—Chapter 3—

CHEMICAL AND BIOLOGICAL ASPECTS OF *NARCISSUS* ALKALOIDS

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I. Introduction

A. GEOGRAPHICAL DISTRIBUTION AND TAXONOMICAL ASPECTS

The genus *Narcissus* L. belongs to the Narcisseae, one of the 15 tribes of the Amaryllidaceae, a widely distributed monocotyledonous family of 59 genera and about 850 species (*1*). The Amaryllidaceae are richly represented in the tropics and have pronounced centers of diversity in South Africa and the Andean region. Some genera are also found in the Mediterranean area and the temperate regions of Asia. The family's phylogenetic relationships closely follow geographic distribution, with much regional endemism, which adds credence to a Gondwana origin for the family at a time when the continents were much closer together (*1*). The hypothesis that the family evolved in Africa and subsequently spread to other continents, further suggesting that South America is the center of secondary diversification is supported by the *matK* sequence data (*2*).

Narcissus comprises approximately 80–100 wild species of perennial geophytes, geographically concentrated in southwestern Europe, with a center of diversity in the Iberian Peninsula and North Africa, which substantiates the hypotheses that landmasses of Europe and Africa were once joined. A few species extend into France and Italy, and even fewer are found in the Balkans and the eastern Mediterranean. Records outside this area, such as *N. tazetta* variants in China and Japan, are almost certainly ancient introductions (*3*,*4*). The native habitats of *Narcissus* species are very varied, ranging from lowland to mountain sites, including grassland, scrub, woods, river banks, and rocky crevices (*3*). Most of the species

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flower in late winter and spring, although a few flower in the autumn (*5*). All species are insect pollinated, with the majority possessing showy flowers, some of which are highly scented (*6*). The major pollinators are bees, butterflies, flies, and hawkmoths (*5*,*7*,*8*).

The taxonomy of the genus *Narcissus* is complex and unsettled because of its very varied wild populations, the ease with which hybridization occurs naturally, accompanied by extensive cultivation, breeding, selection, escape, and naturalization, and also because many descriptions of taxons have been based on garden specimens, several of which were probably of hybrid origin. However, although the status bestowed upon the individual groups may vary somewhat from author to author, the basic content of each group is similar in the various classifications (*3*–*5*). The most recent classification (Scheme 4), which incorporates elements of those of Fernandes and Webb (*9*–*11*), also notes that substantial work of revision is needed for some taxa in the genus. The inferred plastid-based phylogeny, on the other hand, reveals that floral morphology has been remarkably dynamic during the history of *Narcissus*, indicating extensive and repeated diversification and convergent evolution. Polymorphic sexual systems in *Narcissus* have evolved independently from the ancestral monomorphic state on at least six occasions (*5*,*12*). As these morphologies are associated with particular suites of pollinators, the recurring transitions from one floral design to another have probably accompanied pollinator transitions. Additionally, the remarkable resemblance of flower features between unrelated species indicates that pollinator activity might have driven flower convergence (*13*).

Most of the species of *Narcissus* will hybridize but, significantly, there is great variation in the fertility of the offspring, depending upon the degree of relationship between the parents (*4*). Hybridization has become very popular, resulting in thousands of commercial *Narcissus* cultivars that are in most cases larger and more robust than their wild parents (*3*). Moreover, large garden varieties of daffodils have recently been crossed with many of the small wild species to produce delightfully graceful blossoms. Unfortunately, the ability to produce new kinds of miniature daffodils is hampered by the disappearance of many of the tiny wild species (*14*). Thus, the survival of a number of *Narcissus* species is under threat because of overcollection and habitat destruction. There is a need to maintain vigilance in the conservation of wild species and of their many variants (*15*).

Narcissus bulbs have been an important floricultural crop in Western Europe since the late nineteenth century, although the bulbs have been grown in the Netherlands since the sixteenth century. At the start of the twenty-first century, the daffodil remains one of the major ornamental spring-flowering bulb crops grown in temperate regions, with large areas of field-grown crops providing both bulbs and flowers (*15*,*16*). Rees (*17*) estimated that the area of *Narcissus* grown in gardens, parks, cemeteries, etc., is five times the area grown commercially.

The development of the horticultural classification of *Narcissus* cultivars in 13 divisions was described by Kington (*18*) and, in order to avoid confusion due to the re-use of earlier names, since 1998, the International Daffodil Register and Classified List is updated annually by supplements of newly registered names (*4*).

B. THE AMARYLLIDACEAE ALKALOIDS

A particular characteristic of the Amaryllidaceae is a consistent presence of an exclusive group of alkaloids, which have been isolated from the plants of all the genera of this family. The Amaryllidaceae alkaloids represent a large, and still expanding, group of isoquinoline alkaloids, the majority of which are not known to occur in any other family of plants. Since the isolation of the first alkaloid, lycorine, from *Narcissus pseudonarcissus* in 1877, substantial progress has been made in examining the Amaryllidaceae plants, although they still remain a relatively untapped phytochemical source (*1*). At present, over 300 alkaloids have been isolated from plants of this family (*19*) and, although their structures vary considerably, these alkaloids are considered to be biogenetically related.

The large number of structurally diverse Amaryllidaceae alkaloids are classified mainly into nine skeleton types, for which the representative alkaloids are norbelladine, lycorine, homolycorine, crinine, hemanthamine, narciclasine, tazettine, montanine, and galanthamine (Fig. 1). With the aim of unifying the numbering system of the different skeleton types, Ghosal's model will be used in this review (*20*).

As the alkaloids of the Amaryllidaceae family species fall mainly into one of these subgroups, they can serve as a classifying tool for including genera and species in this family. Thus, the genus *Behria*, in spite of having been classified as

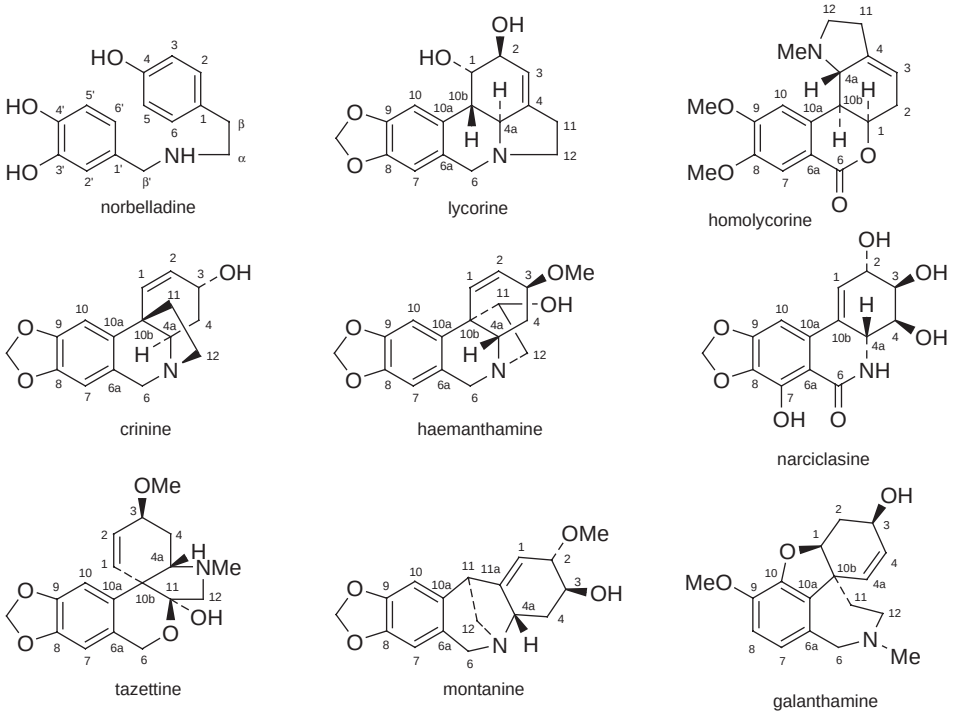


Figure 1. Amaryllidaceae alkaloid types.

Amaryllidaceae (*21*), does not have any Amaryllidaceae alkaloids (*22*) and should therefore be included in the Alliaceae family. Furthermore, although it is unusual to find other types of alkaloids in this family, if present, they are always accompanied by typical Amaryllidaceae alkaloids. The classical example is the reported presence of the mesembrane (*Sceletium*) alkaloids, generally found in the Aizoaceae family (*23*,*24*), in a few species of Amaryllidaceae such as *Hymenocallis arenicola, Crinum oliganthum, N. pallidulus*, and *N. triandrus* (*25–27*). In turn, the unexpected isolation of (−)-capnoidine and (+)-bulbocapnine from *Galanthus nivalis* subsp. *cilicicus* is the first report of the occurrence of classical isoquinoline alkaloids in a typical member of the Amaryllidaceae (*28*). On the contrary, the isolation of the Amaryllidaceae alkaloid crinamine from the wild yam *Dioscorea dregeana* (Dioscoreaceae) has also proven that Amaryllidaceae alkaloids may well be encountered in other plant families (*29*). Both of these results suggest that the definition of the Amaryllidaceae alkaloids should be reconsidered, and also the alkaloidal profile of this plant family.

The presence of alkaloids in plants is believed to be a protective adaptation, which in Amaryllidaceae is connected with the seasonal cycle of development, many species grow in early spring when other genera are only just starting to grow (*30*). Thus, Amaryllidaceae plants present an ontogenic variation of alkaloids, and the effects of stress, such as incisional injuries or insect attacks, on alkaloid metabolism causes almost complete hydrolysis of the alkaloidal conjugates and also produces oxidized metabolites (*31*). Regarding co-evolutionary adaptation, a notable example is the elaboration of a new conjugate alkaloid (telastasine) by the insect *Polytela gloriosa* Fab. (Noctuidae), a smokey-gray moth that is adapted to toxic Amaryllidaceae plants (*32*,*33*). Plants and insects use the same detoxification mechanism. These alkaloids, essential for plant survival, have a wide range of interesting physiological effects, including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory, and antimalarial activities, some of them being of particular interest because of their potential use in clinical therapy (*34*).

Plants of the Amaryllidaceae family have been used for thousands of years as herbal remedies. The alkaloids from their extracts have been the object of active chemical investigation for nearly 200 years. Over the past two decades many have been isolated, screened for different biological activities, and synthesized by a number of research groups. An important handicap is the availability of these alkaloids, which are obtained only in minute quantities from natural sources. Since isolation in larger quantities is not practical, there is a strong case for the development of syntheses or semisyntheses of these alkaloids and their derivatives as potential prodrugs (*35*).

The history of the Amaryllidaceae alkaloids, their structural elucidation, and their biological profiles, as well as their synthesis, have been summarized on several occasions (*20*,*33*,*36–48*) which, together with the regular publications in the journal *Natural Product Reports* (*34*,*49–66*), represent a valuable source of information.

The present review provides coverage of the isolation, spectroscopy, biological activity, and chemical synthesis of the Amaryllidaceae alkaloids present in the genus *Narcissus* up to July 2005.

II. *Narcissus* Alkaloids and their Occurrence

Numerous alkaloids have been isolated from *Narcissus* species as a result of the continuing search for novel alkaloids with pharmacological activity in the Amaryllidaceae family. The alkaloids isolated from this genus, classified in relation to the different skeleton types, are shown in Tables I–VII. Table VIII lists the different *Narcissus* wild species and intersectional hybrids, grouped into subgenera and sections, with their corresponding alkaloids, arranged according to their ring system. The occurrence of alkaloids in *Narcissus* cultivars is shown in Table IX.

A. ALKALOID TYPES AND DISTRIBUTION

The presence of almost 100 alkaloids in this genus (Tables I–VII) means that approximately a third of the total number of alkaloids isolated from Amaryllidaceae have been found in the genus *Narcissus*. Amaryllidaceae alkaloids are present in all the species and varieties of *Narcissus* studied. In general, a series of related alkaloids is found in each plant: often a few major metabolites and several minor components, which differ in the position of their substitutents. Up to now, about 40 wild species and around 100 cultivars have been studied in relation to the presence of alkaloids (Tables VIII and IX), which means that more than half of the *Narcissus* species or varieties have still to be explored in this aspect.

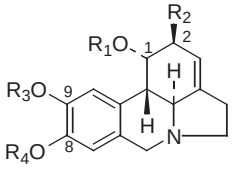
1. Lycorine and Homolycorine Types

The alkaloids of the lycorine and homolycorine groups are, on the whole, the most common alkaloids in this genus. Lycorine (**1**), galanthine (**7**), and pluviine (**11**) (lycorine type) and homolycorine (**26**) and lycorenine (**35**) (homolycorine type) are particularly frequent, lycorine being the most abundant. The presence of these alkaloids is very significant in the sections Narcissus (mainly lycorine type), Pseudonarcissi (mainly homolycorine type), and Tazettae of the wild species, and in the Divisions 1, 2, and 4 of cultivars.

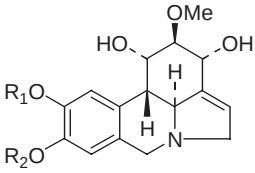
Almost all of the lycorine-type alkaloids isolated from *Narcissus* present a *trans*-union between B/C rings, making them especially vulnerable to oxidative processes. It is interesting to observe that four of these alkaloids, namely vasconine (**22**), tortuosine (**23**), ungeremine (**24**), and roserine (**25**) possess an unusual quaternary nitrogen (*67–71*). The species *N. pallidulus* (section Ganymedes), unusual because it contains mesembrane-type alkaloids, is even more exceptional due to the presence of roserine.

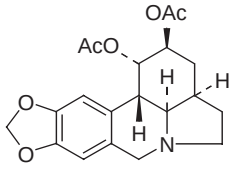
The alkaloids of the homolycorine series, formed by a restructuring of lycorine-type alkaloids, are absent from some tribes of the Amaryllidaceae, such as the Amaryllideae or Hemantheae (*44*). For that reason, the presence of these alkaloids is a distinctive feature of the Narcisseae tribe. Moreover, all the *Narcissus* alkaloids of the homolycorine series display a B/C ring junction with a *cis* stereochemistry. An exceptional homolycorine-type alkaloid is dubiusine (**33**), which has an unusual hydroxybutyryl substituent (*72*).

TABLE I.
Narcissus Alkaloid Structures. Lycorine Type.



1	R_1=H, R_2=OH, R_3+R_4=CH_2	lycorine
2	R_1=Ac, R_2=OH, R_3+R_4=CH_2	poetaminine
3	R_1=H, R_2=OH, R_3=H, R_4=Me	pseudolycorine
4	R_1=Ac, R_2=OH, R_3=H, R_4=Me	1-*O*-acetylpseudolycorine
5	R_1=H, R_2=OAc, R_3=H, R_4=Me	2-*O*-acetylpseudolycorine
6	R_1=H, R_2=OH, R_3=Me, R_4=Me	9-*O*-methylpseudolycorine
7	R_1=H, R_2=OMe, R_3=Me, R_4=Me	galanthine
8	R_1=H, R_2=OMe, R_3=Me, R_4=H	goleptine
9	R_1=Ac, R_2=O, R_3+R_4= CH_2	jonquilline
10	R_1=H, R_2=H, R_3+R_4= CH_2	caranine
11	R_1=H, R_2=H, R_3=Me, R_4=Me	pluviine
12	R_1=H, R_2=H, R_3=Me, R_4=H	norpluviine (= 8-*O*-demethylpluviine)
13	R_1=H, R_2=H, R_3=H, R_4=Me	9-*O*-demethylpluviine
14	R_1=Ac, R_2=H, R_3=H, R_4=Me	1-*O*-acetyl-9-*O*-demethylpluviine
15	R_1=Ac, R_2=H, R_3=Ac, R_4=Me	1,9-*O*-diacetyl-9-*O*-demethylpluviine

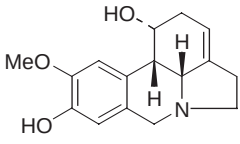




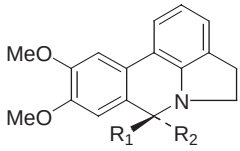
16 R_1=Me, R_2=Me narcissidine

17 R_1+R_2=CH_2 ungiminorine (= ungminorine)

18 nartazine



19 kirkine

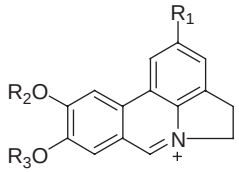


20 R_1=H, R_2=H assoanine

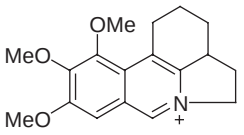
21 R_1+R_2=O oxoassoanine

(*continued*)

TABLE I.
Continued.



22 R_1=H, R_2=Me, R_3=Me vasconine
23 R_1=OMe, R_2=Me, R_3=Me tortuosine
24 R_1=O^-, R_2+R_3=CH_2 ungeremine



25 roserine

2. Hemanthamine, Tazettine, Narciclasine, and Montanine Types

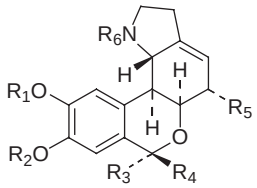
The main groups of alkaloids originating from a *para–para′* oxidative phenolic coupling of *O*-methylnorbelladine (**87**) (hemanthamine, tazettine, and narciclasine types) are frequently represented in this genus by the model alkaloid of each group, hemanthamine (**53**), tazettine (**62**), and narciclasine (**68**), respectively. Their presence is significant in the Pseudonarcissi, Tazettae, and Bulbocodii sections of wild species, and in the Divisions 1, 2, and 8 of cultivars. The hemanthamine-type alkaloids are the most abundant, being the biogenetic source of the other types.

The lack of crinine-type alkaloids (*β*-5,10b-ethano bridge configuration) in this genus, which only has representatives of the α-5,10b-ethano bridge series (hemanthamine type), is a very significant taxonomic feature. Additionally, in *Narcissus*, the hemanthamine-type alkaloids never show any substitution in the aromatic ring at position 7, which is usual in crinine-type alkaloids from tribes such as the Amaryllideae or Hemantheae (*44*). The pairs of alkaloids with a hydroxyl substituent at C-6, like papyramine/6-epipapiramine (**48/49**) or hemanthidine/6-epihemanthidine (**55/56**), always appear as a mixture of epimers in solution (*73*). It is also interesting to mention the unusual structure of bujeine (**61**), an alkaloid of the hemanthamine type that has a modified bridge with a heteroatom between C-11 and C-12 and an acetoxymethyl substituent at the 11- *endo* position (*74*). Ismine (**72**) is considered to be a catabolic product from the hemanthamine series.

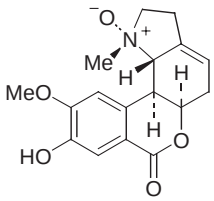
Tazettine (**62**) is a widely reported alkaloid in the Amaryllidaceae family, particularly in *Narcissus* (see Tables VIII and IX), although it is known to be an extraction artifact of pretazettine (**64**) (*75*). All the alkaloids of the tazettine type that are isolated from *Narcissus* species show the typical methylenedioxy group between the C-8 and C-9 positions. Obesine (**67**) is an exceptional tazettine-type alkaloid with a seven-membered ring (*76*).

Narciclasine (**68**) is reasonably abundant in some *Narcissus* spp. and has served as a very useful intermediate for synthetic conversion into (+)-pancratistatin (see Section IV) and to conduct a series of structure–activity relationship studies (*77*,*78*). Bicolorine (**71**), another member of the narciclasine series, is an unusual, completely aromatized quaternary alkaloid with an *N*-methyl group (*79*).

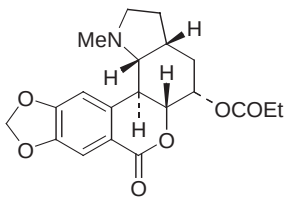
TABLE II.
Narcissus Alkaloid Structures. Homolycorine Type.



26	R_1=Me, R_2=Me, R_3+R_4=O, R_5=H, R_6=Me	homolycorine
27	R_1=Me, R_2=H, R_3+R_4=O, R_5=H, R_6=Me	8-*O*-demethylhomolycorine
28	R_1=Me, R_2=Ac, R_3+R_4=O, R_5=H, R_6=Me	8-*O*-demethyl-8-*O*-acetylhomolycorine
29	R_1=H, R_2=Me, R_3+R_4=O, R_5=H, R_6=Me	9-*O*-demethylhomolycorine
30	R_1+R_2=CH_2, R_3+R_4=O, R_5=H, R_6=Me	masonine
31	R_1+R_2=CH_2, R_3+R_4=O, R_5=H, R_6=H	normasonine (= *N*-demethylmasonine)
32	R_1=H, R_2=Me, R_3+R_4=O, R_5=OH, R_6=Me	9-*O*-demethyl-2α-hydroxyhomolycorine
33	R_1=3OHbut, R_2=Me, R_3+R_4=O, R_5=OAc, R_6=Me	dubiusine
34	R_1+R_2=CH_2, R_3+R_4=O, R_5=OH, R_6=Me	hippeastrine
35	R_1=Me, R_2=Me, R_3=OH, R_4=H, R_5=H, R_6=Me	lycorenine
36	R_1=Me, R_2=Me, R_3=OMe, R_4=H, R_5=H, R_6=Me	*O*-methyllycorenine
37	R_1+R_2= CH_2, R_3=OH, R_4=H, R_5=H, R_6=Me	oduline
38	R_1+R_2= CH_2, R_3=OMe, R_4=H, R_5=H, R_6=Me	6-*O*-methyloduline
39	R_1+R_2= CH_2, R_3=OMe, R_4=H, R_5=OH, R_6=Me	2α-hydroxy-6-*O*-methyloduline



40 8-*O*-demethylhomolycorine-*N*-oxide



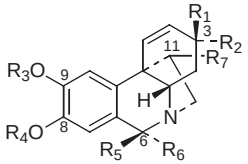
41 poetinatine

The montanine-type alkaloids, also deriving from the hemanthamine series, are very unusual. Only two, namely pancracine (**73**) and nangustine (**74**), have been isolated from two species, both belonging to the Narcissus section of this genus. Nangustine has a unique substitution pattern (*80*), being the first 5,11-methanomorphanthridine alkaloid with a C-3/C-4 substitution, instead of a typical C-2/C-3.

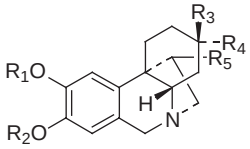
3. Galanthamine Type

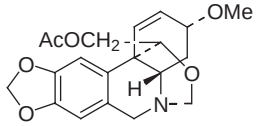
The galanthamine-type alkaloids are the only group among the Amaryllidaceae alkaloids showing two *ortho* aromatic protons in ring A. This type of alkaloid often shows an *N*-methyl group, or occasionally *N*-formyl or *N*-acetyl

TABLE III.
Narcissus Alkaloid Structures. Hemanthamine Type.



42	R_1=OH, R_2=H, R_3+R_4=CH_2, R_5=H, R_6=H, R_7=H	vittatine
43	R_1=OH, R_2=H, R_3+R_4=CH_2, R_5=H, R_6=H, R_7=OH	11-hydroxyvittatine
44	R_1=OH, R_2=H, R_3=Me, R_4=Me, R_5=H, R_6=H, R_7=H	maritidine
45	R_1=OH, R_2=H, R_3=Me, R_4=H, R_5=H, R_6=H, R_7=H	8-*O*-demethylmaritidine
46	R_1=OH, R_2=H, R_3=H, R_4=Me, R_5=H, R_6=H, R_7=H	9-*O*-demethylmaritidine
47	R_1=OMe, R_2=H, R_3=Me, R_4=Me, R_5=H, R_6=H, R_7=H	*O*-methylmaritidine
48	R_1=OMe, R_2=H, R_3=Me, R_4=Me, R_5=H, R_6=OH, R_7=H	papyramine
49	R_1=OMe, R_2=H, R_3=Me, R_4=Me, R_5=OH, R_6=H, R_7=H	6-epipapyramine
50	R_1=OMe, R_2=H, R_3=Me, R_4=Me, R_5=OMe, R_6=H, R_7=H	*O*-methyl-6-epipapyramine
51	R_1=H, R_2=OMe, R_3=Me, R_4=Me, R_5=H, R_6=OH, R_7=H	6α-hydroxy-3-*O*-methylepimaritidine
52	R_1=H, R_2=OMe, R_3=Me, R_4=Me, R_5=OH, R_6=H, R_7=H	6β-hydroxy-3-*O*-methylepimaritidine
53	R_1=OMe, R_2=H, R_3+R_4=CH_2, R_5=H, R_6=H, R_7=OH	haemanthamine
54	R_1=OMe, R_2=H, R_3+R_4=CH_2, R_5=H, R_6=H, R_7=OAc	11-*O*-acetylhaemanthamine
55	R_1=OMe, R_2=H, R_3+R_4=CH_2, R_5=H, R_6=OH, R_7=OH	haemanthidine
56	R_1=OMe, R_2=H, R_3+R_4=CH_2, R_5=OH, R_6=H, R_7=OH	6-epihaemanthidine
57	R_1=H, R_2=OMe, R_3+R_4=CH_2, R_5=H, R_6=H, R_7=OH	crinamine
58	R_1=OMe, R_2=H, R_3=Me, R_4=H, R_5=H, R_6=H, R_7=OH	narcidine



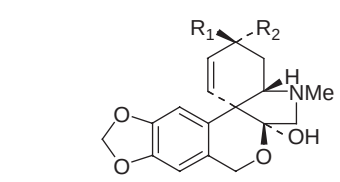


59	R_1=H, R_2=Me, R_3=H, R_4=OAc, R_5=H	cantabricine
60	R_1+R_2=CH_2, R_3=OMe, R_4=H, R_5=$OCH_2CH(OH)Et$	narcimarkine

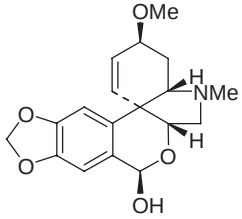
61 bujeine

derivatives. They are frequent in *Narcissus*, galanthamine (**75**) being the most usual and representative of them (*30*,*81*). The concentration of galanthamine in *Narcissus* has been found to vary widely between species and varieties, from trace amounts to 2.5% (*30*). The potential of some *Narcissus* cultivars ('Carlton', 'Gigantic Star', Ice Follies', and 'Fortune') and wild species (*N. confusus*) as sources of galanthamine and related alkaloids has been recognized (*81–84*), and research has been initiated into the agronomic factors that affect their content. *Narcissus* has two important

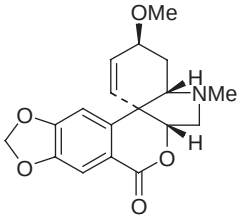
TABLE IV.
Narcissus Alkaloid Structures. Tazettine Type.



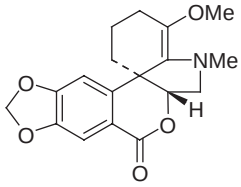
62 R_1=OMe, R_2=H tazettine
63 R_1=H, R_2=OMe criwelline



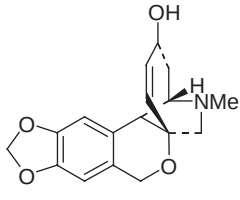
64 pretazettine



65 3-epimacronine



66 3-epimacronine isomer
(structure under revision)



67 obesine

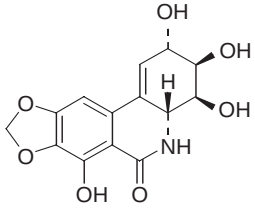
advantages over *Leucojum aestivum*: first, bulbs of many *Narcissus* cultivars are available in commercial quantities, offering the possibility of establishing large-scale cultivation in a short time; second, a comprehensive body of information already exists regarding narcissus propagation, physiology, breeding, and cultivation (*85*).

4. Other Alkaloids

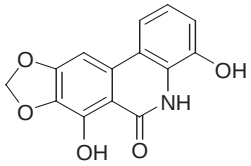
The mesembrane (*Sceletium*)-type alkaloids are also present in *Narcissus* plants. It is noteworthy that the alkaloids of this group (mesembrenone (**90**), mesembrenol (**91**), and mesembrine (**92**)) isolated from *Narcissus* are restricted to the species of the Ganymedes section, which is therefore of chemotaxonomic interest because they are generally found in the Aizoaceae, a dicotyledonous family (*23*,*24*). Both the Amaryllidaceae and *Sceletium*-type alkaloids have common biogenetic precursors, although their biosyntheses are fundamentally different (*33*).

There are also two unclassified alkaloids, namely cherylline (**88**) and pallidiflorine (**89**). Cherylline, a 4-substituted tetrahydroisoquinoline derivative, is a unique representative of rare phenolic Amaryllidaceae alkaloids. Pallidiflorine, a heterobis alkaloid isolated from *N. pallidiflorus* (*86*), is the only bis-alkaloid present in this genus isolated up to now. This alkaloid is formed from two directly joined moieties, one of them being the alkaloid lycoramine (galanthamine type), and the other being the reverse form of the hemiacetal at C-11 of tazettine.

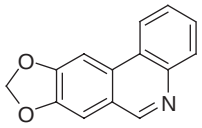
TABLE V.
Narcissus Alkaloid Structures. Narciclasine and Montanine Types.



