THE ALKALOIDS

Edited by
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VOLUME 69

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PREFACE

In this volume of *The Alkaloids: Chemistry and Biology* the recent progress on several quite different alkaloid groups is presented in two excellent chapters.

The first, by Lounasmaa and Hanhinen, updates an area of indole alkaloids which has been neglected in the series for over 30 years, namely, the ajmaline group of alkaloids, where numerous advances in chemistry and biosynthesis have been made recently. The second chapter by Michael reports on the progress made in a vast area of alkaloid chemistry, those alkaloids with either an indolizidine or a quinolizidine nucleus derived from plant, marine animal, and fungal sources.

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CHAPTER 1

THE AJMALINE GROUP OF INDOLE ALKALOIDS

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I. Introduction

The ajmaline alkaloids have been reviewed only twice in "*The Alkaloids*" series (*1,2*). Both articles appeared in the sixties and are substantially out-of-date. The need for a new review in the series is apparent. A review article in the series "*Progress in the Chemistry of Natural Products*" (*3*) was published in 1983, but even that will soon be twenty years old. Yearly summaries have been compiled by Saxton (*4*) and short reviews have occasionally appeared in connection with other topics (*5-9*). The present chapter covers the literature to October, 1999.

Because of their close biogenetic relationship, earlier reviews (*1-3*) treated the ajmaline alkaloids together with the sarpagine alkaloids. The number of known structures in the two series has grown markedly, however, and to do this now would require a long and time consuming editorial process, which would diminish the relevance of the information when published. For this reason, we prefer to treat the

THE ALKALOIDS, VOL. 55
0099-9598/01 $35.00

series separately, as was done in our recent review of the sarpagine alkaloids (*10*). To facilitate a comparative use of the reviews, we have adopted a similar approach to the ajmaline alkaloids as we used for the sarpagine series.

The number of known ajmaline structures (*sensu stricto*) has grown markedly in recent years to a present count of 77 (compounds **1** - **77**). Some of these might be artefacts and a few structures have not been convincingly determined (*vide infra*). In addition, seven bisindole alkaloids (compounds **78** - **84**) containing at least one monomeric ajmalan unit have been isolated, increasing the total number to 84 (77 + 7).

Ajmaline alkaloids contain the polycyclic ajmalan ring system [(except the rearranged perakan ring system (*vide infra*)]. The "biogenetic numbering" of Le Men and Taylor (*11*) is used throughout this article (Figure 1). It is noteworthy that the priority sequence for the C-17 substituents in the Cahn-Ingold-Prelog system is different in the absence and presence of the $COOCH_3$ substituent at C-16. Thus, for example, the 17*R* configuration in the absence of the $COOCH_3$ substituent and the 17*S* configuration in the presence of the $COOCH_3$ substituent correspond to the "same" three-dimensional arrangement of the substituents at C-17 (Figure 2).

The 3-hydroxyajmaline derivatives [*e.g.* herbamine (**85**) and herbadine (**86**) (*4*)], which exist, in part, in the 2-acylindolenine form, and thus behave in a different manner, are not included in this review (Scheme 1). The various alkaloids of the seco ajmalinoid type [*e.g.* rhazicine (**87**), isorhazicine (**88**) and sandwicoline (**89**) (*4*)] are also excluded from the present review (Figure 3). In addition, some doubtful compounds of unknown structures (*e.g.* sandwicensine and ajmalinine), which have persisted in earlier lists of ajmaline alkaloids (*1*), have been rejected.

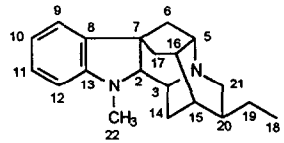


FIG. 1. Ajmalan ring system numbered according to Le Men and Taylor (*11*).

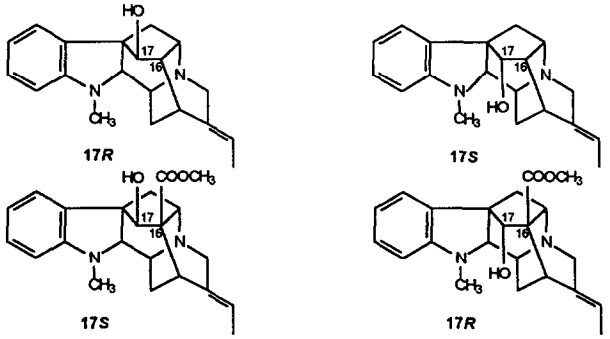
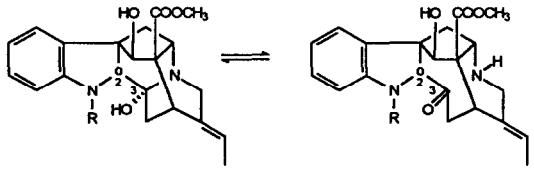


FIG. 2. Application of the Cahn-Ingold-Prelog priority sequence system to mark the C-17 stereochemistry in the absence and presence of the $COOCH_3$ substituent.



SCHEME 1. Equilibrium between the 3-hydroxyajmaline derivatives herbamine (85) and herbadine (86) and their 2-acylindolenine forms.

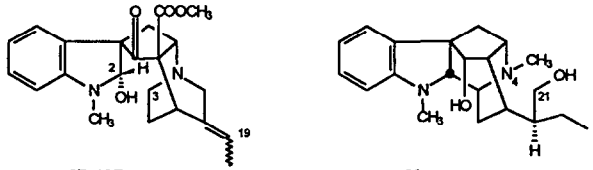


FIG. 3. Structures of rhazicine (87), isorhazicine (88) and sandwicoline (89), representing alkaloids of the 2,3-seco and 4,21-seco ajmalinoid types.

II. Occurrence

All of the ajmaline alkaloids found thus far occur in the plant family Apocynaceae. To date, they have been recognized in the following genera: *Alstonia*, *Aspidosperma*, *Cabucala*, *Melodinus*, *Rauvolfia**, *Tonduzia* (*Alstonia*), and *Vinca*. Of these, by far the most important genus is *Rauvolfia*. A detailed account of the distribution of ajmaline alkaloids among different plant species is presented in order of increasing molecular weight in Table I. The alkaloid structures, with their melting points and $[\alpha]_D$ values where given, are presented in Table II. The CAS Registry numbers of individual compounds are indicated in both tables. The superscripts beside several of the compounds indicate plausible artefacts or structures which, in the writers' opinion, are questionable or in need of supplementary confirmation.

* Of the two orthographies used in the literature, *Rauvolfia versus Rauwolfia*, the former is preferred in the present article.

TABLE I

AJMALINE ALKALOIDS OF PLANT ORIGIN

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
292.4	$C_{19}H_{20}N_2O$	36063-54-4	(+)-**1**	(+)-Rauflorine	*Rauvolfia confertiflora*	*12*
294.4	$C_{19}H_{22}N_2O$	68160-76-9	**2**	Nortetraphyllicine	*Rauvolfia caffra*	*13*
					Rauvolfia cumminsii	*14*
					Rauvolfia macrophylla	*15*
					Rauvolfia mombasiana	*16*
					Rauvolfia nitida	*17*
					Rauvolfia oreogiton	*18*
					Rauvolfia semperflorens var. *semperflorens*	*19*
					Rauvolfia volkensii	*20,21*
					Rauvolfia vomitoria	*22*
308.4	$C_{20}H_{24}N_2O$	509-38-6	(+)-**3**	(+)-Tetraphyllicine [Serpinine] [Semperflorine]	*Rauvolfia caffra*	*23*
					Rauvolfia cumminsii	*24*
					Rauvolfia degeneri	*25*
					Rauvolfia mauiensis	*25*
					Rauvolfia mombasiana	*16*
					Rauvolfia nitida	*17*
					Rauvolfia obscura	*26*
					Rauvolfia oreogiton	*27*
					Rauvolfia sandwicensis	*25*
					Rauvolfia sellowii	*28*
					Rauvolfia serpentina	*29*
					Rauvolfia suaveolens	*30*
					Rauvolfia tetraphylla	*31*

						Rauvolfia verticillata var. *rubrocarpa*	*32*
						Rauvolfia volkensii	*20*
						Rauvolfia vomitoria	*33*
						Rauvolfia yunnanensis	*34*
	308.4	$C_{20}H_{24}N_2O$	6883-73-4	(+)-**4**	(+)-Mauiensine	*Rauvolfia mauiensis*	*25,35*
						Rauvolfia media	*36*
						Rauvolfia semperflorens var. *semperflorens*	*19*
	308.4	$C_{19}H_{20}N_2O_2$	68160-75-8	**5**	Normitoridine	*Rauvolfia cumminsii*	*14*
	310.4	$C_{19}H_{22}N_2O_2$	70509-79-4	**6**	10-Hydroxynortetraphyllicine	*Rauvolfia vomitoria*	*22a*
	310.4	$C_{19}H_{22}N_2O_2$	93552-59-1	(+)-**7**	(+)-Norajmalidine	*Rauvolfia caffra*	*13*
	312.4	$C_{19}H_{24}N_2O_2$	23944-24-3	(+)-**8**	(+)-Norajmaline	*Rauvolfia caffra*	*13*
						Rauvolfia macrophylla	*37*
						Rauvolfia nitida	*17*
						Rauvolfia obscura	*38*
						Rauvolfia suaveolens	*30*
						Rauvolfia vomitoria	*22b*
	322.4	$C_{20}H_{22}N_2O_2$	67627-71-8	**9**	Endolobine	*Rauvolfia cumminsii*	*14*
						Rauvolfia mombasiana	*39*
						Rauvolfia vomitoria	*22b*
	322.4	$C_{20}H_{22}N_2O_2$	65061-33-8	(±)-**10**	(±)-Norpurpeline [N_a-Demethylpurpeline] [1-Demethyl-19,20-didehydro-12-methoxy-ajmalan-17-one]	*Rauvolfia cumminsii*	*14,40*
						Rauvolfia mombasiana	*39*
						Rauvolfia vomitoria	*22*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
322.4	$C_{20}H_{22}N_2O_2$	3911-19-1	(+)-**11**	(+)-Mitoridine	*Rauvolfia cumminsii* *Rauvolfia vomitoria*	*40* *22b,33b,41*
322.4	$C_{20}H_{22}N_2O_2$	70509-81-8	**12**	17-*O*-Deacetyl-12-methoxy-vinorine [17-*O*-Deacetyl-21-deoxy-12-methoxyvomilenine]	*Rauvolfia vomitoria*	*22a*
324.4	$C_{20}H_{24}N_2O_2$	104748-99-4	(+)-**13**	(+)-12-Hydroxymauiensine	*Rauvolfia media*	*36*
324.4	$C_{20}H_{24}N_2O_2$	30171-06-3	(+)-**14**	(+)-Norseredamine [N_a-Demethylseredamine]	*Rauvolfia cumminsii* *Rauvolfia sumatrana* *Rauvolfia vomitoria*	*14* *42* *22*
324.4	$C_{20}H_{24}N_2O_2$	639-30-5	(-)-**15**	(-)-Ajmalidine	*Rauvolfia mauiensis* *Rauvolfia nitida* *Rauvolfia salicifolia* *Rauvolfia sellowii* *Rauvolfia tetraphylla* *Rauvolfia vomitoria*	*35* *17* *43* *28* *31b* *33a*
324.4	$C_{20}H_{24}N_2O_2$	65136-98-3	**16**	Dihydronorpurpeline [N_a-Demethyldihydropurpeline]	*Rauvolfia cumminsii*	*14,40,44*
326.4	$C_{20}H_{26}N_2O_2$	4360-12-7	(+)-**17**	(+)-Ajmaline [Raugalline] [Rauwolfine]	*Aspidosperma spegazzinii* *Melodinus balansae* var. *paucivenosus* *Rauvolfia balansae*	*45* *46* *19*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
					Rauvolfia suaveolens	*30*
					Rauvolfia tetraphylla	*66*
					Rauvolfia verticillata	*67*
					Rauvolfia verticillata var. hainanensis	*68*
					Rauvolfia verticillata var. rubriocarpa	*32*
					Rauvolfia viridis	*69*
					Rauvolfia volkensii	*20*
					Rauvolfia vomitoria	*70*
					Rauvolfia yunnanensis	*34,71*
					Tonduzia longifolia	*72*
326.4	$C_{20}H_{26}N_2O_2$	509-37-5	(+)-**18**	(+)-Sandwicine	*Rauvolfia cubana*	*73*
					Rauvolfia mauiensis	*25*
					Rauvolfia sandwicensis	*25*
					Rauvolfia semperflorens var. *semperflorens*	*19*
					Rauvolfia semperflorens var. *viridis*	*19,74*
					Rauvolfia vomitoria	*33b,75*
326.4	$C_{20}H_{26}N_2O_2$	6989-79-3	(+)-**19**	(+)-Isoajmaline	*Rauvolfia confertiflora*	*54*
					Rauvolfia semperflorens var. *viridis*	*19*
					Rauvolfia serpentina	*65b*
					Rauvolfia vomitoria	*76*

326.4	$C_{20}H_{26}N_2O_2$	6835-90-1	(+)-**20**	(+)-Isosandwicine	*Rauvolfia semperflorens* var. *viridis*	*19*
					Rauvolfia vomitoria	*33b,75*
334.4	$C_{21}H_{22}N_2O_2$	34020-07-0	(-)-**21**	(-)-Vinorine [21-Deoxyvomilenine] [2-Deshydronortetraphyllicine]	*Alstonia yunnanensis*	*77*
					Rauvolfia balansae spp. *balansae*	*19,78*
					Rauvolfia balansae spp. *schumanniana* var. *basicola*	*19,78*
					Rauvolfia caffra	*79*
					Rauvolfia perakensis	*80*
					Rauvolfia semperflorens var. *viridis*	*19,74*
					Rauvolfia sevenetii	*78*
					Rauvolfia spathulata	*78*
					Vinca minor	*81*
336.4	$C_{21}H_{24}N_2O_2$	81525-52-2	(+)-**22**	(+)-17-O-Acetylnortetra-phyllicine	*Rauvolfia nitida*	*17*
336.4	$C_{21}H_{24}N_2O_2$	70522-05-3	(+)-**23**	(+)-Rauflexine	*Rauvolfia reflexa*	*82*
336.4	$C_{21}H_{24}N_2O_2$	2246-33-5	(+)-**24**	(+)-Purpeline	*Rauvolfia cumminsii*	*44*
					Rauvolfia mombasiana	*39*
					Rauvolfia vomitoria	*22,41*
338.5	$C_{21}H_{26}N_2O_2$	3911-20-4	(+)-**25**	(+)-Seredamine	*Rauvolfia cumminsii*	*24,44*
					Rauvolfia vomitoria	*22b,41*
338.5	$C_{21}H_{26}N_2O_2$	3382-93-2	**26**	Vincamajoreine	*Rauvolfia vomitoria*	*22b*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
				[10-Methoxytetraphyllicine]	*Vinca elegantissima* var. *Vinca major*	*83*
					Vinca major	*83,84*
338.5	$C_{21}H_{26}N_2O_2$	6109-18-7	(+)-**27**	(+)-Reflexine	*Rauvolfia reflexa*	*82*
340.5	$C_{21}H_{28}N_2O_2$	99612-65-4	(+)-**28**	(+)-Sandwicolidine	*Rauvolfia serpentina*	*85*
342.4	$C_{20}H_{26}N_2O_3$	73012-74-5	(+)-**29**	(+)-Ajmalinol	*Rauvolfia vomitoria*	*86*
352.4	$C_{21}H_{24}N_2O_3$	135649-95-5	(-)-**30**	(-)-Leepacine	*Rhazya stricta*	*87*
350.4	$C_{21}H_{22}N_2O_3$	4382-56-3	(+)-**31**	(+)-Perakine [Raucaffrine]	*Alstonia yunnanensis*	*77*
					Rauvolfia balansae ssp. *balansae*	*19*
					Rauvolfia biauriculata	*48*
					Rauvolfia caffra	*49b,88*
					Rauvolfia perakensis	*62*
					Rauvolfia sellowii	*89*
					Rauvolfia sprucei	*90*
					Rauvolfia sumatrana	*91*
					Rauvolfia volkensii	*92*
					Rauvolfia vomitoria	*93*
					Voacanga africana	*94*
350.4	$C_{21}H_{22}N_2O_3$	688-50-8	(-)-**32**	(-)-Vomilenine	*Rauvolfia balansae* spp. *balansae*	*78*

					Rauvolfia balansae spp. *schumanniana* var. *basicola*	*78*
					Rauvolfia biauriculata	*48*
					Rauvolfia caffra	*79*
					Rauvolfia sellowii	*89*
					Rauvolfia sevenetii	*78*
					Rauvolfia spathulata	*78*
					Rauvolfia vomitoria	*95*
	350.4	$C_{21}H_{22}N_2O_3$	107585-43-3	**33**	Raucaffriline [*Z*-Vomilenine ?]	*Rauvolfia caffra*	*88a*
	350.5	$C_{22}H_{26}N_2O_2$	25926-60-7	**34**	17-O-Acetyltetraphyllicine	*Rauvolfia volkensii*	*92*
	352.4	$C_{21}H_{24}N_2O_3$	36285-11-7	(+)-**35**	(+)-Raucaffrinoline	*Alstonia venenata*	*96*
						Rauvolfia balansae spp. *balansae*	*78*
						Rauvolfia balansae spp. *schumanniana* var. *basicola*	*78*
						Rauvolfia caffra	*49b,97*
						Rauvolfia nitida	*17*
						Rauvolfia sellowii	*89*
						Rauvolfia semperflorens var. *viridis*	*74*
						Rauvolfia sevenetii	*78*
						Rauvolfia spathulata	*78*
						Rauvolfia volkensii	*92*
						Rauvolfia vomitoria	*98*

(*continues*)

TABLE I (*Continued*)

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
352.4	$C_{21}H_{24}N_2O_3$	4835-69-2	(+)-**36**	(+)-Quebrachidine	*Alstonia constricta*	*99*
					Alstonia macrophylla	*100*
					Alstonia muelleriana	*101*
					Alstonia odontophora	*102*
					Alstonia spectabilis	*103*
					Alstonia sphaerocapitata	*104*
					Aspidosperma quebracho-blanco	*105*
					Cabucala erythrocarpa var. *erythrocarpa*	*106*
					Cabucala striolata	*107*
					Cabucala torulosa	*108*
					Rauvolfia discolor	*109*
					Rauvolfia viridis	*69b*
					Rauvolfia vomitoria	*110*
					Tabernaemontana undulata	*110*
					Vinca libanotica	*111*
352.4	$C_{21}H_{24}N_2O_3$	21641-60-1	(+)-**37**	(+)-Vincarine	*Vinca erecta*	*112*
					Vinca herbacea	*113*
					Vinca major	*114*
352.4	$C_{21}H_{24}N_2O_3$	110044-96-7	**38**	19,20-Dihydrovomilenine [1-Demethyl-2-dehydro-*17-O*-acetylajmaline]	*Rauvolfia balansae* ssp. *balansae*	*78*
					Rauvolfia balansae ssp. *schumanniana* var. *basicola*	*78*

					Rauvolfia sevenetii	*78*
					Rauvolfia spathulata	*78*
354.5	$C_{21}H_{26}N_2O_3$	639-28-1	(+)-**39**	(+)-Vomalidine	*Rauvolfia cumminsii*	*24*
					Rauvolfia mombasiana	*16*
					Rauvolfia obscura	*115*
					Rauvolfia vomitoria	*33b,116*
356.5	$C_{21}H_{28}N_2O_3$	56897-55-3	**40**	12-Methoxyajmaline	*Rauvolfia obscura*	*38,115*
364.4	$C_{22}H_{24}N_2O_3$	163461-46-9	(+)-**41**	(+)-10-Methoxyvinorine	*Vinca erecta*	*117*
					Vinca major	*118*
366.5	$C_{22}H_{26}N_2O_3$	2506-26-5	(-)-**42**	(-)-Vincamajine	*Alstonia angustifolia*	*119*
					Alstonia constricta	*120*
					Alstonia coriacea	*121*
					Alstonia deplanchei	*122*
					Alstonia legouixiae	*123*
					Alstonia macrophylla	*124*
					Alstonia odontophora	*102*
					Alstonia quaternata	*125*
					Alstonia spectabilis	*103*
					Cabucala torulosa	*108*
					Rauvolfia mannii	*126*
					Tonduzia longifolia	*127*
					Vinca difformis	*128*
					Vinca herbacea	*129*
					Vinca libanotica	*111*
					Vinca major	*83,84c,84d,130,131*
					Vinca media	*131*

(*continues*)

TABLE I *(Continued)*

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
366.5	$C_{22}H_{26}N_2O_3$	1784-05-6	**43**	17-Epivincamajine [Vincamajinine]	*Vinca major*	*132*
368.5	$C_{22}H_{28}N_2O_3$	19918-92-4	**44**	17-*O*-Acetylajmaline	*Rauvolfia caffra* *Rauvolfia volkensii* *Rauvolfia vomitoria*	*49b* *92* *33a,133*
380.4	$C_{22}H_{24}N_2O_4$	163461-45-8	(-)-**45**	(-)-10-Methoxyperakine	*Vinca major*	*118*
380.4	$C_{22}H_{24}N_2O_4$	64986-27-2	**46**	Majorinine [10-Methoxyvomilenine]	*Vinca major*	*84c,130b,134*
380.5	$C_{23}H_{28}N_2O_3$	6519-30-8	(-)-**47**	(-)-Majoridine [Majdinine]	*Vinca erecta* *Vinca major* *Vinca pubescens*	*135* *84b,84c,136* *137*
382.5	$C_{22}H_{26}N_2O_4$	108195-74-0	**48**	19-Hydroxy-19,20-dihydro-vincamajine[a]	*Alstonia macrophylla*	*124c*
394.5	$C_{23}H_{26}N_2O_4$	98301-75-8	**49**	21-Acetyl-19,20-dihydro-vomilenine[b]	*Rauvolfia caffra*	*79*
394.5	$C_{23}H_{26}N_2O_4$	not given	(±)-**50**	(±)-Norvincamedine	*Alstonia deplanchei*	*122*
396.5	$C_{23}H_{28}N_2O_4$	57800-02-9	(±)-**51**	(±)-10-Methoxyvincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera* *Alstonia sphaerocapitata*	*138* *104*

396.5	$C_{23}H_{28}N_2O_4$	132242-26-3	(-)-**52**	(-)-11-Methoxyvincamajine	*Alstonia pittieri* = *Tonduzia pittieri*	*139*
396.5	$C_{23}H_{28}N_2O_4$	132268-03-2	(-)-**53**	(-)-11-Methoxy-17-epivincamajine	*Alstonia pittieri* = *Tonduzia pittieri*	*139*
408.5	$C_{24}H_{28}N_2O_4$	912-27-6	(-)-**54**	(-)-Vincamedine [Vincamajine acetate]	*Alstonia constricta* *Alstonia deplanchei* *Alstonia sphaerocapitata* *Alstonia undulata* *Vinca difformis* *Vinca major*	*99* *122* *104* *140* *141* *142*
410.5	$C_{24}H_{30}N_2O_4$	107603-58-7	**55**	Ajmalinimine	*Rauvolfia serpentina*	*143*
410.5	$C_{24}H_{30}N_2O_4$	19775-56-5	**56**	17,21-*O*,*O*-Diacetylajmaline	*Rauvolfia caffra* *Rauvolfia cumminsii*	*49b* *24*
424.5	$C_{24}H_{28}N_2O_5$	164176-14-1	(-)-**57**	(-)-Vincawajine	*Vinca major*	*118*
438.5	$C_{25}H_{30}N_2O_5$	94444-30-1	(-)-**58**	(-)-10-Methoxyvincamedine	*Alstonia sphaerocapitata*	*104*
438.5	$C_{25}H_{30}N_2O_5$	142750-28-5	(-)-**59**	(-)-11-Methoxyvincamedine	*Alstonia pittieri* = *Tonduzia pittieri*	*144*
454.5	$C_{25}H_{30}N_2O_6$	94444-31-2	(-)-**60**	(-)-10-Methoxyvincamedine *N*-oxide	*Alstonia sphaerocapitata*	*104*
470.6	$C_{29}H_{30}N_2O_4$	24190-04-3	(-)-**61**	(-)-17-*O*-Benzoylvincamajine	*Alstonia macrophylla* *Alstonia vieillardii*	*145* *122*

(*continues*)

TABLE I *(Continued)*

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
488.6	$C_{29}H_{32}N_2O_5$	64675-21-4	**62**	Norrauvomitine	*Rauvolfia vomitoria*	*22b,33b*
502.6	$C_{30}H_{34}N_2O_5$	466-57-9	(-)-**63**	(-)-Rauvomitine	*Rauvolfia obscura* *Rauvolfia vomitoria*	*38* *146*
512.6	$C_{27}H_{32}N_2O_8$	31282-07-2	(+)-**64**	(+)-Raucaffricine	*Rauvolfia caffra*	*88a,88b*
520.6	$C_{30}H_{36}N_2O_6$	110941-51-0	(+)-**65**	(+)-Ajmalimine	*Rauvolfia serpentina*	*147*
520.6	$C_{30}H_{36}N_2O_6$	104998-32-5	**66**	17-*O*-(3',4',5'-Trimethoxybenzoyl)ajmaline [Willicourtine]	*Rauvolfia obscura* *Rauvolfia vomitoria*	*38* *148*
530.6	$C_{31}H_{34}N_2O_6$	154849-47-5	**67**	17-*O*-(3',4'-Dimethoxybenzoyl)vincamajine [Vincamajine 17-*O*-veratrate]	*Alstonia macrophylla* *Alstonia vieillardii*	*124b* *122*
532.6	$C_{31}H_{36}N_2O_6$	68160-77-0	**68**	17-*O*-(3',4',5'-Trimethoxybenzoyl)seredamine	*Rauvolfia cumminsii*	*14*
546.6	$C_{31}H_{34}N_2O_7$	144379-35-1	**69**	4'-Hydroxy-3',5'-dimethoxybenzoylvincamajine	*Alstonia angustifolia*	*149*
546.6	$C_{31}H_{34}N_2O_7$	31148-63-7	(-)-**70**	(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)quebrachidine	*Alstonia constricta*	*99,120*

546.6	$C_{31}H_{34}N_2O_7$	not given[c]	(-)-**71**	(-)-1-*N*-(3',4',5'-Trimethoxybenzoyl)quebrachidine [Norvincamajine *N*(1)-tri-*O*-methylgallate][d]	*Alstonia macrophylla*	*124b*
560.7	$C_{32}H_{36}N_2O_7$	71385-80-3	(-)-**72**	(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera* *Alstonia vieillardii*	*138a* *122*
576.7	$C_{32}H_{36}N_2O_8$	57800-05-2	(-)-**73**	(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera*	*138*
586.7	$C_{34}H_{38}N_2O_7$	57800-03-0	(-)-**74**	(-)-17-*O*-(3',4',5'-Trimethoxycinnamoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera* *Alstonia constricta*	*138* *120*
590.7	$C_{33}H_{38}N_2O_8$	71385-81-4	**75**	10-Methoxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera*	*138*
602.7	$C_{34}H_{38}N_2O_8$	57808-41-0	(-)-**76**	(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera*	*138*
616.7	$C_{35}H_{40}N_2O_8$	57800-04-1	**77**	10-Methoxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine	*Alstonia boulindaensis* = *Alstonia lanceolifera*	*138*
672.9	$C_{42}H_{48}N_4O_4$	36474-13-2	(-)-**78**	(-)-Alstonisidine	*Alstonia muelleriana*	*150*
674.8	$C_{41}H_{46}N_4O_5$	80765-85-1	(-)-**79**	(-)-Flexicorine	*Rauvolfia reflexa* *Rauvolfia sumatrana*	*151* *91*
690.9	$C_{42}H_{50}N_4O_5$	199800-14-1	(+)-**80**	(+)-Alstomacroline	*Alstonia macrophylla*	*152*

(*continues*)

TABLE I *(Continued)*

MW	Formula	CAS Registry Number		Compound	Plant source(s)	Refs.
763.0	$C_{45}H_{54}N_4O_7$	142795-96-8	**81**	11-Methoxy-10-(11'-vincorinyl)-vincamajine {11-[10-(11-Methoxyvincamajinyl)]-vincorine}	*Alstonia pittieri* = *Tonduzia pittieri*	*144*
763.0	$C_{45}H_{54}N_4O_7$	142750-29-6	(-)-**82**	(-)-11-Methoxy-10-(11'-vincorinyl)-17-epivincamajine {(-)-11-[10-(11-Methoxy-17-epi-vincamajinyl)]vincorine}	*Alstonia pittieri* = *Tonduzia pittieri*	*144*
763.0	$C_{45}H_{54}N_4O_7$	132242-27-4	(±)-**83**	(±)-11-Methoxy-10-[11'-(10'-methoxy-cathafolinyl)vincamajine {(±)-10-Methoxy-11-[10-(11-methoxy-vincamajinyl)]cathafoline}	*Alstonia pittieri* = *Tonduzia pittieri*	*139*
805.0	$C_{47}H_{56}N_4O_8$	142750-30-9	(-)-**84**	(-)-11-Methoxy-10-(11'-vincorinyl)-vincamedine {(-)-11-[10-(11-Methoxyvincamedinyl)]-vincorine}	*Alstonia pittieri* = *Tonduzia pittieri*	*144*

[a] In reference (*124c*) compound **48** is erroneously called 19-hydroxyvincamajine instead of 19-hydroxy-19,20-dihydrovincamajine.

[b] In reference (*79*) compound **49** is erronneously called 17-acetyl-19,20-dihydrovomilenine instead of 21-acetyl-19,20-dihydrovomilenine.

[c] There is some confusion in the CAS registration concerning compounds **70** and **71**. For the registration number 31148-63-7 there are three references marked, two (*99* and *120*) for compound **70** and one (*124b*) for compound **71**. Apparently, these two compounds are erroneously presented as one and the same compound.

[d] In reference (*124b*) compound **71** is erroneously referred to as vincamajine *N*(1)-tri-*O*-methylgallate instead of norvincamajine *N*(1)-tri-*O*-methylgallate.

III. Syntheses

A. MASAMUNE SYNTHESIS OF AJMALINE (17)

Masamune *et al.* (*158*) were the first to present a total synthesis of ajmaline (**17**). Condensation between *N*-methyl-3-indolacetyl chloride (**90**) and ethyl hydrogen Δ^3-cyclopentenylmalonate (**91**) (in the form of Mg chelate) led to ketoester **92**. Reaction of **92**, first with methoxyamine ($MeONH_2$) and then with $LiAlH_4$, afforded epimeric α,γ-amino alcohols **93**, which were converted into the dibenzoyl derivative **94**. Treatment of **94** with OsO_4 yielded diol **95**, which was cleaved with $NaIO_4$. Spontaneous ring formation followed, leading to the tricyclic aldehyde **96**. Warming **96** with acetic acid at 50°C for 1 h led to the tetracyclic aldehyde **97**. Conversion of **97** into the cyano compound **98** was achieved by treatment first with hydroxylamine (NH_2OH) and then with benzoyl chloride (PhCOCl). Ethylation with EtI, using triphenylmethylsodium in THF as a base, led to monoethyl derivatives **99**. Removal of the benzoyl group from the ester with sodium methoxide afforded the hydroxy compound **100** which was oxidized with dimethyl sulfoxide (DMSO) and acetic anhydride to aldehyde **101**. Acid-catalyzed cyclization of aldehyde **101** (equilibrium between the C-16 isomers) yielded the pentacyclic compound **102** which was hydrogenated to **103**. Reduction of **103** with lithium triethoxyaluminium hydride led to the corresponding benzyl derivative **104**, which, by hydrogenolysis, was converted to compound **105**. Compound **105** was treated with $LiAlH_4$ to afford the non-isolated imine **106** (apparently in the form of a chelate). Addition of water led first to aldehyde **17'** (*chano* form), which mainly exists in the cyclized form **17** (Scheme 2).

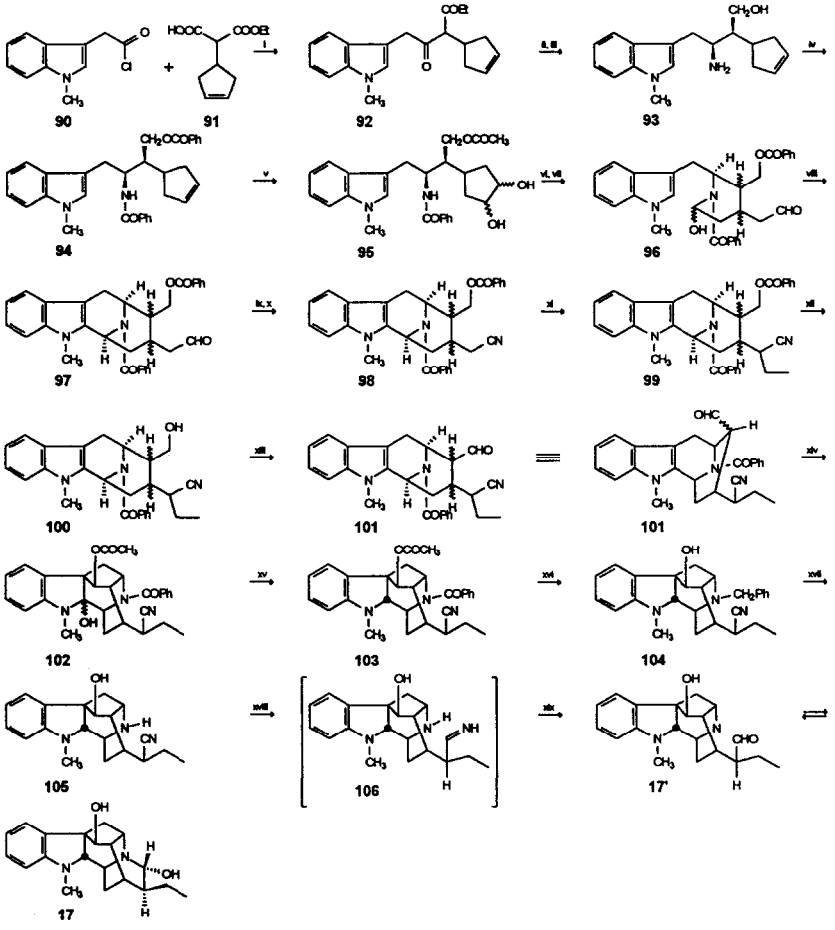
B. MASHIMO AND SATO SYNTHESIS OF ISOAJMALINE (19)

The Mashimo and Sato synthesis of isoajmaline (*159*) starts from the ketone **107**, which is a general synthetic intermediate in the ajmaline (and sarpagine) series. Ketone **107** was condensed with *n*-propanal to yield the propylidene derivative **108**. Hydrocyanation of **108** led to compound **109**, which was converted with dimethyloxosulfonium methylide ($Me_2S^+OCH_2^-$) to the corresponding oxirane **110**. Reductive oxirane cleavage by means of AlH_3 afforded the alcohol **111**. Debenzylation, dibenzoylation, and selective *O*-debenzoylation yielded, *via* compound **112**, alcohol **113**, which proved to be isomeric with the Masamune intermediate **100**. Oxidation of **113** with DMSO-Ac_2O gave aldehyde **114** which was equilibrated (**114** ⇌ **115**) and cyclized to **116**. Compound **116** was hydrogenated to **117**, which was first treated with the Meerwein reagent ($Et_3O^+BF_4^-$) and then reduced with $NaBH_4$ to afford compound **118**. Reductive debenzylation of **118** led to compound **119**, which Robinson (*154*) had earlier transformed to isoajmaline (**19**) *via* **120** (Scheme 3).

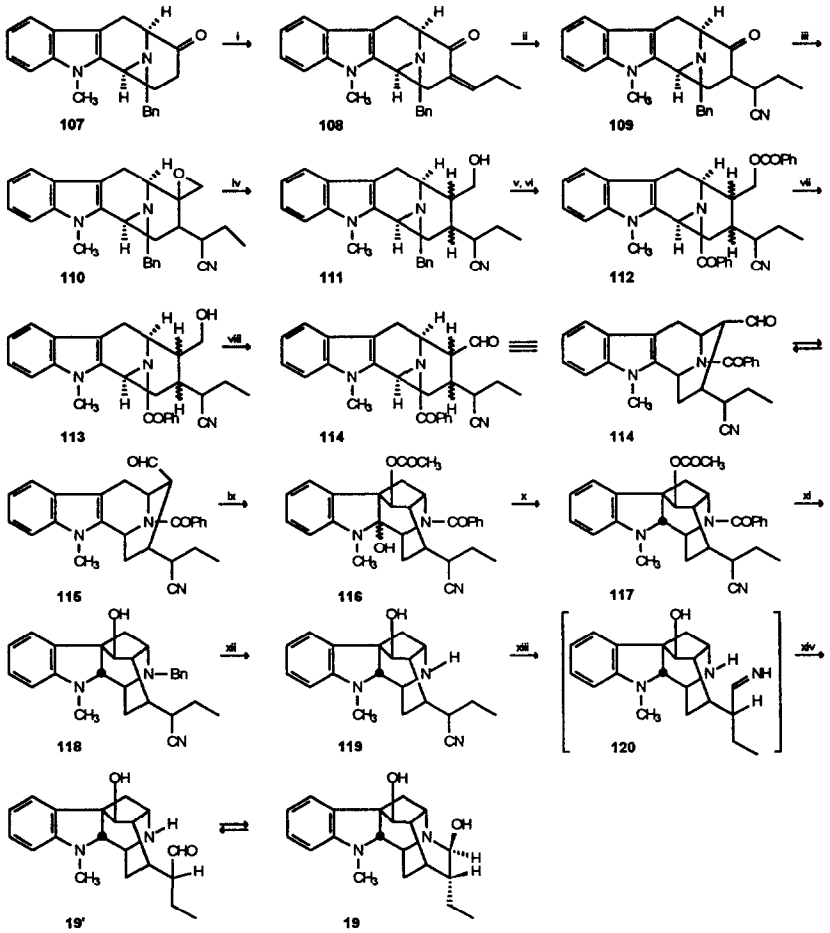
C. MASHIMO AND SATO FORMAL SYNTHESIS OF AJMALINE (17)

Masamune and Sato (*160*) also presented a formal total synthesis of ajmaline

(**17**). The general intermediate **107** (*vide supra*) was transformed into the corresponding pyrrolidine-enamine **121**, which, when reacted with chloroacetonitrile, afforded the nitrile **122**. Epoxide formation led to compound **123**, which was reductively cleaved to the alcohol **124**. Hydrogenolysis of **124** yielded the debenzylated compound **125** which was dibenzoylated to the Masamune intermediate **98** (Scheme 4).



SCHEME 2. Masamune synthesis of ajmaline (**17**). Reagents: i. Δ; ii. $MeONH_2$; iii. $LiAlH_4$; iv. PhCOCl; v. OsO_4; vi. $NaIO_4$; vii. spontaneously; viii. AcOH, 50°C; ix. NH_2OH; x. PhCOCl; xi. $Na^+Ph_3C^-$, THF, EtI; xii. MeONa; xiii. Ac_2O, DMSO; xiv. HCl, AcOH, Ac_2O; xv. H_2/PtO_2; xvi. $LiAl(OEt)_3H$; xvii. H_2/PtO_2; xviii. $LiAlH_4$; xix. H_2O.

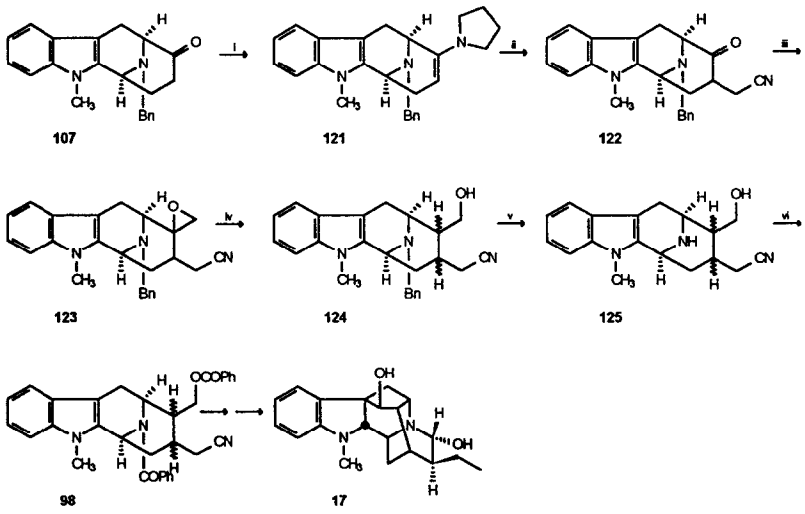


SCHEME 3. Mashimo and Sato synthesis of isoajmaline (19). Reagents: i. EtCHO, triton B; ii. KCN; iii. $Me_2S^+OCH_2^-$; iv. AlH_3; v. H_2/Pd/C; vi. PhCOCl; vii. MeOH (1% NaOH); viii. Ac_2O, DMSO; ix. Ac_2O, AcOH, HCl; x. H_2/PtO_2; xi. $Et_3O^+BF_4^-$, $NaBH_4$; xii. H_2/Pd/C; xiii. $LiAlH_4$; xiv. H_2O.

D. COOK ENANTIOSPECIFIC TOTAL SYNTHESIS OF (+)-AJMALINE (17)

The first enantiospecific total synthesis of (+)-ajmaline [(+)-17] was developed by Cook *et al.* (*161*). D-(+)-Tryptophan methyl ester (**126**) was converted enantiospecifically, *via* intermediate **127**, to the optically active (-)-N_b-benzyltetracyclic ketone (-)-**107**, which was then transformed into the α,β-unsaturated aldehyde (-)-**128**. When compound (-)-**128** was stirred with 3-bromo-4-heptene in the Barbier-Grignard process conditions the 1,4-addition products **129a,b**

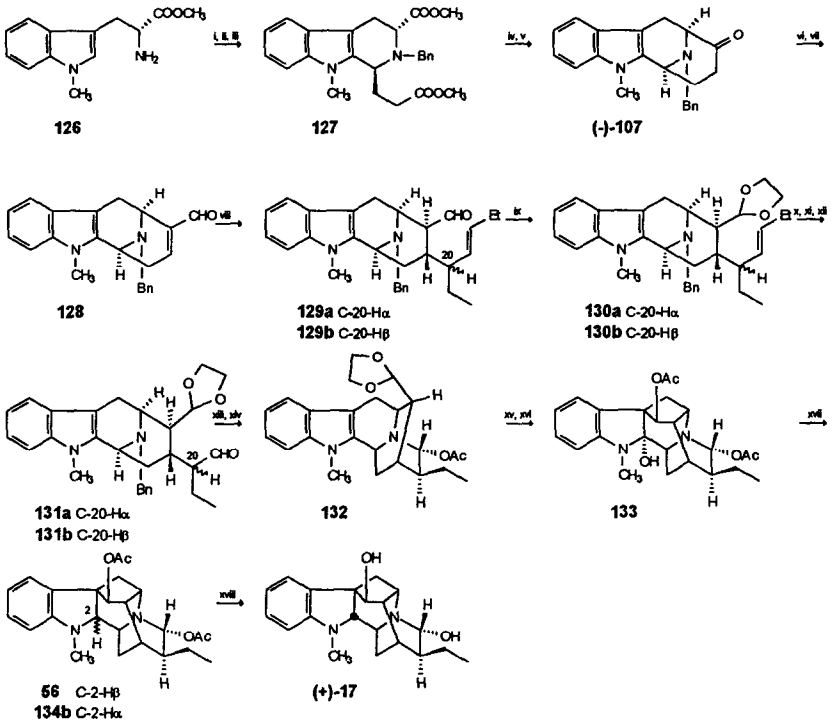
(together with 1,2-addition products) were obtained. The aldehyde function of **129a,b** was protected as the ethylene acetal **130a,b**. Oxidative cleavage (OsO_4, $NaIO_4$) of the olefinic bond in **130a,b** yielded the epimeric aldehydes **131a,b**. Epimerization of the undesired isomer **131b** permitted access to the desired isomer **131a** in >80% total yield. Catalytic debenzylation, followed by addition of acetic anhydride (Ac_2O), led to the sarpagine ring system **132**. When **132** was treated with acetic acid and conc. aqueous HCl for 3 h, and the mixture reacted with Ac_2O/HCl_g, the 2-hydroxyajmaline derivative **133** was obtained in 85% yield. The alcohol **133** was hydrogenated (H_2/PtO_2) in the presence of BF_3/Et_2O to afford diacetylajmaline (**56**) and its 2-epi-analog **134**. Hydrolysis of diacetylajmaline (**56**) (K_2CO_3/H_2O/MeOH) yielded (+)-ajmaline [(+)-**17**] (Scheme 5).



SCHEME 4. Mashimo and Sato formal synthesis of ajmaline (**17**). Reagents: i. pyrrolidine; ii. $ClCH_2CN$; iii. $Me_2S^+OCH_2^-$, DMSO; iv. AlH_3; v. $H_2/Pd/C$; vi. PhCOCl.

E. VAN TAMELEN PROPOSAL FOR A SYNTHETIC ROUTE TO AJMALINE (17)

Thirty years ago van Tamelen and Oliver (*162*) presented a synthetic route, which they claimed to lead, *via* the sarpagan ring system ("deoxyajmalal system"), to the six-ring indole alkaloid ajmaline (**17**). The "crucial steps" in their scheme were the regioselective formation of the $\Delta^{4(5)}$-iminium ion **136** (realized by decarbonylation; **135** → **136**), and subsequent spontaneous bond formation between C-5 and C-16 (spontaneous "biogenetic-type cyclization"; **136** → **137a** ⇌ **137b**) (Scheme 6).

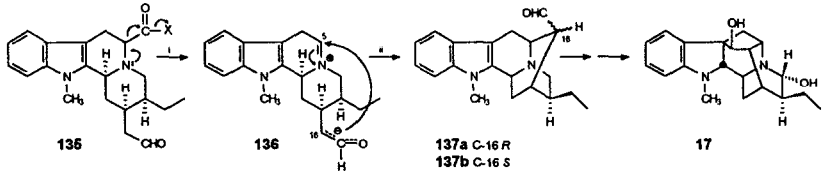


SCHEME 5. Cook enantiospecific total synthesis of (+)-ajmaline (**17**). Reagents: i. PhCHO, MeOH, rt, 2h; ii. $NaBH_4$, -30°C to -10°C, 3 h; iii. $(MeO)_2CHCH_2CH_2COOMe$, TFA, $CHCl_3$, Δ, 12 h; iv. NaH, MeOH, toluene, Δ, 4 h; v. HOAc, HCl, Δ, 12 h; vi. LDA, $ClCH_2SOPh$, KOH; vii. $LiClO_4$, dioxane, Δ; viii. $CH_3CH_2CH{=}CHCHBrCH_2CH_3$, Mg/THF, 0°C; ix. HO-$CH_2$-$CH_2$-OH, pTSA; x. OsO_4/THF/pyridine, $NaHSO_3$; xi. $NaIO_4$/MeOH, 0°C; xii. NaOMe/MeOH, flash chromatographic separation; xiii. H_2/Pd/C, DME, 2 d; xiv. Ac_2O/DMAP; xv. HOAc/HCl, 3 h; xvi. Ac_2O/HCl_g, 18 h; xvii. H_2/PtO_2, CH_2Cl_2, BF_3/Et_2O; xviii. K_2CO_3/H_2O (5%), MeOH.

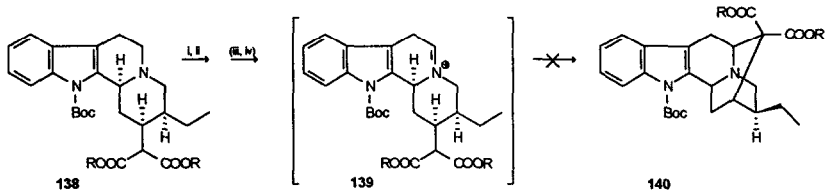
For a long time, the van Tamelen synthesis of ajmaline (**17**) *via* the "deoxyajmalal system" was authoritative in the field. However, in contrast to van Tamelen and Oliver, Lounasmaa and Hanhinen (*163*) were unable to detect a spontaneous "biogenetic-type cyclization", and were unable to cyclize compound **138** (or similar ones) to the "deoxyajmalal ring system" (**138** → **139** → **140**) (Scheme 7).

The failure to realize a spontaneous "biogenetic-type cyclization" casts doubt on the results of van Tamelen and Oliver (*162*). It also places into question the proposed biogenetic formation of the sarpagine/ajmaline skeleton (*vide infra*). In rationalizing their failure to repeat the van Tamelen cyclization, Lounasmaa and Hanhinen argued (*164*) that the shortest possible distance between the reactive sites

C-5 and C-16 in intermediate **139** is about 2.70 Å. This is far too large to permit bond formation between C-5 and C-16 (Fig. 4).



SCHEME 6. van Tamelen synthesis of ajmaline (**17**) *via* the "deoxyajmalal system". Reagents: i. DCC/TsOH; ii. spontaneously.



SCHEME 7. Attempts by Lounasmaa and Hanhinen to effect the spontaneous "biogenetic-type cyclization" of van Tamelen. Reagents: i. *m*-CPBA; ii. TFAA [or i. *m*-CPBA; ii. TFAA; iii. KCN; iv. $AgBF_4$].

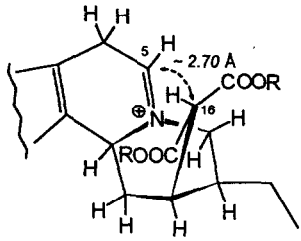
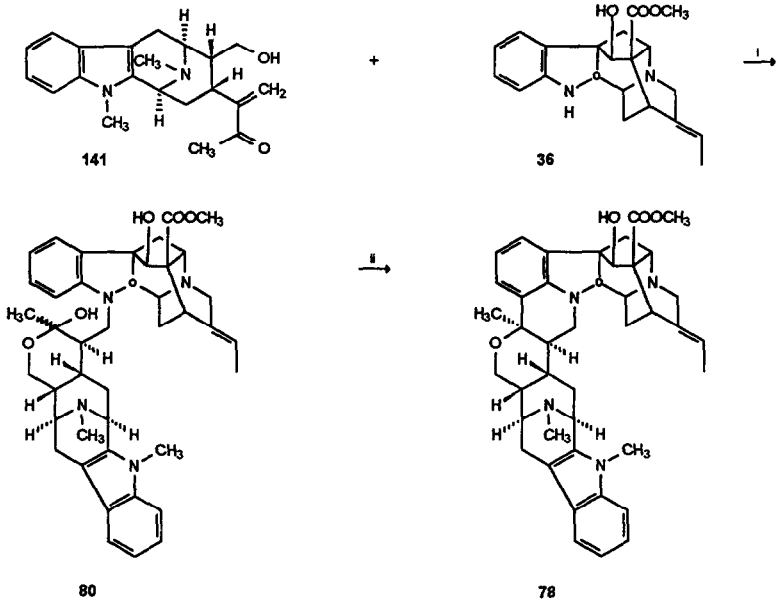


FIG. 4. The shortest possible distance between the reactive sites C-5 and C-16 in intermediate **139**.

F. BIOMIMETIC SEMISYNTHESIS OF ALSTOMACROLINE (**80**) AND ALSTONISIDINE (**78**)

Le Quesne and coll. (*156*, *157*, *165*) found that when macroline (**141**) and quebrachidine (**36**) were allowed to stand for 72 h in a dilute aqueous HCl solution at room temperature, they were converted into alstomacroline (**80**), which is claimed

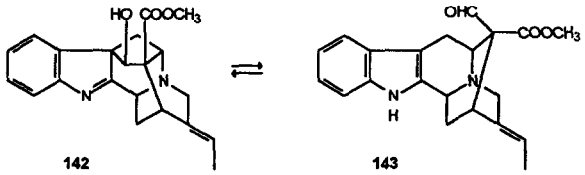
to be naturally occurring in *Alstonia macrophylla* (*152*). In the writers' opinion the mild conditions needed for the reaction strongly suggest that alstomacroline (**80**) is an artefact. Treatment of **80** with BF_3/Et_2O at 0°C for 6 h led to alstonisidine (**78**) (Scheme 8).



SCHEME 8. Biomimetic semisynthesis of alstomacroline (**81**) and alstonisidine (**79**). Reagents: i. 0.2 N HCl, 20°C, 72 h; ii. BF_3/Et_2O.

IV. Reactions

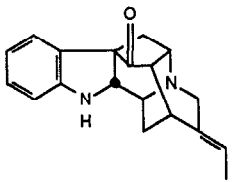
At the outset we would like to emphasize the generally easy interconversion between ajmaline and sarpagine derivatives, schematically presented here for the not yet naturally found 1,2-didehydroquebrachidine (**142**) and polyneuridine aldehyde (**143**) (Scheme 9).



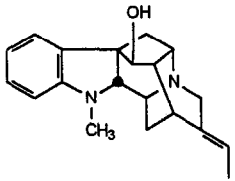
SCHEME 9. Schematic view of the interconversion between ajmaline and sarpagine derivatives.

TABLE II

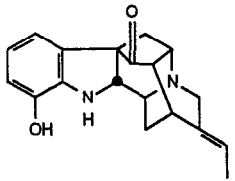
AJMALINE ALKALOID STRUCTURES



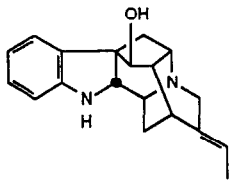
(+)-Rauflorine
[(+)-1]
[36063-54-4]
Mp. 221°C (MeOH)(*12*)
$[\alpha]_D^{20}$ +312° (*c* 1.54, $CHCl_3$)(*12*)



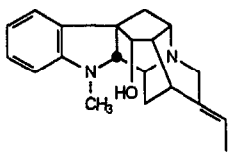
(+)-Tetraphyllicine
[(+)-3]
[509-38-6]
Mp. 320-322°C (acetone)(*31a*)
$[\alpha]_D^{27}$ +21° (py)(*31a*)



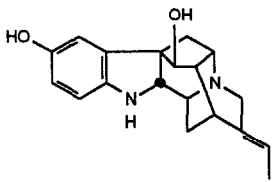
Normitoridine
[5]
[68160-75-8]
Amorphous (*14*)
$[\alpha]_D$ n.r.



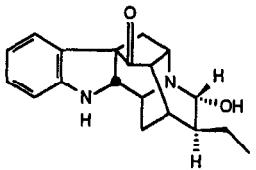
Nortetraphyllicine
[2]
[68160-76-9]
Mp. 280°C dec. (*22a*)
$[\alpha]_D$ n.r.



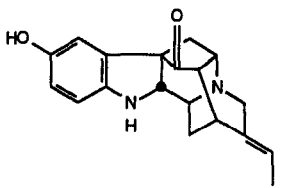
(+)-**Mauiensine** (17*S*)
[(+)-4]
[6883-73-4]
Mp. 240-242°C (acetone)(*25*)
$[\alpha]_D$ +184° (MeOH)(*25*)



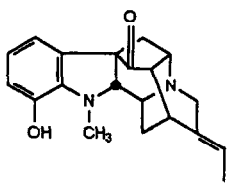
10-Hydroxynortetraphyllicine
[6]
[70509-79-4]
Amorphous (*22a*)
$[\alpha]_D$ n.r.



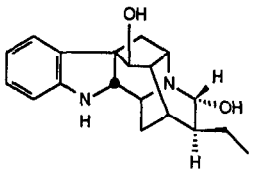
(+)-Norajmalidine
[7]
[93552-59-1]
Amorphous (*13*)
$[\alpha]_D^{24}$ +183.8° (*c* 0.3, $CHCl_3$)(*13*)



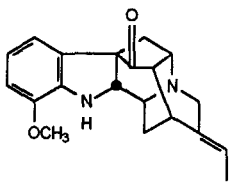
Endolobine
[9]
[67627-71-8]
Mp. 260°C dec. (*39*)
$[\alpha]_D$ n.r.



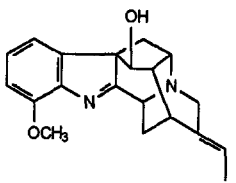
(+)-Mitoridine
[(+)-11]
[3911-19-1]
Mp. 322°C (MeOH + subl.)(*41*)
$[\alpha]_D^{18}$ +175° ± 4° (*c* 1.04, py)(*41*)



(+)-Norajmaline
[(+)-8]
[23944-24-3]
Amorphous (*30*)
$[\alpha]_D$ +36° (*c* 0.67, $CHCl_3$)(*30*)



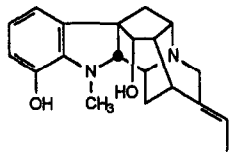
(±)-Norpurpeline
[(±)-10]
[65061-33-8]
Mp. n.d.
$[\alpha]_D$ ±0° (*40*)



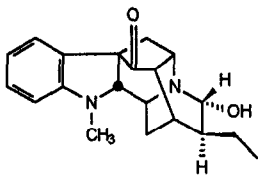
17-*O*-Deacetyl-12-methoxyvinorine
[12]
[70509-81-8]
Amorphous (*22a*)
$[\alpha]_D$ n.r.

(*continues*)

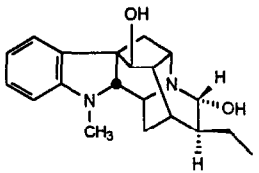
TABLE II (*Continued*)



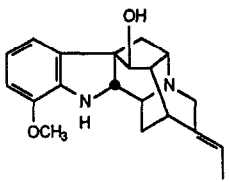
(+)-**12-Hydroxymauiensine** (17*S*)
[(+)-**13**]
[104748-99-4]
Mp. 260°C (*36*)
$[\alpha]_D$ +100° (*c* 1, MeOH)(*36*)



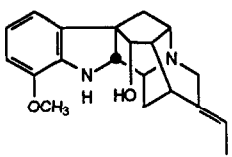
(-)-**Ajmalidine**
[(-)-**15**]
[639-30-5]
Mp. 241-242°C (MeOH)(*28*)
$[\alpha]_D^{25}$ -80° (*c* 1, AcOH)(*153*)



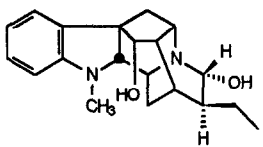
(+)-**Ajmaline**
[(+)-**17**]
[4360-12-7]
Mp. 200-202°C (anh.) (MeOH)(*154*)
$[\alpha]_D$ +144° (*c* 0.8, $CHCl_3$)(*154*)



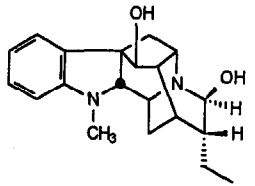
(+)-**Norseredamine**
[(+)-**14**]
[30171-06-3]
Mp. 242-245°C ($CHCl_3$)(*42*)
$[\alpha]_D^{22}$ +32.6° ± 0.5° (*c* 3.65, MeOH)(*42*)



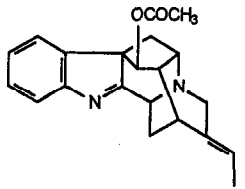
Dihydronorpurpeline (17*S*)
[16]
[65136-98-3]
Amorphous (*40*)
$[\alpha]_D$ n.r.



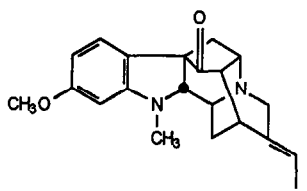
(+)-**Sandwicine** (17*S*)
[(+)-**18**]
[509-37-5]
Amorphous (*75*)
$[\alpha]_D$ +180° ($CHCl_3$)(*25*)



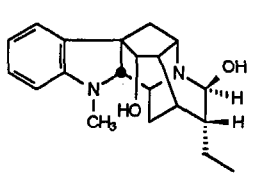
(+)-**Isoajmaline**
[(+)-**19**]
[6989-79-3]
Mp. 265°C dec. (MeOH aq.)(*154*)
$[\alpha]_D^{18}$ +72° (c, 0.7, $CHCl_3$)(*154*)



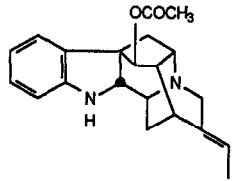
(-)-**Vinorine**
[(-)-**21**]
[34020-07-0]
Mp. 117-119°C (Et_2O)(*77*)
$[\alpha]_D^{15}$ -33° (*c* 0.05, $CHCl_3$)(*77*)



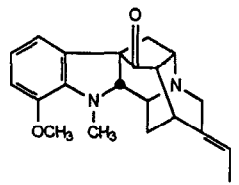
Rauflexine
[23]
[70522-05-3]
Mp. 154-155°C (EtOAc/petr. ether) (*82a*)
$[\alpha]_D$ n. r.



(+)-**Isosandwicine** (17S)
[(+)-**20**]
[6835-90-1]
Mp. 250°C (MeOH aq.)(*75*)
$[\alpha]_D^{20}$ +130° (*c* 1.18, $CHCl_3$)(*75*)



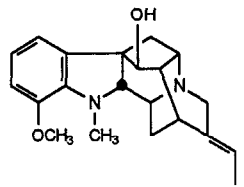
(+)-**17-*O*-Acetylnortetraphyllicine**
[(+)-**22**]
[81525-52-2]
Amorphous (*17*)
$[\alpha]_D^{22}$ +41° (*c* 0.01, MeOH)(*17*)



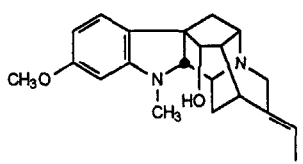
(+)-**Purpeline**
[(+)-**24**]
[2246-33-5]
Mp. 155°C (ether/hexane)(*41*)
$[\alpha]_D^{25}$ +333° ($CHCl_3$)(*41*)

(*continues*)

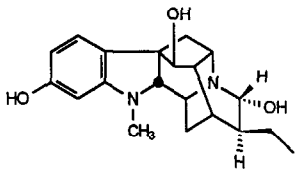
TABLE II (*Continued*)



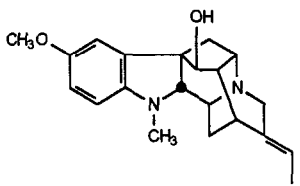
(+)-**Seredamine**
[(+)-**25**]
[3911-20-4]
Mp. 297°C (acetone + subl.)(*41*)
$[\alpha]_D^{18}$ +60° ± 2° (*c* 0.74, $CHCl_3$)(*41*)



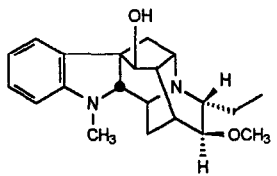
(+)-**Reflexine** (17*S*)
[(+)-**27**]
[6109-18-7]
Mp. 260°C dec. (acetone)(*82a*)
$[\alpha]_D$ +126° ($CHCl_3$)(*82a*)



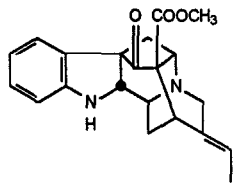
(+)-**Ajmalinol**
[(+)-**29**][a]
[73012-74-5]
Mp. 209-210°C (benzene/MeOH)(*86*)
$[\alpha]_D^{30}$ +132° ($CHCl_3$)(*86*)



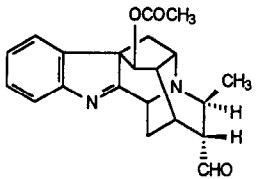
Vincamajoreine
[26]
[3382-93-2]
Mp. 246-247°C (MeOH)(*83*)
$[\alpha]_D$ n.r.



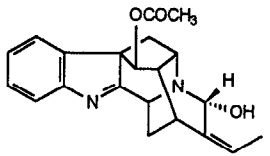
(+)-**Sandwicolidine**
[(+)-**28**][a]
[99612-65-4]
Mp. 213-214°C (EtOH:AcOEt 9:1)(*85*)
$[\alpha]_D^{20}$ 227° ($CHCl_3$)(*85*)



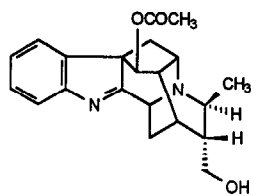
(-)-**Leepacine**
[(-)-**30**][a]
[135649-95-5]
Mp. n.d.
$[\alpha]_D$ -91° (MeOH)(*87*)



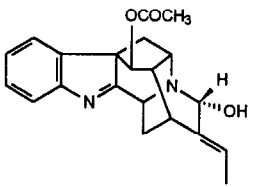
(+)-**Perakine**
[(+)-**31**][b]
[4382-56-3]
Mp. 186-189°C (EtOAc/petr. ether)(*88b*)
$[\alpha]_D$ +120° ($CHCl_3$)(*88b*)



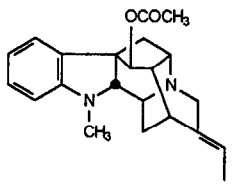
Raucaffriline
[**33**][c]
[107585-43-3]
Mp. 200-201°C (EtOAc)(*88a*)
$[\alpha]_D$ n.r.



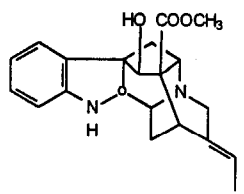
(+)-**Raucaffrinoline**
[(+)-**35**][b]
[36285-11-7]
Mp. 249-251°C (*78*)
$[\alpha]_D$ +11° ($CHCl_3$)(*78*)



(-)-**Vomilenine**
[(-)-**32**]
[6880-50-8]
Mp. 207°C (MeOH)(*95*)
$[\alpha]_D$ -72° (*c* 0.5, py)(*95*)

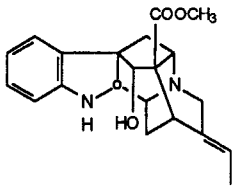


17-*O*-Acetyltetraphyllicine
[**34**]
[25926-60-7]
Mp. n.d.
$[\alpha]_D$ n.r.

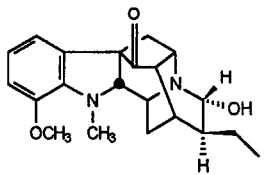


(+)-**Quebrachidine**
[(+)-**36**]
[4835-69-2]
Mp. 276-278°C (benzene)(*105b*)
$[\alpha]_D^{26}$ +54° ($CHCl_3$)(*105b*)

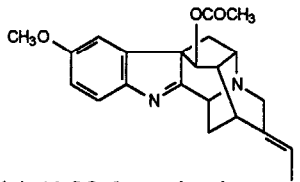
(*continues*)



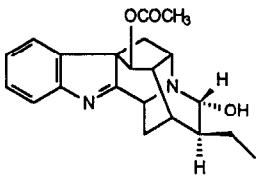
(+)-**Vincarine** (17*R*)
[(+)-**37**][d]
[21641-60-1]
Mp. 263-264°C (MeOH)(*113*)
$[\alpha]_D$ +14° (*c* 0.785, MeOH)(*113*)



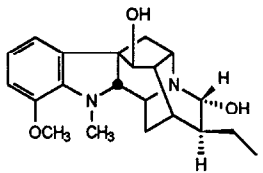
(+)-**Vomalidine**
[(+)-**39**]
[639-28-1]
Mp. 242-243°C (acetone)(*116*)
$[\alpha]_D^{20}$ +318° (*c* 1, $CHCl_3$)(*116*)



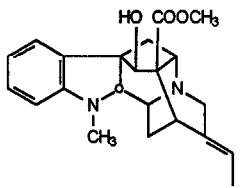
(+)-**10-Methoxyvinorine**
[(+)-**41**]
[163461-46-9]
Amorphous (*118*)
$[\alpha]_D$ +23.5° (*c* 0.2, $CHCl_3$)(*118*)



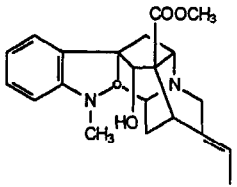
19,20-Dihydrovomilenine
[38]
[110044-96-7]
Mp. n.d.
$[\alpha]_D$ n.r.



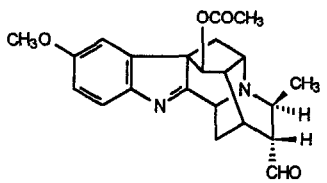
12-Methoxyajmaline
[40]
[56897-55-3]
Amorphous (*38*)
$[\alpha]_D$ n.r.



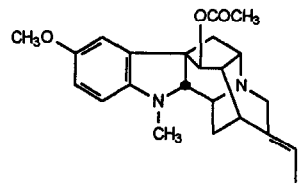
(-)-**Vincamajine**
[(-)-**42**]
[2506-26-5]
Mp. 225°C (MeOH)(*130a*)
$[\alpha]_D$ -55° ± 5° (*c* 0.45, EtOH)(*130a*)



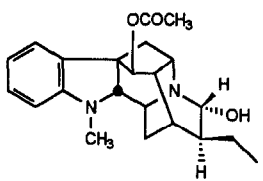
Vincamajinine (17*R*)
[43]
[1748-05-6]
Mp. 274-275°C (MeOH)(*132*)
$[\alpha]_D$ n.r.



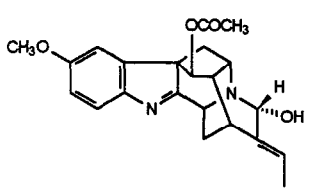
(-)-10-Methoxyperakine
[(-)-45][b]
[163461-45-8]
Mp. n.d.
$[\alpha]_D$ -43° (*c* 0.3, $CHCl_3$)(*118*)



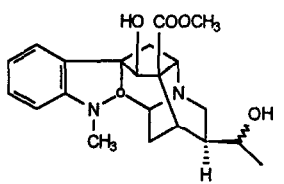
(-)-Majoridine
[(-)-47]
[6519-30-8]
Mp. 222-223°C (EtOH)(*136b*)
$[\alpha]_D^{22}$ -26° ± 2° (*c* 1.05, $CHCl_3$)(*136b*)



(+)-17-*O*-Acetylajmaline
[(+)-44]
[19918-92-4]
Mp. 213-215°C (MeOH)(*33a*)
$[\alpha]_D^{20}$ +52° (*c* 0.5, $CHCl_3$)(*33a*)



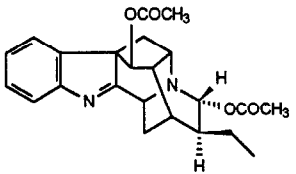
Majorinine
[46]
[64986-27-2]
Mp. 195-196°C (acetone)(*130b*)
$[\alpha]_D$ n.r.



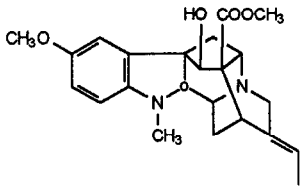
19-Hydroxy-19,20-dihydrovincamajine
[48]
[108195-74-0]
Mp. n.d.
$[\alpha]_D$ n.r.

(*continues*)

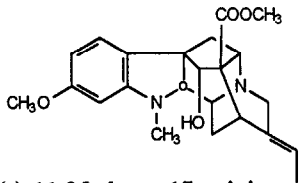
TABLE II (*Continued*)



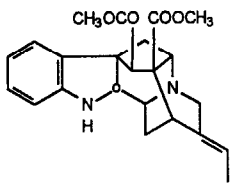
21-Acetyl-19,20-dihydrovomilenine
[49]
[98301-75-8]
Amorphous (*79*)
$[\alpha]_D$ n.r.



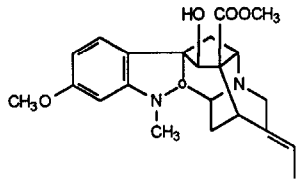
(±)-10-Methoxyvincamajine
[(±)-51]
[57800-02-9]
Amorphous (*138b*)
$[\alpha]_D$ ±0° ± 3°(*c* 1, EtOH)(*138b*)



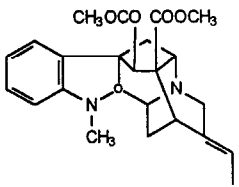
(-)-11-Methoxy-17-epivincamajine (17*R*)
[(-)-53]
[132268-03-2]
Mp. n.d.
$[\alpha]_D$ -12° (*c* 0.5, $CHCl_3$)(*139*)



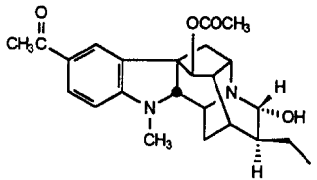
Norvincamedine
[(±)-50]
[not given]
Mp. 185-187°C (*122*)
$[\alpha]_D$ ±0° ($CHCl_3$)(*122*)



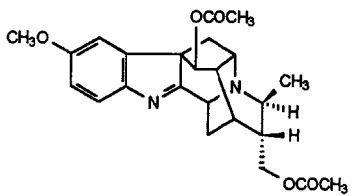
(-)-11-Methoxyvincamajine
[(-)-52]
[132242-26-3]
Mp. n.d.
$[\alpha]_D$ -14° (*c* 0.25, $CHCl_3$)(*139*)



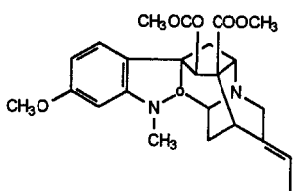
(-)-Vincamedine
[(-)-54]
[912-27-6]
Mp. 185°C (cyclohexane + subl.)(*141*)
$[\alpha]_D$ -66° ± 2° (*c* 0.52, $CHCl_3$)(*141*)



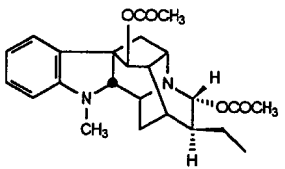
(+)-Ajmalinimine
[(+)-55]
[107603-58-7]
Mp. 198-199°C (MeOH aq)(*143*)
$[\alpha]_D$ +205° (*c* 0.3, $CHCl_3$)(*143*)



(-)-Vincawajine
[(-)-57][b]
[164176-14-1]
Mp. n.d.
$[\alpha]_D$ -10.9° (*c* 0.9, $CHCl_3$)(*118*)

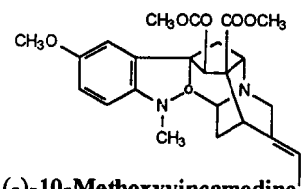


(-)-11-Methoxyvincamedine
[(-)-59]
[142750-28-5]
Mp. n.d.
$[\alpha]_D$ -7.5° (*c* 1, $CHCl_3$)(*144*)



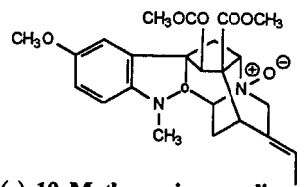
17,21-O,O-Diacetylajmaline

[56]
[19775-56-5]
Amorphous (*24*)
$[\alpha]_D$ n.r.



(-)-10-Methoxyvincamedine

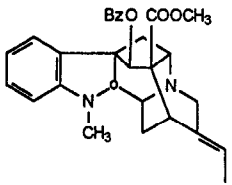
[(-)-58]
[94444-30-1]
Mp. n.d.
$[\alpha]_D$ -9° (*c* 1, $CHCl_3$)(*104*)



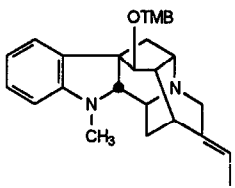
(-)-10-Methoxyvincamedine N_b-oxide
[(-)-60]
[94444-31-2]
Mp. n.d.
$[\alpha]_D$ -2° (*c* 1, $CHCl_3$)(*104*)

(*continues*)

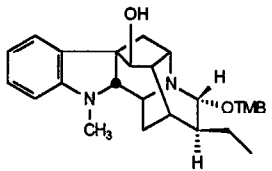
TABLE II (*Continued*)



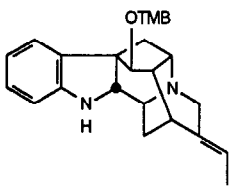
(-)-17-*O*-Benzoylvincamajine
[(-)-61]
[24190-04-3]
Mp. 267-269°C (*145*)
$[\alpha]_D$ -147° ($CHCl_3$)(*145*)



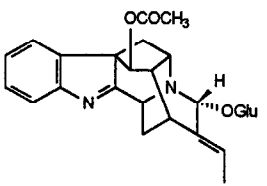
(-)-Rauvomitine
[(-)-63]
[466-57-9]
Mp. 115-117°C (EtOH:H_2O 1:1)(*146b*)
$[\alpha]_D^{20}$ -173.4° ± 1° (*c* 1, $CHCl_3$)(*146b*)



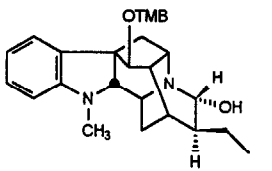
(+)-Ajmalimine
[(+)-65][a]
[110941-51-0]
Mp. 188-189°C (EtOAc:MeOH 1:1)(*147*)
$[\alpha]_D^{20}$ +105° (*147*)



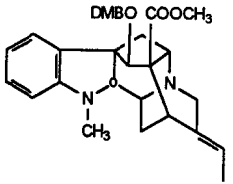
Norrauvomitine
[62]
[64675-21-4]
Amorphous (*33b*)
$[\alpha]_D$ n.r.



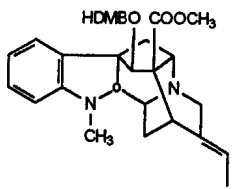
(+)-Raucaffricine
[(+)-64][e]
[31282-07-2]
Mp. 186-220°C (MeOH:EtOAc 1:5)(*88b*)
$[\alpha]_D^{30}$ +14.5° (EtOH)(*88b*)



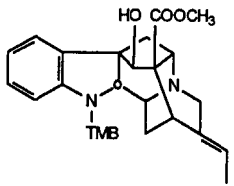
17-*O*-(3,4,5-Trimethoxybenxoyl)ajmaline
[66]
[104998-32-5]
Amorphous (*38*)
$[\alpha]_D$ n.r.



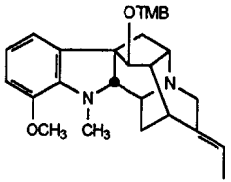
(-)-17-*O*-(3',4'-Dimethoxybenzoyl)-vincamajine
[(-)-67]
[154849-47-5]
Solid (*124b*)
$[\alpha]_D^{25}$ -129.6° (c, 0.68, MeOH)(*124b*)



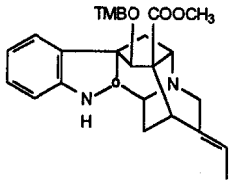
4'-Hydroxy-3',5'-dimethoxybenzoyl-vincamajine
[69]
[144379-35-1]
Mp. n.d.
$[\alpha]_D$ n.r.



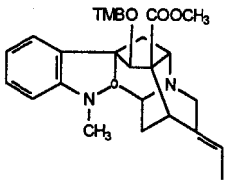
(-)-1-*N*-(3',4',5'Trimethoxybenzoyl)-quebrachidine
[(-)-71]
[not given]
Solid (*124b*)
$[\alpha]_D^{25}$ -98,4° (*c* 0.56, MeOH)(*124b*)



17-*O*-(3',4',5'-Trimethoxybenzoyl)-seredamine
[68]
[68160-77-0]
Amorphous (*14*)
$[\alpha]_D$ n.r



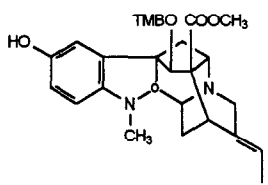
(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)-quebrachidine
[(-)-70]
[31148-63-7]
Mp. 231-232°C (MeOH)(*120*)
$[\alpha]_D$ -36° (*c* 1.3, $CHCl_3$)(*120*)



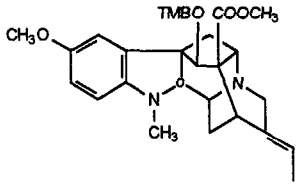
(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)-vincamajine
[(-)-72]
[71385-80-3]
Amorphous (*122*)
$[\alpha]_D^{20}$ -100° (*c* 1, $CHCl_3$)(*122*)

(*continues*)

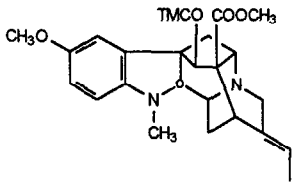
TABLE II (*Continued*)



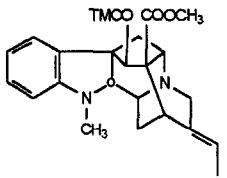
(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine
[(-)-73]
[57800-05-2]
Amorphous (*138b*)
$[\alpha]_D$ -43° (*c* 1, $CHCl_3$)(*138b*)



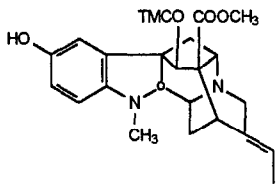
10-Methoxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine
[75]
[71385-81-4]
Mp. n.d.
$[\alpha]_D$ n.r.



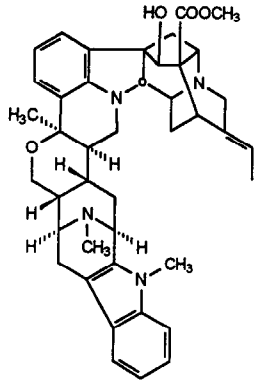
(-)-10-Methoxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine
[(-)-77]
[57800-04-1]
Amorphous (*138b*)
$[\alpha]_D$ -134° (*c* 1, $CHCl_3$)(*138b*)



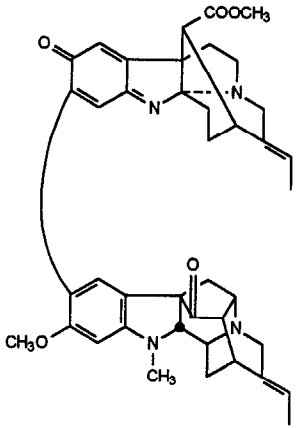
(-)-17-*O*-(3',4',5'-Trimethoxycinnamoyl)-vincamajine
[(-)-74]
[57800-03-0]
Amorphous (*120*)
$[\alpha]_D$ -68° (*c* 2.6, $CHCl_3$)(*120*)



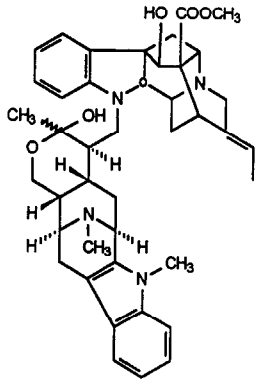
(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine
[(-)-76]
[57808-41-0]
Amorphous (*138b*)
$[\alpha]_D$ -114° (*c* 1, $CHCl_3$)(*138b*)



(-)-Alstonisidine
[(-)-78]
[36474-13-2]
Mp. 325°C dec. (MeOH)(*156*)
$[\alpha]_D$ -133° (*c* 0.208, $CHCl_3$)(*157*)



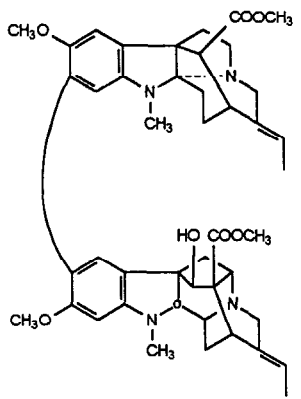
(-)-Flexicorine
[(-)-79]
[80765-85-1]
Amorphous (*151*)
$[\alpha]_D^{25}$ -519.5° ($CHCl_3$)(*151*)



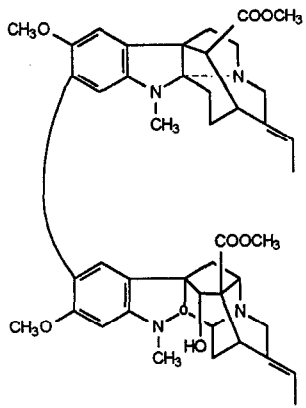
(+)-Alstomacroline
[(+)-80][b]
[199800-14-1]
Amorphous (*152*)
$[\alpha]_D^{20}$ +54.6° (*c* 0.366, $CHCl_3$)(*152*)

(*continues*)

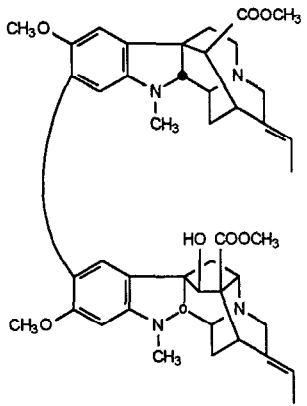
TABLE II (*Continued*)



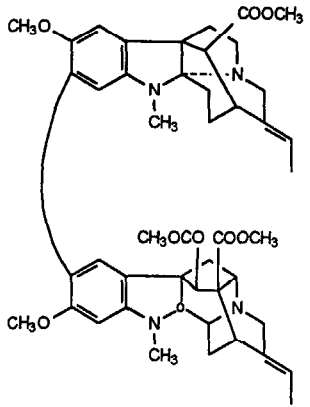
11-Methoxy-10-(11'-vincorinyl)-vincamajine
[81]
[142795-96-8]
Mp. n.d.
$[\alpha]_D$ n.r.



(-)-**11-Methoxy-10-(11'-vincorinyl)-17-epivincamajine** (17*R*)
[(-)-82]
[142750-29-6]
Mp. n.d.
$[\alpha]_D$ -37° (*c* 1, $CHCl_3$)(*144*)



(±)-**11-Methoxy-10-[11'-(10'-methoxycatha-folinyl)]vincamajine**
[(±)-83]
[132242-27-4]
Mp. n.d.
$[\alpha]_D$ ±0° (*c* 1, $CHCl_3$)(*139*)



(-)-11-Methoxy-10-(11'-vincorinyl)vincamedine
[(-)-84]
[142750-30-9]
Mp. n.d.
$[\alpha]_D$ -58° (*c* 1, $CHCl_3$)(*144*)

Abbreviations used: n.d. not determined; n.r. not recorded; py pyridine; Bz benzoyl; TMB 3,4,5,-trimethoxybenzoyl; DMB 3,4-dimethoxybenzoyl; HDMB 4-hydroxy-3,5-dimethoxybenzoyl; TMC 3,4,5-trimethoxycinnamoyl. The sign of the optical rotation [(+) or (-)] is indicated with the compound name if this is given with the CAS number.

[a] In the writers' opinion, the proposed structure is in need of confirmation.

[b] In the writers' opinion, the compound in question is an artefact.

[c] The writers suggest that raucaffriline, whose structure has not been conclusively determined (*88a*), may in fact be identical with *Z*-vomilenine (**33**).

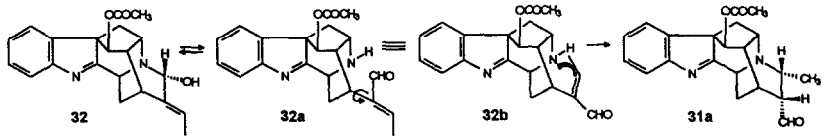
[d] In the recent Russian literature (*113b*) vincarine (**37**) is considered identical, not isomeric, with quebrachidine (**36**).

[e] For the revision of the original structure given for raucaffricine (**64**), see reference (*155b*).

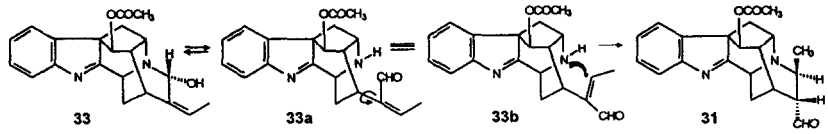
A. TRANSFORMATION OF VOMILENINES INTO PERAKINES

Compounds such as perakine (**31**) and raucaffrinoline (**35**), with their rearranged ajmaline structures, are now considered to be artefacts, formed from *E*-vomilenine (**32**) during the isolation process (*166*).

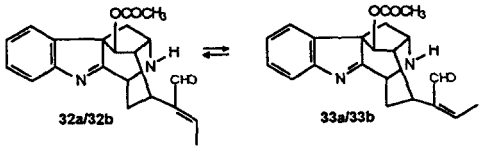
A striking general feature of compounds **31** and **35** is that the C-19 methyl group is β (when the quinuclidine ring system is considered). Another interesting point is that, in their formation, the attack during the recyclization procedure can take place only from the β-side. In the case of *E*-vomilenine (**32**), this would lead, *via* intermediates **32a/32b** (*chano* forms), to 19-epiperakine (**31a**) (C-19α-CH_3), which has never been detected (Scheme 10). In view of this, Lounasmaa and Hanhinen have recently suggested that "alkaloids" **31** and **35** are formed from *Z*-vomilenine (raucaffriline? *vide supra*) (**33**) rather than from *E*-vomilenine (**32**) (*167a*) (Scheme 11). In the case of *E*-vomilenine (**32**), intermediate **32a/32b** has to isomerize to intermediate **33a/33b** before recyclization (Scheme 12).



SCHEME 10. Hypothetical transformation of *E*-vomilenine (**32**) (*via* intermediates **32a/32b**) to 19-epiperakine (**31a**) (C-19α-CH_3).



SCHEME 11. Transformation of *Z*-vomilenine (**33**), *via* intermediate **33a/33b** (*chano* form), to perakine (**31**).



SCHEME 12. Equilibration between intermediates **32a/32b** and **33a/33b**.

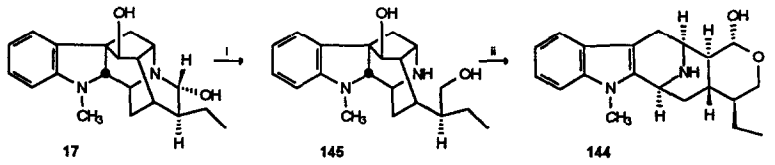
Partial reduction of the formed perakine (**31**) (Cannizzaro reaction) then easily affords raucaffrinoline (**35**).

Takayama *et al.* (*167b*) have shown that both synthetic *E*-vomilenine (**32**) and synthetic *Z*-vomilenine (**33**) are transformed to perakine (**31**), but the latter is transformed much faster and under less drastic conditions. This supports the assumption that perakine (**31**) is "directly" formed from *Z*-vomilenine (**33**) (*vide supra*), which is more or less totally "consumed" during the isolation procedure and which is thus difficult to detect as a naturally occurring alkaloid.

A similar procedure starting from majorinine (10-methoxy-*E*-vomilenine) (**46**) can be expected to lead, also *via* its *Z*-isomer, to 10-methoxyperakine (**45**) and then, after reduction and acetylation [10% acetic acid was used in the applied extraction procedure (*118*)], to vincawajine (**57**) (*167a*).

B. TRANSFORMATION OF AJMALINE INTO RAUMACLINE

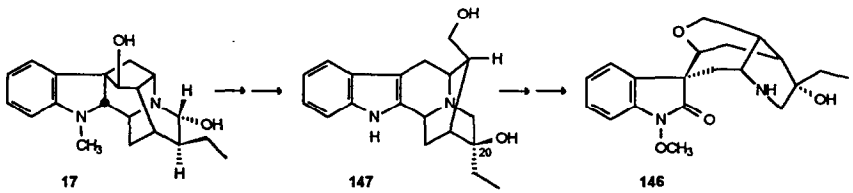
An efficient transformation of ajmaline (**17**) into raumacline (**144**), which is a biotransformation product of ajmaline in cell cultures of *Rauvolfia serpentina*, was developed by Endress and Stöckigt (*168*). Ajmaline (**17**) was reduced with $NaBH_4$ in citrate/phosphate buffered solution (pH 6.0) to 4,21-secoajmaline (**145**), which, by riboflavin-sensitized photo-oxidation, afforded raumacline (**144**) in 86% total yield (Scheme 13).



SCHEME 13. Transformation of ajmaline (**17**) into raumacline (**144**). Reagents: i. $NaBH_4$, MeOH, citrate/phosphate buffer (pH 6.0); ii. riboflavin, hv.

C. USE OF AJMALINE IN THE PARTIAL SYNTHESIS OF (-)-20-HYDROXYDIHYDRORANKINIDINE

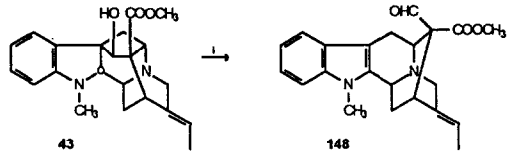
Sakai *et al.* (*169*) used ajmaline (**17**) in their partial synthesis of (-)-20-hydroxydihydrorankinidine (**146**) *via* the sarpagine analog **147** (Scheme 14).



SCHEME 14. Transformation of (-)-ajmaline [(-)-17], *via* the sarpagine analog **147**, into (-)-20-hydroxydihydrorankinidine (**146**).

