Synthetic Approaches toward the Benzo[a]quinolizidine System. A Review

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Introduction

Over the recent years, the benzo[a]quinolizidine ring system 1 (Figure 1) has become of great significance since it was found to be a key subunit in numerous natural and synthetic molecules possessing a variety of physiological activities or being promising candidates for such activity.1–10

![Figure 1](image)

The benzo[a]quinolizidine motif 1 is found in the alkaloids of the Schulzeines species (schulzeines A-C (2)) and Ipecac species (emetine (3), tubulosine (4)). (Figure 2) The Schulzeines 2, isolated from the marine sponge Penares schulzei, are well studied and regarded as potential inhibitors of α-glucosidases which may be crucial for treatment of diabetes, cancer and viral infections.11,12 Emetine (3) has been used in traditional medicine, in the form of a root extract from Ipecac sp., for its antiparasitic and emetic activities. Later more intensive research was initiated to determine its ability to inhibit both ribosomal and mitochondrial protein synthesis and interfere with DNA and RNA synthesis. In their article “Biological Activities of Emetine” Akinboye and Bakare2 showed the diverse biological properties of emetine (3) and some of its analogues, such
as antiparasitic, antiviral, anticancer and contraceptive activity. **Tubulosine** (4) is an indole-containing analogue of *emetine* that shows similar properties.\(^{13,14}\)

![Tubulosine](image)

\[\text{schulzeines A-C (2)}\]

\[2 \text{ A - C}_{11b}-\text{H}; R^1 = \text{Me}, R^2 = \text{H}\]

\[2 \text{ B - C}_{11b}-\text{H}; R^1, R^2 = \text{H}\]

\[2 \text{ C - C}_{11b}-\text{H}; R^1, R^2 = \text{H}\]

Figure 2

Despite the great medicinal value of 3, its toxicity and side-effects led to a search for new medicinally useful analogues. **Figure 3** illustrates some of the latest synthetic compounds containing 1. According to a recent study, *dehydroemetine* (5), *isocephaeline* (6), *NZ71 (emunin)*, (7) and *NZ72* (8) are promising anti-cancer therapeutics because of their inhibitory activity towards heat-shock proteins (Hsp), which enhances sensitivity of the cancer cells towards different drugs.\(^7\) All of the compounds share the tricyclic system 1, which seems to be essential for activity. The benzo[a]quinolizinone derivative *lirequinil* (9) is a potential non-sedative drug which mimics the activity of benzodiazepines and may be effective for people with anxiety and sleep disorders.\(^4\) **Tetrabenazine** (10) is known to inhibit the uptake of serotonin, norepinephrine and dopamine in the CNS by binding to the vesicular monoamine transporter-2. Its chemistry and pharmacology have been widely studied since it is used in medicine for diverse hyperkinetic movement disorders.\(^8,10,15–17\) Another interesting drug candidate, **carmegliptin** (11), is found to inhibit the enzyme dipeptidyl peptidase IV (DPP-IV), which is a new approach for the treatment of type 2 diabetes.\(^5,18,19\)

In the light of this broad spectrum of biological activity, many methods for the construction of benzo[a]quinolizidines have been developed. More than two dozen syntheses of *emetine* (3) have been described in the literature. Many include the closure of ring B by the Bischler-Napieralski reaction, by palladium-catalyzed cyclizations or ring C closure by the Dieckmann condensation, alken metathesis or cycloadditions. There are few review articles on the methods for the preparation of benzo[a]quinolizidines, *e.g.* by Saraf\(^20\), by Popp and Watts\(^21\), and by Fujii.\(^22\) Montalban has more recently provided a short survey on the methods of synthesis for *emetine* (3).\(^1\) Methodological progress
Figure 3. Synthetic Compounds with Benzo[a]quinolizidine System 1.
towards the enantioselective approaches, which include the use of chiral auxiliaries and chiral catalysts at the very early stages of the multistep procedures, has led to the chiral intermediates that could dictate the steric course of the reaction sequences to the final products. The present review will summarize the ring construction and the synthetic transformations of the benzo[a]quinolizidine ring system 1 within the framework of the notable total synthesis of alkaloids and potential drugs created from 1990 up to 2015. Older publications are also discussed in view of historical development of the problem, the improvement of older classic methods via the application of new reagents, or synthesis of some products of medicinal importance.

The synthetic methods leading to ring system 1 are classified into two sections, I. Formation of Ring B and II. Formation of Ring C. However, there are synthetic schemes involving the successive formation of ring B and ring C as a one-pot procedure, so the adopted classification is not strictly followed.

I. Formation of Ring B

1. Bischler–Napieralski Reaction

The Bischler-Napieralski reaction is a Friedel-Crafts type acylation towards the synthesis of isoquinolines. The reaction is a cyclodehydration of 2-phenethylamides in the presence of a dehydrating agent, for example POCl₃, PCl₅ etc. (Scheme 1). The synthesis of 1 using the Bischler–Napieralski reaction relies on the formation of the C₁₁a–C₁₁b bond. The starting compound incorporates an appropriately substituted piperidine derivative which upon cyclodehydration yields the corresponding benzo[a]quinolizidine. Sugasawa and Itoh used the suitably substituted piperidinone 12, which was treated by means of PCl₅ in pyridine to give the protected benzo[a]quinolizidine 13, which was reduced and deprotected to give the 3-ethyl-benzo[a]quinolizidin-2-one 14 (Scheme 2).

The Bischler–Napieralski reaction proceeds smoothly, which makes this methodology widely used in the natural product synthesis, e. g., 3-ethyl derivative 14 can be regarded as a key intermediate for the synthesis of emetine (3) (Scheme 2). Compound 3 is probably the most frequently synthesized benzo[a]quinolizidine alkaloid. The first total synthesis of emetine (3) was achieved by Battersby and Turner by means of Bischler–Napieralski cyclization. In their procedure the starting piperidinone was converted to the ester 15 which had the required trans-stereochemistry. Upon treatment with POCl₃ the ester gave the desired benzo[a]quinolizidine derivative 16 in good yield. The product was isolated as a perchlorate salt due to its greater stability compared
Catalytic hydrogenation using Adams’ catalyst produced the desired saturated derivative 17 selectively and in good yield. It was used in subsequent steps for the preparation of emetine (3) (Scheme 3).

Scheme 2

(i): P₂O₅, sea sand, pyridine, reflux, 6h, 73%;
(ii): Pt/H₂, EtOH, 10% HCl;
(iii): 10% HCl, 1h, steam bath, 46% (over two steps).

to the corresponding free base. Catalytic hydrogenation using Adams’ catalyst produced the desired saturated derivative 17 selectively and in good yield. It was used in subsequent steps for the preparation of emetine (3) (Scheme 3).

