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Use of nitrogen and oxygen dipole ylides for alkaloid synthesis

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Dedicated to Gordon Gribble on the occasion of his 50th year retirement from Dartmouth College

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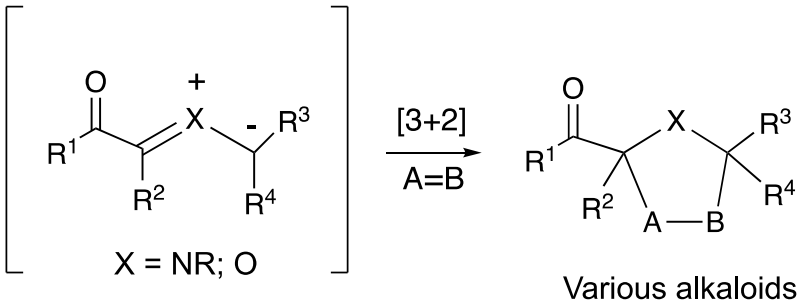
Abstract

As highlighted in this mini review, a growing area of interest in organic synthesis involves the use of substituted azomethine and carbonyl ylides as 1,3-dipoles for the preparation of alkaloidal natural products. Cascade reactions proceeding by an intramolecular 1,3-dipolar cycloaddition of nitrogen and oxygen dipole ylides are of particular interest to the synthetic organic community because of the increase in molecular complexity involved and the high isolated yields.



Keywords: 1,3-Dipole, azomethine ylide, carbonyl ylide, intramolecular, dipolar cycloaddition, alkaloid synthesis

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1. Introduction

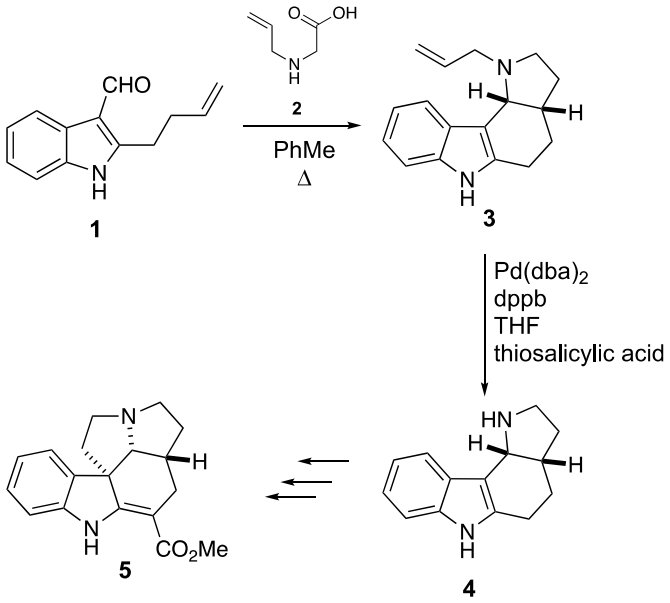
1,3-Dipolar cycloaddition reactions are among the most powerful methods in organic synthesis.[1] A particularly attractive feature is their ability to rapidly increase molecular complexity and lead to a high degree of functionality. These unique reactions were extensively studied by the Huisgen group starting in the early 1960s and their rate and regioselectivity can be understood through FMO analysis.[2-4] [3+2]-Cycloadditions are also extremely useful for the synthesis of natural products such as alkaloids and other biologically important structures employing rather simple starting materials. In addition, dipolar cycloadditions using chiral substrates for enantioselective synthesis has been extensively explored since the 1990s.[5] Because several reviews and related articles have recently been published dealing with the synthetic aspects of dipolar cycloaddition chemistry for the preparation of natural products,[6,7] this mini-review for Gordon Gribble's upcoming 50th year retirement is intended to provide a selective rather than an exhaustive survey of the use of both azomethine and carbonyl ylide dipoles for alkaloid synthesis.

2. Azomethine Ylides

2.1. Dipolar cycloaddition using stabilized azomethine ylides from amino acids

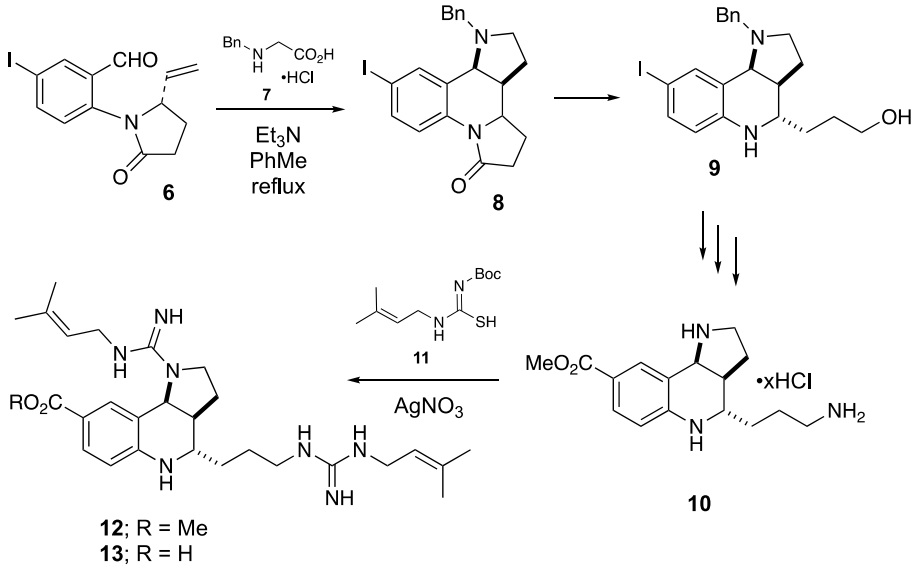
Azomethine ylides have emerged as one of the more useful 1,3-dipoles for the synthesis of a variety of alkaloids.[8] Several methods have been employed to generate azomethine ylides for use in dipolar cycloaddition chemistry.[3] A particularly common method is the condensation of *N*-alkyl amino acid derivatives with aldehydes

followed by decarboxylation to afford the 1,3-dipole. The Coldham group employed this method in their approach toward the synthesis of a variety of alkaloids. In a formal synthesis of deethylibophylidine, for example, heating a toluene solution of aldehyde **1** and *N*-allyl glycine (**2**) at reflux produced **3** in 42% yield (Scheme 1).[9] The *N*-allyl group was subsequently removed to furnish **4** in 40% yield, which represents an intermediate in the synthesis of deethylibophyllidine.



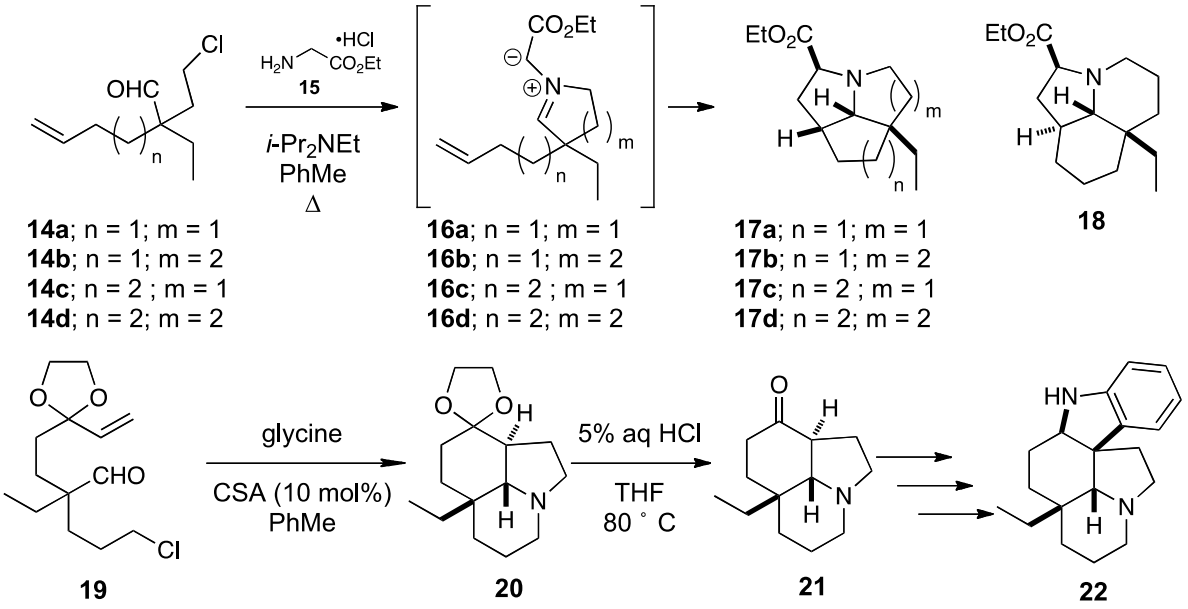
Scheme 1

Lovely *et al.* used a [3+2]-cycloaddition reaction as the key step in an approach to martinellic acid **13**.[10] In this synthesis, the reaction of aldehyde **6** with benzyl glycine **7** produced 65% of **8** which was subsequently reduced to afford tricyclic alcohol **9** in 88% yield (Scheme 2). Compound **9** was then converted in several steps to afford triamine **10**. Finally, a $AgNO_3$ mediated guanylation of **10** with **11** gave **12** in 62% yield. This constitutes a formal synthesis of martinellic acid **13**, as the hydrolysis of the ester was previously reported.



