Amaryllidaceae and *Sceletium* alkaloids

Zhong Jin*

Received (in Cambridge, UK) 12th April 2007
First published as an Advance Article on the web 21st May 2007
DOI: 10.1039/b502163b

Covering: July 2004 to June 2006. Previous review: *Nat. Prod. Rep.*, 2005, **22**, 111–126

A great number of natural products, especially alkaloids, which exhibit a range of biological activities including acetylcholinesterase inhibition and antineoplastic, cardiovascular and immunostimulatory activities, have been isolated from the plants of the Amaryllidaceae family. This review summarizes isolation, biological activity, and synthetic studies of these alkaloids. The primary biosynthetic pathways of each type of alkaloids are also proposed.

1 Introduction

Over the past decade, although encountering drastic challenges from chemical synthesis, combinatorial chemistry, computer-aimed molecular modeling, and other drug discovery approaches, drug discovery from natural products, especially medicinal plants,[1] has continued effectively to provide new drugs and drug leads against various pharmacological targets such as tumors, viruses, fungi, bacteria, *etc.* For thousands of years, extensive plant families, and mostly herbaceous plants, have been used as therapeutical agents against various diseases, which were known as herbal medicines. Plants of the Amaryllidaceae family, including *ca.* 65 genera and about 860 species, are amongst the top 20 in the most widely applied medicinal plant families. A number of pharmacologically active compounds, including alkaloids, phenols, lectins, peptides, *etc.*, have been isolated and characterized from this family. As primary constituents, nearly 500 structurally diverse alkaloids have been isolated and most of them have shown significant biological activity.

This review, following the previous one of this series,[2] reports the latest research progress on the alkaloids from plants of the Amaryllidaceae family, including isolation, structure characterization, biological activities and chemical syntheses.

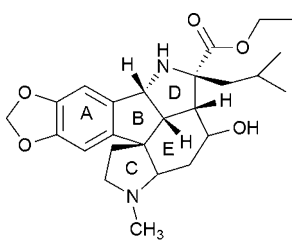
State Key Laboratory and Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China. E-mail: zjin@nankai.edu.cn

2 Amaryllidaceae alkaloids

During the past two years, twenty new alkaloids have been isolated from the various genera of plants of Amaryllidaceae family. Of these, nineteen belong to the known fourteen skeleton structures (Table 1, entries 1–14), and one has a new dinitrogenous pentacyclic skeleton (Table 1, entry 15). This represents the second dinitrogenous framework besides the plicamine-type alkaloids.

2.1 Occurrence, isolation and structure analyses

The genus *Galanthus* of the Amaryllidaceae family has proven to be a promising source of alkaloids with diverse structures, which recently provided a novel subgroup, the graciline-type alkaloids. During the course of phytochemical investigation on the species *G. gracilis*, a novel pentacyclic dinitrogenous alkaloid, namely gracilamine **15**, was identified.[3] The structure of the new alkaloid was elucidated by means of a combination of comprehensive spectroscopic methods including 1D and 2D NMR, MS, UV, and IR.



15 gracilamine

The genus *Nerine* Herbert, the second largest group within the Amaryllidaceae family with *ca.* 23 species, is one of seven representatives of the southern African subtribe Amaryllidinae. Three new alkaloids, *N*-demethylbelladine **16**, 6α-methoxybuphanidrine **17**, and filifoline **18**, have been isolated from fresh bulbs of the plant *Nerine filifolia* along with five known alkaloids, belladine **1**, ambelline **19**, 11-*O*-acetylambelline **20**, 6α-hydroxybuphanidrine **21**, and undulatine **22**.[4] Filifoline **18** is the 11-*O*-nicotinyl analogue of ambelline **19**.

Table 1 Known structure types of the Amaryllidaceae family alkaloids

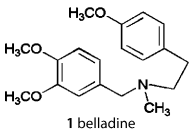
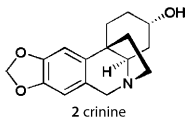
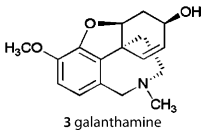
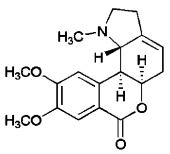
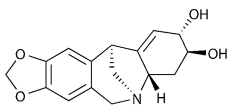
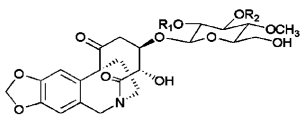
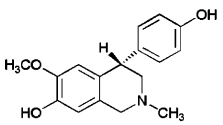
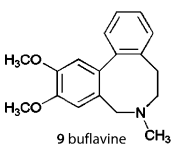
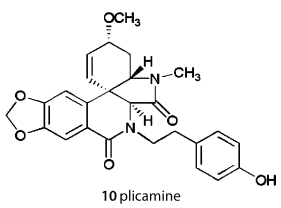
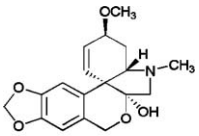
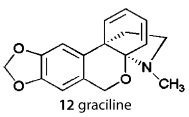
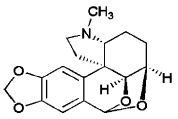
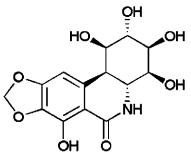
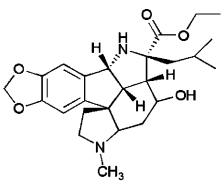
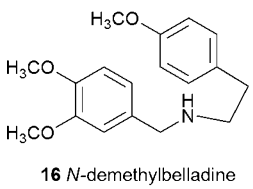
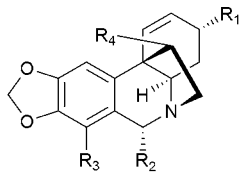
Entry	Framework type	Representative alkaloid	Plant genus
1	Belladine-type	 **1** belladine	*Crinum*, *Nerine*
2	Crinine-type	 **2** crinine	*Ammocharis*, *Brunsvigia*, *Crinum*, *Eucharis*, *Narcissus*, *Nerine*, *Pancratium* (now *Hymenocallis*)
3	Galanthamine-type	 **3** galanthamine	*Crinum*, *Hymenocallis* (*Pancratium*), *Leucojum*, *Lycoris*, *Narcissus*,
4	Lycorine-type	 **4** lycorine	*Amaryllis*, *Ammocharis*, *Brunsvigia*, *Crinum*, *Eucharis*, *Hisppeastrum*, *Hymenocallis* (*Pancratium*), *Leucojum*, *Narcissu Zephyranthes*
5	Homolycorine-type	 **5** homolycorine	*Clivia*, *Galanthus*, *Haemanthus*, *Lycoris*, *Narcissus*
6	Pancracine-type	 **6** pancracine	*Boophane*, *Haemanthus*, *Hymenocallis* (*Pancratium*), *Narcissus*,
7	Cripowellin-type	 **7a** cripowellin A R_1, R_2= -CH_2OCH_2- **7b** cripowellin B R_1, R_2= CH_3	*Crinum*
8	Cherylline-type	 **8** cherylline	*Crinum*
9	Buflavine-type	 **9** buflavine	*Boophane*
10	Plicamine-type	 **10** plicamine	*Cyrtanthus*, *Galanthus*

Table 1 *Cont.*

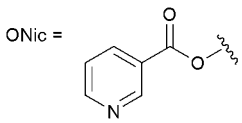
Entry	Framework type	Representative alkaloid	Plant genus
11	Tazettine-type	 **11** tazettine	*Crinum*, *Eucharis*, *Galanthus*, *Hippeastrum*, *Hymenocallis* (*Pancratium*)
12	Graciline-type	 **12** graciline	*Galanthus*
13	Augustamine-type	 **13** augustamine	*Crinum*
14	Pancratistatin-type	 **14** pancratistatin	*Crinum*, *Hisppeastrum*, *Hymenocallis* (*Pancratium*), *Zephyranthes*
15	Gracilamine-type	 **15** gracilamine	*Galanthus*

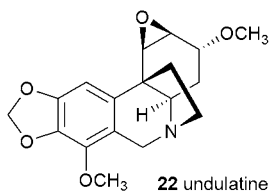


16 *N*-demethylbelladine

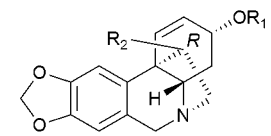


17 R_1, R_2, R_3 = OCH_3, R_4 = H
18 R_1, R_3 = OCH_3, R_2 = H, R_4 = ONic filifoline
19 R_1, R_3 = OCH_3, R_2 = H, R_4 = OH ambelline
20 R_1, R_3 = OCH_3, R_2 = H, R_4 = OAc
21 R_1, R_3 = OCH_3, R_2 = OH, R_4 = H

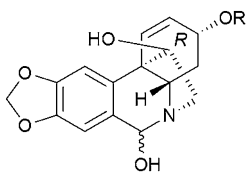




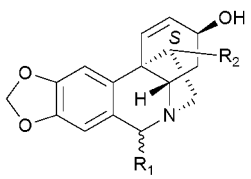
22 undulatine



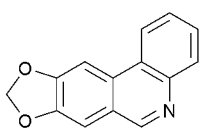
23 R_1 = Ac, R_2 = OH yemenine A
28 R_1 = H, R_2 = OH bulbispermine
29 R_1 = CH_3, R_2 = OH crinamine



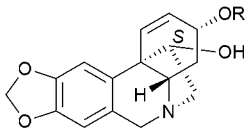
24 R = H yemenine B
30 R = CH_3



25 R_1, R_2 = OH yemenine C
27 R_1, R_2 = H vittatine
33 R_1 = H, R_2 = OH



26 trisphaeridine



31 R = CH_3 haemanthamine
32 R = H hamayne

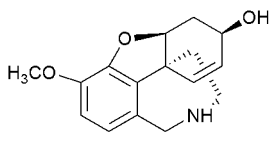
From the aqueous methanolic extract of the bulbs of *Crinum yemense* three new crinine-type alkaloids, yemenines A **23**, B **24**, and C **25**, have been isolated together with six known alkaloids, lycorine **4**, trisphaeridine **26**, vittatine **27**, bulbispermine **28**, crinamine **29**, and 6-hydroxycrinamine **30**.[5] The absolute configurations of the new compounds have been established on

the basis of chemical and physicochemical evidence. Several of them show potent inhibitory activities on nitric oxide (NO) production in lipopolysaccharide-activated macrophages.

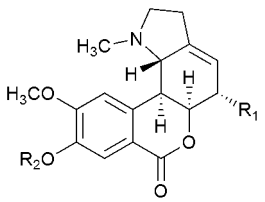
Four known alkaloids, lycorine **4**, crinamine **29**, haemanthamine **31**, and hamayne **32**, have been isolated from the bulbs of two Nigerian *Crinum* species (*C. jagus* and *C. glaucum*).[6] Hamayne **32** and lycorine **4** showed inhibition of acetylcholinesterase with IC_{50} values of 250 μM and 450 μM, respectively, whilst the other alkaloids were comparatively inactive.

From Turkish Amaryllidaceae species *Galanthus nivalis* subsp. *cilicicus*, three known alkaloids, lycorine **4**, vittatine **27** and 11-hydroxyvittatine **33**, were identified together with two unexpected isoquinoline alkaloids which often occur in the Fumariaceae, Papaveraceae, and Lauraceae families.[7] In addition, two known furofurane lignans were also reported to occur for the first time in this species.

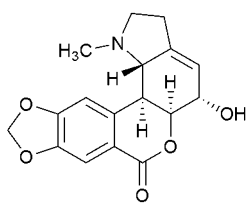
In addition to five known alkaloids, crinine-type 11-hydroxyvittatine **33** and *N*-demethylgalanthamine **34** and homolycorine-type 9-*O*-demethylhomolycorine **35**, 5α-hydroxyhomolycorine **36** and hippeastrine **37**, two new galanthamine-type alkaloids, named leucovernine **38** and acetylleucovernine **39**, were isolated by means of pH-gradient extraction and multistep chromatographic purification, including vacuum liquid chromatography and preparative TLC.[8]



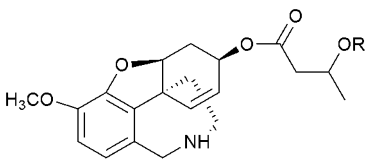
34



35 R_1, R_2 = H
36 R_1 = OH, R_2 = CH_3

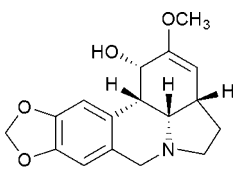


37 hippeastrine



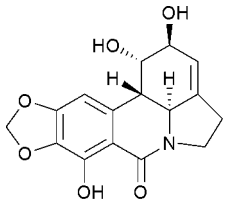
38 R = H leucovernine
39 R = Ac acetylleucovernine

From the bulbs of Egyptian *Amaryllis belladonna* L., a new lycorine-type alkaloid, named amarbellisine **40**, was isolated together with the well known alkaloids lycorine **4**, pancracine **6**, vittatine **27**, 11-hydroxyvittatine **33**, and hippeastrine **37**.[9] It is the first case of a lycorine-type alkaloid with a *cis* B/C ring junction.

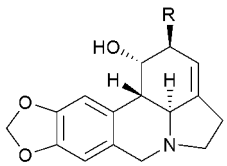


40 amarbellisine

Two new lycorine-type alkaloids, namely 8-hydroxylycorin-7-one **41** and 2-deoxylycorine **42**, were isolated from the bulbs of *Crinum bulbispermum*, along with the known alkaloids vittatine **27**, 11-hydroxyvittatine **33**, and hippamine **43**.[10] Their structures were elucidated by using combined spectroscopic methods of EIMS, UV, and NMR.



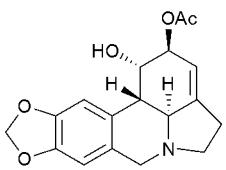
41



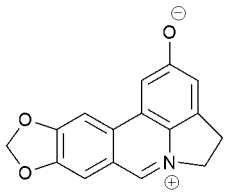
42 R = H
43 R = OCH_3 hippamine

Three known alkaloids lycorine **4**, 2-*O*-acetyllycorine **44**, and homolycorine **5** have been isolated from the bulbs of *Leucojum vermum*.[11] These alkaloids and others isolated from other Amaryllidaceae species have been subjected to tests *in vitro* for HIV-1 growth inhibitory activity on the MT4 human T cell line. Amongst them, lycorine **4**, homolycorine **5**, trisphaeridine **26**, and haemanthamine **31** possess high antiretroviral activities (IC_{50} = 0.4–7.3 μg mL^{-1}), accompanied by low therapeutic indices (TI_{50} = 1.3–1.9).

