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SURVEY OF CHEMICAL SYNTHESES OF THE PYRROLIZIDINE ALKALOIDS TURNEFORCIDINE AND PLATYNECINE†

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Abstract - The necine bases turneforcidine and platynecine have inspired a great deal of synthetic effort. Key challenges include the construction of the bicyclic pyrrolizidine ring system and controlled introduction of three contiguous stereocenters. This review will survey the many diverse strategies by which these natural products have been synthesized.

Pyrrolizidines[1] are a class of alkaloids found in various plant families (Figure 1).[2] A number of polyhydroxylated pyrrolizidines are potent inhibitors of glucosidase I[3] and also have been found in an unidentified African plant that has been beneficial in treating AIDS patients.[4] Additionally, many pyrrolizine imides have displayed amnesia-reversal activity.[5] In general, pyrrolizidine alkaloids represent diverse groups of natural products displaying a broad range of biological activity.[6,7]

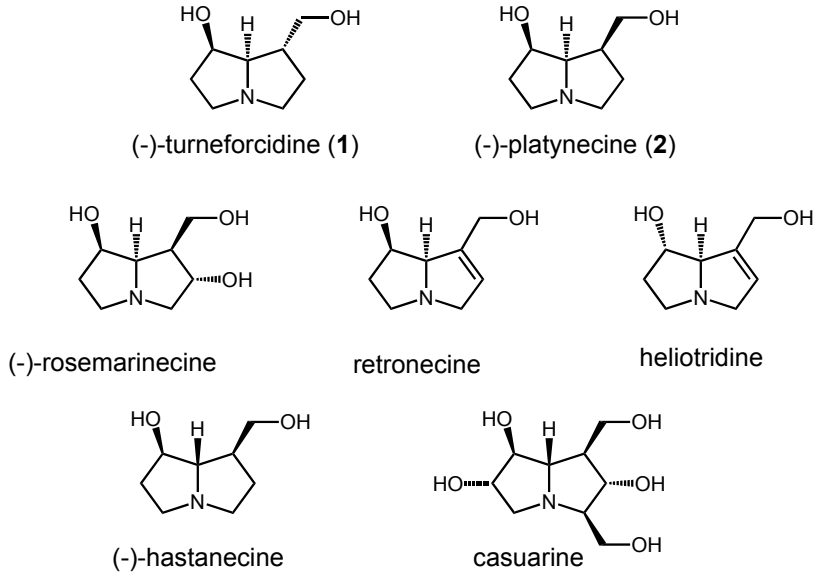


Figure 1. Representative pyrrolizidine alkaloids.

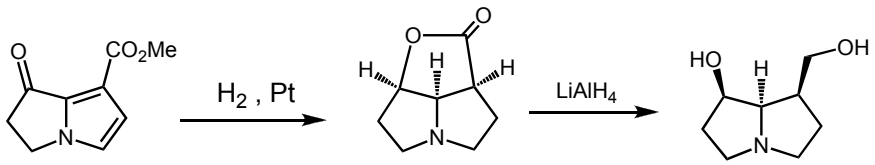
† *This article is dedicated to Professor Ekkehard Winterfeldt in recognition of his many important contributions to the field of heterocyclic chemistry.*

The pyrrolizidines have been targets of synthetic studies for many decades now.[8,9] Their bicyclic core makes these molecules deceptively simple in nature. These small bicyclic ring systems typically include several contiguous stereocenters, which when coupled with their biological relevance, makes them attractive targets for the synthetic chemist. These factors have led to many elegant approaches towards their total synthesis.

The sheer number of different pyrrolizidine natural products has resulted in total syntheses too numerous to be comprehensively covered in this review. Our intent is tocover the syntheses of two epimeric diol pyrrolizidine natural products, turneforcidine (**1**) and platynecine (**2**), in order to demonstrate the many different and unique approaches used in synthesizing these natural products. This will help to educate the reader on how the pyrrolizidines have provided the synthetic chemist with a fertile base to test new synthetic strategies in the synthesis of these small, yet challenging natural products. In order to simplify the writing of this review, the syntheses will appear, for the most part, in a chronological order.

Many pyrrolizidine alkaloids, though isolated in the early part of the twentieth century, did not succumb to total synthesis until many years later. This is the case with the necine base platynecine, whose first synthetic effort was published by Visconti and Buzek in 1972 (Scheme 1).[10] Their synthesis relied on the simple manipulation of bicyclic pyrrole **3** via hydrogenation of the heteroaromatic ring with concomitant chemoselective reduction of the ketone. The resulting lactone **4** was subjected to excess lithium aluminum hydride to give the desired (±)-platynecine in good overall yield. Thus began the efforts towards the synthesis of platynecine and turneforcidine.

Scheme 1

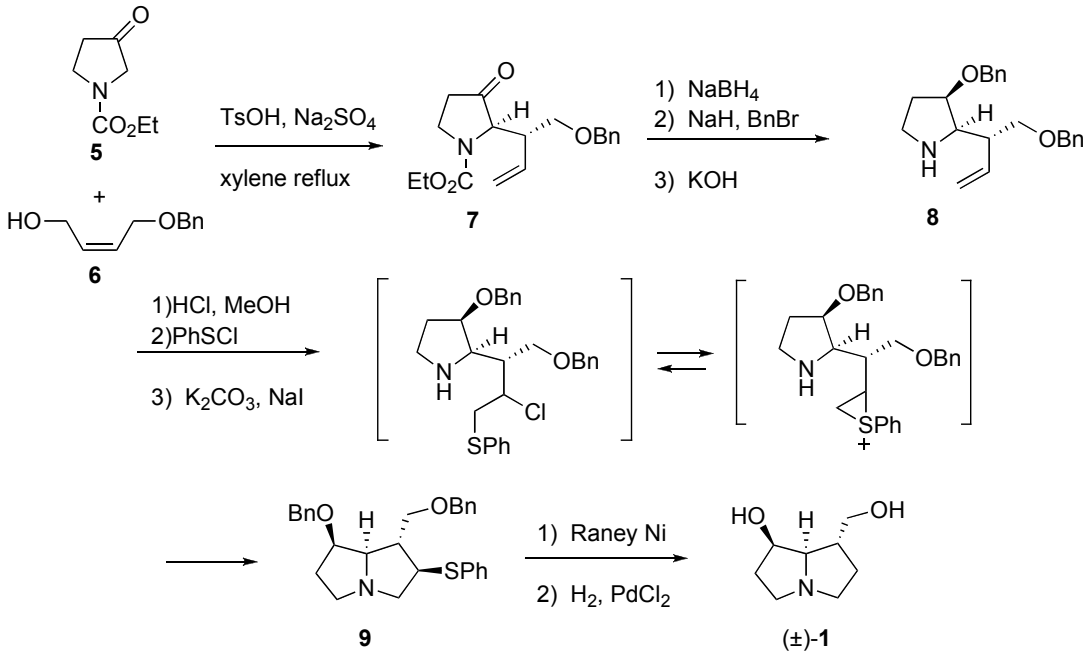


3 **4** (±)-**2**

Ohsawa and Kametani[11] provided an interesting entry into the pyrrolizidines utilizing a sulfenocycloamination reaction en route to synthesizing (±)-turneforcidine (Scheme 2). As was the case with platynecine, turneforcidine had been without a synthesis since its isolation[12] in 1952 and this report marked its first chemical synthesis. Their route began with treatment of pyrrolidinone **5** in xylene and catalytic *p*-toluenesulfonic acid with monoprotected *cis*-butenediol derivative **6** to provide pyrrolidinone **7** by way of a Claisen rearrangement. The regio- and stereoselective reaction is explained through a chairlike transition state. Pyrrolidinone **7** was next converted to **8** by reduction with sodium borohydride, subsequent benzyl ether formation, and finally carbamate removal by treatment with potassium hydroxide.

