CHEMICAL REVIEWS

Review

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Cyclopropanation Strategies in Recent Total Syntheses

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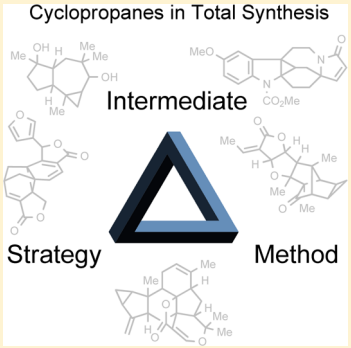
ABSTRACT: Complex molecular architectures containing cyclopropanes present significant challenges for any synthetic chemist. This review aims to highlight the strategic considerations for introduction of the cyclopropane motif in a collection of recent total syntheses. At first, an overview of the most important and widely used cyclopropanation techniques is presented, followed by a discussion of elegant approaches and clever solutions that have been developed to enable the synthesis of various unique cyclopropane natural products or use of cyclopropanes as versatile strategic intermediates.



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1. INTRODUCTION

Molecules incorporating cyclopropanes have always fascinated organic chemists.[1−3] Strain of approximately 27 kcal/mol associated with such rings leads to significant challenges for their construction and manipulation, resulting in certain tactical limitations.[4,5] Synthetic chemists developed remarkable strategies that exploit the spring-loaded cyclopropanes, employing them as key intermediates in routes to access challenging structures, such as medium-sized rings or densely functionalized molecules.[6−12] Since the discovery of (+)-*trans*-chrysanthemic acid by Staudinger and Ruzicka in 1924,[13] a wide variety of cyclopropane-containing secondary metabolites have been isolated from fungi, plants, marine organisms, and microorganisms.[14−16] Over the years, increasingly complex structures have been elucidated that impose tougher challenges in the development of strategies and methods. To enable synthetic access to these target molecules, chemical research has focused

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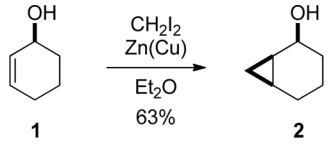
on the development of a broad toolbox for the efficient generation of cyclopropanes from a wide range of intermediates.[17−21] The endless possibilities in chemical space give rise to myriad settings in which cyclopropanes, as with any other functional group, can be embedded. Any practioner of synthesis appreciates that, in crafting synthetic routes to targets, context is everything. The aim of this review is to highlight the strategic considerations in a collection of selected recent total synthesis endeavors that have appeared in the last 15 years. These include, among others, (a) the stage of the synthesis at which a cyclopropane is introduced, an issue directly influenced by the stability of the cyclopropane and the feasibility of its introduction; (b) the methods of choice for the cyclopropanation; (c) the stereoselective synthesis of cyclopropanes and associated directing effects; and (d) the tactical implementation of cyclopropane intermediates in synthetic routes. The syntheses are grouped according to the methods employed for introduction of the cyclopropane. The review will first include an overview of the most important and widely used cyclopropanation techniques. The discussions of the routes that are highlighted are intended to showcase the elegant approaches and clever solutions that have been implemented to solve problems unique to each target.

2. CYCLOPROPANATION METHODS

2.1. Simmons−Smith Cyclopropanation

In 1958, H. E. Simmons and R. D. Smith at DuPont reported the formal cycloaddition of methylene and various olefins by treatment of diiodomethane with the zinc−copper couple Zn(Cu).[22,23] The synthetic utility of this method derives mainly from the wide scope of olefins that can be employed as substrates as well as the stereospecificity of the transformation,[24] so that the stereochemical information on the olefin is transferred to the product. Diastereocontrol is an important strategic feature in the planning of a synthesis, and in olefin cyclopropanation, it is largely governed by steric factors. Additionally, a strong directing effect may be observed when the substrate bears Lewis basic heteroatoms in proximity to the olefin.[25−29] A representative simple example is shown in Scheme 1, in which 2-cyclohexen-1-ol (**1**) is exposed to CH_2I_2 and Zn(Cu), providing **2** as a single diastereomer in 63% yield.

Scheme 1. Simmons−Smith Cyclopropanation of 2-Cyclohexen-1-ol (1)



The rather tedious preparation of the zinc−copper couple, along with reproducibility problems caused by variations in surface features of the alloy, have led to the development of other protocols for generation of the zinc carbenoid. In 1959, Wittig and Schwarzenbach[30] reported that exposure of diazomethane to zinc iodide in ether provided $IZnCH_2I$.[30−34] Furthermore, Furukawa et al.[35,36] developed a method that has been widely adopted for generation of the zinc carbenoid, in which diiodomethane is treated with $ZnEt_2$. The carbenoid species generated under Furukawa conditions displays high reactivity with electron-rich olefins such as styrenes, enol ethers, and enamines as well as for substrates containing Lewis basic directing groups. However, the cyclopropanation of unfunctionalized olefins employing this carbenoid can be challenging. As means of overcoming such limitations when they arise, several elegant methods have been reported. In 1991, Denmark and Edwards[37] showcased the superior cyclopropanation properties of a carbenoid generated from $ZnEt_2$ and $ClCH_2I$.

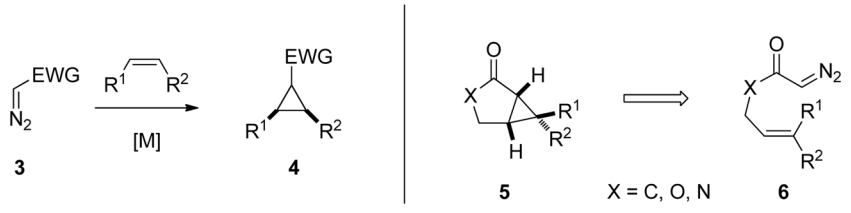
Shi and co-workers[38−40] have noted that the zinc carbenoid can be rendered more reactive by a ligand-exchange process. In their landmark study, 1 equiv of Brønsted acid, such as alcohol, amine, or carboxylic or sulfonic acid, was added to an equimolar amount of $ZnEt_2$, followed by 1 equiv of CH_2I_2. The electron-withdrawing effect of trifluoroacetate as a ligand on zinc is suggested to trigger a dramatic increase in the reaction rate. To date, the generated $(F_3CCO_2)ZnCH_2I$ carbenoid represents one of the most reactive reagents for cyclopropanation. Moreover, Charette and co-workers[41,42] reported phosphoric acid-derived zinc carbenoids also display enhanced reactivity.

2.2. Diazo-Derived Carbenoids

The discovery that metal salts catalyze the decomposition of diazo compounds dates back to 1906, when Silberrad and Roy[43] investigated the effect of copper dust on ethyl diazoacetate: "[...] When the diazoacetate is added to copper dust, no reaction appears to take place below 80 °C, but above that temperature the addition of the first drop of ester is accompanied by an explosion of sufficient violence to shatter the flask.[...]". Another milestone was reached in the 1960s, when catalytic homogeneous diazo decomposition was enabled by soluble copper complexes.[44,45] A decade later, Teyssie and co-workers[46−48] discovered that $Pd(OAc)_2$ and $Rh_2(OAc)_4$ are suitable alternatives to copper salts.

Several important aspects need to be taken into account when consideration is given to use of a diazo-derived carbenoid for a cyclopropanation reaction in the synthesis of complex molecules (Scheme 2). First, because alkyldiazo compounds lacking stabilizing groups are considered capricious, they are typically generated in situ.[49−54] Second, in cases of intermolecular cyclopropanation (such as **3** → **4**), slow addition of the diazo compound to a mixture of the olefin and a metal catalyst may be necessary in order to avoid carbene dimerization.[55] Third, chemoselective discrimination between

Scheme 2. Diazo-derived Carbenoids for Cyclopropanation of Olefins



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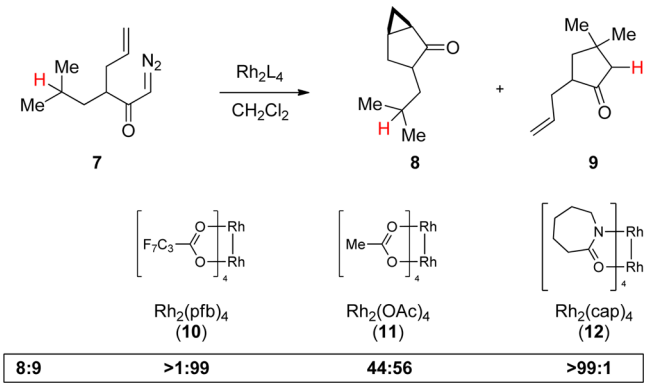
cyclopropanation and C−H insertion pathways can be an important issue. In this respect, elegant studies by Padwa and Doyle and co-workers[56] showcase that chemoselectivity can be significantly influenced by the nature of the catalyst employed. Even for diazoketone **7**, possessing both a γ,δ-olefin and a γ-methine C−H, complete selectivity can be achieved. As shown in Scheme 3, while $Rh_2(OAc)_4$ produces a 1:1 mixture of **8** and **9**, $Rh_2(pfb)_4$ furnishes solely the product of C−H insertion. In contrast, the use of $Rh_2(cap)_4$ produced only cyclopropane **8**.

Scheme 3. Chemoselectivity Study between C−H Insertion and Cyclopropanation[a]



[a]Padwa and Doyle and co-workers.[56]

The intramolecular variant of this transformation (cf. Scheme 2, **6** → **5**) has gained considerable popularity in natural product synthesis, as two rings can be stereoselectively generated in a single step and, depending on the olefin employed, highly substituted cyclopropanes can be accessed.[57−62]

2.3. Free Carbenes

As early as 1862, Geuther[63] discovered that chloroform undergoes decomposition in alkaline alcohol solutions. Almost 100 years later, Doering and Hoffmann[64] treated a mixture of cyclohexene and a solution of KO*t*-Bu in *t*-BuOH with chloroform and observed a vigorously exothermic reaction (Scheme 4). The product formed was identified as 7,7-dichlorobicyclo[4.1.0]heptane (**17**) and its formation was attributed to the generation of dichlorocarbene (**15**) via base-mediated α-elimination. Several years later, Cory and McLaren[65] showcased the enormous potential of this method during their total synthesis of ishwarane (**21**). Olefin **18** was treated with tetrabromomethane and an excess of methyllithium at −78 °C, mediating the formation of dibromocyclopropane **19**. Upon warming of the reaction mixture to −30 °C, lithium−halogen exchange and subsequent α-elimination occurred, generating cyclopropylcarbene **20**, which participated in a C−H insertion reaction to yield ishwarane (**21**).

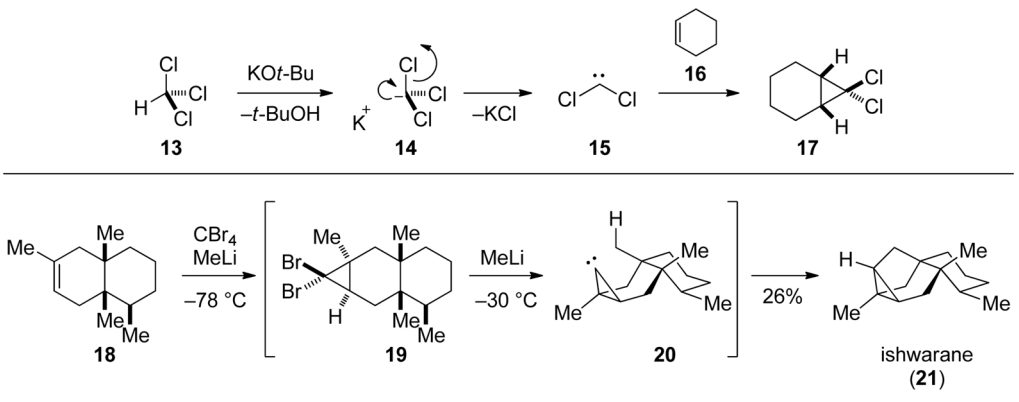
In 1967, Crandall and Lin[66] discovered that α-lithiated epoxides are prone to undergo elimination, leading to carbene formation. When epoxide **22** was exposed to *t*-BuLi, cyclopropanol **23** was isolated as a minor product in 9% yield (Scheme 5). Intriguingly, the anti isomer was the only observed product, a finding attributed to cycloaddition proceeding through the chairlike transition state **24**.[67,68]

During their investigation of the α-deprotonation of epoxides, Mioskowski and co-workers[69−71] discovered that epoxide **25** furnished cyclopropane **26** via carbene **27**, albeit in low yield. In the early 2000s, Hodgson became interested in optimizing this intriguing transformation in light of the fact that enantioenriched epoxides are widely available via Jacobsen hydrolytic kinetic resolution.[72−77] After a laborious screening, Hodgson et al.[72,73] found that high yields (60−84%) can be obtained by slow addition of LiTMP to a solution of the epoxide substrate at 0 °C, followed by warming to ambient temperature. This method provides the anti isomer of the product, a stereochemical outcome that is complementary to that observed in the Simmons−Smith cyclopropanation reaction, which otherwise leads to cis isomer **28** as a consequence of known directing effects in the reaction of allylic alcohols.

2.4. Cycloisomerization

In 1976, Ohloff and co-workers[78] reported a seminal observation in which propargylic acetate **29** was converted to **30** in 70% yield upon exposure to $ZnCl_2$ (Scheme 6).[78,79] Intriguingly, cyclopropane **31** was formed as a side product in minor amounts (5%). Some years later, Rautenstrauch[80] described a novel approach for the synthesis of cyclopentenones, a transformation referred to as the Rautenstrauch rearrangement. When enyne **32** was exposed to a Pd(II) catalyst, cyclopentenone **33** was isolated in 50−61% yield. Rautenstrauch proposed a mechanism in which the alkyne undergoes acetoxy palladation to give intermediate **34**. Subsequent displacement of the acetoxonium by the vinylpalladium species furnishes a putative palladacycle (**35**) that is

Scheme 4. Formation of Dichlorocarbene and Total Synthesis of Ishwarane[a]



[a]Cory and McLaren.[65]

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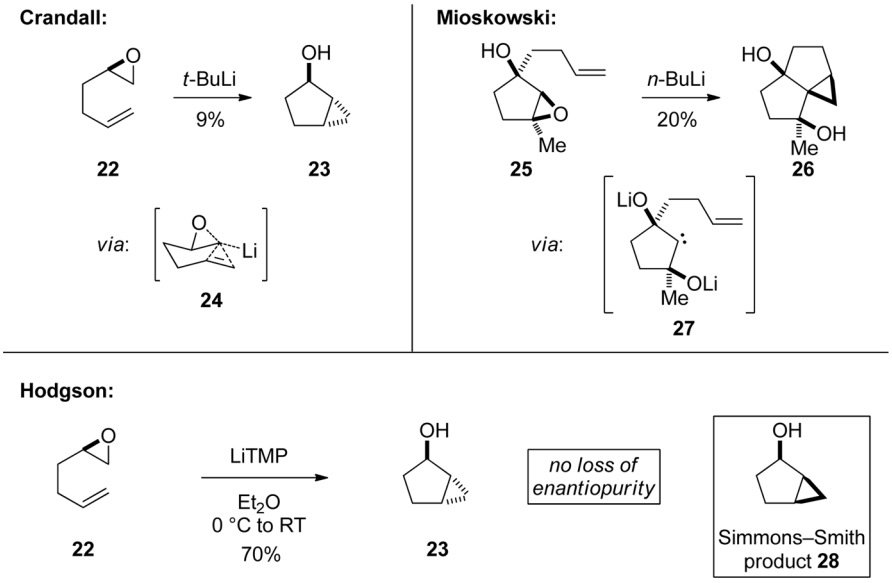
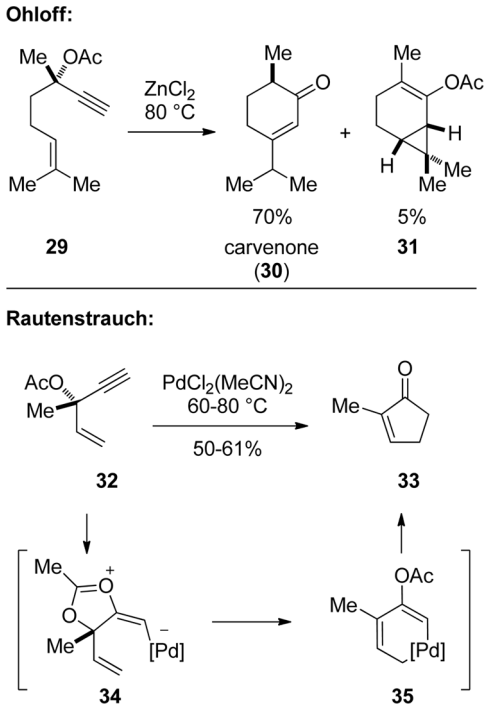
Scheme 5. α-Lithiation and Elimination of Epoxides



Scheme 6. Cycloisomerization of Propargylic Acetates[a]



[a]Ohloff and co-workers[78] and Rautenstrauch.[80]

suggested to undergo reductive elimination and hydrolyze to form **33**.

