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Ring contraction in synthesis of functionalized carbocycles

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Carbocycles are a key and widely present structural motif in organic compounds. The construction of structurally intriguing carbocycles, such as highly-strained fused rings, spirocycles or highly-functionalized carbocycles with congested stereocenters, remains challenging in organic chemistry. Cyclopropanes, cyclobutanes and cyclopentanes within such carbocycles can be synthesized through ring contraction. These ring contractions involve re-arrangement of and/or small molecule extrusion from a parental ring, which is either a carbocycle or a heterocycle of larger size. This review provides an overview of synthetic methods for ring contractions to form cyclopropanes, cyclobutanes and cyclopentanes en route to structurally intriguing carbocycles.

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1. Introduction

Carbocycles are omnipresent in chemical pharmaceuticals, biologically active natural products, and organic functional materials. The construction of structurally intriguing carbocycles, such as highly-strained fused rings,[1,2] spirocycles,[3] and highly-functionalized carbocycles with congested stereocenters,[4,5] remains a challenging task in organic chemistry. Conventional transformations, such as cycloadditions,[6–10] cyclizations,[11–18] cascade reactions,[19–25] ring expansion, and ring contraction, are readily accessible to synthesize carbocycles, which are subjected to further chemical transformations to afford the desired compounds. In particular, ring contraction involves the synthesis of cyclic compounds (*e.g.*, carbocycles, heterocycles, metallocycles, *etc.*) from a parental compound with a larger ring size. Compared with medium and large carbocycles, for which a variety of methods can be resorted to in most cases, the construction of small carbocycles (*i.e.* three to five-membered) has fewer synthetic methods available. Especially when small carbocycles are highly substituted in nature and/or have a number of stereocenters, their synthesis is very challenging. More synthetic steps may be required to prepare these systems using alternative approaches such as direct ring closure chemistry. Moreover, the synthesis of small carbocycles containing two or more contiguous quaternary carbon centers is not trivial because few effective methods are available for achieving such sterically hindered

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structural motifs. The development of novel synthetic methods and/or synthetic strategies for small carbocycles containing two or more contiguous quaternary carbon centers continues to be a research hot spot for synthetic scientists.

It should be noted that contractive synthesis of carbocycles have been used extensively in natural product synthesis to afford highly substituted cyclic compound possessing an array of stereocenters and/or sterically hindered quaternary carbon center(s) (Fig. 1). One remarkable example is the protecting group free, eight-step synthesis of (+)-welwitindolinone A (**1**) featured an oxidative, pinacol-type rearrangement to construct a cyclobutane from the cyclopentane moiety of 12-*epi*-fischerindole I (**39**)[26] showing good atom-economy and good chemoselectivity (Scheme 1(A)). In contrast, the first total synthesis of ***rac*-1** required 22 steps,[27–29] involving the early construction of cyclobutanone **43** and required sequences of functional group transformations. The scarcity of direct synthetic method to forge the spirocyclobutane motif in the early stage poses difficulties for the synthetic route design that may cause more steps to be required to build up the molecule skeleton and embellish the necessary functional groups. Alternatively, the late-stage ring contraction of fused indole **39** affording spirocyclobutane **1** significantly improves the synthetic efficiency. Another representative example of ring contractive synthesis is the four-step synthesis of prostratin (**28**) from crotophorbolone[30] (Scheme 1(B)). The late-stage, highly-chemoselective dinitrogen extrusion on pyrazoline **46** with UV irradiation producing the cyclopropane. Importantly, the dinitrogen extrusion process required no prior protection of reactive hydroxy groups and is redox neutral. The excellent chemoselectivity of contractive synthesis of cyclopropane from pyrazoline was adopted by recently reported 20-step total synthesis of prostratin (**28**)[31] and other cyclopropane natural products. Up-to-date, no alternative synthetic protocol en route to prostratin (**28**) was reported. Noteworthy, the remarkable synthetic efficiency of Baran's synthesis of (+)-welwitindolinone A (8 steps, *versus* 22 steps of non-contractive approach) and Wender's semi-synthesis of prostratin (**28**) (4 steps) could be attributed to the chemoselective ring contraction of advanced and/or late-stage intermediates.

Historically, low synthetic efficiency made these practically useful but synthetically challenging small carbocycles[32] inaccessible. Although various synthetic strategies have been proposed to improve the efficiency of synthetic design,[33–41] and contractive synthesis of carbocycles has seen wide application organic chemistry, they are still often overlooked (Scheme 1(C)). In general, 1,2-rearrangment methods (*e.g.* semi-pinacol rearrangement, benzilic acid rearrangement, Wolff rearrangement, *etc.*) and gas extrusion reactions (*e.g.* Ramberg–Backlund reaction, dinitrogen extrusion, *etc.*), which are well-documented, have mainly contributed to ring contraction methods. However, the use of such reactions often requires intricate synthetic design in which the precursor of ring contraction usually possesses skeletal framework structurally distinct to the final product, for instance, **39** and (+)-welwitindolinone A (**1**) (see Scheme 1(A)). Early recognition of ring contraction as a synthetic tactic for the target compound is essential so that ring contraction methods can be identified and a precursor carrying the necessary functional features for such transformation can be elaborated. After successfully preparing the desired carbocycle *via* ring contraction, the target product could be accomplished by further transformations. (Scheme 1(D)). As a promising strategy to improve synthetic efficiency, a systematic review of the contractive synthesis of carbocycles in organic synthesis could reveal significant success factors and provide insights for scientists in future research.

In this review, the synthetic applications of ring contraction enabling the synthesis of carbocyclic natural products (**1–38**, Fig. 1) from 2011 to 2021 were discussed. Selected examples reported before 2011 are introduced, providing a brief glance at the history of ring contraction in the synthesis of complex natural products. The representative synthesis of complex natural products using ring contraction as key strategy to fabricate skeletal carbocycles are illustrated. Methods used for the ring contraction in natural product synthesis are catalogized into three groups: 1,2-carbon-migrations, gas-extrusions, and miscellaneous rearrangements. Important information including the reaction scheme of ring contraction, the possible reaction intermediate(s) involved that hints at the reaction mechanism, and the resultant natural products are depicted. Although the contractive synthesis of carbocycles in this Review are categorized according to what we deem to be the key contributing factors, it is of note that contractive synthesis of carbocycles could be organized by other ways, for instance, ring contraction based on the changes in ring size. As such, the number of steps of either the first synthesis or, if applicable, the first asymmetric or enantioselective synthesis using an alternative approach (*i.e.* non-contractive) is denoted along with that of its ring contraction synthesis counterpart for comparison. Some elegant synthetic methods enabled contractive synthesis of carbocycles, which have not been applied to natural product synthesis, are also demonstrated. The transformations of each method are outlined, and how each contractive synthesis was

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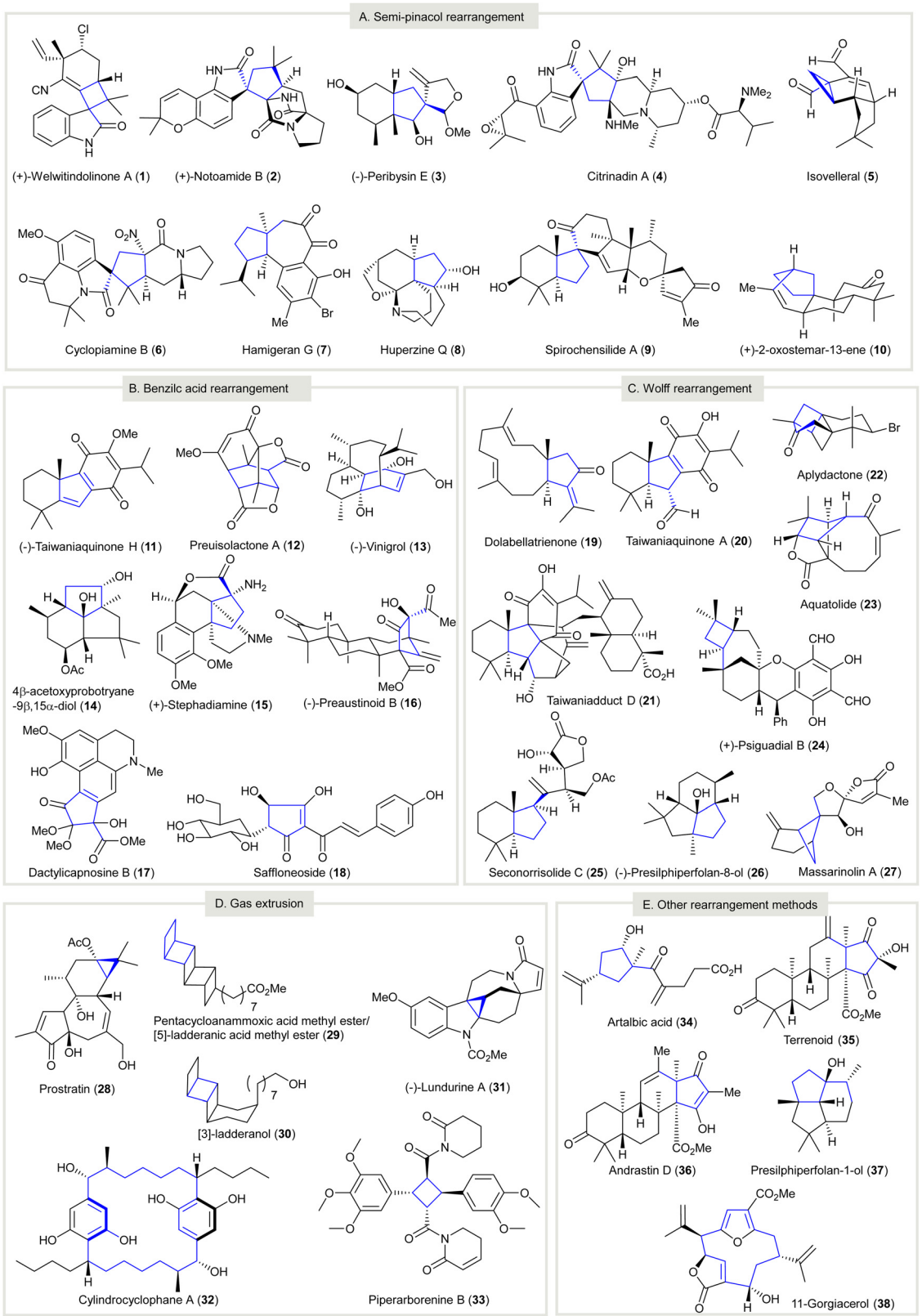
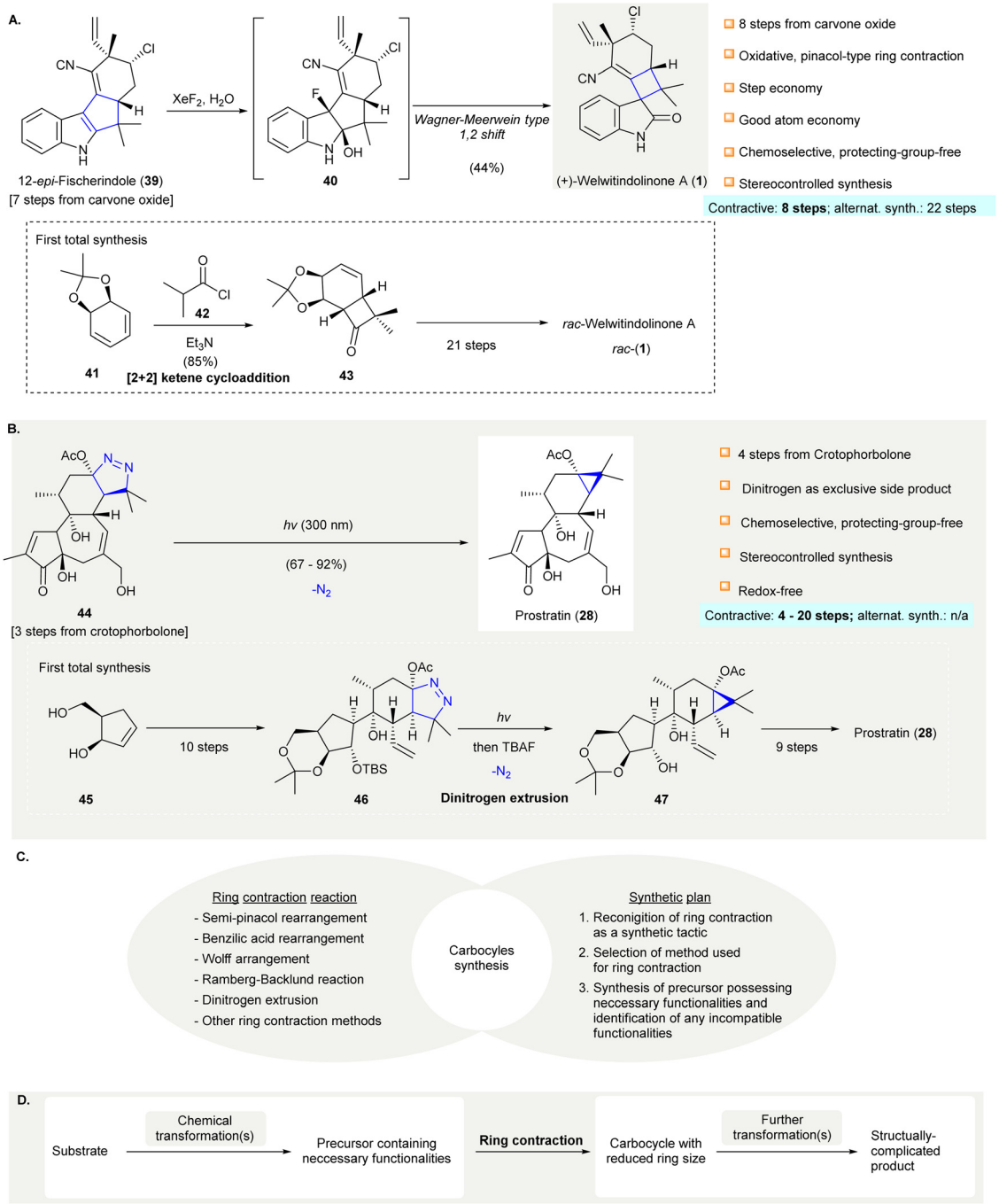


