Diterpenoid alkaloids†

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The lasting attention that researchers have devoted to diterpenoid alkaloids is due to their various bioactivities and toxicities, structural complexity, and intriguing chemistry. From 1998 to the end of 2008, more than 300 new diterpenoid alkaloids were isolated from Nature. This review focuses on their structural relationships, and investigations into their chemical reactions, synthesis, and biological activities. A table that lists the names, plant sources, and structural types is given along with 363 references.

1 Introduction

The important pharmacological activities and structural complexity of the diterpenoid alkaloids have long stimulated scientists' strong interest in their phytochemistry, synthesis, and medicinal chemistry. Since diterpenoid alkaloids were last reviewed in 1999 in this journal by Rahman and Choudhary,[1] they have remained an active area of research. Accordingly, a number of reviews considering various aspects have been published during this period. Hale and Manaviazar have reviewed some important chemical reactions and syntheses of diterpenoid alkaloids, covering the literature from 1985 to early 1998.[2] Ameri summarized the biological activities and mechanisms of action of several diterpenoid alkaloids,[3] while Wang and Xie highlighted the analgesic and anti-inflammatory activities of diterpenoid alkaloids investigated by Chinese researchers.[4] In 1999, Pelletier and coworkers reviewed the past 15 years' work of their research group on the isolation, determination of structures, rearrangement reactions, and spectroscopic studies of diterpenoid alkaloids.[5] Two years later, they compiled an exceedingly useful collection of ^{13}C NMR and ^{1}H NMR data and physical constants of C_{20}-diterpenoid alkaloids.[6] Bessonova and Saidkhodzhaeva listed the hetisine-type C_{20}-diterpenoid alkaloids isolated up to 1998.[7] Wang and Liang have contributed a comprehensive review covering the classification, distribution and occurrence, biosynthesis, spectroscopy, chemical reaction and stereochemistry, and pharmacological

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† Dedicated to the memory of Professor Xiao-Tian Liang (1923–2009).

activity of the C_{20}-diterpenoid alkaloids.[8] In this review, a new system of classification for C_{20}-diterpenoid alkaloids was proposed, and it was also suggested that the diterpenoid alkaloids be classified into three categories: the C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids. In addition, Wang *et al.* have reviewed the advances in various aspects of this field, such as the structures of the C_{19}-diterpenoid alkaloids between 1988 and 1998,[9] single-crystal X-ray analyses of the diterpenoid alkaloids up to 2002,[10] and the pharmacological activities of diterpenoid alkaloids between 1984 and 2002.[11] It is also worthwhile to note here that Brimble and coworkers have published an excellent review on the advances in the synthesis of methyllycaconitine and its analogues.[12]

During the review period, in addition to the great progress in the phytochemical investigations on the diterpenoid alkaloids, the following advances should also be pointed out:

1) From the view of pharmacological activities, 8-*O*-azeloyl-14-benzoylaconine, first isolated from *Aconitum karacolicum* by the French scientists Robert and coworkers, exhibits *in vitro* cytotoxicity (IC_{50} = 10–20 μM).[13] It was reported by Chinese scientists that talatisamine is a potent and specific blocker of the delayed rectifier K^+ channel in rat hippocampal neurons,[14] and songorine, designated as a novel $GABA_A$ receptor antagonist in rat brain, can enhance the excitatory synaptic transmission in rat hippocampus.[15]

2) Guan-fu base A has been developed by Jing-Han Liu *et al.* for the therapeutic treatment of arrhythmia in China.[16]

3) Xiao and Wang *et al.* have already systematically summarized the phytotaxonomic characteristic of diterpenoid alkaloids from Chinese *Aconitum*, and their reliable taxonomic character of the genus.[17]

4) Soft-ionization mass spectrometry (ESI-MS, LC–MS-MS, ESI-MS^n, LC–ESI-MS^n *etc*.) has been extensively applied to the monitoring of diterpenoid alkaloids from mixed samples. Ohta, Wada, Liu, and Katz are among the scientists who are active in this field.

5) Wang and coworkers have converted a C_{19}-diterpenoid alkaloid, deltaline, to the ABC core system of taxanes.[18]

6) The total synthesis of the C_{20}-diterpenoid alkaloid nominine has been completed independently by Muratake and Natsume,[19] as well as by Gin and Peese.[20]

This review focuses on the phytochemical investigations, chemical reactions, synthetic studies, and biological activities of diterpenoid alkaloids, covering the literature from 1998 to 2008. In addition, the advances in soft-ionization MS studies and phytotaxonomic researches during the period are also discussed.

2 Phytochemical investigations

The system of classification of diterpenoid alkaloids we previously proposed is adopted throughout this review.[8] Accordingly, C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids will be discussed by category, and their types and code numbers referred to in the review are shown in Fig. 1. The chemical structures given in the review are predominantly those of new alkaloids. However, structures of known alkaloids are also given when necessary. The structural abbreviations used here

Feng-Peng Wang

Feng-Peng Wang was born in Shanxi Province, China. He studied medicinal chemistry with Professor Xiao-Tian Liang at the Institute of Material Medica, China Union Medical University & Chinese Academy of Medical Sciences, and obtained his PhD in 1984. He then spent two years at the University of Georgia, USA, working with Professor S. W. Pelletier. In 1992, he was promoted to full professor at the West China University of Medical Sciences. His research involves phytochemistry and syntheses of natural products with biological activities. Of specific interest are the toxic and complex diterpenoid alkaloids from Aconitum *and* Delphinium *species.*

Qiao-Hong Chen

Qiao-Hong Chen, born in 1968, received her PhD degree from Sichuan University, China, under the supervision of Professor Feng-Peng Wang. She was a CIHR/Rx&D-HRF Postdoctoral Fellow and an AHFMR Postdoctoral Fellow under Professor Edward Knaus for three years at the University of Alberta in Canada. For another three years, she worked as a senior research fellow in Professor David Kingston's group at Virginia Tech in the USA. Appointed as a lecturer in 2001, she was promoted to the position of full professor in 2003 at Sichuan University. Her research interests are focused on natural product-based drug design and drug discovery.

Xiao-Yu Liu

Xiao-Yu Liu was born in 1985 in Sichuan province of China. After receiving his Bachelor degree in 2006, he joined the group of Professor Wang at West China College of Pharmacy, Sichuan University. He is currently carrying out his doctoral research on the chemistry of diterpenoid alkaloids.

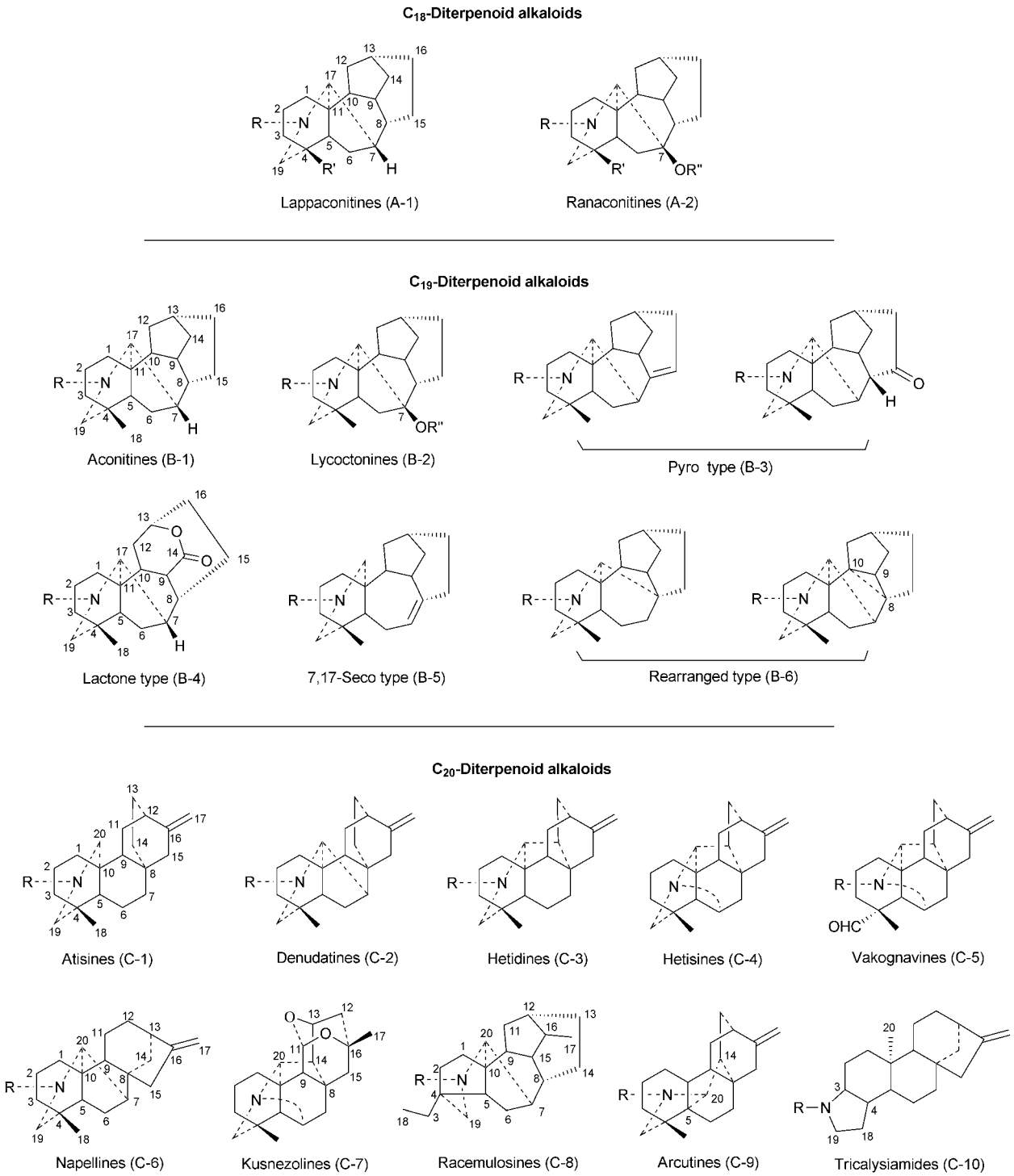


Fig. 1 Types of diterpenoid alkaloids covered in this review (R and R″ can be hydrogen, alkyl, or acyl groups; R′ can be hydrogen, hydroxyl, alkoxy, or acyloxy groups).

are indicated in Fig. 2.‡ Listed in Table 1 are the names, plant sources, types, along with the references of all the new diterpenoid alkaloids reported from 1998 to 2008. Most of the diterpenoid alkaloids during this period were isolated from the genera *Aconitum*, *Consolida* and *Delphinium* of the Ranunculaceae family, and the genus *Spiraea* of the Rosaceae family, with just a few from other genera.

2.1 C_{18}-Diterpenoid alkaloids

2.1.1 Lappaconitines. The lappaconitine-type C_{18}-diterpenoid alkaloids are structurally characterized by the presence of

‡ Throughout this review, the • symbol has been used at ring junctions in chemical structures to indicate a hydrogen atom that is pointing 'up', *i.e.* out of the plane of the paper.

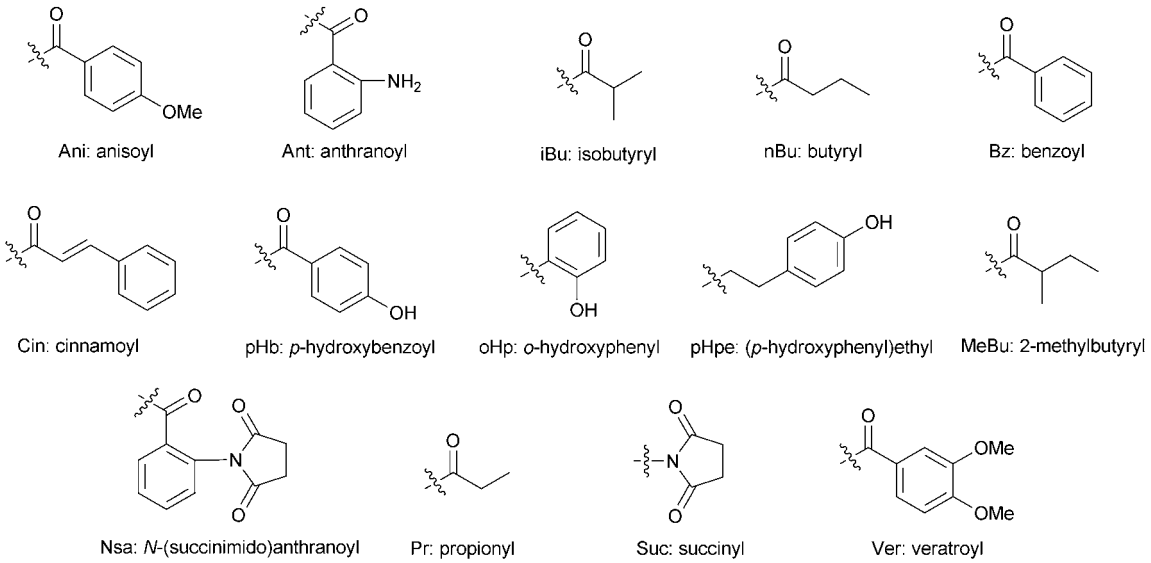
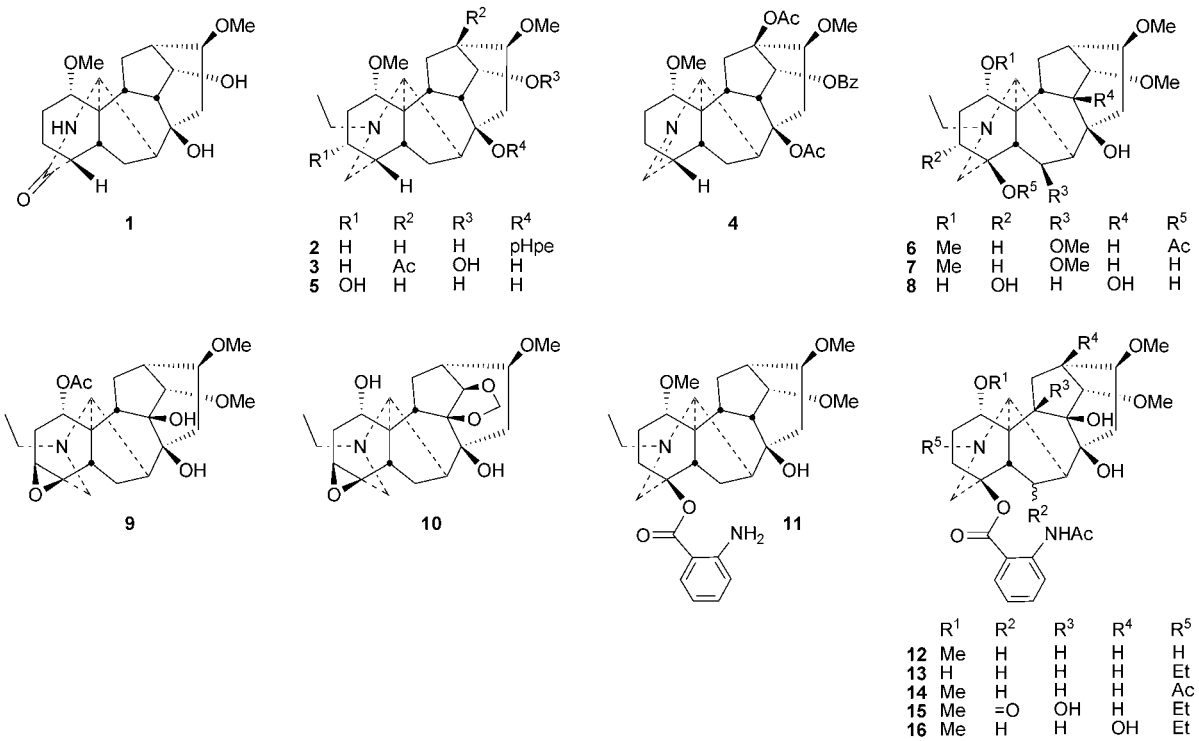


Fig. 2 Structural abbreviations used in this review.

a methine unit at C-7.[21] Sixteen lappaconitine-type alkaloids (**1–16**) were obtained.[22–33] Most of them come from *Aconitum* species, with the exception of alkaloid **11**, which is derived from a *Delphinium* species.

Structurally, piepunendine A (**1**) includes a lactam carbonyl at C-19, while piepunendine B (**2**) is the first example of a C_{18}-diterpenoid alkaloid from Nature with a 2-(*p*-hydroxyphenyl)ethoxy group at C-8.[22] Delavaconitine G (**4**) possesses an azomethine group between *N* and C-19.[23] Akiradin (**9**) and kiridine (**10**) possess a C-3,C-4 epoxide group.[28,29] In addition, kiridine (**10**), whose structure was established by X-ray crystallographic analysis, is also the first example of a diterpenoid alkaloid that contains a 9,14-methylenedioxy group. Lappaconitines **12–16** possess an *N*-acetylanthranoyloxy substituent at C-18.[31–33]

2.1.2 Ranaconitines. The ranaconitine-type C_{18}-diterpenoid alkaloids, featuring an oxygen-containing functionality at C-7,



	R^1	R^2	R^3	R^4	R^5
2	H	H	H	pHpe	
3	H	Ac	OH	H	
5	OH	H	H	H	
6	Me	H	OMe	H	Ac
7	Me	H	OMe	H	H
8	H	OH	H	OH	H
12	Me	H	H	H	H
13	H	H	H	H	Et
14	Me	H	H	H	Ac
15	Me	=O	OH	H	Et
16	Me	H	H	OH	Et

Table 1 New diterpenoid alkaloids isolated from 1998 to 2008

Source	Diterpenoid alkaloid	Type[a]	Ref.
Aconitum arcuatum	Arcutin(e) (**346**)	C-9	220
	Arcutinine (**347**)	C-9	221
Aconitum balfourii	9-Hydroxysenbushine A (**112**)	B-1	84
Aconitum barbatum var. *hispidum*	11α-Hydroxylepenine (**294**)	C-2	182
Aconitum brunneum	3α-Hydroxy-12-*epi*-napelline (**338**)	C-6	210
Aconitum bulleyanum	Talatisamine 8-acetyl-14-*p*-methoxybenzoate (**54**)	B-1	57
	Talatisamine 14-*p*-methoxybenzoate (**55**)	B-1	57
Aconitum carmichaeli	14-*O*-Anisoylneoline (**90**)	B-1	71
	8-*O*-Cinnamoylneoline (**91**)	B-1	72
	14-*O*-Cinnamoylneoline (**89**)	B-1	71
	Lipo-14-*O*-anisoylbikhaconine (**134**)	B-1	71
	Lipoforesaconitine (**135**)	B-1	102
	14-*O*-Veratroylneoline (**88**)	B-1	71
Aconitum cochleare	Acochlearine (**288**)	C-2	180
	Acoleareine (**116**)	B-1	88
	Aconitilearine (**94**)	B-1	74
	Cochleareine (**262**)	C-1	88
	N-Deethylmethyllycaconitine (**211**)	B-2	74
Aconitum coreanum	13-Acetyl-14-hydroxy-2-propionylhetisine (**309**)	C-4	191
	Guan-fu base K (**343**)	C-7	218
	Guan-fu base P (**310**)	C-4	192
	Guan-fu base Q (**312**)	C-4	194
	Guan-fu base R (**311**)	C-4	193
	Guan-fu base S (**315**)	C-4	196
	Guan-fu base T (**313**)	C-4	195
	Guan-fu base U (**314**)	C-4	195
Aconitum delavayi	Delavaconitine F (**3**)	A-1	23
	Delavaconitine G (**4**)	A-1	23
Aconitum episcopale	Liaconitine A (**81**)	B-1	68
	Liaconitine B (**82**)	B-1	68
	Liaconitine C (**83**)	B-1	68
	Secoyunaconitine (**251**)	B-5	157
Aconitum excelsum	6-Demethyldelsoline (**150**)	B-2	35
	Exceconidine (**17**)	A-2	34
	Excecoitine (**150**)	B-2	34
	8-Methyl-10-hydroxyllycoctonine (**168**)	B-2	35
	8-Methyllycoctonine (**169**)	B-2	35
	6-Methylumbrofine (**17**)	A-2	35
Aconitum falconeri	Faleoconitine (**104**)	B-1	76
	3′-Methoxyacoforestinine (**98**)	B-1	76
Aconitum geniculatum	Geniculatine A (**87**)	B-1	52
	Geniculatine B (**88**)	B-1	52
	Geniculatine C (**52**)	B-1	52
	Geniculatine D (**47**)	B-1	52
	Geniculine (**99**)	B-1	77
	Genicunine A (**40**)	B-1	49
	Genicunine B (**41**)	B-1	49
	Genicunine C (**50**)	B-1	49
Aconitum habaense	Habaenine A (**146**)	B-1	81
	Habaenine B (**108**)	B-1	81
	Habaenine C (**147**)	B-1	106
Aconitum hemsleyanum	Hemsleyatine (**130**)	B-1	99
Aconitum hemsleyanum var. *atropurpureum*	Atropurpursine (**103**)	B-1	79
	3-Hydroxyfranchetine (**246**)	B-5	79
Aconitum hemsleyanum var. *circinatum*	Circinadine A (**63**)	B-1	62
	Circinadine B (**64**)	B-1	62
	Circinasine A (**68**)	B-1	61
	Circinasine B (**69**)	B-1	61
	Circinasine C (**65**)	B-1	61
	Circinasine D (**61**)	B-1	61
	Circinasine E (**62**)	B-1	61
	Circinasine F (**70**)	B-1	61
	Circinasine G (**140**)	B-1	61
	Hemsleyanine A (**66**)	B-1	63
	Hemsleyanine B (**67**)	B-1	63
	Hemsleyanine C (**59**)	B-1	60
	Hemsleyanine D (**60**)	B-1	60
Aconitum hemsleyanum var. *leueanthus*	Leueandine (**245**)	B-5	142
	Leueantine A (**100**)	B-1	56
	Leueantine B (**79**)	B-1	56
	Leueantine C (**53**)	B-1	56

Table 1 (*Contd.*)

Source	Diterpenoid alkaloid	Type[a]	Ref.
	Leueantine D (**110**)	B-1	56
Aconitum hemsleyanum var. *pengzhouense*	8-Deacetylsungpaconitine (**97**)	B-1	75
	13-Deoxyludacontine (**96**)	B-1	75
	6-*epi*-Forsticine (**109**)	B-1	82
	Pengshenine A (**136**)	B-1	103
	Pengshenine B (**138**)	B-1	103
Aconitum heterophyllum	6-Dehydroacetylsepaconitine (**15**)	A-1	33
	13-Hydroxylappaconitine (**16**)	A-1	33
Aconitum jaluense	Jaluenine (**316**)	C-4	197
Aconitum karacolicum	8-*O*-Azeloyl-14-benzoylaconine (**133**)	B-1	13
	Secokaraconitine (**250**)	B-5	155,156
Aconitum karakolicum	Acofamine A (**119**)	B-1	90
	Acofamine B (**120**)	B-1	90
Aconitum kirinense	Akiradin (**9**)	A-1	28
	Akiramidine (**7**)	A-1	26
	Akiramine (**6**)	A-1	25
	Kiridine (**10**)	A-1	29
	Kirinine B (**295**)	C-2	183
	Kirinine C (**296**)	C-2	183
Aconitum kongboense	Kongboendine (**244**)	B-5	152
	Kongboentine A (**132**)	B-1	83
	Kongboentine B (**111**)	B-1	83
Aconitum kusnezoffii	3-Acetylaconifine (**124**)	B-1	94
	3-Acetylmesaconitine (**125**)	B-1	94
	Acsonine (**247**)	B-5	154
	Beiwudine (**247**)	B-5	153
	Beiwucine (**122**)	B-1	92
	Beiwusine A (**257**)	C-1	164
	Beiwusine B (**258**)	C-1	164
	6-*epi*-Forsticine (**109**)	B-1	82
Aconitum laeve	Swatinine (**161**)	B-2	113
Aconitum liljestrandii	*N*-Deethyltalatisamine (**56**)	B-1	58
	Liljestrandinine (**58**)	B-1	58
	Liljestrandisine (**57**)	B-1	59
Aconitum leave	*N*-Deethyllycaconitine-*N*-aldehyde (**203**)	B-2	135
	14-Demethyllycaconitine (**204**)	B-2	135
	8-Methyllycaconitine (**222**)	B-2	135
Aconitum lycoctonum	6-*O*-Acetyldemethylenedelcorine (**152**)	B-2	108
	6-*O*-Acetyl-14-*O*-methyldelphinifoline (**151**)	B-2	108
Aconitum macrorhynchum	Macrorhynine A (**142**)	B-1	104
	Macrorhynine B (**143**)	B-1	104
Aconitum manshuricum	Manshuritine (**127**)	B-1	97
Aconitum nagarum	10-Dehydroxyflavaconitine (**126**)	B-1	96
	13-Hydroxyfranchetine (**249**)	B-5	96
Aconitum nagarum var. *lasiandrum*	14-Benzoylsachaconitine (**33**)	B-1	43
	N-Deethyl-*N*-methyl-12-*epi*-napelline (**339**)	C-6	179
	16,17-Dihydro-12β,16β-epoxynapelline (**340**)	C-6	179
	11-*epi*-16α,17-Dihydroxylepenine (**287**)	C-2	179
	Francheline (**248**)	B-5	100
	Lasianine (**131**)	B-1	100
	Lasiansine (**113**)	B-1	85
	Nagadine (**138**)	B-1	43
Aconitum napellus	Merckonine (**144**)	B-1	105
Aconitum nasutum	Trabzonine (**304**)	C-3	187
Aconitum naviculare	Naviculine A (**307**)	C-3	189
	Naviculine B (**306**)	C-3	189
	Navirine (**308**)	C-3	190
Aconitum nemorum	1-*epi*-Deacetylaconitine (**118**)	B-1	89
Aconitum orochryseum	2-*O*-Acetyl-7α-hydroxyorochrine (**319**)	C-4	198
	2-*O*-Acetylorochrine (**318**)	C-4	198
	Orochrine (**317**)	C-4	198
Aconitum ouvrardianum	Ouvrardiandine A (**269**)	C-1	78
	Ouvrardiandine B (**270**)	C-1	78
	Ouvrardiantine (**102**)	B-1	78
Aconitum piepunense	18-Acetylcammaconine (**49**)	B-1	54
	Piepunendine A (**1**)	A-1	22
	Piepunendine B (**2**)	A-1	22
	Piepunensine A (**145**)	B-1	54
Aconitum pseudo-laeve var. *erectum*	18-*O*-2-(2-Methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine (**221**)	B-2	65