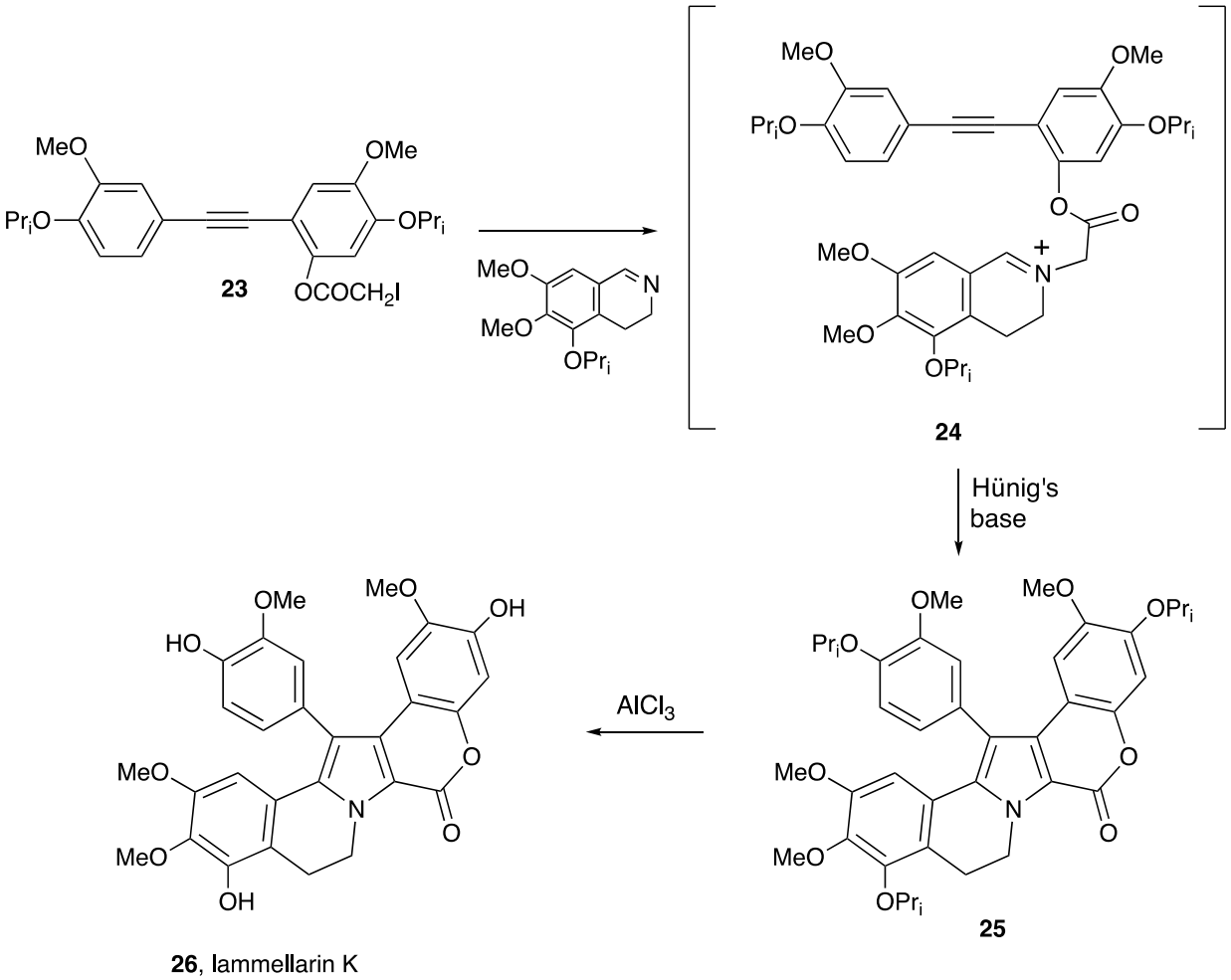
Scheme 2

Stabilized azomethine ylides can easily be formed using amino acids and their esters to generate an imine that is subsequently alkylated to generate an iminium ion. Decarboxylation or deprotonation then affords the reactive azomethine ylide. Coldham and coworkers examined the scope of this type of "*condensation - alkylation – cycloaddition*" cascade wherein the acid-catalyzed condensation of **14a** with glycine ethyl ester **15** followed by intramolecular cyclization generated azomethine ylide **16a.** This 1,3-dipole then cycloadded across the pendant olefin to give **17a** in 81% yield as a single diastereomer (Scheme 3).[11] Likewise, **14b,c** produced **17b,c** in 72% and 51% yield, respectively. Alternatively, **14d** underwent the cascade sequence to produce **18** in 74% yield. Presumably, the increased conformational flexibility in this system allows a transition state that gives rise the *trans*-fused product. Application of this cascade to the synthesis of natural products began with the exposure of **19** to glycine, giving amine **20** in 79% yield. Hydrolysis of the ketal group delivered ketone **21** in 89% yield, which was subsequently converted into aspidospermidine **22** and several other aspidospermine alkaloids through Fischer indole syntheses.



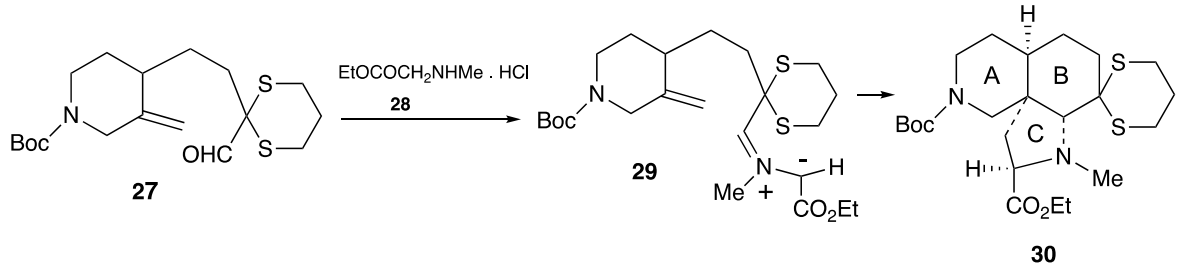
Scheme 3

Another example employing a carbonyl stabilized azomethine ylide for alkaloid synthesis was reported by Banwell in 1997.[12] The pivotal step in his approach to the lamellarin class of alkaloids involved the deprotonation of an iminium ion to generate the dipole. Construction of the central pyrrole moiety of the alkaloid proceeded *via* an intramolecular [3+2]-cycloaddition of an isoquinoline-based azomethine ylide dipole to a suitably tethered alkyne (Scheme 4). Thus, ester **23** was first reacted with 3,4-dihydro-6,7-dimethoxy-5-isopropoxyisoquinoline to give salt **24**. Treatment of **24** with Hunig's base followed by air oxidation of the resulting cycloadduct afforded compound **25** which was subsequently converted to lamellarin K **26** in 96% yield.



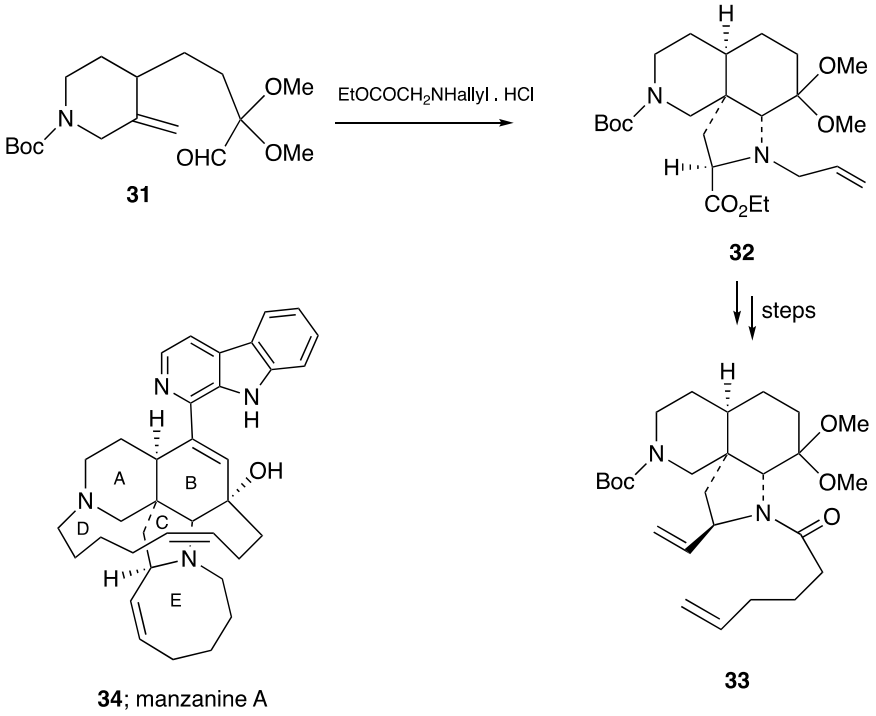
Scheme 4

In an early communication by the Coldham group in 1999, they disclosed that the key step in an approach to the manzamine alkaloids proceeded by an intramolecular azomethine ylide cycloaddition of a carbonyl stabilized dipole.[13] This reaction forms rings B and C simultaneously, together with three new chiral centers and allowed a rapid access to the core ABC ring system of manzamine A. Thus, condensation of the secondary amine sarcosine ethyl ester **28** with aldehyde **27** resulted in the formation of azomethine ylide **29** (Scheme 5). Intramolecular cycloaddition resulted in the generation of the pyrrolidine ring C, together with simultaneous formation of ring B. A single diastereomeric product **30** was obtained which consisted of the desired ABC ring system of the manzamine alkaloids.



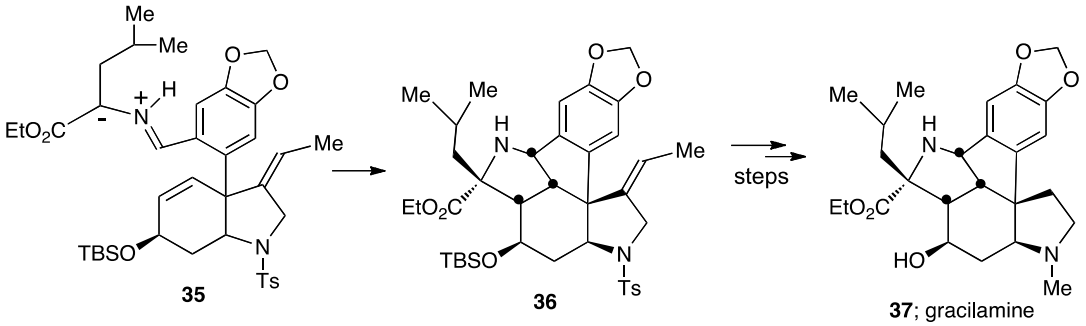
Scheme 5

In a follow up report, this same intramolecular azomethine ylide cycloaddition protocol was used by Coldham in conjugation with a ring closing metathesis to prepare the tetracyclic ABCE ring system of manzanine A **34**.[14] Addition of *N*-allyl glycine ethyl ester to aldehyde **31** afforded the tricyclic compound **32** as the major diastereomer (Scheme 6). This compound was subsequently converted to compound **33** in five subsequent steps. The ring-closing metathesis was carried out in 75% yield thereby providing the critical tetracyclic ABCE ring system of manzamine A **34**.



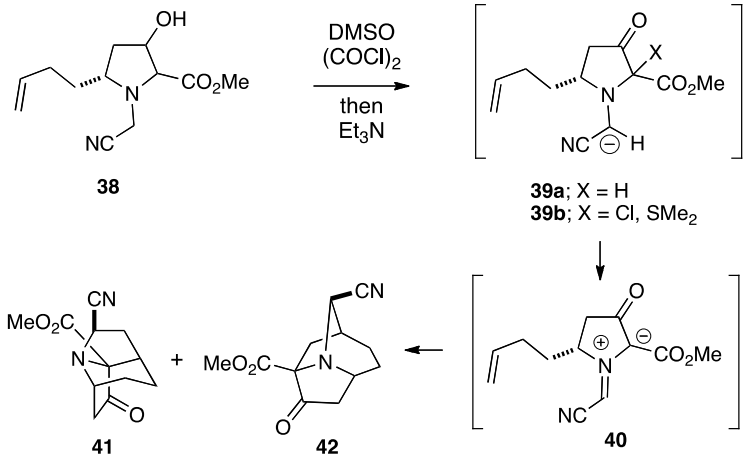
Scheme 6

In 2017, Banwell and coworkers reported a biomimetic total synthesis of the pentacyclic Amaryllidaceae alkaloid derivative gracilamine **37**.[15] Azomethine ylide **35**, produced *via* a Schiff base condensation of the corresponding aldehyde containing C3*α*-arylhexahydroindole with ethyl L-leucinate, engages in a stereoselective intramolecular dipolar cycloaddition reaction to give adduct **36** (Scheme 7). This compound was further elaborated, over eight steps, into the racemic modification of the alkaloid derivative gracilamine **37**. The formation of azomethine ylide **35** and its conversion into compound **36** mimics the proposed biogenesis of the pentacyclic framework of gracilamine **37**.



