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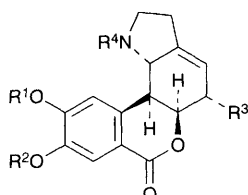
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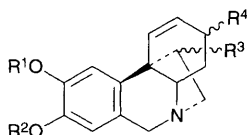
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1 Introduction

In this annual review 23 new alkaloids have been reported as well as known alkaloids that have been found in new sources. Table 1 lists those alkaloids that are reported upon in this review. The identity of the alkaloidal contents of a plant not only has important chemical implications but taxonomic deductions can also be implied. The identification of new skeletal arrangements, which are often associated with specific pharmacological properties, can lead to a deeper understanding of structure-activity relationships with the development of the synthesis of simpler analogues suitable for clinical evaluation. Alkaloids and other naturally occurring compounds can provide useful information on taxonomic classification; thus *Narcissus primigenius* has been classified as a new taxon of the *Narcissus pseudonarcissus* DC section as a result of the four alkaloids, homolycorine **1**, 8-*O*-demethylhomolycorine **2**, haemanthamine **3** and 8-*O*-demethylmaritidine **4**, which were found in extracts of the whole plant.¹

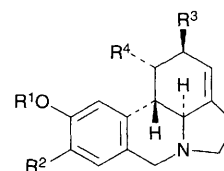


- 1** Homolycorine $R^1 = R^2 = R^4 = \text{Me}$; $R^3 = \text{H}$
- 2** 8-*O*-Demethylhomolycorine $R^1 = R^3 = \text{H}$; $R^2 = R^4 = \text{Me}$
- 37** 9-*O*-Demethylhomolycorine $R^1 = R^4 = \text{Me}$; $R^2 = R^3 = \text{H}$
- 41** 5-Methoxy-9-*O*-demethylhomolycorine
 $R^1 = R^4 = \text{Me}$; $R^2 = \text{H}$; $R^3 = \text{OMe}$
- 48** Hippeastrine $R^1R^2 = \text{CH}_2$; $R^3 = \text{OH}$; $R^4 = \text{Me}$
- 63** Mansonine $R^1R^2 = \text{CH}_2$; $R^3 = \text{H}$; $R^4 = \text{Me}$
- 68** *N*-Demethylmansonine $R^1R^2 = \text{CH}_2$; $R^3 = R^4 = \text{H}$



- 3** Haemanthamine $R^1R^2 = \text{CH}_2$; $R^3 = \alpha\text{-OH}$; $R^4 = \beta\text{-OMe}$
- 4** 8-*O*-Demethylmaritidine $R^1 = \text{Me}$; $R^2 = R^3 = \text{H}$; $R^4 = \beta\text{-OH}$
- 18** 3-*O*-Acetylhamayne $R^1R^2 = \text{CH}_2$; $R^3 = \beta\text{-OAc}$; $R^4 = \alpha\text{-OH}$
- 19** Hamayne $R^1R^2 = \text{CH}_2$; $R^3 = \beta\text{-OH}$; $R^4 = \alpha\text{-OH}$
- 20** Crinamine $R^1R^2 = \text{CH}_2$; $R^3 = \beta\text{-OH}$; $R^4 = \alpha\text{-OMe}$
- 36** 11-Hydroxyvittatine $R^1R^2 = \text{CH}_2$; $R^3 = \alpha\text{-OH}$; $R^4 = \beta\text{-OH}$
- 64** Vittatine $R^1R^2 = \text{CH}_2$; $R^3 = \text{H}$; $R^4 = \beta\text{-OH}$

Microanalytical techniques for the analysis of the alkaloidal content of a plant depends a great deal on their stability under gas chromatography conditions. A new study² using capillary gas chromatography coupled with mass spectrometry has shown that many underivatized Amaryllidaceae alkaloids were stable under the conditions employed. Thus an extract of the bulbs of *Narcissus pseudonarcissus* sub-sp. *pseudonarcissus* was shown to contain 30 alkaloids using direct insertion mass spectrometry. If gas chromatography preceded mass measurement only two alkaloids, haemanthamine **3** and lycorine **5**,

