11.01
Bicyclic 6-6 Systems with One Bridgehead (Ring Junction) Nitrogen Atom: No Extra Heteroatom

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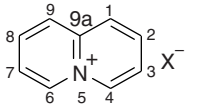
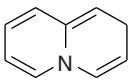
11.01.1 Introduction

According to their level of unsaturation, bicyclic 6-6 systems with one bridgehead nitrogen can be classified as quinolizinium, quinolizine, or quinolizidine derivatives. The quinolizinium ion **1** is the newest benzenoid aromatic heterocyclic system having one nitrogen atom, and the investigation of its properties is still an active research topic. Regarding the quinolizine system, it can exist as three possible tautomeric structures, namely 2*H*-quinolizine **2**, 4*H*-quinolizine **3**, and 9a*H*-quinolizine **4**. None of them has been isolated as a stable species, although **3** may have a transient existence, but a large number of substituted quinolizine derivatives are known. The saturated system, that is, quinolizidine **5** is very important due to the bewildering profusion of quinolizidine alkaloids in nature.



1



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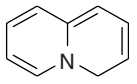

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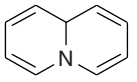

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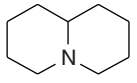
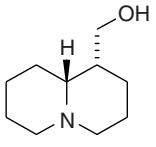


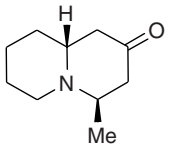
5

It has been estimated that 25–30% of all known alkaloids belong to the quinolizidine–indolizidine group. Some examples of alkaloids containing quinolizidine, quinolizine, or quinolizinium structural fragments are given in structures **6–16**.

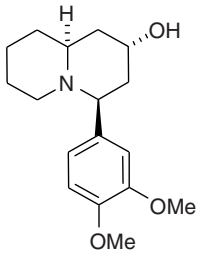
Simple quinolizidine alkaloids



Lupinine
6

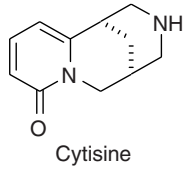


Myrtine
7



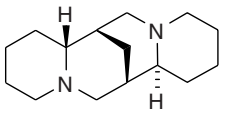
Lasubine II
8

Tricyclic quinolizidine–piperidine alkaloids



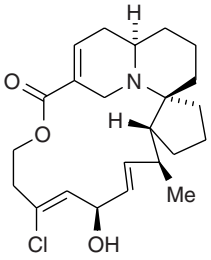
Cytisine
9

Tetracyclic bisquinolizidine alkaloids



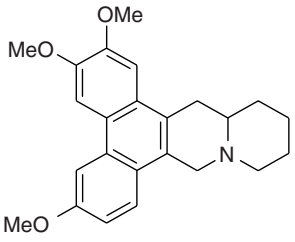
Sparteine
10

Spiroquinolizidine alkaloids



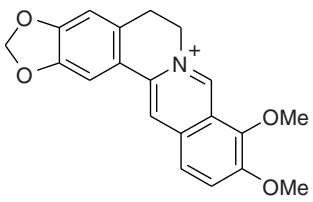
Halichlorine
11

Phenanthroquinolizine alkaloids



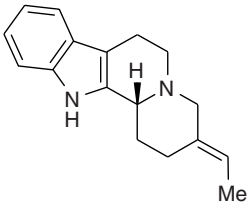
Cryptopleurine
12

Berberine alkaloids

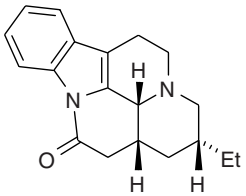


Berberine
13

Indoloquinolizidine alkaloids

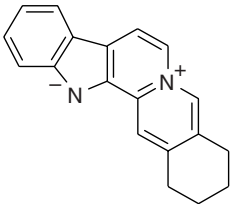


Deplancheine
14



Tacamonine
15

Quinolizinium alkaloids



Sempervirine
16

The occurrence of quinolizidines in nature has stimulated a vast amount of research into their chemistry, biochemistry, and pharmacology, and it is not possible to cover all relevant facts within the scope of a single chapter. For more detailed information, the reader is referred to the numerous comprehensive reviews available on quinolizidine alkaloids and related subjects <1996RCC(4)181, B-2001MI91> and to the periodical reviews covering developments in their chemistry, appearing in *Natural Product Reports* <1996NPR45, 1997NPR619, 1998NPR571, 1999NPR675, 2000NPR579, 2001NPR520, 2002NPR719, 2003NPR458, 2004NPR625, 2005NPR603, 2007NPR191>. Periodical reports on other types of alkaloids from the same sources also contain information on certain arenoquinolizine alkaloids like the berberin and emetan derivatives that are normally classified as isoquinoline alkaloids. For surveys of the literature published prior to 1996, perusal of the corresponding chapters in previous editions of this work <1984CHEC(2)525, 1996CHEC-II(8)507> is recommended.

11.01.2 Theoretical Methods

11.01.2.1 Molecular Mechanics

Molecular mechanics (MM) calculations have been employed for determining dihedral angles and to establish a comparison with values calculated from coupling constants, during conformational studies of tricyclic and tetracyclic quinolizidine alkaloids. The MM results had to be treated with care, as they sometimes predicted ring conformations different to those supported by experimental data <1999JST215>.

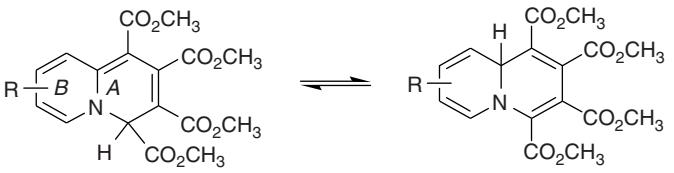
11.01.2.2 Quantum Methods

11.01.2.2.1 *Ab initio* calculations

Ab initio Hartree–Fock calculations have been used to study the stability of the 4*H*- and 9a*H*-tautomers (**17** and **18**, respectively) of a series of derivatives of tetramethyl quinolizine-1,2,3,4-tetracarboxylate. These calculations (**Table 1**) have confirmed that the 4*H*-tautomer is the thermodynamically more stable form <2003JST719>.

Ab initio calculations using the CHF-GIAO approach on the optimized geometrical configurations of the compounds have also allowed to predict the ^{1}H, ^{13}C, and ^{15}N nuclear magnetic resonance (NMR) spectra of the quinolizidine series. The calculated spectra fit fairly well the experimental data, with the exception of some signals

Table 1 *Ab initio* stabilities of the 4*H*- and 9a*H*-tautomers of a quinolizine system



4*H*-Tautomer
17

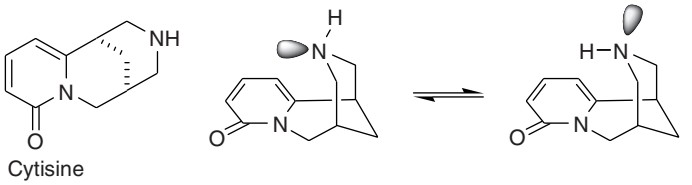
9a*H*-Tautomer
18

	Total RHF/DZ-HB energy (Hartree)		
Substitution	*9aH-Tautomer* (**18**)	*4H-Tautomer* (**17**)	ΔE (*kcal mol*$^{-1}$)
None	−1307.231936	−1307.267951	22.60
6-CH_3	−1346.266212	−1346.309440	27.13
7-CH_3	−1346.275089	−1346.310853	22.44
8-CH_3	−1346.276687	−1346.313841	23.31
9-CH_3	−1346.270554	−1346.298247	17.38

of the 9a*H*-tautomers. This discrepancy was interpreted in terms of conformational differences between the frozen structures of molecules calculated *in vacuo* and flexible molecules measured in a polar medium <2003JST719>.

11.01.2.2.2 Semi-empirical calculations

Cytisine is a tricyclic quinolizidine alkaloid that binds with high affinity and specificity to nicotinic acetylcholine receptors. In principle, this compound can exist in several conformations, but semi-empirical calculations at the AM1 and PM3 levels have shown that structures **19** and **20** are more stable than other possible conformers by more than 50 kcal mol^{-1}. Both structures differ by 3.7 kcal mol^{-1} at the AM1 level and 2.0 kcal mol^{-1} at the PM3 level, although this difference is much smaller when *ab initio* calculations are employed <2001PJC1483>. This conclusion is in agreement with infrared (IR) studies and with ^{1}H NMR data obtained in $CDCl_3$ solution, which are compatible with an *exo–endo* equilibrium <1987JP21159>, although in the solid state cytisine has an *exo* NH proton (structure **19**) (see Section 11.01.3.4.2).



Cytisine
9

19

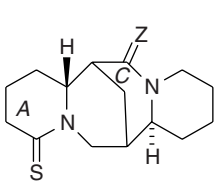
20

11.01.3 Experimental Structural Methods

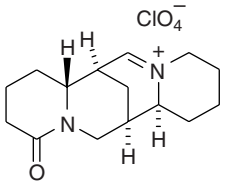
11.01.3.1 X-Ray Analysis

Structural characterization of many quinolizidine derivatives has been established by X-ray diffraction. For example, this technique, in combination with spectroscopic methods, showed that (+)-2-thionosparteine **21** and (+)-2,17-dithionospartine **22** are conformationally rigid and have their lactam and thiolactam groups close to planarity, with the exception of the lactam group in **21**, and that rings A and C adopt distorted sofa conformations <2005JST75>.

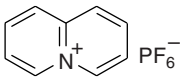
Bisquinolizidine alkaloids have also been widely studied by this technique. For instance, the crystal structure of (−)-$\Delta^{16(17)}$-dehydrolupaninium perchlorate **23** was obtained from sealed-tube and synchroton X-ray diffraction data, and showed that the A, B, C, and D rings assume distorted half-chair, chair, distorted sofa, and chair conformations, respectively; it was also used to determine the most precise dimensions so far known for the iminium group <1999JST245>. The crystal structure of quinolizinium hexafluorophosphate has also been studied <2001CSC174>.



21: Z = O
22: Z = S



23



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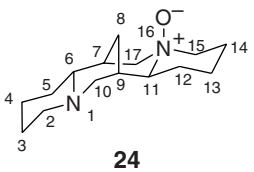
11.01.3.2 NMR Spectroscopy

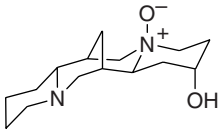
11.01.3.2.1 Proton NMR spectroscopy

On the basis of their ^{13}C NMR assignments (see below), ^{1}H–^{1}H correlation spectroscopy (COSY) and ^{1}H–^{13}C COSY experiments allowed to assign the ^{1}H NMR data of a series of sparteine analogues and derivatives (compounds **24**–**27**). These data are collected in **Table 2** <2003JST275>. Detailed ^{1}H NMR assignments for other sparteine derivatives are also available in the literature (see, for instance, <2005JST75>).

Table 2 ^{1}H-NMR assignments of some sparteine analogues and derivatives



24



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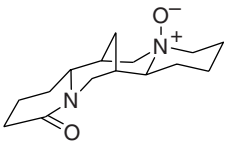

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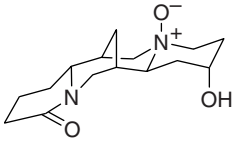
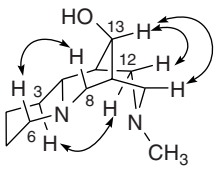


27

H atom	**24** (*$CDCl_3$*)	**25** (*CD_3OD*)	**26** (*CD_3OD*)	**27** (*$CDCl_3$*)
2α	2.69	2.75		
2β	2.07	2.09		
3α	1.47	1.55	2.47	2.48
3β	1.60	1.62	2.40	2.41
4α	1.73	1.75	1.85	1.86
4β	1.27	ca. 1.27	1.67	1.67
5α	1.18	ca. 1.27	1.52	1.60
5β	1.34	1.37	1.88	1.87
6	1.86	1.91	3.49	3.48
7	2.05	2.04	2.30	2.32
8α	3.64	3.38	3.54	3.53
8β	1.15	1.25	1.45	1.47
9	1.63	1.62	1.80	1.79
10α	2.48	2.57	4.43	4.24
10β	2.05	2.06	2.61	2.61
11	3.10	3.68	2.61	2.61
12α	1.41	1.57	1.60	1.65
12β	2.31	2.35	2.13	2.34
13α	1.38		1.44	
13β	1.77	4.02	1.75	4.01
14α	1.51	1.63	1.56	1.64
14β	2.52	2.50	2.30	2.46
15α	3.06	3.58	3.25	3.58
15β	3.27	3.08	3.19	3.06
17α	3.24	3.41	3.16	3.24
17β	3.35	3.32	3.39	3.41

Nuclear Overhauser enhancement spectroscopy (NOESY) experiments play a very important role in structural studies in quinolizidine derivatives. For instance, the *endo*-type structure of compound **28** was proven by the steric proximity of the H-3α and H-12α protons according to the NOESY cross peak, while the spatial proximity of the H-6β and H-8β protons reveals that tha A/B ring junction has a *trans*-stereochemistry. Similarly, compound **28** could be distinguished from its regioisomer **29** on the basis of the NOESY behavior of its H-13 atom <1999JST153>.



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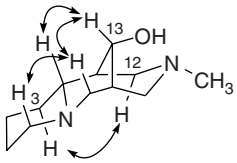
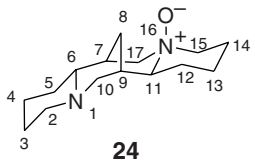


29

11.01.3.2.2 Carbon-13 NMR spectroscopy

The ^{13}C NMR assignments of a series of bisquinolizidine compounds related to sparteine (compounds **24**–**27**) are summarized in **Table 3** <2003JST275>. Detailed ^{13}C NMR assignments for other sparteine derivatives are also available in the literature <2003T5531, 2005JST75>.

Table 3 ^{13}C-NMR assignments of some sparteine-related compounds



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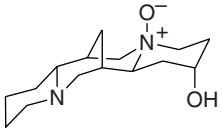

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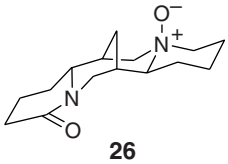

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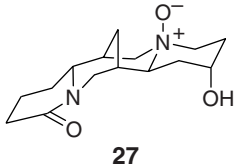


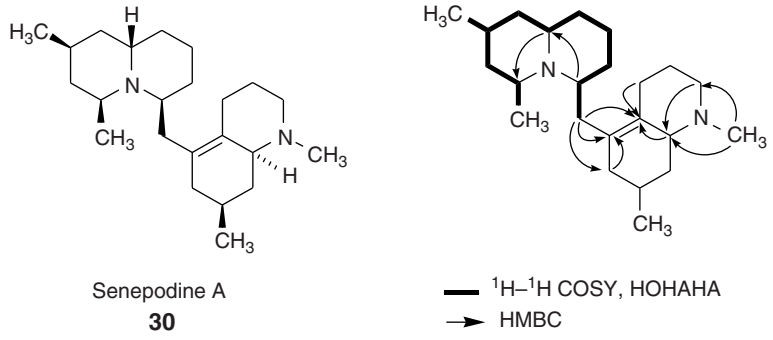
27

Position	**24** (*$CDCl_3$*)	**25** (*CD_3OD*)	**26** (*$CDCl_3$*)	**26** (*CD_3OD*)	**27** (*$CDCl_3$*)
2	55.70	56.74	172.1	174.78	171.6
3	25.77	26.75	33.00	33.60	33.60
4	24.32	25.46	19.40	20.28	20.40
5	29.70	30.65	27.70	28.24	28.30
6	66.25	67.60	61.80	63.06	62.80
7	32.46	33.75	33.60	33.04	33.00
8	26.10	27.05	22.70	26.46	26.30
9	34.61	35.27	31.70	34.96	34.30
10	61.56	62.19	47.00	48.05	47.80
11	71.53	66.46	71.40	72.27	65.70
12	27.87	36.00	27.70	28.59	36.00
13	23.19	63.08	25.70	23.74	62.50
14	20.50	28.76	20.30	21.37	28.50
15	69.37	65.00	69.60	70.44	63.10
17	66.32	67.00	65.20	66.23	66.10

NMR spectroscopy provides an accurate method for studying conformational equilibria. In the case of fast processes, the experimentally observed chemical shifts and coupling constants depend on the chemical shifts and coupling constants of the individual conformers, which are averaged in the NMR timescale according to their contribution to the conformational mixture. Thus, the chemical shift values for C-12 and C-14 in bisquinolizidine alkaloids, together with the values for the coupling constant H_7–$H_{17\beta}$, have been employed for the study of their conformational equilibria <1996JST23>.

The combination of ^1H NMR, ^{13}C NMR data and ^1H–^1H and ^1H–^{13}C correlations has been widely employed for the structural assignment of quinolizidine natural products. One example is the alkaloid senepodine A **30**,

isolated from the club moss *Lycopodium chinense* and assigned the structure indicated on the basis of two-dimensional experiments including COSY, homonuclear Hartmann-Hahn (HOHAHA), heteronuclear multiple bond correlation (HMBC) and NOESY <2001TL4199>. The absolute configuration of senepodine A was subsequently determined by the exciton chirality method, after its derivatization by allylic oxidation at C-6 of the quinoline moiety followed by preparation of the corresponding *p*-bromobenzoyl ester and study of its Cotton effect <2003T3567>.



Senepodine A
30

11.01.3.2.3 Nitrogen-15 NMR spectroscopy

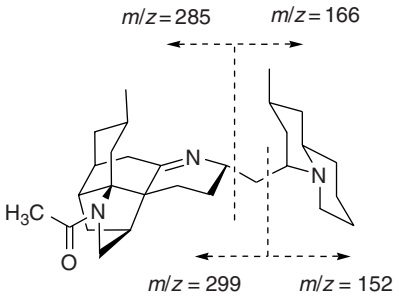
The previously mentioned series of alkyl derivatives of tetramethyl quinolizine-1,2,3,4-tetracarboxylate, which is present as mixtures of the 4*H*- and 9a*H*- tautomers **17** and **18**, was studied by ^{15}N NMR, both experimentally and using *ab initio* calculations. The data are collected in **Table 4**. The *ab initio* ^{15}N NMR chemical shifts reproduce well the trends observed in the experimental data, but their values are ca. 72 ppm smaller than the experimental ones <2003JST719>.

Table 4 Experimental and *ab initio*-calculated ^{15}N-NMR chemical shifts of the 4*H*- and 9a*H*-tautomers of a quinolizine system

	9aH tautomer (**18**)		*4H tautomer* (**17**)	
Substitution	*Experimental*	*Calculated*	*Experimental*	*Calculated*
None	−273.1	−363.2	−221.4	−304.3
6-CH_3	Not measured	−371.1	−216.6	−301.3
7-CH_3	Not measured	−362.8	Not measured	−306.5
8-CH_3	Not measured	−363.4	−223.0	−306.7
9-CH_3	−271.3	−351.7	−209.5	−290.0

11.01.3.3 Mass Spectrometry

The mass spectral fragmentations of several types of quinolizidine derivatives, including derivatives of tricyclic quinolizidine-piperidine alkaloids such as multiflorine and angustifoline <1990OMS453> and tetracyclic bis-quinolizidine alkaloids such as sparteine and lupinine <2000JMP1271, 2005OMS700>, have been determined. Besides, mass spectrometry (MS), used in combination with spectroscopic techniques, has been the key to the structural assignment of a large number of quinolizidine natural products. For example, himeradine A **31**, isolated from the club moss *Lycopodium chinense*, showed a pseudomolecular peak at *m*/*z* 452 $(M + H)^+$ in the fast atom bombardment mass spectroscopy (FABMS) spectrum, and its molecular formula was established as $C_{29}H_{45}N_3O$ by high-resolution FABMS (HRFABMS) (*m*/*z* = 452.3647). Its structure was deduced by the analysis of its IR, ^1H, and ^{13}C NMR data, including two-dimensional COSY, HOHAHA, heteronuclear multiple quantum correlation (HMQC), HMBC, and HMQC–HOHAHA experiments. Further evidence for the proposed structure came from tandem MS experiments, through examination of the collision-induced dissociation (CID) mass spectrum of the $(M + H)^+$ ion. The positive ion FABMS/MS spectrum of himeradine A showed product ion peaks from the bond fissions shown below.



Himeradine A
31

Mass spectral data have also been employed for biological studies aimed at determining the distribution of quinolizidine alkaloids within a plant. For instance, the analysis of stem sections of *Lupinus polyphyllus* and *Cytisus scoparius* by laser desorption mass spectrometry led to the conclusion that these alkaloids are restricted to the epidermis and probably also to the neighboring one or two subepidermal cell layers <1984MI230>.

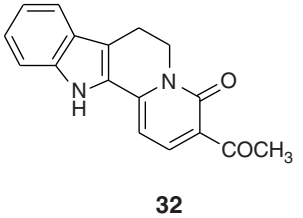
11.01.3.4 Ultraviolet–Visible, Luminescence, and IR/Raman Spectroscopy

11.01.3.4.1 Ultraviolet–visible and luminescence spectroscopy

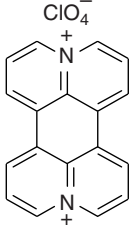
Quinolizine derivatives and quinolizinium salts exhibit native fluorescence, which has been extensively studied. The fluorescence behavior of 3-acetyl-4-oxo-6,7-dihydro-2*H*-indolo[2,3-*a*]quinolizine **32** has shown drastic modifications with changes in solvent polarity. When the fluorescence parameters were plotted against a solvent polarity parameter, the plots showed segmented linearity with two independent slopes. This observation led to the proposal that the fluorescence of this compound originates from two different states, namely a locally excited state and a charge-transfer state. Phosphorescence and heavy atom quenching studies were also carried out, and showed that the charge-transfer state lies above the lowest triplet state, even in very polar environments <2003CPL688>.

Regarding the luminescence properties of quinolizinium systems, the 3*a*,9*a*-diazaperylenium dication **33**, containing two quinolizinium moieties, has been synthesized recently (see Section 11.01.9.5.3), and it shows an interesting luminescence behavior <2002OL4113>. The perchlorate salt of this compound is soluble in several polar solvents, where it showed photoluminescence with 17–20 nm values for the Stokes shift, which are rather large for a rigid system (by way of comparison, the Stokes shift for perylene **34** in cyclohexane is 12 nm). This probably indicates a structural reorganization between the ground and the lowest excited state beyond the usual bond elongation upon photoexcitation. Indeed, *ab initio* calculations supported this interpretation by showing the ground state to be twisted, with a 6.4° tilt between the quinolizinium fragments, while the first excited state displayed a planar geometry (0.04° tilt). Interestingly, luminescence disappeared at liquid nitrogen temperatures, which was explained by assuming that the above-mentioned geometric relaxation upon excitation is not possible in the rigid matrices present at low temperatures.

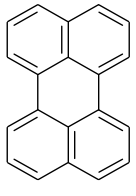
Fluorescence energy transfer experiments, in which the energy transfer from the excited DNA bases to a fluorescent ligand is monitored by fluorescence excitation spectroscopy, has been used to analyze the binding of the bisquinolizinium species **35** to DNA <2004ARK219>.



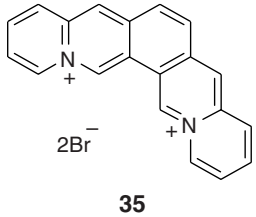
32



33



Perylene
34



35

11.01.3.4.2 Infrared/Raman spectroscopy

Infrared spectroscopy was the first physical technique employed in the study of conformational and configurational problems in quinolizidine derivatives through examination of the so-called Bohlmann bands in the 2700–2800 cm^{-1} region. These bands are characteristic of the *trans*-systems, although this criterion is sometimes unreliable because of the low intensity of the bands and because of their absence in *trans*-quinolizidines with distorted rings or lacking two axial hydrogens α to nitrogen <1996CHEC-II(8)507>.

More recently, infrared data have found further application in conformational studies of complex quinolizine derivatives, such as the previously mentioned alkaloid cytisine **9**. Comparison of experimental values for the $\nu_{(NH)}$ and $\nu_{(CO)}$ frequencies with the theoretical values obtained from semi-empirical calculations for both possible conformers led to the conclusion that both conformers **19** and **20** are present in solution in almost equimolecular amounts, with a slight preference for **19** in nonpolar solvents and for **20** in polar ones <2002TAL609>.

11.01.4 Thermodynamic Aspects

11.01.4.1 Solubility and Chromatographic Behavior

11.01.4.1.1 TLC and related techniques

Two-dimensional thin-layer chromatography (TLC) with adsorbent gradient has allowed the separation of quinolizidine alkaloids in the herb and in several alkaloids from *Genista* sp. <2004MI89>.

11.01.4.1.2 GC and GC-based hyphenated techniques

Quinolizine alkaloids, including sophocarpine, matrine and sophoridine have been determined by GC–MS techniques in *kuhuang*, a traditional Chinese medicine (GC = gas chromatography) <2005MI967>. Similarly, GC–MS has allowed a phytochemical study of the quinolizidine alkaloids of *Genista tenera* <2005MI264>.

11.01.4.1.3 HPLC and HPLC-based hyphenated techniques

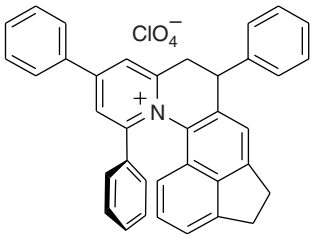
The high-performance liquid chromatography (HPLC) determination of quinolizidine alkaloids in *Radix Sophora flavescens* was assisted by using tris(2,2′-bipyridyl)ruthenium(II) electrochemoluminescence <2004MI237>. Tandem HPLC–MS techniques have allowed the development of a sensitive and specific method for the determination of sophocarpine, matrine, and sophoridine in rabbit plasma <2005MI1595>.

11.01.4.1.4 Capillary electrophoresis

Capillary electrophoresis has been employed for the quantitation of quinolizidine alkaloids in several natural sources, especially Chinese herbs <2004ANA17>, including the separation and simultaneous determination of quinolizine alkaloids in *Cortex Fraxini* and its medicinal preparations <2005MI696>, the determination of quinolizidine alkaloids in medicinal plants belonging to the *Sophora* genus <2004ANA15, 2005MI257>, and the determination of fangchinoline and tetrandine in *Radix Stephaniae* <2005MI639>.

11.01.4.2 Aromaticity

X-Ray diffraction data have been used to study the aromaticity of complex quinolizinium systems, such as the acenaphtho[4,5-*c*]quinolizinium derivative **36**. The rings connected to the molecule by single C–C bonds are more aromatic than those connected by more links as indicated by the homeostatic model assessment (HOMA) aromaticity index <1992AXC2238>.

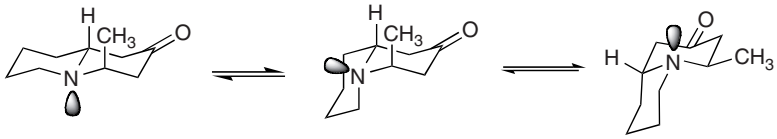


36

11.01.4.3 Conformational Aspects

The quinolizidine system poses an interesting conformational problem, due to the presence of the stereochemically mobile nitrogen atom. Three structures **37–39** are possible, one of them with a *trans*-arrangement between the nitrogen lone pair and the angular hydrogen atom and two others with a *cis*-ring fusion <1981T4287>, as shown for the case of the alkaloids myrtine **7** and epimyrtine. Theoretical calculations using the semi-empirical AM1 method, previously validated on decalin, have shown that the energies of the three conformers of myrtine are very similar, the calculated populations being 29% of **37**, 39% of **38**, and 32% of **39**, which is claimed to be in good agreement with the observed NMR spectral data <1998TA1823>, although the same NMR data were previously considered to be consistent with the presence of conformer **37** as the sole species. The same study <1998TA1823> showed that epimyrtine exists mainly as the *cis*-**41** conformer instead of the *trans*-structure **40**, as previously proposed.

Myrtine

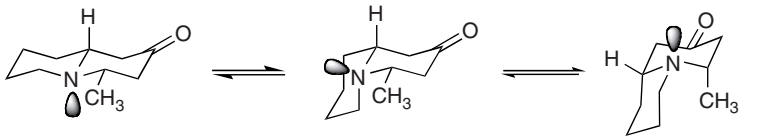


37 *trans* — $\Delta(\Delta H^0_f)$ 0.19 kcal mol^{-1}

38 *cis* — 0 kcal mol^{-1}

39 *cis* — 0.12 kcal mol^{-1}

Epimyrtine

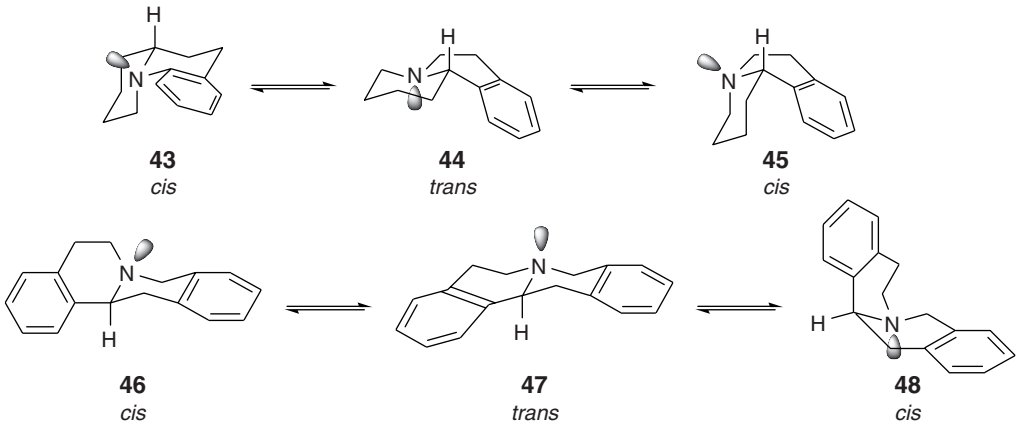


40 *trans* — $\Delta(\Delta H^0_f)$ 1.46 kcal mol^{-1}

41 *cis* — 0 kcal mol^{-1}

42 *cis* — 2.00 kcal mol^{-1}

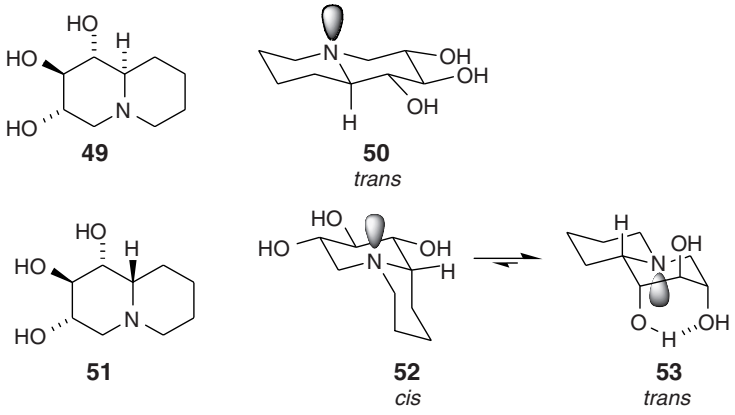
Similar conformational equilibria occur in arenoquinolizidines (e.g., structures **43–45** for benzo[*a*]quinolizidines and **46–48** for dibenzo[*ag*]quinolizidines).



43 *cis* **44** *trans* **45** *cis*

46 *cis* **47** *trans* **48** *cis*

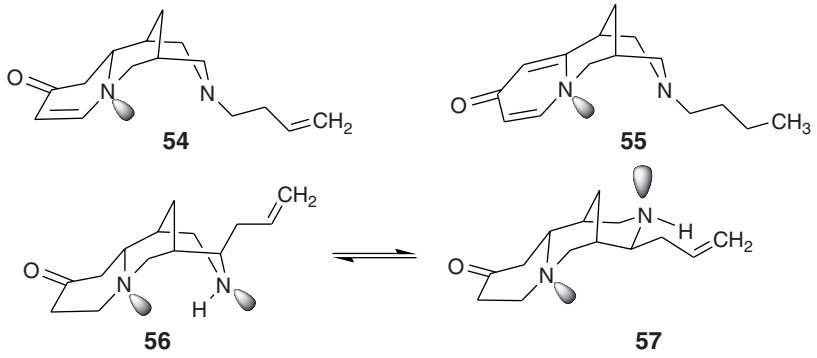
Substituents may play a crucial role in the conformation of quinolizidine systems. Thus, compound **49** shows a *trans*-conformation **50** with all three hydroxyl groups in equatorial positions. For its diastereomer **51**, a *cis*-conformation **52** was initially proposed, but the ^{1}H NMR data point at the *trans*-conformation **53**, with axial orientation of the hydroxy substituents and presumably stabilized by an intramolecular hydrogen bond <2004T3009>.



49 **50** *trans*

51 **52** *cis* **53** *trans*

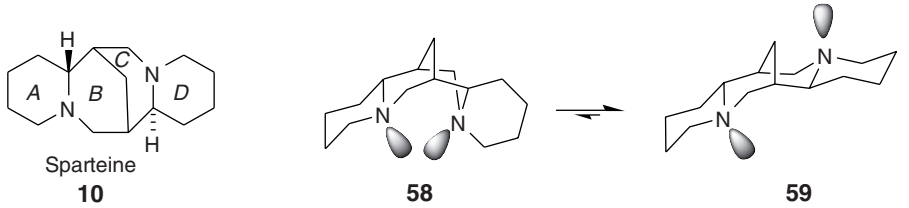
The conformational equilibria and geometry of tricyclic quinolizidine–piperidine systems has been extensively studied using ^{1}H and ^{13}C spectroscopy. Most of these compounds assume a conformation in solution with a chair ring C and a more or less distorted ring B, as in the solid state, as shown for the cases of seco(11,12)-12,13-didehydromultiflorine **54** and seco-(11,12)-5,6-didehydromultiflorine **55**. This result can be considered as surprising, in view of the high conformational flexibility expected for 3,7-diazabicyclo[3.3.1]nonane systems, and was attributed to the lack of steric hindrance for ring C because of the flattening of ring B as a consequence of the presence of double bonds in ring A <1999JST215>. This explanation agrees with the finding that angustifoline seems to be conformationally nonhomogeneous in solution, with the major conformer being **56** and a contribution of about 23% being estimated for the C-ring boat conformer **57** <1999T14501>.



54 **55**

56 **57**

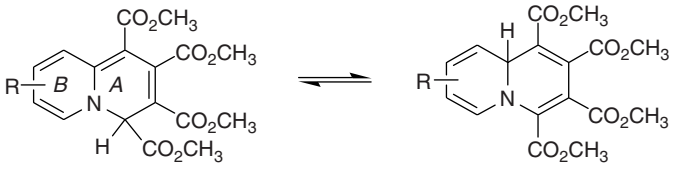
In solution, most tetracyclic bisquinolizidine alkaloids occur in the form of a mixture of conformers that differ mainly in the conformation of the third ring. In some cases, one of these conformers predominates; for example, sparteine **10** adopts almost exclusively the conformation **58**, with a boat structure for ring C and a *trans*-junction for rings C and D <1996JST3213>. For instance, in the case of 2-thionosparteine, ^{1}H and ^{13}C NMR data allowed calculation of the contribution of the C-boat structure **59** as 81% <1999JST207>. As in the case of simpler quinolizidines, conformational changes in this class of compounds involve inversion of the nitrogen lone pair, and therefore these changes are not possible if the lone pair is blocked (e.g., by formation of an *N*-oxide). Monoprotonation of sparteine is accompanied by a boat-to-chair conformational change of ring C <1997JST171>.



Sparteine
10 **58** **59**

11.01.4.4 Tautomerism

Quinolizine exists as a mixture of up to three species, namely the 2*H*-, 4*H*- and 9a*H*-tautomers (**17** and **18**, respectively). This tautomeric equilibrium has been extensively studied in the case of tetramethyl quinolizine-1,2,3,4-tetracarboxylate, where, as previously mentioned, the 4*H*-tautomer **17** has been shown to be thermodynamically more stable than the 9*H*-species **18** through *ab initio* Hartree–Fock calculations. An interesting feature of these compounds is that the rate of the interconversion of the 9a*H*-tautomer **18** into the more stable 4*H*-compound **17** depends on the position of substituents in ring B <2003JST651>.