The authors noted that the borohydride reduction provided a 7:1 mixture favoring the desired diastereomer in this three step sequence.

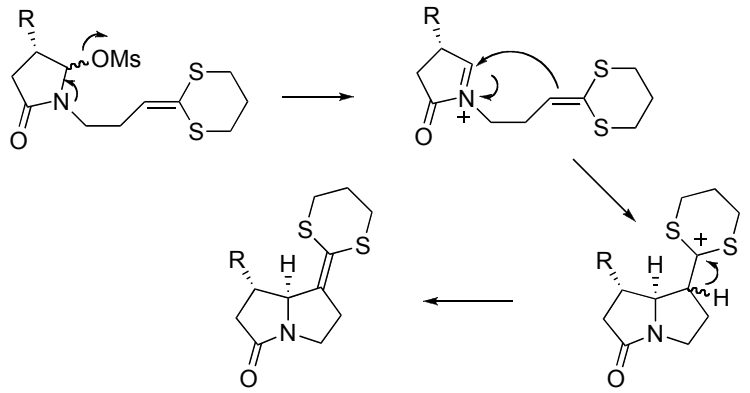
Scheme 2



With pyrrolidine **8** in hand, the authors then induced the key sulfenocycloamination reaction by subjecting **8** to benzenesulfenyl chloride followed by potassium carbonate and sodium iodide to give the desired sulfide **9** as a single isomer in 72% yield. At this point two simple synthetic transformations, reductive removal of the sulfur group followed by debenzylation, were all that was needed to complete the first synthesis of (±)-turneforcidine.

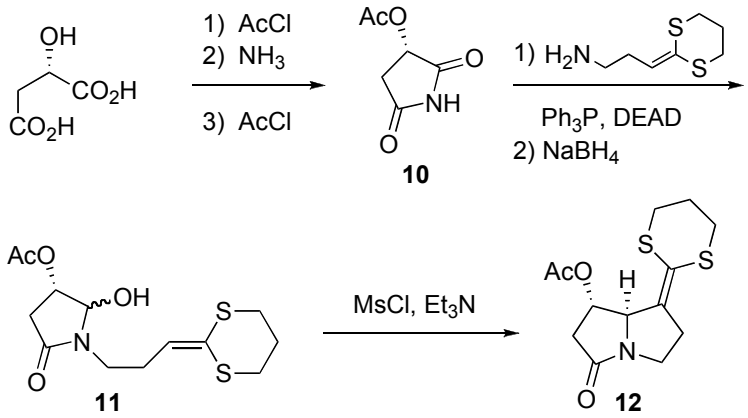
Chamberlin and Chung were able to utilize a key, readily available intermediate in their synthesis of seven different pyrrolizidine diols including (±)-turneforcidine and (±)-platynecine.[13] Their strategy focused on the use of an optically active alcohol group as the control element in an acyliminium ion cyclization utilizing a novel ketene dithioacetal group as the cationic cyclization terminator (Scheme 3).

Scheme 3



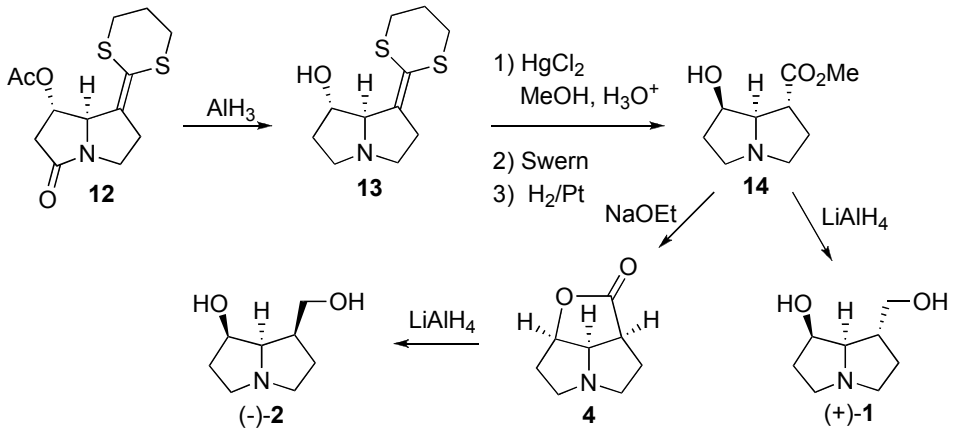
Application of this general strategy is summarized in Scheme 4. Commencing with (*S*)-malic acid,[14] sequential treatment with acetyl chloride, gaseous ammonia, and acetyl chloride again provided succinimide **10**. Mitsunobu coupling using 2-(3-hydroxypropylidene)-1,3-dithiane was followed by reduction with sodium borohydride to provide the pivotal aminal **11**. It is interesting to note that although succinimides are typically sensitive to overreduction by borohydride, the conditions employed by the authors provided clean conversion to a white solid consisting of an 11:1 mixture of diastereomers in excellent yield. Separation of the diastereomers was unnecessary and consequently, treatment of **11** with MsCl and triethylamine in dichloromethane permitted smooth conversion to the desired bicycle **12** in 68% yield with only trace amounts (3%) of the minor diastereomer via the mechanism in Scheme 3.

Scheme 4



With **12** in hand, reduction with AlH_3 provided pyrrolizidine **13** which is the common precursor used in the synthesis of both (–)-platynecine and (+)-turneforcidine (Scheme 5). Conversion of the dithioacetal to the methyl ester, Swern oxidation, and chemoselective reduction of the resulting ketone in the presence of the ester functionality provided the desired alcohol **14** without any racemization at the bridgehead stereocenter (a problem that occurred when oxidation conditions were employed prior to removal of the

Scheme 5

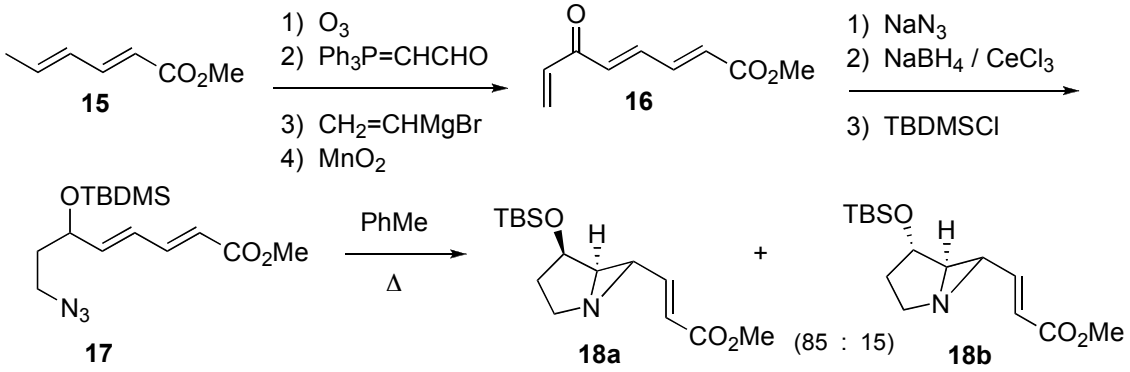


dithioacetal). Reduction of **14** with lithium aluminum hydride provided (+)-turneforcidine or treatment with sodium ethoxide produced the lactone **4**, which can subsequently be treated with $LiAlH_4$ to provide access to (–)-platynecine.

As is apparent in the previous work of Chamberlin and Chung, it is often possible to access multiple pyrrolizidine alkaloid from a single common precursor. Hudlicky and co-workers took full advantage of this fact in their formal syntheses of (±)-turneforcidine and (±)-platynecine.[15] Their approach focused on using an intramolecular [4+1] pyrroline annulation reaction via azide-diene cycloadditions as their key transformation en route to synthesizing the pyrrolizidine ring system.

