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Recent approaches to the construction of 1-azaspiro[4.5]decanes and related 1-azaspirocycles

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Contents

Keywords: Azaspirocyclic ring systems; Spirocycles; 3° Carbon center.

Abbreviations: Ac, acetyl; AIBN, azobisisobutyronitrile(2,2′-azo(2-methylpropionitrile)); Ar, aryl; Bn, benzyl; Boc, *t*-butoxycarbonyl; Bu, butyl; Cbz, benzyloxycarbonyl; Cy, cyclohexyl; DBB, di-*t*-butylbiphenylide; DBU, diazadicycloundecane; DIB, di(acetoxyl)iodobenzene; DMAP, 4-dimethylaminopyridine; DMSO, dimethylsulfoxide; DPPA, diphenylphosphorylazide; DTBHN, di-*t*-butylhyponitrite; Et, ethyl; h, hours; HMDS, hexamethyldisilazide; H–W–E, Horner–Wadsworth–Emmons Reaction; LA, arbitrary Lewis acid; LDA, lithium di(isopropyl)amide; Me, methyl; MOM, methoxymethyl; MS, molecular sieve; NMO, *N*-methyl morpholine *N*-oxide; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NPS, *N*-phenylselenylsuccinimide; Ph, phenyl; PMB, *p*-methoxybenzyl; Pr, propyl; rt, room temperature; SEM, 2-(trimethylsilyl)ethoxymethyl; SIMes, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene; TBAF, tetrabutylammonium fluoride; TBS, *t*-butyldimethylsilyl; TBDPS, *t*-butyldiphenylsilyl; TMS, trimethylsilyl; Tf, trifluoromethanesulfonate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; tol, toluyl; TMG, tetramethylguanidine; TPAP, tetrapropylammonium perruthenate; Ts, *p*-toluenesulfonyl.

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1. Introduction

Natural products are embedded with structural motifs that inspire practitioners of synthetic organic chemistry. The development of new synthetic methods and strategies for the construction of these motifs is a continuing focus of interest for our community. In assessing the strengths and weaknesses of a synthetic approach, criteria that can be used to evaluate each method include conciseness, efficiency, functional group compatibility, cost, 'elegance' as well as other factors. Although in practice each method has its own pros and cons, the instructive value for each is substantial. These studies define within specific contexts 'achievable' and, perhaps more importantly, 'unachievable' processes. 'Unachievable' transformations or strategies present problems that require further examination and, hopefully, innovation.

The 1-azaspiro[4.5]decane ring system, along with related structures such as the 1-azaspiro[5.5]undecane, 1-azaspiro[4.4]nonane and 6-azaspiro[4.5]decane ring systems, represent structural motifs that can be termed, despite obvious nomenclature inaccuracies, as '1-azaspirocycles' (Fig. 1). These cyclic systems incorporate two rings connected by a spiro ring fusion containing a nitrogen atom adjacent to the ring junction. This structural motif has been observed in a number of alkaloid natural products (starred atoms in structures in Fig. 2).

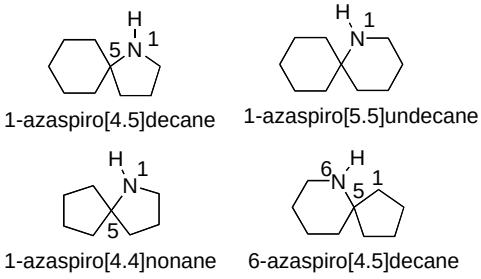


Figure 1. 1-Azaspiro[4.5]decane and structurally related '1-azaspirocycles'.

This ring system is not only observed in natural products that have served as synthetic targets for a number of years, such as histrionicotoxin,[1] cephalotaxine[2] and erythrina alkaloids[3] as exemplified by erysotramidine and cocculidine (Fig. 2), but also within natural products whose structures have only recently been reported. Examples of these compounds include halichlorine,[4] pinnaic acid (not pictured),[5] TAN1251A,[6] FR901483[7] and members of the cylindricine family such as fasicularin,[8] cylindricine A[9] and lepadiformine.[10]

A number of methods have been described recently for the construction of azaspirocyclic ring systems, especially within the context of synthetic approaches to targets in Figure 1. The synthesis of spirocycles that contain more than one heteroatom as exemplified within the natural products in Figure 3 will not be covered in this review.

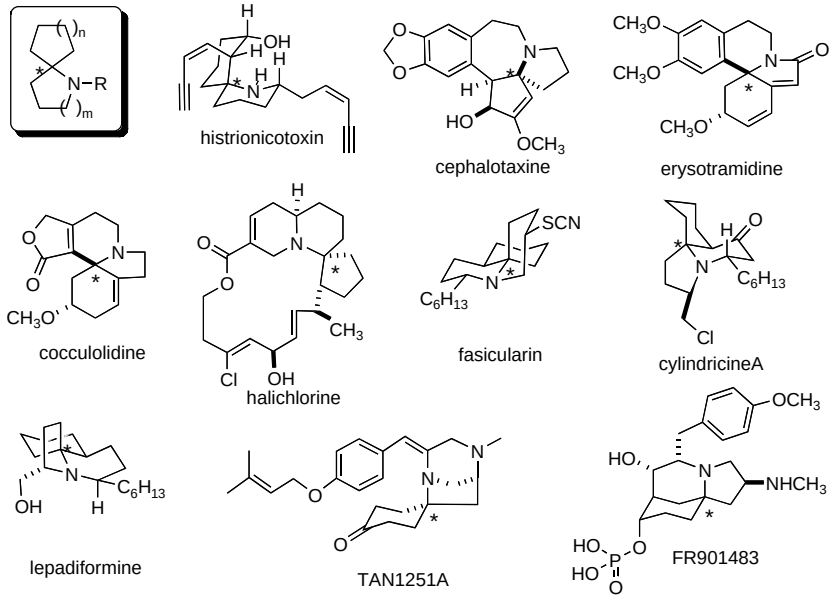


Figure 2. Alkaloids that contain 1-azaspirocycle motifs.

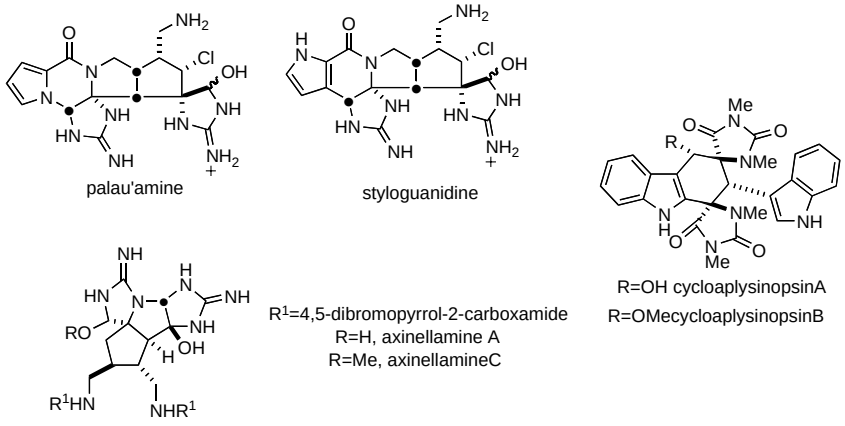


Figure 3. Alkaloids with spirocycle substructures not covered in this review.

Recent reviews dealing with aspects of this general topic are available.[11] This report will present recent developments to provide an overview of the diverse strategies for the construction of these azaspirocyclic structural motifs.

1.1. Organization

In considering a route to construct 1-azaspirocyclic motifs, two synthetic challenges must be considered. The first problem is the construction of the 3° carbon center bearing the nitrogen atom that will ultimately become the spirocycle ring junction. This carbon is often a stereogenic center, thus necessitating stereochemical control in its formation. The second issue is the installation of the 'rings' of the spirocyclic system. By defining these two synthetic problems, approaches to 1-azaspirocycles can be divided into three general possibilities (Fig. 4). The first two strategies require a two-step process where the 3° carbon center and the spirocycle are each constructed in separate events. The establishment of the 3° carbon center could be achieved in an early step, and a subsequent discrete step would close the heterocycle of the spirocyclic system (path a). Formation of the 3° stereogenic center could also conceivably be followed by carbocycle formation in a two-step process (path b). A third approach is to combine both the generation of the 3° stereogenic center and the formation of the spirocyclic ring system within the same reaction (path c). This account is organized on the basis of these three approaches to the formation of 1-azaspirocycles.

2. Approaches that construct the 3° center, then close the heterocycle

In determining a synthetic approach to a 1-azaspirocycle, a useful solution is to break the synthetic challenge into two parts. In this section, the two-step strategy in which the 3° center is established followed by formation of the heterocycle to generate the spiro-ring system is presented. By necessity, installation of the carbon atom bearing the nitrogen atom must precede the formation of the spirocycle. As such, methods that can generate a 3° stereogenic center bearing a nitrogen functionality are used. Common methods to perform this transformation include the Curtius

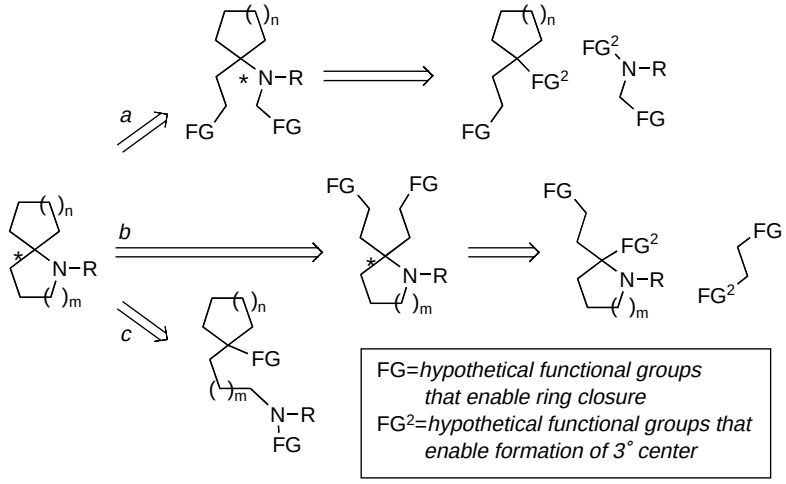
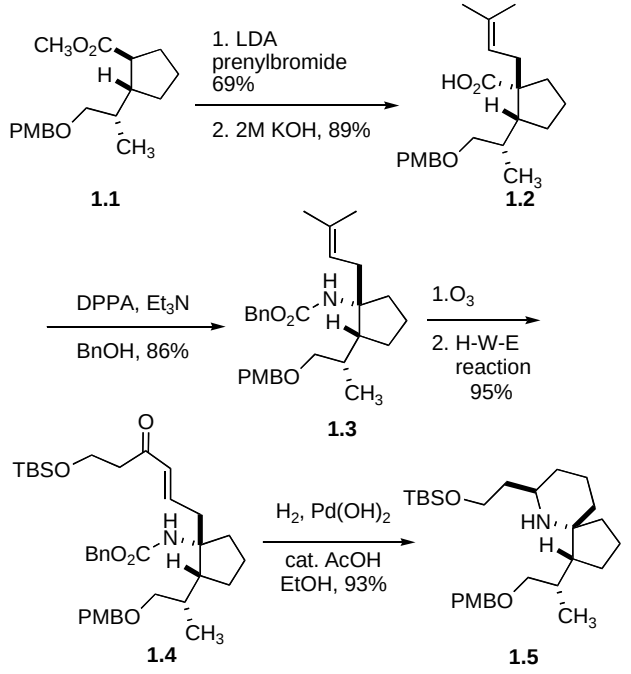


Figure 4. Approaches to target ring system.

rearrangement, addition of organometallic reagents (e.g., Grignard reagents) to imines, or conjugate addition reactions using amine nucleophiles. With formation of the 3° center complete, the heterocyclic ring must be constructed. This can be performed using C–C bond forming reactions such as ring closing metathesis. However, as C–N bond forming processes are comparatively easy, these procedures are often used, as well. Typical examples are reductive amination reactions or lactamization reactions.

2.1. Curtius rearrangement–reductive amination

A classic method of establishing a 3° stereogenic center attached to an amine-derived functional group is the Curtius rearrangement. In the Arimoto route, ester **1.1** was sequentially treated with LDA followed by prenyl bromide to establish the 4° carbon stereocenter in **1.2** (Scheme 1).

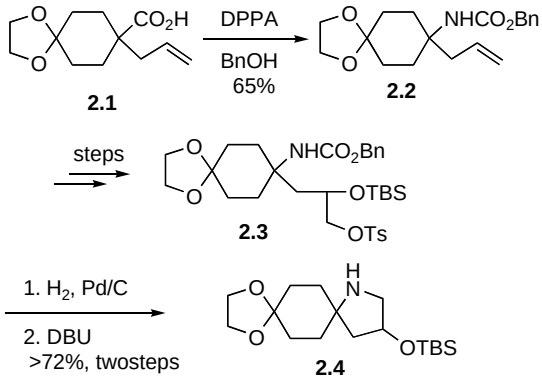


Scheme 1. The arimoto route.

Saponification of the methyl ester followed by reaction with diphenylphosphoryl azide (DPPA), triethylamine and benzyl alcohol produced benzyl carbamate **1.3** in 71% yield.[12] Oxidative cleavage of the alkene followed by a Horner–Wadsworth–Emmons reaction led to ketone **1.4** in good yield. The C–N bond completing the spirocyclic ring system was established using reductive amination. Catalytic hydrogenation of **1.4** smoothly provided **1.5**, reducing the iminium ion intermediate on the least hindered face of the heterocycle.

2.2. Curtius rearrangement–N-alkylation

The 3° stereocenter in **2.2** was similarly established using a Curtius rearrangement (Scheme 2). The conversion of **2.2** to 1° tosylate **2.3** utilized standard procedures. The benzyl carbamate function in **2.3** was deprotected (H_2, Pd/C) and subsequently treated, without purification, with DBU to smoothly produce the desired spirocycle **2.4** in >72% yield (over two steps) from **2.3**.[13]

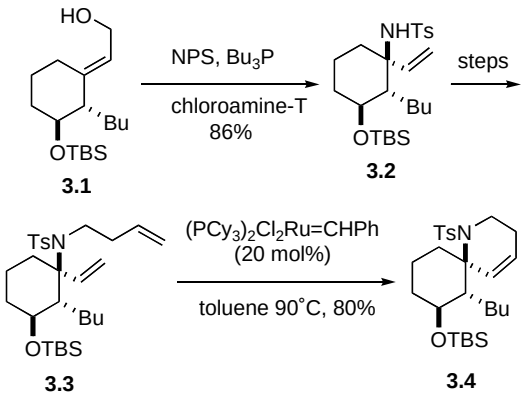


Scheme 2. The Nagumo/Kawahara route.

