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Controllable skeletal reorganizations in natural product synthesis

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Covering: 2016 to 2023

The synthetic chemistry community is always in pursuit of efficient routes to natural products. Among the many available general strategies, skeletal reorganization, which involves the formation, cleavage, and migration of C–C and C–heteroatom bonds, stands out as a particularly useful approach for the efficient assembly of molecular skeletons. In addition, it allows for late-stage modification of natural products for quick access to other family members or unnatural derivatives. This review summarizes efficient syntheses of steroid, terpenoid, and alkaloid natural products that have been achieved by means of this strategy in the past eight years. Our goal is to illustrate the strategy's potency and reveal the spectacular human ingenuity demonstrated in its use and development.

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1. Introduction

Organic synthesis has evolved considerably since Friedrich Wöhler synthesized urea in 1828. Over the centuries, remarkable developments in synthetic methodologies and strategies have enriched the chemist's repertoire of techniques for taming the structural complexity of natural products.[1–9] The resulting impressive achievements in total synthesis have convinced the chemistry community that almost any natural product can be synthesized in the laboratory.[10,11] As a result, the major focus of modern synthetic studies has switched to improving synthetic efficiency,[12–14] which is typically represented by shortening synthetic routes,[15] increasing overall yields, and improving scalability.[16]

Towards this end, there is a continuous need for the development of novel synthetic strategies and methods that make the synthesis of complex molecules more direct. Generally speaking, synthesis of natural products can be divided into two main tasks: assembly of the molecular skeleton and modulation of oxidation states. The former task has received more attention than the latter because rapid construction of the skeleton, which often features formidable fused and bridged polycyclic ring systems, is the key to an efficient synthetic route. Over the years, the art and science of total synthesis have advanced together, and many ingenious strategies have been developed. For example, cyclization reactions can swiftly convert simple linear molecules to involuted cyclic ones;[17–19] and convergent fragment-coupling approaches can shorten the longest linear sequence of steps, thereby improving the overall yield and decreasing synthetic cost.[20–23] Alternatively, reorganization of the skeletons of readily available substrates is also a feasible

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strategy for quickly and efficiently generating scaffold diversity and complexity.[24–29] In fact, skeletal reorganization is one of the most important tools used by nature to generate the huge variety of natural products.[30–33]

Skeletal reorganization can utilize either a natural product or a human-made synthetic intermediate as a substrate. In the former case, generation of target molecules by skeletal reorganization of inexpensive commercially available compounds derived from natural sources is often inspired by proposed biosynthetic pathways. In the latter case, the latent relationship between the target molecule and readily accessible intermediates may become apparent only after careful structural analysis. However, once realized, this tactic can enable really efficient construction of the target skeleton. In addition, it can also be utilized in the late stages of syntheses, thereby allowing the divergent syntheses of a collection of natural products with distinct but closely related scaffolds.[34–36]

Despite the advantages of the skeletal reorganization strategy, it poses some challenges. A major one is controlling oxidation states. Because skeletal reorganization usually relies on controlled rearrangements, appropriate oxidation patterns are necessary to effect the desired reactions. Therefore, careful selection of starting materials and design of the substrates is vital to the successful application of this strategy.

In this review, impressive synthesis examples are selected to showcase the power of the skeletal reorganization strategy in natural product synthesis. The review is divided into sections based on three classes of target natural products: steroids, terpenoids, and alkaloids. In each section, five sets of examples will be introduced to showcase the achievements that have been made with this fantastic strategy.

2. Steroids

Steroids, which feature a 6/6/6/5-tetracyclic skeleton, are ubiquitous natural products found in a wide variety of plants, fungi, and animals (including marine organisms). In recent years, rearranged steroids[37] (*i.e.*, *abeo*-steroids and secosteroids) have

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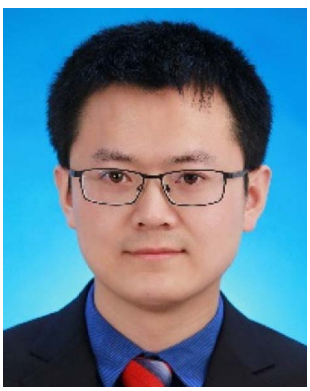
Xiao Qian was born in Yangzhou, Jiangsu Province, China, in 1999. He received his BSc degree in chemistry in 2021 from Fudan University. In 2022, he joined Prof. Jinghan Gui's group at SIOC to pursue his PhD research in the synthesis of natural products, especially those with heavily rearranged steroidal skeletons.



Jinghan Gui

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attracted significant attention because of their interesting structures and biological activities. Given the biosynthetic relationships between classical steroids and rearranged steroids, it is not surprising that the complex core framework of the latter can be efficiently constructed by means of skeletal reorganizations of abundant steroid starting materials; and semisyntheses of rearranged steroids from inexpensive commercially available steroids have been actively pursued by synthetic chemists.

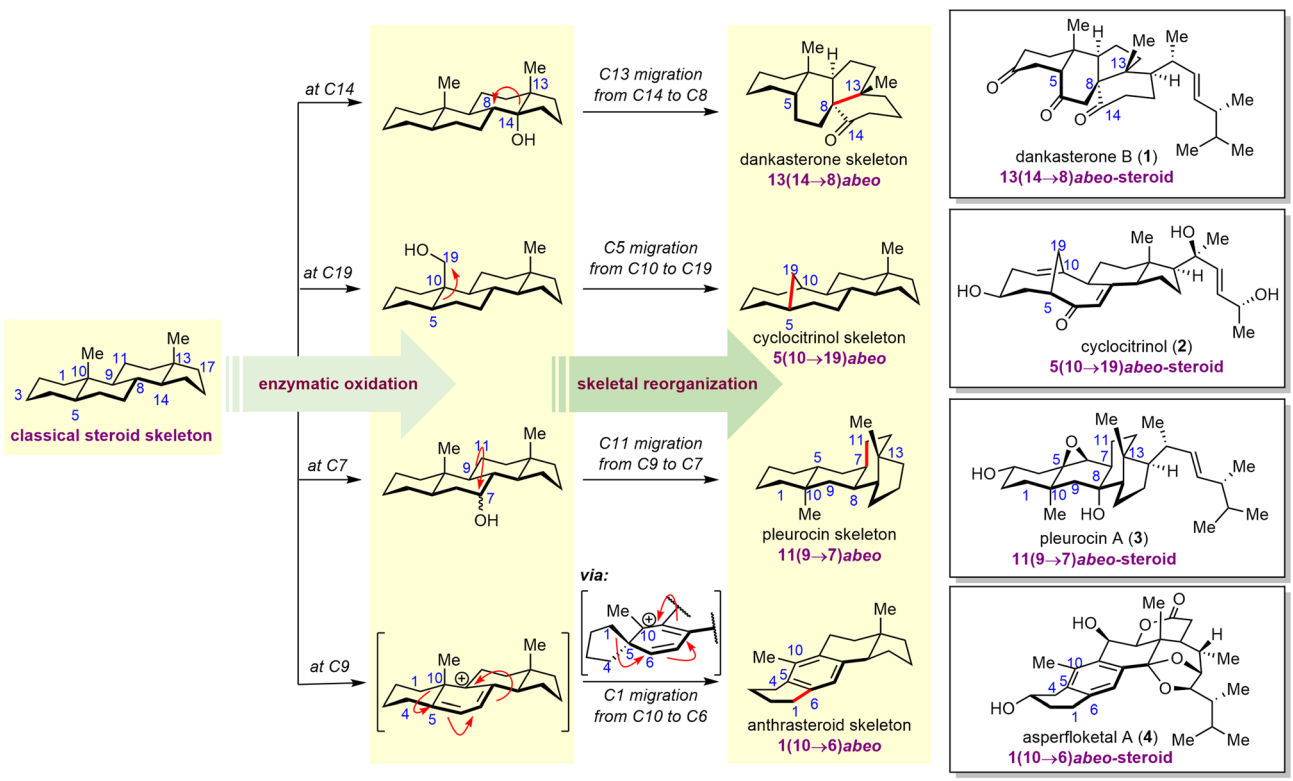
Biosynthetically, site-specific enzymatic C–H oxidation of classical steroids, followed by selective bond migration and cleavage, leads to rapid preparation of molecules with a diverse array of rearranged steroid skeletons (Scheme 1). For example, enzymatic hydroxylation at C14 of the classical steroid skeleton can facilitate migration of C13 from C14 to C8, delivering 13(14→8)*abeo*-steroids such as the natural product dankasterone B (**1**). Alternatively, oxidation at C19, C7 or C9, in combination with subsequent C5, C11, and C1 migration, can afford 5(10→19)*abeo*-, 11(9→7)*abeo*-, and 1(10→6)*abeo*-steroids, respectively. Representative members of these three families include cyclocitrinol (**2**), pleurocin A (**3**), and asperfloketal A (**4**). In this section, five examples will be presented to demonstrate the advantages of skeletal reorganization for efficient synthesis of rearranged steroids.

2.1 Gui's syntheses of cyclocitrinols

Cyclocitrinol (**2**), a C25 5(10→19)*abeo*-steroid with a unique bicyclo[4.4.1]undecane A/B ring system, was first isolated from a terrestrial *Penicillium citrinum* by Gräfe and co-workers in 2000.[38] In 2003, Crews and co-workers revised the structure of **2** on the basis of X-ray crystallographic analysis.[39] To date, more than 30 C25 steroids sharing a bicyclo[4.4.1]undecane A/B ring system have been isolated,[38–46] mostly from *Penicillium* species. Members of this family display diverse bioactivities, including antibacterial, cAMP-inducing, and anti-osteoporosis activities, as well as moderate cytotoxicity against KB and MCF-7 cancer cell lines.[39,41,46,47]

To date, five groups had reported construction of the cyclocitrinol skeleton: the Schmalz group,[48] the Leighton group,[49] the Li group,[50] the Ding group[51] and the Tanino group.[52] In 2018, Li and co-workers reported the first total synthesis of **2**, which was accomplished in 18 steps and featured an intramolecular type II [5 + 2] cycloaddition.[53,54] Soon after, the Gui group disclosed unified syntheses of ten cyclocitrinols from pregnenolone (**5**), an inexpensive commercially available steroid, by means of a bioinspired skeletal reorganization approach.[55]

The key challenge in the semisynthetic approach to **2** lies in the transformation of the decalin motif of classical steroids to the bicyclo[4.4.1]undecane ring system. Inspired by the proposed biosynthetic pathway, Gui and co-workers surmised that the desired skeletal reorganization could be realized through cyclopropane formation and subsequent fragmentation (Scheme 2), that is, formal C5–C19 bond formation and C5–C10 bond cleavage. Their synthetic endeavors commenced with the preparation of a diastereomeric mixture of sulfoxides **6** from **5** in seven steps. Upon treatment with *O*-methylquinine at 130 °C, sulfoxides **6** underwent *syn* elimination followed by



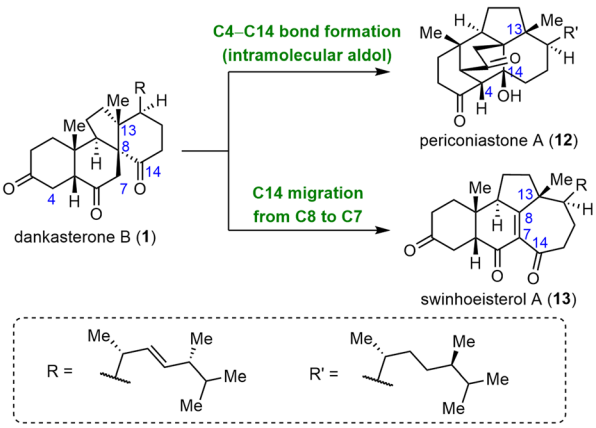
Scheme 1 Proposed biosynthesis of rearranged steroids and structures of representative examples.

cyclopropane formation and ring expansion to deliver trienes **9a** (54%) and **9b** (11%). In this transformation, *O*-methylquinine first acted as a nucleophile to enable the formation of cyclopropane **8** and then as a base and a leaving group to facilitate the cyclopropane fragmentation to afford the trienes. Subsequently, triene **9a** was transformed to ketone **10** *via* a hydroboration/oxidation sequence. Notably, this biomimetic skeletal reorganization strategy enabled the gram-scale preparation of key intermediate **10** in only nine steps from **5**. With ketone **10** in hand, various side chains were introduced to complete divergent syntheses of ten cyclocitrinols in an additional one to three steps (*i.e.*, 10–12 steps overall from **5**).[56]