D. Oxidation of Vincamajine to Voachalotinal

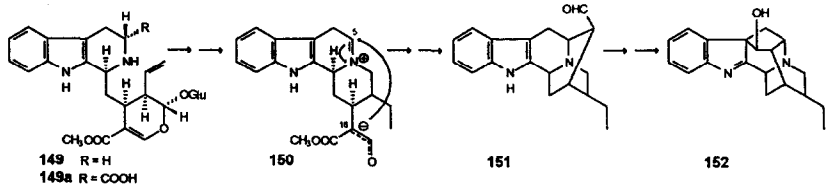
Oxidation of vincamajine (**43**) with CrO_3 in pyridine leads to voachalotinal (**148**) (*131*, *170*) (Scheme 15).



Scheme 15. Oxidation of vincamajine (**43**) to voachalotinal (**148**). Reagents: i. CrO_3/py.

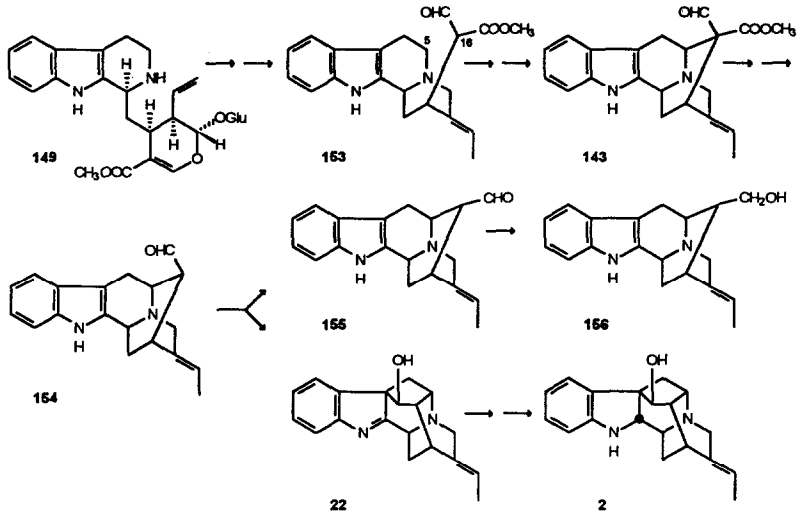
V. Biosynthesis and Biogenesis

The general role of strictosidine (**149**) in the biosynthetic formation of monoterpenoid indole alkaloids is well established (*171-175*). In the biogenetic formation of ajmaline (and sarpagine) alkaloids the van Tamelen proposal has been generally accepted. According to this proposal the formation of a bond between C-5 and C-16 in the intermediate 4,5-dehydrogeissoschizine ($\Delta^{4(5)}$-iminium system) (**150**) leads to the sarpagan ring system ("deoxyajmalal system") **151**, which then can transform to the ajmalan ring system **152**. van Tamelen suggested that 5α-carboxystrictosidine (**149a**), not strictosidine (**149**) itself, was the key intermediate. However, Stöckigt (*176*) has shown that 5α-carboxystrictosidine (**149a**) is not, in fact, involved (Scheme 16).



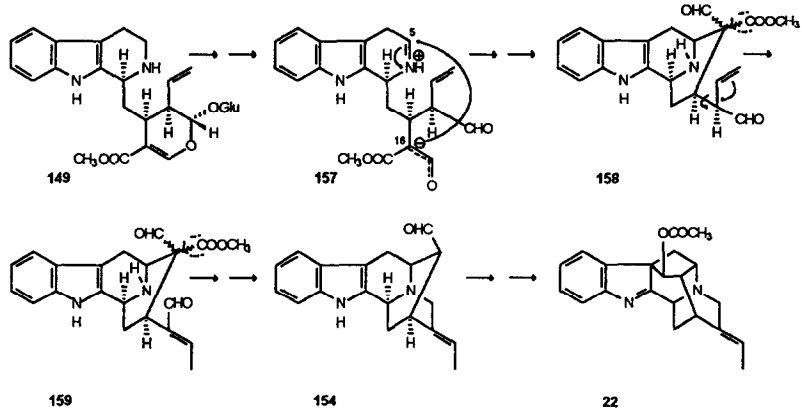
Scheme 16. The van Tamelen proposal for the biogenetic formation of the ajmalan skeleton **152** *via* the sarpagan skeleton **151**.

In a brilliant series of investigations, Stöckigt *et al.* (*7*, *177-181*) clarified the enzymatic transformation of strictosidine (**149**) to sarpagan- (**149** → **153** → **143** → **154** → **155** → **156**) and ajmalan-type (**149** → **153** → **143** → **154** → **22** → **2**) alkaloids. These transformations in many aspects follow the suggestions of van Tamelen (Scheme 17). However, the stage at which the bond formation between C-5 and C-16 takes place, and the participation of geissoschizine (**153**) as an intermediate in general, in our opinion remains unclear.



SCHEME 17. The enzymatic transformation of strictosidine (149) to sarpagan- and ajmalan-type alkaloids according to Stöckigt *et al.*

Lounasmaa and Hanhinen (*163*, *164*) have presented evidence to suggest that the bond formation between C-5 and C-16 takes place not after, as has generally been accepted, but before the D ring formation (**149** → **157** → **158**). As soon as intermediate **158** is formed, transformation to sarpagine and ajmaline structures can take place by normal biogenetic routes (**158** → **159** → **154** → **22**) (Scheme 18).



SCHEME 18. The Lounasmaa and Hanhinen proposal for the bond formation between C-5 and C-16 in the transformation of strictosidine (149) into sarpagine structures [represented by 16-*epi*-vomilenine (154)] and ajmaline structures [represented by vinorine (22)].

The main argument that Lounasmaa and Hanhinen (*163*, *164*) employed in rejecting the van Tamelen proposal was that the shortest possible distance between the reactive sites C-5 and C-16 in intermediate **150** is about 2.70 Å (Fig. 4). This is far too large to permit bond formation between C-5 and C-16. In their alternative proposal, where the bond formation takes place before the D-ring formation, the minimal distance between the reactive sites C-5 and C-16 in intermediate **157** is about 1.50 Å (Fig. 4). This is quite suitable for bond formation.

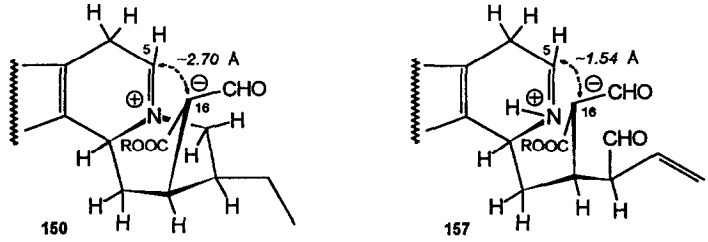
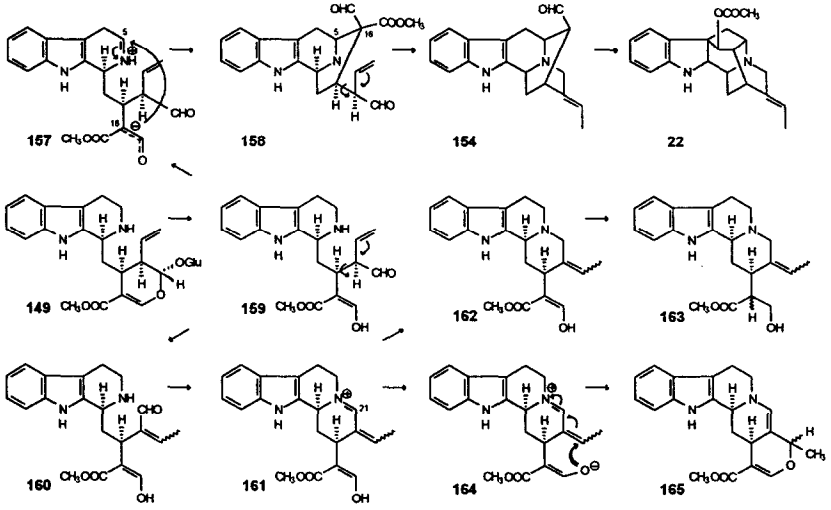


FIG. 5. The shortest possible distances between the reactive sites C-5 and C-16 in intermediates **150** and **157**.

Altogether this means that in the general biogenetic formation of monoterpenoid indole alkaloids possessing the unrearranged skeletal system (*173-175*), the route leading to the sarpagine and ajmaline structures takes a course of its own (**159** → **157** → **158** → **154** → **22**) before the formation of 4,21-dehydrogeissoschizines (**159** → **160** → **161**). Intermediate **161** can then lead, among other things, to geissoschizines (**162**), isositsirikines (**163**), and cathenamines (**165**) (Scheme 19).



SCHEME 19. General biogenetic formation, from strictosidine (**149**), of monoterpenoid indole alkaloids possessing the unrearranged skeletal system.

TABLE III

^{1}H NMR AND MASS SPECTRAL DATA OF INDIVIDUAL ALKALOIDS

(+)-Rauflorine [(+)-**1**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 1.64 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 1.69 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 1.88 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 1 Hz, H-14α), 2.47 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.58 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{15,16}$= 5 Hz, H-16), 3.17 (1H, dd, $J_{14\beta,15}$= $J_{15,16}$= 5 Hz, $J_{14\alpha,15}$~ 1 Hz, H-15), 3.22 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.37 (1H, s(d), $J_{2,3}$< 0.5 Hz, H-2), 3.50 (2H, def, H-21α, H-21β), 3.59 (1H, d(dd), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$~ 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 5.31 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 6.77 (1H, H-12), 6.85 (1H, H-10), 7.10 (1H, H-11), 7.22 (1H, H-9). (*189*), see also (*190*)
MS: 292 (M^+), 263, 184, 183, 169, 168, 144, 130. (*12*)

Nortetraphyllicine (**2**):
^{1}H NMR (60 MHz, CD_3OD): 1.25 (3H, m), 1.65 (3H, d), 1.87 (1H, s), 2.0 (1H, s), 3.1 (2H, d), 3.55 (2H, m), 3.8 (1H, s), 5.3 (1H, dq), 6.6-7.3 (4H, m, H-9, H-10, H-11H-12). (*22a*)
MS: 294 (M^+, 100%), 293, 277, 263, 249, 184, 170, 169, 168, 144, 143, 130, 117. (*22a*)

(+)-Tetraphyllicine [(+)-**3**]:
^{1}H NMR: No data available.
MS: 308 (M^+, 100%), 291, 277, 183, 182, 157, 144, 131. (*42*), see also (*41*)

(+)-Mauiensine [(+)-**4**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.23 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 1.62 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 1.78 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 1 Hz, H-14α), 2.05 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.08 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$~ 4 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 2.44 (1H, dd(d), $J_{16,17}$= 9 Hz, $J_{5,16}$= 7 Hz, $J_{15,16}$~ 4 Hz, H-16), 2.78 (1H, s, N-CH_3), 2.89 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 2.97 (1H, dd(d), $J_{14\beta,15}$= $J_{15,16}$~ 4 Hz, $J_{14\alpha,15}$~ 1 Hz, H-15), 3.07 (1H, s(d), $J_{2,3}$< 0.5 Hz, H-2), 3.34 (1H, d, $J_{21\alpha,21\beta}$= 15 Hz, H-21α), 3.46 (1H, d, $J_{21\alpha,21\beta}$= 15 Hz, H-21β), 3.62 (1H, d(dd), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$~ 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 4.72 (1H, d, $J_{16,17}$= 9 Hz, H-17), 5.22 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 6.66 (1H, H-12), 6.81 (1H, H-10), 7.10 (1H, H-9), 7.16 (1H, H-11). (*189*), see also (*36*), (*19*)
MS: 308 (M^+), 291, 277, 183 (100%), 182, 170, 168, 167, 157, 144, 108. (*19*)

(*continues*)

TABLE III (*Continued*)

Normitoridine (**5**):
^{1}H NMR: No data available.
MS: 308 (M^+, 100%), 279, 265, 200, 199, 198, 173, 172, 160, 146, 108. (*14*)

10-Hydroxynortetraphyllicine (**6**):
^{1}H NMR: No data available.
MS: 310 (M^+, 100%), 309, 279, 256, 200, 199, 186, 185, 184, 164, 159, 146, 113. (*22a*)

(+)-Norajmalidine [(+)-**7**]:
^{1}H NMR: 0.95 (3H, t, H-18), 1.5 (2H, m, 2 x H-19), 2.1 (H, s), 3.15 (1H, m, H-21), 3.55 [(1H, m, H-9 (*sic!*)], 3.8 (1H, d, H-2), 4.3 (1H, q, H-3), 6.5-7.4 (4H, m, H-9, H-10, H-11, H-12). (*13*)
MS: 310 (M^+), 295, 293, 282, 281, 184, 183, 180 (100%), 169, 168, 144, 143, 130. (*13*)

(+)-Norajmaline [(+]-**8**]:
^{1}H NMR: No data available.
MS: 312 (M^+), 297, 283, 183, 182, 169, 168, 144, 143, 131, 130. (*30*), see also (*37*)

Endolobine (**9**):
^{1}H NMR ($CDCl_3$): 1.60 (3H, H-18), 3.75 (3H, s, -OCH_3), 5.18 (1H, q, H-19), 6.64 (3H, m, H-9, H-11, H-12), 8.27 (1H, s, NH). (*39*)
MS: 322 (M^+, 100%), 294, 293, 279, 265, 214, 213, 200, 199, 198, 186, 174, 173, 160, 108. (*39*)

(±)-Norpurpeline [(±)-**10**]:
^{1}H NMR (60 MHz, $(CD_3)_2SO$): 1.6 (1H, m), 2.5 (2H, s), 3.70 (1H, d, H-2), 3.80 (3H, s, Ar-OCH_3), 6.55-6.70 (3H, m, H-9, H-10, H-11), 8.32 (1H, s, NH). (*40*)
MS: 322 (M^+, 100%), 293, 211, 199, 198, 174, 173, 160, 108, 98. (*40*)

(+)-Mitoridine [(+)-**11**]:
^{1}H NMR: No data available.
MS: 322 (M^+), 294, 293, 214, 199, 198, 173, 160. (*41*)

17-*O*-Deacetyl-12-methoxyvinorine (**12**):
^{1}H NMR (60 MHz, CD_3OD): 1.2 (3H, br s), 1.66 (3H, d), 1.88 (1H, s), 3.08 (3H, d), 3.58 (1H, br s), 3.78 (3H, s), 5.35 (1H, m), 6.81-7.87 (3H, m, H-9, H-10, H-11). (*22a*)
MS: 322 (M^+, 100%), 321, 294, 279, 200, 199, 198, 173, 160, 134, 130, 109, 108. (*22a*)

(+)-12-Hydroxymauiensine [(+)-**13**]:
^{1}H NMR (400 MHz, $CDCl_3$:CD_3OD 3:2): 1.25 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 1.65 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 1.85 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 1 Hz, H-14α), 2.00 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.20 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$~ 4.5 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 2.50 (1H, dd(d), $J_{16,17}$= 9 Hz, $J_{5,16}$= 7 Hz, $J_{15,16}$~ 4.5 Hz, H-16), 2.94 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.06 (1H, s, N-CH_3), 3.03 (1H, dd(d),$J_{14\beta,15}$= $J_{15,16}$~ 4.5 Hz, $J_{14\alpha,15}$~ 1 Hz, H-15), 3.07 (1H, s(d), $J_{2,3}$< 0.5 Hz, H-2), 3.32 (1H, d, $J_{21\alpha,21\beta}$= 15 Hz, H-21α), 3.48 (1H, d, $J_{21\alpha,21\beta}$= 15 Hz, H-21β), 3.63 (1H, dd(d), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$~ 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 4.68 (1H, d, $J_{16,17}$= 9 Hz, H-17), 5.25 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 6.63 (1H, H-10), 6.68 (2H, H-9, H-11). (*36*)
MS: 324 (M^+), 307, 293, 199, 198. (*36*)

(+)-Norseredamine [(+)-**14**]:
^{1}H NMR (100 MHz, $(CD_3)_2SO$): 1.61 (3H, d, J = 6 Hz, H-18), 3.74 (3H, s, Ar-OCH_3), 4.22 (1H, s, H-17), 4.9-5.4 (1H, m, -OH), 5.15 (1H, q, J = 6 Hz, H-19), 6.5-6.8 (2H, m, H-10, H-11), 7.05 (1H, q, J = 6.5 Hz, J = 2 Hz, H-9), 8.31 (1H, s, NH). (*42*)
MS: 324 (M^+, 100%), 293, 200, 199, 198, 184, 173, 164, 160. (*42*)

(-)-Ajmalidine [(-)-**15**]:
^{1}H NMR: No data available.
MS: 324 (M^+), 296, 295, 198, 183, 182, 157, 144 (100%). (*205*), see also (*201*)

Dihydronorpurpeline (**16**):
^{1}H NMR: No data available.
MS: 324 (M^+). (*40*)

(*continues*)

(+)-Ajmaline [(+)-**17**]:
^{1}H NMR (400 MHz, $CDCl_3$): 0.95 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.36 (1H, m, $J_{19',20}$= 4.5 Hz, H-19'), 1.48 (2H, m, H-19, H-20), 1.48 (1H, m, $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$= 4.4 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 1.82 (1H, dd, $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 1 Hz, H-14α), 1.93 (1H, dd, $J_{6\alpha,6\beta}$= 12.5 Hz, $J_{5,6\beta}$= 6 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 2.00 (1H, dd(d), $J_{5,16}$~ 6 Hz, $J_{15,16}$= 4.4 Hz, $J_{16,17}$< 0.5 Hz, H-16), 2.05 (1H, d(dd), $J_{6\alpha,6\beta}$= 12.5 Hz, $J_{5,6\alpha}$= $J_{6\alpha,17}$~ 1 Hz, H-6α), 2.24 (1H, ddd, $J_{14\beta,15}$= $J_{15,16}$= 4.4 Hz, $J_{15,20}$= 3.2 Hz, $J_{14\alpha,15}$~ 1 Hz, H-15), 2.63 (1H, s(dd), $J_{2,6\beta}$~ 0.5 Hz, $J_{2,3}$< 0.5 Hz, H-2), 2.79 (1H, s, N-CH_3), 3.04 (1H, m(dd), $J_{5,6\beta}$= 6 Hz, $J_{5,16}$~ 6 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.58 (1H, d, $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$~ 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 4.26 (1H, br s, $J_{20,21}$~ 0.5 Hz, H-21), 4.43 (1H, s(d), $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$< 0.5 Hz, H-17), 6.68 (1H, d, H-12), 6.80 (1H, dd, H-10), 7.17 (1H, dd, H-11), 7.46 (1H, d, H-9). (*189b*), see also (*190*), (*194*)
MS: 326 (M^+), 311, 297, 183, 182, 157, 144 (100%). (*203*), see also (*41*), (*204*)

(+)-Sandwicine [(+)-**18**]:
^{1}H NMR: No data available.
MS: 326 (M^+), 183, 182, 158, 157, 145, 144. (*75*)

(+)-Isoajmaline [(+)-**19**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.18 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$= 4 Hz, $J_{3,14\beta}$< 1 Hz, H-14β), 1.38 (1H, m, $J_{20,21}$= 7 Hz, $J_{15,20}$~ 1 Hz, H-20), 1.42 (1H, m, H-19'), 1.70 (1H, m, H-19), 1.76 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$< 1 Hz, H-14α), 1.95 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 1.98 (1H, br dd(d), $J_{5,16}$~ 6 Hz, $J_{15,16}$~ 4 Hz, $J_{16,17}$~ 0.5 Hz, H-16), 2.12 (1H, m, $J_{14\beta,15}$= 4 Hz, $J_{15,16}$~ 4 Hz, $J_{15,20}$~ 1 Hz, $J_{14\alpha,15}$< 1 Hz, H-15), 2.13 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.62 (1H, s(d), $J_{2,3}$< 0.5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-2), 2.78 (1H, s, N-CH_3), 3.37 (1H, d(dd), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$< 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 3.68 (1H, dd(d), $J_{5,16}$~ 6 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 4.00 (1H, d, $J_{20,21}$= 7 Hz, H-21), 4.38 (1H, s(d), $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$~ 0.5 Hz, H-17), 6.66 (1H, H-12), 6.78 (1H, H-10), 7.17 (1H, H-11), 7.45 (1H, H-9). (*189a*), see also (*190*)
MS: No data available.

(+)-Isosandwicine [(+)-**20**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.00 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.32 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 1.33 (1H, m, $J_{20,21}$= 7 Hz, $J_{15,20}$~ 1 Hz, H-20), 1.41 (1H, m, H-19'), 1.68 (1H, m, H-19), 1.73 (1H, def, H-14α, H-14β), 2.00 (1H, m, $J_{15,16}$~ 5 Hz, $J_{14\beta,15}$~ 4 Hz, $J_{15,20}$~ 1 Hz, $J_{14\alpha,15}$< 1 Hz, H-15), 2.04 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.46 (1H, ddd, $J_{16,17}$= 9 Hz, $J_{5,16}$= 6 Hz, $J_{15,16}$~ 5 Hz, H-16), 2.82 (1H, s, N-CH_3), 3.04 (1H, s(d), $J_{2,6\beta}$~ 0.5 Hz, $J_{2,3}$< 0.5 Hz, H-2), 3.56 (1H, d(dd), $J_{3,14\alpha}$~ 10 Hz, $J_{3,14\beta}$< 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 3.57 (1H, m, $J_{5,16}$= 6 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 4.08 (1H, d, $J_{20,21}$= 7 Hz, H-21), 4.78 (1H, d, $J_{16,17}$= 9 Hz, $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$~ 0.5 Hz, H-17), 6.67 (1H, H-12), 6.80 (1H, H-10), 7.08 (1H, H-9), 7.14 (1H, H-11). (*189*), see also (*75*), (*190*)
MS: 326 (M^+), 183, 182, 158, 157, 145, 144. (*75*)

(-)-Vinorine [(-)-**21**]:
^{1}H NMR (200 MHz, $CDCl_3$): 1.67 (3H, dt, J_1= 7 Hz, J_2= 2 Hz, H-18), 2.04 (2H, m), 2.08 (1H, br s), 2.16 (3H, s, -$OCOCH_3$), 2.54 (1H, t, J= 6.5 Hz), 2.78 (1H, dd, J_1= 12 Hz, J_2= 5 Hz), 3.37 (1H, br t, J= 4 Hz), 3.62 (1H, m), 3.72 (2H, br s, 2 x H-21), 4.46 (1H, br d, J= 7 Hz, H-3), 4.98 (1H, d, J= 1 Hz, H-17), 5.41 (1H, q, J= 7 Hz, H-19), 7.23, 7.40 (2H, dt, J_1= 8 Hz, J_2= 1 Hz, H-11, H-10), 7.45, 7.63 (2H, dd, J_1= 8 Hz, J_2= 1 Hz, H-12, H-9). (*178b*), see also (*81*)
MS: 334 (M^+), 291, 275, 182, 169, 168 (100%). (*81*), see also (*178b*)

(+)-17-*O*-Acetylnortetraphyllicine [(+)-**22**]:
^{1}H NMR: 1.76 (3H, d, J= 6 Hz), 5.65 (1H, m), 6.7-7.6 (5H, m, H-9, H-10, H-11, H-12, NH). (*19*)
MS: 336 (M^+, 100%), 321, 294, 293, 278, 277, 169, 168, 167, 144, 143, 130. (*17*), see also (*19*)

Rauflexine (**23**):
^{1}H NMR: 2.79 (3H, s, N-CH_3), 6.30 (2H, dd, J= 8.5 Hz, J= 2 Hz, H-10, H-12), 7.08 (1H, d, J= 8.5 Hz, H-9). (*82a*), see also (*82b*)
MS: 336 (M^+). (*82a*), see also (*82b*)

(+)-Purpeline [(+)-**24**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.65 (3H, d, H-18), 3.05 (3H, s, N-CH_3), 3.78 (3H, s, Ar-OCH_3), 5.30 (1H, q, H-19), 6.81 (3H, H-9, H-10, H-11). (*41*)
MS: 336 (M^+), 308, 307, 228, 213, 212, 187, 174. (*41*)

(+)-Seredamine [(+)-**25**]:
^{1}H NMR (100 MHz, CF_3COOH): 1.84 (3H, d, J= 6.5 Hz, H-18), 3.71 (3H, s, N-CH_3), 4.05 (3H, s, Ar-OCH_3), 4.75 (1H, br d, J= 10 Hz, H-2), 5.02 (1H, s, H-17), 5.76 (1H, q, J= 6.5 Hz, H-19), 7.20 (1H, dd, J_1= 7.5 Hz, J_2= 1.5 Hz, H-11 or H-9), 7.48 (1H, dd, J_1= 7.5 Hz, J_2= 1.5 Hz, H-9 or H-11), 7.63 (1H, t, J= 7.5 Hz, H-10). (*42*)
MS: 338 (M^+, 100%), 323, 307, 213, 197, 187, 174, 108. (*42*), see also (*41*)

Vincamajoreine (**26**):
^{1}H NMR: 1.65 (3H, d, J= 7 Hz, H-18), 2.75 (3H, s, N-CH_3), 3.78 (3H, s, Ar-OCH_3), 4.47 (1H, -OH), 5.25 (1H, q, J= 7 Hz, H-19), ~ 7 (3H, H-9, H-11, H-12). (*83*)
MS: 338 (M^+), 213, 212, 187, 174. (*83*)

(*continues*)

(+)-Reflexine [(+)-**27**]:
^{1}H NMR (100 MHz, $CDCl_3$): 1.63 (3H, d, J= 7 Hz, H-18), 2.78 (3H, s, N-CH_3), 3.77 (3H, s, Ar-OCH_3), 5.23 (1H, q, J= 7 Hz, H-19), 6.25 (1H, d, J= 2 Hz, H-12), 6.35 (1H, d, J= 8 Hz, H-10), 7.08 (1H, d, J= 2 Hz, H-9). (*82a*), (*82b*)
MS: 338 (M^+, 100%), 337, 293, 226, 213, 212. (*82a*)

(+)-Sandwicolidine [(+)-**28**]:
^{1}H NMR (300 MHz, $CDCl_3$): 0.95 (3H, t, H-18), 1.27 (2H, m, H-19), 2.74 (1H, m, H-20), 2.80 (3H, s, N-CH_3), 3.06 (3H, s, -OCH_3), 3.35 (2H, m, H-3, H-5), 3.74 (1H, dd, $J_{15,21}$= 4.5 Hz, $J_{20,21}$= 1 Hz, H-21), 4.8 (1H, d, J= 9 Hz, H-17), 6.67-7.25 (4H, m, H-9, H-10, H-11, H-12). (*85*)
MS: 340 (M^+), 312, 269, 213, 196 (100%), 168, 144. (*85*)

(+)-Ajmalinol [(+)-**29**]:
^{1}H NMR (CF_3COOD): 7.00 (1H, d, $J_{10,12}$= 2.5 Hz, $J_{9,12}$= 0.6 Hz, H-12), 7.6 (1H, def. q, $J_{9,10}$= 9 Hz, $J_{10,12}$= 2.5 Hz, H-10), 7.9 (1H, d, $J_{9,10}$= 9 Hz, $J_{9,12}$= 0.6 Hz, H-9). (*86*)
MS: 342 (M^+), 327, 324, 314, 313, 253, 216, 199, 198, 174, 160 (100%). (*86*)

(-)-Leepacine [(-)-**30**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.42 (1H, m, H-14α), 1.59 (3H, d, $J_{18,19}$= 6.1 Hz, H-18), 2.07 (1H, m, H-6α), 2.57 (1H, m, H-14α), 2.60 (1H, m, H-6β), 3.03 (1H, m, H-15), 3.24 (1H, ddd, $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$= 1 Hz, $J_{2,3}$< 1 Hz, H-3), 3.26 (1H, m, H-5), 3.45 (1H, d, $J_{21\alpha,21\beta}$= 15.1 Hz, H-21α), 3.60 (3H, s, -$COOCH_3$), 3.95 (1H, br s, H-2), 4.33 (1H, d, $J_{21\alpha,21\beta}$= 15.1 Hz, H-21β), 5.70 (1H, q, $J_{18,19}$= 6.1 Hz, H-19), 6.62 (1H, d, $J_{11,12}$= 7.6 Hz, H-12), 6.90 (1H, dd, $J_{9,10}$= 7.4 Hz, $J_{10,11}$= 7.1 Hz, H-10), 7.15 (1H, dd, $J_{11,12}$= 7.6 Hz, $J_{10,11}$= 7.1 Hz, H-11), 7.23 (1H, d, $J_{9,10}$= 7.4 Hz, H-9), 9.37 (1H, s, NH). (*87*)
MS: 350 (M^+), 322, 292, 291, 263, 214, 182, 167, 122 (100%). (*87*)

(+)-Perakine [(+)-**31**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.30 (3H, d, J= 6.7 Hz, H-18), 1.60 (1H, dddd, J_1= 14.8 Hz, J_2= 5.2 Hz, J_3= 2.0 Hz, J_4= 1.0 Hz, H-14), 1.66 (1H, d, J= 12.1 Hz, H-6), 1.77 (1H, dddd, J_1= 14.8 Hz, J_2= 9.2 Hz, J_3= 2.0 Hz, J_4= 1.0 Hz, H-14), 2.17 (1H, d, J= 9.3 Hz, H-20), 2.19 (3H, s, -$OCOCH_3$), 2.48 (1H, ddd, J_1= 7.0 Hz, J_2= 5.5 Hz, J_3= 1.7 Hz, H-16), 2.82 (1H, dd, J_1= 12.1 Hz, J_2= 5.3 Hz, H-6), 2.91 (1H, dd, J_1= 5.5 Hz, J_2= 5.2 Hz, H-15), 3.34 (1H, dq, J_1= 9.3 Hz, J_2= 6.7 Hz, H-19), 3.64 (1H, dd, J_1= 6.7 Hz, J_2= 5.3 Hz, H-5), 4.20 (1H, d, J= 9.1 Hz, H-3), 4.95 (1H, d, J= 1.7 Hz, H-17), 7.23 (1H, ddd, J_1= 7.7 Hz, J_2= 7.5 Hz, J_3= 1.1 Hz, H-10), 7.40 (1H, ddd, J_1= 7.8 Hz, J_2= 7.5 Hz, J_3= 1.0 Hz, H-11), 7.49 (1H, dd, J_1= 7.2 Hz, J_2= 1.5 Hz, H-9), 7.62 (1H, d, J= 7.8 Hz, H-12), 9.85 (1H, s, -CHO). (*89*), (*93*), see also (*88a*)
MS: 350 (M^+), 335, 321, 308, 291, 196, 182, 169, 168. (*88c*)

(-)-Vomilenine [(-)-**32**]:
^{1}H NMR (500 MHz, $CDCl_3$)[a]: 1.68 (3H, d, J= 6.6 Hz, H-18), 2.17 (3H, s, -$OCOCH_3$), 2.77 (1H, dd, J= 12.1 Hz, J= 4.7 Hz, H-6β), 3.28 (1H, m, H-15), 3.92 (1H, t, J= 5.8 Hz, H-5), 4.31 (1H, dd, J= 7.1 Hz, J=2.8 Hz, H-3), 4.98 (1H, s, H-17), 5.03 (1H, br s, H-21), 5.75 (1H, q, J= 6.6 Hz, H-19), 6.06 (1H, br s, -OH). (*168b*), see also (*95*)
MS[a]: 350 (M^+), 169 (100%). (*168b*)

Raucaffriline (**33**):
^{1}H NMR: No data available.
MS: No data available.

17-O-Acetyltetraphyllicine (**34**):
^{1}H NMR: No data available.
MS: 350 (M^+, 100%), 307, 291, 183, 182, 158, 157, 144. (*136b*)

(+)-Raucaffrinoline [(+)-**35**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.28 (3H, d, J= 6.8 Hz, H-18), 1.51 (1H, ddd, J_1= 9.3 Hz, J_2= 8.6 Hz, J_3= 5.1 Hz, H-20), 1.54 (1H, dd, J_1= 14.7 Hz, J_2= 5.5 Hz, H-14), 1.64 (1H, d, J= 12.1 Hz, H-6), 1.95 (1H, dd, J_1= 14.7 Hz, J_2= 9.3 Hz, H-14), 2.38 (1H, ddd, J_1= 6.5 Hz, J_2= 5.5 Hz, J_3= 1.5 Hz, H-16), 2.49 (1H, dd, J_1= J_2= 5.5 Hz, H-15), 2.54 (1H, dd, J_1= 9.3 Hz, J_2= 6.7 Hz, H-19), 2.81 (1H, dd, J_1= 12.1 Hz, J_2= 5.1 Hz, H-6), 3.66 (1H, dd, J_1= 6.5 Hz, J_2= 5.1 Hz, H-5), 3.75 (2H, dd, J_1= 11.0 Hz, J_2= 5.2 Hz, H-21), 4.13 (1H, d, J= 9.3 Hz, H-3), 5.00 (1H, d, J= 1.2 Hz, H-17), 7.22 (1H, ddd, J_1= J_2= 7.3 Hz, J_3= 1.2 Hz, H-10), 7.39 (1H, ddd, J_1= J_2= 8.0 Hz, J_3= 1.2 Hz, H-11), 7.47 (1H, dd, J_1= 7.0 Hz, J_2= 1.5 Hz, H-9), 7.61 (1H, d, J= 7.6 Hz, H-12). (*89*), see also (*97*)
MS: 352 (M^+), 351, 337, 335, 322, 321 (100%), 306, 293, 292, 280, 279, 264, 263, 262, 261, 250, 249, 248, 247, 238, 234, 233, 232, 223, 197, 194, 193, 192, 191, 182, 181, 180, 169, 168, 154, 152, 150, 130, 129, 121, 115. (*96*)

(+)-Quebrachidine [(+)-**36**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.42 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 2 Hz, H-14α), 1.58 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 1.65 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.49 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$~ 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 2.55 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 3.23 (1H, def, H-21α), 3.25 (1H, def, H-21β), 3.30 (1H, dd(d), $J_{3,14\alpha}$= 10 Hz, $J_{2,3}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-3), 3.43 (1H, d(d), $J_{14\beta,15}$~ 5 Hz, $J_{14\alpha,15}$~ 2 Hz, H-15), 3.44 (1H, d(d), $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.63 (3H, s, -$COOCH_3$), 3.67 (1H, d, $J_{2,3}$= 5 Hz, H-2), 4.18 (1H, s, H-17), 5.22 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 6.72 (1H, H-12), 6.74 (1H, H-10), 7.05 (1H, H-11), 7.19 (1H, H-9). (*189a*)
MS: 352 (M^+, 100%), 222, 190, 143, 130. (*105b*), see also (*201*)

(*continues*)

(+)-Vincarine [(+)-**37**][b]:
^{1}H NMR: No data available.
MS: 352 (M^+, 100%), 222, 190, 143, 130. (*112*)

19,20-Dihydrovomilenine (**38**):
^{1}H NMR: No data available.
MS: No data available.

(+)-Vomalidine [(+)-**39**]:
^{1}H NMR: No data available.
MS: 354 (M^+), 326, 325, 228, 213, 212 188, 187, 175, 174 (100%). (*203*), see also (*205*)

12-Methoxyajmaline (**40**):
^{1}H NMR: No data available.
MS: 356 (M^+), 341, 327, 230, 213, 212, 200, 199, 198, 182, 174, 173, 131, 130. (*115*)

(+)-10-Methoxyvinorine [(+)-**41**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.66 (3H, d, $J_{18,19}$= 6.6 Hz, H-18), 1.67 (1H, d, $J_{6\alpha,6\beta}$= 11.7 Hz, H-6α), 1.91 (2H, br t, J_1= J_2= 3.9 Hz, H-14α, H-14β), 2.16 (3H, s, -$OCOCH_3$), 2.41 (1H, br dd, J_1= J_2= 6.1 Hz, H-16), 2.70 (1H, dd, $J_{6\alpha,6\beta}$= 11.7 Hz, J_2= 5.1 Hz, H-6β), 3.25 (1H, m, H-15), 3.38 (1H, br t, J_1= J_2= 5.1 Hz, H-5), 3.52 (2H, m, H-21α, H-21β), 3.81 (3H, s, Ar-OCH_3), 4.17 (1H, t, $J_{3,14\alpha}$= J_2= 5.5 Hz, H-3), 5.03 (1H, s, H-17), 5.29 (1H, q, $J_{18,19}$= 6.6 Hz, H-19), 6.89 (1H, dd, $J_{11,12}$= 8.4 Hz, $J_{9,11}$= 2.7 Hz, H-11), 7.02 (1H, d, $J_{9,11}$= 2.7 Hz, H-9), 7.50 (1H, d, $J_{11,12}$= 8.4 Hz, H-12). (*118*)
MS: 364 (M^+, 100%), 349, 321, 305, 265, 212, 198, 183. (*118*), see also (*117*)

(-)-Vincamajine [(-)-**42**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.46 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 1.46 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 2 Hz, H-14α), 1.57 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 2.41 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 2.56 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 2.58 (3H, s, N-CH_3), 3.15 (1H, d, $J_{2,3}$= 5 Hz, H-2), 3.34 (2H, def, H-21α, H-21β), 3.45 (1H, dd(d), $J_{3,14\alpha}$= 10 Hz, $J_{2,3}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-3), 3.47 (1H, d(d), $J_{14\beta,15}$= 5 Hz, $J_{14\alpha,15}$~ 2 Hz, H-15), 3.49 (1H, d(d), $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.65 (3H, s, -$COOCH_3$), 4.21 (1H, s, H-17), 5.24 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 6.63 (1H, H-12), 6.78 (1H, H-10), 7.15 (1H, H-9), 7.16 (1H, H-11). (*189a*), see also (*121*), (*124b*), (*190*)
MS: 366 (M^+), 334, 291, 263, 222, 190, 157 (100%), 148, 131, 115, 97, 83. (*124a*)

Vincamajinine (**43**):
^{1}H NMR: 1.62 (3H, d, H-18), 2.64 (3H, s, N-CH_3), 3.69 (3H, s, -$COOCH_3$), 5.31 (1H, q, H-19). (*132*)
MS: 366 (M^+), 222, 190, 158, 157 (100%), 144. (*132*)

17-O-Acetylajmaline (**44**):
^{1}H NMR (400 MHz, 52°C, $CDCl_3$): 0.95 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.37 (1H, m, H-19'), 1.47 (1H, m, H-19), 1.52 (1H, m, H-20), 1.62 (1H, ddd, $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$~ 4 Hz, $J_{3,14\beta}$< 1 Hz, H-14β), 1.85 (1H, m, $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$< 1 Hz, H-14α), 1.89 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 2.07 (1H, dd(d), $J_{5,16}$= 6 Hz, $J_{15,16}$~ 4 Hz, $J_{16,17}$~ 0.5 Hz, H-16), 2.15 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.19 (3H, s, -$OCOCH_3$), 2.44 (1H, *m*, $J_{14\beta,15}$= $J_{15,16}$~ 4 Hz, $J_{15,20}$~ 3 Hz, $J_{14\alpha,15}$< 1 Hz, H-15), 2.72 (1H, *s(d)*, $J_{2,6\beta}$~ 0.5 Hz ,$J_{2,3}$< 0.5 Hz, H-2), 2.78 (1H, s, N-CH_3), 3.06 (1H, m, $J_{5,16}$= 6 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.65 (1H, d(dd), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$< 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 4.33 (1H, s(d), $J_{20,21}$< 1 Hz, H-21), 5.28 (1H, s(d), $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$~ 0.5 Hz, H-17), 6.66 (1H, d, H-12), 6.78 (1H, dd, H-10), 7.15 (1H, dd, H-11), 7.26 (1H, d, H-9). (*189a*), see also (*190*)
MS: 368 (M^+), 325, 195, 182, 157, 144 (100 %). (*206*)

(-)-10-Methoxyperakine [(-)-**45**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.29 (3H, d, $J_{18,19}$= 6.7 Hz, H-18), 1.61 (1H, m, H-14α), 1.65 (1H, m, H-14β), 1.67 (1H, d, $J_{6\alpha,6\beta}$= 4.2 Hz, H-6α), 2.15 (1H, m, H-20), 2.17 (3H, s, -$OCOCH_3$), 2.45 (1H, t, $J_{5,16}$= 5.8 Hz, $J_{15,16}$= 5.5 Hz, H-16), 2.74 (1H, dd, $J_{5,6\beta}$= 11.9 Hz, $J_{6\alpha,6\beta}$= 4.2 Hz, H-6β), 2.86 [1H, t-like, $J_{15,16}$= 5.40 Hz, $J_{14\beta,15}$= 5.38 Hz (*sic!*), H-15), 3.31 (1H, m, H-19), 3.60 (1H, dd, $J_{5,6\beta}$= 11.9 Hz, $J_{5,16}$= 6.0 Hz, H-5), 3.82 (3H, s, Ar-OCH_3), 4.16 (1H, d, $J_{3,14\alpha}$= 9.2 Hz, H-3), 4.97 (1H, s, H-17), 6.91 (1H, dd, $J_{11,12}$= 8.5 Hz, $J_{9,11}$= 2.6 Hz, H-11), 7.02 (1H, d, $J_{9,11}$= 2.6 Hz, H-9), 7.51 (1H, d, $J_{11,12}$= 8.5 Hz, H-12), 9.83 (1H, s, CHO). (*118*)
MS: 380 (M^+), 365, 351, 337, 321, 281, 226, 198. (*118*)

Majorinine (**46**):
^{1}H NMR (360 MHz, $CDCl_3$): 1.67 (3H, dd, J_1= 6.5 Hz, J_2 ~ 2 Hz, H-18), 1.67 (1H, ddd, J_1= 12 Hz, J_2≈ 1.5 Hz, J_3< 0.5 Hz, H-6α), 1.95 (2H, m, H-14α, H-14β), 2.19 (3H, s, -$COOCH_3$), 2.37 (1H, ddd, J_1= J_2= 6 Hz, J_3< 0.5 Hz, H-16), 2.71 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6β), 3.28 (1H, ddd, J_1= J_2= 6 Hz, J_3< 0.5 Hz, H-15), 3.82 (3H, s, Ar-OCH_3), 3.85 (1H, ddd, J_1= 6 Hz, J_2= 5 Hz, J_3< 0.5 Hz, H-5), 4.30 (1H, dd, J_1= 7 Hz, J_2= 3 Hz, H-3), 4.98 (1H, br s, H-17), 4.98 (1H, m, H-21), 5.70 (1H, qd, J_1= 6.5 Hz, J_2 ~ 2 Hz, H-19), 6.90 (1H, dd, J_1= 8.5 Hz, J_2= 2.3 Hz, H-11), 7.02 (1H, d, J= 2.3 Hz, H-9), 7.53 (1H, d, J= 8.5 Hz, H-12). (*130b*)
MS: 380 (M^+, 100%), 362, 352, 351, 350, 337, 321, 213, 199. (*130b*)

(*continues*)

TABLE III (*Continued*)

(-)-Majoridine [(-)-**47**]:
^{1}H NMR (60 MHz, $CDCl_3$): ~1.73 (3H, d, J= 6.6 Hz, H-18), 2.22 (3H, s, -$OCOCH_3$), 2.78 (3H, s, -N-CH_3), 3.76 (3H, s, Ar-OCH_3), 5.0-5.4 (1H, m, H-19), 5.23 (1H, s, H-17), 6.35-6.76 (3H, m, H-9, H-11, H-12). (*136c*), see also (*136b*)
MS: 380 (M^+, 100%), 337, 321, 213, 212, 188, 187, 174. (*136c*)

19-Hydroxy-19,20-dihydrovincamajine (**48**):
^{1}H NMR (60 MHz, $CDCl_3$): 1.0 (3H, d, J= 7 Hz, H-18), 2.6 (3H, s, N-CH_3), 3.2 (1H, d, H-2), 3.3 (1H, m, H-3), 3.5 (2H, m, 2 x H-21), 3.6 (1H, d, H-15), 3.7 (3H, s, -$COOCH_3$), 5.3 (1H, s, H-17), 7.1-8. (*124c*)
MS: 384 (M^+), 366, 349, 222, 190, 157 (100%), 144. (*124c*)

21-Acetyl-19,20-dihydrovomilenine (**49**):
^{1}H NMR (400 MHz, $CDCl_3$): 0.96 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.45 (1H, m, H-19'), 1.51 (1H, m, H-20), 1.66 (1H, m, H-19), 1.69 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 1.82 (2H, def, H-14α, H-14β), 2.09 (3H, s, -$OCOCH_3$), 2.15 (3H, s, -$OCOCH_3$), 2.28 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{15,16}$~ 5 Hz, $J_{16,17}$~ 0.5 Hz, H-16), 2.49 (1H, m, $J_{15,16}$~ 5 Hz, $J_{14\beta,15}$~ 4 Hz, $J_{15,20}$~ 3 Hz, $J_{14\alpha,15}$< 1 Hz, H-15), 2.78 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 3.40 (1H, dd(d), $J_{5,16}$= 7 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 4.26 (1H, d(d), $J_{3,14\alpha}$= 9 Hz, $J_{3,14\beta}$= 2.5 Hz, $J_{2,3}$< 0.5 Hz, H-3), 5.00 (1H, s(d), $J_{20,21}$< 0.5 Hz, H-21), 5.36 (1H, s(d), $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$~ 0.5 Hz, H-17), 7.21 (1H, dd, H-11), 7.39 (1H, dd, H-10), 7.47 (1H, d, H-12), 7.61 (1H, d, H-9). (*189a*)
MS: 394 (M^+), 365, 351, 335 (100%), 322, 321, 292, 291, 275, 263, 249, 225, 221, 206, 196, 182, 181, 180, 169, 168 156, 144, 143, 130, 115. (*79*)

(±)-Norvincamedine [(±)-**50**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.52 (3H, dd, J_1~ 6.6 Hz, J_2~ 1.6 Hz, H-18), 1.83 (3H, s, -$OCOCH_3$), 3.65 (3H, s, -$COOCH_3$), 5.28 (1H, q, J~ 6.6 Hz, H-19), 5.72 (1H, s, H-17), 6.5-7.28 (4H, m, H-9, H-10, H-11, H-12). (*122*)
MS: 394 (M^+, 100%), 335, 264, 222, 190, 169, 168, 156, 144, 143, 130. (*122*)

(±)-10-Methoxyvincamajine [(±)-**51**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.57 (3H, d, J= 7 Hz, H-18), 2.56 (3H, s, N-CH_3), 3.68 (3H, s, Ar-OCH_3), 3.70 (3H, s, -$COOCH_3$), 4.12 (1H, s, H-17), 5.15 (1H, m, H-19), 6.53-6.83 (3H, H-9, H-11, H-12). (*138b*)
MS: 396 (M^+, 100%), 222, 190, 187, 174. (*138b*)

(-)-11-Methoxyvincamajine [(-)-**52**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.49 (1H, dd, J= 14 Hz, J= 10 Hz, H-14'), 1.69 (1H, d, J= 7 Hz, H-18), 1.71 (1H, d, J= 12 Hz, H-6'), 2.40 (1H, dd, J= 14 Hz, J= 5 Hz, H-14), 2.60 (1H, dd, J= 12 Hz, J= 5 Hz, H-6), 2.68 (3H, s, N-CH_3), 3.21 (1H, d, J= 5 Hz, H-2), 3.42 (2H, m, 2 x H-21), 3.48 (1H, d, J= 4 Hz, H-15), 3.51 (1H, d, J= 5 Hz, H-3), 3.59 (1H, d, J= 5 Hz, H-5), 3.69 (3H, s, -$COOCH_3$), 3.78 (3H, s, Ar-OCH_3), 4.15 (1H, s, H-17), 5.24 (1H, q, J= 7 Hz, H-19), 6.21 (1H, d, J= 2 Hz, H-12), 6.30 (1H, dd, J= 8 Hz, J= 2 Hz, H-10), 7.02 (1H, d, J= 8 Hz, H-9). (*139*)
MS: 396 (M^+), 222, 190, 187 (100%), 174. (*139*)

(-)-11-Methoxy-17-epivincamajine [(-)-**53**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.49 (1H, dd, J= 14 Hz, J= 10 Hz, H-14'), 1.59 (1H, d, J= 7 Hz, H-18), 1.71 (1H, d, J= 12 Hz, H-6'), 2.24 (1H, dd, J= 12 Hz, J= 5 Hz, H-6), 2.72 (3H, s, -N-CH_3), 2.92 (1H, dd, J= 14 Hz, J= 5 Hz, H-14), 3.37 (1H, d, J= 5 Hz, H-2), 3.42 (1H, d, J= 5 Hz, H-15), 3.48 (2H, m, 2 x H-21), 3.49 (1H, d, J= 5 Hz, H-5), 3.61 (1H, dd, J= 10 Hz, J= 5 Hz, H-3), 3.68 (3H, s, -$COOCH_3$), 3.78 (3H, s, Ar-OCH_3), 3.98 (1H, s, H-17), 5.24 (1H, q, J= 7 Hz, H-19), 6.31 (1H, d, J= 2 Hz, H-12), 6.35 (1H, dd, J= 8 Hz, J= 2 Hz, H-10), 6.95 (1H, d, J= 8 Hz, H-9). (*139*)
MS: 396 (M^+), 368, 222, 190, 187 (100%), 174. (*139*)

(-)-Vincamedine [(-)-**54**]:
^{1}H NMR (400 MHz, $CDCl_3$): 1.54 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$~ 2 Hz, H-14α), 1.55 (1H, br d, $J_{18,19}$= 7 Hz, H-18), 1.81 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 1.85 (3H, s, -$OCOCH_3$), 2.54 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, H-6β), 2.63 (1H, dd(d), $J_{14\alpha,14\beta}$= 14 Hz, $J_{14\beta,15}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-14β), 2.64 (3H, s, N-CH_3), 3.23 (1H, d, $J_{2,3}$= 5 Hz, H-2), 3.47 (1H, def, H-21α), 3.49 (1H, def, H-21β), 3.50 (1H, d(d), $J_{14\beta,15}$= 5 Hz, $J_{14\alpha,15}$~ 2 Hz, H-15), 3.58 (1H, dd(d), $J_{3,14\alpha}$= 10 Hz, $J_{2,3}$= 5 Hz, $J_{3,14\beta}$~ 1 Hz, H-3), 3.63 (1H, d(d), $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.64 (3H, s, -$COOCH_3$), 5.29 (1H, br q, $J_{18,19}$= 7 Hz, H-19), 5.67 (1H, s, H-17), 6.66 (1H, H-12), 6.73 (1H, H-10), 6.98 (1H, H-9), 7.17 (1H, H-11). (*189a*), see also (*190*)
MS: 408 (M^+, 100%), 349, 264, 222, 190, 157, 144. (*105b*)

Ajmalinimine (**55**):
^{1}H NMR: 0.95 (3H, t, J= 7.0 Hz, H-18), 1.41 (2H, m, H-19), 1.68 (1H, ddd, J_1= 13.6 Hz, J_2= 5.5 Hz, J_3= 1.0 Hz, H-14β), 1.85 (1H, m, H-14α), 1.88 (1H, dd, J_1= 11.5 Hz, J_2= 5.3 Hz, H-6β), 2.15 (1H, dd, J_1= 11.5 Hz, J_2= 1.0 Hz, H-6α), 2.21 (3H, s, -$OCOCH_3$), 2.35 (1H, m, H-15), 2.46 (3H, s, -$COCH_3$), 2.88 (3H, s, N-CH_3), 2.98 (1H, br s, H-2β), 3.05 (2H, m, H-5), 3.70 (1H, br d, J= 10.2 Hz, H-3α), 4.26 (1H, br s, H-21β), 5.32 (1H, s, H-17), 6.71 (1H, d, J= 8.3 Hz, H-12), 7.83 (1H, dd, J_1= 8.3 Hz, J_2= 1.7 Hz, H-11), 7.90 (1H, d, J= 1.7 Hz, H-9). (*143*)
MS: 410 (M^+), 395, 367, 352, 339, 309, 279, 242, 224, 200, 199, 186, 182 (100%). (*143*)

(*continues*)

17,21-O-Diacetylajmaline (**56**):
^{1}H NMR (400 MHz, $CDCl_3$): 0.95 (1H, t, $J_{18,19}$= $J_{18,19'}$= 7 Hz, H-18), 1.40 (1H, m, H-19'), 1.47 (1H, m, H-20), 1.70 (1H, m, H-19), 1.74 (1H, dd(d), $J_{14\beta,15}$~ 4 Hz, $J_{3,14\beta}$< 1 Hz, H-14β), 1.77 (1H, m, $J_{3,14\alpha}$= 10 Hz, $J_{14\alpha,15}$< 1 Hz, H-14α), 1.93 (1H, dd, $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\beta}$= 5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-6β), 2.07 (1H, dd(d), $J_{5,16}$= 6 Hz, $J_{15,16}$~ 4 Hz, $J_{16,17}$~ 0.5 Hz, H-16), 2.10 (3H, s, -$OCOCH_3$), 2.15 (1H, d(d), $J_{6\alpha,6\beta}$= 12 Hz, $J_{5,6\alpha}$~ 1 Hz, H-6α), 2.21 (3H, s, -$OCOCH_3$), 2.50 (1H, m, $J_{14\beta,15}$= $J_{15,16}$~ 4 Hz, $J_{15,20}$~ 3 Hz, $J_{14\alpha,15}$< 1 Hz, H-15), 2.72 (1H, s(d), $J_{2,3}$< 0.5 Hz, $J_{2,6\beta}$~ 0.5 Hz, H-2), 2.78 (1H, s, N-CH_3), 3.05 (1H, dd(d), $J_{5,16}$= 6 Hz, $J_{5,6\beta}$= 5 Hz, $J_{5,6\alpha}$~ 1 Hz, H-5), 3.63 (1H, d(dd), $J_{3,14\alpha}$= 10 Hz, $J_{3,14\beta}$< 1 Hz, $J_{2,3}$< 0.5 Hz, H-3), 5.25 (1H, s(d), $J_{20,21}$< 0.5 Hz, H-21), 5.28 (1H, s(d), $J_{6\alpha,17}$~ 1 Hz, $J_{16,17}$~ 0.5 Hz, H-17), 6.68 (1H, d, H-12), 6.81 (1H, dd, H-10), 7.18 (1H, dd, H-11), 7.30 (1H, d, H-9). (*189a*)
MS: 410 (M^+), 395, 368, 367, 326 (100%), 325, 200, 199, 183, 182, 158, 144, 130. (*24*)

(-)-Vincawajine [(-)-**57**]:
^{1}H NMR (500 MHz, $CDCl_3$): 1.44 (3H, m, H-18), 1.66 (1H, m, H-14α), 1.69 (1H, m, H-20), 1.73 (1H, m, H-6α), 2.03 (1H, m, H-14β), 2.06 (3H, s, -$OCOCH_3$), 2.16 (3H, s, -$OCOCH_3$), 2.45 (1H, m, H-15), 2.48 (1H, m, H-16), 2.79 (1H, dd, $J_{5,6\beta}$= 12.45 Hz, $J_{6\alpha,6\beta}$= 4.25 Hz, H-6β), 2.79 (1H, m, H-19), 3.80 (1H, s, Ar-OCH_3), 3.85 (1H, m, H-5), 4.16 (2H, ddd, $J_{21\alpha,21\beta}$= 20.15 Hz, $J_{21\alpha,21\beta}$= 11.45 Hz, $J_{20,21\alpha}$= 8.7 Hz, H-21), 4.32 (1H, br s, H-3), 4.93 (1H, s, H-17), 6.90 (1H, dd, $J_{11,12}$= 8.5 Hz, $J_{9,11}$= 2.6 Hz, H-11), 7.02 (1H, d, $J_{9,11}$= 2.6 Hz, H-9), 7.51 (1H, d, $J_{11,12}$= 8.5 Hz, H-12). (*118*)
MS: 424 (M^+), 381, 365 (100%), 351, 226, 198. (*118*)

(-)-10-Methoxyvincamedine [(-)-**58**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.55 (3H, d, J= 7 Hz), 1.85 (3H, s), 2.65 (3H, s), 3.6 (3H, s), 3.7 (3H, s), 5.25 (1H, q, J= 7 Hz), 5.68 (1H, s). (*104*)
MS: 438 (M^+, 100%), 423, 379, 264, 222, 200, 190, 187, 174. (*104*)

(-)-11-Methoxyvincamedine [(-)-**59**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.55 (1H, m, H-14), 1.61 (3H, d, J= 6.8 Hz, H-18), 1.79 (1H, br d, J= 12 Hz, H-6), 1.88 (3H, s, -$OCOCH_3$), 2.54 (1H, dd, J= 12 Hz, J= 5 Hz, H-6), 2.62 (1H, m, H-14), 2.64 (3H, s, N-CH_3), 3.22 (1H, d, J= 4.9 Hz, H-2), 3.47 (2H, m, 2 x H-21), 3.62 (1H, d, J= 5 Hz, H-5), 3.65 (3H, s, -$COOCH_3$), 3.78 (3H, s, Ar-OCH_3), 5.29 (1H, br q, J= 6.8 Hz, H-19), 5.63 (1H, d, J= 1.3 Hz, H-17), 6.22 (2H, m, H-10, H-12), 6.85 (1H, m, H-9). (*152*)
MS: 438 (M^+), 395, 380, 264, 222, 200, 190, 187, 174 (100%). (*152*)

(-)-10-Methoxyvincamedine *N*-oxide [(-)-**60**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.55 (3H, d, J= 7 Hz, H-18), 1.85 (3H, s, -$OCOCH_3$), 2.6 (3H, s, N-CH_3), 3.65 (3H, s, -$COOCH_3$), 3.7 (3H, s, Ar-OCH_3), 5.4 (1H, q, J= 7 Hz, H-19), 5.65 (1H, s, H-17). (*104*)
MS: 454 (M^+), 438 (100%), 379, 264, 222, 212, 200, 190, 187, 174. (*104*)

(-)-17-*O*-Benzoylvincamajine [(-)-**61**]:
^{1}H NMR (60 MHz, $CDCl_3$): 1.60 (3H, d, J= 6.5 Hz, H-18), 2.72 (3H, s, N-CH_3), 3.43 (3H, s, Ar-OCH_3), 3.55 (2H), 5.34 (1H, q, J= 6.5 Hz, H-19), 6.3-8.1 (9H, m, H-9, H-10, H-11, H-12, 5 x Bz-H). (*144*)
MS: 470 (M^+), 439, 411, 365, 349, 326, 294, 157, 144, 105, 77. (*144*)

Norrauvomitine (**62**):
^{1}H NMR: No data available.
MS: 488 (M^+), 350, 336, 307, 291, 277, 195 (100%), 182, 181, 160, 157, 144. (*33b*)

(-)-Rauvomitine [(-)-**63**]:
^{1}H NMR: No data available.
MS: No data available.

(+)-Raucaffricine [(+)-**64**]:
^{1}H NMR (300 MHz, pyridine-d_5)[a]: 1.50 (3H, d, J= 6.5 Hz, H-18), 1.69 (1H, d, J= 11.5 Hz, H-6), 1.84 (1H, dd, J_1= 13.5 Hz, J_2= 5 Hz, H-14), 2.16 (3H, s, -$OCOCH_3$), 2.4 (1H, t, J= 6 Hz, H-16), 2.74 (1H, dd, J_1= 11.5 Hz, J_2= 4.5 Hz, H-6), 3.24 (2H, m, H-5, H-15), 3.94 (1H, m, H-5), 4.1 (1H, t, J= 8 Hz H-2'), 4.2-4.35 (2H, m, H-3', H-4'), 4.33 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6'), 4.52 (1H, dd, J_1= 12 Hz, J_2= 2 Hz, H-6'), 5.14 (1H, d, J= 9.5 Hz, H-3), 5.23 (1H, s, H-17), 5.29 (1H, d, J= 8 Hz, H-1'), 5.43 (1H, br s, H-21), 5,86 (1H, q, J= 6.5 Hz, H-19), 7.28 (1H, t, J= 8 Hz, H-11), 7.42 (1H, t, J= 8 Hz, H-10), 7.66 (1H, d, J= 8 Hz, H-12), 7.81 (1H, d, J= 8 Hz, H-9). (*155b*), see also (*155a*)
MS (EI)[a]: 351 (M^+ - $C_6H_{11}O_6$), 291, 273, 183, 170, 169 (100%), 168, 167, 156, 107, 106. (*155b*)
MS (CI)[a]: 569 ($M + C_4H_9)^+$, 513 [(M + H), 100%]. (*155b*)

(+)-Ajmalimine [(+)-**65**]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.02 (3H, t, J= 7 Hz, H-18), 1.40 (2H, m, 2 x H-19), 2.02 (1H, ddd, $J_{5,16}$= 5.9 Hz, $J_{15,16}$= 4.5 Hz, $J_{16,17}$= 0.5 Hz, H-16), 2.41 (1H, dddd, $J_{15,16}$= 4.5 Hz, $J_{14\beta,15}$= 4.2 Hz, $J_{15,20}$= 3 Hz, $J_{14\alpha,15}$= 1.1 Hz, H-15), 2.68 (1H, br s, H-2), 2.75 (3H, s, N-CH_3), 3.67 (1H, ddd, $J_{3,14\alpha}$= 10.4 Hz, $J_{3,14\beta}$= 1.1 Hz, $J_{2,3}$= 0.5 Hz, H-3), 3.90 (6H, s, C3'-OCH_3, C5'-OCH_3), 3.92 (3H, s, C4'-OCH_3), 4.50 (1H, br s, H-17), 5.43 (1H, br s, H-21), 6.66 (1H, dd, $J_{11,12}$= 8.6 Hz, $J_{10,12}$= 1.2 Hz, H-12), 6.80 (1H, ddd, $J_{9,10}$= $J_{10,11}$= 8.6 Hz, $J_{10,12}$= 1.2 Hz, H-10), 7.16 (1H, ddd, $J_{10,11}$= $J_{11,12}$= 8.6 Hz, $J_{9,11}$= 1.2 Hz, H-11), 7.31 (2H, s, H2', H6'), 7.46 (1H, dd, $J_{9,10}$= 8.6 Hz, $J_{9,11}$= 1.2 Hz, H-9). (*147*), see also (*143*)
MS: 520 (M^+), 325 (100%), 297, 226, 212, 198, 182, 160, 158, 144. (*147*), see also (*143*)

(*continues*)

TABLE III (*Continued*)

17-*O*-(3',4',5'-Trimethoxybenzoyl)ajmaline (**66**):
^{1}H NMR (60 MHz, $CDCl_3$): 1.25 (3H, d, H-18), 2.76 (3H, m, N-CH_3), 3.62 (1H, s, H-2), 3.45, 3.85 (9H, C3'-OCH_3, C4'-OCH_3, C5'-OCH_3), 6.95-7.25 (4H, H-9, H-10, H-11, H-12). (*148*)
MS: 520 (M^+), 505, 488, 325, 309, 297, 296, 189, 195 (100%), 182, 181, 168, 157, 144, 143. (*148*), see also (*38*)

(-)-17-*O*-(3',4'-Dimethoxybenzoyl)vincamajine [(-)-**67**]:
^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): 1.55 (3H, dd, J_1= 7 Hz, J_2= 1 Hz, H-18), 1.59 (1H, dd, J_1= 14 Hz, J_2= 11 Hz, H-14), 1.88 (1H, d, J= 12 Hz, H-6), 2.68 (3H, s, N-CH_3), 2.71 (1H, dd, J_1= 14 Hz, J_2= 5 Hz, H-14), 2.72 (1H, dd, J_1= 12 Hz, J_2= 4 Hz, H-6), 3.24 (1H, d, J= 5 Hz, H-2), 3.48 (H, br s, H-21), 3.55-3.60 (2H, m, H-3, H-15), 3.69 (1H, d, J= 4 Hz, H-5), 3.89 (3H, s, -$COOCH_3$), 3.90 (3H, s, C3'-OCH_3), 3.93 (3H, s, C4'-OCH_3), 5.29 (1H, br q, J= 7 Hz, H-19), 5.90 (1H, br s, H-17), 6.52 (1H, br t, J= 7 Hz, H-10), 6.66 (1H, br d, J= 7 Hz, H-12), 6.86 (1H, br d, J= 7 Hz, H-9), 6.88 (1H, d, J= 8 Hz, H-5'), 7.10 (1H, br t, J=7 Hz, H-11), 7.38 (1H, d, J= 2 Hz, H-2'), 7.54 (1H, dd, J_1= 8 Hz, J_2= 2 Hz, H-6'). (*124b*)
MS (FAB): 530 (M^+), 365, 349, 165 (100%), 144. (*124b*)

17-*O*-(3',4',5'-Trimethoxybenzoyl)seredamine (**68**):
^{1}H NMR: No data available.
MS: 532 (M^+, 100%), 337, 323, 307, 213, 197, 195, 187, 174, 108. (*14*)

4'-Hydroxy-3',5'-dimethoxybenzolyvincamajine (**69**):
^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (3H, d, J= 7 Hz, H-18), 2.69 (3H, s, N-CH_3), 3.41 (3H, s, -$COOCH_3$), 3.92 (6H, s, C3'-OCH_3, C5'-OCH_3), 5.37 (1H, q, H-19), 5.88 (1H, s, H-17), 6.56 (1H, t, J= 7 Hz, H-11), 6.65 (1H, d, J= 7 Hz, H-12), 6.85 (1H, d, J= 7 Hz, H-9), 7.13 (1H, t, J= 7 Hz, H-10), 7.15 (2H, s, J= 7 Hz, H-2', H-6'). (*149*)
MS: 546 (M^+), 365, 349, 338, 197, 181 (100%), 157, 153, 144. (*149*)

(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)quebrachidine [(-)-**70**]:
^{1}H NMR (100 MHz, $CDCl_3$): 1.56 (3H, br d, J= 6 Hz, H-18), 3.41 (3H, s, -$COOCH_3$), 3.88 (6H, s, 2 x -OCH_3), 3.91 (3H, s, -OCH_3), 5.28 (1H, br q, J= 6 Hz, H-19), 5.91 (1H, s, H-17), 7.13 (2H, s, H-2', H-6'), 6.40-7.20 (4H, m, H-9, H-10, H-11, H-12). (*120*)
MS: 546 (M^+), 515, 416, 351, 335, 195 (100%), 167, 143, 130. (*120*)

(-)-1-*N*-(3',4',5'-Trimethoxybenzoyl)quebrachidine [(-)-**71**]:
^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$): 1.58 (1H, dd, J_1= 15 Hz, J_2= 9 Hz, H-14), 1.60 (3H, br d, J= 7 Hz, H-18), 1.75 (1H, d, J= 12 Hz, H-6), 2.22 (1H, dd, J_1= 15 Hz, J_2= 5 Hz, H-14), 2.69 (1H, dd, J_1= 12 Hz, J_2= 4 Hz, H-6), 3.43 (2H, br s, H-21), 3.55-3.58 (1H, m, H-15), 3.58 (1H, d, J= 4 Hz, H-5), 3.72 (3H, s, $-COOCH_3$), 3.84 (6H, br s, 2x $-OCH_3$), 3.92 (3H, s, $-OCH_3$), 4.25 (1H, d, J= 4 Hz, H-2), 4.33 (1H, m, H-3), 4.38 (1H, br s, H-17), 5.29 (1H, br q, J= 7 Hz, H-19), 6.39 (1H, m, H-12), 6.93 (2H, br s, H-2', H-6'), 6.97-7.00 (2H, m, H-10, H-11), 7.29 (1H, dd, J_1= 6 Hz, J_2= 3 Hz, H-9). (*124b*)
MS (FAB): 547 (M^+ + H), 413, 195 (100%), 176, 149. (*124b*)

(-)-17-*O*-(3',4',5'-Trimethoxybenzoyl)vincamajine [(-)-**72**]:
^{1}H NMR: 1.54 (3H, d, J~ 7 Hz, H-18), 2.69 (3H, s, $N-CH_3$), 3.40 (3H, s, $-OCH_3$), 3.87 (6H, s, 2 x -OCH3), 3.90 (3H, s, $-COOCH_3$), 5.30 (1H, q, J~ 7 Hz, H-19), 5.89 (1H, s, H-17), 6.5-7.1 (4H, m, H-9, H-10, H-11, H-12), 7.10 (2H, s, H-2', H-6'). (*122*)
MS: 560 (M^+, 100%), 365, 349, 195, 157, 144. (*138b*), see also (*122*)

(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine [(-)-**73**]:
^{1}H NMR (60 MHz, CCl_4): 1.57 (3H, d, J= 7 Hz, H-18), 2.66 (3H, s, $N-CH_3$), 3.58 (3H, s, $-COOCH_3$), 3.86 (3H, s, C4'-OCH_3), 3.89 (6H, s, C3'-OCH_3, C5'-OCH_3), 5.35 (1H, m, H-19), 5.81 (1H, s, H-17), 6.45-6.60 (3H, H-9, H-11, H-12), 7.10 (2H, s, H-2', H-6'). (*138b*)
MS: 576 (M^+, 100%), 381, 365, 195, 173, 160. (*138b*)

(-)-17-*O*-(3',4',5'-Trimethoxycinnamoyl)vincamajine [(-)-**74**]:
^{1}H NMR (100 MHz, CCl_4): 1.57 (3H, d, J= 6 Hz, H-18), 2.66 (3H, s, $N-CH_3$), 3.58 (3H, s, $-COOCH_3$), 3.86 (3H, s, -C4'-OCH_3), 3.89 (6H, s, -C3'-OCH_3, -C5'-OCH_3), 5.35 (1H, m, H-19), 5.81 (1H, s, H-17), 6.16 (1H, d, J= 16 Hz, -*CH*=CH-TMB), 6.40-7.20 (4H, m, H-9, H-10, H-11, H-12), 6.71 (2H, s, H-2', H-6'), 7.42 (1H, d, J= 16 Hz, -CH=*CH*-TMB). (*120*), see also (*138b*)
MS: 586 (M^+), 555, 531, 442, 365 (100%), 349, 221, 165, 157, 144. (*120*), see also (*138b*)

10-Methoxy-17-*O*-(3',4',5'-trimethoxybenzoyl)vincamajine (**75**):
^{1}H NMR: No data available.
MS: 590 (M^+, 100%), 395, 379, 195, 187, 174 (*138b*)

(*continues*)

(-)-10-Hydroxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine [(-)-**76**]:
^{1}H NMR (60 MHz, CCl_4): 1.57 (3H, d, J= 7 Hz, H-18), 2.66 (3H, s, N-CH_3), 3.58 (3H, s, -$COOCH_3$), 3.86 (3H, s, C4'-OCH_3), 3.89 (6H, s, C3'-OCH_3, C5'-OCH_3), 5.35 (1H, m, H-19), 5.81 (1H, s, H-17), 6.16 (1H, d, J= 16 Hz, -*CH*=CH-TMB), 6.45-6.60 (3H, H-9, H-11, H-12), 6.71 (2H, s, H-2', H-6'), 7.42 (1H, d, J= 16 Hz, -CH=*CH*-TMB). (*138b*)
MS: 602 (M^+, 100%), 381, 365, 221, 173, 160. (*138b*)

10-Methoxy-17-*O*-(3',4',5'-trimethoxycinnamoyl)vincamajine (**77**):
^{1}H NMR (60 MHz, CCl_4): 1.57 (3H, d, J= 7 Hz, H-18), 2.66 (3H, s, N-CH_3), 3.56 (3H, s, Ar-OCH_3), 3.58 (3H, s, -$COOCH_3$), 3.86 (3H, s, C4'-OCH_3), 3.89 (6H, s, C3'-OCH_3, C5'-OCH_3), 5.35 (1H, m, H-19), 5.81 (1H, s, H-17), 6.16 (1H, d, J= 16 Hz, -*CH*=CH-TMB), 6.45-6.70 (3H, H-9, H-11, H-12), 6.71 (2H, s, H-2', H-6'), 7.42 (1H, d, J= 16 Hz, -CH=*CH*-TMB). (*138b*)
MS: 616 (M^+, 100%), 395, 379, 221, 187, 174. (*138b*)

(-)-Alstonisidine [(-)-**78**]:
^{1}H NMR ($CDCl_3$): 1.50 (3H, s, -$OCCH_3$), 1.72 (3H, d, J= 7 Hz, H-18), 2.37 (3H, s, N-CH_3), 3.63 (3H, s, -$COOCH_3$), 3.72 (3H, s, N-CH_3), 5.22 (1H, q, J= 7 Hz, H-19), ~ 7.05 (7H, m, aromatic). (*156*)
MS: 674 (M^+), 673, 672, 657, 403, 222, 198, 197 (100%), 183, 182, 181, 170, 168, 167, 158, 144. (*156*)

(-)-Flexicorine [(-)-**79**]:
^{1}H NMR: No data available.
MS: No data available.

(+)-Alstomacroline [(+)-**80**][c]:
^{1}H NMR (400 MHz, $CDCl_3$): 0.66 (1H, d, J= 1 Hz, 17-OH), 1.23 (1H, m, H-20'), 1.26 (2H, m, 2 x H-6), 1.29 (3H, s, 18'-CH_3), 1.35 (1H, br d, J= 12.8 Hz, H-14'), 1.48 (1H, d, J= 11.6 Hz, H-14), 1.63 (3H, d, J= 6.5 Hz, H-18), 2.11 (1H, d, J= 6.1 Hz, H-17), 2.19 (1H, m, H-16'), 2.28 (1H, d, J= 16.0 Hz, H-6'), 2.30 (1H, m, H-15'), 2.34 (1H, m, H-14), 2.41 (3H, s, N-CH_3), 2.71 (1H, dd, J_1= 14.4 Hz, J_2= 5.2 Hz, H-21'), 3.06 (1H, d, J= 5.6 Hz, H-5'), 3.08 (1H, m, H-14'), 3.10 (1H, m, H-6'), 3.12 (1H, d, J= 4.4 Hz, H-2), 3.18 (1H, m, H-15), 3.22 (1H, m, H-3), 3.25 (1H, m, H-21'), 3.28 (1H, m, H-5), 3.32 (2H, m, 2 x H-21), 3.57 (1H, dd, J_1= 11.6 Hz, J_2= 4.1 Hz, H-17'), 3.67 (3H, s, N_a-CH_3), 3.79 (3H, s, -OCH_3), 3.96 (1H, br s, H-3'), 4.50 (1H, t, J= 11.6 Hz, H-17'), 5.21 (1H, q, J= 6.5 Hz, H-19), 6.58 (1H, d, J= 7.9 Hz, H-12), 6.72 (1H, t, J= 7.3 Hz, H-10), 6.77 (1H, t, J= 7.4 Hz, H-10'), 6.87 (1H, d, J= 7.7 Hz, H-9'), 6.94 (1H, d, J=7.1 Hz, H-9), 7.03 (1H, t, J= 7.8 Hz, H-11'), 7.20 (1H, t, J= 7.9 Hz, H-11), 7.34 (1H, d, J= 7.8 Hz, H-12'). (*152*)
MS: 690 (M^+), 672, 365, 324, 292, 197 (100%), 182, 181, 170, 130. (*152*)

11-Methoxy-10-(11'-vincorinyl)vincamajine (**81**)[c]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.54 (1H, dd, J_1= 14 Hz, J_2= 10 Hz, H-14), 1.63 (3H, d, J= 7 Hz, H-18), 1.64 (3H, dd, J_1= 7 Hz, J_2= 2 Hz, H-18'), 1.72 (1H, m, H-3'), 1.73 (1H, m, H-6), 1.74 (1H, m, H-14'), 1.75 (1H, m, H-14'), 2.10 (1H, dd, J_1= 14 Hz, J_2= 8 Hz, H-6'), 2.35 (1H, m, H-3'), 2.47 (1H, dd, J_1= 14 Hz, J_2= 5 Hz, H-14), 2.48 (1H, m, H-6'), 2.61 (3H, s, N'-CH_3), 2.62 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6), 2.71 (3H, s, N-CH_3), 2.80 (1H, m, H-5'), 2.87 (1H, s, H-16'), 3.07 (1H, d, J= 16 Hz, H-21'), 3.35 (1H, m, H-2), 3.45 (1H, m, H-5'), 3.49 (2H, m, 2 x H-21), 3.55 (1H, d, J= 5 Hz, H-5), 3.56 (1H, m, H-3), 3.58 (1H, d, J= 5 Hz, H-15), 3.64 (1H, m, H-15'), 3.65 (3H, s, Ar'-OCH_3), 3.70 (3H, s, -$COOCH_3$), 3.83 (6H, s, -$COOCH'_3$ + Ar-OCH_3), 3.88 (1H, d, J= 16 Hz, H-21'), 4.21 (1H, s, H-17), 5.28 (1H, q, J= 7 Hz, H-19), 5.44 (1H, q, J= 7 Hz, H-19'), 6.18 (1H, s, H-12'), 6.37 (1H, s, H-12), 7.03 (1H, s, H-9'), 7.06 (1H, s, H-9). (*144*)
MS: 762 (M^+), 704, 368, 57 (100%). (*144*)

(-)-11-Methoxy-10-(11'-vincorinyl)-17-epivincamajine [(+)-**82**][c]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.51 (1H, dd, J_1= 14 Hz, J_2= 10 Hz, H-14), 1.61 (3H, d, J= 7 Hz, H-18), 1.62 (3H, dd, J_1= 7 Hz, J_2= 2 Hz, H-18'), 1.72 (1H, m, H-6), 1.73 (1H, m, H-3'), 1.79 (1H, m, H-14'), 1.80 (1H, m, H-14'), 2.05 (1H, dd, J_1= 14 Hz, J_2= 8 Hz, H-6'), 2.22 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6), 2.30 (1H, m, H-3'), 2.44 (1H, m, H-6'), 2.58 (3H, s, N'-CH_3), 2.70 (3H, s, N-CH_3), 2.75 (1H, m, H-5'), 2.84 (1H, s, H-16'), 2.97 (1H, dd, J_1= 14 Hz, J_2= 5 Hz, H-14), 3.02 (1H, d, J= 16 Hz, H-21'), 3.40 (1H, m, H-5'), 3.46 (1H, d, J= 5 Hz, H-15), 3.48 (2H, m, 2 x H-21), 3.50 (1H, d, J= 5 Hz, H-5), 3.59 (1H, m, H-3), 3.62 (1H, m, H-15'), 3.68 (6H, s, Ar-OCH_3 + -$COOCH'_3$), 3.80 (6H, s, -$COOCH_3$ + Ar'-OCH_3), 3.82 (1H, d, J= 16 Hz, H-21'), 3.99 (1H, s, H-17), 5.25 (1H, q, J= 7 Hz, H-19), 5.40 (1H, q, J= 7 Hz, H-19'), 6.15 (1H, s, H-12'), 6.39 (1H, s, H-12), 6.97 (1H, s, H-9), 7.03 (1H, s, H-9'). (*144*)
MS: 762 (M^+), 368, 353, 201, 57 (100%). (*144*)

(±)-11-Methoxy-10-[11'-(10'-methoxycathafolinyl)]vincamajine [(±)-**83**][c]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.52 (1H, m, H-14b), 1.59 (6H, d, J= 7 Hz, H-18, H-18'), 1.70 (1H, d, J= 12 Hz, H-6b), 1.80 (1H, m, H-6'b), 1.82 (1H, m, H-14'b), 2.44 (2H, dd, J_1= 14 Hz, J_2= 5 Hz, H-14a, H-14'a), 2.57 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6a), 2.66 (3H, s, N'-CH_3), 2.68 (3H, s, N-CH_3), 2.70 (1H, s, H-2'), 2.94 (1H, dd, J_1= 16 Hz, J_2= 13 Hz, H-5'b), 3.06 (1H, d, J= 4 Hz, H-16'), 3.18 (1H, m, H-6'a), 3.27 (1H, d, J= 16 Hz, H-21'b), 3.32 (1H, d, J= 5 Hz, H-2), 3.43 (2H, m, 2 x H-21), 3.50 (1H, d, J= 4 Hz, H-15), 3.54 (1H, d, J= 5 Hz, H-5), 3.56 (1H, d, J= 5 Hz, H-3), 3.61 (3H, s, Ar-OCH_3), 3.68 (3H, s, -$COOCH_3$), 3.75 (1H, br s, H-15'), 3.77 (3H, s, Ar-OCH_3), 3.81 (3H, s, -$COOCH'_3$), 4.20 (1H, s, H-17), 4.21 (1H, m, H-21'a), 4.28 (1H, m, H-5'a), 4.59 (1H, d, J= 5 Hz, H-3'), 5.24 (1H, q, J= 7 Hz, H-19), 5.64 (1H, q, J= 7 Hz, H-19'), 6.34 (1H, s, H-12), 6.56 (1H, s, H-12'), 6.66 (1H, s, H-9'), 7.00 (1H, s, H-9). (*139*)
MS: 762 (M^+), 704, 194, 57 (100%). (*139*)

(*continues*)

TABLE III (*Continued*)

(-)-11-Methoxy-10-(11'-vincorinyl)vincamedine [(-)-**84**][c]:
^{1}H NMR (300 MHz, $CDCl_3$): 1.50 (1H, m, H-14), 1.59 (3H, d, J= 7 Hz, H-18), 1.62 (3H, dd, J_1= 7 Hz, J_2= 2 Hz, H-18'), 1.75 (1H, m, H-6), 1.77 (1H, m, H-14'), 1.79 (1H, m, H-14'), 1.94 (3H, s, $-OCOCH_3$), 2.05 (1H, dd, J_1= 14 Hz, J_2= 8 Hz, H-6'), 2.25 (1H, dd, J_1= 12 Hz, J_2= 2 Hz, H-3'), 2.41 (1H, dd, J_1= 8 Hz, J_2= 4 Hz, H-6'), 2.50 (1H, dd, J_1= 12 Hz, J_2= 5 Hz, H-6), 2.53 (3H, s, N'-CH_3), 2.63 (1H, m, H-14), 2.69 (3H, s, N-CH_3), 2.73 (1H, m, H-5'), 2.86 (1H, s, H-16'), 3.10 (1H, d, J= 16 Hz, H-21'), 3.29 (1H, d, J= 5 Hz, H-2), 3.40 (1H, m, H-5'), 3.47 (3H, m, H-15, 2 x H-21), 3.52 (1H, dd, J_1= 10 Hz, J_2= 5 Hz, H-3), 3.58 (3H, s, Ar'-OCH_3), 3.62 (1H, m, H-5), 3.64 (3H, s, $-COOCH_3$), 3.67 (1H, s, H-15'), 3.78 (3H, s, Ar-OCH_3), 3.82 (3H, s, $-COOCH'_3$), 3.85 (1H, m, H-21'), 5.28 (1H, q, J= 7 Hz, H-19), 5.40 (1H, q, J= 7 Hz, H-19'), 5.70 (1H, s, H-17), 6.03 (1H, s, H-12'), 6.30 (1H, s, H-12), 6.88 (1H, s, H-9), 7.03 (1H, s, H-9'). (*144*)
MS: 804 (M^+, 100%), 438, 368, 352, 309, 253, 222. (*144*)

^{1}H NMR signals reassigned by the writers are marked with underlining.
[a] Spectral data given for a synthetic sample.
[b] In recent Russian literature (*113b*) vincarine (**37**) is considered identical, not isomeric, with quebrachidine (**36**).
[c] The non-ajmaline moities of the bisindoles are marked with primes.

VI. Spectroscopy

A. ^{1}H NMR SPECTROSCOPY

Determination of the structures of organic natural products has been greatly simplified by modern high-field ^{1}H NMR techniques. This has clearly been demonstrated in the field of the ajmaline (and sarpagine) alkaloids (*182-188*).

The ^{1}H NMR spectral data for ajmaline alkaloids are presented in Table III. High-field data are reported where available, but for some alkaloids only older data measured with low-field techniques were available. Despite the incompleteness of the older data they were judged to be useful for comparison and are therefore included in Table III. Caution is nevertheless needed in utilizing the older data, as they often contain errors.

In the mid-eighties, Lounasmaa *et al.* (*189*) measured and interpreted the high field ^{1}H NMR spectra of twelve basic ajmaline alkaloids. Several earlier erroneous signal assignments were corrected in the process.

The findings indicated that the four basic skeleta in the ajmaline subgroup, characterized by the 17*R*,21*R*, 17*R*,21*S*, 17*S*,21*R*, and 17*S*,21*S* configurations and corresponding to ajmaline, isoajmaline, sandwichine, and isosandwichine skeleta, respectively, can easily be distinguished by their ^{1}H NMR spectra. In the *R*-configurations, C-17H and C-21H are represented by singlets ($J_{16,17}$ and $J_{20,21}$ are negligible), whereas in the *S*-configurations they are represented by doublets (Table III).

Scrutiny of the spectral data reveals that the main shielding effects, due to the C-17 and/or C-21 OH-groups (or their acetylated counterparts), are in the chemical shifts of C-2H (*e.g.* alkaloids **17**, **19**, **44**, **56**), C-5H (*e.g.* alkaloids **17**, **20**, **44**, **56**), and C-6Hβ (*e.g.* alkaloids **3**, **13**, **20**, **53**, **82**). This is in good agreement with what could be expected on a structural basis.

The quebrachidine subgroup alkaloids (*e.g.* alkaloids **36** and **43**) are easily distinguished from the other ajmaline alkaloids by the C-2H doublets ($J_{2,3}\approx 5$ Hz) and the C-17H singlets. For alkaloids possessing the tetraphyllicine ring skeleton (*e.g.* mauiensine **4**), the C-2H is presented by a slightly broadened singlet ($J_{2,3}< 0.5$ Hz).

Quite recently Lounasmaa *et al.* (*190*) reexamined the ^{1}H NMR spectra of several ajmaline derivatives with new techniques. While most of the earlier assignments were confirmed, a few corrections were required in the interpretation of the signals for vincamajinine (**43**).

References for the ^{1}H NMR spectral data of individual alkaloids, when available, are given in Table III.

B. ^{13}C NMR SPECTROSCOPY

^{13}C NMR spectroscopy has permitted many stereochemical problems with the ajmaline alkaloids to be solved (*e.g. 78, 82b, 121, 191-197*). In addition, identical ^{13}C NMR spectral data of two alkaloids, together with identical optical rotations, would appear to provide the best and most rapid way to establish the

identity of two alkaloids.

As with the ^1H NMR spectra (*vide supra*), there has been much confusion in the literature over the ^{13}C NMR spectra of ajmaline alkaloids (*78, 82b*). Although many errors have been corrected (*192, 193*), caution is still needed, especially in utilizing earlier spectral data.

Recently, Lounasmaa and coll. (*190*) introduced some new corrections for the ^{13}C NMR spectra of isoajmaline (**19**), isosandwicine (**20**), and vincamedine (**54**). Measurements, confirmed by COSY and HETCOR experiments, indicated that the generally accepted assignments for C-14 and C-19 in the spectra of isoajmaline (**19**) and isosandwichine (**20**) (*3, 78, 192*) should be interchanged (*190*). The same applies to the proposed (*104*) assignments of the C-2 and C-17 signals of vincamedine (**54**).

The chemical shift of C-14 is characteristic of the H-2 stereochemistry for the ajmaline derivatives. In cases where H-2 is β (C-2*R*) the C-14 shift value is > 25 ppm [*e.g.* 31.4 ppm for rauflorine (**1**)], whereas when H-2 is α (C-2*S*) the C-14 shift value is ≈ 22 ppm [*e.g.* 22.3 ppm for quebrachidine (**36**)]. The only exception seems to be leepacine (**30**), for which the shift value 22.1 ppm is indicated (Table IV). In the writers' opinion, this (and some other indicated shift values) casts doubt on the proposed structure **30**.

^{13}C NMR spectral data for 31 monomeric and 6 bisindolic alkaloids of the ajmaline type are presented in Table IV.

C. Mass Spectrometry

The mass spectra of ajmaline type alkaloids can be divided into three main groups: namely, ajmaline (**17**) and similar compounds with a H-2β orientation, ajmalidine (**15**) and other compounds with a 17-keto group, and compounds with a H-2α configuration [*e.g.* quebrachidine (**36**)]. For the general features of the mass spectra of ajmaline alkaloids, and the determination of structures with the aid of mass spectra, see Refs. *198-202*.

a. The Ajmaline Group. The base peak in the mass spectrum of ajmaline (**17**) is at *m/z* 144. This corresponds to the fragment ion $C_{10}H_{10}N^+$, which is characterictic of all N_a-methyl indole alkaloids. Other characteristic peaks are at *m/z* 157 ($C_{11}H_{11}N$) and 158 ($C_{10}H_8NO$) (Figure 6).

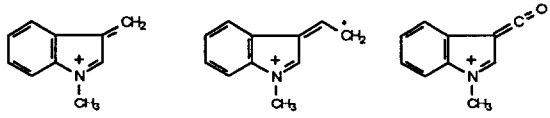
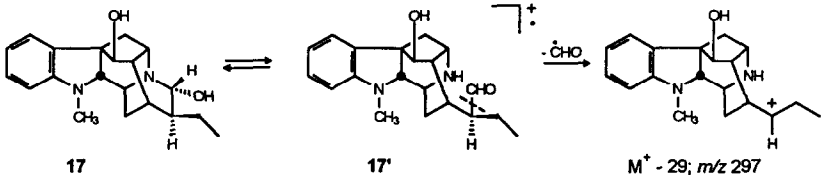


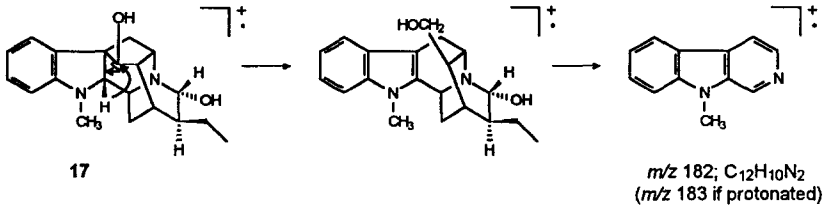
FIG. 6. Characterictic mass fragments for N_a-methyl indole alkaloids.

In the mass spectrum of ajmaline (**17**) there are peaks at *m/z* 311 (M^+-15) and *m/z* 308 (M^+-18), which are due to losses of $CH_3^{\cdot}$ and H_2O, respectively. The cleavage of the aldehyde function (M^+-29; peak at *m/z* 297) can be explained by the prior formation of *chano*-ajmaline (**17'**) (Scheme 20).



SCHEME 20. The cleavage of an aldehyde function from the *chano*-ajmaline (**17'**).

One characterictic peak for ajmaline (**17**) and similar compounds is at *m/z* 182. This peak consists of three different fragments (isobaric species), namely, $C_{12}H_{10}N_2$, $C_{13}H_{12}N$, and $C_{10}H_{16}NO_2$. The $C_{12}H_{10}N_2$ fragment is derived from a sarpagine type skeleton, which is formed by the cleavage of the C-7 - C-17 bond upon the migration of H-2β to C-17. This type of fragmentation is characteristic of alkaloids with a H-2β orientation (Scheme 21) (*203, 204*). In alkaloids with the opposite orientation (H-2α) the hydrogen atom is too far from C-17 to migrate (*vide infra*).

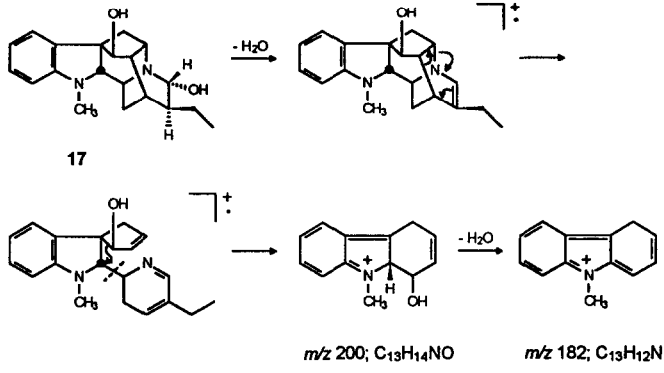


SCHEME 21. Fragmentation of ajmaline (**17**); H-2α migration and formation of the fragment ion $C_{12}H_{10}N_2^+$ (*m/z* 182).

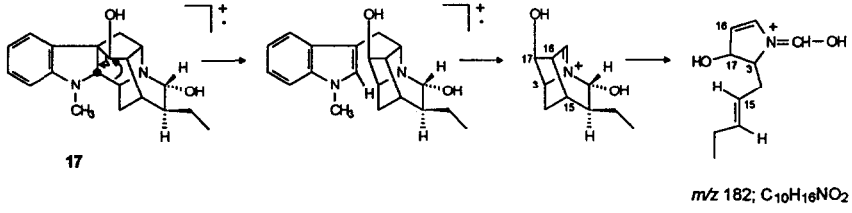
Thermal loss of water from ajmaline (**17**) followed by rearrangement and cleavage gives the fragment ion $C_{13}H_{14}NO^+$ (*m/z* 200), which in turn gives the fragment ion $C_{13}H_{12}N^+$ (*m/z* 182) after water cleavage (Scheme 22).