2.3. Sigmatropic rearrangement–ring closing metathesis

The reaction of allylic alcohol **3.1** with *N*-phenylselenylsuccinimide (NPS) in the presence of tributylphosphine and chloroamine T smoothly produced, via a [2,3] sigmatropic

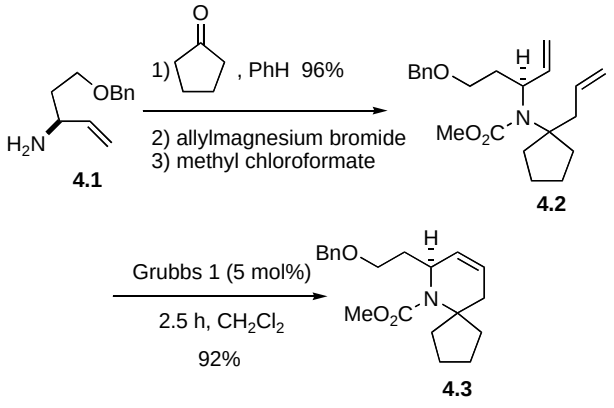
rearrangement, allylic sulfonamide **3.2** in 86% yield, establishing the required 3° stereocenter (Scheme 3).[14] N-alkylation followed by ring closing metathesis using $(PCy_3)_2$ $Cl_2Ru{=}CHPh$ (the Grubbs 'first-generation' precatalyst, 'Grubbs 1') produced spirocycle **3.4** in 80% yield.[15] This material was used in a synthesis of perhydrohistrionicotoxin.



Scheme 3. The Tanner route.

2.4. Imine addition–ring closing metathesis

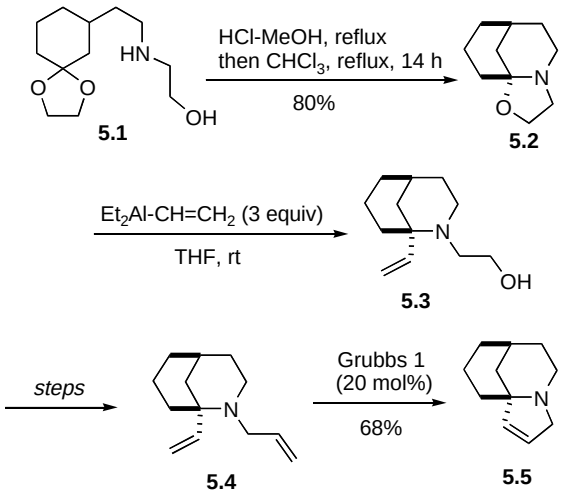
Imine formation using **4.1** and cyclopentanone was followed by the sequential addition of allyl magnesium bromide and methyl chloroformate (Scheme 4). Subjecting alkene **4.2** to the Grubbs 1 precatalyst produced spirocycle **4.3** in 92% yield. Protection of the amine function as its methyl carbamate was important as the corresponding reaction using a free amine in the metathesis substrate required a 60% 'catalyst' load using an acid-copromoter to produce only 33% of cyclized product after 20 days.[16]



Scheme 4. The Wright route.

2.5. Iminium ion addition–ring closing metathesis

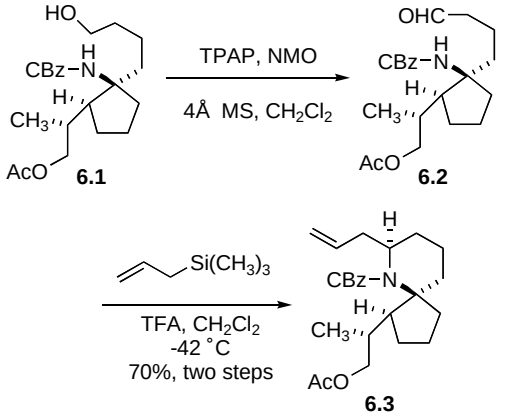
The Kibayashi group presented the following construction of a bridged spirocycle-containing ring system of FR901483 (Scheme 5).[17] Intramolecular transketalization of **5.1** provided bridged ring system **5.2**. Addition of a vinyl group to the iminium ion generated in situ from **5.2** was accomplished using vinyldiethylalane to produce **5.3**. Subsequent manipulation of **5.3** resulted in **5.4**. Ring closing metathesis of **5.4** using a 20 mol% catalyst loading of the Grubbs 1 precatalyst produced **5.5** in 68% yield.



Scheme 5. The Kibayashi metathesis route.

2.6. Not disclosed-iminium ion addition

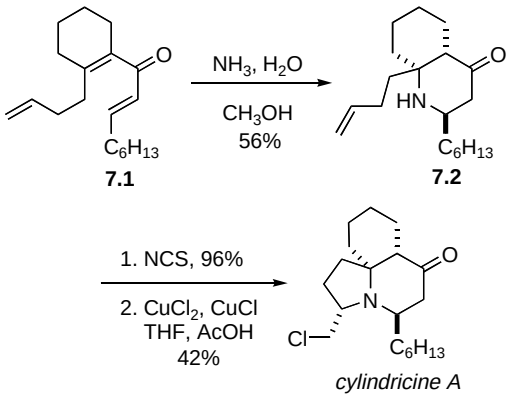
In a preparation of a spirocyclic ring system related to halichlorine, the following sequence was disclosed (Scheme 6).[18] The oxidation of alcohol **6.1** (the preparation was not disclosed) was followed by treatment of aldehyde **6.2** with trifluoroacetic acid and allyltrimethylsilane. The *N*-carbamoyl iminium ion that was formed in situ reacted with allyltrimethylsilane to form azaspirocycle **6.3** in 70% yield as a single diastereomer. The diastereoselectivity of the addition reaction was rationalized via an axial attack on the less hindered face of the *N*-carbamoyl iminium ion.



Scheme 6. The Forsyth route.

2.7. Conjugate addition–radical cyclization

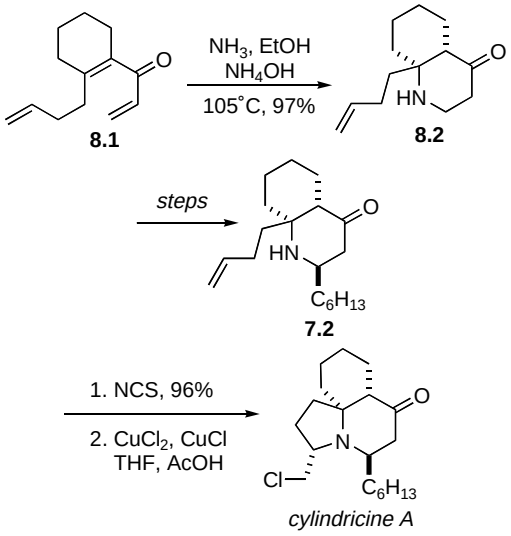
In early syntheses of cylindricines A and B, the 3° stereogenic center of the spirocycle in the natural product was established using a conjugate addition sequence of ammonia to bis-enone **7.1** (Scheme 7).[19] N-chlorination was followed by radical cyclization, using the procedure



Scheme 7. The Snider approach to the cylindricines.

established by Stella,[20] to form the spirocyclic structure within these alkaloids.

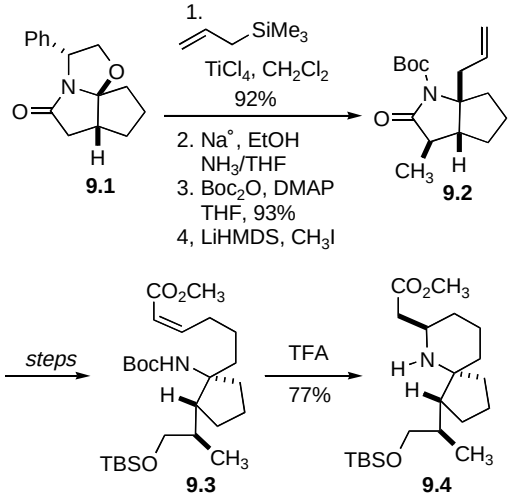
Heathcock and Liu used a conceptually similar approach in another cylindricine synthesis (Scheme 8).[21] A conjugate addition of ammonia to **8.1** installed the required 3° stereocenter. After subsequent manipulation of **8.2**, a Stella procedure was used to form the spirocycle in the natural product.



Scheme 8. The Heathcock route to the cylindricines.

2.8. Iminium ion addition–conjugate addition

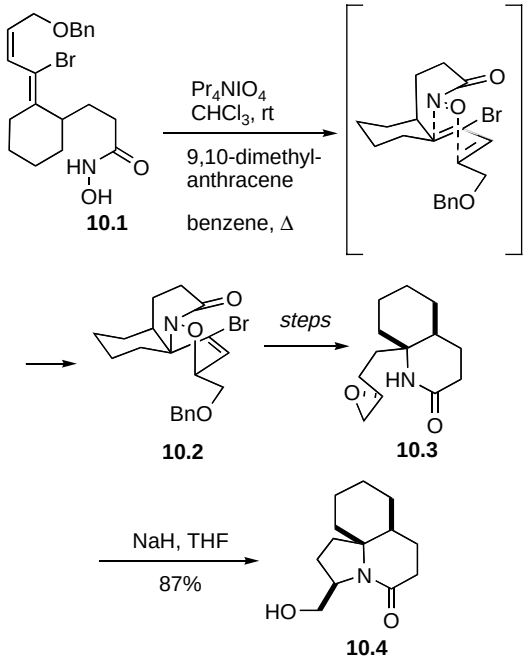
The bias of a [3.3.0] bicyclic ring system was used to ensure control in establishing the stereochemistry of the 3° center in Danishefsky's approach to halichlorine and pinnaic acid (Scheme 9).[22] Titanium tetrachloride promoted addition of allyltrimethylsilane to lactam **9.1** established the stereochemistry of what would become the 3° stereocenter of the natural product. This process was followed by several functional group manipulations to produce enoate **9.3**. Deprotection of the *t*-butylcarbamate group within **9.3** initiated spontaneous intramolecular conjugate addition to the enoate, producing **9.4** in 77% yield.



Scheme 9. The Danishefsky route.

2.9. Cycloaddition–N-alkylation

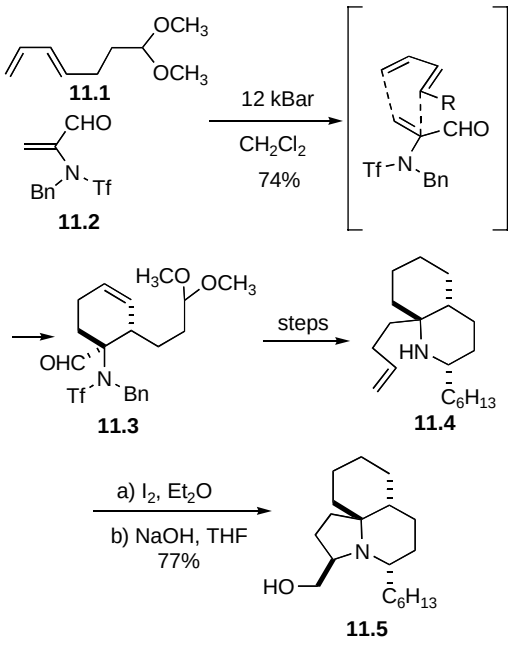
In an early approach to lepadiformine, an *N*-acyl nitroso Diels–Alder reaction was used to establish the 3° center in a stereocontrolled manner (Scheme 10).[23] The major stereochemical result of the cycloaddition reaction can be rationalized by the minimization of $A^{1,3}$ strain between the nitroso containing side chain and the bromine substituent on the diene within **10.1**. Several steps led to the eventual formation of **10.3**. Closure of the spirocyclic ring occurred uneventfully as treatment of **10.3** with NaH in THF led to the requisite spirocycle in 87% yield.



Scheme 10. The Kibayashi *N*-acyl nitroso Diels–Alder route.

2.10. [4+2] Cycloaddition–iodoamination of an alkene

An alternative cycloddition-based approach towards lepadiformine was implemented by the Funk group

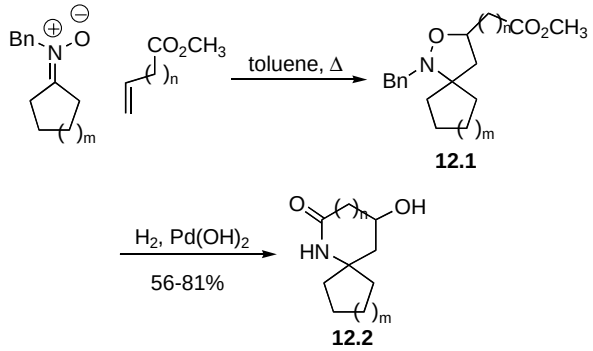


Scheme 11. The Funk α-amidoacrolein cycloaddition route.

(Scheme 11).[24] Specifically, a Diels–Alder reaction between diene **11.1** and dienophile **11.2** under high pressure produced functionalized cyclohexene **11.3** in 74% yield, establishing the requisite 3° center for the spirocycle. Elaboration of **11.3** provided **11.4**, which upon treatment of iodine underwent a smooth cyclization to form the spirocyclic ring system within **11.5**. A very similar transformation was used by the Funk group to establish the spirocyclic ring system of fasicularin.

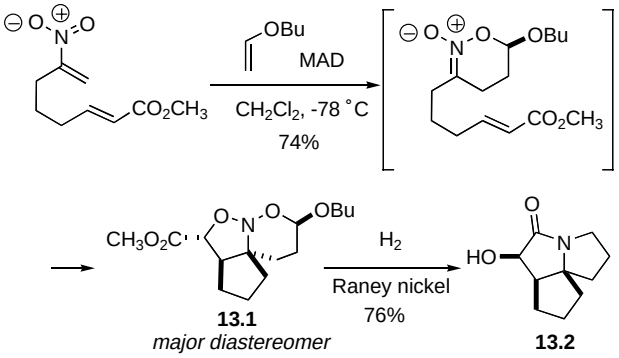
2.11. [3+2] Cycloaddition–amide bond formation

In the late 1980s, the Funk group devised a route to spirocyclic ring systems (Scheme 12).[25] Specifically, a [3+2] dipolar cycloaddition was used to establish the 3° center required in the spirocycle. Hydrogenolysis of the N–O bond followed by spontaneous lactamization resulted in the formation of azaspirocycles of type **12.2**. This procedure was adapted in a more complex setting by the Snider group in a recent synthesis of (−)-FR901483.[26]



Scheme 12. The Funk dipolar cycloaddition route.

