REVIEW

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Samarium(II) iodide-mediated reactions applied to natural product total synthesis

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Natural product synthesis remains a field in which new synthetic methods and reagents are continually being evaluated. Due to the demanding structures and complex functionality of many natural products, only powerful and selective methods and reagents will be highlighted in this proceeding. Since its introduction by Henri Kagan, samarium(II) iodide (SmI$_2$, Kagan's reagent) has found increasing use in chemical synthesis. Over the years, many reviews have been published on the application of SmI$_2$ in numerous reductive coupling procedures as well as in natural product total synthesis. This review highlights recent advances in SmI$_2$-mediated synthetic strategies, as applied in the total synthesis of natural products since 2004.

1. Introduction

Natural product total synthesis remains a challenging field, especially if the structures of natural products are uncertain, and even more so if the target molecules or the late-stage synthetic precursors are highly unstable. As a result, this area of research allows for testing various synthetic methodologies and strategies, together with new chemical reagents according to their versatility, reactivity, reliable selectivities, and compatibility with functional groups, to develop a new route for a total synthesis or to find an achievable pathway for the first time.

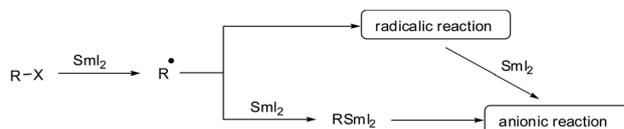Samarium diiodide (SmI$_2$) also known as Kagan's reagent, was reported by Kagan in 1980.[1]

It has been considered among the most valuable reagents and utilized in the development of a broad variety of reactions, *e.g.*, reduction of different functional groups comprising sulfones and sulfoxides, alkyl and aryl halides, epoxides, phosphine oxides, carbonyls, and conjugated double bonds, in addition to C–C bond-construction, and cascade or sequential reactions.

Over the years, several reviews have been published on the application of Kagan's reagent and also its application in the natural product total synthesis.[2,3] In this review, we try to emphasize the crucial role of samarium diiodide in the total synthesis of natural products from 2004 to date.[2] An introduction to the reagent and different classes of SmI$_2$-mediated transformations is also included; however, previous reviews must be considered for a detailed discussion of this field. Samarium diiodide (SmI$_2$) was first introduced by Matignon in 1906.[4] Over seventy years later, in 1977 Kagan *et al.* used this

reagent in organic chemistry,[1] and since then this mild and selective single-electron reducing agent has been used in the development of numerous reactions and has evolved into a prominent reagent for the modification of natural products and the natural products total syntheses. Due to the high versatility of samarium diiodide, the SmI$_2$-mediated reactions are broadly utilized as key steps in total syntheses, delivering extraordinary outcomes that cannot be attributed to other reagents and the large reduction potential of SmI$_2$ (up to −2.05 V in the presence of HMPA)[5] enables access to a large number of reactive intermediates, *e.g.* Accordingly, SmI$_2$ demonstrates a broad application from the total synthesis of natural and bioactive products to fields of materials and polymer science.[3s]

Due to the high oxophilicity of samarium and the ability to coordinate at several Lewis basic centers simultaneously, SmI$_2$-mediated reactions often proceed through well-defined transition states and produce products with excellent stereoselectivity. SmI$_2$ acts as a one-electron transfer reagent, and therefore, radical or anionic reaction mechanisms can come into play (Scheme 1). The SmI$_2$-mediated reduction of alkyl halides occurs through a single-electron transfer to produce a radical species or *via* two successive single-electron transfers to generate organosamarium reactive intermediates (Scheme 1).
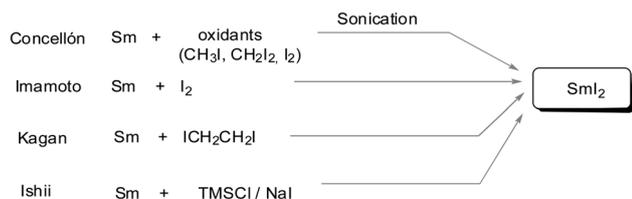
Comparably, a SmI$_2$-mediated reduction of carbonyl compounds results in either ketyl radicals or reactive

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Scheme 1 Possible pathways for SmI$_2$-mediated reactions.

Scheme 2 Preparation of samarium iodide.

carbanions. The resulting radical or organosamarium anionic intermediate can trigger various reductions including many variations of C–C bond-forming processes and cascade or sequential reactions under mild conditions. Generally, SmI$_2$ is prepared as a 0.1 M solution in THF *via* the addition of molecular iodine or 1,2-diiodoethane to samarium powder. Kagan used diiodoethane as a source of iodine.[1] Imamoto introduced a more atom-efficient method using elemental iodine.[6a] Further procedures utilized alternative sources of iodine such as diiodomethane[6b] or a combination of TMSCl and NaI.[6c] There are also methods for faster preparation such as microwave irradiation or ultrasound, and several other methods[7] (Scheme 2).

The strong reactivity of SmI$_2$ can be determined very specifically by carefully optimizing the reaction conditions. The high versatility of samarium diiodide makes a variety of radical and/or ionic reactions selectively accessible. The effective combination of useful reactivity and tunable selectivity of SmI$_2$ makes it one of the most important one-electron reducing agents in synthetic chemistry. One of the extraordinary aspects of SmI$_2$-induced reactions is the power to manipulate the outcome of reactions and to control the rate of reductions using selective cosolvents or additives.[5c] The difference in additives can stimulate the chemo- or stereoselectivity of the SmI$_2$-mediated transformations, can change the reactivity, and even affect the selectivity of one functional group among others, which makes this user-friendly reagent the most intelligent electron transfer (ET) reagent available to the synthetic chemist. The real reduction potential of SmI$_2$ and the chemo- or stereo-selectivity of the reactions mediated by SmI$_2$ can differ based on the temperature of the reaction, the solvent, or any additives, used in the reaction.[8]

Additives, which are generally used to fine-tune the reactivity of samarium diiodide can be categorized into three major groups: (a) Lewis bases, such as hexamethylphosphoramide (HMPA), ethers, and other electron donor ligands, (b) proton sources mainly including alcohols and water, and (c) inorganic additives, such as metal ion salts or complexes such as LiCl, FeCl$_3$, NiI$_2$, and LiBr. The solvent atmosphere can also alter the coordination sphere of the samarium metal, and consequently,
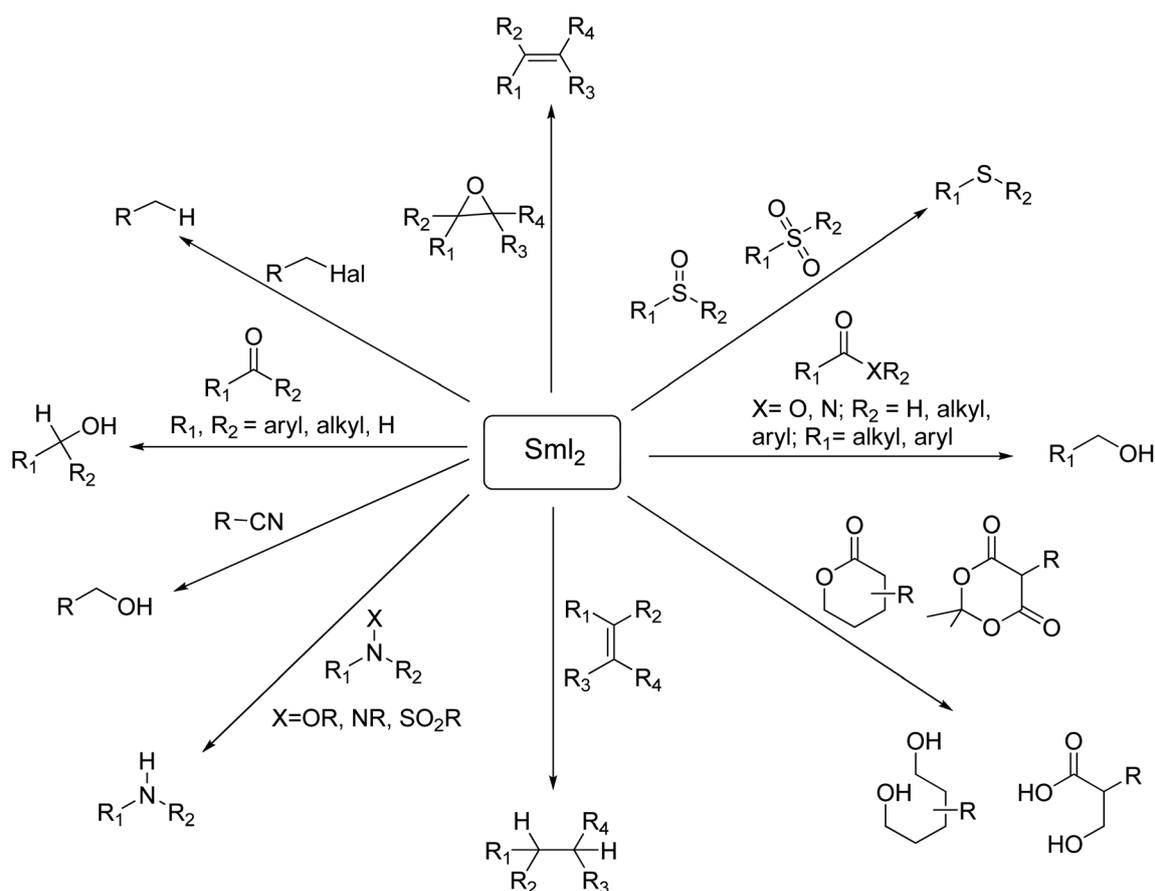
Scheme 3 Selective SmI$_2$-mediated functional group transformations.

SmI₂-mediated radical ketyl Alken /Alkin reaction
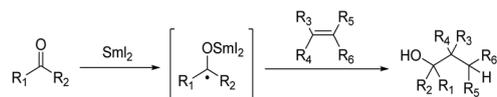
SmI₂-mediated radical none-ketyl Alken /Alkin reaction
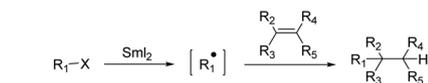
X= Cl, Br, I, SO₂R

Intra- and intermolecular SmI₂-mediated pinacol-type reactions
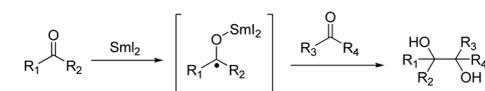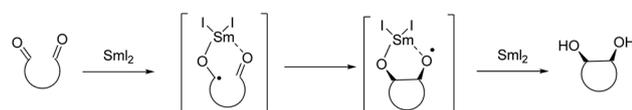
SmI₂-mediated Barbier reaction
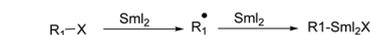
X= Cl, Br, I, SO₂R

SmI₂-mediated Reformatsky and aldol-types reactions
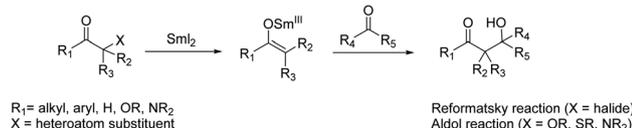
R₁= alkyl, aryl, H, OR, NR₂
X = heteroatom substituent

Reformatsky reaction (X = halide)
Aldol reaction (X = OR, SR, NR₂)

Scheme 4 Selective SmI₂-mediated reactions.

changing the reactivity of the Sm(ɪɪ) reducing agent. HMPA is still a prominent additive that significantly increases the potency of SmI₂ as an electron-transfer reagent *via* coordination to Sm(ɪɪ) and stabilizing the Sm(ɪɪɪ) oxidation state.[5a,8b,c]

SmI₂-mediated reactions can be classified into two major classes: (1) functional group reduction and (2) reductive C–C bond formation. SmI₂ is an extremely chemoselective reagent and its chemoselectivity and reactivity can be determined by the presence or absence of additives and different reaction conditions. This reagent reduces various functional groups such as alkyl and aryl halides, carbonyls, oxides, epoxides, sulfoxides, sulfones, and phosphine, as well as conjugated double bonds.[3f]

Y = CH₂, O, NR
m = 1,2, n = 0,1
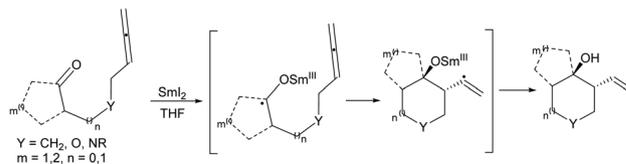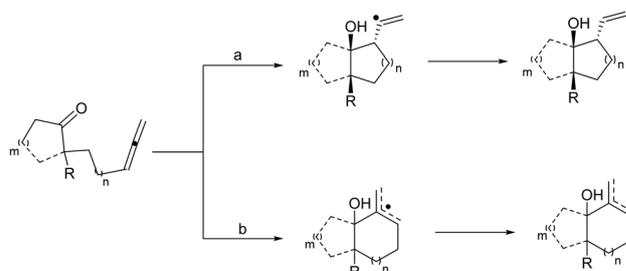
Scheme 5 SmI₂-mediated ketyl–allene cyclizations.

(Scheme 3). Recent advances demonstrate the power and extraordinary potential of Kagan's reagent for the mild and selective electron-transfer reduction of functional groups such as carboxylic acids, esters, amides, and nitriles which have limitations and require violent conditions to be transformed.[3]

The various applications of SmI₂-mediated reactions to construct carbon–carbon bonds have been utilized for the development of synthetic strategies in natural product total synthesis due to the remarkable combination of the high reducing ability of this reagent with an extraordinary control of stereochemistry (Scheme 4).

Samarium diiodide (SmI₂) catalyzed intramolecular reductive coupling reactions of ketyl radicals with unsaturated compounds like alkenes, alkynes, and nitriles develop functionalized carbocycles comprising tertiary alcohols. Intramolecular ketyl–olefin coupling reactions produce carbocycles in great yield and favorable diastereoselectivity. The ketyl–allene coupling reaction catalyzed by SmI₂ delivers stereocontrolled, highly functionalized carbocycles and heterocycles. The reaction conditions play an important role in the regioselectivity of free-radical additions to allenes ranging from complete terminal attack to restricted central carbon addition.[9–11] Molander[12] reported also SmI₂-mediated-ketyl cyclizations with allenes to synthesize highly functionalized carbocycles or heterocycles in acceptable to excellent yield and great stereochemical control (Scheme 5).

Molander introduced a pathway that provided increased selectivity for addition to the proximal sp² center, preventing regio- and stereoisomeric product mixtures, and the prospect of leading to sequential reactions (Scheme 6, pathway a). By using HMPA as an additive, the reactions improve sufficiently and when the toxicity of HMPA is a problem, DMPU can be used instead albeit requiring longer reaction times.

The reactions underwent a chair-like transition state regulated by the samarium alkoxide in the pseudoequatorial

**Scheme 6** Reaction pathways of SmI₂-mediated ketyl–allene cyclizations.
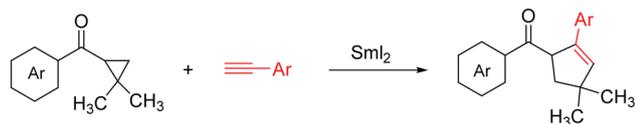
Scheme 7 SmI_2-catalyzed intermolecular coupling of cyclopropyl ketones and alkynes.

position to obtain high diastereoselectivity. The reaction generated two neighboring stereocenters, and the resulting hydroxyl group and alkene moiety can be utilized for additional development. The ketyl–allene coupling can be extended to SmI_2-mediated cascade reactions. In the absence of a hydrogen donor, vinyl radicals are relatively rigid, making them favorable for sequential reactions. The developed SmI_2-catalyzed reactions often desired superstoichiometric amounts of a metal co-reductant to restore the Sm(II) catalyst. Procter[13] recently developed a SmI_2-catalyzed intermolecular radical coupling of aryl cyclopropyl ketones and alkynes to give cyclopentenes using 15–25 mol% of SmI_2 in THF at 45 °C in good to excellent yields without requiring a superstoichiometric co-reductant to regenerate SmI_2. The reactions underwent a reversible single-electron transfer from SmI_2 to the ketone, opening the cyclopropyl ring, intermolecular coupling with the alkan closing of the cyclopentene ring resulting in a ketyl radical. The ketyl radical regenerated the Sm(II) catalyst by transferring an electron back to Sm(III) (Scheme 7).

SmI_2-mediated cascade reactions are remarkable synthetic tools in the total synthesis of natural products and other complex molecules affording ring formation and/or constructing multiple stereocenters. Due to extraordinary properties of samarium(II) iodide such as the excellent functional group

tolerance, high Lewis acidity, fine-tuning the reactivity, the thermodynamic control of single-electron processes, mild reaction conditions, and particularly the ability of this reagent to combine radical and ionic transformations to promote the challenging transformations in any combination or order, it has given rise to this reagent as a crucial tool to achieve the poly-cyclic complex structures bearing multiple stereocenters from simple, linear synthetic precursors *via* one-pot, multistep sequences. Over the past decade in the synthesis of complex natural products, various SmI_2-catalyzed radical cyclizations to develop different radical/anionic sequential strategies have been utilized for the selective synthesis of complex carbocycles bearing quaternary stereocenters. The ability of SmI_2 to mediate both individual reactions in a remarkably particular way and tandem reactions in an equally productive manner has permitted different tandem reactions such as sequential radical reactions, transformations initiated by radical sequences followed by anionic reactions, anionic processes followed by radical reactions and tandem anionic processes to be possible. Several SmI_2 asymmetric reactions in presence of a chiral auxiliary to develop the enantioenriched compounds have also been reported, and are also expected to be a common method for high selectivity. Several C–C bond formations using samarium diiodide as electron-donor in the presence of chiral auxiliary also exist.[3q] In SmI_2-mediated asymmetric reactions, samarium enolates can generate *in situ* which then undergo asymmetric protonation.

The Reformatsky-aldol and the pinacol coupling can be suitable methods to develop asymmetric synthesis considering reasonable synthetic manipulation. Due to the strong oxophilicity of the samarium ion, high stereoselectivities will be achieved using samarium(II) complexes. The intelligent choice of a chiral ligand is important. The suitable ligand should possess
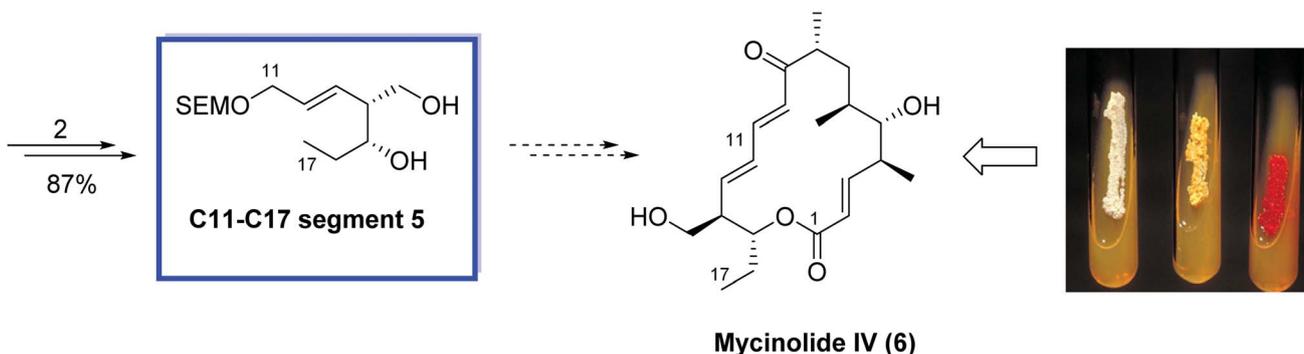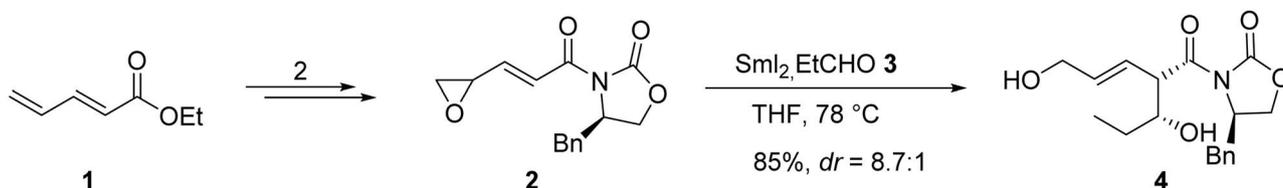
Scheme 8 Enantioselective synthesis of **5** (C11−C17 segment of mycinolide IV (**6**)).

many oxygen or nitrogen atoms to coordinate with the samarium and should not be reducible. The super-stoichiometric amounts of SmI$_2$ and the ligand also has to be considered. The ease of preparation and recyclability of the ligand should also be evaluated in the case of green chemistry and the development of asymmetric catalysis.[3q] Samarium diiodide can be a useful reducing agent in asymmetric synthesis for the mild cleavage of the chiral auxiliaries or certain protecting groups.

In continuation of our interest in total synthesis of natural products,[14] in this reviews we try to underscore the applications of SmI$_2$ in the total synthesis of natural products covering the literature from 2004 to date.

2. Applications of SmI$_2$-mediated reactions in natural products total synthesis

2.1. SmI$_2$-mediated functional groups transformations

Mycinolide IV (**6**),[15] the aglycon of mycinamicin IV, is a 16-membered macrolide antibiotic and was isolated from *Micromonospora griseorubida* sp. nov.[15] In 2005, Mukaiyama and colleagues[16] reported the enantioselective synthesis of the C11–C17 fragment of mycinolide IV using an asymmetric samarium(II) iodide-mediated aldol reaction by installing a chiral oxazolidinone on the unsaturated epoxide. The key steps contain the preparation of samarium enolates by epoxide-
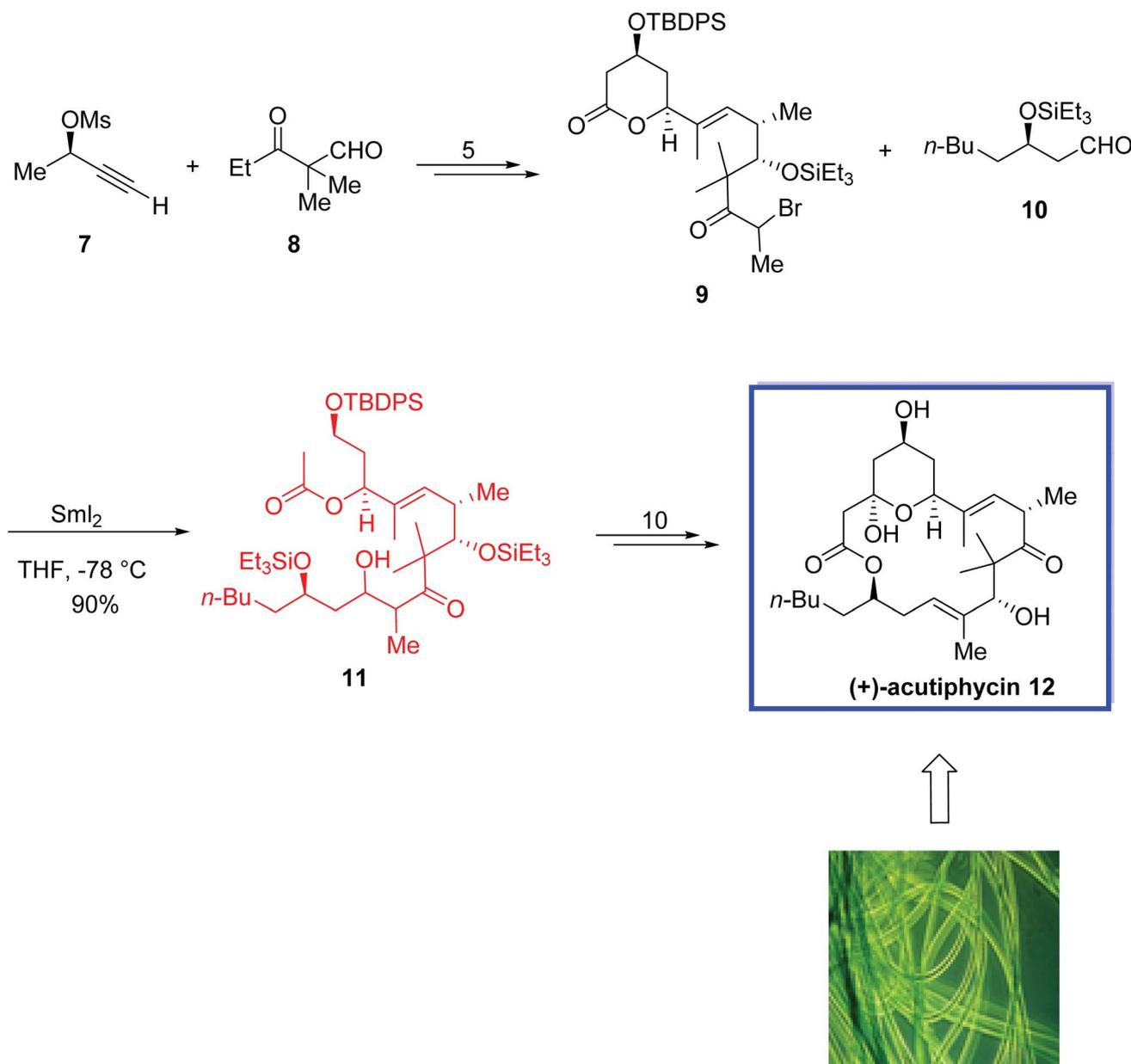
Scheme 9 Total synthesis of (+)-acutiphycin **12**.

fragmentation of, γ.δ-oxiranyl-α,β-unsaturated esters with two moles of SmI$_2$ and a stereoselective synthesis of δ,β'-dihydroxy-β,γ-unsaturated esters by aldol reaction of aldehydes with the samarium enolates. This type of aldol reaction was effectively utilized in the enantioselective synthesis of the C11–C17 segment of mycinolide IV containing two chiral centers and a trans double bond, and in the stereochemical assignment of this compound.

The enantioselective synthesis of **5** (C11–C17 segment of mycinolide IV (**6**)) started with the reaction of 2,4-pentadienoic acid ethyl ester **1** to produce γ.δ-oxiranyl-α,β-unsaturated ester **2** in 2 steps in 52%. Next, an asymmetric SmI$_2$-mediated aldol reaction of **2** and propanal **3** with 2 equiv. of SmI$_2$ at 78 °C provided the aldol adduct **4** in 85% yield and high diastereoselectivity (dr = 8.7 : 1). Compound **4** was then converted to compound **5** in 2 steps and 87% yield (Scheme 8).

The complex macrolide (+)-acutiphycin **12** was originally isolated from the blue-green alga *Oscillatoria acutissima*; however, this alga no longer produces this metabolite. (+)-Acutiphycin **12** shows an antineoplastic effect against murine cancer cells and also exhibits cytotoxicity in contact with KB and NIH/3T3 cell lines.[17]

In 2006, Jamison and colleagues[18] reported a highly convergent synthesis of (+)-acutiphycin **12** in 18 steps and an overall yield of 4.0% from commercial starting materials. Both the relative and absolute stereochemistry of the synthetic (+)-acutiphycin **12** were in good agreement with those reported for the natural product. They used an alkynyl ether for the first time as a macrolactone precursor in total synthesis. They also used an intermolecular, SmI$_2$-mediated Reformatsky reaction as a fragment coupling procedure for the first time. The authors claimed that the developed synthetic route is a standard and compatible synthetic pathway that facilitated the immediate and organized analysis of the structure–activity relationships of (+)-acutiphycin **12**.

The total synthesis of (+)-acutiphycin **12** began with the coupling of alkyne **7** and aldehyde **8** to provide the required α-bromoketone **9** in 5 steps and quantitative yield. While activated
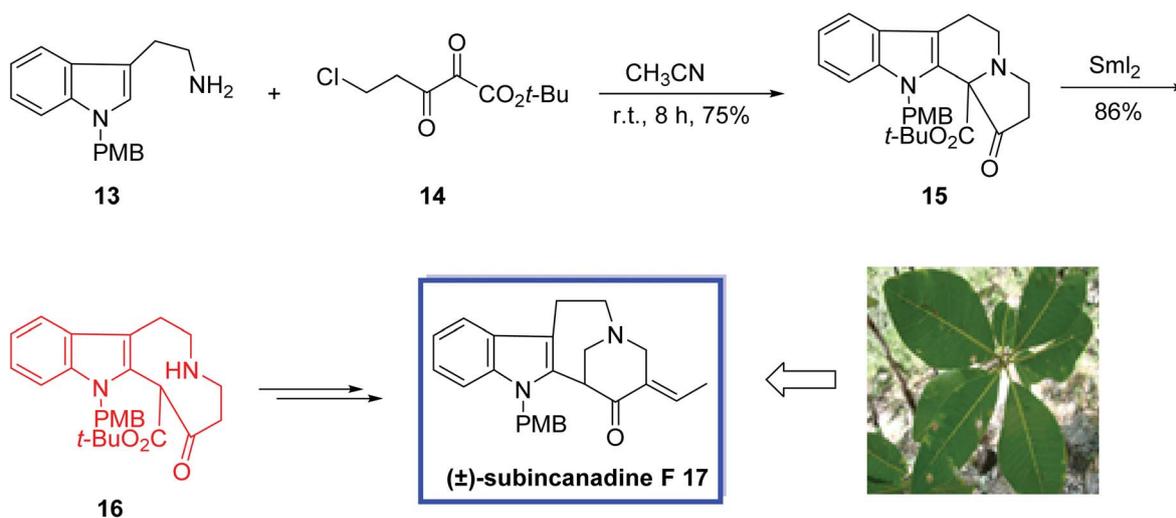
zinc failed to generate the desired enolate, a SmI$_2$-mediated Reformatsky reaction of α-bromoketone **9** and aldehyde **10** afforded the β-hydroxy ketone **11** as a mixture of diastereomers in 90% yield. (+)-Acutiphycin **12** was then synthesized from **11** in 10 steps (Scheme 9).

(±)-Subincanadine F **17**, isolated from the barks of the Brazilian medicinal plant *Aspidosperma subincanum* Mart.,[19] is a bioactive indole alkaloid with cytotoxic activity *in vitro* toward murine lymphoma L1210 cells and human epidermoid carcinoma KB cells. Due to remarkable structural characteristics and extraordinary pharmacological activities of the subincanadine family of alkaloids, they have drawn much interest from synthetic chemists.

In 2006, Zhai and coworkers[20] developed the first total synthesis of (±)-subincanadine F **17**, possessing a 1-azabicyclo [4.3.1]-decane core. The six-step total synthesis of indole alkaloid (±)-subincanadine F **17** began with 1-(para methoxybenzyl) tryptamine **13**, prepared from commercially available tryptamine in one step. Key steps contain a SmI$_2$-mediated ring opening and an acid-mediated Mannich reaction to construct the bridge-containing tetracyclic scaffold of subincanadine F **17**. They also developed the key intermediate tetracyclic ketoester **15** in one step from α,β-diketoester **14**. According to the researchers, the developed strategy to (±)-subincanadine F **17** as well as the synthesized key intermediate tetracyclic ketoester **15** can be potentially useful to synthesize various indole alkaloids with related structures.

A reaction of **13** with α,β-diketoester **14** in acetonitrile at room temperature for 8 h afforded the tetracyclic ketoester **15** in a 75% yield. The tetracyclic core of subincanadine F **17** was easily constructed *via* a samarium diiodide mediated ring-opening of **15** in THF, at r.t. for 3 h and the 6/5/9 tricycle **16** was obtained in 86% yield. Finally (±)-subincanadine F **17** was synthesized from **16** in 3 steps and 28% yield (Scheme 10).