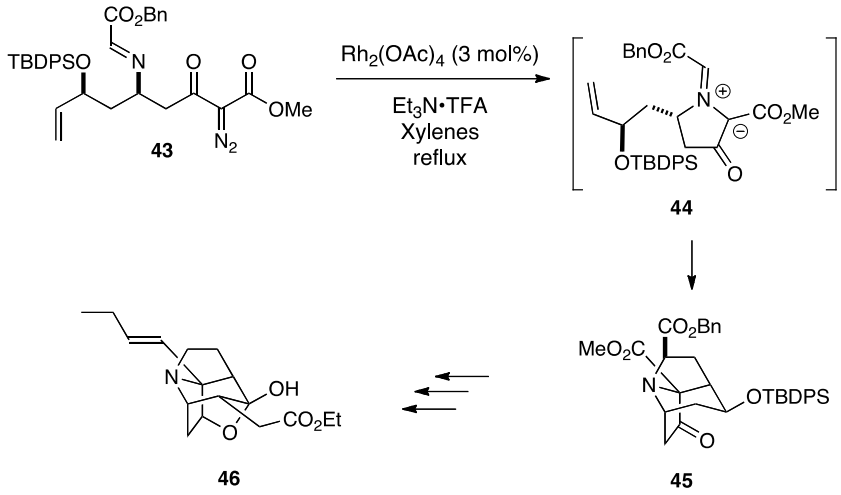
Scheme 7

In an approach to the stemofoline class of alkaloids, the Martin group discovered an unusual set of conditions for generating azomethine ylides. Oxidation of compound **38** under Swern conditions afforded a 5:1 mixture of **41** and **42** in 69% yield (Scheme 8).[16] The formation of these two molecules can be easily rationalized *via* an intramolecular 1,3-dipolar cycloaddition of dipole **40**, but the mechanism through which the azomethine ylide is formed under Swern conditions is not well understood. The authors proposed that the oxidized product **39a** derived from **38** reacted with one of the electrophilic species formed under the reaction conditions to give **39b**. A subsequent loss of a proton as well as the leaving X group would then produce dipole **40**.



Scheme 8

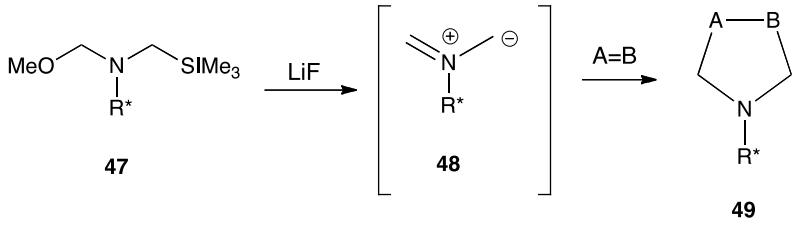
Even with considerable experimentation, the inability to easily remove the cyano group in structures **41** and **42** necessitated an alternate route to the key azomethine ylide intermediate. Ultimately, Martin and coworkers settled on the intramolecular reaction of the imino group in compound **43** with the critical carbenoid intermediate being obtained by a rhodium(II)-catalyzed decomposition of the diazo group in **43** so as to provide dipole **44** (Scheme 9).[17] Subsequent cycloaddition of the resulting azomethine ylide with the tethered alkene afforded **45** in 75% yield. Tricycle **45** was subsequently transformed into (+)-**46**, an intermediate used by Overman in a synthesis of (±)- didehydrostemofoline and isodidehydrostemofoline.[18]



Scheme 9

2.2. Azomethine ylide generation using an iminium ion desilylation protocol

In 1984 the 1,3-dipolar cycloaddition of azomethine ylides derived by a desilylation reaction attracted our attention as a particularly appealing approach for pyrrolidine synthesis. We found that the desilylation of *N*-(trimethylsilyl)methylamino ethers was a very convenient method for azomethine ylide generation.[19-21] Treatment of compounds of type **47** with LiF in the presence of a reactive dipolarophile afforded dipolar cycloadducts in high yield. The overall cycloaddition reaction presumably proceeds by the initial generation of an iminum ion from **47** which then is followed by desilylation to produce dipole **48**. Trapping dipole **48** with a variety of dipolarophiles afforded products of type **49** in high yield. Our interest in the enantioselective synthesis of substituted pyrrolidine derivatives by this process also led us to study the [3 + 2]-cycloaddition of chiral azomethine ylides. The dipole precursors were prepared from enantiomerically pure R-methylbenzylamines, and the diastereoselectivity of the [3 + 2]-cycloaddition was studied in some detail (Scheme 10).



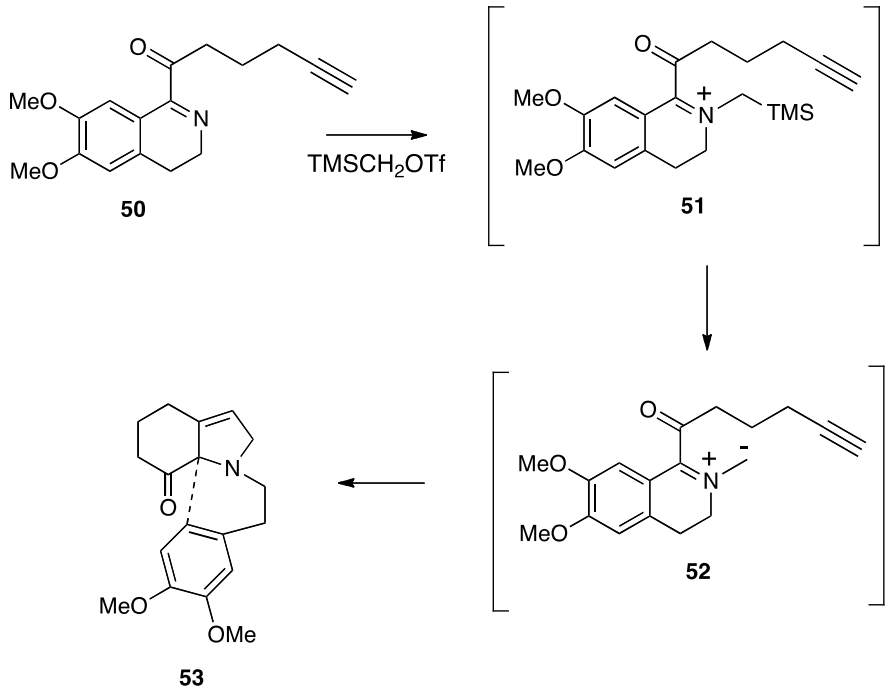
Scheme 10

3. Alkaloid target synthesis

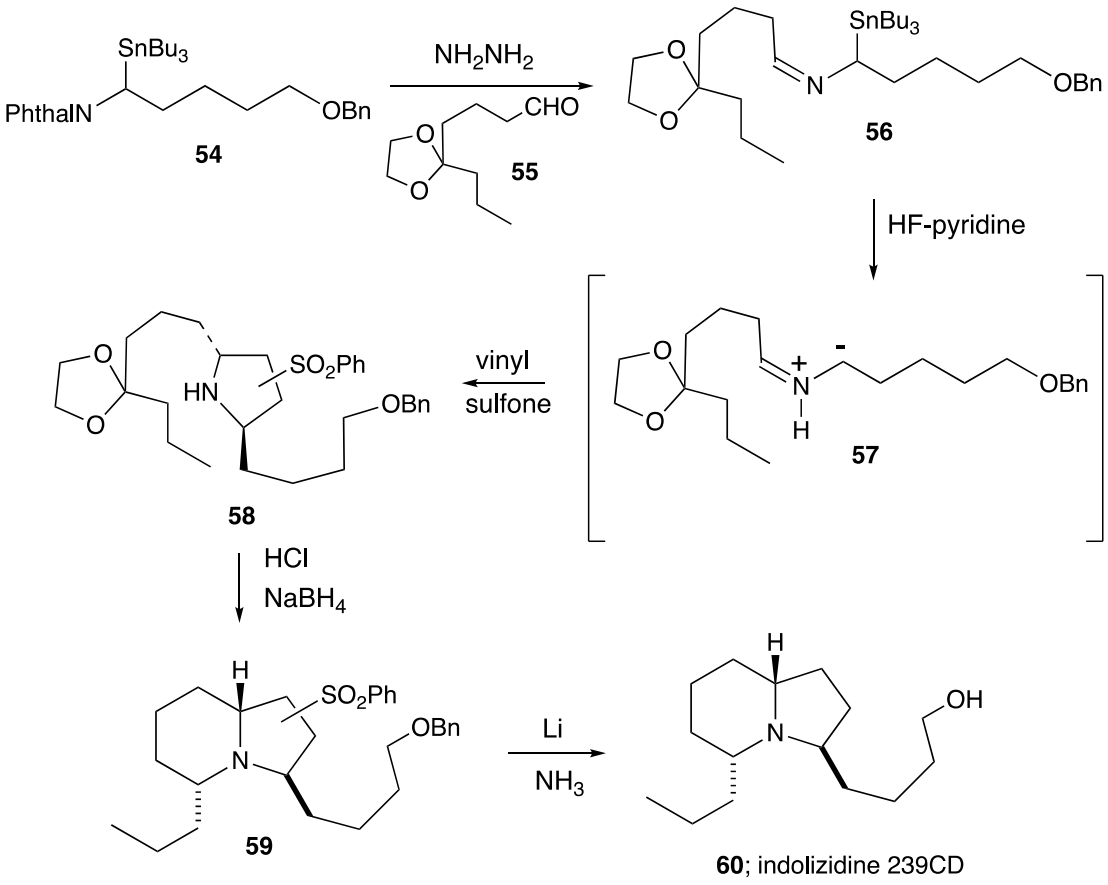
3.1. (±)-Indolizidine 239CD

Livinghouse and coworkers used this iminium ion desilylation protocol to generate the skeleton framework of the erythrinan family of alkaloids.[22] Alkylation of dihydroisoquinoline **50** with trimethylsilylmethyl triflate gave the iminium ion **51**, which was then desilylated with cesium fluoride to form azomethine ylide **52** (Scheme 11). An intramolecular cycloaddition between the ylide and the terminal acetylenic dipolarophile of **52** resulted in the formation of azatetracycle **53** that contains the core of the erythrinane scaffold.

Another related method for the generation and cycloaddition of nonstabilized *N*–unsubstituted azomethine ylides involves the treatment of (2-azaally)stannanes **56** with HF-pyridine by a process involving *N*-protonation and destannylation. [23,24] Compared to other methods for azomethine ylide formation, notable features of this route include the tolerance for aliphatic groups, good *trans* 2,5-diasteroselectivity in the pyrrolidine product, and mild reaction conditions. An early application of this method toward alkaloids was carried out by the Pearson group and involved its use in the synthesis of (+/-)indolizidine 239CD **60**, one of several natural occurring indolizidines that possess a *trans* 2,5-disubstituted pyrrolidine in their structure.[24] Thus hydrazinolysis of phthalimide **54** gave the expected amine which was condensed with aldehyde **55** under typical imine formation conditions to produce the (2-azallyl)stannane **56** (Scheme 12). This imine was then treated with phenyl vinyl sulfone and the mixture was allowed to react with HF-pyridine to provide pyrrolidine **58** *via* ylide **57** as a mixture of diastereomers. Removal of the ketal group and intramolecular reductive amination created compound **59** which was subsequently converted into the desired alkaloid **60**.