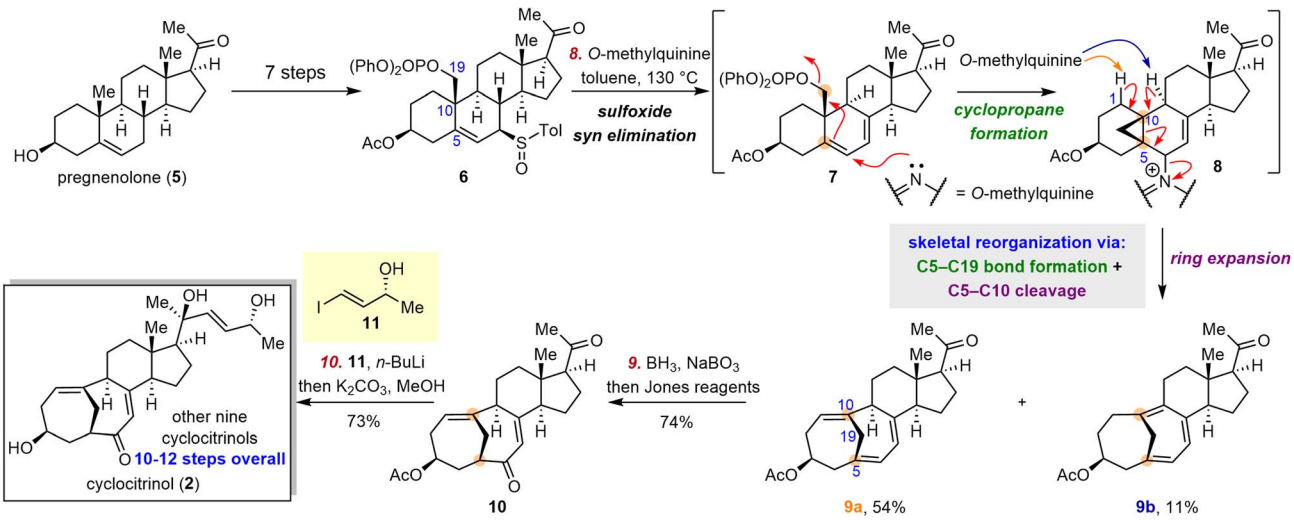
2.2 Heretsch's and Ma's syntheses of dankasterones

Dankasterones A (**23**) and B (**1**), two 13(14→8)*abeo*-steroids with a 6/6/5/6-tetracyclic skeleton, were isolated from *Gymnascella dankaliensis* by the Numata group and found to exhibit significant cytotoxicity against murine P388 leukemia cells and human cancer cell lines.[57,58] Later, 13(14→8),14(8→7)di-*abeo*-steroids swinhoeisterols A–F were isolated from the Xisha sponge *Theonella swinhoei* by the W. Zhang group.[59,60] Two of these compounds, swinhoeisterols A (**13**) and C, show cytotoxicity against A549 and MG-63 cancer cells and inhibit the histone acetyltransferase (h)p300.[60] In 2019, the Y. Zhang group isolated periconiastone A (**12**), which has a 13(14→8)*abeo*-4,14-cyclo-system skeleton, from *Periconia* sp. TJ403-rc01 and demonstrated that it has antibacterial activities.[61] Periconiastone A is proposed to be biosynthesized from dankasterone B by means of an intramolecular aldol reaction that forms the C4–C14 bond, and the swinhoeisterol skeleton might be formed from the dankasterone skeleton *via* C14 migration from C8 to C7 (Scheme 3).

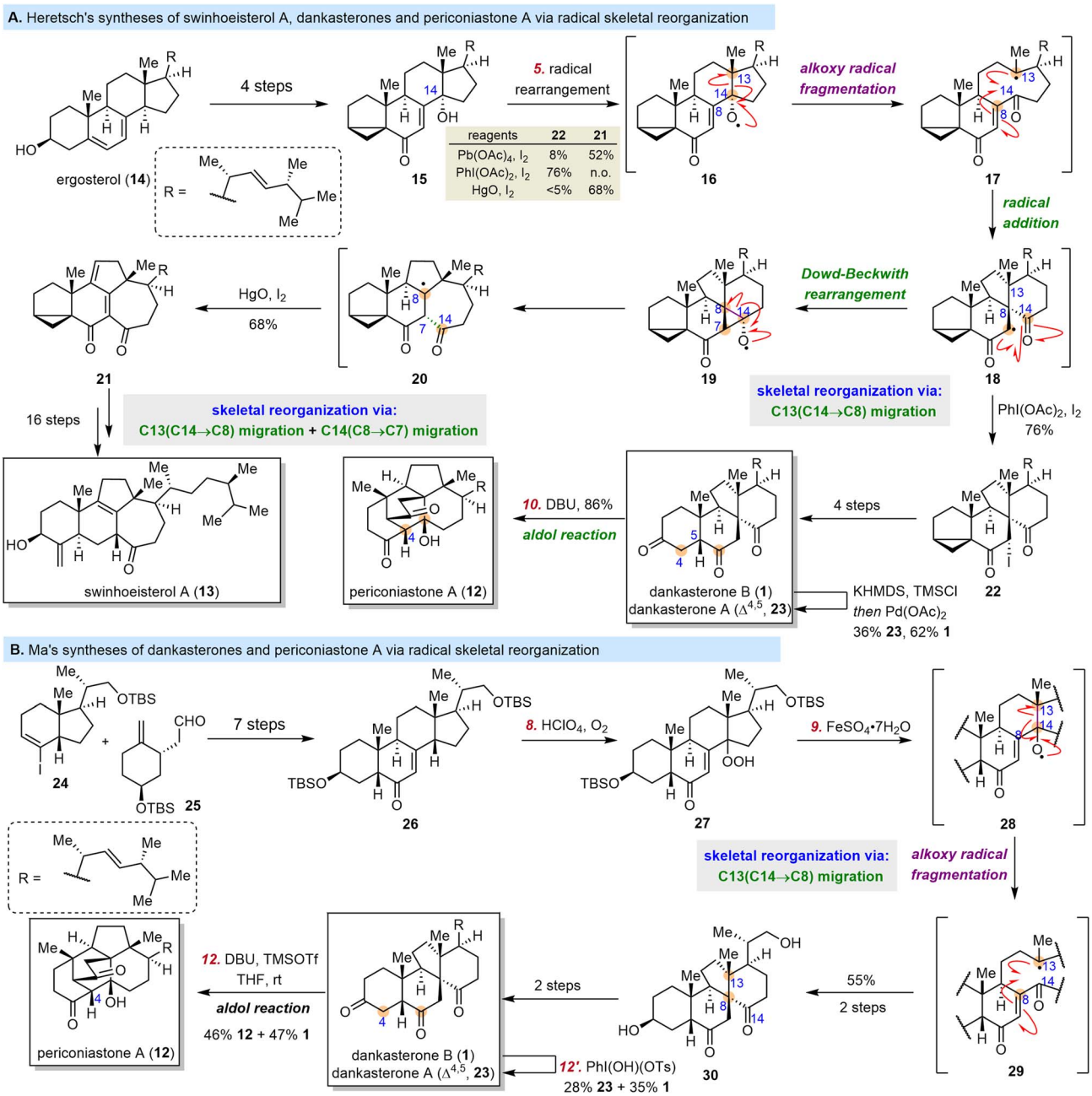
Till now, three groups have finished syntheses of dankasterones including total syntheses by the Ma group,[62,63] the Snyder group[64] and semisynthesis by the Heretsch group.[65,66] From a semisynthetic perspective, three pivotal transformations are necessary to obtain the complex core framework of these rearranged steroids from classical steroids: (1) migration of C13 from C14 to C8 to produce the dankasterone skeleton, (2) formation of a C4–C14 bond in dankasterone skeleton to generate the periconiastone skeleton, and (3) migration of C14 from C8 to C7 in dankasterone skeleton to furnish the swinhoeisterol skeleton. In 2020, Heretsch and co-workers completed elegant bioinspired syntheses of swinhoeisterol A (**13**), dankasterones A (**23**) and B (**1**), and periconiastone A (**12**), which were achieved by means of radical-mediated rearrangements (Scheme 4A).[65,66] The syntheses started with 14-hydroxy steroid **15**, which was prepared from ergosterol (**14**) in four steps. Treatment of **15** with either $PhI(OAc)_2/I_2$ or HgO/I_2 generated 14-alkoxy radical **16**. Subsequent migration of C13 from C14 to C8 *via* an alkoxy radical fragmentation/radical addition sequence afforded **18**, which either was trapped with iodine to afford **22** in 76% yield under the $PhI(OAc)_2/I_2$ conditions or underwent a Dowd–Beckwith rearrangement to produce **21** in 68% yield under the HgO/I_2 conditions. Iodide **22** was converted to **1** in four steps.



Scheme 3 Proposed biosyntheses of periconiastone and swinhoeisterol from dankasterone.



Scheme 2 Gui's syntheses of cyclocitrinols.



Scheme 4 Heretsch's and Ma's syntheses of dankasterones A and B and periconiastone A.

Dehydrogenation of **1** *via* a Saegusa oxidation produced **23**, and an intramolecular aldol reaction of **1** yielded **12**. Compound **21** was transformed to **13** in 16 steps.

In 2021, Ma and co-workers reported total syntheses of dankasterones A (**23**) and B (**1**) and periconiastone A (**12**) (Scheme 4B).[62,63] Notably, this synthesis also involved the use of an alkoxy radical rearrangement to realize the skeletal reorganization. To begin their syntheses, Ma *et al.* prepared **26** through a seven-step fragment-coupling sequence. Subsequently, the C8-hydroperoxyl group of **27** was introduced by reaction of **26** with $HClO_4/O_2$. Treatment of **27** with $FeSO_4 \cdot 7H_2O$ initiated the alkoxy radical rearrangement/radical addition sequence that resulted in migration of C13 from C14 to C8 to generate **30** in 55% yield from **26**. Then **30** was transformed to **1** in two steps or **23** in three steps. Finally, as was the case with the Heretsch group's synthesis,[65] **1** was converted to **12** through an aldol reaction.

2.3 Heretsch's synthesis of asperfloketal A

Anthrasteroids, which possess an aromatic B ring flanked by A and C rings in a linear geometry, can be traced back to 1963, when the first member of this class of compounds was obtained by chemical synthesis.[67,68] The anthrasteroid asperfloketal A (**4**), which was isolated from *Aspergillus flocculosus* 16D-1 by Lin *et al.* in 2020, shows anti-inflammatory activity in $CuSO_4$-

induced transgenic zebrafish.[69] Two years later, the Heretsch group finished the first synthesis of **4**, which was accomplished in a bioinspired manner.[70]

These investigators devised a double Wagner–Meerwein rearrangement strategy as a stepwise version of the rearrangement that reorganizes the classical steroid skeleton into the anthrasteroid skeleton (Scheme 5), that is, migration of C1 from C10 to C5 and migration of C4 from C5 to C6. As in their semisynthesis of strophasterol A,[71] vinyl chloride **31** was prepared from ergosterol (**14**) in nine steps. Treatment of **31** with KOH resulted in C14–C15 bond cleavage, which was followed by keto–enol isomerization, E1cB elimination, and alkene isomerization to produce **35** in quantitative yield. Subsequently, **35** was converted to **36** in three steps; **36** was reduced by $NaBH_4$; and the resulting diol (not shown) underwent cyclopropane opening/C9–OH dehydration, which triggered the double Wagner–Meerwein rearrangement cascade. Notably, the second Wagner–Meerwein rearrangement delivered a 2 : 1 mixture of regioisomeric acetates **39b** and **39a**, which were derived from migration of C1 from C5 to C6 and migration of C4 from C5 to C6, respectively. From **39b**, **4** was synthesized in an additional four steps.