Opening of ring C, followed by cleavage of the C-5 - C-6 bond, gives, after rearrangement, the third component ($C_{10}H_{16}NO_2$) of the peak at *m/z* 182 (Scheme 23).

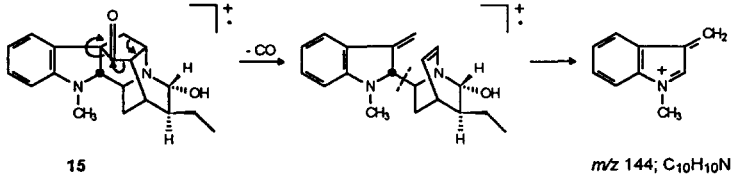
b. The Ajmalidine Group. Ajmalidine (**15**) gives the fragment ion $C_{10}H_{10}N^+$ (*m/z* 144) by elimination of CO and cleavage of the C-2 - C-3 bond (Scheme 24) (*205*).



SCHEME 22. Fragmentation of ajmaline (17); thermal loss of water, followed by formation of the fragment ions $C_{13}H_{14}NO^+$ (*m/z* 200) and $C_{13}H_{12}N^+$ (*m/z* 182).



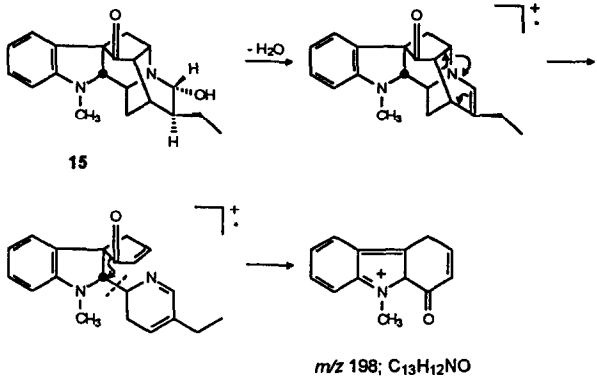
SCHEME 23. Fragmentation of ajmaline (17); formation of the fragment ion $C_{10}H_{16}NO_2^+$ (*m/z* 182).



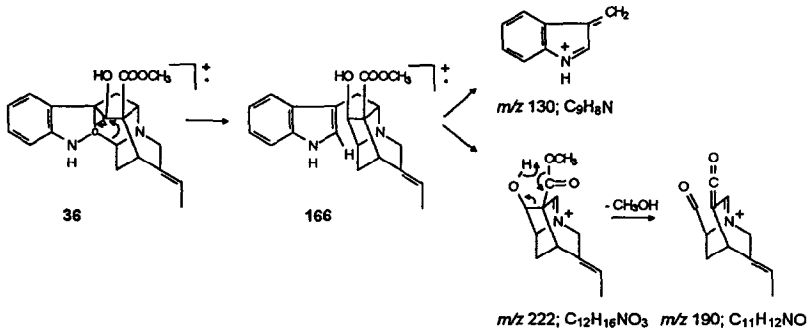
SCHEME 24. Formation of the fragment ion $C_{10}H_{10}N^+$ (*m/z* 144) from ajmalidine (15).

The fragment ion $C_{13}H_{12}NO^+$ (*m/z* 198) in the mass spectrum of ajmalidine (15) (Scheme 25) is formed in an analogous way to the fragment ion $C_{12}H_{14}NO^+$ (*m/z* 200) in the spectrum of ajmaline (17) (*vide supra*).

c. The Quebrachidine Group. In quebrachidine (**36**) and similar alkaloids the H-2α orientation prevents the formation of the sarpagan-type skeleton and fragmentation by this pathway (*Cf.* Scheme 21) (*105b*). Instead, a rearrangement leads to intermediate **166**, which then gives rise to characteristic peaks at *m/z* 130 (C_9H_8N) and 222 ($C_{12}H_{16}NO_3$). Fragment ion $C_{12}H_{16}NO_3^+$ (*m/z* 222) then generates, after loss of CH_3OH, fragment ion $C_{11}H_{12}NO_2^+$ (*m/z* 190) (Scheme 26).



SCHEME 25. Formation of the fragment ion $C_{13}H_{12}NO^+$ (*m/z* 198) from ajmalidine (**15**).

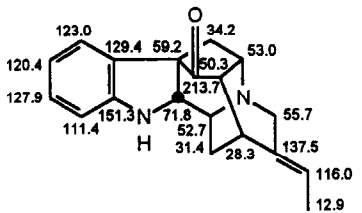


SCHEME 26. Fragmentation of quebrachidine (**36**); formation of fragment ions $C_9H_8N^+$ (*m/z* 130), $C_{12}H_{16}NO_3^+$ (*m/z* 222), and $C_{11}H_{12}NO_2^+$ (*m/z* 190).

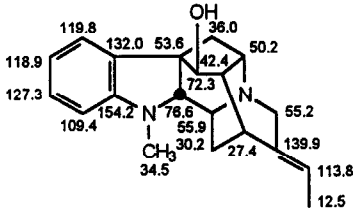
Mass spectral data of individual alkaloids, when available, are presented in Table III.

TABLE IV

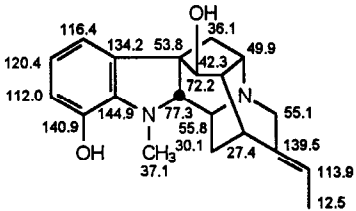
^{13}C NMR SPECTRAL DATA OF INDIVIDUAL ALKALOIDS



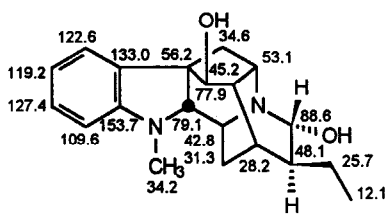
1 (+)-**Raufiorine**
(*190*) 100.577 MHz, $CDCl_3$



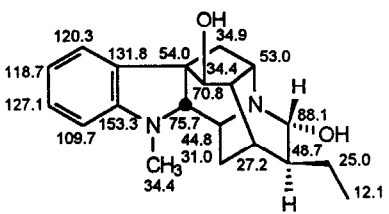
4 (+)-**Mauensine** (17*S*) ¤
(*36*) 100.577 MHz, $CDCl_3$



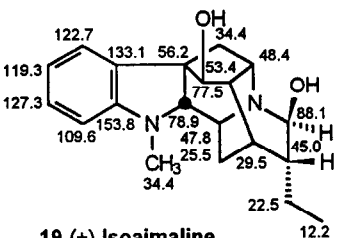
13 (+)-**12-Hydroxymauiensine** (17*S*) ¤
(*36*) 50 MHz, $CDCl_3$: CD_3OD 3:2



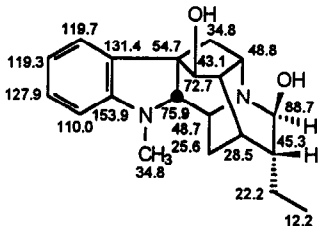
17 (+)-**Ajmaline**
(*190*) 100.577 MHz, $CDCl_3$
see also (*78*), (*82b*), (*193*)



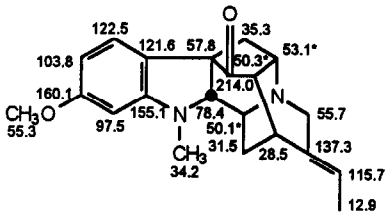
18 (+)-**Sandwicine** (17*S*) ¤
(*193*) 25.2 MHz, $CDCl_3$



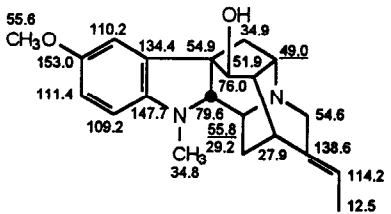
19 (+)-**Isoajmaline**
(*190*) 100.577 MHz, $CDCl_3$
see also (*78*), (*193*)



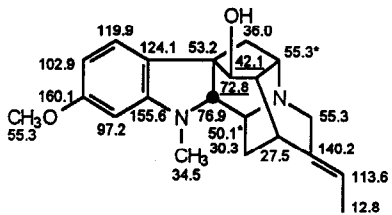
20 (+)-Isosandwicine (17*S*) ¤
(*190*) 100.577 MHz, $CDCl_3$
see also (*193*)



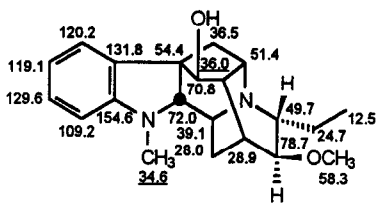
23 Rauflexine
(*82b*) $CDCl_3$, see also (*151*)



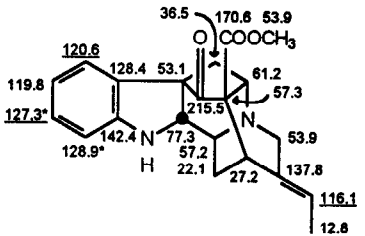
26 Vincamajoreine
(*82b*) $CDCl_3$: CD_3OD 5:1



27 (+)-Reflexine (17*S*) ¤, a
(*151*) 25.2 MHz, $CDCl_3$

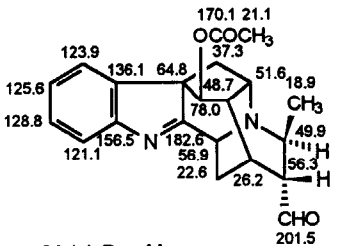


28 Sandwicolidine (17*S*) ¤
(*85*) 75 MHz, $CDCl_3$

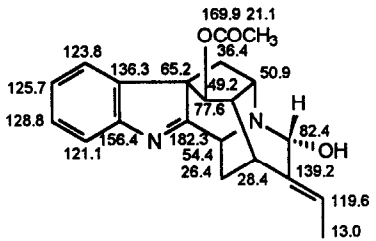


30 (-)-Leepacine
(*87*) 75 MHz, $CDCl_3$

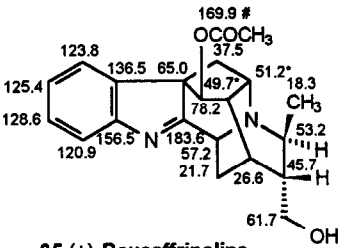
(continues)



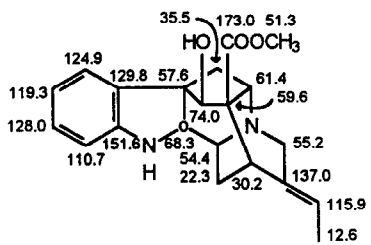
31 (+)-**Perakine**
(*89*) 75.47 MHz, $CDCl_3$
see also (*88b*)



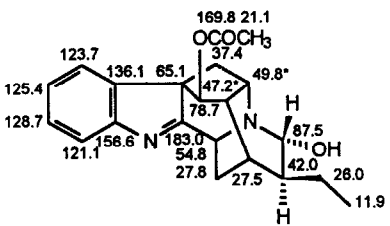
32 (-)-**Vomilenine** ▪
(*167b*) 67.8 MHz, $CDCl_3$
see also (*78*), (*89*)



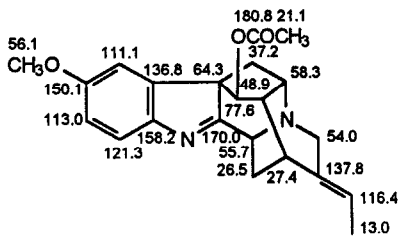
35 (+)-**Raucaffrinoline**
(*78*) $CDCl_3$, see also (*89*)



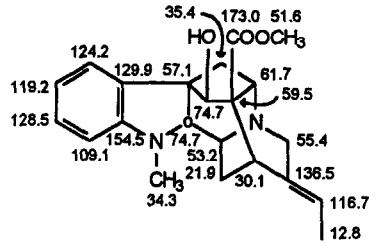
36 (+)-**Quebrachidine**
(*84e*) 100.577 MHz, $CDCl_3$
see also (100)



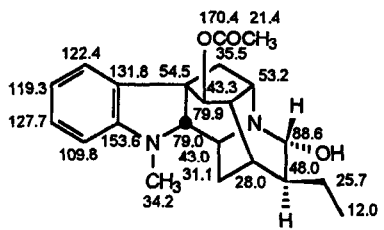
38 19,20-**Dihydrovomilenine**
(*78*) $CDCl_3$



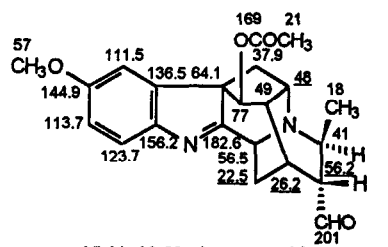
41 (+)-**10-Methoxyvinorine**
(*118*) 25 MHz, $CDCl_3$



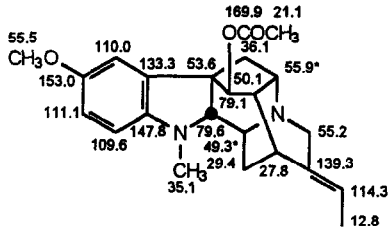
42 (-)-Vincamajine
(*190*) 100.577 MHz, $CDCl_3$
see also (*82b*), (*124b*), (*84e*)



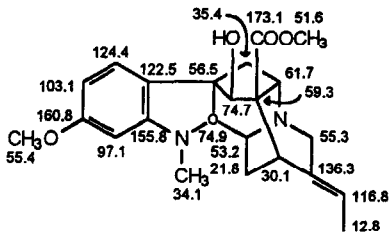
44 17-Acetylajmaline
(*190*) 100.577 MHz, $CDCl_3$



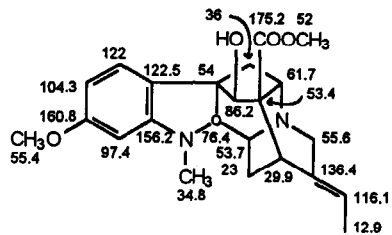
45 (-)-10-Methoxyperakine
(*118*) 125 MHz, $CDCl_3$



47 (-)-Majoridine
(*82b*) $CDCl_3$

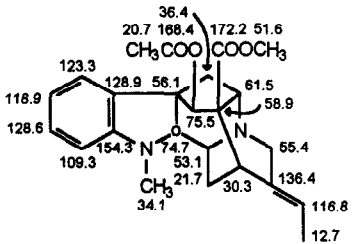


52 (-)-11-Methoxyvincamajine
(*139*) 75 MHz, $CDCl_3$

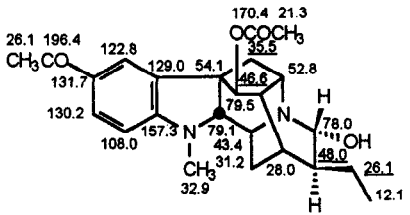


53 (-)-11-Methoxy-17-epi-vincamajine (17*R*) ¤
(*139*) 75 MHz, $CDCl_3$
see also (*144*)

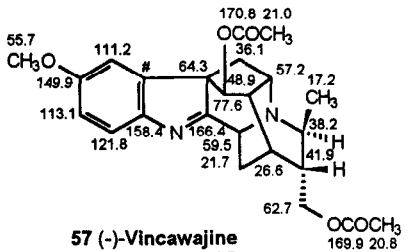
(continues)



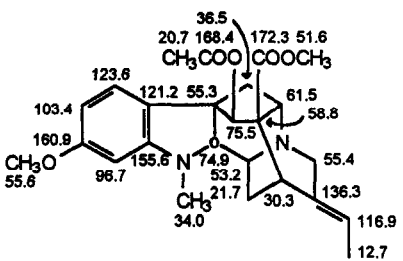
54 (-)-**Vincamedine**
(*190*) 100.577 MHz, $CDCl_3$
see also (*84e*), (*104*)



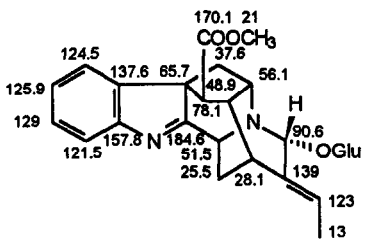
55 Ajmalinimine
(*143*) 75 MHz, $CDCl_3$



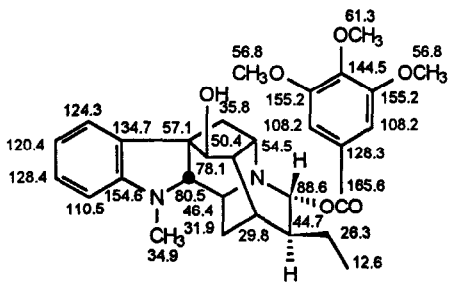
57 (-)-Vincawajine
(*118*) 125 MHz, $CDCl_3$



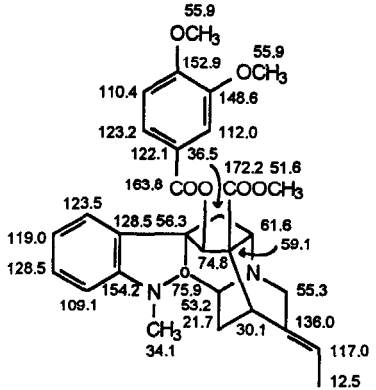
59 (-)-11-Methoxyvincamedine
(*154*) 75 MHz, $CDCl_3$



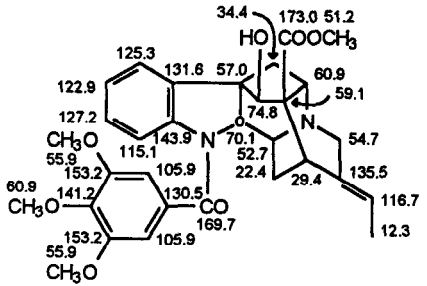
64 (+)-Raucaffricine[b]
(*155b*) C_5D_5N, see also (*88b*)



65 (+)-Ajmalimine
(*147*) 75 MHz, $CDCl_3$



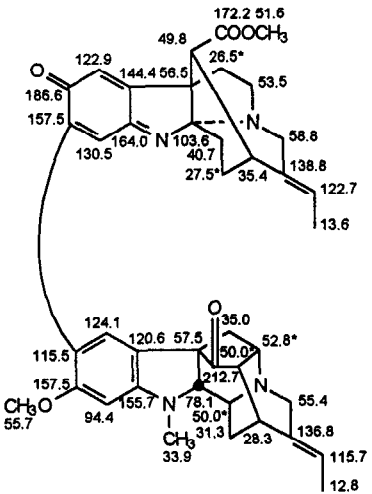
67 17-*O*-(3',4'-Dimethoxybenzoyl)-vincamajine
(*124b*) 100 MHz, $CDCl_3/CD_3OD$



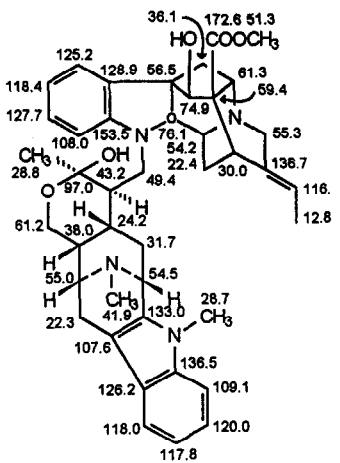
71 1-*N*-(3',4',5'-Trimethoxybenzoyl)-vincamajine
(*124b*) 100 MHz, $CDCl_3/CD_3OD$

(continues)

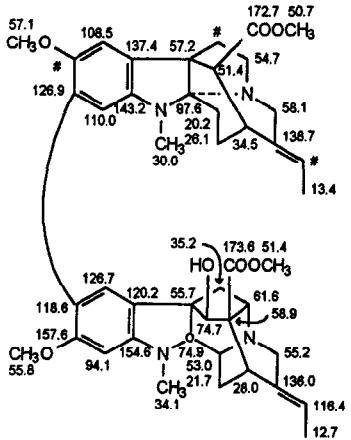
TABLE IV (*Continued*)



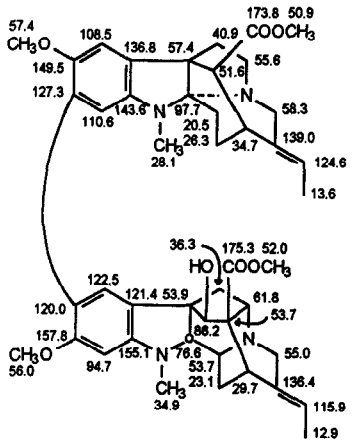
79 (-)-Flexicorine
(*151*) 25.2 MHz, $CDCl_3$



80 (+)-Alstomacroline
(*152*) 100 MHz, $CDCl_3$



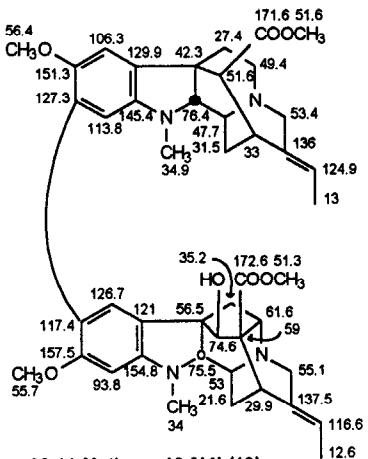
81 11-Methoxy-10-(11'-vincorinyl)vincamajine
(*144*) 75 MHz, $CDCl_3$



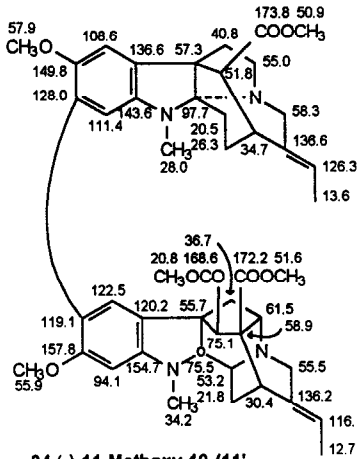
82 (-)-11-Methoxy-10-(11'-vincorinyl)-17-epivincamajine (17*R*) ¤
(*144*) 75 MHz, $CDCl_3$

(continues)

TABLE IV (*Continued*)



83 11-Methoxy-10-[11'-(10'-methoxycathafolinyl)]vincamaline
(*139*) 75 MHz, $CDCl_3$



84 (-)-11-Methoxy-10-(11'-vincorinyl)vincamedine
(*144*) 75 MHz, $CDCl_3$

^{13}C NMR signals reassigned by the writers are marked with underlining.

¤ In order to make the presentation of the ^{13}C NMR data in Table IV more readable, writers present similar drawings for the C-17*R* and C-17*S* isomers.

\# Values not mentioned.

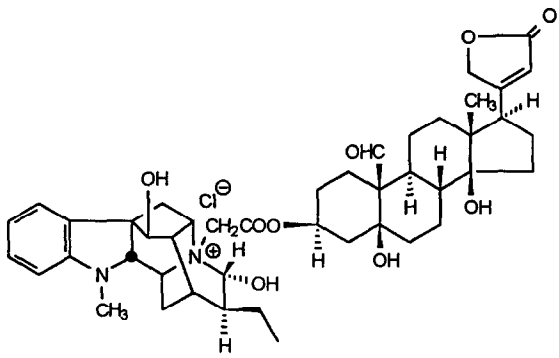
[a] Synthetized compound.

[b] Compound extracted from cell culture.

VII. Pharmacology

Only a few new pharmacological effects have been indicated for the alkaloids of the ajmaline group. Most of them concern ajmaline (**17**) itself, which has been known since 1959 (*207*) and is used in the treatment of cardiac arrhythmia (*208, 209*).

Several cardenolide derivatives of ajmaline alkaloids have been synthesised and tested for their anti-arrhythmic activity. N_b-(Strophanthidin-3β-yloxycarbonylmethyl)ajmalinium chloride (**167**) was found to be one of the most potent of these (*210*).



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VIII. Perspectives

Altogether 84 alkaloids belonging to the ajmaline group (*sensu stricto*) have been isolated from plant sources. Caution is needed in counting the ajmaline alkaloids, however, for at least five (compounds **31**, **35**, **45**, **57**, and **80**; see Table II) of the mentioned 84 are, in the writers' opinion, artefacts. Moreover, some structures (*e.g.* compounds **28**, **29**, **30**, and **65**; see Table II) are in need of confirmation. Of these, especially the structure of sandwicolidine (**28**) would seem incorrect because it goes against what is known of the biogenetic formation of indole alkaloids.

The intensity of the search for new alkaloids of the ajmaline type will certinly not abate. The research on cell culture methods to prepare ajmaline alkaloids is likely to continue. So far, however, the alkaloid content in cultured cells has almost always been low. For the future, we can expect the production of ajmaline derivatives by gene transfer techniques.

Acknowledgments

One of us (P. H.) thanks the Academy of Finland for financial support.

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Correction.

For unexplained reasons the formulae intended for page 122 (Table II) in our recent review "The Sarpagine Group of Indole Alkaloids" in Vol. 52 of the present series were accidently replaced by the formulae intended for page 123, and which were thus presented twice. The correct page 122 is reproduced below (next page).

CHAPTER 2

SIMPLE INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS

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THE ALKALOIDS. VOL. 55
0099-9598/01 $35.00

I. Introduction

The first comprehensive survey of simple indolizidine and quinolizidine alkaloids in this treatise was presented in Volume 28, which was published in 1986 (*1*). In updating the topic for the present Volume, it was necessary to confront afresh the particular problems associated with covering a field that is so heterogeneous and so widely exemplified in nature. Alkaloids of the indolizidine and quinolizidine classes are found in bacteria, fungi, higher plants, invertebrates, and vertebrates; and both terrestrial and marine sources are represented. No common biogenetic pathway links the metabolites within each class, and apparent structural relationships between individual alkaloids are often based on nothing more consequential than their coincidentally possessing a common 1-azabicyclo-[4.3.0]nonane (**1**) or 1-azabicyclo[4.4.0]decane (**2**) core (Fig. 1). The classification into the two broad classes on the basis of substructures **1** or **2** is, in the main, a matter of expedience. A problem with this simplistic approach is that the two substructures are such common motifs in alkaloidal systems that the classification is almost self-defeating—hence the need for the epithet 'simple' in the title of this review. However, what constitutes a 'simple' indolizidine or quinolizidine alkaloid is also open to interpretation. In this chapter the term is applied, with a few justifiable exceptions, to those alkaloids in which the azabicyclic nucleus is *isolated*; that is, not embedded within a fused polycyclic array.

A major difficulty that arises from the diffuse nature of the topic is that simple indolizidine and quinolizidine alkaloids often occur in genera, families, orders, and classes that have merited chapters of their own in this series of volumes. An unfortunate consequence is that some themes introduced in the earlier review in Volume 28 have been selectively updated in the intervening years, while others have remained unsurveyed. This piecemeal coverage means that the present

1 **2**

FIG. 1. Conventional numbering system for the indolizidine (**1**) and quinolizidine (**2**) systems.

overview must either duplicate material presented by other authors elsewhere in this series (*vide infra*), or else itself espouse a piecemeal presentation that picks up where others have left off. In the interests of brevity, the latter approach has perforce been adopted—a mixed blessing since, while there are obvious advantages in having a unified update in a single volume, the sheer profusion of accumulated literature would have been almost impossible to assimilate. Each section of this chapter will thus be prefaced by an explicit statement of the time span being covered, and references to the previous treatment in these volumes will be provided. The intention is to level the playing fields once more by covering the primary literature in all relevant areas up to the middle of 1999.

The following post-1986 reviews in this treatise provide the antecedents for several sections of this chapter. The important contribution of Takahata and Momose in Volume 44, entitled "Simple Indolizidine Alkaloids", covered the period 1986 to 1992, but dealt only with *Elaeocarpus* alkaloids, slaframine, polyhydroxylated indolizidines such as swainsonine and castanospermine, and alkaloids from ants and amphibians (*2*). This partial update is especially valuable as a guide to published total syntheses of these alkaloids. Material of relevance is also to be found in a number of reviews on more specialized topics. Numata and Ibuka reviewed the chemistry of alkaloids from ants and other insects in Volume 31 (*3*), while a substantial survey by Daly, Garraffo, and Spande in Volume 43 concentrated on the sources and structure elucidation of alkaloids from amphibians (*4*). A shorter review by Daly in Volume 50 highlighted advances in this rapidly expanding field, and extended the coverage into 1997 (*5*). Two reviews containing applicable material appeared in Volume 35: Fuji reported on alkaloids of the Lythraceae (*6*), while the *Nuphar* furylquinolizidines and analogous beaver alkaloids were updated by Cybulski and Wróbel (*7*). The lupine alkaloids formed the subject of weighty contributions in Volumes 31 (*8*) and 47 (*9*), and aspects of their biosynthesis were featured prominently in Volume 46 (*10*). A more wide-ranging review on the chemical ecology of alkaloids in Volume 47 included many systems of interest for the current survey (*11*), while information on the distribution of quinolizidine alkaloids in higher plants was included in an article on alkaloid chemosystematics in Volume 50 (*12*).

Indolizidine and quinolizidine alkaloids, simple or otherwise, have been frequently reviewed in other publications throughout the period under consideration. The annual updates in the Royal Society of Chemistry's journal *Natural Product Reports* have ensured ongoing coverage since 1984, and continue to provide the most regular current awareness service in the area (*13*). Several major reviews that appeared between 1986 and 1991 were cited in the review by Takahata and Momose (*2*). More recent surveys include a general overview of indolizidine alkaloids from fungal and plant sources (*14*), and two successive updates on quinolizidine alkaloids in the series "Rodd's Chemistry of Carbon Compounds" (*15,16*). Three important reviews focus largely or exclusively on the synthesis of indolizidine alkaloids (*17–19*), while several other reviews that describe general strategies for the synthesis of azaheterocycles and alkaloids include many simple indolizidine and quinolizidine alkaloids as targets. Worth singling out in this category are surveys on the use of stereoselective acyliminium ion cyclizations

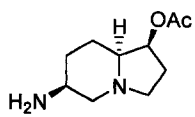
(*20*), hetero Diels–Alder reactions with *N*-acylnitroso dienophiles (*21*), carbohydrate-influenced methodologies (*22*), 1-acylpyridinium salts as intermediates (*23*), 1,3-dipolar cycloadditions (*24*), and ring-closure metathesis (*25*). Other recent reviews on specific topics will be referenced in the appropriate sections of the ensuing presentation.

II. Alkaloids from Fungal and Microbial Sources

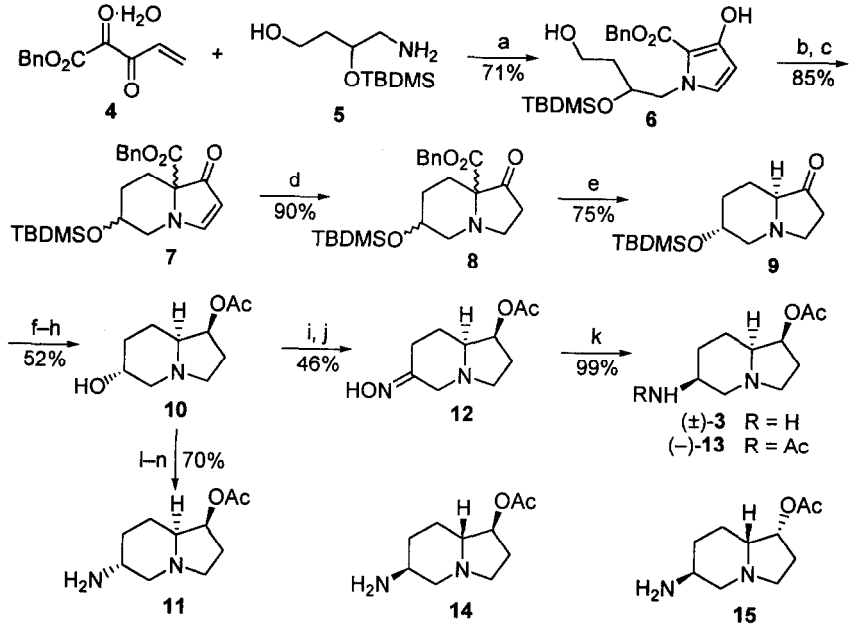
A. SLAFRAMINE

The comprehensive treatment of the isolation, biosynthesis, biological activity and synthesis of the parasympathomimetic fungal metabolite (–)-slaframine (**3**) in Volume 28 of this treatise (*1*) was updated in Volume 44, which extended the coverage into 1992 (*2*). Aspects of the chemistry and biology of the alkaloid have been touched on in other general reviews (*14,18,19*). Effects on livestock, which develop 'slobber syndrome' when foraging on crops contaminated with the slaframine-producing fungus *Rhizoctonia leguminicola*, have also been reviewed (*26,27*). Recent biological studies have concentrated almost entirely on the alkaloid's ability to alter the secretion of saliva and pancreatic fluids in livestock, and the consequent nutritional implications of altering digestion and ruminal function (*28–34*).

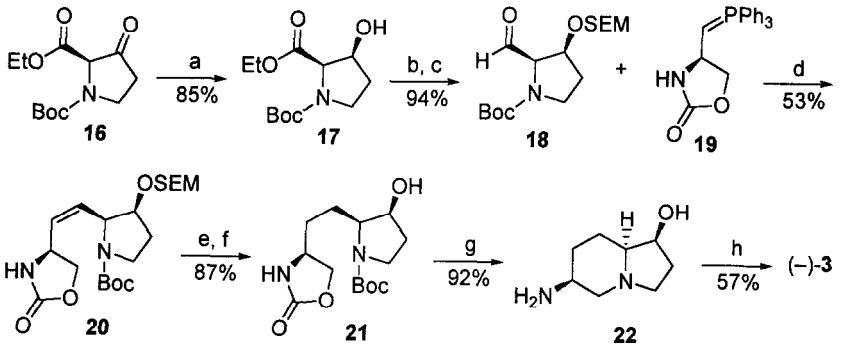
Synthetic studies on slaframine usually target the naturally occurring (1*S*,6*S*,8a*S*)-(–) enantiomer **3**. However, the synthesis of the racemic alkaloid by Wasserman and Yu (Scheme 1) deserves mention for its unique construction of the indolizidine core (*35*). Condensation between the vicinal tricarbonyl compound **4** and amine **5** yielded the 3-hydroxypyrrole **6**, the enolic nucleophilicity of which was exploited in cyclization to form the indolizidine nucleus of product **7**. Although this product was obtained as an equal mixture of two separable diastereomers, reduction of either to **8** followed by cleavage and decarboxylation of the bridgehead ester yielded the same ketone **9**. Reduction of the carbonyl group with the bulky reagent L-Selectride (lithium tri-*sec*-butylborohydride) set up the correct relative stereochemistry at C–1. However, attempted S_N2 displacement of the mesylate of the subsequent alcohol intermediate **10** with azide ion proceeded with retention, rather than the expected inversion, of configuration, eventually leading to the unnatural isomer (±)-6-epislaframine (**11**). The target alkaloid (±)-**3** was finally obtained by catalytic hydrogenation of oxime **12**. Soon afterwards, Gmeiner and co-workers reported a synthesis of (1*S*,6*S*,8a*S*)-(–)-*N*-acetyl-slaframine (**13**) by essentially the same route, but they used the *tert*-butyl ester analog of **4** and (*R*)-4-amino-3-benzyloxybutanol as reactants (*36*). They were also able to prepare (+)-8a-epislaframine (**14**) and (+)-1,8a-diepislaframine (**15**) by making slight modifications to the route (*37*).



3 (–)-Slaframine



SCHEME 1. Reagents: a, CH_2Cl_2, Et_2O, SiO_2; b, PPh_3, CBr_4, THF; c, NaH, THF; d, $BF_3{\cdot}Et_2O$, Super-Hydride, THF, –78°C; e, H_2 (55 psi), 10% Pd/C, EtOAc; f, L-Selectride, THF, –78°C; g, Ac_2O, NEt_3, DMAP, CH_2Cl_2; h, aq. HF, MeCN; i, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78°C; j, $NH_2OH{\cdot}HCl$, pyridine, EtOH, reflux; k, H_2 (40 psi), PtO_2, EtOH, aq. HCl; l, MsCl; m, NaN_3; n, H_2, Pd/C.



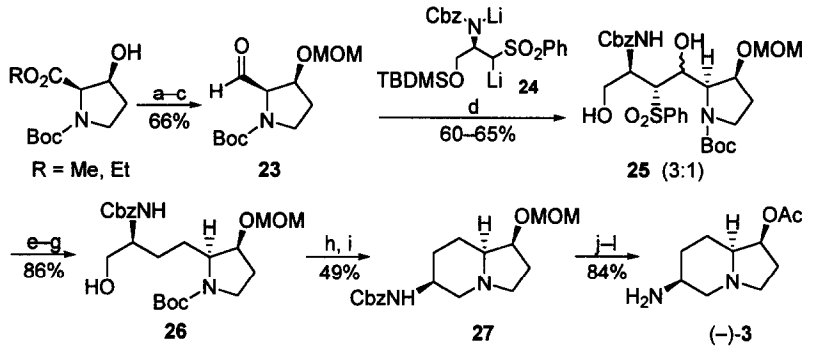
SCHEME 2. Reagents: a, baker's yeast immobilized on sodium alginate, sucrose, H_2O–EtOAc; b, SEM-Cl, Pr^i_2NEt, CH_2Cl_2; c, DIBAL, PhMe, –78°C; d, THF, –43°C to rt; e, H_2, 10% $Pd(OH)_2/C$, EtOAc; f, Bu_4NF, HMPA, 80°C; g, 270°C, 5 min; h, HCl, HOAc, 75°C.

Sibi and co-workers devised an enantiospecific synthesis of (−)-**3** from the 3-oxoproline ester **16**, which was reduced with baker's yeast to give the (2*R*,3*S*)-*cis*-3-hydroxyproline ester **17** in 85% yield (Scheme 2) (*38,39*). Wittig reaction between the subsequent aldehyde derivative **18** and ylide **19** was optimized with difficulty, and gave the *cis*-alkene **20** in 53% yield at best. The feature of chief interest in this synthesis is the unprecedented use of an oxazolidinone as an electrophile in the efficient (92%) thermally-induced cyclization of **21** to deacetylslaframine (**22**). Selective *O*-acetylation under conditions developed by Schneider and Harris (*40*) completed the synthesis of (−)-**3** in an overall yield of 18.4% from **16**. Sibi *et al.* have also applied this novel methodology to the synthesis of several analogs of slaframine, including (−)-*N*-acetylslaframine (**13**), (−)-8a-epi-1-desacetoxyslaframine and (*2R,6S*)-(−)-6-aminoindolizidin-2-ol (*39*).

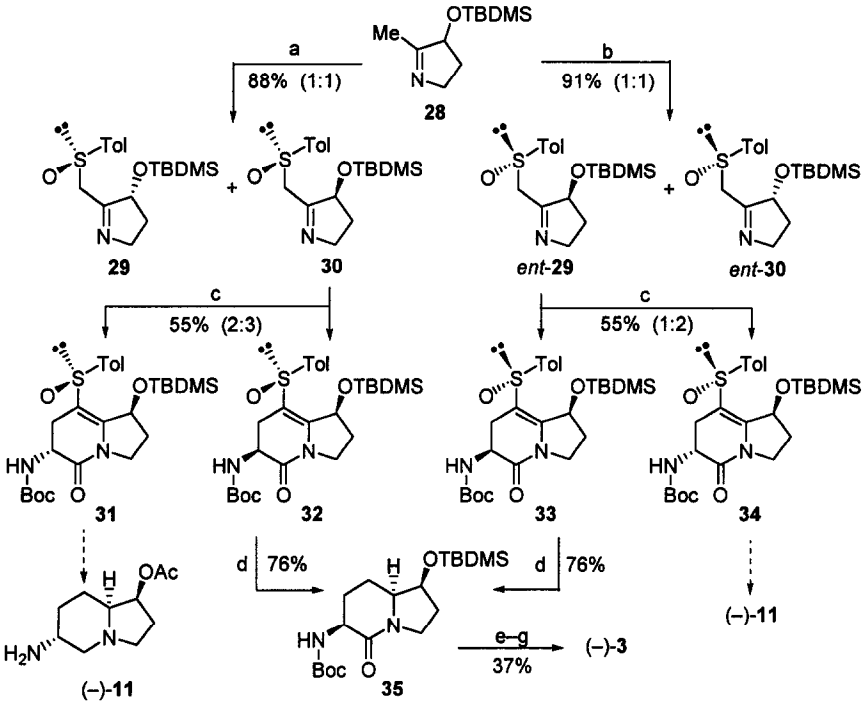
Knight and Sibley began their short asymmetric synthesis of (−)-**3** very similarly (Scheme 3) (*41,42*). Baker's yeast reduction of a 3-oxoproline ester and chemical modification of the resulting (2*R*,3*S*)-3-hydroxyprolinate gave aldehyde **23**, which served as the electrophilic partner in a Julia condensation with dianion **24**, made from the corresponding benzyloxycarbonyl (Cbz) protected serine-derived sulfone. Adduct **25** was obtained as a 3:1 mixture of diastereomers. The modest diastereoselectivity was unimportant since both new stereogenic centers were later defunctionalized to afford alcohol **26**, the mesylate of which was cyclized to give indolizidine **27**. Conventional functional group transformations completed the synthesis of (1*S*,6*S*,8a*S*)-(−)-**3** containing about 10% of the separable 1,8a-diepi isomer **15**, which probably arose from a contaminant formed in the yeast reduction.

In their route to (−)-**3**, Hua and his coworkers demonstrated the usefulness of chiral α-sulfinyl ketimine anions as intermediates in alkaloid synthesis (Scheme 4) (*43*). Treatment of the anion of **28** with (*S*)-(−)-menthyl *p*-toluenesulfinate afforded a 1:1 mixture of the separable diastereomers **29** and **30**, while use of (*R*)-(+)-menthyl *p*-toluenesulfinate afforded the enantiomers *ent*-**29** and *ent*-**30**. Conjugate addition of the anion of **30** to methyl 2-(*tert*-butoxycarbonylamino)acrylate was followed by spontaneous cyclization to give the unsaturated indolizidines **31** and **32** in a ratio of 2:3. Similar treatment of the anion of *ent*-**29** yielded **33** and **34** in the ratio 1:2. Both sets of indolizidine diastereomers were readily separated by chromatography. The synthetic routes converged when reduction of either **32** or **33** with Raney nickel gave the same 5-oxoindolizidine **35**, from which (−)-slaframine (**3**) was derived by simple functional group transformations. Isomers **31** and **34** could likewise be converted into (−)-6-epislaframine (**11**).

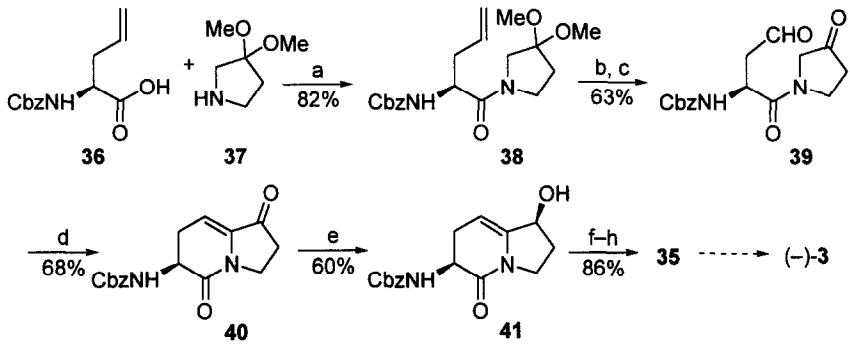
Gallagher and co-workers devised a formal enantioselective synthesis of (−)-**3** in which the stereogenic center at C-6 was derived from Cbz-protected (*S*)-2-amino-4-pentenoic acid (**36**) (*44*). Acylation of 3,3-dimethoxy-pyrrolidine (**37**) with this acid yielded amide **38**, which was converted into aldehyde **39** by cleavage of the terminal alkene with osmium tetroxide and sodium periodate (Scheme 5). The indolizidine nucleus was constructed from **39** by a problematic intramolecular aldol condensation, which was eventually optimized by using 2,2,6,6-tetramethylpiperidine as base followed by adsorption onto, and elution from, silica gel (*45*). Diastereoselective reduction of the ketone group of the aldol product **40** was accomplished in better than 95% enantiomeric excess (ee) with the Corey



SCHEME 3. Reagents: a, MOM-Cl, Pr^i_2NEt, CH_2Cl_2, 20°C; b, DIBAL-H, PhMe, –78°C to 20°C; c, TPAP, NMO, 4Å molecular sieves, CH_2Cl_2–MeCN (9:1); d, THF, –78°C; e, 6% Na–Hg, Na_2HPO_4, MeOH, –20°C; f, trisyl hydrazide, NEt_3, Et_2O; g, Bu_4NF, THF; h, MsCl, pyridine, CH_2Cl_2, –20°C; i, TFA, CH_2Cl_2, then 2M NaOH; j, HCl, MeOH, 60°C; k, Ac_2O, pyridine, CH_2Cl_2; l, H_2, 10% Pd/C, MeOH–HOAc (9:1).



SCHEME 4. Reagents: a, LDA, THF, –25°C, then (*S*)-(–)-menthyl *p*-toluenesulfinate; b, LDA, THF, –25°C, then (*R*)-(+)-menthyl *p*-toluenesulfinate; c, n-BuLi, THF, –78°C, then $H_2C{=}C(CO_2Me)NHBoc$, –78°C to rt; d, H_2 (50 psi), Raney Ni, EtOH, 50°C; e BH_3·THF, 0°C; f, Bu_4NF, THF, 0°C, then Ac_2O, NEt_3, 0°C to 22°C; g, Me_3SiI, $CDCl_3$.

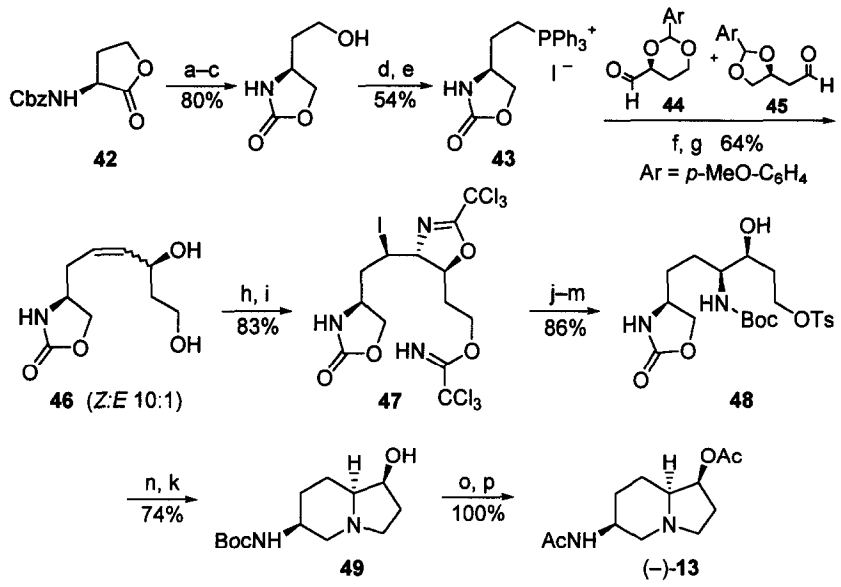


SCHEME 5. Reagents: a, $Me_2N(CH_2)_3N{=}C{=}NEt$, CH_2Cl_2; b, OsO_4 (cat.), $NaIO_4$, THF–H_2O; c, 2M HCl, THF–H_2O; d, 2,2,6,6-tetramethylpiperidine, THF, then SiO_2 chromatography; e, CH_2Cl_2, Corey oxazaborolidine,–20°C; f, TBDMSCl, imidazole, DMF; g, H_2, 10% Pd/C, EtOH; h, $(Boc)_2O$, CH_2Cl_2.

oxazaborolidine reagent (*46*). After silylation of the (1*S*)-alcohol **41**, catalytic hydrogenation of the C=C bond not only set up the (*S*) stereogenic center at the C-8a bridgehead, but also cleaved the benzyloxycarbonyl protecting group. Re-protection as the *tert*-butoxycarbonyl (Boc) derivative **35** completed a formal synthesis of the target alkaloid, since Hua *et al.* had previously converted this intermediate into (–)-slaframine (**3**) (*cf.* Scheme 4) (*43*).

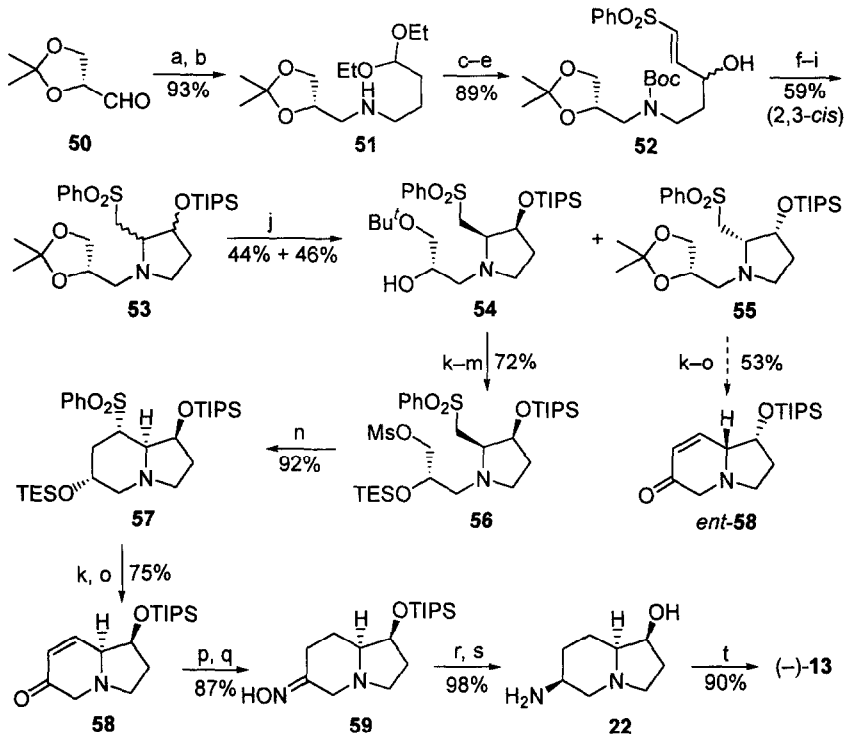
An aspartic acid derivative, the lactone **42**, was the starting material in a recent route to (–)-*N*-acetylslaframine (**13**) by Kang and co-workers (Scheme 6) (*47*). Compound **42** was transformed in four steps into the phosphonium salt **43**, the ylide from which underwent Wittig reaction with a mixture of 1,3-dioxolan- and 1,3-dioxan-containing aldehydes **44** and **45** prepared from *p*-anisaldehyde and (*S*)-butane-1,2,4-triol. A 10:1 mixture of *Z* and *E* alkenes **46** was obtained in 64% overall yield after removal of the benzylidene substituent and oxidative decomposition of the minor 1,2-diol product with periodic acid. Reaction of the isomeric alkenes with trichloroacetonitrile converted them into readily separable bis(trichloroacetimidate) derivatives. The *cis* isomer was cyclized with iodine monobromide to give the *trans*-oxazoline **47** in 83% overall yield. This compound contains the three stereogenic centers of the target alkaloid with the correct absolute configurations. After several standard functional group transformations, the late intermediate **48** underwent a double cyclization on heating at 180°C to give deacetylslaframine, purified as the *N*-Boc derivative **49** (74%). Quantitative hydrolysis and acetylation of this product completed the synthesis of (–)-**13**.

An intriguing stereodivergent approach to both enantiomers of slaframine, devised by Carretero and Gómez Arrayás, commenced with the reductive amination of (*R*)-glyceraldehyde acetonide **50** with the diethyl acetal of 4-aminobutanal (Scheme 7) (*48*). The secondary amine product **51** was transformed in three steps into a 1:1 diastereomeric mixture of α,β-unsaturated γ-hydroxysulfones **52**,



SCHEME 6. Reagents: a, NaOH, MeOH; b, neutralize, then CH_2N_2; c, $LiBH_4$, THF, 0°C to 20°C; d, I_2, Ph_3P, imidazole, DMF; e, Ph_3P, MeCN, reflux; f, BuLi, HMPA, THF, 0°C, then aldehydes **44** + **45**, –78°C to –20°C; g, H_5IO_6, aq. MeOH; h, Cl_3CCN, DBU, MeCN, 0°C; i, IBr, K_2CO_3, EtCN, –78°C; j, HCl (6M), MeOH; k, $(Boc)_2O$, $NaHCO_3$, MeOH, 0°C; l, Ph_3SnH, Et_3B, THF, 0°C; m, *p*-TsCl, pyridine, CH_2Cl_2, 0°C; n, 180°C; o, TFA, CH_2Cl_2; p, Ac_2O, DMAP, Et_3N, CH_2Cl_2.

N-deprotection and cyclization of which gave a mixture of 2,3-*cis*-disubstituted pyrrolidine isomers **53** after further protection steps. Kinetic resolution of this mixture was unexpectedly effected by treatment with trimethylaluminum, which cleaved the dioxolan ring of only one of the isomers. The cleaved product **54** (44%) and the unaffected isomer **55** (46%) were separated by flash chromatography. Differential functionalization of the latent hydroxy groups in the former afforded mesylate **56** (72%), cyclization of which under basic conditions yielded the indolizidine **57** exclusively (92%). After selective removal of the triethylsilyl protecting group, Swern oxidation and *in situ* elimination of the sulfone gave the bicyclic unsaturated (–)-indolizidinone **58** (75%). The same sequence of transformations converted isomer **55** into the (+)-indolizidinone, *ent*-**58**, in 53% overall yield. The synthesis of (–)-*N*-acetylslaframine (**13**) from (–)-**58** was completed *via* oxime **59** and the known (+)-deacetylslaframine **22**, access to which completes a formal synthesis of (–)-slaframine (**3**) itself (*cf.* Ref. *38*). It is to be regretted that the authors did not carry out the conversion of (+)-indolizidinone *ent*-**58** into the unnatural (+)-enantiomer of slaframine, but the transformations should parallel those shown in Scheme 7.



SCHEME 7. Reagents: a, $(EtO)_2CH(CH_2)_3NH_2$, MeOH, 3Å molecular sieves; b, $NaBH_4$, MeOH; c, $(Boc)_2O$, CH_2Cl_2; d, AcOH–H_2O (2:1); e, $PhO_2SCH_2SO_2$-*p*-Tol, piperidine, CH_2Cl_2, 0°C; f, TFA (10 equiv), CH_2Cl_2; g, Et_3N, THF, –78°C; h, *p*-TsOH, $Me_2C(OMe)_2$, CH_2Cl_2; i, TIPS-OTf, 2,6-lutidine, CH_2Cl_2; j, Me_3Al (10 equiv), CH_2Cl_2; k, TFA, H_2O; l, MsCl, Et_3N, CH_2Cl_2, 0°C; m, TES-Cl, imidazole, CH_2Cl_2; n, LHMDS, THF, 0°C; o, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C; p, H_2, PtO_2, EtOAc; q, NH_2OH·HCl, pyridine, MeOH; r, H_2, PtO_2, EtOH, conc. HCl; s, Dowex-OH^-; t, Ac_2O, pyridine.

B. CYCLIZIDINE

The microbial metabolite cyclizidine (**60**), introduced in Volume 28 of this treatise (*1*), was originally isolated from a *Streptomyces* strain found in a hedgerow soil sample in the United Kingdom (*49*). It has since been isolated by Chinese workers from the fermentation broth of *Streptomyces* strain L-892 (*50*).

Biosynthetic studies with ^{13}C-labeled precursors by Leeper and co-workers proved that the carbon skeleton of **60** is derived from acetate and propionate units in a polyketide fashion as shown in Fig. 2 (*51,52*). Doubly-labeled sodium acetate ($^{13}CH_3{}^{13}CO_2Na$) was incorporated into four pairs of carbon atoms (C-2/C-3, C-5/C-6, C-7/C-8, C-12/C-13), while the ^{13}C marker in singly-labeled sodium propionate ($CH_3CH_2{}^{13}CO_2Na$) appeared at C-8a, C-10 and C-14. In addition, the deuterium label of $CD_3CH_2CO_2Na$ was located in the methyl groups at C-9 and C-17, and in the

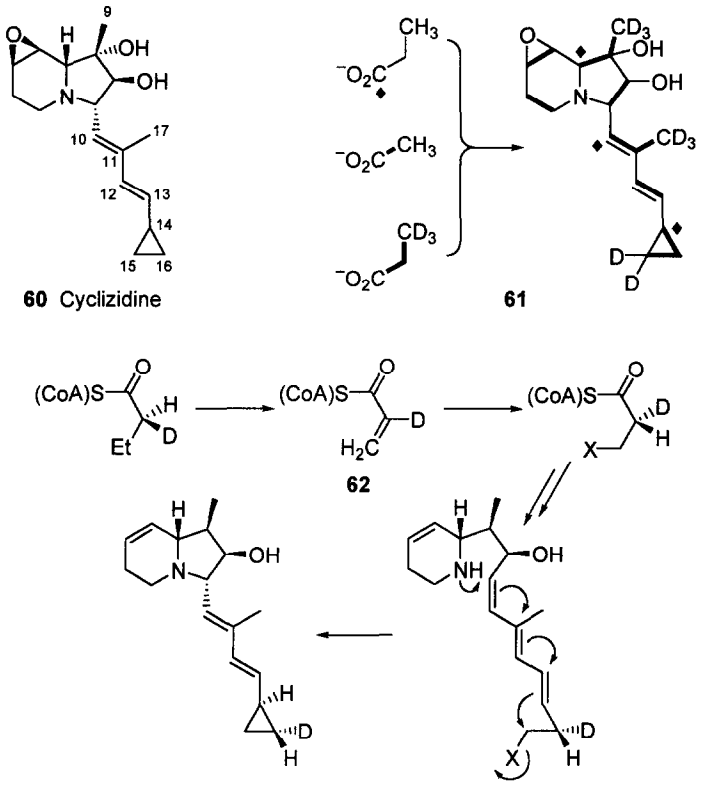


FIG. 2. Aspects of the biosynthesis of cyclizidine (**60**).

cyclopropyl ring at C-16, although the level of incorporation at the latter was approximately half of that at the methyl groups. The results are summarized pictorially in **61**. With sodium acetate doubly labeled at carbon and oxygen ($CH_3{}^{13}C^{18}O_2Na$), only the hydroxy group at C-2 was found to be derived from intact acetate, thus precluding the involvement of a C-2/C-3 epoxide in the formation of the five-membered ring.

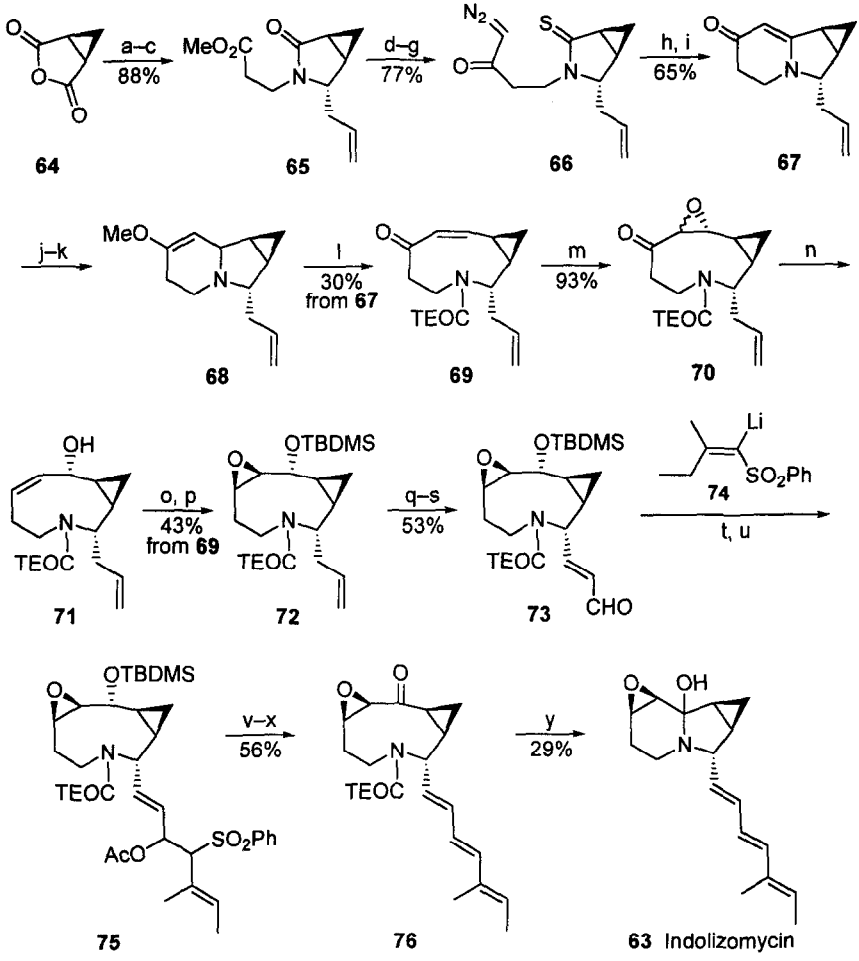
The biosynthesis of the cyclopropyl ring was studied further with propionate doubly labeled with both deuterium and carbon-13 ($CD_3CH_2{}^{13}CO_2Na$) (*52*). The results showed that the propionate unit was incorporated intact, but with low efficiency, apparently because of deuterium-related kinetic effects that accompany an unexpected modification of propionate during incorporation. The stereochemical subtleties were probed by Kuhn–Roth degradation of the labeled natural product, conversion of the cyclopropanecarboxylate thus produced into cyclopropyl phenyl carbinol, and resolution of (1*S*)-camphanate esters—a risky undertaking that was

first perfected with a model system (*53*). The results revealed that C-3 of propionate became the pro-*S* methylene group of the cyclopropyl ring. More surprisingly, incorporation experiments with 2-deuteriated propionate ($CH_3CD_2CO_2Na$) showed that only *one* deuterium atom was incorporated at C-15, and that it ended up specifically *cis* to the hydrogen at C-14. Finally, both (2*R*)-CH_3CHDCO_2Na and (2*S*)-CH_3CHDCO_2Na were incorporated into cyclizidine, but only the latter transferred its label to the natural product, though even then not very efficiently. The pro-*S* deuterium label of propionate thus ends up in the pro-*R* position at C-15 of cyclizidine, a net inversion of configuration. The simplest rationalization for all these observations is shown in Fig. 2, which gives a proposed mechanism for the stereochemical course of events *via* a dehydrogenated propionate equivalent such as **62**, as well as a proposal for the formation of the three- and five-membered rings of cyclizidine.

C. INDOLIZOMYCIN

The isolation, structural elucidation, and biological activity of the extraordinary metabolite indolizomycin (**63**) were described in the earlier review on simple indolizidine and quinolizidine alkaloids in Volume 28 of this series (*1*). The compound was obtained from a mutant *Streptomyces* strain 'bioengineered' by protoplast fusion of two strains that do not normally produce antibiotics (*54*). It was reported to be exceedingly unstable, undergoing decomposition within a few hours under neutral conditions at room temperature.

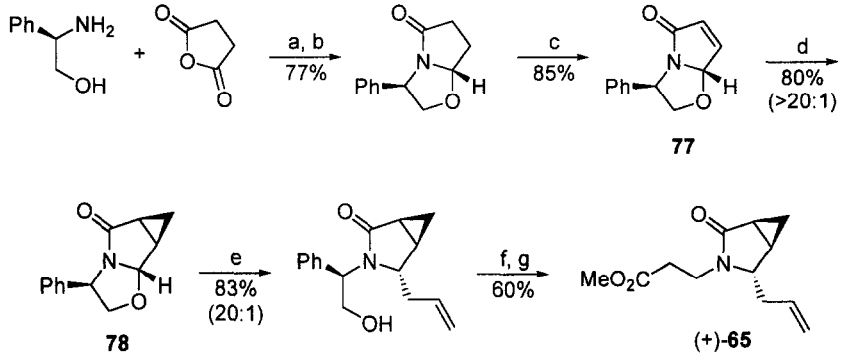
Danishefsky and co-workers, fascinated by the structural complexity of **63** and undaunted by its reported lability, devised the innovative synthesis of the racemic compound shown in Scheme 8 (*55,56*). Surmising that the instability of **63** probably stems largely from the location of the bridgehead carbinolamine in relation to other structural features, they chose to defer the creation of this feature until the final step of their synthesis. The cyclopropane ring, assumed to be the least labile structural unit, was present at the start in the bicyclic anhydride **64**, which was transformed in three steps into the lactam **65** (*vide infra*), and thereafter into the thiolactam **66**. A novel 'aza-Robinson' annulation between the diazoketone and thiocarbonyl groups of **66** was induced by treatment with rhodium(II) acetate followed by desulfurization with Raney nickel to give the tricyclic vinylogous amide **67** in 65% yield. Ironically, the next phase of the synthesis required disassembly of the indolizidine core, which was accomplished by treating enol ether **68** with 2-(trimethylsilyl)ethoxycarbonyl (TEOC) chloride, the use of which proved to be critical to the eventual success of the synthesis. However, the yield of the azonine product **69** from this 'vinylogous McCluskey cleavage', as the authors termed it, was only 30%. Epoxidation of **69** gave a mixture of isomers of **70**, but the subsequent Wharton reaction afforded a single allylic alcohol **71**. The epoxidation of **71** with *m*-chloroperoxybenzoic acid took place *anti* to the hydroxy group, an interesting observation that is apparently precedented for medium-ring allylic alcohols. Also interesting is that the epoxide ring of the product **72** remained unscathed throughout the rest of the synthesis.



SCHEME 8. Reagents: a, Ph_3P, $N_3CH_2CH_2CO_2Me$, C_6H_6, 0°C, then $Bu_4N^+ CN^-$; b, $NaBH_4$, MeOH, –10°C; c, $H_2C{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, 0°C; d, Lawesson's reagent, C_6H_6, reflux; e, 1M NaOH, MeOH; f, Bu^iOCOCl, *N*-methylmorpholine, THF, 0°C; g, CH_2N_2, Et_2O, 0°C; h, $Rh_2(OAc)_2$, C_6H_6, reflux; i, W-2 Raney Ni, $Me_2C{=}O$; j, $Me_3O^+ BF_4^-$; CH_2Cl_2, 0°C; k, $NaBH_4$, MeOH, 0°C; l, $Me_3SiCH_2CH_2OCOCl$, C_6H_6; m, 30% H_2O_2, 3M NaOH, MeOH,; n, $H_2NNH_2{\cdot}H_2O$, cat. AcOH, MeOH; o, MCPBA, CH_2Cl_2, 0°C; p, TBDMS-OTf, Et_3N, CH_2Cl_2, 0°C; q, O_3, CH_2Cl_2–MeOH, $NaHCO_3$, –78°C, then Me_2S; r, $Ph_3P{=}CHOMe$, THF, 0°C; s, $^1O_2$, hv, tetraphenylporphine (10%), C_6H_6, then PPh_3; t, lithium reagent **74**, THF, –78°C; u, Ac_2O, THF; v, 5% Na(Hg), THF–MeOH (3:1), –20°C; w, 1M HIO_4, THF; x, TPAP, CH_2Cl_2; y, Bu_4NF, THF, 0°C.

Ozonolysis of **72** followed by Wittig homologation with methoxymethylene-triphenylphosphorane and ene reaction with singlet oxygen yielded the unsaturated aldehyde **73**. The sensitive conjugated triene side chain was introduced rather late in the sequence by means of Julia methodology, which involved treating **73** with lithiated vinylsulfone **74**, acetylating the condensation product *in situ*, and reductively eliminating the β-acetoxy and sulfone groups of intermediate **75**. Deprotection and oxidation of the alcohol group gave the penultimate intermediate **76**. Finally, cleaving the TEOC group with tetrabutylammonium fluoride initiated a spontaneous transannular ring closure to give (±)-indolizomycin (**63**) in 0.46% overall yield based on **64**. The synthesis did not establish the stereochemistry of the carbinolamine bridgehead. As expected, the purification of **63** was complicated by its propensity to decompose, and its extreme lability precluded direct comparison with the natural product. However, the NMR spectra agreed with those published for natural indolizomycin, and X-ray crystallographic analysis of derivatives of intermediates **69** and **71** confirmed important structural and stereochemical features.

Groaning and Meyers have recently synthesized the (*S*)-(+)-enantiomer of Danishefsky's early intermediate **65** by a short alternative route (Scheme 9) (*57*). In one of the key steps, cyclopropanation of the chiral unsaturated bicyclic oxazolidinone **77** took place preferentially on the convex face (>20:1). Subsequent treatment of the product **78**, a masked acyliminium ion, with allyltrimethylsilane and titanium tetrachloride introduced the allyl group at the angular position, again with good stereocontrol (20:1). The preparation of (+)-**65** in effect represents a formal synthesis of (−)-indolizomycin (**63**).

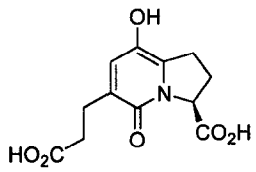


SCHEME 9. Reagents: a, PhMe, Et_3N, reflux; b, $NaBH_4$, EtOH, 2M HCl; c, $PhSO_2Me$, KH, PhMe, reflux; d, dimethylsulfoxonium methylide; e, $H_2C{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, −78°C to 0°C; f, Ca, NH_3; g, KH, $BrCH_2CH_2CO_2Me$.

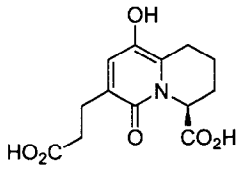
D. *STREPTOMYCES* METABOLITES A58365A AND A58356B

It was reported in 1985 that the culture broth of the soil bacterium *Streptomyces chromofuscus* NRRL 15098 showed inhibitory activity towards angiotensin-converting enzyme (ACE) at sub-nanomolar concentrations (*58*). Two active components, coded as A58365A and A58365B, were detected in the broth, and conditions were developed for their biosynthesis by the microorganism (*59*). After painstaking isolation, preliminary spectroscopic studies revealed them to be the homologous bicyclic pyridones **79** ($[\alpha]_D^{25}$ –199.5°, *c* 1.0, H_2O) and **80** ($[\alpha]_D^{25}$ –141.2°, *c* 0.16, H_2O), respectively (*60*). Full details of their structural elucidation by means of ^1H- and ^{13}C-NMR spectroscopies, UV spectroscopy, and mass spectrometry were subsequently reported (*61*). UV spectroscopic evidence for the 5-hydroxy-2-pyridone chromophore was particularly important; like certain model 5-hydroxy-2-pyridones, **79** and **80** possessed a long-wavelength absorbance maximum near 330 nm that was red-shifted by 25–30 nm upon addition of base. Several ester derivatives of **79** were prepared in order to obtain further spectroscopic correlations, while catalytic hydrogenation gave a deoxytetrahydro derivative **81**. The structure of A58365A was ultimately substantiated by X-ray crystallographic analysis of its dimethyl ester. The absolute configuration, not determined at the time, was reasonably assumed to be the same as in L-proline. This assumption was verified soon thereafter by synthesis (*62*).

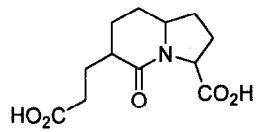
The first synthesis of (–)-**79**, by Fang and Danishefsky, used L-pyroglutamic acid (**82**) as the chiral precursor (Scheme 10) (*62*). The vinylogous urethane derivative **83** underwent annulation with methyleneglutaric anhydride (**84**) to give the hexahydroindolizinone **85** as a 2:1 mixture of diastereomers. Dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) yielded the pyridone-5-carboxylic acid **86**, oxidative decarboxylation of which was effected with dicyclohexylcarbodiimide (DCC) and *m*-chloroperoxybenzoic acid. This, the weakest step in the synthesis, gave a mixture of the desired hydroxypyridone **87** and the corresponding *m*-chlorobenzoate **88** and methyl ether **89** in yields of 15%, 21%, and 5%, respectively. At this stage, ester hydrolysis of the first two products should in principle lead to the target alkaloid. However, in order to preserve the pyridone ring, these two compounds were converted into the corresponding benzyl esters by a mild ester-exchange method, after which hydrogenolysis over a palladium catalyst completed the synthesis of (–)-**79**.



79 (–)-A58365A



80 (–)-A58365B



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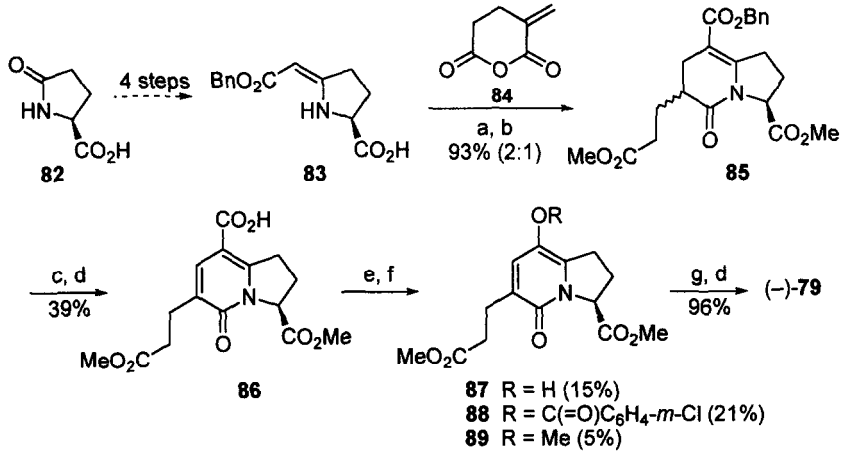
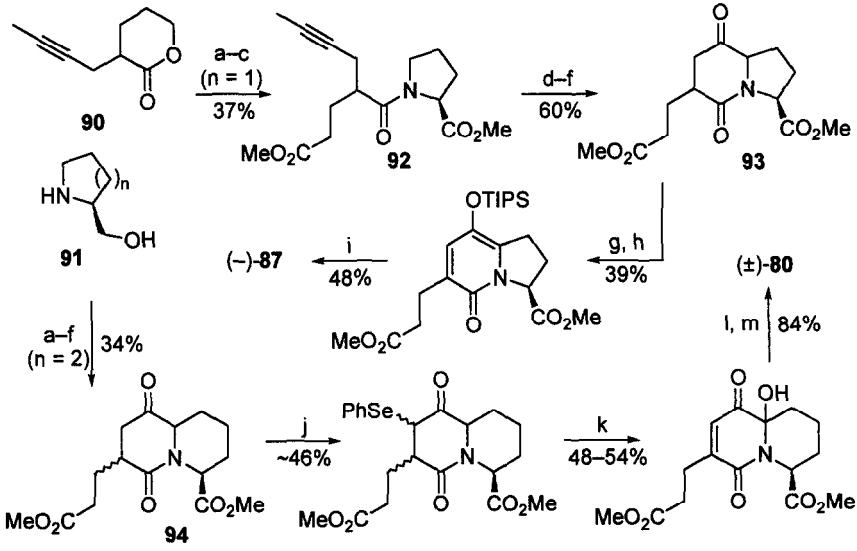


SCHEME 10. Reagents: a, C_6H_6, reflux; b, CH_2N_2; c, DDQ, dioxan, reflux; d, H_2, Pd/C, MeOH; e, DCC, CH_2Cl_2, –20°C; e, MCPBA, CH_2Cl_2, –20°C; f, $PhCH_2OH$, cat. $ClBu_2SnOSnBu_2OH$ (Otera's catalyst), PhMe, reflux.

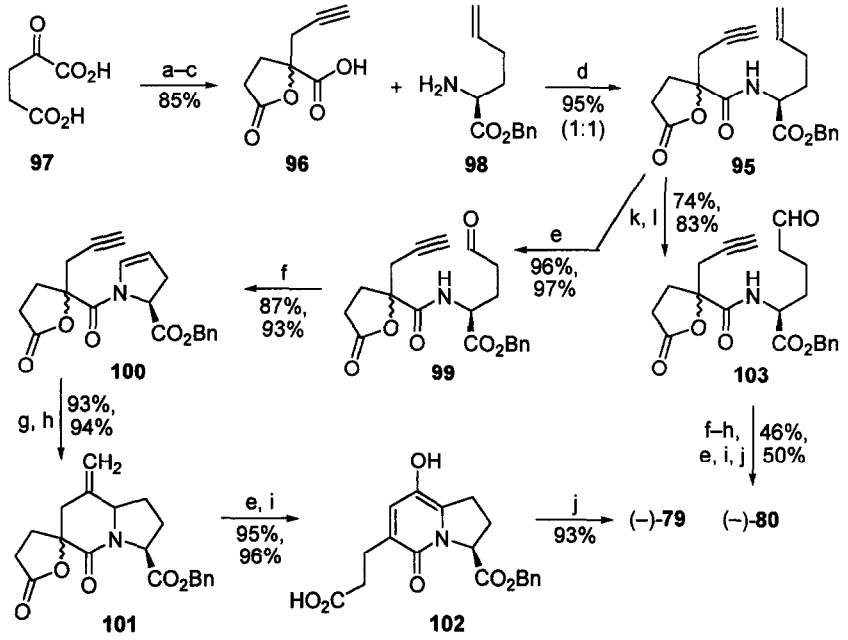


SCHEME 11. Reagents: a, Me_3Al, PhMe, reflux; b, Jones oxidation; c, $Me_2NCH(OMe)_2$, C_6H_6, reflux; d, C anode, Pt cathode, Et_4NOTs (0.03M in MeOH), undivided cell, *ca* 36 mA; e, $TiCl_4$, CH_2Cl_2, –78°C to rt; f, O_3, MeOH, –78°C, then Zn, HOAc, –78°C to rt; g, TIPS-OTf, NEt_3, C_6H_6, 0°C to rt; h, DDQ, dioxan, reflux; i, 0.01M HCl in MeOH–H_2O (1:1), 105°C; j, LiTMP, THF, –78°C to –40°C, then PhSeBr; k, MCPBA, CH_2Cl_2, 0°C to rt; l, Et_3SiH, CF_3CO_2H, $CHCl_3$; m, Bu_4NBr, 9M HBr, 110°C.

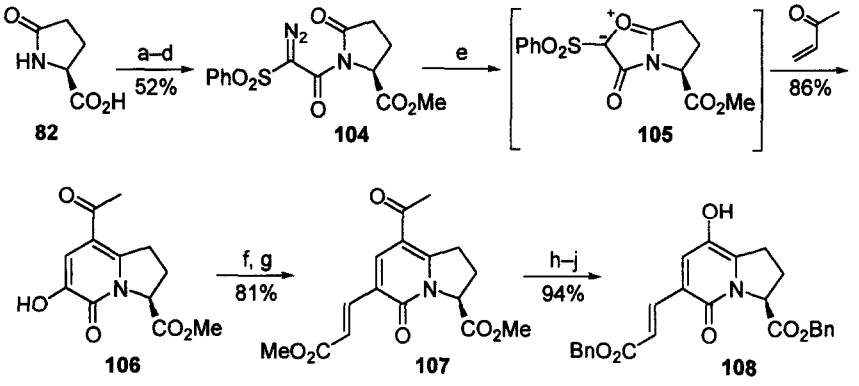
In the later route to (−)-**79** by Wong and Moeller, amide formation between lactone **90** and (*S*)-(+)-prolinol (**91**, n = 1) was followed by oxidation of the alcohol groups and esterification to give **92** (Scheme 11) (*63*). Proline itself was an unsuitable starting material, since it racemized under the reaction conditions. Anodic oxidation α to nitrogen followed by treatment with titanium tetrachloride generated an acyliminium ion *in situ*, capture of which by the alkyne group created the desired indolizidine nucleus. The dione **93** was isolated after ozonolysis of the alkylidene intermediate. The problematic aromatization of the lactam ring was accomplished by converting the ketone into a silyl enol ether, after which oxidation with DDQ and mild hydrolysis yielded the Danishefsky intermediate (−)-**87**. This completed a formal synthesis of (−)-**79** in an ee of approximately 92%. An analogous synthesis of racemic A58365B (**80**) from (±)-piperidine-2-methanol (**91**, n = 2) proceeded along the same lines as far as intermediate **94**, but even greater problems experienced during the aromatization step necessitated the illustrated change in strategy.

After communicating methodology for the synthesis of (±)-A58365A (**79**) (*64*) and A58465B (**80**) (*65*), Clive and co-workers published full details of an improved adaptation that led to both of the levorotatory alkaloids from a common intermediate **95** (*66*). This intermediate, a separable mixture of two diastereomers, was prepared in convergent fashion from the racemic lactone **96** (itself made in three steps from the α-keto acid **97**), and the serine-derived (*S*)-amino ester **98**. Although the separated diastereomers of **95** were individually taken through the illustrated reaction sequence (Scheme 12; yields quoted are for individual isomers), convergence was again achieved in the final stages of the synthesis. Thus, the relative stereochemistry of intermediates from **95** onward (never determined, incidentally) was actually irrelevant in view of the ultimate destruction of the stereogenic center introduced from lactone **96**. For the synthesis of (−)-**79**, intermediates **95** were cleaved with ozone to give the aldehydes **99**, which were smoothly cyclized to the enamides **100** by sonication with barium oxide, followed by continued sonication in the presence of phosphorus pentoxide. A second ring closure involving enyne radical cyclization, initiated with tributyltin hydride and AIBN in boiling toluene, was followed by destannylation to give spirotricyclic compounds **101**. Ozonolysis of the methylene groups and base-initiated cleavage of the lactone rings saw the diastereomers converging to the common intermediate **102**. Hydrogenolysis of the benzyl ester completed the syntheses of (−)-**79**. A similar sequence of reactions was used for making (−)-**80**, but in this case hydroboration and oxidation of the intermediates **95** gave the chain-extended aldehyde diastereomers **103** *en route* to the target alkaloid.

The most recently published route to (−)-**79**, by Straub and Padwa, began with L-pyroglutamic acid (**82**), which was converted into the diazosulfone **104** in four standard steps (Scheme 13) (*67*). Treatment with catalytic quantity of rhodium(II) acetate in benzene at 80°C generated a transient isomünchnone intermediate **105**, which underwent a 1,3-dipolar cycloaddition with methyl vinyl ketone to give the bicyclic pyridone **106** in 86% isolated yield. The product was readily converted into the corresponding triflate, Heck reaction of which with methyl acrylate afforded the prop-2-enoate derivative **107** in 81% yield. Catalytic hydrogenation, Baeyer–Villiger oxidation, transesterification, and acetate cleavage yielded the benzyl ester **108**, at which point the synthesis coincided with the Danishefsky route to (−)-**79**.



SCHEME 12. Reagents: a, *p*-TsOH·H_2O, MeOH, $CHCl_3$, azeotropic distillation; b, $HC{\equiv}CCH_2Br$, Al, $HgCl_2$, THF, –78°C; c, LiOH, THF, H_2O, then Amberlite IR-120; d, 1-($Me_2NCH_2CH_2CH_2$)N=C=NEt·HCl, 1-hydroxybenzotriazole, CH_2Cl_2, DMF; e, O_3, CH_2Cl_2, –78°C, then Ph_3P, –78°C *to* rt; f, BaO, CH_2Cl_2, *ultrasound, then* P_2O_5, *ultrasound*; g, Bu_3SnH, AIBN, PhMe, reflux; h, TFA, THF; i, Et_3N, THF, 60°C; j, H_2 (1 atm), 10% Pd/C, MeOH; k, 9-BBN, THF, 0°C to rt; l, PCC, CH_2Cl_2, 4Å molecular sieves, reflux.



SCHEME 13. Reagents: a, MeOH, Dowex; b, $PhSCH_2COCl$, C_6H_6; c,oxone, MeOH; d, *p*-$MeCONHC_6H_4SO_2N_3$, Et_3N; e, $Rh_2(OAc)_4$, C_6H_6, 80°C; f, $PhN(OTf)_2$, Et_3N; g, $H_2C{=}CHCO_2Me$, $Pd(Ph_3P)_2Cl_2$, Et_3N, MeCN; h, H_2, Pd/C, $CHCl_3$; i, H_2O_2, TFA; j, $PhCH_2OH$, $ClBu_2SnOSnBu_2OH$ (Otera's catalyst), PhMe, 120°C.

III. Hydroxylated Indolizidine Alkaloids

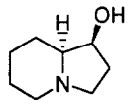
The high profile enjoyed by the hydroxylated indolizidine alkaloids stems from their potent biological activity as inhibitors of glycosidases. The first general survey of this topic appeared in Volume 28 of this treatise (*1*). The update by Takahata and Momose in Volume 44 extended coverage of the literature up to 1992 (*2*). In 1987 Elbein and Molyneux reviewed the chemistry and biochemistry of this group of alkaloids for another important series of volumes (*68*). Other reviews published since 1992 have dealt with the distribution, isolation, purification, structural elucidation, analysis and biological activity of this important group of alkaloids (*69–73*), while large sections of several more general reviews are also devoted to these metabolites (*14,18,22,24,25*).

A. 1-Hydroxyindolizidines

Harris *et al.* postulated that (1*S*,8a*S*)-(+)-1-hydroxyindolizidine (**109**) and (1*R*,8a*S*)-1-hydroxyindolizidine (**110**) were pivotal intermediates in the biosynthesis of slaframine (**3**) and swainsonine (*cf.* Section III.C) in the fungus *Rhizoctonia leguminicola* (*74*). Compound **110** was subsequently isolated as the acetate from extracts of the diablo locoweed, *Astragalus oxyphysus* (*75*).

Pertinent publications since 1992 have dealt exclusively with the synthesis of **109**, invariably as the (+)-enantiomer. The only recent preparation of the racemic alkaloid used a boron trifluoride-promoted condensation between vinylboronate **111** and the *N*-benzyloxycarbonyl-2,3-dihydroxypyrrolidine **112** to produce the *cis*-2-alkenyl-3-hydroxypyrrolidine **113** in 62% yield (Scheme 14) (*76*). Tosylation of the alcohol group followed by catalytic reduction of the alkene with concomitant hydrogenolysis of the *N*-Cbz group and spontaneous cyclization completed this short but effective synthesis of (±)-**109**.

The key step in an enantioselective synthesis of (1*S*,8a*S*)-(+)-**109** by Green *et al.* was the stereoselective addition of the *O,C*-dianion of sulfone **114** to the chiral imine **115** [made in six steps from (*S*)-malic acid], which gave a 2:1 mixture of the separable lactam diastereomers **116** and **117** (Scheme 15) (*77*). Although the isomers were individually taken through the illustrated reaction sequence, removal of the acetal protecting group from the indolizidines **118** followed by desulfonylation ensured convergence to the same product (+)-**109**, which was obtained in an optical purity of greater than 95%.



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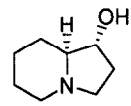

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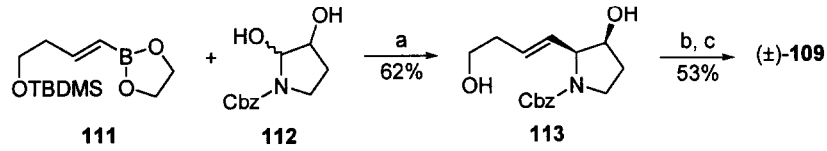
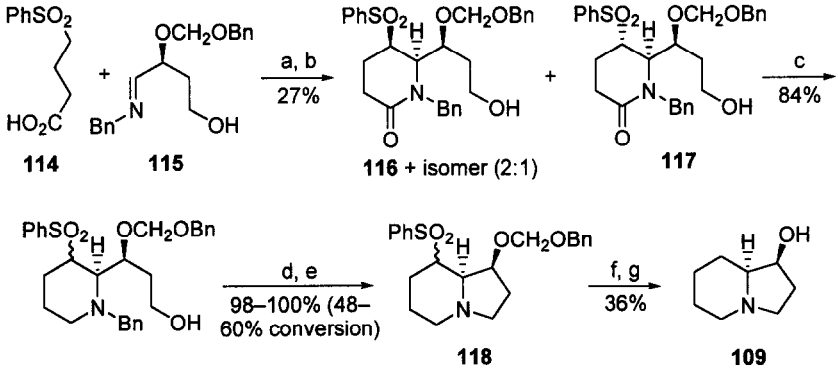
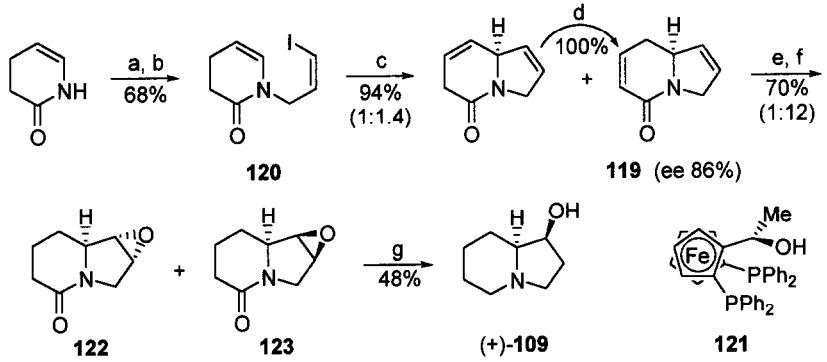


SCHEME 14. Reagents: a, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78°C to rt; b, *p*-TsCl, Et_3N, pyridine, CH_2Cl_2, –78°C to rt; c, H_2, Pd/C, EtOH, 4°C.



SCHEME 15. Reagents: a, **115**, $BF_3{\cdot}Et_2O$, THF, –78°C, added to **114** + BuLi (2 equiv), THF, –78°C to 0°C; b, TFAA, 0°C; c, $BH_3{\cdot}THF$, THF, 0°C; d, MsCl. NEt_3, K_2CO_3, CH_2Cl_2; e, H_2 (39 psi), $Pd(OH)_2$, MeOH; f, H_2 (10–20 psi), 10% Pd/C, MeOH, TFA; g, 6% Na–Hg, MeOH.

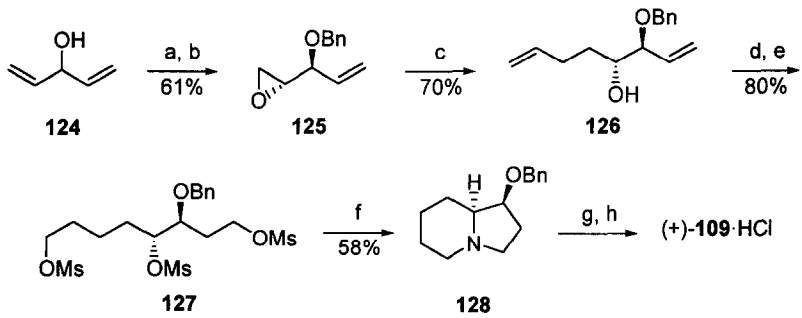


SCHEME 16. Reagents: a, NaH, DMF; b, (*Z*)-$ICH_2CH{=}CHI$; c, $Pd_2(dba)_3$ (4 mol %), **121** (9.6 mol %), Ag-exchanged zeolite (*ca.* 6 equiv Ag), DMSO–DMF (1:1), 0°C, 5 d; d, Pd/C, MeOH, rt; e, K-Selectride (1M in THF), Et_2O, –78°C to 0°C; f, 30% aq. H_2O_2, HCO_2H; g, $BH_3{\cdot}THF$, $LiBH_4$, THF, 0°C, then aq. HCl, 0°C to 60°C.

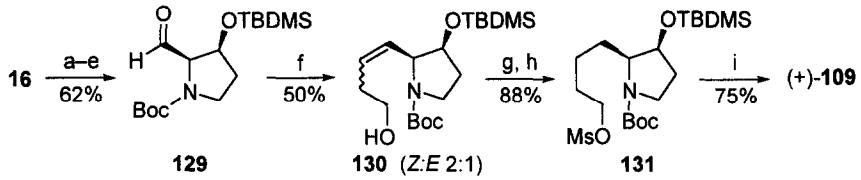
(−)-3,5,8,8a-Tetrahydroindolizin-5-one (**119**), prepared from the (*Z*)-vinyl iodide **120** by an intramolecular asymmetric Heck reaction in the presence of the chiral phosphine ligand **121**, is a potentially versatile intermediate from which to gain access to hydroxylated indolizidines (*78*). For example, selective reduction of the conjugated double bond with K-selectride followed by epoxidation of the unconjugated alkene with peroxyformic acid yielded a 1:12 mixture of epoxides **122** and **123** (*79*). Reduction of the latter with diborane completed a simple synthesis of (+)-**109** (Scheme 16). Other synthetic uses of intermediate **119** or its enantiomer will be described in Sections III.B (*cf.* Scheme 23) and V.B (*cf.* Scheme 76).