A pivotal discovery was made by Fensterbank and Malacria and co-workers[81,82] when dienyne **36** was exposed to $PtCl_2$ at elevated temperatures (Scheme 7). The free alcohol substrate as well as the corresponding methyl and silyl ethers provided **38**, while the acetate derivatives gave **37**. The authors suggested that, in the absence of an acetate, zwitterion **41** cyclizes to cyclopropane **42**. The generated intermediate platinum carbene then participates in a second intramolecular cyclopropanation reaction to yield **38**. For the acetylated substrate, an acetoxonium organoplatinum intermediate is formed (**39**), analogous to **34**, which leads to a metallocarbene that subsequently is engaged in an intramolecular cyclopropanation to afford **37**. Building on these discoveries, Toste and co-workers[83,84] reported a remarkable gold(I)-catalyzed Rautenstrauch rearrangement, generating cyclopentenones from propargylic pivalates in high yields. Additionally, Fürstner and co-workers[85] reported a versatile gold- and platinum-catalyzed method for the synthesis of cyclopropane-substituted cyclopentanones from propargylic acetates.

A conceptually different cycloisomerization was reported by Trauner and Miller and co-workers in 2003,[86−88] inspired by biosynthetic considerations (Scheme 8). The focus of the studies by Trauner was the synthesis of polyketides featuring a bicyclo[3.1.0]hexane core, such as photodeoxytridachione (**43**), tridachiapyrone (**44**), and crispatene (**45**). In order to establish efficient entry into this natural product class, a novel Lewis acid-catalyzed cyclization reaction of hexatrienes was developed. Trauner and Miller discovered that catalytic amounts of Me_2AlCl mediated a $[{}_{\pi}4_a + {}_{\pi}2_a]$ cycloaddition to give cyclopropane **47** in 73% yield.

2.5. Kulinkovich Reaction

In 1989, Kulinkovich et al.[89] reported one of the most intriguing reaction in modern organotitanium chemistry. Treatment of aliphatic esters with ethylmagnesium bromide in the presence of $Ti(OiPr)_4$ generated 1-alkylcyclopropanols such as **49** (Scheme 9).[89−91] The mechanism of this unusual cyclopropanation has been intensively investigated using deuterium labeling studies by Kulinkovich and co-workers[92] and computationally by Wu and Yu,[93] leading to the conclusion that the reaction proceeds through a titanacyclopropane, or Ti(II)-olefin, intermediate.[94] Importantly, Kulinkovich et al.[95] could demonstrate that exchange of ethylene with substituted olefins was possible, thus enabling the generation of more substituted cyclopropanols (cf. **48** → **50**).

Two modifications have been developed, by Chaplinski and de Meijere[96] and Bertus and Szymoniak,[97] in which amides and nitriles serve as starting materials, culminating in the generation of aminocyclopropanes (Scheme 10).

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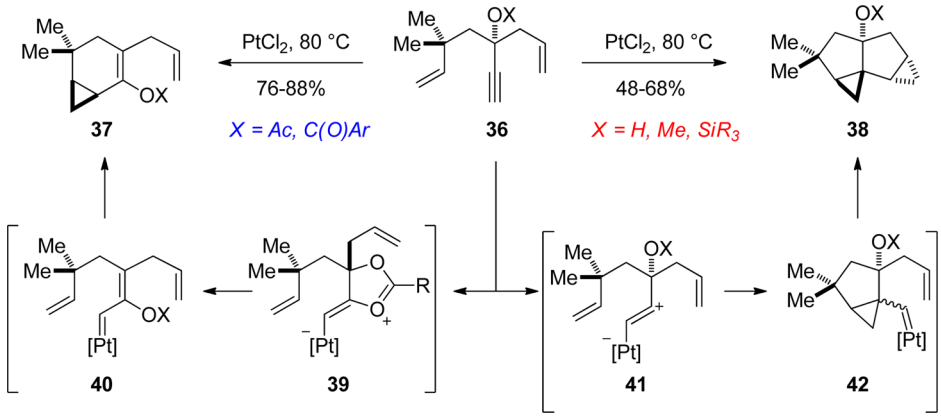
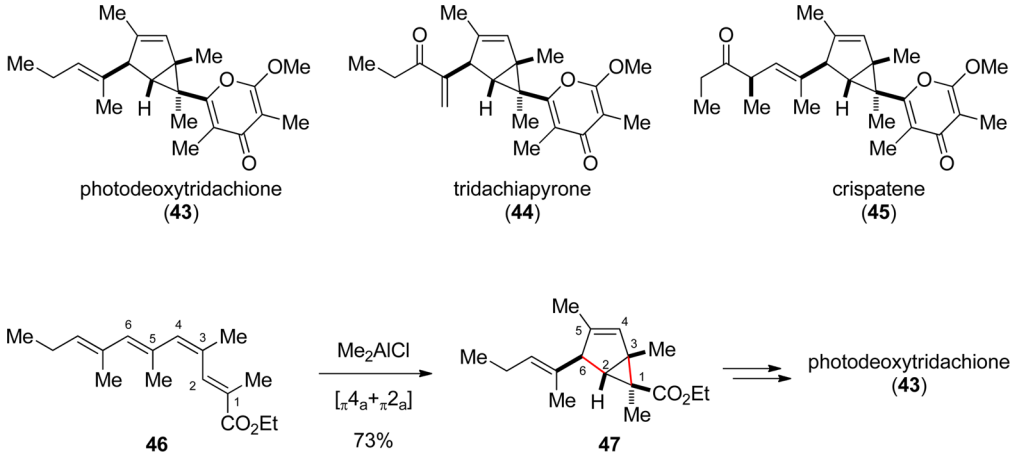
Scheme 7. Pt-catalyzed Cycloisomerization of Enynes and Effect of Oxygen Substitution

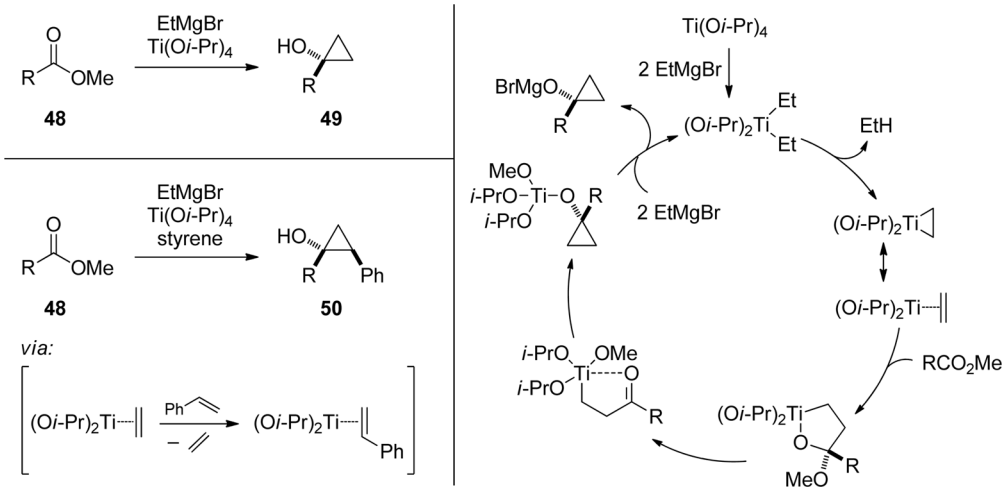


Scheme 8. Polypropionate Natural Products and Lewis Acid-catalyzed Cycloisomerization[a]



[a]Trauner and Miller and co-workers.[86−88]

Scheme 9. Kulinkovich Reaction



2.6. Nucleophilic Displacement Reactions

In 1884, W. H. Perkin[98] reported the cyclopropanation of diethyl malonate with 1,2-dibromoethylene in the presence of NaOEt (Scheme 11). In numerous studies, stabilized carbanions have been shown to undergo analogous double alkylation to furnish cyclopropanes.[99−101] Pirrung et al.[102] discovered that cyclopropanated γ-lactones are formed when malonates are treated with epichlorohydrin and base. A groundbreaking method was introduced by Corey and Chaykovsky,[103,104] who discovered that enones react with dimethylsulfoxonium methylide to form cyclopropanes, a process known as the Corey−Chaykovsky reaction.

A landmark in the synthesis of cyclopropane containing natural products was reported by Büchi et al. in 1966.[105]

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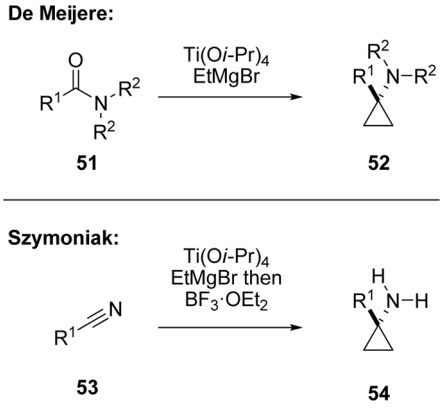
Scheme 10. Modifications of the Kulinkovich Reaction



During the total synthesis of aromadendrene, aldehyde **62** underwent addition of HBr and subsequent exposure of the crude bromide to KO*t*-Bu provided cyclopropane **63** in 41% overall yield.

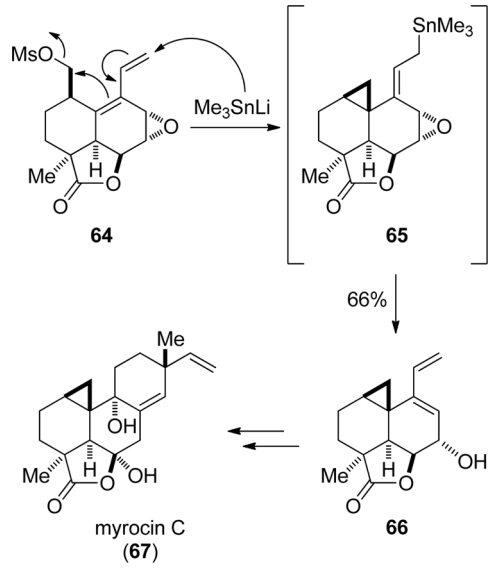
Another remarkable example of a nucleophilic displacement was employed by Chu-Moyer and Danishefsky and co-workers[106,107] during their total synthesis of the diterpene myrocin C (**67**, Scheme 12). When diene **64** was treated with (trimethylstannyl)lithium, cyclopropane **66** was isolated in 66% yield.

In 2009, Hardee and Lambert[108] reported a conceptually different approach for the generation of cyclopropane, relying on the Lewis acid-mediated nucleophilic attack of olefins onto epoxides. As shown in Scheme 13, treatment of epoxide **68** with 5 mol % La(OTf)$_3$ at 40 °C provided cyclopropane **69** in 72% yield. The mechanism as proposed by the authors describes initial attack of the olefin on the activated epoxide, followed by a semipinacol rearrangement to produce the cyclopropyl product. Notable advantages of this method are the high stereospecificity and broad substrate scope.

3. RECENT APPLICATIONS IN TOTAL SYNTHESIS

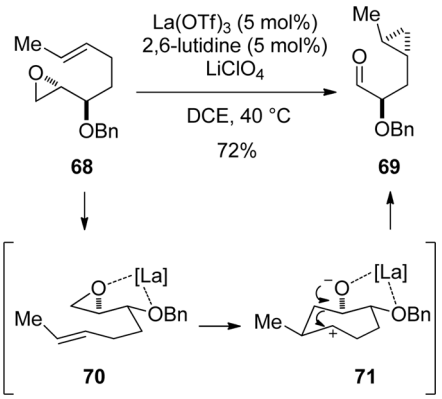
In this section, recent examples of total syntheses have been selected to illustrate contemporary solutions to problems involving cyclopropane synthesis. Collectively, they underscore the creative solutions that have been identified. The challenging structures presented by the natural products compel and inspire discovery and innovation.

Scheme 12. Nucleophilic Cyclopropanation[a] during Total Synthesis of Myrocin C



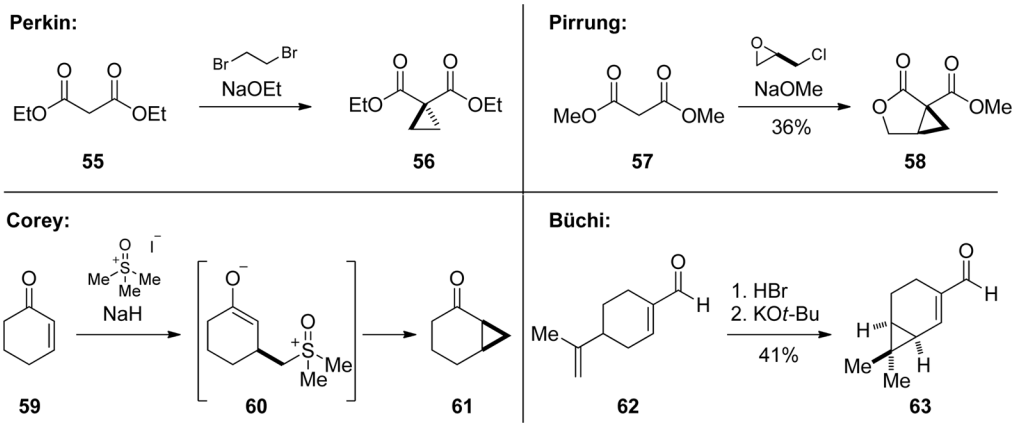
[a]Chu-Moyer and Danishefsky and co-workers.[106,107]

Scheme 13. La(OTf)$_3$-Catalyzed Cyclopropanation of Epoxyolefins[a]



[a]Hardee and Lambert.[108]