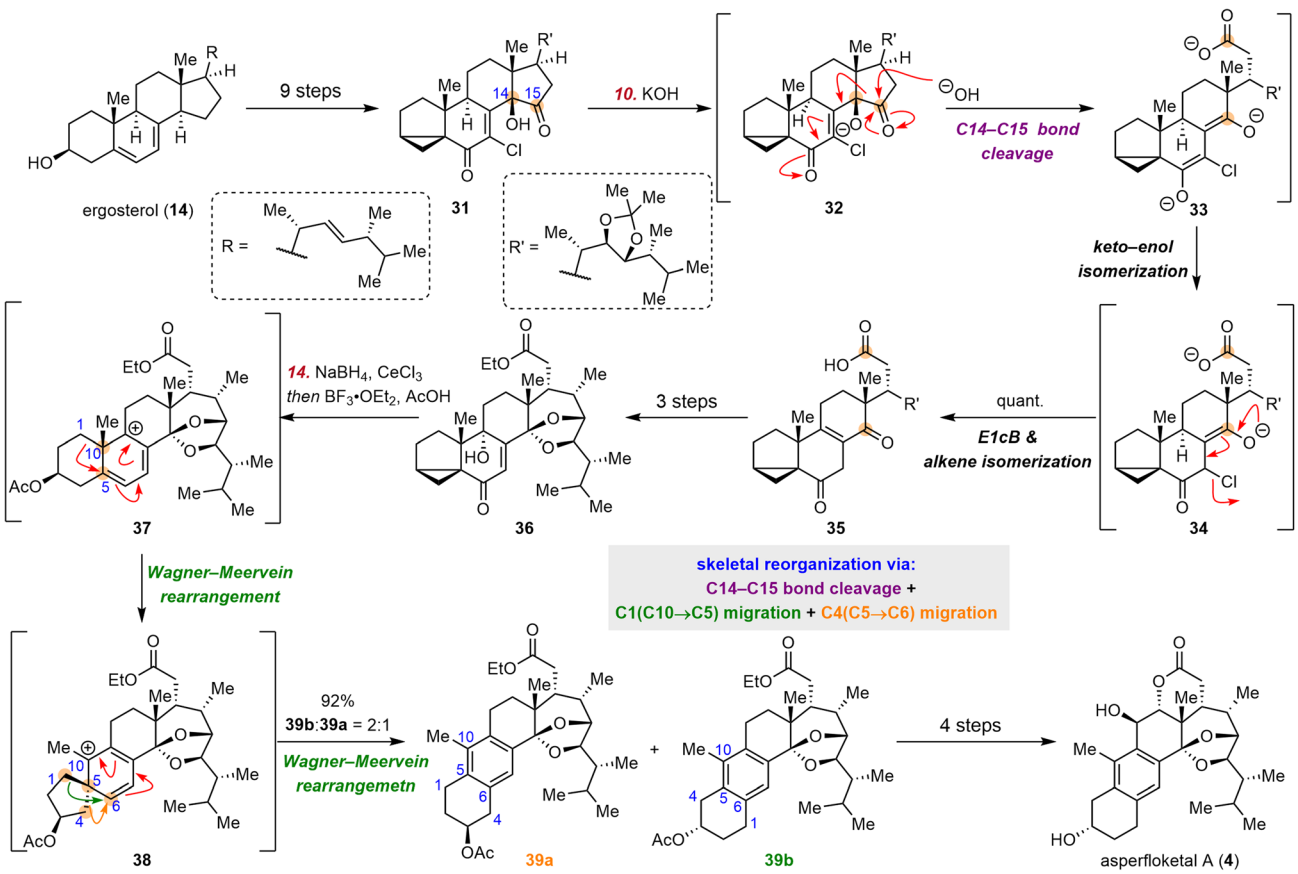
2.4 Heretsch's synthesis of pleurocin A

Pleurocin A (**3**) (also known as matsutakone), which has a unique 11(9→7)*abeo*-steroid skeleton, was first isolated from *Tricholoma matsutake* by the Liu group in 2017.[72] Soon after, Tanaka and co-workers isolated **3** from *Pleurotus eryngii* and found that it inhibits NO production.[73]

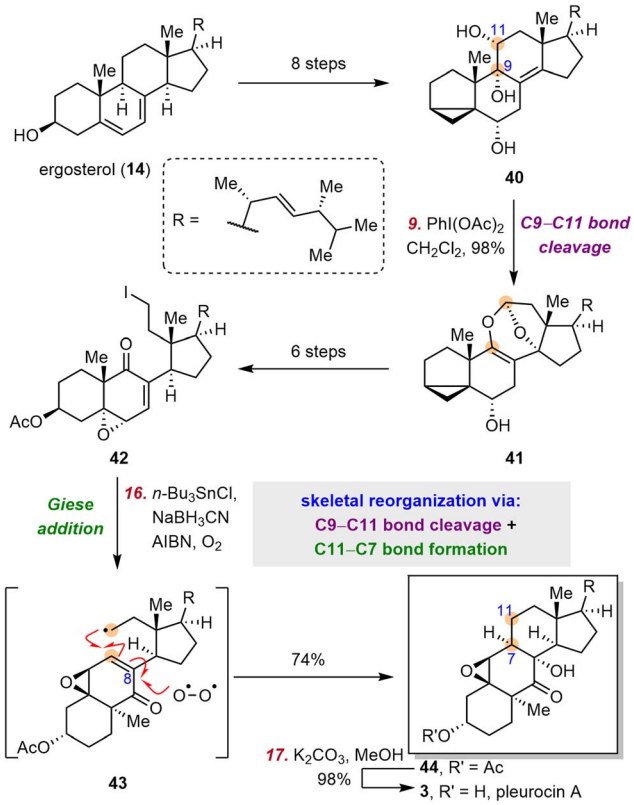
The pivotal task in the semisynthesis of pleurocin A (**3**) lies in reorganization of the classical steroid skeleton to the pleurocin skeleton through C9–C11 bond cleavage and C7–C11 bond formation. Inspired by the proposed polar biosynthesis,[72,73] Heretsch and co-workers devised a biomimetic approach involving polar cleavage of the C9–C11 bond and subsequent radical formation of the C11–C7 bond (Scheme 6).[74] Specifically, starting from ergosterol (**14**), they obtained triol **40** in eight steps. Upon treatment with $PhI(OAc)_2$, **40** was smoothly converted to **41** in 98% yield through C9–C11 bond cleavage and a formal dioxa-[4 + 2]-cycloaddition. Then iodide **42**, which was synthesized in six steps from **41**, underwent a diastereoselective 6-*endo*-trig radical cyclization (Giese addition) initiated by AIBN/*n*-Bu_3SnCl/$NaBH_3CN$; and trapping of the resulting C8-alkyl radical (not shown) by oxygen delivered **44** in 74% yield. During this process, two contiguous stereogenic centers were established stereospecifically. Finally, deacetylation of **44** afforded **3**.

2.5 Gui's syntheses of pinnigorgiols

9,11-Secosteroids, most of which are isolated from marine organisms, are a subfamily of secosteroids. Pinnigorgiols are a group of heavily rearranged 9,11-secosteroids that possess



Scheme 5 Heretsch's synthesis of asperfloketal A.



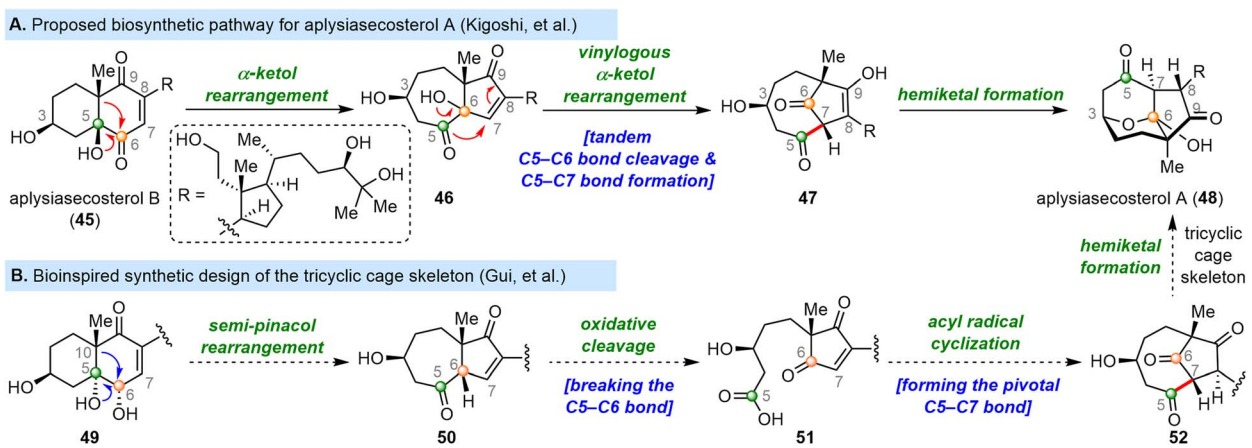
Scheme 6 Heretsch's synthesis of pleurocin A.

a unique tricyclo[5.2.2.0^{4,8}]decane skeleton. Pinnigorgiols B (**60**) and E (**59**), which were isolated by Sung and co-workers from a gorgonian coral *Pinnigorgia* sp., induce apoptosis of hepatic stellate cells.[75,76] Aplysiasecosterol A, which shares its core skeleton with the pinnigorgiols, was convergently synthesized by the Li group[77] and the Kigoshi group.[78] In 2021, the Gui group reported the first synthesis of pinnigorgiols, which they accomplished by means of a bioinspired skeletal reorganization for converting the classical steroid skeleton to the complex cage skeleton.[79] In 2016, the Kigoshi group proposed that the structurally similar natural product aplysiasecosterol A (**48**) might be derived from aplysiasecosterol B (**45**) through an α-ketol rearrangement, followed by a vinylogous α-ketol rearrangement and hemiketal formation (Scheme 7A).[80,81] Inspired by this proposed biosynthesis (Scheme 7A), Gui and co-workers devised a stepwise bond migration, bond cleavage, and bond formation sequence to access the core tricyclo[5.2.2.0^{4,8}]decane framework; this sequence involved C10 migration from C5 to C6, cleavage of the C5–C6 bond, and C5–C7 bond formation/hemiketalization (Scheme 7B).

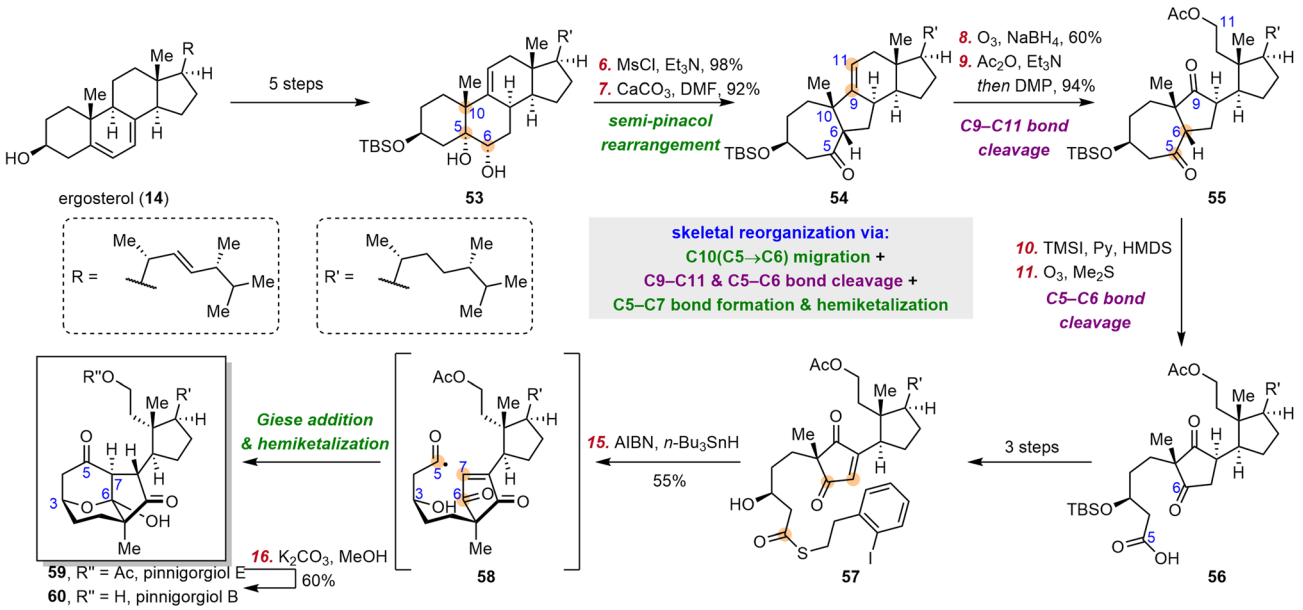
Specifically, ergosterol (**14**) was first converted to diol **53** in five steps (Scheme 8), and **53** was transformed into ketone **54** by means of a semi-pinacol rearrangement. Ozonolysis of the double bond of **54**, followed by acetylation, afforded diketone **55**, which was converted to the corresponding enol silyl ether and subjected to another ozonolysis to cleave the C5–C6 bond, affording diseco intermediate **56**. Then thioester **57** was obtained in three steps from **56**. Upon treatment with AIBN/*n*-Bu_3SnH, **57** underwent an acyl radical cyclization/hemiketalization cascade, thereby completing the semisynthesis of **59** in 15 steps from **14**. Notably, two rings and three contiguous stereogenic centers were established during this process. Hydrolysis of **59** afforded **60** in 60% yield.