Lactone-containing natural products (6*R*)-6-[(1*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one **23**, (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-

Scheme 10 Total synthesis of (±)-subincanadine F **17**.

2-one **24**, isolated from *Ravensara crassifolia*,[21] belong to the group of 5,6-dihydro-α-pyrone-containing natural products with a substituted arylalkyl side chain at C6. These compounds continue to be of great interest because the β-unsaturated α-pyrones can function as Michael-acceptors for the amino acid residues of receptors. α,β-Unsaturated α-pyrones exhibit various biological activities such as antibacterial, anticancer, antifungal, antifeedant, HIV protease inhibition, and antitumor activities. Compounds **23** and **24** show antifungal activities against the phytopathogenic fungus *Cladosporium cucumarinum*.[22]

Scheme 11 Total synthesis of (6R)-6-[(1E, 4R, 6R)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6 dihydro-2H-pyran-2-one **23** and (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2 one **24**.

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In 2014, Venkateswarlu and colleagues[23] reported an efficient stereoselective total synthesis of the 6-alkylated pyranones $(6R)$-6-[(1E, 4R, 6R)-4,6-dihydroxy-10-phenyldec-1-en-1-yl]-5,6 dihydro-2H-pyran-2-one 23 and $(6S)$-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2 one 24 from commercially available 5-phenylpentan-1-ol 18 and l-aspartic acid 21. The key steps include a SmI$_2$-mediated reduction of alkoxy ketone, a Crimmins aldol reaction, and a Grubbs-II-catalyzed olefin crossmetathesis. The spectral data and optical rotation of the synthetic compounds 23 and 24 were in good agreement with those of the natural product. The synthesis of 23 started from 5-phenylpentan-1-ol 18 to provide the ketone 19 in 5 steps and 90% yield. Treatment of 19 with SmI$_2$ in THF and MeOH for 12 h resulted in a stereoselective reduction of the oxo group to the desired anti-1,3-diastereoisomer 20 as the major product in 76%

yield. Compound 20 was then reacted with 5,6-dihydro-6-vinyl-α-pyrone 22, which was prepared from l-aspartic acid 21 in 6 steps and 80% yield, to afford 23 in 2 steps and 78% yield. The natural product 24 was also prepared in 7 steps starting from 5-phenylpentan-1-ol 18 and resulted in a separable mixture of the natural product 24 and bicyclic lactone 25 (7 : 3) in 78% yield (Scheme 11).

Hydroxy(methyl)tetrahydronaphthalene and methoxy(methyl)tetrahydronaphthalene are known classes of natural products with various biological activities.[24] The (+)-aristelegone A 34, (−)-aristelegone B 28, and (−)-aristelegone D 30, isolated from *Aristolochia elegans*; (+)-methylaristelegone A 33 (antispasmodic), isolated from *Aristolochia constructa*;[25] (+)-heritonin 31 and (+)-heritol 32, isolated from *Heritiera littoralis*; (+) mutisianthol 35 (antitumor), isolated from *Mutisia*
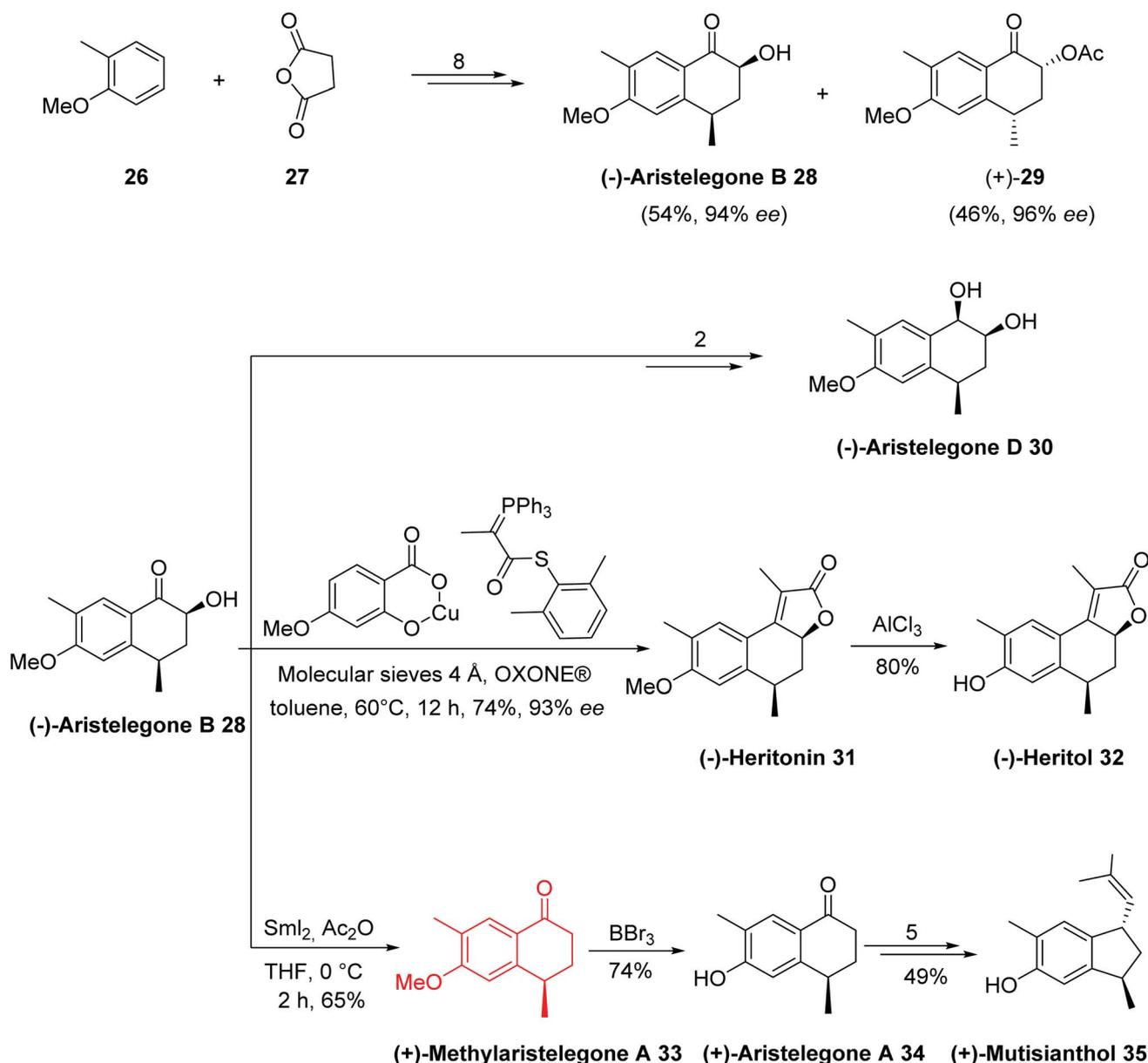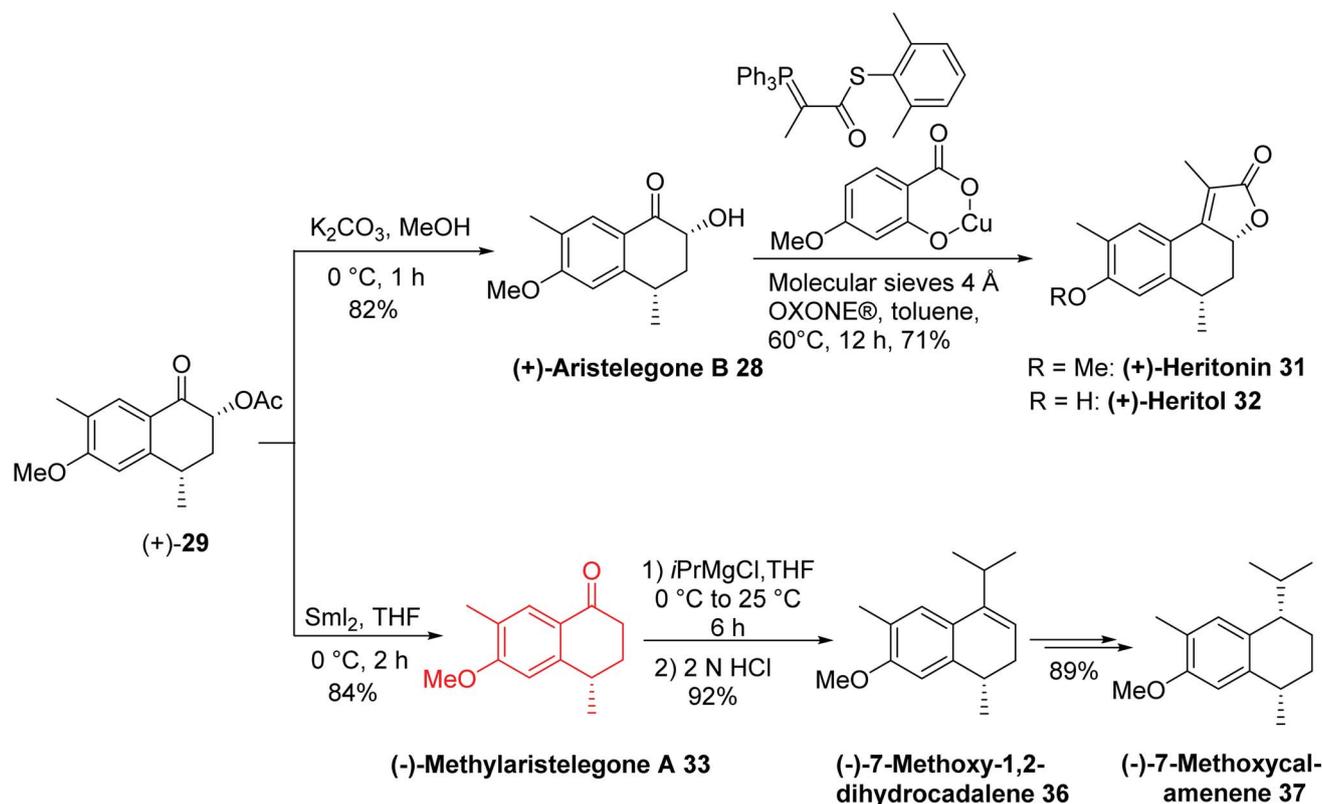

Scheme 12 Total synthesis of tetrahydronaphthalene-based natural products 28–35.

homoeantha;[26] and (−)-7-methoxy-1,2-dihydrocadalene **36** and (−)-7-methoxycalamenene **37**, isolated from a *Heteroscyphus planus* culture[27] belong to the hydroxy(methyl)tetrahydronaphthalene class of natural products.

In 2015, Argade and coworkers[28] developed the chemoenzymatic total synthesis of nine bioactive tetrahydronaphthalene-based natural products using antipode (−)/(+)-aristelegone B **28** as a single common precursor. Both (+)/(−)-isomers as potential building blocks were prepared through the late-stage efficient enzymatic resolution. It was planned to employ (±)/(+)/(−)-**28/29** as

key building blocks bearing well-positioned substituents and necessary functional groups to achieve the stereoselective collective synthesis of target compounds. The key steps were SmI₂-mediated deoxygenations, the *syn*-selective installation of hydroxyl groups at the α-position of the ketone component, a sequence of acylation-Wittig reactions, regioselective benzylic oxidations, enantiomerically pure enzymatic resolutions, and stereoselective reductions. The analytical and spectral data, obtained for the synthetic product, were in good agreement with those reported for the natural product (−)-**28**.

Scheme 13 Total synthesis of tetrahydronaphthalene-based natural products **28**–**37**.

The total synthesis of all assigned target compounds began with the reaction of 2-methylanisole **26** and succinic anhydride **27** to obtain (−)-aristelegone B **28** (54% yield, 94% ee) and (+)-acylaristelegone B **29** (46% yield, 96% ee) in 8 steps. The natural product (−)-aristelegone D **30** was obtained from (−)-aristelegone B **28** within two steps in 84% yield; therefore, the first chemoenzymatic synthesis of (−)-aristelegone D **30** was achieved in ten steps with an 8% overall yield. Tandem acylation-Wittig reaction of (−)-aristelegone B **28** provided (−)-heritonin **31** in a 74% yield (93% ee) and 8% overall yield in nine steps without any racemization. Treatment of (−)-heritonin **31** with AlCl₃ provided (−)-heritol **32** in 80% yield. Cleavage of the hydroxyl group of (−)-aristelegone B **28** with samarium iodide provided (+)-methylaristelegone A **33** in a 65% yield. Further treatment of (+)-methylaristelegone A **33** with BBr₃ gave (+)-aristelegone A **34** in a 74% yield, from which (+)-mutisianthol **35** was then synthesized by a known procedure in 5 additional steps. To synthesize (−)-7-methoxy-1,2-dihydrocadalene **36**, (−)-7 methoxycalamenene **37** and (+)-heritonin **31**, the second enantiomerically pure building block (+)-acylaristelegone B **29** was selected, which was achieved via enzymatic resolution. Cleavage of the acetoxy group of (+)-acylaristelegone B **29** by samarium iodide furnished (−)-methylaristelegone A **33** in an 84% yield. The reaction of isopropylmagnesium bromide with (−)-methylaristelegone A **33** followed by acid-catalyzed in situ dehydration of the formed intermediate tertiary alcohol yielded another natural product, (−)-7-methoxy-1,2-dihydrocadalene **36**, in a 92% yield; therefore, the first chemoenzymatic synthesis of (−)-7-methoxy-1,2-dihydrocadalene **36** was accomplished in ten steps with an 8% overall yield. An enantioselective reduction of the naturally-isolated natural product (−)-**36** gave (−)-7-methoxycalamenene **37** via known procedure. Base-induced deacylation of compound (+)-**29** to establish (+)-aristelegone B **28**, followed by a similarly performed tandem acylation-Wittig reaction provided the natural product (+)-heritonin **31** in a 71% yield. The diastereoselective synthesis of the common precursor (±)-aristelegone B **28** and its efficient enzymatic resolution allowed for the syntheses shown below in Schemes 12 and 13.

(−)-Securinine **43** and (−)-14,15-dihydrosecurinine **44**[29] were isolated from the roots of *Securinega suffructicosa*,[30] and belong to the Securinega alkaloids[31] with a wide range of pharmacological activities. They have received considerable attention from the synthetic community. Most securinine-type alkaloids are characterized by possessing a unique tricyclic skeleton with an α,β-unsaturated-γ-lactone ring that exists only in the Euphorbiaceae in species *Phyllantus* and *Securinega*.[32] (−)-Securinine **43** is the major component of the alkaloid fraction in *S. suffruticosa* and is a potential central nervous system (CNS) stimulant that shows antimalarial, antibacterial, and cytotoxic activities.[33] (−)-14,15-Dihydrosecurinine **44** is also a potent CNS stimulant and an acute poison,[30] and has potent inhibition activities against [3H]GABA[34] and AChE.[35]

In 2015, Zheng and coworkers[36] developed the total synthesis of (−)-14,15-dihydrosecurinine **44** in 12 steps in an overall yield of 14.4%. They also reported the total synthesis of (−)-securinine **43** in 10 steps in an overall yield of 20.2% from the

intermediate **42**. The key steps contain a six-step procedure to construct the piperidine ring A, a SmI₂-induced reductive coupling reaction for the diastereoselective construction of α-hydroxy-6-azabicyclo[3.2.1]octanone and an intramolecular olefination reaction to form the butenolide ring D. The spectral data of **43** and **44** were in good agreement with those previously reported and the enantiopurity of the synthetic 14,15-dihydrosecurinine **44** was greater than 99% ee.

The total synthesis of (−)-14,15-dihydrosecurinine **44** and (−)-securinine **43** started from optically pure maleimide **38** to obtain imides **39a** and **39b** in 4 steps and 92% yield.

Reduction of **39a**/**39b** with DIBAL-H, followed by SmI₂-induced reductive radical coupling with acrylonitrile provided the desired stereoisomer **40** as the major product in a diastereomeric mixture of **40a**/**40b** (d.r. = 75 : 25 for **40a**, d.r. = 88 : 12 for **40b**). Of note, SmI₂-mediated debromination of **39a** occurred if the reaction occurred at a temperature above −40 °C. Compound **40a** was then converted into ketonitrile **41** in 2 steps. Treatment of compound **41** with excess SmI₂ in methanol afforded the cyclized product **42** as a single diastereoisomer in 75% yield, from which (−)-securinine **43** and 14,15-dihydrosecurinine **44** were synthesized in 4 and 3 steps, respectively (Scheme 14).

The vicinal amino alcohol motif occurs in various biologically active natural products, and several bioactive long-chain vicinal amino alcohols such as obscuraminol A **48** have been isolated from marine sources. The sphingolipid class of natural products obtained from long-chain vicinal amino alcohols with the 1-deoxygenated sphingosine core occurs in marine invertebrates, particularly in marine ascidian.[37] Obscuraminol A **48** is a vicinal *anti*-amino alcohol that belongs to the class of sphingoids possessing a polyunsaturated *Z*-skipped side chain in their structure. Obscuraminol A **48** retains the same (2*S*,3*R*)-configuration as spisulosine and was isolated from the chloroform extracts of the marine ascidian *Pseudodistoma obscurum*.[38] This class of substances exhibits several bioactivities such as cytotoxicity, antimicrobial, and antifungal effects.[39]

In 2016, Hansen and colleagues[40] reported the first stereoselective synthesis of the polyunsaturated amino alcohol natural product obscuraminol A **48** in 6% overall yield over 11 steps from the ethyl ester of eicosapentaenoic acid **45**. The key steps were an *anti*- and enantioselective organocatalyzed Henry reaction and a challenging chemoselective SmI₂-mediated reduction of a nitro-group in the Henry product. The configuration of the four *Z*-skipped double bonds of synthesized obscuraminol A **48** was maintained by the starting material, *i.e.*, the ethyl ester of (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid. The synthesized obscuraminol A **48** was in complete agreement with the natural product.

The stereoselective synthesis of obscuraminol A **48** started with the ethyl ester of (all-*Z*)-eicosa-5,8,11,14,17-pentaenoic acid **45** to obtain the (2*S*,3*R*)-nitroaldol **46** in 94% yield and good diastereoselectivity (*anti/syn* 11.5 : 1) in 8 steps. Reduction of vicinal nitroaldols **46** into related amino alcohols with common methods was not successful; therefore, they tried the previously reported SmI₂-mediated reduction method on the nitroaldol product **46**. Treatment of **46** with SmI₂ in MeOH/THF/H₂O gave
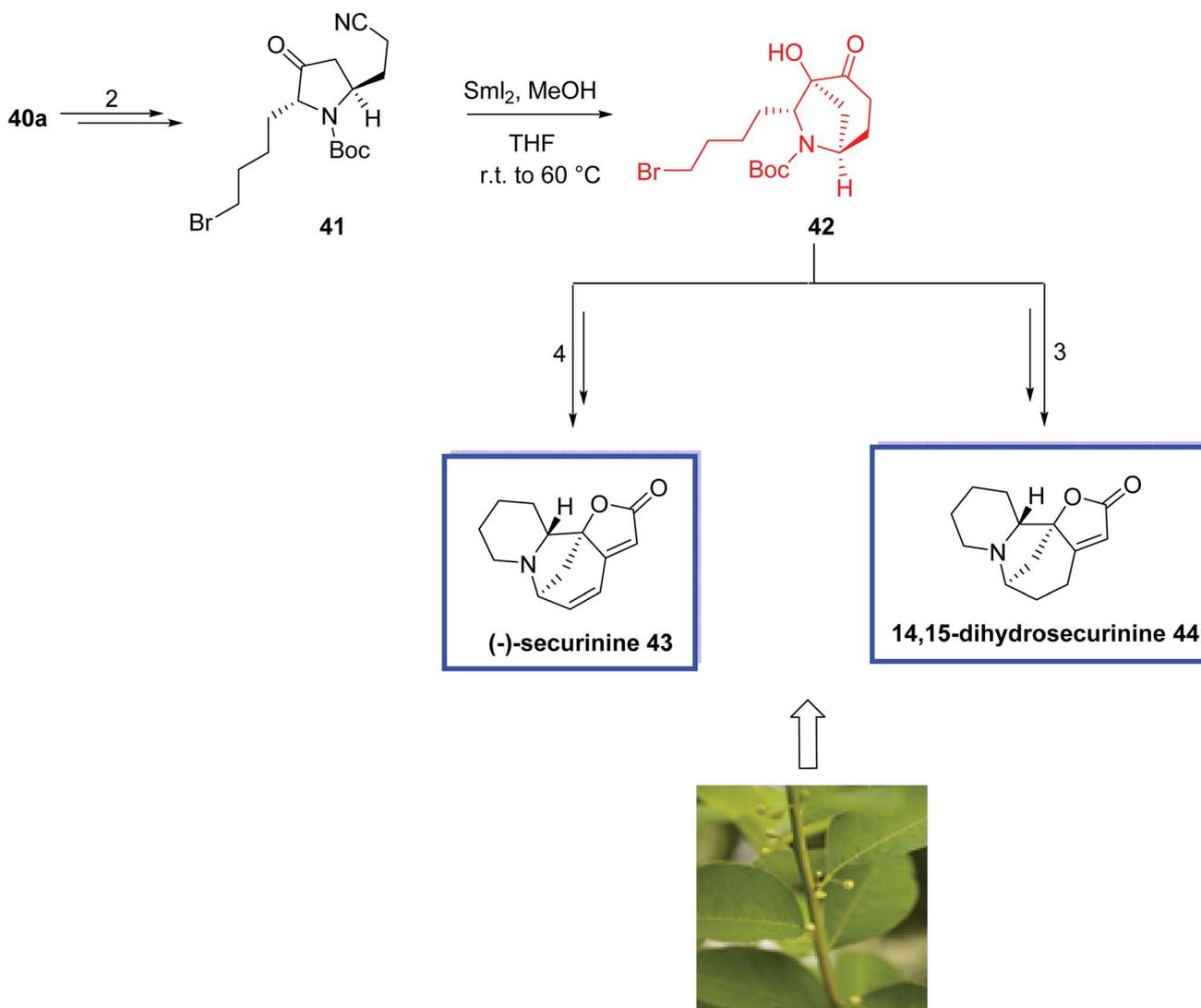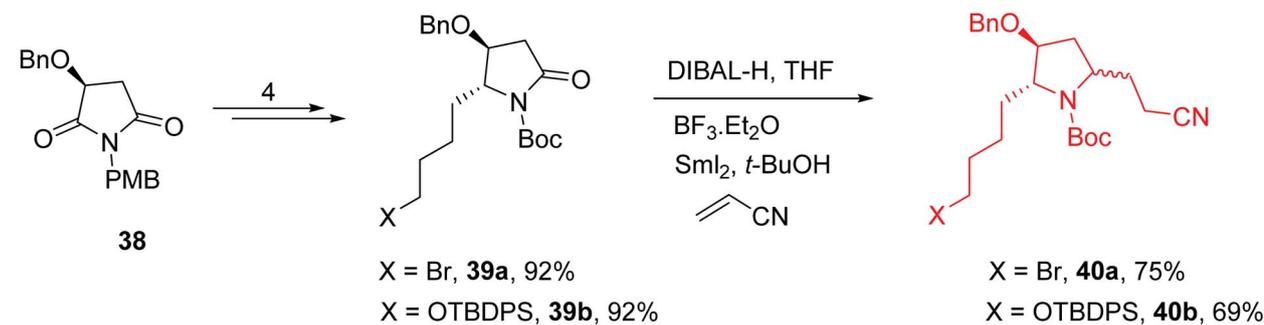
Scheme 14 Total synthesis of (−)-securinine **43** and (−)-14,15-dihydrosecurinine **44**.

the desired amino-alcohol **48** in 60% yield together with the hydroxylamine **47** as a by-product. Increasing the reaction time and molar equivalents of SmI_2 to 10 equivalents did not affect the full conversion to the target molecule **48**. The synthesized obscuraminol A **48** validated the assigned structure of the natural product **48**. With lower diastereoselectivity than anticipated from the starting material defined to be 5.2 : 1 in favor of

the desired *anti*-isomer and the absolute configuration of the stereogenic centers in **48** to be 2S,3R as initially allocated, this provided evidence for the initial assignment of the relative configuration of **46** also as *anti*. Hence, the absolute configuration of the stereogenic centers in **48** is indeed 2S,3R as originally assigned (Scheme 15).
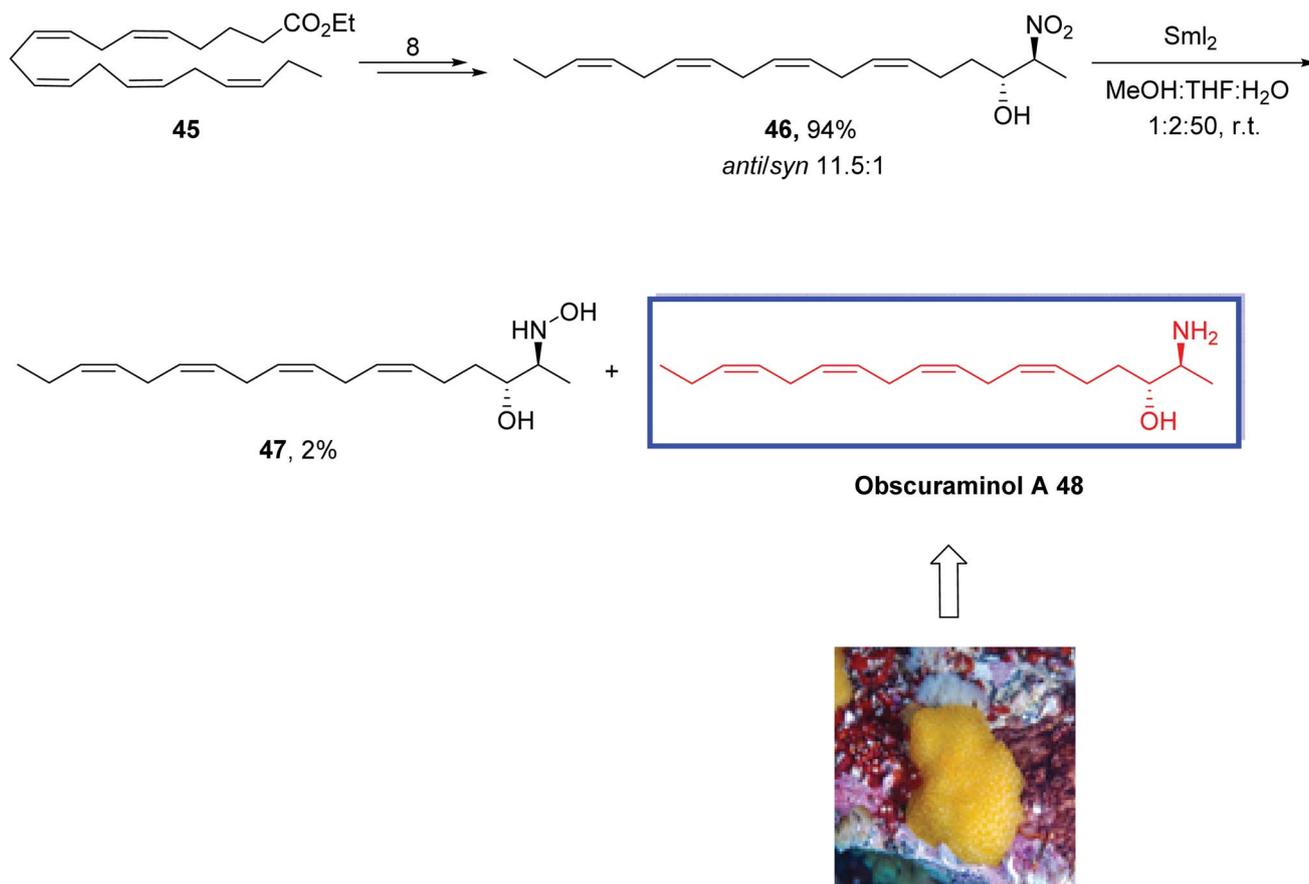
Scheme 15 Total synthesis of obscuraminol A **48**.

Araiosamines A–D were isolated from the methanol extract of a marine sponge, *Clathria* (*Thalysias*) *araiosa*.[41] They relate to a small family of unusual marine alkaloids with extraordinary structures with two guanidine units, three bromoindole heterocycles and six contiguous stereocenters.

In 2016, Baran and coworkers[42] reported the total synthesis of araiosamine A **52** and araiosamines C–D **54–55** in 11 steps. Key steps featured the installation of guanidine through a new chemoselective reagent, a SmI$_2$-mediated stereoselective reduction, chemo- and stereoselective C–H functionalization, and a simple final step to synthesize the biosynthetic intermediate. The absolute configuration of these natural araiosamines was not assigned; therefore, they synthesized (+)-araiosamine C **54**, which was found to be the natural enantiomer, in reference to the optical rotation. They show that the synthetic araiosamines A,C, and D, **52**, **54**, and **55**, respectively, exhibit significant antibacterial activities against both Gram-positive and -negative bacteria.

The total synthesis of araiosamines A, C, and D (**52**, **54**, **55**) began with the commercially available 6-bromotryptophol **49** to obtain oxime **50** in 8 steps. The reduction of the oxime in **50** was a challenging step due to the sterically placed oxime moiety and the existence of other functional groups being prone to be reduced. Using lithium aluminum hydride and sodium or different combinations of sodium borohydride and metal salts

caused debromination. Alone, the combination of SmI$_2$ and H$_2$O reduced oxime **50** to primary amine **51** stereoselectively, from which araiosamine A **52** and 1-*epi*-araiosamine A **53** were then obtained in several steps. Heating the mixture of **52** and **53** resulted in araiosamines C **54** and D **55** (Scheme 16).

Honokiol **59**, isolated from the bark of *Magnolia officinalis*, is a neolignan, which exhibits a significant range of promising biological activities such as antitumor[43] and anti-angiogenic[44] activities. Honokiol **59** was isolated together with its isomeric compound magnolol[45] with similar physical properties, but with different bioactivities.

In 2016, O'Neil and colleagues[46] reported the total synthesis of the honokiol **59** in 4 steps and 42% overall yield. The key steps were a Suzuki coupling to construct the biphenyl core and a samarium-mediated bis-benzoyl ester reduction to install both allyl groups at the same time at the last stage to avoid problems related to allylic deprotonation or isomerization.

This total synthesis demonstrates the capability of this samarium diiodide for organic synthesis, establishing sensitive olefins without any unwanted isomerization. It was anticipated that the procedure could be scaled up for more biological investigations.