Beginning with unsaturated ester **15**, a four step sequence of ozonolysis, Wittig reaction, Grignard addition, and MnO_2 oxidation provided the desired unsaturated ketone **16** in a modest yield of 16% (Scheme 6). The lowest yielding step proved to be the MnO_2 oxidation in this sequence. With the desired ketone in hand, the authors then proceeded by Michael addition of sodium azide in acetic acid followed by reduction with sodium borohydride under Luche conditions. Protection of the alcohol as the TBDMS ether gave azide **17** ready to undergo their azide-diene cycloaddition reaction. Treatment of **17** in toluene at reflux provided cycloaddition adduct vinyl aziridine products **18a** and **18b** as a 85:15 mixture of diastereomers which were separated.

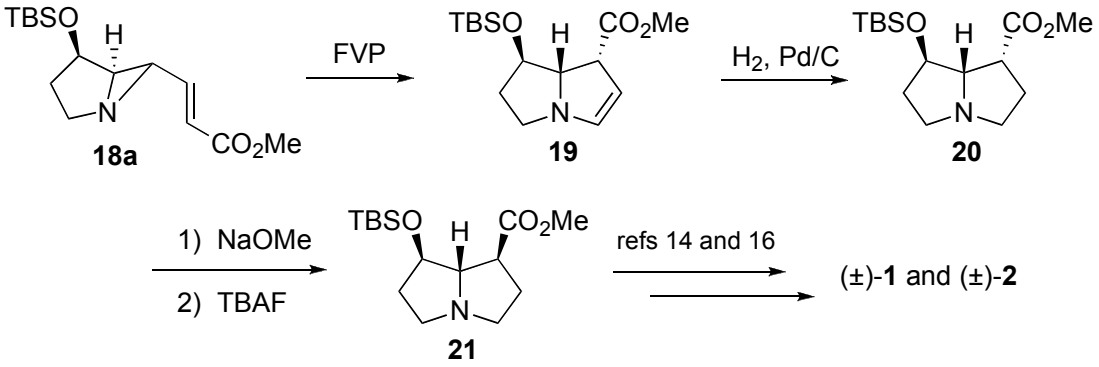
Scheme 6



The major diastereomer **18a** was then treated under flash vacuum pyrolysis conditions to provide the pyrrolizidine **19** (Scheme 7). Due to the instability of this compound, it was immediately subjected to reduction conditions (H_2 30psi, Pd/C) to provide the ester **20**. At this point two simple transformations, epimerization and removal of the silyl group using TBAF, were required to arrive at **21**, which had previously been converted to **1** and **2**.[14,16]

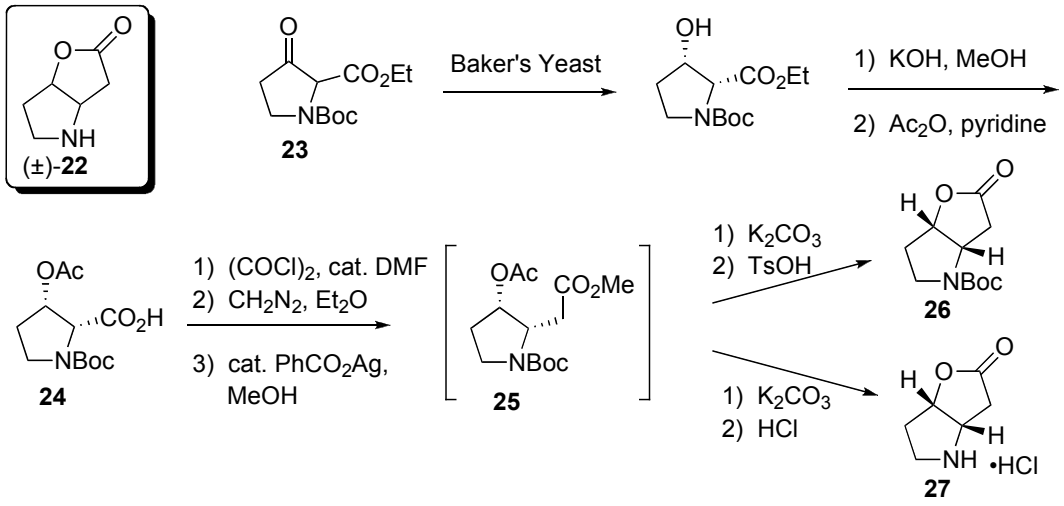
Geissman and Waiss had used lactone **22** (formally known as the Geissman-Waiss lactone) many years earlier in their syntheses of the necine base retronecine.[17] This intermediate was quickly realized as having potential to access many other necine bases and has since then been seen in synthesis many times.

Scheme 7



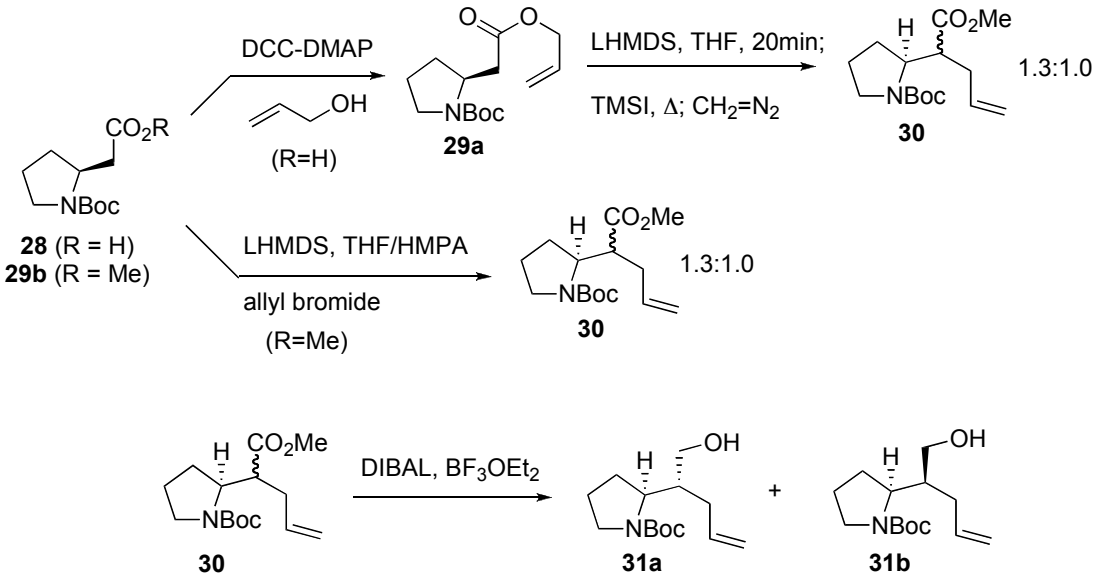
However, access to the optically active lactone through a variety of methods[18,19] has required rather lengthy syntheses. Knight and co-workers realized that an expedient synthesis of this intermediate would allow for efficient syntheses of a variety of optically active necine bases.[20] They reasoned that access to *cis*-3-hydroxyproline could be available in optically active form by reduction of the corresponding racemic ketoproline derivative **23** (Scheme 8), which is available in large quantity via various Dieckmann condensations.[21] To this end, treatment of **23** with Baker's yeast, sucrose, and water provided the desired 3-hydroxyproline as a single diastereomer (80% ee) in 75% isolated yield. Base hydrolysis followed by treatment with acetic anhydride provided the corresponding acetate **24**. Homologation under Arndt-Eistert conditions gave the ester **25** which was subsequently treated with potassium carbonate in methanol and then with acid to provide the protected or unprotected lactones **26** and **27**, respectively, the later being the (–)-enantiomer of the Geissman-Waiss lactone. This then represented a formal synthesis of the unnatural enantiomer of platynecine. The authors were also quick to note that this strategy provides one of the simplest routes to date to enantioenriched 3-hydroxyproline derivatives as at the time none of the four enantiomers of this amino acid was readily available.