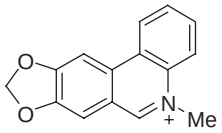
68 narciclasine



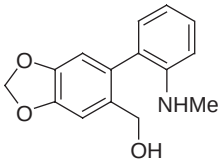
69 narciprimine



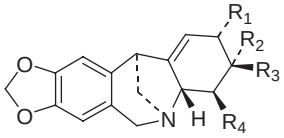
70 trisphaeridine



71 bicolorine



72 ismine



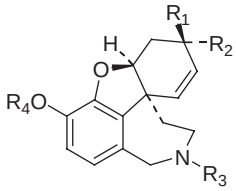
73 R_1=OH, R_2=H, R_3=OH, R_4=H pancracine
74 R_1=H, R_2=OH, R_3=H, R_4=OH nangustine

B. ONTOGENIC VARIATIONS

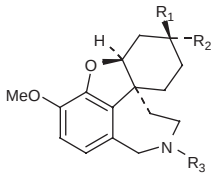
It is well established that profiles of alkaloids vary with time, location, and developmental stage. In many instances, the site of biosynthesis is restricted to a single organ, but accumulation of the corresponding products can be detected in several other plant tissues. Long-distance transport must take place in these instances. There are only a few data on the ontogenic variations and distribution of alkaloids in species of the Amaryllidaceae family, and some results have been obtained in *Narcissus* species, such as *N. assoanus* (with only lycorine-type alkaloids) or *N. confusus* (with alkaloids of the homolycorine, hemanthamine, tazettine, and galanthamine types) (*84*,*87*).

During the vegetative period, the bulb of *N. assoanus* has a lower concentration of alkaloids than the aerial part. Pseudolycorine (**3**), the major alkaloid of both the aerial parts and the bulb, represents around 50% of the total alkaloids. The synthesis of alkaloids might take place mainly in the aerial part, where they accumulate. Once flowers have been fecundated, they are transported to the bulb. It seems that, in order to avoid autotoxicity, pseudolycorine is stored in the bulbs as

TABLE VI.
Narcissus Alkaloid Structures. Galanthamine Type.



75	R_1=OH, R_2=H, R_3=Me, R_4=Me	galanthamine
76	R_1=H, R_2=OH, R_3=Me, R_4=Me	epigalanthamine
77	R_1=OAc, R_2=H, R_3=Me, R_4=Me	*O*-acetylgalanthamine
78	R_1=OH, R_2=H, R_3=H, R_4=Me	norgalanthamine (= *N*-demethylgalanthamine)
79	R_1=H, R_2=OH, R_3=H, R_4=Me	epinorgalanthamine
80	R_1=OH, R_2=H, R_3=CHO, R_4=Me	*N*-formylnorgalanthamine
81	R_1=OH, R_2=H, R_3=Me, R_4=H	sanguinine
82	R_1=OH, R_2=H, R_3=Ac, R_4=Me	narcisine
83	R_1+R_2=O, R_3=Me, R_4=Me	narwedine

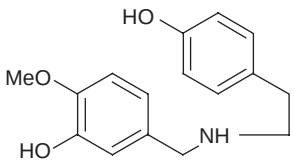


84	R_1=OH, R_2=H, R_3=Me	lycoramine
85	R_1=OH, R_2=H, R_3=H	norlycoramine (=*N*-demethyllycoramine)
86	R_1=H, R_2=OH, R_3=H	epinorlycoramine

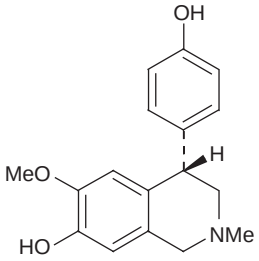
the 1-*O*-Ac (**4**) and 2-*O*-Ac (**5**) derivatives (*87*). The specific localization of alkaloids make sense if their role as defense and/or signal compounds is accepted. As a rule, vulnerable tissues are defended more than old, senescent tissues.

Galanthamine (**75**) and four other alkaloids of *N. confusus* were found to be present in all of the organs at every stage, with the exception of hemanthamine (**53**), which does not occur in senescent flowers. The main alkaloid is galanthamine, followed by *N*-formylnorgalanthamine (**80**) or tazettine (**62**), depending on the sample, while homolycorine (**26**) is in general the least common. The organ with the highest total alkaloid accumulation throughout the ontogenic cycle is the bulb, except at the end of the cycle, when the alkaloids accumulate mainly in the flower stem, reaching a concentration of up to 2.5% by dry weight (*84*).

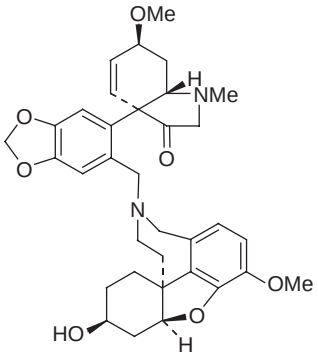
TABLE VII.
Narcissus Alkaloid Structures. Other Types.



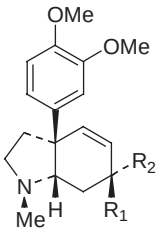
87 *O*-methylnorbelladine



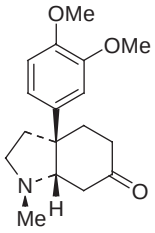
88 cherylline



89 pallidiflorine



90 R_1=R_2=O mesembrenone
91 R_1=OH, R_2=H mesembrenol



92 mesembrine

III. Biosynthetic Pathways

Most of the biosynthetic research done on Amaryllidaceae alkaloids was carried out in the 1960s and early 1970s. Since then, the only noteworthy study has been the biosynthesis of galanthamine (**75**) and related alkaloids (*181*). As in most alkaloid biosyntheses, that of the Amaryllidaceae follows a sequential pattern.

TABLE VIII.
Occurrence of *Narcissus* Alkaloids in Wild Species and Intersectional Hybrids.

Species[a]	Skeleton types: (alkaloids)[b]	References
1. Subgenus *Narcissus*		
a- *Section* Narcissus L.		
N. angustifolius Curtis ex Haw.	GA: (**75**)	(*88*)
N. angustifolius Curtis subsp. *transcarpathicus* Kricsfalusy	LY: (**3, 22, 24**); HL: (**27**); MN: (**73, 74**); OA: (**88**)	(*80*)
N. poeticus L.	LY: (**1, 2, 6, 7, 11, 16, 18**); HL: (**26, 35**); MN: (**73**); GA: (**75, 79**)	(*89–95*)
N. poeticus L. var. *ornatus* Hort.	LY: (**1, 2, 7**); HL: (**26, 35, 41**); HT: (**53**); TZ: (**62**); GA: (**75**)	(*89,96–98*)
b- *Section* Pseudonarcissi DC.		
Group A [Plant small, usually less than 15 cm]		
N. asturiensis (Jordan) Pugsley	HT: (**53, 55**) ; TZ: (**62, 65**); NC: (**70, 72**)	(*99*)
N. cyclamineus DC	NC: (**68**); GA: (**83**)	(*100,101*)
N. jacetanus Fdez. Casas	LY: (**1, 3, 20, 21**)	(*102*)
N. lobularis Hort.	HT: (**53**); GA: (**75**)	(*103*)
N. muñozii-garmendiae Fdez. Casas	HL: (**26, 35, 36**)	(*104*)
N. vasconicus Fdez. Casas	LY: (**1, 22**); HL: (**26, 28**)	(*70*)
Group B [Plant often 15–60 cm or more and/or with large flowers]		
N. bicolor L.	LY: (**22**); HL: (**29**); TZ: (**64, 65**); NC: (**71, 72**)	(*79*)
N. bujei (Fdez. Casas) Fdez. Casas	HL: (**26, 27, 30, 35, 36, 38**); HT: (**53, 54, 57, 61**); TZ: (**62**); GA: (**75**)	(*74,93*)
N. confusus Pugsley	HL: (**26, 29**); HT: (**53**); TZ: (**64**); GA: (**75, 79, 80**)	(*82,83,93*)
N. eugeniae Fdez. Casas	HL: (**26, 35**); GA: (**75**)	(*93,105,106*)
N. leonensis Pugsley	LY: (**1**); GA: (**78, 79, 86**)	(*93,107*)
N. pallidiflorus Pugsley	HL: (**26, 27**); HT: (**53**); TZ: (**64**); NC: (**72**); OA: (**89**)	(*86*)
N. perez-chiscanoi Fdez. Casas	GA: (**75, 79**)	(*93*)
N. primigenius (Laínz) Fdez. Casas & Laínz	HL: (**26, 27**); HT: (**45, 53**)	(*108*)
N. pseudonarcissus L.	LY: (**1**); HL: (**26, 30**); HT: (**53**); OA: (**87**)	(*95,109,110*)
N. radinganorum Fdez. Casas	HL: (**26, 27**); HT: (**46**)	(*111*)
N. tortuosus Haworth	LY: (**1, 23**)	(*68*)
c- *Section* Ganymedes Salisbury ex Schultes and Schultes		
N. pallidulus Graells	LY: (**25**); OA: (**90**)	(*26,67*)
N. triandrus L.	OA: (**90, 91, 92**)	(*112*)

(*continued*)

TABLE VIII.
Continued.

Species[a]	Skeleton types: (alkaloids)[b]	References
d- *Section* Jonquillae De Candolle		
N. assoanus Léon-Dufour = *N. requienii* Roemer	LY: (**3, 4, 5, 20, 21**)	(*87*,*113*,*114*)
N. jonquilla L.	NC: (**68**); GA: (**75, 84**)	(*115*)
2. Subgenus *Hermione* (Salisbury) Spach		
a- *Section* Hermione		
i. Subsection *Hermione* [syn. Section *Tazettae* De Candolle]		
A. Series *Hermione*		
N. aureus Loiseleur = *N. tazetta* L. ssp. *aureus* (Loisel.) Baker	LY: (**1**)	(*116*)
N. canaliculatus Guss.	HT: (**53**); TZ: (**62**); NC: (**68**)	(*89*,*101*)
N. tazetta L.	LY: (**1, 3, 7, 16, 18**); HL: (**26, 27, 30, 34**); HT: (**47, 53, 55, 56**); TZ: (**62, 63, 64**); NC: (**68, 71**) GA: (**75, 82, 83**)	(*89*,*117–129*)
N. tazetta L. ssp. *tazetta*	LY: (**1**); HT: (**43, 53**); TZ: (**62**); GA: (**78**)	(*130*)
N. tazetta L. var. *chinensis* Roem	LY: (**1, 3, 11**); HL: (**26, 35**); HT: (**44, 47, 48, 49, 51, 52, 55, 56**); TZ: (**62, 64**); GA: (**75, 76, 84**)	(*131–133*)
B. Series *Albiflorae*		
N. dubius Gouan	LY: (**3**); HL: (**32, 33**)	(*72*,*134*)
N. panizzianus Parlatore	LY: (**7**); HL: (**26**); HT: (**48, 49**); TZ: (**64**)	(*135*)
N. papyraceus Ker-Gawler.	LY: (**1, 3**); HL: (**26, 27, 40**); HT: (**44, 47, 48, 49, 50, 60**); TZ: (**62**); GA: (**75, 84**)	(*91*,*136*,*137*)
N. tortifolius Fdez. Casas	HL: (**26, 27, 32, 33**); GA: (**75**)	(*138*)
ii. Subsection *Serotini* [syn. Section *Serotini* Parlatore]		
N. serotinus Löfl. ex L.	TZ: (**66**); NC: (**68**)	(*101*,*139*)
3. Subgenus *Corbularia* (Salisb.) Pax [syn. Section *Bulbocodii* De Candolle]		
N. bulbocodium L.	HT : (**53**); TZ : (**62, 64**); NC: (**72**); GA: (**75, 81**)	(*112*)
N. cantabricus DC.	HT: (**42, 57, 59**); TZ: (**62**)	(*140*)
N. nivalis Graells	LY: (**6**); GA: (**75, 78**)	(*141*)
N. obesus Salisbury	HT: (**53**); TZ: (**64, 65, 67**); NC: (**71, 72**); GA: (**75**)	(*76*)
Intersectional hibrids		
Intersection [*Jonquillae* DC. *x Narcissus* L.]		
N. x gracilis Sabine	LY: (**1**); TZ: (**62**); GA: (**75**)	(*142*)

(*continued*)

TABLE VIII.
Continued.

Species[a]	Skeleton types: (alkaloids)[b]	References
Intersection [*Narcissus* L. *x Tazettae* DC.]		
N. x biflorus Curtis	LY: (**1**)	(*116*)
Intersection [*Jonquillae* DC. *x Pseudonarcissii* DC.]		
N. x odorus L. var. *rugulosus*	LY: (**1**); HL: (**26, 34, 37**); TZ: (**62**); NC: (**68**); GA: (**75**)	(*101*,*142*)
Other *Narcissus*		
Narcissus sp.	LY: (**2**); NC: (**68, 69**); GA: (**75**)	(*95*,*125*, *143*,*144*)

[a]Wild *Narcissus* species and hybrids are grouped into Subgenera and Sections according to the *Narcissus* classification of Mathew (*4*). Some taxonomical aspects are also based on the works of Barra and López-González (*145*,*146*), Dorda and Fernández-Casas (*147–152*), Fernandes (*10*,*153*), and Fernández-Casas (*154–157*).

[b]Skeleton types: LY, lycorine; HL, homolycorine; HT, hemanthamine; TZ, tazettine; NC, narciclasine; MN, montanine; GA, galanthamine; OA, other alkaloids. Alkaloid names: see Tables I–VII.

A. ENZYMATIC PREPARATION OF THE PRECURSORS

Although L-phenylalanine (L-phe) and L-tyrosine (L-tyr) are closely related in their chemical structure, they are not interchangeable in plants. In the Amaryllidaceae alkaloids, L-phe serves as a primary precursor of the C_6–C_1 fragment, corresponding to ring A and the benzylic position (C-6), and L-tyr is the precursor of ring C, the two-carbon side chain (C-11 and C-12) and nitrogen, C_6–C_2–N. The conversion of L-phe to the C_6–C_1 unit requires the loss of two carbon atoms from the side chain as well as the introduction of at least two oxygenated substituents into the aromatic ring, which is performed *via* cinnamic acids. The presence of the enzyme phenylalanine ammonia lyase (PAL) has been demonstrated in Amaryllidaceae plants (*182*), and the elimination of ammonia mediated by this enzyme is known to occur in an antiperiplanar manner to give *trans*-cinnamic acid, with loss of the *β-pro*-S hydrogen (*183*). Thus, it may be expected that L-phe would be incorporated into Amaryllidaceae alkaloids with retention of the *β-pro*-R hydrogen. However, feeding experiments in *Narcissus* 'King Alfred' showed that tritium originally present at C-*β* of L-phe, whatever the configuration, was lost in the formation of several hemanthamine- and homolycorine-type alkaloids, which led to the conclusion that fragmentation of the cinnamic acids involves the oxidation of C-*β* to the ketone or acid level, the final product being protocatechuic aldehyde or its derivatives (Fig. 2). On the other hand, L-tyr is degraded no further than tyramine before incorporation into the Amaryllidaceae alkaloids.

B. PRIMARY CYCLIZATION MECHANISMS

Tyramine and protocatechuic aldehyde or its derivatives are logical components for the biosynthesis of the precursor norbelladine (**93**). This pivotal reaction

TABLE IX.
Occurrence of Alkaloids in *Narcissus* Cultivars.

Narcissus cultivars[a]	Skeleton types: (alkaloids)[b]	References
Division 1 – Trumpet Daffodils		
Narcissus 'Celebrity'	NC: (**68**)	(*101*)
Narcissus 'Covent Garden'	LY: (**1, 7, 11**); HL: (**35**); HT: (**53**); GA: (**75, 78, 85**)	(*103*,*158*)
Narcissus 'Dutch Master'	GA: (**75**)	(*81*)
Narcissus 'Early Glory'	LY: (**1, 7**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'Flower Carpet'	NC: (**68**)	(*101*)
Narcissus 'Golden Harvest'	NC: (**68**); GA: (**75**)	(*81*,*101*)
Narcissus 'Grand Maître'	LY: (**1, 7**); HL: (**26**); HT: (**53**); TZ: (**62**); GA: (**75**)	(*103*)
Narcissus 'Imperator'	LY: (**1, 7, 11**); HL: (**26, 35**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'King Alfred'	LY: (**1, 6, 7, 11, 16, 20**); HL: (**26, 27, 34, 35, 37**); HT: (**53, 58**); NC: (**68**); GA: (**75, 78, 85**)	(*92*,*101*,*103*,*125*, *158–161*)
Narcissus 'Magnet'	LY: (**7, 11**); HT: (**53**)	(*103*)
Narcissus 'Magnificience'	LY: (**1, 7, 11**); HT: (**53**); GA: (**75, 78, 85**)	(*103*,*158*)
Narcissus 'Mount Hood'	HL: (**26, 34**); NC: (**68**); GA: (**75, 84, 85**)	(*101*,*162–164*)
Narcissus 'Mrs. Ernst H. Krelage'	LY: (**1, 7, 11**); HT: (**53**); NC: (**68**); GA: (**75**)	(*103*,*163*)
Narcissus 'Music Hall'	LY: (**1, 7**); HT: (**53**)	(*103*)
Narcissus 'Oliver Cromwell'	LY: (**7, 11**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'President Lebrun'	NC: (**68**)	(*101*,*163*)
Narcissus 'Queen of Bicolors'	LY: (**1, 7, 11**); HT: (**53**)	(*103*)
Narcissus 'Rembrandt'	LY: (**1**); HT: (**53**); NC: (**68**); GA: (**75, 78, 85**)	(*101*,*103*)
Narcissus 'Rockery Beauty'	LY: (**7, 16**); HT: (**53**); GA: (**78, 85**)	(*103*)
Narcissus 'Romaine'	LY: (**7, 11**); HL: (**35**); HT: (**53**)	(*103*)
Narcissus 'Spring Glory'	LY: (**1, 7, 11**); HT: (**53**); GA: (**78, 85**)	(*103*)
Narcissus 'Unsurpassable'	LY: (**11**); HL: (**35**); HT: (**53**); GA: (**75**)	(*81*,*103*)
Narcissus 'Victoria'	LY : (**1, 7, 11**); HT: (**53**); GA: (**78, 85**)	(*103*)
Narcissus 'Wrestler'	LY: (**7, 11**); HT: (**53**); GA: (**75**)	(*103*)
Division 2 – Large-Cupped Daffodils		
Narcissus 'Carabiniere'	NC: (**68**)	(*101*)
Narcissus 'Carlton'	LY: (**13, 14, 15**); HL: (**26, 30, 31, 34, 35, 36, 37, 38**); HT: (**42, 53**); NC: (**68**); GA: (**75, 77, 78, 83, 84, 86**)	(*101*,*165–168*)

(*continued*)

TABLE IX.
Continued.

Narcissus cultivars[a]	Skeleton types: (alkaloids)[b]	References
Narcissus 'Clamor'	NC: (**68**)	(*101*,*163*)
Narcissus 'Daisy Schäffer'	LY: (**7, 11**); GA: (**75**)	(*103*)
Narcissus 'Deanna Durbin'	LY: (**1, 7, 11, 16**); HT: (**53**)	(*103*,*158*)
Narcissus 'Flower Record'	LY: (**1, 7, 11**); HT: (**53**); GA: (**75**)	(*81*,*103*)
Narcissus 'Folly'	LY: (**1**); TZ : (**62**)	(*118*)
Narcissus 'Fortune'	LY: (**19**); HL: (**34, 37**); HT: (**53**); GA: (**75**)	(*81*,*103*,*169*,*170*)
Narcissus 'Gigantic Star'	GA: (**75**)	(*81*)
Narcissus 'Helios'	LY: (**7, 11**); HL: (**26, 35**); HT: (**53**); NC: (**68**); GA: (**75**)	(*101*,*103*,*125*)
Narcissus 'Ice Follies'	LY: (**1, 7, 10, 13, 14**); HL: (**34**); HT: (**53**); GA: (**75, 84, 85**)	(*81*,*164*,*171*,*172*)
Narcissus 'John Evelyn'	LY: (**1, 7,11**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'Marion Cran'	LY: (**1, 7**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'Mercato'	NC: (**68**)	(*101*)
Narcissus 'Mrs. R.O. Backhouse'	NC: (**68**)	(*101*)
Narcissus 'Nova Scotia'	LY: (**1, 7**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'Oranje Bruid'	NC: (**68**)	(*101*)
Narcissus 'Pluvius'	LY: (**1, 7, 11, 16**); HT: (**53**); GA: (**75**)	(*103*,*158*)
Narcissus 'Salome'	LY: (**3, 22, 23**); HL: (**34, 39**); HT: (**57**); GA: (**75, 78**)	(*71*,*81*)
Narcissus 'Scarlet Elegance'	NC: (**68**)	(*101*,*163*)
Narcissus 'Sempre Avanti'	LY: (**1, 7, 11, 16**); HT: (**53**); NC: (**68**)	(*101*,*103*,*125*,*163*)
Narcissus 'Suda'	LY: (**7, 11**); HL: (**35**); HT: (**53**); GA: (**75**)	(*103*)
Narcissus 'Toronto'	LY: (**1, 7**); HT: (**53**)	(*103*)
Narcissus 'Tunis'	NC: (**68**)	(*101*,*163*)
Narcissus 'Walt Disney'	NC: (**68**)	(*101*,*163*)
Narcissus 'Yellow Sun'	GA: (**75**)	(*81*)
Division 3 – Small-Cupped Daffodils		
Narcissus 'Barrett Browning'	GA: (**75**)	(*81*)
Narcissus 'Daphne'	LY: (**1**); HL: (**26, 35**); GA: (**75**)	(*103*)
Narcissus 'Verger'	NC: (**68**); GA: (**75**)	(*81*,*101*,*163*)
Division 4 – Double Daffodils		
Narcissus 'Cheerfulness'	NC: (**68**); GA: (**75**)	(*101*,*164*)
Narcissus 'Dick Wilden'	GA: (**75**)	(*81*)
Narcissus 'Flower Drift'	GA: (**75**)	(*81*)
Narcissus 'Inglescombe'	LY: (**1, 11**); HL: (**26, 34, 35**); HT: (**53**); GA: (**75, 84, 85**)	(*103*,*162*)
Narcissus 'Insulinde'	LY: (**1, 7, 11**); HT: (**53**)	(*103*)

(*continued*)

TABLE IX.
Continued.

Narcissus cultivars[a]	Skeleton types: (alkaloids)[b]	References
Narcissus 'Irene Copeland'	LY: (**1**); GA: (**83**)	(*103*)
Narcissus 'Livia'	LY: (**1, 7, 10, 11**); HT: (**53**)	(*103*)
Narcissus 'Sir Winston Churchill'	LY: (**17**)	(*173*)
Narcissus 'Texas'	LY: (**1, 11, 12**); HT: (**53**); NC: (**68**); GA: (**75, 83**)	(*101*,*103*,*163*, *174–176*)
Narcissus 'Twink'	LY: (**1, 7, 11**); HT: (**53**); GA: (**75**)	(*103*,*158*)
Narcissus 'Van Sion'	LY: (**1, 7, 11**); HL: (**26, 35**); HT: (**53**); TZ: (**62**); GA: (**75, 78, 85**)	(*81*,*103*,*158*)
Division 5 – Triandrus Daffodils		
Narcissus 'Thalia'	LY: (**1**); HL: (**26, 35**); HT: (**53**); NC: (**68**)	(*101*,*125*,*142*)
Narcissus 'Tresamble'	HL: (**35**); HT: (**53**); NC: (**68**); GA: (**75**)	(*101*,*125*,*142*)
Division 6 – Cyclamineus Daffodils		
Narcissus 'Beryl'	LY: (**1, 7, 16**)	(*142*)
Narcissus 'Cairhays'	LY: (**7, 11**); HT: (**55, 56**)	(*142*)
Narcissus 'February Gold'	HL: (**26, 35**); GA: (**75, 84**)	(*81*,*142*)
Narcissus 'Peeping Tom'	LY: (**11**); HL: (**35**); TZ: (**62**)	(*142*)
Narcissus 'Tête-a-Tête'	GA: (**75**)	(*81*)
Division 7 – Jonquilla and Apodanthus Daffodils		
Narcissus 'Golden Sceptre'	LY: (**1, 7, 8, 9**); HL : (**26, 30, 34, 35, 37**); HT: (**53**); TZ: (**62**); GA: (**75**)	(*142*,*177–180*)
Narcissus 'Pipit'	GA: (**75**)	(*168*)
Narcissus 'Trevithian'	LY: (**1**); HL: (**35**); TZ: (**62**); NC: (**68**); GA: (**75**)	(*101*,*142*)
Division 8 – Tazetta Daffodils		
Narcissus 'Cragford'	LY: (**1**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Early Perfection'	LY: (**1, 11**); HL: (**26, 34**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Geranium'	LY: (**1, 16**); HL: (**26**); HT: (**53**); TZ: (**62**); NC: (**68**); GA: (**75**)	(*89*,*122*,*143*,*164*)
Narcissus 'La Fiancée'	LY: (**1, 7**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Laurens Koster'	LY: (**1**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'L'innocence'	LY: (**1, 16**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Minnow'	GA: (**75**)	(*81*)

(*continued*)

TABLE IX.
Continued.

Narcissus cultivars[a]	Skeleton types: (alkaloids)[b]	References
Narcissus 'Scarlet Gem'	LY: (**1, 7**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Silver Chimes'	LY: (**1**); HT: (**53**); TZ: (**62**)	(*142*)
Narcissus 'St. Agnes'	LY: (**1**); HL: (**26**); HT: (**53**); TZ: (**62**)	(*89*)
Narcissus 'Totus Albus'	NC: (**68**)	(*101*,*163*)
Division 9 – Poeticus Daffodils		
Narcissus 'Actaea'	LY: (**1, 7, 16**); HL: (**35**); NC: (**68**); GA: (**75**)	(*89*,*101*)
Narcissus 'Sarchedon'	LY: (**1, 7, 16**); HL: (**35**); GA: (**75**)	(*89*)
Division 12 – Other Daffodils		
Narcissus 'Brougshane'	GA: (**75**)	(*81*)
Narcissus 'Kristalli'	LY: (**1**); TZ: (**62**); GA: (**75, 83**)	(*118*)

[a]Horticultural classification of *Narcissus* cultivars according to the International Daffodil Register and Classified List of the Royal Horticultural Society (*18*).
[b]Skeleton types: LY, lycorine; HL, homolycorine; HT, hemanthamine; TZ, tazettine; NC, narciclasine; MN, montanine; GA, galanthamine. Alkaloid names: see Tables I–VII.

represents the entry of primary metabolites into a secondary metabolic pathway. The junction of the amine and the aldehyde results in a Schiff's base, two of which have been isolated up to now from several *Crinum* species: craugsodine (*184*) and isocraugsodine (*185*). The existence of Schiff's bases in nature, as well as their easy conversion into the different ring systems of the Amaryllidaceae alkaloids, suggest that the initial hypothesis about this biosynthetic pathway was correct.

C. ENZYMATIC PREPARATION OF INTERMEDIATES

In 1957, Barton and Cohen (*186*) proposed that norbelladine (**93**) or related alkaloids could undergo oxidative coupling in Amaryllidaceae plants, once ring A had been suitably protected by methylation, resulting in the different skeletons of the Amaryllidaceae alkaloids (Fig. 3). The key intermediate in most of cases is *O*-methylnorbelladine (**87**).

D. SECONDARY CYCLIZATION, DIVERSIFICATION, AND RESTRUCTURING

Secondary cyclization is produced by an oxidative coupling of *O*-methylnorbelladine.

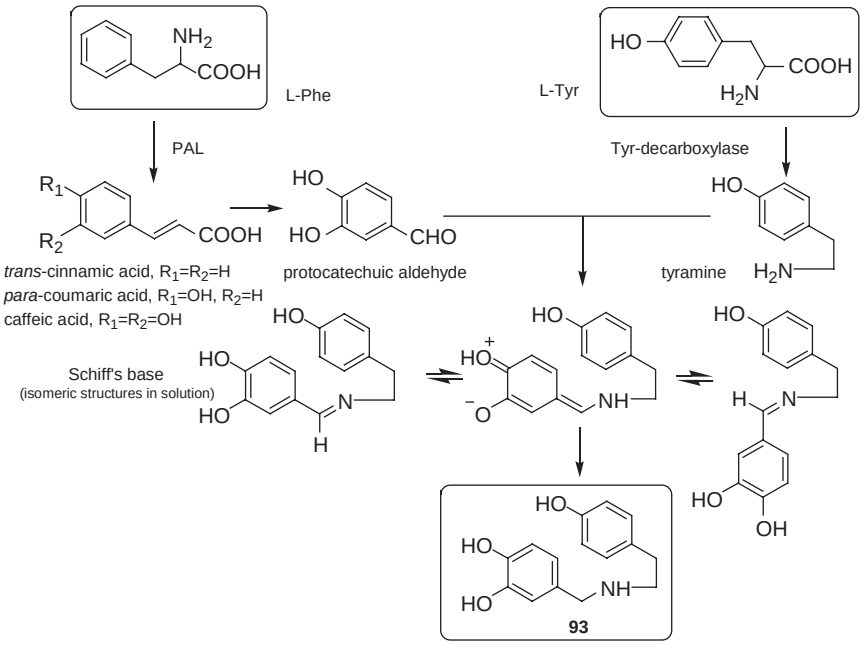


Figure 2. Biosynthetic pathway to norbelladine (**93**).