The total synthesis of honokiol **59** began with the commercially available aldehyde **56** which was utilized to obtain intermediate diol **57** in 3 steps. Acylation of **57** with benzoyl chloride
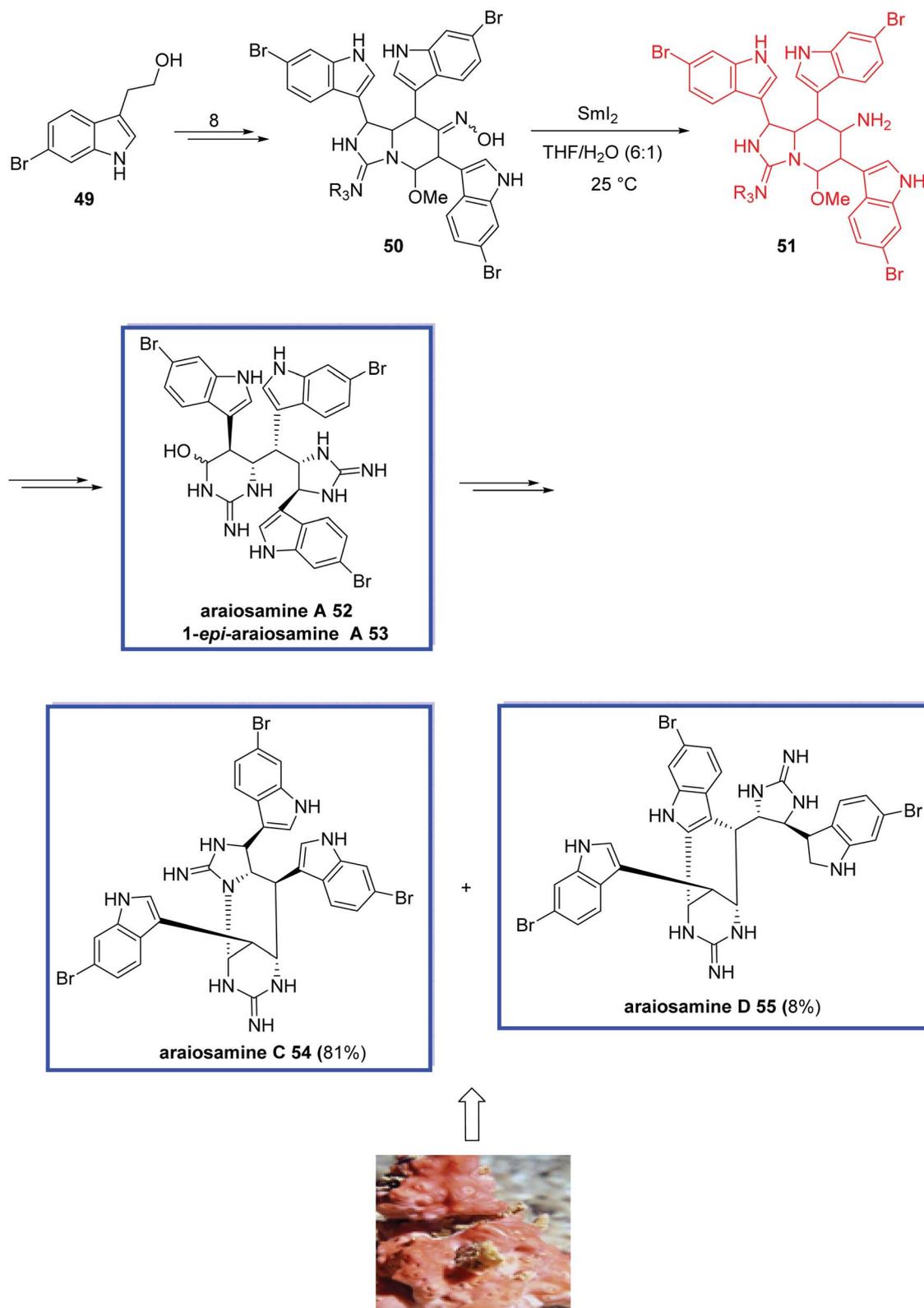
Scheme 16 Total synthesis of araiosamine A **52**, araiosamine C **54**, and araiosamine D **55**.

and reduction of both benzoyl esters with $SmI_2/MeOH$ provided dimethylhonokiol **58** in 98% yield and >10 : 1 selectivity for both nonconjugated allyls substituents (Scheme 17).

The sorbicillins belong to the class of polypeptide metabolites derived from fungi.[47] They exhibit considerable structural variety and biological activities.[48] Rezishanone C **66** relates to
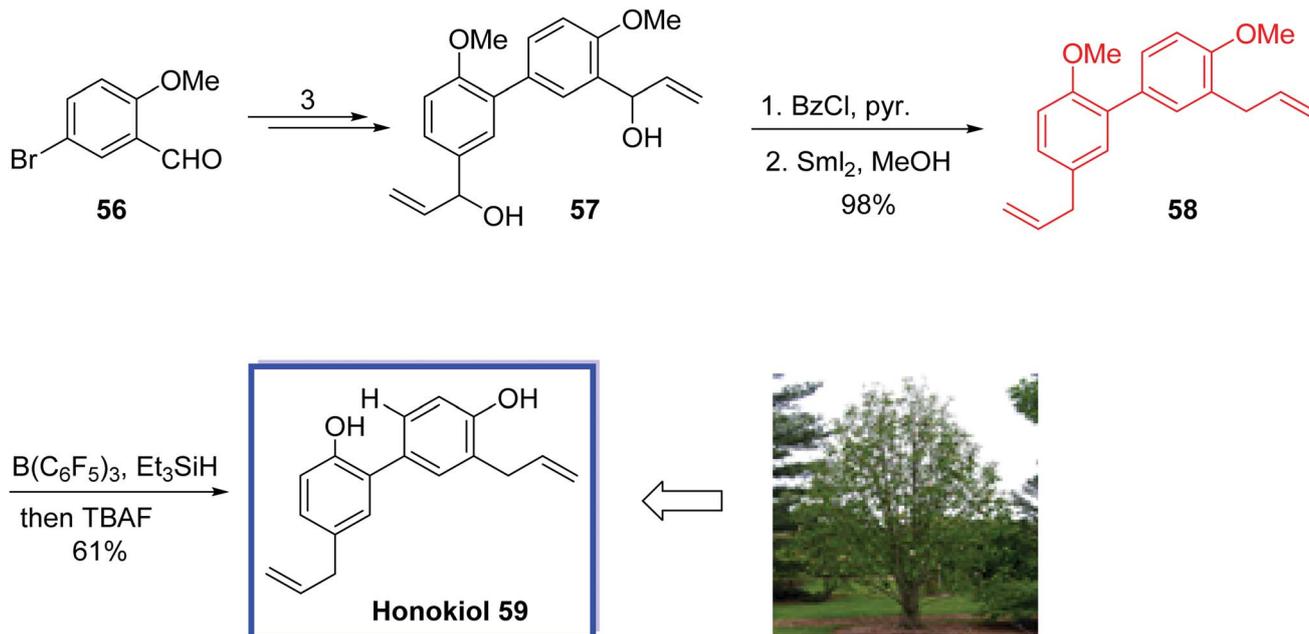
Scheme 17 Total synthesis of honokiol **59**.

a hybrid sub-type[48a] of sorbicillins, which is generated *via* a Diels–Alder reaction between sorbicillinol and several non-sorbicillinoid-derived compounds with a dienophilic residue. In the case of rezishanone C **66**, it has been proposed that an ethyl vinyl ether group is the dienophile included.

In 2017, Banwell and colleagues[49] reported the total synthesis of target compound *ent*-**66**, the enantiomer of the true structure of the sorbicillinoid rezishanone C **66** (sorbivinetone), from a homochiral *cis*-1,2-dihydrocatechol **60**. All the spectral data of compound *ent*-**66** were in complete agreement with the assigned structure and the specific rotation was also comparable but opposite sign to the reported data for rezishanone C **66**. Therefore, they reported the total synthesis of *ent*-rezishanone C (*ent*-**66**) and instead of the originally illustrated structure, compound **66** was demonstrated as the correct structure for rezishanone C **66**. They performed dispersion-corrected DFT calculations to approximate the transition state energies that correlate with the different possible modes of Diels–Alder cycloaddition occurring between sorbicillinol and ethyl vinyl ether. These calculations proposed that the most energetically favorable reaction path was directly to compound **66** instead of the already proposed structures.

The total synthesis of rezishanone C **66** commenced from homochiral *cis*-1,2-dihydrocatechol **60** to convert into the desired ethyl ether **61** in 13 steps, which included several key structural components of the scaffold of *ent*-rezishanone C **66**.

Compound **61** was then subjected to dihydroxylation to obtain a mixture of diols **62** (22%) and **63** (68%), which were separated by chromatography. Diol **63** was then converted into the desired ketone **64** in 7 steps (79%) from which the target *ent*-**66** was synthesized in 3 steps and 52% yield. Diol **62** was also converted into ketone **64** by first converting to ketone **65** in 89% yield over 2 steps. Then treatment of ketone **65** with samarium

diiodide in THF provided ketone **64** in 93% yield. An additional four steps led to *ent*-rezishanone C **66** (Scheme 18).

Pyrrole-containing natural products, isolated from terrestrial and marine origins,[50] show a various range of applications and diverse interesting biological activities such as antimalarial, antifungal, antibacterial, anticancer, antiprotozoal, *etc.*[50] Chlorizidine A **72**, a new pyrrole-containing natural product, was isolated from *Streptomyces* sp. strain CNH-287 and exhibits significant cytotoxicity against HCT-116 adenocarcinoma cell line.[50g] Chlorizidine A **72** retains the 5*H*-pyrrolo[2,1-*a*]isoindol-5-one scaffold, which was found for the first time in the field of natural products and is perhaps responsible for the cytotoxicity.

In 2017, Mhaske and coworkers[51] developed the first total synthesis of the methyl-protected (±) chlorizidine A **72** in 10 steps. The key steps were a Pd-catalyzed decarboxylative coupling Mitsunobu reaction and a samarium iodide-mediated Reformatsky reaction to synthesize the unique 5*H*-pyrrolo[2,1-*a*]isoindol-5-one ring and 2,3-dihydropyrrolizine scaffold. Chlorizidine A **72** is highly prone to degradation; hence, the methyl group of (±)-chlorizidine A **72** was protected. The spectral and analytical data of the synthesized methyl-protected chlorizidine A **72** were in complete agreement with the reported data, which confirms the structure of the isolated natural product chlorizidine A **72**. The designed synthetic route is suitable to synthesize other potential analogues for structure–activity relationship analyses.

The total synthesis of the methyl-protected (±)-chlorizidine A **72** began with the reaction of dichloro ester **67** and alcohol **68**, which were coupled and transformed to the desired aldehyde **69** within 6 steps. With aldehyde **69** in hand, they installed the 2,3-dihydropyrrolizine ring system through the effective use of a samarium iodide-mediated Reformatsky reaction with bromoketone **70** in THF under reflux to synthesize the β-hydroxy
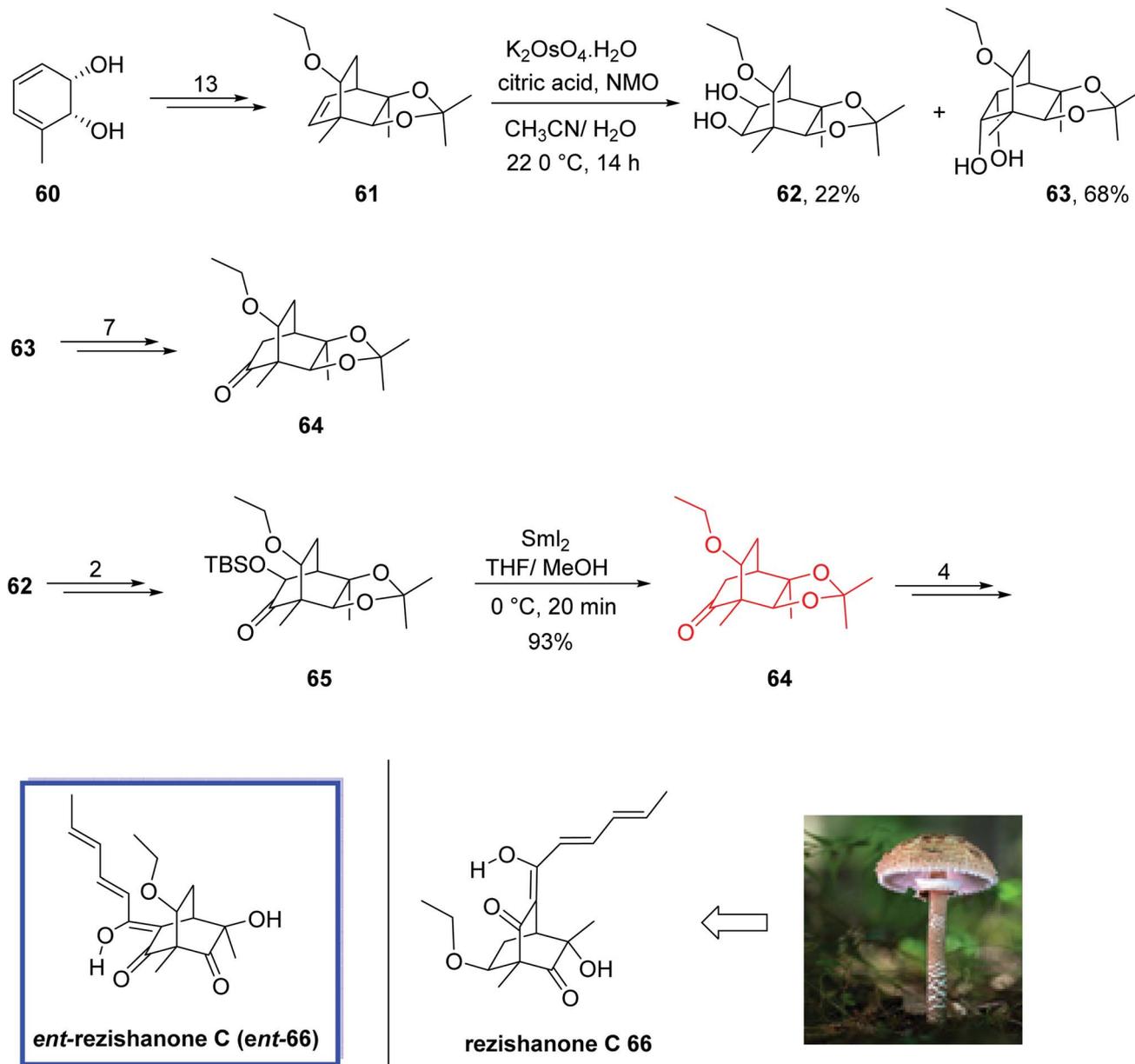
Scheme 18 Total synthesis of *ent*-rezishanone C (*ent*-**66**).

ketone **71** in 70% yield. The methyl-protected (±)-chlorizidine A **72** was then synthesized in 3 steps (Scheme 19).

Kedarcidin **77**, isolated from *Streptoalloteichus* sp. ATCC 53650 (not Saccharothrix),[52] is a nine-membered cyclic enediyne, in which an alkene directly is attached to two alkynyl appendages. The kedarcidin chromophore is a highly unstable natural product. It consists of an ansa-bridged enediyne chromophore and an apoprotein that stabilizes the toxin in the Actinomycete.[52] Kedarcidin **77** is a chromoprotein antitumor antibiotic and shows selective *in vivo* antitumor activity against P388 leukemia and B16 melanoma cells.[52]

In 2019, Lear and coworkers[53] reported the total synthesis of Myers' structure of the kedarcidin chromophore **77** in 17 steps from gram-scale intermediates. Key steps contain

a stereoselective epoxyalkyne formation, an α-selective glycosylation, a Mitsunobu aryl etherification to establish a steric 1,2-*cis*-configuration, a Sonogashira–Shiina cyclization sequence, a Ohfune-mediated amidation, a Ce(III)-mediated nine-membered enediyne cyclization, and a SmI$_2$-mediated reductive olefination. HRMS data of the synthetic natural product **77** was achieved for the first time.

The total synthesis of kedarcidin **77** began with the iodocyclopentenone **73** as its C10-OSET silyl ether to establish the nine-membered enediyne cyclisation and to prepare C4–O-trifluorobenzoate (TFBz) ester **74** or **75** in 15 steps. Deoxygenation of **74** or **75** by SmI$_2$ in THF at −20 °C for 5–10 min gave olefin **76**. Finally, deprotection of **76** under buffered hydrogen
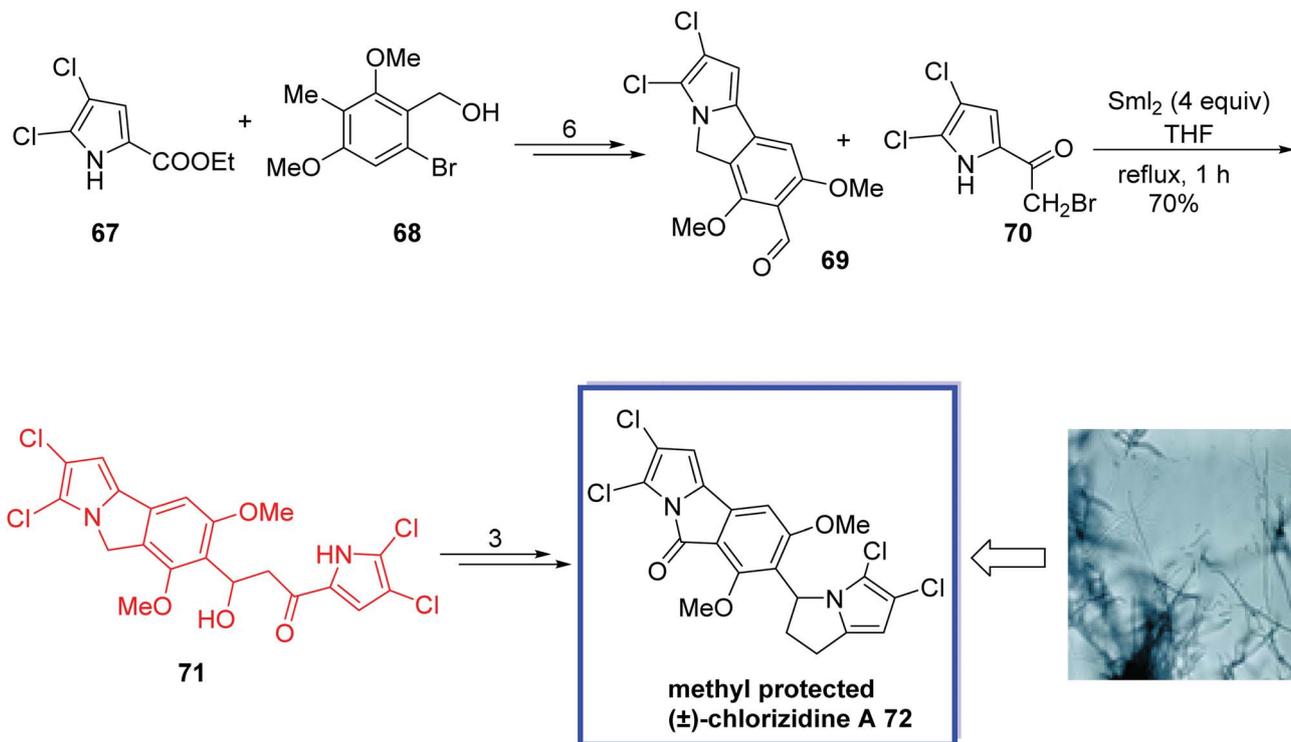
Scheme 19 Total synthesis of methyl-protected (±)-chlorizidine A **72**.

fluoride conditions resulted in kedarcidin chromophore **77** (Scheme 20).

Rumphellclovanes E **82**, a rare marine natural product and family member of clovane-type sesquiterpenoids, was isolated from the gorgonian coral *Rumphella antipathies*.[54] Clovane-type sesquiterpenoids comprise a tricyclo[6.3.1.01,5]dodecane ring system including three to five stereocenters, of which at least two of them are quaternary centers.

Clovane-type sesquiterpenoids exhibit several biological properties such as inhibition of superoxide anion and elastane, produced by human neutrophils,[54] and inhibition of embryonic hippocampal and cortical neurons enlargement.[55]

In 2021, Liu and coworkers[56] reported the first asymmetric total synthesis of rumphellclovane E **82**, in eight steps from commercially available (*R*)-carvone **78** *via* a B–AB–ABC sequence. Key steps included a SmI$_2$-mediated chemo- and diastereoselective reduction of the cyclopentanone to install the desired stereocenter at C2, an iron-catalyzed intramolecular reductive aldol reaction to construct ring C, and a Rh-catalyzed cyclopropanation to construct ring A. The structure of rumphellclovane E was confirmed by X-ray crystallographic analysis. ^{1}H and ^{13}C NMR data of synthetic rumphellclovane E **82** were in good agreement with those of the natural product. However, the optical rotation of the synthetic **82** was different from that of natural product probably because of the insufficient quantity attained from nature. According to the authors, the developed total synthesis will be a general strategy to synthesize the clovane-type sesquiterpenoids.

The total synthesis of rumphellclovane E **82** began with the reaction of (*R*)-carvone **78** and the diazo compound **79** to afford

ketone **80** in 7 steps and 86% yield. Treatment of **80** with SmI$_2$ in THF/H$_2$O (10 : 1) at 0 °C provided the reduction product **81** in 76% yield. The slow addition of diluted SmI$_2$ solution (0.1 mol L^{-1} in THF) in this step was especially important for sufficient yield. Finally, TBS deprotection of the hydroxyl at C9 in **81** using HF·Et$_3$N (10 : 1, v/v) in THF at room temperature delivered rumphellclovane E **82** in 86% yield. Rumphellclovane E **82** was also synthesized in 100 mg-scale in one pot from **80** in 67% yield (Scheme 21).

2.2. SmI$_2$-mediated cyclization reactions

Miharamycins A **87** and B **88**, isolated from *Streptomyces miharaensis* SF-489, are novel 2-aminopurinyl peptidyl nucleoside antibiotics (PNAs) with complex nine-carbon core saccharides and N5-hydroxyarginine. They show significant inhibition effects for the rice blast disease caused by *Pyricularia oryzae*.[57]

In 2008, Blériot and colleagues[58] reported the relative configuration at C-6′ of miharamycin A **87** and the structure of miharamycin A **87** was confirmed. They also attempted to develop the first total synthesis of miharamycin B **88**. They synthesized the remarkable core structure of miharamycin B **88**, though efforts to deprotect the core structure **86** failed to provide the miharamycin B **88**. The key steps contained a SmI$_2$-mediated keto–alkyne coupling to construct the bicyclic sugar moiety and the regio- and stereoselective *N*-glycosylation to form the nucleosidic part of miharamycin B **88**. According to the researchers, the reported synthetic route could be applied to synthesize structurally similar nucleoside natural products, like amipurimycin. First, the relative configuration at C-6′ of miharamycin A **87** was determined. Since both antibiotics have
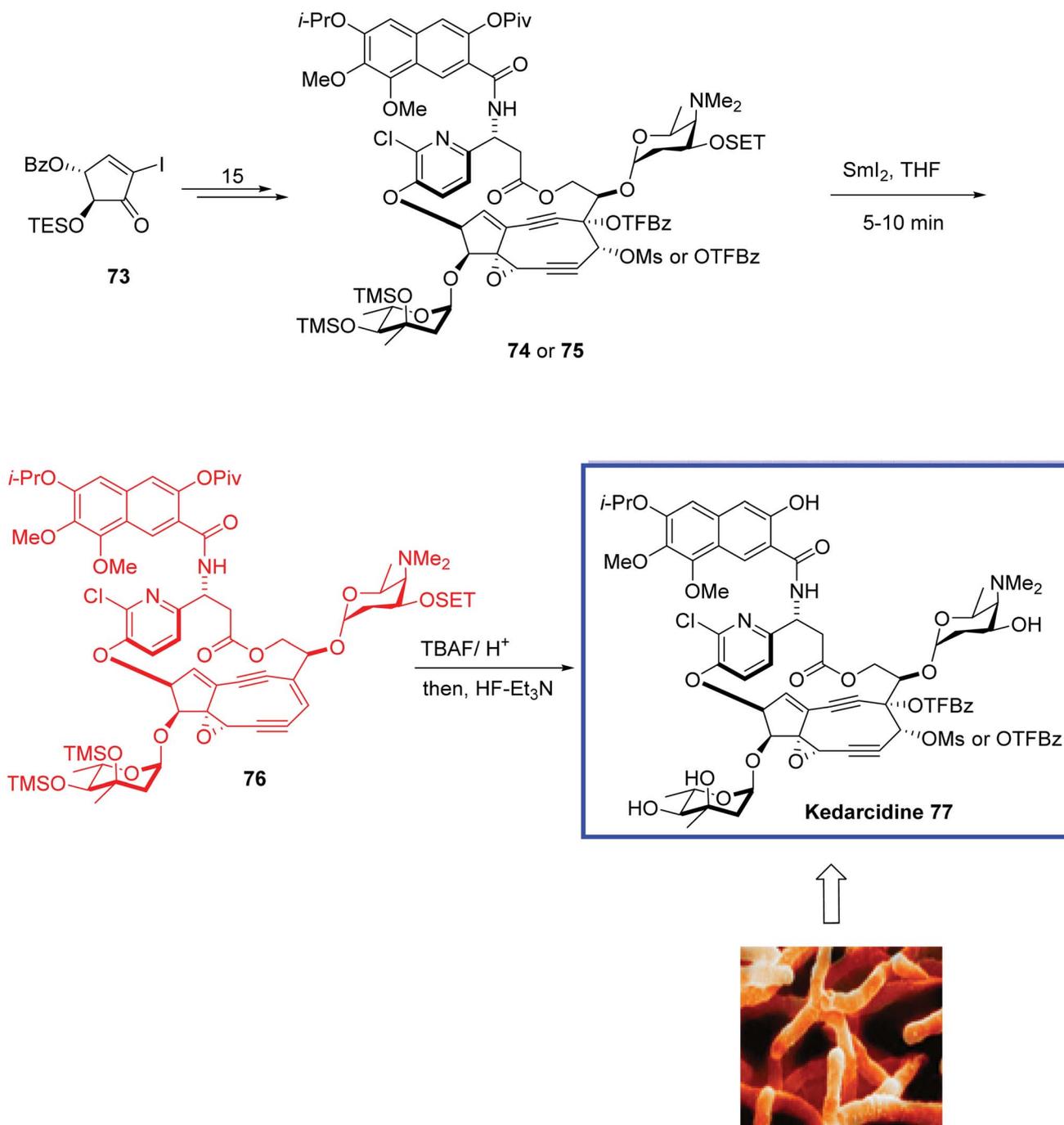
Scheme 20 Total synthesis of kedarcidin **77**.

been isolated from the same microorganism and most of the peptidyl nucleoside family of antibiotics retain *S*-configured natural amino acids, they proposed the *S*- configuration at C-6′ of both miharamycins A **87** and B **88**.

The total synthesis of miharamycins B **88** began with the SmI$_2$-mediated 5-*exo*-dig ketyl–alkyne cyclization of α-propargyloxy ketone **83** in the presence of hexamethylphosphoramide (HMPA) and *t*BuOH at room temperature to give the desired exoalkene **84** in 94% yield. The desired C-6 (*S*)-azido ester **85** was then synthesized from **84** in 6 steps and 82% yield.

Compound **85** was then converted into *N*-benzyloxycarbonyl-protected miharamycin B core **86** in 4 steps and 70% yield (Scheme 22).

(−)-GB 13 **96**[59] and (+)-GB 16 **97**,[60] isolated from the bark of *Galbulimima belgraveana*, belong to the gabulimima alkaloid natural products. GB alkaloids have held the attention of the organic synthesis community due to the extraordinary structures of these alkaloids, but also in the pharmaceutical industry, particularly because the *Galbulimima belgraveana* bark has been used as a medicine and some of the members of these
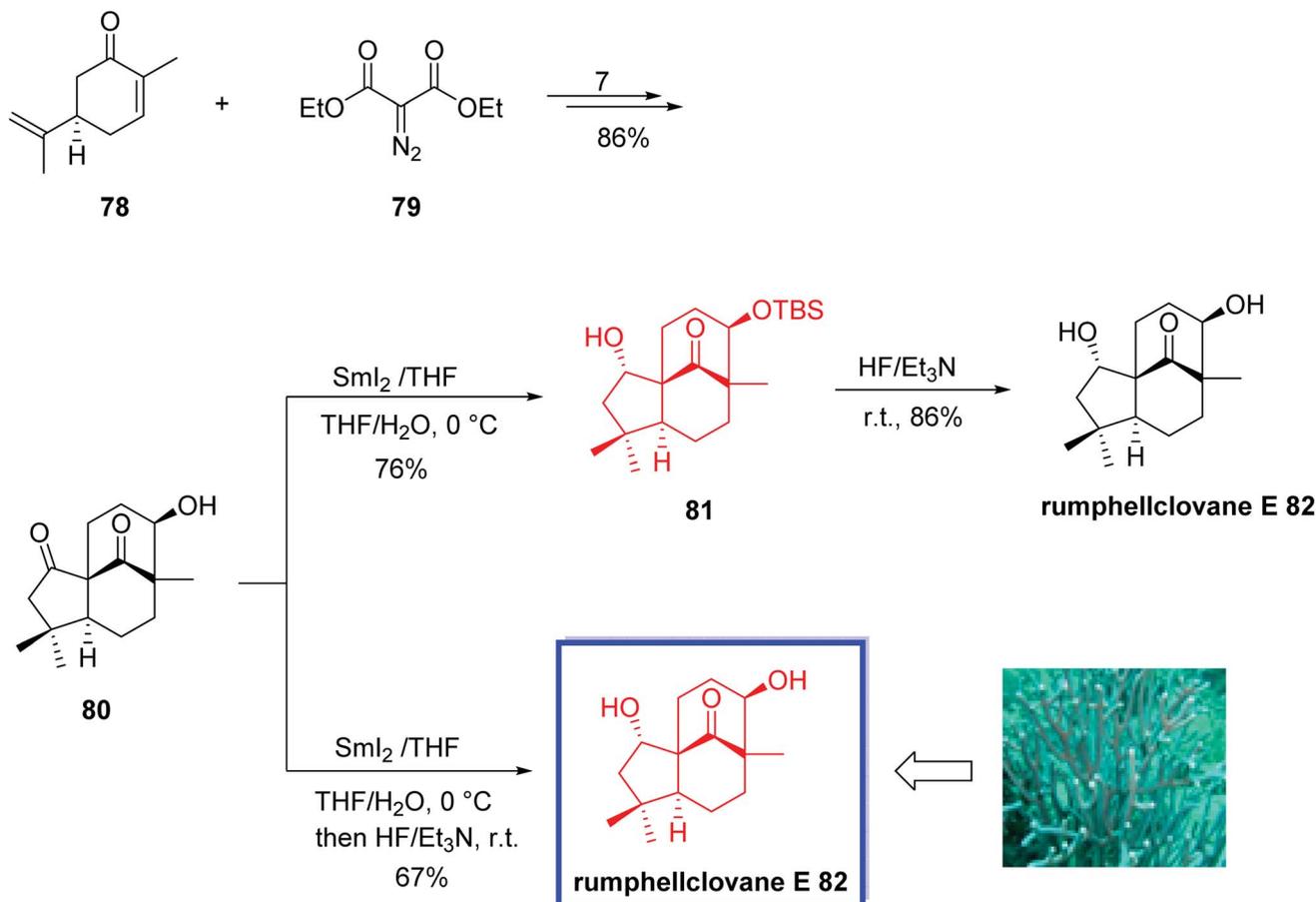
Scheme 21 Total synthesis of rumphellclovanes E **82**.

alkaloids show potent muscarinic or thrombin receptor antagonist activities.[61] Vorapaxar (SCH 530348), based on the natural product himbacine, is a thrombin receptor antagonist, and is used for preventing heart attacks in patients with acute coronary syndrome.

In 2010, Ma and coworkers[62] developed a convergent strategy for the asymmetric total synthesis of the alkaloid (−)-GB 13 **96** in 19 linear steps and an overall yield of 6.1% from the commercially available starting material. The key steps contain a Mukaiyama–Michael addition for connecting two bicyclic fractions and a SmI$_2$-mediated carbonyl–alkene reaction to construct the C ring. They also developed the first total synthesis of (+)-GB 16 **97** using an advanced intermediate from the (−)-GB 13 **96** total synthesis as a starting material. The analytical data of synthetic **96** and **97** were in good agreement with those reported for the natural products. X-ray crystal structure analysis of (+)-GB 16 **97** was also reported.