Scheme 3

(i): POCl₃, anhydrous toluene, reflux, 30 min;
(ii): 10% HCl, HClO₄, EtOH, 87% (over two steps);
(iii): H₂/PtO₂, EtOH/H₂O - 90:10, rt, 15 min, 91%.
Ihara et al. used the Bischler–Napieralski reaction in formation of ring B for the purposes of the formal enantioselective synthesis of (−)-emetine (3).27 The chiral lactone 18 was synthesized so that the configuration of the stereogenic centers C2 and C3 is the same as the one in the target molecules. The chiral lactone 18 was used to acylate homoveratrylamine 19 to furnish amide 20 quantitatively. Its treatment with POCl3 allowed the simultaneous formation of rings B and C of the benzo[a]quinolizidinium salt 21 in one-step (Scheme 4). The configuration of 18 dictated the steric course of the hydrogenation of the iminium bond of 21 which gave rise to 22 as a single diastereomer in 36% overall yield. The latter product incorporated the benzo[a]quinolizidine core used as an important key intermediate for the synthesis of (−)-emetine (3) and tubulosine (4).

![Scheme 4](image)

(i): 155-156 °C, 6h, 100%; (ii): POCl3, reflux, 4h; (iii): LiClO4, CH2Cl2/H2O, 3h reflux, 1h, rt; (iv): H2/PtO2, EtOH, rt.

2. Pomeranz–Fritsch Reaction

The acid-mediated cyclization of aminoacetals to yield isoquinolines is referred to as the Pomeranz–Fritsch reaction (Scheme 5). The reaction is carried out in acidic media, usually trifluoroacetic acid or boron trifluoride.28,29 The procedure works best when the aromatic ring carries electron-donating substituents, which leads to the formation of substituted isoquinolines.
Rubiralta et al. were the first to develop an approach to the benzo[a]quinolizidine structure using formation of the C7-C7a bond by introducing the appropriately substituted trans-piperidine derivatives 23 in a Pomeranz–Fritsch reaction. The necessary compounds 24 were prepared by condensation of aminoacetals 25 with veratraldehyde 26, followed by a diastereoselective Mannich-type cyclization. The trans-piperidines 23 were then converted to the aldehydes 27 which underwent acid-catalyzed cyclization to the 7-hydroxybenzo[a]quinolizidines 28. After reduction and acid hydrolysis the target compounds 29 were obtained (Scheme 6; TFA = trifluoroacetic acid).

Scheme 6

(i): C6H6, 0 °C to reflux (Dean-Stark conditions), R = H (98%), R = Et (90%); (ii): p-TsOH, C6H6, reflux, N2 atm, 1h, R = H (93%), R = Et (67%); (iii): 4N HCl, 0 °C, 4h, R = H (75%), R = Et (87%); (iv): Et3SiH, TFA, CH2Cl2, N2 atm, reflux, 24 h, R = H (50%), R = Et (30%); (v): 4N HCl, MeOH, 40 °C, 7h, R = H (89%), R = Et (83%).
Further development of the method by Hoornaert et al. allowed the stereospecific synthesis of 1,3-substituted benz[a]quinolizidines starting from the suitable oxazinone 30, which was converted to the pyridine derivative 31 in high regioselectivity. Reductive dehalogenation by treatment with hydrogen, Pd/C and PtO₂ resulted in conversion into the all-cis substituted piperidine 32. Upon treatment with glycidol and subsequent periodate cleavage the amino aldehyde 33 was obtained. Cyclization of the latter with hydrochloric acid yielded stereospecifically the trans-fused benz[a]quinolizidine product 34 which was then treated to remove the hydroxyl group. The trans-fused bicyclic system was proven by NMR analysis of the final product 35. This method is applicable for the stereospecific synthesis of different 1,3-disubstituted derivatives (Scheme 7).

Scheme 7

3. Pictet–Spengler Reaction

The Pictet–Spengler reaction is one of the classical methods for the synthesis of tetrahydroisoquinolines. The reaction is an acid-catalyzed condensation between a carbonyl compound and a β-arylethylamine derivative to give a tetrahydroisoquinoline ring (Scheme 8).²⁸,²⁹

Scheme 8

The key intermediate in this reaction is the N-alkyliminium ion 36, which undergoes an intramolecular cyclization upon which the product is formed. A modification of this reaction is the use of N-acyliminium ion 37, which is more electron-deficient and thus more reactive as an electrophile.³² Nucleophiles that are usually unreactive in the
classical Pictet–Spengler reaction, such as unactivated arenes, participate readily in cyclizations with N-acyliminium electrophiles 37 (Scheme 9).

![Scheme 9]

As in the previously mentioned Bischler-Napieralski reaction, ring B is closed via the formation of C$_{11a}$$-$$C_{11b}$ bond. One of the first reports featuring this type of reaction was made by Bithos et al. in the development of a new synthetic pathway to emetine (3). Using amides of type 38, the hydroxylactam aldehyde 39 was prepared and upon treatment with phosphoric acid underwent a Pictet–Spengler type cyclization. The tricyclic product 40 was used for the synthesis of emetine (3) (Scheme 10; DME = 1,2-dimethoxyethane).

![Scheme 10]

Similar hydroxylactam derivative 41 was used by Bowen et al. in order to obtain the benzoquinolizidine skeleton 42 of the schulzeine alkaloids. The key part in their synthetic approach was the chiral amide 43 with the same configuration of the chiral center as C$_3$ of the schulzeine 2. The starting molecule for the preparation of 43 was the L-glutamate derivative 44. The amide 43 is converted into the aldehyde 45, which in acidic medium gave the hydroxylactam 41, i.e., ring C formation preceded the ring B formation (Scheme 11; NPhth = phthalimide-protected amine group).

The cyclized product 42 was a diastereomeric mixture of cis- and trans-benzo[a]quinolizidinones. The cis and trans diastereomers 46 were converted into (+)-schulzeine B
and (−)-schulzines A and C, respectively. The authors suggested an enantioselective total synthesis of the long-chain aliphatic carboxylic acids, thus rendering total enantioselective syntheses of schulzines A and C.

Lete et al. focused their attention on the transformations of imides employing two procedures - addition of organolithium reagents and reduction of imides. Borohydride reduction of the glutarimide 47 followed by acid-mediated cyclization gave the benzo[a]quinolizidinone 48 in good yield. Treatment of 47 with methyllithium and subsequent acidic treatment afforded the 11b-methyl-substituted product 49 (Scheme 12). The compounds obtained were used further in order to obtain the benzo[a]quinolizidine framework of emetine. Because of the availability of a wide array of substituted imides, the two approaches provide access to the heterocyclic framework of different isoquinoline alkaloids.

The potential application of these types of reactions in the synthesis of enantiopure alkaloids has also been studied. The products 48 and 49 were synthetically modified toward alkaloid-like structures. Lete et al. proposed a synthetic strategy which included a formation of an α,β-unsaturated lactam unit in the benzo[a]quinolizidinones 50, 51 followed by a conjugate addition reaction affording another functional group in ring C. The introduction of the double bond was performed in two steps - formation of selenium derivatives 48A and 49A and subsequent selenoxide elimination (Scheme 13; LDA = lithium diisopropylamide; PIDA = (diacetoxyiodo)benzene, phenyliodoso diacetate).