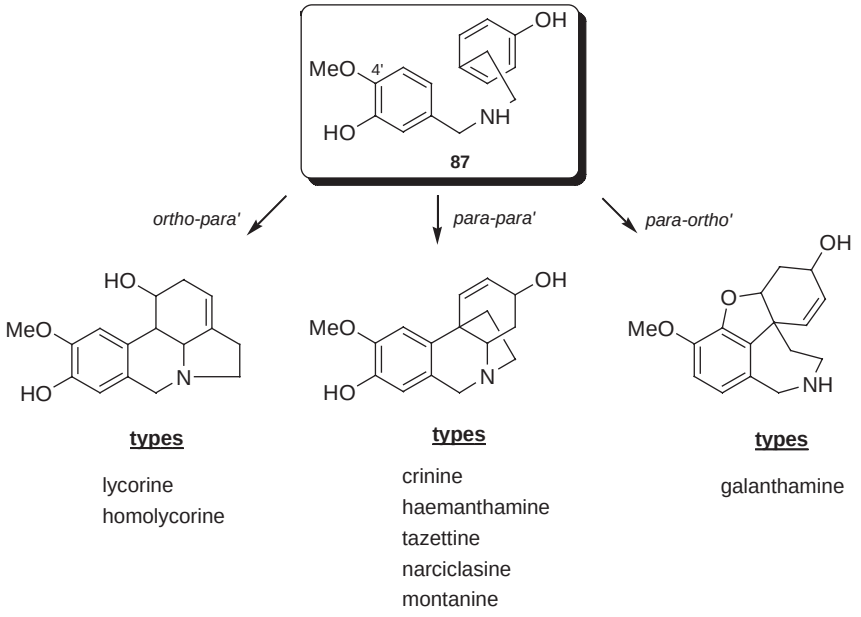


Figure 3. Phenol oxidative coupling in Amaryllidaceae alkaloids.

1. Lycorine and Homolycorine Types

The alkaloids of this group are derivatives of the pyrrolo[de]phenanthridine (lycorine type) and the 2-benzopirano-[3,4-*g*]indole (homolycorine type) skeletons, and both types originate from an *ortho–para′* phenol oxidative coupling (Fig. 4).

The biological conversion of cinnamic acid *via* hydroxylated cinnamic acids into the C_6–C_1 unit of norpluviine (**12**) has been used in a study of hydroxylation mechanisms in higher plants (*187*). When [3-^{3}H, β-^{14}C] cinnamic acid was fed to *Narcissus* 'Texas' a tritium retention in norpluviine (**12**) of 28% was observed, which is very close to the predicted value resulting from *para*-hydroxylation with hydrogen migration and retention.

In the conversion of *O*-methylnorbelladine (**87**) into lycorine (**1**), the labeling position [3-^{3}H] on the aromatic ring of L-tyr afterward appears at C-2 of norpluviine (**12**), which is formed as an intermediate, the configuration of the tritium apparently being β (*176*). This tritium is retained in subsequently formed lycorine (**1**), which means that hydroxylation at C-2 proceeds with an inversion of configuration (*188*) by a mechanism involving an epoxide, with ring opening followed by allylic rearrangement of the resulting alcohol (Fig. 5). Supporting evidence comes from the incorporation of [2β-^{3}H]caranine (**10**) into lycorine (**1**) in *Zephyranthes candida* (*189*). However, hydroxylation of caranine (**10**) in *Clivia miniata* occuring with retention of configuration was also observed (*190*). Further, [2α-^{3}H,11-^{14}C]caranine (**10**) was incorporated into lycorine (**1**) with high retention of tritium at C-2, indicating that no 2-oxo-compound can be implicated as an intermediate.

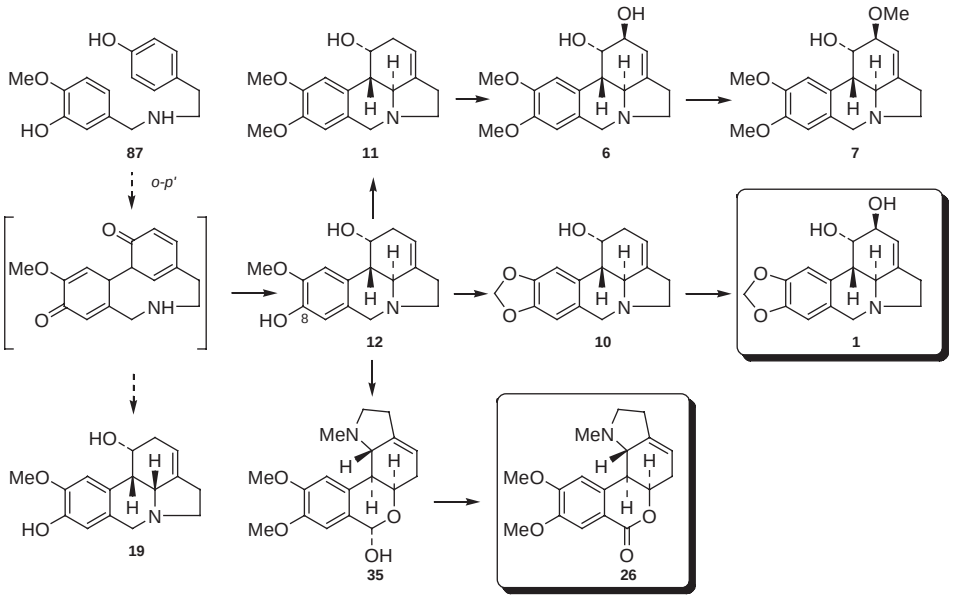


Figure 4. Alkaloids proceeding from an *ortho–para′* coupling.

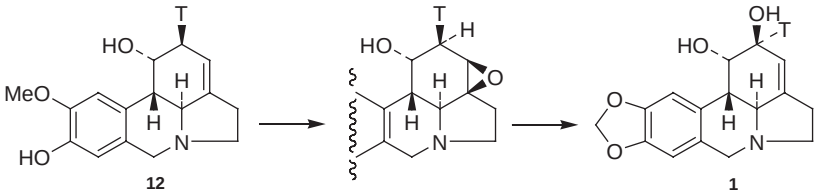


Figure 5. Biosynthesis of lycorine (**1**) with inversion of the configuration.

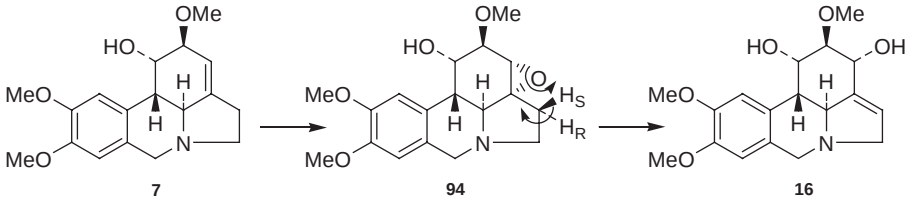


Figure 6. Conversion of galanthine (**7**) to narcissidine (**16**) *via* epoxide (**94**).

The conversion of the *O*-methoxyphenol to the methylenedioxy group may occur late in the biosynthetic pathway. Tritiated norpluviine (**12**) is converted to tritiated lycorine (**1**) by *Narcissus* 'Deanna Durbin', which demonstrates the previously mentioned conversion and also indicates that the C-2 hydroxyl group of lycorine (**1**) is derived by allylic oxidation of either norpluviine (**12**) or caranine (**10**) (*191*).

Regarding the conversion of [2β-^{3}H,8-OMe-^{14}C]pluviine (**11**) into galanthine (**7**), in *Narcissus* 'King Alfred', the retention of 79% of the tritium label confirms that hydroxylation of C-2 may occur with inversion of configuration (*92*).

It was considered (*192*) that another analogous epoxide **94** could give narcissidine (**16**) in the way shown by loss of the *pro*-S hydrogen from C-11, galanthine (**7**) being a suitable substrate for epoxidation. Labeled [α-^{14}C, β-^{3}H]-*O*-methylnorbelladine (**87**), when fed to *Narcissus* 'Sempre Avanti', afforded galanthine (**7**) (98% tritium retention) and narcissidine (**16**) (46% tritium retention). Loss of hydrogen from C-11 of galanthine (**7**) was therefore stereospecific. In the 1990s, Kihara *et al.* (*193*) isolated a new alkaloid, incartine (**94**), from the flowers of *Lycoris incarnata*, which could be considered as the biosynthetic intermediate of this pathway (Fig. 6).

The biological conversion of protocatechuic aldehyde into lycorenine (**35**), which proceeds *via* *O*-methylnorbelladine (**87**) and norpluviine (**12**), first involves a reduction of the aldehyde carbonyl, and afterward, in the generation of lycorenine (**35**), oxidation of this same carbon atom. The absolute stereochemistry of these processes has been elucidated in subsequent experiments (*194*), and the results show that hydrogen addition and removal take place on the *re*-face of the molecules concerned (*195*), the initially introduced hydrogen being the one later removed (*196*). It is noteworthy that norpluviine (**12**), unlike pluviine (**11**), is converted in *Narcissus* 'King Alfred' primarily to alkaloids of the homolycorine type. Benzylic

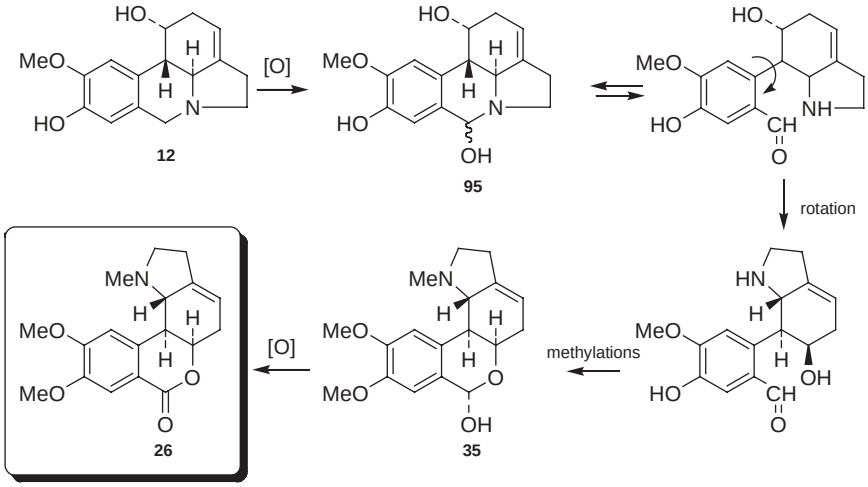


Figure 7. Conversion of norpluviine (**12**) to homolycorine-type alkaloids.

oxidation of position 6 would afford **95**, followed by ring opening to form an amino aldehyde. Hemiacetal formation and methylation could provide lycorenine (**35**) (*92*), and, on subsequent oxidation, could afford homolycorine (**26**), as shown in Fig. 7.

2. Crinine, Hemanthamine, Tazettine, Narciclasine, and Montanine Types

This group includes the alkaloids derived from 5,10b-ethanophenanthridine (crinine and hemanthamine types), 2-benzopyrano[3,4-*c*]indole (tazettine type), phenanthridine (narciclasine type), and 5,11-methanomorphanthridine (montanine type) skeletons, originating from a *para–para′* phenol oxidative coupling (Fig. 8).

Results of experiments with labeled crinine (**96**), and less conclusively with oxovittatine, indicate that the two, naturally occurring enantiomeric series, represented in Fig. 8 by crinine (**96**) and vittatine (**42**), are not interchangeable in *Nerine bowdenii* (*197*).

Incorporation of *O*-methylnorbelladine (**87**), labeled in the methoxy carbon and also in positions [3,5-^{3}H], into the alkaloid hemanthamine (**53**) was without loss of tritium, half of which was sited at C-2 of **53**. Consideration of the possible mechanisms involved in relation to tritium retention led to the suggestion that the tritium which is expected at C-4 of **53** might not be stereospecific (*198*). The conversion of *O*-methylnorbelladine (**87**) into hemanthamine (**53**) involves loss of the *pro*-R hydrogen from the C-β of the tyramine moiety as well as the further entry of a hydroxyl group at this site (*199*). The subsequent benzylic oxidation results in a **55/56** epimeric mixture that even HPLC cannot separate. The epimeric forms were proposed to be interchangeable through **97**. The biosynthetic conversion of the 5,10b-ethanophenanthridine alkaloids to the 2-benzopyrano[3,4-*c*]indole was demonstrated by feeding tritium-labeled alkaloids to *Sprekelia formosissima*. It was shown that this plant converts hemanthamine (**53**) to hemanthidine/epihemanthamine (**55/56**), and subsequently to pretazettine (**64**), in an essentially irreversible

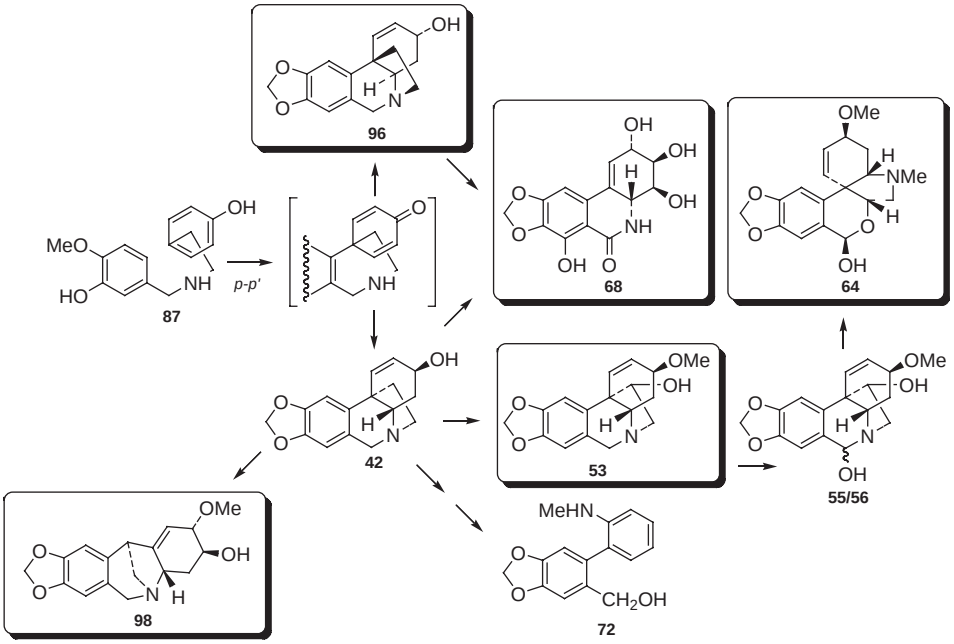


Figure 8. Alkaloids proceeding from a *para–para′* coupling.

manner (*200*). This transformation was considered to proceed through **97** or the related alkoxide anion, although intermediate **97** have never been detected by spectral methods (*201*) (Fig. 9).

It has also been proved that formation of the alkaloid narciclasine (**68**) proceeds from the pathway for crinine- and hemanthamine-type alkaloids, and not through norpluviine (**12**) and lycorine (**1**) derivatives. In fact, in view of its structural affinity to both hemanthamine (**53**) and lycorine (**1**), narciclasine (**68**) could be derived by either of the pathways. When *O*-methylnorbelladine (**87**), labeled in the methoxy carbon and in both protons of positions 3 and 5 of the tyramine aromatic ring, was administered to *Narcissus* plants, all four alkaloids incorporated activity. The isotopic ratio [^{3}H:^{14}C] for norpluviine (**12**) and lycorine (**1**) was, as expected, 50% that of the precursor, because of its *ortho–para′* coupling. On the contrary, in hemanthamine (**53**) the ratio was unchanged. These results show clearly that the methoxy group of **87** is completely retained in the alkaloids mentioned, providing a satisfactory internal standard and showing that the degree of tritium retention is a reliable guide to the direction of phenol coupling. Narciclasine (**68**) showed an isotopic ratio (75%) higher than that of lycorine (**1**) or norpluviine (**12**), though lower than that of hemanthamine (**53**). However, the fact that more than 50% of tritium is retained suggests that *O*-methylnorbelladine (**87**) is incorporated into narciclasine (**68**) *via para–para′* phenol oxidative coupling.

O-methylnorbelladine (**87**) and vittatine (**42**) are implicated as intermediates in the biosynthesis of narciclasine (**68**) (*202–204*), and the loss of the ethane bridge

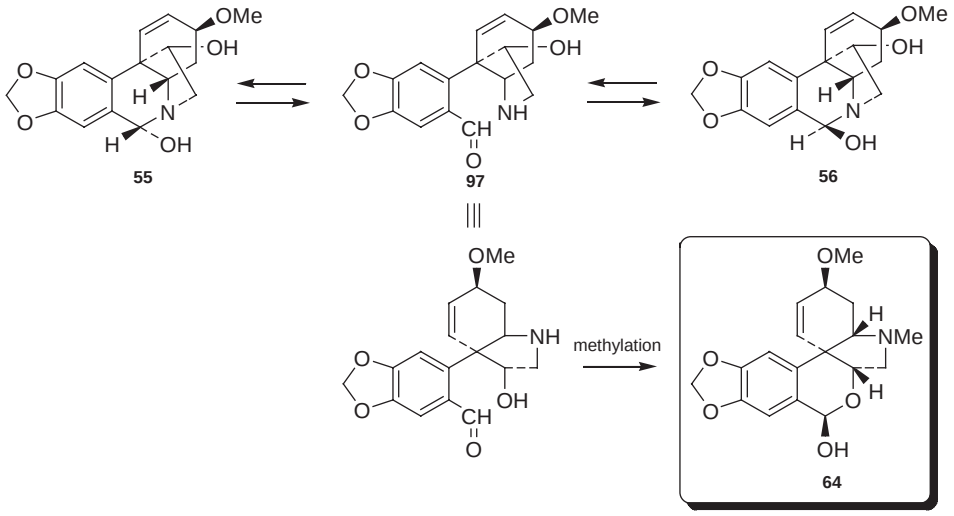


Figure 9. Biosynthesis of pretazettine (**64**).

from the latter could occur by a retro-Prins reaction on 11-hydroxyvittatine (**43**). Strong support for this pathway was obtained by labeling studies. 11-Hydroxyvittatine (**43**) has also been proposed as an intermediate in the biosynthesis of hemanthamine (**53**) and montanine (**98**) (a 5,11-methanomorphanthridine alkaloid) following the observed specific incorporation of vittatine (**42**) into the two alkaloids in *Rhodophiala bifida* (*197*) (Fig. 10).

Fuganti and Mazza (*203*,*204*) concluded that in the late stages of narciclasine (**68**) biosynthesis, the two-carbon bridge is lost from the oxocrinine skeleton, passing through intermediates bearing a pseudoaxial hydroxy-group at the C-3 position and further hydrogen removal from this position does not occur. Noroxomaritidine was also implicated in the biosynthesis of narciclasine (**68**) and further experiments (*205*) showed that it is also a precursor for ismine (**72**).

The alkaloid ismine (**72**) has also been shown (*206*) to be a transformation product of the crinine-hemanthamine series. The precursor, oxocrinine labeled with tritium in the positions 2 and 4, was administered to *Sprekelia formosissima* plants and the radioactive ismine (**72**) isolated was shown to be specifically labeled at the expected positions.

3. Galanthamine Type

These alkaloids have a dibenzofuran nucleus (galanthamine type) and are obtained from a *para–ortho′* phenol oxidative coupling.

The initial studies of this pathway suggested that the *para–ortho′* coupling does not proceed from *O*-methylnorbelladine (**87**), but from *N*,*O*-dimethylnorbelladine (**99**) to finally give galanthamine (**75**) (*207*). *O*,*N*-dimethylnorbella-dine (**99**) was

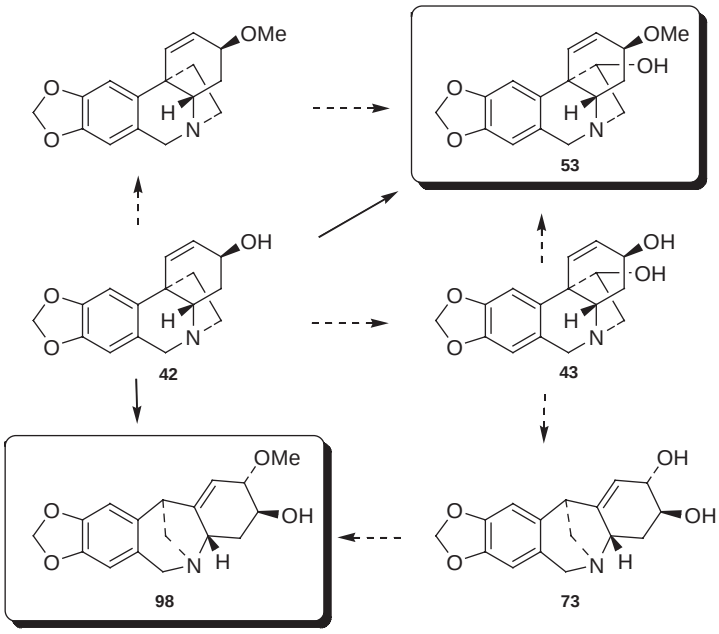


Figure 10. Proposed biosynthetic pathways to hemanthamine (**53**) and montanine (**98**).

first isolated from *Pancratium maritimum* (*208*), a species that also contains galanthamine (**75**).

However, the most recent study seems to contradict the evidence set forth above. Experiments carried out with application of ^{13}C-labeled *O*-methylnorbelladine (**87**) to organs of field-grown *L. aestivum* have shown that the biosynthesis of galanthamine (**75**) involves the phenol oxidative coupling of *O*-methylnorbelladine (**87**) to a postulated dienone, which undergoes spontaneous closure of the ether bridge to yield *N*-demethylnarwedine (**100**), giving norgalanthamine (**78**) after stereoselective reduction. Furthermore, it was shown that norgalanthamine (**78**) is *N*-methylated to galanthamine (**75**) in the final step of biosynthesis (*181*) (Fig. 11). In contrast to the literature, *N*,*O*-dimethylnorbelladine (**99**) was metabolized to a lesser extent in *L. aestivum* and incorporated into galanthamine (**75**) as well as norgalanthamine (**78**) at about one-third of the rate of *O*-methylnorbelladine (**87**).

According to Eichhorn *et al.* (*181*), narwedine (**83**) is not the direct precursor of galanthamine (**75**), and could possibly exist in equilibrium with galanthamine (**75**), a reaction catalyzed by a hypothetically reversible oxido-reductase.

Chlidanthine (**101**), by analogy with the known conversion of codeine to morphine, might be expected to arise from galanthamine (**75**) by *O*-demethylation. This was shown to be true when both galanthamine (**75**) and narwedine (**83**), with tritium labels, were incorporated into chlidanthine (**101**) (*209*).

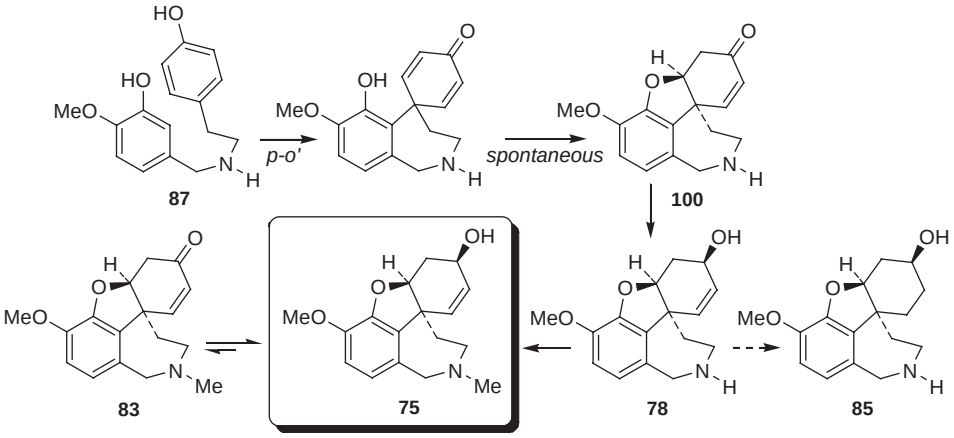


Figure 11. Biosynthesis of galanthamine (**75**) and derivatives.

IV. Synthetic Studies

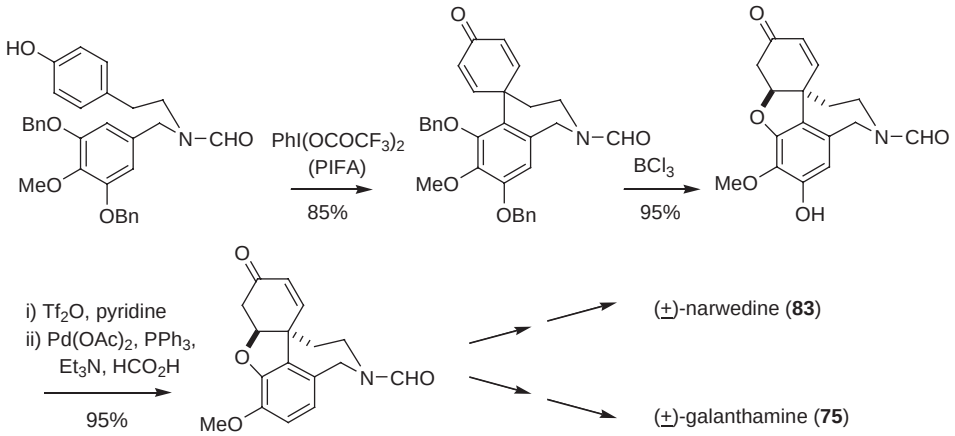
The synthesis of *Narcissus* alkaloids has been the subject of intense efforts over the past few years. An exhaustive report is beyond the scope of this chapter, and the reader is referred to recent and excellent reviews in the field for a more thorough account (*34*,*60–66*,*210*,*211*). Several approaches to the total synthesis of these alkaloids have demonstrated their efficiency. We describe herein some representative examples, classified according to mechanistic criteria.

A. OXIDATIVE COUPLINGS

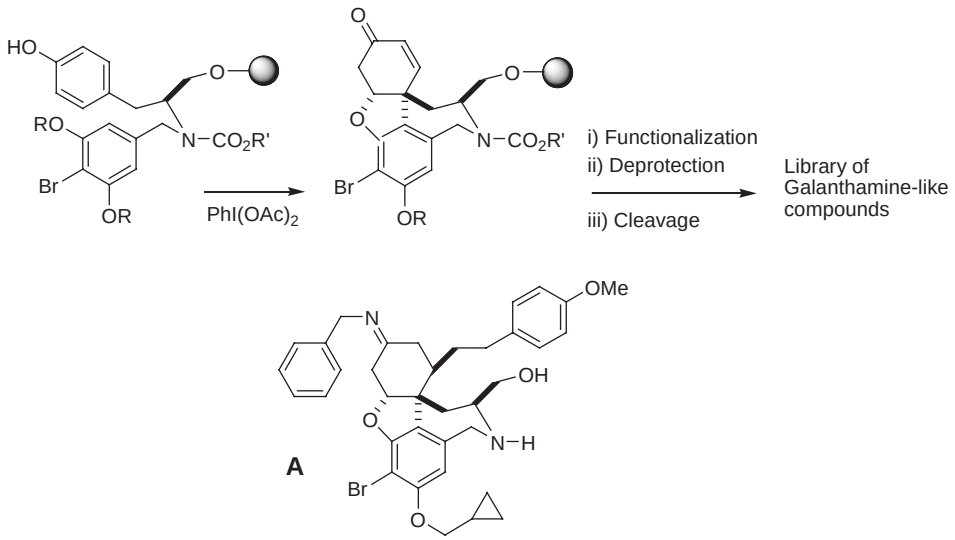
Biomimetic oxidative phenolic coupling still stands as a practical method for the preparation of these alkaloids. New syntheses of (−)-narwedine (**83**) and (−)-galanthamine (**75**) have been disclosed, the former having been prepared in its enantiopure form from the corresponding racemate through a crystallization-induced chiral transformation (*212*). Derivatives of 1-methylgalanthamine (*213*), as well as galanthamine analogues having the N atom at altered positions in the azepine ring (*214*), have also been reported. A significant improvement to the oxidation protocol is the use of PIFA as the oxidant on a symmetrical substrate, allowing efficient synthesis of racemic narwedine and galanthamine (*215*) (Scheme 1).

The same group later reported an efficient route to (−)-galanthamine (**75**) by a variation of the method whereby remote asymmetric induction was used (*216*) as well as the total syntheses of siculine, oxocrinine, epicrinine, and buflavine (*217*).

A solid-phase version of this biomimetic method has been developed in the context of diversity-oriented synthesis to generate a library of galanthamine-like molecules, which allowed the identification of compound **A**, a potent new blocker of protein trafficking from the Golgi apparatus to the plasma membrane. Interestingly, galanthamine (**75**) does not exhibit this biological activity (*218*) (Scheme 2).