Scheme 8



Recognizing the potential of proline-based molecules to gain access to many different necine bases, Knight and co-workers continued their studies with the synthesis turneforcidine beginning with (*S*)-*N*-Boc-homoproline **28** (Scheme 9).[22] Treatment with DCC/DMAP followed by addition of allyl alcohol provided the allyl ester **29a**, which was subsequently treated with base and TMSI to provide **30** via Claisen rearrangement. They also arrived at the same compound by subjecting the methyl ester **29b** to base and allyl bromide. However, in each approach, they were disappointed by the nearly total lack of stereoselectivity, obtaining at best a 1.3:1.0 mixture of difficult to separate diastereomers. Reduction of the mixture with DIBAL did provide readily separable alcohols **31a** and **31b**, which were subsequently converted to the necine bases (–)-trachelanamidine and (–)-isotretronecanol, respectively.

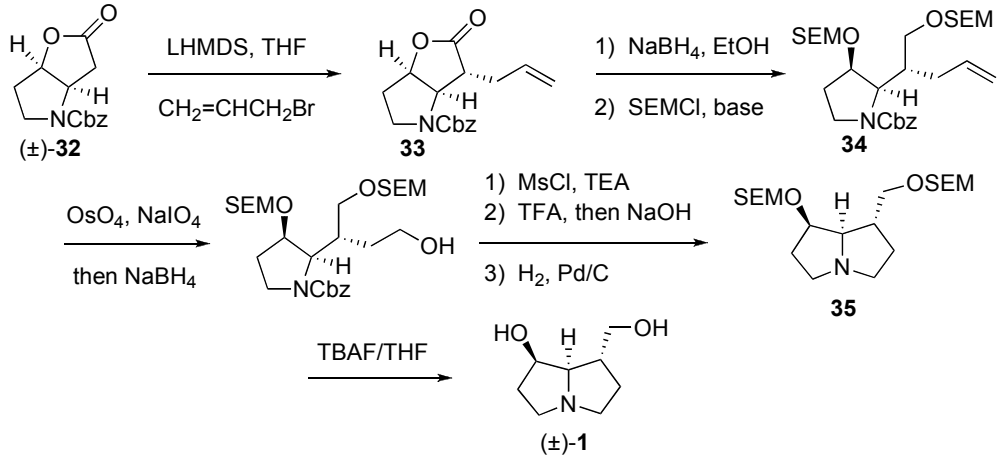
Scheme 9



The lack of stereoselectivity in this sequence however, led them to reconsider their approach to turneforcidine. Ultimately, they chose to begin their synthesis with the readily available racemic Geissman-Waiss lactone derivative **32** (Scheme10). Treatment with LHMDS and allyl bromide gave **33** in high diastereoselectivity, with the expected allylation from the convex face. Reduction to the diol was followed by bis SEM ether formation to give **34**. Johnson-Lemieux cleavage of the diol gave the aldehyde, which was reduced with sodium borohydride to give alcohol **34**. Cyclization via the mesylate furnished bis-SEM protected turneforcidine **35**, and treatment with TBAF in THF gave rise to (±)-**1**.

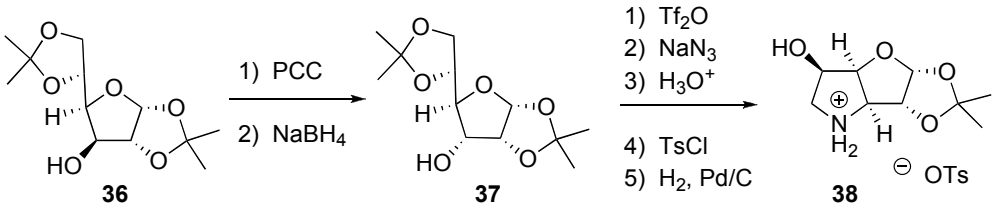
Many of the necine base natural products contain substantial oxygen functionality around the bicyclic core. Accessing these heavily oxygenated compounds in an efficient manner is always a concern when taking on a synthetic endeavor towards the necine bases. Fleet and co-workers recognized the potential of sugars as readily available starting materials to access many different necine bases.[23] Following literature precedents,[24] their synthesis began with diacetone glucose **36** (Scheme 11), which was oxidized

Scheme 10



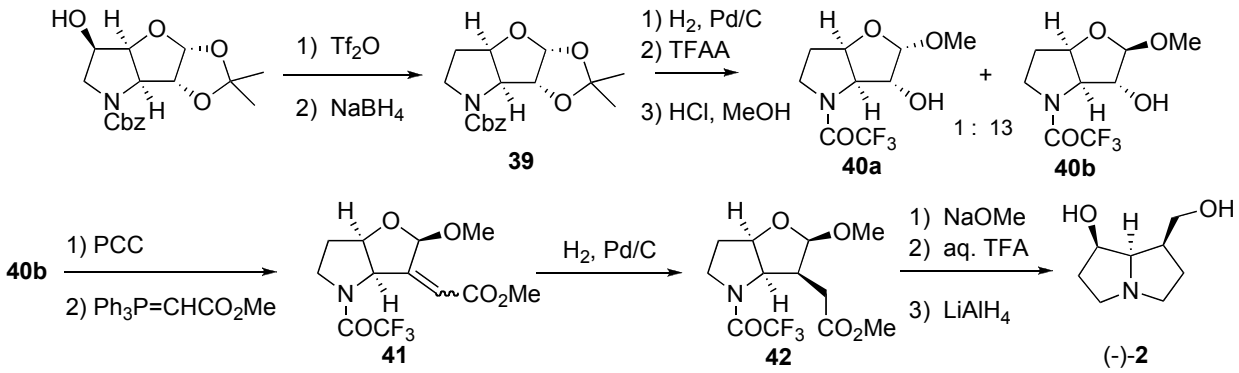
with PCC followed by reduction with $NaBH_4$ to effect inversion and give diacetone allose **37**. Treatment with triflic anhydride followed by sodium azide accomplished a second inversion and introduced latent amine functionality. Mild acid hydrolysis and subsequent reaction with TsCl gave the primary tosylate, and hydrogenation led to pyrrolidiene **38** as the tosylate salt. At this point the authors had generated their key intermediate in their approach towards platynecine.

Scheme 11



Reaction of the Cbz-protected derivative of **38** with triflic anhydride resulted in sulfonylation of both the secondary alcohol (Scheme 12). Deoxygenation using sodium borohydride then furnished **39** in good yield. The Cbz group was then exchanged for a trifluoroacetamide, and methanolysis of the acetonide gave a 1:13 mixture of methyl furanosides **40a** and **40b**, leaving only the C-3 hydroxyl now free for

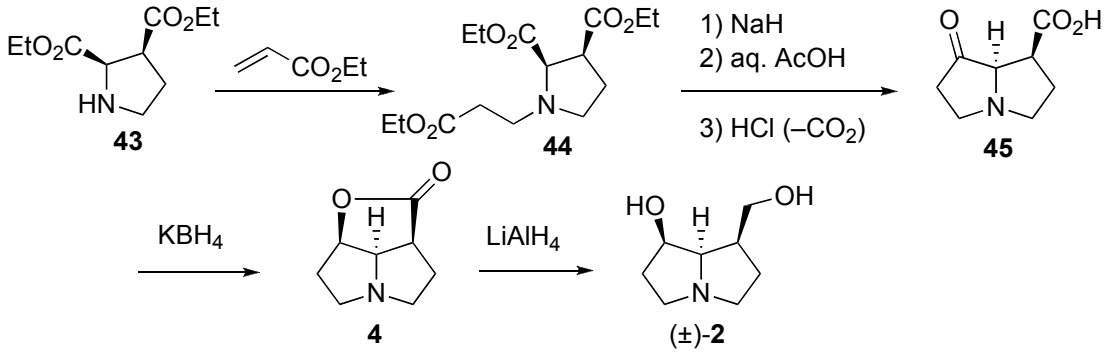
Scheme 12



manipulation. Oxidation of **40b** using PCC was followed by Wittig olefination to give **41** as a mixture of unsaturated esters. Hydrogenation at this point provided ester **42**, though in order to avoid unwanted reduction at the anomeric center, EtOAc had to be employed as the solvent. Under these conditions, **42** was obtained in quantitative yield as a single diastereomer. Treatment of **42** with sodium methoxide afforded the desired lactam by first removal of the acetamide group followed by cyclization onto the ester. This compound was then hydrolyzed with aqueous TFA, and the resulting lactol was reduced (with concomitant reduction of the lactam) using $LiAlH_4$ to afford (–)-platynecine in 20% overall yield from the starting Cbz derivative.