The unsaturated products 50, 51 were studied in conjugate addition reactions with sulfur-stabilized nucleophiles. This allowed the stereocontrolled formation of a carbon-
Deprotection with PIDA gave the aldehyde as a single diastereomer, which was further used to obtain the *emetine* analogue (Scheme 14).

(i): NaBH₄, EtOH/H₂O, HCl, 0 °C; (ii): TFA, CH₂Cl₂, rt, 83%; (iii): MeLi, -78 °C, THF; (iv): TFA, CH₂Cl₂, 87%.

Scheme 12

(i): PhSeBr, LDA, THF, -78 °C, 1h (48A, 70%); (ii): PIDA, TFA, MeCN/H₂O, rt, (50, 56%); H₂O₂, pyridine, 0 °C to rt, (51, 61%, over two steps).

Scheme 13

Carbon bond at C₂ in the resulting product 52. Deprotection with PIDA gave the aldehyde 53 as a single diastereomer, which was further used to obtain the *emetine* analogue 54 (Scheme 14).

(i): (PhS)₂CHLi, THF, -78 °C, 16h, 93%, dr 80:20; (ii): PIDA, TFA, MeCN/H₂O, 80%.

Scheme 14
The reactions used in the asymmetric synthesis of natural products are based either on the use of chiral starting materials or chiral auxiliaries. Lete et al. showed that the cyclization of hydroxylactam derivatives **55A** and **55B** could be catalyzed by chiral phosphoric acids, such as **56**, thus allowing the preparation of optically active products.43 It was found that in the case of pyrrolidine hydroxylactams **55A** the reaction yields the corresponding pyrroloisoquinoline **57A** in good yield but with poor enantioselectivity (12% ee). The cyclization of the piperidine derivative **55B** was unsuccessful and only the enamine product **57B** was isolated (Scheme 15).

Another approach allowing stereospecific synthesis of benzo[a]quinolizidine molecules starts with the preparation of chiral substituted bicyclic lactams of type **58**. They are generated by cyclocondensation of racemic or prochiral oxoester derivatives **59** with (S)-dimethoxyphenylalaninol (**60**), which acts as a chiral inductor. Upon acidic treatment, the final products **61** are assembled by an intramolecular Pictet–Spengler reaction (Scheme 16).44–46

The condensation of the oxoester derivatives **59** with **60** proceeds in good yield and high stereoselectivity, and thus leads to the formation of an enantiopure product. The process involves a dynamic kinetic resolution of the racemic starting substrate **59**.44 Under acidic conditions the oxazolidine ring in **58** is cleaved leading to the formation of an α-acylaminium ion **58A**, which undergoes a stereoselective Pictet–Spengler reaction. The reaction conditions were optimized using different acidic sources. Cyclizations initiated by BF₃·Et₂O or TiCl₄ lead to the formation of a single diastereomer **61**, whereas in the presence of HCl an isomerization of the C₁ stereocenter may occur. The cyclization leads to the formation of a product with a trans-H₁/H₁₁b relative configuration which is guided by the hydroxymethyl substituent.47

Franzén and Fisher suggested the efficient one-pot enantioselective synthesis of benzo[a]quinolizidinone as a mixture of diastereomers **62** in 2:1 ratio in the presence of the basic chiral catalyst **63**.48 In this method the formation of the rings B and C of the benzo[a]quinolizidinone system proceeds in one pot. Yields varied from 53 to 71% and the enantiomeric excess (ee) of the 11bS-isomer of **62** was 90–98% depending on the aryl
substituent (Scheme 17; TMS = trimethylsilyl ether protective group). The configuration of the isomers 62 was established by means of X-ray analysis.48

A possible mechanism for the reaction was also presented according to which the key stage of the reaction is a stereospecific conjugate addition of the starting amide 64 to the iminium ion, which resulted from initial reaction between the catalyst 63 and the conjugated aldehyde 65. The stereospecificity was caused by the steric hindrance of the aryl groups present in the catalyst 63 (Scheme 17).48 The resulting hydroxypiperidinone 66 incorporated the thermodynamically more stable trans configuration between the stereo-centers at C2 and C3. Acid-catalyzed dehydration of 66 gave the acylaminium ion 67 which underwent an intramolecular Pictet–Spengler reaction to the final products 62. The procedure was further developed as a one-pot method for the preparation of indolo[2,3-a]quinolizidines49–51 with application in the synthesis of natural products.52

4. Intramolecular Heck Reaction

The Heck Reaction, a palladium-catalyzed coupling of haloarenes or haloalkenes with alkenes is one of the most widely used methods in the organic synthesis of complex molecules.53,54 Its applications in the preparation of heterocyclic compounds have been extensively reviewed.55–57

Using a three-step synthetic strategy which includes a final Heck Reaction, Kirschbaum and Waldmann obtained functionalized benzo[a]quinolizidinones in good yields.58,59 The first two steps of the synthetic route aimed at the preparation of the enamiones of type 68 starting from the condensation of homoveratryl amine derivative 69 with a series of aliphatic and aromatic aldehydes. Lewis acid-mediated condensation

\[ \text{(i): Toluene, reflux; (ii): TiCl}_4, \text{CH}_2\text{Cl}_2, -10^\circ\text{C, 24h (R}_1^1 = \text{H, R}_2^2 = \text{CH}_2\text{COOEt, 68%); HCl/EtOH, 50^\circ\text{C, 24h (R}_1^1 = \text{Et, R}_2^2 = \text{H, 80%).} \]
of the resulting Schiff bases 70 with electron-rich silyloxydienes 71 furnished the desired enaminones 68 (Scheme 18).58,59

The Heck-type cyclization of enaminones 68 to give products 72 and 73 with an additional double bond in ring C is shown below. When the substituent R 2 is hydrogen, the products 72A, B contain an endocyclic double bond, but when R 2 is an ethyl group, 73A, B with an exocyclic double bond were formed. It was concluded that if the R 1-substituent and the base employed were sterically demanding (for example aromatic substituent and i-Pr 2NEt) the formation of the isomeric product 72B is low. The method is applicable for

(i): 20 mol % 63, CH 2 Cl 2 , 3 °C to rt, 1-5 days; (ii): HCl/Et 2 O, -78 °C, 3h
a) Ar = C 6 H 5 , yield - 69%, dr - 62:38;
b) Ar = 2-NO 2 C 6 H 4 , yield - 53%, dr - 83:17;
c) Ar = 4-AcO-3-MeOC 6 H 3 , yield - 62% dr - 69:31;
d) Ar = 4-MeOC 6 H 4 , yield - 71%, dr - 76:24;
e) Ar = 4-BrC 6 H 4 , yield - 56%, dr - 72:28.

Scheme 17

of the resulting Schiff bases 70 with electron-rich silyloxydienes 71 furnished the desired enaminones 68 (Scheme 18).