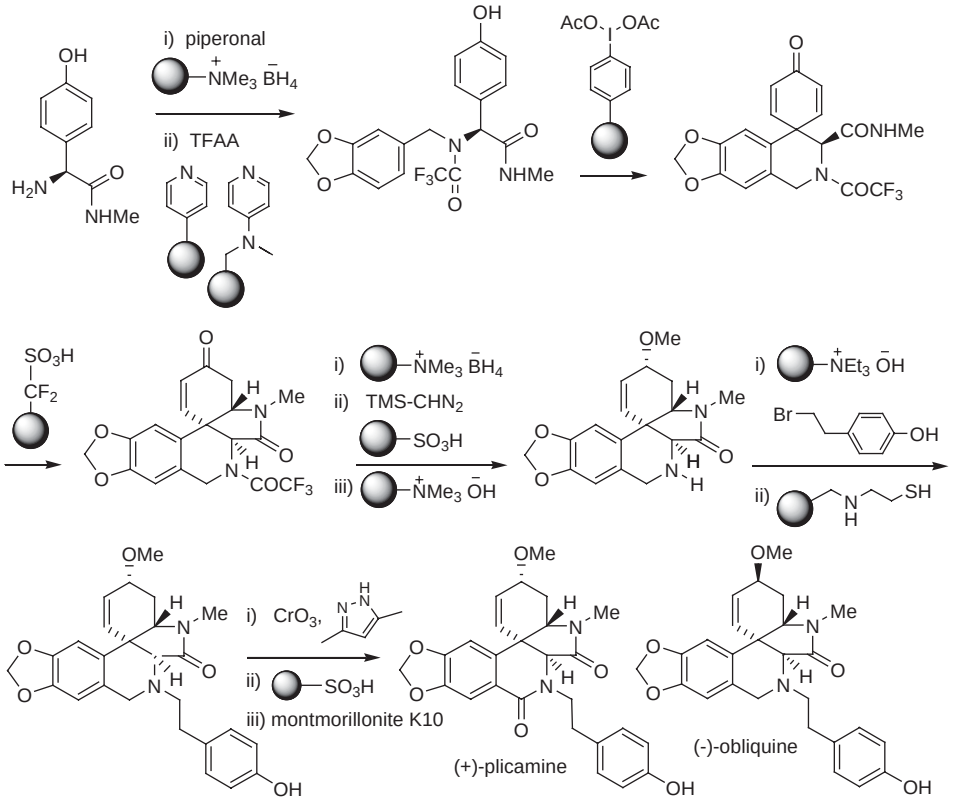
Scheme 1. Synthesis of racemic narwedine (**83**) and galanthamine (**75**).



Scheme 2. Diversity-oriented synthesis of galanthamine-like compounds.

A new oxidative rearrangement has led to the synthesis of (±)-lycoramine (*219*), and a related Lewis-acid-promoted transformation has allowed the preparation of mesembrine (**92**) and crinane in racemic form (*220*).

An impressive demonstration of the use of solid-supported reagents and scavengers in the total synthesis of natural products was provided by the group of Ley (for previous work, see ref. *221*). As an application of this new methodology (intended to expedite synthetic routes, as the only work up required in these protocols involves filtration, followed by evaporation of the solvent), (+)-plicamine was synthesized without the need for chromatography. The sequence starts

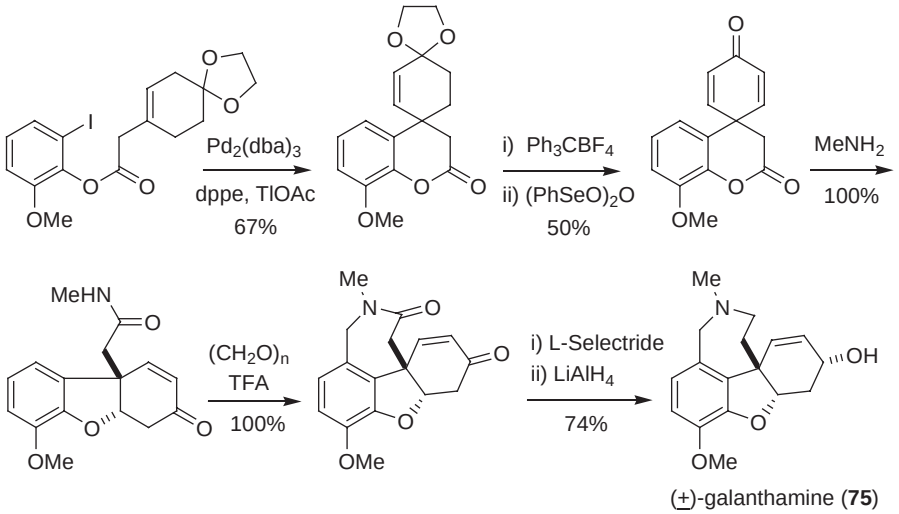


Scheme 3. Synthesis of plicamine and obliquine using solid-supported reagents.

with *p*-hydroxyphenylglycine which, upon functionalization, undergoes a reductive amination with piperonal. The resulting product is subjected to biomimetic phenol oxidative coupling with solid-supported iodonium diacetate. An acid-promoted conjugate addition closed the lactam ring, and subsequent functional group transformations led to the desired product. Every single step used solid-supported reagents or solid-supported scavengers (Scheme 3) (*222*,*223*). The same group later disclosed the syntheses of (−)-obliquine and (+)-plicane (*224*).

B. ORGANOMETALLIC-PROMOTED REACTIONS

Transition metals, especially palladium, have been used for the stereoselective synthesis of these alkaloids with remarkable success. Since Overman's approach to (±)-tazettine (**62**) using an intramolecular Heck reaction (*225*), this methodology for the construction of the critical quaternary stereogenic center has been implemented for the preparation of many alkaloids. Grigg later reported access to (*R,R*)-crinane *via* regiospecific palladium-mediated cyclization (*226*). An efficient total synthesis of racemic galanthamine (**75**) following this approach has been recently disclosed (*227*). After the key intramolecular Heck reaction, deprotection of the

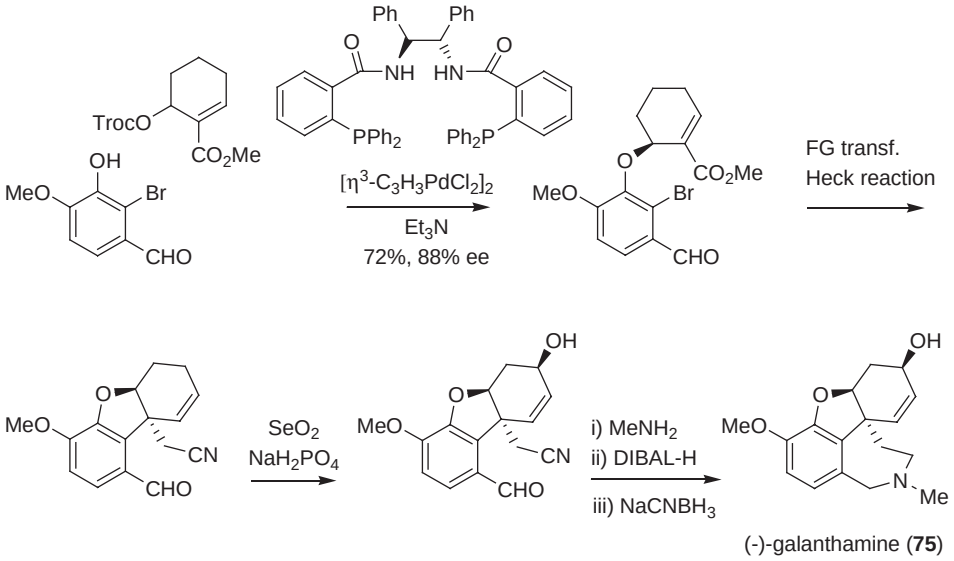


Scheme 4. Palladium-mediated synthesis of galanthamine (**75**).

acetal moiety, followed by oxidation and aminolysis of the lactone, promoted the spontaneous conjugate addition of the phenolic hydroxyl, to afford the tricyclic intermediate. A Pictet–Spengler reaction was then used to close the azepine ring. Subsequent functional group transformations allowed the completion of the total synthesis (Scheme 4).

Related strategies were used to prepare racemic maritidine (**44**) (*228*) and lycoramine (**84**) (*229*,*230*). An elegant and unified approach to synthesize (−)-pancracine (**73**), (−)-montanine (**98**), (−)-coccinine, and (−)-brunsvigine used an intramolecular Heck reaction for the ring closure of the central azepine ring, connecting the bromoarene and terminal alkene moieties. The key precursor was prepared *via* stereospecific intramolecular allenylsilane addition to an imine (*231*). Enders recently reported an asymmetric synthesis of the 1-*epi* aglycon of cripowellins A and B, based on an intramolecular Heck reaction of a functionalized bromoaryl-azacyclononene, which in turn was prepared *via* ring closing metathesis of an open-chain precursor (*232*). Buflavine was prepared in a very short route by assembling a biphenyl intermediate through a Suzuki coupling (*233*).

Recently, palladium-catalyzed asymmetric allylic substitution of an activated cyclohexenol derivative has allowed two enantioselective syntheses of (−)-galanthamine (**75**) (*234*,*235*). Both approaches rely on the enantioselective preparation of the same tricyclic intermediate, which is subsequently converted to the alkaloid *via* stereocontrolled transformations; the most efficient of which comprised stereoselective allylic oxidation of the cyclohexene moiety (Scheme 5). The same methodology allowed the synthesis of (−)-codeine and (−)-morphine (*236*). The same group had earlier reported the synthesis of (+)-pancratistatin following a related strategy (*237*). Use of a tosylamide as the nucleophile in the displacement of an activated aryl-cyclohexenol derivative enabled the preparation of a chiral intermediate which



Scheme 5. Enantioselective synthesis of (−)-galanthamine (**75**).

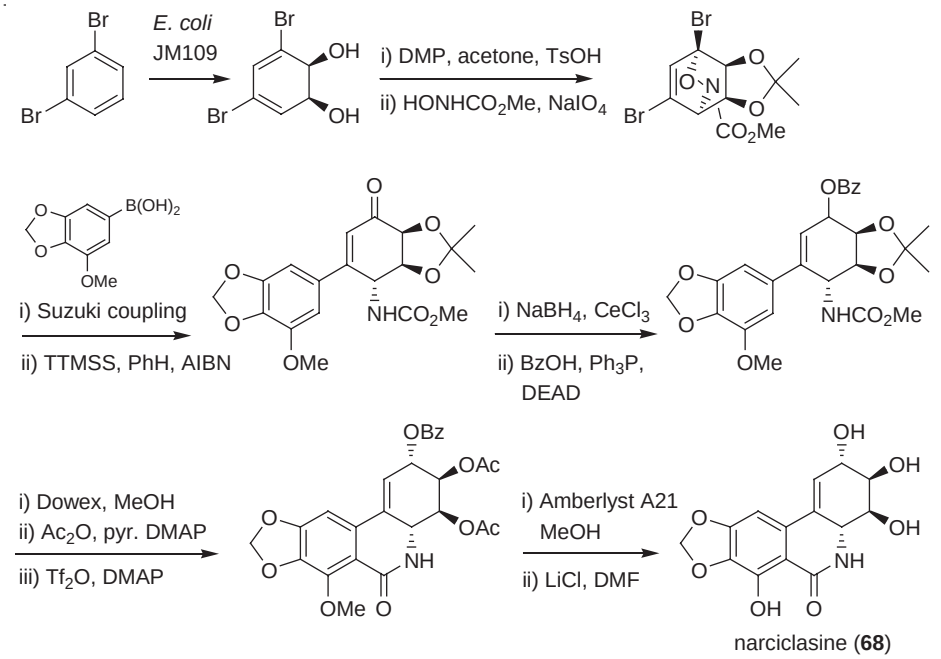
was sequentially converted into (+)-crinamine (**57**), (−)-hemanthidine (**55**), and (+)-pretazettine (**64**) (*238*).

Regioselective C–H activation is often used for intramolecular biaryl preparations in Pd-mediated transformations. Thus concise syntheses of a large collection of alkaloids have been reported using variations of this approach (*239–241*), which differ mainly in terms of the functionalization of the precursor, palladium catalysts, and ligands. An efficient synthesis of racemic γ-lycorane was recently disclosed whereby the key step is the intramolecular α-arylation of a cyclohexanone derivative (*242*). Some heterocyclic synthetic precursors (e.g. substituted indoles, quinolines, quinolones, phenanthridines, and phenanthridinones) have also been prepared *en route* to the alkaloids [hippadine, trisphaeridine (**70**), and crinasiadine] *via* Pd- and Cu-mediated reactions (*243*,*244*).

The use of main group metals has also facilitated alkaloid synthesis, exemplified in the preparation of (−)-brunsvigine by intramolecular anionic cyclization (the addition of an organolithium derivative to an amide) (*245*). Also, a Meyers biaryl coupling has been used as the key step in a total synthesis of buflavine (*246*). The connection of directed *ortho* metalations with cross-coupling reactions is the basis of very elegant syntheses of buflavine, 8-*O*-demethylbuflavine, pratosine, and hippadine (*247*,*248*). Synthesis of (−)-mesembrine has been achieved through a route involving stereoselective ring opening of an aryl-substituted epoxide with a Grignard reagent (*249*).

C. ENZYMATIC DIHYDROXYLATION

The development of enzymatic dihydroxylation of aromatics has enabled synthetic access to a large collection of cyclohexadiene diols in enantiopure form.

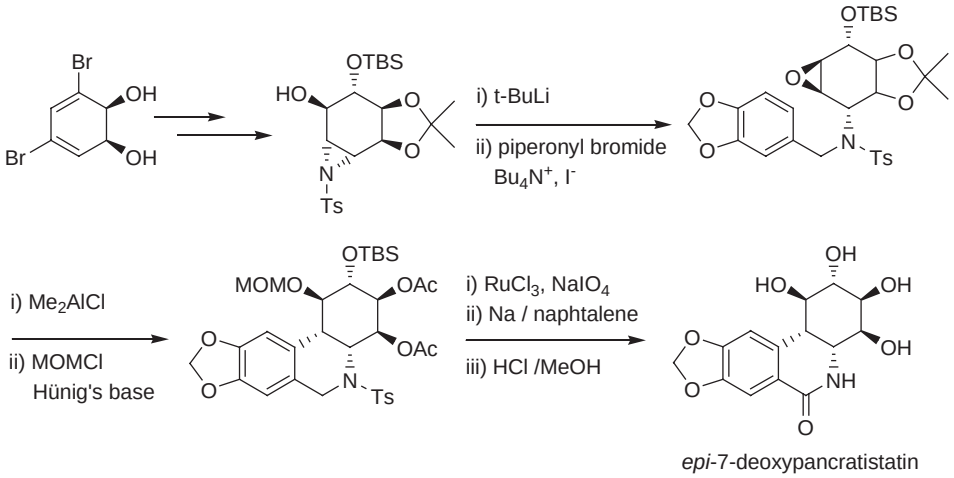


Scheme 6. Synthesis of narciclasine (**68**).

These compounds have become invaluable synthetic materials and are pivotal intermediates in the total syntheses of structurally diverse natural products (*250*). In particular, the group of Hudlicky which developed the methodology has devised short, efficient, and enantioselective total syntheses of alkaloids and related compounds to meet quantity demands for materials used in biological studies. Lycoricidine was prepared in only nine steps from bromobenzene (*251*), and the same starting material was used in straightforward syntheses of pancratistatin and its 7-deoxy derivative (*252*). Recently, the Hudlicky group published the synthesis of narciclasine (**68**), based on the whole-cell fermentation of 1,3-dibromobenzene by a recombinant *Escherichia coli* (Scheme 6). The resulting dienediol was subjected to a hetero-Diels–Alder reaction with a nitroso derivative and the corresponding adduct underwent Suzuki coupling followed by reductive opening of the oxazine N–O bond. Stereoselective reduction of the resulting ketone, exchange of the acetonide moiety with acetate groups, a Bischler–Napieralski-type ring closure and the removal of the ester and phenolic methyl protecting groups led to the desired product (*253*).

The same group also disclosed the synthesis of *epi*-7-deoxypancratistatin *via* an aza-Payne rearrangement (*254*) (Scheme 7). Analogues of narciclasine (**68**), pancrastistatin, and 7-deoxypancratistatin have been synthesized using modifications of the reported procedures as well as new methodologies (e.g. addition of indoles to oxiranes and aziridines derived from cyclohexadiene diols) (*255–258*).

Pancratistatin analogues having a carbohydrate-derived structure in place of the polyhydroxycyclohexane moiety have been prepared for studying the minimum pharmacophore of the parent molecule (*259*).

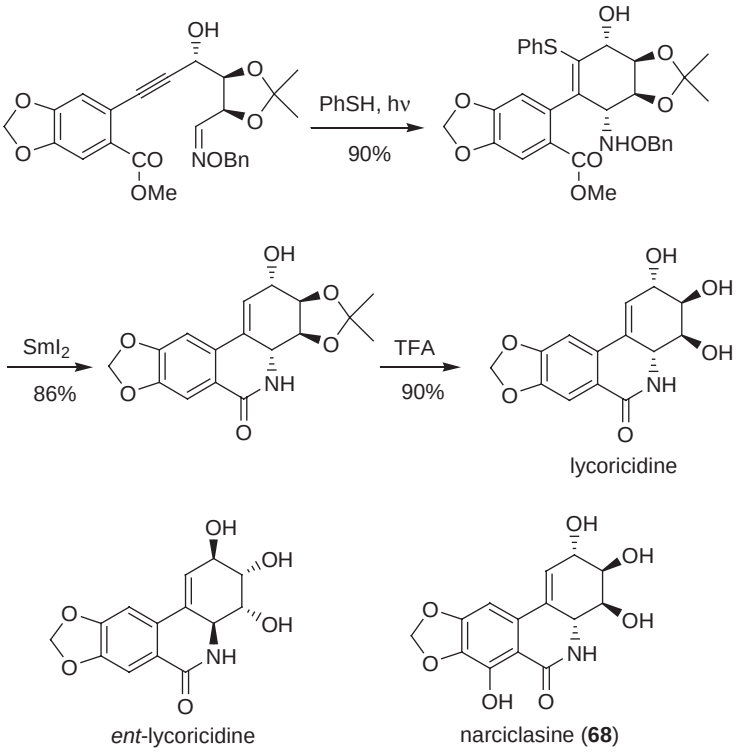


Scheme 7. Synthesis of epi-7-deoxypancratistatin.

D. RADICAL REACTIONS

The well-established radical reactions have been used to drive selective connectivity, often without the need of protecting groups normally required in polar approaches. Also the 'living' nature of some radical additions has triggered elegant and efficient reaction cascades for the formation of multiple C–C bonds.

The group of Magnus has continued to exploit the β-azidonation reaction of silyl enol ethers, which they used in the synthesis of pancratistatin (*260*), and has applied the same type of approach for the synthesis of a lycorane derivative. The pyrrolidine ring was closed *via* a cobalt-promoted intramolecular radical addition-dehydrogenation reaction (*261*). Parsons has reported model studies on the cyclization of diversely substituted 2-amino-cyclohex-2-enone derivatives to yield octahydroindole derivatives related to the Amaryllidaceae alkaloids. In these processes, radical cyclizations were promoted with tributyltin hydride, samarium (II) iodide, or manganese (III) acetate (*262*). Curran has reported a radical cyclization leading to spirocyclohexadienones, which includes the formal synthesis of aza-galanthamine (*263*). Keck reported an impressive radical cascade process as the crucial step in his total synthesis of 7-deoxypancratistatin (*264*). A modified approach led to the synthesis of (+)-lycoricidine, *via* 6-*exo*-cyclizations of substituted alkenyl radicals with oxime ethers (*265*) (Scheme 8). The precursor was prepared from D-gulonolactone, which was protected, selectively transformed, and coupled through a Sonogashira reaction with a substituted iodoarene to yield the key alkyne intermediate. PhSH was added under photochemical activation to generate a vinyl radical, which was then added to the oxime ether moiety to close the six-membered ring with high stereoselectivity. Treatment of the resulting compound with SmI_2 allowed the cleavage of the N–O bond, the removal of the thioether, and the formation of the lactam. The final step was the deprotection of the acetonide group. *Ent*-lycoricidine, and (+)-narciclasine (**68**) have been similarly prepared.



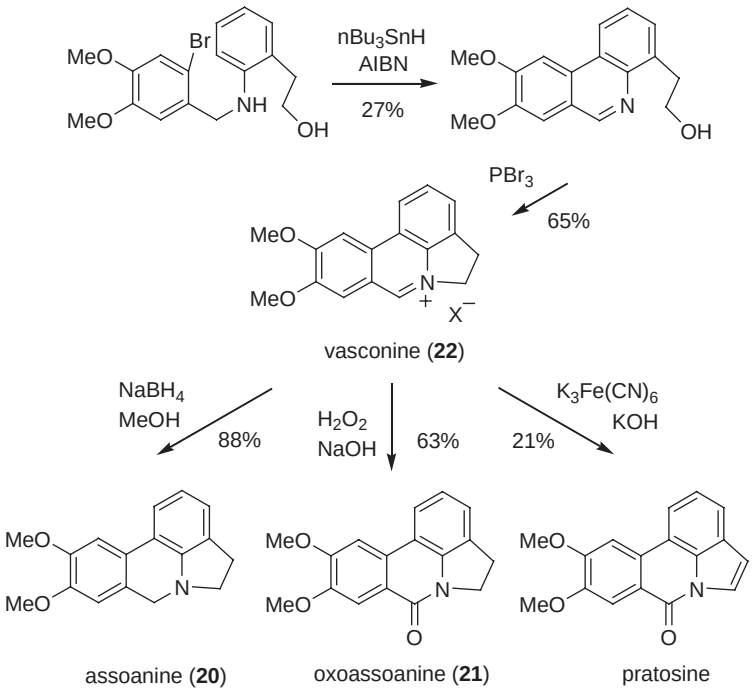
Scheme 8. Radical synthesis of lycoricidine.

The formal synthesis of racemic pancracine (**73**) *via* radical cyclization of a *N*-(2-cyclohexenyl)-α-phenylthioacetamide has been reported (*266*). Racemic montanine (**98**), coccinine, and pancracine (**73**) have been prepared using a phenylthiotetrahydroisoquinoline derivative as the radical precursor (*267*). Recently, Zard has described the construction of the carbon skeleton of kirkine (**19**). In these model studies, thiosemicarbazide proradicals interact with lauroyl peroxide (a tin-free initiator) to trigger a reaction cascade that ultimately yields the desired tetracyclic system of kirkine (**19**) (*268*).

An interesting Csp^2–Csp^2 coupling *via* an aryl radical cyclization has been used as the key step in a unified strategy to synthesize vasconine (**22**), assoanine (**20**), oxoassoanine (**21**), and pratosine. Tin hydride cyclization of an *N*-(*o*-bromobenzyl)-aniline yielded a substituted phenanthridine which was subsequently transformed into vasconine (**22**), from which the remaining natural products were prepared (*269*) (Scheme 9).

E. PERICYCLIC PROCESSES

The aza-Cope–Mannich cyclization protocol, developed by Overman has been strategically applied in the synthesis of racemic and enantiopure pancracine (**73**) (*270*). Later, Kim developed a synthetic approach based on a [3,3]-sigmatropic

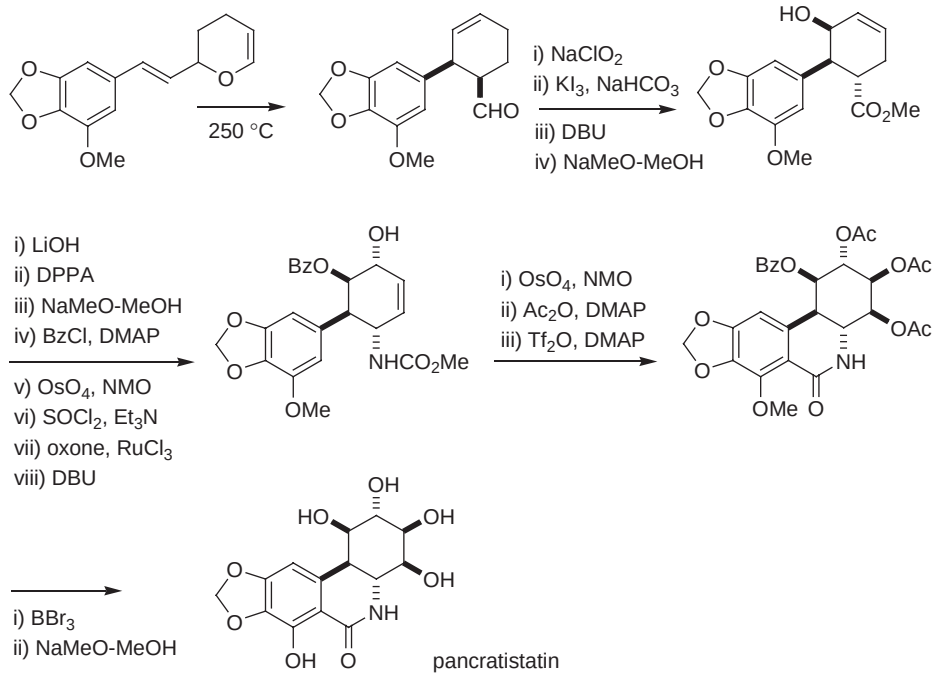


Scheme 9. Radical synthesis of vasconine (**22**), assoanine (**20**), oxoassoanine (**21**), and pratosine.

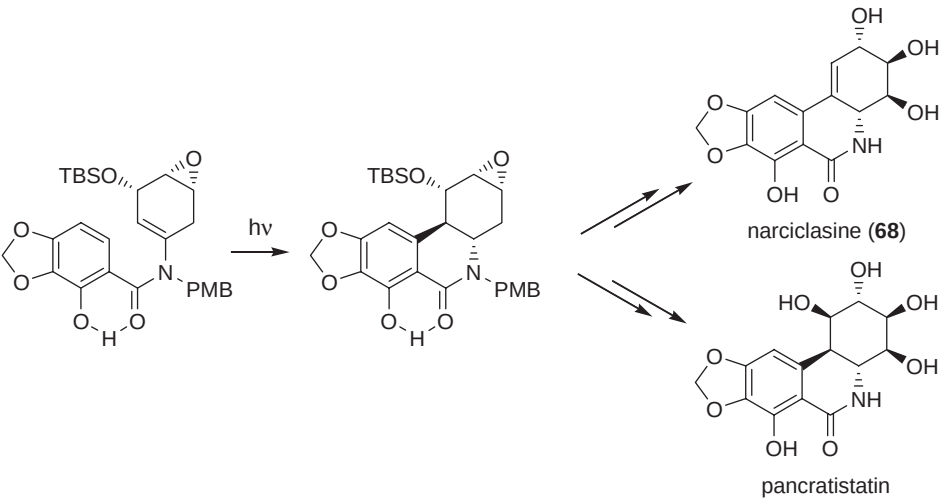
rearrangement as the key step in the stereoselective synthesis of racemic pancratistatin (*271*). Horner–Wasdsworth–Emmons reaction provided a reactive olefin that upon heating afforded the rearranged (aryl)cyclohexenylcarbaldehyde which, in turn, was further oxidized to the corresponding acid and subjected to a halolactonization and elimination protocol to yield the unsaturated lactone. This intermediate was converted into the hydroxyester, and subsequent functional-group transformations allowed the stereocontrolled installation of the remaining stereogenic centers and the final ring closure. The sequence ended with deprotection of the esters and methyl phenolic groups (Scheme 10).

Rigby's studies on the synthesis of alkenylisocyanates fostered the preparation of a suitable substituted aryl enamide, which on photocyclization yielded the polysubstituted pentacyclic system. Key to the success of this process is the hydrogen bond between the phenolic OH and the carbonyl group, which restricts the rotation around the aryl–amide bond and directs the cyclization. Further functionalization allowed the total synthesis of pancratistatin (*272*) and narciclasine (**68**) (*273*) (Scheme 11). The [4 + 1] cycloaddition of bis(alkylthio)carbenes with vinyl isocyanates was the key process in a recent synthesis of (±)-mesembrine (**92**) (*274*).

