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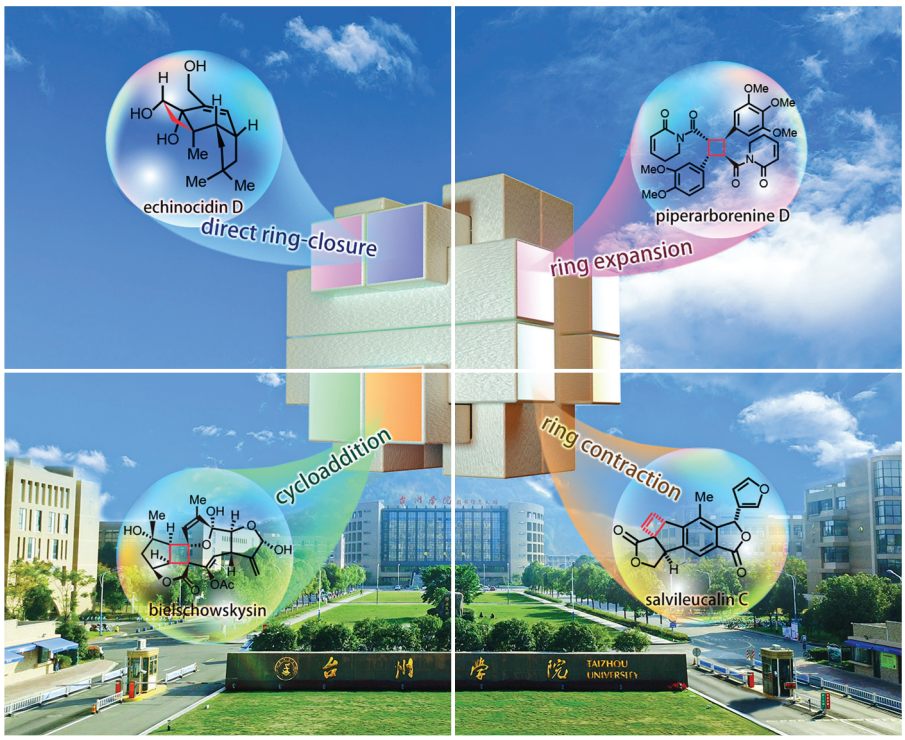

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Recent advances in the total synthesis of cyclobutane-containing natural products

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Complex natural products bearing strained cyclobutane subunits, including terpenoids, alkaloids and steroids, not only display fascinating architectures, but also show potent biological activities. Due to their unique structures as critical core skeletons in these molecules, a variety of new strategies for the construction of cyclobutane rings have greatly emerged during the last decade. In this review, we wish to summarize the recent progress in the cyclobutane-containing natural product synthesis with an emphasis on disconnection tactics employed to forge the four-membered rings, aiming to provide a complement to existing reviews.

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1. Introduction

In the class of strained carbocycles, cyclobutanes have been known as intriguing structural motifs for more than one century but remained relatively less explored in parallel with their homologues.[1] Due to the highly strained ring systems (*ca.* 26.7 kcal mol^{-1}), construction of cyclobutane rings, especially stereoselectively, poses significant challenges in synthetic chemistry. On the other hand, cyclobutanes readily undergo a number of ring-opening reactions by virtue of their tendency to release inherent strain energies. In some cases, however, striking ring strains can be dramatically reduced by the installation of a *gem*-dialkyl substituent (through the Thorpe–Ingold effect),[2] a carbonyl group, a heteroatom, or other functionalities (Fig. 1).[3] Owing to their improved stability, these structures could exist in not only artificial molecules but also many complex natural products.[4] The novel chemical structures as well as remarkable biological activities of the cyclobutane-containing natural products make them extremely attractive targets for total synthesis. Therefore, the development of new strategies for the assembly of these unique structures in a rapid and efficient manner has long been highly desirable.

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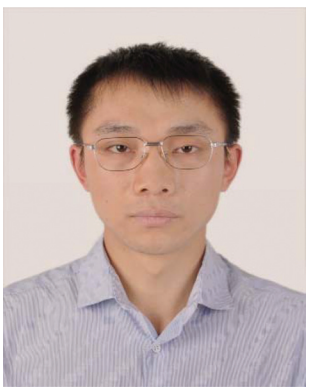

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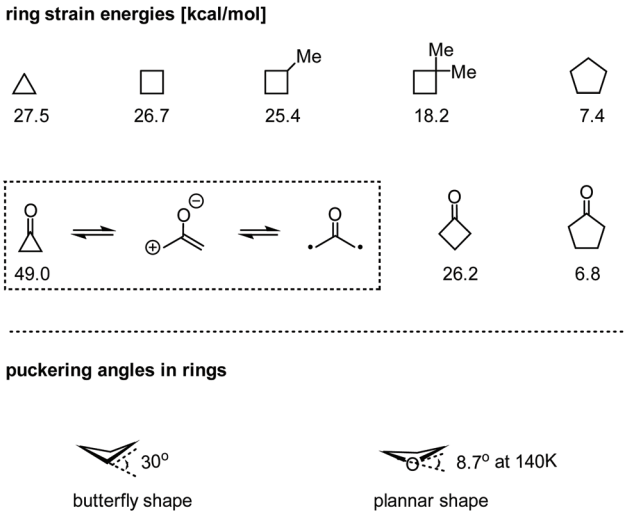

Fig. 1 Comparison of ring strain energies and structural properties of strained carbocycles.

Nowadays, grounded on the strain release, an increasing number of specialized summaries of cyclobutane chemistry have emerged, which presented the synthetic versatilities to forge acyclic and other types of cyclic skeletons. However, few systematic surveys on recent contributions to the total synthesis of natural products possessing four-membered carbocyclic scaffolds have been demonstrated.[5] Therefore, we endeavour to focus on the strategic considerations in a collection of selected total syntheses that have appeared in the last decade (2008–2018, and the representative examples reported in early 2019 are also included), and divide them into four categories: intramolecular direct ring-closure, cycloaddition, ring-contraction and ring-expansion strategies. In this review, the isolation, biological activities and innovative solutions to the problems encountered during the syntheses of the cyclobutane-containing natural products are emphatically described. Due to space limitation, some other classical protocols as well as the syntheses concentrating on the reconstruction of cyclobutanes[6,7] have to be neglected. Besides, the discussions of the performances on hetero four-membered ring systems such as oxetanes[3a–c] and azetidines[3d–f] are beyond the scope of this context and thus will not be covered herein.

2. Intramolecular direct ring-closure strategies

Intramolecular direct ring-closure strategies offer a facile route to the strained cyclobutane skeletons embedded in complex natural products, even though these processes are entropically disfavorable. Such approaches, which mainly include intramolecular nucleophilic cyclization, radical cyclization, cationic cyclization and transition-metal catalyzed cyclization, have become widespread and could be performed in a highly regio- or stereoselective fashion.

2.1 Nucleophilic cyclization

Solanoeclepin A was isolated by Mulder in 1986 as a hatching stimulus for potato cyst nematodes *Globodera rostochiensis* and *G. pallida*, which causes significant damage to potato crops.[8] Structurally, solanoeclepin A contains a heptacyclic ring system with each of the ring sizes from three to seven. In 2011, Tanino and Miyashita reported the first total synthesis of solanoeclepin A (**4**) featuring an intramolecular nucleophilic cyclization to assemble its highly strained tricyclo[5.2.1.$0^{1,6}$]decane skeleton (Scheme 1).[9] Their synthesis commenced with preparation of the crucial precursor **2**, which was derived from the known bicyclic acetoxy nitrile **1** in nine steps. Treatment of **2** with LDA initiated an intramolecular cyclization *via* the carbanion mediated ring opening of the epoxide, followed by silylation to afford cyclobutane **3** in nearly quantitative yield. The above transformation allowed the total synthesis of **4** in 52 steps and 0.18% overall yield.

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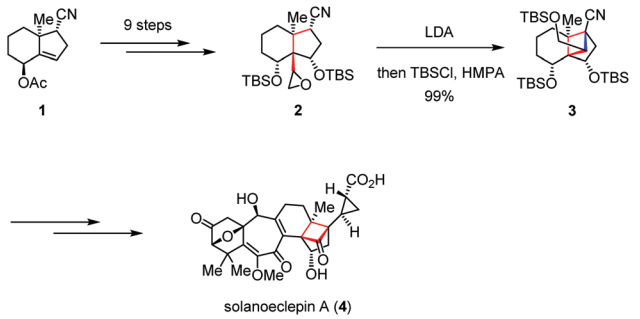
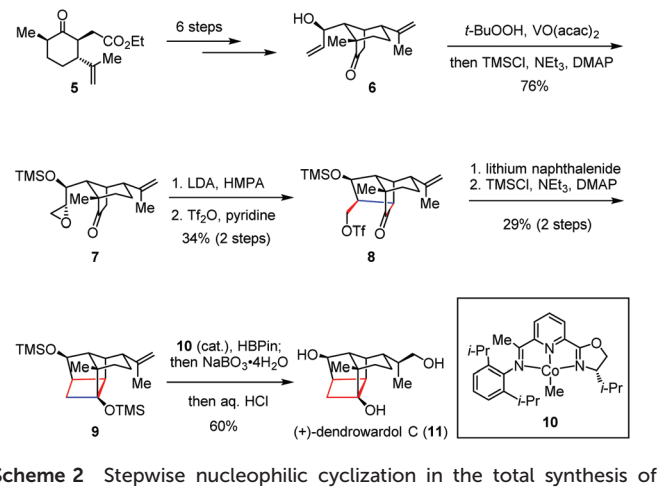


Scheme 1 Intramolecular nucleophilic cyclization in the total synthesis of solanoeclepin A.

Dendrobium species (Orchidaceaeare) have been widely used in traditional Chinese medicine for fever reduction and promotion of saliva secretion.[10] (+)-Dendrowardol C, isolated from the stems of *Dendrobium wardianum* Warner, is a sesquiterpenoid bearing an unprecedented 4/5/5/6 tetracyclic ring skeleton decorated with nine contiguous stereogenic centers.[11] Recently, Carreira and co-workers described the total synthesis of (+)-dendrowardol C (**11**) relying on an intramolecular aldol reaction to forge the central bicyclic scaffold and subsequent cyclization of a γ-triflyoxy ketone to construct the cyclobutane subunit (Scheme 2).[12] Their synthesis began with the preparation of allylic alcohol **6** from known ester **5** in six steps. Direct epoxidation of **6** using $VO(acac)_2$/TBHP and TMS protection proceeded in one pot to give epoxyketone **7** in 76% yield. Treatment of the latter with LDA/HMPA generated a lithium enolate intermediate and induced the following regioselective epoxide opening. Triflation of the resultant primary alcohol provided **8**, which then underwent ring closure in the presence of lithium naphthalenide to deliver the corresponding cyclobutanol. After silylation, **9** was formed in 29% yield over two steps. Finally, a regio- and enantioselective Co(I)-catalyzed hydroboration of **9** followed by oxidative work-up and global deprotection provided (+)-**11** in 60% yield.



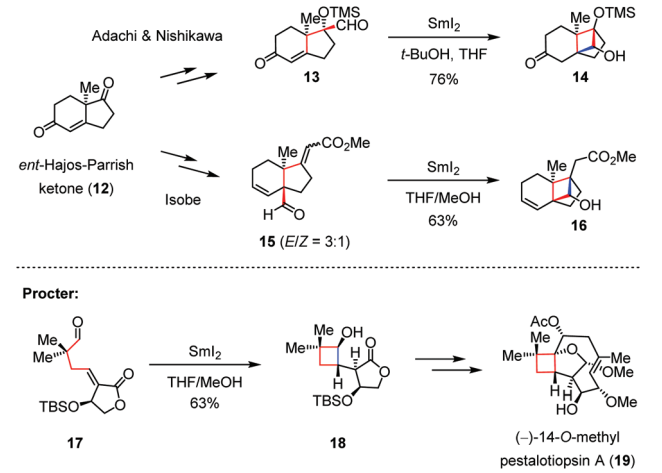
Scheme 2 Stepwise nucleophilic cyclization in the total synthesis of (+)-dendrowardol C.

2.2 Radical cyclization

Radical addition has seldom been used to construct four-membered carbon frameworks, probably because the inherent ring strain of the generated cyclobutane would easily reverse the reaction back to the corresponding acyclic form. To address this problem, electron-withdrawing groups such as carboxylic esters and sulfones can be introduced to stabilize the cyclic radical intermediate, and the *gem*-disubstituents could also be pre-installed on the precursor with the aim of enhancing the velocity of the intramolecular cyclization.

With this concept in mind, the groups of Adachi and Nishikawa,[13] and Isobe[14] independently reported the construction of the tricyclo[5.2.1.$0^{1,6}$]decene skeleton of solanoeclepin A (**4**) from *ent*-Hajos–Parrish ketone (**12**). As shown in Scheme 3, upon treatment with SmI_2, both enone **13** and enoate **15** underwent a 4-*exo*-trig ketyl-olefin radical cyclization to afford cyclobutanols **14** and **16** in 76% and 63% yield, respectively. On the other hand, Procter and co-workers also devised a similar strategy to build up the cyclobutanol skeleton and completed the total synthesis of (−)-14-*O*-methyl pestalotiopsin A (**19**).[15]

Xenicane diterpenoid (+)-plumisclerin A was isolated by Reyes and co-workers from crude extracts of soft coral *Plumigorgia terminosclera* collected on Mayotte Island in 2010.[16] (+)-Plumisclerin A exhibits low-micromolar cytotoxicity against multiple tumor cells, such as A549, HT29 and MDA-MB-231. Featuring a compact 6/5/4/6 tetracyclic ring system, (+)-plumisclerin A is structurally more complex than other xenicane congeners. The highly congested tricyclo[4.3.1.$0^{1,5}$]-decane in (+)-plumisclerin A makes this molecule a challenging target for synthesis. In 2018, Yao and co-workers reported the first total synthesis of (+)-plumisclerin A (**26**), which proceeded enantioselectively and thus allowed the determination of its absolute configuration (Scheme 4).[17] Their synthesis commenced with the asymmetric conjugate addition of malonate **21** to cyclopentenone **20** catalyzed by (*S*,*S*)-La-bis-



Scheme 3 Ketyl-olefin radical cyclizations in the syntheses of solanoeclepin A and (−)-14-*O*-methyl pestalotiopsin A.