The Heck-type cyclization of enaminones 68 to give products 72 and 73 with an additional double bond in ring C is shown below. When the substituent R 2 is hydrogen, the products 72A, B contain an endocyclic double bond, but when R 2 is an ethyl group, 73A, B with an exocyclic double bond were formed. It was concluded that if the R 1-substituent and the base employed were sterically demanding (for example aromatic substituent and i-Pr 2NEt) the formation of the isomeric product 72B is low. The method is applicable for

(i): R 1 CHO, CH 2 Cl 2 , MgSO 4 ; (ii): ZnCl 2 /THF (for aromatic aldehydes);
EtAlCl 2 /CH 2 Cl 2 (for aliphatic aldehydes).

a) R 1 = C 6 H 5 (R 2 = H, 43%); (R 2 = Et, 45%); b) R 1 = 4-MeOC 6 H 4 (R 2 = H, 66%); (R 2 = Et, 52%); c) R 1 = 4-NO 2 C 6 H 4 (R 2 = H, 20%); (R 2 = Et, 73%); d) R 1 = i-Pr (R 2 = H, 65%); (R 2 = Et, 64%); e) R 1 = n-Pr (R 2 = H, 43%); f) R 1 = H (R 2 = H, 47%); (R 2 = Et, 27%).

Scheme 18
the formation of benzo[a]quinolizidines with additional substituents in ring C, by variation of the structure of silyloxydienes 71. In all cases E-73 was formed in excess over the Z-isomer. All attempts to achieve asymmetric induction by using chiral phosphine ligands, such as (R)-BINAP ((R)-(+)-(1,1’-binaphthalene-2,2’-diyl)bis(diphenylphosphine)), were unsuccessful (Scheme 19; dba = dibenzalacetone).58,59

Aiming to achieve enantiomerically enriched benzo[a]quinolizidines, Kirschbaum et al. also performed the Heck reaction of chiral enaminones 74. This method yielded 75 as a mixture of isomers. The major products had an exocyclic double bond and differed in configuration at C11b (ratio 3:4) (Scheme 20).58,59

5. Photochemical Cyclization

A characteristic feature of conjugated hexatriene-containing polyenes is their electrocycloaddition reaction, which has found applications in the synthesis of alkaloids and natural products.
The potential of these reactions for the synthesis of benzo[a]quinolizidines is illustrated by the electrocyclic reaction of a stilbene-like pyridine analogue, where nitrogen is a part of enamide moiety. The benzo[a]quinolinizin-4-ones were prepared by irradiation of substituted pyridine derivatives in acetonitrile or ethanol solution containing hydrochloric acid, O₂ and I₂. Irradiation of under these conditions led to trans-to cis-isomerization, and the latter configuration is favorable for cyclization to (Scheme 21).

6. Parham Cyclization

The intramolecular reaction between an electrophilic site and an aryllithium to generate fused carbo- or heterocyclic rings is referred to as the Parham reaction. The aryllithium is usually derived by metal-halogen exchange and the subsequent cyclization depends on the nature of the side-chain electrophile. When the electrophile is a carbonyl group, the product is a cyclic alcohol, whereas cyclization with a carboxy group yields a cyclic ketone. In the latter case the reaction could be considered an anionic equivalent of the Friedel-Crafts reaction (Scheme 22).

The reaction is very useful for the preparation of aryl or heteroaryl fused carbo- or heterocycles, and has found applications in the synthesis of numerous natural products.

A good example of the usefulness of the Parham cyclization is the procedure by Lete et al. for the preparation of benzo[a]quinolizidine species, which involves aromatic lithiation-cyclization sequence of imides of type 78. The products were hydroxylactam derivatives, which were further dehydrated to yield benzo[a]quinolizidinones and analogs (of type 80) containing a cyclic enamide moiety (Scheme 23).

The authors used a similar synthetic strategy for the preparation of different types of isoquinoline-fused heterocycles. An enantioselective protocol for the preparation of isoindolo[2,1-a]isoquinolines was also developed. The main characteristic of the
sequence was the use of BINOL-derived Brønsted acids in the dehydrogenation of the initial product.67 (BINOL = 1,1′-bi-2-naphthol)

II. Formation of Ring C

1. Dieckmann Condensation

The formation of ring C by the Dieckmann condensation is a classic approach to the benzo[a]quinolizidine ring system.1,20,21 It includes a step of appropriate diester preparation, which then reacts in the Dieckmann condensation. Sodium hydride or ethoxide, or sodium metal are usually employed as basic reagents in solvents such as benzene or toluene. Regioselectivity can be a problem if both side-chains contain active α-hydrogens; then the yield of the target molecule is lower and tedious purification may be necessary.

This approach was used in the preparation of 3- or 1-alkylbenzo[a]quinolizidine-2-ones, which exhibit tranquilizing properties. Thus, 3-isobutylbenzo[a]quinolizidine-2-one under the name tetrabenazine (10) was introduced in medical practice for the treatment of hyperkinetic movement disorder (Huntington disease).8,68 Starting from tetrahydroisoquinolines such as 81 the racemic 3-ethylbenzo[a]quinolizidine derivative 14 was obtained and used as an intermediate in the total syntheses of emetine (3) (Scheme 24).69–72

There are different methods for the construction of side-chains with ester moieties in positions 1 and 2 of the isoquinoline ring as in 81. Aza-Michael addition to esters of unsaturated acids has often been used. Mizukami prepared tetrahydroisoquinoline 82, which underwent Michael addition to give diester 83 which was cyclized in the presence of NaH/toluene to give ethyl ester of benzo[a]quinolizidin-2-one 84 as a sole isomer in 55% yield (Scheme 25).70
Mizukami also prepared compound 85 and cyclized it to the ester 86. The change in regioselectivity, as compared to the synthesis of 84 was rationalized on the basis of steric factors. The 3-methyl derivative 87 was converted into a methyl enol ether 87A (the position of the double bond was not specified) (Scheme 26).

A similar procedure was utilized to prepare a series of 1-alkyl benzo[a]quinolizidinones 88 via the oxoesters 89, in order to obtain compounds for biological activity evaluation. The α-substituent of the 1-(ethoxycarbonylmethyl) group dictated the regioselectivity to compounds 89, obtained in moderate yields (Scheme 27).
The Dieckmann condensation was included in the approach of Schnider et al. as a key step for the total synthesis of \((\pm)-emetine (3)\).\(^{72}\) The authors started from the diester 90 and accomplished the synthesis of \((\pm)-3\) in fifteen steps. Other key points are the early selective reduction of the 1-oxo group in 91, and the elongation of the side-chain at C\(_2\) into 2-(carboxymethyl) compound 92 using the Arndt–Eistert reaction. The acid 92 was transformed into two diastereomers 93, each of which in turn gave \((\pm)-emetine (3)\) and its diastereomer called \((\pm)-isoemetine\) (Scheme 28).\(^{72}\)

![Scheme 28](image)