Fig. 1 Selected natural products created by the contractive synthesis of carbocycles. (A) Semi-pinacol rearrangement. (B) Benzilic acid type rearrangement. (C) Wolff rearrangement. (D) Gas-extrusion. (E) Other rearrangement methods.

successfully applied is discussed. Our motivation to compose this Review is to arouse the attention from the synthetic communities for ring contraction as an efficient approach to making carbocycles, especially the highly functionalized and small carbocycles.



Scheme 1 Examples of contractive carbocycle synthesis that comply with elements of efficient synthesis. (A) An oxidative pinacol-type rearrangement converted 12-*epi*-fisherindole (**39**) to oxindole (+)-welwitindolinone A (**1**)[26] (inset, the non-contractive synthesis of *rac*-welwitindolinone A *rac*-(**1**)).[27–29] (B) Photoinduced dinitrogen extrusion-ring contraction of pyrazoline **44** en route to prostatin (**28**).[30] Dinitrogen extrusion in the 20-step total synthesis of prostratin (**28**).[31] (C) Ring contraction methods and rational synthetic plan direct to successful synthesis of carbocycle. (D) A general strategy of applying ring contraction as a maneuver to prepare structurally complicated product. XeF_2, xenon fluoride; TBAF, tetra-*n*-butylammonium fluoride.

Ring contraction not included in this review are intramolecular cyclizations and cycloadditions, reductive elimination of metals from cyclic organometallic complexes, and intramolecular rearrangements resulting in simultaneous ring contractions and expansions in fused carbocycles. Finally, future method developments and applications of contractive synthesis in carbocycles were considered.

2. Selected early transformations

A 1,2-carbon migration between two vicinal atoms can create structural complexity. This is the principal mechanism of numerous, classical, named rearrangement reactions. One notable reaction is the semi-pinacol rearrangement; an organic transformation involving a 1,2-bond migration (C–C or C–H)

centered on oxygen-containing carbons which migrate to vicinal electrophilic carbons generating carbonyl groups.[42] The semi-pinacol reaction allows the contractive synthesis of smaller carbocycles and is applied widely in organic synthesis (Scheme 2).[43–45]

The synthesis of oxindole (+)-notoamide B (**2**) was accomplished *via* a biomimetic, oxidative semi-pinacol rearrangement using Davis' oxaziridine[46] (**49**)[47,48] (Scheme 2(A)). The regioselective epoxidation of (−)-stephacidin A (**48**) at the less sterically hindered α-face and subsequent epoxide opening gave intermediate **50**. Ring contraction at the α-face of **50** *via* a 1,2-shift successfully synthesized (+)-notoamide B (**2**) with 65% yield as a single diastereomer (contractive synthesis: 18 steps;[47,48] alternative synthesis: not available) The biomimetic conversion of an indole structure to its corresponding oxindole using Davis' oxaziridine was reported thereafter.[49–52]

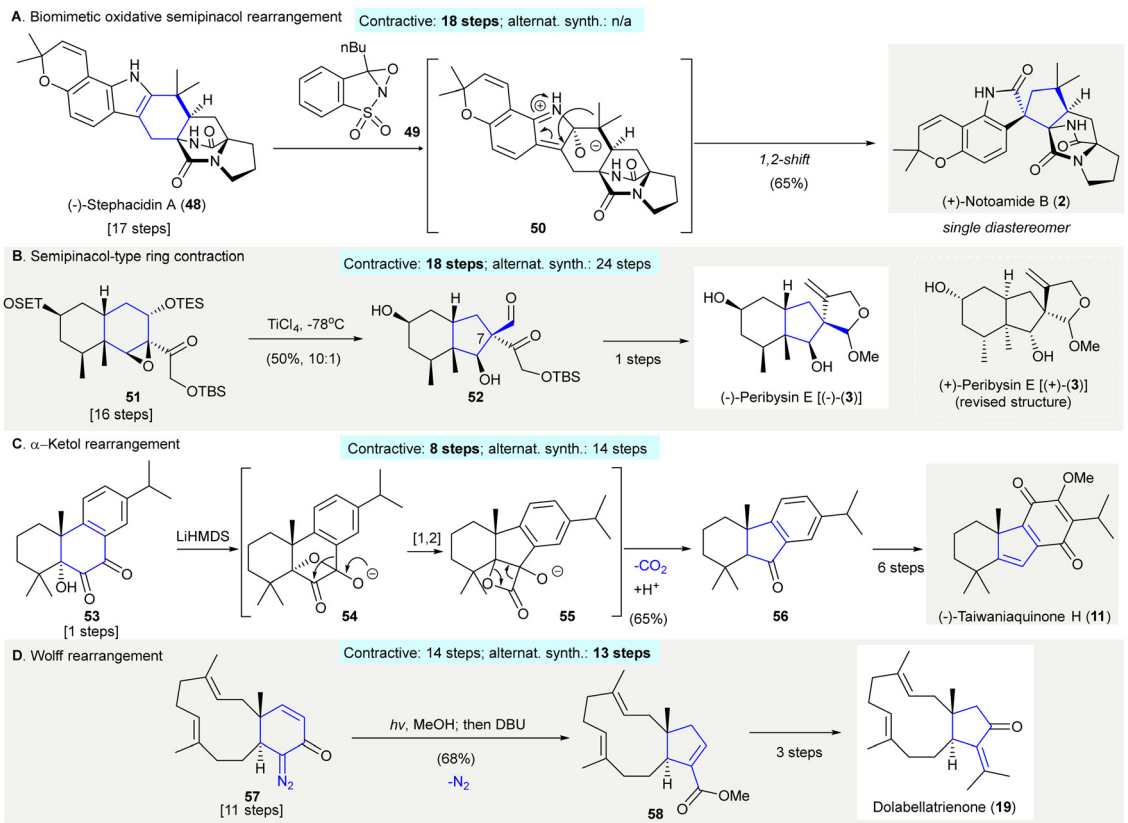
The synthesis of (−)-peribysine E [(−)-(**3**)] used a semi-pinacol-type rearrangement to facilitate the contractive synthesis of a *C*7 quaternary center, on fused cyclopentane **52**[53,54] (Scheme 2(B)). Treatment of epoxide **51** with titanium chloride afforded cyclopentane **52** in 50% yield, and was converted to (−)-peribysine E [(−)-(**3**)] in one step[55] (contractive synthesis: 18 steps;[53,54] alternative synthesis: 24 steps[56]). The revised structure proved to be (+)-perbysine E [(+)-(**3**)] but was misassigned as (−)-peribysine E [(−)-(**3**)].

The synthesis of (−)-taiwaniaquinone H (**11**) featured a benzilic acid rearrangement forming the 6-5-6 tricyclic core of **56**[57] (Scheme 2(C)). Exposure of 1,2-diketone **53** to LiHMDS as a base resulted in the formation of oxetane intermediate **54**, which underwent a 1,2-carbon migration giving intermediate lactone **55**. Successive decarboxylation and protonation of **55** afforded the desired tricyclic ketone **56**, a precursor to (−)-taiwaniaquinone H (**11**) (contractive synthesis: 8 steps;[57] alternative synthesis: 14 steps[58]).

The synthesis of dolabellatrienone (**19**) relied on a Wolff rearrangement producing chiral dolabellane derivative **58** in 68% yield[59] (Scheme 2(D)). Photoirradiation of the α,β-unsaturated diazoketone **57** followed by heating in neat DBU formed the ring-contracted ester **58**, synthesized through an α-keto carbene intermediate (contractive synthesis: 14 steps;[59] alternative synthesis: 13 steps[60]). The Wolff rearrangement is often used to construct 4 and 5 membered carbocycles *via* ring contraction in natural product synthesis.

TBS, *tert*-butyldimethylsilyl; TES, triethylsilyl; $TiCl_4$, titanium tetrachloride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; LiHMDS, lithium bis(trimethylsilyl)amide.

The synthesis of pentacycloanammoxic acid/[5]-ladderanoic acid methyl ester (**29**) featured a photo-induced dinitrogen extrusion giving pentacyclic ladderane ketone **60**[62] (Scheme 3(A)). After ketal protection of the bridged azo ketone **59**, a



Scheme 2 Contractive synthesis of carbocycles *via* 1,2-carbon migrations in organic synthesis. (A) Biomimetic, oxidative semi-pinacol rearrangement facilitated the conversion of (−)-stephacidin A (**48**) to (+)-notoamide B (**2**).[47,48,61] (B) The synthesis of (−)-peribysin E [(−)-(**3**)] involved a semi-pinacol-type reaction to build the [6,5] fused ring in **52** from compound **51** with a [6,6] fused ring.[53] (C) Benzilic acid rearrangement en route to (−)-taiwaniaquinone H (**11**).[57] (D) Wolff arrangement featured as a key reaction in the synthesis of dolabellatrienone (**19**).[59]

photoinduced dinitrogen extrusion followed by deprotection affording fused cyclobutane **60** in 6% yield. It was theorized that the low yield of the dinitrogen extrusion was a result of fragmentation. The formation of unidentified oligomeric materials and problems involving polymerization were also reported in other bridged azo compounds.[63–65] Later, the synthesis of [5]-ladderanoic acid methyl ester (**29**) was accomplished through a modified Ramberg–Bäcklund olefination[66] (see Scheme 9(C)).