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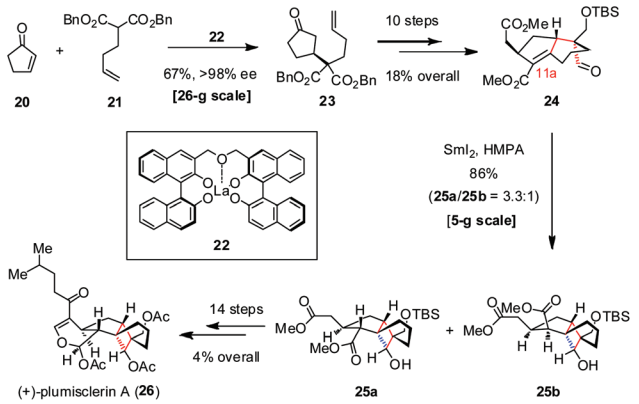
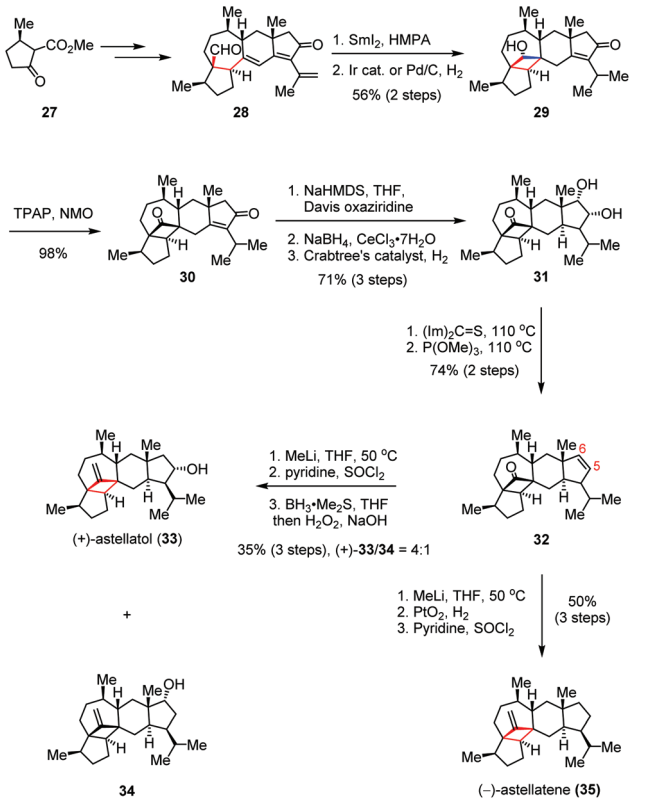


Scheme 4 Ketyl-olefin radical cyclization in the total synthesis of (+)-plumisclerin A.

BINOL **22** (10 mol%), providing **23** with 67% yield and >98% ee on a large scale. The following conversion of **23** to aldehyde **24** was realized in 18% overall yield over ten steps, setting the stage for the subsequent ketyl-olefin radical cyclization. In the presence of SmI_2 and HMPA, the expected 1,4-addition occurred well to give **25a** and **25b** as a 3.3 : 1 mixture of diastereomers at C11a in 86% combined yield on a gram scale. Further elaboration of the desired isomer **25a** gave rise to (+)-**26** uneventfully.

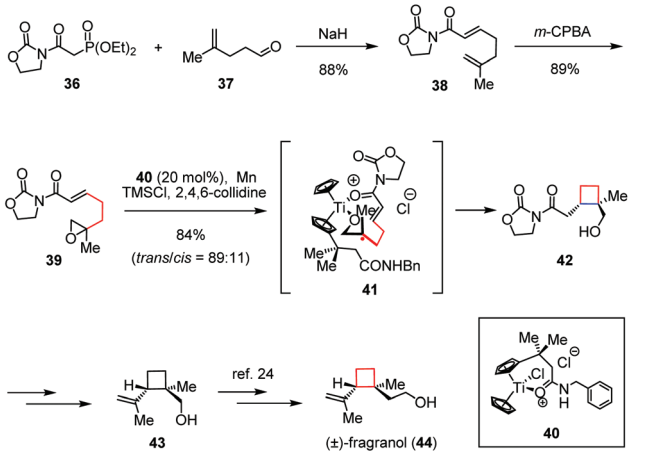
(+)-Astellatol was isolated from *Aspergillus stellatus* and structurally determined by Sadler and Simpson in 1989,[18] while (−)-astellatene was discovered recently by the Osbourn group *via* the genome mining technique.[19] Both of these molecules share a highly congested pentacyclic ring system, which possesses an unprecedented bicyclo[4.1.1]octane skeleton. In 2019, Xu and co-workers reported the first total syntheses of (+)-astellatol (**33**) and (−)-astellatene (**35**) featuring the SmI_2-mediated intramolecular 1,6-radical additions to forge the embedding cyclobutane subunits (Scheme 5).[20] The enantiomeric-enriched precursor **28** was prepared from known β-ketoester **27**. In the forward sense, exposure of **28** to SmI_2 and HMPA initiated the expected ketyl-olefin cyclization, followed by regioselective hydrogenation to afford cyclobutanol **29** in 56% yield over two steps. Subsequent Ley oxidation produced cyclobutanone **30**, which then underwent Davis α-hydroxylation, Luche reduction and direct hydrogenation, delivering *trans*-hydrindane **31** in 70% yield over four steps. After being converted to **32** through a Corey–Winter elimination, an additional three-step core modification led to (+)-**33** and its regioisomer **34** as a 4 : 1 mixture in 35% combined yield. On the other hand, further elaboration of **32** gave rise to (−)-**35** in 50% yield over three steps.

In the field of metal-mediated radical chemistry, much progress has been made toward efficient 4-*exo*-cyclization. Amongst, the application of titanocene(III) chloride constitutes a rapidly expanding field of research, especially for the generation of alkyl radicals from the corresponding epoxides as introduced by Nugent and RajanBabu.[21] (±)-Fragranol, a monoterpene, was first isolated from *Artemisia fragrans* Willd. Due to



Scheme 5 Ketyl-olefin radical cyclization in the total syntheses of (+)-astellatol and (−)-astellatene.

its useful structure which could be considered as a potential alternative to classical pesticides, the total synthesis of this terpene is a matter of recent investigation.[22] In 2009, Gansäuer and co-workers applied template catalysis to the stereoselective 4-*exo* radical cyclization, which led to a formal synthesis of (±)-fragranol (**44**).[23] As depicted in Scheme 6, their synthesis began with epoxide **39**, which was readily prepared through a Horner–Wadsworth–Emmons (HWE) olefination between



Scheme 6 Ti(III)-triggered 4-*exo* radical cyclization in the total synthesis of (±)-fragranol.

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phosphonate **36** and aldehyde **37** followed by epoxidation of the resultant alkene **38** with *m*-CPBA. By treatment of **39** with a catalytic amount of the cationic titanocene complex **40** in the presence of TMSCl and 2,4,6-collidine, the desired *trans*-cyclobutanol **42** was formed with its *cis*-isomer as a 89 : 11 mixture in 84% combined yield *via* the intermediacy of **41**. The known cyclobutanol **43** could be obtained from **42** through late-stage functionalization, which resulted in a formal synthesis of (±)-**44**.[24]

Apart from the ketyl-olefin radical cyclizations described above, the intramolecular pinacol coupling has also been exploited to assess the cyclobutane subunits. The antimicrobial protoilludane and marasmane sesquiterpenoids were isolated in the 1960s from the *Armillaria mellea* and *Lactarius vellereus* species of parasitic basidiomycetes fungi.[25] Due to their densely functionalized perhydrocyclobuta[*e*]indene and related carbon frameworks, great attention has been gained by these compounds. In 2017, Scheidt and co-workers reported a unified strategy to access the protoilludane, mellolide and marasmane families of natural products (Scheme 7).[26] Their syntheses commenced with aldehyde **46**, which could be prepared from 1,5-dienoate **45** through a series of conventional manipulations. By exposure of **46** to the *in situ* generated vanadium(II)/zinc(II) bimetallic complex, the expected intramolecular pinacol-type reductive coupling took place smoothly, affording the common intermediate **47** in 85% yield. Direct TASF-induced desilylation of **47** gave echinocidin D (**51**) in 87% yield. Under Mitsunobu conditions, a semi-pinacol ring contraction occurred as expected. After desilylation and oxidation, isovelleral (**52**) was obtained in 37% yield over three steps. On the other hand, **47** was conveniently transformed to *trans*-diol **48** through an oxidation/reduction sequence in 61% yield. Upon removal of the TBDPS group, echinocidin B (**53**) was formed with high efficiency. Furthermore, the esterification of **48** with orsellinic acid derivative **49** delivered orsellinate ester **50**, which was then advanced to armillaridin (**54**) in 70% yield over two steps.

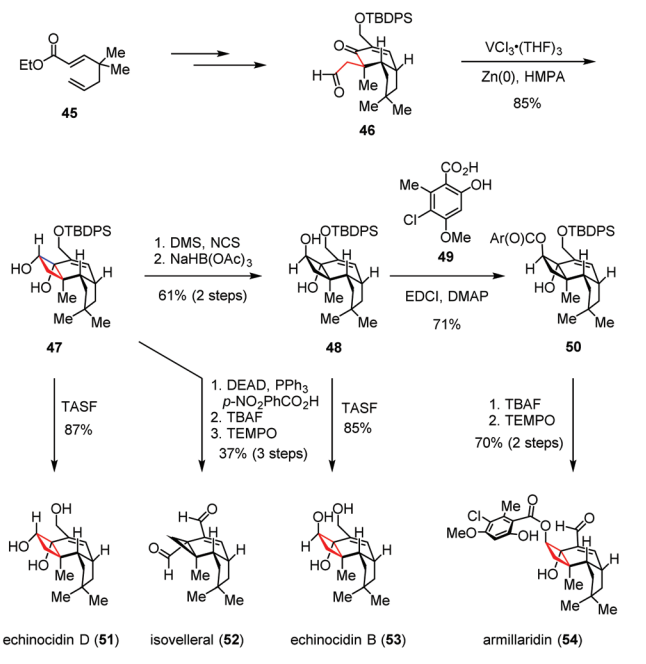
2.3 Cationic cyclization

Although cationic cyclization has been widely applied in the construction of polycyclic skeletons, few examples were described to generate cyclobutanes.[27] In 2012, Isobe and co-workers synthesized an advanced intermediate *en route* to solanoeclepin A (**4**) by using a cationic Hosomi–Sakurai cyclization as the key step (Scheme 8).[28] Allylpropargyl ether **55**, prepared from *ent*-Hajos-Parrish ketone (**12**), underwent TMS protection of the terminal alkyne followed by the [2,3]-Wittig rearrangement to give the *trans*-fused bicyclic precursor **56** as a single diastereomer in 83% yield over two steps. After *in situ* formation of the Nicholas-type cation **57**, subsequent cyclization in the presence of TMSOTf afforded tricycle **58** bearing three quaternary stereocenters as a single diastereomer in 66% yield over three steps.

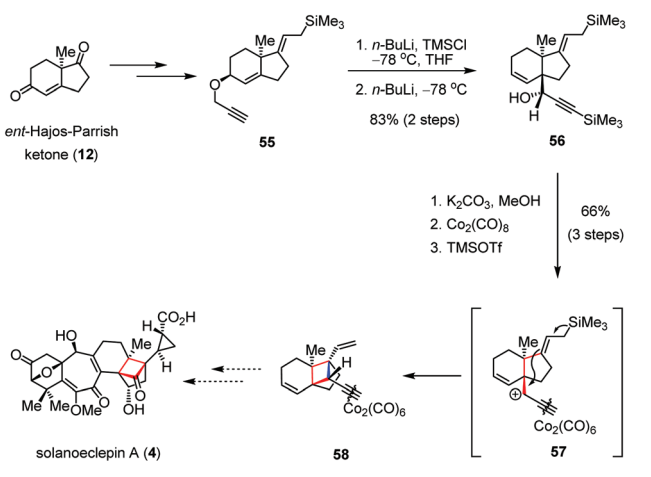
2.4 Transition-metal catalyzed cyclization

Transition-metal catalyzed cyclizations have been widely applied as versatile methods in C–C bond formations. Although the employment of these reactions for the generation of cyclobutane-based systems would encounter the risk of undesired ring cleavage, they still attracted considerable interest from the synthetic community due to their high efficiency in the construction of complex natural skeletons.

Grandisol, a diastereomer of **44** isolated from male boll weevils and other species, is one of the active components of aggregating pheromone and thus of interest to the pesticide industry.[29] The cyclobutane skeleton combined with two adjacent chiral centers makes this molecule structurally intriguing. In 2011, Suh and co-workers synthesized (±)-grandisol (**65**) through a Pd(0)-catalyzed intramolecular allylic alkylation in a



Scheme 7 Intramolecular pinacol coupling in the unified total syntheses of protoilludane natural products.



Scheme 8 Cationic Hosomi–Sakurai type cyclization towards the total synthesis of solanoeclepin A.

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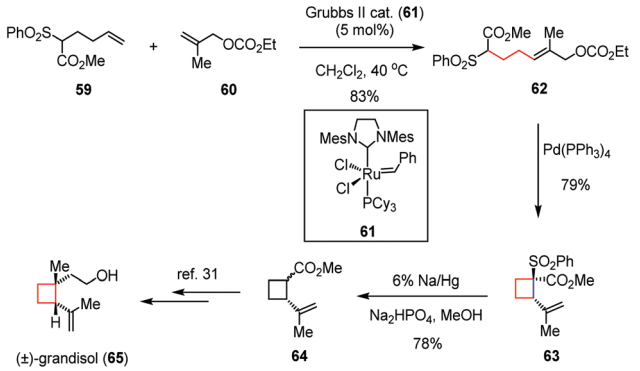
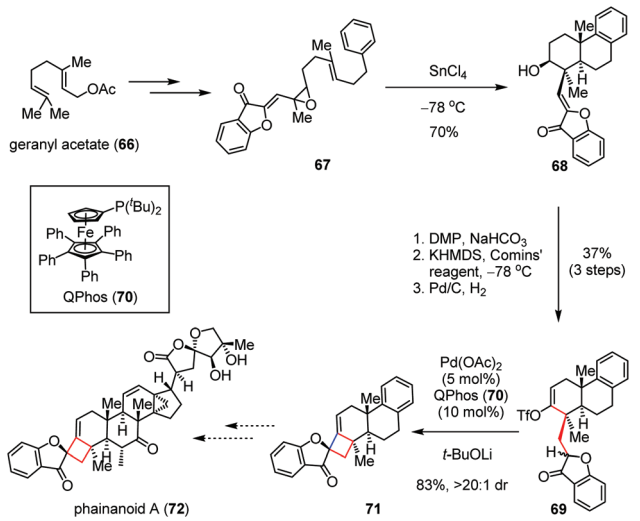


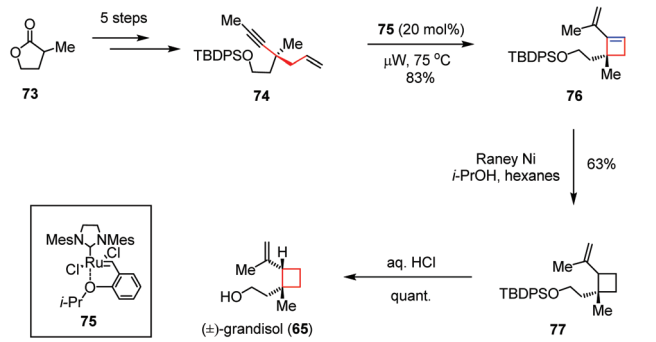
Scheme 9 Pd-Catalyzed intramolecular allylic alkylation in the total synthesis of (±)-grandisol.

highly regioselective manner (Scheme 9).[30] The precursor **62** was prepared in 83% yield through a cross metathesis reaction between the known methyl hexanoate **59** and allyl carbonate **60** in the presence of the Grubbs II catalyst (**61**). Treatment of **62** with $Pd(PPh_3)_4$ in DMSO afforded the required cyclobutane **63** in 79% yield. After desulfonylation by sodium amalgam, the known intermediate **64** was formed in 78% yield, which constitutes a formal synthesis of (±)-**65**.[31]

A similar strategy was devised by Dong and co-workers for the construction of a more rigid spiro-fused cyclobutane skeleton *en route* to phainanoids,[32] a class of novel triterpenoids that were isolated by Yue and co-workers from *Phyllanthus hainanensis* and exhibit potent immuno-suppressive activities.[33] As depicted in Scheme 10, their synthesis toward phainanoid A (**72**) began with vinyl epoxide **67**, which could be prepared from geranyl acetate (**66**) through several conventional transformations. A $SnCl_4$-promoted polyene cyclization of **67** at −78 °C gave tricyclic alcohol **68** bearing a *trans*-decaline core in 70% yield. The latter was then converted to enol-triflate **69**



Scheme 10 Pd-Catalyzed intramolecular coupling reaction towards the total synthesis of phainanoid A.