Total synthesis of the alkaloid (−)-GB 13 **96** began with the preparation of the two needed bicyclic fractions **90** and **92** for the Mukaiyama–Michael addition. The desired enone **90** was prepared using (S)-3-aminobutan-1-ol **89** in 5 steps and 79% yield. In a parallel procedure, the lactone **92** was prepared from olefin **91** in 4 steps and 89% yield. The addition of lactone **92** onto the enone **90** provided ketone **93** in 80% yield. Further

reaction of **93** generated the desired enone **94** in 5 steps and 74% yield. SmI$_2$-mediated ketyl–alkene reductive coupling of enone **94** by slowly adding the enone **94** to a solution of SmI$_2$ in THF at reflux without any additives, followed by the oxidation with Dess–Martin periodinane constructed C ring and resulted in the desired reductive coupling product **95** in 75% yield. Finally, (−)-GB 13 **96**, was synthesized from **95** in 2 steps and 71% yield. (+)-GB 16 **97** was synthesized from lactone **93** in 8 steps and 87% yield (Scheme 23).

Sieboldine A **105**, isolated from club moss *Lycopodium sieboldii*, and alopecuridine, isolated from *L. alopecuroides* (foxtail club moss), are two members of the fawcettimine-type Lycopodium alkaloids with unusual polycyclic structures and a broad range of biological activities.[63] The Lycopodium alkaloids are a growing family of structurally various and complex natural products. To date, more than 250 Lycopodium alkaloids have been isolated and characterized. Due to their exciting molecular structures and significant biological activities, the Lycopodium alkaloids are challenging targets for their total synthesis and have attracted broad attention from biogenetic and biological points of view.

Sieboldine A **105** is a significant acetylcholinesterase (AChE) inhibitor and shows significant cytotoxic activity against murine lymphoma L1210 cells.[63,64] Both alkaloids comprise a unique
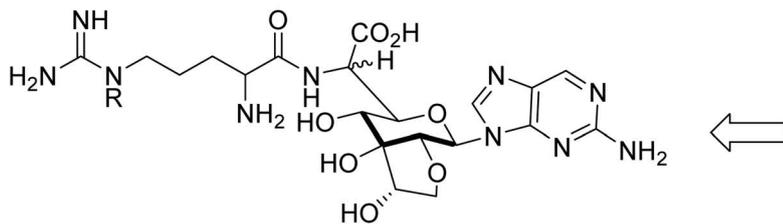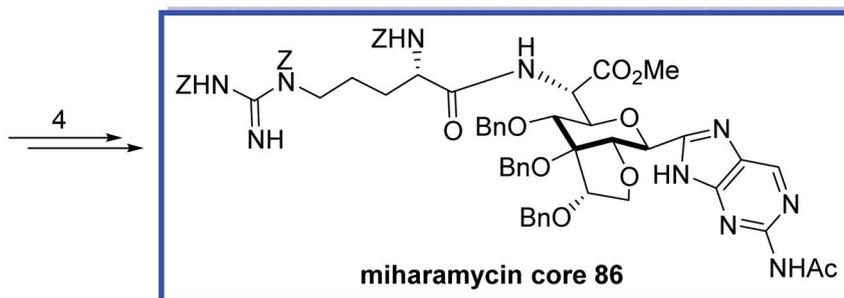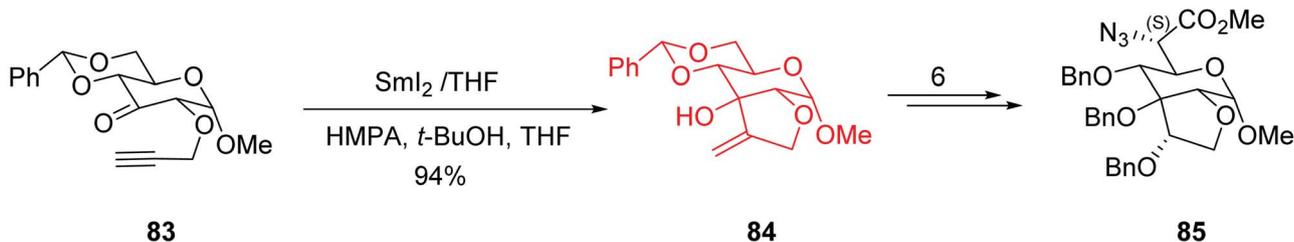
Scheme 22 Total synthesis of miharamycin B core **86**.

tetracyclic skeleton and two contiguous quaternary stereo-centers, additionally, sieboldine A **105** possesses an *N*-hydrox-yazacyclononane ring bridged to a tetrahydrofuran ring.

In 2011, Tu and coworkers[65] reported the first total synthesis of (±)-alopecuridine·TFA **104** and a biomimetic synthesis of (±)-sieboldine A **105** through the known iodide **98** in 13 and 15 steps, respectively. Key steps contain a semipinacol rearrange-ment of a medium-sized ring and a SmI$_2$-mediated intra-molecular pinacol coupling. The spectroscopic data for synthetic alopecuridine·TFA **104** and sieboldine A **105** were identical to those reported for the natural product.

The total synthesis of (±)-alopecuridine·TFA **104** and its biomimetic conversion into (±)-sieboldine A **105** began with the preparation of two coupling fragments **99** and **101**. Iodoalkene **99** was prepared from known iodide **98** in 3 steps and 75% yield. Ketone **101** was prepared from commercially available azepine **100** in 2 steps and 75% yield. The two fragments, **99** and **101**, were then coupled to give aldehyde **102** in 3 steps and 86% overall yield. The key tricyclic core and two contiguous quater-nary carbon atoms of alopecuridine·TFA **104** were constructed

through the SmI$_2$-mediated stereoselective intramolecular pinacol coupling of aldehyde **102** in THF at 0 °C and resulted in *cis*-diol **103**. Finally, alopecuridinium trifluoroacetate **104** was synthesized from diol **103** in 4 steps and 96% yield. The biomimetic transformation of (±)-alopecuridine·TFA **104** to sieboldine A **105** occurred over two steps in 60% yield (Scheme 24).

In 2012, Wang and coworkers[66] developed an efficient strategy for the asymmetric total synthesis of (+)-alopecuridine **108**, (+)-sieboldine A **109**, and (−)-lycojapodine A **110**,[67] in 15, 16, and 16 steps, respectively, starting from chiral enone **106**. All three alkaloids are structurally similar fawcettimine-type alka-loids and possess a unique tetracyclic skeleton and two contiguous quaternary stereocenters. (−)-Lycojapodine A **110**, isolated from the club moss *Lycopodium japonicum*, retains anti-HIV-1 activity. Both (−)-lycojapodine A **110** and (+)-sieboldine A **109**, are also acetylcholinesterase (AChE) inhibitors.
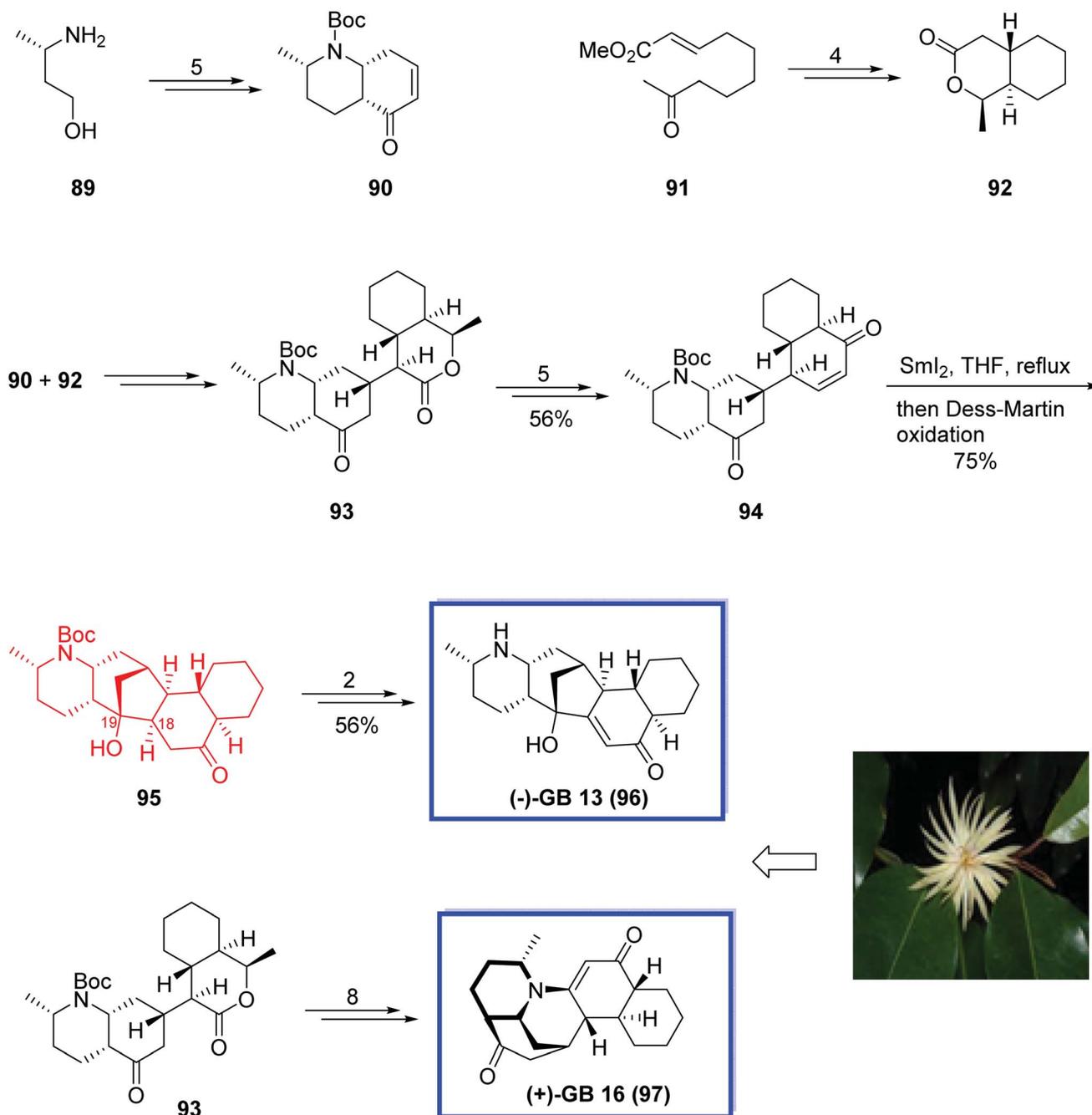
The key steps for the total synthesis of (+)-alopecuridine·TFA **108** contain the construction of the spiro 6,9-azacarbocycles with an all-carbon quaternary center *via* a semipinacol

rearrangement of a hydroxyl epoxide, and the construction of the 5-membered ring through a late-stage SmI$_2$-induced intramolecular pinacol coupling reaction. The biogenetic relationship of these three alkaloids was also confirmed through the biomimetic synthesis of (+)-sieboldine A **109** and (−)-lycojapodine A **110**. An N-oxidation/nitrone formation reaction of (+)-alopecuridine·TFA **108** resulted in the synthesis of (+)-sieboldine A **109**. The biogenetic synthesis of (−)-lycojapodine A **110** from (+)-alopecuridine·TFA **108** through diol formation/diol cleavage strategy was developed for the first time. The spectral data of the synthetic products were in good agreement

with the reported values and their rotations were identical to those of the natural products and confirmed the absolute configurations.

The asymmetric total synthesis of (+)-alopecuridine·TFA **108** and sieboldine A **109** began with the known enone **106** to provide chiral bromoalkene **107** in 6 steps, from which aldehyde **102** was prepared in 5 steps and 86% yield. SmI$_2$-induced intramolecular pinacol coupling of aldehyde **102** provided tricyclic compound **103**. Finally, (+)-alopecuridine·TFA **108** was obtained from **103** in 3 steps and 96% yield. The one-pot synthesis of (+)-sieboldine A **109** occurred through the

Scheme 23 Total synthesis of (−)-GB 13 (**96**) and (+)-GB 16 (**97**).
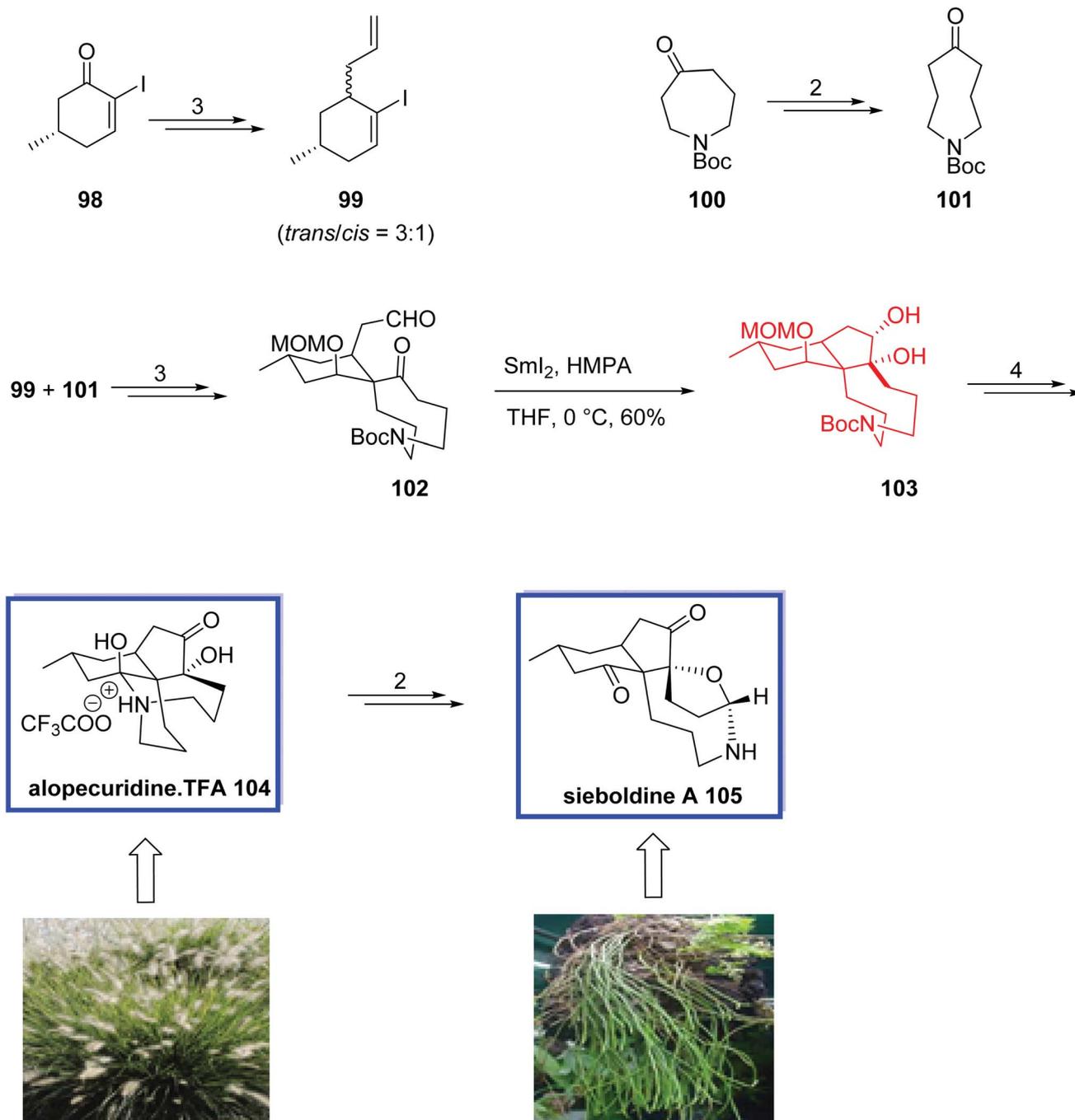
Scheme 24 The total synthesis of (±)-alopecuridine·TFA **104** and (±)-sieboldine A **105**.

biomimetic oxidation of (+)-alopecuridine·TFA **108** using *m*-CPBA in CH₂Cl₂ followed by addition of HgO in MeOH to generate **109** in 60% yield. Lacojapodine A **110** was synthesized in 82% yield through the biomimetic oxidation of (+)-alope-curidine·TFA **108** using MnO₂ in CH₂Cl₂ at room temperature (Scheme 25).

The fawcettimine-type *Lycopodium* alkaloids, containing alopecuridine **108**,[63a,b] sieboldine A **109**,[64d] and lycojapodine A **110**,[66] (+)-fawcettidine **119** and (+)-fawcettimine **120**[67] have continued to be of great interest to synthetic chemists. The

serratinine-type Lycopodium alkaloids, such as (−)-8-deoxy-serratinine **121**,[67d] exemplify another important class of Lyco-podium alkaloids possessing a 6/5/6/5 tetracyclic framework with two contiguous quaternary stereogenic centers. They are structurally comparable to the fawcettimine-type alkaloids. The fawcettimine-type alkaloids are different from other classes of Lycopodium alkaloids because of the extensive ring–chain tautomerism, which is important to their biogenesis.

In 2013, Lei and colleagues[68] reported the total synthesis of both fawcettimine- and serratinine-type *Lycopodium* alkaloids
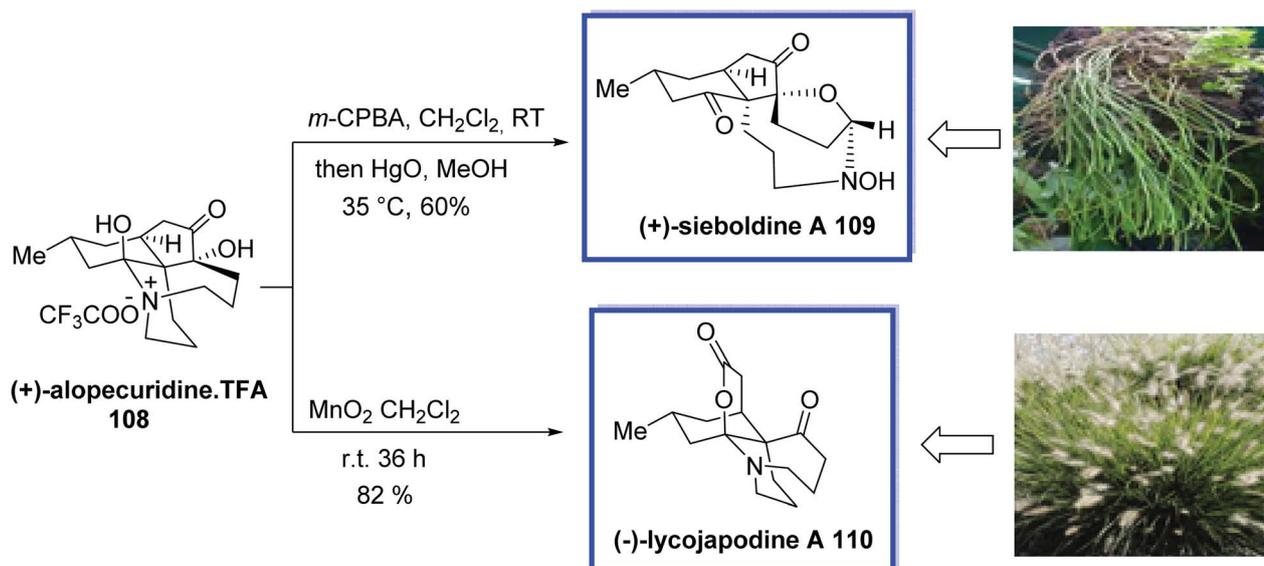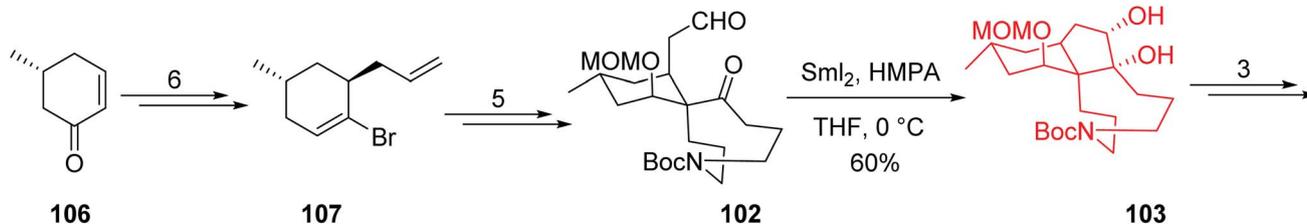
(+)-alopecuridine **108**, (−)-lycojapodine A **110**, (+)-fawcettidine **119**, (+)-fawcettimine **120** and (−)-8-deoxyserratinine **121**, from a known precursor **111** in either 12 or 13 steps employing a very compact pathway stimulated by the suggested biosynthesis of the fawcettimine- and serratinine-type alkaloids. The key steps contain an intramolecular C-alkylation to install the spiro quaternary carbon center and the aza-cyclononane ring, SmI$_2$-mediated pinacol couplings to synthesize the tricyclic skeleton and also to confirm the relative stereochemistry of the oxa-quaternary center, and a sequential transannular N-alkylation to achieve the desired tetracyclic core. The total synthesis of (−)-lycojapodine A **110** was achieved either via a late-stage IBX/TFA-mediated tandem oxidation reaction or through a one-pot biogenetic pathway from (+)-alopecurdine **108**. The spectroscopic data of the synthetic **119**, **120**, and **121** were in good agreement with those already reported.

The total synthesis of **108**, **110** and **119-121** started from the common intermediate **111**, to obtain aldehydes **112** and **113**. Pinacol coupling of **112** using SmI$_2$ in THF at room temperature resulted in diol **114** as the sole product in 86% yield. A pinacol coupling reaction of aldehyde **113** using SmI$_2$ in THF in the presence of HMPA at −78 °C to room temperature resulted in the 4,5-trans diol **115** as the sole product in 67% yield. (−)-Lycojapodine A **110** was synthesized via a late-stage IBX/TFA-mediated tandem oxidation reaction of tautomer-locked

diol **116**, which was synthesized from diol **114** in 3 steps and 54% yield. (−)-Lycojapodine A **110** was also synthesized via a one-pot process using α-ketol **117**, which was obtained from diol **114** in 2 steps and 50% yield. Removal of the Boc group from α-ketol **117** with TFA and neutralization with NaHCO$_3$ afforded (+)-alopecuridine·TFA **108** in 94% yield. Additionally, the successive biomimetic transformation of (+)-alopecur-idine·TFA **108** also resulted in (−)-lycojapodine A **110**. The absolute configuration of **108** was also confirmed (Scheme 26).

The total syntheses of (+)-fawcettimine **119**, (+)-fawcettidine **120**, and (−)-8-deoxyserratinine **121** were achieved using 8-deoxy-13-dehydroserratinine **118**, which retained the key aza-quaternary carbon center at C4 and was prepared from diol **115**. Treatment of **118** with NaBH$_4$ at 0 °C afforded (−)-8-deoxy-yserratinine **121** in 98% yield. The reductive reaction of **118** with Zn/AcOH at 140 °C resulted in (+)-fawcettidine **119** in 95%. Finally, (+)-fawcettimine **120** was attained by treatment of **118** with SmI$_2$ in THF/H$_2$O at 0 °C in 51% yield (Scheme 27).

(−)-Actinophyllic acid **129**, isolated from the leaves of the tree *Alstonia actinophylla*,[69] is a biologically active indole alkaloid with five contiguous stereocenters and a potent inhibitor of the zinc-dependent carboxypeptidase U (CPU). Inhibitors of CPU promote fibrinolysis and inhibit blood clot formation which is a cause of several cardiovascular disorders.[70,71]

Scheme 25 The total synthesis of (+)-alopecuridine·TFA **108**, (+)-sieboldine A **109** and lacojapodine A **110**.
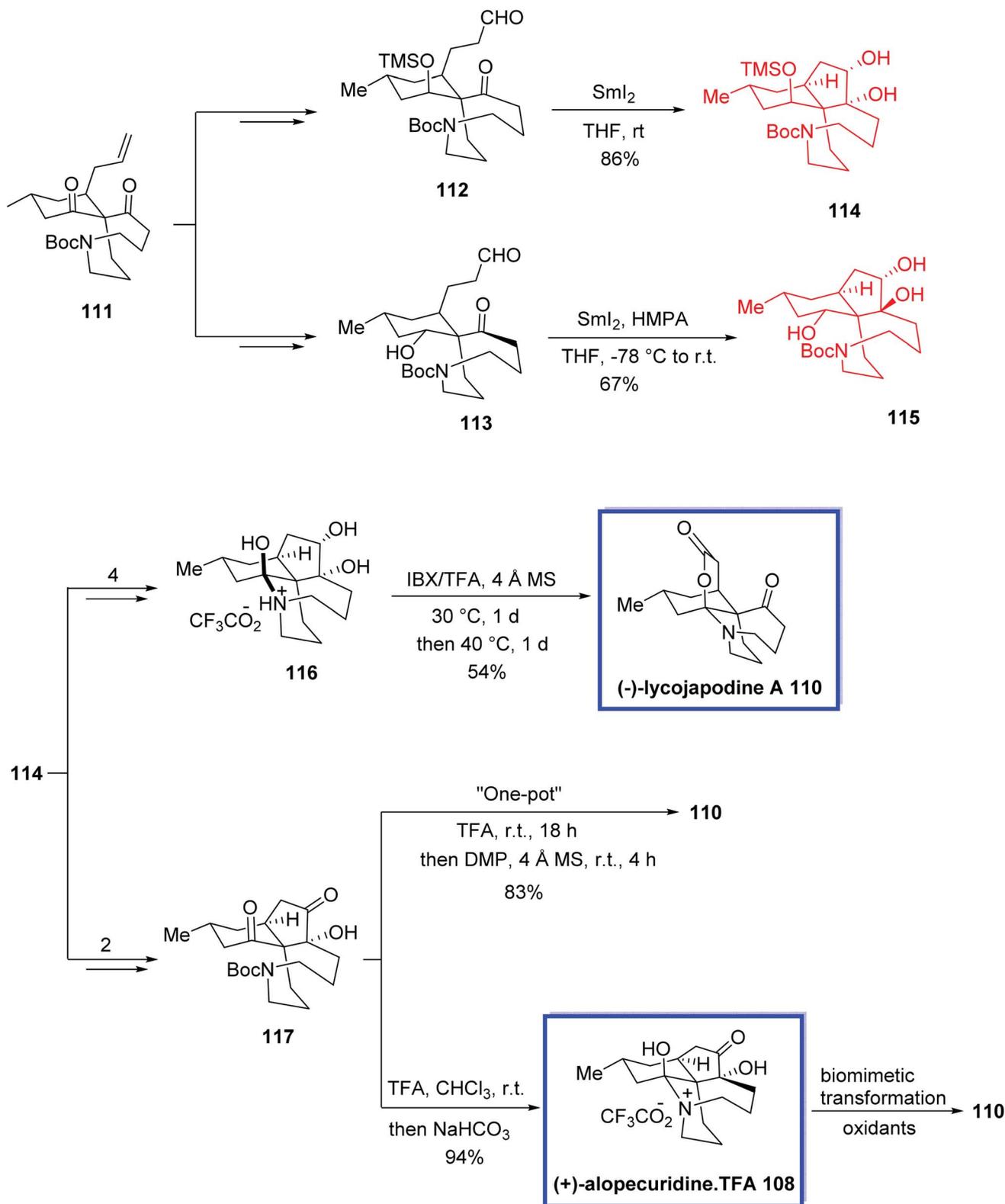
Scheme 26 Total synthesis of (+)-alopecuridine **108**, (−)-lycojapodine A **110**.

In 2016, Kwon and coworkers[72] reported the first enantio-selective total synthesis of (−)-actinophyllic acid **129** in 13 steps from a known aldehyde in 12.4% yield. They used the same

starting materials for the synthesis of (−)-actinophyllic acid **129** as the racemic synthesis of actinophyllic acid. The key steps were a chiral phosphine-catalyzed [3 + 2] annulation of an
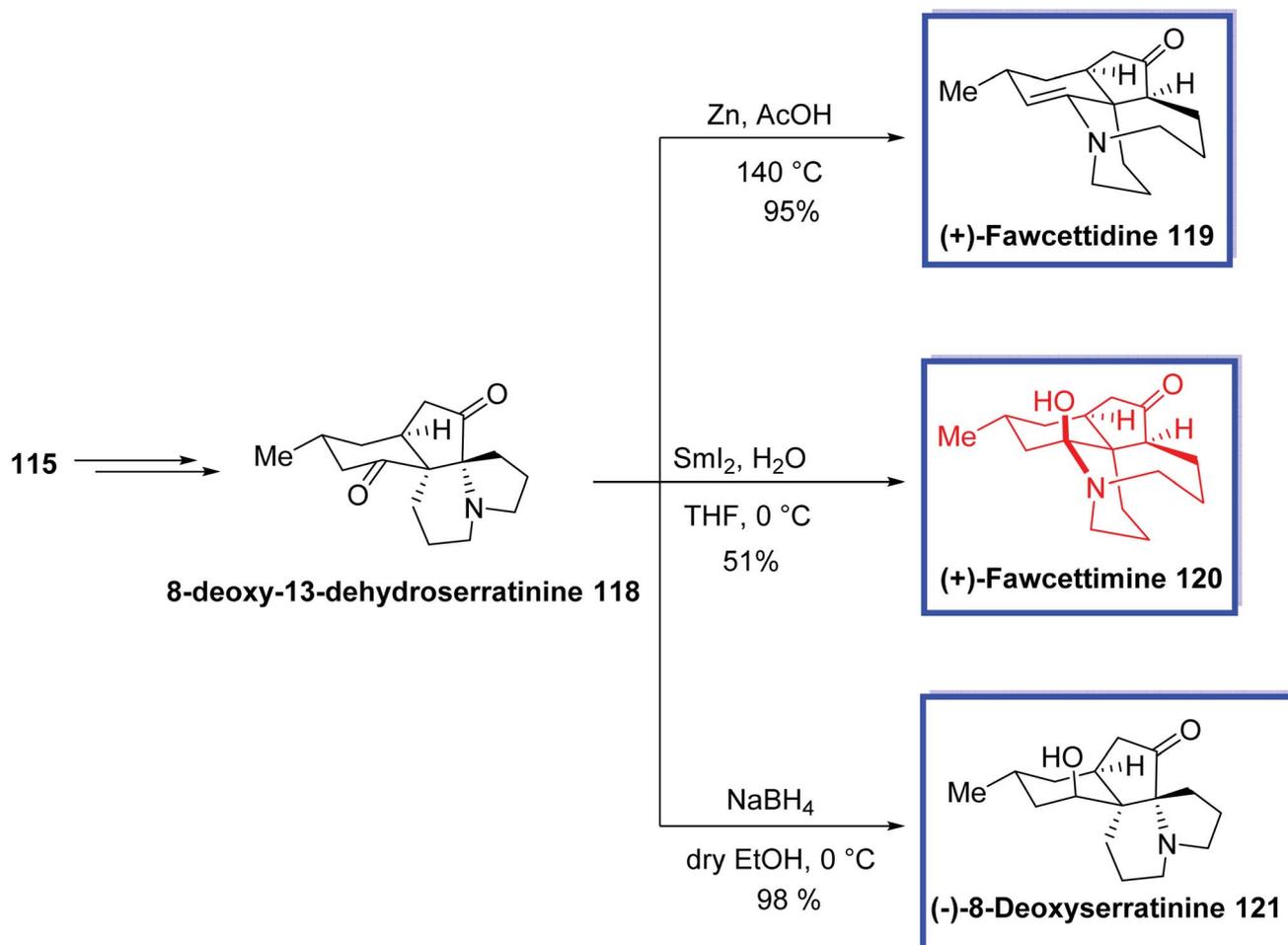
Scheme 27 Total synthesis of (+)-fawcettidine **119**, (+)-fawcettimine **120** and (−)-8-deoxyserratinine **121**.

allenoate and an indole imine to prepare a proline intermediate, a CuI-catalyzed coupling to form the tetrahydroazocine ring, an intramolecular alkylative lactonization, a SmI$_2$-mediated intramolecular pinacol coupling between a ketone and a lactone to construct the caged framework of (−)-actinophyllic acid **129**, and a remarkable regioselective dehydroxylation. The spectral data of the synthesized structures were in complete agreement with those reported in the literature.

