Total Synthesis of Natural Products

Jie Jack Li • E.J. Corey
Editors

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At the Frontiers of Organic Chemistry

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Dedicated to
Professor David Y. Gin (1967–2011)

Preface

The last few decades have witnessed some exciting developments of synthetic methodologies in organic chemistry. Chiefly among these developments are ring-closing metathesis (RCM) and transition metal-catalyzed C–H activation, which have emerged as novel and useful tools.

A touchstone for any synthetic methodology is how practical it is in synthesis, especially total synthesis of natural products. Therefore, it is not surprising that books on total synthesis occupy a place on nearly every organic chemist's bookshelf.

This volume is somewhat different from previous books on total synthesis. We have been fortunate enough to enlist eleven current practitioners in the field of total synthesis to describe one of their best total syntheses. These authors leveraged synthetic methodologies developed in their own laboratories as key operations in their construction of natural products. As such, this book reflects a true sense of what is happening at the frontiers of organic chemistry.

Skillman, NJ, USA — Jie Jack Li
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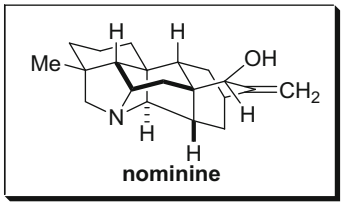
Chapter 1
Nominine

Kevin M. Peese and David Y. Gin



1.1 Introduction and Classification

The genera of *Aconitum* (commonly known as Monkshood) and *Delphinium*, and to a lesser extent *Rumex*, *Consolida*, and *Spiraea*, have long been recognized as a rich source of alkaloid natural products [1]. The diterpenoid alkaloids are generally classified into two major groups: the C_{19}-diterpenoid alkaloids (sometimes referred to as the C_{19}-norditerpenoid alkaloids) and the C_{20}-diterpenoid alkaloids. Within the C_{20}-diterpenoid alkaloids, at least 11 separate classes have been isolated, including the hetisine alkaloids (Chart 1.1).

Among the first hetisine alkaloids isolated were nominine (**1**) [2], kobusine (**2**) [3], pseudokobusine (**3**) [4], hetisine (**4**) [5], and ignavine (**5**) [6] in the 1940s and 1950s (Chart 1.2). Since these early isolations, over 100 distinct hetisine alkaloids have

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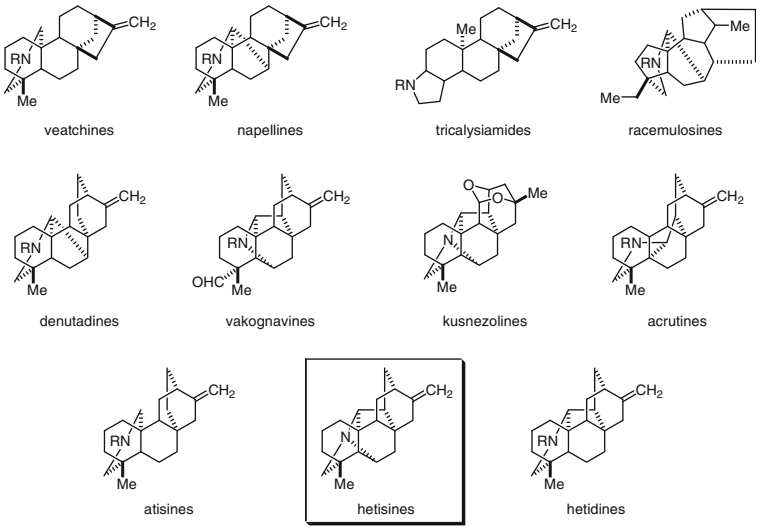


Chart 1.1 C_{20}-diterpenoid alkaloids

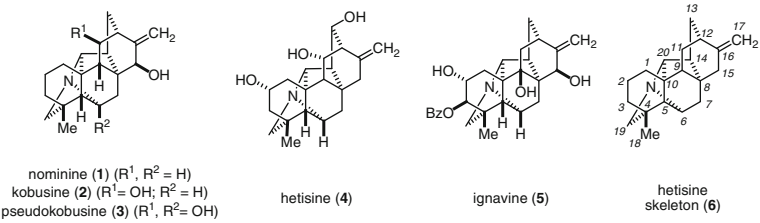


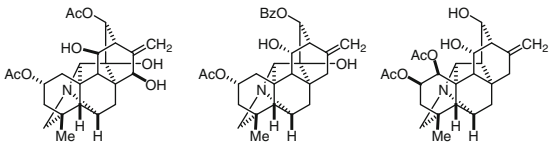
Chart 1.2 Hetisine alkaloids

been isolated and characterized with new alkaloids continuing to be discovered. Structurally, the hetisines are characterized by a highly fused heptacyclic ring system with an embedded tertiary nitrogen core. The separate members of the hetisine alkaloids are distinguished by the number, location, and stereochemical placement of oxygen functionality, primarily alcohols and simple esters.