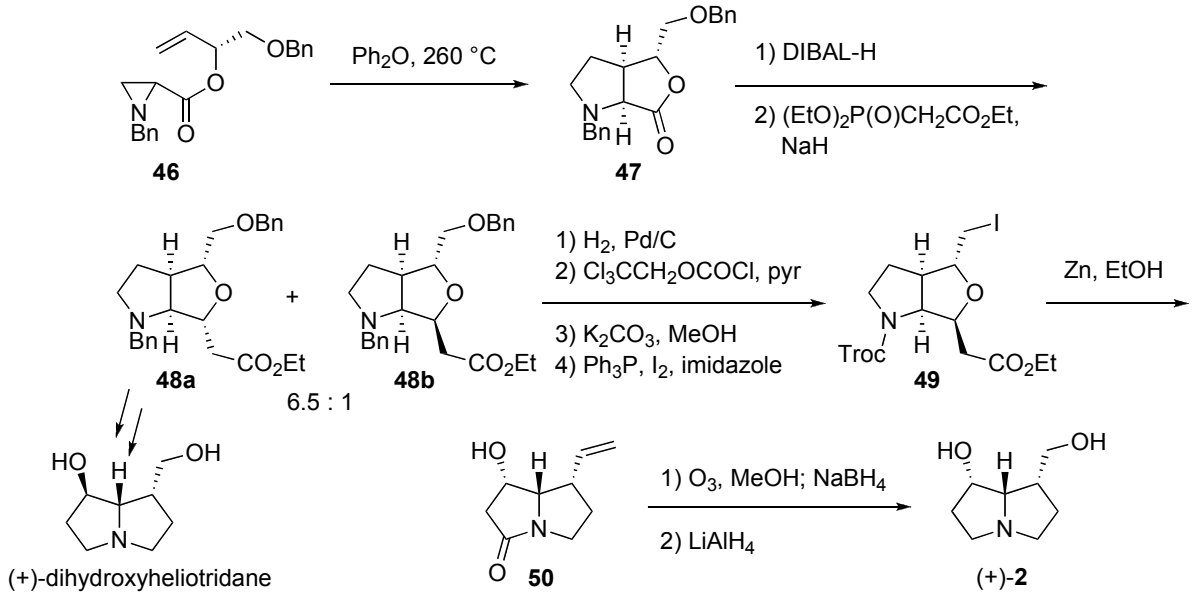
Röder and coworkers reported a short synthesis of (±)-platynecine in 1990 (Scheme 13).[25] Starting with the readily available diethyl ester **43** of *cis*-3-carboxyproline,[26] they carried out a Michael addition to ethyl acrylate, and subjected the resulting triester **44** to Dieckmann cyclization. The intermediate adduct was subjected to saponification with concomitant decarboxylation to furnish ketoacid **45**. Diastereoselective reduction then gave the known lactone **4**, which could be converted to (±)-**2** with $LiAlH_4$.

Scheme 13



A synthesis of (–)-platynecine based upon intramolecular 1,3-dipolar cycloaddition of azomethine ylides was reported by Ogasawara and coworkers.[27] The primary objective of this study was the enantioselective synthesis of the diastereomeric pyrrolizidine alkaloid dihydroxyheliotridane (Scheme 14). Aziridinecarboxylate allyl ester **46** (derived from glycidol) was heated at 260 °C for a short time to yield lactone-fused pyrrolidine **47**. Half-reduction followed by HWE olefination furnished epimeric tetrahydrofurans **48a** and **48b**. The minor isomer, **48b**, could be subjected to protecting group exchange and conversion of the primary alcohol to iodide, giving key intermediate **49**. Treatment with Zn then effected reductive elimination of the iodolactone, with simultaneous deprotection of the pyrrolidine nitrogen. In situ lactamization then furnished pyrrolizidine **50**, which could be converted to (+)-**2** in two steps. Application of the same sequence to the major diastereomer **48a** allowed for the preparation of (+)-dihydroxyheliotridane.

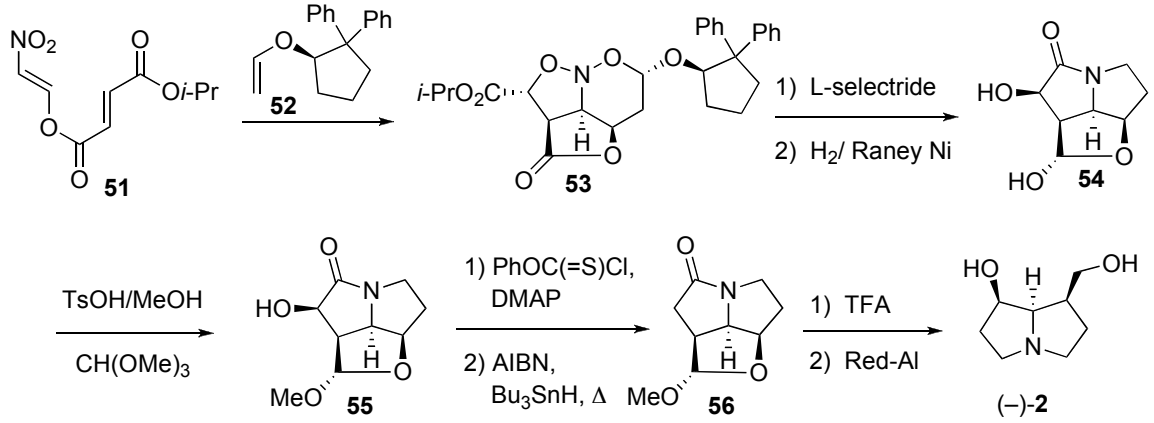
Scheme 14



Denmark and co-workers also described an interesting cycloaddition-based approach to pyrrolizidine natural products, taking advantage of the ability of nitroalkenes to function as 4π components in cycloaddition reactions.[28] They envisioned a tandem [4+2]/[3+2] cycloaddition to rapidly access the pyrrolizidine ring system in enantioselective fashion. This work was the continuation of a previous publication in which they were able to synthesize three other pyrrolizidines.[29]

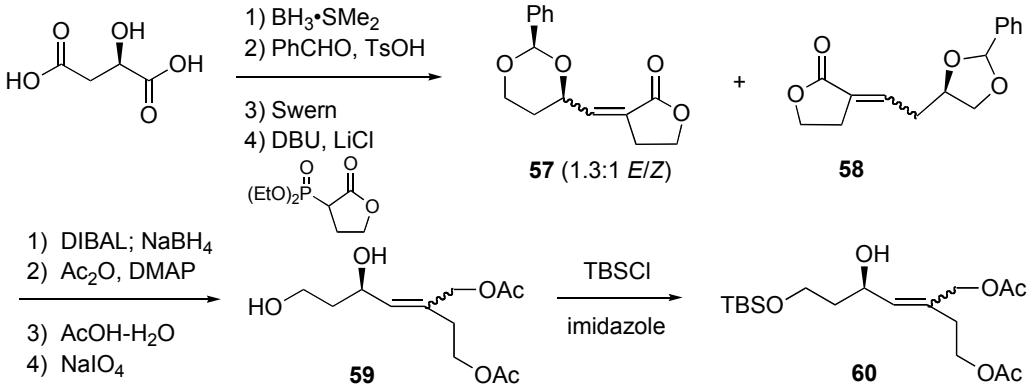
Beginning with nitroalkene **51**, intermolecular cycloaddition with enol ether **52** followed by an intramolecular [3+2] cycloaddition furnished the tricyclic adduct **53** (Scheme 15). Reduction with L-selectride and subsequent hydrogenolytic conditions provided the desired lactol **54** in good overall yield. The lactol was then selectively converted to the methyl acetal **55**, and Barton-McCombie deoxygenation was accomplished in two steps to provide **56**. Deprotection of the methyl acetal using TFA afforded a 10:1 mixture of anomeric lactols which were treated with Red-Al in THF at reflux to afford the desired (–)-**2** in 74% yield after purification.