The Diels–Alder cycloaddition has played an important role in the synthesis of *Narcissus* alkaloids and related structures. Boger has prepared anhydrolycorinone using an intramolecular hetero-Diels–Alder reaction in which a 1,3,4-oxadiazole

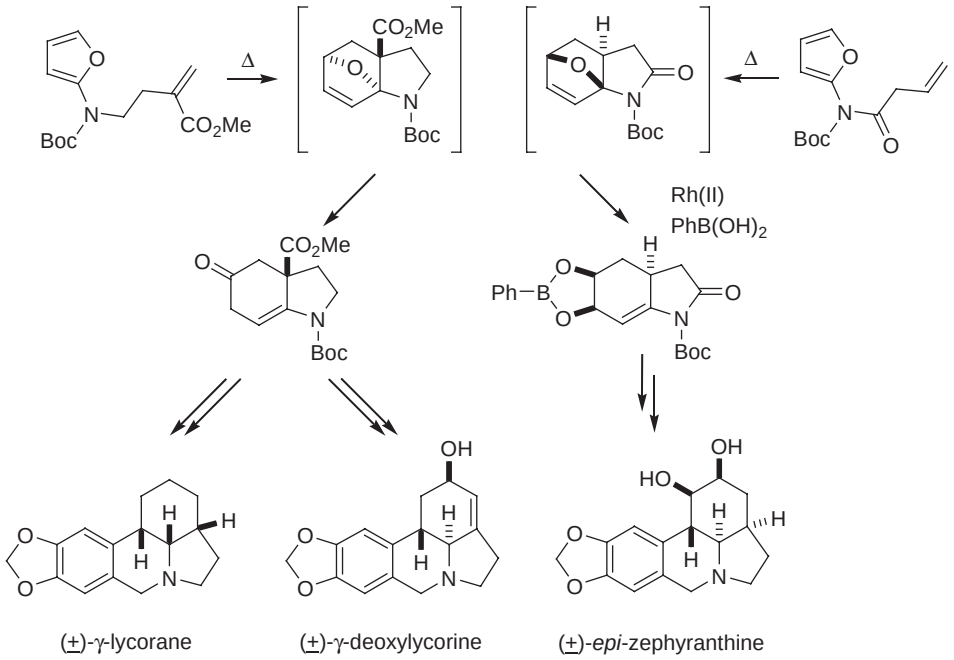


Scheme 10. Synthesis of racemic pancratistatin.



Scheme 11. Synthesis of narciclasine (**68**) and pancratistain.

unit interacted with an electron-rich double bond to yield an intermediate furan adduct that underwent another intramolecular [4 + 2] cycloaddition with a second olefin moiety (*275*). Padwa has reported a conceptually attractive entry to this family of alkaloids based on intramolecular cycloadditions on substituted furanyl



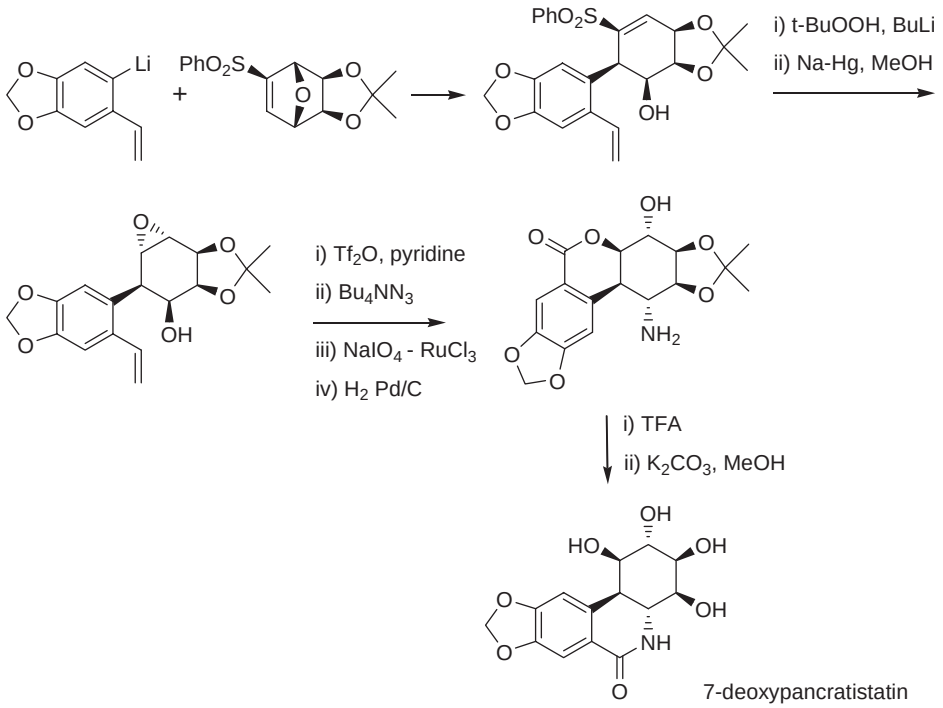
Scheme 12. Synthesis of γ-lycorane, 1-deoxylycorine, and epi-zephyranthine.

carbamates. The resulting adduct can be elaborated into diversely substituted hydroindolinones *via* nitrogen-assisted ring opening (*276*) or Rh(II)-promoted nucleophilic reaction (*277*). The former has provided compounds which on subsequent transformations yielded γ-lycorane and 1-deoxylycorine as racemates, whereas the latter afforded materials for the preparation of *epi*-zephyranthine (Scheme 12).

F. POLAR REACTIONS

Haseltine has described an enantioselective formal synthesis of pancratistatin in which the stereocontrol is driven by the acetonide of conduritol A. The enantioselective hydrolysis (desymmetrization) of this compound was achieved with a lipase, and the aryl–cyclohexane ring bond was formed through an intramolecular cyclization of the activated benzene ring with an allylic triflate (*278*). Plumet reported a total synthesis of (+)-7-deoxypancratistatin based on the conjugate addition of an aryl-lithium species to a bicyclic conjugated sulfone derived from furan, which enabled the efficient installation of the six stereogenic centers of the cyclohexane ring (*279*) (Scheme 13).

The next series of syntheses is based on conjugate additions. A 2-arylcyclohexanone was regio- and stereoselectively added to nitroethylene to access the octahydroindole core present in the alkaloids. This has enabled the total synthesis of (±)-γ-lycorane and (±)-crinane (*280*). Tomioka described a chemoselective conjugate addition – nitro Michael reaction sequence to prepare α- and β-lycoranes in their racemic form (*281*). The addition of an arylcuprate to a D-mannitol-derived

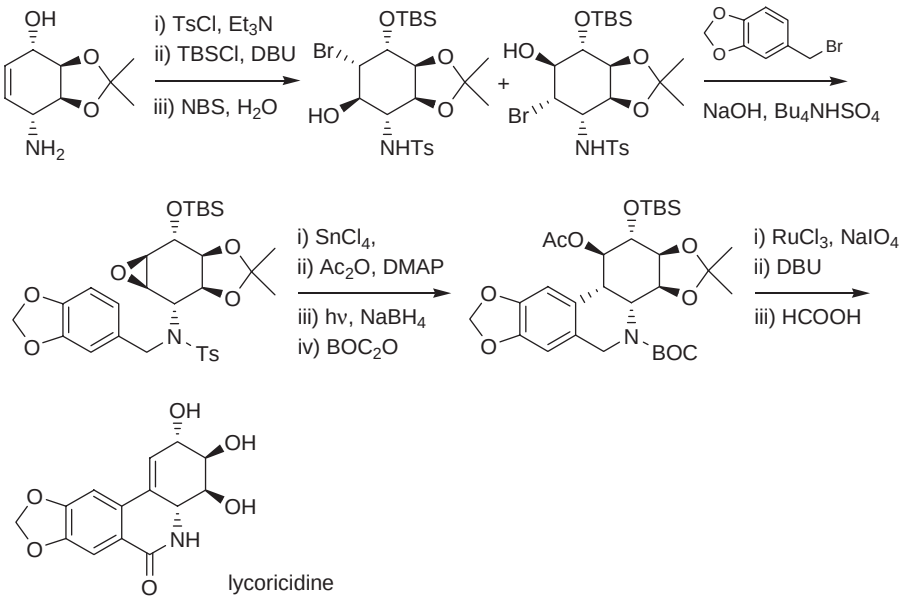


Scheme 13. Synthesis of 7-deoxypancratistatin.

conjugate ester provided access to synthetic precursors of the Amaryllidaceae alkaloids (*282*). Similarly, the addition of arylcuprates to enantiomerically pure conjugate esters derived from D-xylose, allowed, after pertinent FG transformations and ring-closing metathesis, the preparation of novel 1-aryl-1-deoxyconduritols F. These compounds are advanced intermediates *en route* to pancratistatin derivatives (*283*). A 15-step synthesis of racemic mesembrine (**92**) featuring the intramolecular addition of an amine to a cyclohexenone moiety to close the octahydroindolone ring system was recently disclosed (*284*). Taber has described an elegant approach to (−)-mesembrine relying on a conjugate addition and an intramolecular alkylidene C–H insertion (*285*).

Intramolecular additions to *N*-acyliminium ions (generated by Pummerer reaction) were used to prepare highly functionalized tricyclic intermediates for the synthesis of the putative alkaloid jamtine (*286*). Synthesis of cherylline (**88**) in both of its enantiopure forms was achieved using a chiral auxiliary through a sequence involving reductive amination-acid-promoted cyclization (*287*).

Short syntheses of enantiomerically pure narciclasine (**68**) and lycoricidine based on the intramolecular acid-catalyzed arene-epoxide coupling have been described (*288*,*289*). Bromohydroxylation of a protected aminocyclohexenol afforded the corresponding bromohydrin as a mixture of two *trans* stereoisomers, which was subsequently transformed to link an arylmethyl moiety in basic medium with the concomitant formation of the epoxide ring, thereby setting the stage for the



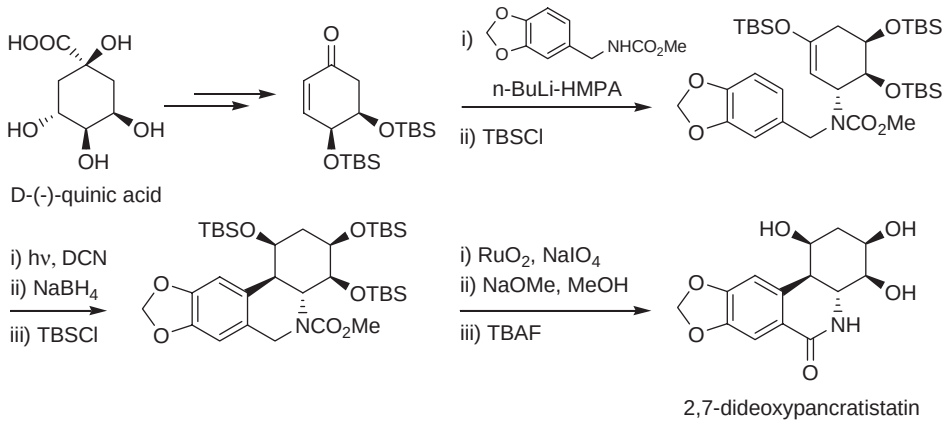
Scheme 14. Total synthesis of lycoricidine.

crucial carbon–carbon bond formation required for cyclization. Subsequent functional group transformations, exchange of protecting groups, oxidation of the benzylic position, and finally deprotection, afforded lycoricidine (Scheme 14). Narciclasine (**68**) has been prepared following a related pathway. The same group has also reported a convenient approach to chiral *O*-isopropylidene-protected 4-aminocyclohexenol (*290*).

G. SEMISYNTHESIS AND CHIRAL POOL APPROACHES

Taking advantage of the availability of narciclasine (**68**) from plant extracts, Pettit used the compound as a starting material in an efficient synthesis of pancratistatin (*77*). The same group has also described related approaches for the preparation of a pancratistatin phosphate prodrug (*291*), as well as for the natural product 7-deoxy-*trans*-dihydronarciclasine and related derivatives (*292*). In another context, an improved protocol for the synthesis of (−)-galanthamine (**75**), based on the spontaneous resolution of either of the enantiomers of narwedine (**83**), has been reported (*293*).

A short route to enantiomerically pure lactone analogues of narciclasine and lycoricidine uses D-gulonolactone as the chiral pool source, as it contains all of the stereogenic centers of the products in their correct configuration. Connectivity with the functionalized aryl moiety arises from the addition of an organolithium reagent to the carbonyl group of the gulonolactone (*294*). The total syntheses of (−)-hemanthidine (**55**), (+)-pretazettine (**64**), and (+)-tazettine (**62**) were successfully achieved



Scheme 15. Synthesis of 2,7-dideoxypancratistatin from D-(−)-quinic acid.

starting from the α-methyl-D-mannopyranoside (*295*). Vittatine (**42**) has been prepared from D-glucose. The sequence involved a Ferrier carbocyclization to yield a cyclohexenone derivative that, after functionalization and a Claisen rearrangement, gave an intermediate with the quaternary carbon atom and the required stereochemistry for the closure of the aryloctahydroindole ring system to provide the desired product (*296*).

D-(−)-Quinic acid has been efficiently used as the synthetic precursor for the incorporation of the aminocyclohexanetriol moiety present in 2,7-dideoxypancratistatin (*297*) (Scheme 15).

V. Spectroscopy and Alkaloid Data

There follows a discussion of proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), and mass spectrometry (MS) of the *Narcissus* alkaloids. A list of the different *Narcissus* alkaloids, their spectroscopic properties, and literature with the most recent spectroscopic data is given in Table X.

A. PROTON NUCLEAR MAGNETIC RESONANCE

^{1}H NMR spectroscopy gives important information about the different types of Amaryllidaceae alkaloids. In the last two decades, the routine use of 2D NMR techniques has facilitated the structural assignments and the establishment of their stereochemistry. A compilation of the different ^{1}H NMR spectra arranged according to the different skeleton types is shown in Tables XI–XVII.

1. Lycorine Type

This group has been subject to several ^{1}H NMR studies and lycorine (**1**), as well as its main derivatives has been completely assigned. The general characteristics of the ^{1}H NMR spectra are

TABLE X.
Narcissus Alkaloid Data.

Alkaloid[a]	MF (MW)[b]	Spectroscopic data	References
1 Lycorine	$C_{16}H_{17}NO_4$ (287)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*298–301*)
2 Poetaminine	$C_{18}H_{19}NO_5$ (329)	UV, IR	(*302*)
3 Pseudolycorine	$C_{16}H_{19}NO_4$ (289)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*113*)
4 1-*O*-acetyl-pseudolycorine	$C_{18}H_{21}NO_5$ (331)	UV, IR, MS, ^{1}H NMR	(*113*)
5 2-*O*-acetyl-pseudolycorine	$C_{18}H_{21}NO_5$ (331)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*113*)
6 9-*O*-methyl-pseudolycorine	$C_{17}H_{21}NO_4$ (303)	UV, IR, MS, ^{1}H NMR	(*159*,*303*)
7 Galanthine	$C_{18}H_{23}NO_4$ (317)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*135*,*304*)
8 Goleptine	$C_{17}H_{21}NO_4$ (303)	IR	(*179*)
9 Jonquilline	$C_{18}H_{17}NO_5$ (327)	UV, IR	(*180*)
10 Caranine	$C_{16}H_{17}NO_3$ (271)	UV, IR, MS, ^{1}H NMR, CD	(*305*,*306*)
11 Pluviine	$C_{17}H_{21}NO_3$ (287)	UV, IR	(*176*,*307*)
12 Norpluviine	$C_{16}H_{19}NO_3$ (273)	UV, IR	(*176*,*308*)
13 9-*O*-demethyl- pluviine	$C_{16}H_{19}NO_3$ (273)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*167*)
14 1-*O*-acetyl-9-*O*-demethylpluviine	$C_{18}H_{21}NO_4$ (315)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*167*)
15 1,9-*O*-diacetyl-9-*O*-demethylpluviine	$C_{20}H_{23}NO_5$ (357)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*167*)
16 Narcissidine	$C_{18}H_{23}NO_5$ (333)	UV, IR, MS, ^{1}H NMR, X-ray	(*309–313*)
17 Ungiminorine	$C_{17}H_{19}NO_5$ (317)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*173*,*314*,*315*)
18 Nartazine	$C_{20}H_{23}NO_6$ (373)	IR	(*89*)
19 Kirkine	$C_{16}H_{19}NO_3$ (273)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*316*)
20 Assoanine	$C_{17}H_{17}NO_2$ (267)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*114*)
21 Oxoassoanine	$C_{17}H_{15}NO_3$ (281)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*114*)
22 Vasconine	$C_{17}H_{16}NO_2$ (266)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*70*,*71*)
23 Tortuosine	$C_{18}H_{18}NO_3$ (296)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*68*,*69*)
24 Ungeremine	$C_{16}H_{11}NO_3$ (265)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*317–320*)
25 Roserine	$C_{18}H_{22}NO_3$ (300)	MS, ^{1}H NMR, ^{13}C NMR	(*67*)
26 Homolycorine	$C_{18}H_{21}NO_4$ (315)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*82*,*300*,*321*,*322*)

27 8-*O*-demethyl-homolycorine	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*111*,*300*,*323*,*324*)
28 8-*O*-demethyl-8-*O*-acetylhomolycorine	$C_{19}H_{21}NO_5$ (343)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*70*)
29 9-*O*-demethyl-homolycorine	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*82*)
30 Masonine	$C_{17}H_{17}NO_4$ (299)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*165*,*321*)
31 Normasonine	$C_{16}H_{15}NO_4$ (285)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*165*)
32 9-*O*-demethyl-2α-hydroxy-homolycorine	$C_{17}H_{19}NO_5$ (317)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*138*)
33 Dubiusine	$C_{23}H_{27}NO_8$ (445)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*72*)
34 Hippeastrine	$C_{17}H_{17}NO_5$ (315)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*71*,*300*,*325*,*326*)
35 Lycorenine	$C_{18}H_{23}NO_4$ (317)	UV, MS, ^{1}H NMR, ^{13}C NMR, X-ray	(*106*,*327–329*)
36 *O*-methyllycorenine	$C_{19}H_{25}NO_4$ (331)	IR, MS, ^{1}H NMR, ^{13}C NMR, X-ray	(*74*,*104*)
37 Oduline	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*165*)
38 6-*O*-methyloduline	$C_{18}H_{21}NO_4$ (315)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*165*)
39 2α-Hydroxy-6-*O*-methyloduline	$C_{18}H_{21}NO_5$ (331)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*71*)
40 8-*O*-demethyl-homolycorine-*N*-oxide	$C_{17}H_{19}NO_5$ (317)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*137*)
41 Poetinatine	$C_{20}H_{23}NO_6$ (373)	IR, MS, ^{1}H NMR	(*98*)
42 Vittatine	$C_{16}H_{17}NO_3$ (271)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*208*,*300*,*330*,*331*)
43 11-Hydroxyvittatine	$C_{16}H_{17}NO_4$ (287)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*208*,*300*)
44 Maritidine	$C_{17}H_{21}NO_3$ (287)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*136*,*332–336*)
45 8-*O*-demethyl-maritidine	$C_{16}H_{19}NO_3$ (273)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*108*,*331*,*337*)
46 9-*O*-demethyl-maritidine	$C_{16}H_{19}NO_3$ (273)	IR, MS, ^{1}H NMR	(*111*)
47 *O*-methylmaritidine	$C_{18}H_{23}NO_3$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*133*,*137*)
48 Papyramine	$C_{18}H_{23}NO_4$ (317)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*135*,*137*)
49 6-Epipapyramine	$C_{18}H_{23}NO_4$ (317)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*135*,*137*)

TABLE X.
Continued.

Alkaloid[a]	MF (MW)[b]	Spectroscopic data	References
50 *O*-methyl-6-epipapyramine	$C_{19}H_{25}NO_4$ (331)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*137*)
51 6α-Hydroxy-3-*O*-methylepimaritidine	$C_{18}H_{23}NO_4$ (317)	UV, IR, MS, ^{1}H NMR, CD	(*133*)
52 6β-Hydroxy-3-*O*-methylepimaritidine	$C_{18}H_{23}NO_4$ (317)	UV, IR, MS, ^{1}H NMR, CD	(*133*)
53 Hemanthamine	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*83*,*331*, *338*,*339*)
54 11-*O*-acetyl- hemanthamine	$C_{19}H_{21}NO_5$ (343)	IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*74*)
55 Hemanthidine	$C_{17}H_{19}NO_5$ (317)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*73*,*300*,*325*, *331*,*340*,*341*)
56 6-Epihemanthidine	$C_{17}H_{19}NO_5$ (317)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*73*,*300*,*325*, *331*,*340*,*341*)
57 Crinamine	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*298*,*342–344*)
58 Narcidine	$C_{17}H_{21}NO_4$ (303)	UV, IR, MS, ^{1}H NMR	(*161*)
59 Cantabricine	$C_{18}H_{23}NO_4$ (317)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*140*)
60 Narcimarkine	$C_{21}H_{29}NO_5$ (375)	IR, MS	(*91*)
61 Bujeine	$C_{20}H_{23}NO_6$ (373)	IR, MS, ^{1}H NMR, ^{13}C NMR, CD	(*74*)
62 Tazettine	$C_{18}H_{21}NO_5$ (331)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*300*,*345–351*)
63 Criwelline	$C_{18}H_{21}NO_5$ (331)	UV, MS, ^{1}H NMR, ^{13}C NMR, CD	(*352–355*)
64 Pretazettine	$C_{18}H_{21}NO_5$ (331)	UV, IR, MS, ^{1}H NMR, CD	(*300*,*347*)
65 3-Epimacronine	$C_{18}H_{19}NO_5$ (329)	IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*79*,*300*,*337*,*356*)
66 3-Epimacronine isomer	$C_{18}H_{19}NO_5$ (329)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*139*)
67 Obesine	$C_{16}H_{17}NO_4$ (287)	MS, ^{1}H NMR, ^{13}C NMR	(*76*)
68 Narciclasine	$C_{14}H_{13}NO_7$ (307)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, X-ray	(*120*,*122*,*125*)
69 Narciprimine	$C_{14}H_9NO_5$ (271)	UV, IR, MS, ^{1}H NMR	(*125*,*357*)
70 Trisphaeridine	$C_{14}H_9NO_2$ (223)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*99*,*358*)

71 Bicolorine	$C_{15}H_{12}NO_2$ (238)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*79*)
72 Ismine	$C_{15}H_{15}NO_3$ (257)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, X-ray	(*99*,*358–360*)
73 Pancracine	$C_{16}H_{17}NO_4$ (287)	UV, MS, ^{1}H NMR, ^{13}C NMR, CD	(*80*,*361*)
74 Nangustine	$C_{16}H_{17}NO_4$ (287)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*80*)
75 Galanthamine	$C_{17}H_{21}NO_3$ (287)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*83*,*354*,*362*,*363*)
76 Epigalanthamine	$C_{17}H_{21}NO_3$ (287)	UV, IR, MS, ^{1}H NMR, CD	(*354*,*364*,*365*)
77 *O*-acetyl-galanthamine	$C_{19}H_{23}NO_4$ (329)	UV, MS, ^{1}H NMR, ^{13}C NMR	(*167*)
78 Norgalanthamine	$C_{16}H_{19}NO_3$ (273)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR, CD, X-ray	(*141*,*366–368*)
79 Epinorgalanthamine	$C_{16}H_{19}NO_3$ (273)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*107*)
80 *N*-formyl-norgalanthamine	$C_{17}H_{19}NO_4$ (301)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*83*)
81 Sanguinine	$C_{16}H_{19}NO_3$ (273)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*369*)
82 Narcisine	$C_{18}H_{21}NO_4$ (315)	UV, IR, MS, ^{1}H NMR, ^{13}C NMR	(*117*)
83 Narwedine	$C_{17}H_{19}NO_3$ (285)	UV, IR, MS, ^{1}H NMR	(*364*,*367*)
84 Lycoramine	$C_{17}H_{23}NO_3$ (289)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*336*,*367*,*369*)
85 Norlycoramine	$C_{16}H_{21}NO_3$ (275)	IR, MS, ^{1}H NMR	(*337*)
86 Epinorlycoramine	$C_{16}H_{21}NO_3$ (275)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*107*)
87 *O*-methyl-norbelladine	$C_{16}H_{19}NO_3$ (273)	^{1}H NMR, ^{13}C NMR	(*181*)
88 Cherylline	$C_{17}H_{19}NO_3$ (285)	IR, MS, ^{1}H NMR, ^{13}C NMR, X-ray	(*370*)
89 Pallidiflorine	$C_{34}H_{40}N_2O_7$ (588)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*86*)
90 Mesembrenone	$C_{17}H_{21}NO_3$ (287)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*26*,*371*)
91 Mesembrenol	$C_{17}H_{23}NO_3$ (289)	UV, IR, MS, ^{1}H NMR, CD	(*372*)
92 Mesembrine	$C_{17}H_{23}NO_3$ (289)	IR, MS, ^{1}H NMR, ^{13}C NMR	(*284*,*285*,*373*)

[a] Alkaloids are listed in numerical order and grouped according to their ring system (see Tables I–VII).
[b] MF (MW) = Molecular formula (Molecular weight).

TABLE XI.
^{1}H NMR Data of Lycorine-Type Alkaloids.

Alkaloid	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**13**	**14**	**15**	**19**
H-1	4.27 br s	4.85 br s	5.58 m	4.43 t	4.53 dd	4.55 s	4.70 m	4.26 dd	5.54 dd	5.51 m	4.37 q
H-2α	3.97 br s	4.50 t	4.15 dd	5.29 dd	4.18 m	3.72 m	2.59 m	2.3–2.6 m	2.3–2.5 m	2.36 m	2.46 ddd
H-2β	—	—	—	—	—	—	2.59 m	2.3–2.4 m	2.3–2.5 m	2.36 m	2.34 dddd
H-3	5.37 br s	5.60 t	5.69 dd	5.45 t	5.55 m	5.55 br s	5.41 m	5.54 br d	5.39 br s	5.32 br t	5.87 br dt
H-4a	2.60 d	3.02 br d	2.90 br s	2.85 d	2.87 dd	2.65 s	2.78 dd	2.70 br d	2.3–2.5 m	2.2–2.3 m	4.24 br d
H-6α	3.32 d	3.68 br d	3.61 dd	3.54 d	3.55 dd	3.40 br d	3.52 dd	3.31 d	3.54 br d	3.5–3.6 br s	4.40 d
H-6β	4.02 d	4.16 d	4.17 d	4.14 d	4.16 d	4.05 d	4.13 d	3.93 d	3.59 br d	3.5–3.6 br s	4.61 dt
H-7	6.68 s	6.71 s	6.70 s	6.61 s	6.75 s	6.52 s	6.58 s	6.59 s	6.64 s	6.71 s	6.60 s
H-10	6.81 s	6.89 s	6.74 s	6.83 s	6.96 s	6.78 s	6.82 s	6.82 s	7.08 s	7.14 br s	7.08 s
H-10b	2.50 m	2.74 br d	2.90 br s	2.69 d	2.76 ddd	2.65 s	2.41 ddd	2.98 dd	3.33 dd	3.27 dd	3.52 dd
H-11 (2H)	2.44 m	2.6–2.7 m	2.66 t	2.63 m	2.64 m	2.4–2.6 m	2.59 m	2.5–2.6 m	2.3–2.5 m	2.2–2.4 m	2.8–2.9 m
H-12α	2.19 ddd	2.6–2.7 m	2.59 br t	2.42 dt	2.42 br q	2.25 dd	2.33 br q	2.3–2.4 m	2.79 m	2.6–2.8 m	3.71 ddd
H-12β	3.19 dd	3.37 dd	3.33 m	3.35 dt	3.35 ddd	3.25 ddd	3.32 ddd	3.32 m	2.79 m	2.6–2.8 m	3.83 ddd
OCH_2O	5.95 s	—	—	—	—	—	5.91 (2d)	—	—	—	—
OMe	—	3.84 s	3.84 s	3.82 s	3.85 s	3.78 s	—	3.89 s	3.86 s	3.74 s	3.87 s
OMe	—	—	—	—	3.80 s	3.74 s	—	—	—	—	—
OMe	—	—	—	—	—	3.40 s	—	—	—	—	—
OAc	—	—	1.92 s	2.06 s	—	—	—	—	1.98 s	2.23 s	—
OAc	—	—	—	—	—	—	—	—	—	1.92 s	—
Solvent	a	b	b	b	c	d	d	d	d	d	c
MHz	300	200	200	200	270	200	270	400	400	400	500
Reference	(*298*)	(*113*)	(*113*)	(*113*)	(*303*)	(*135*)	(*305*)	(*167*)	(*167*)	(*167*)	(*316*)

Solvent a: DMSO-d_6, b: CDC_{13}-CDC_3OD, c: CD_3OD, d: $CDCl_3$

TABLE XI.
Continued.

Alkaloid	**20**	**21**	**22**	**23**	**24**
H-1	7.31 dd	7.85 br d	8.32 d	8.13 d	7.54 s
H-2	6.75 t	7.27 t	7.84 t	—	—
H-3	6.99 dt	7.33 br d	7.70 d	7.59 br s	7.34 s
H-6	4.09 s	—	10.42 s	9.55 s	9.19 s
H-7	6.64 s	7.57 s	8.09 s	7.92 s	7.59 s
H-10	7.17 s	7.81 s	7.86 s	8.34 s	7.88 s
H-11 (2H)	3.00 br t	3.45 br t	3.76 t	3.88 t	3.70 t
H-12 (2H)	3.32 t	4.45 br t	5.42 t	5.35 t	5.12 t
OMe	3.93 s	4.09 s	4.19 s	4.33 s	—
OMe	3.87 s	4.03 s	4.08 s	4.20 s	—
OMe	—	—	—	4.17 s	—
OCH_2O	—	—	—	—	6.32 s
Solvent	d	b	b	c	e
MHz	200	200	500	500	600
Reference	(*114*)	(*114*)	(*71*)	(*68*)	(*320*)

Solvent a: DMSO-d_6, b: CDC_{13}-CDC_3OD, c: CD_3OD, d: $CDCl_3$, e: $D_2O + 0.01\%$ TFA-d_1

TABLE XI.
Continued.