1.2 Pharmacology

The hetisine alkaloids have long been recognized to be active constituents of traditional eastern herbal medicines [7]. Pharmacological investigations of the hetisine alkaloids have shown a diverse range of bioactivities [1b, 7]. Significantly, guan-fu base A (**7**) is reported to be under clinical development in China for arrhythmia [1a]. In addition, kobusine (**2**), pseudokobusine (**3**), as well as multiple

Chart 1.3
Pharmacologically significant hetisine alkaloids



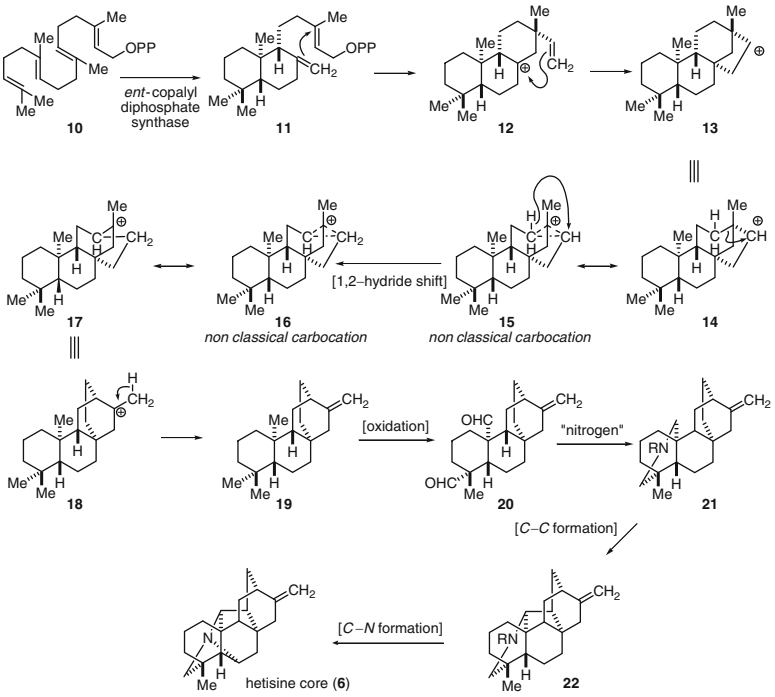
O-acyl derivatives thereof have shown potent vasodilatory activity [8]. A number of other hetisine alkaloids have shown diverse biological activities. These include nominine [9] (**1**) (local anesthetic, anti-inflammatory, and antiarrhythmic), hetisine [9a] (**4**) (hypotensive), ignavine [10] (**5**) (analgesic, anti-inflammatory, antipyretic, sedative, antidiuretic), zeravshanisine [9a] (**8**) (antiarrhythmic and local anesthetic), and tadzhaconine [9a, 11], (**9**) (antiarrhythmic) (Chart 1.3).

1.3 Biosynthesis

The biosynthesis of the atisane class of C_{20}-diterpene alkaloids, including the hetisine family, has been proposed to take place in two principal phases [1a]. The first phase encompasses biogenesis of most of the diterpene framework via a standard, diterpene biosynthesis (Scheme 1.1) [12]. Beginning with geranylgeranyl diphosphate (**10**), cyclization with *ent*-copalyl diphosphate synthase produces *ent*-copalyl diphosphate (**11**). The exocyclic alkene of **11** then undergoes annulation with the allylic diphosphate to afford, after a series of carbocation rearrangements, *ent*-atisir-16-ene (**19**). Noteworthy in this cascade is the nonclassical carbocations **15** and **16**. The second phase of the biosynthesis of the atisane class has been hypothesized, but is not well understood [13]. It has been proposed that an oxidation event occurs on *ent*-atisir-16-ene (**19**) to give a dialdehyde or its synthetic equivalent (**20**). Following a condensation event with a nitrogen source and reduction, the atisine skeleton (**21**) of C_{20}-diterpene alkaloids is accessed. Carbon–carbon bond formation between C-14 and C-20, possibly through a Prins-type intermediate, produces the hetidine skeleton (**22**) of C_{20}-diterpene alkaloids. Finally, bond formation between the nitrogen and C-6 generates the hetisine-type skeleton (**6**).

1.4 Previous Synthetic Work

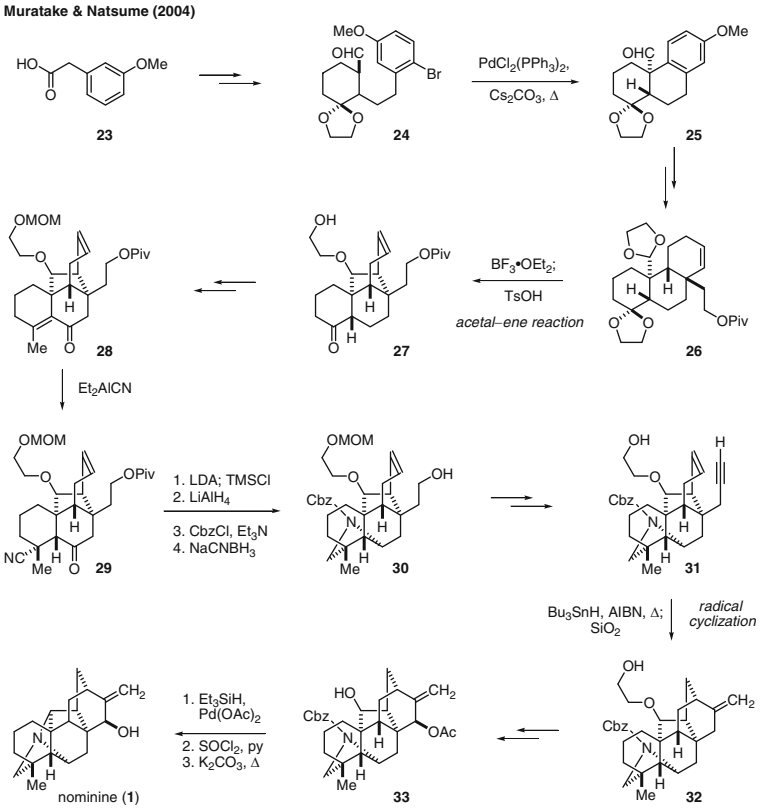
The C_{20}-diterpene alkaloids have long served as classic targets within the field of natural product synthesis [14]. Total syntheses of four C_{20}-diterpene alkaloids have thus far been reported: atisine [15], veatchine [16], garryine [17], and napelline [18]. In spite of this progress, synthetic efforts toward the hetisine alkaloids have been relatively sparse. Prior to our work in the area, these efforts include one total synthesis and five synthetic studies.