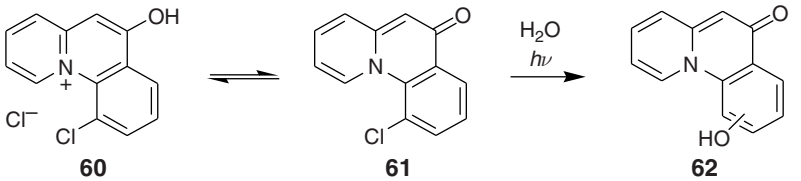


4*H*-Tautomer **17** 9a*H*-Tautomer **18**

11.01.5 Reactivity of Fully Conjugated Rings

11.01.5.1 Photochemical Reactions

Some quinolizinium derivatives such as MPB-07 **60** have importance as chloride channel activators. This compound has been shown to be photolabile in aqueous solution when exposed to daylight, being transformed into the phenolic derivative **62** with the deprotonated form **61** as an intermediate, as shown in **Scheme 1** <2002JPS324>. A highly regioselective solid-state photodimerization of naphthoquinolizinium salts has also been described <2002EJO2624>.

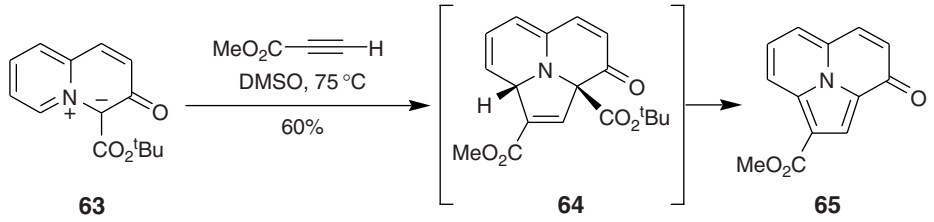


60 **61** **62**

Scheme 1

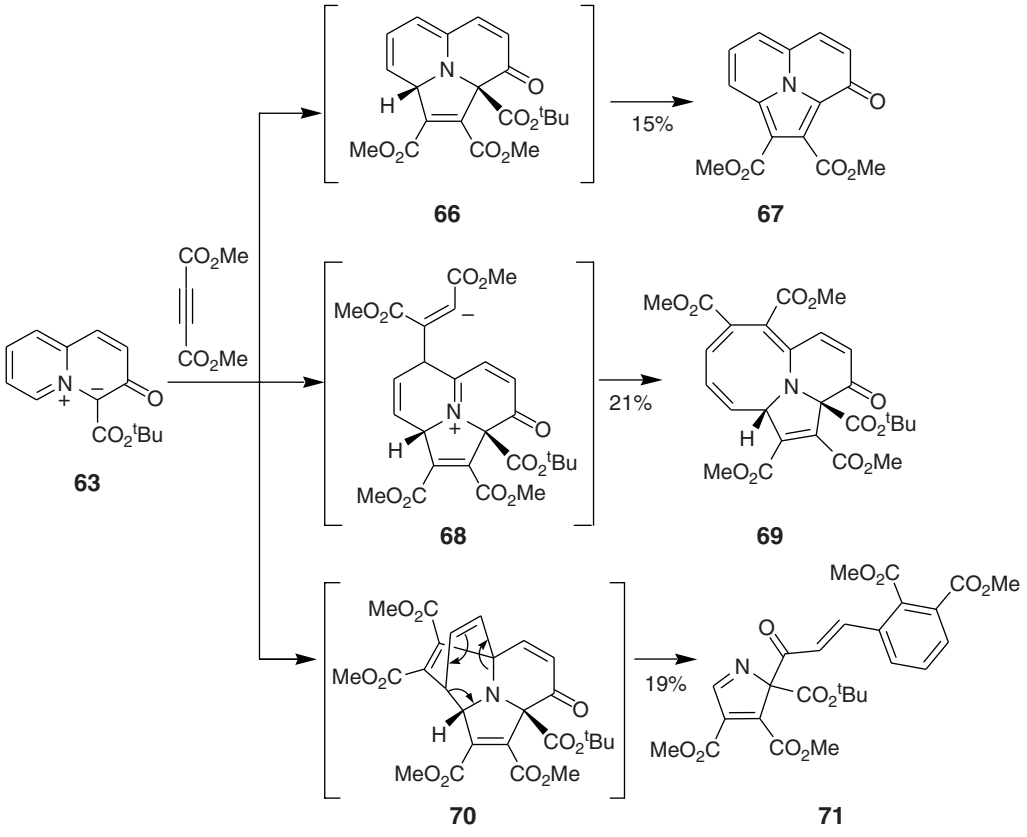
11.01.5.2 Intermolecular Cyclic Transition State Reactions

Acyl-substituted quinolizinium ylide **63** was obtained by treatment of its 1,2-dihydro analogue with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Its 1,3-dipolar cycloaddition with an acetylenic ester in excess was regioselective and was accelerated in polar solvents yielding the intermediate adduct **64** and finally the corresponding cyclazine **65**, as shown in **Scheme 2** <2001JOC1638>.



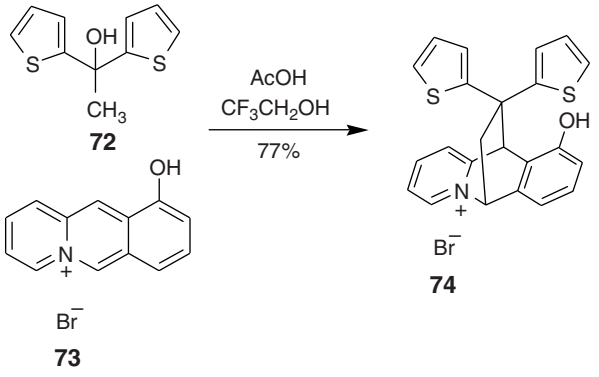
Scheme 2

The reaction of the same ylide **63** with dimethyl acetylenedicarboxylate (DMAD) in chloroform afforded the cyclazine **67**, through aromatization of monoadduct **66**; the azocine **69**, which is formed through a second nucleophilic attack with ring expansion in the bis-adduct **68**; and the pyrrolo derivative **71**, which is formed by evolution of the bis-adduct **70** through a retro-Diels–Alder reaction (**Scheme 3**) <2001JOC1638>.



Scheme 3

The quinolizinium ring can behave as the diene component in reverse electron demand Diels–Alder reactions. For example (Equation 1), the reaction between a dienophile generated *in situ* by acid-catalyzed dehydration of precursor **72** and quinolizinium **73** gave the 1,4-ethanobenzo[*b*]quinolizinium derivative **74** <2001BML519>.



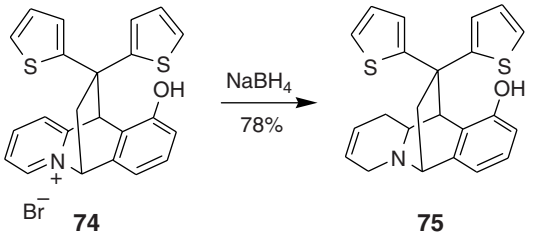
(1)

11.01.6 Reactivity of Nonconjugated Rings

11.01.6.1 Reactivity of Partially Saturated Quinolizines and Quinolizinium Salts

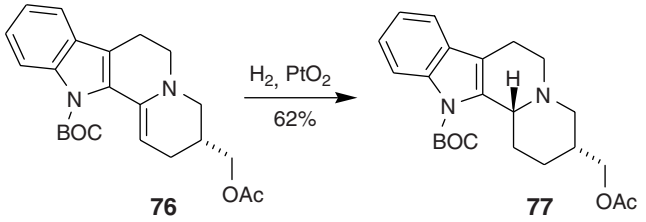
11.01.6.1.1 Reduction

The pyridinium portion of the previously mentioned partially saturated quinolizinium derivative **74** was reduced by sodium borohydride to yield compound **75**, which was employed as a precursor to a radiolabeled methyl ether as a probe for the *in vivo* distribution of quinolizinium prodrugs (Equation 2) <2001BML519>.



(2)

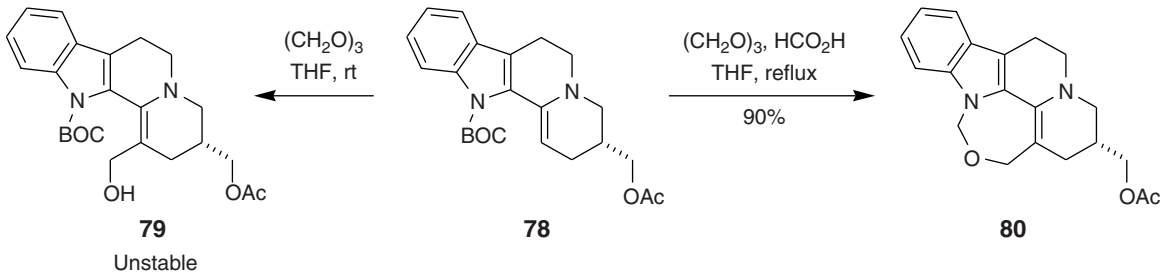
The C/C double bonds in the quinolizine system can be reduced by catalytic hydrogenation. One example, involving the transformation of an indolo[2,3-*a*]quinolizidine substrate **76** into compound **77**, can be found in Equation 3 <2001TL7237>.



(3)

11.01.6.1.2 Reaction with electrophiles

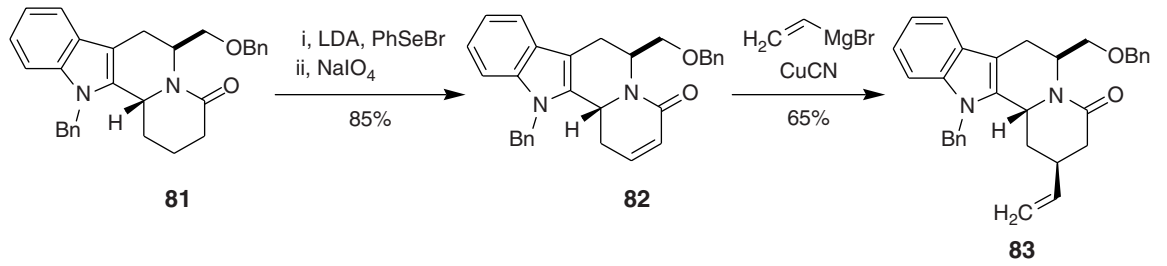
Enamine fragments present in quinolizine systems show their expected behavior as nucleophiles. For example, reaction of the indoloquinolizine derivative **78** with formaldehyde at room temperature afforded the unstable hydroxymethyl derivative **79**, while reflux of **78** with formaldehyde under acidic conditions led to indole deprotection and allowed the isolation of the pentacyclic derivative **80** (**Scheme 4**) <2001TL7237>.



Scheme 4

11.01.6.1.3 Reaction with nucleophiles

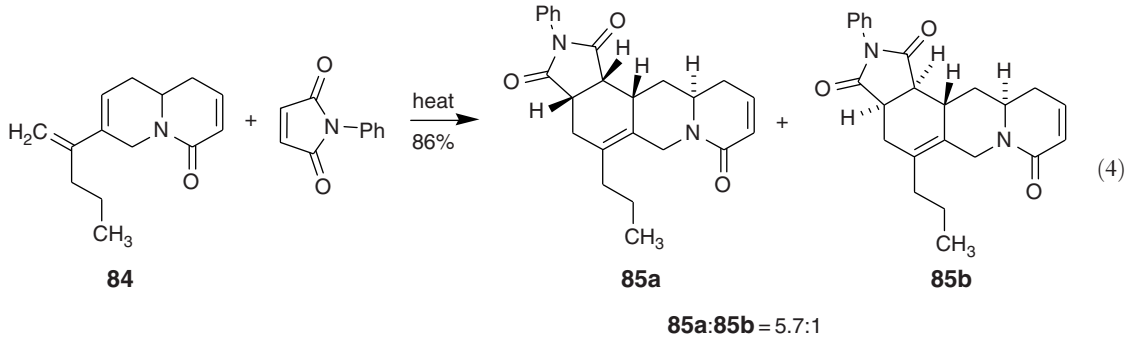
α,β-Unsaturated indoloquinolizine derivative **82**, readily prepared from the corresponding saturated compound **81** by selenoxide elimination, gave stereoselective Michael additions with varying degrees of success. For instance, its treatment with vinylmagnesium bromide in the presence of copper cyanide gave adduct **83** in 65% yield, as shown in **Scheme 5** <2006TL1961>. Similar Michael additions of sulfur-stabilized nucleophiles have also been described <2006JOC6776>.



Scheme 5

11.01.6.1.4 Intermolecular cyclic transition state reactions

1,3-Butadiene moieties contained in quinolizine frameworks give the expected Diels–Alder reactions, behaving as the diene component. For example, compound **84**, readily available from a enyine double ring-closing metathesis (RCM) reaction, reacts with *N*-phenylmaleimide to give the polycyclic compound **85** in good yield and stereoselectivity (Equation 4) <2004JOC6305>.

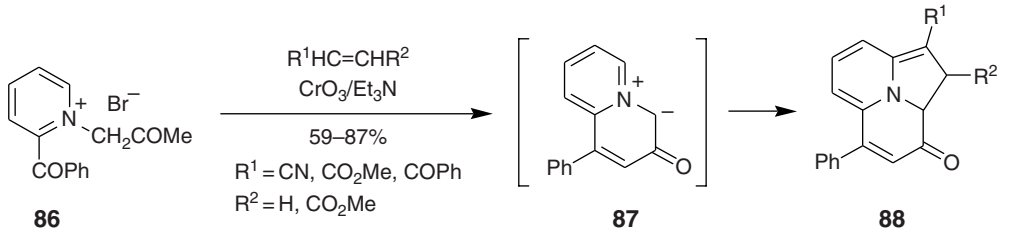


85a:**85b** = 5.7:1 (4)

Derivatives of the pyrrolo[2,1,5-*de*]quinolizine system **88** were obtained from 2-benzoyl-*N*-acetonylpyridinium bromide **86** in a single step through a tandem process of intramolecular aldol condensation and deprotonation, leading to intermediate **87**, followed by 1,3-dipolar cycloaddition and oxidation (**Scheme 6**) <2001JPI1820>.

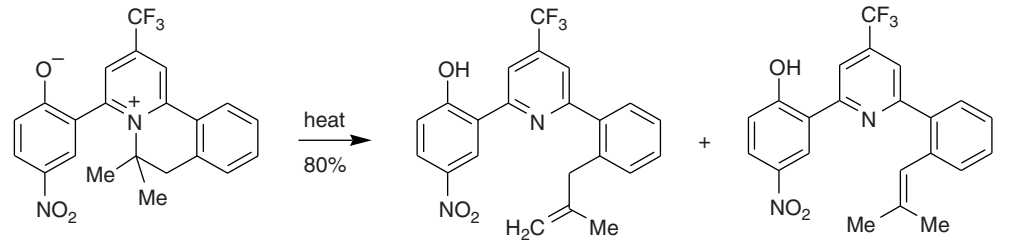
11.01.6.1.5 Ring opening

On heating the 6,7-dihydrobenzo[*a*]quinolizinium zwitterion **89**, ring cleavage occurs through an elimination mechanism, leading to a 4:1 mixture of the 2,6-diarylpiperidine derivatives **90** and **91** (Equation 5). It has been suggested that steric hindrance in **89** may provide a driving force for this reaction <2003OL3123>.



86 **87** **88**

Scheme 6



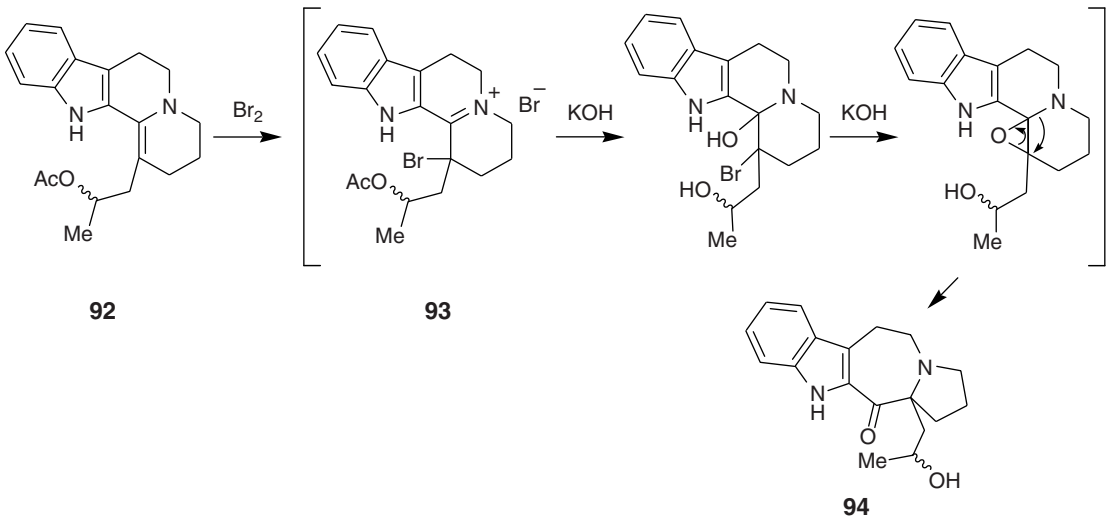
(5)

89 **90** **91**

90:**91** = 4:1

11.01.6.1.6 Ring rearrangement

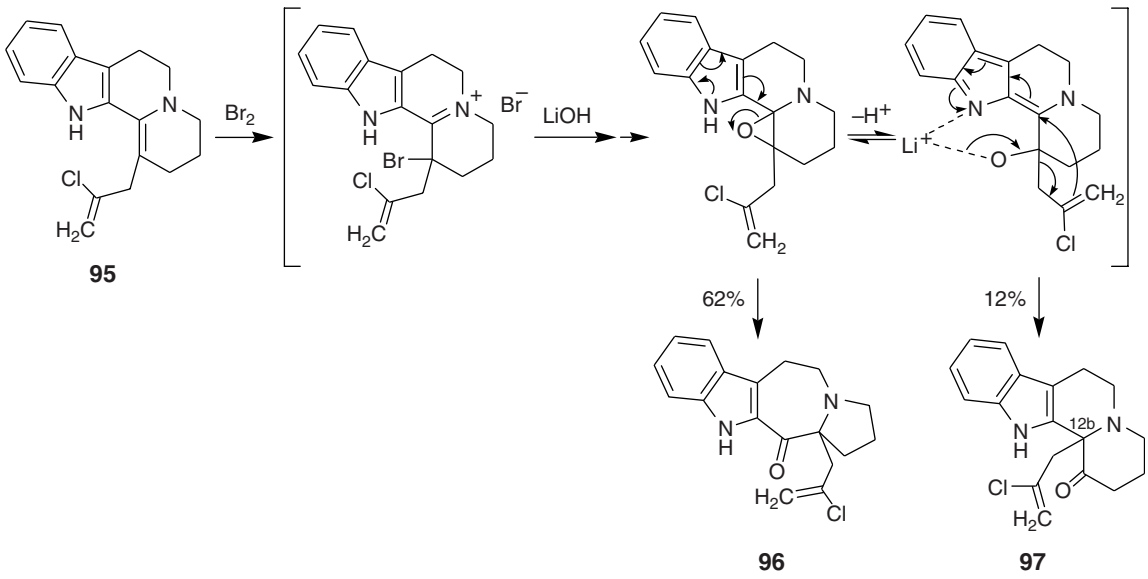
Treatment of indoloquinolizine **92**, containing an enamine function, with bromine followed by aqueous potassium hydroxide gave the rearranged hydroxyketone **94** (no yield given) through a mechanism involving halogenation, hydroxide attack onto the iminium intermediate **93**, epoxide generation, and rearrangement (**Scheme 7**) <1996TL5701>.



92 **93** **94**

Scheme 7

In the case of the related starting material **95**, bearing a chlorovinyl fragment in the side chain, the expected azepinone **96** was accompanied by a new rearranged quinolizine derivative **97** that was generated from allylic transposition of the side chain to C-12b, as shown in **Scheme 8** <1996TL5701>.

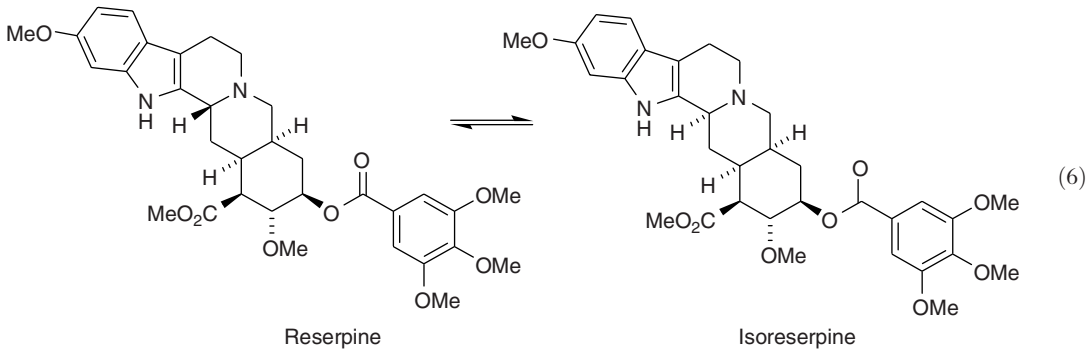


Scheme 8

11.01.6.2 Reactivity of Quinolizidines and Arenoquinolizidines

11.01.6.2.1 Epimerization

Some indolo[2,3-*a*]quinolizidines undergo easy acid-catalyzed epimerization <1998H(50)243>. For instance, the alkaloid reserpine equilibrates to a mixture of starting material and its 3-epimer, isoreserpine, under acid or basic catalysis (Equation 6). A controlled epimerization of this type has been employed as the key step in a total synthesis of (±)-tacamonine <1998T157>.

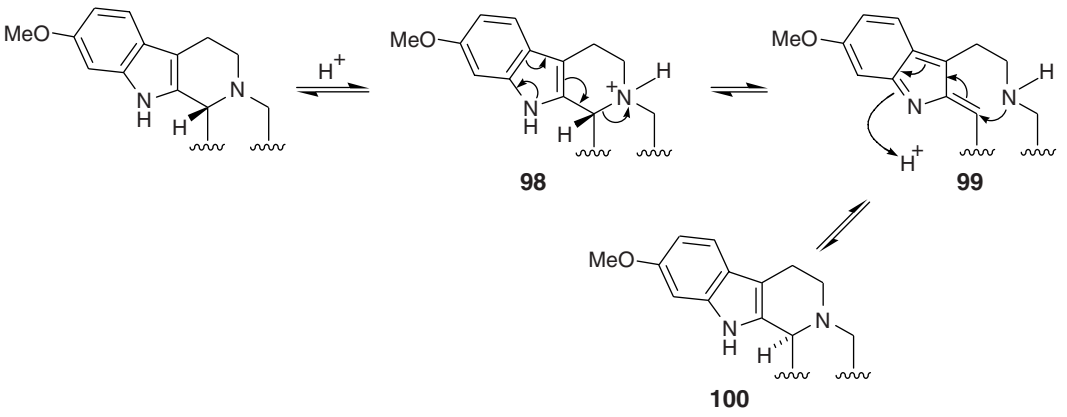


(6)

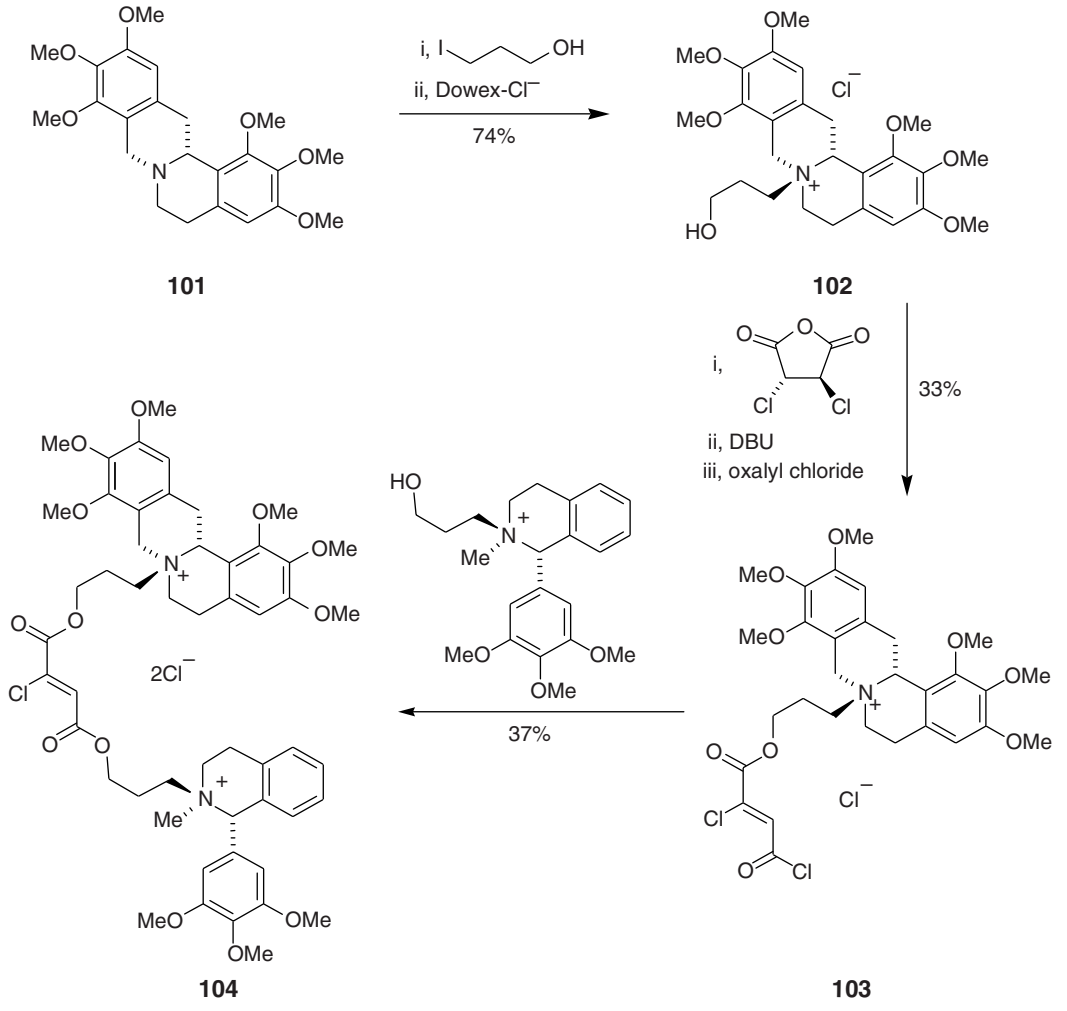
Among several mechanistic proposals that have been put forward to explain this reaction, the one in **Scheme 9** seems to be supported by epimerization experiments involving reserpine analogues with a lactam group <1998T10205>. In this mechanism, the protonated reserpine **98** undergoes ring opening to intermediate **99** and subsequent ring closure to isoreserpine **100**.

11.01.6.2.2 Quaternization

The nitrogen atom in quinolizidine derivatives behaves as a tertiary amine and hence it can undergo quaternization by reaction with alkyl halides. For instance, berberine derivative **101** was transformed into **102** by treatment with 3-iodopropanol followed by anion exchange. Compound **102** was then transformed into intermediate **103**, which was employed as a precursor for the the preparation of bis-ammonium salt **104** (**Scheme 10**). This compound showed ultrashort curare-like activity in rhesus monkeys <2001JOC3495>.



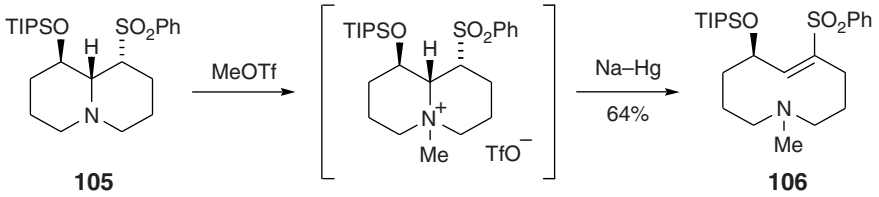
Scheme 9



Scheme 10

11.01.6.2.3 Ring opening

The ten-membered cyclic amine **106** was efficiently prepared from quionolizidine derivative **105** by methylation to a nonisolated intermediate followed by an olefin-forming desulfonylation reaction induced by treatment with sodium amalgam (**Scheme 11**) <2001OL2957>.

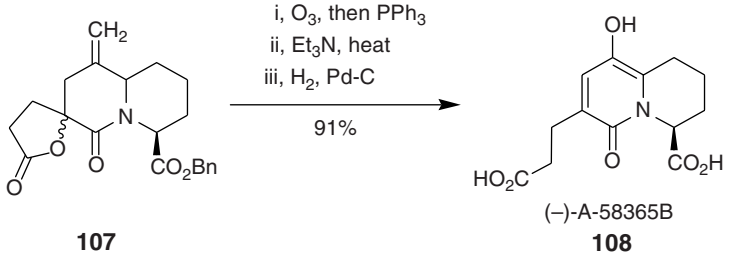


Scheme 11

11.01.7 Reactivity of Substituents Attached to Ring Carbon Atoms

11.01.7.1 Methylene Side Chains

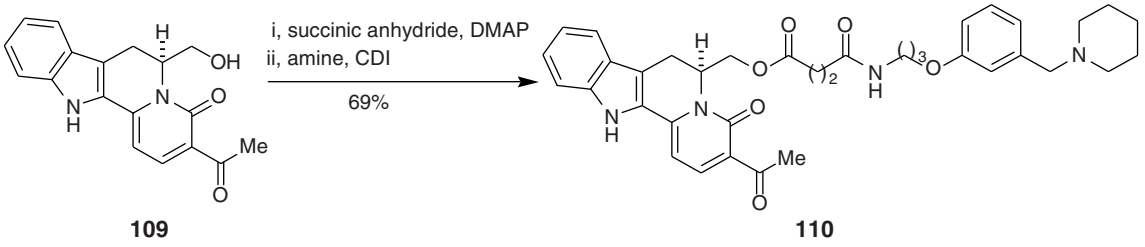
The final stages of the synthesis of (−)-A-58365B, a *Streptomyces* metabolite that inhibits the angiotensin-converting enzyme, involve several reactions at substituents attached to ring carbon atoms of a quinolizidine system. Thus, ozonolysis of the exocyclic methylene side chain of compound **107**, followed by base-induced elimination and carboxyl deprotection, gave **108** (**Scheme 12**) <1999JOC1447>.



Scheme 12

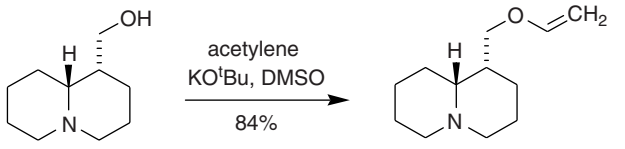
11.01.7.2 Hydroxy and Hydroxyalkyl Groups

Hydroxy or hydroxymethyl groups attached to quinolizine substrates normally show the expected reactivity. For instance, compound **109** was linked to histamine receptor antagonists by esterification with succinic anhydride followed by amidification with the antihistaminic drug to give the fluorescently labeled structure **110** for *in vivo* studies of receptor binding (**Scheme 13**) <2003BML1717>.



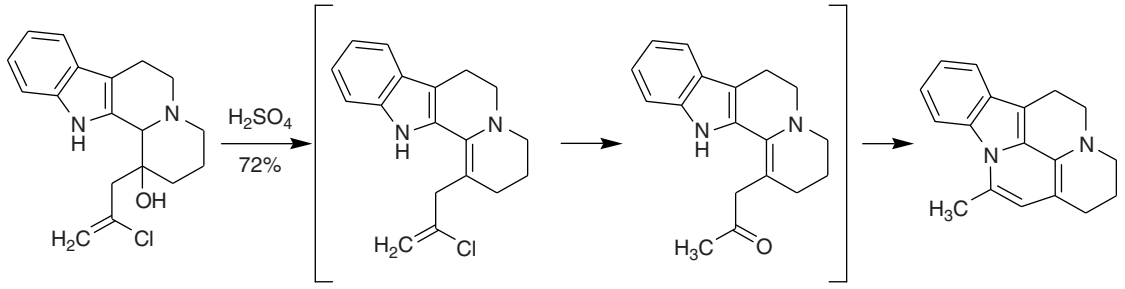
Scheme 13

The primary hydroxymethyl group of lupinine **6** was studied with regard to the addition of acetylene in basic systems to give the vinylated product **111** (Equation 7). As compared with aliphatic amino alcohols, the vinylation of lupinine required more drastic conditions <2004RCB242>.



Lupinine
6 **111** (7)

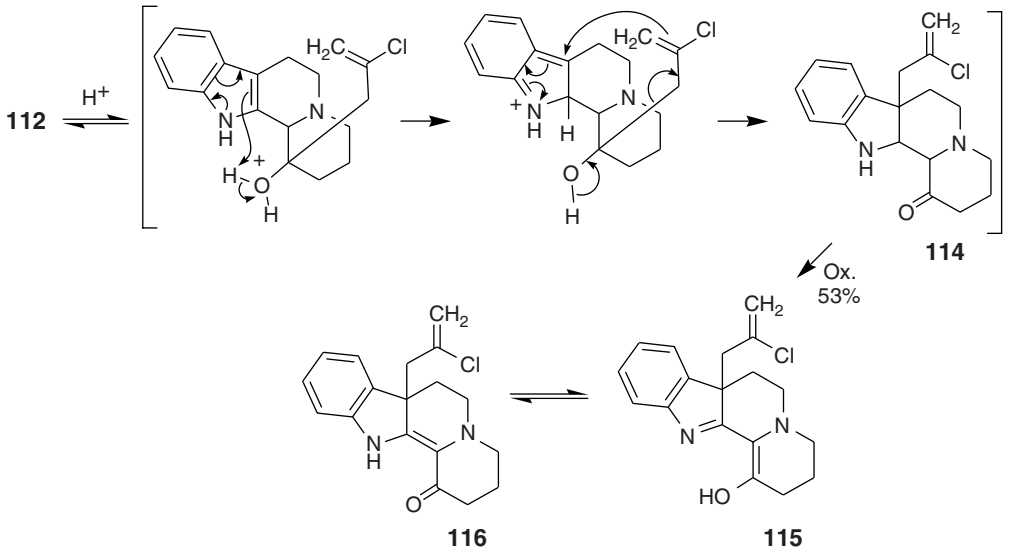
As shown in **Scheme 14**, a sulfuric acid-catalyzed dehydration–cyclization–elimination domino sequence starting from protonation of the secondary hydroxy group of the indolo[2,3-*a*]quinolizidine **112** led to the isolation of the pentacyclic compound **113** in good yield <1999EJO3429>.



112 **113**

Scheme 14

The same starting compound **112** showed a totally different behavior when treated with trifluoroacetic acid (TFA), giving a rearrangement to **114** followed by spontaneous oxidation that afforded an equilibrium mixture of tautomeric compounds **115** and **116** (**Scheme 15**) <1999EJO3429>.