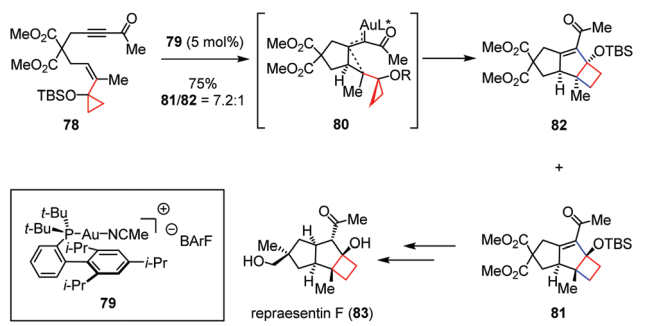


Scheme 11 Enyne metathesis in the total synthesis of (±)-grandisol.

in 37% yield over three steps. Subsequently, the Pd-catalyzed intramolecular ketone alkenylation occurred smoothly with the aid of QPhos (**70**) and *t*-BuOLi, affording the desired 4,5-spirocycle **71** with 83% yield and >20 : 1 dr. The remarkably high diastereoselectivity was presumably ascribed to the stabilizing effects of the adjacent carbonyl moiety.

As another representative of reactive intermediates in organometallic chemistry, the transition-metal carbenoid generated from a alkyne precursor could also be employed to construct the four-membered ring. For instance, Goess and co-workers described a second route to (±)-grandisol (**65**) involving a microwave-assisted enyne metathesis (Scheme 11).[34] The synthesis began with the preparation of enyne **74**, which could be obtained from α-methyl-γ-butyrolactone **73** in five steps. Treatment of **74** with the optimum ruthenium catalyst **75** under microwave irradiation provided vinylcyclobutene **76** in 83% yield. Subsequent regioselective hydrogenation in the presence of RANEY nickel followed by desilylation furnished (±)-**65** in 63% yield over two steps.

An alternative application covered in this class of transformation is the use of gold catalysts. The sesquiterpene repraesentin F was isolated from the fruiting bodies of *Lactarius repraesentaneus* and shows growth regulation on plants by promoting the radicle elongation of lettuce seedlings at low concentration.[35] In 2018, Echavarren and co-workers described the first total synthesis of repraesentin F (**83**), which allowed reassignment of the relative and absolute configuration of this molecule.[36] As shown in Scheme 12, key to the



Scheme 12 Au-Catalyzed cyclization cascade cyclization in the total synthesis of repraesentin F.

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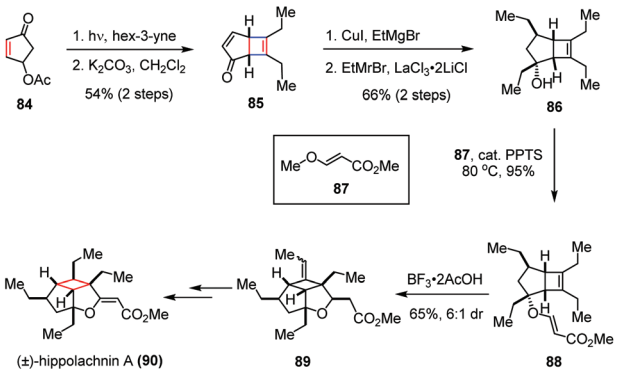
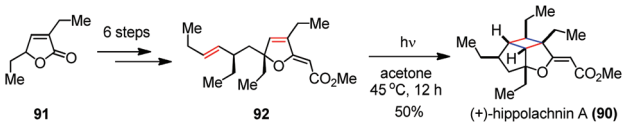
success of their synthesis is a highly diastereoselective Au(I)-catalyzed cyclization cascade to assemble the tricyclic core of the natural product with the requisite *syn*/*anti*/*syn* ring fusion, which delivered cyclobutanes **81** and **82** as a 7.2 : 1 isomeric mixture in 75% combined yield from enyne **78**. DFT calculations revealed that the activation energy for the C–C formation through the intermediate **80** is much lower ($\Delta G^{\ddagger}$ = 10.3 kcal mol^{-1}) than that for the activation of the keto group ($\Delta G^{\ddagger}$ = 20.5 kcal mol^{-1}), which indicated that this reaction abides by the usual activation mode as in other gold-catalyzed enyne cyclizations. It should also be noted that the use of $BArF^{-}$ as a counterion in the structure of the gold catalyst **79** was essential to suppress further rearrangement of cyclobutanes **81** and **82** to the corresponding cyclopropane byproduct.



Scheme 13 [2 + 2] photocycloaddition in the total synthesis of (±)-hippolachnin A.



Scheme 14 [2 + 2] photocycloaddition in the total synthesis of (+)-hippolachnin A.

3. Cycloaddition strategies

In contrast to the direct ring-closure strategies in which a single bond is formed in one step, the hallmark of the cycloadditions involves the formation of two or more bonds in a single operation.[37] Such protocols have proven useful in the intramolecular context and homodimerizations, which were demonstrated by the recent applications in the assembly of four-membered carbocycles.

3.1 [2 + 2] photocycloaddition

The most commonly considered and direct approaches to cyclobutanes are the [2 + 2] photocycloadditions between two alkene moieties.[38] Electron-deficient olefins are favorable substrates in photo-induced cycloadditions due to their convenient excitation by widely available UV sources.

Hippolachnin A was isolated from the South China Sea sponge *Hippospongia lachne* by Lin and co-workers in 2013.[39]

It shows potent antifungal activity at a minimum inhibitory concentration of 0.41 μM against three pathogenic fungi, namely *Cryptococcus neoformans*, *Trichophyton rubrum* and *Microsporum gypseum*. Structurally, this molecule possesses a highly substituted cyclobutane ring decorated with six contiguous stereogenic centers, four of which bear an ethyl substituent projecting in the convex orientation. The congested oxacyclobutapentalene core combined with the promising biological activities made hippolachnin A a highly desirable yet challenging synthetic target. In 2015, Carreira and co-workers accomplished the first total synthesis of (±)-hippolachnin A (**90**).[40] As depicted in Scheme 13, the synthesis commenced with an intermolecular [2 + 2] photocycloaddition of enone **84** and hex-3-yne, followed by β-elimination to establish the key cyclobutene intermediate **85** in 54% yield over two steps. Subsequent introduction of the ethyl side chains to the bicyclic scaffold was achieved by a Cu(I) mediated 1,4-addition and a $LaCl_3$·2LiCl promoted 1,2-Grignard addition, affording alcohol **86** with complete *exo* diastereoselectivity in 66% yield over two steps. After being converted to ester **88** in the presence of catalytic PPTS and (*E*)-methyl-3-methoxyacrylate (**87**) as a solvent, a BF_3·2AcOH induced intramolecular ene cyclization provided tricycle **89** in 65% yield (6 : 1 dr). Further functionalization of the latter led to the formation of (±)-**90** with good efficiency.

Recently, Tang, Enders and co-workers reported a biomimetic approach to (+)-hippolachnin A (**90**) involving another intramolecular [2 + 2] photocycloaddition (Scheme 14).[41] In contrast to Carreira's synthetic sequence, they chose furanone **91** as the starting material and installed the required functionalities to afford the precursor **92** within six steps. By irradiation of **94** with a high pressure mercury lamp (500 W) at 45 °C for 12 h, (+)-**90** was furnished in 50% yield.

A similar approach was disclosed toward the synthesis of the well-known furano-cembranoid bielschowskysin (**100**), which was isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos* and exhibits potent antimalarial activity and selective cytotoxicity against various types of cancer cells.[42] Synthesizing this diterpenoid proved to be difficult owing to its complex tricyclo[9.3.0.0]tetradecane carbon framework bearing numerous oxygen-containing functional groups and 11 stereogenic centers (Scheme 15).[43] A significant advance has been made by Nicolaou and co-workers in the expedient synthesis of the highly functionalized 5/4/8/5 tetracyclic core structure of this molecule.[44] The intramolecular [2 + 2] photocycloaddition of a macrocyclic precursor **95**, which was prepared through a crucial oxidative coupling of β-keto ester **93** and furan **94** followed by a ring-closing metathesis, resulted in a ring contraction to form the polycyclic skeleton in one step. On the other hand, the Roche group also reported a biomimetic route to the bielschowskysin skeleton relying on a late-stage transannular [2 + 2] photocycloaddition.[45] In their approach, the pivotal cycloaddition precursor

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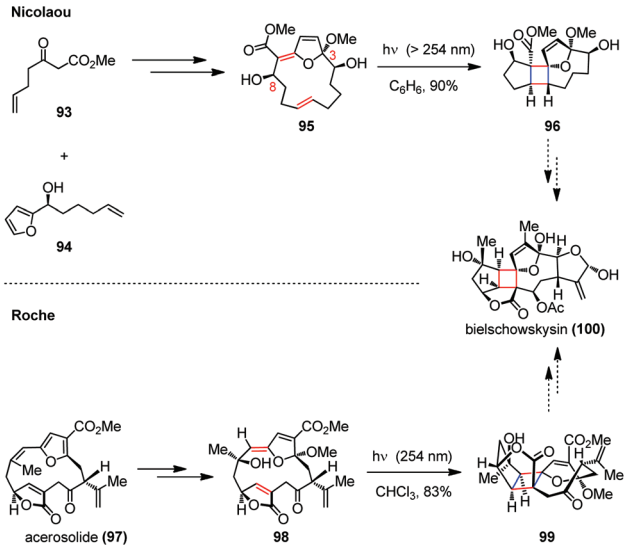
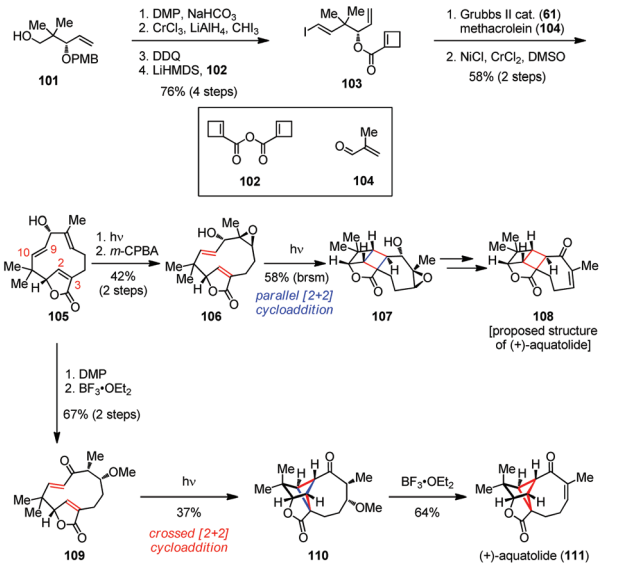


Scheme 15 Transannular [2 + 2] photocycloadditions in the construction of the core structures of bielschowskysin.



Scheme 16 Biomimetic transannular [2 + 2] photocycloaddition in the total synthesis of (+)-aquatolide.

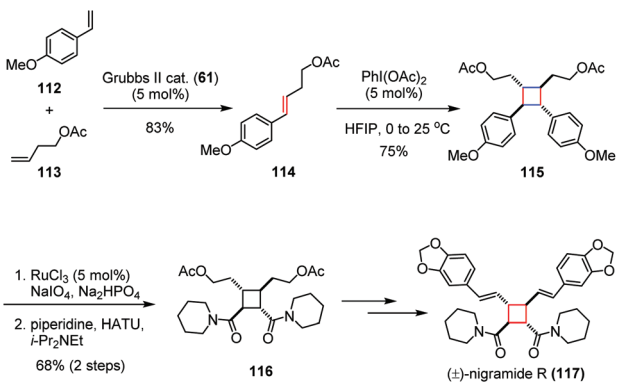
(*Z*)-*exo*-enol ether **98** was prepared through a regio- and stereoselective oxidative dearomatization of the furan-containing natural product acerosolide (**97**). Upon UV irradiation, the advanced intermediate **99** could be obtained in 83% yield.

Aquatolide was first isolated from *Asteriscuc aquaticus* in 1989 and its structure was finally determined by single-crystal X-ray analysis in 2012.[46] Structurally, aquatolide has a cyclobutane moiety embedded concurrently in a bicyclo[5.1.1]nonane and a bicyclo[2.1.1]hexane skeleton, which makes it a challenging target for synthesis. In 2019, Takao and co-workers reported a concise total synthesis of (+)-aquatolide (**111**) by a biomimetic transannular [2 + 2] photocycloaddition to build up its cyclobutane subunit at the late stage (Scheme 16).[47] Their synthesis commenced with vinyl iodide **103**, which was readily prepared from known alcohol **101** in 76% yield over four steps. The subsequent ring-opening/ring-closing/cross-metathesis (ROM/RCM/CM) reaction of **103** proceeded in a cascade manner to produce the desired aldehyde. The latter was then subjected to an intermolecular Nozaki–Hiyama–Kishi (NHK) reaction with methacrolein (**104**) to give macrocycle **105** as a single diastereomer in good yield. The following three-step sequence involving olefin isomerization, epoxidation and parallel [2 + 2] photocycloaddition delivered [2]-ladderane adduct **107** in 24% overall yield. Further functionalization of **107** provided the originally proposed structure of (+)-**108**. Furthermore, oxidation of **105** followed by 1,4-addition to mask the olefin gave **109** as a single isomer. Fortunately, the transannular crossed [2 + 2] photocycloaddition of **109** occurred successfully to construct the bicyclo[2.1.1]hexane core, affording the desired cycloadduct **110** in 37% yield. Finally, the β-elimination of MeOH from **110** proceeded smoothly and led to the completion of the total synthesis of (+)-**111** in 64% yield.

3.2 Oxidative radical cycloaddition

For the [2 + 2] cycloaddition of two electron-rich olefins, harsh reaction conditions are normally needed. An alternative solution is to oxidize one of the substrates to generate a radical cation which is sufficiently reactive even under mild conditions. This method is typically used, for example, to dimerize the unactivated olefins.

Nigramide R, bearing a tetrasubstituted cyclobutane skeleton, was isolated from the roots of *Piper nigrum* and exhibits inhibitory activity against cytochrome P450 2D6, as well as cytotoxicity against a mouse lymphoma cell line (L5178Y).[48] In 2015, Donohoe and co-workers reported a concise synthesis of (±)-nigramide R (**117**) by using a hypervalent iodine-induced oxidative dimerization as the key step (Scheme 17).[49] Their synthesis began with the preparation of **114**, which was derived from a cross metathesis between olefins **112** and **113**. The subsequent $PhI(OAc)_2$ promoted head-to-head dimerization of



Scheme 17 Oxidative radical dimerization in the total synthesis of (±)-nigramide R.

