Synthesis of Polycyclic Natural Products via Skeletal Rearrangement

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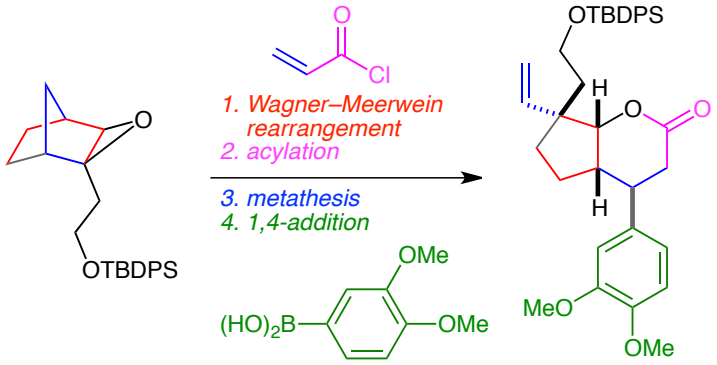

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Abstract Construction of rings via reliable reactions, followed by changing the ring size or the connectivity via skeletal rearrangement provides molecules with a wide range of skeletons. In this Account, our syntheses of polycyclic natural products via skeletal rearrangement are discussed.

Key words alkaloids, cycloaddition, natural products, rearrangement, total synthesis

1 Introduction

Natural products have long been a promising source for novel drug development.[1] Many natural products contain stereogenic centers and fused or bridged rings that form rigid and three-dimensional structures.[2] These rigid three-dimensional structures enable drugs derived from natural products to closely interact with biological molecules by reducing entropy loss upon binding. In addition, these structural features tend to provide favorable drug properties by increasing solubility and decreasing CYP inhibition and non-specific binding to proteins.[3] This background prompted us to conduct synthetic studies on polycyclic natural products.[4]

Although using cyclic compounds as the starting materials in the synthesis of potential drug candidates is an attractive strategy, these starting materials are not always readily available. In addition, the inherent nature of the starting materials may limit the types of transformations and range of modifications they can undergo. Therefore, constructing the ring systems is an important task in synthetic studies on polycyclic natural products.

A variety of ring-forming reactions have been developed and applied to the synthesis of natural products. These reactions are usually limited by the nature of the substituents and functional group tolerance; therefore, not all ring systems can be directly constructed in a single reaction. Skeletal rearrangement can expand the versatility of ring-forming reactions. Construction of rings via reliable reactions, followed by changing the ring size or the connectivity via skeletal rearrangement, can provide a wider range of molecules. In this Account, we present our strategy for the synthesis of polycyclic natural products via skeletal rearrangement.

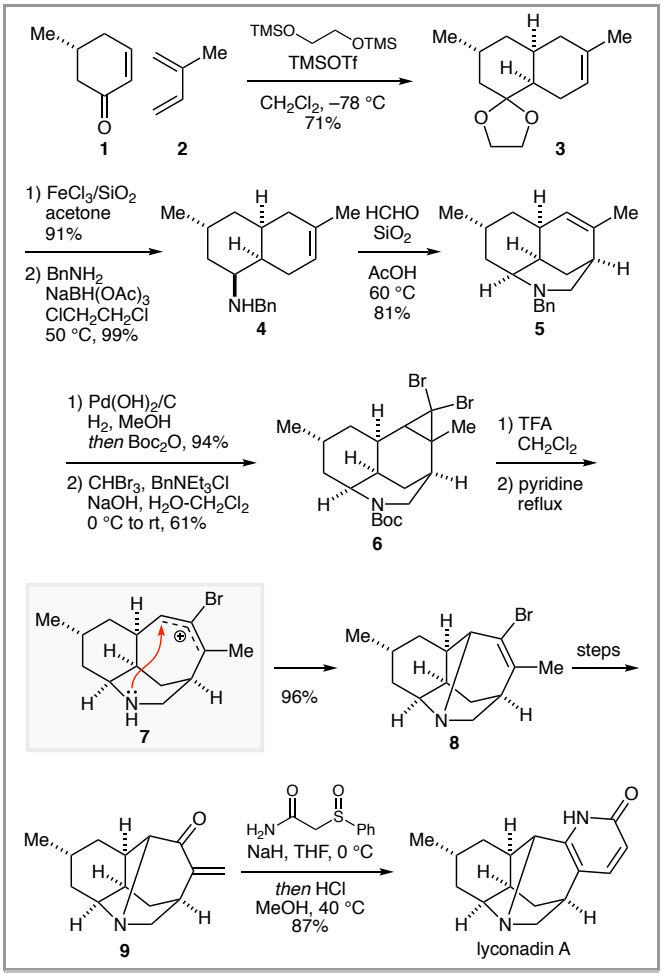
2 Synthesis via changing the ring size

The Diels–Alder reaction is one of the most versatile methods for forming a 6-membered rings.[5] Ring expansion or ring contraction reactions can expand the utility of Diels–Alder reactions.[6] In this section, two syntheses of alkaloids that feature the combination of the Diels–Alder reaction and a ring expansion or contraction reaction are discussed.