Alkaloid	**16**	**17**	**25**
H-1α	—	—	2.85 ddd
H-1β	4.66 m	4.69 br s	3.13 dd
H-2α	3.4–4.2 m	3.69 m	1.8–1.95 m
H-2β	—	—	2.25–2.4 m
H-3α	—	—	1.38 qd
H-3β	4.66 m	4.60 br s	2.25–2.4 m
H-4	—	—	3.4–3.5 m
H-4a	3.4–4.2 m	4.09 m	—
H-6α	3.54 d	3.69 m	9.50 s (1H)
H-6β	4.09 d	4.15 br d	
H-7	6.68 s	6.78 s	6.95 s
H-10	6.88 s	6.93 s	—
H-10b	2.70 d	2.84 br d	—
H-11α	5.56 br s (1H)	5.75 br d (1H)	2.05 ddd
H-11β			2.70 dt
H-12α	3.4–4.2 m (2H)	3.69 m	4.75–4.95 m (2H)
H-12β		4.15 br d	
OMe	3.86 s	—	4.15 s
OMe	3.82 s	—	4.05 s
OMe	3.44 s	3.44 s	3.90 s
OCH_2O	—	5.92 br s	—
Solvent	d	c	d
MHz	400	600	250
Reference	(*313*)	(*173*)	(*67*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$, e: D_2O + 0.01% TFA-d_1.

TABLE XII.
^{1}H NMR Data of Homolycorine-Type Compounds: Lactone Alkaloids.

Alkaloid	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**40**
H-1	4.81 ddd	4.78 m	4.86 br d	4.80 ddd	4.75 m	4.85 s	4.59 br d	4.63 dd	4.58 br s	4.83 m
H-2 (2H)	2.49 m	2.59 m	2.5–2.7 m	2.51 m	2.60 m	2.62 m	4.28 br t (Hβ)	5.46 dd (Hβ)	4.38 br s (Hβ)	2.64 m
H-3	5.50 m	5.50 d	5.63 br d	5.55 m	5.50 br d	5.64 m	5.68 br s	5.62 m	5.63 br s	5.76 br d
H-4a	2.72 dd	2.73 dd	2.96 br d	2.71 br d	2.74 m	5.50 br d	2.66 br d	2.74 br d	2.62 d	3.87 br d
H-7	7.57 s	7.60 s	7.47 s	7.54 s	7.49 s	7.52 s	7.47 s	7.52 s	7.45 s	7.44 s
H-10	6.99 s	6.98 s	7.13 s	6.91 s	6.96 s	7.11 s	6.95 s	6.97 s	6.92 s	7.24 s
H-10b	2.64 dd	2.63 dd	2.86 dd	2.60 dd	2.74 m	2.66 d	2.83 dd	2.79 br d	2.85 dd	3.50 dd
H-11 (2H)	2.6–2.7 m	2.50 m	2.5–2.7 m	2.5–2.6 m	2.50 m	2.52 m	2.5–2.6 m	2.5–2.7 m	2.48 m	3.57 m
H-12α	3.14 ddd	3.14 ddd	3.31 ddd	3.15 ddd	3.18 ddd	3.15 ddd	3.17 ddd	3.19 ddd	3.13 ddd	2.88 m
H-12β	2.24 ddd	2.25 dd	2.45 dd	2.30 ddd	2.27 dd	2.89 dd	2.31 dd	2.37 dd	2.23 ddd	2.72 m
OCH_2O	—	—	—	—	6.07 (2d)	6.05 d	—	—	6.04 (2d)	—
OMe	3.96 s	3.95 s	3.97 s	3.94 s	—	—	3.95 s	3.94 s	—	3.96 s
OMe	3.95 s	—	—	—	—	—	—	—	—	—
NMe	2.00 s	2.00 s	2.16 s	2.01 s	2.06 s	—	2.08 s	2.06 s	2.03 s	2.94 s
OAc	—	—	2.00 s	—	—	—	—	2.00 s	—	—
CH_A	—	—	—	—	—	—	—	2.53 dd	—	—
CH_B	—	—	—	—	—	—	—	2.65 dd	—	—
CHOH	—	—	—	—	—	—	—	5.24 m	—	—
Me	—	—	—	—	—	—	—	1.29 d	—	—
Solvent	d	d	b	b	d	d	b	b	d	b
MHz	200	400	250	200	400	400	200	400	500	200
Reference	(*82*)	(*324*)	(*70*)	(*82*)	(*165*)	(*165*)	(*138*)	(*72*)	(*71*)	(*137*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$

TABLE XII.
Continued.

Alkaloid	35	36	37	38	39
H-1α	4.35 br d	4.29 br d	4.35 d	4.17 d	4.15 br s
H-2α	2.35 m	2.35 m	2.31 dm	2.26 dd	—
H-2β	2.65 m	2.65 m	2.62 dm	2.53 dm	4.21 br s
H-3	5.50 br s	5.50 br d	5.46 br d	5.39 br s	5.69 br s
H-4a	2.78 br d	2.77 dd	2.72 br d	2.69 br d	2.87 d
H-6β	5.93 s	5.54 s	5.99 s	5.39 br s	5.43 s
H-7	6.93 s	6.80 s	6.85 s	6.67 s	6.73 s
H-10	6.99 s	6.93 s	6.90 s	6.77 s	6.94 s
H-10b	2.44 dd	2.44 dd	2.4–2.5 m	2.35 dd	2.85 d
H-11 (2H)	2.4–2.6 m	2.4–2.6 m	2.4–2.5 m	2.3–2.4 m	2.54 m
H-12α	3.15 ddd	3.15 ddd	3.14 ddd	3.08 dd	3.33 m
H-12β	2.27 dd	2.23 dd	2.25 dd	2.17 dd	2.38 dt
OCH_2O	—	—	5.97 d	5.83 d	5.91 (2d)
OMe	3.88 s	3.89 s	—	3.43 s	3.51 s
OMe	3.87 s	3.88 s	—	—	—
OMe	—	3.55 s	—	—	—
NMe	2.08 s	2.10 s	2.11 s	2.05 s	2.22 s
Solvent	c	d	d	d	d
MHz	250	200	400	400	500
Reference	(*106*)	(*104*)	(*165*)	(*165*)	(*71*)

Solvent a: DMSO-d_6; b: $CDCl_3$-CD_3OD; c: CD_3OD; d: $CDCl_3$.

TABLE XIII.
^{1}H NMR Data of Hemanthamine-Type Alkaloids.

Alkaloid	42	43	44	45	46	47	48/49	53	54	55/56	57	58
H-1	6.44 d	6.41 d	6.71 d	6.65 d	6.58 d	6.49 d	6.65 d/6.66 d	6.36 d	6.40 d	6.33 d	6.22 br s	6.48 d
H-2	6.06 dd	6.19 dd	5.93 dd	5.99 dd	5.91 ddd	6.08 dd	6.00 dd	6.25 dd	6.21 dd	6.27 dd	6.22 br s	6.35 dd
H-3	4.46 m	4.28 ddd	4.27 ddd	4.36 m	4.31 td	3.85 m	3.88 m/3.85 m	3.82 m	3.91 m	3.85 m	3.98 m	3.86 m
H-4α	1.85 ddd	2.28 ddd	1.81 ddd	1.75 ddd	1.73 td	1.73 ddd	1.77 ddd/1.60 ddd	2.11 ddd	2.07 ddd	2.36 ddd/2.21 ddd	2.08 m	2.11 ddd
H-4β	2.58 ddd	1.85 ddd	1.95 m	2.03 ddd	1.90 dddd	2.95 ddd	2.21 br d/2.09 m	1.96 ddd	1.98 ddd	2.12 ddd/2.00 ddd	2.08 m	2.04 ddd
H-4a	3.87 m	3.47 dd	3.48 dd	3.37 m	3.43 dd	3.90 dd	3.59 dd/3.90 m	3.25 dd	3.41 m	3.56 dd/3.20 m	3.22 dd	3.38 m
H-6α	4.07 d	3.84 d	3.84 d	3.79 d	3.81 d	4.25 d	—/5.16 s	3.72 d	3.77 d	—/5.02 s	3.66 d	3.70 d
H-6β	4.71 d	4.35 d	4.39 d	4.39 d	4.41 d	4.80 d	5.86 s/—	4.25 d	4.40 d	5.69 s/—	4.28 d	4.31 d
H-7	6.53 s	6.56 s	6.66 s	6.56 s	6.53 s	6.57 s	7.03 s/6.89 s	6.41 s	6.52 s	6.94 s/6.79 s	6.47 s	6.53 s
H-10	6.87 s	6.94 s	6.97 s	6.82 s	6.87 s	6.81 s	6.80 s/6.83 s	6.74 s	6.95 s	6.70 s/6.73 s	6.79 s	6.78 s
H-11 *endo*	2.15 m	3.98 dd	1.95 m	1.95 m	1.8–2.0 m	2.22 ddd	2.00 m	3.96 dd	5.05 dd	3.92 m	3.92 m	3.99 ddd
H-11 *exo*	2.32 m	—	2.17 m	2.15 m	2.19 ddd	2.37 ddd	2.00 m	—	—	—	—	—
H-12 *endo*	3.17 m	3.20 dd	2.93 ddd	2.95 m	2.91 ddd	3.27 ddd	3.02 ddd/2.84 ddd	3.30 dd	3.41 m	4.20 dd/3.30 m	3.40 m	3.39 m
H-12 *exo*	3.87 m	3.50 dd	3.34 m	3.37 m	3.31 ddd	4.08 ddd	3.73 ddd/3.39 m	3.19 dd	3.41 m	2.96 dd/3.20 m	3.40 m	3.26 dd
OCH_2O	5.95 s	5.89 s	—	—	—	—	—	5.81 (2d)	5.95 s	5.83 (2d)/5.86 (2d)	5.86 s	—
OMe	—	—	3.81 s	3.89 s	3.82 s	3.86 s	3.88 s	—	—	—	—	3.86 s
OMe	—	—	3.77 s	—	—	3.82 s	3.88 s	—	—	—	—	—
OMe	—	—	—	—	—	3.34 s	3.37 s/3.31 s	3.36 s	3.41 s	3.32 s/3.28 s	3.40 s	3.35 s
OAc	—	—	—	—	—	—	—	—	2.03 s	—	—	—
Solvent	d	c	c	d	d	d	d	d	d	d	d	d
MHz	360	270	300	360	200	200	200	360	500	360	300	360
Reference	(*331*)	(*376*)	(*336*)	(*331*)	(*111*)	(*137*)	(*135*)	(*331*)	(*74*)	(*331*)	(*298*)	(*161*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$

TABLE XIII.
Continued.

Alkaloid	**59**	**61**
H-1ax	1.77 ddd	6.38 d (1H)
H-1eq	2.39 dt	
H-2ax	1.61 dddd	6.08 dd (1H)
H-2eq	2.06 m	
H-3	4.67 tt (β)	3.89 ddd (α)
H-4ax	1.44 ddd	2.43 ddd
H-4eq	2.23 m	2.06 ddd
H-4a	3.18 dd	3.29 dd
H-6α	3.91 d	4.04 d
H-6β	4.50 d	4.45 d
H-7	6.48 s	6.57 s
H-10	6.74 s	6.81 s
H-11 *exo*	2.30 ddd	3.93 dd
H-11 *endo*	1.83 ddd	—
H-12 *exo*	3.60 m	4.82 d
H-12 *endo*	2.94 m	4.51 d
OMe	3.82 s	3.36 s
OCH_2O	—	5.91 s
CH_A	—	4.27 dd
CH_B	—	3.58 dd
OAc	2.02 s	2.00 s
Solvent	d	d
MHz	500	500
Reference	(*140*)	(*74*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XIV.
^{1}H NMR Data of Tazettine-Type Alkaloids.

Alkaloid	**62**	**63**	**65**	**67**
H-1	5.60 ddd	5.78 d	5.44 ddd	5.86 d
H-2	6.15 ddd	6.20 dd	5.97 d	6.13 d
H-3	4.13 m	3.89 ddd	4.12 m	4.3–4.4 m
H-4α	2.20 m	1.93 ddd	1.70 m	2.39 br d
H-4β	1.60 m	2.09 ddd	2.55 m	1.68 ddd
H-4a	2.83 m	2.95 t	3.10 m	3.15 br s
H-6	4.65 d	4.68 d	—	4.02 d
H-6′	4.95 dd	4.94 d	—	4.38 d
H-7	6.50 br s	6.55 s	7.52 s	6.66 s
H-10	6.85 s	6.52 s	6.73 s	6.70 s
H-10b	—	—	—	2.81 br d
H-11	—	—	4.43 dd	—
H-12	2.65 d	2.83 d	2.76 dd	3.01 d
H-12′	3.30 d	3.30 d	3.16 dd	3.10 d
OCH_2O	5.90 s	5.92 s	6.01 s	5.99 s
OMe	3.45 s	3.45 s	3.40 s	—
NMe	2.40 s	2.38 s	2.50 s	—
Solvent	d	d	d	c
MHz	90	300	100	250
Reference	(*347*)	(*355*)	(*337*)	(*76*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XV.
^{1}H NMR Data of Narciclasine-Type Alkaloids.

Alkaloid	**68**	**70**	**71**	**72**
H-1	6.17 ddd	8.36 dddd	8.73 dd	6.98 dd
H-2	4.23 ddd	7.61 ddd	8.02 td	6.81 ddd
H-3	3.92 ddd	7.67 ddd	8.09 td	7.28 ddd
H-4	3.90 dd	8.11 ddd	8.31 dd	6.73 dd
H-4a	4.35 ddd	—	—	—
H-6	—	9.06 s	10.42 s	4.26 d
H-6′	—	—	—	4.20 d
H-7	—	7.32 s	7.97 s	7.00 s
H-10	6.75 s	7.89 s	8.16 s	6.67 s
OCH_2O	6.01 (2d)	6.15 s	6.41 s	5.99 s
NMe	—	—	4.73 s	2.73 s
Solvent	c	d	b	d
MHz	500	200	200	200
Reference	(*122*)	(*358*)	(*79*)	(*358*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XVI.
^{1}H NMR Data of Montanine-Type Alkaloids.

Alkaloid	**73**	**74**
H-1	5.37 br dddd	5.52 dt
H-2α	—	2.05 ddt
H-2β	3.73 dddd	2.57 dddd
H-3	3.65 ddddd (β)	3.62 ddd (α)
H-4α	1.36 ddd	3.31 t
H-4β	1.83 ddd	—
H-4a	3.20 ddd	3.16 br d
H-6α	4.16 br d	4.32 d
H-6β	3.63 br d	3.83 d
H-7	6.60 br s	6.51 s
H-10	6.67 br s	6.56 s
H-11	3.25 br s	3.33 br d
H-12ax	2.86 br s	3.03 d
H-12eq	2.86 br s	2.94 dd
OCH_2O	5.90 (2d)	5.86 (2d)
Solvent	a	c
MHz	400	500
Reference	(*361*)	(*80*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

a. Two singlets for the *para*-oriented aromatic protons, together with a unique olefinic proton.
b. Two doublets as an AB system corresponding to the benzylic protons of C-6. The deshielding observed in the β-protons of positions 6 and 12 in relation to their α-homologues is due to the effect of the *cis*-lone pair of the nitrogen atom.
c. Like almost all other lycorine-type examples, the alkaloids isolated from the *Narcissus* genus show a *trans* B/C ring junction, the coupling constant being $J_{4a,10b}$ ~11 Hz. Only kirkine (**19**) shows a *cis* B/C ring junction, with a smaller coupling constant $J_{4a,10b}$ 8 Hz.

In the plant, the alkaloid lycorine (**1**) is particularly vulnerable to oxidation processes, giving several ring-C aromatized products.

2. Homolycorine Type

This group includes lactone, hemiacetal, or the more unusual cyclic ether alkaloids. The general traits for this type of alkaloids can be summarized as follows:

a. Two singlets for the *para*-oriented aromatic protons. In lactone alkaloids, the deshielding of H-7 is caused by the *peri*-carbonyl group.
b. The hemiacetal alkaloids always show the substituent at C-6 in an α-disposition.
c. The majority of alkaloids belong to a single enantiomeric series containing a *cis* B/C ring junction, which is congruent with the small size of the coupling constant $J_{1,10b}$. In the *Narcissus* genus, no exception to this rule has been observed.

TABLE XVII.
^{1}H NMR Data of Galanthamine-Type Alkaloids.

Alkaloid	**75**	**76**	**77**	**78**	**79**	**80**	**81**	**83**	**84**	**86**
H-1	4.73 m	4.58 m	4.58 m	4.67 m	4.62 br s	4.50 m	4.52 br s	4.72 m	4.28 m	4.37 t
H-2α	2.12 ddd	1.69 ddd	2.10 ddd	2.24 ddd	2.04 ddd	1.95 ddd	2.10 ddd	2.73 dd	1.4–1.9 m	1.88 m
H-2β	2.80 ddt	2.77 dddd	2.69 ddd	2.60 m	2.68 dd	2.61 ddt	2.49 dm	3.14 m	2.40 br d	2.50 ddd
H-3	4.25 m	4.61 dddd	5.34 dd	4.28 m	4.15 m	4.07 m	4.15 br t	—	3.98 m	4.09 m
H-4	6.10 ddd	6.05 dt	5.92 d	6.06 ddd	5.98 d	6.00 ddd	5.91 dd	6.02 d	1.4–1.9 m (2H)	1.5–1.7 m (2H)
H-4a	6.21 dd	5.79 dt	6.28 d	6.23 dt	6.05 d	5.88 dd	6.11 d	6.92 d	1.4–1.9 m (2H)	1.7–1.9 m (2H)
H-6	3.79 dd	3.61 d	3.77 d	4.21 d	3.93 d	3.94 dd	3.64 d	3.76 d	3.54 d	3.98 s
H-6′	4.21 d	4.06 d	4.22 d	4.44 d	4.04 d	4.80 d E 5.10 d Z	4.06 d	4.12 d	3.92 d	3.98 s
H-7	6.74 d	6.55 d	6.61 d	6.84 d	6.62 d	6.60 d	6.57 d	6.64 d	6.51 d	6.65 d
H-8	6.78 d	6.61 d	6.68 d	6.90 d	6.68 d	6.76 d	6.52 d	6.68 d	6.57 d	6.62 d
H-11α	2.20 ddd	2.16 dt	2.18 dd	2.08 m	1.88 dt	1.71 ddd	1.65 dm	2.26 dt	1.4–1.9 m	1.7–1.9 m
H-11β	1.69 ddd	1.63 ddd	1.65 dd	2.08 m	1.80 td	1.81 ddd	2.05 m	1.87 d	1.4–1.9 m	1.7–1.9 m
H-12α	3.16 dt	3.04 br d	3.14 br d	2.42 m	3.22 m	3.82 ddd E 3.15 ddd Z	3.01 dm	3.14 m	2.96 t	3.19 dt
H-12β	3.39 ddd	3.25 dt	3.40 br t	3.57 m	3.38 dt	3.61 ddd	3.22 br t	3.27 t	3.12 t	3.43 m
OMe	3.95 s	3.82 s	3.85 s	3.91 s	3.84 s	3.84 s	—	3.82 s	3.76 s	3.85 s
NMe	2.52 s	2.56 s	2.45 s	—	—	—	2.38 s	2.45 s	2.29 s	—
NCHO	—	— —	— —	— —	—	8.02 s 8.07 s	— —	— —	— —	— —
OAc	—	—	2.04 s	—	—	—		—	—	—
Solvent	d	d	d	c	d	d	c	d	d	d
MHz	200	400	400	200	200	200	250	400	400	200
Reference	(*83*)	(*365*)	(*167*)	(*141*)	(*107*)	(*83*)	(*377*)	(*367*)	(*367*)	(*107*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

d. The large coupling constant between H-4a and H-10b ($J_{4a,10b}$~10 Hz) is only consistent with a *trans*-diaxial relationship.
e. In general, ring C presents a vinylic proton. If position 2 is substituted by an OH, OMe, or OAc group, it always displays an α-disposition.
f. The singlet corresponding to the *N*-methyl group is in the range of δ 2.0–2.2 ppm, its absence being very unusual.
g. The H-12α is more deshielded than H-12β as a consequence of the *cis*-lone pair of the nitrogen atom.

Homolycorine-type alkaloids with a saturated ring C have been studied by Jeff and coworkers (*374*). They describe empirical correlations of *N*-methyl chemical shifts with stereochemical assignments of the B/C and C/D ring junction.

3. *Hemanthamine Type*

The absolute configuration of these alkaloids is determined through the circular dichroism spectrum. The alkaloids of the *Narcissus* genus are exclusively of the hemanthamine type, while in genera such as *Brunsvigia, Boophane*, etc., the crinine-type alkaloids are predominant. It is also noteworthy that the alkaloids isolated from the *Narcissus* genus do not show additional substitutions in the aromatic ring, apart from those of C-8 and C-9. On the contrary, in the genera where crinine-type alkaloids predominate, the presence of alkaloids with a methoxy substituent at C-7 is quite common. Thus, hemanthamine-type alkaloids show the following characteristics:

a. Two singlets for the *para*-oriented aromatic protons.
b. Using $CDCl_3$ as the solvent, the magnitude of the coupling constants between each olefinic proton (H-1 and H-2) and H-3 gives information about the configuration of the C-3 substituent. Thus, in those alkaloids in which the two-carbon bridge (C-11 and C-12) is *cis* to the substituent at C-3, H-1 shows an allylic coupling with H-3 ($J_{1,3}$~1–2 Hz) and H-2 shows a smaller coupling with H-3 ($J_{2,3}$~0–1.5 Hz), as it occurs in crinamine (**57**). On the contrary, in the corresponding C-3 epimeric series, e.g. hemanthamine (**53**), a larger coupling between H-2 and H-3 ($J_{2,3}$ 5 Hz) is shown, the coupling between H-1 and H-3 not being detectable.
c. There is frequently an additional coupling of H-2 with the equatorial H-4β in a W-mechanism, while the proton H-4α shows a large coupling with H-4a ($J_{4\alpha,4a}$~13 Hz) due to their *trans*-diaxial disposition, characteristic of the hemanthamine series.
d. Two doublets for an AB system corresponding to the benzylic protons of position C-6.
e. The pairs of alkaloids with a hydroxy substituent at C-6, like papyramine/6-epipapyramine (**48/49**), hemanthidine/6-epihemanthidine (**55/56**), etc., appear as a mixture of epimers not separable even by HPLC.
f. Also, in relation to position C-6, it is interesting to note that ismine (**72**), a catabolic product from the hemanthamine series, shows a restricted rotation around the biarylic bond, which makes the methylenic protons at the benzylic position magnetically non-equivalent.

4. *Tazettine Type*

Although tazettine (**62**) is one of the most widely reported alkaloids in the Amaryllidaceae family, it was found to be an extraction artifact from pretazettine (**64**) (*75*).

The presence of an *N*-methyl group (2.4–2.5 ppm) in tazettine-type alkaloids immediately distinguishes them from the hemanthamine type, from which they proceed biosynthetically. Moreover, the ^{1}H NMR spectrum always shows the signal corresponding to the methylenedioxy group.

We have also included the alkaloid obesine (**67**) in this group, although it exhibits some structural differences with the skeleton type.

5. Galanthamine Type

Among the Amaryllidaceae alkaloids, only the galanthamine type shows an *ortho*-coupling constant between both the aromatic protons of ring A. The general characteristics of their ^{1}H NMR spectra are

a. Two doublets for the two *ortho*-oriented aromatic protons with a coupling constant of $J_{7,8}$ ~8 Hz.
b. The assignment of the substituent stereochemistry at C-3 is made in relation with the coupling constants of the olefinic protons H-4 and H-4a. When the coupling constant $J_{3,4}$ is about 5 Hz, the substituent is pseudoaxial, while if it is ~0 Hz this indicates that the substituent at C-3 is pseudoequatorial.
c. Two doublets as an AB system corresponding to the benzylic protons of C-6.
d. The existence of the furan ring results in a deshielding effect in H-1.
e. This type of alkaloid often shows an *N*-methyl group, but occasionally an *N*-formyl group has been reported.

B. CARBON^{13} NUCLEAR MAGNETIC RESONANCE

^{13}C NMR spectroscopy has been extensively used for determining the carbon framework of Amaryllidaceae alkaloids, and there are several major contributions (*330*,*346*,*375*). The preliminary assignments are made on the basis of chemical shifts and multiplicities of the signals (by DEPT experiment). The use of 2D NMR techniques, such as HMQC and HMBC, allow the assignments to be corroborated. Tables XVIII–XXIV show a compilation of the different ^{13}C NMR spectra classified according to the different types.

The ^{13}C NMR spectra of *Narcissus* alkaloids can be divided in two regions. The low-field region (>90 ppm) contains signals of the carbonyl group, the olefinic and aromatic carbons, as well as that of the methylenedioxy group. The other signals corresponding to the saturated carbon resonances are found in the high-field region, the *N*-methyl being the only characteristic group, easily recognizable by a quartet signal between 40 and 46 ppm.

The effect of a substituent (OH, OMe, OAc) on the carbon resonances is of considerable importance in localizing the position of the functional groups.

The analysis of the spectra allows conclusions to be drawn about the following aspects:

- The number of methine olefinic carbons.
- The presence and nature of the nitrogen substituent.

TABLE XVIII.
^{13}C NMR Data of Lycorine-Type Alkaloids.

Alkaloid	**1**	**3**	**5**	**7**	**13**	**14**	**15**	**19**	**21**	**22**	**23**	**24**	**25**
C-1	70.2	70.7	68.5	68.3	69.8	70.3	69.9	65.4	119.4	120.0	102.2	105.4	31.7
C-2	71.7	71.8	73.9	81.0	33.5	28.8	28.8	34.7	123.9	131.2	164.5	163.8	21.8
C-3	118.5	118.6	114.0	115.1	116.2	115.0	114.6	123.2	123.9	125.6	118.0	119.1	23.0
C-4	141.7	141.7	144.6	143.9	139.6	139.2	139.4	133.9	124.3	123.2	139.7	140.9	40.0
C-4a	60.8	61.4	60.9	60.9	59.5	60.4	60.2	71.2	131.3	136.0	133.0	133.2	162.4
C-6	56.7	56.4	56.7	56.6	55.3	51.9	51.8	66.2	157.5	144.7	142.6	143.1	138.5
C-6a	129.7	127.3	127.9	129.3	126.0	125.0	129.2	124.8	129.0	121.3	122.9	125.3	119.3
C-7	107.0	110.5	110.4	110.8	112.4	113.4	111.5	115.3	108.6	110.5	111.0	109.2	96.8
C-8	145.2	146.2	146.0	147.8	146.0	145.4	149.4	149.1	149.8	151.7	153.1	153.1	150.5
C-9	145.6	145.1	146.0	147.6	144.4	144.0	137.5	150.2	153.3	157.9	159.1	158.6	146.8
C-10	105.1	111.3	111.3	108.0	110.2	110.2	121.2	111.9	103.3	102.4	104.6	103.1	142.0
C-10a	129.6	126.5	127.2	126.6	128.8	129.2	132.5	123.7	120.3	130.6	131.4	134.3	127.1
C-10b	40.2	39.4	41.1	41.5	41.6	38.0	38.2	42.1	117.0	136.0	126.1	127.6	135.5
C-11	28.1	28.3	28.8	28.5	27.3	28.4	28.6	26.2	27.5	27.4	27.8	29.4	26.8
C-12	53.3	53.9	53.9	53.8	52.1	52.4	52.3	67.5	46.8	55.4	57.0	58.0	57.4
OCH_2O	100.6	—	—	—	—	—	—	—	—	—	—	106.4	—
OMe	—	56.1	56.0	57.3	55.9	56.0	55.9	56.2	56.3	56.7	57.8	—	62.5
OMe	—	—	—	56.0	—	—	—	—	56.2	56.4	57.4	—	62.4
OMe	—	—	—	55.9	—	—	—	—	—	—	57.0	—	56.8
OOCMe	—	—	170.9	—	—	170.6	170.6	—	—	—	—	—	—
OOCMe	—	—	21.3	—	—	21.4	20.6	—	—	—	—	—	—
OOCMe	—	—	—	—	—	—	169.2	—	—	—	—	—	—
OOCMe	—	—	—	—	—	—	21.3	—	—	—	—	—	—
Solvent	a	b	b	d	d	d	d	c	b	b	c	c	d
MHz	75	50	50	50	100	100	100	50	50	50	50	50	62
Reference	(*298*)	(*113*)	(*113*)	(*135*)	(*167*)	(*167*)	(*167*)	(*316*)	(*114*)	(*71*)	(*68*)	(*319*)	(*67*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XIX.
^{13}C NMR Data of Homolycorine-Type Alkaloids.