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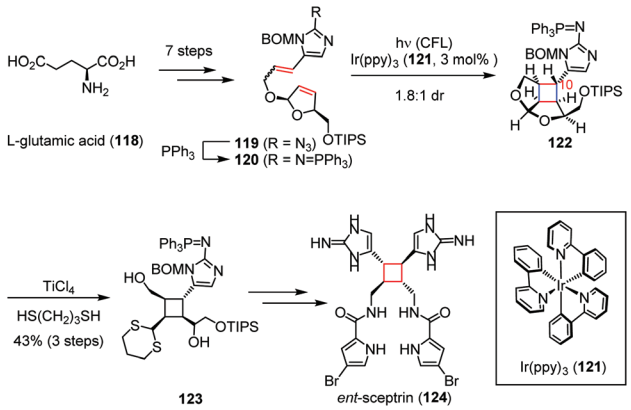


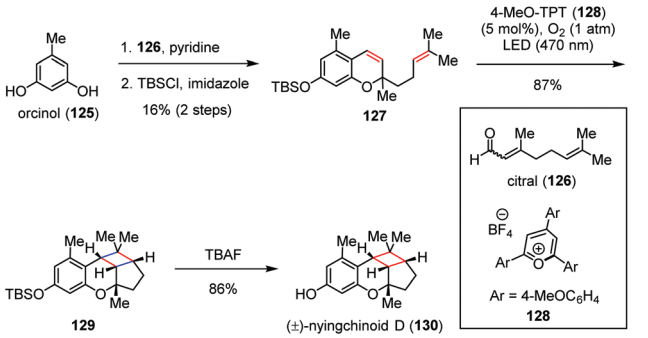
Scheme 18 SET [2 + 2] cycloaddition in the total synthesis of *ent*-sceptrin.

olefin **114** afforded the cyclobutane **115** in 75% yield. The bis (amide) **116** was then obtained in 68% yield over two steps through oxidative cleavage to carboxylic acid and coupling with piperidine. Late-stage derivatization of **116** through additional four steps gave rise to (±)-**117** in 58% overall yield.

Besides, the cyclobutane-containing natural products could also be synthesized *via* photo-induced single-electron transfer (SET) reactions, in which the radical cations are transiently produced by excited photosensitizers. The dimeric pyrrole-imidazole alkaloids are structurally complex molecules produced by marine sponges through reactions that are not well understood.[50] These natural products are highly polar, noncrystalline, redox labile, and pH sensitive owing to their exceptionally high nitrogen content. In 2014, Chen and co-workers demonstrated the biomimetic synthesis of *ent*-sceptrin (**124**).[51] As depicted in Scheme 18, the key intermediate **119** was prepared from L-glutamic acid (**118**) in seven steps. After Staudinger reduction, irradiation of a solution of the resultant **120** with catalytic Ir (ppy)$_3$ (**121**) induced the [2 + 2] cycloaddition to give **122** and its C10-epimer as a 1.8 : 1 mixture. The following *trans*-thioketalization afforded **123** in 43% yield, which was then readily transformed to *ent*-**124** within a few steps.

Recently, Evanno, Poupon, Smietana, Arseniyadis and co-workers developed an interesting DNA-templated cationic [2 + 2] photodimerization process.[52a] Its synthetic utility was further demonstrated by application to the synthesis of cycloaplysinopsin-type natural products such as dictazole B, which was isolated from the sponge *Smenospongia cerebriformis*.[52b,c]

Nyingchinoids belong to a family of polycyclic meroterpenoids that were isolated from *Rhododendron nyingchiense* by Hou and co-workers in 2018, with each molecule identified as a scalemic mixture by chiral HPLC.[53] Very recently, George and co-workers achieved the biomimetic synthesis of (±)-nyingchinoid D (**130**) and its analogues by a photocatalytic aerobic [2 + 2] cycloaddition pathway (Scheme 19).[54] Diene **127** was readily prepared through the known condensation of orcinol (**125**) and citral (**126**) followed by TBS protection. The pyrylium photoredox-catalyzed aerobic [2 + 2] cycloaddition of **128** according to the slightly modified procedure of Nicewicz

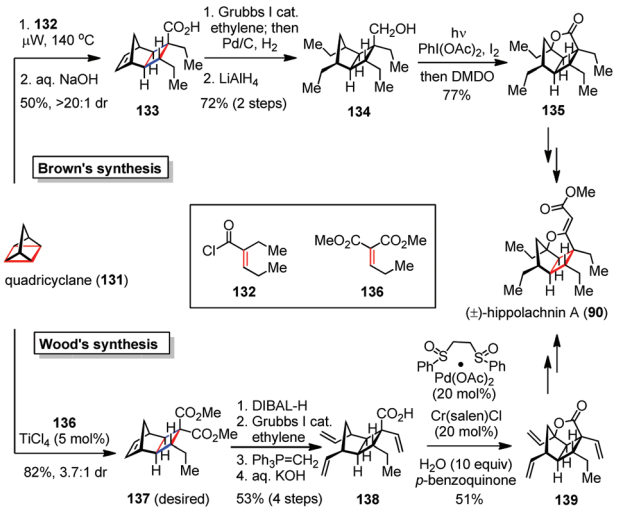


Scheme 19 Photocatalytic aerobic [2 + 2] cycloaddition in the total synthesis of (±)-nyingchinoid D.

[4-MeO-TPT (2 mol%), O_2 (1 atm), LED (470 nm), DCE, 0 °C, 20 min] afforded cyclobutane **129** in 87% yield as the sole product. Desilylation of the latter completed the rapid synthesis of (±)-**130** in 86% yield.

3.3 Strain-releasing cycloaddition

The [2 + 2] cycloadditions can be driven by not only the external factors but also the inherent ring strains in the substrates. In 2016, the Wood and Brown groups independently accomplished the total synthesis of (±)-hippolachnin A (**90**) *via* a strain-releasing cyclobutanation and a late-stage C–H oxidation (Scheme 20).[55] Tricycles **133** and **137** were efficiently obtained through an unusual [2π + 2σ + 2σ] cycloaddition of quadricyclane (**131**) with electron-deficient alkenes **132** and **136**, respectively. In Brown's synthesis, **133** underwent a ring-opening metathesis with ethylene followed by reduction to give alcohol **134** in 72% yield over two steps. Subjection of the latter to Suárez conditions [I_2, PhI(OAc)$_2$, hν] afforded a tetrahydrofuran intermediate, which was oxidized by DMDO to produce the lactone **135** in 77% yield. Further attachment of the side chain furnished (±)-**90**.



Scheme 20 Strain-releasing cycloadditions in the total synthesis of (±)-hippolachnin A.

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In Wood's synthesis, **137** was converted to acid **138** *via* a series of transformations involving regioselective reduction of ester, ring-opening metathesis, Wittig olefination and saponification. Upon exposure of **138** to modified White's conditions [$Pd(OAc)_2$·($CH_2SO_2Ph)_2$ (20 mol%), Cr(salen)Cl (20 mol%), H_2O (10 equiv.), 1,4-benzoquinone (2 equiv.)], the C–H activation/oxidation proceeded smoothly and provided lactone **139** in 51% yield. Of note, the presence of excess water was found to be crucial for the efficiency of this process. Further installation of the remaining vinylogous carbonate completed the synthesis of (±)-**90** within three steps.

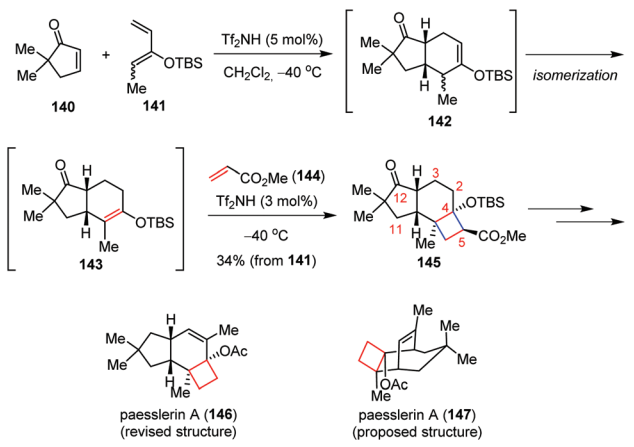
By providing the shortest routes to (±)-hippolachnin A, the above two syntheses demonstrated the capability of the strain-releasing cycloadditions in concise total syntheses of natural products.

3.4 Ionic stepwise [2 + 2] cycloaddition

The acid-catalyzed [2 + 2] cycloaddition reaction of silyl enol ethers with α,β-unsaturated carbonyl compounds provides a promising tool for the syntheses of donor–acceptor (D–A) cyclobutane derivatives in a different stepwise fashion. The strategy involves an intramolecular aldol reaction of δ-ketoenolate, which was formed by the Michael addition of silyl enol ethers with α,β-unsaturated carbonyl compounds in the former step.

Takasu and co-workers have made great efforts on the triflic imide (Tf_2NH) catalyzed [2 + 2] cycloaddition reactions of silyl enol ethers for the construction of various fused cyclobutane rings bearing a silyloxy group at the bridgehead position.[56] This effective method has been successfully applied to the synthetic studies toward penitrems, a family of indole diterpene alkaloids isolated from *Penicillium cyclopium* and *Penicillium crustosum* with strong neurotoxicity.[57]

Most recently, the same group reported the first total synthesis of cytotoxic paesslerin A (**146**) through a Tf_2NH-catalyzed multicomponent reaction between cyclopentenone **140**, 2-siloxy-butadiene **141** and methyl acrylate **144** (Scheme 21).[58] This catalytic three-component reaction consists of a [4 + 2] cycloaddition, an alkene isomerization and an ionic stepwise [2 + 2] cycloaddition. The reaction cascade enables the assembly of the desired tricyclo[6.3.0.$0^{2,5}$]-undecanone **145** as the major product in 34% yield. Further core functionalization led to **146** with good efficiency. The above synthesis led to the revision of the originally proposed tricyclic structure of paesslerin A (**147**).



Scheme 21 Multicomponent domino cycloaddition in the synthesis of paesslerin A.

4. Ring contraction strategies

Aside from the aforementioned cycloaddition reactions, the four-membered cyclic scaffolds can also be accessed from the existing rings by modification of their sizes. In this regard, the ring contraction is one important and common strategy to address this issue. Although such reactions would inevitably intensify the ring strains, appropriate transient reactive intermediates could be devised to trigger the reactions toward the desired direction.

4.1 Electrocyclization

Electrocyclization has been widely used to build up various complex polycyclic scaffolds in a highly stereocontrolled manner, in which the electrocyclic contraction of 4π- and 6π-electron systems can rapidly generate cyclobutanes.[59]

The highly cytotoxic cyclobutane-fused piperaborenines were isolated from the stems of *Piper arborescens*.[60] These molecules were classified into two stereochemical classes including *cis–trans–cis* and *trans–cis–trans*. Both of them were biosynthetically generated through head-to-tail dimerization of piplartine-type monomers with varying degrees of oxidation on the aryl rings. Syntheses of such cyclobutanoid amides through direct coupling of monomeric olefins are challenging due to the difficulties encountered in ensuring the desired heterodimerization to provide the final targets. Baran and co-workers found an ingenious solution by using monoarylated cyclobutane **154** as a common intermediate followed by conducting sequential C(sp^3)–H functionalization (Scheme 22).[61] Inspired by Maulide's creative work on the cyclobutene synthesis[62a] and Corey's pioneering research on pyrone photochemistry,[62b] the desired precursor **149** was obtained from the commercially available methyl coumalate (**148**) *via* a photochemical 4π electrocyclization. This unstable intermediate obtained was immediately hydrogenated and coupled with *o*-thioanisidine **151** to provide cyclobutanoid amide **152** in 61% yield. Selective C–H cross-coupling of **152** with 3,4,5-trimethoxy-iodobenzene **153** delivered the desired monoarylated cyclobutane **154** in 52% yield. Divergent epimerization of **154** in the presence of *t*-BuOLi and KHMDS gave C1- and C3-epimers **155** and **158**, respectively. Further functionalization delivered piperarborenine B (**156**) and the proposed structure of piperarborenine D (**159**).

The Trauner group used another 4π electrocyclization to forge the cyclobutane subunit in the total synthesis of (±)-hippolachnin A (Scheme 23).[63] Based on earlier results from Dauben and colleagues,[64] the researchers obtained the key

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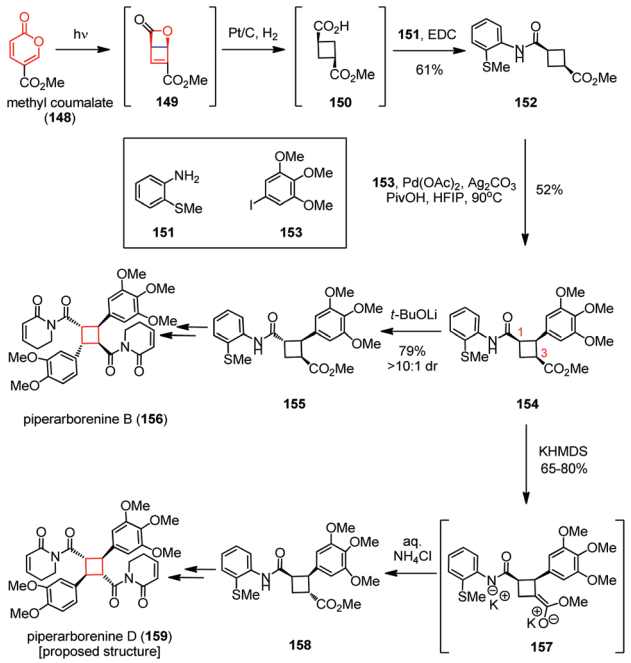
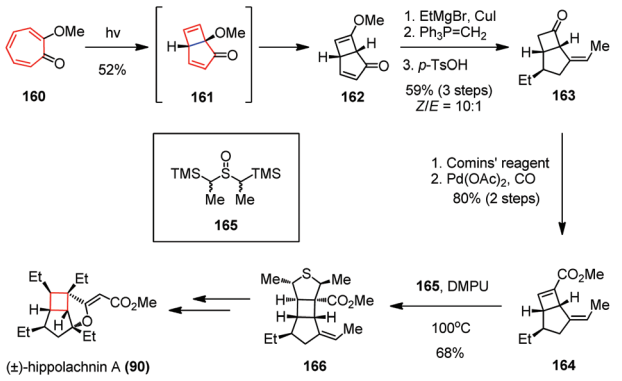
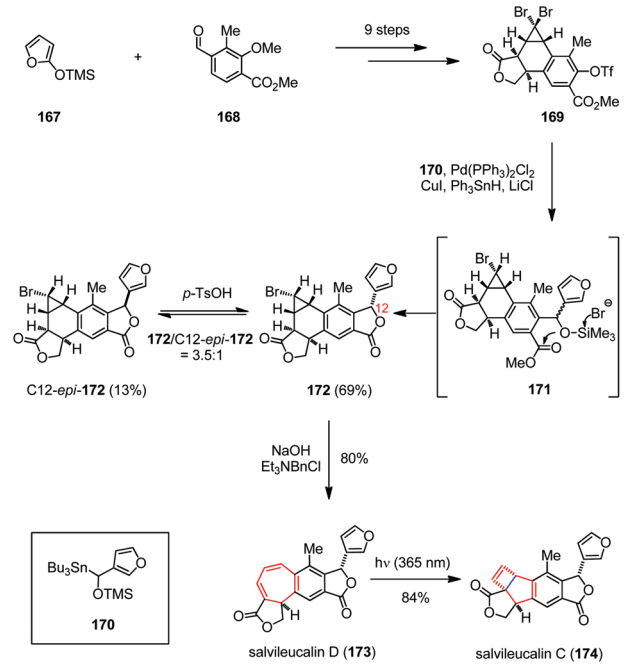


Scheme 22 4π electrocyclization in the total syntheses of piperaborenines.