Lyconadin A is an alkaloid isolated from *Lycopodium complanatum* (Scheme 1).[7] The cage-like pentacyclic skeleton includes a cycloheptane ring fused with a 2-pyridone and a cyclohexane rings. A nitrogen-containing bridge forms two additional rings. Our synthesis of lyconadin A featured the formation of the cycloheptane ring via a ring expansion reaction.[8,9]

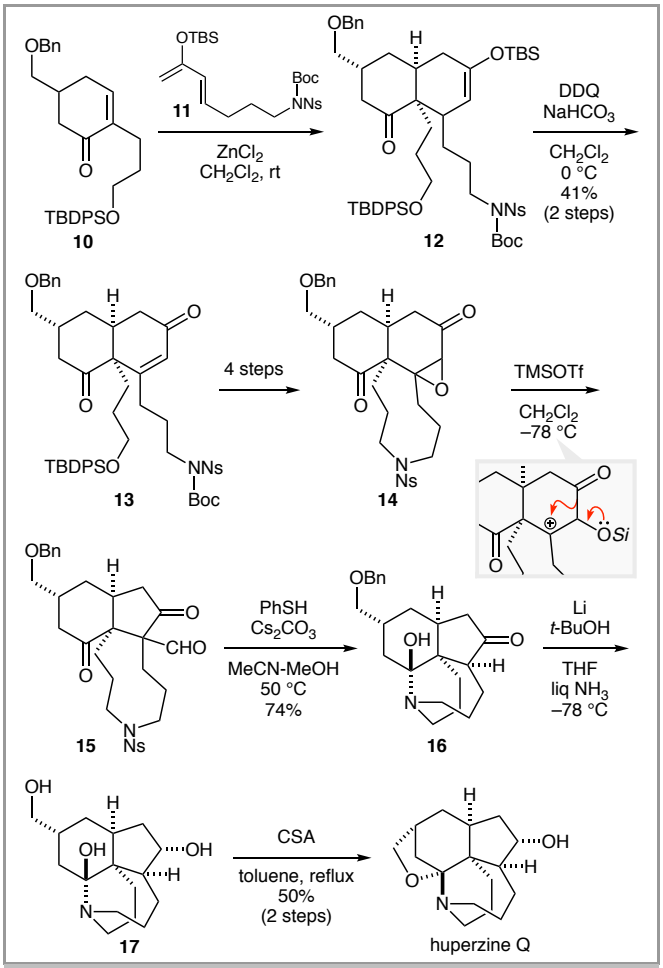
The synthesis commenced with a Diels–Alder reaction of cyclohexenone **1** with isoprene (**2**) to afford *cis*-decaline **3**. In this reaction, trimethylsilyl triflate and ethylene glycol bis(trimethylsilyl) ether were employed to activate the enone moiety and to avoid epimerization of the *cis*-fused product.[10] After hydrolysis of the ethylene acetal in **3** under mildly acidic conditions, the resultant ketone was subjected to reductive amination with benzylamine. The reduction occurred from the convex face of the bicyclic system to furnish secondary amine **4** as a single diastereomer. Compound **4** was subsequently treated

with formalin and acetic acid in an aza-Prins reaction to afford tricyclic compound **5**. This transformation featured movement of the C–C double bond to the adjacent endocyclic C–C bond. After changing protecting groups on the nitrogen atom from a benzyl group to a Boc group, a dibromocyclopropane ring was constructed on the C–C double bond. The Boc protecting group in compound **6** was cleaved with trifluoroacetic acid and the product was refluxed in pyridine to induce electrocyclic ring opening of the dibromocyclopropane ring. The resultant allyl cation **7** was trapped intramolecularly by the nitrogen atom on the bridge to form tetracyclic compound **8**. Thus, the cyclohexane ring that was formed via a Diels–Alder reaction was expanded into a cycloheptane ring with simultaneous formation of a C–N bond across a bridge, to construct the tetracyclic backbone of the natural product. Compound **8** was then converted into α,β-unsaturated ketone **9**, upon which the 2-pyridone ring was constructed,[11] leading to the synthesis of lyconadin A.



Scheme 1 Synthesis of lyconadin A.

Huperzine Q is an alkaloid isolated from *Lycopodium serratum* (Scheme 2).[12] The core structure of huperzine Q is a *cis*-hydrindane, a bicyclic system containing a cyclohexane ring fused with a cyclopentane ring. Huperzine Q also includes an *N*,*O*-acetal moiety, with these two heteroatoms independently forming heterocycles. We used a Diels–Alder reaction and a ring contraction reaction to construct the *cis*-hydrindane skeleton of huperzine Q.[13,14] The Diels–Alder reaction of cyclohexenone **10** with siloxy diene **11** was mediated by zinc chloride to afford **12** as a mixture of isomers, which was oxidized with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to produce α,β-unsaturated ketone **13**. Formation of a nitrogen-containing 9-membered ring via a 3-step sequence followed by nucleophilic epoxidation afforded epoxy ketone **14**. Upon treatment with trimethylsilyl triflate, the epoxy ketone underwent a ring contraction reaction via cleavage of the epoxide at the β position of the carbonyl group and subsequent 1,2-shift of the carbonyl group, affording cyclopentanone **15**.[15] Removal of the Ns group and deformylation were carried out simultaneously under basic conditions in the presence of benzenethiol and the liberated secondary amine attacked the carbonyl group to form hemiaminal **16**. Birch reduction cleaved the benzyl ether and reduced the ketone moiety, leaving the hemiaminal moiety intact. Finally, acidic treatment of **17** under Takayama's conditions formed the *N*,*O*-acetal, giving huperzine Q.[14a]



Scheme 2 Synthesis of huperzine Q.