By application of a fluorometric flow assay system to an on-line coupled preparative HPLC, known alkaloid ungeremine **45** was isolated from the methanol extract of *Nerine bowdenii*. Its structure was assigned by analysis of 1D and 2D NMR spectra, and ungeremine shows stronger inhibitory activity (0.35 μM) against acetylcholinesterase than galanthamine (2.2 μM).[12]

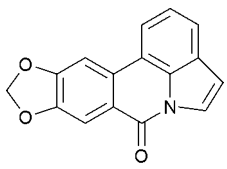


44



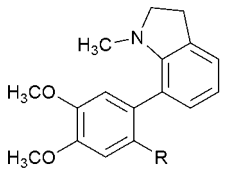
45 ungeremine

Bio-guided isolation of cholinesterase inhibitors from the bulbs of *Crinum powellii* has led to a known lycorine-type alkaloid hippadine **46**, which was isolated for the first time from this plant species.[13] During the screening for antiviral activities against Severe Acute Respiratory Syndrome-associated coronavirus (SARS-CoV), a herbal extract from *Lycoris radiata* was demonstrated to be most potent and the active component was identified as alkaloid lycorine **4**, which has an EC_{50} value of 15.7 ± 1.2 nM against SARS-CoV.[14] Using high performance liquid chromatography (HPLC), lycorine **4** in the total alkaloidal extracts prepared from aerial and underground parts of four Turkish *Galanthus* species, *G. nivalis* ssp. *cilicicus*, *G. gracilis*, *G. elwesii*, and *G. plicatus* ssp. *byzantinus*, collected during two different vegetation periods, has been detected and quantified using external standard calibration.[15]

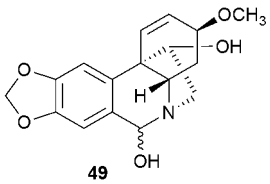


46 hippadine

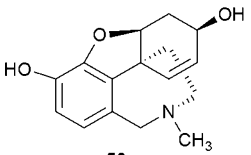
Two new ring-open homolycorine-type alkaloids, designated as lycosinine A **47** and B **48**, accompanied by ten known alkaloids, galanthamine **3**, hippeastrine **37**, haemanthidine **49**, *N*-demethylgalanthamine **34**, *O*-demethylgalanthamine **50**,



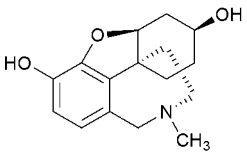
47 R = CH_2OH lycosinine A
48 R = CHO lycosinine B



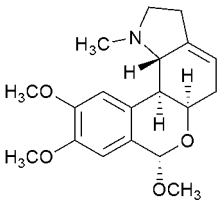
49



50



51 *O*-demethyllycoramine



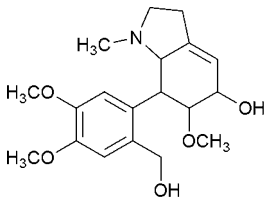
52 *O*-methyllycorenine

haemanthamine **31**, homolycorine **5**, *O*-demethyllycoramine **51**, lycorine **4**, and *O*-methyllycorenine **52**, have been isolated from the ethanol extract of *Lycoris aurea* bulbs.[16]

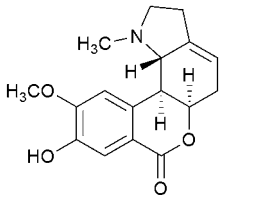
During the course of identifying novel alkaloids for medicinal use, six alkaloids were extracted and isolated individually from the Georgian *Galanthus caucasicus*. Of them, one, designated as galanthusin **53**, was reported for the first time and the other alkaloid derivatives were identified as known galantine, lycorine **4**, tazettine **11**, galanthamine **3**, and 9-demethylhomolycorine **54**.[17]

Screening of acetylcholinesterase (AChE) inhibitors in natural extracts using HPLC-MS methodology has been carried out. From the crude extract of *Narcissus* c.v. "Bridal Crown", galanthamine **3** was identified effectively.[18]

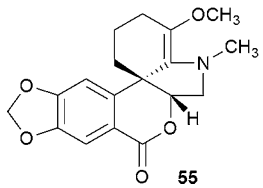
A new tazettine-type alkaloid **55** was recently isolated from *Narcissus serotinus* L. and its structure and stereochemistry were established by a combination of spectroscopic analyses.[19]



53 galanthusin



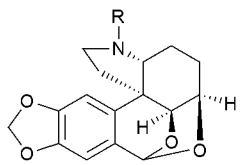
54 9-demethylhomolycorine



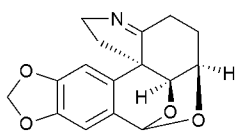
55

Alkaloid augustamine **13**, which was only reported once from *Crinum augustum*, is a rare member of the Amaryllidaceae family. Recently, from the bulbs of *Crinum kirkii* Baker, nineteen Amaryllidaceae alkaloids have been isolated and characterized. Two of them are hitherto unknown augustamine-type alkaloids noraugustamine **56** and 4α,*N*-didehydronoraugustamine **57**, and the others were identified as previously known augustamine **13**, sanguinine **58**, 3-*O*-acetylsanguinine **59**, lycorine **4**, 1-*O*-acetyllycorine **60**, 2-*O*-acetyllycorine **44**, 1,2-di-*O*-acetyllycorine **61**, hippadine **46**, zephyranthine **62**, flexinine **63**, crinine **2**, amabiline **64**, macowine **65**, *O*-methylnorbelladine **66**, hamayne **32**, and kirkine **67**.[20]

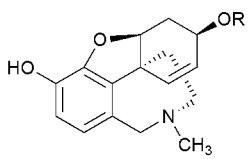
Sixteen known alkaloids, including trisphaeridine **26**, galanthamine **3**, haemanthamine **31**, buphanisine **68**, lycorine **4**, tazettine **11**, crinine **2**, crinan-3-one **69**, zephyranthine **62**, pancracine **6**, 6a-deoxytazettine **70**, galanthane **71**, *N*-demethylgalanthamine **34**, *N*-formylnorgalanthamine **72**, 9-*O*-demethylmaritidine **73**, and graciline **12**, have been identified from the



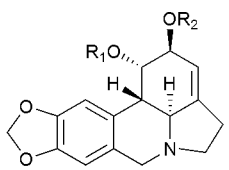
13 R = CH_3 augustamine
56 R = H noraugustamine



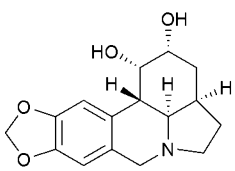
57



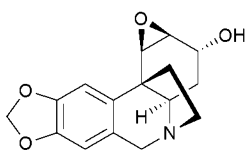
58 R = H sanguinine
59 R = Ac



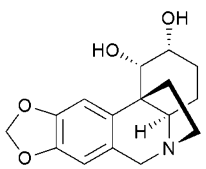
60 R_1 = Ac, R_2 = H
61 R_1, R_2 = Ac



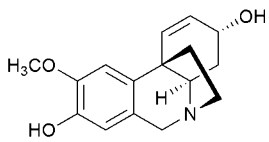
62 zephyranthine



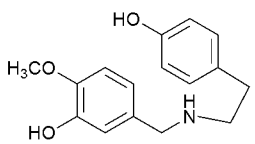
63 flexinine



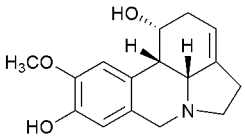
64 amabiline



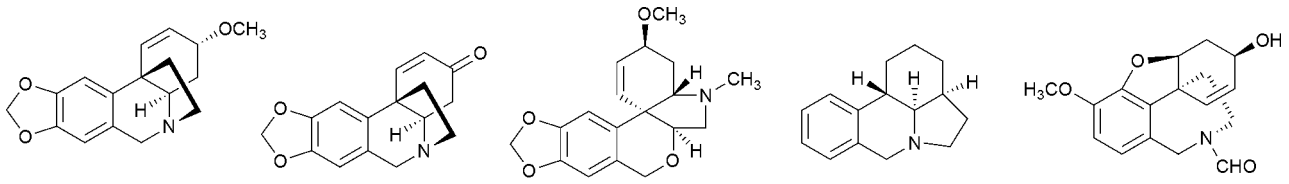
65 macowine



66 *O*-methylnorbelladine



67 kirkine



68 buphanisine **69** **70** 6a-deoxytazettine **71** galanthane **72**

leaves, bulbs, and roots of *Pancratium maritimum* by GC-MS analysis.[21] Haemanthamine was the main alkaloid in the leaves and bulbs whereas galanthane was found to be the main alkaloid in roots of this species.

Phytochemical investigation of three closely allied ethnomedicinal *Haemanthus* species has led to isolation of various alkaloids.[22] Homolycorine **5**, albomaculine **74**, and *O*-methyllycorenine **52** were isolated from *H. albiflos*, homolycorine **5**, montanine **75**, and manthidine **76** from *H. pauculifolius*, and coccinine **77**, montanine **75** and manthidine **76** from *H. deformis*.

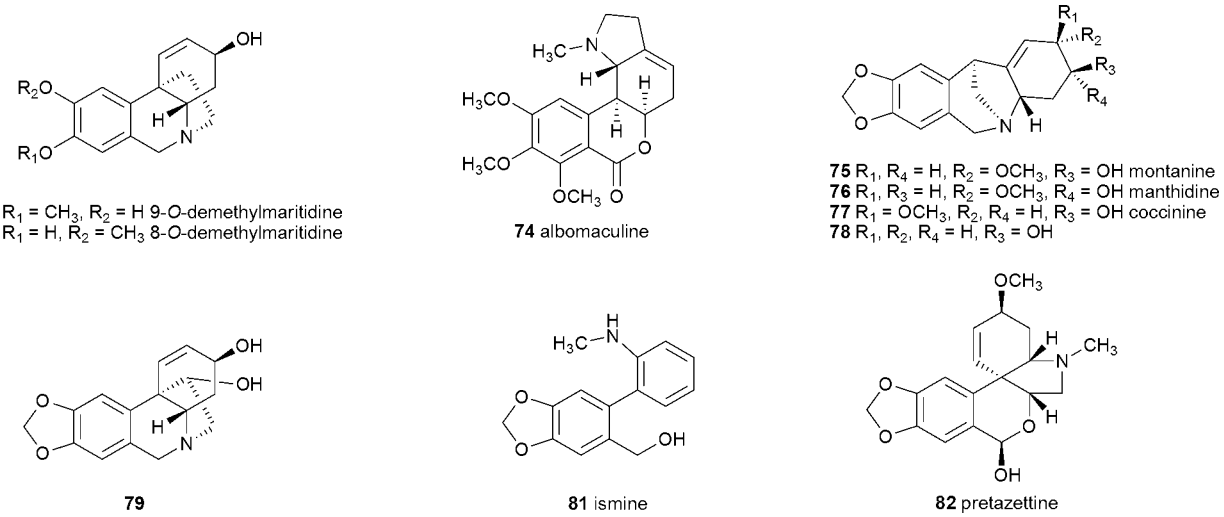
Bioactivity-directed fractionation and isolation studies on the Turkish *Galanthus ikariae* and *Narcissus tazetta* subsp. *tazetta* have afforded eight known Amaryllidaceae alkaloids, 2-demethoxymontanine **78**, 3-*epi*-hydroxybulbispermine **79** (bulbispermine = hamayne **32**), *N*-norgalanthamine **34**, crinine **2**, galanthamine **3**, haemanthamine **31**, lycorine **4**, and tazettine **11**.[23] It was reported that the acetylcholinesterase inhibitory activity of both of the plant extracts was due to the synergistic interaction of the alkaloids isolated.

Four known alkaloids, haemanthamine **31**, crinamine **29** hydrochloride, lycorine **4** and tazettine **11**, have been recently isolated from *Cyrtanthus breviflorus* collected from both moist and dry grasslands of the eastern seaboard region of southern Africa, along with five known lupane triterpenoids.[24] The alkaloid 8-*O*-demethylmaritidine **80** has been isolated from the chloroform extract of the bulbs in the preflowering stage of *Amaryllis belladonna* L. cultivated in Egypt, but it was lacking in the flowering stage.[25] Six major alkaloids, galanthamine **3**, haemanthamine **31**, tazettine **11**, ismine **81**, pretazettine **82**, and sanguinine **58**, have been characterized from *Narcissus bulbocodium* L.[26] From different Bulgarian *Galanthus elwesii* populations, three major alkaloids, galanthamine **3**, crinine **2** and haemanthamine **31**, were isolated by preparative thin layer chromatography and identified by GC-MS.[27] From Nigerian *Crinum jagus*, two known alkaloids, lycorine **4** and hamayne **32**, were identified together with morpholine hydrochloride.[28]

The extracts from the intact plants and *in vitro* cultures of *Leucojum aestivum* have been analyzed by capillary GC-MS. Fourteen known phenanthridine-, crinine-, lycorine-, and galanthamine-type alkaloids, including trisphaeridine **26**, crinine **2**, 9-*O*-demethylmaritidine **73**, anhydrolycorine **83**, *O*-acetylcaranine **84**, *O*-acetylpluviine **85**, pluviine **86**, lycorine **4**, galanthamine **3**, 2-*epi*-galantamine, narwedine **87**, norgalanthamine **34**, *N*-formylnorgalanthamine **72** and its 2-*epi* isomer, have been identified, eleven (galanthamine, 2-*epi*-galanthamine, narwedine, norgalanthamine, anhyudrolycorine, *O*-acetylcaranine, *O*-acetylpluviine, pluviine, lycorine, *N*-formylnorgalanthamine and its 2-*epi* isomer) in the intact plants and eight (trisphaeridine, galanthamine, crinine, narwedine, norgalanthamine, 9-*O*-demethylmaritidine, lycorine, and *N*-formylnorgalanthamine) in the *in vitro* cultures.[29]

Aiming to clarify the potential discrepancies in the reported ion structures, the accurate product ion mass spectra of nine galanthamine analogues including galanthamine **3**, galanthamine *N*-oxide, galanthaminium bromide, *O*-demethylgalanthamine hydrochloride **50**, norgalanthamine **34**, lycoramine **88**, 3-*epi*-galanthamine, narwedine **87**, and 3-acetyl-6-*O*-demethylgalanthamine **59** have been recorded on the basis of the sustained off-resonance (SORI) mass spectra of electrospray-generated $[M + H]^+$ ions.[30]

In a attempt to isolate antineoplastic isocarbostyril-type alkaloids from five *Hymenocallis* Salisbury species *H. bolivariana* Traub., *H. guianensis* Herb., *H. lobata* Klotzsch, *H. tubiflora* Salisb., *H. venezuelensis* Traub., nine naturally occurring



73 $R_1 = CH_3$, $R_2 = H$ 9-*O*-demethylmaritidine
80 $R_1 = H$, $R_2 = CH_3$ 8-*O*-demethylmaritidine

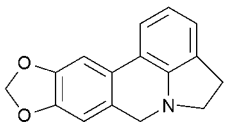
74 albomaculine

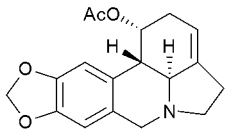
75 R_1, $R_4 = H$, $R_2 = OCH_3$, $R_3 = OH$ montanine
76 R_1, $R_3 = H$, $R_2 = OCH_3$, $R_4 = OH$ manthidine
77 $R_1 = OCH_3$, R_2, $R_4 = H$, $R_3 = OH$ coccinine
78 R_1, R_2, $R_4 = H$, $R_3 = OH$

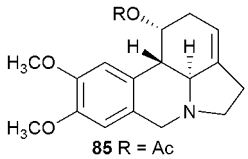
79

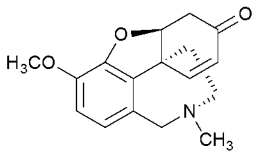
81 ismine

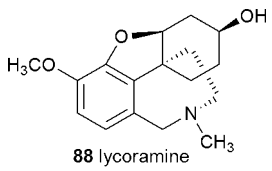
82 pretazettine


83 anhydrolycorine

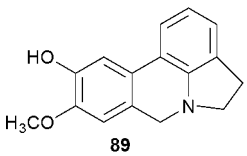

84 *O*-acetylcaranine

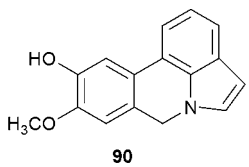

85 R = Ac
86 R = H pluviine

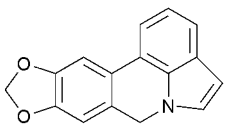

87 narwedine

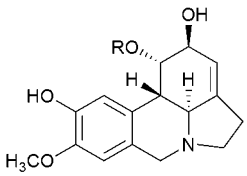

88 lycoramine

alkaloids have been obtained, two of them new, namely anhydro-pseudolycorine **89** from *H. guianensis*, *H. lobata*, and *H. tubiflora*, and 4,5-dehydroanhydropseudolycorine **90** from *H. lobata*. And others were identified as known lycorine **4**, galanthamine **3**, norgalanthamine **34**, anhydrolycorine **83**, 4,5-dehydroanhydrolycorine **91**, 1-*O*-acetylpseudolycorine **92**, and pseudolycorine **93**.[31]

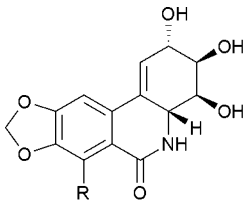

89

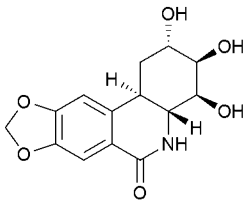

90


91 4,5-dehydroanhydrolycorine


92 R = Ac
93 R = H pseudolycorine

By a biotechnological approach involving an initial tissue culture cloning of *Hymenocallis littoralis* bulbs, subsequently, effective isolation has led to various human cancer cell line inhibitory isocarbostyrils, pancratistatin **14**, narciclasine **94**, 7-deoxynarciclasine **95** (lycorididine, margetine), 7-deoxy-*trans*-dihydronarciclasine **96**. For the purpose of improving aqueous solubility and transport to tumors for cancer antiangiogenesis/vascular targeting, these isocarbostyrils were selected for conversion to 3,4-cyclic phosphate prodrugs.[32] As an extension of structure–activity relationship studies of pancratistatin, the lactam groups in 7-deoxynarciclasine **95** and 7-deoxy-*trans*-dihydronarciclasine **96** were reduced into related amines.[33] These amines, however, were found to show lower cancer cell growth inhibitory activity than the parent natural products by a factor of 10 or more.