Another short route to (+)-**109** used Sharpless asymmetric epoxidation of penta-1,4-dien-3-ol (**124**) with (+)-diisopropyl tartrate to introduce the required stereogenic centers at an early stage of the synthesis (Scheme 17) (*80*). Cleavage of epoxide **125** with allylmagnesium chloride in the presence of copper(I) iodide produced the dienol **126**. Hydroboration of both terminal alkenes followed by mesylation led to the acyclic tris(mesylate) **127**. Treatment with aqueous ammonia brought about a double cyclization to give the indolizidine **128** in 58% yield, the internal stereogenic site undergoing inversion of configuration in the process. After hydrogenolysis of the benzyl protecting group, the target compound (+)-**109** was isolated as the hydrochloride salt.

Sibi and co-workers devised an enantiospecific synthesis of (+)-**109** from the same 3-oxoproline ethyl ester **16** previously used in their synthesis of (+)-slaframine (**3**) (*cf.* Section II.A, Scheme 2) (*39*). In this case, Wittig reaction between the aldehyde **129** and the ylide prepared from 3-hydroxypropyl-phosphonium chloride gave a 2:1 mixture of *cis*- and *trans*-alkenes **130** in 50% yield. Catalytic hydrogenation followed by mesylation of the primary alcohol group set the scene for the ensuing cyclization, which took place spontaneously upon hydrolysis of the *N*-Boc protecting group of **131**. The overall yield of (+)-**109** was 16.3% based on **16** (Scheme 18).



SCHEME 17. Reagents: a, L-(+)-DIPT, Bu^{t}OOH, Ti(OPr^i)$_4$, 4Å molecular sieves, CH_2Cl_2, −20°C; b, BnBr, NaH, Bu_4NI, THF −20°C; c, $H_2C{=}CHCH_2MgCl$, CuI (10%), THF, −78°C; d, dicyclohexylborane (3 equiv), THF, then 3M NaOH, H_2O_2 (30% aq.); e, MsCl, pyridine, CH_2Cl_2; f, aq. NH_3, K_2CO_3, MeOH, 2 d; g, H_2, $PdCl_2$, MeOH; h, HCl (g).

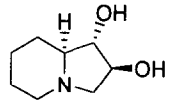


SCHEME 18. Reagents: a, baker's yeast immobilized on sodium alginate, sucrose, H_2O–EtOAc; b, H_2 10% Pd/C, $(Boc)_2O$, MeOH; c, TBDMS-Cl, imidazole, DMF, 0°C to rt; d, $LiBH_4$ (2M in THF), $B(OMe)_3$, Et_2O, reflux; e, DMSO, TFAA, CH_2Cl_2, Et_3N, –78°C to 0°C; f, $HO(CH_2)_3PPh_3^+$ Cl^-, LiHDMS, THF, –78°C to rt; g, H_2, 10% $Pd(OH)_2/C$, EtOAc; h, MsCl, Et_3N, CH_2Cl_2, 0°C; i, 3M HCl, dioxane, then 1M NaOH.

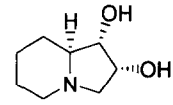
B. 1,2-DIHYDROXYINDOLIZIDINES

1. Structure and Biological Activity

This class of hydroxylated indolizidine alkaloids is represented by two natural products, lentiginosine (**132**) and 2-epilentiginosine (**133**). When lentiginosine was first isolated from the leaves of *Astragalus lentiginosus* var. *diphysus*, the (1*S*,2*S*,8a*S*) absolute configuration shown in **132** was assumed on biogenetic grounds (*81*). The specific rotation was recorded as –3.3° (*c* 0.33, MeOH). Some years afterwards, a total synthesis of the (1*S*,2*S*,8a*S*) enantiomer (*cf.* Scheme 19) yielded a product with a specific rotation of +0.19° (*c* 6.10, MeOH) (*82*), the sign of which was ascribed to contamination by a small quantity of the bridgehead diastereomer. However, when a later synthesis of the same enantiomer (*cf.* Scheme 20) yielded a product with a specific rotation of +3.2° (*c* 0.27, MeOH), it began to look as though either the sign of the optical rotation or the absolute configuration had been incorrectly assigned in the original work (*83*). After Gurjar *et al.* showed that their synthetic sample of (1*R*,2*R*,8a*R*)-(–)-lentiginosine (*cf.* Scheme 22) had an optical rotation very close to that of the natural product ($[\alpha]_D$ –2.6°, *c* 1.0, MeOH) (*84*), opinion favored the hypothesis that the wrong absolute configuration had been assigned to the natural product. However, Brandi and co-workers offered an alternative explanation for the anomalous results based on the biological activity of both the (1*S*,2*S*,8a*S*)-(+) and the (1*R*,2*R*,8a*R*)-(–) enantiomers, which they synthesized from (+)- and (–)-tartaric acids, respectively (*cf.* Scheme 20) (*85*). While both enantiomers were specific inhibitors of amyloglycosidases from various sources, (–)-lentiginosine was about 35 times less potent than (+)-lentiginosine, which had approximately the same activity as that reported for the natural alkaloid. This result strongly suggests that natural lentiginosine is almost certainly the (1*S*,2*S*,8a*S*)-(+) enantiomer **132**. Since the optical rotations of the pure enantiomers are very small, the negative rotation originally reported for lentiginosine is thought to have arisen from impurities in the isolated sample—a plausible explanation, since the published NMR spectrum of the natural product shows that impurities are indeed present (*81*). While the Brandi rationalization is cogent, the matter is likely to be settled only by a more detailed structural investigation of natural lentiginosine.



132 Lentiginosine



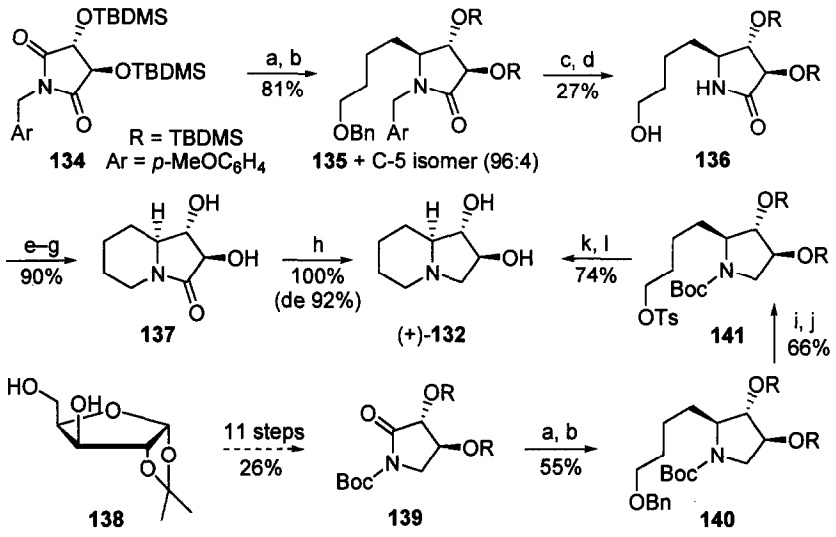
133 2-Epilentiginosine

Glucoamylase, an enzyme that is widely used in industry for the conversion of starch into glucose, is one of the amyloglucosidases inhibited most strongly by (+)-**132**. Starting from published X-ray crystallographic data for the complex formed between a simpler glycosidase inhibitor, deoxynojirimycin, and glucoamylase II from *Aspergillus awamori* var. X100, the Brandi team used molecular dynamics methods to simulate the interaction between **132** and the active site of glycoamylase II (*86*). The ability of the alkaloid to inhibit the enzyme appears to result from strong hydrogen bonding between the *trans*-disposed OH groups and the enzyme's key Arg 54 and Asp 55 residues.

2. Synthesis

No fewer than eight syntheses of (1*S*,2*S*,8a*S*)-(+)-lentiginosine (**132**) and three of (1*R*,2*R*,8a*R*)-(−)-lentiginosine (*ent*-**132**) have been published since 1993. Several of them begin with substrates derived from either L-(+)- or D-(−)-tartaric acid, which provide the target alkaloid's *trans*-1,2-dihydroxy substituents. The first published route to (+)-**132**, by Yoda *et al.*, used the C_2-symmetric imide **134** derived from L-(+)-tartaric acid (Scheme 19, top line) (*82*). Treatment of **134** with 4-benzyloxybutylmagnesium bromide followed by triethylsilane in the presence of boron trifluoride etherate provided the lactam **135** as a 96:4 mixture with its C-5 epimer. Removal of both benzyl protecting groups yielded pyrrolidin-2-one **136**, after which mesylation of the alcohol and base-induced cyclization yielded indolizidin-3-one **137**. Simple transformations completed the synthesis of (+)-**132** in a diastereomeric excess (de) of 92%. A second, more recent, route to (+)-**132** by Yoda *et al.* commenced by converting the commercially available 1,2-*O*-isopropylidene-D-xylofuranose **138** into the *tert*-butyldimethylsilyl (TBDMS)-protected pyrrolidin-2-one **139** in eleven steps and 26% yield (Scheme 19, bottom line) (*87*). Once again, addition of 4-benzyloxybutylmagnesium bromide was followed by highly stereoselective (98:2) reductive deoxygenation of the hydroxypyrrolidine adduct to yield the pyrrolidine **140**. The indolizidine nucleus was formed by *N*-deprotection and ring closure of tosylate **141**, after which removal of the silyl protecting groups completed the synthesis of (+)-**132**.

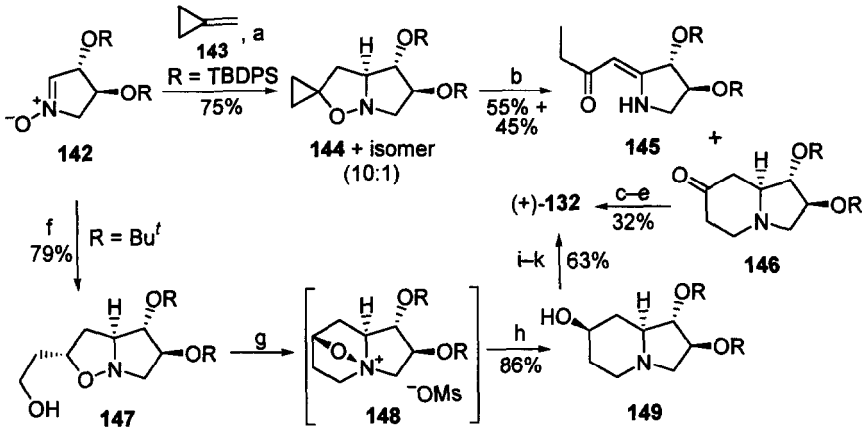
Δ^1-Pyrroline-*N*-oxides (nitrones) derived from tartaric acids feature in several syntheses of **132** and *ent*-**132**. The first of two routes by Brandi and co-workers commenced with a dipolar cycloaddition between the nitrone **142** (R = *tert*-butyldiphenylsilyl, or TBDPS) and methylenecyclopropane (**143**), which afforded a mixture of spirocyclopropylisoxazolidine **144** and its bridgehead epimer (10:1) (Scheme 20, top line) (*83*). When heated in xylene, **144** rearranged cleanly to enaminone **145** and the indolizidinone **146**, the latter undergoing ready conversion *via* the tosylhydrazone into the target diol, (+)-**132**. A subsequent synthesis with



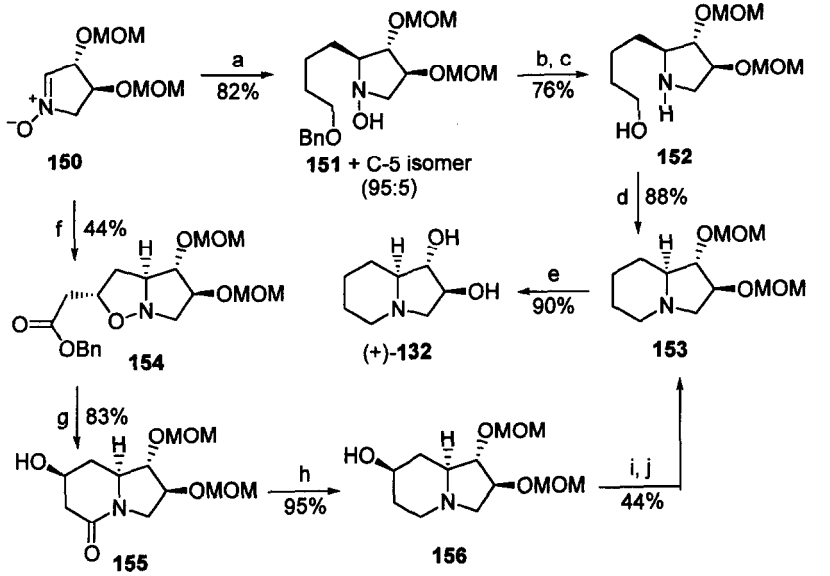
SCHEME 19. Reagents: a, $BnO(CH_2)_4MgBr$, THF, -78°C; b, Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78°C; c, $Ce(NH_4)_2(NO_3)_6$, MeCN–H_2O, 0°C; d, Pd black, HCO_2H, Pr^iOH; e, MsCl, NEt_3, CH_2Cl_2; f, NaH, THF; g, HCl, MeOH; h, $LiAlH_4$, THF, reflux; i, Pd black, HCO_2H (4.4%) in MeOH, 40°C; j, *p*-TsCl, pyridine; k, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –20°C to 0°C; l, KOH, MeOH.

the enantiomeric nitrone *ent*-**142** (R = TBDPS), prepared from D-(−)-tartaric acid, followed essentially the same route, and afforded (1*R*,2*R*,8a*R*)-(−)-lentiginosine (*ent*-**132**) (*85*). However, because the rearrangement of the isoxazolidines **144** showed such poor selectivity, an alternative route involving quantitative dipolar cycloaddition between but-3-en-1-ol and the *tert*-butyl-protected nitrone **142** (R = Bu^t) was developed (Scheme 20, bottom line) (*88*). This gave an easily separated mixture of three diastereomers in the ratio 10:2:1, from which the dominant isomer **147** was isolated in 79% yield. Its mesylate readily rearranged *via* salt **148** to give the protected 7-hydroxyindolizidine **149**, deoxygenation of which was accomplished by radical-initiated defunctionalization of the corresponding thiocarbonylimidazolide. The new route to (+)-**132** required ten steps from L-tartaric acid and gave an overall yield of 25%; by contrast, the previous synthesis took nine steps, and the overall yield was 2.4%.

Petrini and co-workers used the bis(methoxymethyl)-protected nitrone **150**, also derived from L-tartrate, as an electrophile rather than as a 1,3-dipole (Scheme 21, top line) (*89*). In their key step, reaction with 4-benzyloxybutylmagnesium bromide gave the cyclic hydroxylamine **151** in 82% yield (de 90%). Transfer hydrogenation with ammonium formate and a palladium catalyst cleaved both the hydroxylamine and the benzyl ether, affording the aminoalcohol **152**. Cyclization *via* the corresponding primary chloride created the protected indolizidine **153**, acidic hydrolysis of which completed this short synthesis of (+)-**132** in 16%



SCHEME 20. Reagents: a, C_6H_6, rt; b, xylene, 140°C; c, *p*-TsNHNH$_2$, MeOH; d, $NaBH_4$, 65°C; e, 40% aq. HF, MeCN; f, but-3-en-1-ol, 60°C, 2 d; g, MsCl, Et_3N, CH_2Cl_2; h, H_2 (50 psi), 10% Pd/C, MeOH; i, Im_2CS, THF, reflux; j, Bu_3SnH, toluene, reflux; k, TFA.

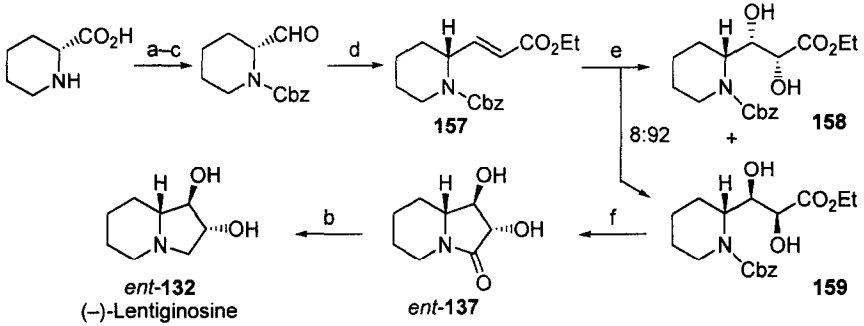


SCHEME 21 (MOM = CH_2OCH_3). Reagents: a, $BnO(CH_2)_4MgBr$, THF, reflux; b, H_2 (1 atm), Raney Ni W2, MeOH, rt; c, NH_4OCOH, 10% Pd/C, EtOH, reflux; d, Ph_3P, CCl_4, NEt_3, DMF; e, conc. HCl, MeOH, reflux; f, $H_2C{=}CHCH_2CO_2Bn$, PhMe, reflux, 4 d; g, Zn, aq. HOAc (10M), 60°C; h, $BH_3{\cdot}Me_2S$, THF, 0°C, then EtOH, reflux; i, Im_2CS, $(CH_2Cl)_2$, reflux; j, Bu_3SnH, AIBN, PhMe, reflux; k, 6M HCl.

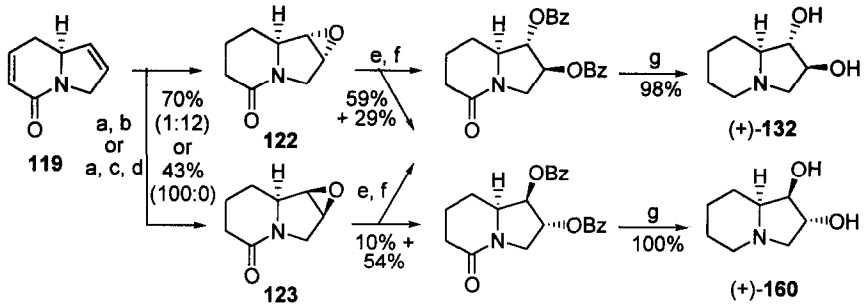
overall yield from L-(+)-tartaric acid. By contrast, McCaig *et al.* chose to exploit the dipolar cycloaddition of **150** with benzyl but-3-enoate (Scheme 21, left and bottom line) (*90*). When the isoxazoline adduct **154** was heated with zinc in aqueous acetic acid, the expected hydrogenolysis was followed by spontaneous cyclization to form the protected 7-hydroxyindolizidin-5-one **155** in 83% yield. Reduction with lithium aluminum hydride removed the carbonyl group, and radical-initiated defunctionalization of the thiocarbonylimidazolide of indolizidin-7-ol **156** gave **153**, thereby converging with Petrini's route to (+)-**132**. The same approach was used by McCaig *et al.* to complete a synthesis of (1*R*,2*R*,8a*R*)-(−)-lentiginosine (*ent*-**132**) in 13% overall yield from the enantiomeric nitrone *ent*-**150**.

Gurjar and co-workers synthesized both (+)-lentiginosine (**132**) and the (−)-enantiomer *ent*-**132** from (*S*)- and (*R*)-pipecolic acids, respectively (*84*). The synthesis of (−)-lentiginosine (the first published route to this enantiomer, incidentally) is illustrated in Scheme 22; the route to (+)-lentiginosine was exactly analogous. The synthesis hinged on Sharpless asymmetric dihydroxylation of the enoate **157** with AD-mix-β™, which yielded the diol **158** and its diastereomer **159** in a ratio of 8:92. Removal of the *N*-Cbz group from the latter proceeded with concomitant cyclization to give the bicyclic lactam *ent*-**137**, the mirror image of the late intermediate from Yoda's first synthesis (*cf.* Scheme 19). Reduction of *ent*-**137** with diborane completed the synthesis of *ent*-**132**. The implications of this synthesis for the absolute configuration of the natural product were discussed in Section III.B.1.

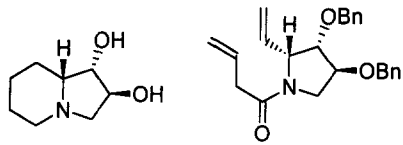
In Section III.A, it was shown how the (−)-3,5,8,8a-tetrahydroindolizin-5-one **119** could be converted into (1*S*,8a*S*)-(+)-indolizidin-1-ol (**109**) *via* epoxides **122** and **123** (*cf.* Scheme 16). The same intermediates have also been transformed into (+)-lentiginosine (**132**) and the unnatural 1,2-diepimer (+)-**160** (Scheme 23) (*79*). The enantiomer of the latter, (1*S*,2*S*,8a*R*)-(−)-indolizine-1,2-diol (*ent*-**160**), has been prepared by a route involving ring-closing metathesis of diene intermediate **161** (*91*).



SCHEME 22 Reagents: a, $ClCO_2Bn$, 4M NaOH; b, $BH_3{\cdot}Me_2S$, THF; c, py·SO_3, DMSO, 0°C; d, $Ph_3P{=}CHCO_2Et$, C_6H_6; e, AD-mix-β™, Bu^{t}OH–H_2O, then separation of acetonides by chromatography; f, H_2 (1 atm), 10% Pd/C, NaOAc, MeOH.

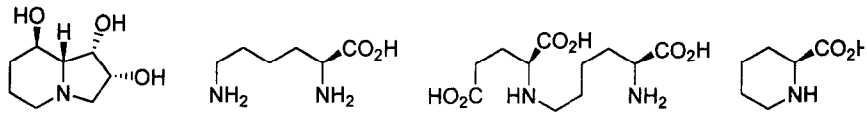


SCHEME 23. Reagents: a, 1M K-Selectride in THF, Et_2O, –78°C to 0°C; b, 30% aq. H_2O_2, HCO_2H; c, NBS, H_2O–THF, H_3PO_4; d, K_2CO_3, MeOH; e, 1% aq. H_2SO_4–Me_2CO (1:1), 70°C; f, PhCOCl, pyridine, DMAP, CH_2Cl_2; g, $LiAlH_4$, Et_2O.



C. SWAINSONINE AND RELATED ALKALOIDS

(–)-Swainsonine (**162**) was originally isolated from the fungus *Rhizoctonia leguminicola*, and subsequently from plants belonging to the genera *Swainsona*, *Astragalus* and *Oxytropis* (family Leguminosae) as well as another fungus, *Metarhizium anisopliae*. The alkaloid is responsible for chronic neurological disorders (*e.g.*, 'locoism' in the USA) in range animals that feed on alkaloid-producing plants or contaminated forage. The deleterious effects arise from swainsonine's potent inhibition of glycosidases, especially α-D-mannosidases, and the consequent interference with the normal course of glycoprotein processing. This important alkaloid continues to elicit interest from a broad sector of the scientific research community. The following account highlights developments in the chemistry and biology of swainsonine in the period following the surveys presented in Volumes 28 and 44 (*1,2*).



1. Distribution and Structural Studies

A review on livestock toxicosis caused by Australian *Swainsona* species presents a general discussion of the isolation, occurrence, synthesis and biological properties of swainsonine (**162**) (*92*). The review also describes the *Swainsona* species known to produce the alkaloid, among which are *S. canescens*, *S. galegifolia*, and *S. greyana* (the richest source). Other toxic species that probably contain the alkaloid are *S. luteola*, *S. procumbens*, and *S. swainsonioides*. A similar review on toxicosis induced by North American locoweeds and related plants lists the following as sources of the alkaloid: *Astragalus asymmetricus*, *A. bicristatus*, *A. bisulcatus*, *A. didymocarpus*, *A. emoryanus*, *A. flavus* (var. *argillosus* and *flavus*), *A. lentiginosus* (var. *diphysus*, *lentiginosus*, *micans*, *nigricalysis*, and *wahweapensis*), *A. mollissimus*, *A. oocarpus*, *A. oxyphysus*, *A. praelongus*, *A. pycnostachyus*, *A. succumbens*, *A. trichopodus*, *A. wootoni*, *Oxytropis kansunsis*, *O. lambertii*, *O. ochrocephala*, and *O. sericea*. (*93*). Swainsonine *N*-oxide has also been detected in most of these species and varieties (*94*). South American and Asian *Astragalus* and *Oxytropis* species in which swainsonine has been detected include *A. pehuenches* and *A. illini* (Argentina), *A. garbancillo* and *A. junin* (Peru), *A. strictus* (Tibet), *A. variabilis* and *O. deflexa* (Inner Mongolia), and *O. ochrocephala, O. kansuensis, O. caerulea*, and *O. imbricata* (China) (*95*). A quantitative bioassay for swainsonine based on the inhibition of jack bean α-mannosidase has shown that the alkaloid is apparently present in the seeds of *S. canescens, S. galegifolia, S. kingii, S. procumbens, A. boeticus,* and *A. garbancillo* (*96*). Very recently, swainsonine was actually isolated in high yield (0.17% by mass) from dried seeds of *S. procumbens* (*97*).

Swainsonine has also been found in plants of the genus *Ipomoea* (Convolvulaceae). The alkaloid, which was accompanied by a hydroxylated tropane (calystegine B_2), made up 0.048% of the weight of dried plant material in the Australian plant *Ipomoea* sp. Q6 [aff. *calobra*] (Weir vine), a species that produced a nervous derangement symptomatic of a lysosomal storage disease when grazed by livestock (*98*). The level of **162** in seeds of *I. polpha* was even higher (0.107% of dry weight). In both cases, the levels are much higher than the 0.001% known to cause neurological damage. Although insufficient material was obtained to establish the alkaloid's absolute stereochemistry, the ability of plant extracts to inhibit various glycosidases suggested that the compound was the expected (−)-enantiomer. Swainsonine and two calystegines were also identified as the causative agents in the outbreak of a lysosomal storage disease in goats feeding on *Ipomoea carnea* in Mozambique (*99*).

Unambiguous proton and carbon NMR spectroscopic assignments for swainsonine (**162**) and swainsonine triacetate have been published (*100*).

2. Biotechnology and Biosynthesis

Potential therapeutic uses for (−)-swainsonine have led to several studies aimed at optimizing the yield of the alkaloid from natural sources. Experiments with root cultures of *Swainsona galegifolia* transformed with *Agrobacterium rhizogenes* produced higher levels of the alkaloid than untransformed cultures and responded favorably to various stimuli (pH, addition of copper sulfate, supplementation with malonic and pipecolic acids), but still did not produce the

levels found in intact plants (*101–103*). More encouraging is a continuing series of fermentation experiments designed to optimize the production of (–)-**162** by the fungus *Metarhizium anisopliae*. These include selection of the growth medium and effect of supplements such as D-glucose and (±)-lysine (*104,105*), as well as reactor design, aeration strategy, and culture homogeneity (*106*), pH (*107*), and rate of stirring (*108*). Yields of swainsonine as high as 61 mg dm^{-3} have been obtained when using a modified starch–casein medium supplemented by (±)-lysine (*109*).

A simple assay based on potent and specific inhibition of jack bean α-mannosidase has been devised for determining low concentrations of **162** (up to 0.5 μg cm^{-3}) in *M. anisopliae* cultures (*110*). The new assay was used to demonstrate that the addition of L-lysine (**163**) to the culture medium stimulated production of the alkaloid by approximately fourfold. Other early metabolic precursors of **162** in this fungus, including α-aminoadipic acid, saccharopine (**164**), L-pipecolic acid (**165**), and L-lysine itself, were quantified by reverse-phase HPLC analysis of mycelial extracts derivatised with 9-fluorenylmethyl chloroformate (FMOC) (*111*).

3. *Synthesis*

Swainsonine (**162**) continues to be a popular synthetic target owing to intense interest in its biological effects, and numerous synthetic stereoisomers, regioisomers and other analogs have also been reported. Only the syntheses of swainsonine itself are discussed below, but the interested reader is referred to the following post-1992 references for the synthesis of the swainsonine diastereomers illustrated in Fig. 3: (–)-1-episwainsonine (**166**) (*112,113*), (–)-8-episwainsonine (**167**, as the triacetate) (*114*), (–)-8a-episwainsonine (**168**) (*115*) and its acetonide (*116*), (+)-1,8-diepiswainsonine (**169**) (*113*), (–)-8,8a-diepiswainsonine (**170**) (*115, 117*), (+)-1,2,8-triepiswainsonine (**171**) (*115*), and (+)-2,8,8a-triepi-swainsonine (**172**) (*112*).

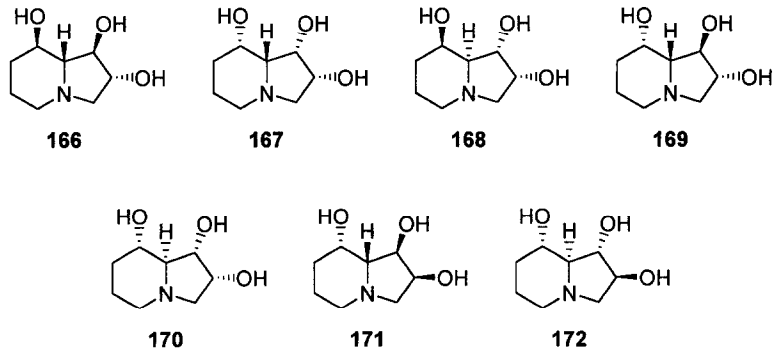
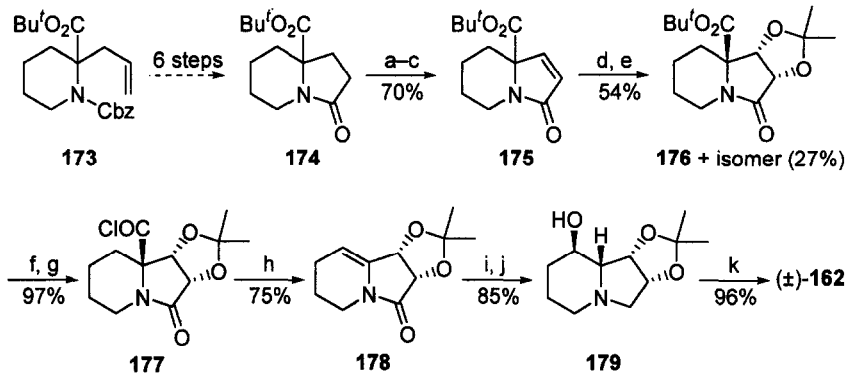
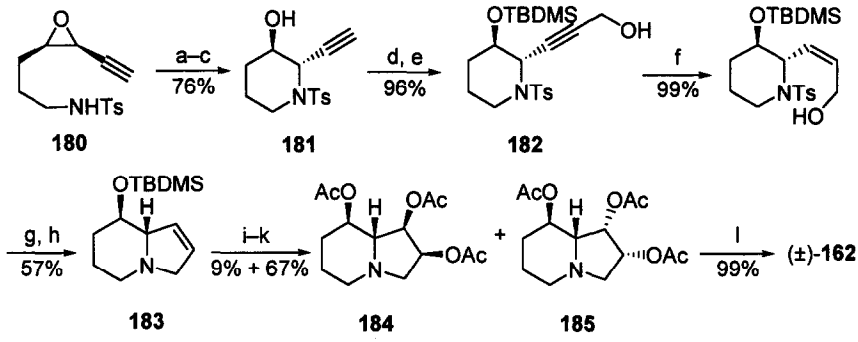


FIG. 3. Synthetic stereoisomers of swainsonine (**162**).

Two interesting routes to (±)-swainsonine have been published. After a six-step conversion of the known pipecolic acid derivative **173** (*118*) into the indolizidin-3-one **174** (*119*), Bermejo and co-workers used standard α-selenenylation and oxidative elimination to produce the unsaturated lactam **175** (Scheme 24) (*120,121*). *cis*-Dihydroxylation of the double bond took place preferentially on the concave face (2:1), probably because of steric interference by the bridgehead ester. The isomers were separated after acetonide formation. Removal of the bridgehead substituent from the major isomer **176** was accomplished *via* the isolable acid chloride **177**, which underwent thermal fragmentation to give **178** (75%) upon heating under reflux in a mixture of xylene and 1,2-dichloroethane. Hydroboration–oxidation produced the indolizidin-8-ol acetonide **179**, deprotection of which completed the synthesis of (±)-**162**. The novel transformation in the stereoselective total synthesis of (±)-**162** by Mukai *et al.* was a 6-*endo* cyclisation of 1,2-*cis*-disubstituted alkynyl epoxide **180** (Scheme 25) (*122*). Successive treatment of this compound with dicobalt octacarbonyl, boron trifluoride and ceric ammonium nitrate produced a 9:1 mixture of *trans*-2-alkynylpiperidin-3-ol **181** and its *cis* isomer. The ratio swung to 3:7 when the reaction was performed on the corresponding *trans* epoxide. Silylation of **181** and condensation at the alkyne terminus with formaldehyde afforded **182**, after which functional group transformations and cyclization gave the unsaturated indolizidine **183**. The ensuing *cis*-dihydroxylation occurred selectively (88:12) on the face of the double bond opposite to the bridgehead hydrogen at C-8a. The isomeric products were characterized as the acetate derivatives **184** and **185**. Basic hydrolysis of the latter completed the synthesis of (±)-**162**.

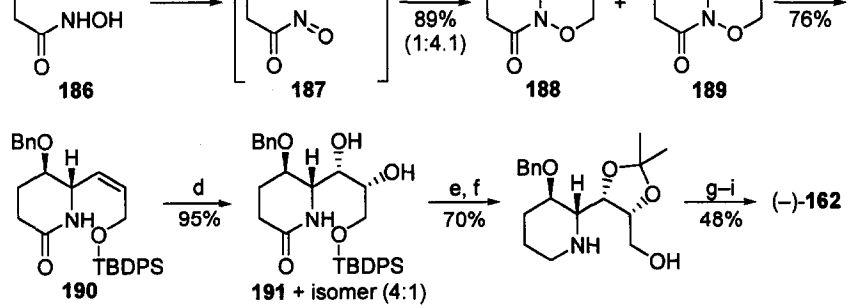


SCHEME 24. Reagents: a, LDA, THF, –78°C; b, PhSeCl, THF; c, 30% aq. H_2O_2, AcOH, 0°C; d, OsO_4 (cat.), Bu^{t}OH, NMO, Me_2CO–H_2O (8:1); e, $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, then chromatography; f, TFA, CH_2Cl_2; g, $(COCl)_2$, $(CH_2Cl)_2$; h, xylene–$(CH_2Cl)_2$ (2:1), reflux; i, B_2H_6, THF; j, 30% aq. H_2O_2, 3M NaOH, EtOH; k, 6M HCl, THF, then ion exchange with Dowex 1X8 200 (OH^-).

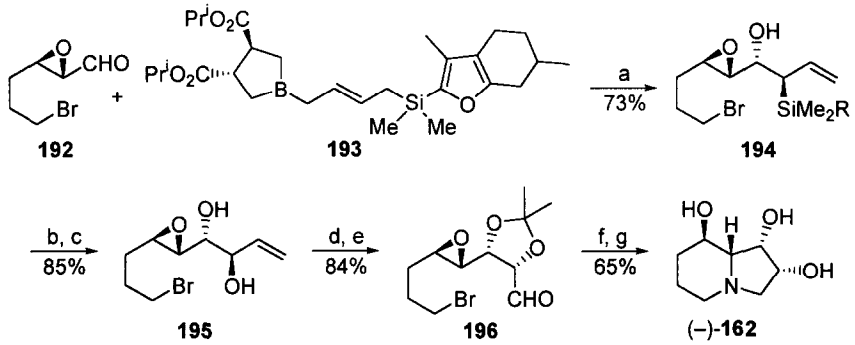


SCHEME 25. Reagents: a, $Co_2(CO)_8$, CH_2Cl_2, rt; b, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78°C to 0°C; c, CAN, MeOH, 0°C, then chromatography on SiO_2; d, TBDMS-Cl, imidazole; e, BuLi, $(H_2CO)_n$, THF, –78°C to rt; f, H_2 (1 atm), Lindlar catalyst, EtOAc; g, Na, naphthalene, THF, –78°C; h, CBr_4, Ph_3P, CH_2Cl_2, 0°C; i, OsO_4 (cat.), NMO, Me_2CO–H_2O (3:1), then $NaHSO_3$; j, TBAF, THF; k, Ac_2O, pyridine, DMAP, CH_2Cl_2, then chromatography on SiO_2; l, K_2CO_3, MeOH.

A route to (–)-**162** devised by Kibayashi and co-workers began with the chiral hydroxylamine **186**, prepared in eleven steps from D-malic acid (*123*). *In situ* oxidation of **186** with periodate produced the transient acylnitroso species **187**, intramolecular Diels–Alder reaction of which yielded stereoisomeric oxazine cycloadducts **188** and **189** (Scheme 26). The observed ratio was 1:1.3 when the oxidation was performed in chloroform, but the dramatic improvement to 1:4.1 in aqueous medium was ascribed to a 'hydrophobic packing effect'. Reductive cleavage of the N–O bond of **189** and silylation of the exposed alcohol group gave (*Z*)-alkene **190**. A moderately diastereoselective osmylation yielded the (7*S*,8*R*)-*cis*-diol **191** and its chromatographically separable (7*R*,8*S*) isomer in a 4:1 ratio. The synthesis of (–)-**162** from isomer **191** was completed as shown in five straightforward steps.



SCHEME 26. Reagents: a, $NaIO_4$, H_2O, 0 C; b, 5% Na–Hg, Na_2HPO_4, EtOH, 0°C; c, TBDPS-Cl, imidazole, DMF; d, OsO_4 (cat.), NMO, MeCN–H_2O (2:1), then chromatography; e, PPTS, $Me_2C(OMe)_2$, C_6H_6, 55°C; f, $LiAlH_4$, THF, reflux; g, CBr_4, PPh_3, NEt_3, CH_2Cl_2, 0°C; h, H_2 (1 atm), $PdCl_2$, MeOH; i, 2M HCl, THF, then chromatography on Dowex 1-X8.

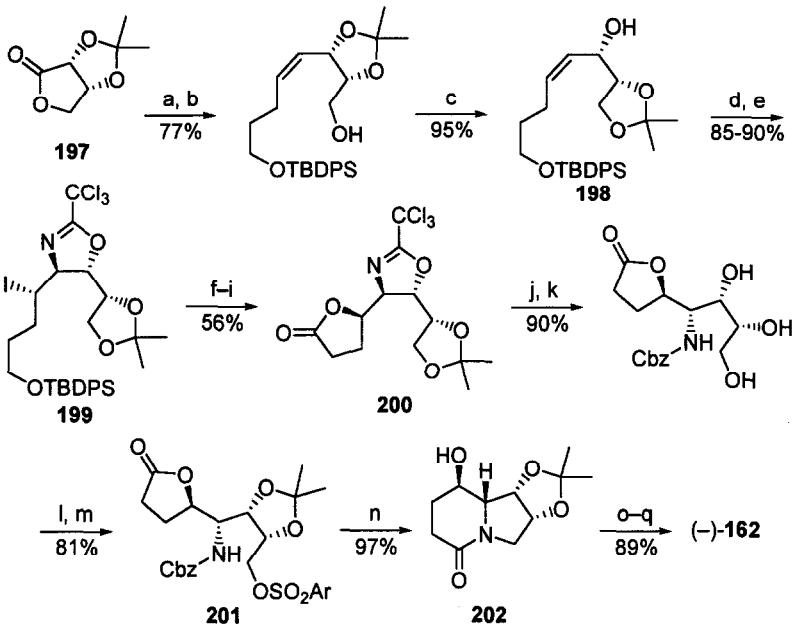


SCHEME 27. Reagents: a, 4Å molecular sieves, PhMe, –78°C; b, TFA, THF, 0°C to rt; c, KF, $KHCO_3$, 30% aq. H_2O_2, THF–MeOH; d, $Me_2C(OMe)_2$, PPTS, CH_2Cl_2; e, O_3, CH_2Cl_2, –78°C, then PPh_3; f, NH_4OAc, 3Å molecular sieves, MeOH, reflux, then $NaBH_3CN$; g, 6M HCl, THF.

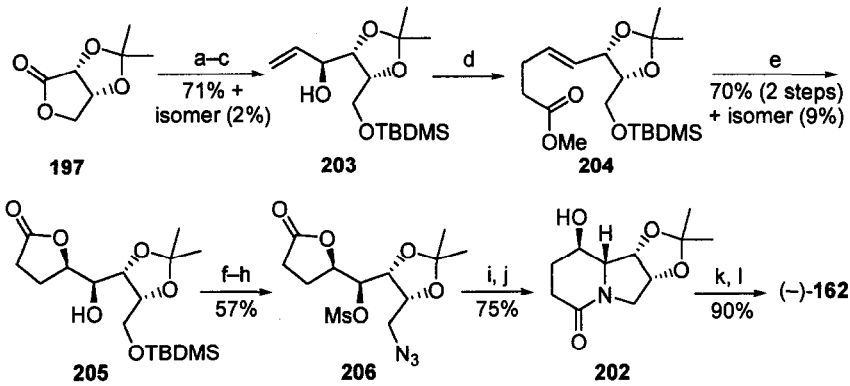
Hunt and Roush exploited *anti*-diastereoselective (9:1) 'matched' alkylation of epoxy-aldehyde **192** with the tartrate-modified (menthofuryldimethylsilyl)allylboronate **193** in their short synthesis of (–)-**162** (Scheme 27) (*124,125*). The exotic substituent on silicon was carefully chosen to facilitate the oxidative replacement of silicon by a hydroxy group with retention of configuration (the Fleming–Tamao reaction) in the transformation of intermediate **194** into the *anti*-diol **195**. Protection of this product as the acetonide and ozonolysis of the terminal vinyl group yielded aldehyde **196**, all three electrophilic centers of which reacted with ammonia (from ammonium acetate) in the presence of sodium borohydride to give the requisite double cyclization leading to the target alkaloid.

The synthesis of (–)-**162** by Kang and Kim (*126*) used methodology similar to that previously illustrated in the group's synthesis of *N*-acetylslaframine (**13**) (*cf.* Scheme 6). Their starting material, 2,3-*O*-isopropylidene-D-erythronolactone (**197**), already possesses the correct absolute stereochemistry for C-1 and C-2 of the target alkaloid. The focus of the route is the iodocyclization of the acetimidate derivative of (*Z*)-allylic alcohol **198** when treated with iodine monobromide (Scheme 28). The use of this reagent rather than iodine itself proved to be critical for the stereocontrolled formation of the *trans*-oxazoline **199**; the reliable *trans* addition across the double bond not only ensured the requisite absolute stereochemistry at the nitrogen-bearing site, but also introduced the halogen in such a way that its subsequent intramolecular S_N2 displacement to give lactone **200** created the final stereogenic center with the correct absolute configuration for swainsonine's C-8 site. Both rings of the indolizidine nucleus were formed simultaneously when the *N*-Cbz intermediate **201** was deprotected. Reduction of lactam **202** and hydrolysis of the ketal completed the synthesis of (–)-**162**.

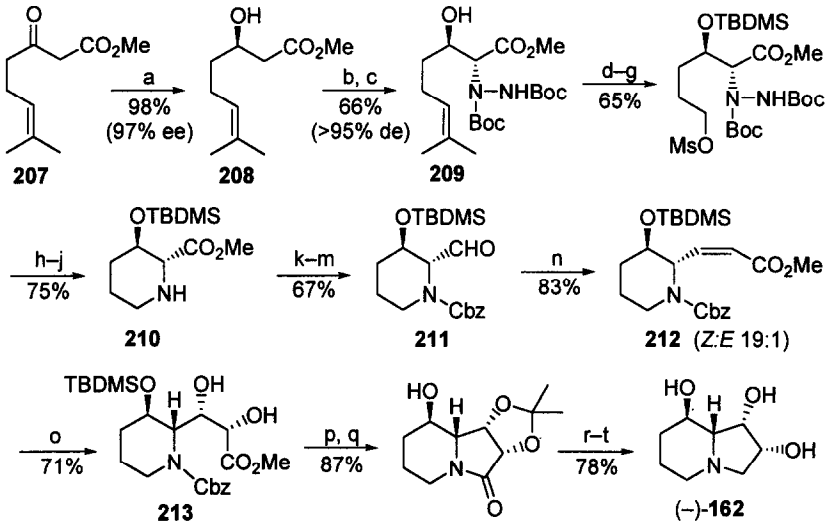
In their short synthesis of (–)-**162**, Pearson and Hembre also began with the protected D-erythronolactone derivative **197**, which was converted in three steps into a mixture (97:3) of diastereomeric allylic alcohols **203** (Scheme 29) (*127*). Separation of the epimers, although possible, was not necessary as both alcohols yielded the same product **204** after Johnson orthoester Claisen rearrangement. Subsequent Sharpless asymmetric dihydroxylation with AD-Mix-β™ gave as major



SCHEME 28. Reagents: a, DIBAL-H, CH_2Cl_2, –78°C; b, $TBDPSO(CH_2)_4PPh_3^+ I^-$, BuLi, HMPA, THF, 0°C; c, *p*-TsOH, Me_2CO; d, Cl_3CCN, DBU, MeCN–CH_2Cl_2, 0°C; e, DBU, IBr, MeCN, –60°C; f, NH_4F, MeOH, 45°C; g, Swern oxidation; h, $NaClO_2$, Me_2C=CHMe, NaH_2PO_4, Bu^{t}OH–H_2O; i, Ag_2CO_3, C_6H_6, 65–70°C; j, TFA, H_2O; k, BnO_2CCl, K_2CO_3, MeOH, 0°C; l, 2,4,6-$Me_3C_6H_2SO_2Cl$, NEt_3, CH_2Cl_2, 0°C; m, *p*-TsOH, $Me_2C(OMe)_2$, Me_2CO; n, H_2, 10% Pd/C, K_2CO_3, reflux; o, BH_3·Me_2S, THF; p, H_2O_2, NaOH, reflux; q, 6M HCl.



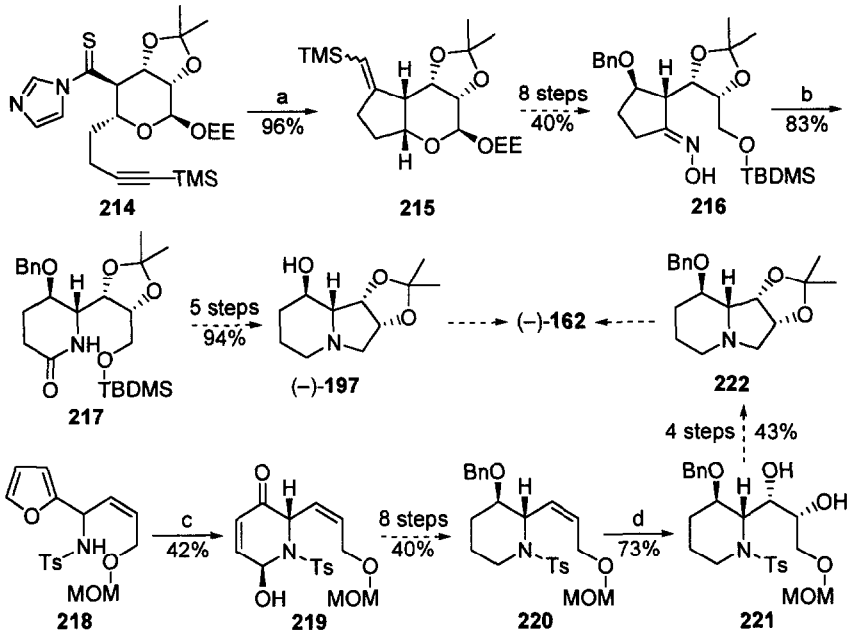
SCHEME 29. Reagents: a, DIBAL-H, toluene–CH_2Cl_2, –78°C, then MeOH; b, H_2C=CHMgBr, THF, –78°C to 0°C; c, TBDMSCl, THF–DMF (3:1), imidazole, 0°C; d, $MeC(OMe)_3$, $C_2H_5CO_2H$, PhMe, reflux; e, AD-Mix-β™, $MeSO_2NH_2$, H_2O, Bu^{t}OH, 0°C to rt, then Na_2SO_3, then chromatography; f, Bu_4NF, THF, 0°C; g, MsCl, DMAP, pyridine, 0°C; h, NaN_3, DMSO, 80°C; i, H_2 (1 atm), $Pd(OH)_2$/C, MeOH; j, NaOMe, MeOH, reflux; k, BH_3·Me_2S, THF, 0°C to rt, then EtOH, reflux; l, 6M HCl, THF, then ion exchange with Dowex 1X8 (OH^-).



SCHEME 30. Reagents: a, $RuBr_2$[(*R*)-Binap], H_2 (1 atm), MeOH, 50°C; b, MeZnBr, THF, 0°C; c, LDA, THF –78°C, then $Bu^tO_2CN{=}NCO_2Bu^t$, THF, –78°C; d, 2,6-lutidine, TBDMS-OTf, CH_2Cl_2, –78°C; e, O_3, CH_2Cl_2, –78°C; f, $BH_3{\cdot}SMe_2$, CH_2Cl_2, –78°C to rt; g, MsCl, pyridine, 0°C; h, TFA, CH_2Cl_2; i, Raney Ni, H_2 (1 atm), MeOH, ultrasound; j Et_3N, CH_2Cl_2; k, $ClCO_2Bn$, DMAP, MeCN; l, $Ca(BH_4)_2$ (6 equiv), THF–EtOH (2:3), –20°C to rt; m, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60°C; n, 18-crown-6, $(CF_3CH_2O)_2POCHCO_2Me^-\ K^+$, THF, –78°C; o, OsO_4 (0.2 equiv), Me_3NO, Me_2CO–H_2O (19:1), ultrasound; p, Pd/C, H_2 (1 atm), NaOAc, MeOH, 35°C; q, $(MeO)_2CMe_2$, Dowex 50W-400 (H^+); r, $BH_3{\cdot}SMe_2$, THF; s, EtOH, reflux; t, 1M HCl, reflux, then Dowex 1X8-200 (OH^-).

product the lactone **205**, which has all the carbon atoms and three of the target alkaloid's four stereogenic centers in place. Hydrogenation of the azide group in the subsequent product **206** and base-induced double cyclization yielded the same protected indolizidin-5-one **202** as prepared by Kang and Kim (*126*) as well as previous workers (*128,129*). Well-precedented transformations completed the synthesis of (–)-**162**. This exceptional route yielded a comparatively large amount (4.5 g) of the alkaloid in eleven steps and an overall yield of 20% based on **197**. The method has also been patented (*130*).

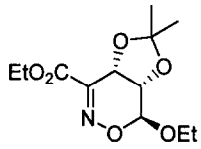
Ferreira *et al.* made the unusual choice of an achiral substrate, the β-keto-ester **207**, to commence their route to (–)-**162** (Scheme 30) (*131*). Reduction of the ketone, destined to become the C-8 hydroxy group of the target alkaloid, was accomplished by hydrogenation over $RuBr_2$[(*R*)-Binap] to give the chiral alcohol **208** in 98% yield and an ee of 97%. Treating the ester enolate of **208** with di-*tert*-butyl azodicarboxylate gave the *anti*-hydroxy hydrazine **209**, thereby effecting the introduction of nitrogen with the correct absolute stereochemistry. A further seven steps completed the synthesis of the protected (2*R*,3*R*)-pipecolic ester **210**. Building the pyrrolidine ring entailed Horner–Wittig homologation of aldehyde **211** with the potassium salt of methyl bis(trifluoroethyl)phosphonoacetate, which ensured that (*Z*)-alkenoate **212** was the favored geometrical isomer (19:1). Simple face-selective



SCHEME 31. Reagents: a, Bu_3SnH, AIBN, C_6H_6, reflux; b, $SOCl_2$, 0°C; c, $Ti(OPr^i)_4$, D-(–)-DIPT, Bu^tOOH, SiO_2, CaH_2, CH_2Cl_2; d, OsO_4 (cat.), NMO, $MeSO_2NH_2$, DBQN–CLB, Me_2CO–H_2O, ultrasound.

dihydroxylation then afforded diol **213**. At this point all the skeletal atoms and stereogenic centers of the target alkaloid had been introduced, and routine functional group transformations completed the synthesis of (–)-**162**.

Key transformations in two formal syntheses of (–)-swainsonine are shown in Scheme 31. The route developed by Honda *et al.* included radical cyclization of the carbohydrate-derived alkynylsilane **214** to create the cyclopentane ring of **215**, and Beckmann rearrangement of oxime **216** to give lactam **217** (*132*). The final product in this synthesis, (–)-swainsonine acetonide (**197**), has featured in many other routes to (–)-**162** (*125–127,129,133,134*). The approach by Zhou *et al.* began with kinetic resolution of the furan **218** under Sharpless epoxidation conditions, the more reactive enantiomer undergoing conversion into the (2*S*,6*S*)-dihydropyridinone **219** (*135,136*). Sharpless asymmetric dihydroxylation on a later intermediate, **220**, introduced the final two stereogenic centers, yielding the (7*S*,8*R*)-diol **221** and its (7*R*,8*S*) isomer in a 10:1 ratio. This formal synthesis terminated with the preparation of benzyloxy-acetonide **222**, which was an intermediate in Kibayashi's synthesis of (–)-**162** (*cf.* Scheme 26) (*123*). A four-step reaction sequence for converting the 1,2-oxazine **223** into the enantiomerically pure pyrrolidine **224**, devised by Reissig and co-workers (*137*), also represents a formal synthesis of (–)-**162**, since the conversion of **224** into the alkaloid was reported previously (*138*).



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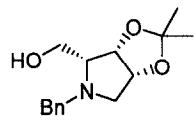

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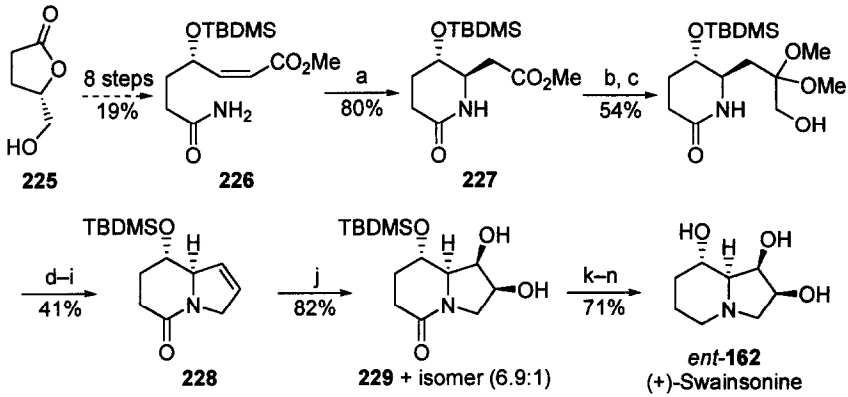
The first synthesis of the unnatural (+)-enantiomer of swainsonine (*ent*-**162**) was reported in 1995 by Hirama and co-workers (Scheme 32) (*117*). Lactone **225**, derived from L-glutamic acid, was converted in eight steps into the (*Z*)-enoate **226**, base-induced cyclization of which gave the (5*S*,6*R*)-disubstituted lactam **227** as the sole product. After a further eight steps involving chain elongation and a second cyclization, the unsaturated bicyclic lactam **228** was converted into the *cis*-diol **229** by simple osmylation, which occurred preferentially on the β-face (6.9:1). The facial selectivity could be altered by performing the reaction in the presence of various chiral ligands. Reduction of the lactam and desilylation completed the synthesis of *ent*-**162**.

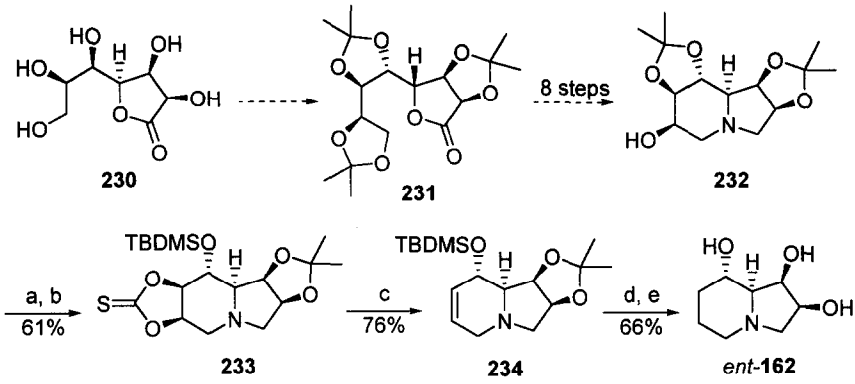
Fleet and co-workers prepared (+)-swainsonine (*ent*-**162**) from the cheap heptonolactone **230** (*139*). Conversion into the octonolactone **231** (*140*) followed by a further eight steps (*141*) yielded the protected pentahydroxyindolizidine **232** (Scheme 33). Selective deprotection and reprotection gave the thionocarbonate **233**, Corey–Winter fragmentation of which was accomplished by heating with triethyl phosphite to give the unsaturated indolizidine **234**. The synthesis of *ent*-**162** was completed by catalytic hydrogenation and deprotection. In tests with naringinase obtained from *Penicillium decumbens*, (+)-swainsonine indeed proved to be a very potent and highly specific inhibitor, showing a K_i of 0.45 μM, while natural (–)-swainsonine failed to inhibit the enzyme.



225 **226** **227**

228 **229** + isomer (6.9:1) *ent*-**162** (+)-Swainsonine

SCHEME 32. Reagents: a, Bu^{t}OK, THF, –55°C; b, $LiCHBr_2$, THF, –90°C, then BuLi, –90°C; c, K_2CO_3, MeOH; d, MsCl, NEt_3, CH_2Cl_2; e, KH, THF; f, *p*-TsOH, Me_2CO; g, $NaBH_4$, MeOH, 0°C; h, NaH, THF, CS_2, then MeI; i, 180°C; j, OsO_4 (cat.), NMO, Me_2CO, H_2O; k, TFA, THF, H_2O; l, Ac_2O, pyridine, CH_2Cl_2; m, BH_3.THF, reflux, then K_2CO_3, MeOH; n, 2M HCl, reflux.

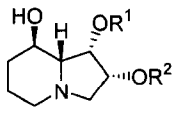


SCHEME 33. Reagents: a, TFA–H_2O (4:1); b, $Im_2C{=}S$, PhMe, then TBDMS-OTf, pyridine, CH_2Cl_2; c, $(EtO)_3P$, heat; d, H_2, Pd black, EtOAc; e, CF_3CO_2D–D_2O (1:1).

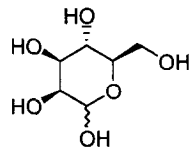
Chemical transformations carried out on the parent alkaloid (–)-**162** are surprisingly uncommon when one considers current levels of interest in the therapeutic properties of the compound and its analogs. The stable hydrohalide salts have been described in a patent relating to the compound's antitumor potential (*142*). Several 2- and 8-*O*-acyl esters of **162** have been reported (*143*). The use of the enzyme subtilisin in pyridine permitted selective synthesis of 2-*O*-butyrylswainsonine (**235**) from **162** in 23% yield, while catalysis by porcine pancreatic lipase gave **235** (6%) and 1,2-di-*O*-butyrylswainsonine (**236**) (31%) (*97*). Swainsonine has been tethered at C-7 to an agarose matrix for evaluation as an affinity material for mannosidases (*144*).

4. *Biological Activity*

The pronounced and diverse biological activity of (–)-swainsonine (**162**) stems from its potency as an inhibitor of α-mannosidases, and its consequent ability to alter the course of glycoprotein processing. Mannosidases partially or wholly characterized during, or detected in, recent inhibition studies with the alkaloid include α-D-mannosidases in the parasite *Trypanosoma cruzi* (*145,146*) and in various insects (*147,148*), a murine lysosomal α-mannosidase (*149*), and α-mannosidases I and II from *Vigna umbellata* (rice beans) (*150*). The alkaloid was used to differentiate



235 $R^1 = H$; $R^2 = CO(CH_2)_2Me$
236 $R^1 = R^2 = CO(CH_2)_2Me$



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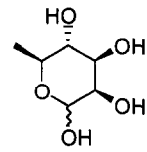

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between a cytosolic α-mannosidase and two distinct α-mannosidases from rat liver endoplasmic reticulum (*151*). However, (−)-**162** failed to inhibit an α-mannosidase prepared from hen oviduct, which suggests that this enzyme is preferentially involved in processing high mannose-type oligosaccharides (*152*). The alkaloid's ability to inhibit the mannosidases implicated in glycoprotein processing has been exploited in studies dealing with *N*-glycan trimming in the function and biosynthesis of the vasopressin V_2 receptor site in renal epithelial cells (*153*).

Other enzymes may also be inhibited by (−)-**162**. For example, it has been shown to affect the processing and transport of the lactase–phlorizin hydrolase from the human small intestine (*154*). However, the time-dependent alteration of intestinal sucrase activity in rats by swainsonine is apparently not due to inhibition of the enzyme itself, but rather to slow alteration of the enzyme's *N*-linked oligosaccharide structure (*155*). An interesting hypothesis that unnatural (+)-swainsonine (*ent*-**162**) might inhibit enzymes whose substrates have absolute configurations mirroring that of D-mannopyranose (**237**) [for example, L-rhamnopyranose (**238**)] was tested by Fleet and co-workers, who showed that *ent*-**162** was a very potent, highly specific inhibitor of L-rhamnosidase (naringinase) (K_i 0.45 μM), while (−)-**162** had no effect on the enzyme (*139*).

The toxicology of swainsonine, especially the effects of locoweeds on livestock, still elicits interest (*156–158*). Neurophysiological responses in rats treated with extracts of the woolly locoweed (*Astragalus mollissimus*) and with (−)-**162** have been compared, and vacuolar degeneration was noted in renal, thyroid, lymph, spleen, lung, liver, and thymus cells; the swainsonine-induced vacuoles all contained mannose-rich oligosaccharides (*159*). Specific effects of (−)-**162** on cell membrane oligosaccharides and lysosomes have also been demonstrated in rats (*160*). Interestingly, insects that feed on *A. mollissimus* var. *earlei* apparently use symbiotic intestinal bacteria (*Klebsiella* and *Pseudomonas* sp.) to break down the toxin, which suggests that the microorganisms use (−)-**162** as an energy and carbon source *in vivo*—a hypothesis confirmed by growing bacterial cultures in media containing swainsonine as the only 'nutrient' (*161*). Wider implications for community health are contained in a study of the reversal of *Oxytropis sericea* poisoning in sheep (*162*). The study showed that the half-life of the alkaloid in different organs varied from 20 hours to 60 hours, which means that animals intended for consumption should be kept for at least 25 days before slaughter (10 $T_{1/2}$) to ensure that the toxin has been cleared from animal tissue.

Rather few new studies on the immunomodulatory effects of swainsonine have appeared since 1992. Modification of cell membrane oligosaccharides by swainsonine was shown to inhibit T-cell–B-cell adhesion, thus blocking the maturation of the B-cells (*163*). The alkaloid increased the susceptibility of various $CD4^-$ human cell lines to infection by the LAV-2/B strain of human immunodeficiency virus type 2 (HIV-2), suggesting the existence of an alternative CD4-independent receptor for HIV-2 (*164*). Swainsonine was shown to lower the liposaccharide-induced humoral immune responses in mice (*165*). Low levels of swainsonine appeared not to affect the immune responses in sheep and cattle, but T-cell function was affected at higher concentrations (*166*). Perhaps the most significant recent finding is that swainsonine not only helped to boost the

proliferation of murine and human bone marrow cells *in vitro*, but also conferred protection against the toxic effects of the anti-AIDS drug AZT; the result suggests a potential use for (–)-**162** as an adjuvant in chemotherapy (*167*).

The most significant manifestation of swainsonine's effects on glycosidases relates to its therapeutic potential in the treatment of tumors. A stream of short reviews illustrates the rapid advances in the area (*168–173*). Themes in current research include the control of metastasis and tumor growth, the connection between malignancy and processing in the carbohydrate portion of glycoproteins, promotion of bone marrow cell proliferation, augmentation of immunomodulatory activity, amelioration of the toxicity of other chemotherapeutic agents, clinical trials, and implications for the design of new carbohydrate processing inhibitors. Some results from the post-1992 primary literature are summarized below.

Much of the published research deals with the effects of swainsonine on cells cultured *in vitro*. The alkaloid's ability to augment the cytotoxicity of various natural and activated killer cells is now beyond dispute; for instance, it activated resident tissue-specific macrophages in several mouse strains (*174*), and enhanced the activity of various human effector cells in a dose-dependent fashion (*175*). The heightened ability of killer cells to contend with invasive tumors has been studied with human melanomas (*176*), leukemia cells (*177*), and autologous thyroid cancer cells (*178*). Specific effects on *N*-glycan trimming have been observed in leukemia cells (*177*), cells from a human colonic adenocarcinoma (*179*), and human mononuclear leukocytes, murine melanoma cells and baby hamster kidney cells (*180*). However, the effects did not extend to the inhibition of tyrosinase activity in certain human melanoma cells (*181*). Swainsonine's alteration of glycoprotein processing also appeared to enhance the transcription of certain genes in selected human, mouse and hamster tumor cell lines, especially the gene for the expression of TIMP (tissue inhibitor of metalloproteinases), which is known to inhibit tumor cell invasion (*182*).

Since the potential clinical uses of swainsonine may be limited by the alkaloid's toxicity, several pharmacokinetic studies with laboratory animals have been performed. In mice, dose-limiting CNS toxicity may present little hazard at the levels needed to prevent metastasis; however, the alkaloid's short half-life and time to reach steady state *in vivo* necessitated continuous infusion for at least 2.5 hours to approach a plateau, though considerable amounts of **162** remained in body organs and tissue even when blood levels were low (*183*). Dose- and time-dependent tumoricidal activity of lung and spleen macrophages was observed after systematic administration of the alkaloid, and *in vivo* activation of macrophages in animals with compromised immune systems suggested that the alkaloid might be acting directly on the macrophages (*174*). Swainsonine's ability to maintain antimetastatic activity for several days after administration was subsequently correlated with its retention in lymphoid tissue, especially the spleen (*184*). Related research from China showed that administration of swainsonine increased splenocyte levels, decreased tumor volume and inhibited metastasis to the liver and peritoneum in nude mice orthotopically implanted with gastric carcinoma in the gastric wall (*185,186*). A recent study showing that swainsonine administration to melanoma-bearing mice increased bone marrow production and white blood cell levels without compromising the anti-tumor effects is significant, since it indicates

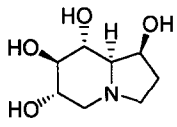
that the alkaloid can confer protection against chemotherapeutic toxicity; concurrent *in vivo* studies showed that swainsonine was able to protect animals from the myelosuppressive effects of the anti-AIDS drug AZT (*167*).

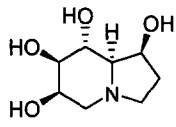
The most important development in the clinical use of swainsonine in cancer chemotherapy has undoubtedly been a phase I clinical trial with nineteen terminally ill patients suffering from advanced malignancies (*187*). The study, involving intravenous infusion of **162** over five days, repeated at 28-day intervals, helped to establish dosage levels and side effects (edema, mild liver dysfunction, a rise in serum amylase, and decreased serum retinol). Benefits included a greater than 50% shrinkage in tumor mass, which persisted for six weeks after treatment, in a patient with head and neck cancer; and improvement in respiratory function continued for a week after treatment in patients with lymphangitis carcinomatosis. The only treatment-related fatality was a patient who had severe hepatic dysfunction before the study began. Urine analysis, which showed decreased leukoagglutinin binding and increased oligomannoside levels, indicated that the alkaloid was altering Golgi oligosaccharide processing and inhibiting lysosomal α-mannosidases, as expected. An important part of the study was the measurement of swainsonine levels in the serum of patients receiving treatment, and accurate GC and GC–MS assays for monitoring the alkaloid in biological fluids were published separately (*188*). A follow-up phase IB study examined the pharmacokinetics, toxicities and biochemical effects of orally administered swainsonine at increasing dose levels between 50–600 $\mu g\ kg^{-1}$ in sixteen cancer patients and two HIV-positive patients (*189*). The maximum tolerated dose was found to be about 300 $\mu g\ kg^{-1}$ per day, after which abnormal serum aspartate transferase levels and breathing difficulties were observed. Other adverse effects included fatigue, anorexia and abdominal pain. Changes in lymphocyte populations cast some light on the alkaloid's ability to increase natural killer cell activity. Unfortunately, malignancies were too advanced for objective responses of the diseases to the drug regime to be evaluated.

Esters of swainsonine appear to offer therapeutic advantages in terms of specificity for Golgi α-mannosidase II, improved pharmacokinetics, and diminished side effects (*143*). Although 2- and 8-acyloxy esters of swainsonine were two to three orders of magnitude less active as α-mannosidase inhibitors *in vitro* than the parent alkaloid, the 2-butanoyl, 2-octanoyl, and 2-*p*-nitrobenzoyl esters, which are soluble enough to enter viable tumor cells, were as effective as swainsonine *in vivo*, apparently because they are hydrolyzed to swainsonine with intracellular esterases. These compounds may thus be advantageous as prodrugs.

D. CASTANOSPERMINE AND RELATED ALKALOIDS

(+)-Castanospermine (**239**) was originally isolated from seeds of the Australian legume *Castanospermum australe* (the Moreton Bay chestnut), and later from plants of the South American genus *Alexa*, which is also a member of the Leguminosae. Two minor diastereomers of (+)-**239**, *viz.* (+)-6-epicastanospermine (**240**) and (+)-6,7-diepicastanospermine (**241**), were subsequently isolated from *C. australe*. Castanospermine owes its status as one of the most widely-investigated


239
(+)-Castanospermine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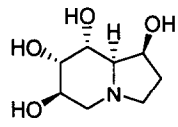
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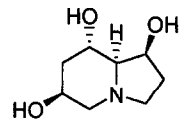
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indolizidine alkaloids to its potent, competitive and reversible inhibition of various glucosidases, which gives it potential therapeutic value in the treatment of ailments as varied as cancer, viral infections (including human immunodeficiency virus-1, or HIV-1), and diabetes. The following survey of recent developments in the chemistry and biology of castanospermine and its naturally-occurring analogs updates the synopses presented in Volumes 28 and 44 of this treatise (*1,2*), and includes some germane information not included in the latter review.

1. Isolation and Structure

An additional minor alkaloid isolated from the seeds of *Castanospermum australe* has proved to be (+)-7-deoxy-6-epicastanospermine (**242**) ($[\alpha]_D$ +18.3°, *c* 0.712, MeOH) (*190*). A combination of chemical and spectroscopic methods revealed the gross structure, while the relative stereochemistry at the four stereogenic centers was assigned on the basis of proton coupling constants. Its absolute stereochemistry was assigned by analogy with other alkaloids from the same plant, and has since been confirmed by synthesis (*vide infra*). The new alkaloid, the first trihydroxyindolizidine to be isolated from *C. australe*, was a moderate inhibitor of amyloglucosidase and yeast α-glucosidase.

(+)-Castanospermine (**239**) has been isolated from callus cultures prepared from leaf and stem explants of young specimens of *C. australe*, or from leaves of mature trees, and cultivated on a supplemented Murashige–Skoog medium (*191*). The alkaloid content of the cultures was approximately 0.004% based on fresh weight, which is slightly higher than that in mature leaf extracts (0.003%). The significant therapeutic potential of **239** makes this a development to follow with interest.

High-resolution single-crystal X-ray diffraction has confirmed both the structure and the absolute configuration of (+)-**239** (*192*), and the structure of the hydrochloride salt of 6-epicastanospermine (**240**) (*193*).

2. Synthesis

The bioactivity of castanospermine and related alkaloids continues to inspire chemists to devise new synthetic routes to the alkaloid, as well as to innumerable structural, stereochemical and other analogs. The ensuing discussion deals only with reported syntheses of the four natural products **239–242**. For syntheses of other reported stereoisomers of the indolizidine-1,6,7,8-tetraols (Fig. 4), the following references should be consulted: (−)-1-epicastanospermine (**243**) (*194*), (±)-7-epicastanospermine (*195*) and (1*S*,6*S*,7*S*,8*R*,8a*R*)-7-epicastanospermine (**244**) (*196*),

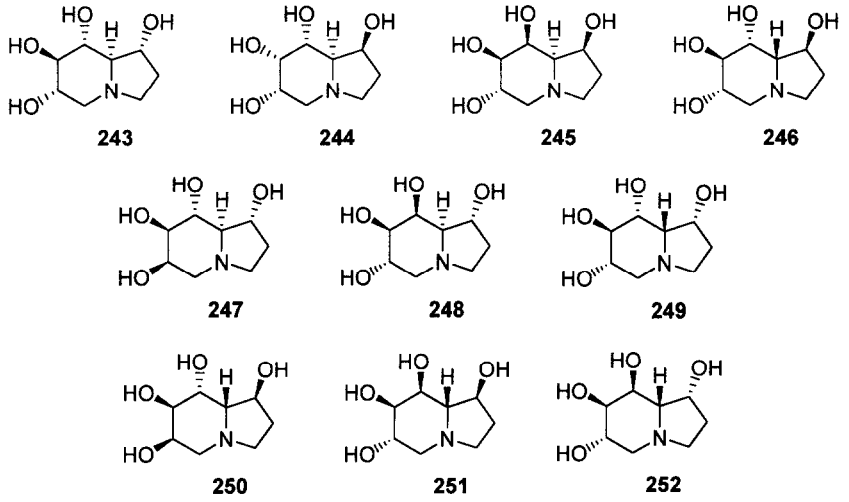
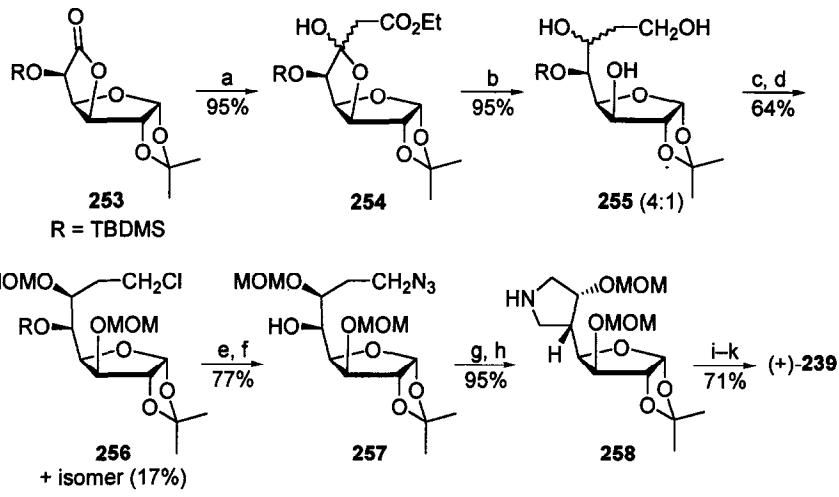


FIG. 4. Synthetic stereoisomers of castanospermine (**239**).

(+)-8-epicastanospermine (**245**) (*197*), (±)-8a-epicastanospermine (*198*) and (+)-8a-epicastanospermine (**246**) (*199,200*), (±)-1,6-diepicastanospermine (*198*) and (−)-1,6-diepicastanospermine (**247**) (*201,202*), (±)-1,8-diepicastanospermine (**248**) (*195*), (+)-1,8a-diepicastanospermine (**249**) (*200*), (±)-6,8a-diepicastanospermine (*198*) and (1*S*,6*R*,7*R*,8*R*,8a*S*)-6,8a-diepicastanospermine (**250**) (*199*), (±)-8,8a-diepicastanospermine (*195*) and (+)-8,8a-diepicastanospermine (**251**) (*203*), and (−)-1,8,8a-triepicastanospermine (**252**) (*197*). A synthesis of [3-^{14}C]-castanospermine and its 6-*O*-butyryl ester, required for pharmacokinetic studies (*204*), essentially followed the 1990 route of Anzeveno *et al.* (*205*), but used cyclohexyl [1-^{14}C]-acetate as the labeled precursor of the C-2/^{14}C-3 fragment. Two model studies having (+)-**239** as the ultimate goal are also worth noting (*144,206*).

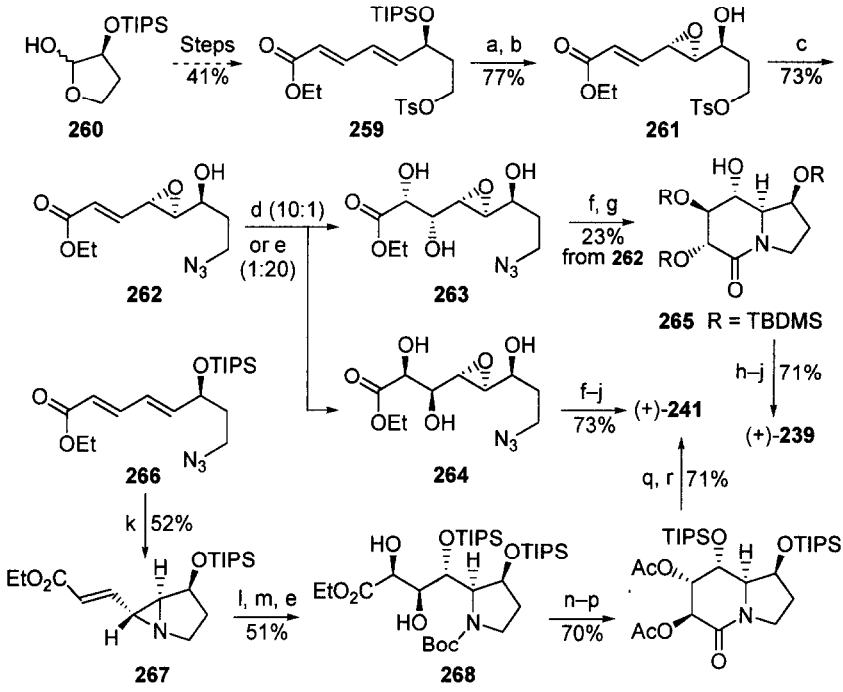
The short synthesis of (+)-**239** by Grassberger *et al.* shown in Scheme 34 commenced with an unusual carbohydrate substrate, the L-idofuranurolactone **253** (*194*). Reformatsky reaction with ethyl bromoacetate yielded the epimeric lactols **254**, which contain all the skeletal carbon atoms of the target alkaloid. After reduction with calcium borohydride, the diastereomeric mixture of alcohols **255** (4:1) was protected and activated to give the primary alkyl chloride **256** (64%) and its separable isomer (17%). Nitrogen was introduced by displacing chloride with azide ion, following which the product **257** was converted in two steps into the pyrrolidine **258**. Removal of the protecting groups and reductive cyclization completed the synthesis of (+)-**239** in an overall yield of 33% from lactone **253**. It should be noted that the same authors' synthesis of (1*R*,6*S*,7*R*,8*R*,8a*R*)-1-epicastanospermine (**243**) from the D-glucofuranurolactone analog of **253** gave a levorotatory product ($[\alpha]_D$ −5°, *c* 0.1, H_2O), whereas other workers have found a positive specific rotation for the same enantiomer (*207*). However, since the sign of the optical rotation appears to depend on pH and solvent (*208*), the contradictory results may not be significant.



SCHEME 34. Reagents: a, Zn, $BrCH_2CO_2Et$, cat. I_2, THF, 65°C; b, $CaCl_2$, $NaBH_4$, THF; c, *p*-TsCl, pyridine, CH_2Cl_2; d, $ClCH_2OMe$, Pr^i_2NEt, CH_2Cl_2, 40°C; e, NaN_3, DMF, 90°C; f, $Bu_4NF{\cdot}3H_2O$, THF; g, $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, –20°C; h, H_2, 10% Pd/C, EtOAc; i, TFA, MeCN–H_2O (1:2), 40°C; j, H_2, 5% Pd/C, MeOH; k, chromatography on Amberlite CG50 [H^+].

In the synthesis of (+)-**239** by Cha and co-workers, Sharpless methodology proved critical for the stereocontrolled oxygenation of both double bonds of diene **259**, which was obtained in several steps from the readily available lactol **260** (Scheme 35) (*209*). Firstly, desilylation of **259** exposed the hydroxy handle needed for asymmetric epoxidation of the adjacent double bond. Performed with (+)-diisopropyl tartrate as the control element, this reaction yielded diastereomer **261**. Conversion of this product into the azide **262** paved the way for asymmetric dihydroxylation of the second double bond with osmium tetroxide. This reaction could be biased in favor of either diol isomer **263** or **264** by varying the chiral ligand. After protection of the hydroxy groups of **263**, reductive double cyclization of the epoxy-azide created the indolizidinone nucleus of **265**. Reduction of the lactam and deprotection completed the synthesis of (+)-castanospermine (**239**). Similar late transformations of **264** resulted in the first total synthesis of the minor alkaloid (+)-6,7-diepicastanospermine (**241**). A related synthesis of (+)-**241** from the same research team proceeded *via* azidodiene **266**, which underwent intramolecular dipolar cycloaddition to give the bicyclic aziridine **267** as the sole product (Scheme 35, bottom line) (*210*). Cleavage of the strained ring with di-*t*-butyl pyrocarbonate followed by protection and asymmetric dihydroxylation yielded diol **268**, which was transformed as shown into the target alkaloid (+)-**241**.

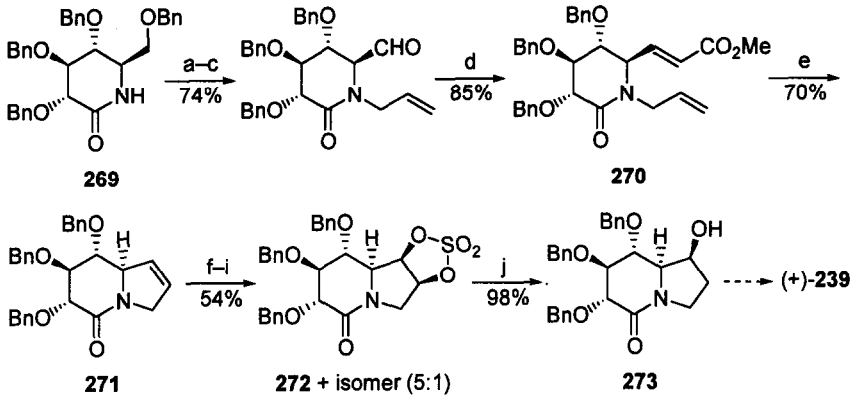
The glucopyranose-derived lactam **269** was the starting material in Overkleeft and Pandit's formal synthesis of (+)-**239** (Scheme 36) (*211*). What makes this synthesis topical is the novel construction of the indolizidine nucleus by metathesis of dialkene **270**. The yield of **271** (70%) is noteworthy when one appreciates that a metathesis in which one of the participating double bonds forms part of an



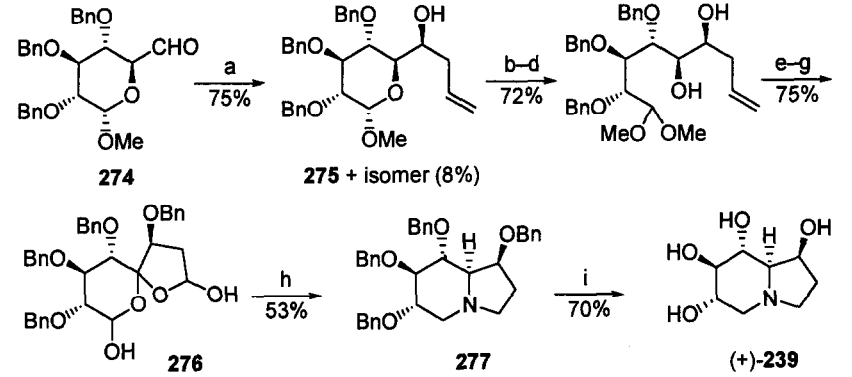
SCHEME 35. Reagents: a, Bu_4NF, THF, 0°C; b, $Ti(OPr^i)_4$, (+)-diisopropyl tartrate, 4Å molecular sieves, CH_2Cl_2, –23°C, then Bu^tOOH; c, NaN_3, DMF; d, $K_2OsO_4{\cdot}2H_2O$, $K_2Fe(CN)_6$, $MeSO_2NH_2$, $(DHQ)_2$-PHAL, H_2O–Bu^tOH (1:1); e, $K_2OsO_4{\cdot}2H_2O$, $K_2Fe(CN)_6$, $MeSO_2NH_2$, $(DHDQ)_2$-PHAL, H_2O–Bu^tOH (1:1); f, TBDMS-OTf, pyridine, CH_2Cl_2, 0°C to rt; g, H_2 (1 atm), 10% Pd/C, MeOH; h, $BH_3{\cdot}Me_2S$, THF; i, TFA–H_2O (9:1), CH_2Cl_2; i, chromatography on Dowex 1-X8; k, pyridine, 50°C, 11 h, then 70°C, 5 h; l, $(Boc)_2O$, THF–H_2O; m, TIPS-OTf, pyridine, CH_2Cl_2; n, HF, MeCN; o, NEt_3, reflux; p, Ac_2O, pyridine; q, $BH_3{\cdot}Me_2S$ or $BH_3{\cdot}THF$; r, NH_3.

α,β-unsaturated ester was unprecedented when this synthesis was reported. After dihydroxylation of the double bond of **271**, formation of the cyclic sulfate in two steps yielded **272** and its 1α,2α-diastereomer in a ratio of 5:1. Reduction of this compound afforded the bicyclic lactam **273**, at which stage the synthesis converged with the synthesis of (+)-**239** previously reported by Miller and Chamberlin (*212*).

Another glucopyranoside derivative, the aldehyde **274**, was converted into (+)-**239** in nine steps and 22% overall yield by Zhao and Mootoo (Scheme 37) (*213*). In this route, ultrasound-promoted allylation of **274** with allyl bromide and tin afforded alcohol **275** as the major diastereomer (9:1), thereby setting up the correct absolute stereochemistry at four of the target alkaloid's five stereogenic centers. The focal step in this synthesis was the triple reductive amination of the spiroketal compound **276**, which is effectively a masked tricarbonyl compound. The reaction, effected with ammonium formate and sodium cyanoborohydride, yielded **277** (53%); less than 5% of the bridgehead epimer was observed. Hydrogenolysis of the benzyl protecting groups completed this straightforward route to (+)-**239**.

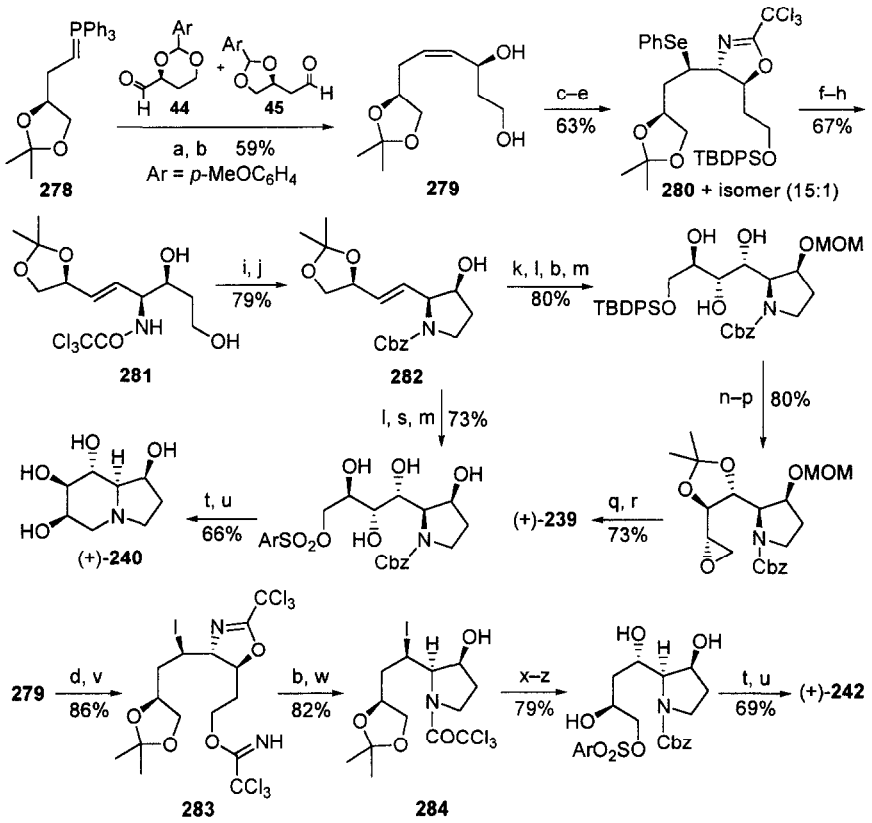


SCHEME 36. Reagents: a, $H_2C{=}CHCH_2Br$, Bu_4NI (cat.), 50% aq. KOH–CH_2Cl_2 (1:1); b, Ac_2O, $FeCl_3$, then NH_3, MeOH; c, Dess–Martin periodinane; d, $Ph_3P{=}CHCO_2Me$; e, Grubbs catalyst $[P(C_6H_{11})_3]_2Cl_2Ru{=}CHCH{=}CPh_2$ (5% w/w), PhMe, Ar, 110°C; f, OsO_4 (cat.), NMO; g, $SOCl_2$, NEt_3; h, $RuCl_3$ (cat.), $NaIO_4$, CH_2Cl_2–H_2O–MeCN (2:3:2); i, separation on SiO_2; j, $NaBH_4$, $MeCONMe_2$, then 20% aq. H_2SO_4, Et_2O.



SCHEME 37. Reagents: a, $H_2C{=}CHCH_2Br$, Sn, MeCN–H_2O (10:1), ultrasound; b, BnBr, NaH, Bu_4NI, DMF, 0°C; c, iodonium dicollidine perchlorate, CH_2Cl_2, MeOH; d, Zn, EtOH, reflux; e, Swern oxidation; f, O_3, CH_2Cl_2, MeOH, –78°C, then Ph_3P; g, 9M HCl, THF; h, NH_4HCO_2 (1.3 equiv), $NaBH_3CN$ (30 equiv), MeOH; i, 10% Pd/C, HCO_2H, MeOH.