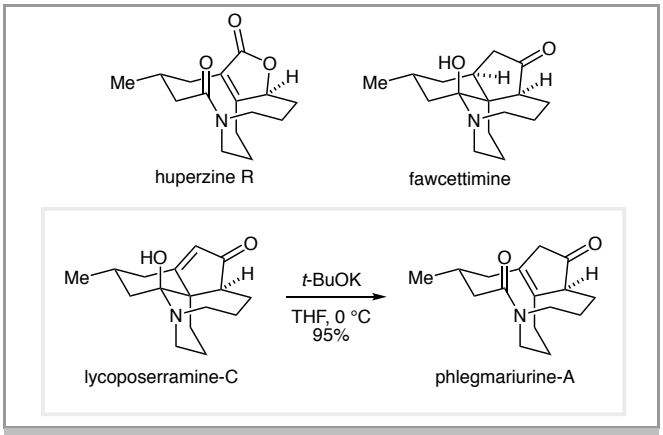
3 Synthesis with biomimetic strategy

Polycyclic natural products are often biogenetically synthesized via cyclization reactions of linear precursors. In addition to the cyclization steps, skeletal rearrangement in biosynthesis helps expand the structural diversity of natural products. The biomimetic synthesis of natural products using skeletal rearrangement has also been explored.[16] When the requisite substrates are easily prepared, we can take advantage of the

potential to construct complex skeletons of natural products through biosynthetic pathways. In this section, our syntheses of two natural products employing biomimetic strategies are described.

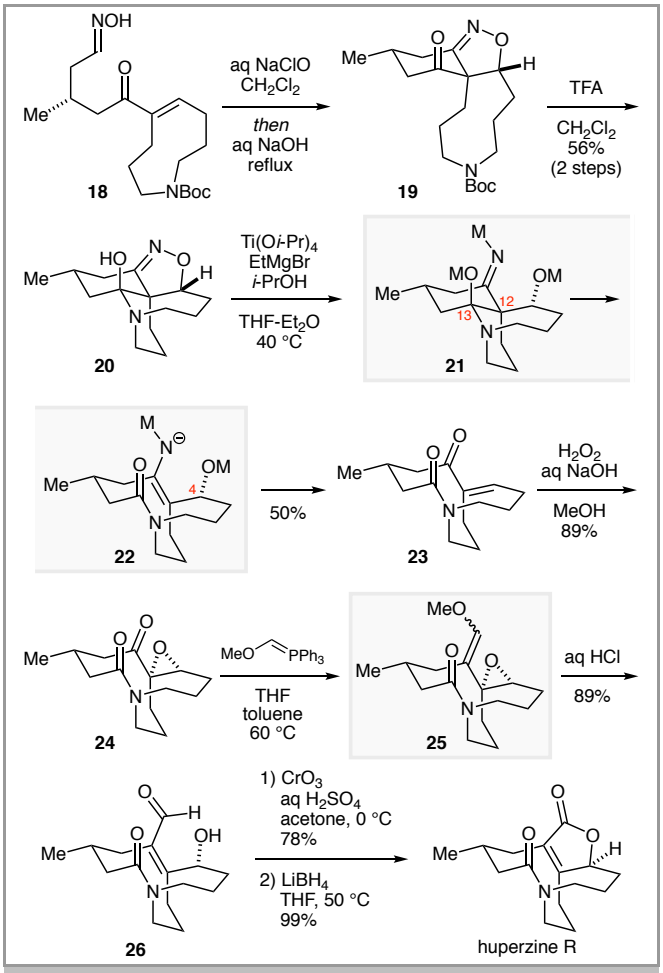
Huperzine R is a natural product isolated from *Lycopodium serratum* that features an amide moiety incorporated into the bridgehead of a 1-azabicyclo[5.4.3]tetradecane skeleton and a butanolide ring fused to the other bridgehead (Scheme 3).[17] Our initial attempt in the synthesis of huperzine R included an intramolecular condensation of the corresponding amino acid to form the lactam. However, the desired condensation could not be achieved under a variety of conditions likely due to the ring strain of the bicyclo [5.4.3] system. After extensive investigations,[18] we found that the synthesis of the core could be achieved using a biomimetic strategy involving cleavage of a cyclohexane ring fused with a 1-azabicyclo[4.3.1]decane was effective.[19,20]

Biogenetically, huperzine R and related natural products are thought to be derived from the fawcettimine skeleton via cleavage of the cyclohexane ring. The chemical transformation of lycoposerramine-C into phlegmariurine-A, in which a vinylogous retro-aldol reaction was conducted by treatment with a base to cleave the cyclohexane ring, has also been reported.[21]



Scheme 3 Biomimetic transformation of lycoposerramine-C into phlegmariurine-A.