3. Terpenoids

Terpenes and terpenoids are the largest classes of natural products. Although the term "terpene" is often used to refer only to compounds with an empirical formula of C_5H_8, "terpenoid" refers to terpenes in which methyl groups have been moved or removed or oxygen atoms have been added. Although all terpenes and terpenoids are conceptually derived from isoprenes, they can have different numbers of isoprene units, complicated linkage patterns, diverse redox states, and rearranged skeletons, all of which result in the existence of many dramatically distinct structural classes. Therefore, the skeletal reorganization strategy is a flexible option for their chemical synthesis. Although proposed biosynthesis



Scheme 7 Kigoshi's proposed biosynthesis of aplysiasecosterol A and Gui's bioinspired strategy for installing the tricyclic cage skeleton.



Scheme 8 Gui's syntheses of pinnigorgiols.

pathways or co-isolation of structurally related species can inspire biomimetic rearrangements for straightforward access to the target molecules, other innovative reorganization approaches have been devised to achieve interconversions of seemingly unrelated skeletons. Furthermore, those approaches have emerged from both semisynthesis and total synthesis studies, which have greatly expanded the scope of the skeletal reorganization strategy. In this section, remarkable recent accomplishments in this area will be demonstrated by five examples.

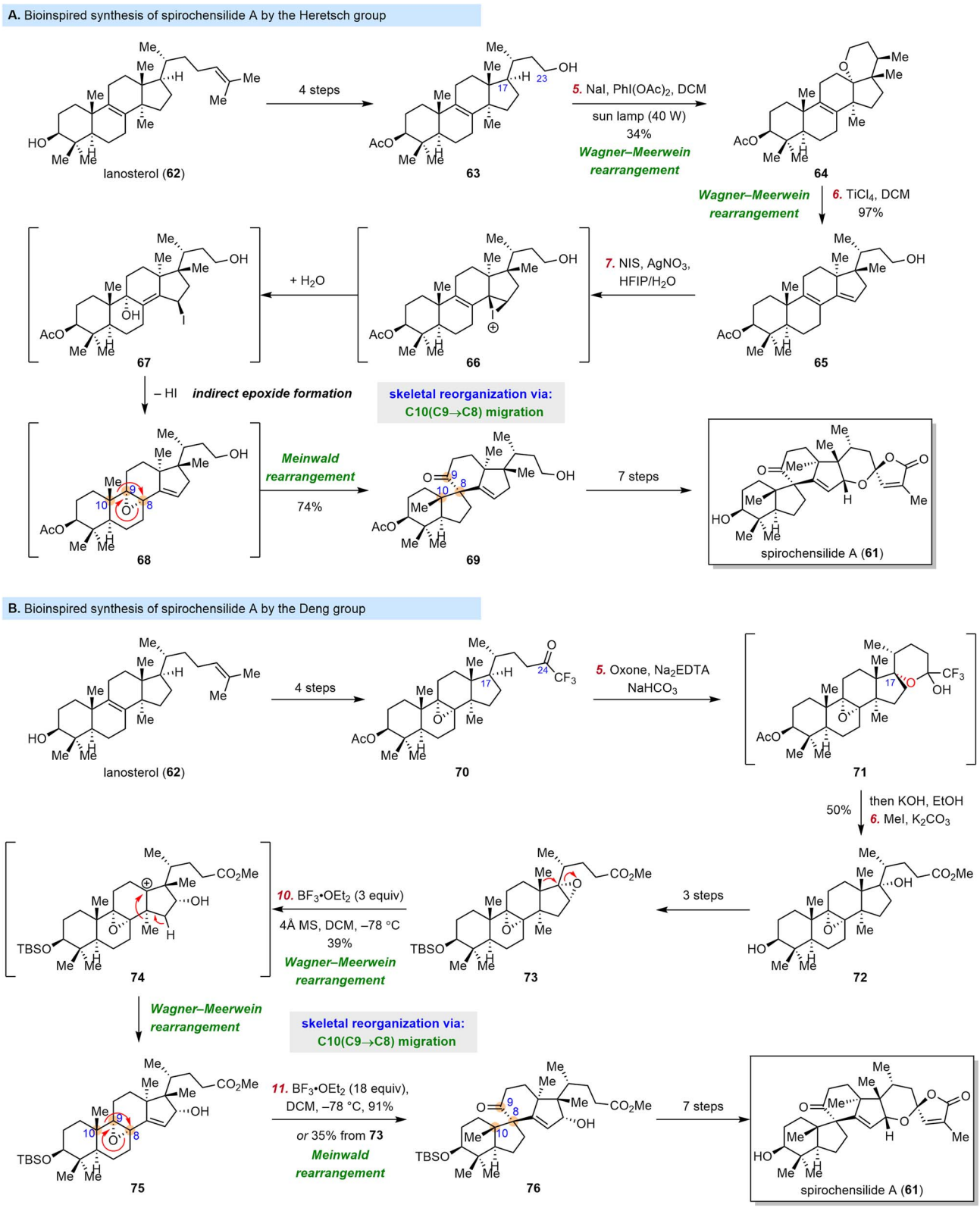
3.1 Heretsch's and Deng's synthesis of spirochensilide A

Triterpenoids are often structurally very similar to steroidal compounds because the triterpene squalene is the biosynthetic precursor of lanosterol (**62**) and cycloartenol, the key intermediates in steroid biosynthesis. Thus, it is not surprising that rapid skeletal reorganization can be used for the synthesis of complex triterpenoids from inexpensive triterpenoid starting materials.

Good examples were reported in 2022, when both the Heretsch group and the Deng group reported synthesis of the triterpenoid spirochensilide A (**61**).[82,83] This compound was isolated from *Abies chensiensis* by Gao and co-workers in 2015 and moderately inhibits NO production.[84] The first total synthesis of **61**, which was reported by Yang and co-workers in 2020, featured a Meinwald rearrangement and a Pauson–Khand reaction.[85–87] In contrast, inspired by the biosynthesis proposed by the investigators who isolated **61**, the Heretsch and Deng groups utilized a semisynthetic strategy to access it from **62** *via* a skeletal reorganization approach (Scheme 9).[82,83]

This approach posed two main challenges: (1) a site- and stereoselective C–H oxidation at C17 to drive the migration of two methyl groups and (2) a Meinwald rearrangement to install the spiro[4.5]decane motif. As shown in Scheme 9A, the Heretsch group surmounted the first challenge by carrying out the C–H oxidation at C17 of **63** (which was prepared in four steps from **62**) through activation of the C23 hydroxyl group, 1,5-hydrogen atom transfer, and radical-polar crossover. Specifically, upon photoirradiation of **63** in the presence of NaI/$PhI(OAc)_2$, the first methyl migration took place spontaneously to generate **64**, and the second migration was initiated by treatment of **64** with $TiCl_4$ to give **65**. Then Heretsch *et al.* investigated the formation of an α-8,9-epoxide, which was the substrate for the desired Meinwald rearrangement. They eventually discovered an indirect epoxidation method involving reaction with *N*-iodosuccinimide/$AgNO_3$ *via* an iodination-double S_N2' mechanism to afford epoxide **68**, which was not isolable and could not be obtained by direct epoxidation of **65**. Interestingly, under the above-described epoxidation conditions, **68** spontaneously underwent a Meinwald rearrangement to give **69**; in this way, the key 10(9→8) migration was achieved. With the target reorganized skeleton in hand, Heretsch *et al.* were able to synthesize spirochensilide A (**61**) in another seven steps.

In contrast, the Deng group sought a reorganization substrate with the required oxidation pattern in place (Scheme 9B), which allowed them to develop a rearrangement cascade. Specifically, they managed to install the α-8,9-epoxide at an early stage, and then they oxidized the C17 position of trifluoromethyl ketone **70**. Dioxirane-mediated intramolecular hydroxylation of **70** delivered hemiketal **71**, which was smoothly elaborated to diepoxide **73**. Upon treatment with $BF_3 \cdot OEt_2$ to activate the less hindered 16,17-epoxide, **73** underwent two consecutive Wagner–Meerwein rearrangements to accomplish the migration of two angular methyl



Scheme 9 Heretsch's and Deng's bioinspired synthesis of spirochensilide A.

groups, furnishing epoxide **75**, which was then transformed into desired spiro[4.5]decane compound **76** *via* a Meinwald rearrangement. Notably, the three rearrangement steps could be achieved in one pot to access **76** directly from **73** in 35% yield. With **73** in hand, Deng *et al.* synthesized spirochensilide A (**61**) in another seven steps.

3.2 Lei's synthesis of jungermannenone C

The jungermannenones are *ent*-kaurane-type diterpenoids isolated from liverwort *Jungermannia* species and are considered to be promising candidates for cancer chemotherapy on the basis of preliminary biological studies.[88–90] In 2016, Lei and co-workers reported the first scalable total syntheses of *rac*-jungermannenones B and C (**77**), which involved a regioselective 1,6-dienyne reductive cyclization reaction as the key assembly step.[91] In 2019, these investigators reported a second-generation route, leading to the total synthesis of **77** and featuring a photoinduced reorganization from the *ent*-kaurane-type skeleton to the jungermannenone-type skeleton.[92] Of note, unlike the skeletal reorganization precursor used in the synthesis of spirochensilide A (**61**), the precursor for the *ent*-kaurane-type skeleton was prepared by total synthesis.

Specifically, as shown in Scheme 10, intermediate **78**, which was prepared in three steps from simple building blocks, underwent an enantioselective bicyclization *via* a radical cation generated by means of organo-SOMO (singly occupied molecular orbital) catalysis according to MacMillan's protocol[93] to give aldehyde **80**. This aldehyde was converted to dienyne **81** in five steps, and **81** underwent a reductive radical cyclization of the dienyne mediated by *n*-Bu_3SnH to afford **82**, which was converted to **83** in three simple steps. Both **82** and **83** have the *ent*-kaurane-type skeleton.

The skeletal reorganization step was accomplished by irradiation of **83** at 254 nm, which afforded **77** in 58% isolated yield, along with a 28% yield of recovered **83**. The photochemical 1,3-acyl migration was an equilibrium reaction, and Lei *et al.* found that **83** could be regenerated from **77** by irradiation at 365 nm in 21% yield, along with a 71% yield of recovered **77**. These results revealed that a photoinduced radical rearrangement is another way to access jungermannenones, in addition to carbocationic rearrangement pathways.

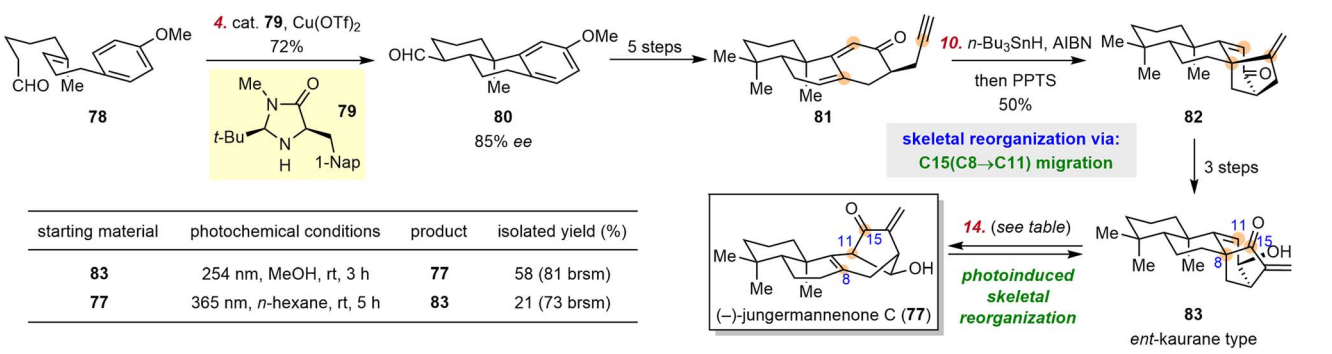
3.3 Sarpong's syntheses of phomactins, xishacorene B, and longiborneol

Naturally occurring "chiral pool terpenes" are widely used as starting materials for total synthesis because they are inexpensive. However, they are typically used in situations where their structures can easily be superimposed on some portion of the target structures. When this is not the case, their use becomes less straightforward and more challenging to implement, but they nevertheless offer access to many possible scaffolds.