Scheme 15



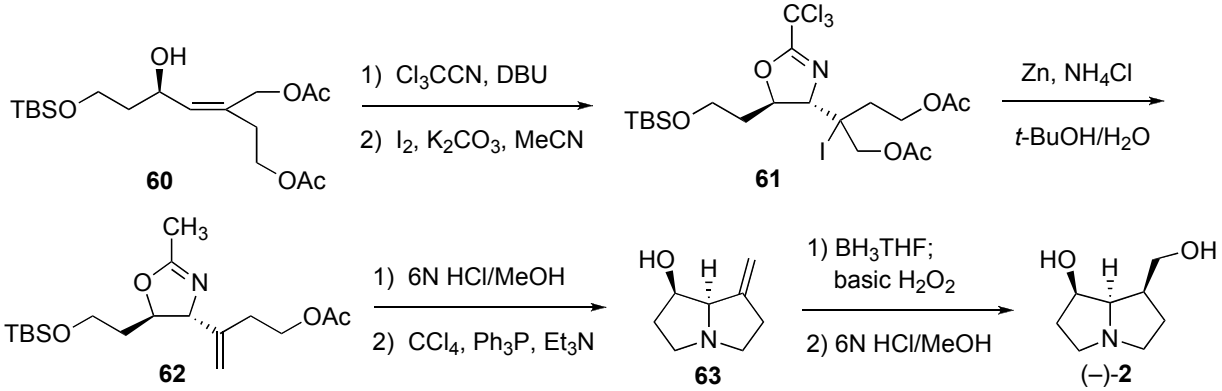
Roughly contemporary with Denmark's work, another synthesis of (–)-platynecine was also published by Kang and co-workers.[30] They chose to begin their synthesis with D-malic acid as a simple, inexpensive chiral starting material (Scheme 16). The diacid could easily be converted to an inseparable mixture of benzylidenes, which were oxidized (Swern) and olefinated to provide the conjugated lactones **57** as a 1.3:1.0 *E*/*Z* mixture, along with lactones **58** formed from the 5-membered benzylidene, in a combined 90% yield. The entire mixture was then reduced with DIBAL followed by sodium borohydride after which the primary hydroxyl groups were acetylated and the benzylidene groups hydrolyzed in aqueous acetic acid to provide a mixture of 1,3- and 1,2-diols. In order to effect facile purification at this point, the mixture of 1,3- and 1,2-diols was treated with sodium periodate, resulting in selective consumption of the 1,2- diol, and allowing for easy separation to give the desired 1,3-diols **59**. Subsequent silylation occurred with complete regioselectivity for the primary alcohol, giving silyl ethers **60**.

Scheme 16



Silyl ethers **60** were then converted to the *trans*-oxazolines **61** by treatment with trichloroacetonitrile and DBU followed by cyclization with iodine and potassium carbonate (Scheme 17). Reaction of **61** with zinc in the presence of ammonium chloride in aqueous *t*-butanol to effect reductive elimination of the β-iodo acetate group as well as concomitant reduction of the trichloromethyl group to the resulting methyl group providing a single *trans*-oxazoline **62**. Global deprotection using methanolic HCl was followed by double cyclization of the resultant amino diol, accomplished using carbon tetrachloride and **Scheme 17**

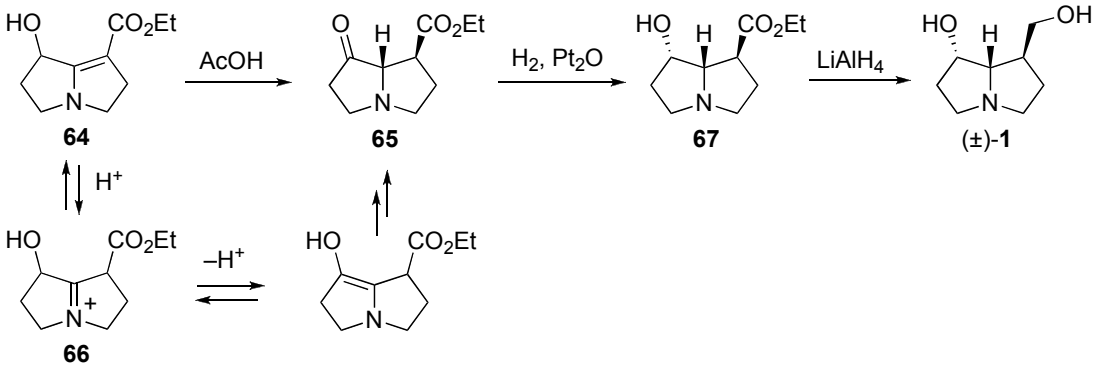
Scheme 17



triphenylphosphine in the presence of TEA to give pyrrolizidine **63**. Hydroboration and subsequent oxidation with basic peroxide gave the platynecine-borane complex, which was treated with methanolic HCl once again to effect decomplexation and provide the desired (–)-**2**. The key intermediate **63** could also be dihydroxylated to form the pyrrolizidine triol (–)-hadinecine.

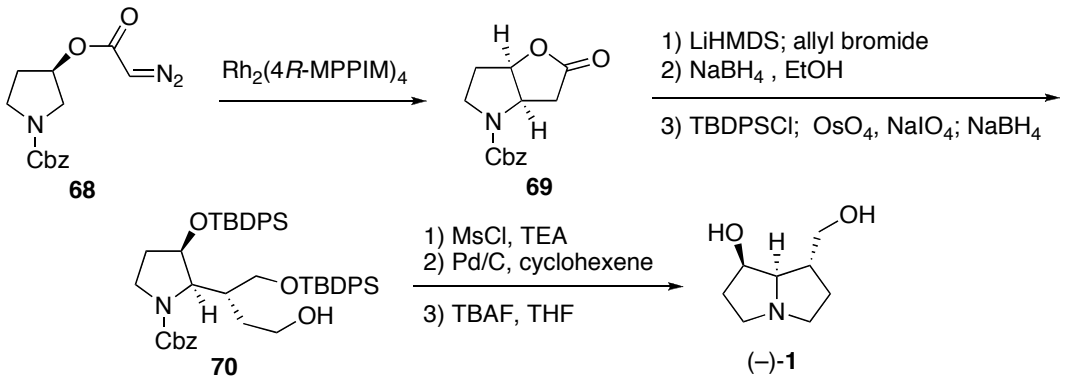
Also in 1997, Niwa and coworkers reported a concise synthesis of (±)-turneforcidine (Scheme 18).[31] The key starting material was unsaturated pyrrolizidine **59**, which had previously been used in the prepartion of (±)-retronecine.[32] Treatment of **59** with acetic acid resulted in its tautomerization to ketoester **60**. The authors suggest that this process occurs via protonation of the vinylogous carbamate, followed by rearrangement of the resulting iminium salt **61** via a series of proton-transfer steps. With **60** in hand, the ketone was reduced diastereoselectively under hydrogenation conditions to give hydroxyester **62**, analogous to ester **14** (see Scheme 5). Reduction of the ester with $LiAlH_4$ then produced (±)-**1**.