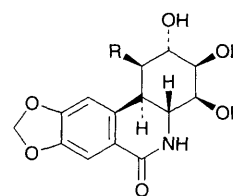


- 5** Lycorine $R^1R^2 = \text{CH}_2\text{O}$; $R^3 = R^4 = \text{OH}$
- 22** Sternbergine $R^1 = \text{Me}$; $R^2 = R^4 = \text{OH}$; $R^3 = \text{OAc}$
- 55** Pseudolycorine $R^1 = \text{H}$; $R^2 = R^4 = \text{OH}$; $R^3 = \text{OMe}$
- 57** 10-Norpluviine $R^1 = \text{Me}$; $R^2 = R^3 = \text{OH}$; $R^4 = \text{H}$
- 58** 1-*O*-Acetyl-10-norpluviine $R^1 = \text{Me}$; $R^2 = R^3 = \text{OH}$; $R^4 = \text{OAc}$
- 59** 1,10-Diacetyl-10-norpluviine $R^1 = \text{Me}$; $R^2 = R^4 = \text{OAc}$; $R^3 = \text{OH}$
- 60** 9-Norpluviine $R^1 = \text{H}$; $R^2 = \text{OMe}$; $R^3 = \text{OH}$; $R^4 = \text{H}$

were found to partly decompose thermally in the column. This method was however found to be better than if the alkaloids were derivatised prior to gas chromatography.

2 Occurrence and structural studies

Pancreatistatin **6** has been found to exhibit a highly characteristic differential cytotoxicity profile against 60 human cancer



- 6** Pancreatistatin $R = \text{OH}$
- 9** 7-Deoxy-*trans*-dihydranarciclasine $R = \text{H}$

lines.³ Unfortunately, an efficient synthetic route has not been established and so an investigation into its production within the plant has taken place.⁴ Monthly analyses of the bulbs of cloned plants from *Hymenocallis littoralis* showed that the alkaloid **6** content varied when these plants were grown in an irrigated semi-arid Arizona desert location. Normally *Hymenocallis littoralis* is found in tropical or sub-tropical regions. Highest yields of the alkaloid were obtained in October after the plant had undergone six months of growth in the period following flowering. On average, a yield of 0.015% of pancreatistatin **6** was achieved; in addition narciclasine **7**,

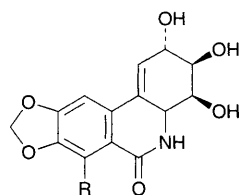
Table 1 Isolation of Amaryllidaceae alkaloids

Species	Alkaloid (structure)	Ref.		
<i>Brunsvigia gregaria</i>	Crinamidine 10	7		
	Crinine 11			
	Flexinine 12			
	Haemanthidine 13			
	Lycoramine 14			
	8-Methylenedioxyphenanthridine 15			
	Tazettine 16			
	Undulatine 17			
	<i>Brunsvigia josephinae</i>		3- <i>O</i> -Acetylhamayne 18	8
			Hamayne 19	
Crinamine 20				
Ambelline 21				
Sternbergine 22				
11- <i>O</i> -Acetylbambelline* 23				
Brunsbelline* 24				
Crinine 11				
Buphanisine 25				
Buphanidrine 26				
<i>Crinum kirkii</i> (bulbs)	Undulatine 17	9		
	Hippadine 27			
	Kirkine* 28			
	8- <i>O</i> -Demethylvasconine* 29			
	Crinine 11			
	Hamayne 19			
	3- <i>O</i> -Acetylhamayne 18			
	(-)-Galanthamine 30			
	(-)-Sanguinine 31			
	(-)-Leucotamine 32			
<i>Galanthus elewesii</i> (whole plants)	(-)- <i>O</i> -Methylleucotamine 33	10		
	(±)-Narwedine 34			
	(-)- <i>N</i> -Demethylgalanthamine 35			
	(+)-11-Hydroxyvittatine 36			
	(+)-9- <i>O</i> -Demethylhomolycorine 37			
	(-)-Lycorine 5			
	(-)-Galanthine 38			
	Hordeanine 39			
	(<i>E</i>)- <i>N</i> -Ferulolytyramine 40			
	(+)-5-Methoxy-9- <i>O</i> -demethylhomolycorine* 41			
(+)-Galwesine* 42				
(+)-9- <i>O</i> -Demethylgalwesine* 43				
(+)-16-Hydroxygalwesine* 44				
(+)-16-Hydroxy-9- <i>O</i> -demethylgalwesine* 45				
Galasine* 46				
<i>Hippeastrum equestre</i> (bulbs)	Phamine* 47	12		
	Lycorine 5			
	Tazettine 16			
<i>Hymenocallis expansa</i> (whole plant)	Hippeastrine 48	13		
	<i>N</i> -Methylcrinasiadine 49			
<i>Hymenocallis littoralis</i> (whole plant)	8,9-Methylenedioxyphenanthridine 15	14		
	Pancreatistatin 6			
<i>Hymenocallis maritimum</i> (whole plant)	Pancreatistatin 6	14		
	Pancreatistatin 6			
<i>Hymenocallis sonorensis</i> (whole plant)	Pancreatistatin 6	14		
	Pancreatistatin 6			
<i>Hymenocallis speciosa</i> (whole plant)	Pancreatistatin 6	14		
	Pancreatistatin 6			
<i>Leucojum autumnale</i> (bulbs)	Narcissidine 50	15		
	Lycorine 5			
<i>Lycoris sanguinea</i> (bulbs)	3- <i>O</i> -Acetylnarcissidine* 51			
	3- <i>O</i> -Acetylnarcissidine <i>N</i> -oxide* 52			
	Norsanguinine* 53			
	Norbutanguinine* 54			
	Sanguinine 31			
	Lycorine 5			
	Pseudolycorine 55			
	Galanthamine 30			
Galanthine 38				