Scheme 1.1 Postulated biosynthesis of hetisine alkaloids

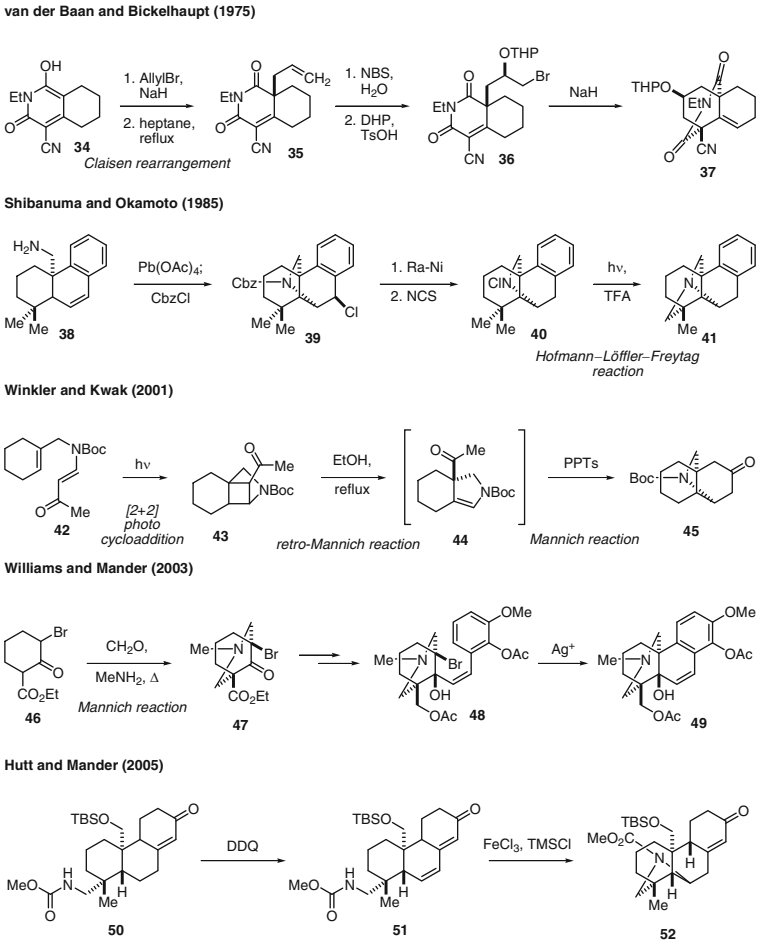
1.4.1 Total Synthesis of Nominine [19a]

In 2004, Muratake and Natsume reported the landmark total synthesis of (±)-nominine (**1**), the first total synthesis of a hetisine alkaloid (Scheme 1.2) [19]. Their approach was based upon two key reactions: α-arylation of an aldehyde [20] for formation of the C-9 and C-10 carbon–carbon bond (i.e., **24**→**25**) and Lewis acid-catalyzed acetal-ene reaction [21] for formation of the key C-14 and C-20 carbon–carbon bond (i.e., **26**→**27**). Beginning with 3-methoxyactetic acid (**23**), aryl bromide aldehyde **24** was prepared in a straightforward nine-step sequence. In the first key reaction of the synthesis, treatment of aryl bromide **24** with $PdCl_2(PPh_3)_2$ and Cs_2CO_3 in refluxing THF-delivered tricyclic **25** in 65 % yield, 4.2:1 *dr*. Next, elaboration through a six-step sequence produced intermediate alkene **26**. Acetal-ene reaction of **26** using $BF_3{\cdot}OEt_2$ in toluene at −18 °C afforded ether **27** in 66 % after subsequent deketalization with *p*-TsOH in acetone. Installation of the nitrogen atom began six steps later with the conjugate cyanation of enone **28** with Et_2AlCN (Nagata reagent) [22] in toluene resulting in β-cyanoketone **29**. Then, following protection of the ketone as the TMS enol ether, the cyano group was reduced to the primary amine



Scheme 1.2 Total synthesis of nominine, first total synthesis of a hetisine alkaloid

with $LiAlH_4$. The amine was condensed with the proximal ketone functionality to furnish the enamine which was immediately protected with a Cbz group leading to the protected enamine. Reduction of the enamine with $NaCNBH_3$ produced Cbz-protected pyrrolidine **30**. Following a ten-step interlude to complete construction of the [2.2.2] bicyclo-octane system, completion of the aza-ring system was addressed. Deprotection of the Cbz group of **33** was accomplished with Et_3SiH, $Pd(OAc)_2$, and NEt_3. The last critical *C–N* bond of the pyrrolidine was then formed via alkylation of the amine with the adjacent alcohol by first activation of the alcohol with $SOCl_2$ and then annulation. The synthesis was then completed with the deprotection of the allylic acetate to the allylic alcohol with K_2CO_3 in refluxing methanol-giving nominine. Overall, Muratake and Natsume were able to accomplish a 40-step synthesis of (±)-nominine in 0.15 % yield.