94 R = OH narciclasine
95 R = H 7-deoxynarciclasine

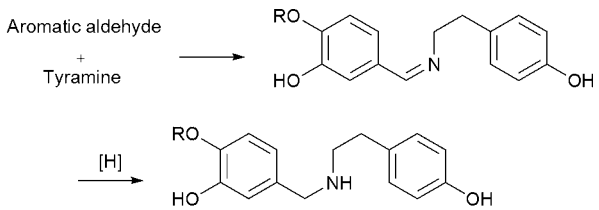

96 7-deoxy-trans-dihydronarciclasine

Bioassay-guided separation from the previously chemically uninvestigated Texas grasshopper *Brachystola magna* has led to isolation of three isocarbostyrils, pancratistatin **14**, narciclasine **94**, and ungeremine **45**.[34] The structure of pancratistatin from the insect grasshopper *B. magna* extract has been verified by X-ray crystal analysis to be identical to the pancratistatin obtained from plant sources. The occurrence of pancratistatin in *B. magna* suggested a defensive strategy and potential new plant source, since Amaryllidaceae species have not been recorded among the plants selected by this grasshopper as preferred foods.

Commonly, naturally occurring alkaloids, such as the important groups of secondary metabolites, are separated and extracted by methods such as Soxhlet and room temperature solvent extraction, or by ultrasound, microwaves, supercritical solvents, or other methods. Due to the significant biological value of the Amaryllidaceae alkaloids, new separating, extracting, and structure analyzing techniques for them from the plant sources have been presented continually. A new methodology was developed using microwave irradiation as a powerful tool for extracting alkaloids such as galanthamine **3**, lycoramine **88**, and lycorine **4** from Amaryllidaceae plants,[35] and another one involved adsorption onto and elution from a cation exchange resin as the key step.[36–38]

2.2 Biosynthetic pathways

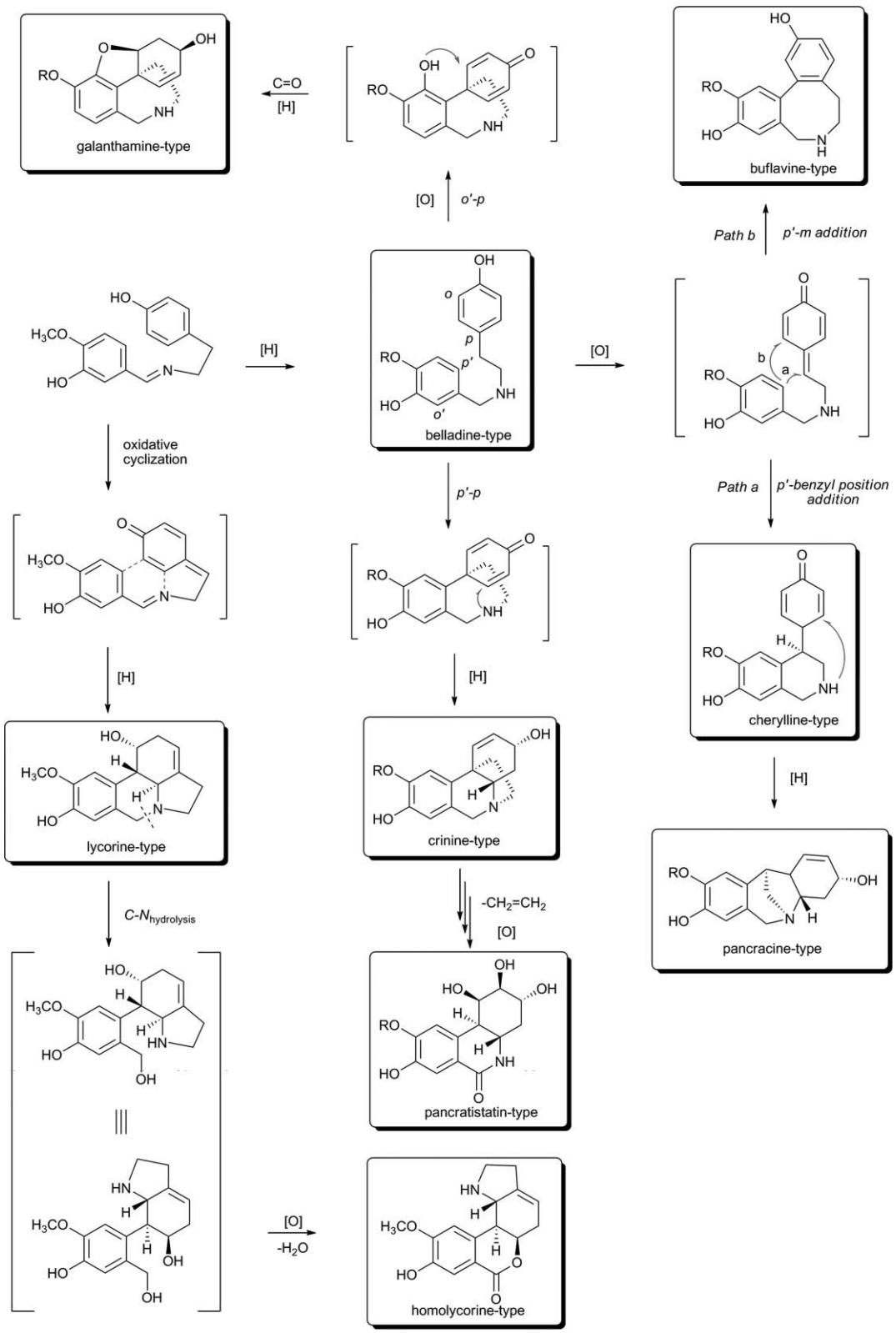
Although the Amaryllidaceae alkaloids have diverse structural architectures, they are all biogenetically derived from norbelladine **97** or its derivatives, which are produced in plants from aromatic aldehydes and tyramine (Scheme 1). The primary metabolic processes leading to the Amaryllidaceae alkaloids include: a) intramolecular phenol oxidative coupling, b) biocatalytic hydrolysis of benzylic C–N bonds, c) reduction of C=O bonds, d) oxidation of C–O and C–H bonds, and e) *O*- and *N*-methylations (Scheme 2 and 3).



97 R = H norbelladine

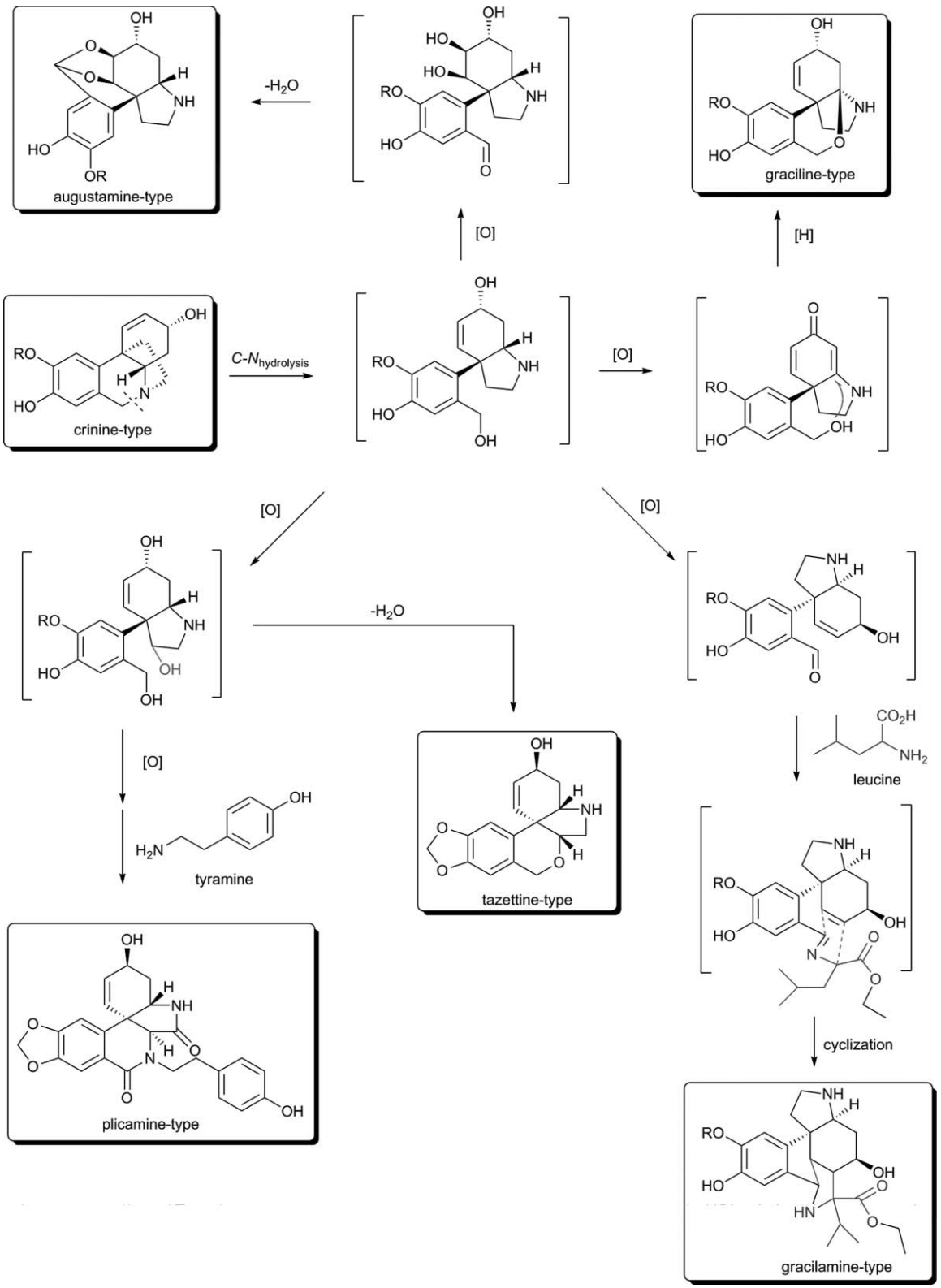
Scheme 1

Intramolecular *p-o′* phenolic oxidative coupling of norbelladine yields the probable dienone intermediate, which provides the galanthamine-type skeleton after hydroxyl cyclization and subsequent carbonyl reduction. Intramolecular addition



Scheme 2 Proposed biosynthetic pathways for the Amaryllidaceae alkaloids (part I).

to the *p*′-position of the electronic-rich aromatic ring to the benzylic position of the oxidised quinonoid form gives 4-aryltetrahydroisoquinoline cherylline-type alkaloids after aromatization (path a). Alternatively, further addition of the secondary amine to the intermediate dienone provides the rare pancracine-type alkaloids. As one of the lesser members of this family, buflavine-type alkaloids might originate from intramolecular addition of the *p*′-position of the electronic-rich aromatic ring to



Scheme 3 Proposed biosynthetic pathways for the Amaryllidaceae alkaloids (part II).

the *m*-position of the quinonoid form (path b) or by rearrangement of some other phenol oxidative coupling intermediate.

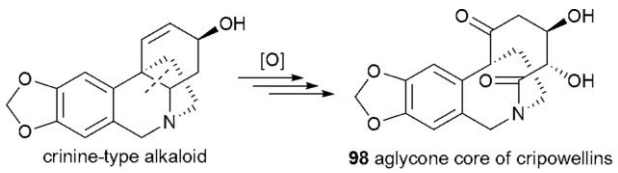
Lycorine-type structures are biosynthesized possibly by intramolecular *p′-o* phenol oxidative coupling of norbelladine or concerted intramolecular cyclization of the iminoquinonoid form; subsequent reduction gives the pyrrolo[*c*]phenanthridine framework. As a derivative species of lycorine-type alkaloids, the biosynthesis of homolycorine-type alkaloids involves biocatalytic oxidation/hydrolysis of the benzylic C–N bond. Cyclization of the hydrogenated 7-arylindole products, which have been isolated as

naturally occurring alkaloids from this plant family,[16] yields the corresponding homolycorine-type skeletons (Scheme 2).

Crinine-type alkaloids, the largest family, are derived from intramolecular oxidative *p′-p* phenolic coupling of norbelladine followed by nucleophilic addition of the amine to the resulting dienone. The rare oxygenated phenanthridine pancratistatin-type alkaloids are probably derived from the crinine-type with loss of a two-carbon unit but further evidence for this hypothesis is required.

Tazettine-type, plicamine-type, augustamine-type, graciline-type and the newly-discovered gracilamine-type alkaloids all come from C–N cleavage products of crinine-type structures, giving hydrogenated 3a-arylindoles, closely related to the *Sceletium* alkaloid skeleton (see section 3). Various oxidative and recyclization processes give the tazettine-type, augustamine-type, and graciline-type alkaloids (Scheme 3). Alternatively, oxidation and insertion of another tyramine unit deliver the unique dinitrogenous plicamine-type alkaloids. Oxidation and cyclization with the amino acid leucine produces another dinitrogenous alkaloid, gracilamine.[3]

The only two members of the glycosidic cripowellin-type alkaloids **7a** and **7b**, isolated by researchers at Bayer AG in 1997, own a unique skeleton among Amaryllidaceae alkaloids. Their common aglycon **98** has a [5.3.2]bicyclic core which might originate from oxidative cleavage of the C2–C3 bond of the tetrahydroisoquinoline moiety in the crinine-type skeleton (Scheme 4).