Table 1 (*Contd.*)

Source	Diterpenoid alkaloid	Type[a]	Ref.
	14-*O*-Acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine (**77**)	B-1	65
Aconitum racemulosum var. *pengzhouense*	Racemulodine (**301**)	C-3	185
	Racemuloline A (**149**)	B-2	50
	Racemuloline B (**42**)	B-1	50
	Racemulosine (**345**)	C-8	219
	Racemulotine (**341**)	C-6	211
Aconitum septentrionale	Acoseptine (**252**)	B-6	158
	Anhydrolycaconitine (**253**)	B-6	159
	Septonine (**254**)	B-6	162
	Septontrionine (**255**)	B-6	162
Aconitum sinomontanum	Sinaconitine A (**31**)	A-2	32
	Sinaconitine B (**14**)	A-1	32
	Sinomontanine A (**12**)	A-1	31
	Sinomontanine B (**13**)	A-1	31
	Sinomontanine C (**75**)	B-1	31
	Sinomontanine D (**23**)	A-2	27
	Sinomontanine E (**8**)	A-1	27
	Sinomontanine F (**29**)	A-2	41
	Sinomontanine G (**28**)	A-2	41
	Sinomontanine H (**30**)	A-2	41
	Sinomontanine I (**205**)	B-2	41
	Sinomontanitine A (**45**)	B-1	31
	Sinomontanitine B (**46**)	B-1	31
Aconitum soongoricum	12-Acetyl-12-*epi*-napelline (**337**)	C-6	209
Aconitum spicatum	Spicatine A (**123**)	B-1	93
	Spicatine B (**126**)	B-1	93
Aconitum sungpanense var. *leucanthum*	Leucanthumsine A (**84**)	B-1	69
	Leucanthumsine B (**85**)	B-1	69
	Leucanthumsine C (**95**)	B-1	69
	Leucanthumsine D (**141**)	B-1	69
	Leucanthumsine E (**107**)	B-1	69
Aconitum taipaicum	Isodelelatine (**179**)	B-2	122
Aconitum tanguticum	Tangutimine (**305**)	C-3	188
	Tangutisine A (**332**)	C-5	205
	Tangutisine B (**333**)	C-5	206
Aconitum toxicum	Acotoxicine (**5**)	A-1	24
	Acotoxinine (**92**)	B-1	73
Aconitum transsectum	*N*-Deethylchasmanine (**80**)	B-1	67
	8-*O*-Ethylyunaconitine (**101**)	B-1	67
	Transconitine D (**137**)	B-1	67
	Transconitine E (**105**)	B-1	67
Aconitum tuberosum	Tuberacontine (**128**)	B-1	98
	Tuberanine (**125**)	B-1	95
	Tubermesaconitine (**129**)	B-1	98
Aconitum variegatum	14-Acetylgenicunine B (**34**)	B-1	44
	N-Deethyl-*N*-19-didehydrosachaconitine (**139**)	B-1	44
	8-Ethoxysachaconitine (**37**)	B-1	44
	16β-Hydroxycardiopetaline (**44**)	B-1	44
	N-Ethyl-1α-hydroxy-17-veratroyldictizine (**291**)	C-2	44
	Variegatine (**300**)	C-3	44
	15-Veratroyl-17-acetyldictizine (**289**)	C-2	44
	15-Veratroyl-17-acetyl-19-oxodictizine (**292**)	C-2	44
	15-Veratroyldictizine (**290**)	C-2	44
Aconitum vilmorinianum	Vilmoraconitine (**256**)	B-6	163
Aconitum vulparia	Acovulparine (**233**)	B-2	145
	Vulparine (**219**)	B-2	140
Aconitum sp. (cultivated in Korea)	8-*O*-Methylhypaconine (**121**)	B-1	91
Ascidian *Lissoclinum* spp.	Haterumaimide A (**354**)	M	225
	Haterumaimide B (**355**)	M	225
	Haterumaimide C (**356**)	M	225
	Haterumaimide D (**357**)	M	225
	Haterumaimide E (**358**)	M	225
	Haterumaimide F (**359**)	M	226
	Haterumaimide G (**360**)	M	226
	Haterumaimide H (**361**)	M	226
	Haterumaimide I (**362**)	M	226
	Haterumaimide J (**363**)	M	227
	Haterumaimide K (**364**)	M	227

Table 1 (*Contd.*)

Source	Diterpenoid alkaloid	Type[a]	Ref.
Chamaecyparis obtusa cv. *tetragon*	Chamobtusin A (**353**)	M	224
Clitocybe concava	Concavine (**352**)	M	223
Consolida ambigua	13-Acetylvakhmatine (**324**)	C-4	199
Consolida armeniaca	Consolarine (**148**)	B-2	107
Consolida glandulosa	9-*O*-Acetylglanduline (**325**)	C-4	200
	9-Deoxyglanduline (**328**)	C-4	200
	11,13-*O*-Diacetylglanduline (**326**)	C-4	200
	Glandulosine (**327**)	C-4	200
Consolida hohenackeri	Consolinine (**86**)	B-1	70
	Hoheconsoline (**93**)	B-1	70
Consolida oliveriana	7α-Hydroxycossonidine (**329**)	C-4	53
	8-*O*-Methylcolumbianine (**48**)	B-1	53
	Olividine (**237**)	B-2	53
	Olivimine (**232**)	B-2	53
Consolida orientalis	14-*O*-Acetyltakaosamine (**162**)	B-2	114
	18-*O*-Benzoyl-14-*O*-deacetyl-18-*O*-demethylpubescenine (**174**)	B-2	39
	14-*O*-Benzoyltakaosamine (**163**)	B-2	39
	Consorientaline (**260**)	C-1	167
	14-Deacetyl-18-demethylpubescenine (**175**)	B-2	118
	14-*O*-Deacetylpubescenine (**172**)	B-2	39
	Dehydrodeltatsine (**226**)	B-2	114
	14-*O*-Demethyldelboxine (**26**)	A-2	39
	18-Demethoxypubescenine (**171**)	B-2	114
	18-Demethylpubescenine (**170**)	B-2	117
	1-*O*-Demethyltricornine (**164**)	B-2	39
	1-*O*,19-Didehydrotakaosamine (**227**)	B-2	39
	8-*O*-Methylconsolarine (**173**)	B-2	39
Consolida scleroclada	Willipelletierine (**293**)	C-2	181
Delphinium alpinum	Alpinine (**225**)	B-2	143
Delphinium anthriscifolium var. *savatieri*	Anthriscifolcine A (**18**)	A-2	36
	Anthriscifolcine B (**19**)	A-2	36
	Anthriscifolcine C (**20**)	A-2	36
	Anthriscifolcine D (**21**)	A-2	36
	Anthriscifolcine E (**22**)	A-2	36
Delphinium bonvalotii	Bonvalotidine A (**196**)	B-2	132
	Bonvalotidine B (**197**)	B-2	132
	Bonvalotidine C (**198**)	B-2	132
Delphinium brunonianum	Delbruninol (**181**)	B-2	124
Delphinium buschianum	Budelphine (**240**)	B-2	147
Delphinium campylocentrum	Campylocine (**230**)	B-2	128
	Campylotine (**185**)	B-2	128
Delphinium carduchorum	Carduchoron (**298**)	C-3	184
	Delcarduchol (**297**)	C-3	184
Delphinium corymbosum	Delcorinine (**180**)	B-2	123
Delphinium crispulum	Crispulidine (**36**)	B-1	30
	Delphicrispuline (**11**)	A-1	30
Delphinium chrysotrichum	Delphatisine A (**267**)	C-1	172
	Delphatisine B (**268**)	C-1	172
Delphinium cuneatum	16-Demethoxymethyllycaconitine (**210**)	B-2	137
	16-Demethoxydelavaine (**218**)	B-2	139
Delphinium cyphoplectrum	Cyphoplectine (**74**)	B-1	64
Delphinium davidii	Davidisine A (**165**)	B-2	115
	Davidisine B (**166**)	B-2	115
Delphinium dissectum	10-Hydroxymethyllycaconitine (**212**)	B-2	112
Delphinium excelsum	10-Hydroxymethyllycaconitine (**212**)	B-2	112
	10-Hydroxynudicaulidine (**160**)	B-2	112
	18-*O*-Methyldelterine (**159**)	B-2	112
Delphinium fangshanense	16-Demethyldelsoline (**153**)	B-2	109
Delphinium giraldii	Giraldine A (**154**)	B-2	110
	Giraldine B (**155**)	B-2	110
	Giraldine C (**156**)	B-2	110
	Giraldine D (**176**)	B-2	111
	Giraldine E (**157**)	B-2	111
	Giraldine F (**158**)	B-2	111
	Giraldine G (**216**)	B-2	51
	Giraldine H (**217**)	B-2	51
	Giraldine I (**43**)	B-1	51
Delphinium gracile	Delphigraciline (**321**)	C-4	47

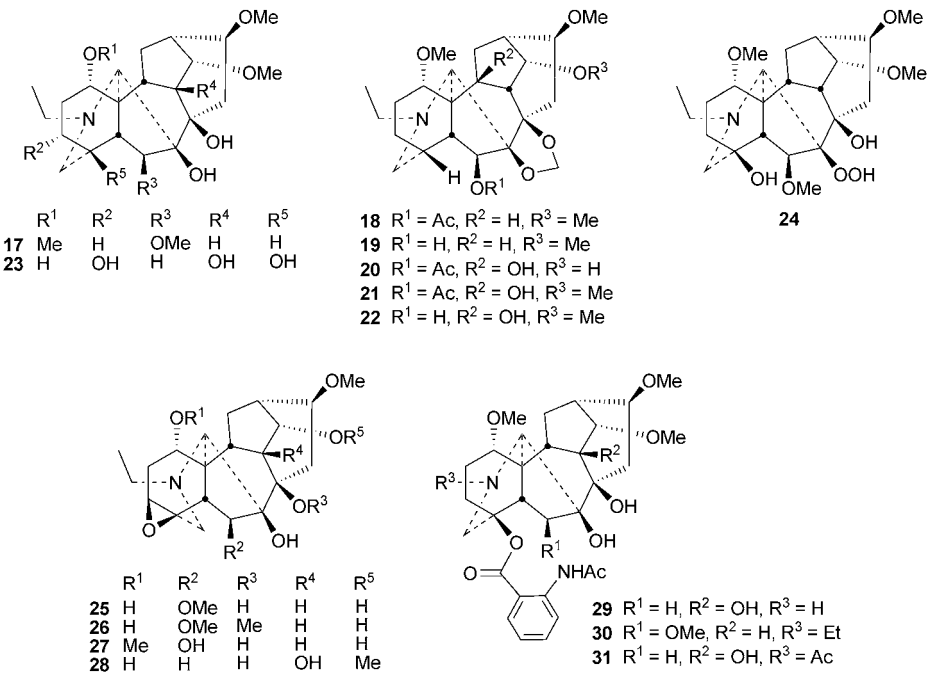
Table 1 (*Contd.*)

Source	Diterpenoid alkaloid	Type[a]	Ref.
	14-Hydroxyhetisinone *N*-oxide (**322**)	C-4	47
	8-Methylkarakoline (**38**)	B-1	47
Delphinium laxicymosum var. *pilostachyum*	Laxicymine (**228**)	B-2	125
	Laxicyminine (**229**)	B-2	125
	Laxicymisine (**182**)	B-2	125
Delphinium linearilobum	Linearilin (**24**)	A-2	37
	Linearilobin (**76**)	B-1	37
Delphinium nordhagenii	Nordhagenine A (**193**)	B-2	131
	Nordhagenine B (**194**)	B-2	131
	Nordhagenine C (**195**)	B-2	131
Delphinium nuttallianum	14-Acetylbearline (**207**)	B-2	136
	Bearline (**209**)	B-2	136
	16-Deacetylgeyerline (**208**)	B-2	136
Delphinium orthocentrum	Deacetylswinanine A (**184**)	B-2	127
	Orthocentrine (**236**)	B-2	127
Delphinium pentagynum	2-Dehydrodeacetylheterophylloidine (**299**)	C-3	146
	14-Demethyl-14-acetylanhweidelphinine (**235**)	B-2	146
	14-Demethyl-14-isobutyrylanhweidelphinine (**234**)	B-2	146
Delphinium poltoratskii	Delpoline (**32**)	B-1	42
Delphinium potaninii	Potanisine F (**223**)	B-2	142
	Potanisine G (**224**)	B-2	142
Delphinium potaninii var. *jiufengshanense*	Jiufengdine (**200**)	B-2	133
	Jiufengsine (**177**)	B-2	119
	Jiufengtine (**199**)	B-2	133
Delphinium pyramidale	8-Acetylcondelphine (**51**)	B-1	55
Delphinium roylei	Royleinine (**106**)	B-1	80
Delphinium scabriflorum	13-(2-Methylbutyryl)azitine (**284**)	C-1	178
Delphinium shawurense	Shawurensine (**220**)	B-2	141
Delphinium siwanense var. *leptogen*	Siwanine A (**186**)	B-2	129
	Siwanine B (**187**)	B-2	129
	Siwanine C (**188**)	B-2	129
	Siwanine D (**189**)	B-2	129
Delphinium souliei	Soulidine (**191**)	B-2	130
	Souline A (**114**)	B-1	86
	Souline B (**243**)	B-4	86
	Souline C (**190**)	B-2	48
	Souline D (**39**)	B-1	48
	Souline E (**35**)	B-1	45,46
	Souline F (**320**)	C-4	45,46
Delphinium stapeliosum	14-Deacetyl-14-isobutyrylajadine (**202**)	B-2	38
	14-Deacetyl-14-isobutyrylnudicauline (**206**)	B-2	38
	14-Demethyltuguaconitine (**25**)	A-2	38
Delphinium staphisagria	22-*O*-Acetyl-19-oxodihydroatisine (**286**)	C-1	177
	Isoazitine (**283**)	C-1	177
	19-Oxodihydroatisine (**285**)	C-1	177
Delphinium tatsienense var. *chinghaiense*	Tatsienine V (**178**)	B-2	121
Delphinium tiantaishanense	Tiantaishandine (**323**)	C-4	40
	Tiantaishanmine (**238**)	B-2	40
	Tiantaishannine (**192**)	B-2	40
	Tiantaishansine (**27**)	A-2	40
Delphinium tongolense	Tongolenine C (**231**)	B-2	144
	Tongolenine D (**239**)	B-2	144
Delphinium trifoliolatum	Trifoliolasine A (**201**)	B-2	134
	Trifoliolasine B (**214**)	B-2	134
	Trifoliolasine C (**215**)	B-2	134
	Trifoliolasine D (**334**)	C-5	207
	Trifoliolasine E (**335**)	C-5	207
	Trifoliolasine F (**336**)	C-5	207
Delphinium uncinatum	14-Acetylchasmanine (**78**)	B-1	66
	Uncinatine (**261**)	C-1	168
Delphinium uralense	Uraline (**213**)	B-2	138
	Uraphine (**183**)	B-2	126
Delphinium virgatum	*N*-Deethylperegrine alcohol (**115**)	B-1	87
Spiraea formosana	Spiraeaine A (**272**)	C-1	173
Spiraea fritschiana var. *parvifolia*	Spirafine II (**302**)	C-3	186
	Spirafine III (**303**)	C-3	186
Spiraea japonica var. *acuta*	Spiramide (**265**)	C-1	166,171
	Spiramine P (**275**)	C-1	175
	Spiramine Q (**276**)	C-1	175

Table 1 (*Contd.*)

Source	Diterpenoid alkaloid	Type[a]	Ref.
	Spiramine T (**278**)	C-1	175
	Spiramine U (**277**)	C-1	175
	Spiramine W (**279**)	C-1	176
	Spiramine X (**273**)	C-1	174
	Spiramine Y (**274**)	C-1	174
	Spiramine Z (**281**)	C-1	174
	Spiratine A (**259**)	C-1	165,166
	Spiratine B (**280**)	C-1	165,166
Spiraea japonica	6-Hydroxylspiraqine (**331**)	C-4	201
var. *fortunei*	Spiraqine (**330**)	C-4	201
Spiraea japonica	Deacetylspiramine F (**271**)	C-1	169,170
var. *ovalifolia*	15-Deacetylspiramine S (**266**)	C-1	169,170
	19-*O*-Deethylspiramine N (**282**)	C-1	169,170
	Spiramidine A/spiramine Z-2 (**263**)	C-1	169,170
	Spiramidine B/spiramine Z-3 (**264**)	C-1	169,170
Tricalysia dubia	Tricalysiamide A (**348**)	C-10	222
	Tricalysiamide B (**349**)	C-10	222
	Tricalysiamide C (**350**)	C-10	222
	Tricalysiamide D (**351**)	C-10	222

[a] M: Miscellaneous.



comprise 15 new members (**17–31**).[27,32,34–41] All of these alkaloids come from the genera *Aconitum*, *Consolida* and *Delphinium*.

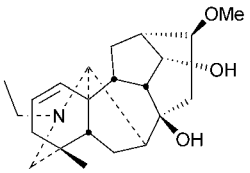
The alkaloid linearilin (**24**) has a rare hydroperoxyl group at C-7, which was confirmed by an iodine test.[37] There are four ranaconitine-type alkaloids that possess a C-3,C-4 epoxide unit, including 14-demethyltuguaconitine (**25**),[38] 14-*O*-demethyldelboxine (**26**),[39] tiantaishansine (**27**),[40] and sinomontanine G (**28**).[41] The structure of sinaconitine A (**31**) was confirmed by X-ray crystallographic analysis.[32]

2.2 C_{19}-Diterpenoid alkaloids

2.2.1 Aconitines. Aconitine-type C_{19}-diterpenoid alkaloids have no oxygen-containing functionality at C-7. Based on the nitrogen patterns, they may be subdivided into the following four subtypes: the amine, the *N*,*O*-mixed acetal, the imine, and the amide subtypes. The majority of these alkaloids are of the amine subtype. Here we will discuss the amine subtype in various groups based on whether oxygenated functionalities are attached at C-6 or C-15.

Alkaloids **32–77** lack oxygenated groups at both C-6 and C-15.[30,31,37,42–54,57,58,60–65] Delpoline (**32**) is the first aconitine-type alkaloid that has a $\Delta^{1,2}$ double bond.[42] Alkaloids **33–44** have a methyl group at C-4, and **36–38** contain an alkoxyl group at C-8. Alkaloids **39**, **42** and **43** have no oxygen-containing group at C-16; unusually, alkaloids **40** and **44** have a hydroxyl group at C-16.[30,43–51]

Sinomontanitines A (**45**) and B (**46**) possess an *N*-(succinimido)anthranoyl moiety at C-8, as well as a hydroxyl group at



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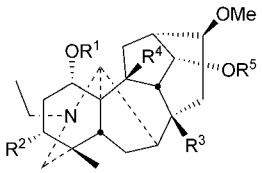
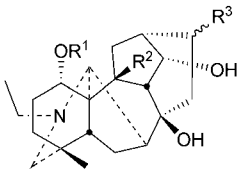


	R^1	R^2	R^3	R^4	R^5
33	Me	H	OH	H	Bz
34	Me	H	OH	OH	Ac
35	H	H	H	H	H
36	H	OH	OMe	H	H
37	Me	H	OEt	H	H
38	H	H	OMe	H	H

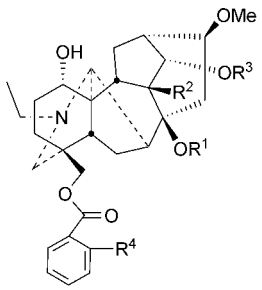


39 R^1 = Me, R^2 = H, R^3 = H
40 R^1 = Me, R^2 = H, R^3 = α-OH
41 R^1 = Me, R^2 = OH, R^3 = β-OMe
42 R^1 = Me, R^2 = OH, R^3 = H
43 R^1 = Me, R^2 = H, R^3 = H
44 R^1 = H, R^2 = H, R^3 = β-OH

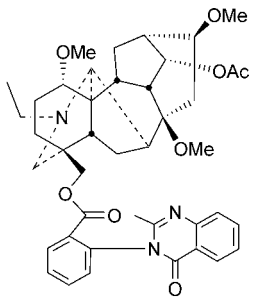
C-18.[31] Geniculatine D (**47**) and 8-*O*-methylcolumbianine (**48**) have a hydroxyl group at C-18; in contrast, the functionality at C-18 of 18-acetylcammaconine (**49**) is an acetate.[52–54]

Alkaloids **50–73** all have a methoxyl group at C-18. All of them were isolated from the genus *Aconitum* with an exception of 8-acetylcondelphine (**51**), which was obtained from *Delphinium pyramidale*. Among these alkaloids, genicunine C (**50**) has a carbonyl group at C-14,[49] while liljestrandinine (**58**) possesses a $\Delta^{15,16}$ double bond.[58] Investigation on the roots of *Aconitum hemsleyanum* var. *circinatum* by Wang *et al.* led to the isolation of twelve new aconitine-type alkaloids (**59–70**), as well as the revision of the structures of hemsleyadine, hemsleyanisine and isohemsleyanisine to the structures shown (**71–73**).[60–63] The structures of **68**, **70** and **71** were confirmed by single-crystal X-ray analysis. Of special interest are the alkaloids **59–62** and **66–70**, which possess an uncommon hydroxyl group at C-5.

Four new aconitine-type alkaloids (**74–77**) have benzoate or anthranilate derivatives at C-18. Sinomontanine C (**75**) contains a C-18 *N*-(succinimido)anthranoyl moiety,[31] and linearilobin (**76**) has an *N*-acetyl anthranoyl group at C-18 as well as a rare catechol unit at C-8.[37] Further investigation on *Aconitum pseudo-laeve* var. *erectum* resulted in the isolation of two unique C_{19}-diterpenoid alkaloids, 14-*O*-acetyl-8-*O*-methyl-18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoylcammaconine (**77**) and 18-*O*-2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoyllycoctonine (**221**). Interestingly, it was found for the first time that the 2-(2-methyl-4-oxo-4*H*-quinazoline-3-yl)benzoate moiety could exist as a substituent of diterpenoid alkaloids.[65]

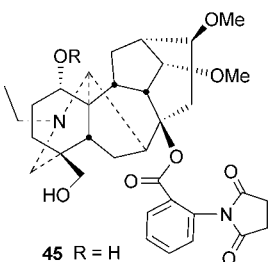


	R^1	R^2	R^3	R^4
74	Me	H	Me	OMe
75	H	OH	Me	Suc
76	oHp	H	H	NHAc

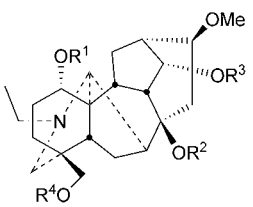


77

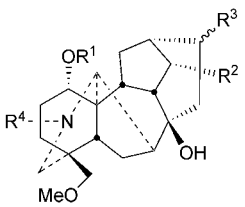
The alkaloids **78–116** possess an oxygenated group at C-6, most of which are configured in the α-orientation.[52,56,66–68,71,72,74,76,77,79,82] Leueantine B (**79**) has a cinnamoyl group at C-8,[56,66] while compound **80** is an *N*-deethyl analogue of chasmanine.[67] Liaconitines A–C (**81–83**) are characterized by the presence of a $\Delta^{2,3}$ double bond.[68] It should be mentioned that 14-*O*-veratroylneoline and geniculatine B have the same structure, **88**.[52,71] Aconitilearine (**94**) contains a C-19 hydroxyl group.[74] Geniculine (**99**) represents the first example of



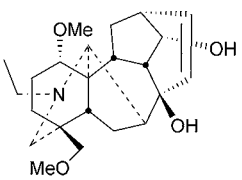
45 R = H
46 R = Me



	R^1	R^2	R^3	R^4
47	Me	H	Ver	H
48	H	Me	H	H
49	Me	H	H	Ac
51	H	Ac	Ac	Me
52	H	Ver	Ac	Me
53	Me	H	Cin	Me
54	Me	Ac	Ani	Me
55	Me	H	Ani	Me



	R^1	R^2	R^3	R^4
50	H	=O	β-OMe	Et
56	Me	OH	β-OMe	H
57	Me	OH	α-OH	Et



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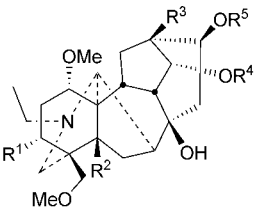
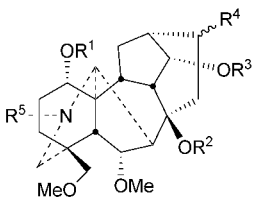


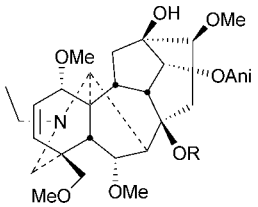
	R^1	R^2	R^3	R^4	R^5
59	H	OH	H	H	Me
60	H	OH	H	Ani	Me
61	H	OH	H	Ani	H
62	H	OH	H	H	H
63	OH	H	OH	Ani	Me
64	OH	H	OH	H	Me
65	OH	H	OH	H	Ani
66	H	OH	OH	pHb	Me
67	H	OH	OH	H	Me
68	H	OH	OH	H	Me
69	OH	OH	OH	Ani	H
70	OH	OH	OH	H	Me
71	H	OH	OH	Ani	Me
72	H	OH	OH	Ani	H
73	H	OH	OH	H	Ani

the occurrence of a *p*-hydroxybenzoyloxy group in the diterpenoid alkaloids.[77] Atropurpursine (**103**) is a rare aconitine-type alkaloid with 2β,3α-dihydroxyl groups.[79] Faleoconitine (**104**) contains a rare *N*-formyl functionality, which was confirmed by X-ray diffraction analysis.[76] Transconitine E (**105**) has a ketone group at C-1.[67]