Scheme 18



An interesting approach to (–)-turneforcidine by Wee[33] relied on the intramolecular regio- and diastereoselective C-H insertion reaction of diazoacetate **68** (Scheme 19). Beginning with enantiomerically pure **68**, reaction with Rh_2(4*R*-MPPIM)$_4$ (MPPIM = methyl (4*R*/4*S*)-1-(3-phenylpropanoyl)-2-oxoimidazolidine-4-carboxylate) provided homochiral Geissman-Waiss lactone **69** (analogous to the previously described (±)-**32**) in good yield as the sole regio- and stereoisomer. Alkylation of **69** with allyl bromide, in analogy to Knight's route, was followed by reduction with $NaBH_4$

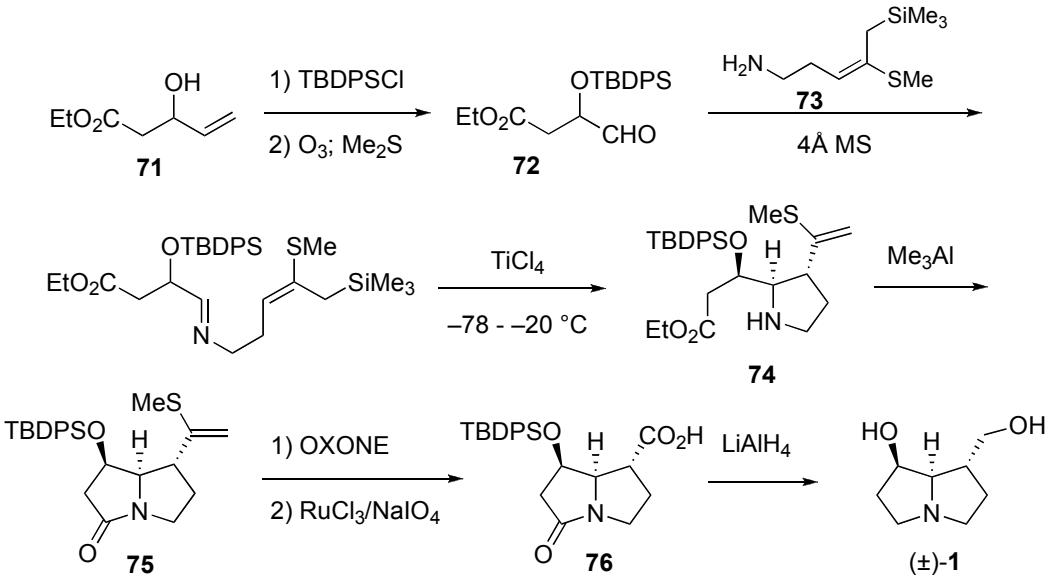
Scheme 19



to provide a diol. Silylation of the resulting diol and oxidative cleavage of the double bond was followed by treatment with $NaBH_4$ to provide the alcohol **70** in good overall yield. Mesylation, reductive removal of the Cbz group with concomitant cyclization to the bicyclic ring system, and silyl deprotection provided enantiomerically pure (–)-**1**.

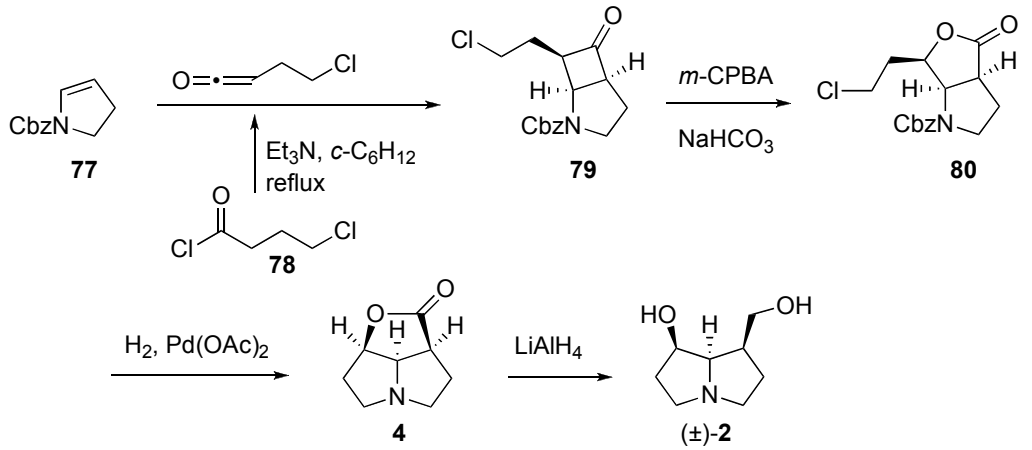
Livinghouse and co-workers provided an efficient approach to turneforcidine relying on a metalloiminium ion cyclization as their key transformation (Scheme 20).[34] The synthesis began from readily available 3-hydroxyester **71**,[35] which was silylated and oxidatively cleaved to provide aldehyde **72**. Formation of the cylization precursor was accomplished by treating **72** with amine **73**[36] in the presence of molecular sieves to give the desired imine in quantitative yield. This imine was immediately treated with $TiCl_4$ to furnish the mono-cyclized product **74** and not the anticipated bicyclic lactam **75**. However, subsequent treatment of pyrrolidine **74** with trimethyl aluminum did provide the desired pyrrolizidone **75** in excellent yield. The authors intent was to then effect direct conversion of the vinyl sulfide to the desired acid. However a wide variety of conditions failed to give the acid, and a two step approach was initiated by first oxidation to the sulfone (OXONE) and then treatment with RuO_4 gave acid **76** in good yield. At this point a global reduction using $LiAlH_4$ then provided access to (±)-**1**.

Scheme 20



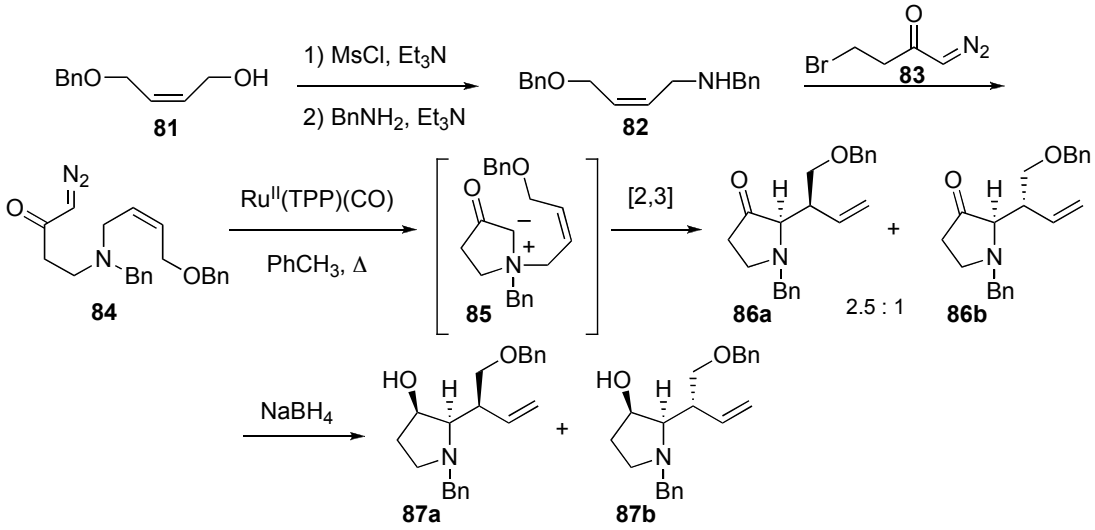
An interesting approach from the labs of Correia[37] centered on the [2+2] cycloaddition of enecarbamates and alkyl ketenes as the key reaction. Their synthesis commenced with reaction of enecarbamate **77** and acid chloride **78** in hexanes at reflux (Scheme 21). Via *in situ* generation of the ketene from **78**, *endo*-azabicyclic cyclobutanone **79** was produced in 72% yield. Baeyer-Villiger oxidation gave lactone **80**, and hydrogenolysis of the Cbz group led to smooth cyclization to tricyclic intermediate **4**. Reduction with $LiAlH_4$ provided the natural product platynecine in four steps and 43% yield from enecarbamate **77**.