Our synthesis of huperzine R commenced with construction of the cyclohexane ring via an intramolecular cycloaddition of a nitrile oxide (Scheme 4). In the reaction, oxime **18** was oxidized with sodium hypochlorite then refluxed in dichloromethane with aqueous sodium hydroxide to afford isoxazoline **19**. Treatment with trifluoroacetic acid liberated the secondary amine moiety, which attacked the ketone moiety to give fawcettimine-like hemiaminal **20**. Reductive cleavage of the N–O bond with a titanium(III) reagent[22] was followed by a retro-aldol type reaction to cleave the C12–C13 bond with concomitant elimination of the oxygen functionality at C4 to give, after aqueous workup, lactam **23**. The enone moiety in **23** was utilized to form the butenolide ring. Nucleophilic epoxidation afforded epoxy ketone **24**, which was then subjected to a Wittig reaction with methoxymethylenetriphenylphosphine and subsequent acid-induced cleavage of the epoxide to furnish hydroxy aldehyde **26**. Oxidation into a keto carboxylic acid, followed by selective reduction of the resultant ketone moiety afforded huperzine R.



Scheme 4 Synthesis of huperzine R.

Cardiopetaline is a norditerpenoid alkaloid isolated from *Delphinium cardiopetalum* (Figure 1).[23] The hexacyclic skeleton of cardiopetaline includes a cycloheptane ring fused with cyclopentane and cyclohexane rings. A C–C bridge between the cyclopentane and the cycloheptane rings forms another ring, and a C–N–C bridge connected to the cyclohexane and the cycloheptane rings at three positions constitutes two more rings. Extensive synthetic efforts toward this skeleton have been made because it is the same skeleton present in the highly toxic plant poison aconitine. Successful construction of the hexacyclic skeleton employed a biomimetic transformation involving the Wagner–Meerwein rearrangement of a bicyclo [2.2.2] system into a bicyclo [3.2.1] system.[24,25] We also conducted the synthesis of cardiopetaline via a Wagner–Meerwein rearrangement (Scheme 5).[26]

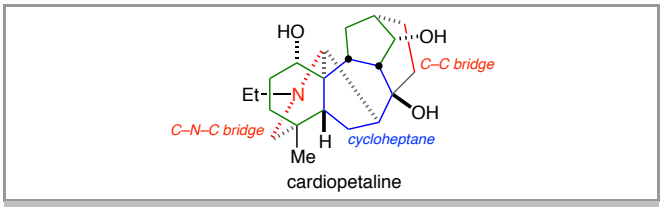
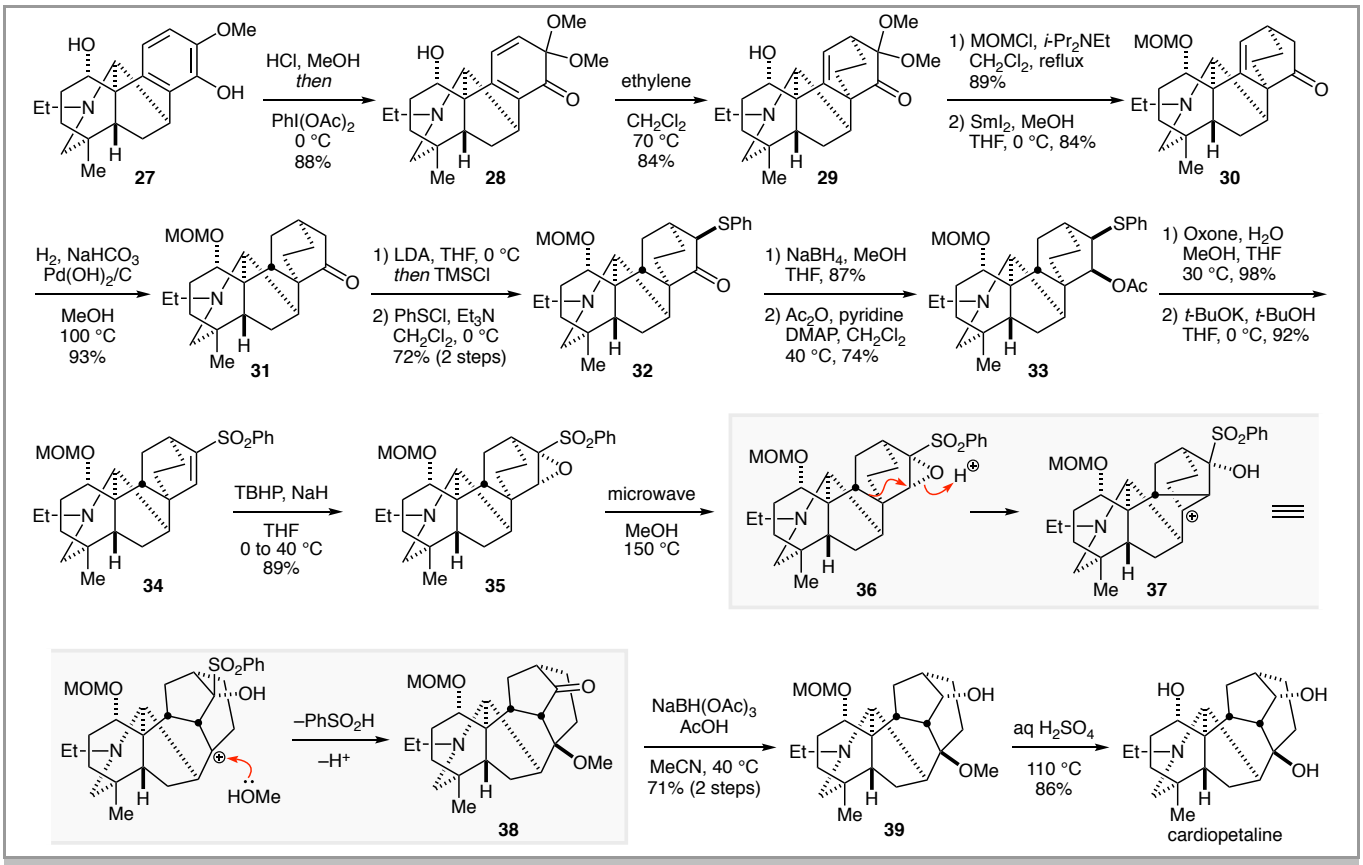