The Overberger reaction[67] produced the 10-membered carbocycle [2,2]-metacyclophane (**62**) *via* reduction/dinitrogen extrusion[68] (Scheme 3(B)). As described by Overberger,[67] this reaction involved the reduction of a *N*-nitroso group using sodium dithionite under alkaline condition. In this reaction, dinitrogen extrusion took place giving a ring-contracted carbocycle. The treatment of *N*-nitroso compound **61** under standard conditions afforded [2,2] metacyclophane (**62**) in 72% yield, which was also synthesized by the photodecarbonylation of diketone **63** (Scheme 3(B)).[69]

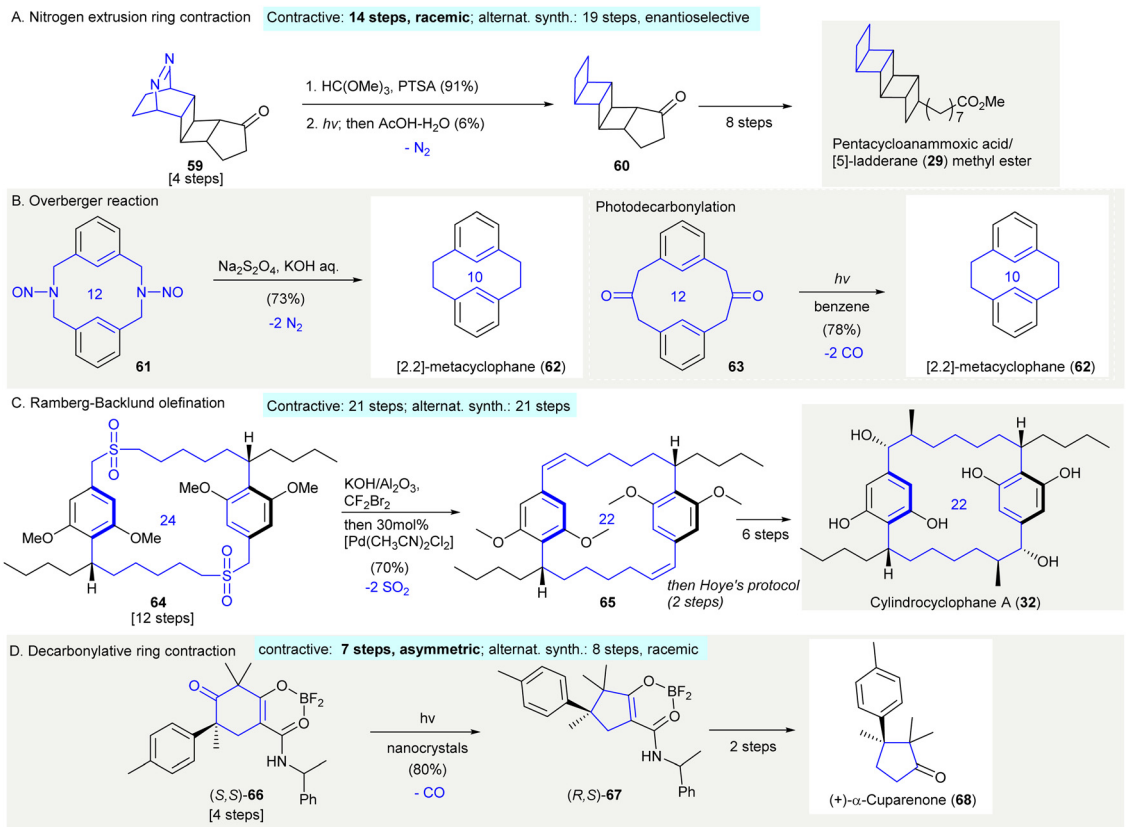
The synthesis of cylindrocyclophane A (**32**) relied on a Ramberg–Bäcklund olefination[70,71] to give bis(olefin) **65**[72] (Scheme 3(C)). The treatment of bis(sulfone) **64** with alumina-supported KOH–CBr_2F_2[73] by removing sulfur dioxide gave a diolefin. This compound was then isomerized by 30 mol% of $[Pd(CH_3CN)_2Cl_2]$ to give exclusively *E*,*E*-**65** in 70% yield. (contractive synthesis: 21 steps;[72] alternative synthesis: 21 steps[74]) The Ramberg–Bäcklund olefination is often employed in the synthesis of cyclophane,[75] and is also used when synthesizing smaller cycloalkenes[76] and fused rings[77] which are not discussed in this review.

The synthesis of (+)-α-cuparenone (**68**) used solid-state photodecarbonylation generating (*R*,*S*)-**67**[78] (Scheme 3(D)). The photoirradiation of (*S*,*S*)-**66** as a nanocrystalline suspension in water using cetrimonium bromide afforded decarbonylated product (*R*,*S*)-**67** in 80% yield, in which all vicinal carbons possessed quaternary centers. The ketone substrate had to be crystalline (*i.e.* (*S*,*S*)-**66**) and contain at least one radical-stabilizing functional group in order to stabilize the possible biradical intermediate (contractive synthesis: 7 steps,[78] asymmetric; alternative synthesis: 8 steps,[79] racemic). This method was also applied in the synthesis of other natural products.[80]

PTSA, *p*-toluenesulfonic acid; CTAB, Cetrimonium bromide.

3. The contractive synthesis of carbocycles *via* 1,2-rearrangements in organic synthesis

Ring contractions *via* 1,2-rearrangements have seen wide application in natural product synthesis. In this section, the use of



Scheme 3 Contractive synthesis of carbocycles *via* gas extrusion in organic synthesis. (A) Dinitrogen extrusion-ring contraction of bridged azo ketone **59** to fused-cyclobutanes **60** in the synthesis of pentacycloanammoxic acid (**29**) methyl ester.[62] (B) Synthesis of cyclophane **62** relied on the Overberger reaction.[68] (inset: a photoinduced decarbonylation)[69] (C) Double Ramberg–Bäcklund olefination resulted in macrocyclic diene **65** in the synthesis of cylindrocyclophane A (**32**).[72] (D) Synthesis of (+)-α-cuparenone (**68**) relying on a solid-state photodecarbonylation.[78]

semi-pinacol rearrangements, benzilic acid rearrangements (including variant α-ketol rearrangements), Wolff rearrangements and miscellaneous 1,2-rearrangement reactions in natural product synthesis are discussed. Additionally, novel 1,2-rearrangement methods capable of contractively synthesizing carbocycles are introduced.

3.1 Semi-pinacol rearrangements in natural product synthesis

The enantioselective synthesis of (−)-citrinadin A (**4**) featured a substrate-controlled, oxidative semi-pinacol rearrangement of indole **69** to oxindole **71** using William's approach[48–50] (Scheme 4(A)). Exposure of indole **69** to an excessive amount of Davis' oxaziridine **49** afforded epoxide (**70**). This compound was then subjected to a semi-pinacol rearrangement with acetic acid forming **71** in 47% yield. A variety of oxidants, besides Davis' oxaziridine **49**, such as *tert*-BuOCl, OsO_4, and NBS, failed to give oxindole **71**[81] (contractive synthesis: 20 steps;[49,50] non-contractive synthesis: N/A).

The synthesis of cyclopiamine B (**6**) utilized a dimethyldioxirane-promoted, one-pot semi-pinacol rearrangement/amine oxidation and synthesized cyclopiamine B precursor **74**[82] (Scheme 4(B)). The treatment of indole **72** with excess dimethyldioxirane (generated *in situ* from acetone and oxone) resulted in the sequential stereoselective epoxidation of the indole C2–C3 bond, and amine oxidation forming a nitro group to give intermediate **73**. This resulted in a semi-pinacol rearrangement giving oxindole **74** in 56% yield with a 4 : 1 diastereomeric ratio.[82] The primary amine group of **72** may have served as a hydrogen-bond donor, facilitating stereoselective epoxidation of the indole C2–C3 bond. Then, the primary amine was oxidized to a nitro group, making hydrogen bonding formation to stabilize the pseudoindoxyl side product (not depicted) no longer possible. Lastly, intermediate **72**[83] was used in a semi-pinacol rearrangement to give product **74**. It was suggested that the chromanone moiety minimized the participation of the indole nitrogen's lone pair through intramolecular H-bonding producing oxindole **74** (contractive synthesis: 21 steps;[82] non-contractive synthesis: N/A).

The synthesis of sesquiterpenoid isovelleral (**5**)[84] detailed the preparation of cyclopropane **76** through a semi-pinacol type rearrangement[85] (Scheme 4(C)). When cyclobutanediol **75** was subjected to Mitsunobu's condition (DEAD, PPh_3 and 4-O_2NPhCO_2H), an unexpected semi-pinacol rearrangement occurred to give cyclopropane **76** in 61% yield, without observing the expected stereo-inverted product (contractive synthesis: 22 steps,[84] enantioselective; non-contractive synthesis: 12 steps,[86] asymmetric). The ring contraction of cyclobutanediol formed a quaternary carbon-containing cyclopropane which could be used as an efficient strategy to prepare fused cyclopropanes.[87]

The synthesis of hamigeran G (**7**) started *via* the construction of cyclopentane **79** with three adjacent stereocenters and occurred through an acid-catalyzed semi-pinacol rearrangement and subsequent ketal protection[88] (Scheme 4(D)). The treatment of epoxide **77** with trifluoromethanesulfonic acid and silylated diol **78** gave ketal **79** in 79% yield as single diastereomer. The stereochemistry of the C9-quaternary center of **79** matched that of hamigeran G (**7**) (contractive synthesis: 25 steps,[88] enantioselective; non-contractive synthesis: N/A). This showed that the stereocongested compound **79** was accessible *via* a semi-pinacol rearrangement of epoxide **77**, which was synthesized from the chiral pool chemical (*R*)-piperitone in three steps.[2]

The synthesis of huperzine Q (**8**) featured selective epoxide cleavage *via* a 1,2-carbon shift in the preparation of product **82**[89] (Scheme 4(E)). Exposure of epoxide **80** to TMSOTf enabled the selective opening of the epoxide, resulting in 1,2-carbon migration giving ketoaldehyde **82** in 91% yield. The cleavage of the tosyl group in **82** in the presence of thiophenol and cesium carbonate resulted in the formation of a hemiketal (not depicted), in which deformylation occurred simultaneously through the addition of methanol giving **83** in 74% yield. The synthesis of huperzine Q (**8**) was achieved *via* an additional two-step synthesis (contractive synthesis: 13 steps, racemic;[89] non-contractive synthesis: 19 steps, asymmetric[90]).

The synthesis of (−)-spirochensilide A (**9**) started with the cleavage of an epoxide *via* a semi-pinacol rearrangement cascade of enyne **84** to generate the bicycle **86**[91] (Scheme 4(F)). The treatment of enyne **84** with *meta*-chloroperoxybenzoic acid produced epoxide **85**. Subsequent addition of a substoichiometric amount of $BF_3{\cdot}OEt_2$ resulted in a semi-pinacol rearrangement to give product **86** in 65% yield as a single diastereomer. Aldehyde **86** was converted to (−)-spirochensilide A (**9**) in further reactions (contractive synthesis: 22 steps;[91] non-contractive synthesis: N/A).