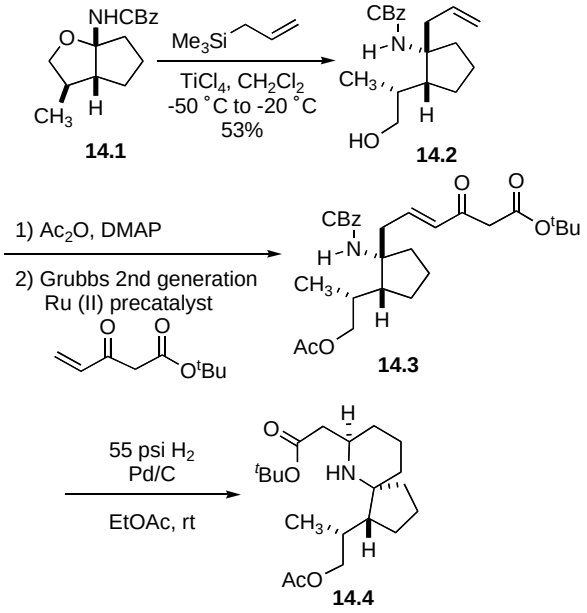
A tandem hetero-[4+2]/[3+2] cycloaddition sequence formed heterocycle **13.1** (Scheme 13).[27] Reductive cleavage of the N–O bonds in this instance resulted in a one-pot reductive amination–lactamization sequence, leading to the efficient formation of the azaspirocycle ring system in **13.2**.



Scheme 13. The Denmark route.

2.12. Iminium ion addition–reductive amination

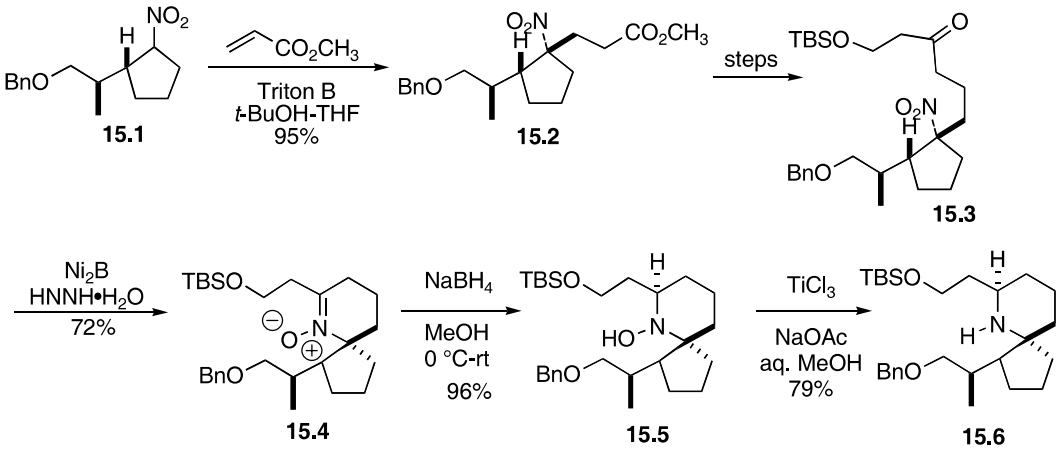
The Heathcock approach to halichlorine and the pinnaic acids outlined in Scheme 14 used the following protocol.[28] Allylsilane addition to **14.1** mediated by titanium tetrachloride gave adduct **14.2**. With the 3° center of the spirocycle established, acetylation and cross-metathesis provided **14.3**, which served as a precursor to reductive amination. Hydrogenation of **14.3** over palladium on carbon provided **14.4**, an intermediate in the Heathcock synthesis.



Scheme 14. The Heathcock route to halichlorine/pinnaic acid.

2.13. Nitroalkane alkylation–imine reduction

Conjugate addition of the anion derived from the nitro function in **15.1** to methyl acrylate resulted in the formation of **15.2** in 95% yield (Scheme 15).

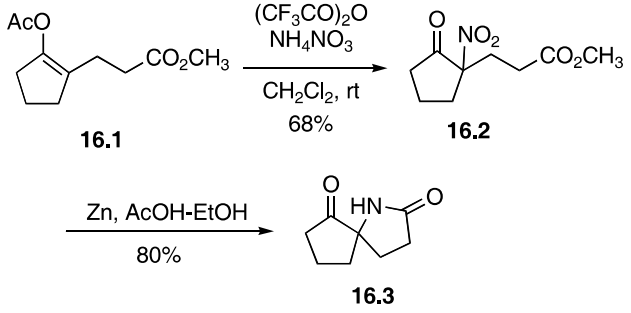


Scheme 15. The Zhao route.

The relative stereochemistry of **15.2** was a result of electrophile approach to the less-hindered face of the anion of **15.1**. Functional group manipulation led to **15.3**. Formation of the spiro compound necessitated three steps. Reduction using nickel boride and hydrazine hydrate generated nitrone **15.4**. Further reduction using sodium borohydride followed by titanium trichloride produced spirocycle **15.6** in good yield.[29] Bonjoch reported a conceptually similar approach.[30] A recent approach to the erythrinan alkaloids also used an alkylation reaction as the key step to establish the critical 3° stereocenter.[31]

2.14. Electrophilic nitration–amide bond formation

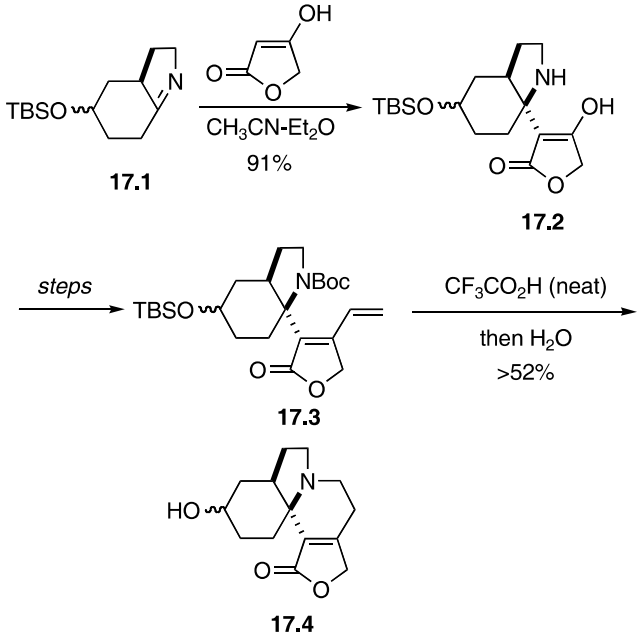
A straightforward approach to azaspirocycles utilized the installation of a nitro function adjacent to a ketone carbonyl moiety using enol acetate **16.1** as a key precursor (Scheme 16).[32] Treatment of **16.1** with ammonium nitrate in the presence of trifluoroacetic anhydride gave ketone **16.2**. Chemoselective reduction of the nitro functional group using Zn in acidic ethanol led to spontaneous amide bond formation to provide **16.3**.



Scheme 16. The Nagasaka route.

2.15. Imine addition–conjugate addition

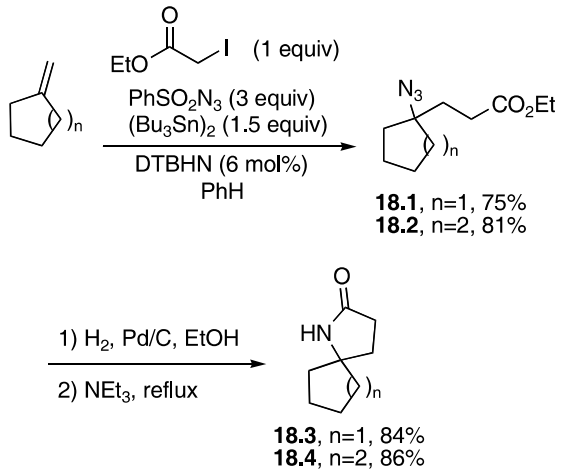
The reaction of imine **17.1** with tetronic acid in an acetonitrile–ether mixture produced adduct **17.2** in excellent yield (Scheme 17).[33] This procedure established the 3° center in the target structure. Compound **17.2** was converted to **17.3** using standard manipulations. Deprotection of the carbamate protecting group using trifluoroacetic acid led to spontaneous 1,6-addition to furnish spirocycle **17.4**.



Scheme 17. The Kitahara route.

2.16. Radical addition to alkene–lactamization

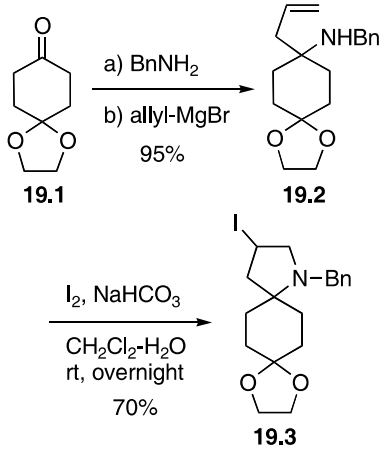
An interesting reaction that results in the addition of azide and methylenecarboxyl functions across alkenes through radical intermediates sets the stage for an azaspirocycle synthesis (Scheme 18).[34] The reaction of methylenecyclopentane or methylenecyclohexane with ethyl 2-iodoacetate, phenylsulfonylazide, and hexabutyldistannane in the presence of di-*tert*-butylhyponitrite (DTBHN) provided azides **18.1** or **18.2** in very good yields. The catalytic reduction of the azide function was followed by lactamization to provide spirocycles **18.3** and **18.4**, each process occurring in excellent yield.



Scheme 18. The Renaud route.

2.17. Imine addition–N-alkylation

In the context of a synthetic approach towards FR901843, Bonjoch and co-workers allylated the intermediary benzylimine produced from **19.1** (Scheme 19). The reaction of the alkene function in **19.2** with iodine then induced an iodoamination to provide alkylated amine **19.3** in excellent yield.[35]



Scheme 19. The Bonjoch route.

3. Approaches that construct the 3° center, then close the carbocycle

After the 3° stereocenter is set, the spirocyclic ring system could be made using C–C bond forming reactions in building the carbocyclic unit of the spirocycle. Efficient procedures such as ring closing metathesis, enamine alkylation or enolate condensation processes are effectively used.

3.1. Lactamization–Claisen condensation

An efficient sequence involving well-established reactions was used by the Fukuyama group in their efforts towards FR901483 (Scheme 20).[36] Nitromethane was induced to undergo multiple conjugate addition reactions upon its treatment with excess methyl acrylate under the influence of catalytic DBU. Reduction of the nitro function and cyclization produced lactam **20.1**. Dieckmann cyclization followed by saponification and decarboxylation produced ketone **20.2**.

3.2. Enolate alkylation–ring closing metathesis

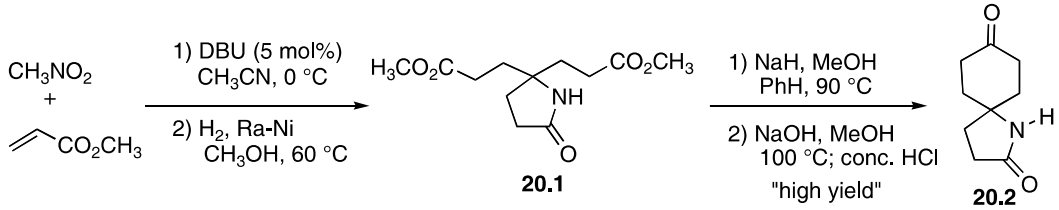
The 3° center of a compound used in a program directed toward the synthesis of halichlorine was established by the desymmetrization of meso diester **21.1** (Scheme 21).[37] Reaction of **21.1** with chiral base **21.2** followed by addition of allyl bromide produced allylated diester **21.3**. Elaboration of **21.3** using straightforward procedures culminated in the formation of **21.4**. Treatment of **21.4** with (SIMes)PCy_3-Cl_2Ru=HPh, a Grubbs second generation precatalyst, produced the spirocycle **21.5** in 80% yield.

3.3. Enolate alkylation–radical addition to an alkene

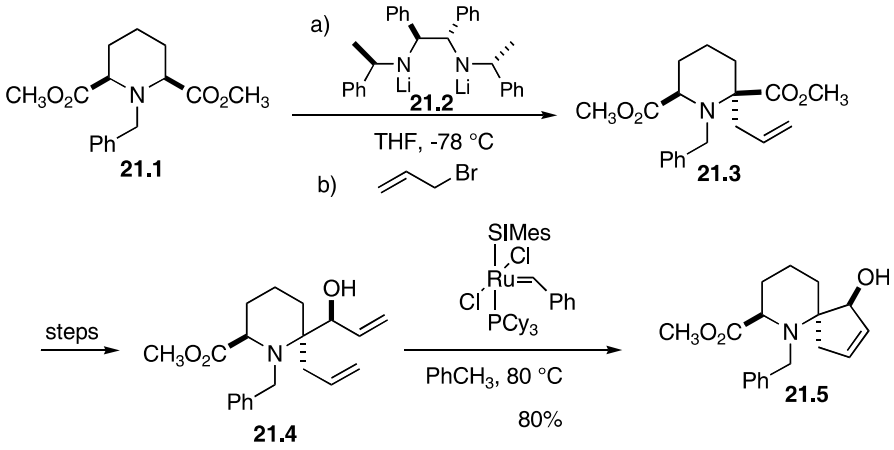
After installing chirality in the same fashion as the Simpkins route to provide **21.3**, the Clive group performed a number of chemical transformations to procure **22.1**, an advanced synthetic intermediate towards halichlorine (Scheme 22).[38] Subjection of **22.1** to the conditions of tri-*n*-butyltin hydride and AIBN generated a mixture of compounds, **22.2** and **22.3**, that had undergone cyclization. Enone **22.3** was the major component within the reaction mixture (46 or 67%, depending on the diastereomer (not known) of **22.1** used as the starting material).