Scheme 23 4π electrocyclization in the total synthesis of (±)-hippolachnin A.



Scheme 24 4π electrocyclization in the total synthesis of salvileucalin C.

bicyclo[3.2.0]heptadiene **162** in 52% yield by irradiation of the readily available tropolone ether **160** with a high pressure mercury lamp (150 W). The reaction process involves a disrotatory 4π electrocyclization, followed by excited state rearrangement. A three-step sequence including a stereoselective 1,4-addition and a Wittig olefination followed by hydrolysis gave **163** as a 10 : 1 mixture of *Z*- and *E*-isomers in 59% yield. Subsequent formation of enol-triflate using Comins' reagent and Pd(0)-catalyzed CO insertion afforded eonate **164** in 80% yield over two steps. The latter underwent a [3 + 2] cycloaddition with thiocarbonyl ylide *in situ* generated from **165** and DMPU at elevated temperature to provide tetrahydrothiophene **166** as a single diastereomer in 68% yield. Final derivatization of **166** accomplished the synthesis of (±)-**90**.

Salvileucalin C, a highly rearranged neoclerodane diterpenoid, was isolated by Takeya and co-workers from *Salvia leucantha*.[65] The structurally closely related salvileucalin D was proposed to be a biosynthetic precursor of salvileucalin C, whose bicyclo[3,2,0]hept-6-ene core structure would be formed through bicyclization of the cycloheptadiene subunit.[66] Inspired by this hypothesis, Ding and co-workers achieved the first total synthesis of salvileucalin C (**174**) *via* a late-stage photo-induced electrocyclic ring contraction (Scheme 24).[67] Their synthesis began with triflate **169**, which was prepared from silyloxyfuran **167** and aldehyde **168** in nine steps. Subjection of **169** to a one-pot diastereoselective Stille coupling/debromination/lactonization process delivered monobromide **172** in 69% yield *via* the intermediacy of **171**, together with 12-*epi*-**172** 13% yield. Exposure of **172** to aqueous NaOH in the presence of Et_3BnNCl led to ring-expansion and gave salvileucalin D (**173**) in 80% yield. Upon UV irradiation (λ = 365 nm), the expected 4π electrocyclization took place smoothly and afforded **174** in 84% yield.

Later, Li and co-workers applied a conceptually similar strategy in their total syntheses of colchicine (**178**) and its derivatives (Scheme 25).[68] The highly toxic tricyclic alkaloid colchicine was the first tubulin-destabilizing agent reported in the literature.[69] Structurally, (−)-**178** contains a single stereocenter at C-7, an a*R*-configured chiral axis and a highly oxidized tropolone ring. The synthesis commenced with **176**, which was prepared with excellent ee from **175** by using an intramolecular oxidopyrylium-mediated [5 + 2] cycloaddition as the key step.[70] Subsequently, a three-step sequence involving a diastereoselective reduction, a methylation and a regioselective Wacker oxidation afforded **177** in 53% yield. Double elimination of the oxa-bridge in **177** proceeded smoothly in

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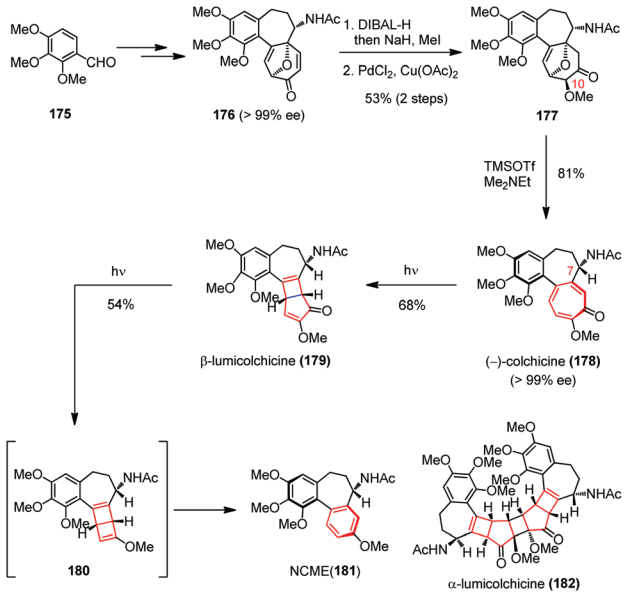


Scheme 25 4π electrocyclization in the total synthesis of colchicine derivatives.

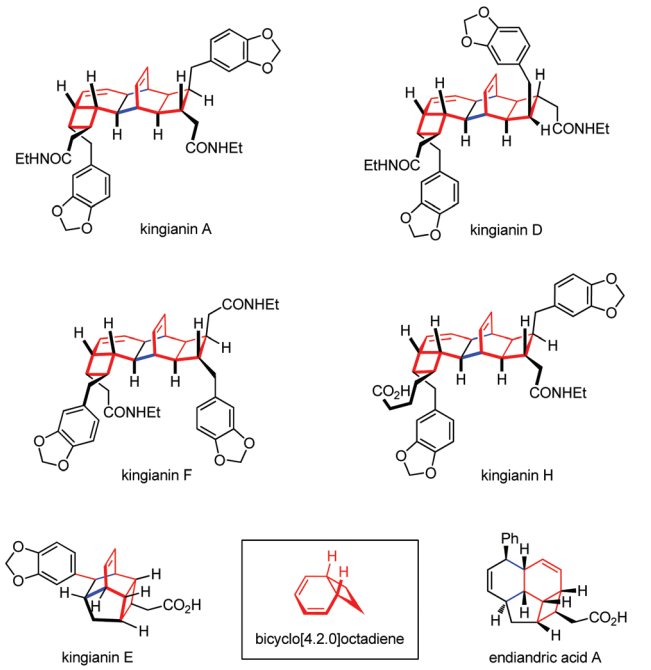


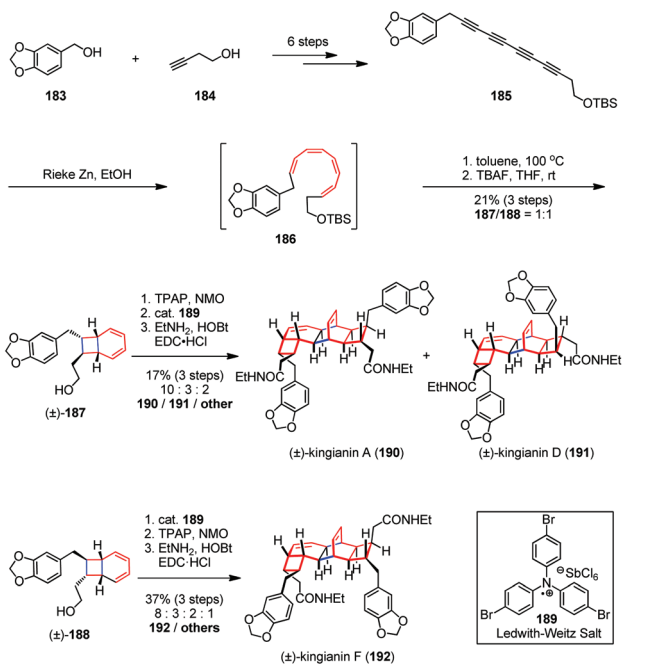
Fig. 2 Structures of representative members of the kingianin family and endiandric acid A.

the presence of TMSOTf and Me_2NEt, providing (–)-**178** in 81% yield with >99% ee.

The biomimetic conversion of (–)-**178** to β-lumicolchicine (**179**), NCME (**181**) and α-lumicolchicine (**182**) was then investigated. Upon irradiating a solution of (–)-**178** in CH_3CN/acetone with a Pyrex water jacket surrounded high-pressure mercury lamp (125 W) for 25 min, the expected ring contraction occurred and afforded **179** in 68% yield. Repeating this procedure with the isolated **179** for 20 min led to a rapid decarbonylation and generated intermediate **180**, which was then transformed to **181** instead of **182** *via* a retro-4π electrocyclization.

Thermal or photo-induced electrocyclic reactions of conjugated tetraenes with 8π systems can readily provide diverse bicyclic scaffolds.[71] Such operations need to be rationally incorporated into a synthesis from the beginning, given that the researchers should choose from among multiple ring-closure reactions and take into account torque and chemoselectivity in the electrocyclization steps.[72] The Nicolaou group first applied an 8π–6π cascade electrocyclization in their landmark biomimetic syntheses of endiandric acids.[73] The above work has inspired other groups a lot to build up related polycyclic skeletons. Kingianins were isolated from the bark of *Endiandra kingiana* (Lauraceae) and show promising activity against the anti-apoptotic protein Bcl-xL (Fig. 2).[74] Retrosynthetically, their unique pentacyclic architecture was proposed to arise from thermal 8π–6π electrocyclization cascade and Diels–Alder dimerization.

In 2013, Sherburn, Lawrence and co-workers reported the total syntheses of (±)-kingianins A (**190**), D (**191**) and F (**192**) in a longest linear sequence (LLS) of ten steps based on a highly divergent biomimetic strategy (Scheme 26).[75] The unsymmetrical tetrayne **185** was readily prepared from the alcohol **183** and



Scheme 26 8π–6π electrocyclization cascade in the total synthesis of kingianins.

184 in six steps on a multi-gram scale. Reduction of **185** with Rieke zinc in ethanol afforded (*Z*,*Z*,*Z*,*Z*)-tetraene **186** in a completely chemoselective and highly diastereoselective manner. The latter was then immediately heated to 100 °C in toluene to bring about the expected 8π–6π electrocyclization cascade.

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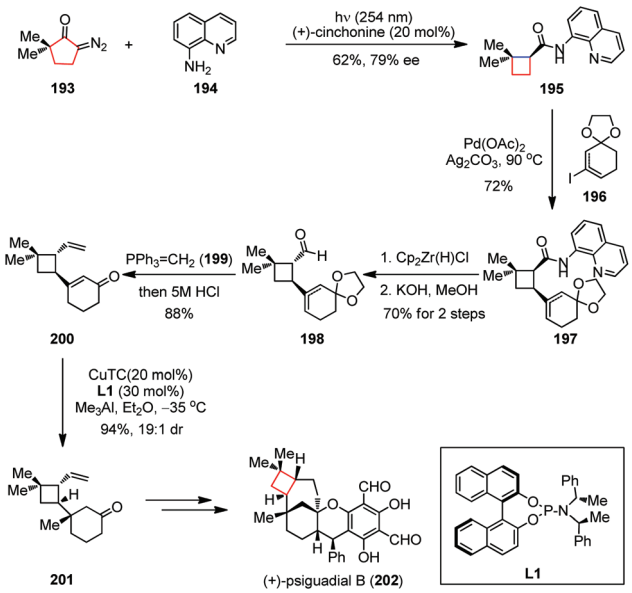
After desilylation, alcohols **187** and **188** were obtained as a 1 : 1 mixture of diastereomers in 21% combined yield. Subsequent oxidation of **187** with TPAP/NMO followed by Ledwith–Weitz aminium salt (**189**) promoted Diels–Alder dimerization to provide a mixture of diacids, which were directly converted into the corresponding diamides and achieved the syntheses of (±)-**190** and (±)-**191**. On the other hand, (±)-**192** was also obtained through dimerization of **188** followed by double oxidation and diamide formation.

4.2 Rearrangement

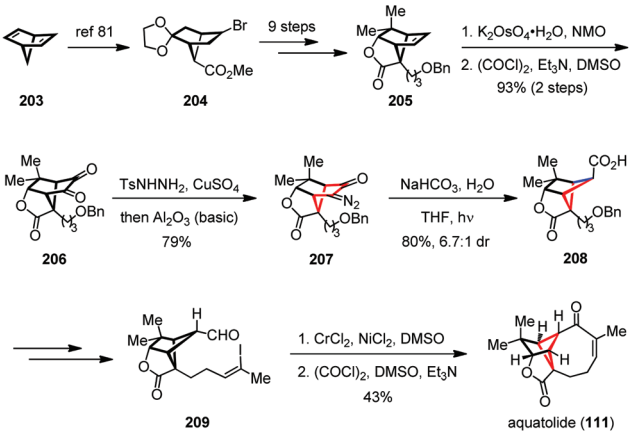
In addition to the concerted electrocyclic processes mentioned above, the migration of a C–C bond between two vicinal atoms has also been extensively investigated when embedding the four-membered rings into complex molecules through ring contraction. These migrations could be initiated by an electrophilic reagent or through a highly reactive neutral intermediate in order to overcome the reaction barriers arising from ring strains.

Under various conditions, the α-diazo ketone would lose its nitrogen and undergo 1,2-shift to yield a ketene intermediate, a process known as the Wolff rearrangement.[76] Although the mechanism of this rearrangement is still under debate,[77] it can effectively generate the ring-strained systems where other approaches fail. (+)-Psiguadial B, a diformyl phloroglucinol meroterpenoid, was isolated from the leaves of *Psidium guajava* and found to inhibit proliferation of HepG2 human hepatoma cancer cells.[78] This natural compound possesses a compact bicyclo[4.3.1]decane core fused to a *trans*-cyclobutane ring, which was probably derived from the biotransformation of β-caryophyllene. In 2016, Reisman and co-workers proposed a synthetic strategy toward (+)-psiguadial B (**202**) featuring *de novo* construction of the *trans*-fused cyclobutane *via* a Wolff rearrangement/asymmetric ketene addition cascade, followed by a Pd-catalyzed C(sp^3)–H alkenylation reaction (Scheme 27).[79] The synthesis started by irradiating a mixture of the known diazoketone **193** and 8-aminoquinoline **194** with UV light (254 nm) in the presence of 10 mol% (+)-cinchonine, providing cyclobutane **195** with 62% yield and up to 79% ee. A solution of **195** and vinyl iodide **196** (isolated as an 8 : 1 mixture of olefin isomers) was then subjected to $Pd(OAc)_2$ and Ag_2CO_3 at 90 °C and furnished the *cis*-fused cyclobutane **197** in 72% yield. Reduction of **197** using Schwartz's reagent followed by treatment with KOH in methanol gave the desired *trans*-aldehyde **198** in 70% yield over two steps. The corresponding aldehyde was telescoped with Wittig olefination and hydrolysis to afford vinyl enone **200** in 88% yield. Subsequently, the copper-catalyzed conjugate addition under Alexakis' conditions delivered the desired ketone **201** in 94% yield (19 : 1 dr), which was finally converted to (+)-**202** within a few steps.