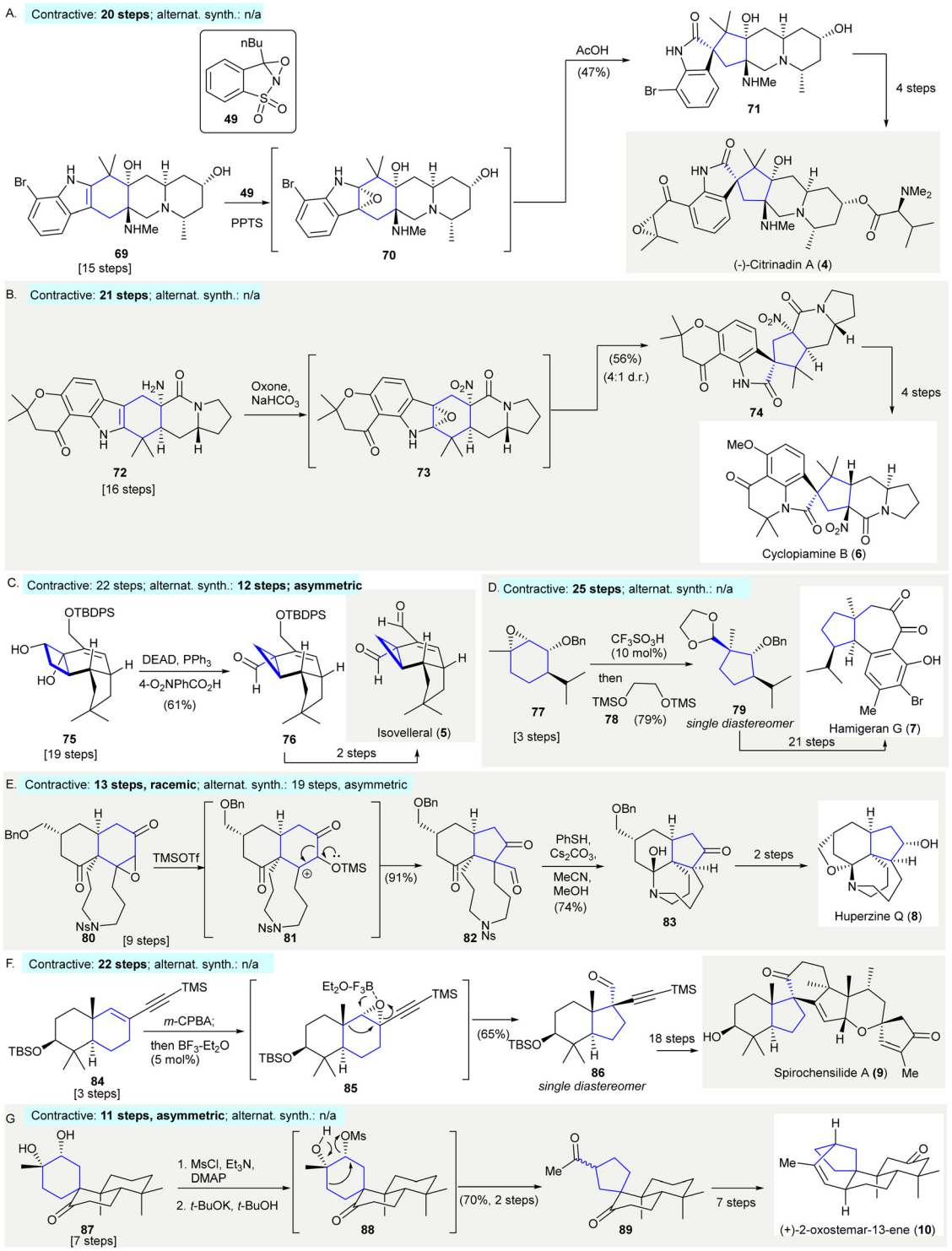
The synthesis of (+)-2-oxostemar-13-ene (**10**) utilized a semi-pinacol rearrangement to prepare spirocyclopentane **89**[92] (Scheme 4(G)). The selective mesylation of the C12 hydroxy group of **87**, followed by treatment with potassium *tert*-butoxide enabled a semi-pinacol rearrangement giving diketone **89** in 70% yield over two steps with a 1 : 1 epimeric ratio (contractive synthesis: 11 steps,[92] asymmetric; non-contractive synthesis: N/A).

TBDPS, *tert*-butyldiphenylsilyl; DEAD, diethyl azodicarboxylate; TMS, trimethylsilyl; PPTS, pyridinium *p*-toluenesulfonate; Bn, benzyl; oxone, potassium peroxymonosulfate; Ph, phenyl; DMAP, 4-(dimethylamino)pyridine.

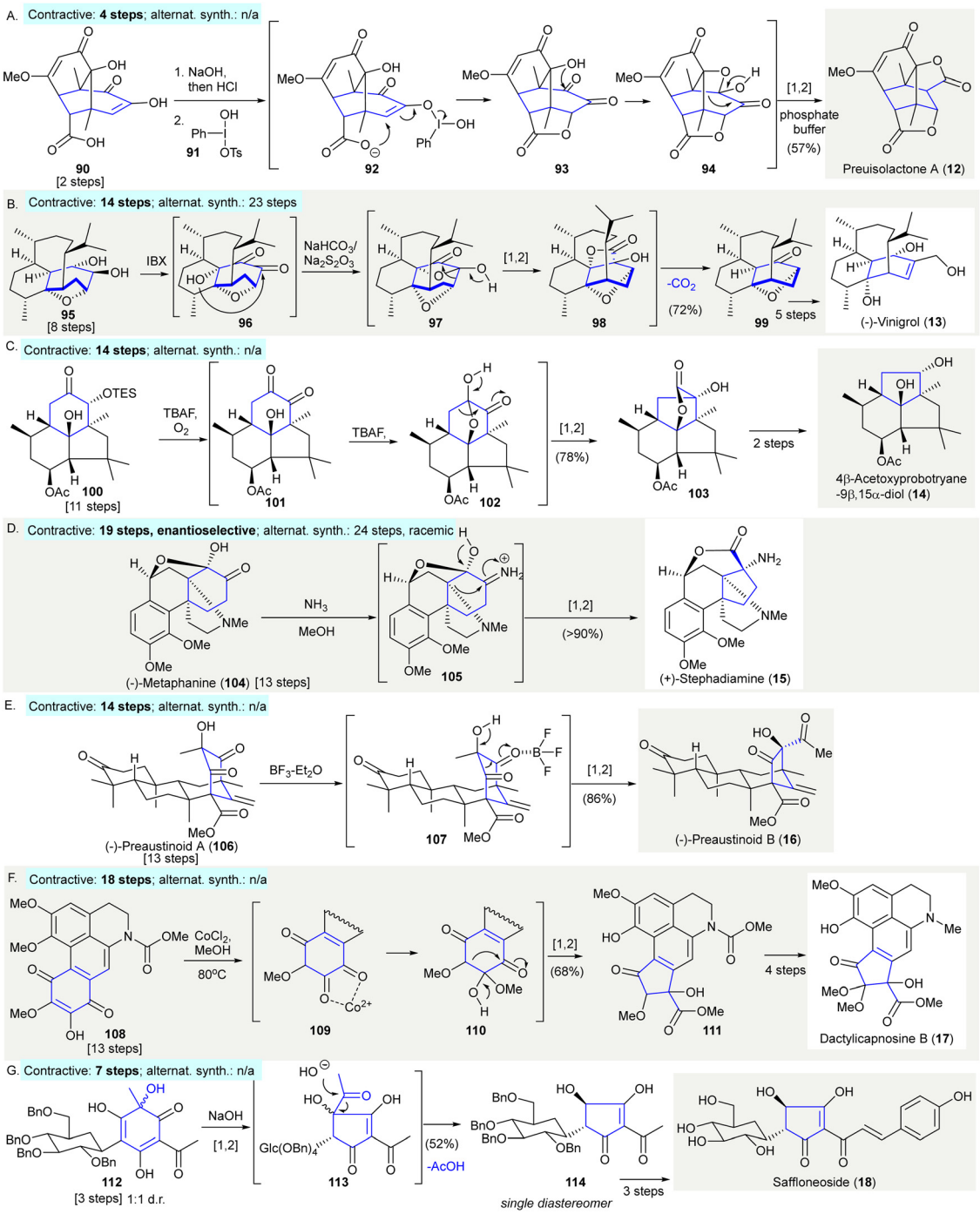
3.2 Benzilic acid rearrangements in natural product synthesis

A ring contractive synthesis was conducted using a benzilic acid rearrangement to synthesize preuisolactone A (**12**)[93] (Scheme 5(A)). Koser's reagent **91** oxidized enol **90**, which is a desirable intermediate formed under the effect of alkaline followed by acidification. It was proposed that lactone **93** formed *via* the activation of the enolized 1,2-diketone with assistance from the hypervalent iodine(III) species **92**. The obtained product **93** was converted to oxetane **94** followed by 1,2-carbon migration upon workup with aqueous phosphate buffer (pH = 8) to give preuisolactone A (**12**) in 57% yield (contractive synthesis: 4 steps;[93] alternative synthesis: N/A).

The asymmetric synthesis of (−)-vinigrol (**13**) featured an unexpected decarboxylative ring contraction, yielding the 1,5-butanodecahydronaphthalene core **99** as a synthetic precursor for other reactions[94] (Scheme 5(B)). The oxidation of diol **95**



Scheme 4 Ring contractions enabled by semi-pinacol rearrangements in natural product synthesis. A. The diastereoselective epoxidation with Davis' oxaziridine **49** and subsequent acid-catalysed rearrangement, resulting in the formation of oxindole precursor **71** in the enantioselective synthesis of (−)-citrinadin A (**4**).[49] (B) The synthesis of cyclopiamine B (**6**) featured the reaction of dimethyldioxirane *via* a one-pot rearrangement and tertiary amine formation to give spiroxoindole **74**.[82] (C) An unexpected semi-pinacol-type reaction occurred under Mitsunobu's condition in the preparation of isovelleral (**5**).[84] (D) Synthesis of hamigeran G (**7**) utilized a semi-pinacol rearrangement followed by hemiketal protection yielding highly functionalized cyclopentane **79**.[88] (E) Selective cleavage of epoxide *via* a 1,2-carbon shift in the synthesis of hyperzine Q (**8**).[89] (F) A semi-pinacol rearrangement converted [6,6]-bicycle **80** to [6,5]-bicycle **82** in the synthesis of spirochensilide A (**9**).[91] (G) Conversion of a diol **87** to a cyclopentane **89** achieved through the selective mesylation *via* a 1,2-carbon migration in the synthesis of (+)-2-oxostemar-13-ene (**10**).[92]



Scheme 5 Ring contractions *via* benzilic acid rearrangements in natural product synthesis. (A) A late-stage benzilic acid rearrangement en route to preuisolacone A (**12**).[93] (B) Synthesis of (−)-vinigrol (**13**) featured an unexpected decarboxylative ring contraction to give precursor **99**.[94] (C) A benzilic acid rearrangement of silyl ether **100** produced a highly-strained *trans*-fused structure **103** in the synthesis of 4β-Acetoxyprobotryane-9β,15α-diol (**14**).[96] (D) An aza-benzilic acid-type rearrangement of (−)-metaphanine (**104**) en route to (+)-stephadiamine (**15**).[97] (E) Conversion of (−)-preaustinoid A (**106**) to (−)-preaustinoid B (**16**) achieved *via* late-stage α-ketol rearrangement.[99] (F) Ring contraction of *p*-quinone **108** *via* cobalt-mediated benzilic acid rearrangement gave cyclopentanone **112** in the synthesis of dactylicapnosine B (**17**).[101] (G) Base-mediated stereospecific acyloin ring contraction in the synthesis of safflоneoside (**18**).[102]

using IBX gave 1,2-diketone **96**, this reaction proceeded *via* the α-hydroxy group attacking the least hindered ketone to give oxetanone **97**. This step was followed by a 1,2-carbon migration to give the unstable β-lactone **98**. The β-lactone **98** was isolated and characterized and underwent spontaneous decarboxylation and epimerization to give desired product **99** in 72% yield (contractive synthesis: 14 steps;[94,95] alternative synthesis: 23 steps[95]).

The synthesis of 4β-acetoxyprobotryane-9β,15α-diol (**14**) used a benzilic acid-type rearrangement to construct the *trans*-fused bicyclo[3.3.0]octane skeleton of **103**[96] (Scheme 5(C)). The treatment of silyl ether **100** with TBAF in the presence of oxygen resulted in desilylation, followed by rearrangement generating the 1,2-diketone **101**, which underwent hemiketalization to give **101**. The rearrangement in ketal **101** proceeded spontaneously, producing lactone **103** in 78% yield which contained a *trans*-fused bicyclo[3.3.0]octane scaffold. The further synthesis of 4β-acetoxyprobotryane-9β,15α-diol (**14**) was completed in two additional steps (contractive synthesis: 14 steps;[96] alternative synthesis: N/A).

