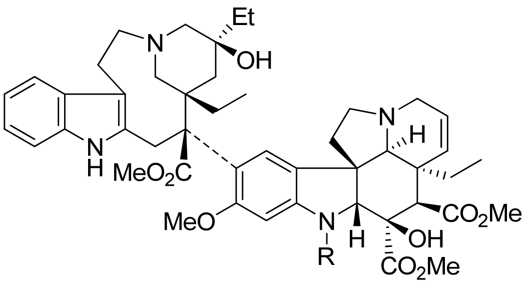
Plants are capable of producing an overwhelming variety of secondary metabolites, both in terms of complexity and quantity. Secondary metabolites can be divided into two main groups; those with nitrogen and those without nitrogen in their structures. Nitrogen-containing compounds include alkaloids, amines, non-protein amino acids, cyanogenic glycosides, glucosinolates, protease inhibitors, and lectins, while nitrogen-free compounds include various terpenoids, polyketides, phenolics, and polyacetylenes.[1] Most secondary metabolites possess biological activities and are therefore of interest due to their potential applications as drugs. Selected examples of biologically active secondary metabolites which have been developed into useful drugs include the antineoplastic agents, Epothilones A and B,[2] Taxol,[3] vincristine and vinblastine,[4] the antiarrhythmic agent, ajmaline,[5] the antitussive agent, codeine,[6] the antihypertensive agent, reserpine,[7] and the antimalarial agents, quinine[8] and artemisinin.[9]



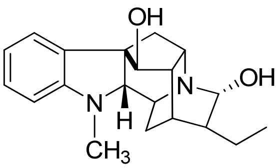
R = H Epothilone A
R = Me Epothilone B



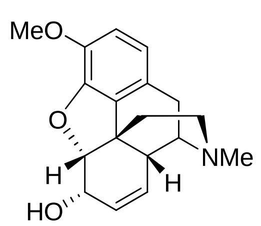
Taxol



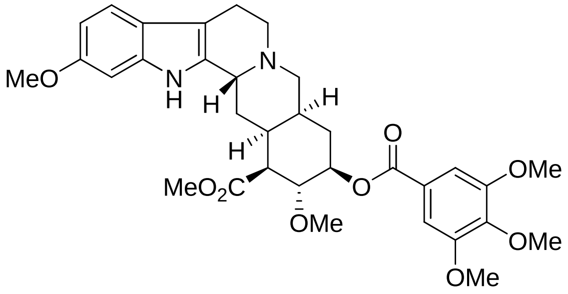
R = CH_3 Vinblastine
R = CHO Vincristine



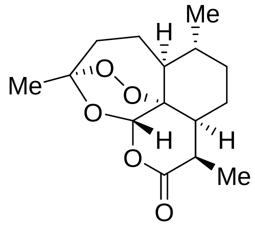
Ajmaline



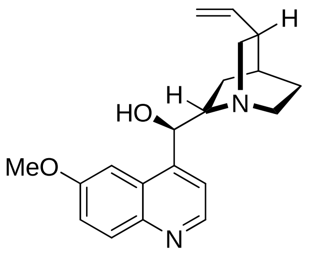
Codeine



Reserpine

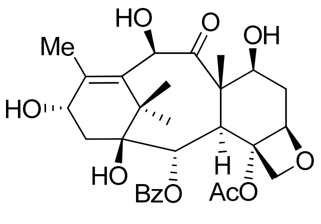


Artemisinin

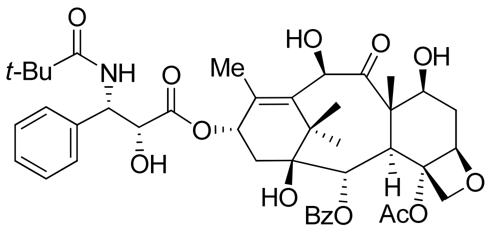


Quinine

These biologically active secondary metabolites are usually isolated in minute amounts from the natural sources, and in a number of such cases, partial synthesis provides a useful solution to the supply problem. For example, Taxol is present only in low concentrations from the bark of the Pacific Yew tree *Taxus brevifolia*.[3] The trees, which are slow growing, must be sacrificed in order to harvest the bark. This supply problem was solved by a partial synthesis of Taxol from the precursor 10-deacetylbaccatin III, which can be extracted from the aerial parts (needles) of the readily available European Yew tree, *Taxus baccata*.[3,10] In addition, by modifying the structure of Taxol via partial synthesis, a more potent drug, Docetaxel was obtained.[10]