Table 1 Continued

Species	Alkaloid (structure)	Ref.
<i>Narcissus primigenius</i> (whole plants)	Homolycorine 1	1
	8- <i>O</i> -Demethylhomolycorine 2	
<i>Narcissus pseudonarcissus</i> (bulbs)	Haemanthamine 3	2
	8- <i>O</i> -Demethylmaritidine 4	
<i>Narcissus pseudonarcissus</i> subsp. <i>pseudonarcissus</i>	Lycorine 5	19
	29 other alkaloids identified by GC-MS	
	<i>O</i> -Acetylgalanthamine* 56	
	10-Norpluviine* 57	
	1- <i>O</i> -Acetyl-10-norpluviine* 58	
	1,10-Diacetyl-10-norpluviine* 59	
	9-Norpluviine 60	
	Lycorenine 61	
	Oduline 62	
	Hippeastrine 48	
	Mansonine 63	
	Homolycorine 1	
	Haemanthamine 3	
	Vittatine 64	
	Galanthamine 30	
	<i>N</i> -Demethylgalanthamine 35	
	Lycoramine 14	
	Epi- <i>N</i> -demethyllycoramine 65	
	Narwedine 34	
<i>O</i> -Methyllycorenine 66		
<i>O</i> -Methyloduline* 67		
<i>N</i> -Demethylmansonine* 68		
<i>Narcissus tortuosus</i> (whole plants)	Lycorine 5	20
	Tortusine* 69	
	Vasconine 70	
	(-)-Lycorine 5	
<i>Pancratium maritimum</i> (bulbs)	(+)-0-Demethylhomolycorine 37	21
	Trisphaeridine 15	
	(+)-Haemanthamine 3	
	(+)-Buphanisine 25	
	(-)-Crinine 11	
	(-)-3β-11α-Dihydroxy-1,2-dehydrocrinane 71	
	(-)-8-Hydroxy-9-methoxycrinane 72	
	(-)-3β-Methoxy-6α,11β-dihydroxy-1,2-dehydrocrinane 73	

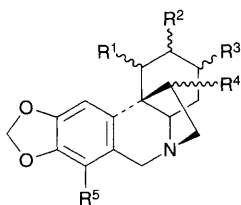
* New alkaloids

**7** Narciclasine R = OH
8 7-Deoxynarciclasine R = H

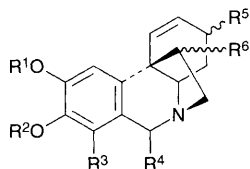
7-deoxynarciclasine **8** and 7-deoxy-*trans*-dihydronarciclasine **9** were also produced. An extraction-separation procedure was consequently developed to allow a scale up of production of the alkaloids.

An alkaloid extract obtained from the bulbs of *Haemanthus albiflos* was reported⁵ to have an antiviral effect on RNA viruses. Further studies have now indicated that its activity is involved at an early stage in the virus' development.⁶ The identity of the active agent(s) remain unknown.

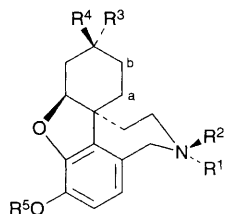
Crinamidine **10**, crinine **11**, flexinine **12**, haemanthidine **13**, lycoramine **14**, 8,9-methylenedioxyphenanthridine **15**, tazettine **16** and undulatine **17** were all isolated from *Brunsvigia gregaria*. Confirmation of their identities was made by their



- 10** Crinamide $R^1R^2 = \beta\text{-O}$; $R^3 = \alpha\text{-OH}$; $R^4 = \text{H}$; $R^5 = \text{OMe}$
12 Flexinine $R^1R^2 = \beta\text{-O}$; $R^3 = \alpha\text{-OH}$; $R^4 = R^5 = \text{H}$
17 Undulatine $R^1R^2 = \beta\text{-O}$; $R^3 = \alpha\text{-OMe}$; $R^4 = \text{H}$; $R^5 = \text{OMe}$

