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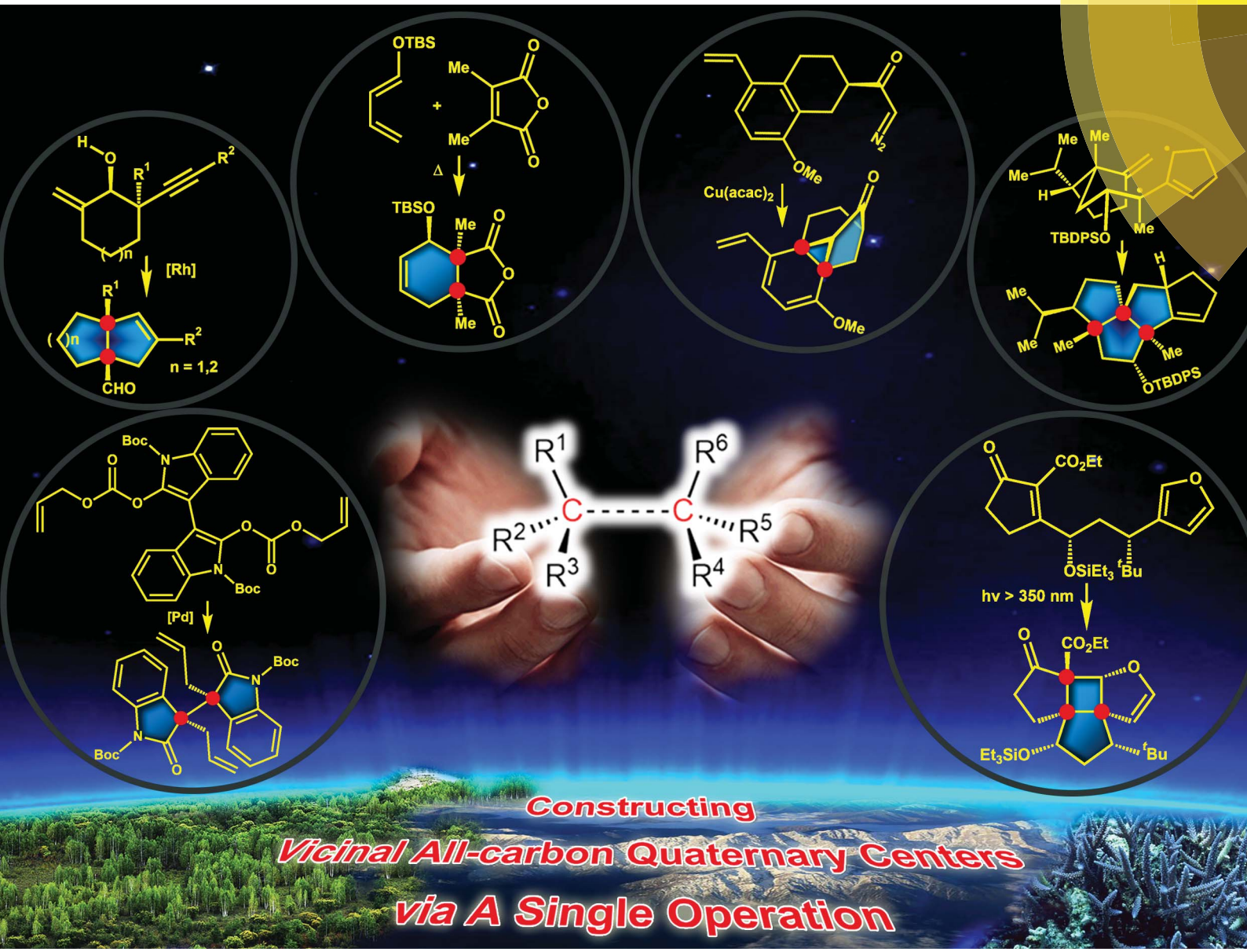

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Direct construction of vicinal all-carbon quaternary stereocenters in natural product synthesis

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Molecules containing vicinal all-carbon quaternary stereocenters are found in many secondary metabolites, and they exhibit a variety of biological and pharmacological activities. However, the construction of such a structural motif remains a significant challenge in natural product synthesis. Only in recent years have considerable efforts been made to construct vicinal quaternary stereocenters in a single-step operation. In this review, we focus on the different types of methods that have been successfully used in the total synthesis of natural products. Based on the classified reactions for the simultaneous generation of vicinal all-carbon quaternary stereocenters, the total syntheses of the natural products are discussed, placing emphasis on the diastereoselective preparation of vicinal quaternary carbon centers and the subsequent total syntheses.

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1. Introduction

Natural products play an important role in biomedical research and drug discovery, mainly because of the structural complexity and diversity that nature has engineered to facilitate the optimal functions of living systems. This structural complexity and diversity enables natural products to modulate the biological targets of human diseases. Natural products have some of the general features of drugs, such as molecular complexity, the ability to bind to proteins, structural rigidity, and three-dimensionality.[1] In this respect, natural products containing rigid vicinal all-carbon quaternary stereocenters are particularly important because of their unique structural features and their tendency to tightly bind to target molecules.[2] Thus, the stereoselective construction of sterically restricted vicinal stereogenic centers has attracted the interest of synthetic chemists because of the prevalence of such structural arrangements in natural

products and bioactive compounds. Consequently, a number of methods have been developed to directly synthesize vicinal all-carbon quaternary centers, including pericyclic, alkylation, photochemical, transition metal-catalyzed, radical, and cyclopropanation reactions.[3]

Despite the remarkable advances that have been made in the formation of all-carbon quaternary stereocenters in a stereoselective fashion,[4] the direct stereocontrolled construction of vicinal all-carbon quaternary stereocenters remains a considerable challenge in contemporary organic synthesis. Further investigations into the development of efficient methods to directly and selectively generate such stereochemical arrays should prove valuable.[5]

In 2004, Overman and Peterson presented a perspective on the direct asymmetrical formation of vicinal all-carbon quaternary stereogenic centers in natural product synthesis.[6] Since then, many elegant methodologies have been developed,[7–15] and methods for the catalytic asymmetric construction of vicinal all-carbon quaternary stereogenic centers have been reported.[16–28]

Although a comprehensive review of the synthesis of vicinal all-carbon quaternary stereogenic centers is beyond the scope of this review, we herein report the powerful reactions that can form this challenging motif in "a single operation" and that have been successfully applied to the total synthesis of complex natural products. This review has been organized based on reaction types, and highlights their usefulness in the construction of structurally diverse vicinal all-carbon quaternary centers. We apologize if we have overlooked any relevant results.

2. Pericyclic reactions

2.1. Diels–Alder reaction

The Diels–Alder reaction is a powerful method for the single-step synthesis of complex polycyclic structures containing many stereogenic centers,[29] and it has been successfully applied for the stereocontrolled introduction of contiguous all-carbon quaternary stereogenic centers.[30] Using this reaction as a key step, many complex natural products can be effectively synthesized. Cyclohexene frameworks with up to four contiguous stereogenic centers can be constructed *via* either intermolecular or intramolecular Diels–Alder reactions and the

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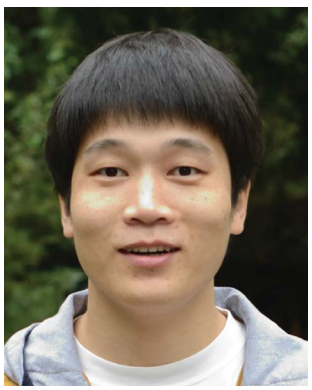
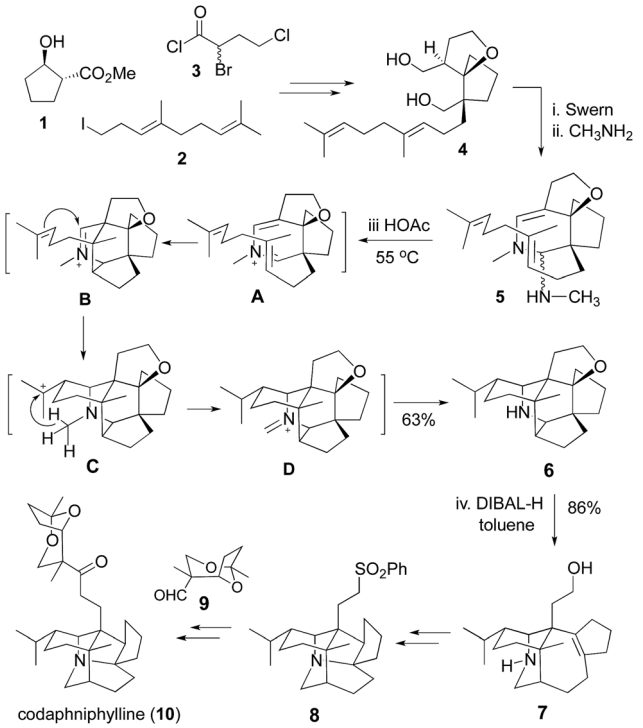
Jianxian Gong received his Ph.D. from Peking University in 2012 under the supervision of Professor Zhen Yang. After a year of postdoctoral research at Memorial Sloan-Kettering Cancer Center, he returned to China and joined Professor Zhen Yang' group as an associate investigator. In 2015, he was appointed as an associate professor at Peking University Shenzhen Graduate School. His research interests include the total synthesis of bioactive natural products and the development of new synthetic methods.

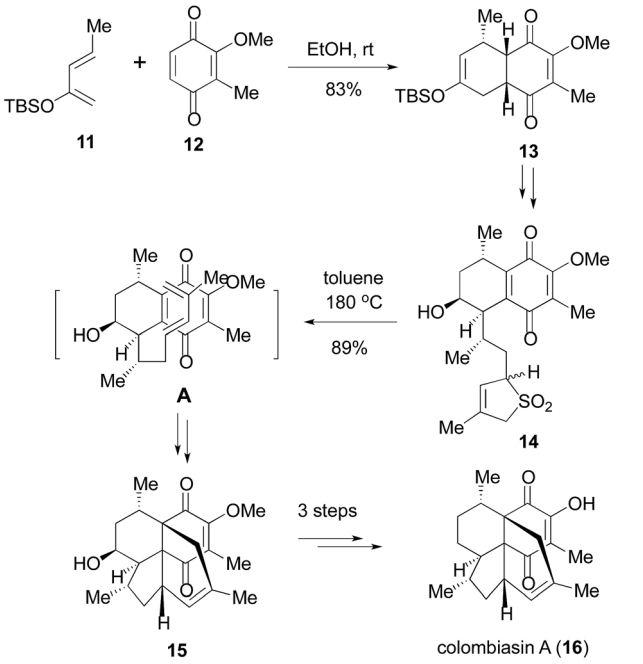


Jun Huang was born in Hubei, China. He received his BS degree in chemistry from China Agricultural University in 2010. He completed his Ph.D. in Organic Chemistry at Peking University under the guidance of Professor Zhen Yang, working on the total synthesis of natural products based on transition-metal catalyzed new processes. Currently, he is undertaking postdoctoral research at State University of New York at Albany.