10-Deacetylbaccatin III



Docetaxel

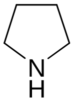
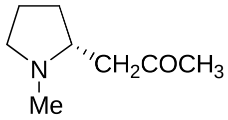
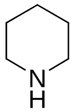
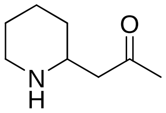
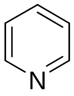
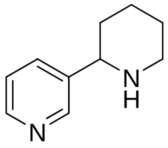
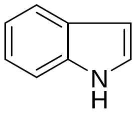
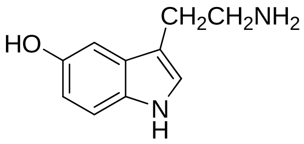
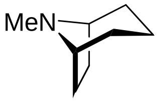
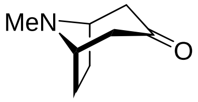
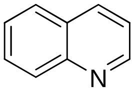
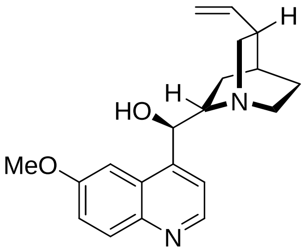
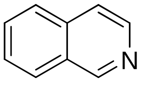
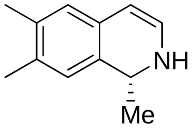
1.1 Alkaloids

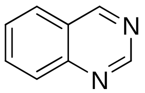
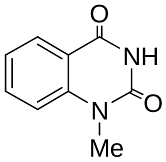
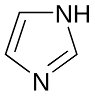
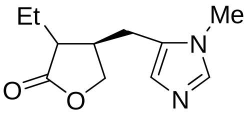
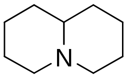
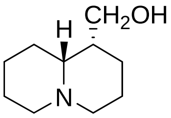
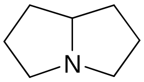
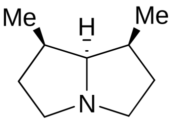
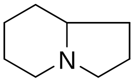
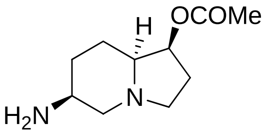
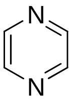
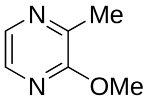
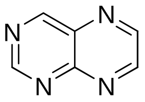
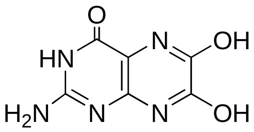
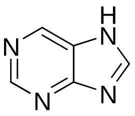
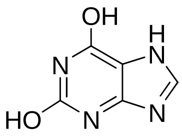
The term alkaloid, or ‘alkali-like’, was first proposed by the pharmacist, W. Meissner in 1819. It is usually applied to basic, nitrogen-containing compounds of plant origin. A simple general definition of an alkaloid has been suggested by Pelletier: “An alkaloid is a cyclic compound containing nitrogen in a negative oxidation state which is of limited distribution in living organisms.”[11] This definition encompasses compounds with nitrogen as part of a heterocyclic system as well as those with extracyclic bond nitrogen such as colchicines or capsaicin. Although most alkaloids are secondary metabolites of plants, many have been isolated from animals, insects, marine invertebrates, and microorganisms.[12]

1.2 Classification of Alkaloids

The number of alkaloids isolated and identified has increased over the years and more continue to be found. Alkaloids can be classified into 15 classes based on the carbon-nitrogen skeleton as shown below.[13]

a. Pyrrolidine
b. Piperidine
c. Pyridine
d. Indole
e. Tropane
f. Quinoline
g. Isoquinoline
h. Quinazoline
i. Imidazole
j. Quinolizidine
k. Pyrrolizidine
l. Indolizidine
m. Pyrazine
n. Pteridine
o. Purine bases

Alkaloid class	Basic ring system	Example
Pyrrolidine		 (+)-(R)-Hygrine
Piperidine		 Methylisopelletierine
Pyridine		 Anabasine
Indole		 Serotonine
Tropane		 Tropinone
Quinoline		 Quinine
Isoquinoline		 (+)-Salsoline