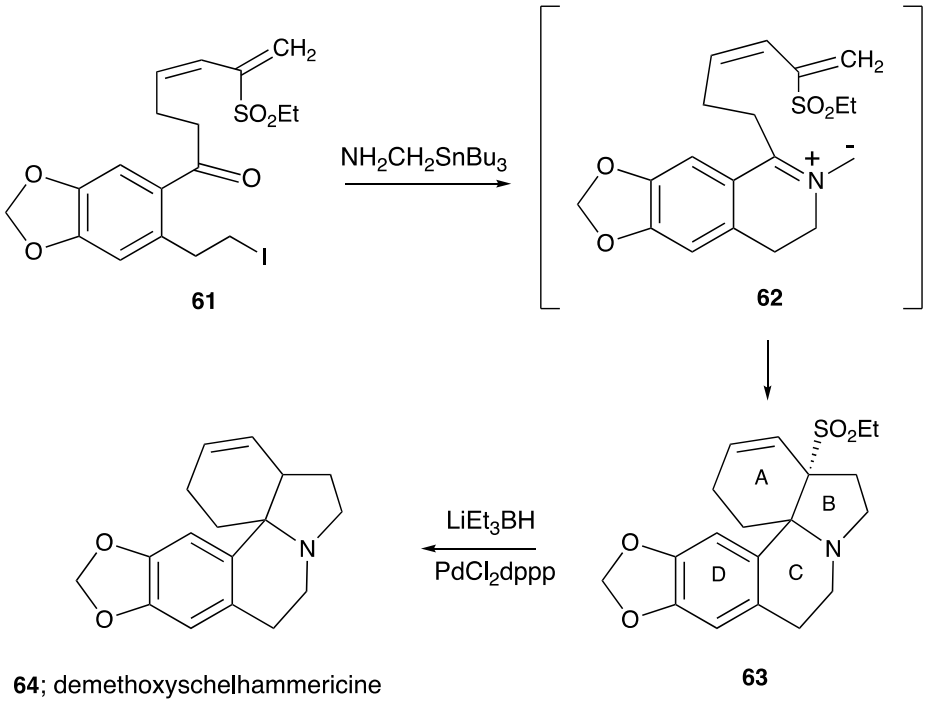
Scheme 11



Scheme 12

3.2. (±)-Demethoxyschelammericine

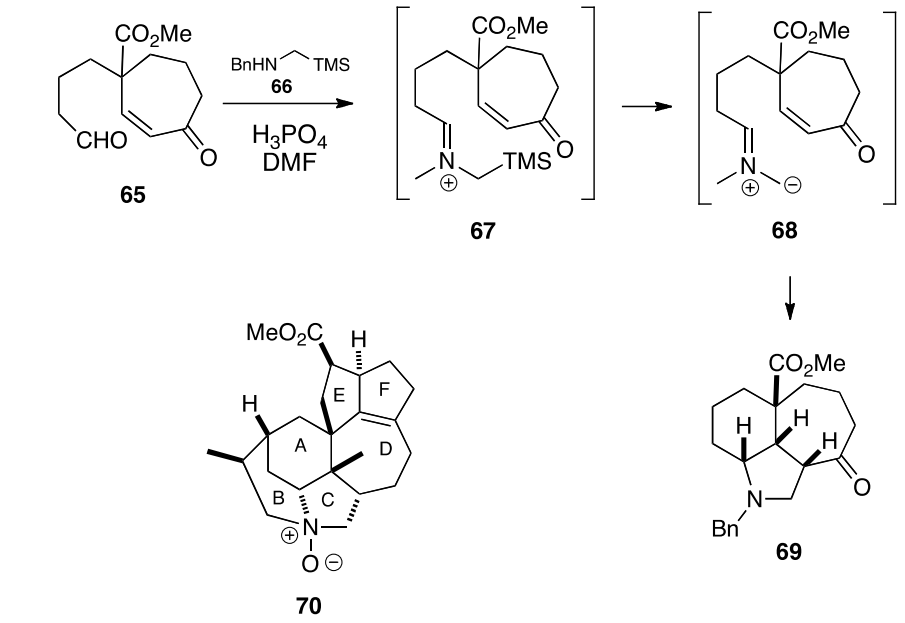
In a later publication Pearson described his efforts toward the total synthesis of the homoerythrina class of alkaloids including the preparation of demethoxyschelhammericine **64**.[25] The key feature of this syntheses involves the successful formation of the A-C rings of the alkaloid using a tandem *N*-alkylation/azomethine ylide [3+2] cycloaddition (Scheme 13). This critical step features both an intramolecular *N*-alkylation of a tethered electrophile and an intramolecular cycloaddition of a tethered dipolarophile.



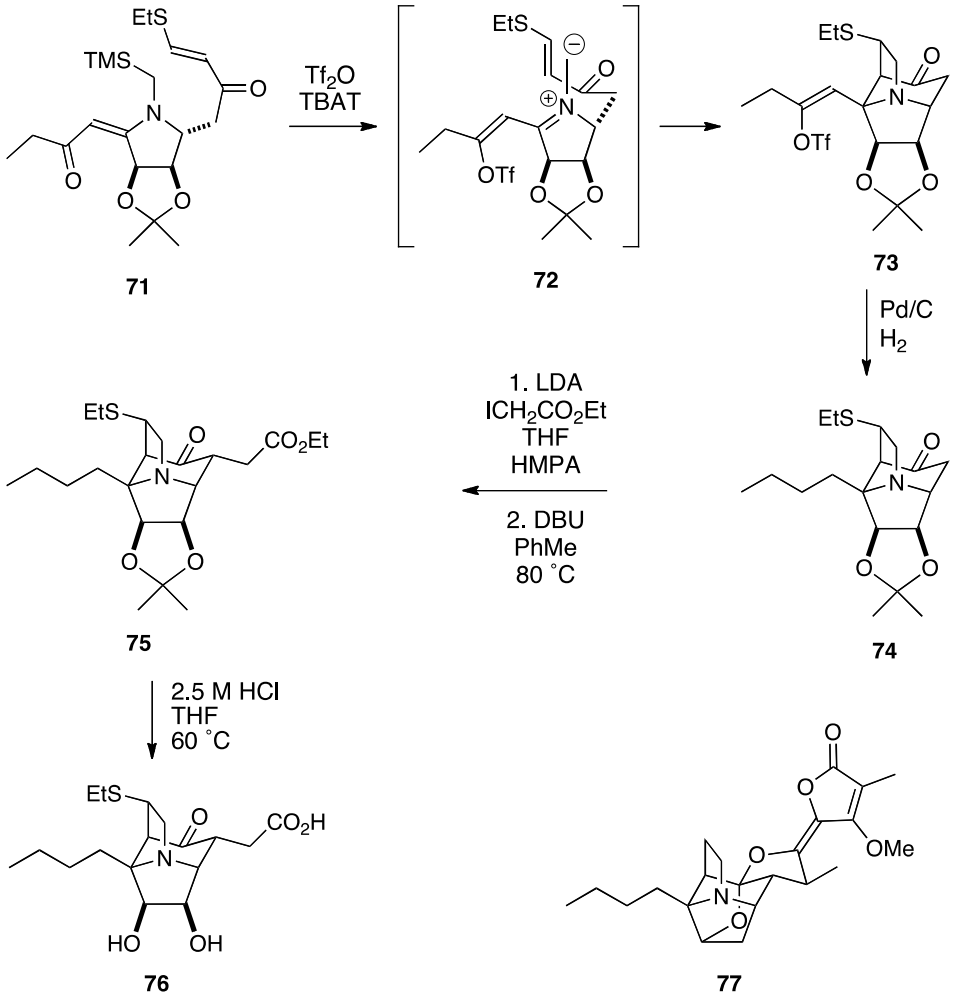
Scheme 13

The condensation of secondary *N*-(trimethylsilyl)methyl amines with carbonyl compounds has also been shown to be an effective method to generate unstabilized azomethine ylides upon desilylation. For example, the *ACD* azatricylic **69**, which represents the core of the calyciphylline type A daphniphyllum alkaloid **70**, was formed in 55 % yield by mixing **65** and amine **66** in DMF at rt in the presence of catalytic amounts of H_3PO_4 (Scheme 14).[26] In this cascade sequence, condensation of the amine with aldehyde **65** produced iminium ion **67**. Cleavage of the silyl group then gave azomethine ylide **68** that underwent cycloaddition across the pendant electron-deficient alkene to produce **69**.

There are also several examples of imidate derived azomethine ylides reported in the literature. For example, the Gin group described a clever use of these 1,3-dipoles in an approach to the azatricyclic core of some stemofoline members of the stemona alkaloid family. The formation of the azomethine ylide **72** occurred upon exposure of pyrrolidine **71** to triflic anhydride and tetrabutylammonium triphenyldifluorosilicate (TBAT; Scheme 15).[27] Cycloaddition of the resulting dipole across the pendant vinyl sulfide furnished **73** in 71% yield. Enol triflate **73** was then reduced to give the saturated side-chain in **74** in 89% yield by the action of Pd/C under an H_2 atmosphere. The enolate derived from **74** was treated with ethyl iodoacetate in the presence of HMPA followed by epimerization of the alkylation product to provide **75** in 58% yield from **74**. Concomitant hydrolysis of the methyl ester and the acetonide protecting group gave **76** in 96% yield, an intermediate that contained suitable functional handles that could be elaborated into stemofoline **77**.