Zhen Yang studied medicinal chemistry at Shenyang College of Pharmacy and earned a Ph.D. at The Chinese University of Hong Kong in 1992 under the guidance of H. N. C. Wong. He carried out postdoctoral research on natural-product synthesis with K. C. Nicolaou at The Scripps Research Institute in La Jolla, CA, and joined its faculty in 1995. In 1998, he moved to the Institute of Chemistry and Cell Biology of Harvard Medical School as an institute fellow before returning to China as a professor at Peking University in 2001. His research is devoted to the total synthesis of natural products and chemical biology.



Scheme 1 Total synthesis of (+)-codaphniphylline.



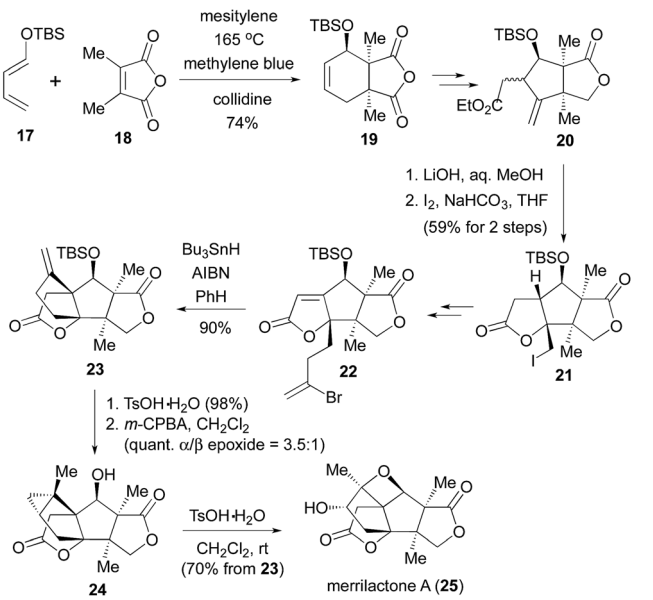
Scheme 2 Total synthesis of colombiasin A.

relative stereochemistry is defined by the typically favored *endo* transition state. The following examples illustrate the use of this powerful reaction in the total synthesis of complex natural products.

2.1.1. *Daphniphyllum* alkaloids. *Daphniphyllum* alkaloids are a large and growing group of complex natural products.[31] Intensive effort has been devoted to the total synthesis of this type of biologically important active[31a] natural product.[32] Among these syntheses, the possibly biomimetic approach for the synthesis of the basic skeleton of the *Daphniphyllum* alkaloids developed by Heathcock[33] is striking, and it demonstrates the capability of synthetic chemistry to effectively construct complex molecules. As demonstrated in the total synthesis of (+)-codaphniphylline (**10** in Scheme 1),[34] the most impressive transformation is the formation of the hexacyclic (+)-codaphniphylline core by the following sequential reactions: Swern oxidation, imine formation, intramolecular Diels–Alder reaction to form the two vicinal all-carbon quaternary stereogenic centers, and acid-mediated hydride transfer to form the immonium ion **D**. This eventually leads to the formation of the key intermediate **6** after hydrolytic workup (Scheme 1). Further synthetic transformations, including a DIBAL-H reduction and Eschenmoser–Grob fragmentation (**6** to **7**), lead to the total synthesis of (+)-codaphniphylline (**10**) in a highly efficient manner.

The impressive synthetic transformation carried out by Heathcock's group has elicited a much deeper understanding of the biomimetic synthesis of *Daphniphyllum* alkaloids and has stimulated much effort toward the development of new synthetic strategies and tactics. The developed chemistry has served to inspire chemists to develop even better total syntheses of *Daphniphyllum* alkaloids.

2.1.2. Colombiasin A. Colombiasin A (**16** in Scheme 2) is a diterpene isolated from a biologically active (against *Mycobacterium tuberculosis* H37Rv) extract obtained from the gorgonian octocoral *Pseudopterogorgia elisabethae* collected off San Andres Island, Colombia.[35] This tetracyclic diterpene contains six stereogenic centers, two of which are adjacent quaternary carbon atoms. Nicolaou *et al.* used a double Diels–Alder reaction to synthesize this molecule, and demonstrated its absolute configuration.[36] In their total synthesis, the cornerstone



Scheme 3 Total synthesis of (±)-merrilactone A.

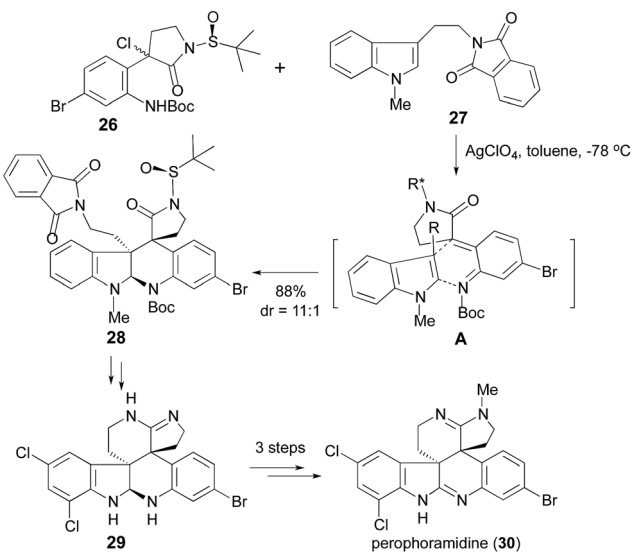
intermediate quinone **13** was constructed from diene **11** and quinone **12** by an intermolecular Diels–Alder reaction, and then converted to cyclic sulfone **14**, which was then subjected to a sequence of extrusion of SO_2 followed by an intramolecular Diels–Alder reaction to produce **15** (89% yield) as a single diastereoisomer with *endo*-selectivity. Thus, through a three-step transformation, the total synthesis of colombiasin A (**16**) was achieved.

The asymmetric total synthesis of colombiasin A was later independently achieved by several research groups,[37–40] and in their syntheses intramolecular Diels–Alder reactions were also used as a key step in the construction of the adjacent quaternary carbon centers.

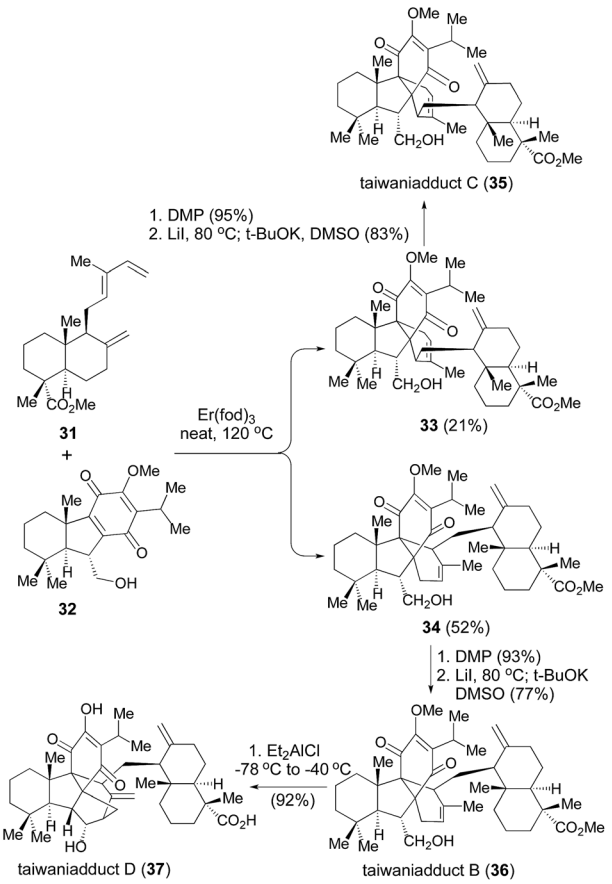
2.1.3. (±)-Merrilactone A. Merrilactone A (**25** in Scheme 3) is a sesquiterpene dilactone isolated from *Illicium merrillianum*.[41] It can greatly promote neurite outgrowth in fetal rat cortical neurons at concentrations as low as 0.1–10 μmol. Merrilactone A has a pentacyclic skeleton with five contiguous stereogenic centers, of which two are vicinal all-carbon quaternary stereocenters.

Many research groups involved in the total synthesis of merrilactone A are motivated by its important biological activity and unusual structure.[42] The first total synthesis of (±)-merrilactone A was accomplished by Birman and Danishefsky in 2001,[42a] where construction of the two vicinal all-carbon quaternary stereogenic centers in compound **19** was accomplished by an intermolecular Diels–Alder reaction using dimethylmaleic anhydride as a dienophile. Through a series of transformations, such as iodolactonization to form **21** from **20**, intramolecular free radical cyclization to synthesize **23** from **22**, and a Payne-like rearrangement to form the oxetane ring, (±)-merrilactone A was synthesized in 20 steps with 10.7% overall yield.

2.1.4. (+)-Perophoramidine. Perophoramidine (**93** in Scheme 15) was isolated from the ascidian *Perophora namei* in 2002,[43a] and this molecule exhibits cytotoxicity toward the HCT



Scheme 4 Total synthesis of (+)-perophoramidine.



Scheme 5 Total synthesis of taiwaniadducts B, C, and D.

116 human colon carcinoma cell line (IC_{50} = 60 μM) and induces apoptosis *via* PARP cleavage.[43b] It contains an intriguing bis-amidine skeleton with two vicinal all-carbon quaternary centers.

The first asymmetric total synthesis of (+)-perophoramidine (**30** in Scheme 4) was accomplished by Qin and co-workers.[44] The key step is the *in situ* generation of precursor A from **26** and **27** in the presence of $AgClO_4$ in toluene. This is followed by a chiral-auxiliary-induced hetero-Diels–Alder reaction to diastereoselectively produce **28** (88% yield), which has two vicinal all-carbon quaternary chiral centers, and the ratio of the diastereoselectivity is 11 : 1. After a further five steps, the asymmetric total synthesis of (+)-perophoramidine (**30**) was achieved in 17 steps with 11% overall yield.

2.1.5. Taiwaniadducts B, C, and D. Taiwaniaquinoids are a class of terpenoids with impressive biological activities that are isolated from the endangered species *Taiwania cryptomerioides*.[45] From a biosynthetic perspective, taiwaniadduct D (**37**, Scheme 5) can be derived from taiwaniadduct B (**36**) through carbonyl-ene cyclization, and **36** can be obtained through an intermolecular Diels–Alder reaction between naturally occurring taiwaniaquinone A or F and *trans*-ozic acid.