Scheme 1.3 Previous synthetic studies

1.4.2 Synthetic Studies Toward the Hetisine Alkaloids

In 1975, van der Baan and Bickelhaupt reported the synthesis of imide **37** from pyridone **34** as an approach to the hetisine alkaloids, using an intramolecular alkylation as the key step (Scheme 1.3) [23]. Beginning with pyridone **34**, alkylation with sodium hydride/allyl bromide followed by a thermal [3,3] Claisen rearrangement gave alkene **35**. Next, formation of the bromohydrin with *N*-bromosuccinimide and subsequent protection of the resulting alcohol as the tetrahydropyranyl (THP) ether produced bromide **36**, which was then cyclized in an intramolecular fashion to give tricylic **37**.

Ten years later in 1985, Shibanuma and Okamoto reported the synthesis of pentacyclic intermediate **41** (Scheme 1.3) [24]. This approach to the hetisine alkaloids, a refinement of work previously reported by Okamoto [25], utilized a Hofmann–Löffler–Freytag reaction to form the polycyclic substructure surrounding the tertiary amine of the hetisine alkaloids. In the key sequence of the synthesis, styrene **38** was subjected to lead tetraacetate [$Pb(OAc)_4$] oxidation to give an aziridine which was immediately fragmented by treatment with benzyl chloroformate (CbzCl) to give benzylic chloride **39**. Reductive cleavage of the benzylic chloride and concomitant cleavage of the carbamate with Raney nickel followed by *N*-chlorination of the amine provided the key Hofmann–Löffler–Freytag precursor *N*-chloramine **40**. Photolysis in acidic media provided the Hofmann–Löffler–Freytag reaction product **41**.

More recently in 2001, Winkler and Kwak reported methodology designed to access the pyrrolidine core of the hetisine alkaloids via a photochemical [2+2], retro-Mannich, Mannich sequence (Scheme 1.3) [26]. In a representative example of the methodology, vinylogous amide **42** was photo-irradiated to give the [2+2] cycloaddition product **43**. Heating cyclobutane **43** in ethanol provided enamine **44** via a retro-Mannich reaction. Exposure of enamine **44** to acidic conditions then effected a Mannich reaction, resulting in pyrrolidine **45**.

In 2003, Williams and Mander reported a method designed to access the hetisine alkaloids (Scheme 1.3) [27]. This approach, based upon a previously disclosed strategy by Shimizu et al. [28], relied on arylation of a bridgehead carbon via a carbocation intermediate in the key step. Beginning with β-keto ester **46**, double Mannich reaction provided piperidine **47**. Following a straightforward sequence, piperidine **47** was transformed to the pivotal bromide intermediate **48**. In the key step, bromide **48** was treated with silver (I) 2,4,6-trinitrobenzenesulfonate in nitromethane (optimized conditions) to provide **49** as the most advanced intermediate of the study, in 54 % yield.

Finally in 2005, Hutt and Mander reported their strategy for the synthesis of nominine (Scheme 1.3) [29]. The approach relies upon construction of the steroidal ABC carbocyclic ring structure followed by stepwise preparation of the fused aza-ring system. In the key sequence of the synthetic study, enone **50** was oxidized to dienone **51** with DDQ followed by Lewis acid-catalyzed intramolecular conjugate addition of the methylcarbamate to the newly formed dienone to deliver pyrrolidine **52**.

1.5 Strategy and Retrosynthesis

The highly fused and bridged architecture of the carbon–nitrogen skeleton within the hetisine alkaloids presents a formidable challenge for the synthetic chemist. While the placement and orientation of the oxygen functionalities of the various hetisine alkaloids presents its own hurdles, the key synthetic challenge of the hetisine family, exemplified by nominine as the simplest member, is construction of the polycyclic ring system, especially the scaffold surrounding the nitrogen.

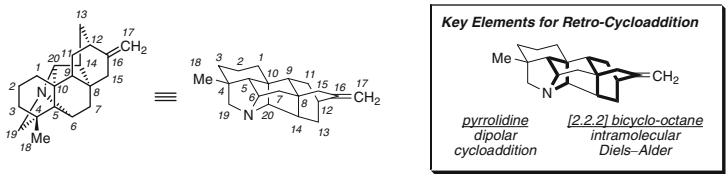
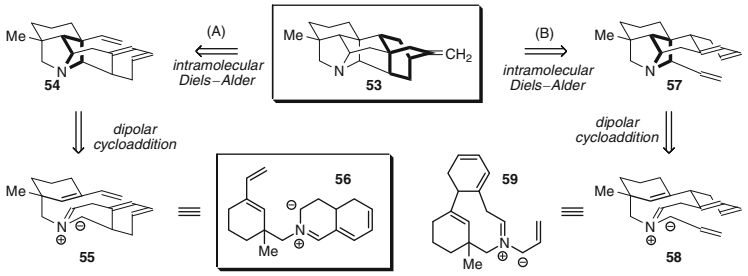