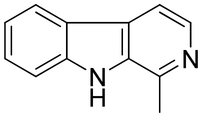
Alkaloid class	Basic ring system	Example
Quinazoline		 Glycosmicine
Imidazole		 Pilocarpine
Quinolizidine		 (–)-Lupinine
Pyrrolizidine		 (–)-Retronecanol
Indolizidine		 (–)-Slaframine
Pyrazine		 2-Methoxy-3-methylpyrazine
Pteridine		 Leucopterin
Purine bases		 Xanthine

1.3 Indole Alkaloids

Indole alkaloids are defined as natural products containing an indole nucleus or an oxidized, reduced, or substituted equivalent of it. The number of indole alkaloids of known structure amounts to approximately 5191 (2001).[14] This figure includes both those compounds that incorporate the actual indole chromophore and those containing its derivatives, namely, dihydroindole, indolenine, α-methyleneindoline, pseudoindoxyl, and oxindole. Also members of this group are alkaloids in which the nucleus incorporates an additional benzene or pyridine ring, for instance, carbazole or β- and γ-carbolines and their derivatives.

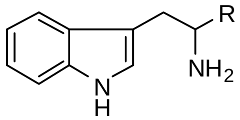
1.4 Structural Classes of the Monoterpenoid Indole Alkaloids

For further subclassification of indole alkaloids, structural and biogenetic criteria are applied. The indole alkaloids can be divided into two main categories. The first comprises the simple indole alkaloids which do not present a structural uniformity, possessing only the indole nucleus or a direct derivative of it as a common feature (e.g., harmane, **1**).

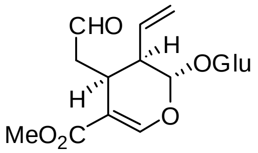


1 Harmane

The indole bases of the second category contain two structural units, viz., tryptamine (**2**) (or tryptophan, **3**) with the indole nucleus, and a C_9 or C_{10} monoterpene moiety derived from secologanin (**4**).