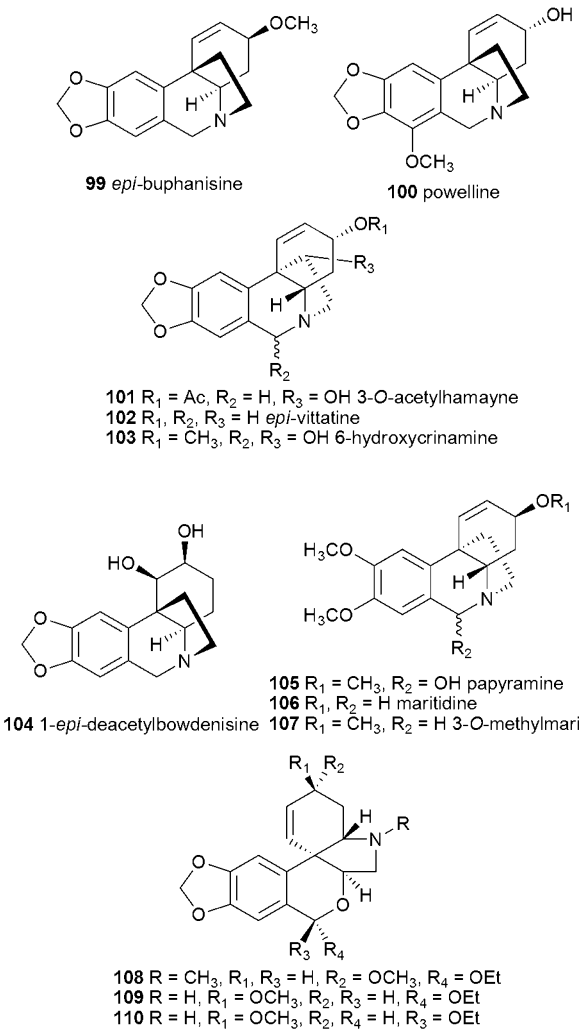
Scheme 4 Biogenetic pathway postulation for the aglycon core of cripowellin alkaloids.

These tentative biogenetic proposals for the known Amaryllidaceae alkaloids were deduced from reported phytochemical investigations and partial chemical syntheses, and should be verified by feeding experiments with isotopically labeled precursors.

2.3 Biological activities

The anti-inflammatory and antibacterial activities of six Amaryllidaceae species in south Africa, *Cyrtanthus falcatus*, *C. mackenii*, *C. suaveolens*, *Gethyllis ciliaris*, *G. multifolia* and *G. villosa*, belonging to two genera of the Amaryllidaceae family, have been investigated.[39] With the exception of the leaf of *C. mackenii*, extracts from all parts of the *Cyrtanthus* species inhibited the growth of at least one bacterium and the bulb/root extracts of *C. suaveolens* showed broad-spectrum antibacterial activity. The extracts from different parts of all species under investigation showed at least 70% anti-inflammatory activity against both COX-1 and COX-2. In addition, the risk associated with the use of these plants in traditional medicine has also been evaluated using *Salmonella*/microsome mutagenicity test methods.

Twenty-one Amaryllidaceae alkaloids, isolated from the different species, have been tested for their affinity to the serotonin reuptake transport protein and for their $GABA_A$-benzodiazepine receptor binding potential.[40] These alkaloids, including crinine **2**, *epi*-buphanisine **99**, powelline **100**, hamayne **32**, 3-*O*-acetylhamayne **101**, *epi*-vittatine **102**, crinamine **29**, 6-hydroxycrinamine **103**, 1-*epi*-deacetylbowdenisine **104**, papyramine **105**, maritidine **106**, 3-*O*-methylmaritidine **107**, tazettine **11**, 8α-ethoxyprecriwelline **108**, *N*-demethyl-8α-ethoxypretazettine **109**, *N*-demethyl-8β-ethoxypretazettine **110**, lycorine **4**, 1-*O*-acetyllycorine **60**, 2-*O*-acetyllycorine **44**, 1,2-*O*-diacetyllycorine **61**, and cherylline **8**, belong to crinine-, tazettine-, lycorine-, and cherylline-type skeletons. Cherylline and *epi*-vittatine showed the highest activity for affinity to the serotonin reuptake transport protein but none of the alkaloids exhibited $GABA_A$-benzodizaepine receptor binding activity.



Molecular mechanism studies against human acute promyelocytic leukemia (APL) cell line HL-60 have shown that alkaloid lycorine **4** could arrest the cell cycle at the G2/M phase and induce apoptosis of HL-60 cells.[41] Lycorine has been shown to differentiate between cells devoid of mtDNA (rho^0) and cells with mtDNA, either rho^+ or rho^-. Wild-type rho^+ cells, neutral rho^- cells, and moderately suppressive rho^- cells are sensitive to lycorine, but rho^0 cells are resistant to high concentrations of alkaloid lycorine due to lack of the RTG retrograde regulator genes.[42] Lycorine isolated from the bulbs of *Pancratium maritimum* collected in the Apulian region has been evaluated for antifungal and antimicrobial activities. The screening data showed that

bacteria are resistant to lycorine, whereas yeasts are very sensitive to it.[43]

Pancratistatin **14**, isolated from the spider lily *Pancratium littorale* (now *Hymenocallis littorale*), has been shown to possess promising antineoplastic activity. Biochemical studies indicated that pancratistatin could induce apoptosis selectively in cancer cells and that the mitochondria may be the site of action.[44,45] Although pancratistatin selectively targets cancerous cells without being cytotoxic to healthy ones, the mechanism of its action is currently unknown. By comparison of synthetic structurally simplified analogues with the natural product itself, the structural elements required for the anticancer activity have been tentatively elucidated.[46]

Strong inhibitory effects of narciclasine **94**, isolated from the bulbs of *Narcissus tazetta*, on callus cells of tobacco and wheat have been observed, showing that narciclasine might be used not only as a new anticancer lead, but also as a new plant growth regulator.[47] In spite of the promising anti-neoplastic activities of the Amaryllidaceae alkaloids such as pancratistatin and narciclasine such secondary metabolites are unavailable in quantity from native bulb tissue and chemical syntheses often require too many chemical steps with extremely disappointing overall yields, which has seriously limited their therapeutic application. An alternative strategy has been proposed which involves enhancing the natural abilities of *Hymenocallis* sp. (tropical spider lily) to produce these bioactive alkaloids by plant tissue culture.[48]

Alzheimer's disease (AD), a progressive neurodegenerative disorder of the central nervous system, is characterized by selective cholinergic neuronal loss, extracellular accumulation of amyloid-β-peptide (Aβ) deposits and abnormal intracellular phosphorylated tau protein. Cholinergic function impairment such as acetylcholine (ACh) deficiency is of critical importance in AD.[49–51] Inhibition of acetylcholinesterase (AChE) will result in a prolongation of the existence of ACh. Over the past decade, a number of AChE inhibitors from chemical synthesis and natural sources have been developed for the treatment of AD.[52–54] Galanthamine **3**, isolated from the plants of the Amaryllidaceae family, is a selective, reversible, competitive, naturally occurring AChE inhibitor.[55–60] It has recently been approved for the symptomatic treatment of AD by the European Union and the United States (Reminyl®).

In studies aimed at increasing the production of galanthamine **3** and other related Amaryllidaceae alkaloids, it has been found that addition of methyl jasmonate increased the amount of alkaloids released to the liquid culture medium and accumulated in the tissues by up to 300% compared to the control explants.[61]

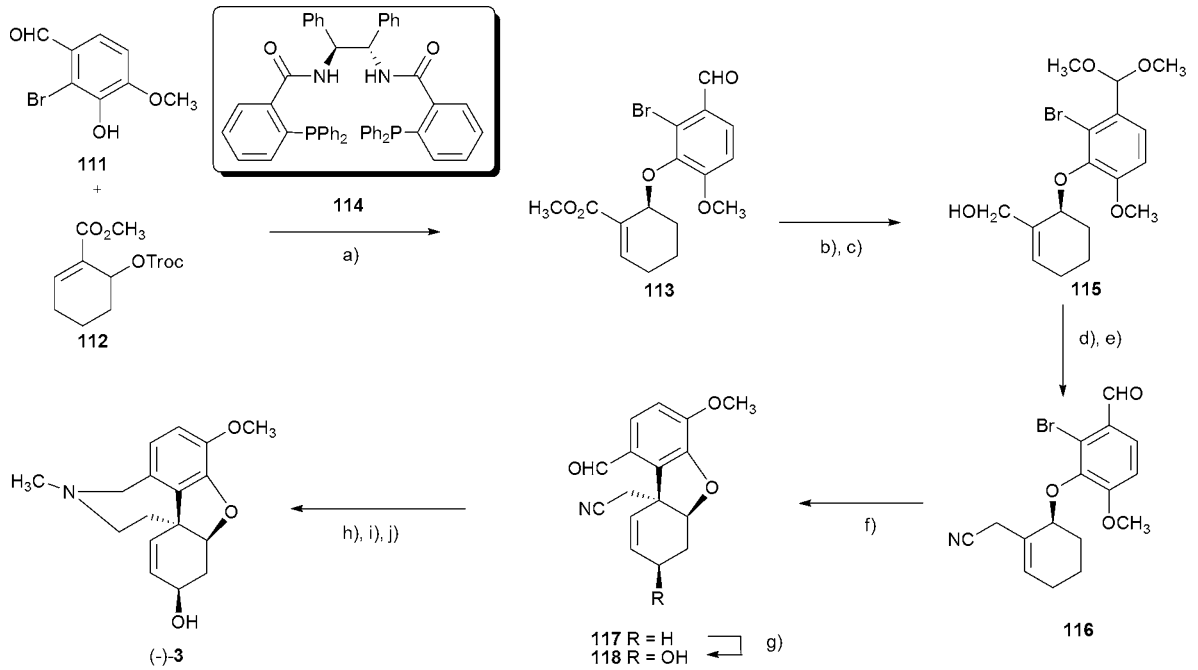
The aqueous leaf extracts of *Crinum bulbispermum* Brum., traditionally used as folk medicine in Sri Lanka, were tested for their antinociceptive activity.[62] The results indicated that the antinociceptive activity of the extracts is mediated both spinally and supraspinally. In addition, the extracts are effective against phasic and continuous non-inflammatory/inflammatory pain. The quantitative determination of galanthamine **3** and lycorine **4** from Turkish *Galanthus nivalis* subsp. *cilicicus* has been carried out using UV spectrometry combined with TLC. On the basis of a brine shrimp lethality bioassay, it was observed that all of the alkaloidal extracts showed meaningful cytotoxic activity.[63] Various extracts of the bulbs and aerial parts of two Amaryllidaceae species, *Sternbergia sicula* and *Sternbergia lutea*, have been prepared and tested for their antimicrobial and antifungal activity.[64] It was concluded that the alkaloid constituents present in *S. sicula* and *S. lutea* might contribute to the observed antimicrobial activity. Because of the putative effects on components of the immune system and inflammatory response, the extracts of the bulb of *Boophane disticha* were examined for their effect on ATP production in isolated human neutrophils.[65] ATP production was significantly decreased by ethanol extracts of the bulbs. *Curculigo orchioides* Gaertn. is a plant species of the Amaryllidaceae family found in India in the subtropical Himalayas. The methanolic extract of rhizomes of *C. orchioides* showed clear immunostimulatory activity and has potential as a protective agent against cytotoxic drugs.[66]

2.4 Total syntheses of alkaloids and their analogues

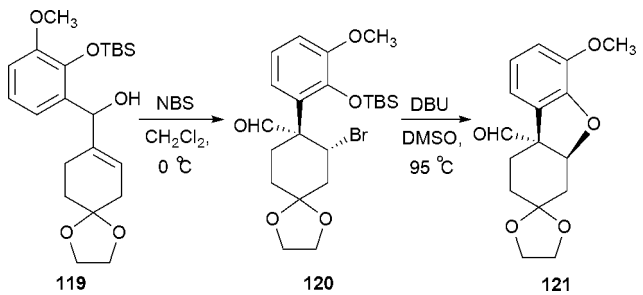
The important biological activities and limited availability from natural sources of the Amaryllidaceae alkaloids have made them attractive synthetic targets for the chemical community. Recently, a large number of novel methods for the efficient construction of *N*-containing heterocycles such as pyrroles, indoles, and carbazoles have been developed using organometallic chemistry methods and applied to total syntheses of natural products including the Amaryllidaceae alkaloids.[67]

2.4.1 Galanthamine-type alkaloids. Galanthamine, a selective, reversible, competitive AChE inhibitor for the treatment of AD, is the first commercial natural product from the Amaryllidaceae family. Much attention has been paid to its chemical synthesis and pharmacology.[68,69] Three enantioselective synthetic strategies for (−)-galanthamine **3** have been developed by Trost's group.[70] All the methodologies featured the sequential palladium-mediated asymmetric allylic alkylation (AAA) and Heck cyclization reactions and all the stereochemistry originated from the AAA reactions as well. Palladium-catalyzed AAA reaction of bromophenol **111** and ester-substituted allylic carbonate **112**, prepared from commercial available glutaraldehyde in two steps, smoothly afforded aryl ether **113** with satisfying enantioselectivity in the presence of the stilbene diamine ligand **114**. The key intermediate **113** was firstly protected as its dimethylacetal and then selectively reduced with diisobutylaluminium hydride (DIBAL-H) to give allylic alcohol **115**. Using a modified Mitsunobu protocol, the β,γ-unsaturated nitrile **116** was obtained after subsequent acid hydrolysis. The Heck-reaction product **117** was produced in high yield under the catalysis of diphenylphosphinopropane (dppp) and $Pd(OAc)_2$. Treatment of olefin **117** with SeO_2 in dioxane provided allylic alcohol **118** in moderate yield. Imine formation with methylamine followed by concomitant reduction of the imine and nitrile by DIBAL-H followed by treatment with sodium cyanoborohydride completed the synthesis of (−)-galanthamine **3** (Scheme 5).

Two new total syntheses of (±)-galanthamine **3** and (±)-lycoramine **88** (3,4-dihydrogalanthamine) have recently been reported and both featured a successive semipinacol rearrangement strategy to construct the core structure.[71,72] NBS-Induced semipinacol rearrangement of allylic alcohol **119** built the quaternary carbon center **120** to deliver the key core unit **121** (Scheme 6). Using intramolecular Heck cyclization to construct the seven-membered benzazepine ring as the key step, another new total synthesis of (±)-lycoramine **88** has been achieved by Liang and

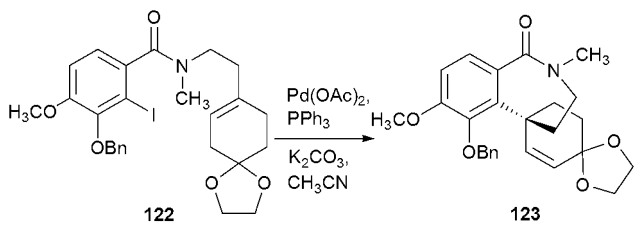


Scheme 5 *Reagents and conditions*: a) 1 mol% $[(\eta^3\text{-}C_3H_5)PdCl]_2$, **114**, Et_3N, CH_2Cl_2; b) 1.5 mol% TsOH, $CH(OCH_3)_3$, CH_3OH; c) DIBAL-H, toluene, −78 °C; d) Ph_3P, acetone cyanohydrin, DIAD, Et_2O; e) 2.20 mol% TsOH, THF, H_2O; f) 15 mol% $Pd(OAc)_2$, 15 mol% dppp, 3 equiv. of Ag_2CO_3, toluene, 107 °C; g) SeO_2, NaH_2PO_4, dioxane, 150 °C, 3 h; h) CH_3NH_2, CH_3OH; i) 4 equiv. DIBAL-H, then NaH_2PO_4; j) $NaCNBH_3$.