3.4. C–H insertion–conjugate addition

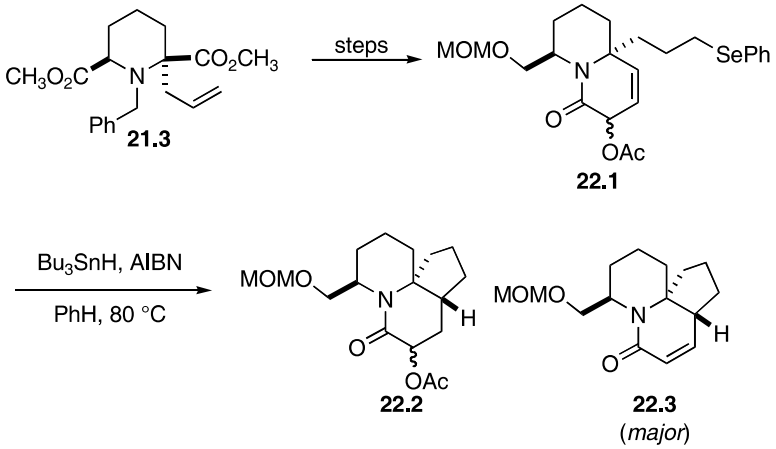
Alkynyliodonium salt **23.1**, upon reaction with sodium *p*-toluenesulfonate, suffered a conjugate addition reaction to produce, after α-elimination, an intermediate represented simplistically as **23.2** (Scheme 23).[39] This carbene-like intermediate underwent a 1,5 C–H insertion process to produce bicycle **23.3**. This process thus established the 3° stereogenic center required for the spirocycle synthesis. In the event, treatment of **23.3** with magnesium bromide induced a smooth 1,4-addition reaction of the alkylstannane to the doubly activated alkene, generating an azaspirocycle. This compound was elaborated to the core structure of halichlorine.



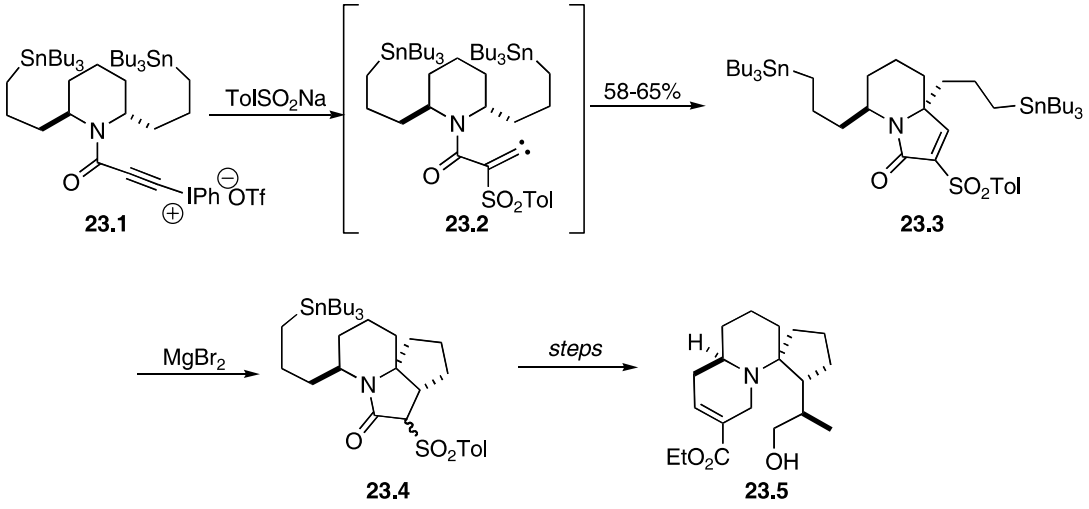
Scheme 20. The Fukuyama route.



Scheme 21. The Simpkins route.



Scheme 22. The Clive desymmetrization approach.



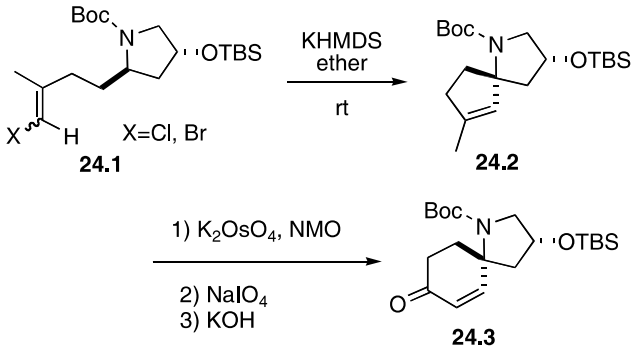
Scheme 23. The Feldman route.

3.5. C–H insertion–aldol condensation

In a somewhat related sequence, the reaction of vinylhalides **24.1** with potassium hexamethyldisilazide produced an intermediary carbene that undergoes C–H insertion to produce spirocycle **24.2** (Scheme 24).[40] This compound was further elaborated by oxidative cleavage of the alkene in **24.2** followed by aldol condensation to produce functionalized cyclohexanone **24.3**.

3.6. Imine addition–alkylation

In the context of synthetic approaches to marine alkaloids, the Kibayashi group has developed a number of routes to



Scheme 24. The Hayes route.

azaspirocycles. This specific procedure involved the addition of allylmagnesium bromide to imine **25.1** under the influence of boron–trifluoride etherate to generate amine **25.2** as a single diastereomer (Scheme 25).[41] Standard manipulations of **25.2** produced **25.3**. This compound, upon reaction with pyrollidine to generate an enamine, underwent a smooth cyclization reaction to produce, after hydrolysis, aldehyde **25.4**.

3.7. Enolate alkylation–carbonyl addition

A recent approach to cephalotaxine utilized an interesting alkylation–carbonyl addition sequence (Scheme 26).[42] The 3° stereocenter of the target spirocycle was established by enolate alkylation within a constrained [3.3.0] bicyclic ring system. With the 3° center in **26.2** established, functional group manipulations provided vinyl iodides **26.3** or **26.4**. Intramolecular carbonyl addition of the vinyl iodide function to the carbonyl group in each case was promoted by trimethylsilyltributylstannane and cesium fluoride. In each case the reactions proceeded very well, providing the target spirocycles in good yields.

3.8. Enolate acylation–ring closing metathesis

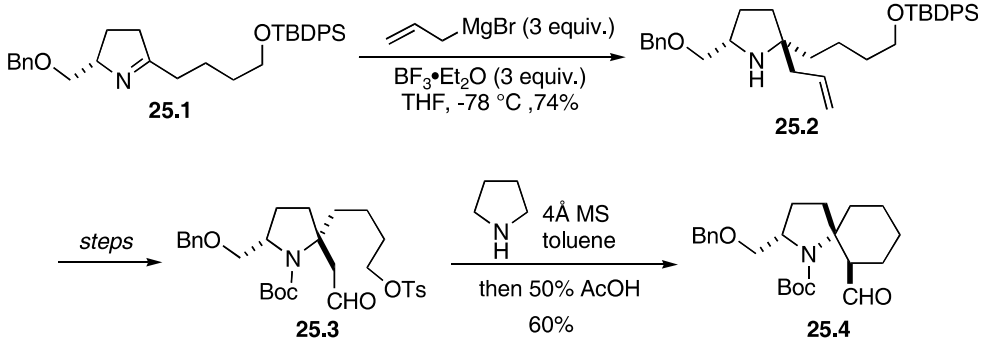
Ring closing metathesis provided the crucial spirocycle in the construction of the ring-system of lepadiformine (Scheme 27).[43] Reaction of the extended silyl enol ether derived from **27.1** with trimethylorthoformate provided **27.2** in excellent yield. Acetal hydrolysis and carbonyl addition then provided diene **27.3**. Closure of the carbocyclic system of the spirocycle was accomplished using standard ring closing metathesis technology. Functional group manipulations provided spirocycle **27.4**.

3.9. Nitrile anion alkylation–Thorpe/Zeigler cyclization

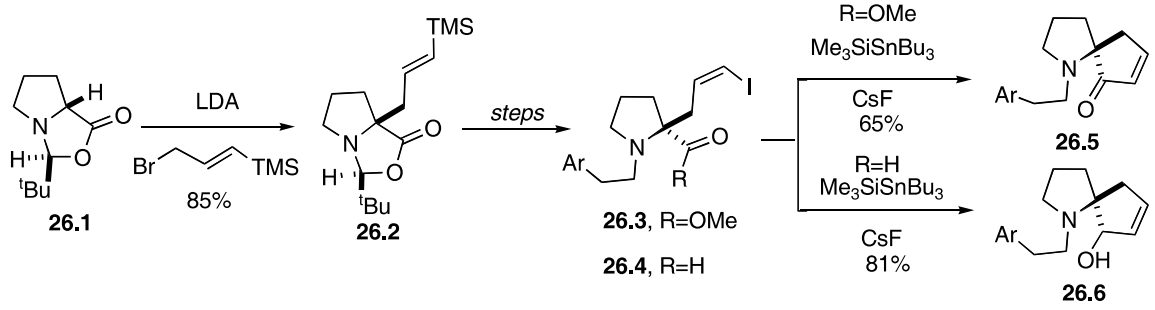
Electrochemical installation of a nitrile function adjacent to the amine moiety in **28.1** allowed for its further functionalization, yielding a spirocycle in the following manner (Scheme 28).[44] Deprotonation and alkylation of **28.2** was followed by conversation to bis-nitrile **28.3**. Thorpe/Zeigler cyclization under the influence of LDA produced spirocycle **28.4** in 70% yield. A thematically related sequence (anion alkylation–aldol condensation) was used in a recent approach to cephalotaxine.[45]

4. Approaches that construct 3° center and spirocycle in the same step

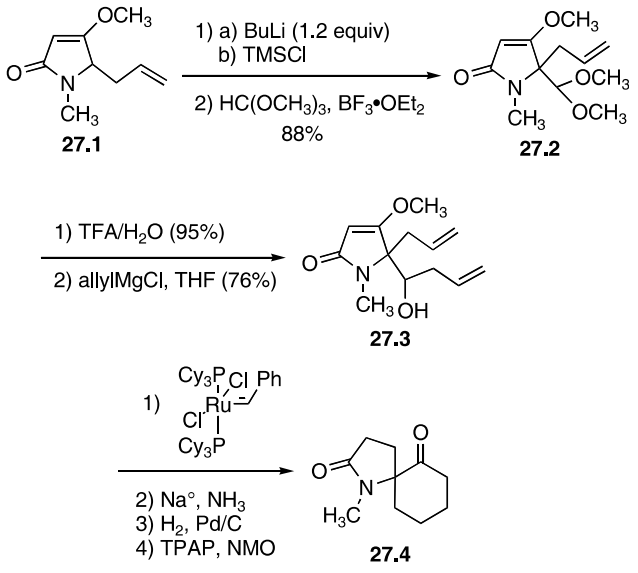
The last general strategies to be presented are those that generate the 3° stereocenter of the spirocycle in conjunction with the two rings of the spirocycle. As these require only one synthetic step, these procedures can have a benefit of efficiency. However, the gain in efficiency can be limited by



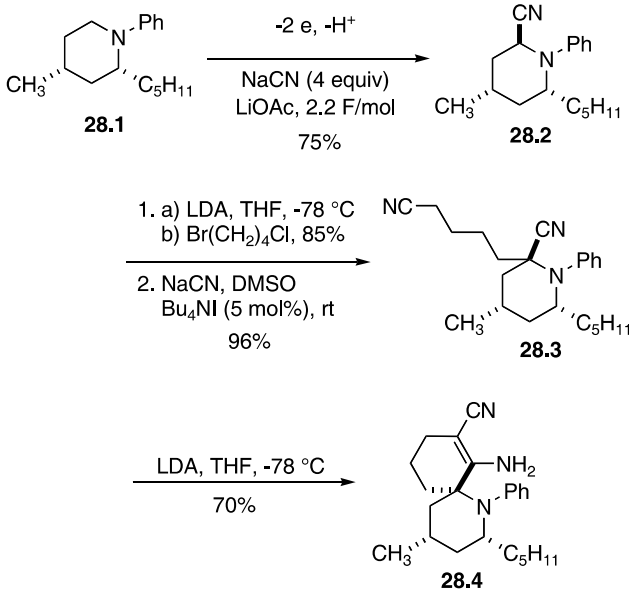
Scheme 25. The Kibayashi route.



Scheme 26. The Mori route.



Scheme 27. The Hunter route.

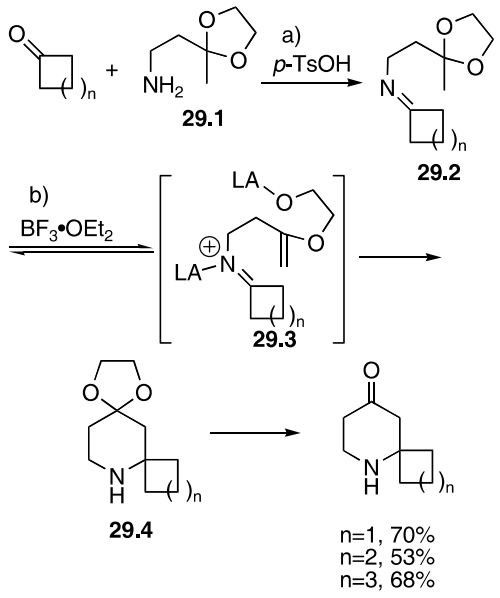


Scheme 28. The Hurvois route.

reaction scope (e.g., the heterocycle or carbocycle ring size) in certain instances.

4.1. Addition to iminium ions

4.1.1. Mannich reaction. The condensation of a cyclic ketone and amine **29.1** under acidic conditions formed, as expected, imine **29.2** (Scheme 29). Although no subsequent productive reaction occurred using *p*-toluenesulfonic acid, the addition of BF_3–OEt_2 (1.5 equiv) then, in sequence, activated the imine and formed (under equilibrating conditions) an enol ether represented as **29.3**. The closure of the spirocycle led to ketals of type **29.4** that can be deprotected using standard chemistry.[46]

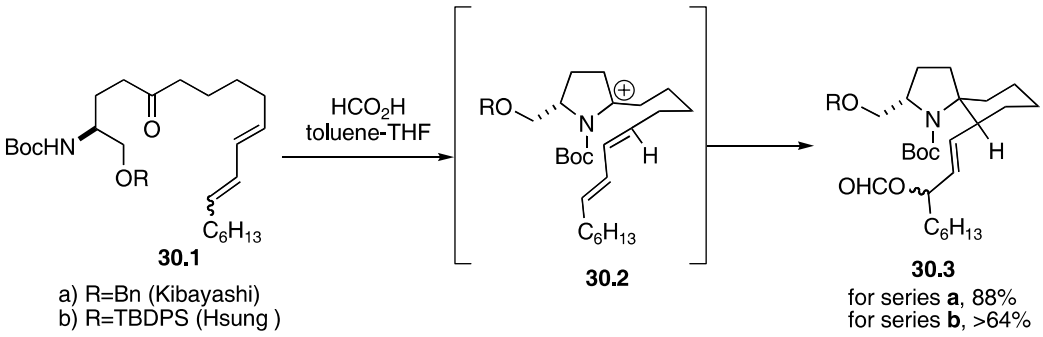


Scheme 29. The Troin route.