Scheme 21



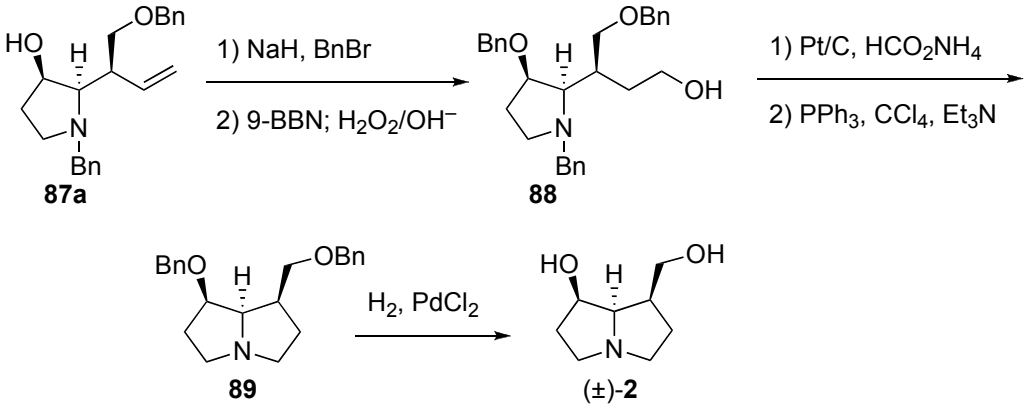
A recent approach towards platynecine comes from the labs of Yu and Che, utilizing a tandem ammonium ylide formation/[2,3]-sigmatropic rearrangement (Scheme 22).[38] Their synthesis began with mesylation of the alkene **81**, followed by nucleophilic substitution with benzylamine to give **82** in good yield. Reaction of the amine with bromodiazoketone **83** gave tertiary amine **84.** Treatment of the diazo ketone with 1 mol % [Ru^{II}(TTP)(CO)] in toluene provided an inseparable mixture of *syn*- and *anti*-pyrrolidones **86a**,**b** (2.5:1 *syn*/*anti*). This process occurred via cyclic ammonium ylide **85**, and it is notable that none of the competing benzyl [1,2]-shift was seen. Stereoselective reduction of the mixture using sodium borohydride gave alcohols **87a**,**b**, and the major *syn* product (**87a**) could be separated and carried on.

Scheme 22



Protection of **87a** as the benzyl ether was followed by hydroboration with 9-BBN to give primary alcohol **88** (Scheme 23). Catalytic transfer hydrogenation (ammonium formate) allowed selective *N*-deprotection to give the secondary amine, which underwent intramolecular alkylation via an *in situ*-generated chloride to give pyrrolizidine **89**. Global debenzylation then gave racemic platynecine in excellent isolated yield.

Scheme 23

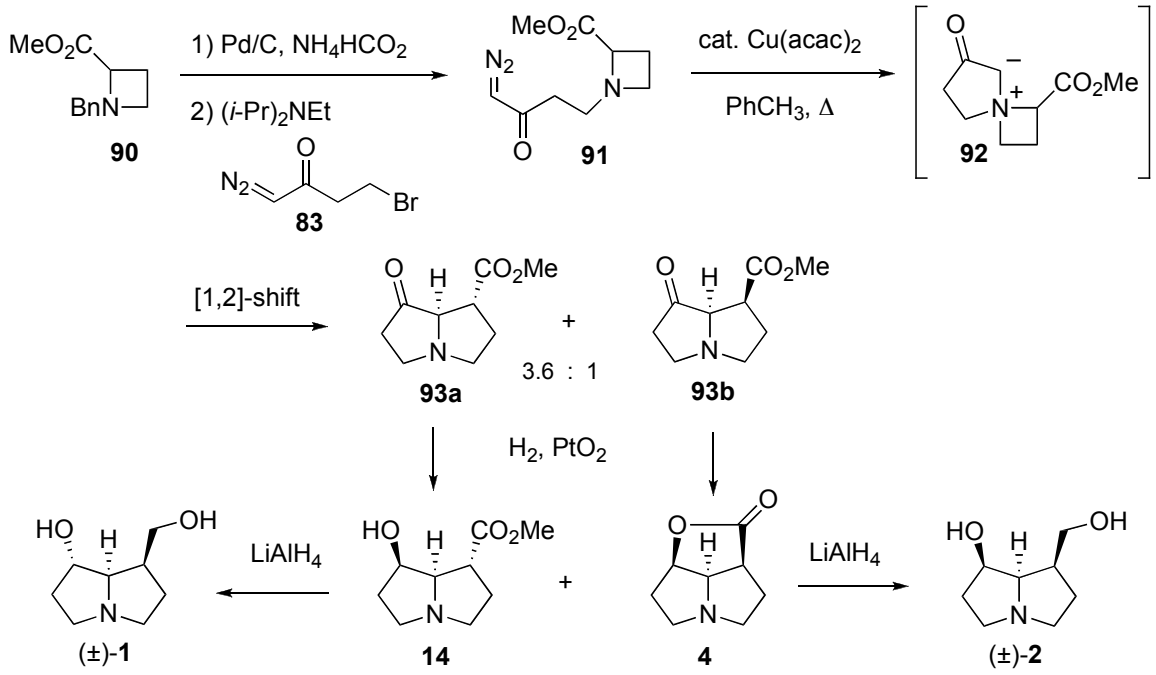


Another recent approach to pyrrolizidines utilizing ammonium ylide chemistry was described by Vanecko and West.[39] They incorporated an azetidine ring expansion strategy via Stevens [1,2]-shift to rapidly access the pyrrolizidine ring system. This methodology was an extension of earlier work from the same group used in the synthesis of the quinolizidine alkaloid epilupinine.[40] The synthesis of the pyrrolizidine natural products began with reductive debenzylation of azetidine **90** under transfer hydrogenation conditions (Pd/C, ammonium formate)[41] to give the free azetidine (Scheme 24). Due to its volatility, the resulting azetidine was immediately carried on to the next step by coupling with diazo compound **83** to provide substrate **91** in excellent yield (96%) over the two steps. Rearrangement of diazoketone **91** could be effected with a number of transition metal catalysts, of which $Cu(acac)_2$ and $Rh_2(OAc)_4$ provided the best results with yields of 82% and 81% respectively. The intermediate spirocyclic ammonium ylide **92** underwent ring expansion by [1,2]-shift of the ester-substituted carbon in preference to either of the unsubstituted methylene carbons. The ratio of diastereomeric pyrrolizidines **93a**,**b** obtained was independent of catalyst or reaction conditions, consistently providing a 3.6:1 ratio in favor of **93a**. Attempts at equilibration according to a literature protocol utilizing NaOMe did improve upon the ratio but gave lower yields.[42]

Having established an efficient route to the pyrrolizidine skeleton, the authors next sought to synthesize the natural products turneforcidine and platynecine. Chemoselective reduction of the ketone with PtO_2/H_2[16] provided a separable mixture of the alcohol **14** (88%) and lactone **4**. These compounds were in turn treated with $LiAlH_4$[32] in THF at reflux to provide (±)-turneforcidine (91%) and (±)-platynecine (94%) respectively.

It is apparent from the few syntheses discussed above that these interesting alkaloid natural products have provided a "playground" in which to develop and experiment with new synthetic methodologies. Though many groups have intercepted similar or identical intermediates en route to synthesizing platynecine or turneforcidine, one hopes that this review has shown just how truly creative organic chemists can be in

Scheme 24



approaching these challenging natural products. A variety of novel strategies based on ionic cyclizations, cycloadditions, or various rearrangements of reactive intermediates are just some of the key reactions covered in this review. Clearly these molecules have provided the foundation for the discovery of fascinating new reactivity and will continue to do so for years to come.

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