Scheme 11. Nucleophilic Cyclopropanations



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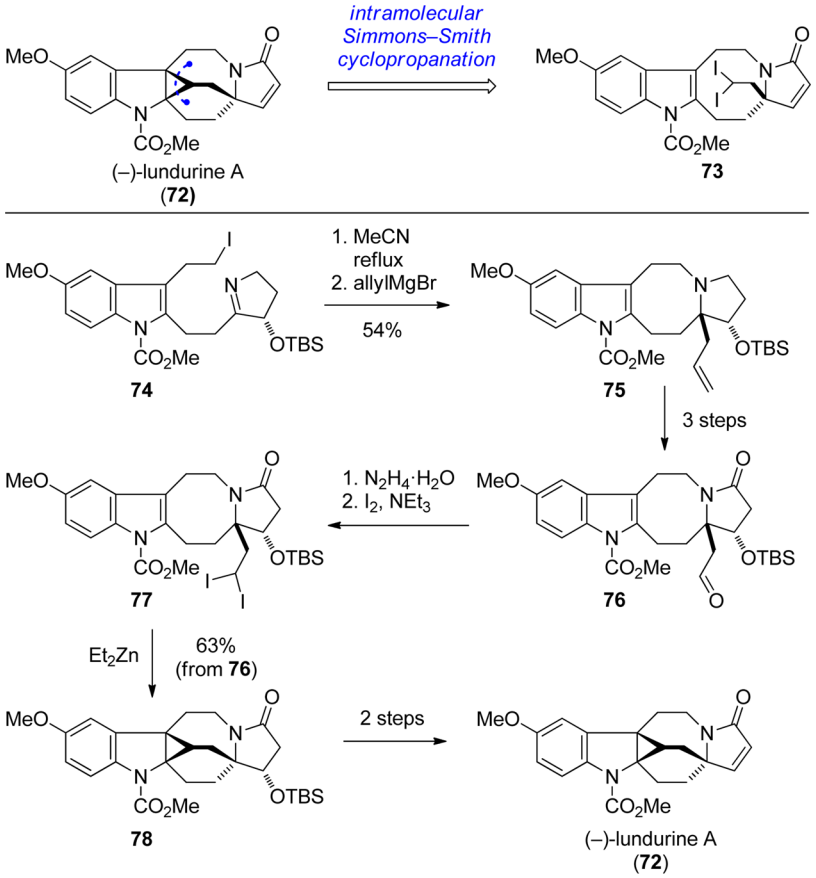
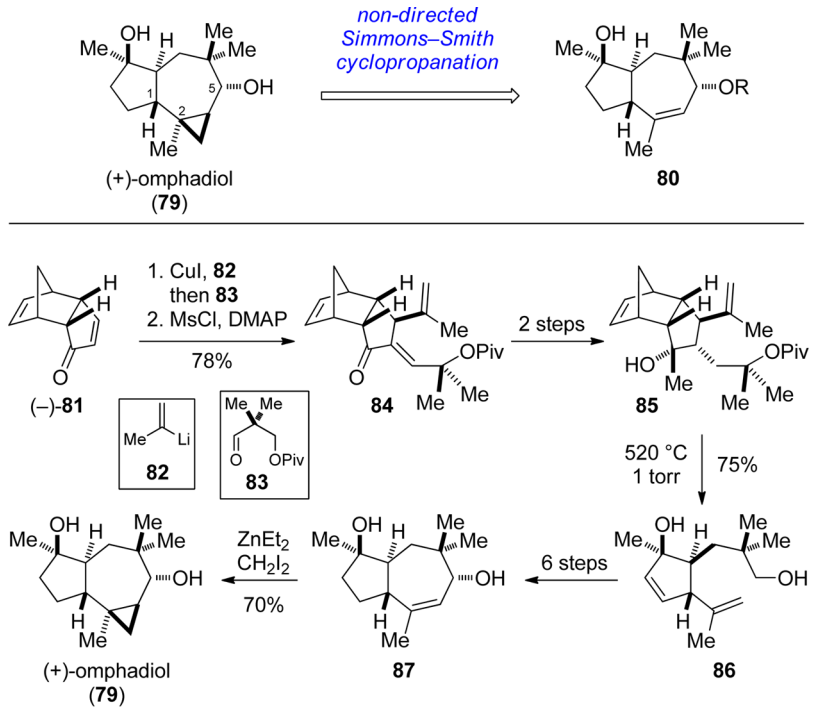
Scheme 14. Total Synthesis of (−)-Lundurine A via Intramolecular Simmons−Smith Cyclopropanation[a]



[a]Qin and co-workers.[110,111]

Scheme 15. Total Synthesis of (+)-Omphadiol[a]



[a]Kalesse and co-workers.[116]

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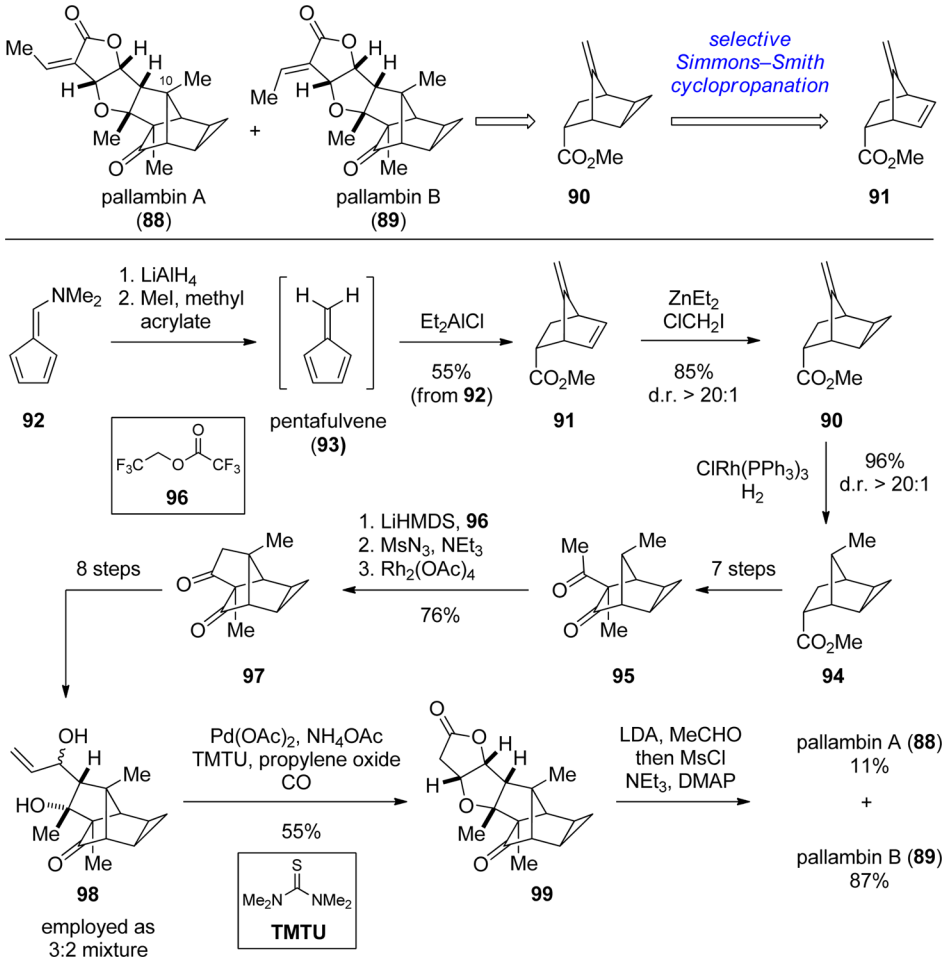
Scheme 16. Total Synthesis of Pallambins A and B[a]



[a]Ebner and Carreira.[118]

3.1. Simmons–Smith Cyclopropanations

3.1.1. Synthesis of (−)-Lundurine A. (−)-Lundurine A (**72**) is an indoline alkaloid, isolated in 1995 from Malaysian *Kopsia tenuis* (Scheme 14).[109] The structure of this natural product is characterized by a tricyclic core, incorporating a densely substituted cyclopropane as well as four stereocenters. Qin and co-workers[110,111] concluded that a late-stage intramolecular Simmons–Smith cyclopropanation reaction of **73**, involving the indole and a carbenoid, would simultaneously solve the problem of installation of the challenging cyclopropane as well as the tricyclic core of the natural product.

The key advanced azocane intermediate was formed via intramolecular nucleophilic displacement of the primary iodide in **74**, available in four steps from a known substituted indole.[112] Subsequent addition of allylMgBr furnished amine **75**, which was further converted into aldehyde **76** in three additional steps. Barton's protocol was employed in order to convert the aldehyde into *gem*-diiodide **77**,[113,114] setting the stage for an intramolecular Simmons–Smith cyclopropanation reaction. Hence, treatment of **77** with an excess of $ZnEt_2$ furnished cyclopropane **78** in 63% yield from aldehyde **76**. After deprotection and dehydration, (−)-lundurine A (**72**) was obtained.

3.1.2. Synthesis of (+)-Omphadiol. The sesquiterpene (+)-omphadiol (**79**) was isolated in 2000 from the fungus *Omphalotus illudens* (Scheme 15).[115] This natural product contains a 5-7-3 ring system and six contiguous stereocenters. In addition to synthesis of the trans-fused cyclopentane moiety, the stereoselective introduction of the cyclopropane represents a challenge. It is noteworthy that the potential directing effect of the C(5) alcohol, which might lead to the undesired stereoisomer, must be taken into account while planning the synthesis route. Recently, Kalesse and co-workers[116] described an approach that allows for a stereoselective generation of the *trans*-cyclopentane. Bicyclic enone (−)-**81** was subjected to conjugate addition, followed by a formal aldol condensation with **83** to give **84**. This sequence exploited the shielding effect of the norbornene to ensure that enone functionalization takes place from the concave face. Flash vacuum pyrolysis of advanced intermediate **85** then provided highly substituted cyclopentane **86** in 75% yield. Interestingly, upon exposure of olefin **87** to Simmons–Smith conditions, the free alcohol at C(5) did not exert any directing effect, providing (+)-omphadiol (**79**) in 12 steps from ketone (−)-**81**. This may result from the steric hindrance associated with the neopentyl-like alcohol or, alternatively, suboptimal disposition between alcohol and olefin of the cycloheptenyl ring to enable directed methenylation.

3.1.3. Synthesis of Pallambins A and B. The norditerpenoids pallambins A (**88**) and B (**89**), isolated in 2012 from extracts of the liverwort *Pallavicinia ambigua*,[117]

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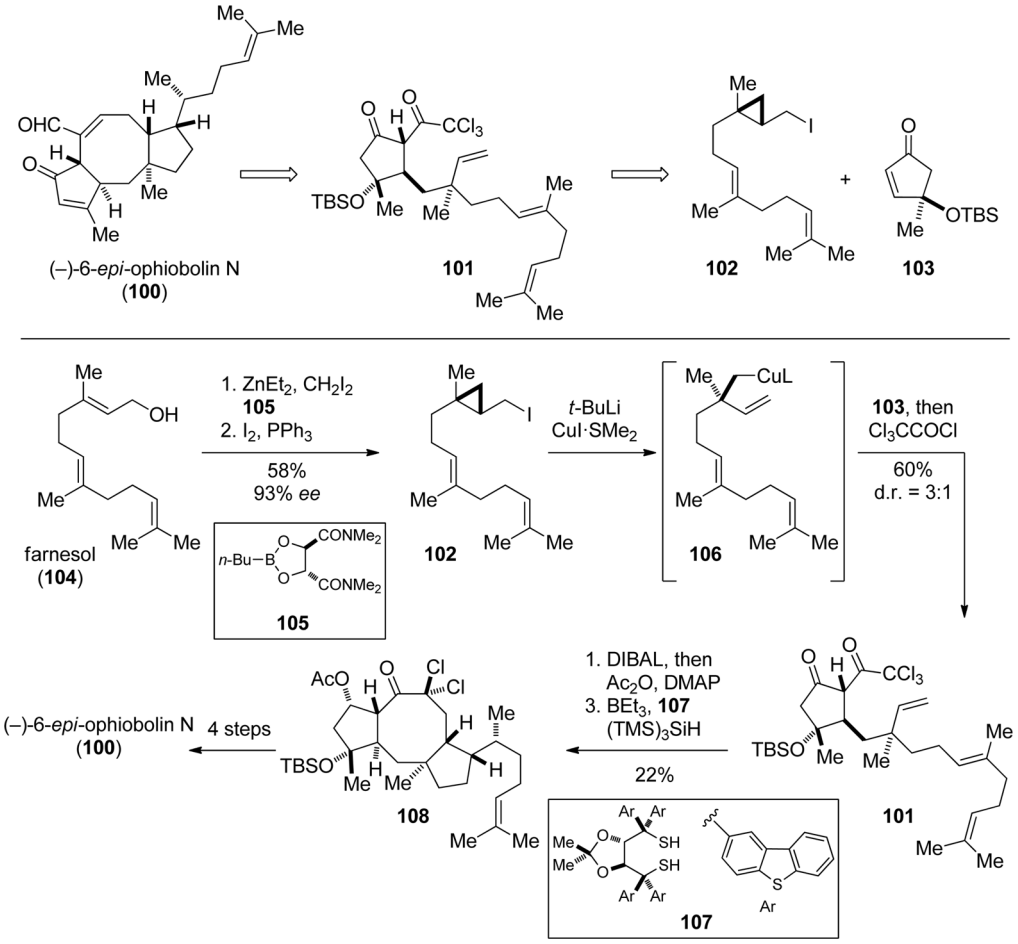
Scheme 17. Total Synthesis of (−)-6-*epi*-Ophiobolin N[a]



[a]Maimone and co-workers.[123]

possess a hexacyclic scaffold equipped with 10 contiguous stereocenters, out of which two are quaternary (Scheme 16).

A formidable challenge in any total synthesis endeavor arises from the tetracyclo[4.4.0^{3,5}.0^{2,8}]decane core, comprising an encumbered cyclopropane that includes double gauche pentane-like interactions with the C(10) methyl group. In their total synthesis of pallambins A and B, Ebner and Carreira[118] planned for introduction of the cyclopropane prior to installation of the C(10) methyl group. Accordingly, chemo- and diastereoselective Simmons−Smith cyclopropanation of diene **91**, followed by diastereoselective hydrogenation of the remaining exo-olefin, was envisioned.

Diene **91** was prepared from an unprecedented Diels−Alder reaction between pentafulvene (**93**) and methyl acrylate. While various cyclopropanation protocols either showed lack of reactivity or chemoselectivity (endo- vs exo-olefin), exposure of **91** to Denmark's conditions[37] provided cyclopropane **90** in 85% yield as a single diastereomer. Subsequent reduction of the remaining olefin with Wilkinson's catalyst furnished ester **94** in 96% yield (dr > 20:1). The tetracyclic core of the natural products was completed by diazo transfer and C−H insertion of **95**, giving diketone **97** in 76% overall yield. Palladium-catalyzed alkoxycarbonylation under the conditions described by Yang and co-workers,[119,120] followed by a formal aldol condensation, then yielded pallambins A (**88**) and B (**89**).

3.1.4. Synthesis of (−)-6-*epi*-Ophiobolin N. The discovery of the ever-expanding ophiobolin class of natural products commenced in 1958 with the isolation of ophiobolin A.[121] These sesterterpenes possess a characteristic fused 5-8-5 ring system, representing an exceptional challenge for total synthesis. In 2016, Maimone and co-workers[123] documented a concise approach toward the recently isolated 6-*epi*-ophiobolin N (**100**),[122] relying on an anionic cyclopropane fragmentation of iodide **102** (Scheme 17).

The use of a halogenated cyclopropane as a synthon for a homoallylic organometal species is a strategic coup that allows straightforward asymmetric access to a key intermediate. Furthermore, the tricyclic skeleton of the targeted natural product was envisioned to be generated from a radical-mediated cyclization cascade of trichloride **101**.

Farnesol (**104**) was subjected to enantioselective Simmons−Smith cyclopropanation conditions by Charette et al.,[124,125] followed by Appel reaction to furnish cyclopropane **102** in 58% yield. Subsequent lithium−halogen exchange triggered anionic cyclopropane opening. After transmetalation with CuI·SMe$_2$, enone **103** was added, followed by trichloroacetyl chloride, providing **101** in 60% yield. Following ketone reduction and alcohol protection, a remarkable radical cascade, initiated by BEt$_3$, generated the 5-8-5 ring system. It is noteworthy that, while several achiral thiols failed to deliver the correct diastereomer, an extensive screening of chiral alternatives provided chiral dithiol **107** as an excellent alternative. After four additional steps, 6-*epi*-ophiobolin N (**100**) was obtained.