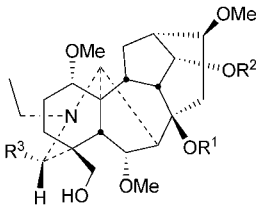
from *Aconitum* species since 1998. 8-*O*-Azeloyl-14-benzoylaconine (**133**) features a zwitterionic structure between the nitrogen atom and the azelaic acid chain at C-8.[13] It was proposed, with support from MS data, that lipo-14-*O*-anisoylbikhaconine (**134**) and lipoforesaconitine (**135**) have long-chain fatty acid esters at C-8.[71,102]



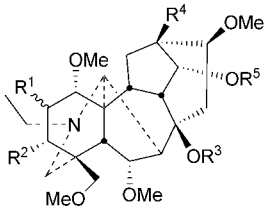
	R^1	R^2	R^3	R^4	R^5
78	Me	H	Ac	β-OMe	Et
79	Me	Cin	Ac	β-OMe	Et
80	Me	H	H	β-OMe	H
84	Me	Ac	Cin	α-OMe	Et
85	Me	H	Cin	α-OMe	Et
86	H	Me	H	β-OMe	Et
87	H	Ac	Ani	β-OMe	Et
88	H	H	Ver	β-OMe	Et
89	H	H	Cin	β-OMe	Et
90	H	H	Ani	β-OMe	Et
91	H	Cin	H	β-OMe	Et
92	H	Ver	H	β-OMe	Et



81 R = Ac
82 R = Ani
83 R = Et



93 R^1 = Me, R^2 = Me, R^3 = H
94 R^1 = H, R^2 = Me, R^3 = OH
95 R^1 = H, R^2 = H, R^3 = H



	R^1	R^2	R^3	R^4	R^5
96	H	OH	H	H	Bz
97	H	OH	H	H	Cin
98	H	OH	Et	OH	Ver
99	H	OH	Ac	OH	pHb
100	H	OH	Cin	H	Ac
101	H	OH	Et	OH	Ani
102	α-OH	H	Ac	OH	Ani
103	β-OH	OH	Ac	OH	Bz

Most of the aconitine-type alkaloids (such as **109–113**) possess an α-oriented hydroxyl group at C-6. In contrast, alkaloids **114–116** are in a minority, with a β-oriented substitutent at C-6. The structure of 6-*epi*-forsticine (**109**) was established by its 2D NMR data and X-ray diffraction analysis. Accordingly, the structure of forsticine was then revised from **109** to **117**.[82]

Compounds **118–129** contain oxygenated functionalities at both C-6 and C-15,[89,91–96,98] which might be regarded as a more evolved group of aconitine-type C_{19}-diterpenoid alkaloids.[17] 1-*epi*-Deacetylaconitine (**118**) is the only aconitine-type alkaloid with a β-oriented methoxyl group at C-1, and an intramolecular hydrogen bond in **118** was observed between the nitrogen atom and the hydrogen of the 3α-hydroxyl group.[89] 8-*O*-Methylhypaconine (**121**) was obtained from the underground parts of an unknown species of *Aconitum* cultivated in Korea, which originated from the Sichuan province of China.[91] Beiwucine (**122**) and 3-acetylaconifine (**124**) have a C-10 hydroxyl group.[92,94] The structure of 3-acetylmesaconitine (**125**) obtained from *Aconitum kusnezoffii* is as the same as that of tuberanine from *Aconitum tuberosum*.[94,95] Similarly, spicatine B (**126**) from *Aconitum spicatum* is structurally identical to 10-dehydroxyflavaconitine from *Aconitum nagarum*.[93,96] Tuberaconitine (**128**) and tubermesaconitine (**129**) feature an acetonide unit at C-8 and C-15, as proved by their spectral data and chemical correlations with aconitine and mesaconitine.[98]

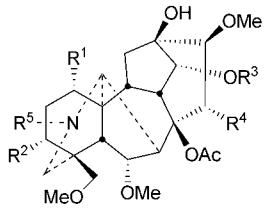
Three alkaloids (**130–132**) that possess an amino group at C-8 were isolated.[83,99,100] Hemsleyatine (**130**) represents the first example of this group,[99] while the possibility of lasianine (**131**) being an artifact was excluded through chemical transformations.[100]

The term "lipo-alkaloid" was originally given by Kitagawa *et al.*,[101] and three new members of this group have been obtained

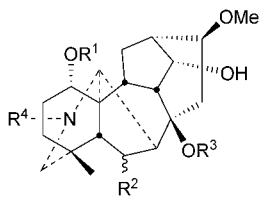
Pengshenine A (**136**) and transconitine D (**137**) are the first two examples of naturally occuring aconitine-type C_{19}-diterpenoid alkaloids with an *N*–C-19–*O*–C-6 mixed acetal moiety.[67,103] Several aconitine-type C_{19}-diterpenoid alkaloids (**138–144**) with a C-19=*N* unit from various plant sources were identified. Among these, nagadine (**138**)[43] from *Aconitum nagarum* var. *lasiandrum* is identical to pengshenine B from *Aconitum hemsleyanum* var. *pengzhouense*.[103] Merckonine (**144**), the first member of the imine group, was determined on the basis of its physical and spectroscopic data and chemical correlation with aconitine.[105] Alkaloid piepunensine A (**145**) has an *N*-deethyl lactam group.[54] Habaenines A (**146**) and C (**147**) are two amide-subtype alkaloids.[81,106]

2.2.2 Lycoctonines. The lycoctonine-type C_{19}-diterpenoid alkaloids are structurally characterized by the presence of an oxygenated group at C-7. They may also be subdivided into the following subtypes according to their nitrogen patterns: amines, *N*,*O*-mixed acetals, imines, and amides. The amine subtype constitutes the majority of this type of alkaloids, and could be further subdivided into various groups according to what kind of C-7/C-8 oxygen-containing groups they possess.

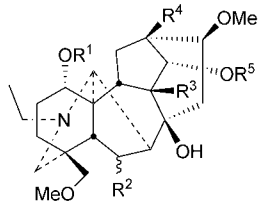
Alkaloids **148–167** are a group of lycoctonine-type alkaloids, isolated from various plants, which each contain a C-7,C-8 diol. Consolarine (**148**) features an α-oriented hydroxyl at C-6,[107] and racemuloline A (**149**) lacks an oxygenated group at C-6.[50] **150–152** were obtained from two *Aconitum* species, among which **150** is identical to excecoitine from the same plant (*Aconitum excelsum*).[34,35] 16-Demethyldelsoline (**153**) is uncommon in having a hydroxyl group at C-16, whose structure was established based on its 1D and 2D NMR data and the correlations with delsoline.[109] Giraldines A–F (**154–156**, **176**, **157–158**) possess a $\Delta^{2,3}$ double bond.[110,111] In addition, **158** has a carbonyl



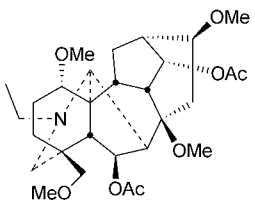
	R^1	R^2	R^3	R^4	R^5
104	OMe	OH	Ver	H	CHO
105	=O	OH	Ani	H	Et
107	OH	OH	Bz	H	Et
108	OMe	H	Ani	H	H
126	OH	H	Bz	OH	H



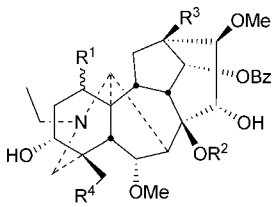
	R^1	R^2	R^3	R^4
106	Me	α-OMe	H	Et
114	Ac	β-OH	Ac	Et
115	Me	β-OH	Me	H



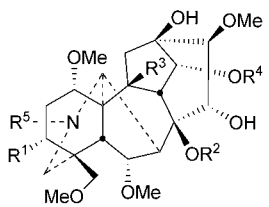
	R^1	R^2	R^3	R^4	R^5
109	Me	α-OH	H	H	H
110	Me	α-OH	H	H	Cin
111	Me	α-OH	H	H	Bz
112	H	α-OH	OH	H	H
113	Me	α-OH	H	OH	H
117	Me	β-OH	H	H	H



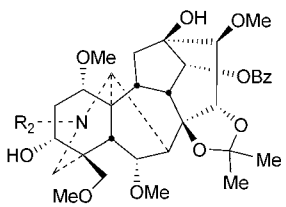
116



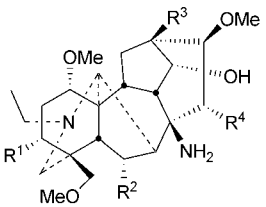
	R^1	R^2	R^3	R^4
118	β-OMe	H	OH	OMe
119	α-OMe	H	H	OMe
120	α-OMe	Me	OH	H



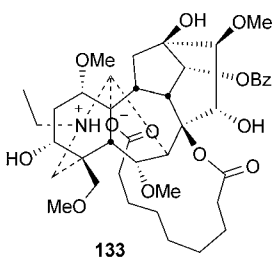
	R^1	R^2	R^3	R^4	R^5
121	H	Me	H	H	Me
122	OH	Et	OH	Bz	Me
123	OH	Et	H	Bz	Et
124	OAc	Ac	OH	Bz	Et
125	OAc	Ac	H	Bz	Me
127	OH	Bz	H	Bz	Me



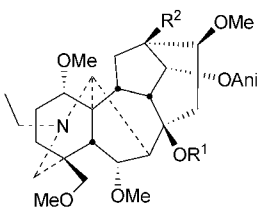
128 R = Et
129 R = Me



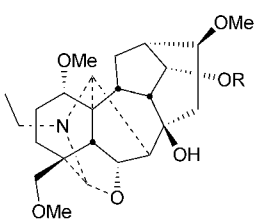
	R^1	R^2	R^3	R^4
130	OH	OMe	OH	H
131	OH	OMe	OH	OH
132	H	H	H	H



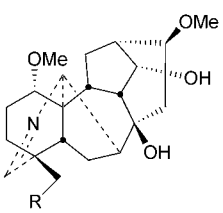
133



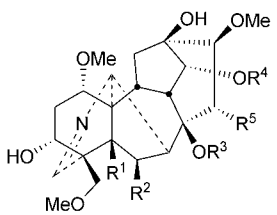
134 R^1 = Lip (linoleoyl, oleoyl, palmitoyl, stearoyl) R^2 = OH
135 R^1 = Lip (arachidoyl, linoleoyl, palmitoyl, stearoyl) R^2 = H



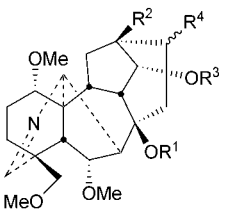
136 R = H
137 R = Ani



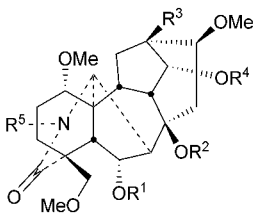
138 R = OMe
139 R = H



	R^1	R^2	R^3	R^4	R^5
140	OH	H	H	Ani	H
144	H	OMe	Ac	Bz	OH



	R^1	R^2	R^3	R^4
141	H	H	H	α-OMe
142	Ac	H	Ani	β-OMe
143	Ac	OH	Ani	β-OMe



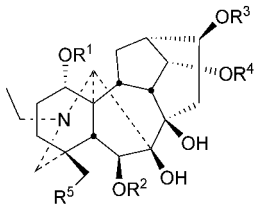
	R^1	R^2	R^3	R^4	R^5
145	H	H	H	H	H
146	OMe	Ac	OH	Ani	Et
147	OMe	Ac	H	Ani	Et

group at C-14, and **176** possesses a methoxy group at C-8.[111] Davidisines A (**165**) and B (**166**) were identified as *N*-deethyllycoctonine and *N*-aldehyde-lycoctonine, respectively,[115] by spectral methods, and the structure of the previously reported potanisine A was revised from **166** to **167**.[116]

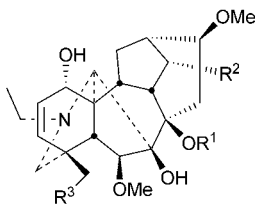
Nine members (**168–176**) were added to the group of lycoctonine-type alkaloids with a 7-OH/8-OMe unit. **170–175** are 6-*epi*-lycoctonine-type alkaloids.[39,114,117,118] Jiufengsine (**177**) is the first example of a naturally occurring lycoctonine-type alkaloid with a C-8 anthranoyl group.[119] The absolute

configuration of C-2″ was suggested to be *S* because such a side chain was supposedly derived from the *N*-(methylsuccinimido)anthranoyl group.[120]

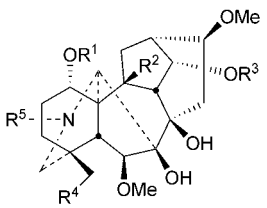
The alkaloids **178–198** fall into the group of lycoctonine-type alkaloids with a 7,8-methylenedioxy moiety. Almost all of these compounds originate from the *Delphinium* species except for isodelatine (**179**), which comes from the roots of *Aconitum taipaicum*.[122] It is really rare for such a lycoctonine-type alkaloid with a 7,8-methylenedioxy group to be found from the *Aconitum* species. Delcorinine (**180**) features a C-16 β-hydroxyl group, and



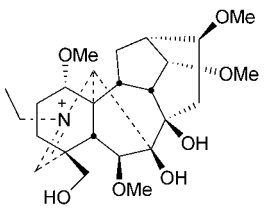
	R^1	R^2	R^3	R^4	R^5
148	H	α-OH	Me	H	H
149	Me	H	Me	H	OMe
150	H	β-OH	Me	Me	OMe
151	H	β-OAc	Me	Me	OMe
152	Me	β-OAc	Me	Me	OMe
153	H	β-OMe	H	Me	OMe



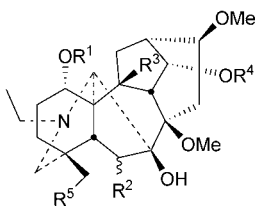
	R^1	R^2	R^3
154	H	OH	H
155	H	OAc	H
156	H	OBz	H
157	H	OMe	OMe
158	H	=O	H
176	Me	OH	H



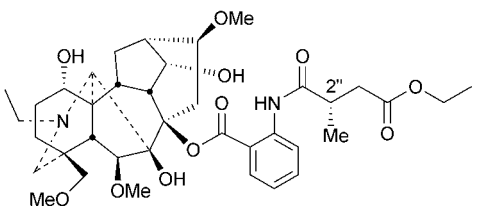
	R^1	R^2	R^3	R^4	R^5
159	Me	OH	Me	OMe	Et
160	Me	OH	H	H	Et
161	Me	OH	Me	OH	Et
162	H	H	Ac	OH	Et
163	H	H	Bz	OH	Et
164	H	H	Me	OAc	Et
165	Me	H	Me	OH	H
166	Me	H	Me	OH	CHO



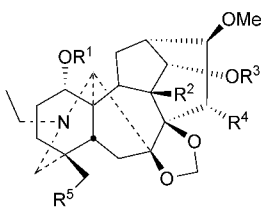
167



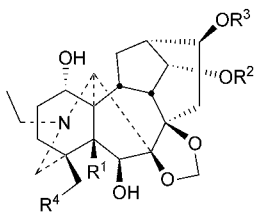
	R^1	R^2	R^3	R^4	R^5
168	Me	β-OMe	OH	Me	OH
169	Me	β-OMe	H	Me	OH
170	H	α-OH	H	Ac	OH
171	H	α-OH	H	Ac	H
172	H	α-OH	H	H	OMe
173	H	α-OH	H	H	H
174	H	α-OH	H	H	OBz
175	H	α-OH	H	H	OH



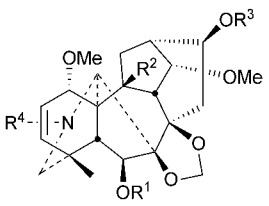
177



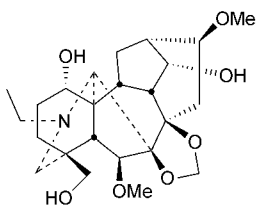
	R^1	R^2	R^3	R^4	R^5
178	H	OH	Me	H	OMe
179	Me	H	H	OH	H



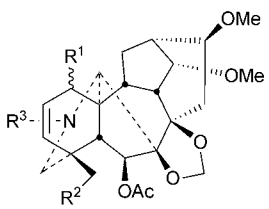
	R^1	R^2	R^3	R^4
180	H	Me	H	OMe
181	H	H	Me	OMe
182	OH	Me	Me	H
183	H	Me	Me	OMe



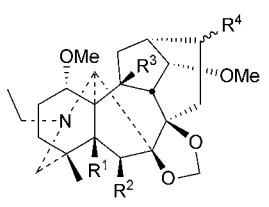
	R^1	R^2	R^3	R^4
184	H	OH	Me	Et
186	Ac	OH	Me	Et
187	Ac	OH	H	Et
188	Ac	H	Me	Me
189	Ac	OH	H	Me



185



190 R^1 = β-OMe, R^2 = H, R^3 = Et
191 R^1 = α-OMe, R^2 = OMe, R^3 = Me
192 R^1 = α-OH, R^2 = H, R^3 = Et



	R^1	R^2	R^3	R^4
193	OH	H	H	α-OMe
194	H	OAc	OH	α-OH
195	OH	OAc	H	β-OH
196	OH	OAc	H	β-OMe
197	OH	OH	H	β-OMe
198	OH	=O	H	β-OMe

its structure was established by its spectral data and the correlations with delcorine and delsoline.[123] Four new alkaloids, siwanines A–D (**186–189**), have a $\Delta^{2,3}$ double bond.[129] The relative stereochemistry of **189** was confirmed by its X-ray crystallographic analysis. Nordhagenines A–C (**193–195**) have an unusual hydroxyl group at C-16,[131] the structures of **194** and **195** being confirmed by X-ray crystallographic analysis. Bonvalotidines A–C (**196–198**) possess a C-5 hydroxyl group.[132]

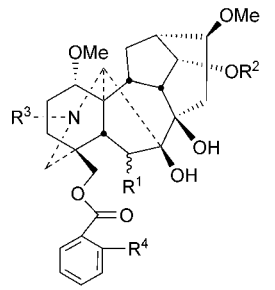
There is a group of lycoctonine-type C_{19}-diterpenoid alkaloids characterized by the presence of an anthranoyl substituent at C-18. It consists of 27 new members (**199–225**), and most of them have a C-7,C-8 diol. Jiufengtine (**199**) and jiufengdine (**200**) are two C-18 anthranoyl-containing alkaloids with an unusual α-oriented methoxy group at C-6.[133] Alkaloid **202** is an analogue of ajadine.[38] The new alkaloids **203**, **204** and sinomontanine I (**205**) possess an *N*-(succinimido)anthranoyl unit at C-18.[41,135] Bearline (**207**), 14-acetylbearline (**208**), and 16-deacetylgeyerline (**209**) are three alkaloids that contain an *N*-(methylsuccinimido)anthranoyl unit.[136] The stereochemistry of C-3″ in both **214** and **215** was deduced as *S* based on comparison of the ^{13}C NMR data with those of the known delsemine B. 16-Demethoxydelavaine (**218a** and **218b**) is a mixture of two regioisomers of lycoctonine-type alkaloids.[139] Four alkaloids in this group (**222–225**) have alkoxy substituents at C-8.[135,142,143]

Five new lycoctonine-type alkaloids **226–230** with an *N*–C-19–*O*–C-1 mixed acetal unit were isolated from the genera *Consolida* and *Delphinium*.[39,114,125,128] Laxicymine (**228**) and laxicyminine (**229**) possess a methylenedioxy group at C-7 and C-8, and the former has an additional C-5 hydroxyl group.[125]

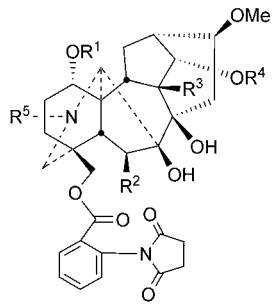
Alkaloids **231–238** have a C-19=*N* imine; they come from various plants. Several *N*-(methylsuccinimido)anthranoyl lycoctonine alkaloids, such as **234**, **235** *etc.*, were isolated from *Delphinium pentagynum* by Herz *et al.* , suggesting that it could be a highly poisonous plant.[146]

There are three alkaloids (**166**, **239** and **240**) that belong to the lycoctonine-type C_{19}-diterpenoid alkaloids with an amide group. Davidisine B (**166**) was established as *N*-formyllycoctonine;[115] tongolenine D (**239**) and budelphine (**240**) feature a lactam moiety.[144,147] In addition, budelphine (**240**) possesses an epoxy unit at C-1,C-2.[147]

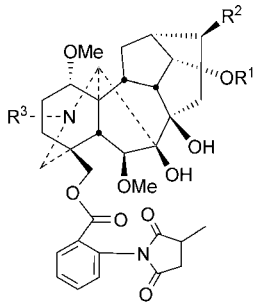
2.2.3 Pyro type. Pyro-type C_{19}-diterpenoid alkaloids that contain a $\Delta^{8,15}$ double bond or an 8-H/15-ketone unit are considered to be derived from the elimination of the C-8



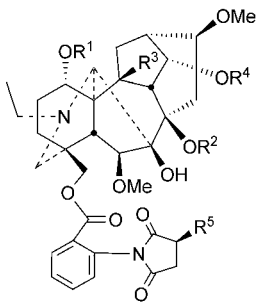
	R^1	R^2	R^3	R^4
199	α-OMe	Me	H	NH_2
200	α-OMe	MeBu	Et	NH_2
201	β-OMe	iBu	Et	NH_2
202	β-OMe	iBu	Et	NHAc



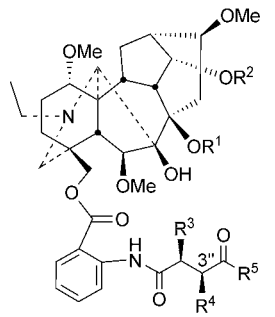
	R^1	R^2	R^3	R^4	R^5
203	Me	OMe	H	Me	CHO
204	Me	OMe	H	H	Et
205	H	H	OH	Me	Et



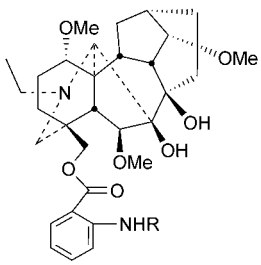
	R^1	R^2	R^3
206	iBu	OMe	Et
207	Ac	OAc	Et
208	Me	OH	Et
209	H	OAc	Et
210	Me	H	Et
211	Me	OMe	H

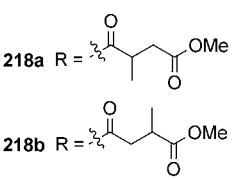


	R^1	R^2	R^3	R^4	R^5
212	Me	Me	OH	Me	Me
213	H	Me	H	Me	Me
222	Me	Me	H	Me	H
223	Me	Me	H	Me	Me
225	Me	Et	H	Pr	Me



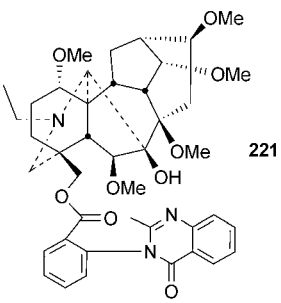
	R^1	R^2	R^3	R^4	R^5
214	H	H	H	Me	NH_2
215	H	MeBu	H	Me	NH_2
216	H	MeBu	Me	H	NH_2
217	H	iBu	Me	H	NH_2
219	H	H	H	H	OMe
220	H	Me	Me	H	OH
224	Me	Me	H	Me	NH_2



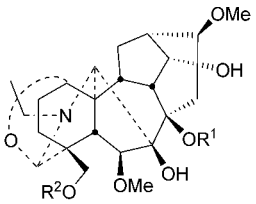


218a R =

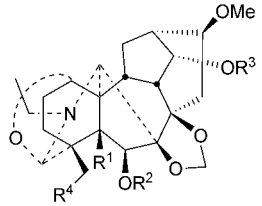
218b R =



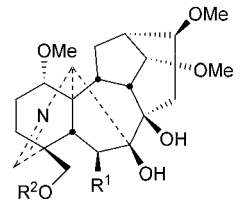
221



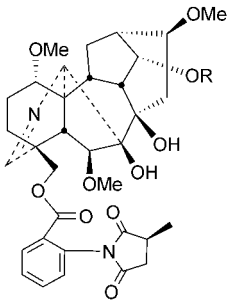
226 R^1 = Me, R^2 = Me
227 R^1 = OH, R^2 = OH



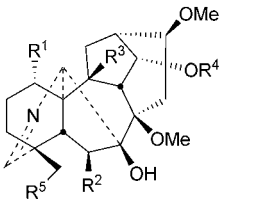
	R^1	R^2	R^3	R^4
228	OH	H	Me	H
229	H	H	Me	H
230	H	Me	H	OMe



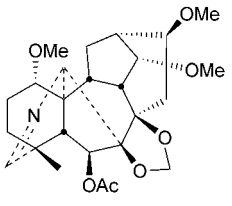
231 R^1 = H, R^2 = Me
232 R^1 = OMe, R^2 = Me
233 R^1 = OMe, R^2 = H



234 R = iBu
235 R = Ac



	R^1	R^2	R^3	R^4	R^5
236	H	H	OH	Me	H
237	OMe	OMe	H	Ac	OMe



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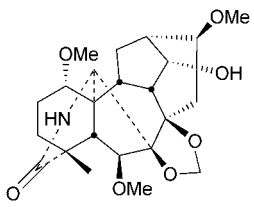

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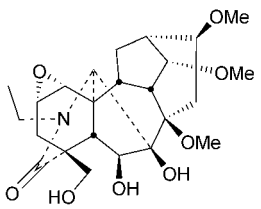