Adopting the biomimetic approach, Li and co-workers achieved the total syntheses of taiwaniaquinones B, C, and D for the first time (Scheme 5).[46] The key intermediates **33** and **34**, containing sequestered and sterically hindered vicinal all-carbon

quaternary centers, were formed by the $Er(fod)_3$-catalyzed intermolecular Diels–Alder reaction of diene **31** (a derivative of *trans*-ozic acid) and dienophile **32** (a derivative of taiwaniaquinone F), and both **31** and **32** were prepared with high enantiopurity by Ir-catalyzed asymmetric polyene cyclization.[47] The Diels–Alder reaction of **31** and **32** was carried out in the presence of $Er(fod)_3$ at 120 °C without solvent to produce **33** and **34** in 21% and 52% yields, respectively. Further treatment of **33** with 2,2-dimethoxypropane followed by demethylation and hydrolysis produced taiwaniadduct C (**35**) in 79% yield. Under similar reaction conditions, product **34** was converted to taiwaniadduct B (**36**) in 72% yield. When taiwaniadduct B (**36**) was treated with Et_2AlCl to initiate the carbonyl-ene cyclization reaction, taiwaniadduct D (**37**) was obtained in 92% yield.

The total synthesis presented above has demonstrated the unique power and robust nature of the Diels–Alder reaction to stereoselectively form sequestered and sterically hindered intermediates from elaborated dienes and dienophiles as coupling partners, which facilitates a highly convergent synthesis of a broad range of complex natural products.

2.2. [3,3]-Sigmatropic rearrangement reaction

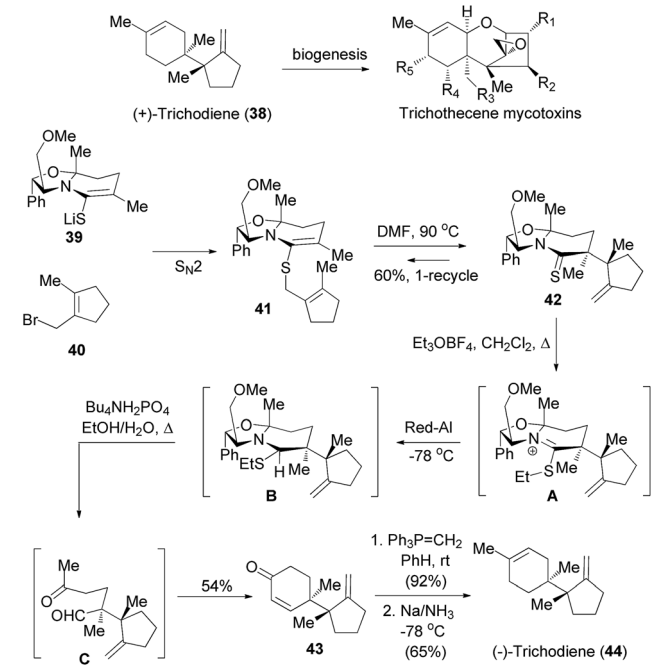
[3,3]-Sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) has emerged as a proven strategy for the stereoselective synthesis of vicinal quaternary carbons.[48] The diastereoselectivity is generally high and predictable in these processes because of the concerted nature of the C–O bond-breaking and C–C bond-forming events, as well as the large energetic preference for chair-like over boat-like transition states. Therefore, the resulting product has the correct relative stereochemical disposition about the vicinal quaternary centers, and carbon–carbon bonds between vicinal stereogenic centers. There are two strategies to achieve the diastereocontrolled synthesis: (1) the use of substrates containing pre-existing stereogenic centers, either as part of cleavable auxiliaries or structural features of the target molecule;[49] and (2) catalytic asymmetric methods for the direct and selective formation of such stereochemical arrays.[17]

2.2.1. (−)-Trichodiene. Trichodiene (**44** in Scheme 6) is a sesquiterpene. It is isolated from the fermentation broth of the mycelium of *Trichothecium roseum*,[50] and it is the postulated biogenetic precursor[51] of the trichothecene mycotoxins, which are fungal metabolites from the genus *Fusarium*.[52] Trichothecene mycotoxins have been shown to exhibit diverse biological activities.[53]

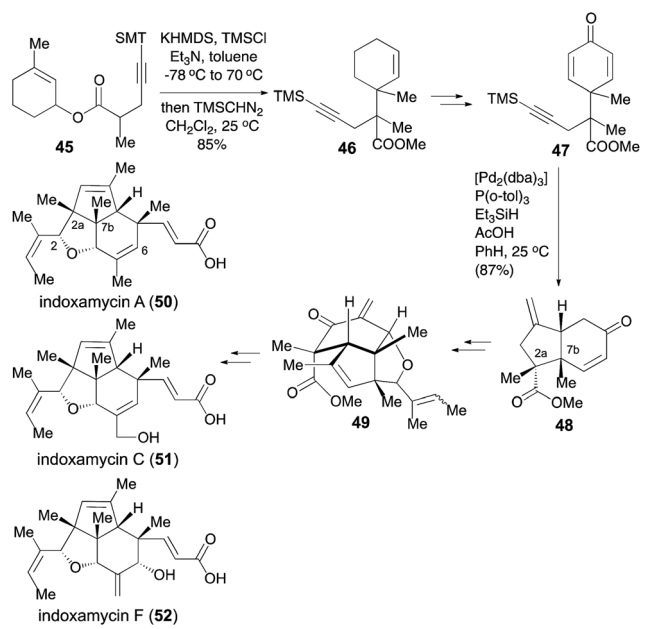
In 1998, Meyers and Lemieux reported the asymmetric total synthesis of (−)-trichodiene from the readily available bicyclic lactam **39** in 10 steps with 14% overall yield.[54] The key step is thio-Claisen rearrangement of thioether **41** to prepare the important synthetic intermediate **42** containing two vicinal stereogenic quaternary carbon centers. The chiral auxiliary was removed by sequential alkylation/reduction/hydrolysis *via* intermediates **A**, **B**, and **C** (Scheme 6). The total synthesis of (−)-trichodiene was achieved by a Wittig reaction followed by Na/NH_3 reduction in 60% yield.

The chiral non-racemic bicyclic lactam has proven to be a versatile chiral template for the asymmetric construction of a variety of optically pure compounds. Thus, the application of the thio-Claisen rearrangement of chiral bicyclic lactam-based thiocarbonyl compound **41** has proved to be an effective tool in the synthesis of a key intermediate bearing two vicinal quaternary chiral centers.

2.2.2. Indoxamycins A, C, and F. Indoxamycins A–F represent a novel class of polyketides, and they are isolated from saline cultures of marine-derived actinomycetes.[55] Within this family, indoxamycins A and F have exhibited promising growth-



Scheme 6 Total synthesis of (−)-trichodiene.



Scheme 7 Total synthesis of indoxamycins A, C, and F.

inhibition activity against HT-29 tumor cell lines (IC_{50} = 0.59 and 0.31 μM, respectively), achieving levels of activity similar to that of mitomycin (IC_{50} = 0.66 μM).

The indoxamycin skeleton consists of a [5,5,6] tricyclic cage-like carbon framework with a trisubstituted olefin and an unsaturated carboxylic acid side chain. The core structure contains six contiguous stereogenic centers, of which three are quaternary, including two vicinal carbon atoms embedded in a sterically congested tetrahydrofuran subunit (Scheme 7).

In 2012, Ding and co-workers reported the divergent total synthesis of indoxamycins A, C, and F.[56] The critical step is the synthesis of two vicinal quaternary centers at the C2a and C7b positions by Ireland–Claisen rearrangement. Substrate **45** was first treated with potassium bis(trimethylsilyl)amide (KHMDS) followed by reaction with trimethylsilyl chloride (TMSCl). The resultant silyl ketene acetal then underwent Ireland–Claisen rearrangement after reaction with trimethylsilyldiazomethane ($TMSCHN_2$) to produce ester **46** as a pair of diastereoisomers in 85% yield. After **46** had been subjected to two oxidation steps, the resultant enyne **47** underwent Pd-catalyzed reductive Alder-ene cyclization to produce cyclohexenone **48** with two vicinal quaternary centers in 87% yield. Further synthetic transformation to convert cyclohexenone **48** to its advanced intermediate **49** eventually led to the total synthesis of indoxamycins A, C, and F.

The Claisen rearrangement has become a powerful method widely used by synthetic organic chemists, and a catalytic version of the asymmetric Claisen rearrangement has emerged.[57] In this aspect, Yamamoto and co-workers have developed a copper-catalyzed enantioselective Claisen rearrangement of enolphosphonates, and a number of α-ketophosphonate bearing vicinal all-carbon quaternary centers were formed in excellent yields and stereoselectivities.[58] This reaction is expected to be applicable in the total synthesis of complex natural products.

3. Photochemical reactions

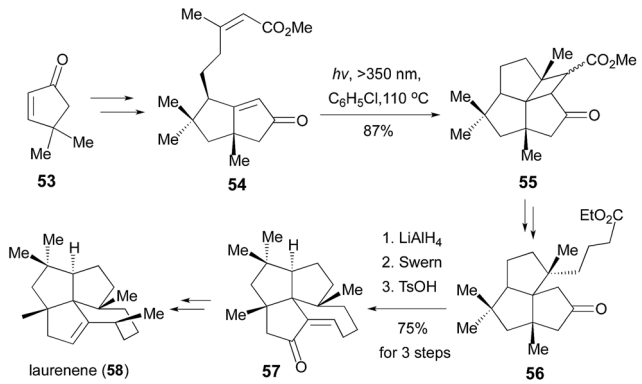
Photochemical reactions are often very useful in organic synthesis. By accessing electronically excited states, modes of reactivity that are not available to molecules in the ground state can be exploited.[59] As a result, astonishing transformations occur that result in the formation of remarkable molecular structures, which barely resemble their precursor molecules. In this regard, [2 + 2] photocycloaddition,[23,60] *meta*-photocycloaddition,[61] and photodecarbonylation reactions[62] have emerged as unique methods for highly chemoselective and stereospecific formation of vicinal quaternary centers. In this section, we highlight some successful examples of the use of [2 + 2] photocycloaddition as a key step in the total synthesis of complex natural products, with particular focus on its unique role in the stereoselective construction of vicinal quaternary all-carbon stereogenic centers.