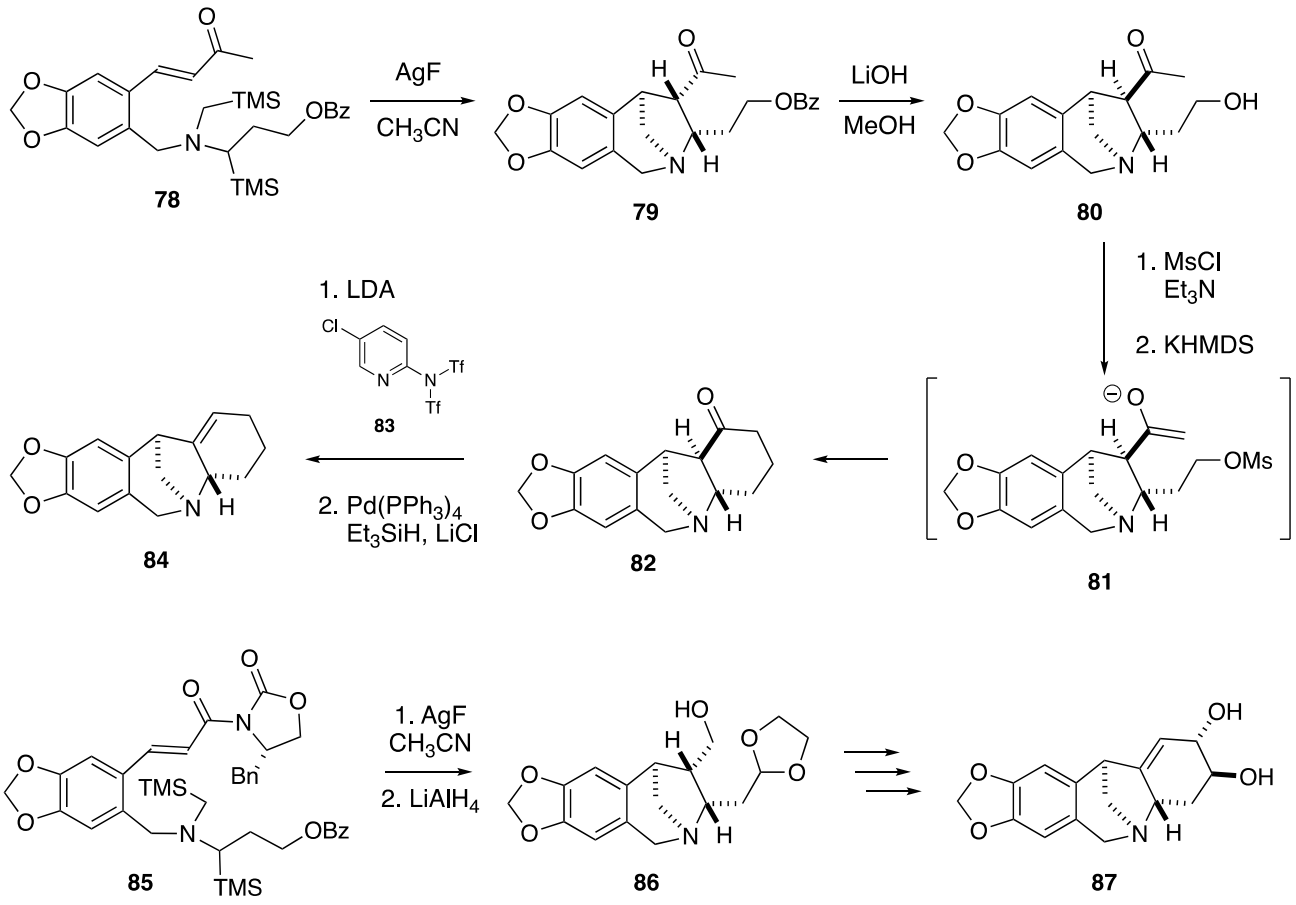
Scheme 14



Scheme 15

3.3. Amaryllidaceae alkaloids

Pandey and coworkers developed a AgF-mediated route to azomethine ylides starting from *N*,*N*′-bis(trimethylsilylmethyl)alkyl amines and applied this method of dipole formation toward a formal total synthesis of the amaryllidaceae class of alkaloids. Exposure of **78** to AgF effected a double desilylation and oxidation to furnish a transient azomethine ylide dipole (Scheme 16).[28,29] Cycloaddition of the dipole to the proximal enone fashioned tetracycle **79** in 56% yield. A base mediated hydrolysis of the benzoyl ester occurred with concomitant epimerization, giving **80** in 98% yield. Conversion of the hydroxyl group in **80** to a mesylate followed by reaction with KHMDS produced **82** in 65% yield *via* enolate **81**. The alkene moiety in compound **84** was installed in 71% yield by a reductive elimination of an enol triflate derived from **83** using $Pd(PPh_3)_4$ and Et_3SiH. The Overman group had previously synthesized pancracine **87** from compound **84**, thereby resulting in a formal synthesis of this alkaloid.[30,31] With the general cycloaddition strategy established, a next generation synthesis employed a chiral auxiliary to control the overall diasteroselectivity. Thus, exposure of compound **85** to AgF followed by reduction with $LiAlH_4$ afforded **86** in 46% yield and with 63% enantiomeric excess after recrystallization. Tetracycle **86** was then used to complete an asymmetric formal synthesis of **87** and several related alkaloids.

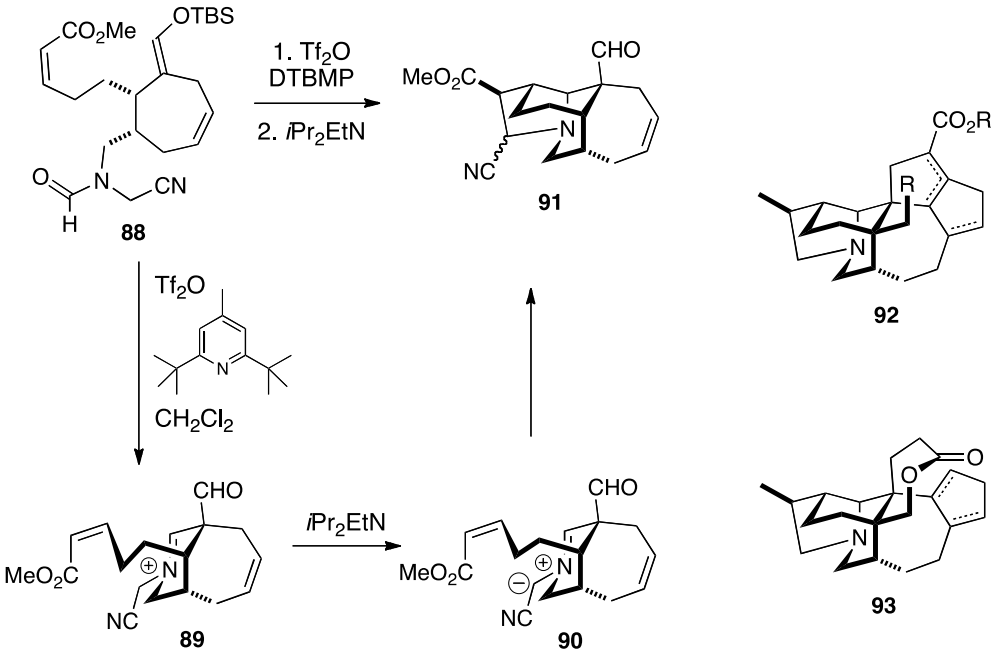


Scheme 16

3.4. Daphnane alkaloids

In an approach to the compact, polycyclic core of some daphnane alkaloids, the Bélanger group employed a sequential "*Vilsmeier-Haack–azomethine ylide cycloaddition*" sequence (Scheme 17).[32] Formamide **88** was reacted with Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at rt to produce an iminium ion which

underwent reaction with the silyl enol ether moiety followed by loss of triflate to produce iminium ion **89**. Addition of *i*Pr_2EtN to the reaction mixture then generated azomethine ylide dipole **90** that reacted with the α,β-unsaturated ester to give tetracyclic **91**, a species common to both the daphnilactone B-type alkaloids **92** and yuzurimine-type alkaloids **93**.

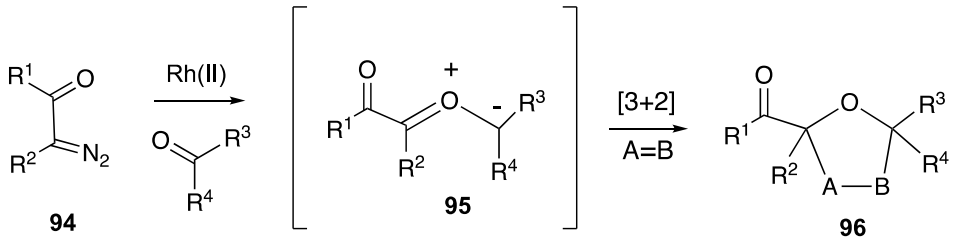


Scheme 17

4. Carbonyl ylides

4.1. Rh(II)-catalyzed reaction of diazo carbonyl substrates for ylide generation

The creation of carbonyl ylide dipoles **95** (Scheme 18) from the reaction of α-diazo compounds with ketones in the presence of Rh(II) catalysts[7,33-38] has significantly broadened their applicability for natural product synthesis.[39-41] The ease of generating the dipole, the rapid accumulation of polyfunctionality in a relatively small molecular framework, the high stereochemical control of the subsequent [3+2]-cycloaddition, and the fair predictability of its regiochemistry have contributed to the popularity of the reaction.[42,43] When the reacting components are themselves cyclic or have ring substituents, complex multicyclic arrays, such as those contained in drugs and natural products, can be constructed in a single step.

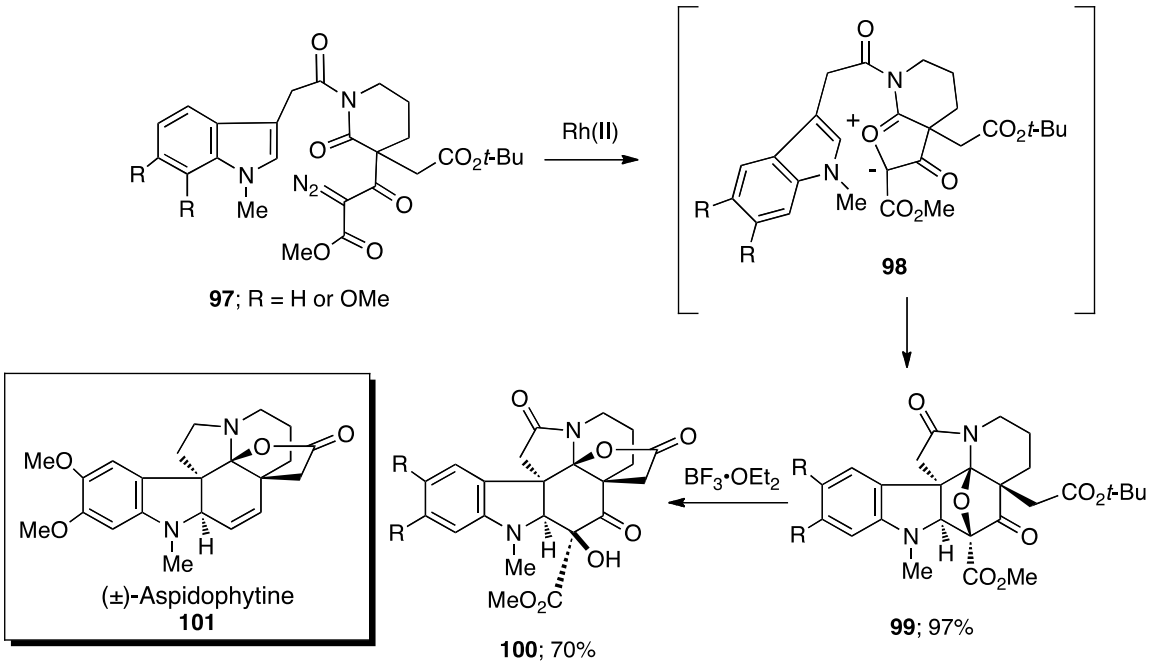


Scheme 18

5. Alkaloid target synthesis

5.1. (±)-Aspidophytine

One of the early examples of the trapping of a carbonyl ylide dipole with a tethered π-bond for alkaloid synthesis was found as the central step in my laboratory's approach toward the complex pentacyclic alkaloid (±)-aspidophytine **101**.[44,45] The key sequence of reactions involved a 1,3-dipolar cycloaddition of the '*push-pull*' dipole **98** across the indole π-system. The *exo*-cycloadduct **99** was the exclusive product isolated from the Rh(II)-catalyzed reaction of **97** (Scheme 19). It was assumed that in this case, the bulky *tert*-butyl ester functionality blocks the *endo* approach thereby resulting in cycloaddition taking place from the less-congested *exo* face. Treatment of the resulting dipolar cycloadduct **99** with $BF_3.OEt_2$ induces a domino fragmentation cascade. The reaction proceeds by an initial cleavage of the oxabicyclic ring and formation of a transient *N*-acyliminium ion, which reacts further with the adjacent *tert*-butyl ester and sets the required lactone ring present in aspidophytine. A three-step sequence was then used to remove both the ester and OH groups from lactone **100**. Subsequent functional group manipulations allowed for the high-yielding conversion of **100** into (±)-aspidophytine **101**.