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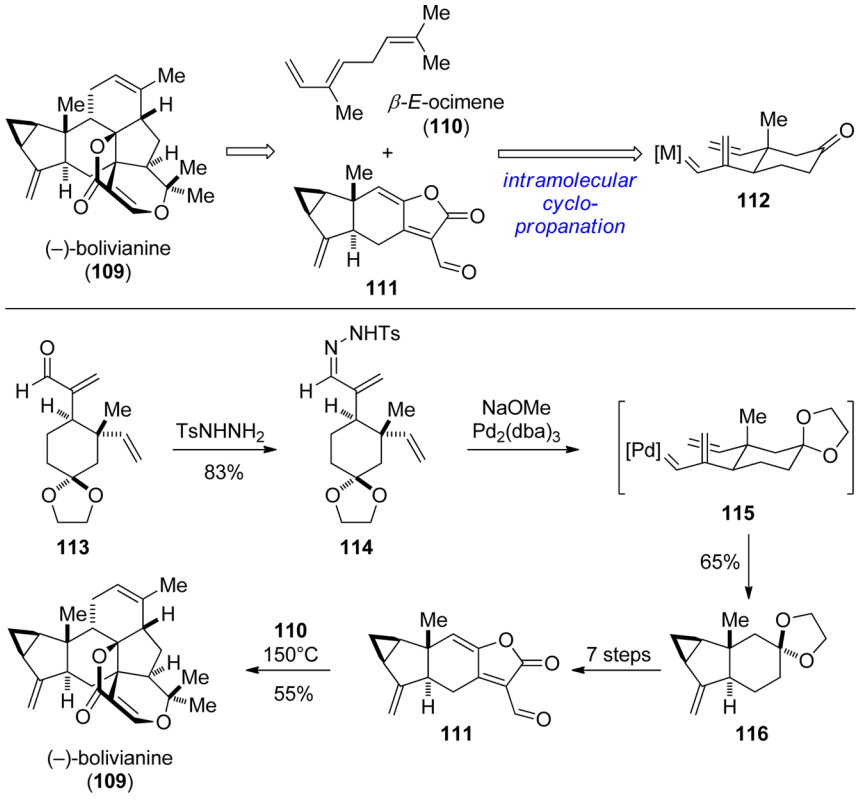
Scheme 18. Total Synthesis of (−)-Bolivianine[a]



[a]Liu and co-workers.[127]

3.2. Diazo-derived Carbenoids

3.2.1. Synthesis of (−)-Bolivianine. The sesterterpenoid (−)-bolivianine (**109**), isolated in 2007 from *Hedyosmum angustifolium* in the Chloranthaceae family, possesses a highly congested seven-membered ring system, including a cyclopropane unit.[126]

In their synthesis of this complex natural product, Liu and co-workers[127] introduced the cyclopropane through the use of allylic carbenoid **112** (Scheme 18). Additionally, a biomimetic Diels−Alder/hetero-Diels−Alder cascade between aldehyde **111** and *β*-*E*-ocimene (**110**) was planned to rapidly generate (−)-bolivianine (**109**).

Aldehyde **113**, available in only four steps from (+)-verbenone, was transformed into tosylhydrazone **114** in 83% yield. Upon exposure to sodium methoxide and $Pd_2(dba)_3$, carbenoid **115** was formed in situ, which selectively gave cyclopropane **116** in 65% yield. After seven additional steps, aldehyde **111** was obtained, which underwent the desired Diels−Alder/hetero-Diels−Alder cascade with **110** to give (−)-bolivianine in impressive 55% yield.

3.2.2. Synthesis of (+)-Salvileucalin B. (+)-Salvileucalin B (**117**) was isolated in 2008 from the aerial parts of *Salvia leucantha*, an evergreen herbaceous plant, by Takeya and co-workers.[128] This cytotoxic natural product is structurally characterized by a central norcaradiene subunit, which is part of a tricyclo[3.2.1.$0^{2,7}$]octane. Strategically, retrosynthetic scission of the central cyclopropane as shown in Scheme 19 would be highly efficient, because it would generate the complex tricyclic core of the natural product in a single step.

In 2011, Reisman and co-workers[129] reported the first enantioselective synthesis of (+)-salvileucalin B, relying on such a strategy. Importantly, such a disconnection requires the cyclopropanation of an arene, a process initially discovered by Büchner and Curtius,[130,131] which engenders several challenges. First, diazo ketone **119** possesses an activated benzylic methylene group, which could potentially undergo competing C−H insertion to form a cyclopentane. Second, the norcaradiene must be formed under conditions where it is precluded from undergoing electrocyclic ring opening to generate the corresponding heptatriene. The central chemoselectivity issue, with regard to cyclopropanation and C−H insertion, had been previously examined by Mander and co-workers[132−134] in an elegant total synthesis of gibberellin GA_{103}. In these studies, the authors discovered that both the nature of the metal catalyst and the arene substitution pattern influence the reaction outcome. While dimeric rhodium catalysts produced mixtures of C−H inserted products and norcaradienes, copper catalysts favored cyclopropanation. For the total synthesis of (+)-salvileucalin B, an electron-withdrawing group adjacent to the ketone in **118** was required in order to form the *γ*-lactone. Reisman and co-workers[135,136] discovered that the nature of this additional functional group has a significant impact on the chemoselectivity of the reaction. While *α*-diazo-*β*-keto esters favor C−H insertion, the corresponding nitriles furnish the norcaradiene products in good yields.

The central arene unit was generated via ruthenium-catalyzed cycloisomerization of diyne **120**, available in seven steps from propargyl alcohol. Following auxiliary removal and introduction of the *α*-diazo-*β*-ketonitrile, **119** was exposed to $Cu(hfacac)_2$ under microwave irradiation to generate norcaradiene **122** in 65% yield. This product could then be converted to (+)-salvileucalin B in five additional steps.

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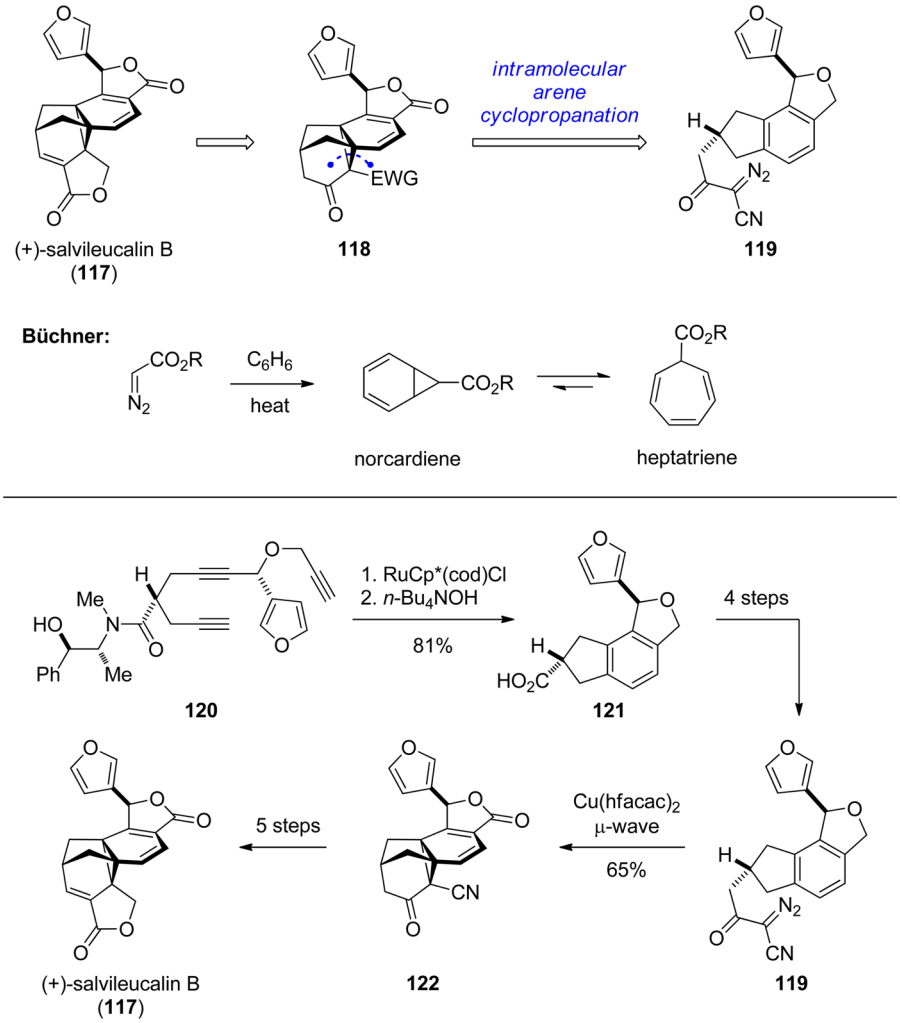
Scheme 19. Total Synthesis of (+)-Salvileucalin B via Intramolecular Arene Cyclopropanation[a]



[a]Reisman and co-workers.[129]

3.2.3. Synthesis of Piperarborenine B. In 2013, Fox and co-workers[137] reported an ingenious enantioselective bicyclopropanation/homoconjugate addition for the generation of tetrasubstituted cyclobutanes (Scheme 20, top). α-Cinnamyl-α-diazo esters were observed to form dicyclopropane intermediates, such as **125**, that could subsequently undergo homoconjugate opening with an added organometal species to form cyclobutylenolate **126**. The latter could be quenched by a collection of electrophiles.

The utility of this method was showcased by Fox and co-workers[138] in an elegant total synthesis of the cyclobutane-containing natural product piperarborenine B (**123**). After diazo ester **128**, available in three steps from veratraldehyde, was exposed to their established conditions, only moderate enantioselectivity was achieved. Thus, a new dimeric rhodium catalyst was developed (**129**), which provided cyclobutane **131** in 69% yield and 92% ee after nucleophilic dicyclopropane opening and BHT-mediated proton quenching. This bulky proton source was necessary in order to enable diastereoselective protonation of the corresponding enolate. In accordance with the work of Baran and co-workers,[139−141] the remaining aryl substituent was introduced by C−H activation approaches.

3.2.4. Synthesis of (−)-Spirotryptostatin. Spirotryptostatin B (**142**), isolated in 1996 by Osada and co-workers,[142] is characterized by a challenging spiro[oxindole-3,3′-pyrrolidine] core. Carreira and Meyers[143−145] reported an innovative approach for the construction of such entities by employing a cyclopropane ring expansion reaction developed in their laboratory. As shown in Scheme 21, rhodium-catalyzed cyclopropanation of diazo-oxindole **135** provided **137** in 71% yield. The key ring expansion of the latter proceeded smoothly to give spirocyclic oxindole **139** in 68% yield upon exposure to MgI_2 in the presence of alkynyl imine **138**. After oxidation of ester **140**, the diketopiperazine was formed by Boc deprotection and subsequent cyclization to provide (−)-spirotryptostatin B.[146−151]

3.3. Free Carbenes by α-Elimination

3.3.1. Synthesis of Steenkrotin A. Steenkrotin A (**143**), a diterpenoid isolated in 2008 by Hussein and co-workers,[152] contains a fused pentacyclic system as well as eight stereocenters (Scheme 22). The stereoselective introduction of the dimethylcyclopropane is an important aspect to consider in planning a synthesis of **143**. Consequently, Ding and co-workers[153] envisioned reacting dimethylcarbene (**146**), generated in situ, with cyclic enol ether derivative **147**. Importantly, the increased nucleophilicity of the enol ether was expected to lead to its chemoselective functionalization in the presence of

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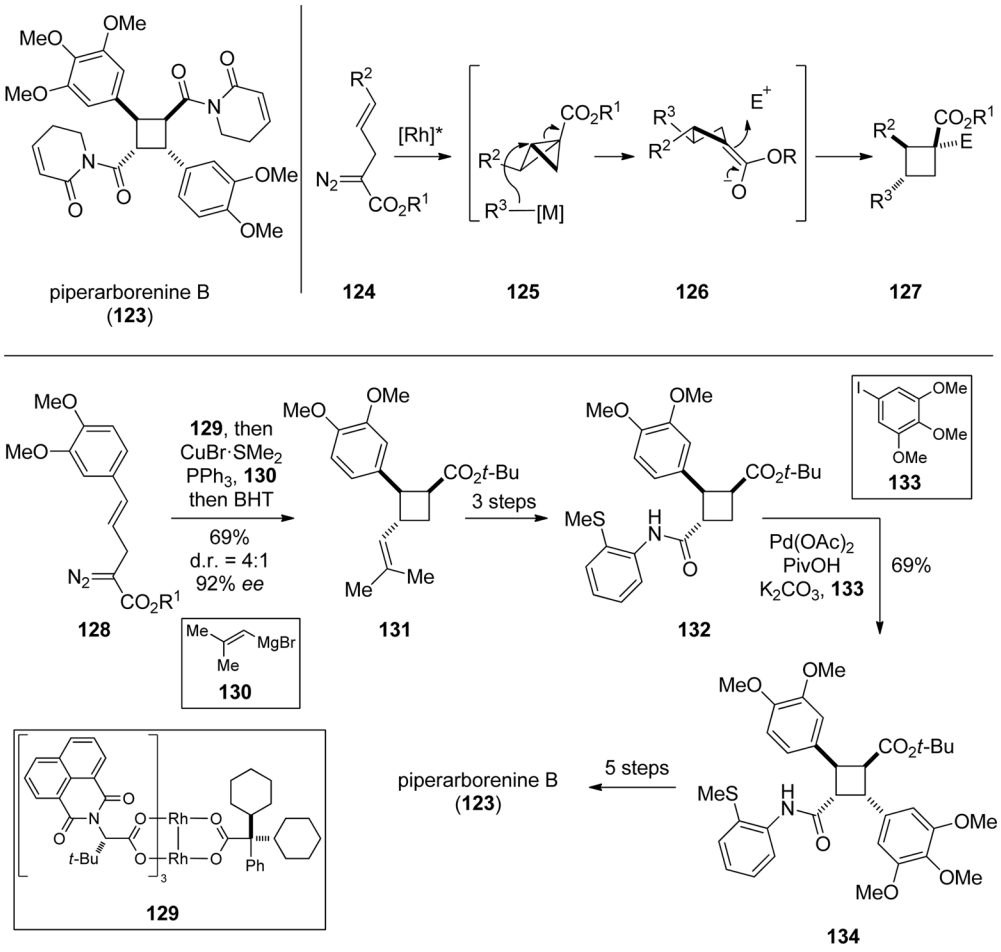
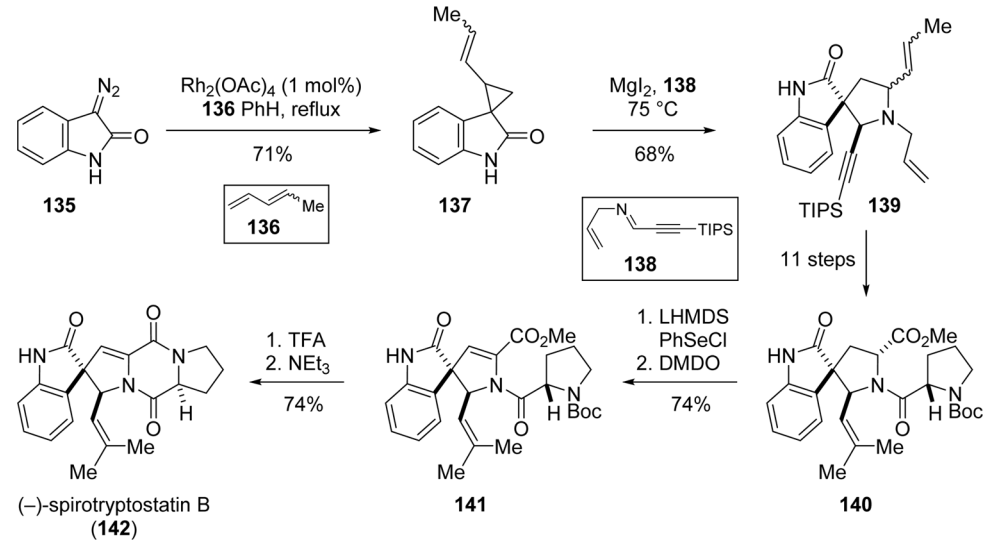
Scheme 20. Total Synthesis of Piperarborenine B[a]



[a]Fox and co-workers.[138]

Scheme 21. Total Synthesis of (−)-Spirotryptostatin[a]



[a]Meyers and Carreira.[143]

the remaining two olefins in **147**. A carbonyl-ene reaction was planned in order to generate the tetrahydrofuran.