Kang and Kim have synthesized both (+)-**239** and (+)-6-epicastanospermine (**240**) by yet another modification of the methodology previously seen in their syntheses of slaframine and swainsonine (*cf.* Schemes 6, 28) (*214*). In this case, Wittig reaction between the mixture of 1,3-dioxolan- and 1,3-dioxan-containing aldehydes **44** and **45** [prepared from *p*-anisaldehyde and (*S*)-butane-1,2,4-triol] and the phosphorus ylide **278** (also derived from butane-1,2,4-triol) gave the *cis*-alkene **279** in 59% yield after selective deprotection and separation from unwanted isomers (Scheme 38). The

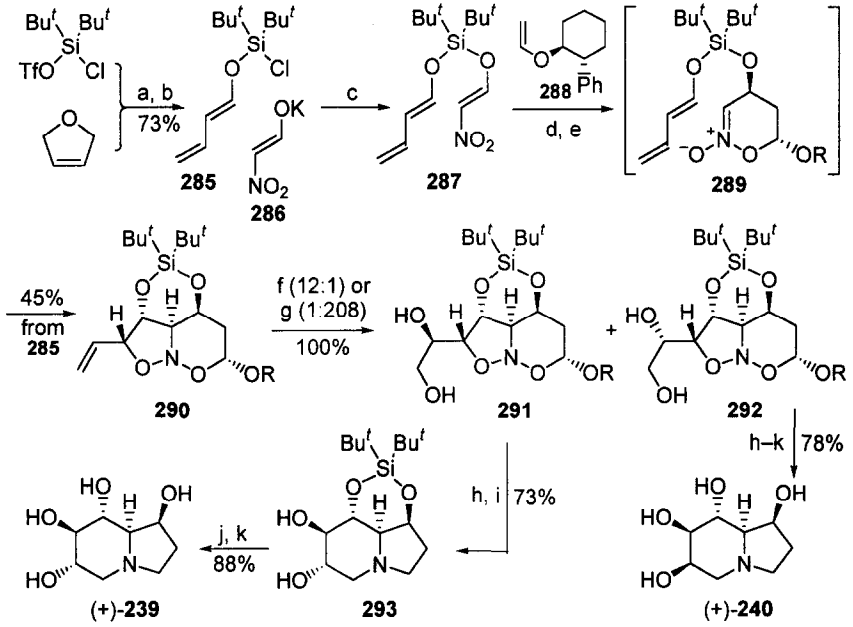


SCHEME 38. Reagents: a, THF, –78°C to 0°C; b, PPTS, MeOH, 0°C; c, TBDPS-Cl, imidazole, DMF, CH_2Cl_2, –60°C; d, Cl_3CCN, DBU, MeCN, 0°C; e, PhSeCl, $MeOC(=NH)CCl_3$, Et_3N, MeCN, –20°C; f, PPTS, H_2O, MeOH; g, 30% H_2O_2, THF, 0°C to 20°C; h, Bu_4NF, THF, –5°C to 0°C, then aq. NaH_2PO_4; i, DIAD, Ph_3P, THF, 0°C; j, NaOBn, THF; k, MOM-Cl, Et_3N, CH_2Cl_2, reflux; l, *p*-TsOH, MeOH; m, OsO_4, NMO, H_2O, Me_2CO, 0°C; n, *p*-TsOH, Me_2CO; o, MsCl, DMAP, Et_3N, CH_2Cl_2; p, Bu_4NF, THF, then 5M NaOH; q, 5% Pd/C, cyclohexene, EtOH, reflux; r, conc. HCl, MeOH, reflux, then Dowex 50WX8-100; s, 2,4,6-Pr^i_3-$C_6H_2SO_2Cl$, pyridine; t, H_2, 10% Pd/C, MeOH; u, Et_3N, reflux; v, IBr, K_2CO_3, EtCN, –78°C; w, DEAD, Ph_3P, THF, 0°C; x, aq. TFA, reflux; y, $ClCO_2Bn$, $NaHCO_3$, MeOH, 0°C; z, 2,4,6-$Me_3C_6H_2SO_2Cl$, pyridine, 0°C.

stereochemical outcome of the route hinged on an unprecedented phenylseleno-amidation of the trichloroacetimidate derivative of **279**, which gave a 15:1 mixture of *trans*-oxazoline **280** and its *cis* isomer in 63% yield. Acidic hydrolysis followed by oxidative elimination of the selenium substituent yielded alkene **281**, from which the 3-hydroxypyrrolidine **282** was readily prepared. Two different sets of transformations, both involving *cis*-dihydroxylation of the double bond, were applied to **282** to complete divergent pathways to (+)-**239** and (+)-**240**. A further interesting twist to this methodology provided access to the minor *Castanospermum* alkaloid (+)-7-deoxy-6-epicastanospermine (**242**) (Scheme 38, bottom line) (*47*). When the bis-

(trichloroacetimidate) of diol **279** was treated with iodine monobromide, *trans*-iodooxazoline **283** was formed exclusively in 86% yield. Partial hydrolysis and cyclization under Mitsunobu conditions then gave hydroxypyrrolidine **284**. The subsequent hydrolytic nucleophilic substitution of iodide took place with complete inversion of stereochemistry, probably assisted by the trichloroacetyl group. The synthesis of (+)-**242**, the first of this compound, was completed as illustrated.

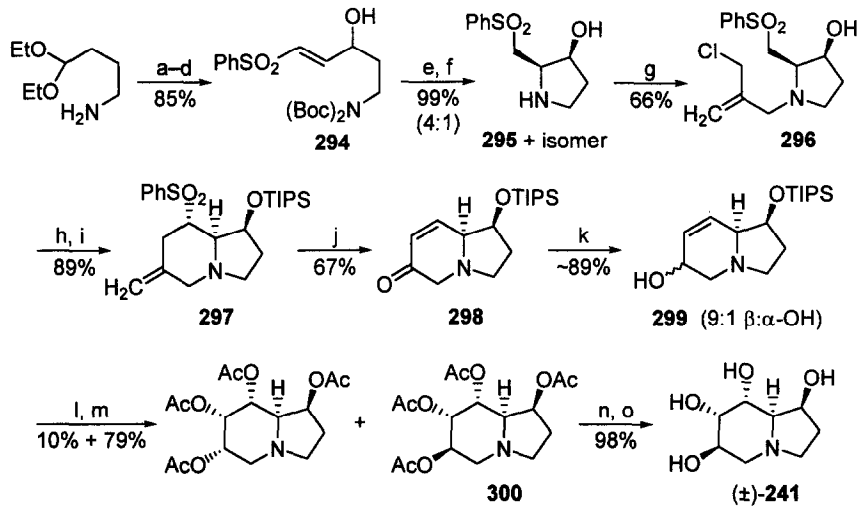
Perhaps the most innovative recent total synthesis of (+)-castanospermine (**239**) is due to Denmark and Martinborough, who devised the convergent route shown in Scheme 39 (*215*). Building blocks **285** (made from 2,5-dihydrofuran) and **286**, intended to become the C5–C6–C7–C8 and N–C8a–C1 skeletal atoms of the indolizidine system, were tethered to a silicon template in intermediate **287**. Methylaluminum bis(2,6-diphenylphenoxide) promoted a diastereofacially selective hetero Diels–Alder reaction between the nitroalkene and optically pure vinyl ether **288**. The intermediate nitronate **289** was then trapped intramolecularly in a 1,3-dipolar cycloaddition to give tricyclic compound (−)-**290** as a 44:1 mixture of diastereomers in 45% overall yield from **285**. Asymmetric dihydroxylation of the vinyl group yielded the diol (−)-**291** and its separable isomer (−)-**292** in a 12:1 ratio when $(DHQD)_2$–AQN was used as the chiral ligand. The isolated yield of **291** was 86%. Tosylation of



SCHEME 39 [R = (1*S*,2*R*)-2-phenylcyclohexyl]. Reagents: a, 2,5-dihydrofuran + BuLi, THF, –23°C; b, $(Bu^t)_2Si(Cl)OTf$, –78°C to 25°C; c, $CHCl_3$, MeCN; d, $MeAl(OC_6H_3\text{-}2,6\text{-}Ph_2)_2$, CH_2Cl_2, –50°C; e, C_6H_6, reflux; f, $K_2OsO_2(OH)_4$, K_2CO_3, H_2O, $NaHCO_3$, $K_3Fe(CN)_6$, Bu^tOH, $(DHDQ)_2$-AQN; g, $K_2OsO_2(OH)_4$, K_2CO_3, H_2O, $NaHCO_3$, $K_3Fe(CN)_6$, Bu^tOH, DHQ-PHN; h, *p*-TsCl, pyridine; i, H_2 (160 psi), Raney Ni, MeOH; j, HF, MeOH; k, AG 50W-X8 resin.

the terminal hydroxy group, then hydrogenolysis of both N–O bonds over Raney nickel, resulted in spontaneous double cyclization and reduction to yielded the (–)-indolizidine **293** (73%). Removal of the silicon tether completed the synthesis of (+)-**239**. Formation of the epimeric diol (–)-**292** from **290** was favored (208:1) when the Sharpless dihydroxylation was mediated by a different ligand, DHQ–PHN. In this case, the pure isomer was isolated in 93% yield after recrystallization. Its transformation into (+)-6-epicastanospermine (**240**) paralleled the conversion of **291** into (+)-**239**. The overall yields of (+)-**239** and (+)-**240** were 18% and 24%, respectively, based on 2,5-dihydrofuran.

Since the minor alkaloid 6,7-diepicastanospermine (**241**) is still an uncommon synthetic target, a recent synthesis of the compound in racemic form deserves mention (*195*). Carretero and co-workers found that deprotection and cyclization of the vinylsulfone **294** produced a 4:1 mixture of 2,3-*cis*-disubstituted pyrrolidine **295** and its *trans* isomer (Scheme 40). *N*-Alkylation of the mixture with 3-chloro-2-chloromethylprop-1-ene followed by chromatography led to isolation of the pure 2,3-*cis* product **296**, silylation and base-initiated cyclization of which gave indolizidine **297**. Ozonolysis and elimination of the sulfone group yielded another pivotal intermediate, the bicyclic enone **298**. Reduction with L-Selectride afforded an inseparable mixture of two diastereomeric alcohols **299** (9:1). Separation was accomplished only after dihydroxylation with osmium tetroxide and peracetylation of the resulting tetrols. The synthesis of (±)-**241** was completed by hydrolysis of the major tetraacetate **300**.



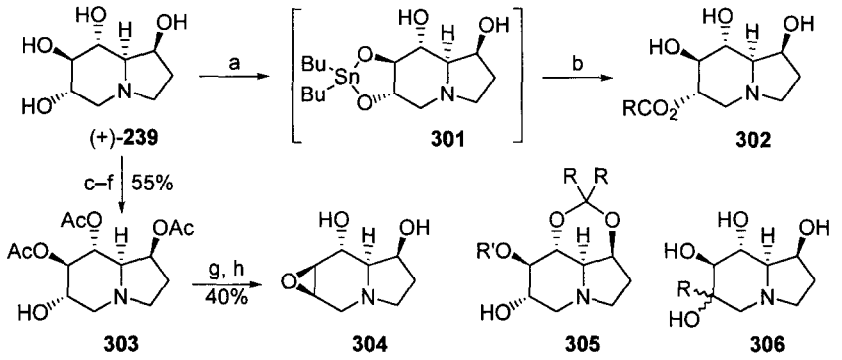
SCHEME 40. Reagents: a, $(Boc)_2O$, CH_2Cl_2, 0°C to rt; b, BuLi, $(Boc)_2O$, THF, 0°C; c, AcOH–H_2O (2:1); d, $PhSO_2CH_2SO$-*p*-Tol, piperidine, CH_2Cl_2, 0°C; e, TFA, CH_2Cl_2; f, Et_3N, THF, –78°C; g, LiI, $(ClCH_2)_2C{=}CH_2$, K_2CO_3, MeCN, 70°C; h, 2,6-lutidine, TIPS-OTf, CH_2Cl_2, –78°C to rt; i, LHDMS, THF, 0°C; j, O_3, TFA, CH_2Cl_2, –20°C, then Ph_3P, then Et_3N, CH_2Cl_2, 0°C to rt; k, L-Selectride, THF, –78°C; l, OsO_4, TMEDA, CH_2Cl_2, –78°C, then Na_2SO_3, THF, reflux; m, Ac_2O, pyridine, DMAP, then chromatography; n, 10% aq. NaOH, MeOH; o, Dowex 1X8-200 (OH^-).

3. *Chemical Transformations of Castanospermine*

Much of the current interest in making simple derivatives of (+)-castanospermine (**239**) can be traced to a seminal publication in 1989, which showed that the alkaloid's anti-HIV activity could be increased by as much as twenty times upon esterification (*216*). Positionally selective acylation procedures usually involve sequential protection, acylation, and deprotection steps; e.g. the preparation of esters at the C-6 and C-7 (*217*) or the C-8 hydroxy groups (*218*). Also of interest are procedures that take advantage of enzyme-catalyzed transesterification with activated esters, e.g. the use of subtilisin for ester formation at C-1, pancreatic porcine lipase for preferential reaction at C-6 and C-7 (*219–221*), and cross-linked enzyme crystals (CLECs) of subtilisin for making the potentially valuable antitumor agent 1-*O*-butanoylcastanospermine (*222*). A cautionary note was sounded, however, when it was observed that 6-*O*-acyl castanospermine esters could equilibrate to a mixture of 6-, 7- and 8-*O*-acyl compounds at physiological pH and temperature (*223*).

Regioselective functionalization of (+)-**239** received a useful boost from the work of Anderson *et al.*, who showed that the dibutylstannyl unit could serve as both protecting and activating group for the alkaloid (*224*). The pre-formed tin complex **301** underwent selective acylation at the C-6 position to give a variety of 6-*O*-acylcastanospermines **302** (R = Me, *n*-Pr, *i*-Bu, *n*-hexyl, *n*-nonyl, *n*-tridecyl, Ph) in yields of between 18% and 44% (Scheme 41). This complexation proved to be a pivotal factor in the extensive series of investigations by Furneaux *et al.*, who used the tin activation method not only to mediate the synthesis of castanospermine esters, but also to make many other derivatives in which one or more of the hydroxy groups was directly or indirectly replaced by various nucleophiles (*e.g.*, Cl, F, CN, OR, NHR, NRR') either with retention of configuration or with inversion (*196,225–227*). For example, acylation of the tin complex with benzyl chloroformate followed by peracetylation of the free hydroxy groups and hydrogenolytic removal of the benzyloxycarbonyl group gave triacetate **303**. The unencumbered 6-OH group of this compound could then be manipulated in several ways [*e.g.*, conversion into epoxide **304**, hydrolysis of which completed another synthesis of 6,7-diepicastanospermine (**241**)] (*225*). Rearrangement of the indolizidine ring to pyrrolizidine systems was observed on occasion. Alternatively, benzoylation of **301** followed by differential protection of the remaining hydroxy groups produced ketal intermediates such as **305**, which further extended the range of accessible derivatives [*e.g.*, oxidation followed by addition of Grignard reagents gave **306** (R = Me, vinyl), while oxidation followed by borohydride reduction gave the minor alkaloid (+)-6-epicastanospermine (**240**)] (*225*). Other publications in this series described selective functionalizations at C-1, C-7 (*196*), and C-8 (*226*).

Another class of castanospermine derivatives to have been explored as potential therapeutic agents are the D-glucopyranosides, six different isomers of which were prepared by coupling the suitably protected alkaloid with 2,3,4,6-*O*-tetrabenzyl (or tetraacetyl) α-D-glucopyranosyl trichloroacetimidate (*228*). Various eliminations from, or degradations of, (+)-**239** have been reported during attempts to oxidize or otherwise functionalize the parent alkaloid or its tetraacetate (*229–231*). Castanospermine *N*-oxide has been made by oxidizing the alkaloid with hydrogen peroxide (*232*).



SCHEME 41. Reagents: a, Bu_2SnO, MeOH, reflux; b, RCOCl, Et_3N; c, $(Bu_3Sn)_2O$, PhMe, reflux; d, $ClCO_2Bn$, PhMe, –20°C; e, Ac_2O, pyridine, 0°C; f, H_2 (60 psi), 5% Pd/C, EtOH, EtOAc; g, MsCl, pyridine; h, KOH, DMF.

4. *Biological Activity*

(+)-Castanospermine's potency as a glucosidase inhibitor underlies its appreciable biological activity and therapeutic potential. For example, its ability to inhibit intestinal sucrase, maltase, and trehalase activity in rats has suggested a possible role in the treatment of diabetes (*155*). It is also an effective competitive inhibitor of pig kidney trehalase (IC_{50} 2.5×10^{-6} M), an enzyme involved in sugar transport across brush border membranes (*233*). It not only inhibited islet lysosomal acid glucan-1,4-α-glucosidase activity *in vitro* (EC_{50} 10^{-7} M), but at the same time also functioned as a slow-acting inhibitor of glucose-induced insulin release (*234,235*). In a more applicable study, intraperitoneal injection of (+)-**239** into streptozotocin-diabetic mice (150 μmol kg^{-1}) revealed the alkaloid's antihyperglycemic effects by reducing blood glucose levels by almost 50% after four hours (*236*). Both 7- and 8-*O*-α-D-glucopyranosylcastano-spermine were recognized as long ago as 1989 to be potent, long-acting sucrase inhibitors that effectively reduced the glycemic response to orally administered sucrose *in vivo* (*237*), although the structural basis for inhibition was not clear (*238*).

Several other glycosidases are affected by castanospermine. The finding that the alkaloid inhibited various insect glycosidases, notably β-glucosidases (*148,239, 240*), makes sense of earlier reports of its efficacy as an insect antifeedant (*241,242*). In adult male rats, (+)-**239** inhibited epididymal α-glucosidase, an enzyme that facilitates the storage of spermatozoa (*243*). There are intriguing implications in the observation of apparent infertility induced during the period of drug administration. The alkaloid can also *induce* the production of α-glucosidases, as was shown when the fungus *Mucor javanicus* was cultured with (+)-**239** (*244*). Castanospermine has been used as a glucosidase inhibiting tool for characterizing the glucosidase I from mung bean seedlings (*245*), for determining the function and biosynthesis of vasopressin V_2-receptors in renal epithelial cells (*153*), and for investigating oligosaccharide trimming in the assembly of nicotinic acetylcholine

receptors (*246*). The alkaloid's ability to alter glycoprotein processing has been exploited in studies on the activation of T-cells (*163,247*), and on the development and differentiation of oligodendrocyte progenitor cells (*248*).

Castanospermine is able to suppress the processing and secretion of lipoprotein lipase (*249–251*). Incubation of aortic endothelial cells with the alkaloid altered the distribution of scavenger receptors for low-density lipoproteins, a finding that has significance in the fight against coronary heart diseases involving the deposition of cholesterol on arterial walls (*252,253*).

Three pivotal papers that appeared in 1987 established the potency of castanospermine in inhibiting the replication of human immunodeficiency virus-1 (HIV-1) (*254–256*), and the intense activity that succeeded these revelations was documented in the previous review (*2*). Castanospermine is recognized as being one of the most powerful inhibitors of HIV-induced syncytium formation (virus-induced cell fusion), a crucial feature in the cell-to-cell transmission of HIV infection (*257*). It subsequently transpired that esters of (+)-**239** were even more effective inhibitors of HIV replication, no doubt because their lipophilic nature facilitates penetration through cell membranes, after which they are probably hydrolyzed to the parent alkaloid (*216*). Much of the current activity centers on 6-*O*-butanoylcastanospermine (the Merrell–Dow drug MDL 28574, also known as BuCast), which is over 30 times as active as castanospermine itself (*258*). It was considerably more effective than (+)-**239** in inhibiting the α-glucosidase I in HIV-infected T cells (*259*). Syncytium formation appears to be compromised because the alteration of glycoprotein processing changes the adhesion molecules implicated in this process and in processes such as antibody–antigen interaction (*260,261*). Indeed, *in vitro* studies with various human and murine cell lines and *in vivo* studies with mice provided evidence for the alteration of both viral ligands and host cell adhesion molecules (*262*). A synergistic effect of MDL 28574 with other anti-AIDS drugs, including 3'-azido-3'-deoxythymidine (AZT), was observed in this study, which parallels effects previously observed for the synergistic effect of (+)-**239** and AZT on HIV replication *in vivo* (*263*). In this regard, a patent describing the combination of castanospermine esters with short peptide analogues for treating retroviral infections is also worthy of note (*264*).

Castanospermine has been screened for efficacy against simian immunodeficiency virus (*265*), and has been shown to prevent syncytium formation in feline astrocyte cultures infected with the feline immunodeficiency virus by modifying the viral cell envelope (*266*). It suppressed syncytium formation and hemolytic activity in baby hamster kidney cells infected with Newcastle disease virus; however, synthesis and cell surface expression of the hemagglutinin–neuraminidase glycoprotein in the viral envelope were not affected, which strengthens the hypothesis that poor transport of the parent alkaloid across membrane barriers may limit its therapeutic use (*267*). Both **239** and its 6-*O*-butanoyl ester had comparable relative toxicities and antiviral effects on Rauscher murine leukemia virus (*268*), but the ester was more potent than the parent alkaloid in inhibiting replication of Moloney murine leukemia virus (*258*). The ester was also active against herpes simplex viruses types 1 and 2 (*269,270*). In the latter case, conclusive evidence was provided for intracellular hydrolysis to **239**.

Castanospermine's antitumor potential continues to receive attention. Recent *in vitro* studies have examined inhibition of tyrosinase activity in human melanoma cells (*181*), effects on intracellular transport of an avian erythroblastosis oncoprotein (*271*), and consequences for biosynthesis, maturation, and transport of α_1-antitrypsin in the human hepatoma HepG2 cell line (*257,272*). The latter study was the first to show the inability of **239** to permeate the plasma membrane in intact HepG2 cells. *In vivo* experiments with nude mice proved that the alkaloid altered the glycosylation of endothelial cells, prevented angiogenesis, and inhibited tumor growth (*273*). However, recent *in vivo* studies failed to reveal cytotoxicity towards two rat prostate adenocarcinoma cell lines, or effects on cell characteristics related to metastatic potential (*274*). Uptake and metabolism of the more lipophilic 6-*O*-butanoylcastanospermine in tumor cell lines and after oral administration to mice was traced with ^{14}C-labeled material, and showed rapid conversion into the parent alkaloid, which is undoubtedly the active metabolite (*275*). Multiple dosing in mice produced additive results.

The anti-inflammatory and immunosuppressant effects of castanospermine have emerged only recently. In 1993 it was shown that subcutaneous administration of (+)-**239** to rats that had undergone heart transplantation suppressed the expression of glycoproteins implicated in allograft rejection (*276*). Anti-inflammatory effects were also observed in mice, for which the alkaloid inhibited rejection of thyroid allografts and leukocyte migration into the peritoneal cavity (*277*). The alkaloid apparently prevents the accumulation of leukocytes at sites of inflammation by inhibiting their passage through the subendothelial basement membrane (*278*). Later investigations with heart transplants in rats proved that interrupting the intracellular processing of oligosaccharides led to 'downregulation' in the expression of adhesion molecules on cell membranes, and hence to suppression of cell-to-cell interactions (*279*). A specific ligand–receptor adhesion molecule pair (LFA-1α $\leftrightarrow$ ICAM-1) was later identified in grafted rats, and limited testing showed dose-dependent effects as well as relatively low toxicity (*280,281*). Influences on other adhesion molecules have also been uncovered (*280–282*). Castanospermine was compatible with other effective but toxic immunosuppressants such as FK-506 and tacrolimus, which suggests the possibility of combined therapies involving reduced dosages of the more toxic component (*283, 284*). The possible utility of (+)-**239** in the treatment of multiple sclerosis and related diseases of the central nervous system has been discussed in a brief review on the development of anti-inflammatory drugs (*285*), while anti-inflammatory effects appear to be involved in its ability to inhibit adjuvant arthritis in the rat (*286*).

Derivatives of (+)-**239** with appreciable ability to inhibit enzymes include the 6-acetamido analog, a potent inhibitor of β-*N*-acetylglucosaminidases from a variety of sources (*287*); and a large number of lipophilic esters (mostly 6-acyl variants), which are effective against α-glucosidases from porcine kidney and mouse melanoma $B_{16}F_{10}$ cells (*288*). The only new biological studies on naturally occurring stereoisomers of (+)-**239** relate to 6-epicastanospermine (**240**), which proved to be a modest inhibitor of some insect glycosidases (*148,239*), isomaltase, palatinase, and lactase (*244*).

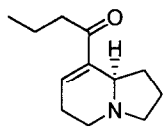
IV. Plant Alkaloids Bearing Alkyl or Functionalized Alkyl Substituents

A. *ELAEOCARPUS* ALKALOIDS

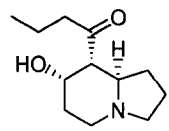
Simple indolizidine alkaloids from the genus *Elaeocarpus* were surveyed in Volumes 28 and 44 of this treatise (*1,2*). The latter survey highlighted a communication on the synthesis of (+)-elaeokanines A (**307**) and C (**308**) by Koizumi and co-workers (*289*) that has since been published with full experimental details (*290*).

A short formal synthesis of (±)-**307** by Brandi and co-workers involved the transformation of spirocyclopropylisoxazolidine **309** into indolizidinone **310** in 45% yield by flash vacuum thermolysis (*291*). The product was easily transformed into alcohol **311**, which was an intermediate in the 1991 synthesis of (±)-**307** by Taber *et al.* (*292*).

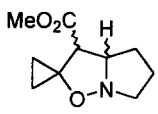
A formal synthesis of (−)-elaeokanine C (*ent*-**308**) by Sato *et al.* showcases an original approach to the construction of the indolizidine nucleus (Scheme 42) (*293, 294*). When the pyroglutamate-derived diene **312** was treated with triethylsilane and $Ni(COD)_2$, a π-allylnickel intermediate was generated *in situ*. Cyclization on to the strategically located aldehyde group yielded a mixture of indolizidinones **313** (37%) and **314** (36%). The former was readily transformed into the latter by a four-step reaction sequence involving Mitsunobu inversion. Compound **314** includes all the skeletal atoms of the target alkaloid as well as the correct relative and absolute stereochemistry. Elaboration of the butanoyl side chain at C-8 entailed unselective epoxidation to give a mixture of diastereomers of **315**, regioselective ring opening to the allylic alcohol **316**, and the appropriate functional group manipulations to give the indolizidinone (−)-**317** as sole product. Since Koizumi's group had previously converted the (+)-enantiomer of **317** into (+)-elaeokanine C (**308**), the unnatural enantiomer (*289,290*), the route shown in Scheme 42 represents a formal synthesis of the naturally occurring (−)-alkaloid, *ent*-**308**. Interestingly enough, there are no total syntheses of (−)-elaeokanine C in the literature; it is a pity, therefore, that the final transformation of (−)-**317** into the natural product was not actually performed.



307 (+)-Elaeokanine A



308 (+)-Elaeokanine C



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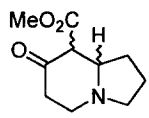

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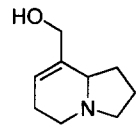

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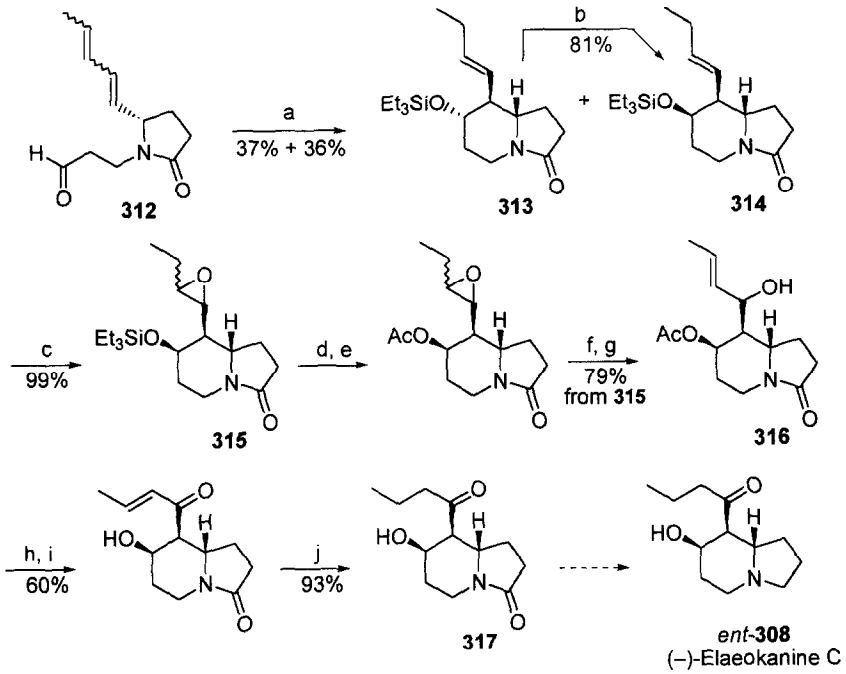


SCHEME 42. Reagents: a, $Ni(COD)_2$ (20%), Ph_3P (40%), Et_3SiH (5 equiv), THF; b, Mitsunobu inversion (4 steps); c, MCPBA, CH_2Cl_2; d, Bu_4NF, THF; e, Ac_2O, pyridine; f, Me_3SiI, DBU, MeCN; g, H_3O^+; h, 10% NaOH, MeOH; i, MnO_2, CH_2Cl_2; j, H_2, Pd/C, EtOAc.

B. *PROSOPIS* ALKALOIDS

Juliprosopine (**318**) and juliprosine (**319**) (Fig. 5), indolizidine alkaloids of the genus *Prosopis* (mesquite; family Leguminosae), had been partially characterized at the time of the previous review on the topic in this serial (*1*). Rather few advances have been made since then; no further stereochemical clarification has been forthcoming, and no further work has been reported on two other putative *Prosopis* indolizidines, isojuliprosopine and isojuliprosine (*295*). However, the alkaloid juliflorine, previously isolated from *Prosopis juliflora* by workers from Pakistan (*296,297*), has since been shown to be identical to juliprosopine (*298*).

The structure of julifloricine, another previously unidentified alkaloid isolated by the Pakistani group, has also been partially elucidated by comparing its spectroscopic characteristics with those of **318** and more typical *Prosopis* piperidine alkaloids such as spectaline (**320**) (*298*). The ^{13}C-NMR spectrum of **318** shows no doubling up of signals for the piperidine rings and the greater part of the attached hydrocarbon chains, which indicated that the two piperidine rings are identically substituted; by contrast, two sets of signals in julifloricine suggested different

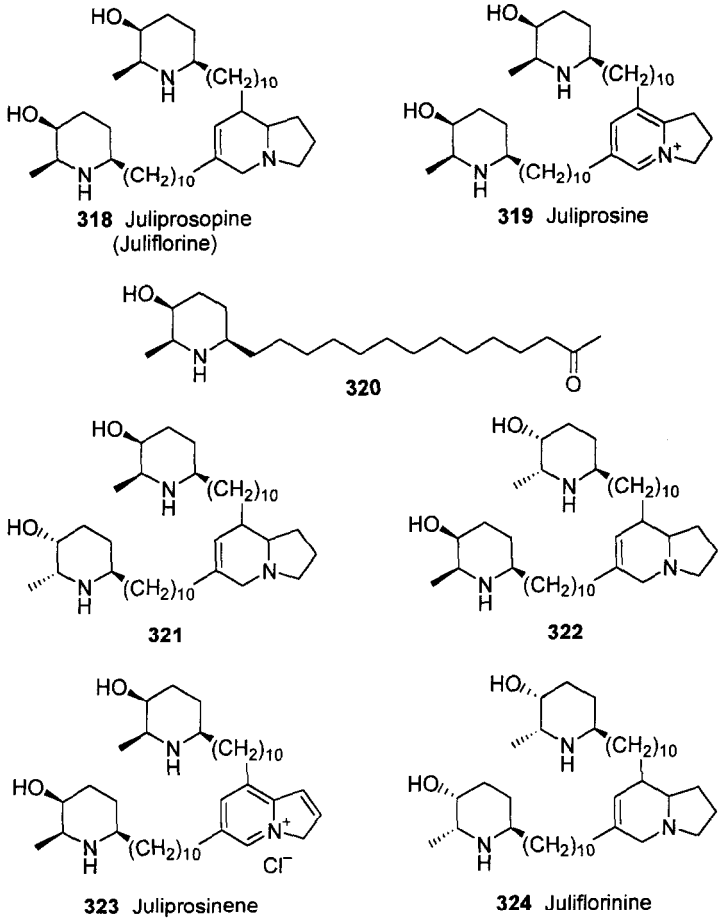


FIG. 5. *Prosopis* alkaloids.

configurations for the piperidine rings. Two alternative structures, **321** and **322**, were proposed for julifloricine, but it was not possible to distinguish between them. The absolute configurations in the piperidine sub-units were tentatively assigned by analogy with known piperidine alkaloids, but the configurations at C-8 and C-8a in the indolizidine nucleus remain unknown.

Two further indolizidine alkaloids, juliprosinene ($[\alpha]_D$ +9.5° for the chloride salt, *c* 0.04, $CHCl_3$) and juliflorinine ($[\alpha]_D$ +3.9°, *c* 0.03, $CHCl_3$), were isolated from the leaves of *Prosopis juliflora* some years after the above work had been reported (*299*). Partial structures were once again deduced on the basis of extensive spectro-scopic comparisons with known alkaloids. Juliprosinene chloride, for instance, gave very similar spectra to juliprosine (**319**) and spectaline (**320**), and showed no doubling up

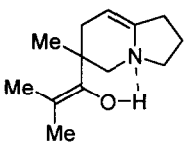
of signals for the pendent piperidine units. The indolizinium structure **323** was proposed. Although the analogous signals in juliflorinine were also not duplicated, they correlated better with those of simple 2,3-*cis*-2,6-*trans*-trisubstituted piperidin-2-ol alkaloids rather than with those of all-*cis*-piperidines. Juliflorinine was thus deduced to be a stereoisomer of juliprosopine, and the structure **324** was proposed.

Prosopis juliflora is a pharmacologically interesting shrub, and several studies on the biological activity of indolizidine alkaloidal fractions from the plant, as well as on isolated alkaloids, have been published. Antibacterial, antifungal, anti-amebic, toxicological, and pharmacokinetic studies have been reported for juliprosopine (**319**), julifloricine (**321/322**), and water-soluble alkaloid mixtures; activity appears to be most significant against Gram-positive bacteria, dermatophytic fungi, and *Candida* (*300–309*). Juliprosinene (**323**), unlike its congeners, showed activity against several common Gram-negative bacteria (*299*).

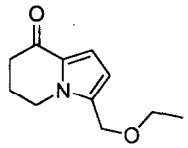
C. Miscellaneous Indolizidine Alkaloids

The unprecedented structure **325** has been proposed for polycanthisine ($[\alpha]_D^{30}$ +16°, *c* 0.75, MeOH; m.p. 160–161°C), one of several structurally diverse indolizidine alkaloids isolated from *Astragalus polycanthus* (Leguminosae) (*cf.* Section VII.C) (*310*). The compound analyzed for $C_{13}H_{21}NO$, and showed a molecular ion at *m/z* 207. The presence of an OH or NH group was suggested by IR absorptions in the region 3100–3380 cm^{-1}. However, Bohlmann bands at 2715 and 2840 cm^{-1}, claimed to be indicative of a *trans*-fused indolizidine system, are clearly incompatible with the bridgehead unsaturation in the proposed structure. The most startling aspect of structure **325** is the free enol, asserted to be stabilized by strong intramolecular hydrogen bonding with nitrogen. The evidence adduced for the enol included a signal at δ 169 in the ^{13}C-NMR spectrum, a D_2O-exchangeable signal at δ 7.4 in the ^1H-NMR spectrum, and another signal at δ 8.0 that was somewhat ambiguously ascribed to hydrogen bonding of the enolic OH group with the indolizidine's nitrogen atom. Strong hydrogen bonding was blamed for the resistance of the alkaloid to acetylation. However, it formed a trimethylsilyl derivative that gave the same mass spectral fragmentation pattern as the parent compound. Although the spectroscopic data obtained for polycanthisine were comprehensive, there are inconsistencies in their interpretation. The proposed structure should be taken *cum grano* until further evidence is produced.

An indolizidine alkaloid isolated from the rhizomes of *Polygonatum sibiricum* (Liliaceae) also has some unusual features (*311*). The unnamed alkaloid, for which the structure **326** has been proposed on the basis of good spectroscopic data (IR, UV, MS; ^1H, ^{13}C and HETCOR NMR), is the first 5,6,7,8-tetrahydroindolizine (cyclohexa[*a*]pyrrole) to have been found as a natural product. In addition, the ethoxymethyl substituent is unique, at least among the natural indolizidines. It should also be pointed out that simple indolizidine alkaloids have never before been isolated from liliaceous species. Although the structure **326** appears to be reasonable in the light of the spectroscopic evidence, judgement should perhaps be reserved until it can be confirmed independently.



325



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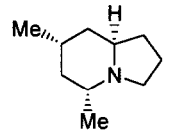
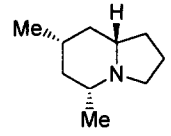


327
(–)-Dendroprimine



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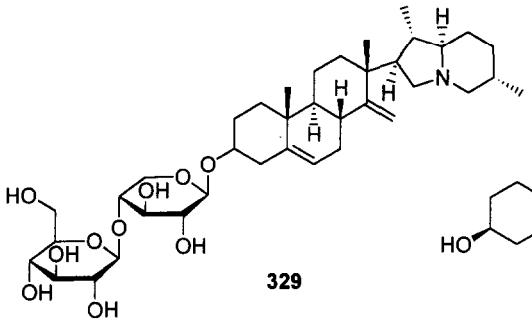

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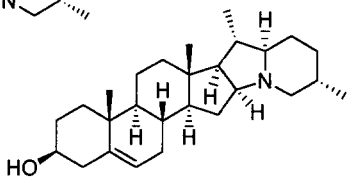


330

The orchid alkaloid (–)-dendroprimine (**327**) was dealt with in Volume 28 of this treatise (*1*). The hydrochloride salt of an epimer, (–)-8a-epidendroprimine (**328**), was recently synthesized from L-proline (*312*).

An atypical steroidal alkaloid, 15,16-*seco*-22αH,25βH-solanida-5,14-dien-3β-ol *O*-β-D-glucopyranosyl-(1→4)-β-D-xylopyranoside (**329**) ($[\alpha]_D^{25}$ –20.5°, *c* 0.40, MeOH) was isolated from the bulbs of *Fritillaria maximowiczii* (Liliaceae) (*313*). This compound contains a uniquely substituted indolizidine nucleus that can be viewed as arising from ring D cleavage between C-15 and C-16 of a more typical steroidal alkaloid precursor such as solanidine (**330**). The structure was deduced from the NMR spectra of both the native metabolite and its aglycone, which was obtained by incubating **329** with hesperidinase. The structures of the sugar units were corroborated by GC analysis.

D. LUPINE ALKALOIDS

Simple bicyclic compounds form a rather small subset of the lupine (or lupin) alkaloids, the overwhelming majority of which have tricyclic or tetracyclic structures based on the quinolizidine motif. These alkaloids are characteristic metabolites of the Papilionoideae, a sub-family of the Leguminosae (Fabaceae), although representative examples have also been isolated from several other plant families. The simple lupine quinolizidines were surveyed in Volume 28 of this treatise (*1*), while later reviews in Volumes 31 (*8*) and 47 (*9*) comprehensively covered all classes of lupine alkaloids, including those containing indolizidine components. Much relevant material is also to be found in the review on the biosynthesis of pyrrolizidine and

quinolizidine alkaloids in Volume 46 (*10*), and in several other short reviews (*314–317*). The present survey, once again limited to fused bicyclic systems, deals primarily with literature published during and after 1993.

1. Isolation and Structural Studies

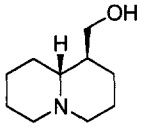
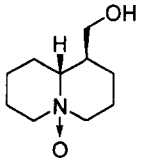
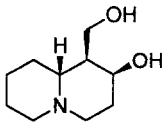
Known and new lupine alkaloids reported from mid-1993 to mid-1999 are listed in Table I together with their plant sources (*318–335*). In a number of cases, alkaloids were not isolated, and their identification was based entirely on their gas chromatographic and/or mass spectrometric (GC–MS) characteristics. Several apparently new alkaloids were identified in this way, and their structures should be regarded as tentative until firmer evidence can be obtained. These include a dehydroepilupinine (**332**), benzoylepilupinine (**336**), and dihydrolusitanine (**347**). The putative 4β-hydroxyepilupinine (**334**) and 4β-hydroxylupinine (**345**) were previously detected in several *Virgilia* species (*336*), and esters of the former were obtained in sufficiently large amounts for unambiguous spectroscopic characterization.

Not included in the Table are the results of a colossal GC–MS chemotaxonomic survey of the alkaloidal profiles of 56 *Lupinus* species (embracing 90 subspecies and chemotypes) representing both Old World and New World taxa (*337*). Of interest in this survey is the finding that bicyclic alkaloids of the lupinine class occurred mainly in Old World species. Genetic evidence has also been obtained for a close relationship between (and probably a common ancestry for) lupines that produce the lupinine complex of metabolites (*338*).

The new glycosidic alkaloid (–)-(3-methoxy-4-α-L-rhamnosyloxycinnamoyl)-epilupinine was isolated as a 5:1 mixture of (*Z*)- and (*E*)-isomers **338** and **339** ($[\alpha]_D$ –37.5°, *c* 0.056, EtOH) from the aerial parts of *Lupinus hirsutus* (*332*). In addition to the customary spectroscopic evidence, the structure was corroborated by hydrolysis with 3% aqueous hydrochloric acid to form rhamnose and the known compound (+)-(4-hydroxy-3-methoxycinnamoyl)epilupinine (**337**). The latter was hydrolyzed in its turn with 7% hydrochloric acid to give (+)-epilupinine (**331**). The (*E*)-isomer **339** ($[\alpha]_D^{24}$ –80°, *c* 0.28, EtOH) was subsequently reported as a new alkaloid from aerial parts of *L. varius* ssp. *orientalis*; similar spectroscopic data were cited, and hydrolysis to L-rhamnose and the corresponding aglycone also supported the structural assignment (*325*).

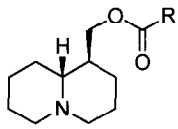
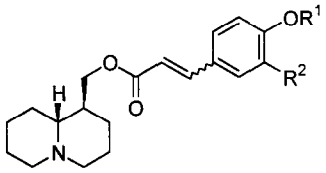
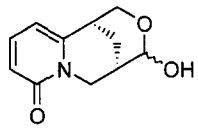
The unusual new alkaloid (+)-hupeol (**341**) ($[\alpha]_D$ +32.3°, *c* 0.263, EtOH), isolated from Chinese *Maackia hupehensis* together with the well-known tricyclic alkaloid (–)-cytisine (**349**), is included in Table I because it is in effect the cyclic hemiacetal of a simple quinolizidinecarbaldehyde system (*326*). Its ^{1}H- and ^{13}C-NMR spectra, recorded in methanolic solution, were very similar to those of cytisine apart from significant downfield shifts of the signals for C-11, C-13, and their attached protons. The new alkaloid comprises two epimeric hemiacetals, as evinced by two sets of NMR signals; the dominant isomer (3:1 in methanol) possesses an axial hydroxy group. Hupeol is suspected to be an advanced metabolite in the biosynthetic pathway for lupine alkaloids; its lack of a basic nitrogen suggests its intermediacy in the breakdown of lupine alkaloids to non-basic components, thus placing it even further down the catabolic path than cytisine.

TABLE I
LUPINE ALKALOIDS AND THEIR SOURCES

Alkaloids	Sources (*Ref.*)
Epilupinine group:	
(+)-Epilupinine (**331**)[a] 	*Anarthrophyllum andicolum, A. cumingii, A. desideratum, A. rigidum, A. umbellatum* (*318*) *Dicraeopetalum stipulare* (*319*) *Harpalyce formosa* (*320*) *Lupinus atlanticus, L. palaestinus, L. pilosus* ssp. *tassilicus, L tassilicus* (*321*); *L. flavoculatus, L. pusillus* ssp. *pusillus, L shockleyi* (*322*); *L. princei* (*323*); *L. varius* ssp. *orientalis* (*324,325*) *Maackia hupehensis* (*326*) *Plagiocarpus axillaris* (*327*) *Poecilanthe amazonica, P. effusa, P. falcata, P. grandiflora, P. hostmannii, P. itapuana, P ovalifolia, P. parviflora, P. subcordata* (*328*) *Retama sphaerocarpa* (*329*) *Sakoanala villosa* (*319*) *Templetonia biloba* (*330*); *T. incana* (*331*)
Dehydroepilupinine (**332**)[b,c]	*Harpalyce formosa* (*320*)
(+)-Epilupinine *N*-oxide (**333**) 	*Lupinus varius* ssp. *orientalis* (*324,325*)
4β-Hydroxyepilupinine (**334**)[d] 	*Poecilanthe amazonica, P. falcata, P. hostmannii, P. itapuana* (*328*)

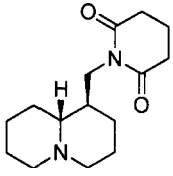
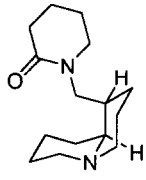
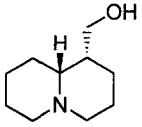
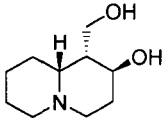
(continued)

TABLE 1 *(continued)*

Alkaloids[a]	Sources (*Ref.*)
Epilupinine esters:	
	
acetate (**335**) (R = Me)	*Poecilanthe amazonica* (*328*)
benzoate (**336**) (R = Ph)[b,d]	*Lupinus varius* ssp. *orientalis* (*325*)
	
(+)-(*E*)-4-hydroxy-3-methoxy-cinnamate (**337**) (R^1 = H, R^2 = OMe)	*Lupinus varius* ssp. *orientalis* (*325*)
(−)-(*Z*)-3-methoxy-4-α-L-rhamnosyloxycinnamate (**338**) (R^1 = α-L-rha, R^2 = OMe)[b]	*Lupinus hirsutus* (*332*)
(−)-(*E*)-3-methoxy-4-α-L-rhamnosyloxycinnamate (**339**) (R^1 = α-L-rha, R^2 = OMe)[b]	*Lupinus varius* ssp. *orientalis* (*325*); *L. hirsutus* (*332*)
(+)-(*E*)-4-α-L-rhamnosyloxy-cinnamate (**340**) (R^1 = α-L-rha, R^2 = H)	*Lupinus varius* ssp. *orientalis* (*325*)
(+)-Hupeol (**341**)[b,e]	*Maackia hupehensis* (*326*)
	

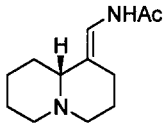
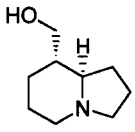
(continued)

TABLE 1 *(continued)*

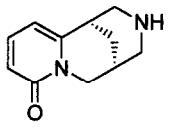
Alkaloids[a]	Sources (*Ref.*)
Lamprolobine group:	
(+)-Lamprolobine (**342**)[a] 	*Anarthrophyllum andicolum, A. cumingii, A. desideratum, A. elegans, A. rigidum, A. umbellatum* (*318*) *Sophora tonkinensis* (*333*)
(+)-17-Desoxy-*cis*-lamprolobine (**343**)[b,e] 	*Bongardia chrysogonum* (Berberidaceae) (*334*)
Lupinine group:	
(−)-Lupinine (**344**)[a] 	*Anarthrophyllum andicolum, A. cumingii, A. desideratum, A. elegans, A. rigidum, A. umbellatum* (*318*) *Argyrolobium uniflorum* (*335*) *Dicraeopetalum stipulare* (*319*) *Lupinus flavoculatus, L. kingii, L. pusillus* ssp. *pusillus, L. pusillus* ssp. *rubens, L shockleyi* (*322*); *L. princei* (*323*) *Plagiocarpus axillaris* (*327*) *Templetonia biloba* (*330*); *T. incana* (*331*)
4β-Hydroxylupinine (**345**)[d] 	*Plagiocarpus axillaris* (*327*)

(continued)

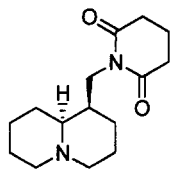
TABLE 1 *(continued)*

Alkaloids[a]	Sources (*Ref.*)
Lusitanine group:	
(−)-Lusitanine (**346**)[a] 	*Anarthrophyllum andicolum, A. cumingii, A. desideratum, A. elegans, A. rigidum, A. umbellatum* (*318*) *Argyrolobium uniflorum* (*335*) *Brongniartia discolor, B. flava, B. lupinoides, B. sousae* (*320*) *Dicraeopetalum stipulare* (*319*) *Lupinus kingii* (*322*) *Maackia hupehensis* (*326*) *Plagiocarpus axillaris* (*327*) *Poecilanthe amazonica, P. effusa, P. grandiflora, P. hostmannii, P. itapuana* (*328*) *Templetonia incana* (*331*)
Dihydrolusitanine (**347**)[b,c]	*Poecilanthe amazonica, P. grandiflora, P. hostmannii* (*328*)
Tashiromine (**348**)[f] 	*Poecilanthe amazonica, P. falcata, P. hostmannii, P. parviflora* (*328*)

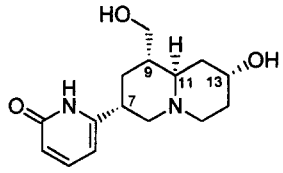
[a]Structure formula shows correct absolute configuration for the indicated enantiomer
[b]New alkaloid
[c]Tentative; unknown structure
[d]Tentative structure
[e]Absolute configuration of natural product is unknown
[f]Absolute configuration of natural product is unknown; synthetic (+)-enantiomer is illustrated



349 (–)-Cytisine



350 (–)-Epilamprolobine



351
(+)-13β-Hydroxymamanine

17-Desoxy-*cis*-lamprolobine (**343**) ([a]$_D$ –70°, *c* 0.9, MeOH) was isolated from Turkish specimens of *Bongardia chrysogonum*, which is a member of the Berberidaceae, a known but uncommon source of lupine alkaloids (*334*). The new alkaloid is all the more unexpected for being a novel representative of the rare lamprolobine class of alkaloids. The structure was deduced from a comprehensive spectroscopic investigation in which long-range NMR spectroscopic experiments played a decisive role. The *cis*-fused quinolizidine ring was inferred from chemical shifts, especially that of 9a-H (δ 3.05), which is deshielded by the *cis* lone pair on nitrogen. This mode of ring fusion is atypical; both lamprolobine (**342**) and (–)-epilamprolobine (**350**) are known to be *trans*-fused quinolizidines (*9*). The *syn* relationship between 1-H and 9a-H, ascertained from nuclear Overhauser effects, in fact means that the new compound, despite its name, is actually a 17-desoxy derivative of epilamprolobine. Alkaloid **343** showed weak activity against a range of bacteria, including *Proteus mirabilis*, *P. vulgaris*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Shigella dysenteriae*.

The absolute stereostructure of (+)-13β-hydroxymamanine (**351**), a metabolite of *Maackia amurensis* var. *buergeri* (*339*), has been established as (7*R*,9*S*,11*R*,13*R*) by X-ray analysis of its hydrated hydrobromide salt (*340*).

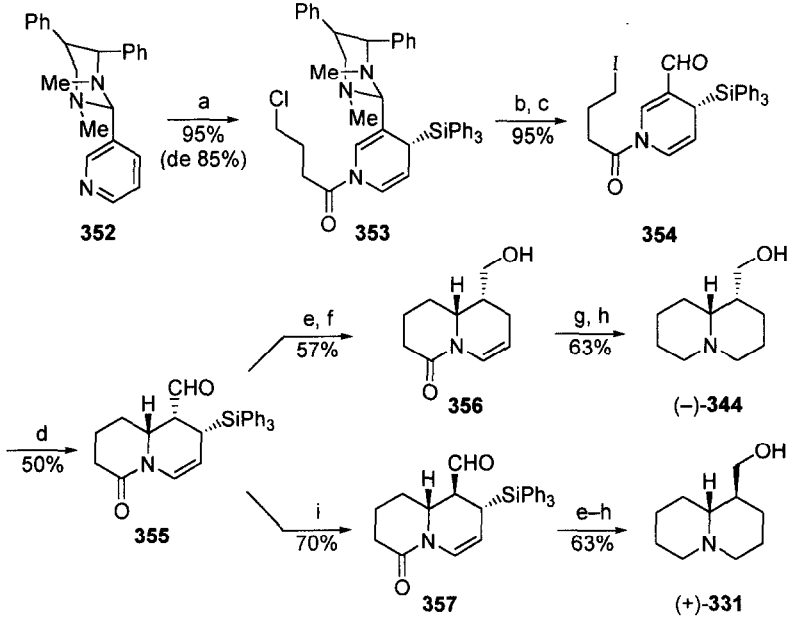
2. *Synthesis*

The diastereomeric alkaloids epilupinine (**331**) and lupinine (**344**) are good candidates for exemplifying new synthetic strategies because of the relative simplicity of their structures. However, few approaches solve the problem of diastereoselectivity completely satisfactorily, and mixtures of both alkaloids are often formed, as was pointed out in a recent review (*341*). Enantioselective syntheses of **331** and **344** also tend to be the exception rather than the rule. The previous survey in this serial included references to syntheses of these two alkaloids reported between 1985 and 1992, but no discussion of the routes was provided (*9*). By contrast, reported syntheses of uncommon alkaloids such as lamprolobine, epilamprolobine, and tashiromine were outlined in some detail. The present survey steers a middle course by individually highlighting all enantioselective syntheses of **331** and **344** reported from 1992 to mid-1999; syntheses of the racemic compounds are noted briefly in the next paragraph. Tashiromine (**348**) is the only other simple alkaloid belonging to the lupine group to have received attention in the same time period, and all recent syntheses of this unique lupine indolizidine will be described.

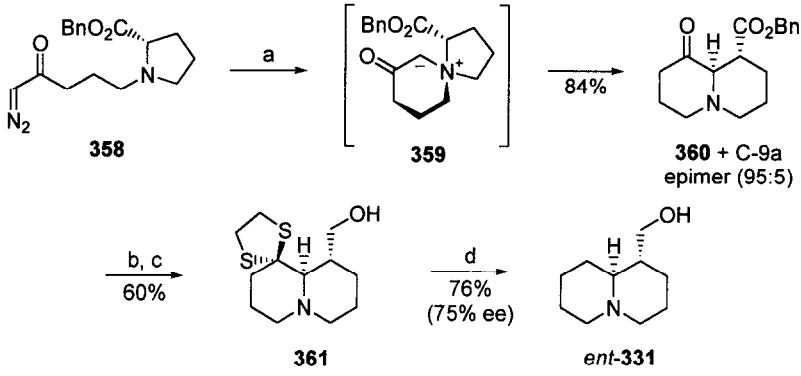
a. Lupinine and epilupinine. Formal syntheses leading to previously exploited precursors for both (±)-**331** and (±)-**344** include strategies based on alkyne–acyliminium ion cyclization (*342,343*) and rearrangement of a spirocyclopropylisoxazolidine (*293*), while a dipolar cycloaddition of an isomünchnone was used in a formal synthesis of (±)-**344** (*344*). Biomimetic syntheses of (±)-**331** and (±)-**344**, as well as *N*-acetyllupinamine and *N*-acetylepilupinamine (perhaps the same as dihydrolusitanine, the tentatively identified new alkaloid **347**?) from Δ^1-piperideine have been reported in ongoing investigations by Wanner and Koomen (*341,345–348*). The dihydro-pyridone methodology of Comins *et al.* (*cf.* Schemes 51, 54, *etc.*) has been applied to syntheses of both (±)-**331** and (±)-**344** (*349*). Intramolecular

cyclization of α-amino radicals made by photosensitized irradiation of α-silyl piperidines resulted in formation of quinolizidines suitable for elaboration to (±)-**331** (*350,351*). A furan–acyliminium ion cyclization was the focal feature in the synthesis of (±)-**331** by Tanis *et al.* (*352*), while the synthesis of (±)-**344** by Molander and Nichols was based on a novel diastereoselective organoyttrium-mediated ring closure of *N*-allyl-2-vinylpiperidine (*353*).

The complementary syntheses of (+)-epilupinine (**331**) and (−)-lupinine (**344**) by Mangeney and co-workers commenced with reaction between the enantiopure pyridine aminal **352** and triphenylsilylcopper(I) in the presence of chlorobutyryl chloride to form the chiral dihydropyridine **353** in 95% yield and a de of 85% (Scheme 43) (*354*). Hydrolysis of the chiral auxiliary followed by transhalogenation with iodide ion afforded **354**, which underwent a radical-mediated cyclization to give the quinolizidinone **355**. The best yield (50%) was obtained by sonicating a mixture of **354**, zinc metal, and copper(I) iodide in water in an ultrasound cleaning bath; reagents such as tributyltin hydride or samarium(II) iodide gave mixtures of the two possible regioisomers. Desilylation of **355** followed by reduction of the intermediate **356** completed the synthesis of (−)-**344** (85% ee) in an overall yield of 16% from **352**. Alternatively, base-induced epimerization of **355** afforded aldehyde **357**, which was similarly transformed into (+)-**331** in 20% overall yield (85% ee).



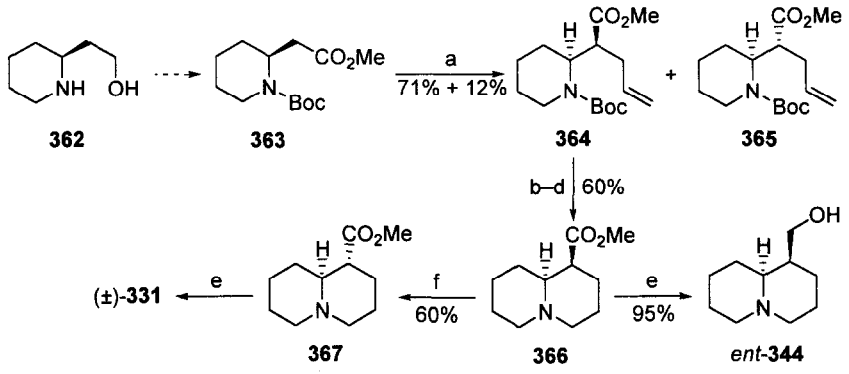
SCHEME 43. Reagents: a, Ph_3SiLi/CuI, THF, −70°C, then $ClCO(CH_2)_3Cl$, −60°C to rt; b, 5% aq. HCl, Et_2O; c, NaI, Me_2CO, reflux; d, Zn, CuI, H_2O, add **354** in Pr^iOH, ultrasound; e, $NaBH_4$, MeOH, 0°C; f, Bu_4NF, THF; g, H_2, 10% Pd/C; h, $LiAlH_4$, Et_2O, reflux; i, DBU, THF, reflux.



SCHEME 44. Reagents: a, $Cu(acac)_2$ (5 mol %), PhMe, reflux; b, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; c, $LiAlH_4$; d, Na, N_2H_4, $HOCH_2CHOH$, heat.

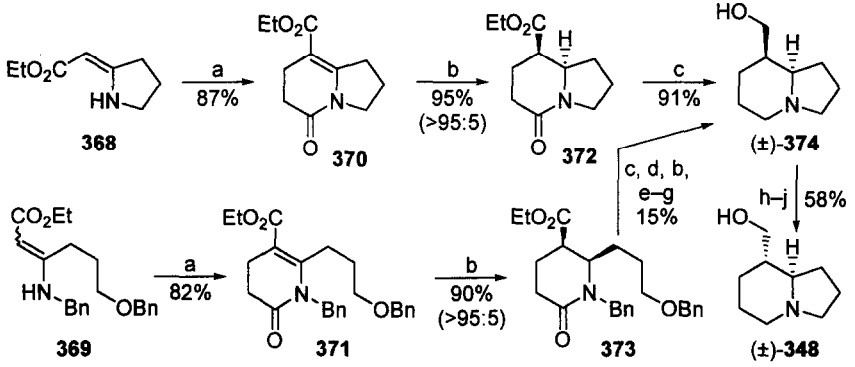
West and Naidu found that the diazoketone **358**, prepared by alkylating the benzyl ester of L-proline with 5-bromo-1-diazopentan-2-one, cyclized to give a transient spirobicyclic ammonium ylide **359** when heated with copper(II) acetylacetonate in toluene (Scheme 44) (*355,356*). This unstable ylide underwent a diastereoselective [1,2]-Stevens rearrangement to give the quinolizidinone **360** and its bridgehead epimer in a ratio of 95:5. However, some racemization (possibly through an achiral diradical intermediate) must have occurred, since **360** had an ee of only 75%. Reduction of the ester and defunctionalization of thioketal **361** with the unusual combination of sodium and hydrazine in hot ethylene glycol completed a synthesis of the unnatural (–)-enantiomer of epilupinine (*ent*-**331**).

Knight and co-workers approached the synthesis of the unnatural (+)-enantiomer of lupinine (*ent*-**344**) by first resolving racemic 2-(piperidin-2-yl)-ethanol with (+)-camphorsulfonic acid (*357,358*). The (*S*)-(+)-enantiomer **362** was then converted into the substituted acetic ester **363**, the enolate of which was stereoselectively allylated to give **364** and **365** in isolated yields of 71% and 12%, respectively (Scheme 45). The major isomer **364** was readily hydroborated and cyclized to the bicyclic ester **366**, reduction of which completed the first reported synthesis of (+)-lupinine (*ent*-**344**). The optical rotation was measured as +19.5° (*c* 1, EtOH), which compared favorably with the rotation of natural (–)-lupinine (–21°) recorded under similar conditions (*359*). It was also hoped that epimerization of **366** would give the thermodynamically more stable compound **377** in which the ester group is equatorial, after which reduction would provide access to (–)-epilupinine (*ent*-**331**). However, the product obtained after these transformations was optically inactive, which indicated that epimerization was accompanied by racemization, probably through base-induced retro-Michael reaction followed by Michael recyclization.



SCHEME 45. Reagents: a, LiHMDS, THF, –78°C, then $H_2C{=}CHCH_2Br$, –78°C to rt; b, $BH_3{\cdot}Me_2S$, hexane, 0°C; c, 30% aq. H_2O_2, 1% aq. NaOH, EtOH, reflux; d, MsCl, NEt_3, CH_2Cl_2, 0°C; e, $LiAlH_4$, THF–Et_2O, reflux, then recrystallization; f, NaOMe, MeOH, reflux.

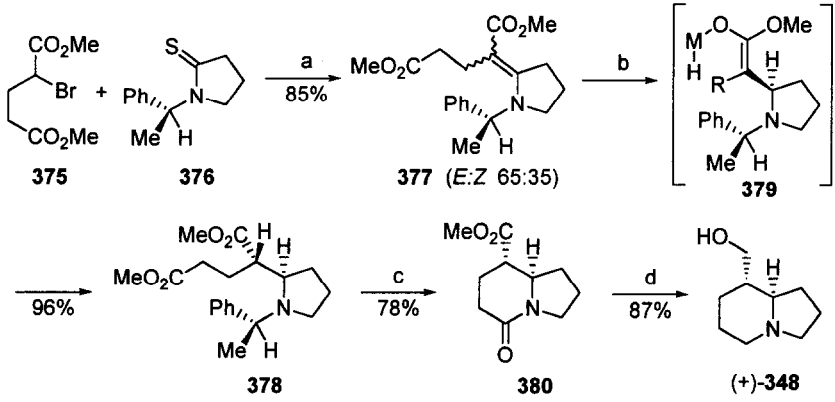
b. Tashiromine. Two complementary routes to racemic tashiromine (**348**) by Paulvannan and Stille used aza-annulation between acryloyl chloride and vinylogous urethanes **368** and **369** for constructing the six-membered ring of intermediates **370** and **371**, respectively (Scheme 46) (*360,361*). Catalytic hydrogenation of both compounds was *cis*-selective (de >90%), both of the piperidone products **372** and **373** subsequently leading to (±)-epitashiromine (**374**), which has not yet been found as a natural product. Swern oxidation of **374**, epimerization of the aldehyde to the more stable equatorial isomer, and reduction with lithium aluminum hydride completed the synthesis of (±)-**348**.



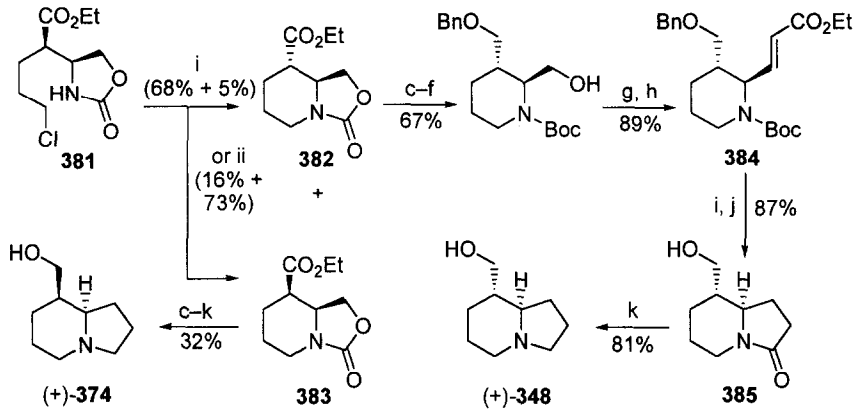
SCHEME 46. Reagents: a, $H_2C{=}CHCOCl$, THF, reflux; b, H_2 (3 atm), 10% Pd/C, Na_2CO_3, MeOH or EtOH; c, $LiAlH_4$, THF, reflux; d, TBDMSCl, imidazole, DMF; e, Li, NH_3, THF, –33°C, then NH_4Cl; f, Ph_3P, CBr_4, NEt_3, CH_2Cl_2, 0°C to rt; g, Bu_4NF, THF; h, $(COCl)_2$, DMSO, CH_2Cl_2, –70°C to –50°C, then NEt_3, –50°C to rt; i, piperidine, *p*-TsOH, C_6H_6, reflux; j, $(CO_2H)_2$–H_2O, CH_2Cl_2, reflux; k, $LiAlH_4$, THF, rt.

In the short synthesis of (+)-**348** by Lhommet and co-workers (Scheme 47), Eschenmoser sulfide contraction between dimethyl 2-bromopentanedioate (**375**) and the (*S*)-pyrrolidine-2-thione **376** yielded the vinylogous urethane **377** (*362*). Although this intermediate was a 65:35 mixture of (*E*)- and (*Z*)-isomers, careful hydrogenation over a palladium–carbon catalyst (0.04 equivalents) gave essentially a single diastereomer of the reduced product **378** (96%), possibly because the species actually undergoing hydrogenation is a metal-bound enolate equivalent such as **379**. Diastereoselectivity was far poorer with other reductants. The absolute stereochemistry of **378** was confirmed by a X-ray crystallographic structure determination on the picrate salt. Further hydrogenation over an increased quantity of palladium–carbon catalyst (0.6 equivalents) effected *N*-debenzylation, which was followed by spontaneous cyclization to the indolizidin-5-one **380**. The synthesis of (+)-**348** was completed by reduction with lithium aluminum hydride. The optical rotation measured for the product was +44.7° (*c* 1.1, EtOH), the highest value reported to date.

The synthesis of (+)-**348** by Ha and co-workers (Scheme 48) employed the substituted oxazolidinone **381**, which was obtained as a 97:3 mixture of diastereomers by alkylating the anion of (*S*)-4-methoxycarbonylmethyl-2-oxazolidinone (derived from aspartic acid) with 1-chloro-3-iodopropane (*363*). Cyclization under basic conditions gave the readily separable bicyclic products **382** and **383**, the degree of epimerization of the ester group depending on the base used to bring about the ring closure. The further elaboration of **382** involved standard functional group chemistry and chain extension to the unsaturated ester **384**, catalytic hydrogenation of which was followed by cyclization to the indolizidin-3-one **385**. (+)-Tashiromine (**348**) ($[\alpha]_D^{20}$ +42.9°, *c* 2.35, EtOH) was obtained by reducing **385** with lithium aluminum hydride. The overall yield of this eleven-step sequence was 18% based on (*S*)-4-methoxycarbonylmethyl-2-oxazolidinone. A similar reaction sequence was used to convert **383** into (+)-5-epitashiromine (**374**).

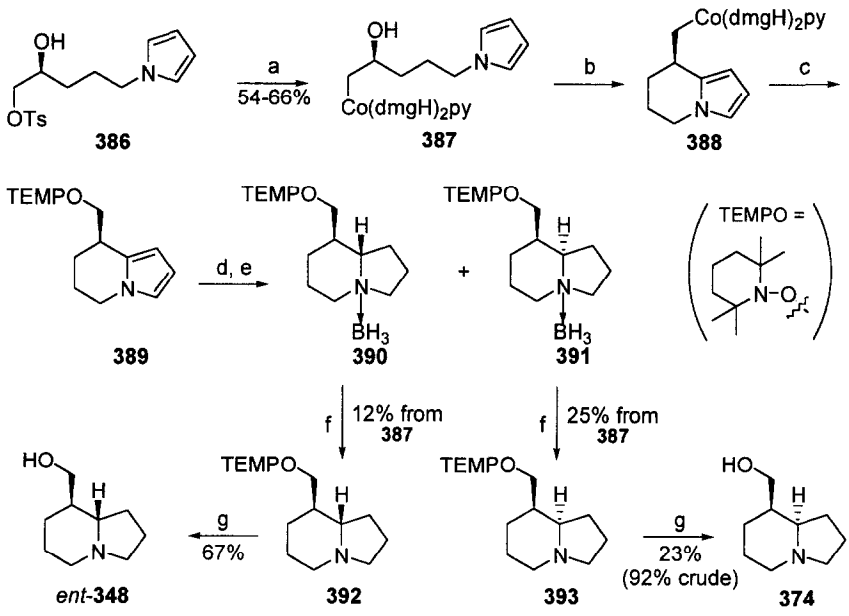


SCHEME 47. Reagents: a, NaI, MeCN, reflux, then dropwise addition of Ph_3P, Et_3N, MeCN; b, H_2 (1 atm), 10% Pd/C (0.04 equiv), MeOH; c, H_2 (1 atm), 10% Pd/C (0.6 equiv), MeOH; d, $LiAlH_4$, THF.



SCHEME 48. Reagents: a, DBU, Bu_4NI, THF, reflux; b, K_2CO_3, Bu_4I, THF, reflux; c, $LiAlH_4$, THF, 0°C; d, NaH, BnBr, Bu_4NI (cat.), THF; e, NaOH, EtOH, reflux; f, $(Boc)_2O$; g, $(COCl)_2$, DMSO, Et_3N; h, $Ph_3P{=}CHCO_2Me$; i, H_2, Pd/C, EtOH; j, Dowex 50-W, BuOH, reflux; k, $LiAlH_4$, THF, reflux.

An unusual synthesis of (−)-tashiromine (*ent*-**348**) by Gage and Branchaud employed a cobaloxime π-cation as a reactive intermediate (Scheme 49) (*364*). The cobalt-containing substituent was introduced by treating (*S*)-tosylate **386** (prepared from L-glutamic acid in seven steps; 17% yield, 96% ee) with $Na[Co(dmgH)_2py]$. The transient cationic species, immediately generated *in situ* by treating the acid-sensitive product (*S*)-**387** with pyridinium *p*-toluenesulfonate, was captured by the pyrrole ring with remarkable enantioselectivity to give the thermally unstable cobalt-containing tetrahydroindolizine **388**. The cobalt–carbon bond was cleaved photochemically in the presence of the stable free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to provide (*R*)-**389**, catalytic hydrogenation of which yielded a mixture of two oxygen-sensitive diastereomeric products. A curious but effective *N*-protection was accomplished by formation of borane complexes **390** and **391**, which were stable enough to survive chromatographic separation. The free bases **392** and **393** were liberated by heating the complexes under reflux in ethanol; the overall yields were 12% and 25%, respectively, based on the cobaloxime **387**. Hydrogenolysis of the hydroxylamine N–O bond was achieved with zinc dust and acetic acid to yield (8*R*,8a*S*)-(−)-tashiromine (*ent*-**348**) from **392**, and (8*R*,8a*R*)-epitashiromine (**374**) from **393**. ^{19}F NMR spectroscopic analysis of the Mosher esters of *ent*-**348** showed its enantiomeric purity to be 96%. It should also be noted that the preparation of (8*R*,8a*R*)-**374** completes a formal synthesis of (+)-**348** in view of the epimerization protocol introduced by Paulvannan and Stille (*361*) (*cf.* Scheme 46).

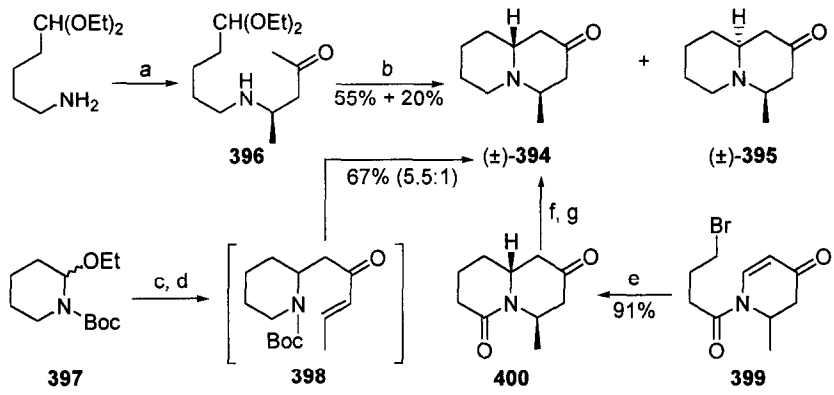


SCHEME 49. Reagents: a, Na[Co(dmgH)$_2$)py], MeOH; b, PPTS, $CHCl_3$; c, TEMPO, hν, MeOH; d, H_2, Rh/Al_2O_3, EtOH; e, BH_3·THF, THF; f, EtOH, reflux; g, Zn, HOAc–H_2O.

E. MYRTINE AND EPIMYRTINE

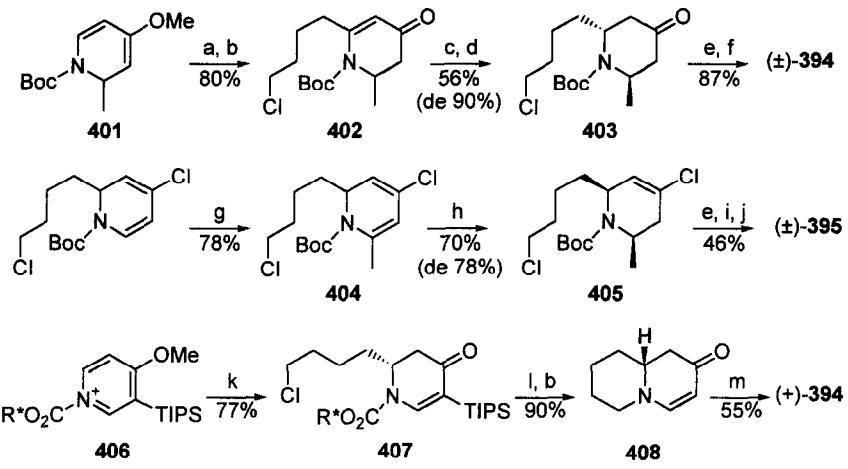
(4*R*,9a*R*)-(+)-Myrtine (**394**) and (4*R*,9a*S*)-(−)-epimyrtine (**395**), simple 4-methylquinolizidin-2-ones isolated from *Vaccinium myrtillus* (*365,366*), received prior coverage in Volumes 28 and 31 of this treatise (*1,8*). The subsequent literature relating to these two alkaloids deals exclusively with their total synthesis.

Two unselective approaches to the two alkaloids are illustrated in Scheme 50. A straightforward synthesis by King relied on acid-induced intramolecular Mannich reaction of aminoketone **396**, prepared from 5-aminopentanal diethyl acetal and pent-3-en-2-one, to give a mixture of (±)-**394** (55%) and (±)-**395** (20%) (*367*). The synthesis by Pilli *et al.* involved a one-pot trimethylsilyl triflate-catalyzed condensation between pent-3-en-2-one and the acyliminium ion derived from *N*-Boc-2-ethoxypiperidine (**397**) (*368,369*). Under the reaction conditions, the intermediate **398** underwent spontaneous *N*-deprotection and cyclization to give a 5.5:1 mixture of (±)-**394** and (±)-**395** (67%). In the same Scheme is also shown the much shorter stereoselective synthesis of (±)-**394** by Beckwith *et al.*, who used a radical-mediated cyclization on the *N*-acylated 2,3-dihydropyridin-4-one **399** to give the bicyclic product **400** as the sole diastereomer (91%) (*370*). Compound **400** was readily converted into the target alkaloid by reduction of both carbonyl groups with lithium aluminum hydride followed by reoxidation of the secondary alcohol at C-2.



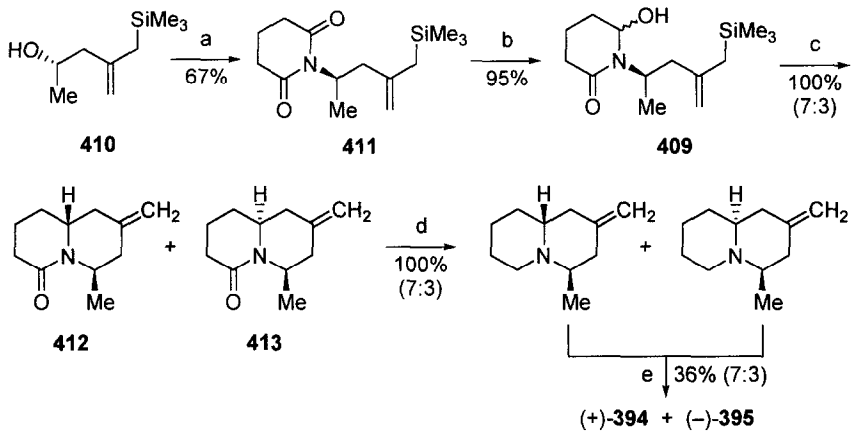
SCHEME 50. Reagents: a, pent-3-en-2-one, Et_2O; b, 2M HCl, 100°C; c, pent-3-en-2-one, TMSOTf, NEt_3, CH_2Cl_2, 0°C; d, $NaHCO_3$, rt, 36 h; e, Bu_3SnH, AIBN (cat.), C_6H_6, reflux; f, $LiAlH_4$; g, PCC.

The first stereoselective route to (±)-**394**) was developed by Comins and LaMunyon, and dates from 1989 (Scheme 51, top line) (*371*). In this early example of the Comins dihydropyridone methodology for alkaloid synthesis, the pyridinium salt prepared from 4-methoxypyridine and *tert*-butyl chloroformate was treated with methyl Grignard to give **401**. Thereafter, lithiation, alkylation with 1-chloro-4-iodobutane and hydrolysis of the enol ether yielded enaminone **402**. This dihydropyridone was reduced with a '$CuH{\cdot}BF_3$' reagent, prepared *in situ*, to give the 2,6-*trans*-disubstituted piperidin-4-one **403** in a de of 90%. The synthesis was completed unexceptionally to give (±)-**394** in 39% isolated yield based on **401**. Comins and co-workers also devised a very similar route to (±)-epimyrtine (**395**) starting with 4-chloropyridine (Scheme 51, middle line) (*372*). The notable differences in this approach are the reversed order of introduction of the 4-chlorobutyl and methyl appendages, and the use of triethylsilane and trifluoroacetic acid at low temperature for reducing dihydropyridine **404** to favor the 2,6-*cis*-disubstituted product **405** (de 78%). The overall yield of (±)-epimyrtine from 4-chloropyridine was 13.6%. The Comins team was also responsible for the first enantioselective synthesis of natural (+)-myrtine (Scheme 51, bottom line) (*373*). In this third variation of their basic methodology, addition of 4-chlorobutylmagnesium bromide to the chiral pyridinium salt **406** [R* = (−)-8-phenylmenthyl] gave dihydropyridone **407** in 77% yield (de 86%). The triisopropylsilyl group served to block conjugate addition at the proximal site. Hydrolytic removal of the auxiliary, cyclization and desilylation then afforded the optically pure vinylogous amide **408**, after which conjugate addition of methylmagnesium chloride completed the short synthesis of (4*R*,9a*R*)-(+)-**394** ($[\alpha]_D$ +19.3°, *c* 1.95, $CHCl_3$). The measured optical rotation was greater than that originally recorded on the natural product ($[\alpha]_D$ +3.1°) (*365*).



SCHEME 51. Reagents: a BuLi, THF, –42°C, then $I(CH_2)_4Cl$; b, oxalic acid, H_2O; c, $BF_3{\cdot}Et_2O$, THF, –78°C; d, $LiAlH_2(OMe)_2$, $CuBr{\cdot}Me_2S$, then $BF_3{\cdot}Et_2O$, –91°C to –78°C; e, TFA, 0°C; f, $NaHCO_3$, H_2O; g, Bu'Li, THF, –42°C, then MeI; h, Et_3SiH, TFA–CH_2Cl_2, –42°C; i, NaI, Li_2CO_3, MeCN, 82°C; j, conc. H_2SO_4, rt; k, $Cl(CH_2)_4MgBr$, THF–PhMe, –78°C; l, KOMe, DMSO; m, MeMgCl, C_6H_6.

In 1992, Remuson and co-workers reported a synthesis of (±)-myrtine and (±)-epimyrtine from the common intermediate (±)-**409**, which underwent a moderately diastereoselective cyclization by attack of the allylsilane unit on to the *N*-acyliminium ion generated in the presence of trifluoroacetic acid (*374*). Six years later they disclosed an enantioselective modification of their earlier route starting with the (*S*)-alcohol **410** (Scheme 52) (*375*). After displacement of the hydroxy group by glutarimide with inversion of stereochemistry under Mitsunobu conditions, partial reduction of the resulting imide **411** gave the optically active hydroxylactams **409**, thereby setting the scene for the pivotal cyclization with trifluoroacetic acid at 0°C. The quinolizidinone diastereomers **412** and **413** were obtained quantitatively in a ratio of 7:3, the diastereoselectivity being ascribed to 1,3-allylic strain between the carbonyl and methyl groups. Subsequent reactions (reduction of the lactam with lithium aluminum hydride followed by osmylation of the methylene group and cleavage with periodate) were performed on this mixture. The final products, (+)-myrtine (**394**) ($[\alpha]_D$ +13.5°, *c* 1.45, $CHCl_3$) and (–)-epimyrtine (**395**) ($[\alpha]_D$ –19°, *c* 0.4, $CHCl_3$) were separated by flash chromatography. This was the first total synthesis of (–)-epimyrtine, and it confirmed the alkaloid's (4*R*,9a*S*) absolute configuration. The optical rotation of (–)-**395** was greater than that of the naturally occurring compounds ($[\alpha]_D$ –2.5°) (*365*), but compared well with that of a synthetic product obtained by resolution of the racemate with (–)-tartaric acid ($[\alpha]_D$ –18°, *c* 5.4, $CHCl_3$) (*366*). In an interesting corollary to this synthesis, conformational analysis of the alkaloids by molecular modeling showed that both alkaloids are likely to exist as mixtures of conformational isomers in which *cis*-fused quinolizidine rings predominate.



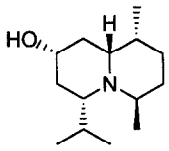
SCHEME 52. Reagents: a, glutarimide, DEAD, Ph_3P, THF; b, $NaBH_4$, MeOH, –5°C; c, TFA, CH_2Cl_2, 0°C; d, $LiAlH_4$, THF, reflux; e, OsO_4 (cat.), $Na_3H_2IO_6$, 80% AcOH, 8°C, then flash chromatography.

F. PLUMERININE

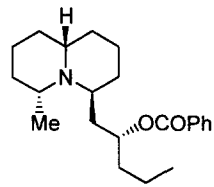
(+)-Plumerinine (**414**) ($[\alpha]_D$ 14.4°, *c* 0.31, CH_3OH) is a unique quinolizidine alkaloid with apparent terpenoid character isolated from *Plumeria rubra* (family Apocyanaceae, sub-family Plumerioideae) (*376*). The compound, a viscous oil, was characterized by a molecular ion at *m/z* 225.2078, corresponding to the molecular formula $C_{14}H_{27}NO$. Fragment ions in its mass spectrum arose from simple pathways involving dehydration, loss of the isopropyl group, cleavage α to nitrogen, and retro-Diels–Alder reactions. A comprehensive range of NMR experiments established the carbon skeleton as well as the positions and orientations of substituents, while Bohlmann bands at 2820 and 2720 cm^{-1} in the IR spectrum indicated a *trans*-fused quinolizidine system. No further information is available for this alkaloid.

G. *PORANTHERA* ALKALOIDS

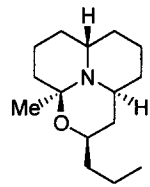
Porantherilidine (**415**), the only bicyclic member of a group of quinolizidine alkaloids from the Australian shrub *Poranthera corymbosa*, was described in the previous chapter on simple indolizidine and quinolizidine alkaloids in Volume 28 of this series (*1*). The related tricyclic alkaloid porantheridine (**416**) is included here as an obvious carbinolamine derivative of the simple bicyclic system.



414 Plumerinine



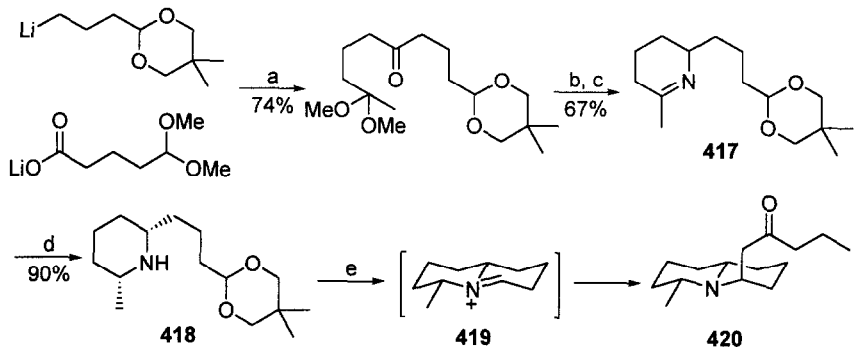
415 Porantherilidine



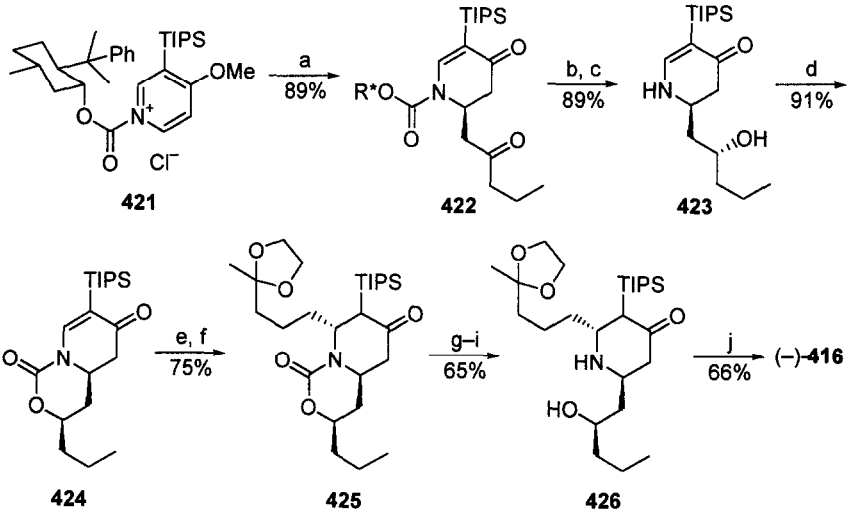
416 Porantheridine

A synthetic approach to porantherilidine by Ryckman and Stevens is illustrated in Scheme 53 (*377*). The route adopted illustrated two applications of the celebrated stereoelectronic principles proposed by Stevens for predicting the trajectory of nucleophilic attack on to tetrahydropyridinium ions (*378*). In the first case, stereoselective reduction of the imine **417** with sodium cyanoborohydride in acidic solution took place from the axial direction to give the 2,6-*cis*-disubstituted piperidine **418**. In the transition state, 1,3-diaxial interactions between the incoming nucleophile and the acetal-bearing side chain are presumably avoided, and orbital interaction between the approaching hydride species and the developing lone pair on nitrogen is maximized in an antiperiplanar alignment. It was theorized that mild hydrolysis of the acetal protecting group of **418** would then result in spontaneous cyclization to a chair-like iminium ion intermediate **419**, which would again be intercepted from the axial direction by an enolic nucleophile. Indeed, treatment of **418** with 1-trimethylsilylpentan-2-one in the presence of tin tetrachloride yielded the expected axially-substituted quinolizidine **420**. It is most unfortunate that the reaction was carried out only on an NMR scale, and was not optimized; the work was indubitably halted by the untimely death of Stevens. In principle, however, conversion of **420** into porantherilidine (**415**) should be a straightforward task.

A novel modification of the well-known Comins dihydropyridone methodology was used in the first asymmetric synthesis of (–)-porantheridine (**416**) (Scheme 54) (*379*). Addition of the kinetically generated zinc enolate of pentan-2-one to the chiral 1-acylpyridinium salt **421** yielded dihydropyridone **422** with a diastereoselectivity of 92%. Stereoselective reduction of the newly introduced ketone group and removal of the chiral auxiliary was followed by mutual protection of the heteroatoms of product **423** to give the bicyclic urethane **424**. The remaining carbon atoms required for the skeleton of porantheridine were introduced by stereoselective (95:5) conjugate addition to give **425**. Hydrolysis of the urethane liberated the amino alcohol **426**, deprotection and reductive amination of which afforded the target alkaloid. The synthesis required eight steps from 4-methoxy-3-(triisopropylsilyl)pyridine, the precursor of **421**, and the overall yield of (–)-**416** was 23%.



SCHEME 53. Reagents: a, THF, –20°C to rt; b, $NaBH_3CN$, NH_4OAc, MeOH, 4Å molecular sieves; c, 10% aq. HCl, THF, pH 5.3; d, pH 5.5, $NaBH_3CN$; e, $SnCl_4$, C_6D_6.



SCHEME 54. Reagents: a, pentan-2-one, LDA, $ZnCl_2$, Et_2O–THF, –78°C; b, K-Selectride, THF, –78°C; c, Na_2CO_3, MeOH, reflux; d, $Im_2C{=}O$, NEt_3, THF, reflux; e, 30% HBr, HOAc, CH_2Cl_2; f, 4-oxopentylmagnesium chloride ethylene acetal, CuBr, $BF_3{\cdot}Et_2O$, THF, –78°C; g, LDA, then *N*-(5-chloro-2-pyridyl)triflimide; h, H_2 (1 atm), 5% Pd/C, Li_2CO_3, EtOAc; i, KOH, EtOH, reflux; j, *p*-TsOH, C_6H_6, 4Å molecular sieves, reflux, then Na_2CO_3.

V. Animal Alkaloids Bearing Alkyl or Functionalized Alkyl Substituents

A. INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS FROM ANTS

Previous treatment of this topic may be found in the review on insect alkaloids by Numata and Ibuka in Volume 31 of this treatise (*3*), and in the general chapters on simple indolizidine and quinolizidine alkaloids in Volumes 28 and 44 (*1,2*).

1. Isolation

All the currently known indolizidine and quinolizidine alkaloids isolated from ants are illustrated in Fig. 6. (+)-Monomorine I (**427**), the well-studied trail pheromone constituent of the Pharaoh ant (*Monomorium pharaonis*), and the analogs **428–431** were described in the earlier volumes in this series. These five compounds are 3,5-disubstituted indolizidines bearing short saturated or mono-unsaturated hydrocarbon chains. The relative stereochemistry in monomorine VI (**430**) still remains unknown, while that of **431** was atypical for the class at the time of its isolation (*380*). The structural resemblance of this group of alkaloids to the 3,5-disubstituted indolizidines isolated from frogs and toads is no longer thought to be coincidental, and the 'dietary hypothesis' for the origin of the amphibian alkaloids will be reviewed in Section V.B. Indeed, monomorine I has been detected as a minor component of skin extracts from bufonid toads of the genus *Melanophryniscus* (*381*), while captive *Dendrobates auratus* frogs were shown to accumulate the alkaloid after feeding on Pharaoh ants (*382*).

The six recently isolated ant alkaloids **432–437** all have structural or stereochemical features that help to dispel the notion of a 'typical' ant indolizidine. Worker ants of a species of *Solenopsis* (*Diplorhoptrum*) collected in Cabo Rojo, Puerto Rico, produced a venom containing two structurally isomeric indolizidines, **432** and **433** (absolute configuration unknown), the ratios of which varied between 6:1 and 1.7:1 depending on the population examined (*383*). The fascinating feature is that 3-butyl-5-propylindolizidines, including both **432** and **433**, had previously been isolated only from amphibians; (−)-**432** is, in fact, the well-known and frequently-synthesized dendrobatid alkaloid indolizidine 223AB (*cf.* Section V.B). The production of alkaloids was found to be caste-specific; **432** and **433** were present only in trace amounts in venom from the queens, which instead contained **429** as the major metabolite. The venom of queens collected from Mona Island, Puerto Rico, also contained **429** as the major component, but workers produced *cis*- and *trans*-piperidines **438**, which are plausible precursors of the indolizidine **429**. Workers of a taxonomically uncertain *Solenopsis* species from California (*S. molesta validiuscula*?) produced two of the remaining three diastereomers of **429**, namely, **434** and **435** (*384*). Different populations contained either one or the other of the new alkaloids, but in some cases a trace of isomer **429** was also detected. The structures of the new alkaloids were deduced on the basis of mass spectrometric and Fourier transform infrared (FTIR) spectroscopic studies, and confirmed by comparison with synthetic samples of all four possible diastereomers of 3-hexyl-5-methylindolizidine. The population-specific distribution may well have some taxonomic significance.