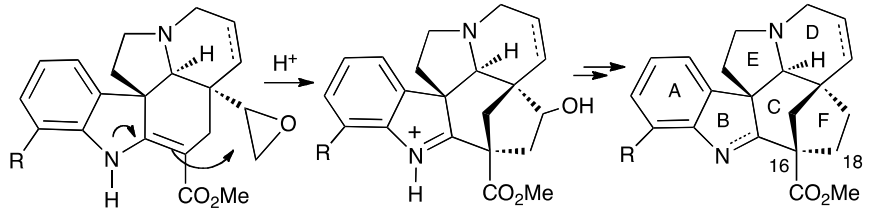


Scheme 19

5.2 Synthesis of the kopsifoline skeleton

As a further extension of *"push-pull"* dipole cycloaddition chemistry, the Rh(II)-catalyzed cyclization/cycloaddition cascade was applied toward the hexacyclic framework of the kopsifoline alkaloids. The kopsifolines **104** are structurally intriguing compounds, related to and possibly derived from an aspidosperma-type alkaloid precursor **102**. A possible biogenetic pathway to the kopsifolines from **102** could involve an intramolecular epoxide-ring opening followed by loss of H_2O as shown in Scheme 20. The interesting biological activity of these compounds combined with their fascinating and synthetically challenging structure, make them attractive targets for synthesis. Using the metal-catalyzed domino reaction as a key step, the heterocyclic skeleton of the kopsifolines could eventually be built by a 1,3-dipolar cycloaddition of a *"push-pull"* carbonyl

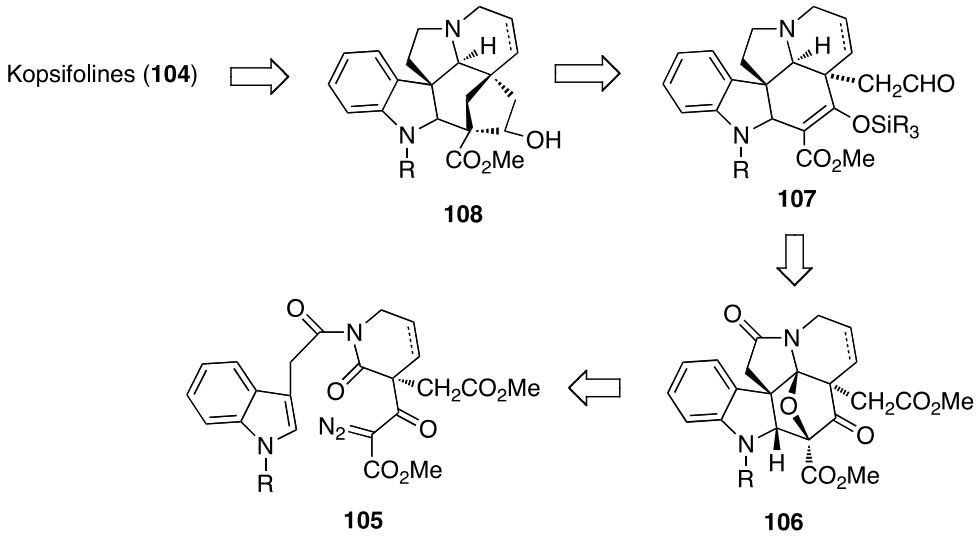
ylide dipole derived from α-diazo ketoester **105** across the indole π-bond. Ring-opening of the resulting cycloadduct **106** followed by a reductive dehydroxylation step produced the critical silyl enol ether **107** necessary for the final F-ring closure. The facility and stereoselectivity of the key cycloaddition reaction was investigated in more detail using some model substrates. It was found that the heterocyclic skeleton of the kopsifoline alkaloid family **108** could readily be constructed by the proposed sequence of reactions outlined in Scheme 21.[46,47] The isolation of **106** as a single diastereomer was rationalized by recognizing that the indole moiety approaches the dipole from the least sterically encumbered position. Ring-opening of the resulting cycloadduct **106** followed by a reductive dehydroxylation step resulted in the formation of the silyl enol ether **107** necessary for the final F-ring closure of the kopsifoline skeleton (*i.e.*, formation of **108**).



102; R = H or OMe **103** **104**; R = H or OMe

Kopsifolines

Scheme 20

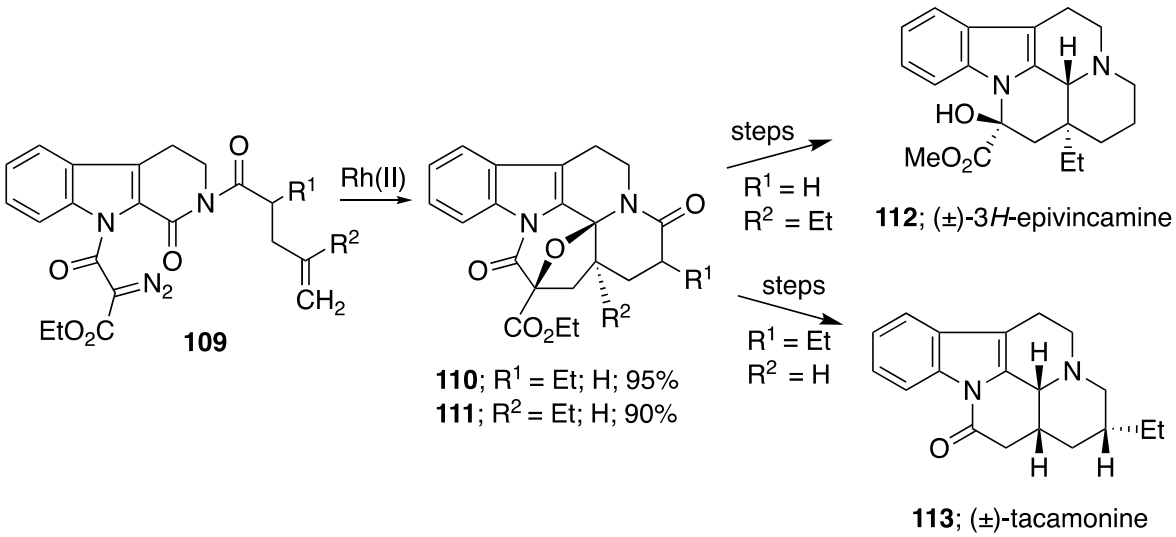


108 **107** **105** **106**

Scheme 21

5.3 Vinca and tacaman alkaloids

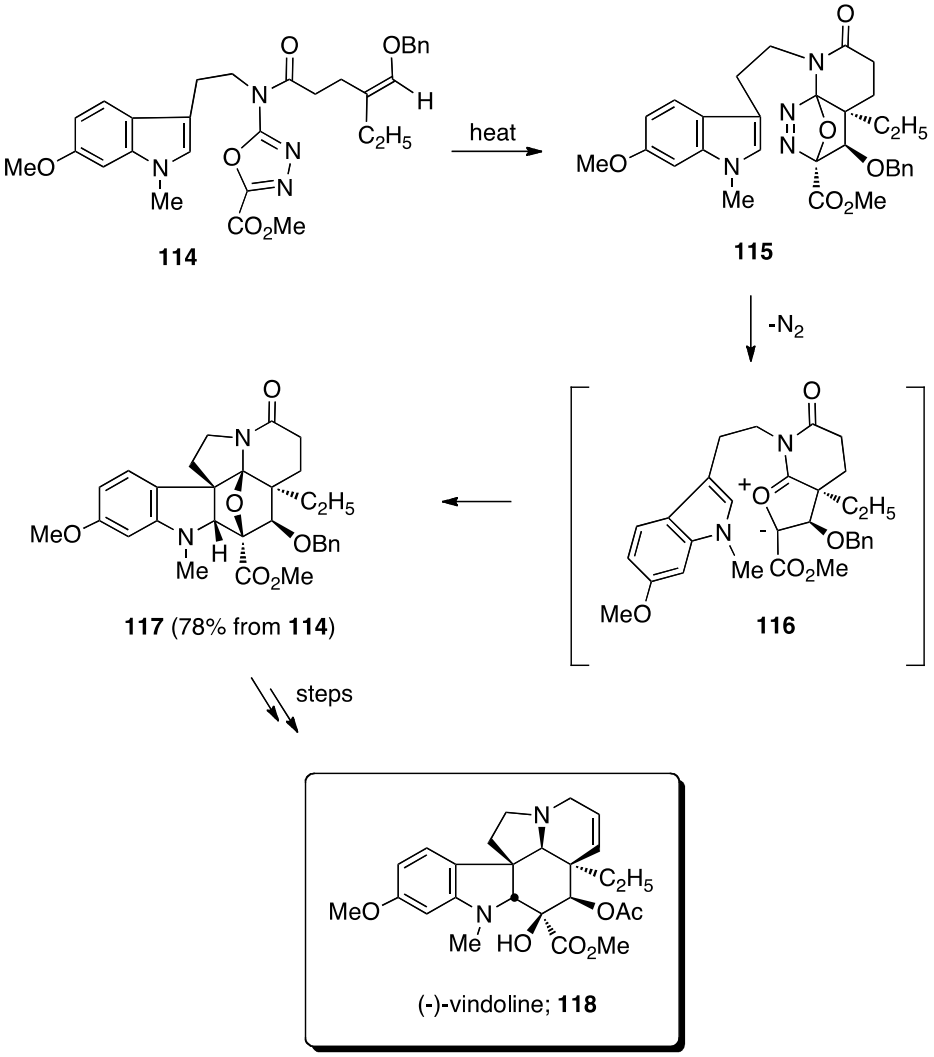
The total synthesis of several members of the vinca and tacaman class of indole alkaloids has also been accomplished using "*push-pull*' dipoles in the critical cycloaddition step.[48,49] The central step in the synthesis consists of an intramolecular [3+2]-cycloaddition reaction of α-diazo indoloamide **109**, which delivers the pentacyclic skeleton of the natural product in excellent yield (Scheme 22). The acid lability of the oxabicyclic structure was exploited to establish the *trans*-D/E-ring fusion of (±)-3*H*-epivincamine **112**. Finally, a base induced ketoamide ring contraction was utilized to generate the *E*-ring of the natural product. A variation of the cascade sequence of reactions used to synthesize (±)-3*H*-epivincamine **112** was also employed for the synthesis of the tacaman alkaloid (±)-tacamonine **113**.