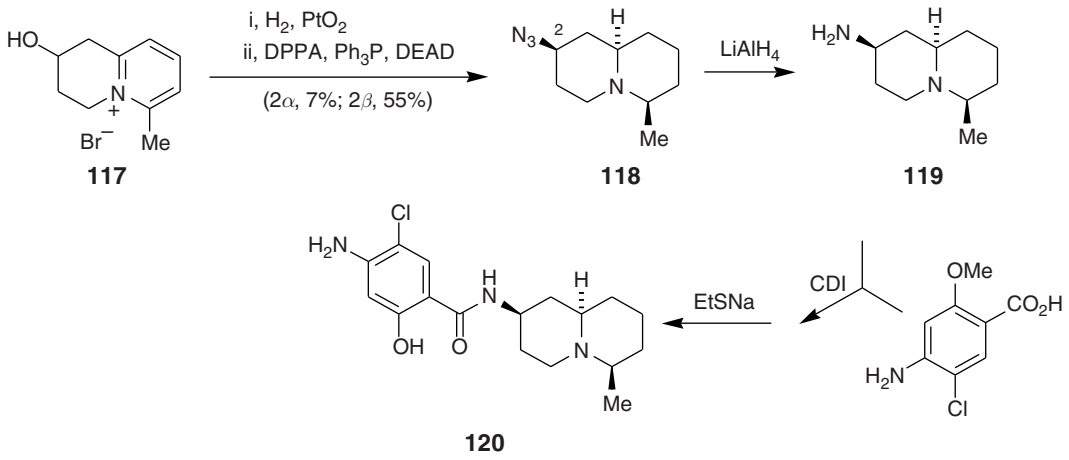


114 **116** **115**

Scheme 15

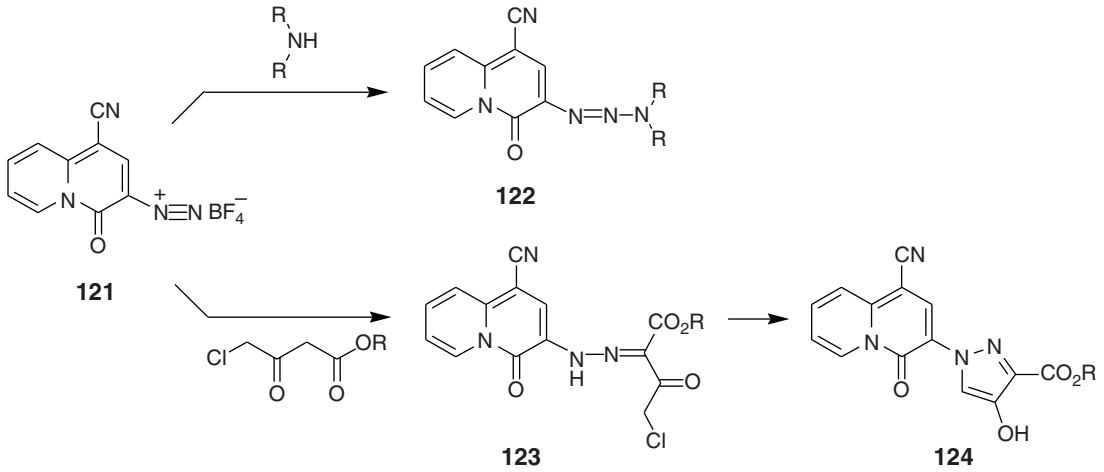
11.01.7.3 Amino, Azido, and Diazonium groups

Hydrogenation of tetrahydroquinolizinium bromide **117** followed by Mitsunobu reaction of the resulting alcohol with diphenylphosphoryl azide (DPPA) gave the corresponding amine **119** and then as a mixture of 2α/2β-epimers. The azido group of compound **118** was reduced to the corresponding amine and then coupled with 4-amino-5-chloro-2-methoxybenzoic acid in the presence of carbonyldiimidazole (CDI) followed by deprotection of the phenolic methyl ether to give quinolizidine salicylamide derivatives **120** (**Scheme 16**). These compounds behave as fusion inhibitors of the influenza virus <1999BML2177>.



Scheme 16

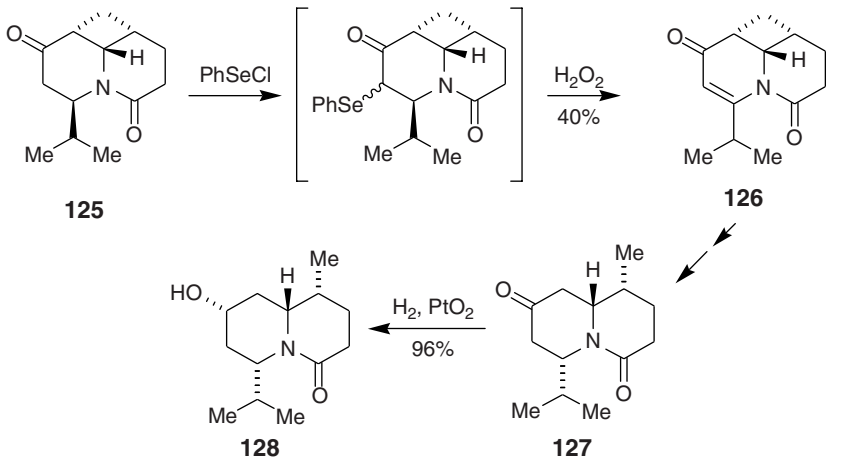
Several interesting reactions have been described for quinolizine-3-diazonium tetrafluoroborate **121**. Thus, its treatment with secondary amines gave the corresponding triazenes **122** <2004ZNB380>, while its reaction with 1,3-dicarbonyl compounds gave the corresponding hydrazones. In the case of alkyl 4-chloro-3-oxobutanoates, the intermediate hydrazone **123** furnished a pyrazole derivative **124**, as shown in **Scheme 17** <2002H(57)2091>.



Scheme 17

11.01.7.4 Ketones and their Derivatives

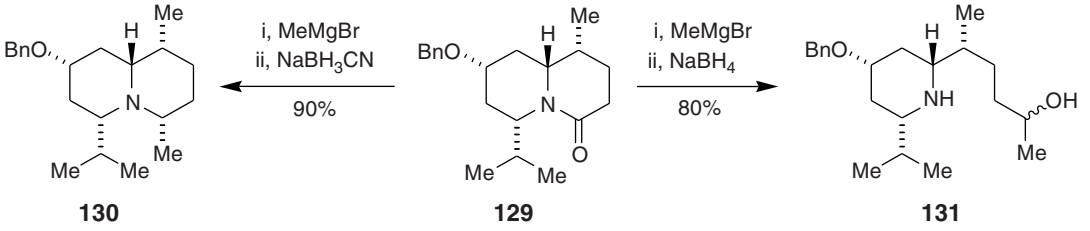
Phenylselenation of the position α to the ketone carbonyl in compound **125** followed by oxidative elimination gave the enone **126** in moderate yield, with a selenide as an intermediate. Compound **127**, obtained by further manipulation of **126**, was stereoselectively hydrogenated over PtO_2 to give the corresponding alcohol **128** (**Scheme 18**) <2002OL1611>.



Scheme 18

11.01.7.5 Carboxylic Acids and their Derivatives

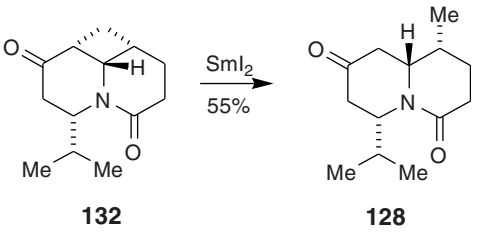
Lactam groups contained in quinolizidine systems exhibit the expected reactivity. This behavior is exemplified by the nucleophilic addition of organomagnesium reagents, which, when combined with a reduction step, can be used to obtain alkyl derivatives in a one-pot sequence. For instance, treatment of compound **129** with methylmagnesium bromide followed by reduction with acidic sodium cyanoborohydride afforded compound **130**, presumably through the generation and reduction of an intermediate iminium species. On the other hand, workup with sodium borohydride gave the open derivative **131** (**Scheme 19**) <2002OL1611>.



Scheme 19

11.01.7.6 Miscellaneous Reactions

Opening of a cyclobutane ring fused to a quinolizine system under reductive conditions has been described. Thus, the previously mentioned compound **128** was obtained by treatment of **132** with samarium diiodide (Equation 8) <2002OL1611>.

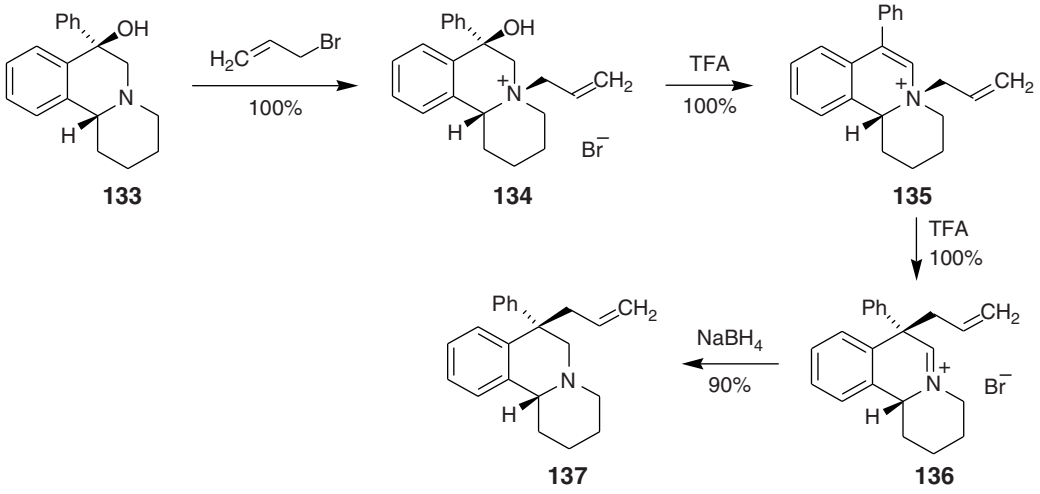


(8)

11.01.8 Reactivity of Substituents Attached to Ring Heteroatoms

11.01.8.1 Rearrangements in *N*-Allylquinolizinium Derivatives

Treatment of benzo[*a*]quinolizine **133** with allyl bromide gave the quaternary ammonium salt **134** in quantitative yield and essentially 100% stereoselectivity. Brief exposure of **134** to trifluoroacetic acid gave its dehydration derivative **135**. A more prolonged treatment induced a 3-aza-Cope rearrangement of **135** to a single iminium salt, which was assigned the *trans*-structure **136** by study of its ^{1}H NMR spectrum. This assignment was confirmed by sodium borohydride reduction of **136** to the stable compound **137**, which showed the expected signals for a *trans*-structure (**Scheme 20**). The intramolecular rearrangement of the allyl group takes place from the same face of the molecule, suggesting that the allyl substituent is not dissociated during the process and that the suprafacial rearrangement is concerted <2000JOC4938>.



Scheme 20

11.01.9 Ring Synthesis from Monocyclic and Acyclic Compounds

The quinolizidine ring system is well represented among alkaloids isolated from both plant and animal sources, and the development of novel strategies for the stereoselective synthesis of compounds containing this important structural motif continues to receive considerable attention (see annual reports in <1996NPR45, 1997NPR619, 1998NPR571, 1999NPR675, 2000NPR579, 2001NPR520, 2002NPR719, 2003NPR458, 2004NPR625, and 2005NPR603>).

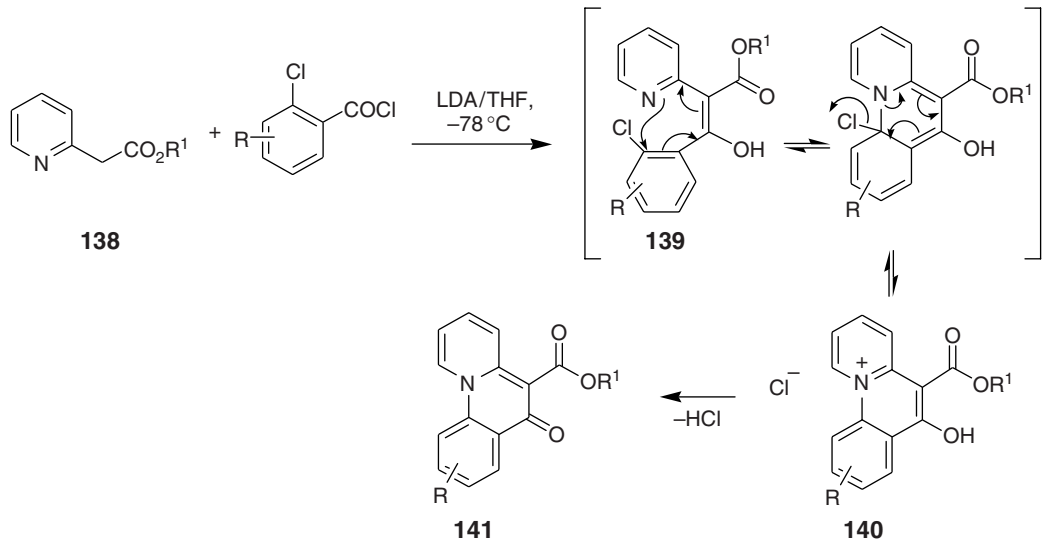
11.01.9.1 Formation of a New Bond α to the Heteroatom

Intramolecular nucleophilic attack of a pyridine or piperidine nitrogen atom onto an electrophilic function placed in the ε-position of a side chain is a common way to achieve quinolizidine compounds. These reactions are systematized below on the basis of the nature of the electrophile.

11.01.9.1.1 By intramolecular displacement of halides

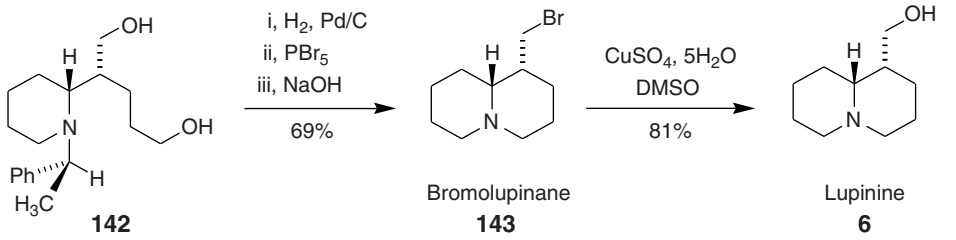
An example of this displacement between a pyridine nitrogen atom and an aryl halide is shown in **Scheme 21**. When 2-pyridyl acetates **138** were *C*-acylated with 2-halobenzoyl chlorides, the enolized products **139** resulting from the reaction suffered an intramolecular nucleophilic attack of the pyridine nitrogen atom onto the ipso-position to give benzo[*c*]quinolizinium salts **140** as intermediates. Loss of HCl gas from **140** afforded benzo[*c*]quinolizine derivatives **141** <2002JOC2082>.

Examples of the more frequent nucleophilic attack of a piperidine nitrogen atom onto an alkyl halide to yield quinolizidine derivatives are described below. Piperidinediol **142**, after debenzylation and treatment with PBr_5



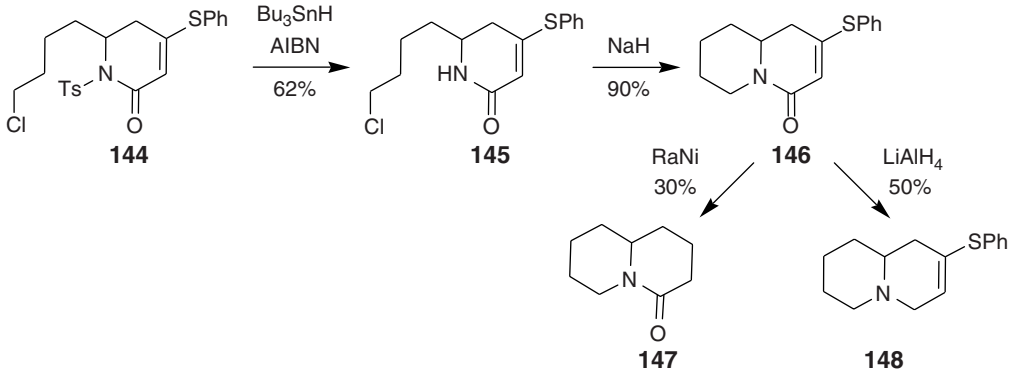
Scheme 21

followed by base, led to the cyclized bromolupinane **143**. This compound gave enantiomerically pure lupinine **6** by treatment with aqueous copper sulfate in dimethyl sulfoxide (DMSO; **Scheme 22**) <2001TL5397>.



Scheme 22

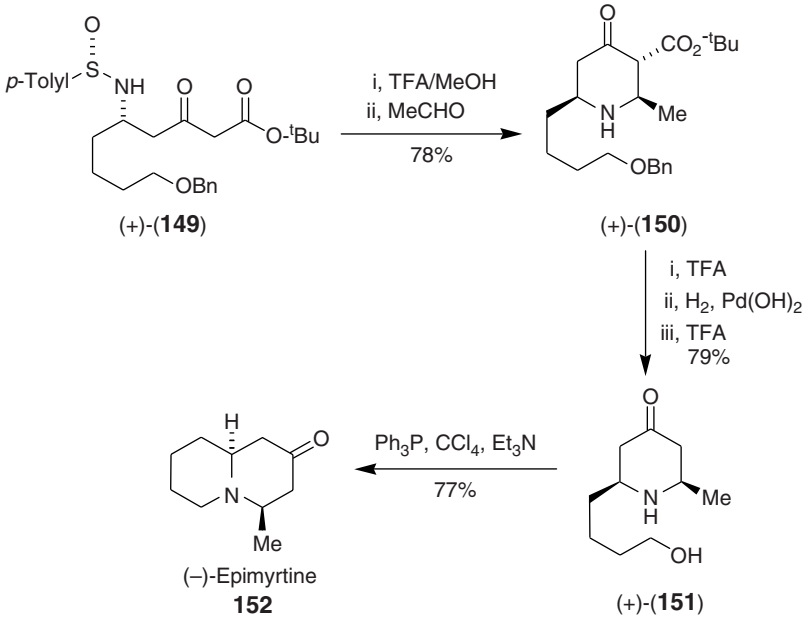
In order to synthesize quinolizidine compounds, some authors have used the Parsons' method (Bu_3SnH/AIBN) to cleave the *N*-tosyl group of 2-piperidones such as **144** (AIBN = 2,2′-azobisisobutyronitrile). After detosylation to **145**, the intramolecular cyclization of the lactam promoted by sodium hydride gave quinolizidinone **146**. Treatment of this compound with Raney nickel both cleaved the C–S bond and reduced the C=C bond to give quinazolinone **147**, while the lactam carbonyl was reduced with $LiAlH_4$ to give **148** (**Scheme 23**) <2005TL8551>.



Scheme 23

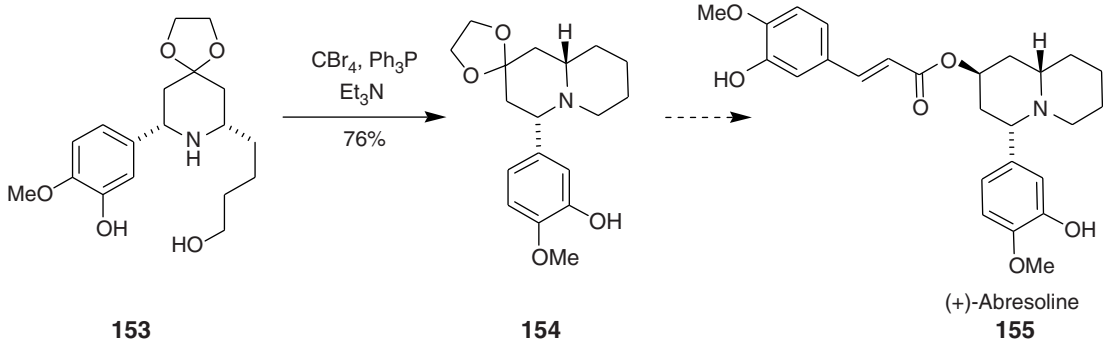
11.01.9.1.2 By intramolecular displacement of activated hydroxy groups

Very often the dehydrocyclization of 2-(4-hydroxybutyl)piperidine compounds has been achieved by activation of the alcohol by treatment with triphenylphosphine and CCl_4 or CBr_4. By using *N*-sulfinyl *δ*-amino *β*-ketoesters such as the (S_S,*S*)-isomer **149** as a chiral building block, efficient access to the quinolizidine alkaloid (−)-epimyrtine has been possible. Removal of the sulfinyl group with TFA and reaction of the crude trifluoroacetate amine salt with acetaldehyde gave the tetrasubsituted piperidine **150** through an intramolecular Mannich reaction. Hydrolysis–decarboxylation by reflux in TFA and subsequent removal of the benzyl group by hydrogenolysis gave the corresponding alcohol **151**, which cyclized to (−)-epimyrtine **152** by treatment with triphenylphosphine and triethylamine in CCl_4 (**Scheme 24**) <2003JOC8061>.



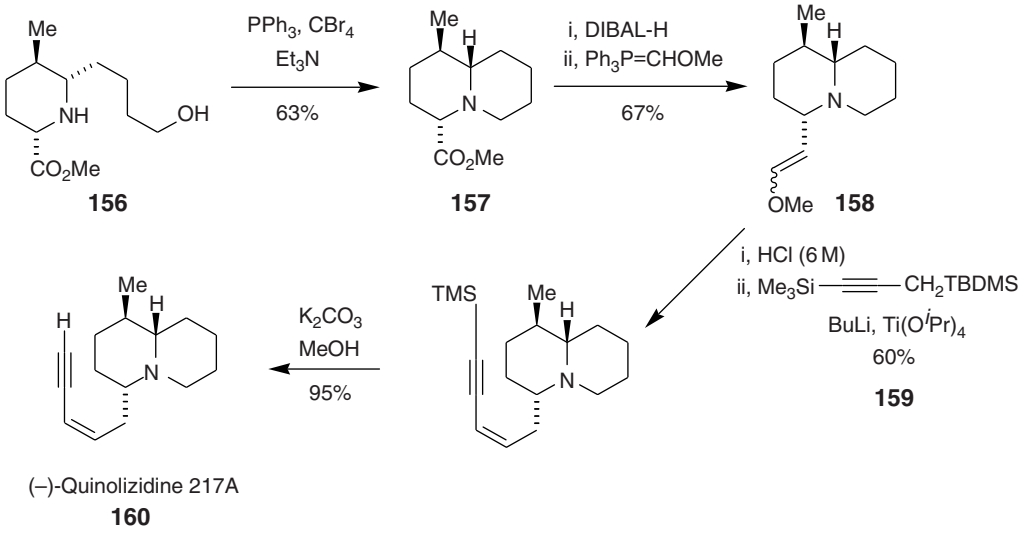
Scheme 24

The first asymmetric synthesis of (+)-abresoline was achieved from the chiral piperidine derivative **153**, which upon treatment of its hydroxy side-chain substituent with carbon tetrabromide, triphenylphosphine, and triethylamine cyclized to the *trans*-quinazolidine **154**. Deketalization and silyl protection of the phenolic group, followed by stereoselective reduction with lithium tri-*sec*-butylborohydride (L-Selectride®), gave an alcohol, which after acylation and deprotection furnished (+)-abresoline **155** (**Scheme 25**) <2005TL2669>.



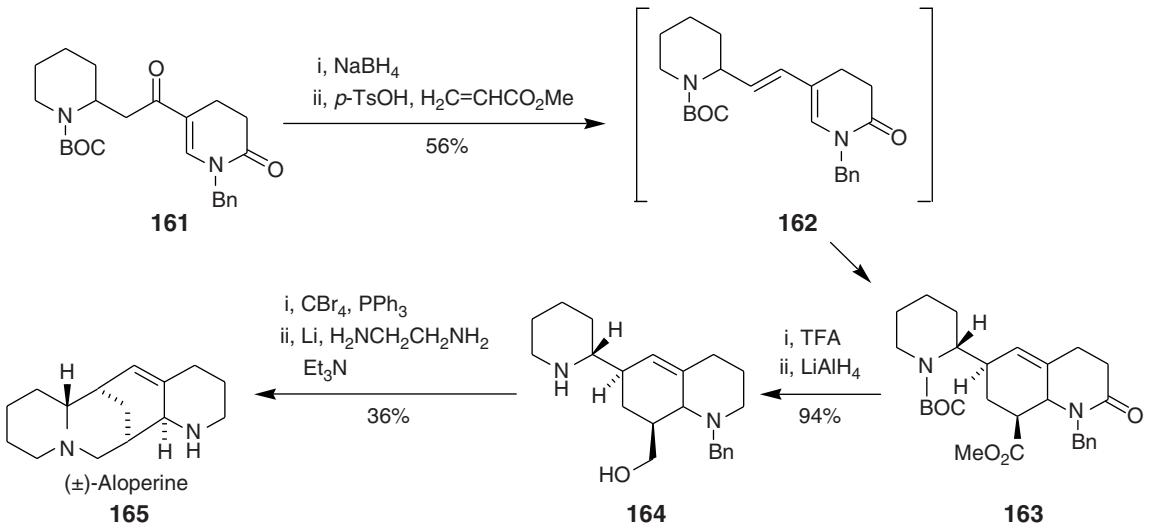
Scheme 25

During the synthesis of the natural product known as (−)-quinolizidine 217A, the 2,6-*cis*-disubstituted tetrahydropyridine **156**, containing a primary alcohol function, was cyclized to quinolizidine **157** via activation of the hydroxyl group with triphenylphosphine and CBr_4. The side-chain of this compound was subsequently manipulated by reduction and Wittig olefination to give **158**, which, after hydrolysis of the enol ether function and Yamamoto olefination with silane **159** followed by deprotection, afforded the natural product **160** (**Scheme 26**) <2003JA626>.



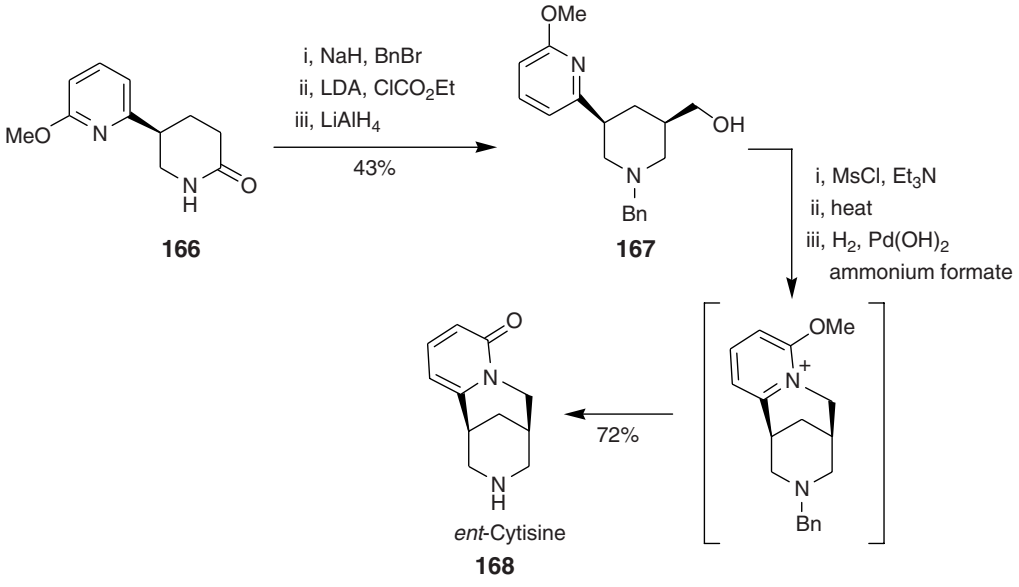
Scheme 26

Construction of the tetracyclic system by a final cyclization of the primary alcohol **164** activated *in situ* as the corresponding bromide was used in a concise synthesis of racemic aloperine **165** from commercially available piperidine-2-ethanol. This starting material was derived to dihydropyridone **161**. After reduction and dehydration, intermediate **162** in the presence of methyl acrylate gave **163** as the major Diels–Alder adduct. Lastly, the *t*-butoxycarbonyl (BOC) protecting group was removed, and the lactam and ester functions were reduced to give alcohol **164**, which was cyclized in the presence of CBr_4 and PPh_3. The problematic removal of the *N*-benzyl substituent was accomplished with lithium in dry ethylenediamine, affording the natural product (**Scheme 27**) <2002OL2925>.



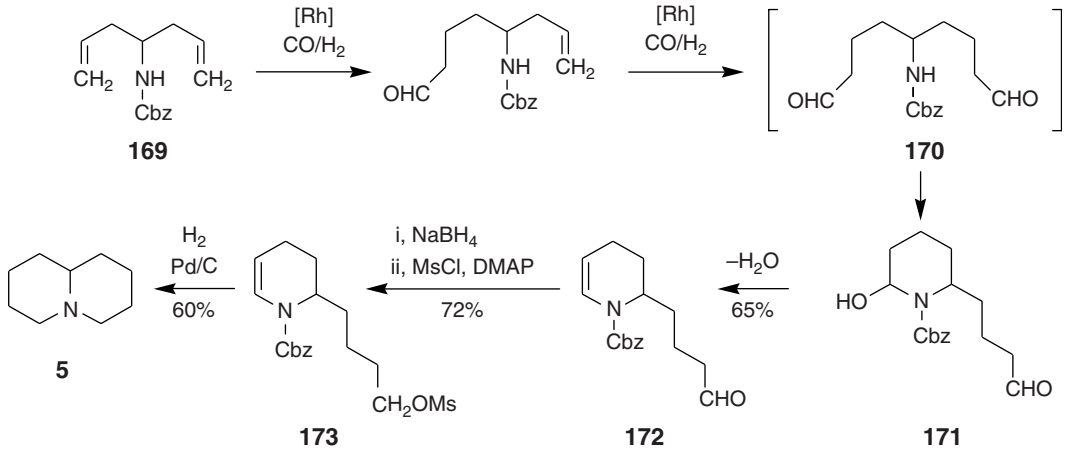
Scheme 27

Activation of a primary alcohol by *in situ* mesylation is another frequent strategy that has been used, for instance, in the synthesis of *ent*-cytisine **168**, which in its final steps follows a previously reported strategy for the racemic form of the alkaloid <2000OL4201>. The chiral piperidine compound **166** was converted into a diastereomeric mixture of hydroxymethyl derivatives, the major one being **167**, by N-benzylation, ethoxycarbonylation, and reduction with $LiAlH_4$. Mesylation of **167**, followed by thermal cyclization, yielded a tricyclic compound that was debenzylated by hydrogenolysis to give *ent*-cytisine **168** (**Scheme 28**) <2005JOC499>. The synthesis of cytosine has been recently reviewed <2007T1885>.



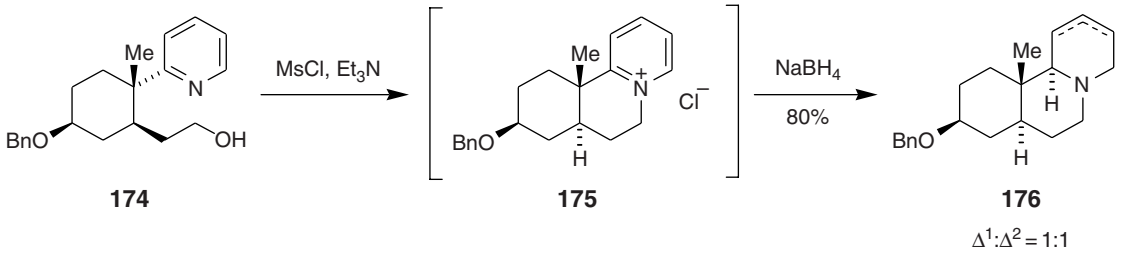
Scheme 28

The unsubstituted quinazolidine system **5** was constructed from mesylate **173**. The key feature in this synthesis is based on a cyclohydrocarbonylation of the protected 4-amino-1,6-heptadiene **169** catalyzed by $Rh(acac)(CO)_2$-BIPHEPHOS. Formation of the hemiamidal-aldehyde **171** took place by hydroformylation of the two olefin moieties and cyclization. Elimination of water gave **172**, which, after treatment with $NaBH_4$, subsequent mesylation to **173,** and catalytic hydrogenation, afforded **5** (**Scheme 29**) <1998TL4599>.



Scheme 29

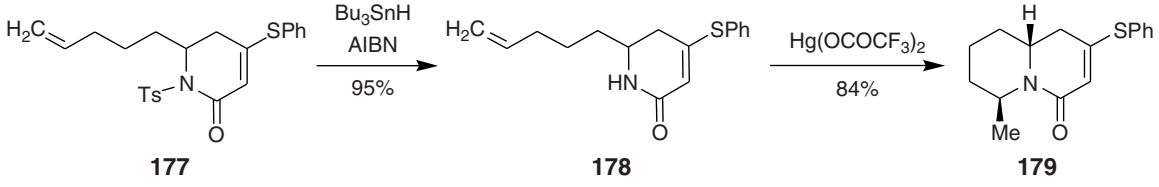
Activation of a primary alcohol **174** by *in situ* mesylation and nucleophilic attack of a pyridine nitrogen atom was used in the last steps of a synthesis of cyclohexa[*a*]quinolizidines **176**. These compounds were obtained by direct $NaBH_4$ reduction of intermediate pyridinium salts **175**, and were proposed as tricyclic models containing the *ABC*-part of 8-azasteroids (**Scheme 30**) <1999T9269>.



Scheme 30

11.01.9.1.3 By nucleophilic addition onto activated alkenes

The Hg(II) cation was used to activate the double bond in lactam **178**, which was obtained by detosylation of **177** using the Parsons' method. This strategy allowed the synthesis of quinolizidine derivative **179**, which was obtained as a single *trans*-diastereoisomer (**Scheme 31**). Besides its higher thermodynamic stability with respect to that of the *cis*-isomer, formation of the *trans*-isomer must involve a lower activation energy since its intermediate precursor, in which the lone pair of electrons of nitrogen must attack from the back side of the mercuronium ion, is sterically less hindered than the precursor of the *cis*-isomer <2003TL4653>.



Scheme 31

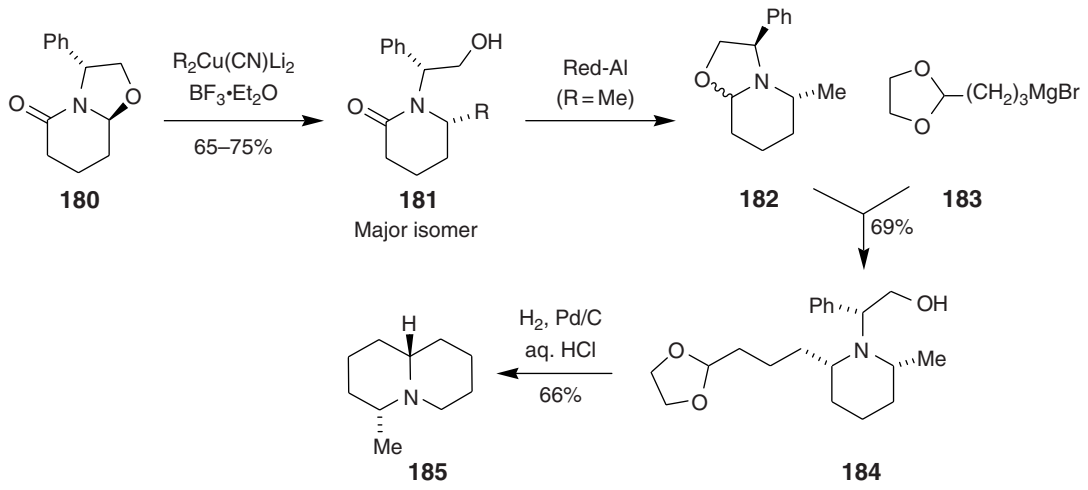
11.01.9.1.4 By nucleophilic attack onto carbonyl groups

Piperidines bearing a masked aldehyde function in the ε-position are easily transformed into quinolizidine compounds through intramolecular reductive amination after deprotection (acetal precursors) or oxidative cleavage (*vic*-diols). Some examples are given below.

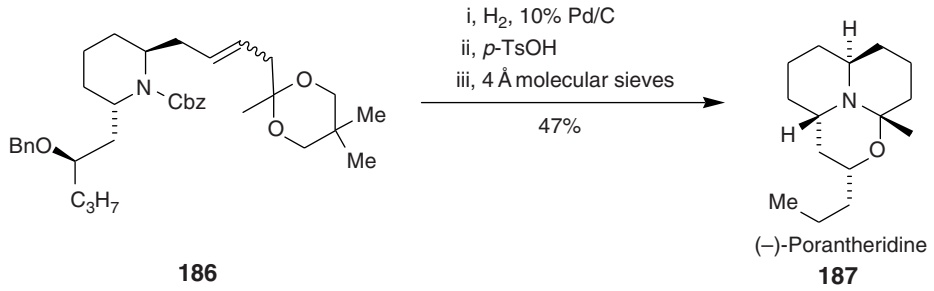
Addition of higher-order cyanocuprates to the enantiopure bicyclic lactam **180**, prepared by cyclocondensation of (*R*)-phenylglycinol with methyl 5-oxo-pentanoate, gave the alkylated compound **181** as the major isomer, which was transformed into the masked iminium ion **182** by reduction. Further alkylation of **182** with a four-carbon Grignard reagent incorporating a protected aldehyde group **183** gave stereoselectively the *cis*-2,6-disubstituted piperidine **184**. This compound, by catalytic hydrogenation under slightly acidic hydrolytic conditions, gave directely the enantiopure *cis*-4-methylquinolizidine **185** through a one-pot debenzylation, deprotection of the carbonyl group, and closure of the second piperidine ring by a reductive amination process (**Scheme 32**) <2003JOC1919>.