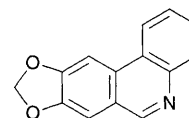


- 11** Crinine $R^1R^2 = \text{CH}_2$; $R^3 = R^4 = R^6 = \text{H}$; $R^5 = \alpha\text{-OH}$
13 Haemanthidine $R^1R^2 = \text{CH}_2$; $R^3 = \text{H}$; $R^4 = R^6 = \beta\text{-OH}$; $R^5 = \alpha\text{-OMe}$
21 Ambelline $R^1R^2 = \text{CH}_2$; $R^3 = \text{OMe}$; $R^4 = \text{H}$; $R^5 = \alpha\text{-OMe}$; $R^6 = \alpha\text{-OH}$
23 11-*O*-Acetylabelline $R^1R^2 = \text{CH}_2$; $R^3 = \text{OMe}$; $R^4 = \text{H}$; $R^5 = \alpha\text{-OMe}$; $R^6 = \alpha\text{-OAc}$
24 Brunsbelline $R^1R^2 = \text{CH}_2$; $R^3 = \text{OMe}$; $R^4 = \text{H}$; $R^5 = \beta\text{-OMe}$; $R^6 = \beta\text{-OH}$
25 Buphanisine $R^1R^2 = \text{CH}_2$; $R^3 = R^4 = R^6 = \text{H}$; $R^5 = \beta\text{-OMe}$
26 Buphanidrine $R^1R^2 = \text{CH}_2$; $R^3 = \text{OMe}$; $R^4 = R^6 = \text{H}$; $R^5 = \alpha\text{-OMe}$
71 (-)-3 β ,11 α -dihydroxy-1,2-dehydrocrinane
 $R^1R^2 = \text{CH}_2$; $R^3 = \text{H}$; $R^4 = \text{H}$; $R^5 = \beta\text{-OH}$; $R^6 = \alpha\text{-OH}$
72 (-)-8-Hydroxy-9-methoxycrinane $R^1 = \text{Me}$;
 $R^2 = R^3 = R^4 = R^5 = R^6 = \text{H}$
73 (-)-3 β -Methoxy-6 α ,11 β -dihydroxy-1,2-dehydrocrinane
 $R^1R^2 = \text{CH}_2$; $R^3 = \text{H}$; $R^4 = \alpha\text{-OH}$; $R^5 = \beta\text{-OMe}$; $R^6 = \beta\text{-OH}$



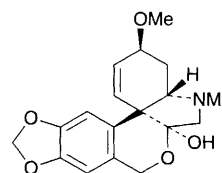
- 14** Lycoramine $R^1 = \text{lone pair}$; $R^2 = R^5 = \text{Me}$; $R^3 = \text{H}$; $R^4 = \text{OH}$; ab sat.
30 Galanthamine $R^1 = \text{lone pair}$; $R^2 = R^5 = \text{Me}$; $R^3 = \text{H}$;
 $R^4 = \text{OH}$; ab unsat.
31 Sanguinine $R^1 = \text{lone pair}$; $R^2 = \text{Me}$; $R^3 = R^5 = \text{H}$;
 $R^4 = \text{OH}$; ab unsat.
32 Leucotamine $R^1 = \text{lone pair}$; $R^2 = \text{Me}$; $R^3 = R^5 = \text{H}$;
 $R^4 = \text{OCOCH}_2\text{CH(OH)Me}$; ab unsat.
33 *O*-Methyleucotamine $R^1 = \text{lone pair}$; $R^2 = R^5 = \text{Me}$; $R^3 = \text{H}$;
 $R^4 = \text{OCOCH}_2\text{CH(OH)Me}$; ab unsat.
34 Narwedine $R^1 = \text{lone pair}$; $R^2 = R^5 = \text{Me}$; $R^3 = R^4 = \text{O}$; ab unsat.
35 *N*-Demethylgalanthamine $R^1 = \text{lone pair}$; $R^2 = R^3 = \text{H}$;
 $R^4 = \text{OH}$; $R^5 = \text{Me}$; ab unsat.
53 Norsanguinine $R^1 = \text{lone pair}$; $R^2 = R^3 = R^4 = R^5 = \text{H}$; ab unsat.
54 Norbutsanguinine $R^1 = \text{lone pair}$; $R^2 = R^4 = R^5 = \text{H}$;
 $R^3 = \text{OCOCH}_2\text{CH(OH)Me}$; ab unsat.
56 *O*-Acetylgalanthamine $R^1 = \text{lone pair}$; $R^2 = R^5 = \text{Me}$; $R^3 = \text{H}$;
 $R^4 = \text{OAc}$; ab unsat.
65 Epi-*N*-demethyllycoramine $R^1 = \text{lone pair}$; $R^2 = R^4 = \text{H}$; $R^3 = \text{OH}$;
 $R^5 = \text{Me}$; ab unsat.