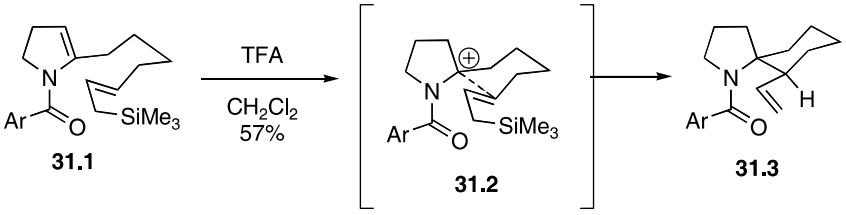
4.1.2. Alkene addition to iminium ions. The cyclization of nucleophilic alkenes onto transiently formed azacarbenium ions is a well-recognized method to form a C–N and C–C bond in the same reaction vessel. The Kibayashi and Hsung groups have each independently used this protocol to generate synthetic intermediates for the construction of lepadiformine and the cylindricines (Scheme 30). In each case, structurally similar substrates (differing in protecting group; the Hsung substrate was described as a stereoisomeric mixture of alkenes at the indicated position) were subjected to similar cyclization conditions using formic acid in a toluene–THF mixture. In each case, in situ formation of the *N*-carbamoyl azacarbenium ion **30.2** led to 'conjugate spirocyclization.' Cyclization was followed by quenching of the intermediate allyl cation to form allylic formate **30.3**.[47,48]

The Hsung and Kibayashi studies also demonstrated that simple alkenes were not nucleophilic enough to capture transiently formed azacarbenium ions. It had been established by Weinreb's group that a more nucleophilic alkene such as an allyltrimethylsilane was sufficiently reactive to capture those electrophiles (Scheme 31).[49] The reaction of enamide **31.1** with trifluoroacetic acid produced an azacarbenium ion that was intercepted by a pendant allylic silane. On the basis of the stereochemistry of **31.3**, the reaction was believed to proceed through a chair topology as represented by structure **31.2**.

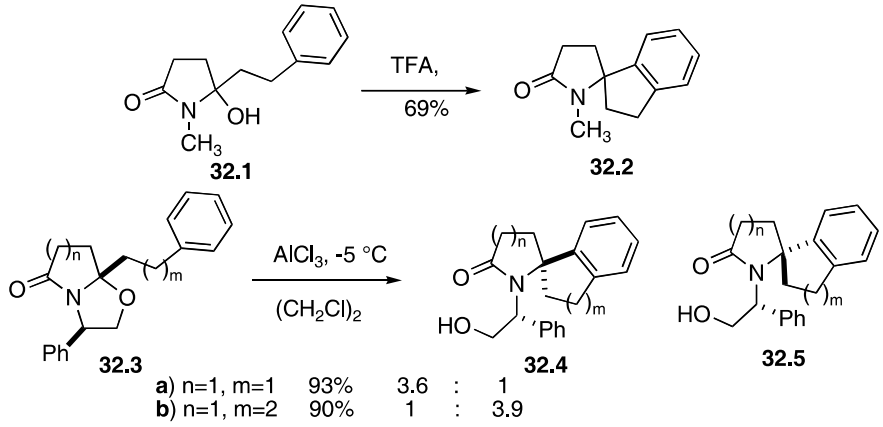
4.1.3. Nucleophilic arenes. Arene nucleophiles were used in the early reports of addition reactions to *N*-acyliminium ions. Further studies examined the problem of stereochemical induction in the spirocycle forming step.[50] The use of chiral auxiliaries attached to the nitrogen atom within substrates similar to **32.1** did not generate products of high de. (Scheme 32). Conversely, acetals of type **32.3** reacted smoothly upon treatment with aluminum chloride at 5 °C to give spirocyclic products **32.4** and **32.5** with modest diastereoselectivities (~3:1). Interestingly, the diastereoselectivity of the ring-forming event was strongly dependant on the size of the ring being produced. Formation



Scheme 30. Kibayashi and Hsung diene addition route.



Scheme 31. The Weinreb allylsilane approach.



Scheme 32. The Vernon route.

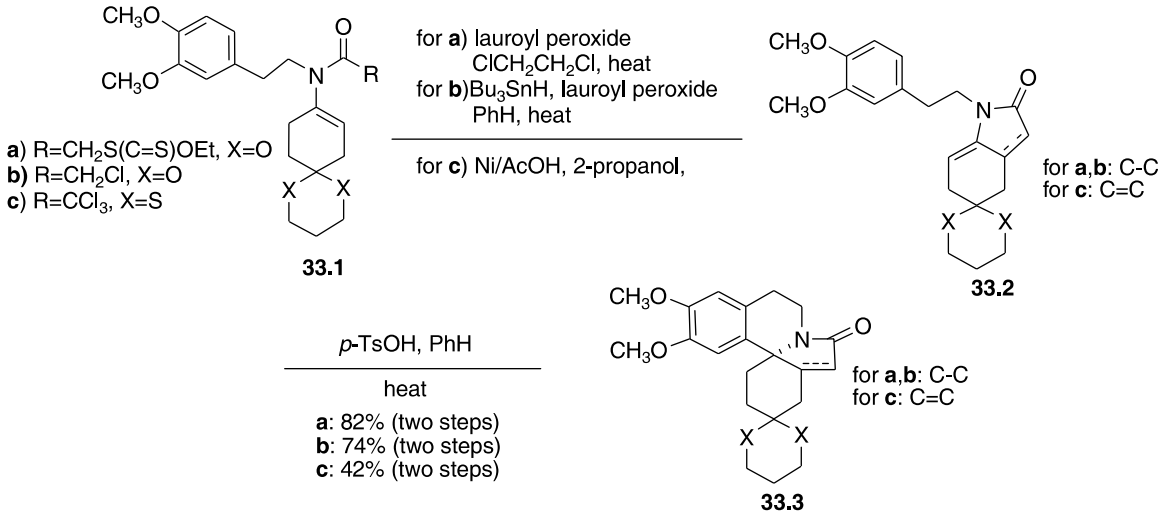
of a five-membered ring generated **32.4a** as the major diastereomer. In contrast, the cyclization of the homologous substrate yielded **32.5b** as the preferred product. A rationale for this observation was not provided.

This process has been exploited extensively in the construction of the erythrinan ring skeletons. Some recent examples are given in Scheme 33.[51] Formation of the critical bicycle **33.2** was accomplished by subjecting starting materials **33.1** to conditions amenable for radical generation. With enamide **33.2** in hand, its conversion to the designated spirocycle target was accomplished in a straightforward manner using catalytic *p*-toluenesulfonic acid in benzene. A mechanistically similar, highly diastereoselective route to the same ring system using an acetal as a chiral auxiliary (cf. to Scheme 32) proceeded in high yield.[52]

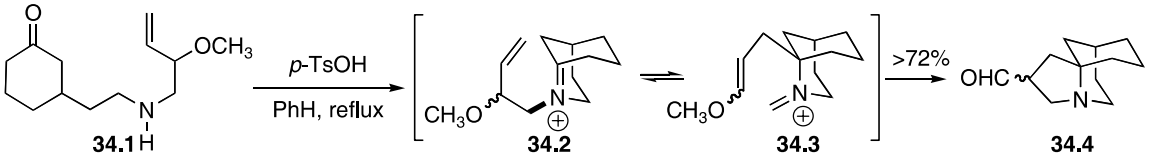
4.1.4. Tandem sigmatropic–aza-Prins process. The formation of a bridgehead iminium ion set the stage for a tandem [3,3] sigmatropic rearrangement followed by an aza-Prins process (Scheme 34).[53] Upon treatment of ketone **34.1** with *p*-toluenesulfonic acid in benzene, the intermediate ketiminium ion **34.2** rearranged to the alternate iminium ion **34.3**. This species suffered intramolecular attack from the pendant enol ether, to produce, after workup a mixture of diastereomeric aldehydes in 72% yield.

4.1.5. Attack on bromonium or iodonium ion intermediates. In the context of a recent cephalotaxine construction, the following sequence was used to build the azaspirocyclic core structure (Scheme 35).[54] The reaction of **35.1** with titanium tetrachloride in an acetic acid–dichloromethane mixture presumably formed an iminium ion in situ that suffered attack from the nearby β-keto ester to ultimately result in the formation of **35.2** in excellent yield (97%). Alternatively, subjection of **35.1** to *N*-iodosuccinimide and titanium tetrachloride generated enone **35.3**. This reaction was thought to proceed through an intermediate in which an iodide atom is located β to the ketone carbonyl moiety.

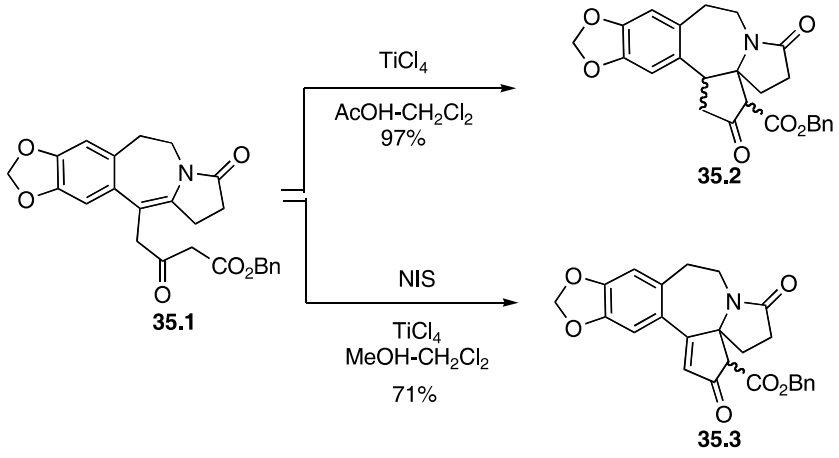
A recent efficient approach to the erythrina alkaloids utilized the attack of a nucleophilic arene to a bromonium



Scheme 33. The Zard/Ishibashi route.



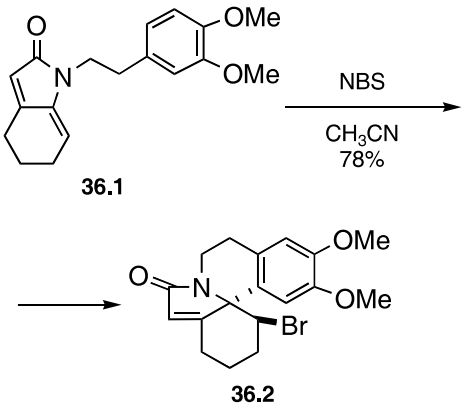
Scheme 34. The Brummond route.



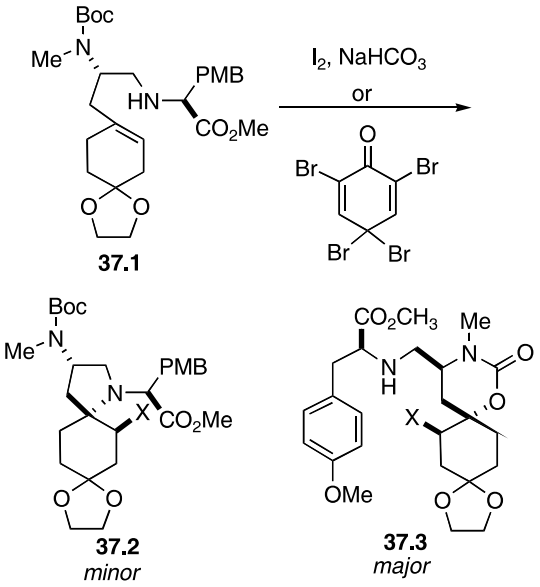
Scheme 35. The Nagasaka route.

ion-containing intermediate (Scheme 36).[55] *N*-Bromosuccinimide in acetonitrile induced a smooth cyclization of enamide **36.1** to produce tetracycle **36.2** in 78% yield. This process was strongly dependant on the solvent, as the use of dichloromethane resulted in the formation of a β-bromoenamide. This product was ultimately used in a construction of erysotramidine.

Spirocyclization of **37.1** occurred upon treatment with either iodine (with sodium bicarbonate) or 2,4,4,6-tetrabromo-2,5-cyclohexadienone (an electrophilic bromine source) to give the desired azaspirocycle **37.2** as the minor component in the reaction mixture (Scheme 37). The major product resulted from interception of the putative halonium ion species with the carbonyl atom of the *t*-butylcarbamate in **37.1**.[56]

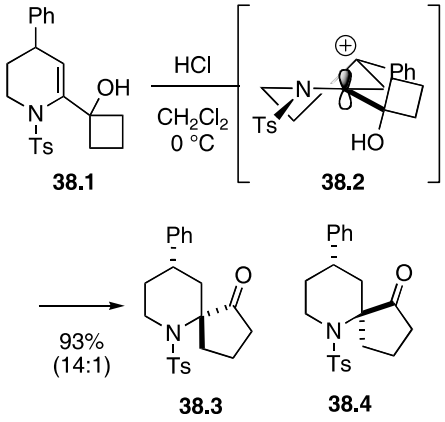


Scheme 36. The Padwa route.



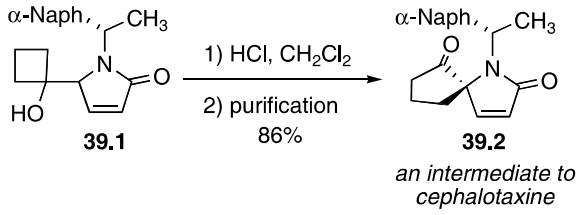
Scheme 37. The Bonjoch route.

4.1.6. Ring expansions. The use of semipinacol rearrangement reactions to form azaspirocycles has been a significant research interest of the Dake group.[57] Protonation of the double bond in **38.1** using concentrated hydrochloric acid at 0 °C generated a putative azacarbenium ion (represented by **38.2**). A 1,2-alkyl shift with concomitant C=O π-bond formation generated azaspirocycles **38.3** and **38.4** in 93% yield as a 14:1 ratio of diastereomers. The diastereoselectivity was rationalized by considering a transition state in which (a) the phenyl group is oriented in a pseudoequatorial orientation and (b) the 1,2-alkyl migration occurs from the 'axial' direction via a chair-like topology (Scheme 38).



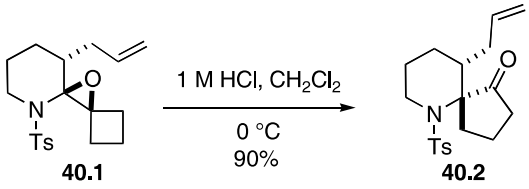
Scheme 38. The Dake routed.