Enone **148** was transformed into the corresponding trimethylsilyl enol ether **150** and then directly treated with dimethylcarbene (**146**), generated in situ from **149** and *n*-BuLi. The formation of cyclopropane **151** in 70% yield as a single diastereomer may be explained by the conformation shown in **150**. In five steps, aldehyde **152** was synthesized, which upon

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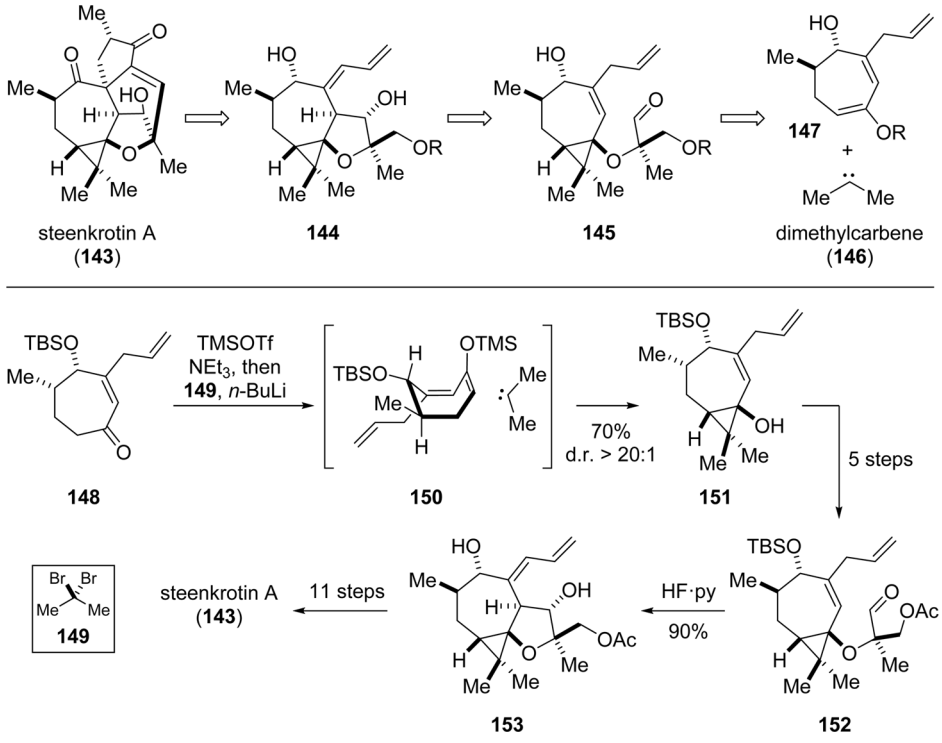
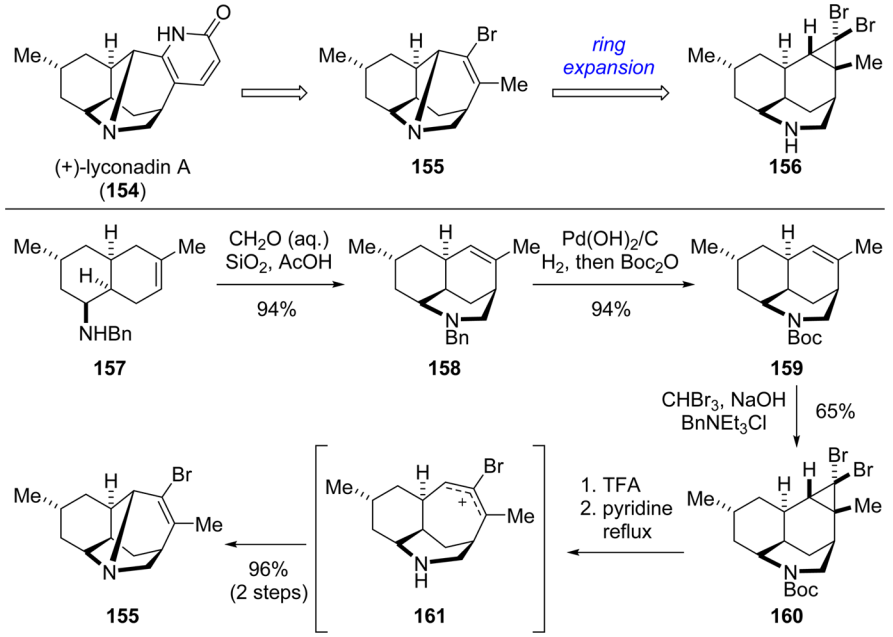
Scheme 22. Total Synthesis of Steenkrotin A[a]



[a]Ding and co-workers.[153]

Scheme 23. Total Synthesis of (+)-Lyconadin A[a]



[a]Fukuyama and co-workers.[157,158]

exposure to HF·pyridine underwent concomitant desilylation and carbonyl-ene reaction to furnish tricycle **153** in excellent 90% yield.

3.3.2. Synthesis of (+)-Lyconadin A. Free carbenes derived from base-mediated α-elimination of HX from CHX_3 (X = halogen) have found widespread application for the one-carbon ring expansion to generate cyclic vinyl halides.[154,155] In 2011, Fukuyama and co-workers[157,158] reported the total synthesis of alkaloid (+)-lyconadin A (**154**), isolated in 2001 from *Lycopodium complanatum*,[156] in which the tetracyclic core was generated from a dibromocyclopropane intermediate (Scheme 23).

Upon exposure of olefin **157** to aqueous formaldehyde under acidic conditions, aza-Prins cyclization occurred, providing tricyclic amine **158** in 94% yield. The cyclopropanation of benzyl-protected **158** proceeded in only 9% yield, a finding that

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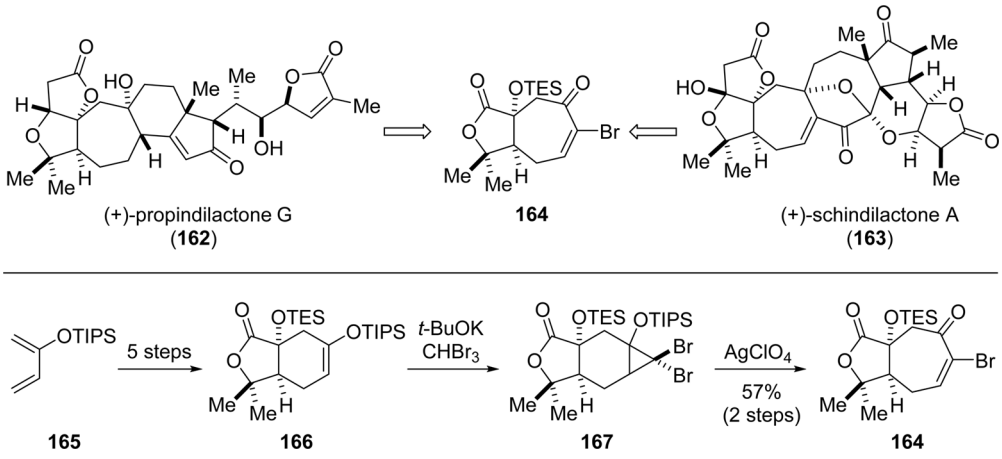
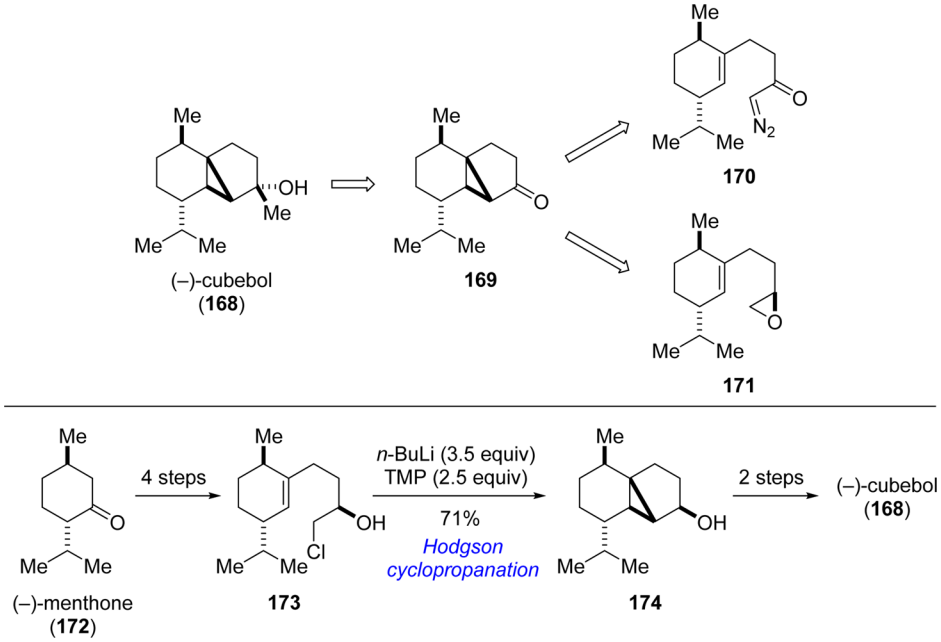
Scheme 24. Total Syntheses of (+)-Propindilactone G and (+)-Schindilactone A[a]



[a]Yang and co-workers.[159,160]

Scheme 25. Synthesis of (−)-Cubebol[a]



[a]Hodgson et al.[171]

was attributed to an undesired side reaction involving the amine and the in situ-generated free carbene. Accordingly, the less nucleophilic Boc-protected amine derivative **159** was prepared. In this case, the desired dibromocyclopropane was isolated in 65% yield upon treatment with bromoform and NaOH under phase-transfer conditions. After deprotection, the corresponding secondary amine was refluxed in pyridine, which resulted in cyclopropane opening to cationic intermediate **161**. Subsequent intramolecular trapping of the latter by the amine then generated tetracycle **155** in excellent overall yield of 96%.

3.3.3. Synthesis of (+)-Propindilactone G and (+)-Schindilactone A. Another conceptually related strategy for the one-carbon expansion of cyclic systems is cyclopropanation of cyclic silyl enol ethers with bromoform and a suitable base. The corresponding dibromocyclopropanes are then treated with a silver(I) salt to ultimately generate α-bromoenones. Yang and co-workers[159,160] employed this procedure during their total syntheses of the nortriperpenoids (+)-propindilactone G (**162**) and (±)-schindilactone A (**163**) (Scheme 24). Accordingly, silyl enol ether **166** is treated with in situ-generated dibromocarbene, forming cyclopropane **167**. $AgClO_4$ is then used to open the latter to the corresponding α-bromoenone **164**.

3.3.4. Synthesis of (−)-Cubebol. (−)-Cubebol (**168**) represents one of the major constitutes of cubeb oil, obtained from the berries of *Piper cubeba*, which is found in Indonesia.[161] Except for two recent syntheses by Fürstner and Hannen[162] and Fehr and co-workers,[163,164] all previous routes have highlighted an α-diazoketone to generate the internal cyclopropane (Scheme 25).[165−170] However, these approaches suffer from moderate yields for the cyclopropanation reaction as well as low diastereoselectivities. In 2010, Hodgson et al.[171] reported a novel synthesis of (−)-cubebol (**168**) starting from (−)-menthone (**172**), which was converted into

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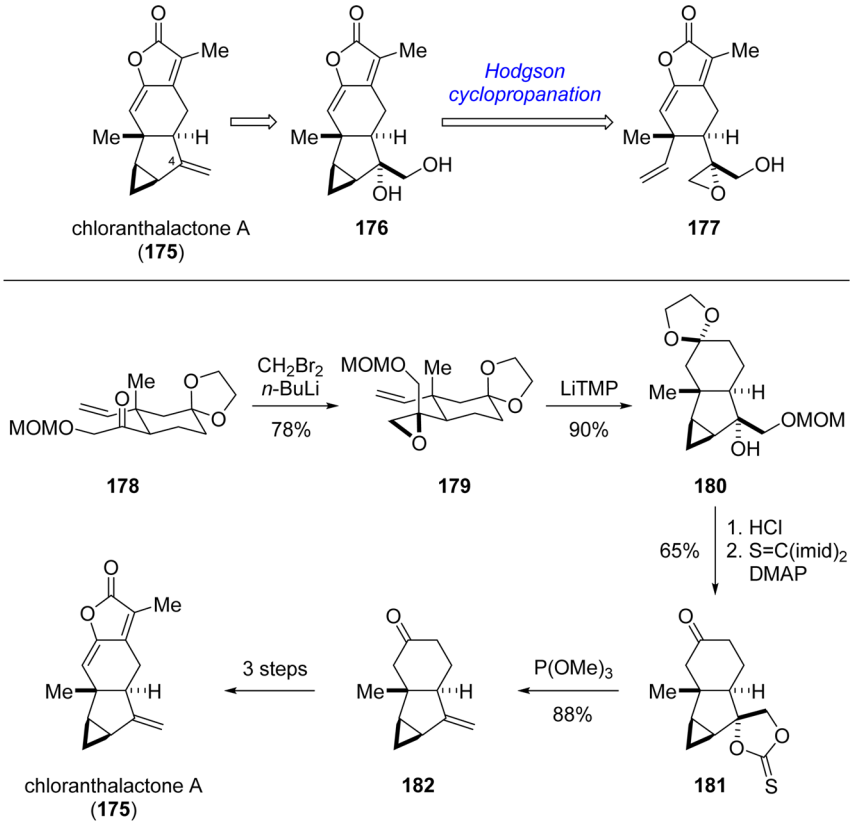
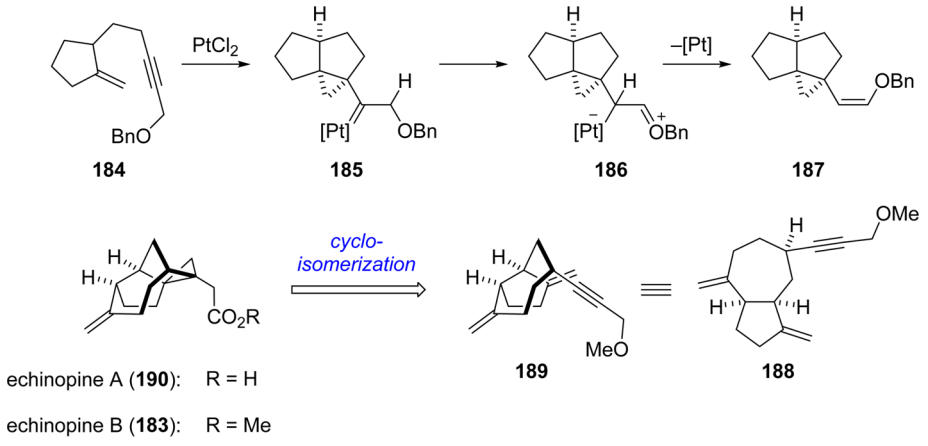
Scheme 26. Total Synthesis of Chloranthalactone A[a]



[a]Liu and co-workers.[172]

Scheme 27. Cycloisomerization Strategy for Total Synthesis of Echinopine B[a]



[a]Vanderwal and co-workers.[177]

chlorohydrin **173** in four steps. Exposure of the latter to *n*-BuLi and TMP-mediated epoxide formation, as well as α-deprotonation with subsequent elimination, formed the carbene, which then underwent clean cyclopropanation to provide alcohol **174** in 71% yield as a single diastereomer.

3.3.5. Synthesis of Chloranthalactone A. A conceptually similar strategy was employed by Liu and co-workers[172] during their total synthesis of the sesquiterpenoid chloranthalactone A (**175**, Scheme 26). Hodgson's cyclopropanation method using epoxide **177** was envisioned. Ketone **178** was first converted into epoxide **179** in 78% yield, before α-lithiation and elimination was affected by treatment of the latter with LiTMP. The desired cyclopropanated product **180** could thus be isolated in impressive 90% yield. Corey–Winter olefination then provided the required *exo*-alkene **182**, which was converted into chloranthalactone A (**175**) in three additional steps.