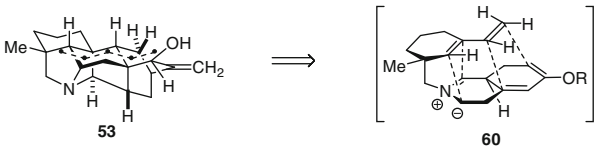
Chart 1.4 Key strategic retrosynthetic elements



Scheme 1.4 Retrosynthetic analysis

Intramolecular cycloadditions are among the most efficient methods for the synthesis of fused bicyclic ring systems [30]. From this perspective, the hetisine skeleton encompasses two key retro-cycloaddition key elements: (1) a bridging pyrrolidine ring accessible via a [3+2] azomethine dipolar cycloaddition and (2) a [2.2.2] bicyclo-octane accessible via a [4+2] Diels–Alder carbocyclic cycloaddition (Chart 1.4). While intramolecular [4+2] Diels–Alder cycloadditions to form [2.2.2] bicycle-octane systems have extensive precedence [3+2], azomethine dipolar cycloadditions to form highly fused aza systems are rare [31–33]. The staging of these two operations in sequence is critical to a unified synthetic plan. As the proposed [3+2] dipolar cycloaddition is expected to be the more challenging of the two transformations, it should be conducted in an early phase in the forward synthetic direction. As a result, a retrosynthetic analysis would entail initial consideration of the [4+2] cycloaddition to arrive at the optimal retrosynthetic C–C bond disconnections for this transformation.

Two possible intramolecular disconnections are available for the [2.2.2] bicyclo-octane ring system (path A and path B, Scheme 1.4). The choice between the initial [4+2] disconnections A and B at first appears inconsequential leading to idealized intermediates of comparable complexity (**54** and **57**). However, when the [4+2] and [3+2] disconnections are considered in sequence, the difference becomes clear. For path A, retrosynthetic [3+2] disconnection of intermediate **54** leads to the conceptual precursor **56**, which embodies a considerable simplification. In contrast, path B reveals a retrosynthetic [3+2] disconnection of intermediate **57** to provide the precursor **59**, a considerably less simplified medium-ring bridged macrocycle. Thus, unification of the [3+2]/[4+2] dual cycloaddition strategy, using the staging



Scheme 1.5 Simplified retrosynthesis

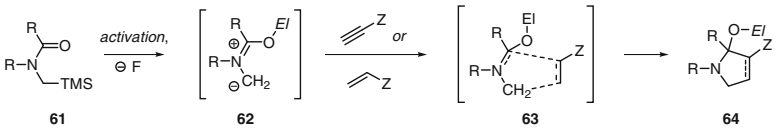
and disconnection approach of path A, leads to a highly streamlined retrosynthetic strategy (Scheme 1.5).

The use of biomimetic strategies in natural product synthesis has been an effective guide in development of total synthesis in recent years [34]. Biomimetic strategies are often the most elegant when the biosynthesis of a natural product imparts most of a molecule's complexity in one reaction or a tandem sequence that has a potential parallel in chemical synthesis. Examples of this can be found in Shair's synthesis of longithorone A [35] and Sorensen's elegant synthesis of (+)-FR182877 [36]. In the case of the proposed biosynthesis of the hetisine alkaloids, however, complexity is generated stepwise over an extended sequence. In fact, for the biosynthesis of the heptacyclic hetisine skeleton, no more than two rings are proposed to be generated in any particular step. Accordingly, following a biomimetic strategy is not likely to hold a privileged position relative to other synthetic strategies.

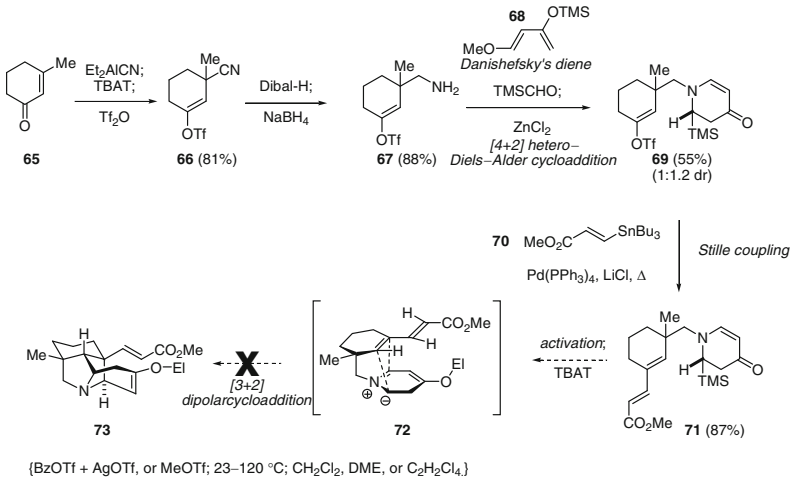
1.6 Synthesis

Synthetic work commenced with evaluation of an azomethine ylide dipole for the proposed intramolecular dipolar cycloaddition. A number of methods exist for the preparation of azomethine ylides, including, *inter alia*, transformations based on fluoride-mediated desilylation of α-silyliminium species, electrocyclic ring opening of aziridines, and tautomerization of α-amino acid ester imines [37]. In particular, the fluoride-mediated desilylation of α-silyliminium species, first reported by Vedejs in 1979 [38], is among the most widely used methods for the generation of non-stabilized azomethine ylides (Scheme 1.6).