The asymmetric total synthesis of (−)-actinophyllic acid **129** began with the [3 + 2] annulation between *N*-nosylimine **122** and benzyl allenoate **123** using phosphine B **124** and 20 mol% *s*-BINOL **125** and as the additive gave the desired (*S*)-enantiomer **126** with the enantioselectivity of 94% ee in 99% yield. With the desired (*S*)-enantiomer **126** in hand, the lactone **127** was synthesized in 35−48% yield in 5 steps. To synthesize the desired coupling product **128** from the lactone **127** *via* a pinacol reaction, Kwon and colleagues evaluated several single-electron-transfer reagents, comprising Ti$_3$$^+$, Li, Na, and Sm^{2+}. Only the reaction of lactone **127** with SmI$_2$ and 10 equiv. of *t*-BuOH in THF furnished the desired hemiketal **128** in quantitative yield, from which (−)-actinophyllic acid hydrochloride **129** was synthesized over 2 steps in 90% yield (Scheme 28).

(+)-Mintlactone **134** and (−)-isomintlactone **135**, isolated from *Bursera graveolens*, are bicyclic monoterpene natural products with two stereocenters.[73] These compounds typically have a sweet aroma and are used as food additives, tobacco additives, and intermediates for the synthesis of dihydrogen mint and menthofuran.[73]

In 2017, Wang and coworkers[74] introduced the divergent procedure for the total synthesis of (+)-mintlactone **134** and (−)-isomintlactone **135** through a SmI$_2$-mediated intramolecular radical cyclization to construct two rings and a stereocenter in one step.

The stereochemistry of the final natural products was controlled by the stereocenter of (−)-citronellol **130** and facilitated by the coordination of the oxygen atoms of the aldehyde and ester with the samarium atom in the transition state. This strategy would be used as a general route for the synthesis of complex natural products with a butenolide moiety. The total synthesis of (+)-mintlactone **134** and (−)-isomintlactone **135** began with (−)-citronellol **130** to obtain aldehyde **131** in 3 steps, from which α,β-unsaturated ester **132** was prepared in 3 steps. SmI$_2$-induced radical cyclization of the key substrate **132** with SmI$_2$ in anhydrous THF and *t*-BuOH at −20 °C under an argon atmosphere provided bicyclic product **133** in 68% yield, from
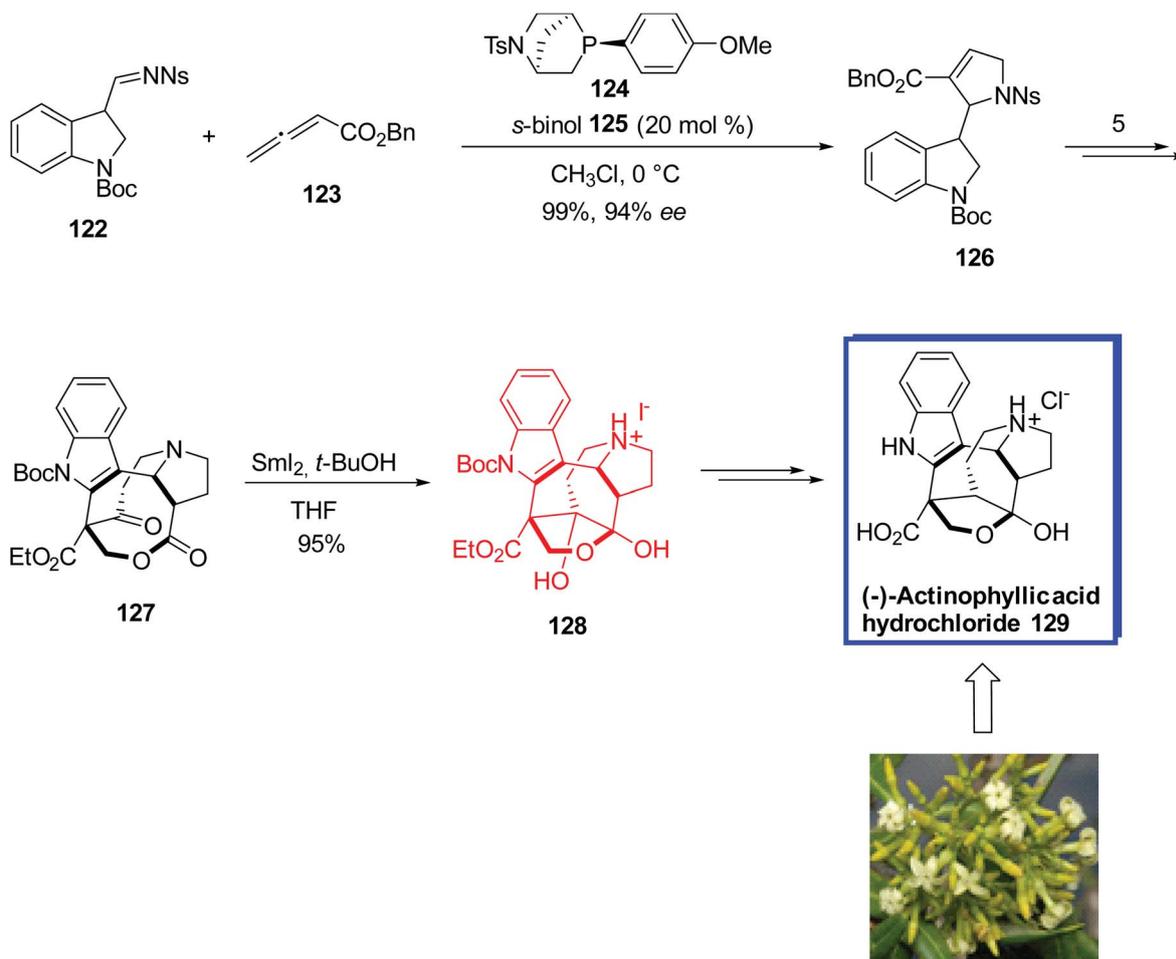
Scheme 28 The total synthesis of (−)-actinophyllic acid **129**.

which a mixture of **134** and **135** (9 : 1) was synthesized in 2 steps and 68% yield.

(−)-Isomintlactone **135** was prepared using aldehyde **131**, which was converted to Z-α,β-unsaturated ester **136** in 3 steps. Treatment of compound **136** with SmI$_2$ in anhydrous THF and t-BuOH at −20 °C under an argon atmosphere provided lactone **137** with an opposite chirality on C8 as expected. With the key substrate **137** in hand, a mixture of **134** and **135** (1 : 5) was synthesized in 2 steps and 51% yield (Scheme 29).

(−)-Kainic acid **142** and its C4-epimer, (+)-allo-kainic acid **143**, are pyrrolidine alkaloids with three contiguous stereocenters, and were isolated initially from the Japanese marine alga *Digenea simplex* (Japanese name, kainin-sou).[75] (−)-Kainic acid **142** promoted a strong activation of neurons and was evaluated as a KA-type ionotropic receptor. Therefore, it was used in neuroscience and neuropharmacology as an effective molecular probe.[76]

In 2017, Matsuda and coworkers[77] developed the total syntheses of (−)-kainic acid **142** and (+)-allo-kainic acid **143** in 12 steps from a commercially available starting material. The key step was a SmI$_2$-mediated reductive 3,4-disubstituted pyrrolidine cyclization. They found that the preference of the 3,4-*cis*- or 3,4-*trans*-selective cyclization can be achieved by

changing the additives from NiI$_2$ to HMPA during the SmI$_2$-promoted pyrrolidine cyclization. Spectroscopic data (1H and 13C NMR, and specific rotation) of synthesized **142** and **143** were in good agreement with those reported from previous total syntheses.

The total syntheses of (−)-kainic acid **142** and (+)-allo-kainic acid **143** began with the amine hydrochloride **138** to obtain *E*-**139** and *Z*-**139** in 3 steps in 60% and 69% yield, respectively. The SmI$_2$-mediated cyclization of *E*-**139** or *Z*-**139** and removal of the TBS group with TBAF resulted in a mixture of only two of the four possible diastereomeric pyrrolidines, **140** and **141**. Using HMPA and H$_2$O, 3,4-*trans*-pyrrolidine **141** was the major diastereomer (*cis* : *trans* = 18 : 82) for the cyclization of *E*-**139**. Then 3,4-*cis*-pyrrolidine **140** was the major diastereomer (*cis* : *trans* = 62 : 38) for the cyclization of *Z*-**139** in the presence of NiI$_2$ and 2,2′-bipyridine. Finally, Jones oxidation of alcohol **140** or **141**, hydrolysis of the ester with LiOH in THF-H$_2$O, and removal of the Boc group with TFA provided (−)-kainic acid **142** or (+)-allo-kainic acid **143** in 60% or 80% yield (3 steps), respectively (Scheme 30).

Isoryanodane diterpenoids contain a rare diterpenoid skeleton. They have been proven to show anti-complementary and antifeedant activities.[78] Vignaticol **150**, isolated from
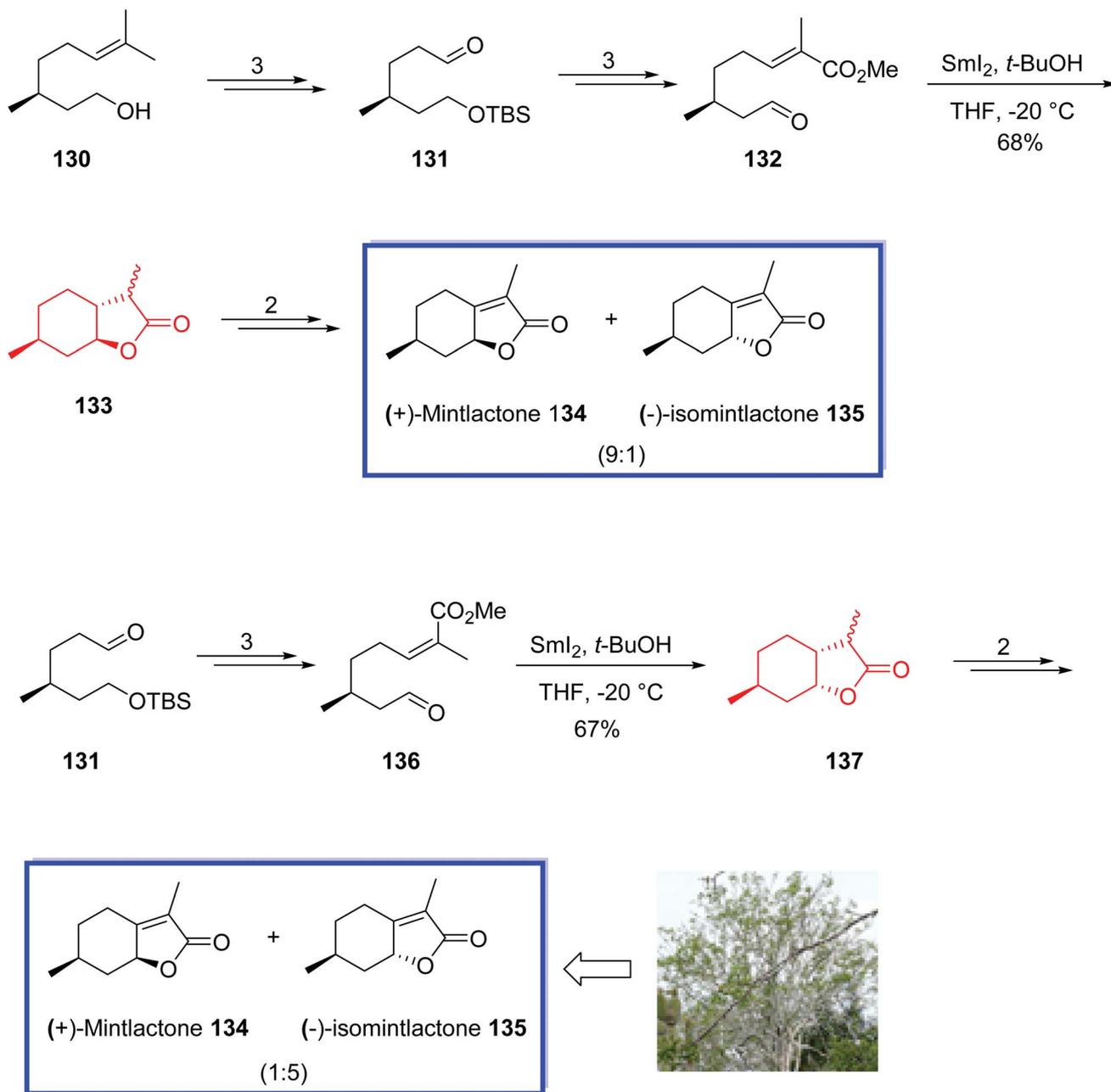
Scheme 29 The total synthesis of (+)-mintlactone **134** and (−)-isomintlactone **135**.

Persea indica (Lauraceae), is an isoryanodane diterpenoid and contains a densely oxygenated and complex fused pentacycle (ABCDE-ring) with 10 contiguous stereogenic centers that are structurally different in the substitution structures of their hydroxyl groups. These compounds demonstrate several important biological activities such as anti-COX-2, anti-complement, and immunosuppressive.[79] In 2018, Inoue and coworkers[80] reported a new procedure for establishing the isoryanodane ABCDE-ring structure of **148** for the first time. They synthesized the 6/5/7-membered isoryanodane BCD-ring system of **148** from the 5/6-membered ryanodane BD-ring system of **146** in 7 steps.

Compound **148** differs from vignaticol **150** only at the C2,3-positions and has 9 of the 10 contiguous stereogenic centers of vignaticol **150**, and thus, it may likely lend itself to be a useful scaffold for the total synthesis of vignaticol **150** and other densely oxygenated and complex fused terpenoids. The key steps were the installation of the C8-vinyl group at the C6-position, an oxy-Cope rearrangement, and SmI$_2$-mediated transannular carbonyl-ene reaction establishing the C6-, C10-, and C11-stereogenic centers. The DFT calculation confirmed that the SmI$_2$ reaction pertained to an intramolecular carbonyl-ene reaction and indicated that the samarium reagent functioned as both a Lewis acid and reluctantly proceeded through

a regio- and stereoselective cyclization without incurring any cation-caused rearrangement or E1cB elimination. The stereo-chemistry of **147** and its C9-(*R*)-stereocenter was determined by X-ray crystallographic analysis.

The total synthesis of isoryanodane pentacycle **148** began with the reaction of 2,5-dimethylbenzene-1,4-diol **144** and maleic anhydride **145** to give the common enantiopure ryano-dane tetracycle **146** within 21 steps. The 9-membered ring of **147** was then synthesized from **146** in 6 steps and 60% yield. Transannular combination of the oxy-Cope rearrangement and transannular carbonyl-ene reaction of **147** using SmI$_2$ in the presence of MeOH gave isoryanodane pentacycle **148** in 79% yield. Alternatively, the transannular cyclization of compound **147** in the presence of *n*-Bu$_3$SnH provided ryanodane pentacycle **149** in 100% yield (Scheme 31).

(−)-Strempeliopine **156**, isolated from the roots of *Strempe-liopsis strempelioides* K. Scrum, is the parent base of the schiz-ozygane alkaloids. The schizozygane alkaloids are biogenetically presumed to be correlated to the Aspidosperma alkaloids.[81] The complex structure of (−)-strempeliopine **156**, containing a highly fused hexacyclic core with an installed transannular ethane bridge, has attracted considerable atten-tion of synthetic chemists.

In 2021, Boger and coworkers[82] developed the total synthesis of (−)-strempeliopine **156** from the intermediate (+)-**153**. Key step was a combined Lewis acid/SmI$_2$-mediated dearomative transannular radical cyclization onto an indole to construct the C19–C2 bond of (−)-strempeliopine **156**. They selected CH$_3$CN as solvent for the SmI$_2$-mediated transannular radical cycliza-tion to prevent the effective complexation of BF$_3$·OEt$_2$ with the
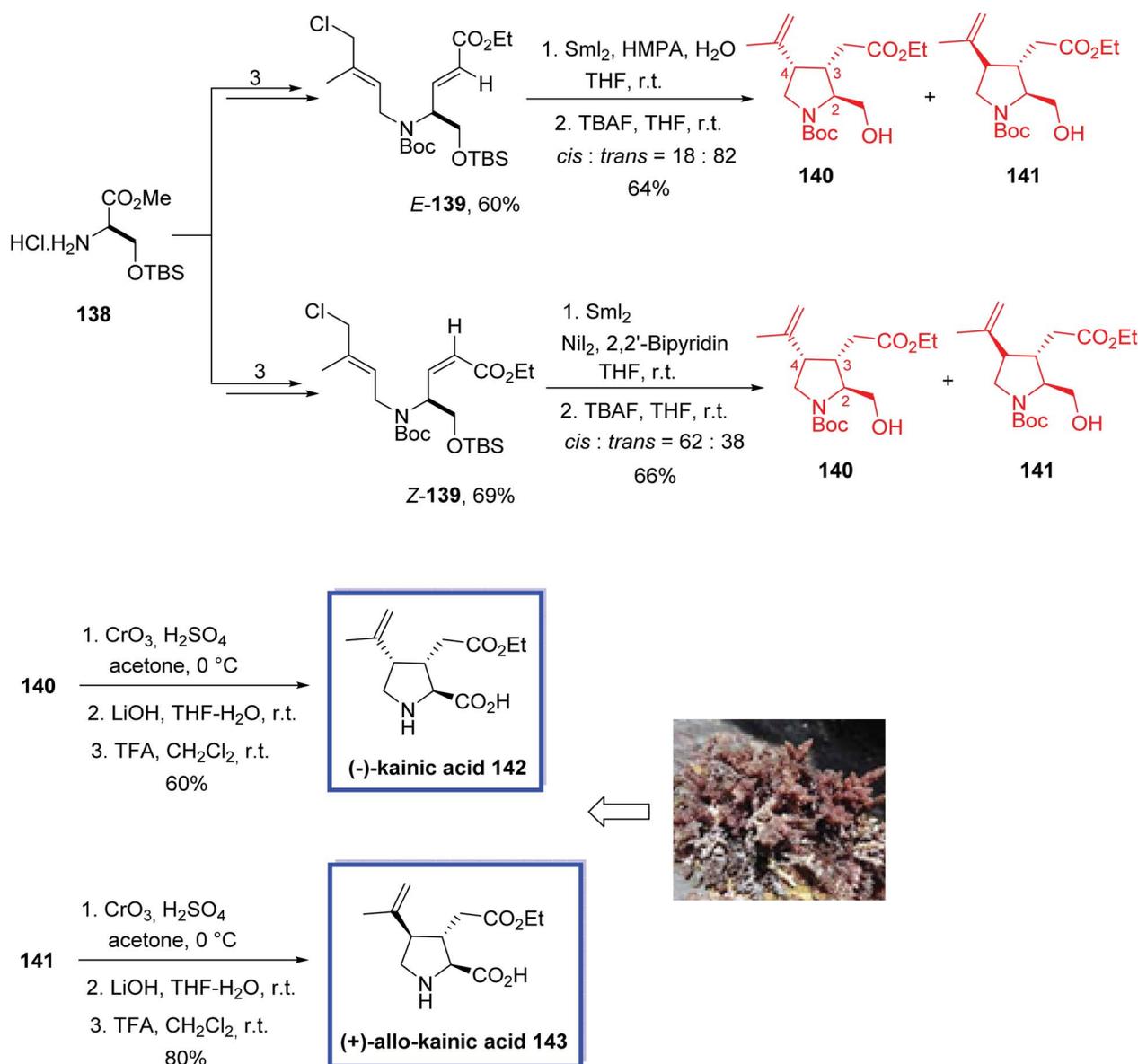
Scheme 30 The total synthesis of (−)-kainic acid **142** and (+)-allo-kainic acid **143**.
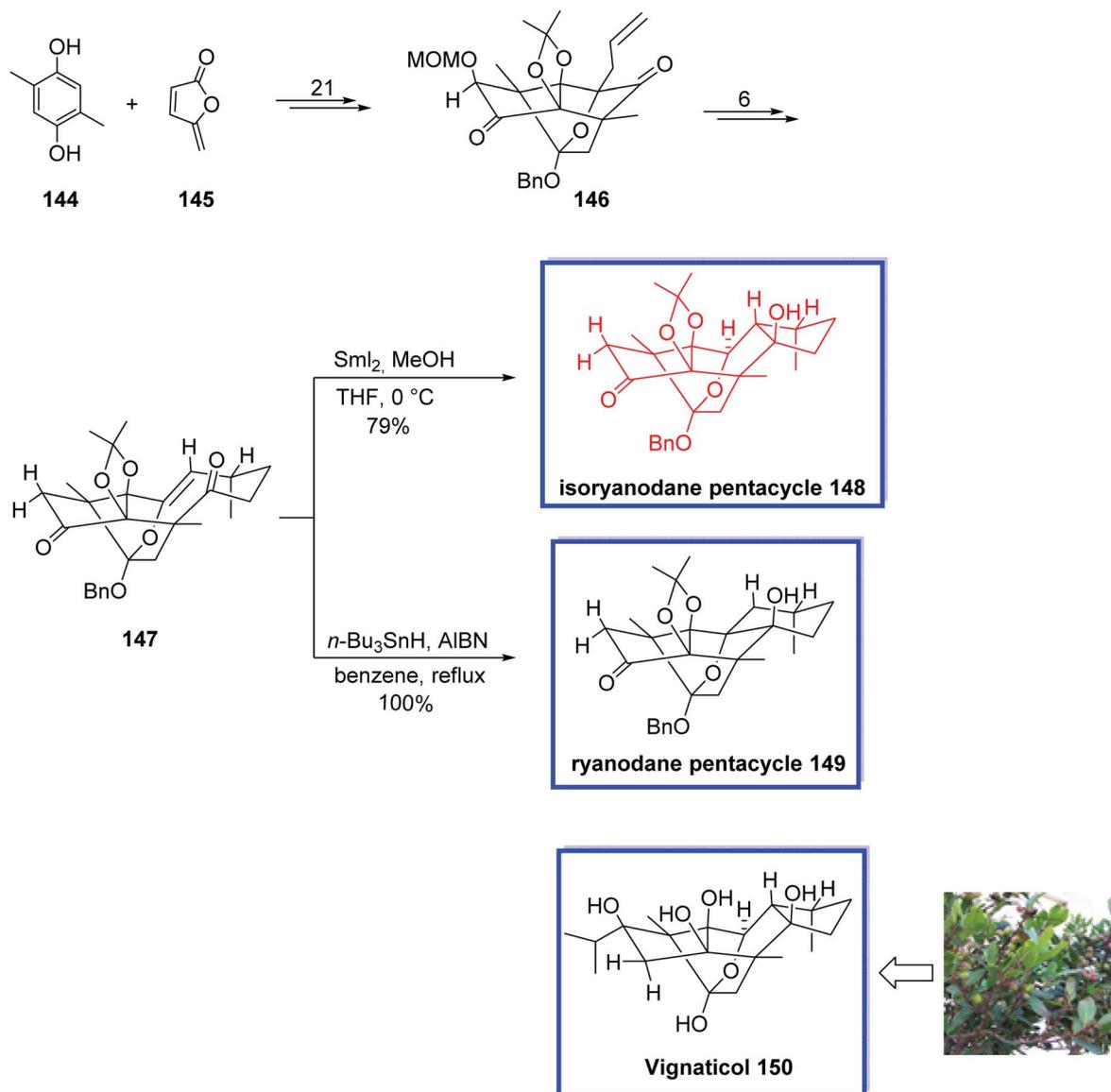
Scheme 31 The total synthesis of isoryanodane pentacycle **148**.

N-acyl hemiaminal, and to reduce its power to facilitate the formation of the iminium ion intermediate.

Total synthesis of (−)-strempeliopine **156** started with the previously reported intermediate (+)-**153**, which was prepared by the reaction of *N*-1,3,4-oxadiazole **151** and 4-(2-*tert*-butyldimethylsilyloxy)pent-4-enoic acid **152** in 7 steps. (+)-**153** was then converted into the carbamate (−)-**154** in 73% yield. Treatment of **154** with BF$_3$·OEt$_2$ to produce the *N*-acyliminium ion and the following SmI$_2$-mediated radical cyclization in CH$_3$CN at 25 °C afforded (+)-**155** regioselectively (8 : 1) and diastereoselectively (>30 : 1) in 63% yield. Finally, (−)-strempeliopine **156** was synthesized from (+)-**155** in 3 steps and 48% yield (Scheme 32).

Kopsia indole alkaloids,[83] isolated from several *Kopsia* (Apocynaceae) species, exhibit various remarkable biological activities, such as cholinergic, anti-rheumatism, and anti-

inflammation antimicrobial, anticancer, anti-inflammatory, and antitussive properties.[84] Based on the scaffold of the kopsine family there are four subtypes: kopsine, isokopsine, chanofruticosine, and fruticosine. Kopsinine **160**, isolated initially from *Kopsia longiflora* Merr.,[85] belongs to the *Aspidosperma* alkaloids family of natural products and shows *in vitro* anticholinergic activity.[84j]

In 2013, Boger and coworkers[86] reported the total synthesis of kopsinine **160**. The key steps included the intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles to form the pentacyclic core and an extraordinary SmI$_2$-induced transannular cyclization reaction to construct the hexacyclic ring system of kopsinine from the bicyclo[2.2.2]octane core, perhaps ensuing from a radical-mediated cyclization with subsequent kinetic protonation of the extra reduced conjugate addition ester enolate from the less overly involved convex face. This
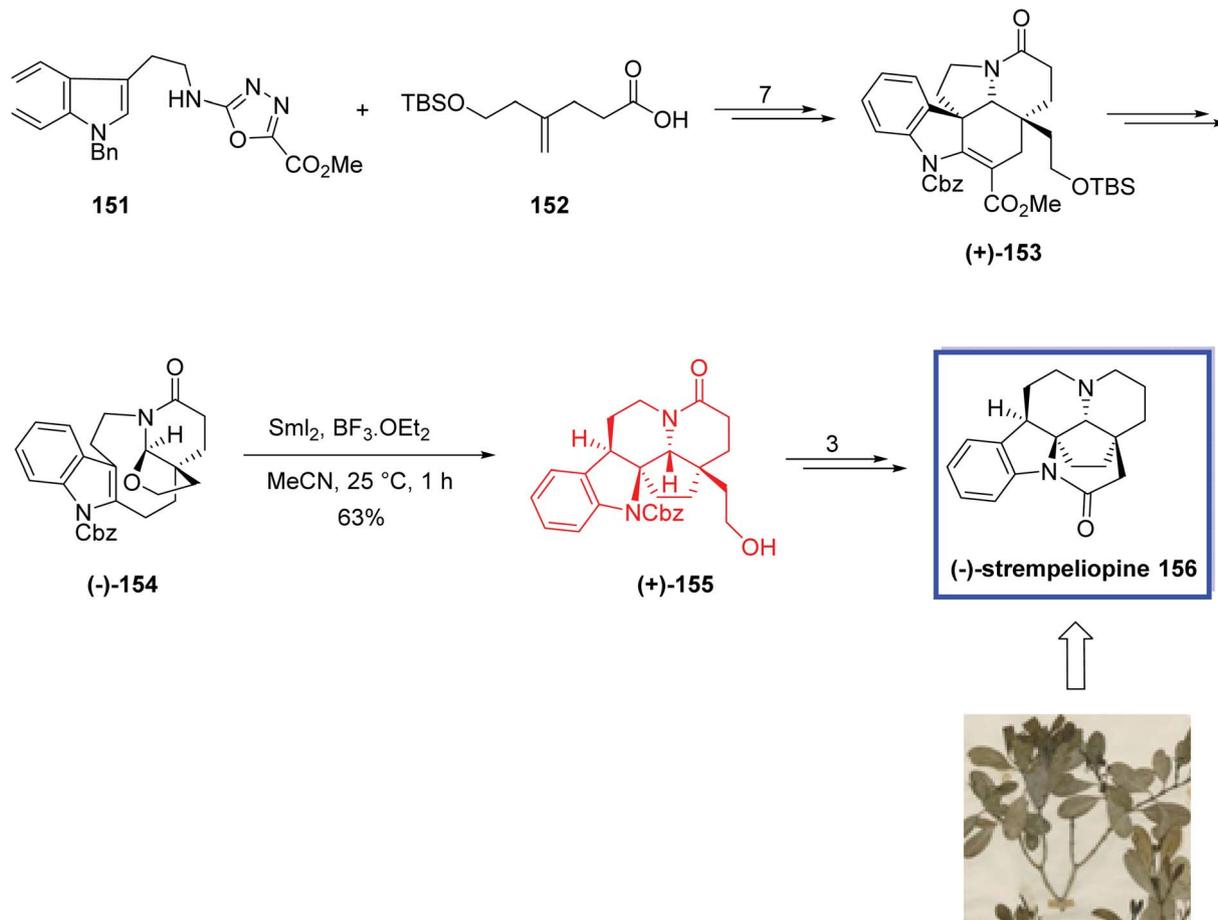
Scheme 32 Total synthesis of (−)-strempeliopine **156**.
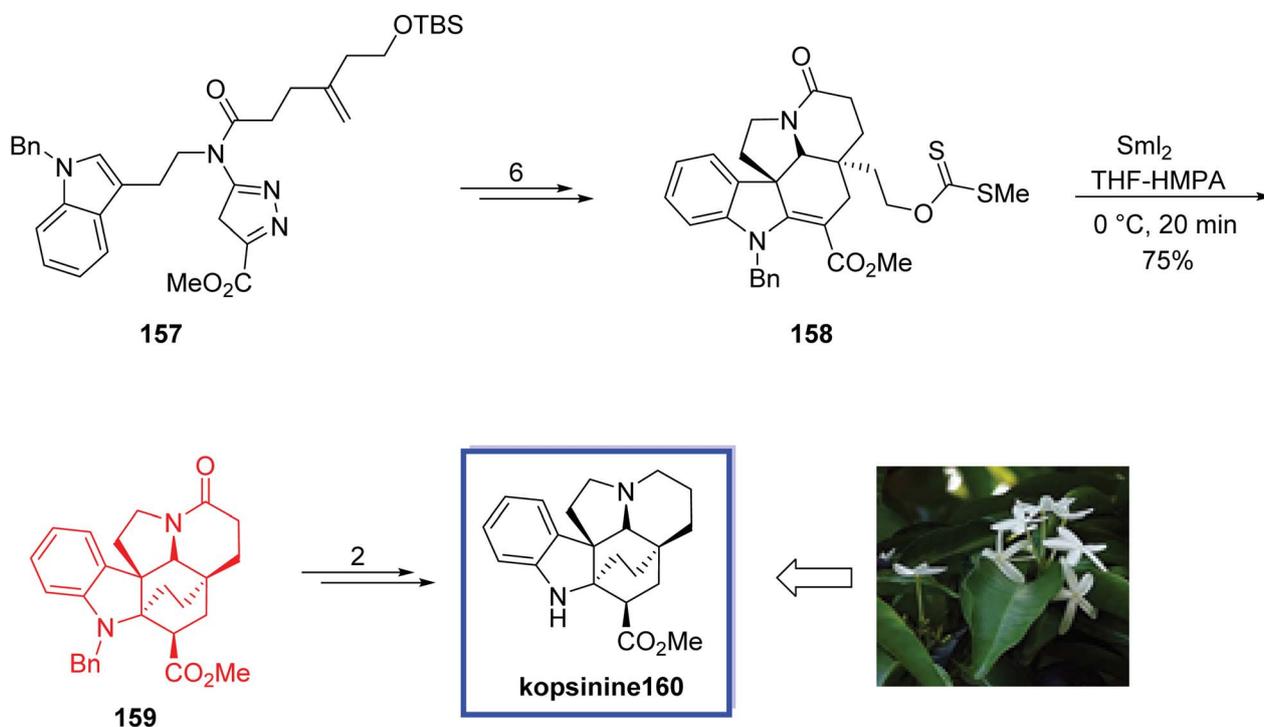
Scheme 33 Total synthesis of kopsinine **160**.

hexacyclic ring system can directly correlate to the structures of the related *Aspidosperma* alkaloids.