3.1. (±)-Laurenene

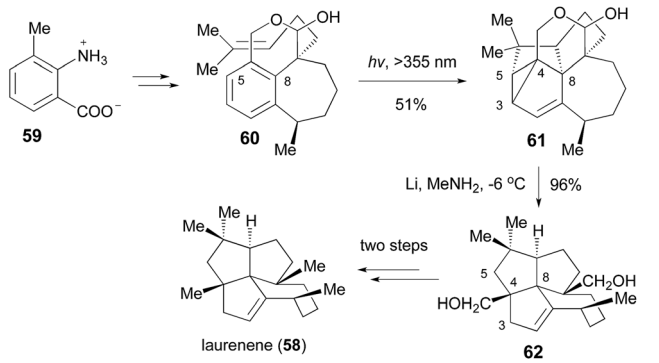
Laurenene (**58** in Scheme 8) is isolated from *Dacrydium cupressinum*. It contains a fenestrane framework with three contiguous all-carbon quaternary stereocenters in the tetracyclic skeleton.[63] Crimmins and Gould achieved the first total synthesis of (±)-laurenene in 1987 using intramolecular [2 + 2] photocycloaddition.[64] The synthesis used dimethylcyclopentanone **53** as the substrate, which was converted to a cyclopentenone derivative (**54**) in several steps. Thus, compound **55** with the core structure of laurenene was constructed by intramolecular photocycloaddition to create the vicinal all-carbon quaternary stereocenters in a single step. Eventually, laurenene (**58**) was successfully produced from **56** after several routine synthetic transformations.

Wender *et al.* reported the total synthesis of laurenene (**58**) in 1988 (Scheme 9).[65] Interestingly, the key step in this total synthesis of laurenene is photo-induced intramolecular *meta*-cycloaddition of the phenyl ring in substrate **60** with a double bond to form the critical intermediate **61**. The reaction is achieved using an aqueous bismuth trichloride filter to give the desired product in 51% yield. After reductive cleavage of the C3–C5 bond, product **62** with the core structure of laurenene was obtained in 96% yield. After further treatment of **62** to convert the hydroxymethyl groups to methyl groups, (±)-laurenene (**58**) was stereoselectively produced in 13 steps with 5% overall yield. Wender *et al.* also achieved the total synthesis of several naturally occurring triquinanes, such as (±)-isocomene, (±)-silphinene, and (±)-retigeranic acid, using *meta*-photocycloaddition as the key step.[66]

A common challenge confronting synthetic organic chemists is the atom-efficient creation of molecular complexity. As



Scheme 8 Total synthesis of laurenene.



Scheme 9 Total synthesis of laurenene.

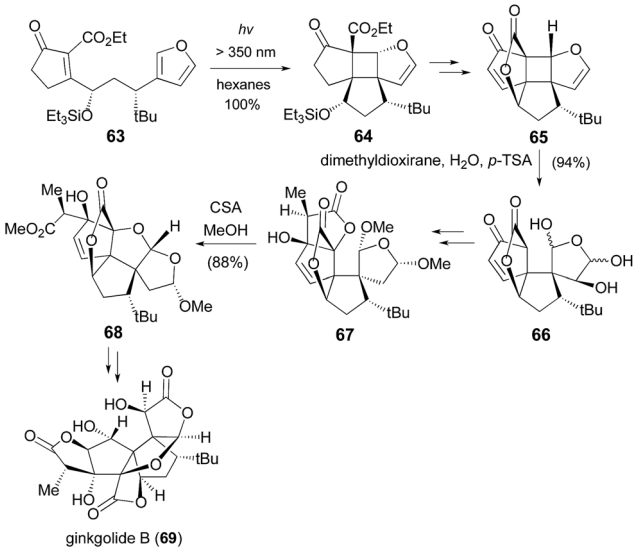
demonstrated in the total synthesis of laurenene, two complex molecular skeletons, **55** and **61**, bearing two vicinal quaternary chiral centers could be generated effectively by using photochemical reactions from their easily prepared precursors **54** and **60**. The syntheses are stereo- and regio-controlled and do not require protecting groups, which is in an agreement with the principles of green chemistry.

3.2. (±)-Ginkgolide B

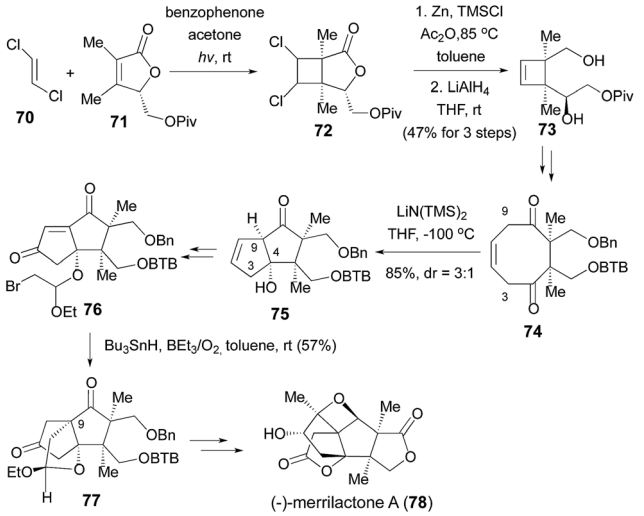
Ginkgolide B is a highly oxygenated natural product that is isolated from the extracts of *Ginkgo biloba*.[67] Ginkgolide B is a C20 hexacyclic trilactone with two vicinal all-carbon quaternary centers in the sterically hindered core of its molecular framework, and it contains a unique *tert*-butyl group on one of its five-membered rings. In addition to its novel and distinctive molecular structure, ginkgolide B is interesting because it is the most active platelet-activating factor antagonist of the isolated ginkgo extracts. Building on their earlier success in the total synthesis of (±)-bilobalide,[68] Crimmins *et al.* used intramolecular [2 + 2] photocycloaddition as the key step to produce the natural product (±)-ginkgolide B (**69** in Scheme 10).[69]

In the total synthesis of ginkgolide B, the most important step is the highly diastereoselective intramolecular [2 + 2] photocyclo-addition of substrate **63** for the quantitative formation of product **64** with two vicinal all-carbon quaternary stereogenic centers. With the synthesis of the key intermediate **64** accomplished, Crimmins *et al.* used state-of-the-art chemistry to complete the total synthesis of (±)-ginkgolide B.

From a synthetic point of view, no other photochemical reaction has had such a large impact on natural product synthesis as the [2 + 2] photocycloaddition of olefins. In the total synthesis of ginkgolide B, the remarkable result of the [2 + 2] photocyclo-addition reaction demonstrates the important impact of photochemical reactions on the outcome of complex scaffold formation. During this process, two carbon–carbon



Scheme 10 Total synthesis of ginkgolide B.



Scheme 11 Total synthesis of (−)-merrilactone A.

bonds, four new rings, and four new stereocenters (including two vicinal quaternary chiral centers) are created, which illustrates that the photocycloaddition reaction is particularly able to produce the polycyclic scaffolds with high rigidity.

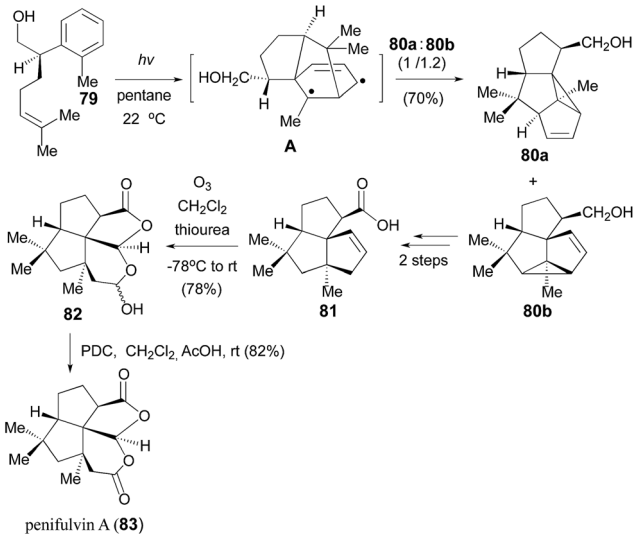
3.3. Merrilactone A

For the total synthesis of merrilactone A, Mehta and Singh,[42e] Inoue *et al.*,[42b–d] and Greaney and co-workers[42h,i] used [2 + 2] cycloaddition to introduce the two vicinal quaternary carbon atoms. Herein, we describe the total synthesis of (−)-merrilactone A accomplished by Inoue *et al.*[42c] (Scheme 11). The total synthesis began with a remarkable [2 + 2] photocycloaddition of dichloroethylene **70** and chiral lactone **71** to asymmetrically generate cyclobutane derivative **72**, which was then subjected to reductive dehalogenation followed by $LiAlH_4$-reduction to give triol **73**. After conversion of **73** to diketone **74**, with a ring-closing metathesis reaction as the key step, the resultant diketone **74** then underwent the following sequential transformations: transannular aldol condensation to synthesize **75** by taking advantage of the bulky 2,6-bis(trifluoromethyl)benzyl (BTB) protecting group, acting as a remote stereocontrol for selective deprotonation of diketone **74**; and radical cyclization to form the sterically congested C9 quaternary carbon atom of **77** from bromide **76**. The complete asymmetric total synthesis of (−)-merrilactone A was achieved with 1.1% overall yield in 31 steps.

3.4. (−)-Penifulvin A

Penifulvin A (**83** in Scheme 12) is a sesquiterpenoid that is isolated from *Penicillium griseofulvum*.[70] It has significant insecticidal activity against *Spodoptera frugiperda*. Penifulvin A has a highly congested dioxa-fenestrane skeleton containing a central quaternary carbon.

Mulzer and Gaich reported the first asymmetric total synthesis of penifulvin A in 2009.[71] The key step in the synthesis is *meta*-photocycloaddition to rapidly form the core structure containing two vicinal quaternary carbon centers. During the



Scheme 12 Total synthesis of (−)-penifulvin A.

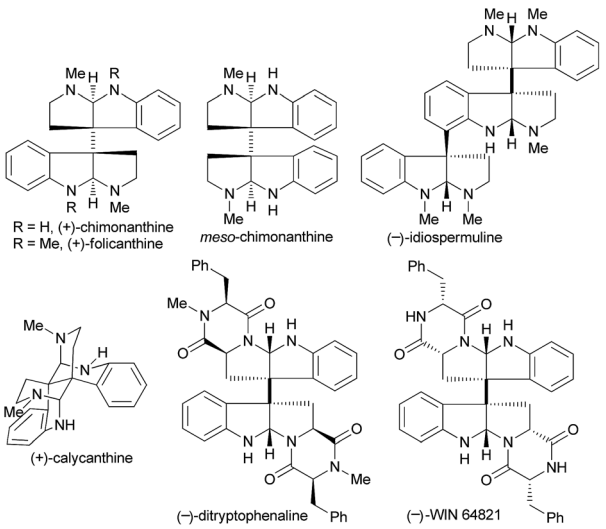
reaction, enantiomerically pure substrate **79** undergoes *meta*-photocycloaddition to produce **80a** and **80b** in a ratio of 1 : 1.2. Compound **80b** is then subjected to Birch-type reduction followed by oxidation to give acid **81**. After ozonolytic cleavage of the double bond followed by pyridinium dichromate oxidation, the yield of (−)-penifulvin A was 64%.