Figure 1 Structure of Cardiopetaline.

The substrate bearing the requisite bicyclo[2.2.2]octane was prepared via oxidative dearomatization of a guaiacol and a subsequent Diels–Alder reaction.[27,28] Thus, compound **27** was oxidized with iodobenzene diacetate in methanol, where the tertiary amine moiety in **27** was protected as its hydrochloride salt *in situ*. Upon heating under an ethylene atmosphere, the resultant *ortho*-quinone monoketal **28** underwent a Diels–Alder reaction, resulting in construction of the bicyclo [2.2.2] system.

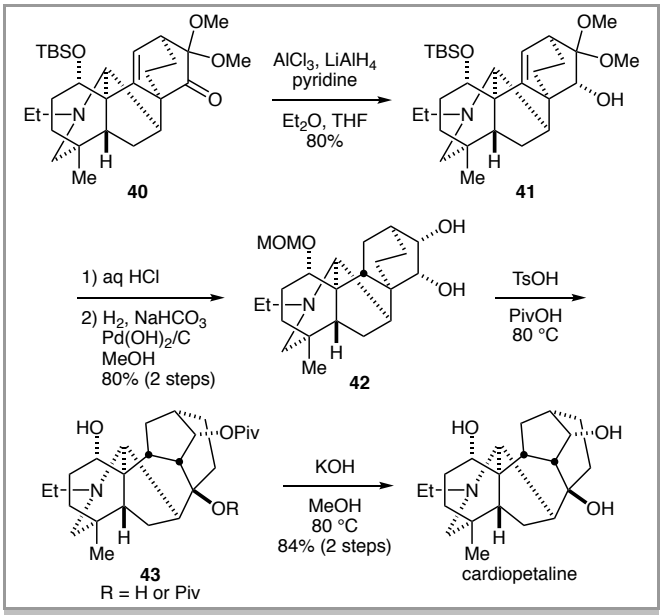
After protection of the hydroxy group in **29** with a methoxymethyl group, the two methoxy groups at the α-position of the carbonyl group were reductively removed with samarium(II) iodide. Hydrogenation of the C–C double bond occurred stereoselectively to give **31**. Installation of a phenylthio group was conducted via formation of a silyl enolate followed by reaction with phenylsulfenyl chloride. Reduction of the ketone moiety in **32** with sodium borohydride afforded an alcohol, which was acetylated by treatment with acetic anhydride. Oxidation of the sulfide moiety in **33** with Oxone gave a sulfone that was treated with potassium *tert*-butoxide to induce elimination of the acetoxy group. Nucleophilic epoxidation of the resultant unsaturated sulfone **34** produced epoxy sulfone **35**.

Heating epoxy sulfone **35** at 150 °C in methanol under microwave irradiation induced the Wagner–Meerwein rearrangement via cleavage of the epoxide at the β-position of the sulfonyl group. The resultant tertiary carbocation **37** was trapped by methanol and the sulfonyl group was eliminated from the intermediate as benzenesulfinic acid, giving ketone **38**, which was reduced with sodium triacetoxyborohydride. Finally, acidic hydrolysis of **39** with sulfuric acid at 110 °C afforded cardiopetaline.[25-26]

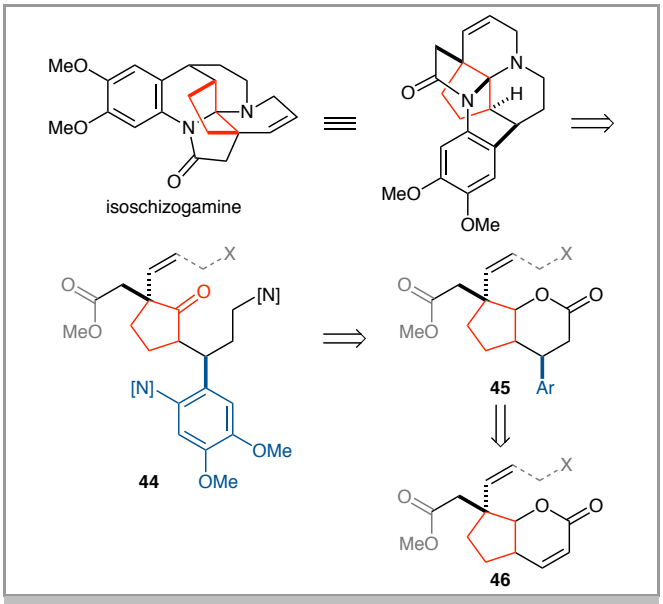


Scheme 5 Synthesis of cardiopetaline via an epoxy sulphone.