3.4. Cycloisomerizations

3.4.1. Synthesis of Echinopine B. The sesquiterpenoid echinopine B (**183**), isolated in 2008 together with the corresponding carboxylic acid (echinopine A, **190**), possesses a unique fused tetracyclic carbon skeleton (Scheme 27).[173] While previous approaches to these intriguing natural products

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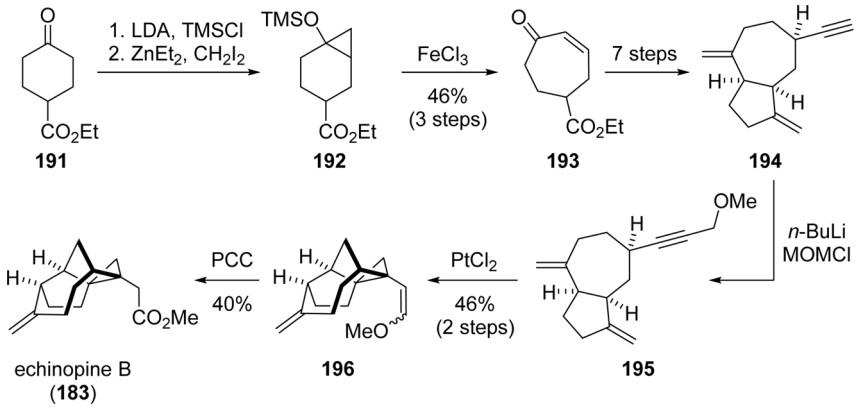
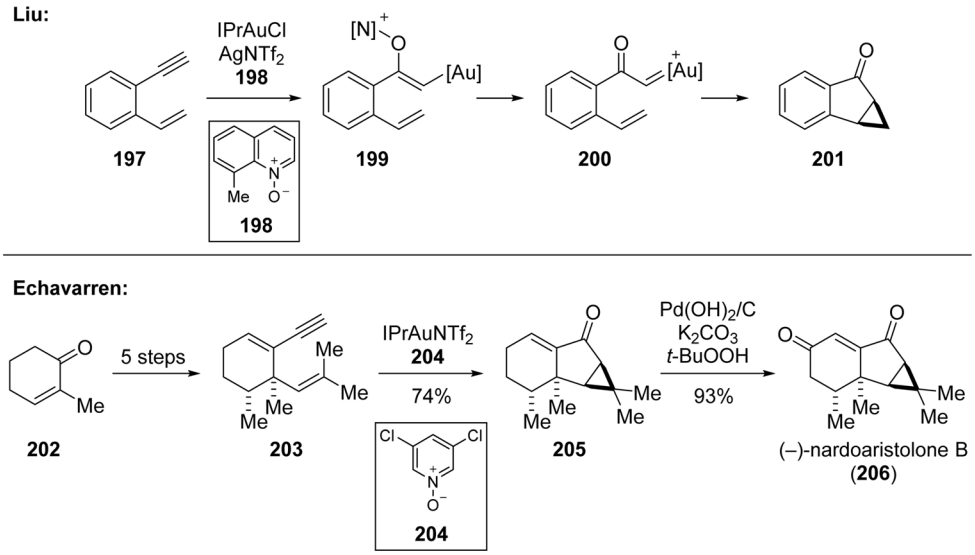
Scheme 28. Total Synthesis of Echinopine B[a]



[a]Vanderwal and co-workers.[177]

Scheme 29. Gold(I)-mediated Oxidative Cyclization of 1,5-Enynes[a] **and Total Synthesis of (−)-Nardoaristolone B**[b]



[a]Liu and co-workers.[179] [b]Echavarren and co-workers.[181]

introduced the cyclopropane moiety by either Simmons−Smith cyclopropanation[174,175] or intramolecular carbenoid cyclopropanation,[176] Vanderwal and co-workers[177,178] employed a Pt-catalyzed cycloisomerization reaction (cf. **184** → **187**).

The synthesis commences with a three-step ring-expansion sequence from cyclohexanone **191** to cycloheptenone **193** (Scheme 28). In the event, the corresponding TMS-enol ether underwent a Simmons−Smith cyclopropanation, followed by $FeCl_3$-mediated ring opening/elimination. Alkyne **194**, obtained in seven additional steps, was alkylated, providing cyclization precursor **195**. The desired cycloisomerization product **196** was subsequently obtained upon exposure of **195** to catalytic amounts of $PtCl_2$. Targeted echinopine B (**183**) could be isolated upon oxidation of the methoxyenol ether with PCC.

3.4.2. Synthesis of (−)-Nardoaristolone B. In 2011, Liu and co-workers[179] reported the gold(I)-catalyzed oxidative cyclization of 1,5-enynes, enabled by N-oxides. As shown in Scheme 29 (top), following metal activation of the alkyne, nucleophilic attack of the oxidant generates **199**, which leads to gold carbene **200** with concomitant N−O bond rupture. An intramolecular cyclopropanation reaction then leads then to the final product **201**.

Echavarren and co-workers[181] realized the potential of this methodology to provide a concise route toward the recently isolated[180] natural product (−)-nardoaristolone B (**206**). In five steps, cyclohexenone **202** was transformed into enantiopure 1,5-enyne **203**. The envisioned gold(I)-catalyzed oxidative enyne cyclization required some optimization. Extensive screening of gold catalysts and N-oxides was necessary in order to achieve a high-yielding cycloisomerization. Accordingly, the use of $IPrAuNTf_2$, in combination with **204** as oxidant, resulted in 74% isolated yield of desired cyclopropane **205**. The remaining allylic oxidation to form (−)-nardoaristolone B (**206**) occurred via palladium-catalyzed radical oxidation in the presence of Pearlman's catalyst.[182]

3.4.3. Synthesis of Gelsenicine. During their total synthesis of the alkaloid gelsenicine (**207**), Ferreira and coworkers[183] reported an impressive example of a cycloisomerization resulting in the stereoselective formation of a highly substituted cyclopropane (Scheme 30). This natural product consists of a tricyclic caged core, which is fused to a spirocyclic oxindole. Advanced diene **208** was envisaged as a

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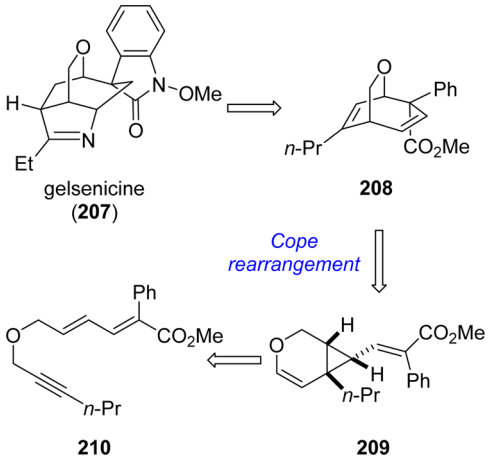
Scheme 30. Retrosynthetic Analysis of Gelsenicine[a]



[a]Ferreira and co-workers.[183]

suitable precursor for gelsenicine (**207**). Cope rearrangement would retrosynthetically lead to cyclopropane **209**, which in turn would be synthesized via a transition metal-catalyzed cycloisomerization from alkyne **210**. It is noteworthy that this two-step sequence (**210** → **208**) might even be realized as a one-pot cascade reaction.

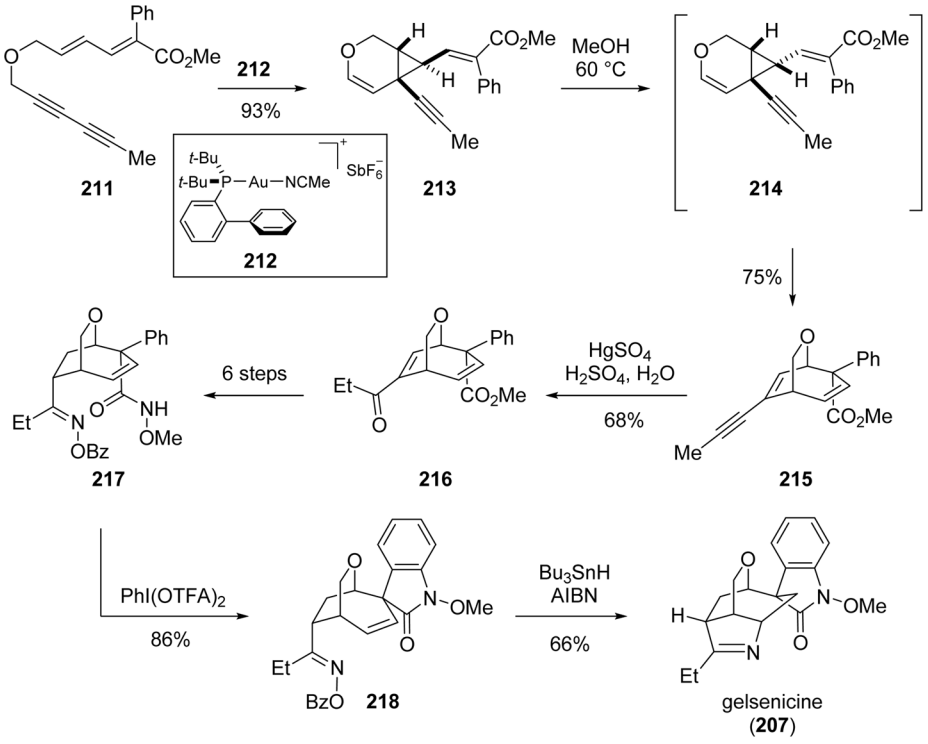
Alkyne **210**, prepared in three steps from commercially available starting materials, was exposed to $PtCl_2$ at 70 °C to induce both the cycloisomerization and the Cope rearrangement. However, the desired bicyclic structure **208** could only be obtained in poor yield of 5%. Hence a two-step sequence was explored next. However, while the cycloisomerization reaction provided **209** in excellent yield, **208** was formed in only minor amounts. This finding could be attributed to competing hydrogen migration from the *n*-propyl group to the enoate olefin. Thus, diyne **211**, which could later also be converted into the required ethyl ketone, was investigated (Scheme 31). Indeed, upon exposure to 2 mol % gold(I) catalyst **212**, cyclopropane **213** could be isolated in 93% yield. Upon heating in methanol, initial isomerization to **214** was followed by Cope rearrangement, providing **215** in 75% yield. Mercury-mediated hydration then installed the crucial ethyl ketone in **216**. The two remaining heterocyclizations were tackled in the final phase of the synthesis. The oxindole was formed in 86% yield upon treatment of **217** with $PhI(OTFA)_2$, and the pyrroline was formed under radical conditions, ultimately providing gelsenicine **207**.

3.5. Kulinkovich Reaction

3.5.1. Synthesis of (−)-β-Araneosene. (−)-β-Araneosene (**219**) is a metabolite isolated from the terrestrial mold *Sordaria araneosa* and belongs to a class of natural products characterized by a trans-fused 11/5 ring system (Scheme 32).[184] In 2005, Kingsbury and Corey[185] reported an elegant total synthesis of this intriguing natural product, generating the cyclopentane by a pinacol rearrangement. Diol **220**, which incorporates a quaternary stereocenter, was envisioned to arise from ring expansion of cyclopropanol **221**.

As indicated in Scheme 32, exposure of ester **222** to $ClTi(O\textit{i}\text{-}Pr)_3$ and EtMgBr furnished Kulinkovich product **223** in 60% yield. While catalysis by Brønsted acids resulted in partial decomposition of the material, treatment of **223** with $AlMe_3$ induced the desired ring expansion to give cyclobutanone **224** in remarkable 90% yield. A salient feature of this sequence is the stereochemically controlled installation of the quaternary center. After four additional steps, diol **220** was obtained, which

Scheme 31. Total Synthesis of Gelsenicine[a]



[a]Ferreira and co-workers.[183]

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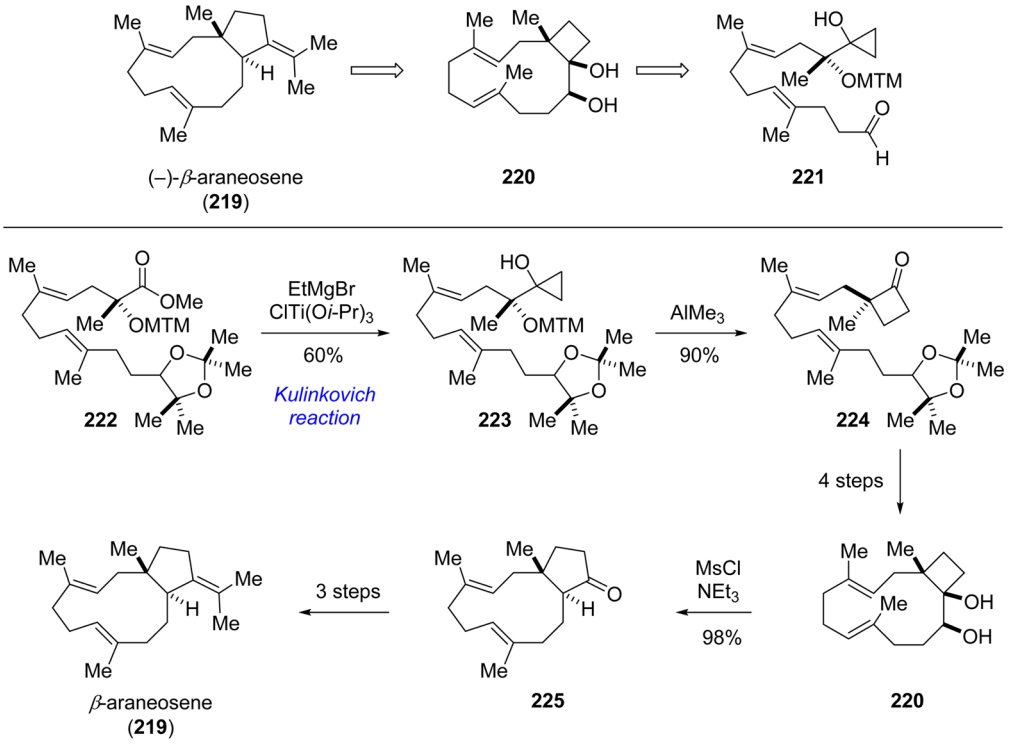
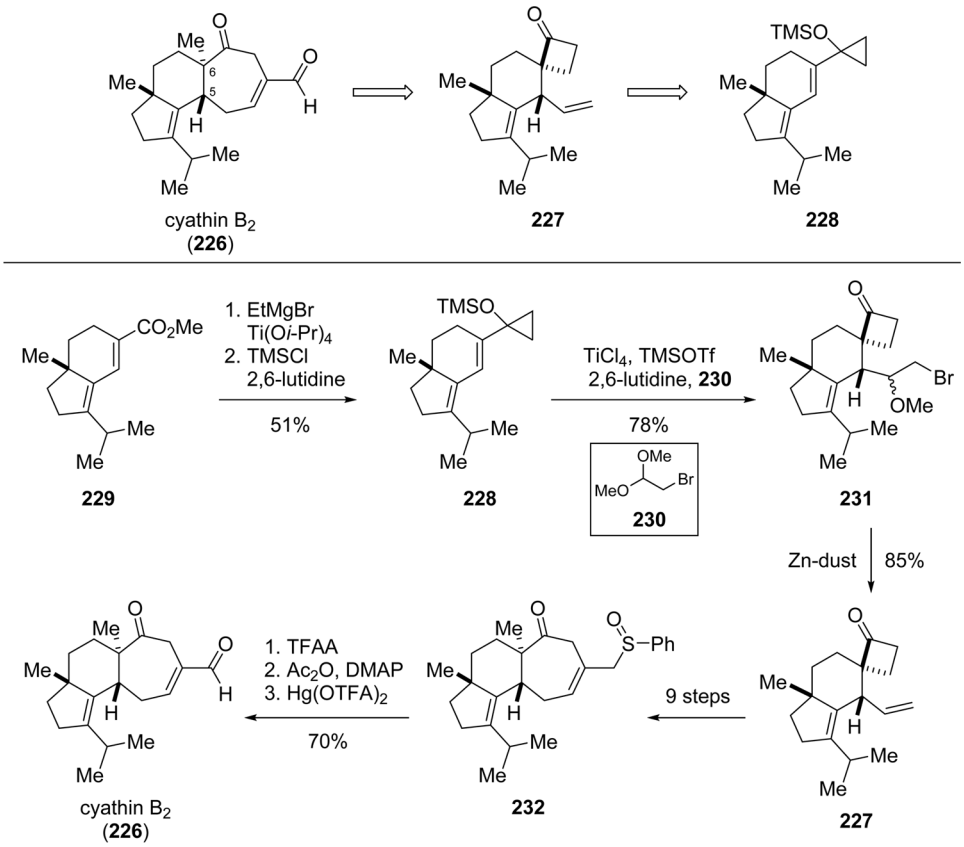
Scheme 32. Total Synthesis of (−)-β-Araneosene[a]