Scheme 6

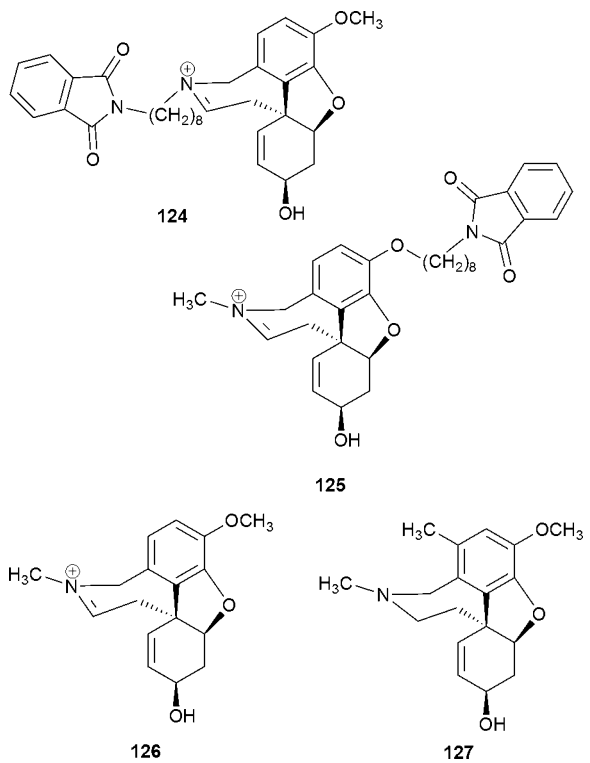
co-workers.[73] Palladium-catalyzed intramolecular Heck coupling of functionalized amide **122** afforded the desired core unit **123** of the natural product (Scheme 7). As the important metabolic precursor of galanthamine **3**, synthesis and resolution of narwedine **87** as well as conversion to galanthamine have been covered in several patent documents.[74–77]

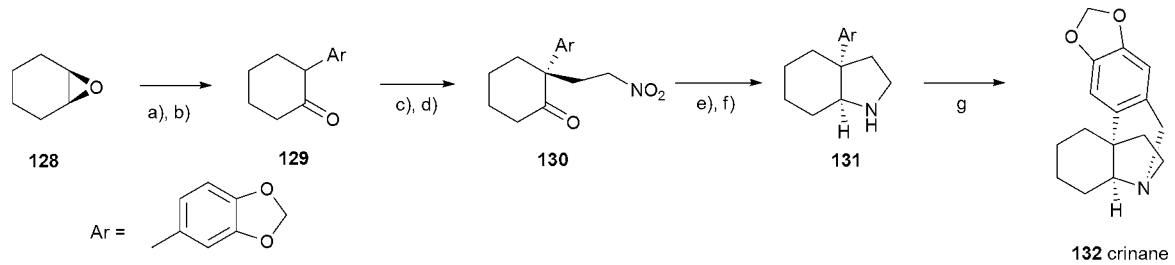


Scheme 7

Based on the chelate effect of bisfunctional groups, three immonium derivatives **124–126** of galanthamine have been prepared and the crystal structures of complexes of *Torpedo californica* AChE (*Tc*AChE) with them have been determined.[78]

The inhibitory constants for inhibition of *Tc*AChE by these three compounds were compared with values obtained for *Electrophorus electricus* AChE (*Ee*AChE). Numerous galanthamine analogues such as 9-methylgalanthamines **127**,[79] 8-substituted galanthamines,[80] isoxazolo[3,2-*a*]-fused derivatives,[81] nitrogen position-altered analogues,[82] and others[83] have been prepared for structure–activity relationship studies.



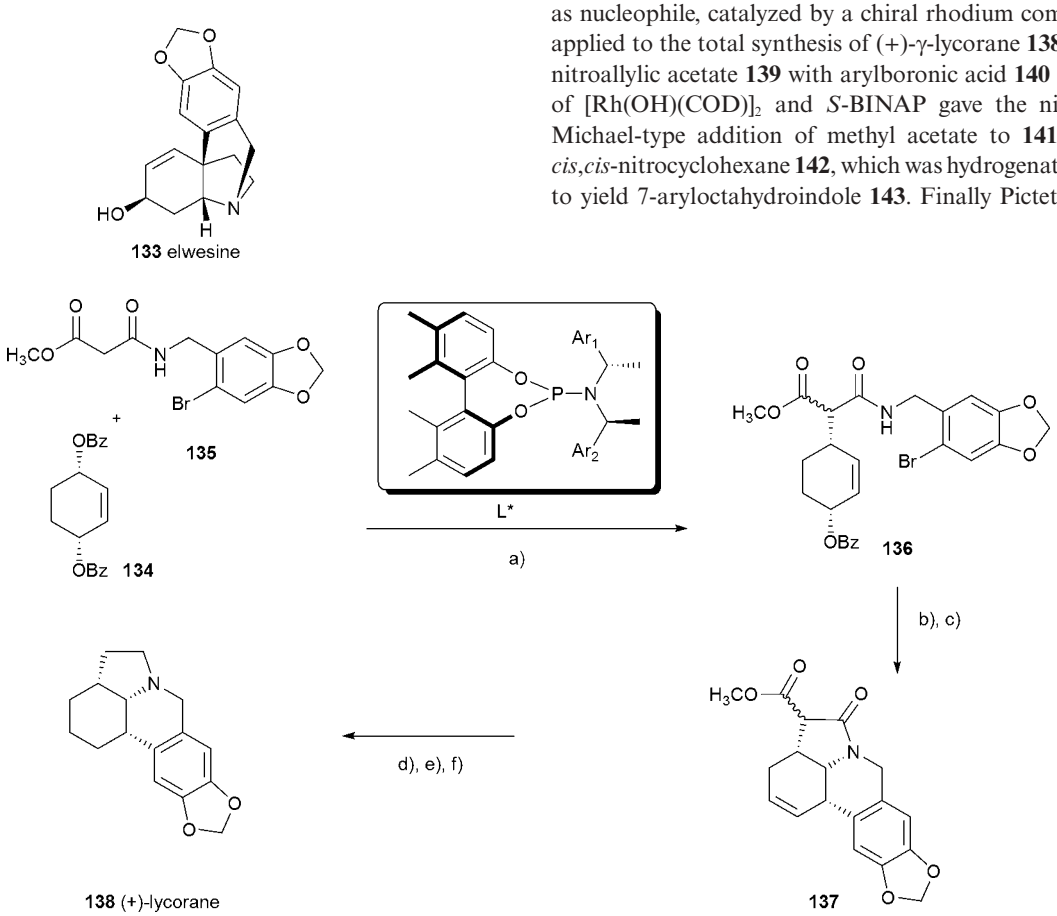


Scheme 8 *Reagents and conditions*: a) ArLi, BF_3Et_2O, THF, −78 °C; b) PCC, CH_2Cl_2; c) TMSCl, DMF, Et_3N, 130 °C; d) CH_3Li, THF, 0 °C, 30 min, then HMPA, −78 °C, 30 min, then nitroethylene; e) Raney-Ni, EtOH, 3 h; f) $NaBH_3CN$, AcOH, 30 min; g) Eschenmoser's salt, THF, 24 h.

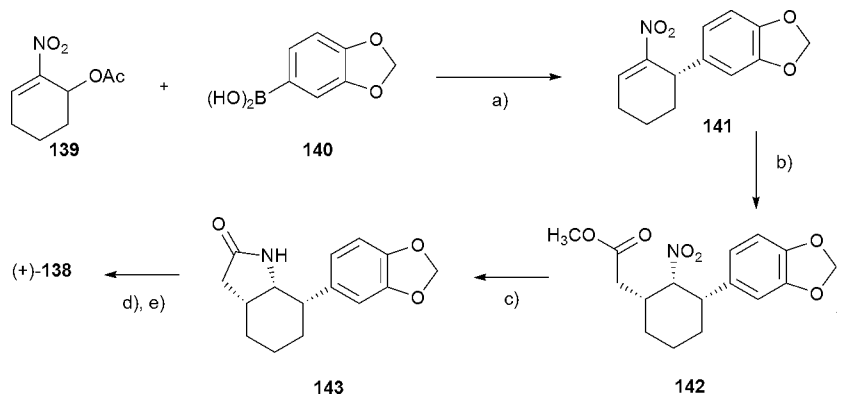
2.4.2 Crinine-type alkaloids. Crinine- and lycorine-type alkaloids, the two largest families of Amaryllidaceae alkaloids, possess *cis*-3a-arylindole and 7-arylindole frameworks, respectively. Tu and coworkers have developed an efficient strategy for the *cis*-3a-aryloctahydroindole structure from commercially available cyclohexene oxide **128** and therefore, a concise total synthesis of (±)-crinane **132** has been accomplished (Scheme 8).[84] The thermodynamic lithium enolate of 2-arylcyclohexanone **129** was trapped by nitroethylene and intramolecular reductive amination then furnished the key 3a-aryloctahydroindole moiety **131**. The corresponding reactions of the kinetic lithium enolate of 2-arylcyclohexanone led to 7-aryloctahydroindole. Additionally, synthetic approaches towards the skeleton of the crinine-type Amaryllidaceae alkaloids from isoquinoline have been extensively explored which led to a total synthesis of (±)-elwesine **133**.[85]

2.4.3 Lycorine-type alkaloids. A fine-tunable biphenol-based chiral monodentate ligand library has been screened for the intramolecular palladium-catalyzed asymmetric allylic alkylation (AAA) reaction. On the basis of the screening results, an efficient enantioselective total synthesis of (+)-γ-lycorane **138** was achieved.[86,87] The desymmetrization of *cis*-1,4-dibenzoyloxycyclohex-2-ene with nucleophile **135** gave product **136** under catalysis of biphenol-based chiral monodentate phosphoramidite ligand/palladium complex. Subsequently, pentacyclic skeleton **137** was built through a one-pot, tandem allylic amination–intramolecular Heck reaction. Finally, sequential demethoxycarbonylation, hydrogenation, and reduction provided the desired (+)-γ-lycorane **138** in six steps with an overall yield of 41% (Scheme 9).

An asymmetric allylation alkylation with an arylboronic acid as nucleophile, catalyzed by a chiral rhodium complex, has been applied to the total synthesis of (+)-γ-lycorane **138**.[88] Reaction of nitroallylic acetate **139** with arylboronic acid **140** in the presence of $[Rh(OH)(COD)]_2$ and *S*-BINAP gave the nitroethene **141**. Michael-type addition of methyl acetate to **141** furnished the *cis*,*cis*-nitrocyclohexane **142**, which was hydrogenated and cyclized to yield 7-aryloctahydroindole **143**. Finally Pictet–Spengler-type



Scheme 9 *Reagents and conditions*: a) 2 mol% $[(\eta^3\text{-}C_3H_5)PdCl]_2$, **L***, LDA, THF; b) 5 mol% $Pd(OAc)_2$, 10 mol% dppb, 1.1 equiv. NaH, DMF, 50 °C, 3 h; c) 2 equiv. Et(*i*-Pr)$_2$N, 110 °C, 8 h; d) 3 equiv. NaCl, DMSO–H_2O (3 : 1), 175 °C, 12 h; e) 5% Pd/C, H_2, MeOH, rt, 1.5 h; f) $LiAlH_4$, THF, reflux, 1.5 h.

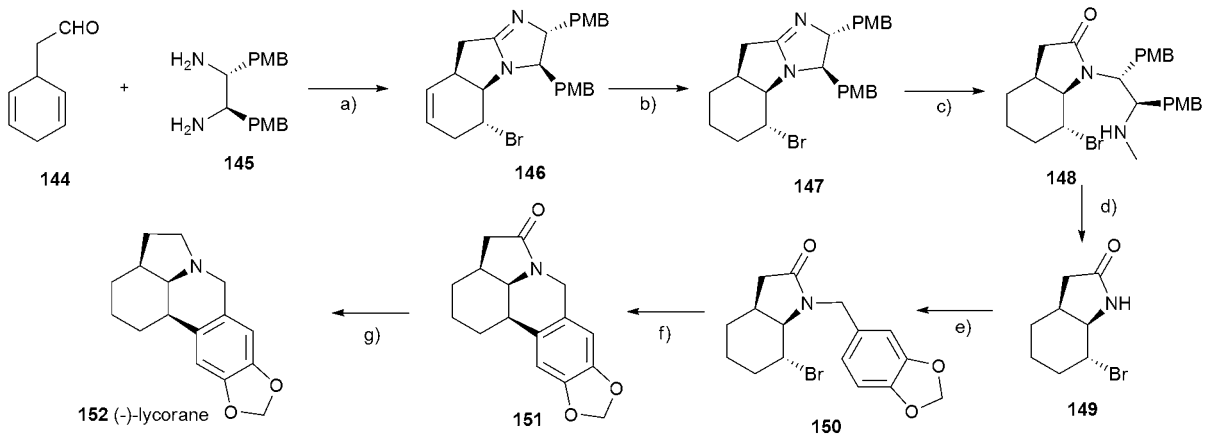


Scheme 10 *Reagents and conditions*: a) 5 mol% $[RhOH(COD)]_2$, 6 mol% *S*-BINAP, dioxane–H_2O (10 : 1), 50 °C, 20 h; b) $CH_3CO_2CH_3$, LDA, THF, −78 °C, 5 h; c) Raney-Ni, H_2 (80 atm), 55 °C, 24 h; d) $(CH_2O)_n$, CF_3CO_2H, $ClCH_2CH_2Cl$, rt, 24 h; e) $LiAlH_4$, THF, reflux, 18 h.

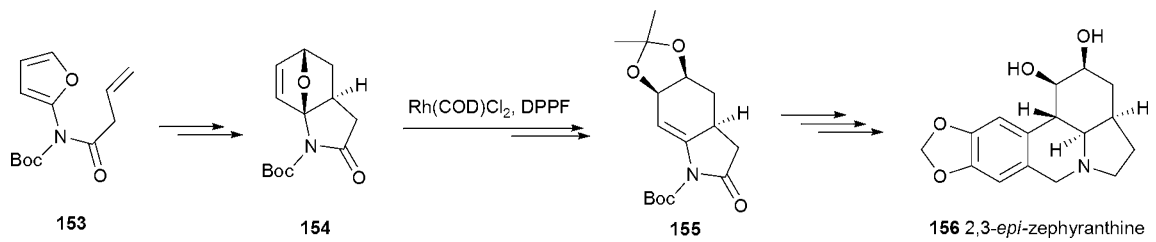
cyclisation and reduction of the amide gave enantiopure (+)-**138** (Scheme 10).

A concise asymmetric total synthesis of (−)-lycorane **152** has been recently reported by Kita's group featuring an asymmetric intramolecular bromo-amination as the key step.[89] One-pot reaction of the cyclohexadiene **144** with enantiopure 1,2-diamine **145** and NBS gave bromide **146** as a single isomer. Hydrogenation followed by methylation and alkaline hydrolysis produced lactam **148** and cleavage of the chiral auxiliary group gave amide **149**. Alkylation of the nitrogen atom and intramolecular Friedel–Crafts-type reaction of **150** finally constructed the all *cis* skeleton of (−)-lycorane (Scheme 11).