The Dieckmann condensation was applied in the synthesis of carmegliptin (11) first developed by Hoffmann-La Roche as a DPP-IV inhibitor in the therapy of type 2 diabetes.\(^{18,74}\) A specific substituent is the pyrrolidinone moiety at the C\(_3\) bearing a fluoromethyl group, which fits in a lipophilic pocket of the enzyme according to X-ray data.\(^{18,75}\) The approach consists of a twenty-one step reaction scheme including a sixteen step linear synthesis. The C-ring was formed by the Dieckmann condensation, with low regioselectivity, and 40% yield of the target product 84 (Scheme 29).\(^{18,75}\)

![Scheme 29](image)

2. Intramolecular Aminolysis

The intramolecular aminolysis is a suitable tool when the starting isoquinoline derivative incorporates a \(\delta\)-amino acid residue, so that the reaction between NH and the carboxylic or ester group will lead to a six-membered ring.\(^{76,77}\) The first total synthesis of schulzeines B and C was accomplished by Gurjar et al. using intramolecular aminolysis as the key step to furnish the tricyclic benzo[a]
The suitably substituted 3,4-dihydroisoquinoline 94 was generated by a two-step reaction sequence starting from amine 95 to yield its amide derivative 96 and subsequent Bischler-Napieralski cyclization. Reduction of the substituted derivative 94 with NaBH₃CN followed by treatment with aq. NaHCO₃ gave the diastereomeric benzo[a]quinolizidines 97-S and 97-R which were separated by column chromatography (Scheme 30; EDC = 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide; HOBt = benzotriazol-1-ol).

Another synthetic strategy using an intramolecular aminolysis involves an initial Corey–Link reaction of a substituted tetrahydroisoquinoline 98 to furnish an α-azido acid 99, which cyclizes readily to form benzo[a]quinolizidinone 100. The tetrahydroisoquinoline 98 was prepared by a Pictet–Spengler reaction with the amine 95 and the vinyl ether 101. Reduction of the azido group of 100 and deprotection of the hydroxyl groups leads to the formation of tricyclic product 102, which was further used for the synthesis of schulzeine B (Scheme 31; TES = triethylsilyl ether protective group; DPPA = diphenyl phosphorazidate).

The key stage in the approach of Itoh et al. towards the synthesis of schulzeine A was also an intramolecular aminolysis of the ester group in 103 initiated by Boc-deprotection to afford a mixture of the diastereomers 104-R and 104-S in very good yield and high enantiomeric excess. The required 103 was prepared using a multi-step synthetic route starting from optically active aldehyde 105. The two diastereomers 104 were separated by means of column chromatography and 104-R was converted into schulzeine A (Scheme 32; COD = 1,5-cyclooctadiene).

The procedure of Li and Yang also includes formation of ring C by aminolysis of ester group as a key step. The ester 106 was alkylated by means of ethyl 4–bromobutanoate to give 107 with very good yields along with the side-product 108. The reaction was carried out in an inert atmosphere to minimize the yield of 108. A possible mechanism for the formation of both 107 and 108 was discussed (Scheme 33).

Shono et al. developed a coupling reaction between iminium salts such as 109 and bromocrotonates 110 promoted by Zn. Investigation of the scope of this novel reaction
(i): AcOH, 100°C, 24h, 33% : 41% mixture of diastereomers; (ii): (Boc)₂O, CH₂Cl₂, 92%; (iii): NaOH, NaN₃, DME/H₂O (1:1); (iv): TFA, CH₂Cl₂, 0°C, (v): Et₃N, DPPA, DMF, 47%; (vi): H₂, Pd/C, MeOH, 99%.

Scheme 31

(i): MeCN, 10 °C to rt, 2h, 93%; (ii): H₂, Rh(COD)₂BF₄ (10 mol.%), R-MONOPHOS (22 mol.%), CH₂Cl₂, rt, 2 days, 99%; (iii): TMSOTf; (iv): K₂CO₃, 18-crown-6.

Scheme 32

(i): tBuOK, DMF, -60 °C; (ii): ethyl 4-bromobutanoate, DMF, N₂ atm.; (107, 69%), (108, 5%).

Scheme 33
entailed the preparation of a series of benzyl-protected tetrahydroisoquinolinium salts 111, which on deprotection cyclized to 112. The products of type 112 were obtained in excellent yields and were further converted to the ketones 113, which have previously been used in a number of methods towards the synthesis of emetine (Scheme 34). The same approach was successfully applied in the synthesis of indoloquinolizidines.

3. Aza-annulation Reactions

Aza-annulation reactions of enamine substrates with molecules containing 1,3-

1
-

bis-electrophilic centers has proven to be a useful one-step method to construct five- or six-membered nitrogen heterocycles. The methodology has been utilized as a key step in the synthesis of various complex structures of this type. Despite its many variations, the procedure involves three fundamental reactions: enamine formation, conjugate addition to an \( \alpha, \beta \)-unsaturated carboxylic acid derivative and acylation at nitrogen.

Two approaches are most often used, namely initial \( N \)-acylation or formation of enamine prior to the important carbon-carbon bond formation. The enamines that result from the second approach are stable and usually isolable, or sometimes readily available. The reactions of enamines with various Michael acceptors have been extensively investigated as a convenient one-step route to six-membered nitrogen heterocycles (Scheme 35).

Heterocyclic enamines are versatile building blocks for the synthesis of various bicyclic and tricyclic structures with a bridgehead nitrogen atom. These reactive N-heterocycles have received considerable attention because they include a push-pull fragment and readily react with different \( \alpha, \beta \)-electrophiles resulting in substituted quinolizidines and indolizidines. “Push-pull” tetrahydroisoquinolines incorporating an enamine fragment, such as \( \beta \)-enaminonitriles and \( \beta \)-enaminoesters, are easily accessible and their reactions with electron-deficient alkenes (unsaturated acyl chlorides, esters and dithioesters, aldehydes (polyenals) and imines (azapolyenes), electron-deficient
Allenes and their precursors or analogues\textsuperscript{84}, azlactones\textsuperscript{87}, etc.) afforded ring C of benzo[a]quinolizidinones and various derivatives thereof in good to high yields. Such cycloadditions, which can be regarded as [3+3] cycloadditions, were also termed "aza-annulation reactions." On the other hand, variation of the electron-withdrawing substituents at the enamine fragment allowed the introduction of substituents at ring C of the benzo[a]quinolizidinones.\textsuperscript{83,84} It should be noted that the presence of double bond(s) in the molecule of the electrophilic partner gives rise to benzoquinolinolizes with one or two double bonds at ring C.\textsuperscript{84}

The aza-annulation reactions of 3,4-dihydroisoquinoline derivatives, such as 114, for the preparation of benzo[a]quinolizidin derivatives have been well documented. Compound 114 is presumed to be in tautomeric equilibrium with its enamine form 114A, which is usually generated \textit{in situ}. The reaction of 114 with crotonic anhydride gave products 115 and 116 with apparent lack of regioselectivity.\textsuperscript{88} Furthermore, the attempted conversion of 115 into 116 proved to be unsuccessful. A regioselective addition was achieved with the doubly activated Michael acceptor 117. The product 118 formed initially underwent spontaneous retro-Michael reaction to afford derivative 119 upon elimination of diethyl malonate.\textsuperscript{89} Reduction of 118 \textit{in situ} with NaBH\textsubscript{4} proved to be useful in order to avoid the latter process (Scheme 36).