Another substrate for the Wagner–Meerwein rearrangement was prepared from the bicyclo [2.2.2] intermediate **29**. After protection of the hydroxy group in **29** with a TBS group (**40**), the carbonyl group was stereoselectively reduced with alane to afford **41** (Scheme 6). Acidic hydrolysis of the dimethyl acetal in **41** afforded a ketone, which was reduced under hydrogenation conditions with Pearlman's catalyst with concomitant reduction of the C–C double bond to furnish the requisite diol **42**. By heating the diol with *p*-toluenesulfonic acid in pivalic acid at 80 °C, the Wagner–Meerwein rearrangement proceeded to give **43**, which was hydrolyzed under basic conditions to produce cardiopetaline.[26b]



Scheme 6 Synthesis of cardiopetaline via a diol.



Scheme 7 Retrosynthetic analysis of isoschizogamine.

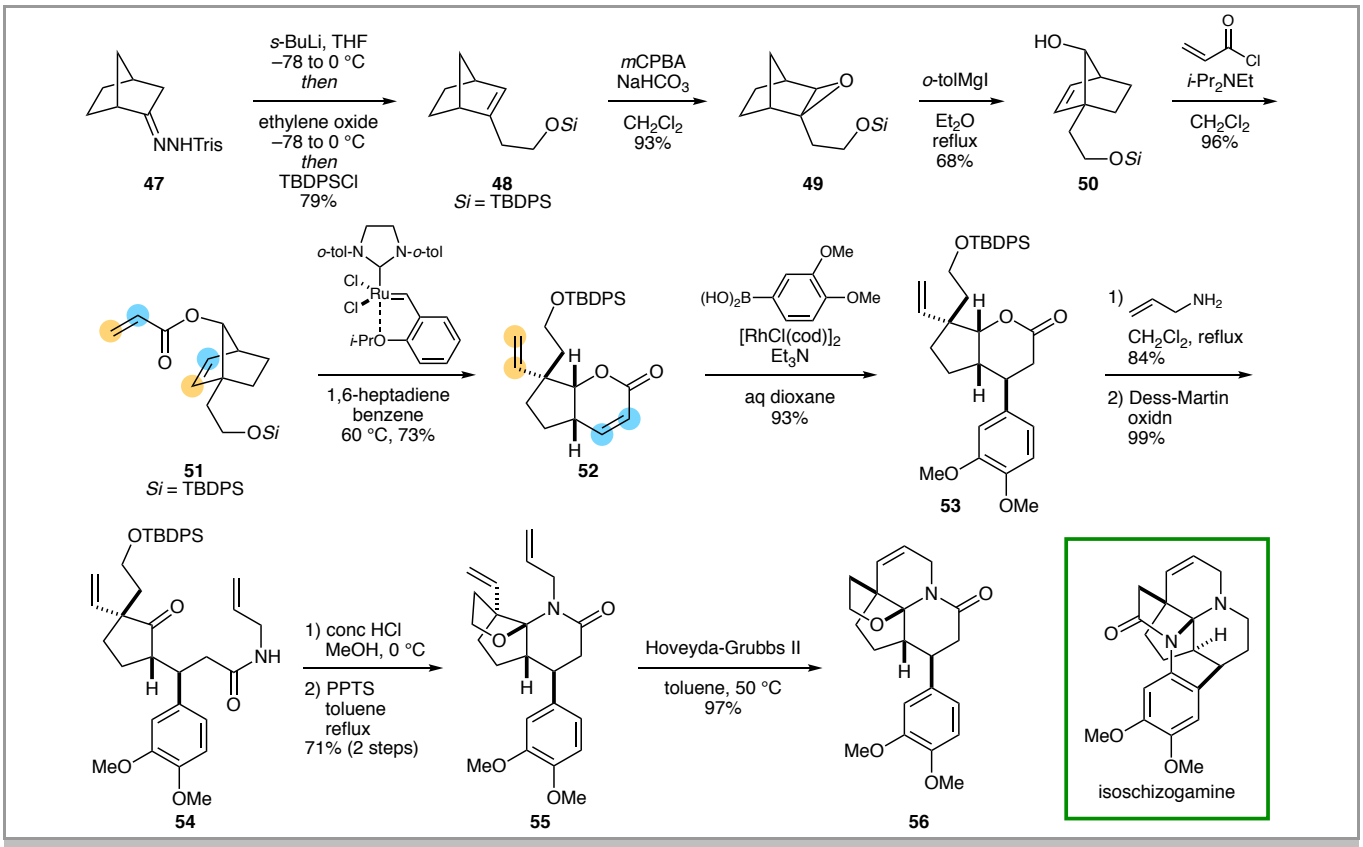
4 Synthesis via metathesis

Ring-closing metathesis is an indispensable method to construct ring systems of natural products.[29] The products consequently have C–C double bonds, which can be used for further functionalization. Herein we discuss our synthesis of isoschizogamine using ring-closing metathesis as a key step.[30,31]

Isoschizogamine is a natural product isolated from *Schizozygia caffaeoides* that features a characteristic tetrahydroquinoline core connected to a piperidine ring via a spiro center (Scheme 7).[32] A γ-lactam fused with the spiro system shares a nitrogen atom on the tetrahydroquinoline. In addition, two C–C bridges constitute piperidine and cyclopentane rings. The two nitrogen atoms on the heterocycles are connected to a carbon on the cyclopentane ring, forming an aminal.