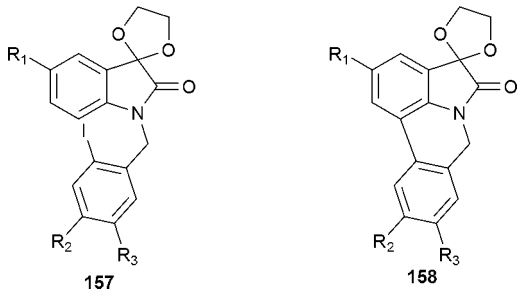
By application of a $[Rh(COD)Cl]_2$-catalyzed ring-opening strategy, oxabicyclo cycloadduct **154** derived from imidofuran **153** has efficiently furnished the key hexahydroindolinone unit **155** which was transformed into the alkaloid *epi*-zephyranthine **156** (Scheme 12).[90] In model studies toward the total synthesis of alkaloid kirkine **67**, a radical cascade reaction strategy has been used to construct the central carbon skeleton of the alkaloid.[91] Pd-mediated biaryl coupling reaction has proven to be efficient method for the synthesis of pyrrolo[3,2,1-*de*]phenanthridine alkaloids.[92–94] The oxopyrrolophenanthridine derivatives **158** could be obtained from related oxoindole substrates **157** in more than 85% yield under the catalysis of $Pd(OAc)_2$.



Scheme 11 *Reagents and conditions*: a) 2.1 equiv. NBS, CH_2Cl_2; b) H_2, $Pd(OH)_2$, AcOH, AcOEt; c) MeI, then 10% NaOH (aq), MeOH; d) H_2SO_4, CF_3CO_2H; e) $ArCH_2Cl$, NaH, NaI, THF, 50 °C; f) $AgBF_4$, CF_3CH_2OH; g) $LiAlH_4$.

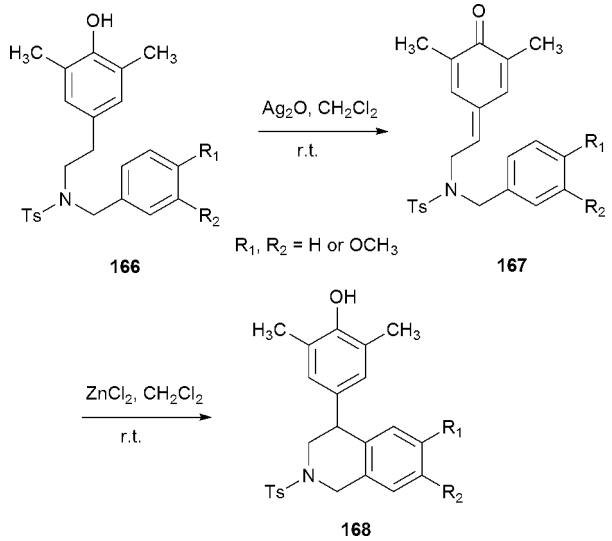


Scheme 12



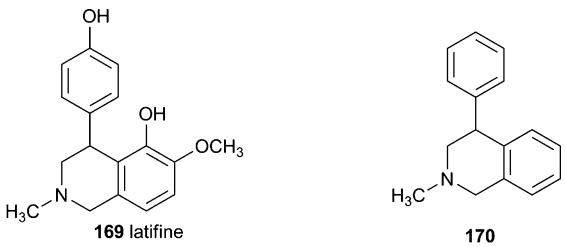
2.4.4 Pancracine-type alkaloids. An intramolecular [2 + 3] 1,3-dipolar cycloaddition strategy involving nonstabilized azomethine ylide and methyl vinyl ketone (MVK) has been applied to construct the core structure of alkaloid pancracine **6** by Pandey and coworkers.[95] Alkylation of **160** followed by protection of the hydroxyl group gave the ester **161**, which was coupled with methyl vinyl ketone using the standard Heck procedure to provide the key cyclization precursor **162**. Ag(I)-mediated [2 + 3] cycloaddition between azomethine ylide and methyl vinyl ketone MVK yielded the corresponding tetracyclic derivative **163**. Subsequently, a cyclisation *via* the kinetic enolate successfully delivered the skeleton **164** of pancracine-type alkaloids. Finally, reduction of the corresponding enol triflate using $Pd(PPh_3)_4/Et_3SiH$ generated deoxypancracine **165** which has previously been transformed into (±)-**6** (Scheme 13). In addition, Chang and coworkers have reported a synthetic study toward pancracine **6** starting from *trans*-2(*S*,4*R*)-4-hydroxyproline.[96]

2.4.5 Cherylline-type alkaloids. A synthetic methodology for producing *p*-quinone methides *in situ* has been developed by Raju and coworkers.[97] Oxidation of *p*-substituted phenol **166** with Ag_2O in dry CH_2Cl_2 at room temperature gave the corresponding isolable *p*-quinone methide **167**, which yielded the tetrahydroisoquinoline skeleton **168** of cherylline-type alkaloids cherylline **8** and latifine **169** after stirring in dry CH_2Cl_2 at room temperature in the presence of $ZnCl_2$ (Scheme 14). This important cyclization process probably relates to the biosynthetic pathway of the cherylline-type Amaryllidaceae alkaloids.

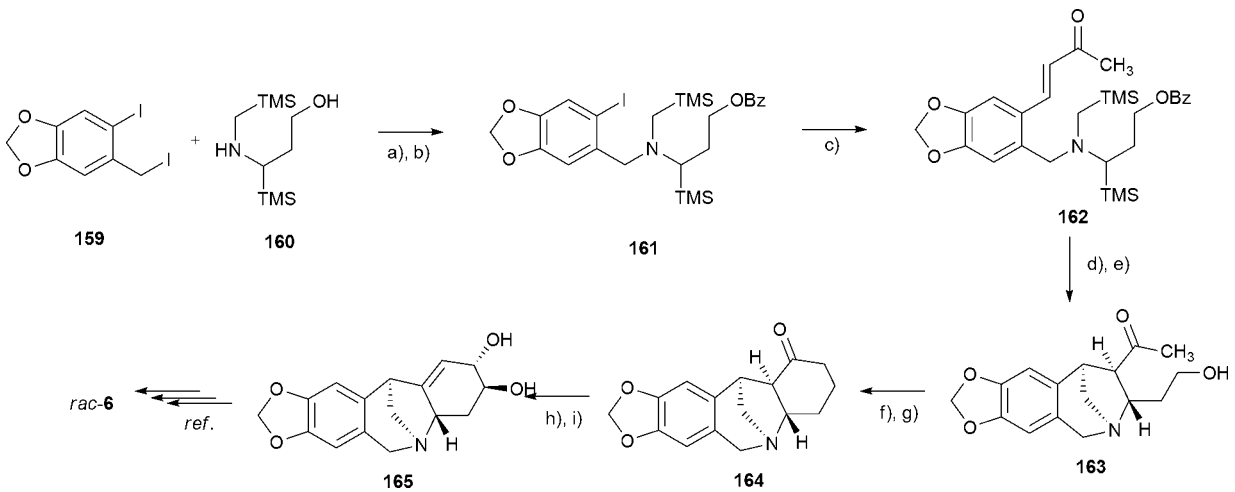


Scheme 14

Using oxazoline as a useful synthetic tool, Seijas and coworkers have synthesized the 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton **170** of cherylline-type alkaloids by 1,6-conjugate addition of a nitrogen nucleophile.[98]

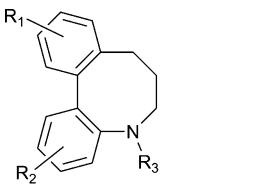


2.4.6 Buflavine-type alkaloids. Buflavine-type alkaloids, *e.g.* **9**, feature a rare 5,6,7,8-tetrahydrodibenzo[*c*,*e*]azocine skeleton composed of a biaryl-incorporated eight-membered *N*-heterocyclic ring. A new six-step synthetic sequence has been developed for the synthesis of *N*-shift buflavine analogues



Scheme 13 *Reagents and conditions*: a) K_2CO_3, CH_3CN; b) BzCl, Et_3N, CH_2Cl_2; c) $Pd(OAc)_2$, Ph_3P, K_2CO_3, MVK; d) AgF, CH_3CN; e) LiOH, MeOH, rt; f) MsCl, Et_3N; g) KHMDS, THF, −78 °C; h) LDA, THF, Comins reagent, −78 °C; i) $Pd(PPh_3)_4$, Et_3SiH, LiCl, THF.

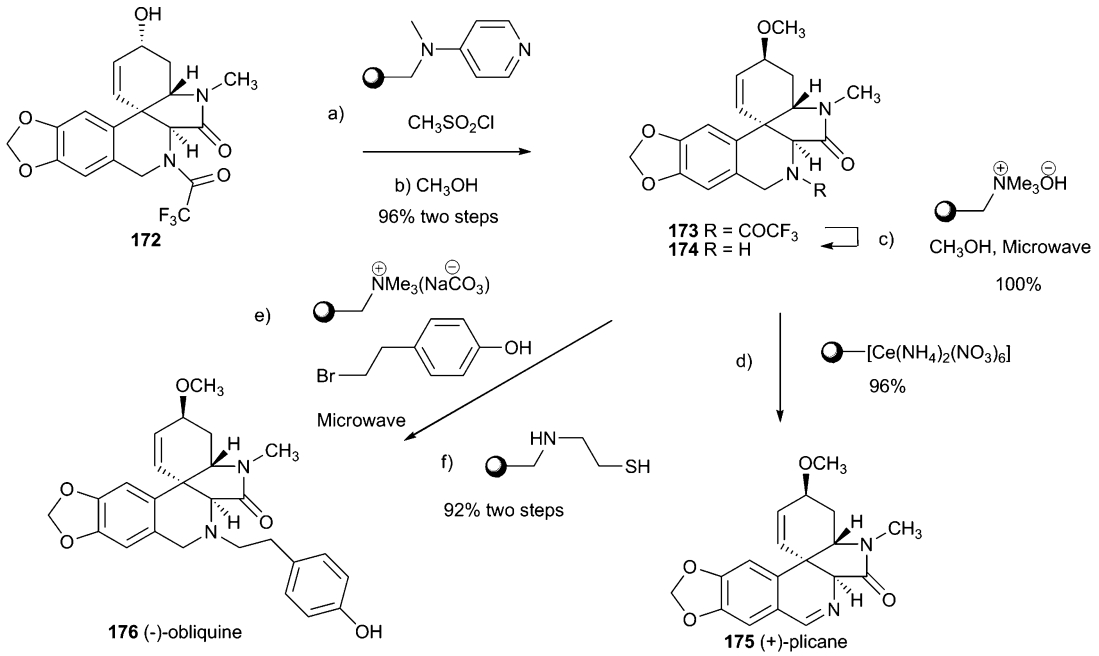
171, which featured microwave-enhanced Suzuki–Miyaura cross-coupling and ring-closing metathesis reactions as the key steps.[99]



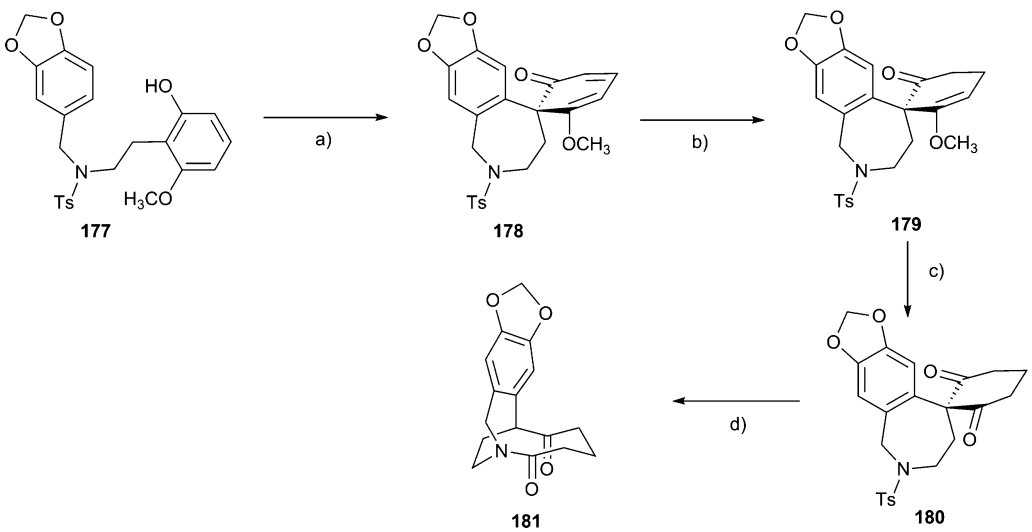
171 R_1, R_2 = H or OCH_3; R_3 = Boc

2.4.7 Plicamine-type alkaloids. Starting from the common intermediate **172**, prepared previously, two naturally occurring Amaryllidaceae alkaloids, (+)-plicane **175** and (−)-obliquine **176**, have been synthesized in high yields and purity by using polymer-supported reagents and scavengers (Scheme 15).[100] In addition, their 3-*epi* isomers have been prepared in an identical manner.

2.4.8 Cripowellin-type alkaloids. Cripowellins A **7a** and B **7b** are structurally unique members of the Amaryllidaceae alkaloids with a 10-membered fused [5.3.2]bicyclic lactam core. Employing an intramolecular phenol oxidative coupling procedure, the [5.3.2]bicyclic lactam unit **181** of the cripowellin-type alkaloids has been constructed by Moon and coworkers.[101] PIFA-Mediated oxidative phenolic coupling of phenol **177** afforded the spirobenzazepin intermediate **178**. Then, 1,4-conjugate reduction by Stryker's reagent [$(Ph_3PCuH)_6$] followed by acidic hydrolysis of methyl enol ether **179** provided spirocyclohexanedione **180**. Finally, removal of the tosyl group caused spontaneous rearrangement to the bicyclic skeleton **181** of the cripowellin alkaloids (Scheme 16).



Scheme 15

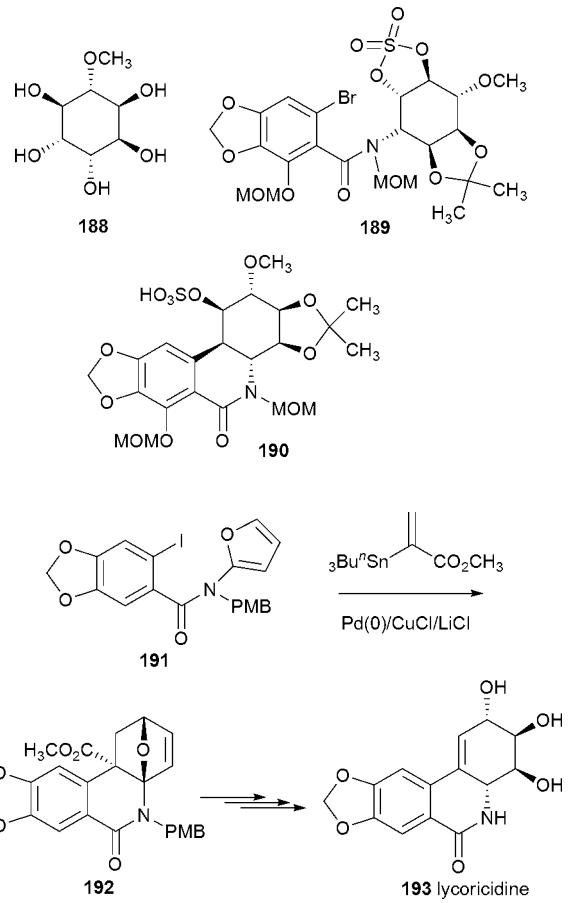


Scheme 16 *Reagents and conditions*: a) PIFA, CF_3CH_2OH, rt; b) $[PPh_3CuH]_6$; c) aq. HCl; d) Na-naphthalene, DME, then H_2O.