The total synthesis of kopsinine **160** began with the cyclo-addition adduct **157** to provide the key intermediate methyl-dithiocarbonate **158** in 6 steps and 86% yield. Treatment of **158** with SmI$_2$ in THF/HMPA (10 : 1) provided **159** in 75% yield as a single diastereomer. Finally, kopsinine **160** was synthesized from **159** in 2 steps (Scheme 33).

Later in 2015, Boger and colleague[87] developed the asymmetric total synthesis of (−)-kopsinine **165** and its unnatural enantiomer from the common *Aspidosperma*-like pentacyclic intermediate **161**. The key steps contain a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles to provide the stereochemically rich C21-functionalized pentacyclic core precursor **161** of the natural product, and the C21–C2 bond formation via a late-stage SmI$_2$-promoted transannular free radical conjugate addition reaction constructing the bicyclo[2.2.2]octane core. The spectral data of synthetic (−)-kopsinine **165** were in good agreement with those reported for the natural product.
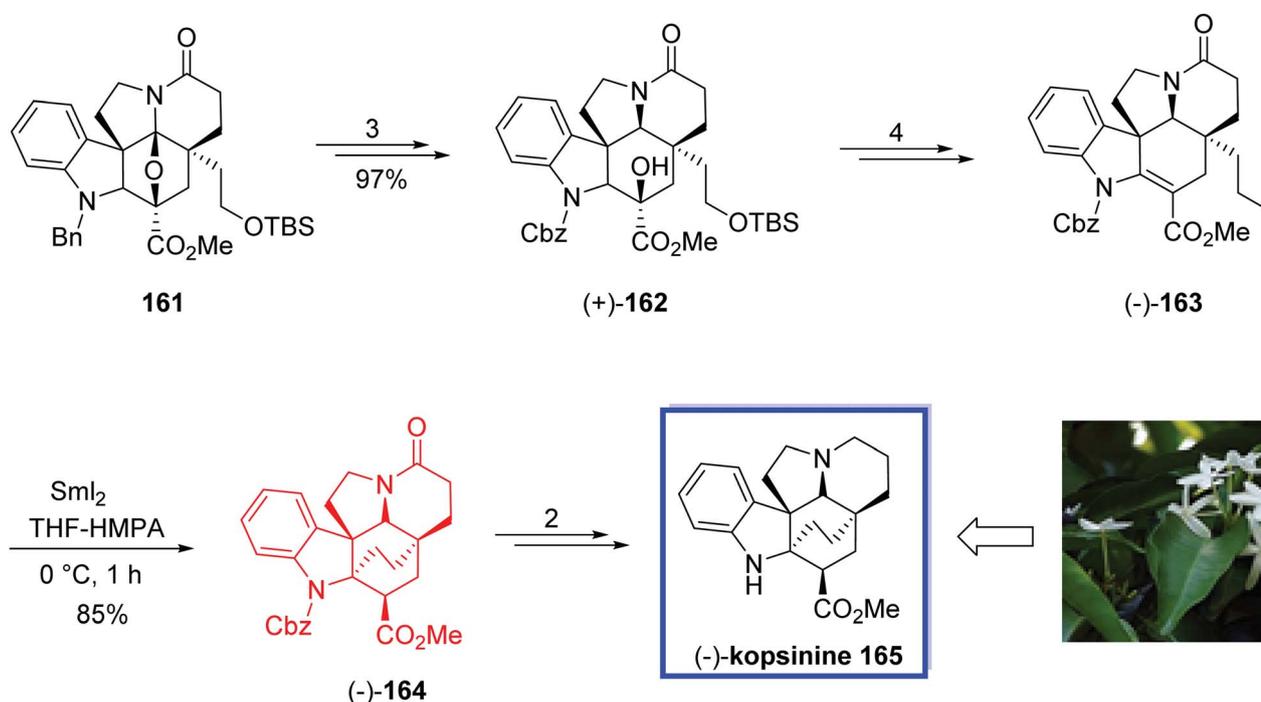
The total synthesis of (−)-kopsinine **165** began with the *Aspidosperma*-like pentacyclic intermediate **161** to provide the natural (+)-**162** and *ent*-(−)-**162** enantiomers in 3 steps and 97% yield. The natural enantiomer (+)-**162** was then converted into the primary iodide (−)-**163** in 4 steps and 81% yield. The key transannular cyclization of (−)-**163** with SmI$_2$ in THF/HMPA (10 : 1) at 0 °C for 1 h smoothly gave (−)-**164** in excellent yield (85%) along with <5% of the C3 diastereomer. This generation of essentially a single diastereomer (>17 : 1). The natural (−)-kopsinine **165** was synthesized from (−)-**164** in 2 steps and 82% yield. The unnatural enantiomer of kopsinine, *ent*-(+)-**165**, was also synthesized in a similar pathway from *ent*-(−)-**162** (Scheme 34).
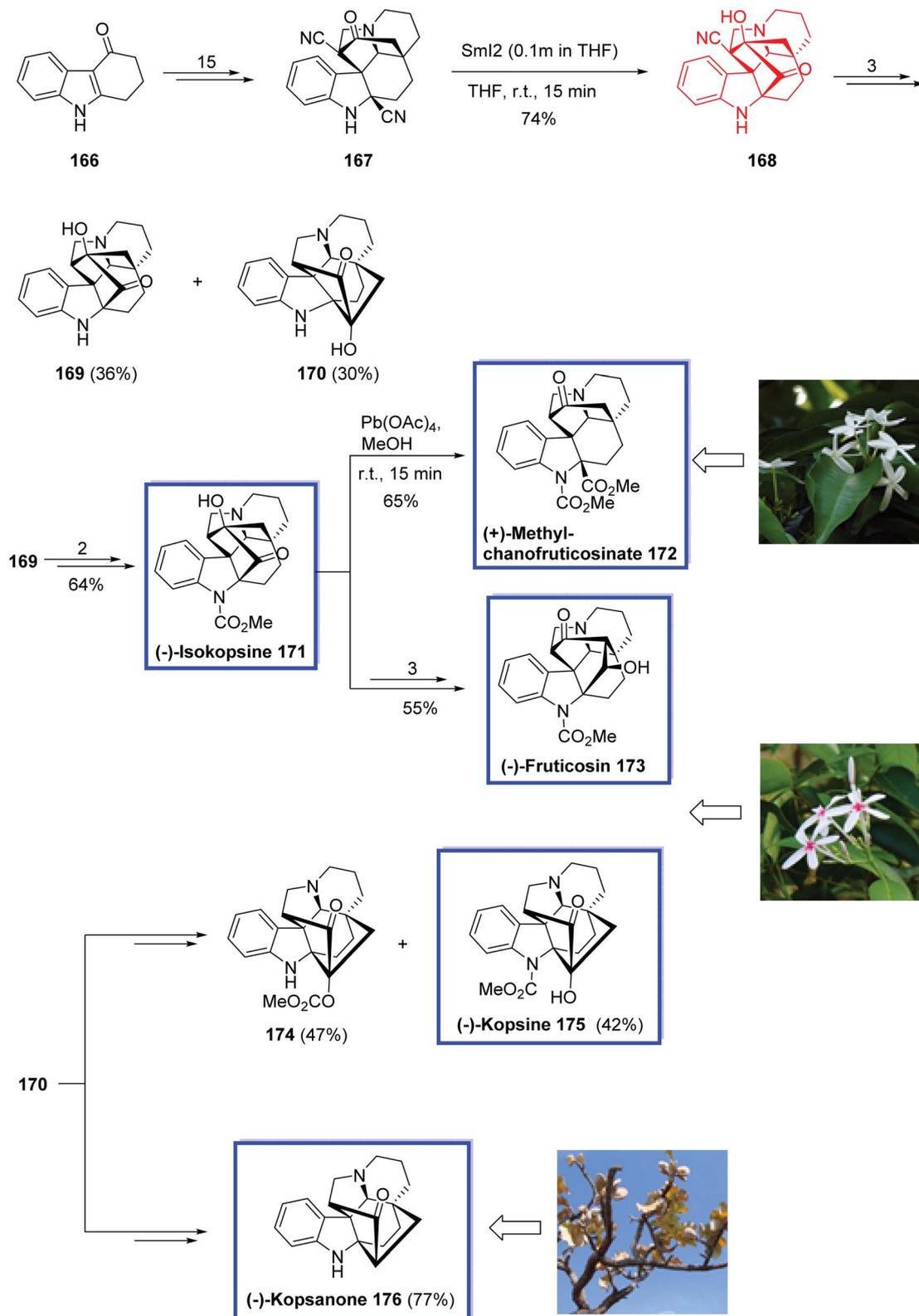
(−)-Fruticosine **173** and (−)-kopsine **175**, isolated from *Kopsia fruticosa*, (−)-kopsanone **176**, isolated from *Aspidosperma macrocarpon* Mart., and (+)-methylchanofruticosinate **172**, isolated from *K. arborea*, belong to the subfamilies of kopsia indole alkaloids.[83] These alkaloids show several impressive types of biological activity, including cholinergic, antirheumatic, and anti-inflammation effects.[84]

In 2017, Qin and colleagues[88] reported the asymmetric total syntheses of all four subfamilies of kopsia indole alkaloids, *i.e.*, (−)-kopsine **175**, (−)-isokopsine **171**, (+)-methyl chanofruticosinate **172**, (−)-fruticosine **173**, and (−)-kopsanone **176**. The key steps contain an asymmetric Tsuji–Trost rearrangement to install the first quaternary carbon center at C20, an intramolecular cyclopropanation by diazo decomposition to generate the second and third quaternary carbon centers at C2 and C7, respectively, and a SmI$_2$-mediated acyloin reaction to form the isokopsine core. They prepared and applied two key intermediates, *N*-decarbomethoxyisokopsine **169** and *N*-decarbomethoxykopsine **170**, to synthesize Kopsia alkaloids with different subtype core structures.

The total synthesis of (−)-isokopsine **171**, (+)-methyl chanofruticosinate **172**, (−)-fruticosine **173**, (−)-kopsine **175** and (−)-kopsanone **176** began with the commercially available tetrahydrocarbazolone **166** to obtain ketone **167** in 15 steps. SmI$_2$-mediated acyloin condensation of **167** in THF at room temperature provided nitrile intermediate **168** in 74% yield, generating the C16–C22 bond. *N*-decarbomethoxyisokopsine **169** was then synthesized from **168** in 3 steps together with *N*-decarbomethoxykopsine **170** in 36% and 30% yield,

Scheme 34   The total synthesis of (−)-kopsinine **165**.

Scheme 35 Total synthesis of (−)-isokopsine 171, (+)-methyl chanofruticosinate 172, (−)-fruticosine 173, (−)-kopsine 175 and (−)-kopsanone 176.

respectively. (−)-Isokopsine, (−)-**171**, was obtained from **169** in 64% yield over two steps. (−)-Fruticosine, (−)-**173**, was synthesized from (−)-isokopsine, (−)-**171**, in 55% overall yield within 3 steps, and treatment of (−)-**171** with Pb(OAc)$_4$ caused the cleavage of the C16–C22 bond and provided (+)-methyl chano-fruticosinate, (+)-**172**, in 65% yield. (−)-Kopsine, (−)-**175**, was

synthesized from **170** in 42% yield together with **174** in 47% yield within 2 steps. (−)-Kopsanone, (−)-**176**, was also synthesized from **170** in two steps and 77% yield (Scheme 35).

In 2018, Ma and coworkers[89] developed a modified thiourea catalyst for the synthesis of 3,3-disubstituted carbazolones *via* the Michael addition of carbazolones to 2-chloroacrylonitrile **182** with excellent enantioselectivity. 3,3-Disubstituted
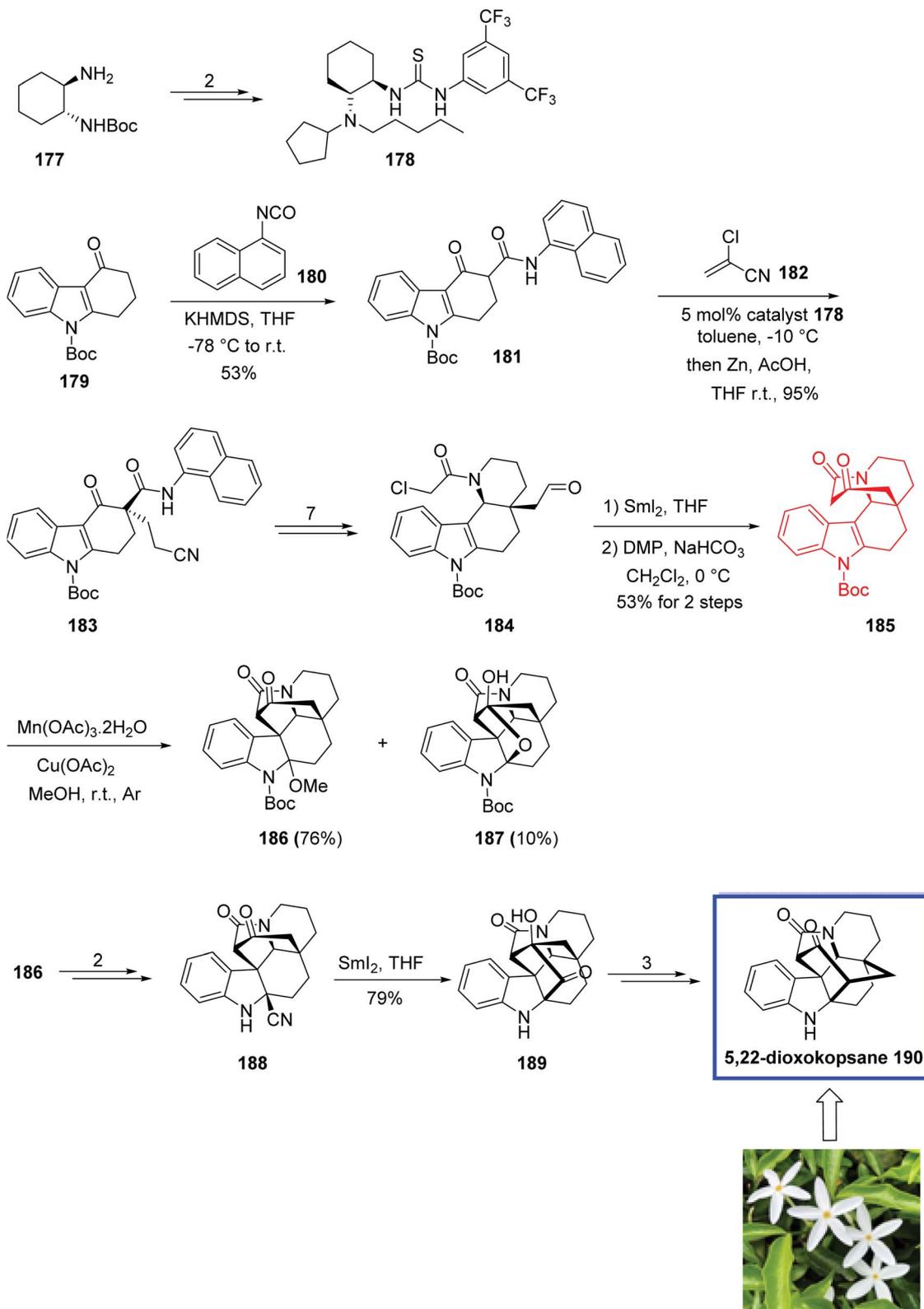
Scheme 36 Total synthesis of 5,22-dioxokopsane **190**.

carbazolones have been used as the valuable building blocks for developing *Aspidosperma* and *Kopsia* indole alkaloids during the past few decades. The key steps for the total syntheses of *Kopsia* alkaloids 5,22-dioxokopsane **190**, isolated from *Kopsia pauciflora*, kopsinidine C **194** and demethoxycarbonylkopsin **193**, isolated from *Kopsia officinalis*, involved the Mn^III-mediated oxidative cyclization to install the caged ring system and a SmI$_2$-mediated reductive coupling.

The total synthesis of 5,22-dioxokopsane **190**, kopsinidine C **194**, and demethoxycarbonylkopsin **193** began with the reaction of tetracarbazolone **179** and 2-naphthyl isocyanate **180** in the presence of KHMDS in THF to provide β-keto amide **181** in 53% yield. Michael addition of β-ketoamide **181** to chloroacrylonitrile **182** on gram scale with 5 mol% of the *n*-pentyl-substituted catalyst **178** at −10 °C and then treatment with zinc powder at room temperature provided 3,3-disubstituted carbazolone **183** in >95% yield and 96% ee. The thiourea catalyst **178** was prepared from commercially available *tert*-butyl ((1*R*, 2*R*)-2-aminocyclohexyl)carbamate **177** in 4 steps and 86% yield. Compound **183** was then converted into aldehyde **184** in 7 steps and 79% yield. A SmI$_2$-mediated Reformatsky-type cyclization of **184**, followed by the Dess–Martin oxidation provided ketoamide

185 in 53% yield. Ketoamide **185** was then converted into two cyclization products **186** and **187** using Mn(OAc)$_3$ as the single-electron oxidant and Cu(OAc)$_2$ as the co-oxidant in methanol in 76% and 10% yield, respectively. Next, aminonitrile **188** was synthesized from amino ketal **186** in two steps and 92% yield. A SmI$_2$-mediated reductive coupling between the keto and nitrile groups of amino nitrile **188** at ambient temperature gave isokopsine lactam **189** in 79% yield, from which 5,22-dioxokopsane **190** was synthesized in 3 steps and 44% yield (Scheme 36). In a parallel process, amino nitrile **191** was synthesized from hemiketal **187** in 2 steps and 91% yield. A SmI$_2$-mediated reductive coupling of **197** in THF at ambient temperature gave hydroxy ketone **198** in 75% yield. Subsequent NaOH-mediated ketol rearrangement of hydroxy ketone **192** in NaOH/dioxane (1 : 1) at room temperature gave demethoxycarbonylkopsin **193** in 80% yield. Further reduction of the ketone with LiAlH$_4$ delivered kopsinidine C **194** and 22-*epi*-kopsinidine C **195** in 40% and 30% yield (Scheme 37).

(−)-Histrionicotoxin 283A (HTX-283A, **206**) belongs to azaspirocyclic histrionicotoxin alkaloids and was first isolated from skin extracts of the Colombian poison arrow frog *Dendrobates histrionicus*. A mixture of six alkaloids including **206** and other
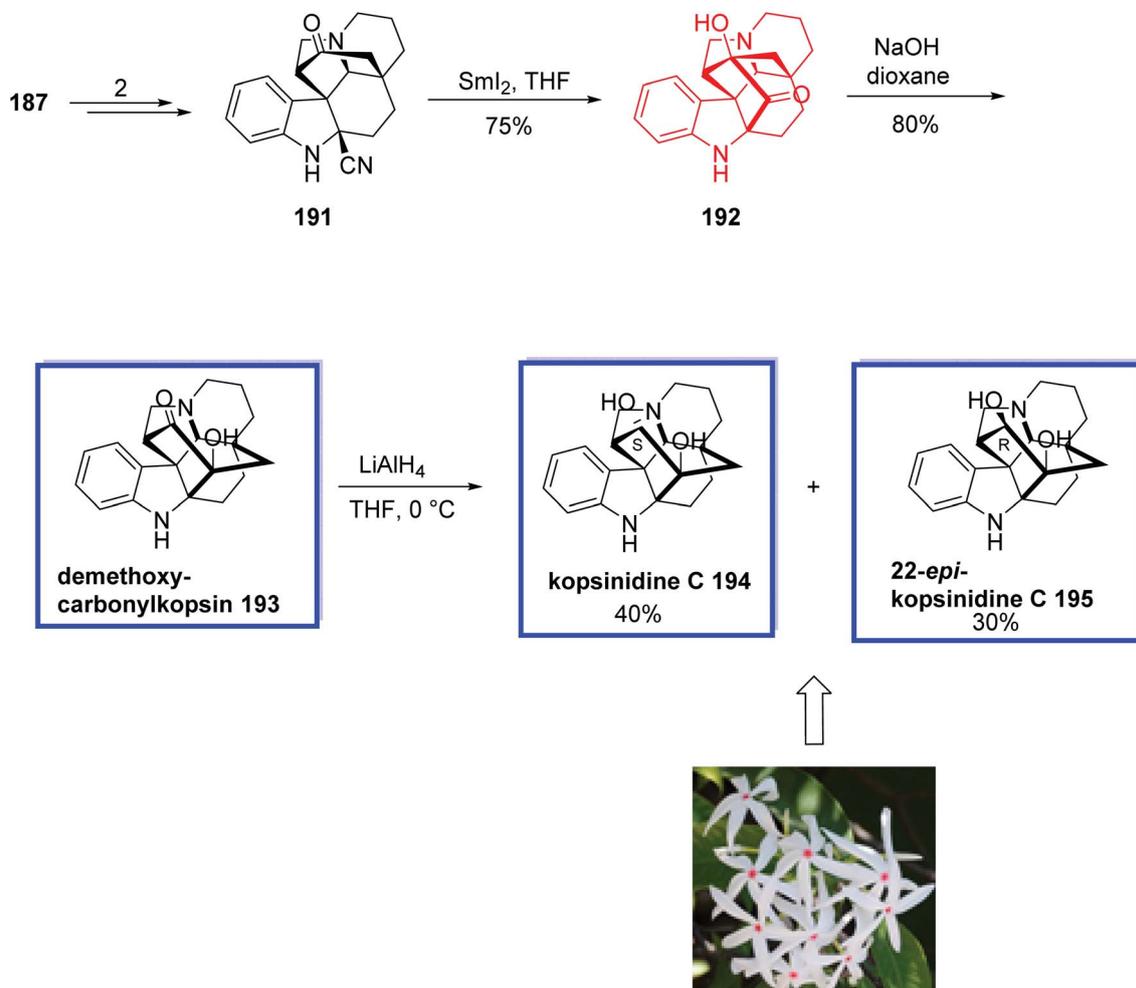
Scheme 37 The total synthesis of demethoxycarbonylkopsin **193**, kopsinidine C **194** and 22-*epi*-kopsinidine C **195**.

members have been isolated and identified so far. (−)-Histri-onicotoxin 283A **206** shows highly selective inhibition of nicotinic acetylcholine receptors.[90a]

(−)-Histrionicotoxin 235A (HTX-235A, **205**) was isolated from another poison frog *Dendrobates auratus*.[90b] It was used towards important investigations into neurophysiology.
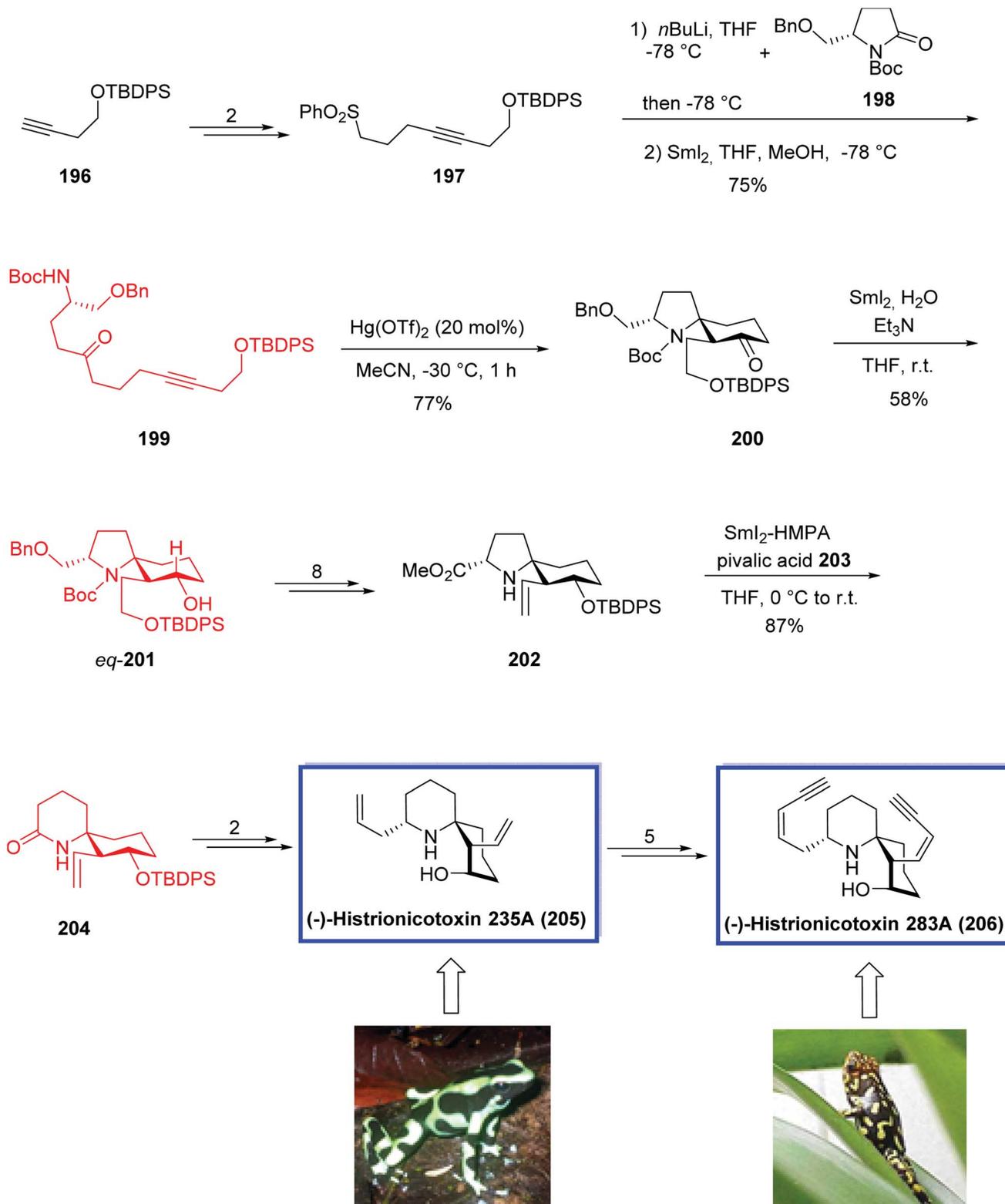
Scheme 38   The total synthesis of (−)-histrionicotoxin 235A (HTX-235A, **205**) and (−)-histrionicotoxin 283A (HTX-283A, **206**).

In 2018, Morimoto and coworkers[91] developed the formal total synthesis of histrionicotoxin alkaloids. The key steps were a Hg(OTf)$_2$-catalyzed cycloisomerization and a SmI$_2$-mediated ring expansion reaction.

The SmI$_2$-mediated ring expansion was used as a key step to synthesize 1-azaspiro[5.5]undecane skeleton **204** in 15 steps and 15% overall yield, based on the known silyl ether **196**, in comparison with Tokuyama's method (5% overall yield and 14 steps based on the ketodiester and benzylamine). This synthetic approach was the first SmI$_2$-mediated radical ring expansion applied to the synthesis of such a complex system as a 1-azaspiro[5.5]undecane skeleton of histrionicotoxins.

The total synthesis of **205** and **206** started from the known silyl ether **196**. Alkylation of a lithium acetylide of silyl ether **196** provided sulfone **197** in 2 steps. Reacrion of 191 with known pyrrolidinone **198** followed by SmI$_2$-mediated desulfonylation provided the desired cyclization precursor **199**. The Hg(OTf)$_2$-catalyzed cycloisomerization reaction of precursor **199** using 20 mol% catalyst in −30 °C provided the desired spirocyclic product **200** in 77% yield. The reaction of **200** with SmI$_2$ in the presence of H$_2$O and triethylamine provided the desired equatorial-alcohol **201** as a major diastereomer in 58% yield. The *eq*-alcohol **201** was then converted into silyl ether **202** in 8 steps. Compound **202** was further converted into 1-azaspiro[5.5] undecane **204** in high yield *via* the key SmI$_2$-mediated ring expansion reaction using HMPA and pivalic acid **203**. The key

intermediate **204** was transformed to (−)-HTX-235A **205** in two steps, and then further converted into HTX-283A, **206** in 5 steps (Scheme 38).

Wickerols A **211** and B **212** are diterpene natural products and were isolated from the fungus *Trichoderma atroviride* FKI-3849,[92] and more recently, from cultures of the marine red alga-epiphytic fungus *Trichoderma koningiopsis* Y10-2.[93] They are similar to the types of molecules with potential activity against the influenza virus.[94]

Wickerol B **212,** possesing a hydroxyl group at C8, is less active than Wickerol A **212** whereas wickerol A **211** shows antiviral activity against the H1N1 type A influenza virus.[92–94] Therefore, different strategies for the synthesis of wickerols and their analogues would extremely promote an extensive investigation of the structure–activity relationships.

In 2020, Gui and coworkers[95] reported a divergent total synthesis of wickerols A **211** and B **212** in 16 and 15 steps, respectively, from sitolactone **207**.