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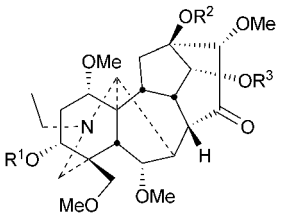
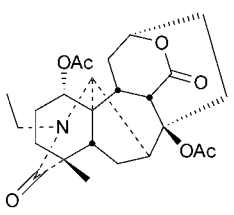


241 R^1 = R^2 = R^3 = H
242 R^1 = R^2 = R^3 = Ac

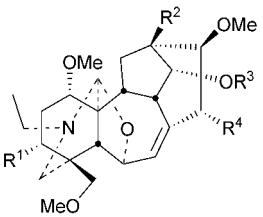


243

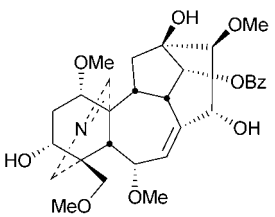
oxygenated group of aconitine-type alkaloids. 16-*epi*-Desbenzoylpyroaconitine (**241**) was initially prepared from aconitine by Katz and Rudin in 1984.[148] It was then isolated from processed aconite by Mori *et al.* in 1989, which was demonstrated to be induced by the heating of aconitine.[149] Further investigation on *Aconitum nagarum* var. *lasiandrum* by Wang *et al.* also led to the isolation of this 15-keto-type alkaloid. Its structure was established by extensive interpretation of its 1D and 2D NMR data, and confirmed by single-crystal X-ray analysis of its derivative **242**.[85]

2.2.4 Lactone type. So far, nine C_{19}-diterpenoid alkaloids with a δ-lactonized C ring have been found. Among these, only souline B (**243**), which possesses a lactam unit as well, was found during the review period.[86]

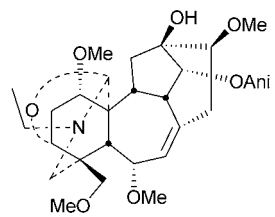
2.2.5 7,17-Seco type. The 7,17-seco-type C_{19}-diterpenoid alkaloids, which also have a $\Delta^{7,8}$ double bond, originated biosynthetically from aconitine-type alkaloids *via* Grob fragmentation. Franchetine, as one of the representatives of this type of alkaloids, was originally isolated from *Aconitum franchetii* by Chen and Sung.[150] Its initial structure was proposed based on its 1D NMR data. Ten years later, it was re-isolated by Wang *et al.* from *Aconitum hemsleyanum* var. *pengshiese*, and its structure was revised based on 2D NMR data and chemical correlations.[151] Six analogues (**244**–**249**) of franchetine were isolated from the genus *Aconitum*. Among them, the structure of acsonine should be revised, and was found to be identical to that of beiwudine (**247**), based on extensive comparison of their NMR data.[153,154] Secokaraconitine (**250**), whose structure was established by X-ray crystallographic analysis, is a new 7,17-seco alkaloid with a C-17=*N* unit. Its rings seem more conformationally flexible than that of the usual lycoctonine skeleton.[155] Secoyunaconitine (**251**) is the second example of C_{19}-diterpenoid alkaloids with an epoxy ring between C-3 and C-17.[157]



	R^1	R^2	R^3	R^4
244	H	H	Ani	H
245	H	H	Cin	H
246	OH	H	Bz	H
247	H	OH	Bz	OH
248	H	OH	H	H
249	H	OH	Bz	H

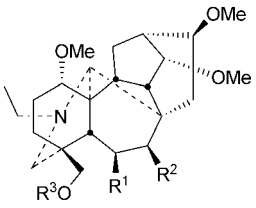


250

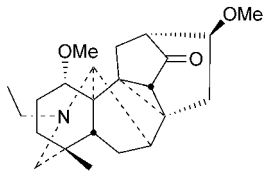


251

2.2.6 Rearranged type. There are five new C_{19}-diterpenoid alkaloids with a rearranged skeleton. Acoseptine (**252**) and anhydrolycaconitine (**253**) contain a C-8–C-17 bridge (instead of a C-7–C-17 bridge) and a carbonyl group at C-7.[158,159] Rearranged skeletons of this type have been prepared from alkaloids with a 7,8-diol system *via* pinacol rearrangement.[160,161] The structure of **253** was confirmed by X-ray diffraction analysis of its hydrolysed derivative, and the possibility of rearrangement having occurred during the isolation procedure was excluded by experiment.[159] Septonine (**254**) and septontrionine (**255**) have a C-8–C-17 bridge, in addition to a ketone at C-6.[162]



	R^1	R^2	R^3
252	OMe	=O	Ant
253	OMe	=O	Nsa
254	=O	OH	Nsa
255	=O	OH	Me



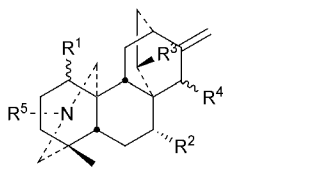
256

Vilmoraconitine (**256**), as a novel rearranged C_{19}-diterpenoid alkaloid, was isolated very recently by Tan and coworker from the roots of *Aconitum vilmorinianum*.[163] As the first representative of C_{19}-diterpenoid alkaloid with a three-membered ring (C-8, C-9, C-10), its structure was determined by 2D NMR data and single-crystal X-ray analysis. It was proposed that **256** might be derived from vilmorrianine D, which can also be obtained from *A. vilmorinianum*.

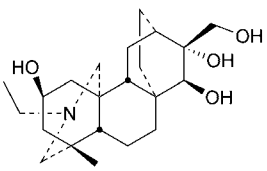
2.3 C_{20}-Diterpenoid alkaloids

2.3.1 Atisines. Atisine-type alkaloids have a pentacyclic core, and are considered to be the simplest group of C_{20}-diterpenoid alkaloids.[8] There are 30 new members (**257–286**) isolated from various species of the genera *Aconitum*, *Consolida*, *Delphinium* and *Spiraea*.

Beiwusines A (**257**) and B (**258**) represent the first examples of atisine-type alkaloids with a hydroxyl group at C-1.[164] Spiratine A (**259**) and consorientaline (**260**), with an uncommon *N*–CH_2CHO group, are epimers at C-15.[165–167] Uncinatine (**261**) possesses a $\Delta^{21,22}$ double bond, whose structure was deduced by 1D and 2D NMR data, and its chemical correlations with dihydroajaconine.[168] Cochleareine (**262**) features a C-16,C-17 diol.[88] Compounds **263–267** all have an oxazolidine ring.[166,169–171] Delphatisine B (**268**) possesses a unique γ-lactone-fused oxazolidine ring.[172] Compounds **269–279**, isolated from the genus *Spiraea* in most cases, have a *N*–C-20–*O*–C-7 unit. Ouvrardiandines A (**269**) and B (**270**) have carbonyl groups at C-2 and



	R^1	R^2	R^3	R^4	R^5
257	α-OH	H	=O	α-OH	CH_2CH_2OH
258	β-OH	H	=O	α-OH	CH_2CH_2OH
259	H	OH	H	α-OH	CH_2CHO
260	H	OH	H	β-OH	CH_2CHO
261	H	OH	H	α-OH	CH=CHOH



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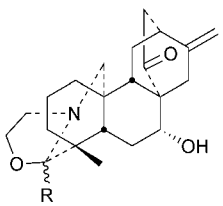
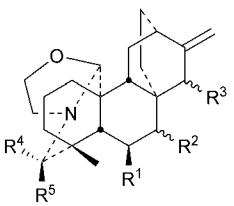
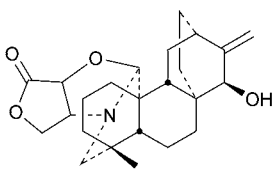


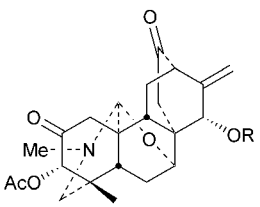
263 R = α-H
264 R = β-H



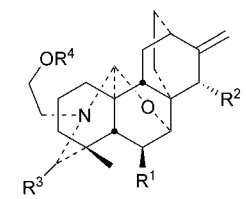
	R^1	R^2	R^3	R^4	R^5
265	OAc	α-OAc	H	=O	–
266	H	α-OH	α-OH	=O	–
267	H	β-OH	β-OH	H	OH



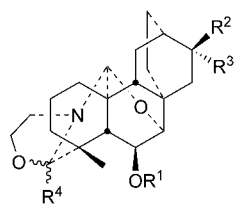
268



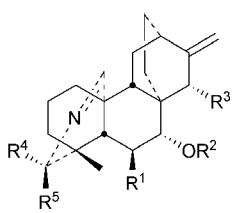
269 R = MeBu
270 R = Bz



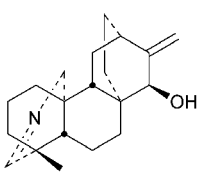
	R^1	R^2	R^3	R^4
271	H	OH	H	H
272	OH	H	H	H
273	OAc	H	=O	Ac
274	OAc	H	=O	H



	R^1	R^2	R^3	R^4
275	H	OH	Me	β-H
276	H	Me	OH	β-H
277	Ac	OH	Me	β-H
278	Ac	Me	OH	α-H
279	H	Me	OH	α-H



	R^1	R^2	R^3	R^4	R^5
280	OAc	Ac	H	H	OH
281	OAc	Ac	H	OEt	H
282	H	H	OH	H	OH



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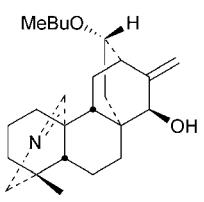

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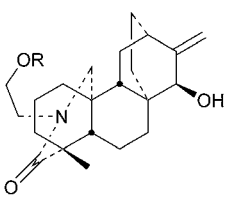


285 R = Ac
286 R = H

C-13.[78] Eleven atisine-type alkaloids (**259**, **265** and **273–281**) were isolated from *Spiraea japonica* var. *acuta* collected in Lijiang, Yunnan Province, China. Spiramine Z (**281**) with an ethoxyl group at C-19 could be an artifact formed during the extraction process.[174] The structures of spiramines P, Q, U and T (**275–278**) were revised based on extensive interpretation of its spectroscopic data and chemical transformations.[175] 13-(2-Methylbutyryl)azitine (**284**) features a C-17═*N* imine.[178]

2.3.2 Denudatines. The denudatine-type alkaloids are a class of hexacyclic C_{20}-diterpenoid alkaloids based on atisines with an additional bond between C-20 and C-7. Ten new alkaloids (**287–296**) have been added to this group since 1998. Among them, only alkaloid **293** was isolated from the genus *Consolida*; the others were all from the genus *Aconitum*.

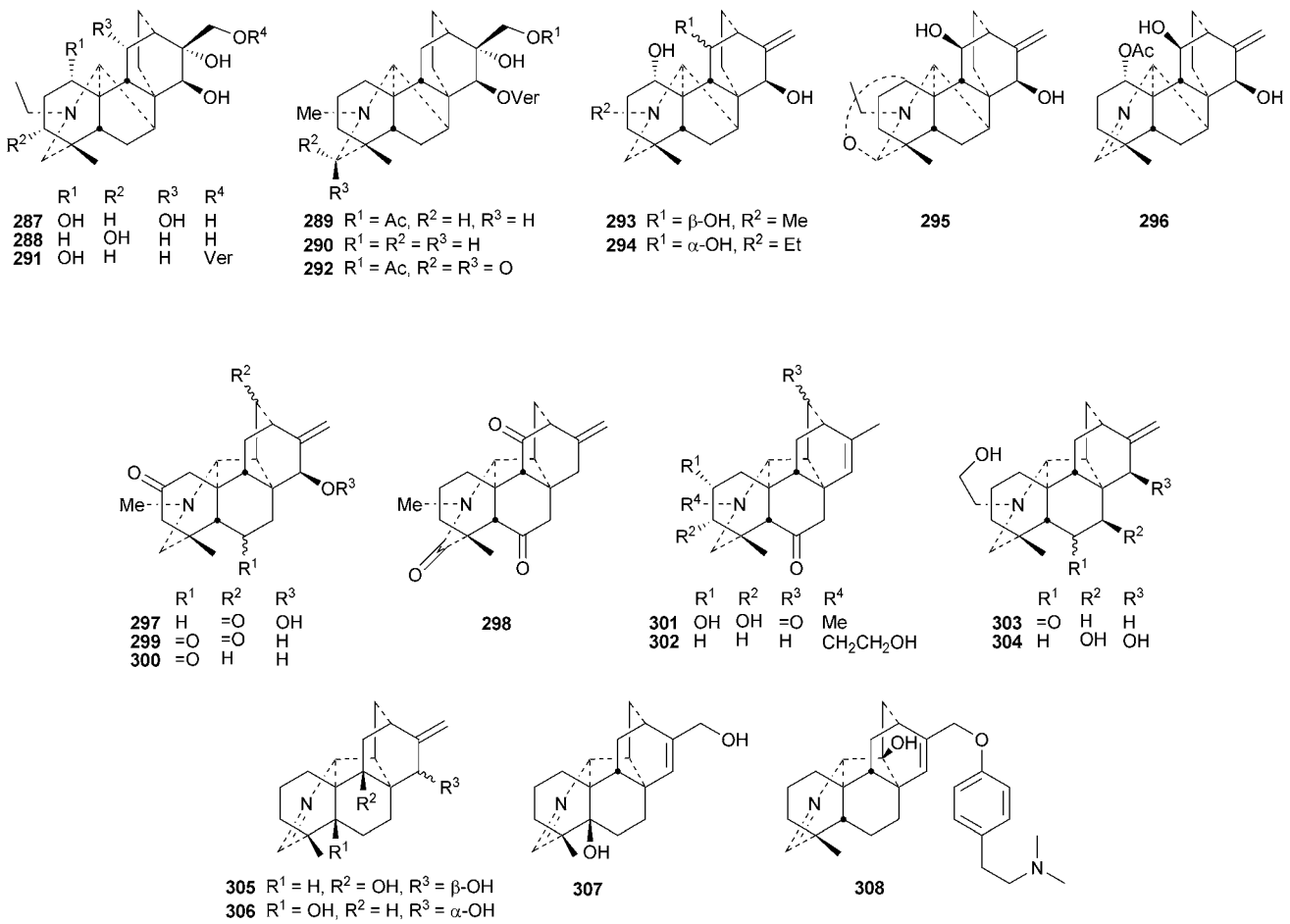
Alkaloids **287–292** possess oxygen-containing groups at both C-16 and C-17, while alkaloids **293–296** have a typical exocyclic double bond. In addition, **292** has a lactam unit.[44] Willipelletierine (**293**) is named after Professor S. W. Pelletier.[181] Kirinines B (**295**) and C (**296**) contain an *N*,*O*-mixed acetal and an imine unit, respectively.[183]

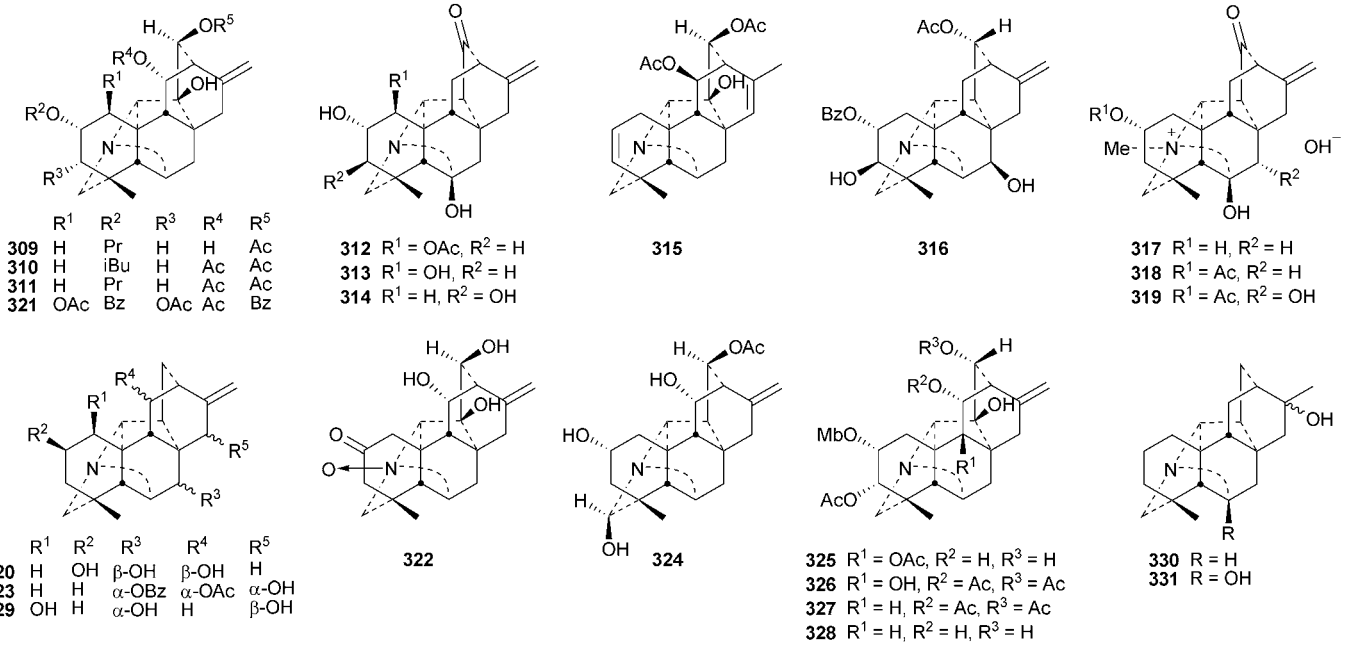
2.3.3 Hetidines. The hetidine-type alkaloids are a class of hexacyclic C_{20}-diterpenoid alkaloids based on atisines with an additional C-20–C-14 bond. Alkaloids of this type include 13 new members: **297–299** from the genus *Delphinium*, **300**, **301** and **304–308** from the genus *Aconitum*, and **302–303** from the genus *Spiraea*.

Delcarduchol (**297**) has two carbonyl groups at C-2 and C-13, while carduchoron (**298**) contains three carbonyl groups at C-6, C-11 and C-19.[184] Racemulodine (**301**) has an endocyclic $\Delta^{15,16}$ double bond, a 2,3-diol, and two carbonyl groups at C-6 and C-11.[185] Spirafine II (**302**) and spirafine III (**303**) possess an *N*–CH_2CH_2OH group and a carbonyl group at C-6.[186] Navirine (**308**) features a hordenine moiety at C-17 of the diterpenoid skeleton.[190] Naviculines A (**307**) and B (**306**) both possess an *N*═C-19 imine unit and a C-5 hydroxyl group.[189]

2.3.4 Hetisines. Hetisine-type C_{20}-diterpenoid alkaloids have a heptacyclic system with an additional N–C-6 bond, compared to the hetidine-type alkaloids, and are one of the most complex groups derived from the atisine skeleton. Twenty-three new members (**309–331**), from various species of the genera *Aconitum*, *Consolida*, *Delphinium* and *Spiraea*, were added to this group during the review period.

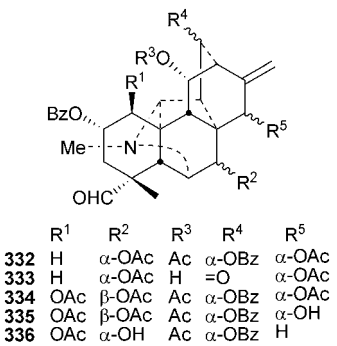
Alkaloids **309–311** have the same substitution patterns and differ in substitutions at C-2 and C-11, while **312–314** differ in substitutions at C-1 and C-3. In contrast, **315** possesses a $\Delta^{2,3}$ double bond.[191–193] The regio-isomers guan-fu bases T (**313**) and U (**314**) were separated by preparative high-speed counter-current chromatography (HSCCC) coupled with evaporative light scattering detection (ELSD).[195] The structure of guan-fu base Q (**312**) was confirmed by single-crystal X-ray diffraction analysis.[194] Guan-fu base S (**315**) was obtained along with a new *ent*-kaurane diterpene, which may support the hypothesis of the



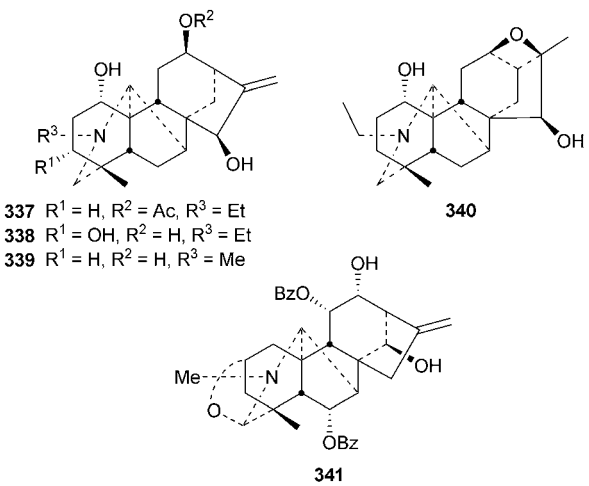


biosynthetic pathway of diterpenoid alkaloids involving a diterpene.[196] Three quaternary ammonium hydroxides, orochrine (**317**), 2-*O*-acetylorochrine (**318**), and 2-*O*-acetyl-7α-hydroxyorochrine (**319**), were isolated from *Aconitum orochryseum*, a Bhutanese traditional medicine.[198] Four hetisine-type alkaloids (**320–323**) were isolated from the genus *Delphinium*, among which **322** from *Delphinium gracile* is a rare hetisine-type *N*-oxide.[40,45–47] 13-Acetylvakhmatine (**324**) contains a C-19 hydroxyl group. High-performance centrifugal partition chromatography (HPCPC) was used in the the isolation of **324**.[199] The four glanduline derivatives **325–328** differ from each other in the substituents at C-9, C-11 and C-13. Their structures were confirmed by single-crystal X-ray diffraction analysis of **326**.[200] Spiraqine (**330**) and 6-hydroxylspiraqine (**331**) differ in the substituent at C-6.[201]

2.3.5 Vakognavines. Vakognavine-type C_{20}-diterpenoid alkaloids have an *N*,19-seco hetisine skeleton in addition to a C-4 aldehyde group, and it was named after the first example of this type, vakognavine.[202–204] During the review period, five new members were added: **332–333** from *Aconitum tanguticum*, and **334–336** from *Delphinium trifoliolatum*. The structure of tangutisine B (**333**) was confirmed by an X-ray crystallographic analysis.[205,206] The structures of trifoliolasines D–E (**334–336**) were established on the basis of spectroscopic data, and by the X-ray diffraction analysis of **334**.[207] The orientation of the axial C-13 benzoyloxyl group is represented as α according to the convention described by Pelletier.[208] In addition, we observed that a transannular effect occurs between the lone pairs of the nitrogen atom and the C-4 aldehyde group in the vakognavine-type alkaloids.[207]

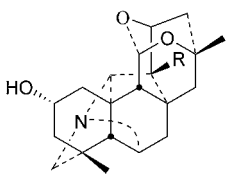


2.3.6 Napellines. The napelline-type C_{20}-diterpenoid alkaloids have a hexacyclic carbon framework with an additional C-20–C-7 bridge as compared with veatchine-type. Five new alkaloids (**337–341**) were added into this group since 1998. All five originated from various species of *Aconitum*. 12-Acetyl-12-*epi*-napelline (**337**) was structurally confirmed by X-ray crystallographic analysis.[209] The structure of **340** features an oxetane

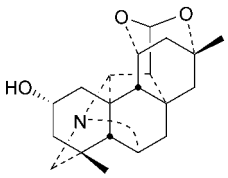


moiety consisting of C-12, C-13 and C-16, as confirmed by X-ray single-crystal analysis. Racemulotine (**341**) has an *N*–C-19–*O*–C-2 mixed acetal.[211]

2.3.7 Kusnezolines and omeielines. Two novel products **342** and **344**, with an adamantane-type skeleton, were prepared by Pelletier *et al.* from hetisine *via* acid-catalyzed rearrangement.[212,213] They were not named at the time, and their structures were established by X-ray crystallographic analysis. Afterwards, we isolated **342** from *Aconitum kusnezoffii*, *Aconitum racemulosum* var. *pengzhouense* and *Delphinium omeiense*,[214,215] and **344** from *Delphinium omeiense*.[216] Meanwhile, we designated them as kusnezoline (**342**) and omeieline (**344**), which belong to the kusnezoline-type and omeieline-type diterpenoids, respectively. Full assignments of ^{1}H and ^{13}C NMR data for these two alkaloids were achieved through extensive interpretation of the 2D NMR data.[217] Guan-fu base K (**343**), whose structure was proved by single-crystal X-ray diffraction analysis, represented the only new example of kusnezoline-type alkaloids from Nature during the period 1998–2008.[218]

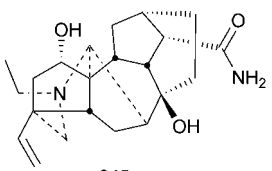


342 R = H
343 R = OH



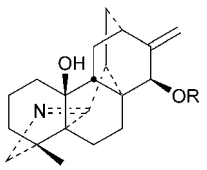
344

2.3.8 Racemulosines. Further investigation of whole plants of *Aconitum racemulosum* var. *pengzhouense* led to the discovery of racemulosine, a novel C_{20}-diterpenoid alkaloid with a unique skeleton (**345**).[219] The structure of **345** was established by 1D and 2D NMR, as well as X-ray crystallographic analysis. It was proposed that racemulosine originates from the denudatine-type diterpenoid alkaloids through double Wagner–Meerwein rearrangements of both rings A and C followed by functionalization of the exocyclic methylene group. This unique compound was assigned to the racemulosine-type, and it is the only example so far.



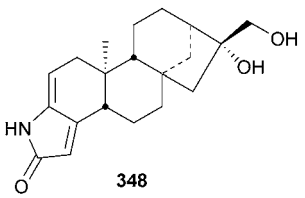
345

2.3.9 Arcutines. Two new alkaloids, arcutin(e) (**346**) and arcutinine (**347**), were isolated from the aerial parts of *Aconitum arcuatum* by Saidkhodzhaeva *et al.*[220,221] They possess an unusual C-5–C-20 bond in lieu of the traditional C-10–C-20 bond typical of this class of alkaloids, and were designated as arcutine-type alkaloids accordingly.[8] The structure of arcutin(e) was determined by single-crystal X-ray diffraction analysis, while that of arcutinine was established by spectral data and comparison with arcutin(e).