An enantioselective synthesis of (−)-lupinine **6** was based on a similar reductive amination process. In this case, (*R*)-phenylglycinol was used to obtain a chiral nonracemic oxazololactam which was cyclized after reduction of N–C and O–C bonds and subsequent hydrolysis of the masked aldehyde <2004T5433>.

In the final steps of a synthesis of (−)-porantheridine **187**, hydrogenation of ketal **186** induced its N- and O-deprotection, which was followed by spontaneous cyclization under acidic conditions (**Scheme 33**) <1999JOC8402>.

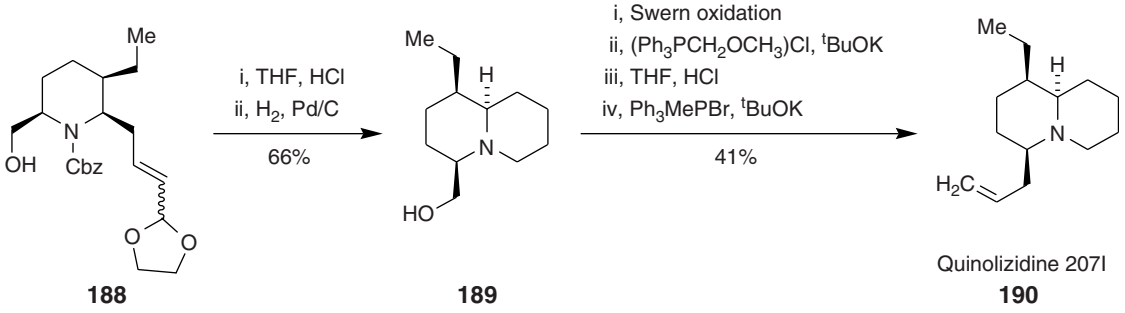


Scheme 32



Scheme 33

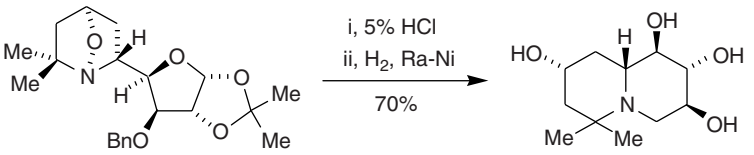
A similar procedure was applied to the synthesis of quinazolidine **189** from precursor **188** in the total synthesis of the natural product known as (±)-quinolizidine 207I **190**, an alkaloid isolated from the skin of the Madagascar mantelline frog *Mantella baroni*, that shows an exceptional axial stereochemistry for the ethyl group at C-1. Quinolizidine **189** was transformed into **190** by oxidation and two consecutive Wittig methylenations (**Scheme 34**) <1999CC2281>.



Scheme 34

Many polyhydroxylated quinolizidines <1995CRV1677>, frequently designed as azasugars, are powerful glycosidase inhibitors and therefore have potential therapeutic application. The 7-oxa-1-azabicyclo[2.2.1]heptane derivative **191**, obtained from 3-*O*-benzyl-1,2-*O*-isopropylidene-1,5-pentadialdo-α-D-xylofuranose with

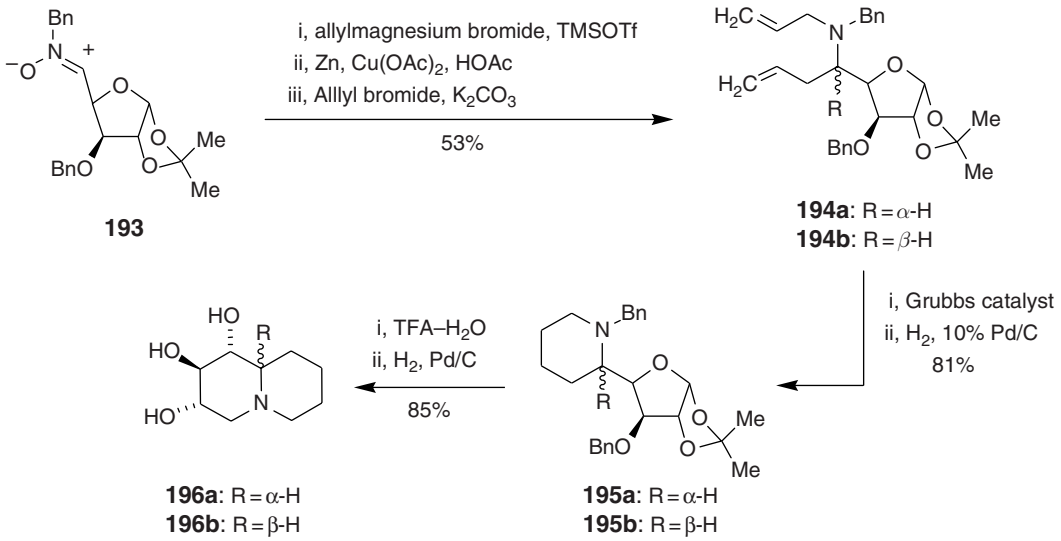
N-(1,1-dimethylbut-3-enyl)-hydroxylamine followed by intramolecular 1,3-dipolar cycloaddition, was easily converted into the polyhydroxylated quinolizidine **192** by removal of the isopropylidene group and hydrogenolysis of the N–O bond in the presence of Raney-nickel accompanied by intramolecular reductive amination (**Scheme 35**) <2001CC915>.



191 **192**

Scheme 35

A related approach was used in the last steps of synthesis of trihydroxyquinolizidines **196**. In this case, the starting material was obtained using as a key step a ring-closing metathesis (RCM) of D-glucose-derived dienes with a nitrogen linkage. Reaction of D-glucose nitrone **193** with allylmagnesium bromide afforded a mixture of diastereomeric adducts that were separated. Reductive cleavage of the N–O bond in both isomers afforded the corresponding *N*-benzylamino sugars that by reaction with allyl bromide gave the N-allylated products **194a** and **194b**. Both isomers were converted through ruthenium-catalyzed RCM into the corresponding dihydropiperidines, which after one-pot reduction of the double bond and removal of the *N*- and *O*-benzyl groups were treated with ethyl chloroformate to give the N-protected precursors **195a** and **195b**. Treatment of these compounds with TFA–water followed by catalytic hydrogenation afforded the azasugars **196a** and **196b** (**Scheme 36**) <2004SL1549>. In a very similar approach, precursors closely related to **195** were obtained via a lactamization approach <2004T3009>.



193

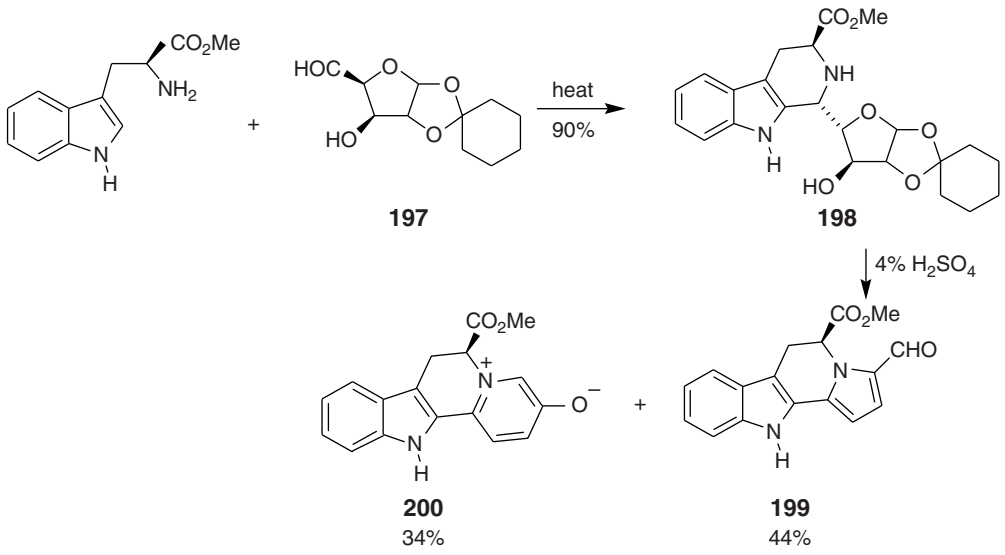
194a: R = α-H
194b: R = β-H

195a: R = α-H
195b: R = β-H

196a: R = α-H
196b: R = β-H

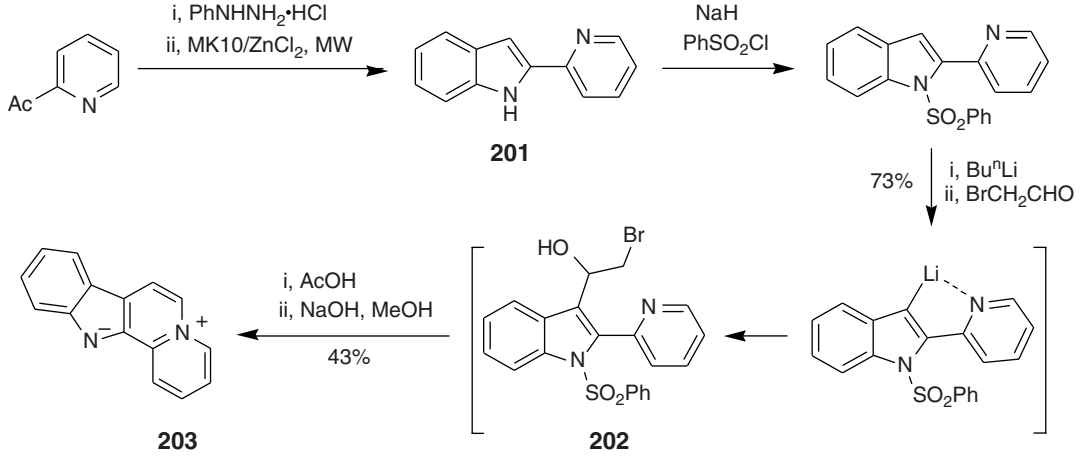
Scheme 36

Condensation of L-tryptophan methyl ester with anhydrosugar **197** afforded the chiral β-carboline **198**, which, upon hydrolysis, gave a mixture of the indolizine aldehyde **199** and the rather unstable quinolizinium salt **200** (**Scheme 37**) <2003ARK150>. Similarly, enantiopure piperidines obtained by applying ruthenium-catalyzed ring-rearrangement metathesis were converted to enantiopure quinolizidines through dihydroxylation of a terminal double bond in the ε-position, oxidative cleavage with sodium periodote of the *vic*-diol thus formed, and *in situ* cyclization <2004T6437>.



Scheme 37

A related strategy that allows the construction of an α-bond in pyridine derivatives is summarized in **Scheme 38** <2004TL8831, 1987TL5259>. The starting material **201** was obtained from 2-acetylpyridine using the Fischer indole synthesis (yield not given). After N-protection, lithium-mediated alkylation of indole with bromoacetaldehyde followed by acid-induced cyclization and dehydration and removal of the N-protecting group gave the indolo[2,3-*a*]quinolizine system **203**, which is a fragment of semperverine and related alkaloids. The precursor of **203** is probably compound **202**, from addition of the lithioindole to the aldehyde group in bromoacetaldehyde <1987TL5259>. A similar strategy allowed the preparation of semperverine analogues containing the complete pentacyclic core <2002TL9565, 2006T5736>.

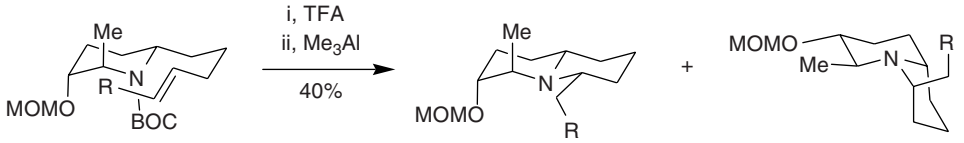


Scheme 38

11.01.9.1.5 By intramolecular Michael additions

The intramolecular Michael-type addition of the nitrogen atom of piperidines to activated alkenes located at a C(2)-side chain is a quite common way of access to the quinolizidine system. Some examples are given below.

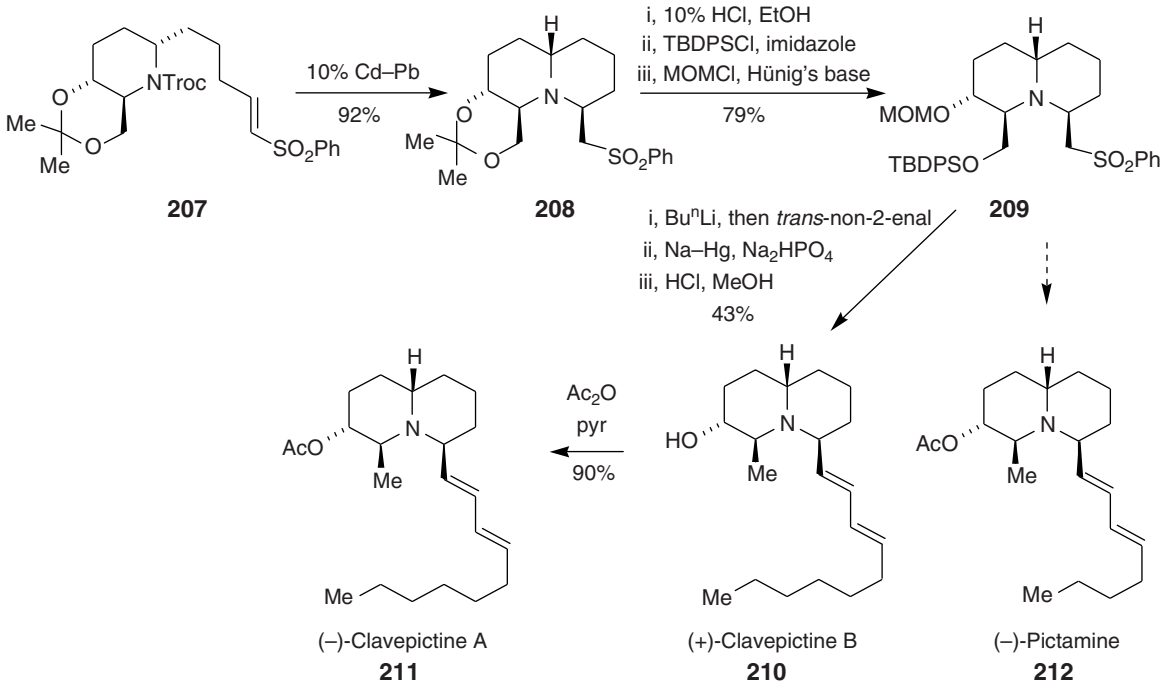
A functionalized piperidine system **204**, on deprotection of the BOC group followed by treatment of the resulting amine with Me_3Al, afforded a 4:1 mixture of *trans*- and *cis*- 4,6-disubstituted quinolizidines **205** and **206** (**Scheme 39**) <1999T15209>.



204 **205** **205**:**206** = 4:1 **206**

Scheme 39

For the application of this method to the synthesis of pictamine and the clavepictines A and B, the starting compound **207** was designed, which bears a protected glycol system on the piperidine ring with the acetonide group and a conjugate sulfone in order to fix the desired conformation. Deprotection of the Troc grop in **207** with Cd–Pb and subsequent intramolecular cyclization by a Michael addition gave the quinolizidine **208** as a single diastereomer. Further manipulation of this product, in which an important step was the Julia coupling between the phenyl sulfone and *trans*-2-nonenal to ensure the requisite (*E*,*E*)-geometry in the decadienyl chain, afforded the marine alkaloids (+)-clavepictine B **210** and (−)-clavepictine A **211**. A similar strategy gave (−)-pictamine **212** (**Scheme 40**) <1999T15209>. Another total synthesis of claviceptines A and B through a silver(I)-mediated cyclization involving a piperidine nitrogen atom and an allene is mentioned in Section 11.01.9.1.8.



207 **208** **209**

(–)-Clavepictine A **211**

(+)-Clavepictine B **210**

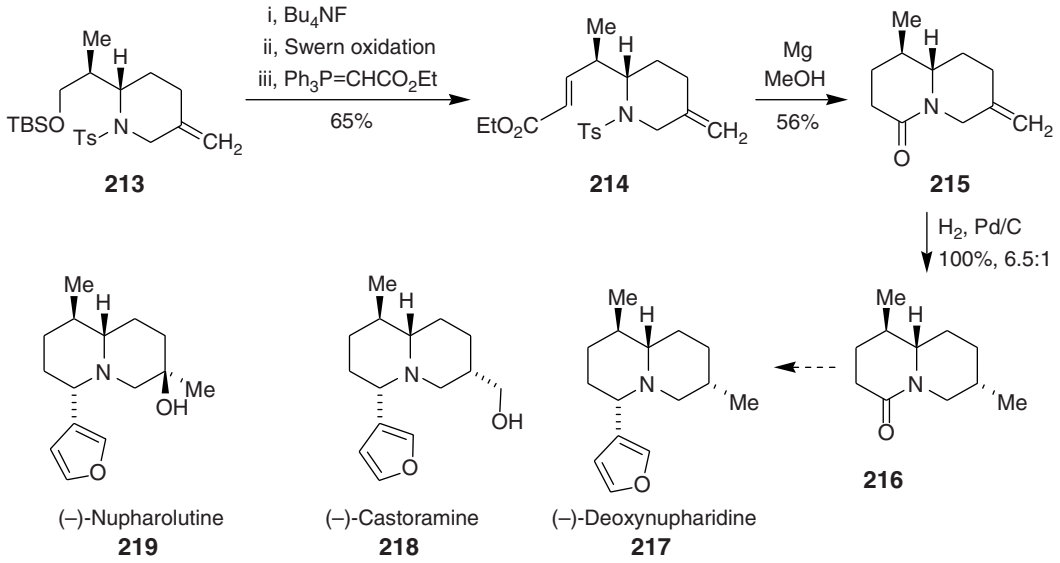
(–)-Pictamine **212**

Scheme 40

11.01.9.1.6 From carboxylic acid derivatives

In an approach to simple *Nuphar* quinolizidine alkaloids, the piperidine compound **213** was converted to compound **214** that underwent one-pot detosylation, conjugate reduction, and cyclization to produce the quinolizidin-4-one **215**

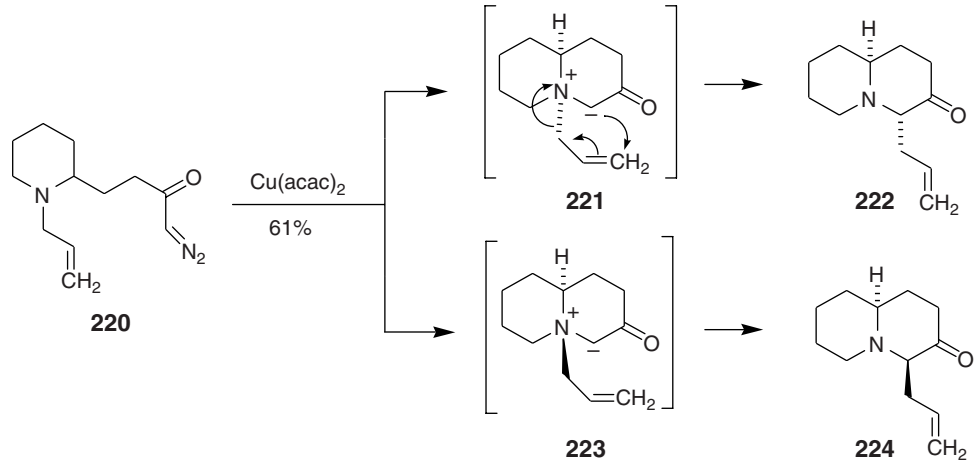
by treatment with magnesium in ethanol. Catalytic hydrogenation of **215** afforded **216** and its (7*R*)-epimer in a 6.5:1 ratio (**Scheme 41**) <2003OL3427>. The preparation of **215** represents a formal synthesis of (−)-deoxynupharidine **217** <1985JOC2719>, (−)-castoramine **218**, and (−)-nupharolutine **219** <2005JOC207>.



Scheme 41

11.01.9.1.7 From metal carbenoids

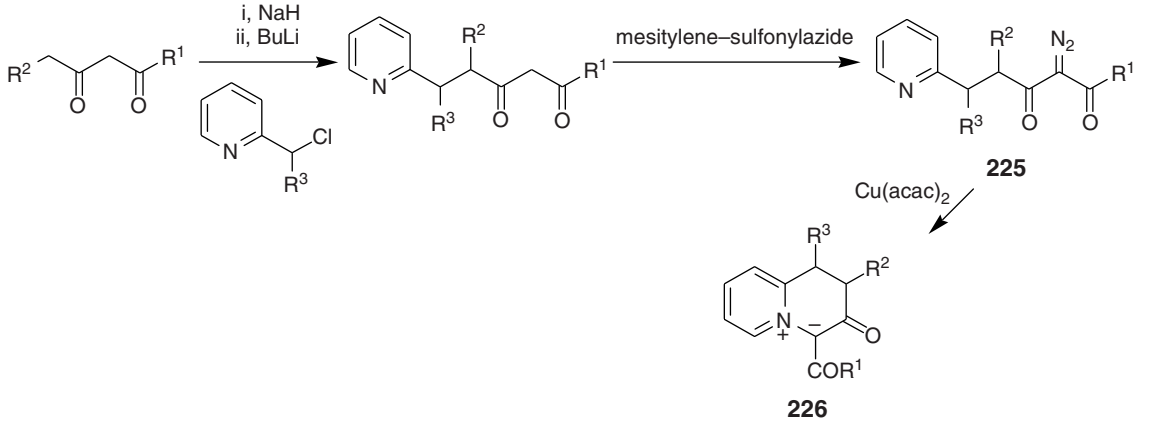
N-Allylpiperidines with a diazo group in a side chain adjacent to nitrogen gave ylides that rearranged to quinolizidine systems with high levels of diastereocontrol. For instance, treatment of diazoketone **220** with $Cu(acac)_2$ in refluxing benzene afforded a mixture (6:1 or 1:6) of two diastereoisomeric quinolizidines **222** and **224** through a [2,3]-rearrangement of the corresponding ammonium ylides **221** and **223** (acac = acetylacetonate; **Scheme 42**). Although both isomers were separable, it was not possible in this case to deduce the relative configuration of the major or minor isomer <2001JPI3325>.



Scheme 42

Using a Cu(II)-catalyzed reaction of 2-(4-diazo-3-oxoalkyl)pyridines **225**, tetrahydroquinolizinium ylides **226** were obtained in high yields. This transition metal-catalyzed decomposition was found to be superior to that promoted by

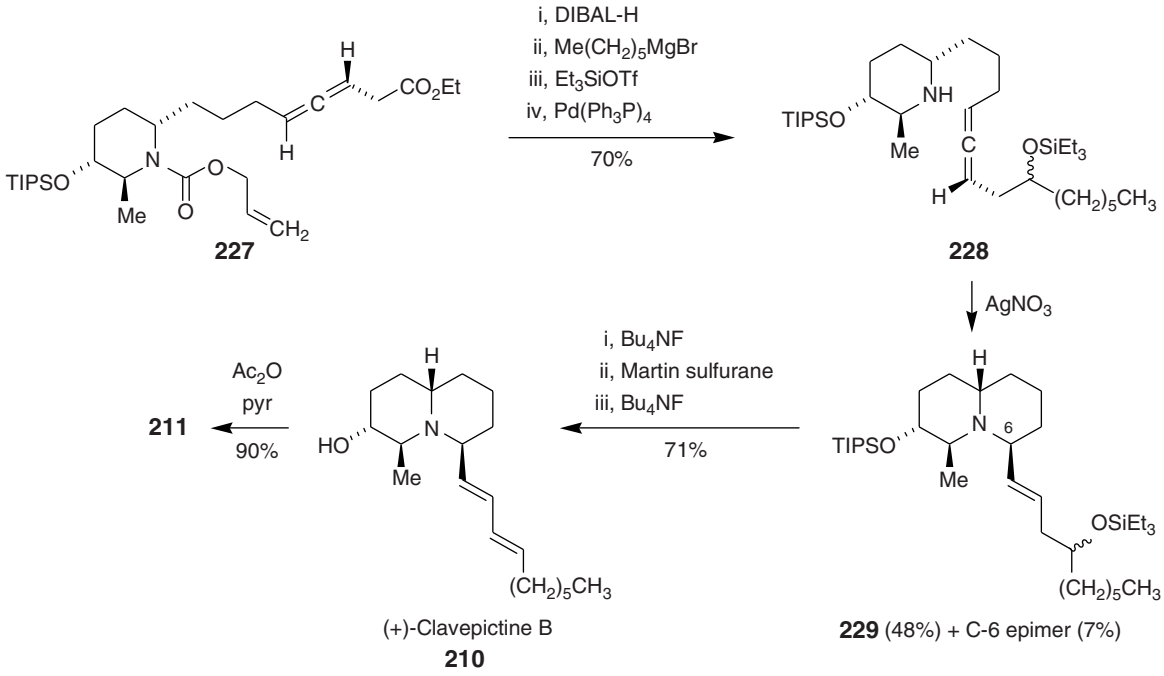
rhodium(II) acetate (**Scheme 43**). The starting compounds were prepared by alkylation of the dianion of 1,3-dicarbonyl compounds with 2-(α-chloroalkyl)pyridines, followed by reaction with arenesulfonyl azides <2001JOC1638>.



Scheme 43

11.01.9.1.8 By allene cyclizations

Clavepictines A and B (**210** and **211**, respectively) were obtained from the allenic ester **227**. The reduction of its ester group to aldehyde, followed of addition to the latter of hexylmagnesium bromide, OH protection, and N-deprotection gave compound **228**. A silver(I)-mediated cyclization of this compound afforded quinolizidine **229** and its C-6 epimer in a 7:1 ratio (**Scheme 44**). The former compound was readily converted into the target alkaloids <1997JOC4550>.

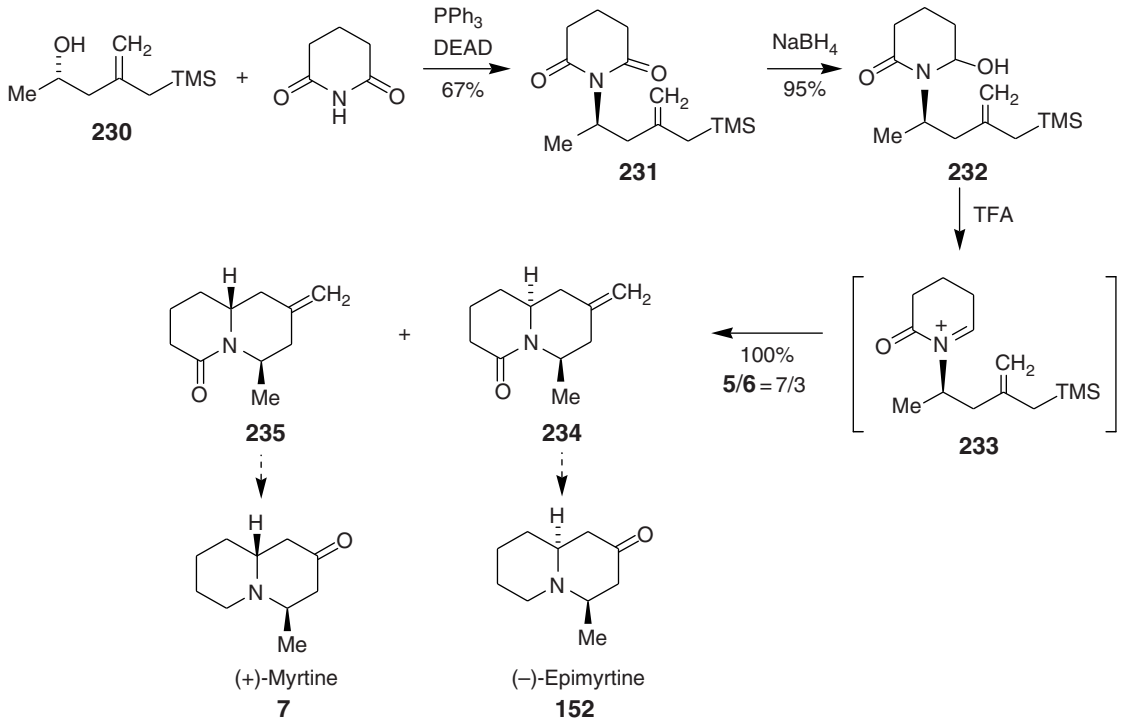


Scheme 44

11.01.9.2 Formation of a New Bond β to the Heteroatom

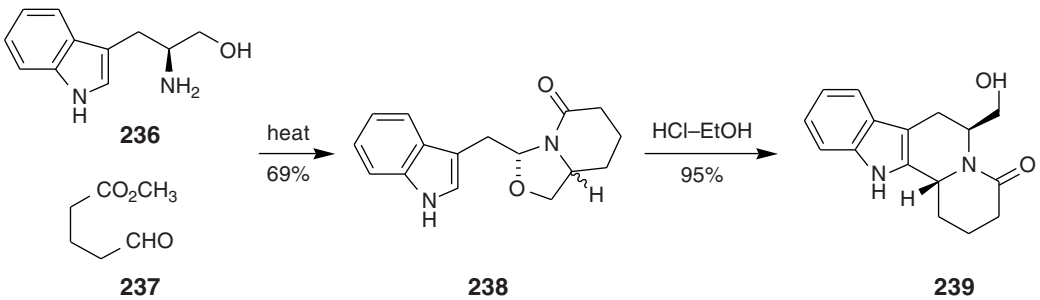
11.01.9.2.1 Intramolecular iminium ion cyclizations

Enantioselective syntheses of the quinolizidine alkaloids (+)-myrtine **7** and (−)-epimyrtine **152** was achieved using an intramolecular allylsilane *N*-acyliminium ion cyclization as the key step. Thus, treatment of the enantiomerically pure silane **230** with glutarimide under Mitsunobu conditions gave compound **231**, with the expected inversion of the stereocenter. Reduction of one carbonyl group in the imide portion of **231** with sodium borohydride afforded hydroxylactam **232**, which upon treatment with trifluoroacetic acid gave a 7:3 mixture of the quinolizidine derivatives **234** and **235**, by intramolecular cyclization of acyliminium species **233** (**Scheme 45**). Compounds **234** and **235** were subsequently transformed into the alkaloids myrtine and epimyrtine in two straightforward steps <1998TA1823>. A similar strategy allowed the asymmetric synthesis of quinolizidine alkaloids belonging to the lasubine and subcosine families <1998TA4361>. Besides silanes, alkynyltungsten compounds have also been found useful for *N*-acyliminium cyclizations leading to quinolizine systems <2001JOC6193>.



Scheme 45

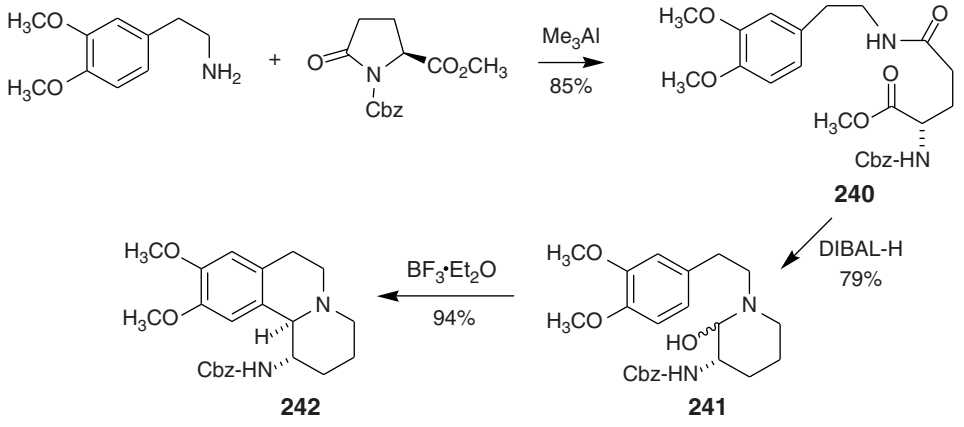
The reaction of (*S*)-tryptophanol **236** with dicarbonyl compound **237** under Dean–Stark conditions afforded the bicyclic lactam **238**, as a mixture of diastereomers. Exposure to acid of this mixture gave the indolo[2,3-*a*]quinolizidine **239** in excellent yield, as a single diastereomer (**Scheme 46**). This chemistry was subsequently applied to



Scheme 46

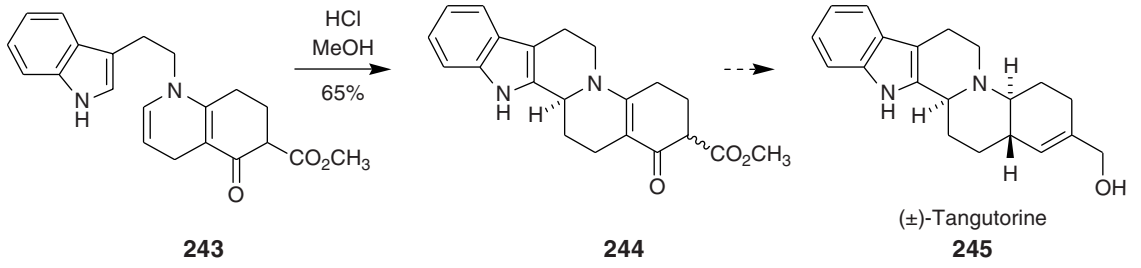
a total synthesis of the main constituent of *Dracontomelum mangiferin B1*, starting from (*R*)-tryptophanol <2004TL7103>.

Enantiospecific syntheses of amino derivatives of benzo[*a*]quinolizidine and indolo[2,3-*a*]quinolizidine compounds have also been achieved via *N*-acyliminium ion cyclization reactions, as an alternative to the more traditional Bischler–Napieralski chemistry (see Section 11.01.9.2.2). One interesting example involves the use of L-pyroglutamic acid as a chiral starting material to construct intermediates **240** via reaction with arylethylamine derivatives. Diisobutylaluminum hydride (DIBAL-H) reduction of the amide function in **240** and subsequent cyclization and further reduction afforded piperidine derivatives **241**, which stereoselectively cyclized to benzo[*a*]quinolizidine **242** upon treatment with boron trifluoride (**Scheme 47**) <1999JOC9729>.



Scheme 47

Another approach to the generation of an iminium cation suitable for cyclization is the protonation of dihydropyridine derivatives. One example can be found in **Scheme 48**, where treatment of compound **243** with acid induced its cyclization to indoloquinolizine **244**, a precursor in the first total synthesis of (±)-tangutorine **245**, an alkaloid isolated from a traditional Chinese medicinal plant <2001TL6593>.