[a]Kingsbury and Corey.[185]

Scheme 33. Total Synthesis of Cyathin B_2[a]



[a]Kim and Cha.[190]

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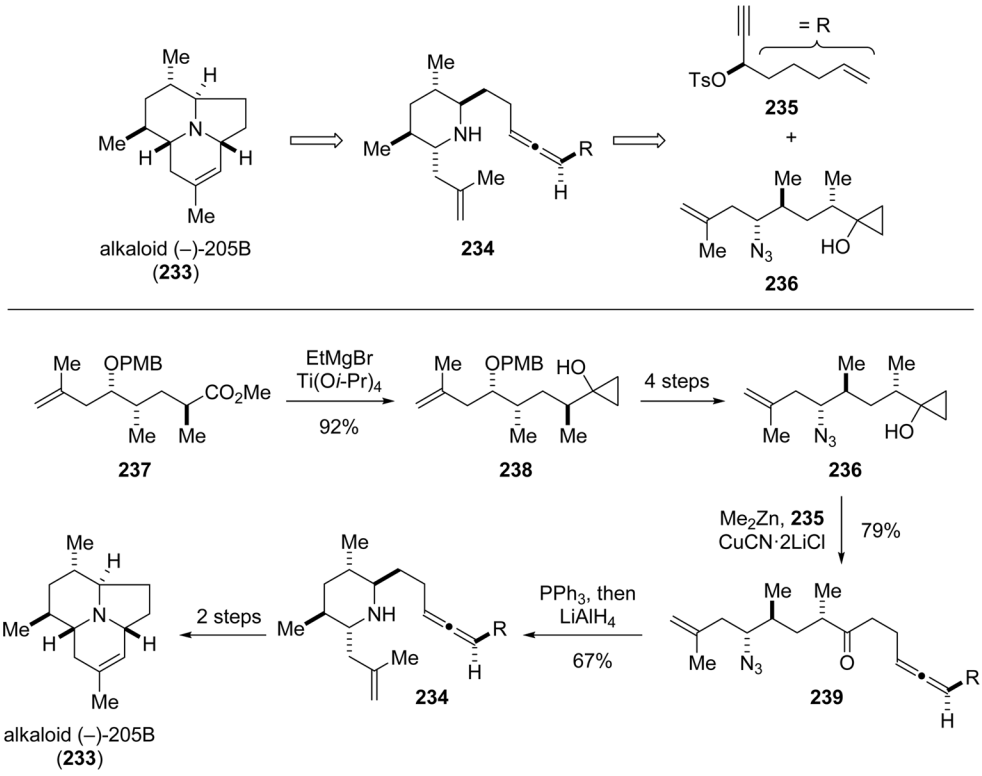
Scheme 34. Total Synthesis of Alkaloid (−)-205B[a]



[a]Rao and Cha.[196]

smoothly underwent a pinacol rearrangement in 98% yield upon treatment with MsCl and triethylamine.

3.5.2. Synthesis of Cyathins A_3 and B_2. Most members of the cyathane metabolites contain a 5/6/7-tricyclic skeleton, with a trans-fused cycloheptene.[186−189] In 2009, Kim and Cha[190] reported the total synthesis of cyathins A_3 and B_2, in which Prins-type cyclopropane expansion (**228** → **227**, Scheme 33) was employed to control the generation of the C(5) and C(6) stereocenters. As in the Corey synthesis of (−)-*β*-araneosene (Scheme 32), the crucial cyclopropanol would arise from the corresponding ester **229** via Kulinkovich reaction.

In the event, known ester **229** underwent cyclopropanation and TMS protection in 51% overall yield. The desired Prins-type ring expansion of **228** occurred in 78% yield upon exposure of the latter to $TiCl_4$ and acetal **230**. The resulting methoxy ether, obtained as a mixture of diastereomers, smoothly underwent zinc-mediated dehalogenation to furnish alkene **227** in 85% yield. In nine steps, sulfoxide **232** was obtained, which underwent a Pummerer rearrangement, giving cyathin B_2 (**226**). Furthermore, the latter could also be transformed into cyathin A_3, another member of this class of diterpenoids.

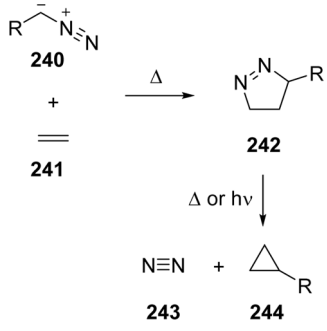
3.5.3. Synthesis of Alkaloid (−)-205B. In 1987, Tokuyama et al.[191] investigated the skin extracts of the poisonous frog *Dendrobates pumilio* and discovered various indolizidine alkaloids. Among these, alkaloid (−)-205B (**233**) gained considerable interest in the synthetic community as a platform to test new methods and strategies (Scheme 34).[192−195] In their retrosynthetic analysis, Rao and Cha[196] disconnected **233** to allene **234**. The synthesis of the latter would be achieved by employing methods involving homoenolates developed in their laboratory.[197,198] The required nucleophiles were generated in situ from cyclopropanols and were shown to react with a variety of electrophiles.

Upon exposure of ester **237** to standard Kulinkovich conditions, cyclopropanol **238** could be isolated in excellent yield of 92%. In four additional steps, the synthesis of azide **236** was achieved, which underwent homoenolate coupling with tosylate **235** in remarkable 79% yield. Piperidine **234** was formed by intramolecular aza-Wittig reaction upon treatment with triphenylphosphine and subsequent imine reduction. Silver-mediated allene cyclization followed by ring-closing metathesis then provided alkaloid (−)-205B (**233**).

3.6. Other Methods

3.6.1. From 1-Pyrazolines. Documented in 1903 by Büchner and Perkel,[199] the thermal decomposition of 1-pyrazolines to generate cyclopropanes under N_2 extrusion is a well-established route (Scheme 35).[199−201] Additionally, Van Auken and Rinehart[202] discovered that this transformation can

Scheme 35. Preparation and Decomposition of 1-Pyrazolines to Cyclopropanes



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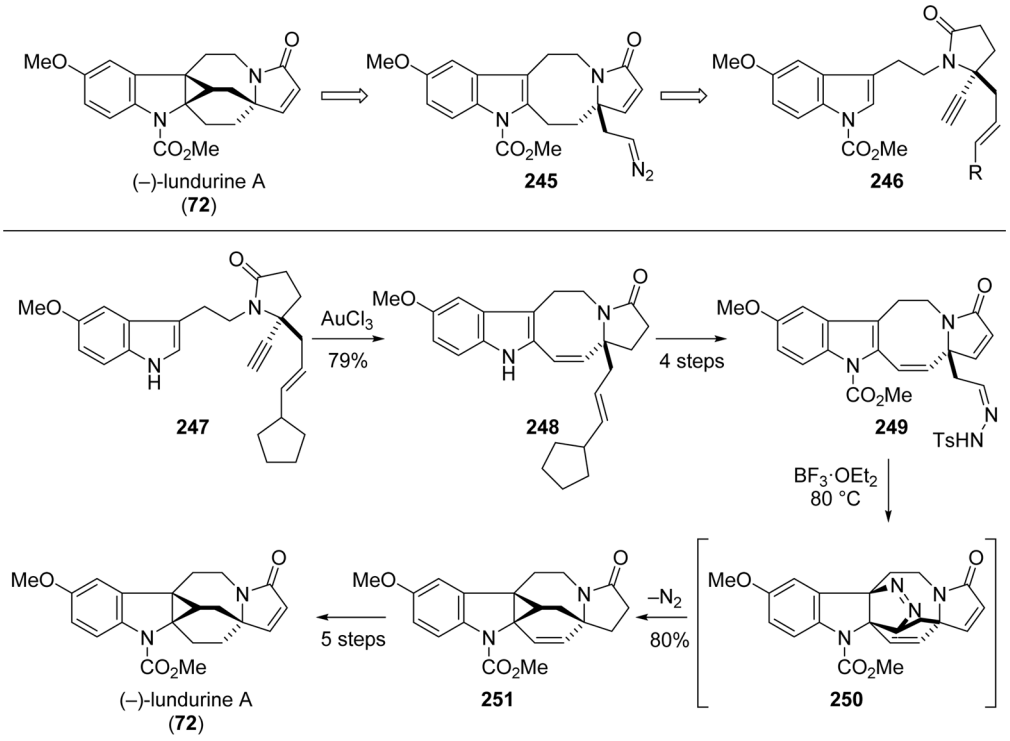
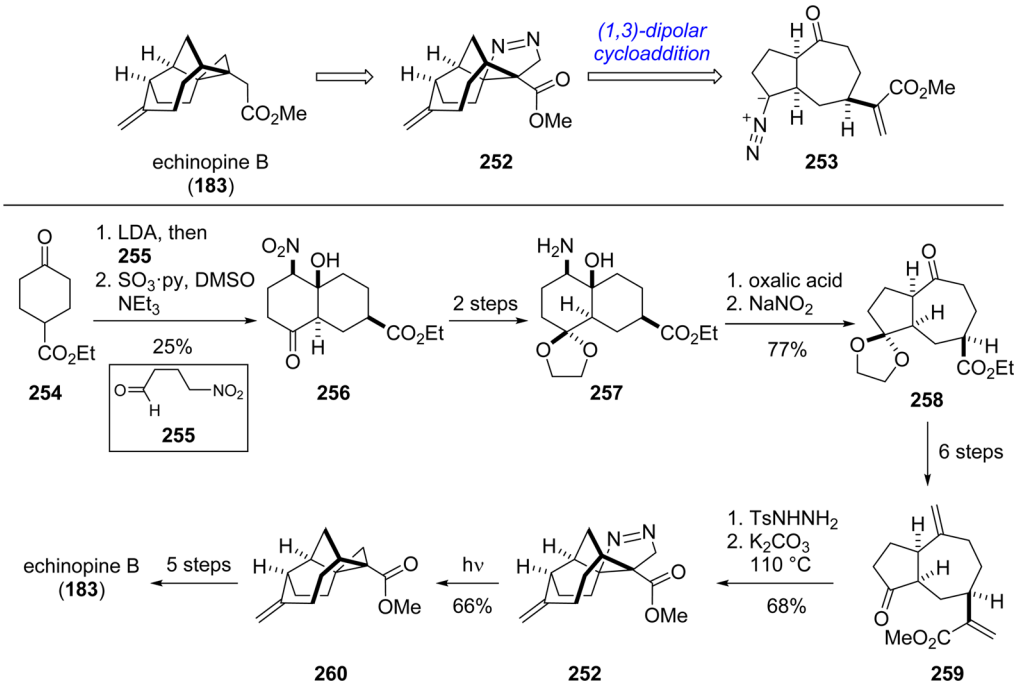
Scheme 36. Total Synthesis of Lundurine A[a]



[a]Echavarren and co-workers.[203]

Scheme 37. Total Synthesis of Echinopine B[a]



[a]Liang and co-workers.[204]

also be effected by irradiation. In this section, we showcase noteworthy examples in which this rather unusual transformation is implemented in the synthesis of complex targets.

3.6.1.1. Synthesis of Lundurines A–C. During the initial retrosynthetic analysis of lundurines A–C, Echavarren and coworkers[203] envisioned employing a diazo-derived carbene precursor such as **245** to generate the crucial cyclopropane motif (Scheme 36). The latter would then be synthesized from alkyne **246** by a gold(I)-mediated hydroarylation.

Indole **247**, obtained in two steps from tryptamine, was treated with 5 mol % $AuCl_3$ and underwent hydroarylation to give **248** in 79% yield. While initial attempts to induce the

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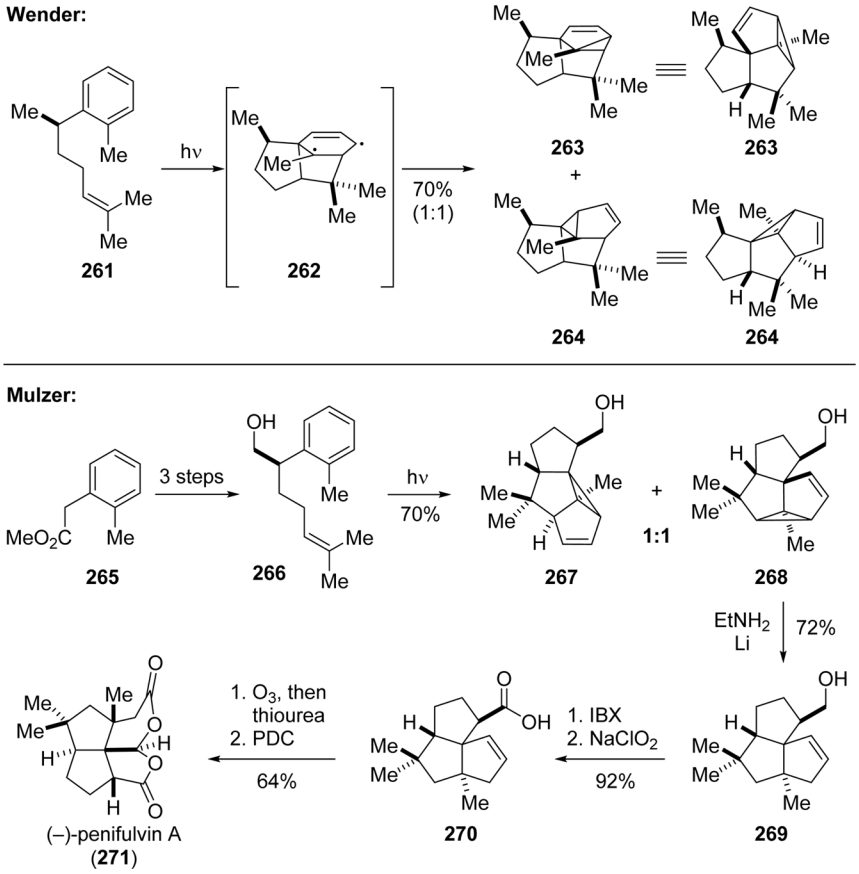
Scheme 38. Photoinduced Cycloaddition of Arene Olefins[a] and Total Synthesis of (−)-Penifulvin A[b]



[a]Wender and Ternansky.[205] [b]Gaich and Mulzer.[207]

cyclopropanation event by various transition-metal processes failed, pyrazoline **250** was formed in the presence of $BF_3{\cdot}OEt_2$ and underwent N_2 extrusion in situ, furnishing cyclopropane **251** in remarkable 80% yield. Advanced intermediate **251** could then be transformed into (−)-lundurine A (**72**) as well as structurally related lundurines B and C.