A variant of this reaction was utilized by the Royer group in the synthesis of cephalotaxine and its derivatives (Scheme 39).[58] Reaction of lactam **39.1** with concentrated hydrochloric acid resulted in formation of ring-expanded products in ~80% diastereomeric excess. Purification of this mixture enabled a recovery of 86% of pure diastereomer **39.2**. This compound served as a key intermediate in their cephalotaxine construction.



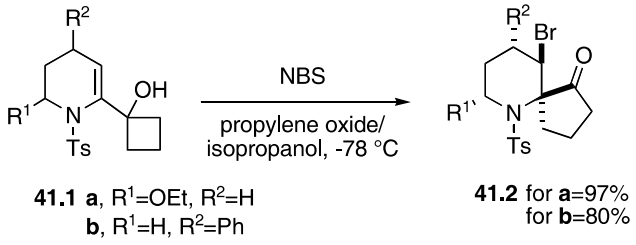
Scheme 39.

A related acid-promoted expansion of epoxide **40.1** smoothly formed azaspirocycle **40.2** in 90% yield (Scheme 40).[59] Noteworthy features for this process are (a) the formation of a spirocycle with an alkyl substituent on the carbon adjacent to the spirocyclic center and (b) the high diastereoselectivity of the process—the migrating alkyl group approaches the face opposite the adjacent alkyl group.



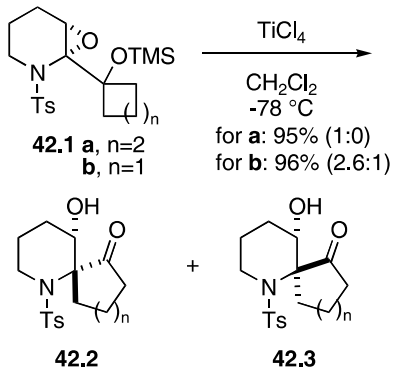
Scheme 40.

Semipinacol rearrangements forming azaspirocycles can also be performed using an electropositive halogen source (Scheme 41).[57b,60] As an example, **41.1a**, when subjected to a slight excess of *N*-bromosuccinimide (NBS) promptly underwent ring expansion to provide ketone **41.2a** in 97% yield. That the *N*-ethoxyaminal did not react is a testament to the mildness of these reaction conditions. In addition, substrates that have substituents at C-4 or C-6 of the heterocycle undergo highly diastereoselective reactions. In these cases, the indicated diastereomers are the only materials observed in the product mixture.



Scheme 41.

Investigations into siloxy-epoxide semipinacol processes uncovered some interesting observations (Scheme 42). For example, the ring expansion of **42.1a** using titanium tetrachloride generated cyclohexanone **42.2a** as a single observable diastereomer in 95% yield.[59] A related process was used to generate an intermediate used in a formal construction of fasicularin.[61] In contrast, the ring expansion of **42.1b** generated a 2.6:1 mixture of diastereomeric ring expansion products **42.2b** and **42.3b**, albeit in good yield (96%).



Scheme 42.

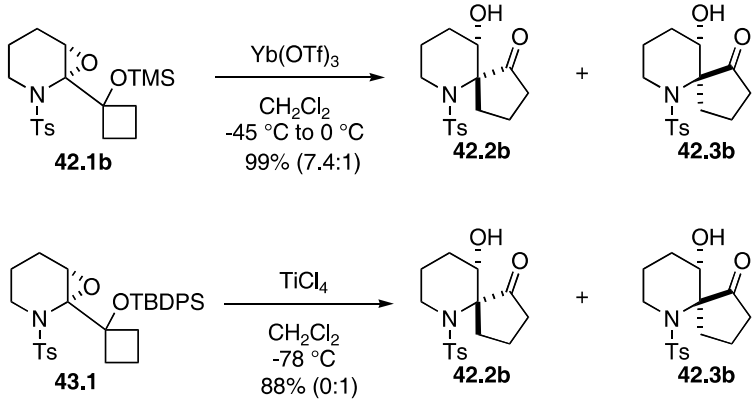
Fortunately, somewhat more selective processes forming **42.2b** or **42.3b** were uncovered by modifying the reaction parameters (Scheme 43). Treatment of **42.1b** with ytterbium(-III) triflate generated **42.2b** as the major product in a 7.4:1 mixture in 99% yield. Conversely, using a *tert*-butyldiphenylsilyl ether in the starting material (**43.1**) using titanium tetrachloride (identical conditions as that for **42.1a**) produced the alternate diastereomer as the only product in 88% yield.

4.1.7. Ring reorganization processes. A recent construction of cephalotaxine used a ring reorganization strategy to establish the azaspirocycle (Scheme 44).[62] A Wacker oxidation and aldol-type condensation was used to form azaspirocycle **44.2**. The ring system was then modified by treatment of **44.2** with zinc metal in acetic acid at 100 °C. Presumably proceeding through an azirdinium ion such as **44.3**, the reorganization process (ring expansion–ring contraction) formed the cephalotaxine skeleton **44.4** in 65% yield.

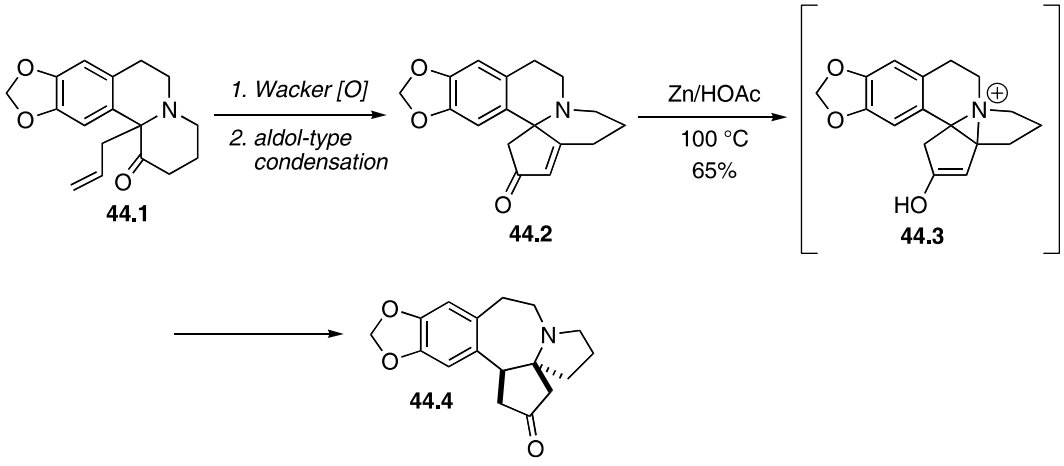
4.2. Cycloaddition strategies

4.2.1. Hetero Diels–Alder reaction. The reaction of Danishefsky's diene with imines generated in situ from amines and cyclic ketones such as **45.1** provided straightforward access to azaspirocycles (Scheme 45).[63] Although the success of the reaction did not depend on whether the imine was preformed or utilized in situ, the efficiency of the process was dependent on the size of the substituent (R^2) on nitrogen. As the diene was interpreted to approach from the equatorial face of the imine, larger substituents (R^2) on the nitrogen atom were detrimental to the process.

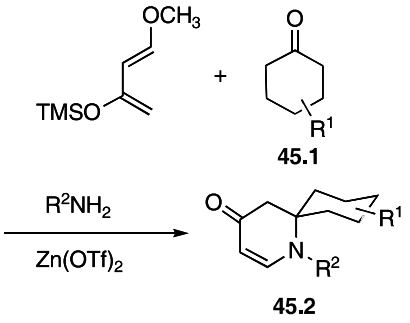
4.2.2. [3+2] Azaallyl cycloaddition. The Pearson group has disclosed fascinating cycloaddition strategies to approach these azaspirocycle ring systems (Scheme 46).[64] Imine formation between **46.1** and **46.2** using trimethylaluminum occurred smoothly. Tin–lithium exchange using butyllithium generated a 2-azaallyl anion that underwent cycloaddition with an electron rich alkene such as vinyl



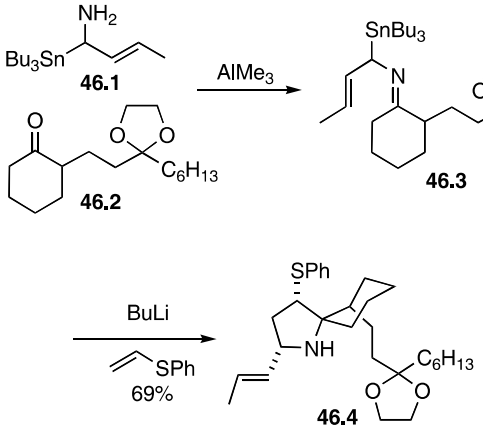
Scheme 43.



Scheme 44.



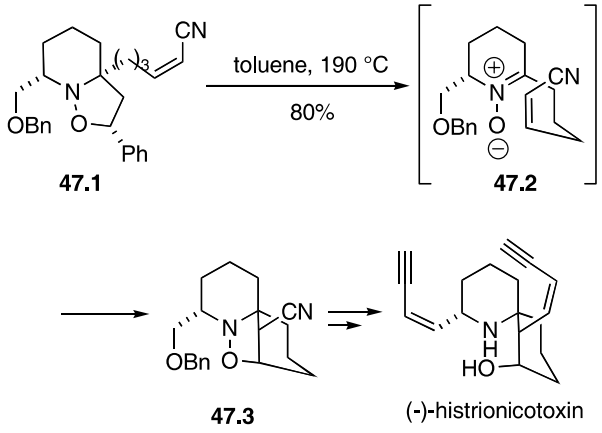
Scheme 45. The Oh approach.



Scheme 46. The Pearson azaallyl cycloaddition route.

phenyl sulfide. Cycloaddition on the face opposite the side chain generated azaspirocycle **46.4**. This work was the first to establish the relative configuration of lepadiformine.

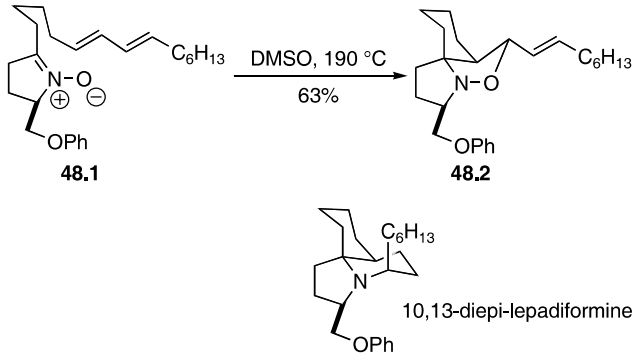
4.2.3. [3+2] Nitrone–alkene cycloadditions. A number of approaches to the azaspirocyclic core of histrionicotoxin utilizing [3+2] cycloadditions have been unsuccessful because of the formation of an undesired regioisomer as the major product.[65] Holmes and co-workers provided a useful and elegant solution to this problem (Scheme 47).[66] Heating **47.1** resulted in the loss of styrene to generate nitrone **47.2** in situ. This nitrone underwent cycloaddition in a regio- and stereochemically defined sense to produce **47.3**



Scheme 47.

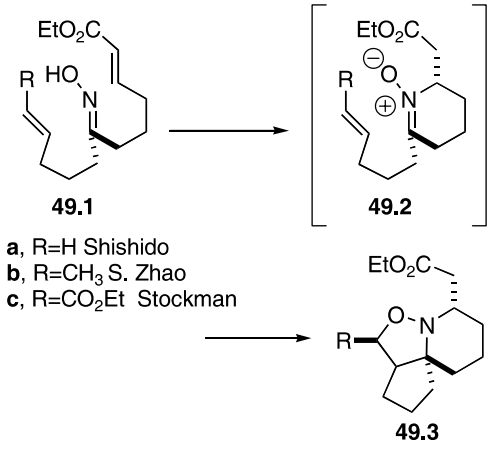
in 80% yield. The use of an α,β unsaturated nitrile was crucial to ensure the appropriate regiochemical result.

Weinreb utilized a [3+2] cycloaddition process to access the skeleton of lepadiformine (Scheme 48).[67] To that end, heating **48.1** in DMSO led to smooth formation of spirocycle **48.2**. This process was used to generate an intermediate used in a synthesis of epimers of lepadiformine, clues that helped to establish the structural and stereochemical identity of the natural product.



Scheme 48. The Weinreb nitrone cycloaddition route.

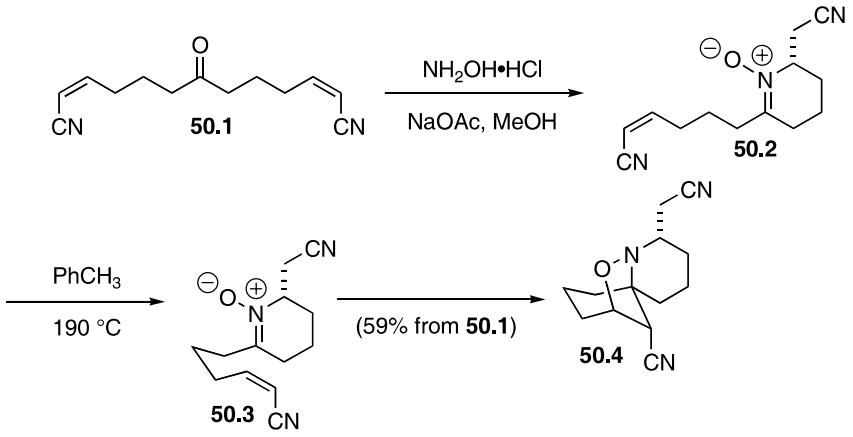
Related approaches to the halichlorine/pinnaic acid core have been developed independently in the Shishido, Zhao and Stockman groups (Scheme 49).[68] At its core, the approach consists of the in situ formation of a 1,3-dipole generated by conjugate addition of the nitrogen atom of an oxime of general structure **49.1** into an adjacent Michael acceptor. At this stage, [3+2] cycloaddition proceeds to generate the requisite azaspirocycle-containing intermediate **49.3**.



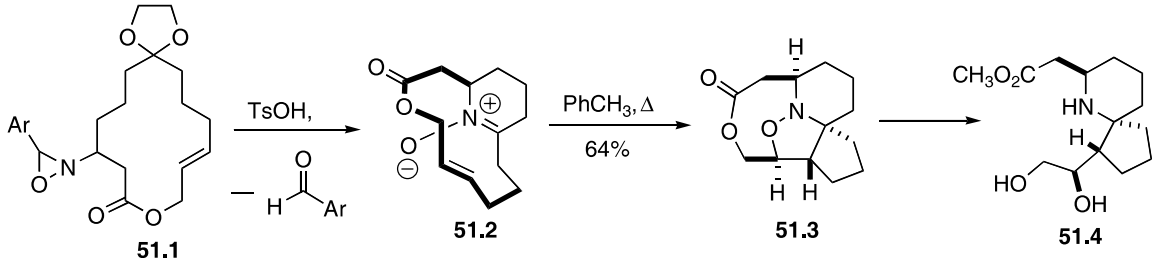
Scheme 49.