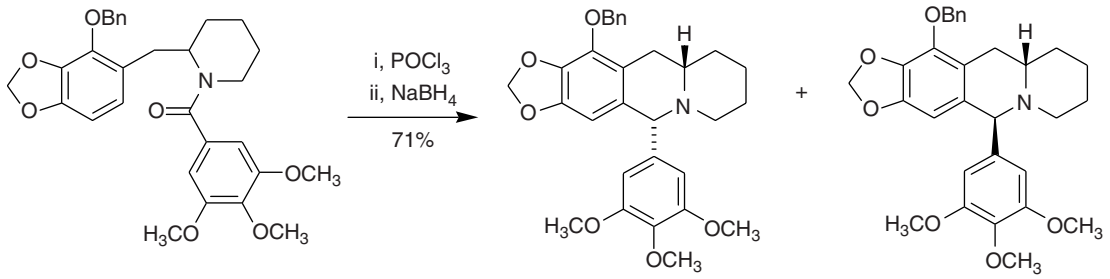


Scheme 48

11.01.9.2.2 Bischler–Napieralski and related reactions

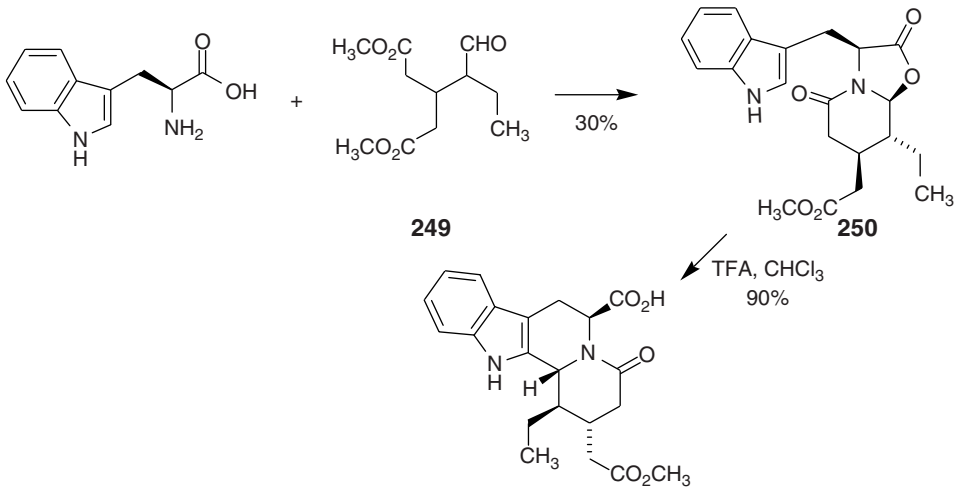
The Bischler–Napieralski reaction is one of the traditional methods for isoquinoline synthesis, and has been applied to the preparation of fused quinolizidine systems. One simple example is the transformation of compound **246** into a 9:1 mixture of diastereomers **247** and **248** by treatment with phosphorus oxychloride followed by sodium borohydride reduction of a nonisolated iminium salt resulting from the cyclization (**Scheme 49**) <2000BMC2113>.

Tryptophan (and also tryptophanol) undergoes a stereoselective cyclocondensation with racemic compound **249**, in a very interesting process involving a kinetic resolution with epimerization of the tryptophan stereocenter and simultaneous desymmetrization of the two diastereotopic acetate chains <2005CC1327>, affording the enantiomerically pure lactam **250**. A subsequent treatment of the latter compound with trifluoroacetic acid led to the indolo[2,3-*a*]quinolizidine **251** through an intermediate acyliminium cation (**Scheme 50**) <2005OL2817>.



246 **247** **248**

Scheme 49

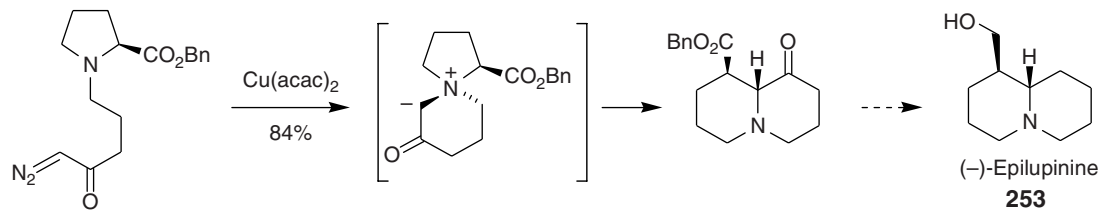


249 **250** **251**

Scheme 50

11.01.9.2.3 Tandem ammonium ylide generation–rearrangement reactions

The key step in the total synthesis of (−)-epilupinine **253** involved the ring expansion of a proline-derived spirocyclic ammonium ylide to give **252** through a [1,2] Stevens rearrangement, as shown in **Scheme 51** <1997T16565>.



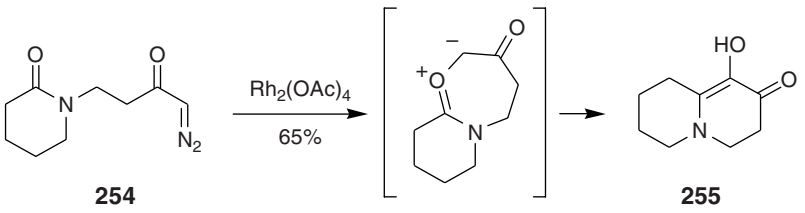
Diastereoselectivity = 95:5

252 **253**

Scheme 51

11.01.9.2.4 Rhodium carbenoid insertion reactions

Treatment of the diazo piperidone **254** with a catalytic amount of rhodium acetate afforded the hydroxyquinolizine derivative **255** through the mechanism summarized in **Scheme 52** <2000JOC7124>.

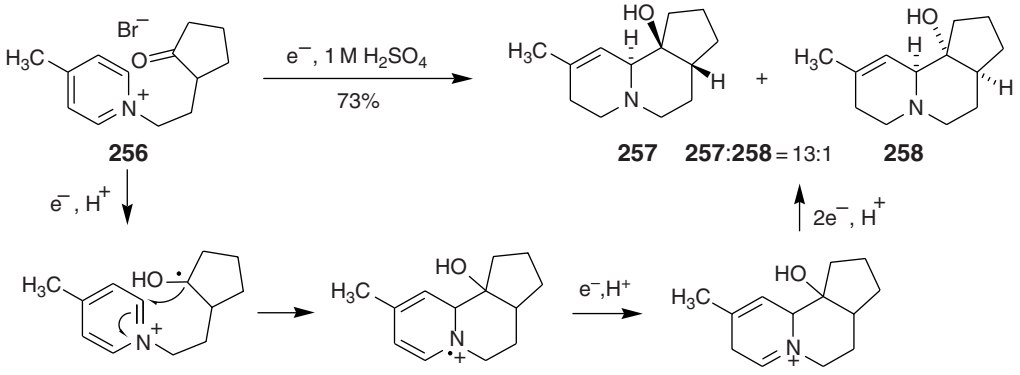


254 **255**

Scheme 52

11.01.9.2.5 Cathodic cyclizations

The cathodic cyclization of several types of *N*-(*δ*-oxoalkyl)pyridinium salts in 1 M sulfuric acid afforded quinolizine derivatives. For example, compound **256**, prepared from 4-methylpyridine, gave a diastereomeric mixture of quinolizines **257** and **258**. Differential pulse polarographic studies allowed a mechanism to be proposed, which is outlined in **Scheme 53** <2003EJO2919>.



Scheme 53

11.01.9.3 Formation of a New Bond γ to the Heteroatom

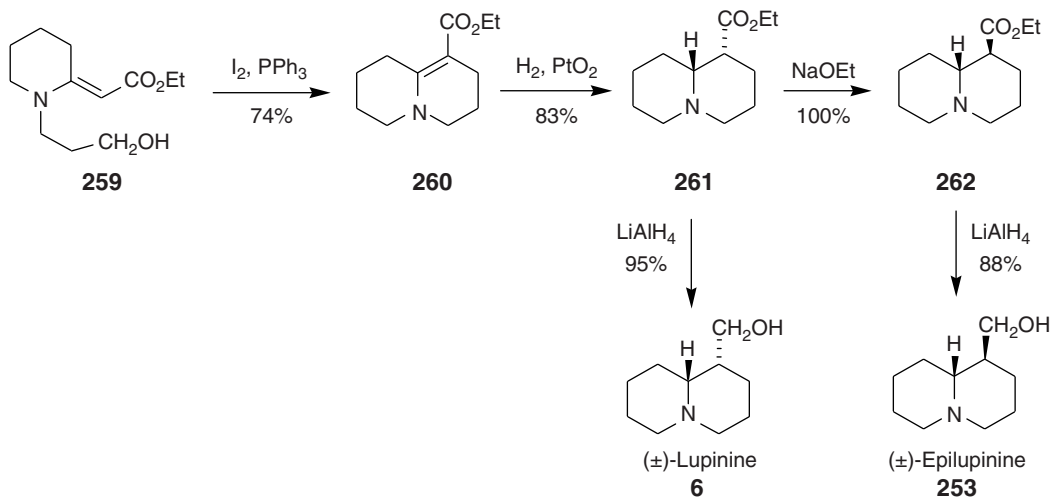
11.01.9.3.1 Intramolecular enamine cyclizations

2-Methylenepiperidines containing a good leaving group at the γ-position of an *N*-alkyl chain undergo an intramolecular cyclization by nucleophilic attack of the enamine portion onto the electrophilic carbon atom. For instance, (±)-lupinine and (±)-epilupinine were obtained from the hydroxy derivative **259** that was activated with iodine and triphenylphosphine. The nonisolated iodide cyclized spontaneously to **260**. This compound, after steroselective *cis*-hydrogenation over the Adams catalyst, yielded (±)-ethyl lupinoate **261**, which was transformed into (±)-lupinine **6** by $LiAlH_4$ reduction. A base-catalyzed epimerization of **261** gave **262**, which was similarly transformed into (±)-epilupinine **253** (**Scheme 54**) <2002ARK62>.

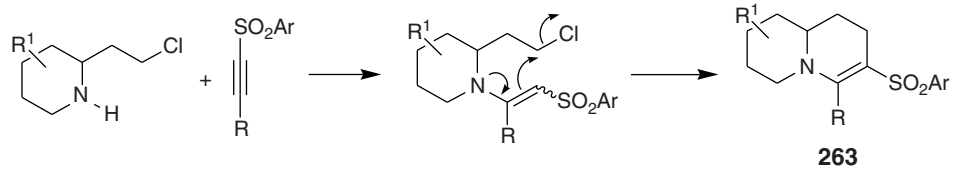
Alternatively, the enamine portion may be located in the *N*-alkyl chain. For instance, piperidines bearing a γ-chloro substituent yielded quinolizidines **263** through a conjugate addition of the nitrogen atom to acetylenic sulfones followed by an intramolecular alkylation (**Scheme 55**) <2000JOC4543>. Other cyclizations that are summarized below used as starting materials piperidine derivatives obtained by similar conjugate additions to vinyl sulfones (see Section 11.01.9.3.6).

11.01.9.3.2 Intramolecular aldol condensations

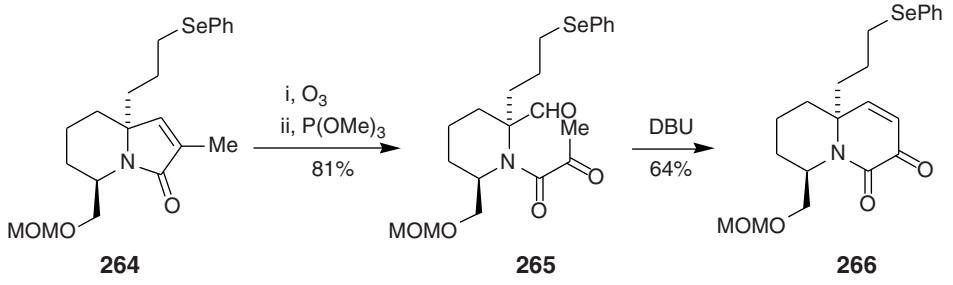
The strategy employed in studies aiming at the synthesis of the spiro segment of halichlorine (see also Section 11.01.11.4) involved a ring expansion in indolizidine **264**. The double bond of this compound was cleaved by ozonolysis yielding compound **265**, which was cyclized to quinolizidine derivative **266** in the presence of base (**Scheme 56**) <2004TL2879>.



Scheme 54

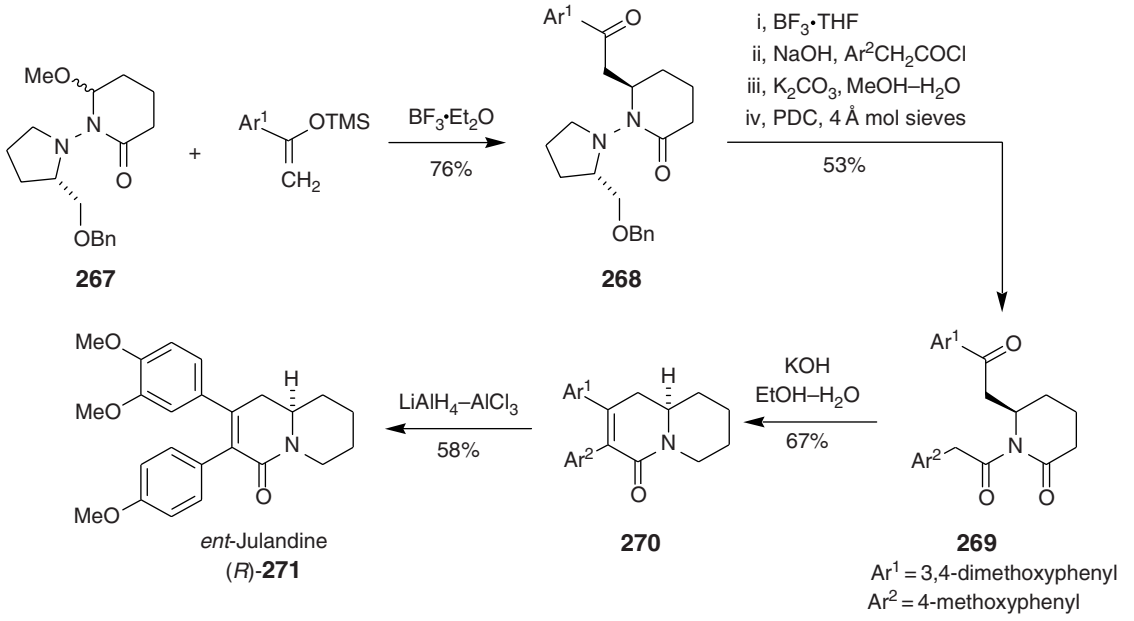


Scheme 55



Scheme 56

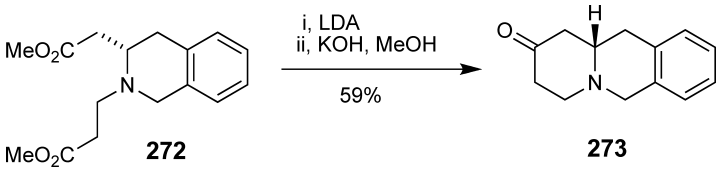
In the first reported enantioselective synthesis of julandine, the seco-analogue of cryptopleurine **12**, the proline-derived lactam **267,** was condensed with a silyl enol ether under Lewis acid catalysis to produce an intermediate acyliminium ion. The diastereoselectively obtained piperidone **268** was treated with borane to reduce both carbonyl groups and remove the chiral auxiliary giving the corresponding (2*R*)-2-substituted piperidine as a mixture of alcohol diastereomers. N,O-Bisacylation, selective hydrolysis of the ester, and benzylic oxidation gave the dicarbonyl compound **269**, which in a base-induced condensation afforded quinolizidone **270**. The synthesis of (*R*)-(−)-julandine **271** was completed by reductive removal of the lactam carbonyl group (**Scheme 57**) <1995JOC6114>. This synthesis allowed assignment of the absolute configuration of natural (+)-julandine as (9a*S*), that is, *ent*-**271**.



Scheme 57

11.01.9.3.3 Dieckman cyclizations

A route for the asymmetric synthesis of benzo[*b*]quinolizidine derivative **273** was planned, having as the key step a Dieckman cyclization of a tetrahydroisoquinoline bis-methyl ester derivative **272**, prepared from (*S*)-phenylalanine in a multistep sequence. This cyclization was achieved by treatment of **272** with lithium diisopropylamide (LDA) as a base, and was followed by hydrolysis and decarboxylation to **273** (**Scheme 58**). Racemization could not be completely suppressed, even though many different reaction conditions were explored <1999JPI3623>.



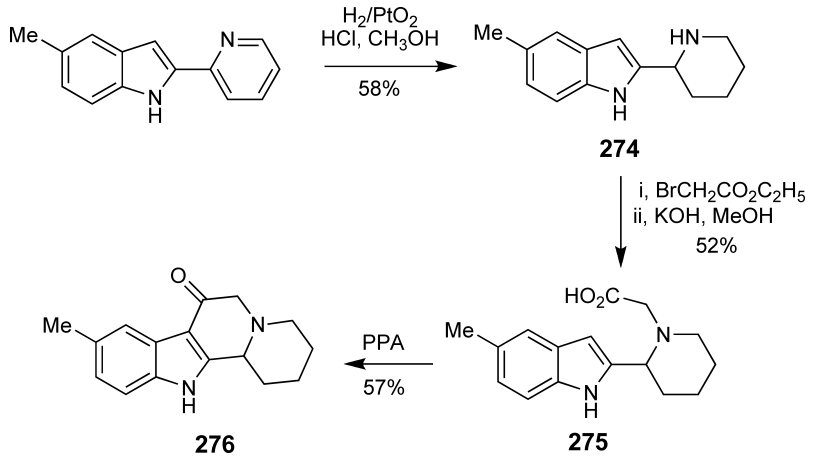
Scheme 58

11.01.9.3.4 Friedel–Crafts and related reactions

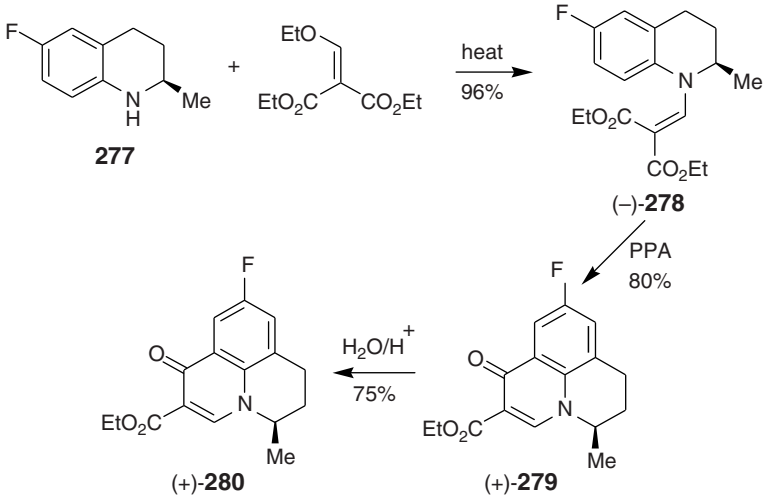
The quinolizine derivative **276** was obtained through a Friedel–Crafts acylation reaction onto the C-3 indole position of **275**. This precursor was obtained by a sequence comprising a Fischer cyclization leading to 5-methyl-2-(2-pyridyl)indole **274**, catalytic hydrogenation, N-alkylation with ethyl bromoacetate, and hydrolysis of the ester group (**Scheme 59**) <1999FA479>.

The antibacterial agent flumequine **280** was synthetized in optically active form by starting with resolution of the two enantiomers of a suitably substituted racemic tetrahydroquinoline through formation of the (1*R*)-3-bromocamphor-8-sulfonates. After N-alkylation of the (2*R*)-tetrahydroisoquinoline enantiomer **277** with diethyl ethoxymethylenemalonate to give **278**, the quinolizidine system **279** was formed by acylation onto the *peri*-position. This compound was finally hydrolyzed to afford **280** (**Scheme 60**) <1999TA1079>.

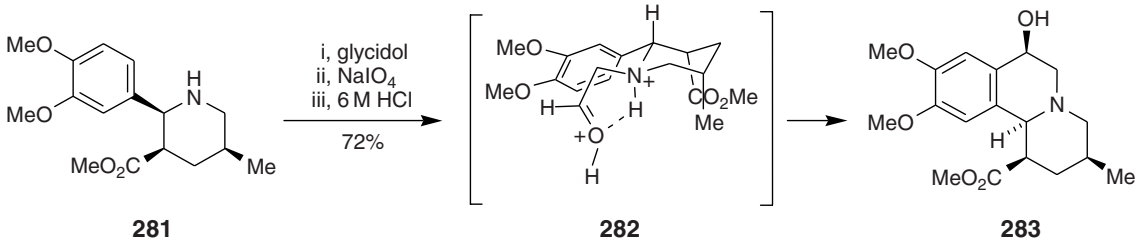
Treatment of 2-arylpiperidine derivatives **281** with glycidol followed by oxidative cleavage of the vicinal diol with $NaIO_4$ afforded the corresponding α-aminoaldehydes that cyclized to the corresponding benzo[*a*]quinolizidine upon acid treatment. Ring closure to **283** was stereospecific, which was rationalized assuming a structure **282** for the protonated aldehyde, with the aryl substituent in an equatorial position (**Scheme 61**) <1999TL9147>.



Scheme 59



Scheme 60

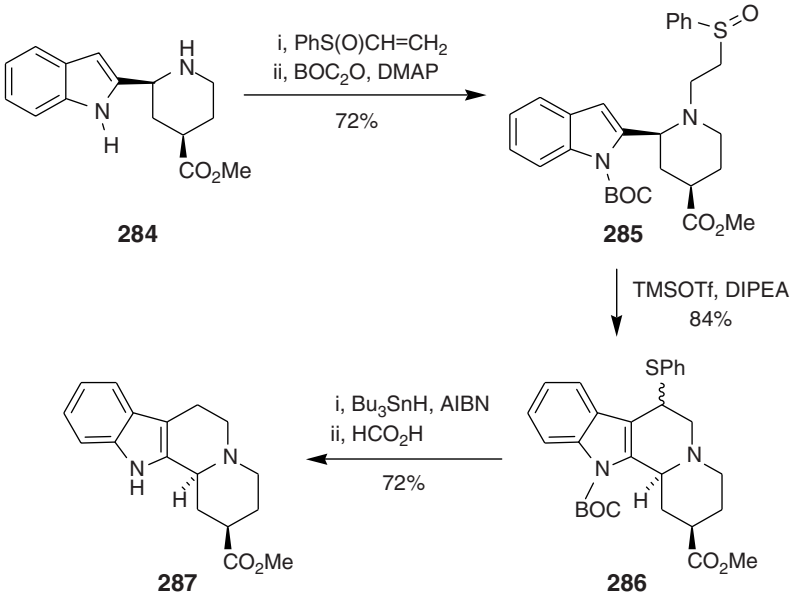


Scheme 61

11.01.9.3.5 Intramolecular Pummerer cyclizations

The intramolecular Pummerer reaction has been applied to the synthesis of simple quinolizidine alkaloids like lupinine <2000JOC2368>, and also to arenoquinolizine alkaloids. Thus, the 2-(2-piperidyl)indole **284** was converted to indolo[2,3-*a*]quinolizidine **287** following a protocol that has as the key step the regioselective cyclization onto the indole 3-position of a thionium ion generated by Pummerer reaction from the appropriately substituted compound

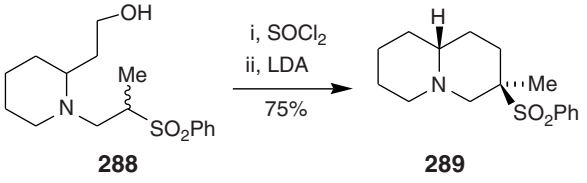
285. This compound was obtained as a mixture of isomers at the sulfur atom by incorporation of the (phenylsulfinyl)-ethyl chain on the piperidine nitrogen and blocking of the indole nitrogen to diminish the nucleophilic character of the indole nucleus. This sulfoxide was subjected to the Pummerer reaction by treatment with TMSOTf (TMS = trimethylsilyl) and *N*,*N*-diisopropylethylamine (DIPEA) giving the indoloquinolizidine **286** as a mixture of epimers at C-7. Finally, elimination of the phenylsulfanyl group by treatment with tributyltin hydride and AIBN, followed by hydrolysis of the BOC group, provided the desired indoloquinolizidine **287** (**Scheme 62**) <2002ARK73>.



Scheme 62

11.01.9.3.6 Intramolecular sulfone cyclizations

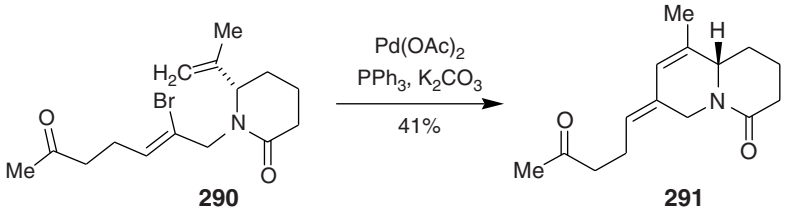
In one example of this type of cyclization aminoalcohol, **288**, which was obtained by conjugate addition of racemic 2-(2-hydroxyethyl)piperidine to allyl phenyl sulfone, was converted into the corresponding chloride and cyclized in the presence of LDA to give **289** as a single diastereomer (**Scheme 63**) <2003JOC9389>. In a related approach, the primary alcohol group was activated for a similar cyclization by transformation into a mesylate <2001OL2957>.



Scheme 63

11.01.9.3.7 Palladium-mediated cyclizations

Dehydrohomopumiliotoxins are the putative structures assigned to alkaloids 235C and 233F isolated as minor components from the skins of Madagascar frogs of the genus *Mantella*. During a total synthesis of these compounds, the core quinolizine system **291** was obtained using an intramolecular Heck cyclization of the (*Z*)-vinyl bromide **290** (**Scheme 64**) <2004TL1627>.

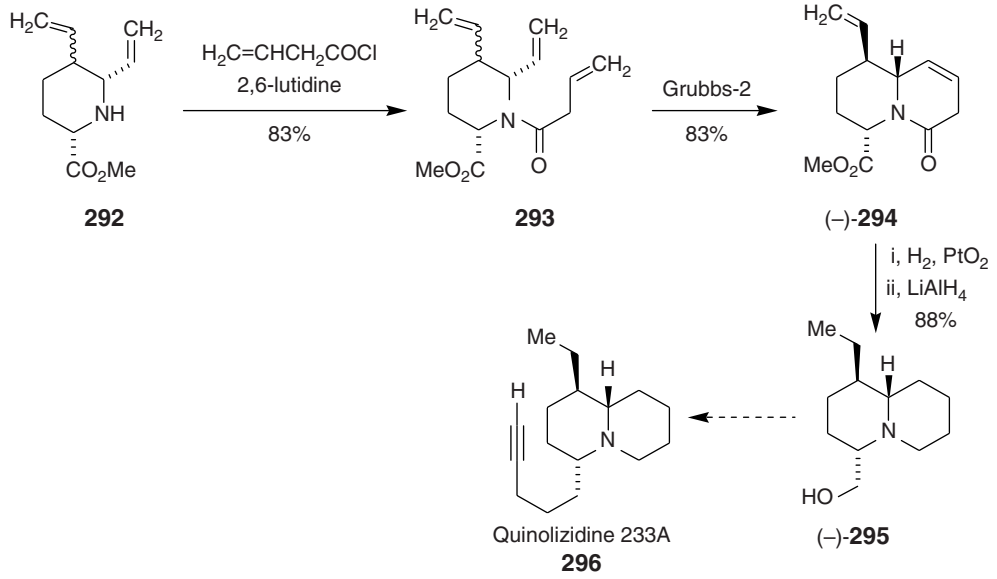


Scheme 64

11.01.9.3.8 Ring-closing metathesis

The application of the RCM reaction to the construction of nitrogen-containing ring systems, including quinolizidine derivatives, has been reviewed <1999EJO959>. From that date, this strategy has become more and more common in quinolizidine synthesis, especially in cases where the cyclization takes place by formation of a bond γ to the heteroatom. Some examples are given below.

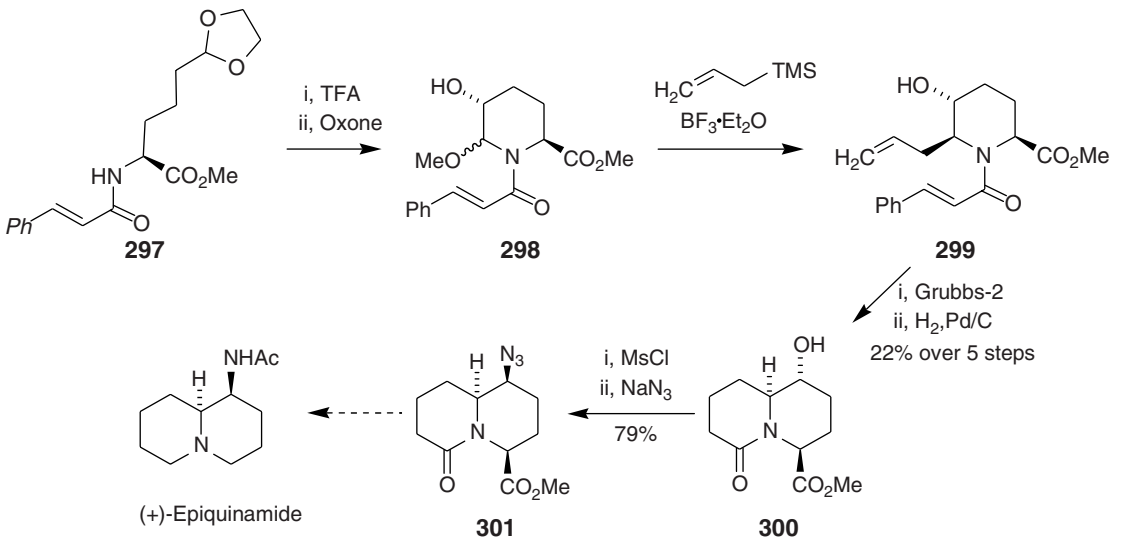
In a formal synthesis of quinolizidine 233A **296**, the 2,6-*cis*-disubstituted piperidine **292**, as a mixture of diastereomers, was transformed into **293** by N-acylation with but-3-enoyl chloride. An RCM afforded **294**, which was transformed into **295** by hydrogenation of the double bonds and hydride reduction of the lactam, thereby completing a formal synthesis <2000JOC8908> of quinolizidine 233A **296** (**Scheme 65**) <2004JA4100>.



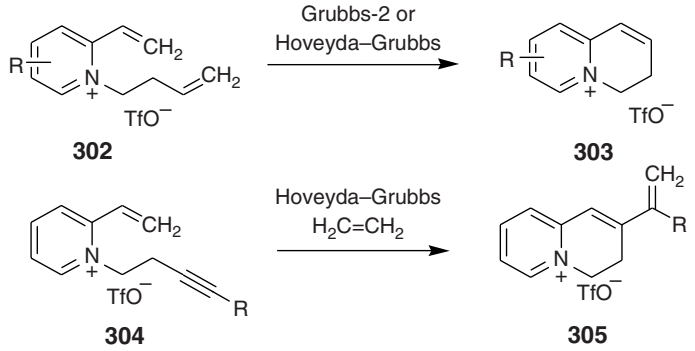
Scheme 65

The stereoselective total synthesis of (+)-epiquinamide **301** has been achieved starting from the amino acid L-allysine ethylene acetal, which was converted into piperidine **298** by standard protocols. Allylation of **297** via an *N*-acyliminium ion gave **298**, which underwent RCM to provide **299** and the quinolizidine **300**, with the wrong stereochemistry at the C-1 stereocenter. This was corrected by mesylation of the alcohol, followed by S_N2 reaction with sodium azide to give **301**, which, upon saponification of the methyl ester and decarboxylation through the Barton procedure followed by reduction and N-acylation, gave the desired natural product (**Scheme 66**) <2005OL4005>.

RCM has also allowed the access to dihydroquinolizinium cations **303** from *N*-alkenyl-α-vinyl azinium salts **302** <2004OL4125>. More recently, the preparation of 2-vinyl-3,4-dihydroquinolizinium salts **305** has been achieved through ring-closing enyne metathesis (RCEYM) of the corresponding precursors **304** (**Scheme 67**), and 4-vinyl-3,4-dihydroquinolizinium salts have also been prepared similarly. The best results were obtained using the Hoveyda–Grubbs catalyst and running the reaction under an atmosphere of ethylene <2006CC2690>.

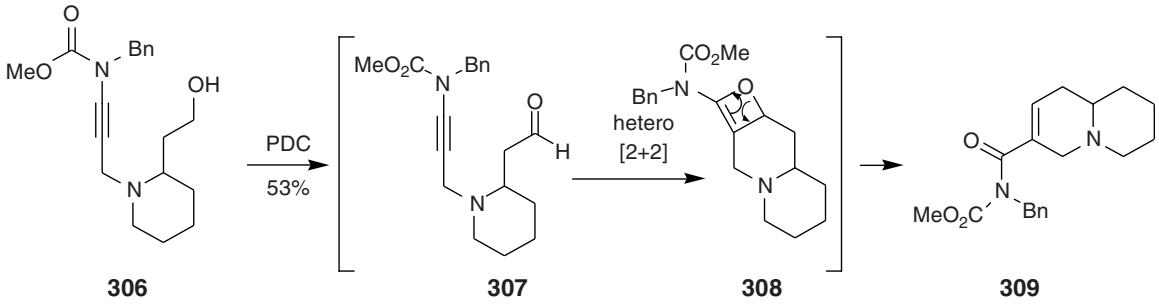


Scheme 66



Scheme 67

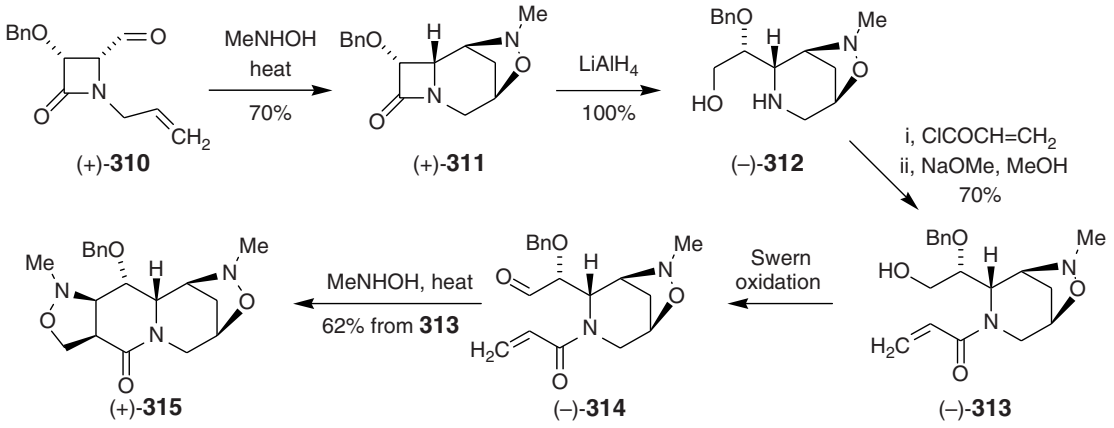
One final, interesting example of a ring-closing ynamide–carbonyl metathesis leading to a quinolizidine system was observed during the pyridinium dichromate (PDC) PDC oxidation of ynamide **306**, which afforded compound **309** in 53% overall yield. Mechanistically, this reaction would proceed from aldehyde **307** through ring opening of an amide-substituted oxetene intermediate **308** formed through a stepwise hetero- [2+2] cycloaddition pathway (**Scheme 68**) <2006OL231>.



Scheme 68

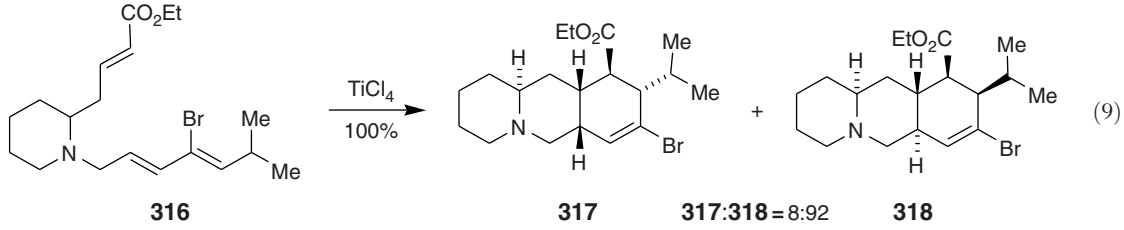
11.01.9.3.9 Intramolecular pericyclic reactions

A new methodology to achieve the preparation of the quinolizidine system was based on the sequential regio- and stereocontrolled intramolecular nitrone–alkene cycloaddition (INAC) reactions of azetidinone-tethered alkenylaldehydes in an extension of the use of β-lactams as chiral synthons. Enantiomerically pure **310** was transformed into the tricyclic bridged cycloadduct **311**, which was quantitatively reduced to piperidyl alcohol **312**. A subsequent reaction with acryloyl chloride afforded the corresponding amido ester, which was converted into the amido alcohol **313** by selective transesterification with sodium methoxide in methanol. Swern oxidation of the alcohol gave the corresponding aldehyde **314**, which afforded quinolizidine **315** after treatment with *N*-methylhydroxylamine (**Scheme 69**) <2002SL85>.