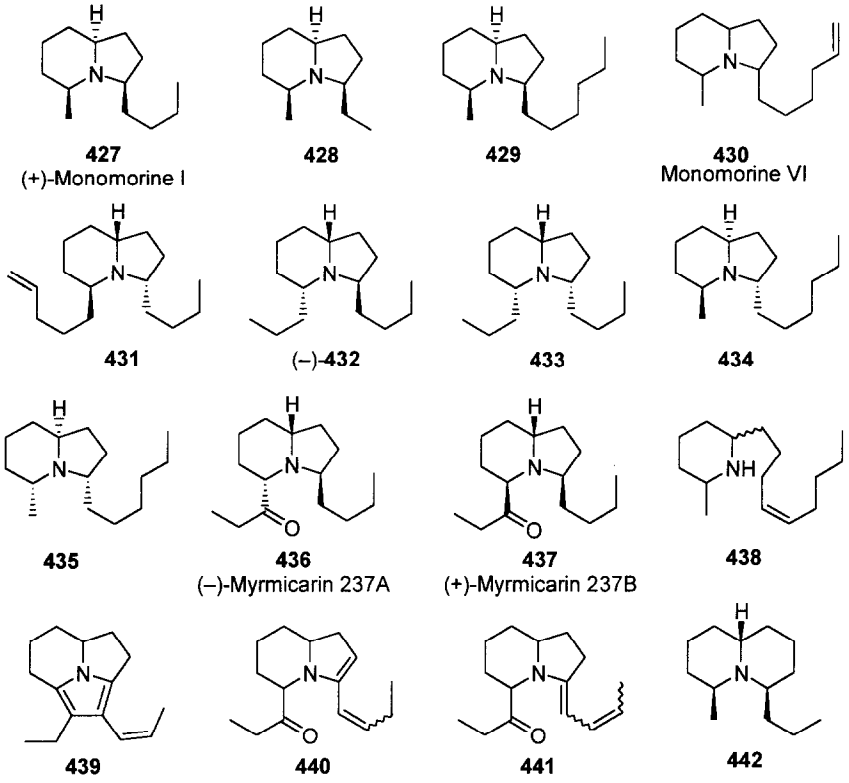


FIG. 6. Indolizidines and related alkaloids isolated from ants.

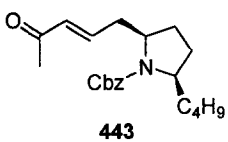
(–)-Myrmicarin 237A (**436**) ($[\alpha]_D^{19}$ –124°, *c* 0.75, *n*-heptane) and (+)-myrmicarin 237B (**437**) ($[\alpha]_D^{19}$ +13.9°, *c* 0.83, *n*-heptane), the first indolizidine alkaloids to be found in the family Myrmicinae, were isolated from the poison glands of the African ant *Myrmicaria eumenoides* (*385*). Although the alkaloids could be separated by column chromatography on neutral alumina, they equilibrated to mixtures of the two compounds within a few hours at ambient temperature. Spectroscopic data revealed the unexpected propanoyl substituent on the indolizidine nucleus, the easily epimerizable stereogenic center adjacent to which accounts for the ready interconversion of the two alkaloids. However, their relative and absolute stereochemistry required confirmation by synthesis (*vide infra*). It should be pointed out that myrmicine ants subsequently yielded a suite of complex tricyclic and polycyclic alkaloids such as myrmicarin 215A (**439**), which are clearly derived from precursors related to **436** and **437** (*386–388*). Intriguingly, myrmicarin 233A, a trace component of *M. opaciventris* gave a mass spectrum that was not inconsistent with structures such as **440** or **441**, which are plausible biosynthetic precursors of the polycyclic alkaloids (*386*).

The first quinolizidine alkaloid to be found in an ant species, alkaloid 195C (**442**), was obtained from an extract of a Brazilian myrmicine ant, *Solenopsis* (*Diplorhoptrum*) sp. *picea* group (*389*). The same compound had previously been detected in the Madagascan frog *Mantella betsileo* (*390*), but its structure remained unknown until the present study made larger quantities available for investigation. The spectroscopic evidence for both the gross structure and relative stereochemistry of **442** was supported by comparison with the four possible synthetic diastereomers of 4-methyl-6-propylquinolizidine. It also seems likely that the new alkaloid possesses a *cis*-fused ring junction.

2. *Synthesis*

a. Monomorine I. Monomorine I (**427**) is one of the most frequently synthesized indolizidine alkaloids. So numerous are the published routes to this popular target that Takahata and Momose chose to ignore syntheses of the racemic compound in their survey in Volume 44 (*2*), and concentrated only on enantioselective routes. The same strategy will be adopted in the ensuing presentation. For the sake of completeness, however, a list of references for syntheses of (±)-**427** published during the period 1986–1999 is appended (*391–403*). It should be noted that several of these routes were not stereoselective, and diastereomers of **427**—all of which are known amphibian alkaloids (*cf.* Section V.B)—were also produced. Diastereomer production was especially common in routes that included the very popular tactic of a late-stage reductive cyclization of an aminoketone, which gives the indolizidine system *via* a cyclic iminium salt (*vide infra*).

The previous review in Volume 44 outlined several communications on the synthesis of (+)-**427** that have since been amplified or reported with full experimental details. A conference contribution by Takahata, Momose *et al.* was expanded to a full paper that included complementary syntheses of the lower and higher homologs (+)-**428** and (+)-**429**; the work unambiguously established the (3*R*,5*S*,8a*S*) configurations of the two alkaloids (*404*). The preliminary communication of another route to (+)-**427** by Momose and co-workers (*405*) was more thoroughly aired in two later publications (*406,407*). A synthesis of (+)-**427** by Lhommet and co-workers involving sequential hydrogenation, cyclization, and diastereoselective reduction of disubstituted pyrrolidine **443** *via* bicyclic iminium ion **444** (*408*) was subsequently elaborated in a paper that included experimental details for these latter steps, as well as useful NMR spectroscopic data for **427** and related alkylindolizidine alkaloids such as indolizidine 223AB (**432**) and indolizidine 167B (*cf.* Section V.B) (*409*).



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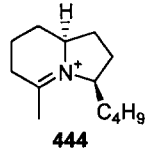

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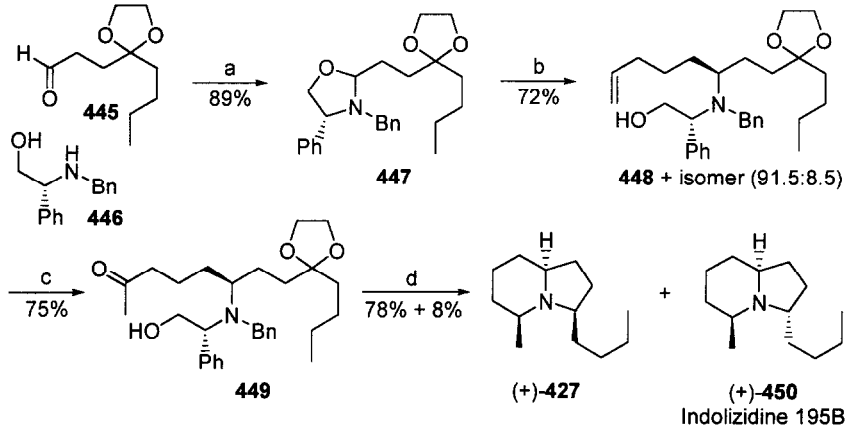
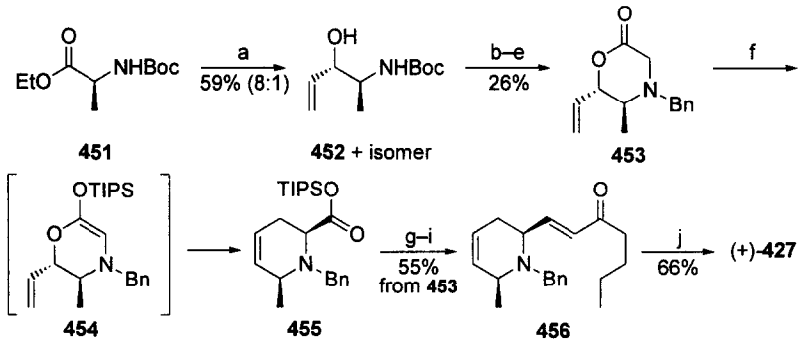


SCHEME 55. Reagents: a, $MgSO_4$, CH_2Cl_2; b, $H_2C{=}CH(CH_2)_3MgBr$, THF, −15°C to rt; c, $PdCl_2(MeCN)_2$, $CuCl_2$, O_2, MeOH; d, H_2, 10% Pd/C, 3% HCl in MeOH.

New routes to (+)-**427** that employ the late-stage reductive cyclization of aminoketones continue to flourish. In the synthesis by Higashiyama *et al.*, ketal **445** and (*R*)-*N*-benzylphenylglycinol **446** were condensed to form the chiral oxazolidine **447** (Scheme 55) (*410*). The heterocycle was cleaved diastereoselectively with pent-4-enylmagnesium bromide to give **448** and its C-6 epimer in a 91.5:8.5 ratio. Separation was achieved after Wacker oxidation to **449**. Hydrogenolytic debenzylation of **449** in acidic medium was accompanied by double reductive cyclization to give (+)-**427** (78%) and the amphibian alkaloid (+)-indolizidine 195B (**450**) (8%).

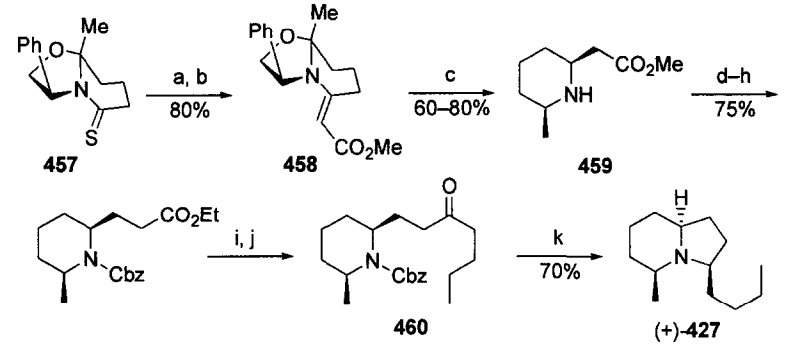
The synthesis of (+)-**427** by Angle and Breitenbucher (Scheme 56) used the protected alanine ester **451** as the chiral precursor (*411*). One-pot reduction and vinylation gave allylic alcohol **452** as an 8:1 mixture of diastereomers, which was carried unseparated through the sequence as far as the lactone **453**. The silyl ketene acetal derivative **454** underwent spontaneous Claisen rearrangement to give the Δ^3-piperideine ester **455** as a single isomer, apparently because the minor *cis*-analog of **454** has the wrong geometry for rearrangement. The synthesis of (+)-**427** was completed by another one-pot reaction, the hydrogenation of aminoketone **456** over a palladium–carbon catalyst, which effected reduction of both alkenes, debenzylation of the amine, reductive cyclization, and stereoselective hydrogenation of the resulting iminium ion without the need for isolation of intermediates. No mention was made of concomitant formation of diastereomer **450**. The overall yield of this nine-step reaction sequence was 5.4% based on **451**.

Piperidine-based aminoketones similar to **456** also featured in syntheses of (+)-**427** by Munchhof and Meyers (Scheme 57) (*412*), and by Solladié and Chu (Scheme 58) (*413*). In the former, the enantiomerically pure bicyclic oxazolidine-thione **457** underwent Eschenmoser sulfide contraction under forcing conditions to produce the vinylogous urethane **458**, which was simultaneously hydrogenated and hydrogenolyzed over Pearlman's catalyst to give the 2,6-*cis*-disubstituted piperidine

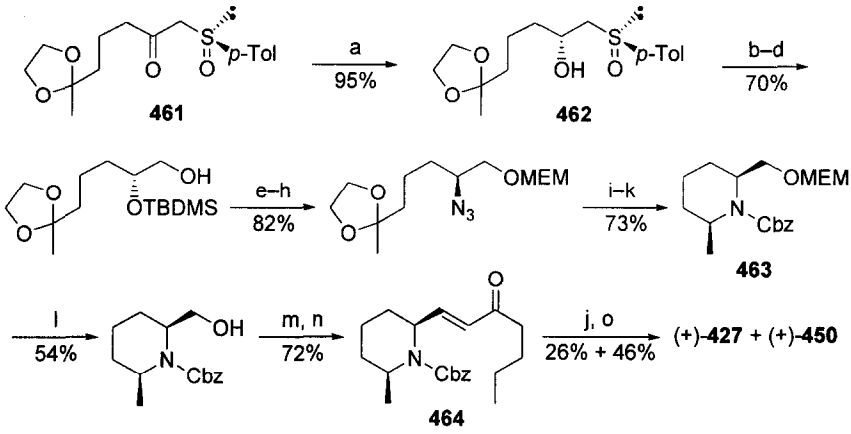


SCHEME 56. Reagents: a, DIBAL-H, H_2C=CHMgCl; b, TFA, CH_2Cl_2, 0°C; c, $PhCO_2Cl$, pyridine; d, $LiAlH_4$, THF, reflux; e, $BrCH_2CO_2Ph$, Pr^i_2NEt, MeCN; f, TIPS-OTf, NEt_3, C_6H_6; g, $LiAlH_4$, Et_2O; h, $(COCl)_2$, DMSO, NEt_3; i, $(EtO)_2POCH_2COC_4H_9$, KH, THF; j, H_2 (1 atm), 10% Pd/C, MeOH/1M HCl (20:1), 5 d.

459. Successive side-chain homologations afforded the aminoketone **460**, the final reductive cyclization of which was performed under conditions previously developed by Kibayashi (*393*) to give the target alkaloid (+)-**427**, apparently as the sole isomer. In the second synthesis, a chiral sulfoxide was used as the asymmetric control element. The (*R*)-(+)-ketosulfoxide **461**, prepared from the anion of (*R*)-(+)-methyl *p*-tolyl sulfoxide and ethyl 4-oxohexanoate ethylene ketal, was reduced to the β-hydroxysulfoxide **462** with excellent stereochemical control (de >95%). Significant later steps included removal of the sulfoxide by Pummerer rearrangement, S_N2 displacement of the hydroxy group with azide ion, and reductive cyclization to the pivotal (2*S*,6*S*)-2,6-*cis*-disubstituted piperidine **463** (for which a second, independent synthesis was also described). Oxidation and Wadsworth–Emmons homologation yielded the unsaturated aminoketone **464**, reductive alkylation of which with hydrogen and palladium on charcoal gave a separable mixture of (+)-monomorine I (**427**) (26%) and (+)-indolizidine 195B (**450**) (46%).



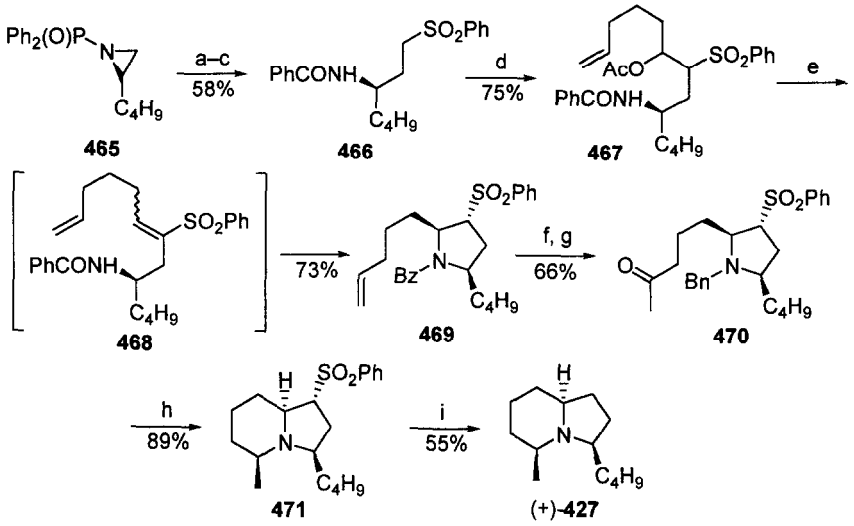
SCHEME 57. Reagents: a, $BrCH_2CO_2Me$ (10 equiv), $CHCl_3$, rt; b, $P(OMe)_3$ (4 equiv), NEt_3 (10 equiv), $CHCl_3$, reflux, 2–3 d; c, H_2 (3 atm), $Pd(OH)_2/C$; d, $ClCO_2Bn$, NaOH; e, hydrolysis; f, $(COCl)_2$; g, CH_2N_2, Et_2O; h, AgO, EtOH; i, HN(Me)OMe; j, BuMgBr; k, H_2, 5% Pd/C.



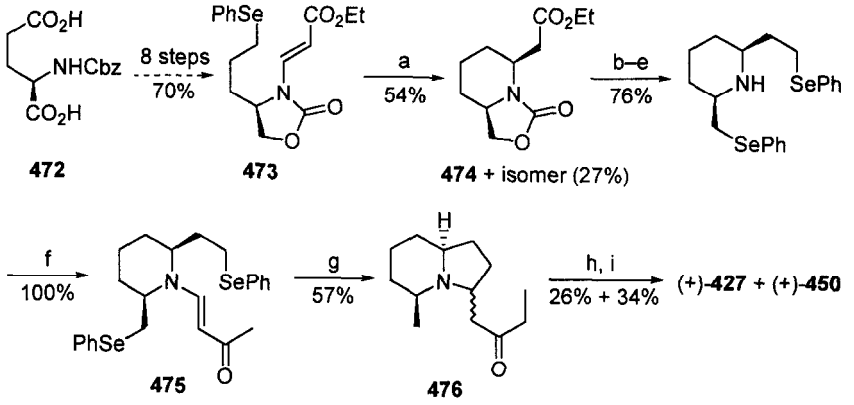
SCHEME 58. Reagents: a, $ZnCl_2$, DIBAL-H, THF; b, TBDMSCl, imidazole, DMF; c, Ac_2O, NaOAc, reflux; d, $LiAlH_4$, PhMe, –35°C; e, MEMCl, Pr^i_2NEt, CH_2Cl_2; f, TBAF, THF; g, MsCl, Et_3N, CH_2Cl_2, 0°C; h, NaN_3, DMF, 80°C; i, *p*-TsOH, Me_2CO; j, H_2, 10% Pd/C, MeOH; k, $ClCO_2Bn$, 20% aq. K_2CO_3, CH_2Cl_2, 0°C; l, $TiCl_4$, CH_2Cl_2, 0°C; m, Swern oxidation; n, $(MeO)_2P(=O)CH_2COC_4H_9$; LiCl, Pr^i_2NEt; o, chromatography on Al_2O_3.

A pyrrolidine-based aminoketone featured in the synthesis of (+)-**427** by Craig and co-workers (Scheme 59) (*414*). The enantiopure aziridine **465**, made in two steps from D-norleucine, was opened by the anion of methyl phenyl sulfone, and the protecting group on nitrogen was exchanged to give **466**. Condensation with hex-5-enal and acetylation of the resulting alcohol then afforded **467**. After base-induced elimination of acetic acid from **467**, the isolable vinyl sulfone **468** underwent 5-*endo*-trig cyclization to give the 2,5-*cis*-disubstituted pyrrolidine **469** as a single isomer (73% from **467**). The stereochemistry was confirmed by X-ray crystallography. Deoxygenation of the benzoyl protecting group followed by modified Wacker oxidation yielded aminoketone **470**, reductive cyclization of which gave a single indolizidine isomer **471**. A less satisfactory alternative strategy involving deprotection of **469** followed by intramolecular aminomercuration yielded a mixture of C-5 epimers of **471**. Brief treatment of **471** with sodium naphthalenide removed the sulfone group, thereby completing the synthesis of (+)-**427**.

Lee *et al.* have developed an iterative radical cyclization to gain access to 3,5-dialkylindolizidine alkaloids. Their synthesis of (+)-**427** commenced with the protected D-glutamic acid derivative **472**, which was transformed in eight steps into the β-aminoacrylate **473** (Scheme 60) (*415*). Cyclization of **473** to a 2:1 mixture of the piperidine derivative **474** and its *trans*-isomer was achieved with tributyltin hydride under conditions of high dilution. The major isomer **474** was then converted in five steps into the next radical precursor, **475**, which under similar conditions afforded the indolizidine **476** as an inseparable mixture of isomers (57%) together with some deselenenylated piperidines (40%). The separable dithiolane derivatives of **476** were reduced with Raney nickel to yield (+)-**427** and (+)-**450** in 26% and 34% yields, respectively.



SCHEME 59. Reagents: a, $PhSO_2Me$, BuLi, TMEDA, THF, –78 °C to rt; b, $BF_3{\cdot}Et_2O$, CH_2Cl_2–MeOH (1:1); c, PhCOCl, pyridine, CH_2Cl_2, workup with $Me_2N(CH_2)_3NH_2$; d, BuLi, TMEDA, THF, then hex-5-enal,–78°C, then Ac_2O, –78°C to rt; e, Bu'OK (2.1 equiv), Bu'OH (10 equiv), THF (0.033 M); f, *DIBAL-H*, CH_2Cl_2, –78 °C to rt; g, $Hg(OAc)_2$, THF–H_2O (3:1), then $PdCl_2$, $CuCl_2$, THF; h, cyclohexa-1,4-diene, 10% Pd/C, MeOH, reflux; i, $NaC_{10}H_8$ (3.5 equiv), THF, rt, 5 min.

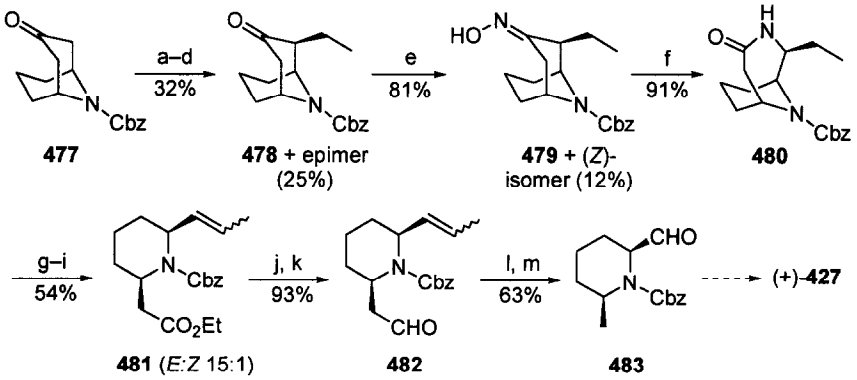


SCHEME 60. Reagents: a, Bu_3SnH (1.3 eq, syringe pump, 5 h), AIBN (0.1 equiv), C_6H_6, reflux; b, $LiAlH_4$, THF, –40°C; c, CBr_4, Ph_3P, CH_2Cl_2; d, $(PhSe)_2$, $NaBH_4$, EtOH, 0°C; e, $PhSeSiMe_3$, ZnI_2 (0.1 equiv), PhMe, reflux; f, $HCOCOC_2H_5$, CH_2Cl_2, reflux; g, Bu_3SnH (2.7 equiv, syringe pump, 6 h), AIBN (0.1 equiv), C_6H_6, reflux; h, $HSCH_2CH_2SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2; i, Raney Ni, EtOH.

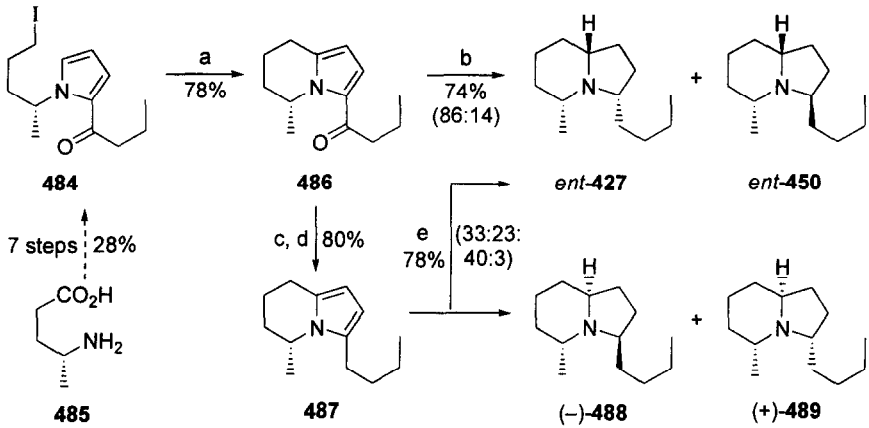
A formal synthesis of (+)-**427** by Muraoka and co-workers (*416*) exploited the asymmetric deprotonation of bridged bicyclic ketone **477** with Koga's chiral lithium amide base (*417*) to prepare the ethyl-substituted product (+)-**478** (Scheme 61) (*418*). Beckmann rearrangement of the oxime derivative **479** followed by Huisgen–White rearrangement of lactam **480** with nitrogen peroxide (an alternative to Baeyer–Villiger oxidation, which failed when attempted on **477**) and cleavage with base yielded the 2,6-*cis*-disubstituted piperidine **481** as a 15:1 *E/Z* mixture after esterification. Reduction of the ester to aldehyde **482**, rhodium-induced decarbonylation (retro-hydroformylation), and ozonolysis gave aldehyde **483**, a compound that Takahata *et al.* have previously converted into (+)-**427** (*404*).

Two syntheses of the unnatural (–)-enantiomer of monomorine I (*ent*-**427**) end this section. The approach of Artis *et al.* hinged on the oxidative radical cyclization of iodoalkyl pyrrole **484**, made in seven steps (*ca.* 28% yield) from (*R*)-4-aminopentanoic acid (**485**) (Scheme 62) (*419*). The bicyclic product **486**, which was formed in 78% yield, was catalytically hydrogenated to give an 86:14 mixture of (–)-monomorine I (*ent*-**427**) and (–)-indolizidine 195B (*ent*-**450**) in 74% yield. Alternatively, thionation of **486** with Lawesson's reagent followed by Raney nickel desulfurization afforded tetrahydroindolizine **487**, catalytic hydrogenation of which gave a separable mixture of *ent*-**427**, *ent*-**450**, and the diastereomers (–)-**488** and (+)-**489** (78% yield; ratio 33:23:40:3). The latter two diastereomers are also natural products, having originally been isolated from the bufonid toad *Melanophryniscus stelzneri* (*381*).

Stereoselective hydrogenation of a pyrrole ring was also the crucial step in the synthesis of (–)-monomorine I (*ent*-**427**) by Jefford *et al.* (Scheme 63) (*420*). The L-glutamate diester **490**, which provided the stereogenic center destined to become C-5 of the target, was converted by a standard method into the *N*-substituted pyrrole

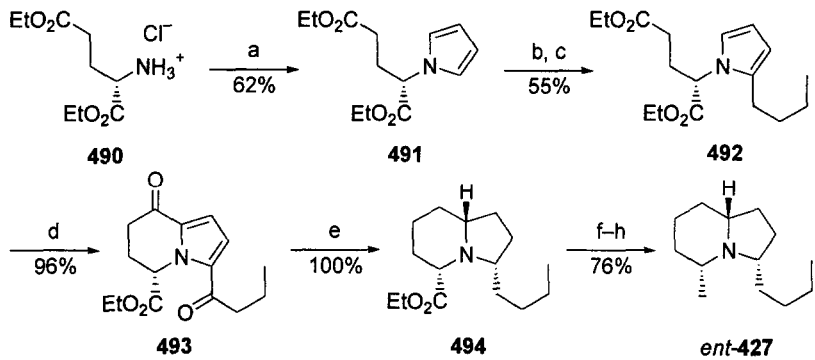


SCHEME 61. Reagents: a, (1*R*)-*N*-(*tert*-butyl)-*N*-lithio-2-(4-methyl-1-piperazinyl)-1-phenylethylamine (Koga's base), Me_3SiCl, HMPA, THF, –100°C; b, MeLi, MeO_2C–CN, DME, HMPA, –60°C; c, NaH, THF, 0°C, then EtI, MeOH, reflux; d, KOH, DMSO, H_2O, 120°C; e, NH_2OH·HCl, NaOAc, EtOH, H_2O, reflux; f, *p*-TsCl, K_2CO_3, $MeOCH_2CH_2OMe$, H_2O, 80°C; g, N_2O_4, NaOAc, DME, 0°C; h, 5% aq. NaOH, –10°C; i, MeOH, HCl; j, DIBAL-H, PhMe, –10°C; k, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –55°C; l, $(Ph_3P)_3RhCl$, BuCN, 140°C; m, O_3, CH_2Cl_2, –60°C, then Ph_3P.



SCHEME 62. Reagents: a, $FeSO_4 \cdot 7H_2O$, DMSO, 30% H_2O_2, ultrasound, <40°C; b, H_2 (55 psi), 10% Pd/C, MeOH, H_2SO_4 (cat.), 7 d; c, Lawesson's reagent, THF, reflux; d, W2 Raney nickel, MeOH; d, H_2 (55 psi), 5% Rh/Al_2O_3, MeOH.

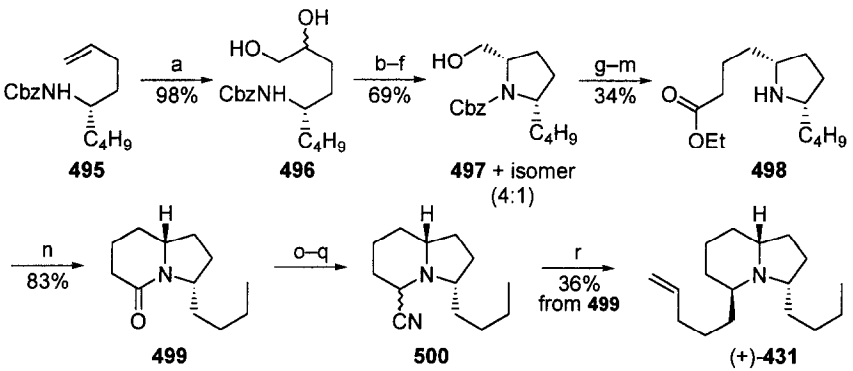
491. Acylation followed by deoxygenation introduced the butyl substituent. Intramolecular acylation of **492** was induced with boron tribromide, thereby creating the bicyclic system **493** in 96% yield and an ee of greater than 99%. Catalytic hydrogenation of **493** over palladium on charcoal in acidic ethanol reduced the ketone to a methylene group and also reduced the pyrrole ring to give indolizidine **494** as the sole isomer in quantitative yield. The synthesis of *ent*-**427** was completed by defunctionalizing the ester group *via* the corresponding alcohol and chloride intermediates.



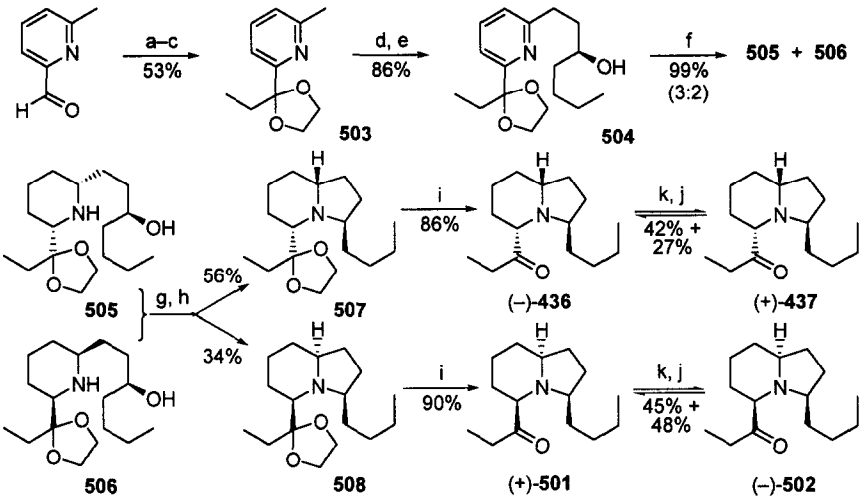
SCHEME 63. Reagents: a, 2,5-dimethoxytetrahydrofuran, H_2O, 80°C; b, PrCOCl, PhMe, reflux; c, $NaBH_3CN$, ZnI_2, $ClCH_2CH_2Cl$, 50°C; d, BBr_3, CH_2Cl_2; d, H_2 (55 psi), Pd/C, EtOH–H_2SO_4 (97:3); f, $LiAlH_4$, THF; g, $SOCl_2$ reflux; h, Bu_3SnH, AIBN, PhMe, reflux.

b. Other ant indolizidine alkaloids. The first total synthesis of (3*S*,5*S*,8a*R*)-(+)-3-butyl-5-(4-pentenyl)indolizidine (**431**), by Takahata *et al.*, commenced with the enantiomerically pure amine derivative **495**, which was made in several steps from L-norleucine (Scheme 64) (*421*). Their usual oxymercuration approach on this substrate was found to yield a 2,5-*trans*-disubstituted pyrrolidine, which necessitated a change of strategy. Sharpless asymmetric dihydroxylation with AD-mix-β™ was less selective than expected, and afforded a diastereomeric mixture of alcohols **496**. However, once the pyrrolidine ring had been formed, the *cis* and *trans* isomers of **497** (ratio 4:1) could be separated. Chain extension at the hydroxymethyl substituent of **497** required a further seven steps to give the ester **498**, which was cyclized to the indolizidin-5-one **499** in the presence of trimethylaluminum. The unsaturated chain at C-5 was introduced by a completely stereoselective reaction of α-aminonitrile **500**, an iminium ion equivalent, with 1-pentylmagnesium bromide.

Franke *et al.* resorted to total synthesis in order to confirm the relative and absolute stereostructures of the new ant alkaloids myrmicarin 237A (**436**) and myrmicarin 237B (**437**) (*385*). Two alternative routes that led to the racemic alkaloids and the unnatural diastereomers **501** and **502** verified the gross structures and the relative stereochemistry. Their third approach, the enantioselective route shown in Scheme 65, used (2*S*)-2-butyloxirane as the source of chirality. Alkylation of the anion of the substituted 2-picoline **503** with the chiral epoxide yielded **504**, catalytic hydrogenation of which gave the two 2,6-*cis*-disubstituted piperidines **505** and **506** in a ratio of 3:2. Cyclization of the mixture *via* the *p*-toluenesulfonate derivatives produced the separable indolizidines **507** and **508**. Finally, deprotection and equilibration yielded pure samples of the four isomers (−)-**436**, (+)-**437**, (+)-**501**, and (−)-**502** (de and ee >98%). The synthetic (3*R*,5*S*,9*R*)-**436** and (3*R*,5*R*,9*R*)-**437** were shown to be identical with natural (−)-myrmicarin 237A and (+)-myrmicarin 237B, respectively, by gas chromatography on a chiral stationary phase.

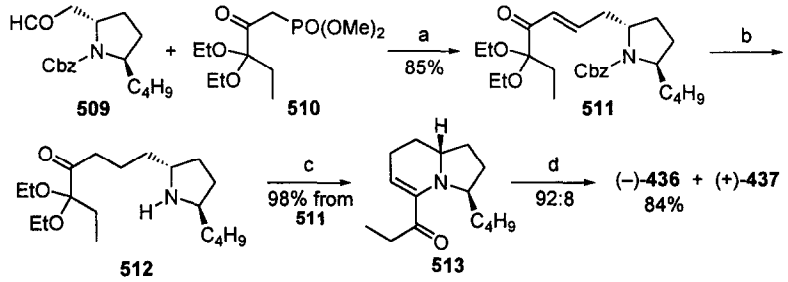


SCHEME 64. Reagents: a, AD-mix-β, Bu'OH–H_2O (1:1); b, TBDMSCl, imidazole, DMF; c, MsCl, NEt_3; d, H_2, $Pd(OH)_2$, MeOH; e, 1% aq. HCl; f, CbzCl, NaOH; g, Jones oxidation, Me_2CO; h, CH_2N_2; i, AgO_2CPh, MeOH; j, $LiBHEt_3$; k, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; l, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C; m, H_2, $Pd(OH)_2$; n, Me_3Al; o, DIBAL-H; p, 60% aq. $HClO_4$; q, KCN; r, $H_2C{=}CH(CH_2)_3MgBr$.



SCHEME 65. Reagents: a, EtMgBr, Et_2O, –10°C to 0°C; b, Swern oxidation; c, $HOCH_2CH_2OH$, *p*-TsOH, PhMe, reflux; d, BuLi, THF, –15°C; e, (2*S*)-2-butyloxirane, DMPU, –50°C to 0°C; f, H_2 (50 atm), 10% Pd/C, EtOH; g, *p*-TsCl, DMAP, pyridine, –10°C to 0°C; h, chromatography on SiO_2; i, 2M HCl, Me_2CO, reflux; j, chromatography on neutral alumina (activity grade III); k, SiO_2, Et_2O, rt, then NEt_3.

Lhommet and co-workers synthesized (–)-**436** by the route shown in Scheme 66 (*422*). Wittig–Horner reaction between the 2,5-*trans*-disubstituted pyrrolidine aldehyde **509**, made from (*S*)-pyroglutamic acid (*423*), and the protected keto-phosphonate **510** introduced all the skeletal carbon atoms of the target. Simultaneous hydrogenation and *N*-deprotection of enone **511** gave the aminoketone **512**, which spontaneously formed the bicyclic enamine **513** in 98% yield when exposed to trifluoroacetic acid—apparently the first time that such an intermediate has actually been isolated *en route* to indolizidines. Reduction with sodium cyanoborohydride in acidic medium acid produced a diastereomeric mixture (92:8) of (–)-**436** and (+)-**437**. The former was isolated in 84% yield after chromatography on silica gel. The overall yield of this 15-step sequence was 8% based on (*S*)-pyroglutamic acid.



SCHEME 66. Reagents: a, KHMDS, THF, 0°C; b, H_2 (1 bar), Pd/C, MeOH; c, CF_3CO_2H, H_2O; d, $NaBH_3CN$, HCl (1 equiv), then chromatography on SiO_2.

B. INDOLIZIDINE AND QUINOLIZIDINE ALKALOIDS FROM AMPHIBIANS

The past fifteen years have seen enormous advances in the discovery, structural elucidation, and synthesis of alkaloids isolated from the skins of anurans and other amphibians. The most significant single publication in this area has been the monumental 1993 survey of amphibian alkaloids by Daly, Garraffo, and Spande in Volume 43 of this treatise; at the time it provided the most comprehensive review of the approximately 300 alkaloids isolated from, or detected in, amphibians (*4*). Daly's subsequent update in Volume 50 (1998) brought the state of knowledge on the structure and origin of the amphibian alkaloids—now estimated at over 400—almost to the present time (*5*). These two chapters, supplemented by reviews on the synthesis of simple amphibian indolizidine alkaloids in Volumes 28 (*1*) and 44 (*2*) of this series, have established the groundwork for the present survey, which covers only those aspects of the topic that postdate the treatment in the four earlier chapters. A further survey of the amphibian alkaloids by Daly and co-workers was published as recently as 1999 in another important series of volumes (*424*). Daly's convention of using a bold-faced font in the nomenclatural code for the alkaloids (*e.g.*, quinolizidine **219A**) will not be followed in order to avoid confusion with the numbering of structure formulae.

1. Isolation, Structure, and Biological Activity

One of the most important recent developments has been the growing realization that the majority of the amphibian alkaloids are not produced by the animals themselves, but are sequestered from the arthropods on which they feed. This topic has been thoroughly covered in Daly's review in Volume 50 (*5*). Evidence for the 'dietary hypothesis' has also been presented in several short reviews dealing with the occurrence, structure, and chemical ecology of toxins isolated from amphibian skins (*425–427*); in this connection, Daly's personal account of thirty years of research in this area deserves special mention (*428*). In the meantime, it has been found that Madagascan frogs of the genus *Mantella*, like the related dendrobatid frogs from the Americas, failed to produce skin alkaloids when raised in captivity, but sequestered indolizidine alkaloids when fed with alkaloid-dusted fruit flies (*429*).

Few new alkaloids have been reported since the publication of the reviews cited above (Fig. 7). The occurrence of the new 4,6-dialkylquinolizidine alkaloid 195C (**442**) both in ants of the genus *Solenopsis* and in the Madagascan frog *Mantella betsileo* was described in Section V.A; it was previously detected as a minor or trace metabolite of unknown structure in the Central and South American frogs *Epipedobates bassleri*, *E. tricolor*, *Minyobates steyermarki*, *Mantella betsileo*, *M. expectata*, *M. laevigata*, *M. pulchra*, and several *Dendrobates* species (*389*). Alkaloid 275A, a putative 4-methyl-6-nonynylquinolizidine, has turned out to be an unprecedented 4-methyl-9-nonynyl-1-azabicyclo[5.3.0]decane of general structure **514** (*424*), but full characterization has not yet been reported.

Novel 1,4-disubstituted quinolizidines were first reported in 1993 (*381,390*), but detailed characterization has only been described quite recently after isolation of larger quantities from another Madagascan frog, *M. baroni* (*430*). Spectroscopic

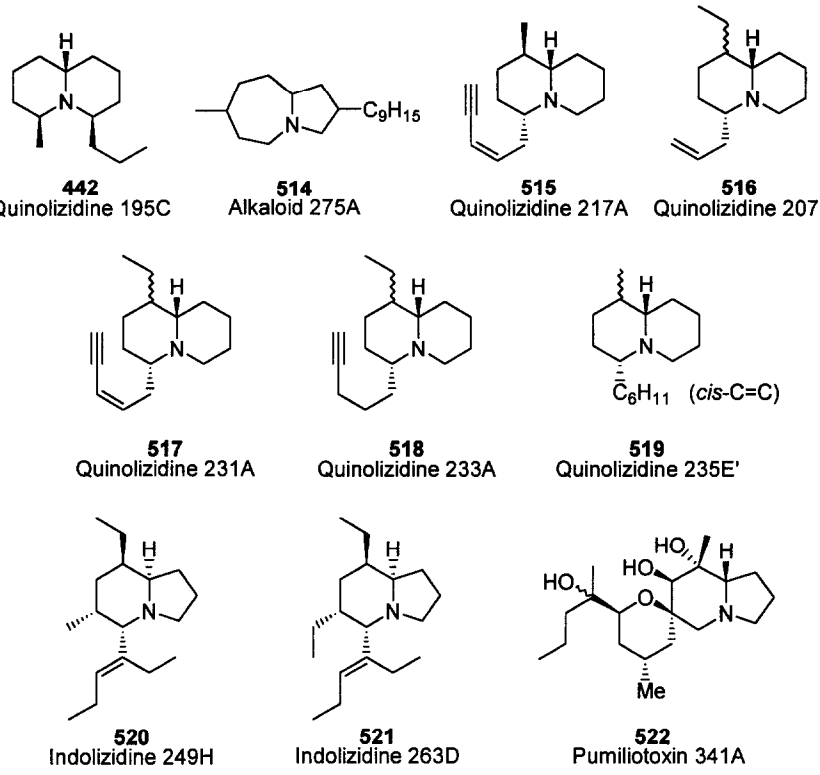


FIG. 7. New quinolizidine, indolizidine, and related alkaloids from amphibians.

evidence for the relative configuration of quinolizidine 217A (**515**) (principally, analysis of Bohlmann bands and coupling constants in the FTIR and NMR spectra, respectively) appears to be unambiguous. Tentative structures have been proposed by analogy for quinolizidines 207I (**516**), 231A (**517**), 233A (**518**), and 235E' (**519**), while alkaloids 231B and 273A are more likely to be 5,6,8-trisubstituted indolizidines. Alkaloid 249H, a minor alkaloid of Panamanian *D. auratus* and a trace component in *M. betsileo*, was also previously thought to be a 1,4-disubstituted quinolizidine (*431*), but it has actually proved to be the trisubstituted indolizidine **520** (*432*). This structure, elucidated on the basis of HRMS and ^{1}H, ^{13}C NMR, and GC–FTIR spectroscopic studies, possesses a unique (*E*)-hex-3-en-3-yl side chain at C-5—the first example of a branched side chain among the simple frog skin indolizidines. An intense NOESY cross peak between 1-H and 5-H was compatible only with a *cis*-fused indolizidine structure, another exceptional feature that was supported by magnetization transfer (TOCSY) NMR spectroscopic studies and molecular modeling. Alkaloid 263D, a trace compound accompanying indolizidine 249H in the extracts from *D. auratus*, may be the 6-ethyl congener **521**.

Alkaloid 341A (**522**), a unique cyclic ether of the allopumiliotoxin class, has been isolated from skin extracts of the Ecuadoran poison frog *Epipedobates tricolor* together with a number of known pumiliotoxins and related compounds, as well as indolizidine 207A, quinolizidine 207I, and several epibatidines (*433*). Exhaustive spectroscopic analysis supported the structural assignment, although the absolute configuration and the relative stereochemistry of the methyl group in the pyran ring were assigned only by analogy with other allopumiliotoxins. The alkaloid was previously detected in certain populations of Central American *Dendrobates auratus*, *D. pumilio*, and *D. granuliferus*, and in Colombian *D. lehmanni*, *Minyobates minutus*, and *M. viridis*, but its structure has remained unknown up to now. A related alkaloid, 341B (from *D. lehmanni* and *D. pumilio*), appears to be a diastereomer, while alkaloid 357, also detected in the present study, is thought to be a hydroxy analogue of 341A.

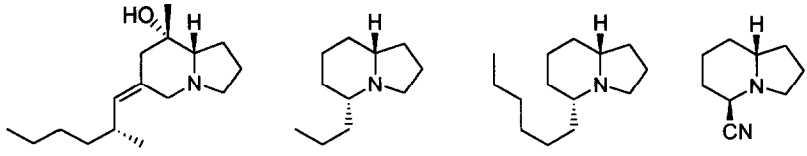
Recent biological studies on amphibian alkaloids and analogs appear to have been confined to pumiliotoxin 251D (**523**) and thirteen synthetic isomers in which the configurations at C-8 and C-2' were varied, or in which the side chain was modified (*434*). In toxicity studies with larvae of the cotton pest *Heliothis virescens* (the tobacco budworm)—the first study of the toxicity of pumiliotoxins towards insects, incidentally—it was found that activity depended on C-2' in the side chain having (*R*) absolute configuration; the nature of the alkyl substituent was less critical. Computational studies suggested that substituents with this configuration were needed in order to attain the active conformation of the side chain. The natural product was found to be the most active neurotoxin in the group, causing convulsions in 50% of larvae at a concentration of 0.01 mg/larva, and having an LD_{50} of 0.15 mg/larva.

2. *Synthesis*

Recent advances in the synthesis of dendrobatid alkaloids have been reviewed by Kibayashi and Aoyagi, who have themselves made substantial contributions in this field over the past few years (*435*). A noteworthy review by Franklin and Overman on the total synthesis of alkaloids of the pumiliotoxin and allopumiliotoxin classes highlights the many imaginative new strategies and methodologies that have been developed for dealing with these challenging targets (*436*).

So popular are the frog alkaloids as synthetic targets, and so numerous are the published approaches to them, that Takahata and Momose discussed only enantioselective syntheses in their survey in Volume 44 (*2*). In the interests of brevity, the ensuing discussion will perforce follow the same course. However, references to syntheses of racemic alkaloids published in the post-1986 period will be cited for completeness. In order to simplify the presentation, the syntheses are grouped according to the structural sub-class of the target alkaloids.

a. 5-Alkylindolizidine alkaloids. This group is represented by two trace alkaloids, indolizidine 167B (**524**) and indolizidine 209D (**525**). The optical rotations and absolute configurations of the natural products are unknown, and even their relative stereochemistries are uncertain, although assumed to be as illustrated by analogy with more abundant dialkylindolizidines. The structural formulae show



523 Pumiliotoxin 251D

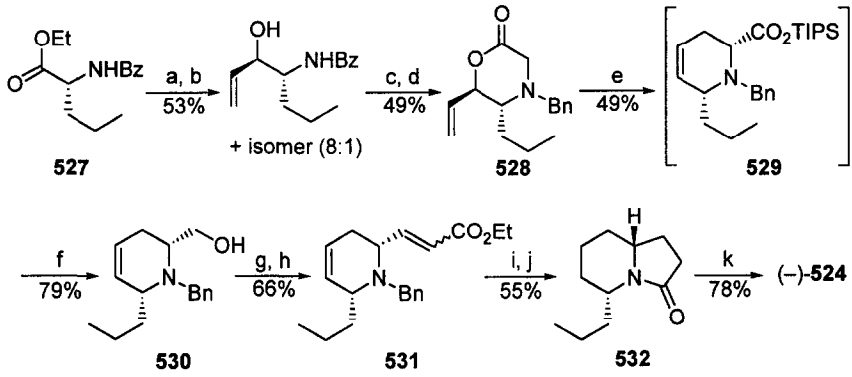
524 Indolizidine 167B

525 Indolizidine 209D

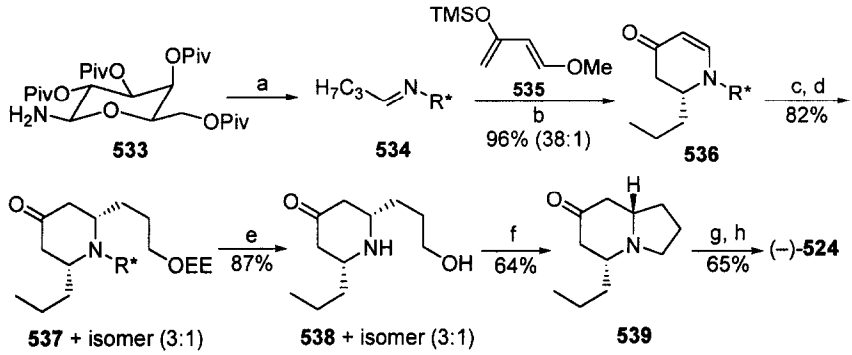
526

the configurations of the synthetic levorotatory isomers. Racemic indolizidine 167B, sometimes accompanied by its diastereomer, has been synthesized on several occasions (*437–442*), while racemic 209D has been prepared only once (*441*). A synthesis of the indolizidine-5-carbonitrile (±)-**526** represents a formal synthesis of both racemic alkaloids (*443*), since Polniaszek and Belmont's important route to the (−)-enantiomers, reported in 1990, proceeded *via* (5*R*,8a*R*)-**526** (*444*). Enantioselective syntheses published before 1993 were reviewed in depth by Takahata and Momose (*2*).

The enantioselective synthesis of (−)-indolizidine 167B (**524**) by Angle and Henry commenced with *N*-benzoyl-D-norvaline ethyl ester (**527**), which was converted in three steps and 26% yield into the oxazinone **528** (Scheme 67) (*445*). Spontaneous Claisen rearrangement of the corresponding triisopropylsilyl enol ether, prepared *in situ*, gave ester **529**, which was immediately reduced with lithium aluminum hydride to yield the 2,6-*cis*-disubstituted 1,2,3,6-tetrahydropyridine **530**. Oxidation and Wadsworth–Emmons homologation afforded a mixture of geometrical isomers of the unsaturated ester **531**, hydrogenation and cyclization of which gave indolizidin-3-one **532**. Simple reduction with lithium aluminum hydride completed the synthesis of the target alkaloid (−)-**524** in nine steps and 5.8% overall yield from the amino ester **527**.



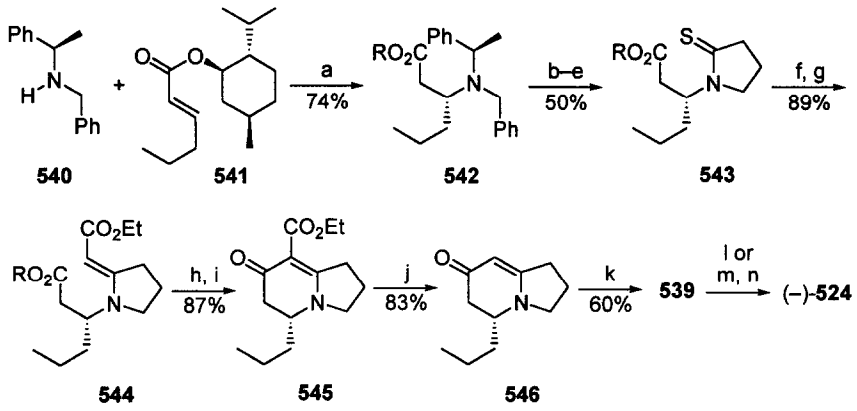
SCHEME 67. Reagents: a, DIBAL-H, CH_2Cl_2, −78°C; b, $H_2C{=}CHMgCl$, THF, −75°C to rt; c, $LiAlH_4$, THF, 0°C to reflux; d, $BrCH_2CO_2Ph$, Pr^i_2NEt, MeCN, 0°C to rt; e TIPS-OTf, Et_3N, C_6H_6; f, $LiAlH_4$, Et_2O, 0°C to rt; g, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C to rt; h, $(EtO)_2POCH_2CO_2Et$, KH, THF, −78°C to rt; i, 5% Pd/C, Na_2CO_3, Et_2O, filter and repeat, then H_2 (30 psi), $Pd(OH)_2/C$, EtOH, 60°C; j, Me_3Al, C_6H_6, 0°C to reflux; k, $LiAlH_4$, Et_2O, 0°C to reflux.



SCHEME 68. Reagents: a, butanal; b, $ZnCl_2$, THF–CH_2Cl_2(1:1), –78°C to –20°C, then 1M aq. HCl; c, $CH_3CH(OEt)OCH_2CH_2CH_2MgBr$, CuBr·$SMe_2$, Me_3SiCl, THF, –78°C; d, Bu_4NF, THF; e, 1M aq. HCl, MeOH, then Na_2CO_3; f, Et_3N, CCl_4, Ph_3P, MeCN, 0°C to rt; g, $(CH_2SH)_2$, BF_3·Et_2O, CH_2Cl_2, 0°C to rt; h, H_2, Raney Ni, Pr^iOH, 70°C.

The synthesis of (–)-**524** by Weymann *et al.* used tetra-*O*-pivaloyl-β-D-galactosylamine **533** as an unusual chiral auxiliary (Scheme 68) (*446*). A highly diastereoselective (38:1) zinc chloride-catalyzed aza-Diels–Alder cycloaddition between its butanal aldimine **534** and Danishefsky's diene **535** gave dihydropyridone **536** in 96% yield. The (*R*) absolute configuration adjacent to nitrogen was confirmed by X-ray crystallography. Diastereoselectivity in the ensuing conjugate addition of 3-(1-ethoxy)ethoxypropylcuprate to **536** was mediocre (3:1), but the reaction nonetheless gave the desired 2,6-*cis*-disubstituted piperidin-4-one **537** as the dominant isomer. Mild acidic hydrolysis removed both the acetal protecting group and the sugar auxiliary, after which the liberated heterocycle **538** (still as a 3:1 mixture of isomers) was cyclized *via* the corresponding chloride to the indolizidin-7-one **539**, isolated as a single isomer. Defunctionalization of the dithiolane derivative of **539** completed the synthesis of (–)-**524**.

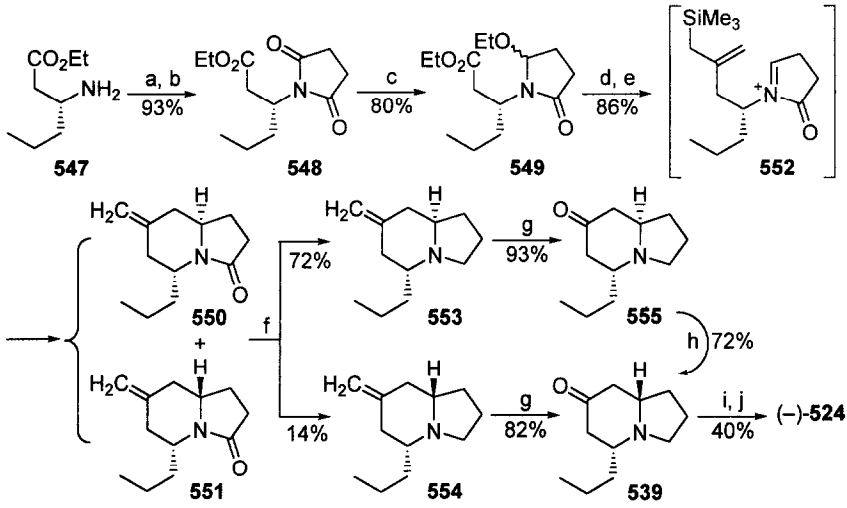
A synthesis of racemic indolizidine 167B by Michael and Gravestock (*442,447*) was later modified to yield the (–)-enantiomer **524** (Scheme 69) (*448*). Highly diastereoselective conjugate addition of the anion of (*R*)-*N*-benzyl-1-phenylethylamine (**540**) to (+)-menthyl (*E*)-hex-2-enoate (**541**) gave adduct **542**, which contains the requisite absolute configuration at the site adjacent to nitrogen, in accordance with the precedents set by Davies *et al.* (*449*). Hydrogenolysis of both benzyl substituents from **542**, lactam formation between the resulting primary amine and 4-chlorobutyryl chloride, and thionation led to thiolactam **543**. Eschenmoser sulfide contraction with ethyl bromoacetate then yielded vinylogous urethane **544**, acylative ring closure of which created the unsaturated indolizidinone **545**. After hydrolysis and decarboxylation gave bicyclic vinylogous amide **546**, careful reduction yielded the volatile indolizidinone **539** as a single diastereomer. The route converged at this point with that of Weymann *et al.*, thereby completing a formal synthesis of (–)-**524**. However, when defunctionalization of **539** *via* the propylene dithioketal was actually attempted, the target alkaloid was obtained with some loss of optical activity.



SCHEME 69. Reagents: a, **540** + BuLi, THF, –78°C, then **541**; b, H_2 (7 atm), 10% Pd/C, HOAc; c, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$; d, KOBu^t, Bu^{t}OH; e, Lawesson's reagent, PhMe, reflux; f, $BrCH_2CO_2Et$, MeCN; g, Ph_3P, Et_3N, MeCN; h, KOH, EtOH, reflux; i, Ac_2O, MeCN, 50°C; j, KOH, H_2O, reflux, then HCl, reflux; k, $LiAlH_4$, THF, rt; l, ref. *446*; m, $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, TFA; n, Raney Ni W-2, EtOH, reflux.

The synthesis of (–)-**524** by Remuson and co-workers also began with the Davies conjugate addition, this time between the lithium amide of **540** and ethyl (*E*)-hex-2-enoate (*450*). The primary amine **547** formed after removal of the benzyl groups was converted into the succinimide derivative **548** by treatment with succinic anhydride followed by acetyl chloride, and thence into the ethoxylactam **549** by reduction with sodium borohydride in acidic ethanol (Scheme 70). Treatment with the organocerium reagent made from trimethylsilylmethylmagnesium chloride and cerium(III) chloride followed by acidic hydrolysis produced an inseparable mixture of the 7-methylene indolizidinones **550** and **551** (4:1; 86%) *via* the acyliminium ion intermediate **552**. When the mixture of lactams was reduced with lithium aluminum hydride, the resulting indolizidines **553** and **554** were easily separated by flash chromatography. Cleavage of the methylene groups with osmium tetroxide and periodate gave the ketones **555** and **539**, the former undergoing epimerization to the latter on prolonged treatment with dilute hydrochloric acid. Defunctionalization of **539** *via* the corresponding ethylene dithioketal completed the synthesis of (–)-**524**.

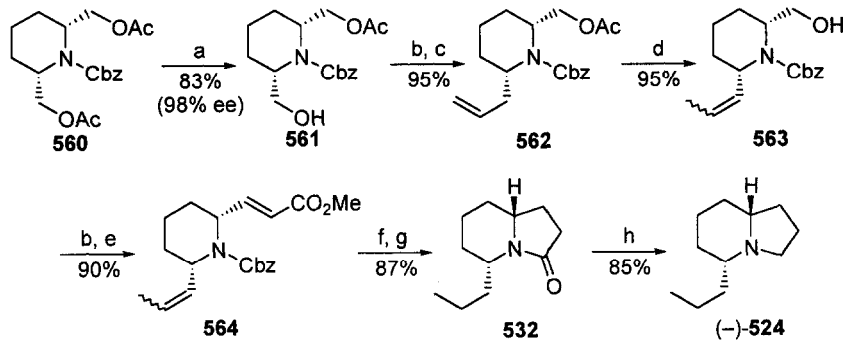
In the short synthesis of (–)-**524** by Back and Nakajima, an efficient cyclization between the proline-derived chloroamine **556** and the alkynylsulfone **557** yielded the unsaturated indolizidine **558** (94%) (Scheme 71) (*451*). Stereoselective reduction of the conjugated double bond with sodium cyanoborohydride followed by cleavage of the sulfone with sodium in ammonia yielded a mixture of (–)-**524** and the unsaturated analog **559**. Catalytic hydrogenation ensured complete conversion of **559** into (–)-indolizidine 167B (**524**).



SCHEME 70. Reagents: a, succinic anhydride, PhMe, reflux; b, AcCl, PhMe, reflux; c, $NaBH_4$, H_2SO_4, EtOH, –30°C; d, Me_3SiCH_2MgCl, $CeCl_3$; e, 1M HCl; f, $LiAlH_4$, THF, then flash chromatography; g, cat. OsO_4, IO_4^-, HOAC; h, 1M HCl, reflux, 6 d; i, $HSCH_2CH_2SH$, BF_3; j, H_2, Raney Ni.

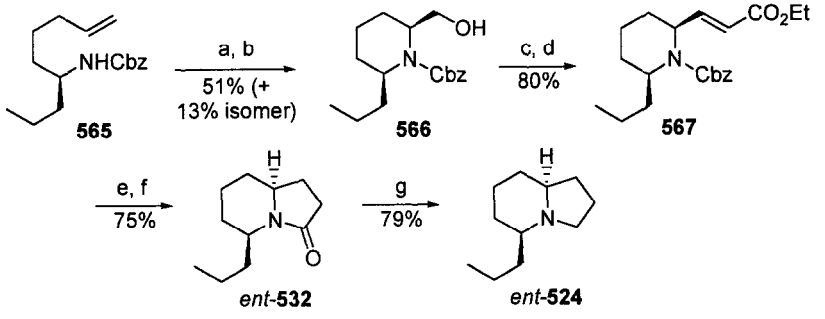
SCHEME 71. Reagents: a, CH_2Cl_2, rt; b, LDA, THF, –78°C, 2 min; c, $NaBH_3CN$, CH_2Cl_2, rt to reflux; d, Na, NH_3, –33°C, then NH_4Cl; e, H (1 atm), 10% Pd/C, EtOH.

The novel feature of an enzyme-mediated synthesis of (–)-**524** was the desymmetrization of the *cis*-2,6-diacetoxymethylpiperidine **560** with *Aspergillus niger* lipase to achieve absolute stereocontrol (Scheme 72) (*452*). The resulting alcohol **561** was obtained in 83% yield and an ee of 98%. Swern oxidation and Wittig reaction with ethylidenetriphenylphosphorane afforded the alkene-ester **562**, a second enzymatic reaction (this time with pig liver esterase) then effecting both hydrolysis of the acetate and isomerization of the double bond to give alcohol **563** (95%). Another Swern oxidation and Wittig homologation produced enoate **564**, which was hydrogenated and cyclized to the same indolizidin-3-one **532** that featured in the synthesis by Angle and Henry (*cf.* Scheme 67) (*445*). Reduction of this bicyclic lactam with lithium aluminum hydride completed the synthesis of (–)-**524** in eight steps and a remarkable 60% overall yield from enantiopure **561**.

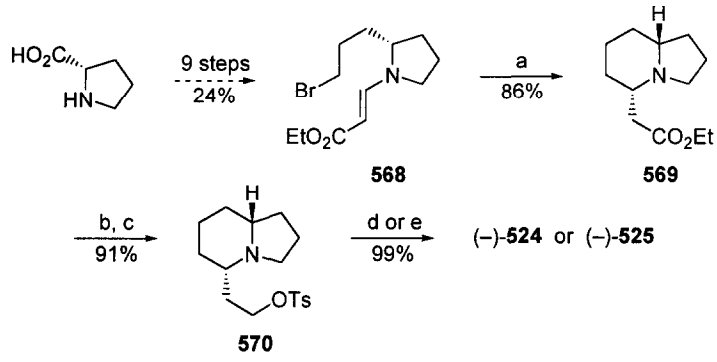


SCHEME 72. Reagents: a, *Aspergillus niger* lipase, phosphate buffer (pH 7), 7% MeCN, 5 d; b, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78°C to rt; c, $Ph_3PEt^+ Br^-$, $KOBu^t$, C_6H_6, rt to reflux; d, pig liver esterase, phosphate buffer, pH 7, rt; e, $Ph_3P{=}CHCO_2Me$, C_6H_6, reflux; f, H_2 (40 psi), 20% $Pd(OH)_2/C$, EtOH; g, Me_3Al, PhMe, reflux; h, $LiAlH_4$, Et_2O, 0°C to reflux.

The only recent synthesis of (+)-indolizidine 167B (*ent*-**524**), by Takahata *et al.*, used their familiar strategy of stereoselective electrophile-mediated heterocyclization of Cbz-protected alkenylamines (*453*). In this case, urethane **565**, readily available from L-norvaline, underwent intramolecular amidomercuration with mercuric trifluoroacetate (Scheme 73). Treatment of the organomercury intermediate with sodium borohydride and molecular oxygen gave the 2,6-*cis*-disubstituted hydroxymethylpiperidine **566** (51%) accompanied by a small amount of the *trans* isomer (13%). Swern oxidation and Wadsworth–Emmons chain extension yielded the piperidine **567**, which was hydrogenated and cyclized to the indolizidin-3-one *ent*-**532**. Standard reduction with lithium aluminum hydride completed this route to *ent*-**524**.



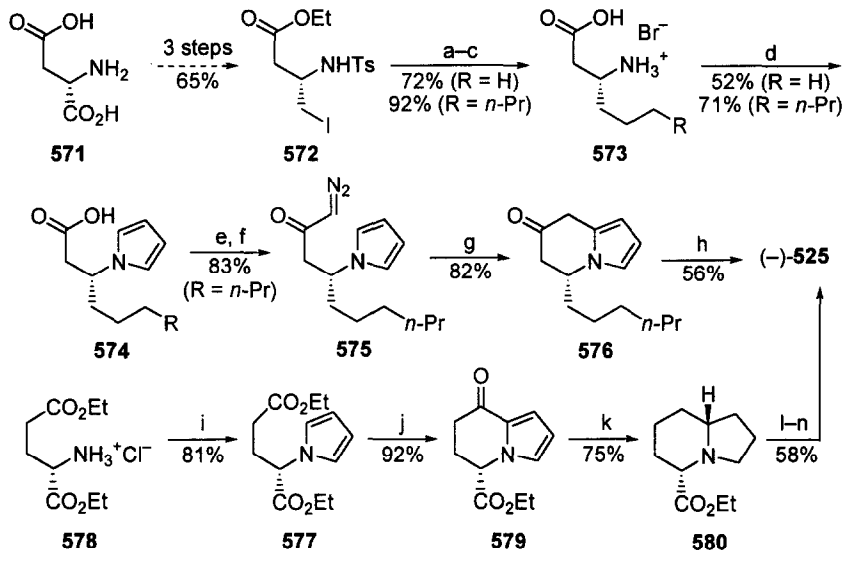
SCHEME 73. Reagents: a, $Hg(OCOCF_3)_2$, $MeNO_2$, then aq. $NaHCO_3$, KBr; b, O_2, $NaBH_4$, DMF; c, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78°C; d, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C; e, H_2 (1 atm), $Pd(OH)_2$, EtOH; f, Me_3Al (1M in hexane), CH_2Cl_2, rt to reflux; g, $LiAlH_4$, Et_2O, rt to reflux.



SCHEME 74. Reagents: a, Bu_3SnH (1,2 equiv, syringe pump, 4 h), AIBN (0.1 equiv), C_6H_6, reflux; b, $LiAlH_4$; c, *p*-TsCl, NEt_3, CH_2Cl_2; d, Me_2CuLi, Et_2O, 0°C; e, Bu_2CuLi, Et_2O, 0°C.

Some routes to the 5-alkylindolizidine alkaloids proceed through intermediates from which both indolizidine 167B (**524**) and indolizidine 209D (**525**) can be made. One such approach, by Lee *et al.*, began with (*S*)-proline, which was converted in nine steps into the β-aminoacrylate **568** (Scheme 74) (*454*). The transformation of importance is intramolecular conjugate addition of the radical derived from the primary bromide on to the β-aminoacrylate under conditions of high dilution to form indolizidine **569** as the sole stereoisomer. Reduction of the ester, activation of the resulting alcohol as the *p*-toluenesulfonate **570**, and reaction with the appropriate dialkylcuprates completed the syntheses of (–)-**524** and (–)-**525**. In the light of this route, an earlier synthesis of **569** can now be considered to represent formal syntheses of the same two alkaloids (*455*).

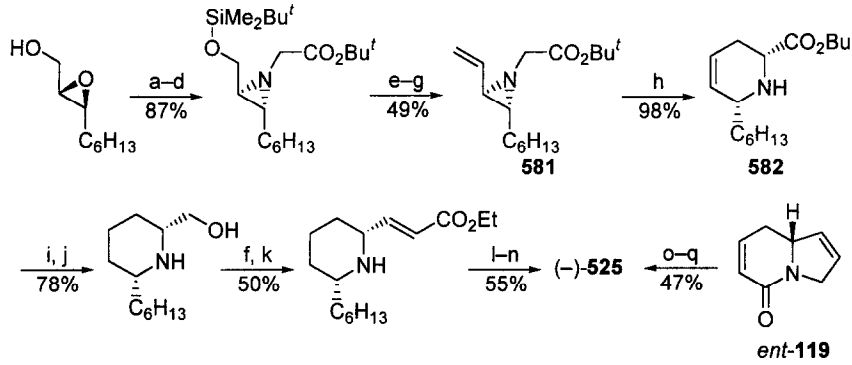
Jefford and Wang prepared both (–)-**524** and (–)-**525** from L-aspartic acid (**571**) by the route shown in Scheme 75 (*456,457*). The pendent chains were introduced by displacing iodide from intermediate **572** with the appropriate dialkylcuprates, after which the sulfonamide and ester groups were hydrolyzed to give the (*R*)-β-aminoacid hydrobromide salts **573**. Standard pyrrole formation with 2,5-dimethoxytetrahydrofuran afforded **574**. At this point a formal synthesis of (–)-indolizidine 167B was achieved, since Jefford *et al.* had previously converted **574** (R = *n*-Pr) into the alkaloid **524** (*458*). The other intermediate **574** (R = *n*-Pr) was treated with isobutyl chloroformate followed by diazomethane to give the diazoketone **575**, following which rhodium(II)-induced cyclization *via* a carbenoid intermediate yielded the bicyclic ketopyrrole **576**. Catalytic hydrogenation of the latter product not only brought about stereospecific reduction of the pyrrole ring, but also accomplished the unexpected defunctionalization of the ketone group, thereby affording (–)-indolizidine 209D (**525**) directly. The overall yield of this eleven-step synthesis from **571** was 16%. An even shorter approach to (–)-**525** by Jefford *et al.*, also shown in Scheme 75, proceeded *via* a different pyrrole intermediate, **577**, which was made from diethyl L-glutamate hydrochloride (**578**) (*459,460*). After acylative cyclization to **579**, hydrogenation in acetic acid over



SCHEME 75. Reagents: a, Et_2CuLi (for R = H) or $(n\text{-}C_5H_{11})_2CuLi$ (for R = *n*-Pr), THF –30°C; b, K_2CO_3, MeOH, H_2O; c, 47% aq. HBr, PhOH, reflux; d, 2,5-dimethoxytetrahydrofuran, NaOAc, AcOH, reflux, 5 min; e, $ClCO_2Bu^i$, *N*-methylmorpholine; f, CH_2N_2; g, $Rh_2(OAc)_4$, CH_2Cl_2; h, H_2 (15 atm.), Pt, AcOH, 6M HCl; i, 2,5-dimethoxytetrahydrofuran, H_2O–$ClCH_2CH_2Cl$, 80°C; j, BBr_3, CH_2Cl_2, 5°C to rt; k, H_2 (55 psi), 10% Pd/C, AcOH; l, DIBAL-H, Et_2O, –70°C, then MeOH, –70°C to reflux; m, Ph_3P=CHBu, THF, –78°C; n, H_2 (40 psi), PtO_2, EtOAc.

10% palladium on carbon proceeded with complete hydrogenolysis of the ketone group, and yielded the indolizidine ester **580** as a single stereoisomer (75%). Standard elaboration of the ester substituent completed this synthesis of (–)-indolizidine 209D (**525**) in six steps and 32% overall yield from **578**. In view of Jefford's results, two other recent syntheses of the indolizidine-5-carboxylate **580** (*461,462*) can be regarded as having also completed formal syntheses of **525**.

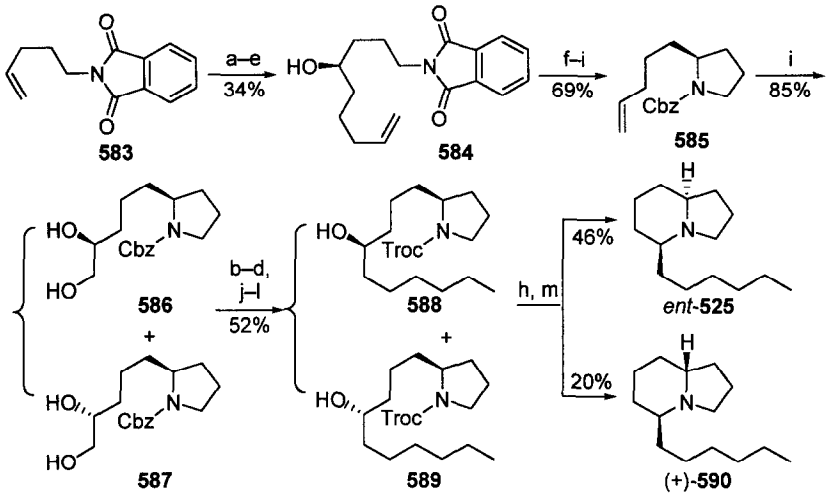
Åhman and Somfai constructed the indolizidine skeleton of (–)-**525** by the novel and efficient base-induced aza-[2,3]-Wittig rearrangement of the vinylaziridine **581** (Scheme 76) (*463,464*). The product (98% yield) was the unsaturated 2,6-*cis*-disubstituted piperidine **582**, which possesses the correct relative and absolute stereochemistry required for the target alkaloid. The synthesis was completed by side chain homologation, reduction, and cyclization in a manner reminiscent of that already seen in the synthesis of related frog skin alkaloids (*cf.* Schemes 72 and 73). Another short route to (–)-**525**, also shown in Scheme 76, made use of (*R*)-**119**, the (*S*)-enantiomer of which was used in routes to hydroxylated indolizidine alkaloids (*cf.* Schemes 16 and 23) (*79*). In this case, the synthesis of the target alkaloid entailed catalytic hydrogenation of both double bonds, addition of a hexylcerium(III) reagent, and reduction with sodium cyanoborohydride.



SCHEME 76. Reagents: a, NaN_3, NH_4Cl, $MeOCH_2CH_2OH$–H_2O; b, TBDMS-Cl, CH_2Cl_2, NEt_3, DMAP; c, Ph_3P, PhMe, reflux; d, $BrCH_2CO_2Bu^t$, K_2CO_3, 18-crown-6, THF; e, Bu_4NF, THF; f, DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78°C; g, $Ph_3P{=}CH_2$, THF; h, LDA, THF, –78°C; i, H_2, 5% Pd/C, EtOH; j, $LiAlH_4$, THF, 0°C to rt; k, $Ph_3P{=}CHCO_2Et$; l, H_2 (4 psi), 5% Pd/C, EtOH; m, Me_3Al, C_6H_6; n, $LiAlH_4$, THF, reflux; o, H_2, PtO_2, EtOAc; p, $C_6H_{13}Li$, $CeCl_3$, THF, –78°C to –30°C; q, $NaBH_3CN$, MeOH, HCl.

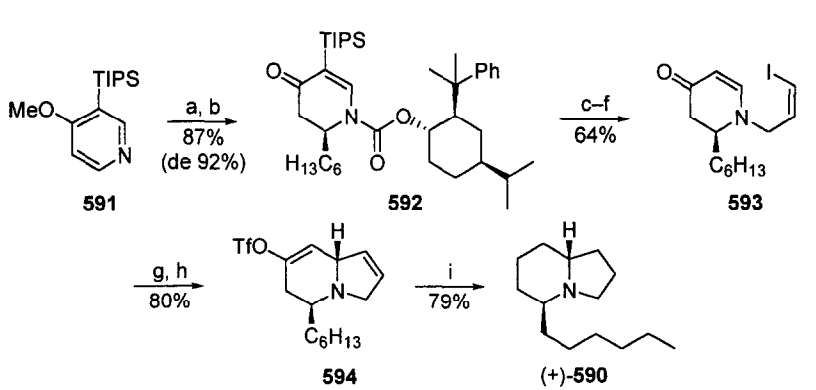
Takahata and co-workers have synthesized all four stereoisomers of indolizidine 209D by stereodivergent routes in which iterative Sharpless asymmetric dihydroxylation was used to establish the absolute configurations of the stereogenic centers (Scheme 77) (*465*). Treatment of *N*-(pent-4-enyl)phthalimide (**583**) with AD-mix-α™ followed by epoxide formation and ring-opening with bis(but-3-enyl)cuprate yielded the (*R*)-alcohol **584** in 34% overall yield. Liberation of the primary amine from the phthalimide was followed by cyclization and *N*-protection to give the (*S*)-pyrrolidine **585**, after which another asymmetric dihydroxylation with AD-mix-α™ produced diol **586** contaminated with the inseparable diastereomer **587**. Conversion of the diols into the corresponding epoxides, ring opening with pentylmagnesium bromide, and protecting group manipulations yielded alcohols **588** and **589**, from which (5*S*,9*S*)-(+)-indolizidine 209D (*ent*-**525**) and the separable (5*S*,9*R*)-(+) isomer **590** were produced in two further steps. Replacing AD-mix-α™ by AD-mix-β™ in either or both asymmetric dihydroxylation steps similarly permitted access to the (5*R*,9*S*)-(–) and (5*R*,9*R*)-(–) isomers of both products. NMR analysis of Mosher esters of various intermediates *en route* to the targets suggested that the ee's of the four indolizidine isomers were between 92% and 98%. All four isomers were found to inhibit the binding of tritiated thienylcyclohexylpiperidine to binding sites on carbamylcholine-activated nicotinic acetylcholine receptor (nAChR) channel complex from the electric eel *Torpedo californica*; the calculated K_i values lay in the range 0.42–0.67 μM, with (–)-indolizidine 209D (**525**) showing the greatest activity.

The 209D diastereomer (+)-**590** has also been made by Comins and Zhang (Scheme 78) (*466,467*). After *N*-acylation of the 4-methoxypyridine **591** with (1*S*,2*R*,4*S*)-4-isopropyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroformate, the resulting pyridinium salt was intercepted with hexylmagnesium chloride to give the optically active enaminone **592**. Removal of the chiral auxiliary and *N*-alkylation with (*Z*)-1,3-diiodopropene yielded **593**, thereby setting the scene for a novel anionic



SCHEME 77. Reagents: a, AD-mix-α™, Bu'OH, H_2O, 0°C; b, $(MeO)_3CMe$, PPTS, CH_2Cl_2; c, AcBr, CH_2Cl_2; d, K_2CO_3, MeOH; e, $H_2C{=}CH(CH_2)_2MgBr$, CuI, THF, –78°C to –35°C; f, $H_2NNH_2{\cdot}H_2O$, EtOH, 60°C; g, $ClCO_2Bn$, 2M NaOH, 0°C to rt; h, MsCl, DMAP, pyridine, 0°C; i, NaH, THF, 0°C to 50°C; j, $Me(CH_2)_4MgBr$, CuI, THF, –78°C to –35°C; k, H_2, $Pd(OH)_2$, MeOH; l, $ClCO_2CH_2CCl_3$, K_2CO_3, CH_2Cl_2, H_2O, 0°C to rt; m, 1M NH_4OAc, 10% Pb/Cd, THF.

cyclization initiated by halogen-metal exchange with *tert*-butyllithium. The transient organolithium species underwent stereospecific intramolecular conjugate addition to the enaminone to give an intermediate enolate, which was trapped as the vinyl triflate **594**. Catalytic reduction afforded the target indolizidine (+)-**590** directly. The overall yield of this brief but effective reaction sequence was 35% based on **591**.



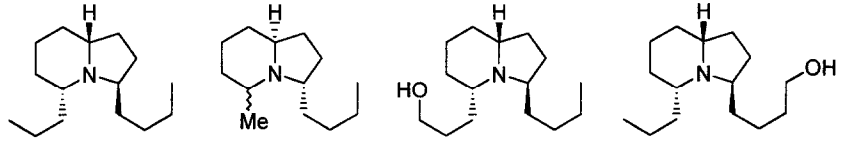
SCHEME 78. Reagents: a, (1*S*,2*R*,4*S*)-4-isopropyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroformate; b, $C_6H_{13}MgCl$; c, NaOMe, MeOH; d, 10% HCl; e, NaHDMS, THF, –78°C; f, (*Z*)-1,3-diiodopropene, THF, –78°C to 0°C; g, Bu'Li, THF, –78°C; h, (5-Cl-2-pyridyl)NTf_2; i, H_2, Pt/C, Li_2CO_3, EtOAc.

b. 3,5-Disubstituted indolizidine alkaloids. Although about fifteen 3,5-disubstituted indolizidine alkaloids have been isolated from, or detected in, amphibian skin extracts, only those shown in Fig. 8 have been the targets of recent syntheses. The naturally occurring alkaloids (3*R*,5*R*,8a*R*)-(−)-indolizidine 223AB (**432**), (3*S*,5*S*,8a*S*)-(+)-indolizidine 195B (**450**), (3*S*,5*R*,8a*S*)-(+)-indolizidine 195B (**595**), (3*R*,5*S*,8a*R*)-(−)-indolizidine 239AB (**596**), and (3*R*,5*R*,8a*R*)-(−)-indolizidine 239CD (**597**) are illustrated.

The synthesis of indolizidine 195B (**450**) has in general been the fortuitous result of indifferent diastereoselectivity in routes to its diastereomer monomorine I (**427**). The racemic alkaloid accompanied (±)-monomorine I, and sometimes other diastereomers, in several post-1985 syntheses (*393,397,399,400,402,403*). Enantioselective syntheses of **450** published during the period 1985–1993, most of them also producing **427**, were discussed in Volume 44 of this treatise (*2*), while post-1993 enantioselective syntheses leading to mixtures of **427** and **450** were detailed in Section V.A of this chapter (*404,410,413,415,419*). A conference paper describing the synthesis of (+)-**450** and the C-5 epimer (+)-**595** was also highlighted in Volume 44; this work has subsequently been published with full experimental details (*468*).

Nine routes to racemic indolizidine 223AB (*rac*-**432**), occasionally accompanied by diastereomers, were published between 1985 and 1994 (*393,469–476*), but subsequent syntheses all appear to have been enantioselective (*vide infra*). The only recent synthesis of indolizidine 239CD yielded the racemic alkaloid (±)-**597** (*477*).

Bloch *et al.* commenced a synthesis of (+)-indolizidine 195B (**450**) with the enantiomerically pure tricyclic lactol **598**, which was obtained by asymmetric reduction or enzymatic resolution from the Diels–Alder adduct of furan and maleic anhydride (*478*). Addition of butylmagnesium bromide to the disguised aldehyde was followed by oxidation of the liberated 4-hydroxy group to give a second lactol, **599** (Scheme 79). Stereoselective addition of a 4-oxygenated pentylmagnesium bromide yielded the diol **600**. Retro-Diels–Alder reaction by flash vacuum pyrolysis and hydrogenation of the resulting alkene afforded diol **601**, which contains all of the skeletal carbon atoms of the target alkaloid. Formation of the pyrrolidine ring of intermediate **602** was accomplished with inversion of configuration at both stereogenic centers by treating the bis(mesylate) of **601** with benzylamine. To complete the synthesis, the keto-pyrrolidine **603** was hydrogenated over palladium on charcoal, which simultaneously removed the *N*-benzyl group and



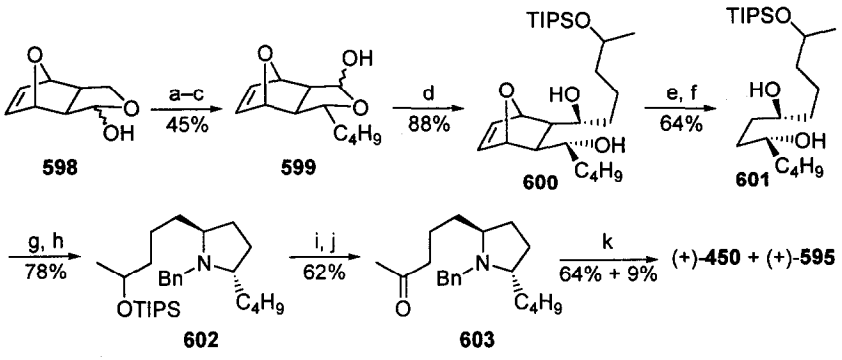
(−)-**432** Indolizidine 223AB

(+)-**450** β-Me
(+)-**595** α-Me
Indolizidines 195B

(−)-**596** Indolizidine 239AB

(+)-**597** Indolizidine 239CD

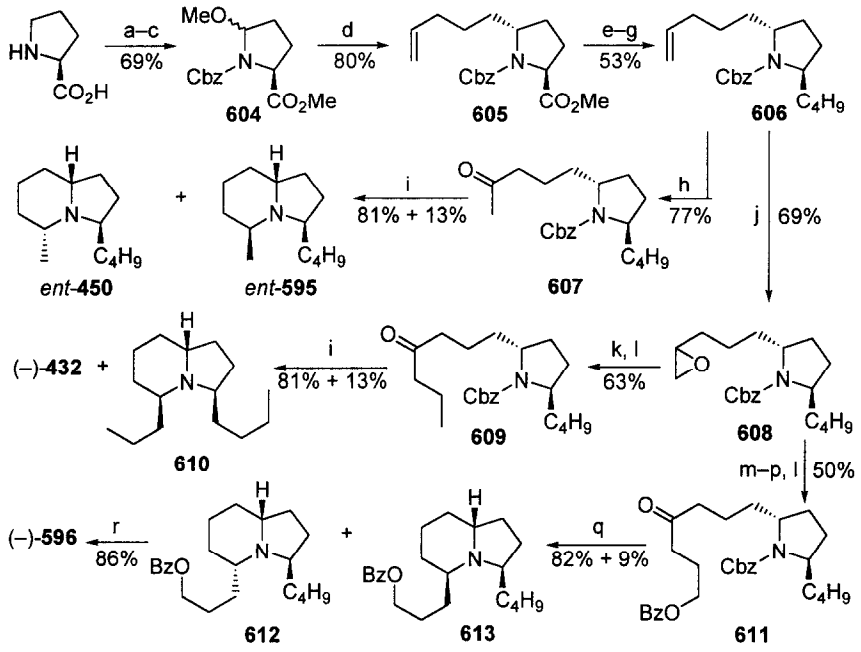
FIG. 8. Recently synthesized 3,5-disubstituted indolizidine alkaloids from amphibians.



SCHEME 79. Reagents: a, BuMgBr; b, TPAP, NMO; c, DIBAL-H; d, $MeCH(OTIPS)(CH_2)_3MgBr$, Et_2O, 0°C to rt; e, 500°C, 10^{-3} torr; f, H_2 (1 atm), 5% Pt/C, EtOAc; g, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0°C; h, $PhCH_2NH_2$, 50°C; i, Bu_4NF, THF, 0°C to rt; j, DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, –78°C to rt; k, H_2 (1 atm), 10% Pd/C, $MeOH–CO_2$.

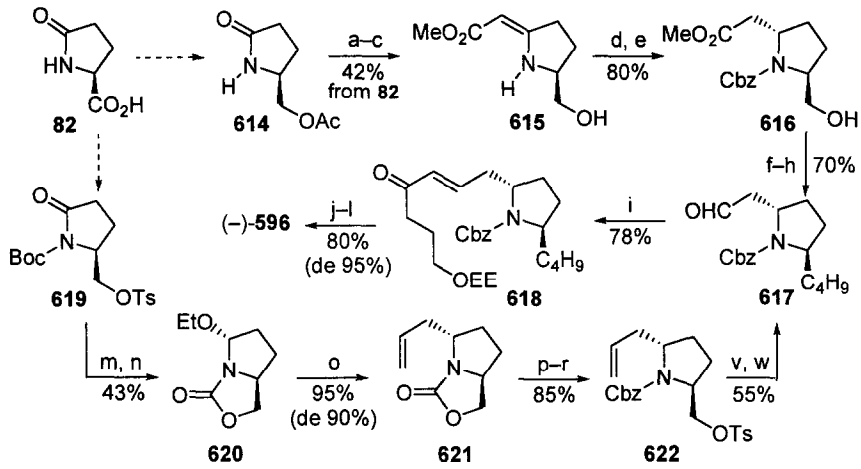
reduced the resulting iminium ion intermediate to give an 88:12 mixture of (+)-**450** and the minor alkaloid **595**. The overall yield of (+)-**450** from **598** was 8%.

Lhommet and co-workers have devised several related routes to 3,5-disubstituted indolizidine alkaloids (including monomorine I; *cf.* Section V.A), all of which also involve diastereoselective hydrogenation of a transient bicyclic iminium ion in the final stages to introduce the stereogenic center at C-5. Their approach to the unnatural levorotatory enantiomer of indolizidine 195B (*ent*-**450**) from L-proline is shown in Scheme 80 (*479,480*). Lewis acid-induced reaction between the iminium ion derived from **604** and pent-4-enylcopper set up the 2,5-*trans* stereochemistry of pyrrolidine **605** (*trans:cis* 96:4), after which modification of the ester group produced the 2-butylpyrrolidine **606**. Wacker oxidation of the alkene then afforded the ketone **607**. The final deprotection and intramolecular reductive alkylation, performed by hydrogenating **607** over a palladium–barium sulfate catalyst, was originally reported as being completely stereoselective (*479*), but was later shown to produce an 86:14 mixture of (–)-**450** (= *ent*-**450**) and (–)-**595** (= *ent*-**595**) (*480,481*). In a variation of this route, epoxidation of **607** produced a mixture of diastereomers of oxirane **608**. Ring opening with diethylcuprate and oxidation of the resulting alcohol gave keto-pyrrolidine **609**, reductive cyclization of which yielded (–)-indolizidine 223AB (**432**) and its C-5 epimer **610** in a ratio of 86:14 (*480*). [Earlier alternatives to this route made keto-pyrrolidine **609** in fourteen steps from (*S*)-pyroglutamic acid, and examined different conditions for the reductive cyclization to (–)-**432** (*409,482*).] In yet another modification, epoxide **608** was opened with divinylcuprate, after which hydroboration and oxidation of the vinyl group, protection of the resulting primary alcohol, and oxidation of the secondary alcohol gave ketone **611**. The familiar one-pot hydrogenolysis–hydrogenation procedure then afforded a separable mixture of the bicyclic ester **612** (82%) and its C-5 epimer **613** (9%). (–)-Indolizidine 239AB (**596**) was finally obtained by cleaving the benzoate **612** with sodium methoxide.



SCHEME 80. Reagents: a, $ClCO_2Bn$, NaOH, 0°C; b, $BF_3{\cdot}Et_2O$, MeOH, reflux; c, $Me_4N^+OTs^-$, MeOH, graphite anode (20 cm^2), 0.5A, –5°C; d, $H_2C{=}CH(CH_2)_3Cu$, $BF_3{\cdot}Et_2O$, Et_2O, –78°C; e, $NaBH_4$, $CaCl_2$, THF, EtOH, –5°C; f, *p*-TsCl, NEt_3; g, Pr_2CuLi, –40°C; h, O_2, $PdCl_2(PhCN)_2$, $CuCl_2$, H_2O, DMF, 70°C; i, H_2 (1 atm), 5% $Pd/BaSO_4$, MeOH; j, MCPBA, phosphate buffer (pH 8), CH_2Cl_2, 0°C to rt; k, EtMgBr, CuI, Et_2O, –40°C to –15°C; l, PDC, CH_2Cl_2; m, $H_2C{=}CHMgBr$, CuI, THF, –40°C to –20°C; n, $BH_3{\cdot}Me_2S$, Et_2O; o, 3M NaOH, 30% H_2O_2, reflux; p, PhCOCl (BzCl), pyridine, CH_2Cl_2, –40°C to rt; q, H_2 (1 atm), 10% Pd/C, MeOH; r, NaOMe, MeOH.