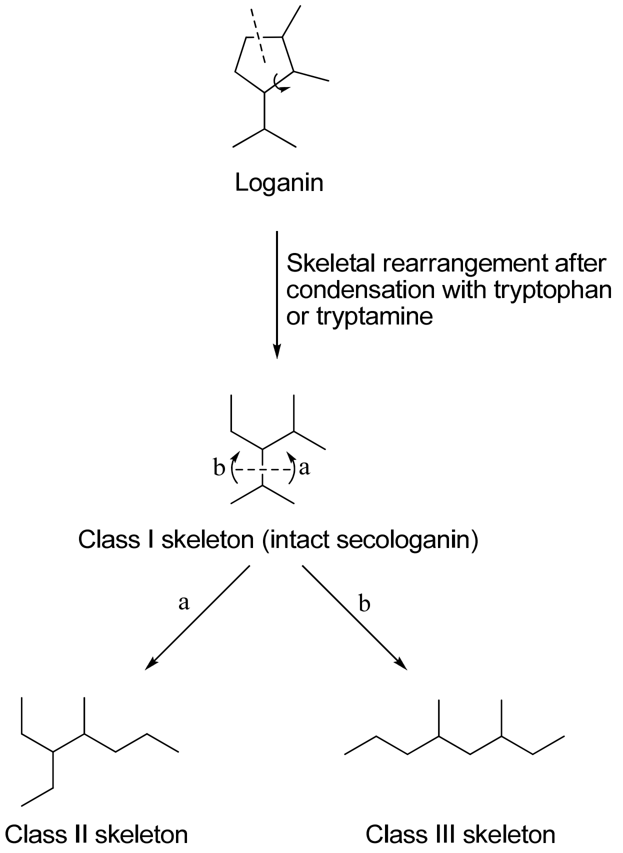


2 R = H
3 R = COOH



4 Secologanin

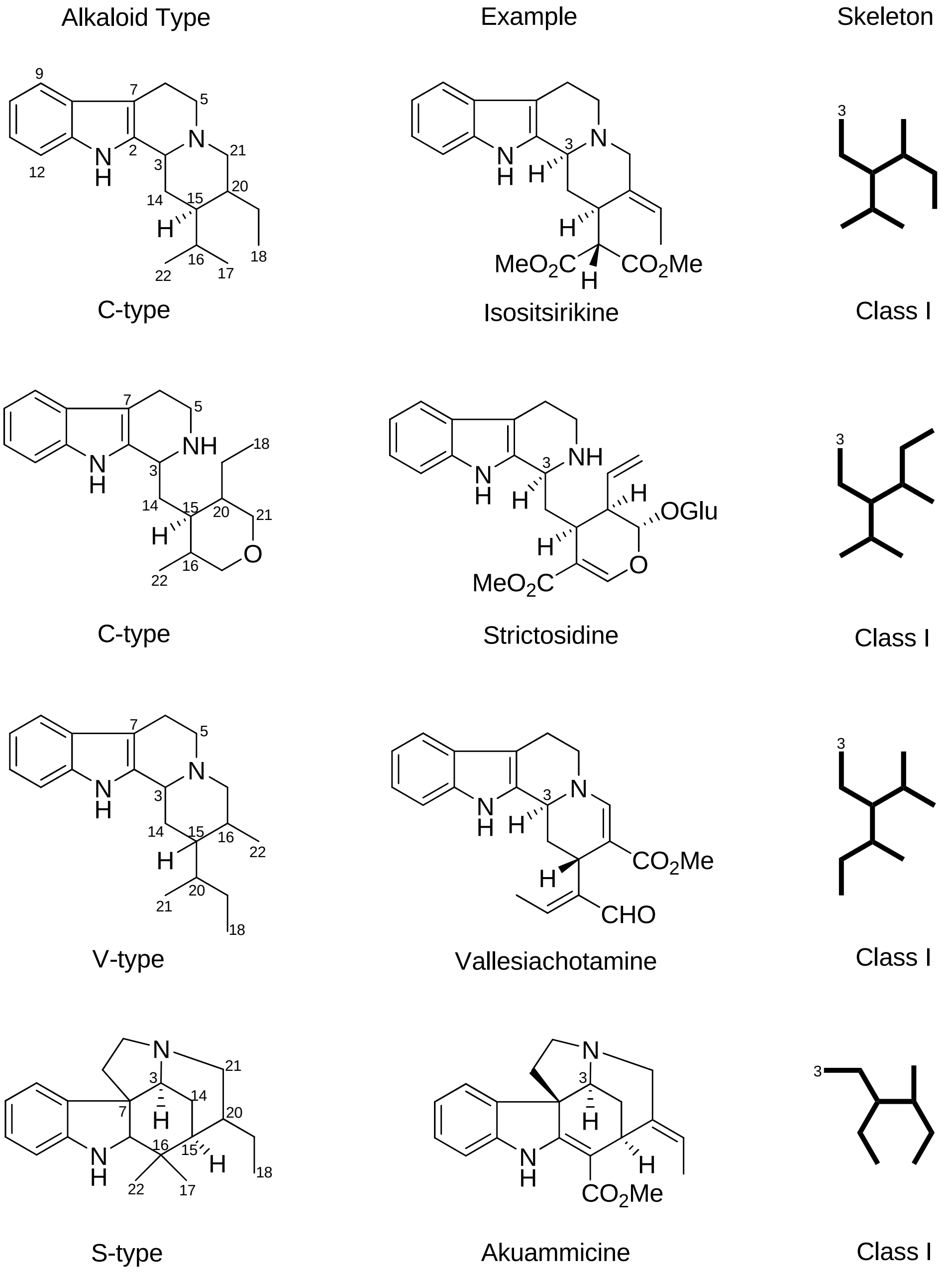
The majority of the indole alkaloids from plants of the Apocynaceae belong to this category and can be classified into nine main types depending on the structural characteristic of their skeletons.[15-17]