The 3,4-dihydroisoquinoline 114 has found application in the synthesis of several natural products. Upon reaction with 120 the cyclized product 121, which incorporates a lactam C-ring (i.e., acylated nitrogen atom), was obtained in one step and in high yield.\textsuperscript{90} The product was then converted to 122, identified as a key intermediate for the synthesis of (±)-emetine (3, 28%), (±)-tubulosine (4, 18%) and (±)-dihydroprotoemetine 123 (Scheme 37). Ninomiya et al. reported a photochemically-induced aza-annulation starting with the acylation of 114, which was carried out by means of unsaturated acid chlorides chosen in a way to introduce specific substituents at ring C of the resulting benzo[a]quinolizinone 124, suitable for the total synthesis of emetine (3).\textsuperscript{91} The irradiation of the acylated products gave rise to 124, which were transformed stereoselectively into 125. The steric course of the transformations was established in order to prepare synthetic bioactive benzo[a]quinolizidines (Scheme 38).\textsuperscript{91}

The aza-annulation reaction of 114 with the unsymmetrical β-oxodithioesters 126 gave regioselectively the benzo[a]quinolizin-4-thiones 127 in one step and in very good yields.\textsuperscript{92,93} The pattern of substitution of oxodithioesters 126 dictates the C\textsubscript{2} and C\textsubscript{3}
substituents of the thiones 127, so a tetracyclic structure could be obtained as well. It is interesting to note that ethyl acetoacetate did not participate in the reaction with 114. Further the thiolactams 127 were converted smoothly into lactams (Scheme 39).

Scheme 36

Scheme 37
The aza-annulation reaction of tetrahydroisoquinolines of type 128, which contain an acyl group at the enamine fragment, with bis-1,3-electrophiles proceeded smoothly to yield benzo[a]quinolizin-4-ones 129-131 in very good yields and high regioselectivity. Unexpectedly the reaction of 128 (X = COPh) with malonyl chloride gave the tetracyclic product 131 in moderate yield. It is presumed that the initially formed benzo[a]quinolizidinone 132 underwent further addition of malonyl chloride (Scheme 40).

The aza-annulation reaction of 128 with a mixture of formaldehyde and primary amines (Mannich-type of electrophile) allowed the formation of 1-acylpyrimido[6,1-a]isoquinolin-4-ones 133 in very good yields under mild reaction conditions. The reaction of 128 with benzoyl isothiocyanate gave 4-phenylpyrimido[6,1-a]isoquinolin-2-thiones 134. This feature of the reactivity of the enamiones 128 is important, because pyrimido[6,1-a]isoquinolines were shown to be potent inhibitors of c-AMP phosphodiesterase and to exhibit excellent anti-hypertensive activity (Scheme 41).

Unlike enamiones 128, cyanoenamines 135 showed a varying reactivity towards different unsaturated acyl chlorides. While cinnamoyl chlorides gave rise to 2-oxo derivatives 136, the acryloyl chlorides gave 4-oxo derivatives 137 (Scheme 42).

Dihydroisoquinolinium mesylates of type 138 reacted with unsaturated aldehydes (polyenals) to give the intermediate conjugated polyenes, which further underwent
Electrocyclization to 4-styryl derivatives 139 in moderate yields. The method was successfully applied for the synthesis of indoloquinolizines as well (Scheme 43).98

Conjugated aza-triennes and aza-tetraenes 140 reacted with formaldehyde and primary amines to give 2-styryl pyrimido[6,1-a]isoquinolines 141. The authors demonstrated that the reaction started with addition of the Mannich reagent to the nitrogen atom of the starting compounds 140 and the intermediate adducts cyclized with formation of the 6-membered pyrimidine ring (Scheme 44).98

Aza-annulation of tetrahydroisoquinoline enamines was used for the preparation of lirequinil (9), as well as its analogs, 7-oxothieno[2,3-a]quinolizine and 4-oxoindolo[2,3-a]quinolizine.4,99 The synthesis of 9 started with the preparation of 7-chloro-3,4-dihydroisoquinoline-1(2H)-thione (142), which was converted into the enamo ester 143. The aza-annulation reaction of 143 with sodium α-phenylacrylate (144) gave ring C of the target benzo[a]quinolizinone as its ethyl ester 145, which after aminolysis was converted into 9 (Scheme 45; PPA = polyphosphoric acid; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).99
In another preparation of 9 developed by Spurr, oxazolidinedione 146 was easily cyclized to the oxazolo[2,3-a]isoquinoline-2,3-dione 147 in high yield. After methanolyisis of 147, the resulting dihydroisoquinoline 148 reacted with ethyl 3-(dimethylamino)-α-phenylacrylate (149) to form ring C of the benzoquinolizinone system of 150. Further
transformations of 150 into the bromoderivative 151 allowed the introduction of the carboxylic group of the acid 152, which gave rise to the carboxamido group of 9. All the steps proceeded in very good to high yields and were suitable for larger scale production of 9 (Scheme 46; NBS = N-bromosuccinimide; dppp = 1,3-bis(diphenylphosphino) propane).4

(i): CS₂, Et₃N, ClCO₂Et, CH₂Cl₂, 0 °C to rt, 1.5h then reflux 15 min; (ii): AlCl₃ then 2M HCl (58%) or PPA (40%); (iii): BrCH₂CO₂Et, Ph₃P, Et₃N, CH₃CN, reflux, 40-70h (78%); (iv): 144, ClCO₂Et, THF, rt (81%); (v): DDQ, toluene, reflux (64%).

Scheme 45

The acylated Meldrum acids and their analogs, which are known to give upon heating the reactive acyl ketenes species, form benzo[a]quinolizin-4-ones in cycloaddition reactions with the dihydroisoquinoline 114.92 Pemberton et al.100 investigated acylated Meldrum acids 153 in reaction with 114 under microwave irradiation (MWI) in an acidic

Scheme 46
medium and obtained mixtures of benzo[a]quinolizin-4-ones 154 and [1,3]oxazino[2,3-a] isoquinolin-4-ones 156 (Scheme 47).100

![Chemical Structure](image1)

(i): 114, MWI, Cl(CH$_2$)$_2$Cl, then HCl$_{(gas)}$ (R = Ph, Me) or TFA (R = cyclohexyl), 140-160 °C (R = Ph, 91 %).