Alkaloid	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
C-1	77.7	79.2	77.5	77.9	77.3	75.6	82.5	79.7	82.2	67.6	66.6	66.7	66.4	72.8	78.8
C-2	31.3	32.1	30.9	31.3	31.1	31.2	66.2	69.2	66.2	32.6	31.3	31.7	31.3	68.3	31.4
C-3	115.2	117.1	116.5	116.1	115.6	115.1	118.5	115.1	119.4	117.2	115.7	115.7	115.6	119.4	121.0
C-4	140.9	141.3	138.7	140.0	140.2	139.4	143.3	147.4	142.4	140.8	140.7	140.6	140.3	144.0	135.6
C-4a	66.6	68.0	66.8	66.9	66.8	59.1	66.4	67.5	67.1	68.5	67.3	67.5	67.5	68.3	79.3
C-6	165.9	167.9	166.3	167.0	165.4	165.1	165.7	165.4	165.0	92.3	98.2	91.8	98.2	98.5	167.1
C-6a	116.9	117.9	116.5	115.6	118.5	118.0	118.5	115.4	118.0	131.3	130.5	132.0	131.8	126.9	117.6
C-7	111.9	116.9	115.9	112.7	109.7	109.9	112.0	115.0	109.8	111.9	109.7	107.4	107.3	107.6	117.1
C-8	148.9	147.9	146.3	148.1	151.8	152.2	147.6	148.2	148.0	149.6	148.3	147.0	146.8	147.1	147.9
C-9	153.1	153.8	152.2	152.0	147.8	147.8	151.8	152.0	151.9	149.6	148.3	147.0	146.7	147.1	153.4
C-10	110.8	112.3	110.9	115.0	108.6	107.4	114.7	112.7	108.5	114.0	112.4	109.8	109.5	109.8	112.6
C-10a	137.8	137.6	135.7	138.0	139.7	138.7	137.2	136.7	138.8	128.6	125.6	128.2	126.9	131.2	134.9
C-10b	43.8	43.7	42.2	43.0	43.8	43.0	38.2	39.9	38.4	44.7	44.0	44.2	43.9	39.2	37.4
C-11	28.1	28.6	27.4	27.9	27.9	29.6	27.0	28.0	27.3	28.7	27.8	28.1	27.9	27.7	26.2
C-12	56.6	57.3	56.0	56.5	56.3	44.1	55.8	56.3	55.9	57.6	56.6	56.7	56.5	56.3	70.7
OCH_2O	—	—	—	—	102.0	102.0	—	—	102.1	—	—	101.0	100.8	101.1	—
OMe	56.4	56.7	56.0	56.2	—	—	55.2	56.2	—	56.5	55.8	—	55.2	55.5	56.8
OMe	56.2	—	—	—	—	—	—	—	—	56.5	55.5	—	—	—	—
OMe	—	—	—	—	—	—	—	—	—	—	55.1	—	—	—	—
NMe	44.2	44.1	42.9	43.3	43.5	—	42.2	43.3	42.9	44.3	43.8	44.3	44.0	43.8	56.2
O<u>OC</u>Me	—	—	174.9	—	—	—	—	169.4	—	—	—	—	—	—	—
OO<u>CMe</u>	—	—	21.0	—	—	—	—	21.1	—	—	—	—	—	—	—
O<u>OCCH</u>$_2$CHOHMe	—	—	—	—	—	—	—	170.8	—	—	—	—	—	—	—
OOC<u>CH</u>$_2$CHOHMe	—	—	—	—	—	—	—	40.8	—	—	—	—	—	—	—
OOCCH$_2$<u>CH</u>OHMe	—	—	—	—	—	—	—	66.7	—	—	—	—	—	—	—
OOCCH$_2$CHOH<u>Me</u>	—	—	—	—	—	—	—	19.9	—	—	—	—	—	—	—
Solvent	d	c	b	b	d	d	b	b	d	c	d	d	d	d	b
MHz	63	50	62	50	100	100	50	50	50	62	50	100	100	50	50
Reference	(*321*)	(*324*)	(*70*)	(*82*)	(*165*)	(*165*)	(*138*)	(*72*)	(*71*)	(*106*)	(*104*)	(*165*)	(*165*)	(*71*)	(*137*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XX.
^{13}C NMR Data of Hemanthamine-Type Alkaloids.

Alkaloid	**42**	**43**	**44**	**45**	**47**	**48**	**49**	**50**	**53**	**54**	**55**	**56**	**57**	**59**	**61**
C-1	132.1	133.2	132.3	130.3	128.2	132.4	132.0	132.4	128.0	127.5	126.7	126.3	123.6	25.4	131.4
C-2	127.4	127.6	128.6	127.6	127.3	125.6	125.9	125.2	127.2	129.5	132.3	132.8	136.0	26.4	129.1
C-3	64.0	64.6	64.5	63.3	70.7	72.4	72.4	72.4	73.0	72.4	72.5	72.5	76.0	69.9	72.5
C-4	32.7	32.8	33.5	31.6	25.6	28.7	28.1	28.5	29.5	28.2	27.8	27.6	30.1	30.3	26.7
C-4a	62.3	64.0	64.1	62.8	64.8	62.2	56.3	57.1	62.7	62.8	61.6	56.2	66.1	66.0	53.4
C-6	62.8	63.7	62.6	60.9	57.1	87.0	88.9	96.4	63.3	61.0	85.8	88.4	63.4	59.1	57.6
C-6a	126.3	126.3	125.8	121.1	116.5	127.4	126.5	125.5	126.9	126.2	129.2	127.8	126.5	118.4	131.8
C-7	106.9	107.9	111.9	109.8	110.0	111.0	112.5	112.4	106.9	106.6	108.2	109.5	106.9	109.0	105.7
C-8	145.6	147.9	149.2	144.8	148.9	147.8	147.8	147.3	146.5	146.5	146.5	146.4	146.2	146.3	146.2
C-9	146.0	148.4	149.1	146.0	149.0	148.5	148.7	148.2	147.0	146.5	147.4	147.7	146.5	145.4	145.5
C-10	102.7	104.4	107.8	109.2	106.2	105.4	105.4	105.0	103.3	103.4	102.7	102.9	103.2	109.6	105.4
C-10a	138.3	136.9	138.7	136.5	138.0	136.4	137.4	138.1	135.0	134.2	134.7	135.8	135.3	137.1	129.1
C-10b	44.2	51.4	45.4	44.0	44.9	44.7	44.1	43.7	50.0	49.2	50.7	50.3	50.3	42.4	36.9
C-11	44.2	80.8	45.0	42.8	40.6	42.3	40.9	41.1	80.0	80.2	79.2	78.3	80.0	35.5	75.3
C-12	53.5	61.5	54.0	52.8	52.3	42.0	47.9	48.4	61.5	60.4	52.0	57.8	61.2	50.8	81.0
OCH_2O	100.6	102.4	—	—	—	—	—	—	101.0	100.8	101.0	101.0	100.9	—	100.8
OMe	—	—	56.8	55.8	56.1	56.6	56.6	56.8	56.0	56.5	56.8	56.5	55.8	55.8	56.5
OMe	—	—	56.5	—	56.1	56.6	56.6	56.0	—	—	—	—	—	—	—
OMe	—	—	—	—	56.1	56.1	56.0	55.8	—	—	—	—	—	—	—
OMe	—	—	—	—	—	—	—	55.7	—	—	—	—	—	—	—
O<u>OC</u>Me	—	—	—	—	—	—	—	—	—	170.0	—	—	—	170.5	—
OOC<u>Me</u>	—	—	—	—	—	—	—	—	—	21.2	—	—	—	21.0	—
<u>CH_2</u>OOCMe	—	—	—	—	—	—	—	—	—	—	—	—	—	—	64.6
CH_2O<u>OC</u>Me	—	—	—	—	—	—	—	—	—	—	—	—	—	—	170.8
CH_2OOC<u>Me</u>	—	—	—	—	—	—	—	—	—	—	—	—	—	—	20.9
Solvent	d	c	c	b	d	d	d	d	d	d	d	d	d	d	d
MHz	20	67.5	75	50	50	50	50	50	20	50	125	125	75	50	50
Reference	(*330*)	(*376*)	(*336*)	(*108*)	(*137*)	(*135*)	(*135*)	(*137*)	(*330*)	(*74*)	(*73*)	(*73*)	(*298*)	(*140*)	(*74*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

TABLE XXI.
^{13}C NMR Data of Tazettine-Type Alkaloids.

Alkaloid	**62**	**63**	**65**	**67**
C-1	130.5	130.1	131.3	132.4
C-2	128.4	128.9	126.0	136.5
C-3	72.4	72.1	72.7	63.6
C-4	26.6	25.4	29.8	34.4
C-4a	69.9	68.2	63.3	68.5
C-6	65.0	62.6	168.5	62.2
C-6a	127.8	126.2	118.6	131.0
C-7	103.7	108.5	103.8	107.3
C-8	146.3	146.6	147.1	148.4
C-9	146.3	146.2	152.3	147.3
C-10	109.1	104.2	111.0	111.0
C-10a	125.4	130.9	142.2	125.0
C-10b	50.1	50.0	46.2	50.3
C-11	101.7	102.6	80.1	82.7
C-12	61.7	64.5	53.5	55.7
OCH_2O	100.6	100.9	102.1	101.9
OMe	55.6	56.7	56.2	—
NMe	41.9	40.6	42.8	—
Solvent	d	d	d	c
MHz	16	75	50	62
Ref.	(*346*)	(*355*)	(*79*)	(*76*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

- The existence of a lactonic carbonyl group.
- The presence of a quaternary carbon signal assignable to C-10b in the chemical shift range of 42–50 ppm.

C. MASS SPECTROMETRY

Extensive studies on the mass spectrometry of Amaryllidaceae alkaloids by electron impact were reported in the 1960s and 1970s (*94*,*310*,*328*,*353*,*378–385*). The fragmentation patterns in the electron impact mass spectrometry (EIMS) of various skeletal types are fairly well documented and have considerable diagnostic value.

1. Lycorine Type

The molecular ion appears as a quite intense peak, and generally suffers the loss of water, as well as C-1 and C-2 and their substituents, by a retro-Diels–Alder fragmentation (Fig. 12). The loss of water is not present in the spectra of acetyl derivatives.

TABLE XXII.
^{13}C NMR Data of Narciclasine-Type Alkaloids.

Alkaloid	**68**	**70**	**71**	**72**
C-1	124.7	122.0	120.2	129.9
C-2	69.1	126.7	125.9	118.0
C-3	72.3	128.1	131.0	129.1
C-4	68.8	129.9	133.0	110.7
C-4a	52.8	143.8	136.5	146.7
C-6	172.1	151.8	152.8	63.5
C-6a	129.2	123.1	126.6	134.0
C-7	168.9	105.5	108.3	109.7
C-8	152.3	148.1	159.2	147.5
C-9	144.8	148.2	152.0	147.4
C-10	95.7	99.9	102.2	110.2
C-10a	132.1	130.3	122.0	131.2
C-10b	133.3	124.3	135.3	127.2
OCH_2O	102.0	101.9	105.7	101.3
NMe	—	—	45.9	30.8
Solvent	a	d	c	d
MHz	68	50	50	50
Reference	(*122*)	(*99*)	(*79*)	(*79*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

The ease of the loss of water from the molecular ion was found to be greatly dependent on the stereochemistry of the C-2 hydroxyl group. Thus, in the mass spectrum of lycorine (**1**) the relative intensity is low, while in 2-epilycorine it is the base peak (*310*).

2. *Homolycorine Type*

In this type of structure, the cleavage of the labile bonds in ring C by a retro-Diels–Alder reaction is dominant, generating two fragments: one, the most characteristic, represents the pyrrolidine ring (together with the substituents in position 2), and the other (a less-abundant fragment) encompasses the aromatic lactone or hemilactone moiety (Fig. 13). A further general and noteworthy feature is the low abundance of the molecular ion in all alkaloids with a double bond $\Delta^{3,4}$ (*378*).

3. *Hemanthamine Type*

The following observations about this type of alkaloids should be considered:

(i) In most cases, the molecular ion is the base peak.
(ii) The aromatic ring plays an important role in the stabilization of the ions, which is retained in all fragments of high mass, while the nitrogen atom is often lost.

TABLE XXIII.
^{13}C NMR Data of Montanine-Type Alkaloids.

Alkaloid	**73**	**74**
C-1	115.6	114.7
C-2	68.2	35.5
C-3	70.4	72.3
C-4	29.3	75.5
C-4a	58.5	70.0
C-6	59.2	62.0
C-6a	122.2	125.2
C-7	106.2	107.8
C-8	146.8	148.3
C-9	146.3	147.6
C-10	106.8	108.3
C-10a	131.1	133.6
C-11	44.7	46.4
C-11a	150.0	147.5
C-12	54.5	56.9
OCH_2O	100.7	102.1
Solvent	c	c
MHz	50	50
Reference	(*80*)	(*80*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

(iii) The fragmentation mechanisms are initiated by the rupture of a bond β to the nitrogen atom, which implies the opening of the C-11/C-12 bridge (*382*,*383*).

a. *Alkaloids with a saturated ring C and no bridge substituent*. The configuration of the ring C substituent plays a minor role in the fragmentation process.
b. *Alkaloids with a double bond ($\Delta^{1,2}$) in ring C and no bridge substituent*. The fragmentation pattern involves ruptures of C-4a/C-10b and C-3/C-4 bonds. A characteristic feature is the loss of a nitrogen-containing moiety, C_3H_5N [M^+-55].
c. *Alkaloids with a double bond ($\Delta^{1,2}$) in ring C and a hydroxyl substituent at C-11*. The presence of a hydroxyl group on C-11 is responsible for dramatic changes in the fragmentation pattern (Fig. 14), and it is profoundly influenced by the stereochemistry. There are three fundamental patterns of fragmentation:

- Loss of CH_3OH: it is more favorable when the two-carbon bridge and the substituent on C-3 are on the same side of the molecule.
- Loss of C_2H_6N: the relative significance of the loss of this neutral nitrogen moiety is governed by the ease with which the methanol is eliminated.
- Loss of CHO: A peak at m/z [M^+-29] due to the loss of an aldehyde radical is present in all alkaloids of this type.

TABLE XXIV.
^{13}C NMR Data of Galanthamine-Type Alkaloids.

Alkaloid	**75**	**77**	**78**	**79**	**80**	**81**	**82**	**83**	**84**	**86**
C-1	88.1	86.2	88.2	88.4	87.9/88.7	88.8	88.7	88.0	89.8	90.0
C-2	30.0	27.7	30.3	29.9	29.8	31.3	29.2	37.3	31.5	31.7
C-3	62.2	63.2	61.7	61.9	61.4	62.6	61.4	194.4	65.2	65.5
C-4	126.8	123.3	129.2	127.6	128.0/128.2	128.6	128.2	127.1	27.6	27.8
C-4a	126.0	121.8	125.9	127.1	125.8/126.2	128.1	125.1	144.3	31.7	37.5
C-6	60.5	59.9	51.6	53.5	41.0/52.8	61.6	58.4	60.7	60.4	53.8
C-6a	129.5	127.2	123.6	132.1	127.4	128.0	127.1	129.4	129.1	127.2
C-7	121.6	130.2	122.8	120.9	119.9/121.6	123.1	121.2	122.0	121.6	120.8
C-8	110.5	111.7	112.2	111.3	111.4	116.7	111.3	111.8	111.3	110.9
C-9	145.5	146.7	146.9	146.2	146.2/146.5	146.8	146.8	147.0	146.2	146.6
C-10	144.0	144.4	145.3	144.1	144.3/144.5	142.6	144.5	144.0	144.0	144.2
C-10a	132.7	131.9	133.1	133.1	131.8/131.9	134.2	131.2	130.5	136.3	136.6
C-10b	48.2	47.8	48.2	48.5	48.0/48.1	47.9	48.1	49.0	46.7	47.4
C-11	34.0	33.7	35.6	39.7	46.6/46.7	35.5	35.1	33.2	23.9	24.2
C-12	54.3	53.4	45.9	46.8	35.7/39.1	55.2	35.2	54.1	54.1	47.4
OMe	55.5	56.0	56.2	55.9	55.8	—	55.6	56.0	55.9	56.1
NMe	42.2	40.9	—	—	—	43.1	—	42.4	41.9	—
NCHO	—	—	—	—	162.1/162.7	—	—	—	—	—
OCMe	—	170.9	—	—	—	—	161.2	—	—	—
OCMe	—	21.4	—	—	—	—	21.4	—	—	—
Solvent	d	d	b	d	b	c	d	d	d	d
MHz	—	100	50	50	50	75	50	90	25	50
Reference	(*362*)	(*167*)	(*141*)	(*107*)	(*83*)	(*377*)	(*117*)	(*181*)	(*367*)	(*107*)

Solvent a: DMSO-d_6, b: $CDCl_3$-CD_3OD, c: CD_3OD, d: $CDCl_3$.

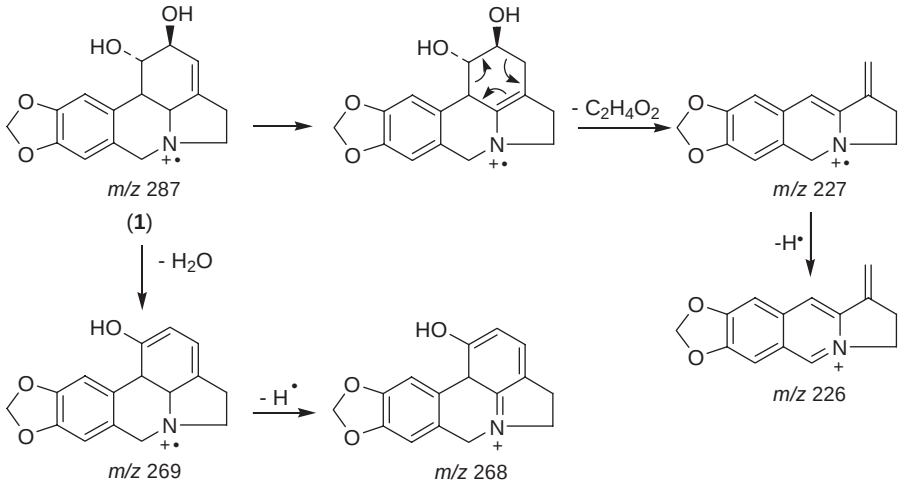


Figure 12. Mass fragmentation pattern of lycorine (**1**).

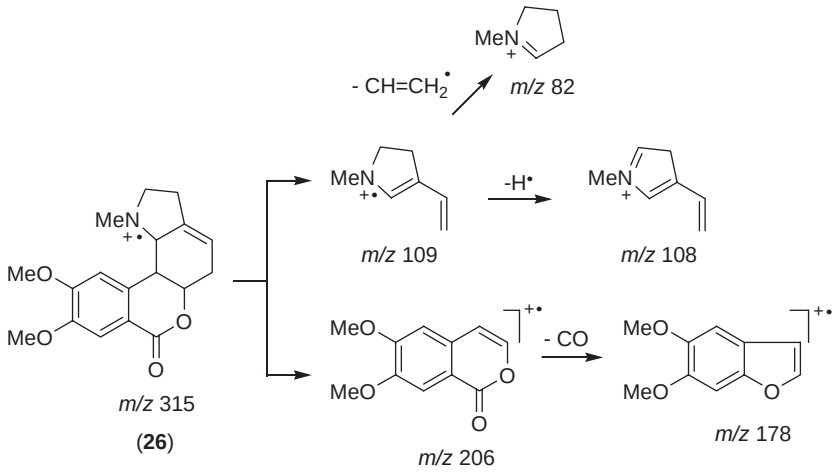


Figure 13. Mass fragmentation pattern of homolycorine (**26**).

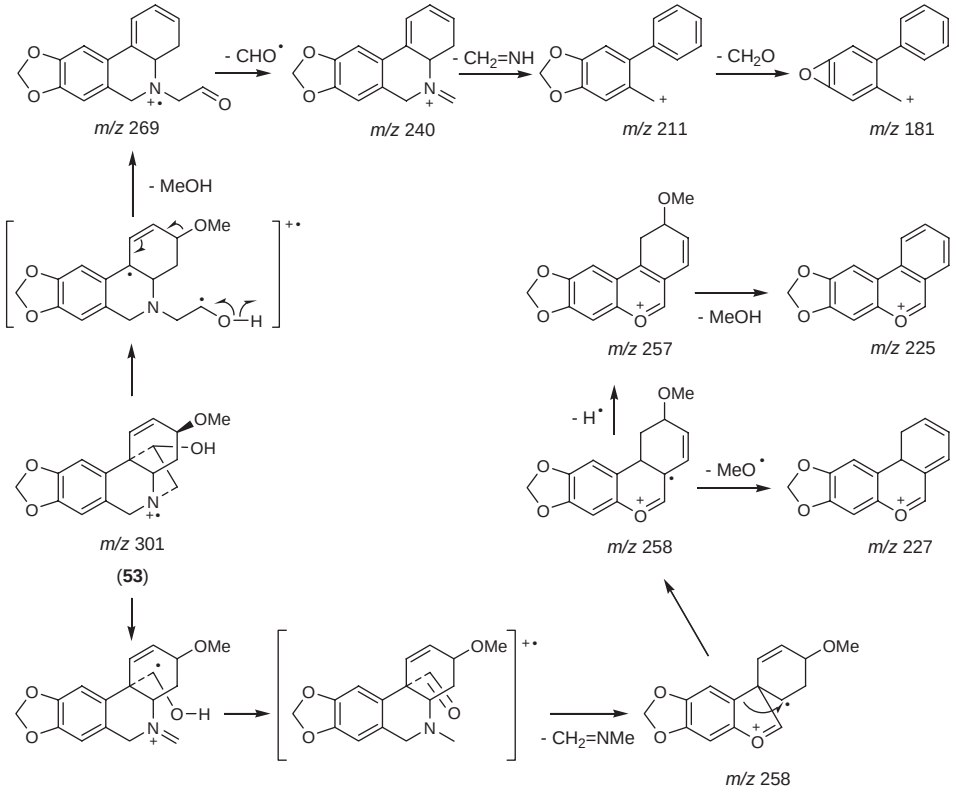


Figure 14. Mass fragmentation pattern of hemanthamine (**53**).

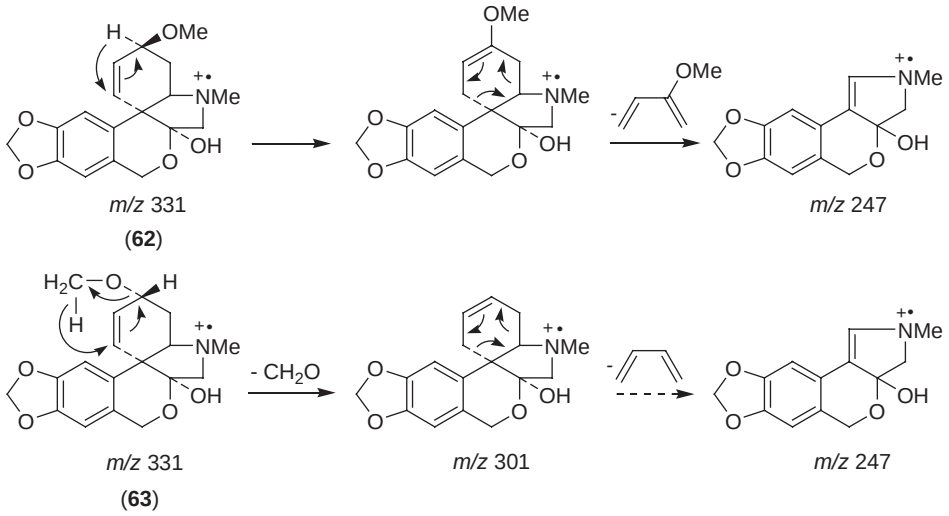


Figure 15. Mass fragmentation pattern of tazettine (**62**) and criwelline (**63**).

4. *Tazettine Type*

Minor changes in stereochemistry are sufficient to cause appreciable differences in the stereoisomers in this kind of structure. Thus, in the MS of tazettine (**62**), with a β-configuration of the methoxyl group at C-3, the dominant ion occurs at m/z [M^+-84], following a C-ring fragmentation by a retro-Diels–Alder process. In contrast, the mass spectrum of its epimer criwelline (**63**) contains a peak of low abundance at m/z [M^+-84] (Fig. 15). Ions occur in both stereoisomers owing to the successive loss of a methyl radical and water from the molecular ion (*353*).

5. *Montanine Type*

The mass spectral fragmentation patterns observed for alkaloids containing the 5,11-methanomorphanthridine nucleus greatly depend on the nature and particular configuration of the substituents at C-2 and C-3. Thus, all the alkaloids that possess a methoxyl group give rise to an M^+-31 ion.

The configuration of the C-2 substituent has a considerable effect on the extent to which the retro-Diels–Alder fragmentation ion is observed (Fig. 16). There is a definite enhancement of this fragmentation when the C-2 has an α-configuration (*94*).

6. *Galanthamine Type*

In this type of structure, the intense molecular ion as well as the [M^+-1] peak, the breaking of ring C (losing a C_4H_6O fragment), and the elimination of elements of ring B (including the nitrogen atom) are characteristic (Fig. 17). This behavior is similar for the dihydro derivatives (*380*).

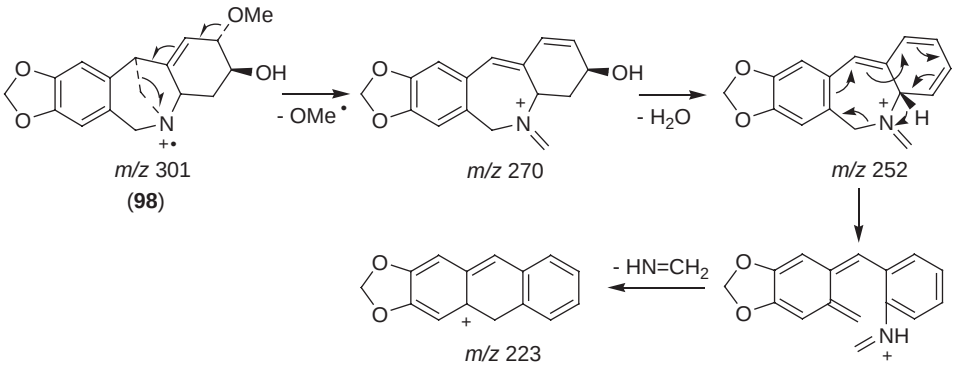


Figure 16. Mass fragmentation pattern of montanine (**98**).

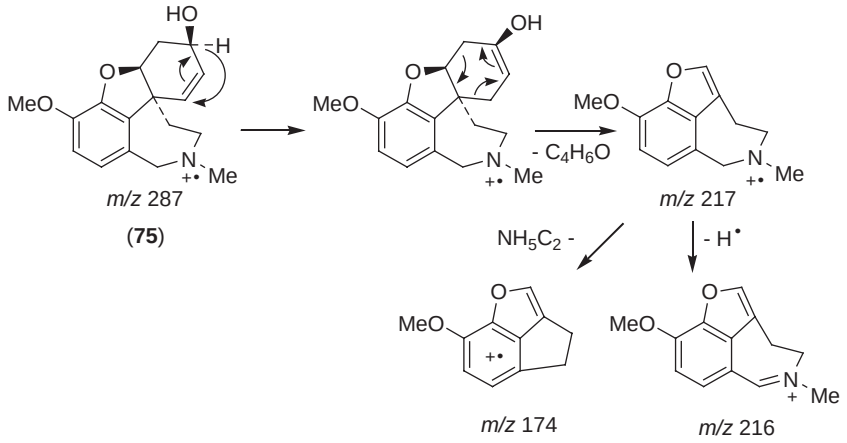


Figure 17. Mass fragmentation pattern of galanthamine (**75**).

VI. Biological and Pharmacological Activities

A. TRADITIONAL USES

1. Traditional Medicinal Usage

Considering that the *Narcissus* species are a rich source of alkaloids, it is not surprising that, despite their lethal potential, plants of this genus have been used throughout history in traditional medicine to treat a variety of medicinal problems (*386*). *N. poeticus*, for example, is described in the Bible as a well-established treatment for symptoms that would now be defined as cancer (*387*). In the fourth century BC, Hippocrates of Cos (the 'Father of Medicine') recommended a pessary prepared from *Narcissus* oil (probably *N. poeticus*) for the management of uterine tumors (*388*). In the first century AD, Pliny the Elder also recorded the topical use of

N. poeticus and *N. pseudonarcissus* for this purpose. It is now known that *N. poeticus* contains 0.012% of the antineoplastic agent narciclasine (**68**) in the fresh bulb (*14*,*101*). Arabian, North African, and Chinese medical practitioners of the Middle Ages continued using *Narcissus* oil in cancer treatment (*389*). For example, bulbs of *N. tazetta* L. var. *chinensis*, cultivated in China as a decorative plant, were used topically for the treatment of tumors in folk medicine. In this case, pretazettine (**64**) was established to be one of the antitumor active compounds (*133*,*390*). The bulbs of *N. tazetta* continue to be used in Turkey as a home remedy for the treatment of abscesses because of their antiphlogistic and analgesic properties (*391*).

Narcissus species have also been used as applications for wounds, hard imposthumes, strained sinews, stiff or painful joints, and other local ailments, being the basis of an ancient ointment called 'Narcissimum' (*14*). The powdered flowers have been used as an emetic, and, in the form of syrup or infusions, have been considered useful for relieving the congestive bronchial catarrh in children, and also epidemic dysentery (*392*). In France, narcissus flowers have been used as an antispasmodic (*14*). The Arabians commended the oil as a cure for baldness and as an aphrodisiac (*393*). In John K'Eogh's Irish Herbal, the roots pounded with honey were recommended to treat burns, bruised sinews, dislocations and old aches, remove freckles, heal abscesses and sores, and draw out thorns and splinters (*14*,*394*). The bulbs of *N. tazetta* have also been used as a contraceptive. The influence of the daffodil on the nervous system has led to the use of its flowers and bulbs for hysterical affections and even epilepsy. A homeopathic medicine is also made from the bulbs and used for respiratory disease, particularly bronchitis and whooping cough (*14*).