In 2016, Zhang and Gu reported the total synthesis of aquatolide (**111**) by using a Wolff ring contraction to build up the cyclobutane subunit and an intramolecular NHK coupling to forge the medium sized ring (Scheme 28).[80] Their synthesis commenced with the known bromo ester **204**, which was



Scheme 27 Wolff rearrangement/asymmetric ketene addition cascade in the total synthesis of (+)-psiguadial B.



Scheme 28 Wollf rearrangement in the total synthesis of aquatolide.

readily prepared from 2,5-norbornadiene (**203**) on a multigram scale.[81] After being converted to **205**, a two-step dihydroxylation/Swern process followed by condensation with tosyl hydrazine and detosylation delivered diazo **207** in 79% yield. Irradiation of the latter with a high-pressure mercury lamp (125 W) in the presence of $NaHCO_3$ gave the desired cyclobutane **208** with 80% yield and a satisfactory dr value. Subsequent incorporation of functionalities led uneventfully to aldehyde **209**, which underwent an intramolecular NHK cyclization followed by Swern oxidation to afford the eight-membered enone and thus completed the synthesis of **111**.

Aplydactone a brominated sesquiterpenoid was isolated from the sea hare *Aplysia dactylomela.* It contains a novel [2]-ladderane moiety with two fused cyclobutanes connected to a *cis*-decalin system, which bears four quaternary centers and a secondary neopentyl bromide.[82] In 2016, the Trauner group

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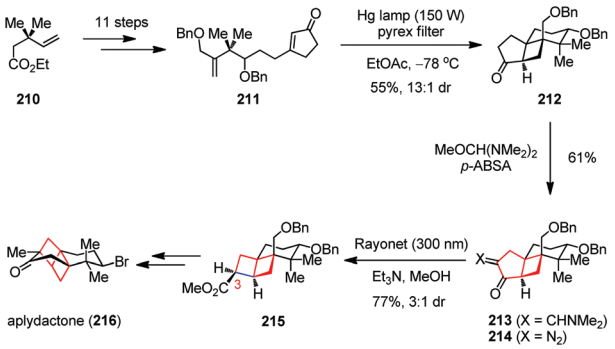
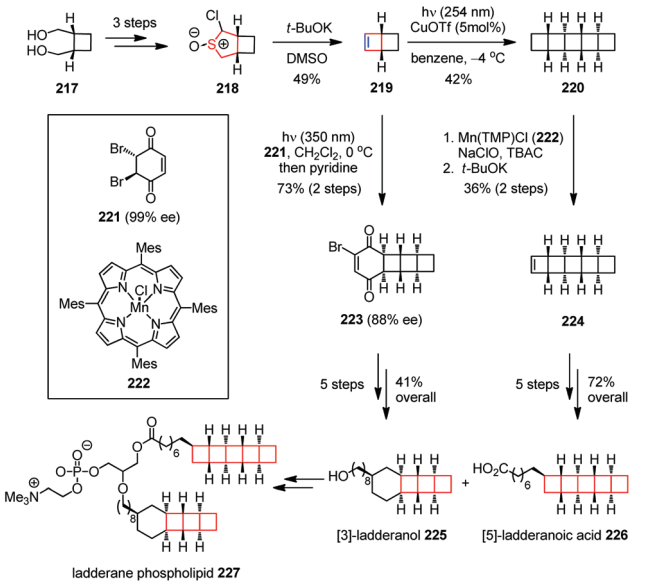


Scheme 29 Wolff rearrangement in the total synthesis of aplydactone.

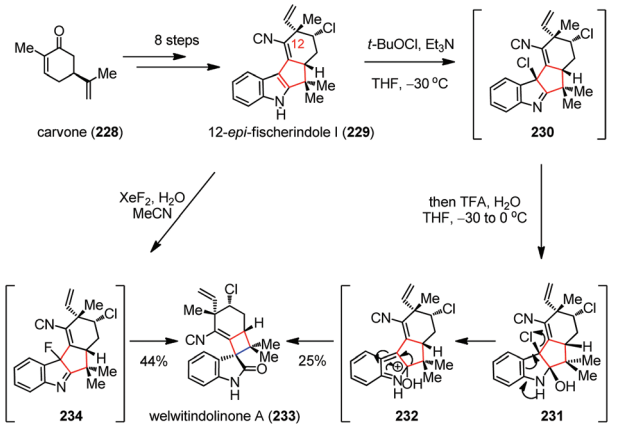
described an intriguing approach that relied on two photochemical key-steps to establish the two cyclobutane rings in the total synthesis of aplydactone (**216**).[83] As depicted in Scheme 29, the cyclopentenone **211** was readily prepared from the known ester **210**, which then upon irradiation with a high-pressure mercury lamp (150 W) gave the photochemical [2 + 2] cycloadduct **212** with decent yield and excellent diastereoselectivity. After being converted to enaminone **213**, the addition of *p*-ABSA led to α-diazo ketone **214** in 61% yield. The expected Wolff rearrangement proceeded smoothly and generated the ladderane **215** and its C3-epimer as a 3 : 1 mixture in 77% combined yield. Late-stage core modification of **215** then completed the total synthesis of **216**. In 2017, the Zhang group developed an alternative synthetic route to this molecule, in which the [2]-ladderane core was also installed readily by the same ring-contraction strategy at the early stage.[84] Remarkably, the two fused four-membered scaffolds remained intact in continuous ring contraction courses, providing a new perspective on the inherent ring strain in cyclobutanes.

Ladderane lipids are produced by anaerobic ammonium oxidizing (anammox) bacteria as a significant fraction of their membrane lipids. Ladderane phospholipid **227**, isolated from anammox enrichment cultures, comprises a mixture containing [5]-ladderane tail as in acid **226** and [3]-laddrane tail as in alcohol **225**.[85] Attracted by the interesting ladder-like structures and potential bioactivities, Gonzalez-Martinez, Boxer, Burns and co-workers reported a highly selective total synthesis of the ladderane lipid tails **225** and **226**, as well as a full phosphatidycholine to render further biophysical studies on these molecules (Scheme 30).[86] Their synthesis commenced with the preparation of the key building block **219**. The α-chlorocyclosulfoxide **218** was obtained from readily available diol **217** as a mixture of diastereomers in 89% yield over three steps. Treatment of **218** with excess *t*-BuOK effected an atypical sulfoxide Ramberg–Bäcklund ring contraction, providing olefin **219** with 49% yield. The latter was subjected to dimerization upon UV irradiation in the presence of CuOTf to afford [5]-ladderane core **220**. A manganese-catalyzed C–H chlorination and elimination delivered **224**. Then, an additional five-step transformation produced the [5]-ladderanoic acid **225** enantioselectively in 72% overall yield. On the other hand, the photocycloaddition between **219** and chiral dibromobenzoquinone **221** followed by selective elimination through proton abstraction from the convex face afforded vinyl bromide **223** in 73% yield over two steps. Further elaboration of the latter gave [3]-ladderanol **226** in 41% overall yield. Coupling of the two ladderane tails by a short sequence ultimately furnished ladderane phospholipid **227**.



Scheme 30 Ramberg–Bäcklund ring contraction in the total synthesis of ladderane phospholipid.

Hapalindole-type natural products were discovered from soil samples in a myriad of habitats around the globe and exhibit potent anticancer and insecticidal activities.[87] In 2008, Baran and co-workers accomplished the total syntheses of welwitindolinones and other hapalindole-type alkaloids (Scheme 31).[88] Their synthesis towards welwitindolinone A (**233**) began with the multi-step conversion of carvone (**228**) to 12-*epi*-fisherindole I (**229**). Subsequently, a Pinacol-type oxidative ring contraction process delivered **233** in 25% yield.



Scheme 31 Pinacol-type oxidative ring contraction in the total synthesis of welwitindolinone A.

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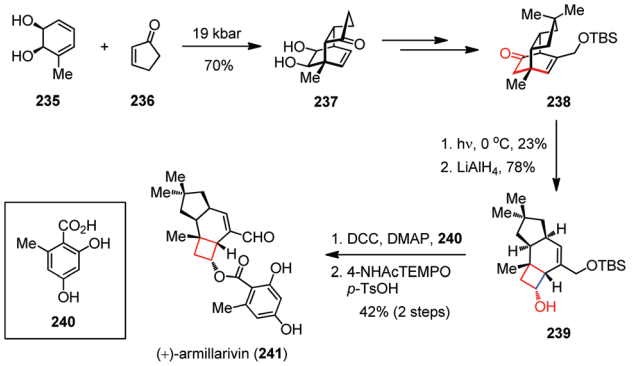
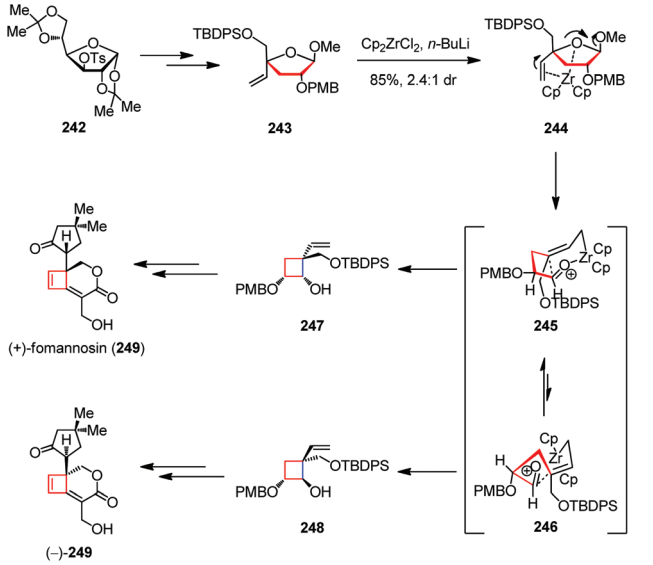


Scheme 32 1,3-Acyl migration in the total synthesis of armillarivin.



Scheme 33 Zirconium-mediated ring contraction in the total syntheses of (+)-fomannosin and its antipode.

This transformation most likely proceeds through chlorination of **229** in the presence of *t*-BuOCl and Et_3N to give **230**, which was then transformed to **231** upon attack of water. Further elimination of chloride generated **232**, followed by [1,5]-sigmatropic rearrangement to install the spirocyclobutane skeleton of **233**. Given that fluorohydroxylation of indole rather than chlorohydroxylation should suppress the formation of isonitrile-derived byproducts, a milder approach was developed. Thus, by treatment of indole **229** with a solution of XeF_2 in wet MeCN, the desired **233** was obtained in 44% yield *via* the intermediacy of **234**.

Besides, the 1,3-acyl migration (known as the Givens rearrangement) has also been utilized for the construction of cyclobutanes in natural product synthesis.[89] (+)-Armillarivin was isolated from *Armillaria tabescens*, a pathogenic basidiomycete that causes root disease in several commercially significant plants.[90] In 2013, the group of Banwell completed the synthesis of (+)-armillarvin (**241**) in 20 steps from the enantiopure *cis*-1,2-dihydrocatechol **235**.[91] As shown in Scheme 32, their synthesis commenced with a high-pressure Diels–Alder cycloaddition between **235** and **236**, affording **237** in 70% yield. After being converted to **238**, the pivotal photochemical Givens rearrangement occurred by UV irradiation. Upon ketone reduction, cyclobutanol **239** was formed as a single isomer in 18% yield over two steps. Coupling of compound **239** with readily prepared acid **240** in the presence of DCC and DMAP provided the ester, which was then oxidized directly to (+)-**241** through treatment with the *in situ* generated oxammonium salt *via* *p*-TsOH-induced disproportionation of 4-acetamido-TEMPO.

(+)-Fomannosin is the pathogen of *Fomes annonsus*, which was grown from still cultures of the wood-destroying Basidiomycetes fungus by Bassett and co-workers in 1967.[92] It is a sesquiterpene metabolite and can cause the death of host cells prior to hyphal invasion. In 2008, Paquette and co-workers disclosed an enantiodivergent strategy for the syntheses of both naturally occurring (+)-fomannosin (**249**) and its (−)-antipode (Scheme 33).[93] The synthesis started with the known tosylate **242**, which was readily available from D-glucose. After being transformed to the advanced intermediate **243**, the zirconocene-mediated ring contraction afforded a 2.4 : 1 diastereomeric mixture of **247** and **248** in 85% combined yield. The product distribution rests upon consideration of the ring-closure transition states. The adoption of **246** is less favored owing to the existing steric interactions between the methylene group of the developing cyclobutane and the allylic methylene group α to the zirconium, as well as the dipole–dipole interactions between the oxygen atoms resident in PMB and TBDPS ethers. Thus, **248** was formed as the less dominant product. Late-stage elaboration of **247** and **248** led to (+)- and (−)-**249**, respectively.

5. Ring expansion strategies

It makes sense to examine possible routes to the cyclobutane ring systems through not only contraction of larger rings but also expansion of cyclopropanes due to their higher strain energies. Such ring expansion has rarely been explored presumably because the resultant cyclobutane intermediates are normally unstable under the strain-releasing conditions.

Pipercyclobutanamides, piperchabamides, nigramides and dipiperamides are tetrasubstituted cyclobutanes that are isolated from *Piper nigrum* and *Piper chaba*.[60] These natural cyclobutanes have a broad range of pharmacological activities. Among them, pipercyclobutanamide A and dipiperamide E are selective inhibitors against CYP2D6 and CYP3A4, respectively, and piperchabamide G was found to have a hepatoprotective effect and inhibit D-GalN/tumor necrosis factor-α-induced death of hepatocytes. In 2012, Tang and co-workers developed a new general strategy for the diastereo- and enantioselective introduction of four different substituents to a cyclobutane ring, and realized the total syntheses of the proposed structures of pipercyclobutanamide A (**256**) and piperchabamide G (**258**).[94] As depicted in Scheme 34, the synthesis began with the preparation of ketoester **251** from the monoprotected diol

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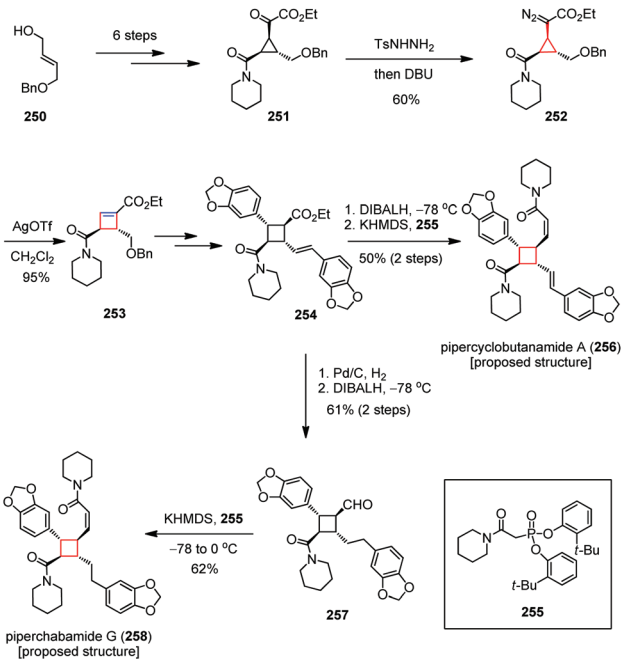
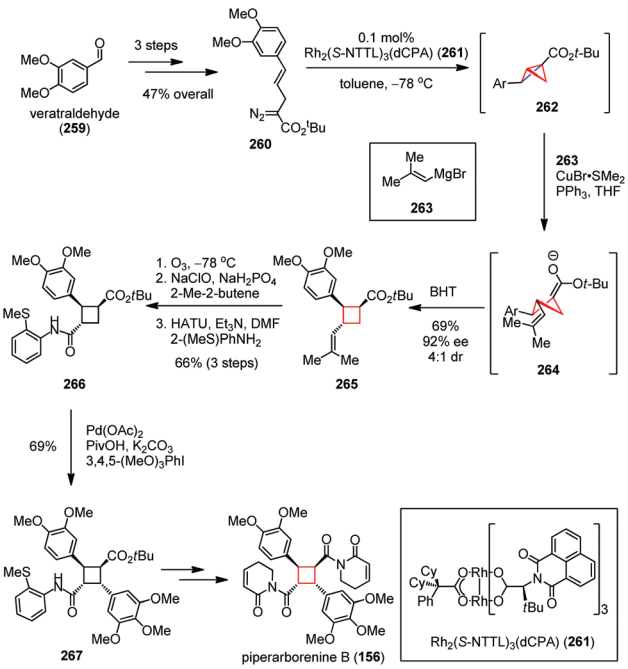


Scheme 34 Ring expansion in the total syntheses of the proposed structures of pipercyclobutanamide A and piperchabamide G.