chromatographic behaviour and UV spectra.⁷ An original investigation into the alkaloids present in the bulbs of *Brunsvigia josephinae* established the presence of 3-*O*-acetylhamayne **18**,

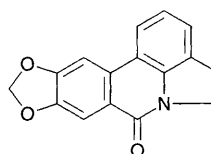


15 8,9-Methylenedioxyphenanthridine (trispharidine)

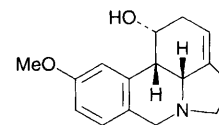
hamayne **19**, crinamine **20**, ambelline **21** and sternbergine **22**. A re-investigation of this plant bulb extract⁸ has produced two new alkaloids 11-*O*-acetylabelline **23** and brunsbelline **24**. Also present were crinine **11**, buphanisine **25**, buphanidrine **26**, undulatine **17** and hippadine **27**.



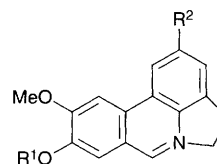
16 Tazettine



27 Hippadine



28 Kirkine



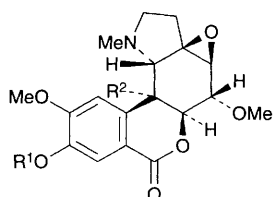
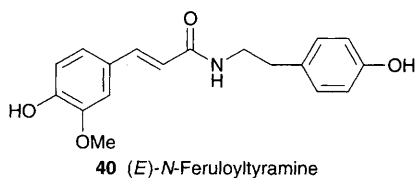
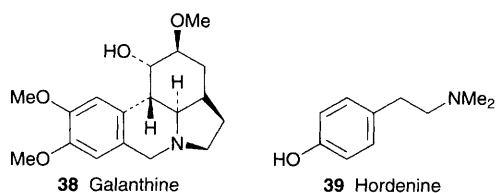
29 8-*O*-Demethylvasconine $R^1 = R^2 = \text{H}$

69 Tortusine $R^1 = \text{Me}$; $R^2 = \text{OMe}$

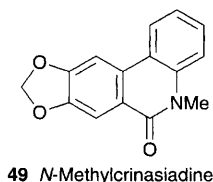
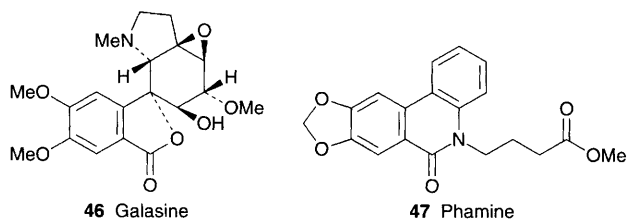
70 Vasconine $R^1 = \text{Me}$; $R^2 = \text{H}$

Two new alkaloids have been characterised as being present in the bulbs of *Crinum kirkii*.⁹ Both belong to the crinan group and are named kirkine **28** and 8-*O*-demethylvasconine **29**. Also found in this extract were crinine **11**, hamayne **19** and 3-*O*-acetylhamayne **18**.

Six new lycorenine-type alkaloids have been isolated from whole plant extracts of *Galanthus elwesii*. Also present were the 12 known alkaloids: (-)-galanthamine **30**, (-)-sanguinine **31**, (-)-leucotamine **32**, (-)-*O*-methyleucotamine **33**, (\pm)-narwedine **34**, (-)-*N*-demethylgalanthamine **35**, (\pm)-11-hydroxyvittatine **36**, (+)-9-*O*-demethylhomolycorine **37**, (-)-lycorine **5**, (-)-galanthine **38**, hordenine **39** and (*E*)-*N*-feruloyltyramine **40**. Galanthamine **30** and lycorine **5** had previously been found in this plant. The new alkaloids were (+)-5-methoxy-9-*O*-demethylhomolycorine **41**, (+)-galwesine **42**, (+)-9-*O*-demethylgalwesine **43**, (+)-16-hydroxygalwesine **44**, (+)-16-hydroxy-9-*O*-demethylgalwesine **45** and galasine **46**. All compounds were characterised by spectroscopic analysis and in the cases of **33**, **43** and **46**, confirmation was made by X-ray crystallography.¹⁰ Galasine **46** is the first spirocyclic lycorenine-type ring system to be reported to date. Five seemingly different colourless crystalline samples were obtained from five different subfractions of the alkaloidal extract obtained from the whole plant *Galanthus elwesii*.¹¹ All were shown to be (+)-9-*O*-demethylhomolycorine **37** having identical CD, UV, ¹H and ¹³C NMR spectral data. They were chromatographically identical but differed in melting point



- 42 Galwesine** $R^1 = \text{Me}; R^2 = \text{H}$
43 9-O-Demethylgalwesine $R^1 = R^2 = \text{H}$
44 (+)-16-Hydroxygalwesine $R^1 = \text{Me}; R^2 = \text{OH}$
45 (+)-16-Hydroxy-9-O-demethylgalwesine $R^1 = \text{H}; R^2 = \text{OH}$

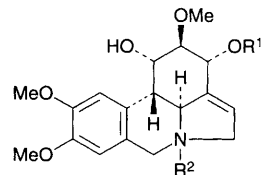


and in optical activity. X-Ray data were obtained from four of these samples and it was seen that solvent molecules were or were not packed into the crystal and that the *N*-methyl-conformation was either axial or equatorial and this depended upon the conditions of crystallisation.