**Scheme 47**

The formation of the benzo[a]quinolizin-4-ones 154 was strongly favored in acidic medium while 156 were major products in the presence of triethylamine; in a neutral medium complex mixtures were obtained. Furthermore, compounds 156 upon heating under microwave irradiation (MWI) in acidic medium, were converted into 154, albeit not completely. It was suggested that oxazinones 156 were intermediate products of cycloaddition.100

The disubstituted acylketene 157 derived from 1,3-dioxin-4-one 158 was used in reaction with 114 under similar reaction conditions - microwave irradiation followed by TFA addition at elevated temperature. In this way the alkylsubstituted benzo[a]quinolizine-4-one 159 was obtained in 69% yield (Scheme 48). The procedure was applied also for the preparation of a series of indoloquinolizidinones.100

![Chemical Structure](image2)

**Scheme 48**

In a search for inhibitors of mitochondrial respiratory chain, Moreno et al. reinvestigated the reaction of 1-substituted dihydroisoquinolines 160 and 6-substituted 1,3-dioxin-4-ones 161 - a source of acylketenes 162.103 By variation of the conditions the authors could direct the reaction towards either benzoquinolizine or oxazinoquinolizine products. When the reaction was carried out under neutral conditions, only benzo[a]quinoliziones 163 were obtained. In the presence of triethylamine, the oxazinones 164 were the sole products (Scheme 49).101 A stepwise mechanism for the reaction via a common intermediate for both products was accepted.

The synthesized compounds were assayed *in vitro* against the NADH oxidase activity of beef-heart submitochondrial particles as a model of mammalian respiratory chain. Most of the compounds tested inhibited the whole respiratory chain at micromolar concentrations. In general, compounds 164 displayed greater NADH oxidase inhibition...
than their respective analogs 163. Because of their moderate toxicity, compounds 163 and 164 could be regarded as potential anti-tumor agents.\textsuperscript{101}

Azlactones (2,5-disubstituted oxazol-4(5\textsubscript{H})-ones) are another type of bis-electrophiles, that react readily with 1-alkyl-3,4-dihydroisoquinolines to give benzo[a]quinolizin-4-ones. Azlactones are easily prepared by cyclodehydration of \(\alpha\)-(N-acylamino)acids in the presence of an aldehyde.

Ruchirawat \textit{et al.}\textsuperscript{87} carried out the cyclocondensation of enolizable dihydroisoquinolines 165 with azlactones 166 and obtained the benzo[a]quinolizinones 167 as mixtures of \textit{cis}- and \textit{trans}-isomers. Ring C of 167 acquired the substitution pattern of the starting azlactone 166 and the \textit{cis}/\textit{trans} ratio depended on the steric size of the substituents. The authors proposed a stepwise mechanism with the formation of \(\textit{N}\)-acylenamines as intermediates, which undergo cyclization to benzo[a]quinolizin-4-ones 167 (Scheme 50).\textsuperscript{87}

The reactions of 166 with dihydroisoquinolines, which cannot give tautomeric enamines, led to the formation of imidazoloisoquinolin-3-ones.\textsuperscript{87}

cis- and trans-Acylamino compounds 167 containing \(o\)-bromophenyl substituent were shown to give benzoindoloquinolizinones 168 on treatment with CuTC (copper(I) thiophene-2-carboxylate) under MWI. \textit{trans}-167 was cyclized to 168 in much lower yield than the \textit{cis}-isomer. The formation of the side-product 169 was also observed (Scheme 51).\textsuperscript{102}
4. Other Cycloaddition Reactions

The cyclocondensation of enolizable mono- and bicyclic anhydrides with cyclic imines is a useful one-step reaction for the formation of compounds with an annulated pyridinone cycle. The mechanism of the reaction is still under discussion.\textsuperscript{103} Kametani \textit{et al.}\textsuperscript{88} reacted 1-methyl-3,4-dihydroisoquinoline (114) with glutaric anhydride (170) to give in one step 11b-methylbenzo[a]quinolizin-4-one 171 in 56\% yield. The authors assumed that compound 171 was formed by a nucleophilic attack of the methylene (CH\_2) carbon of 170 at C-1 of the dihydroisoquinoline 114 followed by cyclization and decarboxylation (Scheme 52).\textsuperscript{88}

\begin{equation}
\text{MeO} \quad \text{MeO} \quad \text{N} \quad \text{Me} \\
\text{114} + \quad \text{170} \quad \text{pyridine, 100\degree C, - CO}_2 \\
\text{MeO} \quad \text{MeO} \quad \text{N} \quad \text{Me} \\
\text{171 (56 \%)}
\end{equation}

\textbf{Scheme 52}

Stanoeva \textit{et al.} carried out the reaction of 1-chloroisouquinoline (172) with 170 in toluene at reflux. The cycloaddition took place with elimination of CO\_2 and HCl to give 4H-benzo[a]quinolizin-4-one (173) in 36\% yield in one step (Scheme 53).\textsuperscript{104,105}

\begin{equation}
\text{172} + \quad \text{170} \quad \text{toluene, \Delta} \quad \text{- CO}_2, \text{- HCl} \\
\text{173 (36 \%)}
\end{equation}

\textbf{Scheme 53}

Similar approach was successfully applied for the total syntheses of dibenzoquinolizine alkaloids (thalictricavine, thalictrifoline, berlambine, canadine, cavidine,
corydaline, xylopinine in racemic and optically active forms) from 3,4-dihydroisoquinolines and suitably substituted homophthalic anhydrides.106

Two successive cycloaddition steps were employed in the synthesis of 3-ethyl-benzoquinolizidin-2,6-dione 174 in an approach towards emetine. The reaction of benzaldoxime 175 with 2,3-bis(phenylsulfonyl)-1,3-butadiene led to the adduct 176 in very good yield. Subsequent reductive N-O cleavage furnished the rings B and C of benzo[a]quinolizinedione 177 as a mixture of diastereomers. The introduction of an ethyl group at position 3 was carried out with a moderate regioselectivity and subsequent desulfurization afforded 3-ethylketone 174 (Scheme 54; AIBN = 2,2′-azobis(2-methylpropionitrile), azobisisobutyronitrile).107

![Scheme 54](image)

(i): SO₃Ph, toluene, 125 °C, 24h; (ii): H₂, Ra/Ni, THF, reflux, 12h;
(iii): Et₃, NaH, DMF, 25 °C, 1 h; (iv): AIBN, Bu₃SnH, toluene, reflux, 20 min.

The three-component condensation of isoquinoline, diethyl acetylenedicarboxylate and substituted butenone 178 led to diethyl benzo[a]quinolizine-3,4-dicarboxylate (179) in 47% yield (Scheme 55).108 However, dimethyl acetylenedicarboxylate gave a 1,3-oxazinoisoquinoline. It was suggested that the reaction included the formation of a dipolar intermediate and a conjugate addition to give benzo[a]quinolizine 179, or a direct addition to the oxazine product. No explanation or rationalization was offered about the influence of the ester group on the reaction product.