3.6.1.2. Synthesis of Echinopines A and B. The strategy of Liang and co-workers[204] for the introduction of the cyclopropane in echinopines A and B also relies on a pyrazoline decomposition reaction (Scheme 37). Hence, diazo compound **253** was introduced so that it would participate in an intramolecular 1,3-dipolar cycloaddition reaction to establish the tricyclic core of the echinopines. The synthesis commenced with the preparation of ketone **256** by an aldol/Henry sequence, followed by oxidation. The cis-fused 5/7 system was synthesized by Tiffeneau−Demjanov rearrangement (**257** → **258**). Condensation of ketone **259** with $TsNHNH_2$ and in situ liberation of the corresponding diazo compound delivered, upon heating, pyrazoline **252** in 68% yield. Subsequent irradiation mediated the desired decomposition to provide cyclopropane **260** in 66% yield, from which echinopines A and B could be accessed in four and five steps, respectively.

3.6.2. Cycloadditions. *3.6.2.1. Synthesis of (−)-Penifulvin A.* In 1985 in pioneering studies, Wender and Ternansky[205] investigated the irradiation of arene olefins. When **261** was exposed to UV light, highly congested tetracyclic systems **263** and **264** were isolated in 70% yield as a 1:1 mixture (Scheme 38, top). This remarkable transformation was then brilliantly used to enable the synthesis of (+)-silphinene.

Gaich and Mulzer[207] exploited this cycloaddition reaction in a remarkably efficient nine-step synthesis of (−)-penifulvin A (**271**), a sesquiterpenoid isolated from the fungus *Penicillium griseofulvum*.[206] Irradiation of arene **266**, available as enantioenriched material in three steps from **265**, provided a 1:1 mixture of cyclopropanes **267** and **268** in a combined yield of 70%. Reductive cyclopropane opening of the latter then gave alcohol **269**, which was oxidized to the corresponding carboxylic acid in excellent yield. Ozonolysis of the cyclopentene was followed by PDC-mediated lactol oxidation to furnish (−)-penifulvin A (**271**) in 64% yield.

3.6.2.2. Synthesis of Neofinaconitine. The norditerpenoid alkaloid neofinaconitine (**272**) was isolated in 1988 (Scheme 39).[208] Surprisingly, the first total synthesis was only reported in 2013 by Shi and Gin and co-workers.[209] In order to provide rapid entry to the pentacyclic skeleton of the natural product, an intramolecular radical addition with concomitant cyclopropane fragmentation (**273** → **272**) was envisioned. This cyclopropane would be installed by an unusual Diels−Alder reaction involving cyclopentadiene **275** and cyclopropene **276**.[210,211] Several possible issues needed to be taken into account while planning this transformation. First, regioselective approach of the dienophile to the cyclopentadiene is required. Second, cyclopropenes are highly reactive intermediates, which are ideally prepared in situ or immediately consumed. Third, substituted cyclopentadienes are known to undergo thermally allowed 1,5-hydrogen shifts, an event that entails the formation of regioisomeric cycloadducts.

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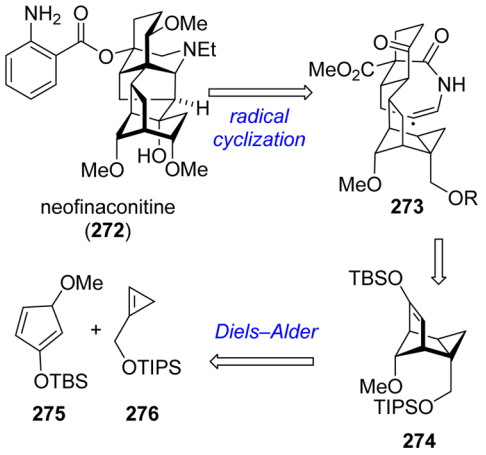
Scheme 39. Retrosynthetic Analysis of Neofinaconitine[a]



[a]Shi and Gin and co-workers.[209]

In initial studies, attempts were made to isolate **275** and allow it to react with cyclopropene **276**; however, only intractable mixtures of cyclopentadiene dimers were obtained. Thus, Shi and Gin and co-workers[209] subsequently prepared the cyclopentadiene under standard conditions (TBSOTf, NEt_3) and directly introduced cyclopropene **276** to the reaction mixture (Scheme 40). The targeted cycloadduct **274** was isolated as the major component of an isomeric mixture. After four additional synthetic steps, Weinreb amide **278** could be accessed in 42% yield from cyclopentenone **277**. As a first-generation synthesis including direct cyclopropane fragmentation failed, a new strategy was devised. Accordingly, TBAF-mediated desilylation was followed by acid-catalyzed fragmentation, which cleaved the internal cyclopropyl C−C bond to give bromide **279** in 62% overall yield. The latter was then converted into bromide **280**, which underwent a highly efficient radical 1,4-conjugate addition to ketone **281** upon exposure to *n*-Bu_3SnH/AIBN.

3.6.3. Iodonium Ylides. *3.6.3.1. Synthesis of (+)-Crotogoudin.* The diterpene (+)-crotogoudin (**282**), isolated in 2010 from plants of the *Croton* genus, possesses a unique tetracyclic skeleton, incorporating two quaternary stereocenters, which flank a hindered tertiary oxygen functionality (Scheme 41).[212] In 2013, Breitler and Carreira[213] reported an annulative cascade commencing from cyclopropane **283** to generate the central cyclohexane ring. The propensity of cyclopropanes substituted with acceptor groups to participate in either radical or ionic transformations was exploited. Chemoselective cyclopropanation of the 1,1-disubstituted olefin in **284** would generate **283**. Accordingly, ketone **285** underwent selective nucleophilic addition upon exposure to isopropenylmagnesium bromide **286** and $LaCl_3$·2LiCl. Subsequent protection of the secondary alcohol provided olefin **287** in 86% yield. Phenyliodonium malonate **288** was chosen as a suitable carbenoid precursor as a consequence of the reported selectivity for 1,1-disubstituted olefins.[214] Thus, exposure of the latter to olefin **287** in the presence of 0.1 mol % $Rh_2(esp)_2$ furnished cyclopropylmalonate **289** in 66% yield and 4.4:1 dr. In three steps, lactone **290** was obtained. While initial approaches in which the cyclopropane would be used as a homo-Michael acceptor in the course of nucleophilic attack by the trisubstituted olefin were not productive, SmI_2-mediated a radical annulation, providing desired **291** in 80% yield. Targeted (+)-crotogoudin (**282**) could then be accessed in seven more steps.

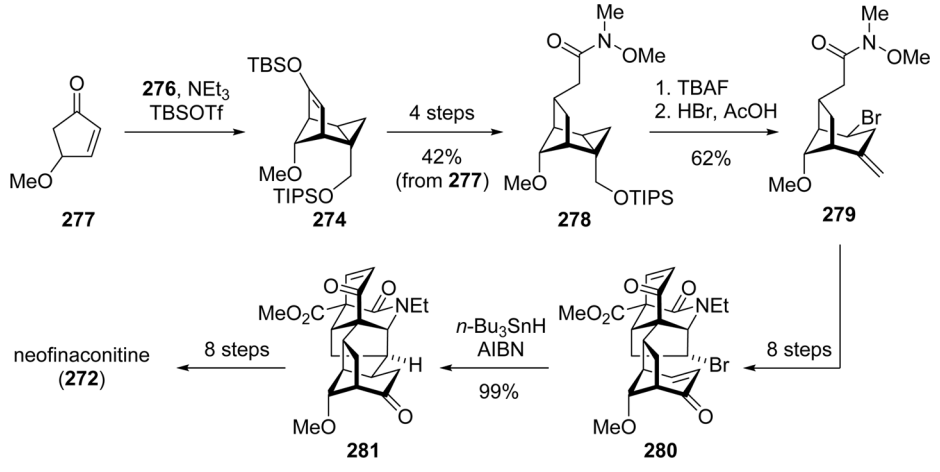
3.6.4. Reductive Cyclopropanation. *3.6.4.1. Synthesis of Steviol.* In 2013, Baran and co-workers[215] reported the total synthesis of the *ent*-kaurane steviol (**292**, Scheme 42). At the heart of their strategy is fragmentation of highly substituted cyclopropane **293**, which was envisoned to be accessible from diketone **294** by reductive cyclopropanation.

Enone **295**, obtained by polyene cyclization and reduction, underwent a photo [2 + 2] cycloaddition with allene in 82% yield. The methylene cyclobutane obtained was transformed into the corresponding diketone via ozonolysis. Subsequent fragmentation under acidic conditions generated diketone **297** in 62% yield. Reductive cyclopropanation with zinc and HCl in acetic anhydride afforded key cyclopropane intermediate **298**. After extensive screening of fragmentation conditions, it was found that treatment of diacetate **298** with methanolic HCl at 0−6 °C gave cyclopentanone **299** in 79% yield, from which steviol (**292**) could be accessed in three additional steps.

4. CONCLUSION

Cyclopropanes present both challenges and opportunities. Although numerous methods have become available, context is

Scheme 40. Total Synthesis of Neofinaconitine[a]



[a]Shi and Gin and co-workers.[209]

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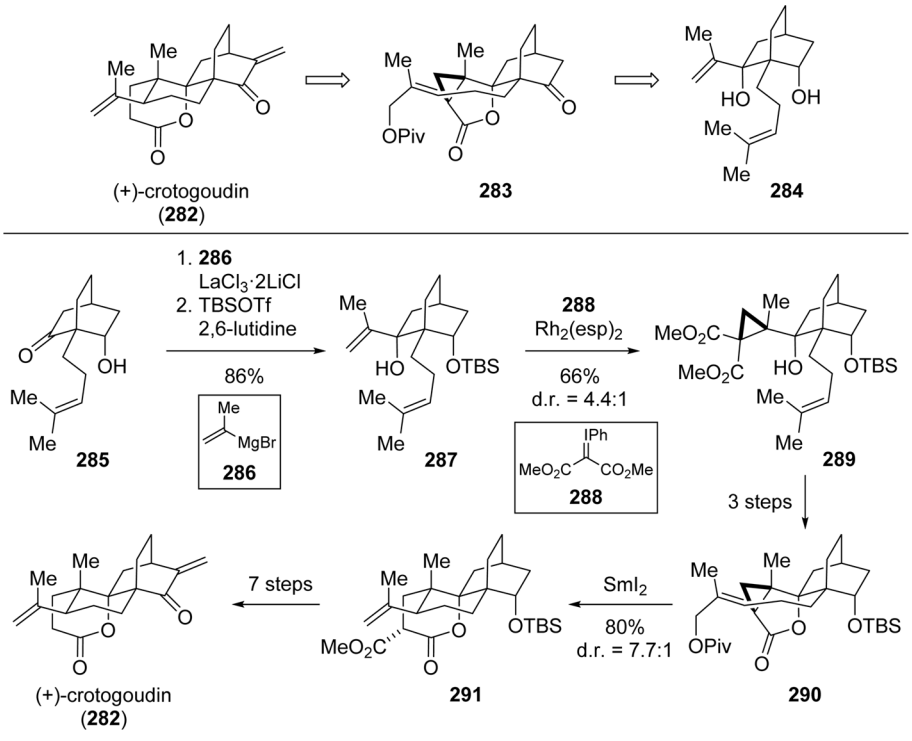
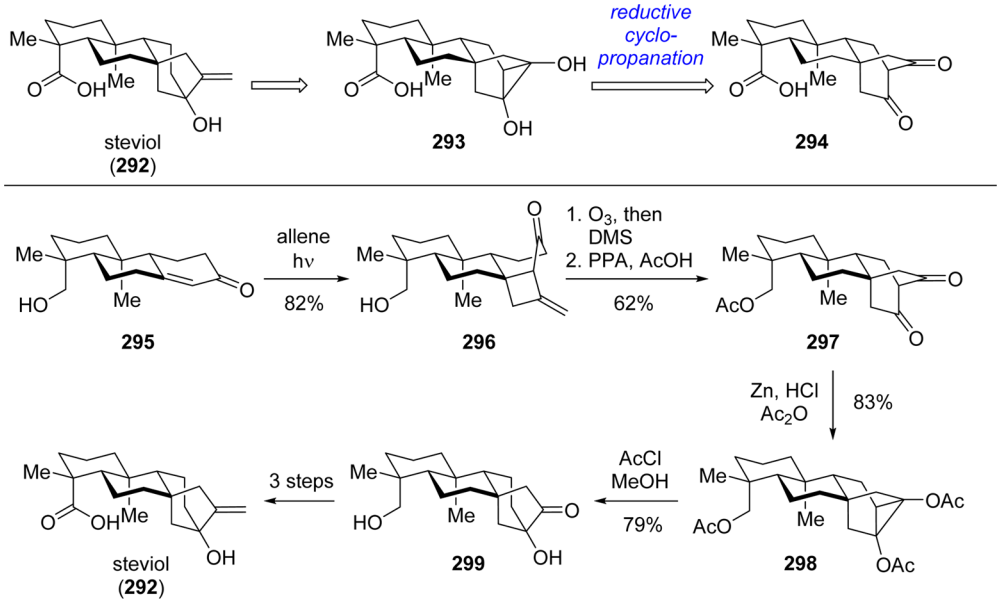
Scheme 41. Total Synthesis of (+)-Crotogoudin[a]



[a]Breitler and Carreira.[213]

Scheme 42. Total Synthesis of Steviol[a]



[a]Baran and co-workers.[215]

everything, and the myriad substitution patterns that can be envisioned are endless, with each presenting unique problems. Consequently, one can anticipate the further discovery and development of new approaches. But the development of methods in isolation inevitably falls short of addressing strategies in complex settings, be they natural products or molecules of anthropogenic origins, such as pharmaceuticals, agrochemicals, fragrances, materials, and sensors. As showcased for the examples in this review, chemical synthesis of complex molecules can be counted upon to meet the challenges in discovery and development.

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Notes

The authors declare no competing financial interest.

Biographies

Professor Erick M. Carreira obtained a B.S. in 1984 from the University of Illinois at Urbana−Champaign under the supervision of Scott E. Denmark and a Ph.D. in 1990 from Harvard University under the supervision of David A. Evans. After carrying out postdoctoral work with Peter Dervan at the California Institute of Technology through late 1992, he joined the faculty at the same institution as an assistant professor of chemistry and subsequently was promoted to the rank of associate professor of chemistry in spring 1996 and full professor in spring 1997. Since September 1998, he has been professor of chemistry at ETH Zurich in the Institute of Organic Chemistry. Since 2011, he has been also been a member of the Competence Center for Systems Physiology and Metabolic Diseases at ETH Zurich.

Christian Ebner was born in 1988 in southern Germany. During his undergraduate studies at ETH Zurich, Switzerland, he moved to the Scripps Research Institute in La Jolla, CA, to conduct his masters thesis in the laboratory of Professor K. C. Nicolaou involving the development of a novel macroheterocyclization. He obtained his Ph.D. in 2016 from ETH Zurich under the supervision of Professor Erick M. Carreira, working on the total synthesis of terpenoid natural products. He was awarded the Otto Bayer Scholarship as well as the scholarship of the Swiss Chemical Industry.

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ABBREVIATIONS

Ac	acetyl
AIBN	azobis(isobutyronitrile)
Ar	aryl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
cap	caprolactam
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
dba	dibenzylideneacetone
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMP	Dess−Martin periodinane
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
esp	$\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate
Et	ethyl
EWG	electron-withdrawing group
hfacac	hexafluoroacetylacetonato
IBX	2-iodoxybenzoic acid
imid	imidazole
IPr	*N*,*N*′-bis(2,6-diisopropylphenyl)imidazol-2-ylidiene
LDA	lithium diisopropylamide
Me	methyl
MOM	methoxymethyl acetal
Ms	methanesulfonyl
MTM	methylthiomethyl
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pfb	perfluorobutyrate
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPA	polyphosphoric acid
Pr	propyl
py	pyridine
RT	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TIPS	triisopropylsilyl
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMTU	tetramethylthiourea
Ts	*p*-toluenesulfonyl

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