The key cycloaddition reaction to form the pyrrolidine ring within the hetisine alkaloids involves the generation and reaction of an extended *endocyclic* azomethine ylide, a class of reactive intermediate with relatively little precedent [32, 33]. As a consequence, a suitable model system was explored to assess the feasibility of this cycloaddition approach (Scheme 1.7). To this end, 3-methylcylcohexen-2-one **65** underwent conjugate addition with cyanide using $Al(CN)Et_2$ in benzene affording an aluminum enolate [22]. Treatment of the enolate with TBAT generated an activated aluminum enolate, which upon treatment with Tf_2O, furnished vinyl triflate **66** in 81 % yield. Reduction of the nitrile with diisobutylaluminum hydride (DIBAL-H) followed by $NaBH_4$/MeOH produced amine **67** in 88 % yield. To construct the endocyclic



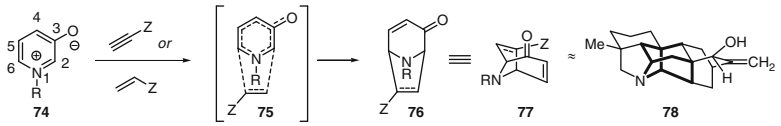
Scheme 1.6 Azomethine dipolar cycloaddition utilizing desilylation



Scheme 1.7 Intramolecular azomethine dipolar cycloaddition

dipole portion of the cycloaddition model substrate, a novel hetero Diels–Alder approach was developed to prepare a suitable 2,3-dihydro-2-silylpyridin-4-one. Condensation of amine **67** with TMSCHO generated the corresponding *C*-silyl aldimine, which was trapped in situ with Danishefsky's diene (**68**) in a hetero Diels–Alder cycloaddition under $ZnCl_2$ catalysis to provide the 2,3-dihydro-2-silylpyridin-4-one **69** [39]. The *C*-silyl vinylogous amide **69** was isolated in 55 % yield as an inseparable yet inconsequential 1.2:1 mixture of diastereomers. Subsequent introduction of the dipolarophile functionality in this model substrate was performed by Stille coupling [40] of vinyl triflate **69** with stannane **70** to afford the conjugated dienoate **71** (87 %), the requisite precursor to the proposed endocyclic azomethine ylide formation and intramolecular dipolar cycloaddition.

The feasibility of azomethine ylide generation from **7** and intramolecular dipolar cycloaddition was examined under a variety of conditions. For example, activation of vinylogous amide **71** with BzOTf [41] followed by desilylation with TBAT led to complex mixtures of products. Likewise, using MeOTf as the activating agent yielded similar results. Significantly, none of these protocols furnished the desired pyrrolidine **73**. Only decomposition of the silylpyridinone to form unidentified products was observed, despite the fact that quantitative *O*-methylation of the



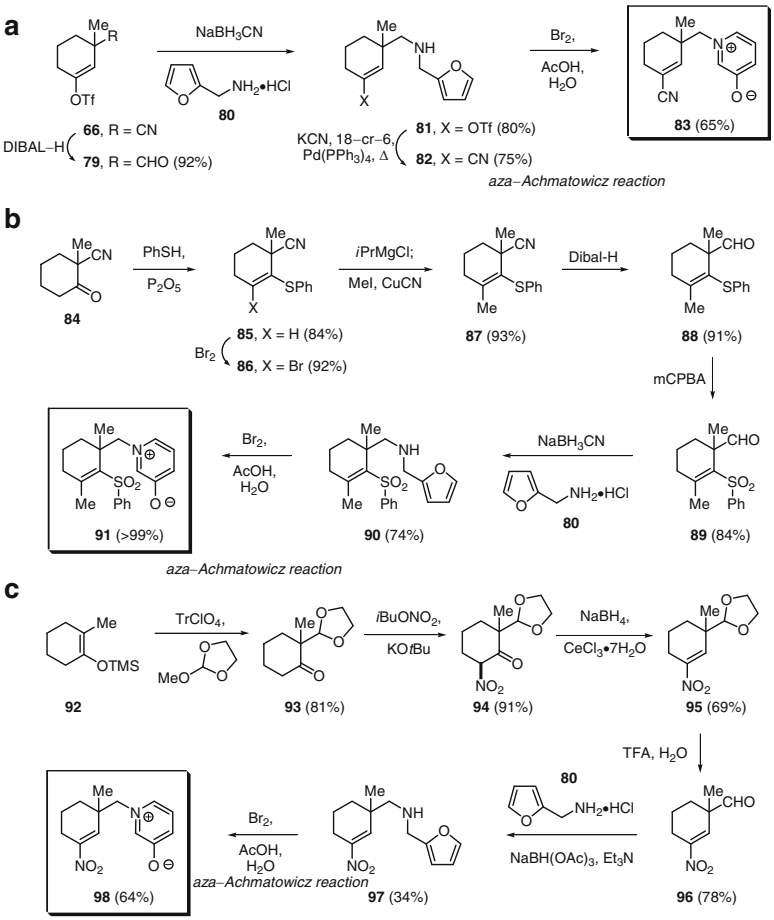
Scheme 1.8 Dipolar cycloaddition of 3-oxidopyridinium betaine

vinylogous amide was verified to occur by NMR analysis in the first stage of the process.