In 2010, Gaich and Mulzer also achieved the total synthesis of (−)-penifulvin B and C using *meta*-photocycloaddition as the key step to stereoselectively construct the vicinal all-carbon quaternary chiral center.[72]

4. Alkylations

Tryptamines are subunits in numerous bioactive natural products, such as the polypyrrolidinoindoline alkaloids[3b,73] in Scheme 13.

Structurally, this type of alkaloid contains two vicinal quaternary carbon centers. Because of their biological importance, intensive effort has been devoted to their total synthesis.[74] One of the typical reactions for the construction of the two vicinal quaternary carbon centers is direct alkylation, and typical examples are discussed below.



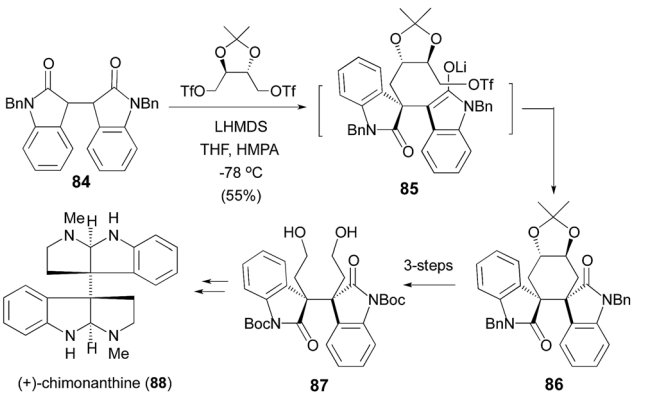
Scheme 13 Naturally occurring cyclotryptamine alkaloids.

4.1. *meso*-Chimonanthine

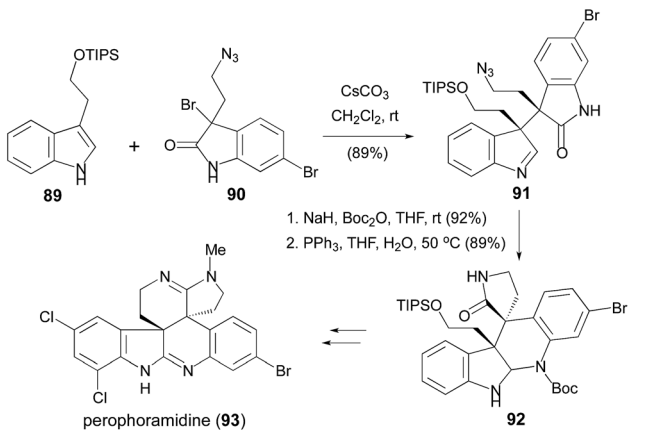
In 1996, Overman *et al.* reported the stereoselective total synthesis of *meso*-chimonanthine for the first time.[75] In 2000, the same group reported the asymmetric total synthesis of (+)-chimonanthine (**88** in Scheme 14).[76] The key step is the asymmetric construction of intermediate **86** using ((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(trifluoromethanesulfonate) as a chiral dielectrophile to effect the dialkylation of **84**. Thus, after several routine synthetic transformations, the asymmetric total synthesis of (+)-chimonanthine was achieved. In addition, using a similar diastereoselective dialkylation strategy, the same group achieved the asymmetric total synthesis of (−)-idiospermuline, ditryptophenaline, and *ent*-WIN 64821.[77–79]

4.2. Perophoramidine and dehaloperophoramidine

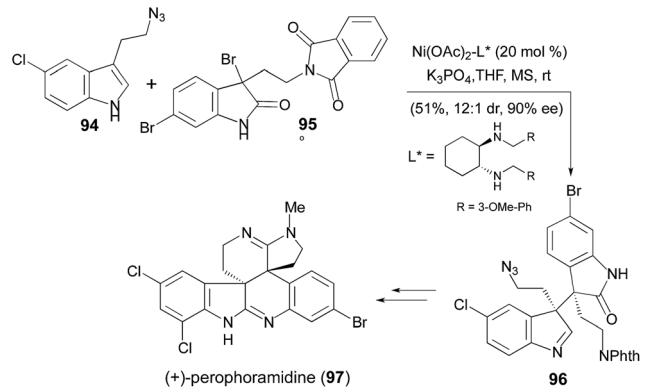
In 2004, Fuchs and Funk reported the first total synthesis of (±)-perophoramidine[80] (Scheme 15).



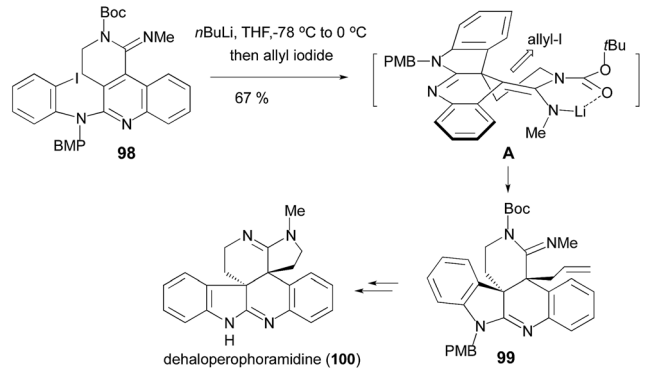
Scheme 14 Total synthesis of (+)-chimonanthine (**88**).



Scheme 15 Total synthesis of perophoramidine.



Scheme 16 Total synthesis of (+)-perophoramidine.



Scheme 17 Total synthesis of dehaloperophoramidine.

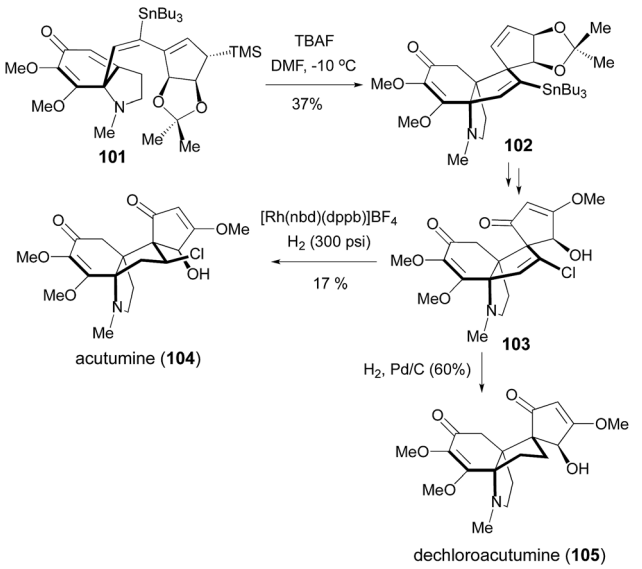
The key step is coupling indole **89** and 3-bromoindolin-2-one **90** in the presence of Cs_2CO_3 to stereoselectively generate product **91** with two vicinal all-carbon quaternary centers (89% yield). **91** is converted to the corresponding *tert*-butyloxycarbonyl (BOC)-imide derivative, which undergoes a cascade reaction sequence upon reduction of the azido group involving transamidation and closure of the resulting carbamate on the indolenine to give aminal **92**. The racemic perophoramidine (**93**) is synthesized by a series of routine synthetic transformations.

The asymmetric total synthesis of (+)-perophoramidine (**97**) was reported by Wang and co-workers in 2013 (Scheme 16).[25] The key step is nickel-catalyzed coupling of substituted indole **96** with the *in situ*-generated indol-2-one (**95**) in the presence of a chiral diamine ligand to produce **96** (51% yield) with excellent enantioselectivity.

In 2013, Takemoto and co-workers reported the total synthesis of dehaloperophoramidine (**100** in Scheme 17) through a tandem dearomatizing arylation allylation sequence,[81] which comprises lithium–iodine exchange, nucleophilic addition, and allylation, producing pentacyclic bisamidine **99** with vicinal all-carbon quaternary centers in one step.

4.3. (−)-Acutumine and (−)-dechloroacutumine

(−)-Acutumine (**104** in Scheme 18) and (−)-dechloroacutumine (**105** in Scheme 18) are spirocyclopentenone-based tetracyclic alkaloids isolated from the roots of *Sinomenium acutum* and



Scheme 18 Total synthesis of (−)-acutumine and (−)-dechloroacutumine.

Menispermum dauricum, respectively. The former inhibits human T-cell proliferation and improves recognition in the Wistar rat model.[82]

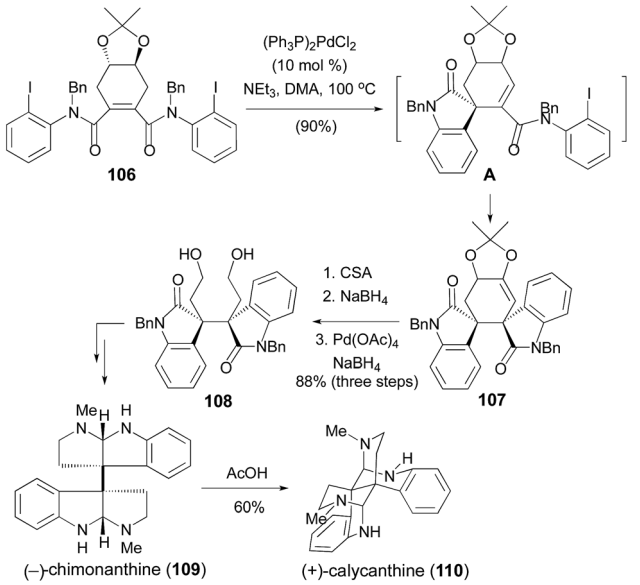
In 2013, Herzon and co-workers reported the total synthesis of (−)-acutumine and (−)-dechloroacutumine (Scheme 18).[83] Notable features of the syntheses include the strategic application of 5-trimethylsilyl-cyclopentadiene as a stabilization and stereocontrol element to induce regio- and stereoselective Hosomi–Sakurai cyclization of **101** to form the two contiguous quaternary centers in key intermediate **102**. Through a couple of critical transformations, **102** was converted to enone **103**. Homogeneous hydrogenation of **103** produced (−)-acutumine (**104**) in 17% yield, and heterogeneous hydrogenation of **103** led to (−)-dechloroacutumine (**105**) in 60% yield.

5. Transition-metal-catalyzed reactions

The development of transition-metal-catalyzed reactions that enable rapid production of complex molecules with multiple stereogenic centers is a principal goal of asymmetric catalysis and green chemistry. These processes become more useful and challenging if the target molecules contain two vicinal all-carbon quaternary stereogenic centers. In the past two decades, transition-metal-catalyzed asymmetric reactions have emerged for the stereoselective construction of vicinal all-carbon quaternary stereogenic centers.[26–28] The following section highlights the progress that has been made in this field by the application of this type of reaction to the total synthesis of complex natural products.