Further adaptations of Lhommet's basic strategy are shown in Scheme 81, which illustrates another two ways in which his group has accomplished the synthesis of 3,5-disubstituted indolizidines. In the first example, (*S*)-pyroglutamic acid (**82**) was converted in six steps *via* derivative **614** into the vinylogous urethane **615** (*483*). Although reduction of **615** with sodium borohydride in acidic medium yielded a mixture of *cis*- and *trans*-2,5-disubstituted pyrrolidines (de 80%), kinetically controlled *N*-carbamoylation of the dominant *trans* product permitted chromatographic separation of **616**, which was obtained in 80% yield. A further three steps gave aldehyde **617**, Wittig reaction of which with 5-(1-ethoxyethoxy)-2-oxopentylidenetriphenylphosphorane afforded keto-pyrrolidine **618**. After catalytic hydrogenation of the alkene, the usual diastereoselective one-pot reductive alkylation procedure followed by acidic work-up yielded (–)-indolizidine 239AB (**596**) in a de of 95%. The overall yield from **82** was 5.6%. In the second example, reduction of the pyroglutamate derivative **619** with lithium triethylborohydride and ethanolysis of the product afforded the bicyclic carbamate **620** (*484*). Reaction of this compound, effectively a disguised *N*-acyliminium species, with allyltrimethylsilane

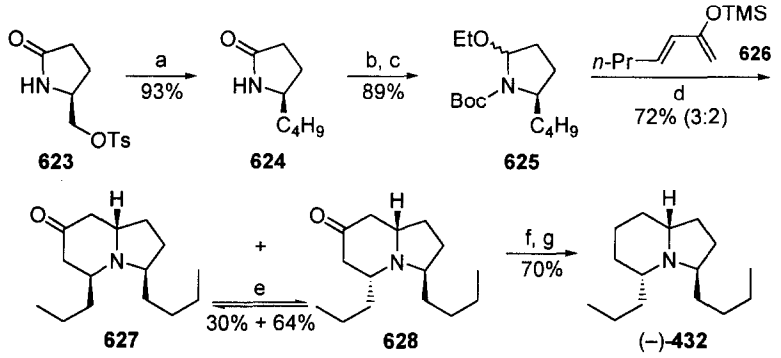


SCHEME 81. Reagents: a, Me_2SO_4, then K_2CO_3; b, Meldrum's acid, $Ni(acac)_2$, $CHCl_3$, reflux; c, NaOMe, MeOH, reflux; d, $NaBH_4$, AcOH, MeCN, 0°C; e, $ClCO_2Bn$, $NaHCO_3$, H_2O, 0°C; f, *p*-TsCl, Et_3N; g, Pr_2CuLi, Et_2O, –80°C; h, DIBAL-H, PhMe, –78°C; i, $Ph_3P{=}CHCO(CH_2)_3OCH(Me)OEt$, PhMe, 80°C; j, H_2, PtO_2, MeOH; k, H_2, Pd/C, MeOH; l, 0.5M HCl in CH_2Cl_2 (2.5:1); m, $LiEt_3BH$, $CHCl_2$, –78°C, then $NaHCO_3$, 35% H_2O_2; n, EtOH, $CHCl_3$, reflux; o, $H_2C{=}CHCH_2SIMe_3$, $TiCl_4$, CH_2Cl_2, –78°C to rt; p, 30% aq. KOH, diozane, reflux; q, $ClCO_2Bn$, $NaHCO_3$, CH_2Cl_2; r, *p*-TsCl, Et_3N, CH_2Cl_2; s, Pr_2CuLi, Et_2O, –20°C; t, OsO_4 (cat.), $NaIO_4$, THF–H_2O (1:1).

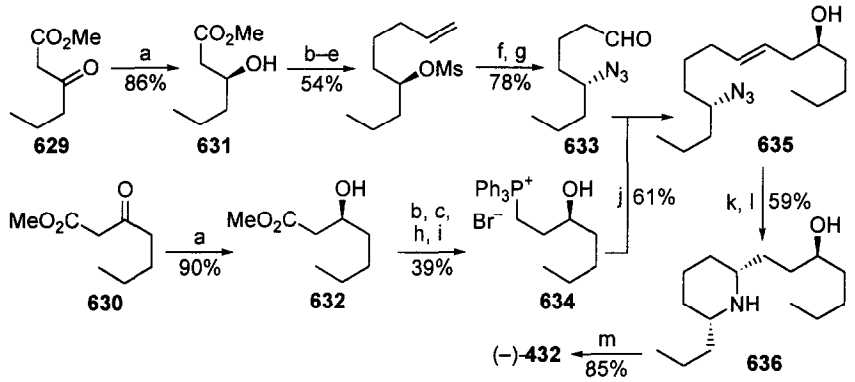
in the presence of titanium tetrachloride gave the allylated compound **621** diastereoselectively (*ca* 95:5) in 90% yield. Manipulation of the oxazolidinone ring led to the 2,5-*trans*-disubstituted pyrrolidine **622**, which was transformed into aldehyde **617** by chain extension at the *p*-toluenesulfonyloxymethyl substituent and oxidative cleavage of the alkene. This synthesis not only converged with the illustrated route to (−)-**596**, but also completed a formal synthesis of (−)-indolizidine 223AB (**432**) (*482*).

(*S*)-(−)-Pyroglutamic acid also served as the starting material in the synthesis of (−)-**432** by Pilli *et al.* (Scheme 82) (*369*). In this case, the butyl substituent was elaborated at an early stage in the transformation of **623** into **624**. The key reaction, however, was a condensation between the *N*-acyliminium ion derived from the 2-ethoxylactam **625** and trimethylsilyl enol ether **626**, which yielded a 3:2 mixture of the indolizidin-7-ones **627** and **628**. The distribution was swung in favor of **628** by equilibration with aqueous ammonia in methanol at room temperature. Deoxygenation of the ketone group of **628** by reduction of the corresponding *p*-toluenesulfonylhydrazone completed the synthesis of (−)-**432**.

Taber and co-workers developed a convergent route to (−)-**432** based on the enantioselective hydrogenation of the β-ketoesters **629** and **630** over a ruthenium–BINAP catalyst, which introduced two of the required stereogenic centers with excellent enantioselectivity (ee 98%) (Scheme 83) (*485*). The products **631** and **632** were transformed into aldehyde **633** and phosphonium salt **634**, respectively, after



SCHEME 82. Reagents: a, $Pr_2Cu(CN)Li_2$, THF, –40°C to rt; b, LDA, THF, –78°C, then $(Boc)_2O$, THF, –78°C to rt; c, $NaBH_4$, EtOH, –23°C, then HCl, EtOH; d, TMSOTf, CH_2Cl_2, –78°C to rt; e, NH_4OH, MeOH, rt; f, *p*-$TsNHNH_2$, EtOH; g, $NaBH_4$, EtOH, 0°C to reflux.

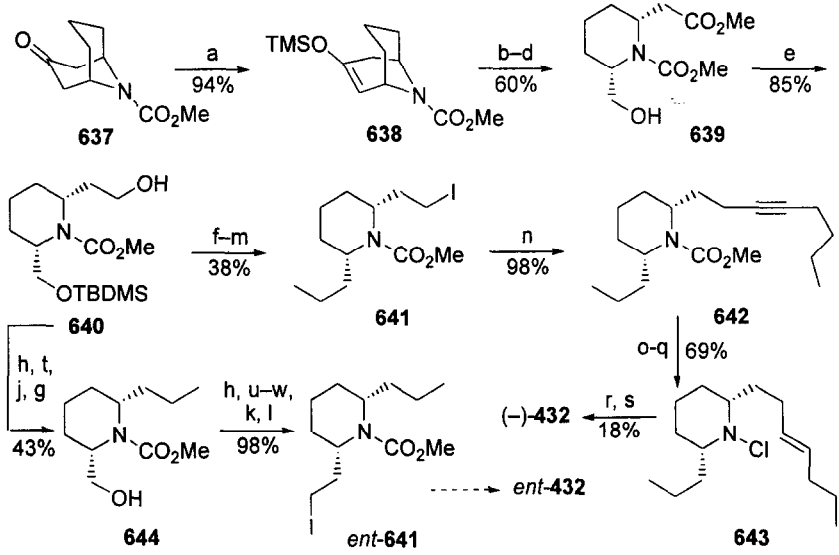


SCHEME 83. Reagents: a, Ru–BINAP, H_2 (50 psi), MeOH, Dowex-50, 80°C; b, $LiAlH_4$, THF, 0°C to rt; c, *p*-TsCl, pyridine, NEt_3, CH_2Cl_2, 0°C; d, $H_2C{=}CHCH_2MgCl$, THF, reflux; e, MsCl, Et_2O, 0°C; f, NaN_3, HMPA, 40°C; g, O_3, MeOH, –78°C, then Me_2S; h, $MgBr_2$, THF, 0°C to rt; i, PPh_3, MeCN, 150°C (sealed tube); j, $LiN(SiMe_3)_2$ (2.2 eq) + **634**, THF, 0°C, then add aldehyde **633**, –78°C to 0°C; k, 1,2-$Cl_2C_6H_4$, 160°C (sealed tube); l, DIBAL-H, CH_2Cl_2, –78°C to 0°C; m, PPh_3, CCl_4, NEt_3, MeCN, 0°C to rt.

which a Wittig reaction between them yielded the azido-alkene **635**. Intramolecular dipolar cycloaddition followed by reduction produced the 2,6-*cis*-disubstituted piperidine **636**, which was cyclized *via* the corresponding chloride with inversion of configuration to give the target alkaloid (–)-**432**. Most unusually, this interesting synthesis made no use of protecting groups.

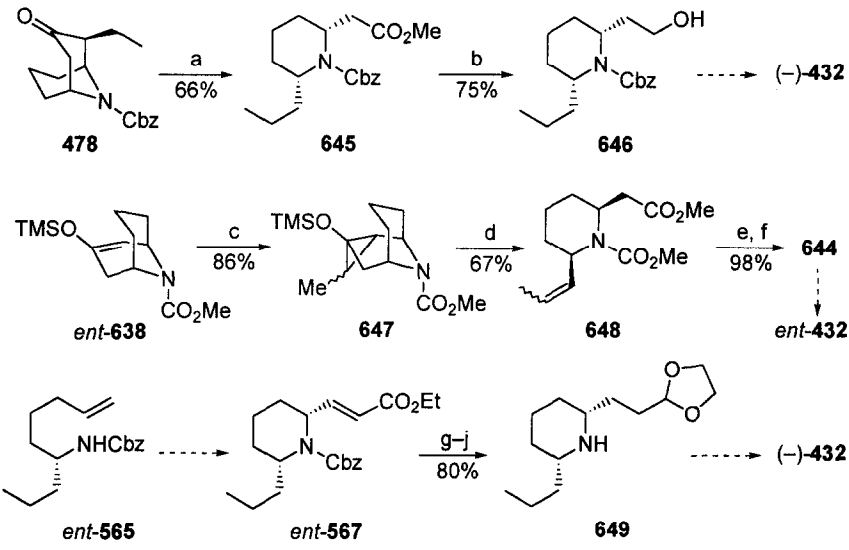
Momose *et al.* have reported a synthesis of both enantiomers of indolizidine 223AB (**432**) by a route that is very similar to the one by which they prepared (+)-monomorine I (*cf.* Scheme 61) (*407*). Desymmetrization of the azabicyclo[3.3.1]-

nonan-3-one **637** by enantioselective deprotonation with Koga's base (*417*) followed by ozonolysis of the silyl enol ether **638** yielded the 2,6-*cis*-disubstituted piperidine **639** (Scheme 84) (*406*). Chain extensions on both sides of the ring were accomplished *via* alcohol **640** to give iodide **641**, coupling of which with pent-1-ynyllithium produced **642**. Treament with sodium in ammonia effected partial reduction of the triple bond to the (*E*)-alkene, while removal of the *N*-protecting group and treatment with *N*-chlorosuccinimide yielded the pivotal intermediate **643**. The indolizidine nucleus was formed by stereoselective cyclization of the aminyl radical derived from **643** on to the alkene. Dechlorination of the resulting product completed this unusual synthesis of (−)-**432**. An engaging feature of this route is that a different set of manipulations on the alcohol **640** effectively permitted 'switching' of the C-2 and C-6 substituents, the hydroxyethyl group serving as the precursor of the propyl substituent in **644**. A more extensive range of transformations at the hydroxymethyl group culminated in the formation of *ent*-**641**, thereby realizing a formal synthesis of the unnatural (+)-enantiomer of indolizidine 223AB (*ent*-**432**).



SCHEME 84. Reagents: a, (1*R*)-*N*-(*tert*-butyl)-*N*-lithio-2-(4-methyl-1-piperazinyl)-1-phenylethylamine (Koga's base), HMPA, THF, −100°C, then TMSCl; b, O_3, CH_2Cl_2–MeOH (10:1), −78°C; c, $NaBH_4$, −78°C; d, CH_2N_2, Et_2O, 0°C to rt; e, $LiEt_3BH$, THF, 0°C to rt; f, MOM-Cl, CH_2Cl_2, $EtNPr^i_2$, 0°C to rt; g, Bu_4NF, THF, 0°C to rt; h, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78°C to 0°C; i, $Ph_3P{=}CHMe$, THF, 0°C to rt; j, H_2 (1 atm), 5% Pd/C, MeOH; k, conc. HCl, MeOH, 60°C; l, MsCl, pyridine, CH_2Cl_2; m, NaI, Me_2CO; n, $Me(CH_2)_2C{\equiv}CLi$, THF, 0°C to rt; o, Na, NH_3, −50°C, then aq. NH_4Cl; p, PrSLi, HMPA, THF, 0°C; q, NCS, Et_2O, 0°C; r, CuCl, $CuCl_2$, THF, AcOH, −45°C; s, Bu_3SnH, AIBN, C_6H_6, reflux; t, $Ph_3P{=}CH_2$, THF, 0°C to rt; u, $Ph_3P{=}CHOMe$, THF, 0°C to rt; v, conc. HCl, CH_2Cl_2; w, $NaBH_4$, MeOH, 0°C to rt.

The desymmetrization of azabicyclic ketones was also the principal feature in two additional formal syntheses of indolizidine 223AB by research associates of Momose. Once again using the ethyl-substituted product **478** (*cf.* Scheme 61) as a key intermediate, Muraoka *et al.* applied a Norrish I photocleavage in methanol to produce the 2,6-*cis*-disubstituted piperidine **645** in 66% yield (Scheme 85) (*486*). Reduction of the ester group with diisobutylaluminum hydride gave alcohol **646**, an intermediate in an earlier synthesis of (−)-**432** by Momose *et al.* (*487*). Kirihara *et al.* cyclopropanated the enantiomer of silyl enol ether **638** with 1,1-diiodoethane under Simmons–Smith conditions to give the tricyclic product (+)-**647** as a 1:1 mixture of methyl epimers (*488*). Oxidative ring cleavage of the cyclopropanol unit was accomplished under acid catalysis with phenyliodine(III) bis(trifluoroacetate) in methanol to produce the 2,6-*cis*-disubstituted piperidine **648** in 67% yield. A further two steps yielded alcohol **644** *en route* to (+)-indolizidine 223AB (*ent*-**432**) (*407*). A third formal synthesis of **432**, by Tahakata *et al.*, used methodology similar to that previously illustrated in Scheme 73 (*453*). In this route, the alkene *ent*-**565** (made from D-norvaline) was converted *via* the 2,6-*cis*-disubstituted piperidine *ent*-**567** into **649**, a compound that Royer and Husson had converted into (−)-**432** as long ago as 1985 (*489*).



SCHEME 85. Reagents: a, hv, Pyrex filter, MeOH; b, DIBAL-H, −10°C; c, Et_2Zn, CH_3CHI_2, CH_2Cl_2; d, $PhI(OCOCF_3)_2$, MeOH, cat. CF_3SO_3H; e, H_2, 5% Pd/C, MeOH; f, $LiEt_3BH$, THF, 0°C; g, Red-Al®, CuBr; h, DIBAL-H; i, *p*-TsOH, $(CH_2OH)_2$; j, H_2, $Pd(OH)_2$.

c. 5,8-Disubstituted indolizidine alkaloids and 1,4-disubstituted quinolizidine alkaloids. Alkaloids in this group that have recently capitulated to total synthesis include (±)-quinolizidine 217A (**515**) and the (*5R*,*8R*,*8aS*)-(−)-indolizidines 205A (**650**), 207A (**651**), 209B (**652**), 235B' (**653**), and 235B" (also known as 235B) (**654**), as well as and the hitherto imperfectly characterized indolizidine 223J (**655**) (Fig. 9). The absolute configurations of natural levorotatory **650**, **651**, and **653** have been established conclusively by synthesis. However, the optical rotation of natural **654** apparently has a positive sign (*4*); this is probably due to a dextrorotatory impurity in the natural sample, since it is most unlikely that the natural product has an anomalous absolute configuration (*2*). Although the optical rotation and relative configuration of the trace alkaloid **652** remain unknown, the illustrated structure is generally taken to be correct by analogy with its more fully investigated congeners. Enantioselective syntheses of amphibian 5-substituted 8-methylindolizidine alkaloids published up to 1993 were reviewed in Volume 44 of this series (*2*), but relatively few syntheses of racemic alkaloids have been published (*437,438,447,490,491*). Related work of relevance includes the synthesis of two (+)-8-ethyl-5-propylindolizidines **656** and **657** by Marazano and co-workers (*492*).

Taber and co-workers used geraniol (**658**) as the starting material in their synthesis of (−)-indolizidine 207A (**651**) (Scheme 86) (*493*). Sharpless asymmetric epoxidation of the allylic alcohol followed by diastereoselective reductive cleavage of the strained ring introduced the stereogenic centers at the future C-8 and C-8a sites with the formation of diol **659**. Chain extension with allylmagnesium chloride *via* an epoxide intermediate produced dienol **660**. Once the alcohol group had been displaced by azide ion with inversion of configuration, the internal double bond of product **661** was epoxidized, and the terminal bond was cleaved with ozone. Reduc-

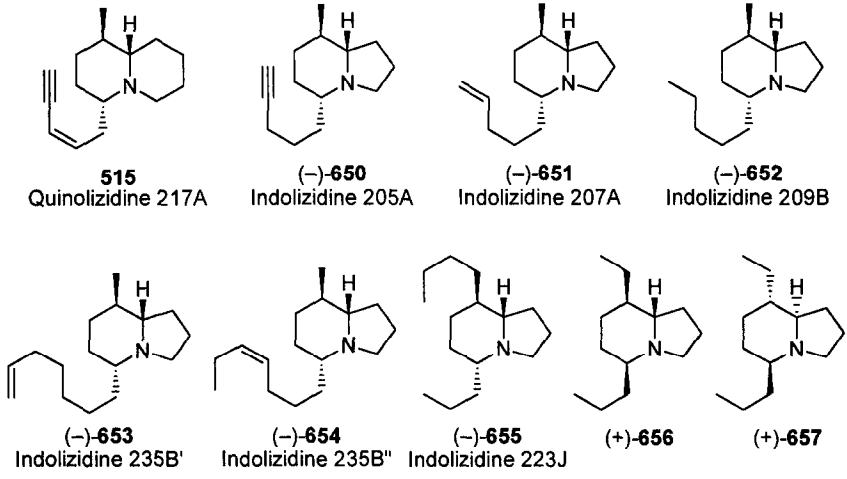
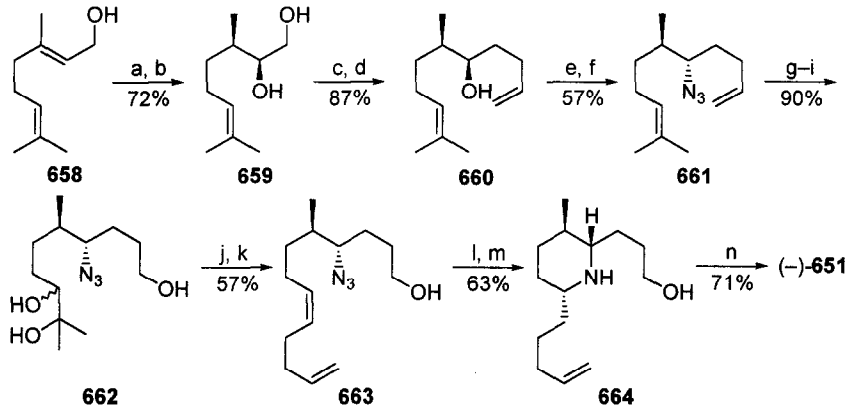
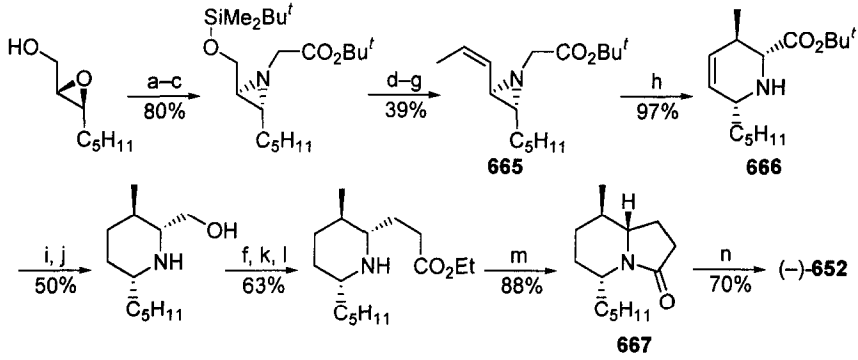


FIG. 9. Recently synthesized 1,4-disubstituted quinolizidine and 5,8-disubstituted indolizidine alkaloids and related compounds.



SCHEME 86. Reagents: a, Sharpless asymmetric epoxidation; b, $NaBH_3CN$, $BF_3{\cdot}Et_2O$; c, *p*-TsCl, CH_2Cl_2, NaOH (aq., 50%), 0°C to rt; d, $H_2C{=}CHCH_2MgCl$, THF, 0°C to rt; e, MsCl, NEt_3, Et_2O, 0°C; f, NaN_3, HMPA, 40°C; g, *m*-CPBA, CH_2Cl_2, –10°C; h, O_3, MeOH, Sudan III indicator, –78°C, then $NaBH_4$; i, $HClO_4$ (aq., 5%), THF; j, $NaIO_4$–SiO_2, CH_2Cl_2; k, $H_2C{=}CH(CH_2)_2CH{=}PPh_3$, THF, –78°C to rt; l, 1,2-$Cl_2C_6H_4$, 160°C; m, DIBAL-H, CH_2Cl_2, –65°C to 0°C, then NaF; n, PPh_3, NEt_3, CCl_4, MeCN.

tion of the resulting carbonyl group and hydrolysis of the epoxide yielded triol **662**. Periodate cleavage of the 1,2-diol component and Wittig reaction of the unmasked aldehyde yielded azidodiene **663**. Intramolecular dipolar cycloaddition followed by reduction with diisobutylaluminum hydride took care of the requisite stereochemistry at the remaining stereogenic center; the all-equatorially trisubstituted piperidine **664** was isolated free of isomers in 63% yield. Straightforward ring closure completed the synthesis of (–)-**651**.

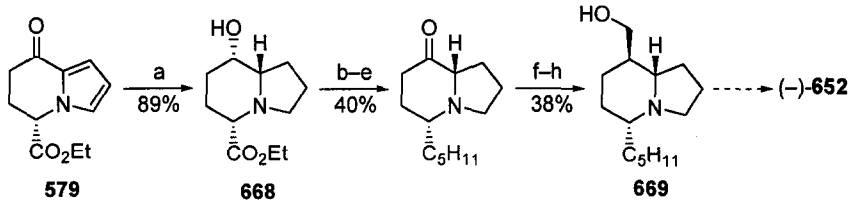


SCHEME 87. Reagents: a, NaN_3, NH_4Cl, $MeOCH_2CH_2OH$–H_2O, reflux; b, TBDMSCl, DMAP, NEt_3, CH_2Cl_2; c, PPh_3, PhMe, reflux; d, $BrCH_2CO_2Bu^t$, 18-crown-6, K_2CO_3, THF; e, $Bu_4NF{\cdot}3H_2O$, THF; f, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78°C; g, $Ph_3P{=}CHMe$, THF; h, LDA, THF, –78°C; i, H_2 (1 atm.), 5% Pd/C, EtOH; j, $LiAlH_4$, THF, 0°C to rt; k, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, –78°C to rt; l, H_2 (4 kg cm^{-1}), 10% Pd/C, EtOH; m, Me_3Al (1M in hexane), C_6H_6, rt to reflux; n, $LiAlH_4$, THF, reflux.

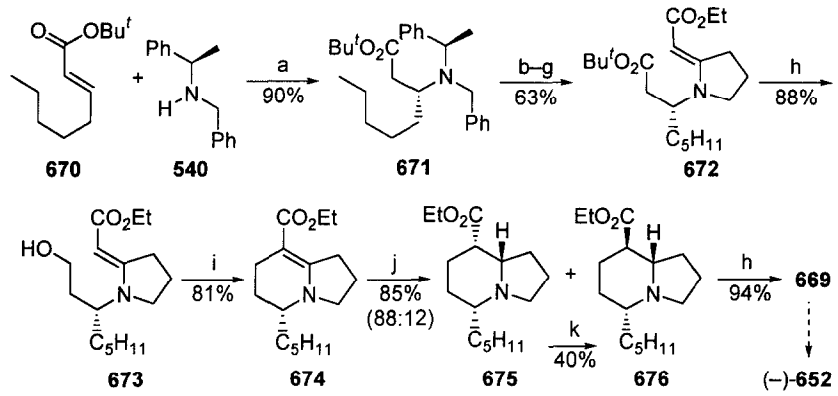
The most frequently synthesized 5,8-disubstituted indolizidine alkaloid is alkaloid 209B, the saturated compound (−)-**652**. Three of the new syntheses of this compound are akin in many respects to syntheses of simpler amphibian alkaloids described earlier in this section. Åhman and Somfai, for example, devised a synthesis of the alkaloid (Scheme 87) that paralleled their approach to (−)-indolizidine 209D (**525**) (*cf.* Scheme 76) (*464*). At the heart of their strategy was the aza-[2,3]-Wittig rearrangement of vinylaziridine **665**. The rearrangement was initiated by treatment with lithium diisopropylamide, and produced the unsaturated trisubstituted piperidine **666** as a single diastereomer in 97% yield. The three stereogenic centers in this compound possess the correct absolute configuration for the target alkaloid. Standard chemical transformations and cyclization yielded the indolizidin-3-one **667**, which was reduced with lithium aluminum hydride to complete the synthesis of (−)-**652**.

The route to (−)-**652** by Jefford and co-workers proceeded *via* the 5,6,7,8-tetrahydroindolizin-8-one **579**, which had also been used in their synthesis of (−)-indolizidine 209D (**525**) (*cf.* Scheme 75) (*459,460*). In the present case, hydrogenation over rhodium on alumina in ethanol containing a trace of acid stereoselectively reduced the pyrrole ring and the ketone to give indolizidinol **668** (89%); very little hydrogenolysis (5%) to **580** occurred under these conditions (Scheme 88). The alcohol **668** was transformed in seven steps into **669**, which previously featured in the pioneering synthesis of (−)-indolizidine 209B (**652**) by Holmes and co-workers (*438*).

A synthesis of (±)-indolizidine 209B by Michael and Gravestock (*491*) was subsequently modified to give the levorotatory alkaloid (*447*). Conjugate addition of the anion of (*R*)-*N*-benzyl-1-phenylethylamine (**540**) to *tert*-butyl (*E*)-oct-2-enoate (**670**) afforded **671** as the only detectable diastereomer (Scheme 89). The synthesis thereafter paralleled that previously illustrated in Scheme 70 for (−)-indolizidine 167B (**524**) up to the vinylogous urethane **672**. Chemoselective reduction of the saturated ester group gave alcohol **673**, which was cyclized *via* the corresponding primary alkyl iodide to give the unsaturated indolizidine **674**. Catalytic hydrogenation produced an 88:12 mixture of esters **675** and **676**; but the former could be epimerized to the latter with sodium ethoxide. Reduction of the ester group finally yielded **669**, thereby completing a formal synthesis of (−)-**652**, as described above.

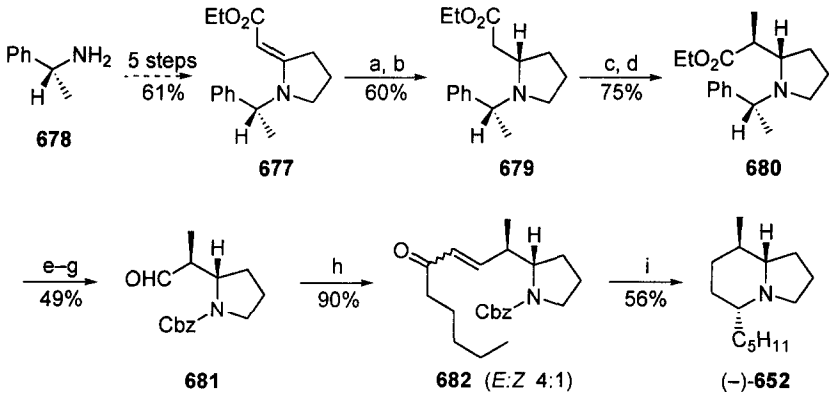


SCHEME 88. Reagents: a, H_2 (55 psi), 5% Rh/Al_2O_3, EtOH–AcOH (99:1), rt; b, DIBAL-H, Et_2O, –70°C, then MeOH, –70°C to reflux; c, Ph_3P=CHPr, THF, –78°C; d, H_2 (40 psi), PtO_2, EtOAc; e, Jones oxidation; f, Ph_3P=CHOMe, THF, –78°C; g, 6M HCl, Et_2O; h, $NaBH_4$, EtOH.



SCHEME 89. Reagents: a, **540** + BuLi, THF, –78°C, then **670**; b, H_2 (7 atm), 10% Pd/C, HOAc; c, $Cl(CH_2)_3COCl$, $NaHCO_3$, $CHCl_3$; d, KOBu^t, Bu^{t}OH; e, Lawesson's reagent, PhMe, reflux; f, $BrCH_2CO_2Et$, MeCN; g, Ph_3P, Et_3N, MeCN; h, $LiAlH_4$, THF; i, I_2, imidazole, Ph_3P, MeCN; j, H_2 (1 atm), PtO_2, AcOH; k, NaOEt (cat.) EtOH, reflux.

Another chiral vinylogous urethane, **677**, played a central role in the synthesis of (–)-**652** by Lhommet and co-workers (Scheme 90) (*494*). This compound, prepared from (*R*)-α-methylbenzylamine (**678**) (*495*), was diastereoselectively hydrogenated over platinum oxide to give the amino-ester **679** (de >95%). More significantly, methylation of the anion of **679** under conditions of kinetic control afforded **680** (de *ca* 98%) in 33% overall yield from the chiral amine (*496*). Wittig reaction of the aldehyde derivative **681** with the stabilized ylide 1-(triphenylphosphoranylidene)-2-heptanone yielded **682** (90%) as a 4:1 mixture of *E* and *Z* isomers. When this product



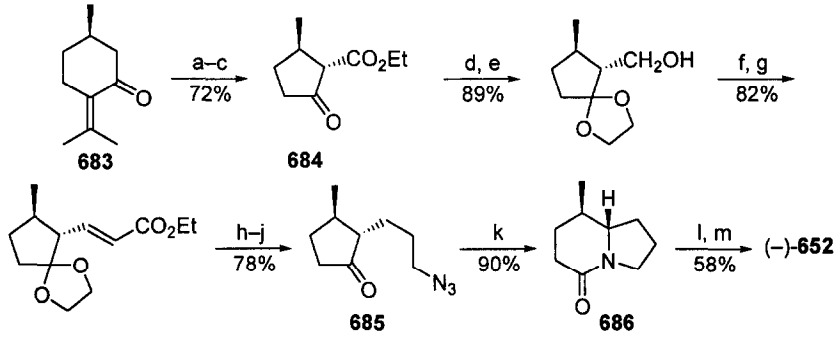
SCHEME 90. Reagents: a, H_2, PtO_2; b, picric acid, recrystallization from hexane, then K_2CO_3; c, LDA, THF, –78°C; d, MeI, –70°C; e, H_2, Pd/C, EtOH; f, $ClCO_2Bn$, K_2CO_3, $CHCl_3$; g, DIBAL-H, PhMe –78°C; h, $Ph_3P{=}CHCOC_5H_{11}$, PhMe, 80°C; i, H_2, PtO_2, MeOH, 50°C.

was treated with hydrogen and platinum oxide at 50°C, four transformations (hydrogenation of the alkene, cleavage of the *N*-protecting group, cyclization, and diastereoselective reduction of the ensuing iminium ion intermediate) occurred in a one-pot process to give (−)-**652** in 56% yield after separation from a minor isomer. The entire sequence from the (*R*)-amine **678** to (−)-indolizidine 209B proceeded in 8% overall yield.

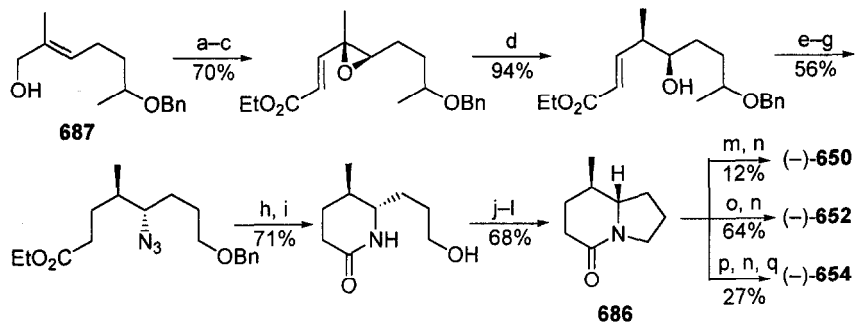
Aubé and co-workers approached the synthesis of (−)-**652** by transforming (*R*)-(+)-pulegone (**683**) into the ring-contracted β-keto-ester **684**, following which side-chain homologation and functional group interconversions yielded the keto-azide **685** (Scheme 91) (*497*). Intramolecular Schmidt reaction under acidic conditions was regioselective, and gave the bicyclic lactam **686** in 90% yield after recrystallization. Addition of *n*-pentylmagnesium bromide was followed by reduction of the ensuing iminium ion intermediate from the pseudoaxial direction, as expected, to yield (−)-**652** in an overall yield of 22% based on pulegone.

Syntheses of several 5,8-disubstituted indolizidine alkaloids from a single pivotal intermediate have been reported by a number of groups. Satake and Shimizu began a twelve-step synthesis of the bicyclic lactam **686** by asymmetric epoxidation of alcohol **687** under Sharpless conditions (Scheme 92) (*498*). Addition of Grignard reagents to **686** followed by reduction of the intermediate iminium ions with sodium cyanoborohydride at pH 3 completed syntheses of (−)-indolizidines 205A (**650**), 209B (**652**), and 235B" (**654**).

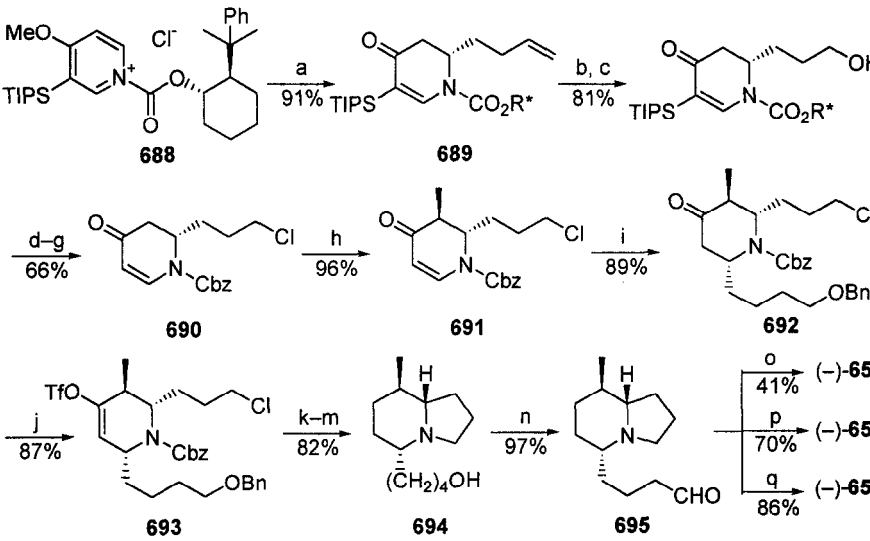
By incorporating a chiral auxiliary, (+)-*trans*-2-(α-cumyl)cyclohexyl (TCC), into pyridinium salt **688**, Comins and co-workers were assured of excellent asymmetric induction in a divergent synthesis of three 5,8-disubstituted amphibian indolizidine alkaloids (Scheme 93) (*467,499*). Addition of but-3-enylmagnesium bromide to **688** yielded the dihydropyridone **689** as a single diastereomer in 91% yield after recrystallization. After a series of functional group manipulations, the C-8 methyl group was introduced stereoselectively by enolate alkylation (**690** → **691**),



SCHEME 91. Reagents: a, Br_2; b, NaOMe; c, O_3, Me_2S; d, $HOCH_2CH_2OH$, H^+; e, $LiAlH_4$; f, PCC, CH_2Cl_2; g, $(EtO)_2POCH_2CO_2Et$, DBU, LiBr, MeCN; h, Li, NH_3, EtOH, Et_2O; i, HN_3, DEAD, PPh_3, C_6H_6, 0°C; j, $LiBF_4$, MeCN, H_2O (2%); k, TFA, 0°C, then recrystallization from hexane; l, $C_5H_{11}MgBr$, Et_2O, 0°C to rt, then HOAc; m, $NaBH_4$.



SCHEME 92. Reagents: a, $Ti(OPr^i)_4$, (–)-DET, Bu^tOOH, CH_2Cl_2; b, DMSO, $(COCl)_2$, CH_2Cl_2; c, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0°C; d, $Pd_2(dba)_3CHCl_3$, Bu_3P, HCO_2H, Et_3N, dioxan; e, *p*-TsCl, pyridine, DMAP, CH_2Cl_2; f, H_2 (1 atm), Pd/C, Et_3N, EtOAc; g, NaN_3, DMF; h, H_2 (1 atm), Pd/C, EtOAc; i, H_2 (1 atm), Pd/C, EtOH; j, MsCl, Et_3N, CH_2Cl_2; k, NaI, Me_2CO; l, NaH, THF; m, $Me_3SiC{\equiv}C(CH_2)_3MgBr$, THF; n, $NaBH_3CN$, pH 3, MeOH; o, $Me(CH_2)_4MgBr$, THF; p, (*Z*)-$MeCH_2CH{=}CH(CH_2)_2MgBr$, THF; q, Bu_4NF.

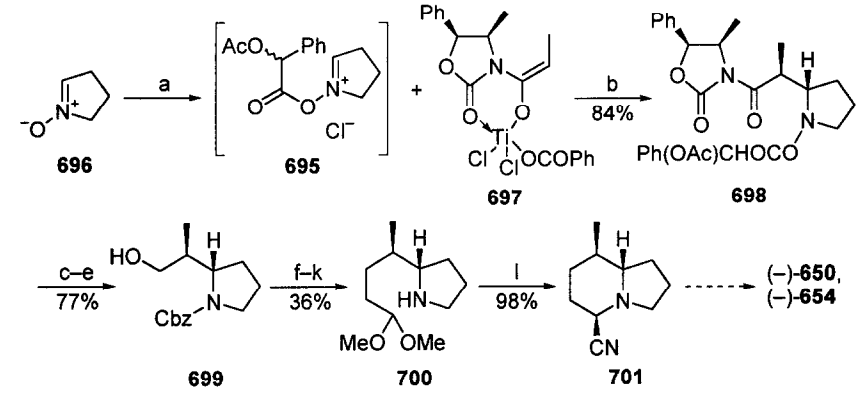


SCHEME 93 [R* = (+)-*trans*-2-(α-cumyl)cyclohexyl]. Reagents: a, $H_2C{=}CH(CH_2)_2MgBr$, THF, –78°C; b, OsO_4 (cat.), $NaIO_4$, H_2O–THF (1:1); c, L-Selectride, THF, –78°C; d, NaOMe, MeOH, reflux; e, 10% aq. HCl; f, BuLi, THF –78°C, then $ClCO_2Bn$; g, Ph_3P, NCS, CH_2Cl_2, –42°C to rt; h, LiHMDS, THF, –78°C, then MeI, –78°C to rt; i, $BnO(CH_2)_4MgBr$, $CuBr{\cdot}SMe_2$, $BF_3{\cdot}Et_2O$, THF –78°C; j, LiHMDS, THF, –78°C, then *N*-(2-pyridyl)triflimide; k, H_2 (1 atm), 5% Pt/C, EtOH; l, H_2 (1 atm), 20% $Pd(OH)_2/C$, EtOH; m, Na_2CO_3, EtOH, reflux; n, Dess–Martin periodinane, CH_2Cl_2; o, $(MeO)_2POCHN_2$, $KOBu^t$, THF, –78°C; p, $Ph_3P{=}CH_2$, THF, 0°C to rt; q, $Ph_3P{=}CHCH_2CH_3$, THF, –78°C to rt.

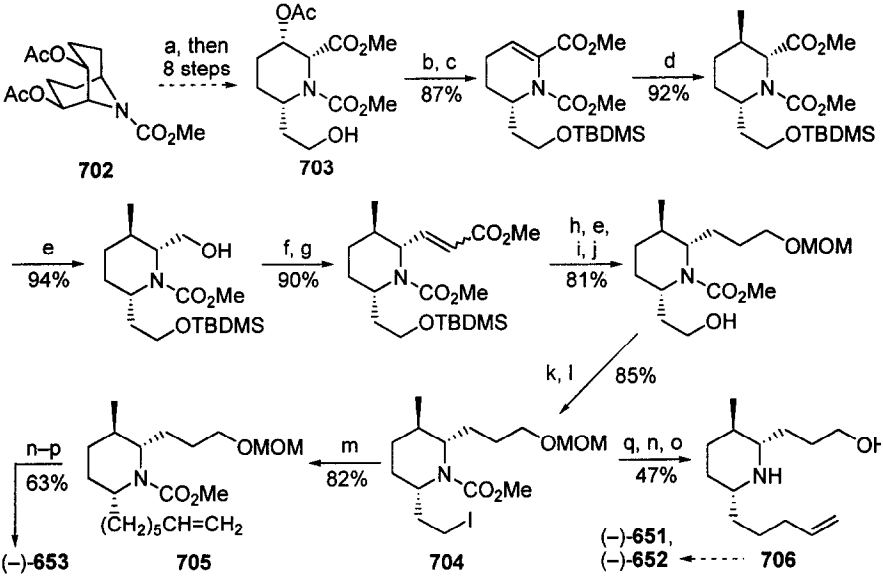
while the precursor of the C-5 substituent was attached by conjugate addition of a 4-benzyloxybutyl group to the enaminone (**691** → **692**). The indolizidine nucleus was formed from vinyl triflate **693** in a one-pot sequence involving defunctionalization of the vinyl triflate, removal of benzyl protecting groups, and cyclization to give the amino alcohol **694** in an overall yield of 82%. Oxidation of this compound with Dess–Martin periodinane yielded aldehyde **695**, which served as a common precursor for the three target alkaloids, (–)-indolizidines 205A (**650**), 207A (**651**), and 235B" (**654**).

A new asymmetric synthesis of β-aminoacids by the addition of enolates bearing chiral auxiliaries to *N*-acyloxyiminium ions has been applied by Murahashi and co-workers to the formal synthesis of 5,8-disubstituted indolizidine alkaloids (Scheme 94) (*500*). The iminium species **695** was prepared *in situ* by acylating the nitrone **696** with (±)-acetylmandelyl chloride, following which addition of the kinetically-generated titanium enolate of oxazolidinone **697** gave adduct **698** in 84% yield and an impressive de of 96%. Reductive cleavage of the N–O bond, protection at nitrogen, and removal of the chiral auxiliary yielded alcohol **699**, chain elongation and functional group manipulation of which produced the amino-acetal **700**. Treatment with potassium cyanide and acid efficiently gave the indolizidine-5-carbonitrile **701** (98% yield), an intermediate previously used by Polniaszek and Belmont in their 1991 synthesis of (–)-indolizidines 205A (**650**) and 235B" (**654**) (*501*).

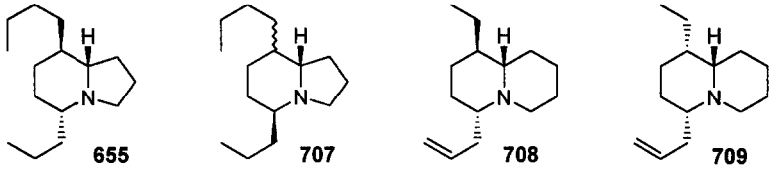
A communication by Momose and Toyooka on the synthesis of three 5,8-disubstituted indolizidine alkaloids (*502*) was later expanded to include approaches to several related indolizidines and quinolizidines (*503*). The synthesis commenced with lipase-catalyzed hydrolytic desymmetrization of the *meso* bicyclic diacetate **702**, the product of which was transformed in eight steps into the chiral piperidine (–)-**703** (Scheme 95) (*504*). A further twelve steps involving a series of functional group interconversions and chain extensions produced the focal iodoalkyl intermediate **704** in an overall yield of 49% from **703**. Copper(I)-catalyzed cross-coupling of this intermediate with pent-4-enylmagnesium bromide yielded **705**, which was deprotected and cyclized to complete the first total synthesis of (–)-indolizidine 235B' (**653**). Alternatively, coupling of **704** with allylmagnesium chloride yielded the trisubstituted piperidine **706**, which had previously been converted into (–)-indolizidines 207A (**651**) and 209B (**652**) by Shishido and Kibayashi (*505*). An interesting feature of this route is the light that it has cast on the structures of several other minor amphibian alkaloids of uncertain structure. For example, suitable synthetic modifications provided access to the (–)-indolizidine **655**, the IR spectrum of which was essentially identical to that of indolizidine 223J, a very minor frog skin alkaloid. In particular, Bohlmann bands in the spectrum of the natural product suggested the *cis*-diaxial relative configuration of the hydrogen atoms at C-5 and C-8a. Another trace alkaloid, indolizidine 223I, lacks Bohlmann bands; 5-H and 8a-H are thus probably *trans* to each other, and the tentative structure **707** has now been proposed for this compound. A different adaptation of the illustrated synthesis yielded the (–)-quinolizidine **708**, the spectroscopic properties of which did *not* agree with those of an imperfectly characterized alkaloid, quinolizidine 207I, despite the presence of Bohlmann bands in both the natural and the synthetic compounds. The tentative structure **709** has in consequence been suggested for quinolizidine 207I.



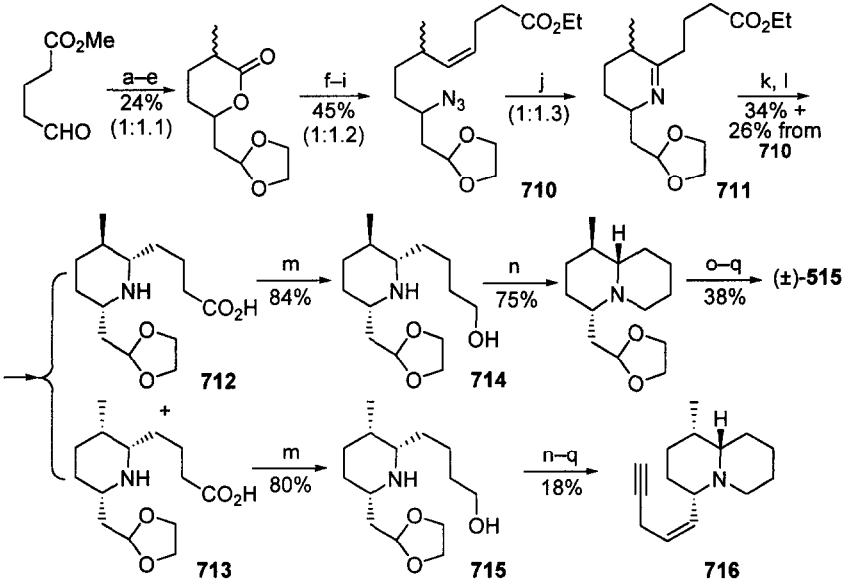
SCHEME 94. Reagents: a, (±)-PhCH(OAc)COCl; b, CH_2Cl_2, –78°C; c, Zn, 4M HCl, MeOH, 60°C; d, $ClCO_2Bn$, K_2CO_3, THF–H_2O (1:1); e, $NaBH_4$, THF–H_2O (1:1), 5°C; f, Ph_3P, CBr_4, THF, 0°C to rt; g, $NaCH(CO_2Et)_2$, DME, 60°C; h, NaCl, H_2O, DMSO, 170°C; i, DIBAL-H, CH_2Cl_2, –78°C; j, *p*-TsOH, MeOH, reflux; k, H_2 (1 atm), 10% Pd/C, MeOH; l, KCN, HCl (pH 3), CH_2Cl_2–H_2O (1:1).



SCHEME 95. Reagents; a, CE-lipase, 0.25M phosphate buffer, pH 7; b, TBDPSCl, DMAP, Et_3N; c, NaH, DMF, C_6H_6, 0°C to 50°C; d, Me_2CuLi, Et_2O, –78°C to –30°C; e, $LiEt_3BH$, THF, 0°C; f, $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, –78°C to 0°C; g, $(EtO)_2POCH_2CO_2Me$, NaH, THF, 0°C; h, H_2 (4 atm), 5% Pd/C, MeOH; i, MOM-Cl, Pr^i_2NEt, CH_2Cl_2, 0°C to rt; j, Bu_4NF, THF, 0°C to rt; k, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C; l, NaI, Me_2CO, 50°C; m, $H_2C{=}CH(CH_2)_3MgBr$, CuI, THF, –40°C to –30°C; n, LiSPr, HMPA, THF, 0°C to rt; o, conc. HCl (cat.), MeOH, reflux; p, CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 0°C; q, $H_2C{=}CHCH_2MgCl$, CuI, THF, –40°C to –30°C.



Pearson and Suga have devised a potentially general approach to the amphibian 1,4-disubstituted quinolizidine alkaloids based on intramolecular azide cycloaddition (Scheme 96) (*506*). When the mixture of azide diastereomers **710** was heated in a sealed tube in benzene at 130°C, slow cycloaddition gave detectable triazoline intermediates that lost nitrogen gas to yield a 1:1.3 mixture of imine diastereomers **711**. Reduction of the imines was followed by ester hydrolysis to afford the carboxylic acids (±)-**712** and (±)-**713** in overall yields of 34% and 26%, respectively, from azide **710**. The relative configurations were assigned on the basis of literature precedents and analysis of coupling constants for the alcohols **714** and **715**, obtained



SCHEME 96. Reagents: a, $H_2C{=}CHCH_2SiMe_3$, $TiCl_4$, CH_2Cl_2, –78°C to –20°C; b, *p*-TsOH, C_6H_6, reflux, Dean–Stark trap; c, LDA, THF, –78°C, then MeI; d, OsO_4 (cat.), NMO, THF–Bu^{t}OH; e, $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, reflux, Dean–Stark trap; f, DIBAL, CH_2Cl_2, –78°C to rt; g, $Ph_3P(CH_2)_3CO_2Et^+\ Br^-$, KHMDS, THF, –78°C to 0°C; h, MsCl, Et_3N, CH_2Cl_2, –40°C to rt; i, $Bu_4N^+N_3^-$, THF; j, C_6D_6, 130°C, 66 h; k, $NaBH_4$, $PdCl_2$, EtOH, 0°C to rt; l, NaOH, EtOH, reflux, then chromatography on SiO_2; m, $LiAlH_4$, THF, 0°C to rt; n, CCl_4, Ph_3P, Et_3N, MeCN, 0°C to rt; o, 1M HCl, THF, 50°C; p, $Me_3SiC{\equiv}CCH_2TBDMS$, Bu^{t}Li, THF, –78°C, then $Ti(OPr^i)_4$, then substrate, –78°C to rt; q, Bu_4NF, THF, DMF.

by reduction of the acids. These alcohols were converted by routine transformations into the quinolizidines **515** and **716**, both of which showed the Bohlmann bands indicative of the *cis* relationship of the hydrogen atoms on C-4 and C-9a. The former product was spectroscopically and chromatographically identical to the natural quinolizidine 217A. Intriguingly, when the racemic synthetic material was resolved on a chiral GC column, the more highly retained enantiomer co-eluted with the natural product—but the absolute configuration still remains unknown for now.

d. Pumiliotoxins, allopumiliotoxins, and homopumiliotoxins. The relative structural complexity of the alkaloids belonging to this group has made them less amenable to synthesis than the other amphibian alkaloids described in this Section. Takahata and Momose described the comparatively few syntheses of these alkaloids published before 1992 in Volume 44 of this treatise (*2*). The structures of natural products whose total synthesis has subsequently been reported are shown in Fig. 10. They include (+)-pumiliotoxins 251D (**523**), 307A (**717**), and 323A (**718**), (+)-allopumiliotoxins 267A (**719**), 323B' (**720**), and 339A (**721**), and (+)-homopumiliotoxin 223G (**722**). As mentioned previously, total syntheses of pumiliotoxins and allopumiliotoxins were reviewed by Franklin and Overman in 1996 (*436*).

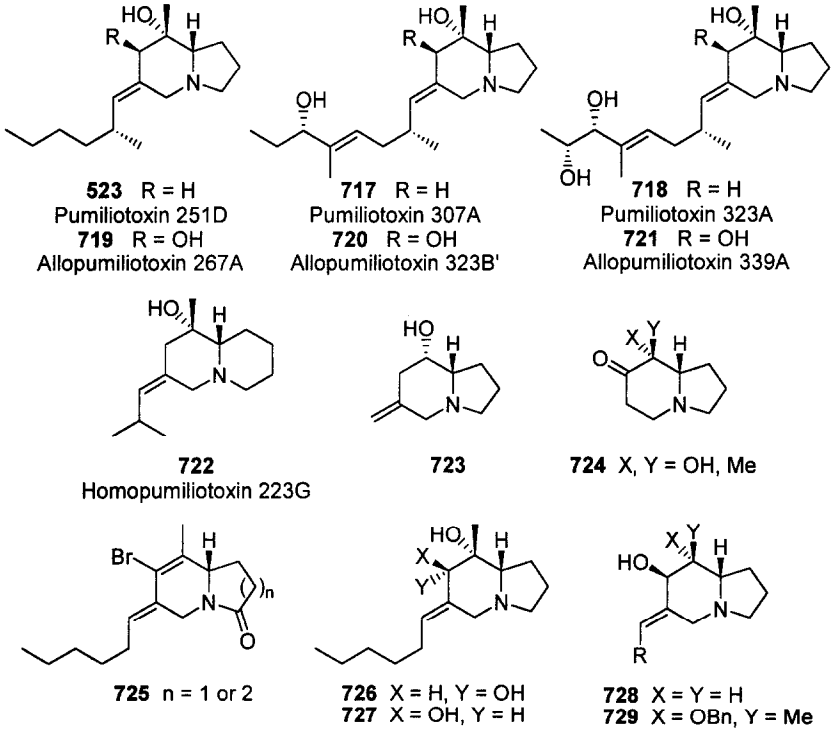
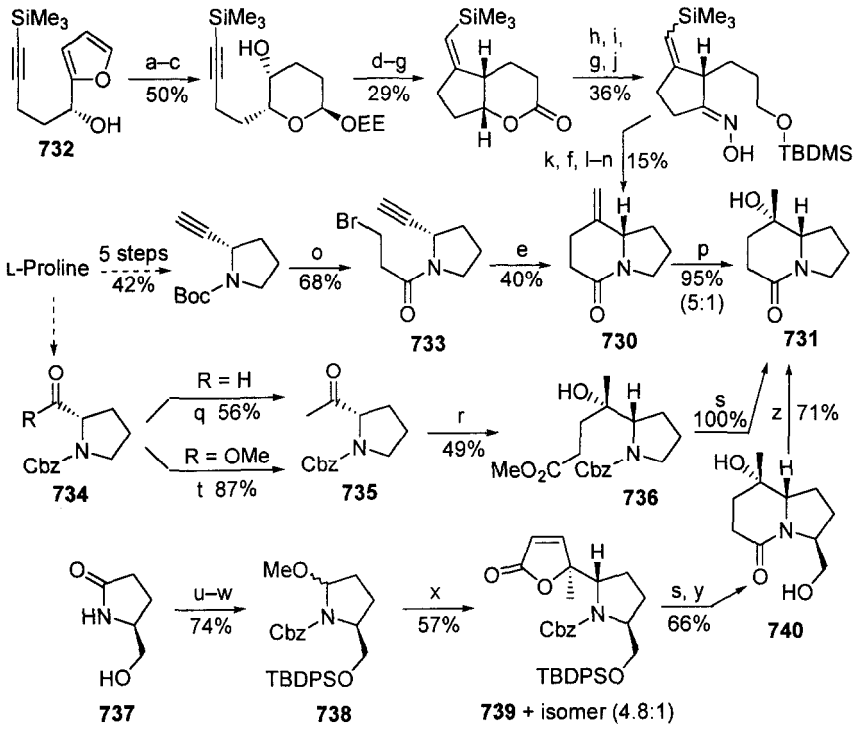


FIG. 10. Recently synthesized pumiliotoxins, allopumiliotoxins, homopumiliotoxins, and synthetic analogs.

Exploratory studies designed to facilitate access to alkaloids of the pumiliotoxin class are frequently of interest in their own right. Examples range from the preparation of simple pumiliotoxin models such as **723** (*507*) and **724** (*508*) to quite complex systems such as **725** (*509*). The crux of most model studies is methodological development, as exemplified by Overman's approaches to the allopumiliotoxin-like compounds **726** and **727** by vinylsilane–iminium ion cyclizations (*510*), and by Kibayashi's investigation of the use of organochromium(III) intermediates in forming indolizidines such as **728** and **729** (*511*) (*vide infra*). Previously developed methodology for making pumiliotoxin 251D (**523**) (*512,513*) has been adapted for the preparation of a range of diastereomers and analogs with modified side chains for toxicity studies towards insects (*434*).

All recent syntheses of pumiliotoxin 251D (**523**) are formal ones that converge with either or both of the two bicyclic lactams **730** or **731** that featured in the 1991 route to the alkaloid by Gallagher and co-workers (*514*). Some of the chiral precursors and key steps in these syntheses are shown in Scheme 97. The lengthy approach of Honda *et al.* began with the (*R*)-furfuryl alcohol **732**, which was obtained from the corresponding racemate by kinetic resolution under Sharpless epoxidation conditions in the presence of (+)-diisopropyl tartrate (*132,515*). Among the important subsequent transformations were oxidative cleavage of the furan ring, radical cyclization involving the alkynylsilane, and Beckmann rearrangement. Yields were affected by poor stereoselectivity in several of the intervening steps. A more economical synthesis by Cossy and co-workers used tributyltin hydride to induce a 6-*exo*-dig radical cyclization of the L-proline derivative **733** to give lactam **730** (40%) (*516,517*). Barrett and Damiani devised two alternative routes to alcohol **731** from L-proline derivatives **734** (*518*). The longer (seven steps, 19% overall yield) involved elaboration *via* aldehyde **734** (R = H) to the ketone **735**, reaction of which with a titanium(IV) homoenolate prepared *in situ* from 1-ethoxy-1-trimethylsilyloxycyclopropane and titanium tetrachloride yielded adduct **736** as a single diastereomer (49%). Hydrogenolysis of the *N*-protecting group was followed by spontaneous cyclization to **731** in quantitative yield. In the shorter route (six steps, 41% overall yield), the proline methyl ester **734** (R = OMe) was methylenated with the Tebbe reagent to give the same ketone **735** (87%) after acidic work-up. Martin and Bur transformed the pyroglutamic acid derivative **737** into the acyliminium ion equivalent **738** in three steps, following which a vinylogous Mannich condensation with 2-trimethylsilyloxyfuran was induced with Lewis acids (*519*). Both **739** and its C-5 epimer were produced, but the unwanted isomer was minimized by catalyzing the reaction with trimethylsilyl trifluoromethanesulfonate at 0°C (isomer ratio 4.8:1). Reduction of the double bond with concomitant *N*-deprotection and spontaneous lactone–lactam rearrangement gave the bicyclic lactam **740** (66%). Finally, an unusual removal of the hydroxymethyl substituent was accomplished by heating **740** with Raney nickel in toluene to give **731** in 71% yield.

The pioneering syntheses of the pumiliotoxins and allopumiliotoxins by Overman and his co-workers during the 1980s incorporated stereospecific vinylsilane–iminium ion cyclizations for making the (*Z*)-alkylidene-substituted indolizidine ring (*520,521*). The 'second-generation' syntheses by this group made

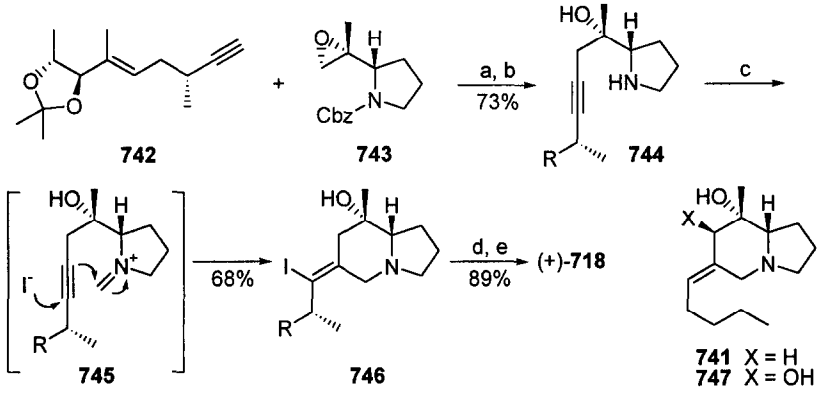


SCHEME 97. Reagents: a, NBS, NaOAc, THF–H_2O (4:1), 0°C; b, H_2C=CHOEt, PPTS, CH_2Cl_2, 0°C, then chromatography; c, $LiAlH_4$, CuI, THF–HMPA (1:1), –78°C, then $NaBH_4$, THF, 0°C; d, Im_2C=S, DMAP, $ClCH_2CH_2Cl$, reflux; e, Bu_3SnH, AIBN, C_6H_6, reflux; f, 2M HCl, THF, 0°C; g, PCC, NaOAc, celite, CH_2Cl_2, then chromatography; h, $LiAlH_4$, Et_2O; i, TBDMSCl, DMAP, Et_3N, CH_2Cl_2; j, NH_2OH·HCl, pyridine, MeOH, then chromatography; k, $SOCl_2$, THF, 0°C; l, MsCl, Et_3N, CH_2Cl_2, 0°C; m, K_2CO_3, dioxane–H_2O (4:1), 90°C; n, *p*-$TolSO_2H$, MeCN–H_2O (50:1), reflux; o, 8M HCl, EtOH, reflux, then $Br(CH_2)_2COCl$, Et_3N, 0°C; p, $Hg(OAc)_2$, H_2O, THF, then $NaBH_4$, aq. NaOH; q, MeMgBr, THF, –78°C to 0°C, then Jones reagent, Me_2CO, 0°C to rt; r, $TiCl_4$, 1-EtO-1-TMS-cyclopropane, CH_2Cl_2, 21°C, then add ketone **735**, –78°C to rt; s, H_2 (1 atm), 10% Pd/C, MeOH; t, $Cp_2Ti(Cl)CH_2AlMe_2$, THF–PhMe, 0°C to rt, then 1M HCl, Me_2CO; u, TBDPSCl, imidazole, DMF; v, $NaN(SiMe_3)_2$, THF, –78°C, then $ClCO_2Bn$, –78°C to rt; w, $NaBH_4$, MeOH, –10°C, then conc. HCl; x, 2-Me_3SiO-furan, TMS-OTf, Et_2O, 0°C; y, 1M HCl, MeOH; z, Raney Ni (W-2), PhMe, 140°C.

use of generally more effective iodide-promoted alkyne–iminium ion cyclizations. A preliminary communication on the synthesis of (+)-pumiliotoxin A (= pumiliotoxin 307A) (**717**) based on this methodology was reported in 1988 (*512*); full experimental details were subsequently published in a paper that also described syntheses of (+)-pumiliotoxin B (= pumiliotoxin 323A) (**718**) and the model compound nor-11-methylpumiliotoxin 237A (**741**) (*522*). Some of the significant late steps in the synthesis of (+)-**718** are shown in Scheme 98. The alkyne **742**, made in eight steps and 46% overall yield from (2*R*)-2-methylpent-4-enol, and the proline-derived epoxide **743** (a pivotal intermediate in several of the earlier

Overman syntheses) were coupled to give pyrrolidine **744** in 73% yield after removal of the protecting group on nitrogen. Treatment with paraformaldehyde in aqueous acidic medium generated the iminium ion intermediate **745** *in situ*. Iodide ion, present in a large excess in the reaction medium, induced a highly stereoselective cyclization by attacking the alkyne bond, which in turn reacted with the iminium ion. The best yields were obtained with pyridinium *p*-toluenesulfonate as the proton source; under these conditions, the acetonide protecting group was also removed. The isolated product, vinyl iodide **746**, was obtained as a single isomer in 68% yield. Since it proved to be light-sensitive, it was immediately deiodinated with *tert*-butyllithium followed by degassed aqueous ammonium chloride solution to give the target alkaloid (+)-pumiliotoxin 323A (**718**). This route to (+)-**718** was comparatively short and efficient (four steps and 44% overall yield based on **742** and **743**); it also yielded a reasonably large amount of the target, 500 mg of which was prepared for biological and structural investigations. Pumiliotoxin 307A (**717**) and model compound **741** were similarly prepared from the appropriate analogs of alkyne **742**.

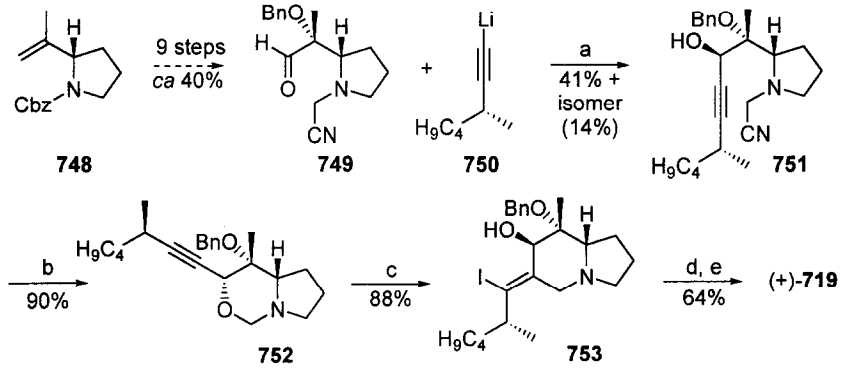
Iodide-promoted iminium ion–alkyne cyclization was also used by the Overman group for the synthesis of alkaloids of the allopumiliotoxin class. A communication on the synthesis of (+)-allopumiliotoxin 339A (**721**) (*523*) was highlighted in Volume 44 of this treatise (*2*). Full experimental details were later reported in a publication that included related syntheses of (+)-allopumiliotoxins 267A (**719**) and 323B' (**720**), as well as the unnatural analog nor-11-methylallopumiliotoxin 253A (**747**) (*524*). The syntheses all commenced with the same L-proline derivative **748**, which was transformed in nine steps and about 40% yield into the *N*-cyanomethylpyrrolidine **749**. Late steps in the synthesis of (+)-**719** are shown in Scheme 99. Chelation-controlled addition of the lithiated alkyne **750** (generated *in situ* from the corresponding 1,1-dibromoalkene) to the aldehyde group of **749** was fairly diastereoselective (3.5:1), yielding propargyl alcohol **751** with (*R*)



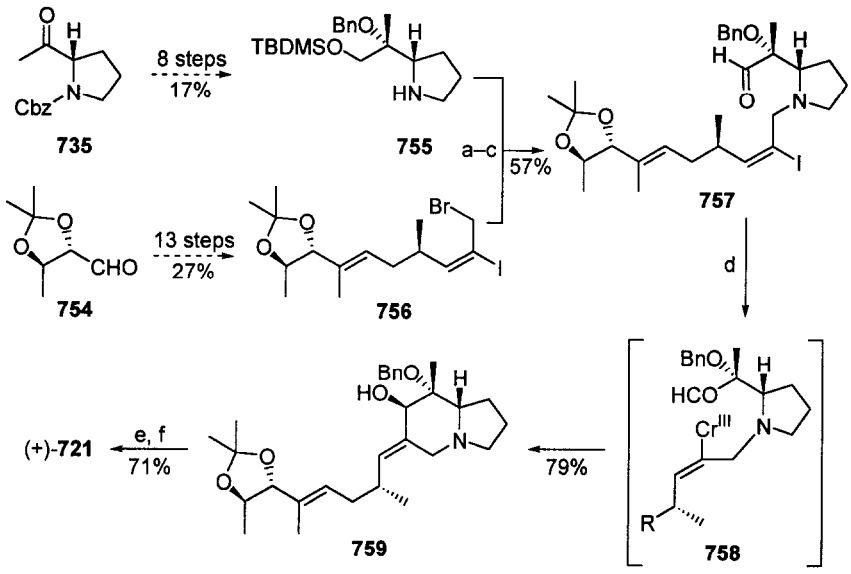
SCHEME 98. Reagents: a, *n*-BuLi (1 equiv), Et_2AlCl (1 equiv), PhMe–hexane, 0°C; b, $Ba(OH)_2$, H_2O–dioxane (1:1.5), 100°C; c, NaI (10 equiv), $(CH_2O)_n$ (5 equiv), PPTS (3 equiv), H_2O, 105°C; d, Bu'Li, THF, –78°C; e, aq. NH_4Cl.

absolute configuration at the newly created stereogenic center. The *N*-cyanomethyl substituent in this product is effectively a protected iminium ion; upon treatment with silver(I) nitrate, cyanide ion was expelled, and the bicyclic oxazine **752** was formed. This product itself contains a latent iminium ion, which was unmasked in the key cyclization step involving reaction with camphorsulfonic acid, sodium iodide, and additional paraformaldehyde (*cf.* Scheme 98). The labile vinyl iodide product **753** was immediately deiodinated by lithium–halogen exchange; protonation then yielded the target alkaloid (+)-**719**. Complementary syntheses of alkaloids **720** and **721**, and the simpler model compound **747**, were launched from appropriate analogs of the lithiated alkynes **750**. These were the first reported syntheses of **720** and **721**; the results confirmed the full stereostructures of the alkaloids, and in particular the absolute configurations at the hydroxylated sites in the side chains.

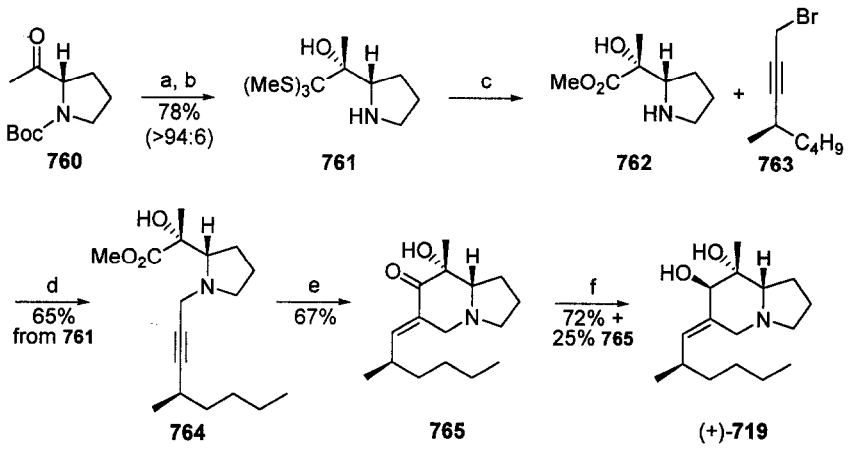
Kibayashi and co-workers communicated a synthesis of (+)-allopumiliotoxin 339A (**721**) in 1992 (*525*), and followed it up with publications that included full experimental details, model studies on their novel cyclization methodology, and an extension to the synthesis of (+)-allopumiliotoxin 267A (**719**) (*511,526*). In their convergent route to (+)-**721** (Scheme 100), two chiral precursors, the proline derived ketone **735** (*cf.* Scheme 97) and the protected aldehyde **754**, were transformed diastereoselectively into the building blocks **755** and **756**, respectively. *N*-Alkylation of **755** with **756** followed by deprotection and oxidation of the primary alcohol yielded the advanced intermediate **757**, thereby opening the way for an unusual ring closure mediated by chromium(II) chloride and catalyzed by nickel(II) chloride. This process formally proceeds through the organochromium(III) intermediate **758**. Remarkably, stereocontrol over both the (*E*) geometry of the alkylidene side chain and the axial orientation of the 7-hydroxy group was essentially complete (>99% de), a feature ascribed to the absence of allylic 1,3-strain in the transition state leading to product **759**. The synthesis of (+)-**721** was completed by removing the protecting groups from **759**. Alkaloid **719** was made analogously from the appropriate analog of vinyl iodide **756**.



SCHEME 99. Reagents: a, THF, –78°C to –50°C; b, $AgNO_3$, EtOH; c, NaI (10 equiv), $(CH_2O)_n$ (2-3 equiv), camphorsulfonic acid, H_2O, 100°C; d, *sec*-BuLi in cyclo-C_6H_{12}, THF, –78°C, then MeOH; e, Li, NH_3, THF, –78°C.



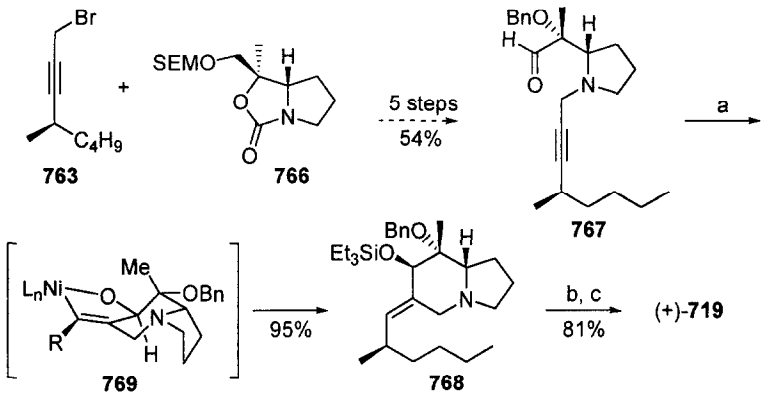
SCHEME 100. Reagents: a, Pr^i_2NEt, THF; b, Bu_4NF, THF; c, $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, –78°C; d, $CrCl_2$ (5 equiv), $NiCl_2$ (cat), DMF; e, 3M HCl, THF; f, Li, NH_3, THF, –78°C.



SCHEME 101. Reagents: a, TFA, anisole, CH_2Cl_2; b, $(MeS)_3CH$/BuLi, –78°C to –40°C; c, $Hg(ClO_4)_2 \cdot 3H_2O$, MeOH, $CHCl_3$; d, Pr^i_2NEt, THF; e, $Ti(OPr^i)_4$, Pr^iMgCl, Et_2O, –78°C to –50°C to –5°C; f, $Me_4N^+ BH(OAc)_3^-$, HOAc, Me_2CO.

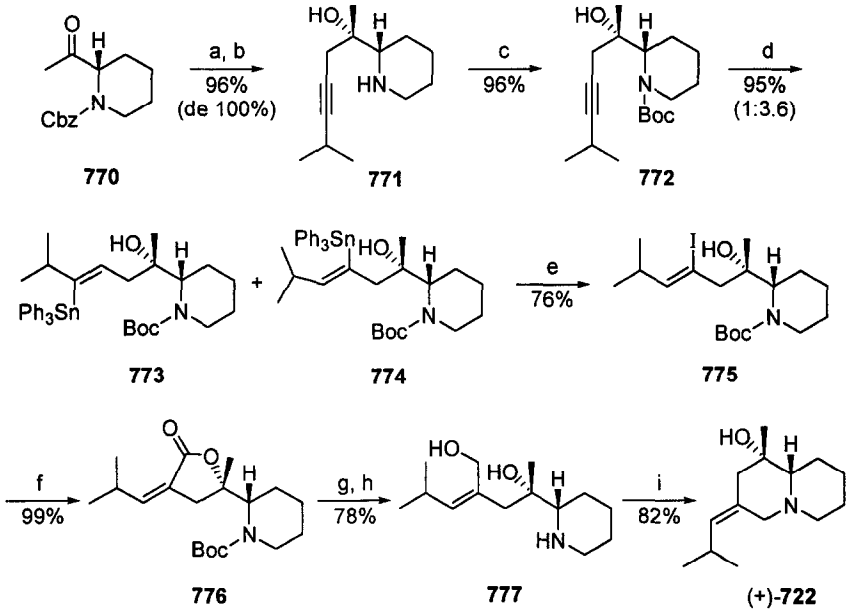
Sato and co-workers began their synthesis of (+)-allopumiliotoxin 267A (**719**) with the L-proline derivative **760**, which was homologated with tris(methylthio)-methane to give the ortho-thioester **761** (Scheme 101) (*527*). Treatment with mercuric perchlorate in methanol unmasked the methyl ester **762**, which was immediately *N*-alkylated with the substituted propargyl bromide **763** to give the focal intermediate **764**. Reaction with titanium(IV) isopropoxide and isopropyl-magnesium chloride, the combination of which produces a (η^2-propenyl)-titanium(II) species *in situ*, apparently occurs at the alkyne site to produce a titana-cyclopropene, intramolecular nucleophilic substitution of which at the nearby ester site completes a novel cyclization. The indolizidinone **765** was isolated in 67% overall yield. Since this compound had previously featured in one of the earlier syntheses of (+)-**719** from the Overman group (*528*), the two routes converge at this point. However, the Japanese workers chose to complete the synthesis by reducing **765** with tetramethylammonium triacetoxyborohydride and glacial acetic acid in acetone. This route to (+)-allopumiliotoxin 267A, the shortest on record, required only seven steps from Boc-protected L-proline, and the overall yield was 27%.

The principal feature in the short synthesis of (+)-**719** by Tang and Mont-gomery (Scheme 102) was the diastereoselective formation of the 6-alkylidene-indolizidine system by a novel nickel-catalyzed reaction (*529*). The precursors, the propargyl bromide **763** and the bicyclic L-proline derivative **766**, were converted in five steps into the ynal **767**. When **767** was treated with triethylsilane and catalytic quantities of $Ni(COD)_2$ and tributylphosphine, the indolizidine **768** was obtained as a single diastereomer in 95% yield. The stereoselectivity was ascribed to oxidative cyclization of **767** through a *cis*-hydrindane conformation to give the oxametallacycle **769**. The silane is thought to cleave the Ni–O bond, after which reductive elimination from the metal affords the observed product. The synthesis of (+)-**719** was completed by straightforward removal of protecting groups. This potentially valuable new cyclization was also applied to ten model substrates to produce a variety of alkylidene-substituted pyrrolizidines, indolizidines, and quinolizidines.



SCHEME 102. Reagents: a, $Ni(COD)_2$ (0.2 equiv), Bu_3P (0.4 equiv), Et_3SiH (5 equiv), THF, 0°C, 18 h; b, HF·pyridine, THF; c, Li, NH_3, THF.

The first (and, to date, the only) reported synthesis of a homopumiliotoxin has been accomplished by Kibayashi and co-workers (Scheme 103) (*530*). Lewis acid-initiated addition of 1-isopropyl-1-trimethylsilylallene to the ketone **770** afforded homopropargylic alcohol **771** as the sole diastereomer in almost quantitative yield. Hydrostannylation of the Boc-protected derivative **772** gave a mixture of the (*Z*)-alkenylstannane **773** and its regioisomer **774** (1:3.6). Halogen–metal exchange of the latter product gave the corresponding iodoalkene **775**, after which a remarkably efficient palladium-catalyzed carbonylation produced the lactone **776** (99% yield). The synthesis was completed by removing the *N*-Boc protecting group, reducing the lactone to diol **777**, formation of the allylic bromide, and cyclization to give (1*S*,9a*S*)-(+)-homopumiliotoxin 223G (**722**). Although the absolute configuration of the natural product remains unknown, the spectroscopic properties of the synthetic and natural products were identical, thus confirming the relative configuration.



SCHEME 103. Reagents: a, H_2, Pd/C, TFA, MeOH; b, 1-isopropyl-1-trimethylsilylallene, $TiCl_4$, CH_2Cl_2, –78°C; c, $(Boc)_2O$, K_2CO_3; d, Ph_3SnH, Et_3B, PhMe; e, NIS; f, CO, $Pd(OAc)_2$, Ph_3P, Bu_3N, HMPA, 100°C; g, TFA; h, DIBAL-H; i, CBr_4, Ph_3P.

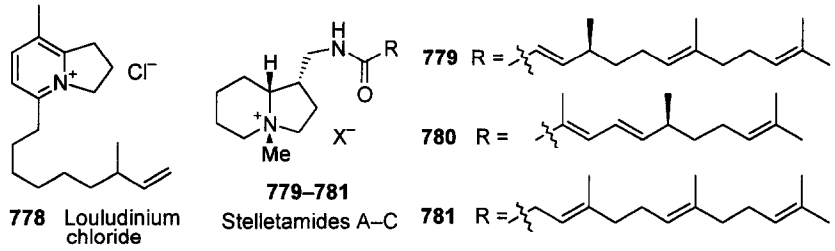
VI. Marine Alkaloids Bearing Alkyl or Functionalized Alkyl Substituents

A. LOULUDINIUM CHLORIDE

(+)-Louludinium chloride (**778**), ($[\alpha]_D$ +97°, *c* 0.65, MeOH), is the only known 2,3(1*H*)-dihydroindolizinium alkaloid from a marine source. This crystalline compound was isolated from specimens of the blue-green alga *Lyngbya gracilis* collected from the Palmyra atoll lagoon in Polynesia (*531*). Its structure was elucidated with the aid of spectroscopic techniques, especially ^1H and ^{13}C NMR spectroscopy. The absolute configuration of the methyl substituent in the side chain is unknown.

B. STELLETTAMIDES

Stellettamides A–C (**779–781**) are related indolizidinium alkaloids obtained from sponges belonging to the genus *Stelletta*. Stellettamide A (**779**), isolated from a Japanese specimen as the dihydrogen phosphate salt ($[\alpha]_D$ +23.1°, *c* 0.3, EtOH) after HPLC purification, has the distinction of being the first simple indolizidine alkaloid to have been found in a marine organism (*532*). The gross structure was elucidated by spectroscopic methods, while the (1*S*,4*S*,8a*R*,4'*S*) absolute stereostructure was later established by total synthesis (*vide infra*) (*533*). Accompanying stellettamide A was stellettamide C (**781**), which was isolated after HPLC purification as the perchlorate salt ($[\alpha]_D$ +1.1°, *c* 0.32, MeOH) (*534*). The two alkaloids, which are double-bond structural isomers, were correlated chemically by catalytic hydrogenation followed by acidic hydrolysis of the amide group to give the same *N*-methylindolizidinium product, the absolute configuration of which was also known from total synthesis (*533*). For both metabolites, chloride is probably the counter-ion *in vivo*. An energy-dispersive spectroscopic experiment performed on a scanning electron microscope proved that chloride is indubitably the counter-ion in (−)-stellettamide B (**780**) ($[\alpha]_D$ −24.2°, *c* 0.5, $CHCl_3$), obtained from an unidentified *Stelletta* sponge collected in Korean waters (*535*). NMR spectroscopic experiments revealed the *rel*-(1*S*,4*S*,8a*R*) configuration in the indolizidine core and the (2'*E*,4'*E*) geometry in the norsesquiterpene chain. Oxidation with sodium periodate and ruthenium trichloride yielded (*S*)-(+)-2-methylglutaric acid, thus proving the absolute stereochemistry at C-13'.



778 Louludinium chloride

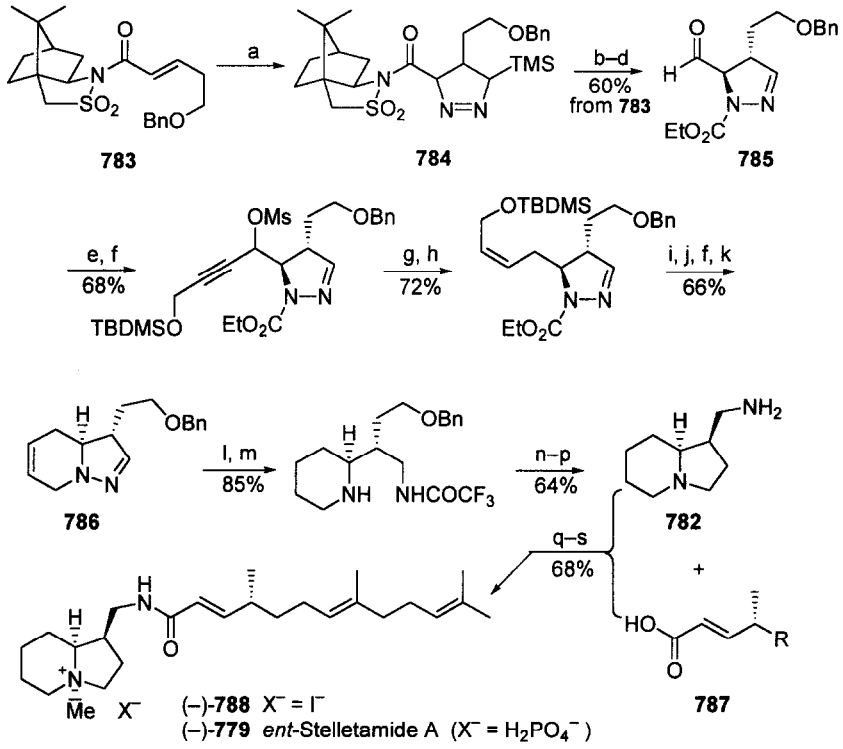
779–781 Stelletamides A–C

All three stellettamides are bioactive. Stellettamides A and B showed antifungal and cytotoxic activity; stellettamide B, for example, was active against *Candida albicans* at a concentration of 25 μg ml^{-1}, and also cleaved both single- and double-stranded RNA at a concentration of 50 μg ml^{-1} (*535*). Stellettamide A inhibited calmodulin (*536*), while stellettamide C inhibited the growth of the bacterium *E. coli* (*534*).

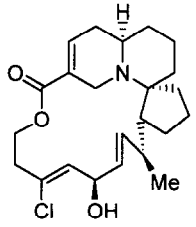
The synthesis of *ent*-stellettamide A (*ent*-**779**) by Whitlock and Carreira (Scheme 104) helped to establish the natural product's absolute stereochemistry and the configuration of the stereogenic center in the side chain (*533*). A novel but lengthy synthesis of (1*R*,8a*S*)-1-aminomethylindolizidine (**782**), the heterocyclic core of the target alkaloid, commenced with dipolar cycloaddition between (trimethylsilyl)diazomethane and the substituted acrylamide **783**, which incorporates the Oppolzer camphorsultam as chiral auxiliary. Manipulation of the pyrazoline adduct **784**, removal of the auxiliary and Swern oxidation yielded aldehyde **785** (60%, four steps), after which the piperidine ring of the bicyclic intermediate **786** was assembled in a further eight steps. Treatment of **786** with hydrogen and Raney nickel simultaneously reduced both double bonds and cleaved the N–N linkage, following which standard transformations yielded the pivotal indolizidine **782**. Since the relative configuration of the alkaloid's side chain was unknown, both (*R*)- and (*S*)-trienoic acids **787** were prepared. DCC-mediated amidation of each acid with **782** followed by treatment of the products with iodomethane yielded two diastereomeric quaternary methiodide salts. When isomer **788** was subjected to anion exchange with potassium dihydrogen phosphate, the product obtained (*ent*-**779**) proved to be spectroscopically and chromatographically identical to natural stellettamide A, but its optical rotation had the opposite sign. The natural product must therefore have the (1*S*,4*S*,8a*R*,4'*S*) absolute configuration.

C. HALICHLORINE

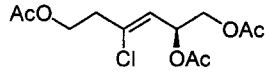
Halichlorine (**789**) ($[\alpha]_D$ +240.7°, *c* 0.54, MeOH), isolated from the Japanese sponge *Halichondria okadai*, is a complex alkaloid possessing a novel spiro-quinolizidine macrolide structure (*537*). Elucidation of the structure was based on detailed analysis of coupling constants and NOE effects in the NMR spectrum The absolute configuration of the ansa chain was inferred by degradation to the (*S*) fragment **790**, the identity of which was established by direct comparison with both enantiomers of samples made by multi-step syntheses from enantiomerically pure tartaric acids (*538*). Three studies aimed at the synthesis of the alkaloid have since appeared (*539–541*). Halichlorine inhibits the induction of vascular cell adhesion molecule-1 (VCAM-1) with an IC_{50} of 7 μg ml^{-1}, and thus may be a useful lead in the search for drugs for treating atherosclerosis, coronary heart diseases and angina, among others (*537*).



SCHEME 104. Reagents: a, $N_2CHSiMe_3$, 4Å molecular sieves, CH_2Cl_2–hexanes; b, EtOCOCl, AgOTf, CH_2Cl_2; c, $LiAlH_4$, THF; d, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e, TBDMS–$OCH_2C{\equiv}CMgBr$, THF; f, MsCl, Et_3N, CH_2Cl_2; g, Bu_3P, $Pd_2(dba)_3$, NH_4O_2CH, C_6H_6; h, H_2 (1 atm.), Pd/$BaSO_4$, quinoline, MeOH; i, $Ba(OH)_2$, dioxane–H_2O; j, $(Boc)_2O$, aq. NaOH, THF; k, 10% H_2SO_4, dioxane, then 2M NaOH; l, Raney Ni, H_2 (1 atm.), EtOH; m, CF_3CO_2Et, THF; n, $Pd(OH)_2/C$, NH_4O_2CH, MeOH, reflux; o, Ph_3P, CBr_4, Et_3N, MeCN; p, 5% K_2CO_3, aq. MeOH; q, DCC, DMAP, CH_2Cl_2; r, MeI, K_2CO_3, MeOH; s, KH_2PO_4, 25% MeOH, then extract with CH_2Cl_2.



789 (+)-Halichlorine



790

D. PETROSINS, SARAINES, AND ISOSARAINES

1. Isolation, Structure, and Biological Activity

Tentative structures for the petrosins (also known as petrosines; Fig. 11), three diastereomeric bis(quinolizidine) metabolites of the sponge *Petrosia seriata* (*542,543*), were presented in the earlier chapter in Volume 28 of this series (*1*). Two-dimensional NMR spectroscopic methods were subsequently used to correct the structure of petrosin A to **791**, and to confirm the structure of petrosin B as **792** (*544*). Petrosin (**793**) and petrosin A have since been isolated from an Okinawan sponge belonging to the genus *Xestospongia*, which also yielded a hybrid quinolizidine/1-oxaquinolizidine alkaloid, aragupetrosine A (**794**) ($[\alpha]_D$ −18.8°, $CHCl_3$) (*545*). Since *Xestospongia* also produces bis(1-oxaquinolizidine) alkaloids such as araguspongine H (**795**) (*546*), the isolation of aragupetrosin is undoubtedly of biogenetic significance. Bohlmann bands in the IR spectrum of **794** indicated a *trans*-fused quinolizidine nucleus, while the 3α-methyl-*trans*-1-oxaquinolizidine unit was deduced from NMR spectroscopic comparisons with known araguspongines. The absolute configuration was determined by reducing the ketone group to the equatorial alcohol and analyzing the NMR spectra of the esters formed with both (+)- and (−)-α-methoxy-α-trifluorophenylacetyl chloride (Mosher esters).

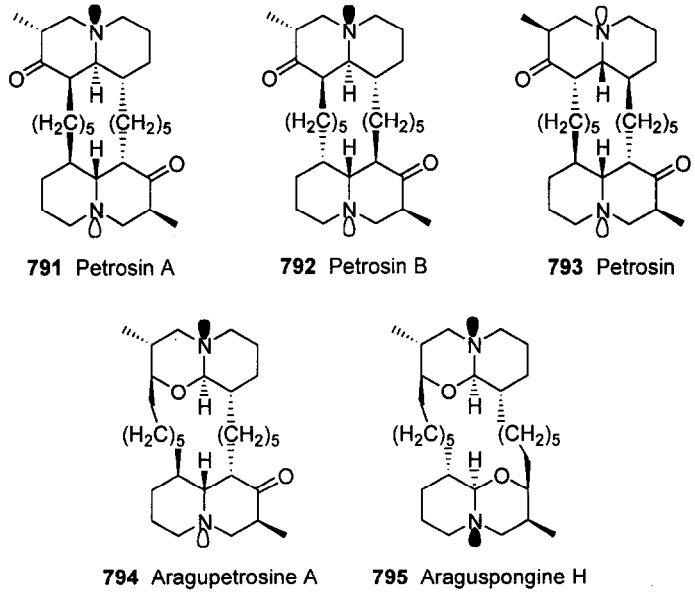


FIG. 11. Structures of the petrosins and related sponge metabolites.