250 in six steps. Treatment of **251** with $TsNHNH_2$ and DBU gave diazo **252** in 60% yield, which then underwent a ring expansion by subjection to catalytic AgOTf, affording cyclobutenoate **253** in 95% yield. After being converted to **254**, the proposed structure of pipercyclobutanamide A (**256**) was obtained in 50% yield over two steps through reduction of the ester followed by olefination of the resultant aldehyde with Ando's reagent **255**. On the other hand, a hydrogenation/reduction/olefination sequence afforded the proposed structure of piperchabamide G (**258**) in 38% yield over three steps.



Scheme 35 Bicyclobutanation/homoconjugate addition cascade in the total syntheses of piperarborenine B.

In 2016, Fox and co-workers reported an elegant total synthesis of piperarborenine B (**156**) featuring a bicyclobutanation/homoconjugate addition cascade to construct its trisubstituted cyclobutane core structure (Scheme 35).[95] The synthesis commenced with the preparation of diazoester **260** from veratraldehyde (**259**) in 47% yield over three steps. Exposure of **260** to 0.1 mol% Rh_2(*S*-NTTL)$_3$(dCPA) (**261**) afforded a bicyclobutane intermediate **262**, followed by copper-mediated nucleophilic homo addition of Grignard **263** and kinetic protonation using BHT to afford the enantiomerically enriched cyclobutane **265** in 69% yield (92% ee, 4 : 1 dr). The latter was then converted to amide **266** in 66% yield over three steps through oxidative cleavage, Pinnick oxidation and amide formation. Subsequent Pd-catalyzed C(sp^3)–H functionalization delivered the densely substituted cyclobutane **267** in high yield, which could be forwarded to **156** within several conventional steps.

6. Conclusions

In conclusion, this review has summarized the recent advances in the total syntheses of cyclobutane-containing natural products. The rapid generation of molecular complexity in a relatively diverse manner has made the construction of cyclobutane skeletons a highly useful tool, which was highlighted with the latest progress in various strategies including direct ring closure, cycloaddition, ring contraction and ring expansion. As demonstrated in these examples, the structures of the substituted cyclobutane core are remarkably stable in a series of strain-releasing reactions, particularly in comparison with their smaller homologues. On the other hand, the biomimetic syntheses have proven to be elegant protocols for the construction of highly complex fused cyclobutane frameworks.

With the deeper understanding of the cyclobutane chemistry and the development of novel synthetic methodologies, we believe that new disconnection strategies would certainly emerge and be successfully applied to the total syntheses of more structurally complex and biologically important cyclobutane-containing natural products.

Conflicts of interest

There are no conflicts to declare.

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References

1 For a recent review on the chemistry of strained ring systems, see: (*a*) G. Fumagalli, S. Stanton and J. F. Bower, *Chem. Rev.*, 2017, **117**, 9404–9432. For reviews on the chemistry of cyclopropanes, see: (*b*) D. J. Mack and J. T. Njardarson, *ACS Catal.*, 2013, **3**, 272–286; (*c*) D. Qian and J. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 677–698; (*d*) A. P. Thankachan, K. S. Sindhu, K. K. Krishnan and G. Anilkumar, *Org. Biomol. Chem.*, 2015, **13**, 8780–8802; (*e*) C. Ebner and E. M. Carreira, *Chem. Rev.*, 2017, **117**, 11651–11679; (*f*) M. Bos, T. Poisson, X. Pannecoucke, A. B. Charette and P. Jubault, *Chem. – Eur. J.*, 2017, **23**, 4950–4961; (*g*) W.-Q. Wu, Z.-M. Lin and H.-F. Jiang, *Org. Biomol. Chem.*, 2018, **16**, 7315–7329.

2 A. L. Ringer and D. H. Magers, *J. Org. Chem.*, 2007, **72**, 2533–2537.

3 For recent reviews on the chemistry of oxetanes, see: (*a*) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2010, **49**, 9052–9067; (*b*) A. Mahal, *Eur. J. Chem.*, 2015, **6**, 357–366; (*c*) J. A. Bull, R. A. Croft, O. A. Davis, R. Doran and K. Morgan, *Chem. Rev.*, 2016, **116**, 12150–12233. For recent reviews on the chemistry of azetidines, see: (*d*) A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev.*, 2008, **108**, 3988–4035; (*e*) D. Antermite, L. Degennaro and R. Luisi, *Org. Biomol. Chem.*, 2017, **15**, 34–50; (*f*) D. Didier, A. N. Baumann and M. Eisold, *Tetrahedron Lett.*, 2018, **59**, 3975–3987. For other related reviews, see: (*g*) E. M. Carreira and T. C. Fessard, *Chem. Rev.*, 2014, **114**, 8257–8322; (*h*) D. Hazelard and P. Compain, *Org. Biomol. Chem.*, 2017, **15**, 3806–3827.

4 (*a*) V. M. Dembitsky, *Phytomedicine*, 2014, **21**, 1559–1581; (*b*) Y.-Y. Fan, X.-H. Gao and J.-M. Yue, *Sci. China: Chem.*, 2016, **59**, 1126–1141; (*c*) M. A. Beniddir, L. Evanno, D. Joseph, A. Skiredj and E. Poupon, *Nat. Prod. Rep.*, 2016, **33**, 820–842.

5 (*a*) T. Seiser, T. Saget, D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 7740–7752; (*b*) M. Luparia, D. Audisio and N. Maulide, *Synlett*, 2011, 735–740; (*c*) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2014, **114**, 7317–7420; (*d*) C. M. Rasik and K. M. Brown, *Synlett*, 2014, 760–765; (*e*) Y. Xu, M. L. Conner and K. M. Brown, *Angew. Chem., Int. Ed.*, 2015, **54**, 11918–11928; (*f*) M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254–259; (*g*) E. N. Hancock, J. M. Wiest and M. K. Brown, *Nat. Prod. Rep.*, 2019, **36**, 1383–1393.

6 For selected examples on the Favorskii rearrangements employed in the construction of cyclobutanes, see: (*a*) L. M. Zhang and M. Koreeda, *Org. Lett.*, 2002, **4**, 3755–3758; (*b*) M. harmata and S. Wacharasindhu, *Org. Lett.*, 2005, **7**, 2563–2565.

7 For a representative review on the application of the 1,2-carbon atom migration strategies for construction of cyclobutanes, see: X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, Z.-H. Chen and S.-H. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2272–2305.

8 J. G. Mulder, P. Diepenhorst, P. Plieger and I. E. M. Bruggemann-Rotgans, *PCT Int. Appl*, WO1993002083A1, 1993.

9 K. Tanino, M. Takahashi, Y. Tomata, H. Tokura, T. Uehara, T. Narabu and M. Miyashita, *Nat. Chem.*, 2011, **3**, 484–488.

10 (*a*) C. J. Bulpitt, Y. Li, P. F. Bulpitt and J. Wang, *J. R. Soc. Med.*, 2007, **100**, 558–563; (*b*) S. Shailajan, S. Kumaria, D. Gurjar, M. Joshi, P. Paul and N. Khongthaw, *J. Appl. Pharm. Sci.*, 2015, **5**, 32–38.

11 W.-W. Fan, F.-Q. Xu, F.-W. Dong, X.-N. Li, Y. Li, Y.-Q. Liu, J. Zhou and J.-M. Hu, *Nat. Prod. Bioprospect.*, 2013, **3**, 89–92.

12 H. Wolleb and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2017, **56**, 10890–10893.

13 T. Komada, M. Adachi and T. Nishikawa, *Chem. Lett.*, 2012, **41**, 287–289.

14 H. Y. Chuang and M. Isobe, *Org. Lett.*, 2014, **16**, 4166–4169.

15 T. M. Baker, D. J. Edmonds, D. Hamilton, C. J. O'Brien and D. J. Procter, *Angew. Chem., Int. Ed.*, 2008, **47**, 5631–5633.

16 M. J. Martín, R. Fernández, A. Francesch, P. Amade, S. S. de Matos-Pita, F. Reyes and C. Cuevas, *Org. Lett.*, 2010, **12**, 912–914.

17 M. Gao, Y.-C. Wang, K.-R. Yang, W. He, X.-L. Yang and Z.-J. Yao, *Angew. Chem., Int. Ed.*, 2018, **57**, 13313–13318.

18 (*a*) I. H. Sadler and T. J. Simpson, *J. Chem. Soc., Chem. Commun.*, 1989, 1602–1604; (*b*) I. H. Sadler and T. J. Simpson, *Magn. Reson. Chem.*, 1992, **30**, s18–s23.

19 A. C. Huang, S. A. Kautsar, Y. J. Hong, M. H. Medema, A. D. Bond, D. J. Tantillo and A. Osbourn, *Proc. Natl. Acad. Sci. U. S. A.*, 2017, **114**, 6005–6014.

20 (*a*) N. Zhao, S.-Q. Yin, S.-L. Xie, H. Yan, P. Ren, G. Chen, F. Chen and J. Xu, *Angew. Chem., Int. Ed.*, 2018, **57**, 3386–3390; (*b*) N. Zhao, S.-L. Xie, P.-L. Tian, R.-B. Tong, C.-Q. Ning and J. Xu, *Org. Chem. Front.*, 2019, **6**, 2014–2022.

21 (*a*) W. A. Nugent and T. V. RajanBabu, *J. Am. Chem. Soc.*, 1988, **110**, 8561–8562; (*b*) T. V. RajanBabu and W. A. Nugent, *J. Am. Chem. Soc.*, 1989, **111**, 4525–4527; (*c*) T. V. RajanBabu and W. A. Nugent, *J. Am. Chem. Soc.*, 1994, **116**, 986–997.

22 (*a*) D. P. G. Hamon and K. L. Tuck, *J. Org. Chem.*, 2000, **65**, 7839–7846; (*b*) I. Petschen, M. P. Bosch and A. Guerrero, *Tetrahedron: Asymmetry*, 2000, **11**, 1691–1695; (*c*) A. M. Bernard, A. Frongia, F. Secci, G. Delogu, J. Ollivier, P. P. Piras and J. Salaün, *Tetrahedron*, 2003, **59**, 9433–9440.

23 A. Gansäuer, A. Greb, I. Huth, D. Worgull and K. Knebel, *Tetrahedron*, 2009, **65**, 10791–10796.

24 H. J. Knölker, G. Baum, O. Schmitt and G. Wanzl, *Chem. Commun.*, 1999, 1737–1738.

25 (*a*) J. Yang, Y. Chen, X. Feng, D. Yu and X. Liang, *Planta Med.*, 1984, **50**, 288–290; (*b*) M. Bohnert, S. Miethbauer, H.-M. Dahse, J. Ziemen, M. Nett and D. Hoffmeister, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2003–2006.

26 M. T. Hovey, D. T. Cohen, D. M. Walden, P. H.-Y. Cheong and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2017, **56**, 9864–9867.

27 For selected reviews, see: (*a*) R. A. Yoder and J. N. Johnston, *Chem. Rev.*, 2005, **105**, 4730–4756; (*b*) C. N. Ungarean,

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Published on 12 November 2019. Downloaded on 2/11/2026 11:02:22 PM.