With the failure of **72** to undergo the desired intramolecular dipolar cycloaddition, the strategy of employing an endocyclic non-stabilized azomethine ylide in the key cycloaddition step was reevaluated. Since the difficulties in this approach were likely associated with lack of stability of the azomethine ylide, a new route involving the generation and cycloaddition of a more stabilized substrate was pursued. In this context, oxidopyridinium ylides display reactivity patterns similar to azomethine ylides with the exception that oxidopyridinium ylides tend to be less reactive due to their enhanced stability. Dipolar cycloadditions of 3-oxidopyridinium betaines (**74**) were introduced by Katritzky in 1970 [42] and have since been shown to be useful in numerous synthetic transformations (Scheme 1.8) [43]. Oxidopyridinium betaines **74** are moderately reactive aza–1,3–dipoles that undergo dipolar cycloaddition reactions at the 2,6-positions of the pyridinium ring with electron-deficient alkene and alkyne dipolarophiles to afford tropane cycloadducts **76** = **77**. These cycloadditions are generally under *HOMO*–dipole *LUMO*–dipolarophile control and preferentially provide *endo* products.

To investigate the feasibility of employing 3-oxidopyridinium betaines as stabilized 1,3-dipoles in an intramolecular dipolar cycloaddition to construct the hetisine alkaloid core (Scheme 1.8, **77** ≈ **78**), a series of model cycloaddition substrates were prepared. In the first (Scheme 1.9a), an ene-nitrile substrate (i.e., **83**) was selected as an activated dipolarophile functionality. Nitrile **66** was subjected to reduction with DIBAL-H, affording aldehyde **79** in 79 % yield. This was followed by reductive amination of aldehyde **x** with furfurylamine (**80**) to afford the furan amine **81** in 80 % yield. The ene-nitrile was then readily accessed via palladium-catalyzed cyanation of the enol triflate with KCN, 18–crown–6, and $Pd(PPh_3)_4$ in refluxing benzene to provide ene-nitrile **82** in 75 % yield. Finally, bromine-mediated aza-Achmatowicz reaction [44] of **82** then delivered oxidopyridinium betaine **83** in 65 % yield.

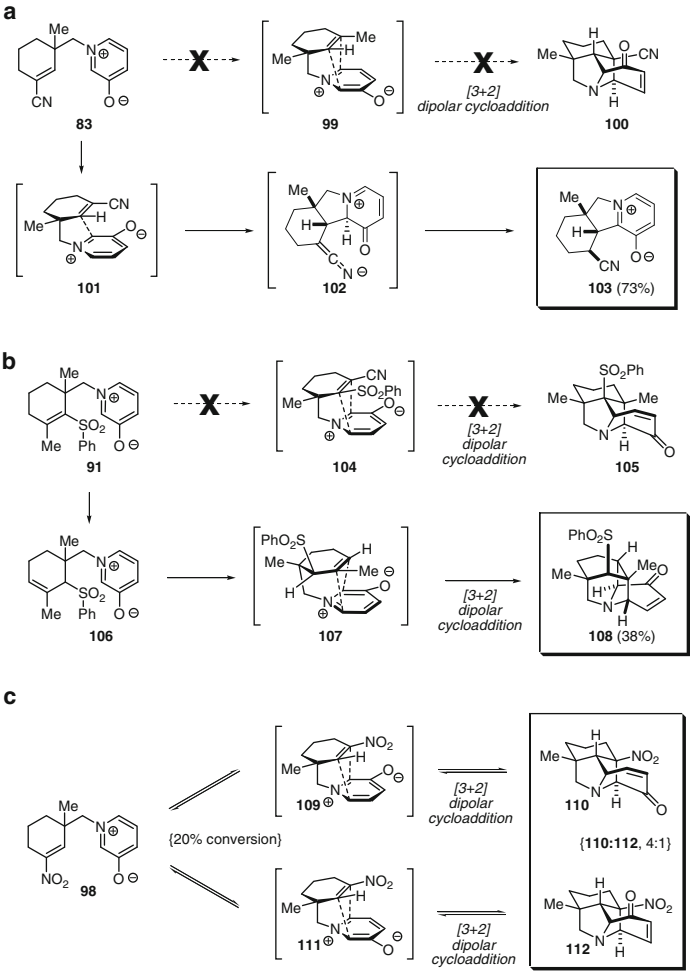
The second cycloaddition substrate took to form of **91** (Scheme 1.9b), incorporating a vinyl sulfone dipolarophile. Beginning with cyano ketone **84**, which was readily prepared from 1,5-dicyanopentane via a previously reported three-step sequence [45], condensation with thiophenol produced vinyl sulfide **85** in 84 % yield. Vinyl sulfide **85** underwent bromination in acetonitrile to afford bromo-vinyl sulfide **86** (86 %), which was then treated with isopropylmagnesium chloride [46] to effect metal-halogen exchange affording an intermediate vinyl magnesium bromide species. Subsequent alkylation with MeI in the presence of catalytic CuCN provided the alkylated vinyl sulfide **87** in 93 % yield. The nitrile within vinyl



Scheme 1.9 Preparation of model cycloaddition substrates

sulfide **87** was reduced with DIBAL-H to furnish aldehyde **88** (91 %), which was followed by oxidation of the sulfide with *m*-CPBA-generated sulfone **89** (84 %), and subsequent reductive amination with furfuryl amine hydrochloride (**80**) to afford substituted furfuryl amine **90** (74 %). Finally, bromine-mediated aza-Achmatowicz [44] reaction of furfuryl amine **90** produced oxidopyridinium betaine **91** in quantitative yield.