(+)-Stephadiamine (**15**) was prepared from (−)-metaphanine (**104**) through an *aza*-benzilic acid-type rearrangement[97] (Scheme 5(D)). The exposure of (−)-metaphanine (**104**) to ammonia in methanol *in situ* generated imine **105**, which underwent another aza-benzilic acid-type rearrangement giving (+)-stephadiamine (**15**) in over 90% yield. The author mentioned that stephadiamine (**15**) was not stable upon purification using silica gel under acidic, or basic condition (contractive: 19 steps,[97] enantioselective; alternative synthesis: 24 steps,[98] racemic).

The conversion of (−)-preaustinoid A (**106**) to (−)-preaustinoid B (**16**) was achieved *via* late-stage α-ketol rearrangement[99] (Scheme 5(G)). The treatment of (−)-preaustinoid A (**106**) with $BF_3{\cdot}Et_2O$ led to an α-ketol rearrangement affording (−)-preaustinoid B (**16**), presumably *via* intermediate **107**. However, attempts to use acidic, basic, or thermal conditions failed to give the desired rearrangement product (contractive: 14 steps;[99] alternative synthesis: N/A).

The synthesis of dactylicapnosine B (**17**) made use of a cobalt-mediated benzilic acid rearrangement[100] preparing tetracyclic precursor **111**[101] (Scheme 5(F)). *p*-Quinone **108** was treated with cobalt chloride in methanol providing 1,2-diketone **109**. The addition of methanol to the diketone **109** gave hemiacetal **110**, which underwent a benzilic acid rearrangement to give cyclopentenone **111** in 68% yield. The synthesis of dactylicapnosine B (**17**) was completed in seven steps (contractive synthesis: 18 steps;[101] alternative synthesis: N/A).

The synthesis of saffloneoside (**18**) relied on a stereospecific acyloin ring contraction yielding cyclopentanone **114**[102] (Scheme 5(G)). The treatment of the cyclohexadienone **112** with aqueous sodium hydroxide gave the cyclopentenone-containing intermediate **113** *via* α-ketol rearrangement. After the cleavage of the acyl moiety of **113** under basic conditions, cyclopentenone **114** was produced in 52% yield as a single diastereomer. The cyclopentenone **114** was converted to saffloneoside (**18**) in three steps. (Contractive synthesis: 7 steps;[102] alternative synthesis: N/A)

Ph, phenyl; Ts, *p*-toluenesulfonyl; IBX, 2-iodoxybenzoic acid; TBAF, tetra-*n*-butylammonium fluoride.

3.3 Wolff rearrangements in natural product synthesis

The synthesis of taiwaniaquinone A (**20**)[103] and taiwaniadduct D (**21**)[104] used a Wolff rearrangement to prepare the 6-5-6 tricyclic core **116a** or **116b** from the 6-6-6 tricyclic diazo compound **115** (Scheme 6(A)). Irradiation of diazo compound **115** with a mercury lamp in methanol gave **116a** in 30% yield as a single diastereomer. Due to decreased efficiency upon scale-up under photoirradiation, thermal conditions (BnOH, 2,4,6-collidine, 160 °C) were tested and the desired benzyl ester **116b** was isolated in 56% yield as a single diastereomer (taiwaniaquinone A (**20**): contractive synthesis: 11 steps,[103] racemic; alternative synthesis: 14 steps,[105] asymmetric).

Trauner's synthesis of aplydactone (**22**) featured a Wolff rearrangement to synthesize fused cyclobutane **118**[106] (Scheme 6(B)). Upon photoirradiation of the α-diazo cyclopentanone **117**, the ladderane **118** was formed in 77% yield with a 3 : 1 diastereomeric ratio. The same strategy was adopted to prepare a fused cyclobutane by Zhang[107] in the total synthesis of aplydactone (**22**) (contractive synthesis: 24 steps,[106] racemic; alternative synthesis: 11 steps,[108] enantioselective).

The synthesis of aquatolide (**23**) featured a Wolff rearrangement to create the bicyclo[2.1.1]hexane structure of **120**[109] (Scheme 6(C)). Irradiation of the diazo compound **119** with a high-pressure mercury lamp in the presence of $NaHCO_3$ gave bridged carboxylic acid **120** in 80% yield with a 20 : 3 diastereomeric ratio (contractive synthesis: 22 steps,[109] alternative synthesis: 16 steps[110]).

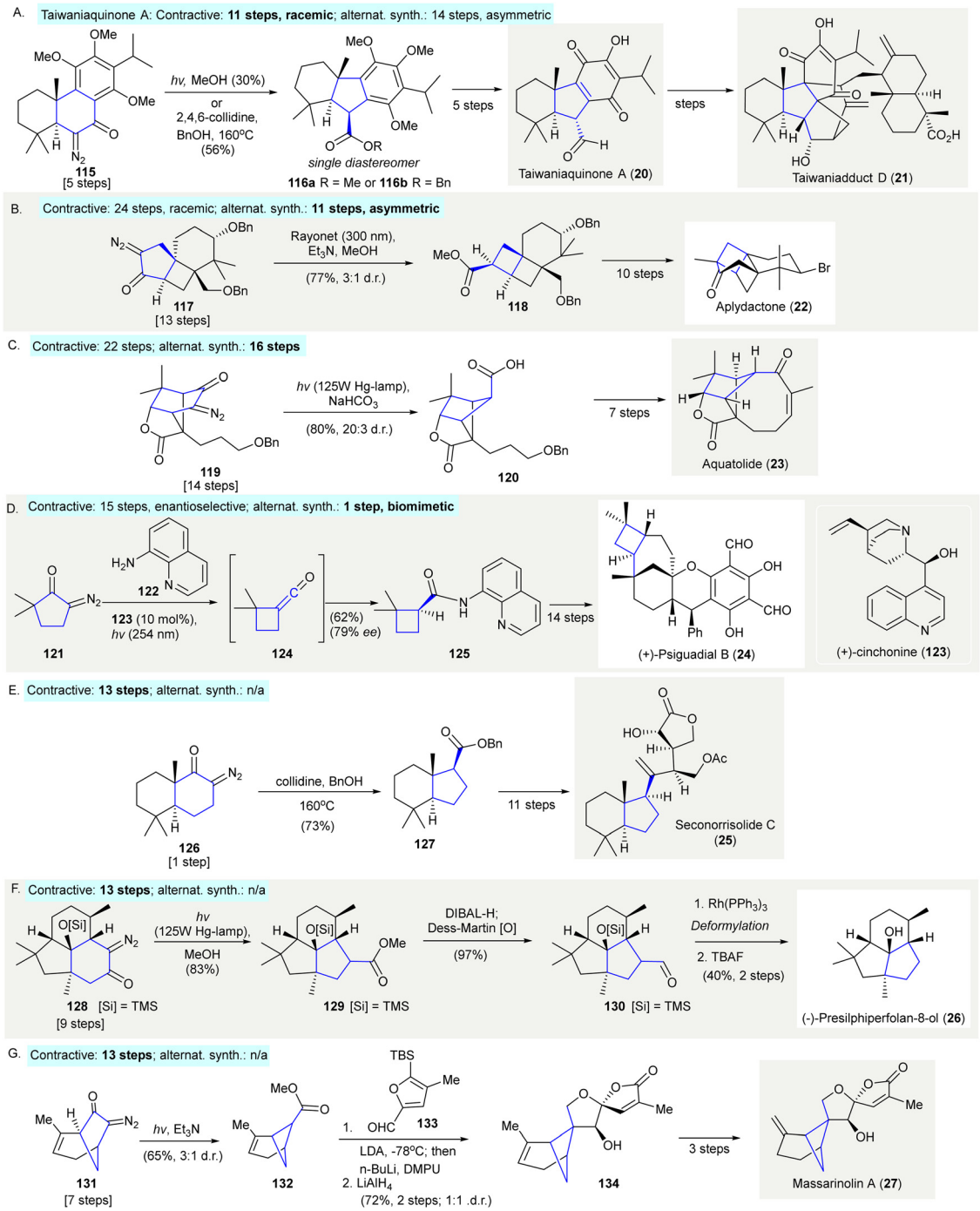
The enantioselective synthesis (+)-psiguadial B (**24**) began with a tandem Wolff rearrangement/catalytic asymmetric ketene addition to afford the cyclobutane on **125**[111] (Scheme 6(D)). This reaction was conducted in the presence of 8-aminoquinoline (**122**) using (+)-cinchonine (**123**) as chiral organocatalyst, resulting in asymmetric nucleophilic addition to ketene **124**[112,113] *via* photolysis of the α-diazo ketone, **121** giving product **125** in 66% yield and 81% ee. Further recrystallization of **125** provided enantiomerically pure material used in the enantioselective synthesis of (+)-psiguadial B (**24**) (contractive synthesis: steps, 15 steps;[111] alternative synthesis: 1 steps[114]).

The synthesis of seconorrisolide C (**25**) used a Wolff rearrangement to prepare the [6,5]-bicycle **127**[115] (Scheme 6(E)). Similar to Li's approach in the synthesis of taiwaniaquinone A (**20**)[103] and taiwaniadduct D (**21**)[104] (see Scheme 6(A)), the treatment of diazoketone **125** with collidine and benzyl alcohol at 160 °C produced ester **127** in 73% yield, a synthetic precursor of seconorrisolide C (**25**) (contractive synthesis: steps, 13 steps;[115] alternative synthesis: N/A).

The enantiospecific synthesis of (−)-presilphiperfolan-8-ol (**26**) used a Wolff rearrangement to prepare the tricyclic core of **128**[116] (Scheme 6(F)). Photoirradiation of diazoketone **128** gave ring contraction product **129** in 83% yield. After a two-step redox manipulation intermediate **129** was formed and when deformylated and desilylated afforded (−)-presilphiperfolan-8-ol (**26**) (contractive synthesis: 13 steps;[116] alternative synthesis: N/A).

Very recently, Dai and co-workers reported the first total syntheses of complex bergamotane sesquiterpenes massarinolin A (**27**) and its congeners featuring a scalable flow photochemical Wolff rearrangement as a key reaction[117] (Scheme 6(G)) (contractive synthesis: steps, 13 steps;[117] alternative synthesis: N/A).

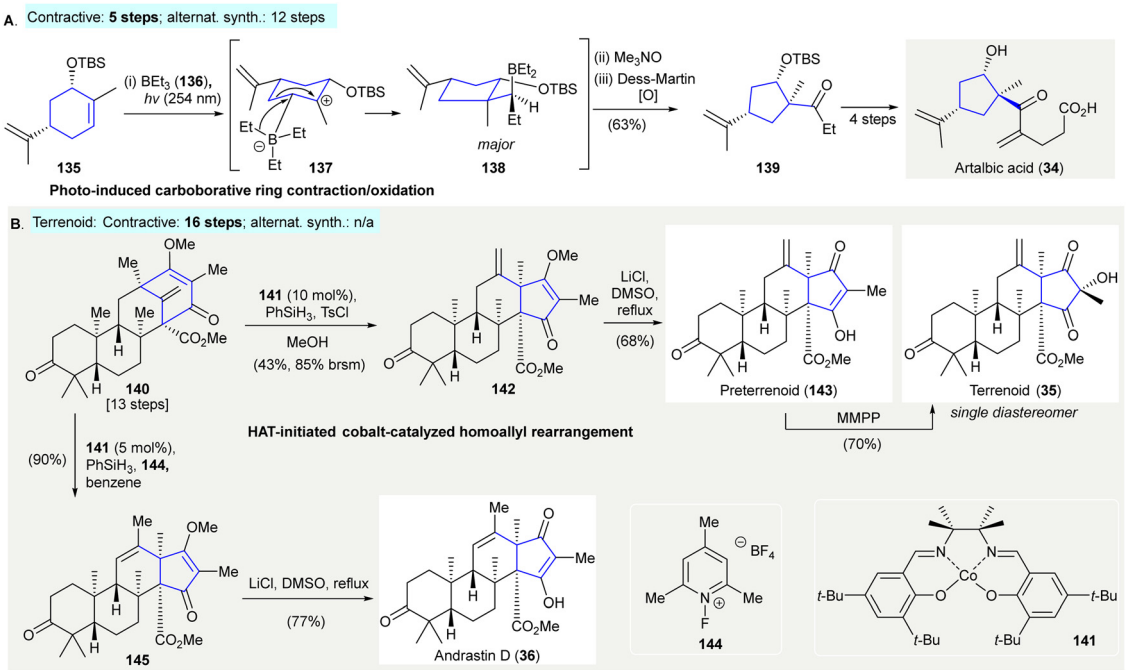
2,4,6-Collidine, 2,4,6-trimethylpyridine; Bn, benzyl.