346 R = MeBu
347 R = iBu

2.3.10 Tricalysiamides. From the wood of *Tricalysia dubia* collected in Okinawa, Japan, four rearranged veatchine-type C_{20}-diterpenoid alkaloids with a cafestol-type diterpene framework, tricalysiamides A–D (**348–351**), were isolated recently.[222] These novel compounds are designated, after the first example, as tricalysiamide-type diterpenoids, which are characterized by the nitrogen atom being between C-3 and C-19. Their structures were determined based on their 2D NMR spectroscopic data and chemical correlations, as well as the single-crystal X-ray analysis of **348**.



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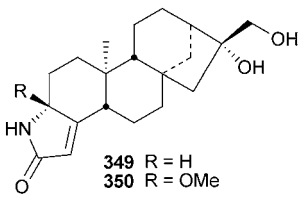
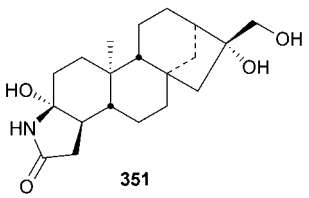


349 R = H
350 R = OMe

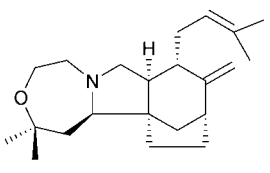


351

2.4 Miscellaneous diterpenoid alkaloids

A series of nitrogen-containing diterpenes that do not belong to the typical diterpenoid alkaloids are discussed in this section.

A novel alkaloid concavine (**352**) with an unprecedented ring system, consisting of dodecahydro-7-oxa-9a-aza-benzo[*a*]azulene, was isolated from cultures of *Clitocybe concava* (Basidiomycetae).[223] Biosynthetically, it could be regarded as a C_{20}-diterpenoid alkaloid, with an additional hydroxyethylamine group as part of the aza-azulene ring. The four isoprenic moieties are evident in the formula, but their sequence is different from that common in most C_{20}-diterpenoid alkaloids. This is the first report of a diterpenoid alkaloid from the Basidiomycetae.



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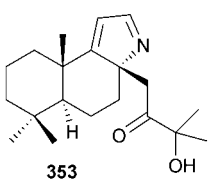
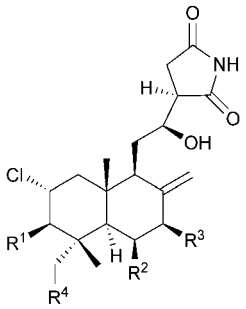


353

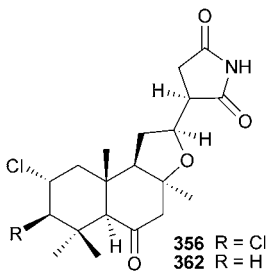
Investigation of *Chamaecyparis obtusa* cv. *tetragon* by Tan and coworkers resulted in the isolation of chamobtusin A (**353**), a diterpenoid alkaloid with a novel skeleton featuring a

2*H*-pyrrole fused with a decalin unit.[224] The structure was mainly established by MS, 2D NMR and X-ray methods, and it is the first naturally occurring diterpenoid alkaloid from the Cupressaceae family.

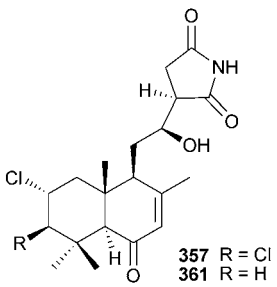
Eleven new nitrogen-containing diterpenes, haterumaimides A–K (**354–364**), were isolated from ascidian *Lissoclinum* species by Ueda and coworkers.[225–227] They could be considered to have derived from the labdane-type diterpenes, and structurally they contain a succinimide moiety as well as chlorine atoms.



	R^1	R^2	R^3	R^4
354	Cl	H	OAc	H
355	Cl	=O	H	H
358	Cl	OH	H	H
359	H	OH	H	H
360	H	=O	H	H
363	H	H	H	OH
364	H	H	H	OAc



356 R = Cl
362 R = H



357 R = Cl
361 R = H

Recently, the Hao group isolated nine known diterpenoid alkaloids (one veatchine-type alkaloid and eight aconitines) from the fruits of *Daphniphyllum longeracemosum*.[228] It is worth noting that this is the first report of diterpenoid alkaloids from the genus *Daphniphyllum*.

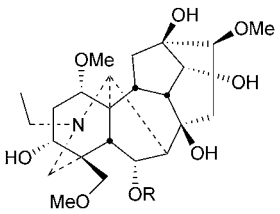
3 Chemical reactions

3.1 *O*-Demethylation

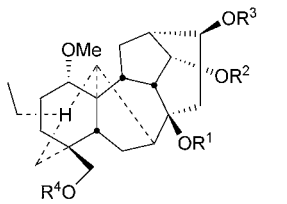
The 6-*O*-methyl group of pseudaconine (**365**) could be selectively removed with 50% H_2SO_4 to give the 6-*O*-demethyl product **366** in high yield (96%).[229] HBr–glacial acetic acid was reported to be an effective *O*-demethylation method for C_{19}-diterpenoid alkaloids.[230] When this method [HBr–AcOH (20 equiv.), 50–80 °C, 7–20 h] was applied to the demethylation of the aconitine- and lycoctonine-type alkaloids (**367–369**), the corresponding *O*-demethylated products (**370–372**) were obtained in high yields (81–90%). However, when the 7,17-seco C_{19}-diterpenoid alkaloids **373** and **374** were exposed to similar conditions, the *O*-demethylated products **375** and **376** were obtained only in low yields.

3.2 Oxidation involving the nitrogen atom

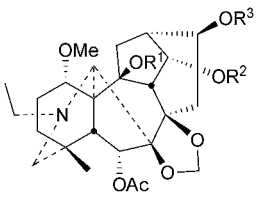
3.2.1 *N*-Deethylation. During our investigation on the chemical reactions of diterpenoid alkaloids, a series of *N*-deethylation products were prepared using various oxidants such as $KMnO_4$ and NBS.[231–233] The resulting products depended greatly upon the reagents, reaction conditions and methods. It was found that treatment of **377** with NBS at room temperature produced the deethylated product **378**, and the subsequent imine product **379**.[232] In addition, an *N*-deethylation product **381**, with a rare *N*,*O*-mixed acetal, could be prepared in high yield (98%) by prolonged treatment of isotalatizidine (**380**) with $KMnO_4$ at 40 °C.[233]



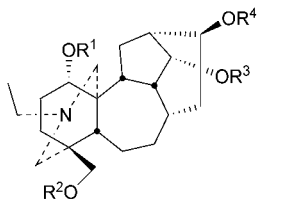
365 R = Me
366 R = H



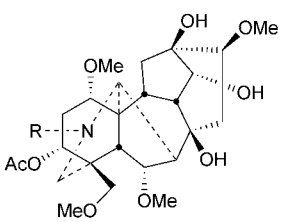
367 $R^1 = R^2 = H$, $R^3 = R^4 = Me$
368 $R^1 = Ac$, $R^2 = Ms$, $R^3 = R^4 = Me$
370 $R^1 = R^2 = R^3 = R^4 = Ac$
371 $R^1 = R^3 = R^4 = Ac$, $R^2 = Ms$



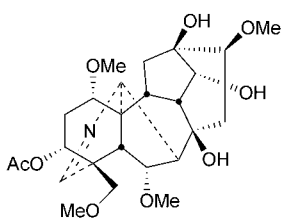
369 $R^1 = H$, $R^2 = R^3 = Me$
372 $R^1 = R^2 = R^3 = Ac$



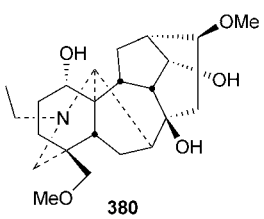
373 $R^1 = R^2 = R^4 = Me$, $R^3 = Ac$
374 $R^1 = R^2 = R^4 = Me$, $R^3 = Ms$
375 $R^1 = R^2 = Me$, $R^3 = R^4 = Ac$
376 $R^1 = R^2 = Me$, $R^3 = Ms$, $R^4 = Ac$



377 R = Et
378 R = H



379



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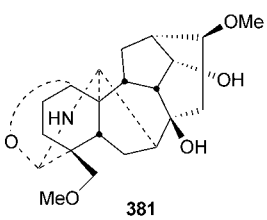


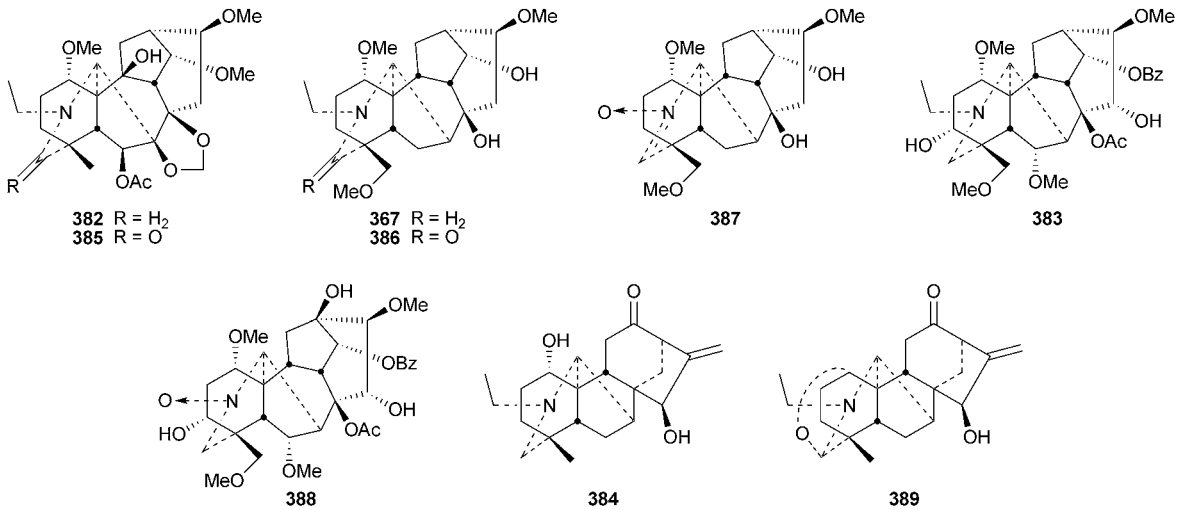
381

3.2.2 Formation of amides, imines, nitrones and *N*,*O*-mixed acetals. Oxidation of eldeline (deltaline, **382**), talatisamine (**367**), aconitine (**383**) and songorine (**384**) with dimethyldioxirane yielded the compounds **385** (lactam, 19%), **386** (lactam, 26%) and **387** (nitrone, 45%), **388** (nitrone, 65%), and **389** (*N*,*O*-mixed acetal, 19%), respectively.[234] The authors have proposed a mechanism, which involves the oxidation of C-19 atom or the methylene moiety of *N*-ethyl group followed by elimination of acetaldehyde and reoxidation of dimethyldioxirane.[235] For

example, two nitrones **393** and **397** were prepared from lappaconitine (**390**) and elatine (**394**), respectively, using the method developed by Osadchii *et al.* The key reactions might include *N*-oxidation, Cope elimination (heat, in *vacuo*), and oxidation with $K_3Fe(CN)_6/NaHCO_3$ (Scheme 1).[235] Interestingly, alkaline hydrolysis of **396** produces a mixture of *N*-deethyl-*N*-hydroxyelatidine **398** and nitrone **399** in a ratio of 3 : 1. Oxidation of **398** with $K_3Fe(CN)_6$ afforded **399** in quantitative yield, while reduction of **399** with $NaBH_4$ gave **398** in 87% yield.[235]

lappaconitine (**390**) with HIO_4. Subsequent reaction of this aldol with Br_2–HOAc could give diketone **423** (31%) and demethylated aldol product **424** (13%) (Scheme 4).[240] Very interestingly, a one-pot reaction of lappaconitine (**390**) with $NaIO_4$ and Br_2–HOAc afforded the *N*-deethylated derivative **425** with a brominated aromatic ring.[241]

Wang *et al.* reported that the oxidation of pseudaconine (**365**) with HIO_4 generated various products (**426–431**) using different reaction media and work-up conditions (Scheme 5).[242]



Wang and coworkers showed that the corresponding imines can be readily prepared in 65–83% yield by heating (100–170 °C, 3–7 h) of certain diterpenoid alkaloids with DMSO.[236] Several imines, such as **402–404**, could be prepared as major products from talatisamine (**367**) and its derivatives **400** and **401** by this method. In the cases of **367** and **400**, trace amounts of immonium salts were also isolated. However, heating deltaline (**382**) and lappaconitine (**390**) with DMSO yields exclusively the *N*-deethyl derivatives instead of the imines.[236]

It was found that treatment of acetyllycoctonine (**405**) with *m*CPBA at room temperature yielded acetyllycoctonine *N*-oxide **406** as a major product, together with other interesting by-products (**407–413**). The key steps are proposed to be nitrogen oxidation, Cope elimination, and Polonovski-like fragmentation (Scheme 2).[237]

Six new products (**408**, **411**, **414–417**) were obtained from the reaction of acetyllycoctonine (**405**) with NBS (Scheme 3).[238] The products and yields of this reaction depend greatly upon the reaction conditions and the nature of the substrates.

In addition, it was also reported that the oxidation of elatidine (**418**) with CrO_3 in acetic acid gives elatidal (**419**), from which two diamines, **420** and **421**, were prepared by the formation of the Schiff base followed by reduction with $NaBH_4$.[239]

3.3 Oxidation of alcohols

The intriguing aldol product **422**, as confirmed by crystal X-ray analysis, could be obtained in 41% yield from the reaction of

Structurally, the product **431** is the first representative of a C/D-nor-rearranged C_{19}-diterpenoid alkaloid.

3.4 Ester-exchange reaction

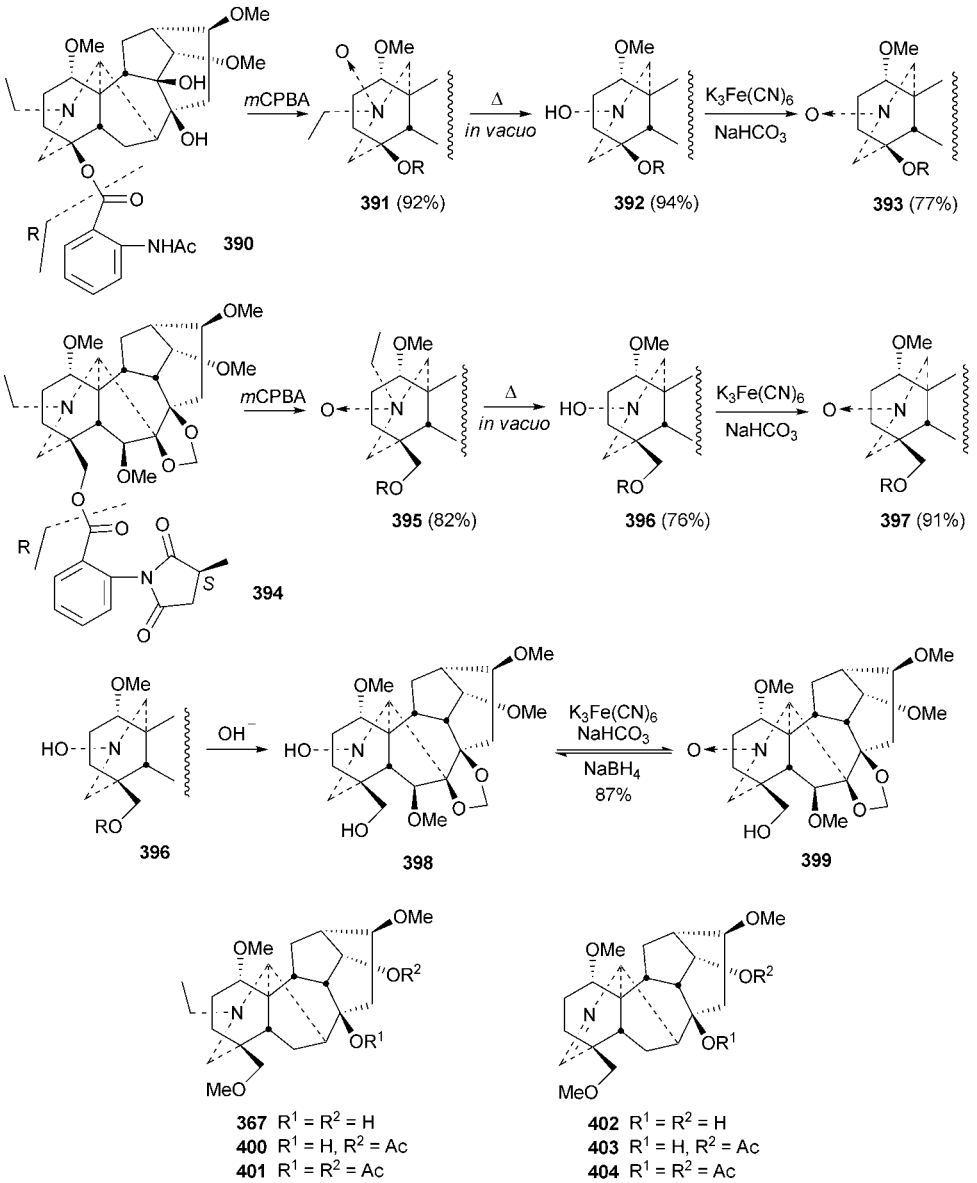
Liu *et al.* reported for the first time that certain diterpenoid alkaloids could be converted into the corresponding lipo-alkaloids during the process of decocting aconite root (involving the addition of palmitic acid to aconitine), or the mixing of mesaconitine and hypaconitine with liquorice roots.[243] A similar ester-exchange reaction was also observed in the biotransformation of aconitine in the presence of human intestinal bacteria.[244]

3.5 Biotransformation

It was demonstrated by ESI-MS/MS^n studies that the incubation of aconitine with human intestinal bacteria *in vitro* produces very complex metabolites. More than 20 types of new compounds, such as mono- and di-ester aconitines, as well as lipo-alkaloids, were observed. The key transformations involve deacetylation, dehydroxylation, demethylation and esterification.[244]

3.6 Stability of aconitine, mesaconitine and hypaconitine

HPLC–ESI-MS/MS^n showed that the decomposition products of aconitine, mesaconitine and hypaconitine mainly derived from hydrolysis and pyrolysis. The stability of these alkaloids depends on the pH value of buffer, the solvent, the storage time, and the substituents at C-3 and the nitrogen atom.[245]



Scheme 1 Formation of nitrones from lappaconitine (**390**) and elatine (**394**).

3.7 Cleavage of the *N*=C-19 bond

The *N*=C-19 bond of **432** and **437** could be broken to yield *N*,19-seco C_{19}-diterpenoid alkaloids **436** and **438** with an oxaziridine ring, respectively. The sequence involves the formation of imine, quaternization of imine, formation of *N*,*O*-mixed acetal, and oxidation with *m*CPBA (Scheme 6).[246]

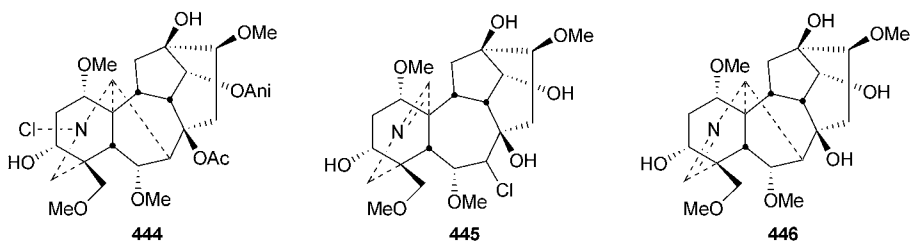
According to the method described in the literature,[247] the *N*,19-seco C_{19}-diterpenoid alkaloids **442** or **443** with a nitro or oxime group at C-17 were also prepared from **439** (Scheme 6).[248]

Some other *N*,19-seco C_{19}-diterpenoid alkaloids were also prepared employing the above-mentioned procedures.[249]

3.8 Cleavage of the C-7–C-17 bond

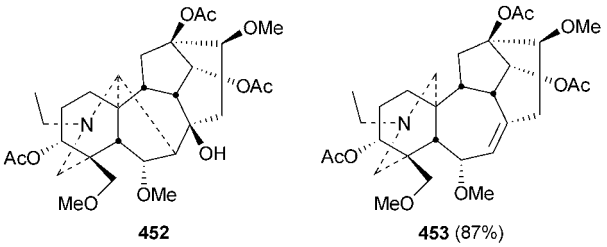
A mixture of 7,17-seco compound **445** and imine **446** was generated *via* the microwave irradiation of **444** in 1.2 M NaOMe for 30 s, but the yield was poor.[250]

Wang and co-workers developed a route to 7,17-seco C_{19}-diterpenoid alkaloids by a reaction sequence that included



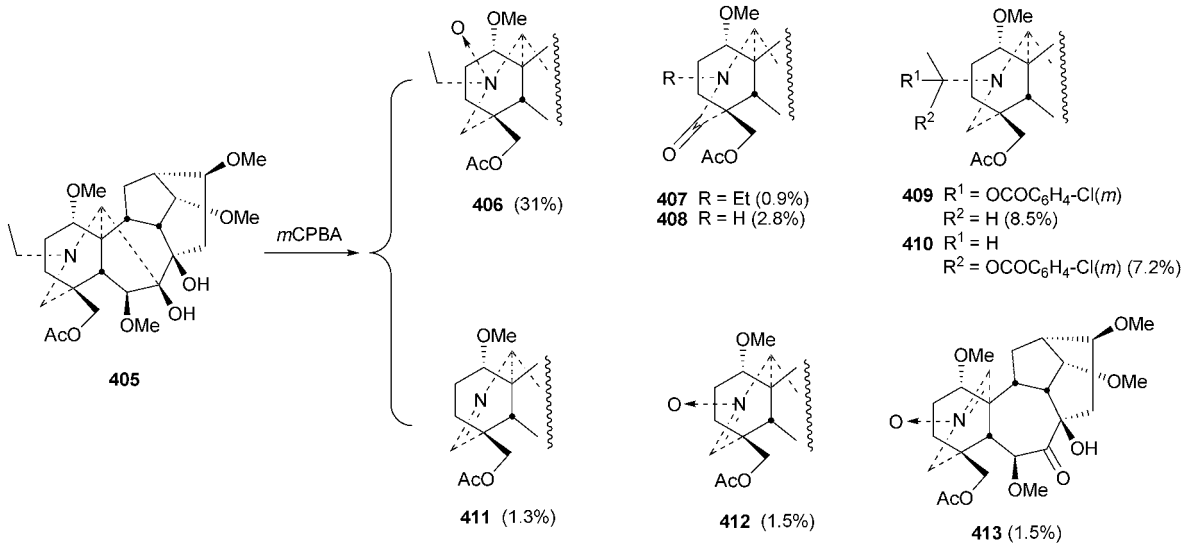
selective hydrolysis, chlorination, Grob fragmentation, and $NaBH_4$ reduction (Scheme 7). By this approach, 7,17-seco C_{19}-diterpenoid alkaloid **448** was generated from **447** in 60% yield; **450** and **451** were produced from isotalatizidine (**449**).[251] Reaction optimization suggested that the replacement of methanol with THF as solvent would significantly increase the yields.

Compound **453** was generated by the rupture of the C-7–C-17 bond of alkaloid **452** in 87% yield.[252]

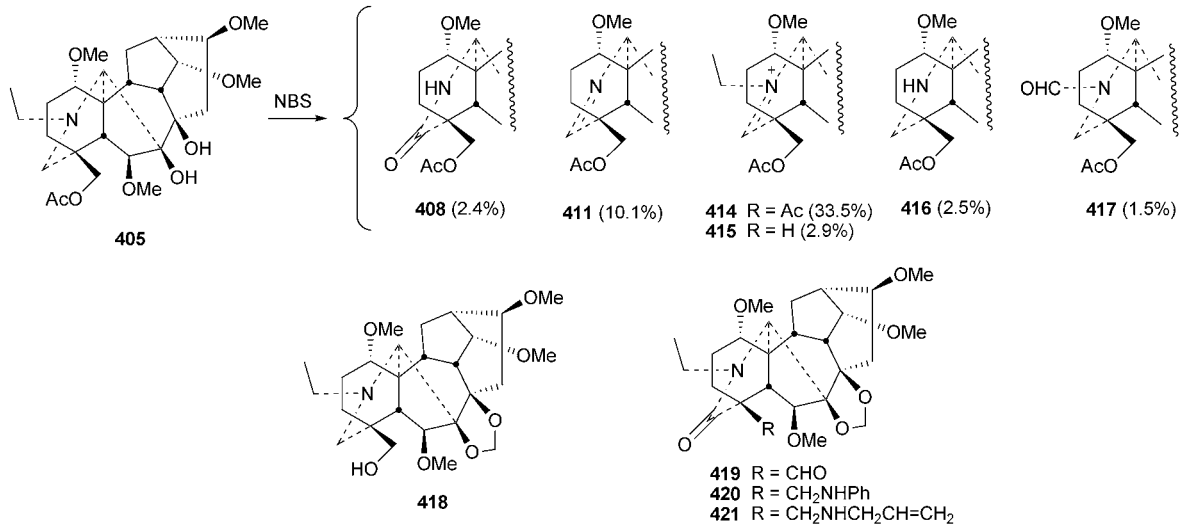


3.9 Rearrangement of ring A

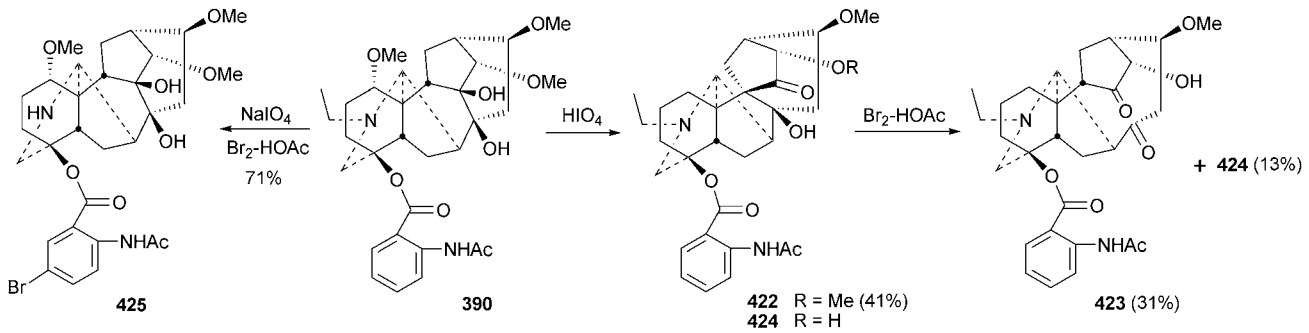
An intriguing rearranged alkaloid **456**, whose structure was confirmed by single-crystal X-ray analysis of its acetylated derivative, was observed from a sequence of reactions starting from **454**. As shown in Scheme 8, the sequence involves the treatment of **454** with NBS followed by methyl iodide and reaction of the resulting iminium salt **455** with 5% NaOH/MeOH.[253] A mechanism for this rearrangement was proposed, which involves double Grob fragmentations, formation of a new ring A by aldol reaction, coupled with an elimination of a molecule of methanol.