Retrosynthetic cleavage of the C–N bonds of isoschizogamine generated a cyclopentanone intermediate. Strategic connection of the functional groups in the retrosynthetic sense would produce lactone **45**. The aromatic ring in **45** could be installed via 1,4-addition to unsaturated lactone **46**, which was our first target for the synthesis of isoschizogamine.

The synthesis of isoschizogamine commenced with a Shapiro reaction of hydrazone **47** to generate an alkenyllithium species, which was reacted with ethylene oxide (Scheme 8). After protection of the resultant alcohol with a TBDPS group, epoxidation with *m*-chloroperbenzoic acid furnished epoxide **49**. Activation of the epoxide with *o*-tolylmagnesium iodide induced the Wagner–Meerwein rearrangement to afford 7-hydroxynorbornene **50**.[33] A subsequent reaction with acryloyl chloride produced acrylate **51**, the substrate for tandem metathesis. The reaction was conducted with a ruthenium catalyst with sterically less demanding aromatic rings on the *N*-heterocyclic carbene was used to enhance reactivity toward the congested substrate and in the presence of 1,6-heptadiene to promote generation of a ruthenium methylidene complex.[34] The reaction proceeded in benzene at 60 °C to give product **52** in 73% yield. The subsequent rhodium-catalyzed 1,4-addition of arylboronic acid stereoselectively occurred from the convex face of the bicyclic system of **52** to afford **53**.[35]



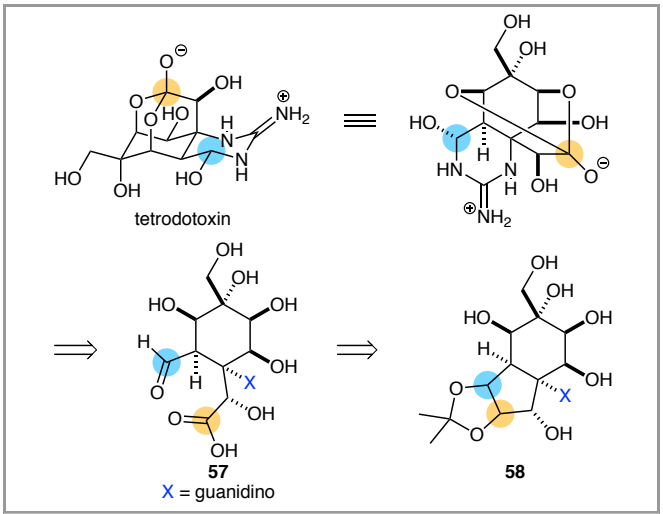
Scheme 8 Synthesis of isoschizogamine.

After ring opening of the lactone ring with allylamine, the liberated alcohol moiety was oxidized to a ketone. Attempted ring-closing metathesis of **54** to form a 10-membered ring, however, did not proceed. To bring the two terminal olefins closer together, the ketone was converted into *N*,*O*-acetal **55** under acidic conditions. The ring-closing metathesis of **55** proceeded smoothly to form the requisite 6-membered ring. Further transformation of compound **56** included the introduction of a nitrogen atom on the aromatic ring and formation of the aminal moiety to afford isoschizogamine.

5 Synthesis via temporary formation of a ring

As shown in the latter part of our synthesis of isoschizogamine, formation of rings often helps to control reactivity or selectivity in reactions. In our synthesis of tetrodotoxin, we successfully controlled both reactivity and selectivity via formation of a ring that the natural product does not have, and then completed the synthesis via rearrangement of the ring system.[36]