2. *Toxic and Hallucinogenic Effects*

Plants of this genus have been used throughout history as a stimulant to induce trance and hallucinations, and as an agent in suicide. Socrates called the narcissus the 'Chaplet of the infernal Gods', because of its narcotic effects. Pliny, in turn, describes the narcissus as '*narce narcissum dictum, non a fabuloso puero*', which translated means 'named narcissus from *narce*, not from the fabulous boy'. The Greek *narkao*, meaning to be numb, originates in the narcotic properties of the plant (*14*).

It has been known for a long time that daffodil ingestion is very dangerous, resulting in toxic symptoms in both man and warm-blooded animals such as cattle, goats, cats, and pigs (*393*,*395*,*396*). After ingestion of *Narcissus* species such as *N. pseudonarcissus* or *N. jonquilla* (*115*), the first visible symptoms are salivation, acute abdominal pains, nausea, vomiting, and diarrhea, followed by neurological (trembling, convulsions, paralysis, etc.) and cardiac sequels, and sometimes resulting in death, if eaten in larger quantities. There have been many cases of poisoning or death when the bulbs have been cooked by mistake in the place of leeks or onions (*393*). Recovery, however, is usually complete within a few hours without any treatment being necessary (*14*,*397*), but in cases of massive ingestion, activated charcoal, salts, and laxatives are administered. When symptoms are severe, atropine sulphate is given by intravenous injection and it may be necessary to induce vomiting or remove stomach contents (*398*).

The good news is that the bulb tastes awful, making it highly unlikely that anyone could even keep down one bite. In an experiment performed with several

plant species that are not consumed by animals, the plant with the most repellent activity was the daffodil, specifically *N. pseudonarcissus* (*399*). As a consequence, an animal repellent containing alkaloids isolated from members of the genus *Narcissus* has been designed to repel animals from vegetation by rendering it unpalatable, being also effective against fungi, molds, and bacteria (*400*,*401*).

Not all *Narcissus* species are equally dangerous. The bulbs of *N. poeticus*, for example, are more dangerous than those of *N. pseudonarcissus*. Neither do all plant tissues have the same concentration or profile of alkaloids. Thus, the alkaloid content of *N. papyraceus* is five times higher in the aerial part than in the bulbs, being toxic for herbivorous mammals (*137*). The distribution of the alkaloids in the plant tissues can be related with the plant defense mechanism.

Some *Narcissus* species, such as *N. pseudonarcissus*, can produce harmful effects without being swallowed. Thus, those who pick and pack the flowers are liable to develop dermatitis, probably due to the irritant effects of the sap or an allergic reaction (*397*,*402–406*). The compounds responsible for the irritation are not known, but alkaloids are thought to be involved (*110*). When extracts of the bulbs are applied to open wounds they can produce staggering, numbness of the whole nervous system, and paralysis of the heart (*393*). Furthermore, the scent of flowers of species such as *N. bulbocodium* can produce headaches and even vomiting if they are placed in confined spaces. Indeed, many people refuse to have daffodils in their house, considering them to be unlucky for the way they hang their heads, which suggests tears and unhappiness (*14*).

The mucilage secreted by bulbs can also produce harmful effects in plant species such as rose, rice, and cabbage, inhibiting seed germination and seedling growth (*120*,*407*).

3. *Other Uses*

The olfactory qualities of the *Narcissus* flower have made it a valuable component of luxury perfumes since time immemorial, although the main components of the volatile part of narcissus absolute are not of alkaloidal origin. However, alkaloids are present, together with essential oils, in some *Narcissus*-derived perfumes, such as jonquil absolute (*408–410*).

B. BIOLOGICAL ACTIVITIES OF PLANT EXTRACTS

Several *Narcissus* extracts have shown the following activities: antiviral (*390*,*411–417*), prophage induction (*418*), antibacterial (*418–420*), antifungal (*419*, *421*,*422*), antimalarial (*419*,*423*), insecticidal (*419*), cytotoxic (*390*,*411*, *419*,*424*), antitumor (*390*,*395*,*412*,*413*,*415*,*425*), antimitotic (*426*), antiplatelet (*419*), hypotensive (*427*), emetic (*395*), acetylcholine esterase inhibitory (*93*), antifertility (*428*), antinociceptive (*391*), chronotropic (*427*), pheromone (*429*), plant growth inhibitor, and allelopathic (*120*,*143*,*407*,*427*).

C. BIOLOGICAL AND PHARMACOLOGICAL ACTIVITIES OF ALKALOIDS

The alkaloids from the genus *Narcissus* are the compounds responsible for the majority of the above-mentioned activities, although the mannosa-binding lectins have also received much interest recently (*430–435*).

In spite of the great variety of pharmacological and/or biological properties exhibited by these alkaloids, only some of the activities of a reduced number have been reported, and the most extensively studied effect is that of non-specific inhibition. The relationship of chemical structure and biological activity is largely unknown, and further studies are needed to explore the full therapeutic potential of these alkaloids. The most-studied alkaloids in this group are galanthamine (**75**), lycorine (**1**), narciclasine (**68**), and pretazettine (**64**), which possess a diversity of pharmacological activities.

1. Lycorine Type

Lycorine (**1**), the most frequent and characteristic of the Amaryllidaceae alkaloids, has been reported to be a powerful inhibitor of ascorbic acid (L-Asc) biosynthesis (*436*,*437*), and thus has proved to be a useful tool in studying Asc-dependent metabolic reactions in L-Asc-synthesizing organisms (*438*,*439*). Lycorine is actually a powerful inhibitor of the activity of L-galactono-γ-lactone dehydrogenase, the terminal enzyme of L-Asc biosynthesis (*440–443*), which appears to be localized in the mitochondrial membrane (*444*,*445*). Galanthine (**7**) also has a high capacity to inhibit ascorbic acid biosynthesis (*437*).

It is well documented that lycorine (**1**) is a powerful inhibitor of cell growth, cell division, and organogenesis in higher plants, algae, and yeasts, inhibiting the cell cycle during interphase, which seems to be related with the L-Asc levels (*438*,*446–450*). In plants, it also inhibits cyanide-insensitive respiration, peroxidase activity, and protein synthesis (*451–453*). The effects of lycorine on L-Asc biosynthesis have been reported to occur at concentrations below those at which protein synthesis is affected, but it seems difficult to completely rule out non-specific effects of this alkaloid since it has been reported that, at least in yeasts, lycorine is able to interact directly with mitochondrial DNA. Thus, differing sensitivity to the alkaloid among cells devoid of mitochondrial DNA (rho^0) and cells with mitochondrial DNA either rho^+ or rho^- has been found in yeasts (*440*,*448*,*454*,*455*), rho^0 cells being resistant to high concentrations of the drug (*450*,*456–458*). Some strains can even adapt to the presence of lycorine, because they are able to degrade the alkaloid and use its biotransformation products as growth-stimulating factors (*458*).

Lycorine-1-*O*-β-D-glucoside, on the other hand, promotes cell growth, seed germination, and the rate of development of root and root hairs in higher plants. The glucosyloxy derivatives of lycorine (**1**) and pseudolycorine (**3**) and their aglycones form stable complexes with phytosterols and with divalent metal ions, and are able to translocate them from the rhizosphere to the aerial part (*347*). Palmilycorine and some acylglucosyloxy conjugates of lycorine, in turn, are frequently encountered among the phytosterols exhibiting membrane-stabilizing action. Additionally,

lycorine-1-*O*-β-D-glucoside and acylglucosyloxy conjugates of lycorine are used by plants for recognition to reject the vast majority of microorganisms and parasites (*459*).

In animals, lycorine (**1**) shows antitumor activity (*460*,*461*), reported to inhibit the *in vivo* and *in vitro* growth of a variety of tumor cells, such as BL6 mouse melanoma, Lewis lung carcinoma, murine ascites, or HeLa cells (*20*,*298*,*459*,*462–465*). It induces flat morphology in K-ras-NRK cells (transformed fibroblasts) (*466*), and reduces the cellular activity in femoral bone marrow tissue that results in granulocytic leucopenia and a decrease in the number of erythrocytes. This alkaloid's mechanism of action is thought to be through the inhibition of protein synthesis at the ribosomal level, even though the cytotoxic effects of calprotectin can also be suppressed using lycorine (*424*,*460*,*461*,*467*,*468*). Lycorine also inhibits murine macrophage production of tumor necrosis factor alpha (TNF-α) (*469*), and shows inhibitory effects on nitric oxide production and induction of inducible nitric oxide synthase (NOS) in lipopolysaccharide-activated macrophages (*470*). The molecular mechanism of lycorine against leukemia (human cell line HL-60) shows that it can suppress cell growth and reduce cell survival by arresting the cell cycle at the G2/M phase and inducing apoptosis of tumor cells (*471*). It displays pronounced cell growth inhibitory activities against both parental and multidrug resistant L5178 mouse lymphoma cell lines, but is almost inactive in inhibiting the glycoprotein responsible for the efflux-pump activity of tumor cells. Assays for interactions with tRNA revealed that the antiproliferative effects of lycorine result from its complex formation with tRNA (*73*). Interaction of lycorine (**1**), pseudolycorine (**3**), and 2-*O*-acetylpseudolycorine (**5**) with DNA has also been observed (*472*,*473*).

Some other alkaloids of this series, such as caranine (**10**), galanthine (**7**), pseudolycorine (**3**), and 2-*O*-acetylpseudolycorine (**5**), are also active against a variety of tumor cells (*415*,*463*,*474*). Pseudolycorine inhibits the protein synthesis in tumor cells at the step of peptide bond formation, but it has a different binding site than lycorine (*467*,*475*). Ungeremine (**24**), a natural metabolite of lycorine (**1**), is responsible, at least in part, for the growth-inhibitory and cytotoxic effects of lycorine, being active against leukemia (*476*,*477*). Lycorine-1-*O*-β-D-glucoside, in turn, has the reverse effect of lycorine, and may produce mitogenic activity in animal cells (*478*).

Lycorine (**1**) and pseudolycorine (**3**) exert antiviral effects on several RNA- and DNA-containing viruses (*479*). Antiviral activity has been observed in tests with flaviviruses, and to a slightly lesser degree, bunyaviruses. Lycorine and pseudolycorine also show inhibitory activity against the Punta Toro and Rift Valley fever viruses, but with low selectivity (*480*,*481*). Lycorine, in turn, acts as an anti-SARS-CoV (Severe Acute Respiratory Syndrome-associated Coronavirus) and shows pronounced activity against poliomyelitis, coxsackie, and herpes type 1 viruses (*20*,*482*). It possesses high antiretroviral activity accompanied by low therapeutic indices (*483*). The relationship between its structure and the mechanism of activity has been studied in the *Herpes simplex* virus, suggesting that alkaloids that may eventually prove to be antiviral agents have a hexahydroindole ring with two functional hydroxyl groups (*484*). The activity was found to be due to the inhibition of

multiplication, and not to the direct inactivation of extracellular viruses, and the mechanism of the antiviral effect was partially explained as a blocking of viral DNA polymerase activity (*33*,*413*,*479*,*485*).

Lycorine (**1**) has appreciable inhibitory activity against acetylcholinesterase (*486*). Cholinesterase activity appears to be associated with the two free hydroxyl groups present in some of the alkaloids of this structural type (*487*). The higher cholinesterase activity of assoanine (**20**) and oxoassoanine (**21**) with respect to the other lycorine-type alkaloids could be explained by an aromatic ring C, which gives a certain planarity to those molecules (*93*). Another alkaloid, galanthine (**7**), exhibits powerful cholinergic activity and has therefore attracted much interest in the treatment of myasthenia gravis, myopathy, and diseases of the central nervous system (*488*). Caranine (**10**), pseudolycorine (**3**), ungiminorine (**17**), and in particular, ungeremine (**24**), also show an inhibitory effect on acetylcholinesterase (*93*,*173*,*320*).

Lycorine (**1**) is an analgesic, more so than aspirin, and a hypotensive (*489*,*490*), as are caranine (**10**) and galanthine (**7**). The analgesic activity exhibited by the Amaryllidaceae alkaloids is attributed to their resemblance to the morphine and codeine skeletons. Lycorine also has antiarrhythmic action, and lycorine hydrochloride is a strong broncholytic (*30*). In fact, lycorine shows a relaxant effect on an isolated epinephrine-precontracted pulmonary artery and increases contractility and the rate of an isolated perfused heart. These effects are mediated by stimulation of β-adrenergic receptors (*491*).

Lycorine (**1**) also has a strong inhibitory effect on parasite (*Encephalitozoon intestinalis*) development (*492*) and antifungal activity against *Candida albicans* (*326*). Additionally, lycorine has antifeedant (*493*), antimalarial (*423*,*494*), emetic (*495*), anti-inflammatory (*496*), antiplatelet (*419*), as well as antifertility (*490*) activities. Galanthine (**7**), in turn, shows mild *in vitro* activity against *Tripanosoma brucei rhodesiense* and *Plasmodium falciparum* (*497*).

2. *Homolycorine Type*

It is reported that some alkaloids of this series, such as homolycorine (**26**), 8-*O*-demethylhomolycorine (**27**), 9-*O*-demethyl-2α-hydroxyhomolycorine (**32**), dubiusine (**33**), hippeastrine (**34**), lycorenine (**35**), or *O*-methyllycorenine (**36**), present cytotoxic effects against non-tumoral fibroblastic LMTK cells (*463*), also being moderately active in inhibiting the *in vivo* and *in vitro* growth of a variety of tumor cells, such as Molt 4 lymphoma, HepG2 human hepatoma, LNCaP human prostate cancer, or HT (*341*,*463*,*490*). Dubiusine, lycorenine, 8-*O*-demethylhomolycorine and 9-*O*-demethyl-2α-hydroxyhomolycorine also show DNA binding activity comparable to that of vinblastine (*472*). Homolycorine possesses high antiretroviral activity, accompanied by low therapeutic indices (*483*). Hippeastrine, in turn, displays antiviral activity against *Herpes simplex* type 1 (*484*).

Dubiusine (**33**), homolycorine (**26**), 8-*O*-demethylhomolycorine (**27**), and lycorenine (**35**) have a hypotensive effect on the arterial pressure of normotensive rats (*498*). Lycorenine also shows a vasodepressor action ascribed to the maintenance of its α-adrenergic blocking action, and produces bradycardia by modifying vagal activity (*499*). Another feature of lycorenine is its analgesic activity (*20*).

Homolycorine (**26**) and masonine (**30**) are other inductors of delayed hypersensitivity in animals (*110*). Hippeastrine (**34**), in turn, shows antifungal activity against *C. albicans* and it also possesses a weak insect antifeedant activity (*326*).

3. Hemanthamine Type

Hemanthamine (**53**), hemanthidine (**55**), crinamine (**57**), maritidine (**44**), and papyramine (**48**) display pronounced cell growth inhibitory activities against a variety of tumor cells, such as Rauscher viral leukemia, Molt 4 lymphoma, BL6 mouse melanoma, HepG2 human hepatoma, HeLa, LNCaP human prostate cancer, or HT (*298*,*336*,*341*,*424*,*462*,*463*,*500*). Some of these alkaloids, namely crinamine, hemanthamine, and papyramine, also present a cytotoxic effect against non-tumoral fibroblastic LMTK cells (*463*). The mechanism of action of hemanthamine is thought to be through the inhibition of protein synthesis, blocking the peptide bond formation step on the peptidyl transferase center of the 60S ribosomal subunit (*467*,*475*). Hemanthamine and hemanthidine also display the same pronounced cell growth inhibitory activities against both parental and multidrug resistant L5178 mouse lymphoma cell lines as described above for lycorine (**1**) (*73*). Crinamine, in turn, shows inhibitory effects on nitric oxide (NO) production and induction of inducible nitric oxide synthase (NOS) in lipopolysaccharide-activated macrophages (*470*).

The antimalarial activity against strains of chloroquine-sensitive *P. falciparum* observed in hemanthamine (**53**) and hemanthidine (**55**) can be attributed to the methylenedioxybenzene part of the molecule and the tertiary nitrogen without methyl (*423*). Crinamine (**57**) also exhibits moderate antimalarial activity (*494*,*501*). Hemanthidine also works *in vitro* against *Trypanosoma brucei rhodesiense*, and to a lesser extent against *Trypanosoma cruzi* (*497*). Vittatine (**42**) has antibacterial activity against the Gram-positive *Staphylococcus aureus* and the Gram-negative *E. coli* (*326*), and the alkaloid crinamine shows strong activity against *Bacillus subtilis* and *S. aureus* (*502*).

Like lycorine (**1**), hemanthidine (**55**) has stronger analgesic and anti-inflammatory activity than aspirin (*489*,*496*), and vittatine has been found to potentiate the analgesic effect of morphine (*60*). Moreover, some alkaloids of this series, such as hemanthamine (**53**) or papiramine (**48**) have a hypotensive effect (*41*,*498*), and hemanthamine shows strong antiretroviral activity (*483*).

4. Tazettine Type

Tazettine (**62**) is mildly active against certain tumor cell lines (*341*,*424*,*503*), with a slight cytotoxicity when tested on fibroblastic LMTK cell lines (*463*). Tazettine also displays weak hypotensive and antimalarial activities and interacts with DNA (*419*,*472*,*498*). Its chemically labile precursor, pretazettine (**64**), is far more interesting due to its antiviral and anticancer activities. In fact, when pretazettine is stereochemically rearranged to tazettine, the biological activity of the precursor is to a large extent reduced (*504*,*505*).

Pretazettine (**64**) shows cytotoxicity against fibroblastic LMTK cell lines and inhibits HeLa cell growth, being therapeutically effective against advanced Rauscher

leukemia, Ehrlich ascites carcinoma, spontaneous AKR lymphocytic leukemia, and Lewis lung carcinoma (*412*,*503*,*506–510*). It is one of the most active of the Amaryllidaceae alkaloids against Molt4 lymphoid cells (*463*), and is used in combination with DNA-binding and alkylating agents in treating the Rauscher leukemia virus (*412*,*503*). In fact, pretazettine strongly inhibits the activity of reverse transcriptase from various oncogenic viruses by binding to the enzyme (*20*). It inhibits both the growth of the Rauscher virus and cellular protein synthesis in eukaryotic cells by a mechanism that does not affect DNA and RNA synthesis, even though it has a pronounced DNA-binding activity (*415*,*424*,*467*,*472*,*481*,*507*,*511*). Pretazettine has also been shown to be active against selected RNA-containing flavoviruses (Japanese encephalitis, yellow fever, and dengue) and bunyaviruses (Punta Toro and Rift Valley fever) in organ culture (*481*). It also possesses pronounced activity against *Herpes simplex* type 1 virus (*484*). This activity may reflect a general ability to inhibit protein synthesis during viral replication (*512*).

5. *Narciclasine Type*

Narciclasine (**68**), an antimitotic and antitumoral alkaloid (*143*), affects cell division at the metaphase stage and inhibits protein synthesis in eukaryotic ribosomes by directly interacting with the 60S subunit and inhibiting peptide bond formation by preventing binding of the 3′ terminal end of the donor substrate to the peptidyl transferase center (*467*,*475*,*513–515*). It also retards DNA synthesis (*516*) and inhibits calprotectin-induced cytotoxicity at a more than 10-fold lower concentration than lycorine (**1**) (*468*). The peculiar effects of narciclasine seem to arise from the functional groups and conformational freedom of its C-ring (*122*), with the 7-hydroxyl group believed to be important in its biological activity (*253*). This alkaloid, related to pancratistatin (*516*), is one of the most important antineoplastic Amaryllidaceae alkaloids (*460*) and shows some promise as an anticancer agent. It inhibits HeLa cell growth, has antileukemic properties and is active against a variety of tumor cells, such as human and murine lymphocytic leukemia, larynx, and cervix carcinomas, and Ehrlich tumor cells (*33*,*77*,*386*,*388*,*389*,*516*). No effect has been observed toward solid tumors. Narciclasine-4-*O*-β-D-glucopyranoside shows very similar cytotoxic and antitumoral activity to narciclasine (*517*).

Narciclasine (**68**) has a prophylactic effect on the adjuvant arthritis model in rats, significantly suppressing the degree of swelling of adjuvant-treated, as well as untreated, feet (*468*). This alkaloid is also active against *Corynebacterium fascians,* inhibits the pathogenic yeast *Cryptococcus neoformans,* and modifications, like 2,3,4,7-tetra-*O*-acetylnarciclasine inhibit, the growth of the pathogenic bacterium *Neisseria gonorrhoeae* (*78*). Antiviral activity has been observed against RNA-containing flaviviruses and bunyaviruses (*481*).

At the plant level, narciclasine (**68**) is a potent inhibitor, showing a broad range of effects, including the ability to inhibit seed germination and seedling growth of some plants in a dose-dependent manner, interacting with hormones in some physiological responses (*518*). Thus, indole-3-acetic acid cannot overcome the inhibition of elongation of wheat coleoptile sections caused by narciclasine. Additionally, narciclasine suppresses the gibberellin-induced α-amylase production in barley seeds and cytokinin-induced expansion and greening of excised radish cotyledons (*120*). Like lycorine (**1**), narciclasine also inhibits ascorbic acid biosynthesis (*305*).

Narciclasine, present in daffodil mucilage, can delay tepal senescence in cut *Iris* flowers by attenuation of protease activity, which, in turn, is apparently related to the inhibition of the protein synthesis involved in senescence (*519*). At the organelle level, narciclasine inhibits both isocitrate lyase (ICL) activity in glyoxysomes and hydroxypyruvate reductase (HPR) activity in peroxysomes. It also blocks the formation of chloroplasts, markedly reducing the chlorophyll content of light-grown wheat seedlings, probably due to the inhibition of the formation of 5-aminolevulinic acid, an essential chlorophyll precursor (*520*). The formation of light-harvesting chlorophyll a/b binding protein (LHCP) is also inhibited by this alkaloid (*521*).

Some alkaloids of this series, such as trisphaeridine (**70**), possess high antiretroviral activities, accompanied by low therapeutic indices (*483*). Ismine (**72**), in turn, shows a significant hypotensive effect on the arterial pressure of normotensive rats (*498*) and is cytotoxic against Molt 4 lymphoid and LMTK fibroblastic cell lines (*463*).

6. *Montanine Type*

There is little information about the montanine-type alkaloids, only some data about pancracine (**73**), which shows antibacterial activity against *S. aureus* and *Pseudomonas aeroginosa* (*326*), as well as weak activity against *Tripanosoma brucei rhodesiense, T. cruzi*, and *P. falciparum* (*80*).

7. *Galanthamine Type*

Galanthamine (**75**), originally isolated from *Galanthus nivalis* L. in the 1940s, is a long-acting, selective, reversible and competitive inhibitor of acetylcholinesterase. This enzyme is responsible for the degradation of acetylcholine at the neuromuscular junction, in peripheral and central cholinergic synapses and in parasympathetic target organs (*522–524*). Galanthamine has the ability to cross the blood–brain barrier and act within the central nervous system (*525*,*526*). It binds at the base of the active site gorge of acetylcholinesterase, interacting with both the choline-binding site and the acyl-binding pocket, having a number of moderate-to-weak interactions with the protein (*527–529*). In addition, galanthamine stimulates pre- and postsynaptic nicotinic receptors which can, in turn, increase the release of neurotransmitters, thus directly stimulating neuronal function (*524*,*530*). It is also suggested that the stimulation of nicotinic receptors protects against apoptosis induced by β-amyloid toxicity (*524*,*531*,*532*). Its dual mode of action (*527*), coupled with the evidence that galanthamine has reduced side effects, make it a promising candidate for the treatment of nervous diseases, paralysis syndrome, schizophrenia, and other forms of dementia, as well as Alzheimer's disease (*524*,*527*,*528*).

Galanthamine (**75**) has other noteworthy pharmacological actions, including an ability to amplify the nerve-muscle transfer (*20*), affecting membrane ionic processes (*533*). It is also known to cause bradycardia or atrioventricular conduction disturbances (*41*), has long been used as a reversal agent in anesthetic practice (*181*), inhibits traumatic shock, and has been patented for use in the treatment of nicotine dependence. Besides this, galanthamine acts as a mild analeptic, shows an analgesic power as strong as morphine, compensates for the effects of opiates on respiration, relieves jet lag, fatigue syndrome, male impotence, and alcohol dependence, and

when applied in eye drops, reduces the intraocular pressure (*20*,*81*,*85*,*534*). It also acts as a hypotensive and has a weak antimalarial activity (*419*,*498*).

At present, there is no preventative or curative treatment available for Alzheimer's disease, leaving the symptomatic relief offered by AChEI therapy as the only approved therapeutic option. Owing to the relative lack of alternative treatment, galanthamine (**75**) is a reasonable approximation of the ideal concept of symptomatic Alzheimer's disease therapy (*523*,*535*). Galanthamine hydrobromide (a third-generation cholinesterase inhibitor used against Alzheimer's disease) offers superior pharmacological profiles and increased tolerance compared to the original acetylcholinesterase inhibitors, physostigmine or tacrine (*536–540*). Galanthamine is effective and well tolerated, resulting in short-term improvements in cognition, function, and daily life activities in patients with mild to moderate symptoms (*530*,*541*,*542*). However, long-term benefits beyond 6 months are in question (*543*), because persistent elevation of acetylcholine may lead to over-stimulation of both nicotinic and muscarinic acetylcholine receptors, the former causing receptor desensitization and the latter potentially causing an increased frequency of cholinergic side effects (*524*,*530*,*544*). The safety profile of galanthamine, as well as its clinical effectiveness, will only be demonstrated after large-scale clinical trials (*544–546*).

Broadly speaking, the development of galanthamine (**75**) into a widely used Alzheimer's drug can be divided into three main periods: (1) the early development in Eastern Europe for its use in the treatment of poliomyelitis; (2) the pre-clinical development in the 1980s; and (3) the clinical development in the 1990s (*544*). Galanthamine hydrobromide was first used by Bulgarian and Russian researchers in the 1950s and exploited for a variety of clinical purposes. It has been used clinically for postsurgery reversal of tubocurarine-induced muscle relaxation and for treating post-polio paralysis, myasthenia gravis, and other neuromuscular diseases, as well as traumatic brain injuries (*547*,*548*). As early as 1972, Soviet researchers demonstrated that galanthamine could reverse scopolamine-induced amnesia in mice, a finding that was demonstrated in man 4 years later. However, this alkaloid was not applied to Alzheimer's disease until 1986, long after the widely accepted cholinergic hypothesis had been first postulated, when researchers in Western Europe switched their attention to galanthamine because of its ability to penetrate the blood–brain barrier and specifically to augment the central cholinergic function (*544*,*549*). This led to clinical trials of galanthamine in the treatment of Alzheimer's disease. In 1996, Sanochemia Pharmazeutika in Austria first launched galanthamine as 'NIVALIN®', but its strictly limited availability meant the international pharmaceutical community adopted a cautions approach (*181*,*550*), until Sanochemia Pharmazeutika developed a method to synthetically produce the compound in 1997 (*551*). Later, galanthamine was co-developed by Shire Pharmaceuticals (Great Britain) and the Janssen Research Foundation (Belgium), who have launched galanthamine as 'REMINIL®' in many countries (*524*,*544*). This renewed interest is reflected in the increasing number of scientific reviews concerned exclusively with galanthamine and its derivatives (*522*,*525*,*526*,*530*,*538*,*539*,*547*,*552–555*).

Sanguinine (**81**) has a more potent acetylcholinesterase inhibitory activity than galanthamine (**75**) due to an extra hydroxyl group available for potential interaction with acetylcholinesterase (*93*,*555*). Sanguinine, in turn, is 10-fold more selective than galanthamine for acetylcholinesterase (AChE) vs. butyrylcholinesterase (BuChE)

(*556*). The lack of AChE inhibitory activity of lycoramine (**84**) and epinorlicoramine (**86**) could be due to the occurrence of a double bond in ring C, which does not allow these alkaloids to have the same spatial configuration as the active alkaloids of this series (*93*).

Narwedine (**83**), the biogenetic precursor of galanthamine (**75**), has been studied as a respiratory stimulator. It increases the amplitude and decreases the frequency of cardiac contractions and would therefore be of value in reducing blood loss during surgery (*41*). It also inhibits the action of narcotics and hypnotics, and increases the analgesic effect of morphine (*60*) as well as the pharmacological effects of caffeine, carbazole, arecoline, and nicotine (*30*).

8. *Other Alkaloids*

Cherylline (**88**) is a 4-arylisoquinoline derivative, a group with several potential medicinal properties (*80*), including a weak acetylcholinesterase inhibitory activity (*486*). Mesembrenone (**90**), in turn, is mildly active against Molt 4 lymphoid and non-tumoral fibroblastic LMTK cells (*463*), has a moderate hypotensive effect on arterial pressure, and interacts slightly with DNA (*472*,*498*).

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