E. H. Southgate and D. Sarlah, *Org. Biomol. Chem.*, 2016, **14**, 5454–5467; (*c*) A. G. M. Barrett, T. Ma and T. Mies, *Synthesis*, 2019, 67–82.
28 K. W. Tsao, C. Y. Cheng and M. Isobe, *Org. Lett.*, 2012, **14**, 5274–5277.
29 (*a*) J. A. Katzenellenbogen, *Science*, 1976, **194**, 139–148; (*b*) G. Rosini and E. Marotta, *Tetrahedron*, 1985, **41**, 4633–4638; (*c*) G. Rosini, E. Marotta, A. Raimondi and P. Righi, *Tetrahedron: Asymmetry*, 1991, **2**, 123–138.
30 Y. T. Han, N.-J. Kim, J.-W. Jung, H. Yun, S. Lee and Y.-G. Suh, *Arch. Pharmacal Res.*, 2011, **34**, 1437–1442.
31 K. Mori and K. Fukumatsu, *Liebigs Ann. Chem.*, 1992, 489–493.
32 J.-X. Xie, J.-C. Wang and G.-B. Dong, *Org. Lett.*, 2017, **19**, 3017–3020.
33 Y.-Y. Fan, H. Zhang, Y. Zhou, H.-B. Liu, W. Tang, B. Zhou, J.-P. Zuo and J.-M. Yue, *J. Am. Chem. Soc.*, 2015, **137**, 138–141.
34 T. J. A. Graham, E. E. Gray, J. M. Burgess and B. C. Goess, *J. Org. Chem.*, 2010, **75**, 226–228.
35 (*a*) M. Hirota, Y. Shimizu, T. Kamo, H. Makabe and H. Shibata, *Biosci., Biotechnol., Biochem.*, 2003, **67**, 1597–1600; (*b*) M. Kashiwabara, T. Kamo, H. Makabe, H. Shibata and M. Hirota, *Biosci., Biotechnol., Biochem.*, 2006, **70**, 1502–1505.
36 S. Ferrer and A. M. Echavarren, *Org. Lett.*, 2018, **20**, 5784–5788.
37 (*a*) P. Lu and T. Bach, *Angew. Chem., Int. Ed.*, 2012, **51**, 1261–1264; (*b*) S. Poplata, A. Tröster, Y.-Q. Zou and T. Bach, *Chem. Rev.*, 2016, **116**, 9748–9815.
38 V. Ramamurthy and J. Sivaguru, *Chem. Rev.*, 2016, **116**, 9914–9993.
39 (*a*) S.-J. Piao, H.-W. Lin, H. Lu, X.-F. Liu and W.-S. Chen, *CN*A 102603689, Shanghai Changzheng Hospital, P. R. China, 2012; (*b*) S.-J. Piao, Y.-L. Song, W.-H. Jiao, F. Yang, X.-F. Liu, W.-S. Chen, B.-N. Han and H.-W. Lin, *Org. Lett.*, 2013, **15**, 3526–3529.
40 S. A. Ruider, T. Sandmeier and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2015, **54**, 2378–2382.
41 Q.-G. Li, K. Zhao, A. Peuronen, K. Rissanen, D. Enders and Y.-F. Tang, *J. Am. Chem. Soc.*, 2018, **140**, 1937–1944.
42 J. Marrero, A. D. Rodríguez, P. Baran, R. G. Raptis, J. A. Sánchez, E. Ortega-Barria and T. L. Capson, *Org. Lett.*, 2004, **6**, 1661–1664.
43 For synthetic studies, see: (*a*) B. Doroh and G. A. Sulikowski, *Org. Lett.*, 2006, **8**, 903–906; (*b*) R. Maio, S. G. Gramani and M. J. Lear, *Tetrahedron Lett.*, 2009, **50**, 1731–1733; (*c*) A. Jana, S. Mondal, M. F. Hossain and S. Ghosh, *Tetrahedron Lett.*, 2012, **53**, 6830–6833; (*d*) S. D. Townsend and G. A. Sulikowski, *Org. Lett.*, 2013, **15**, 5096–5098; (*e*) A. Jana, S. Mondal and S. Ghosh, *Org. Biomol. Chem.*, 2015, **13**, 1846–1859.
44 K. C. Nicolaou, V. A. Adsool and C. R. H. Hale, *Angew. Chem., Int. Ed.*, 2011, **50**, 5149–5152.
45 P. Scesa, M. Wangpaichitr, N. Savaraj, L. M. West and S. P. Roche, *Angew. Chem., Int. Ed.*, 2018, **57**, 1316–1321.
46 (*a*) A. San Feliciano, M. Medarde, J. M. Miguel del Corral, A. Aramburu, M. Gordaliza and A. F. Barrero, *Tetrahedron Lett.*, 1989, **30**, 2851–2854; (*b*) M. W. Lodewyk, C. Soldi, P. B. Jones, M. M. Olmstead, J. Rita, J. T. Shaw and D. J. Tantillo, *J. Am. Chem. Soc.*, 2012, **134**, 18550–18553.
47 K. Takao, H. Kai, A. Yamada, Y. Fukushima, D. Komatsu, A. Ogura and K. Yoshida, *Angew. Chem., Int. Ed.*, 2019, **58**, 9851–9855.
48 K. Wei, W. Li, K. Koike, Y. Chen and T. Nikaido, *J. Org. Chem.*, 2005, **70**, 1164–1176.
49 I. Colomer, R. C. Barcelos and T. J. Donohoe, *Angew. Chem., Int. Ed.*, 2016, **55**, 4748–4752.
50 A. Al-Mourabit, M. A. Zancanella, S. Tilvi and D. Romo, *Nat. Prod. Rep.*, 2011, **28**, 1229–1260.
51 Z.-Q. Ma, X.-L. Wang, X. Wang, R. A. Rodriguez, C. E. Moore, S.-H. Gao, X.-H. Tan, Y.-Y. Ma, A. L. Rheingold, P. S. Baran and C. Chen, *Science*, 2014, **346**, 219–224.
52 (*a*) N. Duchemin, A. Skiredj, J. Mansot, K. Leblanc, J.-J. Vasseur, M. A. Beniddir, L. Evanno, E. Poupon, M. Smietana and S. Arseniyadis, *Angew. Chem., Int. Ed.*, 2018, **57**, 11786–11791; (*b*) E. M. Boyd and J. J. Sperry, *Chem. N. Z.*, 2010, **74**, 109–112; (*c*) J. Dai, J. I. Jimenez, M. Kelly and P. G. Williams, *J. Org. Chem.*, 2010, **75**, 2399–2402.
53 G.-H. Huang, Z. Hu, C. Lei, P.-P. Wang, J. Yang, J.-Y. Li, J. Li and A.-J. Hou, *J. Nat. Prod.*, 2018, **81**, 1810–1818.
54 J. D. Hart, L. Burchill, A. J. Day, C. G. Newton, C. J. Sumby, D. M. Huang and J. H. George, *Angew. Chem., Int. Ed.*, 2019, **58**, 2791–2794.
55 M. E. McCallum, C. M. Rasik, J. L. Wood and M. K. Brown, *J. Am. Chem. Soc.*, 2016, **138**, 2437–2442.
56 K. Takasu, *Isr. J. Chem.*, 2016, **56**, 488–498.
57 Y. Yoshii, T. Otsu, N. Hosokawa, K. Takasu, K. Okano and H. Tokuyama, *Chem. Commun.*, 2015, **51**, 1070–1073.
58 Y. Mogi, K. Inanaga, H. Tokuyama, M. Ihara, Y. Yamaoka, K. Yamada and K. Takasu, *Org. Lett.*, 2019, **21**, 3954–3958.
59 For reviews on electrocyclic reactions, see: (*a*) W. R. Dolbier Jr., H. Koroniak, K. N. Houk and C. Sheu, *Acc. Chem. Res.*, 1996, **29**, 471–477; (*b*) C. M. Beaudry, J. P. Malerich and D. Trauner, *Chem. Rev.*, 2005, **105**, 4757–4778; (*c*) S. Thompson, A. G. Coyne, P. C. Knipe and M. D. Smith, *Chem. Soc. Rev.*, 2011, **40**, 4217–4231; (*d*) N. S. Sheikh, *Org. Biomol. Chem.*, 2015, **13**, 10774–10796; (*e*) M. Bian, L. Li and H. Ding, *Synthesis*, 2017, 4383–4413.
60 (*a*) F. P. Lee, T. C. Chen, J. J. Chen, I. L. Tsai and I. S. Chen, *Helv. Chim. Acta*, 2004, **87**, 463–468; (*b*) I.-L. Tsai, F.-P. Lee, C.-C. Wu, C.-Y. Duh, T. Ishikawa, J.-J. Chen, Y.-C. Chen, H. Seki and I.-S. Chen, *Planta Med.*, 2005, **71**, 535–542.
61 (*a*) W. R. Gutekunst and P. S. Baran, *J. Am. Chem. Soc.*, 2011, **133**, 19076–19079; (*b*) W. R. Gutekunst and P. S. Baran, *J. Org. Chem.*, 2014, **79**, 2430–2452.
62 (*a*) F. Frébault, M. Luparia, M. T. Oliveira, R. Goddard and N. Maulide, *Angew. Chem., Int. Ed.*, 2010, **49**, 5672–5676; (*b*) E. J. Corey and J. Streith, *J. Am. Chem. Soc.*, 1964, **86**, 950–951.
63 N. Winter and D. Trauner, *J. Am. Chem. Soc.*, 2017, **139**, 11706–11709.

Published on 12 November 2019. Downloaded on 2/11/2026 11:02:22 PM.

64 W. G. Dauben, K. Koch, S. L. Smith and O. L. Chapman, *J. Am. Chem. Soc.*, 1963, **85**, 2616–2621.
65 Y. Aoyagi, A. Yamazaki, R. Kato, F. Tobe, H. Fukaya, T. Nishikawa, A. Nakahashi, N. Miura, K. Monde and K. Takeya, *Tetrahedron Lett.*, 2011, **52**, 1851–1853.
66 R. A. Hill and A. Sutherland, *Nat. Prod. Rep.*, 2011, **28**, 1031–1034.
67 C. Fu, Y. Zhang, J. Xuan, C. Zhu, B. Wang and H. Ding, *Org. Lett.*, 2014, **16**, 3376–3379.
68 X. Liu, Y.-J. Hu, B. Chen, L. Min, X.-S. Peng, J. Zhao, S.-P. Li, H. N. C. Wong and C.-C. Li, *Org. Lett.*, 2017, **19**, 4612–4615.
69 (*a*) O. Boye and A. Brossi, in *The Alkaloids*, ed. A. Brossi and G. A. Cordell, Academic Press, San Diego, 1992, vol. 41, pp. 125–176; (*b*) C. Le Hello, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, San Diego, 2000, vol. 53, pp. 287–352; (*c*) R. B. G. Ravelli, B. Gigant, P. A. Curmi, I. Jourdain, S. Lachkar, A. Sobel and M. Knossow, *Nature*, 2004, **428**, 198–202; (*d*) B. Bhattacharyya, D. Panda, S. Gupta and M. Banerjee, *Med. Res. Rev.*, 2008, **28**, 155–183.
70 (*a*) X. Liu, J.-Y. Liu, J. Zhao, S. Li and C.-C. Li, *Org. Lett.*, 2017, **19**, 2742–2745; (*b*) J.-Y. Liu, j. L. Wu, J.-H. Fan, X. Yan, G.-J. Mei and C.-C. Li, *J. Am. Chem. Soc.*, 2018, **140**, 5365–5369.
71 (*a*) R. Huisgen, A. Dahmen and H. Huber, *J. Am. Chem. Soc.*, 1967, **89**, 7130–7131; (*b*) E. N. Marvell, J. Seubert, G. Vogt, G. Zimmer, G. Moy and J. R. Siegmann, *Tetrahedron*, 1978, **34**, 1307–1322; (*c*) J. E. Moses, J. E. Baldwin, R. M. Adlington, A. R. Cowleyb and R. Marqueza, *Tetrahedron Lett.*, 2003, **44**, 6625–6627; (*d*) A. K. Milker and D. Trauner, *Angew. Chem., Int. Ed.*, 2005, **44**, 4602–4606.
72 (*a*) G. Pohnert and W. Boland, *Tetrahedron*, 1994, **50**, 10235–10244; (*b*) G. Pohnert and W. Boland, *Nat. Prod. Rep.*, 2002, **19**, 108–122.
73 (*a*) K. C. Nicolaou, N. A. Petasis, R. E. Zipkin and J. Uenishi, *J. Am. Chem. Soc.*, 1982, **104**, 5555–5557; (*b*) K. C. Nicolaou, N. A. Petasis, J. Uenishi and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5557–5558; (*c*) K. C. Nicolaou, R. E. Zipkin and N. A. Petasis, *J. Am. Chem. Soc.*, 1982, **104**, 5558–5560; (*d*) K. C. Nicolaou, R. E. Zipkin and N. A. Petasis, *J. Am. Chem. Soc.*, 1982, **104**, 5560–5562.
74 (*a*) A. Leverrier, K. Awang, F. Guéritte and M. Litaudon, *Phytochemistry*, 2011, **72**, 1443–1452; (*b*) A. Leverrier, M. E. Tran huu Dau, P. Retailleau, K. Awang, F. Guéritte and M. Litaudon, *Org. Lett.*, 2012, **12**, 3638–3641.
75 S. L. Drew, A. L. Lawrence and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2013, **52**, 4221–4224.
76 W. Kirmse, *Eur. J. Org. Chem.*, 2002, 2193–2256.
77 G. B. Gill, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Flemming, Pergamon Press, 1991, vol. 3, pp. 887–912.
78 M. Shao, Y. Wang, Z. Liu, D.-M. Zhang, H.-H. Cao, R.-W. Jiang, C.-L. Fan, X.-Q. Zhang, H.-R. Chen, X.-S. Yao and W.-C. Ye, *Org. Lett.*, 2010, **12**, 5040–5043.
79 L. M. Chapman, J. C. Beck, L. Wu and S. E. Reisman, *J. Am. Chem. Soc.*, 2016, **138**, 9803–9806.
80 B. Wang, Y. Xie, Q. Yang, G. Zhang and Z. Gu, *Org. Lett.*, 2016, **18**, 5388–5391.
81 (*a*) R. Peel and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 1974, 151–153; (*b*) P. A. Grieco, C. S. Pogonowski, S. D. Burke, M. Nishizawa, M. Miyashita, Y. Masaki, C.-L. J. Wang and G. Majetich, *J. Am. Chem. Soc.*, 1977, **99**, 4111–4118.
82 S. N. Fedorov, O. S. Radchenko, L. K. Shubina, A. I. Kalinovsky, A. V. Gerasimenko, D. Y. Popov and V. A. Stonik, *J. Am. Chem. Soc.*, 2001, **123**, 504–505.
83 R. Meier and D. Trauner, *Angew. Chem., Int. Ed.*, 2016, **55**, 11251–11255.
84 C.-G. Liu, R.-Z. Chen, Y. Shen, Z.-H. Liang, Y.-H. Hua and Y.-D. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 8187–8190.
85 J. S. S. Damsté, M. Strous, W. I. C. Rijpstra, E. C. Hopmans, J. A. J. Geevebasen, A. C. T. van Duin, L. A. van Niftrik and M. S. M. Jetten, *Nature*, 2002, **419**, 708–712.
86 (*a*) J. A. M. Mercer, C. M. Cohen, S. R. Shuken, A. M. Wager, M. W. Smith, F. R. Moss III, M. D. Smith, R. Vahala, A. Gonzalez-Martinez, S. G. Boxer and N. Z. Burns, *J. Am. Chem. Soc.*, 2016, **138**, 15845–15848; (*b*) F. R. Moss III, S. R. Shuken, J. A. M. mercer, C. M. Cohen, T. M. Weiss, S. G. Boxer and N. Z. Burns, *Proc. Natl. Acad. Sci. U. S. A.*, 2018, **115**, 9098–9103.
87 (*a*) R. E. Moore, C. Cheuk and G. M. L. Patterson, *J. Am. Chem. Soc.*, 1984, **106**, 6456–6457; (*b*) J. I. Jimenez, U. Huber, R. E. Moore and G. M. L. Patterson, *J. Nat. Prod.*, 1999, **62**, 569–572; (*c*) A. Raveh and S. Carmeli, *J. Nat. Prod.*, 2007, **70**, 196–201.
88 (*a*) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2005, **127**, 15394–15396; (*b*) P. S. Baran, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404–408; (*c*) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 17938–17954.
89 For a recent review on the Givens rearrangement and related photochemical processes, see: M. G. Banwell and D. J.-Y. D. Bon, in *Molecular Rearrangements in Organic Synthesis*, ed. C. M. Rojas, Wiley, Hoboken, NJ, 2015, ch. 9, pp. 261–288.
90 (*a*) J. S. Yang, Y. L. Su, Y. L. Wang, X. Z. Feng, D. Q. Yu and X. T. Liang, *Acta Pharmacol. Sin.*, 1991, **26**, 117–122; (*b*) P. Cremin, D. M. X. Donnelly, J.-L. Wolfender and K. Hostettmann, *J. Chromatogr., A*, 1995, **710**, 273–285; (*c*) D. M. X. Donnelly, T. Konishi, O. Dunne and P. Cremin, *Phytochemistry*, 1997, **44**, 1473–1478.
91 B. D. Schwartz, E. Matoušová, R. White, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2013, **15**, 1934–1937.
92 C. Bassett, R. T. Sherwood, J. A. Kepler and P. B. Hamilton, *Phytopathology*, 1967, **57**, 1046–1052.
93 L. A. Paquette, X. Peng, J. Yang and H.-J. Kang, *J. Org. Chem.*, 2008, **73**, 4548–4558.
94 R.-H. Liu, M. Zhang, T. P. Wyche, G. N. Winston-McPherson, T. S. Bugni and W.-P. Tang, *Angew. Chem., Int. Ed.*, 2012, **51**, 7503–7506.
95 R. A. Pansih, S. R. Chintala and J. M. Fox, *Angew. Chem., Int. Ed.*, 2016, **55**, 4983–4987.

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