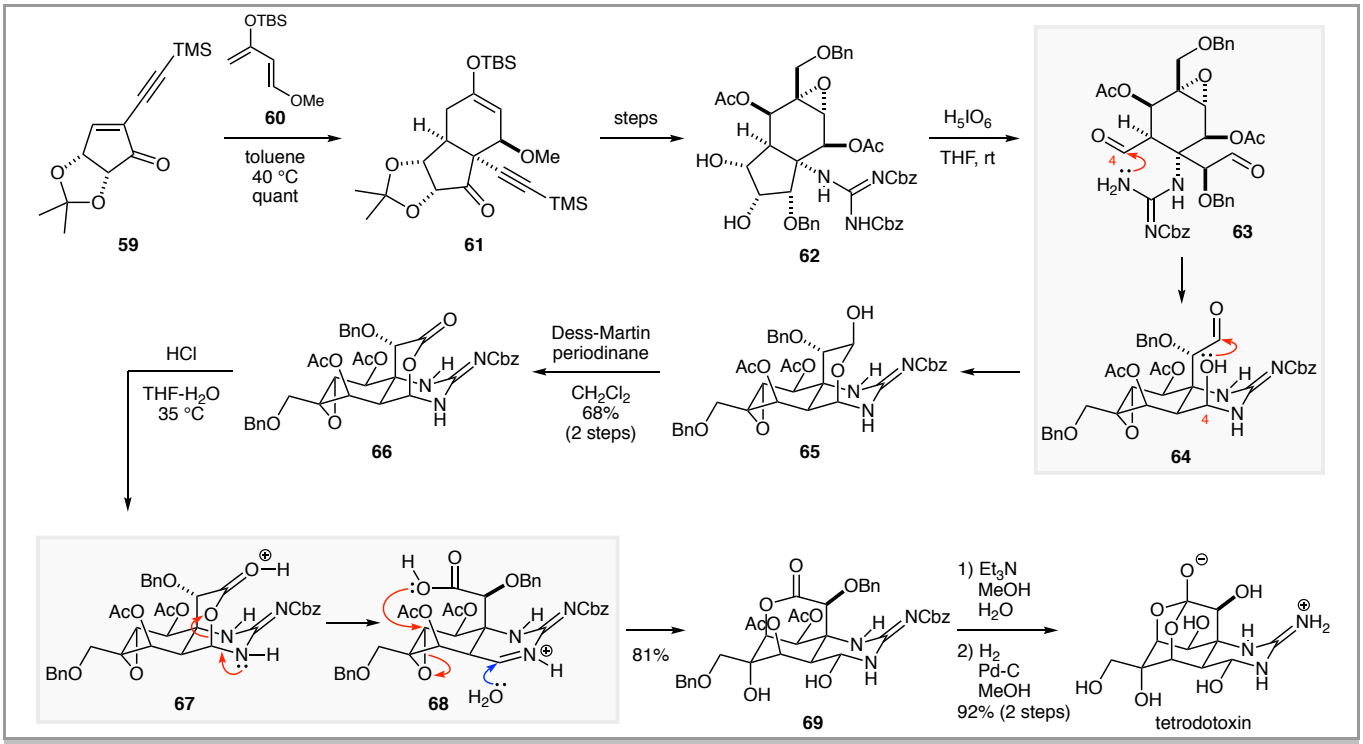
The core structure of tetrodotoxin is a highly functionalized cyclohexane ring (Scheme 9). To form the characteristic hemiaminal and orthoester moieties in tetrodotoxin, the cyclohexane core should have aldehyde and carboxylic acid equivalents, respectively (**57**). In our retrosynthesis of tetrodotoxin, these two carbonyl groups were connected to produce bicyclic compound **58**, where a 1,2-diol was installed for oxidative cleavage. The drawback of this strategy was that a dialdehyde was generated after cleavage of the C–C bond, and the two formyl groups must be differentiated. This problem could be solved by the temporary formation of a ring.



Scheme 9 Retrosynthetic analysis of tetrodotoxin.

As shown in Schcme 10, the cyclohexane ring was constructed via a Diels–Alder reaction of cyclopentenone **59** with siloxydiene **60**. The substituents on the rings were stereoselectively introduced in several steps using the steric bias of the *cis*-fused bicyclic system, leading to diol **62**. Oxidative cleavage of the diol with orthoperiodic acid proceeded smoothly at room temperature. Under these conditions, the two formyl groups and the guanidino group cooperatively formed a lactol intermediate. The guanidino group, which appeared to take the equatorial position, attacked the more accessible C4 formyl group to form hemiaminal **64**, and the hydroxy group of this

hemiaminal then attacked the other formyl group. This strategy enabled the two formyl groups to be efficiently differentiated. Lactol **65** was subsequently oxidized into lactone **66** with Dess-Martin periodinane. Upon treatment with hydrochloric acid, the lactone was cleaved via electron donation from the guanidino group, with the liberated carboxy group attacking the epoxide intramolecularly to give hydroxylactone **69**. Finally, global deprotection afforded tetrodotoxin.



Scheme 10 Synthesis of tetrodotoxin.

6 Conclusion

Our syntheses of polycyclic natural products via skeletal rearrangement are described in this personal account.[37] In the syntheses of lyconadin A and huperzine Q, a ring-expansion or ring-contraction reaction of a cyclohexane ring, which was built by a Diels-Alder reaction, was employed. In the synthesis of huperzine R, cleavage of a C–C bond in a cyclohexane ring led to forming a bicyclo [5.4.3] system. In the synthesis of cardiopetaline, a bicyclo [2.2.2] system, which was constructed by a Diels-Alder reaction, was rearranged into a bicyclo [3.2.1] system via Wagner–Meerwein rearrangement. The synthesis of isoschizogamine demonstrated the utility of metathesis to prepare a functionalized cyclic system. Temporary formation of a ring can control the reactivity of a reaction, and this strategy was applied to the synthesis of tetrodotoxin to differentiate two aldehyde moieties. Skeletal rearrangement of the resultant ring system provided the natural product. Skeletal rearrangement enabled transformation of precursors, which are readily prepared by ubiquitous reactions, into the desired ring systems. This means that the utility of ubiquitous reactions can be expanded by skeletal rearrangement. To access a wide range of ring systems, not only formation of rings but also rearrangement of them should be explored.

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