Enders and coworkers have recently devised an asymmetric synthetic approach to the 1-*epi*-aglycone **187** of the cripowellin alkaloids.[102,103] With catalysis by the second-generation Grubbs' catalyst, the RCM precursor diene **182**, whose stereochemistry arose from a highly enantioselective Sharpless dihydroxylation, was transformed into nine-membered lactam **183**. Subsequently, trisubstituted olefin **184** was formed by a Heck reaction. Olefin **184** was transformed into the α-hydroxy ketone **185** in a two-step sequence consisting of dihydroxylation and Swern oxidation. Deoxygenation of **185** with SmI_2 proceeded smoothly to give **186**, which delivered the 1-*epi*-aglycone **187** after deprotection of the acetonide group (Scheme 17).

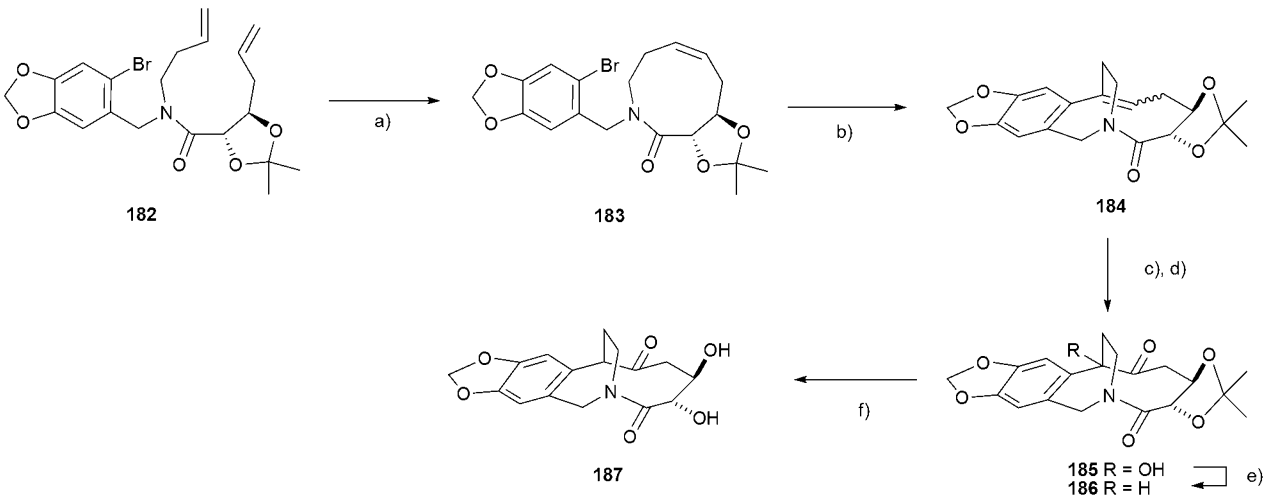
2.4.9 Pancratistatin-type alkaloids. Due to their antitumor activity, as well as their complicated stereochemistry, pancratistatin-type alkaloids have been an intriguing focus for synthetic chemists.[104,105] A concise total synthesis of (+)-pancratistatin **14** has been completed from pinitol **188** by employing an arylcerium induced substitution reaction.[106] Cyclic sulfate **189** was treated with one equivalent of *t*-BuLi followed by addition of anhydrous $CeCl_3$ to effect the key nucleophilic substitution to give **190**. Additionally, several other strategies,[107–109] such as ring-closing metathesis and conjugate addition of arylcuprates, have been investigated for building the multi-functionalized ring C of the pancratistatin skeleton.

An efficient total synthesis of (±)-lycoricidine has been reported by Zhang and Padwa, with the highlights being a Pd(0)-mediated Stille coupling and a tandem [4 + 2]-cycloaddition reaction of 2-amidofuran.[110,111] Amidofuran **191** was coupled with methyl 2-tri-*n*-butylstannylacrylate using a combination of CuCl/Pd(0)/LiCl to give the expected cross-coupled amidofuran intermediate, which spontaneously underwent an intramolecular [4 + 2]-cycloadditon to furnish cycloadduct **192**. Finally, stereocontrolled installation of the other functionality in the C ring of the alkaloid provided (±)-lycoricidine **193** (Scheme 18). In a similar manner, the same authors have accomplished the total synthesis of (±)-7-deoxypancratistatin **194**.[112]



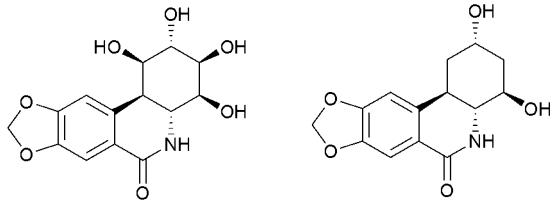
Scheme 18

Additionally, a number of naturally occurring pancratistatin-type alkaloids and their analogues, including (+)-7-deoxy-*trans*-dihydronarciclasine **96**,[113] 3-deoxydihydrolycoricidine **195**,[114] lactone analogues **196** of narciclasine and lycoricidine,[115] β-carboline-1-one mimic **197** of pancratistatin,[116,117] aromatic deoxygenated



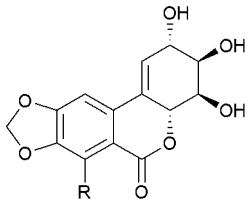
Scheme 17 *Reagents and conditions*: a) 0.1 equiv. 2nd generation Grubbs' catalyst, CH_2Cl_2, reflux, 2.5 h, then 5.0 equiv. DMSO, 25 °C, 12 h; b) 0.15 equiv. $Pd(OAc)_2$, 0.2 equiv. dppp, 3.0 equiv. Ag_2CO_3, toluene, 124 °C, 4 h; c) 0.05 equiv. $K_2OsO_4{\cdot}2H_2O$, 3.1 equiv. NMO, acetone–H_2O (10 : 7), 25 °C, 3 h, then 2.3 equiv. Na_2SO_3; d) 2.5 equiv. CO_2Cl_2, 5.3 equiv. DMSO, 10.0 equiv. Et_3N, CH_2Cl_2, −78 to 25 °C, e) excess SmI_2, 3.0 equiv. *t*BuOH, THF, 25 °C, 12 h; f) Dowex-50, H_2O, 25 °C, 4.25 h.

analogue **198** of pancratistatin,[118] and others,[119,120] have been synthesized and evaluated for antitumor activities.

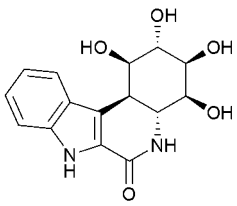


194 7-deoxypancratistatin

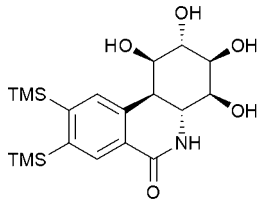
195



196 R = H or OCH_3

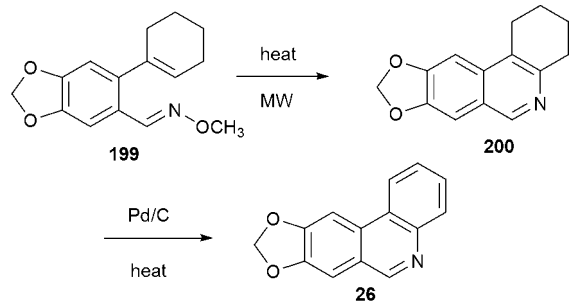


197



198

A highly efficient total synthesis of phenanthridine alkaloid trisphaeridine **26** has been completed in a four-step cascade utilizing a microwave-assisted thermal electrocyclic reaction of an aza 6π-electron system **199** as the key step (Scheme 19).[121]

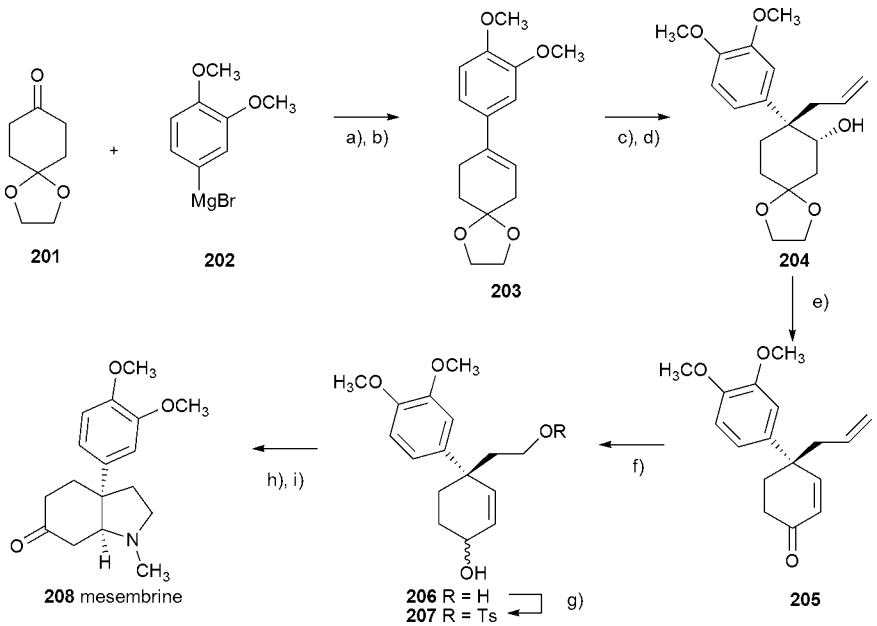


199 **200** **26**

Scheme 19

3 *Sceletium* alkaloids

An efficient enantioselective total synthesis of *Sceletium* alkaloid (−)-mesembrine **208**, isolated as the major component from *Sceletium tortuosum*, has been achieved by Taber and He.[122] The key step of the synthetic strategy was construction of the quaternary stereogenic center by a preferential addition of allyl Grignard reagent to an epoxide at the more hindered benzylic position (Scheme 20). The cyclohexanone **201** reacted with the aromatic Grignard reagent **202** to give the alkene **203** after dehydration in the presence of PTSA. Shi epoxidation of **203** followed by allylmagnesium chloride gave the enantiomerically enriched secondary alcohol **204**, which was well-resolved by chiral HPLC in 96% ee. Exposure of **204** to aqueous HCl gave the enone **205**. Selective ozonolysis of the terminal double bond in **205** followed by treatment of the resulting ozonide *in situ* with $NaBH_4$ in the presence of $CeCl_3$ delivered the diol **206**. The primary hydroxyl group in **206** was selectively converted into the corresponding tosylate **207**, which finally provided (−)-mesembrine **208** on heating with aqueous methylamine followed by oxidation using activated MnO_2.



201 **202** **203** **204** **205** **206** R = H **207** R = Ts **208** mesembrine

Scheme 20 *Reagents and conditions*: a) THF, 0 to 20 °C, overnight; b) PTSA, benzene, ethylene glycol, reflux; c) Shi's catalyst, DME–acetonitrile–H_2O, 0 °C, 4 h; d) allymagnesium chloride, THF, 0 to 20 °C, overnight; e) 10% aq. HCl, THF, reflux, 1 h; f) O_3, MeOH, −78 °C, then 1.0 equiv. $CeCl_3 \cdot 7H_2O$, 8.0 equiv. $NaBH_4$, 0 °C; g) 1.0 equiv. TsCl, Et_3N, CH_2Cl_2, 20 °C, overnight; h) 40% aq. $MeNH_2$, THF, 65 °C; i) MnO_2, CH_2Cl_2, 20 °C, 3 h.