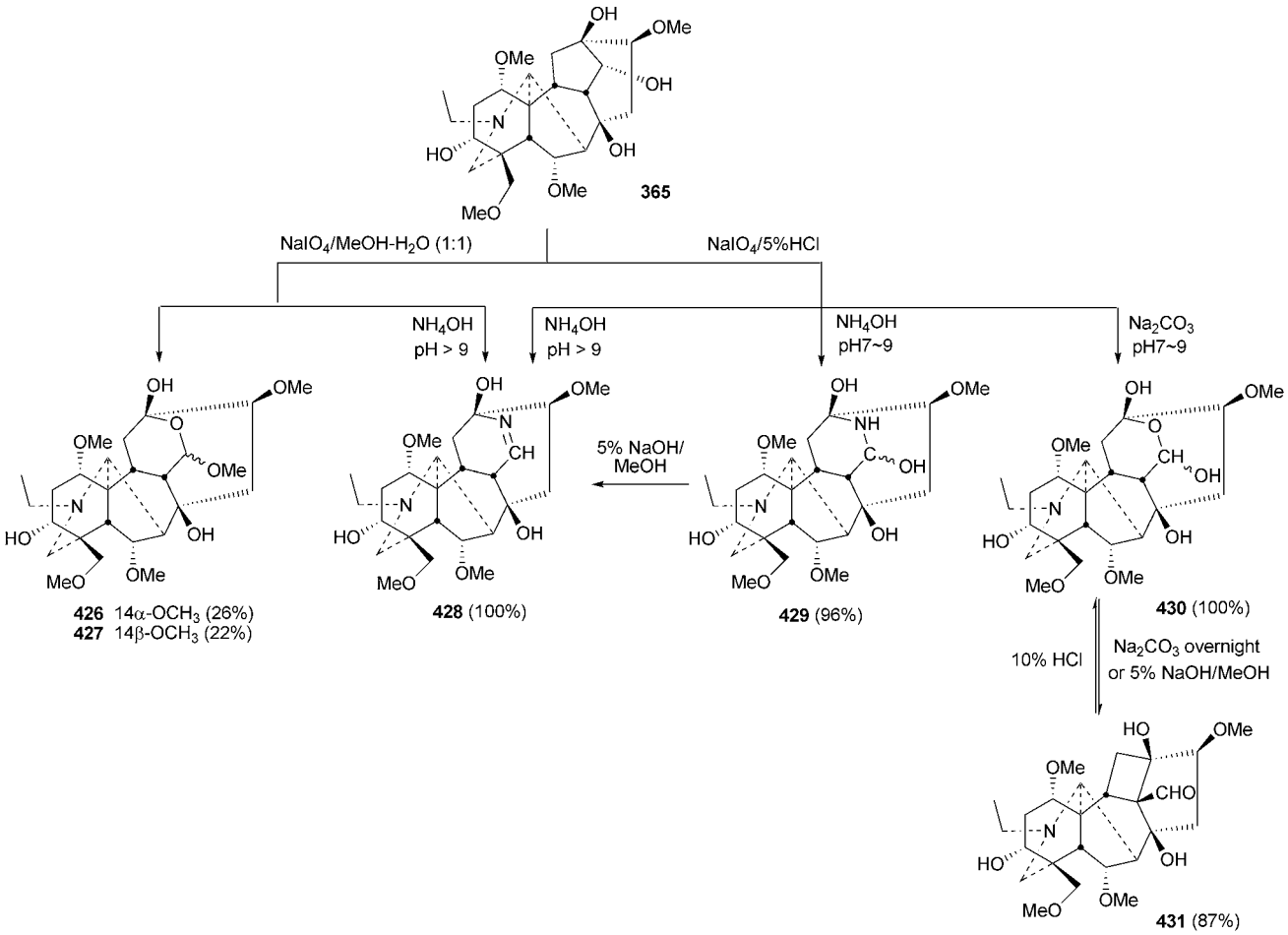
Scheme 2 Oxidation of acetyllycoctonine (**405**) with *m*CPBA.



Scheme 3 Oxidation of acetyllycoctonine (**405**) with NBS.



Scheme 4 $NaIO_4$-catalyzed bromination and HIO_4 oxidation of lappaconitine (**425**).



Scheme 5 Oxidation of pseudaconine (**365**) with HIO_4.

4 Synthetic studies

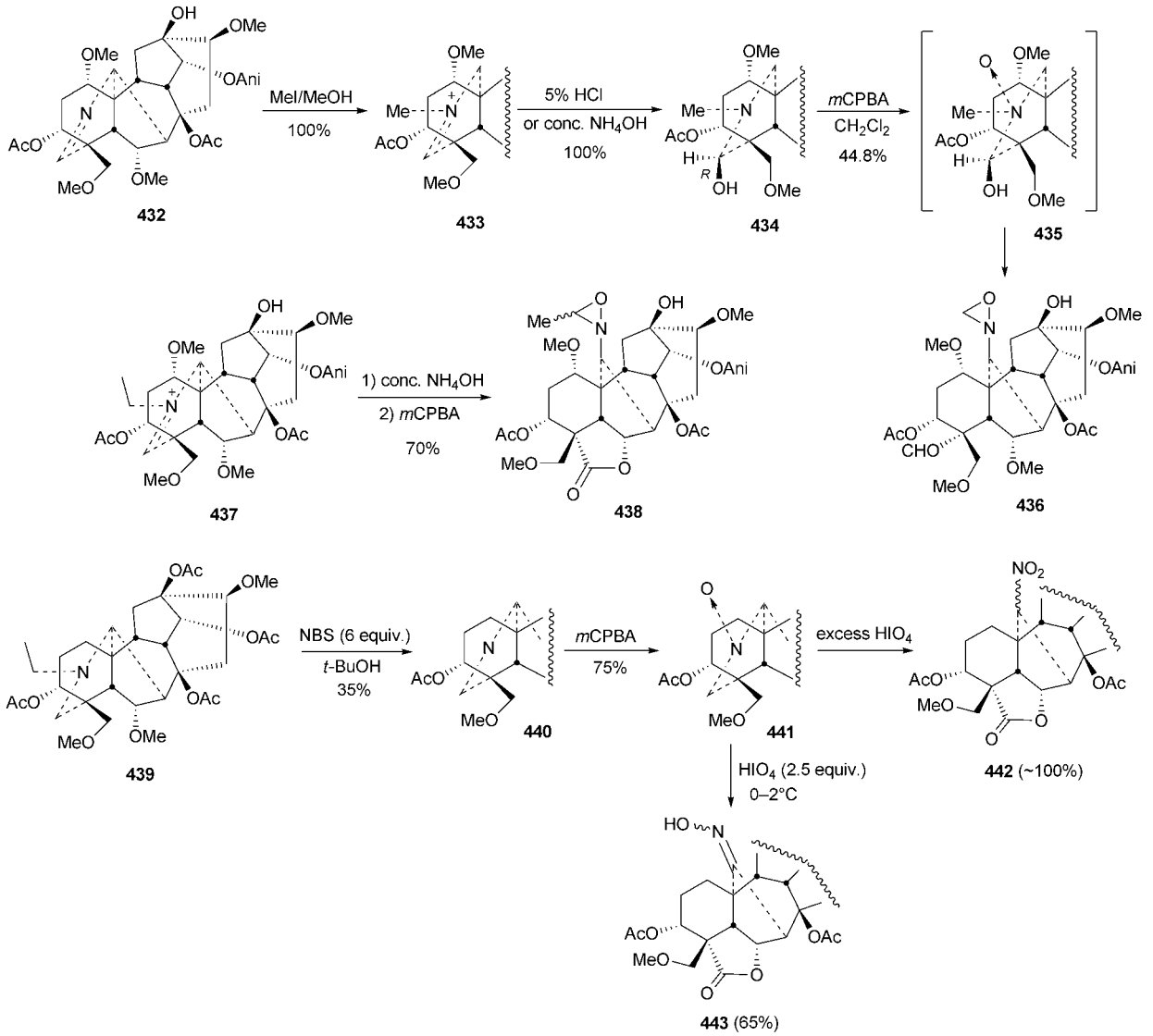
4.1 Synthesis of 12,13-seco C_{19}-diterpenoid alkaloids

As shown in Scheme 9, Wang and coworkers developed a route to the 12,13-seco C_{19}-diterpenoid alkaloids **458** and **459**, and the D ring aromatized **460–462**, *via* semipinacol rearrangement of the pseudaconine derivative **457** followed by reaction with Br_2–HOAc.[254]

The structures of **458** and **461** were confirmed by their 2D NMR data and single-crystal X-ray analysis.[254] Further studies led to the preparation of a series of 12,13-seco C_{19}-diterpenoid alkaloids and their corresponding aromatic products in good to high yields.[249]

4.2 Conversion of C_{19}-diterpenoid alkaloids into aconane-type diterpenes

Two novel aconane-type diterpenes (**463** and **464**) could be generated from *N*,19-seco nitro-compound **442** or nitrone **441**



Scheme 6 Cleavage of the *N*=C-19 bond of compounds **432**, **437** and **439**.

through a Nef reaction or oxidation with HIO_4, respectively, in moderate yields (Scheme 10).[255]

4.3 Exploration on the approaches to taxoids from C_{19}-diterpenoid alkaloids

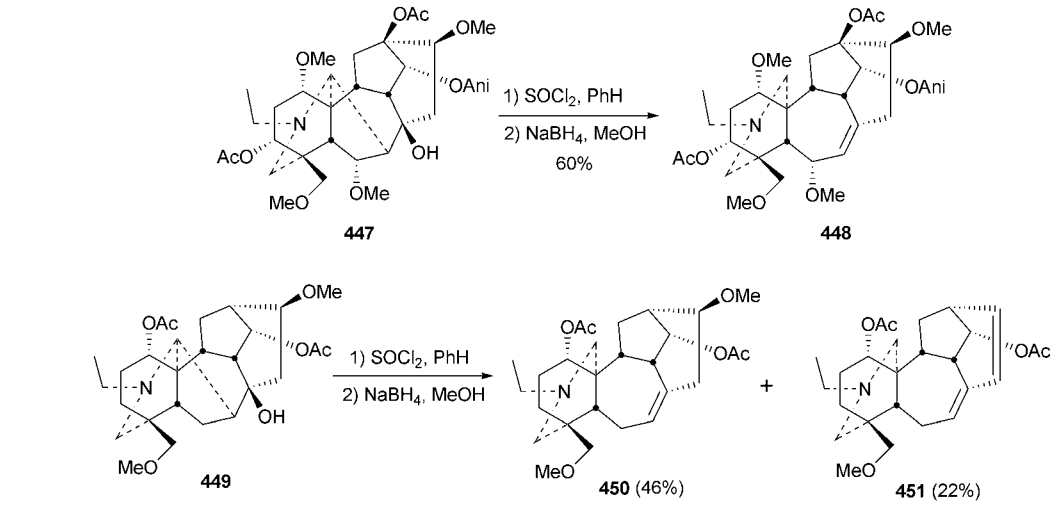
After the exploration of four routes (ABC, ACB, BCA, and CAB) towards taxoids, Wang *et al.* reported that the vital intermediate **473** or **476** could be synthesized starting from yunaconitine (**465**) by the CAB approach, as shown in Scheme 11.[256] The key steps include the semipinacol rearrangement of **467** with NaOH/DMF, and the rupture of the *N*–C-19 bond (**472** → **473**, **475** → **476**).

4.4 Conversion of C_{19}-diterpenoid alkaloid deltaline to the taxane ABC core system

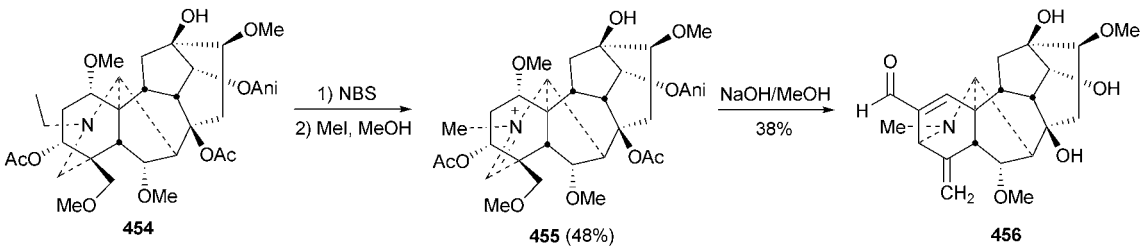
Following a long series of investigations into the chemistry of rings A,[233,236,246,248,254,256] B,[249–251,256] and C[253,255,256] of the C_{19}-diterpenoid alkaloids and the preparation of key intermediates towards the taxoid analogs,[256] Wang and coworkers recently reported a novel approach toward the taxane ABC core system employing deltaline (**382**) as the starting material in 18% overall yield.[18] As shown in Scheme 12, the key reactions included Grob fragmentation (**478** → **479**), fission of the $\Delta^{9,14}$ double bond followed by aldol condensation (**479** → **480**), and Pelletier cleavage (**481** → **482**). The structure of the taxoid analog **482** was confirmed by 2D NMR and single-crystal X-ray analysis.[18]

4.5 Total synthesis of C_{20}-diterpenoid alkaloid nominine

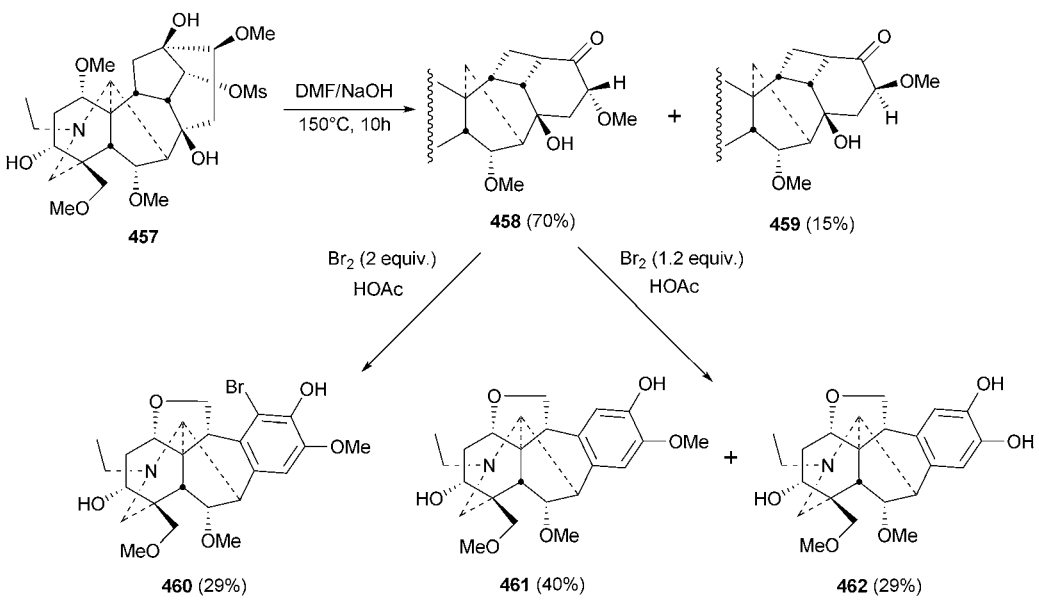
4.5.1 Muratake and Natsume's synthesis of nominine. Nominine (**498**), a hetisine-type diterpenoid, was first isolated from *Aconitum sanyoense* by Ochiai *et al.* in 1956.[257] In 2004, the total synthesis of (±)-nominine was completed by Muratake and Natsume in 40 steps and 0.15% overall yield.[19,258–260] The key steps in the construction of the architecturally complex polycyclic structure of this diterpenoid alkaloid were a palladium-catalyzed intramolecular α-arylation at the aldehyde group,



Scheme 7 Cleavage of the C-7–C-17 bond of compounds **447** and **449**.

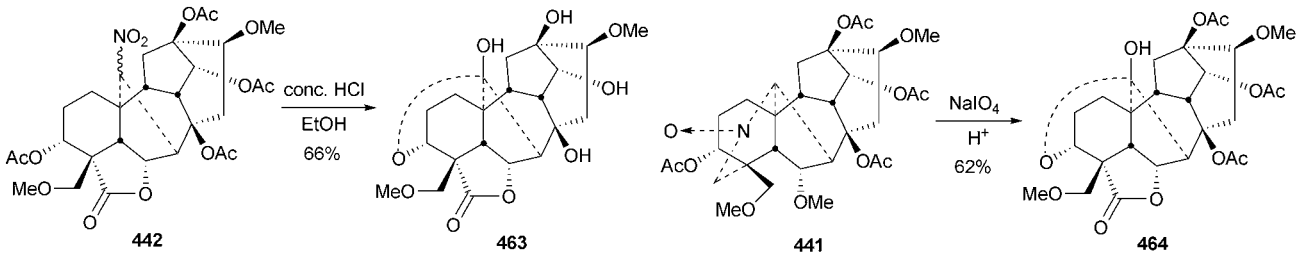


Scheme 8 Rearrangement of ring A of compound **454**.

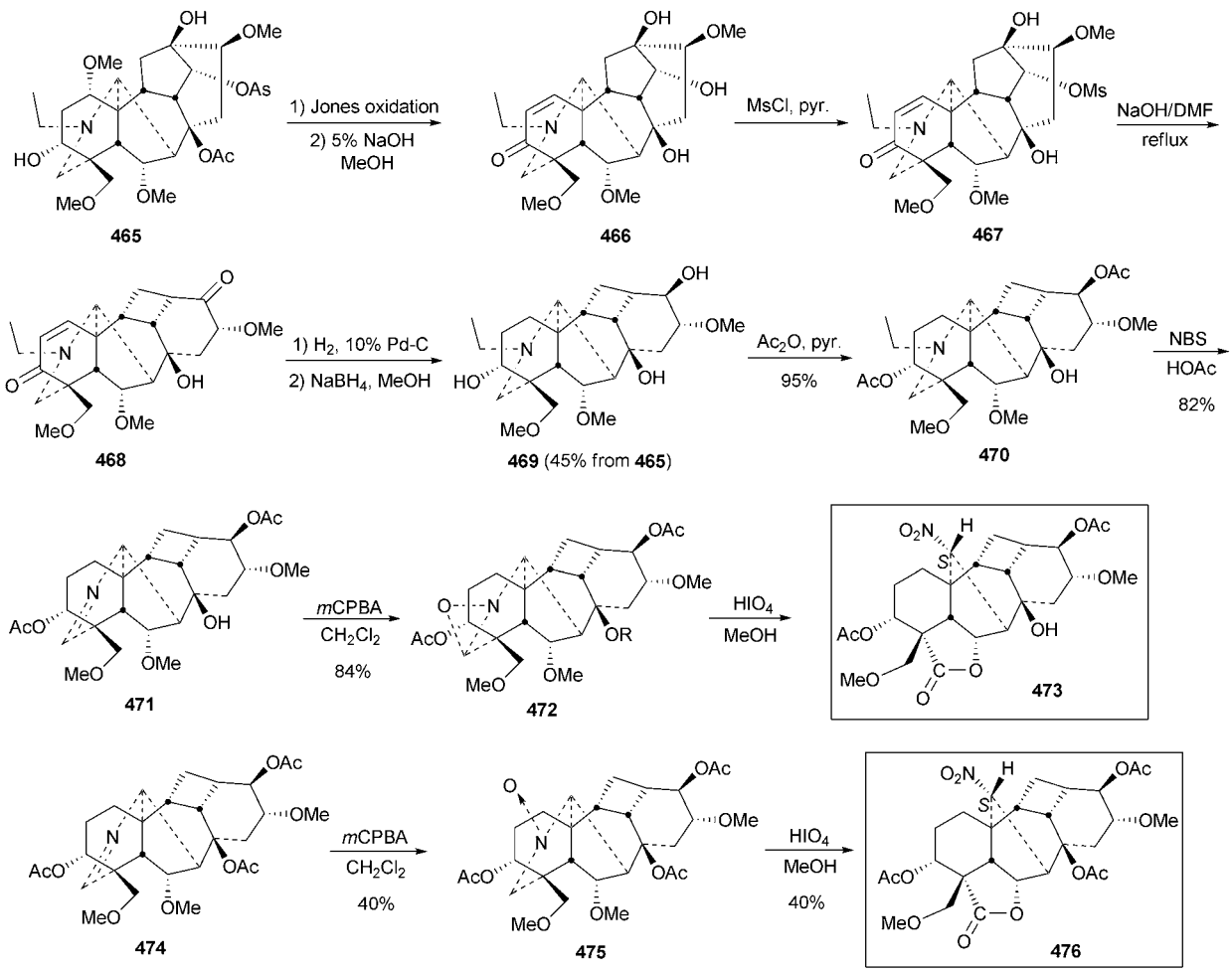


Scheme 9 Synthesis of 12,13-seco diterpenoid alkaloids.

a Lewis acid-mediated acetal–ene reaction to form the C-14–C-20 bond, and a radical cyclization of an enyne. As depicted in Scheme 13, aldehyde **484**, prepared from 1-bromo-2-(2-iodoethyl)-4-methoxybenzene, could be readily converted to the desired isomer **485** *via* palladium-catalyzed intramolecular α-arylation and repeated acetalization. Following the transformation of **485** into **487**, the C-14–C-20 bond was constructed by an intramolecular acetal–ene reaction to form tetracycle **488**. After obtaining the enone **489** in an eight-step sequence from **488**, stereoselective hydrocyanation of **489** with Et_2AlCN afforded the *trans* isomer **490** with the desired C-4 stereochemistry.



Scheme 10 Conversion of diterpenoid alkaloids into aconane-type diterpenes.

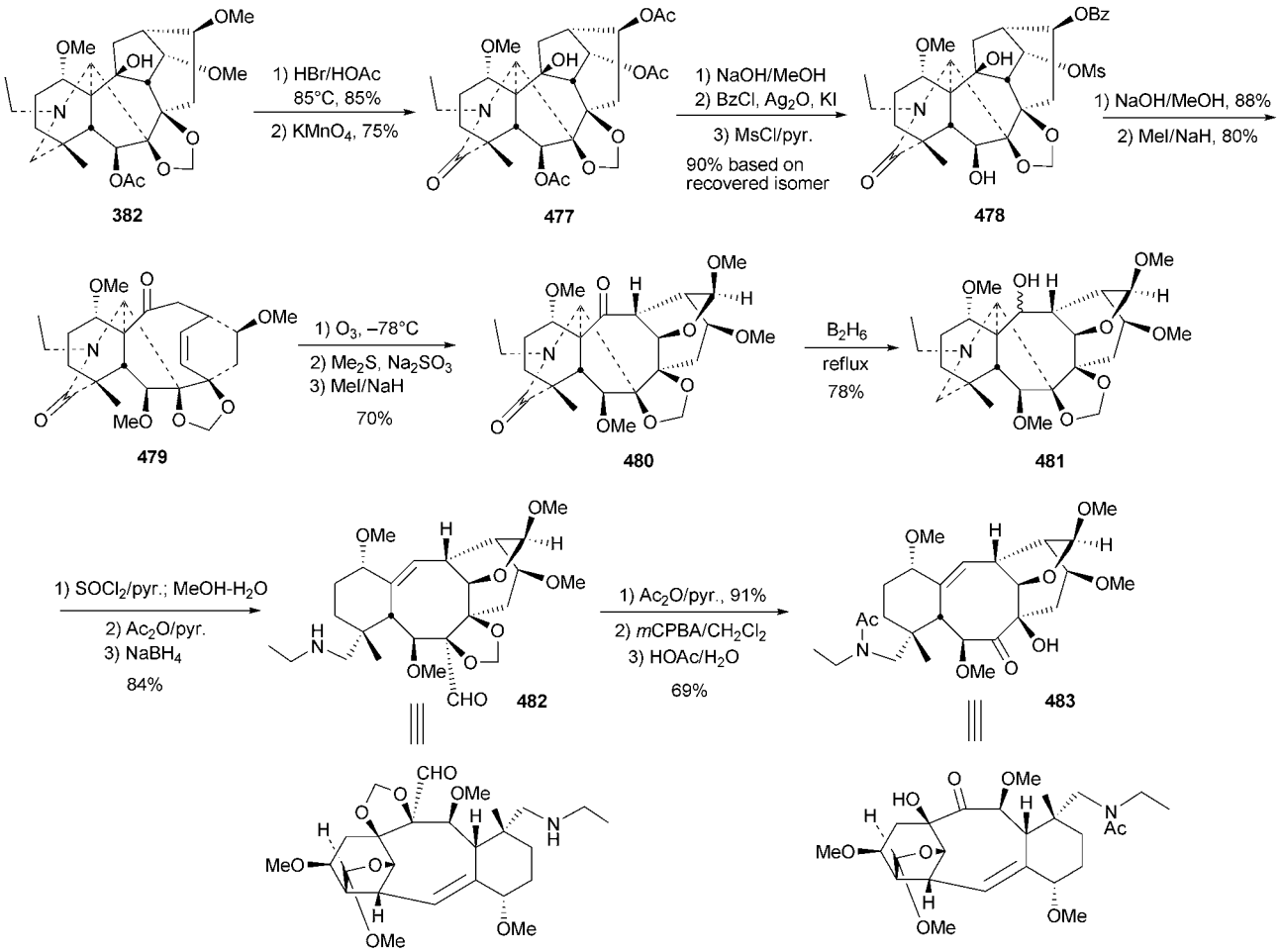


Scheme 11 Synthesis of **473** and **476**.