In 2006, Bermejo and co-workers discovered that epoxidation of the isopropenyl moiety of (*S*)-carvone (**84**) and subsequent Ti(III)-mediated radical epoxide opening/cyclization could furnish pinene cyclobutanols **85** (as the major diastereomer) and **86** (as the minor diastereomer) (Scheme 11A).[94] This cascade reorganizes the carvone skeleton to the α-pinene skeleton and, more importantly, introduces two hydroxyl groups, one at C1 and one at C9. The more intuitive route to **85** and **86**, through selective C–H oxidation of α-pinene (**87**), is clearly much more synthetically challenging.

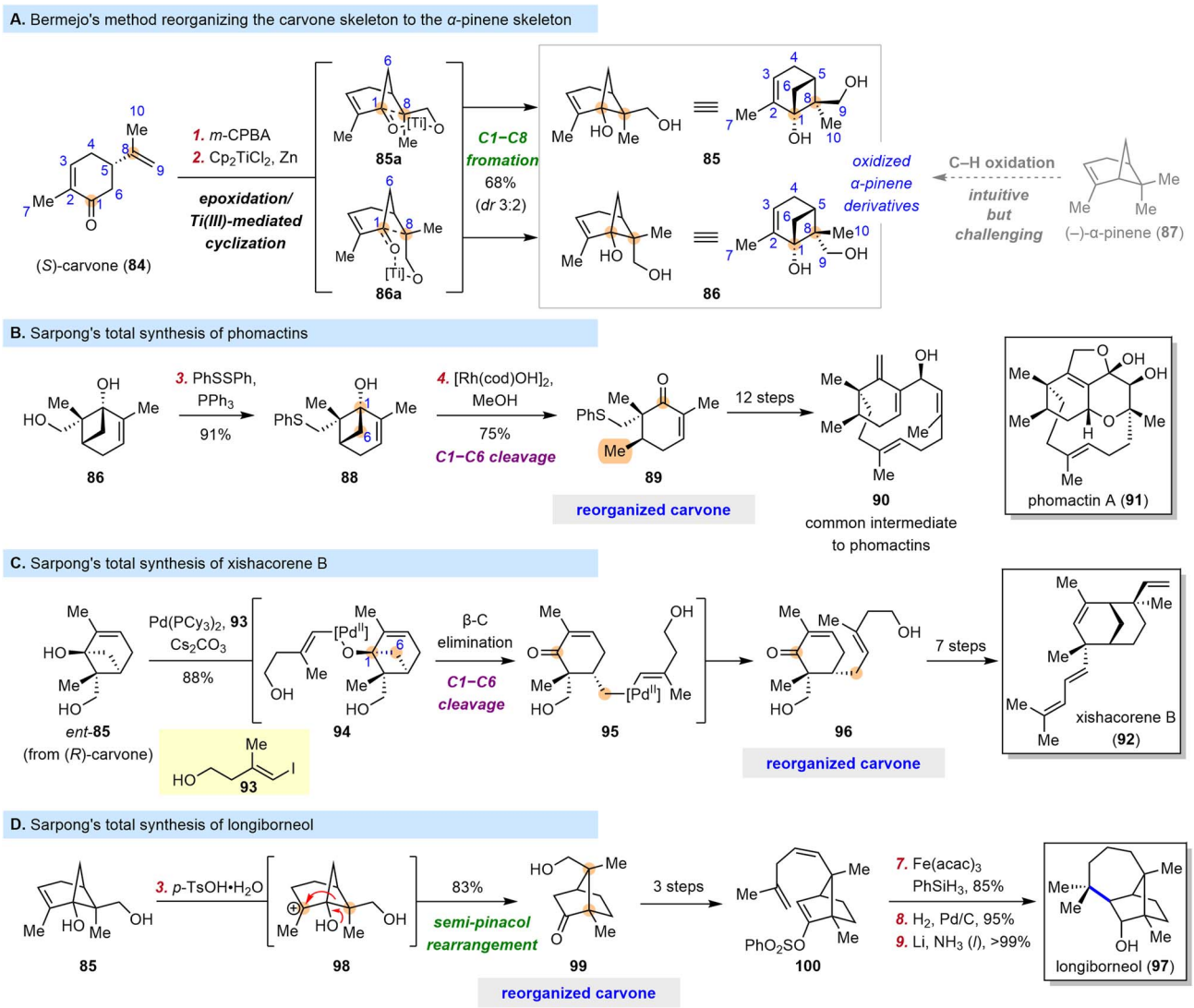
In 2009, Bermejo *et al.* showcased the power of this tactic in a concise synthesis of paeonisuffrone, which contains a bicyclo [3.1.1] motif;[95] and the Sarpong group recognized that cyclobutanols such as **85** and **86** could provide a platform for further elaboration. In fact, in 2018, the latter group published efficient syntheses of phomactin diterpenoids from diol **86** (Scheme 11B).[96] They prepared compound **88** from **86** by a Mitsunobu-type reaction and subjected it to rhodium-catalyzed C1–C6 bond cleavage *via* a β-carbon elimination to obtain cyclohexenone **89**, which appears similar to carvone but actually bears a completely reorganized skeleton and a six-membered ring with an unusual substitution pattern. Intermediates with analogous cyclohexenyl cores are common in previously reported synthetic investigations of the phomactin family,[97–104] but the approach reported by Sarpong *et al.*[96] arguably stands out as a creative, simplified solution to the synthetic challenge posed by these compounds. From compound **89**, 12 straightforward transformations led to **90**, which served as a common intermediate in the syntheses of five phomactins.

The C1–C6 bond cleavage described above resulted in a methyl group at C6, and the Sarpong group proposed that a C–C coupling reaction could be integrated into the bond cleavage process to extend its application. In 2018, they reported the total synthesis of xishacorene B (**92**) from (*R*)-carvone (Scheme 11C).[105] This time, palladium was used as the transition-metal catalyst for the coupling reaction. The synthesis began with treatment of *ent*-**85** (obtained from (*R*)-carvone) and **93** with $Pd(PCy_3)_2$, generating Pd(II)-alkoxide **94** through oxidative addition followed by ligand exchange.



starting material	photochemical conditions	product	isolated yield (%)
83	254 nm, MeOH, rt, 3 h	**77**	58 (81 brsm)
77	365 nm, *n*-hexane, rt, 5 h	**83**	21 (73 brsm)

Scheme 10 Lei's synthesis of jungermannenone C.



Scheme 11 Sarpong's syntheses of phomactins, xishacorene B and longiborneol.

Cleavage of the C1–C6 bond through β-carbon elimination afforded alkyl-Pd(II) intermediate **95**, which, upon reductive elimination, furnished enone **96**, another compound with a reorganized carvone skeleton. Subsequently, **96** was converted to **92** in seven steps.

In addition to the cyclobutanol cleavage reactions leveraged above, polar rearrangements of the bicyclo[3.1.1] carboskeleton of **85** and **86** can obviously be used to produce other bicyclic compounds, and such rearrangements have long been recognized as reliable synthetic tools. Indeed, in 2022, the Sarpong group reported a nine-step synthesis of longiborneol (**97**) by means of such a strategy (Scheme 11D).[106] They found that treatment of **85** with *p*-TsOH led to reorganized carvone **99**, which has a bicyclo[2.2.1] skeleton, through a semi-pinacol rearrangement pathway. Recognizing a carvone in **99** is difficult even though only three reactions were involved in its preparation from (*S*)-carvone (**84**), but the resemblance of **99** to **97** is comparatively obvious. Compound **99** was converted to **100** in three steps, and a subsequent cyclization induced by metal hydride hydrogen atom transfer furnished the seven-membered ring of the target molecule; vinyl phenylsulfonate was used as a novel radical acceptor for this reaction. Overall, **97** was synthesized in nine steps, and this route was much shorter than previously reported routes,[107–109] owing to the efficiency of the skeletal reorganization process at the outset.

3.4 Maimone's syntheses of berkeleyone A, andrastin D, and terretonin L

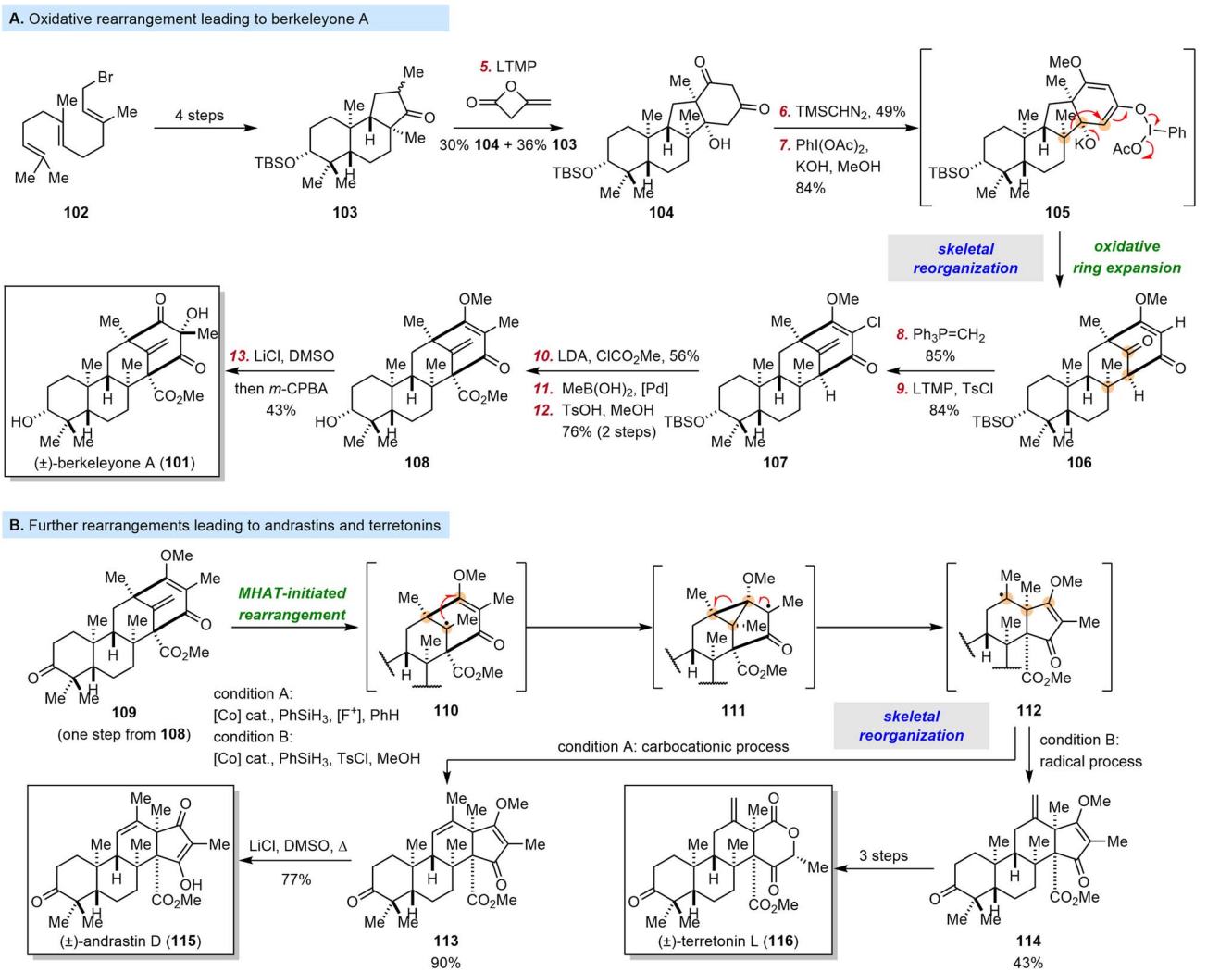
In the examples described above, all the substrates for the skeletal reorganizations were related to natural products. However, if this limitation could be removed, the possibilities would be much broader. In nature, the union of 3,5-dimethylorsellinic acid (DMOA) with farnesyl pyrophosphate leads to the assembly of over 100 meroterpenoid natural products.[110] Although these DMOA-derived meroterpenoids have been the subject of a number of biosynthetic studies, few chemical synthesis have been disclosed.[111,112] In 2016, the Maimone

group described the first total synthesis of a complex DMOA-derived meroterpenoid, berkeleyone A (**101**).[113] The berkeleyones were isolated in 2011 from the fungus *Penicillium rubrum*, which is found in deep water acid mine waste.[114] Berkeleyones were found to inhibit caspase-1 and interleukin-1β production, and **101** was the most potent of the tested compounds.[114]

As depicted in Scheme 12A, the Maimone group's synthesis commenced with farnesyl bromide **102**, which was converted to **103** *via* a polyene cyclization. A ring-opening/annulation process was effected by treatment of **103** with lithium tetramethylpiperidide and diketene, and this formal [4 + 2] reaction afforded **104**. At this stage, Maimone *et al.* explored the conversion of the 5,6-fused ring system of **104** to the hallmark bicyclo[3.3.1]nonane skeleton of **101**.