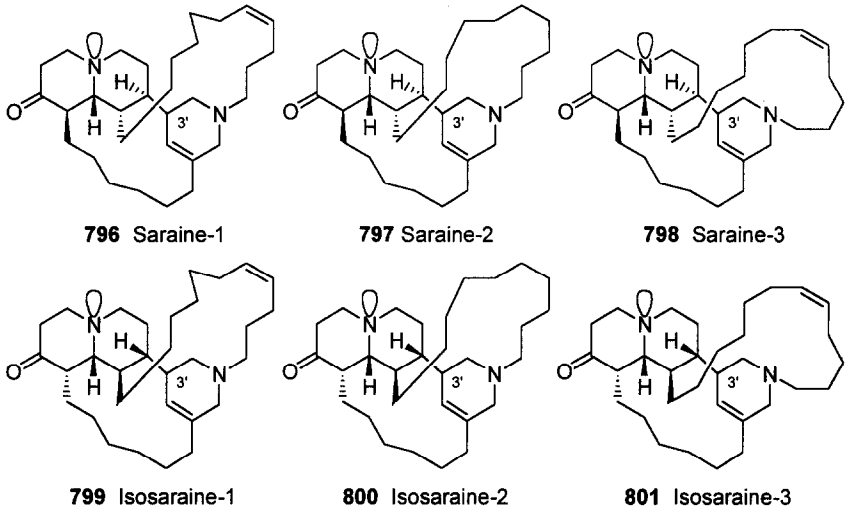


FIG. 12. Structures of the saraines and isosaraines.

(−)-Saraine-1 (**796**) ($[\alpha]_D$ −47.8°, *c* 1.2, $CHCl_3$), (−)-saraine-2 (**797**) ($[\alpha]_D$ −117°, *c* 1.1, $CHCl_3$), (−)-saraine-3 (**798**) ($[\alpha]_D$ −27.4°, *c* 0.8, $CHCl_3$) (*547,548*), (−)-isosaraine-1 (**799**) ($[\alpha]_D$ −23.1°, *c* 1.2, $CHCl_3$) (*549,550*), (−)-isosaraine-2 (**800**) ($[\alpha]_D$ −34.6°, *c* 2.0, $CHCl_3$) (*551*), and (−)-isosaraine-3 (**801**) ($[\alpha]_D$ −16.3°, *c* 1.34, $CHCl_3$), (*552*) are quinolizidine-containing metabolites isolated from the Mediterranean sponge *Reniera sarai* (Fig. 12). These alkaloids are thought to protect the sponge against fouling organisms. Their gross structures and relative stereochemistries were elucidated principally with the aid of NMR spectroscopy, while Bohlmann bands in the IR spectra provided evidence for the *trans*-fused quinolizidinone nucleus. The (1*S*,2*S*,9*R*,9a*R*) absolute configurations of saraine-1 and saraine-2 were ascertained by NMR analysis after reduction of the alkaloids with sodium borohydride, separation of the epimeric alcohols, and formation of complementary pairs of Mosher esters (*552*). It should be noted that the correct structures shown in **796** and **797** have the opposite configuration to what is conventionally shown in the earlier literature. Similar investigations have revealed the (1*R*,2*R*,9*S*,9a*R*) absolute configurations for isosaraine-1 and isosaraine-2 (*553*). The stereochemistry at C-3' remains unknown for all alkaloids in this series, although the proton at C-3' is axially orientated.

Saraines and isosaraines are thought to be biogenetically related by equilibration involving retro–Mannich/Mannich reactions through iminium ion intermediates such as **802** and the corresponding enamine **803** (*553*). Moreover, a common biogenetic origin feasibly links all alkaloids of the petrosin, saraine and 1-oxaquinolizidine class, with a macrocycle containing two piperidine rings, *e.g.* **804**, serving as a pivotal precursor for these metabolites (Fig. 13) (*548*). The dotted lines in Fig. 13 indicate the sites between which putative bond formation in **804** may lead to the formation of the petrosin, 1-oxaquinolizidine, and saraine systems, respectively.

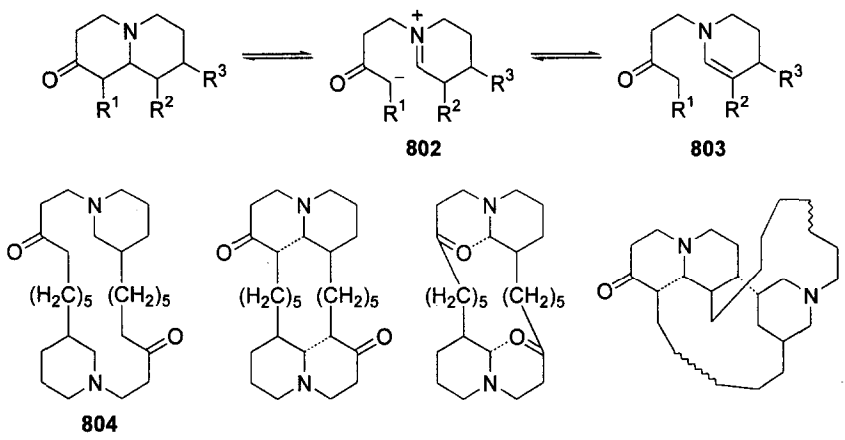


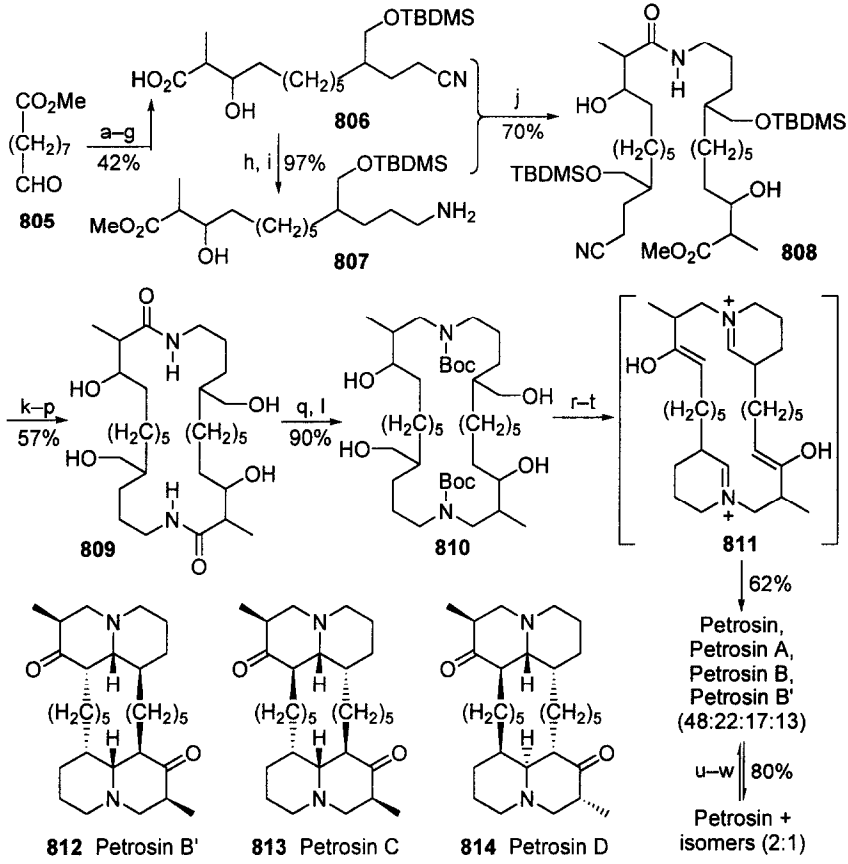
FIG. 13. Putative biogenetic relationships of the sponge quinolizidine alkaloids.

Diverse biological activity is shown by the saraines (*554*). All three alkaloids were active in lethality assays with the brine shrimp *Artemia salina*. They also showed insecticidal activity towards the potato aphid (*Macrosiphum euphorbiae*) and the yellow-fever mosquito (*Aedes aegypti*), and all three functioned as acaricides towards juvenile forms of the two-spotted spider mite (*Tetranychus urticae*). Saraine-1 (**796**) and saraine-3 (**798**) inhibited crown gall tumor formation induced on potato discs by *Agrobacterium tumefaciens*, and also suppressed development of fertilized sea urchin eggs. Saraine-3 was moderately active as an antibacterial agent towards *Staphylococcus aureus*.

2. *Synthesis*

In approaching the synthesis of the naturally racemic sponge alkaloid petrosin (**793**), Heathcock and co-workers daringly elected to disregard the alkaloid's stereochemistry (*555,556*). Their reasoning, fully supported by molecular mechanics calculations, was that **793**, among the many possible alternative diastereomers, is thermodynamically the most stable; it should therefore be the dominant product if equilibration were to form the final step of the synthesis. The synthesis they devised commenced with ozonolysis of methyl oleate to give methyl azelaldehyde (**805**) (Scheme 105). After a series of functional group transformations, two related moieties, **806** and **807**, were coupled to give amide **808**, which was itself modified and cyclized under conditions of high dilution to give the important 28-membered macrolactam **809**. This compound contains all the skeletal atoms of the target alkaloid. Reduction of the amide groups and *N*-protection gave tetraol **810**, oxidation of which with Dess–Martin periodinane, removal of the *N*-Boc protecting groups and *in situ* Mannich reaction (presumably by way of an intermediate such as **811**) yielded a mixture of petrosin isomers (62%). As expected, the main product was crystalline petrosin **793** (isolated yield 23%), while minor products included the *meso* alkaloid petrosin A **791**, petrosin B **792**, and an unnatural isomer **812**, which was named

petrosin B'. The ratio of these isomers in the kinetic cyclization mixture was 48:22:17:13. Although attempted acid-induced equilibration of the isomer mixture either had no effect or resulted in decomposition, conversion of the ketone groups into *t*-butyl imines provided material that underwent the desired equilibration. The yield of crystalline petrosin was thereby increased to 33% based on **810**. Overall, this noteworthy synthesis of (±)-petrosin proceeded in 20 steps and approximately 4.6% yield from methyl oleate. It is also worth noting that Heathcock's team has recently synthesized two further unnatural petrosin diastereomers, petrosin C (**813**) and petrosin D (**814**), by a quite different route (*557*).



SCHEME 105. Reagents: a, pyrrolidine, K_2CO_3; b, $H_2C{=}CHCN$, MeCN; c, H_2O; d, $NaBH_4$, MeOH; e, TBDMS-Cl, imidazole, DMF; f, DIBAL-H, CH_2Cl_2, –95°C; g, dianion of propanoic acid, THF; h, CH_2N_2, Et_2O; i, H_2, PtO_2, EtOAc, HOAc; j, DCC, hydroxybenzotriazole, THF; k, H_2, PtO_2, HCl, EtOH; l, $(Boc)_2O$, dioxane, H_2O; m, NaOH, MeOH, THF; n, DCC, C_6F_5OH, THF; o, 6M HCl, dioxane; p, high dilution into dioxane/pyridine, 90°C; q, $LiAlH_4$, THF; r, Dess–Martin periodinane, CH_2Cl_2; s, 1M HCl, EtOH, H_2O; t, 0.2M HOAc, EtOH; u, Bu^tNH_2, 3Å molecular sieves; v, $PrNH_3^+$ OAc^-, $Cl(CH_2)_2Cl$; w, H_2O.

E. ALKALOIDS FROM TUNICATES

1. Isolation, Structure, and Biological Activity

The tunicate (sea-squirt) *Clavelina picta* is the source of a number of simple quinolizidine and indolizidine alkaloids (Fig. 14). The first representatives, isolated from Bermudan specimens, were the cytotoxic and antimicrobial metabolites clavepictine A (**815**) ($[\alpha]_D$ −75.6°, *c* 0.7, CH_2Cl_2) and clavepictine B (**816**) ($[\alpha]_D$ +27.1°, *c* 0.03, CH_2Cl_2) (*558*), while pictamine (**817**) ($[\alpha]_D$ −87°, *c* 0.1, EtOAc), a lower homologue of clavepictine A, was obtained from a Venezuelan specimen (*559*). The structure of the rather unstable clavepictine A was deduced from spectroscopic data obtained on the natural product and its tetrahydro derivative. NOE effects indicated a *cis*-fused quinolizidine system, an equatorial disposition of the alkadienyl side chain, and axial methyl and acetoxy groups, as illustrated in **818**. Molecular modeling studies showed that this unusual conformation was energetically stable relative to alternative possibilities. Basic hydrolysis of clavepictine A yielded clavepictine B, which gave crystals suitable for X-ray diffraction analysis. The results confirmed the relative configuration deduced from the NOE studies, but did not reveal the (3*R*,4*S*,6*S*,9a*S*) absolute configuration, which was later ascertained by synthesis (*vide infra*) (*560,561*).

Bermudan specimens of *C. picta* subsequently yielded three groups of diastereomeric indolizidines bearing unsaturated hydrocarbon chains at C-5 (*562*). These compounds, the piclavines, appeared to be the most powerful antimicrobial agents in the tunicate extracts, and showed specific activity against Gram-positive bacteria. The piclavine A group of alkaloids ($[\alpha]_D$ +15°, *c* 1.0, CH_2Cl_2) has four members,

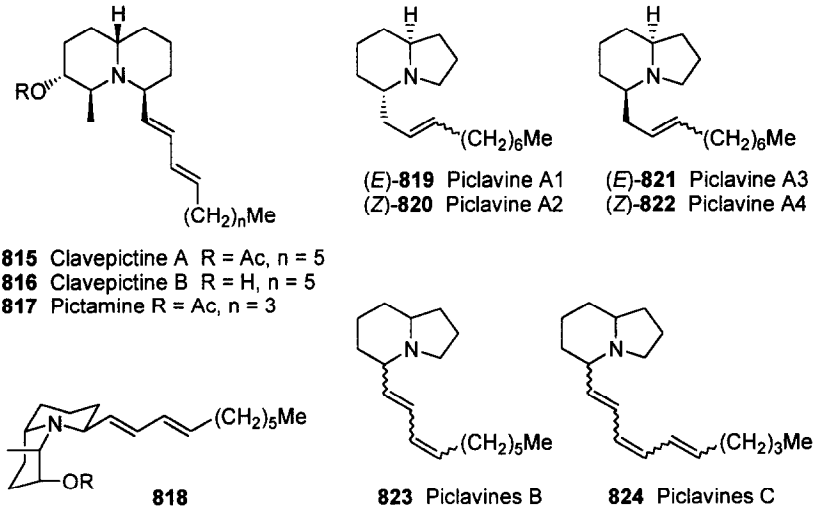


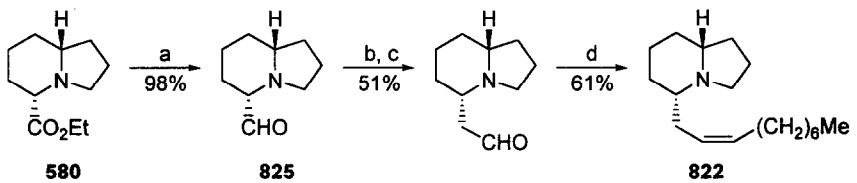
FIG. 14. Quinolizidine and indolizidine alkaloids isolated from tunicates.

which occurred in the ratio 1:3:6:6 as determined by GC. The isomers were designated in order of elution as piclavines A1–A4. Spectroscopic studies provided evidence for the gross structures, alkene geometry and relative stereochemistry, and structures were tentatively assigned. However, a total synthesis of (−)-piclavine A4 (see below) led to a reassessment of the structural proposals (*459*). Piclavines A1 and A2, possessing axial substituents at C-5, are actually the major isomers in the mixture, and the 1:3:6:6 ratio appears to correlate with piclavines A3, A4, A1 and A2, respectively. The structures for piclavines A1–A4 are now thought to be **819–822**. Piclavines B ($[\alpha]_D$ +33.5°, *c* 1.0, CH_2Cl_2) and C ($[\alpha]_D$ +36°, *c* 5.0, CH_2Cl_2), also consisting of mixtures of diastereomers, have not been investigated fully as yet, and only the gross structures shown in **823** and **824** have been proposed (*562*).

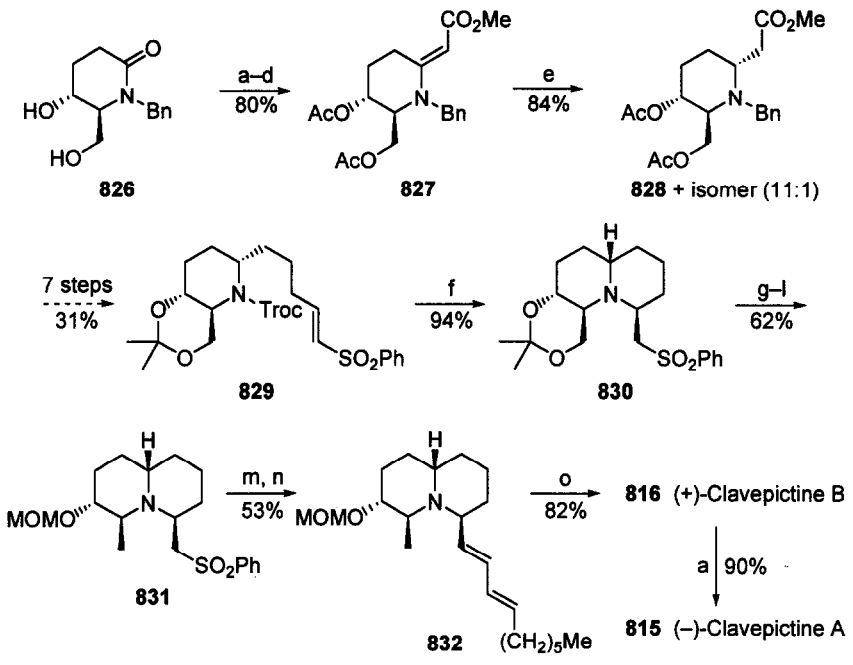
2. *Synthesis*

In the only synthesis of a piclavine to date, Jefford and co-workers followed essentially the same procedure that they used for the synthesis of the frog alkaloid 209D (**525**) (*cf.* Scheme 75) (*459,460*). Significant late steps involved the conversion of the indolizidine-5-carboxylic ester **580** into the corresponding aldehyde **825**, following which chain extension and Wittig reaction completed the synthesis of the (−)-piclavine **822** (Scheme 106). The NMR spectra obtained revealed that this isomer was identical with natural piclavine A4. Jefford's data allowed the tentative structures of piclavines A1–A4 to be reassigned, as described above.

In the first published synthesis of (−)-clavepictine A (**815**) and (+)-clavepictine B (**816**), Momose and co-workers converted the enantiopure piperidinone **826** into vinylogous urethane **827** by a route involving Eschenmoser sulfide contraction (Scheme 107) (*560*). Reduction of **827** with sodium cyanoborohydride produced mainly the *trans* diastereomer **828** (11:1). Further chain extension eventually yielded the vinyl sulfone **829**, which underwent spontaneous and completely stereoselective cyclization to give the quinolizidine **830** on removal of the *N*-protecting group. The stereochemistry of **830** was confirmed by X-ray diffraction analysis, which also substantiated the (3*R*,4*S*,6*S*,9a*S*) absolute configuration. An important step in the late stages of the synthesis was the Julia coupling of sulfone **831** with *trans*-2-nonenal, which ensured the requisite (*E*,*E*)-geometry in the decadienyl side chain. Removal of the methoxymethyl protecting group from the product **832** completed the synthesis of (+)-**816**, after which acetylation afforded (−)-clavepictine A (**815**).

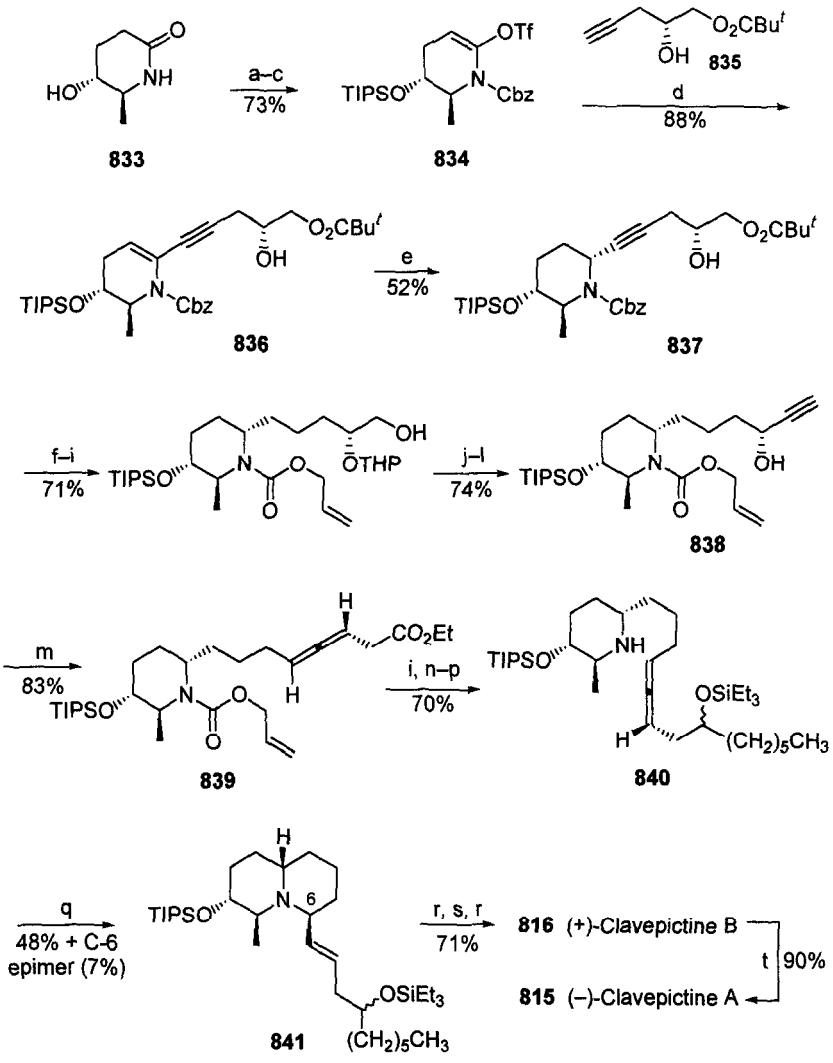


SCHEME 106. Reagents: a, DIBAL-H, Et_2O, −70°C, then MeOH; b, Ph_3P=CHOMe, THF; c, 6M HCl, Et_2O; d, Ph_3P=$CH(CH_2)_6Me$, THF.



SCHEME 107. Reagents: a, Ac_2O, pyridine; b, Lawesson's reagent, THF; c, $BrCH_2CO_2Me$; d, PPh_3, NEt_3, MeCN; e $NaBH_3CN$, TFA; f, 10% Cd–Pb, THF–NH_4OAc (aq., 1M); g, 10% HCl, EtOH; h, TBDPSCl, imidazole, DMF; i, MOM-Cl, Pr^i_2NEt, $CHCl_3$; j, HF (40%), pyridine, THF; k, I_2, PPh_3, imidazole, C_6H_6; l, Bu_3SnH, AIBN, PhMe, reflux; m, BuLi, *trans*-2-nonenal; n, 5% Na–Hg, Na_2HPO_4, MeOH; o, conc. HCl, MeOH.

The more recent total synthesis of clavepictines A and B by Cha and co-workers proceeded *via* lactam **833**, prepared from ethyl sorbate in several steps commencing with Sharpless asymmetric dihydroxylation (*561*). Palladium-catalyzed cross coupling of vinyl triflate **834** with the enantiomerically pure alkyne **835**, made in three steps from (*S*)-(–)-glycidol, gave enamide **836** (88%) (Scheme 108). Stereoselective reduction with sodium cyanoborohydride in trifluoroacetic acid ensured the 2,6-*trans*-substitution pattern in the piperidine ring of product **837**. Significant later steps included conversion of propargyl alcohol **838** into the allenic ester **839** by orthoester Claisen rearrangement, and a novel silver(I)-mediated cyclization of the δ-aminoallene **840** to produce quinolizidine **841** and its C-6 epimer in a 7:1 ratio (55%). The former was readily converted into the target alkaloids (+)-**816** and (–)-**815** as shown.



SCHEME 108. Reagents: a, TIPS-OTf, 2,6-lutidine, CH_2Cl_2; b, BuLi, $ClCO_2Bn$, THF; c, LiHMDS, THF, then 5-Cl-2-(NTf_2)pyridine; d, $Pd(Ph_3P)_4$, CuI, Et_3N, THF; e, $NaBH_3CN$, TFA, CH_2Cl_2; f, H_2 (1 atm.), 10% Pd/C, MeOH; g, $ClCO_2CH_2CH{=}CH_2$, Na_2CO_3, THF–H_2O; h, dihydropyran, PPTS, CH_2Cl_2; i, DIBAL-H, CH_2Cl_2; j, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; k, $(MeO)_2PCHN_2$, Bu^{t}OK, THF; l, *p*-TsOH, MeOH; m, $MeC(OEt)_3$, $EtCO_2H$ (cat.), 145°C; n, $Me(CH_2)_5MgBr$, Et_2O; o, Et_3Si–OTf, 2,6-lutidine, CH_2Cl_2; p, $Pd(Ph_3P)_4$, dimedone, THF; q, $AgNO_3$, acetone–H_2O; r, Bu_4NF, THF; s, Martin sulfurane, C_6H_6; t, Ac_2O, pyridine.

VII. Alkaloids Bearing Aromatic or Heteroaromatic Substituents

A. IPALBIDINE AND RELATED *IPOMOEA* ALKALOIDS

The earlier literature pertaining to this small group of indolizidine alkaloids was described in Volume 28 of this treatise (*1*). More recent coverage may be found in a general survey of indolizidine alkaloids from plant and fungal sources (*14*), and in a review on the synthesis of indolizidine alkaloids (*563*).

1. Isolation and Structural Studies

Known alkaloids from the genus *Ipomoea* are illustrated in Fig. 15. (+)-Ipalbidine (**842**), the aglycone of naturally occurring (+)-ipalbine (**843**), has been shown to have (*S*) absolute configuration by chemical correlation with (*S*)-proline (see below) (*564*), circular dichroism studies (*565*), and X-ray crystallographic analysis of its hydrobromide monohydrate (*566*).

Ipalbidine and ipalbine have been re-isolated from *Ipomoea alba* (Convolvulaceae) together with ipomine (**844**), not previously known from this source, and four new alkaloids (*567*). In this study, ^{13}C NMR spectra were reported for the first time for naturally occurring **842** and **843**, and further interesting facts about the chiroptical properties of the alkaloids emerged. For ipalbidine, the major alkaloid (26% of the total), the optical rotation was measured as –18° (*c* 0.64, EtOH), a smaller value than that reported for (–)-ipalbidine obtained by resolution of a synthetic racemate ($[\alpha]_D$ –237°, *c* 1, $CHCl_3$) (*568*). Since (+)-ipalbidine is a known natural product (*565*), the authors suspected that the compound they isolated was in fact scalemic, in line with earlier speculations about the partially racemic

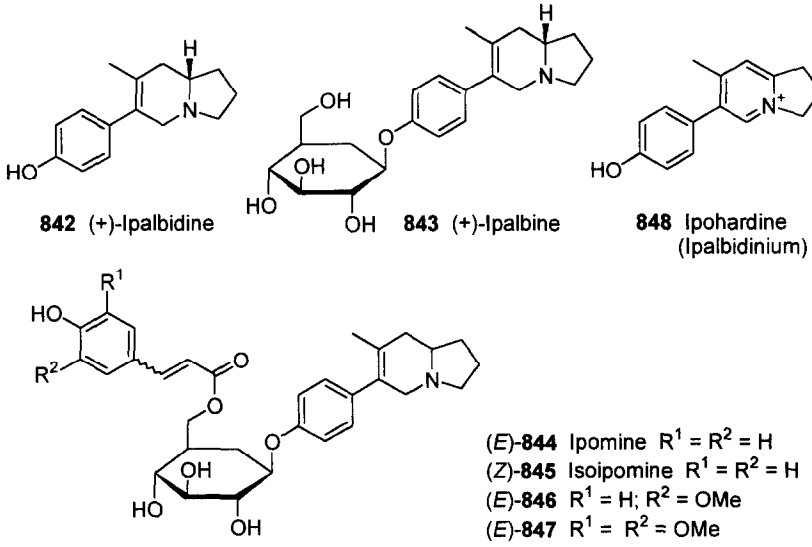
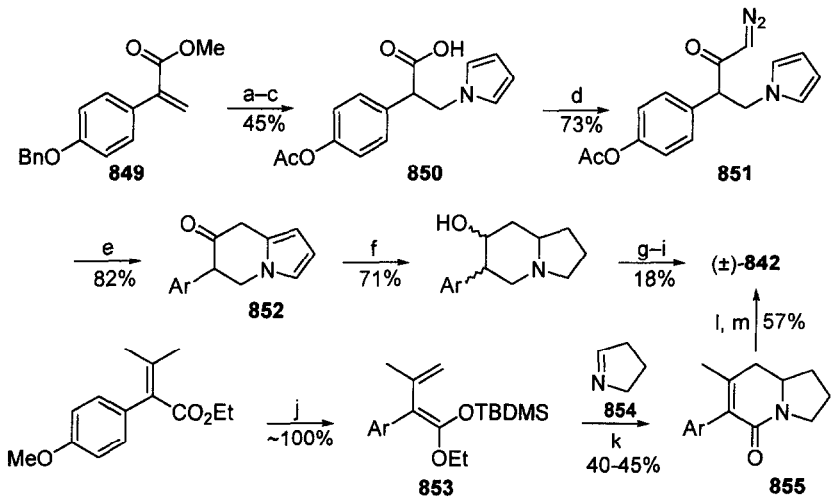


FIG. 15. Indolizidine alkaloids obtained from the genus *Ipomoea*.

nature of natural ipalbidine (*568*). The same appears to be true for the β-D-glucoside alkaloid ipalbine (**843**) ($[\alpha]_D$ –28°, *c* 0.7, EtOH in this work; *cf.* +32.5° (*569*) for natural ipalbine, and +65.8° (*568*) for synthetic (+)-ipalbine), and for ipomine ($[\alpha]_D$ –46°, *c* 0.5, EtOH in this work; *cf.* $[\alpha]_D$ +46° (*570*) for the alkaloid isolated from *I. muricata*). Some doubts were raised in the past about whether the *trans-p*-coumaroyl substituent in ipomine is attached to the hydroxy group at C-4 or C-6 in the sugar unit (*571*); the present work favors the latter, as shown in **844**.

Among the new alkaloids from *I. alba* is isoipomine (**845**), which could not be completely separated from ipomine (*567*). It was characterized by ^{1}H NMR spectroscopy (δ_H 5.51, d, *J* 12 Hz; and δ_H 6.58, d, *J* 12 Hz) as the *cis-p*-coumaroyl isomer of ipomine, possibly formed by photoisomerization. Two further alkaloids, named methoxyipomine (**846**) and dimethoxyipomine (**847**), appeared from spectroscopic data to be the *trans*-feruloyl and *trans*-sinapoyl analogues of ipomine, respectively. A fourth new alkaloid, ipalbidinium (**848**), is one of a mere handful of naturally occurring indolizinium compounds. ^{1}H NMR and UV spectra confirmed the presence of a *p*-substituted phenol, while reduction with sodium borohydride gave a product indistinguishable from ipalbidine. The new alkaloid appears to be the same as the indolizinium alkaloid ipohardine, isolated by Chinese workers from *Ipomoea hardwickii* (*572*). The Chinese group examined the X-ray crystal structures of its picrate and chloride (*573*), and also demonstrated the conversion of ipalbidine into ipohardine, and *vice versa*, by treatment with sodium borohydride and mercuric acetate, respectively (*572*).



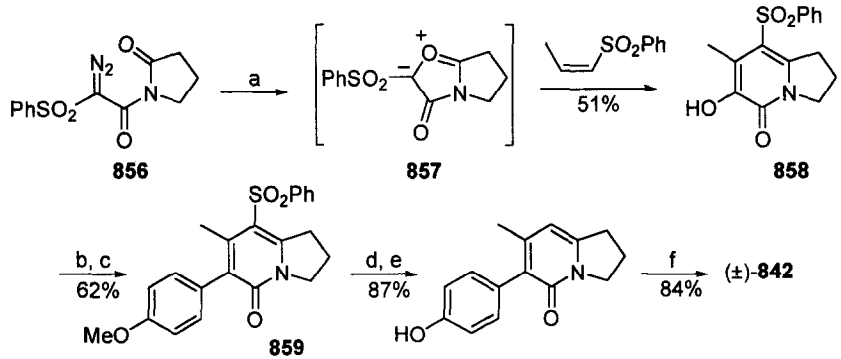
SCHEME 109. Reagents: a, pyrrole, KOBu^t, aq. DMSO; b, H_2, Pd/C, EtOH; c, *N*-methylmorpholine, AcCl, CH_2Cl_2; d, $ClCO_2Bu^i$, *N*-methylmorpholine, Et_2O; e, $Rh_2(OAc)_2$, CH_2Cl_2; f, H_2, PtO_2, EtOAc; g, CrO_3, H_2SO_4, Me_2CO; h, MeLi, THF, then Ac_2O; i, 48% HBr, 80°C; j, LDA, HMPA, THF, then TBDMS-Cl; k, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –78°C; l, $LiAlH_4$, $AlCl_3$; m, BBr_3, CH_2Cl_2.

2. *Synthesis*

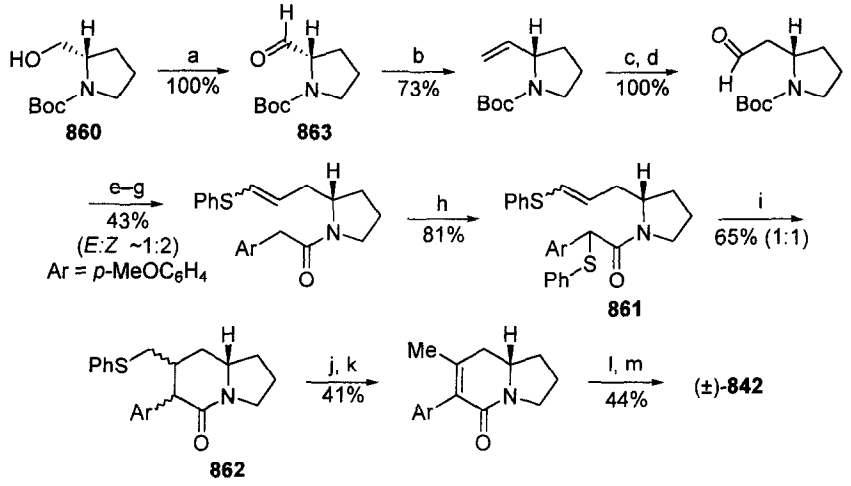
Two short syntheses of racemic ipalbidine (±)-(**842**) are shown in Scheme 109. The synthesis by Jefford *et al.* commenced with conjugate addition between pyrrole and the atropate ester **849** followed by homologation of the acid **850** with diazomethane and rhodium-induced intramolecular carbene cyclization of the resulting diazoketone **851** (*574*). The bicyclic product **852** was converted into (±)-**842** in a further four steps. The approach taken by Danishefsky and Vogel centered on acid-catalyzed cyclocondensation between the silyl ketene acetal **853** and Δ^1-pyrroline (**854**) to give indolizidinone **855** (*575*). Reduction of the lactam and cleavage of the aryl ether completed the synthesis of (±)-**842**.

The synthesis of (±)-ipalbidine by Sheehan and Padwa incorporates several interesting new transformations (Scheme 110) (*576*). When the diazo compound **856** was heated with a catalytic quantity of rhodium(II) acetate, the resulting isomünchnone intermediate **857** underwent a [3 + 2] dipolar cycloaddition with *cis*-1-phenylsulfonylprop-1-ene to yield the 3-hydroxy-2-pyridone **858**. Another novel step involved palladium-catalyzed Stille coupling between the triflate derived from **858** and tributyl(*p*-methoxyphenyl)tin to yield **859**. Although cross couplings with simple vinyl triflates and organotin compounds are well known, there are no precedents for coupling with pyridone-derived triflates. The synthesis of (±)-**842** was completed as shown in an overall yield of 23% based on diazoimide **856**.

An attempted enantioselective synthesis of ipalbidine from the protected (*S*)-prolinol **860** was based on the regioselective 6-*exo-trig* cyclization of the radical intermediate derived from the reaction of the phenylthio compound **861** with tributyltin hydride (Scheme 111) (*577*). The reaction gave a 1:1 mixture of two indolizidin-5-one diastereomers **862** in 65% yield. At the end of the synthesis, the target **842** was found to possess virtually no optical activity. The most likely candidate for racemization is the aldehyde **863**, which might scramble under the basic conditions required for the subsequent Wittig reaction.

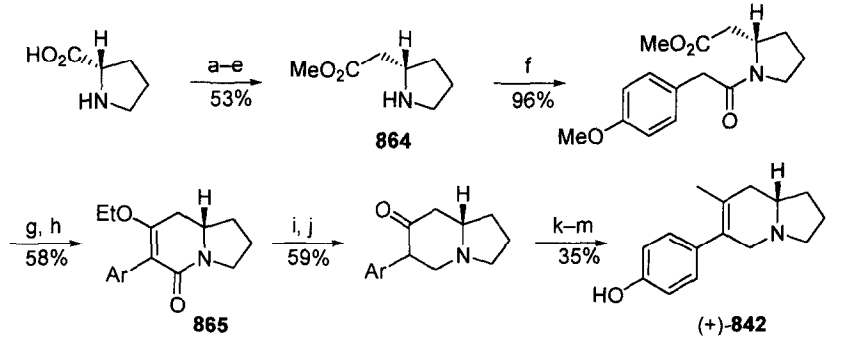


SCHEME 110. Reagents: a, $Rh_2(OAc)_4$, C_6H_6, reflux; b, $(TfO)_2NPh$, Et_3N, CH_2Cl_2; c, $Pd(Ph_3P)_4$, *p*-$MeOC_6H_4SnBu_3$, LiCl, *N*-methylpyrrolidin-2-one, 150°C; d, Raney Ni, EtOH, reflux; e, 48% HBr, reflux; f, $LiAlH_4$, $AlCl_3$, THF, reflux.



SCHEME 111. Reagents: a, SO_3·pyridine, DMSO, Et_3N; b, $Ph_3P^+Br^-$, NaH, DMSO; c, Sia_2BH, THF, then H_2O_2, NaOH; d, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; e, $Ph_2P(O)CH_2SPh$, NaH, DMSO; f, TMSI, MeCN; g, *p*-$MeOC_6H_4COCl$, Et_3N, CH_2Cl_2; h, LDA, then $(PhS)_2$, THF; i, Bu_3SnH, AIBN, C_6H_6, reflux; j, $NaIO_4$, MeOH–H_2O; k, ClC_6H_5, 160°C; l, $LiAlH_4$, $AlCl_3$, THF, reflux; m, BBr_3, CH_2Cl_2.

The first (and still the only genuinely) enantioselective synthesis of (*S*)-(+)-ipalbidine was reported in the Chinese literature in 1985 (Scheme 112) (*564,578*). (*S*)-Proline was homologated to the pyrrolidinylacetic ester **864**, after which *N*-acylation with *p*-methoxyphenylacetyl chloride, intramolecular condensation and enol ether formation created the indolizidinone system of **865**. Standard transformations completed the synthesis of the alkaloid (+)-(**842**), which was isolated as the hydrobromide salt ($[\alpha]_D$ +54.1°, *c* 1, EtOH).



SCHEME 112. Reagents: a, $ClCO_2Bn$, NaOH, H_2O; b, $ClCO_2Bu^i$, Et_3N; c, CH_2N_2, Et_2O; d, $PhCO_2Ag$, Et_3N, MeOH; e, H_2, Pd, MeOH; f, *p*-$MeOC_6H_4CH_2COCl$, K_2CO_3, MeCN; g, NaH, THF; h, $(EtO)_3CH$, HCl, EtOH; i, AlH_3, THF; j, HCl, H_2O; k, MeLi, Et_2O; l, aq. H_2SO_4; m, $AlBr_3$, CS_2.

B. SEPTICINE AND RELATED SECOPHENANTHROINDOLIZIDINE ALKALOIDS

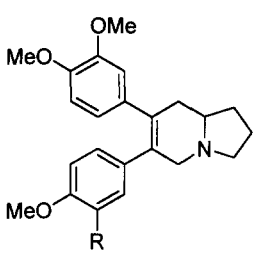
Secophenanthroindolizidine alkaloids and their secophenanthroquinolizidine analogs were last surveyed in Volume 28 of this series (*1*). A comprehensive review on the occurrence, structural elucidation, biosynthesis, synthesis, and biological activity of the phenanthroindolizidine alkaloids, including their seco variants, was published in 1987 (*579*). The topic was also included in several more general reviews on indolizidine alkaloid chemistry (*14,19,563*).

1. Isolation, Structural Studies, and Biological Activity

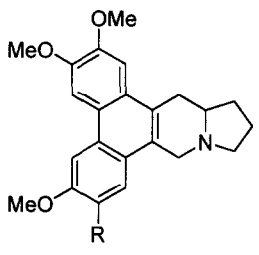
Septicine (**866**), the prototypical alkaloid in this group, is a seco variant of the more populous phenanthroindolizidine class of alkaloids, of which tylophorine (**867**) and antofine (**868**) are commonly encountered examples. All the known analogs of septicine are metabolites of the unrelated genera *Cryptocarya* (Lauraceae), *Ficus* (Moraceae), and *Tylophora* (Asclepiadaceae). In addition to the previously described alkaloids 8a-hydroxysepticine (**869**) and hispidine (**870**) (*1*), seven new members of the family have been isolated (Table II and Fig. 16).

TABLE II
NEW SECOPHENANTHROINDOLIZIDINE ALKALOIDS

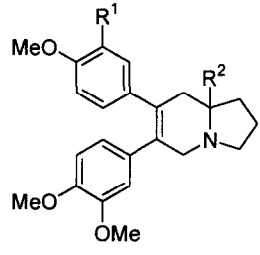
Name	Source	$[\alpha]_D$ (concentration, solvent)	Reference
Phyllostemine (**871**)	*Cryptocarya phyllostemon*	–8° (*c* 0.28, EtOH)	*580*
Phyllosteminine (**872**)	*Cryptocarya phyllostemon*	–49° (*c* 0.4, EtOH)	*580*
Tylohirsuticine (**873**)	*Tylophora hirsuta* (aerial parts)	+20.8° (*c* 0.8, MeOH)	*581*
Tyloindicine B (**874**)	*Tylophora indica*	+14.3° (*c* 1.05, MeOH)	*582*
Tyloindicine F (**875**)	*Tylophora indica* (aerial parts)	–0.5° (*c* 0.05, HOAc)	*583*
Tyloindicine I (**876**)	*Tylophora indica* (aerial parts)	–2.2° (*c* 0.44, HOAc)	*583*
Tyloindicine J (**877**)	*Tylophora indica* (aerial parts)	–2.85° (*c* 0.57, HOAc)	*583*



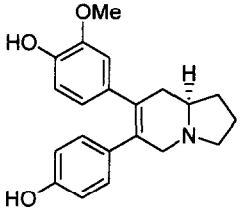
866 Septicine R = OMe
890 R = H



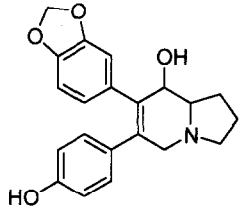
867 Tylophorine R = OMe
868 Antofine R = H



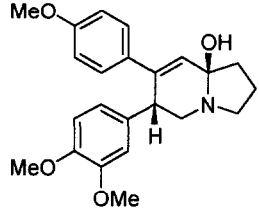
869 R^1 = OMe; R^2 = OH
870 $R^1 = R^2$ = H



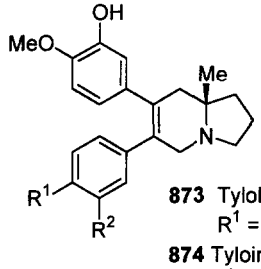
871 Phyllostemine



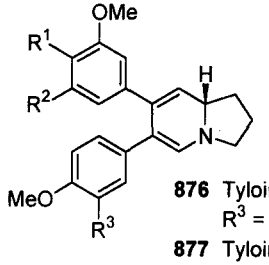
872 Phyllosteminine



875 Tyloindicine F



873 Tylohirsuticine
$R^1 = R^2$ = OMe
874 Tyloindicine B
R^1 = H; R^2 = OAc



876 Tyloindicine I R^1 = R^3 = OMe; R^2 = OH
877 Tyloindicine J R^1 = OH; R^2 = H; R^3 = OAc

FIG. 16. Secophenanthroindolizidine alkaloids and analogs.

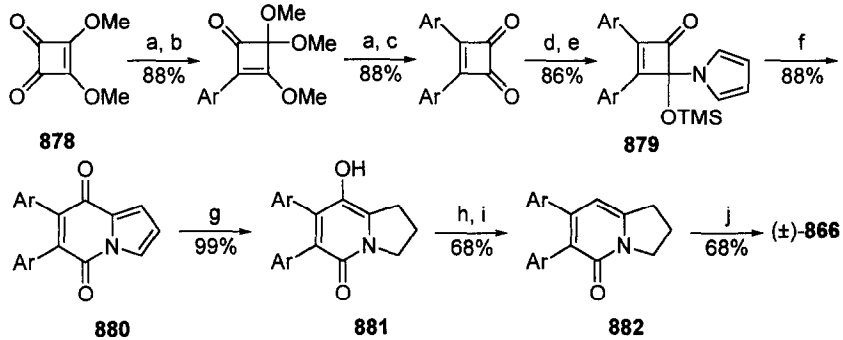
All the new alkaloids possess unusual structural features. These include the 8-hydroxy substituent in phyllosteminine (**872**), the angular methyl groups in tylohirsuticine (**873**) and tyloindicine B (**874**), the acetoxy substituents in tyloindicines B and J (**877**), the bridgehead hydroxy group in tyloindicine F (**875**), and unsaturation between positions other than the customary $\Delta^{6,7}$-position in the later tyloindicines. The location of phyllostemine's *para* phenolic groups was inferred from negative Gibbs test results (*580*), and tylohirsuticine's *meta* phenolic group from a positive Gibbs test (*581*). For none of the new alkaloids was the absolute configuration determined, although the (8a*R*) absolute configuration of phyllostemine was proposed on the basis of the negative specific rotation. For this

alkaloid, there was some uncertainty about which aromatic ring the methoxy group is attached to, but the structure shown as **871** was preferred on the grounds of structural and spectroscopic analogies with known alkaloids. The locations of the two substituted aromatic rings in phyllosteminine (**872**) were also chosen in terms of spectroscopic analogies.

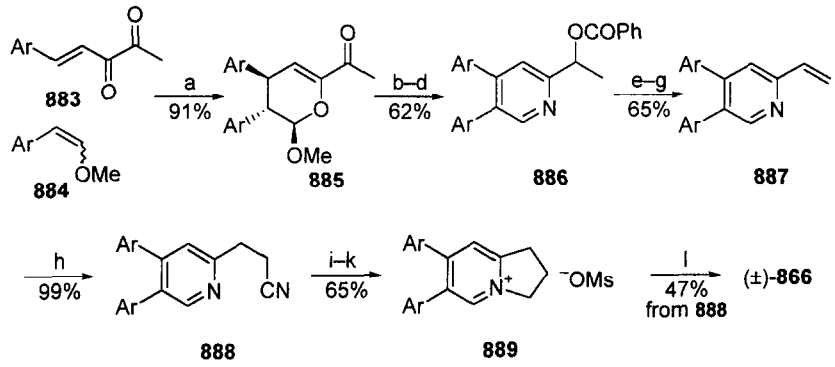
2. *Synthesis*

An unusual synthesis of (±)-septicine (**866**) from dimethyl squarate (**878**) exploits rearrangement of a 4-(1-pyrrolo)cyclobutenone **879** to the indolizine-5,8-dione **880**, presumably *via* a ketene intermediate formed by electrocyclic ring opening of **879** (Scheme 113) (*584*). Partial reduction of **880** yielded the 4-hydroxypyridone **881**, the triflate ester of which was deoxygenated with a palladium(II)–formic acid system to yield the 1,2,3,5-tetrahydroindolizin-5-one **882**. Mild reduction with aluminum hydride completed the synthesis of (±)-**866** in an excellent overall yield of 27% from **878**.

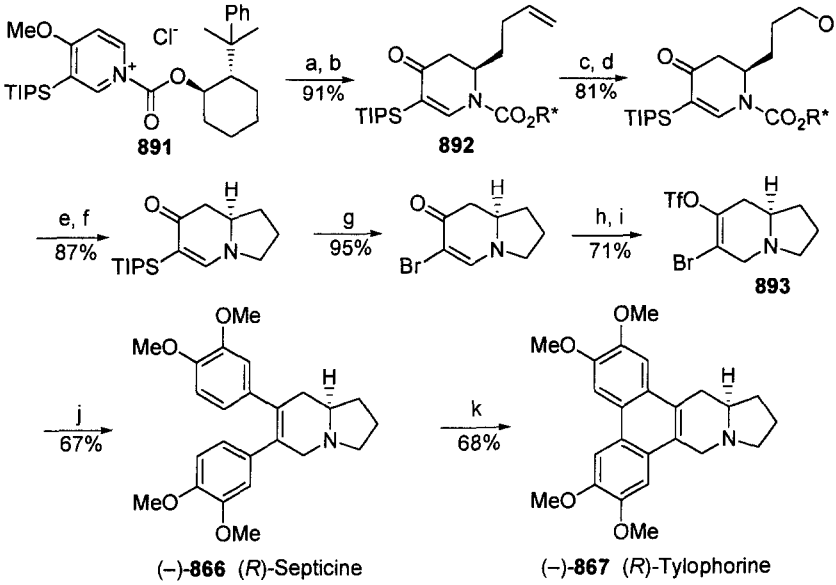
In the synthesis of racemic septicine by Ciufolini and Roschangar, a slow but completely stereoselective ytterbium(III)-catalyzed cyclocondensation between unsaturated diketone **883** and enol ether **884** yielded the all-*trans* adduct **885** (91%) (Scheme 114) (*585*). The acetyl substituent served as the precursor of the pyrrolidine ring *via* pivotal pyridine intermediates **886** and **887**, the latter undergoing a conjugate addition with cyanide ion to form the 2-cyanoethyl-4,5-diarylpyridine **888**. Standard transformations of the nitrile group led to the dihydroindolizinium salt **889**, from which the target alkaloid (±)-**866** was obtained by reduction with sodium borohydride. A similar series of reactions with appropriate precursors yielded the diarylindolizidine **890** (Fig. 16), which has not yet been found as a natural product. Products **866** and **890** could be oxidatively cyclized to the corresponding racemic phenanthroindolizidine alkaloids, tylophorine (**867**) and antofine (**868**), respectively.



SCHEME 113 [Ar = 3,4-$(MeO)_2C_6H_3$]. Reagents: a, 4-bromoveratrole, *n*-BuLi, THF, –78°C, then $(CF_3CO)_2O$, THF; b, MeOH, 0°C; c, 10% aq. HCl; d, pyrrole, *n*-BuLi, THF, –78°C; e, Me_3SiCl, THF, –78°C to 25°C; f, xylene, reflux, then aq. $FeCl_3$; g, H_2 (1 atm), 10% Pd/C, EtOH; h, $(CF_3SO_2)_2O$, C_5H_5N, 0°C; i, $Pd(OAc)_2$, Et_3N, HCO_2H, 1,3-bis(diphenylphosphino)propane, DMF, 90°C; j, $LiAlH_4$, $AlCl_3$, THF, 0°C.



SCHEME 114 [Ar = 3,4-$(MeO)_2C_6H_3$]. Reagents: a, $Yb(fod)_3$, $ClCH_2CH_2Cl$, reflux; b, DIBAL-H, CH_2Cl_2, –78°C, then MeOH, aq. $NaHCO_3$; c, PhCOCl, pyridine, CH_2Cl_2; d, $NH_2OH{\cdot}HCl$, MeCN, reflux; e, 1% aq. NaOH, MeOH; f, $SOCl_2$, pyridine, C_6H_6, reflux; g, Bu^tOK, THF, reflux; h, LiCN, AcOH, DMF, 140°C; i, conc. HCl, dioxan, 40°C; j, $LiAlH_4$, THF, reflux; k, MsCl, Et_3N, CH_2Cl_2, 0°C; l, $NaBH_4$, EtOH, reflux.

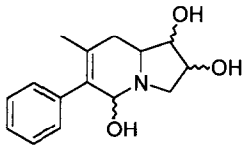


SCHEME 115. Reagents: a, $H_2C{=}CH(CH_2)_2MgBr$, THF–PhMe, –78°C; b, oxalic acid, H_2O; c, OsO_4 (cat.), HIO_4, THF–H_2O (1:1); d, L-Selectride, THF, –78°C, then $NaBO_3{\cdot}4H_2O$, H_2O; e, Ph_3P, NCS, CH_2Cl_2, –23°C to 25°C; f, NaOMe, MeOH, reflux; g, $py{\cdot}HBr_3$, CH_2Cl_2, –23°C to rt; h, L-Selectride, THF, –23°C; i, 5-Cl-2-(NTf_2)pyridine, THF, –23°C; j, 3,4-$(MeO)_2C_6H_3ZnBr$, $Pd(Ph_3P)_4$, THF, 25°C to reflux; k, VOF_3, TFA, CH_2Cl_2, 0°C to rt.

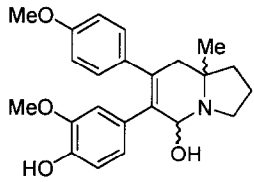
After developing a successful synthesis of (±)-septicine in 1991 (*586*), Comins and co-workers adapted their route to yield the alkaloid's (–)-enantiomer (*587*). Addition of but-3-enylmagnesium bromide to pyridinium salt **891**, which bears (–)-*trans*-2-(α-cumyl)cyclohexanol as the chiral auxiliary, yielded the dihydropyridone **892** (91%) as a single diastereomer (Scheme 115). Simple functional group interconversions led to the important bromovinyl triflate **893** (seven steps, 48%), into which both aryl groups were simultaneously introduced by an elegant palladium-catalyzed cross-coupling with (3,4-dimethoxyphenyl)zinc bromide. The product, (–)-**866**, thus possesses the (*R*) absolute configuration. This is an important finding, since the only previously reported enantioselective synthesis of (–)-septicine, which dates from 1969 (*588*), assigned the (*S*) absolute configuration to the levorotatory alkaloid. The optical rotation of the synthetic alkaloid ($[\alpha]_D^{28}$ –172°) was also significantly higher than that reported for the natural product ($[\alpha]_D$ –16° to –42°). Further confirmation for the revised absolute stereochemistry of (–)-septicine was provided by oxidative coupling with vanadium(V) oxyfluoride, which afforded the known alkaloid (*R*)-tylophorine, (–)-(**867**), in 68% yield (ee >98%).

C. POLYCANTHINE AND POLYCANTHIDINE

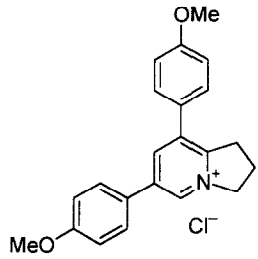
(–)-Polycanthine (**894**) ($[\alpha]_D$ –33°, *c* 0.66, MeOH) and (–)-polycanthidine (**895**) ($[\alpha]_D$ –380°, *c* 0.02, MeOH) were isolated together with several other uncharacterized alkaloids (possibly *N*-oxides) from the aerial parts of Indian *Astragalus polycanthus* (Leguminosae) (*590,591*). The former compound, obtained as a viscous brown gum, was characterized by spectroscopic methods. The substitution pattern was deduced from NMR spectroscopy, and from the retro Diels–Alder cleavage apparent in the mass spectrum. The relative and absolute configuration were not ascertained. Polycanthine formed a diacetate, apparently on the C-1 and C-2 hydroxy groups, but efforts to prepare a hydrochloride salt resulted in oxidation to a lactam. The crystalline alkaloid polycanthidine (**895**) (m.p. 278°C) was also characterized by spectroscopic methods, and by conversion into monoacetyl and monomethoxy derivatives; on standing at room temperature, all three compounds underwent partial oxidation to give lactams. The relative and absolute configuration of polycanthidine also remain unknown. The basic skeletons proposed for alkaloids **894** and **895** , the evidence for which is perhaps not entirely convincing, are obviously akin to those found in the *Ipomoea* and seco-phenanthroindolizidine alkaloids, respectively. However, the occurrence of two such structurally different arylindolizidine alkaloids in the same plant species should give one pause. In this regard it should be noted that the only indolizidine alkaloids previously isolated from the genus *Astragalus* were swainsonine (**162**) and its *N*-oxide (*cf.* Section III.C), and that the structure proposed for a third new *A. polycanthus* alkaloid, polycanthisine (**325**) (*cf.* Section IV.C), is also quite different.



894 Polycanthine



895 Polycanthidine



896 Ficuseptine

D. FICUSEPTINE

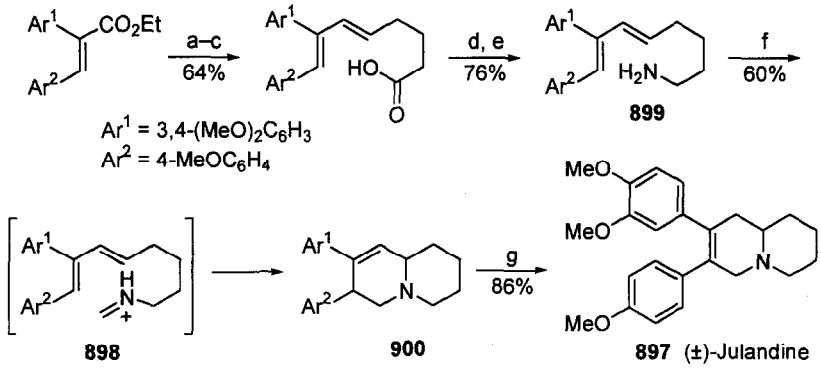
Ficuseptine (**896**) is a unique indolizinium alkaloid with a substitution pattern quite unlike that of other *Ficus* alkaloids, which are phenanthroindolizidines or seco analogs. It was located by bioactivity-guided fractionation of an extract from the leaves of *Ficus septica*, a small Papua New Guinean tree (*589*). The structure of the alkaloid was elucidated by a combination of electron-impact and FAB mass spectrometry, UV and IR spectroscopies, and extremely comprehensive NMR spectroscopic experiments. MS and chemical evidence indicated chloride as the counter-ion. The biogenesis of this new type of indolizidine alkaloid is thought to be from two *p*-hydroxyphenylpyruvate units and ornithine. Ficuseptine showed significant antifungal and antibacterial activity.

E. JULANDINE

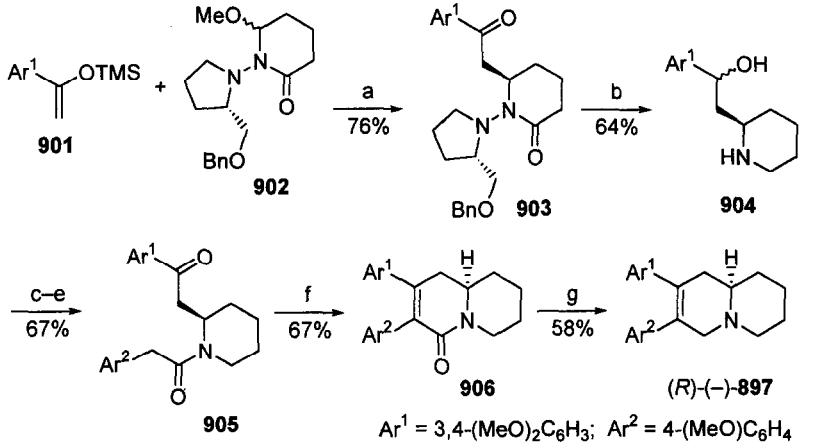
Julandine (**897**), a quinolizidine relative of the septicine group of alkaloids, can also be viewed as a seco variant of the rare phenanthroquinolizidine alkaloids. Racemic julandine has been synthesized twice since the previous review in this series was published. The synthesis by Ciufolini and Roschangar is essentially the same as that shown in Scheme 114 for (±)-septicine (**866**), with the anion of acetonitrile replacing cyanide ion in the conjugate addition step with the appropriately substituted analog of vinylpyridine **887** (*585*). An earlier synthesis, by Grieco and Parker, was built around an intramolecular Diels-Alder cycloaddition of a transient iminium intermediate **898**, formed by acid-catalyzed reaction of amine **899** with formaldehyde (Scheme 116) (*592*). The product formed at 110°C (60%) was isojulandine (**900**), acid-induced isomerization of which gave crystalline (±)-**897** in 86% yield.

The only enantioselective synthesis of julandine to date is due to Kibayashi and co-workers (*593*). Lewis acid-catalyzed condensation between silyl enol ether **901** and the acyliminium ion formed from the proline-derived lactam **902** was highly diastereoselective (>99% de), giving a 76% yield of the piperidin-2-one **903** (Scheme

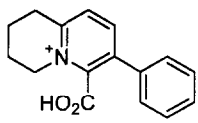
117). Treatment with borane not only reduced both carbonyl groups but also removed the chiral auxiliary to give the (2*R*)-2-substituted piperidine **904** as a mixture of alcohol diastereomers (64%). *N,O*-Bisacylation with 4-methoxyphenylacetyl chloride, selective hydrolysis of the ester, and benzylic oxidation gave the dicarbonyl compound **905** (67%), base-induced condensation of which afforded quinolizidinone **906** (67%). The synthesis of (*R*)-(−)-julandine (**897**) was completed by reductive removal of the lactam carbonyl group. This synthesis permitted the absolute configuration of natural (+)-julandine to be assigned as (9a*S*), *i.e.*, *ent*-**897**.



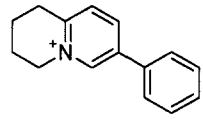
SCHEME 116. Reagents: a, DIBAL-H, PhMe, 0°C; b, MnO_2, C_6H_6–$CHCl_3$; c, $HO_2C(CH_2)_4PPh_3^+$ Br^-, LDA, TMEDA, THF, 0°C; d, $ClCO_2Et$, pyridine, THF, 5°C, then NH_4OH; e, $LiAlH_4$, THF, 0°C; f, 37% aq. H_2CO, EtOH, HCl, 110°C; g, *p*-TsOH, C_6H_6, reflux.



SCHEME 117. Reagents: a, $BF_3{\cdot}Et_2O$, CH_2Cl_2; b, BH_3, THF, rt to reflux; c, 5% aq. NaOH, 4-$MeOC_6H_4CH_2COCl$, CH_2Cl_2, 0°C; d, K_2CO_3, MeOH–H_2O, reflux; e, PDC, CH_2Cl_2, 4Å molecular sieves; f, 5% aq. KOH, EtOH, reflux; g, $LiAlH_4$–$AlCl_3$ (3:1), THF, 0°C to rt.



907 Clathyrimine A



908 Clathyrimine B

F. CLATHYRIMINES

The only arylquinolizidine alkaloid to have been isolated from a marine source is clathyrimine A (**907**), a unique tetrahydroquinolizinium alkaloid isolated from the Indonesian sponge *Clathria basilana* (*594*). This compound was unstable in solution, and underwent partial decarboxylation to clathyrimine B (**908**) during NMR spectroscopic studies. The reaction could be driven to completion merely by heating at 40°C in deuteriated chloroform.

G. LASUBINES AND RELATED LYTHRACEOUS ALKALOIDS

Alkaloids of the family Lythraceae were reviewed in Volumes 18 and 35 of this series (*595,6*). The latter review, published in 1989, was devoted to developments during the period 1979–1987, and overlapped to some extent with the review on simple indolizidine and quinolizidine alkaloids in Volume 28 (*1*). Also worth noting is a phytochemical and phytopharmacological review on the New World flowering shrub *Heimia salicifolia*, an important source of these alkaloids (*596*).

Lythraceous alkaloids include several 4-arylquinolizidin-2-ols and their esters, as well as a variety of piperidine- and quinolizidine-based macrocyclic variants (macrolides, cyclophanes) possessing biaryl linkages. Only the former group is relevant to this review. No new simple quinolizidine metabolites have been reported for over two decades, and recent publications have dealt almost exclusively with the synthesis of four alkaloids, lasubine I (**909**), lasubine II (**910**), and their 3,4-dimethoxycinnamate esters subcosine I (**911**) and subcosine II (**912**) (Fig. 17). The naturally occurring enantiomers are represented in the diagrams.

Recent biosynthetic studies on the Lythraceae alkaloids have concentrated on the macrolide alkaloids. Of interest is a demonstration that the *cis*- and *trans*-fused quinolizidinones **913** and **914** were effective and specific precursors for biaryl macrolide alkaloids such as vertine (**915**) and lythrine (**916**) in *H. salicifolia*, respectively, whereas the four possible monomethyl ethers of **913** and **914** were not incorporated effectively (*597*). Another *in vitro* incorporation study on *H. salicifolia* with labeled lysine, phenylalanine, and *p*-coumaric acid showed that 4-arylquinolizidinols, their *p*-coumarate esters, and biaryl macrolide alkaloids are formed from different precursor pools, but *cis*- and *trans*-fused alkaloids within each class originate from a common metabolic pool (*598*).

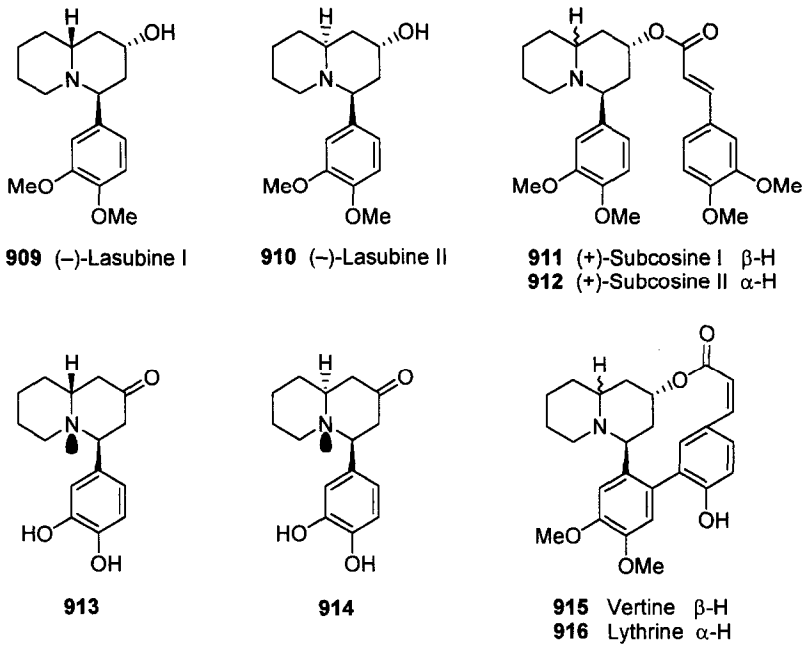
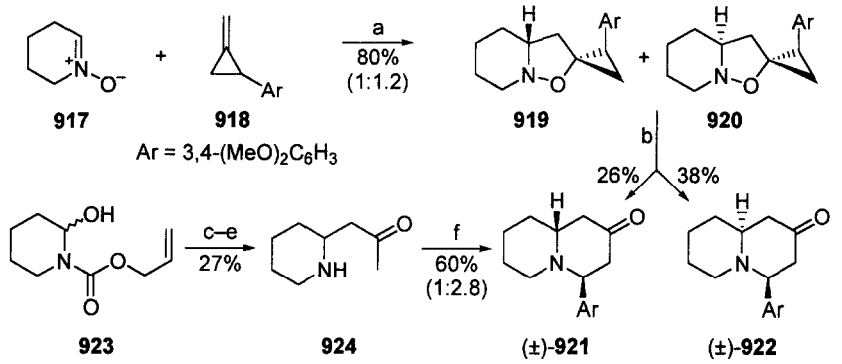


FIG. 17. Lythraceous quinolizidine alkaloids and analogs.

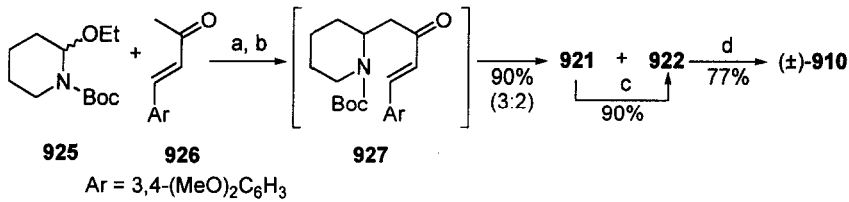
Two formal syntheses of racemic lasubines I and II are shown in Scheme 118. 1,3-Dipolar cycloaddition of nitrone **917** to methylenecyclopropane **918** was marginally stereoselective, and gave a 1:1.2 mixture of isoxazolidine adducts **919** and **920** in 80% yield (*599*). Thermal rearrangement of the mixture afforded the separable ketones **921** (26%) and **922** (38%). Conversion of these into lasubines I and II, respectively, had been reported some years previously (*600*). The second route, also not very stereoselective, used a Wittig reaction between acetylmethylenetriphenylphosphorane and *N*-protected piperidin-2-ol **923** to make pelletierine (**924**), Mannich condensation of which with veratraldehyde gave a 1:2.8 ratio of the ketones **921** and **922** (60%) (*601*).

The same two ketones featured again in a synthesis of (±)-lasubine II (**910**) by Pilli *et al.* (Scheme 119) (*368,369*). In this case, reaction of *N*-Boc-2-ethoxypiperidine (**925**) with enone **926** in the presence of trimethylsilyl triflate sparked off a remarkably efficient (90%) one-pot synthesis involving condensation (*via* an *N*-acyliminium ion to give the intermediate **927**), deprotection, and intramolecular conjugate addition. The familiar products **921** and **922** were obtained as a 3:2 mixture. Base-induced epimerization of the mixture enriched the latter component, which was converted into (±)-**910** by reduction with LS-Selectride (lithium trisiamylborohydride) according to the procedure developed by Comins (*vide infra*).



917 **918** **919** **920** **923** **924** **(±)-921** **(±)-922**

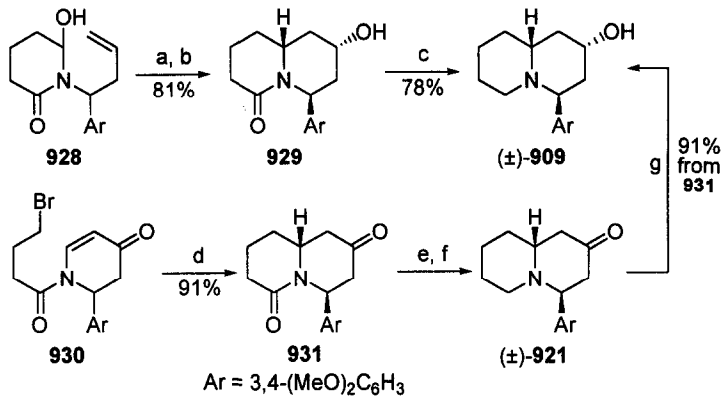
SCHEME 118. Reagents: a, CH_2Cl_2, 4 days; b, mesitylene, reflux; c, $Ph_3P{=}CHCOCH_3$, PhMe, reflux; d, NaH, rt; e, 25% HBr–AcOH; f, veratraldehyde, 1% aq. NaOH, 70°C.



925 **926** **927** **921** **922** **(±)-910**

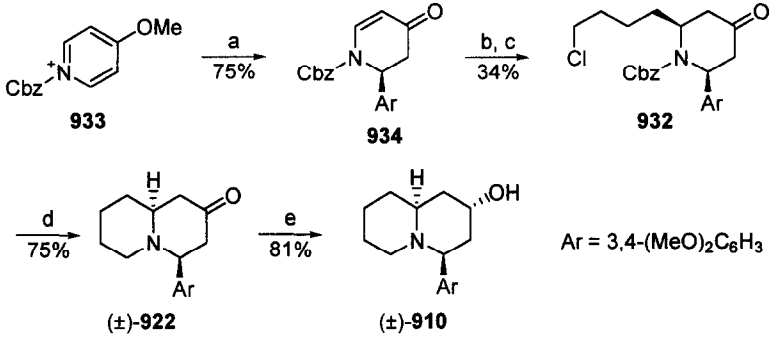
SCHEME 119. Reagents: a, TMSOTf, NEt_3, CH_2Cl_2, 0°C; b, $NaHCO_3$; c, 2M NaOH (or NH_4OH), MeOH; d, LS-Selectride, THF, –78°C, then MeOH, rt, 36 h.

An *N*-acyliminium ion intermediate was also involved in the highly stereoselective synthesis of (±)-lasubine I (**909**) by Speckamp and co-workers (Scheme 120) (*602*). When the glutarimide derivative **928** was treated with formic acid, quinolizidin-2-one **929** was obtained as the sole product (81%). This useful transformation simultaneously set up all three of the target alkaloid's stereogenic centers with the correct relative stereochemistry. Reduction of **929** with lithium aluminum hydride completed the synthesis of **909** in 63% yield based on **928**. In the same Scheme is shown the route to (±)-**909** devised by Beckwith and co-workers, which used a highly diastereoselective radical-mediated cyclization of the *N*-acylated 2,3-dihydropyridin-4-one **930** to give the bicyclic compound **931** as the sole product (91%) (*370*). The cyclization appears to take place *anti* to the aryl substituent because of non-bonded interactions with the amide carbonyl group. Reduction of both carbonyl groups with lithium aluminum hydride was followed by re-oxidation of the mixture of secondary alcohols at C-2 to give ketone **921**, which—rather surprisingly, in view of reports by other workers—was selectively reduced with sodium borohydride to complete the synthesis of the target alkaloid.

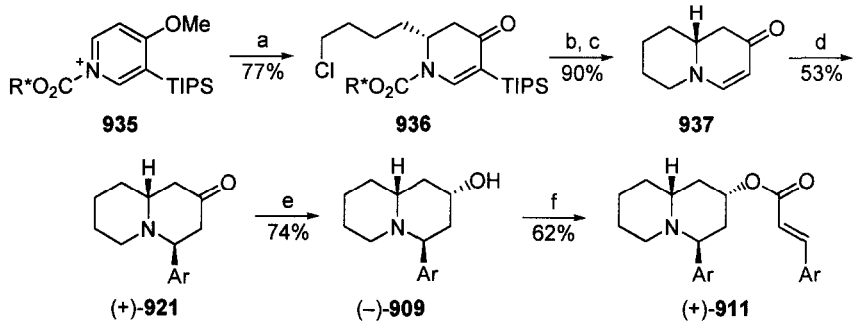


SCHEME 120. Reagents: a, HCO_2H, rt; b, KOH, EtOH, 0°C; c $LiAlH_4$, THF, reflux; d, Bu_3SnH, AIBN (cat.), C_6H_6, reflux; e, $LiAlH_4$; f, PCC; g, $NaBH_4$.

In an equally stereoselective synthesis of (±)-lasubine II (**910**), Comins and co-workers prepared the 2,6-*cis*-disubstituted piperidine **932** by sequential addition of 3,4-dimethoxyphenylmagnesium bromide to the *N*-acylpyridinium salt **933**, followed by conjugate addition of a 4-chlorobutylcuprate to the resulting dihydropyridone **934** (Scheme 121) (*603*). Removal of the protecting group on nitrogen and cyclization gave ketone **922** (75%). Equatorial delivery of hydride to the carbonyl group (96% diastereoselectivity) was effected by reaction with LS-Selectride at –78°C to give alkaloid **910** in 81% yield. With sodium borohydride as reductant, the yields of lasubine II and its C-2-epimer were 19% and 70%, respectively.



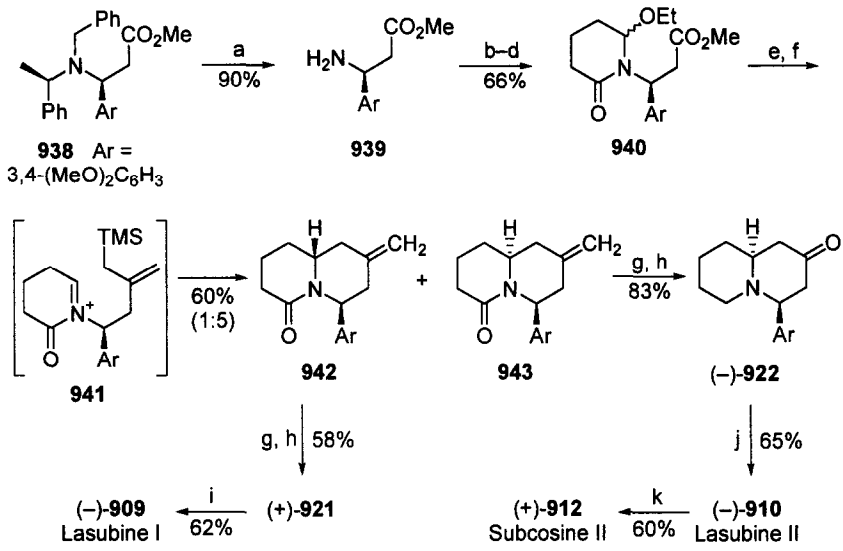
SCHEME 121. Reagents: a, 3,4-$(MeO)_2C_6H_3MgBr$, THF, –23°C; b, $Cl(CH_2)_4MgBr$, Et_2O–THF, CuBr·Me_2S, BF_3·Et_2O; c, NCS, DMF, PPh_3, 0°C to 50°C; d, H_2 (40 psi), 5% Pd/C, Li_2CO_3, EtOAc; e, LS-Selectride, THF, –78°C.



SCHEME 122 [R* = (–)-8-phenylmenthyl; Ar = 3,4-$(MeO)_2C_6H_3$]. Reagents: a, $Cl(CH_2)_4MgBr$, THF–PhMe, –78°C; b, KOMe, DMSO, rt; c, $(CO_2H)_2$; d, 3,4-$(MeO)_2C_6H_3Li$, CuBr, TMSCl; e, L-Selectride; f, 3,4-dimethoxycinnamic anhydride, pyridine, DMAP, reflux.

The Comins team later adapted their dihydropyridone methodology to provide the first enantioselective synthesis of lythraceous alkaloids (Scheme 122) (*373*). A diastereoselective reaction between 4-chlorobutylmagnesium bromide and the chiral pyridinium salt **935** [R* = (–)-8-phenylmenthyl] gave the optically active dihydropyridone **936** (86% de), the triisopropylsilyl group serving to block addition at the proximal site. Hydrolytic removal of the auxiliary, cyclization, and desilylation then afforded the optically pure vinylogous amide **937**. The 4-aryl group was introduced by conjugate addition, thereby producing the (+)-enantiomer of quinolizidinin-2-one **921**. Reduction with L-Selectride completed this short synthesis of (–)-**909**, the naturally occurring enantiomer of lasubine I. Finally, acylation with 3,4-dimethoxycinnamic anhydride gave (+)-subcosine I (**911**), also the natural enantiomer. This synthesis established the (2*S*,4*S*,9a*R*) absolute configurations of the two alkaloids.

In 1998, Remuson and co-workers described a route to (±)-lasubines I and II that involved intramolecular nucleophilic attack of a vinylsilane onto an acyliminium ion to create the quinolizidine nucleus (*604*). Shortly thereafter, an enantioselective modification of the same basic strategy was revealed (Scheme 123) (*605*). The chiral β-aminoester reactant **938** was made by conjugate addition of the anion of (*R*)-*N*-benzyl-1-phenylethylamine (**540**) to methyl (*E*)-3,4-dimethoxycinnamate (*cf.* Schemes 69, 70). The primary amine **939** formed after removal of the benzyl groups was converted into the ethoxylactam **940** in three steps. When this lactam was treated with trimethylsilylmethylmagnesium chloride and cerium(III) chloride followed by dilute hydrochloric acid, the intermediate acyliminium ion **941** cyclized spontaneously to give a 1:5 mixture of the 2-methylenequinolizidin-5-ones **942** and **943** in 60% overall yield. The isomers were separated by flash chromatography, and then converted into (–)-lasubine I (**909**) and (–)-lasubine II (**910**), respectively, *via* the ketones (+)-**921** and (–)-**922**. The overall yields from **938** were 7% and 14%. In addition, acylation of (–)-**910** with *trans*-3,4-dimethoxycinnamic anhydride yielded (+)-subcosine II (**912**). This synthesis confirmed the (2*S*,4*S*,9a*S*) absolute configurations of naturally occurring (–)-lasubine II and (+)-subcosine II, which had never before been synthesized in optically pure form.



SCHEME 123. Reagents: a, H_2 (4 bar), $Pd(OH)_2/C$, AcOH, MeOH; b, glutaric anhydride, PhMe, reflux; c, AcCl, PhMe, reflux; d, $NaBH_4$, EtOH, H_2SO_4 (2 M), –10°C; e, $TMSCH_2MgCl$, $CeCl_3$, THF, –78°C to rt, 3d; f, 1M HCl, 0°C; g, $LiAlH_4$, THF, reflux; h, OsO_4 (cat.), $NaIO_4$, 80% HOAc, 10°C; i, L-Selectride, THF, –78°C to 0°C; j, LS-Selectride, THF, –78°C to 0°C; k, (*E*)-3,4-dimethoxycinnamic anhydride, DMAP, pyridine, reflux.

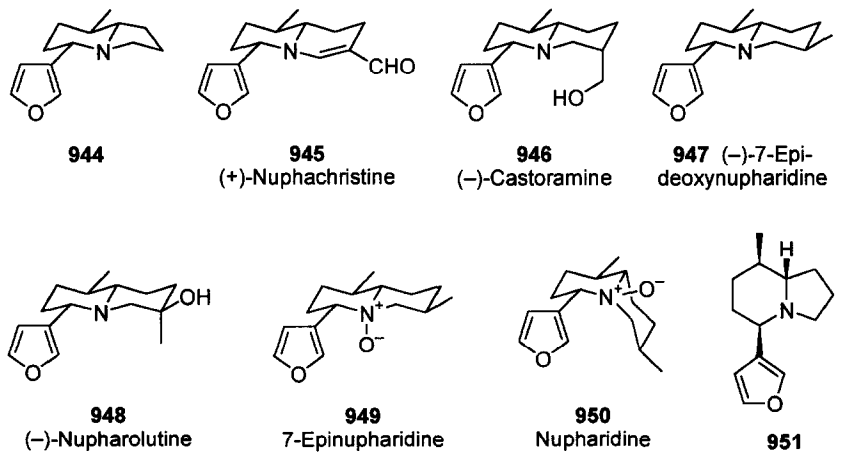
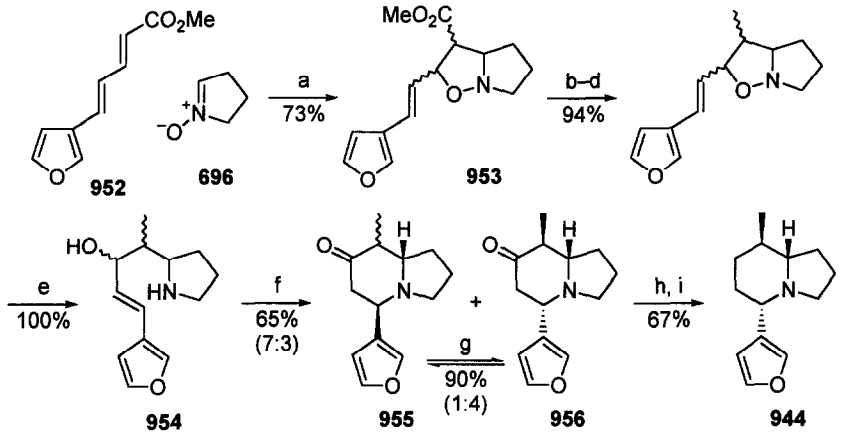


FIG. 18. *Nuphar* indolizidine and quinolizidine alkaloids.

H. *NUPHAR* ALKALOIDS

The previous review on *Nuphar* (water-lily) alkaloids in this treatise appeared in Volume 35, and covered the period 1974–1987 (*7*). It overlapped in part with the treatment of simple bicyclic *Nuphar* metabolites in Volume 28 (*1*). *Nuphar* alkaloids include sesquiterpenoid monomeric (C_{15}) piperidine and quinolizidine alkaloids as well as more complex dimeric (C_{30}) sulfur-containing metabolites. Related metabolites isolated from the scent glands of the Canadian beaver, *Castor fiber*, also include a unique indolizidine alkaloid **944** (*606*). Only the indolizidine and simple quinolizidine alkaloids are relevant to the present review. Compounds mentioned in the ensuing discussion are illustrated in Fig. 18.

No new simple *Nuphar* alkaloids have been recorded since 1988, when (+)-nuphachristine (**945**) was reported from the rhizomes of *N. luteum*. Since the previous review in this treatise reported the results as being in press (*7*), the reference to the subsequently published article is given here (*607*). The known alkaloids (−)-castoramine (**946**), (−)-7-epideoxynupharidine (**947**) and (−)-nupharolutine (**948**) were isolated more recently from rhizomes of *N. japonicum* by bioassay-guided fractionation (*608*). The isolation of castoramine is especially interesting, as its only natural source before this study had been the Canadian beaver (*606*). When the purified alkaloids were tested for insecticidal activity, the most active compound against larvae of the house-fly, *Drosophila melanogaster*, was castoramine (LC_{50} 1.00 μmol per ml of diet). However, 7-epideoxynupharidine had the greatest acute toxicity towards adult flies (LD_{50} 0.86 μg per adult), and was also the most potent inhibitor of acetylcholinesterase isolated from the flies.



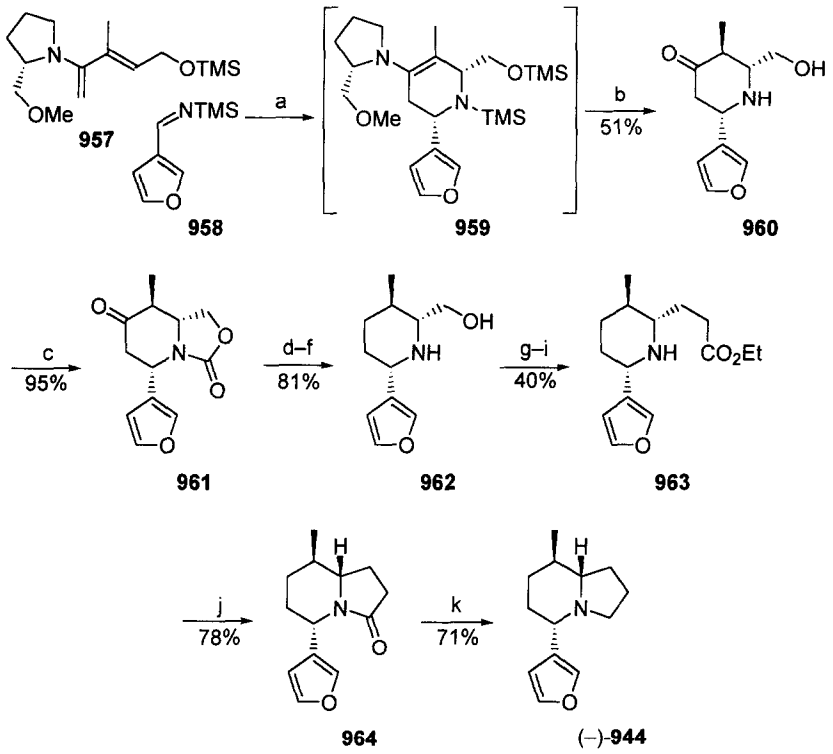
SCHEME 124. Reagents: a, C_6H_6, reflux; b, $LiAlH_4$, Et_2O; c, MsCl, Et_3N; d, Super-Hydride, THF; e, Zn, AcOH–H_2O; f, MnO_2, then chromatography; g, 10% aq. NaOH, MeOH, reflux; h, $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$; i, Bu_3SnH.

The role of mass spectrometry in the stereochemical elucidation of C_{15} and thio-C_{30} *Nuphar* alkaloids was highlighted in a short review dealing with some individual alkaloids, and with general fragmentation patterns (*609*). Mass-analyzed ion kinetic energy (MIKE) spectrometry has been used for analyzing metastable ion decomposition for several C_{15} *Nuphar* alkaloids and their *N*-oxides (*610*). The technique is useful for estimating spatial relationships from the charge separation between doubly-charged ions; it demonstrated, for example, differences between *trans*- and *cis*-fused quinolizidine rings in 7-epinupharidine (**949**) and nupharidine (**950**), respectively.

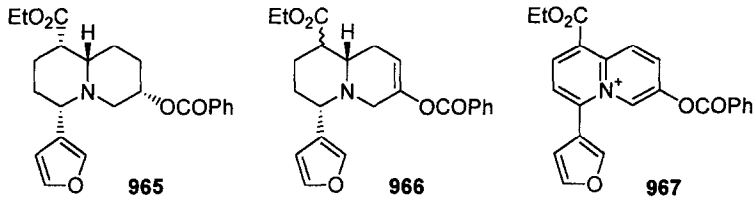
Some uncertainty remains about the relative and absolute configuration of the beaver indolizidine (also frequently called the *Nuphar* indolizidine), since too little natural product was isolated for unambiguous structural elucidation (*606*). Diagram **944** shows the generally accepted structure, assigned by analogy with the well-characterized *Nuphar* quinolizidines. However, other isomeric structures cannot be ruled out, and so two recent syntheses of the racemic diastereomer **951** must be pointed out (*611,612*). A route to the more commonly accepted structure **944**, devised by Tufariello and Dyszlewski, began with regiospecific cycloaddition of nitrone **696** to methyl (2*E*,4*E*)-5-(3-furyl)penta-2,4-dienoate (**952**) (Scheme 124) (*613*). The mixture of isoxazolidine products **953** was carried through a five-step sequence of transformations involving defunctionalization of the ester, hydrogenolysis of the heterocycle's N–O bond, and oxidation of the resulting alcohols **954** to give a separable mixture of indolizidine diastereomers **955** and **956** in a ratio of 7:3. Equilibration of these isomers in favor of the latter was readily effected with methanolic hydroxide, after which removal of the carbonyl group by way of a dithiolane yielded the target indolizidine **944** in an overall yield of approximately 24%. The mass spectrum of synthetic **944** was identical to that reported for the natural compound, and other spectra matched those of the product made by an independent route (*614*).

The only asymmetric synthesis of the *Nuphar* indolizidine to date is due to Barluenga and co-workers (*615*). Their route to the (5*S*,8*R*,8a*S*)-(–) enantiomer of **944** commenced with cycloaddition between the proline-derived 2-amino-butadiene **957** and imine **958** (Scheme 125). Hydrolysis of the adduct **959** gave piperidinone **960** in 51% yield and an ee of better than 99%. Once the alcohol and amine groups had been mutually protected as the cyclic carbamate **961**, defunctionalization of the ketone was accomplished *via* an enol triflate. Chain-extension of the deprotected piperidine **962** at the hydroxymethyl substituent afforded **963**, which was cyclized to the bicyclic lactam **964** simply by heating in toluene. Reduction with lithium aluminum hydride completed the synthesis of (–)-**944** ($[\alpha]_D$ –99°, *c* 1.3, CH_2Cl_2).

Quinolizidines **965** and **966**, potentially useful intermediates for the synthesis of *Nuphar* alkaloids, have been prepared by reducing the quinolizinium salt precursor **967** with sodium cyanoborohydride in ethanol–acetic acid (*616*). Compound **967** was itself prepared by Hantzch condensation of ethyl (5-benzoyloxy-2-pyridyl)acetate with the ethyl enol ether of 3-furoylacetaldehyde.



SCHEME 125. Reagents: a, $ZnCl_2$, THF, –80°C to 25°C; b, aq. $NaHCO_3$, then SiO_2; c, triphosgene; d, LiHMDS, 2-(NTf_2)-pyridine, THF, –80°C; e, H_2 (1 atm.), PtO_2, EtOH, rt; f, KOBu^t, THF, 0°C; g, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –65°C to rt; h, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2; i, H_2 (1 atm.), Pd/C. EtOH; j, PhMe, reflux; k, $LiAlH_4$, THF, reflux.



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