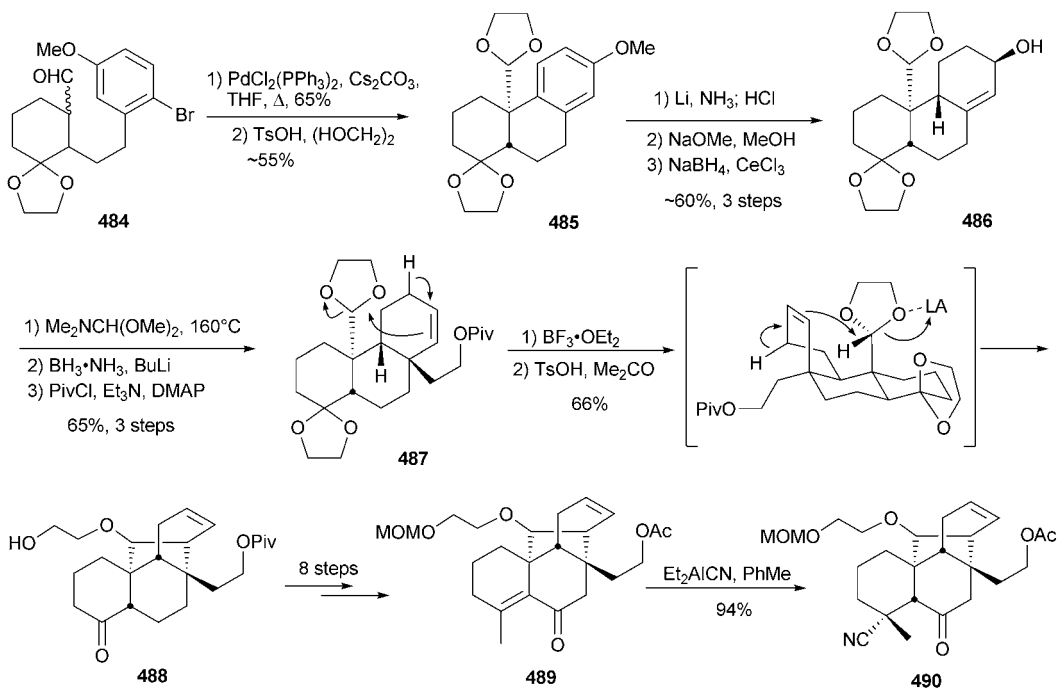
Due to the failure of D ring construction at a later stage,[261] the authors turned to a new strategy to complete the end-game of the synthesis (Scheme 14).[19] The pyrrolidine ring in pentacyclic intermediate **491** was constructed in a three-step sequence from **490** in 63% yield. Then compound **491** was converted *via* Ohira alkynation to enyne precursor **493**, which was subjected to radical cyclization to yield the hexacyclic intermediate **494** in 57% yield. Eventually, the construction of (±)-nominine (**498**) was completed by selective introduction of a 15β-hydroxyl group and the azabicyclic ring.

4.5.2 Gin and Peese's synthesis of nominine. Following the above-mentioned landmark achievement of Muratake and Natsume, a short total synthesis of (±)-nominine in a 15-step sequence was accomplished by Gin and Peese two years later.[20] This elegant route features a reversible intramolecular 4-oxidoisoquinolinium betaine 1,3-dipolar cycloaddition (**506** → **508**) as well as a pyrrolidine-induced dienamine isomerization – Diels–Alder cascade (**511** → **513**).

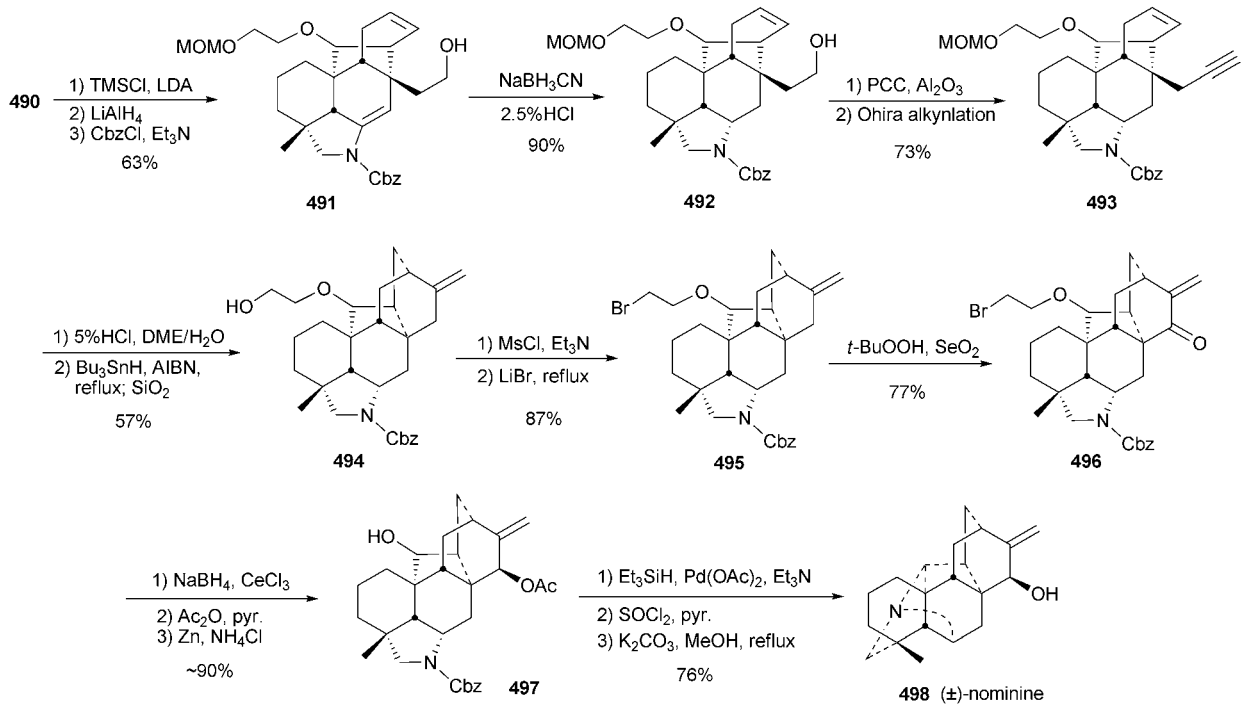
As shown in Scheme 15, the synthetic efforts commenced with the preparation of a substrate incorporating the requisite dipole–dipolarophile complement in conjunction with a latent diene–dienophile pair. Aryl ketone **500** was synthesized in 52% yield by *ortho*-lithiation of *p*-anisaldehyde dimethyl acetal (**499**), followed by nucleophilic addition to 2-chloro-*N*-methoxy-*N*-methylacetamide. Cyclic bis-acetal **501** was achieved by the replacement



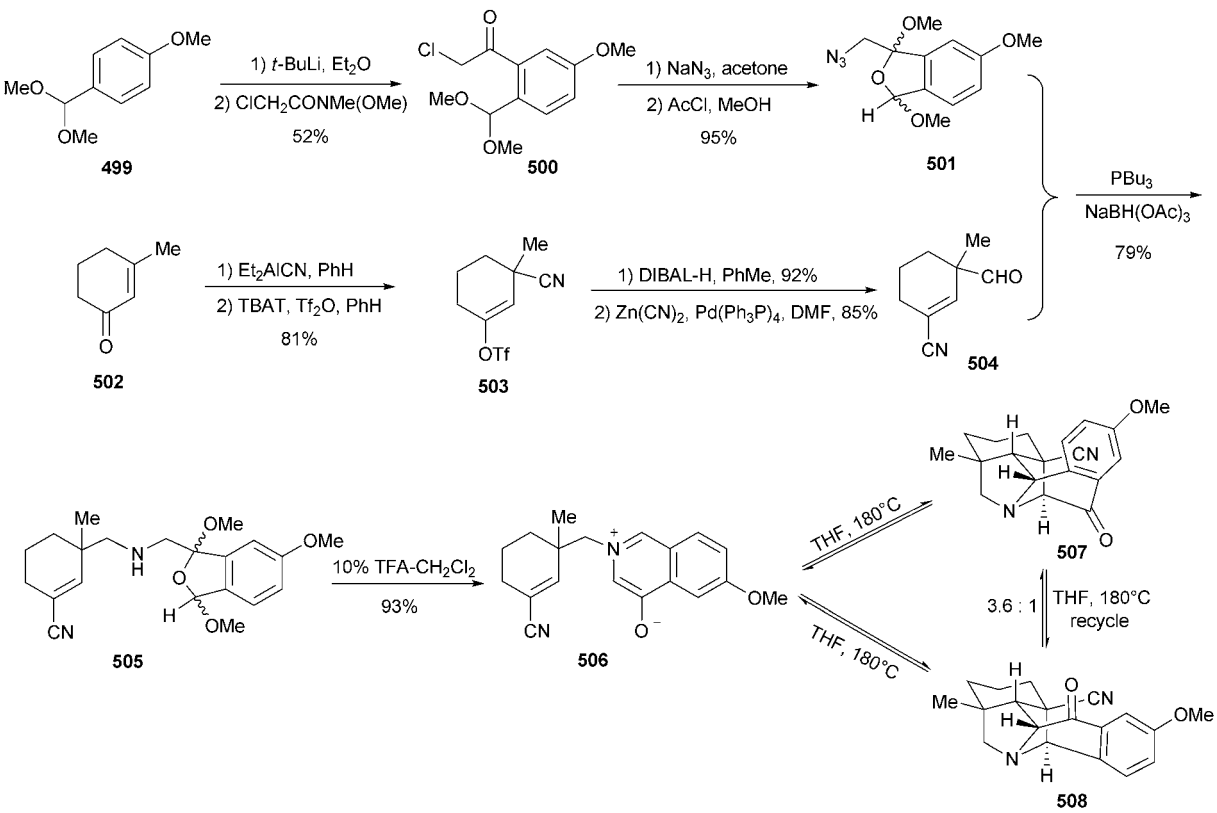
Scheme 12 Conversion of deltaline (**382**) to taxane ABC core system.



Scheme 13 Synthesis of intermediate **490**.



Scheme 14 The first total synthesis of (±)-nominine by Muratake and Natsume.



Scheme 15 Synthesis of key intermediate **508**.

of the α-chloro substituent in **500** with its α-azido counterpart and acid-catalyzed rearrangement. Meanwhile, the ene–nitrile dipolarophile **504** was prepared from **502** in 63% total yield by cyanation, enolate trapping, and Pd^0-catalyzed cross-coupling with $Zn(CN)_2$. Staudinger–aza-Wittig coupling of **501** with **504** followed by reduction of the corresponding imine afforded amine **505** (79%) as a mixture of four diastereomers. The mixture was then converted to 4-oxidoisoquinolinium betaine **506** (93%),

which served as a suitable aza-1,3-dipole, *via* TFA-catalyzed MeOH extrusion and isomerization. The key intramolecular 1,3-dipolar cycloaddition of **506** at 180 °C provided a separable mixture of pyrrolidine isomers **507** and **508** with 97% conversion rate. The isomer **507** could be reconverted to the desired cycloadduct **508** through thermal equilibration.

The β,γ-unsaturated cyclohexenone **511** was achieved from **508** in a six-step sequence (Scheme 16). With compound **511** in hand, the stage was set for the intramolecular Diels–Alder cycloaddition. Upon exposure of **511** to pyrrolidine in MeOH at 60 °C, the adduct **513** was generated in 78% yield, *via* the presumed dienamine intermediate **512**. The end game of the synthesis toward (±)-nominine (**498**) was completed by Wittig methylenation of the ketone **513** followed by diastereoselective SeO_2 allylic hydroxylation.

The first asymmetric total synthesis of (+)-nominine was also completed by the Gin group through an early-stage introduction of the desired chiral centers.[262] The ene–nitrile (+)-**504** served as a key chiral material, which was synthesized using a novel asymmetric conjugate addition methodology developed by Hoveyda *et al.*[263] This enantioselective transformation was applicable in the context of multi-step synthesis, culminating in the asymmetric synthesis of (+)-nominine.

4.6 Syntheses directed towards hetisine-type C_{20}-diterpenoid alkaloids

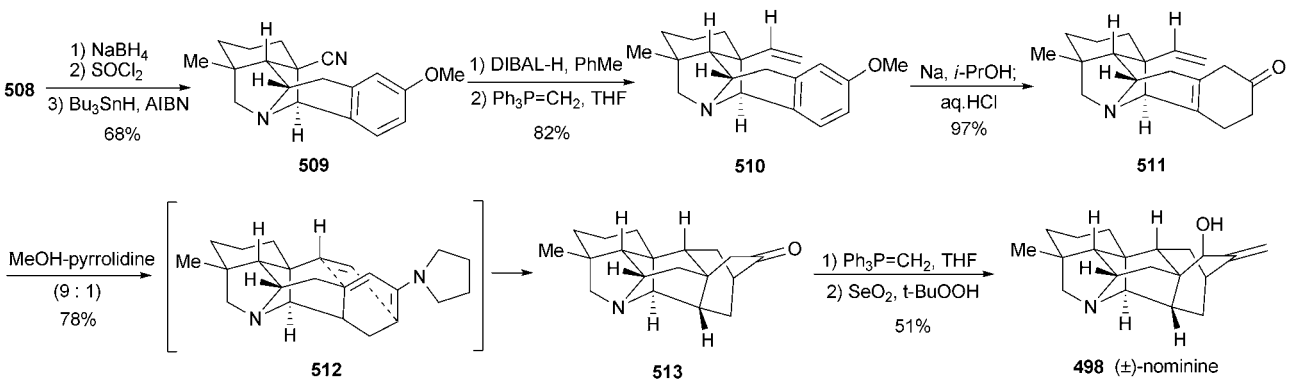
4.6.1 Synthetic studies towards hetisine by Kwak and Winkler. Kwak and Winkler have disclosed a route to the bridged pyrrolidine **518** from **514**, employing a highly efficient intramolecular [2 + 2]-photocycloaddition of a vinylogous imide as a key reaction (**515** → **516**) (Scheme 17).[264] This methodology might be applicable to the synthesis of hetisine alkaloids.

4.6.2 Synthetic studies towards hetisine by the Williams group. The advanced intermediate **525** with an ABCE C_{20}-diterpenoid ring system was prepared from **519** and **520** by Williams and co-workers, employing an intramolecular bridgehead arylation as a key reaction (Scheme 18).[265,266] Deprotonation of arylacetylene **520** with methylmagnesium bromide and subsequent addition to **519** in toluene afforded **521**. Catalytic hydrogenation of **521** gave the *cis*-alkene **522** in 74% yield. Elaboration of **522** using routine procedures afforded **523** and **524**. Intramolecular arylation of **524** with silver 2,4,6-trinitrobenzenesulfonate (AgTNBS) produced the target compound **525** in 53% yield.

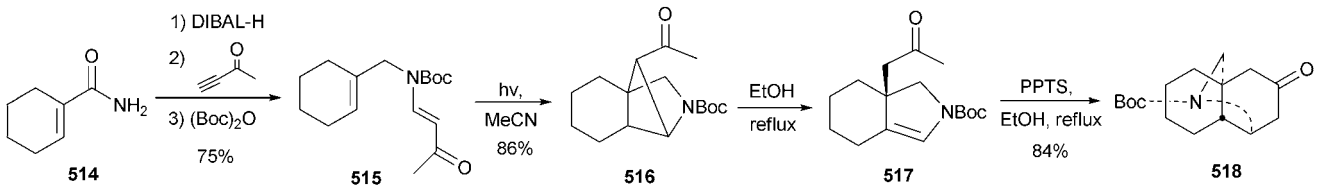
4.6.3 Synthetic studies towards nominine by Hutt and Mander. Recently, attempts to synthesize nominine (**498**) by Hutt and Mander led to the preparation of the key intermediate **537** (Scheme 19).[267] The alcohol **527** was prepared in 27% overall yield from **526** in a six-step sequence. Protection of **527** using standard conditions followed by removal of the ketal functionality afforded the enone **528** in 42% yield, which was smoothly converted to the β-keto ester **529**. Treatment of **529** with NaH/MOMCl in HMPA followed by reduction delivered the alcohol **531**, which was converted into the nitrile **532** in three steps – oxidation, conversion of the aldehyde to the oxime, and dehydration in the presence of $RuCl_2(p\text{-cymene})_2$. The construction of the key intermediate **537** was then achieved by a sequence of reactions involving alkylation (**532** → **533**), Birch reduction (**534** → **535**), DDQ oxidation (**535** → **536**), and intramolecular Lewis acid-catalyzed 1,6-addition (**536** → **537**).

4.7 Synthetic studies towards C_{19}-diterpenoid alkaloids

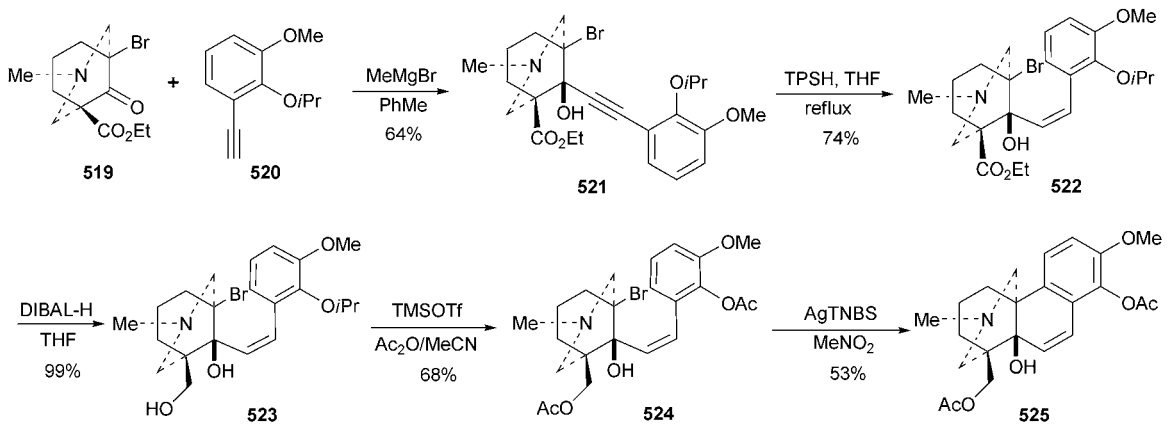
4.7.1 Synthetic studies towards *N*-deacetyllappaconitine. Taber *et al.* presented a model study leading to the preparation of the AEF rings of *N*-deacetyllappaconitine, using conjugate



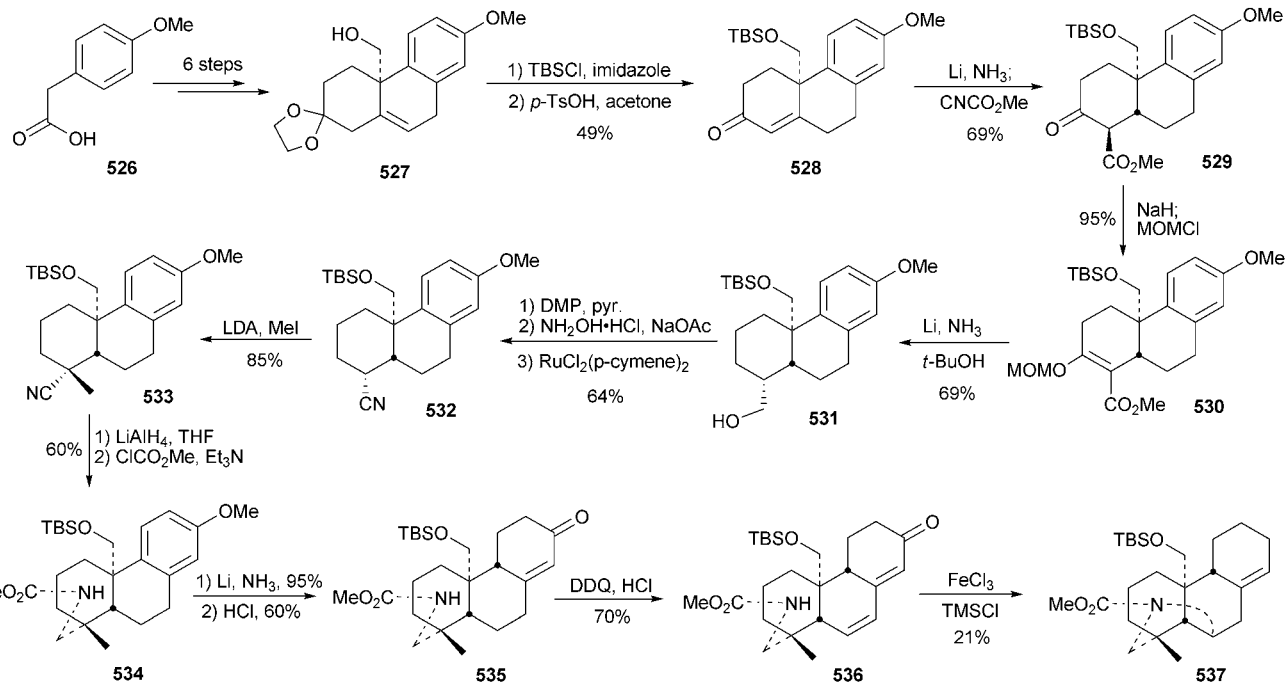
Scheme 16 Completion of the total synthesis of (±)-nominine by Gin and Peese.



Scheme 17 Synthesis of intermediate **518** by Kwak and Winkler.



Scheme 18 Synthesis of ABCE ring system of hetisines by Williams.



Scheme 19 Synthetic studies towards nominine by Hutt and Mander.

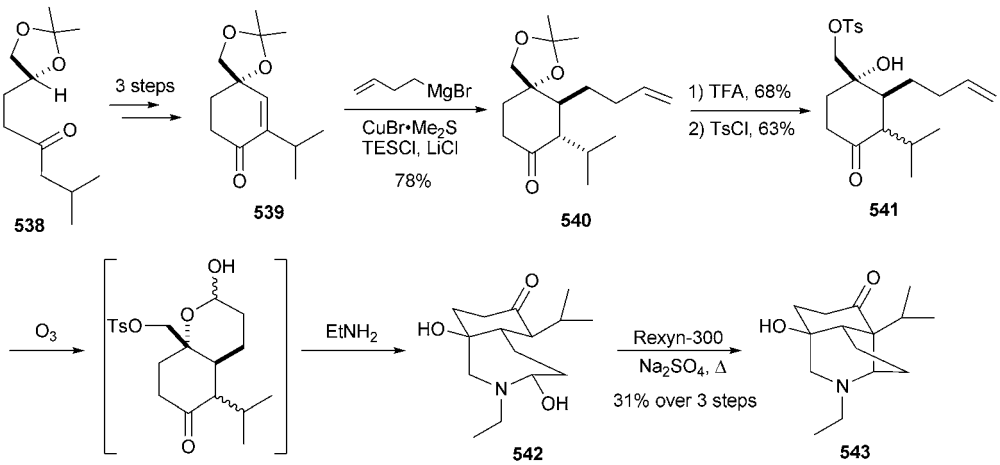
addition and Mannich cyclization as key reactions (Scheme 20).[268] The synthesis of the substituted cyclohexanone intermediate **539** was successfully accomplished using an alkylidene carbene C–H insertion – ozonolysis – aldol condensation sequence. The conjugate addition to the **539** proceeded with high diastereoselectivity. The key intermediate **543** was constructed by Mannich cyclization of the intermediate **542** in the presence of Rexyn-300 and Na_2SO_4.

4.7.2 Synthetic studies towards aconitine. Conrad and Du Bois described a strategy for preparation of the BCD ring system of aconitine during their attempts to exploit chemoselective C–H amination for assembling the complex framework of natural products.[269] As shown in Scheme 21, treatment of sulfamate **544** with $Rh_2(esp)_2$, PhI $(OAc)_2$ and MgO furnished the corresponding *N*,*O*-acetal **545** in high yield and with exquisite chemoselectivity. Subsequent Lewis acid-mediated cyclization failed to obtain the desired **546**; instead, the unexpected rearranged product **547** with a BCD ring system of typical C_{19}-diterpenoid alkaloids was isolated.