The key steps included a SmI$_2$-induced intramolecular reductive cyclization, a Claisen rearrangement, and an intra-molecular alkylation/aldol reaction to develop the tetracyclic core stereoselectively, and the absolute configurations of wickerols A **211** and B **212** were assigned. Under optimized conditions, they observed that the key SmI$_2$-induced intramolecular reductive cyclization can be performed on a gram scale with similar yields. All the spectroscopic data and for synthetic
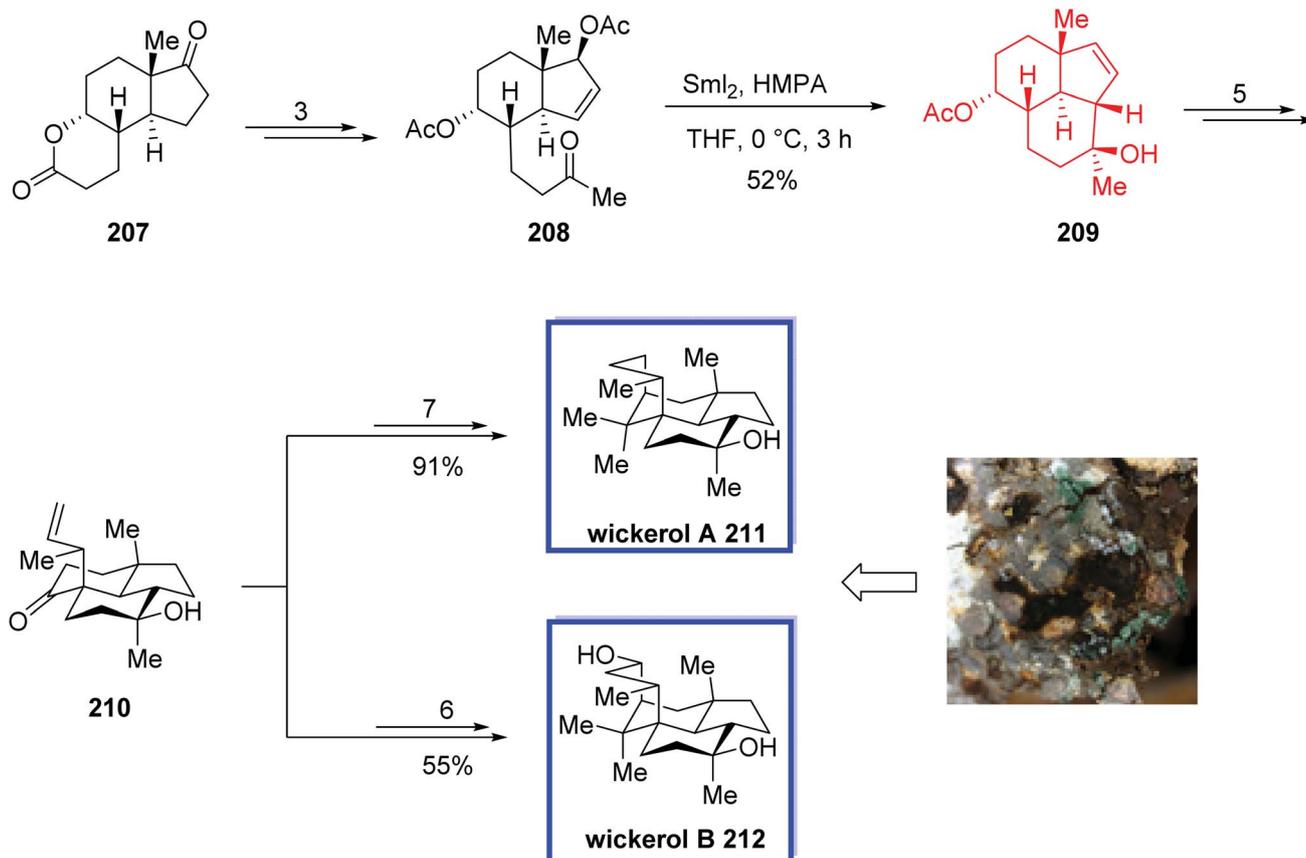
Scheme 39 The total synthesis of wickerol A **211** and wickerol B **212**.

wickerol A **211** and wickerol B **212** were in good agreement with those reported for the natural products, and they had absolute configurations the same as the natural isolates.

The total synthesis of wickerol A **211** and wickerol B **212** began with the commercially available sitolactone **207** to obtain ketone **208** in 3 steps and 95% yield. SmI$_2$-mediated
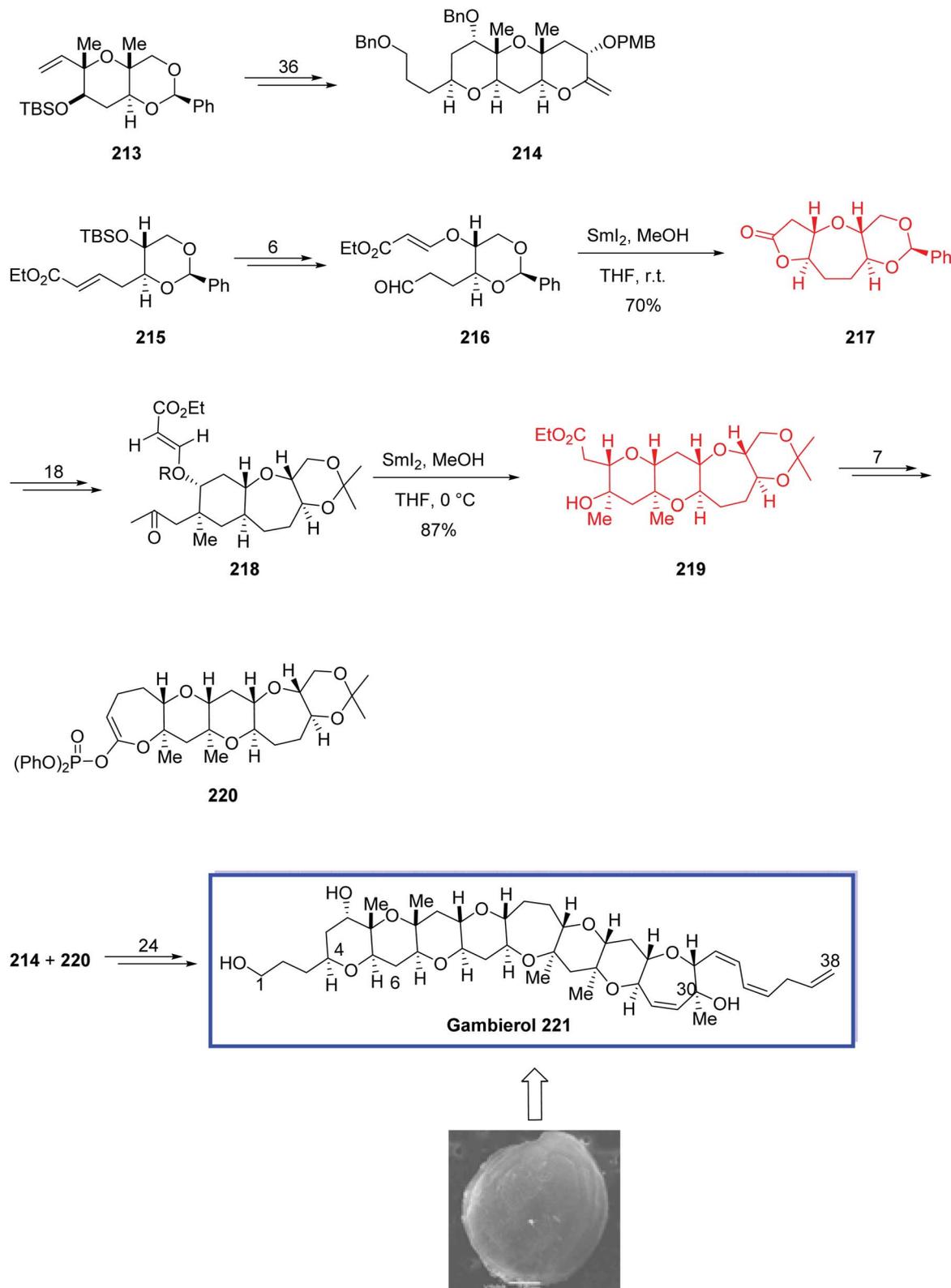
Scheme 40 Total synthesis of (−)-gambierol **221**.

intramolecular ketone–allylic acetate reductive cyclization of ketone **208** using hexamethylphosphoramide (HMPA) in THF under the optimized conditions afforded desired compound **209** in 52% yield, from which ketone **210** was then synthesized in 5 steps and 70% yield. The terminal olefin **210** was then used to complete the synthesis of wickerols A **211** and B **212** in 7 and 6 steps and 91% and 55% yields, respectively (Scheme 39).

Gambierol **221**, a neurotoxin isolated from the cultured cells of the ciguatera causative dinoflagellate *Gambierdiscus toxicus*, belongs to the fused polycyclic ether marine natural products, is a potent blocker of voltage-gated potassium channels, and also is responsible for ciguatera fish poisoning.[96] Due to the molecular complexity of structures of this class of marine natural products and their potent and multiple biological activities, they continue to be of great interest to synthetic chemists. Gambierol **221** contains a trans-fused octacyclic ring system with 18 stereogenic centers, a partly conjugated triene side chain, and two 1,3-diaxial dimethyl-substituted tetrahydropyranyl rings.

In 2002, Sasaki and colleague[97] developed the first total synthesis of (−)-gambierol **221**. Key steps contain B-alkyl Suzuki–Miyaura cross-coupling of the ABC and EFGH ring fragments, **214** and **220**, respectively, to construct the octacyclic polyether scaffold, a SmI₂-mediated reductive cyclization to improve the synthetic method to construct the F and H rings (the EFGH ring fragment **220**), and a late-stage installation of the sensitive triene side chain *via* Pd(PPh₃)₄/CuCl/LiCl-induced Stille coupling. This very efficient route enabled the synthesis of **214** and **220** in multigram quantities and easy access to a variety of structural analogues of gambierol **221**. The spectral data of synthetic gambierol **221** was in good agreement with that of the natural product. The absolute configuration of gambierol **221** was also confirmed.

The total synthesis of (−)-gambierol **221** began with the preparation of the ABC and EFGH ring fragments, **214** and **220**, respectively. The ABC ring exocyclic enol ether **214** was synthesized from the known olefin **213** in 36 steps and 18% overall yield.

Synthesis of the EFGH ring fragment **220** started from the known ester **215** to provide aldehyde **216** in 6 steps and 91% yield. Stereoselective reductive cyclization of **216** using SmI₂ in the presence of methanol/THF and at room temperature afforded the desired γ-lactone **217** in 70% yield, which was then converted to β-alkoxy acrylate **218** in 18 steps and almost quantitative yield. Stereoselective ring closure of the F ring containing 1,3-diaxial angular methyl groups occurred through the treatment of **218** with SmI₂ in methanol/THF at 0 °C and gave the FGH ring system **219** in 87% yield as a single stereoisomer. The EFGH ring ketene acetal phosphate **219** was then achieved in 7 steps. Accordingly, the EFGH ring fragment **220** was synthesized in 33 steps and 22% overall yield from **215**. With the coupling of two key intermediates **214** and **220**, and construction of the octacyclic polyether core, the total synthesis of (−)-gambierol **221** was then completed in 24 steps and 43% yield (Scheme 40).

The *ent*-kaurene diterpenoids, one special classification of the diterpenoid family, have gained increasing attention due to their structural variety and complexity, together with comprehensive bioactivity outlines. The Isodon species of plants produce an enormous collection of terpene natural products that are biosynthetically originated from the familiar *ent*-kaurene nucleus. Among these *ent*-kaurene diterpenoids,
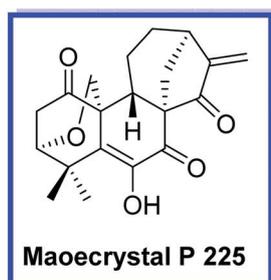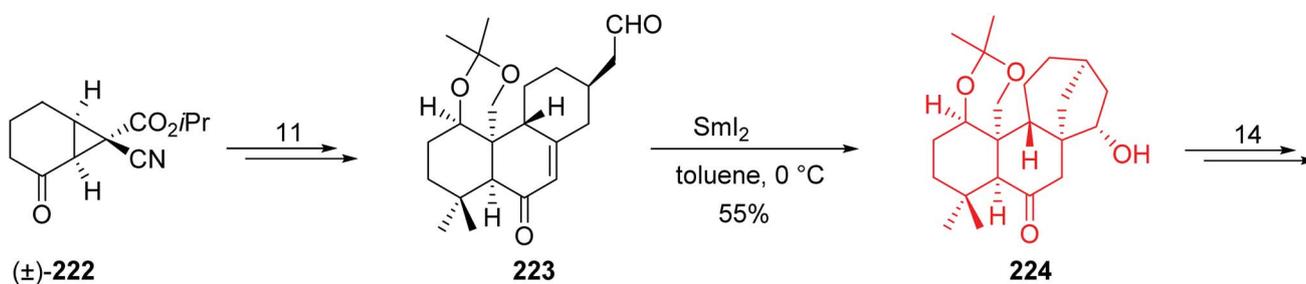
Scheme 41 Total synthesis of maoecrystal P **225**.

maoecrystal P **225**, isolated from the Chinese medicinal plant *Isodon eriocalyx*, exhibits promising cytotoxicity against human tumor cells.[98]

In 2018, Luo and co-workers[99] introduced a new strategy for the total synthesis of maoecrystal P **225** with 27 steps from commercially available 2-bromocyclohex-2-one **222**. The total synthesis of maoecrystal P **225** included a highly regio- and diastereoselective intermolecular Diels–Alder cycloaddition, redox manipulations, a SmI$_2$-mediated carbonyl–alkene cyclization, and isomerization reactions. This novel strategy could be used for the synthesis of other highly oxidized *ent*-kauranoids for biological evaluation.

The total synthesis of maoecrystal P **225** began with ketone **222** and delivered the cyclization precursor **223** in 11 steps. The reaction of **223** with excess SmI$_2$ in toluene at 0 °C provided ketol **224** as a single diastereomer in the modest yield of 50–60% with the completion of the *ent*-kauranoid skeleton. The modest yield of **224** can be justified due to the difficulty of building a hindered quaternary center and a forced ring construction. Finally, maoecrystal P **225** was synthesized from **224** in 14 steps and 55% yield, completing the *ent*-kauranoid skeleton with a hindered quaternary center and a strained ring system (Scheme 41).

Grayanane diterpenoids (grayanoids), with unique carbon skeletons, were isolated from plants of the Ericaceae family. Grayanoids show various biological properties such as anticancer, antiviral, antifeedant, antinociceptive, analgesic, insecticidal, toxicity, and protein tyrosine phosphatase 1B (PTP1B)

properties. Principinol D **233**, isolated from *Rhododendron principis*, belongs to the grayanane diterpenoid natural products with a broad range of biological activities.[100] Grayananes are a wider class of rearranged kaurane natural products. More than one thousand kaurane diterpenoids have been isolated; however, only a few of them have been synthesized. Structurally, principinol D **233** contains a highly oxidized tetracyclic core, consisting of a bicyclo[3.2.1]octane ring system with five stereocenters. It inhibits protein tyrosine phosphatase 1B (PTP1B) *in vitro*, which is a potential target for obesity and types 2 diabetes therapy.[101]

In 2019, Newhouse and colleagues[102] reported the first asymmetric total synthesis of principinol D **233** in 19-steps. The key steps contain a SmI$_2$-mediated reductive cyclization to construct the central seven-membered ring of the grayanane skeleton, a convergent fragment coupling protocol through a 1,2-addition reaction between a bicyclo[3.2.1]octane fragment **229** and a cyclopentyl fragment **230**, and Ni-catalyzed α-vinylation reaction to establish the bicyclo[3.2.1]octane. Reductive strategies involved a diastereoselective SmI$_2$-induced ketone reduction of a bicyclic ketone and a new procedure for selective ester reduction in the presence of ketones. The NMR spectra of the product were in good agreement with those reported for the isolated natural product. According to the researchers, the reported fragment-based strategy is expected to be utilized for SAR-investigations and the synthesis of various grayanane derivatives.
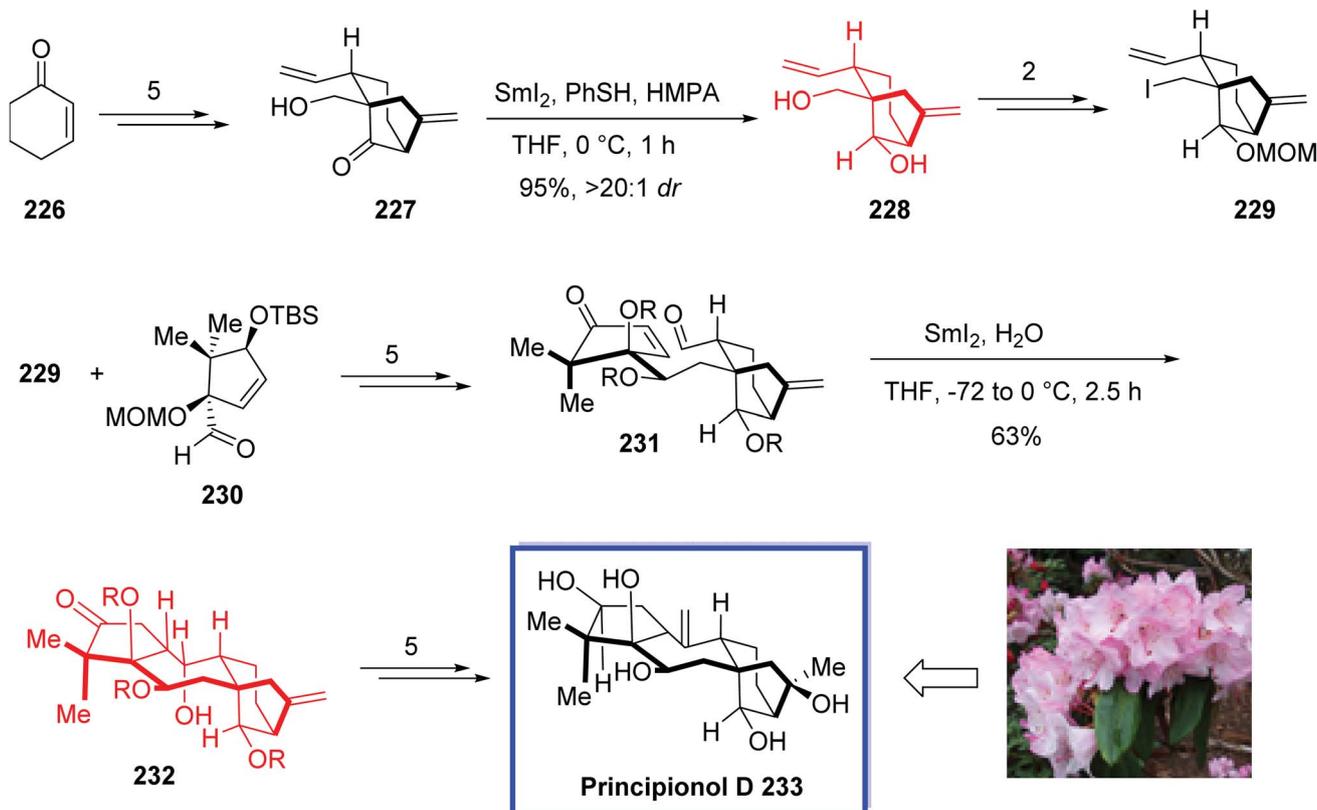
Scheme 42 Total synthesis of principinol D **233**.

The synthesis of bicyclo[3.2.1]octane fragment **229** began with cyclohexenone **226** to afford ketone **227** in 5 steps. Diastereoselective reduction of ketone **227** with SmI$_2$ in the presence of HMPA and PhSH provided the desired alcohol **228** in an excellent yield (95%, >20 : 1 d.r.). From alcohol **228**, the bicyclo [3.2.1]octane **229** was obtained in 2 steps and 87% yield. The racemic bicyclo[3.2.1]octane **229** was then coupled with the enantioenriched cyclopentyl aldehyde **230** (er = 93 : 7) to give enone-aldehyde **231** in 5 steps. Closure of the seven-membered ring occurred through treatment of **231** with SmI$_2$ in the presence of water to produce the desired tetracycle **232** in 63% yield as a single diastereomer, from which principinol D **233** was synthesized in 5 steps and 78% yield (Scheme 42).
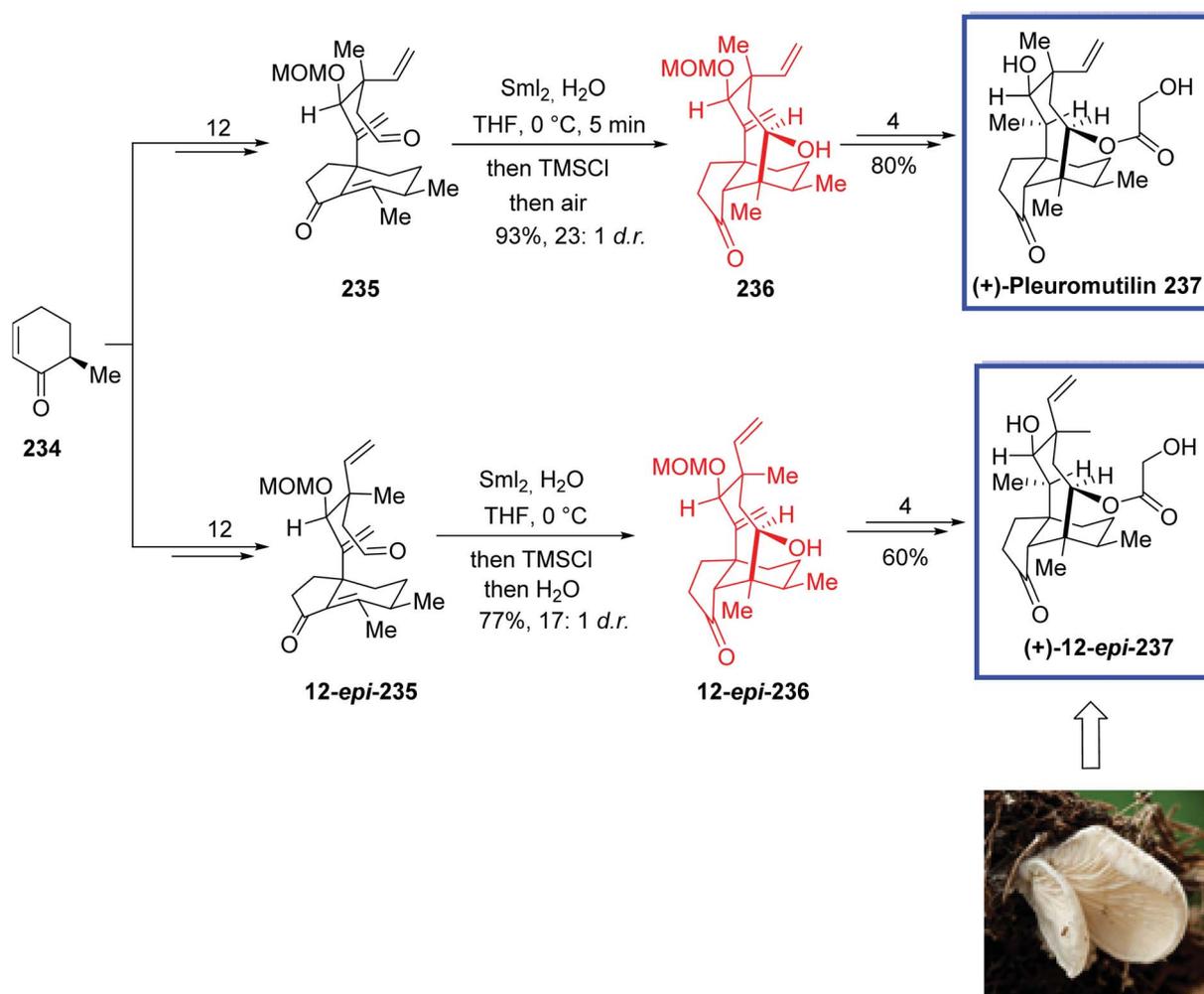
(+)-Pleuromutilin **237**, isolated from the fungus *Clitopilus passeckerianus*,[103] is a diterpene natural product with antibiotic activity. This antibiotic prevents protein synthesis, by which it connects to the peptidyl transferase center of bacterial ribosomes.[104]

In 2018, Reisman and colleagues[105] developed the total synthesis of the antibiotics (+)-pleuromutilin **237** and (+)-12-*epi*-pleuromutilin **12-*epi*-237** each in 18 steps from (+)-*trans*-dihydrocarvone. The key steps included the construction of the

eight-membered ring through a highly stereoselective SmI$_2$-promoted cyclization and the installation of the C10 stereocenter *via* a stereospecific transannular [1,5]-hydrogen atom transfer. According to researchers the shortness and modularity of the reported strategy will facilitate the design and synthesis of new mutilin antibiotics.

The total syntheses of (+)-pleuromutilin **237** and (+)-12-*epi*-pleuromutilin **12-*epi*-237** began with the enone **234**. Aldehydes **235** and **12-*epi*-235** were then synthesized from enone **234** each in 12 steps. It was found that dropwise addition of SmI$_2$ (3 equiv.) to **235** with 6 equivalents of H$_2$O in THF at 0 °C in the absence of oxygen, followed by quenching with trimethylsilyl chloride (TMSCl) and water provided tricycle **236** as a separable mixture of diastereomers (23 : 1) in 93% yield. H$_2$O played a significant role to attain high diastereoselectivity. (+)-Pleuromutilin **237** was then synthesized from **236** in 4 steps and 80% yield. SmI$_2$ cyclization of **12-*epi*-235** under optimal conditions provided **12-*epi*-236** in 77% yield (17 : 1 d.r.), and **12-*epi*-237** was synthesized from **12-*epi*-236** in 4 steps (Scheme 43).

Paucidirinine **244**, isolated from the stem bark of *Kopsia pauciflora*, is a member of the aspidofractinine alkaloid family containing a constricted five-membered lactam ring. The

Scheme 43 Total synthesis of (+)-pleuromutilin **237** and (+)-12-*epi*-pleuromutilin **237**.

Review
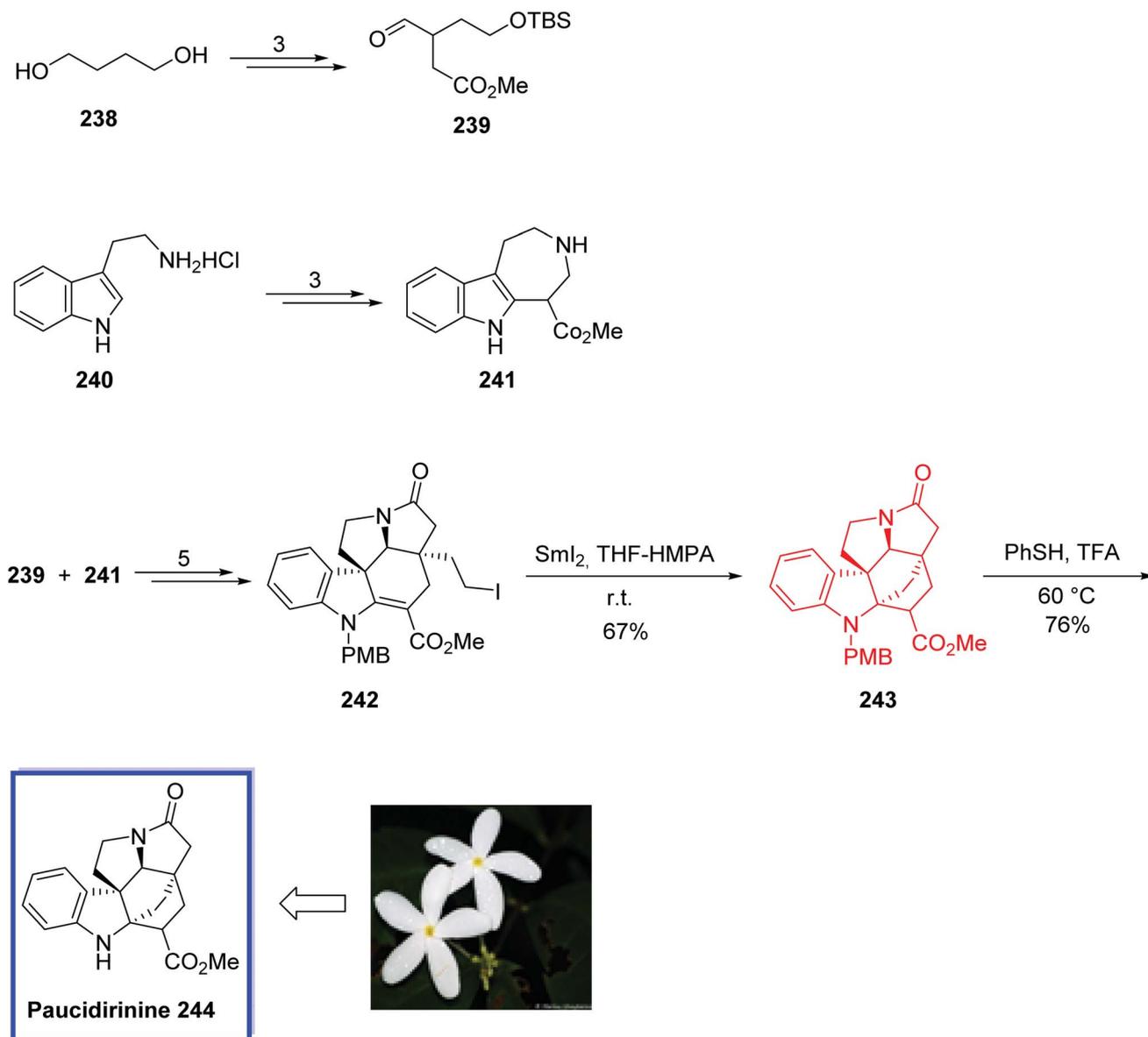
Scheme 44 Total synthesis of paucidirinine **244**.

aspidofractinine alkaloids are a class of structurally complex alkaloids isolated from the leaves of *Pleiocarpa tubicana* and *Aspidosperma refractum*.[106] They display considerable medicinal properties and biological activity, and several members of this family can reverse multidrug resistance in human cancer.[107]

In 2019, She and coworkers[108] developed the first total synthesis of paucidirinine **244** in 10 steps and 8% overall yield from tryptamine hydrochloride salt. Key steps of this potentially scalable strategy contain a highly stereocontrolled intramolecular [4 + 2] Diels–Alder reaction, an acid-catalyzed lactamization, and a challenging late-stage SmI$_2$-induced radical cyclization to construct the bicyclic[2.2.2]octane core. The relative configuration of this potentially bioactive alkaloid was also confirmed through X-ray diffraction analysis.

The total synthesis of paucidirinine **244** began with 1,4-butanediol **238** to obtain aldehyde **239** in 3 steps and 61% yield.

The key indole precursor **241** was prepared in 3 steps and 98% yield using tryptamine hydrochloride salt **240** as the starting material. Indole **241** was then coupled with aldehyde **239** to obtain alkyl iodide **242** in 5 steps. The SmI$_2$-mediated cyclization of **242** in THF/HMPA (10 : 1) for 1 h at 25 °C provided the desired cycloadduct **243** in 2 steps and 67% yield. Finally, removal of the *p*-methoxybenzyl group with TFA provided paucidirinine **244** in 76% yield (Scheme 44).

Kopsinitarine E **248**, isolated from *K. teoi* L. Allorge,[109] is a new member of the *Kopsia* species. Kopsinitarines A–E are *Kopsia* alkaloids, comprising a cage-like system that contains two five-membered rings and three six-membered rings.