Scheme 22

5.4 (-)-Vindoline

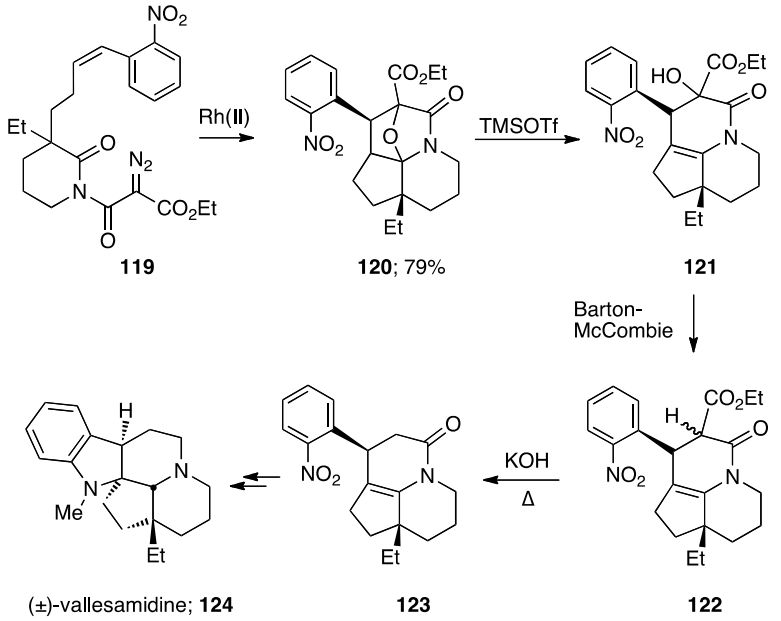
Even though the Boger group's synthesis of the vinca alkaloid family does not involve a Rh-carbenoid intermediate, their approach proceeds through a related "*push-pull*" dipole intermediate and is based on an intramolecular [4 + 2]/[3 + 2]-cycloaddition reaction of a 1,3,4-oxadiazole heterocycle.[50-55] This unique domino cascade was used to assemble the fully functionalized pentacyclic ring system of vindoline **118** in a single step that forms four C-C bonds and three rings while introducing all the requisite functionality and setting all six stereocenters within the central ring including three contiguous and four total quaternary centers (Scheme 23). The reaction leading to **117** is initiated by an intramolecular inverse electron demand Diels-Alder cycloaddition of the 1,3,4-oxadiazole **114** with the tethered enol ether. Loss of nitrogen from the initial Diels-Alder cycloadduct **115** provides the "*push-pull*" carbonyl ylide **116**, which then undergoes a subsequent 1,3-dipolar cycloaddition with the tethered indole. Importantly, the diene and dienophile substituents complement and reinforce the [4+2]-cycloaddition regioselectivity dictated by the linking tether. The relative stereochemistry in the cycloadduct is controlled by a combination of (1) the dienophile geometry and (2) an exclusive *endo* indole [3+2]-cycloaddition sterically directed to the *R*-face opposite the newly formed fused lactam. This *endo* diastereoselection for the 1,3-dipolar cycloaddition has been attributed to a conformational (strain) preference dictated by the dipolarophile tether.[54] Cycloadduct **117** was eventually transformed into the natural product vindoline **118** in several additional steps. Extension of these cascade studies by the Boger group also provided for a total synthesis of the *bis*-indole alkaloids vinblastine and vincristine.[55]



Scheme 23

5.5 (±)-Vallesamidine

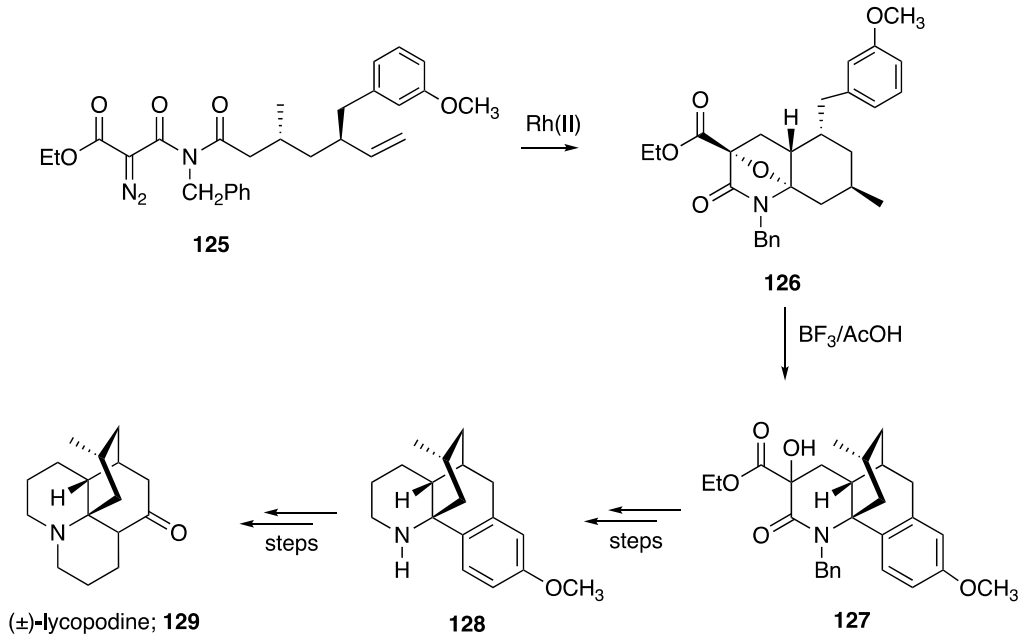
Given the success in forming novel azabicyclic systems derived from an intramolecular isomünchnone cycloaddition/*N*-acyliminium ion cyclization sequence, this domino strategy was also used for a formal synthesis of vallesamidine **124** *via* the key Heathcock intermediate **123** (Scheme 24).[56,57] Thus, *N*-malonylacylation of the precursor amide was carried out followed by a standard diazo transfer reaction to produce the requisite α-diazoimide **119**. The reaction of **119** with a Rh(II)-catalyst gave cycloadduct **120**, which underwent a TMSOTf catalyzed ring opening to furnish enamide **121** in 78% yield. With the ring-opened lactam in hand, a Barton-McCombie deoxygenation reaction delivered **122** in 88% yield.[58] Utilization of the sequential saponification/ decarboxylation protocol afforded enamide **123**.[59] This sequence constitutes a formal synthesis of (±)-vallesamidine **124**, based on the successful conversion of **123** into **124** by Heathcock and Dickman.[56,57]



Scheme 24

5.6 (±)-Lycopodine

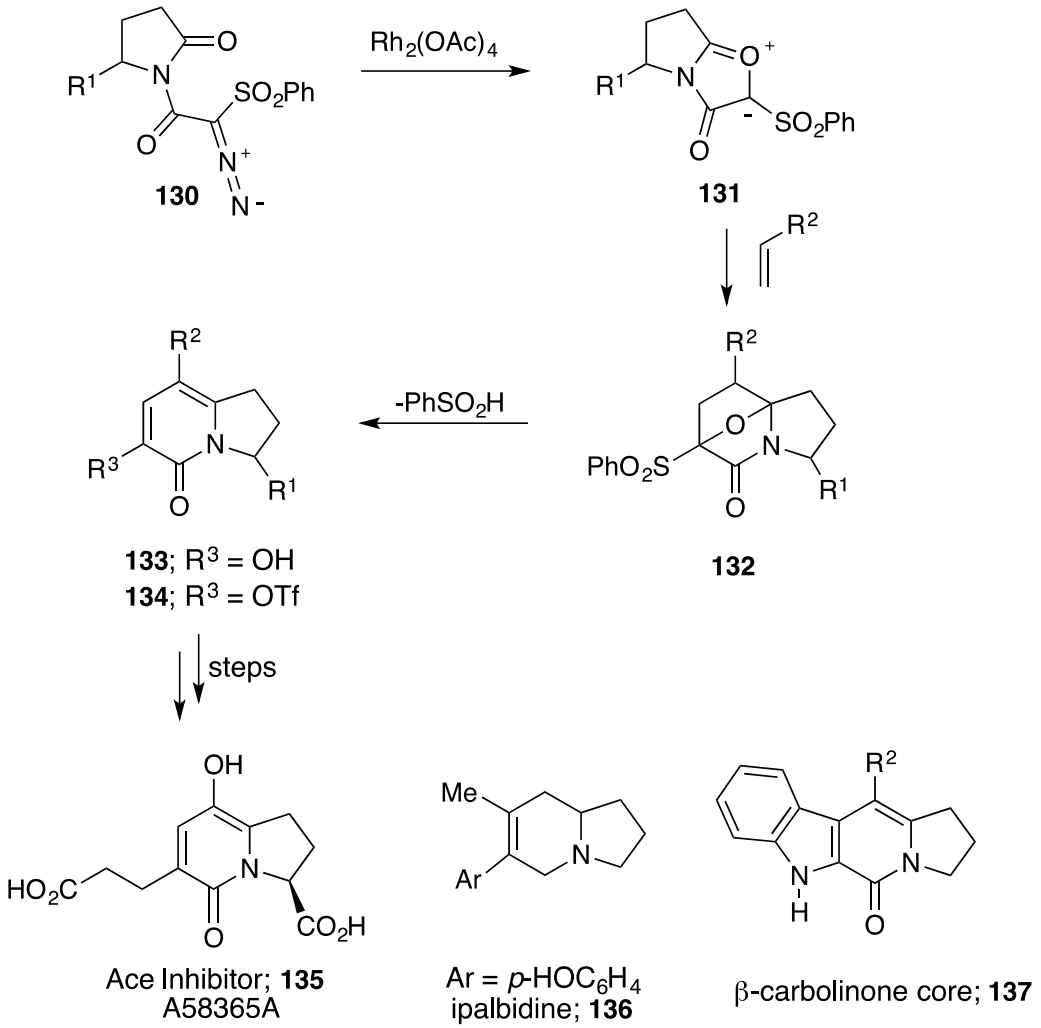
Another application of the domino cascade process toward the construction of alkaloids involved the synthesis of (±)-lycopodine **129** (Scheme 25).[60] The isomünchnone cycloadduct **126** was formed from the Rh(II)-catalyzed reaction of diazo imide **125** and was found to be the precursor of the key Stork intermediate **128** (*via* **127**). Formation of **128** from **127** occurred by way of a Pictet-Spengler cyclization of the *N*-acyliminium ion derived from **126**. Central to this strategy was the expectation that the bicyclic iminium ion originating from **126** would exist in a chairlike conformation.[61-63] Indeed, cyclization of the aromatic ring onto the *N*-acyliminium ion center readily occurred from the axial position.[64-66] The rearranged product **127** was then converted into the key intermediate **128** previously used by Stork for the synthesis of (±)-lycopodine **129**.[61,62]



Scheme 25

5.7 Indolizidine alkaloids

A further implementation of the cascade methodology involves the efficient assembly of the indolizidine ring system by using the Rh(II)-catalyzed [3+2]-dipolar cycloaddition of the phenylsulfonyl substituted diazopyrrolidinone **130** with an appropriately substituted dipolarophile (Scheme 26). The resultant pyridone **133** represents a very versatile synthon. As depicted in Scheme 26, structural manipulation of the pyridinone ring and subsequent functional group interconversions provides access to several indolizidine alkaloids.[67-70] The C_6 hydroxyl substituent, protected as triflate **134**, allows for an assortment of cross coupling-possibilities. The Padwa group demonstrated the versatility of the method through the synthesis of the angiotensin converting enzyme inhibitor (-)-A58365A **135**, (±)-ipalbidine **136**, β-carbolinone **137** and a variety of other novel indolizidine-based compounds.[70]