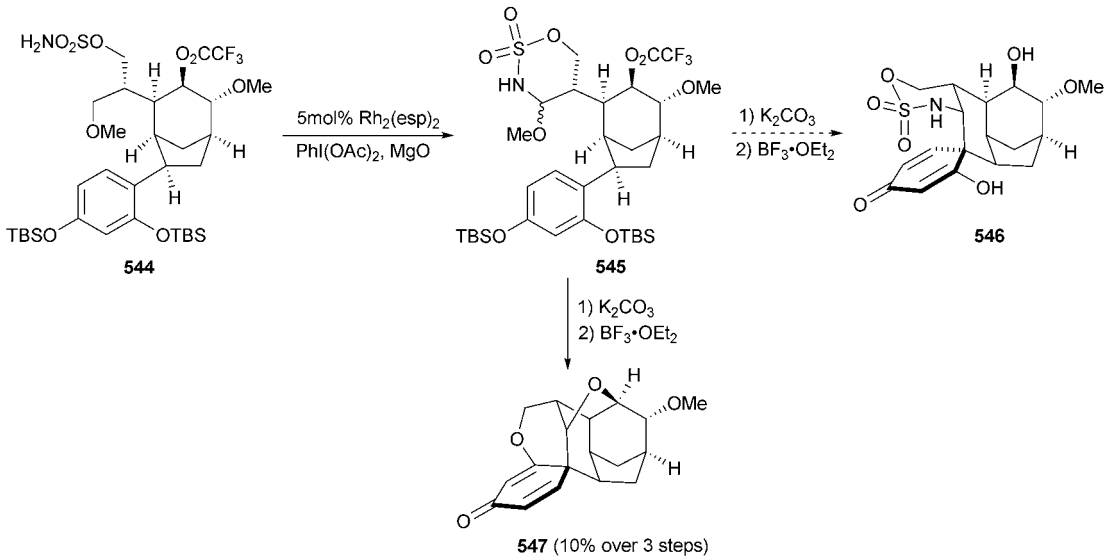
4.7.3 Synthesis of methyllycaconitines. Since Blagbrough *et al.* reported that methyllycaconitine is a potential nAChR inhibitor,[270] the synthesis of methyllycaconitine and its analogues have attracted a lot of interest. An excellent review on the synthesis of methyllycaconitine and its analogues has been presented.[12]

5 Studies of soft-ionization MS (ESI, ESI-MS^n)

Since it was established in 1997 by Ohta *et al.* that soft-ionization mass spectrometry makes it possible to detect therapeutic levels



Scheme 20 Construction of AEF rings of C_{19}-diterpenoid alkaloids by Taber *et al.*



Scheme 21 Synthetic efforts towards aconitine by Du Bois.

of diterpenoid alkaloids in blood and urine,[271] various soft-ionization techniques and their combinations with other techniques have been extensively applied to determine diterpenoid alkaloids in mixed samples (including extracts and metabolites).[243–245,272–289] This technique has been found to be superior to other analytical methods with regard to sample amount, speed, sensitivity, and convenience.

5.1 Aconitine-type alkaloids

"*Chuan wu*" (the roots of *Aconitum carmichaeli*), "*fu zi*" (radix of *Aconitum lateralis*), and "*cao wu*" (the roots of *Aconitum kusnezoffii*) have been widely used in clinical therapy as Traditional Chinese Medicines. They all have toxic and bioactive diester-type diterpenoid alkaloids, such as aconitine, mesaconitine, hypaconitine, deoxyaconitine, beiwutine and aconifine, together with their derivatives, lipo-alkaloids. Structurally, all of these alkaloids possess a hydroxyl group at C-15α, a benzoyl group at C-14, and an acetoxyl or a long-chain fatty acid ester at C-8. Liu *et al.* have extensively investigated the analysis of diterpenoid alkaloids, including pure alkaloid or mixed samples (especially for the alkaloids from "*chuan wu*", "*fu zi*", and "*cao wu*") by ESI-MS^n.[243–245,272,274–279,283,284]

The most important fragmentation features in the ESI-MS^n of this kind of diterpenoid alkaloids are that the characteristic ion peaks come from the cleavage of substituents (such as OH, OMe, OAc, OBz, NMe, NEt); in a very few cases ring fragmentation is involved.

In addition, on the basis of the calculation of the stability of fragment ions by quantum chemistry, Chen *et al.* discovered that the cleavage order of the substituents in the ESI-MS^n was as follows: 8-OAc → 14-OBz → NEt/NMe and that the methoxy group located at C-16 would be lost more readily than those at other positions (such as C-1, C-6 and C-18).[290]

ESI-MS^n characteristics of three aconitine-type alkaloids, including isotalatizidine, neoline and senbusine A, have been

presented. The main fragments in ESI-MS^n spectra of these alkaloids originate from the loss of H_2O (−18 u), MeOH (−32 u), and HOAc (−60 u). The relative abundance of these fragments is influenced by the nature and position of the substituents.[291]

The lycoctonine-type alkaloid virescenine possesses an α-OH at C-6, while the aconitine-type alkaloid senbusine A has a β-OH at C-7. The relative intensity of the fragments at *m/z* 370 $[P - 3H_2O]^+$ in the MS^2 of senbusine A, as well as of the ions at *m/z* 388 $[P_2 - H_2O]^+$ and at *m/z* 370 $[P_2 - 2H_2O]^+$ in its MS^3, is significantly higher than those of virescenine. This suggests that the elimination of the hydroxyl group occurs more readily at C-6 than at C-7.[291]

5.2 Lipo-alkaloids

Most of the lipo-alkaloids belong to the aconitine-type group. The characteristic ion peak at $[M + H - OR/C\text{-}8]^+$ of the lipo-alkaloids in the MS^2 spectra is usually derived by the loss of the long-chain fatty acid ester at the C-8 position.[272–274,277,278] Except for this point, the other fragmentation patterns in their MS^n spectra are similar to those of aconitine-type alkaloids.

Employing various ESI-MS^n techniques, a few dozen lipo-alkaloids have been detected and determined from "*chuan wu*", "*fu zi*", and "*cao wu*".[271,274,276,279,280]

5.3 Lycoctonine-type alkaloids

On the basis of careful analysis of fragmentation patterns in the mass spectra of some lycoctonine-type diterpenoid alkaloids by Gardner *et al.*,[274] it was found that the first two tandem mass experiments of lycoctonine-type alkaloids yield a significant fragment ion peak at $[M + H - H_2O]^+$ from loss of water, or at $[M + H - HOAc]^+$ due to loss of acetic acid. It was also shown that the first three tandem mass experiments produce most abundant ions at $(MH^+ - 32)$ derived from sequential losses of methanol, while MS^4 shows principal losses of water, methanol, and methanol–water. The generation of fragmentation ion peaks of the lycoctonine-type alkaloids is closely correlated with the pattern and position of substituents.

5.4 The stereochemistry of diterpenoid alkaloids

The Japanese scientists Wada *et al.* successfully applied HPLC–APCI-MS to the stereochemical investigation on C_{19}-diterpenoid alkaloids.[292] It was showed that the abundance of fragment ions is significantly higher for C-1β-type alkaloids than for C-1α-type alkaloids. The characteristic fragment ions are formed by the loss of a molecule of water, acetic acid or methanol at C-8. The reason for this kind of difference might be attributed to the stability of $[M + H]^+$.[293] This method was also successfully applied to C-6 stereoisomeric C_{19}-diterpenoid alkaloids by Wada and coworkers.[293] For the diterpenoid alkaloids with 6-OMe/8-OH moieties, comparison of the APCI spectra showed that the abundance of fragment ions at $[M + H - H_2O]^+$ is significantly higher for C-6β alkaloids than for C-6α alkaloids. However, for those with 6-OMe/8-OAc moieties, the abundance of fragment ions at $[M + H - H_2O]^+$ is not correlated with its configuration at all.[292]

Similarly, HPLC–APCI-MS was also successfully applied to seven napelline-type stereoisomeric diterpenoid alkaloids at C-1 or C-12. The APCI spectra of alkaloids consist predominantly of the $[M + H]^+$ ion, the major fragment ion corresponding to the $[M + H–H_2O]^+$ ion or the $[M + H - CH_3COOH]^+$ ion. Comparison of the APCI spectra shows that the abundance of fragment ions is significantly higher for C-1β-type alkaloids than for C-1α-type alkaloids, and for C-12β-type alkaloids than for C-12α-type alkaloids.[294]

In addition, there are some other reports on the application of GC/SIM,[295] HPCE,[296] HPLC,[297–301] countercurrent chromatography,[302–304] and LC[305] for the analysis and separation of diterpenoid alkaloids.

6 Phytotaxonomic studies

During the review period, only one paper on the phytotaxonomic characteristics of diterpenoid alkaloids was presented, by Xiao, Wang *et al.*[17] This report described the taxonomic characteristics of diterpenoid alkaloids from Chinese *Aconitum*, and a reliable taxonomic character of the genus based on the reported diterpenoid alkaloids of 84 species of *Aconitum* grown in China.

7 Biological activities

7.1 Pharmacological activities

7.1.1 Anti-inflammatory, analgesic, and de-addictive activities. Shaheen and co-workers have evaluated the anti-inflammatory activities of six C_{19}-diterpenoid alkaloids in an *in vitro* assay.[113] The results showed that only lappaconitine and puberanine exhibited anti-inflammatory activity as good as indomethacin. Russian scientists have investigated on the effects of water–ethanol extracts and alkaloids extracted from tall *Delphinium* on acute inflammation induced by carrageenin, acetic acid, serotonin and histamine.[306] The bioassay results show that these plant extracts and alkaloids could have significant anti-inflammatory activity, comparable to that of non-steroid anti-inflammatory drugs.

The Wang group has recently published their research results on the structure–analgesic activity relationship of 28 C_{18}- and C_{19}-diterpenoid alkaloids.[307] It was found that a tertiary amine in ring A, an acetoxy or an ethoxy group at C-8, an aromatic ester at C-14, and the saturation state of the ring D are structural features necessary for their analgesic activities. The analgesic activity of several alkaloids of *Aconitum* was assumed to be attributed to the interference with voltage-gated Na^+ channels.[308] Aconitine, 3-acetylaconitine and hypaconitine seem to inhibit neuronal conduction by persistent depolarization, whereas lappaconitine might block Na^+ channels. A QSAR analysis of the effect of chemical substitutes in the analgesic potency of 12 diterpenoid alkaloids, which were previously evaluated in a model of acetic acid-induced writhing in rats, corroborates that analgesic effect is primarily peripheral and secondarily central.[309]

It has been reported that *Delphinium denudatum*, a rich source of diterpenoid alkaloids, might significantly reduce the aggregate scores for all parameters in morphine withdrawal syndrome in rats or mice by central action, and thus may prove to be an alternative remedy in morphine de-addiction.[310–312]

7.1.2 Cardiovascular action. Pelletier and co-workers have tested the *in vivo* cardiovascular action (hypotensive,

bradycardic, and ventricular arrhythmias) of 13 C_{19}-diterpenoid alkaloids in male Sprague-Dawley rats.[313] It was found that 3,8-diacetylfalconerine can cause arrhythmias at doses of 200 and 400 μg kg^{-1}, and that the following compounds exhibit prominent hypotensive and bradycardic activity without prominent arrhythmias: heteratisine *N*-oxide, 8-deacetyl-8-*p*-aminobenzoyldelphinine, 8-deacetyl-8-anthranoyldelphinine, 8-stearoylfalconerine, 8-linolenylfalconerine, pyrodelphinine, 16-*epi*-pyroaconitine, and 8,9-(methylenedioxy)-lappaconitine. It was shown that cardiotoxicity of lappaconitine and *N*-deacetyllappaconitine is much lower than aconitine, and that lappaconitine is a naturally occurring compound with class-I antiarrhythmic action.[314] It was established that several napelline-type alkaloids produce a more-or-less significant antiarrhythmic effect. Among them, 1-*O*-benzoylnapelline showed the most potent activity, which markedly exceeded that of napelline itself and the reference class-I antiarrhythmic drugs novocainamide, quinidine and lidocaine.[315] 12-Acetyl-12-*epi*-napelline was also found to have better antiarrhythmic activity than quinidine and novocainamide.[209] As mentioned in the introduction, guan-fu base A has been developed by Liu *et al.* for the therapeutic treatment of arrhythmia in China.[16]

7.1.3 Anticancer activity. The bioassay-guided fractionation of the MeOH extract of the roots of *Aconitum pseudo-laeve* var. *erectum* led to the isolation of lycaconitine as an active compound (IC_{50} = 74 μg mL^{-1}) toward multidrug-resistant human fibrocarcinoma KB V20C.[316] Lycaconitine was found to have potent inhibitory activity on Pgp-MDR but not on MRP-MDR. Later, 8-*O*-azeloyl-14-benzoylaconine was found to have *in vitro* cytotoxicity, with an IC_{50} value of about 10–20 μM.[13] Two more reports on the effects of the diterpenoid alkaloids on cancer cells have appeared in recent years.[317,318] Several C_{19}-diterpenoid alkaloids (such as neoline, pubescenine, 14-deacetylajadine, lycoctonine, dehydrotakaosamine and ajadelphinine) exhibited selective cytotoxicity to cancerous cells, and some of these had irreversible effects on SW480, HeLa and SkMel25 cell lines.[319] These cytotoxic effects were related to the inhibition of ATP production. Interestingly, it was reported that the C_{19}-diterpenoid alkaloids showed a lower suppression effect against certain human tumor cell lines (such as A172, A549, HeLa and Raji) relative to the C_{20}-diterpenoid alkaloids.[320]

7.1.4 Anti-epileptiform activity. It was reported that mesaconitine shows significant anti-epileptiform activity, which becomes obvious in the low Mg^{2+}-model and is not blocked by the β-adrenoceptor antagonist timolol, but is blocked instead by the α-adrenoceptor antagonist yohimbine.[321] These findings indicate that noradrenergic inhibitory actions in the CA1 and CA3 subfield of the hippocampus are involved in the anti-epileptiform action of diterpenoid alkaloid mesaconitine, which are likely to be α-receptor-mediated. The alkaloid 6-benzoylheteratisine was also reported to be able to exert an inhibitory and anti-epileptiform effect in hippocampal slices by antagonizing the activation of Na^+ currents by aconitine.[322] The effect is likely to be mediated by a direct or indirect interaction at the neurotoxin binding site 2 of the voltage-dependent Na^+ channel. A subfraction (FS-1, 600 mg kg^{-1} i.p.) from the aqueous fraction of the roots of *Delphinium denudatum* exhibits comparable anticonvulsant activity in CF 1 mice to that of phenytoin (the well-known anti-epileptic drug, 20 mg kg^{-1}) in the maximal electroshock test, and it also protected 100% of animals from the hind limb tonic extension phase of this model.[323] Further studies suggest that FS-1 can block sustained repetitive firing in hippocampal neurons in a use-dependent and voltage-dependent manner similar to phenytoin (the prototype anticonvulsant drug).[324] The blockade of sustained repetitive firing is one of the basic mechanisms of anti-epileptic drugs at the cellular level.

7.1.5 Antiparasite and insect repellent. The diterpenoid alkaloids cardiopetamine and 15-acetylcardiopetamine were found to strongly inhibit the feeding activity of *Spodoptera littoralis* and *Leptinotarsa decemlineata*, respectively.[325] Structure–activity studies with *S. littoralis* showed that the C-13 and C-15 hydroxyl groups are essential features of the active molecule, while a C-13 hydroxyl and/or a C-15 acetate might determine their effect on *L. decemlineata*. The C-11 benzoate group may enhance the biological effect on both insect species. The repellent activities against *Tribolium casteneum* of 29 C_{19}- and C_{20}-diterpenoid alkaloids were assessed.[326] Twenty-one alkaloids among them showed promising insect repellent activity, with hetisine as the most potent compound (59.37%). The Spanish scientist González-Coloma and co-workers tested the insect antifeedant and toxic activity of 21 C_{20}-diterpenoid alkaloids and 43 C_{19}-diterpenoid alkaloids on *S. littoralis* and *L. decemlineata*.[319,327,328] The antifeedant effects of the test alkaloids were structure- and species-dependent. Overall, C_{19}-diterpenoid alkaloids are better insect antifeedants and post-ingestive toxicants than the related C_{20}-diterpenoid alkaloids. The most active antifeedants to *L. decemlineata* are 1,14-diacetylcardiopetaline and 18-hydroxy-14-*O*-methylgadesine (C_{19}-diterpenoid alkaloid, EC_{50} <1 μg cm^{-2}) and the rearranged form of hetisine (C_{20}-diterpenoid alkaloid, EC_{50} = 1.7 μg cm^{-2}), while 19-oxodihydroatisine (EC_{50} = 0.1 μg cm^{-2}) is the most active against *S. littoralis*. The *in vitro* anti-proliferative effects were described for several atisine-type diterpenoid alkaloids against the protozoan parasite *Leishmania infantum*.[329] From a total of 43 compounds tested, including several classes of C_{19}- and C_{20}-diterpenoid alkaloids, only 15,22-*O*-diacetyl-19-oxodihydroatisine, azitine and isoazitine are highly active against cultures of the parasite (promastigote form), with IC_{50} values within the range of the reference drug pentamidine-isothionate (7.39–12.80 mg L^{-1} for the test compounds, 11.32 mg L^{-1} for the positive control). González-Coloma and co-workers also screened anti-*Trypanosoma cruzi* activities of 64 C_{19}- or C_{20}-diterpenoid alkaloids.[330] It was found that five C_{20}-diterpenoid alkaloids are active against *T. cruzi* epimastigotes: azitine, isoazitine, and 15,22-*O*-diacetyl-19-oxodihydroatisine have moderate effects on the parasite, while atisinium chloride and 13-oxocardiopetamine are potent *T. cruzi* epimastigote growth inhibitors, with activity levels similar to that of the reference drug benznidazole.

7.1.6 Effects on cutaneous blood flow in mice. Continuing their investigation on the effects of C_{20}-diterpenoid alkaloid kobusine and pseudokobusin derivatives on cutaneous blood flow in mice, the Wada group established that the hydroxyl groups of these alkaloids, especially a free hydroxyl group at C-6,

are important for action on the peripheral vasculature leading to dilatation, and that the alkaloids with a 15-aromatic ester group (*e.g.* acetate, benzoate, anisoate, veratroate or *p*-nitrobenzoate) may enhance their activities relative to the parent alkaloids.[331,332]

7.1.7 Other bioactivities. Certain diterpenoid alkaloids were reported to have antibacterial activity,[33,333] antiviral activity,[334] or antioxidant ability.[113] Bulleyaconitine A was reported to display long-acting local anesthetic properties *in vitro* and *in vivo*.[335] The screening of various structural types of diterpenoid alkaloids and their derivatives for local anesthetic activity identified 26 compounds with distinct activity for surface anesthesia in rabbit eye cornea. Of these, 15 compounds have activities and durations of action that are greater than those of cocaine. However, their rates of onset of anesthesia are slower than that of cocaine.[336] The exceptions are 1-*O*-benzoylnappeline and tadzhaconine, which have similar rates of onset and durations of anesthesia, but higher activities, as compared with cocaine.

7.2 Toxicity

Aconitum species have been used since ancient times as poisons for spears and arrows, and later in homicides. *Aconitum* alkaloids (diterpenoid alkaloids) and especially aconitine (a C_{19}-diterpenoid alkaloid) are neurotoxins that cause conduction block and paralysis by activating voltage-dependent sodium channels. Aconitine poisoning occurs mainly because of confusion with an edible plant,[337] deliberate or accidental ingestion by children,[297] and ingestion for a desired phytotherapeutic effect.[338] It was reported that the toxicity of *A. coreanum* is mainly due to alkaloids that have myorelaxant activity based on the experimental data, and the myorelaxant activity for hetisine, atisine and coryphine diterpenoid alkaloids was found for the first time.[339]

Larkspurs (*Delphinium* spp.) are toxic plants that are responsible for the majority of cattle deaths in western North America. Cattle deaths may exceed 15% in areas where larkspurs are abundant.[340] C_{19}-diterpenoid alkaloids occur as prominent constituents of poisonous larkspurs in one of two structural types: the lycoctonine and the 7,8-methylenedioxylycoctonine (MDL) types. Of the 40 different diterpenoid larkspur alkaloids, the one that is thought to be responsible for much of the toxicity was identified as methyllycaconitine (MLA). MLA is a potent neuromuscular blocker, causing paralysis and rapid death from respiratory failure.[341] The study on the toxicokinetics of MLA excretion indicates that the MLA is rapidly distributed and excreted.[342] Four *N*-(methylsuccinimido)anthranoyllycoctonine C_{19}-diterpenoid (MSAL) alkaloids – geyerline, grandiflorine, bearline and 14-acetylbearline – were recently reported to possess toxicity comparable to that of MLA.[136,343] Evaluation of the toxicity data establishes two structural features (an *N*-ethyl bicyclo-substituted tertiary alkaloid nitrogen atom and a C-18 anthranilic acid ester) to be necessary to impart toxicity to the lycoctonine-type C_{19}-diterpenoid alkaloids. Additionally, the toxicity data establish that two other structural features (functionality at the anthranilic acid amine nitrogen and at C-14) can enhance that toxicity of the lycoctonine-type C_{19}-diterpenoid alkaloids. Toxic alkaloid levels above 3 mg g^{-1} pose a threat to grazing cattle. Diterpenoid alkaloid concentrations in larkspur plants vary with environment, plant and location.[136,341,344,345] Alkaloids in tall larkspur appear to be synthesized during the first three to four weeks of early growth. Pools of alkaloids increase during this period, peak at four to six weeks, then decline as the alkaloids are apparently catabolized or translocated back to the roots.[346] Significantly, three competitive inhibition enzyme-linked immunosorbent assays (CIELISA) for toxic larkspur alkaloids were developed.[347] One assay is class-specific toward the MSAL alkaloids, and two assays are specific for individual alkaloids. It was reported that vaccinating mice with larkspur toxin–protein carrier conjugates appeared to provide a mild protective effect against MLA toxicity.[348]

QSAR analysis performed for the diterpenoid alkaloids showed that a linear relationship and high correlation coefficients were observed for: (1) LD_{50} and analgesic activity ($r = 0.96$); (2) LD_{50} and local anesthetic activity ($r = 0.71$); (3) toxicity and antiarrhythmic activity data ($r = 0.88$); (4) toxicity and three therapeutic actions ($r = 0.88$–0.97).[309,349–353] In addition, descriptors related to "drug-likeness" of molecules were selected to discriminate between "drugs" and "non-drugs" amongst diterpenoid alkaloids studied. A list of boundaries calculated for seven conventional "drug-likeness" parameters has shown that curariform and antiarrhythmic alkaloids are more drug-like compounds, while arrhythmogenic alkaloids are all likely to be classified as "non-drugs". This is in a good agreement with the experimental data. When deciding whether a particular compound is a potential drug, a therapeutic index should also be considered. Thus, therapeutic indexes reported for some of "drug-like" diterpenoid alkaloids from the investigated series were in the range 100–230, mostly for those with benzoyl group. These findings also suggest that "drug-like" series of alkaloids should be further pursued as promising therapeutic agents.

7.3 Mechanisms of action

In 1998, Ameri summarized the effects of diterpenoid alkaloids on the central nervous system.[3] He subdivided the diterpenoid alkaloids into three subgroups based on the chemical features as well as their mechanisms of action: (1) diester diterpenoid alkaloids (with analgesic activity and high toxicity) that are able to activate voltage-dependent sodium channels even at resting potential and inhibit noradrenaline re-uptake; (2) monoester diterpenoid alkaloids (less toxic) which have been shown to possess strong antinociceptive, antiarrhythmic and anti-epileptiform properties due to a blockade of the voltage-dependent sodium channel; (3) de-esterified diterpenoid alkaloids which possess markely reduced toxicity when compared with the two other groups, and fail to affect neuronal activity, but are reported to have antiarrhythmic actions. It was also demonstrated that 14-benzoyltalatisamine and talatisamine are strongly different in their mode of action even though their structures differ only in the presence or absence of a benzoyloxy group at the C-14 position.[354] It was shown that aconitine and 3-acetylaconitine, which are known to activate sodium channels, have comparable inhibitory potencies toward [^{3}H]noradrenaline uptake.[355] In contrast, lappaconitine and *N*-desacetyllappaconitine were found to fail to inhibit [^{3}H]noradrenaline uptake. When either lappaconitine or *N*-desacetyllappaconitine was applied in combination with aconitine, [^{3}H]noradrenaline uptake was not affected. The

inhibitory and anti-epileptiform effect of ajacine and lappaconitine were shown to be mediated by a frequency-dependent inhibition of the voltage-dependent sodium channel.[356] Four diterpenoid alkaloids – songorine, 14-benzoyltalatisamine, pyrochasmaconitine and talatisamine – were shown to be able to depress markedly delayed rectifier K^+ current (I_K) and fast transient K^+ current (I_A) during the investigation using the whole-cell voltage-clamp recording in rat dissociated hippocampal neurons.[357] Very recently, it was further identified that talatisamine is a specific blocker for the delayed rectifier K^+ channel in rat hippocampal neurons.[14] An antagonist modulation of voltage-gated sodium channels exhibited by diterpenoid alkaloids from *Aconitum* and *Delphinium* species were investigated by means of two computational approaches: analysis of frontier MOs generated at B3LYP/6-31G(d, p) level and QSAR study.[358] The research results confirmed the experimental findings that neurotoxins acting at type 2 receptor site of voltage-dependent sodium channel are activators and blockers with common structural features and differ only in efficacy. Five alkaloids, methyllycaconitine, nudicauline, 14-deacetylnudicauline, barbinine and deltaline, were demonstrated to be likely nicotinic receptor antagonists that reduce synaptic efficacy and block neuromuscular transmission.[359] Songorine was suggested to be a novel non-competitive antagonist at the $GABA_A$ receptor in rat brain.[15]

MLA is an α7-type nAChR subtype selective antagonist.[12,270,360] Unlike the α-conotoxins, MLA shows consistent affinity for the α7 subtype across species. Unlike α-Bgt, MLA can discriminate between muscular and neuronal nAChRs, and the association and dissociation kinetics are very rapid. MLA is a very potent antagonist, binding to α7 nAChRs with nanomolar affinity. Although methyllycaconitine is itself too toxic for clinical therapeutic use as a drug in humans, several semi-synthetic efforts have been undertaken to increase the understanding of the structure–activity relationship. The synthesis of small analogues has also been undertaken in the search for less toxic but equally potent drugs.[12,361,362]

It was reported that lappaconitine and puberanine can exhibit mild inhibition against the tyrosinase.[113] Further investigation carried out by Sultankhodzhaev *et al.* on the tyrosinase inhibition of 15 lycoctonine-type diterpenoid alkaloids and six napelline-type alkaloids led to the discovery that lappaconitine HBr is the most potent member of the series ($IC_{50} = 13.30\ \mu M$), with a comparable inhibitory activity to that of kojic acid ($IC_{50} = 16.67\ \mu M$).[363]

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