Scheme 6 Ring contractions *via* Wolff rearrangements in natural product synthesis. (A) The synthesis of taiwaniaquinone A (**20**) and taiwaniadduct D (**21**) revealed a conversion of [6.6.6]-tricyclic fused ring **115** to [6.5.6] tricyclic fused ring **116a** or **116b**.[103,104] (B) The synthesis of aplydactone (**22**) demonstrated the preparation of [4.4.6] tricyclc fused ring **118**.[106,107] (C) A Wolff rearrangement enabled the ring contraction of bridged [2.2.1] bicycle **119** to bridged [2.1.1] bicycle **120** in the synthesis of aquatolide (**23**).[109] (D) The enantioselective synthesis of precursor **125** of (−)-psiguadial B (**24**) through tandem Wolff rearrangement/asymmetric ketene addition.[111] (E) Synthesis of seconorrisolide C (**25**) used a Wolff rearrangement to prepare the [6.5] bicycle **127**.[115] (F) Wolff rearrangement used to prepare tricycle **129** in the enantiospecific synthesis of (−)-presilphiperfolan-8-ol (**26**).[116] A flow Wolff rearrangement of **131** to give 132 as an key intermediate toward the preparation of massarinolin A (**27**).[117]

3.4 Other 1,2-carbon migration methods in natural product synthesis

The synthesis of artalbic acid (**34**) utilized a photoinduced carboborative ring contraction/oxidation to give the highly-functionalized cyclopentane **139**[118] (Scheme 7(A)). The exposure of (*S*,*S*)-carveol-derived TBS ether **135** to UV-irradiation resulted in an isomerization.[119] This was followed by boration with triethylborane **136** to generate a carbocation intermediate **137**, which



Scheme 7 Other 1,2-carbon migration methods in natural product synthesis. (A) Photo-induced carboborative ring contraction/oxidation in the synthesis of artalbic acid (**34**).[118] (B) HAT-initiated cobalt-catalyzed homoallyl rearrangement en route to terrenoid (**35**) and andrastin D (**36**).[121]

underwent 1,2-carbon migration yielding product **138**. The successive oxidation of borane **138** with trimethylamine *N*-oxide and Dess–Martin periodinane afforded cyclopentane **139** in 69% yield (contractive synthesis: 5 steps;[118] alternative synthesis: 12 steps[120]).

The synthesis of andrastin (**36**) and terretonin meroterpenes (*e.g.* terrennoid (**35**)) utilised HAT-initiated homoallyl rearrangements[121] (Scheme 7(B)). The treatment of **140** with 10 mol% of cobalt(II) catalyst **141** and phenylsilane in the presence of tosyl chloride[122] afforded **142** in 43% yield. The demethylation of **142** with lithium chloride under reflux yielded preterrenoid (**143**), which was subjected to stereoselective oxidation with magnesium monoperoxyphthalate giving terrenoid (**35**). Alternatively, the treatment of **140** with 5 mol% of cobalt(II) catalyst **141** in the presence of phenylsilane and **144** as an oxidant (*i.e.* modified Shigehisa conditions[123]) avoided the use of the alcohol as a trapping agent, producing the rearrangement product **145** in 90% yield. Demethylation of **145** afforded andrastin (**36**) in 77% yield. (Terrenoid: contractive synthesis: steps, 16 steps;[121] alternative synthesis: N/A).

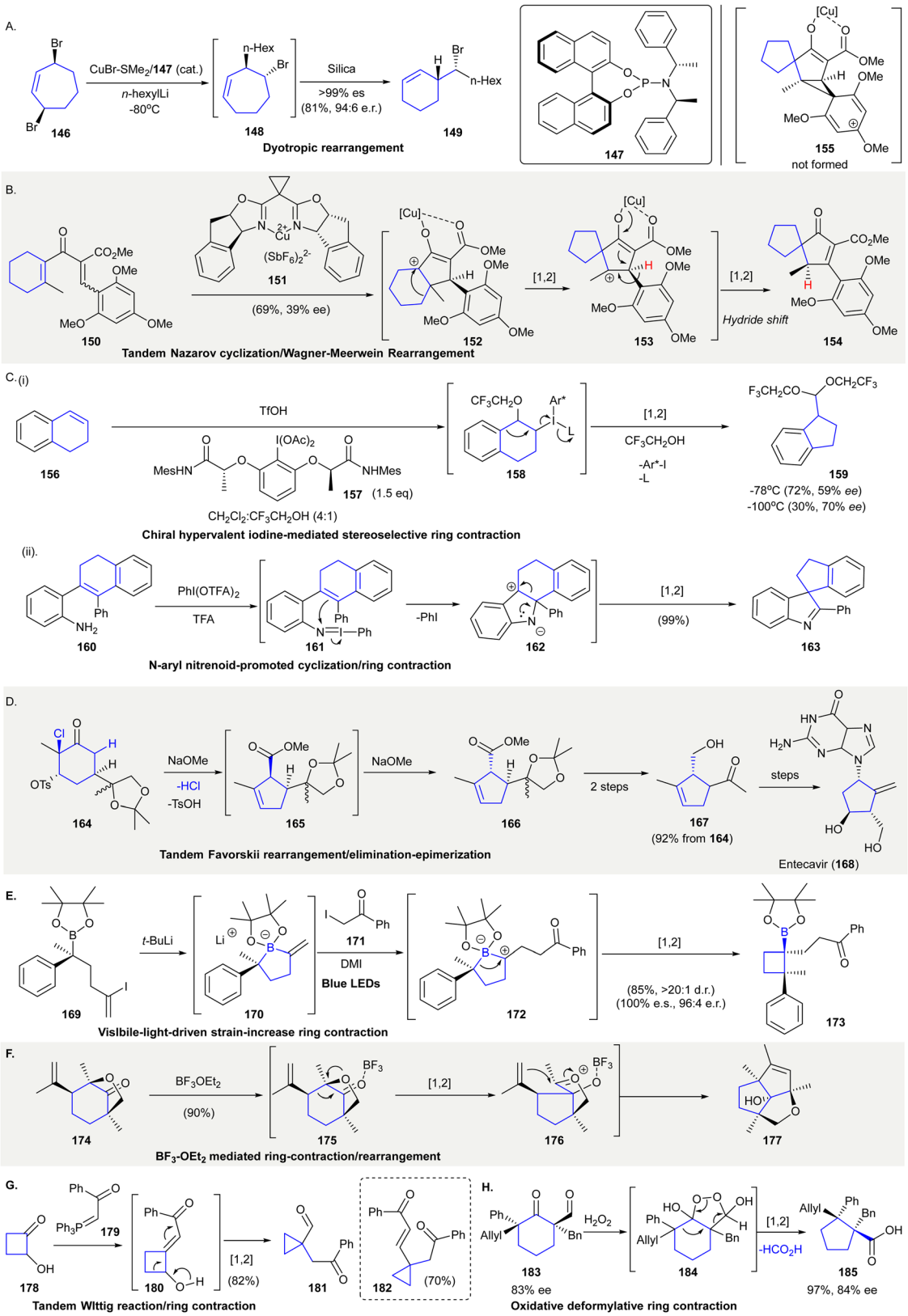
HAT, hydrogen atom transfer; DMSO, dimethyl sulfoxide; Ph, phenyl; MMPP, magnesium monoperoxyphthalate.

3.5 Novel 1,2-carbon migration synthetic methods in organic synthesis

The chiral substituted cyclohexene **149** was prepared from a tandem desymmetrization[124]/dyotropic rearrangement from *meso*-3,7-dibromocycloheptene **146**[125] (Scheme 8(A)). Upon treatment of **146** with substoichiometric amount of $CuBr{\cdot}SMe_2$/**147** and *n*-hexyllithium, the bromocycloheptene **148** (formed by asymmetric allylic substitution (AAS)) was exposed to silica giving **149** *via* stereospecific ring contraction. This dyotropic rearrangement occurred *via* a double 1,2-alkene migration followed by a 1,2-bromide migration.

A copper-mediated Nazarov cyclization followed by a double Wagner–Meerwein migration converted divinyl ketone **150** into spirocycle **154** in 69% yield with 39% ee[126] (Scheme 8(B)). The treatment of divinyl ketone **150** with stochiometric amount of copper complex **151** resulted in a Nazarov cyclization and produced intermediate **152**. The carbocation of **152** initiated a 1,2-carbon migration, generating the cationic spirocycle **153**, in which a 1,2-hydride migration took place to give spirocycle **154** as the final product. It is reported that the 1,2-hydride migration was favorable due to the electron-poor aromatic substitutions present while 1,2-carbon migration was favored with electron-rich aromatic substitutions. Unexpectedly, 1,2-hydride migration took place when electron-rich 2,4,6-trimethoxyphenyl group used as substituent (*i.e.* **153** to **154**). Authors rationalized that phenyl migration is also affected by steric factors that hinder the formation of the bridged cation intermediate **153**, resulting in the formation of 1,2-hydride shift product **154**.

Hypervalent iodine(III) reagents have been used extensively in rearrangement reactions.[127] The ring contraction of tetralone **156** relied on stoichiometric amounts of chiral hypervalent iodine(III) reagent **157** using TfOH as a Lewis acid. The reaction was theorized to proceed through phenyliodinated Intermediate **158** to afford cyclopropane **159** in 30% yield with 70% ee at −100 °C[128] (Scheme 8C(i)). Another example involved the *in situ* generation of electrophilic iodonitrene to facilitate tandem C–N bond formation and 1,2-carbon migration to give spirocyclopentane **163**[129] (Scheme 8(C)(ii)). A reaction between 2-substituted



Scheme 8 Novel 1,2-carbon migration synthetic methods in organic synthesis. (A) Desymmetrization and stereospecific ring contraction through dyotropic rearrangement.[125] (B) Tandem Nazarov cyclization/Wagner–Meerwein rearrangement.[138] (C) (i) Chiral hypervalent iodine(III) reagent **157** mediated stereoselective ring contraction.[128] (ii) *N*-aryl nitrenoid-enabled cyclization/ring contraction.[129] (D) A tandem Favorskii rearrangement/tosylate elimination-epimerization was used in the synthesis of Entecavir (**168**).[139] (E) Visible light-driven ring-contraction triggered by a 1,2-metalate rearrangement.[130] (F) A BF_3·OEt_3-mediated tandem ring contraction/rearrangement produced diquinane **177**.[133] (G) Tandem Wittig reaction/ring contraction.[134] (H) Oxidative and deformylative ring contraction gave cyclopentane **185** containing vicinal quaternary carbon centers.[135]

anilines **160** and bis(trifluoroacetoxy)iodobenzene generated the electrophilic *N*-aryl nitrenoid intermediate **161**, which enabled an intramolecular reaction to give tetracycle intermediate **162**. Intermediate **162** then underwent a 1,2-carbon migration to afford spirocycle **163** in 99% yield. Trifluoroacetic acid was added in stoichiometric amounts, improving the reaction yield by enabling the substitution of TFA on bis(trifluoroacetoxy)iodobenzene with aniline generating the iodonitrene reactant.

The synthesis of Entecavir (**168**), which is an approved drug for the treatment of hepatitis B (HBV), applied a tandem Favorskii rearrangement/elimination/epimerization to prepare the cyclopentene fragment of **166** (Scheme 8(D)). Treatment of α-chlorohexanone **164** with sodium methoxide initially produced the *cis*-substituted Favorskii rearrangement product **165**, which upon isomerization gave the more thermodynamically stable cyclopentanecarboxylate **166**. Sequential transformations, including reduction, hydrolysis of the ketal, and oxidative cleavage afforded **167** in 92% yield over three steps.