Stockman expanded this idea further.[69] His interest in two-directional synthesis led to his use of bis-*Z*-configured enenitrile **50.1** to generate, in rapid fashion, a common intermediate to that used in the Holmes' construction of histrionicotoxin (Scheme 50).

White and co-workers utilized a nitrone–alkene cycloaddition in a perceptive context as a synthetic approach towards the halichlorine/pinnaic acid spirocyclic core



Scheme 50. The Stockman route.



Scheme 51. The White approach.

(Scheme 51).[70] Deprotection of the ketal function within **51.1** under acidic conditions accompanied by concomitant cleavage of aldehyde enabled the generation of nitrone **51.2**. Transannular cycloaddition produced tetracycle **51.3**. Subsequent functional group manipulations produced the desired spirocycle **51.4**.

4.3. Other concerted reactions

Oxidation of hydroxylamine **52.1** led to the generation of *N*-acylnitroso compound **52.2**. The juxtaposition of the nitroso functional group and the alkene in **52.2** resulted in a nitroso-ene process (Scheme 52). This reaction established the azaspirocyclic ring system appropriately functionalized for its conversion to the ring system of halichlorine.[71]

The Knoevanagel condensation of iminium ion **53.1** and lactone **53.2** initiated a cascade process (Scheme 53). After condensation, an electrocyclic ring closure of **53.3** lead to spirocycle **53.4** in good yield. The hydrogenation of the double bond in **53.4** to produce **53.5** was the first in a series of reactions to produce 2-epi-perhydrohistrionicotoxin.[72]

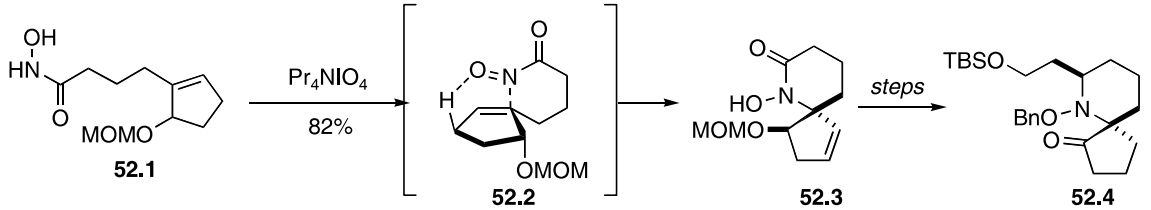
4.4. Intramolecular conjugate addition

In the Molander approach to the spirocycles, a double intramolecular conjugate addition reaction was used to establish both the 3° center and the spirocyclic ring system of the cylindricines in one step (Scheme 54).[73]

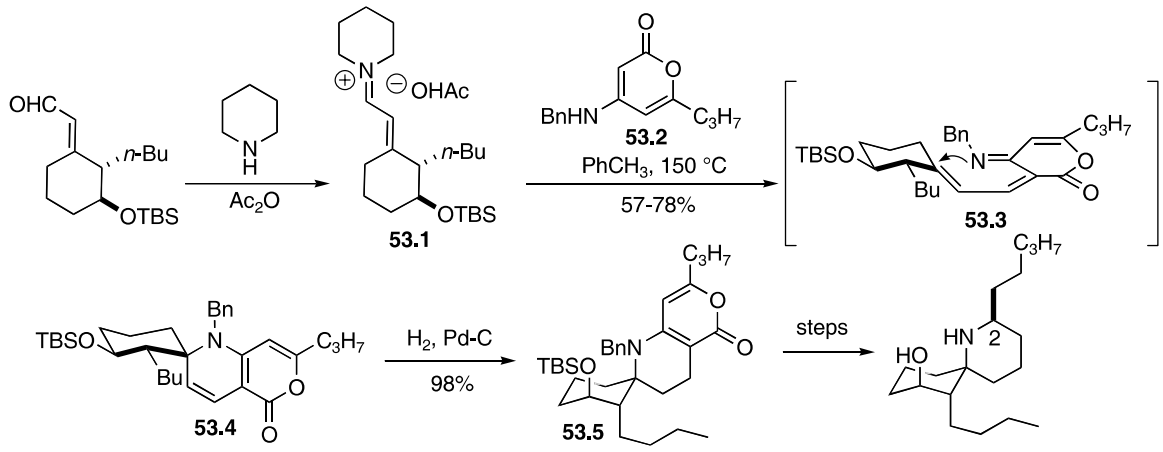
The Tietze group used a domino amide-bond formation–intramolecular conjugate addition reaction to generate spirocycles such as **55.3** (Scheme 55). Yields ranged from moderate to excellent, and the reaction was found to proceed particularly well with unhindered amines.[74]

4.5. Dearomatizations

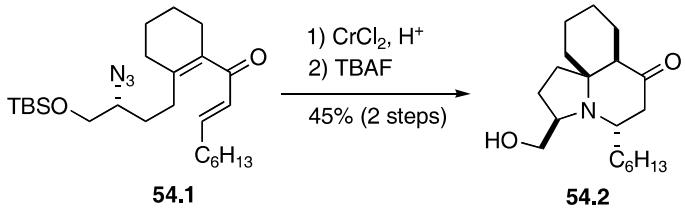
4.5.1. Electrophilic addition processes. The interaction between silver salts and *N*-chloro-*N*-methoxyamides generates an intermediary azetidium ion that, if juxtaposed with an appropriate nucleophile, will suffer nucleophilic attack. In the case of amide **56.1**, this reaction proceeded to generate azaspirocycle **56.2** in



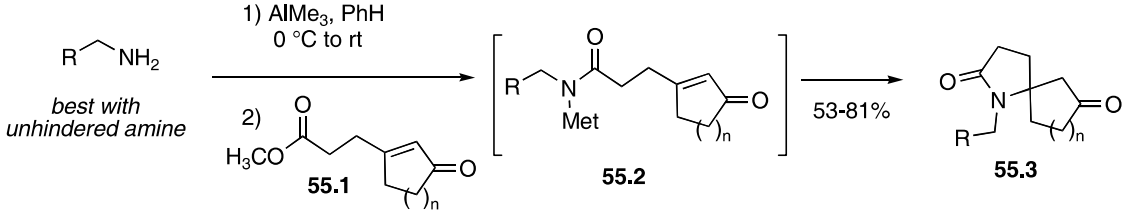
Scheme 52. The Kibayashi nitroso-ene approach.



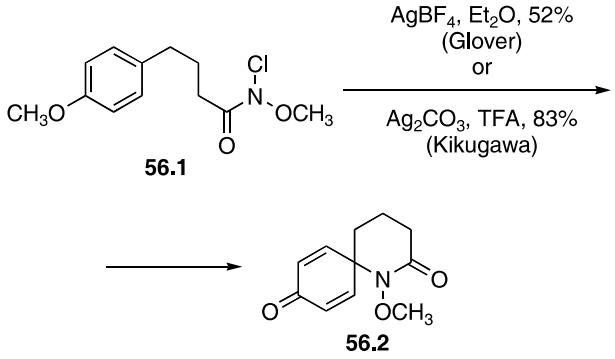
Scheme 53. The Hsung '3+3' annulation route.



Scheme 54. The Molander route.



Scheme 55. The Tietze route.



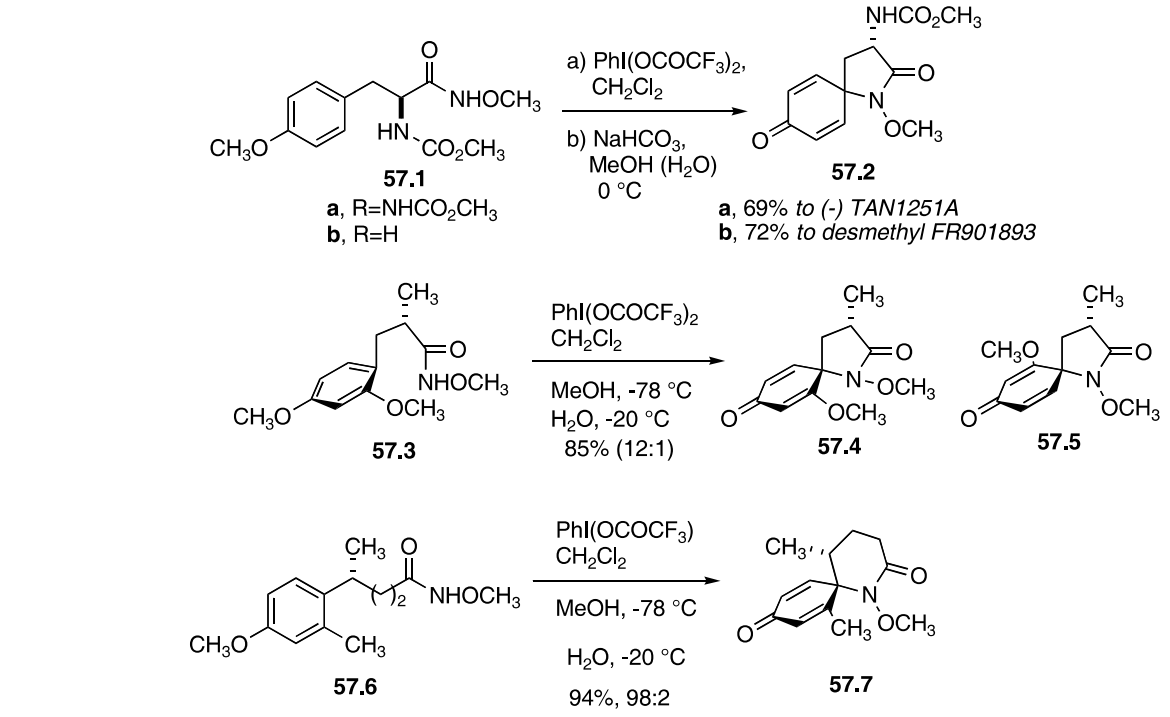
Scheme 56. Dearomatizing route to spirocycles.

excellent yield (Scheme 56).[75] The *p*-methoxy group is necessary as it directs *para* rather than alternative *ortho* attack of the aromatic ring.

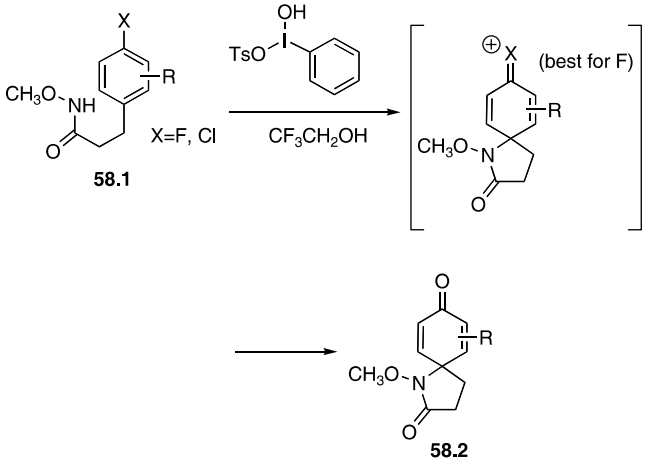
Wardrop and his group have recently expanded upon this concept.[76] In these cases, the use of the phenyliodinebis(trifluoroacetate) (PIFA), a hypervalent iodine reagent, leads to the formation of an identical type of compound (Scheme 57). This reagent system avoids *N*-chlorinated intermediates and aromatic chlorination. These compounds undergo attack by pendant electron-rich arenes. In certain cases, the diastereoselectivity can be quite good. These reactions have been used to generate key intermediates in the synthesis of desmethylamino FR901483 and (−)-TAN 1251A.

In a recent development, the Kikugawa group has uncovered that *p*-halo substrates can be induced to cyclize using hydroxy(*p*-toluenesulfonyloxy)iodobenzene as the oxidant (Scheme 58).[77] The reaction is most efficient using fluoroarenes as substrates.

4.5.2. Nucleophilic addition to arenes. The interaction between diacetoxyiodobenzene (DIB) and phenols in polar solvents produces an electrophilic species that can engage amide equivalents such as imino ethers in an intramolecular manner (Scheme 59).[78] As a specific example, the reaction of phenol **59.1** with DIB produces a transient electrophile that rapidly reacts with its pendant imidate moiety. The putative transient structure is then hydrolyzed with water, and acetylation furnishes the spirocycle **59.3**.[79] Indoles can also be used as internal nucleophiles.[80]



Scheme 57. The Wardrop route.



Scheme 58. The Kikugawa route.

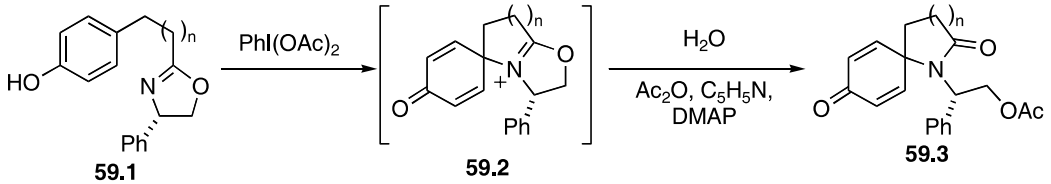
Secondary amines will also react in this context, but the yields are somewhat reduced (Scheme 60).[81] The selection of solvent can be crucial—the cyclization of **60.1** proceeded in highest yield using hexafluoroisopropanol. A similar observation was uncovered in a synthetic approach to TAN1251A (Scheme 61).[82]

This process proceeds particularly well using sulfonamide nucleophiles (Scheme 62).[83] A construction of the cylindricine alkaloids utilized a methanesulfonyl function in a dual role. It served as a protecting group and as a means to desymmetrize the dienone in the reaction product.[84] In general, though, cyclizations to form heterocyclic rings larger than five-membered are low yielding. Recently, an important, two-step variation of this methodology has been described that solves that particular problem. On appropriately functionalized substrates, intermolecular addition of nitriles to the intermediate electrophiles can be followed by a simple amide N-alkylation process to generate spirocycles in which the heterocyclic ring is larger than five-membered.[85]

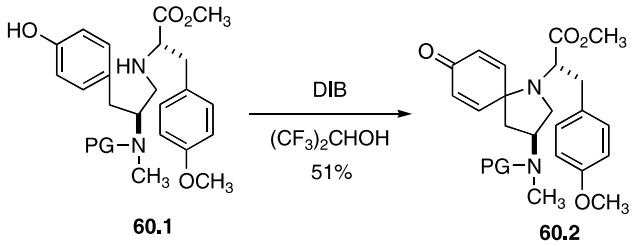
4.6. Radical cyclizations

In an approach to the azaspirocyclic core of halichlorine and the pinnaic acids, the reaction of the intermediary radical generated from **63.1** resulted in the formation of the fused ring system in **63.2** (Scheme 63).[86] This result presumably derived from 6-*endo* addition to the enamide, followed by expulsion of *p*-toluenesulfinate anion. In contrast, the radical initiation of **63.3** resulted in the smooth formation of spirocycle **63.4**.