Phamine **47** is a new phenanthridone alkaloid isolated from the bulbs of the Vietnamese plant *Hippeastrum equestre*.¹² Also present were lycorine **5**, tazettine **16** and hippeastrine **48**. In a second publication by the same group, *N*-methylcrinasiadine **49** and 8,9-methylenedioxyphenanthridine **15** were extracted and identified as alkaloidal constituents of the bulbs of *Hippeastrum equestre*.¹³ The newly reported alkaloidal constituent phamine (*loc cit*) was also present.

Following on from the earlier investigations on *Hymenocallis littoralis*⁴ (*loc cit*) coupled to the efficacy of pancratistatin **6** as an antitumour agent the Pettit group has initiated a survey of the alkaloidal content of bulbs of the genus *Hymenocallis* to ascertain the extent of the occurrence of the active alkaloid **6** and its related isocarbostryls narciclasine **7**, 7-deoxynarciclasine **8** and 7-deoxy-*trans*-dihydronarciclasine **9**.¹⁴ *Hymenocallis speciosa* from Singapore contained **6** and *Hymenocallis expansa* from Bermuda contained **6** and **7**, while

Hymenocallis sonorensis from Mexico, a variegated variety of *Hymenocallis* from Singapore, *Hymenocallis pedalis* from the Seychelles and *Pancratium maritimum* from Israel, all contained only **6**. 7-Deoxynarciclasine **8** was found in the *Ismene* variety 'Sulphur Queen' from the Netherlands but the variety *Ismene* 'Advance' did not contain any of the sought after alkaloids, neither did a 'Tropical Giant' variety of *Hymenocallis* from Singapore.¹⁴ Fresh bulbs of *Leucojum autumnale* contain four alkaloids:¹⁵ narcissidine **50**, lycorine **5** and, hitherto unreported, 3-*O*-acetylnarcissidine **51** and 3-*O*-

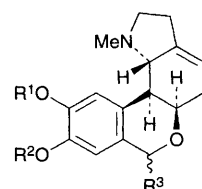


- 50 Narcissidine** $R^1 = \text{H}; R^2 = \text{Ione pair}$
51 3-O-Acetylnarcissidine $R^1 = \text{Ac}; R^2 = \text{Ione pair}$
52 3-O-Acetylnarcissidine-N-oxide $R^1 = \text{Ac}; R^2 = \text{O}$

acetylnarcissidine *N*-oxide **52**. Seven alkaloids have been found to be constituents of the bulbs of *Lycoris sanguinea*;¹⁶ two are new namely norsanguinine **53** and norbutsanginine **54**; the others were sanguinine **31**, lycorine **5**, pseudolycorine **55**, galanthamine **30** and galanthine **38**.

The identities of four alkaloids obtained from the bulbs of the daffodil *Narcissus pseudonarcissus* were determined by GC-MS.¹⁷ They are the known *O*-acetylgalanthamine **56**, which is reported here as a natural product for the first time, 10-norpluviine **57**, 1-*O*-acetyl-10-norpluviine **58** and 1,10-diacetyl-10-norpluviine **59**. A synthesis of **56** and **59** was accomplished by acetylation of galanthamine **30** and 10-norpluviine **57**, respectively. This investigation enabled the alkaloid that was previously called 10-norpluviine¹⁸ to be redesignated as 9-norpluviine **60**.

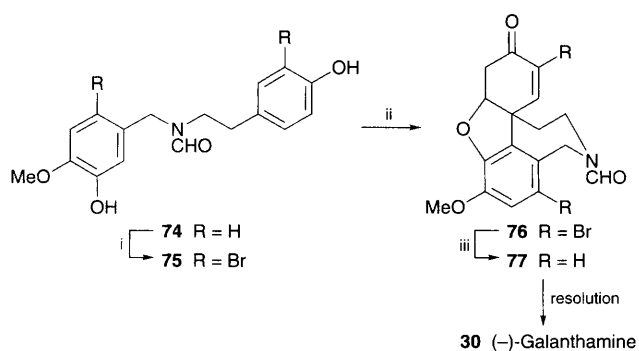
The large cultivated daffodil *Narcissus pseudonarcissus* sub-sp. *pseudonarcissus* variety 'Carlton' has only been examined once previously and narciclasine **7** was identified as a constituent. The new investigation¹⁹ of the bulbs has resulted in the isolation of 15 alkaloids, namely lycorenine **61**,