Scheme 69

Compound **316** contains two suitable ene–diene functions that yielded two diastereomeric tetrahydrobenzo[*b*]quinolizidines in quantitative yield and in a 8:92 ratio in a $TiCl_4$-catalyzed intramolecular Diels–Alder (IMDA) reaction (Equation 9) <1998T9529>.

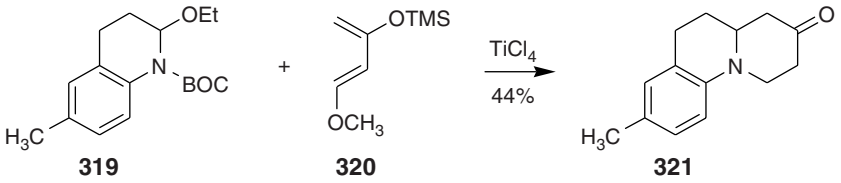


(9)

11.01.9.4 Formation of Two New Bonds from Monocyclic Precursors

11.01.9.4.1 Two new bonds from [6+4] fragments

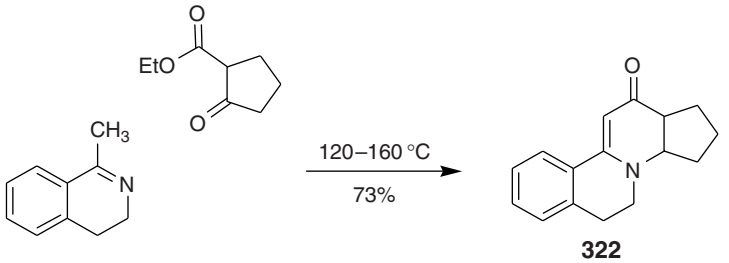
Hetero-Diels–Alder reactions have been succesfully employed for the synthesis of arenoquinolizine systems. For example, as shown in Equation 10, treatment of tetrahydroquinoline **319** with Danishefsky's diene **320** in the presence of a Lewis acid gave the benzo[*c*]quinolizidine derivative **321** <2000JME3718>.



(10)

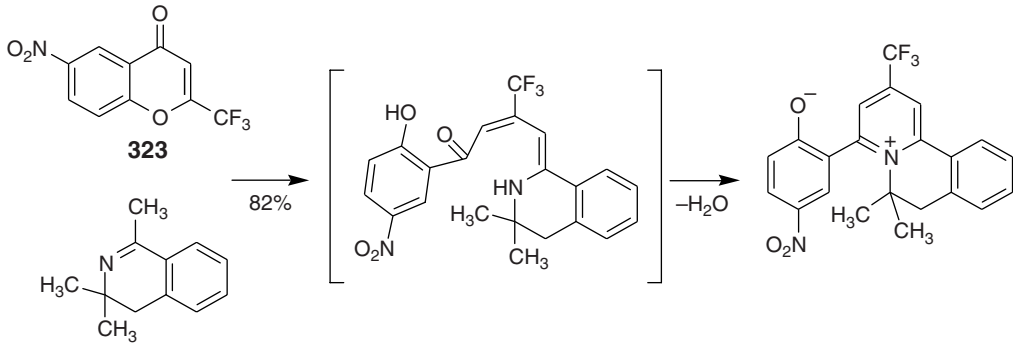
11.01.9.4.2 Two new bonds from [7+3] fragments

Annelation of cyclic imines with β-dicarbonyl compounds <2004RCB393>, with cyclic β-oxodithioesters <2001OL229>, or with arylmethylene-β-dinitriles <2002SC581> provides a one-pot route to quinolizidine systems, as exemplified in Equation 11 for the preparation of the 8-azasteroid **322**.



322 (11)

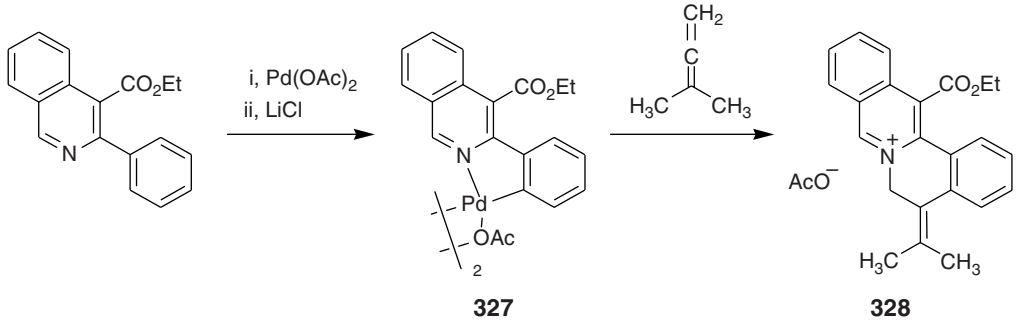
The reaction of 2-polyfluoroalkylchromones (e.g., **323**) with 1,3,3-dimethyl-3,4-dihydroisoquinolines (e.g., **324**) gave zwitterionic 6,7-dihydrobenzo[*a*]quinolizinium compounds such as **326** (**Scheme 70**). The mechanism proposed for this transformation involves an addition–elimination displacement of the chromane heterocyclic oxygen by the enamine tautomer of the dihydroisoquinoline, followed by intramolecular cyclization of the intermediate **325** <2003OL3123>.



Scheme 70

11.01.9.4.3 Two new bonds from [8+2] fragments

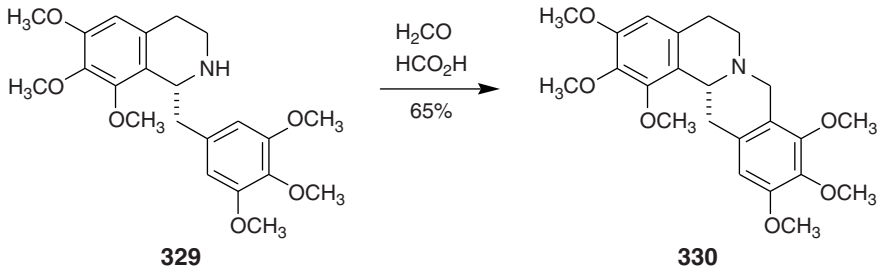
The insertion of allenes in the Pd–C bond of cyclopalladated 3-arylisoquinoline derivatives **327** afforded compounds **328**, derived from the berberinium cation (**Scheme 71**). This reaction takes place via the formation of an intermediate (η^3-allyl)palladium complex <2003JOM313>. This chemistry has been extended to the preparation of other cationic N-heterocycles, including naphtho[*def*]quinolizinium derivatives <2004EJO1724>.



Scheme 71

11.01.9.4.4 Two new bonds from [9+1] fragments

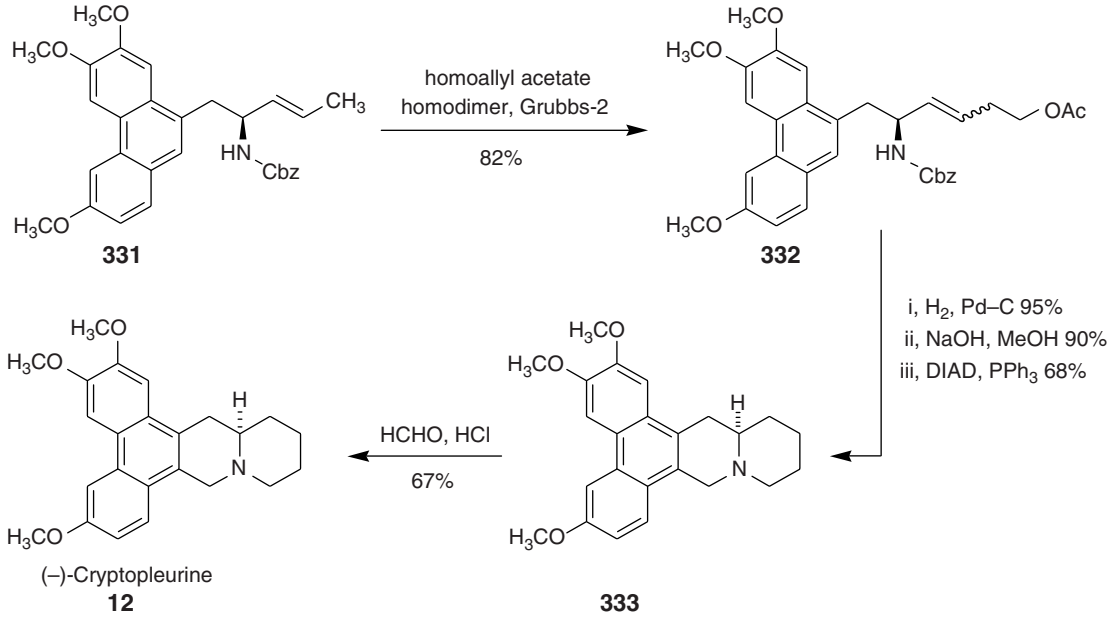
This strategy normally involves the generation of an iminium species from a tetrahydroisoquinoline and formaldehyde, followed by its Pictet–Spengler cyclization. It can be exemplified by the preparation of the berberine derivative **330** from tetrahydroisoquinoline **329** (**Scheme 72**) <2001JOC3495>.



329 **330**

Scheme 72

A similar strategy served to carry out the last step of an asymmetric synthesis of the alkaloid (−)-cryptopleurine **12**. Compound **331**, prepared from the known chiral starting material (*R*)-(*E*)-4-(tributylstannyl)but-3-en-2-ol, underwent cross-metathesis to **332** in the presence of Grubbs second-generation catalyst. Catalytic hydrogenation of the double bond in **332** with simultaneous N-deprotection, followed by acetate saponification and cyclization under Mitsunobu conditions, gave the piperidine derivative **333**, which was transformed into (−)-cryptopleurine by reaction with formaldehyde in the presence of acid (**Scheme 73**) <2004JOC3144>.



331 **332**

(–)-Cryptopleurine
12

333

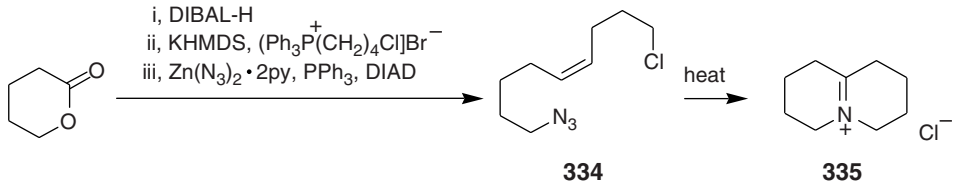
Scheme 73

11.01.9.5 Formation of Two New Bonds from Acyclic Precursors

11.01.9.5.1 Formation of α,α-bonds

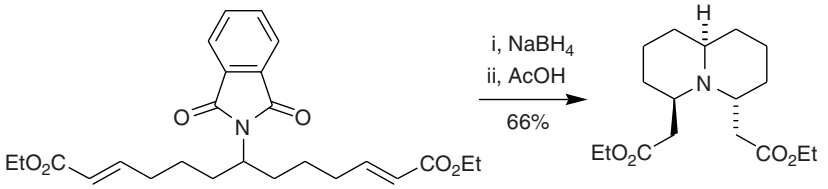
A simple cyclization was carried out to test the ability of chloro azidoalkene cyclization to generate quinolizidines. Reduction of δ-valerolactone to the corresponding lactol was followed by a Wittig reaction onto the carbonyl function employing an appropriate phosphonium salt, and the intermediate primary alcohol thus formed afforded the chloro

azidoalkene **334** through a Mitsunobu reaction with zinc azide. Heating this azide at 100 °C in a sealed tube cleanly afforded the octahydroquinolizinium salt **335** as the sole product (**Scheme 74**) <1998JOC9910>. This simple method could not be applied when δ-allyl-δ-valerolactone was the starting material.



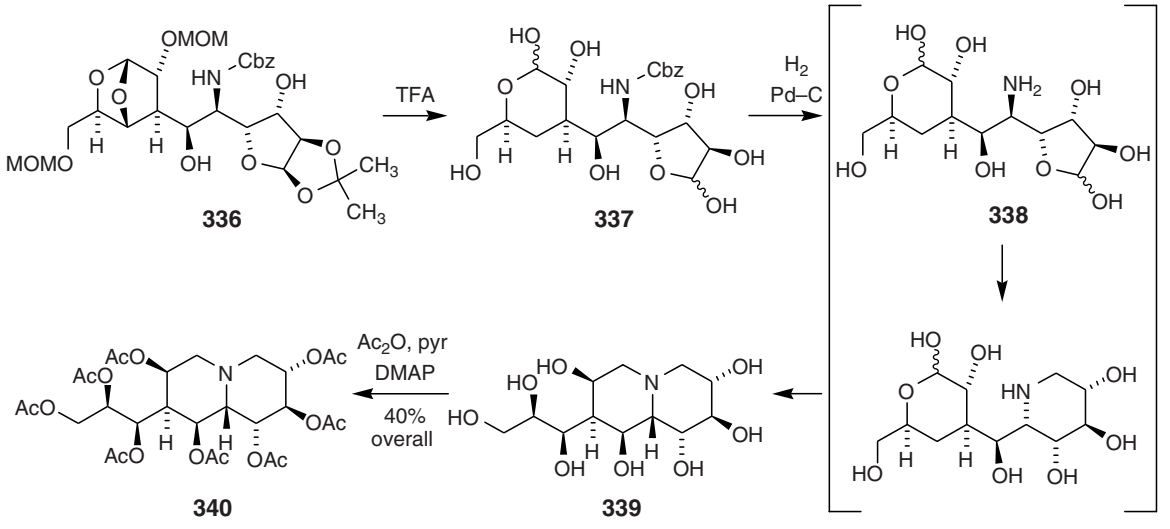
Scheme 74

Another method that yields quinolizidine derivatives by creation of two α-bonds from acyclic precursors is based on a domino process involving a sequence of a double N-deprotection and a double intramolecular Michael addition sequence of reactions, as summarized in **Scheme 75** <2002TL6505>.



Scheme 75

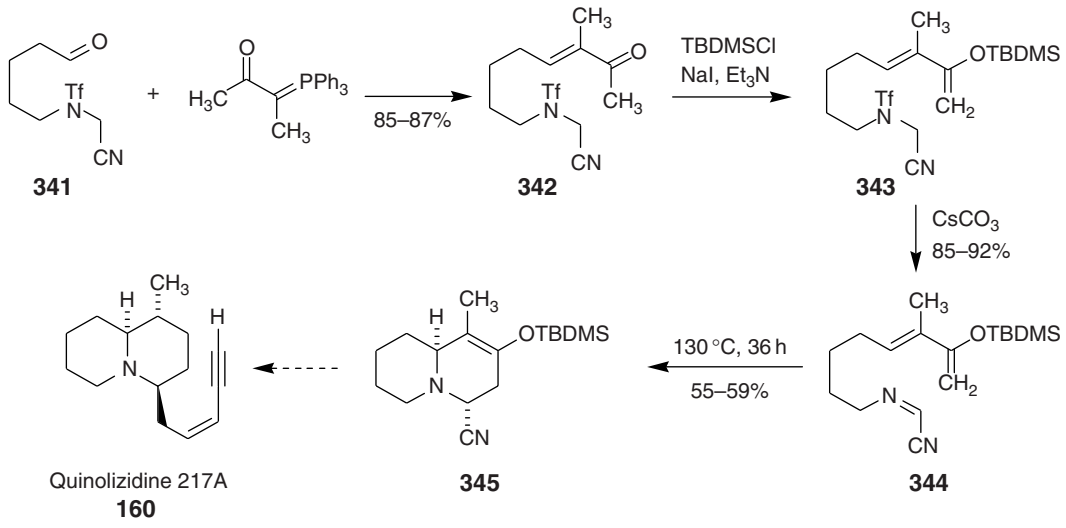
A strategy involving the creation of a quinolizidine system by generation of two α-bonds was applied to the synthesis of a polyhydroxyquinolizine system **340**, which was considered of interest for its study as a glycohydrolase inhibitor. In the last stages of this synthesis, acid deprotection of the hydroxyl functions in intermediate **336** afforded a complex mixture of dialdoses **337**, whose catalytic hydrogenation afforded the quinolizidine **340** as the only product (**Scheme 76**). This complex reaction must start by transformation of **337** into the deprotected amine **338**, which was expected to cyclize by reaction of the amino group with a lactol moieties to give an imine that would be hydrogenated to afford piperidine derivative, which would then again cyclize to **339** through a similar process <1999SL1219>.



Scheme 76

11.01.9.5.2 Formation of α,β-bonds

Intramolecular imino Diels–Alder reactions have also been employed as key steps in the preparation of quinolizidine systems. One example is the synthesis of quinolizidine (−)-217A **160**, which started by the generation of α,β-unsaturated ketone **342** through a Wittig reaction of the trifluoromethylsulfonyl-protected precursor **341**. Transformation of the carbonyl group in **342** into an enol ether completed the preparation of the diene component (compound **343**), while a base-catalyzed elimination reaction afforded the imino group that acts as a dienophile. Heating of compound **344**, thus obtained, triggered the desired Diels–Alder reaction, which afforded compound **345**, a precursor to the natural product (**Scheme 77**) <2005OL3115>.



Scheme 77

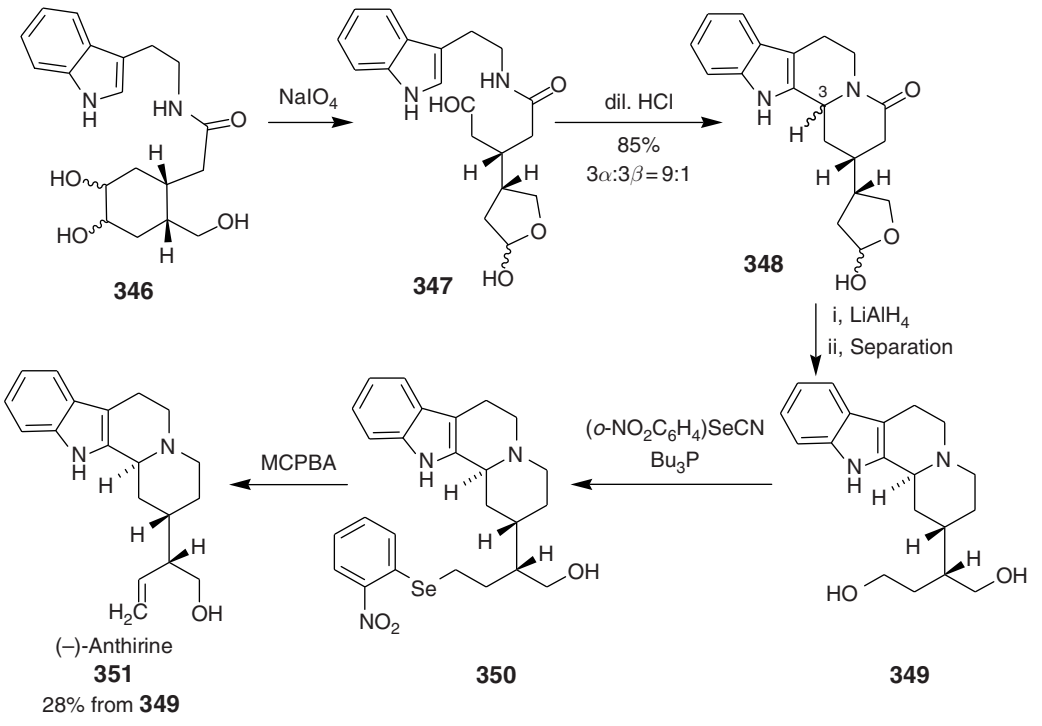
(−)-Antirhine **351**, the major alkaloid of *Antirhea putaminosa*, possesses an indoloquinozilidine skeleton that has been approached through formation of two α,β-bonds in a Pictet–Spengler reaction. The starting enantiomericallypure material was **346**, whose chirality was obtained from enzymatic asymmetrization of *cis*-1,2-cyclohex-4-ene dimethanol. Compound **346** was transformed into aldehyde **347** by oxidative degradation with sodium periodate and then cyclized in acid to give **348**. Reduction of the masked aldehyde and the amide carbonyl group gave the expected diol, also as a mixture of two diastereomers. After separation, the 3α-epimer **349** was monoselenated to give **350** which, by oxidation with *meta*-chloroperbenzoic acid (MCPBA), afforded (−)-antirhine **351** (**Scheme 78**) <2000COR231>.

An intramolecular Mannich reaction of carboline derivative **352** afforded a complex bridged system containing an indolo[2,3-*a*]quinolizidine moiety, as a mixture of two diastereomers. One of them, **353**, was transformed into the alkaloid tacamonine **15** (**Scheme 79**) <2002T4969>.

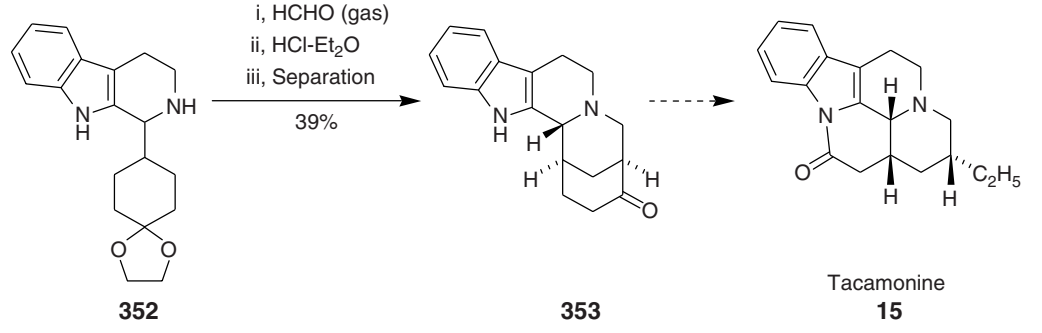
11.01.9.5.3 Formation of α,γ-bonds

An intramolecular formal aza-[3+3] cycloaddition reaction based on the cyclization of a vinylogous amide tethered with an α,β-unsaturated iminium moiety was applied to the synthesis of the indoloquinolizidine alkaloids tangutorine <2003OL4709> and deplancheine **14** <2005OBC2140>. The key step of the latter synthesis (**Scheme 80**) involved the double enamine cyclization of precursor **354** to **356** in the presence of piperidinium acetate, through the intermediacy of **355**, followed by catalytic hydrogenation. The use of chiral amine salts allowed the preparation of (+)-deplancheine, although in modest enantiomeric excess <2005OBC2140>.

A lanthanide-mediated, sequential hydroamination/C–C cyclization reaction served to prepare the benzo[*a*]quinolizine derivative **358** from precursor **357**, using a Nd species as a catalyst (Equation 12). This cascade process proceeded in good yield and with high diastereoselectivity <2003T10581>.



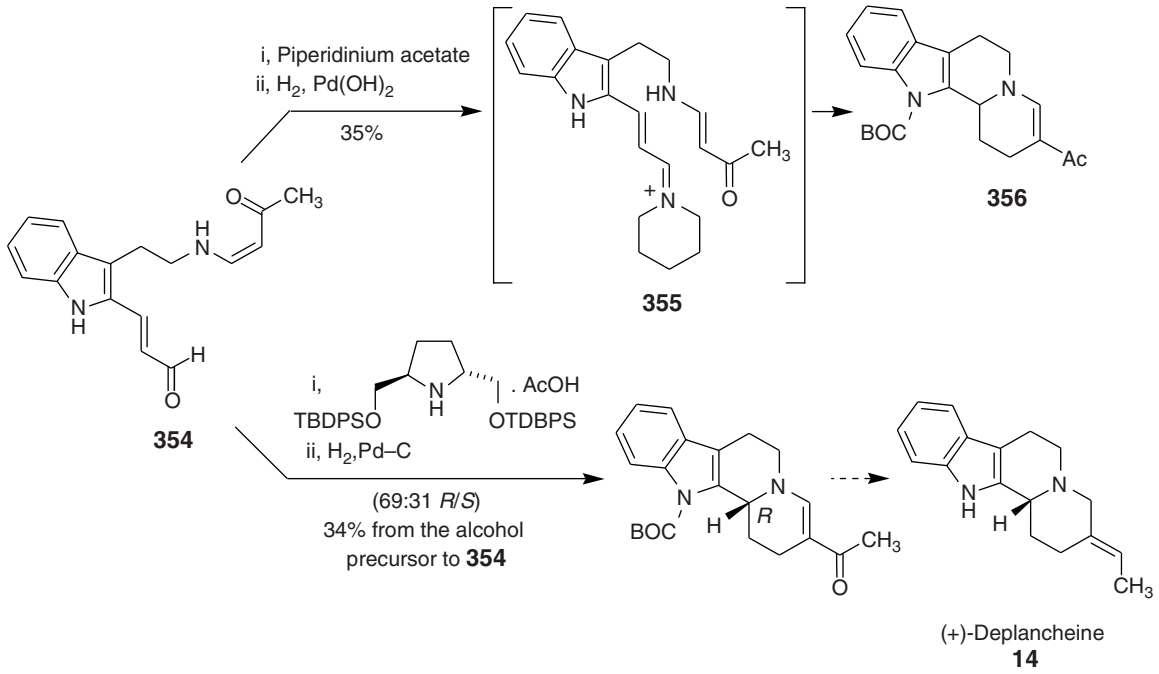
Scheme 78



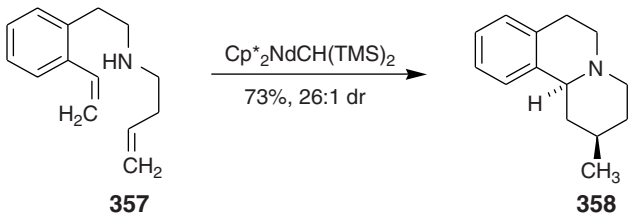
Scheme 79

The 3*a*,9*a*-diazaperylenium dication **33** was synthesized for the first time in two steps from *p*-phenylenediamine. When reacted with 1-bromo-3-chloropropane, this diamine gave the diazaperylene **359**, containing two quinolizidine fragments <2001CC1742>, and this product was oxidized with HgO in acetic acid to give a low yield of a mixture of quinolizinium products **33** and **360** in a 1:3 molar ratio (**Scheme 81**) <2002OL4113>.

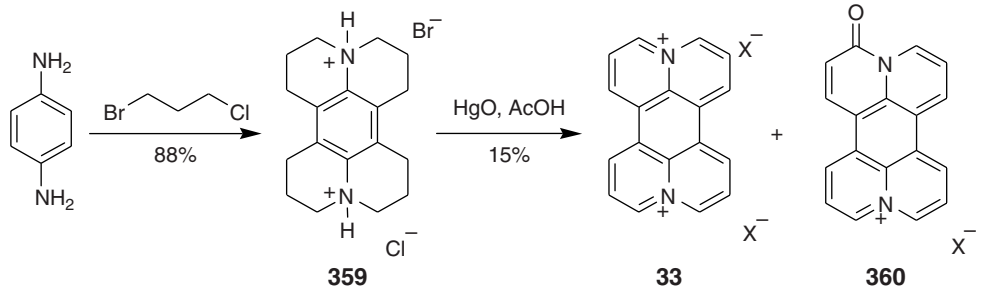
Another approach to a fused quinolizine system **363** through the generation of α,γ-bonds in the key step is the reaction between 2-cyanomethylpyridine and 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-one **361** under basic conditions (**Scheme 82**). This process involves the initial displacement of the methylthio group by the 2-cyanomethylpyridine anion to give intermediate **362**, followed by base-induced cyclization onto the nitrile group <1999S1884>.



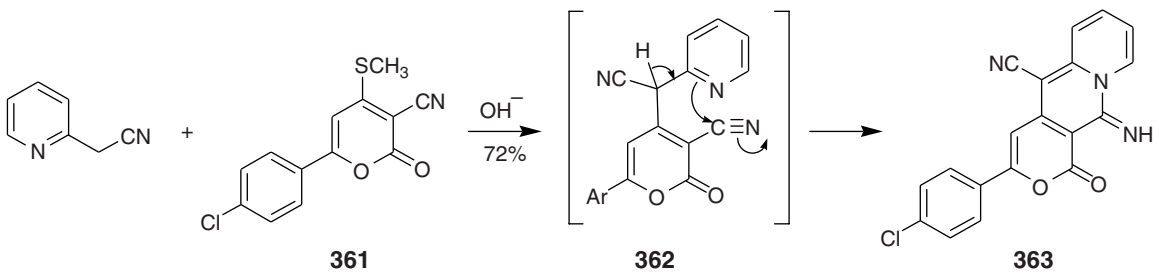
Scheme 80



(12)



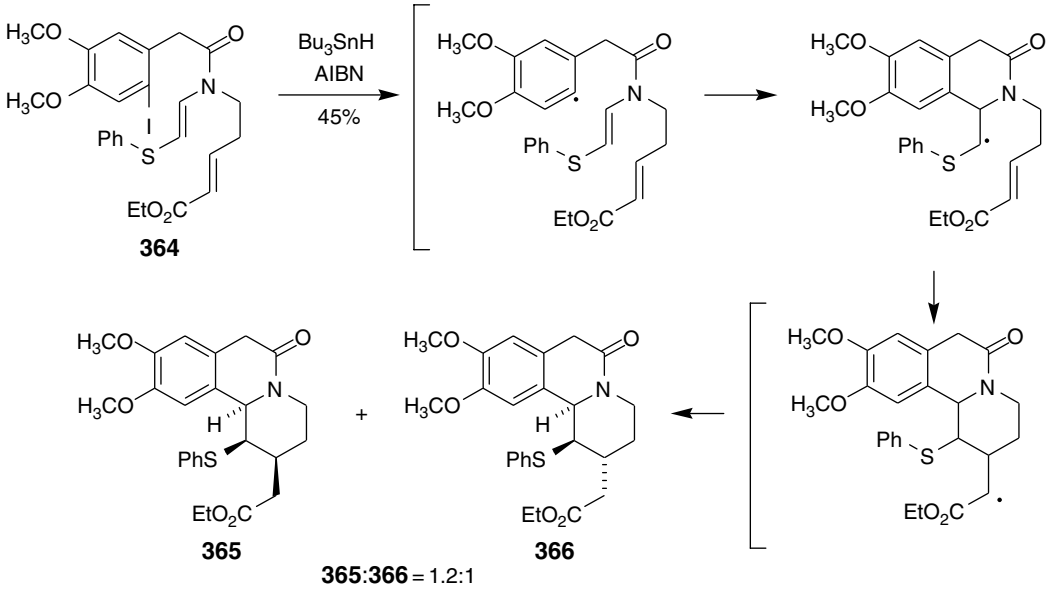
Scheme 81



Scheme 82

11.01.9.5.4 Formation of β,γ-bonds

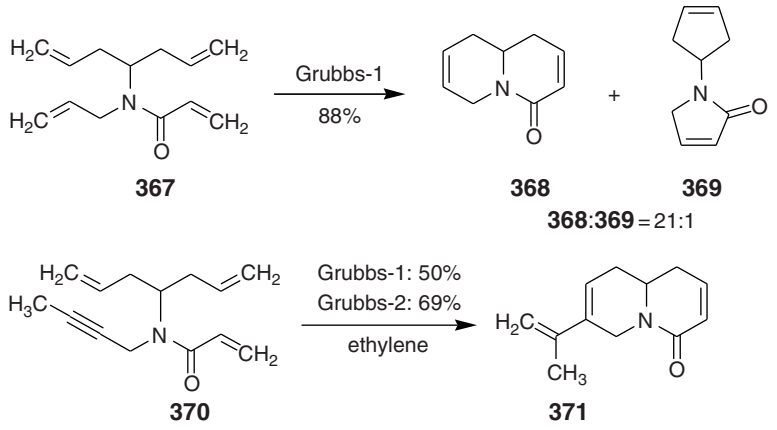
The reaction of compound **364** with a radical initiator gave a mixture of diastereomeric benzo[*a*]quinolizidines **365** and **366** through the radical cascade process summarized in **Scheme 83** <1999TL1149>.



Scheme 83

11.01.9.5.5 Formation of γ,γ-bonds

A double RCM reaction of **367** permitted the efficient construction of the fused bicyclic quinolizidine skeleton **368** as the major product, together with a small amount of the other possible double-metathesis product **369** (**Scheme 84**) <2002OL639, 2004CEJ3286>. Similarly, an RCEYM process from substrate **370**, carried out in an atmosphere of ethylene, afforded the quinolizine derivative **371** <2004JOC6305>.



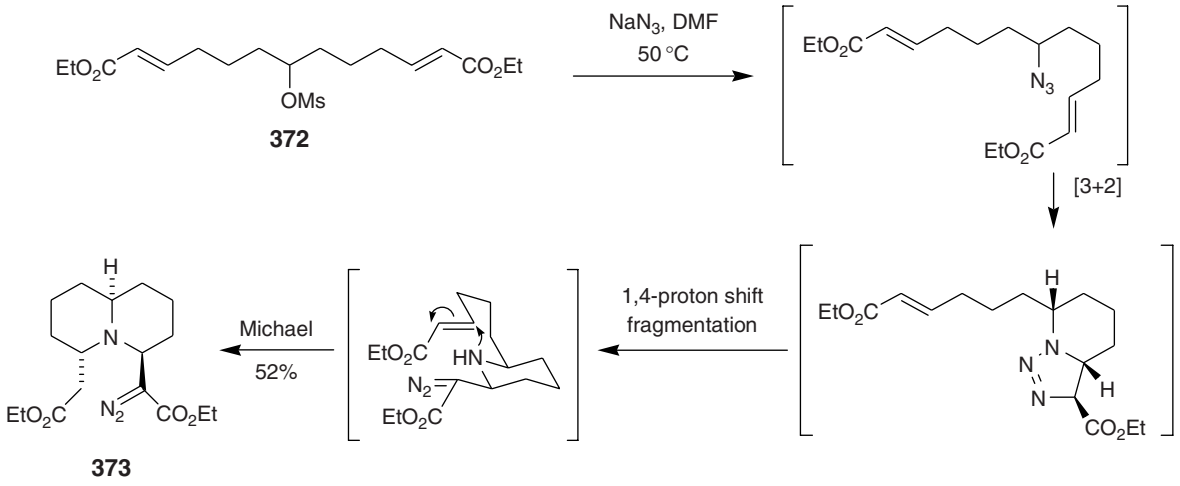
Scheme 84

11.01.9.6 Formation of Three New Bonds from Acyclic Precursors

The increasing current interest in processes that are able to generate complex molecular architectures in one pot has stimulated the development of domino-like procedures that create three bonds in one synthetic operation, with considerable advantages in terms of synthetic efficiency and environmental friendliness. This section describes some examples of the application of these concepts to the preparation of quinolizidine compounds.

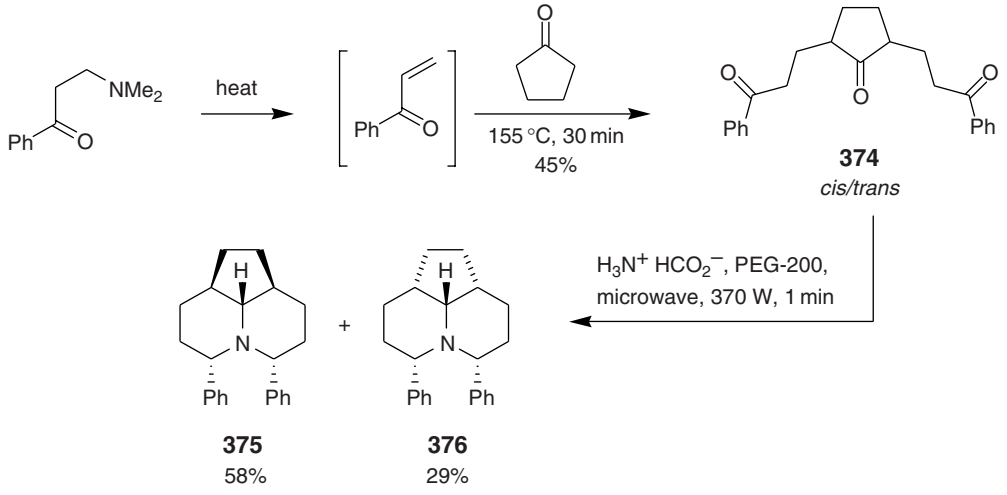
11.01.9.6.1 Formation of three α-bonds

The nonsymmetrical quinolizidine **373** was obtained from the acyclic symmetrical precursor **372** by means of a reaction sequence comprising azide formation, intramolecular 1,3-dipolar cycloaddition, thermal triazoline fragmentation to a diazoalkane, and Michael addition individual steps, as shown in **Scheme 85** <2005CC4661>.