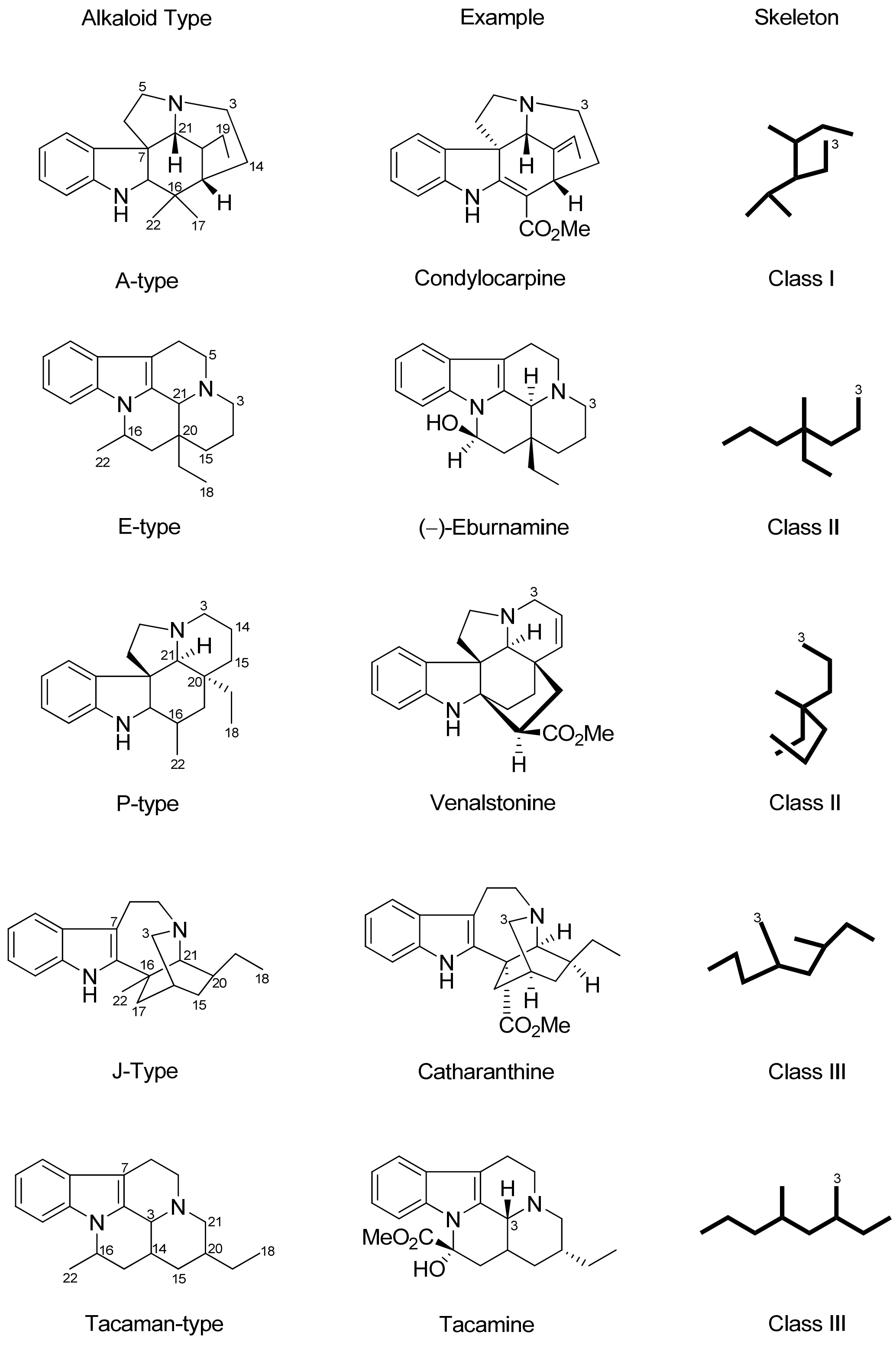
Scheme 1.1: The three major skeletal classes from loganin

Following Hesse,[15,16,18] eight main types have been defined: vincosan, vallesiachotaman, corynanthean, strychnan, aspidospermatan (all belonging to the class I skeleton with an intact secologanin), plumeran, eburnan (belonging to the class II skeleton, corresponding to a rearranged secologanin), and ibogan (belonging to the class

III skeleton, corresponding to a further rearranged monoterpene). A ninth type, tacaman (with class III skeleton) was added by Verpoorte and Van Beek to account for the isolation of a few tacamines.[18,19] The nine main skeletal types are given in Scheme 1.2.