Following *O*-methylation of the 1,3-diketone moiety, they tested their previously developed I(III)-mediated oxidative ring expansion method (with $PhI(OAc)_2$ and KOH in MeOH)[115–117] in this polycyclic setting and isolated **106** in 84% yield. This skeletal reorganization probably proceeded through intermediate **105**. Subsequently, six steps transformed **106** into **101** *via* intermediates **107** and **108**.

A year later, the Maimone group, together with the Newhouse group, reported syntheses of the meroterpenoids andrastin D (**115**) and terretonin L (**116**) (Scheme 12B).[118] These molecules are biogenetically related to **101** but have 6,5-fused C/D rings instead of a bicyclo[3.3.1] ring system. Inspired by Shigehisa's work,[119] the authors reasoned that with an oxidative variant of the classic Mukaiyama hydration process, the bicyclo [3.3.1] motif could be reorganized into the 6,5-fused C/D rings. Their endeavors started from **109**, which was prepared easily from **108**. Tertiary radical **110**, which was formed *via* Co–H addition to **109**, underwent a 1,4-addition to give cyclopropylcarbinyl radical **111**; and a subsequent radical fragmentation gave radical **112**. This process can be thought of as a vinylogous Dowd–Beckwith rearrangement. Depending on the reaction conditions, intermediate **112** could undergo either a carbocation-based process to give **113** (90% yield) or a radical-based process to give **114** (43% yield, 85% based on recovered starting material). This concise process accomplished the



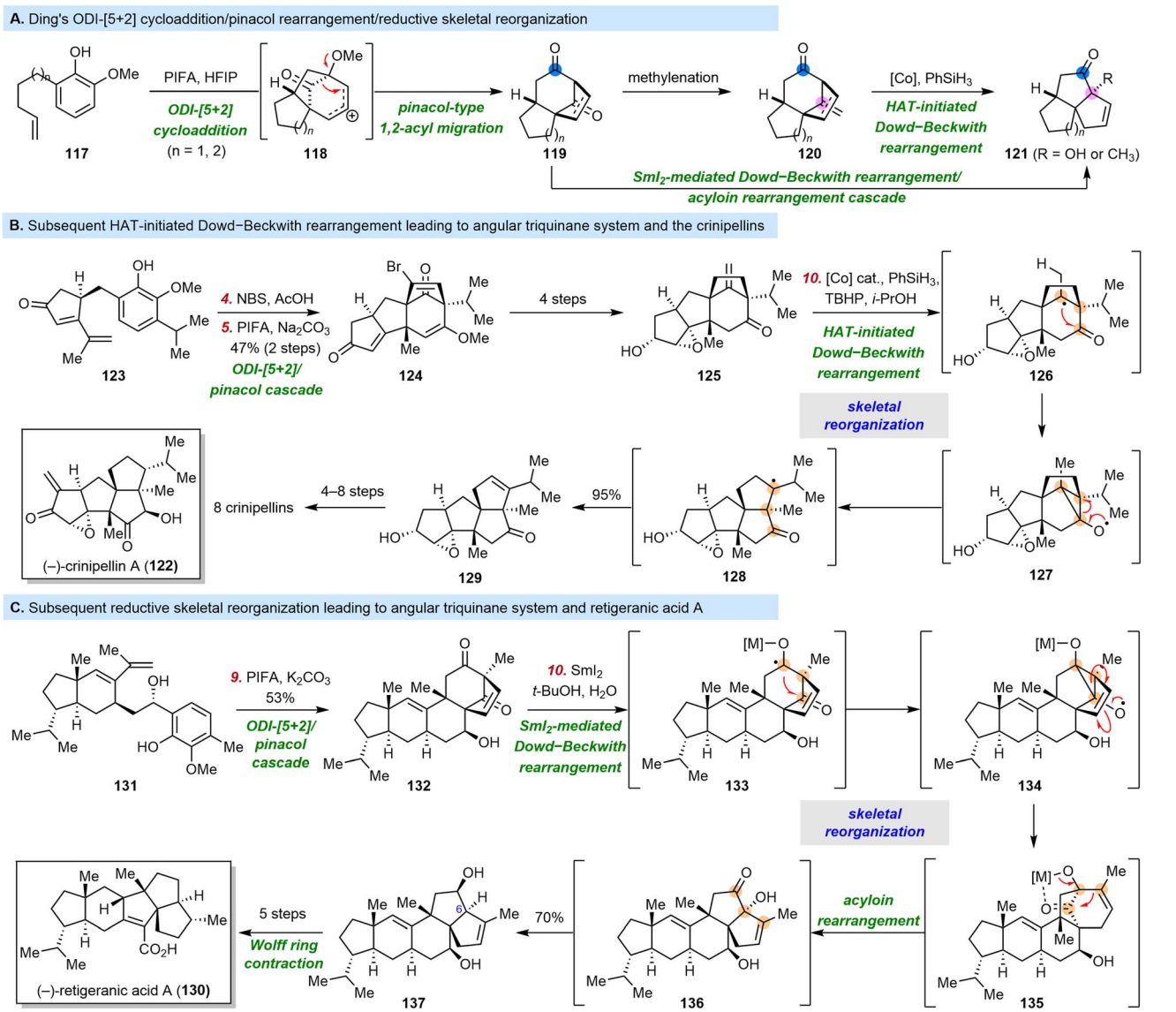
Scheme 12 Maimone's synthesis of berkeleyone A, and Maimone and Newhouse's syntheses of andrastin D and terretonin L.

reorganization of the berkeleyone skeleton to the andrastin/terrenoid skeleton. Compound **113** was then converted to **115** by a simple Krapcho-type demethylation, and **114** was converted to **116** in three steps.

3.5 Ding's syntheses of crinipellins and retigeranic acid A

Tetracyclic diterpenoids, especially those with bridged ring systems, have received considerable attention from the synthetic community. In 2017, the Ding group disclosed a novel oxidative-dearomatization-induced (ODI) [5 + 2] cycloaddition/pinacol rearrangement cascade reaction,[120] and have since synthesized the diterpenoid natural products pharicin A,[120] stemarin,[121] rhodomolleins XX and XXII,[122] and rhodomollanol A.[123] The general pattern of reactions is shown in Scheme 13A.[124] Vinylphenols **117** were subjected to oxidative dearomatization conditions, and the resulting oxidized phenol moiety (not shown) underwent [5 + 2] cycloaddition with the pendant olefin to give cationic intermediates **118**. A subsequent pinacol-type 1,2-acyl migration gave products **119**, which had a cyclopentane- or cyclohexane-fused bicyclo[3.2.1] ring system with a sufficient number of oxidized sites for further elaboration. In addition to developing this ingenious skeletal reorganization process, the Ding group also exploited the synthetic potential of the skeleton of **119** by reorganizing it into angular triquinanes **121**.

Crinipellins are a class of natural products that have a linear *cis*,*anti*,*cis*-triquinane (ABC rings) and an angular triquinane (BCD rings) system and were isolated from a basidiomycete *Crinipellis* species.[125–127] Piers and Renaud in 1993,[128] Piers in 1998,[129] Lee in 2014,[130] and Yang in 2018 [131] accomplished total syntheses of crinipellin A (**122**) or B in racemic or enantiopure form. In 2022, the Ding group reported collective, divergent syntheses of crinipellins A–F and dihydrocrinipellins A and B.[132] As shown in Scheme 13B, Ding *et al.* started by subjecting



Scheme 13 Ding's syntheses of crinipellins and retigeranic acid A.

vinylphenol **123** to bromination followed by the above-mentioned ODI-[5 + 2]/pinacol rearrangement cascade, which afforded **124**. Notably, the bromine atom installed prior to the cascade was used to control the diastereoselectivity of the cycloaddition reaction. Compound **124** was converted to vinylketone **125** in four steps, which set the stage for the key hydrogen-atom-transfer-initiated Dowd–Beckwith rearrangement. The tertiary radical of compound **126**, which formed under metal hydride hydrogen atom transfer conditions, added to the ketone to form a cyclopropane ring, fragmentation of which gave rise to **129** in a remarkable 95% yield *via* radical **128**. An additional four to eight transformations afforded eight members of the crinipellin family.

Notably, this type of skeletal reorganization usually led to products with quaternary stereocenters. However, in the vast majority of angular triquinanes—including retigeranic acid A (**130**), silphinenes, and bipolarolides—at least one of these stereocenters is tertiary or oxa-quaternary. Therefore, to synthesize **130**,[133–138] the Ding group developed a new rearrangement in 2023, when they reported a reductive skeletal reorganization strategy (Scheme 13C).[139] First, vinylphenol **131**, which was prepared in eight steps from commercially available compounds, was exposed to the ODI-[5 + 2]/pinacol rearrangement cascade conditions, which furnished diketone **132**. This time, there was no ketone olefination step; instead, **132** was directly treated with SmI_2 to effect a reductive coupling of the two ketone groups, giving intermediate **134**. Cyclopropane fragmentation completed a Dowd–Beckwith rearrangement process, and resulting intermediate **135** underwent an acyloin rearrangement to afford **136**, which was then doubly reduced to diol **137**. In this new skeletal reorganization, one tertiary bridgehead stereocenter (C6) was retained. After another five steps—including a Wolff ring contraction—**130** was obtained in a total of 15 steps.

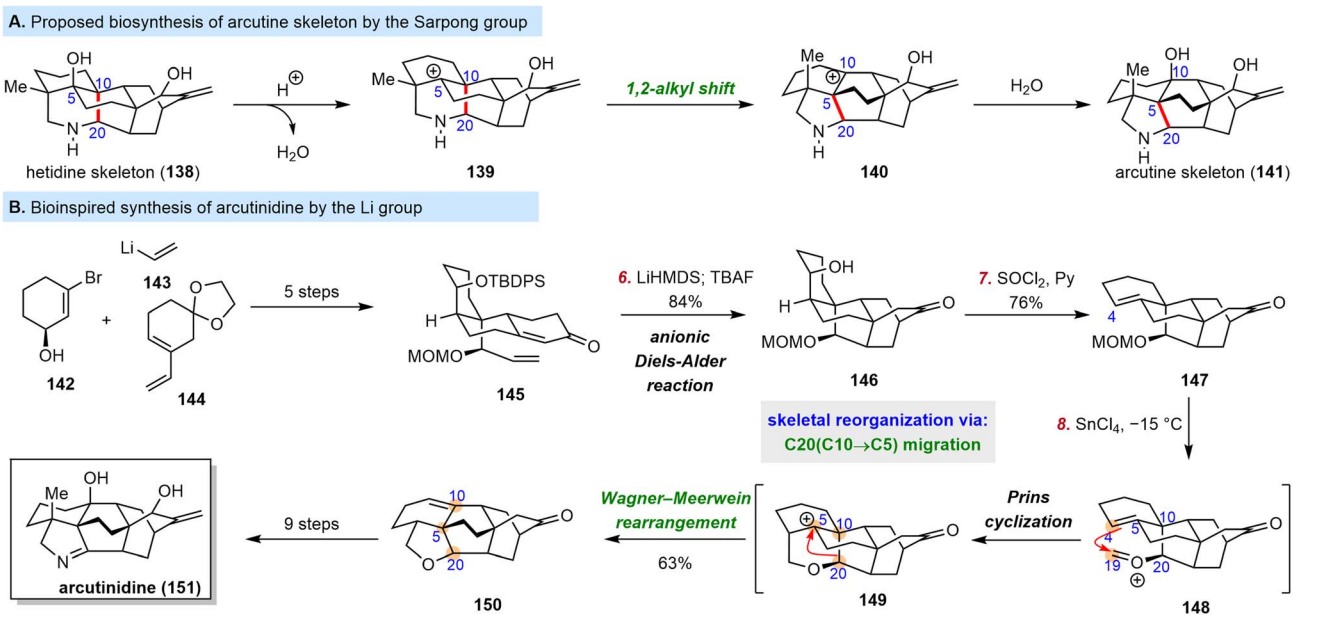
4. Alkaloids

Alkaloid natural products contain at least one nitrogen atom and are usually basic. They are characterized by a greater structural diversity than most other classes of natural products because they generally do not share the same biosynthetic precursors. However, biogenetic relationships between different molecular scaffolds are common, and this renders skeletal reorganization an important strategy for the chemical synthesis of alkaloids. Moreover, the nitrogen atoms not only can act as polar handles to facilitate C–C bond reorganization but also can be directly involved in C–N bond reorganization. In this section, the power and diversity of skeletal reorganizations in alkaloid synthesis will be demonstrated with five examples.