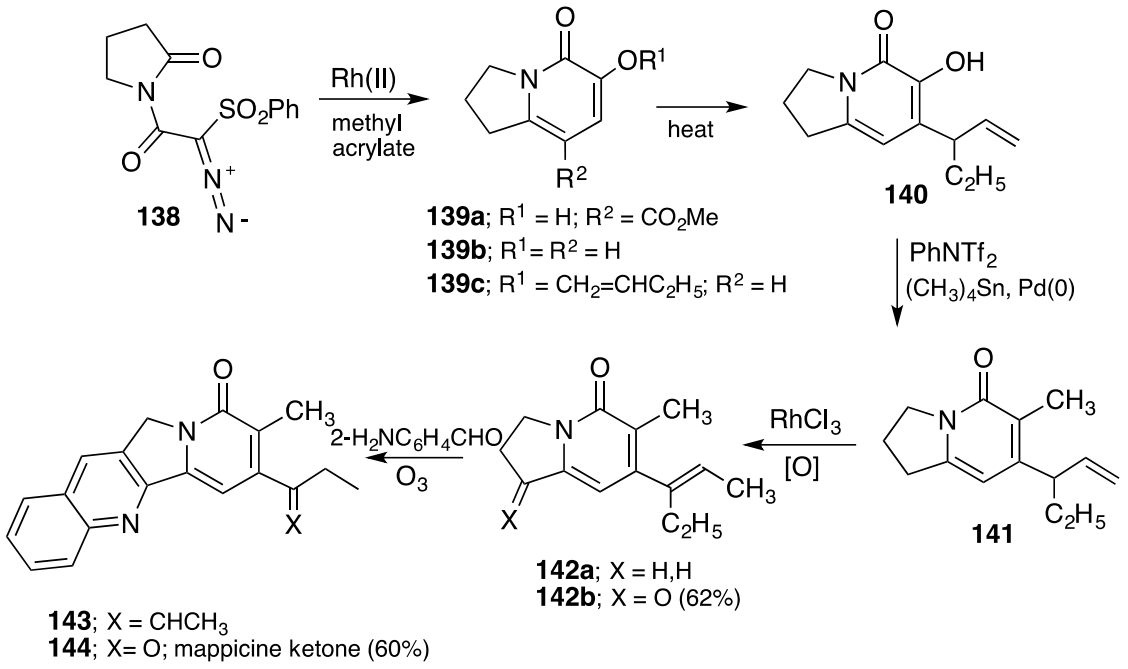


Scheme 26

5.8 Mappicine ketone

An efficient synthesis of the naturally occurring oxoindolizino quinoline mappicine ketone **144** has been carried out by Greene and coworkers by making use of pyridone **139a** as a key intermediate.[71] The synthesis of **144** began with formation of the known cycloadduct **139a** (R_1 = H; R_2 = CO_2Me) by cycloaddition of the isomünchnone dipole derived from diazo sulfone **138** with methyl acrylate (Scheme 27).[67-70] This multistep sequence proceeded smoothly and in high yield when catalyzed by rhodium(II) acetate. Hot aqueous

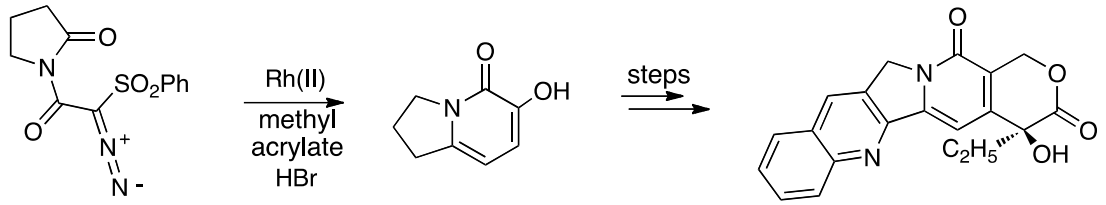
hydrobromic acid then effected decarbomethoxylation of **139a** to give **139b** in 82% yield. Etherification of **139b** with commercially available (*E*)-1-bromo-2-pentene and cesium carbonate in dimethylformamide produced the expected substitution product **139c**, which cleanly underwent a Claisen rearrangement in refluxing chlorobenzene to afford the desired rearranged derivative **140** in 74% overall yield. This transformation is a rare example of a Claisen rearrangement taking place in a hydroxypyridone system[70,72,73] The α-hydroxypyridone **140** was then converted into its triflate derivative under standard conditions. This was followed by Stille coupling with tetramethyltin to provide α-methyl pyridone **141** in 84% yield. In the presence of rhodium(III) chloride in hot ethanol, compound **141** was rapidly isomerized to olefin **142a** (91%). The success of this key transformation derives from the carbon symmetry of the β-substituent in pyridone **141**. Oxidation of **142a** in two steps then selectively generated the Friedländer substrate **142b**, which was reacted with *o*-aminobenzaldehyde to give oxoindolizino quinoline **143** in 73% yield. Ozonolysis of **143** in CH_2Cl_2/MeOH at -78 °C accomplished selective double-bond cleavage in **143** to provide mappicine ketone **144**.



Scheme 27

5.9 (±)-Campothecin

A related synthesis of racemic camptothecin **145** was also carried out by Greene and coworkers soon thereafter and is similarly based on the isomünchnone dipole strategy.[74] The starting point commenced from the readily available hydroxyl-pyridone **139b** (Scheme 28). Subsequent steps include a Claisen rearrangement of a functionalized allylic ether, a hindered Heck coupling, and a Friedländer condensation.

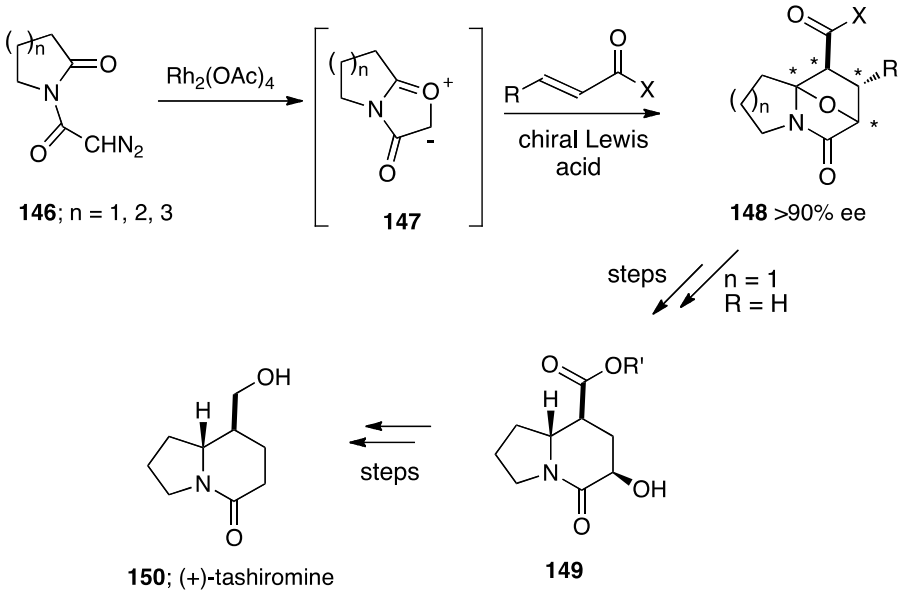


138 **139b** (±)-camptothecin; **145**

Scheme 28

5.10 (±)-Tashiromine

Recently, Suga and coworkers have reported on a highly enantioselective 1,3-dipolar cycloaddition reaction between several 3-(2-alkenoyl)-2-oxazolidinones and carbonyl ylides that were generated from the Rh(II)-catalyzed reaction of *N*-diazoacetyl lactams (Scheme 29).[75] *N*-Diazoacetyl lactams that possess 5-, 6-, and 7-membered rings were transformed to the corresponding epoxy-bridged indolizidines, quinolizidines, and 1-azabicyclo[5.4.0]undecanes **148** with good to high enantioselectivities according to this method. A regio- and stereoselective ring-opening of the epoxy-bridged indolizidine cycloadduct **148** gave the corresponding alcohol as a single diastereomer. The sequence of an asymmetric cycloaddition reaction followed by ring-opening was applied to the syntheses of several chiral indolizidine derivatives, including (+)-tashiromine **150**.[75]



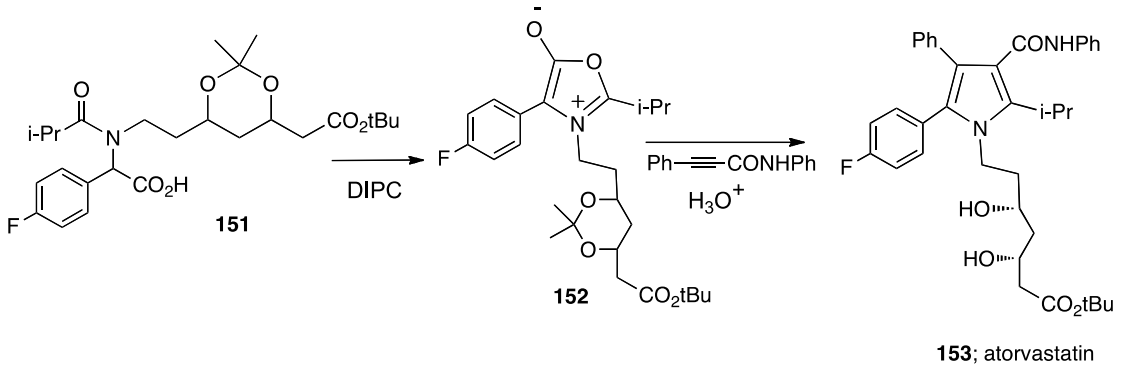
146; n = 1, 2, 3 **147** **148** >90% ee **149** **150**; (+)-tashiromine

Scheme 29

5.11 Atorvastatin

The well known pharmaceutical drug Atorvastatin, marketed under the trade name Lipitor, is a member of the drug class known as statins, which are used primarily for lowering blood cholesterol and for prevention of events associated with cardiovascular disease. Since Atorvastatin **153** is one of the top selling pharmaceuticals, it has been the subject of many synthetic studies aimed to improve its preparation, particularly the pyrrole core and pendant chiral diol. In a recent report, Gribble and Lopchik described the preparation of **153** in seven steps from commercially 4-fluorophenylacetic acid.[76] The key step involved the treatment of **151** with *N,N*'-

diisopropylcarbodiimide (DIPC) followed by a 1,3-dipolar cycloaddition of the resulting münchnone mesoionic heterocycle **152** with *N*,3-diphenylpropiolamide as shown in Scheme 30.[77]



Scheme 30

6. Conclusions

The application of the cycloaddition of both azomethine and carbonyl ylide dipoles for the synthesis of various alkaloids as described in this mini-review article spans a broad spectrum of organic chemistry. The regio- and stereoselectivity of the 3+2-cycloaddition reaction is now well established, making it an attractive strategic disconnection for synthetic design of various alkaloids. As is the case in all new areas of research, future investigations of the chemistry of these dipolar cycloadditions for complex heterocyclic synthesis will be dominated by the search for enantioselective synthesis. Future developments will also depend on gaining a greater understanding of the mechanistic details of this fascinating and synthetically important process.

7. Acknowledgements

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8. References

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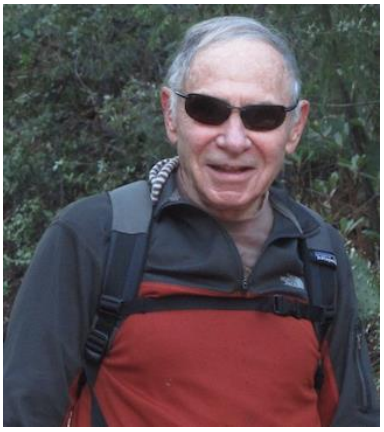
Author's Biography



Albert Padwa was born in New York City. He received both his B.A. and Ph.D. degrees from Columbia University. Following an NSF postdoctoral position at the University of Wisconsin, he was appointed as an Assistant Professor of Chemistry at the Ohio State University. He moved to SUNY Buffalo as Associate Professor and was promoted to Professor in 1969. Since 1979, he has been the William Patterson Timmie Professor of Chemistry at Emory University. The research interests of Al Padwa have encompassed heterocyclic chemistry, alkaloid synthesis, tandem organometallic chemistry, and organic photochemistry. Among other awards, he has been the recipient of an Alfred P. Sloan Fellowship, a John S. Guggenheim Fellowship, an Alexander von Humboldt Senior Scientist Award, a Senior Award in Heterocyclic Chemistry from the International Society of Heterocyclic Chemistry and an ACS Arthur C. Cope Scholar Award. He served as the Chairman of the Organic Division of the ACS and as President of the International Society of

Heterocyclic Chemistry. He is currently one of the Associate Editors for *Organic Reactions*. His hobbies include climbing tall mountains and building Calder like mobiles.