5.1. Cyclotryptamine alkaloids

After the synthesis of *meso*-chimonanthine (**88** in Scheme 14) by SmI_2-mediated reductive dialkylation in 1996,[75] Overman *et al.*



Scheme 19 Asymmetric total synthesis of (–)-chimonanthine and (+)-calycanthine.

used Pd-catalyzed double Heck cyclization as the key step to achieve the stereo- and enantio-controlled total synthesis of *meso*- and (–)-chimonanthine, and (+)-calycanthine (Scheme 19).[84] This catalytic reaction provides a new strategy for the enantioselective synthesis of polypyrroloindoline alkaloids bearing two contiguous all-carbon quaternary stereocenters. As shown in Scheme 19, substituted phenyl iodide **106** was subjected to typical double Heck cyclization to produce the desired annulated product **107** in 90% yield *via* intermediate **A**. Using their previously developed chemistry, **107** was first converted to diol **108**, and then to (–)-chimonanthine (**109**). By treating **109** with acetic acid, (+)-calycanthine (**110**) was produced in 60% yield.

In 2013, Trost and Osipov demonstrated Pd-catalyzed decarboxylative asymmetric allylic alkylation by constructing vicinal all-carbon quaternary centers in cyclotryptamine alkaloids (Scheme 20).[26c] In the synthesis, dienol dicarbonate **111** undergoes an annulation reaction in the presence of $[Pd_2(dba)_3 \cdot CHCl_3]$, chiral ligand L1, and $(n\text{-hex})_4NBr$ to give bisoxindole **113** in 96% yield in a diastereo- and enantioselective manner. Subsequent steps then convert **113** to dialdehyde **114** or diol **115**, and ultimately (–)-folicanthine, (–)-chimonanthine, (+)-calycanthine, (–)-ditryptophenaline, and (–)-WIN 64821.

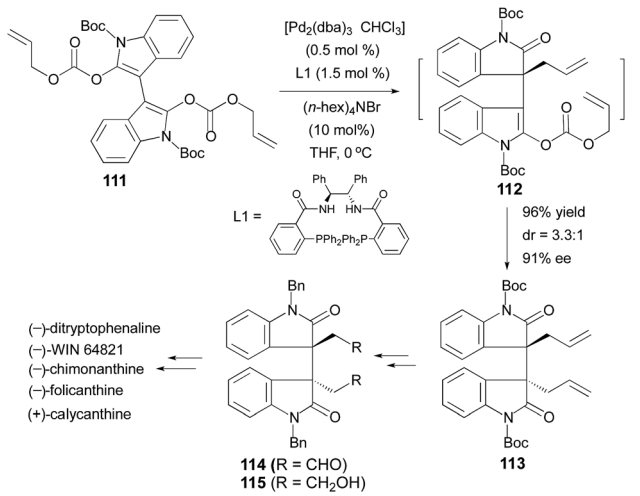
An important difference between these newly developed Pd-catalyzed annulation reactions and the direct allylation of lithium enolates is that under Pd catalysis, these annulation reactions proceeded under neutral conditions. This largely prevents the common side reactions associated with the basic conditions of direct allylation as described in Schemes 14 and 17. The much milder reaction conditions, as well as the much broader substrate scope, also represent the advantages of the Pd-catalyzed annulation reaction over direct allylation. Thus, the newly developed Pd-catalyzed annulation reactions not only allow the desired bisoxindoles to be made stereoselectively in high yields, but also provide opportunities to design novel synthetic strategies for total synthesis of cyclotryptamine alkaloids.

5.2. (–)-Sordarin

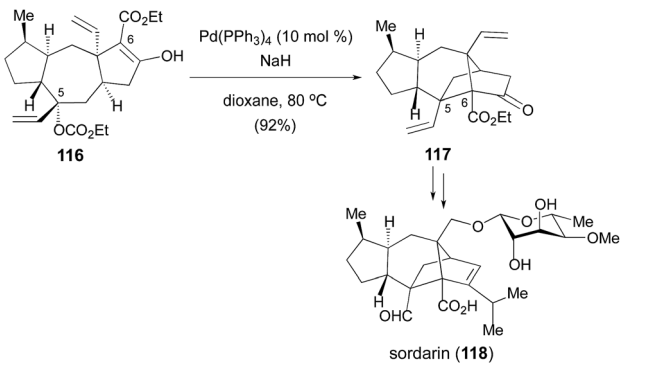
Sordarin (**118** in Scheme 21) is a fungus metabolite first isolated from *Sordaria araneosa* in 1971.[85] It exhibits a selective inhibitory effect on fungal protein synthesis. The molecule contains a diterpene core with three contiguous quaternary carbon centers. In 2006, Narasaka and co-workers reported the total synthesis of (–)-sordarin.[86] The key step is the intramolecular Pd(0)-catalyzed Tsuji–Trost allylation of substrate **116**. Treatment of substrate **116** with $Pd(PPh_3)_4$ in the presence of NaH produces the highly strained bicyclo[2.2.1]-heptan-2-one **117** bearing two vicinal quaternary chiral centers in 92% yield. Subsequent steps produce the natural product (–)-sordarin (**118**).

5.3. (–)-Lingzhiol

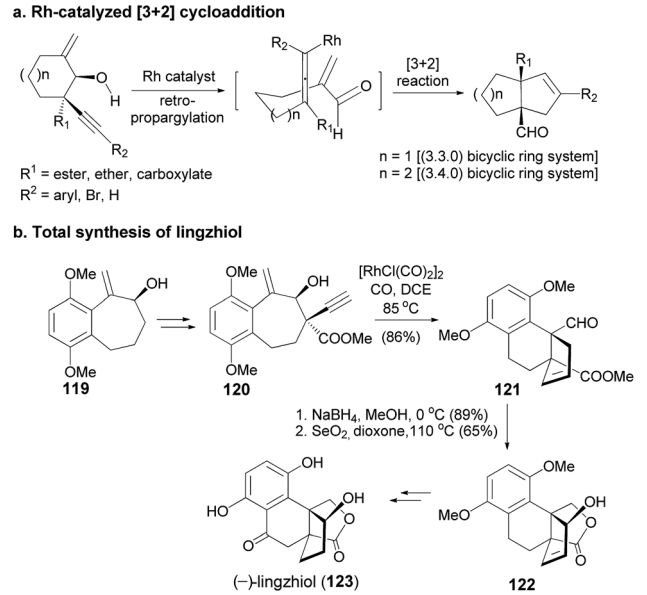
(–)-Lingzhiol (**123** in Scheme 22) is isolated from *Ganoderma lucidum*, a type of mushroom used in Asia as a very effective



Scheme 20 Formal synthesis of cyclotryptamine alkaloids.



Scheme 21 Total synthesis of (–)-sordarin.



Scheme 22 Total synthesis of (−)-lingzhiol.

medicine.[87] It has potent and selective inhibitory activity against the phosphorylation of Smad3 in TGF-β1-induced rat renal proximal tubular cells and activates Nrf2/Keap1 in mesangial cells under diabetic conditions. The molecule contains two vicinal all-carbon quaternary centers.

Very recently, our group disclosed the first asymmetric total synthesis of lingzhiol.[88] The key step in this total synthesis is a novel Rh-catalyzed [3 + 2] cycloaddition between an *in situ*-formed enal and an alleno rhodium species, which was generated *in situ* from the corresponding enynol *via* a retro metal-propargylation reaction (Scheme 22a), to form [3.3.0] and [4.3.0] bicyclic ring systems containing two *syn*-configured vicinal all-carbon quaternary centers at the bridgehead carbons (Scheme 22a). In the total synthesis, enynol **120** (derived from **119**) was treated with $[RhCl(CO)_2]_2$ under an atmosphere of CO (balloon) to give product **121** in 86% yield in a highly diastereoselective manner. Reductive lactonization and allylic oxidation produced alcohol **122** and then oxidation and deprotection gave (−)-lingzhiol (**123**) (Scheme 22b).

The developed novel type of Rh-catalyzed [3 + 2] cycloaddition between an *situ*-formed enal and an alleno rhodium species represents a general synthetic pathway for the stereoselective construction of structural motifs containing [3.3.0] and [4.3.0] bicyclic ring systems with two *syn*-configured vicinal all-carbon quaternary centers at the bridgehead carbons, and may find application to the total synthesis of complex natural products bearing this type of scaffold.

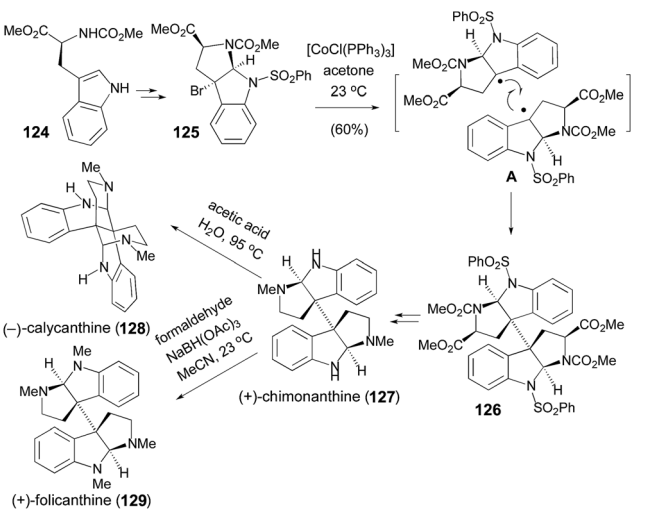
6. Radical reactions

Radicals have a strong tendency to form chemical bonds. However, selective bond formation from radical intermediates is less developed compared with ionic intermediates.[89] Because single electron transfer processes are common in chemical transformations, direct coupling of two radicals is a powerful approach to form bonds, and has wide applications in the total synthesis of complex molecules, particularly for biologically active natural products. Usually, selective radical couplings obey the persistent radical effect: only radical coupling between a persistent radical and a transient radical leads to selective bond formation.[90] However, owing to the sterically favorable effect of the radical-based coupling reaction, this type of reaction might be particularly suitable for the formation of vicinal quaternary all-carbon centers. The following examples represent the successful application of radical coupling reactions in the total synthesis of natural products.