4.1 Li's synthesis of arcutinidine

Diterpenoid alkaloids, which originate from the amination of tetracyclic diterpenes, are a large group of natural products with complex structures and various biological activities. In 2000, a new arcutine-type C20 diterpenoid alkaloid, which features a unique skeleton with a C5–C20 bond rather than the usual C10–C20 bond, was isolated from *Aconitum arcuatum* and *Aconitum carmichaelii*.[140,141]

In 2015, Sarpong and co-workers proposed that the arcutine skeleton is biosynthesized from the hetidine skeleton (Scheme 14A).[142,143] In their proposal, protonation of the C5–OH group of **138** leads to **139**, which has a C5 carbocation that induces a 1,2-alkyl shift of C20 from C10 to C5, generating a compound **140** with a carbocation at C10. Trapping **140** with H_2O then completes the skeletal reorganization to give arcutine skeleton **141**. From 2019 to 2021, three elegant total syntheses of arcutine alkaloids were published by the Qin group,[144–146] the Sarpong group[147,148] and the Li group.[149] Unlike Qin's and Sarpong's



Scheme 14 Sarpong's proposed biosynthesis of the arcutine skeleton and Li's bioinspired total synthesis of arcutinidine.

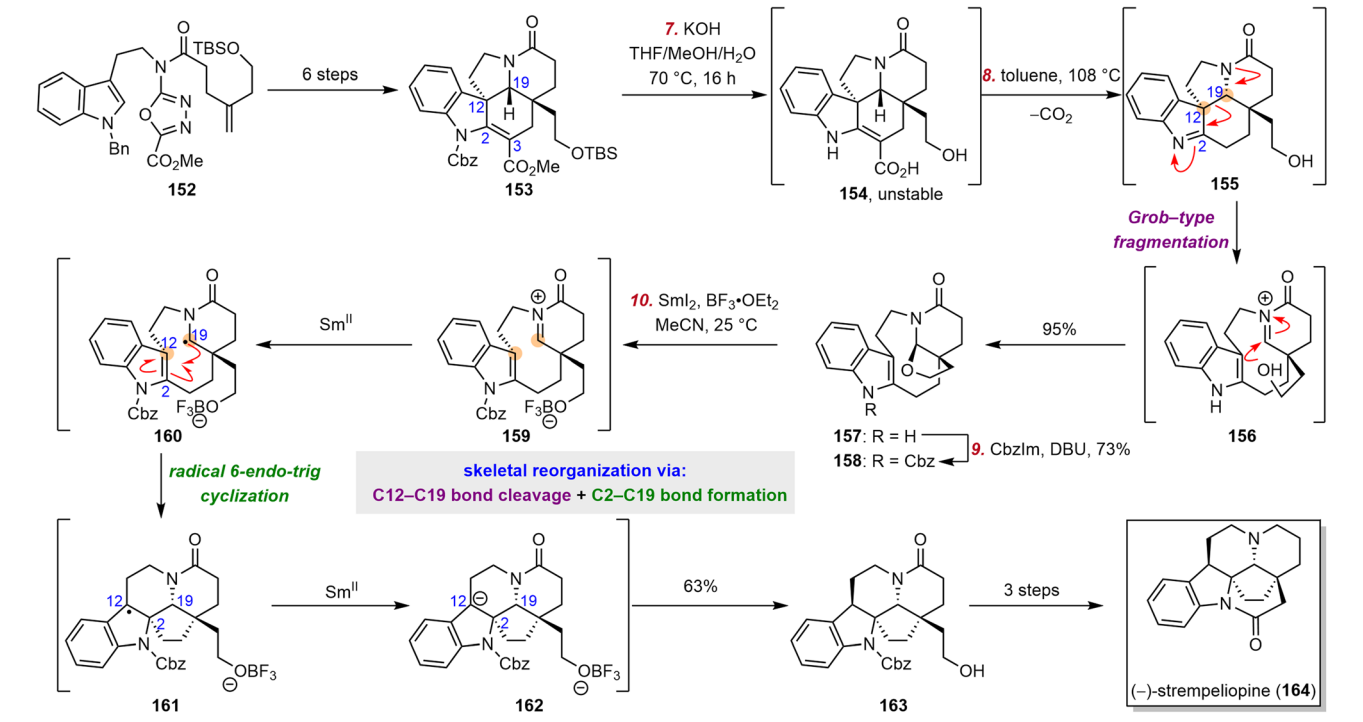
syntheses, Li's synthesis employed an intriguing bioinspired strategy based on consideration of the interrelationship of diterpenoid alkaloids[150] and the biosyntheses postulated by Liang and Wang[151] and by the Sarpong group.[142,143]

Li's synthesis utilized a Prins cyclization/Wagner–Meerwein rearrangement cascade to convert the hetidine skeleton to the arcutine skeleton (Scheme 14B). The synthesis began with the preparation of α,β-unsaturated enone **145** through the convergent coupling of **142**, **143**, and **144**. Upon deprotonation with lithium hexamethyldisilazane, **145** underwent an intramolecular, anionic Diels–Alder reaction to afford an 84% yield of **146**, which has the key hetidine skeleton. Dehydration of **146** with $SOCl_2$/pyridine afforded **147** regioselectively. Notably, the methoxymethyl group was designed for use as a precursor of the oxonium ion of **148**, the formation of which triggered a skeletal reorganization involving C20 migration from C10 to C5. Treatment of **147** with the Lewis acid $SnCl_4$ smoothly produced oxonium ion **148**, initiating the Prins cyclization; and the resultant C5 tertiary carbocation of **149** induced the desired Wagner–Meerwein rearrangement to afford a 63% yield of **150**, which has the arcutine skeleton. Arcutinidine (**151**), arcutinine, and arcutine (not shown) were synthesized from **150**.

4.2 Boger's synthesis of strempeliopine

Strempeliopine (**164**), the parent schizozygane alkaloid, was first isolated by Laguna and co-workers from the roots of *Strempeliopsis strempelioides* K. Schum.[152] Later, its absolute configuration was established by Hájíček and Trojánek through stereoselective synthesis.[153–155]

To date, six groups have reported syntheses of strempeliopine (**164**).[153–160] In 2021, Boger and co-workers disclosed a total synthesis of **164** enabled by a Grob-type fragmentation of the C12–C19 bond and a reductive radical cyclization mediated by $BF_3 \cdot Et_2O/SmI_2$ to form the C2–C19 bond (Scheme 15).[159] Hájíček and Trojánek reported a similar reductive rearrangement strategy, but it suffered from poor reproducibility.[153–155] To address this issue, Boger and co-workers developed a stepwise version of the skeletal reorganization. This version commenced with the preparation of pentacyclic intermediate **153**, which has the core skeleton of the aspidoperma alkaloids, from 1,3,4-oxadiazole **152** in six steps by means of a [4 + 2]/[3 + 2]cycloaddition cascade.[161–165] Removal of the protecting groups from **153** afforded acid **154**, which was unstable and was therefore immediately subjected to thermal decarboxylation to generate **155**. Grob-type fragmentation of **155** cleaved the C12–C19 bond to afford **156**, the iminium ion of which was trapped by the pendent primary alcohol to furnish **157** in 95% yield from **153**. Protection of the indole moiety of **157** as a benzyl carbamate delivered **158**, which was the precursor for the reductive coupling. When subjected to Huang's conditions,[166–168] **158** underwent a radical cyclization to afford **163** in 63% yield. Boger *et al.* proposed that the transformation proceeded by the following mechanism: (1) **158** was activated by $BF_3 \cdot OEt_2$ to yield iminium ion **159**, which was reduced by SmI_2 to α-aminoalkyl radical **160**; (2) radical **160** underwent a radical 6-*endo*-trig cyclization that formed the C2–C19 bond; and (3) the resulting radical at C12 was reduced by SmI_2 to afford anion **162**, protonation of which generated **163**. With **163** in hand, these investigators completed the synthesis of **164** in three additional steps.



Scheme 15 Boger's synthesis of strempeliopine.

4.3 Fan's synthesis of lycojaponicumin D

Lycopodium alkaloids have been known for centuries and have drawn significant attention from both synthetic and medicinal chemists. In 2012, the structurally unprecedented *Lycopodium* alkaloid lycojaponicumin D (**165**), which features a unique 5/7/6/6 tetracyclic skeleton and an unusual C3–C13 linkage, was isolated from *Lycopodium japonicum* Thunb. ex Murray by Yu *et al.*[169] These investigators proposed a plausible biosynthetic pathway from fawcettimine to **165**,[169] but Fan *et al.* instead proposed a possible biogenetic relationship[170] between lycojaponicumin D (**165**), lycoposerramine F (**166**) (also known as miyoshianine A),[171] and lycodoline (**167**), a proposal that provided valuable inspiration for the chemical synthesis of **165**.

Fan *et al.* set out to develop a new, efficient synthetic route to lycodoline (**167**) and to realize its biomimetic conversion to lycojaponicumin D (**165**) (Scheme 16).[170] To this end, they began by developing a novel bridgehead C–H heterofunctionalization reaction for the formation of the challenging bridgehead C–heteroatom bond. Specifically, hemiacetal ketone **168**, which was prepared in six steps from 4-methylcyclohexanone, underwent a Saegusa–Ito oxidation to produce a highly strained bicyclo[3.3.1] bridgehead enone (not shown), which was immediately attacked by acetate anion *via* an oxa-Michael addition to give β-functionalized product **169**. Lycodoline (**167**) was then obtained in three steps from **169**, which set the stage for biomimetic conversion of **167** to **166** and **165**. The synthesis of **166** was smoothly achieved *via* double oxidation. After extensive investigation of reaction conditions, Fan *et al.* used triphosgene as an activating reagent to facilitate cleavage of the N–O bond of **166**, which triggered the C4–C13 bond fragmentation to give intermediate **171**. Subsequent keto–enol tautomerization and a Mannich reaction effected the C3–C13 bond linkage, thus completing the synthesis of **165** in three steps from **167** by a bioinspired skeletal reorganization strategy.