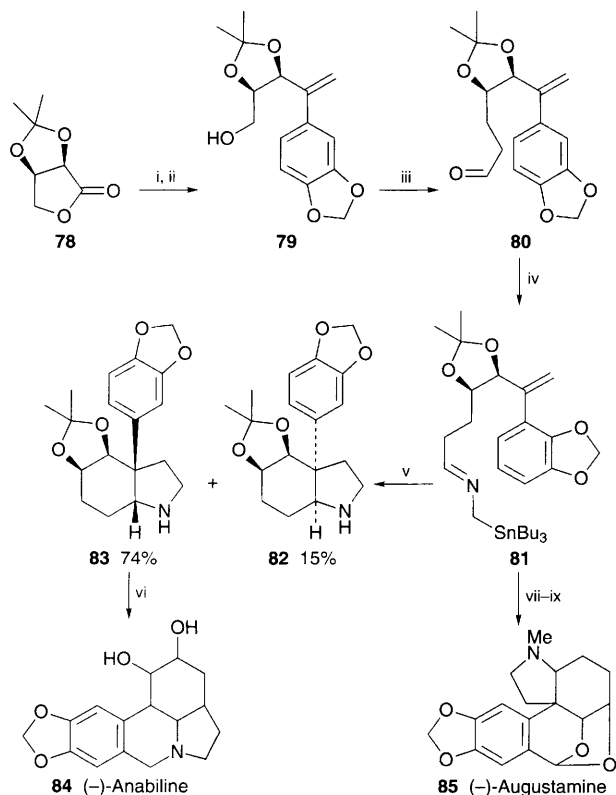
- 61 Lycorenine** $R^1 = R^2 = \text{Me}; R^3 = \beta\text{-OH}$
62 Oduline $R^1 R^2 = \text{CH}_2; R^3 = \alpha\text{-OH}$
66 O-Methyllycorenine $R^1 = R^2 = \text{Me}; R^3 = \beta\text{-OMe}$
67 O-Methyloduline $R^1 R^2 = \text{CH}_2; R^3 = \alpha\text{-OMe}$

oduline **62**, hippeastrine **48**, mansonine **63**, homolycorine **1**, haemanthamine **3**, vittatine **64**, galanthamine **30**, *N*-demethylgalanthamine **35**, lycoramine **14**, epi-*N*-demethyllycoramine **65**, narwedine **34** and *O*-methyllycorenine **66**. The two new compounds were *O*-methyloduline **67** and *N*-demethylmansonine **68**.

Whole plants of *Narcissus tortuosus* contain two alkaloids lycorine **5** and a new anhydrolycorinium salt tortusine **69** whose structure was deduced by comparison with related vasconine **70**.²⁰



Scheme 1 Reagents: i, Br_2 , CHCl_3 , MeOH , room temp.; ii, $\text{K}_3\text{Fe}(\text{CN})_6$, H_2O , NaHCO_3 , 60°C then **75**, stir 2 h; iii, Zn (active), EtOH , reflux, 15 h



Scheme 2 Reagents: i, 3,4-methylenedioxy-4-bromobenzene, Bu^tLi ; ii, $\text{CH}_2=\text{C}(\text{PPH}_3)$, THF ; iii, Tf_3O , py , $\text{C}_6\text{H}_{11}\text{N}=\text{CHCH}_2\text{Li}$, dil. acid; iv, $\text{Bu}_3\text{SnCH}_2\text{NH}_2$ (1 equiv.), 4 Å mol. sieve, Et_2O ; v, BuLi (1.9 equiv.), THF , -78°C , then H_2O ; vi, $\text{Me}_2\text{N}^+=\text{CH}_2\text{I}^-$, MeCN , heat, then HCl , MeOH ; vii, BuLi (1.9 equiv.), THF , -78°C then MeI (1.9 equiv.); viii, conc. HCl , MeOH then $\text{CH}(\text{OMe})_3$; ix, MeSO_3H (10 equiv.), CH_2Cl_2 , room temp.