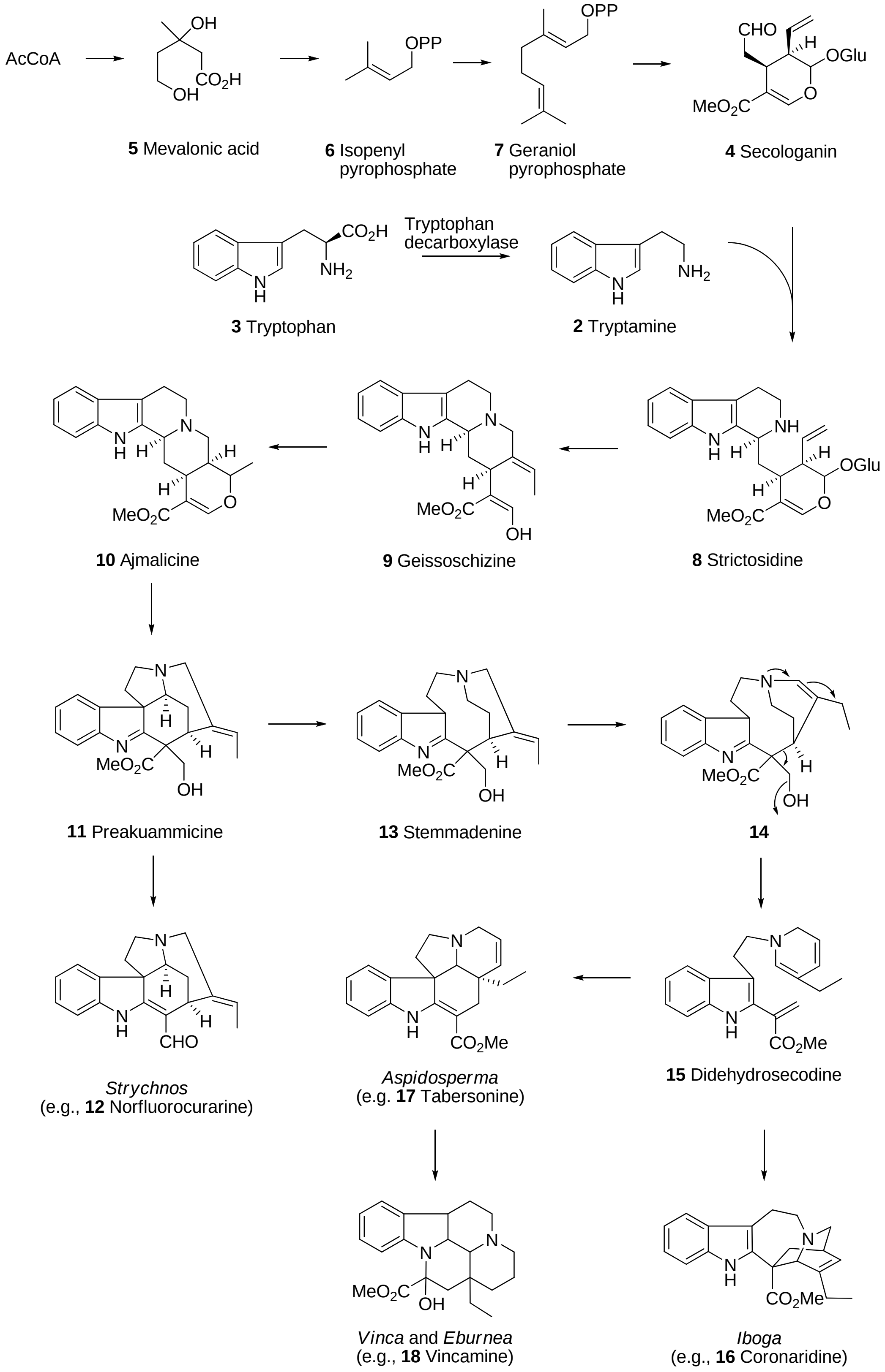
Scheme 1.2: Classification of indole alkaloids



Scheme 1.2, continued: Classification of indole alkaloids

1.5 Biogenesis of the Monoterpenoid Indole Alkaloids

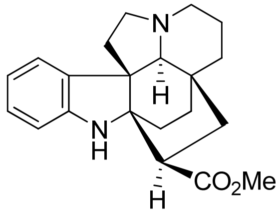
The biogenesis of indole alkaloids is shown in Scheme 1.3. Although there are more than 1000 known structural types of indole alkaloids, they are nevertheless all derived from a common intermediate, namely, strictosidine (**8**). Wenkert, Scott, and others[20,21] suggested that **8** is transformed to geissoschizine (**9**), ajmalicine (**10**) and preakuammicine (**11**), and eventually to stemmadenine (**13**), whose isomerization and collapse via enamine **14** provides didehydrosecodine (**15**), from which the *Aspidosperma*, *Iboga*, and *Vinca/Eburnea* alkaloids are in turn derived.