The synthesis of cycloboronic ester **173** was achieved *via* a visible-light-driven ring contraction of five-membered alkenyl boronate complex **170**[130] (Scheme 8(E)). Reactions between vinyl iodide **169** and *tert*-butyllithium produced cyclic alkenyl boronate **170**. Further reactions with iodido-compound **171** were followed by single electron oxidation to give the zwitterionic intermediate **172**. Ring-contractive 1,2-metalate rearrangement[131,132] of freshly prepared **172** afforded cyclobutyl boronic ester **173** in 85% yield with $>20:1$ diastereomeric ratio. The synthetic versatility of boronic esters enabled transformations to produce other functionalities, including the construction of adjacent quaternary stereocenters.

The Lewis acid-catalyzed 1,2-carbon migration/cyclization of substituted 1-methyl-4-isopropenyl-6-oxabicylo[3.2.1]octan-8-ones **174** produced bridged diquinane **177**[133] (Scheme 8(F)). The treatment of the cyclohexanone **174** with $BF_3{\cdot}OEt_2$ facilitated 1,2-carbon migration to give an oxocarbenium ion **176**, which underwent an ene-type reaction yielding bridged diquinane **177** in 90% yield.

The ring contraction of α-hydroxycyclobutanone **178** to cyclopropanecarbaldehyde **181** was achieved *via* simultaneous Wittig reaction and 1,2-carbon migration[134] (Scheme 8(G)). The reaction between cyclobutanone **178** and the phosphonium ylide **179** gave olefination product **180**, which underwent a 1,2-carbon migration to give cyclopropanecarbaldehyde **181** in 82% yield. The ring contraction product **182** was formed in 70% yield using two equivalents of phosphonium ylide **179**.

A stereospecific oxidative ring contraction converted α-formyl cyclic ketone **183** to **185** *via* the elimination of formic acid[135] (Scheme 8(H)). The treatment of α-formyl cyclic ketone **183** with hydrogen peroxide resulted in an intramolecular cyclization. The reaction was theorized to give 1,2-dioxolane **184** as an intermediate,[136,137] undergoing subsequent 1,2-carbon migration affording **185** in 97% yield. The relative configuration of both stereocenters were completely preserved, the chirality of the two stereocenters could then be transferred to other products.

TfOH, trifluoromethanesulfonic acid; Mes, mesityl; Ac, acetyl; Ph, phenyl; TFA, trifluoroacetic acid, *t*-Bu, *tert*-butyl; DMI, 1,3-dimethyl-2-imidazolidinone; Ph, phenyl; Bn, benzyl.

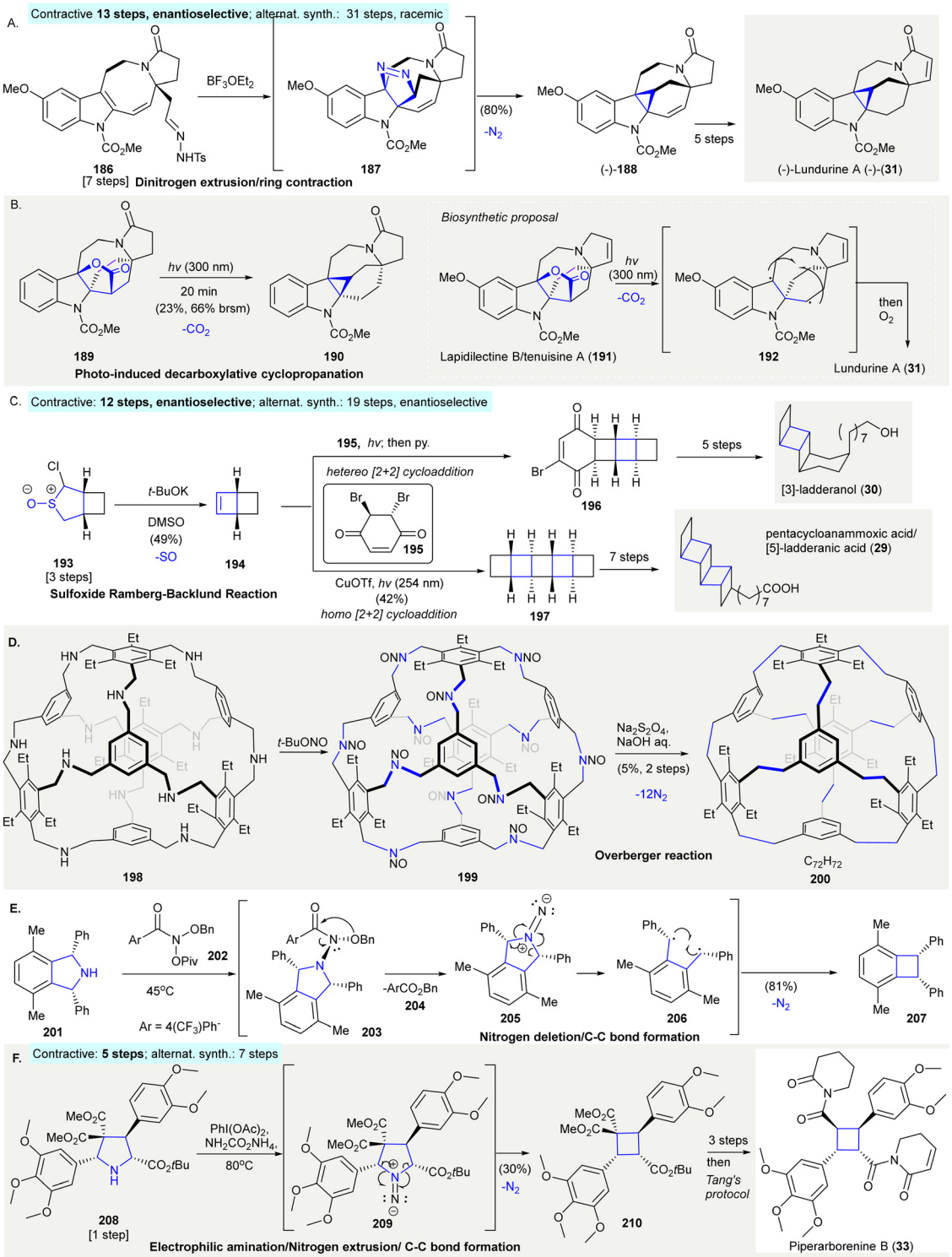
4. The contractive synthesis of carbocycles *via* gas extrusion in organic synthesis

The synthesis of (−)-lundurine A ((−)-**31**) featured indole cyclopropanation, involving a Lewis acid-mediated formal [3+2]-cycloaddition of the indole C2–C3 bond with tosyl hydrazine. Subsequent dinitrogen extrusion gave cyclopropane (−)-**188**[140] (Scheme 9(A)). Exposure of tosyl hydrazine **186** to $BF_3{\cdot}OEt_2$[141] gave an isolatable pyrazoline intermediate **187**, which underwent dinitrogen extrusion producing cyclopropane (−)-**188** in 80% yield (contractive synthesis: 13 steps,[140] enantioselective; alternative synthesis: 31 steps, racemic[142]). Later, the same research group reported a homolytic photochemical decarboxylation of γ-lactone **189** producing cyclopropane **190** in 23% yield, providing a possible biosynthetic pathway to produce *Kopsia* pyrroloazocine indole alkaloids, including lundurine A (**31**)[143] (Scheme 9(B)).

The synthesis of petacycloanammoxic acid/[5]-ladderanic acid (**29**) and [3]-ladderanol (**30**) relied on an atypical sulfoxide Ramberg–Bäcklund olefination[144] to produce bicyclohex-[2.2.0]ene **194**[66] (Scheme 9(C)). α-Chlorosulfoxide **193** was treated with excess potassium *tert*-butoxide in DMSO to afford cyclobutene **194** in 49% yield, which then underwent either a hetero [2+2] cycloaddition with **195**, followed by selective elimination of a proton with pyridine to give vinyl bromide **196**. Or, the homodimerization of **194** gave [5]-ladderane pentacycle **197**. Pentacycle **197** and vinyl bromide **196** which was converted to pentacycloanammoxic acid/[5]-ladderanic acid (**29**) and [3]-ladderanol (**30**) in further steps, respectively. Compared to typical Ramberg–Bäcklund olefinations using sulfone as precursors, this modified sulfoxide approach resulted in a high yield for olefin product **194** (contractive synthesis: 12 steps,[66] enantioselective; alternative synthesis: 19 steps,[145] enantioselective).

Overberger reaction facilitated the conversion of imine cages to hydrocarbon cages[146] (Scheme 9(D)). Nitrosoamine **199**, was prepared by the treatment of truncated tetrahedral [4+4] imine cages **198**[147] with *t*BuONO. **199** underwent reduction/dinitrogen extrusion under Overberger's conditions[67] to give "cubic" cage derivative **200** in 5% yield over two steps. This application of Overberger's reaction enabled the synthesis of less symmetric compounds from multiple building blocks. This provided access to a large variety of structures, despite the fact that alkyne metathesis can provide higher yields when synthesizing carbon cages.[148]

The nitrogen deletion of secondary amines using *N*-pivaloyloxy-*N*-alkoxyamide **202** led to C–C bond formation and was applied to the ring contraction of cyclic secondary amine to carbocycles[149] (Scheme 9(E)). The treatment of pyrrolidine **201** with **202** provided N–N bond containing compound **203**, which underwent 1,2-rearrangement to give 1,1-diazene **205** *via* the



Scheme 9 Ring contractions *via* gas extrusion reactions in organic synthesis. (A) The preparation of (−)-lundurine A (**31**) *via* dinitrogen extrusion.[140] (B) Photoinduced decarboxylative cyclopropanation produced cyclopropane **190**, structurally similar to (−)-lundurine A (**31**)[143] (inset, a new biosynthetic proposal). (C) An atypical sulfoxide Ramberg–Bäcklund olefination in the synthesis of [3]-ladderanol (**30**) and pentacycloanammoxic acid (**29**).[66] (D) Synthesis of cage structures facilitated by an Overberger reaction.[146] (E) Dinitrogen deletion from secondary amine **201** using *N*-pivaloyloxy-*N*-alkoxyamide **202** produced cylcobutane **207** through 1,4-diradical C–C bond formation.[149] (F) Stereoselective contraction of pyrrolidine **208** afforded cyclobutanes and was applied in the formal synthesis of piperarborenine B (**33**).[150]

elimination of ester **204**. Additionally, the dinitrogen extrusion of **205** produced 1,4-diradical **206** as a hypothetical intermediate. The intramolecular radical coupling of the 1,4-diradical in **206** produced **207** in 81% yield.

The iodonitrene-induced ring contraction of pyrrolidine resulted in the stereoselective synthesis of cyclobutene **210**, this method was then adopted in the formal synthesis of piperarborenine B (**33**)[150] (Scheme 9(F)). The electrophilic amination of pyrrolidine **208** was achieved *via* the generation of iodonitrene *in situ* from phenyliodiodiacetate and ammonium carbamate in 2,2,2-trifluoroethanol. This formed **209** as a suggested intermediate, in which dinitrogen extrusion from **209** afforded cylcobutane **210** in 30% yield. A further three-step synthesis from **210** formed a synthetic precursor, which was converted to piperarborenine B (**33**) in one step using Tang's protocol[151] (contractive synthesis: 6 steps;[150] alternative synthesis: 7 steps[152])

Ts, *p*-toluenesulfonyl; *t*-Bu, *tert*-butyl; DMSO, dimethyl sulfoxide; Bn, benzyl; Ph, phenyl; Ac, acetyl; Piv, pivaloyl.