In 2020, Ma and colleagues[110] reported the first total synthesis of kopsinitarine E **248** in 20 steps from commercially available carbazolone **245**. The key steps comprised a remarkable SmI$_2$-mediated radical cyclization cascade, followed by
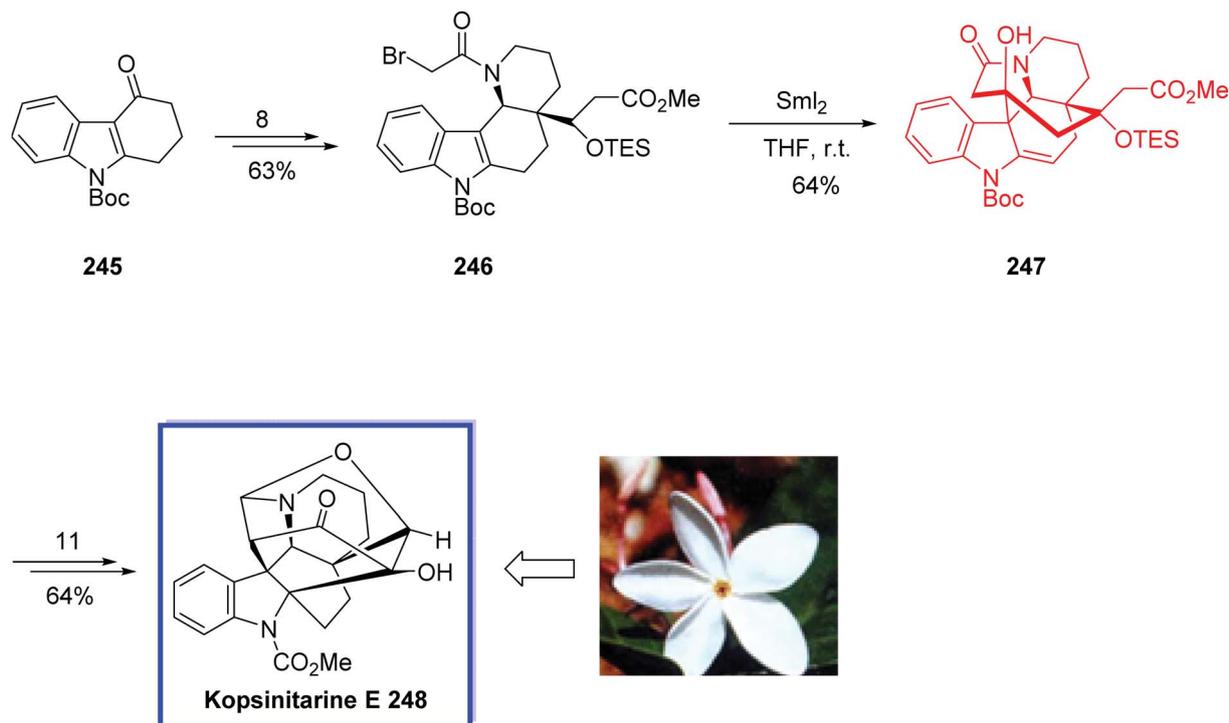
Scheme 45 Total synthesis of kopsinitarine E **248**.

semi-pinacol rearrangement to install the 5,7-fused ring system, a chemoselective hydrosilyl amide reduction to establish the hemiaminal ether bridge, and an intramolecular Mannich reaction for closure of the highly strained cage system. According to the authors, the SmI_2-key procedure would be useful for developing other *Kopsia* alkaloids containing this key skeleton. The spectral data of synthetic kopsinitarine E **248** were in good agreement with those reported for natural kopsinitarine E.

The total synthesis of kopsinitarine E **248** commenced with a known Boc-protected carbazolone **245** to provide the bromide **246** in 8 steps and 63% yield. A SmI_2-mediated Dieckmann-like condensation of **246** gave alcohol **247** in 64% yield. Finally, kopsinitarine E **248** was synthesized from **247** in 10 steps and 64% yield (Scheme 45).

Q-1047H-A-A **253** and Q-1047H-R-A **254**, isolated from a culture of *Pseudonocardia* sp. Q-1047 (type strain deposited under FERM-2331),[111] belong to a class of macrolactam bacterial metabolites and are members of the macrolactam natural products, which exhibit various biological and pharmacological activities.[112]

Q-1047H-A-A **253** and Q-1047H-R-A **254** contain 13-membered lactams with four stereogenic centers. The general structural scaffold of Q-1047H-A-A **253** makes it a key intermediate to access other natural products.

In 2013, Yang and colleagues[113] reported the first total synthesis of Ansamacrolactams (+)-Q-1047H-A-A **255** and (+)-Q-1047H-R-A **256** in 17 steps. The key steps in the synthetic work included an asymmetric chelation-controlled vinylogous Mukaiyama aldol reaction for the stereoselective synthesis of

the *syn*-aldol adduct and an intramolecular SmI_2-mediated Reformatsky reaction for the formation of the macrocyclic lactam **252**. The spectral data for the synthetic Q-1047H-A-A **255** were in good agreement with those reported for the natural product, but with the opposite sign of its optical rotation. Therefore, it was found that the synthetic ansamacrolactams (+)-Q-1047H-A-A **253** and (+)-Q-1047H-R-A **254** were the enantiomers of the compounds reported as the natural products, and the relative stereochemistry and absolute configuration of the natural products (+)-Q-1047H-A-A **253** and (+)-Q-1047H-R-A **254** were reassigned as compounds **255** and **256**. According to researchers, the developed synthetic strategy should be used for the syntheses and SAR analysis of other structurally and biologically related products.

The total synthesis of (+)-Q-1047H-A-A **253** and (+)-Q-1047H-R-A **254** began with the reaction of N,O-acetal **249** with benzaldehyde **250** to afford aldehyde **251** in 11 steps and 60% overall yield. The key SmI_2-promoted Reformatsky reaction of **251** occurred *via* the addition of **251** to the solution of SmI_2 in THF under reflux, and the desired cyclization product **252** was obtained in 84% yield as a mixture of two pairs of diastereomers (3.9 : 1 : 4.0 : 3.3) related to the C2 and C3 carbon centers. Q-1047H-A-A **253** was then synthesized from the mixture of **252** in 2 steps and 51% yield. Finally, the reduction of Q-1047H-A-A **253** with $Na_2S_2O_4$ afforded Q-1047H-R-A **254** in 64% yield (Scheme 46).

2.3. SmI_2-mediated sequential reactions

Strychnine **263**, isolated from the seeds of the *Strychnos nux-vomica* tree belong to the family of Strychnos alkaloids,[114] which
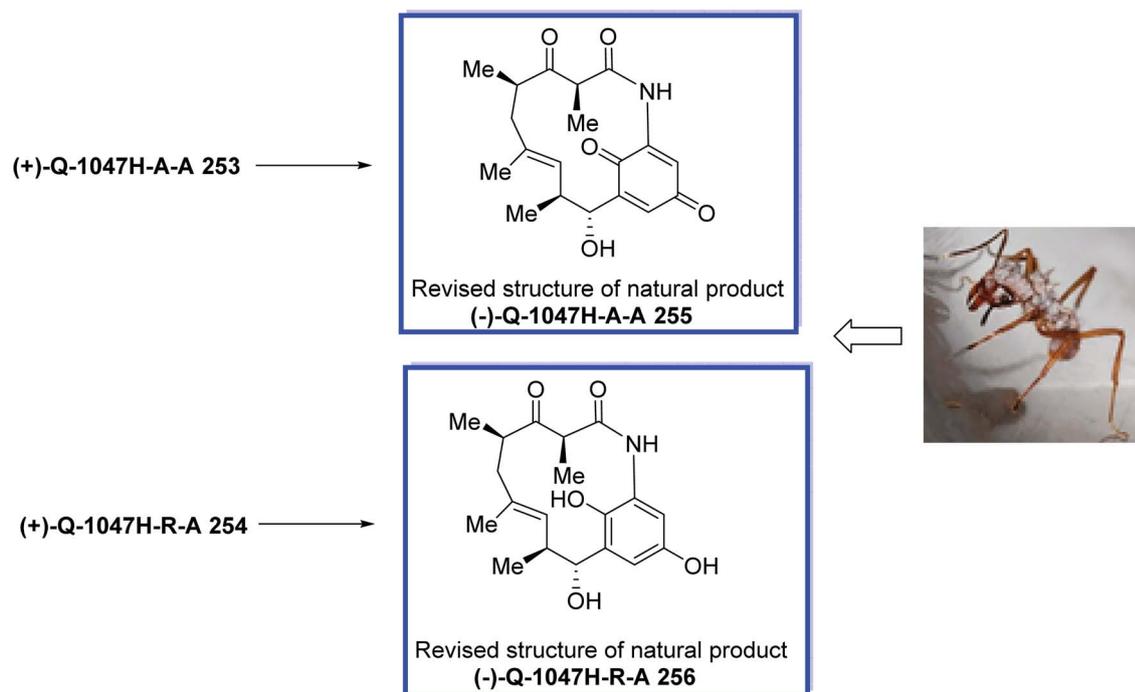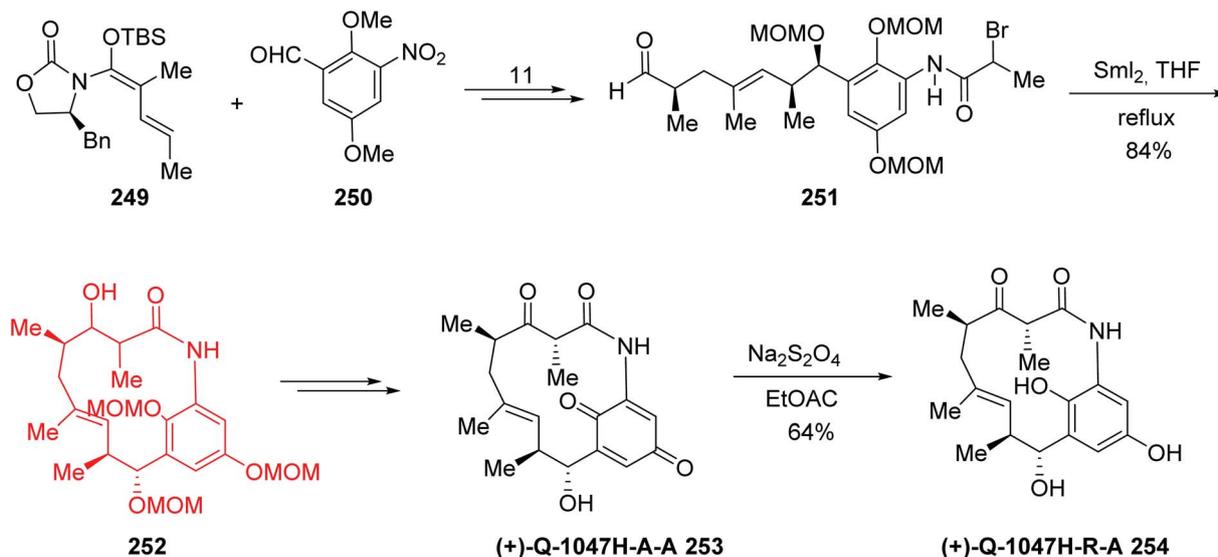
Scheme 46 Total syntheses of (+)-Q-1047H-A-A **253** and (+)-Q-1047H-R-A **254**.

are one of the most fascinating classes of natural products. Strychnine **263** is the most complex natural product of this size, and its elevated level of complexity has continued to persuade synthetic chemists. Its structure retains seven fused rings and six asymmetric centers; hence, it is one of the most complex natural products of this size.

In 2010, Reissig and coworkers[115] developed the shortest formal total synthesis of strychnine **263**. In this strategy, they show the power of SmI$_2$-promoted cascade reaction to construct two new rings, three stereocenters, and a quaternary carbon atom in one step from a commercially available indole

derivative. The key strychnine precursor **259** was accomplished from commercially available indolylacetonitrile in only five steps in an overall yield of 33%, and its incorrectly reported configuration at C-13a was also revised. By examination of the scope of this SmI$_2$-induced ketyl–aryl coupling/acylation cascade reaction, it was accepted that this method could be applied to various highly functionalized tetracyclic indole derivatives stereoselectively.

The total synthesis of strychnine **263** began with a rapid SmI$_2$-promoted cascade reaction of indole derivative **257**. Treatment of **257** with 2.4 equivalents of samarium diiodide
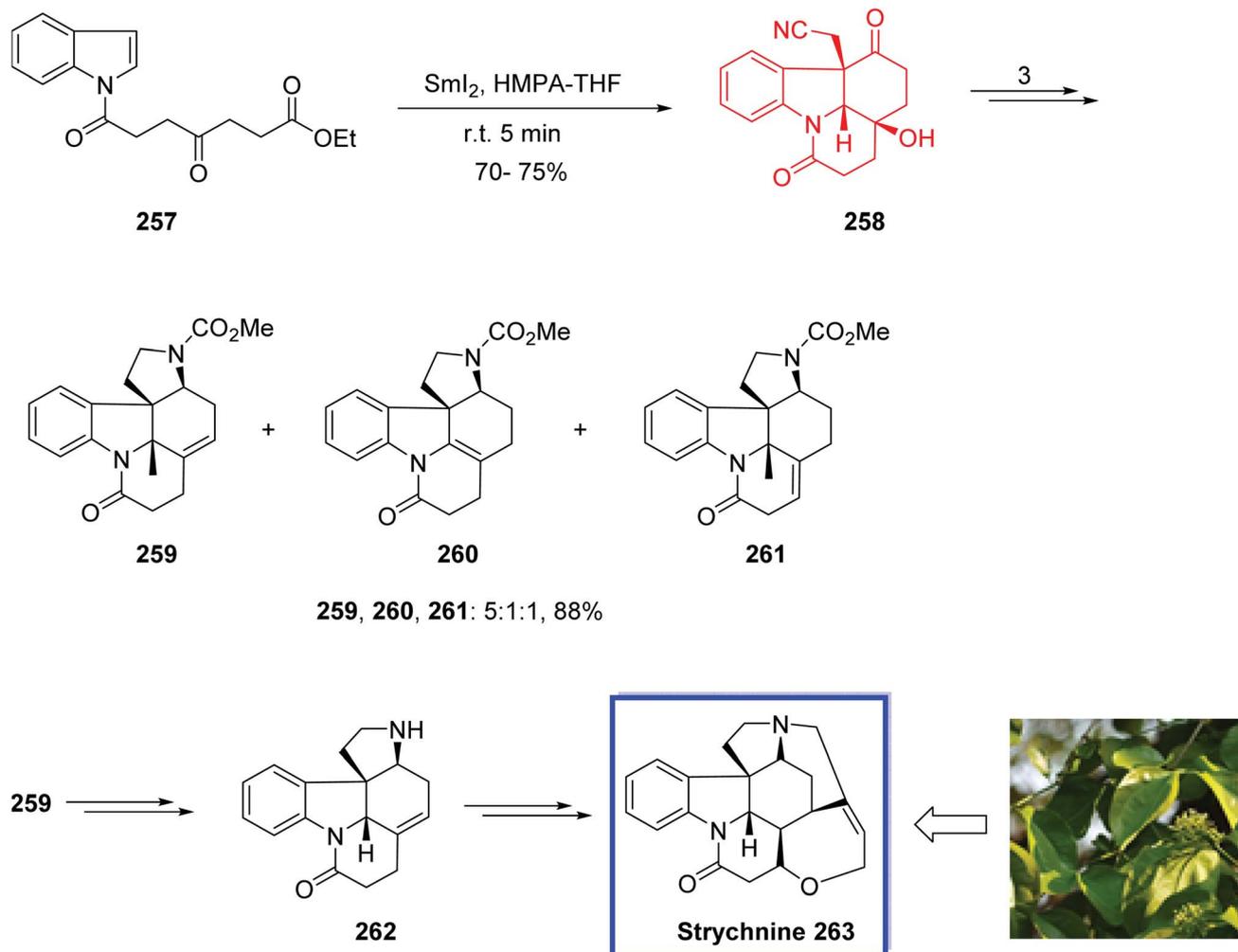
Scheme 47 Total synthesis of strychnine **263**.

and hexamethylphosphoramide (HMPA) provided diastereomerically pure tetracycle **258** as the major product in 70–75%. The tetracyclic building block **258** was then converted to the desired key building block **259** as the major product in good selectivity (5 : 1 : 1 ratio). Finally, carbamate **259** was converted into the pentacyclic strychnine precursor **262**, known as Rawals key building block, to complete the formal total synthesis of strychnine **263** (Scheme 47).

(+)-Crotogoudin **268**, derived from the Madagascan *Croton* plant,[116] belongs to the unusual 3,4-seco atisane family of diterpenoid natural products. Species of the Croton genus are a rich source of secondary metabolites with a broad spectrum of biological activities.[116,117] (+)-Crotogoudin **268** exhibits antiproliferative activity *in vitro* against different human cancer cell lines.[116,117] Structurally, (+)-crotogoudin **268** consists of a tetracyclic ring system with four contiguous stereocenters and with a six-membered ring fused to a bicyclo[2.2.2]octane core.

In 2013, Carreira and coworkers[118] reported the first total synthesis of *ent*-crotogoudin **268**. The key step involved a radical cyclopropane-opening/annulation/elimination cascade for the diastereoselective synthesis of the tetracyclic carbon core. They

also used an efficient pathway to synthesize 1-substituted bicyclo[2.2.2]octa-2,6-diones. The absolute configuration of the (+)-crotogoudin natural product was also assigned. Spectral data for synthetic (+)-crotogoudin **268** were in good agreement with those reported for the natural product. Comparison of the optical rotation shows identical signs for both synthetic and natural material, but with significantly different magnitude. Therefore, the absolute configuration of the natural product (+)-crotogoudin (*ent*-**268**) was assigned to 5R, 10R, belonging to the *ent*-atisane family.

The total synthesis of (+)-crotogoudin **268** began with the reaction of ketoester **264** with enal **265** to afford allylic pivaloate **266** in 12 steps. Tetracyclic compound **267** was synthesized in 80% yield and high diastereoselectivity (d.r. = 7.7 : 1) *via* a SmI$_2$-mediated cascade reaction of allylic pivaloate **266** under optimized reaction conditions (THF/1,3-dimethyl-2-oxohexahydropyrimidine 9 : 1, 0 °C to r.t.) and due to steric hindrance of the allylic leaving group of **266**. The reaction was found to be sensitive to the method of preparation of SmI$_2$. Finally, methyl carboxylate **267** was converted into (+)-crotogoudin **268** in 54% and 4 steps (Scheme 48).
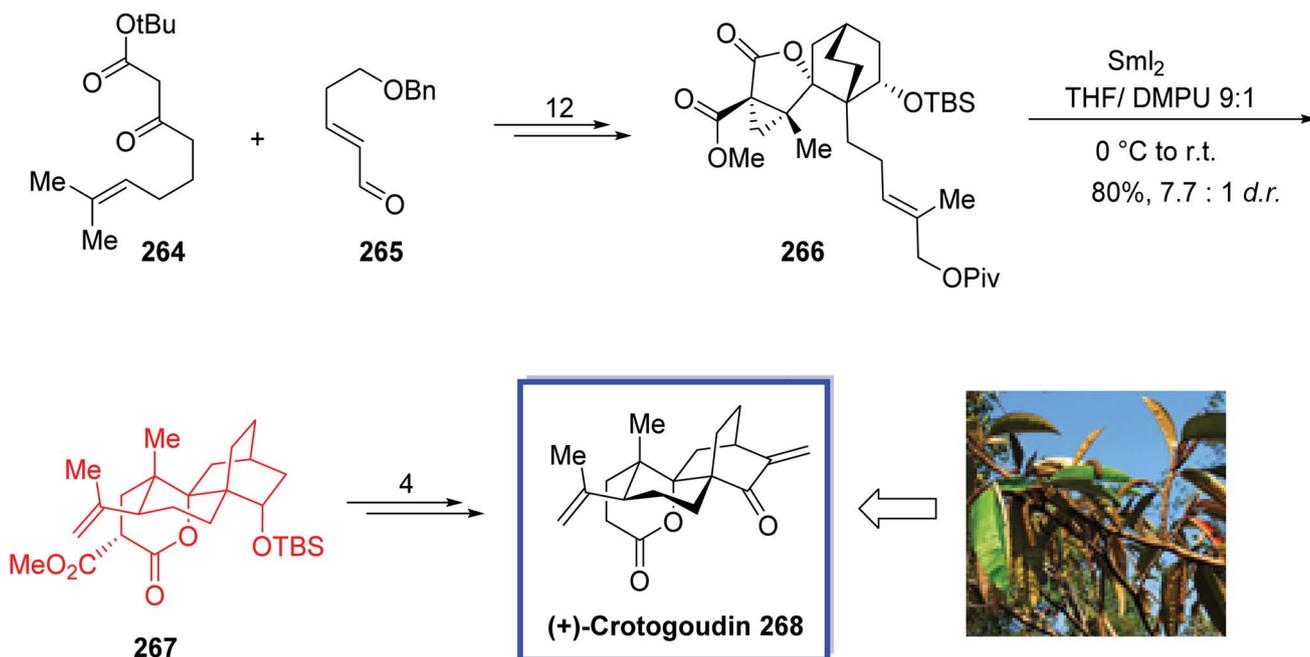
Scheme 48 Total synthesis of (+)-crotogoudin 268.
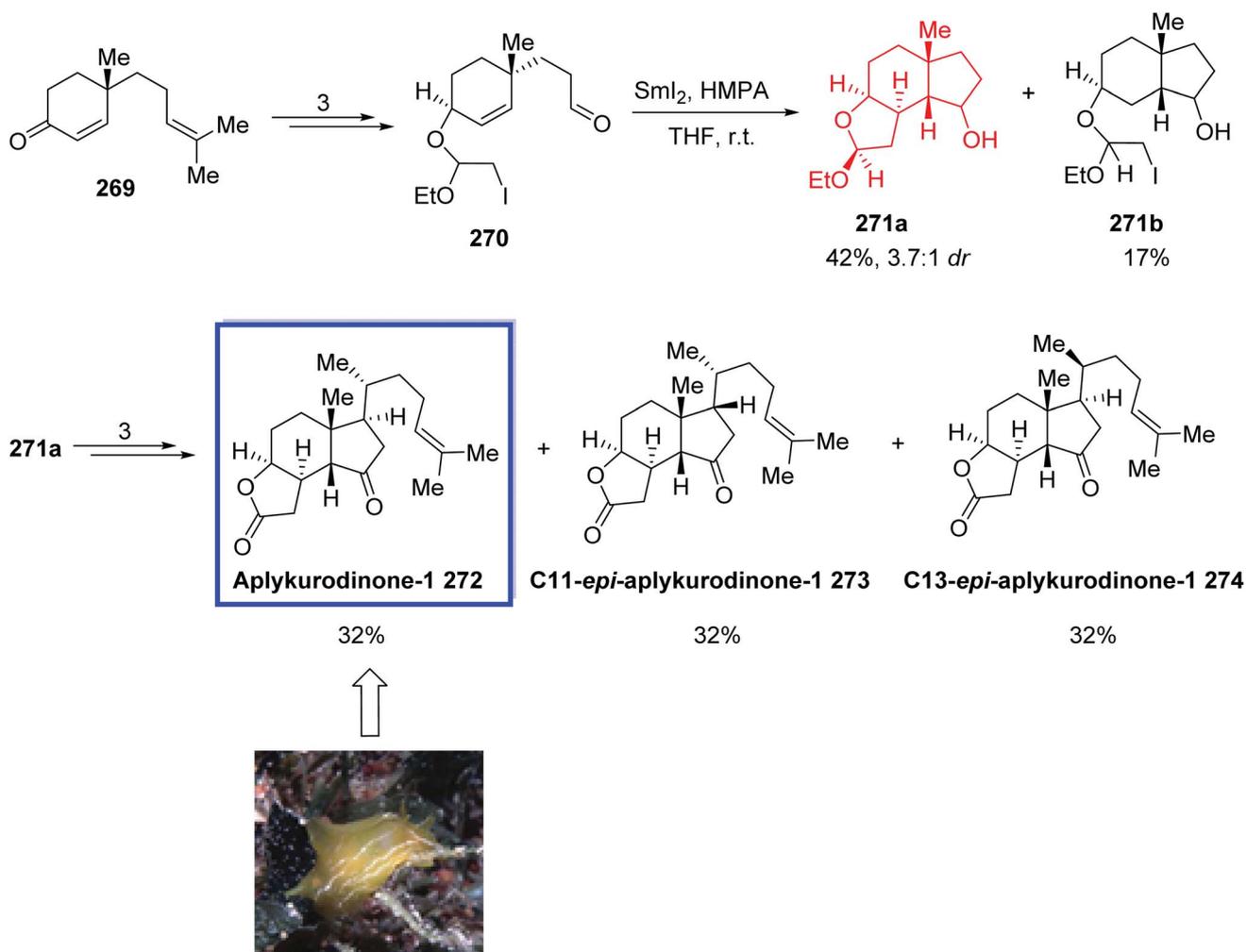
Scheme 49 Total synthesis of aplykurodinone-1 272.

Aplykurodinone-1 **272**, isolated from the sea hare *Syphonota geographica*, belongs to a family of highly degraded marine steroids with cytotoxic activities against the various human cancer cell lines.[119] Structurally, the aplykurodines have gained much interest in the synthetic community. Aplykurodinone-1 **272** includes six contiguous stereocenters, a quaternary carbon center, and an unusual *cis*-fused C–D ring with epimeric C8 and unsaturated side chain.

In 2014, Li and coworkers[120] developed an extraordinary method for the total synthesis of aplykurodinone-1 **272** in 8 steps from known enone **269** without applying any protecting group. The key steps contain a SmI$_2$-mediated reductive cyclization cascade reaction to synthesize an advanced intermediate and a direct cuprate-induced 1,4-addition for the direct installation of the C11 side chain. Their work was the first SmI$_2$-promoted intramolecular cascade cyclization reaction between halide, alkene, and aldehyde functional groups.

The total synthesis of aplykurodinone-1 **272** began with the easily available enone **269** to prepare the haloacetal-aldehyde **270**, as an inseparable 1 : 1 mixture of diastereomeric haloacetal **271** in 3 steps. The SmI$_2$-mediated reductive cascade cyclization reaction of precursor **270** with 2.0 equiv. of SmI$_2$ in THF in the presence of 2.0 equiv. of HMPA easily constructed the tricyclic core and afforded the desired cyclization product **271a** (C9-diastereoisomers 3.7 : 1 d.r.) in 42% yield together with the monocyclization byproduct **271b** in 17% yield. The total synthesis of aplykurodinone-1 **272** was completed from **271a** in 3 steps installing the C11 side chain to afford **272**, C13-

epi-aplykurodinone-1 **273** and undesired facial isomer C11-*epi*-aplykurodinone-1 **274** each in 32% yield (Scheme 49).

Longeracemine **280**, isolated from the fruits of *Daphniphyllum longeracemosum*, is a member of the Daphniphyllum alkaloids[121] with 35 unique carbon frameworks to date, and over 320 members that have been isolated from evergreen shrubs and trees from southeast Asia. These alkaloids with diverse structures and plenty of polycyclic fused structures display various biological activities, such as antioxidant and anti-HIV activities, cytotoxicity against various cancer cell lines, insecticidal, and also known platelet aggregation inhibitors.[121d,e] Longeracemine retains a 5/6/5/5/6/5 skeleton, which comprises a highly functionalized 2-azabicyclo[2.2.1]heptane core and three contiguous quaternary carbons.

In 2020, Wood and coworkers[122] reported the total synthesis of the 2-azabicyclo[2.2.1]heptane core of longeracemine **280**. The key steps contained a stereoselective SmI$_2$-mediated cascade reaction to synthesize the 2-azabicyclo[2.2.1]heptene from azabicyclo[2.2.1]heptadiene. The key SmI$_2$-induced spirocyclization/rearrangement cascade created two adjacent all-carbon quaternary centers and provided the C-15 hydroxyl stereochemistry essential to synthesize **280**. The spectral analysis shows the strong NOE correlation between the C15 hydrogen and the equatorial C1 hydrogen in both spirocycles **278a** and **278b**.

The total synthesis of 2-azabicyclo[2.2.1]heptanes **278a** und **278b** began with the reaction of *N*-Boc pyrrole **275** and ethyl 3-bromopropiolate **276** to obtain aldehyde **277** in 8 steps and 50% yield as a 3 : 2 mixture of diastereomers. The key SmI$_2$-mediated
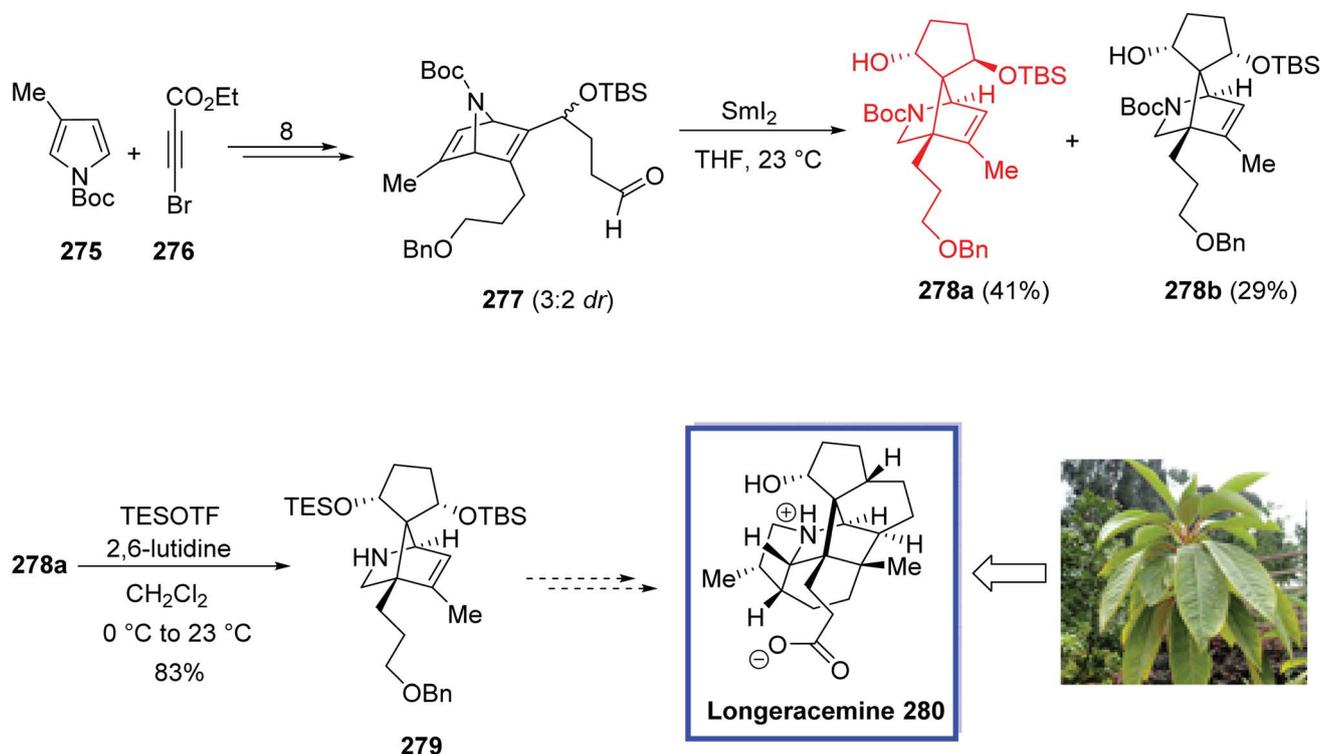
Scheme 50 Total synthesis of 2-azabicyclo[2.2.1] heptane core of longeracemine **280**.

spirocyclization/rearrangement cascade of **277** occurred under very mild conditions using three molar equivalents of SmI$_2$ in THF at 23 °C for 1 h and stereoselectively provided the desired 2-azabicyclo[2.2.1]heptenes **278a** (41%) and **278b** (29%) in good yield with excellent selectivity. C15 hydroxyl protection of **278a** as a triethylsilyl (TES) ether and removal of the Boc group resulted in secondary amine **279**, which could establish the stage for additional development of **279** to **280** (Scheme 50).

3. Conclusion

Manipulation and fine-tuning of the reduction potential, reaction rate, yield, high chemoselectivity, and stereoselectivity of SmI$_2$ can be affected by varying the different additives and cosolvents of a reaction mixture. The very extensive reactivity window of this reagent and the remarkable ability of SmI$_2$ to mediate both anionic and radical processes promote this highly chemoselective reagent a wide spectrum of synthetic strategies varying from functional group modifications to carbon–carbon bond-forming reactions, and in the case of natural products total synthesis, facilitating an otherwise impossible reaction or clean switching of reaction procedure.

Knowing the enormous potential of SmI$_2$-mediated reactions in modifications of functional groups, a survey of new reaction types and mechanistic routes and developing more general and powerful strategies with non-toxic additives are crucial for the application to large-scale synthesis. Additionally, to expand the use of the SmI$_2$-mediated reactions in the future synthesis of complex, biologically active, and chiral target compounds in asymmetric syntheses and natural product total syntheses, it would be expected that this area is still very much considered a work in progress.

Conflicts of interest

There are no conflicts to declare.

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