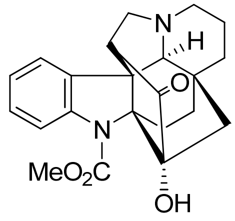
Scheme 1.3: Biogenesis of indole alkaloids

1.6 Representative Alkaloids of the Genus *Kopsia*

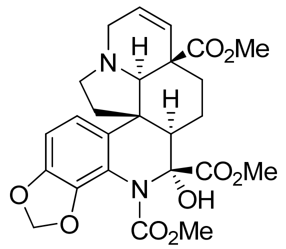
Plants of genus *Kopsia* furnish mainly indole alkaloids of the plumeran and eburnan skeletal-types, with alkaloids of the plumeran type predominating.[22,23] In addition to the monomeric alkaloids, a number of bisindole alkaloids have also been isolated, for example tenuiphylline[24] (**26**) and kopsoffinol (**27**).[25] Some representative alkaloids from plants of this genus are shown below.



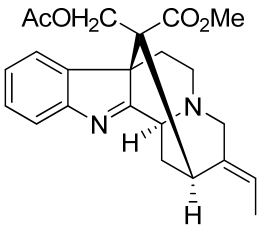
19 Kopsinine
(plumeran type)



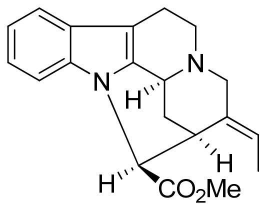
20 Kopsine
(plumeran type)



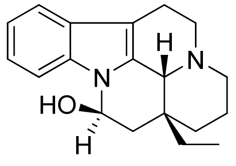
21 Mersinine A
(plumeran type)



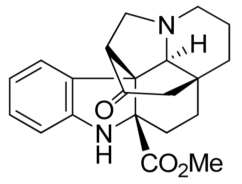
22 Akuammiline
(corynanthean type)



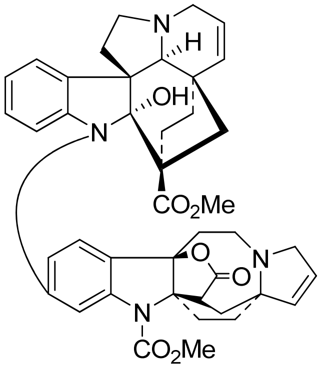
23 Pleiocarpamine
(corynanthean type)



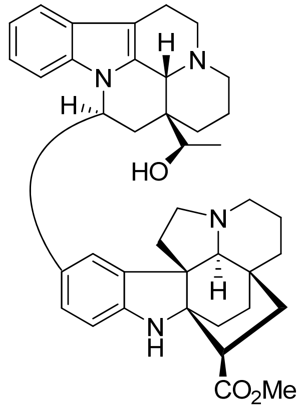
24 (–)-Eburnamine
(eburnan type)



25 Methyl *N*(1)-decarbomethoxy-chanofruticosinate
(plumeran type)



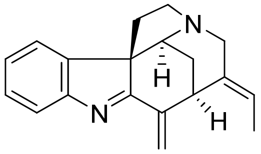
26 Tenuiphylline
(plumeran-plumeran bisindole alkaloid)



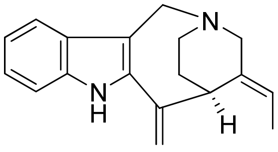
27 Kopsoffinol
(plumera-eburnan bisindole alkaloid)

1.7 Objective of the Present Study

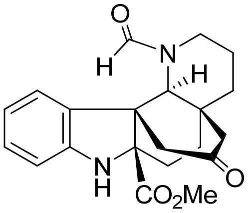
The objective of the present study is to implement biomimetic partial synthesis of selected indole alkaloids from *Kopsia* species recently isolated from our laboratory, such as valparicine (**28**), apparicine (**29**), and danuphylline B (**30**).



28 Valparicine



29 Apparicine



30 Danuphylline B