5. The ring contraction *via* miscellaneous rearrangement reactions in organic synthesis

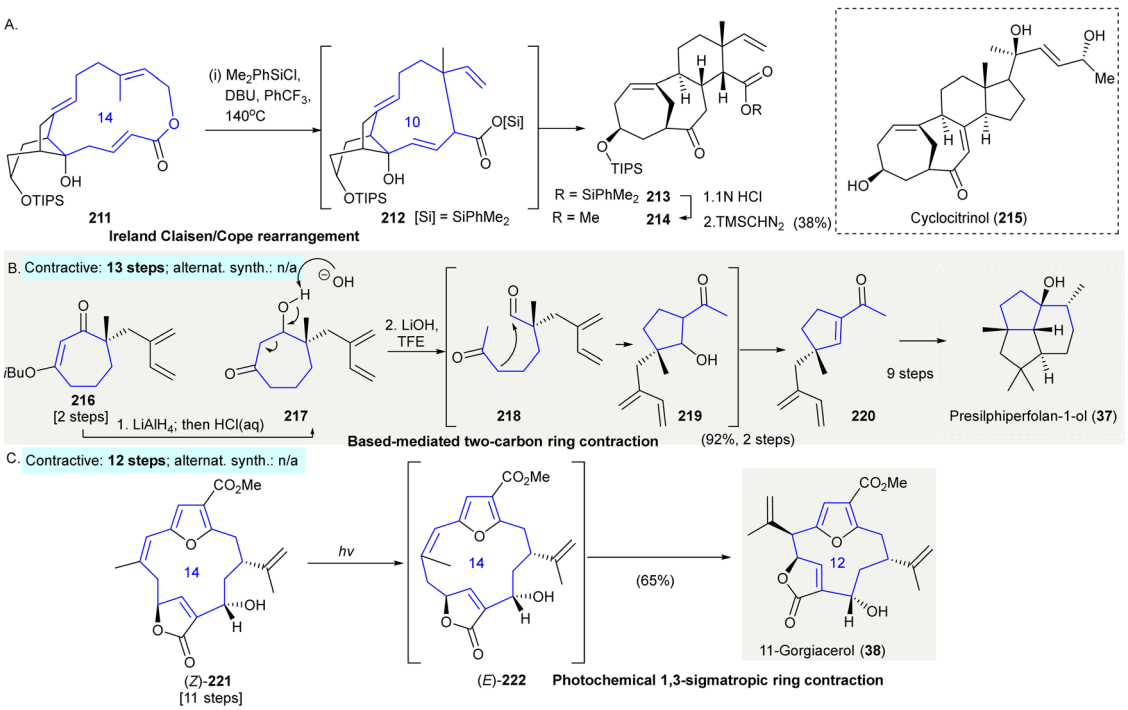
The synthesis of the cyclocitrinol core **215** involved a tandem Ireland Claisen/strain-accelerated Cope rearrangement[153] (Scheme 10(A)). An Ireland-Claisen rearrangement[154] converted macrolactone **211** to the strained 10-membered ring intermediate **212**. The resulting strain then drove the Cope rearrangement under unusually mild thermal conditions to give the tricyclic core **213**. Successive hydrolysis of the silyl ester of **213**, followed by methylation afforded methyl ester **214** in 38% yield over three steps.

The synthesis of presilphiperfolan-1-ol (**37**) used a base-mediated two-carbon ring contraction to give acylcyclopentene **220**[155,156] (Scheme 10(B)). The reduction of compound **216** by $LiAlH_4$ gave intermediate β-hydroxyketone **217**. When **217** was exposed to lithium hydroxide in 2,2,2-trifluoroethanol gave highly functionalized chiral acylcyclopentene **220** in 92% yield over two steps. The synthesis of presilphiperfolan-1-ol (**37**) was achieved from **220** in 9 additional steps (contractive synthesis: 13 steps,[155,156] enantioselective; alternative synthesis: N/A)

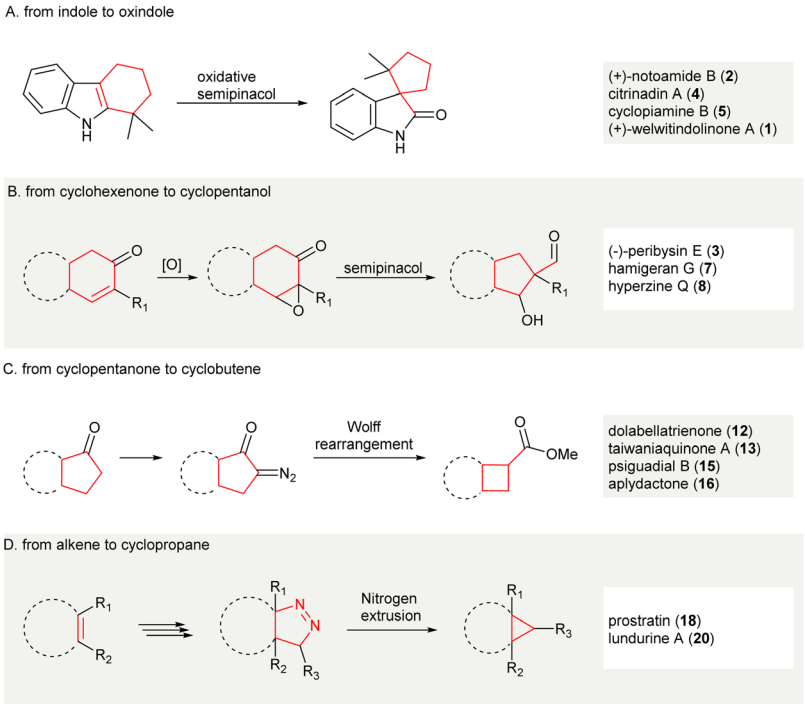
The synthesis of 11-gorgiacerol (**38**) featured a photochemical 1,3-sigmatropic ring contraction (Rodriguez–Pattenden rearrangement[157,158]) as a key synthetic step[159] (Scheme 10(C)). Photoirradiation of **221** led to olefin *Z*-to-*E* isomerization followed by a [1,3]-sigmatropic shift giving 11-gorgiacerol (**38**) in 65% yield (contractive synthesis: 12 steps;[159] alternative synthesis: N/A)

6. Summary and outlook

In this review, the contractive synthesis of carbocycles and their respective applications were discussed. Ring contractions have played important roles in organic synthesis, enabling the creation of small carbocycles with highly condensed functionalities and stereocenters (Scheme 11). Providing the efficient synthesis of complex carbocycles[26] which otherwise required multi-step,



Scheme 10 Ring contractions enabled by miscellaneous rearrangement reactions in organic synthesis. (A) A tandem ring contractive Ireland Claisen/strain-accelerated Cope rearrangement produced cyclocitrinol core **213**.[153] (B) A base-mediated two-carbon ring contraction provided access to acylcyclopentene **214** as a key intermediate in the synthesis of presilphiperfolan-1-ol (**37**).[155,156] (C) A photochemical 1,3-sigmatropic ring contraction en route to 11-gorgiacerol (**38**).[159] TIPS, triisopropylsilyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; Ph, phenyl; iBu, iso-butyl; TFE, 2,2,2-trifluoroethanol; TBS, *tert*-butyldimethylsilyl.



Scheme 11 Strategic applications of contractive synthesis in carbocycles.

time-consuming syntheses when following conventional methods.[27–29] The synthesis of carbocycles through ring contraction using well-planned methods is very practical, as they encompass one to two concepts of efficient synthesis. Including; step economy,[36] chemoselectivity,[39] protecting group-free synthesis,[40] atom economy[34] and/or redox economy.[38] Methods such as semi-pinacol rearrangements and dinitrogen extrusions demonstrate late-stage modifications of complex structures, provide the possibility of late-stage diversification,[160] and enable access to a diverse array of structural analogues which could be useful for compound libraries.

This review summarizes the contractive synthesis of carbocycles, highlighting synthetic methods in organic synthesis including natural product synthesis. The example that we discussed in this Review, ring contraction appear to be either a more efficient approach in term of synthetic steps or an

Table 1 Comparison of step-efficiency of the complex natural product synthesis using or without using ring contraction approach

Natural products	Reaction	Ring contraction	Steps of total synthesis (alter. syn)	Scheme
(+)-Welwitindolinone A	Oxidative pinacol-type rearrangement	5 → 4	**8** (22)	**1a**
(−)-Peribysin E	Semi-pinacol-type reaction	6 → 5	**18** (24)	**2b**
(−)-Taiwaniaquinone H	Benzilic acid rearrangement	6 → 5	**9** (14)	**2c**
Dolabellatrienone	Wolff arrangement	6 → 5	14 (**13**)	**2d**
Pentacycloanammoxic acid/[5]-ladderane methyl ester	Dinitrogen extrusion of 1,2-diazene	6# → 4 (fused bicyclo-hexane)	**14** (19)	**3a**
Cylindrocyclophane A	Double Ramberg-Backlund olefination	24 → 22	21 (21)	**3c**
(+)-α-Cuparenone	Decarbonylative ring contraction	6 → 5	**7**, asymmetric; (8, racemic)	**3d**
Huperzine Q	Semi-pinacol rearrangement	6 → 5	**13**, racemic (19, asymmetric)	**4e**
(+)-2-Oxostemar-13-ene		6 → 5	**11**, asymmetric; (n/a)	**4g**
(−)-Vinigrol	Benzilic acid rearrangement	7 → 6	**15** (23)	**5b**
(+)-Stephadiamine	*aza*-Benzilic acid-type rearrangement	6 → 5	**19**, enantioselective (24, racemic)	**5d**
Taiwaniaquinone A	Wolff rearrangement	6 → 5	**11**, racemic (14, asymmetric)	**6a**
Aplydactone		5 → 4	25, racemic; (**11**, enantioselective)	**6b**
Aquatolide		6 → 5	22 (**16**)	**6c**
(+)-Psiguadial B		5 → 4	15 (**1**)	**6d**
Artalbic acid	Photo-induced carboborative ring contraction	6 → 5	**5** (12)	**7a**
(−)-Lundurine A	Dinitrogen extrusion of 1,2-diazene	5# → 3	**13**, enantioselective; (31, racemic)	**9a**
[5]-Ladderane acid	Sulfoxide Ramberg–Backlund reaction	5# → 4	**12**, enantioselective (19, enantioselective)	**9c**
Piperarborenine B	Dinitrogen extrusion of 1,1-diazene	5# → 4	**5** (7)	**9f**

# denotes heterocycles.

exclusive strategy towards complex natural product synthesis. The comparison of step-efficiency of the complex natural product synthesis using or without using ring contraction approach is tabulated (Table 1). In most cases, the ring contraction involves the preparation of small carbocycles of three to five membered (*i.e.* cyclopropane, cyclobutane and cyclopentane). The behind rationale might be a result of two reasons: first, ring contraction would be a more efficient approach to prepare highly functionalized small carbocycles while more available methods and/or strategies are eligible to prepare the carbocycles of larger ring size, for instance, cycloaddition and ring-closing metathesis. Second, the synthesis of the ring contraction precursor, for example, a seven-membered ring which undergoes ring contraction to a six-membered carbocycles, would be more challenging that the product itself because of the higher kinetic and thermodynamic barriers associated the synthesis of medium-sized ring compared to other rings sizes. More importantly, chemoselective ring contraction of advanced and/or late-stage intermediates might provide a concise synthetic approach compared to the synthesis of the target natural products adopting alternative approaches, such as direct ring closure.

Ring contractive synthesis often required stoichiometric amounts of reagents to facilitate rearrangements, suggesting the possibility of developing catalytic versions. This could enable the simultaneous addition of functionalities during ring contraction, which could be useful for further method development. Ring contractions using gas extrusion required the prior introduction of heteroatom(s), however, the valuable transformations provided can offset this limitation.[30,31,66,140,143,146] Transformations with an emphasis on remodeling carbon skeletons were discussed, aiming to inspire innovative method development and method replacement in the synthesis of important, but synthetically elusive organic molecules. We anticipate ring contractions to function alongside conventional synthetic methods assisting in the further advancement of organic synthesis.

Conflicts of interest

There are no conflicts to declare.

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