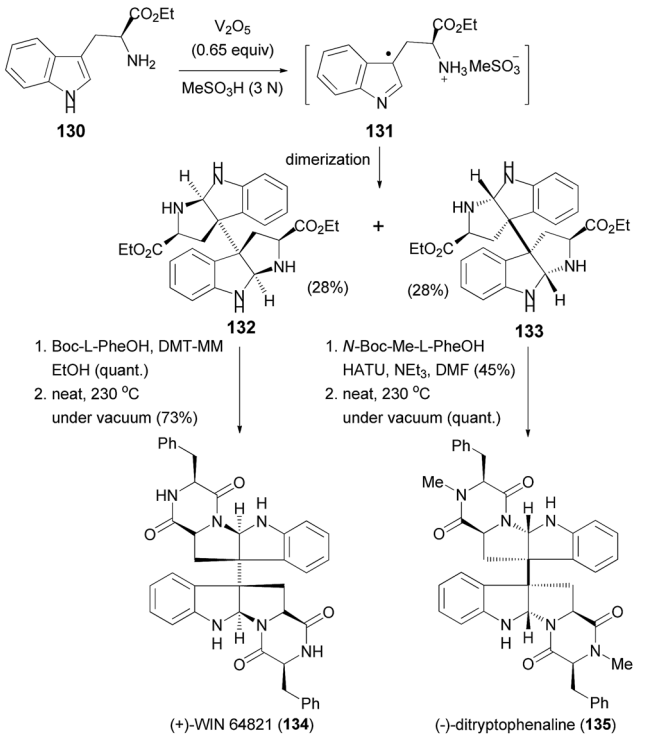
6.1. Cyclotryptamine alkaloids

In 2007, Movassaghi and Schmidt described the total synthesis of (+)-chimonanthine (**127**), (−)-calycanthine (**128**), and (+)-folicanthine (**129** in Scheme 23).[91] The key step in the total synthesis is Co^{I}-promoted reductive dimerization of chiral bromide **125** to asymmetrically produce **126** with the desired vicinal quaternary all-carbon stereocenters. In the total synthesis, bromide **125** was reduced with $CoCl(PPh_3)_3$ in acetone to generate radical species A (Scheme 23), which then underwent dimerization to give product **126** in 60% yield with 99% ee. (+)-Chimonanthine (**127**) was obtained through sequential routine transformations. Following further treatment under the conditions listed in Scheme 19, (−)-calycanthine (**128**) and (+)-folicanthine (**129**) were produced.

The classical approach to access the chimonanthine core structure mostly relies on the oxidative dimerization strategy which was inspired by the biosynthetic hypothesis. This reaction has suffered from harsh reaction conditions, low yields and poor diastereoselectivities. The emergence of the Co^{I}-promoted reductive dimerization of optically active substrates has enabled the enantio- and diastereoselective synthesis of vicinal quaternary stereocenters with high efficiency, which provides a new entry to dimeric diketopiperazine alkaloids.



Scheme 23 Total synthesis of (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine.



Scheme 24 Total syntheses of (−)-ditryptophenaline and (+)-WIN 64821.

By applying the same reductive coupling reaction, Movassaghi and co-workers also performed a series of complex natural product total syntheses to produce, for example, (+)-WIN 64821 (**1**) and (+)-chaetocin A, (−)-ditryptophenaline, (+)-chaetocin A, (+)-11,11′-dideoxyverticillin A, (+)-12,12′-dideoxychetracin, and (+)-chaetocin C and A.[92]

This powerful reductive dimerization reaction has also been used by several groups for the total synthesis of complex natural products, such as the synthesis of (+)-chaetocin A by Sodeoka and co-workers,[93] the synthesis of (+)-WIN 64821, (+)-WIN 64745, and (+)-asperdimin by de Lera and co-workers,[94] and the synthesis of (−)-chimonanthine by Ma and co-workers.[95]

Early synthesis of simple cyclotryptamine alkaloids mainly relied on the oxidative dimerization of indole[96] or oxindole derivatives,[97] usually leading to the formation of racemic C_2-symmetric products. Ishikawa and co-workers used oxidative dimerization of biradicals to form two vicinal quaternary carbon centers in cyclotryptamine alkaloids, and applied the methodology to the total synthesis of (+)-WIN 64821 (**134**) and (−)-ditryptophenaline (**135**) from a tryptophan ester (**130** in Scheme 24) in three steps.[98]

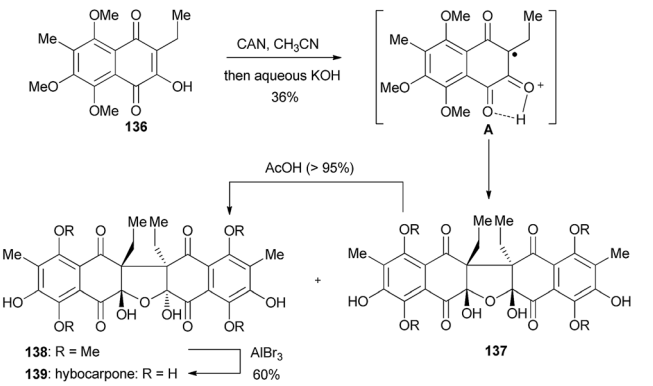
In this synthesis, tryptophan ester **130** was subjected to oxidation by V_2O_5 in aqueous $MeSO_3H$ solution to produce the C_2-symmetric products **132** and **133** in 28% and 28% yields, respectively. Product **132** was condensed with *N*-Boc-phenylalanine in the presence of DMT-MM (Kunishima's reagent)[99] followed by thermal amide bond formation to give product (+)-WIN 64821 (**134**) in 73% yield. Condensation of amino ester **133** with *N*-Boc-methylphenylalanine in the presence of HATU followed by thermal amide bond formation produced the diketopiperazine ring of (−)-ditryptophenaline in 45% yield.

The assembly of the cyclotryptamine alkaloids utilizing the biomimetic oxidative dimerization strategy represents an efficient and attractive approach toward the synthesis of a wide variety of cyclotryptamine alkaloids, and their intriguing structures continue to inspire efforts toward the development of new synthetic strategies based on biosynthetic considerations.

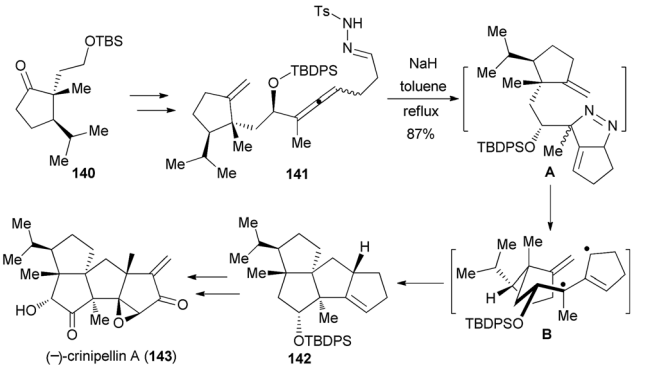
6.2. (±)-Hybocarpone

Hybocarpone (**139** in Scheme 25) is a novel naphthazarin containing two vicinal all-carbon quaternary stereocenters on the furan ring. The molecule is isolated from *Lecanora hybocarpa* and has potent cytotoxicity towards the growth of the P815 cell line with $IC_{50} = 0.15$ mg mL^{-1}.[100]

Nicolaou and Gray reported the total synthesis of hybocarpone using radical dimerization as the key step to incorporate the two hindered vicinal quaternary carbon centers.[101] Quinone **136** was treated with CAN in an aqueous KOH solution to initiate a single electron transfer reaction, and the generated active cation radical intermediate **A** then underwent dimerization to give products **137** and **138** in 36% yield with a ratio of **137** to **138** of 3 : 2. Under acidic conditions, **137** was converted to its corresponding more thermodynamically stable isomer **138** in 95% yield. After removal of the methyl group of **138** with $AlBr_3$, natural product hybocarpone (**139**) was obtained in 60% yield.



Scheme 25 Total synthesis of hybocarpone.



Scheme 26 Total synthesis of (−)-crinipellin A.

The strategy based on the dimerization–hydration cascade reaction in the total synthesis of hybocarpone bears resemblance to its biosynthetic origins, and such a synthetic design may find application in the total synthesis of other natural products which have a similar structural features.

6.3. (−)-Crinipellin A

Crinipellin A (**143** in Scheme 26) contains a unique tetraquinone skeleton with three contiguous all-carbon quaternary stereogenic centers, and it was first isolated from the fungus *Crinipellis stipitaria* in 1985.[102]

In 2014, Lee and co-workers reported the first total synthesis of (−)-crinipellin A.[103] The key step is tandem cycloaddition of allene **141** to stereoselectively synthesize the tetracyclic core of crinipellin A *via* a trimethylenemethane (TMM) diyl intermediate. Allene **141** was treated with NaH by refluxing in toluene to produce annulated product **A** in 87% yield. After a series of routine synthetic transformations, the total synthesis of (−)-crinipellin A (**143**) was asymmetrically achieved.

This powerful transformation enables the diastereoselective formation of three rings with three contiguous all-carbon quaternary stereogenic centers in a single step operation and offers new bond disconnections for the total synthesis of various polyquinane natural products. Since the stereochemistry of the generated tetraquinanes is highly dependent on the substrate chirality, a more general strategy for the synthesis of contiguous stereocenters in a congested tetraquinane skeleton is desirable.

7. Cyclopropanations

Although the three-membered ring is highly strained, many cyclopropanation reactions have been developed.[104] The classical Simmons–Smith reaction[105] has been used to synthesize cyclopropane containing vicinal quaternary stereocenters from tetra-substituted alkenes. The transition-metal-catalyzed decomposition of diazo compounds[106] occupies an important and unique position in the synthesis of highly functionalized cyclopropane, especially in the enantiomeric catalytic construction of such a skeleton.[107] In addition, transition-metal-catalyzed enyne cycloisomerization has been further developed in recent years,[108] and even applied to the total synthesis of cyclopropane-containing natural products.[109] The following examples highlight cyclopropanation reactions in the total synthesis of complex natural products.

7.1. (+)-Salvileucalin B

Salvileucalin B (**148** in Scheme 27) is a diterpenoid obtained from the aerial parts of *Salvia leucantha*, and it exhibits cytotoxic activities against human lung and colon adenocarcinoma cells (A549 and HT-29).[110]

In 2011, Reisman and co-workers reported the first asymmetric synthesis of (+)-salvileucalin B.[111]

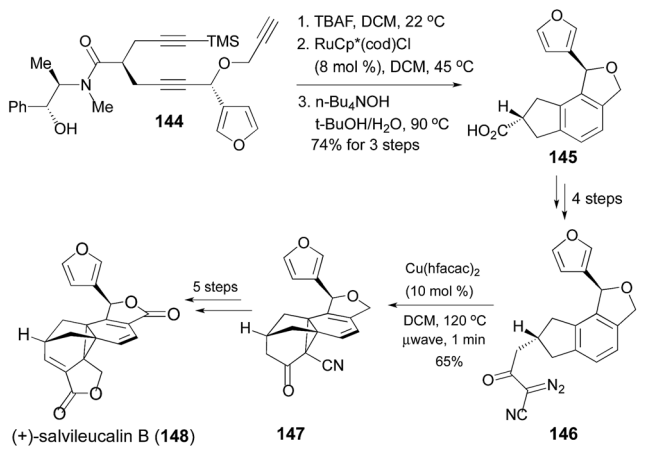
The key step is an intramolecular copper-catalyzed arene cyclopropanation (Buchner reaction)[112] to produce the fully substituted cyclopropane. The benzenoid ring was constructed by Ru-catalyzed cycloisomerization after desilylation of **144**. Under basic conditions, the amide moiety was hydrolyzed to its corresponding acid **145** in 74% yield in three steps. After addition of the diazo side chain, substrate **146** was subjected to microwave irradiation in the presence of $Cu(hfacac)_2$ to initiate the arene cyclopropanation reaction, giving cyclopropane **147** in 65% yield. Late-stage transformations produced (+)-salvileucalin B (**148**) in a total of 18 steps.