5. via Multicomponent Reactions

The Mannich reaction is very useful for the closure of ring C via the formation of the C₃-C₄ bond. Gilles and Meyers performed an enantioselective synthesis of (−)-emetine (3) from the cyclization of tetrahydroisoquinolinum salt 180. The authors started from the 1-substituted tetrahydroisoquinoline 181 with the desired (S)-configuration. The
aminomethylation of the 181 in a modification of the Mannich reaction was executed for the closure of ring C to 3-ethyl-benzoquinolizidin-2-one 182 in a moderate ee (Scheme 56).109

The chiral (S)-1-allyl tetrahydroisoquinoline 183 was prepared and the allyl substituent was catalytically transformed via alkene metathesis into the unsaturated ester 184. The aza-Michael reaction of 184 with acrolein gave the 1,2-disubstituted tetrahydroisoquinoline 185. Ring closure was carried out stereo- and enantioselectively using a second Michael reaction to the aldehyde 186, identified as a key intermediate towards (−)-emetine (3) (Scheme 57).110

Tietze et al. synthesized twelve optically active diastereomers of emetine (3) using combinatorial chemistry. Thus, (S)- and (R)-tetrahydroisoquinolines 187 were prepared enantioselectively and further transformed to give the stereoisomers of emetine.111 A representative synthetic path from (S)-187 is given in Scheme 58. Lactone 188 generated from a domino reaction (sonicated) was methanolyzed and hydrogenated to give methyl ester 189 as a mixture of three diastereomers, which were separated chromatographically (EDDA = ethylenediamine-N,N′-diacetic acid).111

In another example of multicomponent synthesis, the aza-Michael reaction was coupled with the Darzens condensation in a one-pot process to give 2,3-epoxybenzo[a]quinolizidine in high yield.112

6. via Alkene Metathesis

Ring-closing metathesis (RCM) is now a well-established process allowing the synthesis of a wide variety of cyclic systems from acyclic dienes.113 The reaction proceeds well for the formation of 5-, 6-, and 7-membered rings and proved to be a very concise approach to the benzo[a]quinolizidine ring system.
1,2-Dihydro- and 1,2,3,4-tetrahydroisoquinolines containing allylic and homoallylic groups at positions 1 and 2 were used as starting compounds for the ring closing metathesis leading to benzo[a]quinolizidines.\textsuperscript{114} The 1,2-diallyl isoquinoline derivatives of type \textsuperscript{190} were prepared and treated with Grubbs' catalyst at room temperature. The yields of \textsuperscript{191} were high, except for the cases of more basic starting compounds (Scheme 59).\textsuperscript{114}

In the total enantioselective synthesis of \textit{schulzeines}, the asymmetric allylic amination of \textsuperscript{192} was used for the enantioselective B ring closure to 1-vinyl-3,4-dihydroisoquinolines \textsuperscript{193}.\textsuperscript{115} The reaction was catalyzed by a Pd catalyst in the presence of a chiral...
ligand (diphosphonite-substituted biphenyl), to give either (S)- or (R)-193 with very high enantiomeric excess. Each enantiomer of 193 was hydrolyzed and the respective free base 194 was acylated to dienes 195. Subsequent Grubbs’ catalysts-mediated RCM was used for ring C formation. The resulting tricyclic diastereomers 196 were precursors for the synthesis of schulzeines A–C (Scheme 60; PMB = 4-methoxybenzyl ether protective group).115

7. Protoberberine Ring D Degradation

Takano et al. prepared the benzoquinolizidine core of emetine from the intermediate protoberberine 197, which was obtained via ring C formation by Pictet-Spengler reaction.116 A key step in their synthetic strategy included ring D degradation of the protoberberine skeleton of 197 (Scheme 61). Birch reduction of 197, coupled with treatment of
(i): Li, NH₃ (liq.), THF, tBuOH, 6h, 98%; (ii): NCS, CH₂Cl₂, -10 °C to rt, 10h, 63%; (iii): H₂, 10% Pd/C, MeOH, rt, 13h, 89%; (iv): pyrrolidine, C₈H₆, reflux, 2h; (v): TsS(CH₂)₃STs, Et₃N, CH₃CN, reflux, 4h, then HCl, 65% (over two steps); (vi): KOH, tBuOH, THF, 60 °C, then HCl; (vii): CH₂N₂, Et₂O, 94% (over two steps); (viii): Ra-Ni, MeOH, 20h, reflux, 92%.

Scheme 61

*N*-chlorosuccinimide (NCS), afforded the protoberberin-11-one 198 in a moderate yield. Highly *trans* stereoselective hydrogenation was achieved to give ketone 199. The thioacetal moiety was introduced via intermediate enamine formation to 200. Ring D was opened by alkaline treatment and the resultant benzoquinolizidine thioacetal 201 was reduced using Raney-nickel to afford 202 as a precursor of emetine (3) (Scheme 61). Despite the high yields, all the intermediate products were obtained as mixtures of diastereomers and the necessary isomers were isolated by means of column chromatography.

8. *Synthesis of 8-Azasteroids*

The cyclocondensation of 3,4-dihydroisoquinolines 203 with various 2-acyl-1,3-cycloalkanediones was studied by Mikhal’chuk *et al.* and it has been shown that it gives 8-azasteroid products 204-205, which incorporate an annulated benzo[a]quinolizidine ring system. Depending on the structure of the starting cyclic 2-acylcycloalkanedione, different 8-azagonanediones were prepared (Scheme 62). The authors showed that ring D could not be smaller than 5-membered ring. The products
possess both steroid and alkaloid *isosteric* fragments and are structurally similar to bioregulators of animal and plant origin. Compounds 204 (X = CH₂CH₂) showed immunomodulation activity.¹¹⁷–¹²⁰

![Diagram of chemical structures](image)

(i): AcOH, reflux, 9h, 75.6-78.5%.

Scheme 62

9. Radical Cyclization

Ishibashi *et al.* investigated the radical cyclization of *(E)*- and *(Z)*-N-vinylarylacetamides 206 by means of Bu$_3$SnH, which gave the diastereomeric benzoquinolizidines (2S)- and (2R)-207 under the action of different radical initiators.¹²¹ It was shown that *(Z)*-206 reacted more readily under the different conditions used. The best yield with excellent diastereoselectivity in favor of *(S)*-207 was obtained when Et$_3$B was used as an initiator at −78°C. The authors suggested that tetrahydroisoquinoline 208 was an intermediate product and the Z-configuration allowed it to adopt a less hindered conformation during the formation of ring C with S-configuration at C₂ (Scheme 63).

![Diagram of chemical structures](image)

(i): Bu$_3$SnH, Et$_3$B, toluene, -78°C, 46%, S/R = 37/1.

Scheme 63

**Conclusion**

There has been a continuing interest in the synthesis of benzo[a]quinolizidines over the years due to their occurrence in many alkaloids and drugs. The present review has
highlighted numerous reports in the literature to summarize the construction and transformations of the benzo[a]quinolizidine ring system as part of notable total synthesis of alkaloids and pharmaceutically active products, from 1990 up to the end of 2015. This review illustrates a great variety of methods used for the preparation of benzo[a]quinolizidines. Reactions such as the Bischler-Napieralski and Pictet-Spengler reactions, aza-annulations between dihydroisoquinolines and electron-deficient alkenes, ring-closing metathesis, aminolysis of carboxylic acid derivatives or other multi-component processes have proved to be very fruitful. A growing number of synthetic approaches have used chiral reagents to improve the stereochemical outcome of some of these reactions.

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