Scheme 85

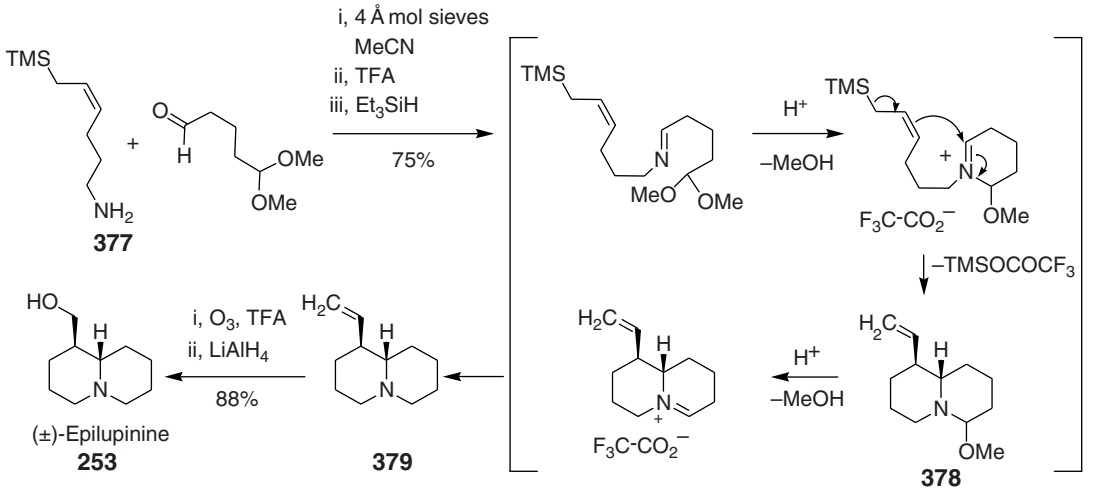
Reaction of phenyl vinyl ketone with cyclopentanone under thermal conditions resulted in a diastereomeric mixture of 1,5,9-triketones **374** via a double Michael reaction. Treatment of this mixture with ammonium formate in polyethyleneglycol-200 under microwave irradiation conditions led to the very fast and efficient formation of a 2:1 diastereomeric mixture of cyclopenta[*ij*]quinolizidines **375** and **376** <2002T2189>. When this reductive amination–cyclization procedure was carried out starting from the purified *trans*-isomer of **374**, the result was identical to that obtained from the *cis–trans* mixture, showing the operation of thermodynamic control (**Scheme 86**).



Scheme 86

11.01.9.6.2 Formation of two α- and one β- bonds

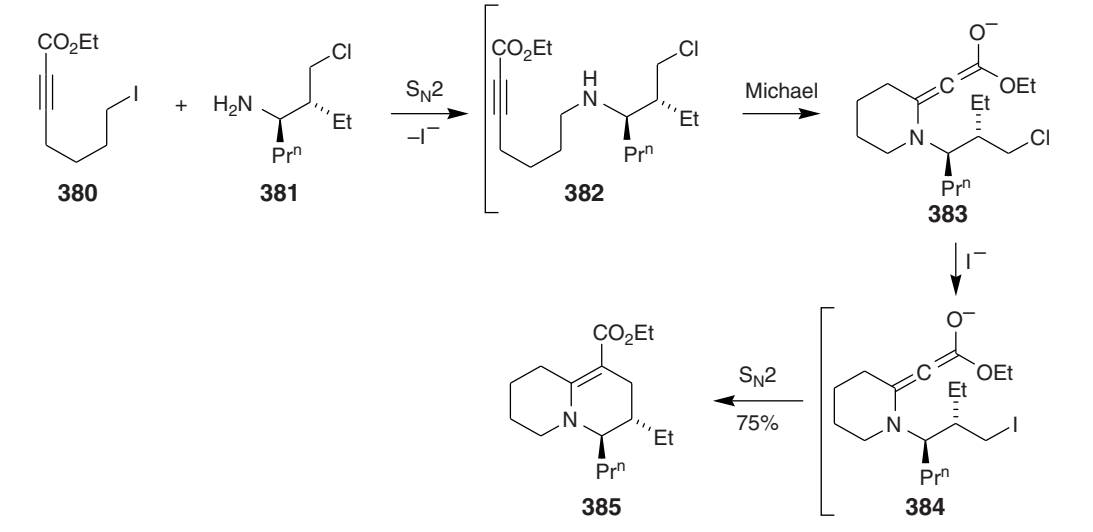
A domino reaction involving iminium intermediates has been employed for achieving a very efficient synthesis of compound **379**, a known intermediate in a previous (±)-epilupinine synthesis <1996JP1219>. Starting from amino allylsilane **377** and glutaraldehyde mono(dimethylacetal), simple addition of molecular sieves followed by trifluoroacetic acid initiated a cascade of reactions in which three new bonds and two rings were created in a single operation, leading to quinolizine derivative **378**. The subsequent *in situ* reduction by triethylsilane of the putative iminium ion arising from loss of a second molecule of methanol led to **379** in 75% overall yield. Remarkably, this compound was obtained as a single diastereomer with a *trans*-relationship between the hydrogen atoms at the two stereocenters thus created. It was also shown that other nucleophiles such as cyanide could also be employed to capture the above-mentioned iminium species. Finally, compound **379** was transformed into the natural product **253** by reductive ozonolysis of its trifluoroacetate salt (**Scheme 87**) <2005OL2031>.



Scheme 87

11.01.9.6.3 Formation of two α- and one γ- bonds

7-Iodo-2-alkynoates (e.g., compound **380**) react with δ-chloropropylamines (e.g., compound **381**) to give quinolizine derivatives in a single synthetic operation (**Scheme 88**). The process comprises a sequence of an S_N2 reaction that yields secondary amine **382**, an intramolecular Michael addition to give the piperidine derivative **383**, halogen

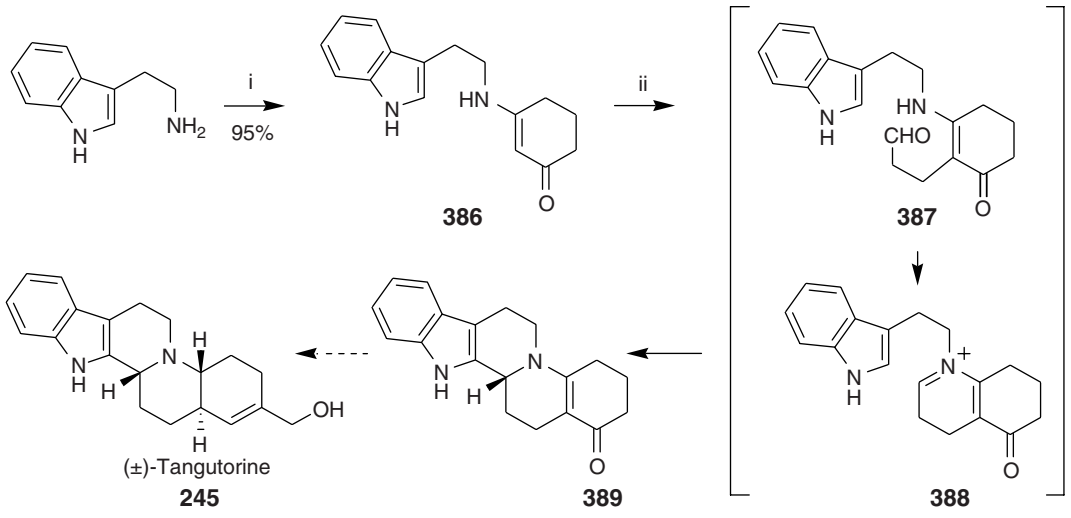


Scheme 88

exchange affording iodide **384** through a second S_N2 reaction, and final cyclization to quinolizine **385** by a third S_N2 reaction <2006T5697>.

11.01.9.6.4 Formation of α-, δ-, and γ-bonds

A domino process comprising an intermolecular formal aza-[3+3] cycloaddition followed by an intramolecular Pictet–Spengler reaction allowed the one-pot construction of a derivative of the unusual benzo[*f*]indolo[2,3-*a*]quinolizidine system **389**. Treatment of keto enamine **386**, prepared from tryptamine and 1,3-cyclohexanedione, with acrolein in the presence of boron trifluoride gave compound **387**, presumably via an enamine Michael addition followed by dehydration of the resulting 2-hydroxyquinoline to an iminium species **388** and subsequent Pictet–Spengler cyclization (**Scheme 89**) <2004JOC4548>. The initial formal aza-[3+3] cycloaddition may be alternatively rationalized as the result of a 1,2-addition of the enamine onto the aldehyde group of acrolein, followed by dehydration of a 4-hydroxyquinoline intermediate <2002JA10435>. Compound **389** is significant because its *N*-BOC derivative had been previously employed as the key intermediate of a total synthesis of the alkaloid (±)-tangutorine **245** <2002JA10435>.



i, 1-3-cyclohexanedione, toluene, reflux; ii, acrolein, BF_3•Et_2O, rt

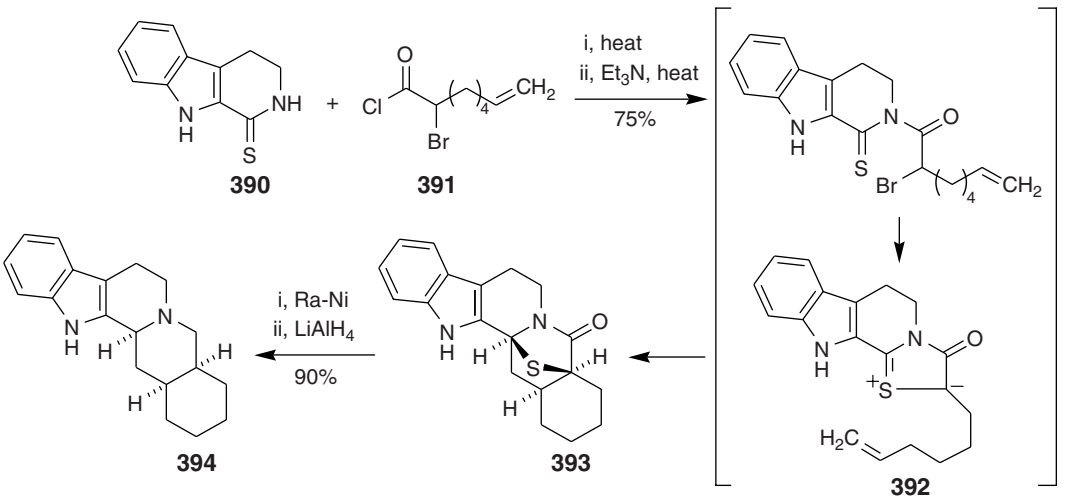
Scheme 89

A highly efficient method for the synthesis of the indolo[2,3-*a*]quinolizidine core of yohimbine is based upon the use of cyclic thioamide **390** and bromoalkenoyl chloride **391** to generate thioisomünchone **392** as a transient 1,3-dipole that readily undergoes an intramolecular cycloaddition across the tethered olefin to give the thiobicycloannulated product **393**. This compound was finally transformed into alloyohimbine **394** under reductive conditions (**Scheme 90**) <2000JOC2684>.

11.01.10 Ring Synthesis by Transformations of Another Ring

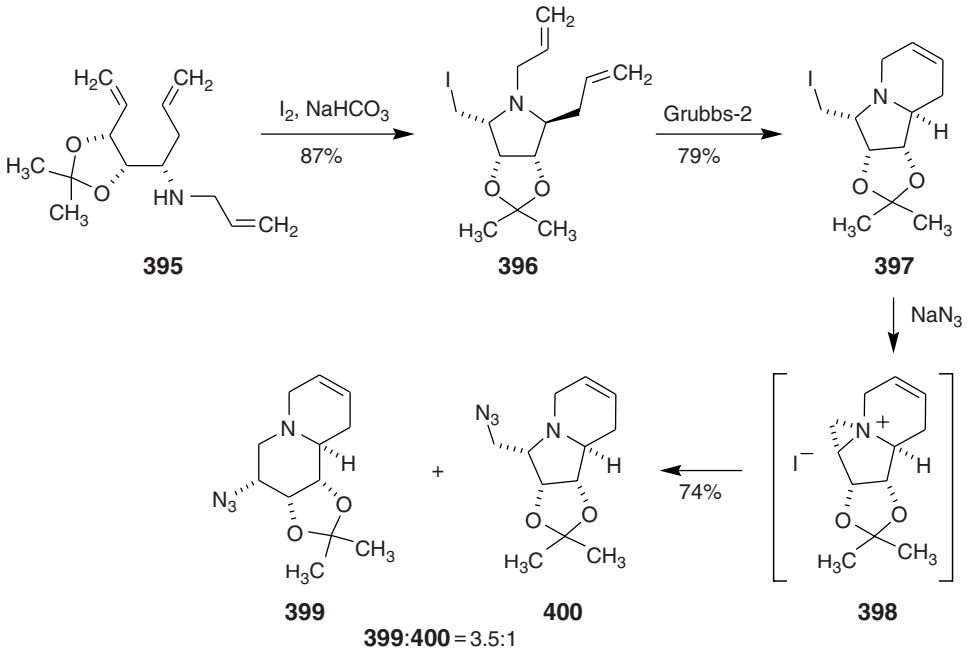
11.01.10.1 Ring Expansion Reactions

Enantiomerically pure triene **395**, whose chirality stems from that of β-D-ribofuranose, was transformed into the chiral pyrrolidine **396** by intramolecular iodoamination. A subsequent RCM reaction gave indolizine derivative **397**. Treatment of this compound with nucleophiles afforded mixtures of indolizine and quinolizine derivatives in



Scheme 90

varying amounts, that depended on the nature of the nucleophile. In the case more favorable for ring expansion to a quinolizine system, the reaction of **397** with sodium azide gave a 3.5:1 mixture of compounds **399** and **400** (**Scheme 91**). Assistance to the nucleophilic attack by the indolizine nitrogen was proved by the detection of intermediate **398** by ^{1}H NMR spectroscopy; quinolizine formation requires attack of the nucleophile to the more substituted carbon atom of the aziridinium ring, which was explained by the development of a partial positive charge in the transition state, which is more stabilized at the most substituted carbon atom <2003JOC9598>.



Scheme 91

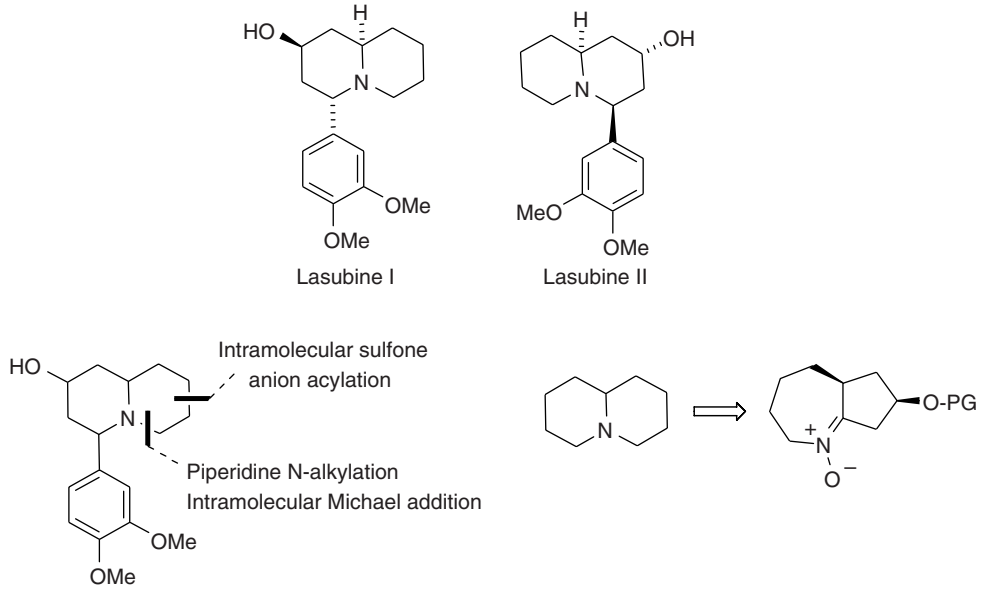
11.01.10.2 Ring Contraction Reactions

Nitrones derived from 2-azabicyclo[5.3.0]decane give quinolizidine compounds by photochemical Beckmann rearrangement which implies simultaneous ring expansion and ring contraction reactions. Intramolecular Schmidt reactions in 2(4-azidobutyl)-cyclopentanones also give quinolizidinone derivatives by ring expansion. Examples of both types of reactions are given in Sections 11.01.11.1 and 11.01.11.3, respectively.

11.01.11 Synthesis of Particular Classes of Compounds and Critical Comparison of the Various Routes Available

11.01.11.1 Simple Quinolizidine Alkaloids: Lasubines

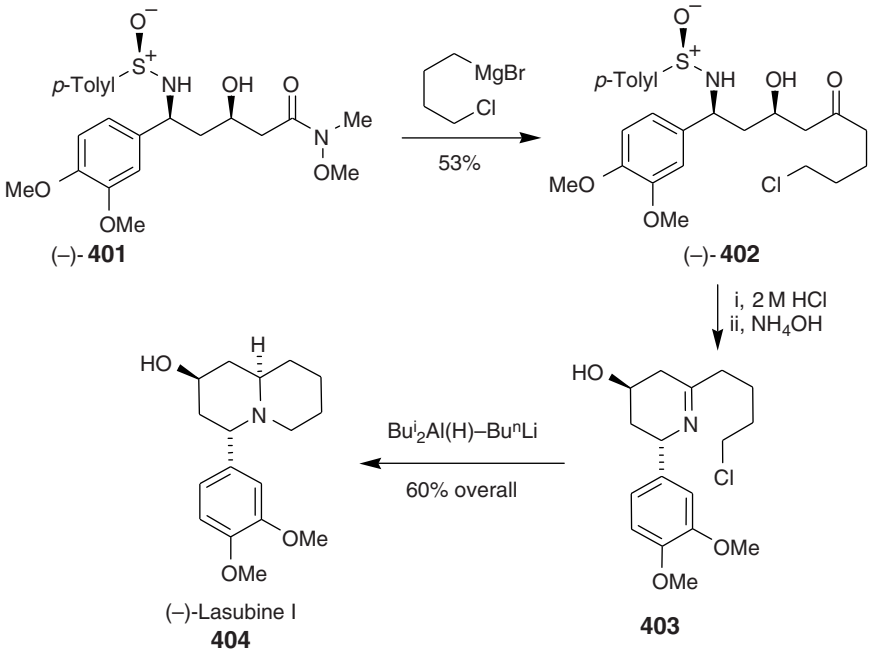
Lasubines I and II are alkaloids containing a 4-arylquinolizidine substructure that have been isolated from plants of the *Lythraceae* family and have attracted the attention of synthetic chemists for some time. While numerous racemic syntheses of these and related compounds have been reported, only a few enantioselective syntheses are known. Some examples of these syntheses are given below, and the strategies involved in these examples are summarized in **Scheme 92**. Three of these syntheses involve the creation of the quinolizidine system by formation of one bond at the α- or γ-positions, while the fourth approach is based on a ring transformation associated with a photochemical Beckmann rearrangement.



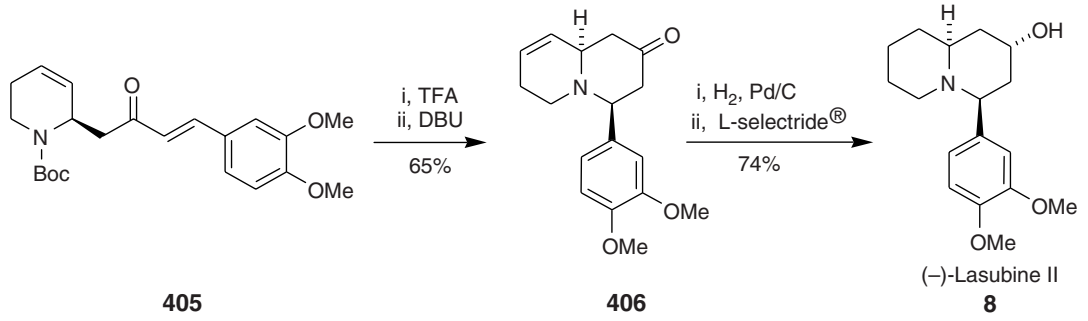
Scheme 92

Construction of a *trans*-2,6-disubstituted piperidine ring bearing a chlorine atom at the nitrogen ε-position was the strategy applied to the synthesis of (−)-lasubine I **404**. The chiral Weinreb amide **401** gave chloroketone **402** that after removal of the sulfinyl group afforded the 4-hydroxy-1,2-dehydropiperidine **403**. The hydroxyl group directed the reduction of the double bond with the $^{i}Bu_2Al(H)$–$^{n}BuLi$ complex and the saturated piperidine cyclized to **404** (**Scheme 93**) <2003OL3855>.

After deprotection of the carbamate group, intramolecular Michael addition of compound **405**, which was obtained in a one-pot domino metathesis step from a chiral cyclopentenone compound, gave a mixture of cyclized quinolizidine compounds from which the more stable diasteroisomer **406** was obtained by equilibration in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), presumably through a retro-Michael fragmentation–recyclization. Catalytic hydrogenation of the double bond and stereoselective reduction of the carbonyl group with L-selectride® provided (−)-lasubine II **8** (**Scheme 94**) <2004T9629>. Other trisubstituted quinolizidine alcohols have been obtained by a similar cyclization process <2004SL1343>.



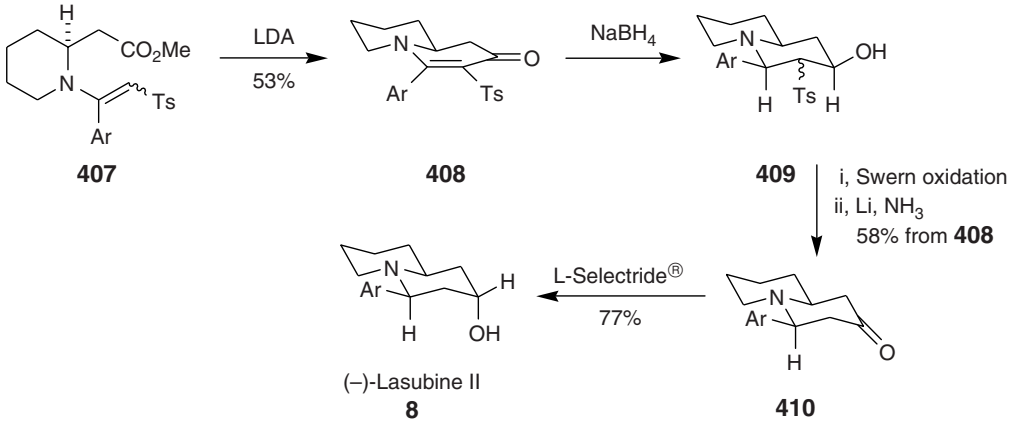
Scheme 93



Scheme 94

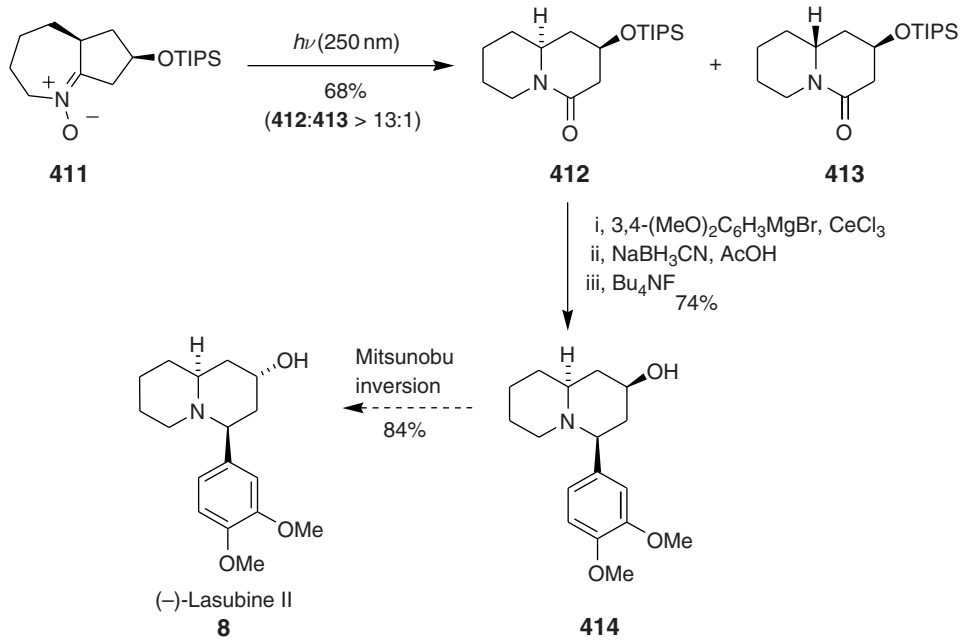
A related example in which the electrophilic function is an ester group has been used in the total synthesis of (−)-lasubine II **8** from compound **407**, which was cyclized by treatment with LDA at −78 °C to give **408**. Treatment with $NaBH_4$ produced the stereoselective reduction of the enaminone moiety from the α-face to give a nonisolated intermediate ketone, in which the equatorial position of the bulky aryl substituent directs the subsequent reduction of the carbonyl group yielding the alcohol **409**. A Swern oxidation to the corresponding ketone followed by desulfonylation with lithium in liquid ammonia afforded a mixture of epimers at C-4 in which **410** was the major isomer. Finally, stereoselective reduction of the carbonyl group in **410** with L-Selectride® produced the desired (−)-lasubine II **8** (**Scheme 95**) <2002OL1779, 2005JOC967>.

A formal synthesis of (−)-lasubine II **8** involved a photochemical Beckmann rearrangement of nitrone **411**, which gave a mixture of diastereomers **412** and **413** in a 13:1 ratio. After separation, the major compound **412** was treated with 3,4-dimethoxyphenylmagnesium bromide and cerium trichloride followed by reduction with sodium cyanoborohydride and removal of the silyl protecting group to yield the lasubine epimer **414,** as a single isomer, as shown in **Scheme 96** <2003OL4999>. This is a formal synthesis of (−)-lasubine II since compound **414** can be converted into the natural product by Mitsunobu inversion <2001OL3927>.



407 **408** **409** **410** **8**

Scheme 95



411 **412** **413** **414** **8**

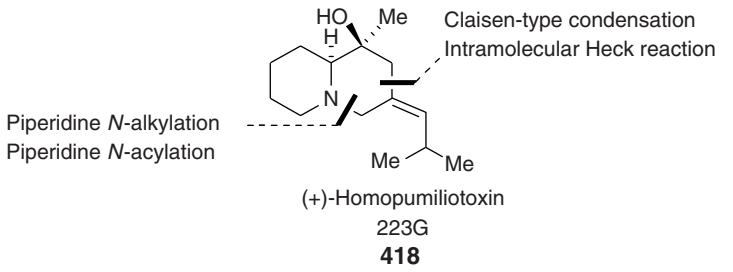
Scheme 96

11.01.11.2 Simple Quinolizidine Alkaloids: Homopumiliotoxins

The pumiliotoxins, allo- and homopumiliotoxins, are alkaloids isolated from the skin of amphibians, such as neotropical frogs of the *Dendrobatidae* family, and are believed to serve as a chemical defence against predators. These natural products have interesting pharmacological properties, including myotonic and cardiotonic activities.

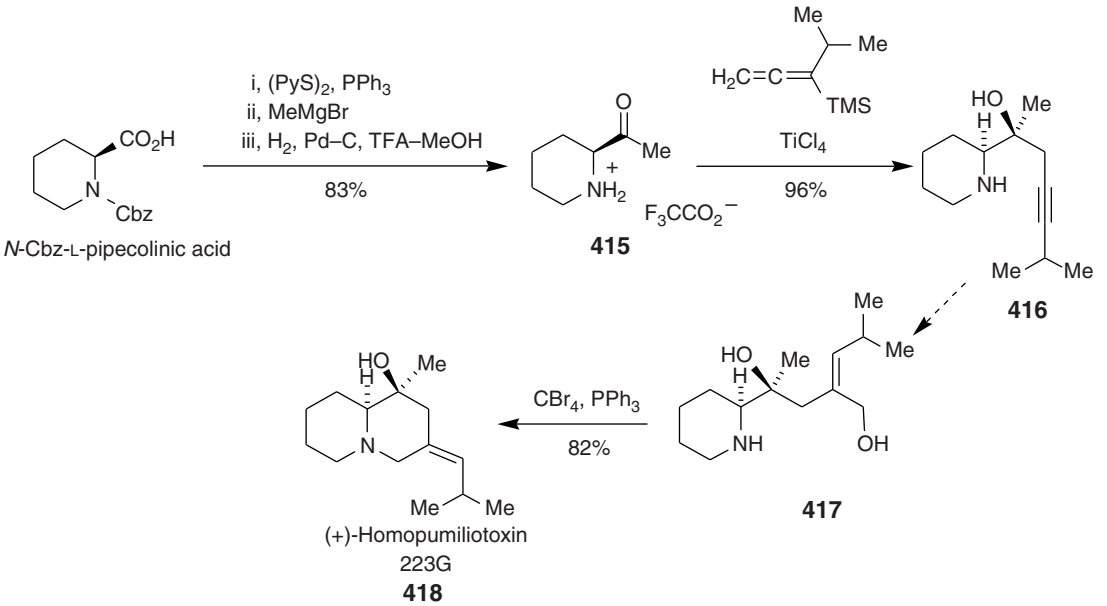
Three syntheses of homopumiliotoxin alkaloids are compared below, and one more reaction leading to homopumiliotoxin-related compounds was mentioned in Section 11.01.9.3.7. The strategies involved for the ring-closure procedures leading to the quinolizidine system involved the formation of α- or γ-bonds from piperidine precursors and are summarized in **Scheme 97**.

The key feature of the first total synthesis of (+)-homopumiliotoxin 223G **418** was a Lewis acid-induced, chelation-controlled propargylation of the trifluoroacetate salt of (*S*)-2-acetylpiperidine **415**, derived from *N*-Cbz-L-pipecolinic acid. Alkyne **416** thus formed was transformed after several steps into **417**, which was cyclized by activation of the primary hydroxyl with the carbon tetrabromide–triphenylphosphine system to give the natural product (**Scheme 98**) <1998TL2149>.



(+)-Homopumiliotoxin
223G
418

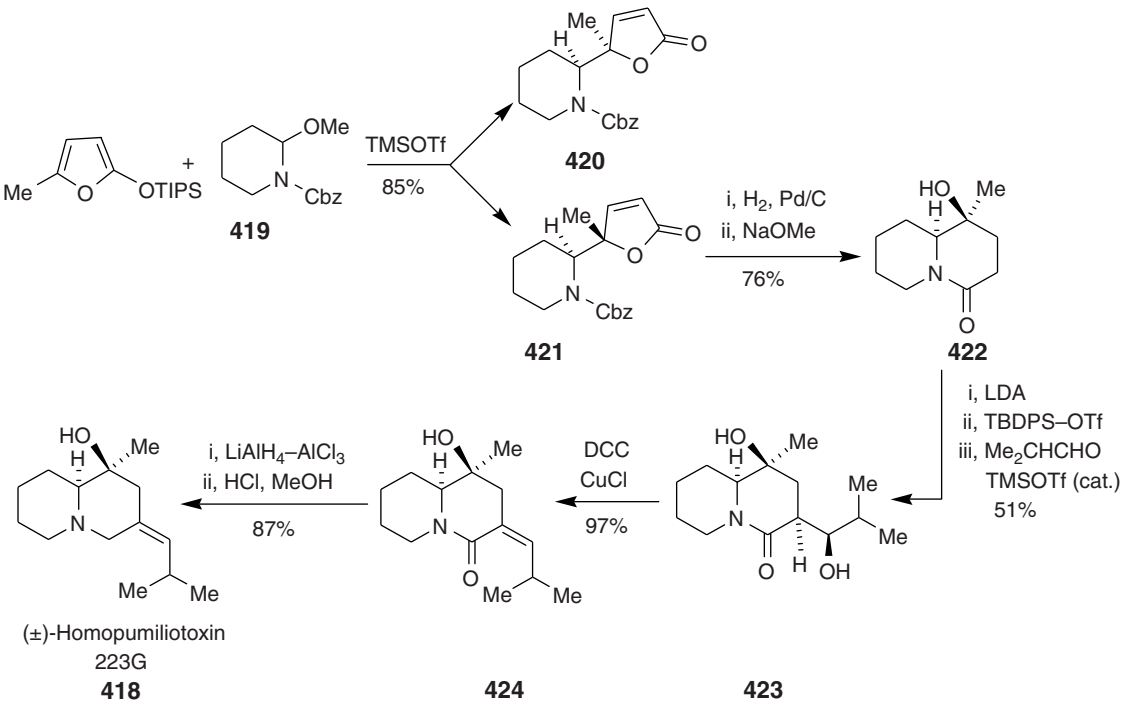
Scheme 97



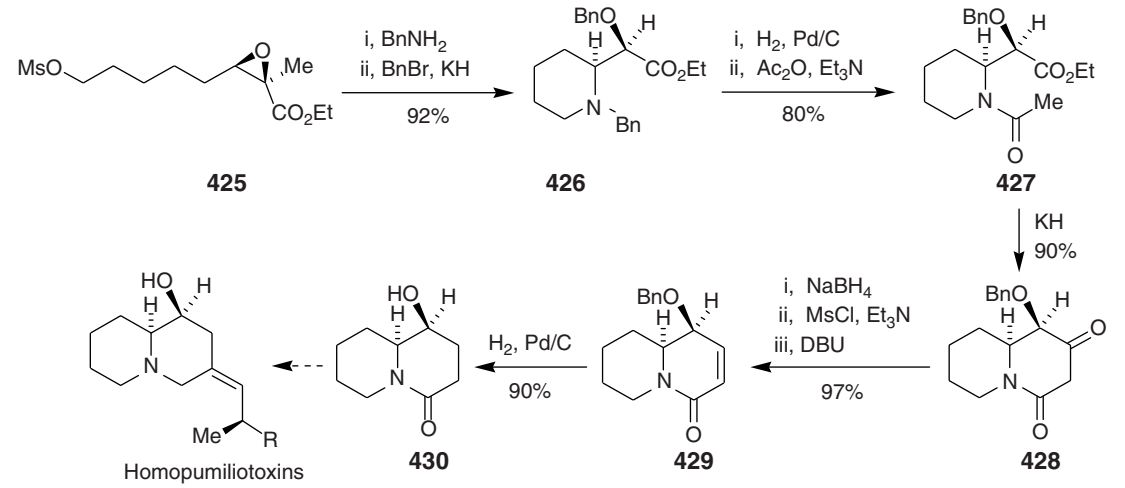
Scheme 98

A systematic investigation of the diastereoselectivity resulting from the addition of *N*-acyliminium ions in five-, six-, and seven-membered ring systems <2001TL6995> paved the way for another synthesis of (±)-homopumiliotoxin 223G **418**. The reaction between a substituted furan and the acyliminium ion precursor **419** produced varying amounts of the diastereomeric adducts **420** and **421**, depending on the solvent and Lewis acid catalyst used. Hydrogenation of **421**, removal of the *N*-Cbz group, and base-induced cyclization gave the hydroxyquinolizidin-4-one **422**. A Mukaiyama aldol condensation between its silyl enol ether and isobutyraldehyde afforded a 1:3 mixture of compounds in which **423** was the major component. Elimination of water from this compound in the presence of DCC–CuCl afforded the desired (*Z*)-product **424**, which by reduction of the lactam function yielded the natural product (DCC = dicyclohexylcarbodiimide; **Scheme 99**) <2001TL6999>.