As highlighted in this total synthesis, the intramolecular Buchner reaction represents a general strategy with efficiency and brevity for the preparation of polycyclic targets, and has proven to be a useful transformation in the context of natural product total synthesis.

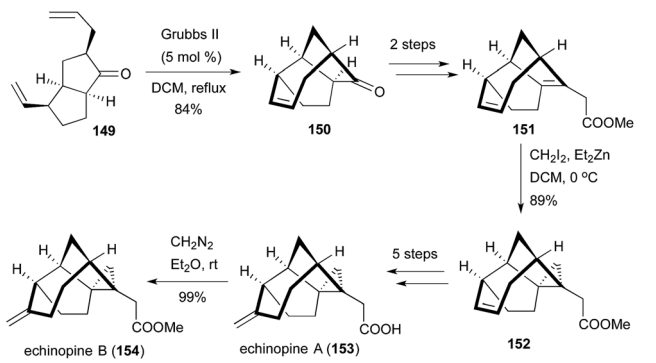
7.2. Echinopine A and B

Echinopine A and B (**153** and **154** in Scheme 28) are sesquiterpenes isolated from the root of the plant *Echinops spinosus*.[113] Despite the lack of reported biological activity, their novel structure has inspired several research groups to embark upon and complete syntheses of these compounds,[114–116] involving different strategies for the formation of the cyclopropane ring.

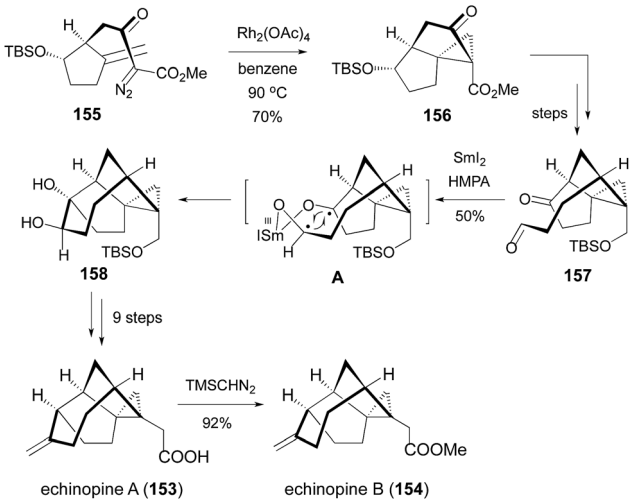
In 2009, Magauer *et al.* reported the first total syntheses of echinopines A and B and determined their absolute stereochemistries.[114]



Scheme 27 Total synthesis of (+)-salvileucalin B.



Scheme 28 Total synthesis of echinopines A and B.

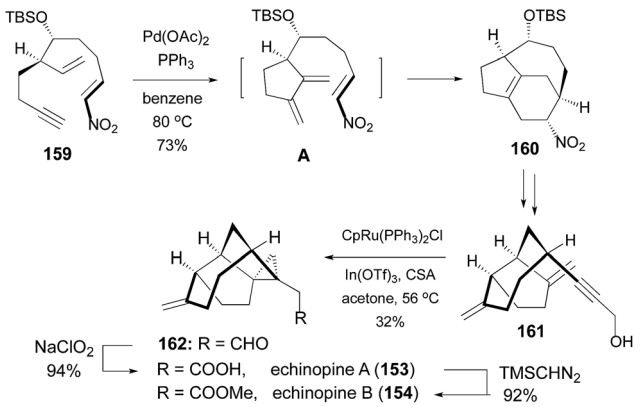


Scheme 29 Total synthesis of echinopines A and B.

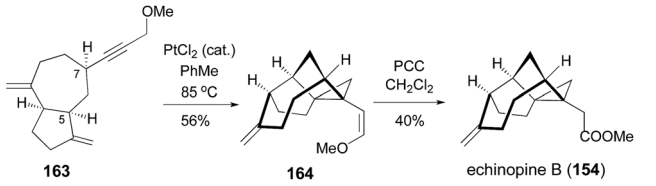
The highly strained seven-membered ring was formed by a ring-closing metathesis strategy, providing alkene **150** in 84% yield. Compound **151** was obtained by regioselective cyclopropanation of ester **150** using modified Furukawa–Simmons–Smith's reagent.[117] Alternatively, the three-membered ring can be constructed by Corey–Chaykovsky cyclopropanation[118] of the corresponding α,β-unsaturated methyl ester. Several subsequent transformation steps produce the natural product echinopine A (**153**), and further treatment with diazomethane gives echinopine B (**154**).

In 2010, Nicolaou *et al.* reported the total synthesis of echinopines A and B (**153** and **154** in Scheme 29).[115a] In the total synthesis, an intramolecular rhodium-catalyzed cyclopropanation was used to form the three-membered ring containing two vicinal quaternary centers. Product **156** was obtained in 70% yield. Several subsequent transformation steps produced aldehyde **157**. Then, SmI_2-mediated ring closure generated the cycloheptane ring, giving diol **158** in 50% yield. Subsequent late-stage transformations produced echinopine A (**153**), and further treatment with $TMSCHN_2$ gave echinopine B (**154**).

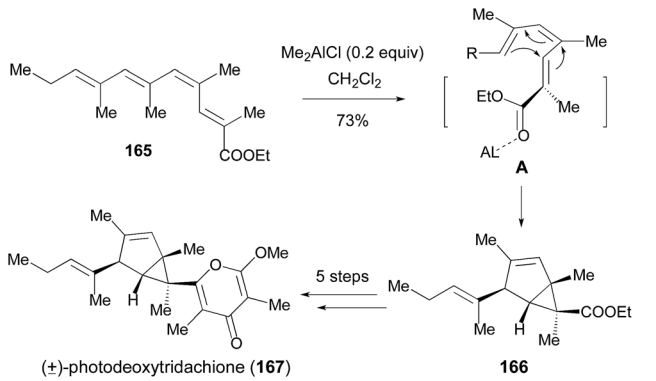
In 2011, Chen and co-workers reported another total synthesis of (±)-echinopines A and B (**153** and **154** in Scheme 30).[115c]



Scheme 30 Total synthesis of echinopines A and B.



Scheme 31 Total synthesis of echinopine B.



Scheme 32 Total synthesis of photodeoxytridachione.

The key reaction is an intramolecular Ru-catalyzed ene–yne cycloisomerization/cyclopropanation. Tricylic **160** was obtained in 73% yield by a Pd-catalyzed cycloisomerization reaction of enyne **159**, which was followed by the intramolecular Diels–Alder reaction of the *in situ*-formed diene **A**.[115b] Several subsequent transformation steps led to Ru-catalyzed precursor **161**. The use of the two-metal catalyst system reported by Trost *et al.*[108c] produced aldehyde **162** in 32% yield. Further oxidation provided echinopine A (**153**) in 94% yield, and its conversion to echinopine B (**154**) was completed by treatment with $TMSCHN_2$.

In 2012, Vanderwal and co-workers reported the concise total synthesis of echinopine B (**154** in Scheme 31).[116] The key step is stereoselective Pt^{II}-catalyzed cycloisomerization[108b] of enyne **163** in a complex setting to generate core structure **164** of echinopine B in 56% yield. After pyridinium chlorochromate oxidation of **164**, echinopine B (**154**) was obtained in 40% yield.

The studies highlighted above capture only some of the most impressive achievements associated with the application of the transition metal-catalyzed cyclopropanations to the synthesis of complex natural products. As our overall understanding of these reaction mechanisms improves, our ability to discover and achieve new creative disconnections for target molecules will be dramatically enhanced.

7.3. Photodeoxytridachione

Photodeoxytridachione (**167** in Scheme 32) was first isolated from the Pacific mollusk *Plakobranchus ocellatus*.[119] It contains a bicyclo[3.1.0]hexene core with two vicinal all-carbon quaternary stereocenters on the three-membered ring. It exhibits activity in an ichthyotoxicity assay at 5 ppm.

In 2003, Trauner and co-workers reported the total synthesis of (±)-photodeoxytridachione by Lewis-acid-catalyzed cycloisomerization.[120] Tetraene **165** was treated with Me_2AlCl, and the bicyclo[3.1.0]hexane system was successfully constructed, giving product **166** in 73% yield as a single diastereoisomer. This process may be a concerted $[_\pi4_a + _\pi2_a]$ cycloaddition *via* the intermediate A. However, the stepwise manner cannot be fully excluded. The addition of the α-methoxy-γ-pyrone moiety in five steps completed the total synthesis of (±)-photodeoxytridachione (**167**). A similar strategy has been used in the total synthesis of (−)-crispatene.[121]

8. Conclusions

The stereoselective formation of vicinal all-carbon quaternary stereocenters is an enduring challenge due to the increased steric nonbonded interactions between the carbon substituents and the difficult introduction of requisite diastereocontrol, and has spurred considerable interest among the chemical community. In this regard, a number of methods have been developed to directly synthesize vicinal all-carbon quaternary centers, including pericyclic reactions, alkylation reactions, photochemical reactions, radical reactions, and transition metal catalysed reactions, to name but a few. In addition, the Nazarov cyclization may emerge as a powerful reaction for the construction of vicinal all-carbon quaternary stereocenters, which may contribute to the total synthesis of complex natural products.[122] All this progress clearly shows that synthetic organic chemistry has now reached extraordinary levels of sophistication with regard to our capability to create vicinal all-carbon quaternary stereocenters in a single step.

Given the intriguing chemical structures and potential biological activities of natural products bearing vicinal all-carbon quaternary stereocenters, in combination with their scarcity in nature that limits their further biological investigation, the identification of fast and efficient synthetic methodologies and strategies for the synthesis of natural products bearing these stereocenters will represent one of the most stimulating and dynamic areas in organic synthesis, and the ability to selectively construct them is one benchmark by which the new synthetic methods are judged. We can predict that more efficient and concise synthetic methods and strategies adhering to the criteria of green chemistry and atom economy will emerge in the near future.

9. Notes and references

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