Treatment of **64.1** with tri-*n*-butyltin hydride and AIBN leads to spirocycles **64.2** and **64.3** in excellent yield

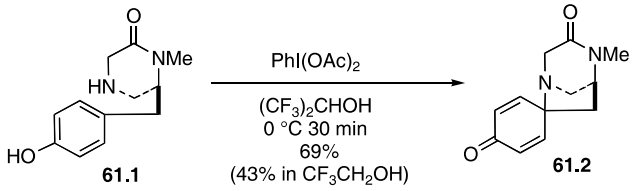


Scheme 59. The Ciufolini route.



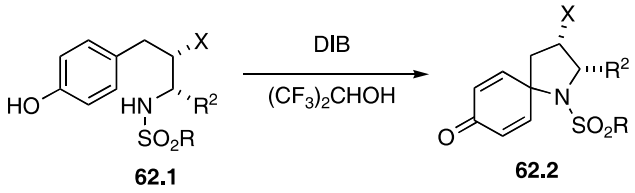
60.1 60.2

Scheme 60. The Sorensen approach.



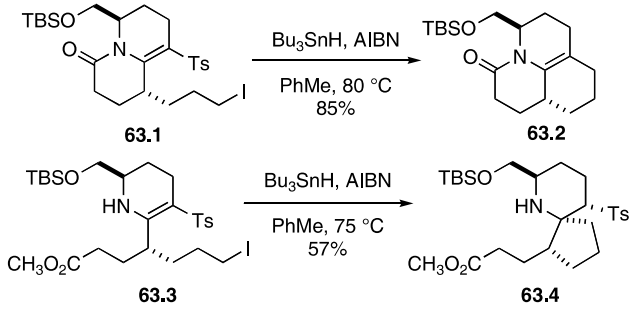
61.1 61.2

Scheme 61.



62.1 62.2

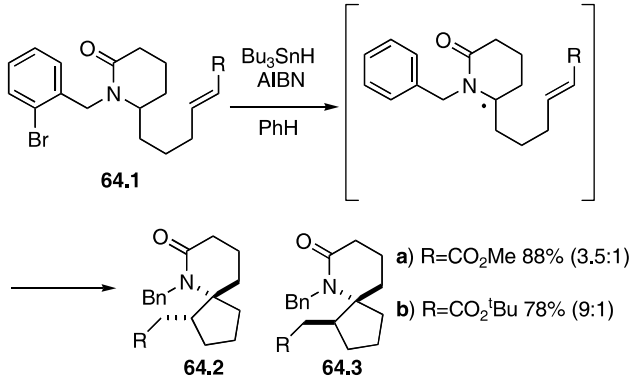
Scheme 62. The Ciufolini sulfonamide approach.



63.1 63.2 63.3 63.4

Scheme 63. The Clive approach.

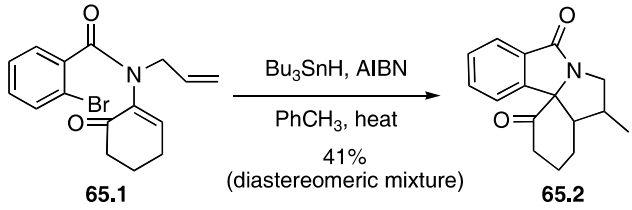
(Scheme 64).[87] After generation of an aryl radical, a 1,5-hydrogen abstraction generated a radical adjacent to the nitrogen atom. Cyclization in a 5-*exo* mode then produced the spirocycles.



64.1 64.2 64.3

Scheme 64. The Ihara route.

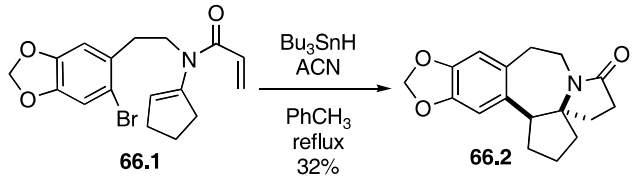
Spirocycles related to the erythrinan skeleton were formed, albeit in low yield and as a diastereomeric mixture, using a tandem bond-forming process via radical intermediates (Scheme 65).[88] As might be expected, initial 6-*endo* cyclization competed with the desired 5-*exo* cyclization process.



65.1 65.2

Scheme 65. The Parsons' approach.

A recent approach to cephalotaxine utilized a radical-mediated 7-*endo* cyclization reaction (Scheme 66).[89] Treatment of aryl bromide **66.1** with tri-*n*-butyl tin hydride generated the requisite natural product skeleton in **66.2** in 32% yield.



66.1 66.2

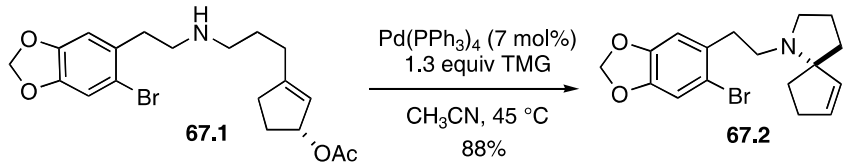
Scheme 66. The Ishibashi route.

4.7. Metal catalysis

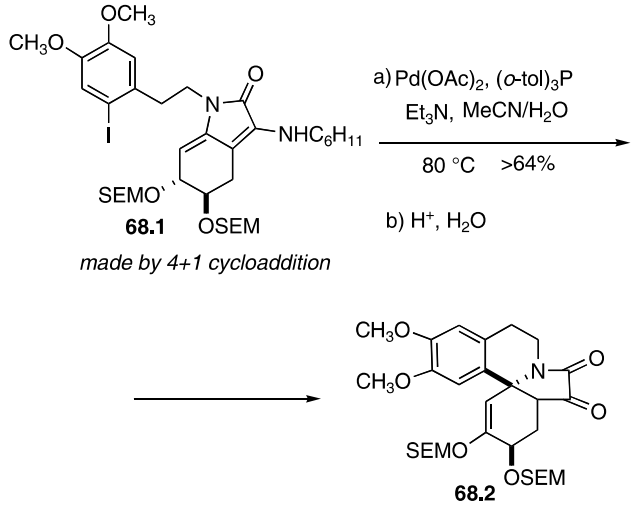
A recent construction of cephalotaxine utilized the following sequence to generate the required spirocycle (Scheme 67). Palladium(0) catalyzed allylic alkylation of amine **67.1** generated spiro compound **67.2** in excellent yield.[90] The aryl bromide function was a necessity for success—attempted reactions with the corresponding aryl iodide did not produce the desired spirocycle. In addition, the reaction temperature was key. Heating the reaction above 50 °C resulted in incomplete conversion, perhaps because of a competing process involving the haloarene.

The Rigby group recently investigated a synthetic approach to erythrinan alkaloids that incorporate a Pd(0) catalyzed Heck reaction as a key process (Scheme 68).[91] The stereochemistry of the spirocycle junction was established using the stereochemistry of the allylic siloxy function in **68.1**. The combination of catalytic palladium(II) acetate and tri-*o*-tolylphosphine in the presence of triethylamine generated a palladium(0) complex in situ that undergoes oxidative insertion into the aryl iodide bond. The sequence of migratory insertion (preferentially a *syn* process) followed by β-hydride elimination (also preferentially a *syn* process) thus defined the stereochemistry of the spirocycle ring junction. Initial unsuccessful studies utilized TBS ethers in place of the sterically less hindering SEM ethers.

Ring closing metathesis reactions have been used in two-step 1-azaspirocycle formation (vida supra). A process that utilizes

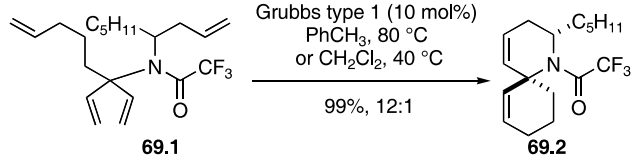


Scheme 67. The Tietze allylic alkylation route.



Scheme 68. The Rigby approach.

metathesis chemistry to generate both the heterocycle and the carbocycle of the spirocycle in a single step has been developed (Scheme 69).[92] This process proceeds with good diastereoselectivity (12:1 favoring **69.2**). The diastereoselectivity increases further when the metathesis chemistry is carried out in two discrete steps. The heterocycle is formed first through metathesis, then the carbocycle.



Scheme 69. The Harrity route.

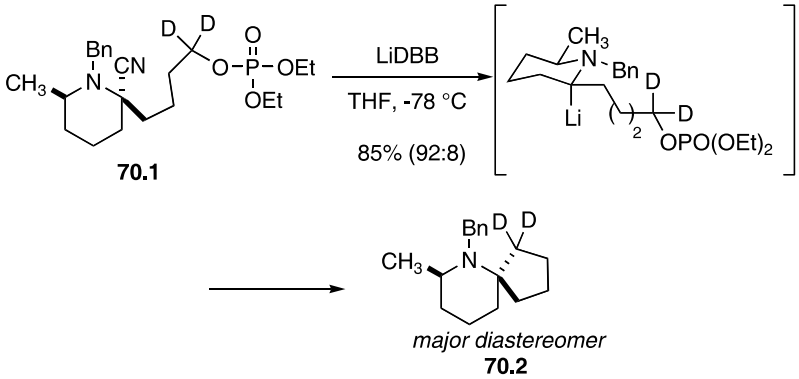
4.8. Miscellaneous

4.8.1. Intramolecular nucleophilic substitution. Rychnovsky's reductive decyanation/lithiation–electrophilic trapping protocol has recently been used for the construction of 1-azaspirocycles (Scheme 70).[93] In an interesting study, the treatment of deuterated substrate **70.1** with lithium di-*tert*-butylbiphenylide presumably produced predominantly axially lithiated α-aminoorganolithium intermediate. Cyclization proceeds with retention of configuration to produce **70.2** in 85% yield.

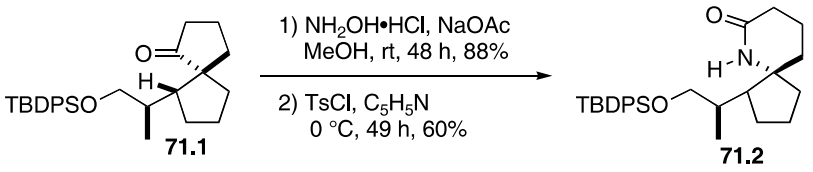
4.8.2. Beckmann rearrangement. Although it necessitates the stereocontrolled construction of a quaternary center, the conversion of an 'all-carbon' spirocyclic system to one containing a heteroatom can be a useful process. A recent example of this process was described by Pilli (Scheme 71).[94] In the event, ketone **71.1** was converted to its corresponding oxime using hydroxylamine in the presence of sodium acetate. Reaction of the hydroxylamine with *p*-toluenesulfonyl chloride with pyridine initiated a Beckmann rearrangement to produce amide **71.2** in 60% yield.

4.8.3. Nazarov reaction. An ingenious method for the installation of an embedded spirocyclic system utilized a Nazarov cyclization (Scheme 72).[95] Specifically, the treatment of the vinylogous amide **72.1** with diethylaluminum chloride induced cyclization to produce **72.2** in good yield.

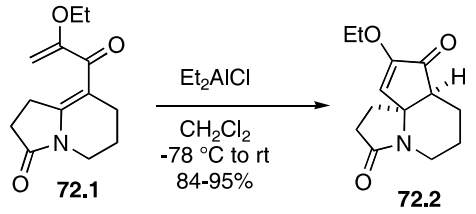
4.8.4. Photochemical cycloaddition–fragmentation. A photochemical formal [5+2] cycloaddition was used to build three rings common to cephalotaxine (Scheme 73).[96] The irradiation of a solution of **73.1** in toluene generated an excited state species (represented by **73.2**) that is presumably organized via hydrogen bonding. After a [2+2] cycloaddition between the C=N bond of the imide-ol tautomer of **73.1** and the pendant alkene, spontaneous fragmentation of **73.3** produced the cephalotaxine ring system within **73.4**.



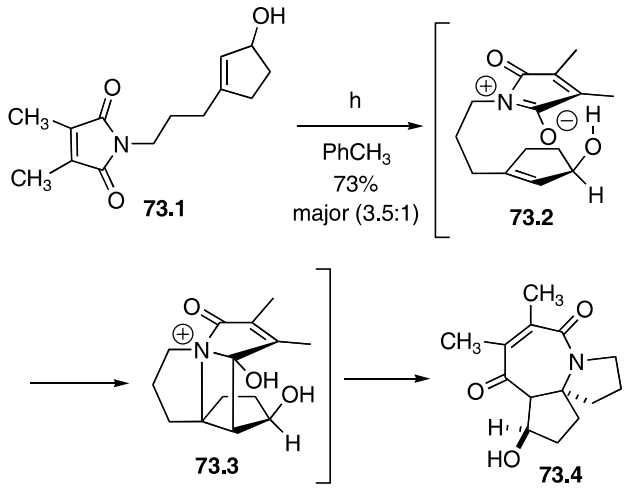
Scheme 70. The Rychnovsky approach.



Scheme 71. The Pilli route.



Scheme 72. The Cha route.



Scheme 73. The Booker-Milburn approach.

5. Concluding remarks

The wide range of approaches presented in the preceding schemes is a clear demonstration of the inspiration of 1-azaspirocycles for synthetic organic chemists. In most cases, a method was developed in order to solve a specific synthetic problem, generally within the context of a total synthesis exercise. These solutions, taken as a whole, help to set new boundaries for the organic chemist. Even so, the prospect of future developments that will enable the synthesis of these motifs within any structural context in a highly selective, economical manner, is an exciting one.

Acknowledgements

I acknowledge Prof. Richard Bunt (Middlebury College), Prof. Matthias McIntosh (University of Arkansas) and Prof. Robert Batey (University of Toronto) for their efforts in evaluating early drafts of this manuscript.

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Biographical sketch

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