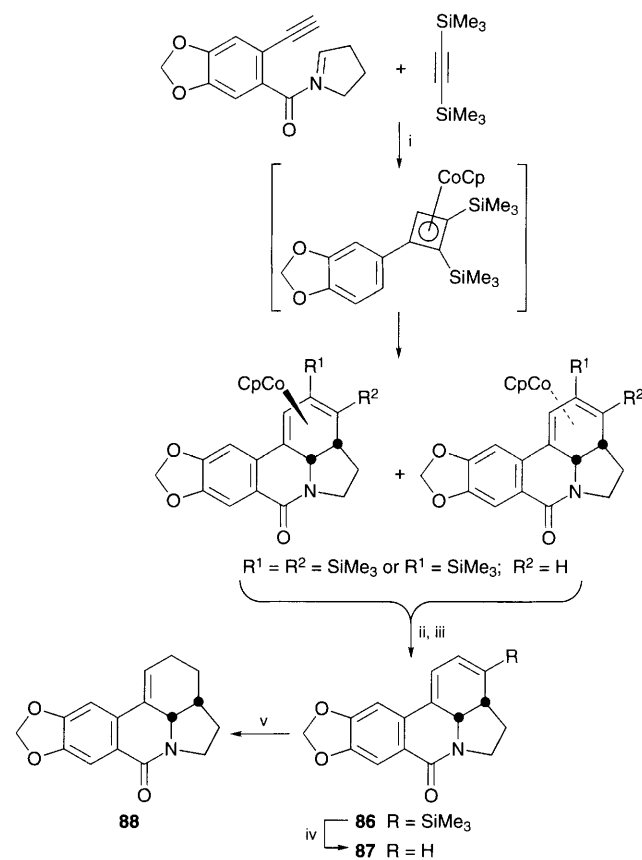
Pancreatum maritimum, found in Turkey, has been investigated extensively over the past three years. The bulbs were first shown to contain two alkaloids, (-)-lycorine **5** and (+)-9-*O*-demethylhomolycorine **37**, and the ariel parts contain trisphaeridine **15**.²¹ The latest publication²² has identified six alkaloids in its bulbs, namely (+)-haemanthamine **3**, (+)-buphanisine **25**, crinine **11**, (-)-3 β ,11 α -dihydroxy-1,2-dehydrocrinane **71**, (-)-8-hydroxy-9-methoxycrinane **72**, which were accompanied by the new alkaloid, (-)-3 β -methoxy-6 α ,11 β -dihydroxy-1,2-dehydrocrinane **73**.

3 Synthetic studies

The biomimetic synthesis of galanthamine **30**, first proposed and achieved by Barton and his group in 1962, has been re-examined several times and the yield of the critical oxidative

coupling step has been increased from 0.2 to 5%. In a recent publication²³ this oxidative coupling process has been increased to 39% but only through modification of the amide precursor **74** ($\text{R}=\text{H}$), derived from isovanillin and tyramine, by using an *N*-formyl- and dibromo-substituted **75** (Scheme 1). Debromination of the oxidatively coupled product **76** gave racemic galanthamine **77** which on resolution gave (-)-galanthamine **30**.

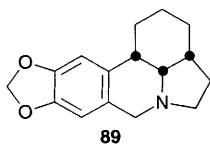
A short and efficient total synthesis of anabiline **87** has been accomplished using as a key step a cycloaddition procedure involving a 2-azaallyl anion with an alkene (Scheme 2). Starting with lactone **78**, introduction of the 3,4-methylenedioxyphenyl substituent was followed by a Wittig reaction to create hydroxy alkene **79** and hence aldehyde **80**, prior to stannane formation **81**. Addition of butyllithium in THF at -78°C to this stannane produced, by transmetalation, a 2-azaallyl anion which cyclised intramolecularly to give two diastereoisomers **82** and **83**. Treatment of **83** with Eschenmoser's salt in boiling acetonitrile, with subsequent removal of acetonide, resulted in the formation of (-)-anabiline **84** in 92% yield. The eight steps involved in this synthesis proceeded in a 43% overall yield.²⁴ (-)-Augustamine **85** was synthesised from the same 2-azaallyl anion by working up the cycloaddition product in the presence of iodomethane.



Scheme 3

Scheme 3 Reagents: i, $\text{CpCo}(\text{CO})_2$, THF , 25°C or reflux, $h\nu$; ii, Bu_4NF , THF , 25°C ; iii, $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$, $\text{THF}-\text{H}_2\text{O}$, 0°C ; iv, $\text{CF}_3\text{CO}_2\text{H}$, CDCl_3 , 55°C ; v, H_2 , $\text{ClRh}(\text{PPh}_3)_3$, PhMe , 25°C

The attractive concept of using a cobalt-mediated [2+2+2] cycloaddition reaction of the double bond of an enamine with two alkynes has been explored and has culminated in the construction of the galanthan skeleton, as exemplified by the synthesis of **88** which is a known precursor of γ -lycorane **89** (Scheme 3).²⁵ The mild protodesilylation sequence is to be noted.



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