The third cycloaddition substrate explored the feasibility of a vinyl nitro functionality as an activated dipolarophile (**98**, Scheme 1.9c). Preparation of nitroalkene oxidopyridinium betaine **98** began with silylenol ether **92**, which was treated with methoxydioxolane in the presence of Lewis acid catalyst, $TrClO_4$, to afford keto dioxolane **93** in 58 % yield [47]. Ketone **93** then underwent α-nitration by treatment with *i*-BuONO_2 and KO*t*-Bu to provide nitro ketone **84** (91 %), which was then converted to the nitroalkene functionality via reduction under Luche conditions to



Scheme 1.10 Evaluation of intramolecular dipolar cycloadditions of model substrates

furnish nitroalkene **95** (69 %) [48]. Deprotection of the dioxolane group with aqueous trifluoroacetic acid produced aldehyde **96** (78 %), which underwent reductive amination of with furfuryl amine hydrochloride (**80**) to furnish the substituted furfuryl amine **97** in 34 % yield. Bromine-mediated aza-Achmatowicz reaction [44] of furfuryl amine **97** provided oxidopyridinium betaine **98** (64 %) to serve as the 1,3-dipole.

Each of the 3-oxidopyridinium betaine substrates **83**, **91**, and **98** were extensively investigated for their potential to engage in intramolecular dipolar cycloaddition (Scheme 1.10). Heating a solution of ene-nitrile **83** in variety of solvents failed to effect the desired intramolecular [3+2] dipolar cycloaddition to form the bridged pyrrolidine **100**, as tricyclic oxidopyridinium betaine **103** was the only

isolated product (Scheme 1.10a). For example, when the reaction was conducted in toluene at 170 °C over 5 days, a 73 % yield of tricyclic betaine **103** could be isolated. Formation of tricyclic betaine **103** was the result of direct conjugate addition of the oxidopyridinium betaine into the ene-nitrile followed by re-aromatization. It had been envisioned that the use of the ene-nitrile would disfavor the conjugate addition pathway by excluding an intramolecular protonation event. This is to some extent true, given the high temperature and extended reaction time required to effect the formation of **103**. Unfortunately, even though the conjugate addition pathway of the ene-nitrile moiety was entailed a high activation barrier, it was still the dominant reaction manifold.

Investigation of the vinyl sulfone cycloaddition substrate (**91**, Scheme 1.10b) led to an alternate reaction manifold, albeit still inappropriate for the synthesis of the hetisine core. Heating a dilute solution of oxidopyridinium betaine **91** in refluxing toluene led to the formation of cycloadduct **108** in 38 % yield as the principal product. Formation of this undesired isomeric cycloadduct **108** is likely the result of an alkene isomerization process wherein the α,β-π-system of dipolarophile **91** migrates to the β,γ-position relative to the sulfone to provide tri-substituted dipolarophile **106**. This unactivated alkene **106** then intramolecular dipolar cycloaddition at elevated temperature to furnish undesired isomeric cycloadduct **108**. The alkene isomerization event is likely driven by a relief of steric strain present in the tetra-substituted alkene **91**. Moreover, it has been shown that sulfones generally have no significant conjugative stabilization with adjacent alkenes due to lack of significant orbital overlap between the sulfone and the alkene π-system, so it is not surprising that such an isomerization would occur [49]. Indeed, this reactivity has on occasion been synthetically exploited [50]. Unfortunately, an extensive survey of a wide array of solvents showed no improvement; in no experiment could desired cycloadduct **105** be observed.

Despite the lack of success in the attempts at intramolecular cycloaddition with substrates **83** and **91**, a moderately promising outcome was observed for the nitroalkene substrate (**98**, Scheme 1.10c). Heating a dilute solution of oxidopyridinium betaine **98** in toluene to 120 °C produced a 20 % conversion to a 4:1 mixture of two cycloadducts (**110** and **112**), in which the major cycloadduct was identified as **110**. While initially very encouraging, it became apparent that the dipolar cycloaddition reaction proceeded to no greater than 20 % conversion, an outcome independent of choice of reaction solvent. Further investigation, however, revealed that the reaction had reached thermodynamic equilibrium at 20 % conversion, a fact verified by resubmission of the purified major cycloadduct **110** to the reaction conditions to reestablish the same equilibrium mixture at 20 % conversion.

In an effort to shift the cycloaddition equilibrium toward the cycloaddition products, a strategy was formulated to lower the energetic cost of breaking aromaticity of the betaine moiety. It was surmised that if an aromatic ring were fused to the oxidopyridinium betaine, the energetic cost of de-aromatization of the betaine would be lowered. In this context, use of a 4-oxidoisoquinolinium betaine in an aza–1,3–dipolar cycloaddition was first reported by Katritzky in 1972 [51] during his seminal studies on oxidopyridinium betaines. Dipolar cycloadditions of