4 References

1 M. J. Balunas and A. D. Kinghorn, *Life Sci.*, 2005, **78**, 431–441.
2 Z. Jin, *Nat. Prod. Rep.*, 2005, **22**, 111–126.
3 N. Unver and G. I. Kaya, *Turk. J. Chem.*, 2005, **29**, 547–553.
4 J. J. Nair, W. E. Campbell, R. Brun, F. Viladomat, C. Codina and J. Bastida, *Phytochemistry*, 2005, **66**, 373–382.
5 O. B. Abdel-Halim, T. Morikawa, S. Ando, H. Matsuda and M. Yoshikawa, *J. Nat. Prod.*, 2004, **67**, 1119–1124.
6 P. J. Houghton, J. M. Agbedahunsi and A. Adegbulugbe, *Phytochemistry*, 2004, **65**, 2893–2896.
7 G. I. Kaya, N. Unver, B. Gozler and J. Bastida, *Biochem. Syst. Ecol.*, 2004, **32**, 1059–1062.
8 P. Forgo and J. Hohmann, *J. Nat. Prod.*, 2005, **68**, 1588–1591.
9 A. Evidente, A. Andolfi, A. H. Abou-Donia, S. M. Touema, H. M. Hammoda, E. Shawky and A. Motta, *Phytochemistry*, 2004, **65**, 2113–2118.
10 M. A. Aboul-Ela, A. M. El-Lakany and H. M. Hammoda, *Pharmazie*, 2004, **59**, 894–896.
11 L. Szlavik, A. Gyuris, J. Minarovits, P. Forgo, J. Molnar and J. Hohmann, *Planta Med.*, 2004, **70**, 871–873.
12 K. Rhee, N. Appels, B. Hofte, B. Karabatak, C. Erkelens, L. M. Stark, L. A. Flippin and R. Verpoorte, *Biol. Pharm. Bull.*, 2004, **27**, 1804–1809.
13 J. Kissling, J.-R. Ioset, A. Marston and K. Hostettmann, *Phytother. Res.*, 2005, **19**, 984–987.
14 S. Li, C. Chen, H. Zhang, H. Guo, H. Wang, L. Wang, X. Zhang, S. Hua, J. Yu, P. Xiao, R. Li and X. Tan, *Antiviral Res.*, 2005, **67**, 18–23.
15 G. I. Kaya, A. Fillik, Y. Hisil and N. Unver, *Turk. J. Pharm. Sci.*, 2004, **1**, 105–114.
16 Y. Yang, S.-X. Huang, Y.-M. Zhao, Q.-S. Zhao and H.-D. Sun, *Helv. Chim. Acta*, 2005, **88**, 2550–2553.
17 D. M. Tsakadze, S. A. Samsoniya, R. Ziaev and A. Abdusamatov, *Mol. Diversity*, 2005, **9**, 41–44.
18 C. F. de Jong, R. J. E. Derks, B. Bruyneel, W. Niessen and H. Irth, *J. Chromatogr., A*, 2006, **1112**, 303–310.
19 A. Vrondeli, P. Kefalas and E. Kokkalou, *Pharmazie*, 2005, **60**, 559–560.
20 A. K. Machocho, J. Bastida, C. Codina, F. Viladomat, R. Brun and S. C. Chhabra, *Phytochemistry*, 2004, **65**, 3143–3149.
21 S. Berkov, L. Evstatieva and S. Popov, *Z. Naturforsch., C: Biosci.*, 2004, **59**, 65–69.
22 N. R. Crouch, T. L. Pohl, D. A. Mulholland and E. Ndlovu, *S. Afr. J. Bot.*, 2005, **71**, 49–52.
23 O. Ilkay and S. Bilge, *Acta Hortic.*, 2005, **678**, 59–64.
24 N. R. Crouch, D. A. Mulholland and J. Chetty, *S. Afr. J. Bot.*, 2005, **71**, 104–106.
25 A. H. Abou-Donia, S. M. Toaima, H. M. Hammoda and E. Shawky, *Alexandria J. Pharm. Sci.*, 2005, **19**, 147–152.
26 J. A. Seijas, M. P. Vazquez-Tato, J. Seijo-Muras, P. Ramil-Rego and M. I. Bujan, *International Electronic Conferences on Synthetic Organic Chemistry*, ed. J. A. Seijas, Universidad de Santiago de Compostela, Spain, 2004, pp. 623–624 (*Chem. Abstr.*, 2005, **143**, 363377).
27 S. Berkov, L. Evstatieva, B. Sidjimova and S. Popov, *God. Sofii. Univ. "Sv. Kliment Okhridski", Biol. Fak., Kniga 3*, 2005, **96**, 89–94.
28 M. O. Edema and F. E. Okieimen, *Niger. J. Chem. Res.*, 2004, **7–9**, 25–29, (*Chem. Abstr.*, 2005, **143**, 352948).
29 S. Berkov, A. Pavlov, M. Ilieva, M. Burrus, S. Popov and M. Stanilova, *Phytochem. Anal.*, 2005, **16**, 98–103.
30 A. Jegorov, M. Buchta, P. Sedmera, M. Kuzma and V. Havlicek, *J. Mass Spetrom.*, 2006, **41**, 544–548.
31 N. Rivero, M. Gomez and J. D. Medina, *Pharm. Biol.*, 2004, **42**, 280–285.
32 G. R. Pettit and N. Melody, *J. Nat. Prod.*, 2005, **68**, 207–211.
33 G. R. Pettit, S. A. Eastham, N. Melody, B. Orr, D. L. Herald, J. McGregor, J. C. Knight, D. L. Doubek, G. R. Pettit, III, L. C. Garner and J. A. Bell, *J. Nat. Prod.*, 2006, **69**, 7–13.
34 G. R. Pettit, Y. Meng, D. L. Herald, J. C. Knight and J. F. Day, *J. Nat. Prod.*, 2005, **68**, 1256–1258.
35 H. Fu, W. Kuang, X. Wang, X. He and N. Wang, *Chin. Pat.*, 1 583 749, 2005; H. Fu, W. Kuang, X. Wang, X. He and N. Wang, *Chem. Abstr.*, 2005, **143**, 435398.
36 H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chin. Pat.*, 1 611 504, 2005; H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chem. Abstr.*, 2006, **144**, 428527.
37 H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chin. Pat.*, 1 611 502, 2005; H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chem. Abstr.*, 2006, **144**, 428526.
38 H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chin. Pat.*, 1 611 503, 2005; H. Fu, N. Wang, X. He, X. Wang and W. Kuang, *Chem. Abstr.*, 2006, **144**, 428525.
39 E. E. Elgorashi and J. van Staden, *J. Ethnopharmacol.*, 2004, **90**, 27–32.
40 E. E. Elgorashi, G. I. Stafford, A. K. Jager and J. van Staden, *Planta Med.*, 2006, **72**, 470–473.
41 J. Liu, W. Hu, L. He, M. Ye and Y. Li, *FEBS Lett.*, 2004, **578**, 245–250.
42 L. Del Giudice, D. R. Massardo, P. Pontieri and K. Wolf, *Gene*, 2005, **354**, 9–14.
43 N. De Laurentis, A. Rosato, C. Vitali, L. Leone and M. A. Milillo, *Riv. Ital. EPPOS*, 2004, **38**, 19–23; N. De Laurentis, A. Rosato, C. Vitali, L. Leone and M. A. Milillo, *Chem. Abstr.*, 2005, **143**, 129863.
44 A. Mclachlan, N. Kekre, J. McNulty and S. Pandey, *Apoptosis*, 2005, **10**, 619–630.
45 N. Kekre, C. Griffin, J. McNulty and S. Pandey, *Cancer Chemother. Pharmacol.*, 2005, **56**, 29–38.
46 M. A. Ogasawara, M. Manpadi and A. Kornienko, *Abstracts of Papers, 231st ACS National Meeting*, Atlanta, GA, USA, March 26–30, 2006, MEDI-295.
47 Y. Wan, Y. Bi and Z. Liu, *Shanghai Daxue Xuebao, Ziran Kexueban*, 2004, **10**, 493–496; Y. Wan, Y. Bi and Z. Liu, *Chem. Abstr.*, 2005, **143**, 23164.
48 P. I. Higgs, *Abstracts Of Papers, 231st ACS National Meeting*, Atlanta, GA, USA, March 26–30, 2006, CHED-345.
49 C. E. Olsen, H. D. Poulsen and H. K. F. Lublin, *Nord. J. Psychiatry*, 2005, **59**, 71–77.
50 I. Bernd and H. Ekkehard, *Curr. Pharm. Des.*, 2004, **10**, 231–251.
51 M. Colombres, J. P. Sagal and N. C. Inestrosa, *Curr. Pharm. Des.*, 2004, **10**, 3121–3130.
52 P. J. Houghton, Y. Ren and M.-J. Howes, *Nat. Prod. Rep.*, 2006, **23**, 181–199.
53 K. Hostettmann, A. Borloz, A. Urbain and A. Marston, *Curr. Org. Chem.*, 2006, **10**, 825–847.
54 C. Viegas, Jr., V. da S. Bolzani, E. J. Barreiro and C. A. M. Fraga, *Mini-Rev. Med. Chem.*, 2005, **5**, 915–926.
55 L. Marco and M. do C. Carreiras, *Recent Pat. CNS Drug Discovery*, 2006, **1**, 105–111.
56 R. Bullock, *Expert Rev. Neurother.*, 2004, **4**, 153–163.
57 M. Heinrich and H. L. Teoh, *J. Ethnopharmacol.*, 2004, **92**, 147–162.
58 H. Geerts, *Brain Res. Bull.*, 2005, **64**, 519–524.
59 M. M. Oh, W. W. Wu, J. M. Power and J. F. Disterhoft, *Neuroscience*, 2006, **137**, 113–123.
60 K. Mann, K. Ackermann, A. Diehl, D. Ebert, G. Mundle, H. Nakovics, T. Reker, G. Richter, L. G. Schmidt, M. Driessen, K. Rettig, K. Opitz and B. Croissant, *Psychopharmacology*, 2006, **184**, 115–121.
61 R. Colque, F. Viladomat, J. Bastida and C. Codina, *Planta Med.*, 2004, **70**, 1180–1188.
62 W. D. Ratnasooriya, S. A. Deraniyagala, S. D. N. K. Bathige and H. D. I. Hettiarachchi, *J. Ethnopharmacol.*, 2005, **97**, 123–128.
63 G. I. Kaya and B. Gozler, *Fitoterapia*, 2005, **76**, 340–343.
64 N. Unver, G. I. Kaya and H. T. Ozturk, *Fitoterapia*, 2005, **76**, 226–229.
65 E. W. Botha, C. P. Kahler, W. J. du Plooy, S. H. du Plooy and L. Mathibe, *J. Ethnopharmacol.*, 2005, **96**, 385–388.
66 A. R. Bafna and S. H. Mishra, *J. Ethnopharmacol.*, 2006, **104**, 1–4.
67 S. Agarwal, S. Caemmerer, S. Filali, W. Froehner, J. Knoell, M. P. Krahl, K. R. Reddy and H.-J. Knoelker, *Curr. Org. Chem.*, 2005, **9**, 1601–1614.
68 J. Marco-Contelles, M. do C. Carreiras, C. Rodriguez, M. Villarroya and A. G. Garcia, *Chem. Rev.*, 2006, **106**, 116–133.
69 J. Marco-Contelles, C. Rodriguez and A. G. Garcia, *Expert Opin. Ther. Pat.*, 2005, **15**, 575–587.
70 B. M. Trost, W. Tang and F. D. Toste, *J. Am. Chem. Soc.*, 2005, **127**, 14785–14803.
71 X. Hu, Y. Q. Tu, E. Zhang, S. Gao, S. Wang, A. Wang, C. Fan and M. Wang, *Org. Lett.*, 2006, **8**, 1823–1825.
72 C. Fan, Y. Q. Tu, Z. Song, E. Zhang, L. Shi, M. Wang, B. Wang and S. Zhang, *Org. Lett.*, 2004, **6**, 4691–4694.
73 P. Liang, J. Liu, L. Hsin and C. Cheng, *Tetrahedron*, 2004, **60**, 11655–11660.

74 G. Schloemer and T. Hsiao, *US Pat.*, 2005070522, 2005; G. Schloemer and T. Hsiao, *Chem. Abstr.*, 2005, **142**, 341838.
75 S. Lahiri, M. Prasad, N. Maheshwar and Y. Kumar, *WO Pat.*, 2006046096, 2006; S. Lahiri, M. Prasad, N. Maheshwar and Y. Kumar, *Chem. Abstr.*, 2005, **144**, 450696.
76 S. Lahiri, M. Prasad, N. Maheshwar and Y. Kumar, *WO Pat.*, 2006013546, 2006; S. Lahiri, M. Prasad, N. Maheshwar and Y. Kumar, *Chem. Abstr.*, 2005, **144**, 212936.
77 V. B. Bolugoddu, S. Shukla, M. R. Jambula, R. R. Sagyam, R. R. Pingili and A. B. Thirunavakarasu, *US Pat.*, 2006009640, 2006; V. B. Bolugoddu, S. Shukla, M. R. Jambula, R. R. Sagyam, R. R. Pingili and A. B. Thirunavakarasu, *Chem. Abstr.*, 2005, **144**, 129140.
78 H. M. Greenblatt, C. Guillou, D. Guenard, A. Argaman, S. Botti, B. Badet, C. Thal, I. Silman and J. L. Sussman, *J. Am. Chem. Soc.*, 2004, **126**, 15405–15411.
79 M. Hemetsberger, M. Treu, U. Jordis, K. Mereiter, C. Hametner and J. Frohlich, *Monatsh. Chem.*, 2004, **135**, 1275–1287.
80 C. Hametner, M. Hemetsberger, M. Treu, K. Mereiter, U. Jordis and J. Frohlich, *Eur. J. Org. Chem.*, 2005, 404–409.
81 M. Hemetsberger, M. Treu, C. Hametner, U. Jordis, K. Mereiter and J. Frohlich, *Heterocycles*, 2004, **63**, 2217–2224.
82 A. H. Lewin, J. Szewczyk, J. W. Wilson and F. I. Carroll, *Tetrahedron*, 2005, **61**, 7144–7152.
83 M. Shair, N. Westwood and H. E. Pelish, *US Pat.*, 6 797 819, 2004; M. Shair, N. Westwood and H. E. Pelish, *Chem. Abstr.*, 2004, **141**, 296194.
84 S. Gao, Y. Q. Tu, Z. Song, A. Wang, X. Fan and Y. Jiang, *J. Org. Chem.*, 2005, **70**, 6523–6525.
85 Y. Zhang, *Diss. Abstr. Int., B*, 2005, **65**, 5161, (*Chem. Abstr.*, **143**, 230032).
86 B. D. Chapsal and I. Ojima, *Org. Lett.*, 2006, **8**, 1395–1398.
87 B. D. Chapsal, Z. Hua and I. Ojima, *Tetrahedron: Asymmetry*, 2006, **17**, 642–657.
88 L. Dong, Y. Xu, L. Cun, X. Cui, A. Mi, Y. Jiang and L. Gong, *Org. Lett.*, 2005, **7**, 4285–4288.
89 H. Fujioka, K. Murai, Y. Ohba, H. Hirose and Y. Kita, *Chem. Commun.*, 2006, 832–834.
90 Q. Wang and A. Padwa, *Org. Lett.*, 2004, **6**, 2189–2192.
91 G. L. Barclay, B. Quiclet-Sire, G. Sanchez-Jimenez and S. Z. Zard, *Org. Biomol. Chem.*, 2005, **3**, 823–835.
92 T. Harayama, *Recent Res. Dev. Org. Chem.*, 2005, **9**, 15–25.
93 T. Harayama, A. Hori, H. Abe and Y. Takeuchi, *Heterocycles*, 2006, **67**, 385–390.
94 J. C. Torres, A. C. Pinto and S. J. Garden, *Tetrahedron*, 2004, **60**, 9889–9900.
95 G. Pandey, P. Banerjee, R. Kumar and V. G. Puranik, *Org. Lett.*, 2005, **7**, 3713–3716.
96 M. Chang, H. Chen, C. Lin and C. Pai, *Heterocycles*, 2005, **65**, 1999–2004.
97 B. C. Raju, P. Neelakantan and U. T. Bhalerao, *Tetrahedron Lett.*, 2004, **45**, 7487–7489.
98 J. A. Seijas, M. P. Vazquez-Tato, M. M. Martinez and M. G. Pizzolatti, *Tetrahedron Lett.*, 2005, **46**, 5827–5830.
99 P. Appukkuttan, W. Dehaen and E. Van der Eycken, *Org. Lett.*, 2005, **7**, 2723–2726.
100 I. R. Baxendale and S. V. Ley, *Ind. Eng. Chem. Res.*, 2005, **44**, 8588–8592.
101 B. Moon, S. Han, Y. Yoon and H. Kwon, *Org. Lett.*, 2005, **7**, 1031–1034.
102 D. Enders, A. Lenzen and G. Raabe, *Angew. Chem., Int. Ed.*, 2005, **44**, 3766–3769.
103 D. Enders, A. Lenzen, M. Backes, C. Janeck, K. Catlin, M. Lannou, J. Runsink and G. Raabe, *J. Org. Chem.*, 2005, **70**, 10538–10551.
104 U. Rinner and T. Hudlicky, *Synlett*, 2005, 365–387 .
105 T. Hudlicky, *ARKIVOC*, 2006, 276–291.
106 M. Li, A. Wu and P. Zhou, *Tetrahedron Lett.*, 2006, **47**, 3707–3710.
107 O. N. Nadein, A. S. Kireev and A. Kornienko, *Abstracts Of Papers, 228th ACS National Meeting*, Philadelphia, PA, USA, August 22–26, 2004, ORGN-372.
108 M. Manpadi and A. Kornienko, *Tetrahedron Lett.*, 2005, **46**, 4433–4437.
109 B. P. Branchaud and S. R. Woodcock, *Abstracts Of Papers, 227th ACS National Meeting*, Anaheim, CA, USA, March 28–April 1, 2004, ORGN-441.
110 H. Zhang and A. Padwa, *Abstracts of Papers, 231st ACS National Meeting*, Atlanta, GA, USA, March 26–30, 2006, ORGN-439.
111 H. Zhang and A. Padwa, *Org. Lett.*, 2006, **8**, 247–250.
112 H. Zhang and A. Padwa, *Tetrahedron Lett.*, 2006, **47**, 3905–3908.
113 T. Fujimura, M. Shibuya, K. Ogasawara and Y. Iwabuchi, *Heterocycles*, 2005, **66**, 167–173.
114 J. McNulty, V. Larichev and S. Pandey, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5315–5318.
115 S. Ibn-Ahmed, M. Khaldi, F. Chretien and Y. Chapleur, *J. Org. Chem.*, 2004, **69**, 6722–6731.
116 U. Rinner, T. Hudlicky, H. Gordon and G. R. Pettit, *Angew. Chem., Int. Ed.*, 2004, **43**, 5342–5346.
117 T. Hudlicky, U. Rinner, K. J. Finn and I. Ghiviriga, *J. Org. Chem.*, 2005, **70**, 3490–3499.
118 M. Moser, X. Sun and T. Hudlicky, *Org. Lett.*, 2005, **7**, 5669–5672.
119 M. Manpadi and A. Kornienko, *Abstracts of Papers, 231st ACS National Meeting*, Atlanta, GA, USA, March 26–30, 2006, ORGN-440.
120 U. Rinner, H. L. Hillebrenner, D. R. Adams, T. Hudlicky and G. R. Pettit, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2911–2915.
121 T. Kumemura, T. Choshi, J. Yukawa, A. Hirose, J. Nobuhiro and S. Hibino, *Heterocycles*, 2005, **66**, 87–90.
122 D. F. Taber and Y. He, *J. Org. Chem.*, 2005, **70**, 7711–7714.