Taking advantage of the fact that α,α-disubstituted esters are nonenolizable and nonepimerizable, the Claisen-type condensation of acetamide **427** resulted in an efficient synthesis of precursors of homopumiliotoxins. The route began with a Sharpless asymmetric dihydroxylation (AD-mix-α) of a trisubstituted olefin, which afforded a chiral diol that was transformed into epoxide **425**. Upon treatment of the mesylate group in **425** with benzylamine, a stepwise substitution–ring-opening sequence afforded regioselectively a substituted piperidine whose tertiary hydroxyl was protected as a benzyl ether to give **426**. Selective removal of the *N*-benzyl protecting group and acetylation of the free NH gave the desired precursor **427**. The Claisen condensation was completed by using KH as a base, which effected irreversible deprotonation. The ketone group of the cyclized compound **428** was reduced with $NaBH_4$, and the resulting alcohol was converted into an olefin **429** through elimination of its mesylate under basic conditions. One-pot saturation of the double bond and debenzylation gave **430** which may be transformed into several homopumiliotoxins (**Scheme 100**) <2003TL7981>.



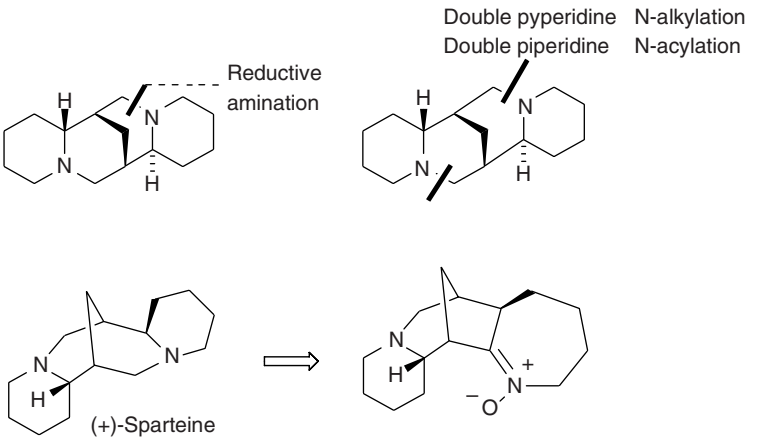
Scheme 99



Scheme 100

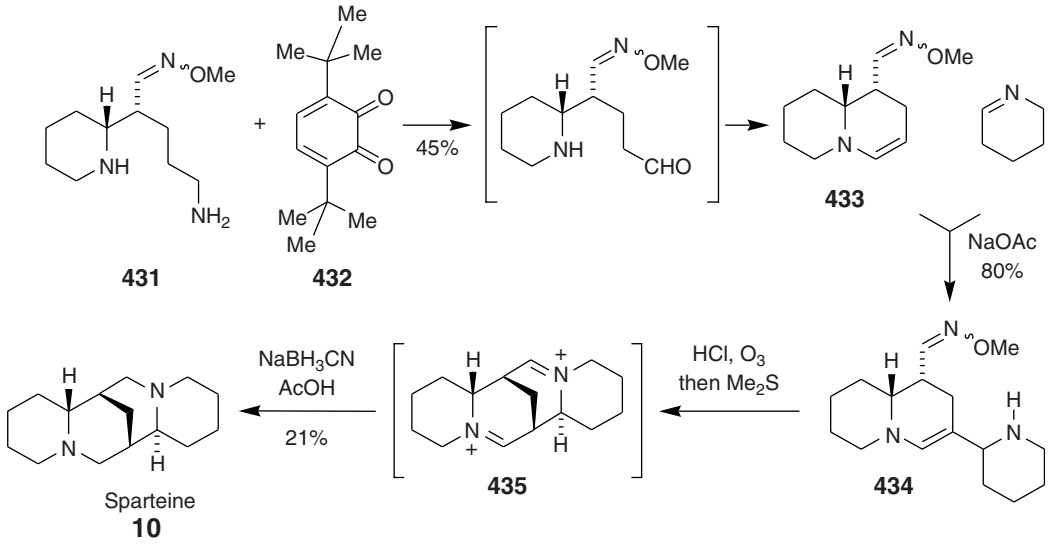
11.01.11.3 Bisquinolizidine Alkaloids: Sparteine

(−)-Sparteine is the best known of the naturally occurring lupin alkaloids, isolated from leguminous plants. This natural product is a cardiovascular agent and it is also important due to its widespread use as a chiral ligand in asymmetric synthesis. Four sparteine syntheses are summarized below, one of which is based on the cyclization of a quinolizidine compound while two others take advantage of the symmetry of the molecule to create simultaneously the two quinolizidine units in a single step. Another route, that has been used for the preparation of (+)-sparteine, is based upon a photochemical Beckmann rearrangement (**Scheme 101**).



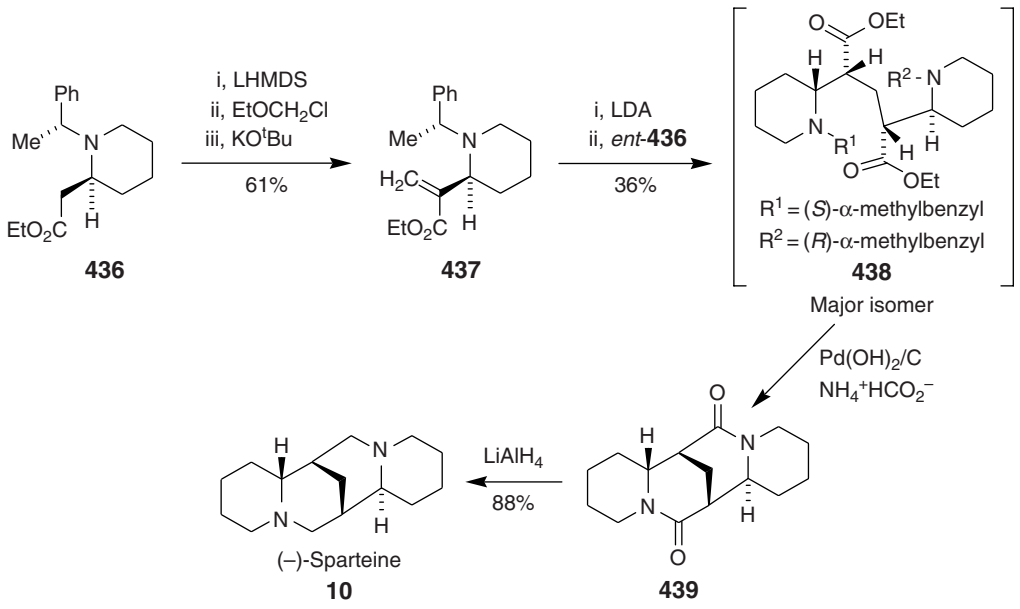
Scheme 101

Several lupin alkaloids have been derived from the unsaturated quinalozidine **433**, that was obtained in the treatment of amine **431** with ortho-quinone **432**. This quinone behaves as a model of topaquinone, the cofactor of copper-containing amine oxidases. The cyclization step involved a nucleophilic attack of the piperidine nitrogen of **431** onto a side-chain aldehyde function that is unmasked by the oxidative deamination. Quinolizine **433**, when treated with dehydropiperidine, gave the oxime ether **434** that, on ozonolysis followed by reduction, afforded sparteine **10,** presumably via the bis(iminium) system **435** (**Scheme 102**) <1996JOC5581>.



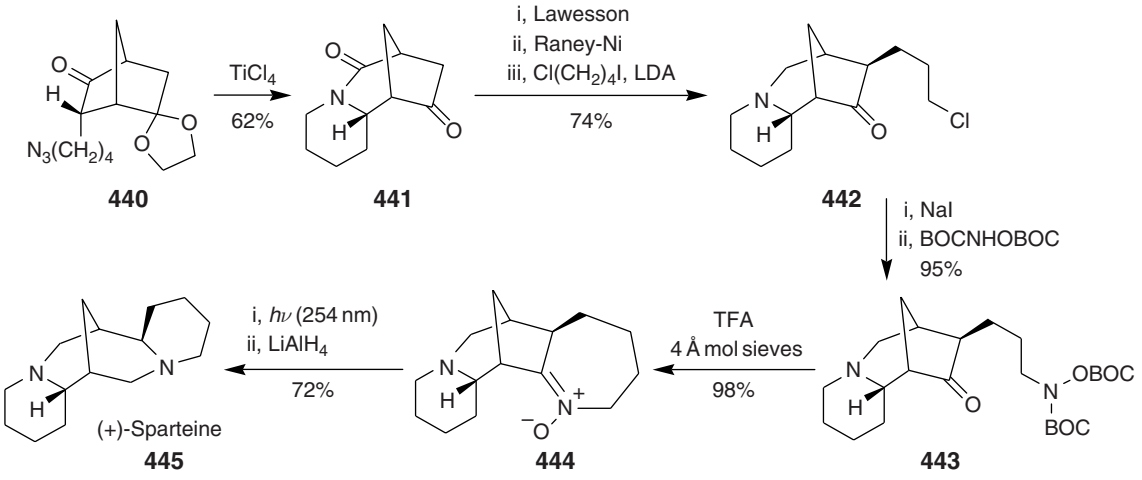
Scheme 102

In a more concise asymmetric synthesis of (−)-sparteine, the bislactam precursor **439** was obtained by a double nucleophilic attack of a piperidine nitrogen onto a carboxylate function. The starting materials (**436** and *ent*-**436**) were obtained as the major products from 7-iodohept-2-enoate and (*R*)- and (*S*)-α-methylbenzylamines, respectively. Compound **437** was derived from **436** by alkylation with $EtOCH_2Cl$ and subsequent ethoxide elimination. The major isomer of the Michael adduct from **437** and *ent*-**436** was compound **438** that cyclized after hydogenolysis of the α-methylbenzyl groups to give **439**. Finally, lithium aluminum hydride reduction yielded (−)-sparteine **10** (**Scheme 103**) <2004CC1830>.



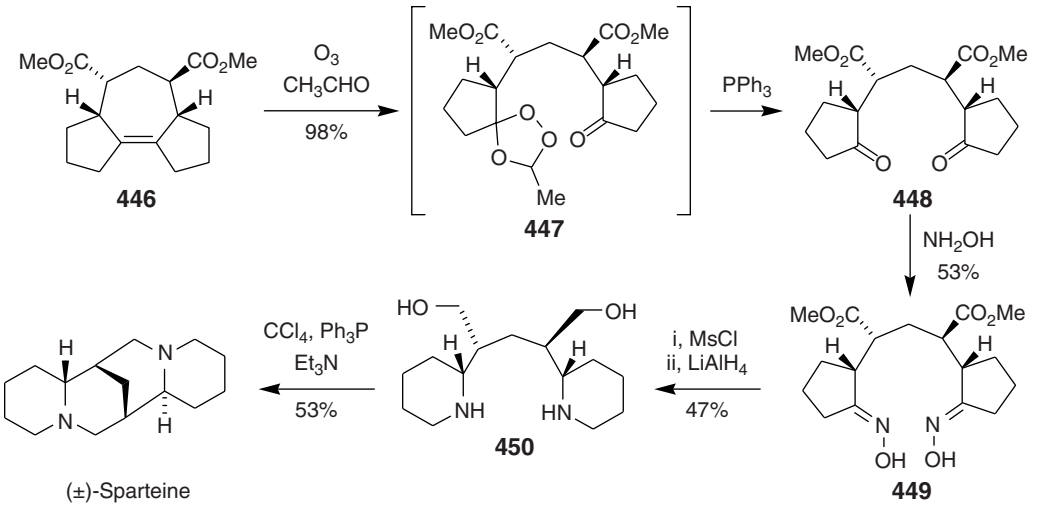
Scheme 103

The first *de novo* asymmetric total synthesis of (+)-sparteine **445**, the naturally occurring but rarely encountered enantiomer of the more common and commercially available (−)-sparteine, was based on rearrangement of nitrone **444**. The starting material was optically pure (+)-norbornane-2,5-dione, which was transformed in six steps into ketoazide **440**. An intramolecular Schmidt reaction with titanium tetrachloride with simultaneous removal of the ketal protecting group formed the tricyclic quinolizidine lactam **441**, which was converted into a 4-chlorobutyl derivative **442** using standard procedures. Although the corresponding azide was prepared from this intermediate, a second intramolecular Schmidt reaction could never be achieved probable because of the preferential coordination of the tertiary amine to protic or Lewis acids. As an alternative, deprotection of the hydroxylamine derivative **443** afforded the nitrone **444**, which gave the desired (+)-sparteine **445** though photochemical Beckmann rearrangement to a tetracyclic lactam followed by standard reduction of the lactam function (**Scheme 104**) <2002OL2577>.



Scheme 104

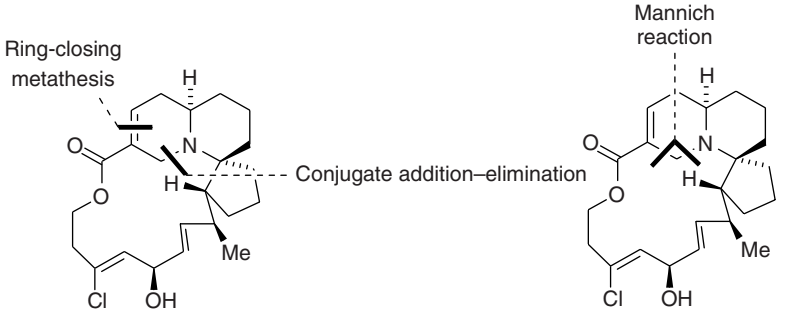
Ozonolysis of alkene **446** in the presence of acetaldehyde afforded diketone **448** through the intermediacy of **447**. Ring expansion through Beckmann rearrangement took place when bis-oxime **449** was mesylated and warmed in aqueous tetrahydrofuran (THF). The bis-lactam so formed gave piperidinediol **450** on reduction with lithium aluminum hydride, and this compound was transformed into (±)-sparteine by treatment with triphenylphosphine, CCl_4, and triethylamine (**Scheme 105**) <2005OBC1557>.



Scheme 105

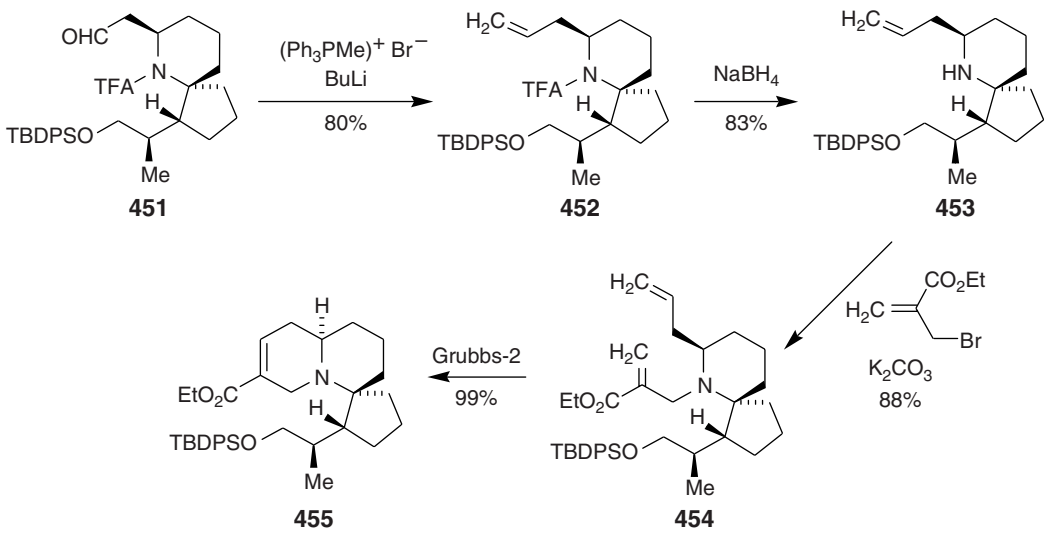
11.01.11.4 Alkaloids Containing an Azaspiro[4.5]decane Ring System: Halichlorine

Halichlorine **11** is a structurally unique alkaloid that was isolated from the sponge *Halichondria okadai* and found to act as an inhibitor of the induction of vascular cell adhesion molecule (VCAM-1), a potential target in the development of drugs for the treatment of several vascular diseases. The strategies employed for the construction of its spiroquinolizidine unit are summarized in **Scheme 106**.



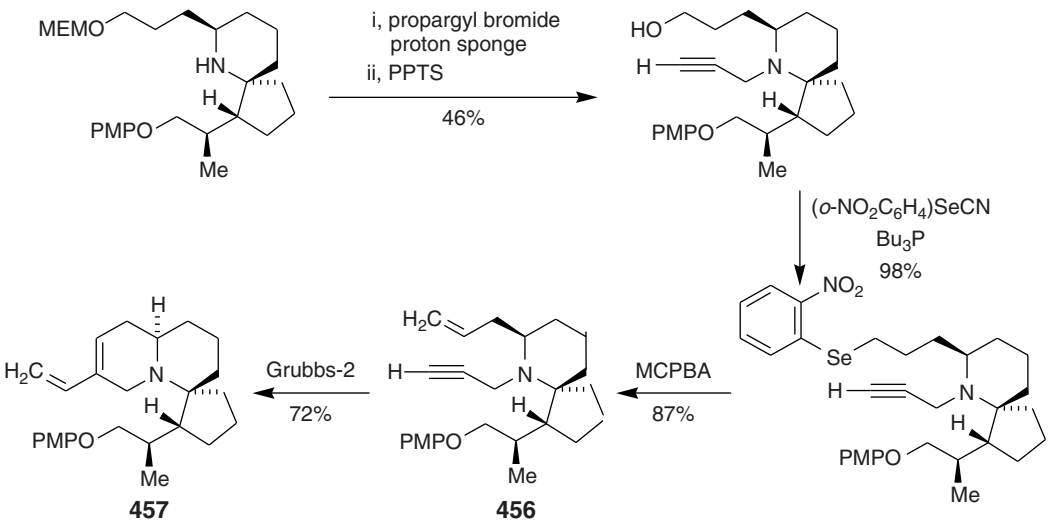
Scheme 106

In one example of application of the RCM strategy, summarized in **Scheme 107**, the key intermediate **454** was obtained from **451** by sequential Wittig methylenation to **452**, reductive *N*-deprotection to **453**, and introduction of an alkenyl chain onto the secondary amine. The RCM reaction of **454** to **455** proceeded in quantitative yield in the presence of the second-generation Grubbs catalyst <2004OL965>.



Scheme 107

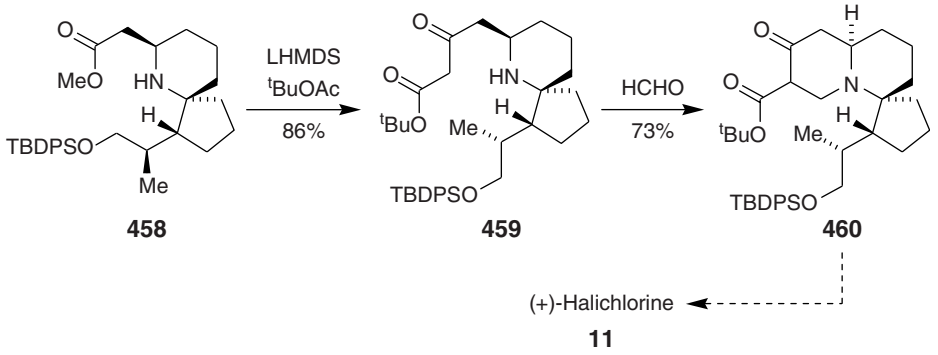
In a closely related approach, the *N*-propargylpiperidine derivative **456**, prepared as shown in **Scheme 108**, was used as the starting material for a ene–yne RCM leading to the spiroquinonolizidine fragment of halichlorine (compound **457**) <2004CC1222>.



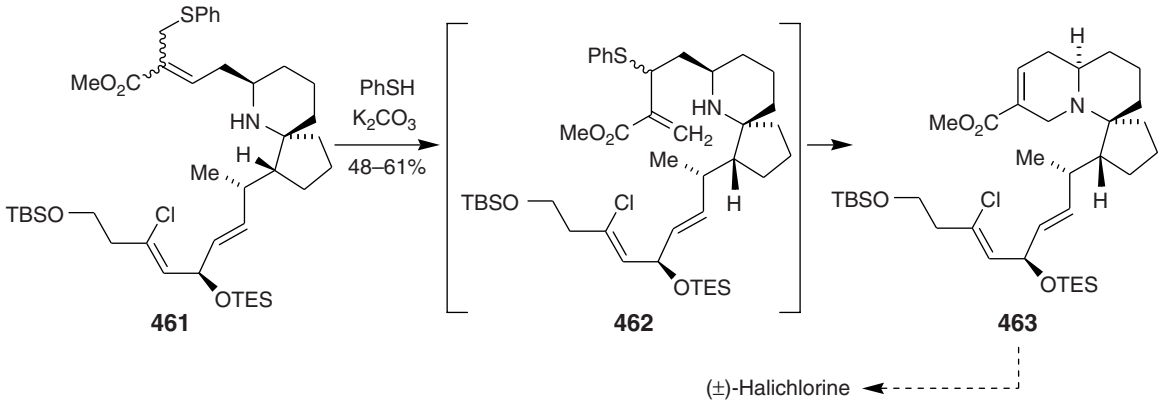
Scheme 108

In the course of the first total synthesis of (+)-halichlorine <1999TL6513, 1999AGE3542>, the spiroquinolizidine unit **460** was constructed by a two-carbon chain extension in compound **458** through a crossed Claisen condensation, leading to **459**, and an intramolecular Mannich reaction of this compound with formaldehyde (**Scheme 109**).

A more elaborate spiroquinolizidine unit **463** was obtained by simply heating a basic thiophenoxide solution of thioether **461**, presumably by addition–elimination of thiophenoxide to give **462**, which then cyclized by a second addition–elimination sequence involving the piperidine nitrogen atom, giving **463**, an advanced intermediate, in a total synthesis of (±)-halichlorine (**Scheme 110**) <2004PNAS12079>.



Scheme 109



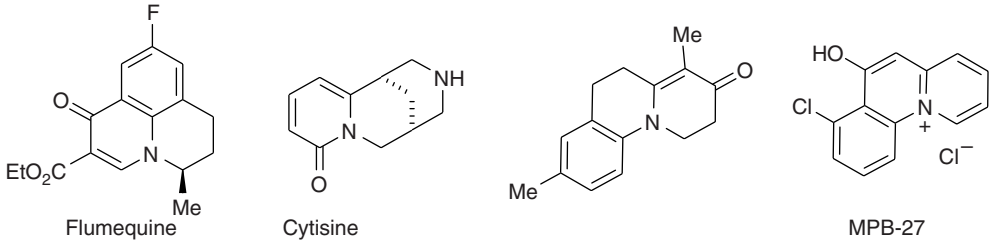
Scheme 110

11.01.12 Important Compounds and Applications

11.01.12.1 Compounds with Biological Activity

Some quinolizine derivatives are employed as drugs. One of them is flumequine **280**, a member of the quinolone family of antibacterial agents. Cytisine **9** is a ligand of the nicotinic acetylcholine receptor that acts primarily as a cholinomimetic at the ganglionar level, being used as a respiratory stimulant in some countries. Cytisine analogues with improved ability to cross the blood–brain barrier have also been developed <1999FA438>.

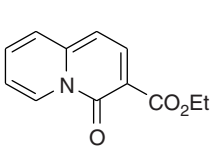
Other quinolizine derivatives, although not in therapeutic use, show interesting pharmacological properties. For example, benzo[*c*]quinolizin-3-ones constitute a novel class of nonsteroidal inhibitors of human steroid 5α-reductase. One example is compound **464**, which has a K_i value of 5.8 nM and inhibits the enzyme through a reversible competitive mechanism <2000JME3718>. The structurally related benzo[*c*]quinolizinium compounds **465** are activators of the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel <1999JBC27415>. Other derivatives with interesting biological properties have been mentioned previously, including compounds **104** (ultrashort curare-like activity), **108** (angiotensin-converting enzyme inhibition), **192**, **196,** and **340** (glycosidase inhibition).



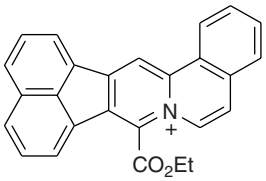
11.01.12.2 Quinolizines and Quinolizinium Salts as Fluorescent Probes

4-Oxoquinolizine-3-carboxylates (e.g., **466**) are excellent fluorophores that show a strong fluorescent response to Mg^{2+} but not to Ca^{2+}, avoiding the very frequent interference between both cations <2001BCC203>. The fluorescence of indolo[2,3-*a*]quinolizines has also been used for the design of fluorescent histamine H_2 receptor antagonists as probes of this receptor <2003BML1717>.

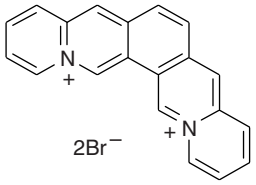
The annelated quinolizinium ion is a versatile platform for the design of DNA intercalators. For this reason, quinolizinium salts (e.g., **467**) <1988ANA105>, and also their heteroanalogues <2002MI37>, have been proposed as DNA fluorescent probes, since they undergo changes in their fluorescence spectra upon DNA intercalation <2005MI1107>. Other quinolizinium derivatives, including compound **468**, which contains two quinolizinium moieties, have been shown to have DNA photodamaging properties upon UV irradiation <2004ARK219>.



466



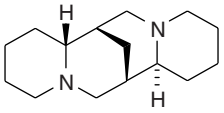
467



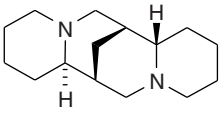
468

11.01.12.3 Quinolizidines as Chirality Inducers

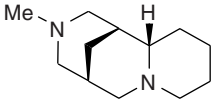
Sparteine has been widely studied as a catalyst for asymmetric synthesis. Because only (−)-sparteine **10** is commercially available, there has been much interest in the development of (+)-sparteine mimics, among which the most important is diamine **467**, which has been employed as a chiral reagent or catalyst in a large number of asymmetric synthesis procedures <2006S2233>.



(–)Sparteine
10



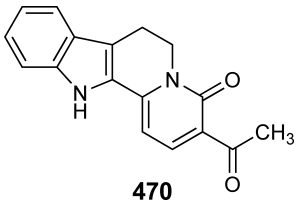
(+)Sparteine
445



469

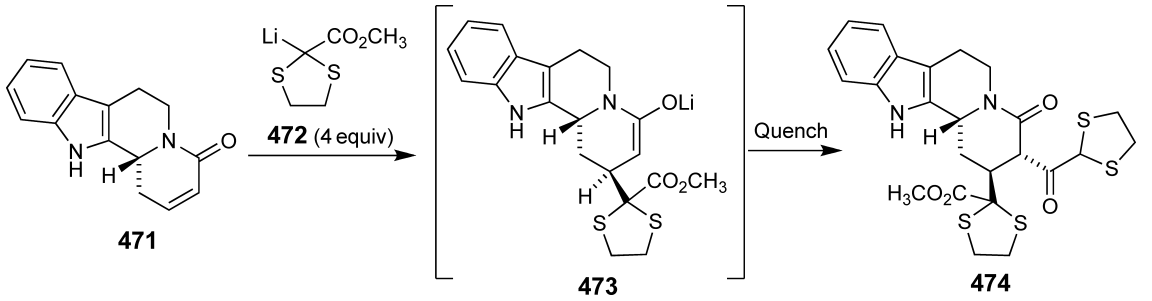
11.01.13 Further Developments

Some recent spectroscopic studies have taken advantage of the high fluorescence of arenoquinolizidine systems. Fluorescence (Förster) resonance energy transfer (FRET) is a distance-dependent interaction between the different electronic excited states of two molecules in which excitation energy is transferred from one molecule (donor) to the other (acceptor) extinguishing the emission of a photon from the former. It is a very sensitive technique that is extensively used to study the structure, conformation, spatial distribution and assembly of proteins and has been exploited as a 'spectroscopic ruler' for mapping cell surface elements. Some recent studies have shown the existence of FRET phenomena between the bioactive indoloquinolizidine derivative **470** and a coumarin derivative <2006MI165>, and also between **470** and non-ionic triton X-100 micelles <2007JML48>.

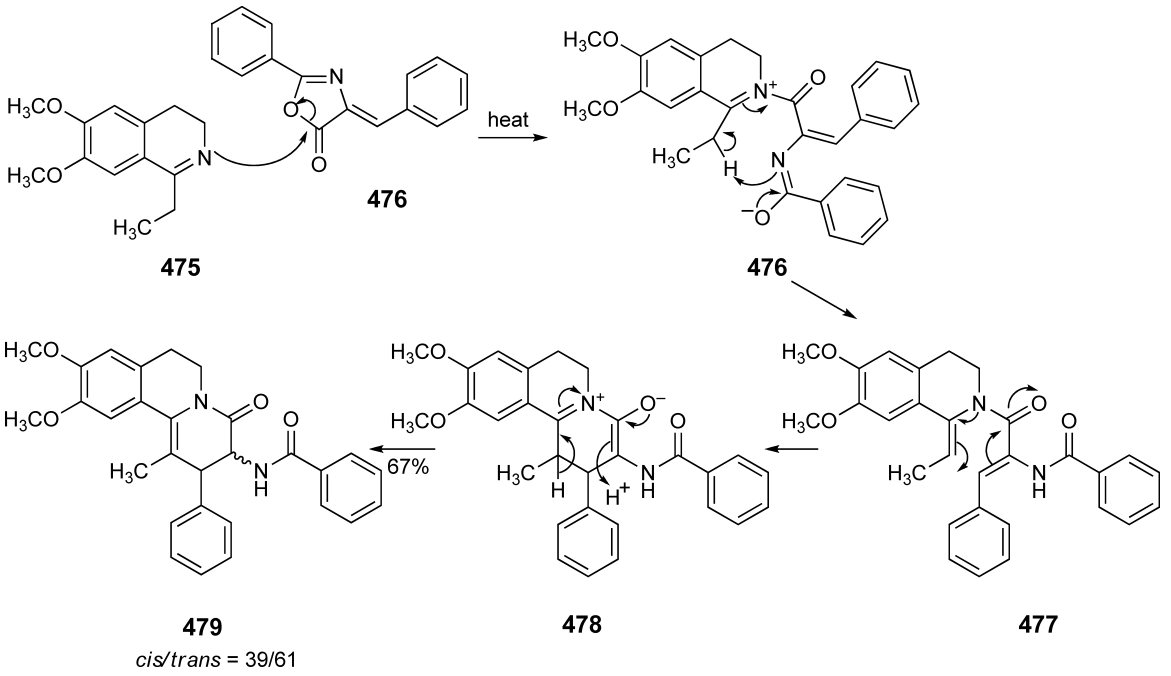


470

The readily available, nonracemic indoloquinolizidine template **471** has been studied as a substrate for the construction of frameworks related to bioactive natural products. The lithiated dithiolane **472** served a dual role in its reaction with **471**, both as a nucleophile giving the non-isolated intermediate **473**, and, in the same pot, as an electrophile during the quench process. This reaction afforded compound **474** as a single diastereomer <2006TL1961>.

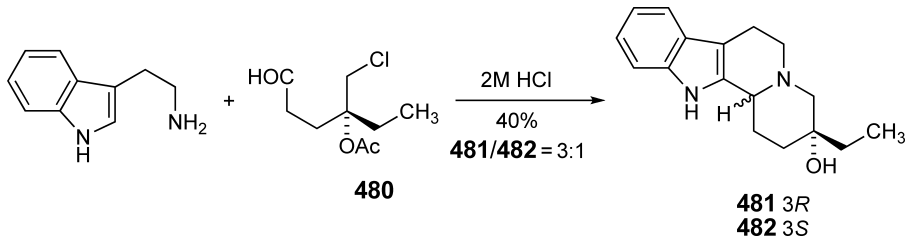


Among the many recent developments in synthetic methods that allow the synthesis of quinolizine and quinolizidine systems <2007NPR191>, we will mention two representative examples. In the first of them, the reaction between 1-alkyl-3,4-dihydroisoquinolines were an imine–enamine equilibrium is possible (e.g., **475**), and azlactones **476** gives benzo[*a*]quinolizidines. The process (**Scheme 111**) is carried out by simply refluxing the starting materials in acetonitrile and involves generation of the acyliminium salt **476**, which is transformed into enamide **477** *via* an intramolecular proton transfer. An intramolecular Michael-type cyclization affords **478**, which is then transformed into the final product **479** <2006OL5845>.



Scheme 111

A recent formal synthesis of the alkaloid (−)-mitralactonine relied on a reaction that allowed the simultaneous creation of three new bonds, two of them α and one β with respect to the quinolizine nitrogen. As shown in **Scheme 112**, treatment of triptamine with chiral aldehyde **480** in the presence of acid directly gave a mixture of diastereomeric indoloquinolizidines **481** and **482** through a mechanism involving a Pictet–Spengler cyclization and a N-alkylation reaction <2007SL79>.



480

481 3*R*
482 3*S*

Scheme 112

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Biographical Sketch

Prof. Mª del Carmen Avendaño López studied Pharmacy at Universidad Complutense (Madrid) and obtained her Ph.D. from the same university in 1970. After holding various teaching positions, she became a Full Professor at the Organic and Medicinal Chemistry Department at UCM in 1986. Her research interests are centered in the development of heterocycle-based synthetic methodologies aimed at the preparation of natural products or bioactive compounds. She has made contributions to the fields of hydantoins, triarylmethane dyes, microbial secondary metabolites containing quinone or quinonimine moieties with antitumor activity, MDR reversors related to *N*-acetylardeemin and antitumor compounds related to the tetrahydroisoquinoline alkaloids from the saframycin-ecteinascidin group. She has co-authored about 200 research articles, reviews and book chapters and 10 patents. She has also written or edited several Medicinal Chemistry textbooks, including two for McGraw-Hill Interamericana and a third one for Elsevier that is scheduled for publication in early 2008. Since 1993 she has been a member of the Profarma Scientific Commitee for the promotion of research in pharmaceutical companies based in Spain. She is a Fellow of the Spanish Royal Academy of Pharmacy since 1999, and in 2005 she was appointed Vice-Chancellor of postgraduate studies at the Universidad Internacional Menéndez y Pelayo.

José Carlos Menéndez Ramos was born in Madrid, in 1960. He obtained degrees in Pharmacy (Universidad Complutense, 1982) and Chemistry (UNED, 1985) and submitted his Ph.D. thesis in 1988 under Dr. Mónica Söllhuber. Later the same year he joined the group of Professor Steven Ley at Imperial College, London, where he worked on the total synthesis of the natural ionophore antibiotic routiennocin. In 1989 he returned as a Profesor Titular to the Organic and Medicinal Chemistry Department at UCM, where he has pursued his teaching and research career ever since. He has varied research interests, mostly related to synthetic work aimed at the development of new antitumor drugs, including heterocyclic quinones, antitumor marine natural products (pyridoacridines, pyrroloquinonimines, flustramines, tetrahydroisoquinoline alkaloids) and natural product-related MDR reversors (ardeemins, tryprostatins, welwistatin). Other projects place more emphasis on the development of new synthetic methodology, and include work on hetero Diels–Alder reactions, microwave-assisted organic synthesis and new domino and multicomponent reactions for the preparation of biologically relevant bicyclic systems and nitrogen heterocycles. This work has been documented in about 120 research papers, reviews and chapters and eight patents, many of them in collaboration with Profesor Avendaño. Additionally, he has co-authored two textbooks in Medicinal Chemistry for McGraw-Hill Interamericana, and a third one for Elsevier that is scheduled for publication in early 2008. He has some long-standing collaborations with several leading chemical and pharmaceutical Spanish companies and is the head of the Organic Microanalysis service at UCM since its creation in 1994. Since 2004, he is a Corresponding Member of the Spanish Royal Academy of Pharmacy. In 2007 he was appointed a Visiting Professor at the Université Paul Cézanne (Aix-Marseille III).