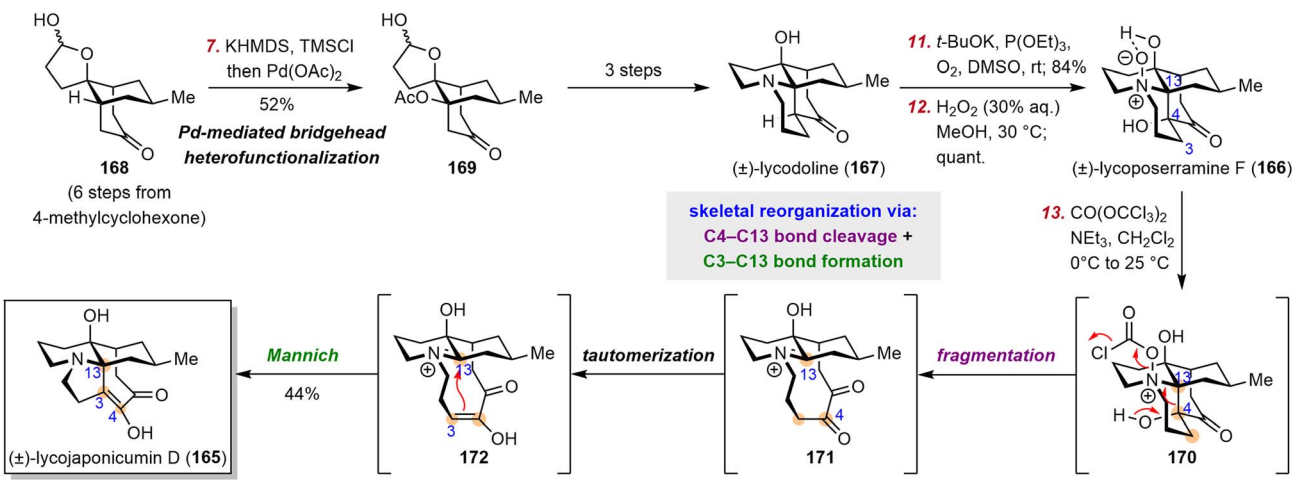
4.4 Zhu's syntheses of condyfoline and tubifoline

The aspidospermatan-type alkaloid condyfoline (**173**) was first synthesized in 1963, by Schumann and Schmid, who subjected condylocarpine (**174**) to hydrogenation and acidic decarboxylation (Scheme 17A).[172] Subsequently, condyfoline (**173**) was found to be readily converted to tubifoline (**175**), whose configuration was established through derivatization of akuammicine (**176**). In this way, the absolute configuration of **174** was also established. Since then, five groups have reported synthetic studies of **173**, which culminated in racemic syntheses by the Harley-Mason group[173] and the Ban group,[174] enantioselective syntheses by the Amat group[175,176] and the Zhu group,[177] and epimer synthesis by the Andrade group.[178] The elegant enantioselective synthesis of **173** by Zhu *et al.*[177] is notable in featuring a $TiCl_3$-mediated intramolecular reductive cyclization, leading to C2–N1 bond formation and C21 migration from C2 to C3 in one pot.

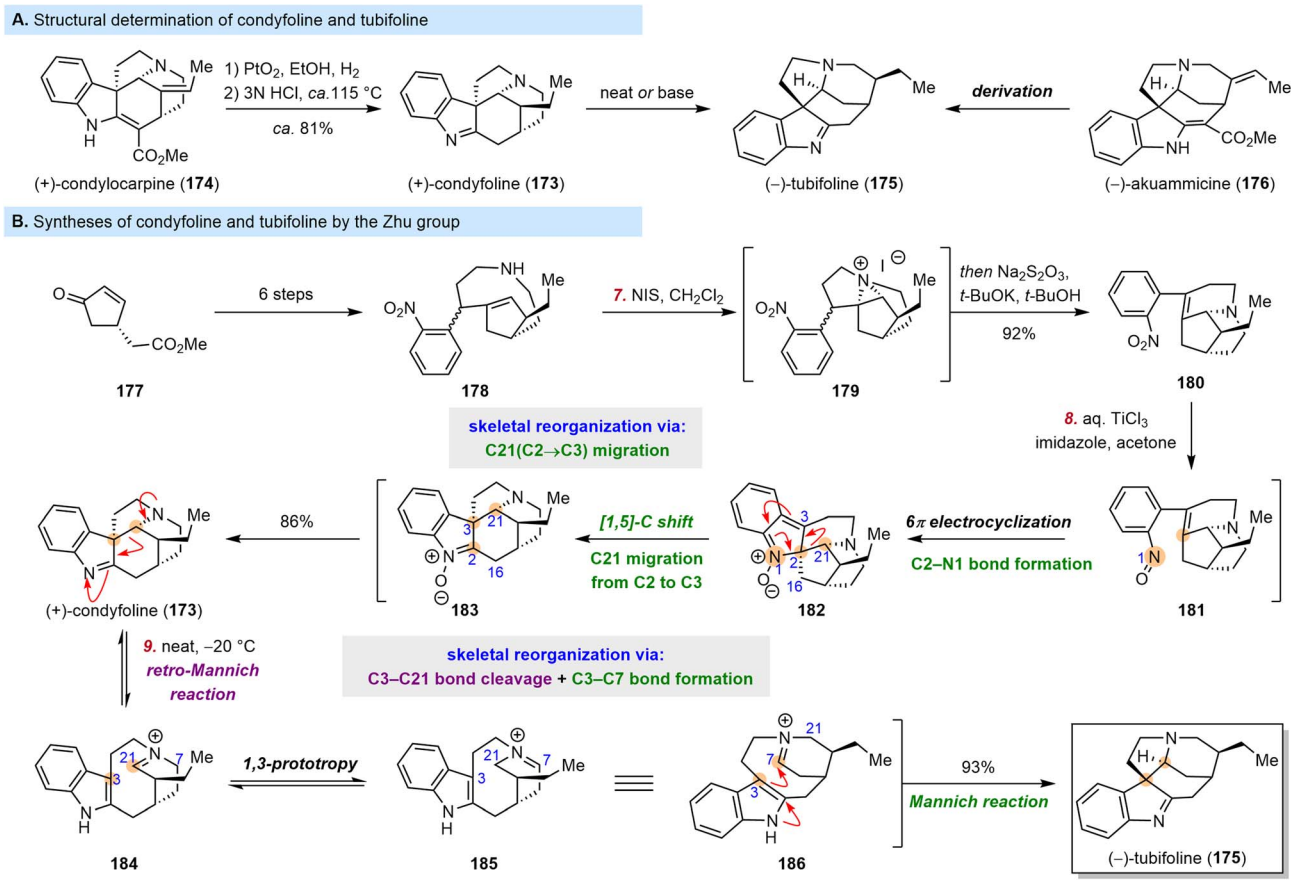
Starting from **177**, Zhu and co-workers prepared 2-nitrophenyl alkene **178** in six steps (Scheme 17B). Subsequently, **178** was treated with *N*-iodosuccinimide to afford putative intermediate **179**. Treatment of this aziridinium salt with *t*-BuOK resulted in an elimination reaction to produce desired alkene **180**. To complete the synthesis of **173**, Zhu *et al.* developed an efficient cascade reaction to install the indolenine moiety. Upon treatment with aqueous $TiCl_3$, **180** underwent 6π electrocyclization and a [1,5]-carbon shift, accomplishing C2–N1 bond formation and C21 migration from C2 to C3, to furnish **173** in 86% yield. Schumann and Schmid had reported the conversion of **173** to **175** in a low yield,[172] but Zhu and co-workers reinvestigated this transformation and found that upon storage at −20 °C for 20 days, **173** was cleanly converted to **175** in 93% yield; they proposed that this transformation occurred through a *retro*-Mannich/1,3-prototropy/Mannich cascade reaction.

4.5 Jiang's synthesis of calycanthine

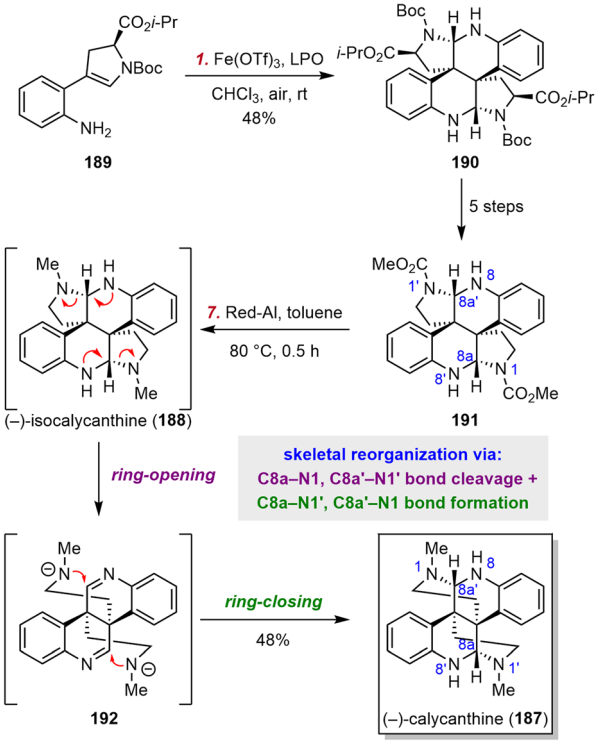
Dimeric cyclotryptamine alkaloids have had a rich history since the isolation of calycanthine (**187**) in 1888.[179] Five basic dimeric scaffolds have been identified from various isolated natural products.[180–184] Numerous pioneering studies suggest that tryptamine, tryptophan, and oxindole derivatives are the biosynthetic precursors for cyclotryptamine dimerization.[185]



Scheme 16 Fan's synthesis of lycojaponicumin D.



Scheme 17 Determination of the structures of condyfoline and tubifoline and Zhu's syntheses of the two molecules.



Scheme 18 Jiang's synthesis of calycanthine.

Despite these precedents, the Jiang group developed a different dimerization tactic to access the relatively underexplored isocalycanthine scaffold.[185]

They selected isocalycanthine (**188**) as their first synthetic target (Scheme 18). They designed chiral substrate **189**, a constitutional isomer of tryptophan, as their dimerization substrate. When **189** was exposed to a combination of $Fe(OTf)_3$ as the catalyst and dilauroyl peroxide as the terminal oxidant, dimeric product **190** was obtained in 48% yield. Notably, this reaction constructed two vicinal all-carbon quaternary centers with superb stereocontrol. Compound **190** was then converted smoothly to **191** in five steps, and at this point, it seemed that **188** was only one reduction step away. Several promising reductants were tested, and Jiang *et al.* were surprised to find that only Red-Al afforded a major product, which was identified as **187**. They proposed that the driving force for this unexpected skeletal reorganization, which involved sequential ring opening and ring closing, was release of strain in the congested skeleton. Intriguingly, this transformation is as an example wherein the nitrogen atoms themselves were directly involved in the reorganization process.

5. Conclusions

In this review, we have highlighted recent examples of efficient syntheses of steroid, terpenoid, and alkaloid natural products by means of a skeletal reorganization strategy, which offers an

expedient approach for quick, easy access to structurally complex molecular frameworks. This strategy can be expected to continue to inspire synthetic chemists to realize additional creative syntheses of complex molecules.

Admittedly, many of the skeletal reorganizations described above may not have been obvious upon first inspection of the molecule, but clues to the emergence of their application can be discerned. The foremost source of reorganization strategies for the construction of complex core frameworks may be based on the proposed biosynthetic pathways, which account for the majority of the steroid and alkaloid syntheses discussed in this review. Similarly, structural comparison between co-isolated or structurally related molecules can provide insights into late-stage interconversions between natural products, processes that frequently involve skeletal reorganizations. Apart from these biogenesis-guided strategies, in-depth exploration of rearrangement reactions opens up a much larger space for the development of skeletal reorganizations. Detailed investigation of a given rearrangement reaction, elaborative design of substrates, and creative derivatization of rearrangement products can bring about impressive reorganizations that can facilitate access to architecturally distinct natural products. Related inspirations may come from careful study of the literature, from the chemist's imagination, and from openness to serendipitous discoveries.

Although significant progress has been made in the development of the skeletal reorganization strategy, inefficient preparation of reorganization precursors somewhat hampers its application. Among the various difficulties encountered, precise installation of appropriate oxidation patterns has proven to be exceedingly challenging. Chemoenzymatic approaches that combine chemical transformations with enzymatic oxidation appear to be an attractive solution to this challenge, owing to the boom in research on enzyme engineering.[186–192] Moreover, integration of functionalization and rearrangement processes into a single transformation can result in synthetic routes that are much more concise and direct. The thriving field of transition-metal catalysis is sure to facilitate such integration because transition-metal catalysts can activate C–H and C–C bonds that are traditionally considered to be inert and can also mediate various C–C bond forming reactions. Such activities have been exhibited by many transition metals, including (but not limited to) Cu,[193,194] Rh,[195–197] Pd,[198,199] Pt,[200] and Au;[200–202] and some of these metals have already found applications in natural product synthesis. Enzymes are another potential tool. Various enzymatic transformations involving oxidation or functionalization followed by rearrangements have been reported over the years.[203–211] To date, such transformations have made only limited contributions to natural product synthesis, but they will undoubtedly receive increasing attention from synthetic chemists. Overall, if the reorganization precursors could be more accessible, skeletal reorganizations will play a more important role in organic synthesis.

6. Conflicts of interest

There are no conflicts to declare.

7. Acknowledgements

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